# DEVELOPMENT OF ENANTIOSELECTIVE TRANSITION-METAL CATALYZED ALLYLIC ALKYLATION METHODOLOGIES

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*To my mom*

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## ABSTRACT

Research in the Stoltz group is directed, generally, at the development of synthetic methods for the preparation of stereochemically rich molecules, and the total synthesis of complex natural products. One major theme of our group's methods development is transition-metal catalyzed allylic alkylation, of which we have reported Pd, Ir, Cu, and Ni catalyzed strategies. Described in this thesis are projects related to these interests, primarily focused on new approaches toward acyclic stereocenters via palladium catalysis; however also include an iridium-catalyzed formal γ-alkylation of malonates and β-ketoesters, as well as an Overman rearrangement strategy for synthesizing α-amino ketones. A majority of asymmetric enolate functionalization methods, developed by our group and others, pertain to cyclic systems in which only one enolate geometry isomer is possible due to the constrained ring. In acyclic systems, however, this issue of enolate geometry becomes a major challenge that must be addressed. When one seeks to prepare a tetrasubstituted acyclic enolate, which would lead to a fully-substituted stereocenter following functionalization, one must contend with the issue of non-selective formation of a mixture of enolates which generally leads toward less selective transformations. Strategies toward overcoming this issue, as well as new insights gained regarding the palladium-catalyzed alkylation of acyclic enolates, are described in the subsequent chapters.

## PUBLISHED CONTENT AND CONTRIBUTIONS

1. Liu, W.–B. Okamoto, N.; Alexy, E. J.; Hong, A. Y.; Tran, K.; Stoltz, B. M. "Enantioselective γ-Alkylation of α,β-Unsaturated Malonates and Ketoesters by a Sequential Ir-Catalyzed Asymmetric Allylic Alkylation/Cope Rearrangement." *J. Am. Chem. Soc.* **2016**, *138*, 5234–5237. DOI: 10.1021/jacs.6b02153.

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3. Alexy, E. J.; Zhang, H.; Stoltz, B. M. "Catalytic Enantioselective Synthesis of Acyclic Quaternary Centers: Palladium-Catalyzed Decarboxylative Allylic Alkylation of Fully Substituted Acyclic Enol Carbonates." *J. Am. Chem. Soc.* **2018**, *140*, 10109–10112. DOI: 10.1021/jacs.8b05560.

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## *CHAPTER 4*

*Palladium-Catalyzed Decarboxylative Allylic Alkylation of Fully-Substituted N-Acyl Indole-Derived Enol Carbonates*

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### *CHAPTER 5*

*Palladium-Catalyzed Enantioselective Decarboxylative Allylic Alkylation of Protected Benzoin-Derived Enol Carbonates*.

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*X-Ray Crystallography Reports Relevant to Chapter 6*

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## *CHAPTER 7*

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| | |
|---|---|
| $[\alpha]_D$ | specific rotation at wavelength of sodium D line |
| °C | degrees Celsius |
| Å | Ångstrom |
| app | apparent |
| aq | aqueous |
| Ar | aryl |
| atm | atmosphere |
| Bn | benzyl |
| Boc | *tert*-butyloxycarbonyl |
| bp | boiling point |
| br | broad |
| Bz | benzoyl |
| *c* | concentration for specific rotation measurements |
| calc'd | calculated |
| cat | catalytic |
| CBS | Corey–Bakshi–Shibata catalyst |
| $cm^{-1}$ | wavenumber(s) |
| cod | 1,5-cyclooctadiene |
| d | doublet |
| D | deuterium |
| dba | dibenzylideneacetone |
| DDQ | 2,3-dichloro-5,6-dicyano-*p*-benzoquinone |

| | |
|---|---|
| DMAP | 4-diethylaminopyridine |
| DME | 1,2-dimethoxyethane |
| DMF | *N,N*-dimethylformamide |
| DMS | dimethylsulfide |
| Dr | diastereomeric ratio |
| EDC | *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodimide |
| *ee* | enantiomeric excess |
| EI+ | electron impact |
| equiv | equivalent(s) |
| ESI | electrospray ionization |
| Et | ethyl |
| EtOAc | ethyl acetate |
| FAB | fast atom bombardment |
| G | gram(s) |
| GC | gas chromatography |
| H | hour(s) |
| HG-II | Hoveyda-Grubbs catalyst 2$^{nd}$ generation |
| HPLC | high-performance liquid chromatography |
| HRMS | high-resolution mass spectroscopy |
| Hz | hertz |
| IPA | isopropanol |
| IR | infrared (spectroscopy) |
| *J* | coupling constant |

| | |
|---|---|
| K | Kelvin(s) (absolute temperature) |
| kcal | kilocalorie |
| KHMDS | potassium hexamethyldisilazide |
| L | liter; ligand |
| L* | chiral ligand |
| LDA | lithium diisopropylamide |
| M | multiplet; milli |
| *m* | meta |
| *m/z* | mass to charge ratio |
| Me | methyl |
| mg | milligram(s) |
| MHz | megahertz |
| min | minute(s) |
| MM | mixed method |
| mol | mole(s) |
| MOM | methoxymethyl acetal |
| mp | melting point |
| n | nano |
| *n*-Bu | butyl |
| NBS | *N*-bromosuccimide |
| NMR | nuclear magnetic resonance |
| Nu | nucleophile |
| *o* | ortho |

| | |
|---|---|
| *p* | para |
| Pd/C | palladium on carbon |
| Ph | phenyl |
| pH | hydrogen ion concentration in aqueous solution |
| PHOX | phosphinooxazoline ligand |
| Pmdba | bis(4-methoxybenzylidene)acetone |
| ppm | parts per million |
| Pr | propyl |
| q | quartet |
| R | generic for any atom or functional group |
| RCM | ring-closing metathesis |
| Ref. | reference |
| $R_f$ | retention factor |
| s | singlet |
| sat. | saturated |
| SFC | supercritical fluid chromatography |
| t | triplet |
| *t*-Bu | *tert*-butyl |
| TBAF | tetrabutylammonium fluoride |
| TBD | 1,3,4-triazabicyclo[4.4.0]dex-5-ene |
| TBHP | *tert*-butyl hydroperoxide |
| TBME | *tert*-butyl methyl ether |
| TBS | *tert*-butyldimethyl silyl |

| | |
|---|---|
| THF | tetrahydrofuran |
| TLC | thin-layer chromatography |
| TMS | trimethylsilyl |
| TOF | time-of-flight |
| $t_R$ | retention time |
| UV | ultraviolet |
| *v/v* | volume to volume |
| w/v | weight to volume |
| λ | wavelength |
| μ | micro |

# *CHAPTER 1*

## *Enantioselective γ-Alkylation of α,β-Unsaturated Malonates and Ketoesters by a Sequential Ir-Catalyzed Asymmetric Allylic Alkylation/Cope Rearrangement*[†]

### 1.1 INTRODUCTION

Enantioenriched unsaturated carbonyl compounds are valuable synthetic intermediates owing to their multiple reactive sites poised for further manipulation to synthesize complex molecules with contiguous stereocenters.[1] Direct asymmetric functionalization at the γ-position of α,β-unsaturated carbonyl derivatives would be a straightforward way to access such motifs. However, this transformation has proven challenging, likely due to the absence of proximal functionality to interact with a catalyst in order to induce facial selectivity. Furthermore, issues arise with regard to regioselectivity (α- versus γ-functionalization) and chemoselectivity (C vs O-alkylation). To date, this transformation has only been achieved in a handful of examples.[2,3] In particular, work from the Tunge group demonstrated the ability of α,β-unsaturated

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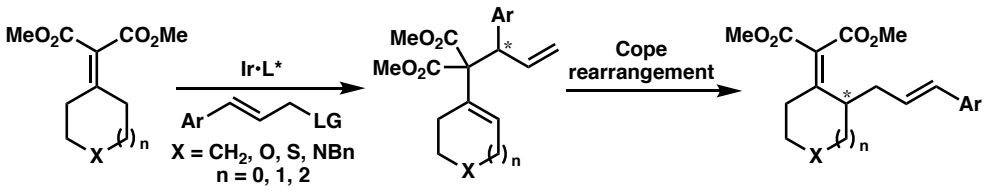
[†]This research was performed in collaboration with Wen-Bo "Boger" Liu, Noriko Okamoto, Allen Hong, and Kristy Tran. Portions of this chapter have been reproduced with permission from Liu, W.–B. Okamoto, N.; Alexy, E. J.; Hong, A. Y.; Tran, K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2016**, *138*, 5234–5237.

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carbonyls to undergo a palladium-catalyzed decarboxylative allylation/Cope rearrangement, but only one asymmetric example with alkylidene malononitriles was provided with poor enantiocontrol.[2b] Recently, the Jørgensen group reported an asymmetric γ-allylation of α,β-unsaturated aldehydes via organocatalysis combined with either iridium or palladium catalysis, providing branched or linear products respectively.[3g] Alternatively, a Birch–Cope sequence has been developed by the Malachowski group as an efficient method to access γ-alkylated α,β-unsaturated ketoesters, although stoichiometric alkali metals and chiral auxiliaries were required.[4] Despite these reports, a general strategy to selectively produce γ-functionalized unsaturated carbonyl derivatives has remained elusive.

Since the initial report in 1997, iridium-catalyzed allylic alkylation has emerged as a successful strategy for the assembly of chiral chemical architectures.[5,6] Numerous studies have been performed in this field elucidating a wide range of suitable nucleophiles.[5,7] However, the use of α,β-unsaturated carbonyls as nucleophiles has seen little attention. We hypothesized that α-alkylation of an extended enolate derived from such compounds could provide chiral 1,5-dienes poised to undergo a [3,3]-sigmatropic rearrangement, producing γ-alkylation products (Scheme 1).[8] A similar approach was utilized by Arseniyadis and Cossy to produce γ-substituted 2(5H)-furanones.[9]

***Scheme 1.1*** *Sequential Asymmetric Allylic Alkylation/Cope Rearrangement.*



## 1.2 REACTION OPTIMIZATION

We began our studies with the seven-membered cyclic alkylidene malonate **1a** and cinnamyl carbonate **2a** as the model substrates (Table 1.1). A variety of conditions including different bases, solvents, and substrate ratios were examined with iridacycle catalysts[10] generated in situ by the treatment of $[Ir(cod)Cl]_2$ and phosphoramidites (Figure 1.1) with 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD).[11, 12] Using *N*-aryl phosphoramidite ligand **L1**, developed by the You group,[12,13] α-alkylation product **3aa** is furnished in perfect enantioselectivity and moderate regioselectivity (entry 1). An investigation of solvents revealed that THF affords optimal reactivity and selectivity. The use of Feringa-type ligands[14] **L2** and **L3** resulted in either a lack of reactivity or formation of a complex mixture of side products (entries 2 and 3). Moreover, ligands **L4** and **L5** led to diminished regio- and enantioselectivity, respectively (entries 4 and 5). The use of the more sterically congested 3,3'-diphenyl-substituted phosphoramidite **L6**[15] resulted in a dramatic improvement in regioselectivity, and a modest improvement in yield (entry 6). After a careful analysis of the crude reaction mixture, we found that the moderate yield was due to hydrolysis of the carbonate under the reaction conditions. Thus, by increasing the quantity of the carbonate (1.5–2 equiv) and switching the base (LiO*t*-Bu), we were able to obtain the desired product **3aa** in 93% yield, >99% ee, and >20:1 regioselectivity (entries 8 and 9). The absolute configuration of α-alkylated product (*R*)-**3aa** was determined by X-ray crystallography.[16]

***Figure 1.1*** *Representative Phosphoramidite Ligands.*

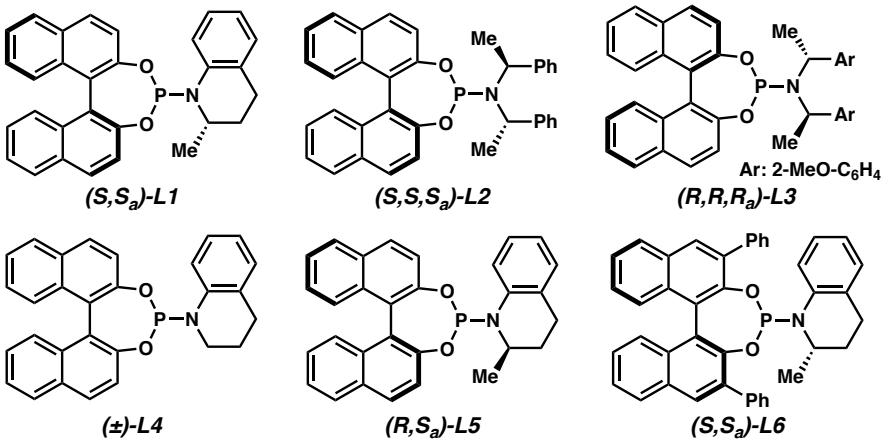
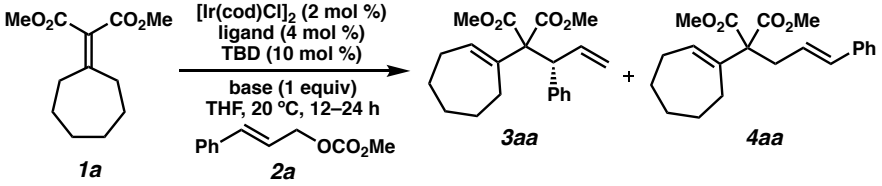



***Table 1.1*** *Optimization of Ir-Catalyzed Allylic Alkylation.*[a]




| entry | ligand | base | conv (%)[b,c] | *3aa*:*4aa*[b] | ee of *3aa* (%)[d] |
|---|---|---|---|---|---|
| 1 | *L1* | KO*t*-Bu | >95 (57) | 3:1 | >99 |
| 2 | *L2* | KO*t*-Bu | <10[e] | – | – |
| 3 | *L3* | KO*t*-Bu | >95[e] | >20:1 | >99 |
| 4 | *(±)-L4* | KO*t*-Bu | >95 | 1:1 | – |
| 5 | *L5* | KO*t*-Bu | 52 | 2:1 | 40 |
| 6 | *L6* | KO*t*-Bu | >95 (69) | >20:1 | >99 |
| 7[f] | *L6* | KO*t*-Bu | 89 (84) | >20:1 | >99 |
| 8[f] | *L6* | LiO*t*-Bu[g] | 92 (90) | >20:1 | >99 |
| 9[h] | *L6* | LiO*t*-Bu[g] | >95 (93) | >20:1 | >99 |

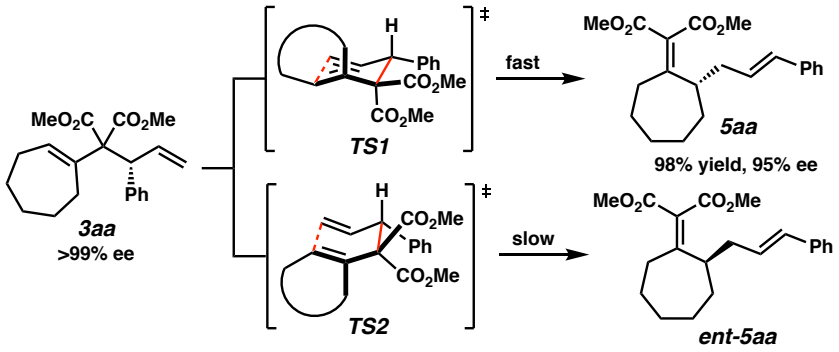
[a] Reactions performed with 0.1 mmol of **2a**, 0.2 mmol of **1a**, 0.1 mmol of base in 1 mL of THF at 20 °C for 12–24 h. [b] Regioselectivity determined by 1H NMR analysis of the crude reaction mixture. [c] Yields of isolated product **3aa** given in parentheses. [d] Determined by SFC. [e] Complex mixture. [f] With 0.1 mmol of **1a** and 0.15 mmol of **2a**. [g] 1.2 equiv. [h] With 0.1 mmol of **1a** and 0.2 mmol of **2a**.

## 1.3 INVESTIGATION OF COPE REARRANGEMENT AND REACTION SCOPE

With optimized conditions for the α-alkylation procedure established, we next examined the possibility of intramolecular chirality transfer by a Cope rearrangement. To our delight, 1,5-diene **3aa** was converted to the rearranged γ-alkylated product **5aa**[17] in

98% yield and 95% ee after heating in toluene (Scheme 1.2). The high degree of chirality transfer (96%)[18] can be rationalized by the preferential rearrangement of the diene **3aa** through a chair-like transition state (**TS1**), over the corresponding boat-like transition state (**TS2**). A one-pot procedure for the allylic alkylation/Cope rearrangement is also possible, providing the product **5aa** in 91% overall yield and 96% ee (Scheme 1.3).

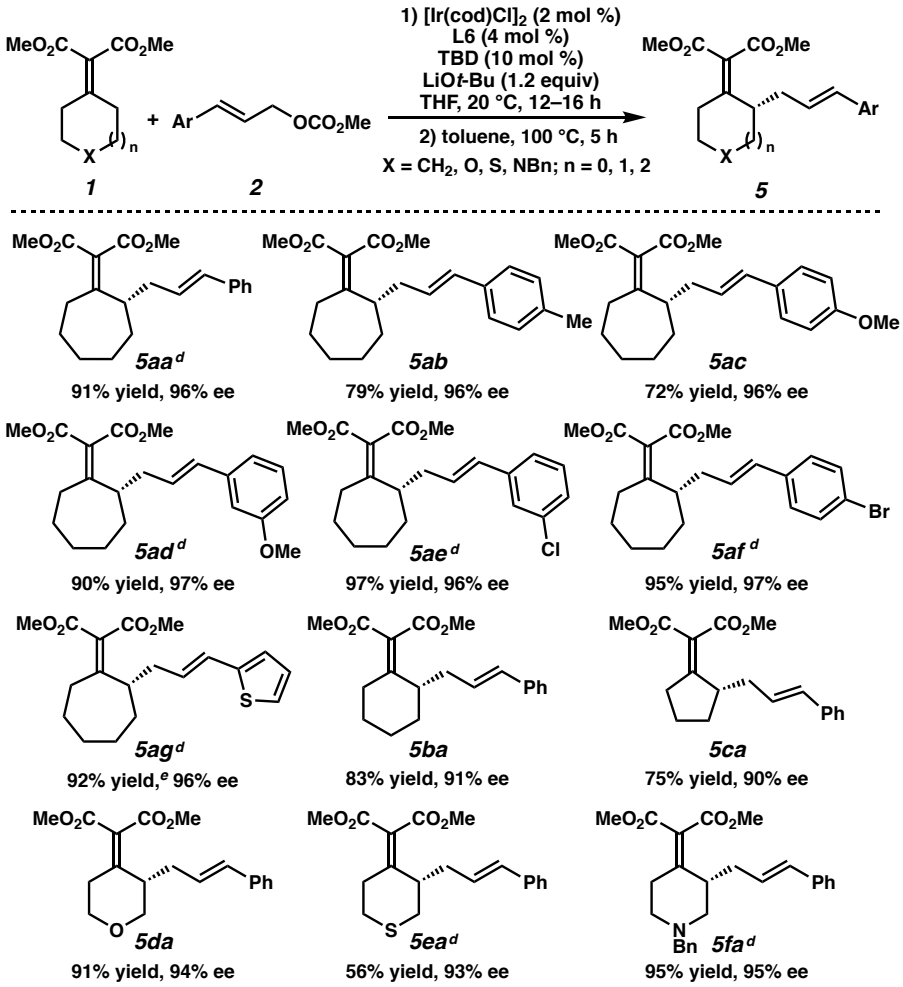
***Scheme 1.2*** *Cope Rearrangement of* ***3aa***.[a]




[a] Reactions conditions: 0.1 mmol of ***3aa*** in toluene at 100 °C for 5 h.

We next explored the impact of functional groups and ring size on this sequential protocol (Scheme 1.3).[19] A variety of cinnamyl carbonates containing either electron-rich or electron-deficient substituents are well tolerated, and the corresponding γ-alkylation products (**5ab**–**5af**) were obtained in high yield and excellent enantioselectivity. Moreover, a thienyl-substituted allylic carbonate is also compatible in this reaction, delivering product **5ag** in good yield and enantioselectivity. Five- and six-membered unsaturated malonates provide the desired products (**5ca** and **5ba**), albeit in slightly decreased yield (75% and 83%) and enantioselectivity (90% ee and 91% ee), respectively. Notably, oxygen, sulfur, and nitrogen containing heterocycles were compatible, providing the corresponding products (**5da**–**5fa**) in excellent ee and yield, except for **5ea** which was obtained in moderate yield.

***Scheme 1.3*** *Substrate Scope of Sequential Ir-Catalyzed Allylic Alkylation/Cope Rearrangement.*[a, b, c]

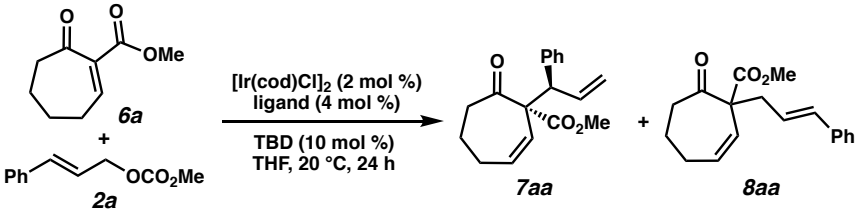



[a] Reactions performed on a 0.2 mmol scale in 2 mL of THF at 20 °C for 12–16 h, followed by stirring in toluene at 100 °C for 5 h, see SI for details. [b] Regioselectivity of the allylic alkylation determined by $^1$H NMR analysis of the crude mixture (>20:1 b:l for all cases), and ee determined by SFC. [c] Yields of isolated product. [d] One-pot procedure employed. [e] Inseparable mixture with carbonate **2g**, NMR yield.

Concurrent with these studies, we investigated the reactivity of endocyclic α,β-unsaturated β-ketoesters, a more challenging class of nucleophiles. It is widely appreciated that iridium-catalyzed allylic alkylation of prochiral nucleophiles can be problematic due to a lack of diastereocontrol during the formation of vicinal stereocenters.[5] Until recently, success has been limited to only a few examples.[13,20,21] Subjecting α,β-unsaturated β-ketoester **6a** to a slightly modified version of our optimized

conditions, the branched product **7aa** was formed exclusively, but as a 1:1 mixture of diastereomers (entry 1, Table 1.2). When ligand **L1** was used, a slight increase in diastereo- and enantioselectivity was obtained (entry 2). Lowering the reaction temperature gave modest improvement in diastereoselectivity, however the reaction required days to reach a satisfactory conversion (entry 3).

***Table 1.2*** *Ir-catalyzed Allylic Alkylation of Cyclic α,β-Unsaturated Ketoester* ***6a***.[a]



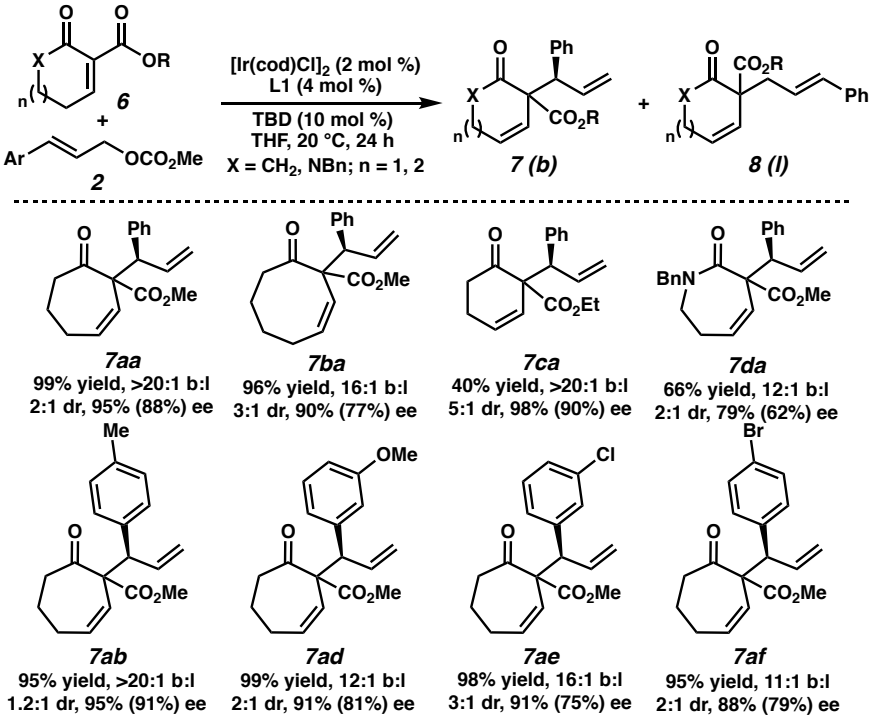

| entry | ligand | conv (%)[b] | *7aa*:*8aa*[b] | dr of *7aa*[b] | ee of *7aa* (%)[c] |
|---|---|---|---|---|---|
| 1 | *L6* | >95 | >20:1 | 1:1 | 89 (70) |
| 2 | *L1* | >95 (99)[d] | >20:1 | 2:1 | 95 (88) |
| 3[e] | *L1* | >95 | >20:1 | 5:1 | 98 (89) |

[a] Reactions performed with 0.4 mmol of **6a** and 0.2 mmol of **2a** in 2 mL of THF. [b] Determined by 1H NMR analysis. [c] Determined by SFC. [d] Combined yields of isolated diastereomers. [e] At 0 °C for 7 days.

Unfortunately, despite extensive attempts to further enhance the diastereoselectivity, no improved conditions were identified. We therefore decided to move forward with this moderate diastereoselectivity and evaluate the substrate scope of the reaction with regard to both reaction partners (Scheme 1.4). It is worth noting that in each case, both diastereomers were isolated and characterized. The reaction with an eight-membered unsaturated β-ketoester gave desired product **7ba** with high branched selectivity and moderate diastereoselectivity. Six-membered substrate afforded the corresponding alkylation product **7ca**[22] with an increased diastereo- and regioselectivity, but in only moderate yield due to the decomposition of the β-ketoester during the reaction. Lactam derivative **7da** was also accessed, although with diminished enantioselectivities for both diastereomers. Finally, several carbonates bearing various

electronically differentiated substituents were found to be well tolerated, and the corresponding products **7ad**–**7af** were furnished in good yield, with high enantioselectivity and moderate diastereoselectivity.

***Scheme 1.4*** *Substrate Scope of Ir-Catalyzed Allylic Alkylation of Cyclic α,β-Unsaturated β-Ketoesters.*[a, b, c, d]

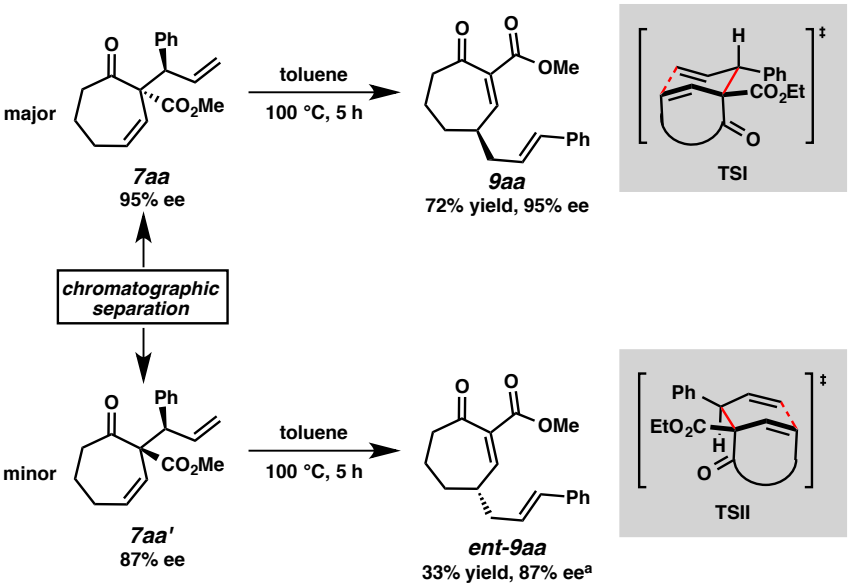



[a] Reactions performed with 0.4 mmol of **6a** and 0.2 mmol of **2a** in 2 mL of THF. [b] Regioselectivity (b:l) was determined by $^1$H NMR analysis of the crude mixture and ee was determined by SFC. [c] Combined yields of isolated diastereomers. [d] ee of the minor diastereomer given in parenthesis.

Having investigated the allylic alkylation, we next turned to the Cope rearrangement (Scheme 1.5). The major isomer (**7aa**) undergoes the rearrangement more readily than the minor isomer **7aa'**. Again, this is likely due to geometrical differences of a chair-like transition state of the major isomer (**TSI**) in contrast to a boat-like transition state of the minor isomer (**TSII**). The rigidity of the transition state plays a key role in enabling the chirality transfer (>99%).[4b] It is worth noting that the rearranged γ-alkylation products from the major isomer **7aa** and the minor isomer **7aa'** have opposite

absolute configurations (Scheme 1.5a and 1.5b). Since the diastereomers **7aa** and **7aa'** have identical tertiary chiral centers, the outcome of the rearrangement is controlled solely by the quaternary center.

***Scheme 1.5*** *Cope Rearrangement of Diastereomeric 1,5-Dienes.*




## 1.4 CONCLUSIONS

In summary, we have developed a sequential iridium-catalyzed allylic alkylation/Cope rearrangement to synthesize enantioenriched γ-substituted α,β-unsaturated malonates and β-ketoesters. The initial alkylation reaction provides efficient access to chiral 1,5-dienes with high regio- and enantioselectivities, with *N*-aryl phosphoramidite ligands being crucial for selectivity. Selective translocation of the newly established chirality to the γ-position was realized by a subsequent thermal Cope rearrangement. Further studies toward the application of this useful method in natural product synthesis are currently ongoing in our laboratory.

## 1.5 EXPERIMENTAL SECTION

### 1.5.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 μm) was used for flash chromatography. $^1$H NMR spectra were recorded on Varian Inova 500 MHz and Bruker 400 MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm). $^{13}$C NMR spectra were recorded on a Varian Inova 500 MHz spectrometer (125 MHz) and Bruker 400 MHz spectrometers (100 MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm). Data for $^1$H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet, app = apparent. Data for $^{13}$C NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer or Nicolet 6700 FTIR spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption ($cm^{-1}$). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell and are reported as: $[\alpha]_D^T$ (concentration in 10 mg/1 mL, solvent). Analytical SFC was performed with a Mettler SFC supercritical $CO_2$ analytical

chromatography system utilizing Chiralpak (AD-H, AS-H or IC) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+), or obtained from Caltech mass spectrometry laboratory. Ligands **L1**, **L4–L6**, and allyl carbonates, were prepared by known methods.

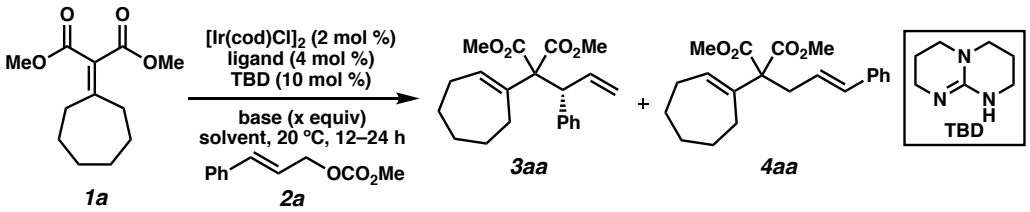
## 1.5.2 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

### 1.5.2.1 General Procedure for Optimization Reactions

*All experiments were performed in a nitrogen-filled glove box.*

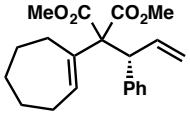
To a 2 dram vial (vial A) equipped with a magnetic stirring bar was added $[Ir(cod)Cl]_2$ (1.4 mg, 0.002 mmol, 2 mol%), ligand **L** (0.004 mmol, 4 mol%), TBD (1.4 mg, 0.01 mmol, 10 mol%), and 0.5 mL of THF. Vial A was stirred at 20 °C (~10 min) while another 2 dram vial (vial B) was charged with base, 0.5 mL of THF, alkylidene malonate **1a**, and carbonate **2a**. The pre-formed catalyst solution (vial A) was then transferred to vial B. The vial was sealed, stirred at 20 °C and monitored by TLC or UHPLC-MS. Upon completion of the reaction, the vial was removed from the glovebox and concentrated under reduced pressure. The resulting residue was dissolved in $Et_2O$ and filtered through a pad of silica, rinsing with $Et_2O$. The regioselectivity (branched to linear) was determined by $^1H$ NMR analysis of this crude mixture. The residue was purified by silica gel flash chromatography (gradient elution, 0→5→10% $Et_2O$ in hexanes) to afford the desired product.

***Table 1.3*** *Optimization of reaction parameters.*




| entry[a] | ligand | solvent | base (x equiv) | equiv of *1a* | equiv of *2a* | conv (%)[b,c] | *3aa*:*4aa*[b] | ee of *3aa* (%)[d] |
|---|---|---|---|---|---|---|---|---|
| 1 | *L1* | THF | LiO*t*-Bu (1) | 2 | 1 | >95 (28) | 1:1 | 95 |
| 2 | *L1* | THF | NaO*t*-Bu (2) | 2 | 1 | >95 (47) | 3:1 | 94 |
| 3 | *L1* | THF | NaH (2) | 2 | 1 | <5 | – | – |
| 4 | *L1* | THF | KO*t*-Bu (2) | 2 | 1 | >95 (43) | 3:1 | 97 |
| 5 | *L1* | THF | KO*t*-Bu (1) | 2 | 1 | >95 (57) | 3:1 | >99 |
| 6 | *L1* | THF | KO*t*-Bu (1) | 1.2 | 1 | 89 | 3:1 | >99 |
| 7 | *L1* | THF | KO*t*-Bu (0.3) | 1.2 | 1 | 32 | 3:1 | – |
| 8 | *L1* | THF | $Cs_2CO_3$ (1) | 1.2 | 1 | 14 | 1:1 | – |
| 9 | *L1* | THF | CsOH·$H_2O$ (1) | 1.2 | 1 | 74 | 3:1 | – |
| 10 | *L1* | dioxane | KO*t*-Bu (1) | 2 | 1 | >95 (54) | 3:1 | >99 |
| 11 | *L1* | $Et_2O$ | KO*t*-Bu (1) | 2 | 1 | 90 | 2:1 | >99 |
| 12 | *L1* | MTBE | KO*t*-Bu (1) | 2 | 1 | 86 | 2:1 | 95 |
| 13 | *L1* | $CH_2Cl_2$ | KO*t*-Bu (1) | 2 | 1 | >95 | 2:1 | 97 |
| 14 | *L1* | DCE | KO*t*-Bu (1) | 2 | 1 | 59 | 2:1 | 98 |
| 15 | *L1* | toluene | KO*t*-Bu (1) | 2 | 1 | 94 | 2:1 | 97 |
| 16 | *L1* | cyclohexane | KO*t*-Bu (1) | 2 | 1 | 94 | 2:1 | 97 |
| 17 | *L1* | MeCN | KO*t*-Bu (1) | 2 | 1 | >95 | 1:1 | 94 |
| 18 | *L1* | DMF | KO*t*-Bu (1) | 2 | 1 | >95 | 1:1 | 99 |
| 19 | *L2* | THF | KO*t*-Bu (1) | 2 | 1 | <10[e] | – | – |
| 20 | *L3* | THF | KO*t*-Bu (1) | 2 | 1 | >95[e] | >20:1 | >99 |
| 21 | *(±)-L4* | THF | KO*t*-Bu (1) | 2 | 1 | >95 | 1:1 | – |
| 22 | *L5* | THF | KO*t*-Bu (1) | 2 | 1 | 52 | 2:1 | 40 |
| 23 | *L6* | THF | KO*t*-Bu (1) | 2 | 1 | >95 (69) | >20:1 | >99 |
| 24 | *L6* | THF | KO*t*-Bu (1) | 1 | 1.5 | 89 (84) | >20:1 | >99 |
| 25 | *L6* | THF | LiO*t*-Bu (1.2) | 1 | 1.5 | 92 (90) | >20:1 | >99 |
| 26 | *L6* | THF | LiO*t*-Bu (1.2) | 1 | 2 | >95 (93) | >20:1 | >99 |

[a] Reactions performed at 0.1 mmol scale in THF (1 mL) at 20 °C for 12–24 h. [b] Determined by $^1$H NMR analysis of the crude reaction mixture. [c] Yield of isolated product **3aa** given in parenthesis. [d] Determined by SFC analysis (Chiralpak AD-H). [e] Complex mixture.

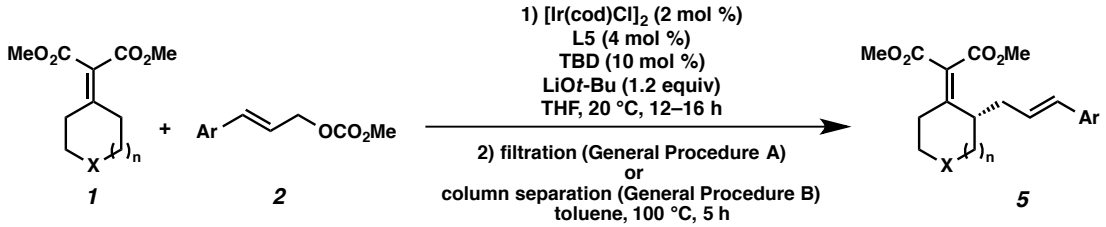



**Dimethyl (R)-2-(cyclohept-1-en-1-yl)-2-(1-phenylallyl)malonate (3aa)**

White solid, >99% ee, $[\alpha]_D^{25}$ –72.1 (*c* 0.76, $CHCl_3$); $R_f$ = 0.3 (10% $Et_2O$ in hexanes); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 2H), 7.26 – 7.21 (m, 2H), 7.20 – 7.14 (m, 1H), 6.36 (ddd, *J* = 17.0, 10.2, 8.9 Hz, 1H), 6.17 (t, *J* = 6.8 Hz, 1H), 5.06 (ddd, *J* = 10.2, 1.8, 0.8 Hz, 1H), 5.00 (ddd, *J* = 17.1, 1.8, 1.1 Hz, 1H), 4.29 (d, *J* = 8.9 Hz, 1H), 3.68 (s, 3H), 3.61 (s, 3H), 2.18–2.10 (m, 2H), 1.96–1.81 (m, 2H), 1.75–1.66 (m, 1H), 1.64–1.55 (m, 1H), 1.54–1.31 (m, 3H), 1.31–1.20 (m, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 170.7, 170.3, 140.5, 139.2, 138.6, 132.2, 130.2, 127.9, 126.8, 116.9, 70.1, 53.9, 52.3, 52.2, 32.7, 32.4, 28.7, 26.3, 26.2; IR (Neat Film, NaCl) 2925, 1737, 1728, 1451, 1433, 1241, 1050 $cm^{-1}$; HRMS (ESI-APCI+) *m/z* calc'd for $C_{21}H_{27}O_4$ $[M+H]^+$: 343.1904, found 343.1905; SFC conditions: 2% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 7.34, major = 8.12.

### 1.5.2.2 General Procedure for the Ir-Catalyzed Asymmetric Allylic Alkylation/Cope Rearrangement of Cyclic Alkylidene Malonates.

*Please note that the absolute configuration was determined only for compound* **5a** *via X-ray analysis of its derivative (vide infra). The absolute configuration for all other products* ***5*** *has been inferred by analogy.*

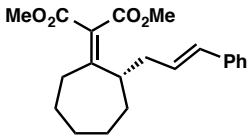


*General Procedure A (One-pot):* In a nitrogen-filled glove box, $[Ir(cod)Cl]_2$ (2.7 mg, 0.004 mmol, 2 mol%), ligand **L6** (4.9 mg, 0.008 mmol, 4 mol%), and TBD (2.8 mg, 0.02 mmol, 10 mol%) were added to a 2 dram vial equipped with a magnetic stirring bar. The vial was then charged with THF (1 mL) and stirred at 20 °C for 10 min, generating a brown solution. To another 2 dram vial was added LiO*t*-Bu (19.2 mg, 0.24 mmol, 1.2 equiv), alkylidene malonates **1** (0.2 mmol, 1 equiv), allylic carbonates **2** (0.3–0.4 mmol, 1.5–2 equiv), and 1 mL of THF. Then, the above pre-formed catalyst solution was transferred to this vial by syringe. The vial was capped and stirred at 20 °C until the alkylidene malonate was fully consumed, as indicated by TLC or UHPLC-MS analysis. Upon completion of the reaction, the vial was removed from the glovebox and the THF removed under reduced pressure. The regioselectivity (branched to linear, b:l >20:1 for all cases) was determined by $^1$H NMR of the crude reaction mixture. The crude sample was recovered from the NMR tube and concentrated. The resulting residue was dissolved in 2 mL of toluene, placed in a sealed vial, and stirred at 100 °C for 5 h. After removal of the solvent, the residue was purified by silica gel flash chromatography to afford the desired product.

*General Procedure B (Column Separation):* In a nitrogen-filled glove box, $[Ir(cod)Cl]_2$ (2.7 mg, 0.004 mmol, 2 mol%), ligand **L6** (4.9 mg, 0.008 mmol, 4 mol%), and TBD (2.8 mg, 0.02 mmol, 10 mol%) were added to a 2 dram vial equipped with a magnetic stirring bar. The vial was then charged with THF (1 mL) and stirred at 20 °C for 10 min, generating a brown solution. To another 2 dram vial was added LiO*t*-Bu (19.2 mg, 0.24 mmol, 1.2 equiv), alkylidene malonates **1** (0.2 mmol, 1 equiv), allylic carbonates **2** (0.3–0.4 mmol, 1.5–2 equiv), and 1 mL of THF. Then the above pre-formed

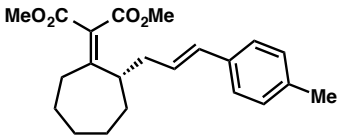
catalyst solution was transferred to this vial by syringe. The vial was capped and stirred at 20 °C until the alkylidene malonate was fully consumed, as indicated by TLC or UHPLC-MS analysis. Upon completion of the reaction, the vial was removed from the glovebox and the THF removed under reduced pressure. The regioselectivity (branched to linear: b:l >20:1 for all cases) was determined by $^{1}$H NMR of the crude reaction mixture. The residue was then purified by silica gel flash chromatography to afford the desired allylation product, which was then dissolved in 2 mL of toluene, sealed, and stirred for 5 h at 100 °C. After removal of the solvent, the residue was purified by silica gel flash chromatography to afford the desired product.

### 1.5.2.3 Spectroscopic Data for the Ir-Catalyzed Asymmetric Allylic Alkylation/Cope Rearrangement Products.

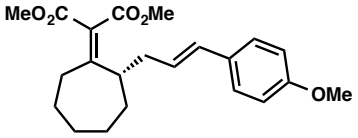



**Dimethyl (*S*)-2-(2-cinnamylcyclohexylidene)malonate 5aa**: General Procedure A was followed. Purified by silica gel flash chromatography (10→20% $Et_2O$ in hexanes) to afford the product as a colorless oil (62.4 mg, 91% yield); 96% ee, $[\alpha]_D^{25}$ –111.1 (*c* 0.72, $CHCl_3$); $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 2H), 7.31 – 7.27 (m, 2H), 7.22 – 7.16 (m, 1H), 6.37 (d, *J* = 15.7 Hz, 1H), 6.17 (ddd, *J* = 15.5, 8.1, 6.8 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.13 (ddt, *J* = 11.0, 8.4, 5.7 Hz, 1H), 2.99 – 2.90 (m, 1H), 2.45 – 2.40 (m, 1H), 2.28 – 2.22 (m, 1H), 2.11 – 1.96 (m, 3H), 1.87 – 1.69 (m, 2H), 1.51 – 1.39 (m, 1H), 1.36 – 1.24 (m, 2H), 1.17 – 1.04 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 168.3, 166.5, 165.8, 137.7, 131.8, 128.6, 127.9, 127.1, 126.2, 124.6, 52.2, 52.1, 44.4, 39.9, 31.7, 30.9, 29.8, 29.6, 25.9; IR (Neat Film, NaCl) 2924, 1723, 1618, 1433, 1231, 1192, 1068

$cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{21}H_{27}O_4$ $[M+H]^+$: 343.1909, found 343.1919; SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 254 nm, $t_R$ (min): major = 4.55, minor = 4.88.

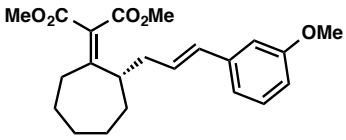



**Dimethyl (*S*,*E*)-2-(2-(3-(*p*-tolyl)allyl)cycloheptylidene)malonate 5ab**: General Procedure B was followed. Purified by silica gel flash chromatography (10% $Et_2O$ in hexanes) to afford the product as a colorless oil (56.5 mg, 79% yield); 96% ee, $[\alpha]_D^{25}$ – 107.2 (*c* 1.67, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.21 (m, 2H), 7.14 – 7.06 (m, 2H), 6.34 (d, *J* = 15.7 Hz, 1H), 6.11 (ddd, *J* = 15.4, 8.1, 6.8 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.14 – 3.08 (m, 1H), 3.01 – 2.89 (m, 1H), 2.44 – 2.38 (m, 1H), 2.32 (s, 3H), 2.28 – 2.17 (m, 1H), 2.11 – 1.94 (m, 3H), 1.87 – 1.70 (m, 2H), 1.50 – 1.39 (m, 1H), 1.36 – 1.23 (m, 2H), 1.15 – 1.03 (m, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 168.3, 166.5, 165.7, 136.8, 134.9, 131.6, 129.3, 126.7, 126.0, 124.5, 52.1, 52.0, 44.5, 39.9, 31.6, 30.8, 29.7, 29.6, 25.9, 21.3; IR (Neat Film, NaCl) 3022, 2924, 2855, 1727, 1615, 1513, 1434, 1294, 1276, 1231, 1192, 1070, 1045, 1028, 967, 790 $cm^{-1}$; HRMS (MM: ESI-APCI+) calc'd for $C_{22}H_{29}O_4$ $[M+H]^+$: 357.2060, found 357.2059; SFC conditions: 5% IPA, 2.5 mL/min, Chiralpak IC column, λ = 254 nm, $t_R$ (min): major = 7.54, minor = 10.52.



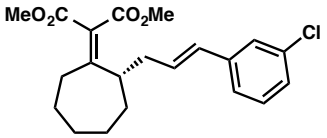

**Dimethyl (*S*)-2-(2-(3-(4-methoxyphenyl)allyl)cycloheptylidene)malonate 5ac**: General Procedure B was followed. Purified by silica gel flash chromatography (10→20% $Et_2O$ in hexanes) to afford the product as a colorless oil (53.6 mg, 72% yield); 96% ee, $[\alpha]_D^{25}$ –

72.7 (*c* 1.42, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.17 (m, 2H), 6.79 – 6.73 (m, 2H), 6.24 (dt, *J* = 15.7, 1.3 Hz, 1H), 5.94 (ddd, *J* = 15.6, 8.1, 6.8 Hz, 1H), 3.72 (s, 3H), 3.69 (s, 3H), 3.66 (s, 3H), 3.06 – 3.00 (m, 1H), 2.91 – 2.83 (m, 1H), 2.35 – 2.30 (dddd, *J* = 13.5, 6.8, 5.3, 1.5 Hz, 1H), 2.15 (dtd, *J* = 13.5, 8.3, 1.2 Hz, 1H), 2.02 – 1.88 (m, 3H), 1.77 – 1.62 (m, 2H), 1.43 – 1.30 (m, 1H), 1.29 – 1.15 (m, 2H), 1.05 – 0.98 (m, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 168.4, 166.5, 165.7, 158.9, 131.1, 130.5, 127.3, 125.6, 124.5, 114.0, 55.4, 52.2, 52.1, 44.5, 39.9, 31.6, 30.8, 29.7, 29.6, 25.9; IR (Neat Film, NaCl) 2928, 2854, 1725, 1608, 1577, 1511, 1434, 1292, 1276, 1233, 1192, 1174, 1139, 1070, 1034, 967 $cm^{-1}$; HRMS (MM: ESI-APCI+) calc'd for $C_{22}H_{29}O_5$ $[M+H]^+$: 373.2010, found 373.2016; SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak IC column, λ = 254 nm, $t_R$ (min): major = 7.39, minor = 9.02.

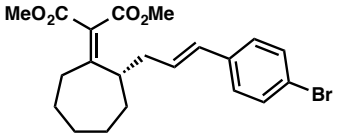



**Dimethyl (*S*,*E*)-2-(2-(3-(3-methoxyphenyl)allyl)cycloheptylidene)malonate 5ad**: General Procedure A was followed. Purified by silica gel flash chromatography (10→20% $Et_2O$ in hexanes) to afford the product as a colorless oil (67.3 mg, 90% yield); 97% ee, $[\alpha]_D^{25}$ –98.0 (*c* 1.35, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.20 (t, *J* = 7.9 Hz, 1H), 6.94 (dt, *J* = 7.5, 1.3 Hz, 1H), 6.88 (dd, *J* = 2.6, 1.6 Hz, 1H), 6.76 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 6.35 (dt, *J* = 15.9, 1.3 Hz, 1H), 6.16 (ddd, *J* = 15.7, 8.1, 6.7 Hz, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 3.74 (s, 3H), 3.19 – 3.08 (m, 1H), 3.00 – 2.86 (m, 1H), 2.45 – 2.39 (m, 1H), 2.29 – 2.18 (m, 1H), 2.12 – 1.92 (m, 3H), 1.86 – 1.68 (m, 2H), 1.51 – 1.37 (m, 1H), 1.37 – 1.19 (m, 2H), 1.16 – 1.03 (m, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 168.2, 166.4, 165.7, 159.9, 139.1, 131.7, 129.5, 128.2, 124.5, 118.9, 112.8, 111.5, 55.3, 52.2, 52.1, 44.3,

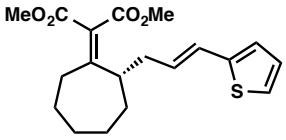
39.8, 31.6, 30.8, 29.8, 29.6, 25.9; IR (Neat Film, NaCl) 2997, 2945, 2927, 2854, 1725, 1598, 1579, 1488, 1434, 1289, 1231, 1192, 1165, 1155, 1070, 1044, 968, 940, 775 $cm^{-1}$; HRMS (MM: ESI-APCI+) calc'd for $C_{22}H_{29}O_5$ $[M+H]^+$: 373.2010, found 373.2001; SFC conditions: 5% MeOH, 2.5 mL/min, Chiralpak IC column, λ = 254 nm, $t_R$ (min): major = 9.50, minor = 10.16.




**Dimethyl (*S*,*E*)-2-(2-(3-(3-chlorophenyl)allyl)cycloheptylidene)malonate 5ae**: General Procedure A was followed. Purified by silica gel flash chromatography (10% $Et_2O$ in hexanes) to afford the product as a colorless oil (73.3 mg, 97% yield); 96% ee, $[\alpha]_D^{25}$ – 88.1 (*c* 1.27, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.30 (m, 1H), 7.24 – 7.18 (m, 2H), 7.18 – 7.11 (m, 1H), 6.31 (dt, *J* = 15.6, 1.2 Hz, 1H), 6.18 (ddd, *J* = 15.7, 8.0, 6.8 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 3.15 (ddt, *J* = 11.3, 8.4, 5.8 Hz, 1H), 2.95 – 2.87 (m, 1H), 2.41 (dddd, *J* = 13.5, 6.8, 5.5, 1.4 Hz, 1H), 2.24 (dtd, *J* = 13.5, 8.1, 1.0 Hz, 1H), 2.09 – 1.94 (m, 3H), 1.85 – 1.72 (m, 2H), 1.50 – 1.37 (m, 1H), 1.36 – 1.20 (m, 2H), 1.15 – 1.03 (m, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 167.9, 166.4, 165.8, 139.6, 134.5, 130.5, 129.8, 129.6, 127.1, 126.1, 124.7, 124.4, 52.2, 52.1, 44.1, 39.8, 31.7, 30.8, 29.8, 29.6, 25.9; IR (Neat Film, NaCl) 2927, 2854, 1726, 1619, 1615, 1593, 1434, 1294, 1276, 1231, 1192, 1140, 1070, 1045, 1028, 964, 776 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{21}H_{26}ClO_4$ $[M+H]^+$: 377.1520, found 377.1503; SFC conditions: 3% IPA, 4 mL/min, Chiralpak IC column, λ = 254 nm, $t_R$ (min): major = 12.00, minor = 17.72.

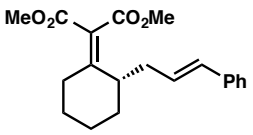



**Dimethyl (*S*,*E*)-2-(2-(3-(4-bromophenyl)allyl)cycloheptylidene)malonate 5af**: General Procedure A was followed. Purified by silica gel flash chromatography (10% $Et_2O$ in hexanes) to afford the product as a colorless oil (80.2 mg, 95% yield); 97% ee, $[\alpha]_D^{25}$ – 69.9 (*c* 1.66, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.35 (m, 2H), 7.25 – 7.16 (m, 2H), 6.30 (d, *J* = 15.6 Hz, 1H), 6.15 (ddd, *J* = 15.6, 8.0, 6.8 Hz, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.17 – 3.11 (m, 1H), 2.96 – 2.87 (m, 1H), 2.42 – 2.36 (m, 1H), 2.27 – 2.20 (m, 1H), 2.08 – 1.94 (m, 3H), 1.85 – 1.71 (m, 2H), 1.50 – 1.37 (m, 1H), 1.35 – 1.22 (m, 2H), 1.13 – 1.05 (m, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 167.9, 166.4, 165.8, 136.6, 131.7, 130.6, 128.8, 127.7, 124.7, 120.8, 52.2, 52.1, 44.2, 39.8, 31.8, 30.8, 29.7, 29.6, 25.9. IR (Neat Film, NaCl) 2927, 2855, 1726, 1619, 1615, 1593, 1567, 1434, 1294, 1276, 1231, 1193, 1140, 1070, 1028, 964, 777 $cm^{-1}$; HRMS (MM: ESI-APCI+) calc'd for $C_{21}H_{24}O_4Br$ $[M–H_2+H]^+$: 419.0852, found 419.0847; SFC conditions: 9% MeOH, 2.5 mL/min, Chiralpak IC column, λ = 254 nm, $t_R$ (min): major = 5.33, minor = 5.85.



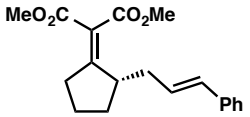

**Dimethyl (*S*,*E*)-2-(2-(3-(thiophen-2-yl)allyl)cycloheptylidene)malonate 5ag**: General Procedure A was followed. Purified by silica gel flash chromatography (10% $Et_2O$ in hexanes) to afford the product as an inseparable mixture with starting material **1a** (65.7 mg of mixture containing 64.0 mg of **5ag** based on $^1H$ NMR integration, 92% yield). Analytically pure product was obtained by preparative HPLC (ACE 5 C18, 250 x 21 2mm id column; gradient, 15–100% MeCN in $H_2O$ for 2 min, then 100% MeCN; flow

rate = 10 mL/min; λ = 254 nm) as a colorless oil; 96% ee, $[\alpha]_D^{25}$ –97.3 (*c* 1.82, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.09 (dt, *J* = 5.1, 0.9 Hz, 1H), 6.92 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.87 (d, *J* = 3.3 Hz, 1H), 6.50 (d, *J* = 15.5 Hz, 1H), 5.99 (ddd, *J* = 15.3, 8.1, 6.9 Hz, 1H), 3.75 (s, 3H), 3.75 (s, 3H), 3.15 – 3.08 (m, 1H), 3.00 – 2.84 (m, 1H), 2.42 – 2.36 (m, 1H), 2.28 – 2.10 (m, 1H), 2.10 – 1.90 (m, 3H), 1.90 – 1.65 (m, 2H), 1.54 – 1.37 (m, 1H), 1.34 – 1.23 (m, 2H), 1.17 – 0.94 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.1, 166.4, 165.7, 142.8, 127.7, 127.3, 125.0, 124.7, 124.6, 123.5, 52.2, 52.1, 44.3, 39.7, 31.6, 30.8, 29.8, 29.6, 25.9; IR (Neat Film, NaCl) 2927, 2855, 1726, 1619, 1615, 1593, 1567, 1434, 1294, 1276, 1231, 1193, 1140, 1070, 1028, 964, 777 $cm^{-1}$; HRMS (MM: ESI-APCI+) calc'd for $C_{19}H_{25}O_4S$ $[M+H]^+$: 349.1468, found 349.1469; SFC conditions: 3% MeOH, 2.5 mL/min, Chiralpak IC column, λ = 254 nm, $t_R$ (min): major = 11.55, minor = 12.69.

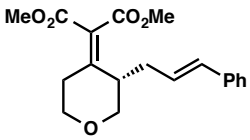



**Dimethyl (*S*)-2-(2-cinnamylcyclohexylidene)malonate 5ba**: General Procedure B was followed. Purified by silica gel flash chromatography (10%→20% $Et_2O$ in hexanes) to afford the product as a colorless oil (54.3 mg, 83% yield); 91% ee, $[\alpha]_D^{25}$ –36.3 (*c* 0.73, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.32 (m, 2H), 7.32 – 7.27 (m, 2H), 7.23 – 7.16 (m, 1H), 6.40 (d, *J* = 15.7 Hz, 1H), 6.14 (ddd, *J* = 15.6, 7.8, 6.8 Hz, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.29 – 3.21 (m, 1H), 3.05 – 2.96 (m, 1H), 2.55 – 2.42 (m, 2H), 2.17 (td, *J* = 13.9, 4.9 Hz, 1H), 1.98 – 1.91 (m, 1H), 1.91 – 1.84 (m, 1H), 1.74 – 1.56 (m, 3H), 1.53 – 1.39 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 166.3, 166.2, 164.4, 137.7, 131.7, 128.6, 128.2, 127.2, 126.2, 122.2, 52.24, 52.18, 39.7, 35.6, 30.5, 27.9, 27.8, 20.3; IR (Neat Film, NaCl) 2933, 2858, 1727, 1626, 1599, 1495, 1449, 1434, 1365, 1336, 1296, 1271, 1251,

1216, 1143, 1103, 1085, 1058, 1016, 966, 743 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{20}H_{25}O_4$ $[M+H]^+$: 329.1753, found 329.1750; SFC conditions: 15% IPA, 2.5 mL/min, Chiralcel OJ-H column, λ = 254 nm, $t_R$ (min): minor = 2.87, major = 4.16.

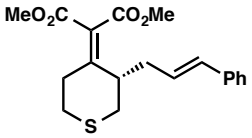



**Dimethyl (*S*)-2-(2-cinnamylcyclopentylidene)malonate 5ca**: General Procedure B was followed. Purified by silica gel flash chromatography (10%→20% $Et_2O$ in hexanes) to afford the product as a colorless oil (47.2 mg, 75% yield); 90% ee, $[\alpha]_D^{25}$ –49.9 (*c* 1.13, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.33 (m, 2H), 7.31 – 7.28 (m, 2H), 7.23 – 7.18 (m, 1H), 6.38 (dt, *J* = 15.8, 1.3 Hz, 1H), 6.16 (ddd, *J* = 15.7, 8.2, 6.3 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.36 – 3.32 (m, 1H), 2.82 – 2.74 (m, 1H), 2.74 – 2.60 (m, 1H), 2.46 – 2.40 (m, 1H), 2.18 – 2.11 (m, 1H), 1.87 – 1.68 (m, 4H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 172.3, 165.9, 137.5, 131.9, 131.9, 128.6, 128.2, 127.2, 126.2, 120.6, 52.2, 52.1, 44.6, 36.9, 33.5, 30.3, 22.8; IR (Neat Film, NaCl) 2951, 2877, 1725, 1634, 1598, 1494, 1435, 1317, 1274, 1232, 1194, 1173, 1061, 1013, 968, 743 $cm^{-1}$; HRMS (MM: ESI-APCI+) calc'd for $C_{19}H_{23}O_4$ $[M+H]^+$: 315.1591, found 315.1600; SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 254 nm, $t_R$ (min): minor = 4.41, major = 4.79.



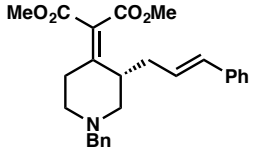

**Dimethyl (*S*)-2-(3-cinnamyltetrahydro-4*H*-pyran-4-ylidene)malonate 5da**: General Procedure B was followed. Purified by silica gel flash chromatography (10%→20% $Et_2O$ in hexanes) to afford the product as a colorless oil (60.3 mg, 91% yield); 94% ee, $[\alpha]_D^{25}$ –52.9 (*c* 1.26, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 2H), 7.30 –

7.27 (m, 2H), 7.24 – 7.14 (m, 1H), 6.46 (dt, *J* = 15.7, 1.3 Hz, 1H), 6.16 (ddd, *J* = 15.7, 8.2, 6.6 Hz, 1H), 4.11 (dd, *J* = 11.1, 6.1 Hz, 1H), 3.99 (dt, *J* = 11.6, 1.3 Hz, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 3.53 (dd, *J* = 11.6, 2.8 Hz, 1H), 3.47 (ddd, *J* = 12.5, 11.1, 2.5 Hz, 1H), 3.09 (t, *J* = 7.3 Hz, 1H), 2.94 (d, *J* = 14.8 Hz, 1H), 2.68 (dtd, *J* = 13.7, 8.4, 1.2 Hz, 1H), 2.61 – 2.52 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 165.7, 158.8, 137.4, 132.6, 128.6, 127.3, 127.2, 126.2, 123.3, 70.2, 68.4, 52.4, 52.3, 41.1, 35.0, 29.0; IR (Neat Film, NaCl) 2952, 2847, 1725, 1633, 1495, 1434, 1384, 1299, 1245, 1228, 1102, 1067, 1047, 1031, 967 $cm^{-1}$; HRMS (MM: ESI-APCI+) calc'd for $C_{19}H_{23}O_5$ $[M+H]^+$: 331.1540, found 331.1544; SFC conditions: 15% IPA, 2.5 mL/min, Chiralcel OJ-H column, λ = 254 nm, $t_R$ (min): minor = 2.79, major = 4.44.



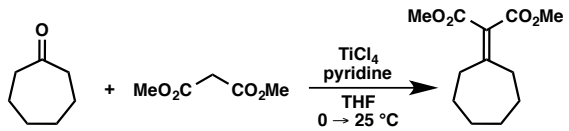

**Dimethyl (*S*)-2-(3-cinnamyltetrahydro-4*H*-thiopyran-4-ylidene)malonate 5ea**: General Procedure A was followed. Purified by silica gel flash chromatography (25% $Et_2O$ in hexanes) to afford the product as a colorless oil (38.7 mg, 56% yield); 93% ee, $[\alpha]_D^{25}$ –50.9 (*c* 0.67, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.29 (m, 4H), 7.26 – 7.19 (m, 1H), 6.50 (dd, *J* = 15.8, 1.3 Hz, 1H), 6.14 (ddd, *J* = 15.7, 8.1, 6.6 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.45 (ddt, *J* = 9.3, 6.5, 3.4 Hz, 1H), 3.28 (dt, *J* = 13.8, 3.2 Hz, 1H), 3.02 (dd, *J* = 13.9, 3.5 Hz, 1H), 2.96 – 2.79 (m, 2H), 2.79 – 2.62 (m, 3H), 2.54 (ddd, *J* = 14.0, 12.4, 4.3 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 165.8, 165.7, 160.5, 137.4, 132.7, 128.6, 127.3, 127.0, 126.2, 124.1, 52.4,4 52.43, 39.6, 34.7, 33.9, 30.4, 29.0; IR (Neat Film, NaCl) 3024, 2950, 2905, 2841, 1727, 1626, 1599, 1494, 1434, 1255, 1231, 1208, 1146, 1061, 1022, 967, 930, 745 $cm^{-1}$; HRMS (MM: ESI-APCI+) calc'd for $C_{19}H_{23}O_4S$

$[M+H]^+$: 347.1312, found 347.1303; SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak IC column, λ = 254 nm, $t_R$ (min): major = 2.75, minor = 2.92.

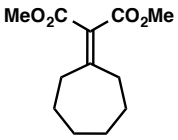



**Dimethyl (*S*)-2-(1-benzyl-3-cinnamylpiperidin-4-ylidene)malonate 5fa**: General Procedure A was followed. Purified by silica gel flash chromatography (15% EtOAc in hexanes) to afford the product as a yellow oil (79.2 mg, 95% yield); 95% ee, $[\alpha]_D^{25}$ –26.1 (*c* 1.18, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 4H), 7.29 – 7.22 (m, 5H), 7.21 – 7.15 (m, 1H), 6.31 (dt, *J* = 15.8, 1.3 Hz, 1H), 6.06 (ddd, *J* = 15.4, 8.1, 6.8 Hz, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.57 (d, *J* = 13.1 Hz, 1H), 3.37 (d, *J* = 13.1 Hz, 1H), 3.14 – 2.94 (m, 3H), 2.91 (dt, *J* = 11.6, 2.2 Hz, 1H), 2.80 – 2.67 (m, 1H), 2.62 – 2.45 (m, 2H), 2.12 (ddd, *J* = 23.7, 11.2, 3.1 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 166.0, 165.9, 161.2, 138.7, 137.6, 132.0, 129.0, 128.5, 128.4, 128.0, 127.2, 127.1, 126.2, 122.6, 62.5, 55.8, 54.4, 52.3, 52.2, 40.8, 35.8, 28.5; IR (Neat Film, NaCl) 3026, 2949, 2802, 1737, 1732, 1722, 1716, 1633, 1494, 1434, 1366, 1348, 1300, 1226, 1066, 1038, 1009, 966, 745 $cm^{-1}$; HRMS (MM: ESI-APCI+) calc'd for $C_{26}H_{30}NO_4$ $[M+H]^+$: 420.2169, found 420.2172; SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak IC column, λ = 254 nm, $t_R$ (min): major = 6.64, minor = 7.42.

### 1.5.2.4 General Procedure for the Synthesis of Cyclic Alkylidene Malonates.



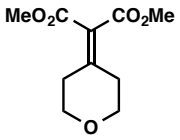

A known procedure was followed with a slight modification:[4] A flame-dried flask containing 25 mL of THF was cooled to 0 °C with an ice-bath, then $TiCl_4$ (13.5 mmol, 3 equiv.) was added slowly. To the resulting mixture was added dropwise a solution of ketone (4.5 mmol), demethyl malonate (13.5 mmol, 3 equiv), and pyridine (13.5 mmol, 3 equiv) in THF (8 mL). Following the addition, the reaction mixture was allowed to slowly warm to room temperature. Upon completion, as determined by TLC, the reaction was quenched with a slow addition of water until a homogenous solution was obtained. The THF was then removed *in vacuo* and the resulting aqueous solution was extracted with EtOAc. The combined organic layers were washed with 1 M HCl and then brine, and dried over $Na_2SO_4$. The crude residue was purified by silica gel flash chromatography to afford the desired product.




**Dimethyl 2-cycloheptylidenemalonate (1a).**

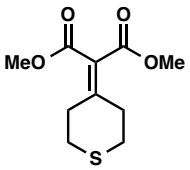
Purified by silica gel flash chromatography (6% EtOAc in hexanes) to afford the product as a colorless oil (45% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 3.76 (s, 6H), 2.65 – 2.58 (m, 4H), 1.70 (dt, $J$ = 4.3, 2.3 Hz, 4H), 1.55 – 1.51 (m, 4H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 166.1, 165.2, 123.4, 52.0, 34.1, 28.9, 26.6; IR (Neat Film, NaCl) 2926.3, 2856.8, 1729.0, 1622.0, 1435.3, 1275.5, 1234.1, 1194.3, 1169.8, 1150.3, 1103.5, 1074.1, 1037.7, 1023.5,

941.5, 749.6 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{12}H_{19}O_4$ $[M+H]^+$: 227.1283, found 227.1273.



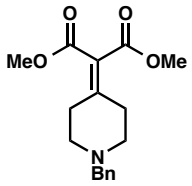

**Dimethyl 2-(tetrahydro-4*H*-pyran-4-ylidene)malonate (1d).**

Purified by silica gel flash chromatography (10% EtOAc in hexanes) to afford the product as a colorless oil (42% yield); $^1H$ NMR (300 MHz, $CDCl_3$) δ 3.80 – 3.76 (m, 10H), 2.68 (t, *J* = 5.5 Hz, 4H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 165.7, 156.4, 122.5, 68.3, 52.3, 33.0; IR (Neat Film, NaCl) 2955.2, 2914.9, 2849.5, 1726.3, 1639.6, 1634.0, 1435.2, 1382.8, 1357.7, 1295.0, 1259.1, 1242.4, 1205.3, 1097.7, 1061.6, 1031.0, 1005.6, 982.5, 947.1, 912.4, 838.8, 765.5 $cm^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{10}H_{14}O_5$ $[M+H]^+$: 215.0914, found 215.0907.




**Dimethyl 2-(tetrahydro-4*H*-thiopyran-4-ylidene)malonate (1e).**

Purified by silica gel flash chromatography (25% EtOAc in hexanes) to afford the product as a colorless oil (83% yield); $^1H$ NMR (400 MHz, $CDCl_3$) δ 3.76 (d, *J* = 0.7 Hz, 6H), 2.96 – 2.83 (m, 4H), 2.83 – 2.70 (m, 4H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 165.7, 158.5, 123.4, 52.4, 34.5, 30.8; IR (Neat Film, NaCl) 3000, 2951, 2915, 2841, 1725, 1633, 1434, 1321, 1294, 1256, 1228, 1203, 1168, 1060, 1031, 1007, 973, 942 $cm^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{10}H_{15}SO_4$ $[M+H]^+$: 231.0686, found 231.0684.

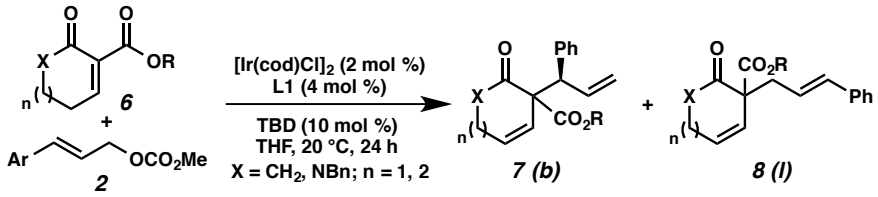



**Dimethyl 2-(1-benzylpiperidin-4-ylidene)malonate (1f)**

Purified by silica gel flash chromatography (25% EtOAc in hexanes) to afford the product as a colorless oil (56% yield); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.21 (m, 5H), 3.75 (s, 6H), 3.52 (s, 2H), 2.67 (d, *J* = 5.7 Hz, 4H), 2.56 (t, *J* = 5.6 Hz, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 166.0, 158.9, 138.1, 129.2, 128.4, 127.3, 122.1, 62.5, 54.0, 52.3, 31.9. IR (Neat Film, NaCl) 2951, 1907, 2801, 2760, 1732, 1639, 1634, 1494, 1435, 1365, 1347, 1295, 1254, 1231, 1208, 1144, 1063, 1033, 997 $cm^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{22}NO_4$ $[M+H]^+$: 304.1543, found 304.1545.

### 1.5.2.5 General Procedure for the Ir-Catalyzed Asymmetric Allylic Alkylation of Endocyclic α,β-Unsaturated β-Ketoesters

*Please note that the absolute configuration was determined only for the major isomer of compound* ***7ca*** *(vide infra). The absolute configuration for all other products has been inferred by analogy.*



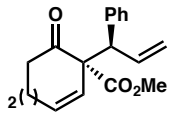

In a nitrogen-filled glove box, $[Ir(cod)Cl]_2$ (2.69 mg, 0.004 mmol, 2 mol %), ligand **L1** (3.71 mg, 0.008 mmol, 4 mol %), and TBD (2.78 mg, 0.02 mmol, 10 mol %) were added to a 2 dram scintillation vial equipped with a magnetic stirring bar. The vial was then charged with THF (1 mL) and stirred at 25 °C for 10 min. To a 20 mL scintillation vial

was added α,β-unsaturated β–ketoester (0.4 mmol, 2.0 eq), cinnamyl carbonate **2a** (38.4 mg, 0.2 mmol, 1.0 equiv) and 1 mL of THF, then the above pre-formed catalyst solution was transferred to this vial. The vial was sealed and stirred at 25 °C for 24 h. The reaction mixture was filtered through a pad of silica gel, rinsed with hexane/ethyl acetate (5:1, v/v), and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography and preparative HPLC.

### 1.5.2.6 Spectroscopic Data for the Endocyclic α,β-Unsaturated β-Ketoester Alkylation Products

**Methyl (*S*)-7-oxo-1-((*R*)-1-phenylallyl)cyclohept-2-ene-1-carboxylate (7aa) and methyl (*R*)-7-oxo-1-((*R*)-1-phenylallyl)cyclohept-2-ene-1-carboxylate (7aa').**

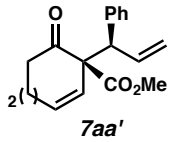
Products **7aa** and **7aa'** were isolated by silica gel chromatography (3% EtOAc in hexanes) as a mixture of diastereomers (2:1), which were separated by preparative HPLC (3% EtOAc in hexanes).




***7aa***

The major diastereomer was isolated as a colorless oil, 95% ee, $[\alpha]_D^{25}$ –15.4 (*c* 1.79, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H), 7.25 – 7.15 (m, 3H), 6.22 (ddd, *J* = 16.7, 10.3, 9.1 Hz, 1H), 6.04 – 5.91 (m, 2H), 5.15–5.04 (m, 2H), 4.39 (d, *J* = 9.1 Hz, 1H), 3.68 (s, 3H), 2.71 (dt, *J* = 12.6, 7.5 Hz, 1H), 2.28 (dt, *J* = 12.5, 6.2 Hz, 1H), 1.98 – 1.87 (m, 1H), 1.73 – 1.61 (m, 2H), 1.48 – 1.37 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 205.8, 170.4, 139.1, 137.0, 132.3, 130.5, 127.8, 127.0, 126.1, 117.8, 71.3, 54.3, 52.9, 40.4, 25.3, 22.9; IR (Neat Film, NaCl) 3030, 2948, 2359, 2341, 1738, 1716, 1493, 1453,

1433, 1296, 1226, 1194, 1123, 1056 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{18}H_{21}O_3$ $[M+H]^+$: 285.1491, found 285.1496; SFC conditions: 5% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 4.99, major = 7.08.

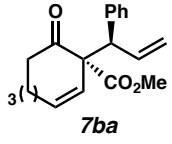


***7aa'***

The minor diastereomer was isolated as a colorless oil, 88% ee, $[\alpha]_D^{25}$ –75.1 (*c* 0.61, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.16 (m, 5H), 6.20 (ddd, *J* = 17.0, 10.2, 8.4 Hz, 1H), 6.12 – 6.01 (m, 2H), 5.22 – 5.10 (m, 2H), 4.38 (d, *J* = 8.5 Hz, 1H), 3.50 (s, 3H), 2.79 (ddd, *J* = 12.7, 8.8, 7.2 Hz, 1H), 2.39 (ddd, *J* = 12.7, 6.5, 5.1 Hz, 1H), 2.16 – 1.98 (m, 2H), 1.96–1.85 (m, 1H), 1.85 – 1.71 (m, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 205.7, 170.0, 139.5, 137.1, 131.7, 129.6, 128.2, 127.2, 126.2, 118.5, 70.6, 53.3, 52.7, 40.0, 25.2, 23.5; IR (Neat Film, NaCl) 3030, 2948, 1737, 1719, 1493, 1453, 1434, 1296, 1230, 1194, 1121 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{18}H_{21}O_3$ $[M+H]^+$: 285.1491, found 285.1498; SFC conditions: 5% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): major = 5.62, minor = 7.98.

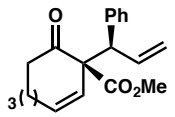
**Methyl (*S*,*Z*)-8-oxo-1-((*R*)-1-phenylallyl)cyclooct-2-ene-1-carboxylate (7ba)** and **methyl (*R*,*Z*)-8-oxo-1-((*R*)-1-phenylallyl)cyclooct-2-ene-1-carboxylate (7ba')**.

Products **7ba** and **7ba'** were isolated by silica gel chromatography (2% EtOAc in hexanes) as a mixture of diastereomers (3:1), which were separated by preparative HPLC (3% EtOAc in hexanes).



***7ba***

The major diastereomer was isolated as a colorless oil, 90% ee, $[\alpha]_D^{25}$ +59.3 (*c* 1.60, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.38 (m, 2H), 7.24 – 7.18 (m, 2H), 7.18 – 7.11 (m, 1H), 6.15 (dt, *J* = 16.8, 10.1 Hz, 1H), 6.08 (dd, *J* = 11.4, 1.0 Hz, 1H), 5.87 – 5.76 (m, 1H), 5.14 – 5.03 (m, 2H), 4.46 (d, *J* = 10.1 Hz, 1H), 3.68 (s, 3H), 2.63 – 2.52 (m, 1H), 2.23 – 2.13 (m, 1H), 1.80 – 1.69 (m, 2H), 1.49 – 1.37 (m, 2H), 1.20 – 1.07 (m, 1H), 0.66 – 0.55 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 208.5, 169.8, 139.1, 137.4, 135.4, 131.0, 127.5, 126.7, 124.7, 117.2, 70.8, 53.7, 53.0, 39.0, 27.6, 25.4, 24.8; IR (Neat Film, NaCl) 3029, 2931, 2859, 1740, 1712, 1492, 1453, 1432, 1331, 1224, 1176, 1123, 1061 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{23}O_3$ $[M+H]^+$: 299.1647, found 299.1645; SFC conditions: 5% IPA, 2.5 mL/min, Chiralpak IA column, λ = 210 nm, $t_R$ (min): minor = 4.52, major = 6.36.



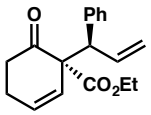

***7ba'***

The minor diastereomer was isolated as a colorless oil, 77% ee, $[\alpha]_D^{25}$ –114.2 (*c* 0.52, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.15 (m, 5H), 6.17 – 6.02 (m, 2H), 6.01 – 5.91 (m, 1H), 5.29 (ddd, *J* = 17.0, 1.9, 0.9 Hz, 1H), 5.11 (ddd, *J* = 10.1, 1.8, 0.7 Hz, 1H), 4.43 (d, *J* = 8.9 Hz, 1H), 3.49 (s, 3H), 2.66 (td, *J* = 12.2, 2.5 Hz, 1H), 2.25 (ddd, *J* = 12.3, 7.0, 2.6 Hz, 1H), 2.05 – 1.81 (m, 3H), 1.74 – 1.53 (m, 2H), 1.31 – 1.21 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 208.2, 169.5, 140.0, 137.0, 134.0, 129.3, 128.3, 127.1, 124.9, 118.1, 69.5, 52.8, 52.7, 39.2, 27.6, 26.0, 25.3; IR (Neat Film, NaCl) 3028, 2931, 2859, 1740, 1715, 1491, 1453, 1432, 1228, 1177, 1432, 1228, 1177, 1133, 1059 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{23}O_3$ $[M+H]^+$: 299.1647, found 299.1654; SFC conditions:

5% IPA, 2.5 mL/min, Chiralpak IA column, λ = 210 nm, $t_R$ (min): major = 5.79, minor = 7.41.

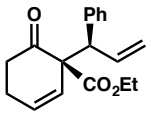
**Ethyl (*S*)-6-oxo-1-((*R*)-1-phenylallyl)cyclohex-2-ene-1-carboxylate (7ca) and Ethyl (*R*)-6-oxo-1-((*R*)-1-phenylallyl)cyclohex-2-ene-1-carboxylate (7ca')**.

Products **7ca** and **7ca'** were isolated by silica gel chromatography (3% EtOAc in hexanes) as a mixture of diastereomers (5:1), which were separated by preparative HPLC (4% EtOAc in hexanes).



*7ca*

The major diastereomer was isolated as a colorless oil, 98% ee, $[\alpha]_D^{25}$ –35.8 (*c* 0.71, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.14 (m, 5H), 6.25 – 6.16 (m, 1H), 6.17 – 6.11 (m, 1H), 6.05 (ddd, *J* = 10.1, 1.9, 1.3 Hz, 1H), 5.23 – 5.10 (m, 2H), 4.49 (dt, *J* = 8.2, 1.2 Hz, 1H), 4.16 (qd, *J* = 7.1, 2.2 Hz, 2H), 2.37 – 2.23 (m, 2H), 1.94 – 1.76 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 205.9, 169.3, 138.8, 136.4, 130.5, 130.3, 128.1, 127.1, 126.1, 118.5, 65.6, 62.0, 54.4, 38.3, 24.5, 14.2; IR (Neat Film, NaCl) 3033, 2980, 1743, 1719, 1493, 1454, 1416, 1391, 1365, 1342, 1299, 1213, 1165, 1130, 1096, 1044, 1016 $cm^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{18}H_{21}O_3$ $[M+H]^+$: 285.1485, found 285.1482; SFC conditions: 2% IPA, 3.0 mL/min, Chiralpak IA column, λ = 210 nm, $t_R$ (min): minor = 6.82, major = 13.26.



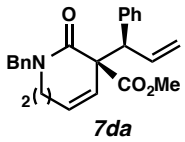
*7ca'*

The minor diastereomer was isolated as a colorless oil, 91% ee, $[\alpha]_D^{25}$ +28.9 (*c* 0.30, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.16 (m, 5H), 6.29 – 6.18 (m, 1H), 6.15 –

6.07 (m, 1H), 5.94 (ddd, *J* = 10.0, 2.4, 1.0 Hz, 1H), 5.15 – 5.07 (m, 2H), 4.34 (d, *J* = 9.0 Hz, 1H), 4.03 (q, *J* = 7.1 Hz, 2H), 2.60 – 2.49 (m, 1H), 2.47 – 2.34 (m, 2H), 2.29–2.17 (m, 1H), 1.14 (t, *J* = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 205.6, 169.2, 139.2, 136.8, 130.0, 129.7, 128.2, 127.4, 127.2, 118.2, 65.0, 61.9, 54.5, 39.2, 24.8, 14.0; IR (Neat Film, NaCl) 3032, 2980, 2931, 1736, 1719, 1637, 1601, 1493, 1453, 1444, 1419, 1389, 1365, 1342, 1298, 1218, 1166, 1118, 1097, 1045, 1018 $cm^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{18}H_{21}O_3$ $[M+H]^+$: 285.1485, found 285.1480; SFC conditions: 2% IPA, 3.0 mL/min, Chiralpak IA column, λ = 210 nm, $t_R$ (min): major = 6.95, minor = 11.43.

**Methyl (*R*)-1-benzyl-2-oxo-3-((*R*)-1-phenylallyl)-2,3,6,7-tetrahydro-1*H*-azepine-3-carboxylate (7da) and methyl (*S*)-1-benzyl-2-oxo-3-((*R*)-1-phenylallyl)-2,3,6,7-tetrahydro-1*H*-azepine-3-carboxylate (7da')**.

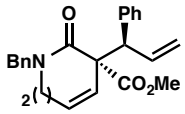
Products **7da** and **7da'** were isolated by silica gel chromatography (3% EtOAc in hexanes) as a mixture of diastereomers (2:1), which were separated by preparative HPLC (12% EtOAc in hexanes).



***7da***

The major diastereomer was isolated as a colorless oil, 79% ee, $[\alpha]_D^{25}$ –14.6 (*c* 0.19, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.19 (m, 10H), 6.27 (ddd, *J* = 17.3, 10.6, 5.4 Hz, 1H), 5.99 – 5.90 (m, 2H), 5.24 (dt, *J* = 10.6, 1.7 Hz, 1H), 5.09 (d, *J* = 14.9 Hz, 1H), 5.02 (dt, *J* = 17.3, 1.7 Hz, 1H), 4.74 (dt, *J* = 5.4, 1.9 Hz, 1H), 4.34 (d, *J* = 14.9 Hz, 1H), 3.54 – 3.44 (m, 1H), 3.39 (s, 3H), 3.09 – 3.00 (m, 1H), 2.26 – 2.07 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 171.7, 170.7, 139.3, 138.9, 137.7, 132.0, 130.4, 128.7, 128.3,

127.9, 127.5, 127.4, 124.7, 118.1, 62.3, 54.7, 52.4, 51.4, 44.0, 28.3; IR (Neat Film, NaCl) 3029, 2048, 1737, 1728, 1656, 1652, 1495, 1480, 1431, 1416, 1357, 1242, 1227, 1164, 1045,1001 $cm^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{24}H_{26}NO_3$ $[M+H]^+$: 376.1907, found 376.1917; SFC conditions: 10% MeCN, 2.5 mL/min, Chiralcel OD-H column, λ = 210 nm, $t_R$ (min): minor = 13.74, major = 16.85.

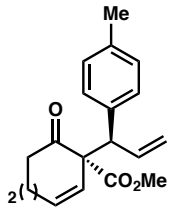



***7da'***

The minor diastereomer was isolated as a colorless oil, 62% ee, $[\alpha]_D^{25}$ –42.3 (*c* 0.12, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.49 – 7.42 (m, 2H), 7.36 – 7.16 (m, 8H), 6.40 (ddd, *J* = 16.9, 10.1, 9.1 Hz, 1H), 5.88 (dddd, *J* = 11.8, 4.7, 3.1, 1.3 Hz, 1H), 5.73 (dt, *J* = 11.9, 2.2 Hz, 1H), 5.23 – 5.05 (m, 2H), 4.99 (d, *J* = 14.8 Hz, 1H), 4.45 (d, *J* = 9.1 Hz, 1H), 4.32 (d, *J* = 14.9 Hz, 1H), 3.63 (s, 3H), 3.51 – 3.42 (m, 1H), 3.10 – 3.02 (m, 1H), 2.22 – 2.04 (m, 2H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 172.0, 170.3, 140.2, 137.7, 137.7, 131.1, 130.3, 128.7, 128.0, 127.9, 127.5, 126.7, 126.2, 118.2, 63.1, 56.6, 52.7, 51.4, 44.2, 28.2; IR (Neat Film, NaCl) 3028, 2948, 1732, 1656, 1652, 1495, 1480, 1429, 1417, 1357, 1241, 1226, 1163, 1044, 1002 $cm^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{24}H_{26}NO_3$ $[M+H]^+$: 376.1907, found 376.1915; SFC conditions: 10% MeCN, 2.5 mL/min, Chiralcel OD-H column, λ = 210 nm, $t_R$ (min): major = 12.34, minor = 15.02.

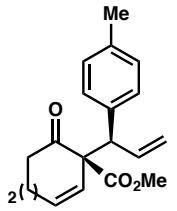
**Methyl (*S*)-7-oxo-1-((*R*)-1-(*p*-tolyl)allyl)cyclohept-2-ene-1-carboxylate (7ab) and methyl (*R*)-7-oxo-1-((*R*)-1-(*p*-tolyl)allyl)cyclohept-2-ene-1-carboxylate (7ab').**

Products **7ab** and **7ab'** were isolated by silica gel chromatography (2% EtOAc in hexanes) as a mixture of diastereomers (1.2:1), which were separated by preparative HPLC (3% EtOAc in hexanes).




***7ab***

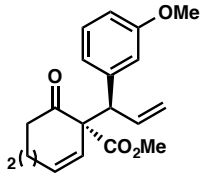
The major diastereomer was isolated as a colorless oil, 95% ee, $[\alpha]_D^{25}$ –17.5 (*c* 0.195, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.1 Hz, 2H), 7.03 (d, *J* = 7.7 Hz, 2H), 6.21 (ddd, *J* = 16.7, 10.4, 9.1 Hz, 1H), 6.00 – 5.90 (m, 2H), 5.13 – 5.04 (m, 2H), 4.33 (d, *J* = 9.0 Hz, 1H), 3.69 (s, 3H), 2.71 (dt, *J* = 12.7, 7.3 Hz, 1H), 2.36 – 2.25 (m, 4H), 2.01 – 1.89 (m, 1H), 1.73 – 1.62 (m, 2H), 1.56 – 1.43 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 205.9, 170.5, 137.2, 136.6, 136.1, 132.3, 130.2, 128.6, 126.2, 117.6, 71.1, 54.0, 52.9, 40.6, 25.6, 22.9, 21.2; IR (Neat Film, NaCl) 2948, 1738, 1716, 1514, 1435, 1225, 1123 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{23}O_3$ $[M+H]^+$: 299.1647, found 299.1655; SFC conditions: 8% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 4.13, major = 4.50.




The minor diastereomer was isolated as a colorless oil, 91% ee, $[\alpha]_D^{25}$ –76.0 (*c* 0.17, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.13 – 7.00 (m, 4H), 6.17 (ddd, *J* = 17.0, 10.2, 8.5 Hz, 1H), 6.11 – 6.00 (m, 2H), 5.17 (ddd, *J* = 17.0, 1.8, 1.0 Hz, 1H), 5.12 (ddd, *J* = 10.2, 1.8, 0.8 Hz, 1H), 4.35 (d, *J* = 8.5 Hz, 1H), 3.52 (s, 3H), 2.79 (ddd, *J* = 12.7, 8.7, 7.1 Hz, 1H), 2.39 (ddd, *J* = 12.6, 6.4, 5.2 Hz, 1H), 2.30 (s, 3H), 2.17 – 2.00 (m, 2H), 1.96 – 1.85 (m, 1H), 1.85 – 1.73 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 205.8, 170.0, 137.2, 136.7, 136.4, 131.6, 129.3, 129.0, 126.3, 118.2, 70.6, 52.9, 52.7, 40.0, 25.2, 23.5, 21.2; IR (Neat Film, NaCl) 2948, 1736, 1720, 1716, 1513, 1435, 1230, 1194, 1123 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{23}O_3$ $[M+H]^+$: 299.1647, found 299.1640; SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 3.43, major = 4.49.

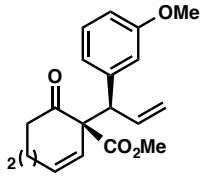
**Methyl (*S*)-1-((*R*)-1-(3-methoxyphenyl)allyl)-7-oxocyclohept-2-ene-1-carboxylate (7ad) and methyl (*R*)-1-((*R*)-1-(3-methoxyphenyl)allyl)-7-oxocyclohept-2-ene-1-carboxylate (7ad')**

Products **7ba** and **7ba'** were isolated by silica gel chromatography (2% EtOAc in hexanes) as a mixture of diastereomers (2:1), which were separated by preparative HPLC (7% EtOAc in hexanes).




***7ad***

The major diastereomer was isolated as a colorless oil, 91% ee, $[\alpha]_D^{25}$ –14.9 (*c* 0.29, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.14 (t, *J* = 8.1 Hz, 1H), 6.93 – 6.87 (m, 2H), 6.74 (ddd, *J* = 8.2, 2.5, 1.1 Hz, 1H), 6.26 – 6.14 (m, 1H), 6.02 – 5.91 (m, 2H), 5.15 – 5.06 (m, 2H), 4.35 (d, *J* = 9.1 Hz, 1H), 3.78 (s, 3H), 3.69 (s, 3H), 2.71 (dt, *J* = 12.7, 7.3 Hz, 1H), 2.30 (dt, *J* = 12.6, 6.2 Hz, 1H), 2.04 – 1.92 (m, 1H), 1.74 – 1.63 (m, 2H), 1.56 – 1.47 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 205.7, 170.4, 159.0, 140.7, 136.9, 132.3, 128.8, 126.2, 122.8, 117.9, 116.2, 112.4, 71.1, 55.3, 54.4, 52.9, 40.5, 25.6, 22.8; IR (Neat Film, NaCl) 2949, 1738, 1716, 1599, 1583, 1489, 1455, 1435, 1225, 1050 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{23}O_4$ $[M+H]^+$: 315.1596, found 315.1592; SFC conditions: 8% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 4.28, major = 4.75.



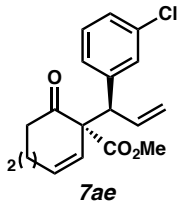

***7ad'***

The minor diastereomer was isolated as a colorless oil, 81% ee, $[\alpha]_D^{25}$ –64.5 (*c* 0.135, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.17 (t, *J* = 7.9 Hz, 1H), 6.84 – 6.71 (m, 3H), 6.15 (ddd, *J* = 17.0, 10.2, 8.6 Hz, 1H), 6.11 – 6.02 (m, 2H), 5.21 (ddd, *J* = 17.1, 1.8, 1.0 Hz, 1H), 5.13 (ddd, *J* = 10.2, 1.7, 0.8 Hz, 1H), 4.37 (d, *J* = 8.6 Hz, 1H), 3.78 (s, 3H), 3.53 (s, 3H), 2.79 (ddd, *J* = 12.5, 8.8, 7.3 Hz, 1H), 2.39 (ddd, *J* = 12.4, 6.6, 4.9 Hz, 1H), 2.17 – 2.01 (m, 2H), 1.98 – 1.86 (m, 1H), 1.86 – 1.72 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ

205.7, 169.9, 159.3, 141.1, 136.8, 131.5, 129.2, 126.3, 121.8, 118.5, 115.6, 112.3, 70.7, 55.3, 53.2, 52.7, 39.8, 25.1, 23.6; IR (Neat Film, NaCl) 2949, 1735, 1719, 1599, 1583, 1491, 1453, 1434, 1230, 1049 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{23}O_4$ $[M+H]^+$: 315.1596, found 315.1603; SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak IC column, λ = 210 nm, $t_R$ (min): minor = 5.40, major = 5.99.

**Methyl (*S*)-1-((*R*)-1-(3-chlorophenyl)allyl)-7-oxocyclohept-2-ene-1-carboxylate (7ae) and methyl (*R*)-1-((*R*)-1-(3-chlorophenyl)allyl)-7-oxocyclohept-2-ene-1-carboxylate (7ae')**

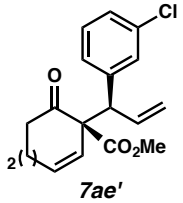
Products **7ae** and **7ae'** were isolated by silica gel chromatography (2% EtOAc in hexanes) as a mixture of diastereomers (3:1), which were separated by preparative HPLC (3.5% EtOAc in hexanes).




*7ae*

The major diastereomer was isolated as a colorless oil, 91% ee, $[\alpha]_D^{25}$ –4.9 (*c* 0.325, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 1H), 7.25 – 7.20 (m, 1H), 7.18 – 7.14 (m, 2H), 6.15 (ddd, *J* = 16.8, 10.2, 9.2 Hz, 1H), 6.05–5.93 (m, 2H), 5.16 – 5.06 (m, 2H), 4.35 (d, *J* = 9.2 Hz, 1H), 3.69 (s, 3H), 2.74 (ddd, *J* = 12.6, 8.0, 7.4 Hz, 1H), 2.31 (dt, *J* = 12.5, 6.0 Hz, 1H), 2.01 – 1.87 (m, 1H), 1.75 – 1.63 (m, 2H), 1.48 – 1.35 (m, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 205.5, 170.1, 141.3, 136.3, 133.5, 132.6, 130.4, 129.0, 128.8, 127.1, 125.8, 118.4, 71.2, 53.8, 53.0, 40.2, 25.2, 22.9; IR (Neat Film, NaCl) 2949, 1738, 1716, 1594, 1571, 1432, 1228, 1195, 1123, 1094 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for

$C_{18}H_{20}O_3Cl$ $[M+H]^+$: 319.1101, found 319.1112; SFC conditions: 7% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 4.14, major = 4.85.

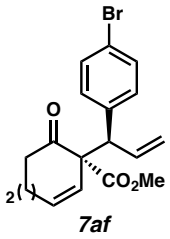



***7ae'***

The minor diastereomer was isolated as a colorless oil, 75% ee, $[\alpha]_D^{25}$ –56.2 (*c* 0.105, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.15 (m, 3H), 7.15 – 7.08 (m, 1H), 6.15 (ddd, *J* = 17.0, 10.2, 8.6 Hz, 1H), 6.09 (ddd, *J* = 11.4, 7.2, 5.5 Hz, 1H), 5.99 (dd, *J* = 11.5, 2.1 Hz, 1H), 5.23 – 5.13 (m, 2H), 4.34 (d, *J* = 8.6 Hz, 1H), 3.55 (s, 3H), 2.80 (ddd, *J* = 12.6, 8.8, 7.2 Hz, 1H), 2.40 (ddd, *J* = 12.7, 6.5, 5.0 Hz, 1H), 2.17 – 2.08 (m, 1H), 2.08 – 1.97 (m, 1H), 1.97 – 1.86 (m, 1H), 1.86 – 1.73 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 205.3, 169.9, 141.7, 136.4, 133.9, 132.1, 129.7, 129.4, 127.7, 127.4, 125.8, 119.0, 70.4, 53.0, 52.8, 39.9, 25.2, 23.4; IR (Neat Film, NaCl) 2949, 1738, 1720, 1594, 1571, 1476, 1455, 1432, 1231, 1194, 1121, 1095 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{18}H_{20}O_3Cl$ $[M+H]^+$: 319.1101, found 319.1089; SFC conditions: 7% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): major = 4.67, minor = 5.28.

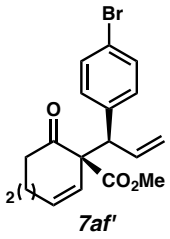
**Methyl (*S*)-1-((*R*)-1-(4-bromophenyl)allyl)-7-oxocyclohept-2-ene-1-carboxylate (7af) and methyl (*R*)-1-((*R*)-1-(4-bromophenyl)allyl)-7-oxocyclohept-2-ene-1-carboxylate (7af')**

Products **7af** and **7af'** were isolated by silica gel chromatography (2% EtOAc in hexanes) as a mixture of diastereomers (2:1), which were separated by preparative HPLC (4% EtOAc in hexanes).




***7af***

The major diastereomer was isolated as a colorless oil, 88% ee, $[\alpha]_D^{25}$ –20.4 (*c* 0.31, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.14 (ddd, *J* = 16.8, 10.2, 9.2 Hz, 1H), 6.03 – 5.93 (m, 2H), 5.15 – 5.04 (m, 2H), 4.36 (d, *J* = 9.2 Hz, 1H), 3.68 (s, 3H), 2.73 (ddd, *J* = 12.5, 8.1, 7.4 Hz, 1H), 2.29 (dt, *J* = 12.5, 5.9 Hz, 1H), 1.98 – 1.86 (m, 1H), 1.76 – 1.63 (m, 2H), 1.47 – 1.33 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 205.7, 170.1, 138.3, 136.4, 132.5, 132.2, 130.9, 125.9, 121.0, 118.2, 71.3, 53.5, 53.0, 40.06, 25.2, 23.1; IR (Neat Film, NaCl) 2948, 1738, 1720, 1716, 1487, 1432, 1227, 1194, 1010 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{18}H_{20}BrO_3$ $[M+H]^+$: 363.0596, found 363.0588; SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 4.68, major = 5.17.



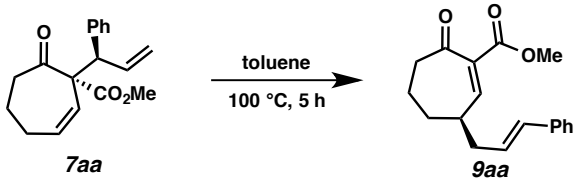

***7af'***

The minor diastereomer was isolated as a colorless oil, 79% ee, $[\alpha]_D^{25}$ –76.3 (*c* 0.16, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.5 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 6.22 – 6.11 (m, 1H), 6.06 (ddd, *J* = 11.4, 7.2, 5.4 Hz, 1H), 5.97 (dd, *J* = 11.5, 2.1 Hz, 1H), 5.19 – 5.10 (m, 2H), 4.30 (d, *J* = 8.5 Hz, 1H), 3.54 (s, 3H), 2.80 (ddd, *J* = 12.7, 8.7, 7.1 Hz, 1H), 2.40 (ddd, *J* = 12.7, 6.4, 5.2 Hz, 1H), 2.17 – 2.07 (m, 1H), 2.04 – 1.94 (m, 1H), 1.94 – 1.85 (m, 1H), 1.84 – 1.73 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 205.5,

170.0, 138.6, 136.6, 132.1, 131.4, 131.3, 125.9, 121.2, 118.8, 70.4, 52.9, 52.8, 40.0, 25.3, 23.3; IR (Neat Film, NaCl) 2948, 1737, 1716, 1488, 1230, 1194, 1075, 1010 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{18}H_{20}BrO_3$ $[M+H]^+$: 363.0596, found 363.0604; SFC conditions: 10% IPA, 2.5 mL/min, Chiralpak IC column, λ = 210 nm, $t_R$ (min): minor = 4.43, major = 5.01.

### 1.5.2.7 General Procedure for the Cope Rearrangement of β-Ketoesters.

A solution of compound **7** in toluene (0.1 M) was heated at 100 °C for five hours in a sealed vial. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*, and the crude residue was purified by silica gel flash chromatography to afford the desired product.




*7aa* *9aa*

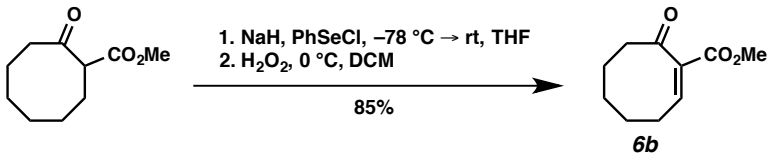
**Methyl (*R*)-3-cinnamyl-7-oxocyclohept-1-ene-1-carboxylate (9aa)**

**9aa** was isolated by silica gel chromatography (3→9→17% EtOAc in hexanes, 72% yield) as a colorless oil, 95% ee; $[\alpha]_D^{25}$ –23.6 (*c* 0.49, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 4H), 7.27 – 7.18 (m, 2H), 6.46 (d, *J* = 15.8 Hz, 1H), 6.15 (dt, *J* = 15.7, 7.2 Hz, 1H), 3.77 (s, 3H), 2.74 – 2.57 (m, 3H), 2.54 – 2.34 (m, 2H), 2.00 – 1.80 (m, 3H), 1.56 – 1.48 (m, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 203.0, 165.5, 151.9, 137.2, 135.4, 133.1, 128.7, 127.6, 126.8, 126.3, 52.5, 43.3, 39.6, 39.1, 30.2, 21.5; IR (Neat Film, NaCl) 3024, 2929, 2858, 1722, 1716, 1495, 1435, 1377, 1256, 1202, 1027 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{18}H_{21}O_3$ $[M+H]^+$: 285.1491, found 285.1491; SFC conditions:

10% IPA, 2.5 mL/min, Chiralcel OB-H column, λ = 210 nm, $t_R$ (min): major = 13.72, minor = 15.18.

### 1.5.2.8 Synthesis of Endocyclic α,β-Unsaturated β-Ketoesters.

The α,β-unsaturated β–ketoesters **6a** and **6c** were prepared following literature procedures.

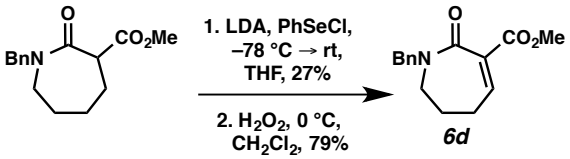



*6b*

**Methyl (*E*)-8-oxocyclooct-1-ene-1-carboxylate (6b)**

Following a modified literature procedure,[8] NaH (60% in mineral oil, 440 mg, 1.1 equiv) was added to a 250 mL round bottom flask and flushed with $N_2$. THF (27 mL) was then added, and the resulting suspension cooled to 0 °C. A solution of methyl 2-oxocyclooctane-1-carboxylate (1.84 g, 10 mmol) in THF (5 mL) was added slowly at 0 °C, and then the reaction mixture was warmed to room temperature. After stirring for 1 h, the enolate solution was cooled to –78 °C and a solution of PhSeCl (2.01 g, 1.05 equiv) in THF (8 mL) was added. After stirring for 1 h at –78 °C, the reaction mixture was warmed to room temperature and stirred for an additional 1 h. Upon completion, the solution was diluted with $Et_2O$ and washed twice with 1 M HCl, followed by brine. The organic layer was dried over $Na_2SO_4$ and concentrated. The crude product was dissolved in $CH_2Cl_2$ (100 mL), cooled to 0 °C, and treated with a solution of $H_2O_2$ (35% in water, 1.84 mL, 2.1 equiv) dropwise over 30 min. After stirring for an additional 1 h, water was added and the aqueous layer extracted with $CH_2Cl_2$. The combined organic layers were washed with saturated $NaHCO_3$, water, and brine, then dried with $Na_2SO_4$. The crude

product was purified by silica gel flash chromatography (5→9% EtOAc in hexanes) to provide **6b** as a colorless oil (1.54 g, 85%); $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.22 (t, $J$ = 4.7 Hz, 1H), 3.73 (s, 3H), 2.60 – 2.53 (m, 2H), 2.43 – 2.36 (m, 2H), 1.94 – 1.85 (m, 2H), 1.73 – 1.61 (m, 4H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 209.2, 165.0, 147.3, 131.3, 52.4, 44.6, 30.4, 29.3, 22.2, 21.8; IR (Neat Film, NaCl) 2946, 1719, 1696, 1638, 1434, 1411, 1376, 1266, 1237, 1219, 1157, 1068 cm$^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{10}H_{14}O_3$ $[M+H]^+$: 183.1021, found 183.1029.




**Methyl 1-benzyl-2-oxo-2,5,6,7-tetrahydro-1*H*-azepine-3-carboxylate (6d)**

To a solution of LDA [1.2 equiv, prepared fresh from diisopropylamine (513 μL) and *n*-BuLi, (2.5 M in hexanes, 1.46 mL) in THF (10 mL) at 0 °C for 15 min] was added dropwise a solution of methyl 1-benzyl-2-oxoazepane-3-carboxylate (798 mg, 3.05 mmol) in THF (3 mL) at –78 °C and the resulting mixture was stirred for 1 h at –78 °C. A solution of PhSeCl (615 mg, 1.05 equiv) in THF (3 mL) was then added, and the reaction was slowly allowed to warm to room temperature. The mixture was diluted with ethyl acetate, washed twice with 1 M HCl, followed by brine, and dried over $Na_2SO_4$. The crude mixture was purified by silica gel flash chromatography (9→17→20% EtOAc in hexanes) to provide methyl 1-benzyl-2-oxo-3-(phenylselanyl)azepane-3-carboxylate as a yellow oil (343 mg, 27%). The isolated compound was carried forward by dissolving in $CH_2Cl_2$ (8 mL) and cooling to 0 °C. A solution of $H_2O_2$ (35% in water, 145 μL, 2.1 equiv) was added dropwise over 30 min. After stirring for an additional 1 h, water was

added and the aqueous later extracted with $CH_2Cl_2$. The combined organic layers were washed with saturated $NaHCO_3$, water, brine and dried with $Na_2SO_4$. The crude product was purified by silica gel flash chromatography (25→50% EtOAc in hexanes) to provide **9** as a pale yellow oil (170 mg, 79%); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 6H), 4.72 (s, 2H), 3.83 (s, 3H), 3.30 (t, *J* = 6.3 Hz, 2H), 2.26 (q, *J* = 7.4 Hz, 2H), 1.74 – 1.64 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 166.5, 165.1, 143.8, 138.0, 132.4, 128.9, 128.5, 127.8, 52.5, 49.8, 45.4, 27.9, 23.7; IR (Neat Film, NaCl) 3493, 3029, 2952, 1721, 1650, 1621, 1471, 1435, 1359, 1274, 1251, 1193, 1159, 1103, 1067, 1053 cm$^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{18}NO_3$ $[M+H]^+$: 260.1281, found 260.1285.

## 1.5.3 Determination of Enantiomeric Excess

***Table 1.4*** *Determination of enantiomeric excess*

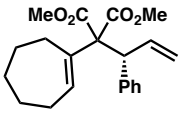
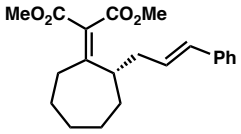
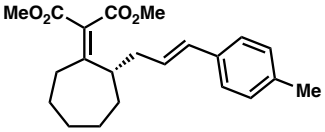
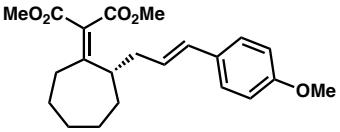
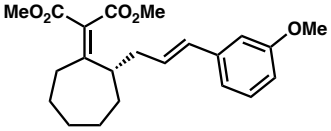
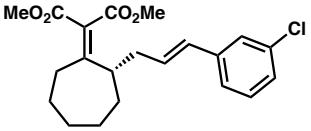
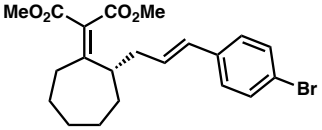
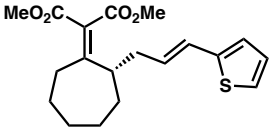
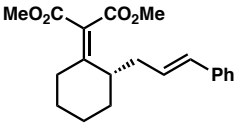
| Entry | Compound | Assay Conditions | $t_R$ of major isomer (min) | $t_R$ of minor isomer (min) | %ee |
|---|---|---|---|---|---|
| 1 |  | SFC<br>Chiralpak AD-H<br>2% IPA<br>isocratic, 2.5 mL/min | 8.12 | 7.34 | >99 |
| 2 |  | SFC<br>Chiralpak AD-H<br>10% IPA<br>isocratic, 2.5 mL/min | 4.55 | 4.88 | 96 |
| 3 |  | SFC<br>Chiralpak IC<br>5% IPA<br>isocratic, 2.5 mL/min | 7.54 | 10.52 | 96 |
| 4 |  | SFC<br>Chiralpak IC<br>10% IPA<br>isocratic, 2.5 mL/min | 7.39 | 9.02 | 96 |
| 5 |  | SFC<br>Chiralpak IC<br>5% MeOH<br>isocratic, 2.5 mL/min | 9.50 | 10.16 | 97 |
| 6 |  | SFC<br>Chiralpak IC<br>3% IPA<br>isocratic, 2.5 mL/min | 12.00 | 17.72 | 97 |
| 7 |  | SFC<br>Chiralpak IC<br>9% MeOH<br>isocratic, 2.5 mL/min | 5.33 | 5.85 | 97 |
| 8 |  | SFC<br>Chiralpak IC<br>3% MeOH<br>isocratic, 2.5 mL/min | 11.55 | 12.69 | 96 |
| 9 |  | SFC<br>Chiralcel OJ-H<br>15% IPA<br>isocratic, 2.5 mL/min | 4.16 | 2.87 | 91 |

***Table 1.4*** *Determination of enantiomeric excess (continued)*

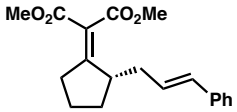
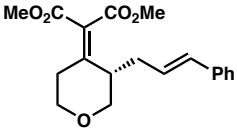
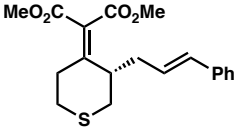
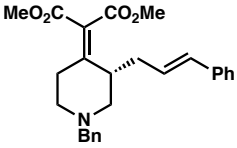
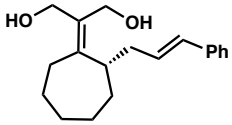
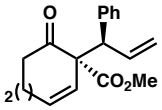
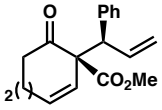
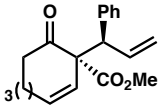
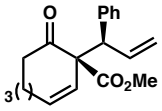
| Entry | Compound | Assay Conditions | $t_R$ of major isomer (min) | $t_R$ of minor isomer (min) | %ee |
|---|---|---|---|---|---|
| 10 |  | SFC<br>Chiralpak AD-H<br>10% IPA<br>isocratic, 2.5 mL/min | 4.79 | 4.41 | 90 |
| 11 |  | SFC<br>Chiralcel OJ-H<br>15% IPA<br>isocratic, 2.5 mL/min | 4.44 | 2.79 | 94 |
| 12 |  | SFC<br>Chiralpak IC<br>10% IPA<br>isocratic, 2.5 mL/min | 2.75 | 2.92 | 93 |
| 13 |  | SFC<br>Chiralpak IC<br>10% IPA<br>isocratic, 2.5 mL/min | 6.64 | 7.42 | 95 |
| 14 |  | SFC<br>Chiralpak IC<br>20% IPA<br>isocratic, 2.5 mL/min | 8.97 | 6.98 | >99 |
| 15 |  | SFC<br>Chiralpak AD-H<br>5% IPA<br>isocratic, 2.5 mL/min | 7.08 | 4.99 | 95 |
| 16 |  | SFC<br>Chiralpak AD-H<br>5% IPA<br>isocratic, 2.5 mL/min | 5.62 | 7.98 | 88 |
| 17 |  | SFC<br>Chiralpak IA<br>5% IPA<br>isocratic, 2.5 mL/min | 6.36 | 4.52 | 90 |
| 18 |  | SFC<br>Chiralpak IA<br>5% IPA<br>isocratic, 2.5 mL/min | 5.79 | 7.41 | 77 |

***Table 1.4*** *Determination of enantiomeric excess (continued)*

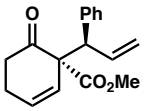
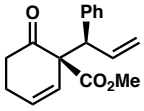
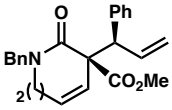
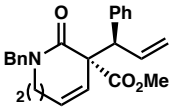
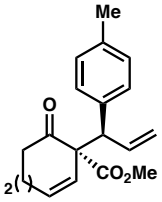
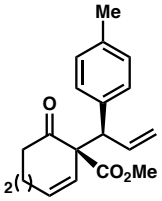
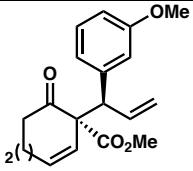
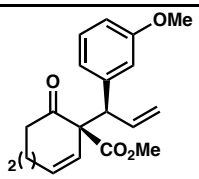
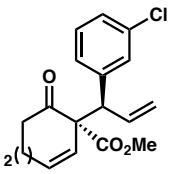
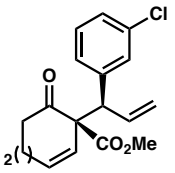
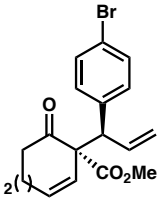
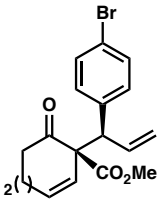
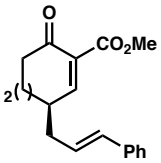
| Entry | Compound | Assay Conditions | $t_R$ of major isomer (min) | $t_R$ of minor isomer (min) | %ee |
|---|---|---|---|---|---|
| 19 |  | SFC<br>Chiralpak IA<br>2% IPA<br>isocratic, 3.0 mL/min | 13.26 | 6.82 | 98 |
| 20 |  | SFC<br>Chiralpak IA<br>2% IPA<br>isocratic, 3.0 mL/min | 6.95 | 11.43 | 91 |
| 21 |  | SFC<br>Chiralcel OD-H<br>10% MeCN<br>isocratic, 2.5 mL/min | 16.85 | 13.74 | 79 |
| 22 |  | SFC<br>Chiralcel OD-H<br>10% MeCN<br>isocratic, 2.5 mL/min | 12.34 | 15.02 | 62 |
| 23 |  | SFC<br>Chiralpak AD-H<br>8% IPA<br>isocratic, 2.5 mL/min | 4.50 | 4.13 | 95 |
| 24 |  | SFC<br>Chiralpak AD-H<br>10% IPA<br>isocratic, 2.5 mL/min | 4.40 | 3.43 | 91 |
| 25 |  | SFC<br>Chiralpak AD-H<br>8% IPA<br>isocratic, 2.5 mL/min | 4.75 | 4.28 | 91 |
| 26 |  | SFC<br>Chiralpak IC<br>10% IPA<br>isocratic, 2.5 mL/min | 5.99 | 5.40 | 81 |

***Table 1.4*** *Determination of enantiomeric excess (continued)*

| Entry | Compound | Assay Conditions | $t_R$ of major isomer (min) | $t_R$ of minor isomer (min) | %ee |
|---|---|---|---|---|---|
| 27 |  | SFC<br>Chiralpak AD-H<br>7% IPA<br>isocratic, 3.0 mL/min | 4.85 | 4.14 | 91 |
| 28 |  | SFC<br>Chiralpak AD-H<br>7% IPA<br>isocratic, 2.5 mL/min | 4.67 | 5.28 | 75 |
| 29 |  | SFC<br>Chiralpak AD-H<br>10% IPA<br>isocratic, 2.5 mL/min | 5.17 | 4.68 | 88 |
| 30 |  | SFC<br>Chiralpak IC<br>10% IPA<br>isocratic, 2.5 mL/min | 5.01 | 4.43 | 79 |
| 31 |  | SFC<br>Chiralcel OB-H<br>10% IPA<br>isocratic, 2.5 mL/min | 13.72 | 15.18 | 95 |

## 1.6 REFERENCES AND NOTES

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(16) See Experimental Section for details.

(17) The absolute structure of **5aa** was assigned by X-ray analysis of its derivative, see Appendix 2 for details.

(18) Chirality transfer = $(ee_{product}/ee_{substrate}) \times 100\%$.

(19) Certain γ-alkylation products and starting materials were inseparable, thus a two-step procedure was required, see SI.

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(22) See Appendix 2 for the assignment of the absolute structure of **7ca**.

# *APPENDIX 1*

*Spectra Relevant to Chapter 1:*

*Enantioselective γ-Alkylation of α,β-Unsaturated Malonates and Ketoesters by a Sequential Ir-Catalyzed Asymmetric Allylic Alkylation/Cope Rearrangement*

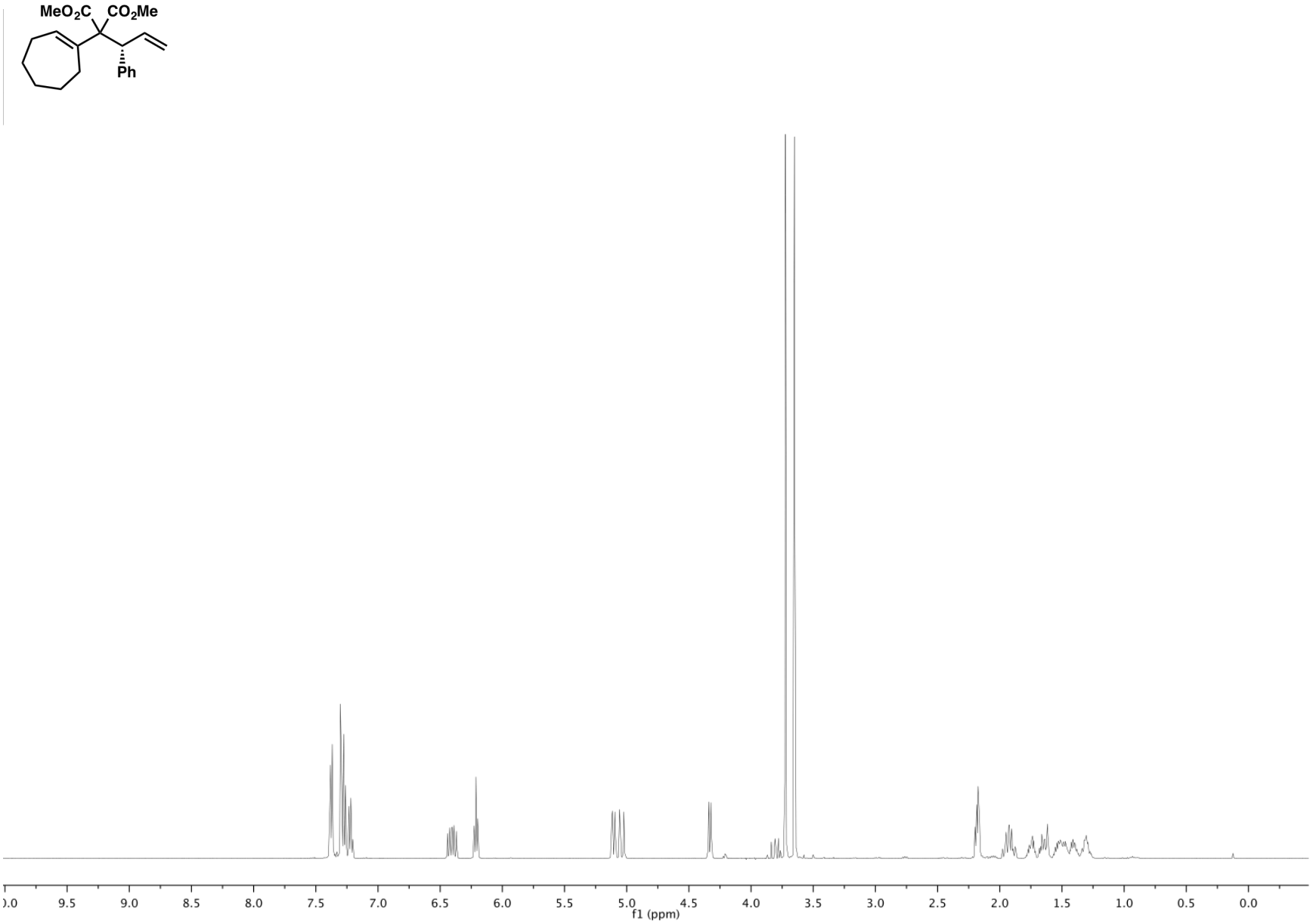



***Figure A1.1*** *$^{1}H$ NMR (500 MHz, $CDCl_3$) of compound* ***3aa***.

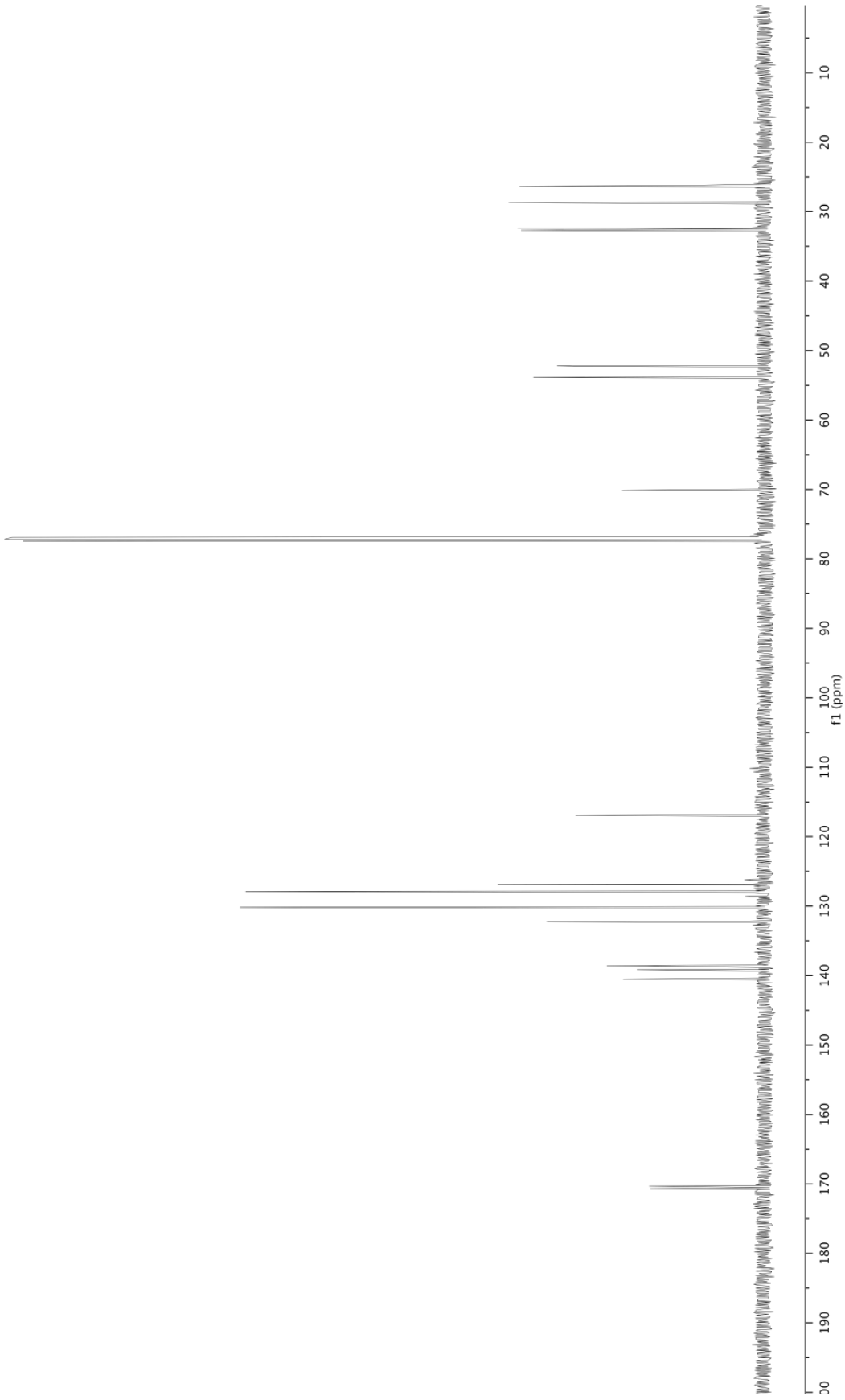



***Figure A1.2*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***3aa****.*

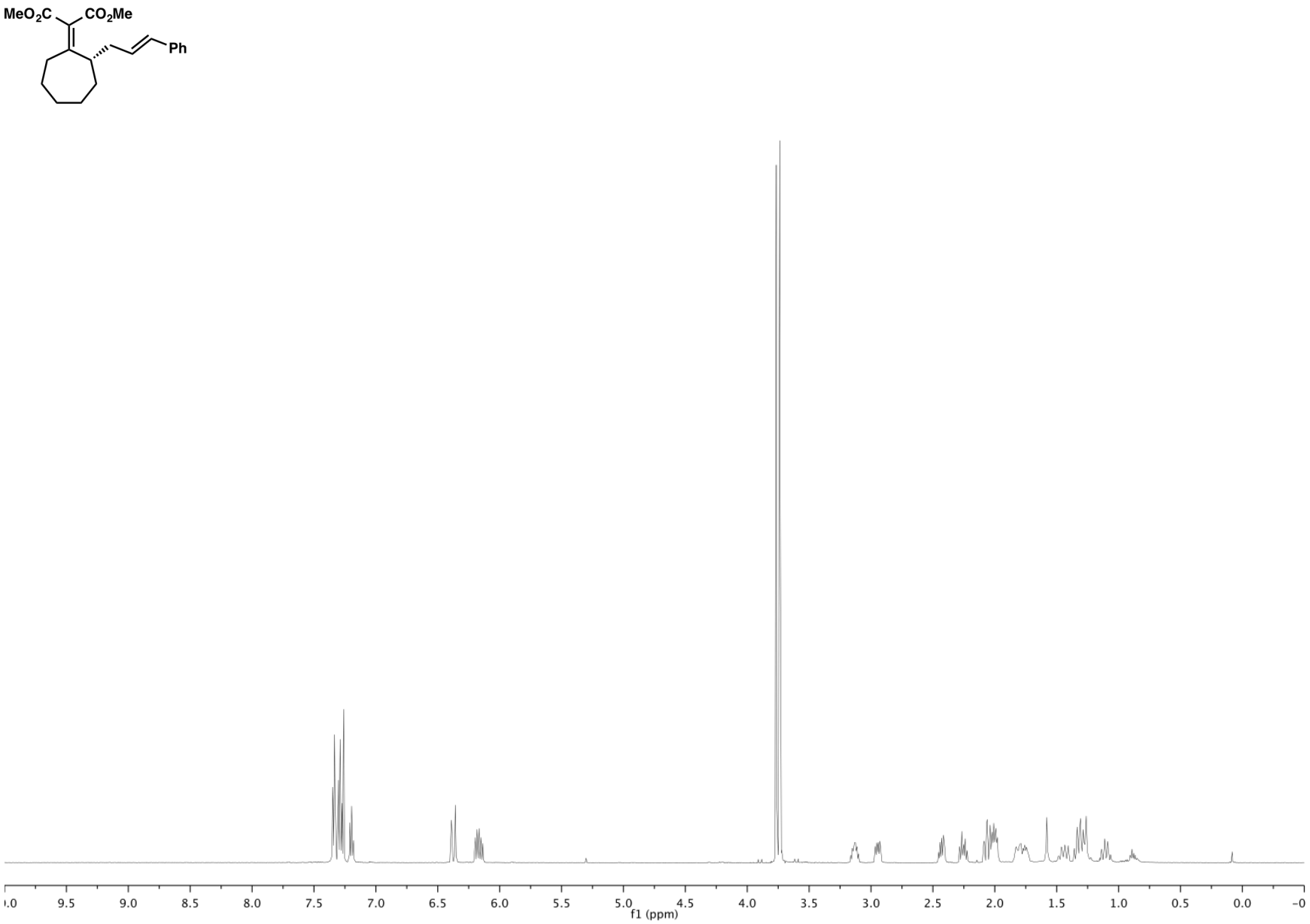



***Figure A1.3*** *$^{1}H$ NMR (500 MHz, $CDCl_3$) of compound* ***5aa***.

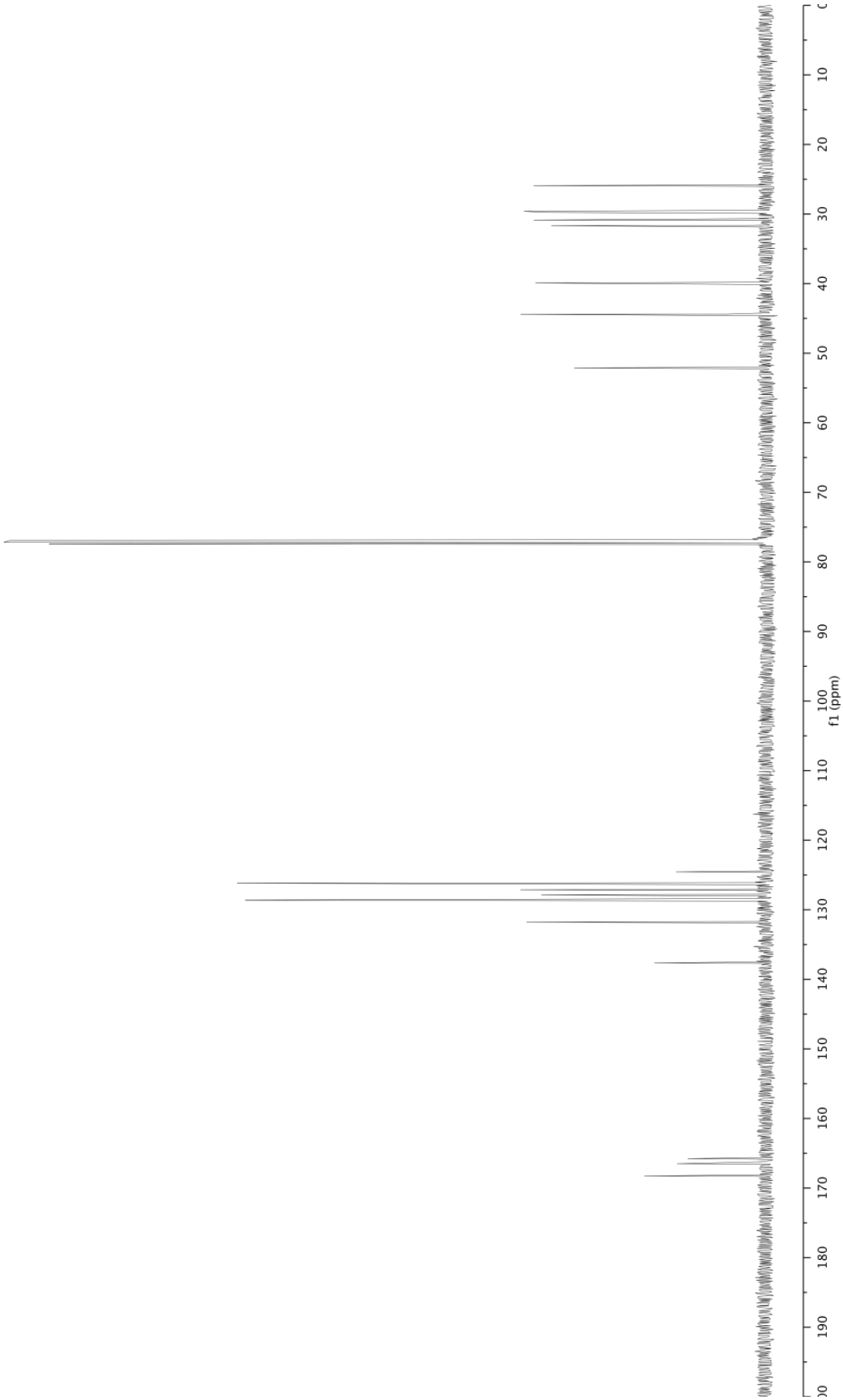



***Figure A1.4*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***5aa****.*

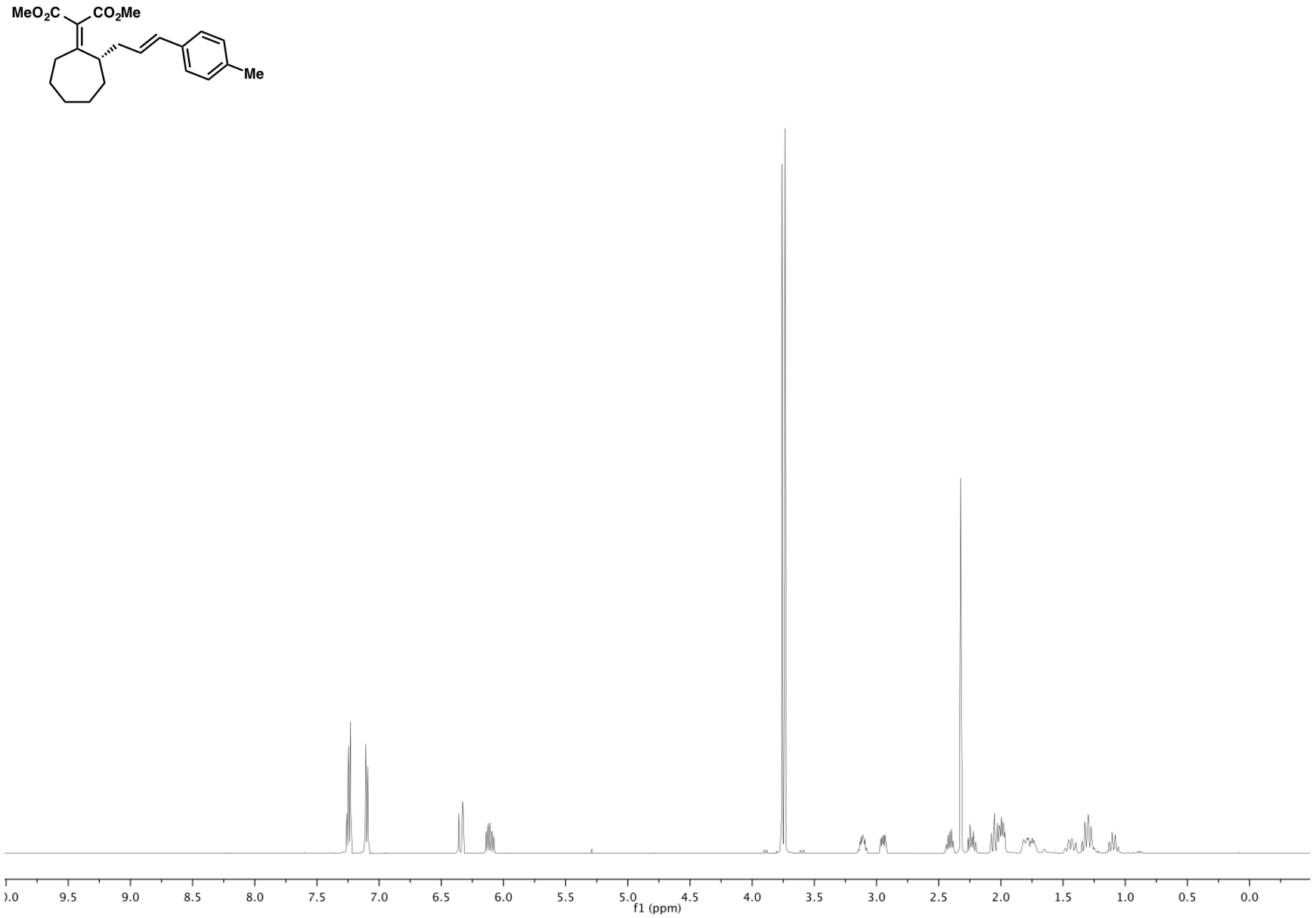



***Figure A1.5*** *$^1$H NMR (500 MHz, $C_6D_6$) of compound* ***5ab.***

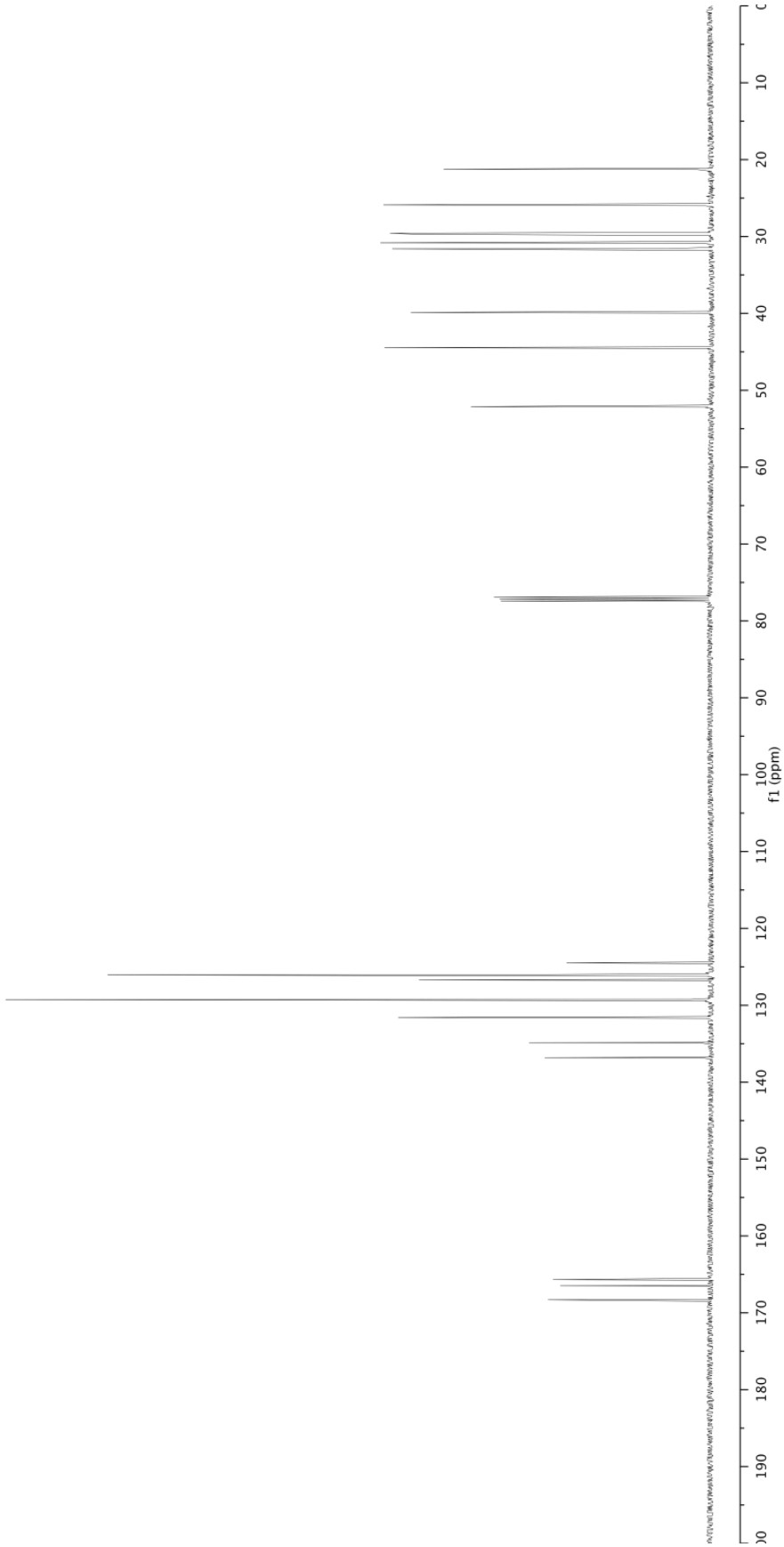



***Figure A1.6*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***5ab****.*

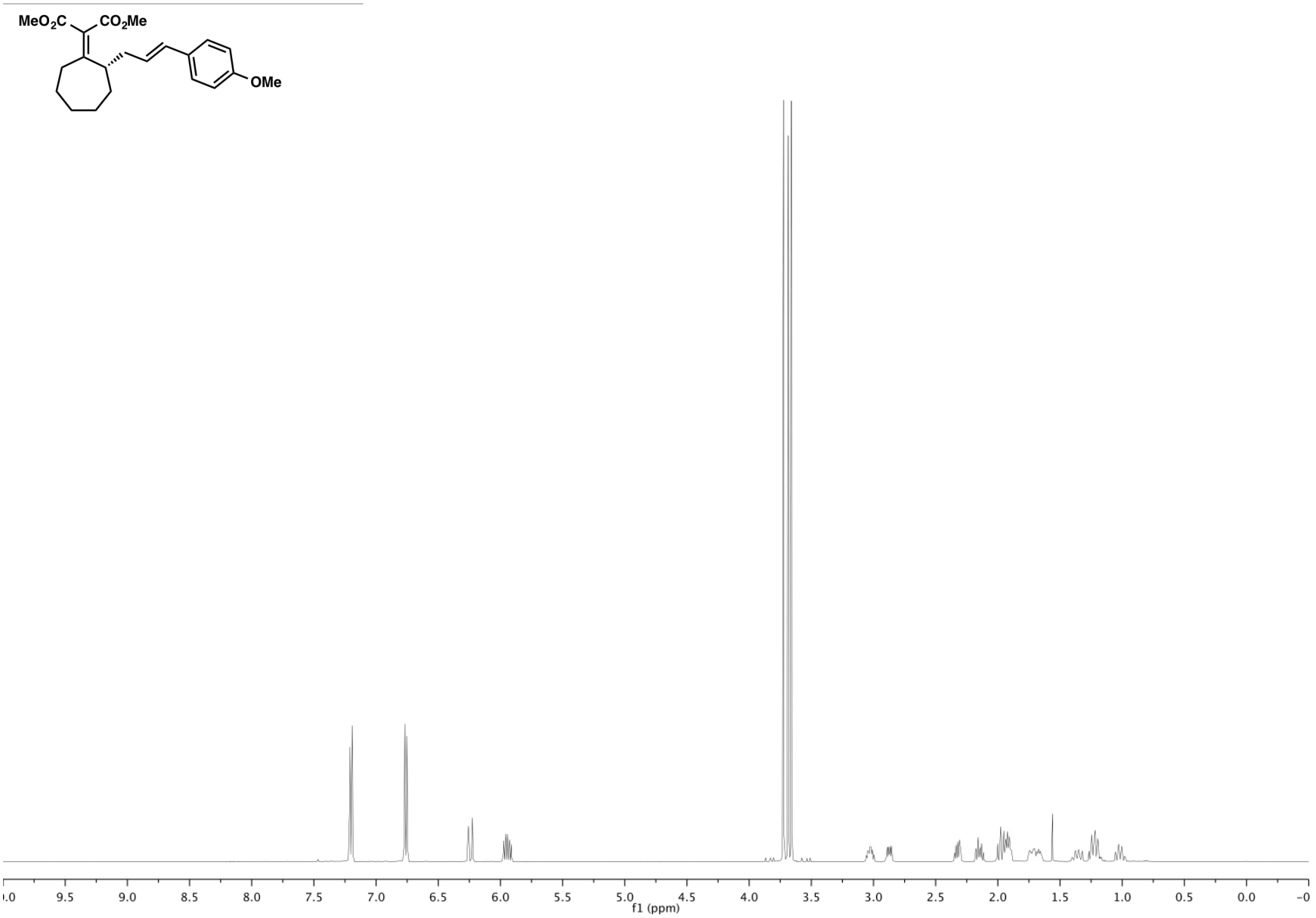



***Figure A1.7*** *$^1$H NMR (500 MHz, $C_6D_6$) of compound* ***5ac*****.**

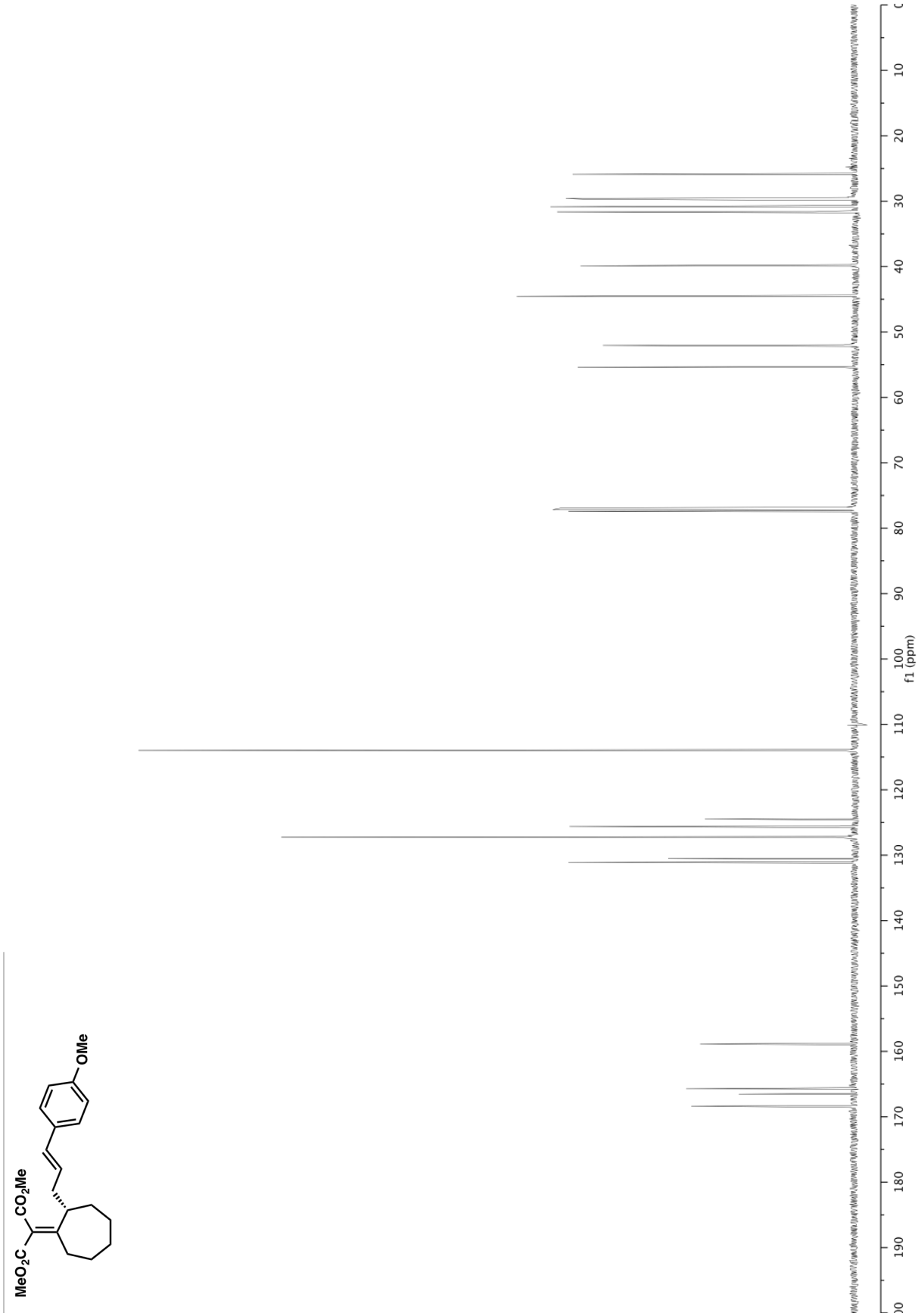



***Figure A1.8*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***5ac****.*

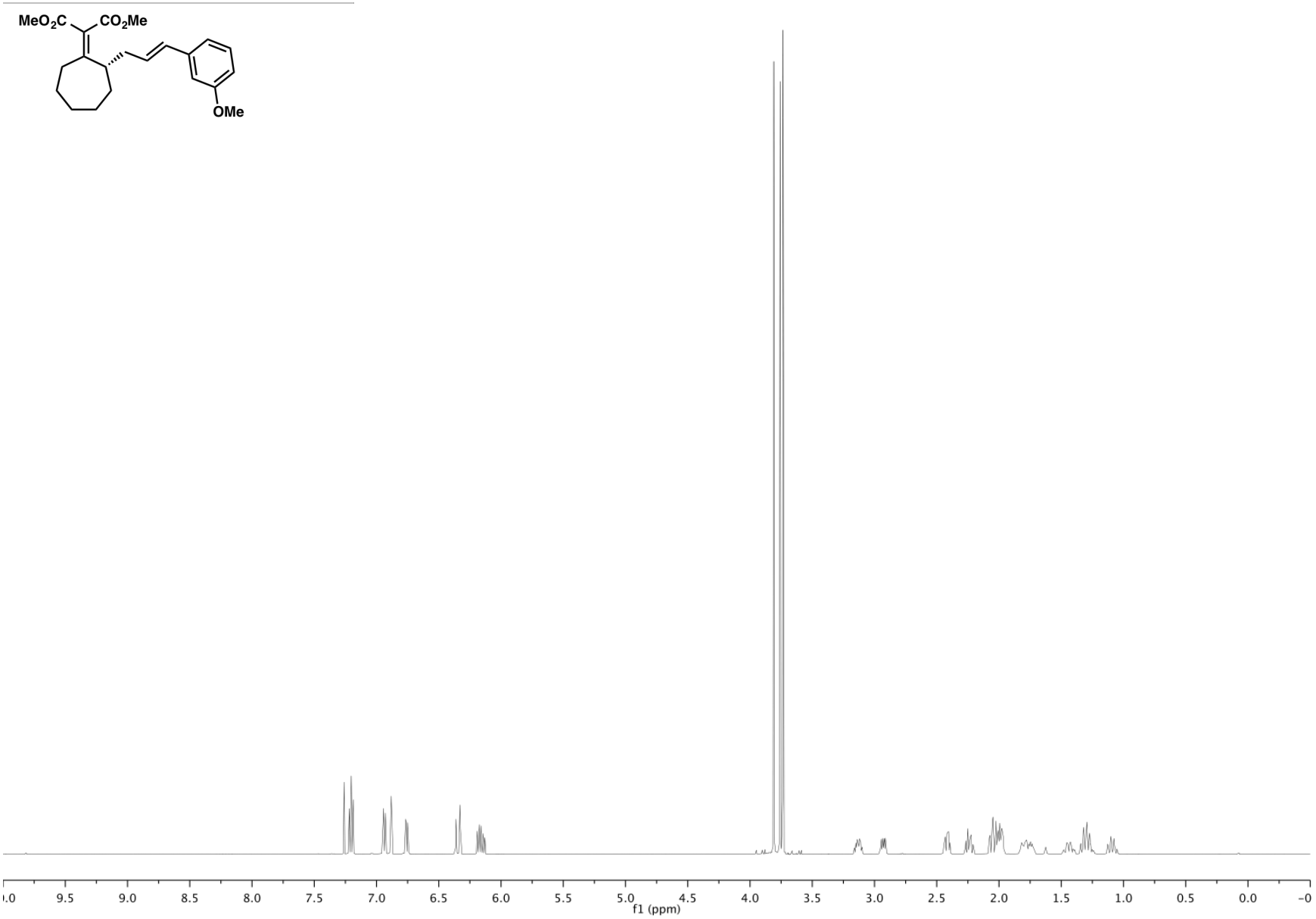



***Figure A1.9*** *$^1$H NMR (500 MHz, $C_6D_6$) of compound* ***5ad.***

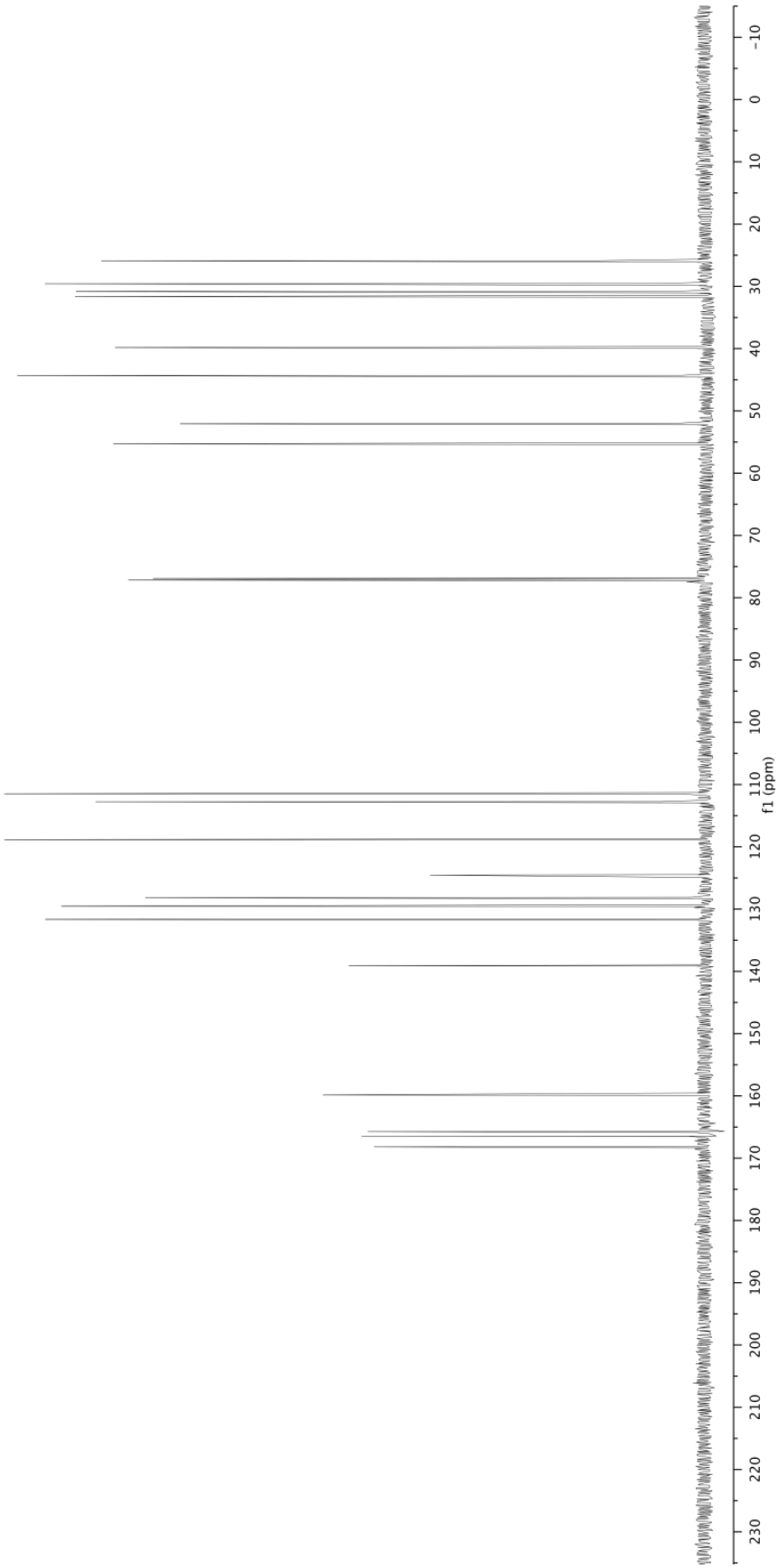



***Figure A1.10*** *$^{13}C$ NMR (125 MHz, $C_6D_6$) of compound* ***5ad****.*

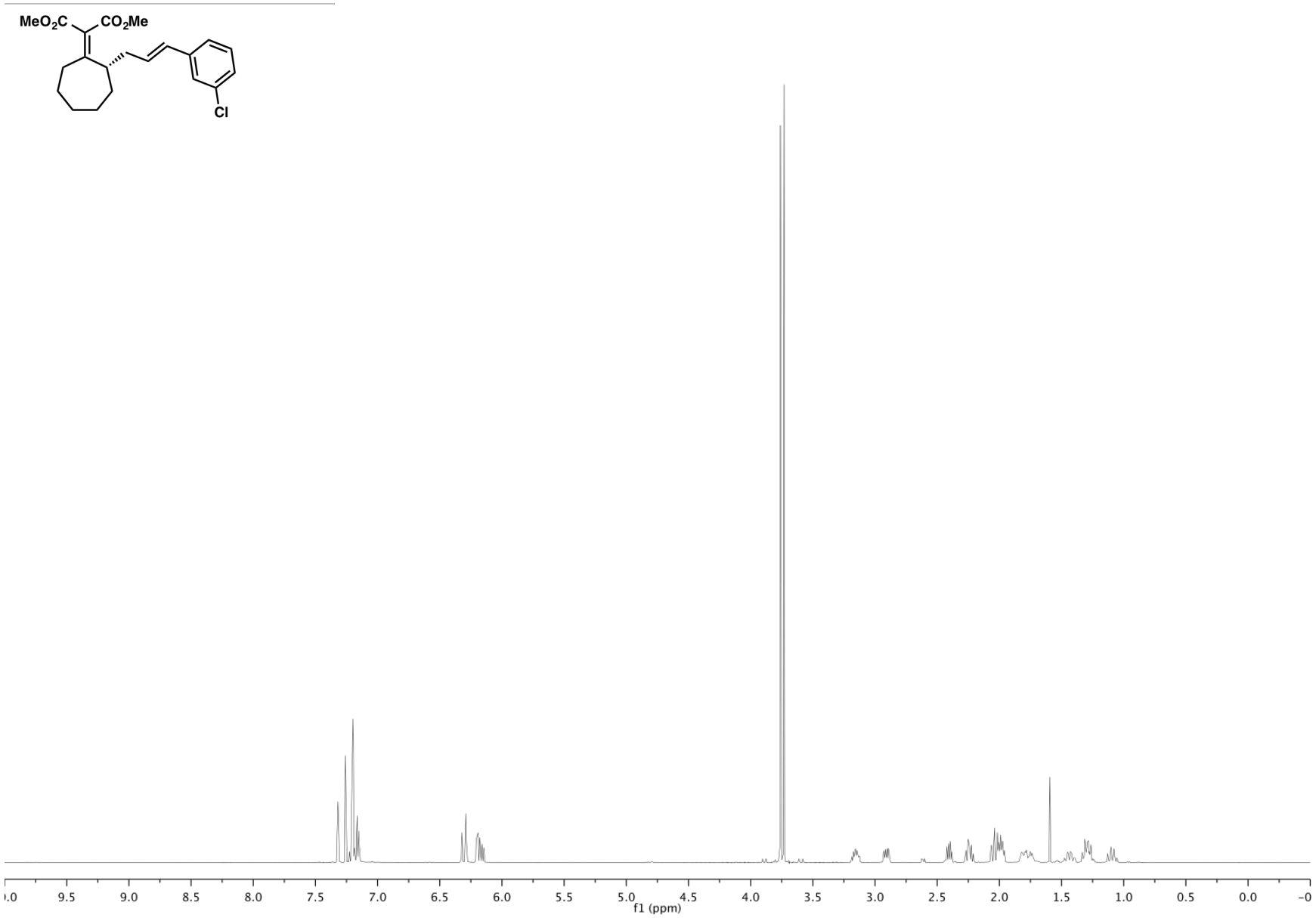



***Figure A1.11*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***5ae***.

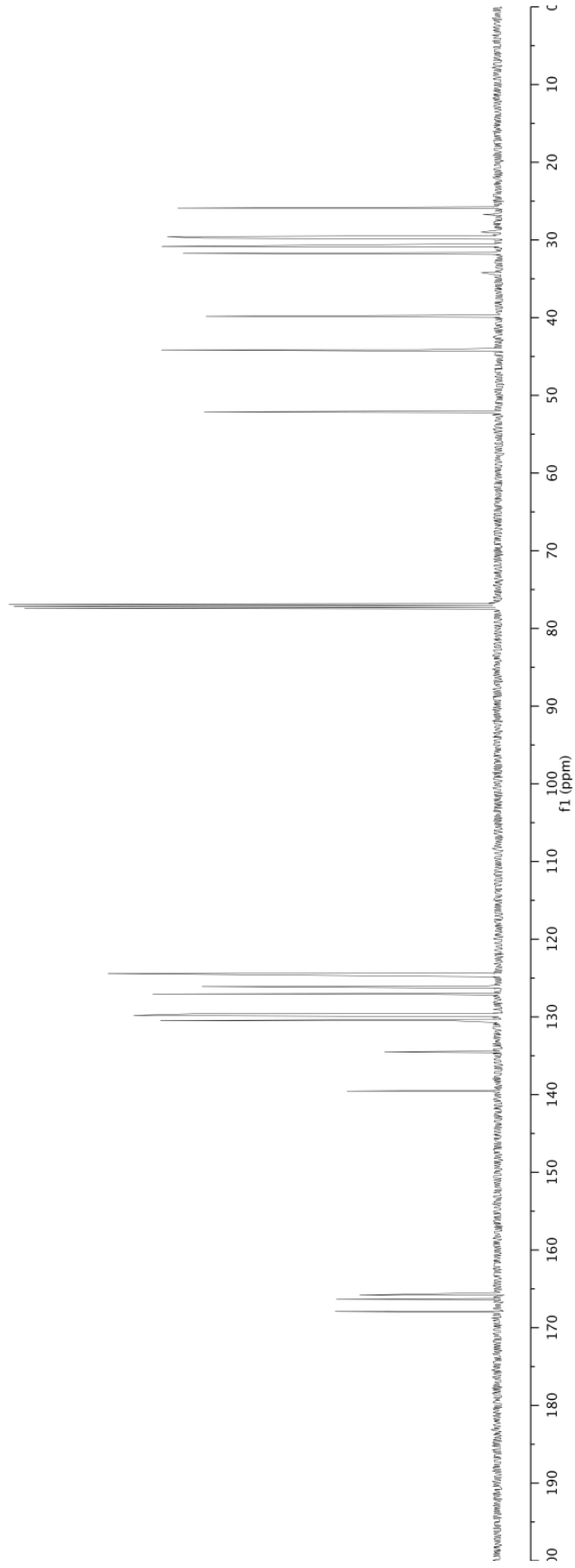



***Figure A1.12*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***5ae***.

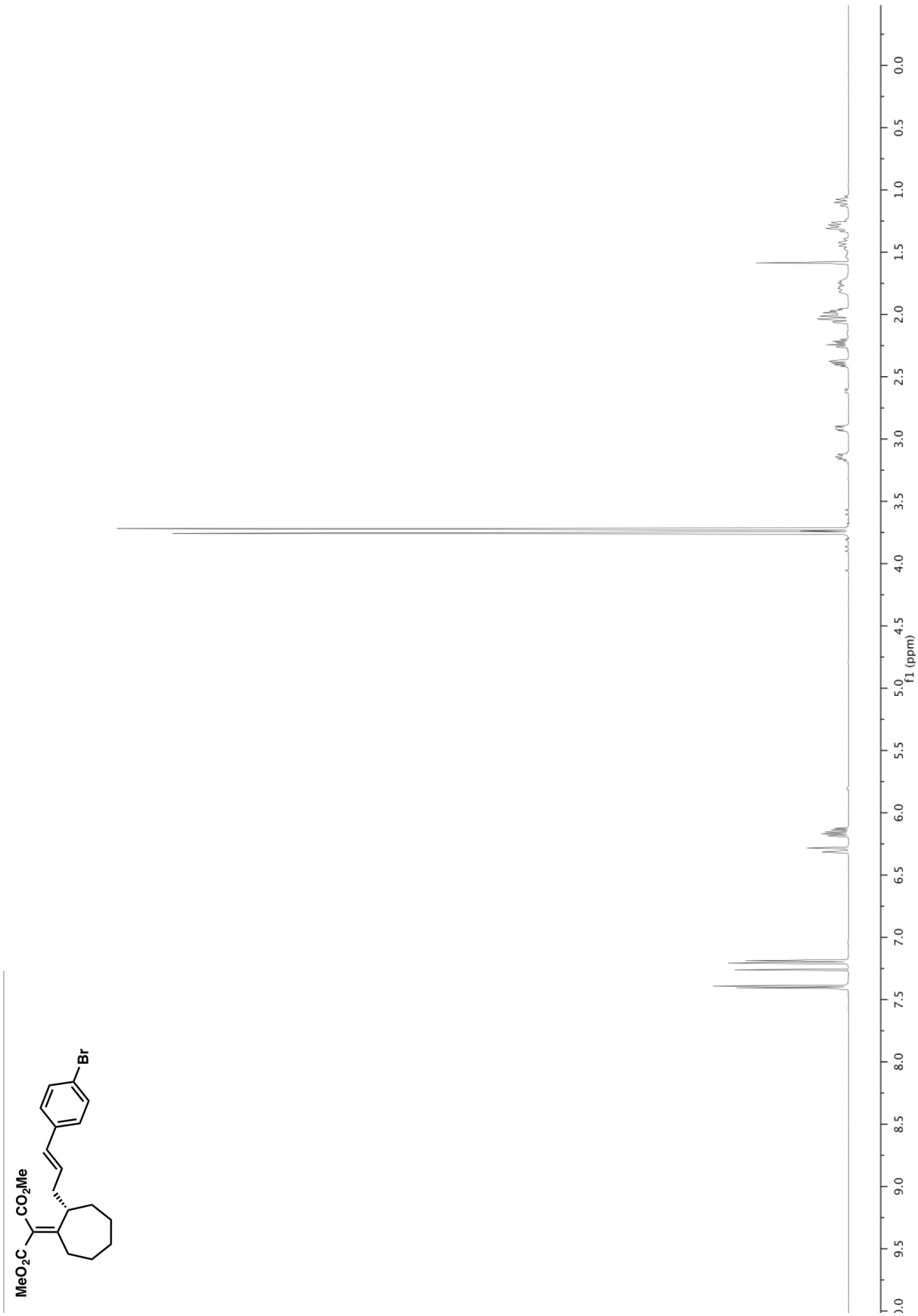



***Figure A1.13*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***5af****.*

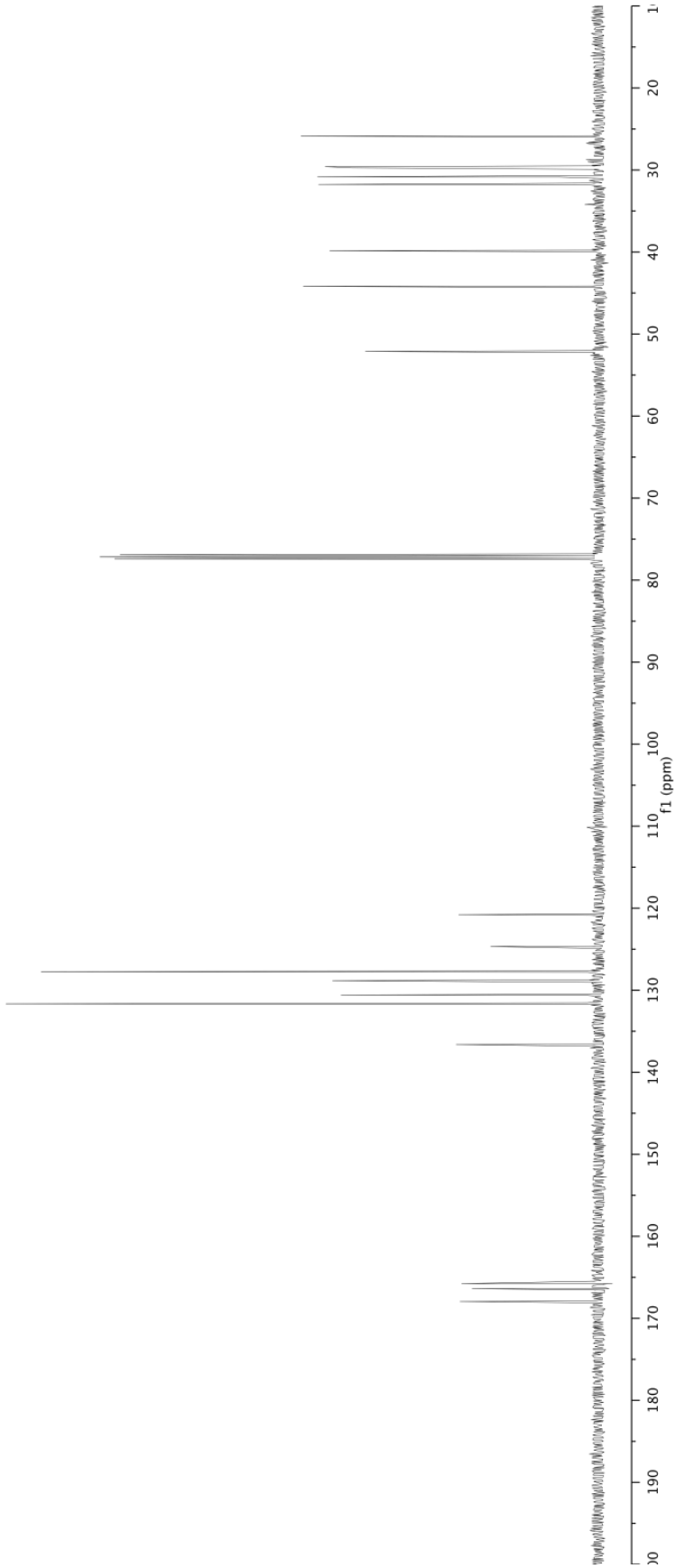



***Figure A.1.14*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***5af****.*

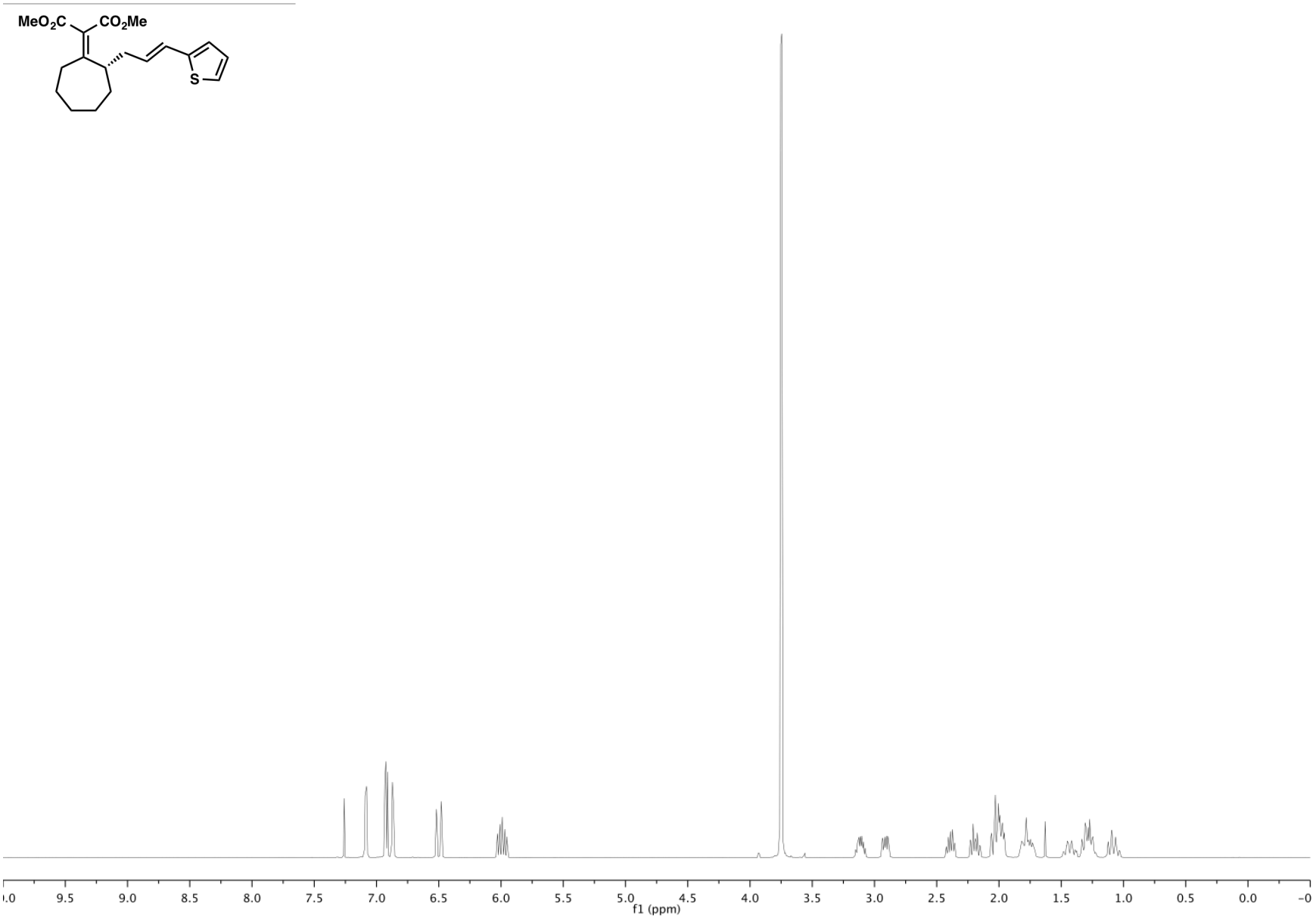



***Figure A1.15*** *$^1$H NMR (400 MHz, $CDCl_3$) of compound* ***5ag***.

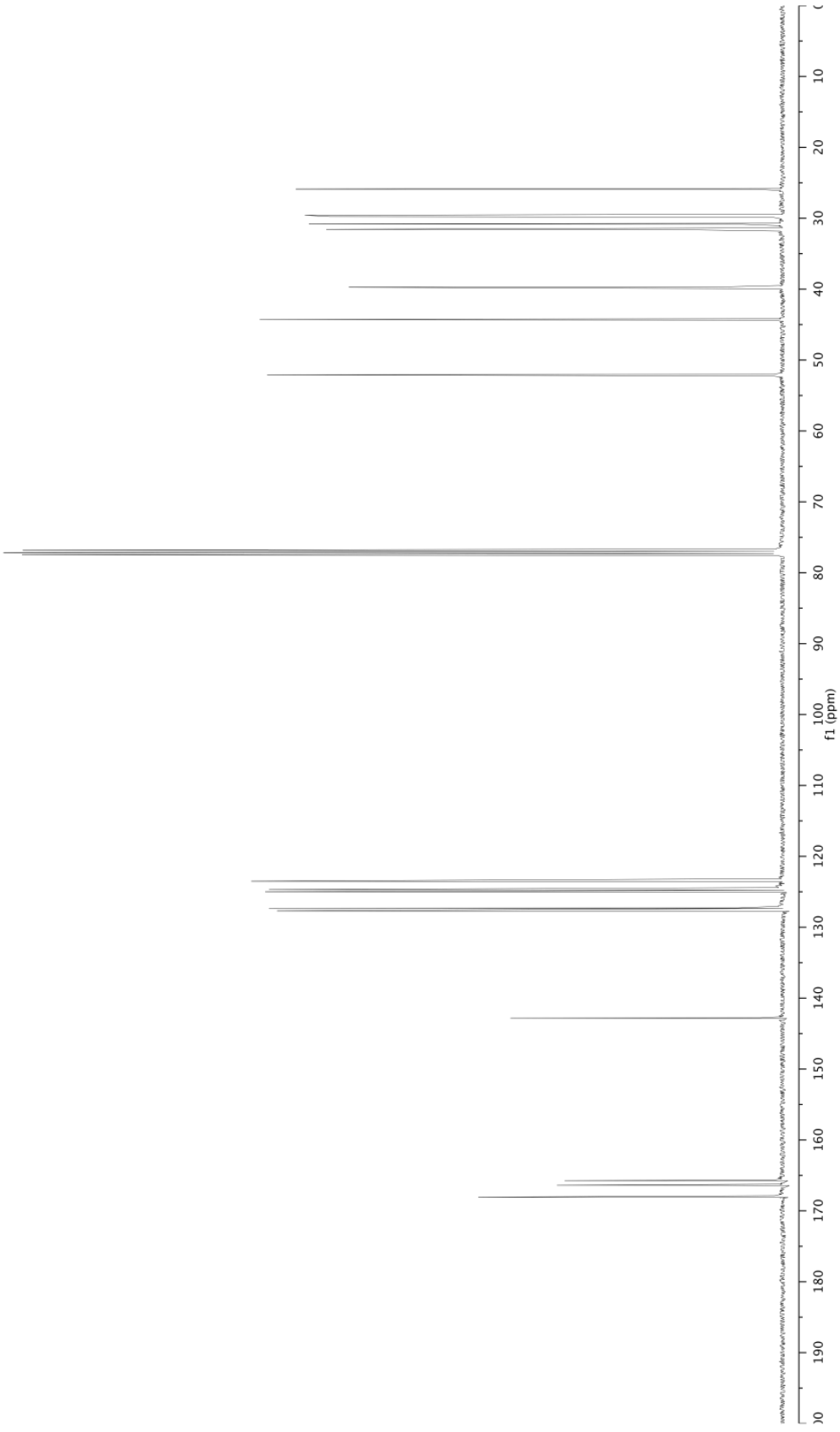



***Figure A1.16*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***5ag***.

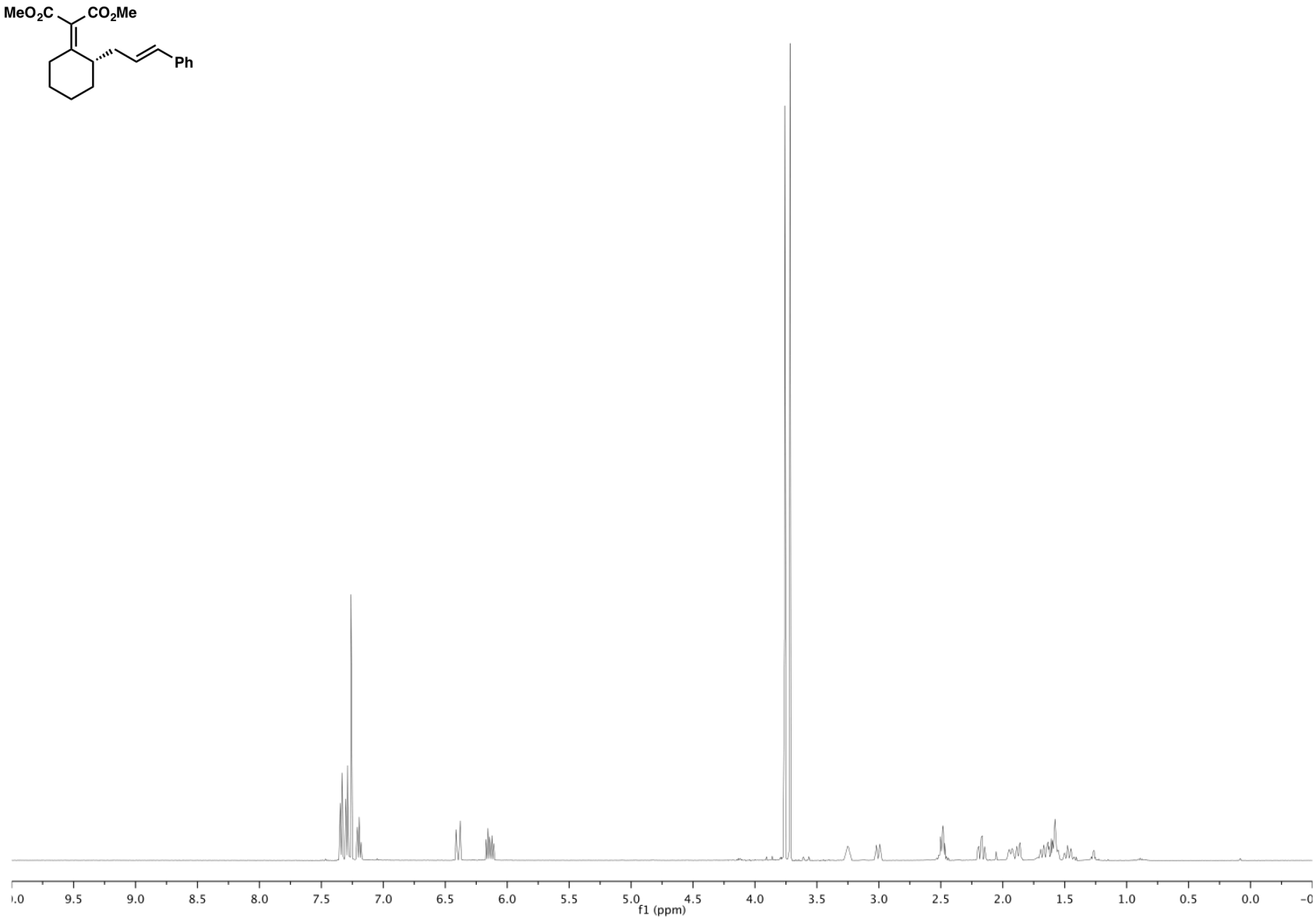



***Figure A1.17*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***5ba***.

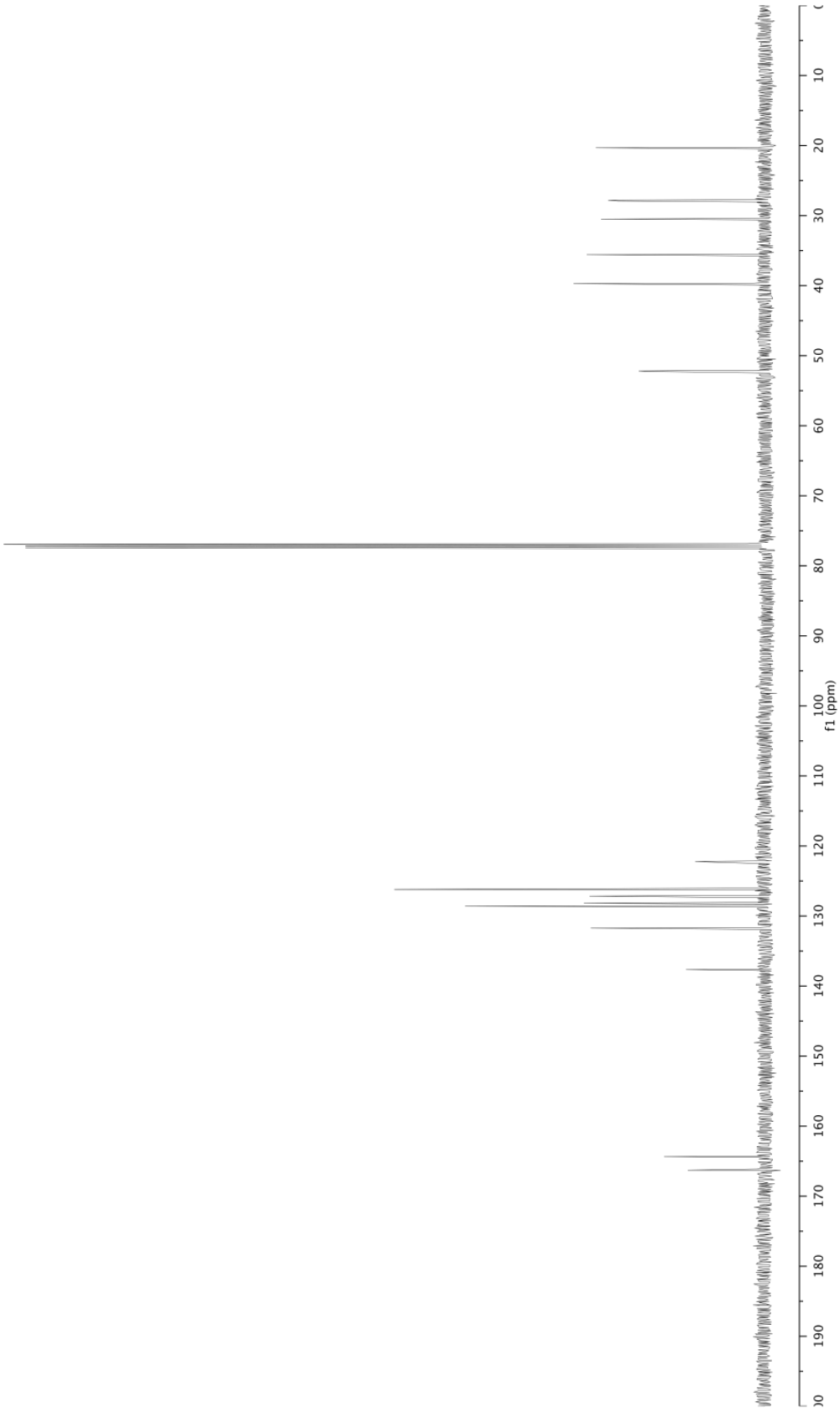



***Figure A1.18*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***5ba***.

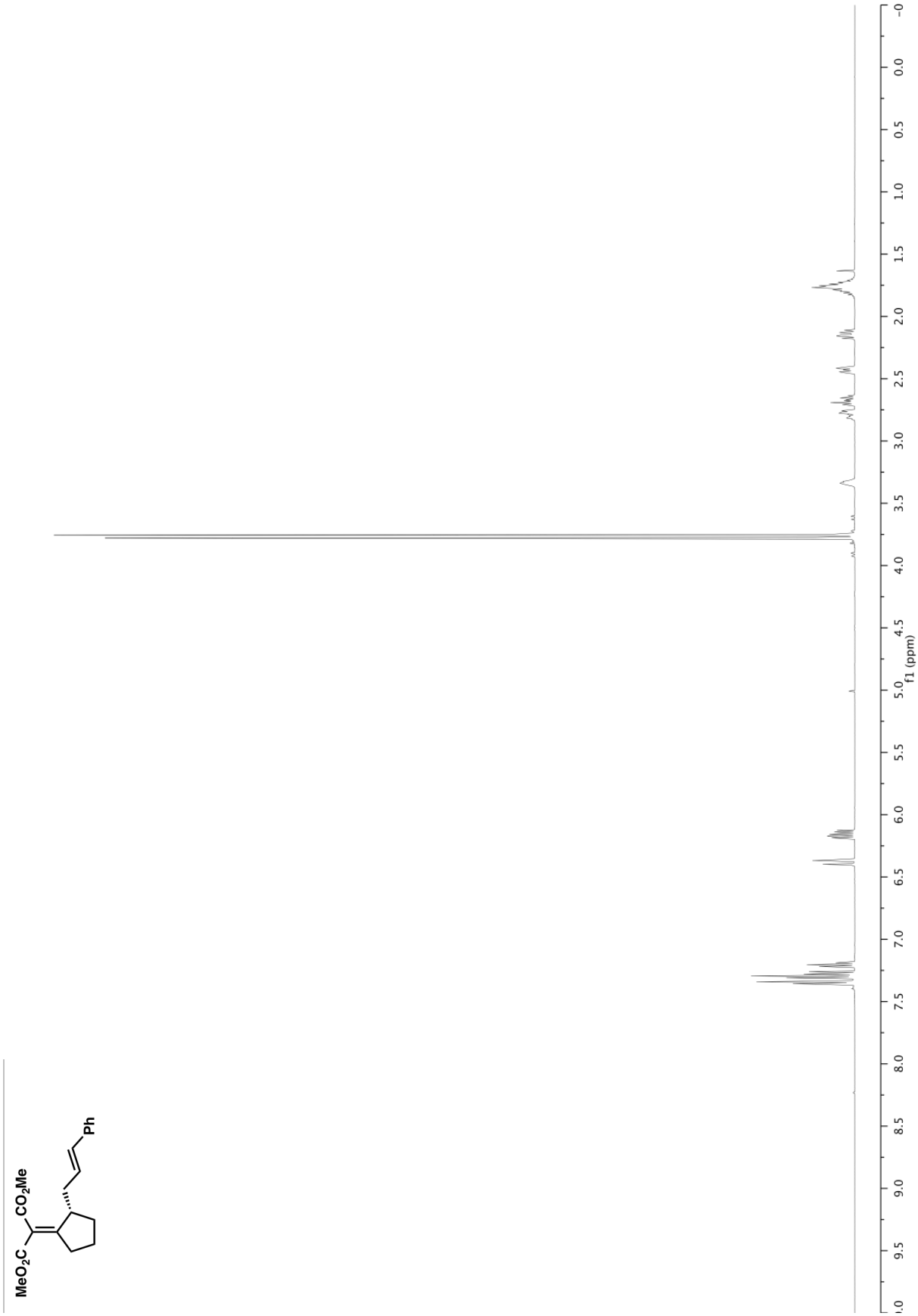



***Figure A1.19*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***5ca****.*

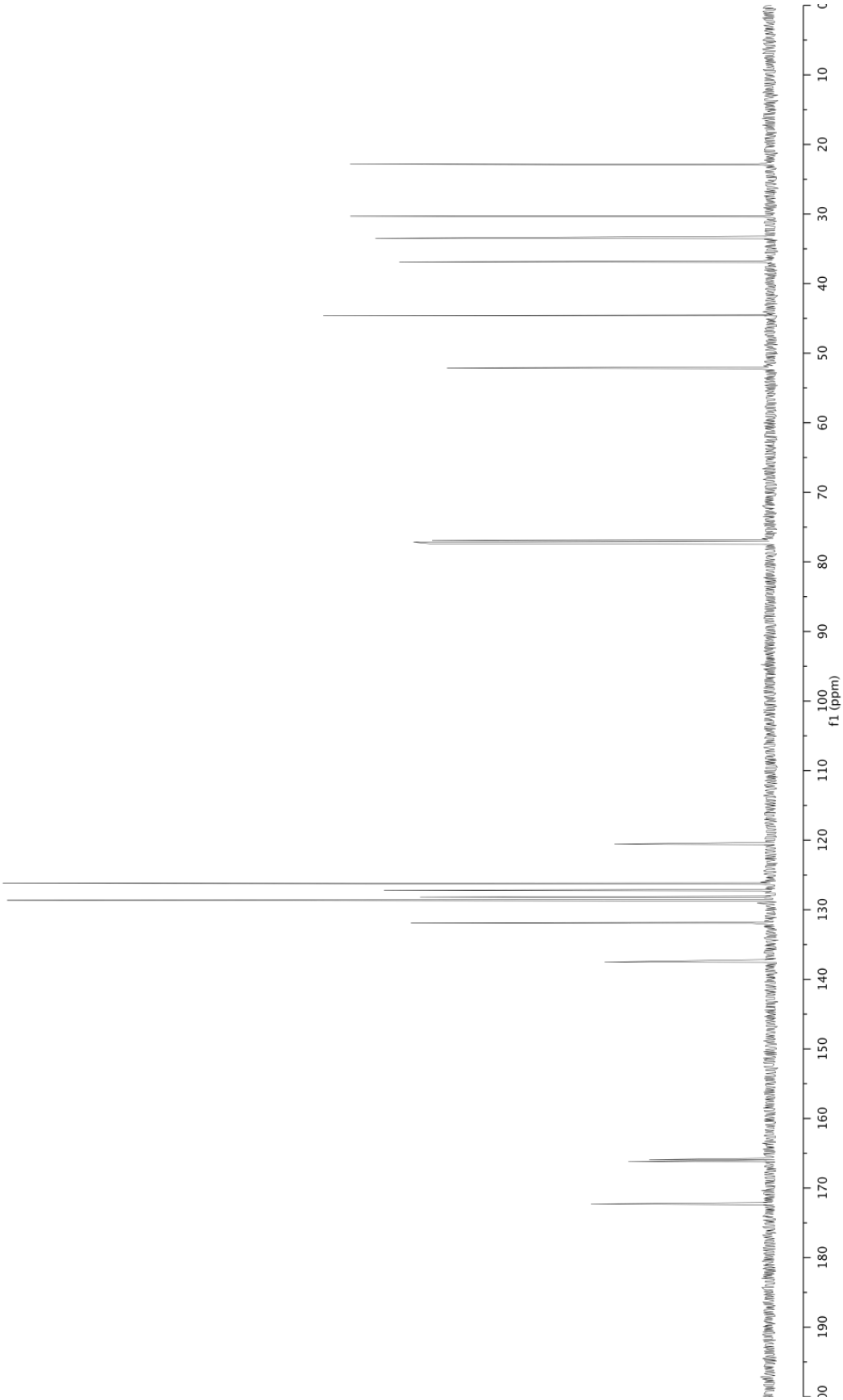



***Figure A1.20*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***5ca***.

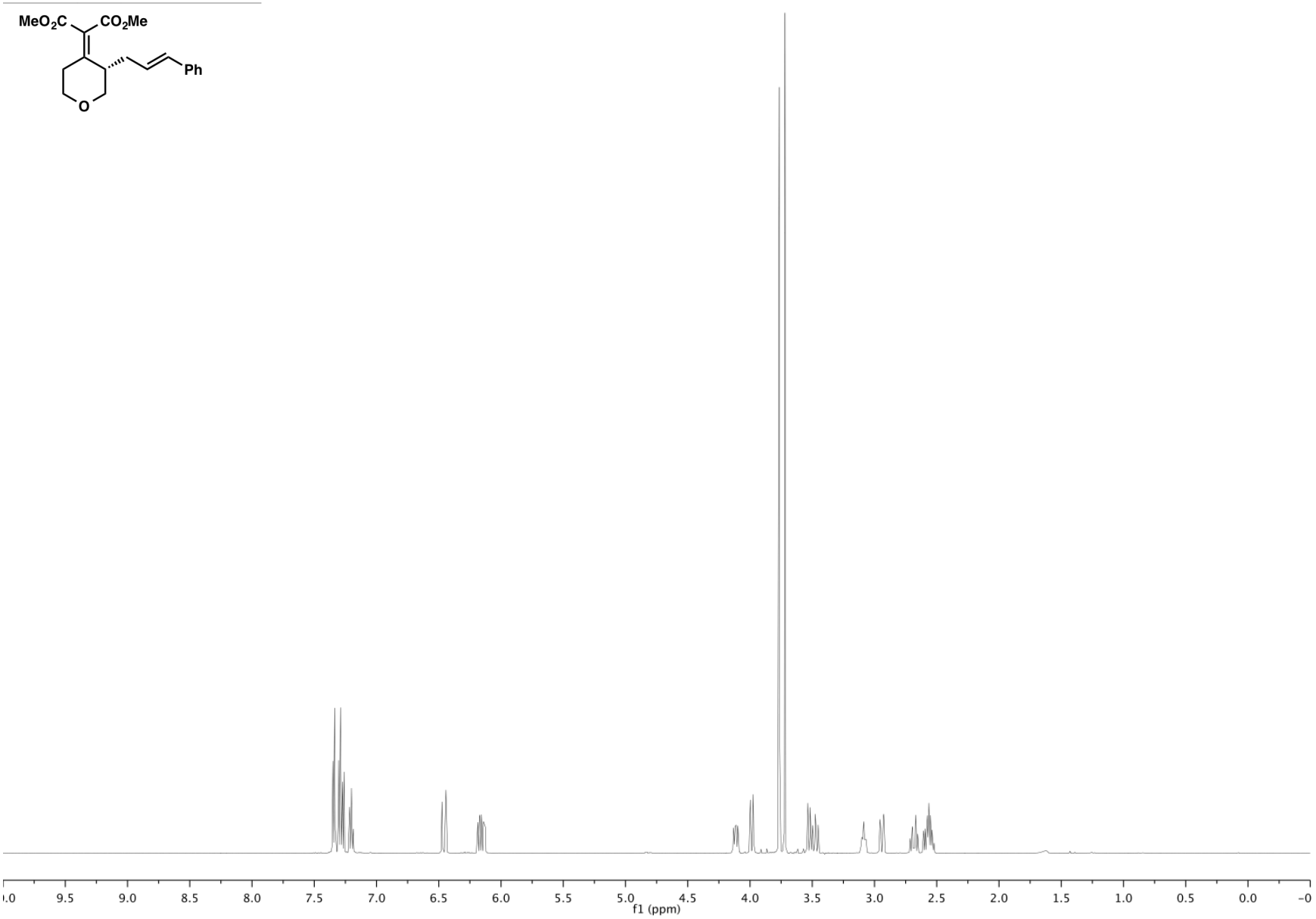



***Figure A1.21*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***5da***.

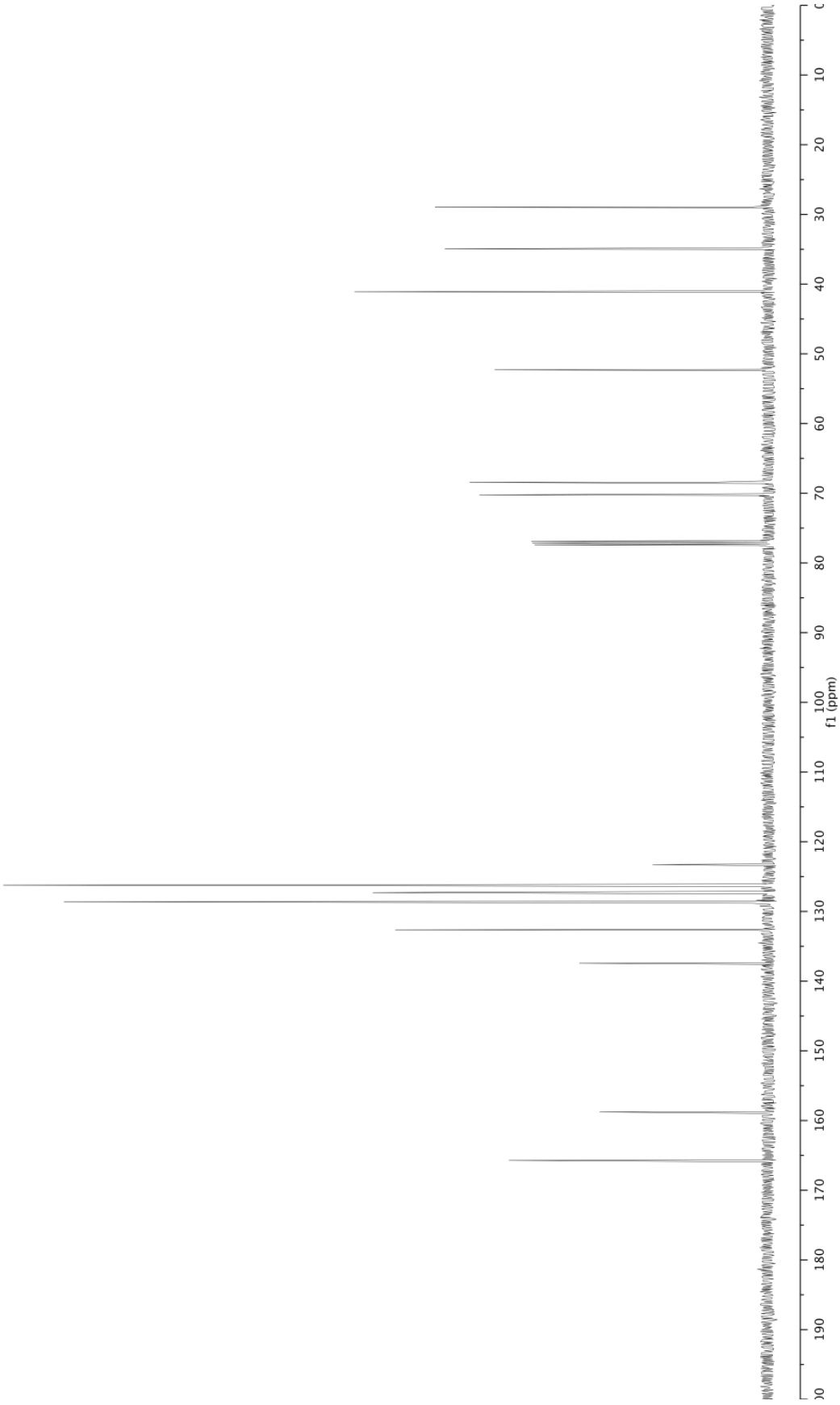



***Figure A1.22*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***5da****.*

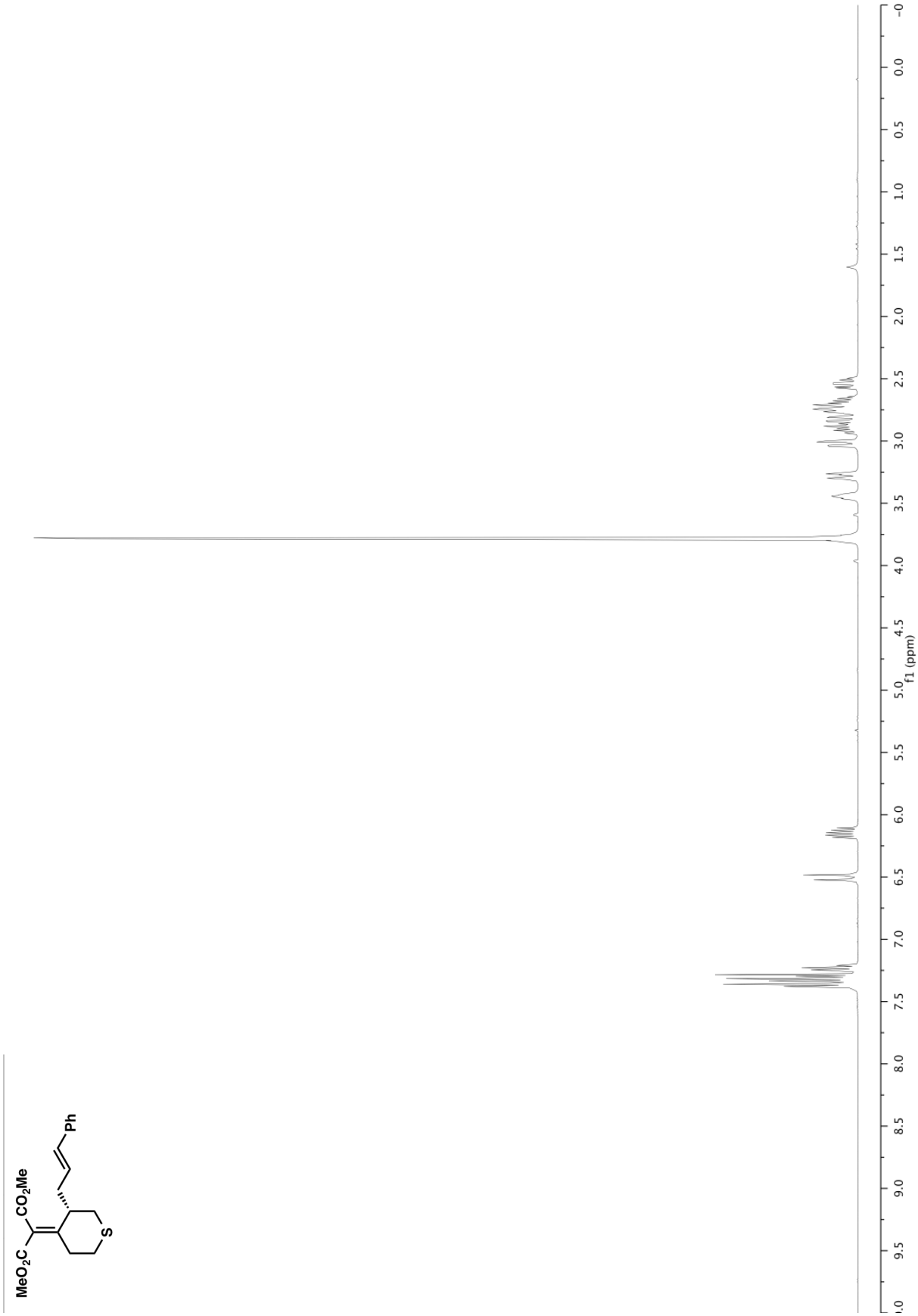



***Figure A1.23*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***5ea***.

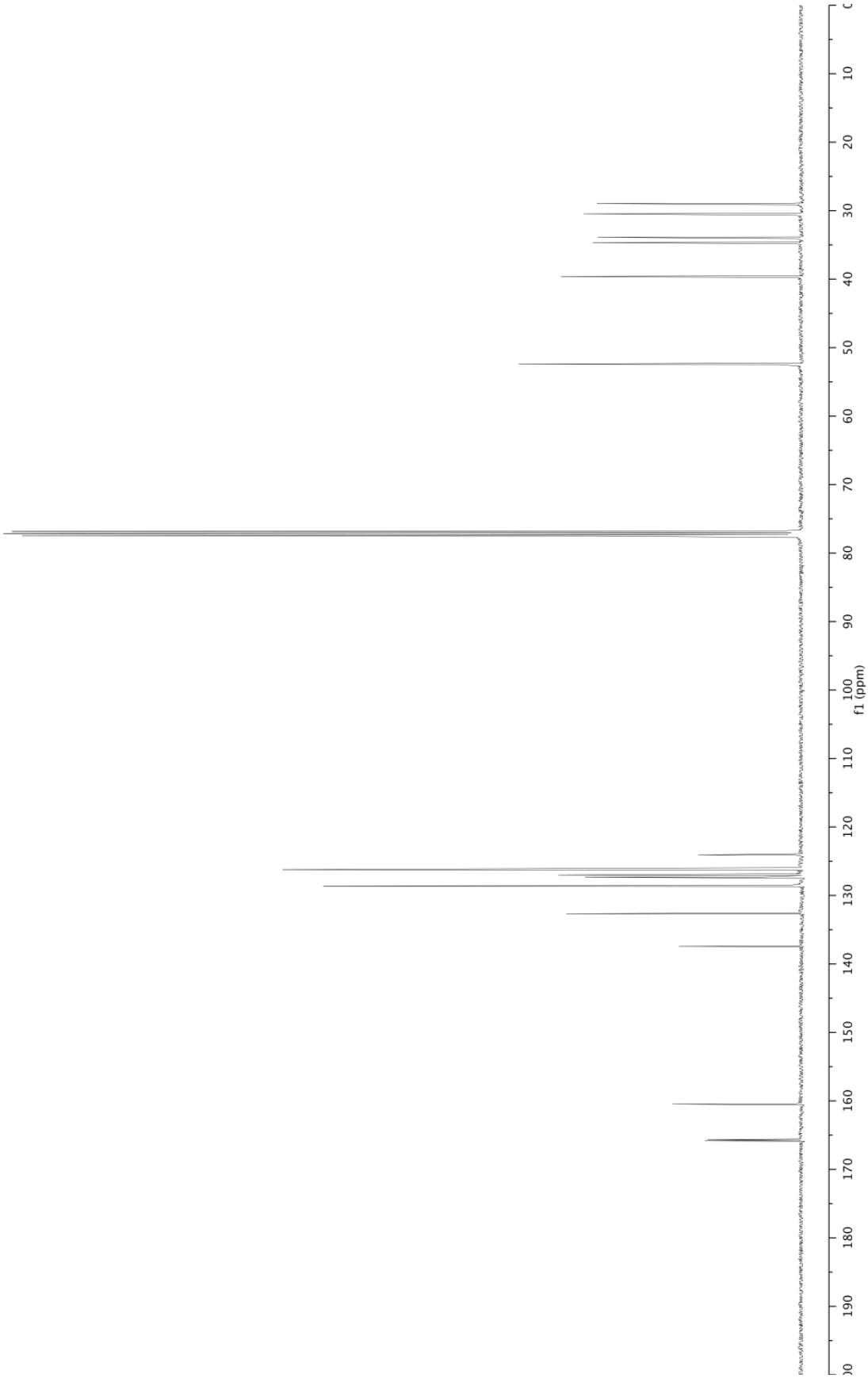



***Figure A1.24*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***5ea***.

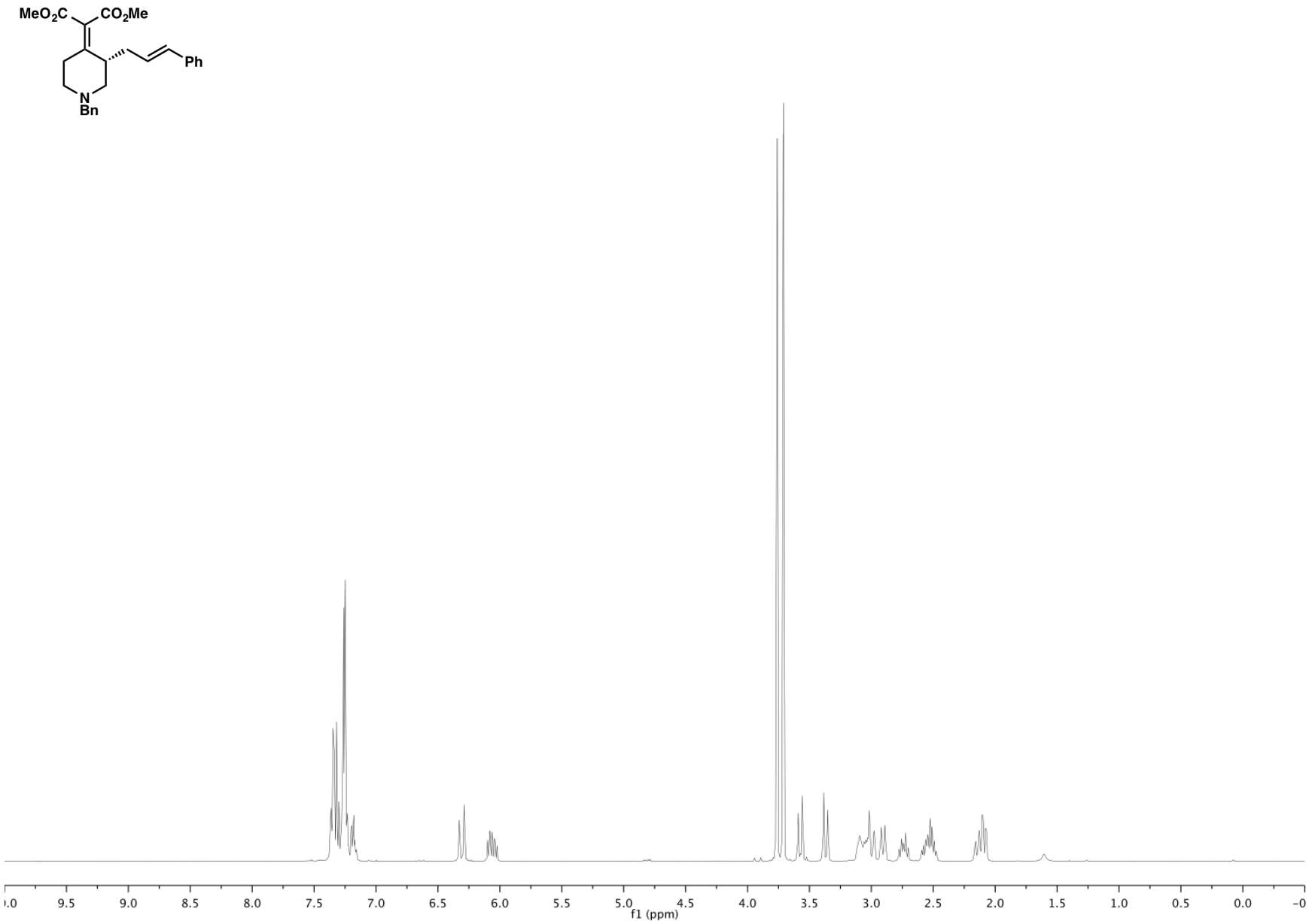



***Figure A1.25*** *$^1$H NMR (400 MHz, $CDCl_3$) of compound* ***5fa***.

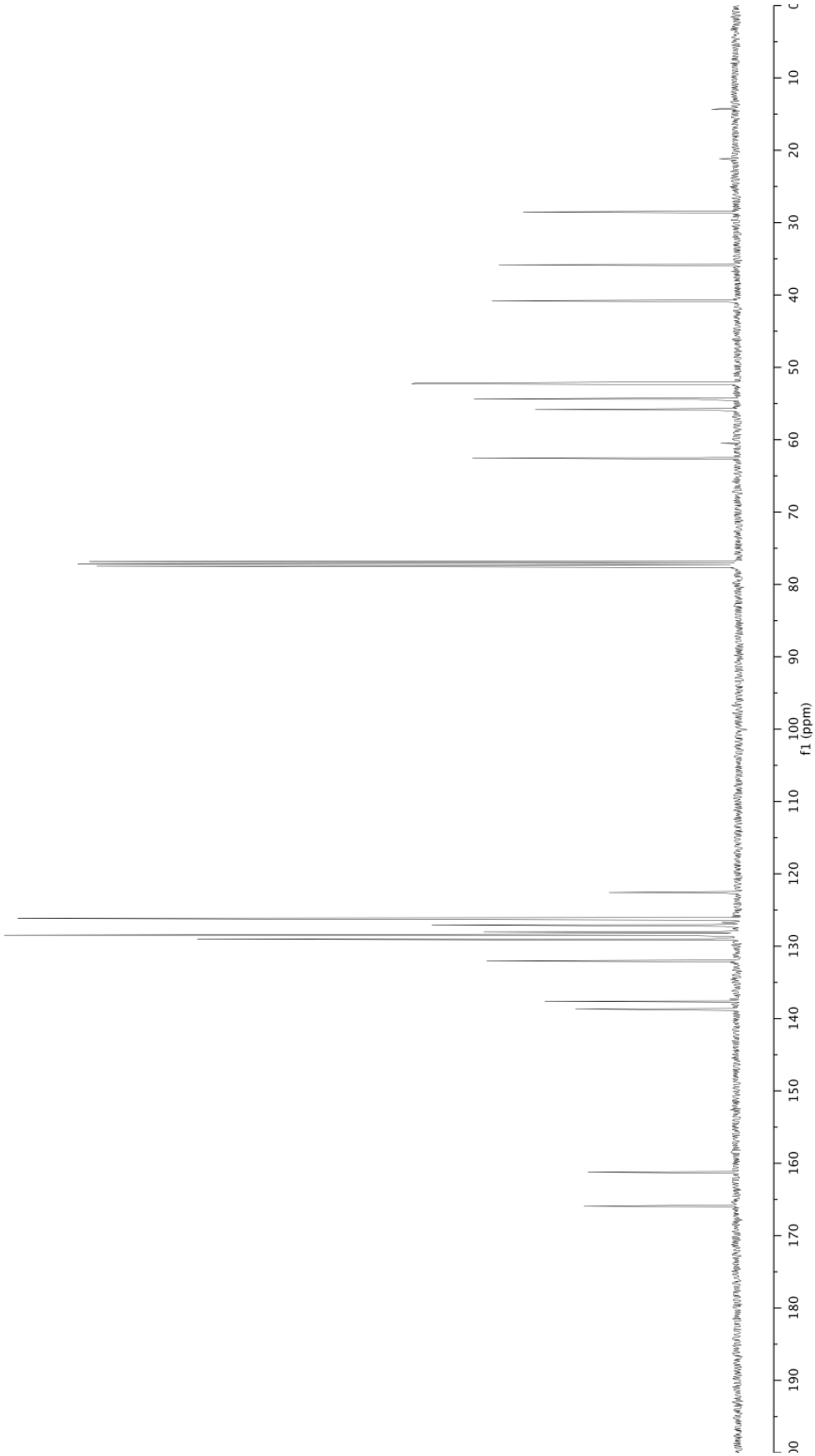



***Figure A1.26*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***5fa****.*

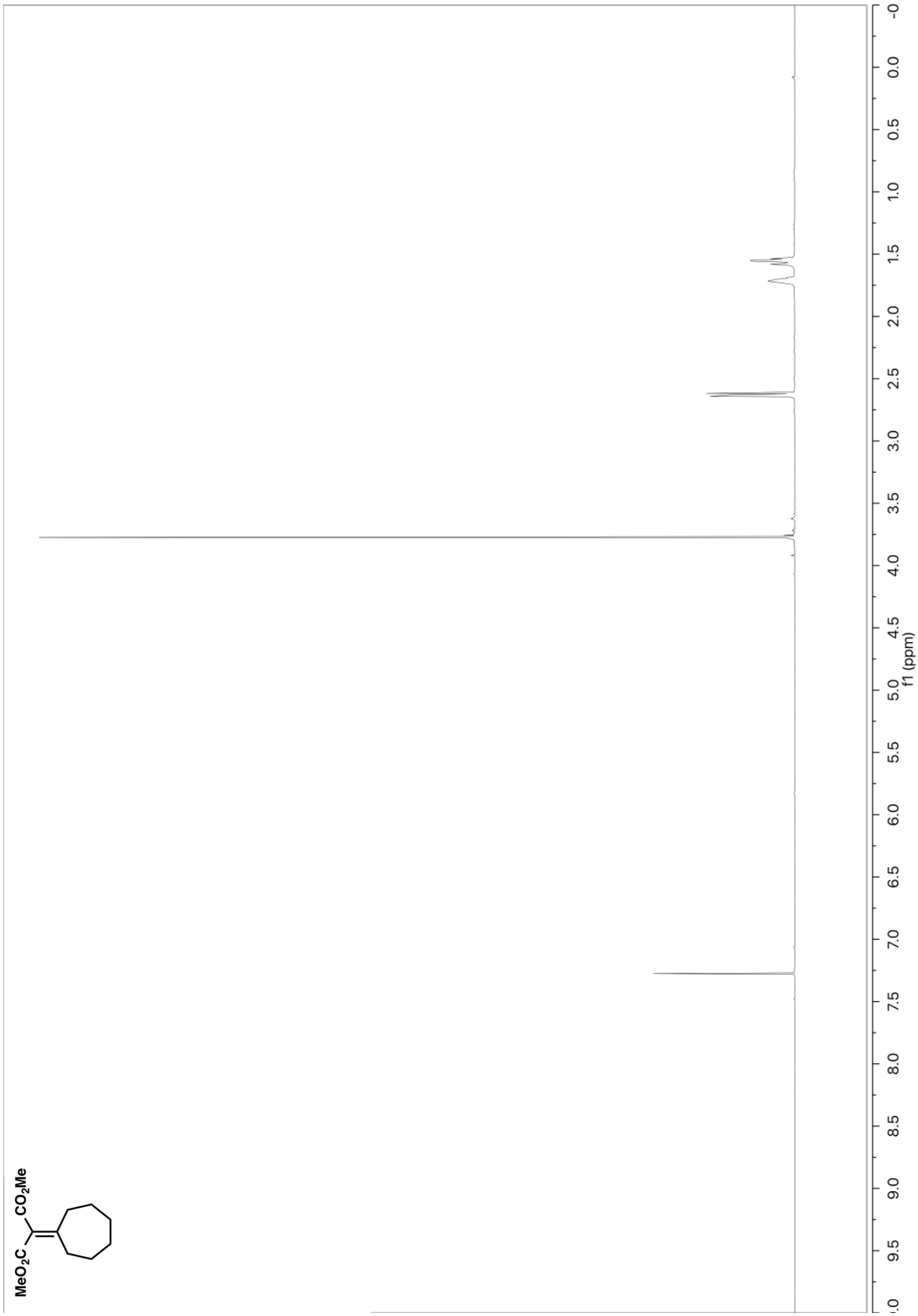



***Figure A1.27*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***1a****.*

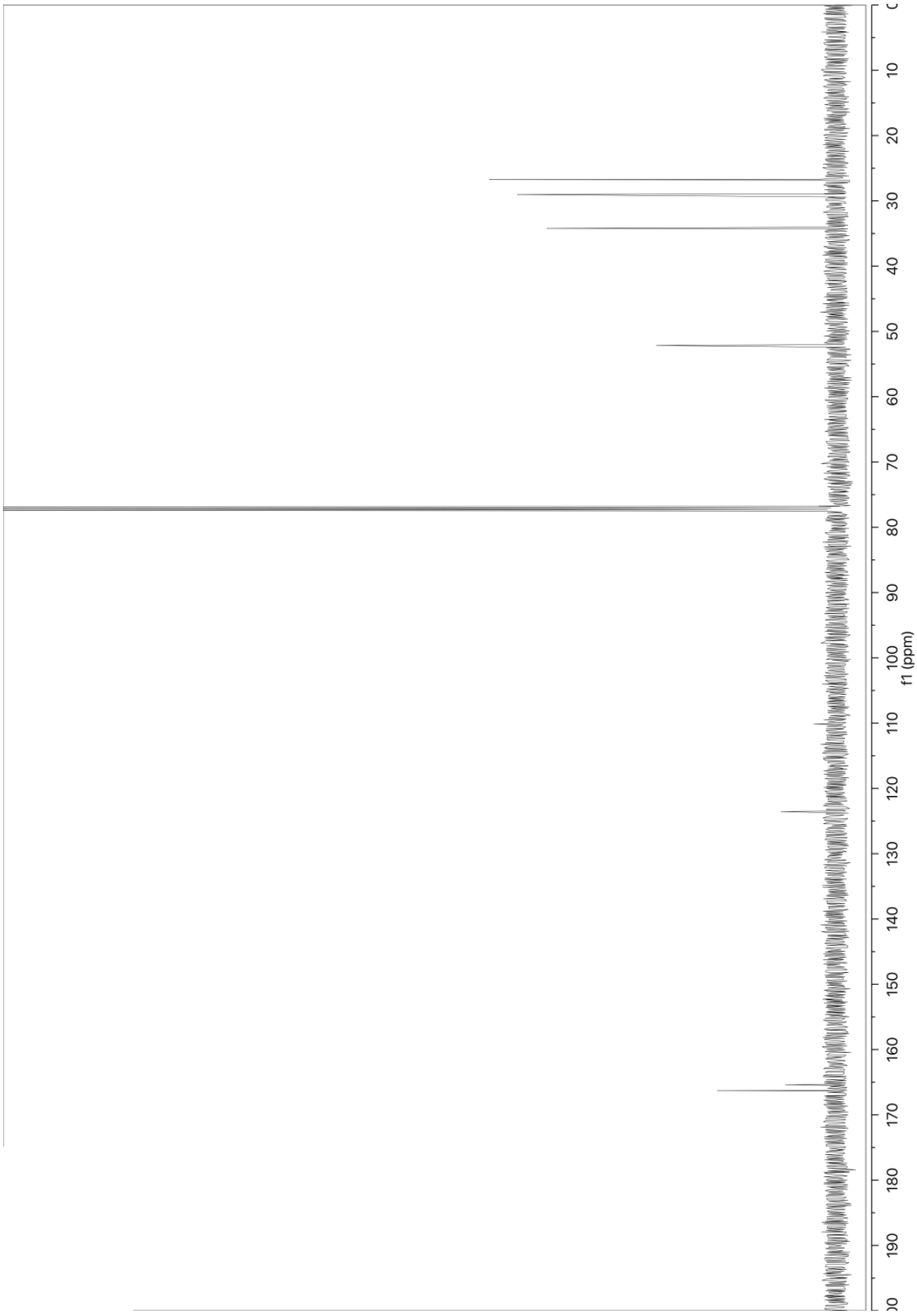



***Figure A1.28*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***1a***.

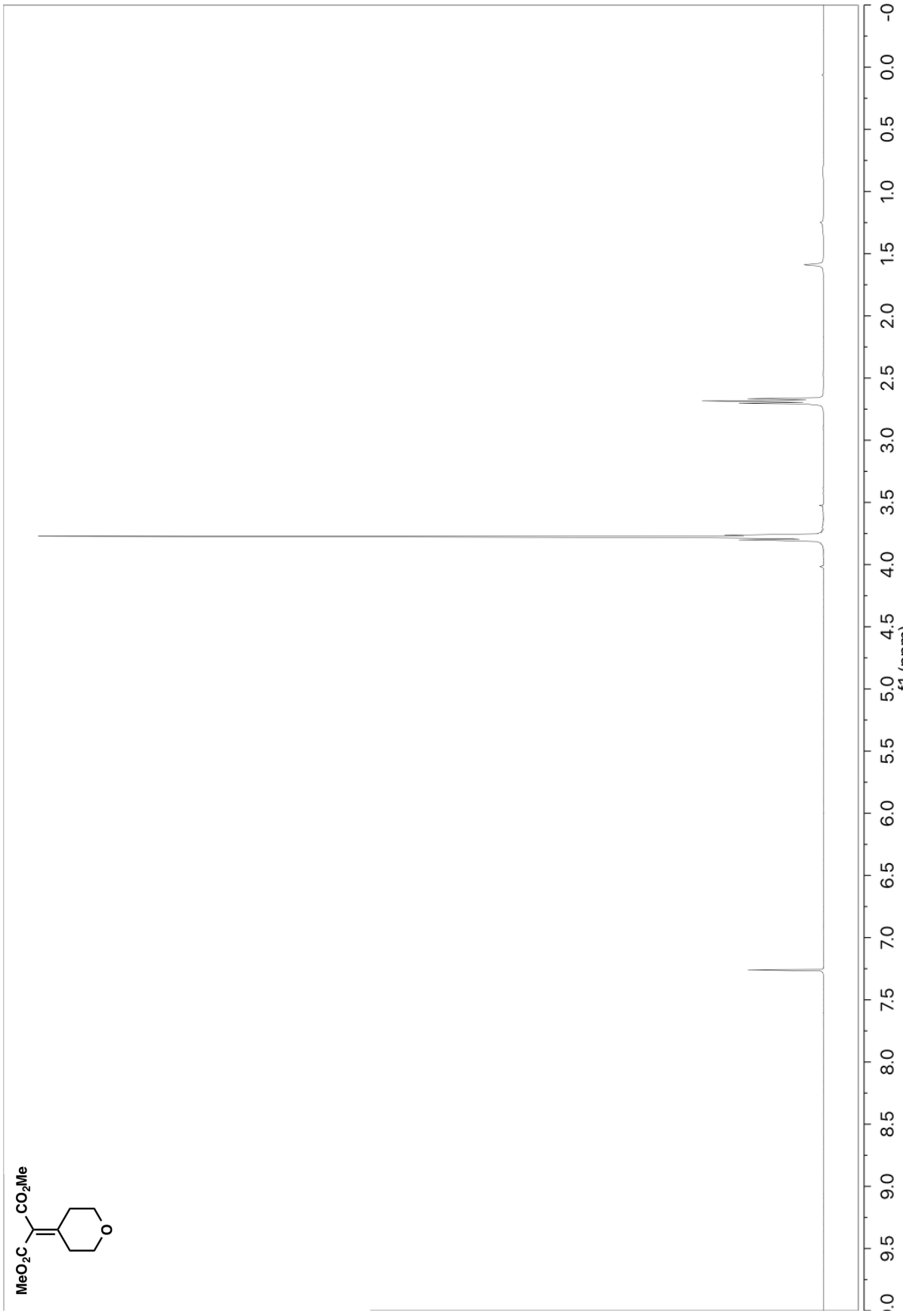



***Figure A1.29*** *$^1$H NMR (400 MHz, $CDCl_3$) of compound* ***1d***.

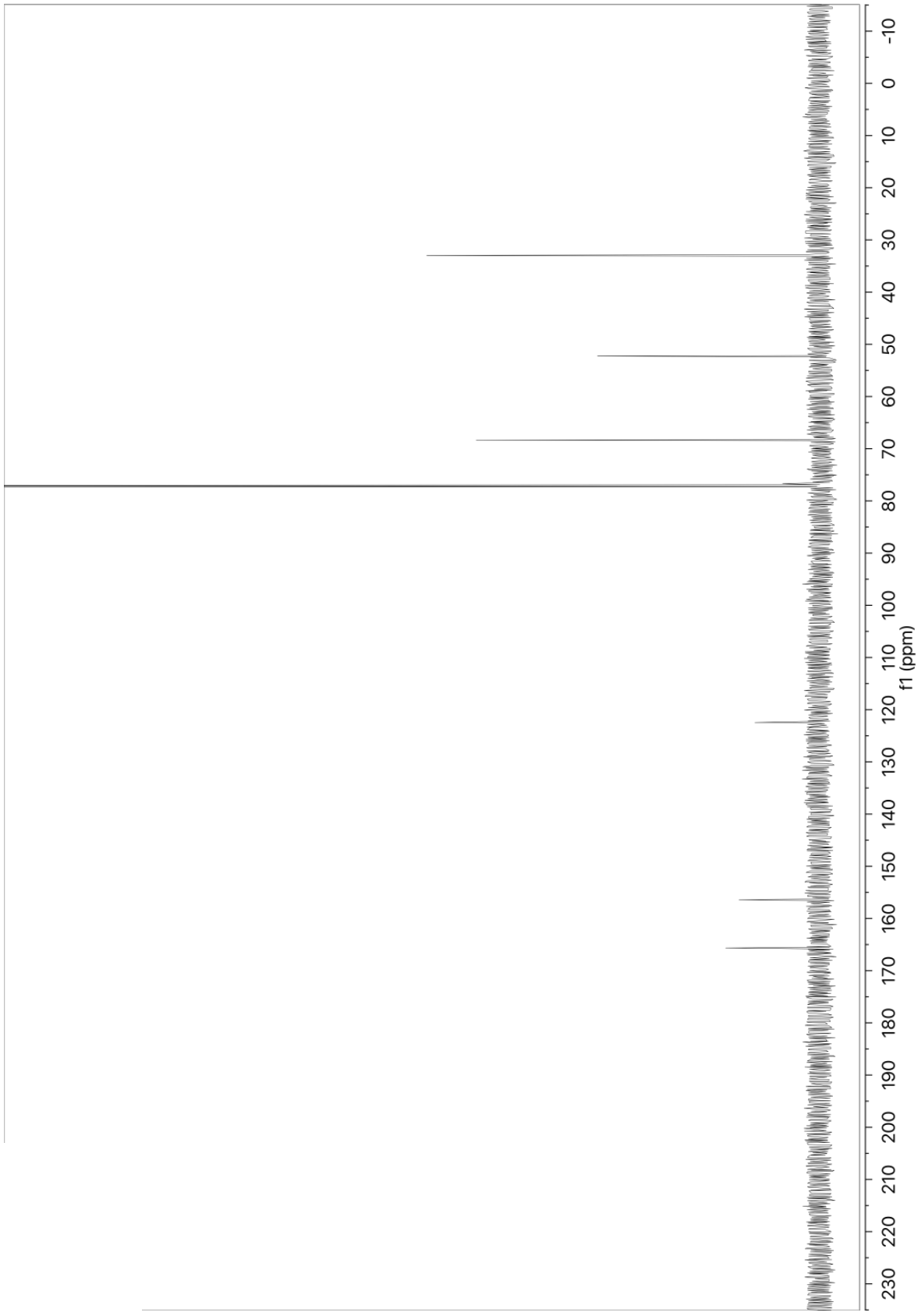



***Figure A1.30*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***1d***.

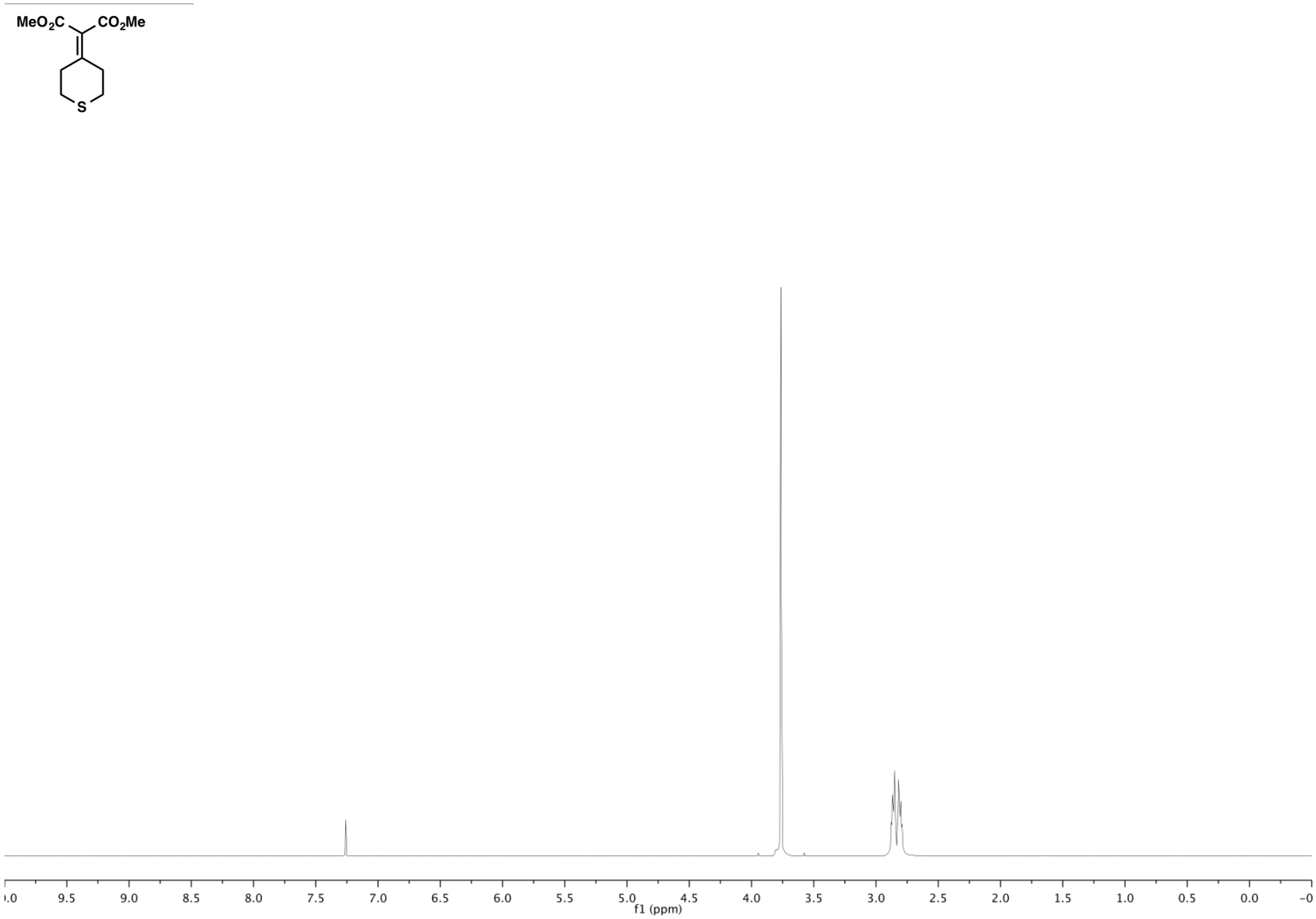



***Figure A1.31*** *$^1$H NMR (400 MHz, $CDCl_3$) of compound* ***1e****.*

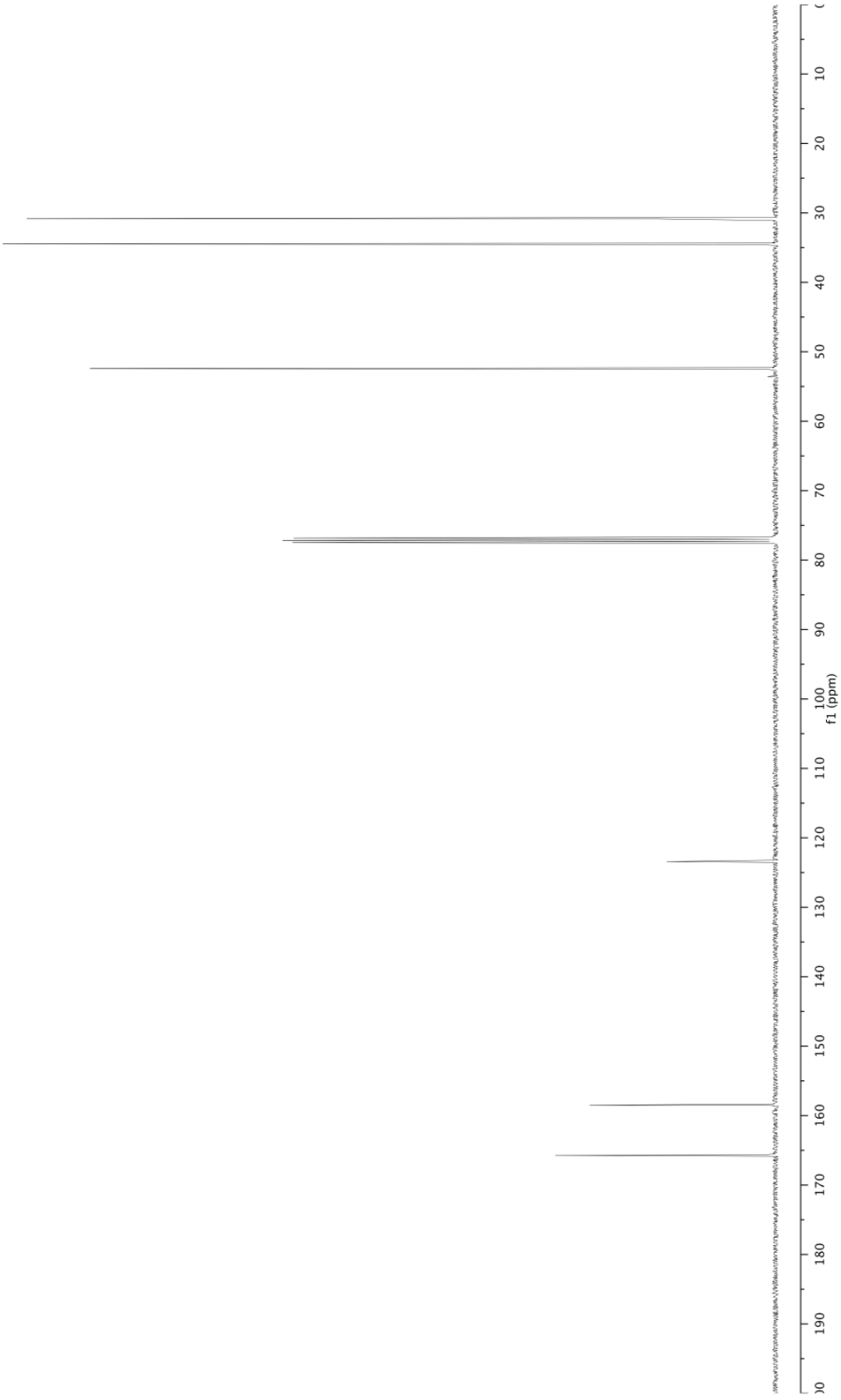



***Figure A1.32*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***1e***.

***Figure A1.33*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***1f.***

***Figure A1.34*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***1f****.*

***Figure A1.35*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***S5aa.***

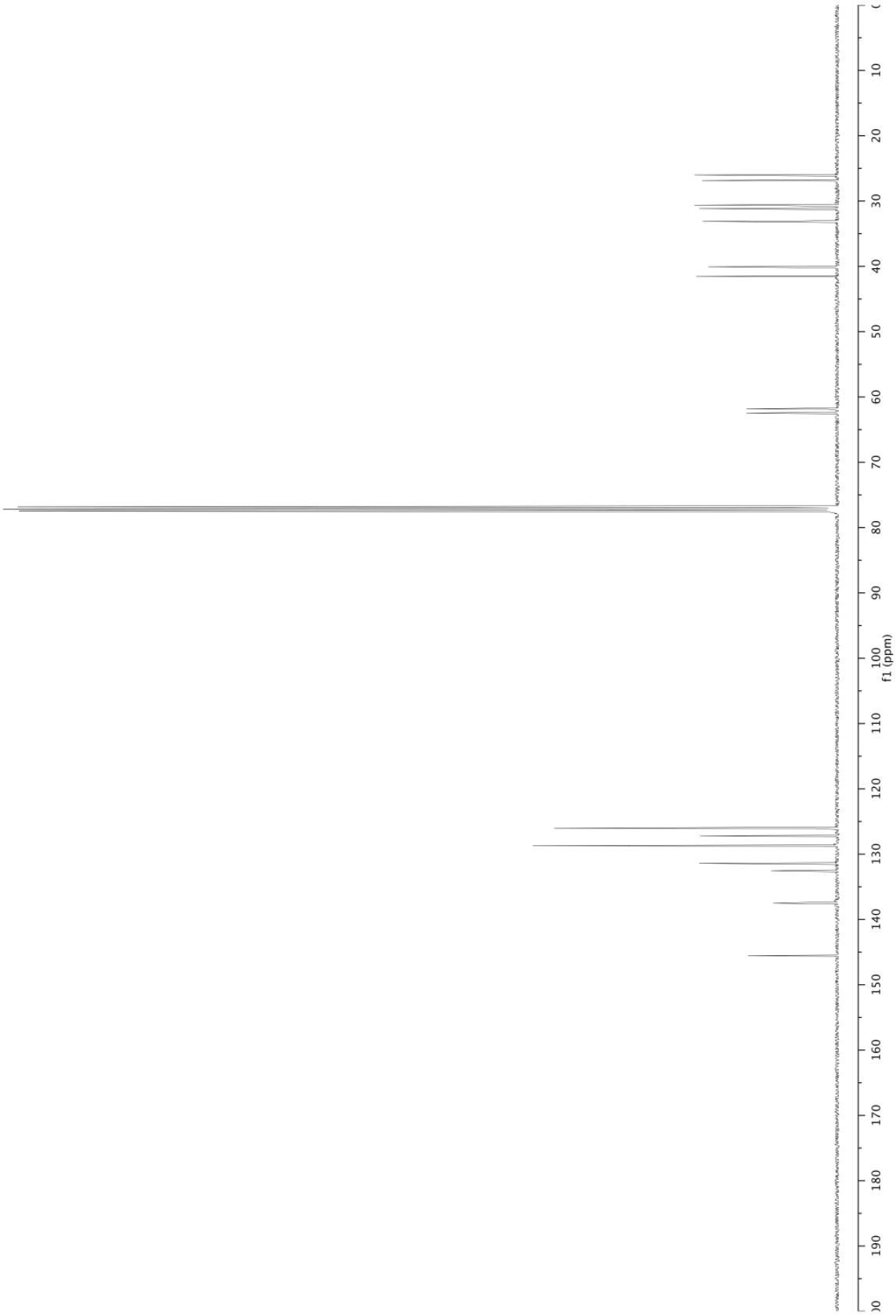



***Figure A1.36*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***S5aa***.

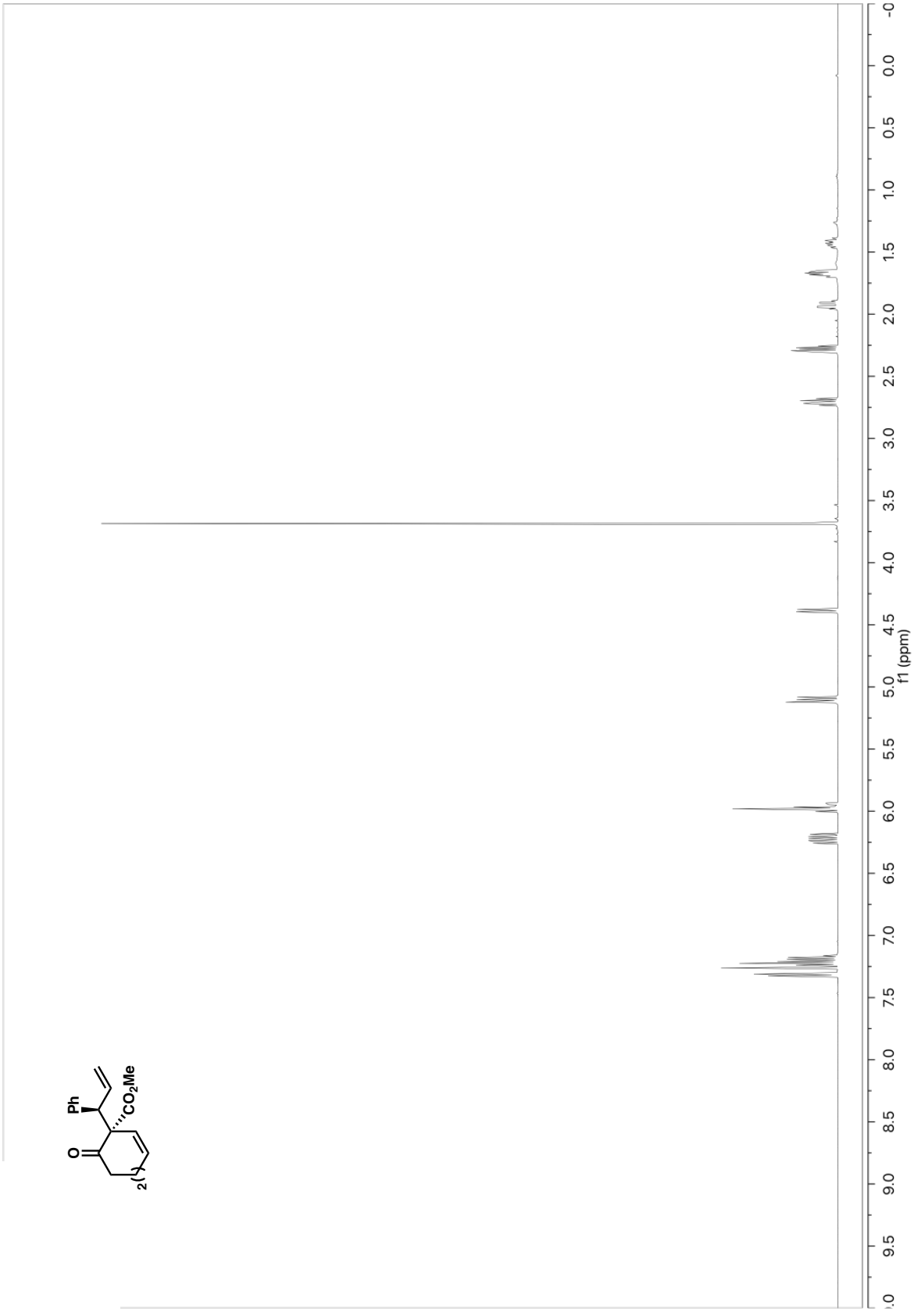



***Figure A1.37*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***7aa.***

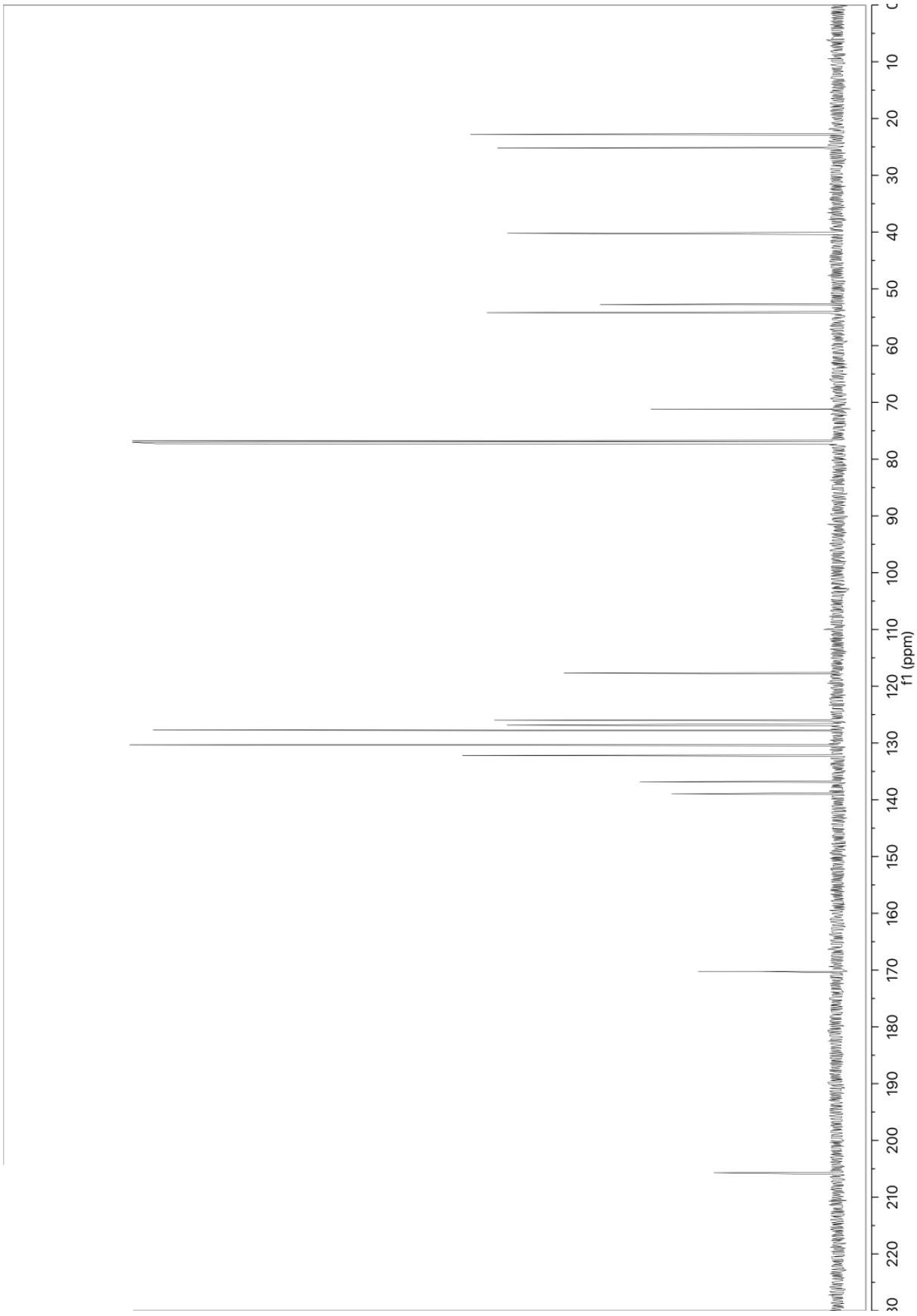



***Figure A1.38*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***7aa****.*

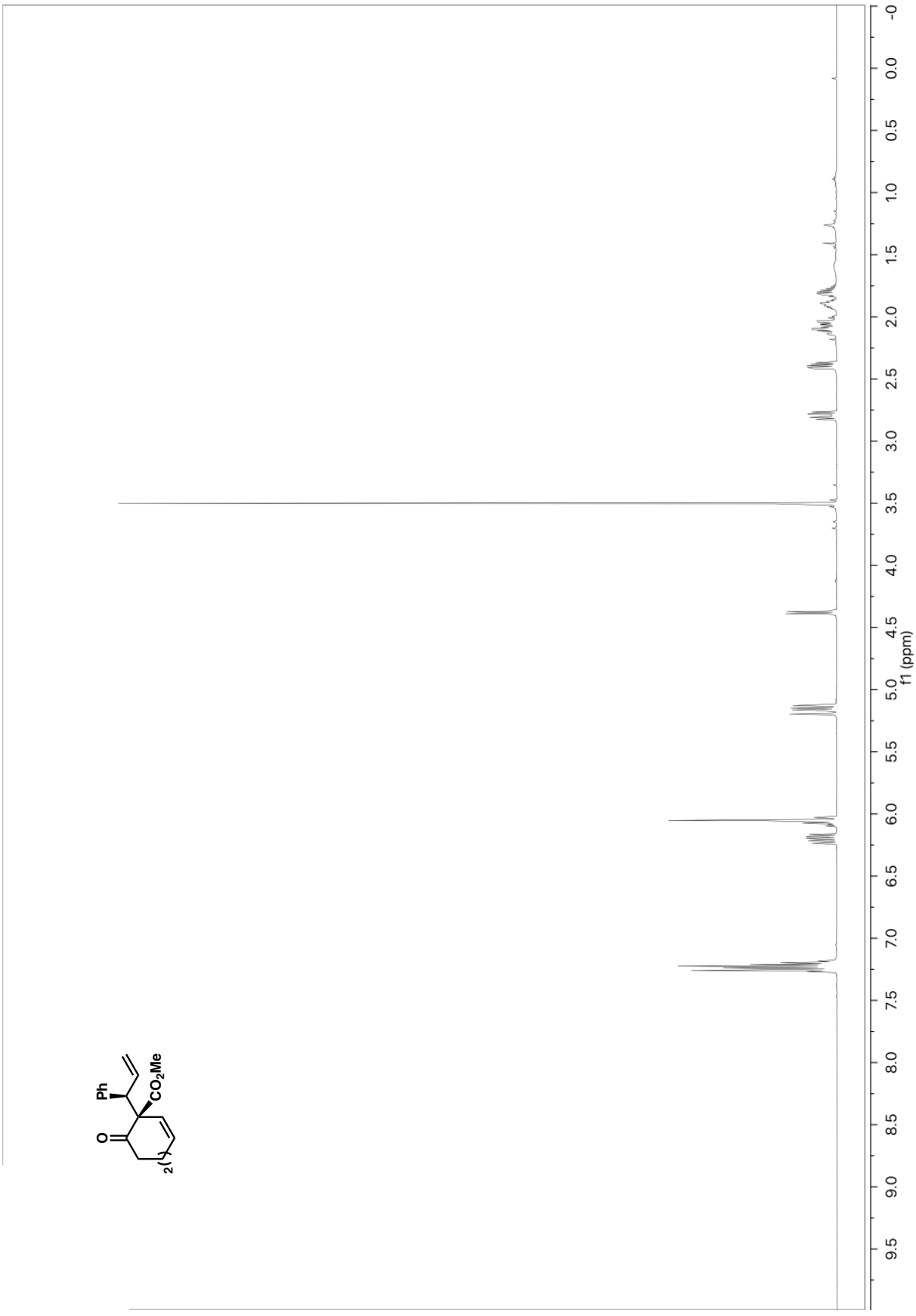



***Figure A1.39*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***7aa'.***

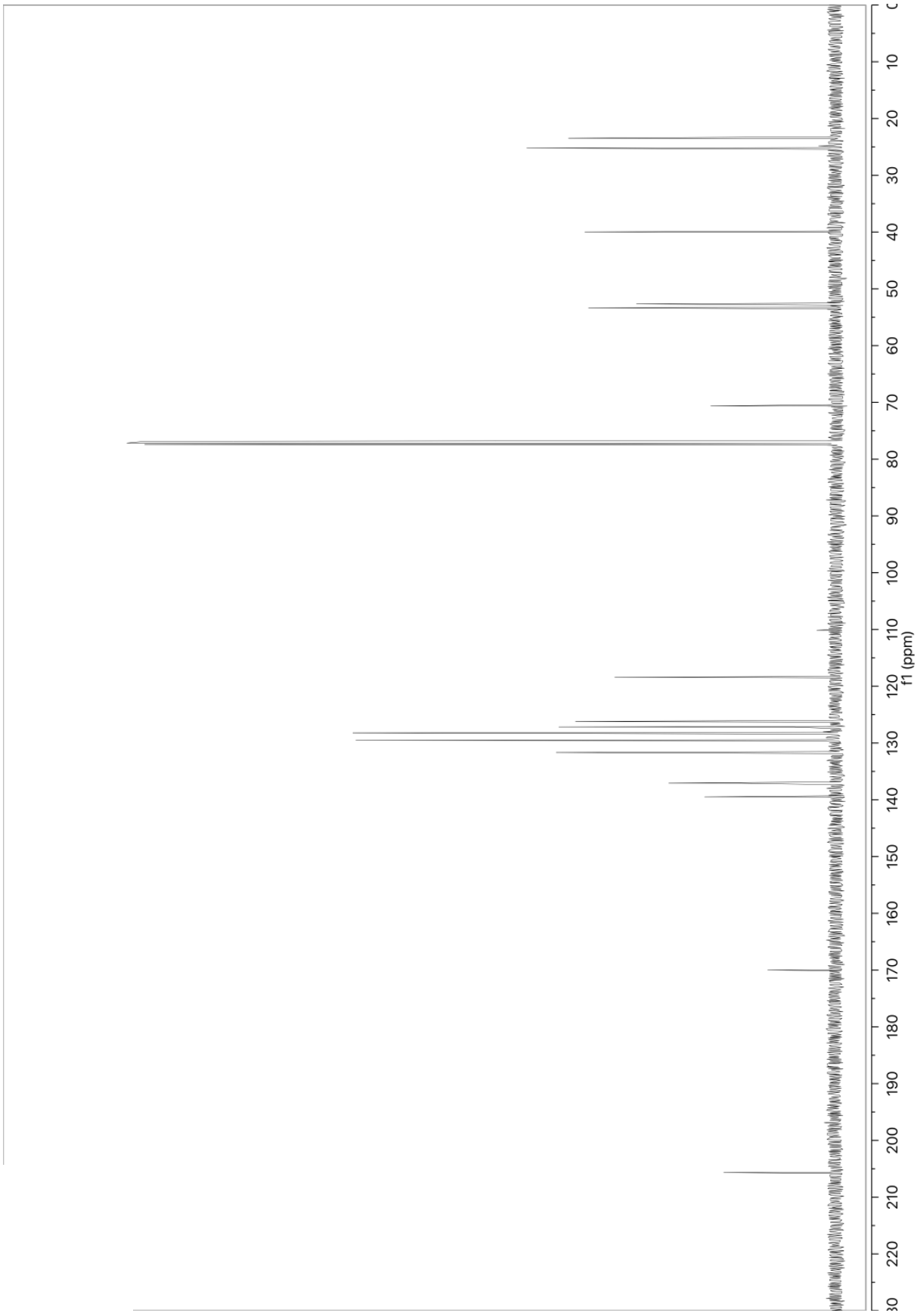



***Figure A1.40*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***7aa'****.*

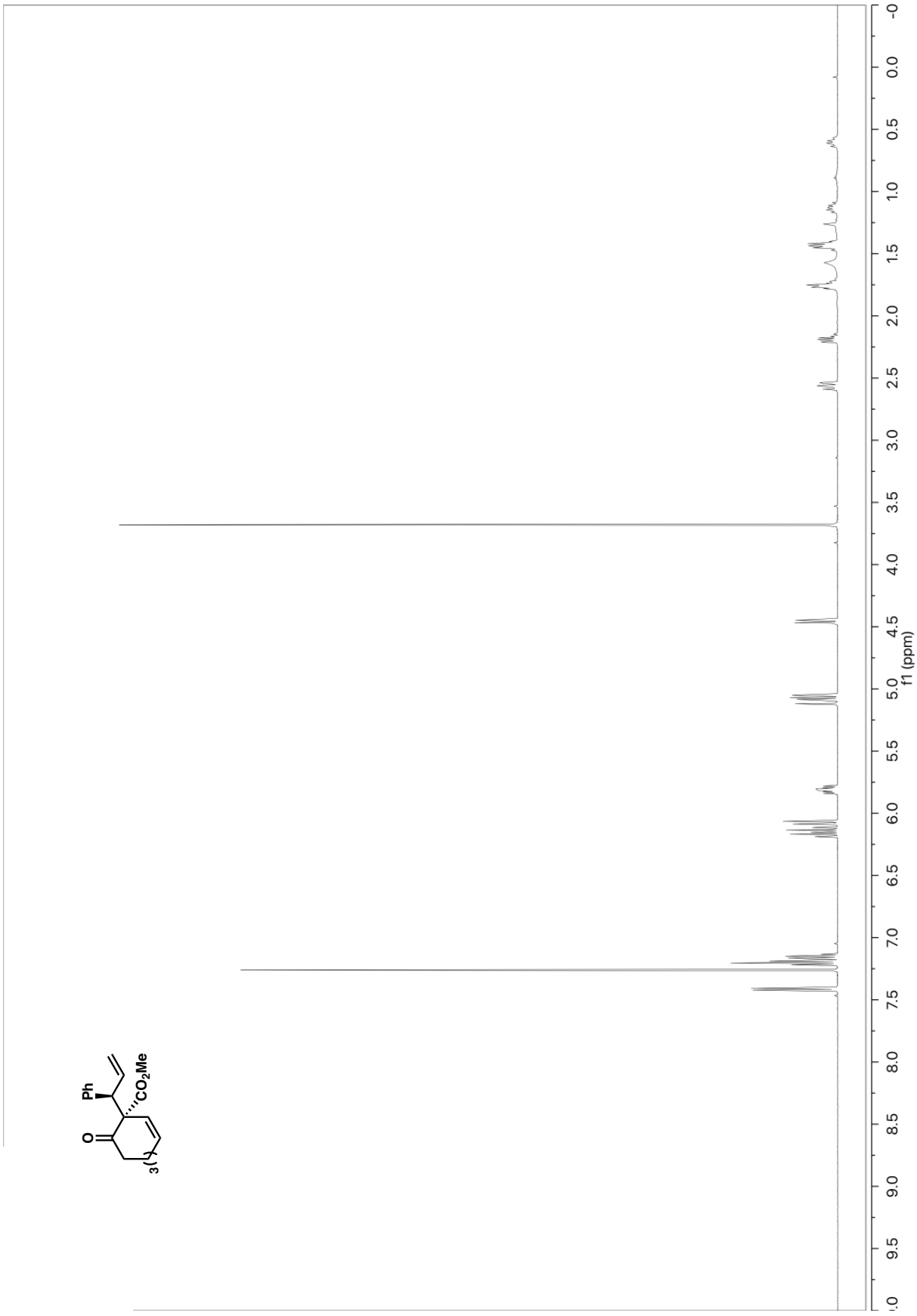



***Figure A1.41*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***7ba.***

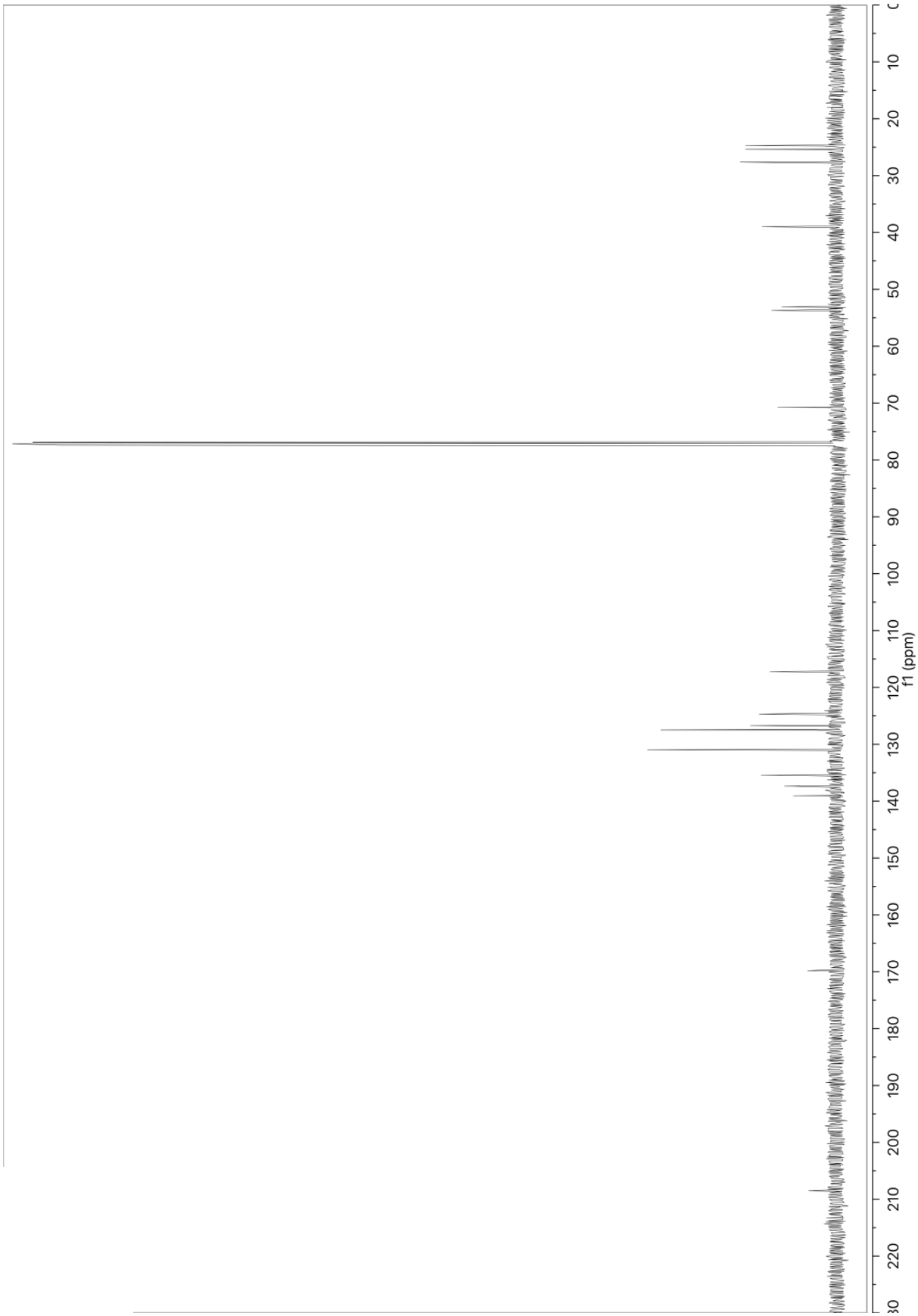



***Figure A1.42*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***7ba***.

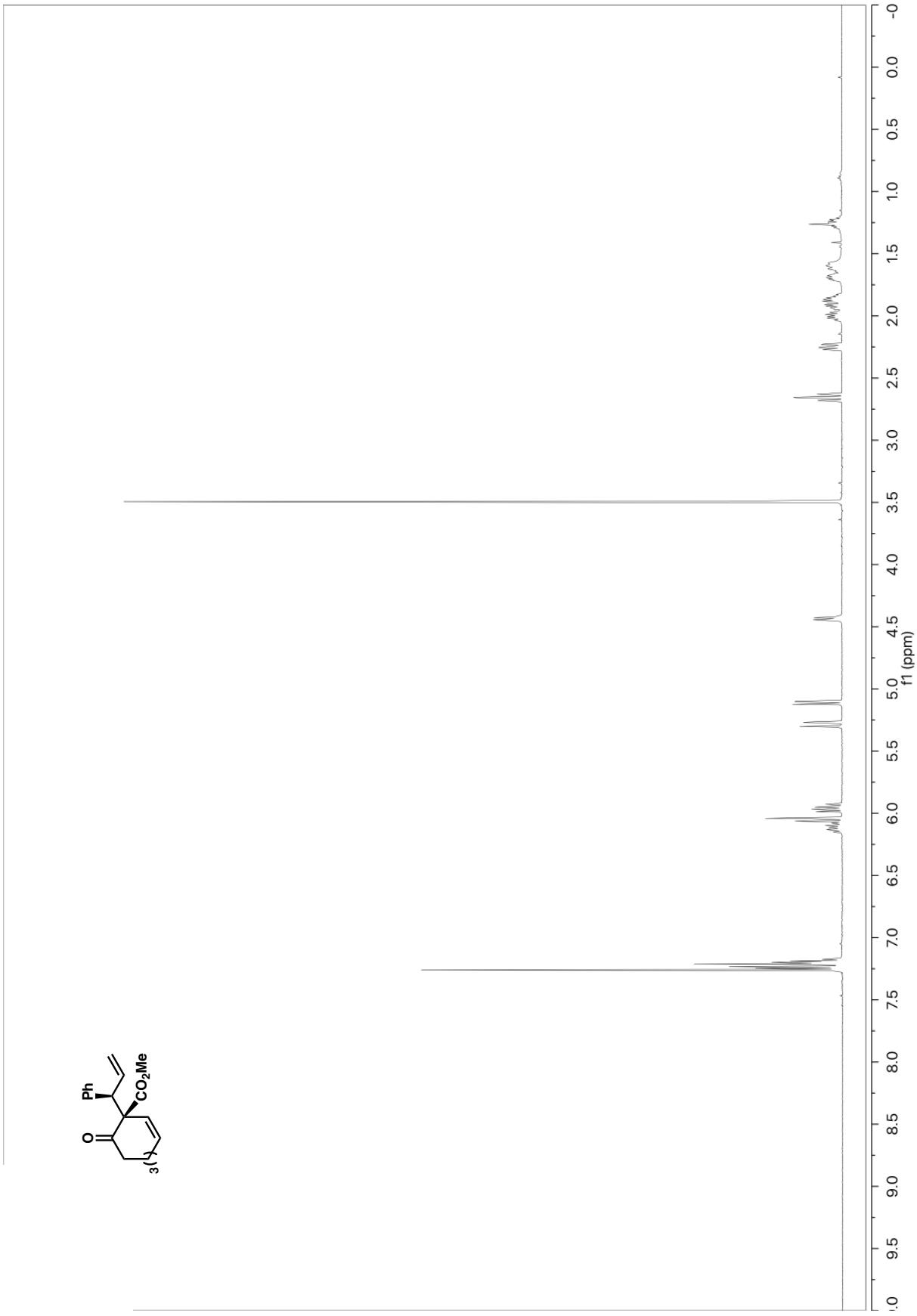



***Figure A1.43*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***7ba'.***

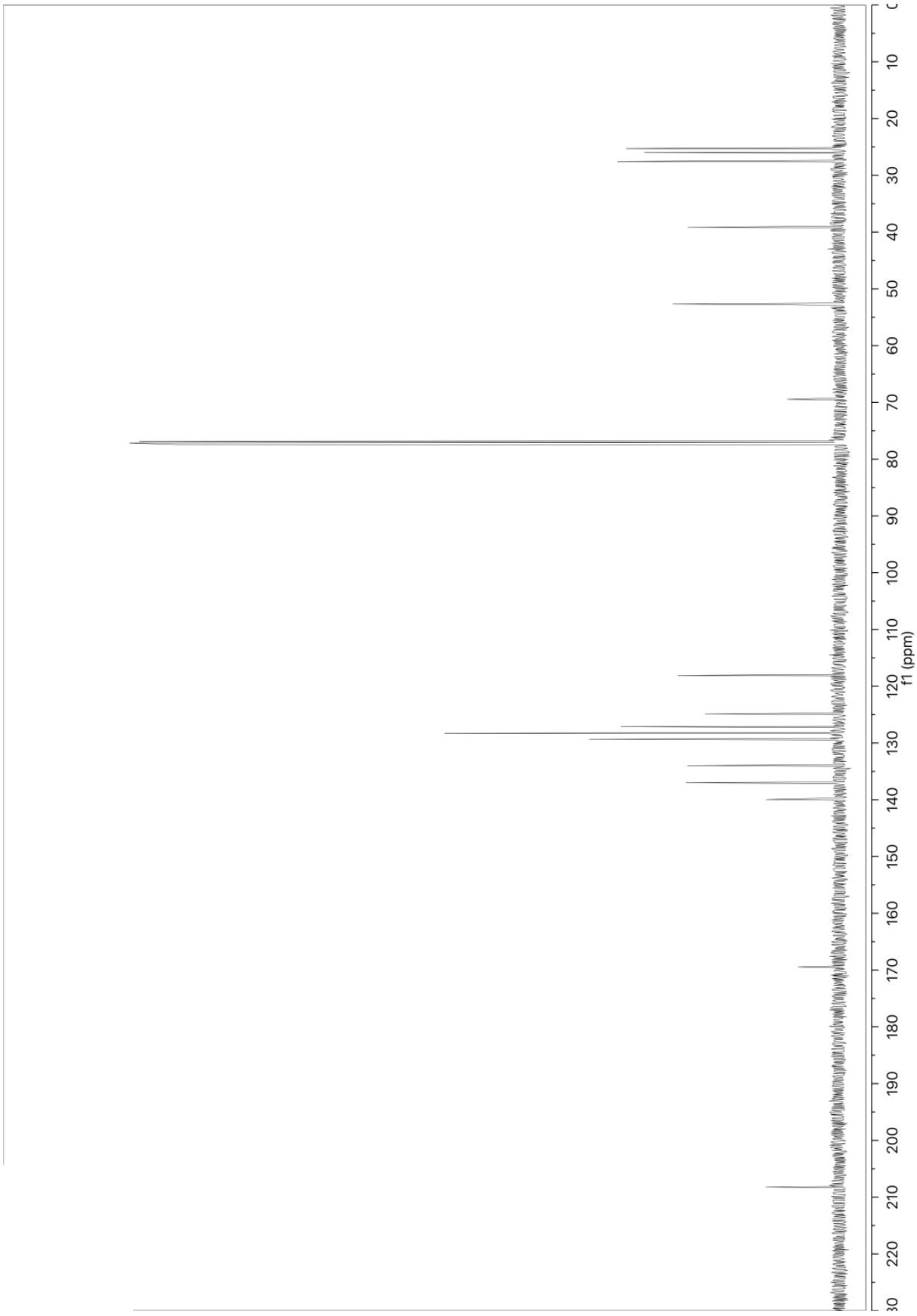



***Figure A1.44*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***7ba'****.*

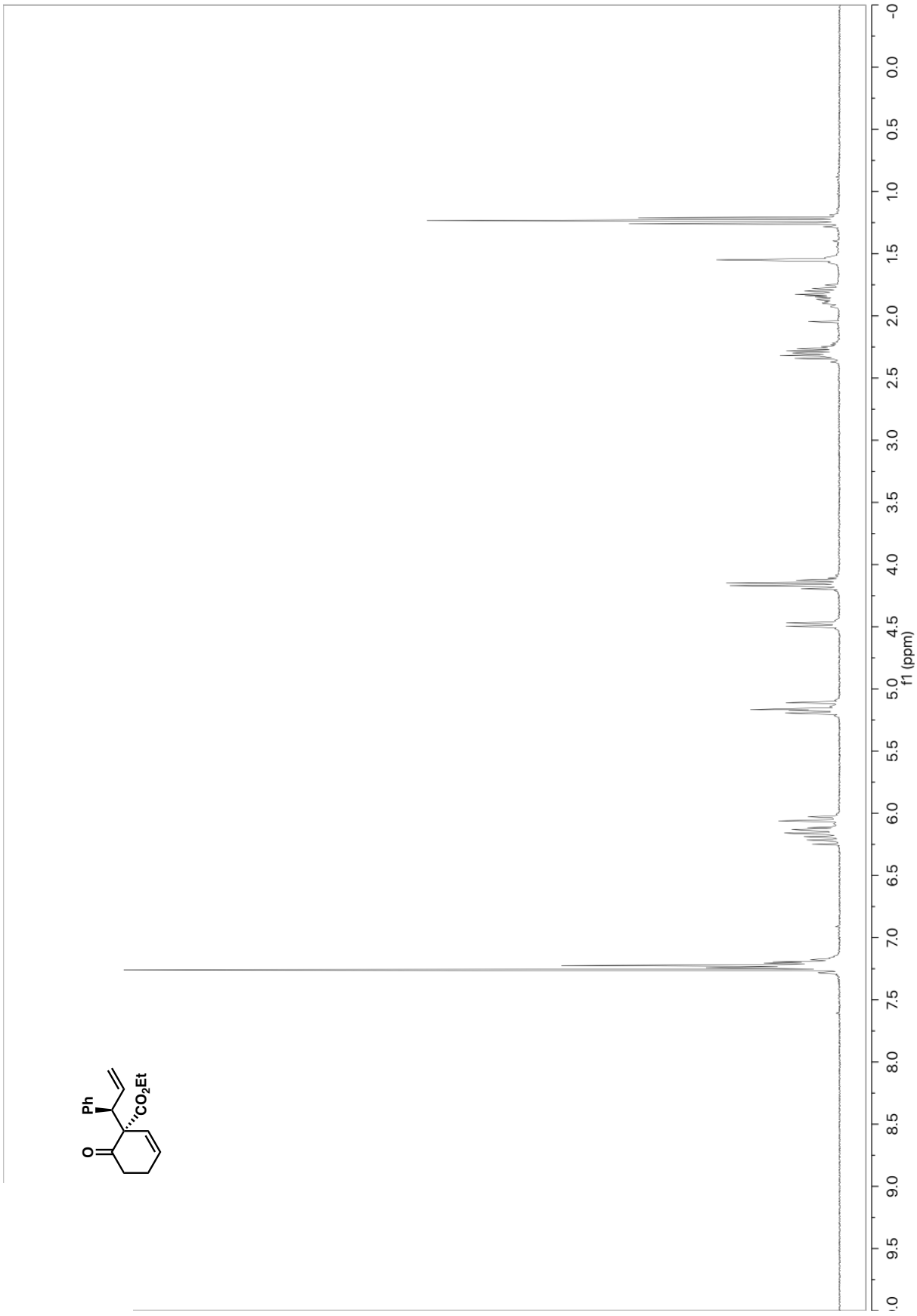



***Figure A1.45*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***7ca.***

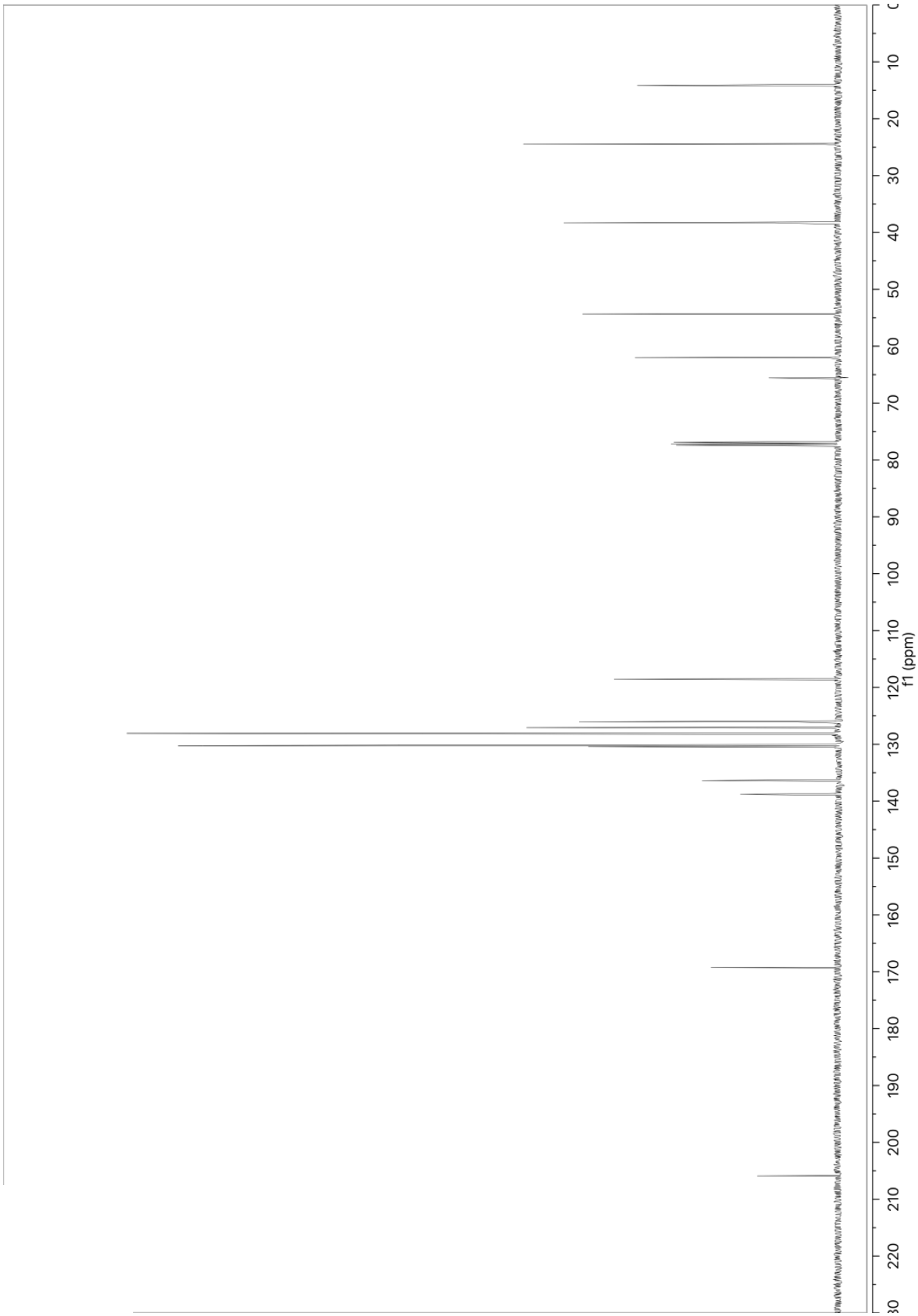



***Figure A1.46*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***7ca****.*

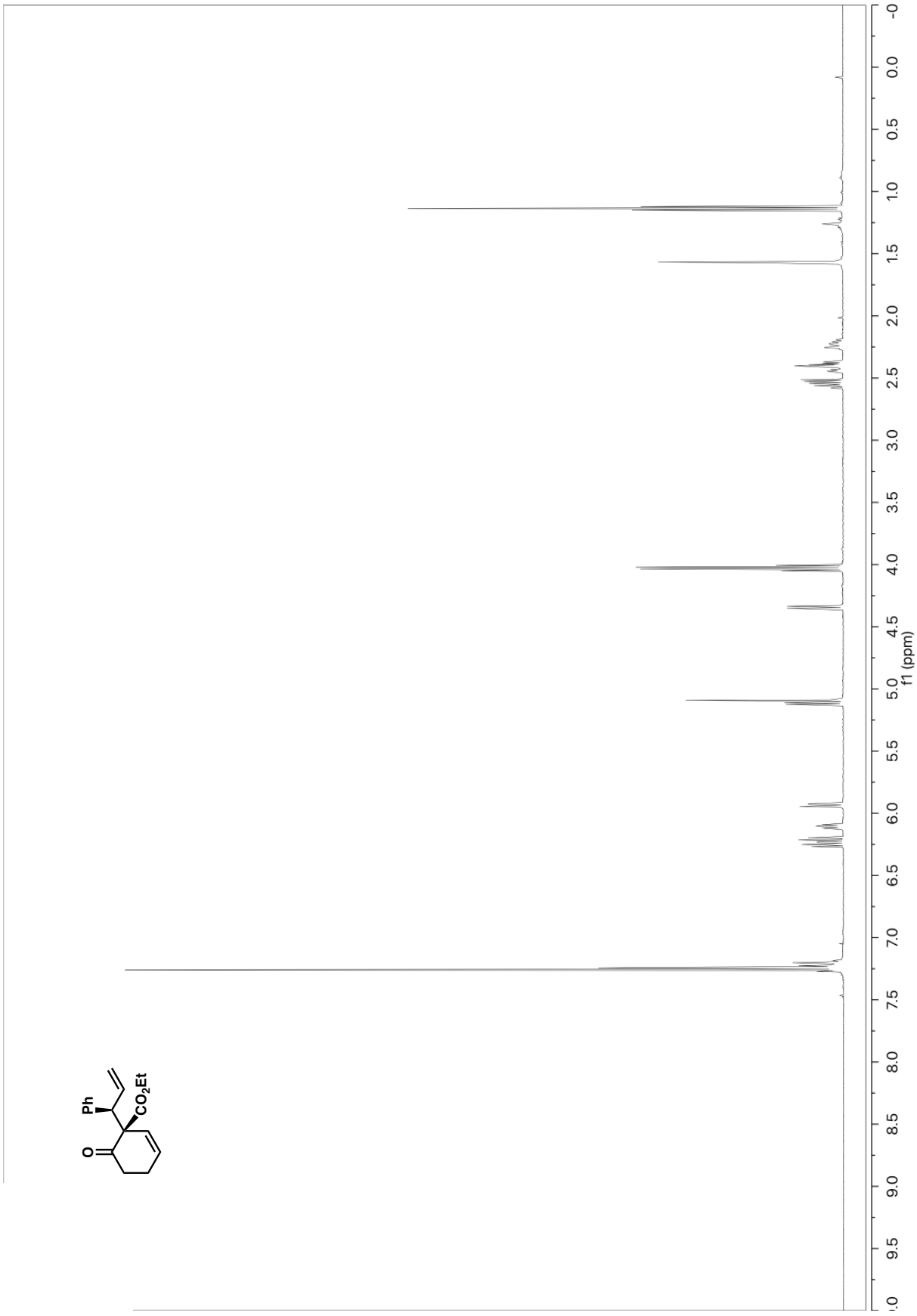



***Figure A1.47*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***7ca'.***

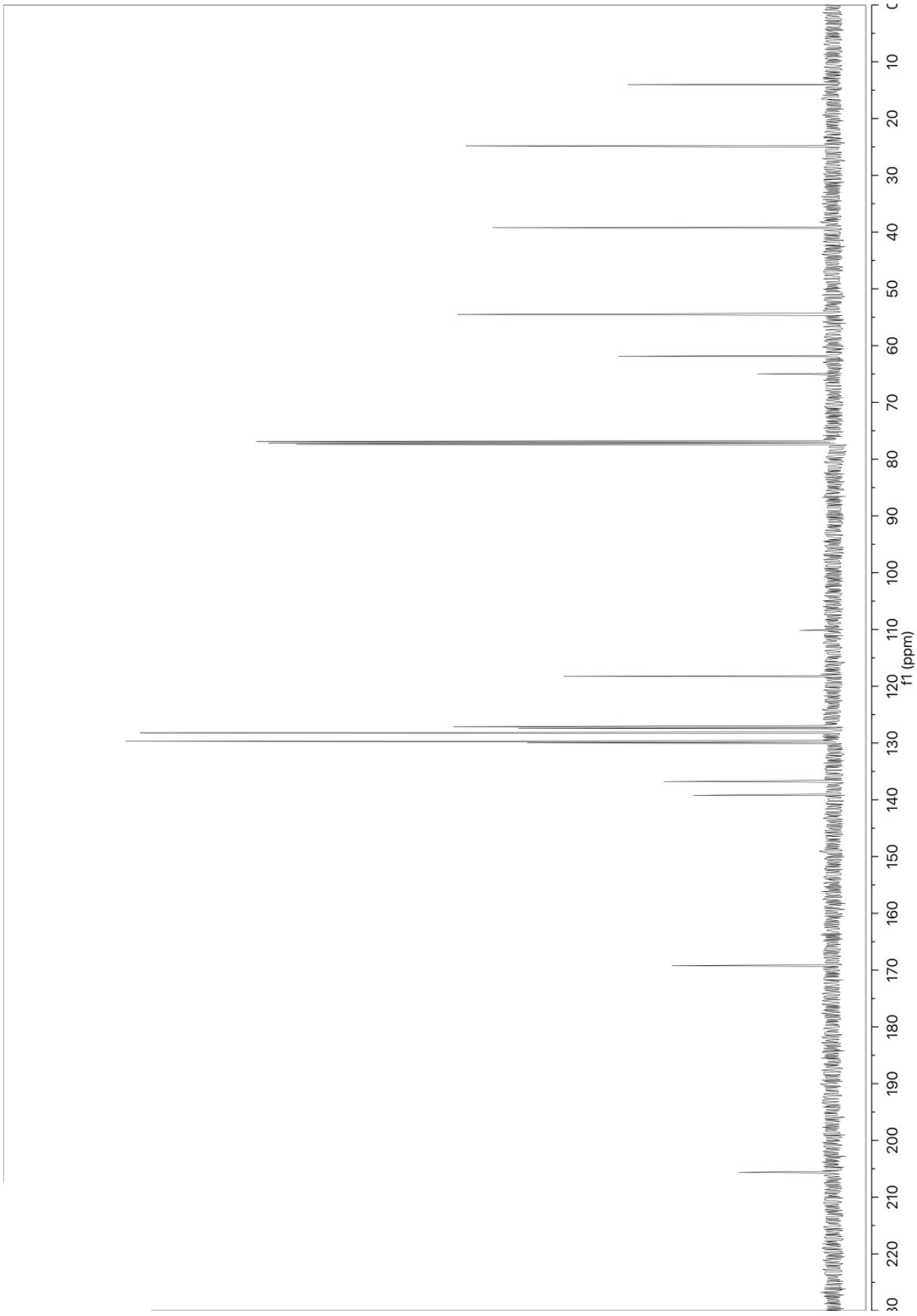



***Figure A1.48*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***7ca'****.*

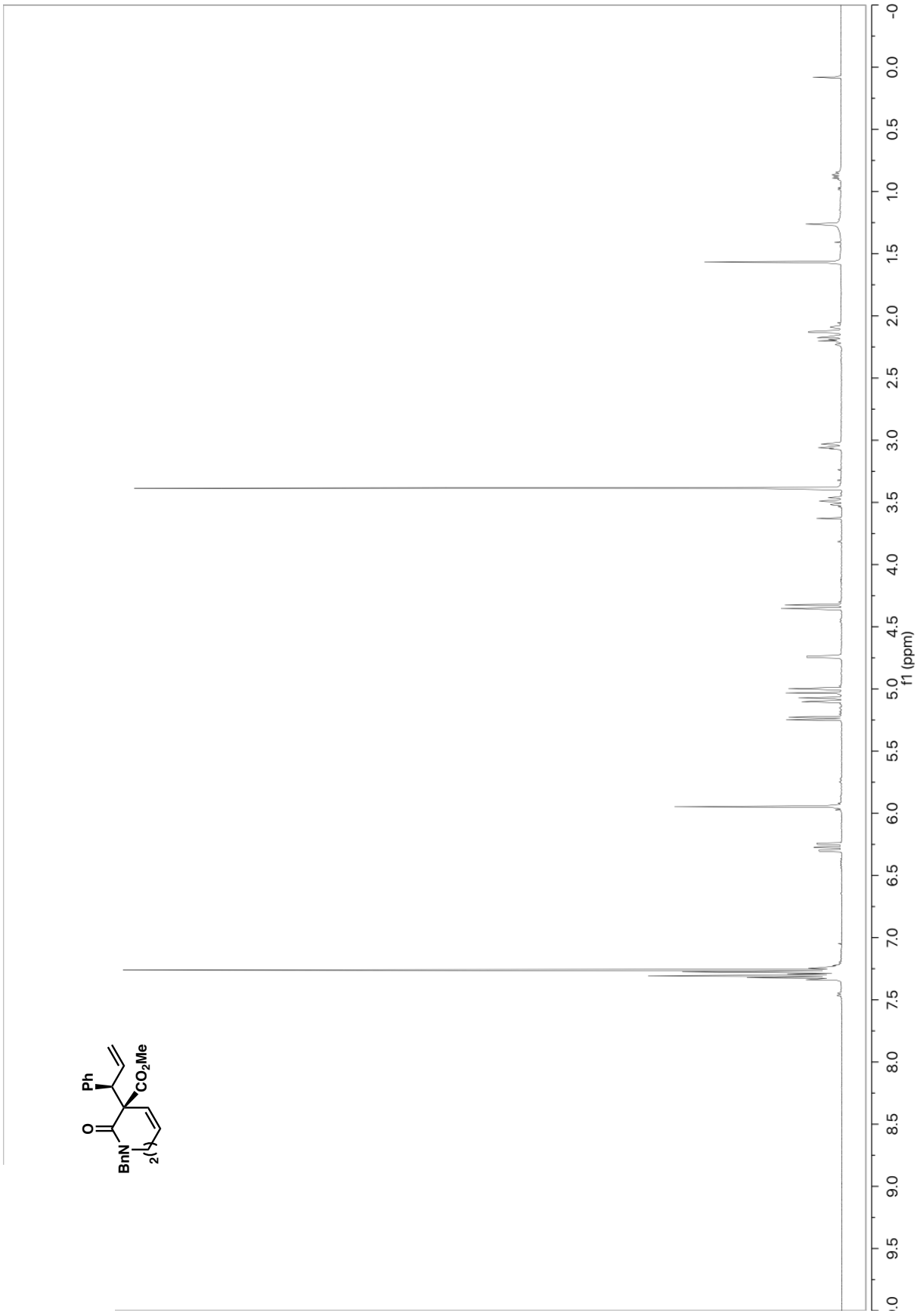



***Figure A1.49*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***7da.***

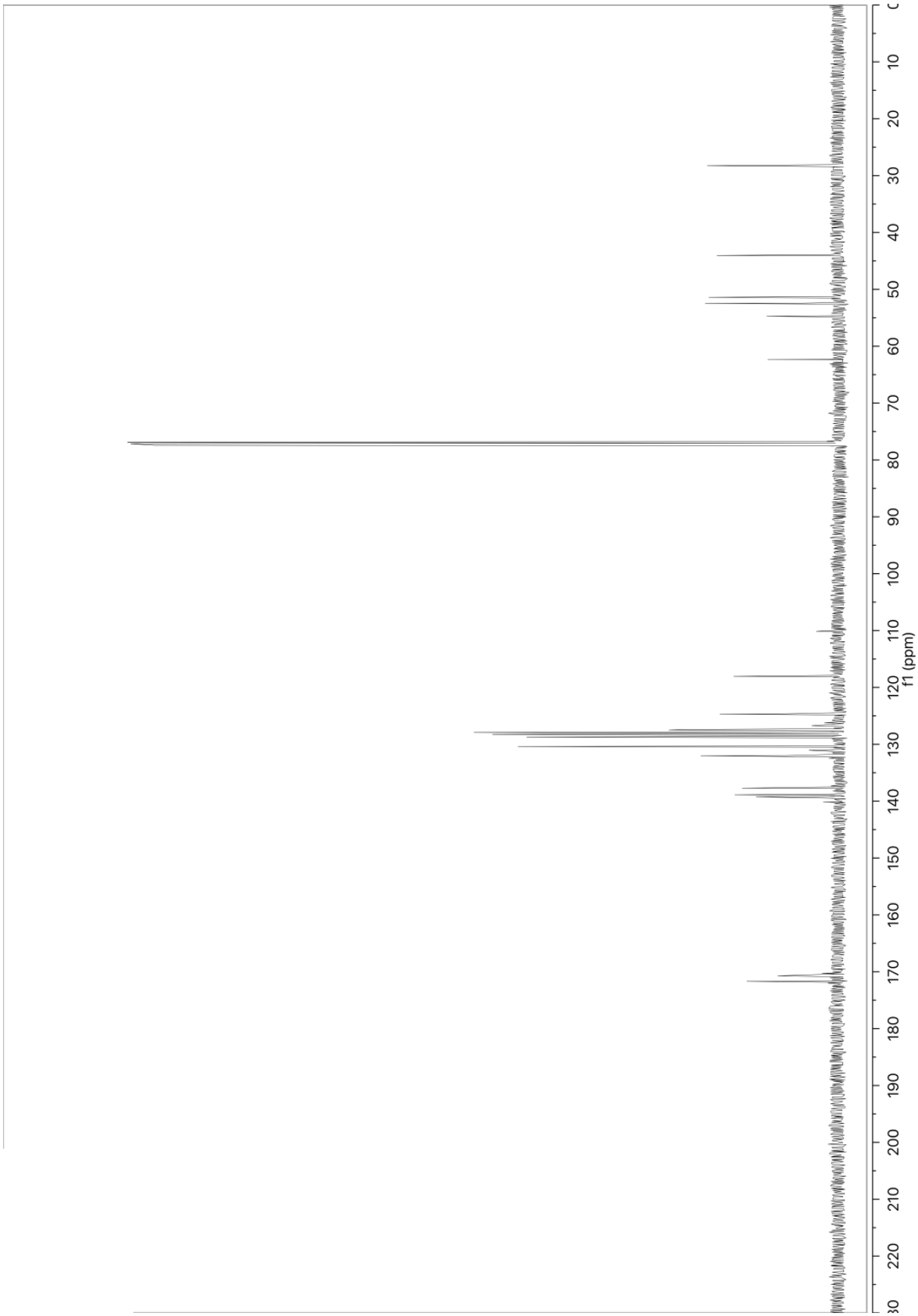



***Figure A1.50*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***7da***.

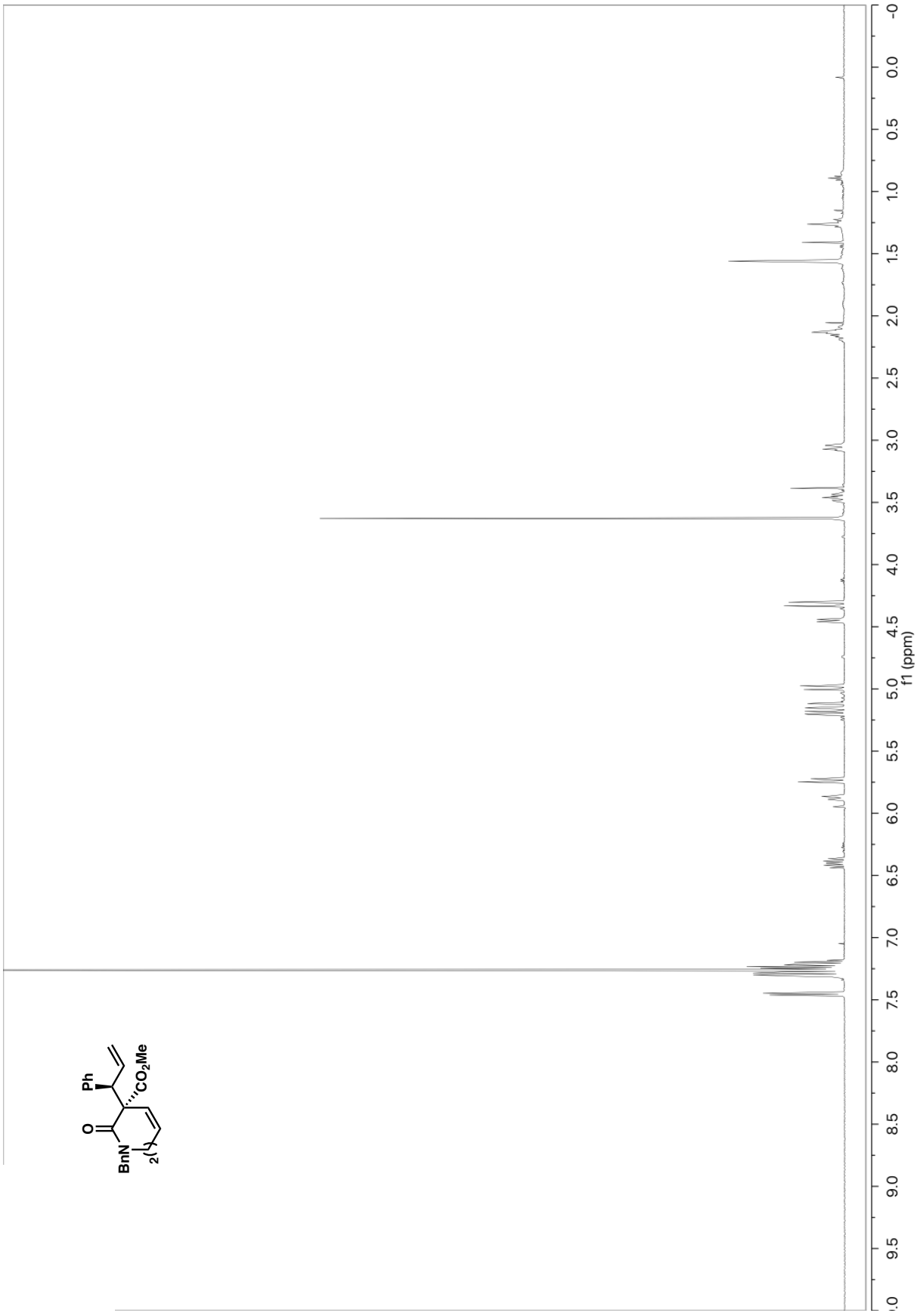



***Figure A1.51*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***7da'.***

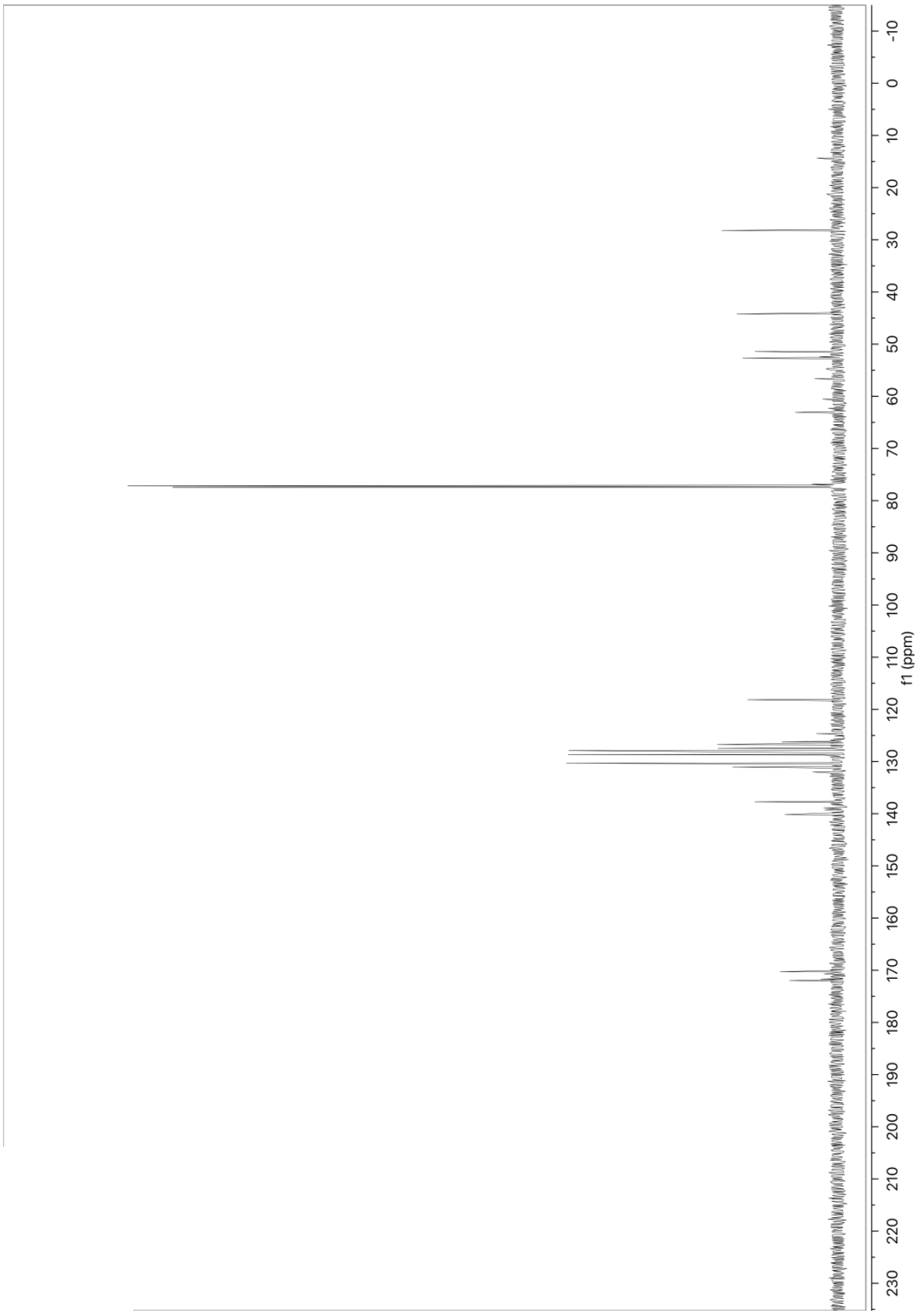



***Figure A1.52*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***7da'***.

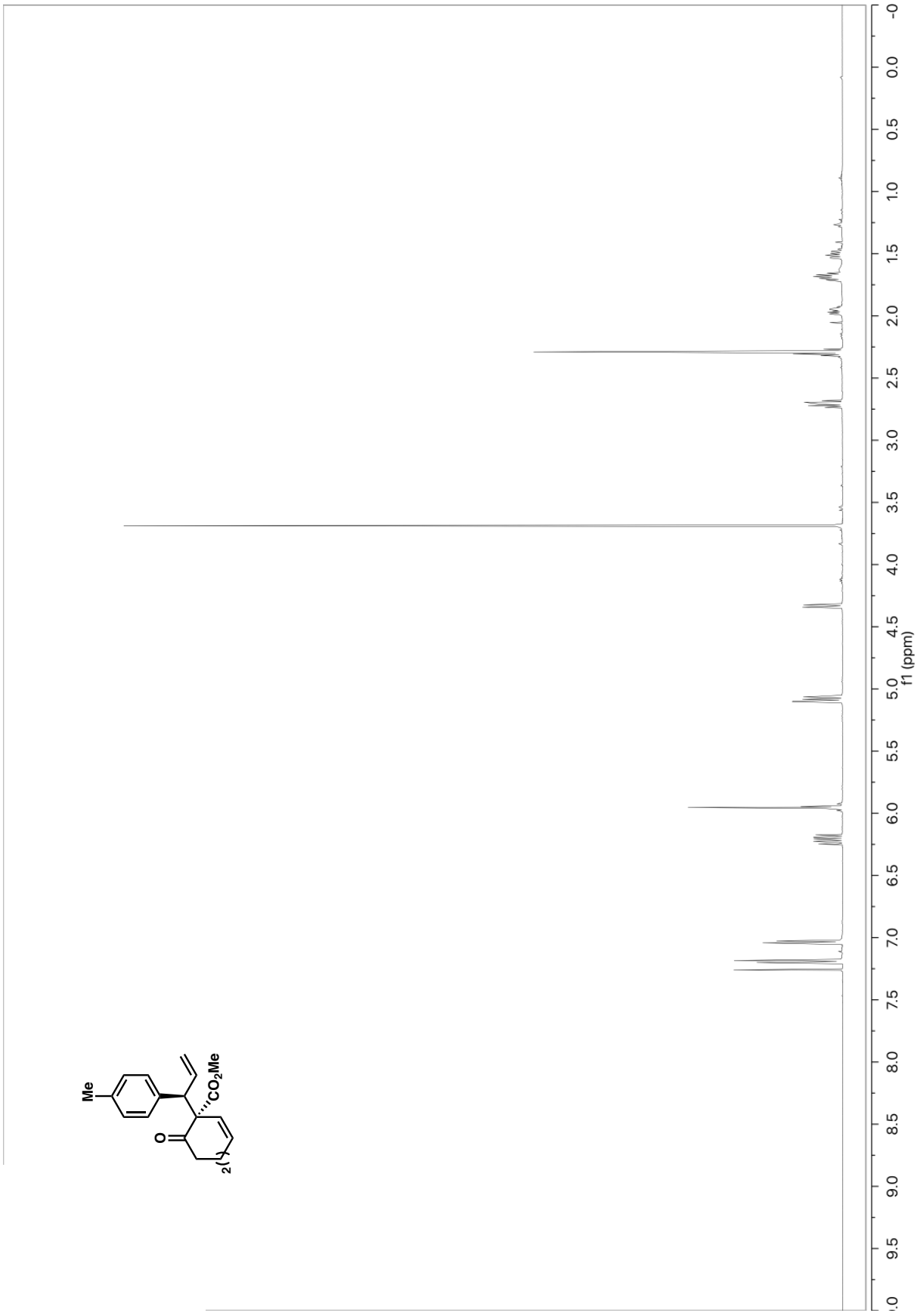



***Figure A1.53*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***7ab.***

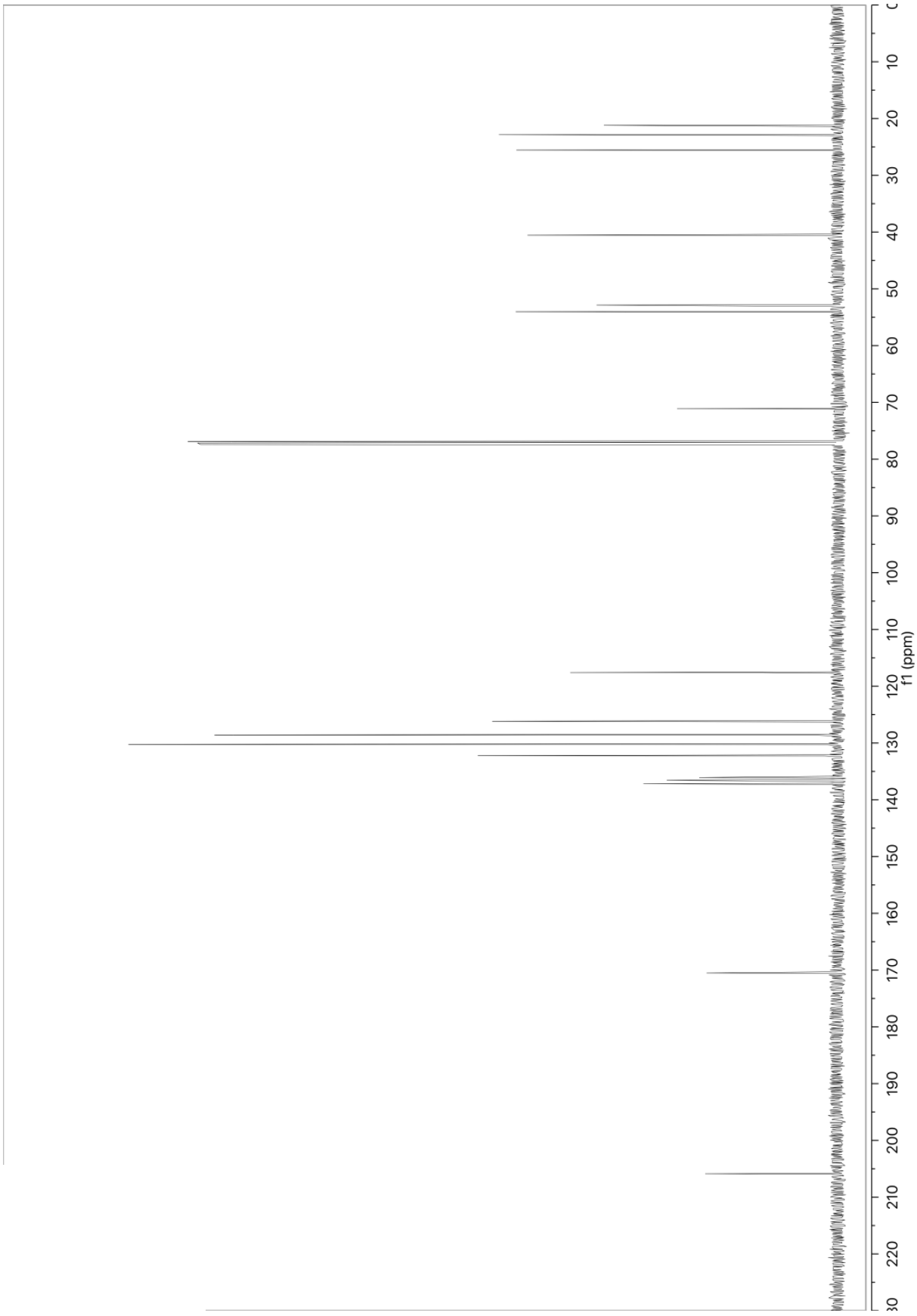



***Figure A1.54*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***7ab****.*

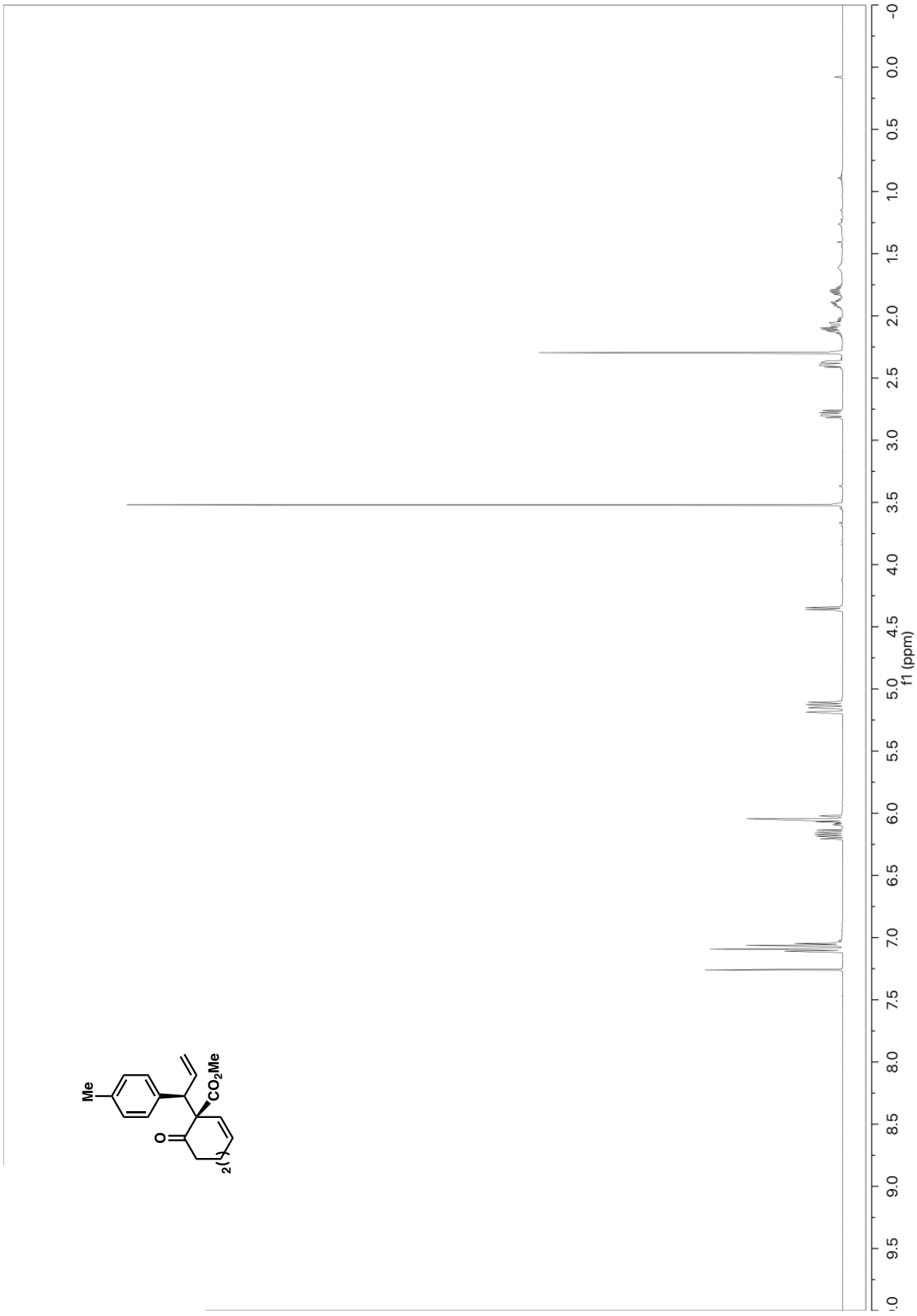



***Figure A1.55*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***7ab'.***

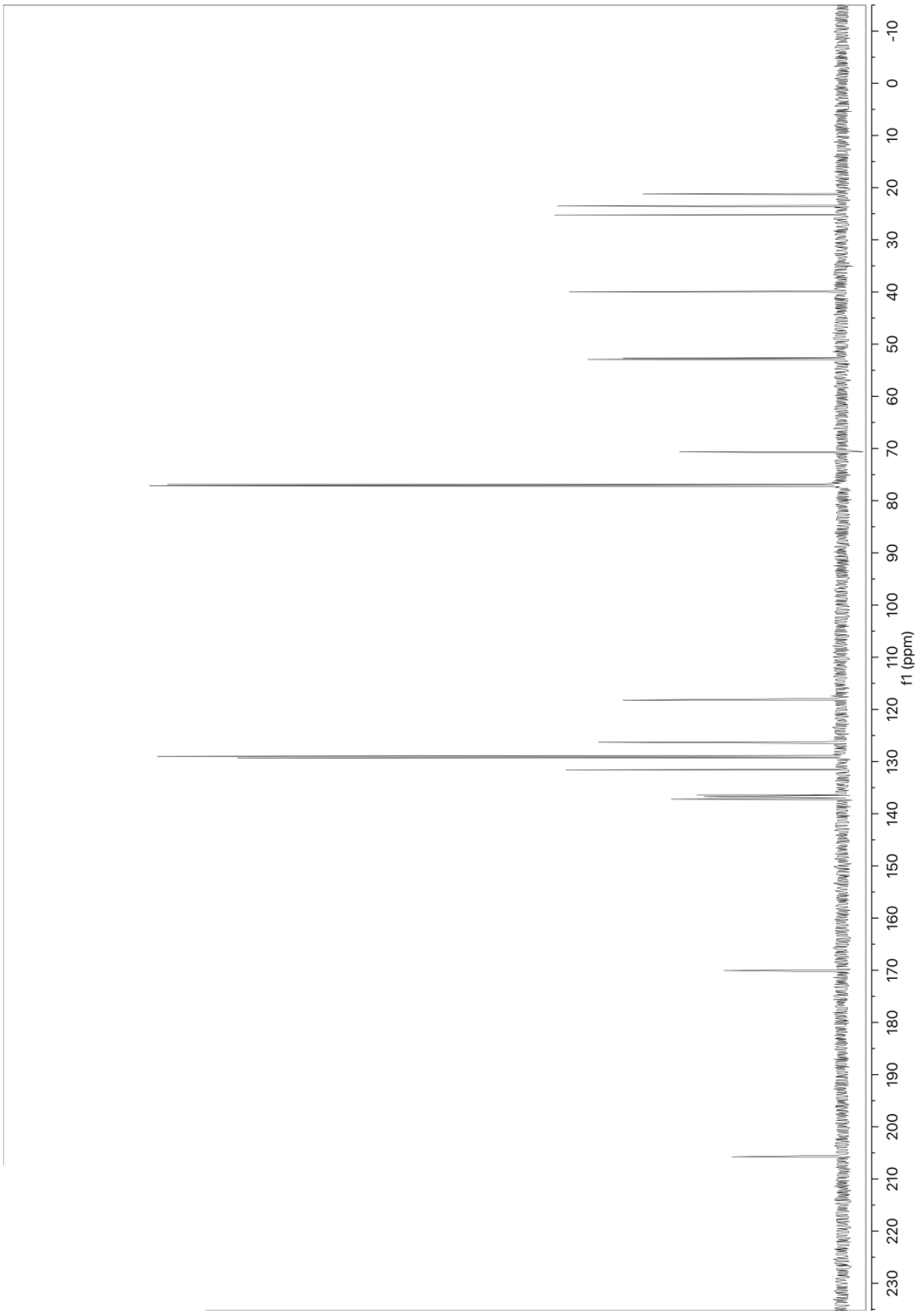



***Figure A1.56*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***7ab'****.*

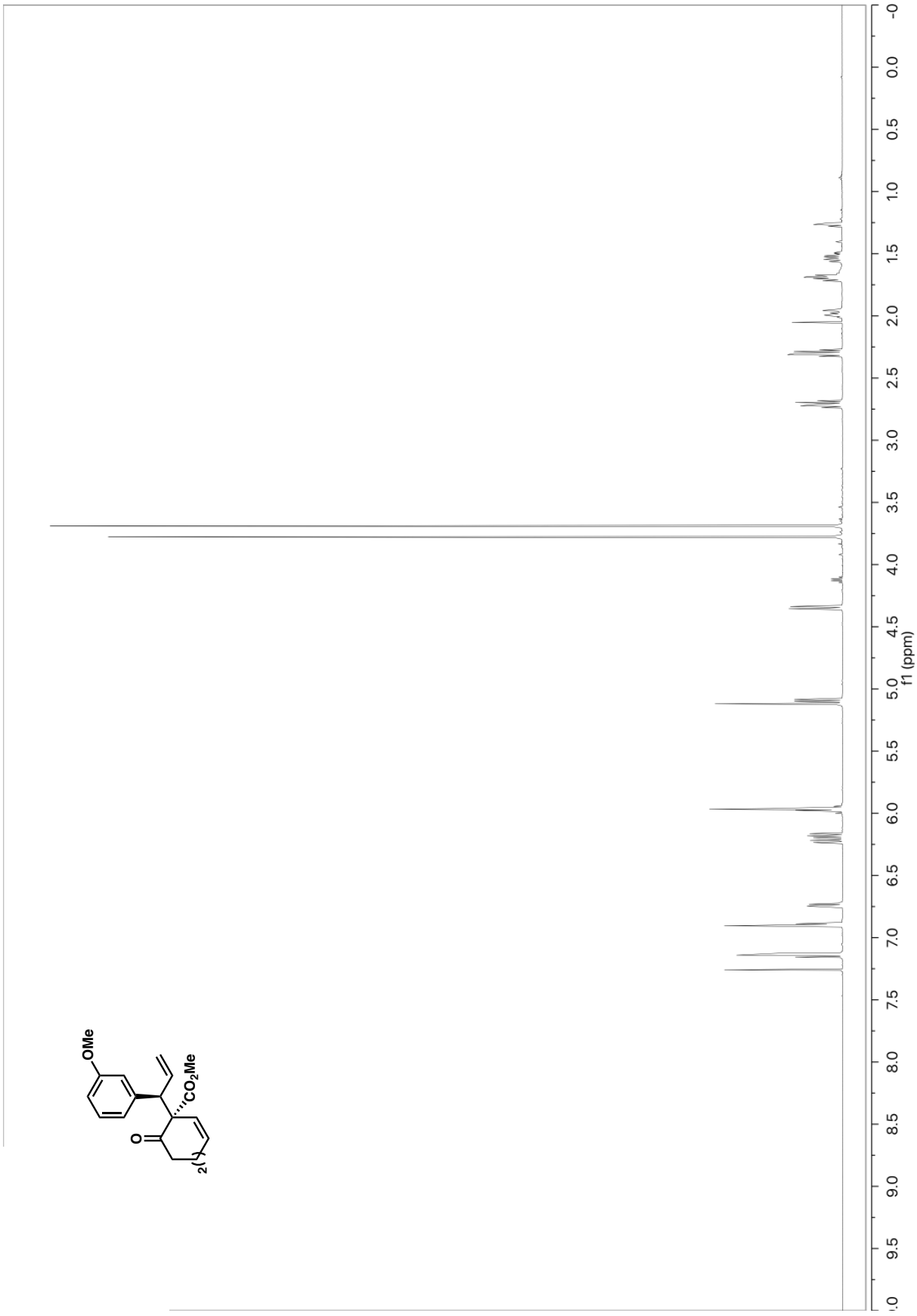



***Figure A1.57*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***7ad.***

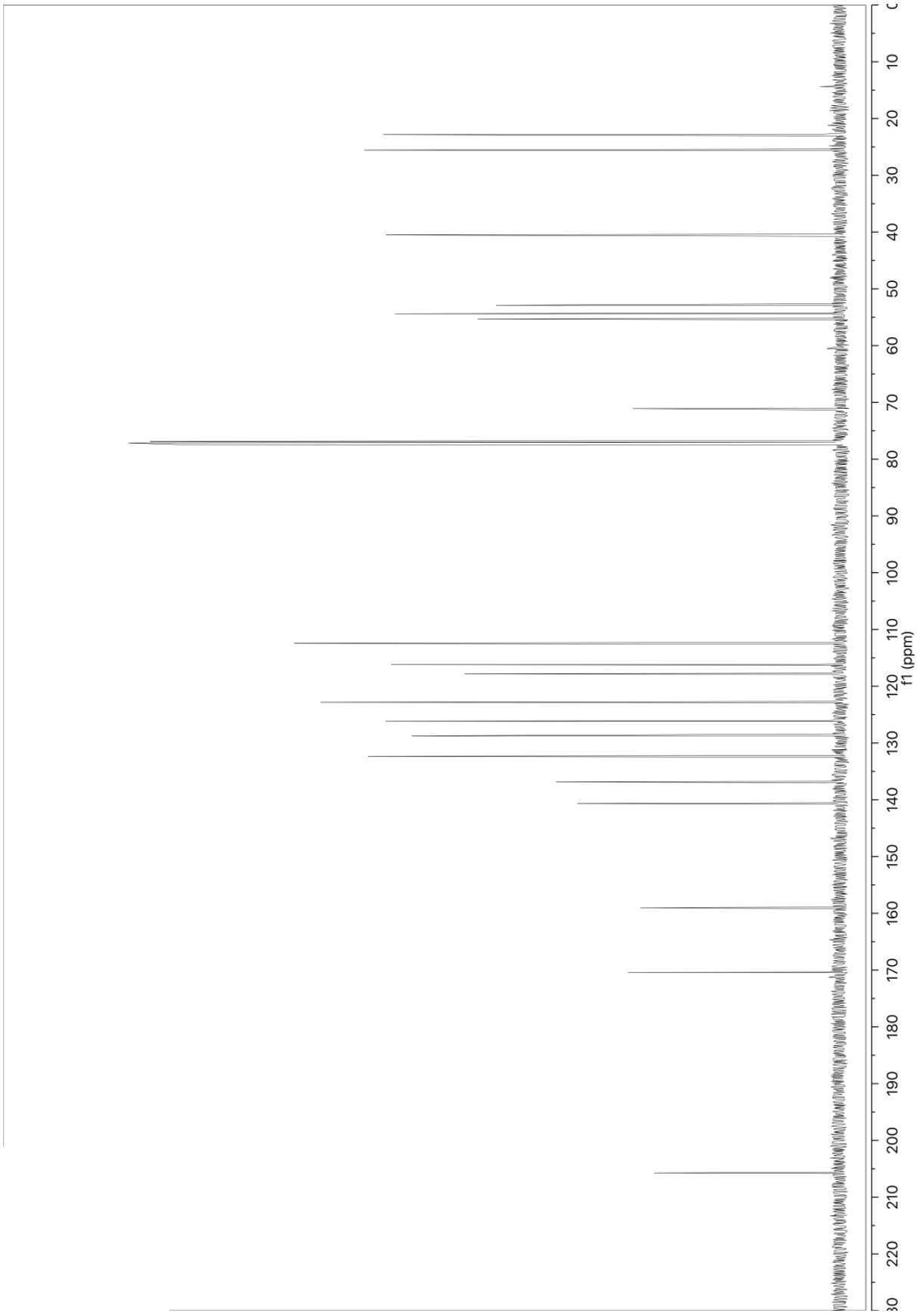



***Figure A1.58*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***7ad****.*

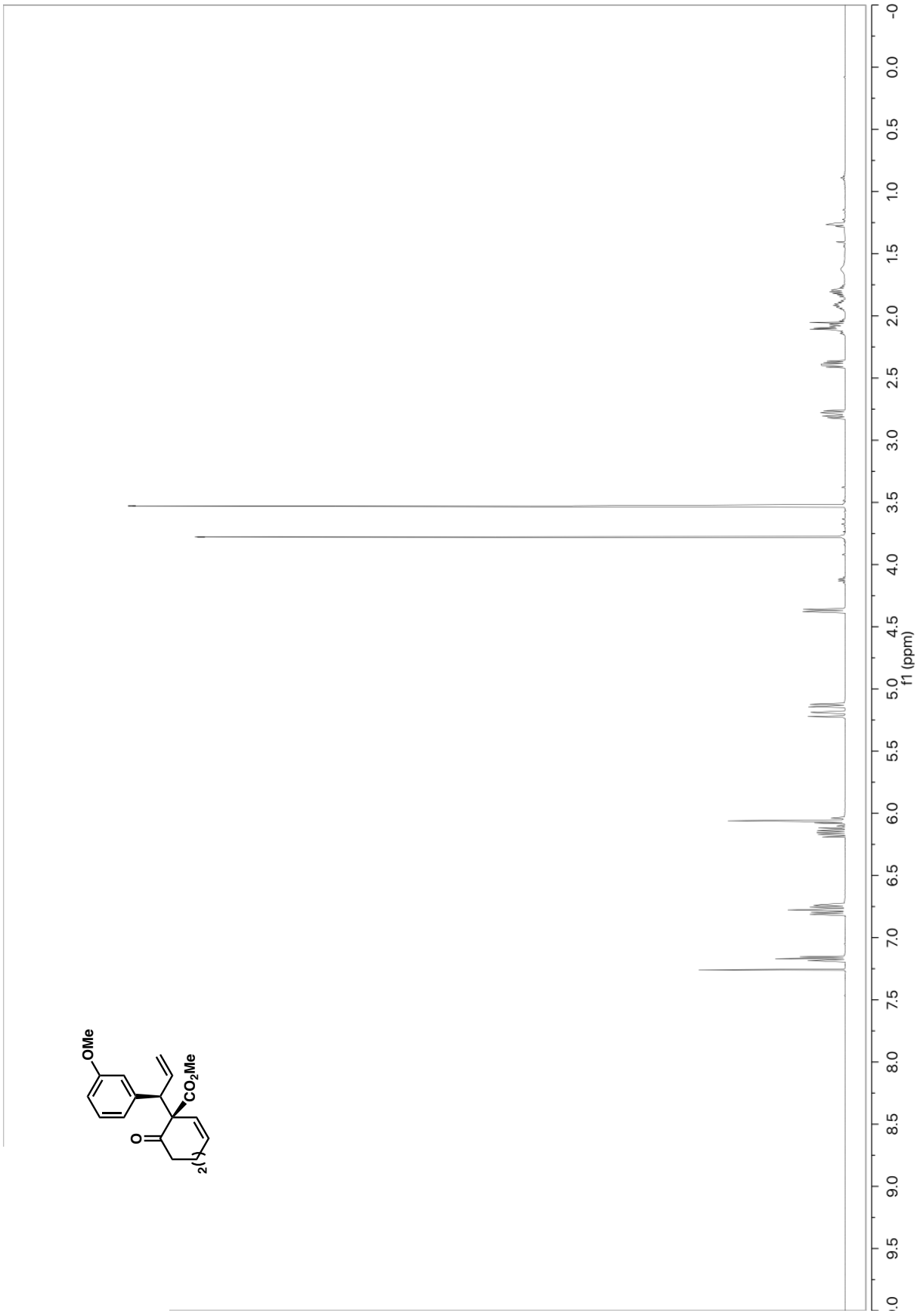



***Figure A1.59*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***7ad'.***

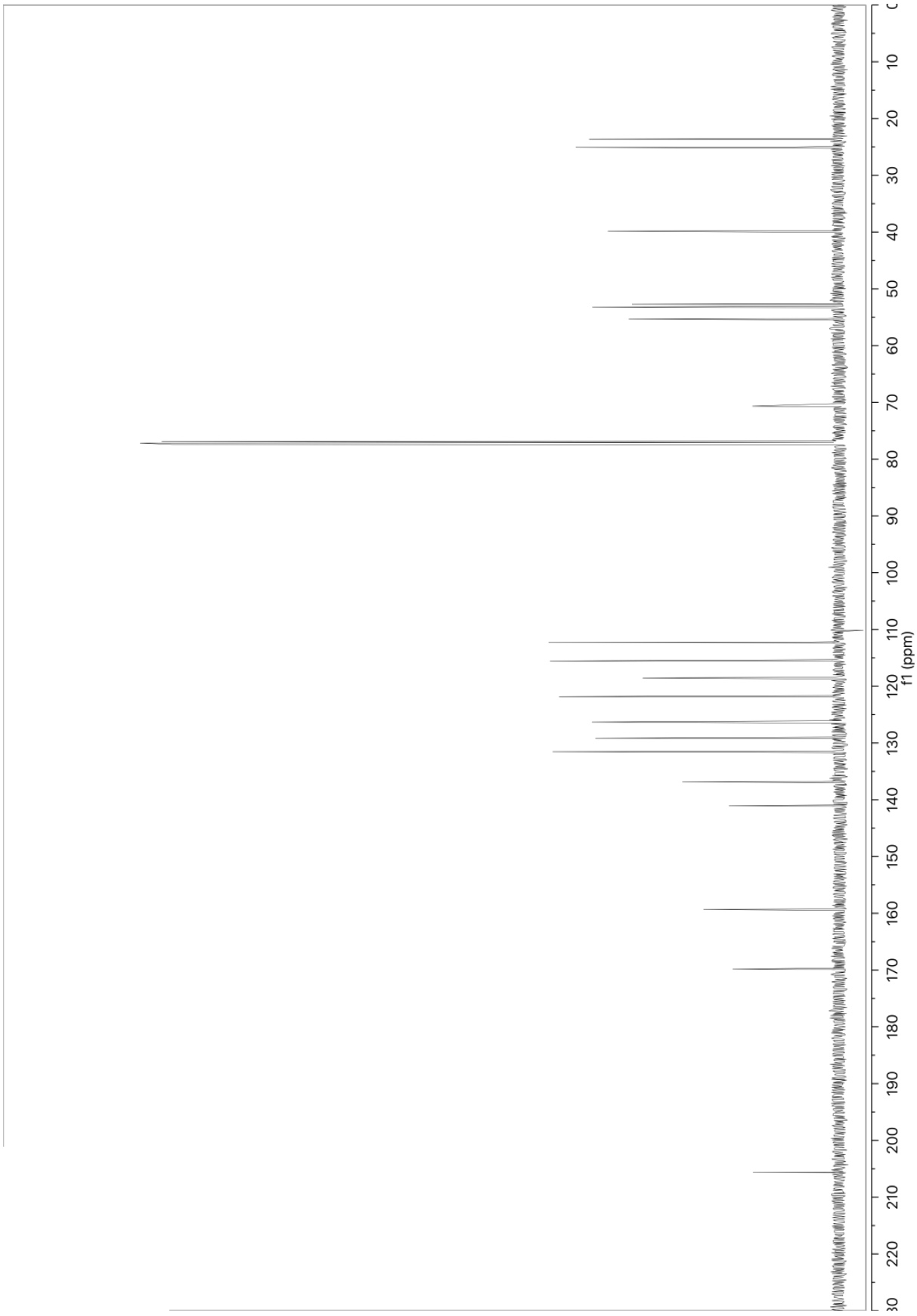



***Figure A1.60*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***7ad'****.*

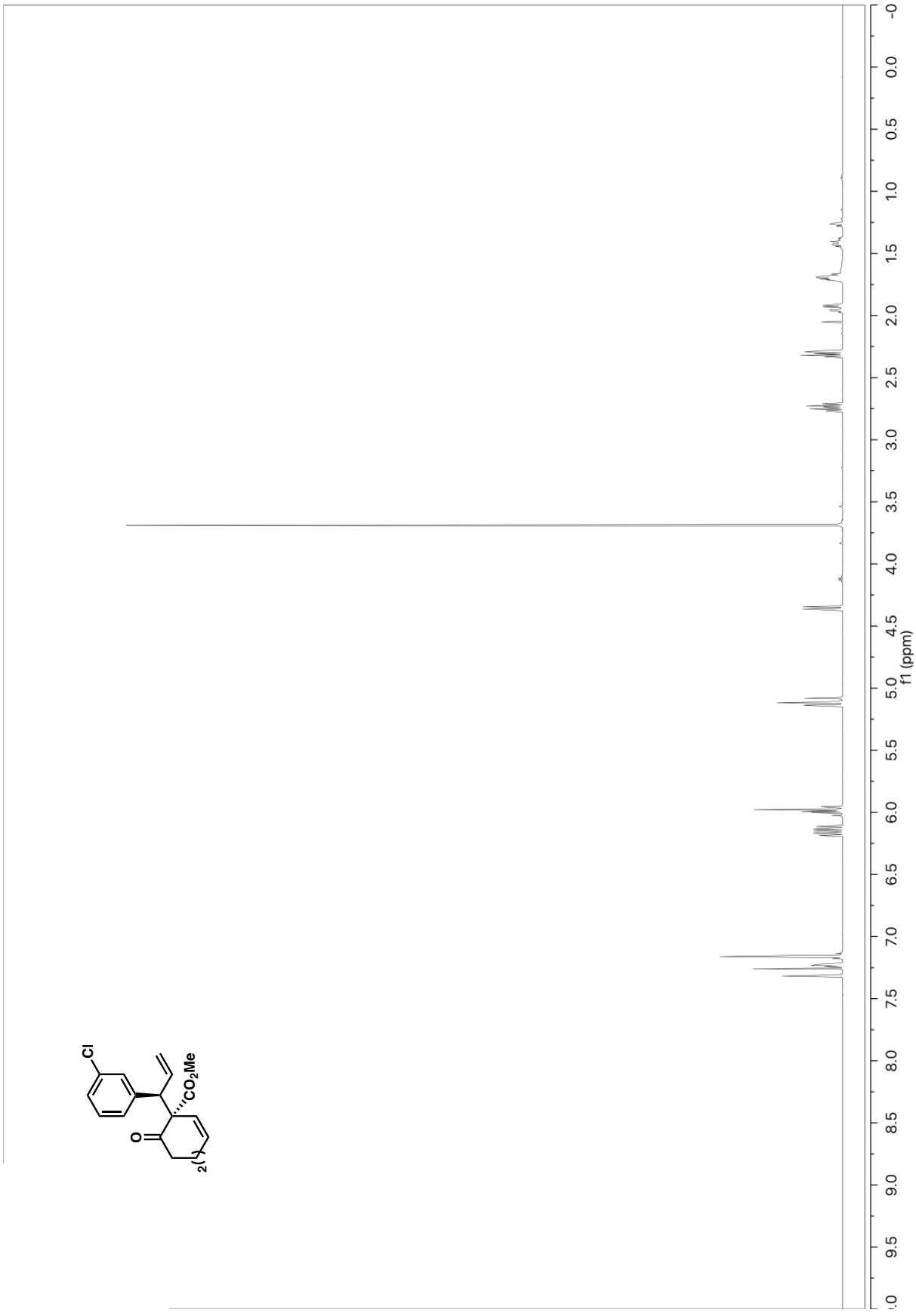



***Figure A1.61*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***7ae.***

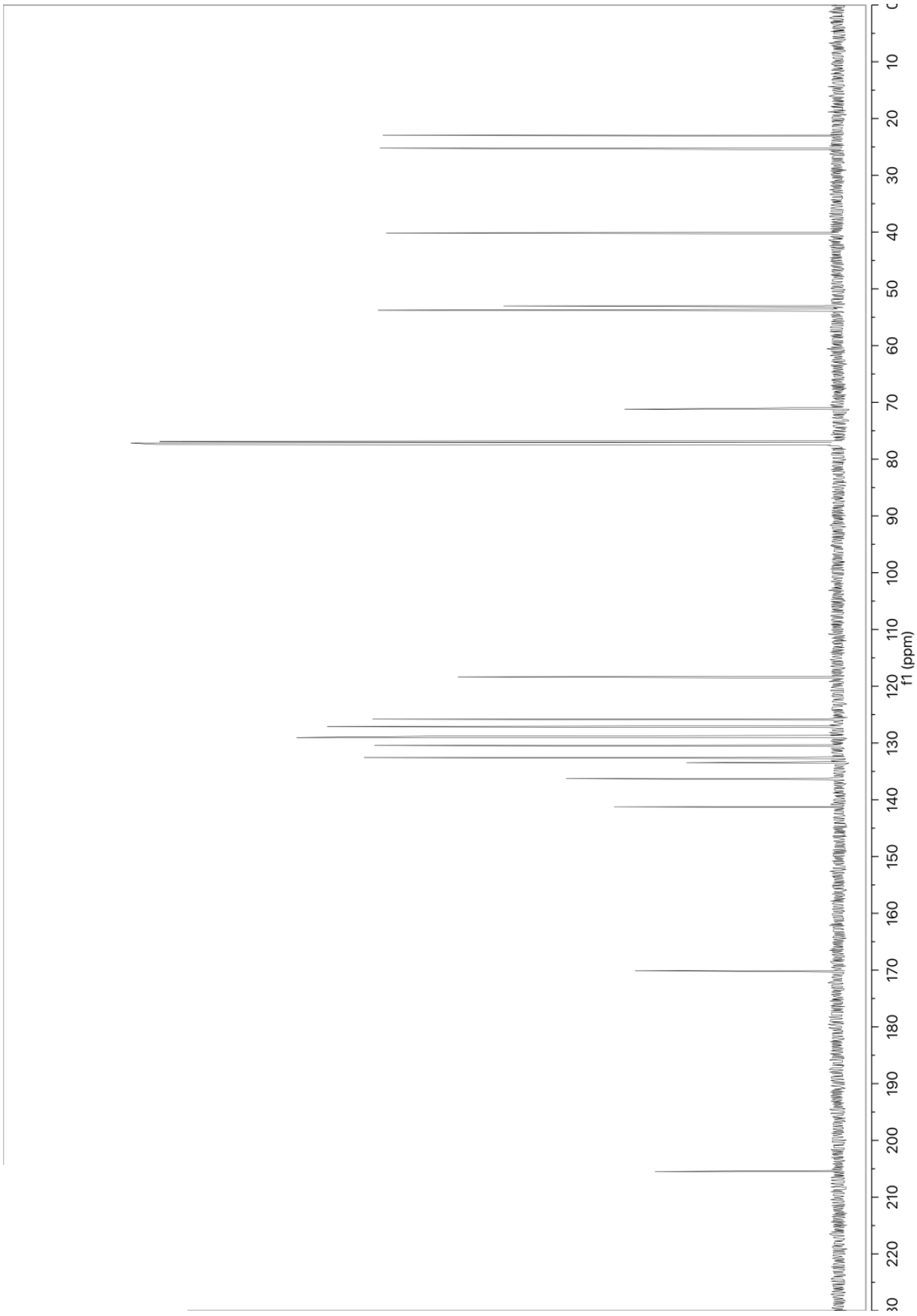



***Figure A1.62*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***7ae***.

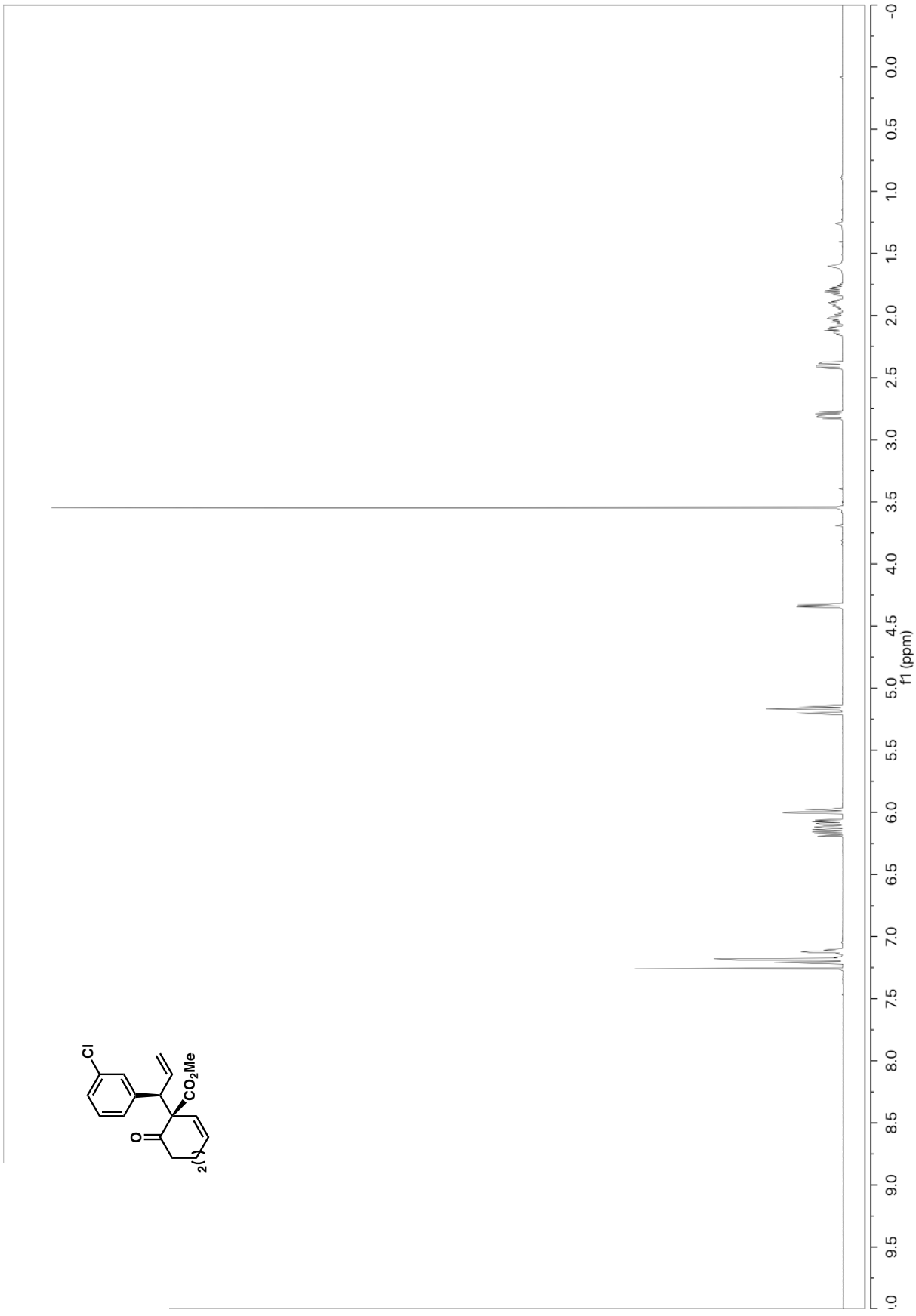



***Figure A1.63*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***7ae'.***

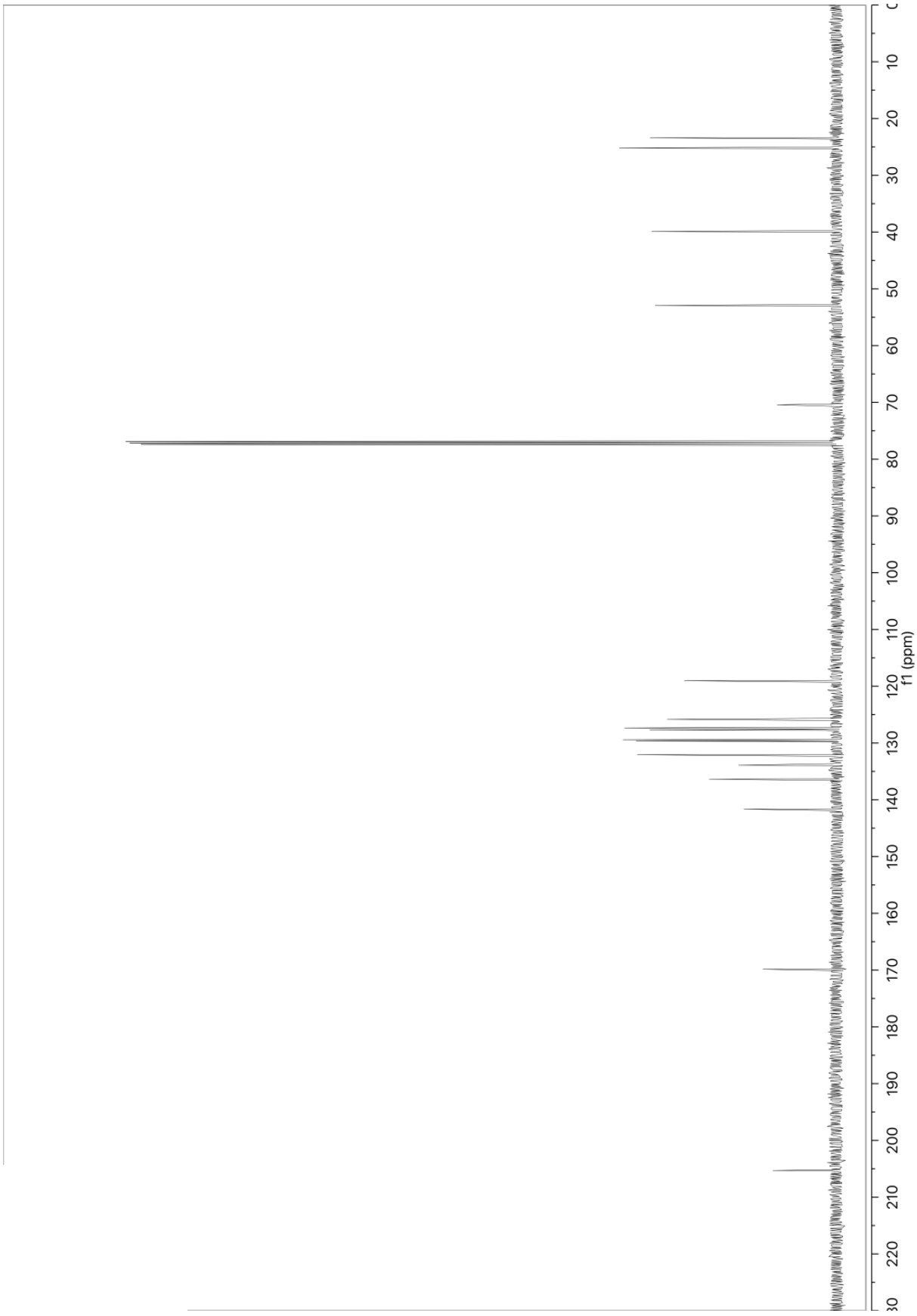



***Figure A1.64*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***7ae'****.*

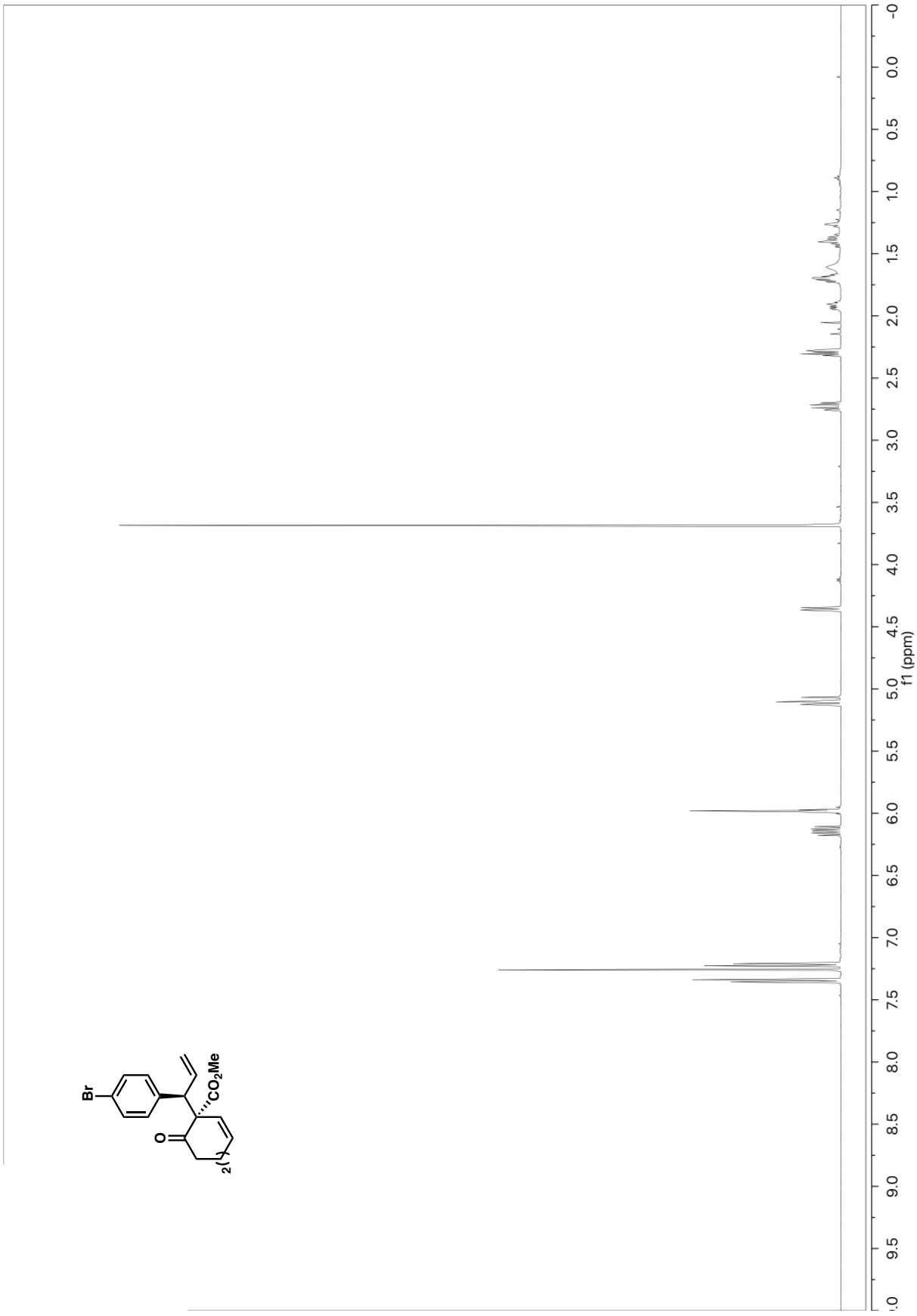



***Figure A1.65*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***7af.***

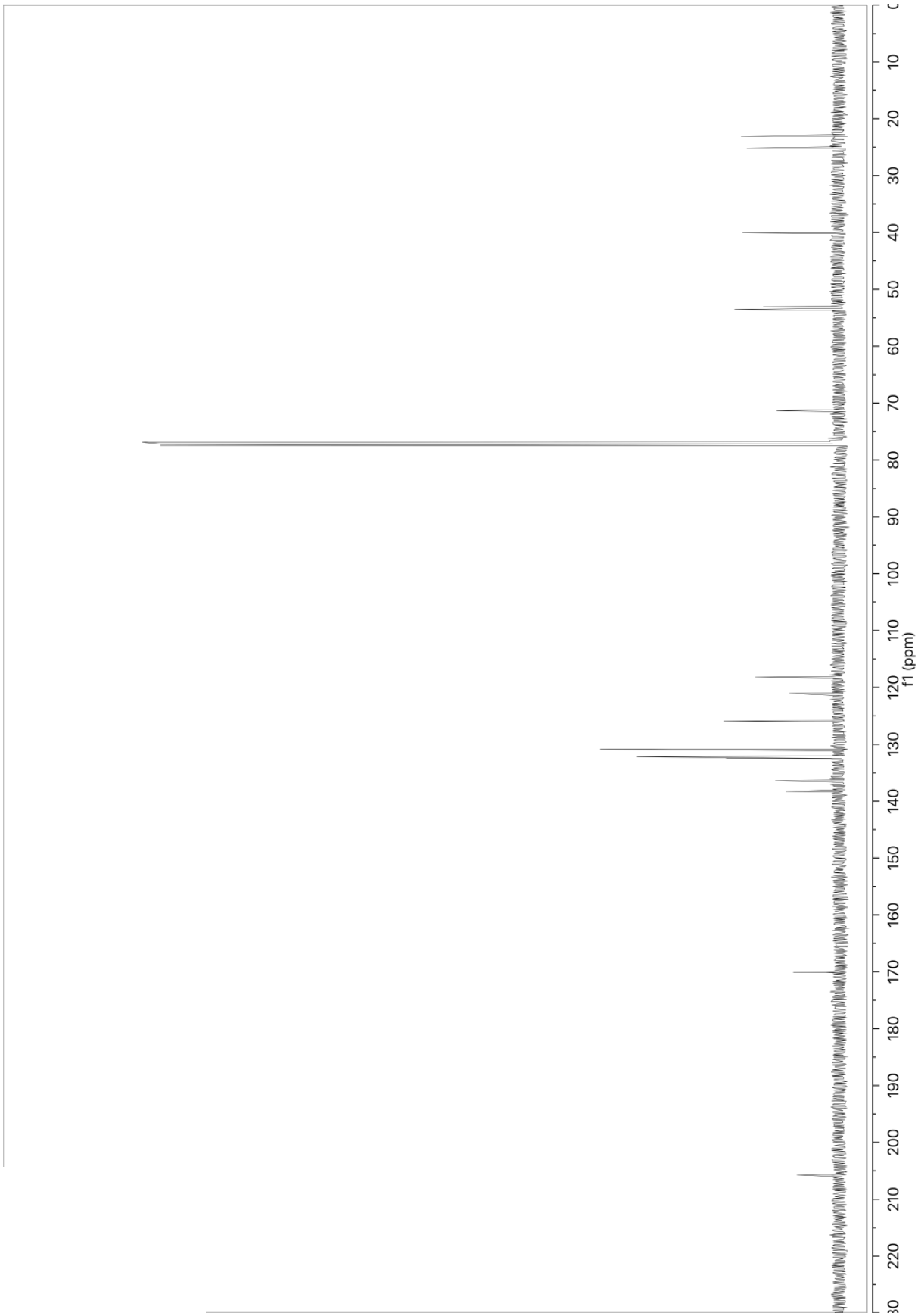



***Figure A1.66*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***7af****.*

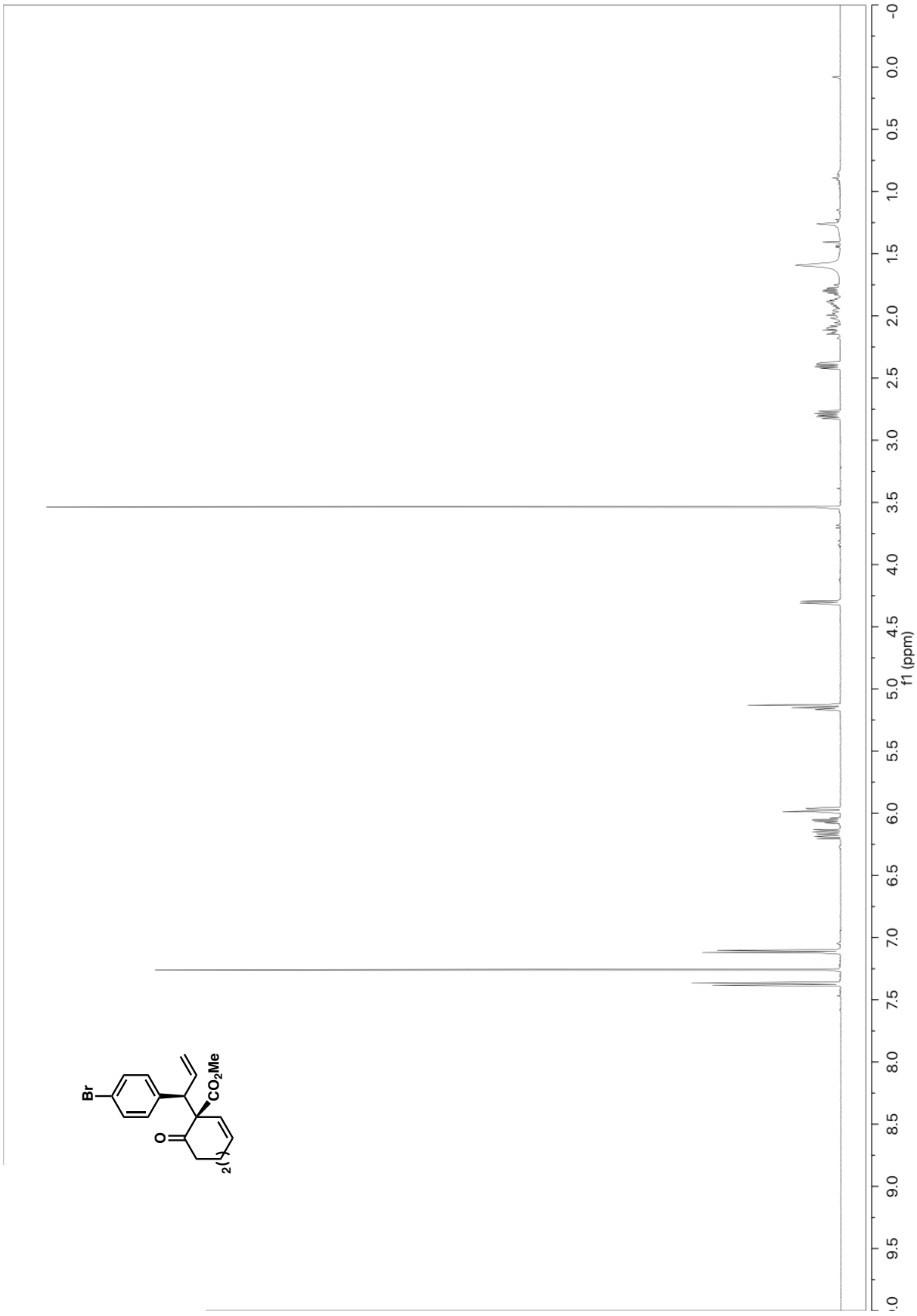



***Figure A1.67*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***7af'.***

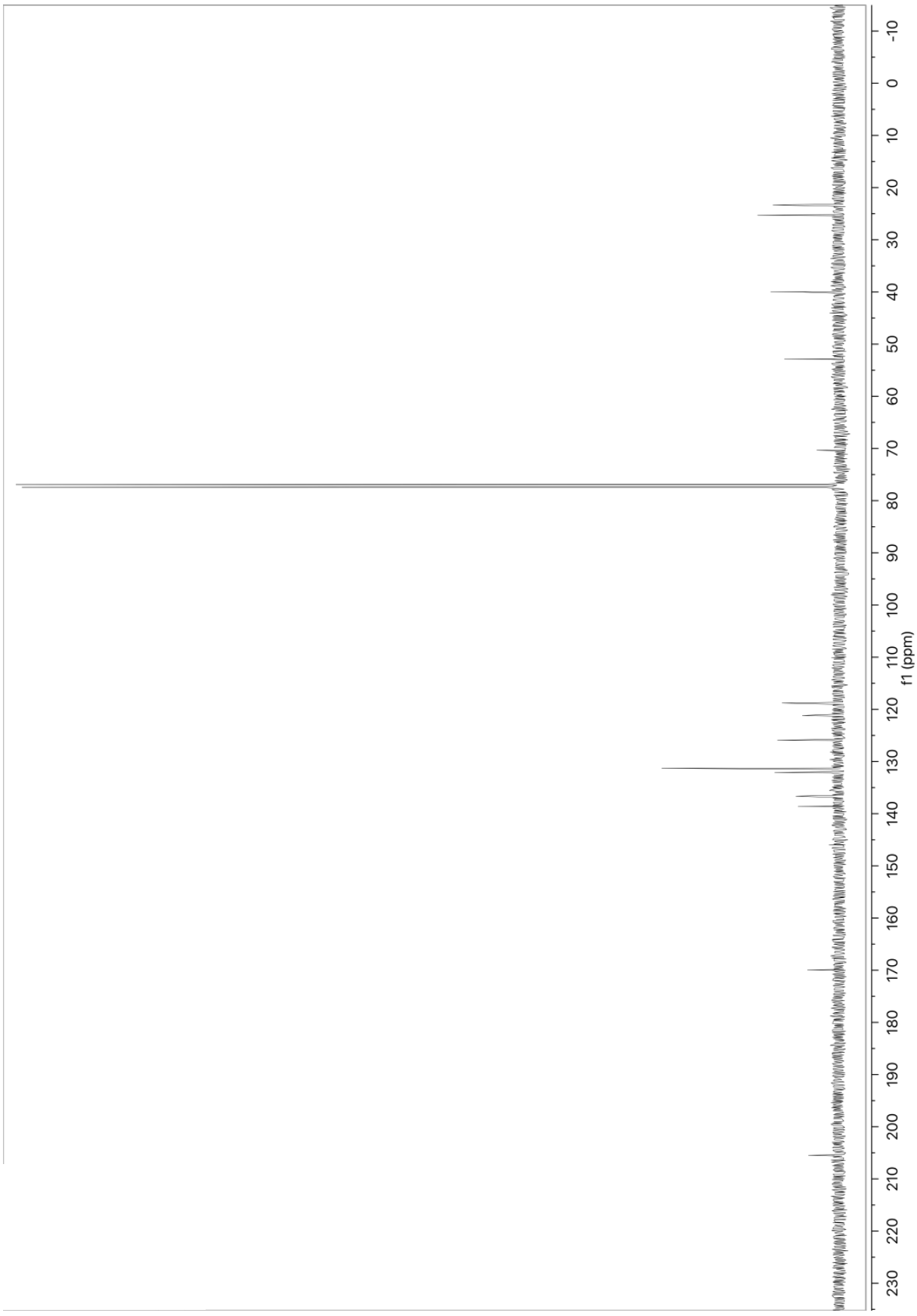



***Figure A1.68*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***7af'***.

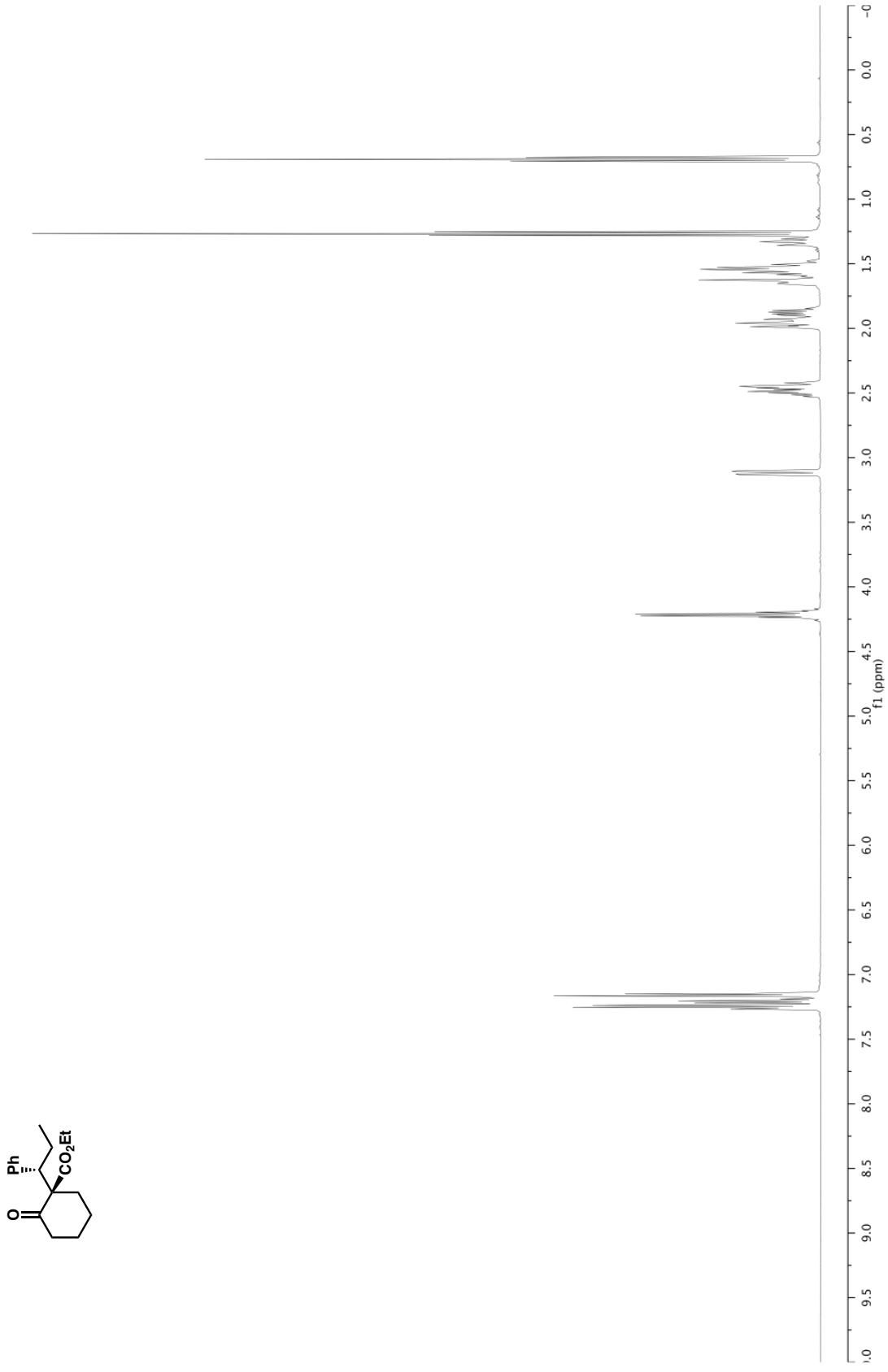



***Figure A1.69*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***S2.***

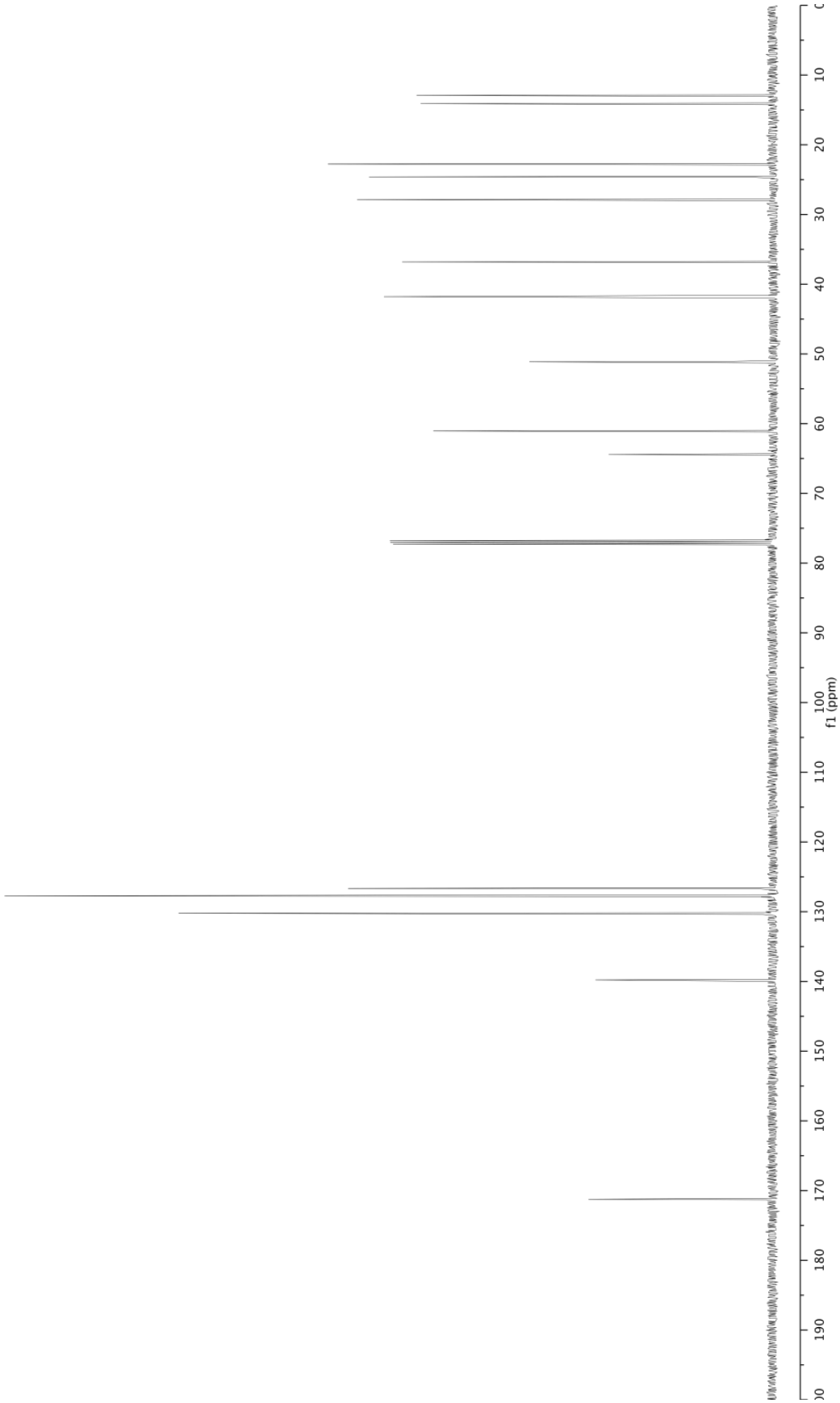



***Figure A1.70*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***S2****.*

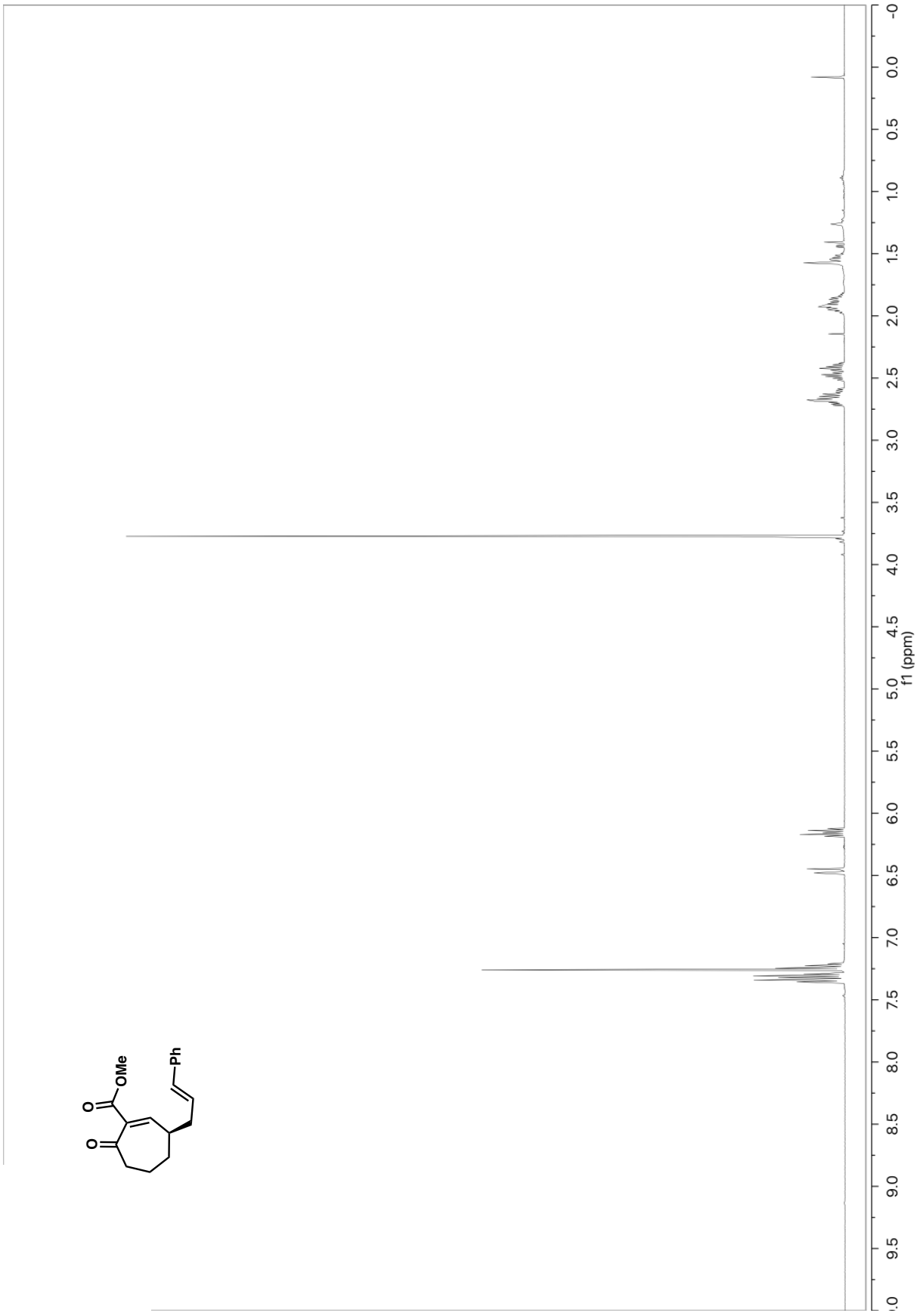



***Figure A1.71*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***9aa.***

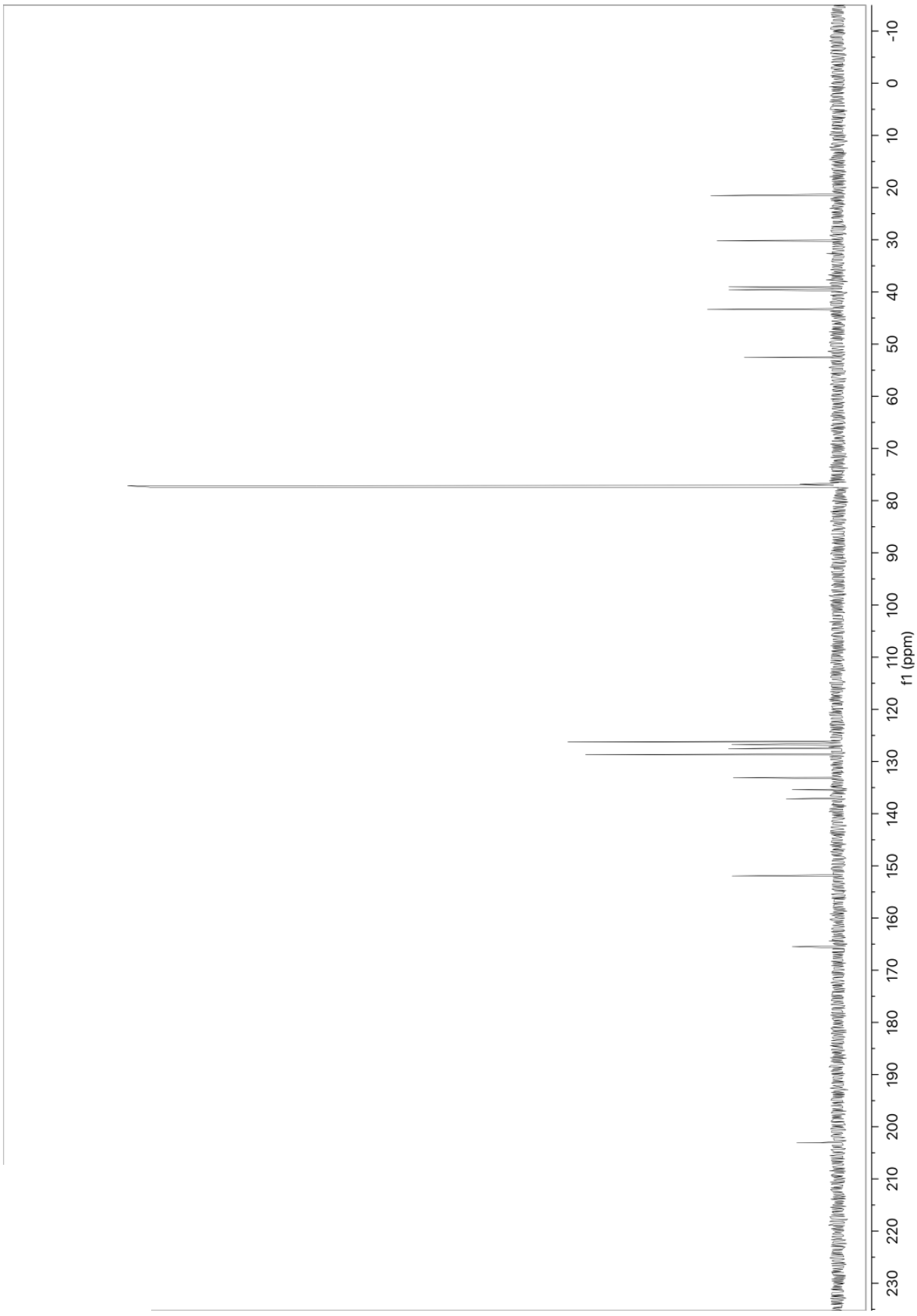



***Figure A1.72*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***9aa***.

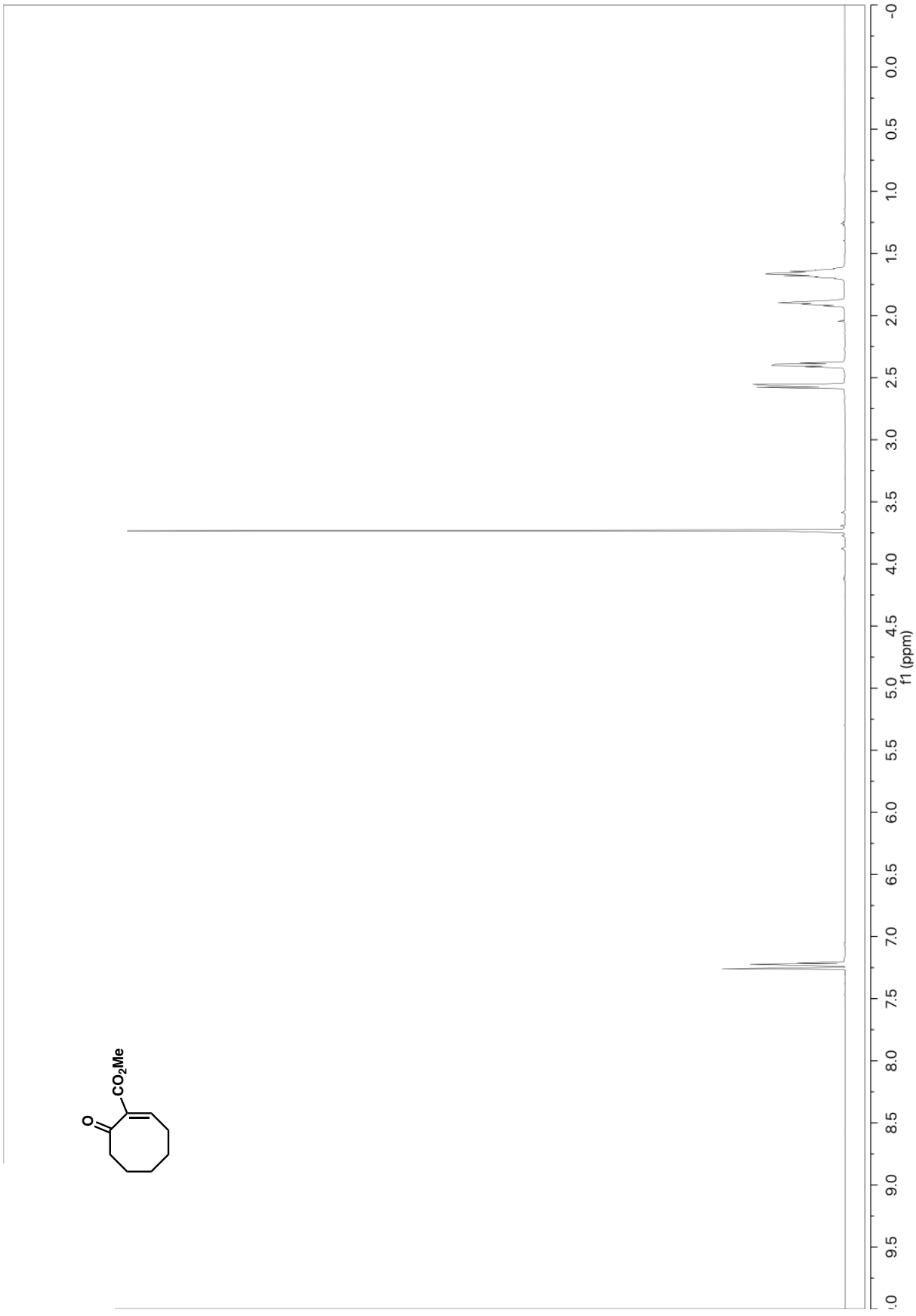



***Figure A1.73*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***6b.***

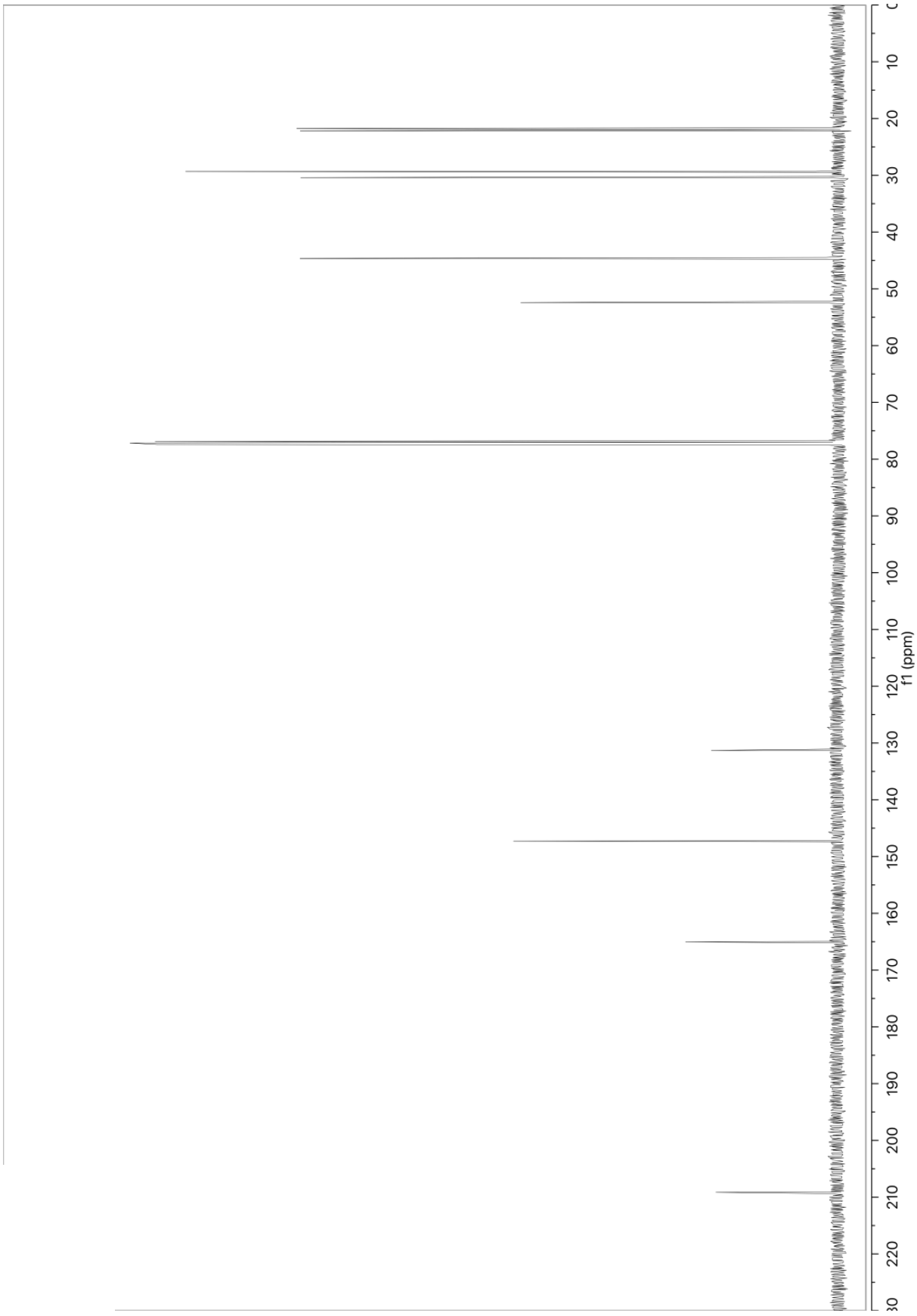



***Figure A1.74*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***6b****.*

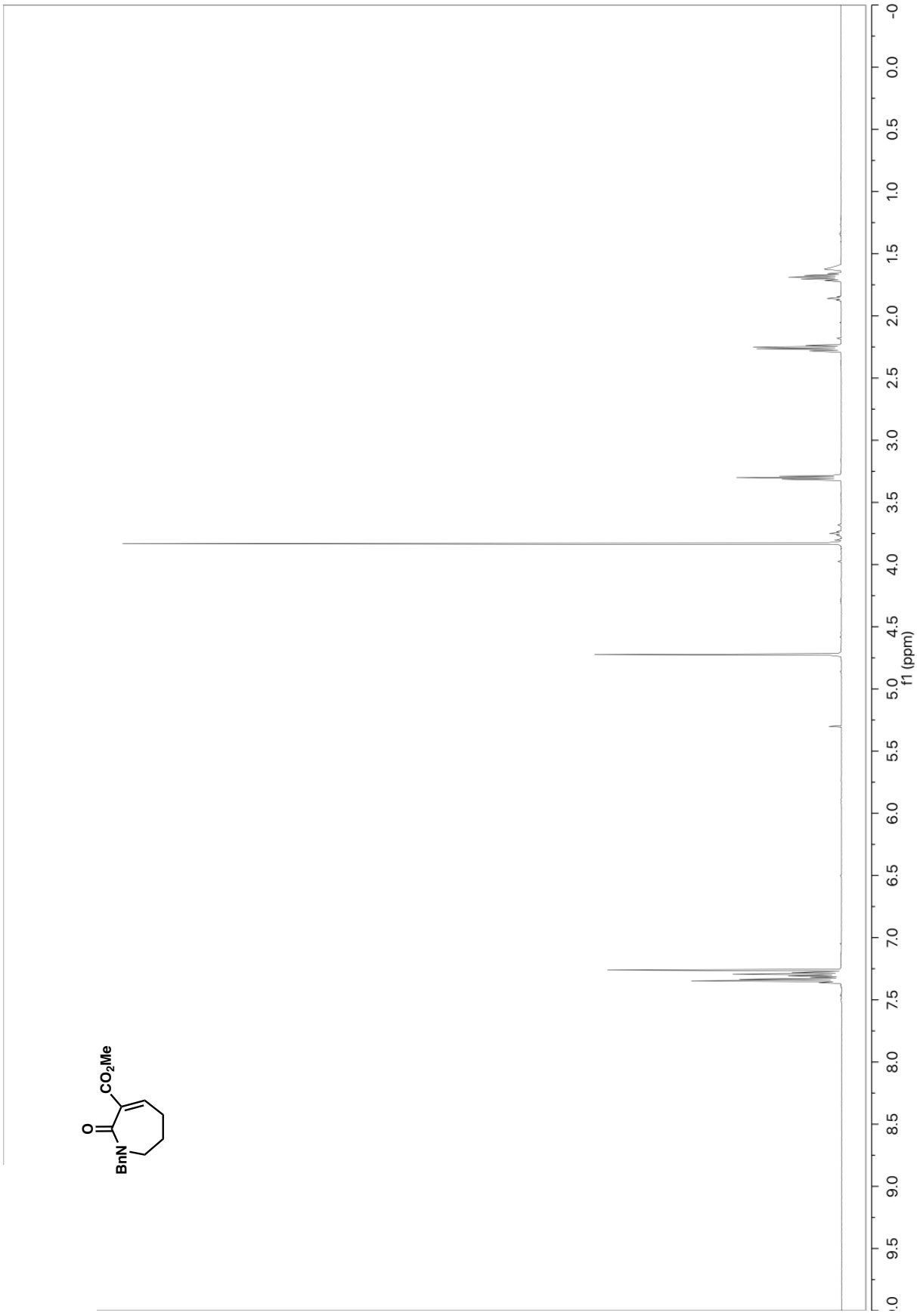



***Figure A1.75*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***6d.***

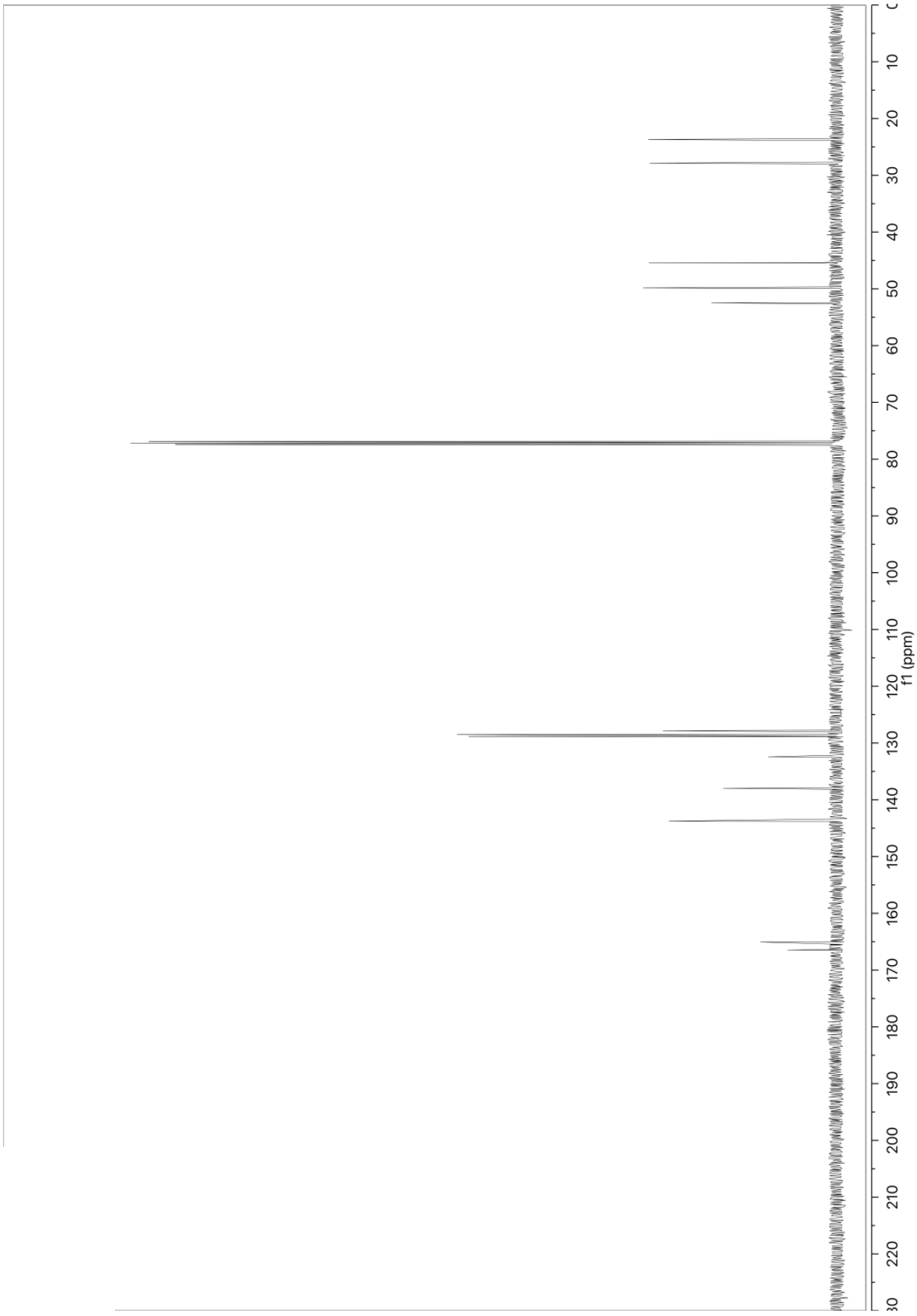



***Figure 1.76*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***6d****.*

# *APPENDIX 2*

*X-Ray Crystallography Reports Relevant to Chapter 1: Enantioselective γ-Alkylation of α,β-Unsaturated Malonates and Ketoesters by a Sequential Ir-Catalyzed Asymmetric Allylic Alkylation/Cope Rearrangement*

## A2.1 GENERAL EXPERIMENTAL

X-ray crystallographic analysis was obtained from the Caltech X-Ray Crystallography Facility using a Bruker D8 Venture Kappa Duo Photon 100 CMOS diffractometer.

### A2.1.1 X-RAY CRYSTAL STRUCTURE ANALYSIS OF ALLYLIC ALKYLATION PRODUCT 3aa

The α-alkylated malonate **3aa** (>99% ee) was recrystallized from $Et_2O$/hexanes (liquid/liquid diffusion) at 0 ºC to provide suitable crystals for X-ray analysis, m.p. = 53 – 55 ºC (hexanes/$Et_2O$).

***Figure A2.1*** *X-ray crystal structure of malonate* ***3aa***

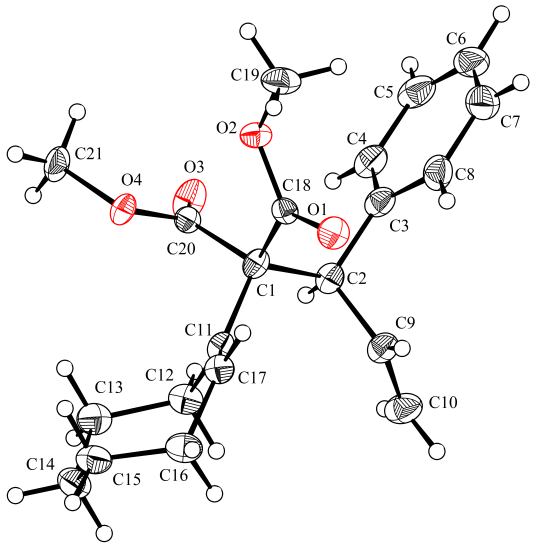



***Table A2.1*** *Crystal data and structure refinement for malonate* ***3aa***

| | |
|---|---|
| Empirical formula | C21 H26 O4 |
| Formula weight | 342.42 |
| Temperature | 100 K |

| | | |
|---|---|---|
| Wavelength | 1.54178 Å | |
| Crystal system | Orthorhombic | |
| Space group | $P2_12_12_1$ | |
| Unit cell dimensions | a = 7.7585(6) Å | α= 90° |
| | b = 9.1039(7) Å | β= 90° |
| | c = 26.2256(17) Å | γ = 90° |
| Volume | 1852.4(2) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.228 $Mg/m^3$ | |
| Absorption coefficient | 0.674 $mm^{-1}$ | |
| F(000) | 736 | |
| Crystal size | 0.21 x 0.19 x 0.17 $mm^3$ | |
| Theta range for data collection | 3.370 to 78.511°. | |
| Index ranges | -9<=h<=9, -11<=k<=11, -32<=l<=33 | |
| Reflections collected | 39232 | |
| Independent reflections | 3967 [R(int) = 0.0517] | |
| Completeness to theta = 67.000° | 99.9 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.9612 and 0.9073 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3967 / 0 / 228 | |
| Goodness-of-fit on $F^2$ | 1.078 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0402, wR2 = 0.1023 | |
| R indices (all data) | R1 = 0.0418, wR2 = 0.1032 | |
| Absolute structure parameter | 0.12(7) | |
| Extinction coefficient | n/a | |
| Largest diff. peak and hole | 0.476 and -0.182 e.$Å^{-3}$ | |

***Table A2.2*** *Atomic coordinates (x$10^5$) and equivalent isotropic displacement parameters (Å$^2$x $10^4$) for* ***3aa****. U(eq) is defined as one third of the trace of the orthogonalized U$^{ij}$ tensor.*

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(1) | 47530(20) | 48207(19) | 71564(6) | 265(4) |
| O(2) | 59320(20) | 31380(18) | 66418(6) | 230(3) |
| O(3) | 40030(20) | 33780(20) | 54882(7) | 328(4) |
| O(4) | 64670(20) | 44547(18) | 57227(6) | 219(3) |
| C(1) | 40600(30) | 48920(30) | 62552(8) | 203(4) |
| C(2) | 20770(30) | 45310(30) | 62993(9) | 228(5) |
| C(3) | 17000(30) | 29830(30) | 64929(10) | 254(5) |
| C(4) | 11800(30) | 19040(30) | 61504(11) | 301(5) |
| C(5) | 8120(30) | 4840(30) | 63209(13) | 365(6) |
| C(6) | 9650(40) | 1220(30) | 68287(12) | 378(6) |
| C(7) | 14440(40) | 11840(30) | 71745(12) | 363(6) |
| C(8) | 17930(30) | 26150(30) | 70102(10) | 305(5) |
| C(9) | 11240(30) | 56730(30) | 66066(10) | 263(5) |
| C(10) | -2930(30) | 63250(30) | 64348(12) | 344(6) |
| C(11) | 43340(30) | 65720(30) | 61761(9) | 216(4) |
| C(12) | 35600(30) | 71790(30) | 56886(9) | 270(5) |
| C(13) | 48620(40) | 78740(30) | 53139(9) | 297(5) |
| C(14) | 55050(40) | 93870(30) | 54684(10) | 308(5) |
| C(15) | 65400(30) | 94390(30) | 59605(10) | 292(5) |
| C(16) | 55380(30) | 90340(30) | 64394(10) | 289(5) |
| C(17) | 52000(30) | 74110(30) | 65029(9) | 237(5) |
| C(18) | 49700(30) | 43240(20) | 67335(8) | 184(4) |
| C(19) | 68200(40) | 25170(30) | 70738(10) | 337(6) |
| C(20) | 48010(30) | 41220(20) | 57798(8) | 191(4) |
| C(21) | 73250(30) | 37220(30) | 53078(9) | 288(5) |

***Table A2.3*** *Bond lengths [Å] and angles [°] for* ***3aa***

| | |
|---|---|
| O(1)-C(18) | 1.210(3) |
| O(2)-C(18) | 1.334(3) |
| O(2)-C(19) | 1.441(3) |
| O(3)-C(20) | 1.194(3) |
| O(4)-C(20) | 1.336(3) |
| O(4)-C(21) | 1.440(3) |
| C(1)-C(2) | 1.577(3) |
| C(1)-C(11) | 1.558(3) |
| C(1)-C(18) | 1.530(3) |
| C(1)-C(20) | 1.541(3) |
| C(2)-H(2) | 1.0000 |
| C(2)-C(3) | 1.526(3) |
| C(2)-C(9) | 1.509(3) |
| C(3)-C(4) | 1.391(3) |
| C(3)-C(8) | 1.400(4) |
| C(4)-H(4) | 0.9500 |
| C(4)-C(5) | 1.397(4) |
| C(5)-H(5) | 0.9500 |
| C(5)-C(6) | 1.377(5) |
| C(6)-H(6) | 0.9500 |
| C(6)-C(7) | 1.377(4) |
| C(7)-H(7) | 0.9500 |
| C(7)-C(8) | 1.398(4) |
| C(8)-H(8) | 0.9500 |
| C(9)-H(9) | 0.9500 |
| C(9)-C(10) | 1.328(4) |
| C(10)-H(10A) | 0.9500 |
| C(10)-H(10B) | 0.9500 |
| C(11)-C(12) | 1.517(3) |
| C(11)-C(17) | 1.330(3) |
| C(12)-H(12A) | 0.9900 |
| C(12)-H(12B) | 0.9900 |
| C(12)-C(13) | 1.545(4) |
| C(13)-H(13A) | 0.9900 |

| | |
|---|---|
| C(13)-H(13B) | 0.9900 |
| C(13)-C(14) | 1.520(4) |
| C(14)-H(14A) | 0.9900 |
| C(14)-H(14B) | 0.9900 |
| C(14)-C(15) | 1.521(4) |
| C(15)-H(15A) | 0.9900 |
| C(15)-H(15B) | 0.9900 |
| C(15)-C(16) | 1.522(4) |
| C(16)-H(16A) | 0.9900 |
| C(16)-H(16B) | 0.9900 |
| C(16)-C(17) | 1.510(3) |
| C(17)-H(17) | 0.9500 |
| C(19)-H(19A) | 0.9800 |
| C(19)-H(19B) | 0.9800 |
| C(19)-H(19C) | 0.9800 |
| C(21)-H(21A) | 0.9800 |
| C(21)-H(21B) | 0.9800 |
| C(21)-H(21C) | 0.9800 |
| C(18)-O(2)-C(19) | 116.30(18) |
| C(20)-O(4)-C(21) | 115.29(18) |
| C(11)-C(1)-C(2) | 110.31(18) |
| C(18)-C(1)-C(2) | 108.65(18) |
| C(18)-C(1)-C(11) | 112.22(18) |
| C(18)-C(1)-C(20) | 109.73(18) |
| C(20)-C(1)-C(2) | 109.16(18) |
| C(20)-C(1)-C(11) | 106.72(18) |
| C(1)-C(2)-H(2) | 106.4 |
| C(3)-C(2)-C(1) | 113.83(19) |
| C(3)-C(2)-H(2) | 106.4 |
| C(9)-C(2)-C(1) | 111.94(19) |
| C(9)-C(2)-H(2) | 106.4 |
| C(9)-C(2)-C(3) | 111.37(19) |
| C(4)-C(3)-C(2) | 119.5(2) |
| C(4)-C(3)-C(8) | 118.1(2) |
| C(8)-C(3)-C(2) | 122.3(2) |
| C(3)-C(4)-H(4) | 119.8 |

| | |
|---|---|
| C(3)-C(4)-C(5) | 120.4(3) |
| C(5)-C(4)-H(4) | 119.8 |
| C(4)-C(5)-H(5) | 119.6 |
| C(6)-C(5)-C(4) | 120.9(3) |
| C(6)-C(5)-H(5) | 119.6 |
| C(5)-C(6)-H(6) | 120.3 |
| C(7)-C(6)-C(5) | 119.5(3) |
| C(7)-C(6)-H(6) | 120.3 |
| C(6)-C(7)-H(7) | 119.9 |
| C(6)-C(7)-C(8) | 120.2(3) |
| C(8)-C(7)-H(7) | 119.9 |
| C(3)-C(8)-H(8) | 119.6 |
| C(7)-C(8)-C(3) | 120.8(3) |
| C(7)-C(8)-H(8) | 119.6 |
| C(2)-C(9)-H(9) | 118.9 |
| C(10)-C(9)-C(2) | 122.2(2) |
| C(10)-C(9)-H(9) | 118.9 |
| C(9)-C(10)-H(10A) | 120.0 |
| C(9)-C(10)-H(10B) | 120.0 |
| H(10A)-C(10)-H(10B) | 120.0 |
| C(12)-C(11)-C(1) | 114.59(19) |
| C(17)-C(11)-C(1) | 123.1(2) |
| C(17)-C(11)-C(12) | 122.3(2) |
| C(11)-C(12)-H(12A) | 108.5 |
| C(11)-C(12)-H(12B) | 108.5 |
| C(11)-C(12)-C(13) | 115.3(2) |
| H(12A)-C(12)-H(12B) | 107.5 |
| C(13)-C(12)-H(12A) | 108.5 |
| C(13)-C(12)-H(12B) | 108.5 |
| C(12)-C(13)-H(13A) | 108.6 |
| C(12)-C(13)-H(13B) | 108.6 |
| H(13A)-C(13)-H(13B) | 107.6 |
| C(14)-C(13)-C(12) | 114.6(2) |
| C(14)-C(13)-H(13A) | 108.6 |
| C(14)-C(13)-H(13B) | 108.6 |
| C(13)-C(14)-H(14A) | 108.4 |

| | |
|---|---|
| C(13)-C(14)-H(14B) | 108.4 |
| C(13)-C(14)-C(15) | 115.3(2) |
| H(14A)-C(14)-H(14B) | 107.5 |
| C(15)-C(14)-H(14A) | 108.4 |
| C(15)-C(14)-H(14B) | 108.4 |
| C(14)-C(15)-H(15A) | 108.5 |
| C(14)-C(15)-H(15B) | 108.5 |
| C(14)-C(15)-C(16) | 115.0(2) |
| H(15A)-C(15)-H(15B) | 107.5 |
| C(16)-C(15)-H(15A) | 108.5 |
| C(16)-C(15)-H(15B) | 108.5 |
| C(15)-C(16)-H(16A) | 108.6 |
| C(15)-C(16)-H(16B) | 108.6 |
| H(16A)-C(16)-H(16B) | 107.6 |
| C(17)-C(16)-C(15) | 114.6(2) |
| C(17)-C(16)-H(16A) | 108.6 |
| C(17)-C(16)-H(16B) | 108.6 |
| C(11)-C(17)-C(16) | 125.4(2) |
| C(11)-C(17)-H(17) | 117.3 |
| C(16)-C(17)-H(17) | 117.3 |
| O(1)-C(18)-O(2) | 123.1(2) |
| O(1)-C(18)-C(1) | 124.1(2) |
| O(2)-C(18)-C(1) | 112.58(18) |
| O(2)-C(19)-H(19A) | 109.5 |
| O(2)-C(19)-H(19B) | 109.5 |
| O(2)-C(19)-H(19C) | 109.5 |
| H(19A)-C(19)-H(19B) | 109.5 |
| H(19A)-C(19)-H(19C) | 109.5 |
| H(19B)-C(19)-H(19C) | 109.5 |
| O(3)-C(20)-O(4) | 123.9(2) |
| O(3)-C(20)-C(1) | 125.6(2) |
| O(4)-C(20)-C(1) | 110.38(18) |
| O(4)-C(21)-H(21A) | 109.5 |
| O(4)-C(21)-H(21B) | 109.5 |
| O(4)-C(21)-H(21C) | 109.5 |
| H(21A)-C(21)-H(21B) | 109.5 |

H(21A)-C(21)-H(21C) 109.5
H(21B)-C(21)-H(21C) 109.5

---

***Table A2.4*** *Anisotropic displacement parameters (Åx10$^4$) for* ***3aa****. The anisotropic displacement factor exponent takes the form* $-2\pi^2[h^2a^{*2}U^{11} + ... +2\ h\ k\ a^*\ b^*U^{12}]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| O(1) | 333(9) | 280(8) | 183(7) | -48(7) | -16(7) | -5(7) |
| O(2) | 272(8) | 184(7) | 234(8) | -17(6) | -28(7) | 29(7) |
| O(3) | 275(9) | 437(10) | 271(9) | -183(8) | 0(7) | -67(8) |
| O(4) | 200(8) | 270(8) | 189(7) | -67(6) | 31(6) | 6(7) |
| C(1) | 184(10) | 259(11) | 166(9) | -48(8) | -11(8) | 10(9) |
| C(2) | 192(10) | 258(11) | 234(11) | -40(9) | -7(8) | -12(9) |
| C(3) | 190(10) | 242(11) | 330(12) | -54(10) | 10(9) | 2(9) |
| C(4) | 232(11) | 291(12) | 382(13) | -85(11) | 19(10) | 2(10) |
| C(5) | 244(12) | 264(12) | 587(18) | -120(12) | 35(12) | -9(10) |
| C(6) | 279(13) | 229(12) | 625(18) | 26(12) | 73(12) | -13(11) |
| C(7) | 288(13) | 336(13) | 466(16) | 53(12) | 30(12) | -15(11) |
| C(8) | 250(12) | 326(13) | 339(13) | -26(11) | 54(10) | -43(10) |
| C(9) | 224(11) | 237(11) | 329(12) | -54(10) | 16(10) | -12(9) |
| C(10) | 238(12) | 258(12) | 536(16) | -36(12) | -13(12) | 9(10) |
| C(11) | 175(10) | 247(11) | 227(10) | -37(9) | 15(9) | 7(8) |
| C(12) | 261(12) | 250(12) | 298(12) | 3(10) | -70(10) | -14(10) |
| C(13) | 365(13) | 291(12) | 237(11) | -11(10) | -38(10) | 32(11) |
| C(14) | 373(14) | 258(11) | 294(12) | 53(10) | 1(11) | 2(10) |
| C(15) | 274(12) | 220(11) | 383(14) | 14(10) | -49(10) | -2(10) |
| C(16) | 335(13) | 211(11) | 320(12) | -46(10) | -59(11) | -18(10) |
| C(17) | 229(11) | 236(11) | 247(11) | -5(9) | -12(9) | -2(9) |
| C(18) | 209(10) | 154(9) | 189(10) | -23(8) | -5(8) | -42(8) |
| C(19) | 455(15) | 255(12) | 301(13) | 35(11) | -67(12) | 103(12) |
| C(20) | 218(10) | 189(10) | 165(10) | -10(8) | -2(8) | -3(9) |
| C(21) | 313(13) | 338(13) | 213(11) | -62(10) | 103(10) | 6(10) |

***Table A2.5*** *Hydrogen coordinates (x $10^4$) and isotropic displacement parameters ($Å^2$ x$10^3$) for* ***3aa****.*

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(2) | 1602 | 4583 | 5945 | 27 |
| H(4) | 1074 | 2134 | 5798 | 36 |
| H(5) | 452 | -242 | 6083 | 44 |
| H(6) | 741 | -853 | 6940 | 45 |
| H(7) | 1538 | 944 | 7526 | 44 |
| H(8) | 2097 | 3345 | 7253 | 37 |
| H(9) | 1551 | 5935 | 6934 | 32 |
| H(10A) | -738 | 6077 | 6108 | 41 |
| H(10B) | -862 | 7040 | 6638 | 41 |
| H(12A) | 2691 | 7930 | 5780 | 32 |
| H(12B) | 2950 | 6373 | 5511 | 32 |
| H(13A) | 5865 | 7209 | 5281 | 36 |
| H(13B) | 4312 | 7949 | 4974 | 36 |
| H(14A) | 4498 | 10046 | 5505 | 37 |
| H(14B) | 6230 | 9779 | 5189 | 37 |
| H(15A) | 7007 | 10443 | 6003 | 35 |
| H(15B) | 7532 | 8761 | 5928 | 35 |
| H(16A) | 6187 | 9387 | 6740 | 35 |
| H(16B) | 4419 | 9556 | 6434 | 35 |
| H(17) | 5641 | 6951 | 6801 | 28 |
| H(19A) | 7662 | 1791 | 6955 | 51 |
| H(19B) | 5985 | 2039 | 7300 | 51 |
| H(19C) | 7417 | 3299 | 7260 | 51 |
| H(21A) | 6846 | 4065 | 4983 | 43 |
| H(21B) | 7153 | 2659 | 5338 | 43 |
| H(21C) | 8561 | 3943 | 5320 | 43 |

***Table A2.6*** *Torsion angles [°] for* ***3aa****.*

| | |
|---|---|
| C(1)-C(2)-C(3)-C(4) | -103.3(3) |
| C(1)-C(2)-C(3)-C(8) | 79.2(3) |
| C(1)-C(2)-C(9)-C(10) | 128.7(3) |
| C(1)-C(11)-C(12)-C(13) | -119.0(2) |
| C(1)-C(11)-C(17)-C(16) | 178.5(2) |
| C(2)-C(1)-C(11)-C(12) | -62.6(2) |
| C(2)-C(1)-C(11)-C(17) | 118.5(2) |
| C(2)-C(1)-C(18)-O(1) | -67.1(3) |
| C(2)-C(1)-C(18)-O(2) | 107.8(2) |
| C(2)-C(1)-C(20)-O(3) | 0.4(3) |
| C(2)-C(1)-C(20)-O(4) | 177.69(18) |
| C(2)-C(3)-C(4)-C(5) | -179.4(2) |
| C(2)-C(3)-C(8)-C(7) | -179.8(2) |
| C(3)-C(2)-C(9)-C(10) | -102.6(3) |
| C(3)-C(4)-C(5)-C(6) | -0.3(4) |
| C(4)-C(3)-C(8)-C(7) | 2.7(4) |
| C(4)-C(5)-C(6)-C(7) | 1.6(4) |
| C(5)-C(6)-C(7)-C(8) | -0.8(4) |
| C(6)-C(7)-C(8)-C(3) | -1.4(4) |
| C(8)-C(3)-C(4)-C(5) | -1.8(4) |
| C(9)-C(2)-C(3)-C(4) | 129.0(2) |
| C(9)-C(2)-C(3)-C(8) | -48.5(3) |
| C(11)-C(1)-C(2)-C(3) | -167.21(18) |
| C(11)-C(1)-C(2)-C(9) | -39.8(3) |
| C(11)-C(1)-C(18)-O(1) | 55.1(3) |
| C(11)-C(1)-C(18)-O(2) | -129.96(19) |
| C(11)-C(1)-C(20)-O(3) | -118.8(3) |
| C(11)-C(1)-C(20)-O(4) | 58.5(2) |
| C(11)-C(12)-C(13)-C(14) | -75.8(3) |
| C(12)-C(11)-C(17)-C(16) | -0.3(4) |
| C(12)-C(13)-C(14)-C(15) | 64.0(3) |
| C(13)-C(14)-C(15)-C(16) | -64.8(3) |
| C(14)-C(15)-C(16)-C(17) | 75.6(3) |
| C(15)-C(16)-C(17)-C(11) | -59.5(3) |

| | |
|---|---|
| C(17)-C(11)-C(12)-C(13) | 59.9(3) |
| C(18)-C(1)-C(2)-C(3) | -43.8(2) |
| C(18)-C(1)-C(2)-C(9) | 83.6(2) |
| C(18)-C(1)-C(11)-C(12) | 176.12(19) |
| C(18)-C(1)-C(11)-C(17) | -2.8(3) |
| C(18)-C(1)-C(20)-O(3) | 119.4(3) |
| C(18)-C(1)-C(20)-O(4) | -63.3(2) |
| C(19)-O(2)-C(18)-O(1) | -4.3(3) |
| C(19)-O(2)-C(18)-C(1) | -179.2(2) |
| C(20)-C(1)-C(2)-C(3) | 75.8(2) |
| C(20)-C(1)-C(2)-C(9) | -156.8(2) |
| C(20)-C(1)-C(11)-C(12) | 55.9(2) |
| C(20)-C(1)-C(11)-C(17) | -123.0(2) |
| C(20)-C(1)-C(18)-O(1) | 173.6(2) |
| C(20)-C(1)-C(18)-O(2) | -11.5(3) |
| C(21)-O(4)-C(20)-O(3) | -6.4(3) |
| C(21)-O(4)-C(20)-C(1) | 176.25(19) |

### A2.1.2 X-RAY CRYSTAL STRUCTURE ANALYSIS OF DIOL S5aa

The diol **S5aa** (>99% ee) was recrystallized from $Et_2O$/hexanes (liquid/liquid diffusion) at 0 ºC to provide suitable crystals for X-ray analysis, m.p. = 91 – 92 ºC (hexanes/$Et_2O$).

***Figure A2.2*** *X-ray crystal structure of malonate* ***S5aa***

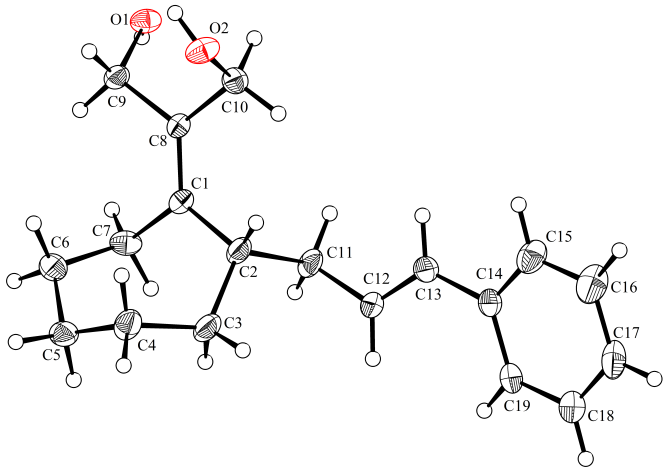



***Table A2.7*** *Crystal data and structure refinement for diol* ***S5aa***

| | | |
|---|---|---|
| Empirical formula | C19 H26 O2 | |
| Formula weight | 286.40 | |
| Temperature | 100 K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Orthorhombic | |
| Space group | $P2_12_12_1$ | |
| Unit cell dimensions | a = 6.1787(8) Å | α= 90° |
| | b = 9.0018(11) Å | β= 90° |
| | c = 29.470(3) Å | γ = 90° |
| Volume | 1639.1(3) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.161 $Mg/m^3$ | |
| Absorption coefficient | 0.569 $mm^{-1}$ | |
| F(000) | 624 | |

| | |
|---|---|
| Crystal size | 0.17 x 0.15 x 0.10 $mm^3$ |
| Theta range for data collection | 2.999 to 79.168°. |
| Index ranges | -7<=h<=6, -11<=k<=11, -37<=l<=37 |
| Reflections collected | 42476 |
| Independent reflections | 3528 [R(int) = 0.0365] |
| Completeness to theta = 67.000∞ | 100.0 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 1.0000 and 0.9358 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 3528 / 0 / 274 |
| Goodness-of-fit on $F^2$ | 1.065 |
| Final R indices [I>2sigma(I)] | R1 = 0.0269, wR2 = 0.0674 |
| R indices (all data) | R1 = 0.0276, wR2 = 0.0680 |
| Absolute structure parameter | 0.06(3) |
| Extinction coefficient | n/a |
| Largest diff. peak and hole | 0.151 and -0.151 e.$Å^{-3}$ |

***Table A2.8*** *Atomic coordinates (x$10^5$) and equivalent isotropic displacement parameters ($Å^2$x $10^4$) for* ***S5aa****. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.*

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(1) | 98299(14) | 29698(10) | 46715(3) | 231(2) |
| O(2) | 39847(15) | 37085(11) | 45850(3) | 264(2) |
| C(1) | 77350(20) | 60425(14) | 40871(4) | 185(2) |
| C(2) | 62050(20) | 65375(14) | 37135(4) | 240(3) |
| C(3) | 58950(30) | 82309(16) | 36918(4) | 332(4) |
| C(4) | 55850(20) | 89964(16) | 41547(5) | 297(3) |
| C(5) | 77130(20) | 94951(15) | 43706(4) | 263(3) |
| C(6) | 91700(20) | 82470(15) | 45366(5) | 257(3) |
| C(7) | 96570(20) | 70494(14) | 41772(5) | 241(3) |
| C(8) | 73960(20) | 47967(13) | 43291(4) | 179(2) |
| C(9) | 87550(20) | 43732(14) | 47335(4) | 211(3) |

| | | | | |
|---|---|---|---|---|
| C(10) | 56100(20) | 36983(14) | 42365(4) | 218(3) |
| C(11) | 70390(70) | 59480(50) | 32407(13) | 248(7) |
| C(12) | 54900(30) | 62780(20) | 28662(5) | 255(5) |
| C(13) | 39140(40) | 53410(20) | 27498(8) | 242(5) |
| C(14) | 23070(60) | 55120(40) | 23888(11) | 233(5) |
| C(15) | 5980(50) | 45320(40) | 23756(10) | 316(6) |
| C(16) | -10090(70) | 46330(50) | 20517(16) | 387(9) |
| C(17) | -9830(90) | 57330(60) | 17220(20) | 343(11) |
| C(18) | 8040(100) | 67220(60) | 17270(13) | 372(9) |
| C(19) | 24250(60) | 66010(40) | 20567(14) | 323(7) |
| C(11A) | 64700(300) | 57900(200) | 32940(70) | 420(50) |
| C(12A) | 44830(140) | 55960(90) | 29580(30) | 261(19) |
| C(13A) | 43160(110) | 60900(80) | 25420(20) | 240(20) |
| C(14A) | 23680(160) | 59780(130) | 22540(40) | 143(19) |
| C(15A) | 5200(300) | 51020(120) | 23290(40) | 340(30) |
| C(16A) | -12300(300) | 52140(130) | 20330(60) | 290(30) |
| C(17A) | -9100(500) | 61600(200) | 16800(90) | 470(60) |
| C(18A) | 6600(400) | 69300(200) | 15880(50) | 340(40) |
| C(19A) | 23080(170) | 68610(120) | 18680(40) | 210(20) |

***Table A2.9*** *Bond lengths [Å] and angles [°] for* ***S5aa***

| | |
|---|---|
| O(1)-H(1) | 0.8400 |
| O(1)-C(9) | 1.4389(16) |
| O(2)-H(2) | 0.8400 |
| O(2)-C(10) | 1.4365(16) |
| C(1)-C(2) | 1.5181(17) |
| C(1)-C(7) | 1.5171(18) |
| C(1)-C(8) | 1.3455(17) |
| C(2)-H(2A) | 1.0000 |
| C(2)-H(2B) | 1.0000 |
| C(2)-C(3) | 1.5376(19) |
| C(2)-C(11) | 1.577(4) |
| C(2)-C(11A) | 1.42(2) |
| C(3)-H(3A) | 0.9900 |

| | |
|---|---|
| C(3)-H(3B) | 0.9900 |
| C(3)-C(4) | 1.5403(18) |
| C(4)-H(4A) | 0.9900 |
| C(4)-H(4B) | 0.9900 |
| C(4)-C(5) | 1.528(2) |
| C(5)-H(5A) | 0.9900 |
| C(5)-H(5B) | 0.9900 |
| C(5)-C(6) | 1.5205(19) |
| C(6)-H(6A) | 0.9900 |
| C(6)-H(6B) | 0.9900 |
| C(6)-C(7) | 1.5410(19) |
| C(7)-H(7A) | 0.9900 |
| C(7)-H(7B) | 0.9900 |
| C(8)-C(9) | 1.5067(16) |
| C(8)-C(10) | 1.5066(17) |
| C(9)-H(9A) | 0.9900 |
| C(9)-H(9B) | 0.9900 |
| C(10)-H(10A) | 0.9900 |
| C(10)-H(10B) | 0.9900 |
| C(11)-H(11A) | 0.9900 |
| C(11)-H(11B) | 0.9900 |
| C(11)-C(12) | 1.491(5) |
| C(12)-H(12) | 0.9500 |
| C(12)-C(13) | 1.333(3) |
| C(13)-H(13) | 0.9500 |
| C(13)-C(14) | 1.463(4) |
| C(14)-C(15) | 1.376(5) |
| C(14)-C(19) | 1.387(4) |
| C(15)-H(15) | 0.9500 |
| C(15)-C(16) | 1.380(6) |
| C(16)-H(16) | 0.9500 |
| C(16)-C(17) | 1.389(6) |
| C(17)-H(17) | 0.9500 |
| C(17)-C(18) | 1.418(9) |
| C(18)-H(18) | 0.9500 |
| C(18)-C(19) | 1.400(5) |

| | |
|---|---|
| C(19)-H(19) | 0.9500 |
| C(11A)-H(11C) | 0.9900 |
| C(11A)-H(11D) | 0.9900 |
| C(11A)-C(12A) | 1.59(2) |
| C(12A)-H(12A) | 0.9500 |
| C(12A)-C(13A) | 1.307(12) |
| C(13A)-H(13A) | 0.9500 |
| C(13A)-C(14A) | 1.477(12) |
| C(14A)-C(15A) | 1.405(19) |
| C(14A)-C(19A) | 1.387(13) |
| C(15A)-H(15A) | 0.9500 |
| C(15A)-C(16A) | 1.39(2) |
| C(16A)-H(16A) | 0.9500 |
| C(16A)-C(17A) | 1.36(3) |
| C(17A)-H(17A) | 0.9500 |
| C(17A)-C(18A) | 1.22(4) |
| C(18A)-H(18A) | 0.9500 |
| C(18A)-C(19A) | 1.31(2) |
| C(19A)-H(19A) | 0.9500 |
| C(9)-O(1)-H(1) | 109.5 |
| C(10)-O(2)-H(2) | 109.5 |
| C(7)-C(1)-C(2) | 116.03(11) |
| C(8)-C(1)-C(2) | 122.15(12) |
| C(8)-C(1)-C(7) | 121.82(11) |
| C(1)-C(2)-H(2A) | 107.9 |
| C(1)-C(2)-H(2B) | 103.1 |
| C(1)-C(2)-C(3) | 113.50(11) |
| C(1)-C(2)-C(11) | 109.8(2) |
| C(3)-C(2)-H(2A) | 107.9 |
| C(3)-C(2)-H(2B) | 103.1 |
| C(3)-C(2)-C(11) | 109.72(19) |
| C(11)-C(2)-H(2A) | 107.9 |
| C(11A)-C(2)-C(1) | 114.9(8) |
| C(11A)-C(2)-H(2B) | 103.1 |
| C(11A)-C(2)-C(3) | 116.7(9) |
| C(2)-C(3)-H(3A) | 108.5 |

| | |
|---|---|
| C(2)-C(3)-H(3B) | 108.5 |
| C(2)-C(3)-C(4) | 114.97(11) |
| H(3A)-C(3)-H(3B) | 107.5 |
| C(4)-C(3)-H(3A) | 108.5 |
| C(4)-C(3)-H(3B) | 108.5 |
| C(3)-C(4)-H(4A) | 108.9 |
| C(3)-C(4)-H(4B) | 108.9 |
| H(4A)-C(4)-H(4B) | 107.8 |
| C(5)-C(4)-C(3) | 113.15(13) |
| C(5)-C(4)-H(4A) | 108.9 |
| C(5)-C(4)-H(4B) | 108.9 |
| C(4)-C(5)-H(5A) | 108.5 |
| C(4)-C(5)-H(5B) | 108.5 |
| H(5A)-C(5)-H(5B) | 107.5 |
| C(6)-C(5)-C(4) | 115.23(11) |
| C(6)-C(5)-H(5A) | 108.5 |
| C(6)-C(5)-H(5B) | 108.5 |
| C(5)-C(6)-H(6A) | 108.7 |
| C(5)-C(6)-H(6B) | 108.7 |
| C(5)-C(6)-C(7) | 114.29(11) |
| H(6A)-C(6)-H(6B) | 107.6 |
| C(7)-C(6)-H(6A) | 108.7 |
| C(7)-C(6)-H(6B) | 108.7 |
| C(1)-C(7)-C(6) | 112.66(10) |
| C(1)-C(7)-H(7A) | 109.1 |
| C(1)-C(7)-H(7B) | 109.1 |
| C(6)-C(7)-H(7A) | 109.1 |
| C(6)-C(7)-H(7B) | 109.1 |
| H(7A)-C(7)-H(7B) | 107.8 |
| C(1)-C(8)-C(9) | 122.91(11) |
| C(1)-C(8)-C(10) | 124.41(11) |
| C(10)-C(8)-C(9) | 112.66(10) |
| O(1)-C(9)-C(8) | 112.27(10) |
| O(1)-C(9)-H(9A) | 109.1 |
| O(1)-C(9)-H(9B) | 109.1 |
| C(8)-C(9)-H(9A) | 109.1 |

| | |
|---|---|
| C(8)-C(9)-H(9B) | 109.1 |
| H(9A)-C(9)-H(9B) | 107.9 |
| O(2)-C(10)-C(8) | 112.23(10) |
| O(2)-C(10)-H(10A) | 109.2 |
| O(2)-C(10)-H(10B) | 109.2 |
| C(8)-C(10)-H(10A) | 109.2 |
| C(8)-C(10)-H(10B) | 109.2 |
| H(10A)-C(10)-H(10B) | 107.9 |
| C(2)-C(11)-H(11A) | 109.2 |
| C(2)-C(11)-H(11B) | 109.2 |
| H(11A)-C(11)-H(11B) | 107.9 |
| C(12)-C(11)-C(2) | 112.2(3) |
| C(12)-C(11)-H(11A) | 109.2 |
| C(12)-C(11)-H(11B) | 109.2 |
| C(11)-C(12)-H(12) | 118.9 |
| C(13)-C(12)-C(11) | 122.2(2) |
| C(13)-C(12)-H(12) | 118.9 |
| C(12)-C(13)-H(13) | 116.0 |
| C(12)-C(13)-C(14) | 128.0(2) |
| C(14)-C(13)-H(13) | 116.0 |
| C(15)-C(14)-C(13) | 118.3(3) |
| C(15)-C(14)-C(19) | 118.3(3) |
| C(19)-C(14)-C(13) | 123.5(3) |
| C(14)-C(15)-H(15) | 119.0 |
| C(14)-C(15)-C(16) | 121.9(3) |
| C(16)-C(15)-H(15) | 119.0 |
| C(15)-C(16)-H(16) | 119.2 |
| C(15)-C(16)-C(17) | 121.5(4) |
| C(17)-C(16)-H(16) | 119.2 |
| C(16)-C(17)-H(17) | 121.6 |
| C(16)-C(17)-C(18) | 116.7(4) |
| C(18)-C(17)-H(17) | 121.6 |
| C(17)-C(18)-H(18) | 119.5 |
| C(19)-C(18)-C(17) | 121.0(4) |
| C(19)-C(18)-H(18) | 119.5 |
| C(14)-C(19)-C(18) | 120.5(3) |

| | |
|---|---|
| C(14)-C(19)-H(19) | 119.8 |
| C(18)-C(19)-H(19) | 119.8 |
| C(2)-C(11A)-H(11C) | 107.2 |
| C(2)-C(11A)-H(11D) | 107.2 |
| C(2)-C(11A)-C(12A) | 120.5(11) |
| H(11C)-C(11A)-H(11D) | 106.8 |
| C(12A)-C(11A)-H(11C) | 107.2 |
| C(12A)-C(11A)-H(11D) | 107.2 |
| C(11A)-C(12A)-H(12A) | 116.2 |
| C(13A)-C(12A)-C(11A) | 127.6(9) |
| C(13A)-C(12A)-H(12A) | 116.2 |
| C(12A)-C(13A)-H(13A) | 117.3 |
| C(12A)-C(13A)-C(14A) | 125.5(9) |
| C(14A)-C(13A)-H(13A) | 117.3 |
| C(15A)-C(14A)-C(13A) | 127.6(11) |
| C(19A)-C(14A)-C(13A) | 117.0(9) |
| C(19A)-C(14A)-C(15A) | 115.4(9) |
| C(14A)-C(15A)-H(15A) | 120.3 |
| C(16A)-C(15A)-C(14A) | 119.4(10) |
| C(16A)-C(15A)-H(15A) | 120.3 |
| C(15A)-C(16A)-H(16A) | 122.8 |
| C(17A)-C(16A)-C(15A) | 114.4(18) |
| C(17A)-C(16A)-H(16A) | 122.8 |
| C(16A)-C(17A)-H(17A) | 115.1 |
| C(18A)-C(17A)-C(16A) | 130(3) |
| C(18A)-C(17A)-H(17A) | 115.1 |
| C(17A)-C(18A)-H(18A) | 121.7 |
| C(17A)-C(18A)-C(19A) | 116.5(17) |
| C(19A)-C(18A)-H(18A) | 121.7 |
| C(14A)-C(19A)-H(19A) | 117.8 |
| C(18A)-C(19A)-C(14A) | 124.4(11) |
| C(18A)-C(19A)-H(19A) | 117.8 |

***Table A2.10*** *Anisotropic displacement parameters (Åx10$^4$) for* ***S5aa****. The anisotropic displacement factor exponent takes the form* $-2\pi^2[h^2a^{*2}U^{11} + ... +2\ h\ k\ a^*\ b^*U^{12}]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| O(1) | 172(4) | 230(4) | 292(4) | 75(4) | -21(4) | 6(3) |
| O(2) | 173(4) | 331(5) | 289(5) | 115(4) | 15(4) | -10(4) |
| C(1) | 175(5) | 219(6) | 162(5) | 19(4) | 8(4) | 23(5) |
| C(2) | 308(7) | 249(6) | 164(5) | 9(5) | -43(5) | 76(5) |
| C(3) | 542(10) | 269(7) | 186(6) | 19(5) | -72(6) | 135(7) |
| C(4) | 369(8) | 290(7) | 232(6) | -21(5) | -40(6) | 122(6) |
| C(5) | 343(7) | 220(6) | 227(6) | 15(5) | 68(6) | -12(6) |
| C(6) | 238(6) | 254(6) | 279(6) | 15(5) | -9(5) | -67(5) |
| C(7) | 189(6) | 230(6) | 305(6) | 53(5) | 47(5) | -20(5) |
| C(8) | 166(6) | 211(6) | 161(5) | 10(4) | -4(5) | 3(5) |
| C(9) | 220(6) | 216(6) | 198(6) | 37(4) | -40(5) | -3(5) |
| C(10) | 190(6) | 225(6) | 238(6) | 3(5) | -7(5) | -27(5) |
| C(11) | 340(20) | 275(11) | 130(13) | -19(10) | 32(13) | 83(12) |
| C(12) | 381(11) | 220(9) | 163(8) | -7(6) | -23(7) | -7(9) |
| C(13) | 335(11) | 196(10) | 196(10) | -24(8) | 23(9) | 16(8) |
| C(14) | 301(12) | 217(14) | 179(13) | -48(10) | 27(11) | 12(12) |
| C(15) | 287(11) | 446(19) | 215(11) | 25(13) | 44(8) | -46(15) |
| C(16) | 284(14) | 590(20) | 284(12) | 10(20) | 20(10) | -146(19) |
| C(17) | 314(15) | 490(30) | 228(16) | -88(19) | -10(10) | -106(17) |
| C(18) | 550(20) | 312(17) | 250(20) | -34(15) | -60(20) | -42(15) |
| C(19) | 457(14) | 261(16) | 252(18) | -39(14) | -111(17) | -76(13) |
| C(11A) | 310(80) | 680(90) | 270(50) | 240(50) | 220(50) | 280(60) |
| C(12A) | 310(40) | 210(40) | 260(40) | -60(30) | 60(30) | -70(30) |
| C(13A) | 220(30) | 260(40) | 230(40) | -60(30) | 20(30) | -20(30) |
| C(14A) | 230(30) | 110(50) | 100(50) | 20(30) | -30(40) | -50(40) |
| C(15A) | 670(80) | 170(50) | 170(40) | 70(40) | 100(40) | 80(50) |
| C(16A) | 260(50) | 320(60) | 300(60) | -130(60) | 80(40) | -110(50) |
| C(17A) | 770(110) | 430(110) | 220(70) | -200(80) | 120(60) | -150(80) |
| C(18A) | 560(90) | 260(60) | 190(60) | -60(50) | 220(70) | -10(50) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C(19A) | 230(50) | 160(40) | 250(50) | -110(40) | 30(50) | -70(30) |

***Table A2.11*** *Hydrogen coordinates (x $10^4$) and isotropic displacement parameters ($Å^2$ x$10^3$) for* ***S5aa****.*

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1) | 11102 | 3117 | 4581 | 35 |
| H(2) | 4453 | 3262 | 4815 | 40 |
| H(2A) | 4760 | 6077 | 3773 | 29 |
| H(2B) | 4766 | 6175 | 3822 | 29 |
| H(3A) | 4617 | 8447 | 3500 | 40 |
| H(3B) | 7174 | 8673 | 3541 | 40 |
| H(4A) | 4637 | 9873 | 4115 | 36 |
| H(4B) | 4844 | 8300 | 4363 | 36 |
| H(5A) | 8525 | 10093 | 4146 | 32 |
| H(5B) | 7375 | 10152 | 4631 | 32 |
| H(6A) | 8476 | 7766 | 4801 | 31 |
| H(6B) | 10556 | 8681 | 4641 | 31 |
| H(7A) | 10085 | 7541 | 3890 | 29 |
| H(7B) | 10894 | 6439 | 4281 | 29 |
| H(9A) | 9852 | 5155 | 4787 | 25 |
| H(9B) | 7819 | 4318 | 5006 | 25 |
| H(10A) | 4927 | 3938 | 3942 | 26 |
| H(10B) | 6237 | 2689 | 4214 | 26 |
| H(11A) | 8452 | 6413 | 3171 | 30 |
| H(11B) | 7262 | 4860 | 3260 | 30 |
| H(12) | 5630 | 7187 | 2705 | 31 |
| H(13) | 3823 | 4452 | 2923 | 29 |
| H(15) | 522 | 3763 | 2596 | 38 |
| H(16) | -2160 | 3933 | 2055 | 46 |
| H(17) | -2106 | 5820 | 1503 | 41 |
| H(18) | 901 | 7479 | 1503 | 45 |

| | | | | |
|---|---|---|---|---|
| H(19) | 3615 | 7269 | 2053 | 39 |
| H(11C) | 7024 | 4783 | 3363 | 50 |
| H(11D) | 7625 | 6313 | 3125 | 50 |
| H(12A) | 3276 | 5059 | 3071 | 31 |
| H(13A) | 5551 | 6561 | 2415 | 29 |
| H(15A) | 465 | 4438 | 2579 | 41 |
| H(16A) | -2533 | 4673 | 2075 | 35 |
| H(17A) | -2083 | 6235 | 1473 | 56 |
| H(18A) | 686 | 7555 | 1327 | 41 |
| H(19A) | 3543 | 7451 | 1802 | 26 |

***Table A2.12*** *Torsion angles [°] for* ***S5aa****.*

| | |
|---|---|
| C(1)-C(2)-C(3)-C(4) | -43.6(2) |
| C(1)-C(2)-C(11)-C(12) | 174.6(2) |
| C(1)-C(2)-C(11A)-C(12A) | 151.8(11) |
| C(1)-C(8)-C(9)-O(1) | -119.85(13) |
| C(1)-C(8)-C(10)-O(2) | -110.60(13) |
| C(2)-C(1)-C(7)-C(6) | 90.17(13) |
| C(2)-C(1)-C(8)-C(9) | -173.18(11) |
| C(2)-C(1)-C(8)-C(10) | 5.28(19) |
| C(2)-C(3)-C(4)-C(5) | 90.06(17) |
| C(2)-C(11)-C(12)-C(13) | -90.1(3) |
| C(2)-C(11A)-C(12A)-C(13A) | 119.6(12) |
| C(3)-C(2)-C(11)-C(12) | -60.0(3) |
| C(3)-C(2)-C(11A)-C(12A) | -71.7(15) |
| C(3)-C(4)-C(5)-C(6) | -69.81(15) |
| C(4)-C(5)-C(6)-C(7) | 52.74(15) |
| C(5)-C(6)-C(7)-C(1) | -73.65(14) |
| C(7)-C(1)-C(2)-C(3) | -36.48(17) |
| C(7)-C(1)-C(2)-C(11) | 86.7(2) |
| C(7)-C(1)-C(2)-C(11A) | 101.4(8) |
| C(7)-C(1)-C(8)-C(9) | 5.86(18) |
| C(7)-C(1)-C(8)-C(10) | -175.69(11) |
| C(8)-C(1)-C(2)-C(3) | 142.60(14) |

| | |
|---|---|
| C(8)-C(1)-C(2)-C(11) | -94.2(2) |
| C(8)-C(1)-C(2)-C(11A) | -79.5(8) |
| C(8)-C(1)-C(7)-C(6) | -88.92(15) |
| C(9)-C(8)-C(10)-O(2) | 67.99(13) |
| C(10)-C(8)-C(9)-O(1) | 61.53(13) |
| C(11)-C(2)-C(3)-C(4) | -166.9(2) |
| C(11)-C(12)-C(13)-C(14) | -179.2(2) |
| C(12)-C(13)-C(14)-C(15) | -169.1(2) |
| C(12)-C(13)-C(14)-C(19) | 11.5(4) |
| C(13)-C(14)-C(15)-C(16) | 178.8(3) |
| C(13)-C(14)-C(19)-C(18) | -178.5(3) |
| C(14)-C(15)-C(16)-C(17) | 0.0(6) |
| C(15)-C(14)-C(19)-C(18) | 2.1(5) |
| C(15)-C(16)-C(17)-C(18) | 1.6(7) |
| C(16)-C(17)-C(18)-C(19) | -1.3(8) |
| C(17)-C(18)-C(19)-C(14) | -0.5(7) |
| C(19)-C(14)-C(15)-C(16) | -1.8(5) |
| C(11A)-C(2)-C(3)-C(4) | 179.2(8) |
| C(11A)-C(12A)-C(13A)-C(14A) | -175.2(11) |
| C(12A)-C(13A)-C(14A)-C(15A) | -13.2(14) |
| C(12A)-C(13A)-C(14A)-C(19A) | 165.1(8) |
| C(13A)-C(14A)-C(15A)-C(16A) | 175.8(10) |
| C(13A)-C(14A)-C(19A)-C(18A) | -177.1(11) |
| C(14A)-C(15A)-C(16A)-C(17A) | 2.3(19) |
| C(15A)-C(14A)-C(19A)-C(18A) | 1.4(15) |
| C(15A)-C(16A)-C(17A)-C(18A) | -1(3) |
| C(16A)-C(17A)-C(18A)-C(19A) | 0(3) |
| C(17A)-C(18A)-C(19A)-C(14A) | 0(2) |
| C(19A)-C(14A)-C(15A)-C(16A) | -2.5(15) |

***Table A2.13*** *Hydrogen bonds for* ***S5aa*** *[Å and °]*

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| O(1)-H(1)...O(2)#1 | 0.84 | 1.86 | 2.6640(13) | 160.0 |
| O(2)-H(2)...O(1)#2 | 0.84 | 1.89 | 2.7121(13) | 165.9 |

Symmetry transformations used to generate equivalent atoms:
#1 x+1,y,z #2 x-1/2,-y+1/2,-z+1

# *CHAPTER 2*

## *Enantioselective Pd-Catalyzed Decarboxylative Allylic Alkylation of Thiopyranones. Access to Acyclic, Stereogenic α-Quaternary Stereocenters*[†]

### 2.1 INTRODUCTION

The enantioselective construction of all-carbon quaternary stereogenic centers, particularly acyclic ones, is a significant challenge in organic synthesis.[1] Among the most reliable methods available for forming all-carbon quaternary stereocenters, such as conjugate addition and sigmatropic rearrangements, palladium-catalyzed decarboxylative allylic alkylation has become a widely adopted and studied transformation owing to its mild nature, broad scope, and versatility of the introduced allyl group for further synthetic manipulations.[2] The mild nature of this transformation was hypothesized to allow access to α-quaternary 4-thiopyranones, which are troublesome to access through standard enolate chemistry owing to the β-disposed sulfur and the propensity for forming ring-opened sulfur alkylation products.[3] Despite these disadvantages, such heterocyclic ketones have been shown to undergo aldol[4] and Mannich[5] reactions, although degradation of the products by retro-aldol processes during purification is common.[6] The

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[†]This research was performed in collaboration with Dr. Scott Virgil and Dr. Michael Bartberger. Portions of this chapter have been reproduced with permission from Alexy, E. J.; Virgil, S. C.; Bartberger, M. D.; Stoltz, B. M. *Org. Lett.* **2017**, *19*, 5007–5009. © 2017 American Chemical Society.

thiopyranone motif has also been shown to tolerate amine–thiourea dual catalysis for enantioselective conjugate addition forming an α-quaternary 4-thiopyranone in an enantioenriched fashion.[7] The value of this motif has been demonstrated by its use as a building block in medicinal chemistry applications,[8] and therefore new methods for constructing chiral, enantioenriched thiopyranone derivatives would allow access to new chemical space.

Our approach would entail a palladium-catalyzed decarboxylative allylic alkylation of a thiopyranone allyl β-ketoester (**15a**, Table 2.1), which would allow access to a diverse range of α-quaternary 4-thiopyranones in an enantioselective fashion. Indeed, a general strategy that has been reported to access alkylated 4-thiopyranones is by first α–functionalization of the corresponding β-ketoester followed by decarboxylation[9] or tin hydride mediated addition of alkyl and aryl halides.[10]

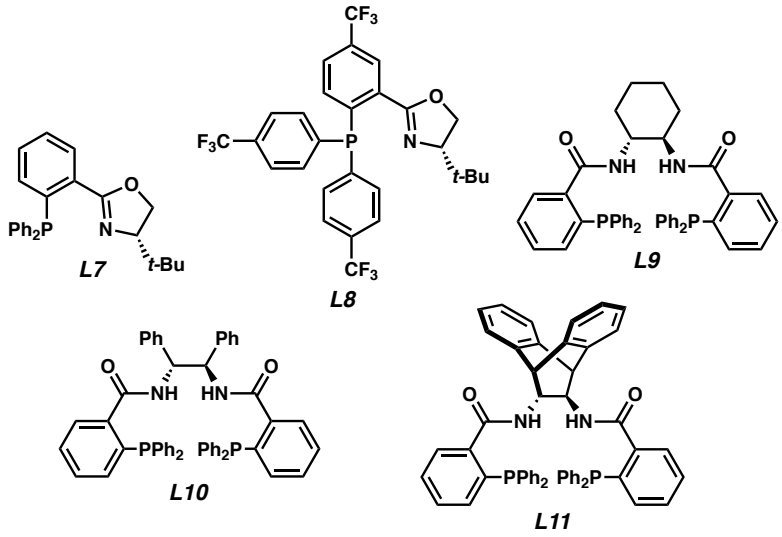
In addition to accessing a synthetically challenging quaternary stereocenter, we also envisioned utilizing the sulfur as a removable handle to access acyclic, all-carbon quaternary stereocenters,[1c] by treatment with Raney nickel. Exploiting a rigid, cyclic thioether to access stereodefined acyclic systems is a valuable strategy utilized in organic synthesis to access polypropionates, most notably Woodward's synthesis of Erythromycin,[11] with this chemistry later expanded upon by other research groups.[12] By using a cyclic system, the issue of controlling tri- and tetrasubstituted enolate geometry, a difficult task in acyclic molecules, is circumvented. While certain acyclic tri-substituted enolates can be formed with a high degree of stereochemical fidelity (e.g. oxizolidinones), the methodology to produce tetra-substituted enolates en route to all-carbon quaternary stereocenters is less developed. A notable example comes from the

Marek lab, in which a stereoselective carbometalation of alkynes is exploited en route to a number of different motifs including homoallylic alcohols[13] and aldol adducts.[14] In fact, only a couple reports of forming enantioenriched acyclic α-quaternary ketones exist in the literature.[15]

## 2.2 REACTION OPTIMIZATION

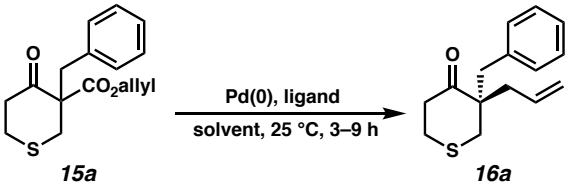
We initiated our investigations with α-benzyl β-ketoester **15a** and phosphinooxazoline (PHOX) ligands **L7** and the electronically deficient **L8**, used previously by our group for asymmetric allylic alkylation (Table 2.1).[2a] Initial reactions employed 5 mol% $Pd(dba)_2$ and 6 mol% ligand in THF. The presence of the Lewis basic sulfur was envisioned to be trivial owing to prior examples of such functionalities (i.e. thioethers) being tolerated under analogous conditions.[2a] Unfortunately, in this case both PHOX ligands performed poorly, producing either no reaction with **L7** (entry 1) or low conversion with **L8** (entry 2), albeit in moderate enantiomeric excess.

***Figure 2.1*** *Representative Ligands Examined.*



Bisphosphine ligands **L9** and **L10**[2b] were found to perform equally poorly, providing very low conversion to product (>5%) and enantiomeric excesses of 24 and 66%, respectively (entries 3 and 4). On the other hand, anthracene diamine deriviced bisphosphine **L11** was found to affect the desired transformation in 85% isolated yield and 69% enantiomeric excess (entry 5). Despite obtaining a lower enantiomeric excess with **L11** compared to **L8**, the improved reactivity was promising and further optimization efforts focused on **L11** (36 additional ligands were examined, see experimental section for details).

**Table 2.1** Optimization of Alkylation Conditions.[a]




*15a* *16a*

| entry | Pd source | ligand | solvent | *yield*[b] | ee[c,d] |
|---|---|---|---|---|---|
| 1 | $Pd(dba)_2$ | (*S*)-L7 | THF | NR | - |
| 2 | $Pd(dba)_2$ | (*S*)-L8 | THF | 24 | –78 |
| 3 | $Pd(dba)_2$ | (*R,R*)-L9 | THF | <5 | 24 |
| 4 | $Pd(dba)_2$ | (*R,R*)-L10 | THF | <5 | 66 |
| 5 | $Pd(dba)_2$ | (*R,R*)-L11 | THF | 85 | 69 |
| 6 | $Pd(dba)_2$ | (*R,R*)-L11 | dioxane | –[e] | 54 |
| 7 | $Pd(dba)_2$ | (*R,R*)-L11 | EtOAc | –[e] | 73 |
| 8 | $Pd(dba)_2$ | (*R,R*)-L11 | toluene | –[e] | 83 |
| 9 | $Pd(dba)_2$ | (*R,R*)-L11 | benzene | –[e] | 78 |
| 10 | $Pd(dba)_2$ | (*R,R*)-L11 | hexane/toluene (2:1) | –[e] | 80 |
| 11 | $Pd(dba)_2$ | (*R,R*)-L11 | TBME | 78 | 87 |
| 12 | $[PdCl(allyl)]_2$ | (*R,R*)-L11 | TBME | –[e] | 90 |
| 13 | $Pd(dmdba)_2$ | (*R,R*)-L11 | TBME | –[e] | 91 |
| 14 | $Pd_2(pmdba)_3$ | (*R,R*)-L11 | TBME | 90 | 93 |
| 15[f] | $Pd_2(pmdba)_3$ | (*R,R*)-L11 | TBME | 92 | 94 |

[a] Conditions: 0.1 mmol **15a,** 2.5 mol % $Pd_2(dba)_3$, 6 mol % ligand, 1 mL solvent. [b] Yield of isolated product. [c] Determined by chiral SFC. [d] Absolute configuration determined by vibrational circular dichroism. [e] Conversion not monitored. [f] Reaction performed with 0.2 mmol **15a**, 1.0 mol % $Pd_2(pmdba)_3$, 2.4 mol % ligand and 2 mL solvent.

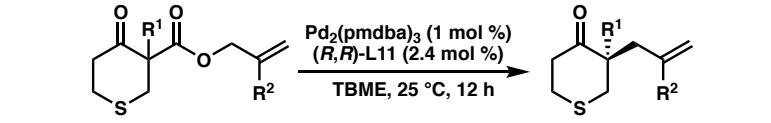
With the ideal ligand identified, the remaining reaction parameters were examined. More polar solvents such as dioxane and EtOAc were found to give decreased enantiomeric excesses of 54% and 73%, respectively (entries 6 and 7). The use of toluene resulted in an increased enantiomeric excess of 83% (entry 8), while benzene and a 2:1 mixture of hexane/toluene were found to give slightly lower levels of selectivity (entries 9 and 10). TBME provided an elevated enantiomeric excess of 87% (entry 11) and was advanced further as the solvent of choice. Additional improvements in enantioselectivity were achieved with different palladium sources (entries 12–14), with $Pd_2(pmdba)_3$ providing the best result and furnishing the α-quaternary thiopyranone in 90% isolated yield and 93% enantiomeric excess (entry 14). Lastly, it was found that lowering the loading of catalyst and ligand by 2.5 times resulted in no loss of either yield or enantiomeric excess, with only a modest increase in reaction time from 3 h to 9 h (entry 15), therefore this lowered loading was used for the remainder of the experiments. The absolute stereochemistry of **16a** was determined via by vibrational circular dichroism (see SI for details).

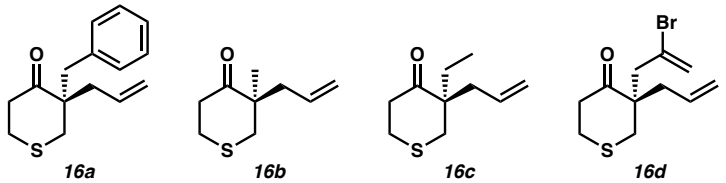
## 2.3 INVESTIGATION OF REACTION SCOPE

With the optimized conditions identified, a variety of different α-substituents were examined in order to evaluate the scope of the chemistry (Scheme 2.1).[16] Simple alkyl groups,[17] such as methyl (**16b**) and ethyl (**16c**), provided the desired product in moderate yields and moderate to excellent enantiomeric excess. Substituted olefins such as vinyl bromide **16d** and prenylated ketone **16e** were tolerated, however only moderate enantiomeric excess was obtained. An ester (**16f**) and an α,β-unsaturated ethyl ester

(**16g**) provided the desired products, again with only moderate selectivity. Alkyl substitution on the 2-position of the allyl was not well tolerated in the reaction, providing the product (**16h**) in low yield. Lastly, a variety of different benzyl derivatives performed well in the reaction, furnishing the corresponding alkylated products with good to excellent yields and excellent enantioselectivities (**16i–16l**).

**Scheme 2.1** Substrate Scope.[a]



***16a*** 92% yield 94% ee



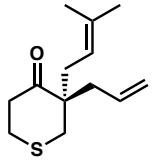
***16b*** 74% yield 93% ee



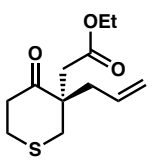
***16c*** 70% yield 82% ee



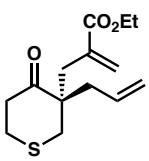

***16d*** 82% yield 50% ee



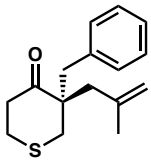
***16e*** 76% yield 78% ee



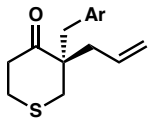

***16f*** 91% yield 69% ee




***16g*** 87% yield 66% ee



***16h*** 29% yield 80% ee




| Ar | % yield | % ee |
|---|---|---|
| 4-$MeC_6H_4$ (*16i*) | 86 | 90 |
| 4-$BrC_6H_4$ (*16j*) | 91 | 91 |
| 4-$FC_6H_4$ (*16k*) | 83 | 91 |
| 4-$CF_3C_6H_4$ (*16l*) | 80 | 93 |

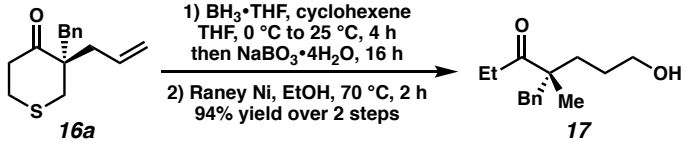
[a] Conditions: 0.2 mmol β-ketoester, 1.0 mol % $Pd_2(pmdba)_3$, 2.4 mol % ligand, 2 mL TBME.

## 2.4 SYNTHESIS OF ACYCLIC KETONE

With the scope established, we sought to examine our hypothesis pertaining to the formation of acyclic all-carbon quaternary stereocenters through reductive cleavage of the thioether (Scheme 2.2). When alkylation product **16a** was treated directly with Raney nickel in methanol at reflux, the desired desulfurization occurred, however concomitant

olefin hydrogenation was also observed. All attempts to prevent olefin hydrogenation while still achieving the desired desulfurization failed. To circumvent this issue, the allyl group can be functionalized prior to the desulfurization step, exemplified by the hydroboration-oxidation of **16a** prior to treatment with Raney nickel, providing acyclic ketone **17** with a synthetic handle for further manipulations.

**Scheme 2.2** Transformation of Alkylation Product to an Acyclic Ketone.[a]




## 2.5 CONCLUSIONS

In summary, we have developed an enantioselective Pd-catalyzed decarboxylative allylic alkylation of thiopyranones. Conditions were identified that tolerate the presence of the Lewis basic thioether, providing alkylated products in moderate to excellent levels of selectivity, with no issues of ring-opening β-elimination. While the cyclic products formed have multiple handles for further derivatization, the thioether can be reduced to afford desulfurized molecules containing an acyclic, all-carbon quaternary stereocenter. We envision that such acyclic α-quaternary ketones, as well as the parent thiopyranones, will find use in synthesis and medicinal chemistry.

## 2.6 EXPERIMENTAL SECTION

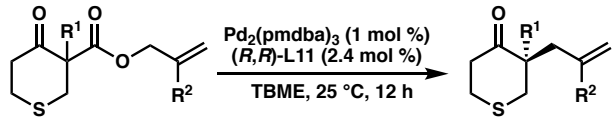
### 2.6.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 μm) was used for flash chromatography. $^1$H NMR spectra were recorded on Varian Inova 500 MHz and Bruker 400 MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm). $^{13}$C NMR spectra were recorded on a Varian Inova 500 MHz spectrometer (125 MHz) and Bruker 400 MHz spectrometers (100 MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm). Data for $^1$H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet, app = apparent. Data for $^{13}$C NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer or Nicolet 6700 FTIR spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption ($cm^{-1}$). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell and are reported as: $[\alpha]_D^T$ (concentration in 10 mg/1 mL, solvent). Analytical SFC was performed with a Mettler SFC supercritical $CO_2$ analytical

chromatography system utilizing Chiralpak (AD-H, AS-H or IC) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+), or obtained from Caltech mass spectrometry laboratory. Ligands **(*S*)-L7**, **(*S*)-L8**, **(*R,R*)-L10**, and **(*R,R*)-L11** and substrate **15a** were prepared by known methods.

## 2.6.2 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

### 2.6.2.1 General Procedure for Pd-Catalyzed Allylic Alkylation Reactions



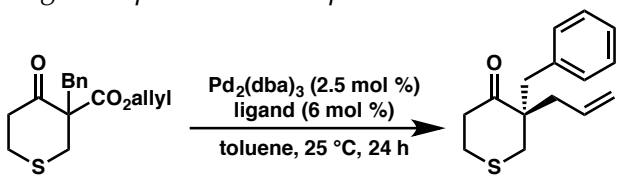

In a nitrogen-filled glovebox, $Pd_2(pmdba)_3$ (1.0 mol %, 2.2 mg) and **(*R,R*)-*L*11** (2.4 mol %, 3.9 mg) were added to a 1 dram vial followed by 1.0 mL of TBME. The resulting mixture was stirred at 25 °C for 30 minutes at which time a solution of β-ketoester substrate (0.2 mmol) in 1.0 mL TBME was added. The vial was then sealed with a Teflon-lined cap and electrical tape, removed from the glovebox, and stirred at 25 °C for 12 h. The crude reaction mixture was filtered through Celite®, and the Celite® rinsed with $Et_2O$. The crude product was purified by silica gel flash chromatography to provide the desired alkylation product.

### 2.6.2.2 Procedure for Preparatory Scale Allylic Alkylation

In a nitrogen-filled glovebox, $Pd_2(pmdba)_3$ (1.0 mol %, 33.0 mg) and **(*R,R*)-*L*11** (2.4 mol %, 58.5 mg) were dissolved in 15.0 mL of TBME, and the resulting mixture was stirred at 25 °C. After 30 minutes, a solution of β-ketoester substrate **15a** (3.0 mmol, 871.1 mg)

in 15.0 mL TBME was added, and the reaction flask sealed and removed from the glovebox. After stirring at 25 °C for 12 h, the crude reaction mixture was filtered through Celite®, and the Celite® rinsed with $Et_2O$. The crude product was purified by silica gel flash chromatography (10% $Et_2O$ in hexanes) to provide **16a** as a colorless oil (649.0 mg, 88% yield): 91% ee.

***Table 2.2*** *Additional ligand optimization experiments*

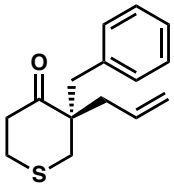



| entry | ligand | e.e |
|---|---|---|
| 1 | (*R*)-BINAP | 9 |
| 2 | (*S*)-DTBM-BIPHEP | 22 |
| 3 | (*R*)-BTFM-Garphos | NR |
| 4 | (*S*)-C3-TunePhos | 19 |
| 5 | (*R*)-SEGPHOS | –17 |
| 6 | (*R*)-bis(Diisopropylphosphino)-SEGPHOS | low conv |
| 7 | (*R*)-P-Phos | –16 |
| 8 | (*R*)-PhanePhos | –7 |
| 9 | (*R*)-SDP | –3 |
| 10 | (*S,S,S*)-(-)-Ph-SKP | 25 |
| 11 | (*R,R*)-Chiraphos | low conv |
| 12 | (*S,S*)-BDPP | 27 |
| 13 | catASium D(*R*) | 28 |
| 14 | (*S,S*)-BPPM | 12 |
| 15 | (*R,R*)-Norphos | 10 |
| 16 | (*S,S*)-Et-BPE | 23 |
| 17 | R,R-$Me_2$NXyl$^F$R | NR |
| 18 | (*S,S*)-Me-Ferrocelane | –1 |
| 19 | (*R,R*)-Me-DuPhos | low conv |
| 20 | (*S,S*)-Et-Ferrotane | –6 |
| 21 | (1*R*,1'*R*,2*S*,2'*S*)– DuanPhos | 29 |
| 22 | (*S*)–BINAPINE | –15 |

***Table 2.2*** *Additional ligand optimization experiments (continued)*

| entry | ligand | e.e |
|---|---|---|
| 23 | (*R*)-(*S*)-Ph, Cy Josiphos (J-001-1) | –6 |
| 24 | (*R*)-(*S*)-$MeOMe_2C_6H_2$, Cy Josiphos (SL-J007-1) | –13.6 |
| 25 | (*R*)-(*R*)-Ph, Ph Walphos (W-002-1) | 10 |
| 26 | (*R*)-(*R*)-Ph, $Xyl^F$ Walphos (W-001-1) | low conv |
| 27 | (*R*)-(*R*)-Ph, Norbornyl Walphos (W-022-1) | 8 |
| 28 | (*S*)-(*R*)-Ph Mandyphos (M-001-2) | 19 |
| 29 | (*S*)-(*R*)-$Xyl^F$ Mandyphos (M-003-2) | NR |
| 30 | (*R*)-(*R*)-Ph, Ph Taniaphos (T-001-1) | –17 |
| 31 | (*R*,*R*)–ChenPHOS | 6 |
| 32 | (*S*)-Quinap | low conv |
| 33 | (*S*,*S*)-CpFe(4-$^i$Pr-oxazolinyl)$C_5H_3PPh_2$ | 38 |
| 34 | (*R*)-Difluorphos | –16 |
| 35 | (*R*)-Synphos | –12 |
| 36 | Josiphos (SL-J212-1) | 1 |

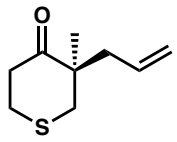
### 2.6.2.3 Spectroscopic Data for the Pd-Catalyzed Allylic Alkylation of Thiopyranones




**(*S*)-3-allyl-3-benzyltetrahydro-4*H*-thiopyran-4-one (16a)**

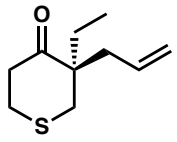
Purified by column chromatography (10% $Et_2O$ in hexanes) to provide a colorless oil (45.2 mg, 92% yield); 94% ee, $[\alpha]_D^{25}$ +11.0 (*c* 1.05, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.32–7.19 (m, 3H), 7.17–7.10 (m, 2H), 5.72 (dddd, *J* = 16.9, 10.3, 7.9, 6.7 Hz, 1H), 5.17–5.07 (m, 2H), 3.14 (d, *J* = 13.8 Hz, 1H), 3.02 (d, *J* = 13.8 Hz, 1H), 2.95–2.85 (m, 2H), 2.83–2.69 (m, 4H), 2.56 (ddt, *J* = 14.4, 7.8, 1.2 Hz, 1H), 2.47 (ddt, *J* = 14.4, 6.7, 1.4 Hz, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 211.1, 136.7, 133.2, 130.8, 128.3, 126.8, 119.2,

54.0, 41.6, 40.2, 38.8, 38.0, 29.7; IR (Neat Film, NaCl) 3062, 3028, 2976, 2946, 2913, 1703, 1638, 1604, 1582, 1495, 1453, 1434, 1419, 1312, 1274, 1223, 1129, 1086, 1031, 988, 965, 918, 806, 750, 726, 703 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{15}H_{19}OS$ $[M+H]^+$: 247.1157, found 247.1168; SFC Conditions: 15% IPA, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, $t_R$ (min): minor = 2.87, major = 3.48.



**(*R*)-3-allyl-3-methyltetrahydro-4*H*-thiopyran-4-one (16b)**

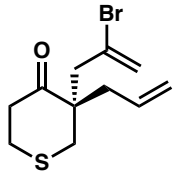
Purified by column chromatography (10% $Et_2O$ in hexanes) to provide a colorless oil (25.1 mg, 74% yield); 93% ee, $[\alpha]_D^{25}$ +33.6 (*c* 1.25, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 5.66 (ddt, *J* = 17.0, 10.2, 7.4 Hz, 1H), 5.14–5.06 (m, 2H), 2.96–2.83 (m, 2H), 2.81–2.61 (m, 5H), 2.45–2.37 (m, 1H), 1.19 (s, 3H); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 211.9, 132.9, 119.0, 50.0, 41.3, 41.2, 40.9, 30.6, 22.0; IR (Neat Film, NaCl) 3075, 2976, 2929, 2907, 1703, 1638, 1452, 1432, 1420, 1376, 1324, 1270, 1221, 1133, 1090, 996, 976, 919, 811 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_9H_{14}OS$ $[M+H]^{\bullet}$: 170.0765, found 170.0790; SFC Conditions: 2% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 5.09, major = 6.37.



**(*R*)-3-allyl-3-ethyltetrahydro-4*H*-thiopyran-4-one (16c)**

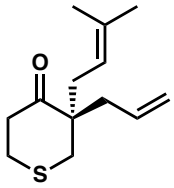
Purified by column chromatography (5% $Et_2O$ in hexanes) to provide a colorless oil (26.0 mg, 70% yield); 82% ee,* $[\alpha]_D^{25}$ +18.3 (*c* 0.85, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ

5.71–5.56 (m, 1H), 5.08 (dddd, *J* = 13.3, 3.7, 2.2, 1.0 Hz, 2H), 2.94–2.82 (m, 2H), 2.81 (dd, *J* = 14.1, 1.0 Hz, 1H), 2.78–2.67 (m, 2H), 2.69–2.59 (m, 1H), 2.54 (ddt, *J* = 14.3, 7.8, 1.1 Hz, 1H), 2.42–2.33 (m, 1H), 2.10 (dq, *J* = 14.9, 7.5 Hz, 1H), 1.66–1.54 (m, 1H), 0.80 (t, *J* = 7.5 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 211.6, 133.3, 118.8, 53.1, 41.3, 39.4, 37.9, 30.4, 26.9, 7.9; IR (Neat Film, NaCl) 3385, 3075, 2966, 2942, 1702, 1639, 1460, 1433, 1420, 1384, 1339, 1313, 1279, 1244, 1104, 1082, 996, 918, 812, 782, 723, 673 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{10}H_{16}OS$ $[M+H]^{\bullet}$: 184.0922, found 184.0941; SFC Conditions*: 20% IPA, 2.5 mL/min, Chiralpak IC column, λ = 210 nm, $t_R$ (min): minor = 7.87, major = 8.61. *ee determined following cross-metathesis with methyl acrylate.



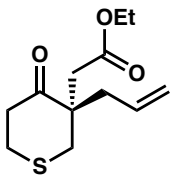

**(*S*)-3-allyl-3-(2-bromoallyl)tetrahydro-4*H*-thiopyran-4-one (16d)**

Purified by column chromatography (5% $Et_2O$ in hexanes) to provide a colorless oil (45.2 mg, 82% yield); 50% ee, $[\alpha]_D^{25}$ +6.2 (*c* 2.26, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 5.71–5.59 (m, 2H), 5.58 (d, *J* = 1.7 Hz, 1H), 5.16–5.07 (m, 2H), 3.17 (dd, *J* = 15.3, 0.9 Hz, 1H), 2.96 (d, *J* = 1.0 Hz, 1H), 2.94–2.84 (m, 5H), 2.81–2.68 (m, 2H), 2.57 (ddt, *J* = 14.4, 7.0, 1.3 Hz, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 210.2, 132.5, 128.3, 122.0, 119.7, 53.1, 45.1, 41.7, 39.3, 38.5, 30.4; IR (Neat Film, NaCl) 3387, 3075, 3004, 2976, 2947, 2911, 2836, 1703, 1637, 1623, 1431, 1420, 1332, 1311, 1275, 1221, 1136, 1105, 993, 966, 920, 897, 809, 739, 673, 618 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{11}H_{16}BrOS$ $[M+H]^+$: 275.0105, found 275.0110; SFC Conditions: 1% IPA, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, $t_R$ (min): minor = 5.16, major = 5.68.




**(*S*)-3-allyl-3-(3-methylbut-2-en-1-yl)tetrahydro-4*H*-thiopyran-4-one (16e)**

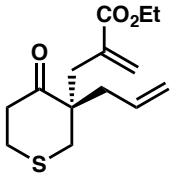
Purified by column chromatography (10% $Et_2O$ in hexanes) to provide a colorless oil (33.9 mg, 76% yield); 78% ee, $[\alpha]_D^{25}$ –6.0 (*c* 1.65, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 5.73–5.59 (m, 1H), 5.11–5.03 (m, 2H), 4.97 (tdq, *J* = 7.5, 2.9, 1.5 Hz, 1H), 2.87 (t, *J* = 6.3 Hz, 2H), 2.82–2.74 (m, 2H), 2.76–2.63 (m, 2H), 2.67–2.53 (m, 2H), 2.41 (ddt, *J* = 14.1, 7.0, 1.3 Hz, 1H), 2.36–2.27 (m, 1H), 1.70 (t, *J* = 1.4 Hz, 3H), 1.62 (d, *J* = 1.3 Hz, 3H); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 211.4, 135.3, 133.3, 118.8, 118.3, 53.6, 41.4, 39.1, 38.8, 32.8, 30.3, 26.2, 18.3; IR (Neat Film, NaCl) 3387, 3075, 2975, 2912, 2857, 1703, 1638, 1435, 1420, 1377, 1326, 1311, 1274, 1221, 1130, 1116, 989, 917, 848, 810, 783, 729, 676, 616 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{13}H_{21}OS$ $[M+H]^+$: 225.1313, found 225.1335; SFC Conditions: 2% IPA, 2.5 mL/min, Chiralcel OB-H column, λ = 210 nm, $t_R$ (min): major = 2.77, minor = 3.21.




**Ethyl (*S*)-2-(3-allyl-4-oxotetrahydro-2*H*-thiopyran-3-yl)acetate (16f)**

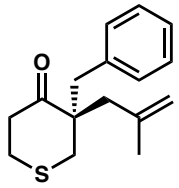
Purified by column chromatography (20% $Et_2O$ in hexanes) to provide a colorless oil (44.2 mg, 91% yield); 69% ee, $[\alpha]_D^{25}$ +43.5 (*c* 2.21, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 5.68–5.56 (m, 1H), 5.15–5.07 (m, 2H), 4.08 (qd, *J* = 7.1, 1.6 Hz, 2H), 3.22 (d, *J* = 13.8 Hz, 1H), 3.00 (ddd, *J* = 13.3, 10.0, 3.8 Hz, 1H), 2.89–2.58 (m, 7H), 2.52 (dd, *J* = 14.0,

7.9 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 209.8, 171.6, 132.1, 119.9, 60.7, 51.6, 41.2, 39.5, 39.2, 38.4, 30.0, 14.2; IR (Neat Film, NaCl) 3077, 2980, 2916, 1732, 1706, 1639, 1438, 1418, 1372, 1345, 1317, 1279, 1247, 1222, 1182, 1135, 1114, 1096, 995, 920 cm$^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{12}H_{19}O_3S$ $[M+H]^+$: 243.1055, found 243.1053; SFC Conditions: 2% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): major = 5.66, minor = 7.67.



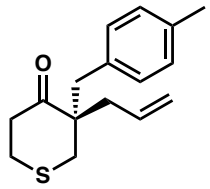

**Ethyl (*S*)-2-((3-allyl-4-oxotetrahydro-2*H*-thiopyran-3-yl)methyl)acrylate (16g)**

Purified by column chromatography (15% $Et_2O$ in hexanes) to provide a colorless oil (46.8 mg, 87% yield); 66% ee, $[\alpha]_D^{25}$ +7.8 (*c* 2.34, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 6.26 (d, *J* = 1.4 Hz, 1H), 5.72–5.59 (m, 1H), 5.59 (q, *J* = 1.1 Hz, 1H), 5.13–5.04 (m, 2H), 4.16 (qt, *J* = 7.2, 1.5 Hz, 2H), 3.10 (dd, *J* = 14.2, 1.1 Hz, 1H), 2.93–2.81 (m, 4H), 2.77 (dd, *J* = 19.6, 1.3 Hz, 1H), 2.73–2.65 (m, 1H), 2.62 (d, *J* = 14.1 Hz, 1H), 2.55–2.41 (m, 2H), 1.28 (td, *J* = 7.2, 1.1 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 210.4, 167.5, 136.9, 133.0, 129.2, 119.2, 61.1, 53.3, 41.5, 38.9, 38.8, 36.1, 29.7, 14.3; IR (Neat Film, NaCl) 3076, 2979, 2938, 2910, 1712, 1638, 1626, 1436, 1417, 1369, 1333, 1308, 1276, 1209, 1174, 1159, 1096, 1027, 992, 960, 920, 858.9, 819, 684, 665 cm$^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{14}H_{21}O_3S$ $[M+H]^+$: 269.1211, found 269.1204; SFC Conditions: 10% IPA, 3.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): major = 3.04, minor = 3.95.



**(*S*)-3-benzyl-3-(2-methylallyl)tetrahydro-4*H*-thiopyran-4-one (16h)**

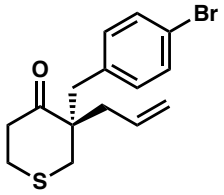
Purified by column chromatography (10% $Et_2O$ in hexanes) to provide a colorless oil (15.3 mg, 29% yield); 80% ee, $[\alpha]_D^{25}$ –1.0 (*c* 0.77, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 2H), 7.26–7.19 (m, 1H), 7.17–7.11 (m, 2H), 4.89 (m, 1H), 4.70–4.66 (m, 1H), 3.23 (d, *J* = 13.7 Hz, 1H), 2.95 (d, *J* = 13.7 Hz, 1H), 2.92–2.78 (m, 3H), 2.77–2.67 (m, 3H), 2.64 (dd, *J* = 15.2, 1.1 Hz, 1H), 2.52 (dd, *J* = 15.2, 1.2 Hz, 1H), 1.70 (t, *J* = 1.0 Hz, 3H); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 212.1, 141.7, 136.9, 131.0, 128.3, 126.7, 114.9, 53.8, 42.1, 41.5, 40.8, 38.2, 29.7, 25.1; IR (Neat Film, NaCl) 3063, 3027, 2915, 1702, 1640, 1494, 1452, 1376, 1311, 1274, 1216, 1124, 1079, 1031, 988, 897, 808, 748, 704 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{16}H_{21}OS$ $[M+H]^+$: 261.1313, found 261.1323; SFC Conditions: 5% IPA, 2.5 mL/min, Chiralcel OB-H column, λ = 210 nm, $t_R$ (min): major = 4.18, minor = 5.16.



**(*S*)-3-allyl-3-(4-methylbenzyl)tetrahydro-4*H*-thiopyran-4-one (16i)**

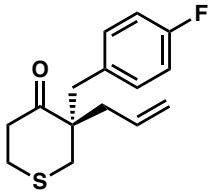
Purified by column chromatography (10% $Et_2O$ in hexanes) to provide a colorless oil (44.8 mg, 86% yield); 90% ee, $[\alpha]_D^{25}$ +3.9 (*c* 2.20, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.08 (d, *J* = 7.8 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 5.72 (dddd, *J* = 16.9, 10.2, 7.8, 6.6 Hz, 1H), 5.16–5.06 (m, 2H), 3.09 (d, *J* = 13.9 Hz, 1H), 2.99 (d, *J* = 13.8 Hz, 1H), 2.89

(m, 2H), 2.83–2.68 (m, 4H), 2.58–2.49 (m, 1H), 2.46 (ddt, $J$ = 14.4, 6.7, 1.4 Hz, 1H), 2.32 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 211.2, 136.3, 133.5, 133.3, 130.6, 129.0, 119.0, 54.0, 41.6, 39.8, 38.7, 38.0, 29.7, 21.1; IR (Neat Film, NaCl) 3075, 3049, 3020, 3005, 2946, 2918, 1703, 1638, 1514, 1434, 1419, 1313, 1274, 1222, 1128, 1115, 989, 919, 830, 797 cm$^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{16}H_{21}OS$ $[M+H]^+$: 261.1313, found 261.1331; SFC Conditions: 10% IPA, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, $t_R$ (min): minor = 3.34, major = 4.14.



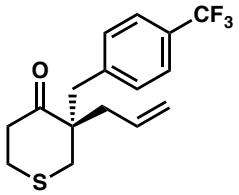

**(*S*)-3-allyl-3-(4-bromobenzyl)tetrahydro-4*H*-thiopyran-4-one (16j)**

Purified by column chromatography (10% $Et_2O$ in hexanes) to provide a colorless oil (58.8 mg, 91% yield); 91% ee, $[\alpha]_D^{25}$ +4.6 (*c* 2.94, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.42–7.35 (m, 2H), 7.05–6.98 (m, 2H), 5.68 (dddd, $J$ = 16.9, 10.2, 7.7, 6.7 Hz, 1H), 5.17–5.06 (m, 2H), 3.11 (d, $J$ = 13.8 Hz, 1H), 2.95–2.84 (m, 3H), 2.78–2.69 (m, 4H), 2.55 (ddt, $J$ = 14.4, 7.7, 1.2 Hz, 1H), 2.43 (ddt, $J$ = 14.3, 6.7, 1.3 Hz, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 210.7, 135.8, 132.8, 132.5, 131.4, 120.8, 119.4, 53.8, 41.5, 39.6, 38.9, 37.9, 29.7; IR (Neat Film, NaCl) 3075, 2946, 2914, 1703, 1638, 1487, 1434, 1404, 1313, 1274, 1073, 1012, 989, 921, 837, 788 cm$^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{15}H_{18}BrOS$ $[M+H]^+$: 325.0262, found 325.0265; SFC Conditions: 7% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 11.06, major = 11.92.




**(*S*)-3-allyl-3-(4-fluorobenzyl)tetrahydro-4*H*-thiopyran-4-one (16k)**

Purified by column chromatography (10% $Et_2O$ in hexanes) to provide a colorless oil (43.9 mg, 83% yield); 91% ee, $[\alpha]_D^{25}$ +9.3 (*c* 2.20, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.14–7.06 (m, 2H), 7.00–6.91 (m, 2H), 5.69 (dddd, *J* = 17.0, 10.3, 7.7, 6.7 Hz, 1H), 5.17–5.06 (m, 2H), 3.13 (d, *J* = 14.0 Hz, 1H), 2.95 (d, *J* = 14.0 Hz, 1H), 2.88 (dd, *J* = 7.6, 5.0 Hz, 2H), 2.79–2.70 (m, 4H), 2.58–2.49 (m, 1H), 2.44 (ddt, *J* = 14.4, 6.7, 1.4 Hz, 1H); $^{19}F$ (282 MHz, $CDCl_3$) δ –116.25 (tt, *J* = 8.8, 5.4 Hz); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 210.9, 161.9 (d, *J* = 245.1 Hz), 133.0, 132.3 (d, *J* = 3.3 Hz), 132.2 (d, *J* = 7.9 Hz), 119.3, 115.2 (d, *J* = 21.0 Hz), 53.9, 41.5, 39.4, 38.8, 37.9, 29.7; IR (Neat Film, NaCl) 3075, 2947, 2915, 1703, 1638, 1604, 1509, 1435, 1417, 1335, 1314, 1275, 1223, 1160, 1130, 1098, 1016, 988, 965, 921, 843, 813, 772 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{15}H_{18}FOS$ $[M+H]^+$: 265.1062, found 265.1055; SFC Conditions: 10% IPA, 2.5 mL/min, Chiralcel OB-H column, λ = 210 nm, $t_R$ (min): major = 2.70, minor = 3.75.

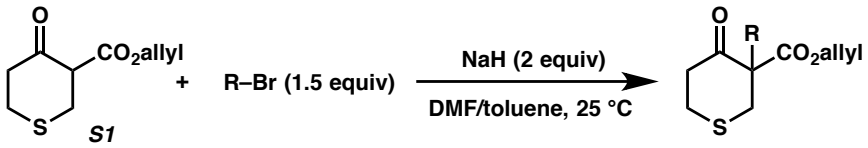



**(*S*)-3-allyl-3-(4-(trifluoromethyl)benzyl)tetrahydro-4*H*-thiopyran-4-one (16l)**

Purified by column chromatography (10% $Et_2O$ in hexanes) to provide a colorless oil (50.5 mg, 80% yield); 93% ee, $[\alpha]_D^{25}$ +12.5 (*c* 2.53, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 5.69 (dddd, *J* = 17.0, 10.2, 7.7, 6.8

Hz, 1H), 5.19–5.09 (m, 2H), 3.22 (d, $J$ = 13.7 Hz, 1H), 3.03 (d, $J$ = 13.8 Hz, 1H), 2.89 (t, $J$ = 6.2 Hz, 2H), 2.84–2.67 (m, 4H), 2.60 (ddt, $J$ = 14.4, 7.7, 1.2 Hz, 1H), 2.44 (ddt, $J$ = 14.4, 6.7, 1.3 Hz, 1H); $^{19}$F NMR (282 MHz, $CDCl_3$) δ –62.48 (s); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 210.5, 141.1 (d, $J$ = 1.4 Hz), 132.6, 131.1, 129.1 (q, $J$ = 32.5 Hz), 125.2 (q, $J$ = 3.7 Hz), 122.9 (q, $J$ = 272.7), 119.6, 53.9, 41.5, 40.0, 38.9, 38.1, 29.7; IR (Neat Film, NaCl) 3076, 2917, 1703, 1638, 1618, 1436, 1417, 1326, 1275, 1165, 1123, 1068, 1019, 922, 856 cm$^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{16}H_{18}F_3OS$ $[M+H]^+$: 315.1030, found 315.1042; SFC Conditions: 2% IPA, 2.5 mL/min, Chiralcel OD-H column, λ = 210 nm, $t_R$ (min): major = 10.24, minor = 11.19.

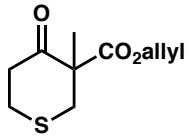
### 2.6.2.4 General Procedure for the Preparation of Thiopyranone β-Ketoester Substrates




To an oven dried 20 mL vial was added NaH (3 mmol) and the vial evacuated and backfilled with argon three times. To the vial was added anhydrous DMF (1.0 mL), toluene (1.0 mL), and alkyl bromide (3 mmol) and the resulting suspension stirred for 5 minutes. A solution of **S1** (2 mmol) in anhydrous toluene (1.0 mL) was then added dropwise over 10 min. Following the addition, the reaction was continued until all **S1** was consumed as seen by TLC. If necessary, additional toluene (1.0 to 2.0 mL) was added to ensure proper stirring of the reaction mixture. After diluting with $Et_2O$, the reaction was quenched with 1.0 M HCl, and the layers separated. The aqueous layer was extracted with $Et_2O$, and the combined organic layers were washed with water and then

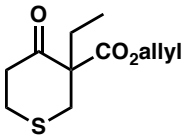
brine, and dried over $Na_2SO_4$. The resulting crude residue was then purified by silica gel flash chromatography to provide the desired product.

### 2.6.2.5 Spectroscopic Data for the Thiopyranone β-Ketoester Substrates




**Allyl 3-methyl-4-oxotetrahydro-2*H*-thiopyran-3-carboxylate (15b)**

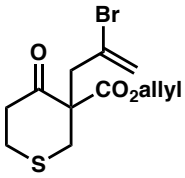
Purified by column chromatography (15% $Et_2O$ in hexanes) to provide a colorless oil (224.3 mg, 52% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 5.91 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.34 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.26 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.74–4.62 (m, 2H), 3.33 (dd, *J* = 13.9, 2.9 Hz, 1H), 3.01–2.82 (m, 3H), 2.84–2.76 (m, 1H), 2.71 (d, *J* = 13.9 Hz, 1H), 1.41 (s, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 205.5, 171.8, 131.5, 119.1, 66.3, 59.2, 42.9, 40.0, 30.8, 21.0; IR (Neat Film, NaCl) 3086, 2985, 2937, 1731, 1714, 1649, 1454, 1417, 1374, 1358, 1315, 1294, 1277, 1233, 1192, 1160, 1125, 1100, 1064, 974, 938, 855, 817, 770, 738, 713, 682 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{10}H_{15}O_3S$ $[M+H]^+$: 215.0742, found 215.0741.




**Allyl 3-ethyl-4-oxotetrahydro-2*H*-thiopyran-3-carboxylate (15c)**

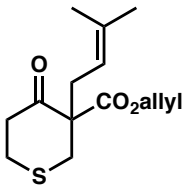
Purified by column chromatography (7% $Et_2O$ in hexanes) to provide a colorless oil (157.4 mg, 35% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 5.92 (ddt, *J* = 17.3, 10.5, 5.8 Hz, 1H), 5.35 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.27 (dq, *J* = 10.3, 1.2 Hz, 1H), 4.75–4.62 (m, 2H), 3.30 (dd, *J* = 13.9, 2.9 Hz, 1H), 3.01–2.89 (m, 2H), 2.89–2.82 (m, 1H), 2.81–2.70 (m, 2H), 2.08–1.97 (m, 1H), 1.74 (dq, *J* = 14.6, 7.5 Hz, 1H), 0.90 (t, *J* = 7.5 Hz, 3H); $^{13}$C

NMR (101 MHz, $CDCl_3$) δ 205.5, 170.8, 131.6, 119.2, 66.1, 63.4, 43.4, 38.4, 31.0, 27.6, 9.3; IR (Neat Film, NaCl) 3085, 2967, 2940, 2883, 1727, 1712, 1460, 1425, 1381, 1360, 1308, 1270, 1248, 1227, 1196, 1149, 1128, 986, 971, 936, 814, 796, 779, 732, 682 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{11}H_{17}O_3S$ $[M+H]^+$: 229.0898, found 229.0894.




**Allyl 3-(2-bromoallyl)-4-oxotetrahydro-2*H*-thiopyran-3-carboxylate (15d)**

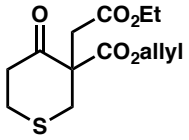
Purified by column chromatography (10% $Et_2O$ in hexanes) to provide a colorless oil (330.1 mg, 52% yield); $^1H$ NMR (500 MHz, $CDCl_3$) δ 5.99–5.86 (m, 1H), 5.68 (dt, *J* = 1.7, 0.8 Hz, 1H), 5.60 (d, *J* = 1.7 Hz, 1H), 5.37 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.27 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.75–4.63 (m, 2H), 3.53 (dd, *J* = 14.0, 2.7 Hz, 1H), 3.23 (dd, *J* = 15.0, 0.7 Hz, 1H), 3.02 (dd, *J* = 15.0, 0.7 Hz, 1H), 3.01–2.72 (m, 5H); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 203.7, 169.2, 131.4, 126.3, 122.8, 119.4, 66.7, 62.5, 44.7, 43.3, 37.7, 30.6; IR (Neat Film, NaCl) 3085, 2952, 2923, 1714, 1649, 1624, 1425, 1360, 1313, 1298, 1279, 1263, 1196, 1143, 1115, 1054, 985, 969, 936, 901, 854, 839, 814, 736, 683 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{12}H_{14}O_3S^{81}Br$ $[(M+H)–H_2]^+$: 318.9827, found 318.9828.




**Allyl 3-(3-methylbut-2-en-1-yl)-4-oxotetrahydro-2*H*-thiopyran-3-carboxylate (15e)**

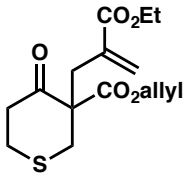
Purified by column chromatography (15% $Et_2O$ in hexanes) to provide a colorless oil (369.8 mg, 69% yield); $^1H$ NMR (500 MHz, $CDCl_3$) δ 5.90 (ddt, *J* = 17.1, 10.4, 5.8 Hz, 1H), 5.34 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.25 (dq, *J* = 10.4, 1.2 Hz, 1H), 5.06 (dddt, *J* = 8.4,

7.0, 2.9, 1.5 Hz, 1H), 4.69–4.61 (m, 2H), 3.30 (dd, *J* = 13.9, 2.8 Hz, 1H), 2.98–2.86 (m, 2H), 2.90–2.81 (m, 1H), 2.84–2.72 (m, 2H), 2.65–2.49 (m, 2H), 1.68 (m, *J* = 1.3 Hz, 3H), 1.70–1.59 (m, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 205.3, 170.5, 135.8, 131.6, 119.1, 118.0, 66.2, 63.3, 43.4, 37.9, 33.0, 30.8, 26.1, 18.1; IR (Neat Film, NaCl) 2912, 1712, 1426, 1377, 1315, 1263, 1223, 1185, 1114, 933 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{14}H_{21}O_3S$ $[M+H]^+$: 269.1211, found 269.1204.



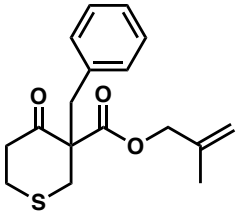

**Allyl 3-(2-ethoxy-2-oxoethyl)-4-oxotetrahydro-2*H*-thiopyran-3-carboxylate (15f)**

Purified by column chromatography (30% $Et_2O$ in hexanes) to provide a colorless oil (472.0 mg, 83% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 5.92 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.35 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.26 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.69 (qdt, *J* = 13.1, 5.8, 1.4 Hz, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.30 (dd, *J* = 13.9, 2.6 Hz, 1H), 3.18 (dd, *J* = 13.9, 0.6 Hz, 1H), 3.08 (ddd, *J* = 14.0, 11.0, 5.5 Hz, 1H), 2.96 (m, 2H), 2.94–2.85 (m, 1H), 2.82 (ddd, *J* = 14.0, 4.6, 3.5 Hz, 1H), 2.75 (d, *J* = 16.3 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 204.2, 170.2, 170.2, 131.5, 119.1, 66.7, 61.0, 60.9, 42.5, 38.9, 38.1, 30.3, 14.2; IR (Neat Film, NaCl) 3085, 2982, 2936, 1736, 1718, 1711, 1420, 1373, 1346, 1281, 1182, 1132, 1097, 1047, 1028, 987, 970, 934, 870, 850, 821 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{13}H_{19}O_5S$ $[M+H]^+$: 287.0953, found 287.0951.




**Allyl 3-(2-(ethoxycarbonyl)allyl)-4-oxotetrahydro-2*H*-thiopyran-3-carboxylate (15g)**

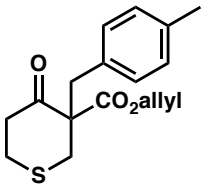
Purified by column chromatography (20% $Et_2O$ in hexanes) to provide a white, waxy solid (431.1 mg, 69% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 6.28 (d, *J* = 1.3 Hz, 1H), 5.91 (ddt, *J* = 17.1, 10.4, 5.8 Hz, 1H), 5.58 (q, *J* = 1.1 Hz, 1H), 5.34 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.26 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.62 (dq, *J* = 5.8, 1.3 Hz, 2H), 4.26–4.10 (m, 2H), 3.31 (dd, *J* = 13.9, 3.1 Hz, 1H), 3.18 (dd, *J* = 14.2, 0.9 Hz, 1H), 3.01–2.85 (m, 2H), 2.89–2.76 (m, 2H), 2.75–2.63 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 204.4, 169.7, 167.0, 135.8, 131.5, 129.3, 119.2, 66.4, 62.5, 61.2, 43.6, 38.1, 35.2, 30.6, 14.3; IR (Neat Film, NaCl) 2982, 2938, 2908, 1714, 1649, 1628, 1434, 1416, 1370, 1337, 1311, 1294, 1278, 1262, 1194, 1175, 1156, 1117, 1096, 1058, 1025, 947, 860, 812, 683 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{15}H_{21}O_5S$ $[M+H]^+$: 313.1110, found 313.1115.




**2-Methylallyl 3-benzyl-4-oxotetrahydro-2*H*-thiopyran-3-carboxylate (15h)**

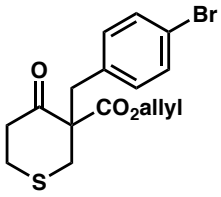
Purified by column chromatography (15% $Et_2O$ in hexanes) to provide a colorless oil (301.2 mg, 49.5% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.34–7.11 (m, 5H), 4.93 (dt, *J* = 12.0, 1.5 Hz, 2H), 4.47 (s, 2H), 3.35 (d, *J* = 13.7 Hz, 1H), 3.31–3.24 (m, 1H), 3.11 (d, *J* = 13.7 Hz, 1H), 2.99–2.82 (m, 4H), 2.85–2.73 (m, 1H), 1.68 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 204.8, 170.0, 139.1, 135.7, 130.6, 128.3, 127.1, 114.2, 69.0, 64.3, 43.6, 39.9,

38.1, 30.7, 19.7; IR (Neat Film, NaCl) 3084, 3062, 3029, 2924, 1713, 1657, 1495, 1454, 1432, 1378, 1364, 1329, 1311, 1275, 1262, 1230, 1190, 1132, 1117, 1092, 1076, 1046, 1032, 965, 912, 810, 771, 741, 702 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{21}O_3S$ $[M+H]^+$: 305.1211, found 305.1220.




**Allyl 3-(4-methylbenzyl)-4-oxotetrahydro-2*H*-thiopyran-3-carboxylate (15i)**

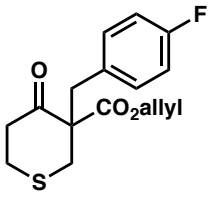
Purified by column chromatography (15% $Et_2O$ in hexanes) to provide a white solid (299.4 mg, 49% yield); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.09 – 6.95 (m, 4H), 5.83 (ddt, *J* = 17.1, 10.4, 5.9 Hz, 1H), 5.29 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.24 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.64–4.54 (m, 2H), 3.33–3.22 (m, 2H), 3.08 (d, *J* = 13.8 Hz, 1H), 2.97–2.78 (m, 4H), 2.75 (d, *J* = 13.9 Hz, 1H), 2.31 (s, 3H); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 205.0, 170.0, 136.7, 132.5, 131.5, 130.5, 129.0, 119.3, 66.3, 64.3, 43.6, 39.4, 38.0, 30.7, 21.12; IR (Neat Film, NaCl) 2922, 1710, 1514, 1422, 1359, 1272, 1229, 1181, 1112, 1048, 967, 931, 828 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{21}O_3S$ $[M+H]^+$: 305.1211, found 305.1208.




**Allyl 3-(4-bromobenzyl)-4-oxotetrahydro-2*H*-thiopyran-3-carboxylate (15j)**

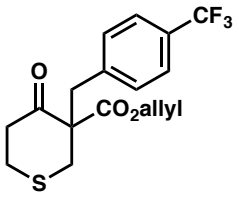
Purified by column chromatography (15% $Et_2O$ in hexanes) to provide a white solid (502.0 mg, 68% yield); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.39–7.31 (m, 2H), 7.09–7.02 (m,

2H), 5.79 (ddt, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.32–5.16 (m, 2H), 4.61–4.49 (m, 2H), 3.33–3.22 (m, 2H), 3.01 (d, *J* = 13.7 Hz, 1H), 2.98–2.78 (m, 4H), 2.73 (d, *J* = 13.8 Hz, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 204.7, 169.8, 134.8, 132.4, 131.4, 131.2, 121.2, 119.5, 66.4, 64.2, 43.6, 39.2, 38.3, 30.8; IR (Neat Film, NaCl) 2926, 1711, 1488, 1426, 1359, 1311, 1295, 1271, 1230, 1190, 1108, 1072, 1048, 1012, 968, 937, 832, 792, 711, 682, 624 cm$^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{16}H_{16}O_3S^{81}Br$ $[(M+H)-H_2]^+$: 368.9983, found 368.9967.




**Allyl 3-(4-fluorobenzyl)-4-oxotetrahydro-2*H*-thiopyran-3-carboxylate (15k)**

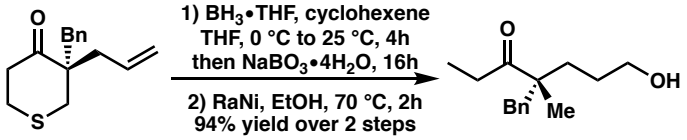
Purified by column chromatography (15% $Et_2O$ in hexanes) to provide a colorless oil (383.7.5 mg, 62% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.18 – 7.10 (m, 2H), 6.97 – 6.88 (m, 2H), 5.79 (ddt, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.31–5.19 (m, 2H), 4.61–4.49 (m, 2H), 3.33 (d, *J* = 13.8 Hz, 1H), 3.26 (dd, *J* = 13.9, 2.7 Hz, 1H), 3.03 (d, *J* = 13.8 Hz, 1H), 2.99–2.77 (m, 4H), 2.74 (d, *J* = 13.9 Hz, 1H); $^{19}$F NMR (282 MHz, $CDCl_3$) δ –115.82 (tt, *J* = 8.6, 5.4 Hz); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 204.9, 169.8, 163.3, 160.8, 132.2 (d, *J* = 7.9 Hz), 131.5 (d, *J* = 3.3 Hz), 115.1 (d, *J* = 20.9 Hz), 66.3, 64.4 (2C), 43.6, 39.0, 38.3, 30.8; IR (Neat Film, NaCl) 2928, 1709, 1601, 1508, 1421, 1273, 1221, 1185, 1158, 1116, 1100, 1048, 1016, 934, 840 cm$^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{16}H_{18}O_3SF$ $[M+H]^+$: 309.0961, found 309.0958.




**Allyl 4-oxo-3-(4-(trifluoromethyl)benzyl)tetrahydro-2*H*-thiopyran-3-carboxylate (15l)**

Purified by column chromatography (15% $Et_2O$ in hexanes) to provide a white solid (481.9 mg, 67% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.55–7.43 (m, 2H), 7.34–7.27 (m, 2H), 5.74 (ddt, *J* = 17.2, 10.4, 6.0 Hz, 1H), 5.29–5.14 (m, 2H), 4.53 (dq, *J* = 6.0, 1.5 Hz, 2H), 3.41 (d, *J* = 13.6 Hz, 1H), 3.27 (dd, *J* = 13.8, 2.7 Hz, 1H), 3.07 (d, *J* = 13.6 Hz, 1H), 3.02–2.77 (m, 4H), 2.75 (d, *J* = 13.8 Hz, 1H); $^{19}$F NMR (282 MHz, $CDCl_3$) δ –62.57; $^{13}$C NMR (101 MHz, $CDCl_3$) δ 204.6, 169.7, 140.1 (d, *J* = 1.5 Hz), 131.0 (2C), 129.4 (q, *J* = 32.3 Hz), 125.1 (q, *J* = 3.8 Hz), 122.9 (q, *J* = 272.7 Hz) 119.5, 66.4, 64.3, 43.6, 39.6, 38.5, 30.8; IR (Neat Film, NaCl) 2929, 1715, 1618, 1420, 1326, 1293, 1276, 1232, 1191, 1165, 1114, 1068, 1020, 969, 939, 855, 732, 684, 630, 607 $cm^{-1}$; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{18}O_3SF_3$ $[M+H]^+$: 359.0929, found 359.0939.

### 2.6.2.6 Derivatization of Alkylation Products




***17***

**(*R*)-4-benzyl-7-hydroxy-4-methylheptan-3-one (17)**

To an oven dried vial was added a 1 M solution of $BH_3$•THF (0.25 mmol, 250 μL) and the vial cooled to 0 °C. Cyclohexene (0.5 mmol, 50.6 μL) was then added neat dropwise and the mixture stirred for 1 h at 0 °C. A solution of ***2a*** (0.2 mmol, 49.2 mg) in 1.0 mL

THF was then added, the cooling bath removed, and the reaction continued at room temperature for 4h. Water (500 μL) was then added followed by $NaBO_3 \bullet 4H_2O$ (1.0 mmol, 153.9 mg), and the reaction continued at room temperature for 12h at which point the reaction was diluted with water and extracted with $Et_2O$. The combined organic layers were dried with $Na_2SO_4$ and concentrated. The crude reaction mixture was then dissolved in 3 mL of EtOH, treated with a suspension of Raney Ni (1.0 mL settled volume) and to 70 °C for 2h. The reaction was then allowed to settle, and the supernatant removed via pipette and filtered through a plug of Celite®. Additional EtOH was added to the reaction vial and stirred for ~5 mins before again being allowed to settle and the supernatant removed. This process was repeated an additional two times, and the combined filtrates concentrated. The crude residue was purified by column chromatography (30% EtOAc in hexanes) to afford the desired linear alcohol (43.9 mg, 94% yield over two steps); $[\alpha]_D^{25}$ -20.4 (*c* 1.39, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.27–7.16 (m, 3H), 7.05 (d, *J* = 7.0 Hz, 2H), 3.59 (h, *J* = 4.5 Hz, 2H), 2.95 (d, *J* = 13.3 Hz, 1H), 2.66 (d, *J* = 13.3 Hz, 1H), 2.42 (dq, *J* = 18.5, 7.1 Hz, 1H), 2.26 (dq, *J* = 18.4, 7.1 Hz, 1H), 1.82 (td, *J* = 11.3, 10.5, 2.9 Hz, 1H), 1.61 (s, 1H), 1.55 – 1.36 (m, 3H), 1.13 (s, 3H), 0.97 (t, *J* = 7.1 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 216.3, 137.6, 130.3, 128.2, 126.5, 63.1, 51.8, 45.3, 34.9, 32.2, 28.0, 20.7, 7.8; IR (Neat Film, NaCl) 3421 (br), 3029, 2972, 2938, 1701, 1496, 1454, 1409, 1378, 1352, 1097, 1059, 1031, 1019, 973, 753, 703 $cm^{-1}$; HRMS (MM) *m/z* calc'd for $C_{15}H_{23}O_2$ $[M+H]^+$: 235.1693, found 235.1685.

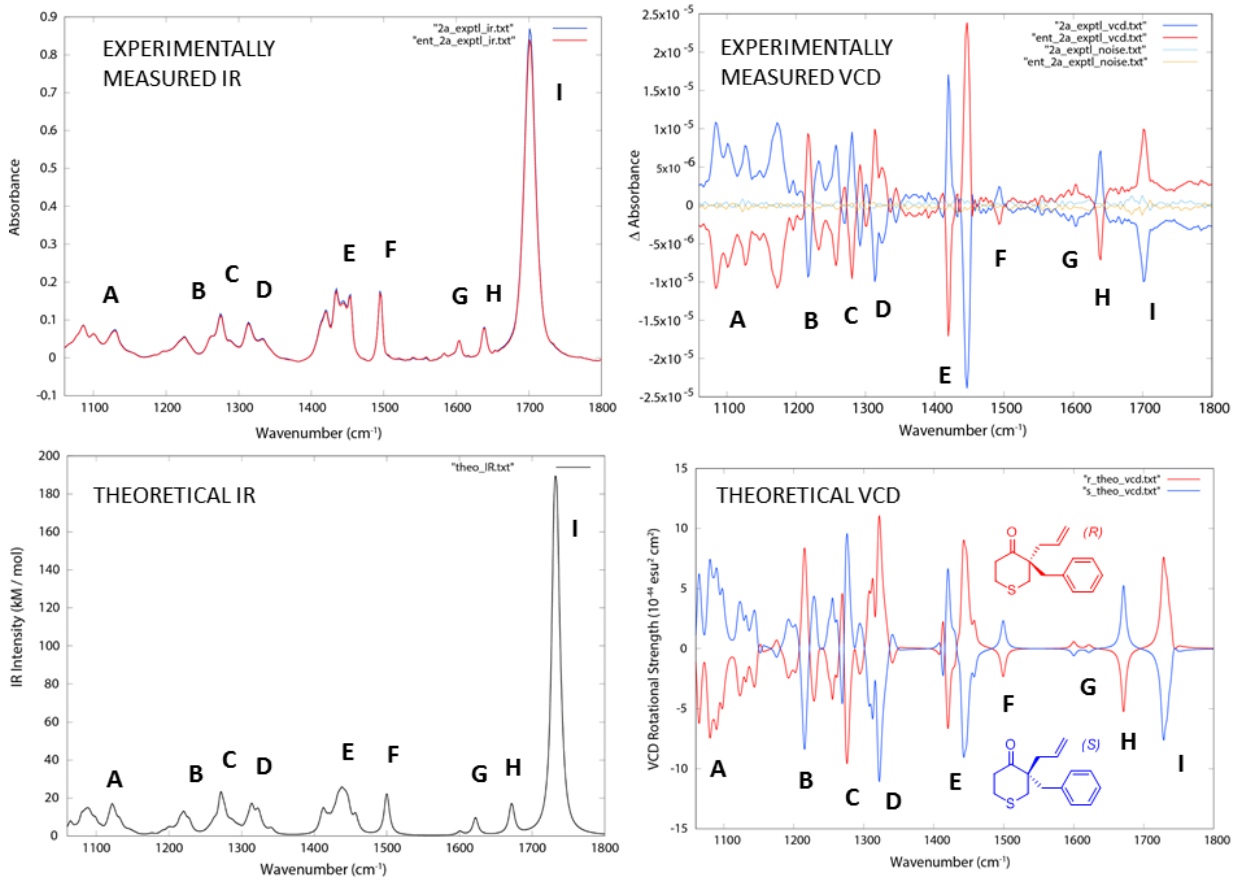
### 2.6.2.7 Determination of Absolute Configuration of Alkylation Product 16a

**Experimental Protocol.** Samples (15.2 mg each) of **16a** (generated from the reaction of **15a** with ligand (*R,R*)-**L11**; Scheme 1, entry 5) and ***ent*-16a** (generated from **15a** with ligand (*S,S*)-**L11**) were subjected to absolute configuration determination via vibrational circular dichroism (VCD) using a ChiralIR-2X spectrometer (BioTools, Inc) at 4 $cm^{-1}$ resolution and optimized at 1400 $cm^{-1}$. Each sample was dissolved in 280 μL of $CDCl_3$ (54 mg/mL), loaded into an SL-4 cell (International Crystal Laboratories) with $BaF_2$ windows and 100 μm path length, and infrared (IR) and VCD spectra acquired in 24 one-hour blocks which were averaged at the completion of the run. A 15-minute acquisition of neat (+)-α-pinene control yielded a VCD spectrum in agreement with literature spectra. IR and VCD spectra were background-corrected using a 5-minute block acquisition of the empty instrument chamber. IR spectra of **16a** and ***ent*-16a** were solvent corrected utilizing a 1-hour block acquisition of $CDCl_3$. VCD spectra of **16a** and ***ent*-16a** were enantiomer subtracted (half-difference).

**Computational Protocol**. The arbitrarily chosen (*S*) enantiomer of **16a** was subjected to an exhaustive initial molecular mechanics-based conformational search (MMFF94 force field, 0.08 Å geometric RMSD cutoff, and 30 kcal/mol energy window) as implemented in MOE (Chemical Computing Group, Montreal, CA). All conformers retained the (*S*) configuration. All MMFF94 conformers were then subjected to geometry optimization, harmonic frequency calculation, and VCD rotational strength evaluation with density functional theory. All quantum mechanical calculations utilized the B3PW91 functional, cc-pVTZ basis, and implicit IEFPCM chloroform solvation model as implemented in the *Gaussian 09* program system (Rev. E.01; Frisch *et al*., Gaussian, Inc., Wallingford, CT).

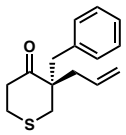
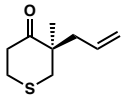
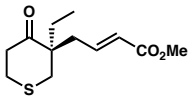
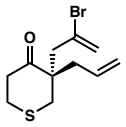
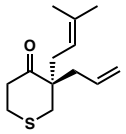
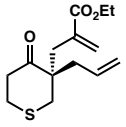
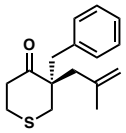
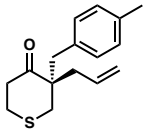
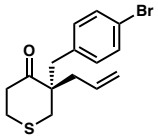
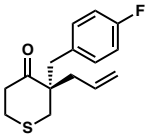
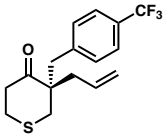
Resultant harmonic frequencies were scaled by 0.98. All structurally unique conformers were Boltzmann weighted by relative free energy at 298.15 K. The predicted IR and VCD frequencies and intensities were convolved using Lorentzian line shapes ($\gamma$ = 4 $cm^{-1}$) and summed using the respective Boltzmann weights to yield the final predicted IR and VCD spectra of the (*S*) enantiomer of **2a**. The predicted VCD of the corresponding (*R*) enantiomer was generated by inversion of sign. From the excellent agreement between the predicted and measured IR and VCD spectra (see below) the absolute configuration of **16a** was unambiguously established as (*S*).

***Figure 2.2*** *Experimental (top) and Computed (bottom) IR and VCD Spectra for* ***16a*** *and* ***ent-16a***.



## 2.6.3 DETERMINATION OF ENANTIOMERIC EXCESS

***Table 2.3*** *Determination of enantiomeric excess*

| Entry | Compound | Assay Conditions | $t_R$ of major isomer (min) | $t_R$ of minor isomer (min) | %ee |
|---|---|---|---|---|---|
| 1 |  | SFC<br>Chiralcel OJ-H<br>15% IPA<br>isocratic, 2.5 mL/min | 3.48 | 2.87 | 94 |
| 2 |  | SFC<br>Chiralpak AD-H<br>2% IPA<br>isocratic, 2.5 mL/min | 6.37 | 5.09 | 93 |
| 3 |  | SFC<br>Chiralpak IC<br>20% IPA<br>isocratic, 2.5 mL/min | 8.61 | 7.87 | 82 |
| 4 |  | SFC<br>Chiralcel OJ-H<br>1% IPA<br>isocratic, 2.5 mL/min | 5.68 | 5.16 | 50 |
| 5 |  | SFC<br>Chiralcel OB-H<br>2% IPA<br>isocratic, 2.5 mL/min | 2.77 | 3.21 | 78 |
| 6 |  | SFC<br>Chiralpak AD-H<br>2% IPA<br>isocratic, 2.5 mL/min | 5.66 | 7.67 | 69 |
| 7 |  | SFC<br>Chiralcel OB-H<br>5% IPA<br>isocratic, 2.5 mL/min | 4.18 | 5.16 | 80 |
| 8 |  | SFC<br>Chiralcel OJ-H<br>10% IPA<br>isocratic, 2.5 mL/min | 4.14 | 3.34 | 90 |
| 9 |  | SFC<br>Chiralpak AD-H<br>7% IPA<br>isocratic, 2.5 mL/min | 11.92 | 11.06 | 91 |
| 10 |  | SFC<br>Chiralcel OB-H<br>10% IPA<br>isocratic, 2.5 mL/min | 2.70 | 3.75 | 91 |
| 11 |  | SFC<br>Chiralcel OD-H<br>2% IPA<br>isocratic, 2.5 mL/min | 10.24 | 11.19 | 93 |

## 2.7 REFERENCES AND NOTES

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(16) Substrate synthesis required the use of a Dieckmann cyclization to form the cyclic β-ketoester, with other strategies such as α-acylation of the parent thiopyranone being unsuccessful. Additionally, attempts to prepare thiochromanone derivatives also failed.

(17) Bulkier alkyl groups were poorly tolerated in the reaction, providing low levels of enantioselectivity.

# *APPENDIX 3*

*Spectra Relevant to Chapter 2:*

*Enantioselective Pd-Catalyzed Decarboxylative Allylic Alkylation Of Thiopyranones. Access to Acyclic, Stereogenic α-Quaternary Stereocenters*

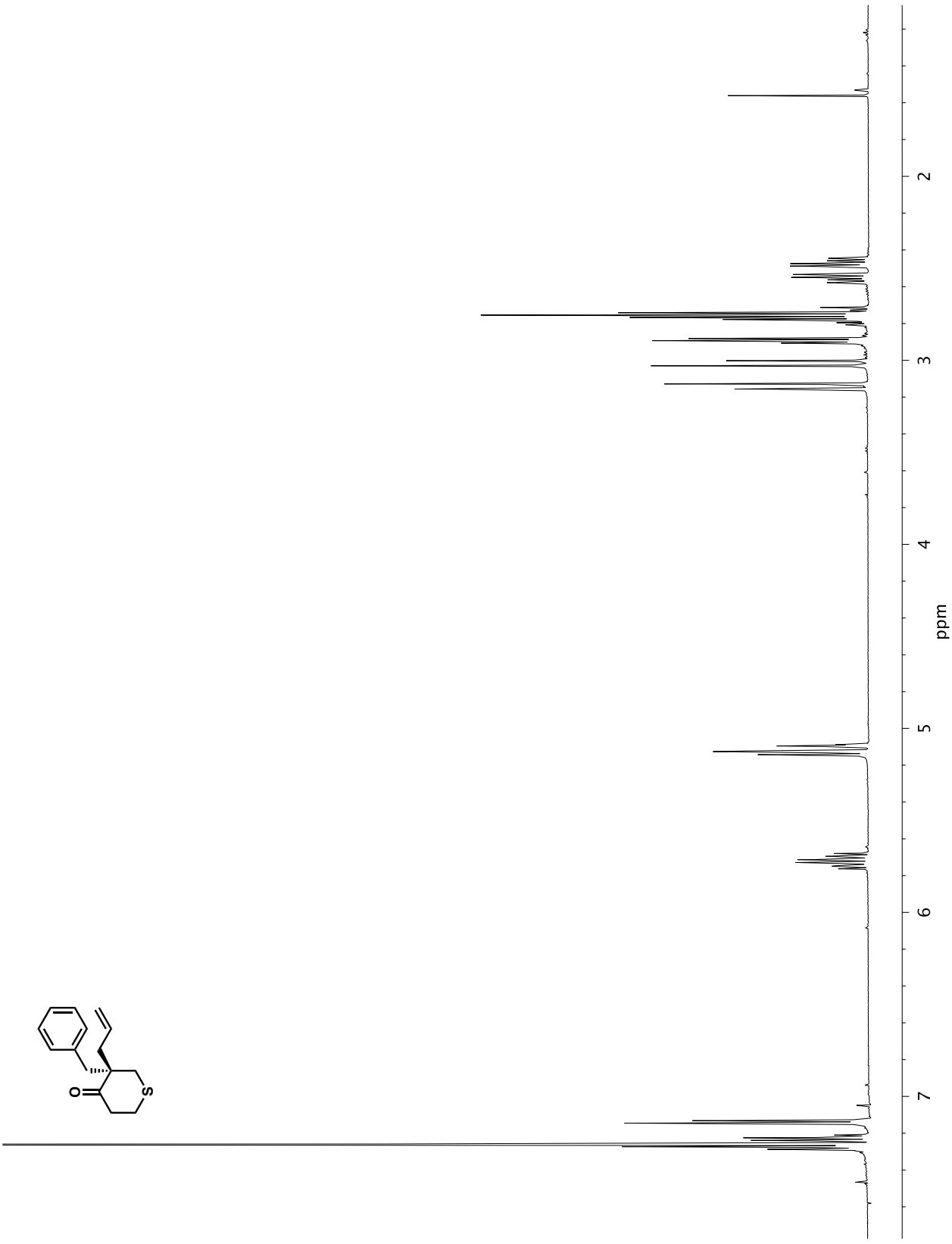



***Figure A3.1*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***16a***.

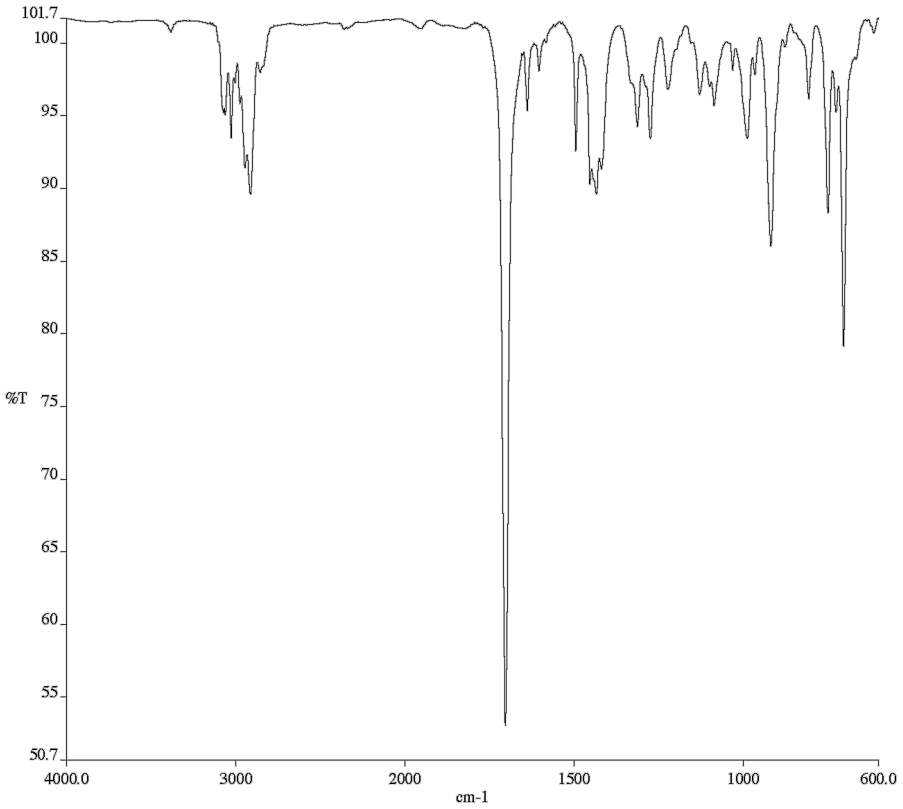



***Figure A3.2*** *Infrared spectrum (Thin Film, NaCl) of compound* ***16a***.

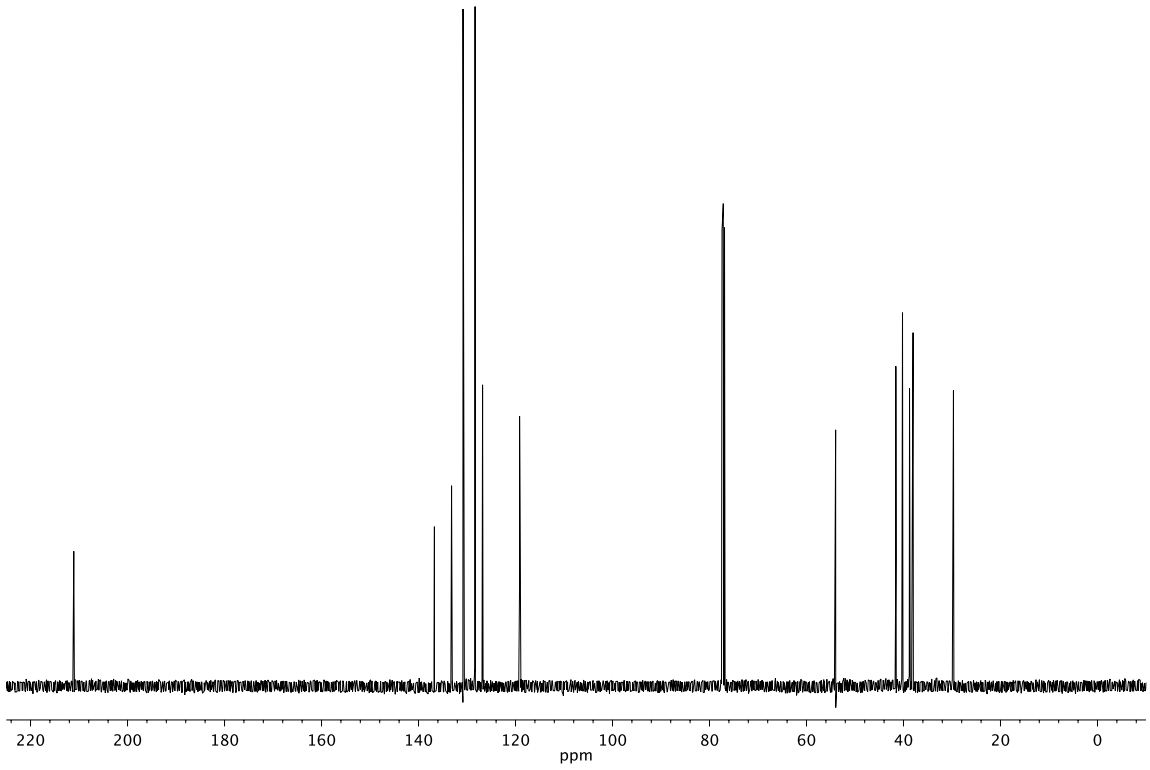



***Figure A3.3*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***16a***.

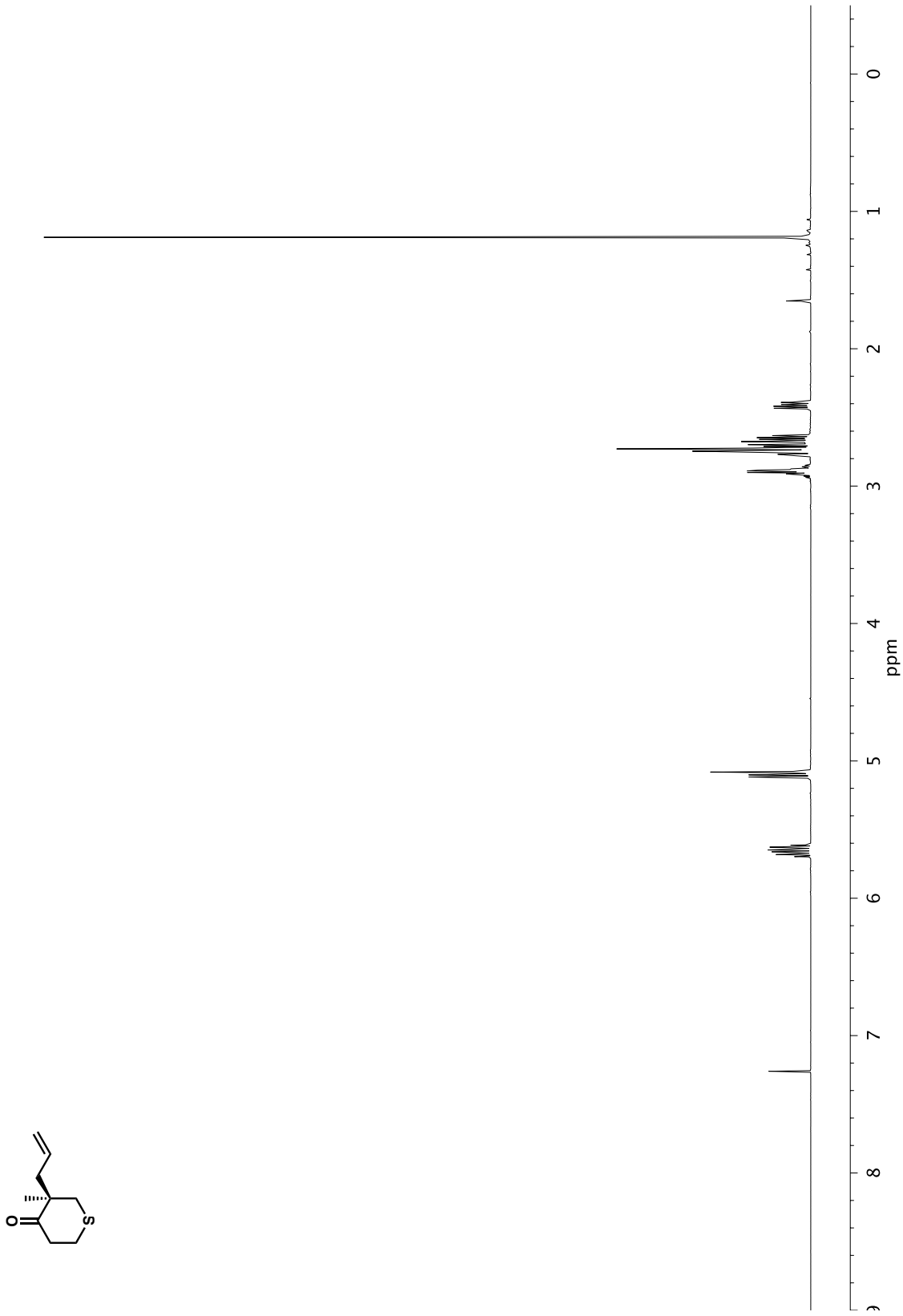



***Figure A3.4*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***16b***.

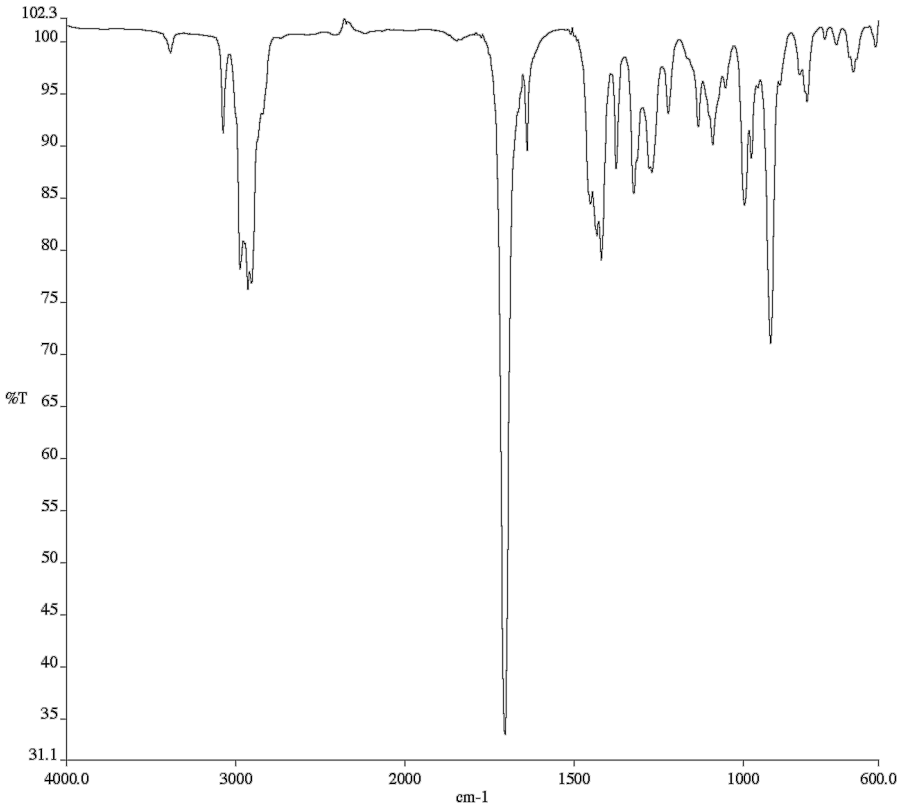



***Figure A3.5*** *Infrared spectrum (Thin Film, NaCl) of compound* ***16b****.*

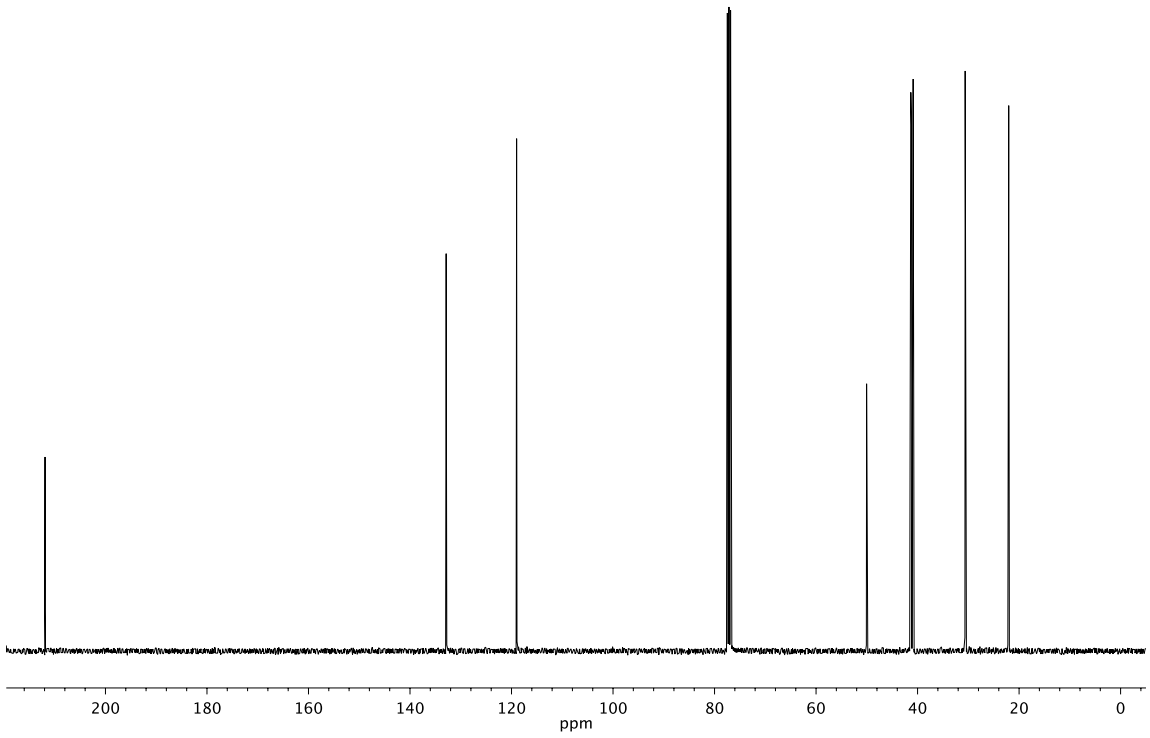



***Figure A3.6*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***16b****.*

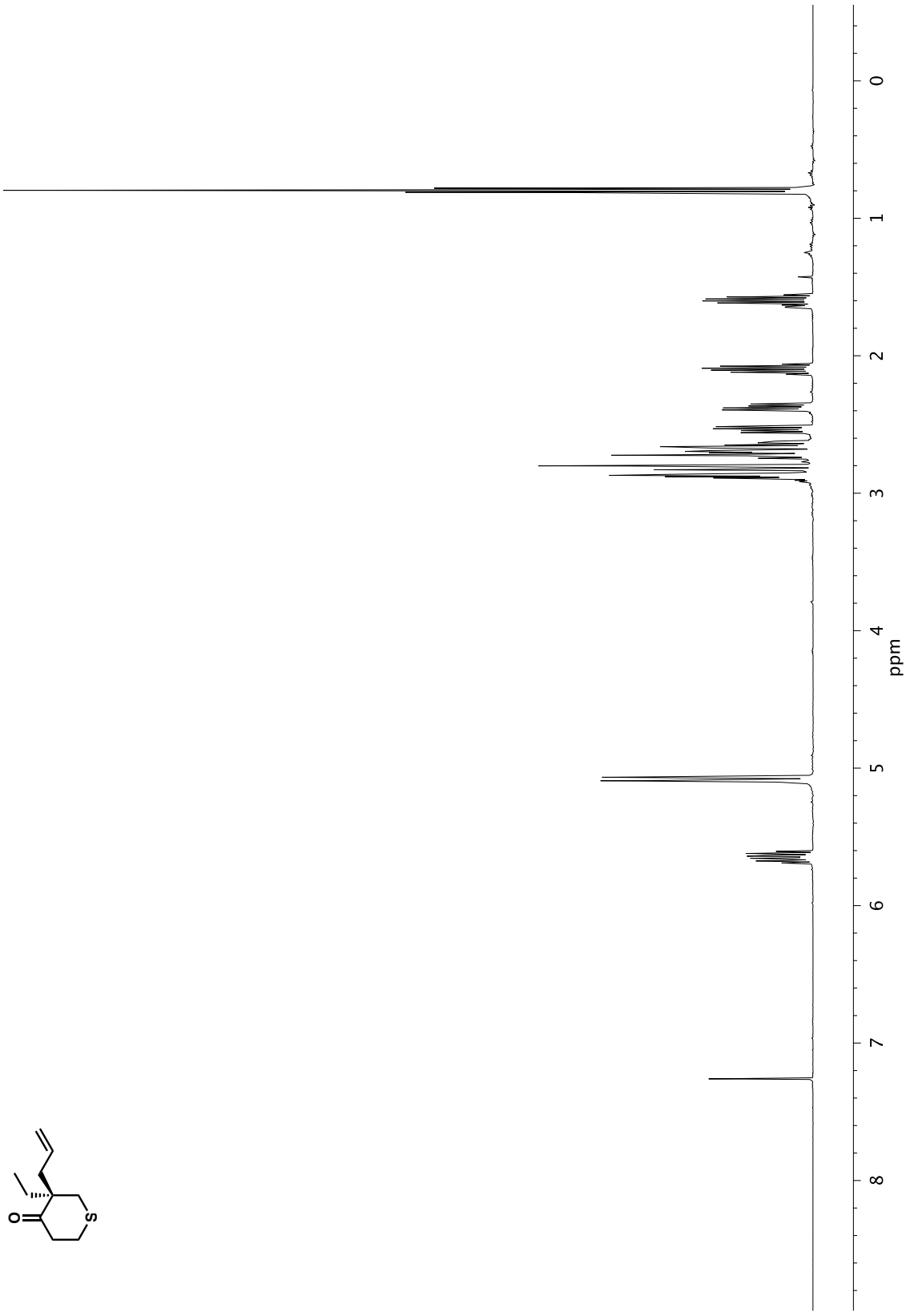



***Figure A3.7*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***16c****.*

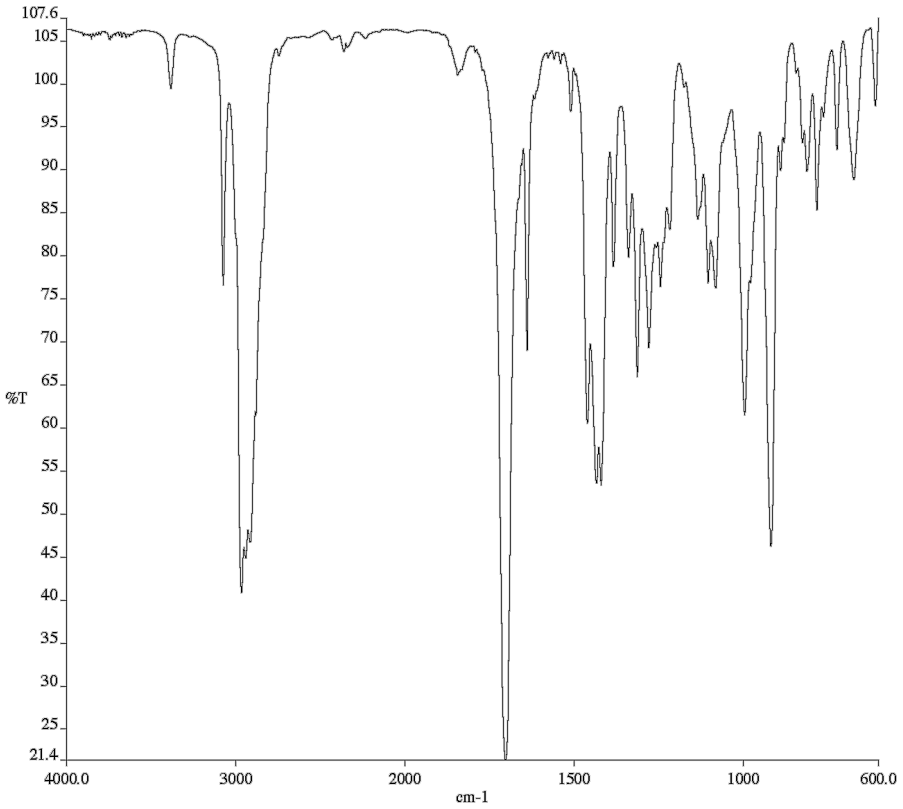



***Figure A3.8*** *Infrared spectrum (Thin Film, NaCl) of compound* ***16c****.*

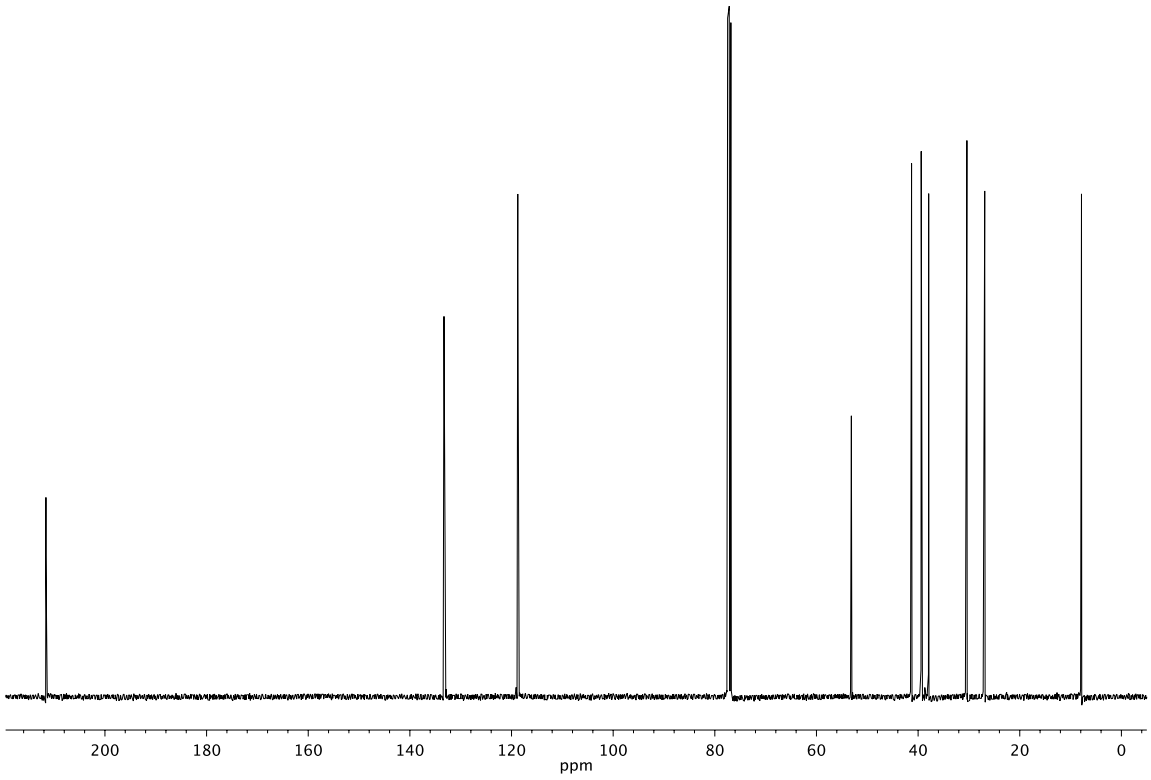



***Figure A3.9*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***16c****.*

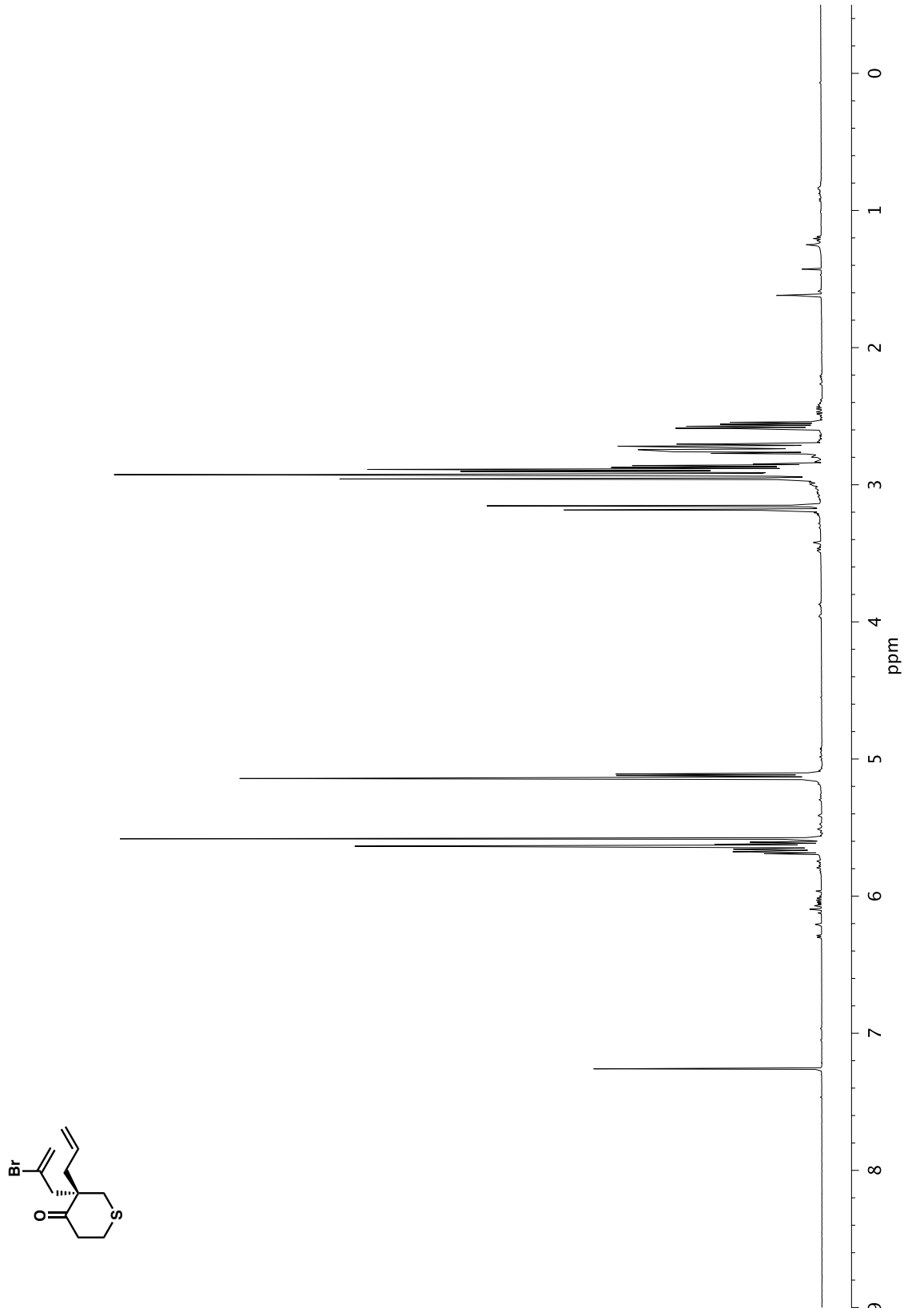



***Figure A3.10*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***16d****.*

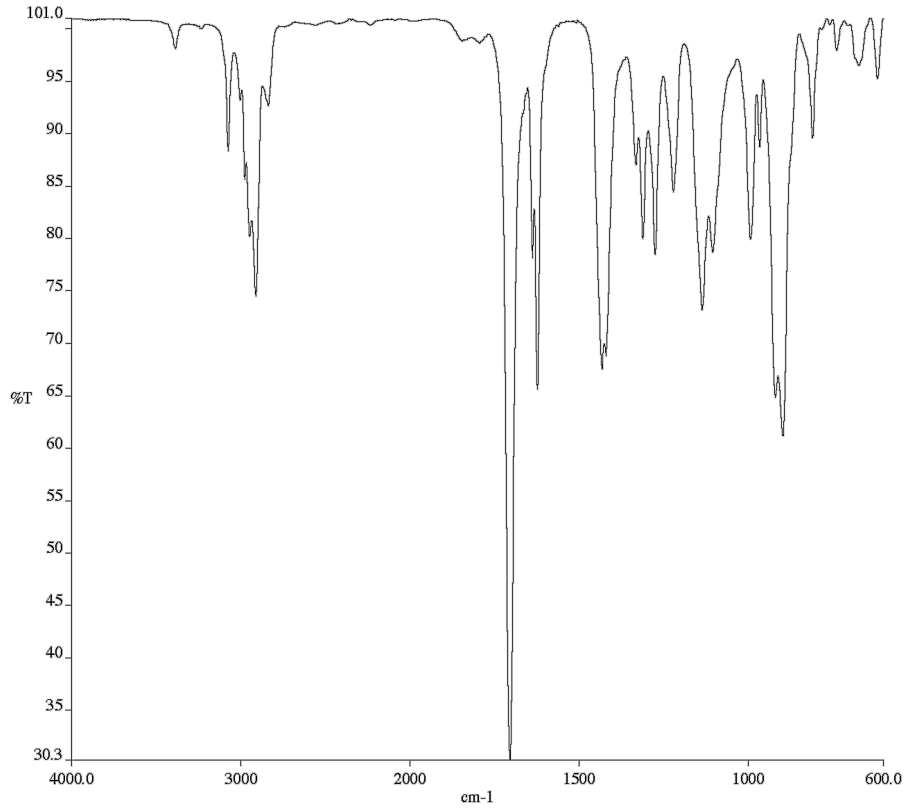



***Figure A3.11*** *Infrared spectrum (Thin Film, NaCl) of compound* ***16d****.*

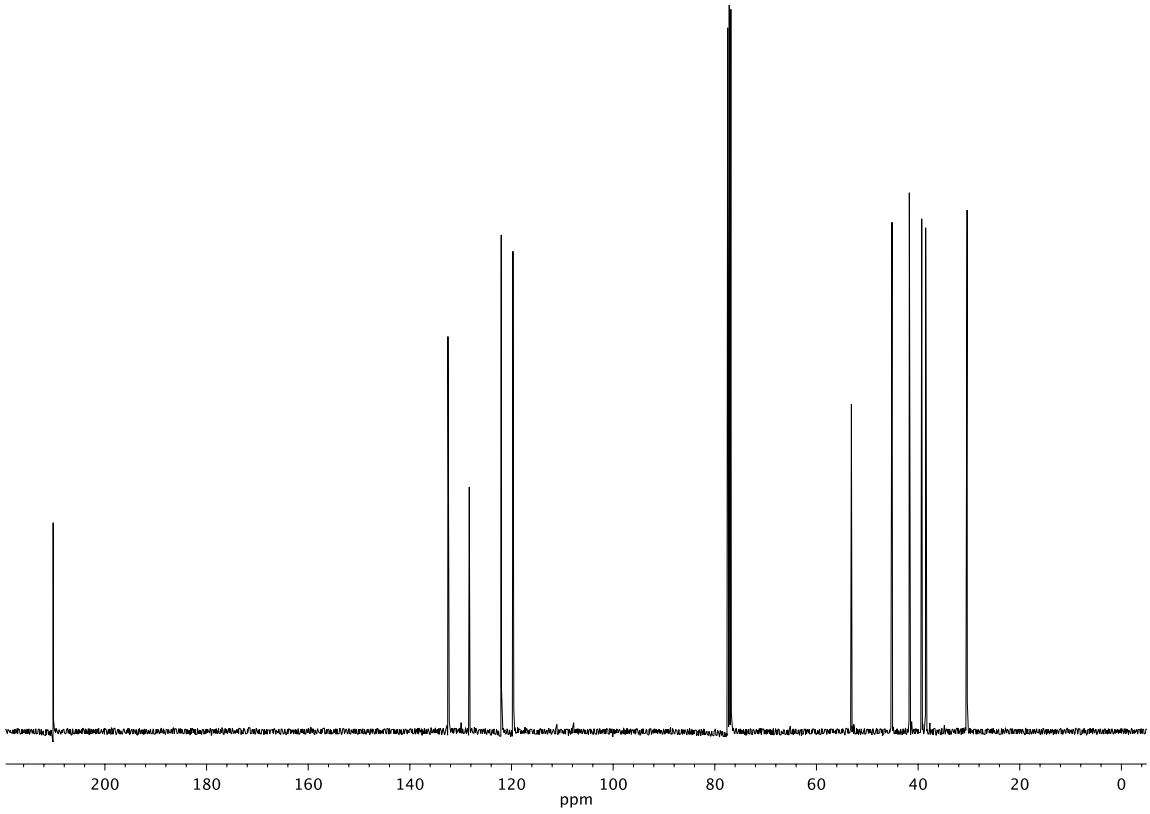



***Figure A3.12*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***16d****.*

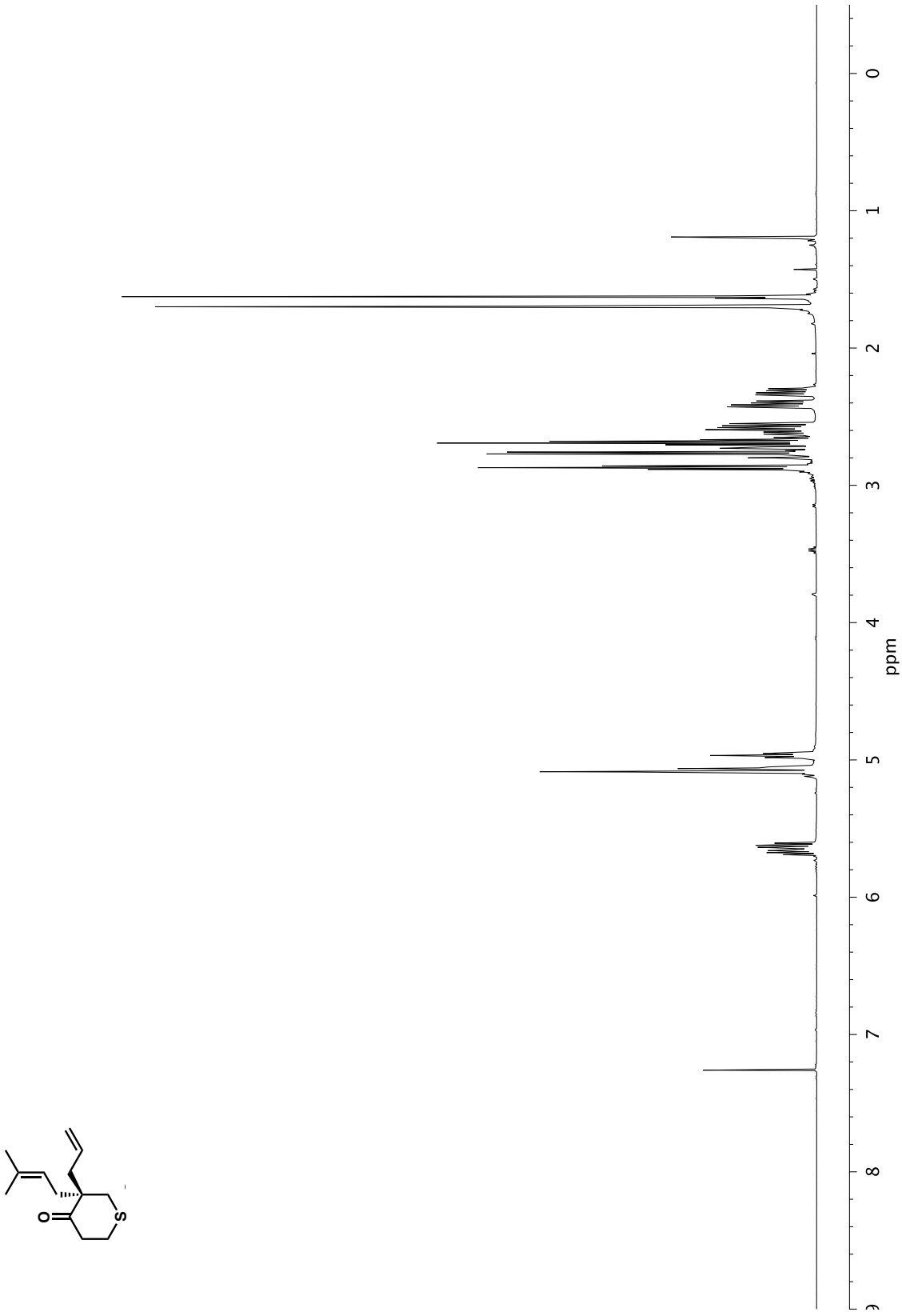



***Figure A3.13*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***16e***.

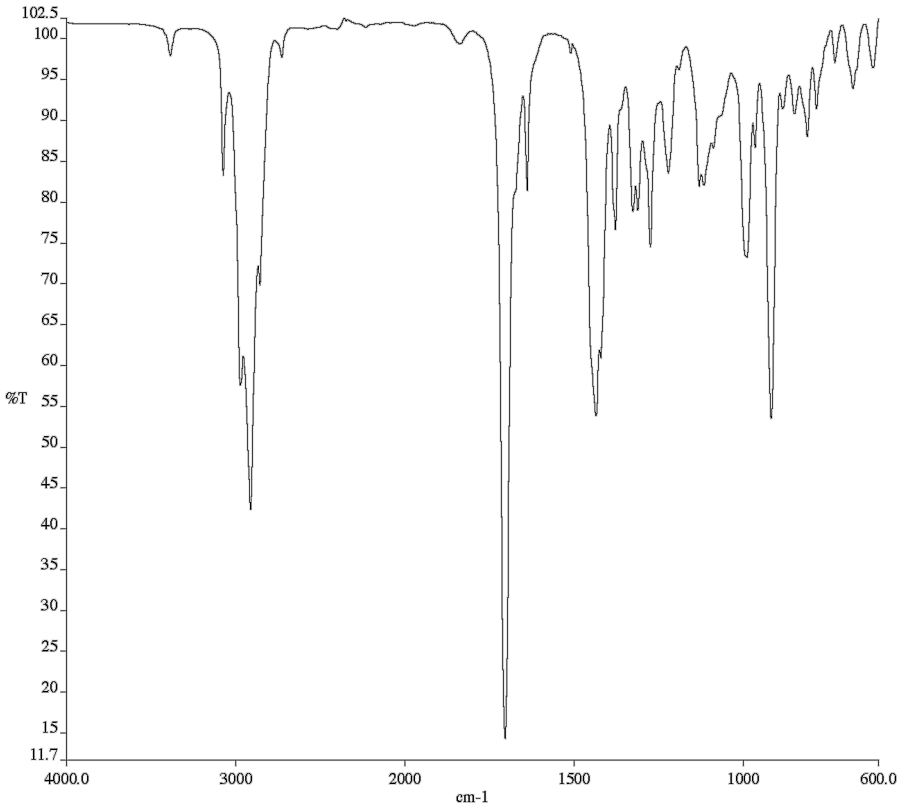



***Figure A3.14*** *Infrared spectrum (Thin Film, NaCl) of compound* ***16e****.*

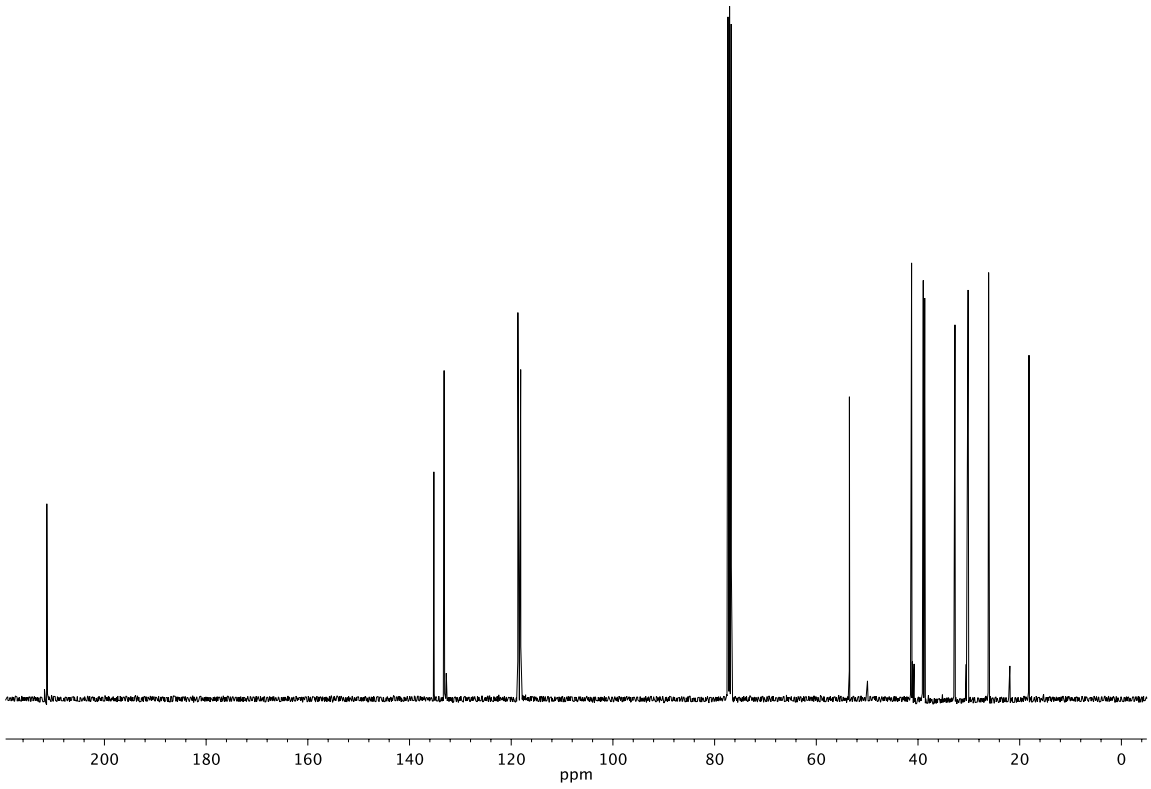



***Figure A3.15*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***16e****.*

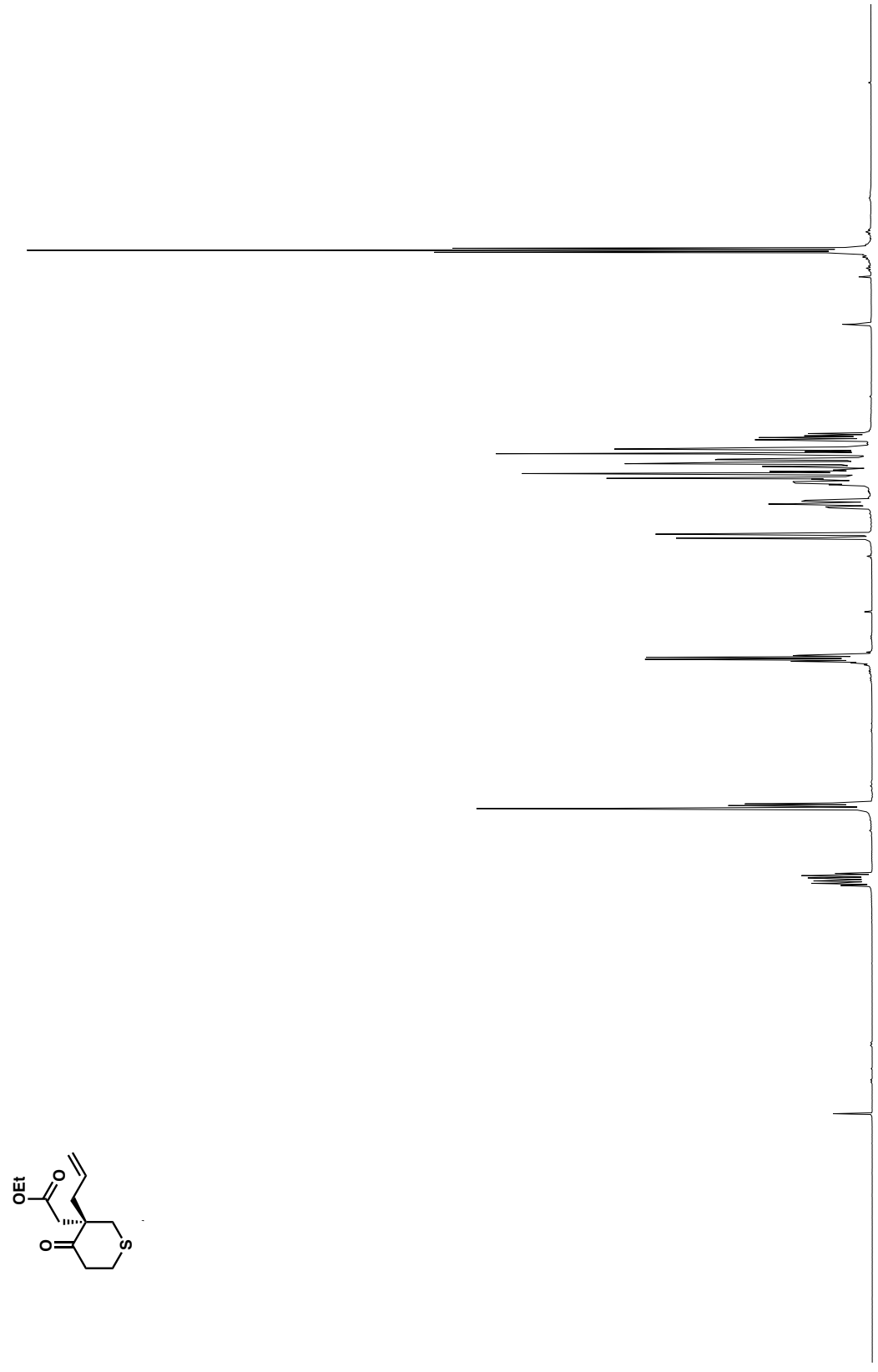



***Figure A3.16*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound **16f**.*

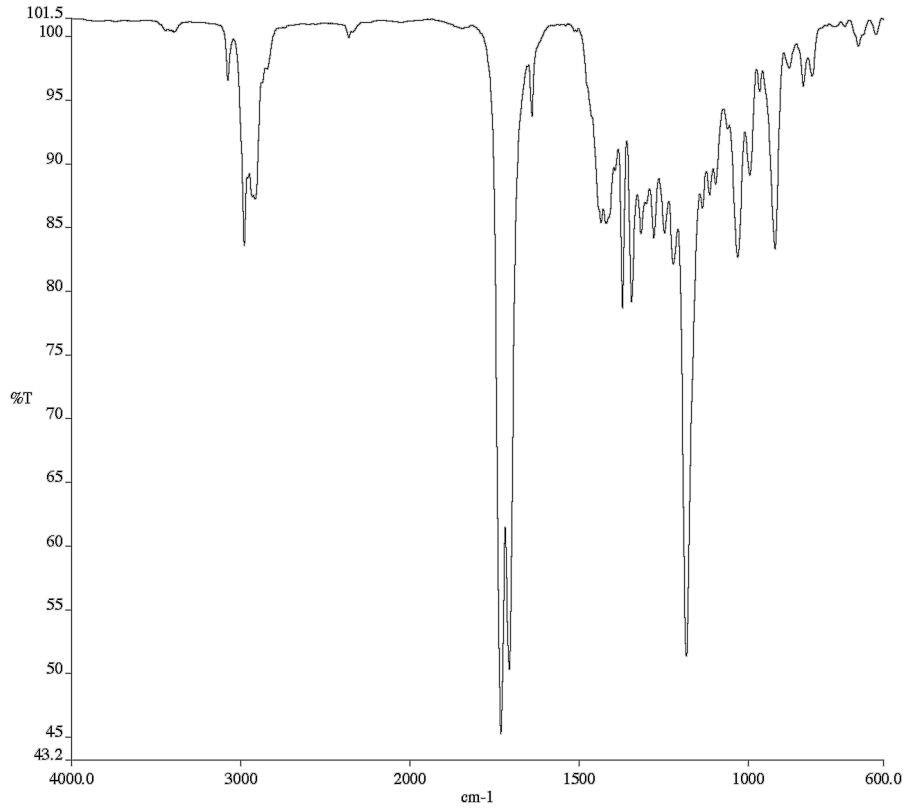



***Figure A3.17*** *Infrared spectrum (Thin Film, NaCl) of compound* ***16f****.*

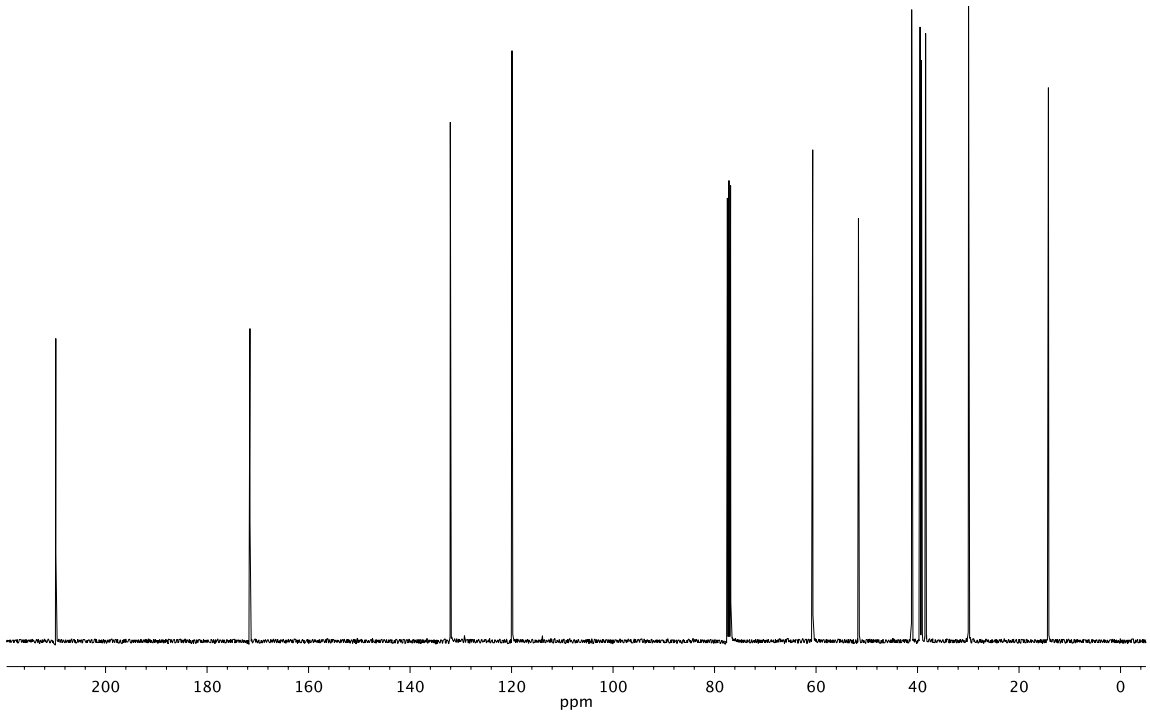



***Figure A3.18*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***16f****.*

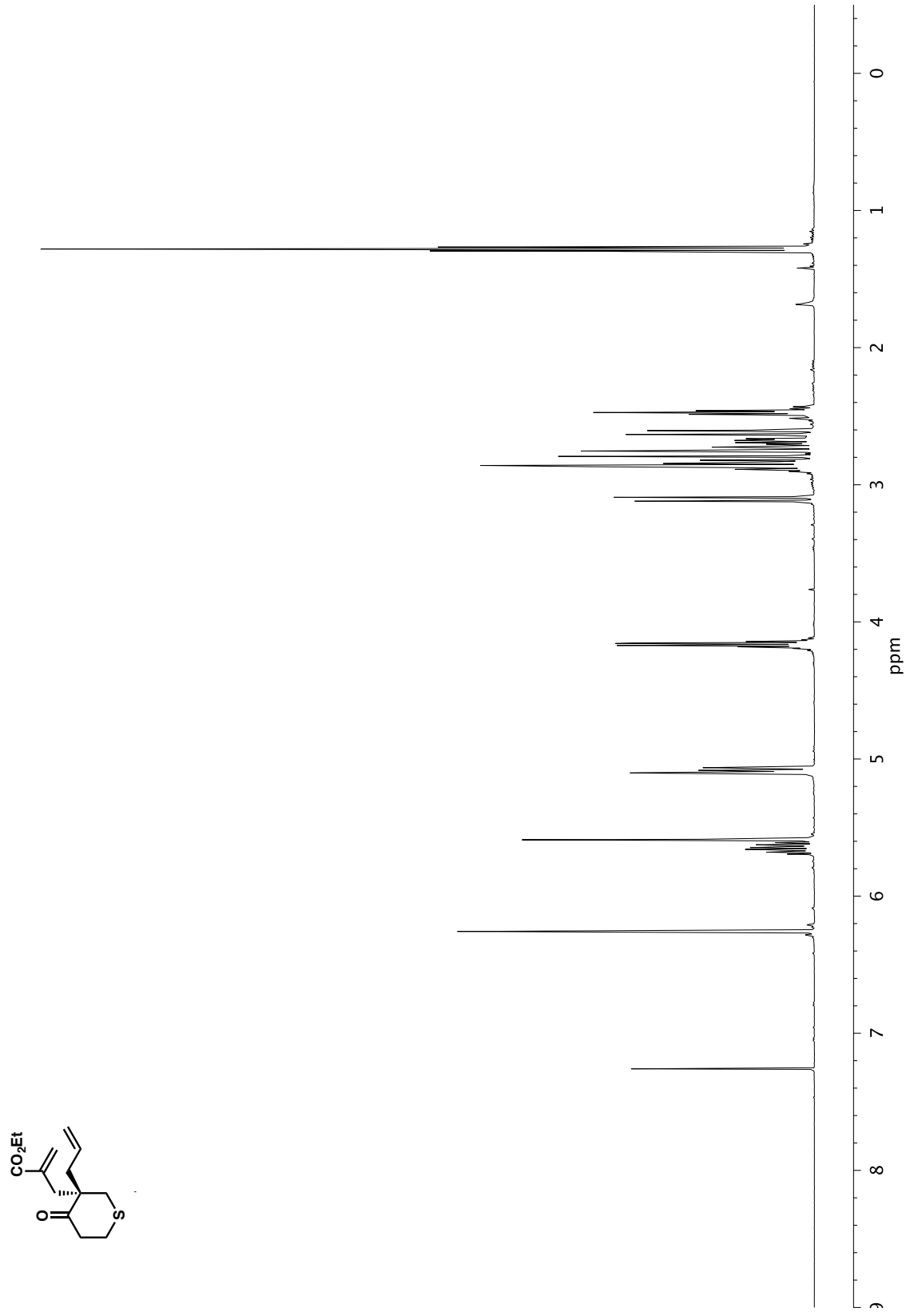



***Figure A3.19*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***16g***.

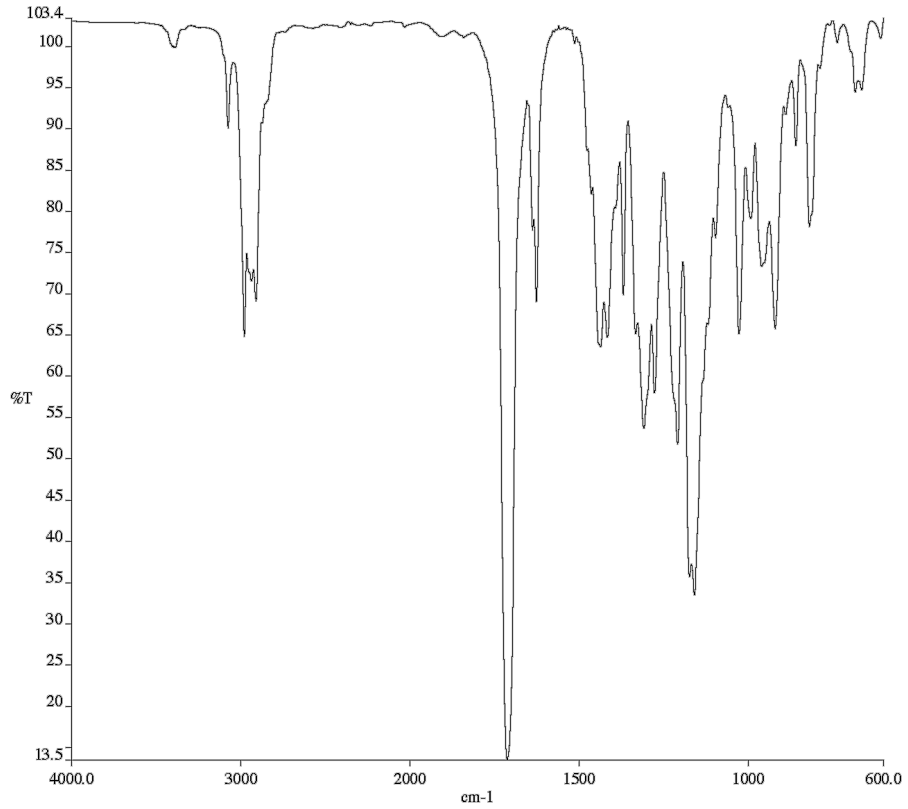



***Figure A3.20*** *Infrared spectrum (Thin Film, NaCl) of compound* ***16g****.*

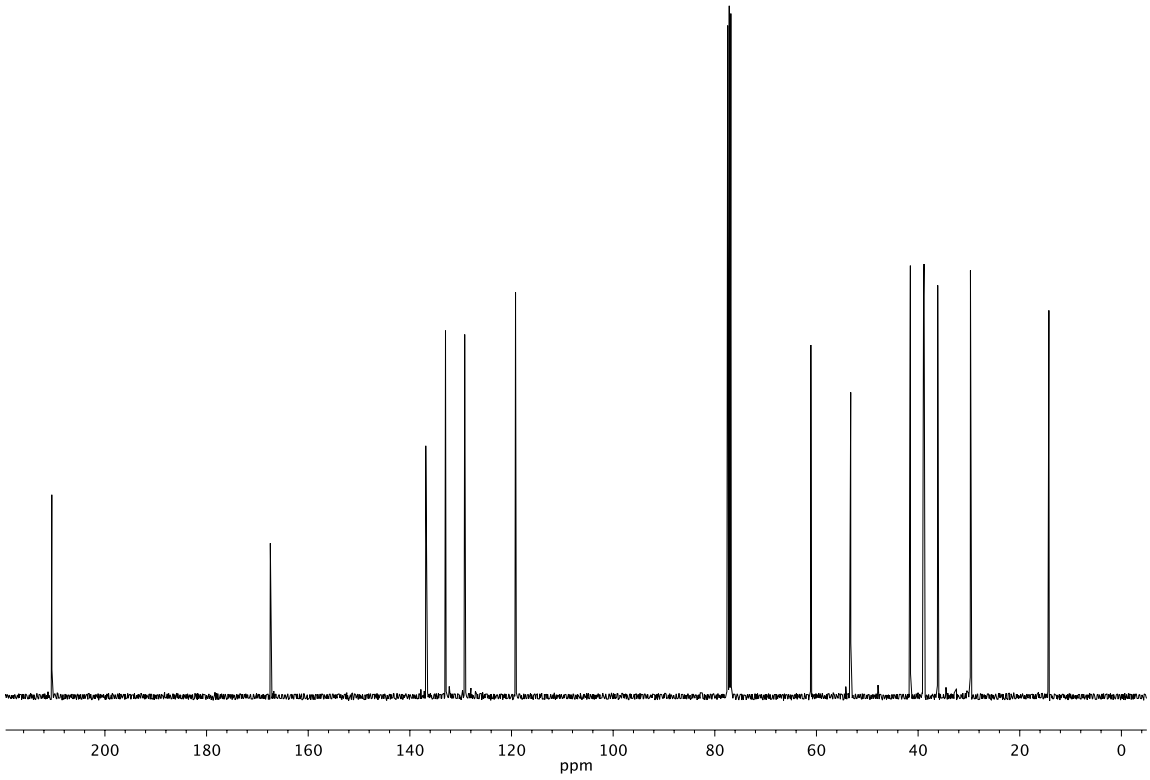



***Figure A3.21*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***16g****.*

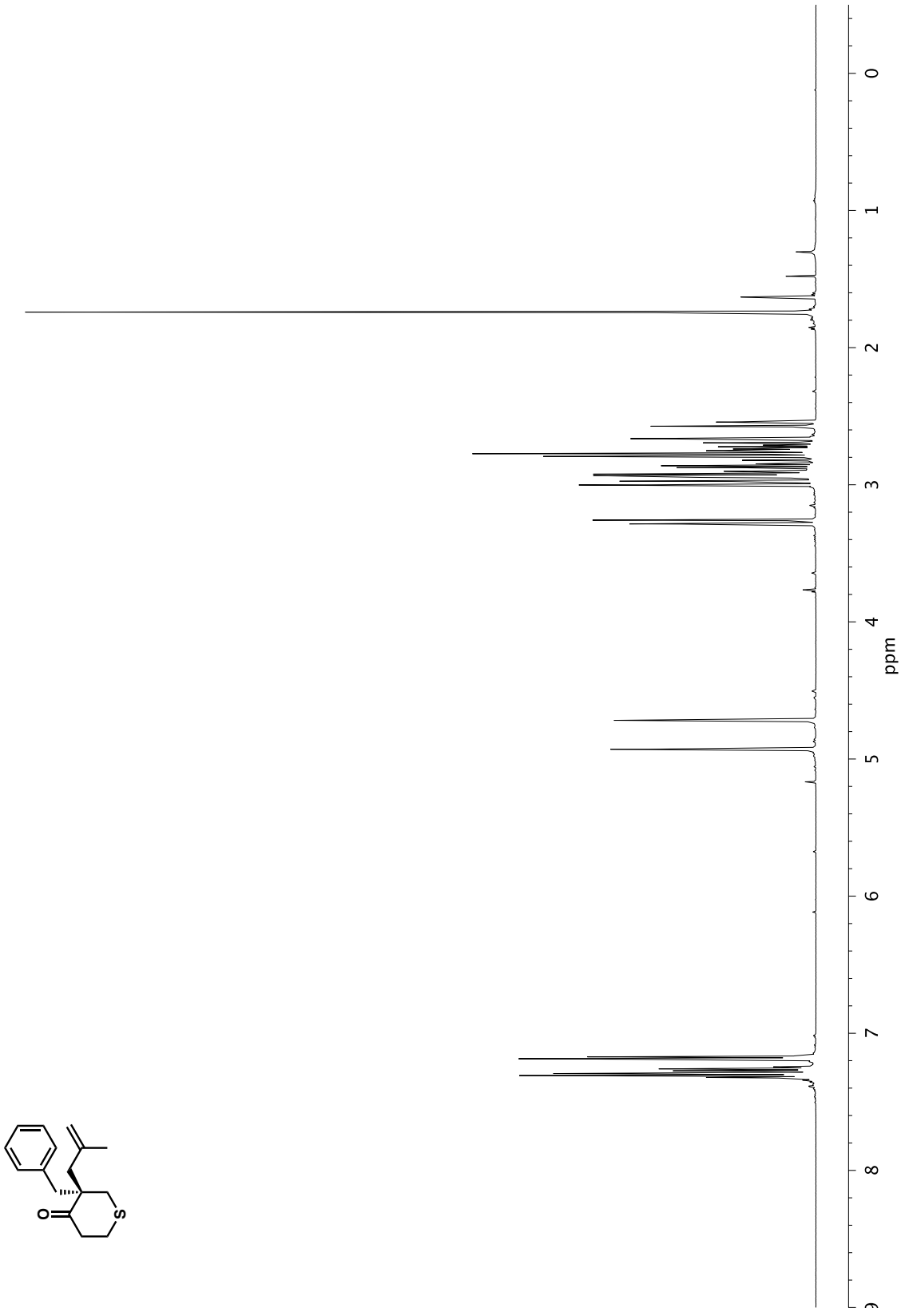



***Figure A3.22*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***16h***.

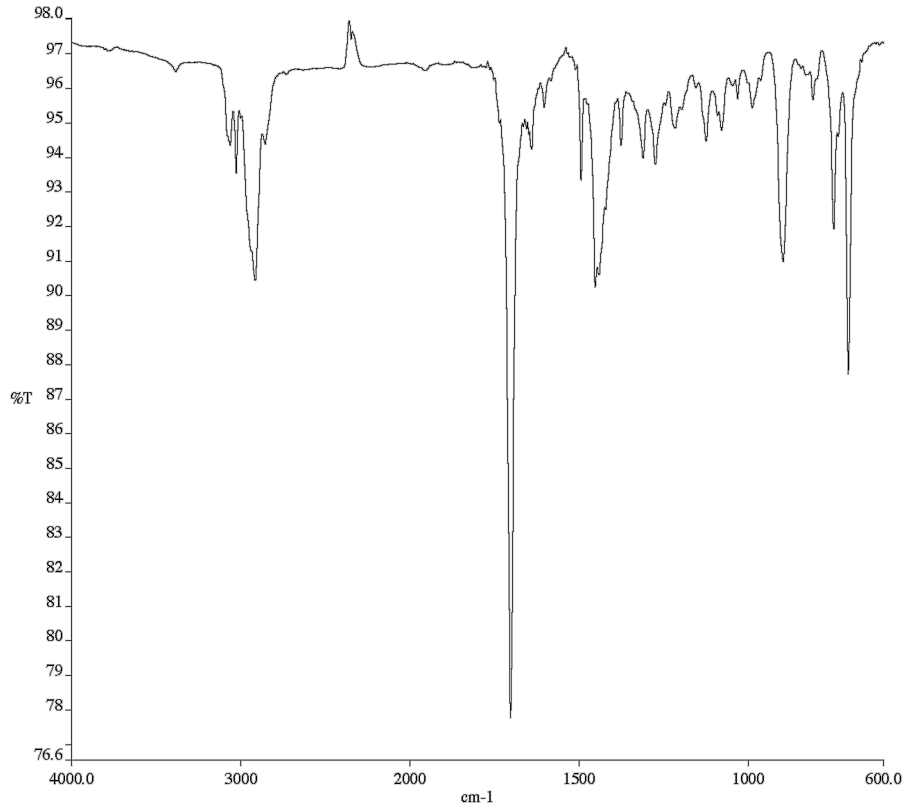



***Figure A3.23*** *Infrared spectrum (Thin Film, NaCl) of compound* ***16h***.

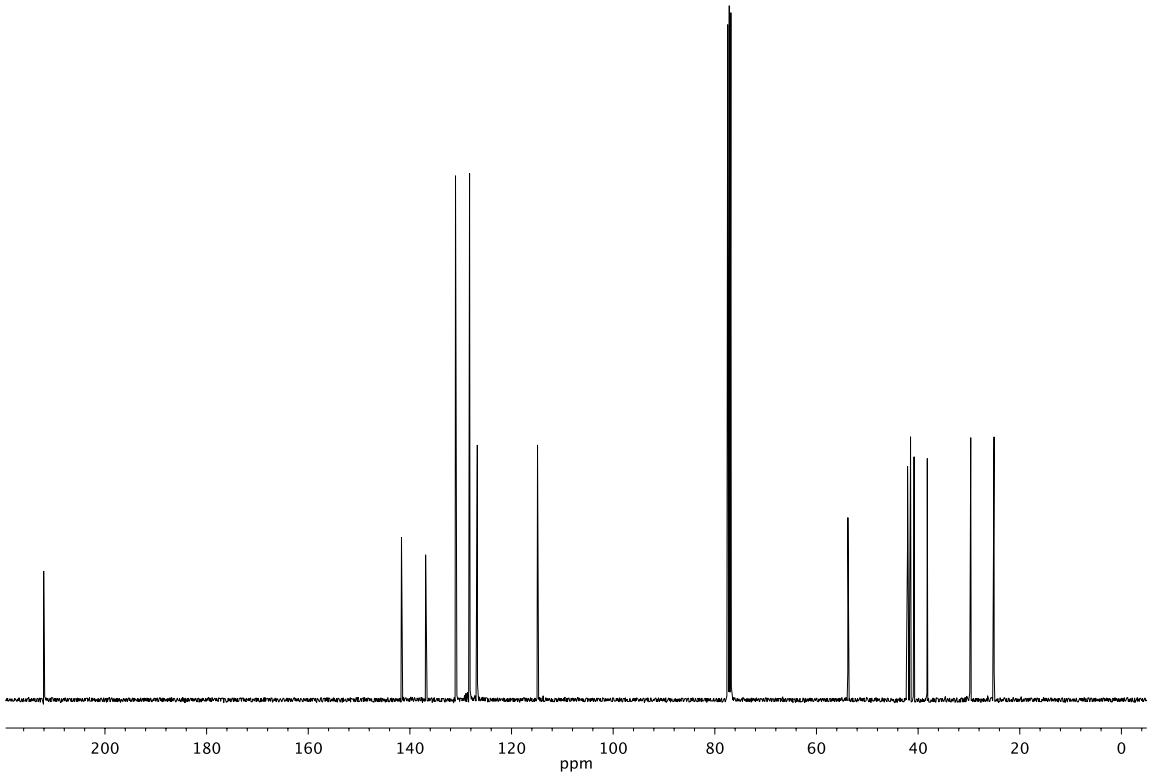



***Figure A3.24*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***16h***.

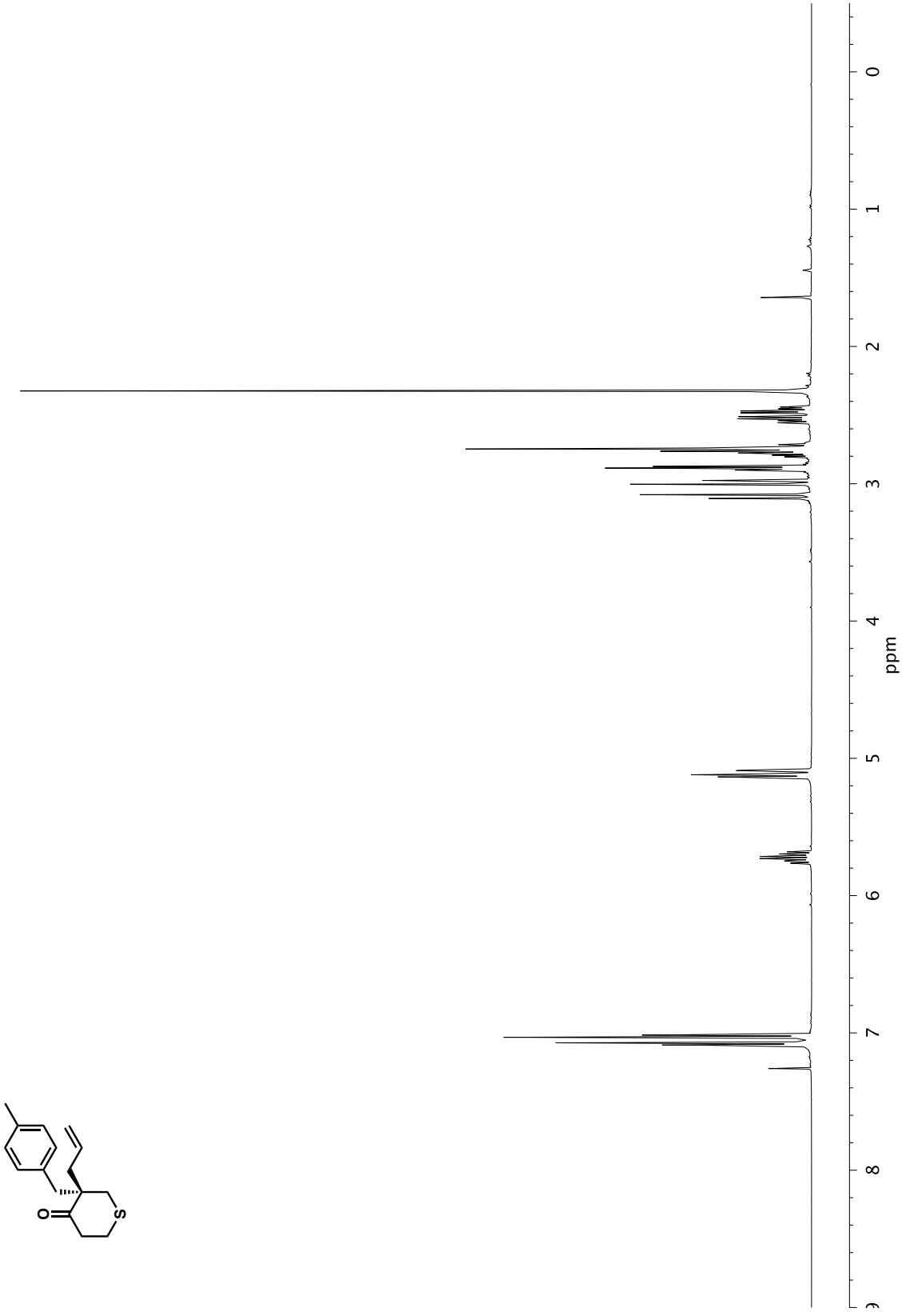



***Figure A3.25*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***16i****.*

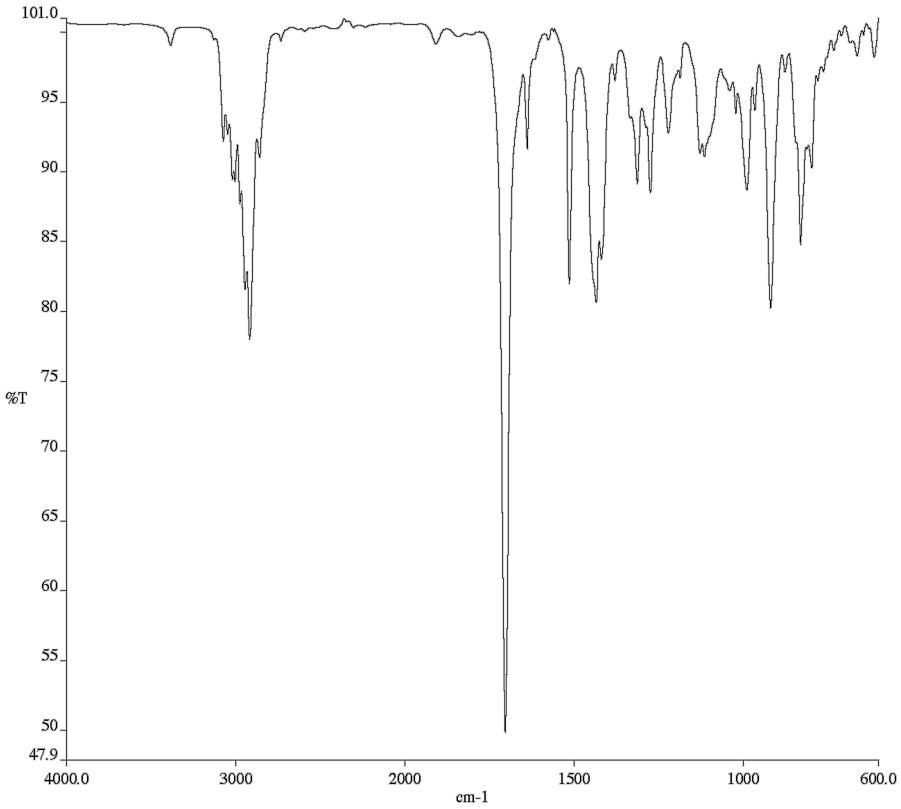



***Figure A3.26*** *Infrared spectrum (Thin Film, NaCl) of compound* ***16i***.

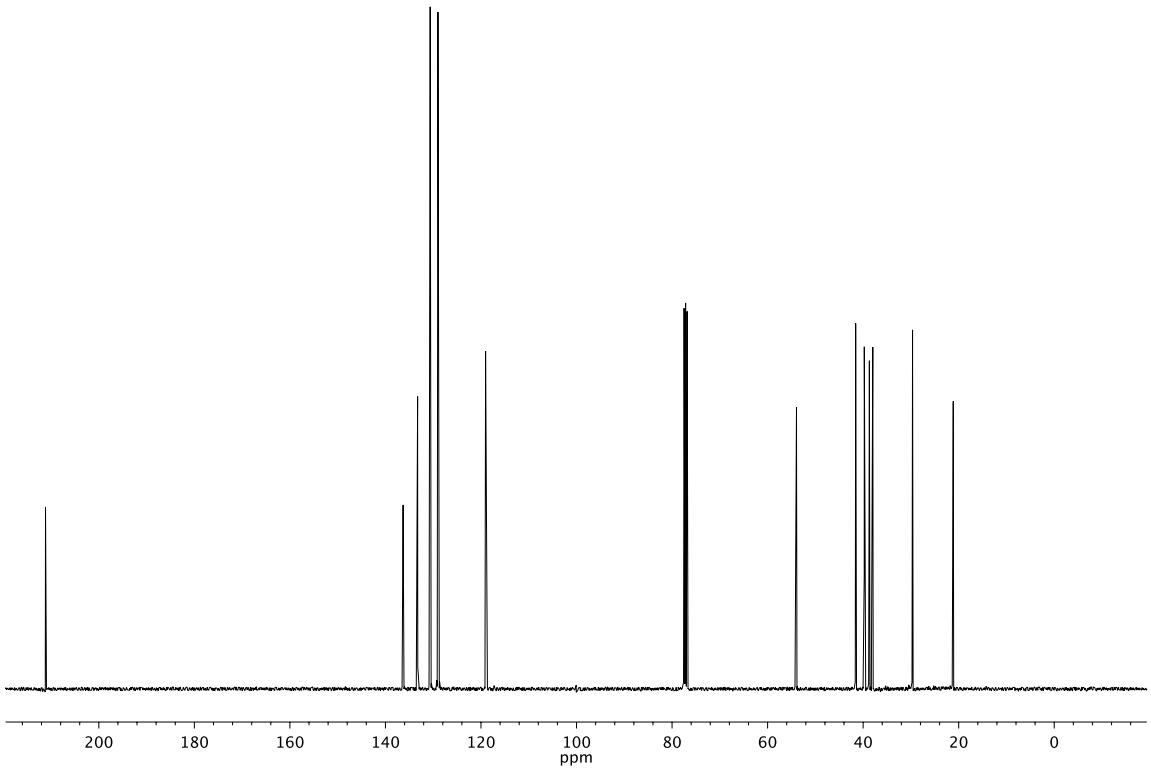



***Figure A3.27*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***16i***.

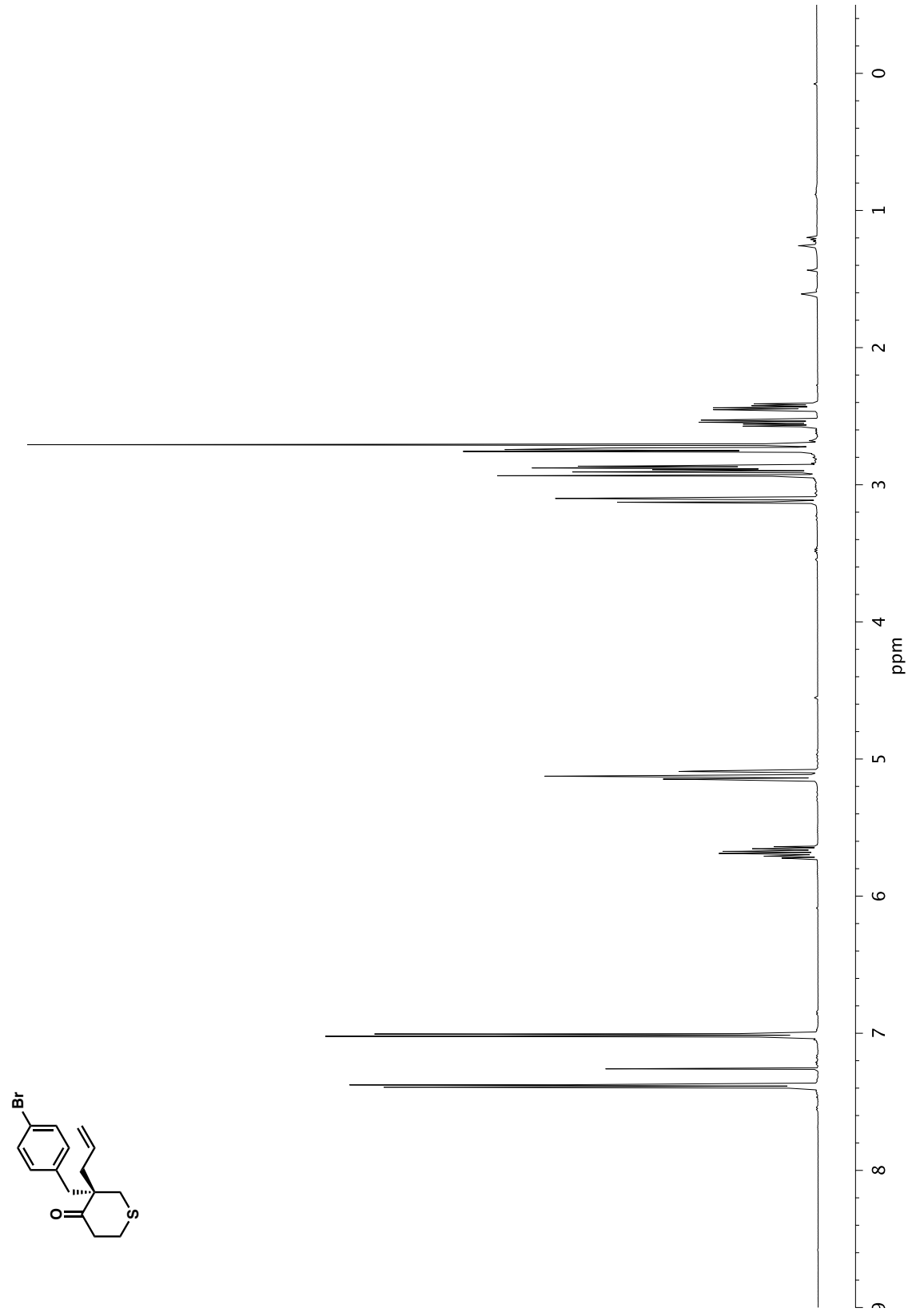



***Figure A3.28*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***16j****.*

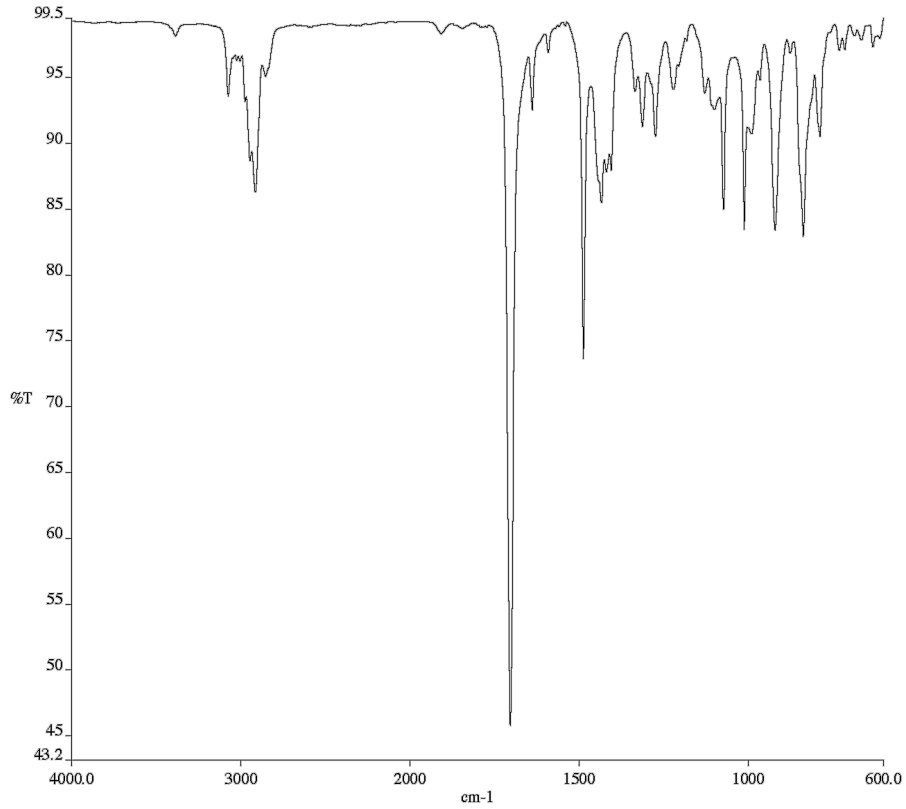



***Figure A3.29*** *Infrared spectrum (Thin Film, NaCl) of compound* ***16j****.*

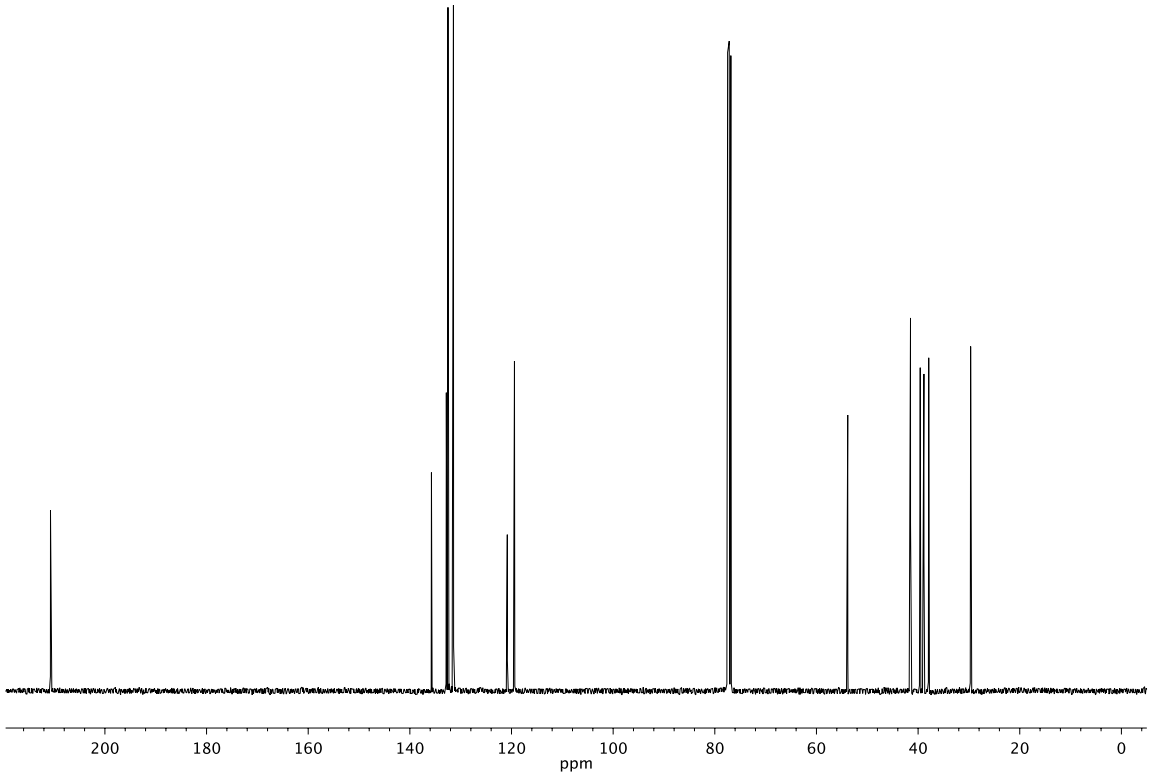



***Figure A3.30*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***16j****.*

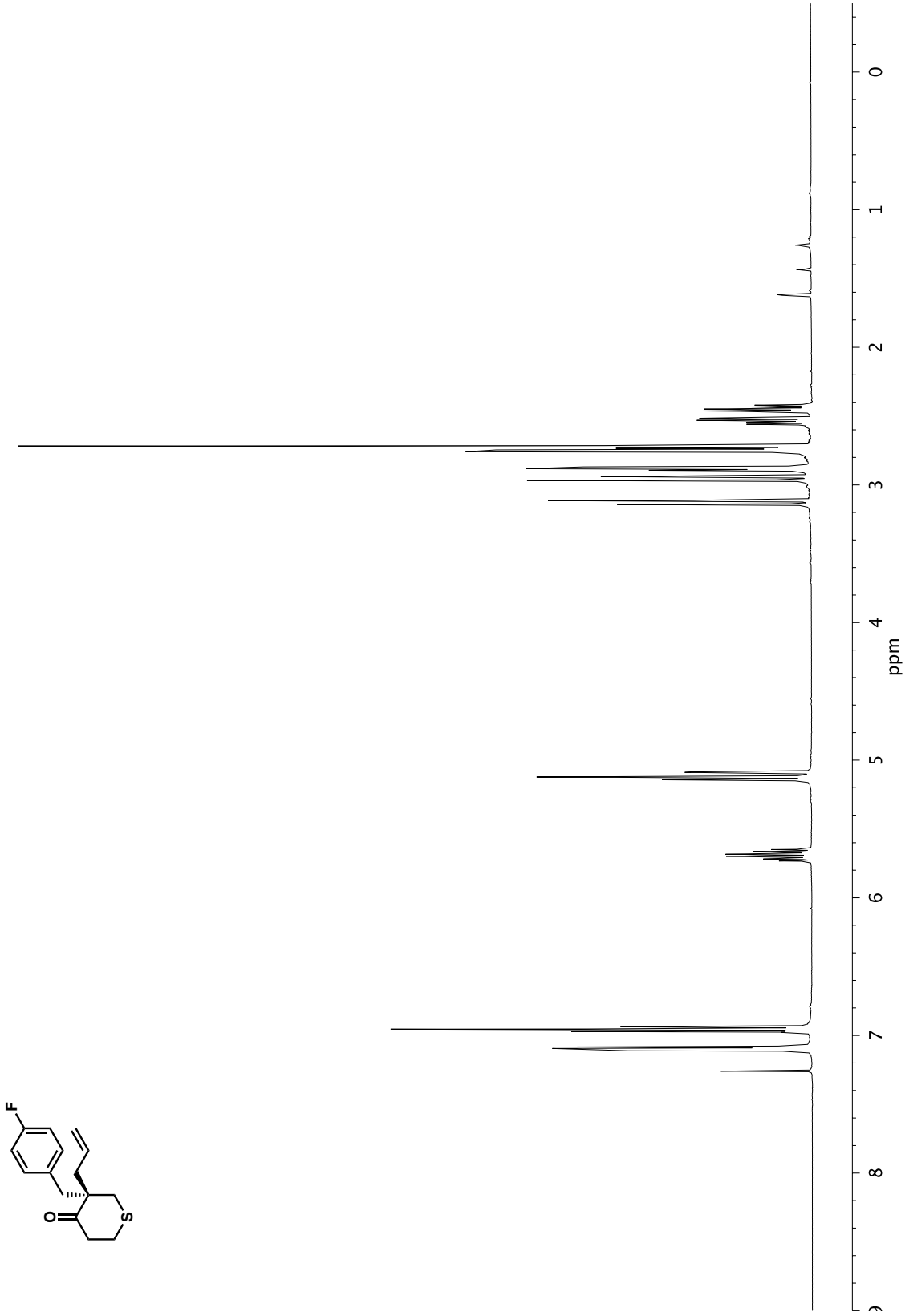



***Figure A3.31*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***16k****.*

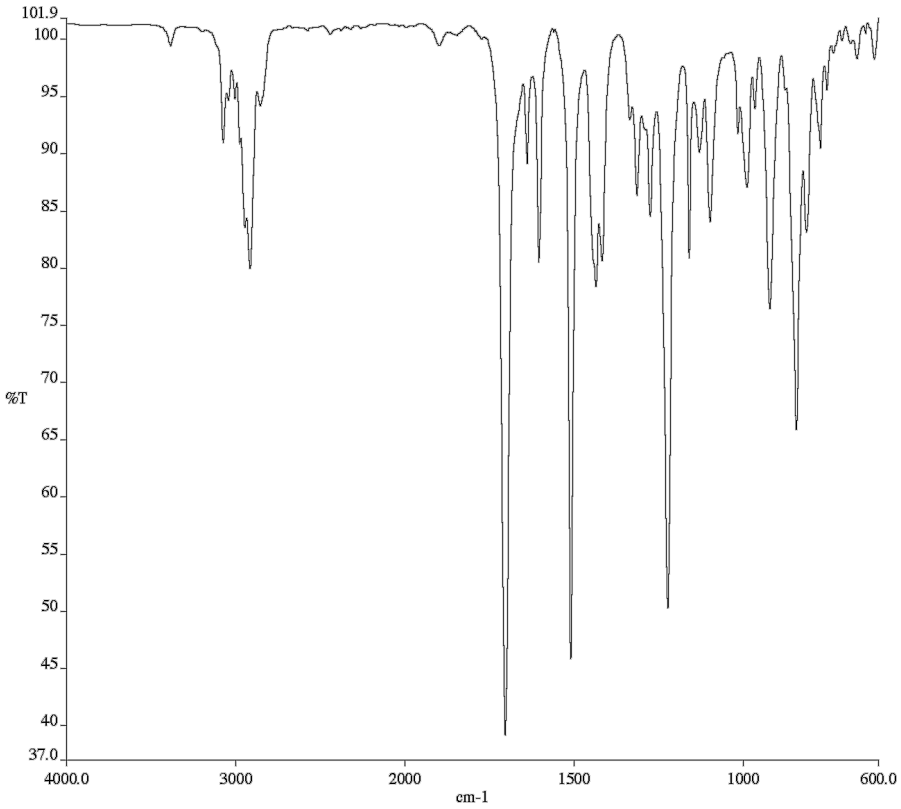



***Figure A3.32*** *Infrared spectrum (Thin Film, NaCl) of compound* ***16k****.*

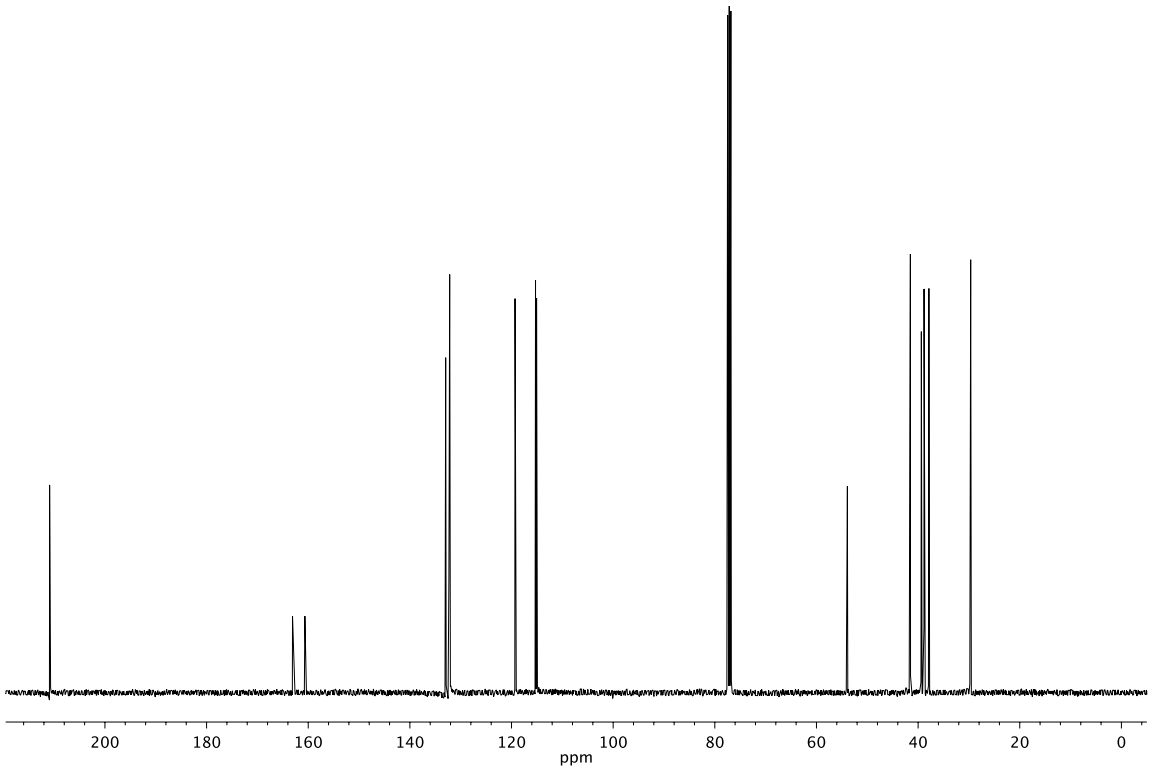



***Figure A3.33*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***16k****.*

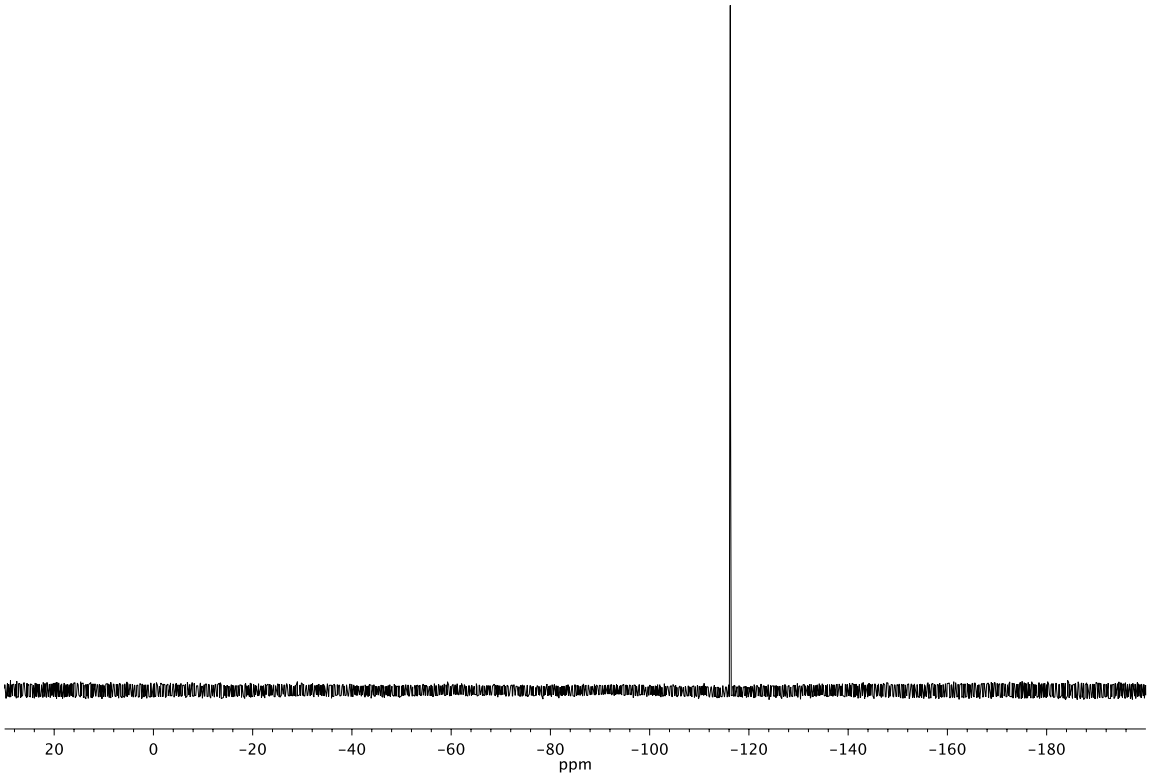



***Figure A3.34*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***16k****.*

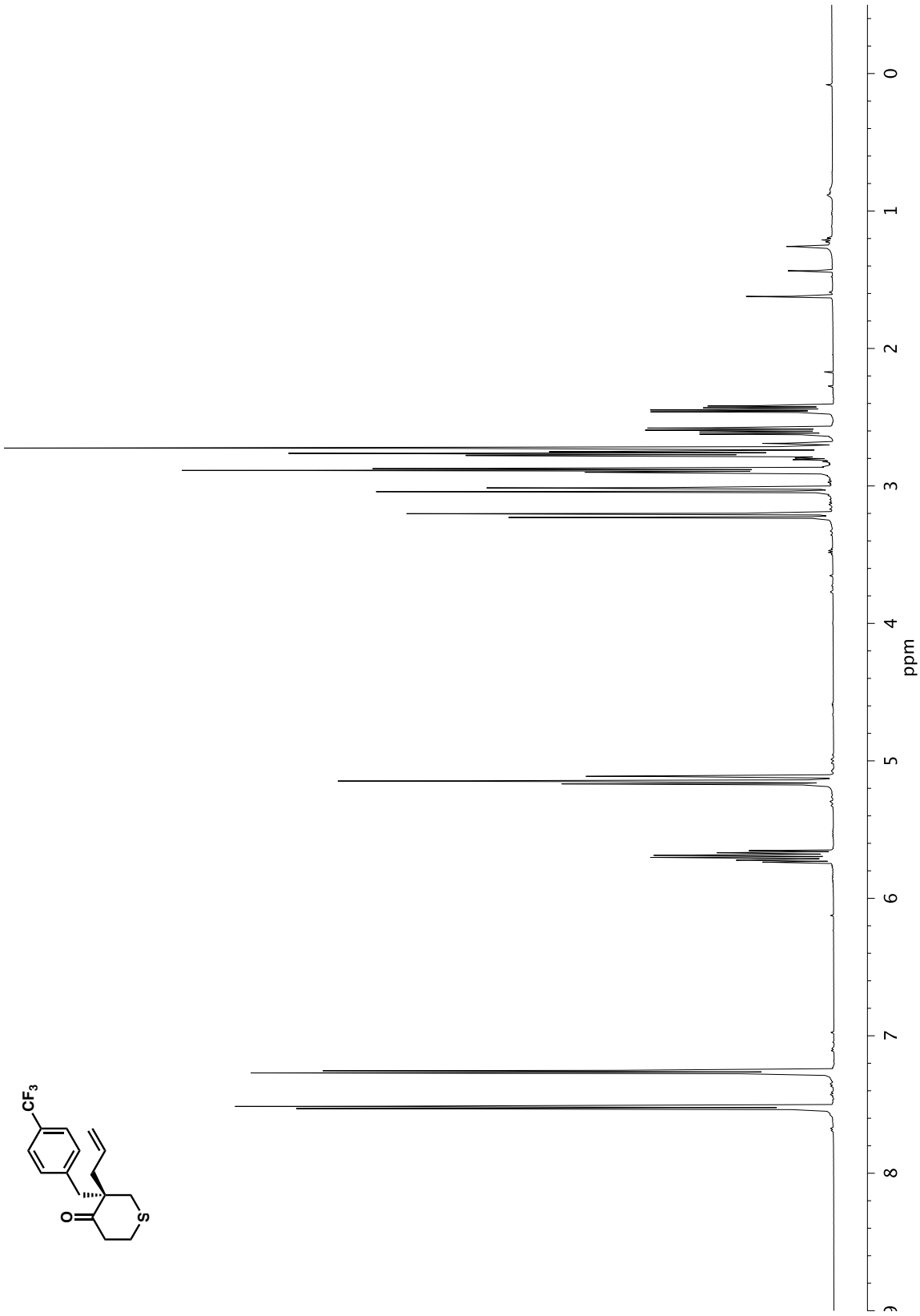



***Figure A3.35*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound **16l**.*

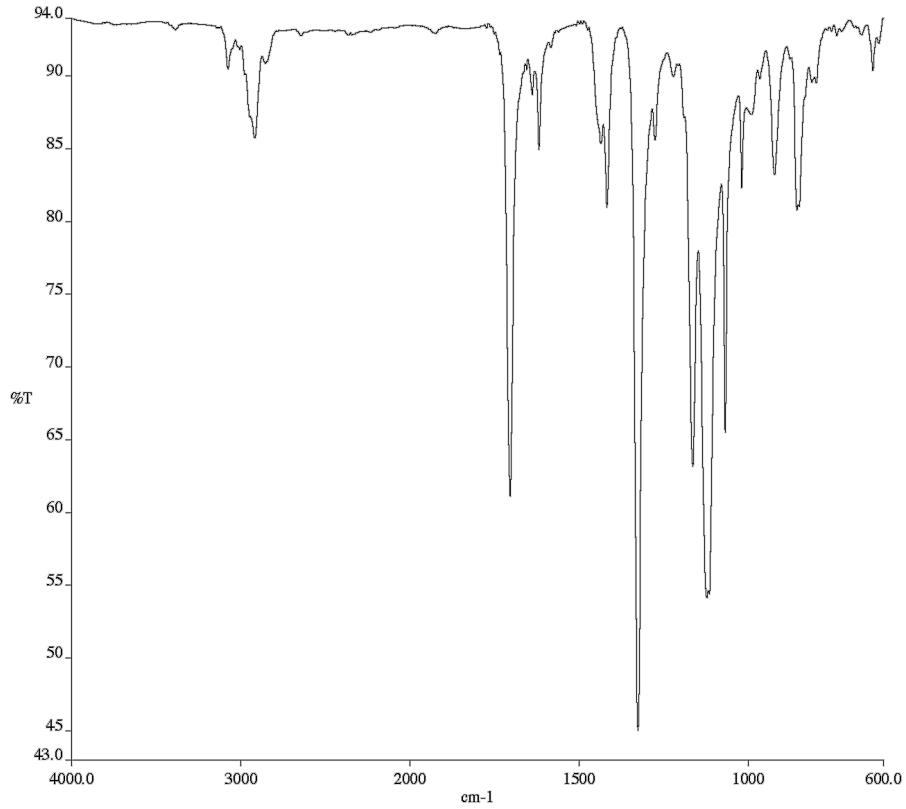



***Figure A3.36*** *Infrared spectrum (Thin Film, NaCl) of compound* ***16l***.

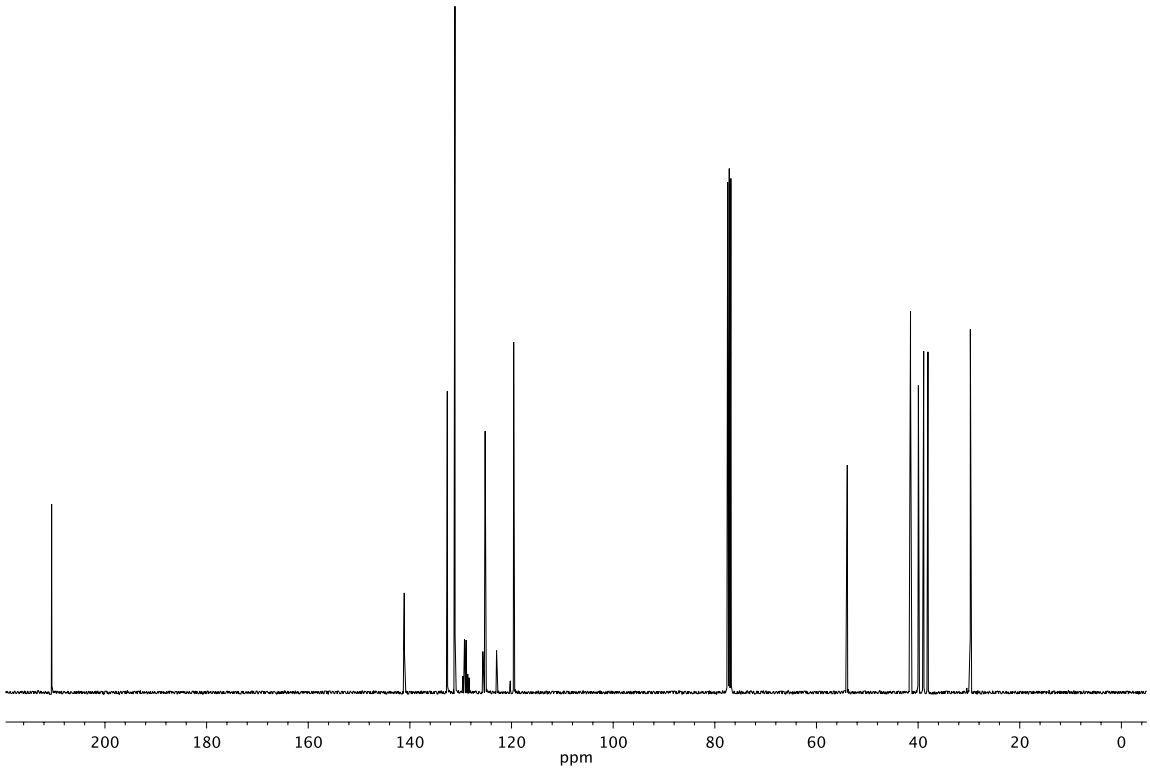



***Figure A3.37*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***16l***.

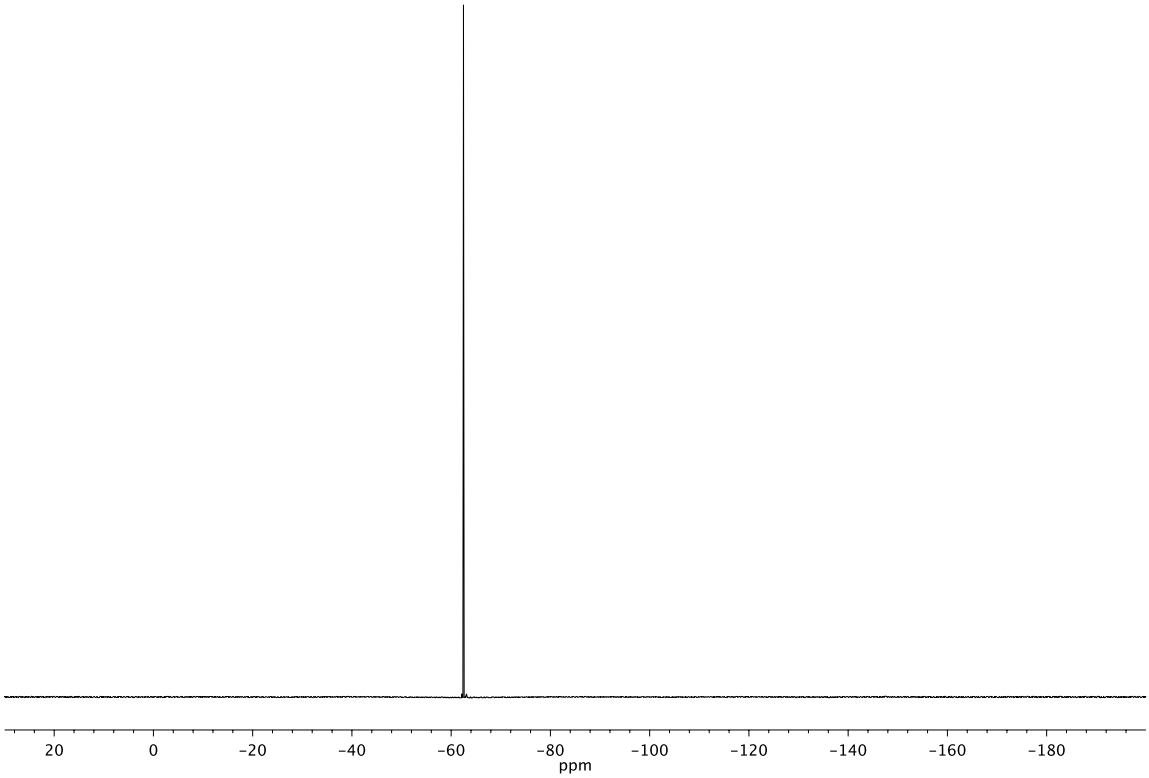



***Figure A3.38*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***16l****.*

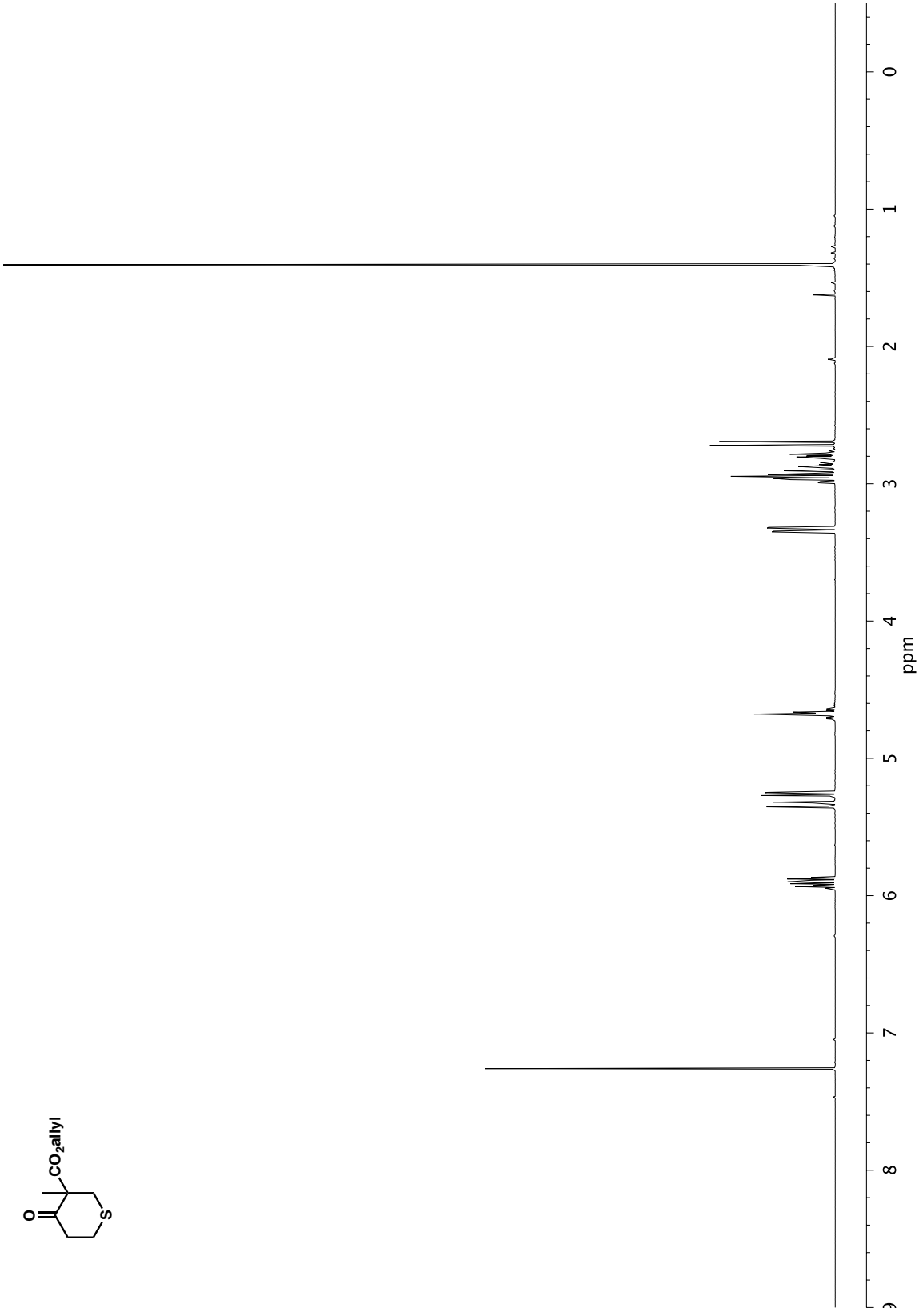



***Figure A3.39*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound **15b**.*

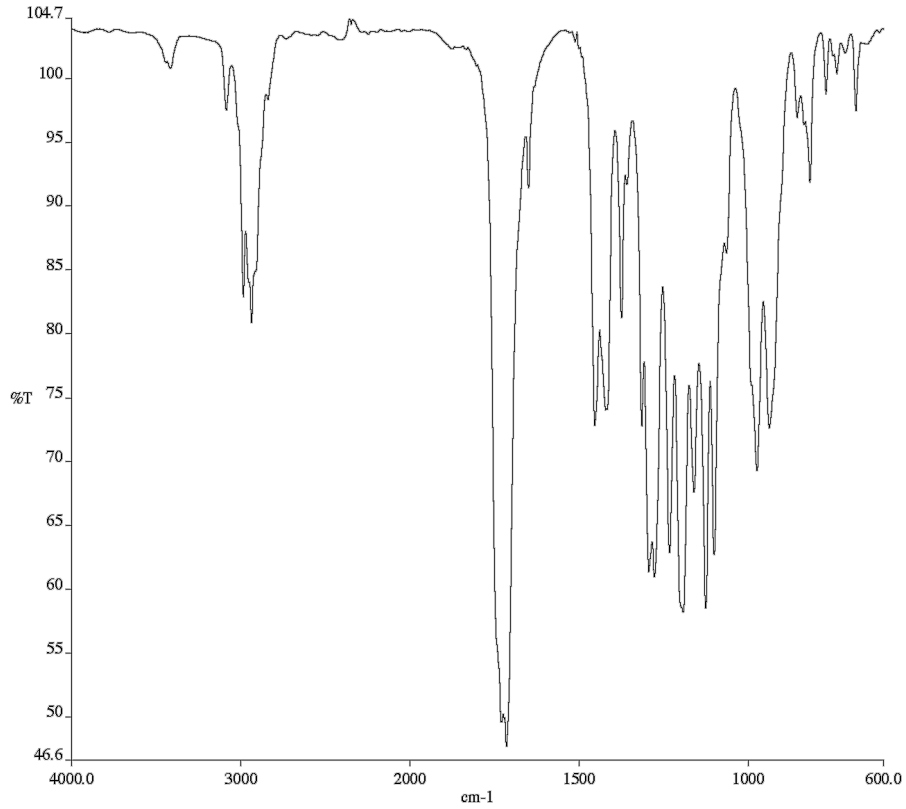



***Figure A3.40*** *Infrared spectrum (Thin Film, NaCl) of compound* ***15b***.

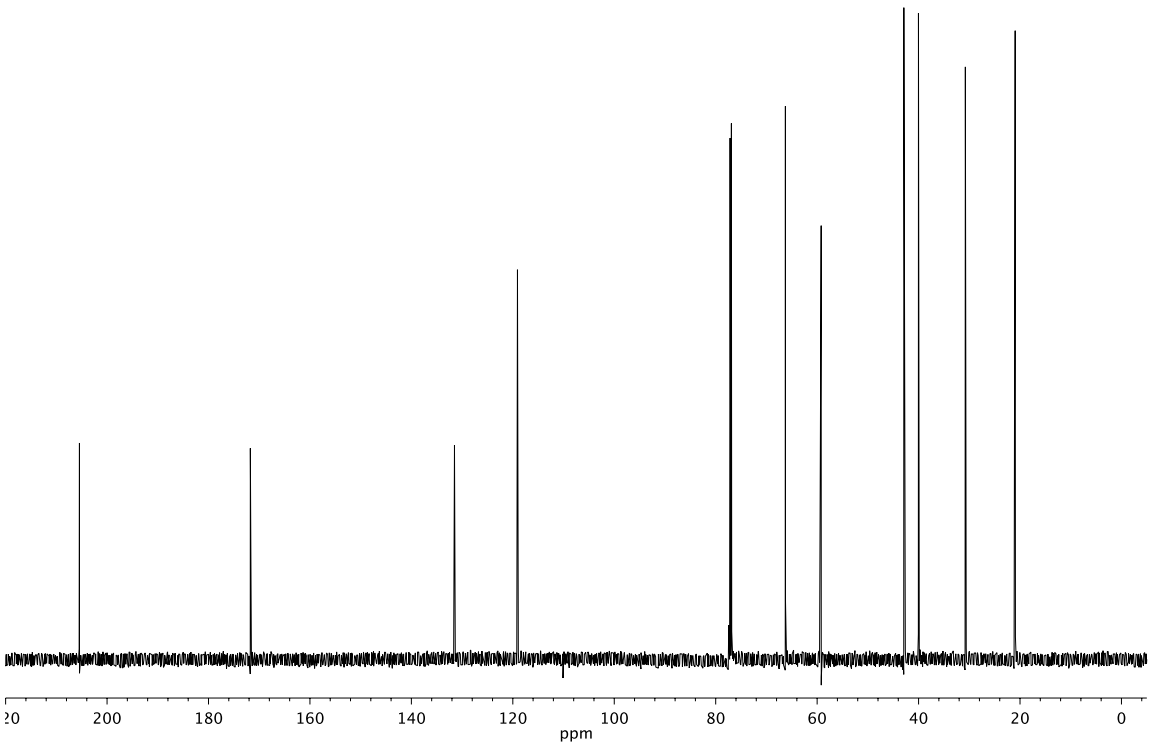



***Figure A3.41*** *$^{13}C$ NMR (125 MHz, $CDCl_3$) of compound* ***15b***.

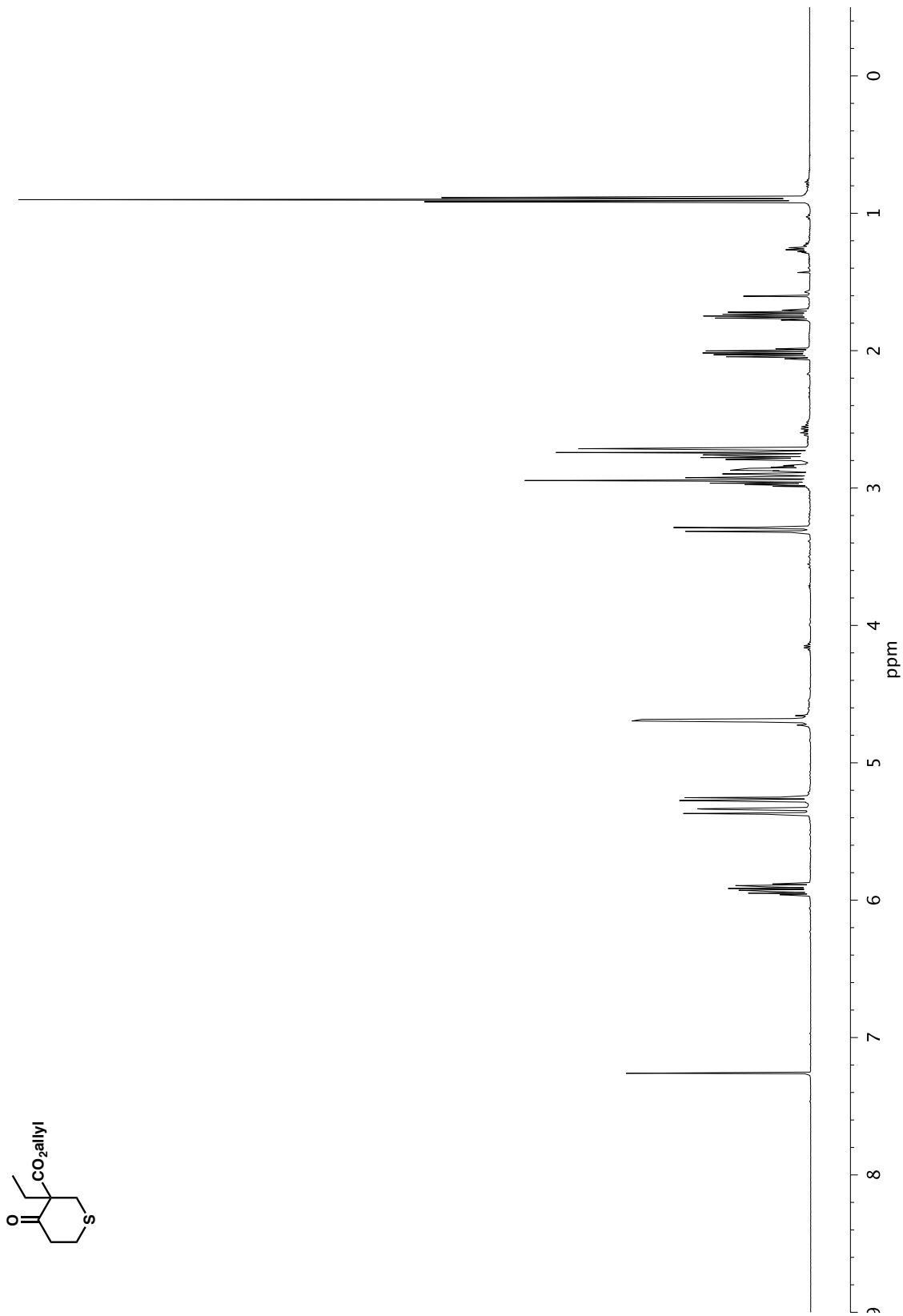



***Figure A3.42*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***15c****.*

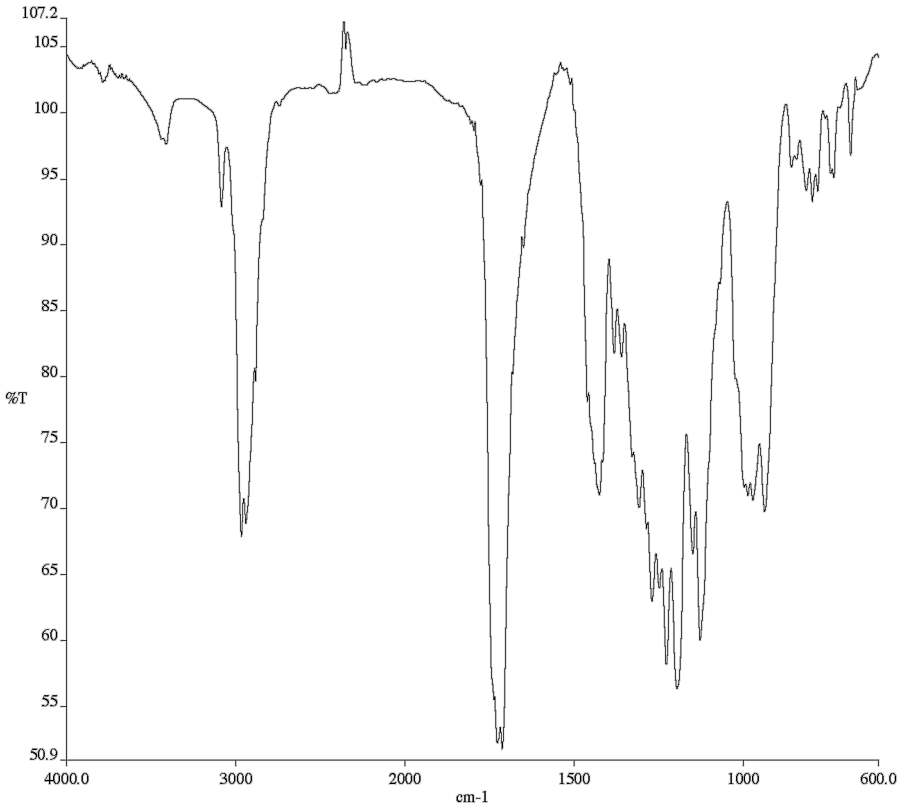



***Figure A3.43*** *Infrared spectrum (Thin Film, NaCl) of compound* ***15c****.*

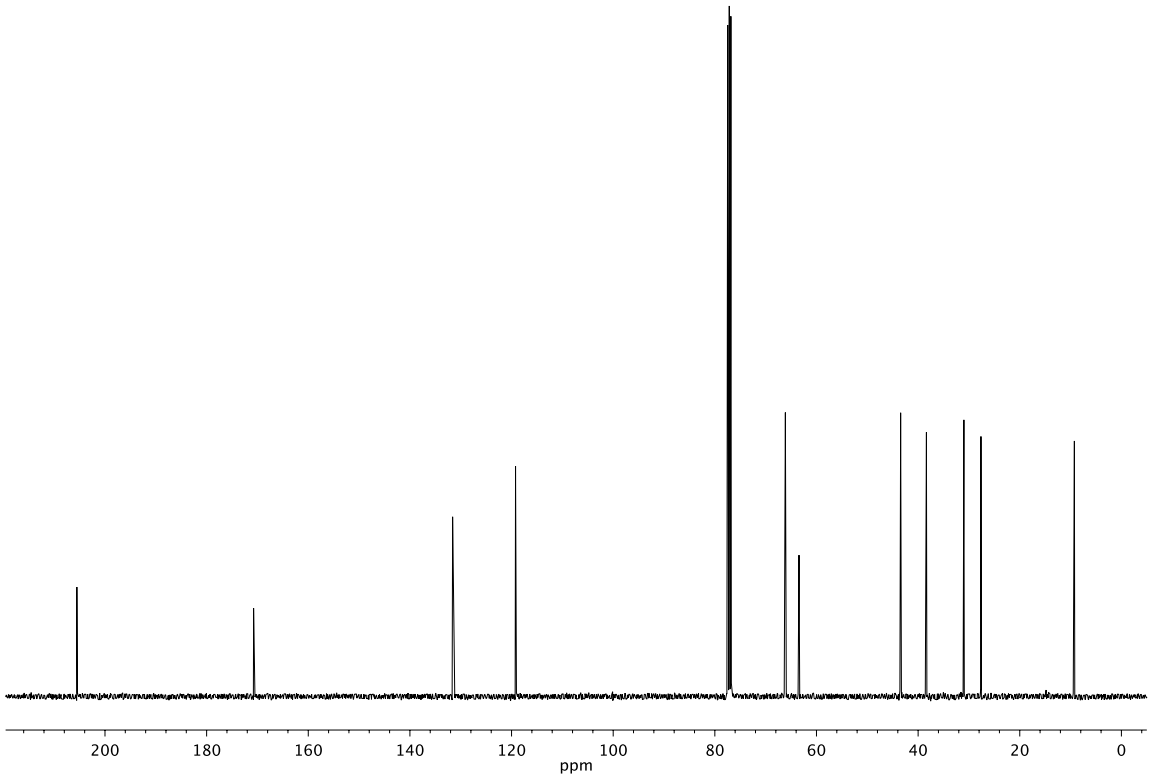



***Figure A3.44*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***15c****.*

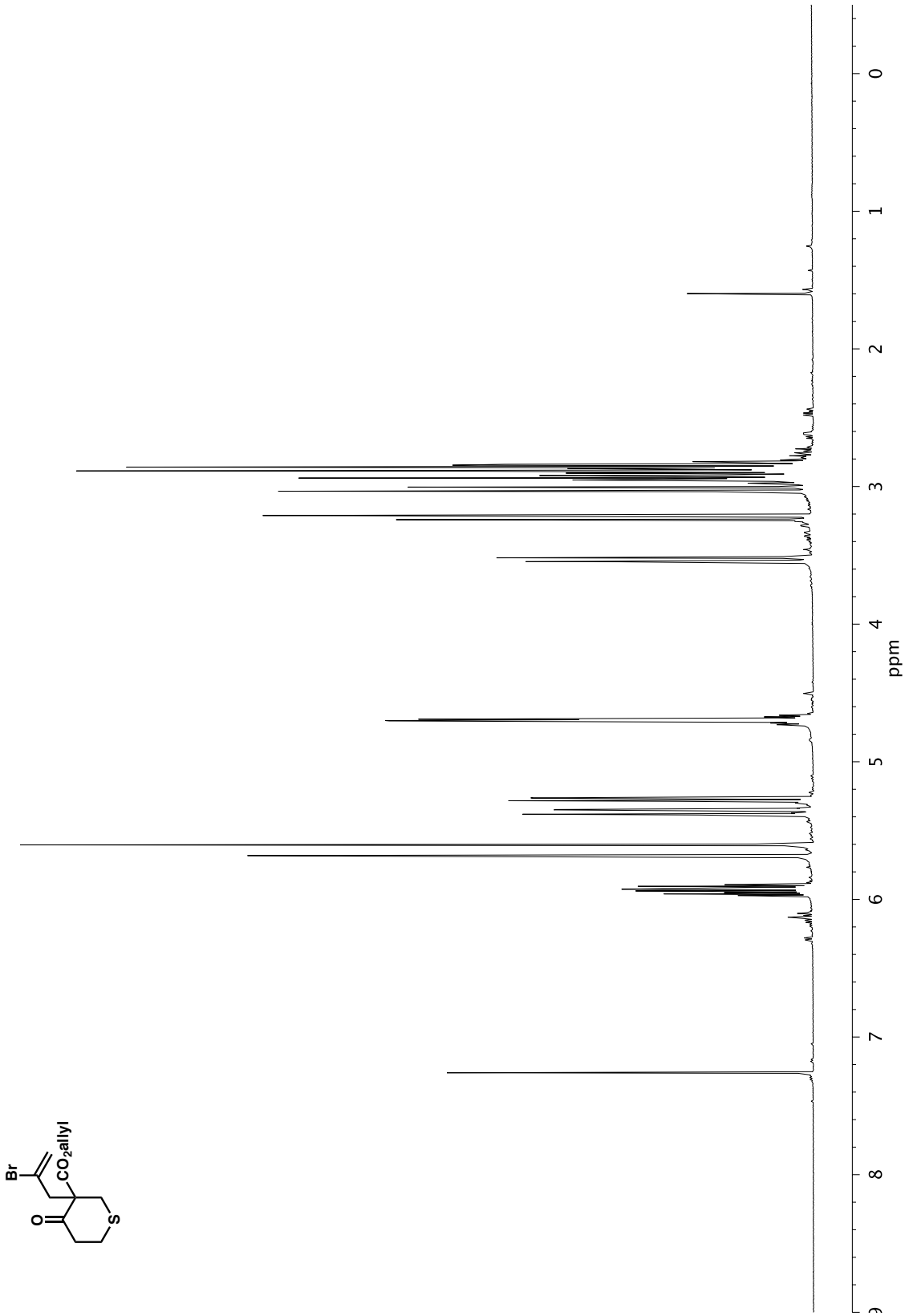



***Figure A3.45*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***15d***.

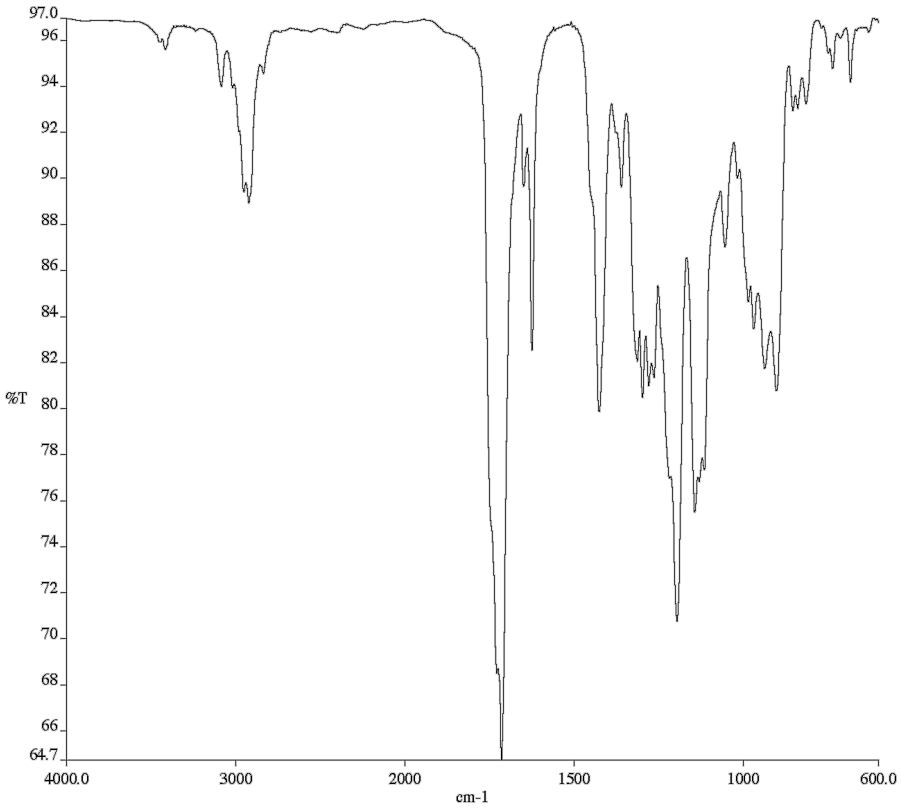



***Figure A3.46*** *Infrared spectrum (Thin Film, NaCl) of compound* ***15d****.*

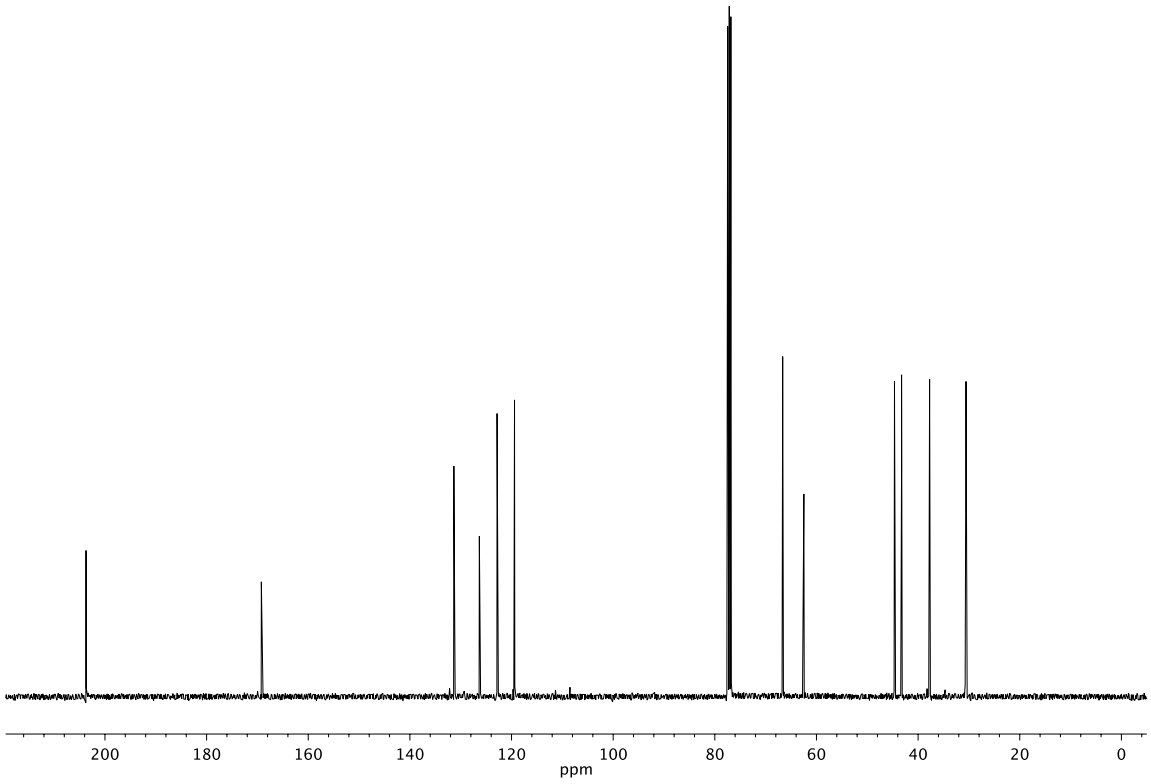



***Figure A3.47*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***15d****.*

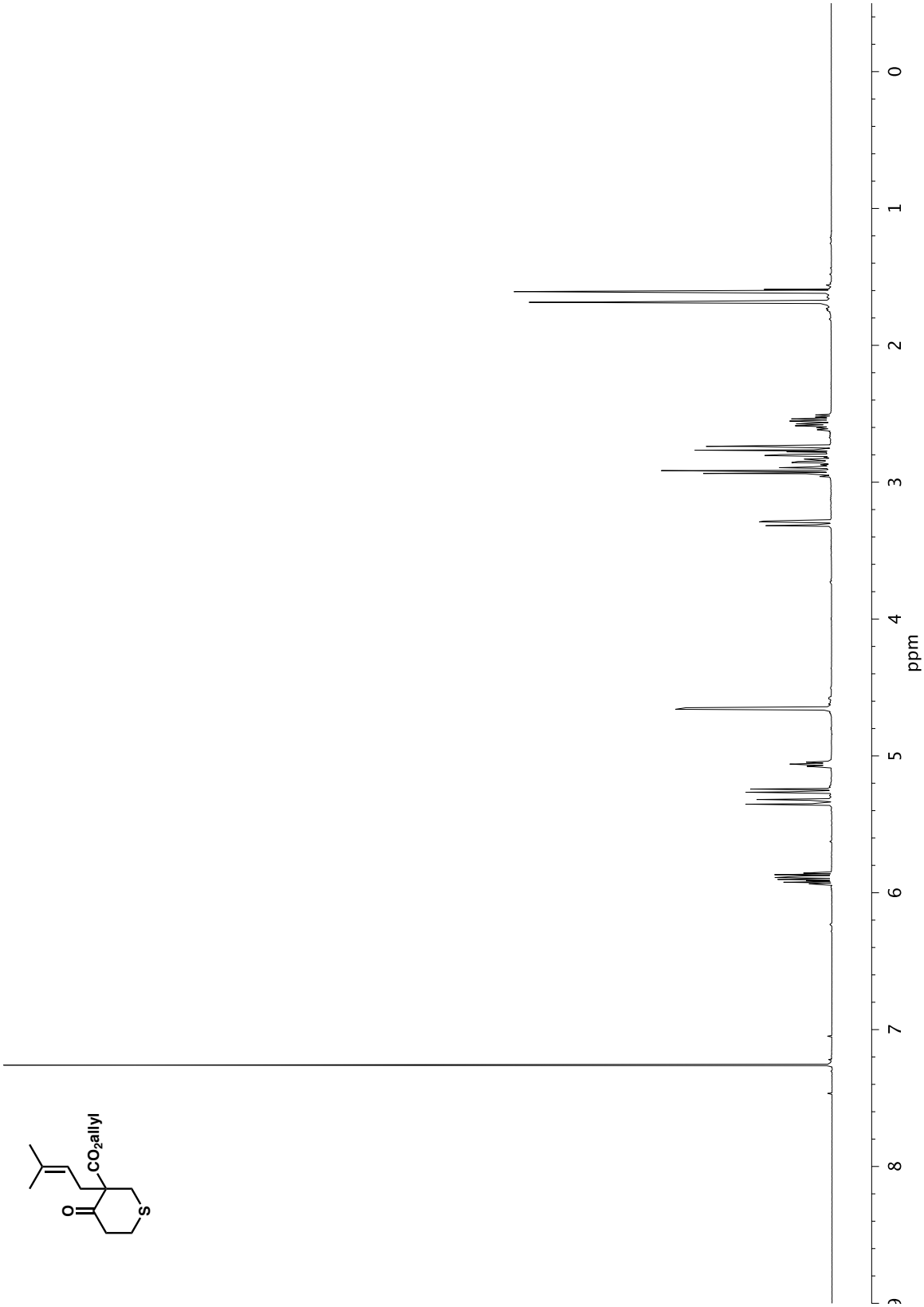



***Figure A3.48*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***15e***.

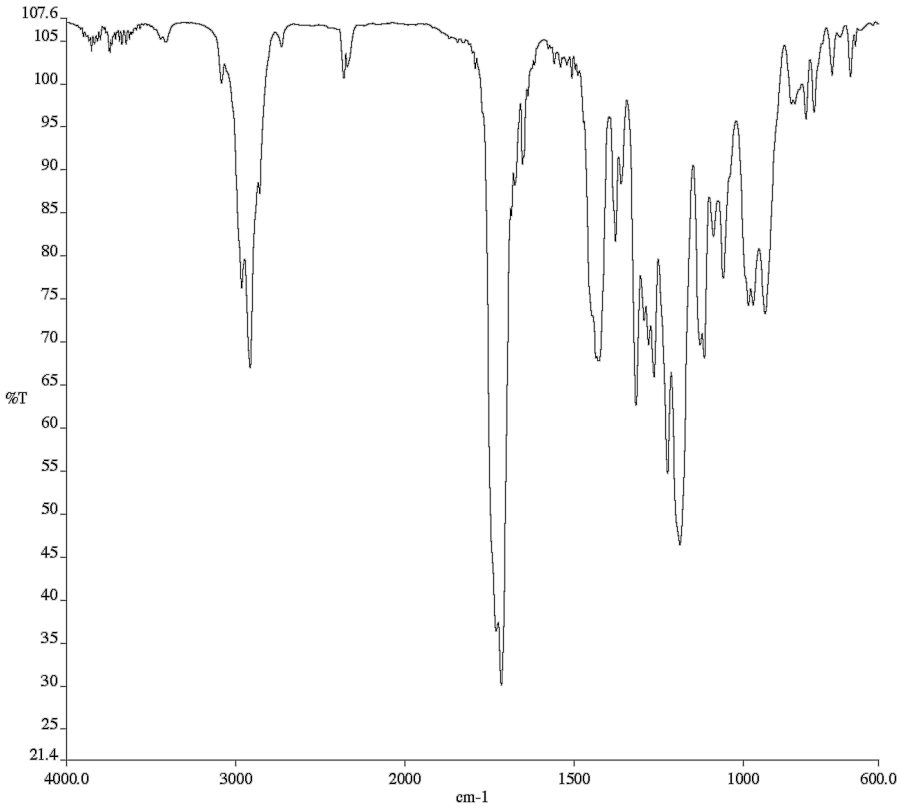



***Figure A3.49*** *Infrared spectrum (Thin Film, NaCl) of compound* ***15e****.*

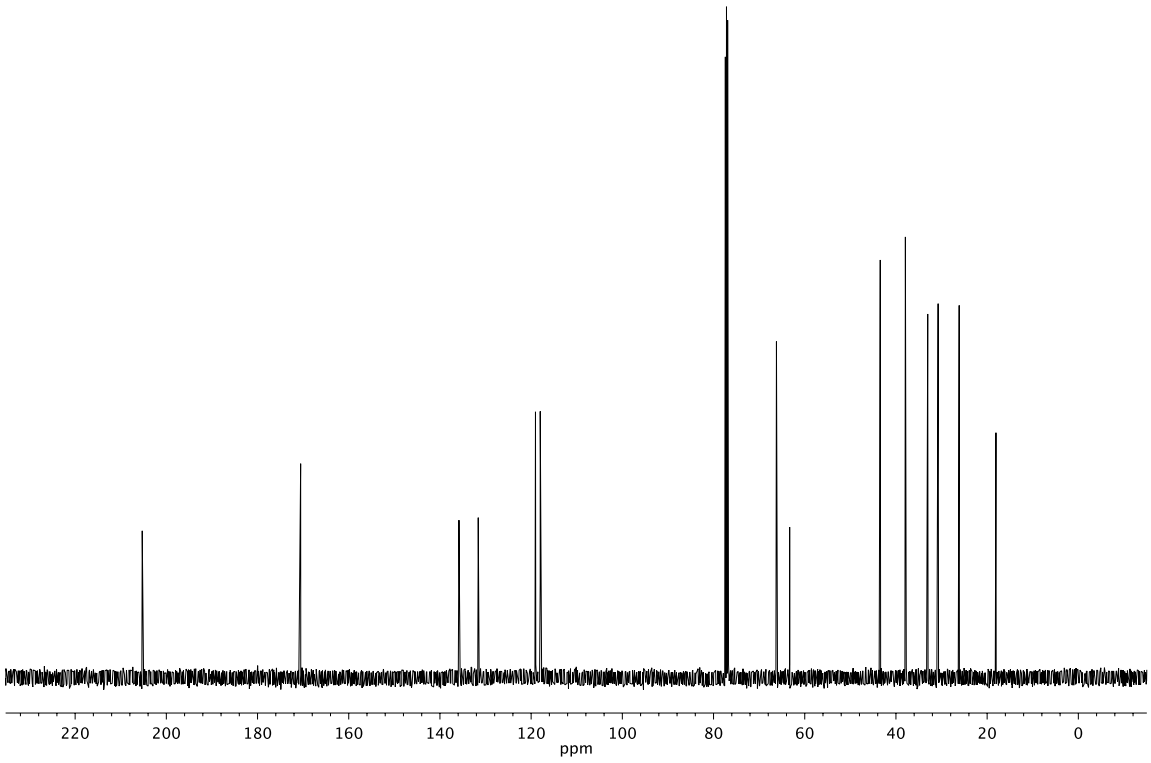



***Figure A3.50*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***15e****.*

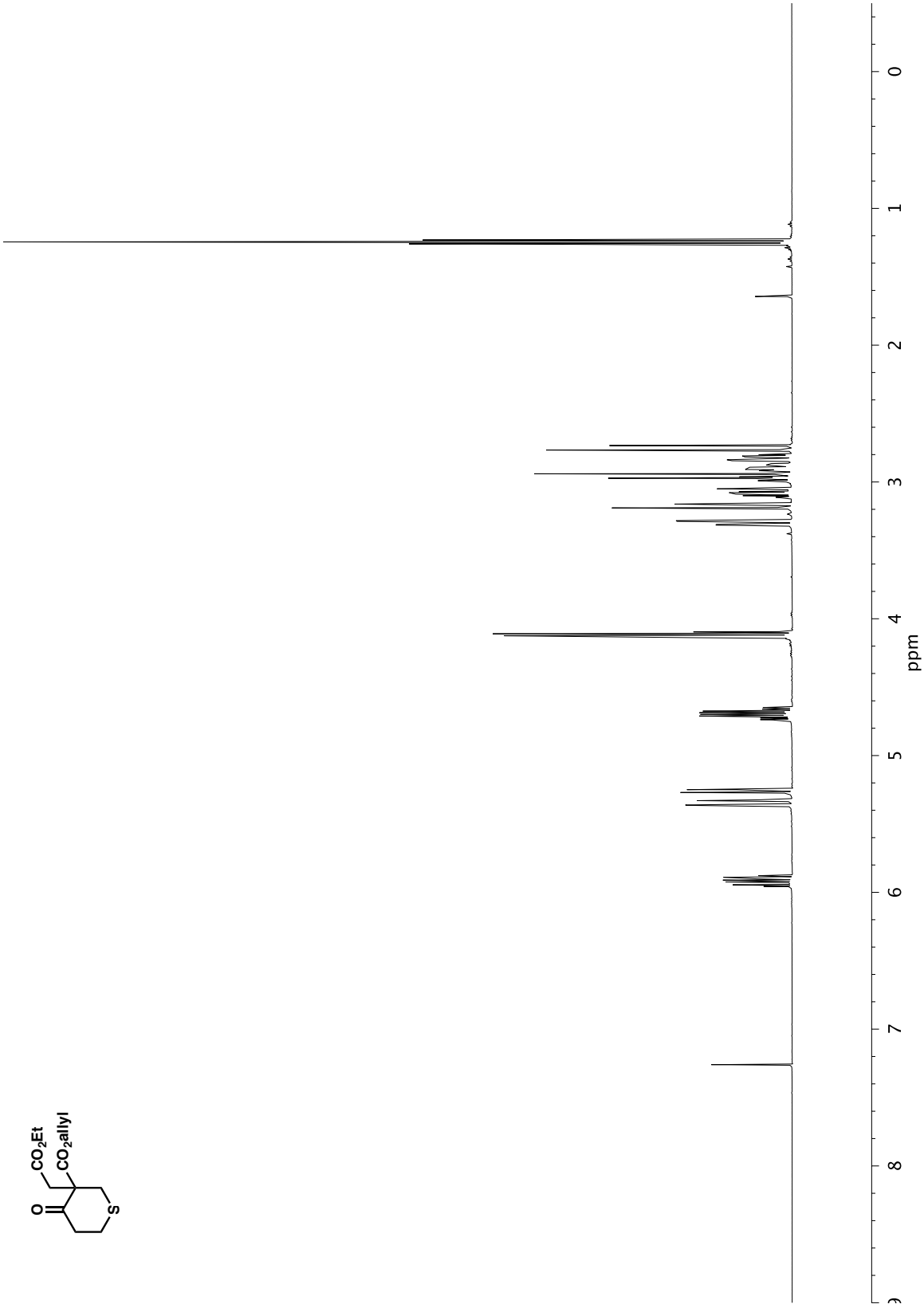



***Figure A3.51*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***15f****.*

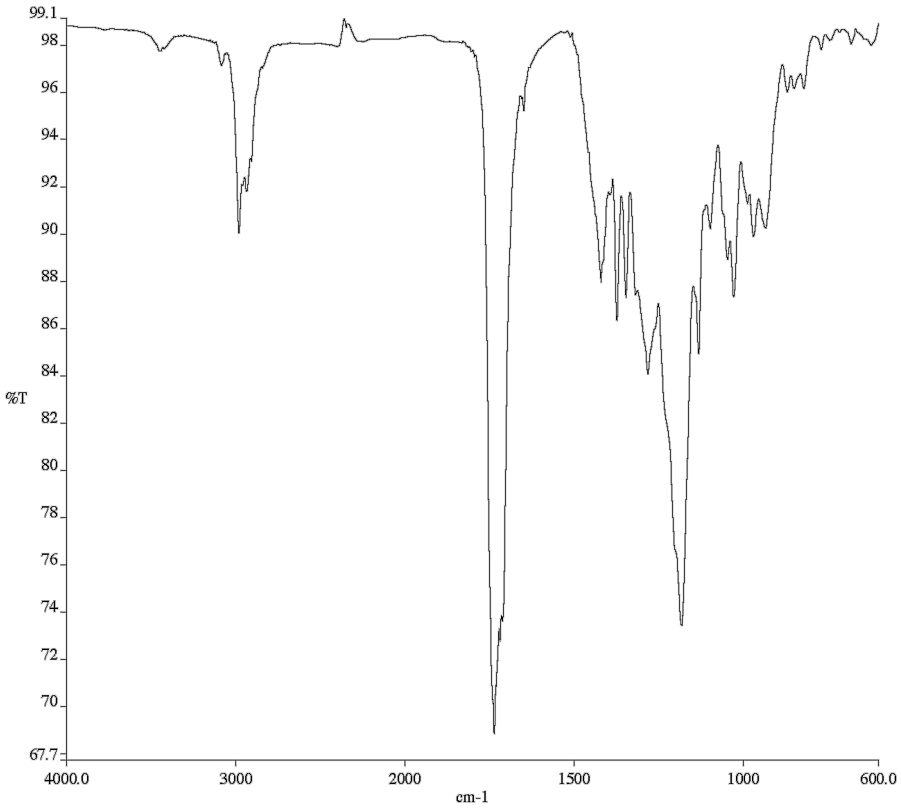



***Figure A3.52*** *Infrared spectrum (Thin Film, NaCl) of compound* ***15f****.*

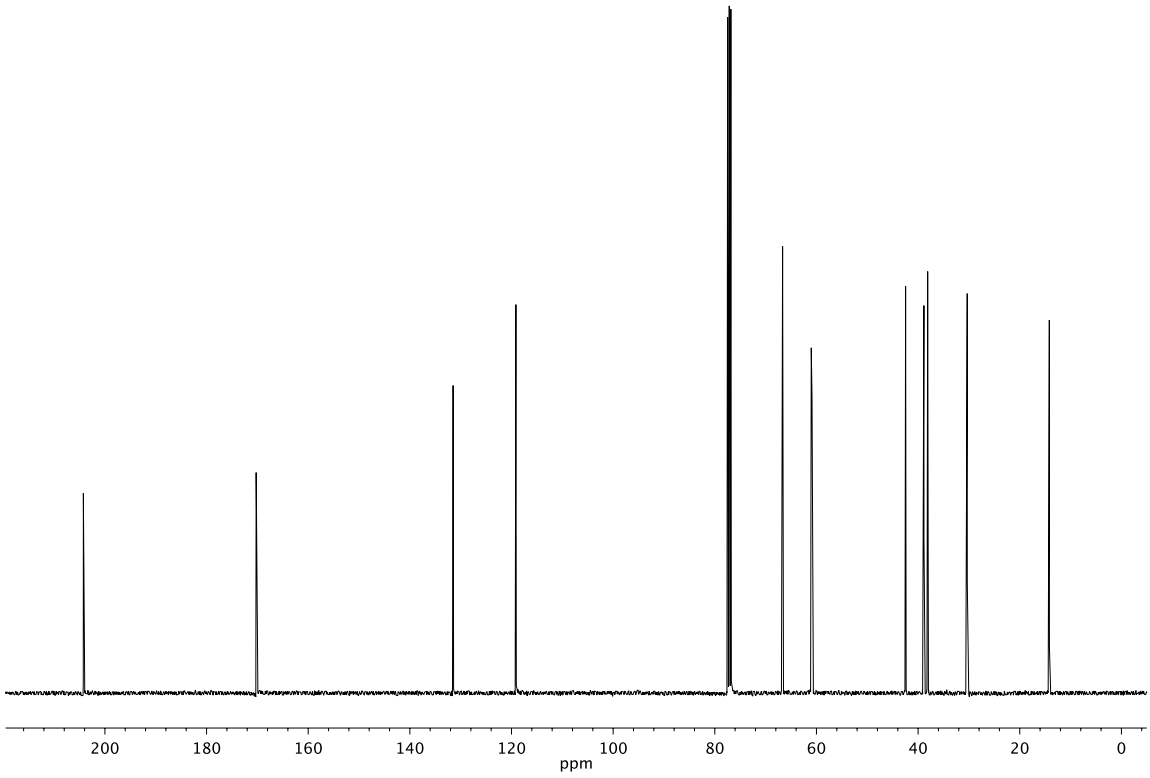



***Figure A3.53*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***15f****.*

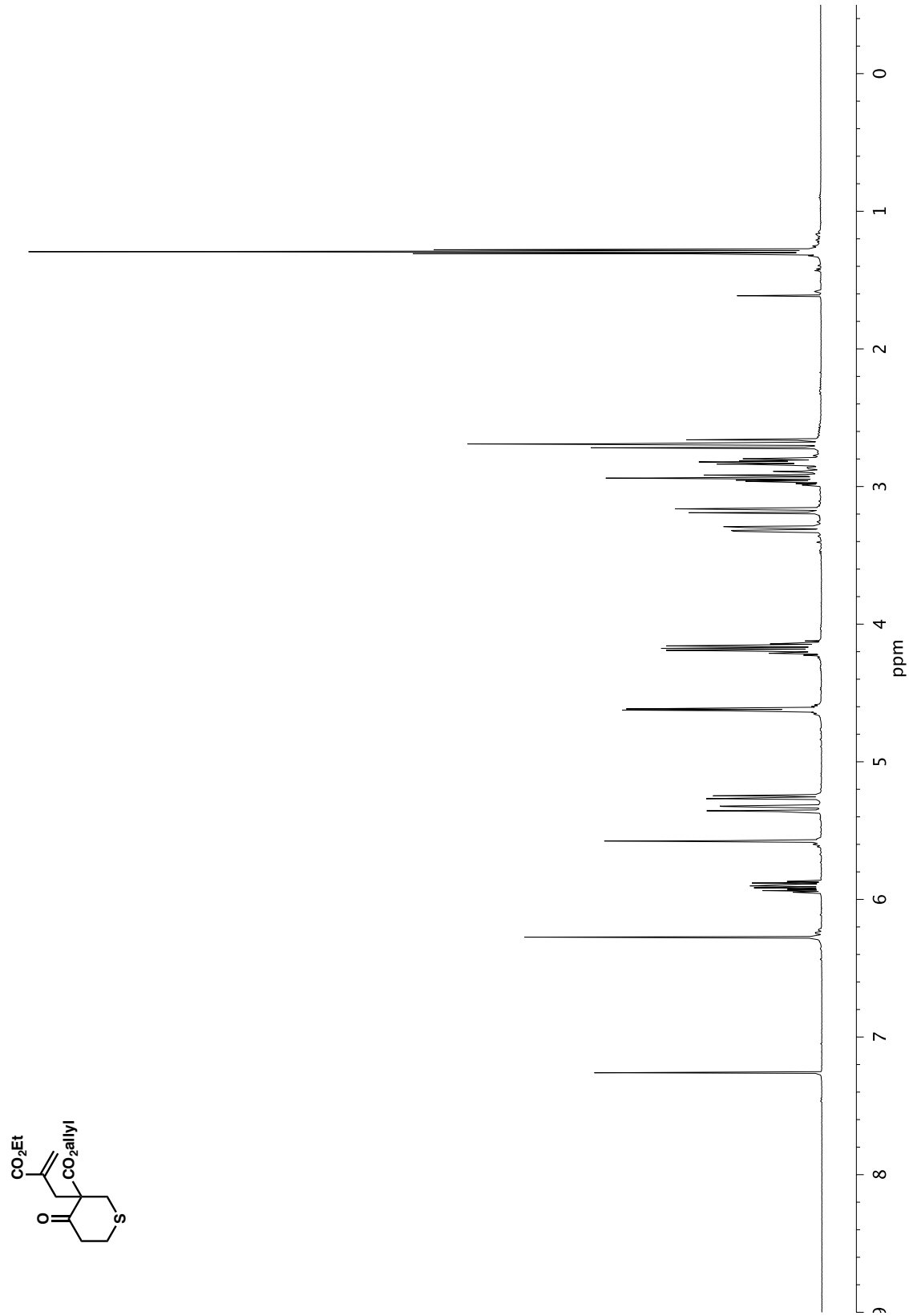



***Figure A3.54*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***15g***.

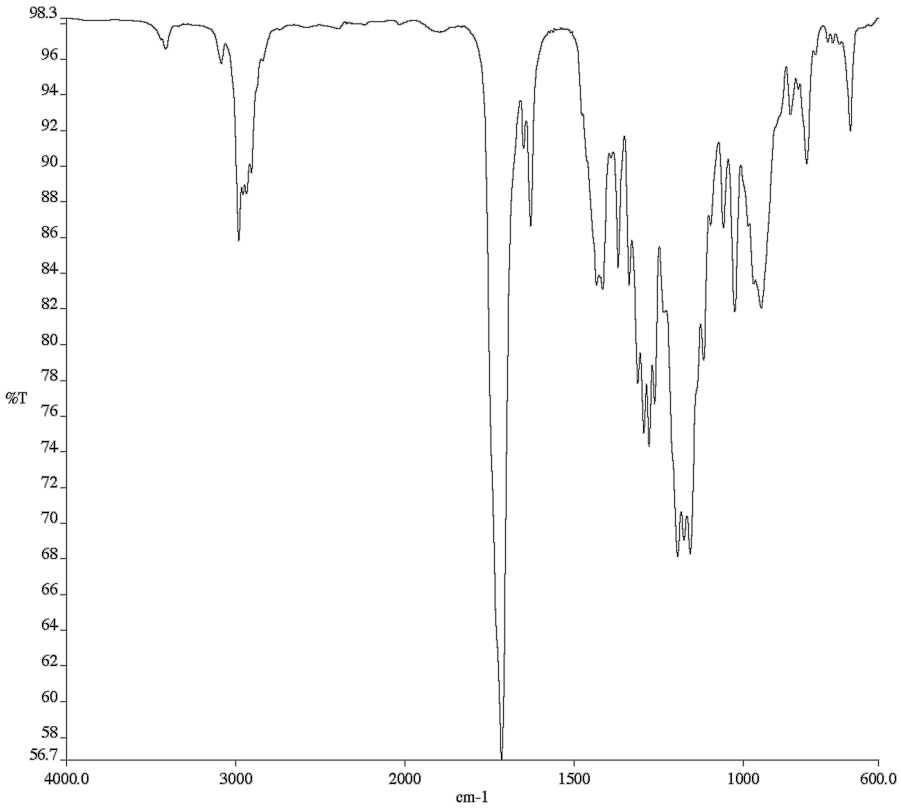



***Figure A3.55*** *Infrared spectrum (Thin Film, NaCl) of compound* ***15g****.*

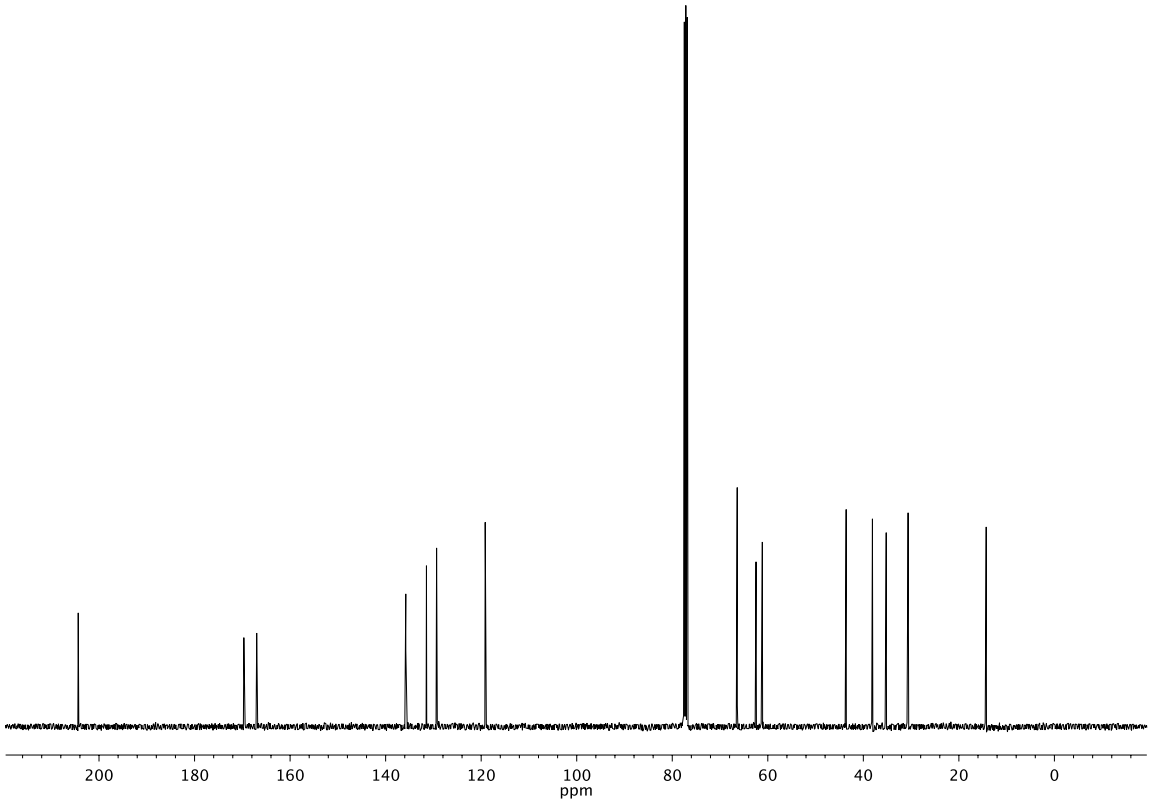



***Figure A3.56*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***15g****.*

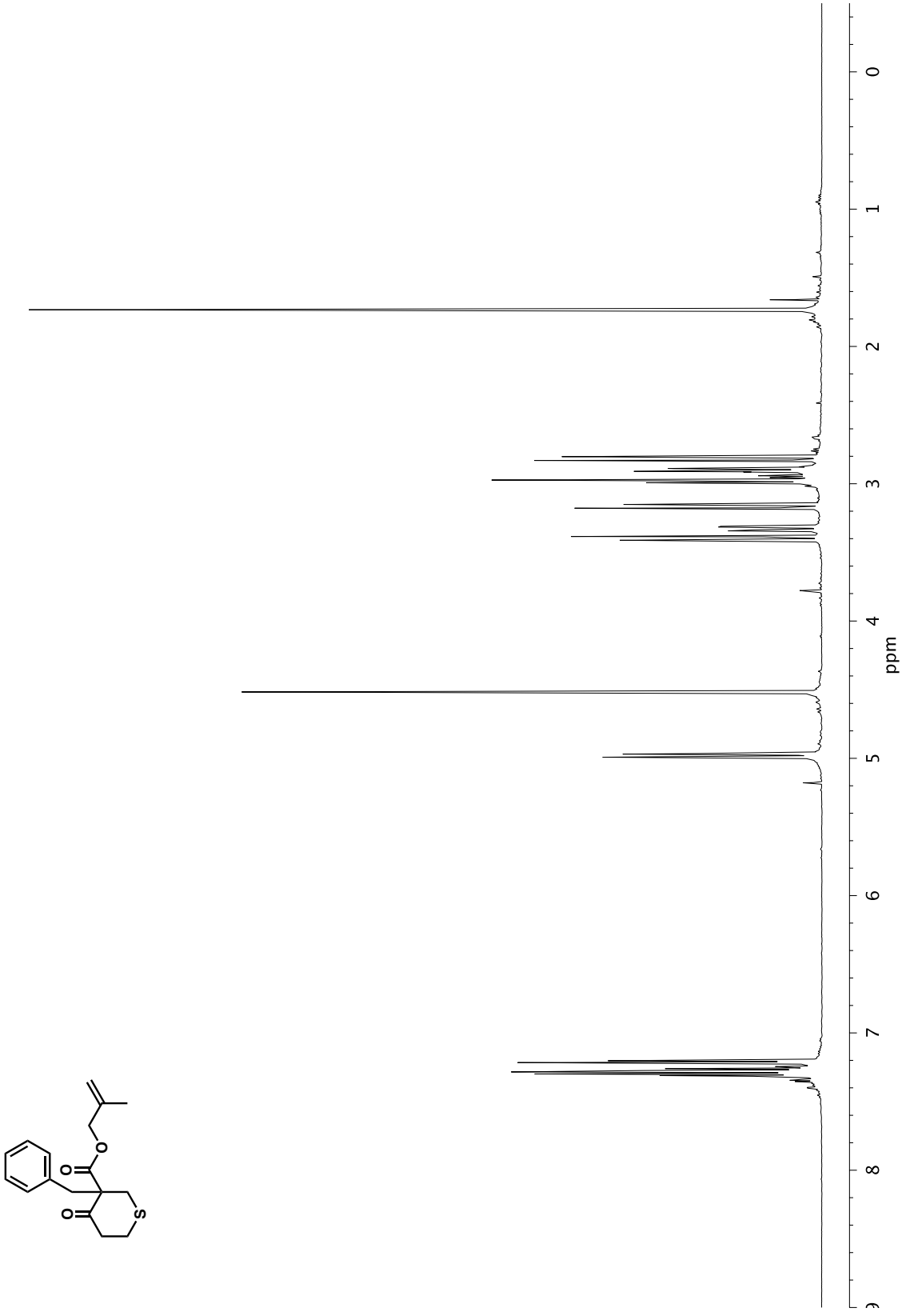



***Figure A3.57*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***15h***.

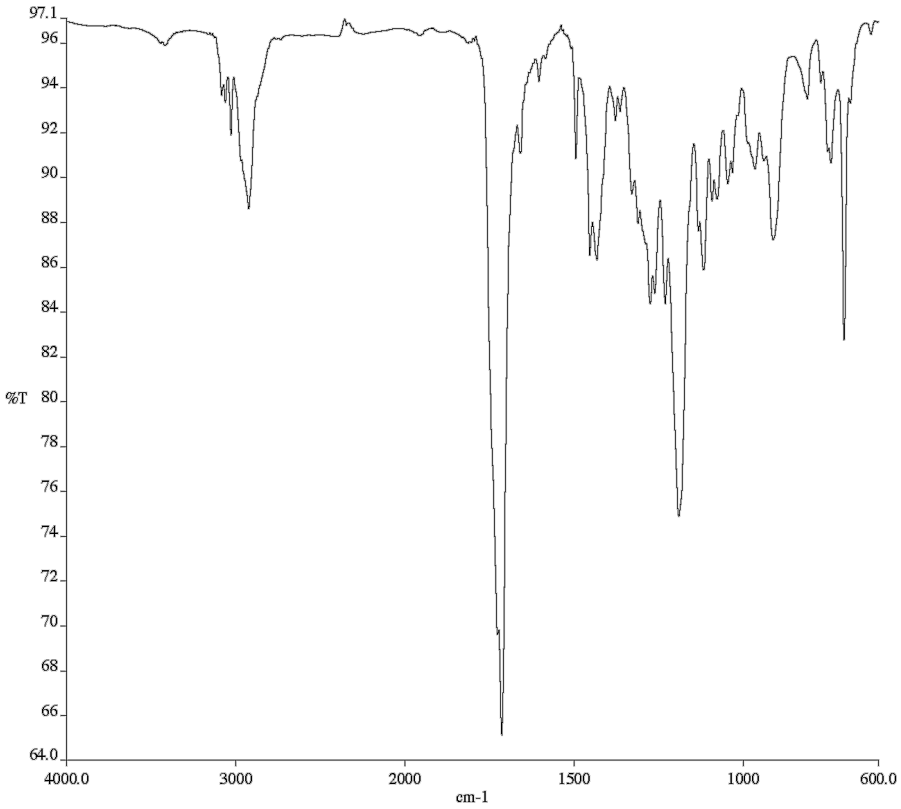



***Figure A3.58*** *Infrared spectrum (Thin Film, NaCl) of compound* ***15h****.*

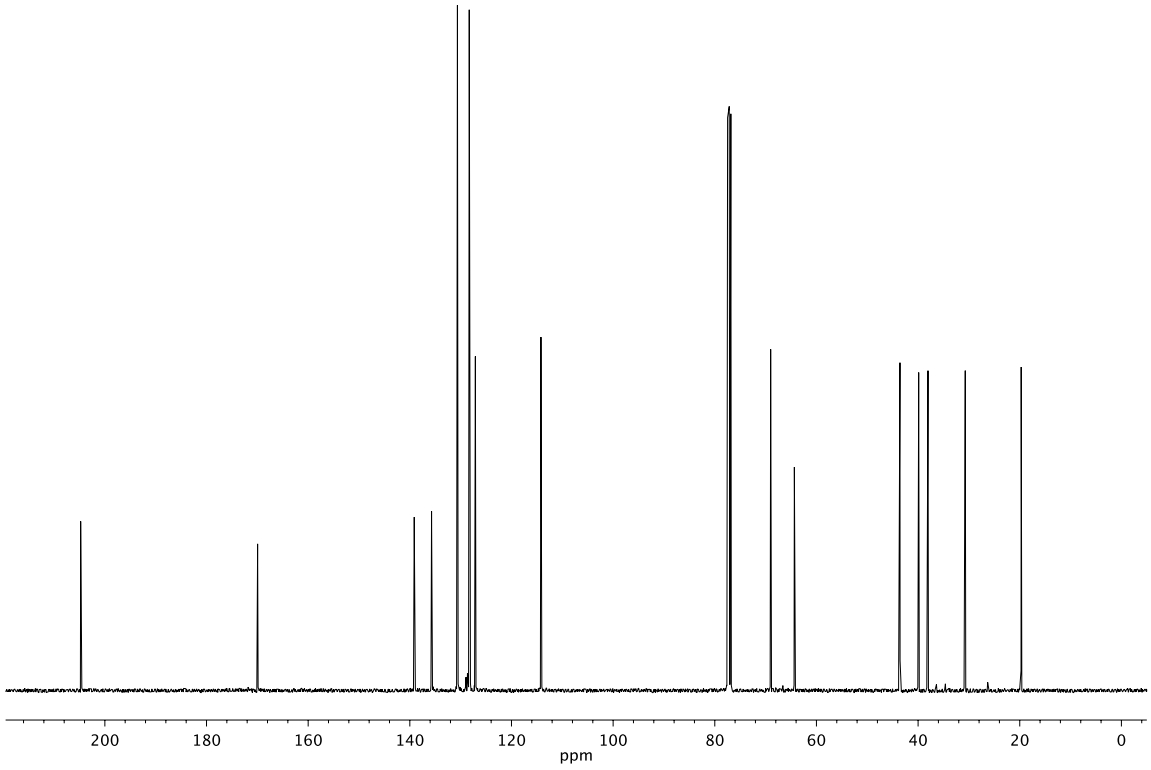



***Figure A3.59*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***15h****.*

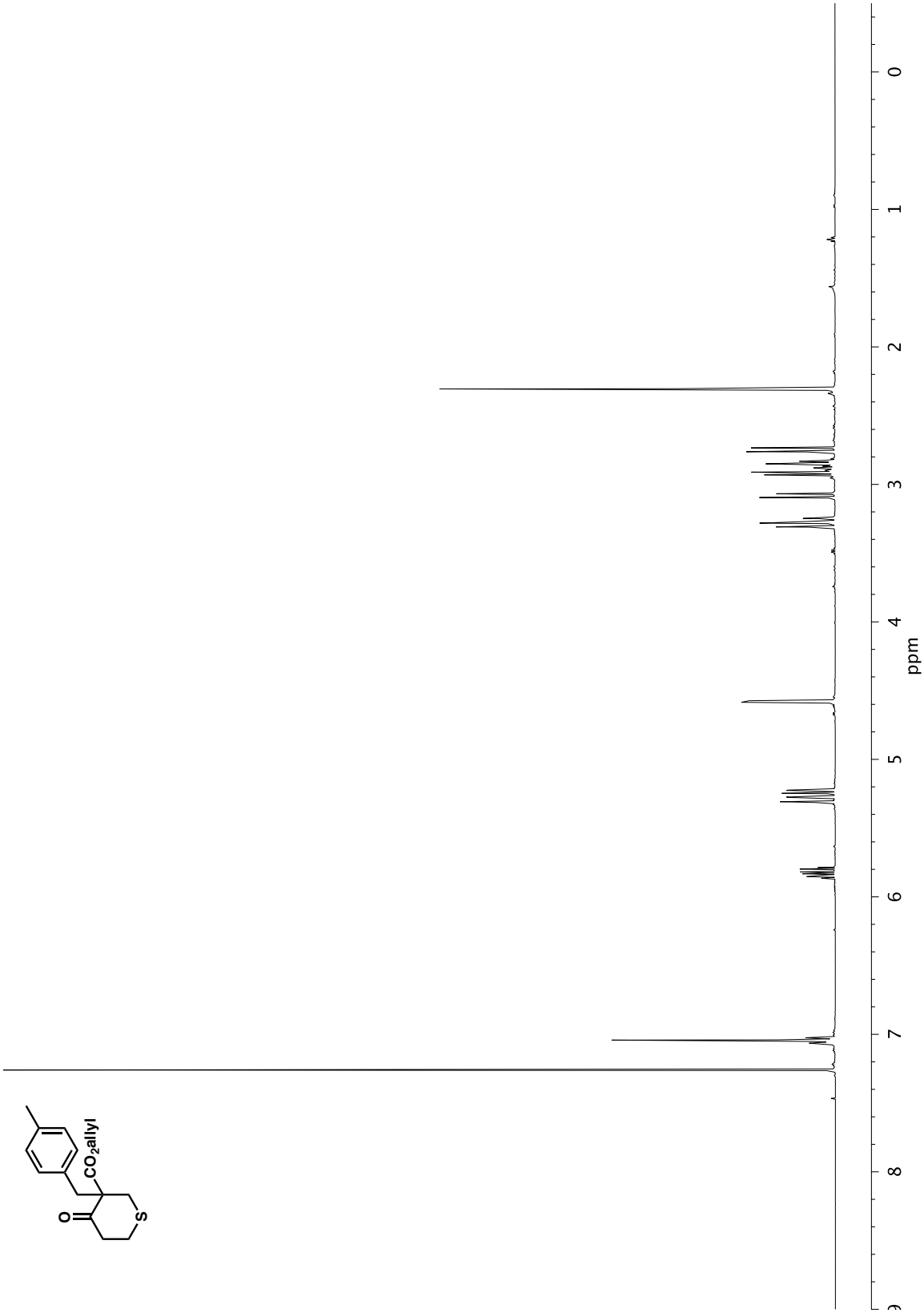



***Figure A3.60*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***15i****.*

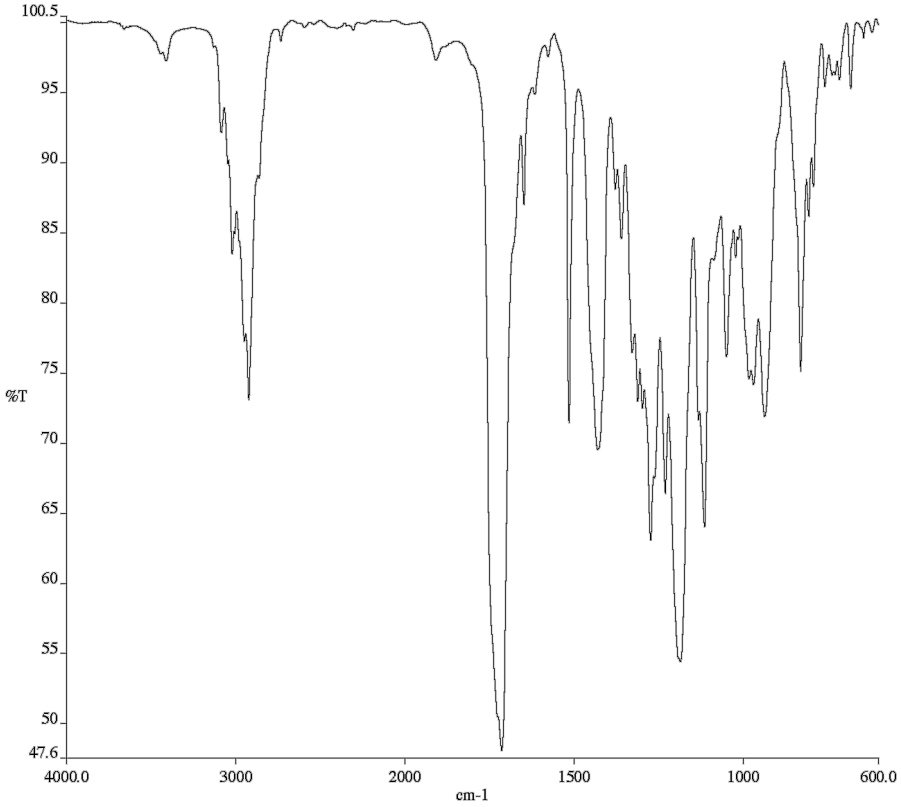



***Figure A3.61*** *Infrared spectrum (Thin Film, NaCl) of compound* ***15i***.

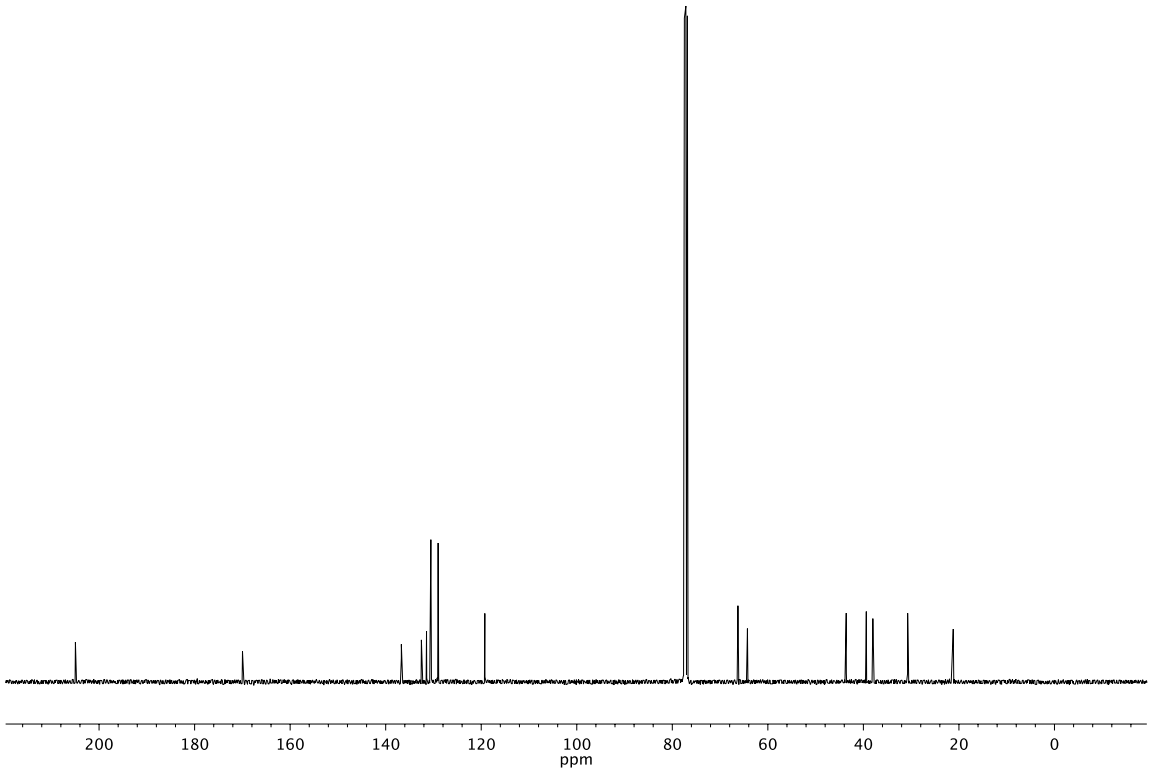



***Figure A3.62*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***15i***.

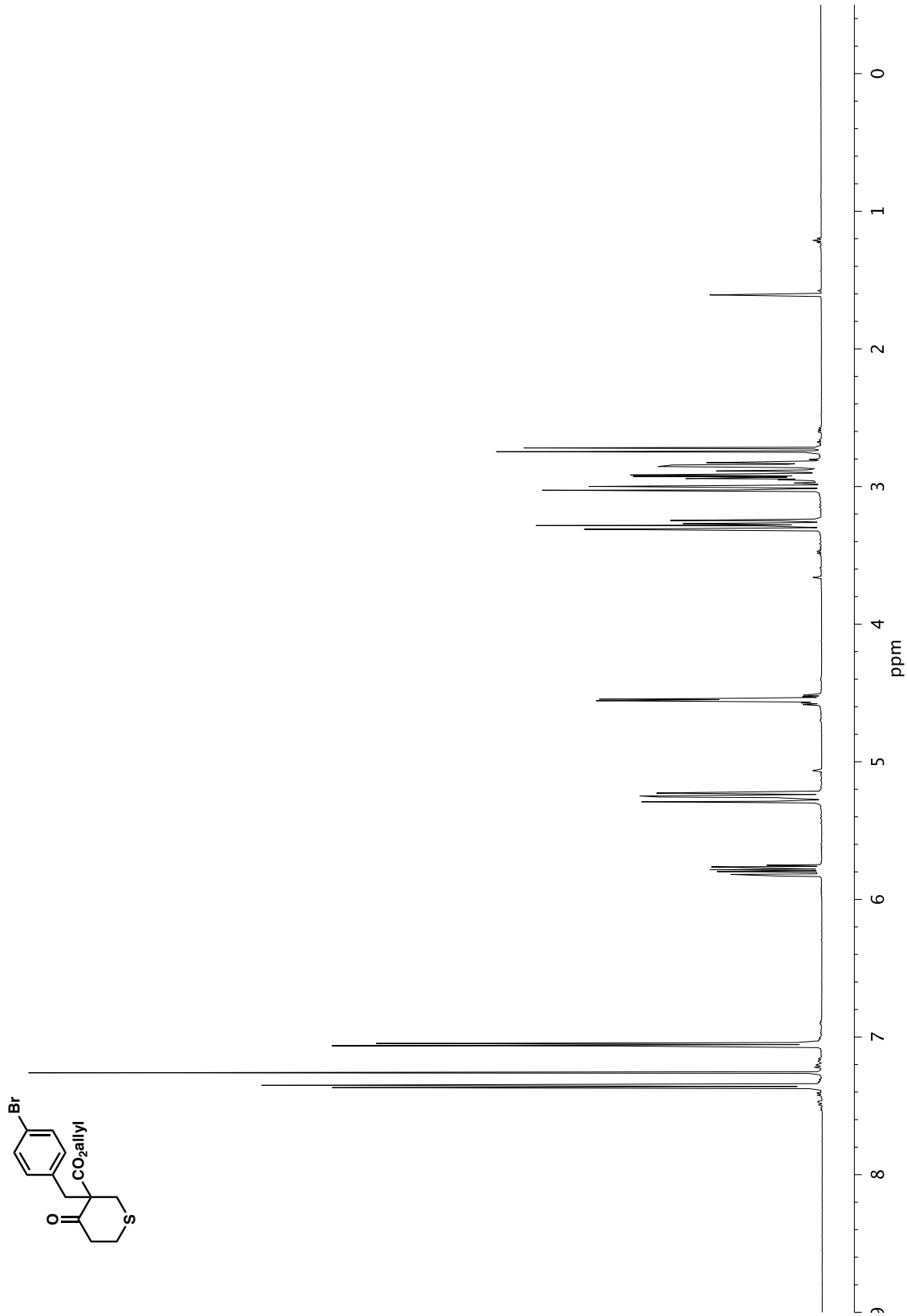



***Figure A3.63*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***15j****.*

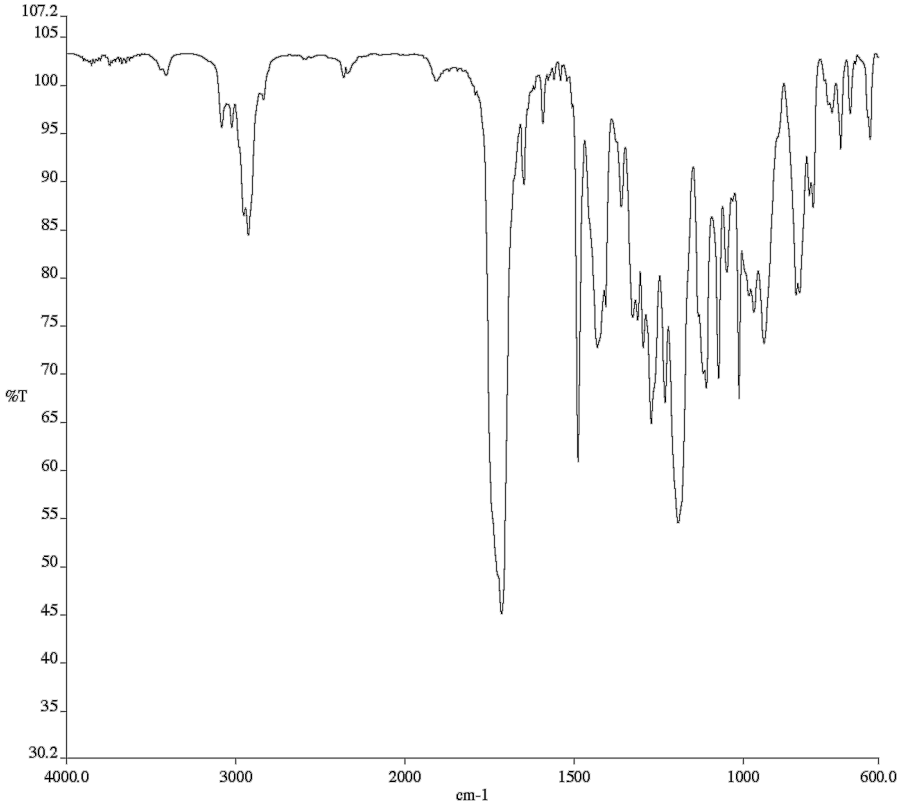



***Figure A3.64*** *Infrared spectrum (Thin Film, NaCl) of compound* ***15j****.*

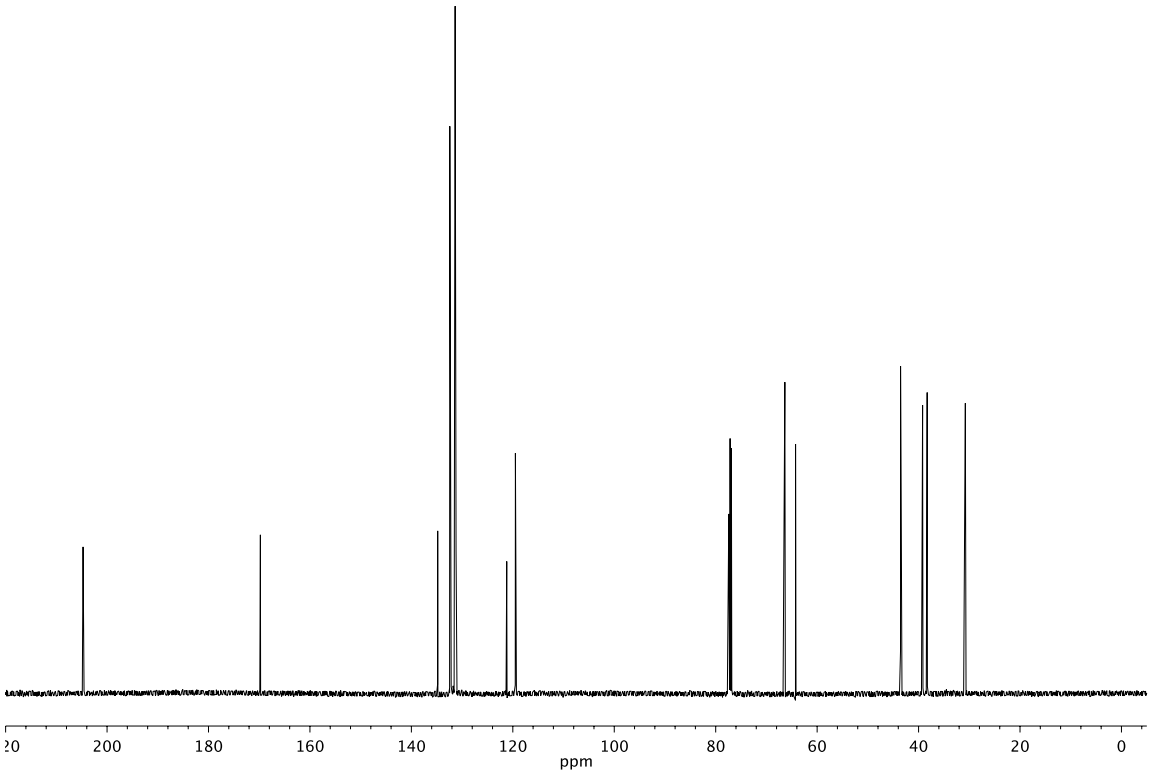



***Figure A3.65*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***15j****.*

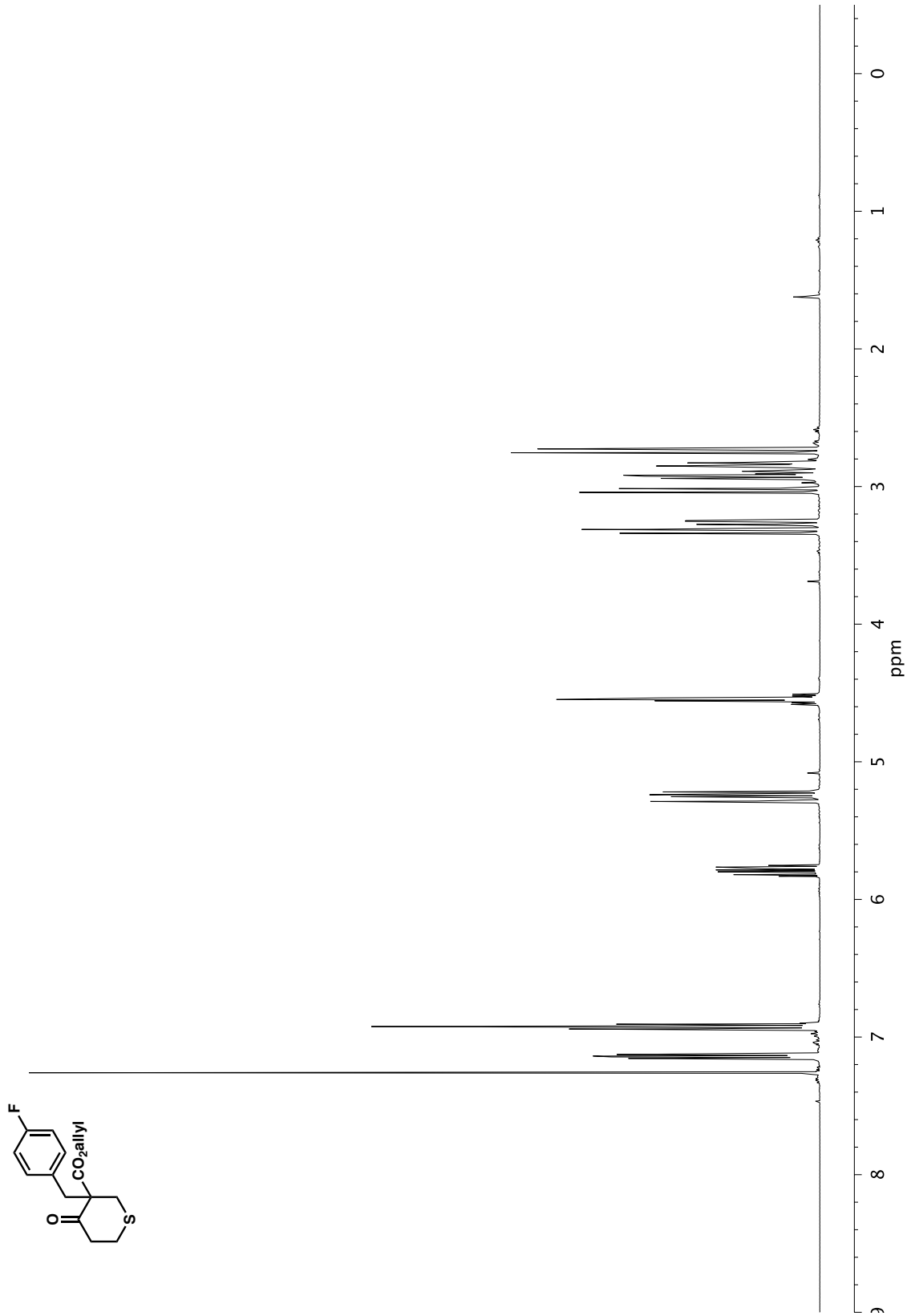



***Figure A3.66*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***15k***.

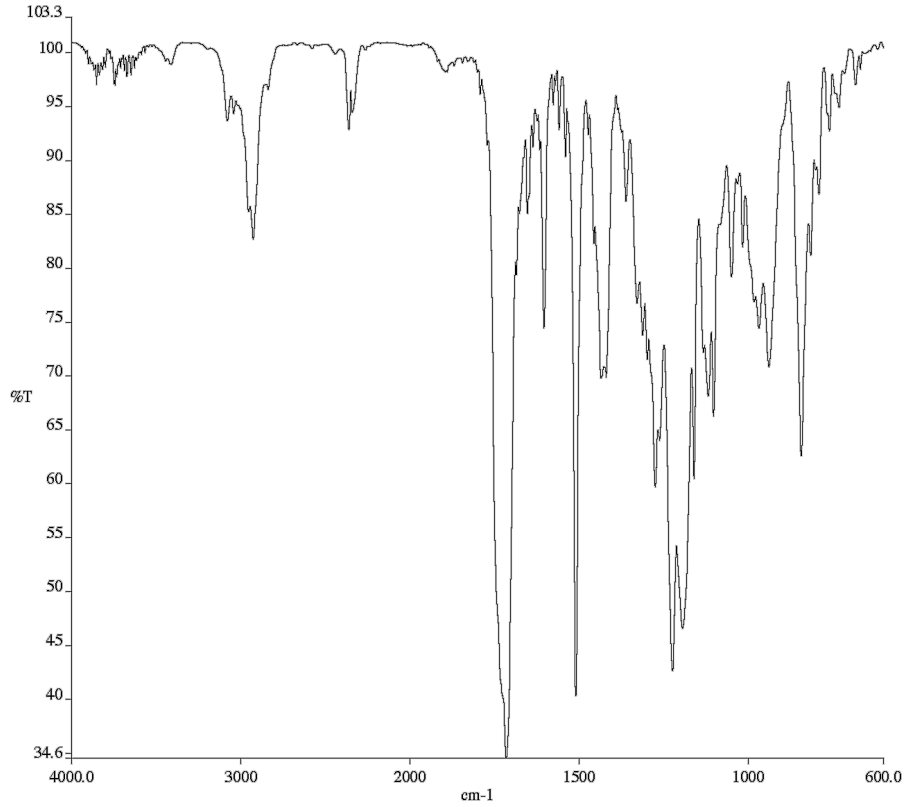



***Figure A3.67*** *Infrared spectrum (Thin Film, NaCl) of compound* ***15k****.*

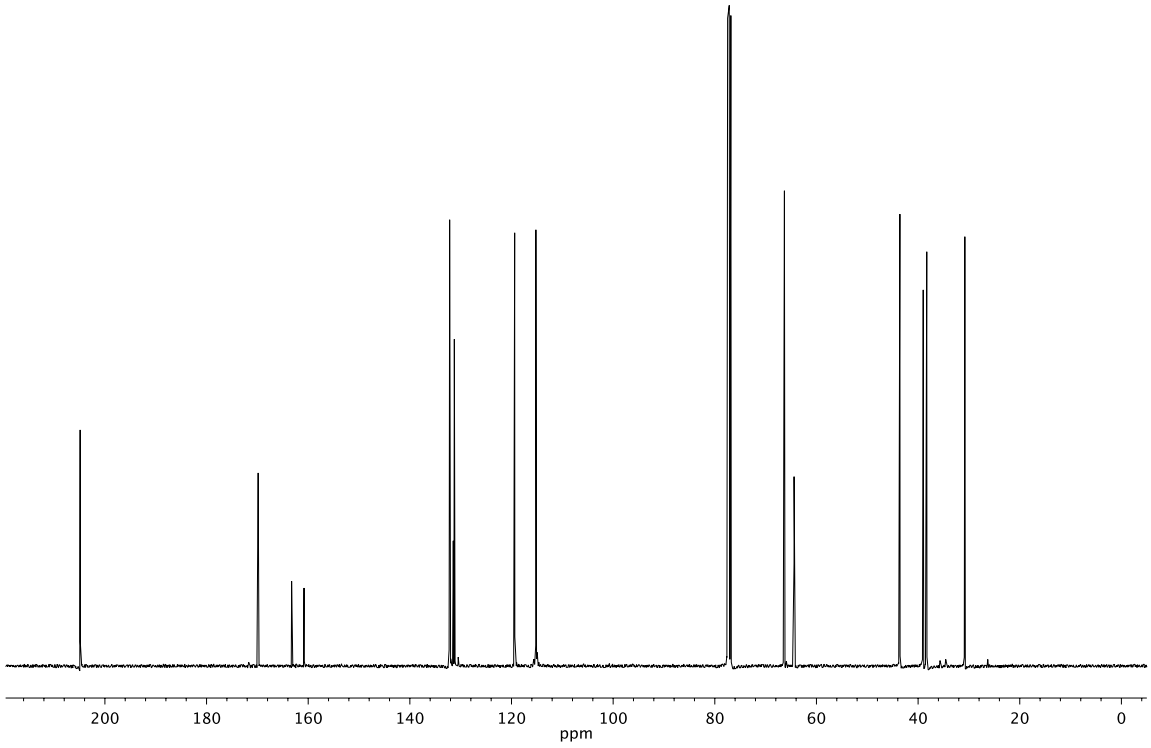



***Figure A3.68*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***15k****.*

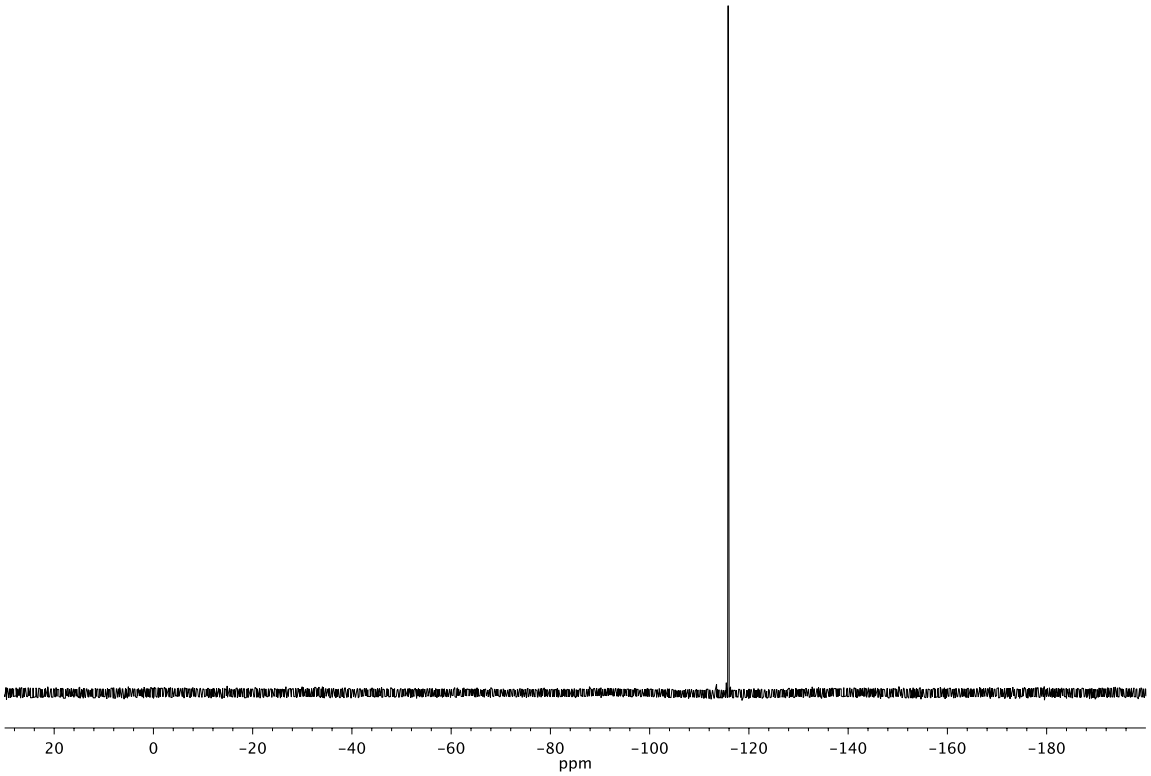



***Figure A3.69*** *$^{19}F$ NMR (282 MHz, $CDCl_3$) of compound* ***15k****.*

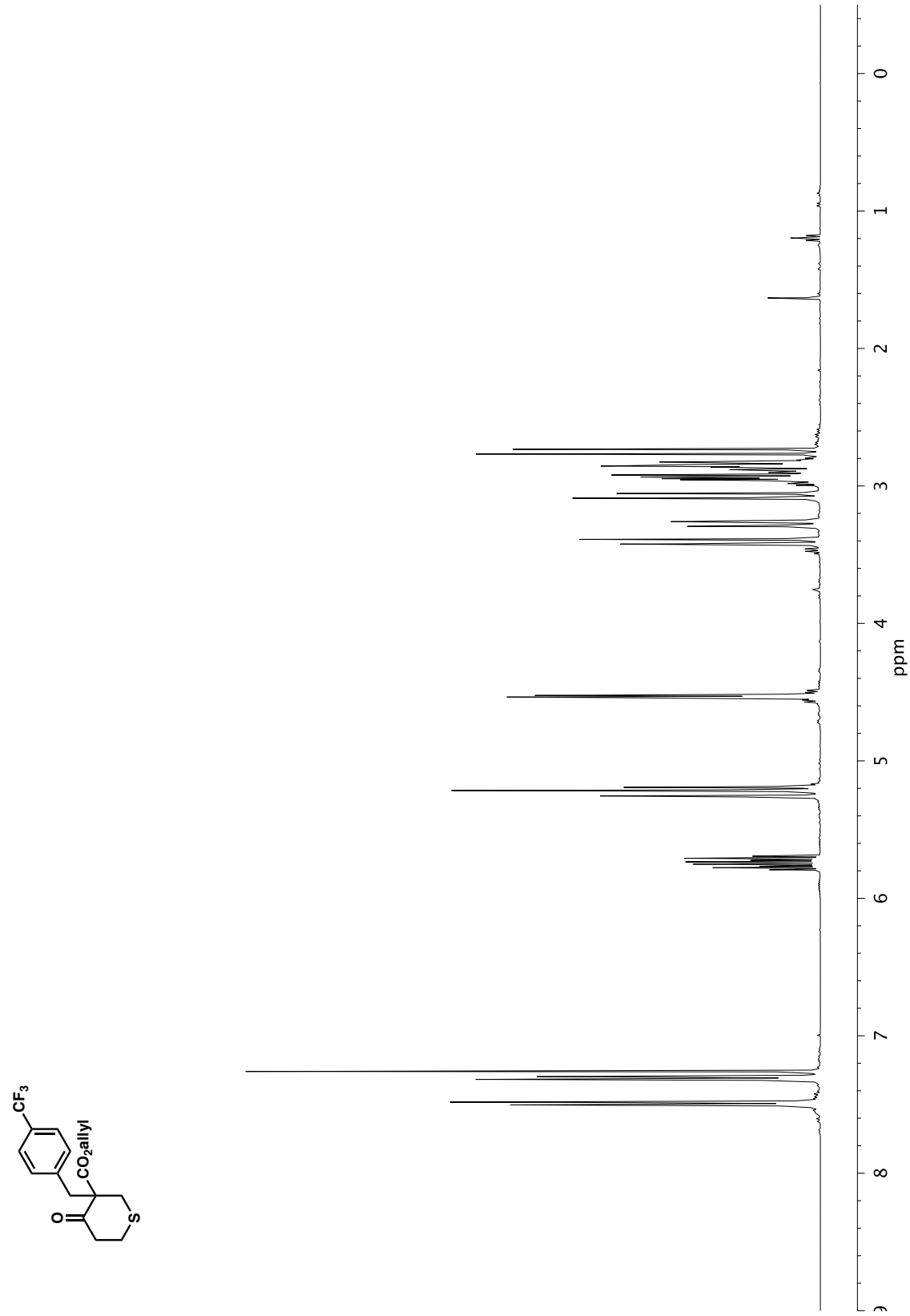



***Figure A3.70*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***15l****.*

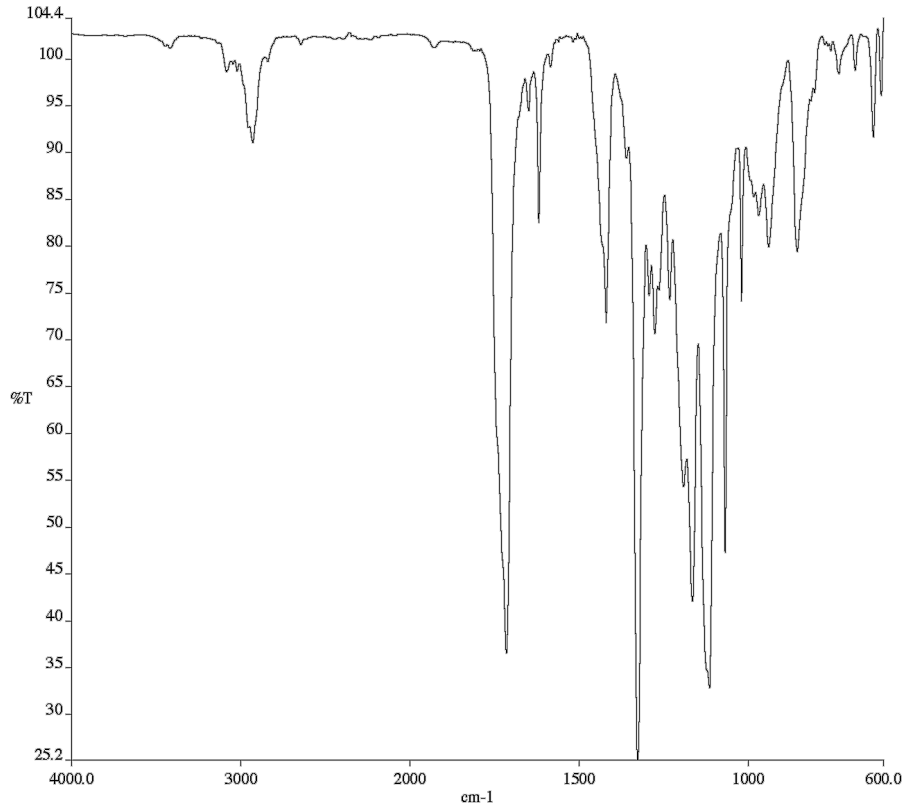



***Figure A3.71*** *Infrared spectrum (Thin Film, NaCl) of compound* ***15l****.*

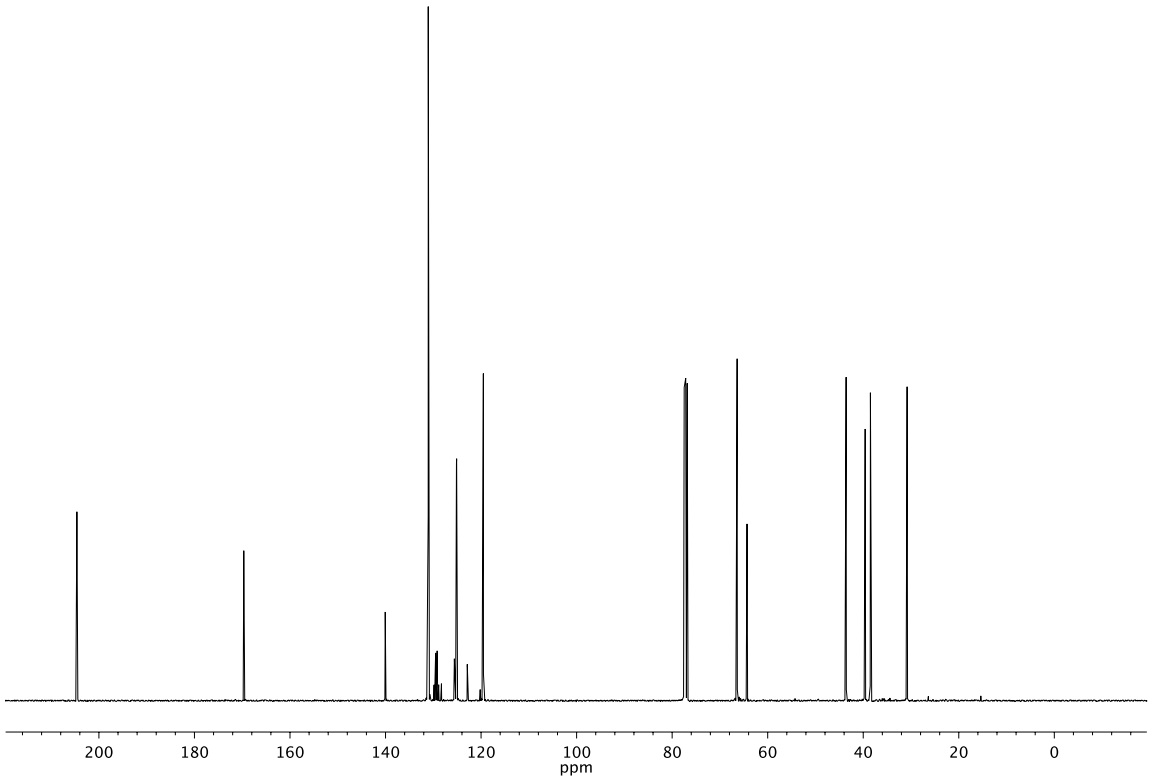



***Figure A3.72*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***15l****.*

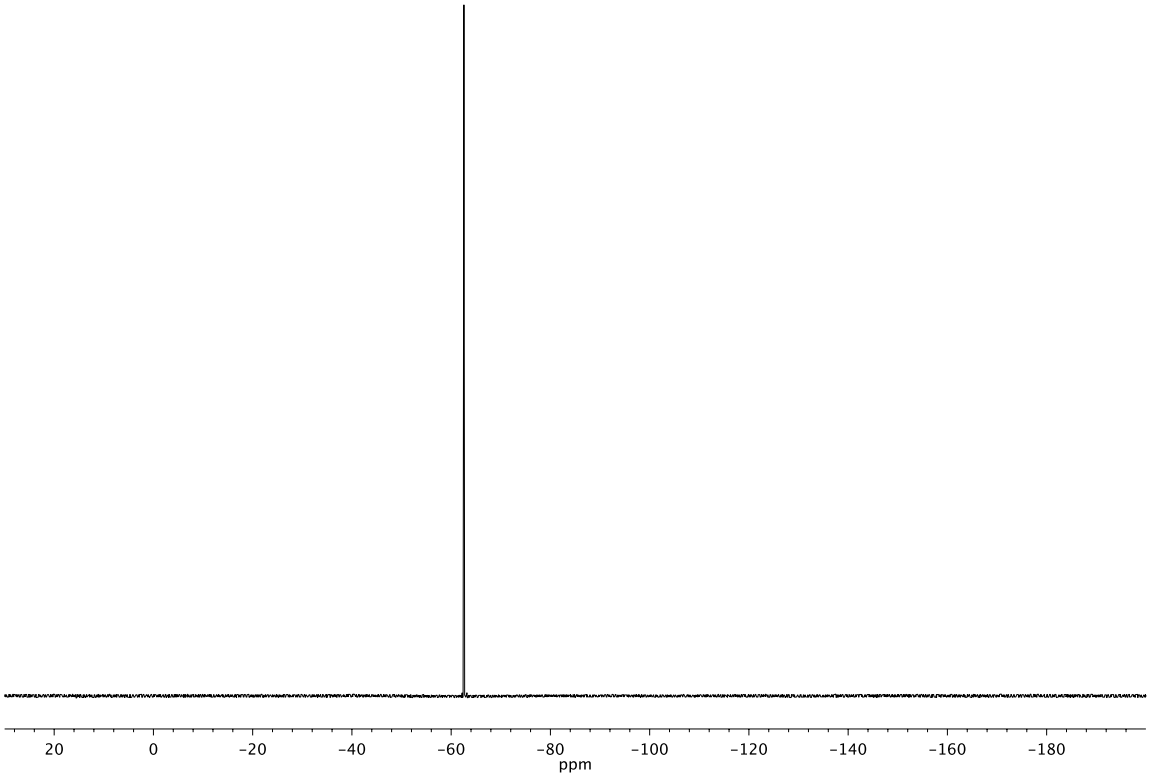



***Figure A3.73*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***15l****.*

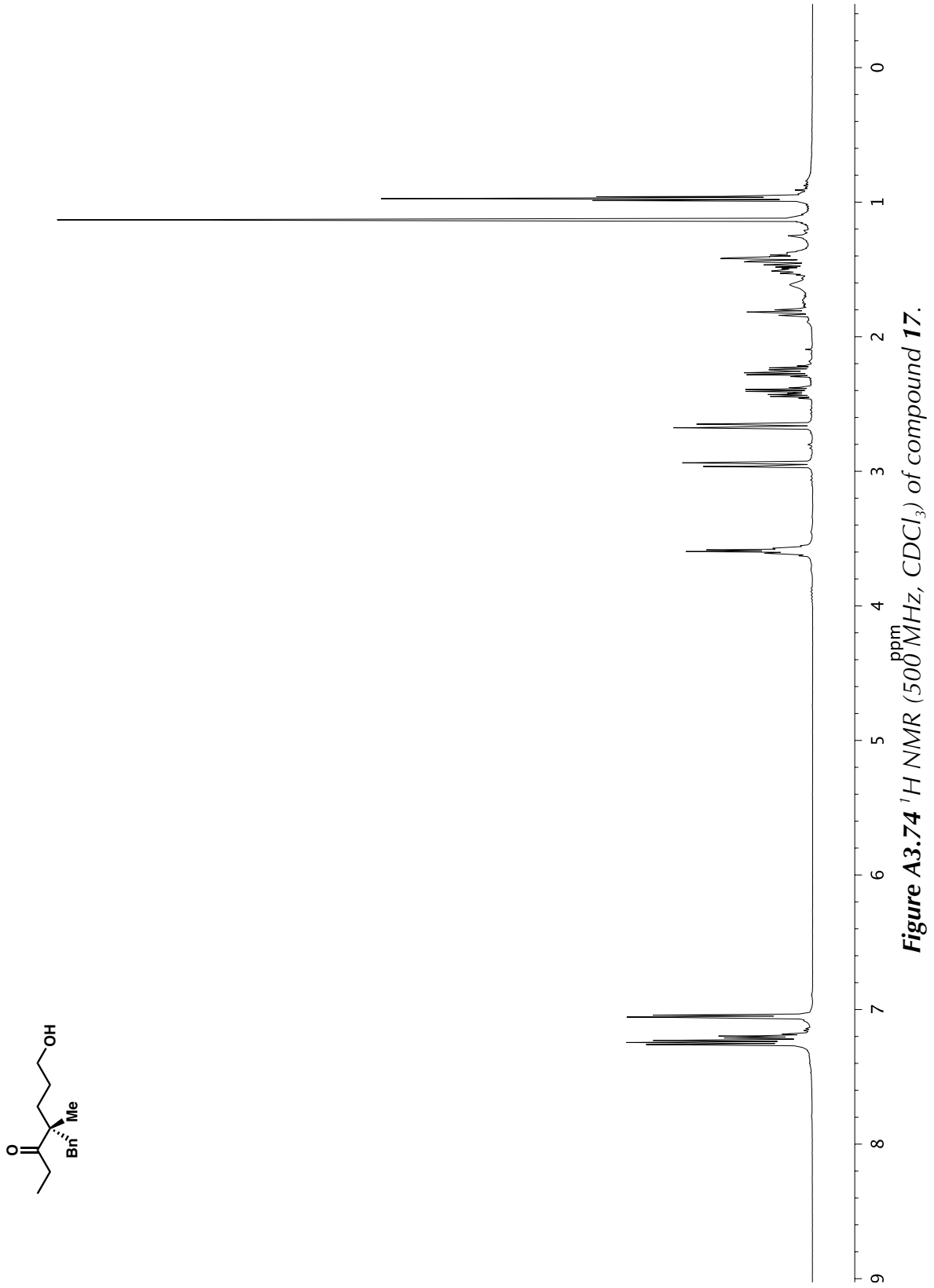



***Figure A3.74*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound **17**.*

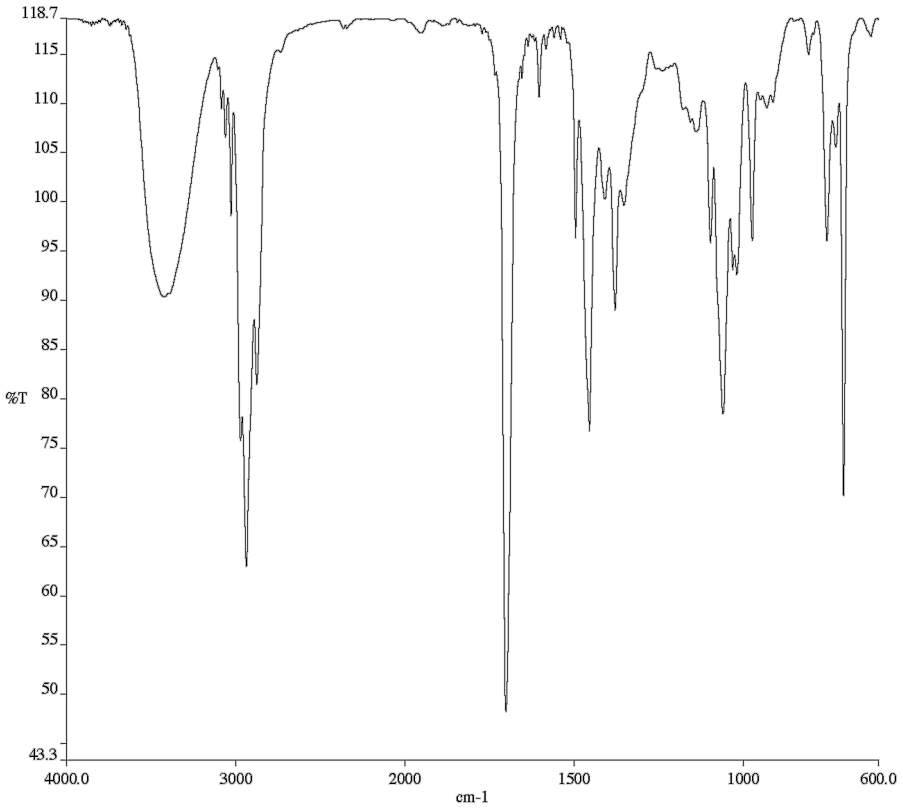



***Figure A3.75*** *Infrared spectrum (Thin Film, NaCl) of compound* ***17****.*

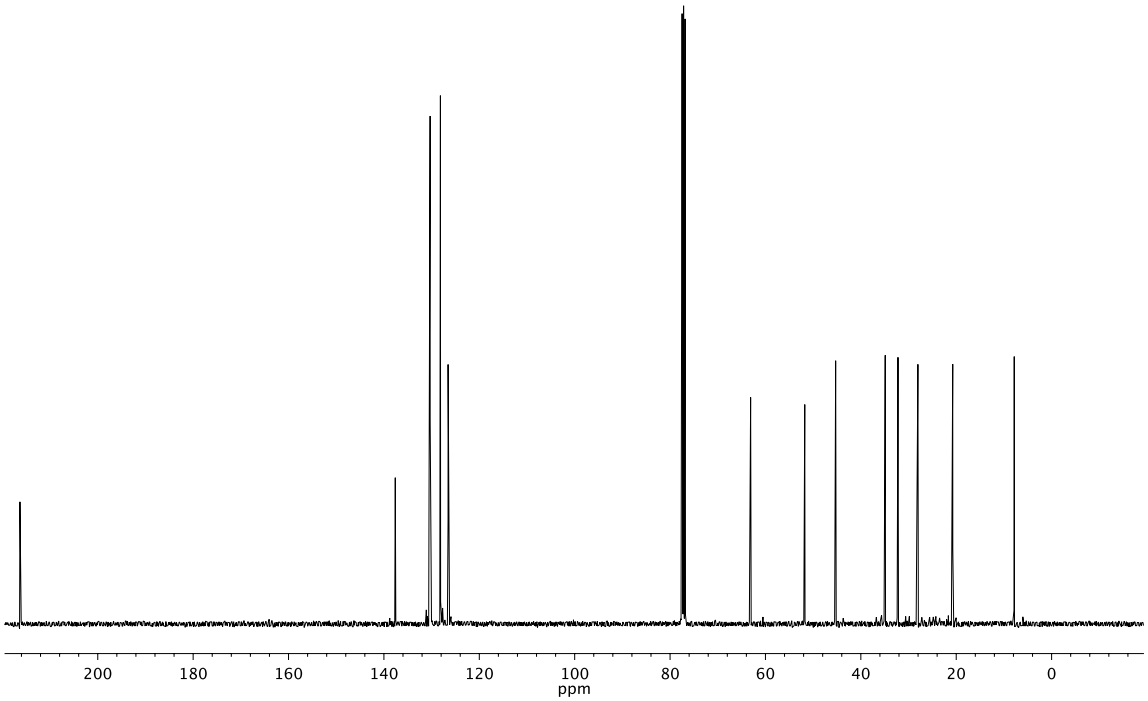



***Figure A3.76*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***17****.*

# CHAPTER 3

## *Catalytic Enantioselective Synthesis of Acyclic Quaternary Centers: Palladium-Catalyzed Decarboxylative Allylic Alkylation of Fully Substituted Acyclic Enol Carbaontes*[†]

### 3.1 INTRODUCTION

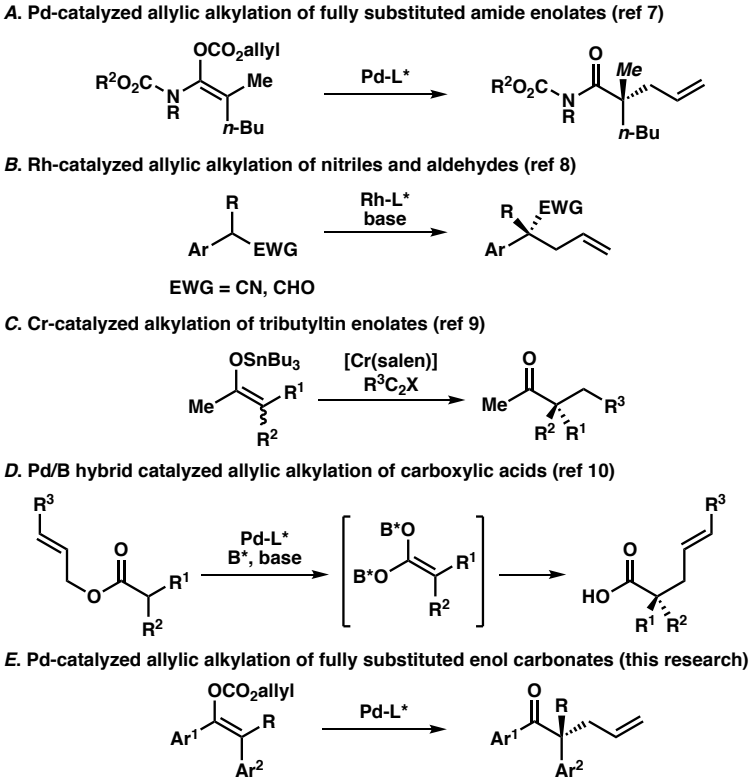
All-carbon quaternary stereocenters are prominent features in many natural products and can provide beneficial biochemical stability and three-dimensionality to molecules for medicinal chemistry applications. As a result, a number of methods to address their synthesis have been developed, particularly in cyclic systems.[1] In acyclic systems, however, the synthesis of this motif is less explored.[2] This is in part due to additional problems that often arise in acyclic systems such as reduced rigidity of particular substrates leading to lower levels of selectivity. Additionally, selectively controlling the formation of fully substituted olefins/enolates is required for high selectivity in many catalytic processes. In the case of electrophilic functionalization of fully substituted enolates, the general and selective formation of such enolates as pure geometric isomers is highly challenging and has slowed progress. Although selective

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[†]This research was performed in collaboration with Dr. Haiming Zhang. Portions of this chapter have been reproduced with permission from Alexy, E. J.; Zhang, H.; Stoltz, B. M. *J. Am. Chem Soc.* **2018**, *140*, 10109–10112. © 2018 American Chemical Society.

enolizations have been reported, these typically require highly specialized substrates, often incorporating chiral auxiliaries to impart selectivity in the enolate formation step.[3]

***Figure 3.1*** *Preparation of Acyclic α-Quaternary Carbonyl Derivatives.*




Recently, our group has become interested in strategies for preparing fully substituted acyclic enolates and applying them toward the synthesis of acyclic quaternary stereocenters, particularly via transition-metal catalyzed allylic alkylation (Figure 3.1). While palladium-catalyzed allylic alkylation has been employed in the synthesis of acyclic tertiary stereocenters,[4] the formation of all-carbon quaternary stereocenters has proven more challenging. Utilizing chemistry developed by the Marek group[5] for the synthesis of stereodefined acyclic enolates, we demonstrated the palladium-catalyzed enantioselective decarboxylative allylic alkylation of acyclic amide enolates utilizing an electron deficient $C_2$-symmetric bisphosphine ligand (Figure 3.1A).[6] Not surprisingly, it

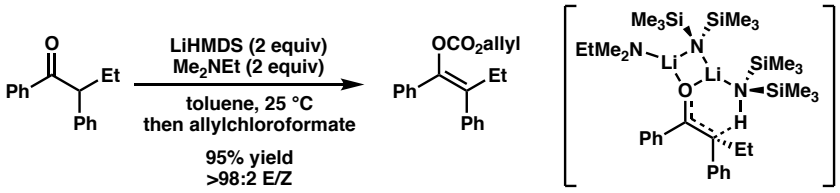
was observed that opposite enolate geometries of the substrate favored formation of the opposite enantiomers of the product, indicating a lack of significant dynamic kinetic resolution of the enolates during the reaction, and different facial selectivity between the two enolates. In fact, an analogous phenomenon regarding different enolate geometries was observed by the Trost lab when forming acyclic tertiary stereocenters via palladium-catalyzed allylic alkylation.[7] Additionally, the Evans lab has reported the use of rhodium-catalyzed allylic alkylation to furnish acyclic α-quaternary nitriles and aldehydes (Figure 3.1B).[8] In the latter work, they showed that both enolate geometries form the same enantiomer of product in essentially the same level of selectivity, which they believe is a consequence of substrate selectivity and not the result of an enolate equilibration event. In contrast, a dynamic equilibration of tributyltin enolates has been invoked by the Jacobsen group to directly alkylate fully substituted acyclic enolates with alkyl halides catalyzed by a [Cr(salen)] complex, affording α-quaternary ketones in high enantioselectivity starting with mixtures of enolates (Figure 3.1C).[9] Recently, Shimizu and Kanai demonstrated the preparation of acyclic α-quaternary carboxylic acids via allylic alkylation utilizing a hybrid boron-palladium catalytic system (Figure 3.1D).[10]

## 3.2 SYNTHESIS OF ACYCLIC KETONES

While acyclic ketone products can be obtained from the derivatization of α-quaternary nitriles and other carbonyl derivatives, we sought to prepare stereodefined acyclic ketone enolates and demonstrate their utility in palladium-catalyzed allylic alkylation (Figure 3.1E). To accomplish this goal, we utilized recently developed chemistry toward the synthesis of tetrasubstituted acyclic all-carbon olefins via sequential

selective enol-tosylate formation and cross-coupling.[11] We were pleased to find that the reported enolization conditions could be modified to trap the resultant enolate as the allyl enol carbonate with excellent *E/Z* ratios (Scheme 3.1), thereby allowing us to investigate palladium-catalyzed conditions toward furnishing the acyclic quaternary stereocenter.

***Scheme 3.1*** *Selective Enolization of Fully Substituted Acyclic Ketones.*

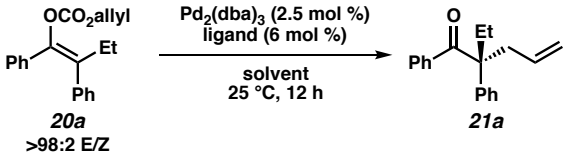



## 3.3 ALLYLIC ALKYLATION OPTIMIZATION

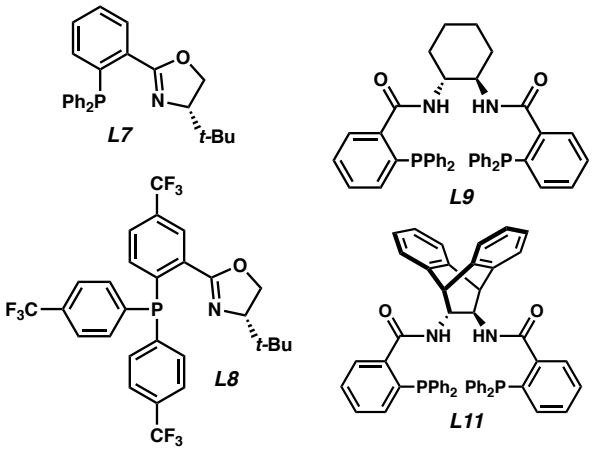
We began our studies with an initial ligand screen using 2.5 mol % $Pd_2(dba)_3$ and 6 mol % of a variety of common ligands, finding that phosphinooxazoline ligand ***L1*** gave high conversion of the substrate albeit with very low enantioselectivity (Table 1, entry 1). This result is unsurprising since ligand ***L7*** has previously been shown to perform poorly with α-aryl stabilized enolates, albeit on cyclic motifs.[1a] We were pleased to find, however, that electron-deficient phosphinooxazoline ***L8*** gave the product in similarly excellent conversion with a promising enantiomeric excess of 54% (entry 2). Bisphosphine ligand ***L9*** gave high conversion of the substrate but only a moderate 45% ee (entry 3), whereas ***L11*** gave a more promising 73% ee but in poor conversion (entry 4). To our delight, we found that non-polar solvents were superior for the transformation (entries 5–9) with a 3:1 mixture of hexane/toluene providing the highest and most reproducible yields. In this solvent system, ***L11*** provided the product in 89% isolated yield and 86% ee (entry 7). Gratifyingly, using ligand ***L8*** gave enhanced results with the desired product obtained in 98% isolated yield and 90% ee. Moreover, the catalyst

loading could be reduced to 0.5 mol % $Pd_2(dba)_3$ and 1.2 mol % of ***L8*** (entry 9) without altering the yield and selectivity or significantly increasing reaction time.

***Table 3.1*** *Optimization of Acyclic Decarboxylative Alkylation.*[a]




| entry | ligand | solvent | yield[b] | % ee[c] |
|---|---|---|---|---|
| 1 | *L7* | THF | – | 6 |
| 2 | *L8* | THF | – | 54 |
| 3 | *L9* | THF | – | –45 |
| 4 | *L11* | THF | 42 | –73 |
| 5 | *L8* | MeCy[d] | 83 | 89 |
| 6 | *L8* | 3:1 MeCy/PhMe | 90 | 89 |
| 7 | *L11* | 3:1 hexane/PhMe | 89 | –86 |
| 8 | *L8* | 3:1 hexane/PhMe | 98 | 90 |
| 9[e] | *L8* | 3:1 hexane/PhMe | 97 | 91 |



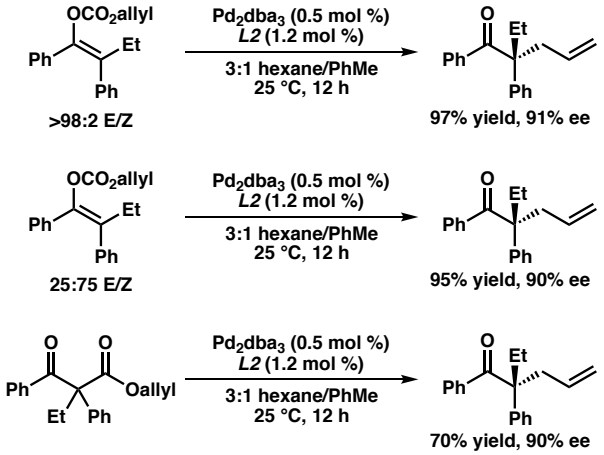

[a] Conditions: 0.1 mmol ***1***, 2.5 mol % Pd(dba), 6 mol % ligand, 1.0 mL solvent. [b] Yield of isolated product. [c] Determined by chiral SFC analysis. [d] methylcyclohexane. [e] Reaction performed with 0.2 mmol ***1***, 0.5 mol % Pd(dba), 1.2 mol % ligand, and 2.0 mL solvent.

## 3.4 IMPORTANCE OF SUBSTRATE ENOLATE GEOMETRY

With optimal conditions identified, we next sought to examine the importance of enolate geometry on the transformation (Figure 2). Under the standard conditions, the

desired product is obtained in 97% isolated yield and 91% ee favoring the *S*-absolute stereochemistry when the starting material consists of a >98:2 *E/Z* ratio of enolates. When the same starting material is prepared in a 25:75 *E/Z* ratio via a non-selective enolization, the alkylation product is obtained in 95% isolated yield and 90% ee, forming the same enantiomer of product (i.e. *S*) as in the standard case. Furthermore, the corresponding β-ketoester substrate again provides the same enantiomer (i.e. *S*) of product in high selectivity, albeit with a diminished yield (70% yield, 90% ee). This surprising result is exclusive to the electron-deficient phosphinooxazoline ***L8***. With bisphosphine ***L11***, the 25:75 *E/Z* ratio of enolates provides the product in a diminished 64% yield and 50% ee (compared to 89% yield and 86% ee). Additionally, when the 25:75 *E/Z* ratio substrate is used with ***L8***, the ee of the product remains the same throughout the time course of the reaction (see experimental). Based on these findings and prior examples of differing selectivities obtained with different enolate geometries in palladium-catalyzed allylic alkylation, we believe that a dynamic kinetic resolution of the two enolate geometries occurs in the reaction when ***L8*** is used as the ligand, possibly due to facile equilibration between *O*-bound and *C*-bound palladium enolates.

***Figure 3.2*** *Importance of Enolate Geometry.*

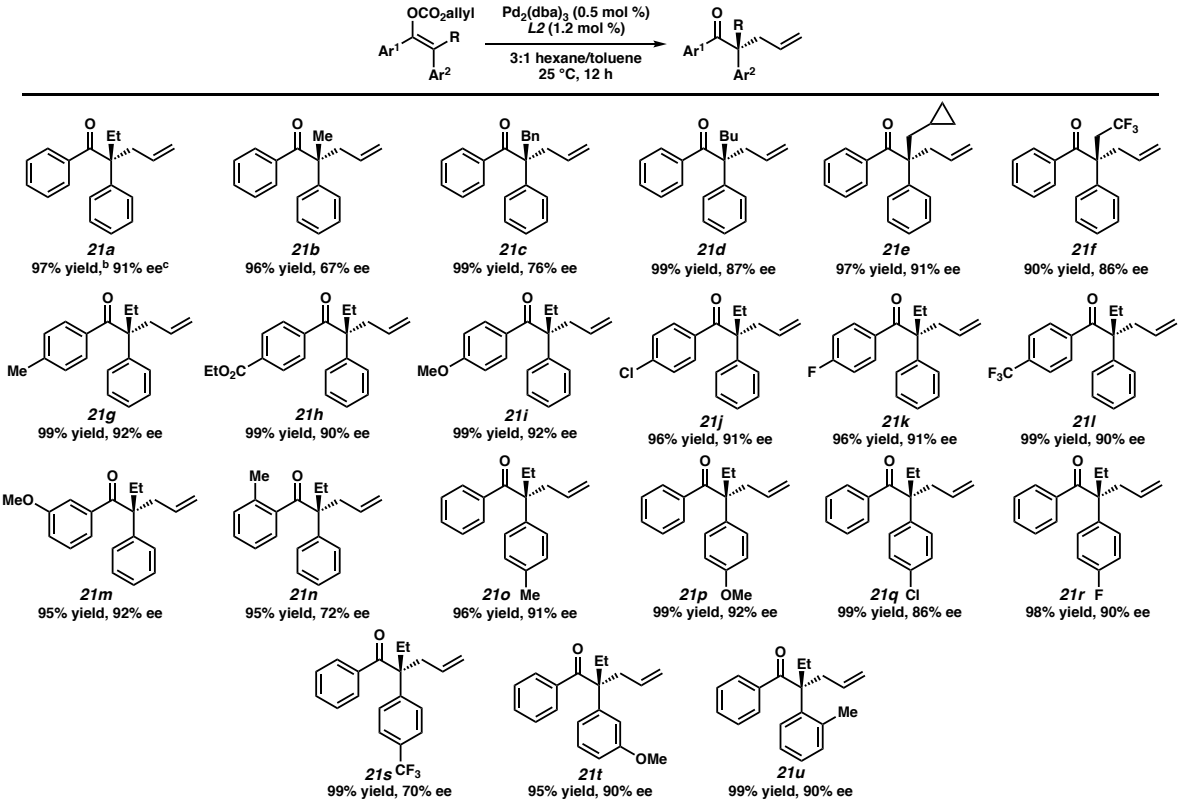


## 3.5 INVESTIGATION OF REACTION SCOPE

While β-ketoesters and enolate mixtures can be used to furnish the desired acyclic ketones in high enantioselectivity, due to ease of preparation and characterization, the substrate scope of the reaction was investigated with allyl enol carbonates formed via the aforementioned selective enolization. Substrates were enolized in generally high levels of selectivity (see experimental section for details). A variety of substrates containing different alkyl and aryl substituents were examined, with all alkylated products obtained in excellent yields (Table 3.2). Smaller α-alkyl groups such as methyl (**21b**) yielded a lower 67% ee, along with the α-benzyl substrate (**21c**) providing the alkylated product in only 76% ee. Longer alkyl chains such as *n*-butyl (**21d**) and trifluoroethyl (**21f**) as well as cyclopropyl methyl substrate (**21e**) all provided the desired alkylation products in high enantioselectivity. Examining electronic effects on the acetophenone (i.e., $Ar^1$) portion of the substrate revealed that a variety of electron-withdrawing and donating substituents were well tolerated. Substitution at the *para*-position led to consistently high yields and selectivities with the *p*-Me (**21g**), *p*-ethyl ester (**21h**), *p*-OMe (**21i**), *p*-chloro (**21j**), *p*-fluoro (**21k**), and *p*-$CF_3$ (**21i**) substrates providing products in 96–99% yield and 90–92% ee. The *m*-OMe (**21m**) substrate also performed well yielding the product in 96% yield and 91% ee. *Ortho*-substitution on this aryl ring, however, resulted in lower enantioselectivity with the *o*-Me (**21n**) substrate obtained excellent yield but only 72% ee. Lastly, α-aryl substitutions were surveyed (i.e. $Ar^2$) with electron donating groups such as *p*-Me (**21o**) and *p*-OMe (**21p**) proceeding with excellent yields and 91% and 92% ee, respectively. While a *p*-fluoro (**21r**) substituent was well tolerated (90% ee), other electron-withdrawing substituents led to lower selectivity with the *p*-chloro (**21q**)

substrate at 86% ee and the *p*-$CF_3$ (**21s**) substrate significantly lower at 70% ee. Again, *meta*-substitution was tolerated with the *m*-OMe (**21t**) substrate delivering the product in 95% yield and 90% ee. Interestingly, ortho substituion is tolerated on the α-aryl substituent with *o*-Me (**21u**) substrate proceeding with excellent yield and 90% ee. Unfortunately, attempts to form fully alkyl quaternary stereocenters has proven challenging (experimental section).

***Table 3.2*** *Substrate Scope of Asymmetric, Decarboxylative Allylic Alkylation.*[a]



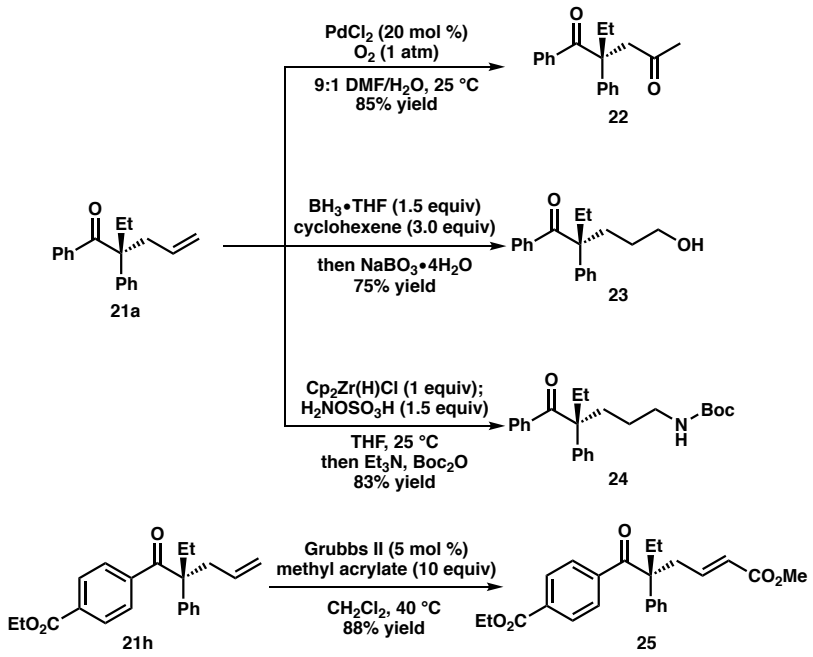

[a] Reactions performed on 0.2 mmol scale. [b] Yield of isolated product. [c] Determined by chiral SFC analysis. [d] Absolute configuration of **21b** determined by comparison to literature value,[9] all other compounds are assigned by analogy.

## 3.6 DERIVATIZATION OF ALKYLATION PRODUCTS

With the scope of the transformation established, we sought to demonstrate the utility of the produced acyclic α-quaternary ketones toward further functionalization (Scheme 3.2).

Treatment of the standard alkylation product **21a** to Wacker oxidation conditions[13] employing catalytic $PdCl_2$ under $O_2$ (1 atm) provided methyl ketone **22** in 85% isolated yield. In addition, treatment of ketone **21a** to a hydroboration-oxidation protocol with $BH_3$•THF and cyclohexene, followed by sodium perborate provided primary alcohol **23** in 75% isolated yield. A hydrozirconation/amination protocol using conditions developed by the Hartwig group[14] allows access to *anti*-Markovnikov amination product **24** in 83% yield following *in situ* Boc protection. Lastly, olefin metathesis of alkylation product **21h** with methyl acrylate and Grubbs' second generation catalyst[6] yields α,β-unsaturated methyl ester **25** in 88% yield.

***Scheme 3.2*** *Derivatization of Alkylation Products.*




## 3.7 CONCLUSIONS

In summary, we have developed the first enantioselective palladium-catalyzed decarboxylative allylic alkylation toward the synthesis of chiral acyclic α-quaternary ketones. The use of electron-deficient phosphinooxazoline ligand ***L2*** is critical to achieve

high yields and enantioselectivity. The allyl enol carbonate substrates could be prepared in high levels of *E/Z* geometrical selectivity, however a proposed dynamic kinetic enolate equilibration during the palladium catalyzed reaction allows the use of enolate mixtures and racemic β-ketoesters as substrates as well. Further exploration into the scope, mechanism, and applications of this process are underway.

## 3.8 EXPERIMENTAL SECTION

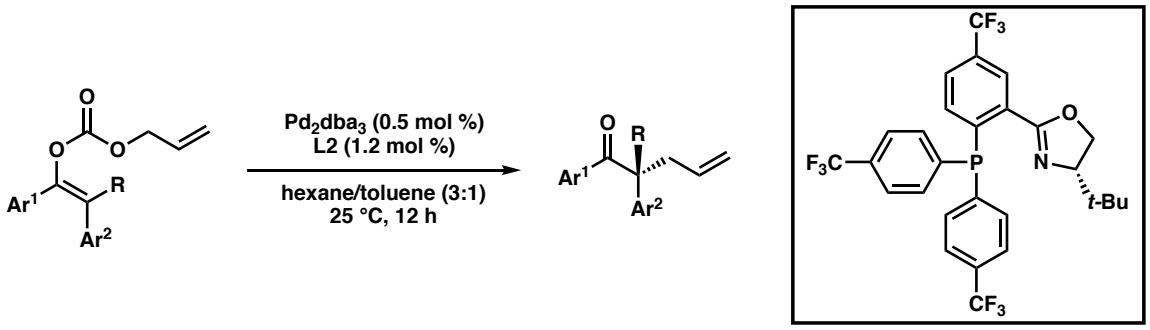
### 3.8.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 μm) was used for flash chromatography. $^1$H NMR spectra were recorded on Varian Inova 500 MHz and Bruker 400 MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm). $^{13}$C NMR spectra were recorded on a Varian Inova 500 MHz spectrometer (125 MHz) and Bruker 400 MHz spectrometers (100 MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm). Data for $^1$H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet, app = apparent. Data for $^{13}$C NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer or Nicolet 6700 FTIR spectrometer using thin films deposited on

NaCl plates and reported in frequency of absorption ($cm^{-1}$). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell and are reported as: $[\alpha]_D^T$ (concentration in 10 mg/1 mL, solvent). Analytical SFC was performed with a Mettler SFC supercritical $CO_2$ analytical chromatography system utilizing Chiralpak (AD-H, AS-H or IC) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+), or obtained from Caltech mass spectrometry laboratory. Ligands and trisubstituted ketones were prepared by known methods.

## 3.8.2 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

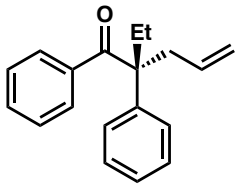
### 3.8.2.1 General Procedure for Pd-Catalyzed Allylic Alkylation Reactions




In a nitrogen-filled glovebox, a solution of $Pd_2(dba)_3$ (1.8 mg/mL) and **L8** (2.8 mg/mL) in toluene was stirred for 30 minutes at 25 °C, then 0.5 mL of the resulting catalyst solution was added to a one dram vial containing allyl enol carbonate substrate (0.2 mmol) dissolved in hexanes (1.5 mL). The vial was sealed with a Teflon-lined cap, removed from the glovebox, and stirred at 25 °C for 12 h. The crude reaction mixture

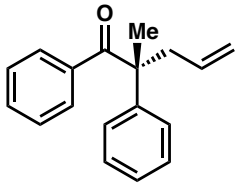
was concentrated then purified by silica gel flash chromatography to provide the desired alkylation product.

### 3.8.2.2 Spectroscopic Data for the Allylic Alkylation Products




**(*R*)-2-ethyl-1,2-diphenylpent-4-en-1-one (21a)**

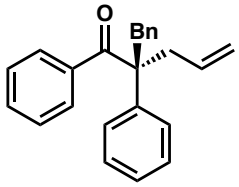
Purified by column chromatography (4% $Et_2O$ in hexanes) to provide a colorless oil (51.1 mg, 97% yield); 91% ee, $[\alpha]_D^{25}$ –107.5 (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.44–7.33 (m, 5H), 7.31–7.25 (m, 3H), 7.24–7.17 (m, 2H), 5.38 (dddd, *J* = 16.8, 10.3, 8.2, 6.5 Hz, 1H), 5.03–4.85 (m, 2H), 2.91–2.72 (m, 2H), 2.16 (qd, *J* = 7.4, 3.3 Hz, 2H), 0.69 (t, *J* = 7.5 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 203.3, 142.7, 137.3, 133.6, 131.8, 129.5, 129.0, 128.1, 127.1, 127.0, 118.3, 58.2, 39.3, 26.9, 8.0; IR (Neat Film, NaCl) 3065, 2973, 2940, 2879, 1675, 1597, 1578, 1496, 1446, 1227, 1182, 1142, 1004, 917, 839, 764, 714, 702, 654 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{21}O$ $[M+H]^+$: 265.1587, found 265.1577; SFC Conditions: 2% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 5.33, major = 5.76.




**(*R*)-2-methyl-1,2-diphenylpent-4-en-1-one (21b)**

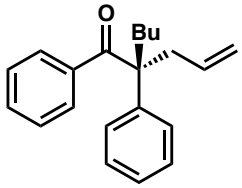
Purified by column chromatography (3% $Et_2O$ in hexanes) to provide a colorless oil (48.3 mg, 96% yield); 67% ee, $[a]_D^{25}$ –111.9 (*c* 1.00, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.48–7.42 (m, 2H), 7.40–7.33 (m, 3H), 7.33–7.27 (m, 3H), 7.24–7.18 (m, 2H), 5.51

(dddd, *J* = 17.0, 10.2, 7.7, 6.9 Hz, 1H), 5.08–4.87 (m, 2H), 2.89–2.71 (m, 2H), 1.58 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 203.3, 143.6, 136.9, 134.1, 131.8, 129.7, 129.1, 128.1, 127.1, 126.4, 118.5, 54.4, 44.8, 23.8; IR (Neat Film, NaCl) 3065, 3024, 2977, 2935, 1677, 1638, 1597, 1578, 1496, 1446, 1376, 1240, 1182, 1139, 1078, 1028, 1001, 970, 917, 762, 716, 701 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{18}H_{19}O$ $[M+H]^+$: 251.1430, found 251.1418; SFC Conditions: 2% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 7.02, major = 7.44.



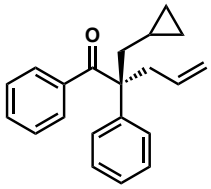

**(*S*)-2-benzyl-1,2-diphenylpent-4-en-1-one (21c)**

Purified by column chromatography (3% $Et_2O$ in hexanes) to provide a white solid (64.9 mg, 99% yield); 76% ee, $[\alpha]_D^{25}$ +102.5 (*c* 1.00, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.48–7.40 (m, 2H), 7.37–7.23 (m, 4H), 7.23–7.13 (m, 2H), 7.12–6.97 (m, 5H), 6.58–6.49 (m, 2H), 5.64 (ddt, J = 17.2, 10.2, 7.1 Hz, 1H), 5.07–4.97 (m, 1H), 4.84 (dd, *J* = 17.0, 1.8 Hz, 1H), 3.41–3.26 (m, 2H), 2.90–2.67 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 202.2, 142.2, 137.2, 137.1, 133.2, 131.9, 130.9, 129.9, 129.0, 128.1, 127.6, 127.4, 127.3, 126.3, 119.4, 59.0, 42.1, 37.9; IR (Neat Film, NaCl) 3062, 1674, 1597, 1579, 1496, 1446, 1269, 1216, 1180, 1078, 1026, 912, 768, 722, 701 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{24}H_{23}O$ $[M+H]^+$: 327.1743, found 327.1748; SFC Conditions: 10% IPA, 2.5 mL/min, Chiralcel OD-H column, λ = 210 nm, $t_R$ (min): minor = 5.47, major = 5.97.




**(*R*)-2-allyl-1,2-diphenylhexan-1-one (21d)**

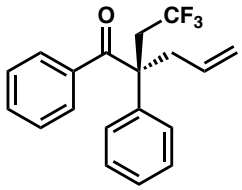
Purified by column chromatography (3% $Et_2O$ in hexanes) to provide a colorless oil (58.2 mg, 99% yield); 87% ee, $[\alpha]_D^{25}$ –112.6 (*c* 1.00, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.41–7.28 (m, 5H), 7.28–7.20 (m, 3H), 7.16 (dd, *J* = 8.2, 7.0 Hz, 2H), 5.35 (dddd, *J* = 16.8, 10.3, 7.9, 6.7 Hz, 1H), 4.98–4.80 (m, 2H), 2.92–2.67 (m, 2H), 2.06 (dt, *J* = 9.9, 4.9 Hz, 2H), 1.23–0.99 (m, 3H), 0.96–0.78 (m, 1H), 0.71 (t, *J* = 7.1 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 203.3, 142.8, 137.3, 133.7, 131.7, 129.5, 129.0, 128.0, 127.1, 126.9, 118.3, 57.8, 40.0, 33.8, 25.6, 23.2, 13.9; IR (Neat Film, NaCl) 3064, 2956, 2871, 2861, 1676, 1639, 1597, 1578, 1496, 1466, 1446, 1254, 1240, 1212, 1181, 1144, 1001, 918, 764, 720, 701 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{21}H_{25}O$ $[M+H]^+$: 293.1900, found 293.1898; SFC Conditions: 5% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 4.44, major = 5.27.




**(*S*)-2-(cyclopropylmethyl)-1,2-diphenylpent-4-en-1-one (21e)**

Purified by column chromatography (3% $Et_2O$ in hexanes) to provide a colorless oil (56.5 mg, 97% yield); 91% ee, $[\alpha]_D^{25}$ –57.6 (*c* 1.00, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.48–7.43 (m, 2H), 7.37–7.33 (m, 3H), 7.30–7.25 (m, 3H), 7.22–7.17 (m, 2H), 5.42 (ddt, *J* = 17.3, 10.2, 7.2 Hz, 1H), 5.04–4.80 (m, 2H), 3.04 (dt, *J* = 7.2, 1.3 Hz, 2H), 2.16 (dd, *J*

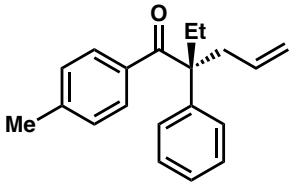
= 14.1, 6.1 Hz, 1H), 2.03 (dd, *J* = 14.1, 7.0 Hz, 1H), 0.49–0.38 (m, 1H), 0.36–0.22 (m, 2H), -0.09 (dtd, *J* = 8.4, 5.0, 3.7 Hz, 1H), –0.18 – -0.27 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 202.9, 143.1, 137.1, 133.8, 131.8, 129.8, 129.0, 128.1, 127.1, 126.9, 118.5, 58.8, 40.1, 39.3, 5.9, 4.9, 4.5; IR (Neat Film, NaCl) 3075, 3003, 2936, 1676, 1639, 1597, 1579, 1496, 1446, 1273, 1221, 1181, 1151, 1019, 919, 762, 719, 701 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{21}H_{23}O$ $[M+H]^+$: 291.1743, found 291.1743; SFC Conditions: 5% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 6.27, major = 6.97.




**(*S*)-1,2-diphenyl-2-(2,2,2-trifluoroethyl)pent-4-en-1-one (21f)**

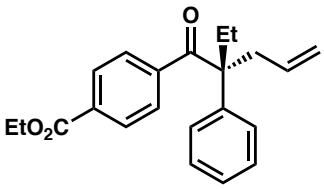
Purified by preparative TLC (10% $Et_2O$ in hexanes) to provide a colorless oil (57.1 mg, 90% yield); 86% ee, $[a]_D^{25}$ +78.0 (*c* 1.00, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.49–7.31 (m, 8H), 7.24–7.18 (m, 2H), 5.45 (ddt, *J* = 17.3, 10.2, 7.3Hz, 1H), 5.08 (ddt, *J* = 10.2, 1.9, 1.0 Hz, 1H), 4.96 (dq, *J* = 17.0, 1.5 Hz, 1H), 3.27–3.16 (m, 1H), 3.15 – 2.88 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 200.4, 139.8, 136.4, 132.1, 131.8, 129.7, 129.4, 128.3, 128.0, 126.8 (q, *J* = 272.9 Hz), 126.7, 120.6, 55.5 (d, *J* = 1.5 Hz), 39.1 (q, *J* = 26.7 Hz), 38.5 (d, *J* = 1.8 Hz); $^{19}$F NMR (282 MHz, $CDCl_3$) δ –58.4 (t, *J* = 11.1 Hz); IR (Neat Film, NaCl) 3067, 3027, 2985, 1678, 1642, 1598, 1579, 1498, 1371, 1272, 1260, 1219, 1202, 1184, 1142, 1118, 1087, 1045, 1025, 982, 926, 765, 727, 701 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{18}F_3O$ $[M+H]^+$: 319.1304, found 319.1293; SFC

Conditions: 5% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 1.73, major = 2.17.




**(*R*)-2-ethyl-2-phenyl-1-(*p*-tolyl)pent-4-en-1-one (21g)**

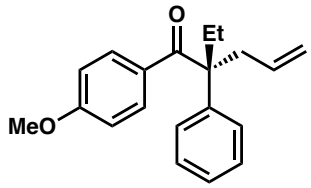
Purified by column chromatography (4% $Et_2O$ in hexanes) to provide a colorless oil (52.1 mg, 94% yield); 90% ee, $[\alpha]_D^{25}$ –99.1 (*c* 1.00, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.39–7.31 (m, 4H), 7.31–7.21 (m, 3H), 7.04–6.97 (m, 2H), 5.38 (dddd, *J* = 16.7, 10.2, 8.3, 6.4 Hz, 1H), 4.99–4.88 (m, 2H), 2.87 (ddt, *J* = 14.2, 8.3, 1.0 Hz, 1H), 2.78 (ddt, *J* = 14.2, 6.3, 1.4 Hz, 1H), 2.28 (s, 3H), 2.20–2.11 (m, 2H), 0.69 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 202.7, 143.1, 142.4, 134.4, 133.7, 129.7, 128.9, 128.8, 127.0, 127.0, 118.2, 58.1, 39.5, 27.0, 21.6, 8.0; IR (Neat Film, NaCl) 3063, 3026, 2973, 2879, 1673, 1640, 1606, 1496, 1446, 1230, 1182, 1001, 916, 824, 774, 740, 704 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{20}H_{23}O$ $[M+H]^+$: 279.1743, found 279.1754; SFC Conditions(for cross-metathesis product): 5% IPA, 2.5 mL/min, Chiralcel OB-H column, λ = 210 nm, $t_R$ (min): minor = 4.14, major = 4.95.




**ethyl (*R*)-4-(2-ethyl-2-phenylpent-4-enoyl)benzoate (21h)**

Purified by column chromatography (5% $Et_2O$ in hexanes) to provide a white solid (66.4 mg, 99% yield); 90% ee, $[\alpha]_D^{25}$ –79.7 (*c* 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ

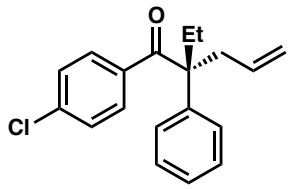
7.90–7.84 (m, 2H), 7.45–7.34 (m, 4H), 7.33–7.24 (m, 3H), 5.44–5.30 (m, 1H), 5.07–4.83 (m, 2H), 4.33 (q, $J$ = 7.1 Hz, 2H), 2.83 (dt, $J$ = 7.6, 1.2 Hz, 2H), 2.14 (qq, $J$ = 14.4, 7.3, 6.9 Hz, 2H), 1.34 (t, $J$ = 7.1 Hz, 3H), 0.69 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 203.0, 165.9, 142.1, 140.9, 133.2, 132.9, 129.3, 129.3, 129.1, 127.4, 127.0, 118.5, 61.4, 58.4, 39.0, 26.7, 14.4, 7.9; IR (Neat Film, NaCl) 3076, 2977, 2940, 2879, 1722, 1581, 1649, 1599, 1580, 1570, 1495, 1462, 1446, 1404, 1367, 1312, 1276, 1225, 1180, 1107, 1017, 1001, 918, 833, 788, 767, 727, 703 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{22}H_{25}O_3$ $[M+H]^+$: 337.1798, found 337.1786; SFC Conditions(for cross-metathesis product, see pg S34): 7% IPA, 2.5 mL/min, Chiralcel OD-H column, λ = 210 nm, $t_R$ (min): minor = 9.38, major = 10.31.




**(*R*)-2-ethyl-1-(4-methoxyphenyl)-2-phenylpent-4-en-1-one (21i)**

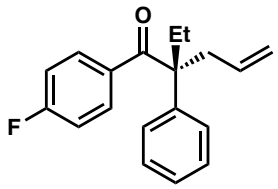
Purified by column chromatography (5% $Et_2O$ in hexanes) to provide a colorless oil (58.4 mg, 99% yield); 91% ee, $[\alpha]_D^{25}$ –91.9 (*c* 1.00, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.51–7.45 (m, 2H), 7.38–7.31 (m, 2H), 7.26 (tt, $J$ = 6.5, 1.1 Hz, 4H), 6.69 (d, $J$ = 9.0 Hz, 1H), 5.38 (dddd, $J$ = 16.8, 10.3, 8.3, 6.3 Hz, 1H), 5.03–4.85 (m, 2H), 3.76 (s, 3H), 2.87 (ddt, $J$ = 14.2, 8.3, 1.0 Hz, 1H), 2.77 (ddt, $J$ = 14.2, 6.4, 1.4 Hz, 1H), 2.19–2.12 (m, 2H), 0.69 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 201.5, 162.3, 143.4, 133.8, 132.0, 129.7, 128.9, 126.9, 118.1, 113.2, 57.9, 55.4, 39.6, 27.2, 8.0; IR (Neat Film, NaCl) 3075, 3004, 2971, 2938, 2839, 1667, 1600, 1574, 1508, 1496, 1459, 1445, 1417, 1307, 1258, 1238, 1174, 1142, 1033, 998, 916, 837, 778, 750, 703 cm$^{-1}$; HRMS (MM:ESI-

APCI+) *m/z* calc'd for $C_{20}H_{23}O_2$ $[M+H]^+$: 295.1693, found 295.1688; SFC Conditions: 5% IPA, 2.5 mL/min, Chiralpak OJ-H column, λ = 210 nm, $t_R$ (min): minor = 4.35, major = 4.60.




**(*R*)-1-(4-chlorophenyl)-2-ethyl-2-phenylpent-4-en-1-one (21j)**

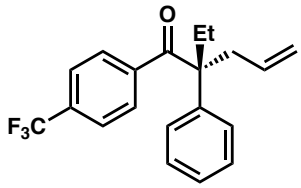
Purified by column chromatography (4% $Et_2O$ in hexanes) to provide a colorless oil (57.1 mg, 96% yield); 91% ee, $[a]_D^{25}$ –91.3 (*c* 1.00, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.39–7.34 (m, 4H), 7.31–7.27 (m, 1H), 7.27–7.23 (m, 2H), 7.19–7.15 (m, 2H), 5.36 (dddd, *J* = 16.8, 10.2, 8.2, 6.4 Hz, 1H), 5.00–4.87 (m, 2H), 2.86–2.76 (m, 2H), 2.23–2.04 (m, 2H), 0.69 (t, *J* = 7.4 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 201.9, 142.5, 138.1, 135.4, 133.3, 131.0, 129.1, 128.4, 127.3, 126.9, 118.5, 58.2, 39.2, 26.9, 8.0; IR (Neat Film, NaCl) 3074, 2973, 2940, 2878, 1677, 1640, 1586, 1486, 1446, 1398, 1225, 1178, 1093, 1001, 917, 827, 775, 744, 703 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{20}ClO$ $[M+H]^+$: 299.1197, found 299.1201; SFC Conditions: 10% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 6.09, major = 6.64.




**(*R*)-2-ethyl-1-(4-fluorophenyl)-2-phenylpent-4-en-1-one (21k)**

Purified by column chromatography (4% $Et_2O$ in hexanes) to provide a colorless oil (54.1 mg, 96% yield); 91% ee, $[\alpha]_D^{25}$ –111.7 (*c* 1.00, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ

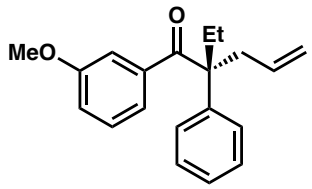
7.50–7.43 (m, 2H), 7.40–7.31 (m, 2H), 7.32–7.23 (m, 3H), 6.91–6.82 (m, 2H), 5.37 (dddd, $J$ = 16.8, 10.2, 8.2, 6.4 Hz, 1H), 5.00–4.87 (m, 2H), 2.91–2.72 (m, 2H), 2.27–1.97 (m, 2H), 0.69 (t, $J$ = 7.5 Hz, 3H); $^{19}$F NMR (282 MHz) δ –107.1 (tt, $J$ = 8.5, 5.5 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 201.5, 164.7 (d, $J$ = 253.6 Hz), 142.7, 133.4, 133.3 (d, $J$ = 3.3 Hz), 132.2 (d, $J$ = 8.9 Hz), 129.1, 127.2, 126.9, 118.4, 115.1 (d, $J$ = 21.5 Hz), 58.1, 39.3, 27.0, 8.0; IR (Neat Film, NaCl) 3076, 2973, 2940, 1677, 1639, 1598, 1504, 1446, 1231, 1158, 1143, 1000, 917, 841, 777, 747, 704 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{20}FO$ $[M+H]^+$: 283.1493, found 283.1479; SFC Conditions (on cross-metathesis product): 5% IPA, 2.5 mL/min, Chiralcel OD-H column, λ = 210 nm, $t_R$ (min): minor = 7.43, major = 8.03.




**(*R*)-2-ethyl-2-phenyl-1-(4-(trifluoromethyl)phenyl)pent-4-en-1-one (21l)**

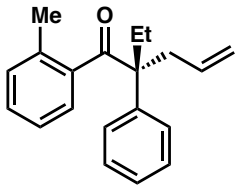
Purified by column chromatography (4% $Et_2O$ in hexanes) to provide a colorless oil (65.5 mg, 99% yield); 90% ee, $[\alpha]_D^{25}$ –95.1 (*c* 1.00, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.47 (s, 4H), 7.41–7.36 (m, 2H), 7.34–7.29 (m, 1H), 7.29–7.25 (m, 2H), 5.37 (ddt, $J$ = 17.0, 10.2, 7.3 Hz, 1H), 5.02 4.87 (m, 2H), 2.83 (dt, $J$ = 7.3, 1.2 Hz, 2H), 2.26–2.05 (m, 2H), 0.70 (t, $J$ = 7.4 Hz, 3H); $^{19}$F NMR (282 MHz) δ –63.2 (s); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 202.4, 141.9, 140.3, 133.1, 133.1 (q, $J$ = 32.6 Hz) 129.7, 129.2, 127.5, 126.9, 125.1 (q, $J$ = 3.7 Hz), 123.7 (q, $J$ = 272.5) 118.6, 58.4, 39.0, 26.7, 7.9; IR (Neat Film, NaCl) 3078, 2974, 2942, 2880, 1683, 1641, 1599, 1580, 1494, 1461, 1446, 1407, 1326, 1227, 1170, 1131, 1069, 1016, 1001, 918, 849, 834, 781, 754, 702 cm$^{-1}$; HRMS

(MM:ESI-APCI+) *m/z* calc'd for $C_{20}H_{23}F_3NO$ $[M+NH_4]^+$: 350.1726, found 350.1723; SFC Conditions (on cross-metathesis product): 5% IPA, 2.5 mL/min, Chiralpak AD-H column, $\lambda = 210$ nm, $t_R$ (min): minor = 4.47, major = 5.90.



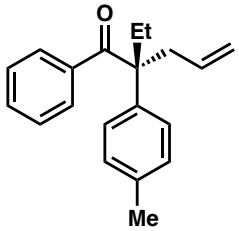

**(*R*)-2-ethyl-1-(3-methoxyphenyl)-2-phenylpent-4-en-1-one (21m)**

Purified by column chromatography (4% $Et_2O$ in hexanes) to provide a colorless oil (55.9 mg, 95% yield); 91% ee, $[\alpha]_D^{25}$ –89.4 (*c* 1.00, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.39–7.34 (m, 2H), 7.31–7.26 (m, 3H), 7.09 (ddd, *J* = 8.2, 7.4, 0.7 Hz, 1H), 7.00–6.96 (m, 2H), 6.90 (ddd, *J* = 8.2, 2.5, 1.2 Hz, 1H), 5.38 (dddd, *J* = 16.8, 10.3, 8.2, 6.4 Hz, 1H), 5.04–4.87 (m, 2H), 3.62 (s, 3H), 2.98–2.74 (m, 2H), 2.16 (q, *J* = 7.5 Hz, 2H), 0.70 (t, *J* = 7.4 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 203.1, 159.1, 142.8, 138.5, 133.6, 129.0, 129.0, 127.1, 127.0, 122.1, 118.4, 118.3, 113.9, 58.2, 55.3, 39.2, 26.9, 8.0; IR (Neat Film, NaCl) 3074, 2970, 2940, 1677, 1640, 1596, 1580, 1487, 1462, 1446, 1425, 1318, 1288, 1258, 1206, 1180, 1046, 917, 790, 773, 738, 703 $cm^1$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{20}H_{23}O_2$ $[M+H]^+$: 295.1693, found 295.1681; SFC Conditions: 2% IPA, 2.5 mL/min, Chiralcel OJ-H column, $\lambda = 210$ nm, $t_R$ (min): minor = 5.57, major = 5.95.




**(*R*)-2-ethyl-2-phenyl-1-(*o*-tolyl)pent-4-en-1-one (21n)**

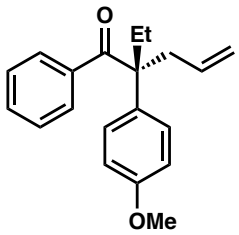
Purified by column chromatography (3% $Et_2O$ in hexanes) to provide a colorless oil (53.0 mg, 95% yield); 73% ee, $[\alpha]_D^{25}$ –62.0 (*c* 1.00, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.30–7.24 (m, 4H), 7.22–7.15 (m, 1H), 7.11–7.04 (m, 2H), 6.74 (dtd, *J* = 8.6, 4.0, 0.7 Hz, 1H), 6.54 (dt, *J* = 7.8, 1.0 Hz, 1H), 5.35 (dddd, *J* = 16.9, 10.3, 7.9, 6.6 Hz, 1H), 4.92–4.75 (m, 2H), 2.75 (ddt, *J* = 7.9, 6.9, 1.3 Hz, 2H), 2.26 (s, 3H), 2.14–1.87 (m, 2H), 0.62 (t, *J* = 7.4 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 207.2, 141.9, 138.3, 138.1, 133.7, 131.9, 130.0, 128.9, 127.6, 127.1, 127.0, 124.6, 118.2, 58.7, 38.5, 26.7, 21.1, 7.9; IR (Neat Film, NaCl) 3061, 2972, 2939, 2879, 1680, 1640, 1599, 1493, 1456, 1446, 1381, 1287, 1226, 1121, 997, 916, 847, 764, 755, 734, 702, 652 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{20}H_{23}O$ $[M+H]^+$: 279.1743, found 279.1746; SFC Conditions (on cross metathesis product): 10% IPA, 2.5 mL/min, Chiralpak IC column, λ = 210 nm, $t_R$ (min): minor = 5.74, major = 6.49.




**(*R*)-2-ethyl-1-phenyl-2-(*p*-tolyl)pent-4-en-1-one (21o)**

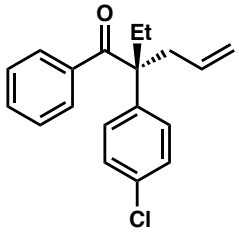
Purified by column chromatography (4% $Et_2O$ in hexanes) to provide a colorless oil (53.5 mg, 96% yield); 91% ee, $[\alpha]_D^{25}$ –107.3 (*c* 1.00, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.44–7.41 (m, 2H), 7.37–7.33 (m, 1H), 7.23–7.18 (m, 2H), 7.17 (s, 4H), 5.38 (dddd, *J* =

16.8, 10.2, 8.2, 6.4 Hz, 1H), 5.01–4.84 (m, 2H), 2.92–2.74 (m, 2H), 2.35 (s, 3H), 2.20–2.03 (m, 2H), 0.68 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 203.6, 139.5, 137.5, 136.7, 133.8, 131.7, 129.7, 129.5, 128.0, 126.8, 118.1, 57.8, 39.2, 26.9, 21.2, 8.0; IR (Neat Film, NaCl) 3069, 2973, 2878, 1676, 1640, 1597, 1578, 1514, 1446, 1228, 1182, 1143, 1020, 1004, 914, 815, 779, 734, 708, 692 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{20}H_{23}O$ $[M+H]^+$: 279.1743, found 279.1733; SFC Conditions: 5% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 7.07, major = 8.66.



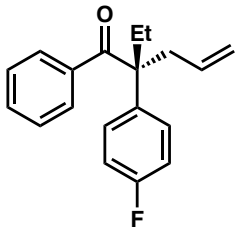

**(*R*)-2-ethyl-2-(4-methoxyphenyl)-1-phenylpent-4-en-1-one (21p)**

Purified by column chromatography (4% $Et_2O$ in hexanes) to provide a colorless oil (59.0 mg, 99% yield); 92% ee, $[\alpha]_D^{25}$ –109.6 (*c* 1.00, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.45–7.31 (m, 3H), 7.24–7.16 (m, 4H), 6.94–6.87 (m, 2H), 5.39 (dddd, $J$ = 16.9, 10.3, 8.0, 6.6 Hz, 1H), 5.04–4.80 (m, 2H), 3.81 (s, 3H), 2.80 (ddt, $J$ = 6.7, 5.7, 1.2 Hz, 2H), 2.26–2.01 (m, 2H), 0.68 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 203.6, 158.6, 137.5, 134.5, 133.7, 131.6, 129.5, 128.1, 128.0, 118.1, 114.3, 57.4, 55.3, 39.3, 26.9, 8.0; IR (Neat Film, NaCl) 3069, 2970, 2836, 1674, 1639, 1609, 1578, 1513, 1262, 1445, 1295, 1251, 1229, 1182, 1143, 1035, 1004, 915, 827, 781, 741, 709, 693 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{20}H_{23}O_2$ $[M+H]^+$: 295.1693, found 295.1683; SFC Conditions: 5% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 9.85, major = 11.03.




**(*R*)-2-(4-chlorophenyl)-2-ethyl-1-phenylpent-4-en-1-one (21q)**

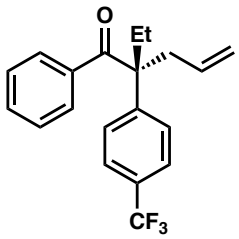
Purified by column chromatography (3% $Et_2O$ in hexanes) to provide a colorless oil (59.1 mg, 99% yield); 86% ee, $[\alpha]_D^{25}$ –92.7 (*c* 1.00, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.44–7.40 (m, 2H), 7.40–7.36 (m, 1H), 7.36–7.32 (m, 2H), 7.25–7.19 (m, 4H), 5.36 (dddd, *J* = 16.8, 10.2, 8.3, 6.4 Hz, 1H), 5.02–4.84 (m, 2H), 2.89–2.67 (m, 2H), 2.13 (q, *J* = 7.4 Hz, 2H), 0.69 (t, *J* = 7.4 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 202.7, 141.4, 136.9, 133.1, 133.0, 132.0, 129.5, 129.2, 128.3, 128.2, 118.7, 57.8, 39.3, 27.0, 8.0; IR (Neat Film, NaCl) 3071, 2972, 2940, 2879, 1676, 1596, 1492, 1446, 1402, 1227, 1181, 1096, 1014, 1004, 917, 821, 784, 725, 691 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{20}ClO$ $[M+H]^+$: 299.1197, found 299.1187; SFC Conditions: 5% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 7.08, major = 8.41.




**(*R*)-2-ethyl-2-(4-fluorophenyl)-1-phenylpent-4-en-1-one (21r)**

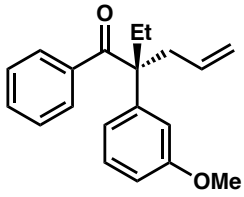
Purified by column chromatography (4% $Et_2O$ in hexanes) to provide a colorless oil (55.3 mg, 98% yield); 90% ee, $[\alpha]_D^{25}$ –104.7 (*c* 1.00, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.43–7.35 (m, 3H), 7.26–7.19 (m, 4H), 7.09–7.03 (m, 2H), 5.36 (dddd, *J* = 16.8, 10.2, 8.2, 6.4 Hz, 1H), 5.05–4.84 (m, 2H), 2.90–2.71 (m, 2H), 2.14 (q, *J* = 7.4 Hz, 2H), 0.69 (t,

$J$ = 7.4 Hz, 3H); $^{19}$F NMR (282 MHz) δ –115.6 (tt, $J$ = 8.4, 5.2 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 203.0, 161.9 (d, $J$ = 246.2 Hz), 138.5 (d, $J$ = 3.4 Hz), 137.1, 133.3, 131.9, 129.5, 128.5 (d, $J$ = 7.9 Hz), 128.1, 118.5, 115.9 (d, $J$ = 21.2 Hz), 57.7, 39.4, 27.1, 8.0; IR (Neat Film, NaCl) 3073, 2974, 2880, 1675, 1598, 1510, 1446, 1230, 1164, 1004, 917, 829, 816, 782, 737, 707, 692 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{20}FO$ $[M+H]^+$: 283.1493, found 283.1491; SFC Conditions: 5% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 4.07, major = 4.47.



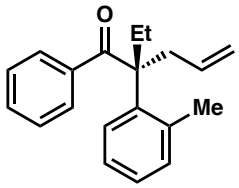

**(*R*)-2-ethyl-1-phenyl-2-(4-(trifluoromethyl)phenyl)pent-4-en-1-one (21s)**

Purified by column chromatography (4% $Et_2O$ in hexanes) to provide a colorless oil (65.7 mg, 99% yield); 70% ee, $[\alpha]_D^{25}$ –57.1 (*c* 1.00, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.63 (m, 2H), 7.45–7.35 (m, 5H), 7.25–7.20 (m, 2H), 5.35 (dddd, $J$ = 16.8, 10.2, 8.3, 6.5 Hz, 1H), 5.05–4.85 (m, 2H), 3.01–2.71 (m, 2H), 2.19 (q, $J$ = 7.4 Hz, 2H), 0.71 (t, $J$ = 7.5 Hz, 3H); $^{19}$F NMR (282 MHz) δ –62.5 (s); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 202.2, 147.1 (d, $J$ = 1.4 Hz), 136.6, 132.8, 132.2, 129.5, 129.3 (q, $J$ = 32.9 Hz), 128.3, 127.3, 125.9 (q, $J$ = 3.7 Hz), 124.2 (q, $J$ = 272.1 Hz) 118.9, 58.3, 39.4, 27.1, 8.0; IR (Neat Film, NaCl) 3075, 2975, 2942, 1678, 1641, 1617, 1597, 1579, 1447, 1411, 1328, 1228, 1168, 1127, 1070, 1017, 920, 828, 712, 656 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{20}H_{20}F_3O$ $[M+H]^+$: 333.1461, found 333.1455; SFC Conditions: 5% IPA, 3.0 mL/min, Chiralpak AD-H column (2 columns combined), λ = 210 nm, $t_R$ (min): minor = 3.59, major = 3.76.




**(*R*)-2-ethyl-2-(3-methoxyphenyl)-1-phenylpent-4-en-1-one (21t)**

Purified by column chromatography (4% $Et_2O$ in hexanes) to provide a colorless oil (56.1 mg, 95% yield); 90% ee, $[\alpha]_D^{25}$ –103.0 (*c* 1.00, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.48–7.42 (m, 2H), 7.39–7.33 (m, 1H), 7.31–7.27 (m, 1H), 7.25–7.17 (m, 2H), 6.90–6.79 (m, 3H), 5.38 (dddd, *J* = 16.8, 10.3, 8.0, 6.6 Hz, 1H), 5.02–4.82 (m, 2H), 3.78 (s, 3H), 2.90–2.70 (m, 2H), 2.25–2.04 (m, 2H), 0.68 (t, *J* = 7.4 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 203.2, 160.1, 144.4, 137.3, 133.6, 131.8, 129.9, 129.4, 128.1, 119.5, 118.2, 113.1, 112.0, 58.1, 55.3, 39.2, 26.9, 8.0; IR (Neat Film, NaCl) 3070, 2971, 2939, 2878, 2835, 1676, 1640, 1598, 1581, 1487, 1462, 1446, 1433, 1292, 1261, 1229, 1168, 1050, 1004, 917, 776, 727, 701 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{20}H_{23}O_2$ $[M+H]^+$: 295.1693, found 295.1683; SFC Conditions: 5% IPA, 3.0 mL/min, Chiralpak AD-H column (2 columns combined), λ = 210 nm, $t_R$ (min): minor = 7.91, major = 8.48.

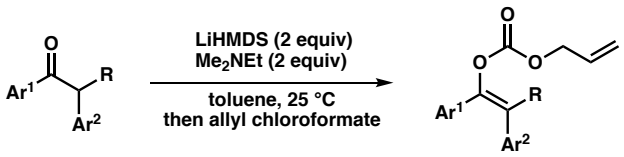



**(*R*)-2-ethyl-1-phenyl-2-(*o*-tolyl)pent-4-en-1-one (21u)**

Purified by column chromatography (4% $Et_2O$ in hexanes) to provide a colorless oil (55.9 mg, 99% yield); 90% ee, $[\alpha]_D^{25}$ –100.6 (*c* 1.0, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.63–7.58 (m, 2H), 7.51–7.48 (m, 1H), 7.41–7.35 (m, 1H), 7.33–7.28 (m, 1H), 7.22–7.16 (m, 3H), 7.07–7.02 (m, 1H), 5.34 (ddt, *J* = 17.5, 10.3, 7.4 Hz, 1H), 5.06–4.84 (m, 2H),

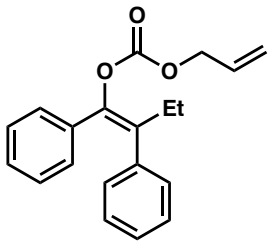
2.93–2.86 (m, 2H), 2.28 (dt, *J* = 14.8, 7.4 Hz, 1H), 2.14 (dt, *J* = 13.9, 7.3 Hz, 1H), 2.09 (s, 3H), 0.69 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 203.1, 141.4, 136.7, 133.9, 132.7, 132.3, 129.1, 128.1, 127.1, 126.6, 126.4, 118.2, 57.9, 37.3, 26.6, 21.1, 8.1; IR (Neat Film, NaCl) 3068, 2975, 2879, 1674, 1639, 1596, 1578, 1487, 1446, 1384, 1225, 1181, 1136, 1059, 1004, 915, 841, 760, 733, 710, 692 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{20}H_{23}O$ $[M+H]^+$: 279.1743, found 279.1736; SFC Conditions: 5% IPA, 3.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 3.76, major = 4.05.

### 3.8.2.3 General Procedure for the Preparation of Allyl Enol Carbonates



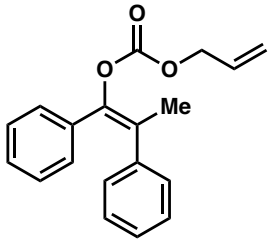

To a flame-dried flask was added LiHMDS (335 mg, 2 mmol) followed by toluene (3.0 mL) and N,N-dimethylethylamine (0.213 mL), and the resulting mixture stirred at 25 °C for 5 minutes. A solution of ketone (1 mmol) in toluene (2.0 mL) was then added, and the reaction stirred at 25 °C for an additional 30 minutes. The flask was then submerged in a room temperature water bath, and allyl chloroformate (0.217 mL, 2 mmol) was added neat, and the reaction continued until no starting material remained by TLC (typically less than 30 minutes). The crude reaction mixture was diluted with $Et_2O$ and quenched with water. The layers were separated, and the aqueous layer was extracted with $Et_2O$ twice. The combined organic layers were dried over $Na_2SO_4$ and concentrated. The crude product was purified by silica gel flash chromatography to afford the desired enol carbonate. The *E/Z* ratio of enol carbonates was determined by $^1$H NMR and is >95:5 unless stated otherwise.

### 3.8.2.4 Spectroscopic data for the Allyl Enol Carbonates




**(*E*)-allyl (1,2-diphenylbut-1-en-1-yl) carbonate (20a)**

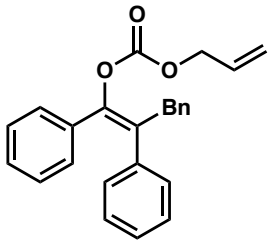
Run on 2.0 mmol scale. Purified by column chromatography (8% $Et_2O$ in hexanes) to provide a colorless oil (586.3 mg, 95% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.23–7.17 (m, 3H), 7.14–7.10 (m, 7H), 5.93 (ddt, *J* = 17.2, 10.5, 5.7 Hz, 1H), 5.40–5.22 (m, 2H), 4.64 (dt, *J* = 5.7, 1.4 Hz, 2H), 2.58 (q, *J* = 7.5 Hz, 2H), 0.99 (t, *J* = 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.2, 142.9, 138.9, 135.1, 133.3, 131.3, 129.5, 128.9, 128.2, 127.8, 127.8, 127.0, 119.0, 68.9, 26.0, 12.2; IR (Neat Film, NaCl) 3083, 3057, 2972, 2936, 2875, 1756, 1651, 1600, 1577, 1493, 1445, 1364, 1257, 1220, 1122, 1091, 1075, 1044, 988, 858, 766, 697 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{20}H_{24}NO_3$ $[M+NH_4]^+$: 326.1751, found 326.1756.




**(*E*)-allyl (1,2-diphenylprop-1-en-1-yl) carbonate (20b)**

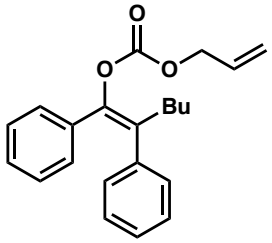
Purified by column chromatography (5% $Et_2O$ in hexanes) to provide a colorless oil (210.3 mg, 71% yield, 81:17 *E/Z* ratio); $^1$H NMR major isomer (300 MHz, $CDCl_3$) δ 7.46–7.34 (m, 1H), 7.23–7.17 (m, 2H), 7.17–7.09 (m, 7H), 5.94 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.44–5.23 (m, 2H), 4.65 (dt, *J* = 5.7, 1.4 Hz, 2H), 2.16 (s, 3H); $^{13}$C NMR major

isomer (100 MHz, $CDCl_3$) δ 153.1, 143.6, 140.4, 135.1, 131.4, 129.1, 128.6, 128.4, 128.0, 127.4, 127.3, 127.2, 119.2, 69.0, 19.2; IR (Neat Film, NaCl) 3082, 3057, 3024, 2992, 2947, 1759, 1493, 1444, 1381, 1364, 1229, 1122, 1030, 966, 777, 765, 698 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{22}NO_3$ $[M+NH_4]^+$: 312.1594, found 312.1583.



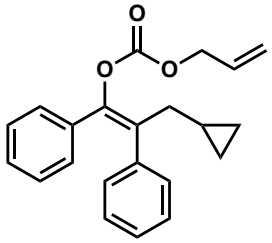

**(*E*)-allyl (1,2,3-triphenylprop-1-en-1-yl) carbonate (20c)**

Purified by column chromatography (4% $Et_2O$ in hexanes) to provide a colorless oil (305.8 mg, 83% yield); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.25–7.09 (m, 13H), 7.04–6.98 (m, 2H), 5.90 (ddt, *J* = 17.2, 10.5, 5.7 Hz, 1H), 5.46–5.15 (m, 2H), 4.61 (dt, *J* = 5.8, 1.4 Hz, 2H), 3.91 (s, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 153.2, 144.4, 138.8, 138.6, 134.9, 131.3, 130.3, 129.7, 129.1, 128.4, 128.2, 128.1, 128.0, 127.2, 126.2, 119.3, 69.1, 39.1; IR (Neat Film, NaCl) 3027, 1760, 1601, 1495, 1444, 1364, 1227, 1118, 1030, 971, 776, 698 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{25}H_{26}NO_3$ $[M+NH_4]^+$: 388.1907, found 388.1898.




**(*E*)-allyl (1,2-diphenylhex-1-en-1-yl) carbonate (20d)**

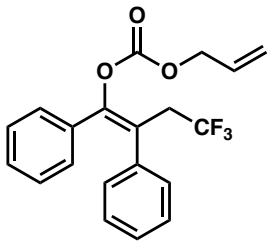
Purified by column chromatography (5% $Et_2O$ in hexanes) to provide a colorless oil (301.3 mg, 90% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.23–7.16 (m, 3H), 7.15–7.09 (m, 7H), 5.92 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.40–5.23 (m, 2H), 4.64 (dt, *J* = 5.7, 1.4 Hz, 2H), 2.59–2.47 (m, 2H), 1.38–1.28 (m, 4H), 0.98–0.83 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.3, 143.4, 139.2, 135.2, 132.2, 131.4, 129.5, 129.0, 128.3, 127.9, 127.8, 127.1, 119.1, 69.0, 32.6, 29.6, 22.7, 14.0; IR (Neat Film, NaCl) 3082, 3057, 3024, 2957, 2930, 2861, 1760, 1493, 1444, 1380, 1364, 1292, 1240, 1227, 1207, 1122, 1000, 964, 772, 698 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{22}H_{28}NO_3$ $[M+NH_4]^+$: 354.2064, found 354.2047.




**(*E*)-allyl (3-cyclopropyl-1,2-diphenylprop-1-en-1-yl) carbonate (20e)**

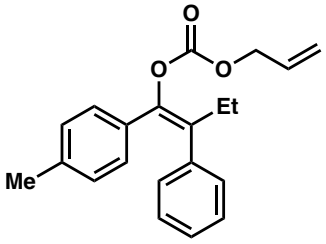
Purified by column chromatography (5% $Et_2O$ in hexanes) to provide a colorless oil (299.4 mg, 90% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.24–7.09 (m, 10H), 5.92 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.39–5.22 (m, 2H), 4.63 (dt, *J* = 5.7, 1.4 Hz, 2H), 2.47 (d, *J* = 6.9 Hz, 2H), 0.78–0.67 (m, 1H), 0.41–0.31 (m, 2H), 0.13 – -0.03 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.3, 143.3, 139.6, 135.1, 131.9, 131.4, 129.6, 129.0, 128.2, 127.9,

127.0, 119.2, 69.0, 37.5, 9.6, 4.7; IR (Neat Film, NaCl) 3079, 3003, 2950, 1760, 1491, 1444, 1364, 1292, 1247, 1222, 1127, 1056, 1018, 972, 936, 826, 771, 698 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{22}H_{26}NO_3$ $[M+NH_4]^+$: 352.1907, found 352.1903.




**(*E*)-allyl (4,4,4-trifluoro-1,2-diphenylbut-1-en-1-yl) carbonate (20f)**

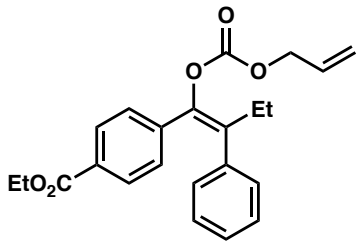
Purified by column chromatography (5% $Et_2O$ in hexanes) to provide a colorless oil (299.0 mg, 82% yield); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.24–7.19 (m, 3H), 7.19–7.11 (m, 7H), 5.90 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.44–5.21 (m, 2H), 4.62 (dt, *J* = 5.8, 1.4 Hz, 2H), 3.40 (q, *J* = 10.3 Hz, 2H); $^{19}F$ NMR (282 MHz, $CDCl_3$) δ –63.1 (t, *J* = 10.4 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 152.5, 148.5, 137.7, 134.1, 131.0, 129.6, 129.1, 128.8, 128.6, 128.1, 127.8, 125.7 (q, *J* = 278.5 Hz), 120.6 (q, *J* = 2.6 Hz), 119.6, 69.4, 37.3 (q, *J* = 30.0 Hz); IR (Neat Film, NaCl) 3085, 3059, 3026, 1764, 1651, 1494, 1446, 1258, 1224, 1136, 1110, 1056, 972, 956, 940, 777, 700 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{20}H_{21}F_3NO_3$ $[M+NH_4]^+$: 380.1468, found 380.1455.




**(*E*)-allyl (2-phenyl-1-(*p*-tolyl)but-1-en-1-yl) carbonate (20g)**

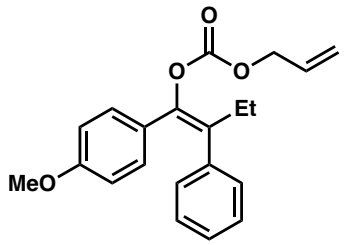
Purified by column chromatography (4% $Et_2O$ in hexanes) to provide a colorless oil (291.6 mg, 90% yield); $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.25–7.17 (m, 3H), 7.16–7.10 (m,

2H), 7.04–6.98 (m, 2H), 6.96–6.89 (m, 2H), 5.93 (ddt, $J$ = 17.2, 10.4, 5.7 Hz, 1H), 5.42–5.23 (m, 2H), 4.64 (dt, $J$ = 5.7, 1.4 Hz, 2H), 2.56 (q, $J$ = 7.5 Hz, 2H), 2.23 (s, 3H), 0.97 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.4, 143.1, 139.2, 137.7, 132.7, 132.2, 131.5, 129.6, 128.8, 128.7, 128.3, 127.0, 119.2, 69.0, 26.1, 21.4, 12.3; IR (Neat Film, NaCl) 3082, 3055, 3026, 2972, 2875, 1760, 1650, 1511, 1491, 1443, 1308, 1291, 1258, 1226, 1184, 1122, 1089, 1045, 988, 946, 929, 862, 826, 784, 768, 701 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{21}H_{26}NO_3$ $[M+NH_4]^+$: 340.1907, found 340.1896.



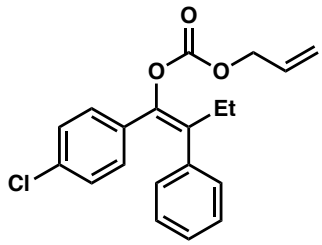

**ethyl (*E*)-4-(1-(((allyloxy)carbonyl)oxy)-2-phenylbut-1-en-1-yl)benzoate (20h)**

Purified by column chromatography (8% $Et_2O$ in hexanes) to provide a colorless oil (291.2 mg, 77% yield); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.82–7.74 (m, 2H), 7.25–7.15 (m, 5H), 7.14–7.05 (m, 2H), 5.92 (ddt, $J$ = 17.2, 10.4, 5.8 Hz, 1H), 5.48–5.20 (m, 2H), 4.64 (dt, $J$ = 5.8, 1.4 Hz, 2H), 4.31 (q, $J$ = 7.1 Hz, 2H), 2.59 (q, $J$ = 7.5 Hz, 2H), 1.33 (t, $J$ = 7.1 Hz, 3H), 0.98 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 166.3, 153.2, 142.0, 139.7, 138.5, 135.4, 131.2, 129.5, 129.4, 129.2, 128.8, 128.5, 127.5, 119.4, 69.2, 61.0, 26.3, 14.4, 12.2; IR (Neat Film, NaCl) 3081, 3057, 2978, 2937, 2876, 1761, 1718, 1609, 1444, 1407, 1366, 1276, 1224, 1180, 1125, 1108, 1045, 1022, 990, 947, 860, 769, 702 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{23}H_{28}NO_5$ $[M+NH_4]^+$: 398.1962, found 398.1952.




**(*E*)-allyl (1-(4-methoxyphenyl)-2-phenylbut-1-en-1-yl) carbonate (20i)**

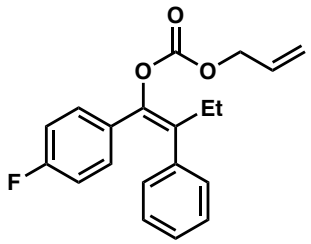
Purified by column chromatography (5% $Et_2O$ in hexanes) to provide a colorless oil (254.3 mg, 75% yield); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.25–7.16 (m, 3H), 7.16–7.10 (m, 2H), 7.09–7.01 (m, 2H), 6.72–6.58 (m, 2H), 5.94 (ddt, *J* = 17.3, 10.5, 5.7 Hz, 1H), 5.49–5.20 (m, 2H), 4.64 (dt, *J* = 5.7, 1.4 Hz, 2H), 3.72 (s, 3H), 2.55 (q, *J* = 7.5 Hz, 2H), 0.97 (t, *J* = 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 159.0, 153.4, 142.9, 139.2, 132.1, 131.5, 130.3, 129.6, 128.3, 127.6, 127.0, 119.2, 113.3, 69.0, 55.2, 26.0, 12.3; IR (Neat Film, NaCl) 2970, 2936, 1760, 1651, 1609, 1576, 1511, 1462, 1443, 1364, 1294, 1252, 1226, 1176, 1123, 1044, 1014, 988, 946, 862, 836, 784, 767, 701 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{21}H_{26}NO_4$ $[M+NH_4]^+$: 356.1856, found 356.1845.




**(*E*)-allyl (1-(4-chlorophenyl)-2-phenylbut-1-en-1-yl) carbonate (20j)**

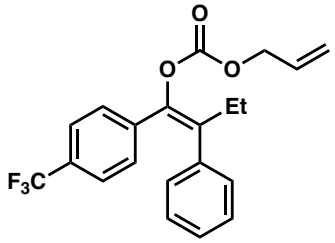
Purified by column chromatography (5% $Et_2O$ in hexanes) to provide a colorless oil (310.0 mg, 90% yield); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 5.3, 1.9 Hz, 3H), 7.14–7.00 (m, 6H), 6.04–5.82 (m, 1H), 5.45–5.24 (m, 2H), 4.64 (dd, *J* = 5.7, 1.5 Hz, 2H), 2.56 (q, *J* = 7.5 Hz, 2H), 0.97 (t, *J* = 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.3, 141.9, 138.6, 134.2, 133.7, 133.6, 131.3, 130.3, 129.5, 128.5, 128.2, 127.4, 119.4, 69.2,

26.1, 12.2; IR (Neat Film, NaCl) 3081, 3057, 2972, 2936, 2875, 1760, 1649, 1594, 1490, 1443, 1364, 1292, 1275, 1257, 1224, 1180, 1123, 1092, 1045, 1015, 989, 946, 930, 860, 835, 768, 701 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{20}H_{23}ClNO_3$ $[M+NH_4]^+$: 360.1361, found 360.1372.



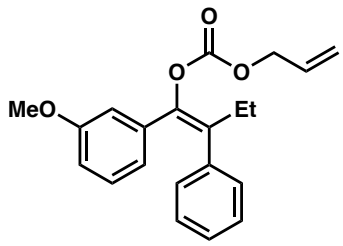

**(*E*)-allyl (1-(4-fluorophenyl)-2-phenylbut-1-en-1-yl) carbonate (20k)**

Purified by column chromatography (5% $Et_2O$ in hexanes) to provide a colorless oil which solidifies in a freezer (303.7 mg, 93% yield); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.25–7.18 (m, 3H), 7.10 (ddq, *J* = 5.3, 4.6, 2.9 Hz, 4H), 6.85–6.74 (m, 2H), 5.93 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.50–5.14 (m, 2H), 4.64 (dt, *J* = 5.7, 1.4 Hz, 2H), 2.56 (q, *J* = 7.5 Hz, 2H), 0.97 (t, *J* = 7.5 Hz, 3H); $^{19}F$ NMR (282 MHz) δ –113.3 (m); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 162.1 (d, *J* = 248.1 Hz), 153.3, 142.1, 138.8, 133.6, 131.3, 131.3, 130.9 (d, *J* = 8.3 Hz), 129.5, 128.4, 127.2, 119.3, 115.0 (d, *J* = 21.6 Hz), 69.1, 26.0, 12.2; IR (Neat Film, NaCl) 3081, 3058, 3024, 2973, 2937, 2876, 1760, 1651, 1605, 1444, 1364, 1292, 1259, 1225, 1159, 1122, 1096, 1045, 989, 946, 930, 864, 842, 809, 785, 767, 701 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{20}H_{23}FNO_3$ $[M+NH_4]^+$: 344.1656, found 344.1659.




**(*E*)-allyl (2-phenyl-1-(4-(trifluoromethyl)phenyl)but-1-en-1-yl) carbonate (20l)**

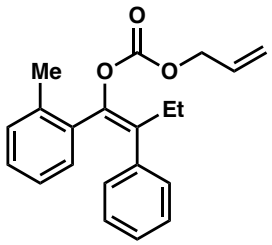
Purified by column chromatography (5% $Et_2O$ in hexanes) to provide a colorless oil which solidifies in a freezer (354.0 mg, 94% yield); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.40–7.33 (m, 2H), 7.25–7.19 (m, 5H), 7.15–7.06 (m, 2H), 5.93 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.48–5.15 (m, 2H), 4.65 (dt, *J* = 5.8, 1.4 Hz, 2H), 2.59 (q, *J* = 7.5 Hz, 2H), 0.98 (t, *J* = 7.5 Hz, 3H); $^{19}$F NMR (282 MHz) δ –62.8 (s); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.3, 141.6, 138.8, 138.3, 135.6, 131.2, 129.6 (q, *J* = 32.4 Hz), 129.4, 129.1, 128.6, 127.6, 124.9 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 271.6 Hz), 119.5, 69.3, 26.3, 12.1; IR (Neat Film, NaCl) 3083, 2059, 3025, 2975, 2938, 2878, 1760, 1651, 1618, 1577, 1492, 1444, 1408, 1365, 1327, 1292, 1260, 1226, 1168, 1127, 1068, 1046, 1018, 989, 946, 931, 847, 782, 769, 702, 613 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{21}H_{23}F_3NO_3$ $[M+NH_4]^+$: 394.1625, found 394.1608




**(*E*)-allyl (1-(3-methoxyphenyl)-2-phenylbut-1-en-1-yl) carbonate (20m)**

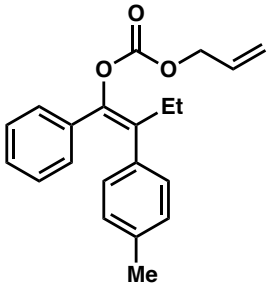
Purified by column chromatography (10% $Et_2O$ in hexanes) to provide a colorless oil (320.2 mg, 95% yield); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.25–7.18 (m, 3H), 7.17–7.11 (m, 2H), 7.04 (ddd, *J* = 8.2, 7.7, 0.4 Hz, 1H), 6.78–6.59 (m, 3H), 5.94 (ddt, *J* = 17.2, 10.4, 5.7

Hz, 1H), 5.47–5.20 (m, 2H), 4.65 (dt, *J* = 5.7, 1.4 Hz, 2H), 3.51 (s, 3H), 2.56 (q, *J* = 7.5 Hz, 2H), 0.98 (t, *J* = 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 158.9, 153.4, 142.8, 139.1, 136.3, 133.5, 131.4, 129.5, 128.9, 128.4, 127.2, 121.1, 119.2, 114.5, 114.0, 69.1, 55.1, 26.2, 12.2; IR (Neat Film, NaCl) 2970, 2937, 1760, 1600, 1580, 1486, 1464, 1454, 1444, 1428, 1364, 1323, 1288, 1234, 1204, 1178, 1120, 1043, 994, 948, 892, 863, 784, 769, 701 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{21}H_{26}NO_4$ $[M+NH_4]^+$: 356.1856, found 356.1844



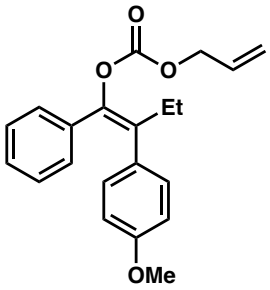

**(*E*)-allyl (2-phenyl-1-(*o*-tolyl)but-1-en-1-yl) carbonate (20n)**

Purified by column chromatography (5% $Et_2O$ in hexanes) to provide a colorless oil (299.3 mg, 93% yield, 80:20 *E/Z* ratio); $^1$H NMR major isomer (300 MHz, $CDCl_3$) δ 7.41–7.28 (m, 1H), 7.21 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.16–7.06 (m, 4H), 7.04 – 6.97 (m, 3H), 5.91 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.41 – 5.22 (m, 2H), 4.60 (dt, *J* = 5.8, 1.4 Hz, 2H), 2.62 (q, *J* = 7.5 Hz, 2H), 2.18 (s, 3H), 1.02 (t, *J* = 7.5 Hz, 3H); $^{13}$C NMR major isomer (100 MHz, $CDCl_3$) δ 153.1, 142.9, 138.5, 137.5, 134.4, 134.3, 131.5, 131.5, 130.0, 129.0, 128.5, 127.9, 126.9, 125.2, 119.2, 68.9, 25.1, 20.0, 12.9; IR (Neat Film, NaCl) 3022, 2971, 1758, 1493, 1457, 1443, 1380, 1364, 1292, 1258, 1225, 1131, 1044, 988, 946, 862, 769, 700 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{21}H_{26}NO_3$ $[M+NH_4]^+$: 340.1907, found 340.1892.




**(*E*)-allyl (1-phenyl-2-(*p*-tolyl)but-1-en-1-yl) carbonate (20o)**

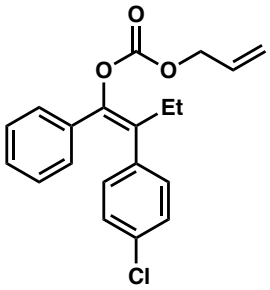
Purified by column chromatography (5% $Et_2O$ in hexanes) to provide a colorless oil (295.7 mg, 92% yield); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.15 – 7.11 (m, 5H), 7.03–6.99 (m, 4H), 5.93 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.41–5.24 (m, 2H), 4.64 (dt, *J* = 5.7, 1.4 Hz, 2H), 2.56 (q, *J* = 7.5 Hz, 2H), 2.30 (s, 3H), 0.98 (t, *J* = 7.5 Hz, 3H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 153.4, 142.7, 136.8, 135.9, 135.3, 133.3, 131.4, 129.4, 129.1, 129.0, 127.9, 127.8, 119.2, 69.0, 26.1, 21.3, 12.3; IR (Neat Film, NaCl) 3024, 2971, 2935, 2874, 1760, 1512, 1292, 1445, 1364, 1291, 1258, 1224, 1122, 1044, 988, 946, 928, 818, 778, 697 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{21}H_{23}O_3$ $[M+H]^+$: 323.1642, found 323.1630.




**(*E*)-allyl (2-(4-methoxyphenyl)-1-phenylbut-1-en-1-yl) carbonate (20p)**

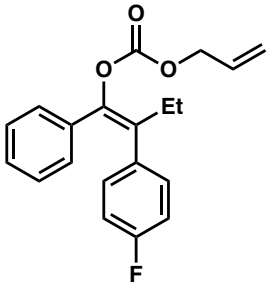
Purified by column chromatography (8% $Et_2O$ in hexanes) to provide a colorless oil (295.0 mg, 87% yield); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.16–7.11 (m, 5H), 7.07–7.00 (m, 2H), 6.78–6.71 (m, 2H), 5.93 (ddt, *J* = 17.2, 10.5, 5.7 Hz, 1H), 5.40–5.23 (m, 2H), 4.64 (dt, *J* = 5.7, 1.4 Hz, 2H), 3.77 (s, 3H), 2.55 (q, *J* = 7.5 Hz, 2H), 0.98 (t, *J* = 7.5 Hz, 3H);

$^{13}$C NMR (100 MHz, $CDCl_3$) δ 158.7, 153.4, 142.6, 135.4, 132.9, 131.4, 131.1, 130.7, 129.0, 127.9, 127.7, 119.2, 113.8, 69.0, 55.3, 26.1, 12.3; IR (Neat Film, NaCl) 2970, 1758, 1650, 1608, 1574, 1511, 1493, 1462, 1444, 1364, 1289, 1245, 1223, 1177, 1122, 1044, 987, 831, 778, 698 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{21}H_{23}O_4$ $[M+H]^+$: 339.1591, found 339.1574.



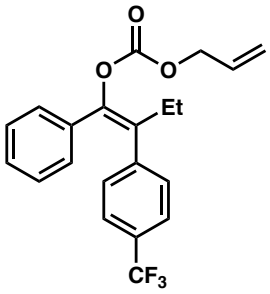

**(*E*)-allyl (2-(4-chlorophenyl)-1-phenylbut-1-en-1-yl) carbonate (20q)**

Purified by column chromatography (8% $Et_2O$ in hexanes) to provide a colorless oil which solidifies in a freezer (315.0 mg, 92% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.20–7.10 (m, 7H), 7.07–7.02 (m, 2H), 5.92 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.46–5.19 (m, 2H), 4.64 (dt, *J* = 5.7, 1.4 Hz, 2H), 2.56 (q, *J* = 7.5 Hz, 2H), 0.97 (t, *J* = 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.2, 143.5, 137.5, 134.8, 133.0, 132.2, 131.3, 131.0, 129.1, 128.6, 128.1, 128.1, 119.3, 69.1, 25.9, 12.2; IR (Neat Film, NaCl) 2973, 2936, 1760, 1490, 1445, 1364, 1292, 1256, 1224, 1123, 1090, 1043, 988, 947, 928, 861, 828, 774, 697 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{20}H_{20}ClO_3$ $[M+H]^+$: 343.1095, found 343.1087.




**(*E*)-allyl (2-(4-fluorophenyl)-1-phenylbut-1-en-1-yl) carbonate (20r)**

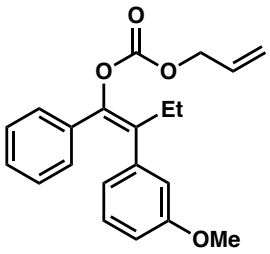
Purified by column chromatography (6% $Et_2O$ in hexanes) to provide a colorless oil (305.7 mg, 94% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.16–7.10 (m, 5H), 7.10–7.05 (m, 2H), 6.93–6.85 (m, 2H), 5.92 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.46–5.16 (m, 2H), 4.64 (dt, *J* = 5.7, 1.4 Hz, 2H), 2.56 (q, *J* = 7.5 Hz, 2H), 0.98 (t, *J* = 7.5 Hz, 3H); $^{19}$F NMR (282 MHz, $CDCl_3$) δ –115.1 (tt, *J* = 8.8, 5.5 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 162.0 (d, *J* = 246.2 Hz), 153.3, 143.3, 135.0, 134.8 (d, *J* = 3.4 Hz), 132.4, 131.4, 131.2 (d, *J* = 7.9 Hz), 129.0, 128.0, 119.3, 115.4 (d, *J* = 21.4 Hz), 69.1, 26.0, 12.2; IR (Neat Film, NaCl) 2973, 2936, 1759, 1602, 1508, 1445, 1364, 1292, 1259, 1222, 1158, 1122, 1043, 988, 945, 835, 767, 698 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{20}H_{20}FO_3$ $[M+H]^+$: 327.1391, found 327.1396.




**(*E*)-allyl (1-phenyl-2-(4-(trifluoromethyl)phenyl)but-1-en-1-yl) carbonate (20s)**

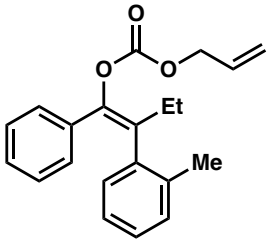
Purified by column chromatography (8% $Et_2O$ in hexanes) to provide a white solid (359.9 mg, 96% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.49–7.44 (m, 2H), 7.25–7.22 (m, 2H), 7.19–7.08 (m, 5H), 5.93 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.49–5.22 (m, 2H), 4.65 (dt, *J*

= 5.7, 1.4 Hz, 2H), 2.60 (q, *J* = 7.5 Hz, 2H), 0.99 (t, *J* = 7.5 Hz, 3H); $^{19}$F NMR (282 MHz, $CDCl_3$) δ –62.5 (s); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.1, 144.0, 143.0 (d, *J* = 1.6 Hz), 134.6, 132.2, 131.3, 130.0, 129.2 (q, *J* = 32.2 Hz), 129.1, 128.4, 128.1, 125.3 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 272.1 Hz), 119.4, 69.2, 25.9, 12.2; IR (Neat Film, NaCl) 2975, 2939, 1760, 1616, 1446, 1406, 1365, 1326, 1260, 1225, 1166, 1125, 1109, 1067, 1044, 988, 947, 930, 839, 779, 696 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{21}H_{23}F_3NO_3$ $[M+NH_4]^+$: 394.1625, found 394.1612.




**(*E*)-allyl (2-(3-methoxyphenyl)-1-phenylbut-1-en-1-yl) carbonate (20t)**

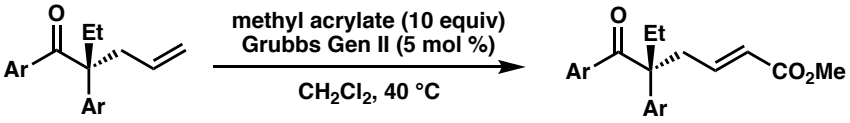
Purified by column chromatography (8% $Et_2O$ in hexanes) to provide a colorless oil (288.3 mg, 85% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.18–7.05 (m, 6H), 6.77–6.62 (m, 3H), 5.93 (ddt, *J* = 17.2, 10.5, 5.7 Hz, 1H), 5.43–5.21 (m, 2H), 4.64 (dt, *J* = 5.7, 1.4 Hz, 2H), 3.66 (s, 3H), 2.56 (q, *J* = 7.5 Hz, 2H), 0.99 (t, *J* = 7.5 Hz, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 159.5, 153.3, 143.0, 140.3, 135.2, 133.3, 131.4, 129.3, 128.9, 127.9, 122.1, 119.2, 115.0, 113.0, 69.1, 55.2, 26.0, 12.3; IR (Neat Film, NaCl) 2970, 1759, 1598, 1577, 1486, 1463, 1446, 1427, 1260, 1225, 1180, 1120, 1048, 988, 780, 698 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{21}H_{26}NO_4$ $[M+NH_4]^+$: 356.1856, found 356.1845.



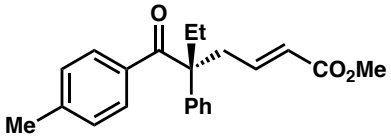

**(*E*)-allyl (1-phenyl-2-(*o*-tolyl)but-1-en-1-yl) carbonate (20u)**

Purified by column chromatography (5% $Et_2O$ in hexanes) to provide a colorless oil (225.3 mg, 70% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.21–7.04 (m, 9H), 5.96 (ddt, $J$ = 17.2, 10.4, 5.7 Hz, 1H), 5.47–5.19 (m, 2H), 4.68 (dq, $J$ = 5.7, 1.2 Hz, 2H), 2.67–2.41 (m, 2H), 2.13 (d, $J$ = 0.6 Hz, 3H), 1.00 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.4, 142.7, 138.1, 136.2, 135.2, 132.3, 131.4, 130.3, 129.7, 127.8, 127.8, 127.4, 125.8, 119.1, 69.0, 26.2, 19.6, 11.6; IR (Neat Film, NaCl) 2970, 1758, 1494, 1444, 1363, 1259, 1222, 1132, 1088, 1044, 987, 918, 858, 762, 730, 694 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{21}H_{26}NO_3$ $[M+NH_4]^+$: 340.1907, found 340.1912.

### 3.8.2.5 Derivatization of Alkylation Products

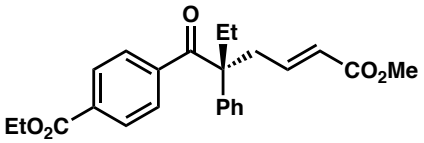



To an oven dried vial was added the alpha-quaternary ketone (0.1 mmol) followed by $CH_2Cl_2$ (1.0 mL) and methyl acrylate (1.0 mmol, 90 μL). The resulting solution was stirred for five minutes at ambient temperature then treated with a solution of Grubb's second generation catalyst (4.2 mg) in 500 μL $CH_2Cl_2$. The reaction was then heated to 40 °C and stirred for five hours. The crude reaction mixture was directly concentrated and then purified by silica gel flash chromatography to obtain the desired product.




**methyl (*R*,*E*)-5-(4-methylbenzoyl)-5-phenylhept-2-enoate (26)**

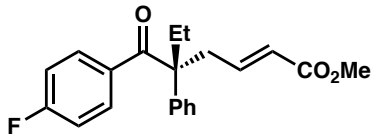
Purified by column chromatography (4% $Et_2O$ in hexanes) to provide a white solid (25.4 mg, 76% yield; 90% ee, $[\alpha]_D^{25}$ –117.37 (*c* 1.00, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.39–7.32 (m, 4H), 7.32–7.24 (m, 3H), 7.04–6.99 (m, 2H), 6.56 (ddd, *J* = 15.5, 9.0, 6.4 Hz, 1H), 5.71 (ddd, *J* = 15.5, 1.7, 1.1 Hz, 1H), 3.67 (s, 3H), 2.99 (ddd, *J* = 14.5, 9.1, 1.2 Hz, 1H), 2.86 (ddt, *J* = 14.6, 6.4, 1.3 Hz, 1H), 2.29 (s, 3H), 2.27–2.12 (m, 2H), 0.72 (t, *J* = 7.4 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 201.9, 166.6, 145.1, 142.7, 142.3, 133.9, 129.7, 129.2, 128.9, 127.4, 126.8, 124.0, 58.2, 51.6, 38.8, 26.9, 21.6, 8.2; IR (Neat Film, NaCl) 2970, 2949, 1724, 1672, 1606, 1495, 1446, 1435, 1335, 1270, 1199, 1183, 1167, 1140, 1036, 1000, 969, 854, 821, 773, 740, 702 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{22}H_{25}O_3$ $[M+H]^+$: 337.1798, found 337.1785; SFC Conditions: 5% IPA, 2.5 mL/min, Chiralcel OB-H column, λ = 210 nm, $t_R$ (min): minor = 4.14, major = 4.95.




**ethyl (*R*,*E*)-4-(2-ethyl-6-methoxy-6-oxo-2-phenylhex-4-enoyl)benzoate (25)**

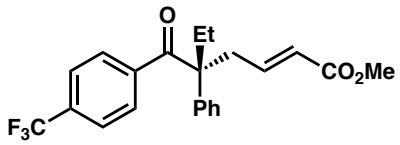
Purified by column chromatography (7% $Et_2O$ in hexanes) to provide a white solid (34.8 mg, 88% yield; 90%, $[\alpha]_D^{25}$ –113.62 (*c* 1.00, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.90–7.85 (m, 2H), 7.45–7.36 (m, 4H), 7.35–7.27 (m, 3H), 6.54 (ddd, *J* = 15.5, 8.9, 6.5 Hz, 1H), 5.71 (dt, *J* = 15.6, 1.5 Hz, 1H), 4.33 (q, *J* = 7.2 Hz, 2H), 3.67 (s, 3H), 3.02–2.82 (m, 2H), 2.17 (q, *J* = 7.4 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H), 0.72 (t, *J* = 7.4 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 202.2, 166.5, 165.8, 144.4, 141.3, 140.3, 133.2, 129.4, 129.4,

129.3, 127.8, 126.8, 124.2, 61.4, 58.5, 51.6, 38.4, 26.5, 14.4, 8.2; IR (Neat Film, NaCl) 2974, 1723, 1681, 1657, 1495, 1446, 1436, 1337, 1312, 1276, 1228, 1199, 1170, 1106, 1020, 1001, 867, 839, 768, 729, 703 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{24}H_{27}O_5$ $[M+H]^+$: 395.1853, found 395.1870; SFC Conditions: 7% IPA, 2.5 mL/min, Chiralcel OD-H column, $\lambda$ = 210 nm, $t_R$ (min): minor = 9.38, major = 10.31.



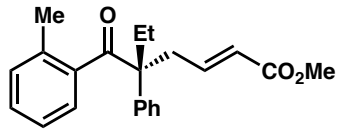

**methyl (*R*,*E*)-5-(4-fluorobenzoyl)-5-phenylhept-2-enoate (27)**

Purified by column chromatography (10% $Et_2O$ in hexanes) to provide a white solid (28.4 mg, 83% yield; 91% ee, $[\alpha]_D^{25}$ –136.18 (*c* 1.00, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.50–7.43 (m, 2H), 7.42–7.29 (m, 3H), 7.27–7.20 (m, 2H), 6.94–6.83 (m, 2H), 6.54 (ddd, *J* = 15.5, 9.1, 6.5 Hz, 1H), 5.71 (ddd, *J* = 15.6, 1.7, 1.2 Hz, 1H), 3.67 (s, 3H), 3.08–2.80 (m, 2H), 2.18 (q, *J* = 7.4 Hz, 2H), 0.72 (t, *J* = 7.4 Hz, 3H); $^{19}F$ NMR (282 MHz, $CDCl_3$) δ –106.5 (tt, *J* = 8.4, 5.4 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 200.8, 166.6, 164.8 (d, *J* = 254.4 Hz), 144.7, 141.9, 132.8 (d, *J* = 3.2 Hz), 132.2 (d, *J* = 9.0 Hz), 129.4, 127.7, 126.7, 124.2, 115.3 (d, *J* = 21.6 Hz), 58.3, 51.6, 38.7, 26.9, 8.2; IR (Neat Film, NaCl) 2970, 2950, 1724, 1676, 1656, 1598, 1504, 1435, 1336, 1271, 1232, 1199, 1158, 1001, 848, 748, 703 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{21}H_{22}FO_3$ $[M+H]^+$: 341.1548, found 348.1534; SFC Conditions: 5% IPA, 2.5 mL/min, Chiralcel OD-H column, $\lambda$ = 210 nm, $t_R$ (min): minor = 7.43, major = 8.03.




**methyl (*R*,*E*)-5-phenyl-5-(4-(trifluoromethyl)benzoyl)hept-2-enoate (28)**

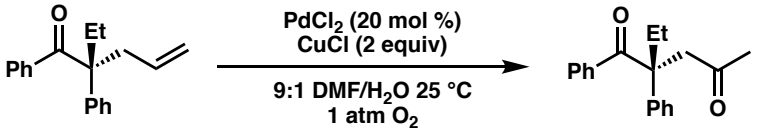
Purified by column chromatography (10% $Et_2O$ in hexanes) to provide a white solid (32.2 mg, 82% yield) containing 6% dimethyl fumarate as an impurity; 90% ee, $[\alpha]_D^{25}$ –116.94 (*c* 1.00, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.48 (s, 4H), 7.43–7.37 (m, 2H), 7.36–7.31 (m, 1H), 7.29–7.26 (m, 2H), 6.54 (ddd, *J* = 15.5, 9.0, 6.4 Hz, 1H), 5.78–5.66 (m, 1H), 3.67 (s, 3H), 3.04–2.81 (m, 2H), 2.27–2.10 (m, 2H), 0.73 (t, *J* = 7.4 Hz, 3H); $^{19}$F NMR (282 MHz, $CDCl_3$) δ –63.3 (s); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 201.7, 166.5, 144.3, 141.2, 139.7, 133.3 (q, *J* = 32.7 Hz), 129.7, 129.5, 127.9, 126.8, 125.3 (q, *J* = 3.7 Hz), 124.3, 123.6 (d, *J* = 272.8 Hz), 58.5, 51.6, 38.4, 26.5, 8.2; IR (Neat Film, NaCl) 2972, 2952, 1725, 1682, 1657, 1446, 1407, 1326, 1272, 1227, 1199, 1169, 1131, 1068, 1001, 858, 755, 702 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{22}H_{25}F_3NO_3$ $[M+NH]^+$: 408.1781, found 408.1771; SFC Conditions: 5% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): major = 4.47, minor = 5.90.




**methyl (*R*,*E*)-5-(2-methylbenzoyl)-5-phenylhept-2-enoate (29)**

Purified by column chromatography (7% $Et_2O$ in hexanes) to provide a colorless oil (25.8 mg, 77% yield); 73% ee, $[\alpha]_D^{25}$ –66.93 (*c* 1.00, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.42–7.30 (m, 5H), 7.20 (dd, *J* = 4.1, 1.0 Hz, 2H), 6.90–6.81 (m, 1H), 6.65–6.55 (m, 2H), 5.72 (dt, *J* = 15.6, 1.4 Hz, 1H), 3.68 (s, 3H), 3.07–2.88 (m, 2H), 2.37 (s, 3H), 2.13 (q, *J* = 7.4 Hz, 2H), 0.74 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 206.3, 166.6, 144.9,

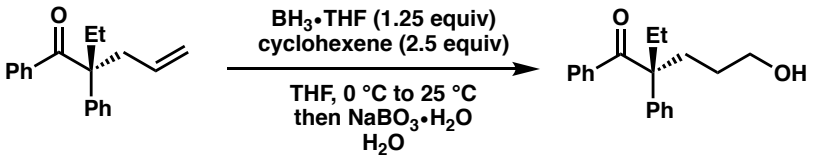
141.2, 138.2, 137.7, 132.1, 130.3, 129.2, 127.6, 127.5, 126.8, 124.8, 124.0, 58.8, 51.6, 37.7, 26.7, 21.1, 8.1; IR (Neat Film, NaCl) 3059, 3022, 2970, 2950, 1725, 1681, 1656, 1494, 1446, 1436, 1337, 1269, 1229, 1197, 1170, 1036, 995, 763, 734, 702 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{22}H_{25}O_3$ $[M+H]^+$: 337.1798, found 337.1813; SFC Conditions: 10% IPA, 2.5 mL/min, Chiralpak IC column, $\lambda$ = 210 nm, $t_R$ (min): major = 5.74, minor = 6.49.




**(*R*)-2-ethyl-1,2-diphenylpentane-1,4-dione (22)**

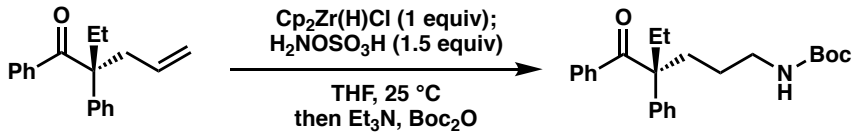
To a 20 mL vial containing alpha quaternary ketone **21a** (0.2 mmol, 52.8 mg) dissolved in 5 mL of 9:1 DMF/$H_2O$ was added $PdCl_2$ (0.04 mmol, 7.1 mg) and CuCl (0.4 mmol, 39.6 mg), and the vial sealed with a Teflon-lined septum cap. The vial was then quickly evacuated and backfilled three times with a balloon of $O_2$, and then stirred at 25 °C under a balloon of $O_2$ for 16 h. The crude reaction was then diluted with EtOAc, followed by water and brine. The layers were separated, and the aqueous layer extracted with EtOAc twice. The combined organic layers were dried over $Na_2SO_4$ and concentrated. The crude product was purified by silica gel flash chromatography (20% $Et_2O$ in hexanes) to afford the desired product as a white, waxy solid in a 14:1 ketone/aldehyde ratio (47.4 mg, 85% yield); $[\alpha]_D^{25}$ –87.8 (*c* 1.00, $CHCl_3$); $^1$H NMR of ketone (500 MHz, $CDCl_3$) δ 7.43–7.27 (m, 8H), 7.23–7.16 (m, 2H), 3.32 (d, *J* = 16.2 Hz, 1H), 3.18 (d, *J* = 16.2 Hz, 1H), 2.59–2.46 (m, 1H), 2.28–2.17 (m, 1H), 1.82 (s, 3H), 0.72 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR of ketone (100 MHz, $CDCl_3$) δ 207.3, 202.7, 141.4, 137.5, 131.5, 129.2, 129.2, 128.0, 127.5, 126.9, 57.0, 47.5, 31.8, 27.2, 8.7; IR (Neat Film, NaCl) 3059, 2971, 2940,

2880, 1716, 1682, 1598, 1579, 1495, 1462, 1446, 1415, 1361, 1260, 1229, 1214, 1180, 1033, 1003, 986, 913, 783, 764, 716, 703, 646 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{21}O_2$ $[M+H]^+$: 281.1536, found 281.1534.




**(*R*)-2-ethyl-5-hydroxy-1,2-diphenylpentan-1-one (23)**

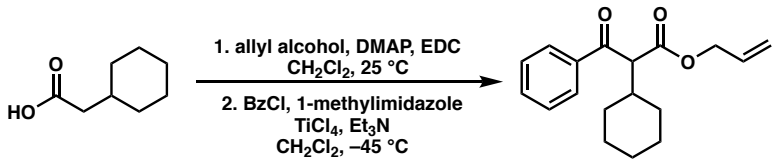
To a one dram vial was added a 1 M solution of $BH_3$•THF (0.25 mmol, 250 μL) and the vial cooled to 0 °C. Cyclohexene (0.5 mmol, 51 μL) was then added neat, dropwise and the mixture stirred at 0 °C for 1 h. A solution of alpha quaternary ketone **21a** (0.2 mmol, 52.8 mg) in 1.0 mL THF was then added, and the reaction was allowed to warm to room temperature and stirred for 4 h. Water (500 μL) was then added to the vial followed by $NaBO_3$•$4H_2O$ (1 mmol, 153.9 mg) and the resulting mixture stirred vigorously for 18 h. The crude reaction was diluted with $Et_2O$ and water, and the layers separated. The aqueous layer was extracted with $Et_2O$ twice, and the combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated. The crude product was purified by preparative TLC (30% acetone in hexanes) to afford the desired product as a colorless oil (42.2 mg, 75% yield); $[\alpha]_D^{25}$ –11.8 (*c* 1.00, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.42–7.32 (m, 5H), 7.31–7.26 (m, 3H), 7.22–7.15 (m, 2H), 3.52 (td, *J* = 6.6, 2.4 Hz, 2H), 2.22–2.09 (m, 4H), 1.32–1.23 (m, 2H), 0.69 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 203.9, 142.9, 137.2, 131.8, 129.4, 129.0, 128.1, 127.1, 127.0, 63.4, 58.1, 30.5, 27.1, 27.0, 8.1; IR (Neat Film, NaCl) 3336 (br) ,3059, 2965, 2878, 1673, 1597, 1578, 1495, 1446, 1383, 1229, 1180, 1060, 1004, 913, 761, 702 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{23}O_2$ $[M+H]^+$: 283.1693, found 283.1688.




**_tert_-butyl (_R_)-(4-benzoyl-4-phenylhexyl)carbamate (24)**

In a nitrogen-filled glovebox, ketone **21a** (0.1 mmol, 26.4 mg) was added to a one dram vial followed by THF (1 mL). $Cp_2Zr(H)Cl$ was then added (0.1 mmol, 25.7 mg) and the resulting suspension stirred at room temperature for 30 minutes, at which point the reaction became a homogeneous yellow solution. Hydroxylamine-*O*-sulfonic acid was then added (0.15 mmol, 17.0 mg) and the vial removed from the glovebox and stirred at room temperature for 1 hr. $Et_3N$ (0.3 mmol, 42 μL) was then added followed by $Boc_2O$ (0.3 mmol, 69 μL) and the reaction continued for 2 hr and then filtered through a plug of silica. The crude product was purified via preparative TLC (12% $Et_2O$ in hexanes) to afford the desired product at a viscous colorless oil (83% yield, 31.5 mg): $[\alpha]_D^{25}$ 24.5 (*c* 1.00, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.46–7.36 (m, 5H), 7.33 (td, *J* = 6.7, 1.1 Hz, 3H), 7.29–7.19 (m, 2H), 4.41 (s, 1H), 3.21–2.96 (m, 2H), 2.16 (dq, *J* = 42.9, 9.0, 8.2 Hz, 4H), 1.46 (s, 9H), 1.22 (ddd, *J* = 10.1, 6.6, 2.9 Hz, 1H), 0.73 (t, *J* = 7.4 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 203.8, 155.9, 142.8, 137.2, 131.8, 129.4, 129.0, 128.1, 127.1, 127.0, 79.1, 58.1, 41.0, 31.4, 28.5, 26.9, 24.1, 8.1; IR (Neat Film, NaCl) 3377 (br), 2972, 1701, 1676, 1597, 1578, 1516, 1446, 1391, 1365, 1270, 1248, 1173, 761, 732, 703; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{24}H_{32}NO_3$ $[M+H]^+$: 382.2377, found 382.2375.

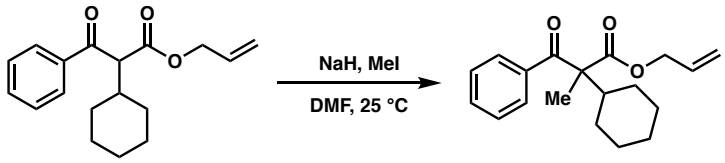
### 3.8.2.6 Preliminary Investigation of Fully Alkyl Quaternary Stereocenters




**allyl 2-cyclohexyl-3-oxo-3-phenylpropanoate (30)**

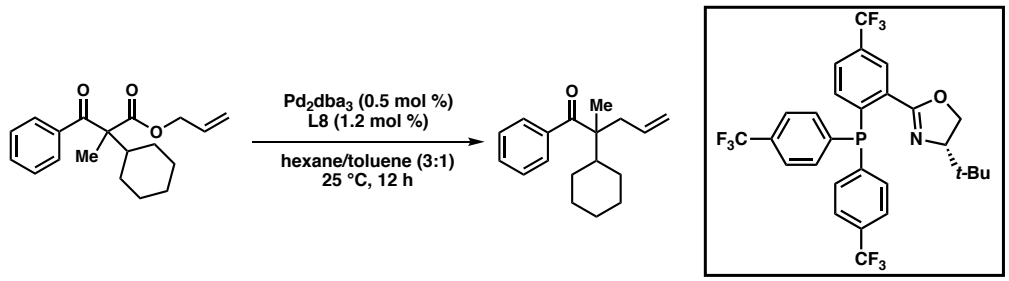
To a flame-dried flask containing cyclohexaneacetic acid (10 mmol, 1.4220 g), DMAP (1 mmol, 122 mg), and EDC-HCl (11 mmol, 2.1087 g) was added $CH_2Cl_2$ (30 mL) and the resulting mixture stirred for 10 minutes at 25 °C. Allyl alcohol (10 mmol, 680 μL) was then added and the reaction continued at 25 °C for 1 h, then diluted with water and extracted with $CH_2Cl_2$. The combined organic layers were washed with brine, then dried with $Na_2SO_4$. The crude product was filtered through a plug of silica and concentrated to a colorless oil (1.5733 g, 86% crude yield) which was then transferred to a flame-dried flask containing benzoyl chloride (8.61 mmol, 1.0 mL) dissolved in 40 mL $CH_2Cl_2$. The reaction was cooled to –45 °C and 1-methylimidazole (10.34 mmol, 824 μL) was added followed by sequential slow addition of $TiCl_4$ (30.15 mmol, 3.31 mL) over 20 minutes and $Et_3N$ (34.5 mmol, 4.8 mL) over 1 h. The resulting mixture was stirred for 1 h at –45 °C then slowly quenched with water. The aqueous layer was extracted with $Et_2O$ and the combined organic layers washed with water then brine, and dried over $Na_2SO_4$. The crude product was purified by silica gel flash chromatography (10% $Et_2O$ in hexanes) to afford the desired product as a colorless oil (2.2396 g, 78% yield over two steps): $^1$H NMR (500 MHz, $CDCl_3$) δ 8.04–7.96 (m, 2H), 7.62–7.53 (m, 1H), 7.51–7.40 (m, 2H), 5.81 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.28–5.07 (m, 2H), 4.57 (ddt, *J* = 5.8, 2.9, 1.4 Hz, 2H), 4.21 (d, *J* = 9.6 Hz, 1H), 2.46–2.33 (m, 1H), 1.76 (tdt, *J* = 8.6, 3.5, 1.7 Hz, 1H), 1.66 (dddd, *J* = 12.9, 8.6, 4.2, 2.5 Hz, 4H), 1.40–1.24 (m, 2H), 1.23–1.06 (m, 2H), 1.01–0.86

(m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 194.7, 168.7, 137.2, 133.6, 131.7, 128.8, 128.6, 118.6, 65.8, 60.5, 38.5, 31.5, 31.0, 26.2, 26.1, 26.0; IR (Neat Film, NaCl) 2927, 2852, 1736, 1686, 1596, 1448, 1284, 1239, 1199, 1154, 1128, 990, 928, 670 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{18}H_{26}NO_3$ $[M+NH_4]^+$: 304.1907, found 304.1913.




**allyl 2-cyclohexyl-2-methyl-3-oxo-3-phenylpropanoate (31)**

To a flame-dried flask containing NaH (2 mmol, 80 mg, 60% dispersion in mineral oil) and DMF (6 mL) was added beta-ketoester **SI5** (1 mmol, 286.4 mg) neat at 25 °C, and the resulting suspension stirred for 30 minutes. MeI (2 mmol, 125 μL) was then added and the reaction continued at 25 °C for 1.5 h. The reaction was quenched with saturated $NH_4Cl$ and diluted with water and $Et_2O$. The aqueous layer was extracted with $Et_2O$ and the combined organic layers dried over $MgSO_4$. The crude product was purified by silica gel flash chromatography (6% $Et_2O$ in hexanes) to afford the desired product as a colorless oil (240.6 mg, 80%) containing some of the undesired *O*-alkylated product: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.82–7.73 (m, 2H), 7.56–7.44 (m, 1H), 7.43–7.34 (m, 2H), 5.68 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.22–5.08 (m, 2H), 4.60–4.49 (m, 2H), 2.46 (tt, *J* = 11.9, 2.7 Hz, 1H), 1.87–1.64 (m, 5H), 1.64–1.49 (m, 1H), 1.46 (s, 3H), 1.42–1.22 (m, 2H), 1.19–0.94 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.7, 173.3, 136.7, 132.3, 131.3, 128.4, 128.3, 118.7, 65.6, 60.9, 42.6, 28.6, 28.0, 26.8, 26.8, 26.5, 17.7; IR (Neat Film, NaCl) 2930, 2853, 2360, 1734, 1684, 1447, 1258, 1233, 1186, 1153, 1121, 1081, 964, 700 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{25}O_3$ $[M+H]^+$: 301.1798, found 301.1787.

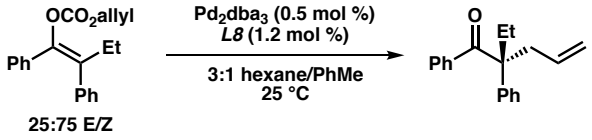



**2-cyclohexyl-2-methyl-1-phenylpent-4-en-1-one (32)**

In a nitrogen-filled glovebox, a solution of $Pd_2(dba)_3$ (1.8 mg/mL) and **L8** (2.8 mg/mL) in toluene was stirred for 30 minutes at 25 °C, then 0.5 mL of the resulting catalyst solution was added to a one dram vial containing beta-ketoester **31** (0.2 mmol) dissolved in hexanes (1.5 mL). The vial was sealed with a Teflon-lined cap, removed from the glovebox, and stirred at 25 °C for 12 h. The crude reaction mixture was concentrated then purified by preparative TLC to provide the desired alkylation product as a colorless oil (27.0 mg, 53% yield); 37% ee, $[\alpha]_D^{25}$ –7.7 (*c* 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.67–7.58 (m, 2H), 7.49–7.32 (m, 3H), 5.77–5.53 (m, 1H), 5.13–4.87 (m, 2H), 2.72 (dd, *J* = 13.9, 6.6 Hz, 1H), 2.40–2.19 (m, 1H), 2.00 (tt, *J* = 11.3, 2.9 Hz, 1H), 1.84–1.56 (m, 4H), 1.48 (dt, *J* = 9.1, 3.2 Hz, 1H), 1.35–1.03 (m, 8H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 209.3, 140.3, 134.5, 130.8, 128.2, 127.6, 118.0, 55.3, 45.5, 42.2, 28.8, 27.5, 27.1, 27.0, 26.7, 18.5; IR (Neat Film, NaCl) 2929, 2853, 1672, 1446, 1379, 1216, 1002, 967, 916, 772, 723, 694 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{18}H_{25}O$ $[M+H]^+$: 257.1900, found 257.1894; SFC Conditions : 5% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): major = 6.16, minor = 6.92.

### 3.8.2.7 Enantioselectivity Time Course Measurement

***Table 3.3*** *Variance in Enantioselectivity Over Time.*




| entry | time (min) | ee |
|---|---|---|
| 1 | 10 | 89.5 |
| 2 | 20 | 89.3 |
| 3 | 30 | 89.2 |
| 4 | 60 | 89.8 |
| 5 | 120 | 89.7 |
| 6 | 180 | 89.6 |

In a nitrogen-filled glovebox, a solution of $Pd_2(dba)_3$ (1.8 mg/mL) and **L8** (2.8 mg/mL) in toluene was stirred for 30 minutes at 25 °C, then 2.5 mL of the resulting catalyst solution was added to a vial containing 25:75 E/Z enol carbonate **20a** (1.0 mmol) dissolved in hexanes (7.5 mL). The vial was sealed with a Teflon-lined cap, removed from the glovebox, and stirred at 25 °C. At the indicated time intervals, 250 μL of the reaction mixture was removed, filtered through a plug of silica, and purified by preparative TLC (10% $Et_2O$ in hexanes). Analysis by chiral SFC showed that the ee of the product is initially high, and remains constant throughout the course of the reaction.

### 3.8.3 Determination of Enantiomeric Excess

***Table 3.4*** *Determination of Enantiomeric Excess.*

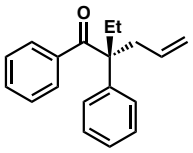
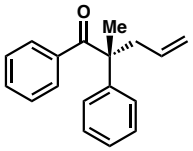
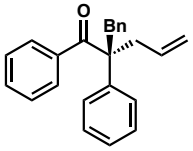
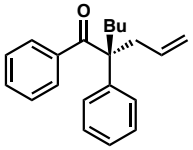
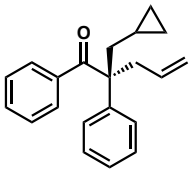
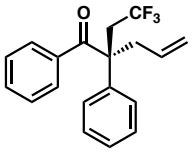
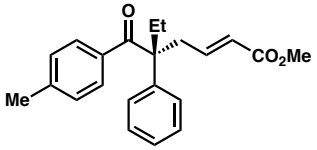
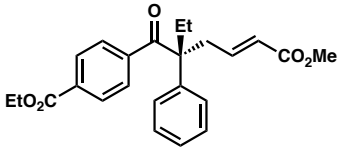
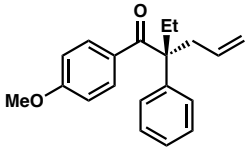
| Entry | Compound | Assay Conditions | $t_R$ of major isomer (min) | $t_R$ of minor isomer (min) | %ee |
|---|---|---|---|---|---|
| 1 |  | SFC<br>Chiralpak AD-H<br>2% IPA<br>isocratic, 2.5 mL/min | 5.76 | 5.33 | 91 |
| 2 |  | SFC<br>Chiralpak AD-H<br>2% IPA<br>isocratic, 2.5 mL/min | 7.44 | 7.02 | 67 |
| 3 |  | SFC<br>Chiralcel OD-H<br>10% IPA<br>isocratic, 2.5 mL/min | 5.97 | 5.47 | 76 |
| 4 |  | SFC<br>Chiralpak AD-H<br>5% IPA<br>isocratic, 2.5 mL/min | 5.27 | 4.44 | 87 |
| 5 |  | SFC<br>Chiralpak AD-H<br>5% IPA<br>isocratic, 2.5 mL/min | 6.97 | 6.27 | 91 |
| 6 |  | SFC<br>Chiralpak AD-H<br>5% IPA<br>isocratic, 2.5 mL/min | 2.17 | 1.73 | 86 |
| 7 |  | SFC<br>Chiralcel OB-H<br>5% IPA<br>isocratic, 2.5 mL/min | 4.95 | 4.14 | 90 |
| 8 |  | SFC<br>Chiralcel OD-H<br>7% IPA<br>isocratic, 2.5 mL/min | 10.31 | 9.38 | 90 |
| 9 |  | SFC<br>Chiralcel OJ-H<br>5% IPA<br>isocratic, 2.5 mL/min | 4.60 | 4.35 | 91 |

***Table 3.4*** *Determination of Enantiomeric Excess (continued)*

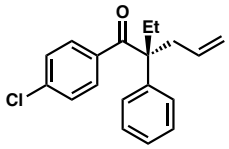
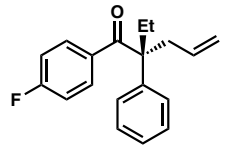
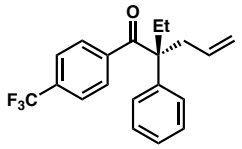
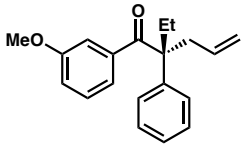
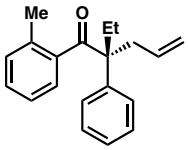
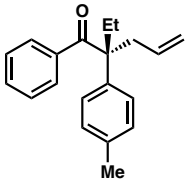
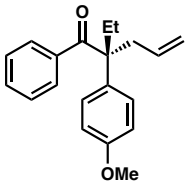
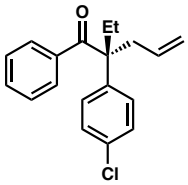
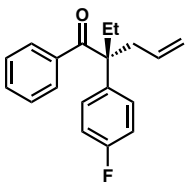
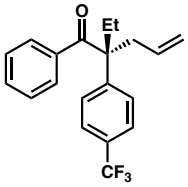
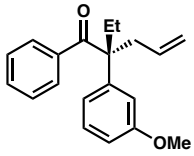
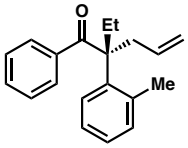
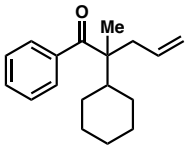
| Entry | Compound | Assay Conditions | $t_R$ of major isomer (min) | $t_R$ of minor isomer (min) | %ee |
|---|---|---|---|---|---|
| 10 |  | SFC<br>Chiralpak AD-H<br>10% IPA<br>isocratic, 2.5 mL/min | 6.64 | 6.09 | 91 |
| 11 |  | SFC<br>Chiralcel OD-H<br>5% IPA<br>isocratic, 2.5 mL/min | 8.03 | 7.43 | 91 |
| 12 |  | SFC<br>Chiralpak AD-H<br>5% IPA<br>isocratic, 2.5 mL/min | 5.90 | 4.47 | 90 |
| 13 |  | SFC<br>Chiralcel OJ-H<br>2% IPA<br>isocratic, 2.5 mL/min | 5.95 | 5.57 | 91 |
| 14 |  | SFC<br>Chiralpak IC<br>10% IPA<br>isocratic, 2.5 mL/min | 6.49 | 5.74 | 73 |
| 15 |  | SFC<br>Chiralpak AD-H<br>5% IPA<br>isocratic, 2.5 mL/min | 8.66 | 7.07 | 91 |
| 16 |  | SFC<br>Chiralpak AD-H<br>5% IPA<br>isocratic, 2.5 mL/min | 11.03 | 9.85 | 92 |
| 17 |  | SFC<br>Chiralpak AD-H<br>5% IPA<br>isocratic, 2.5 mL/min | 8.41 | 7.08 | 86 |
| 18 |  | SFC<br>Chiralpak AD-H<br>5% IPA<br>isocratic, 2.5 mL/min | 4.47 | 4.07 | 90 |

***Table 3.4*** *Determination of Enantiomeric Excess (continued)*

| Entry | Compound | Assay Conditions | $t_R$ of major isomer (min) | $t_R$ of minor isomer (min) | %ee |
|---|---|---|---|---|---|
| 19 |  | SFC<br>Chiralpak AD-H<br>(2 columns in series)<br>5% IPA<br>isocratic, 3.0 mL/min | 3.76 | 3.59 | 70 |
| 20 |  | SFC<br>Chiralpak AD-H<br>(2 columns in series)<br>5% IPA<br>isocratic, 3.0 mL/min | 8.48 | 7.91 | 90 |
| 21 |  | SFC<br>Chiralpak AD-H<br>5% IPA<br>isocratic, 3.5 mL/min | 4.05 | 3.76 | 90 |
| 22 |  | SFC<br>Chiralpak AD-H<br>5% IPA<br>isocratic, 3.5 mL/min | 6.16 | 6.92 | 37 |

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# *APPENDIX 4*

*Spectra Relevant to Chapter 3:*

*Catalytic Enantioselective Synthesis of Acyclic Quaternary Centers:*

*Palladium-Catalyzed Decarboxylative Allylic Alkylation of*

*Fully Substituted Acyclic Enol Carbonates*

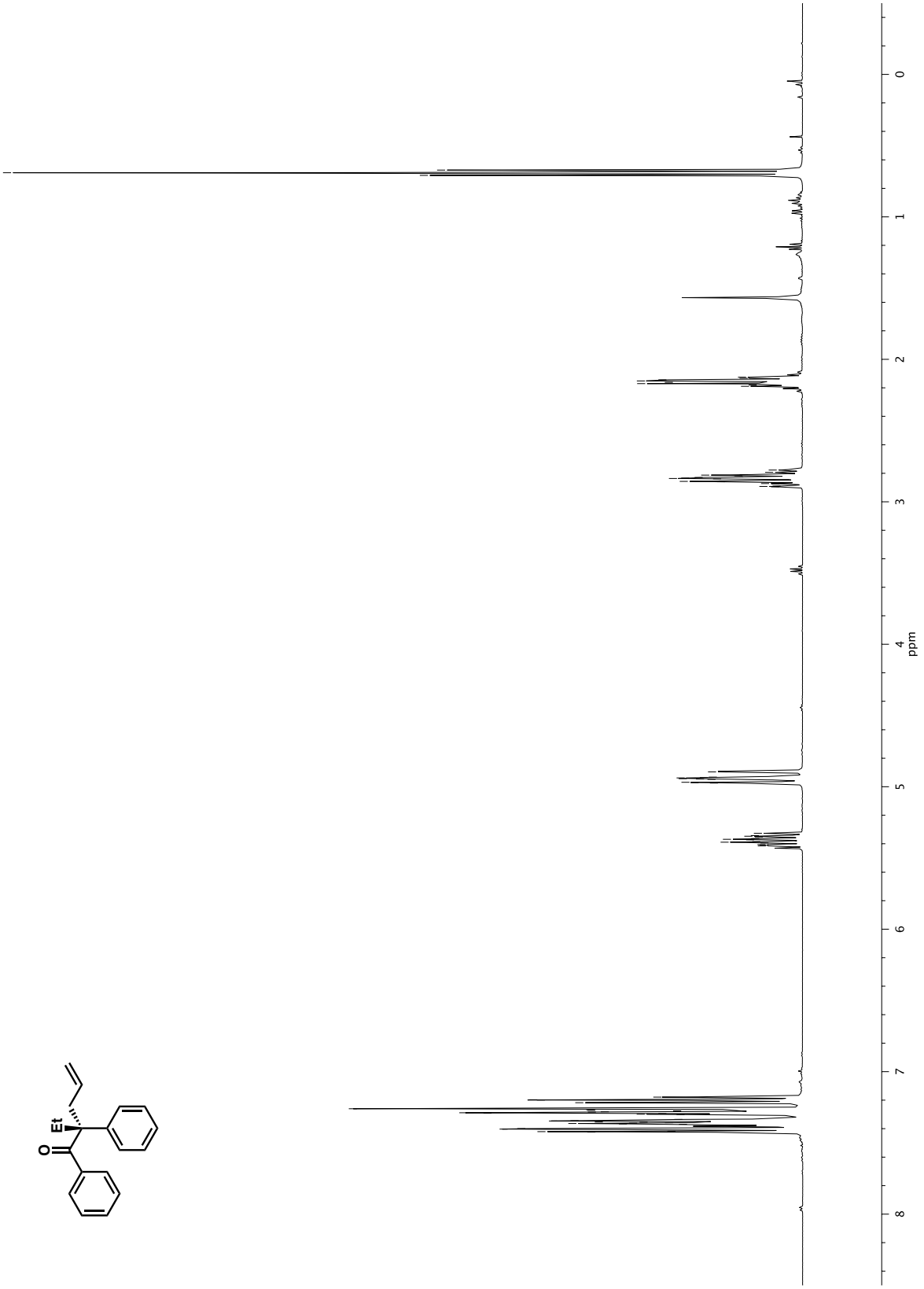



***Figure A4.1*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***21a***.

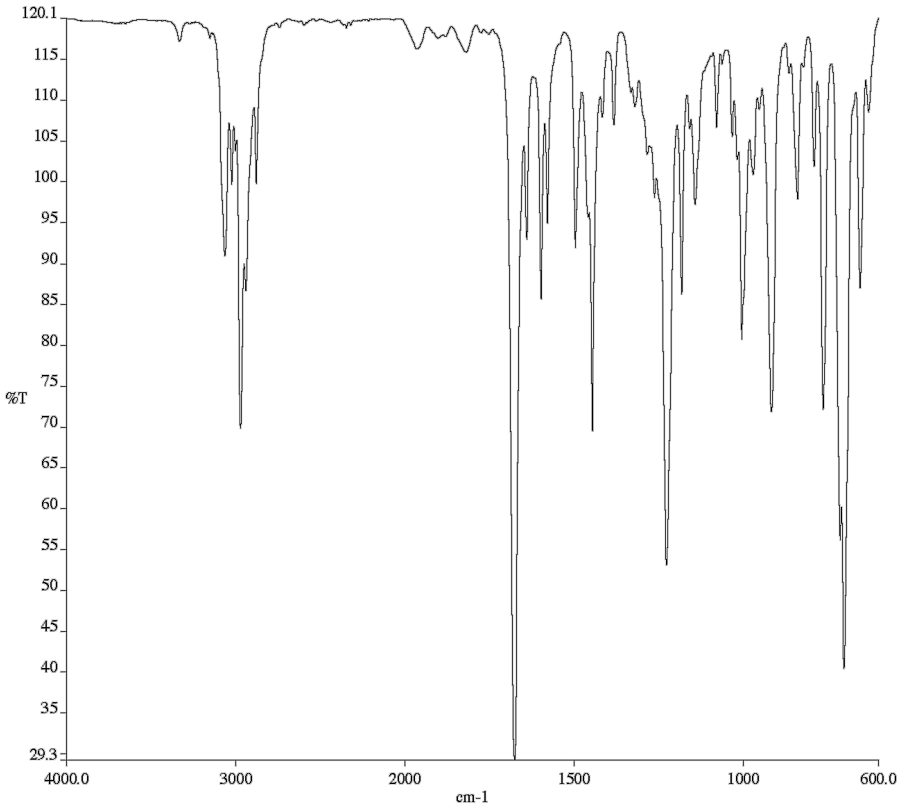



***Figure A4.2*** *Infrared spectrum (Thin Film, NaCl) of compound* ***21a****.*

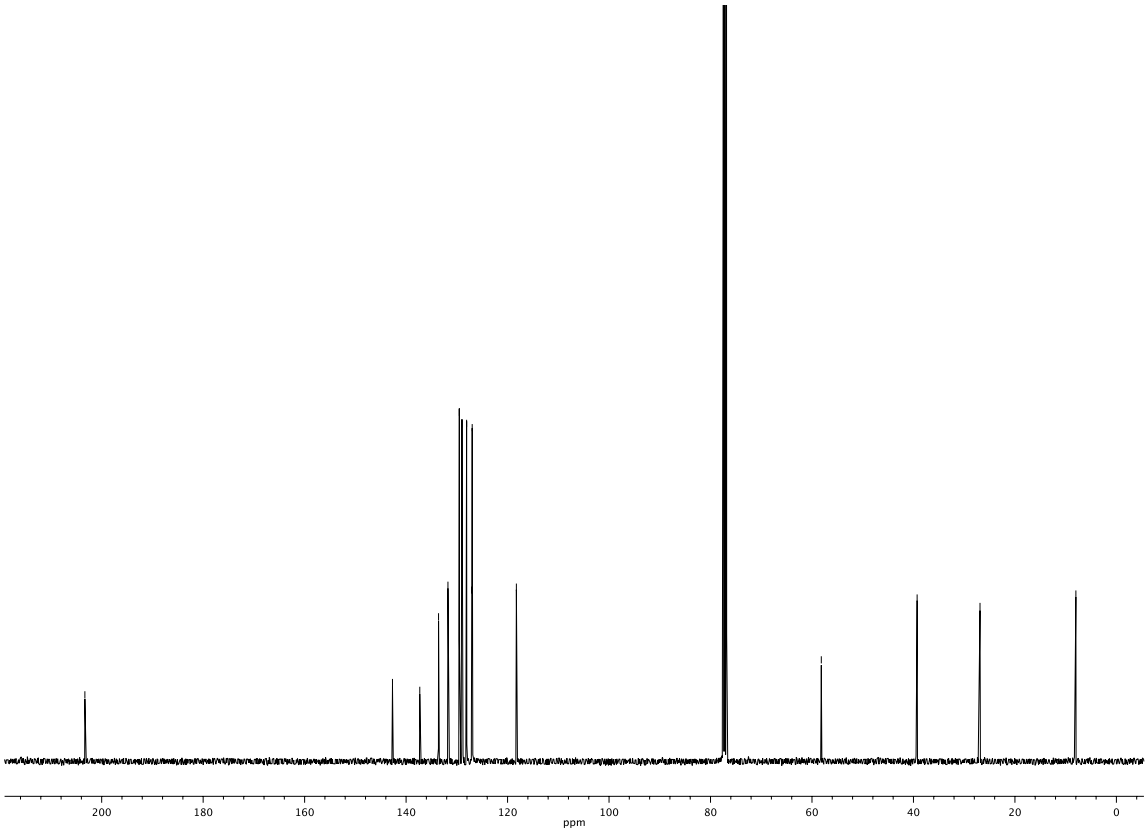



***Figure A4.3*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***21a****.*

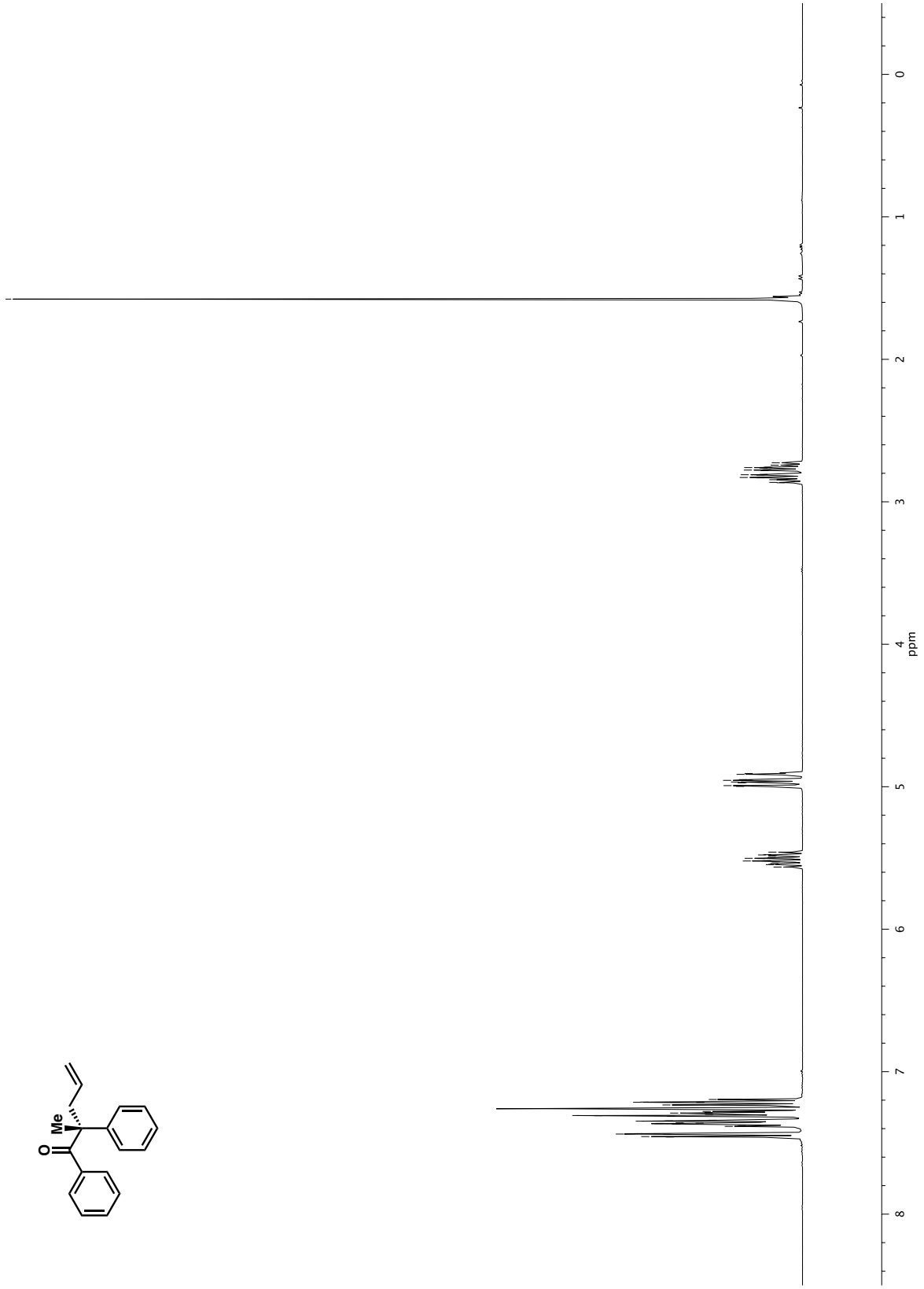



***Figure A4.4*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***21b***.

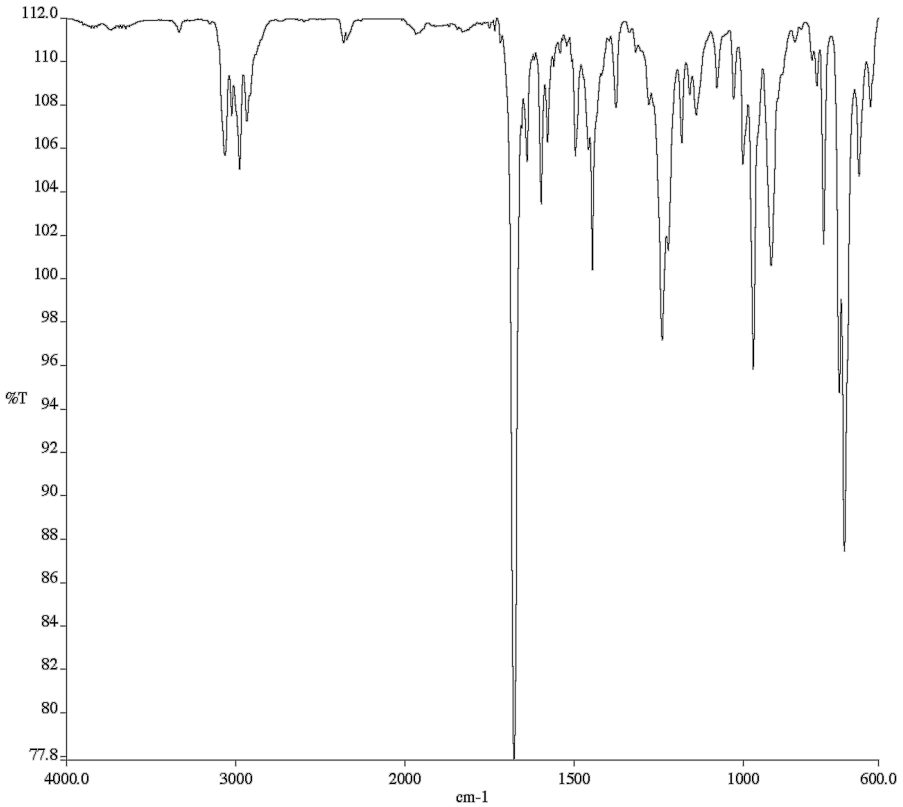



***Figure A4.5*** *Infrared spectrum (Thin Film, NaCl) of compound* ***21b****.*

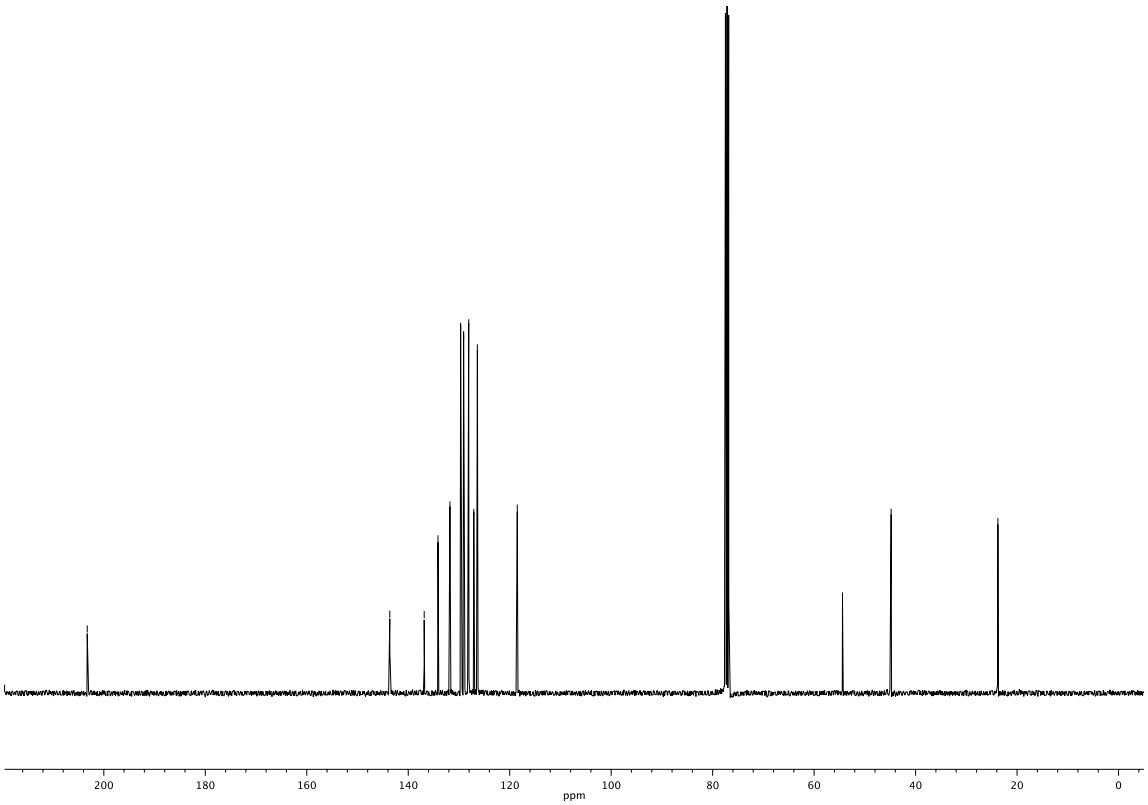



***Figure A4.6*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***21b****.*

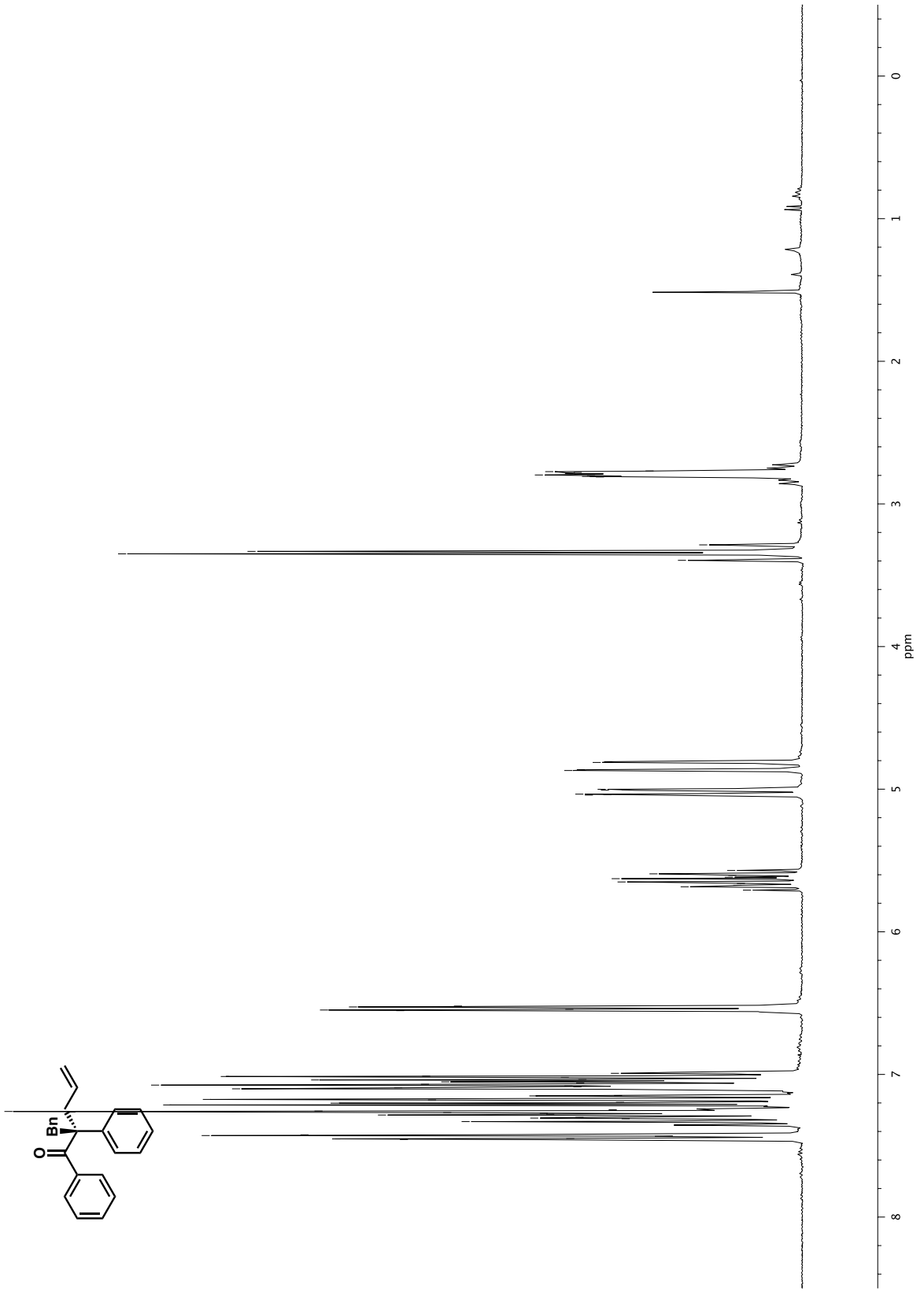



***Figure A4.7*** *$^{1}H$ NMR (400 MHz, $CDCl_3$) of compound* ***21c****.*

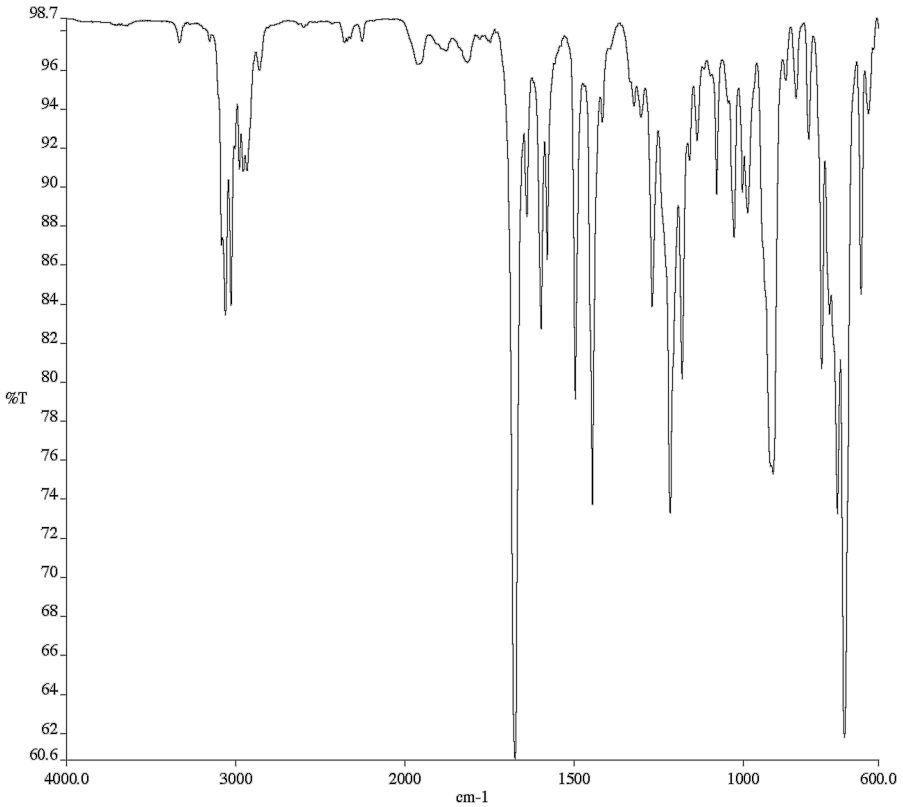



***Figure A4.8*** *Infrared spectrum (Thin Film, NaCl) of compound* ***21c****.*

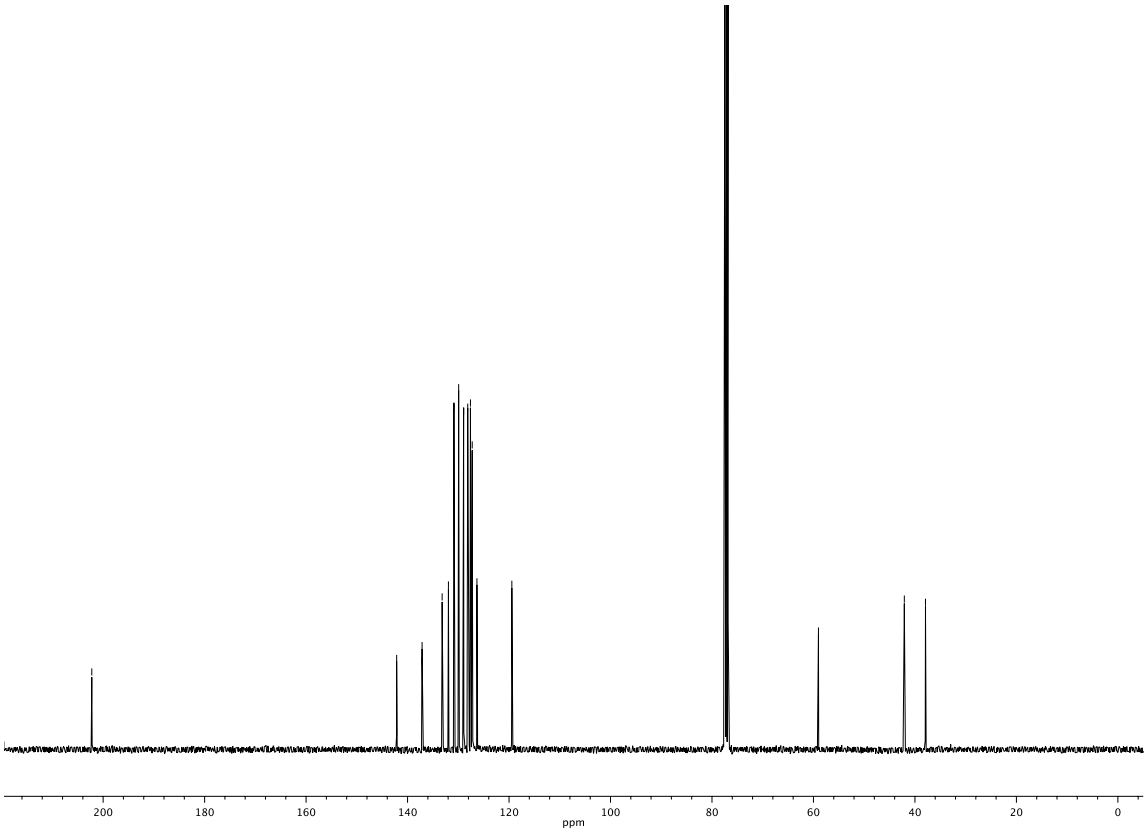



***Figure A4.9*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***21c****.*

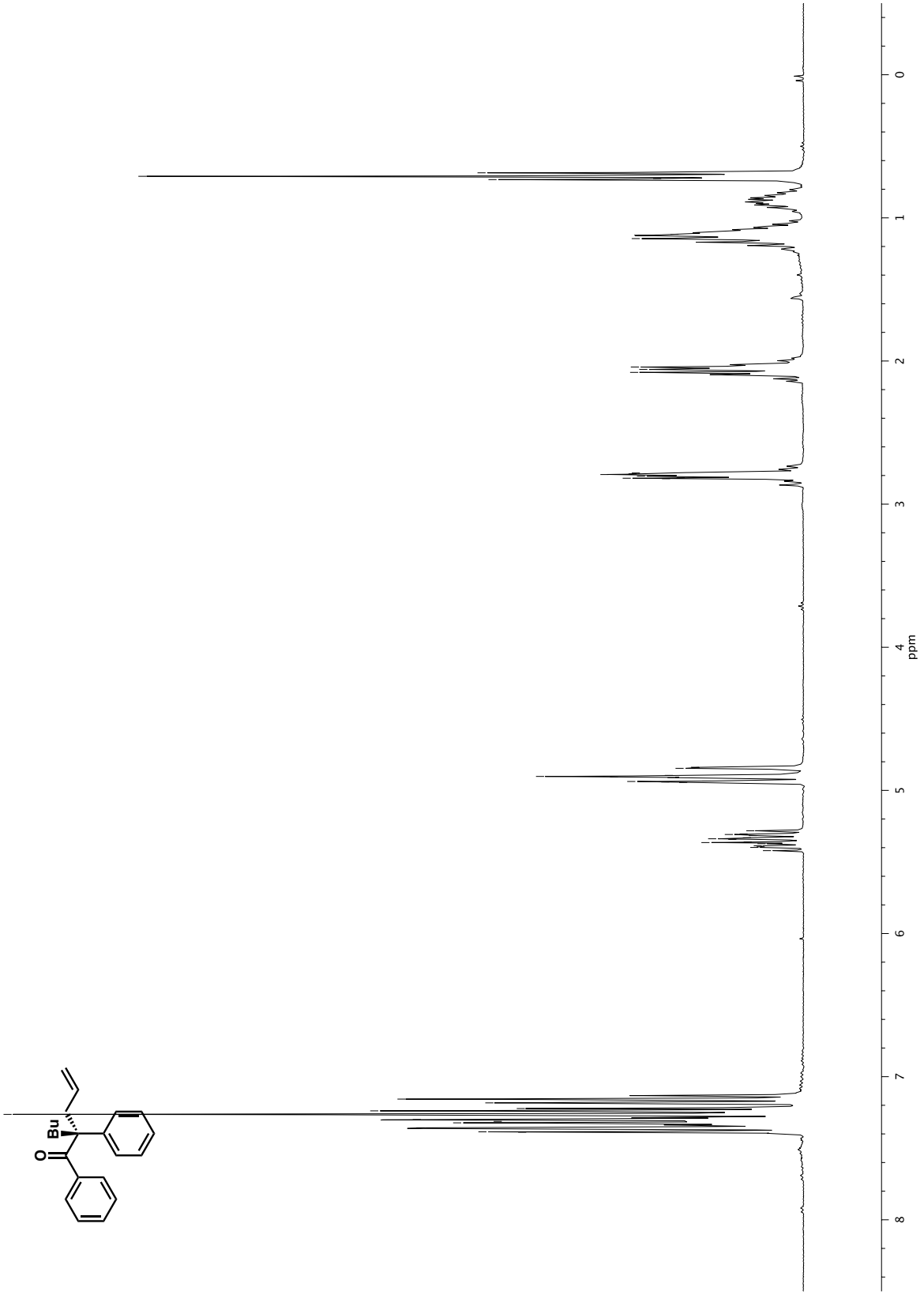



***Figure A4.10*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***21d***.

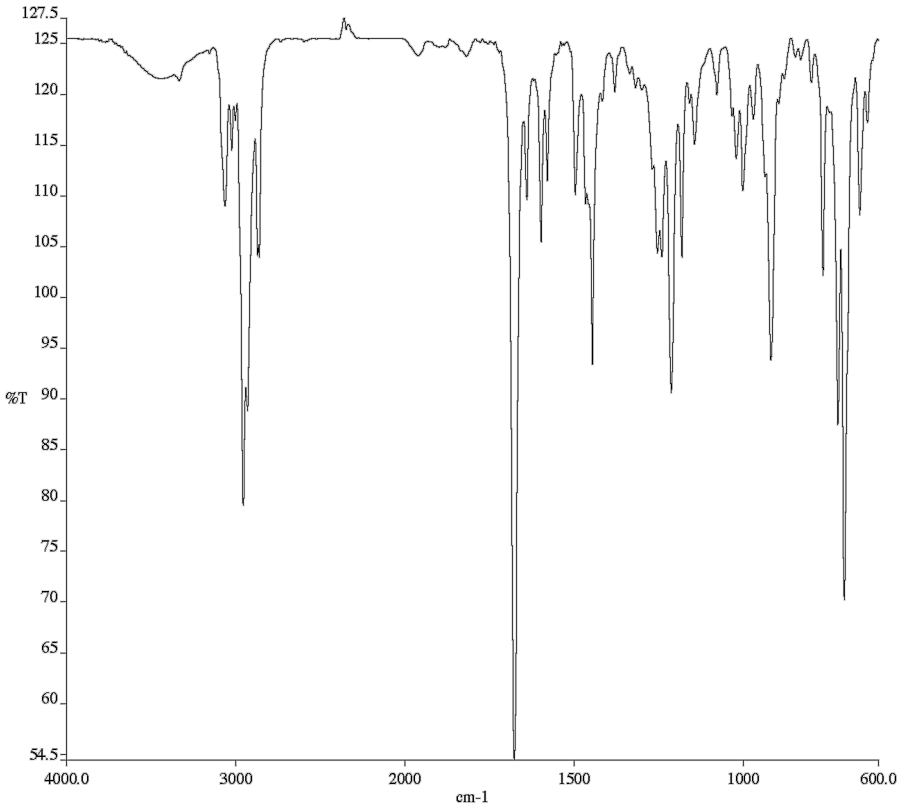



***Figure A4.11*** *Infrared spectrum (Thin Film, NaCl) of compound* ***21d****.*

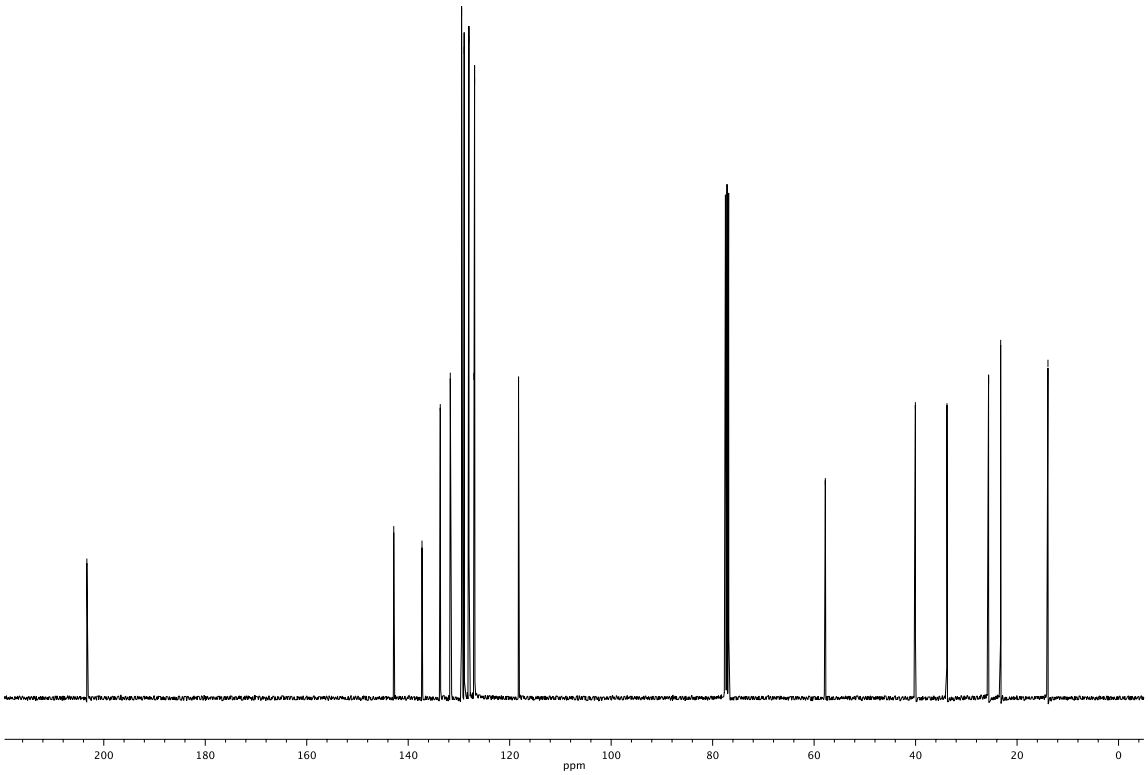



***Figure A4.12*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***21d****.*

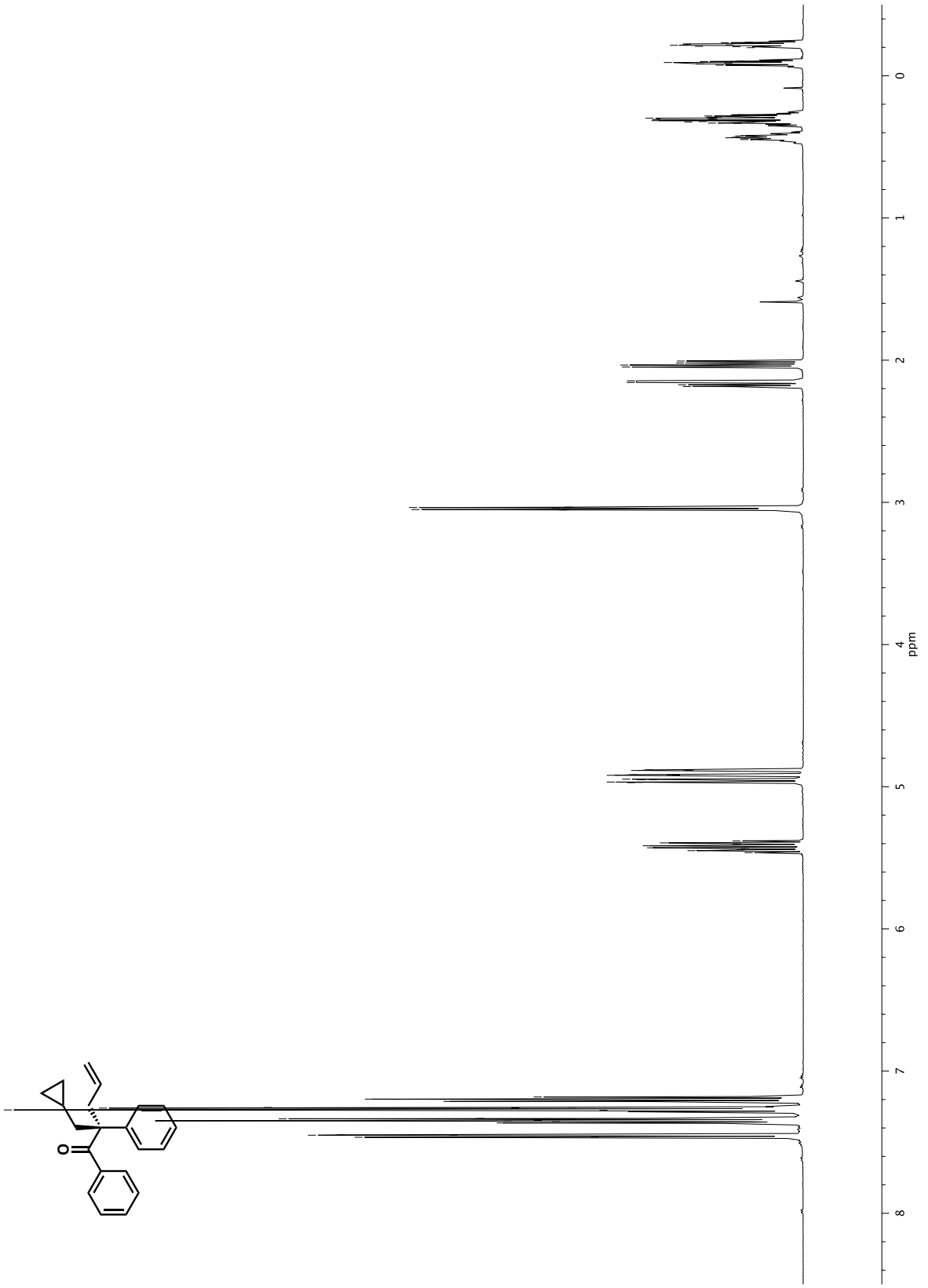



***Figure A4.13*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***21e***.

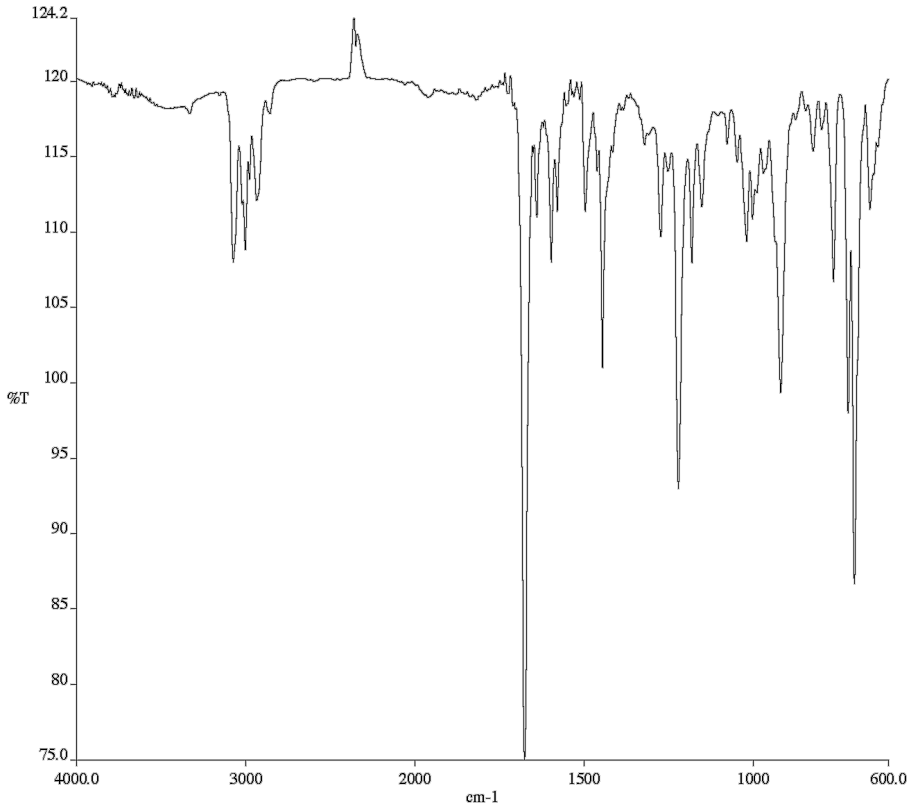



***Figure A4.14*** *Infrared spectrum (Thin Film, NaCl) of compound* ***21e****.*

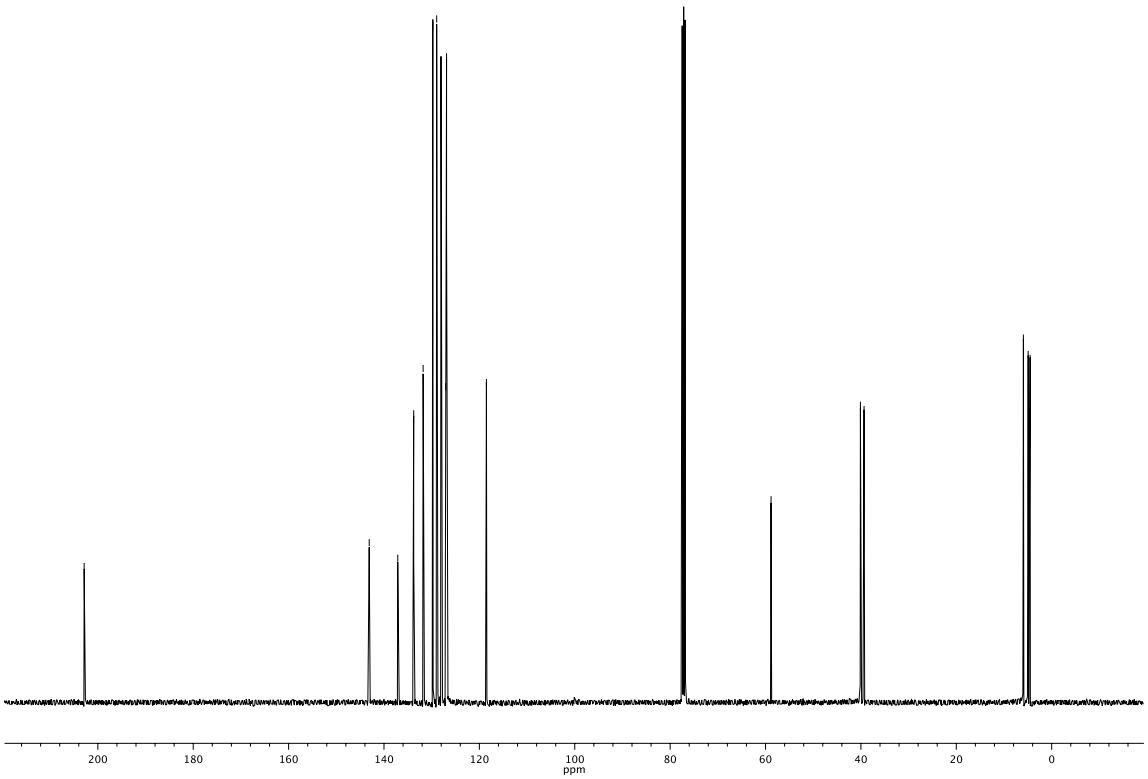



***Figure A4.15*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***21e****.*

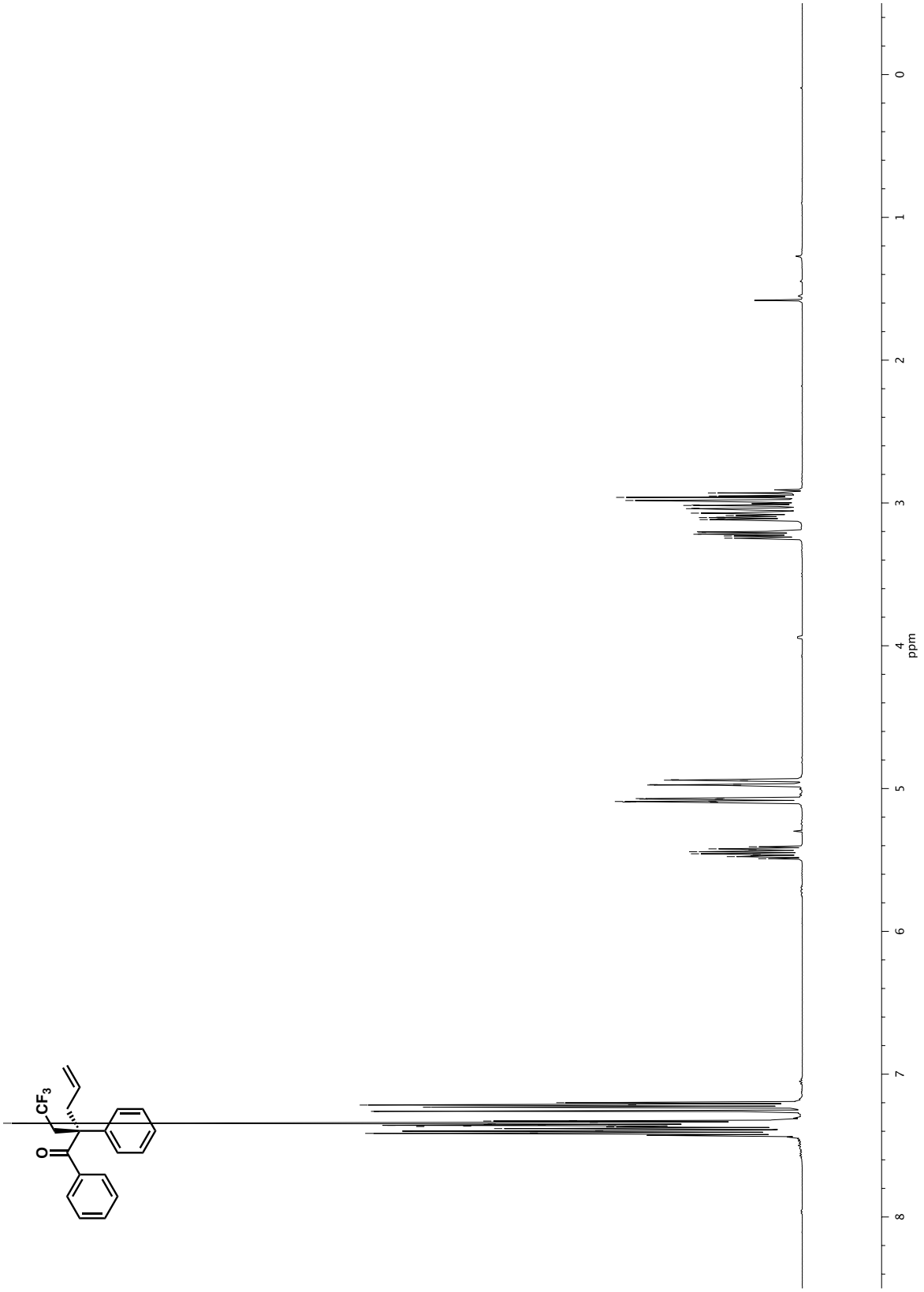



***Figure A4.16*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***21f****.*

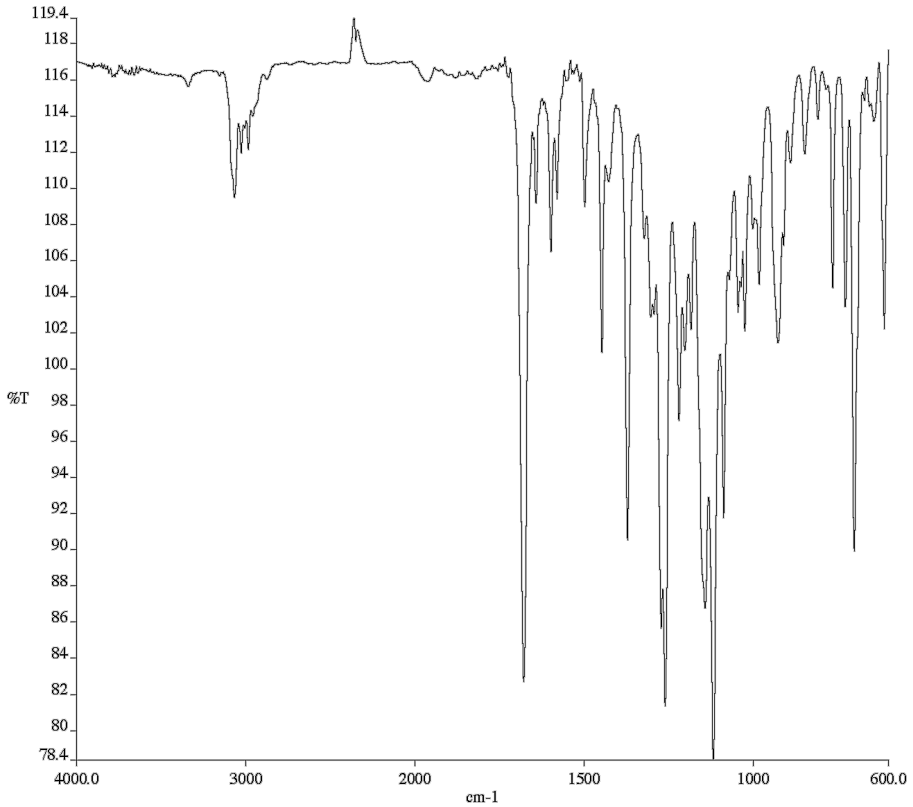



***Figure A4.17*** *Infrared spectrum (Thin Film, NaCl) of compound* ***21f****.*

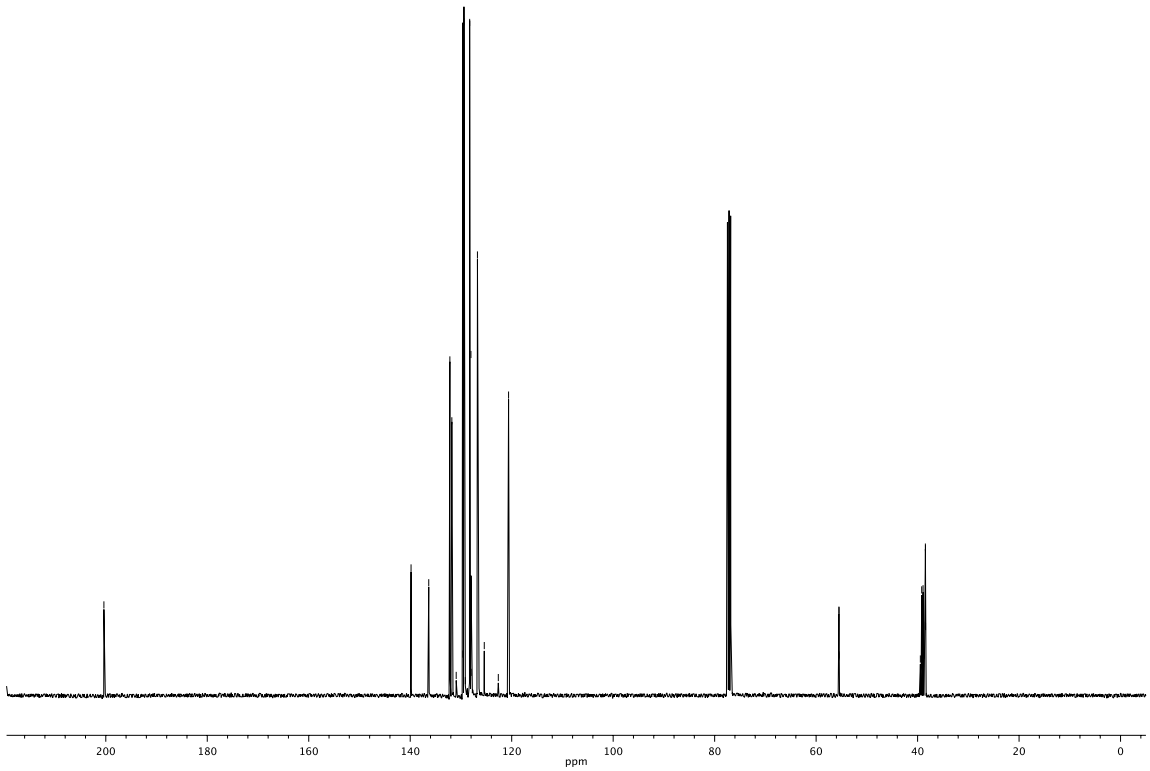



***Figure A4.18*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***21f****.*

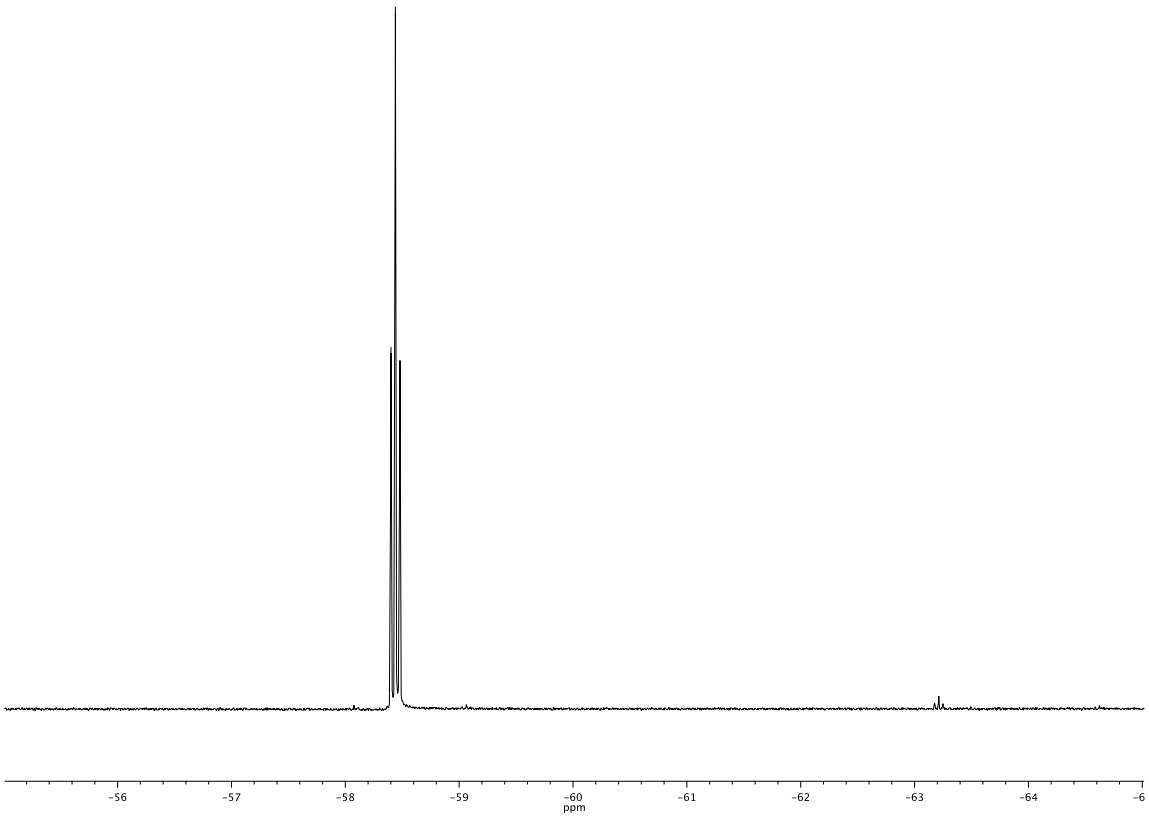



***Figure A4.19*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***21f****.*

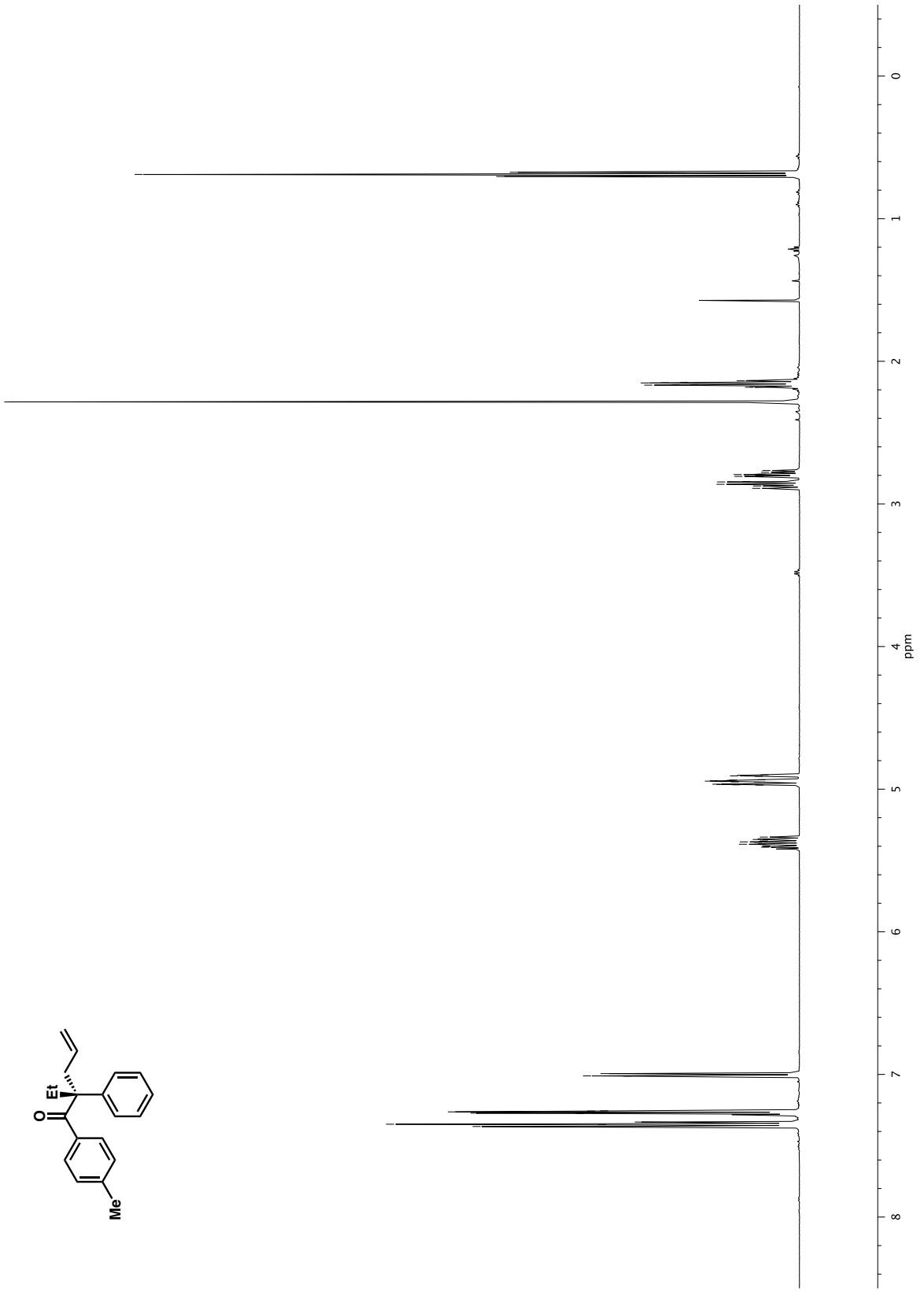



***Figure A4.20*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***21g***.

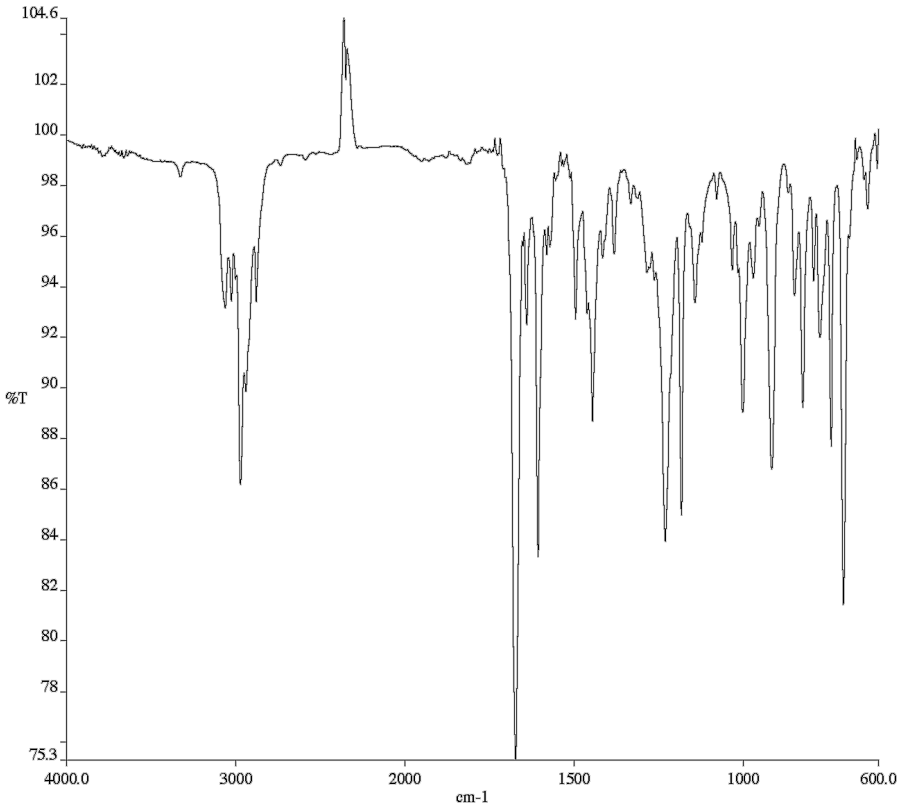



***Figure A4.21*** *Infrared spectrum (Thin Film, NaCl) of compound* ***21g****.*

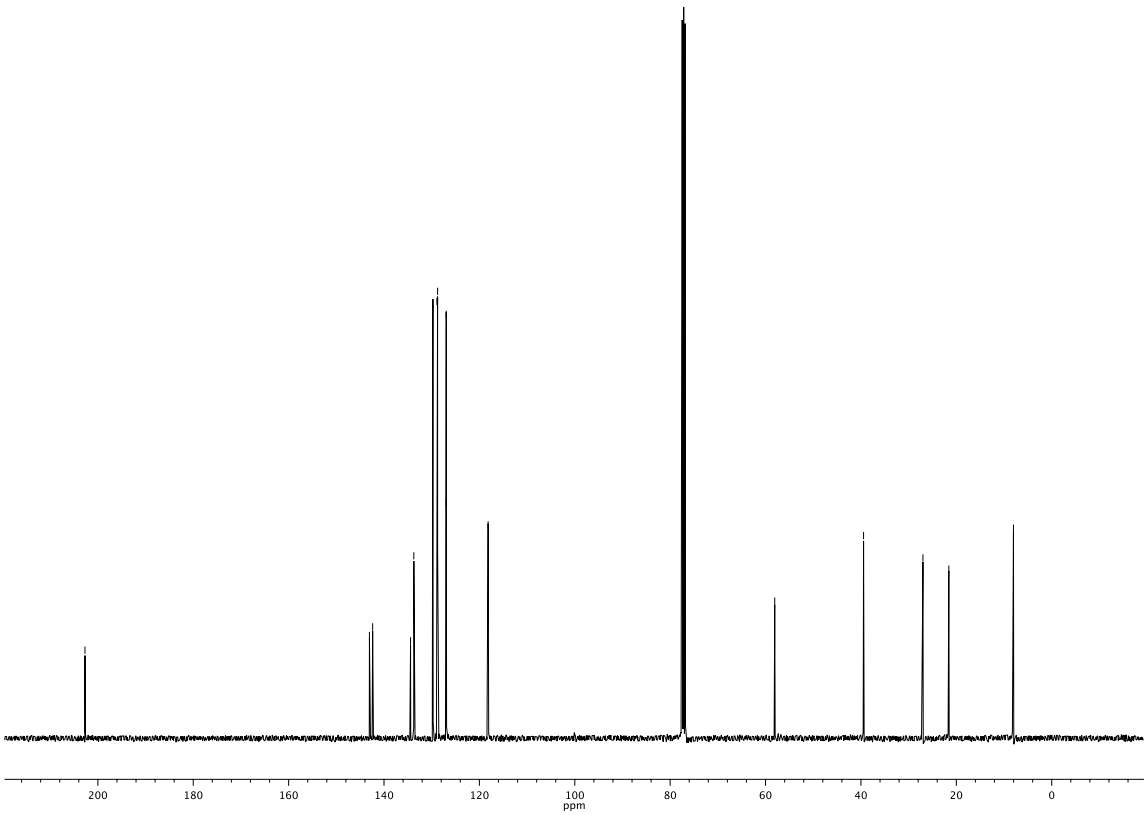



***Figure A4.22*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***21g****.*

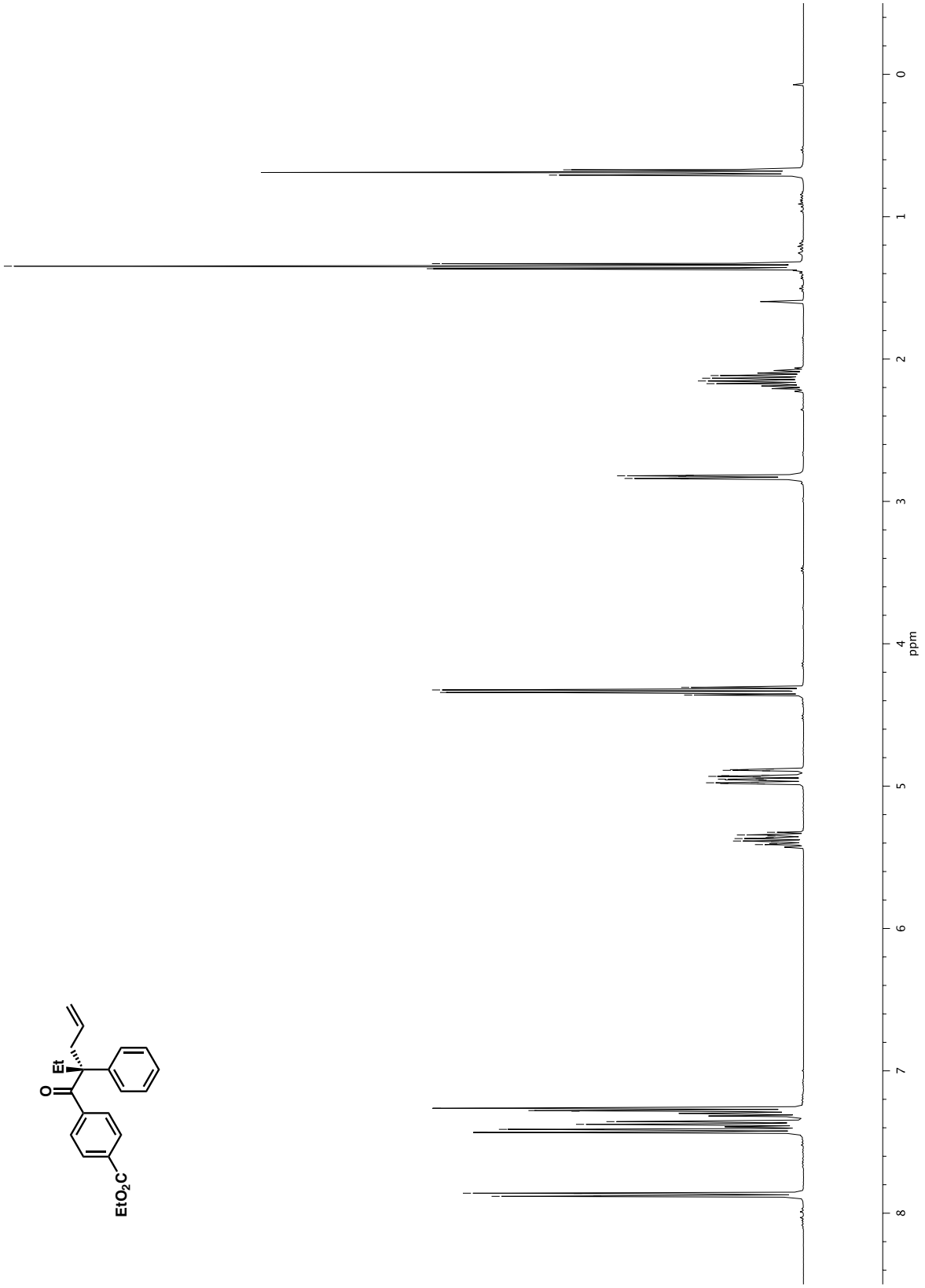



***Figure A4.23*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***21h***.

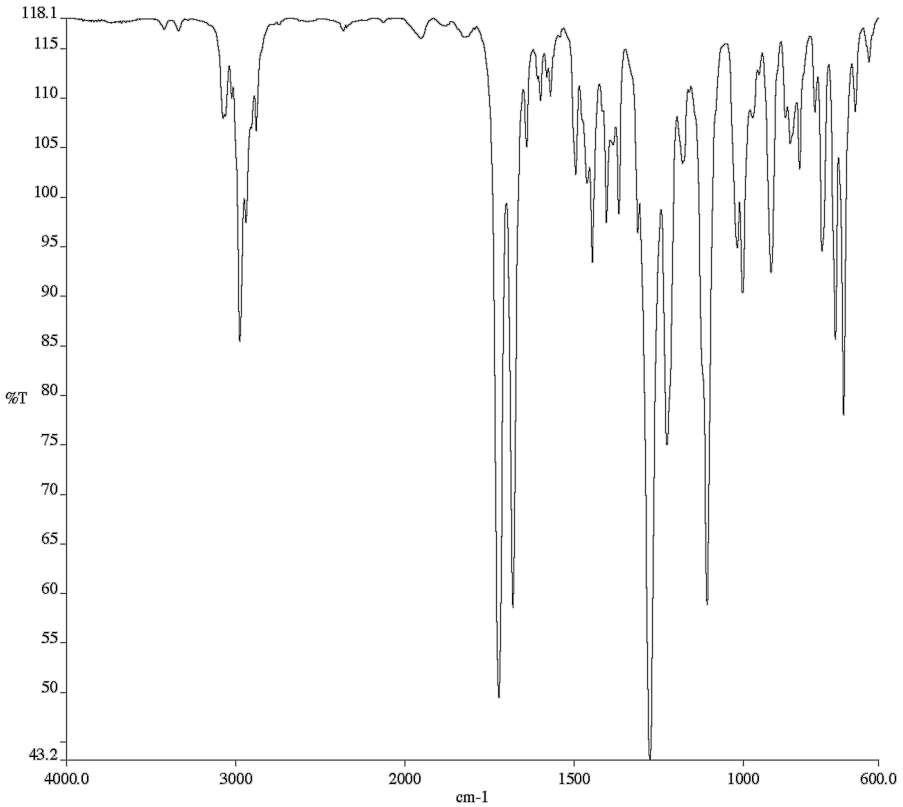



***Figure A4.24*** *Infrared spectrum (Thin Film, NaCl) of compound* ***21h***.

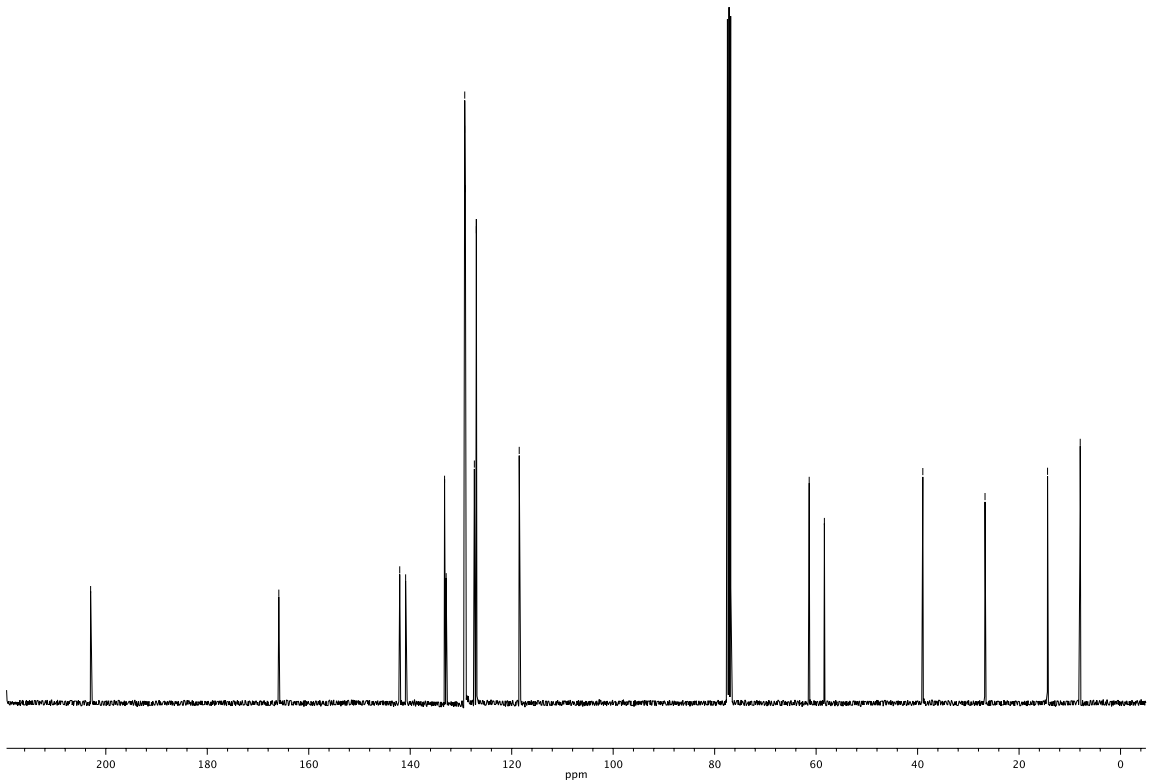



***Figure A4.25*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***21h***.

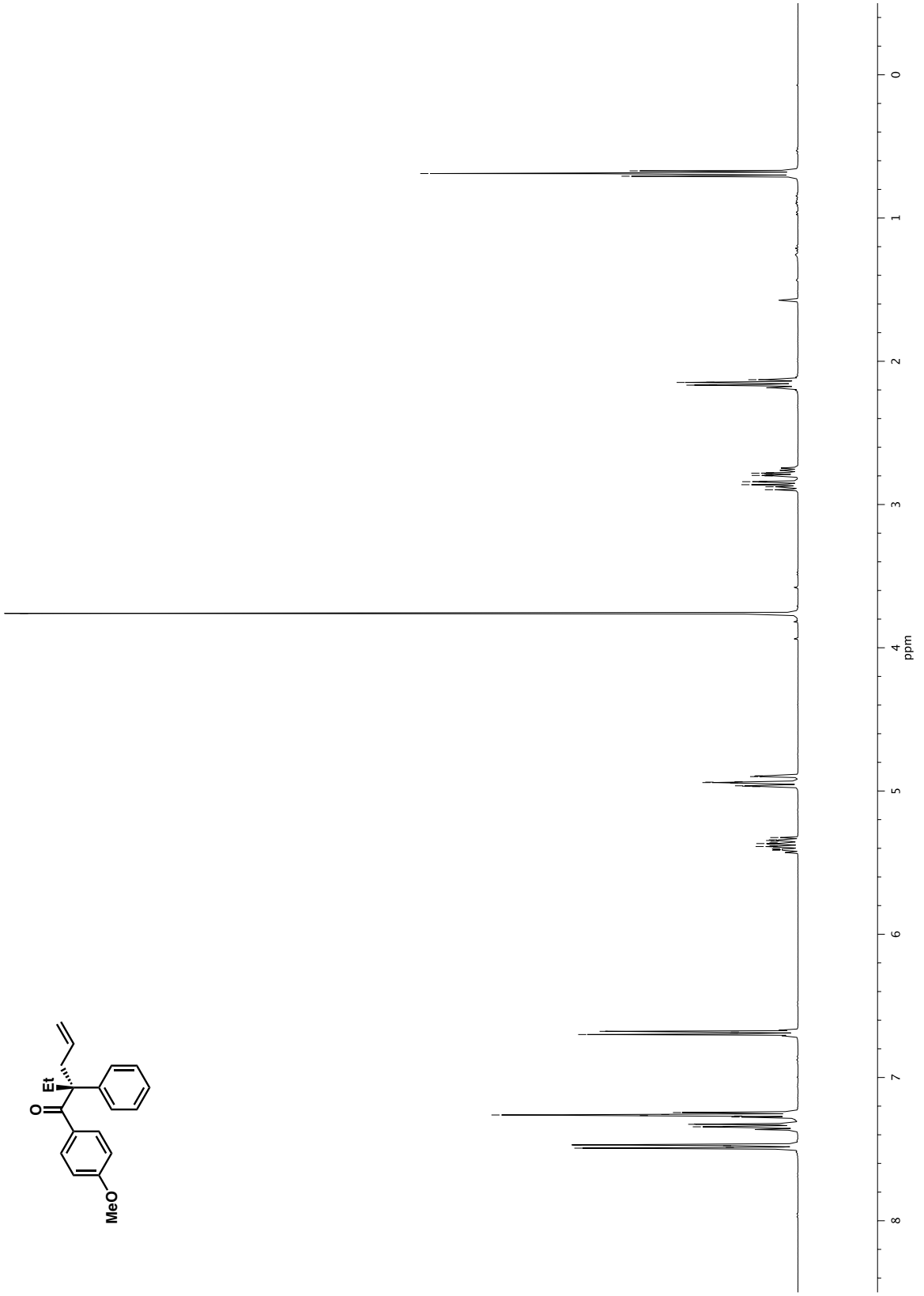



***Figure A4.26*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***21i****.*

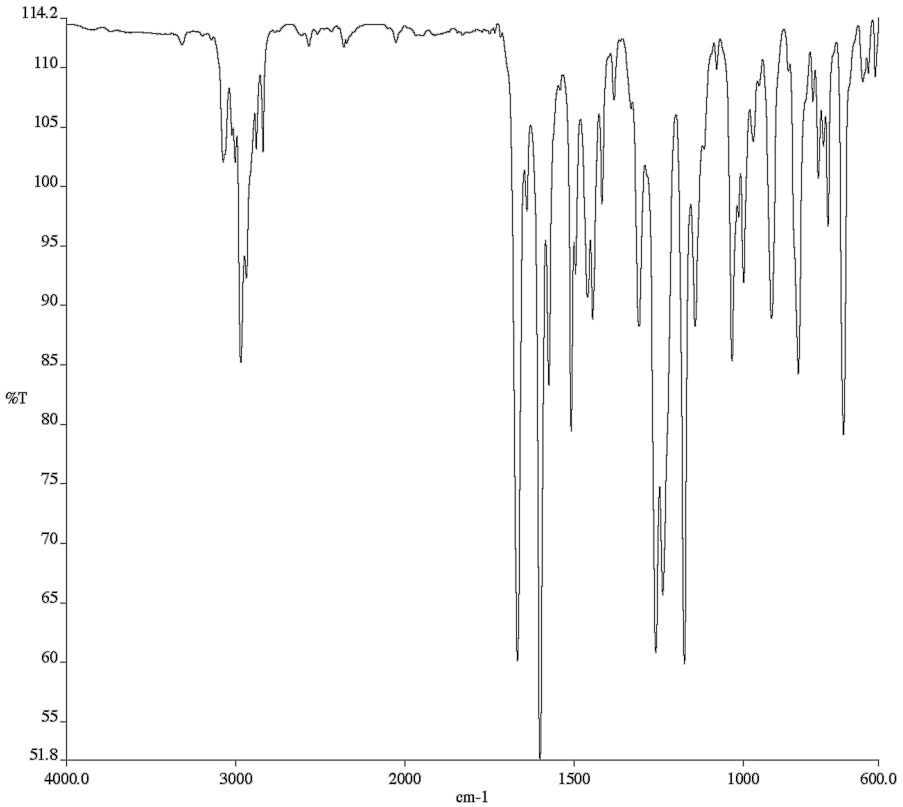



***Figure A4.27*** *Infrared spectrum (Thin Film, NaCl) of compound* ***21i****.*

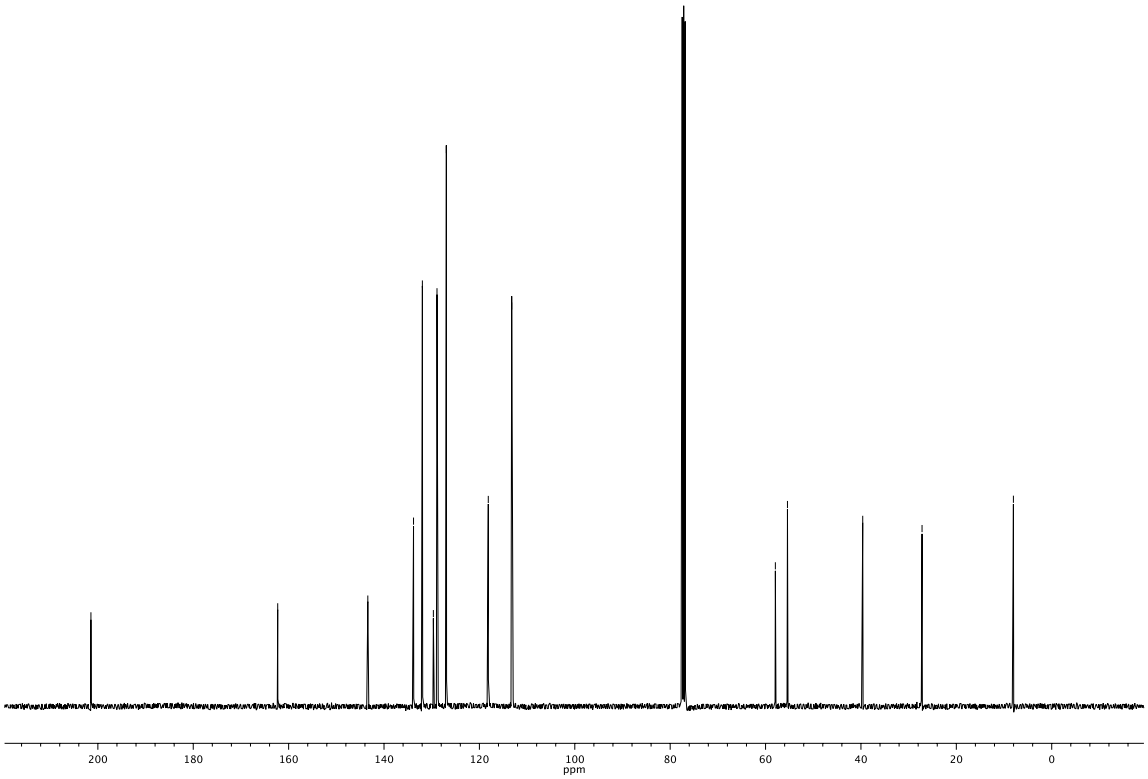



***Figure A4.28*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***21i****.*

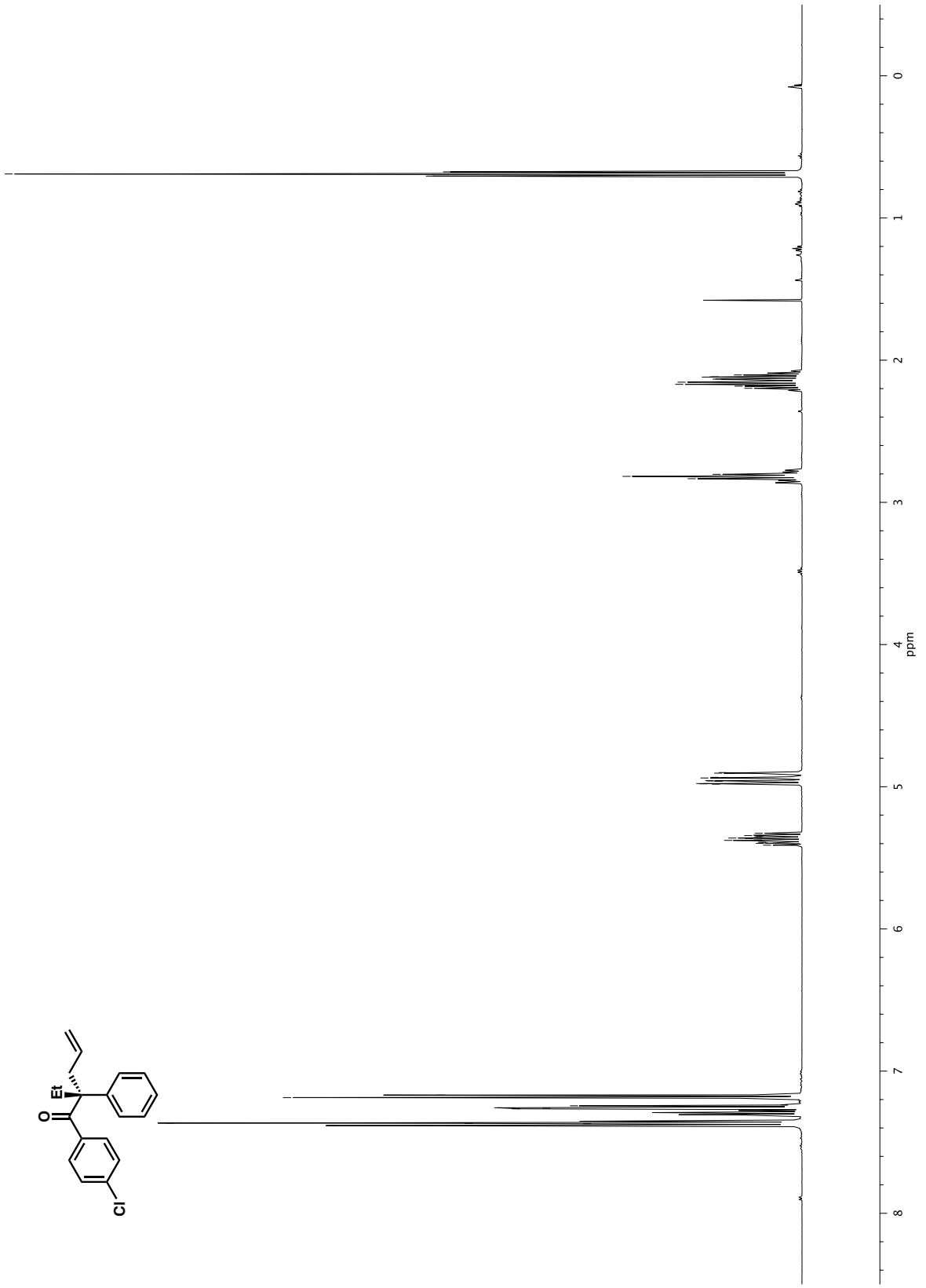



***Figure A4.29*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***21j****.*

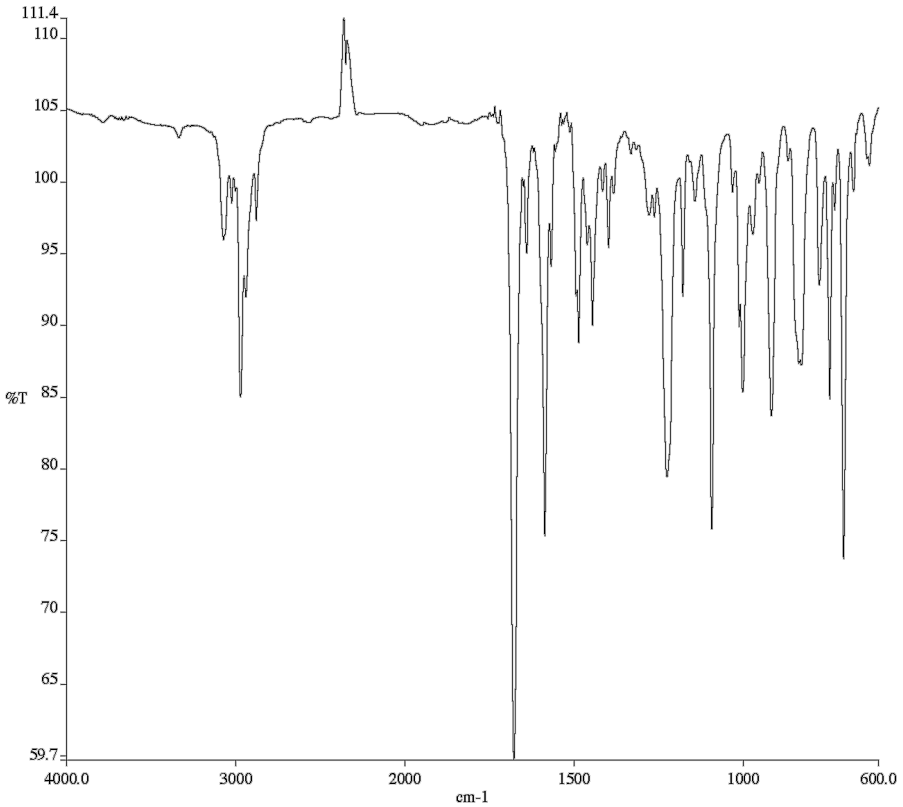



***Figure A4.30*** *Infrared spectrum (Thin Film, NaCl) of compound* ***21j****.*

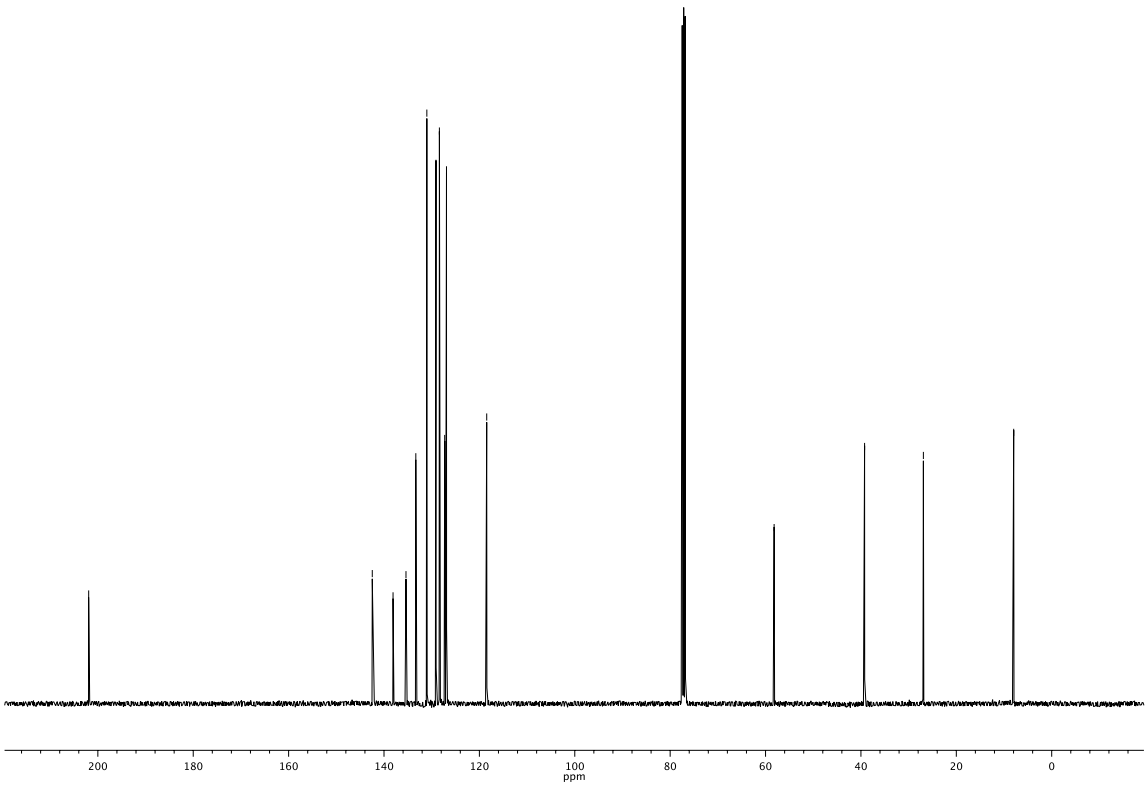



***Figure A4.31*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***21j****.*

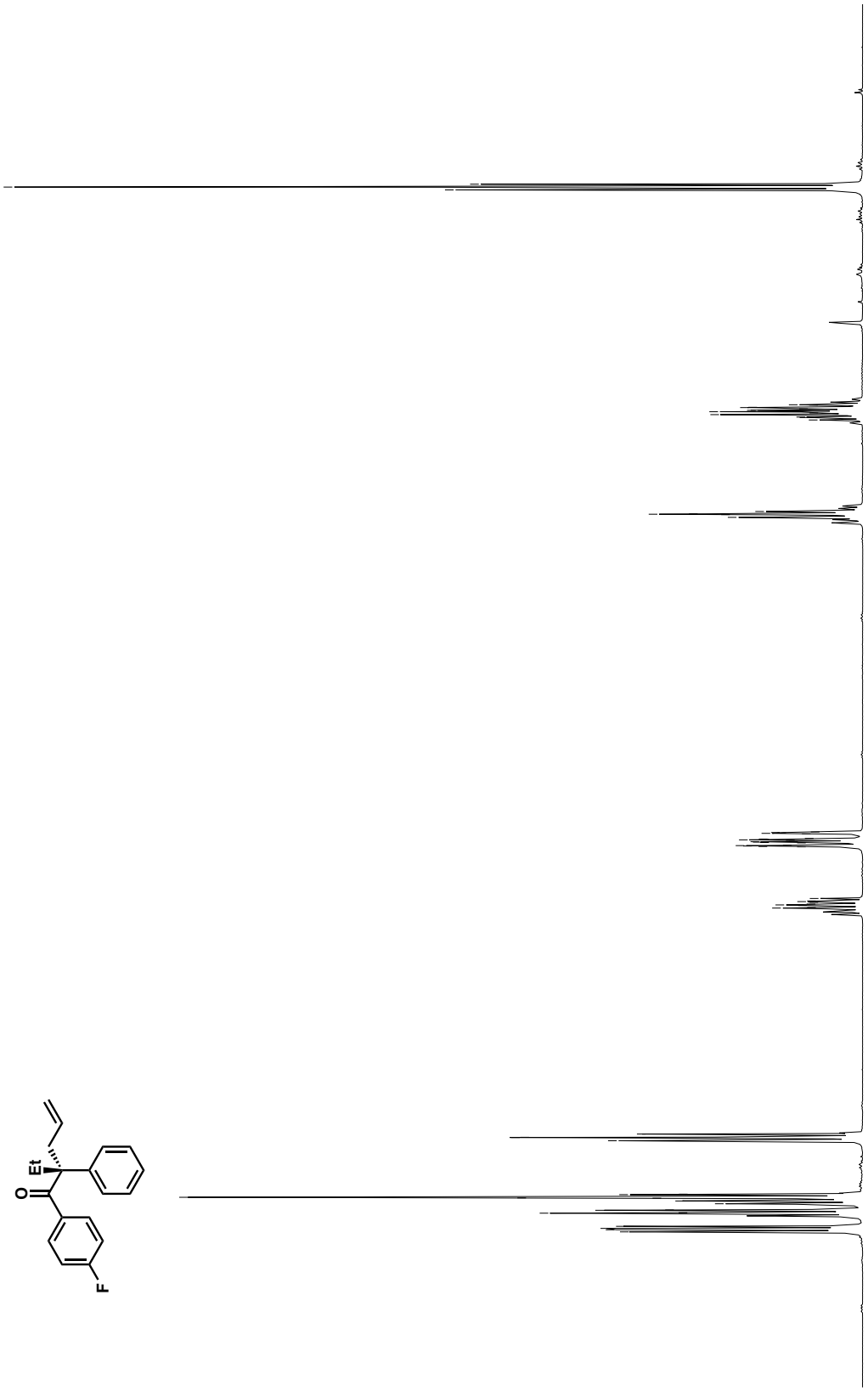



***Figure A4.32*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***21k****.*

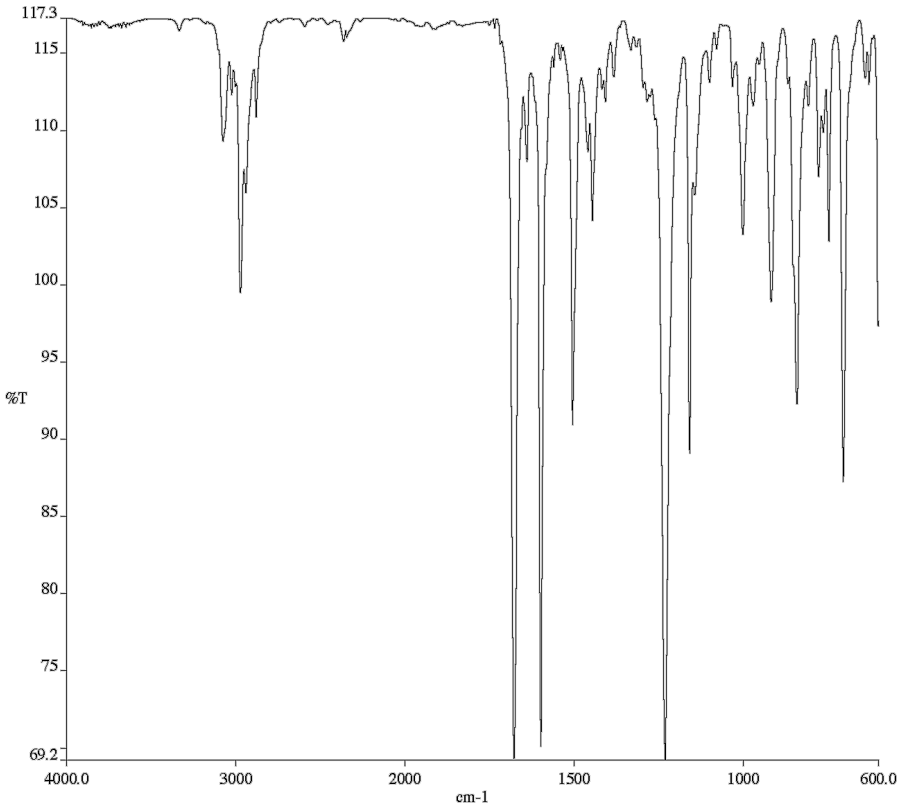



***Figure A4.33*** *Infrared spectrum (Thin Film, NaCl) of compound* ***21k****.*

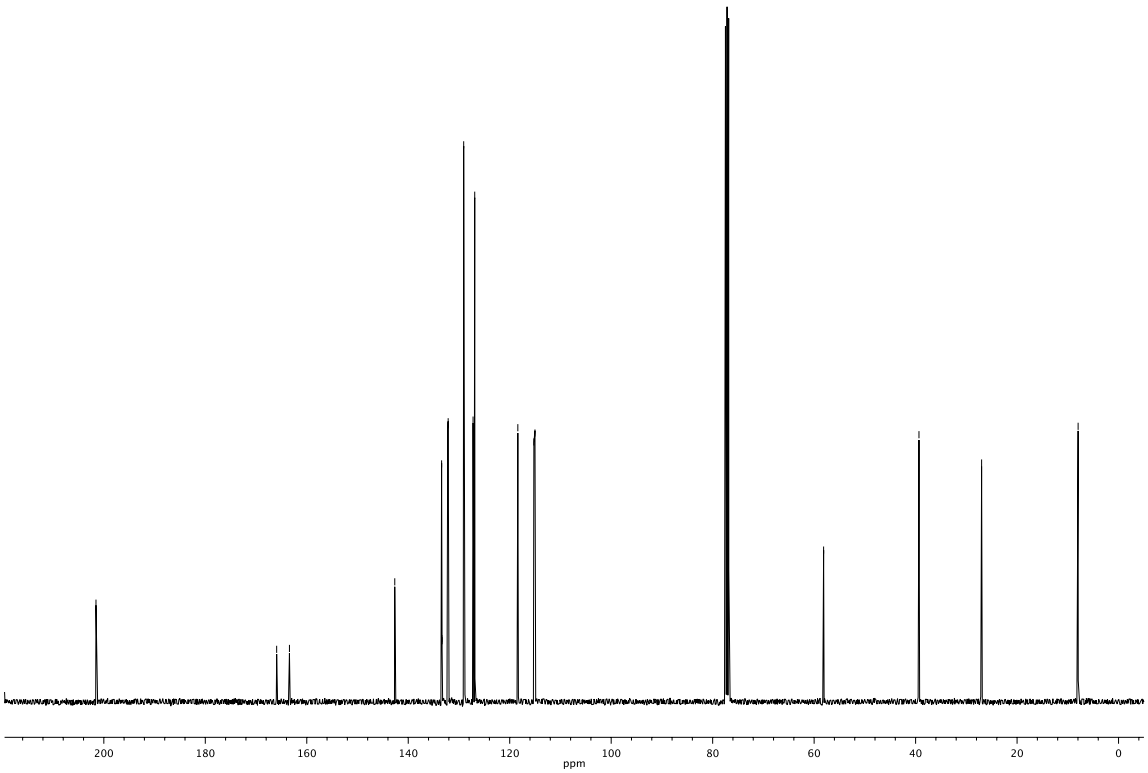



***Figure A4.34*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***21k****.*

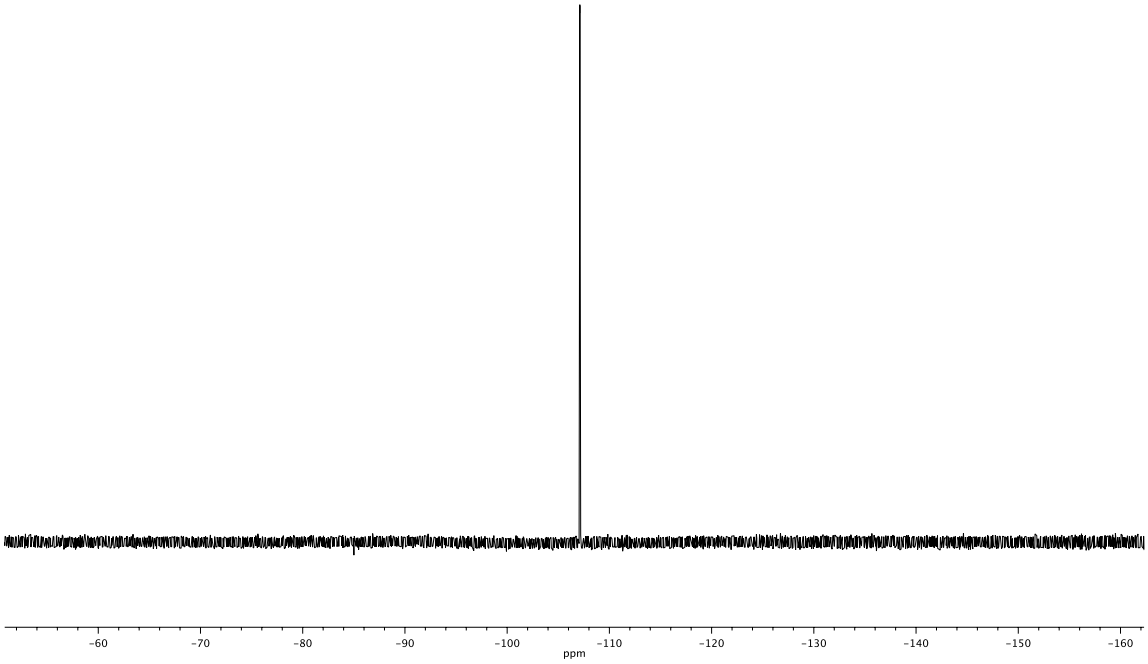



***Figure A4.35*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***21k***.

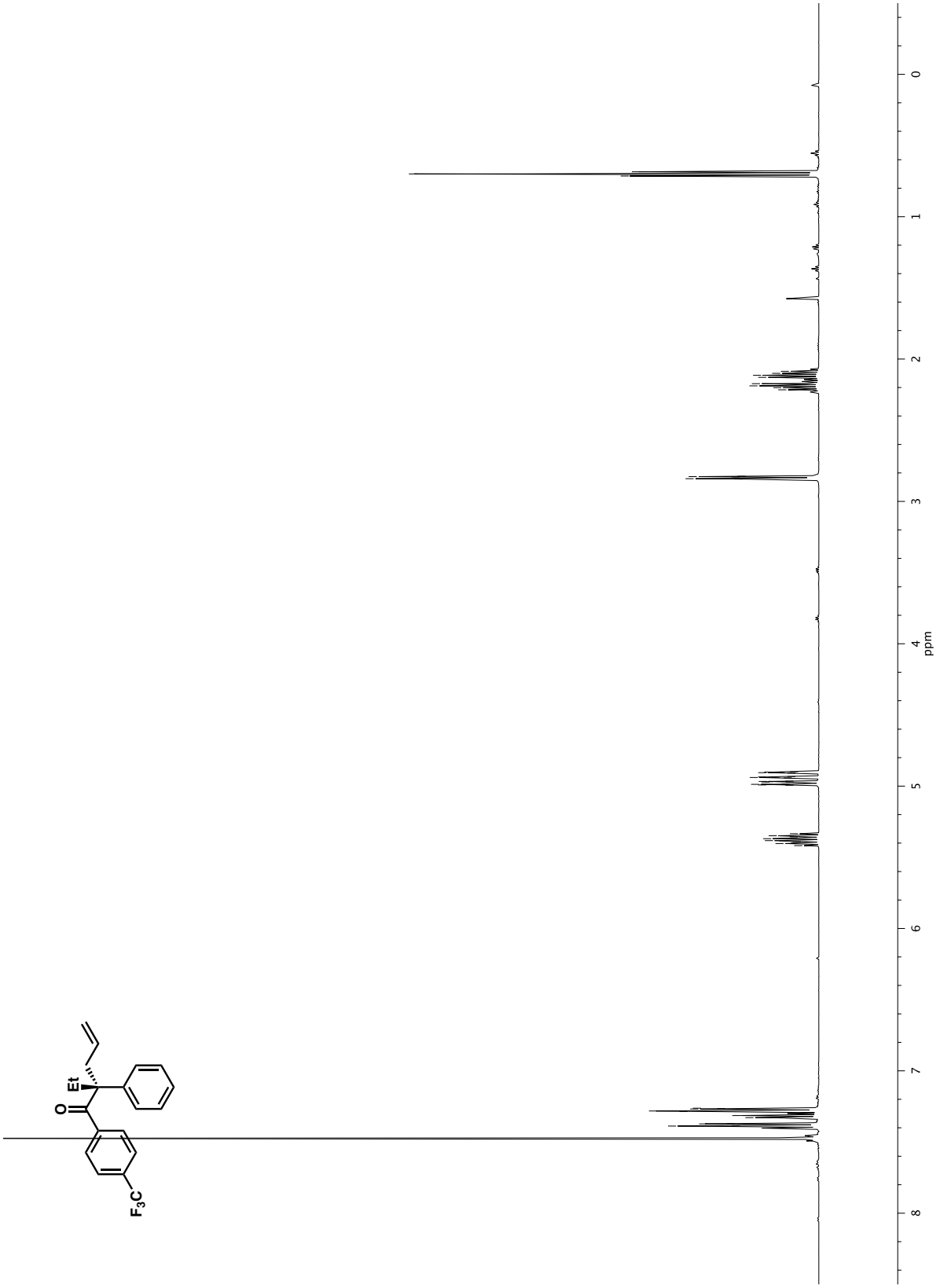



***Figure A4.36*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***21l****.*

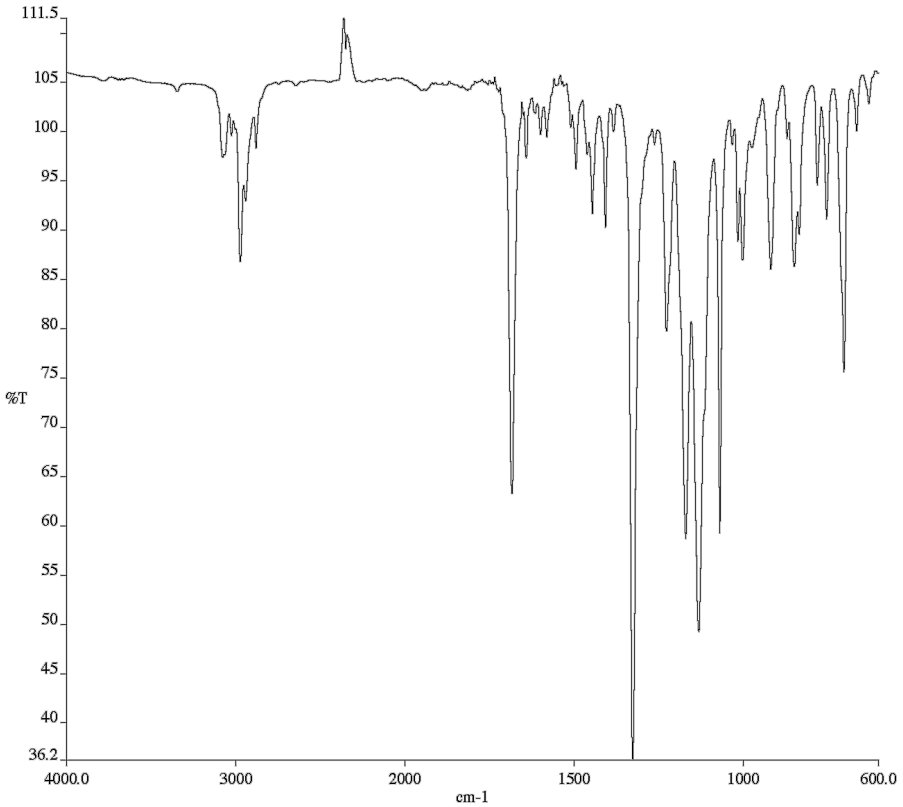



***Figure A4.37*** *Infrared spectrum (Thin Film, NaCl) of compound* ***21l****.*

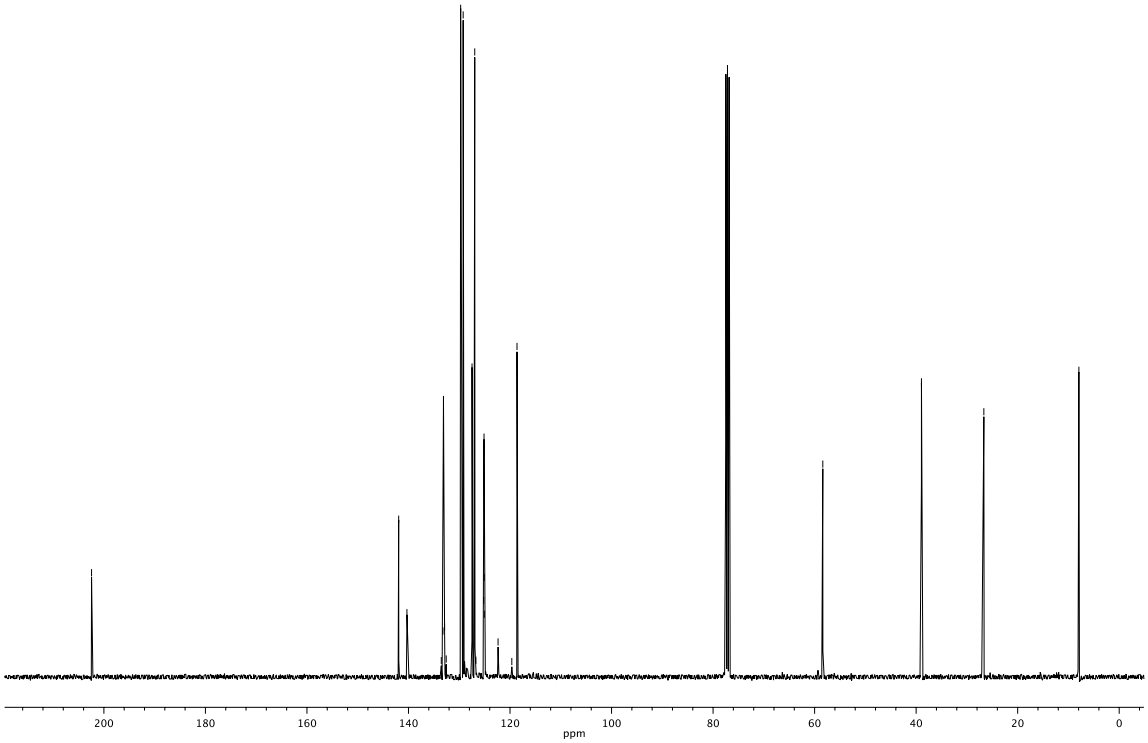



***Figure A4.38*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***21l****.*

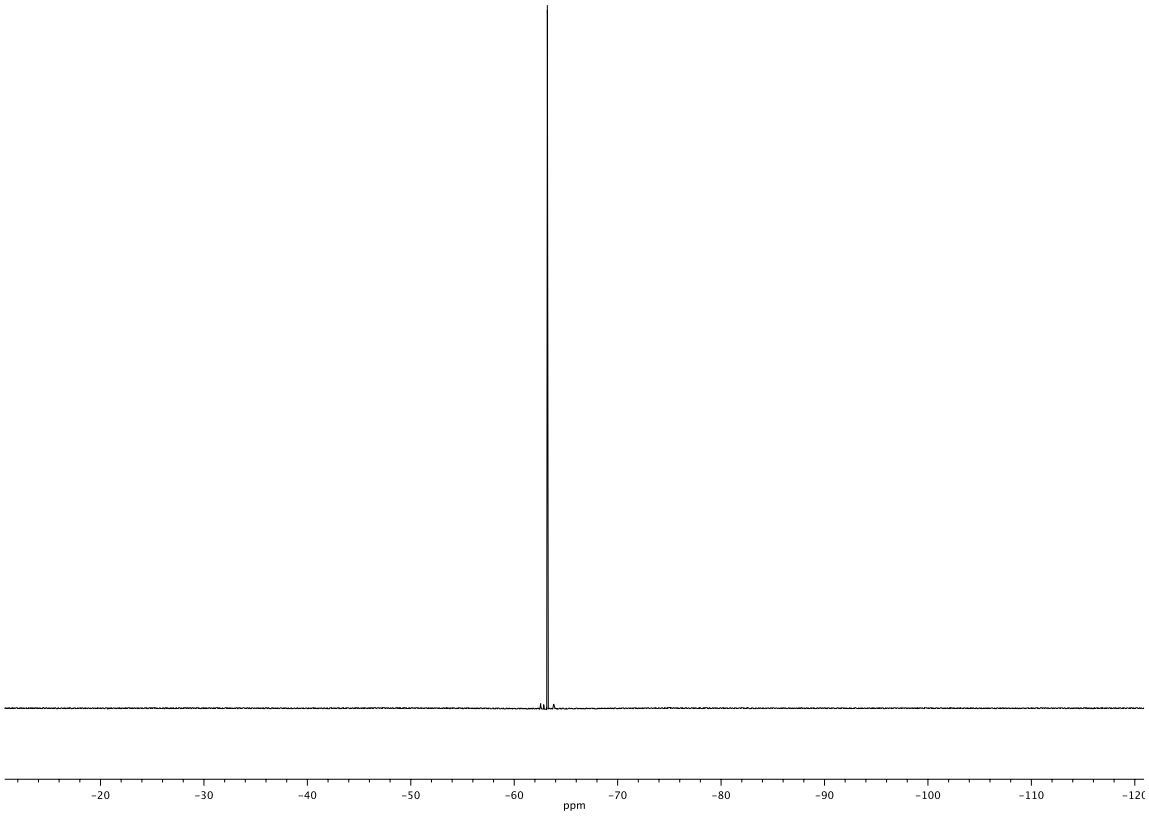



***Figure A4.39*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***21l****.*

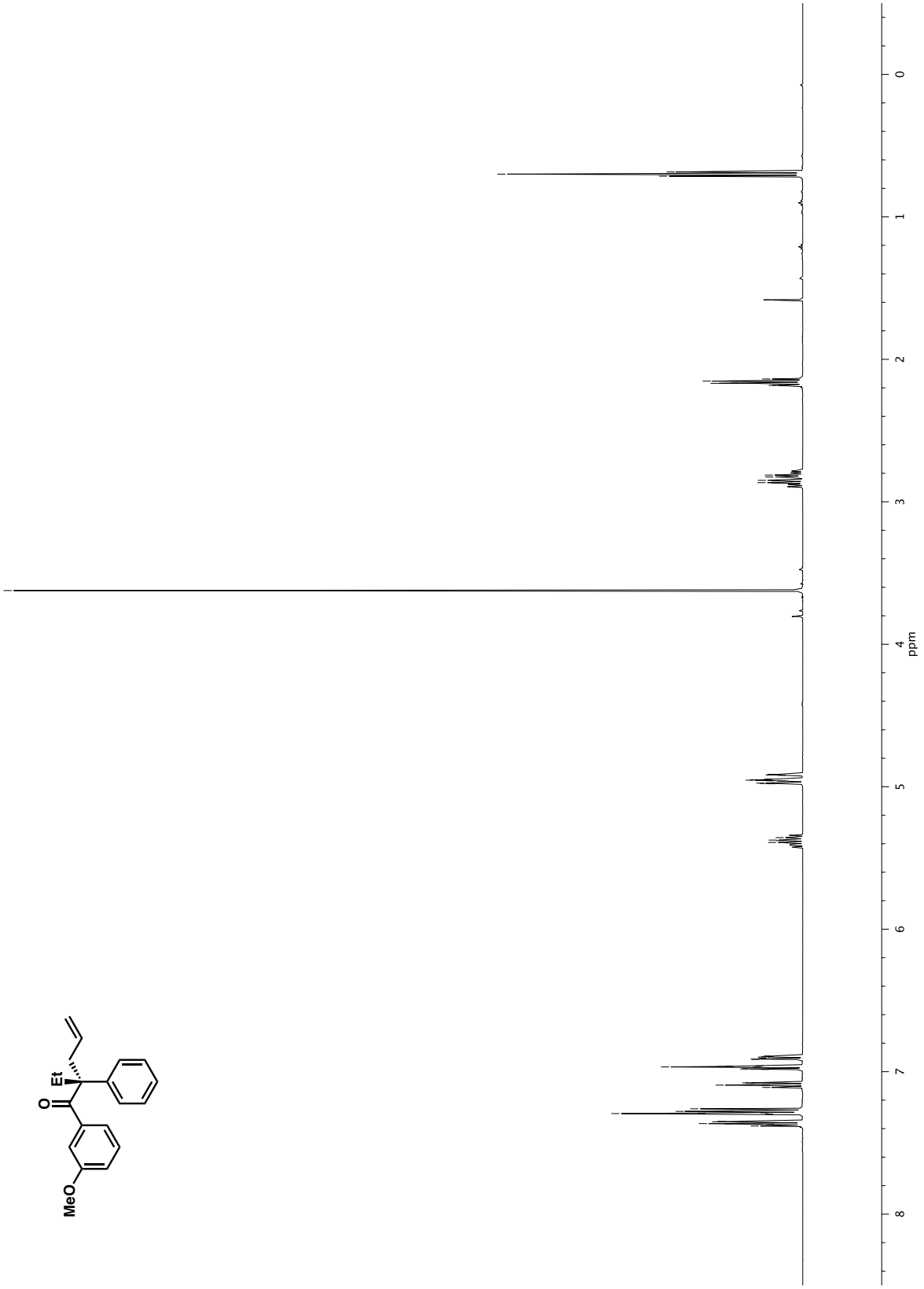



***Figure A4.40*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***21m****.*

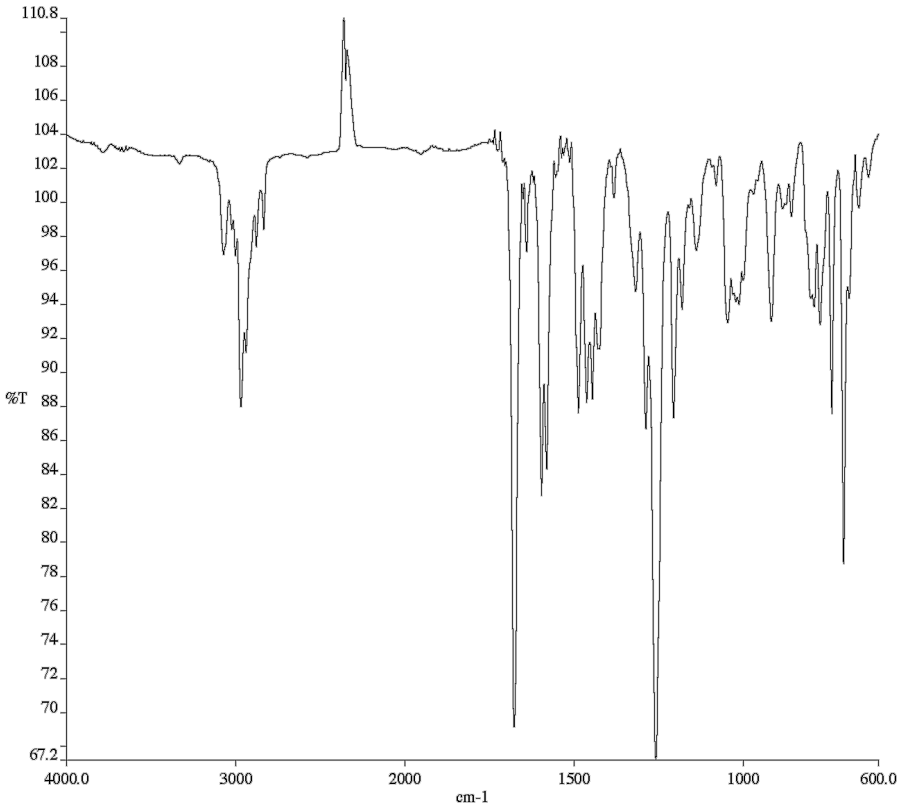



***Figure A4.41*** *Infrared spectrum (Thin Film, NaCl) of compound* ***21m****.*

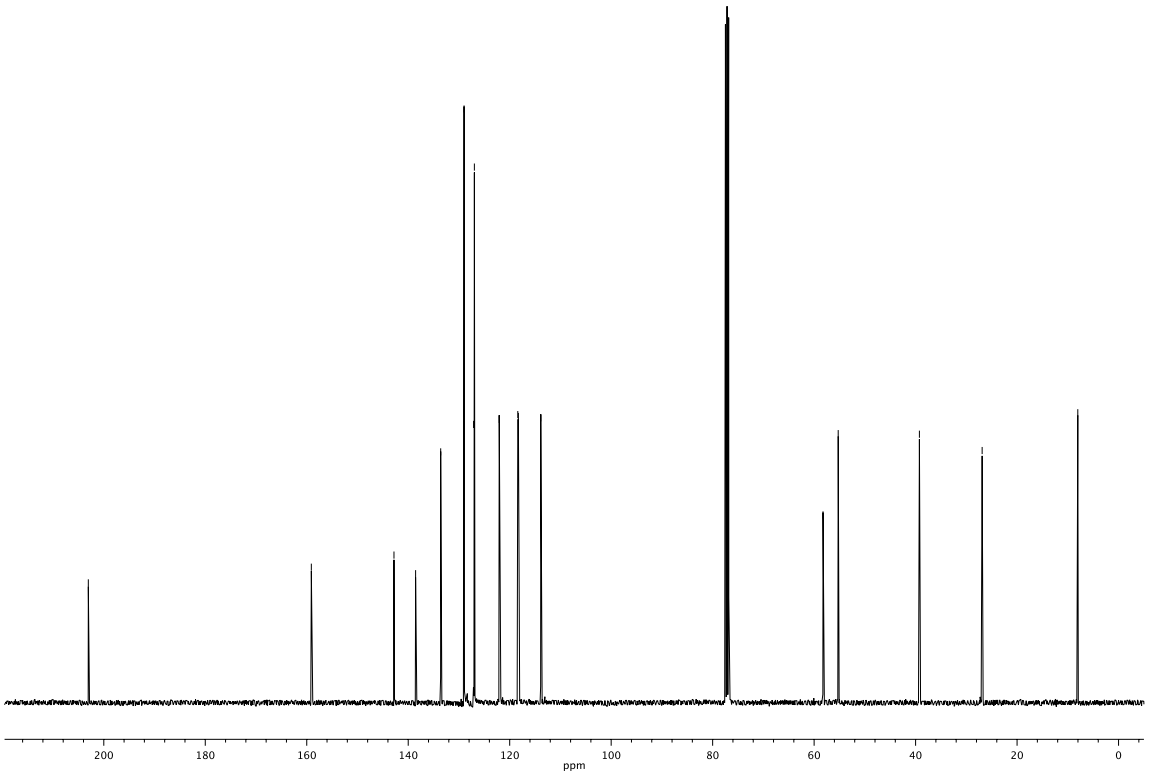



***Figure A4.42*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***21m****.*

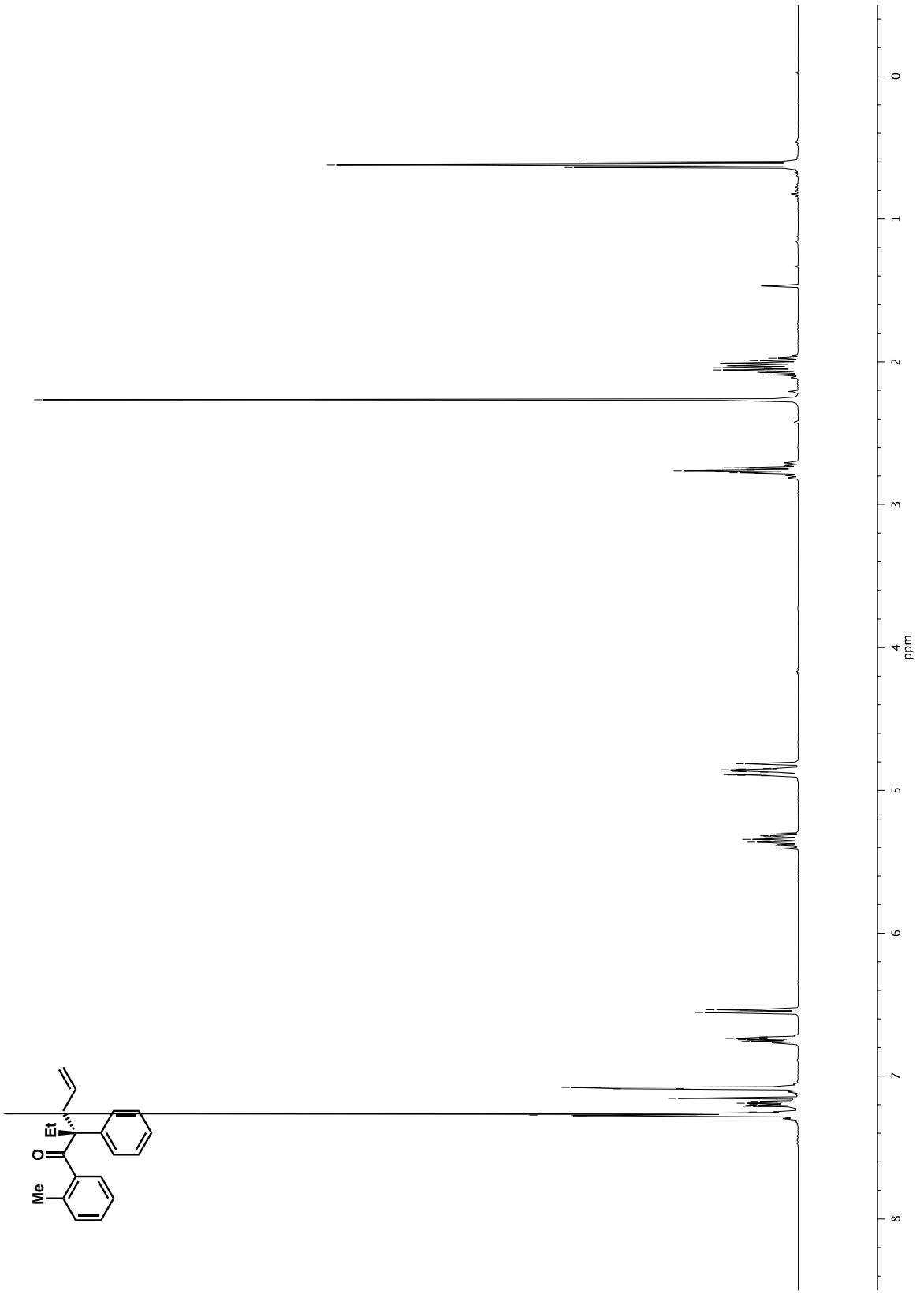



***Figure A4.43*** *$^{1}H$ NMR (400 MHz, $CDCl_3$) of compound* ***21n***.

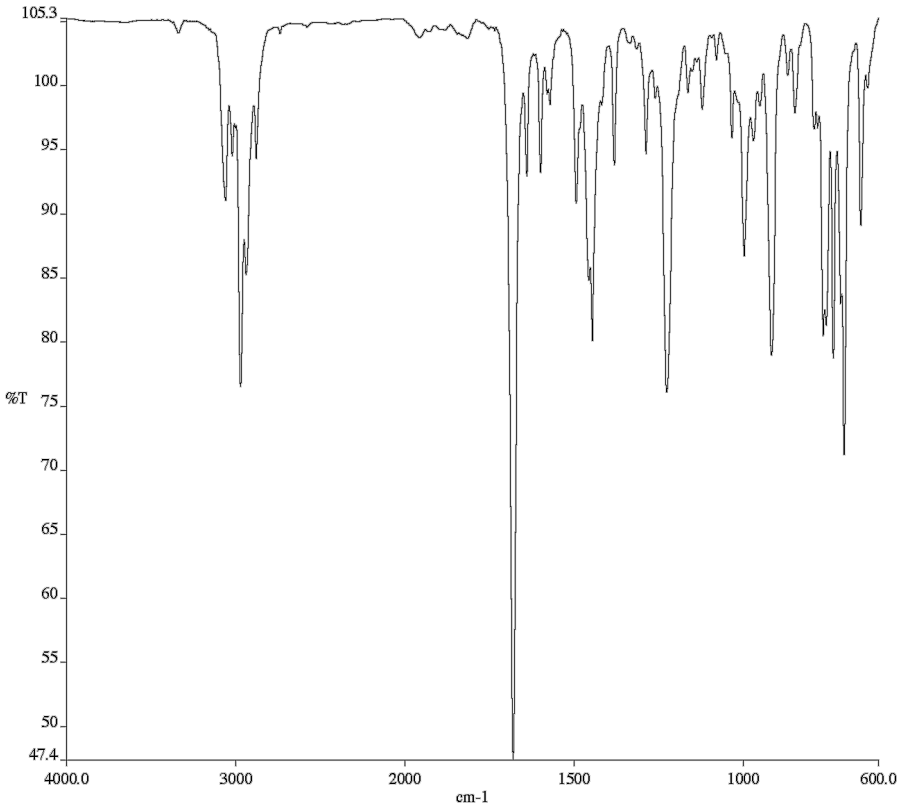



***Figure A4.44*** *Infrared spectrum (Thin Film, NaCl) of compound* ***21n***.

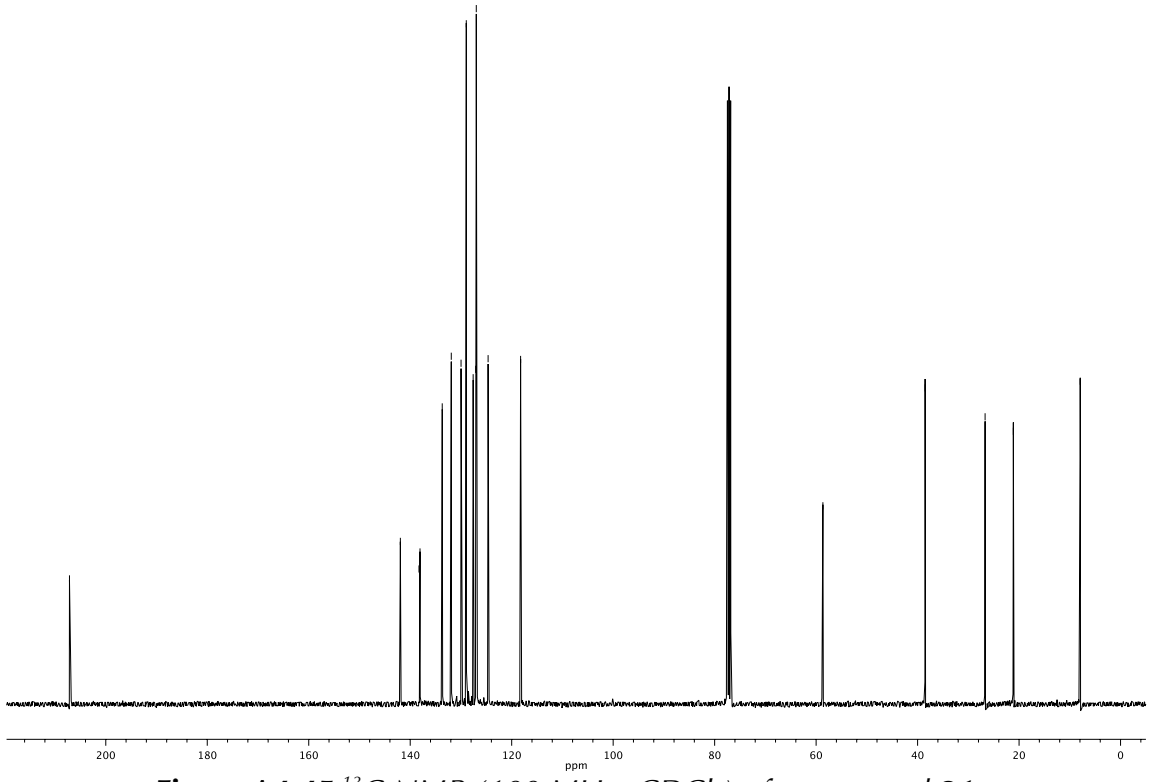



***Figure A4.45*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***21n***.

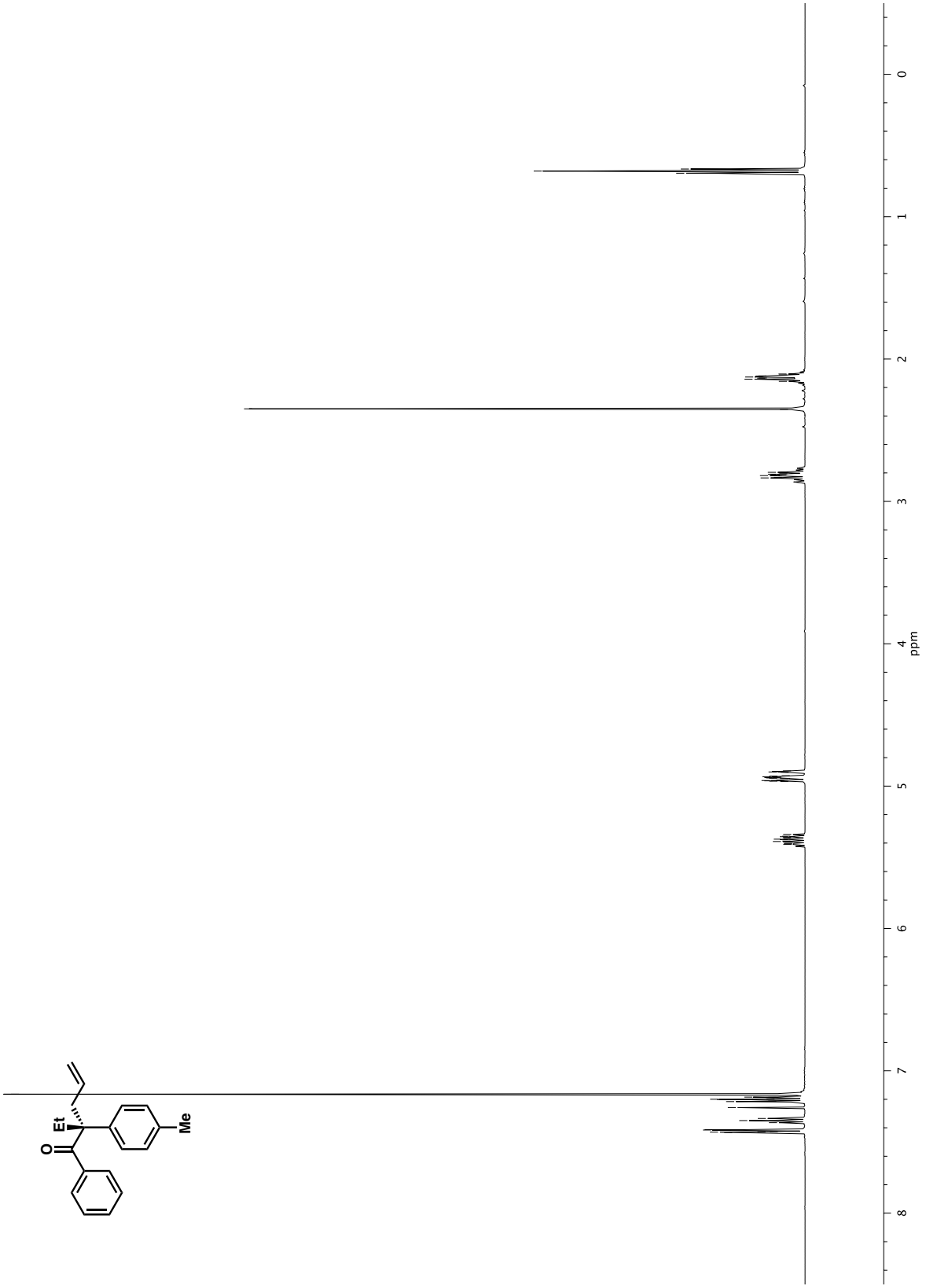



***Figure A4.46*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***21o***.

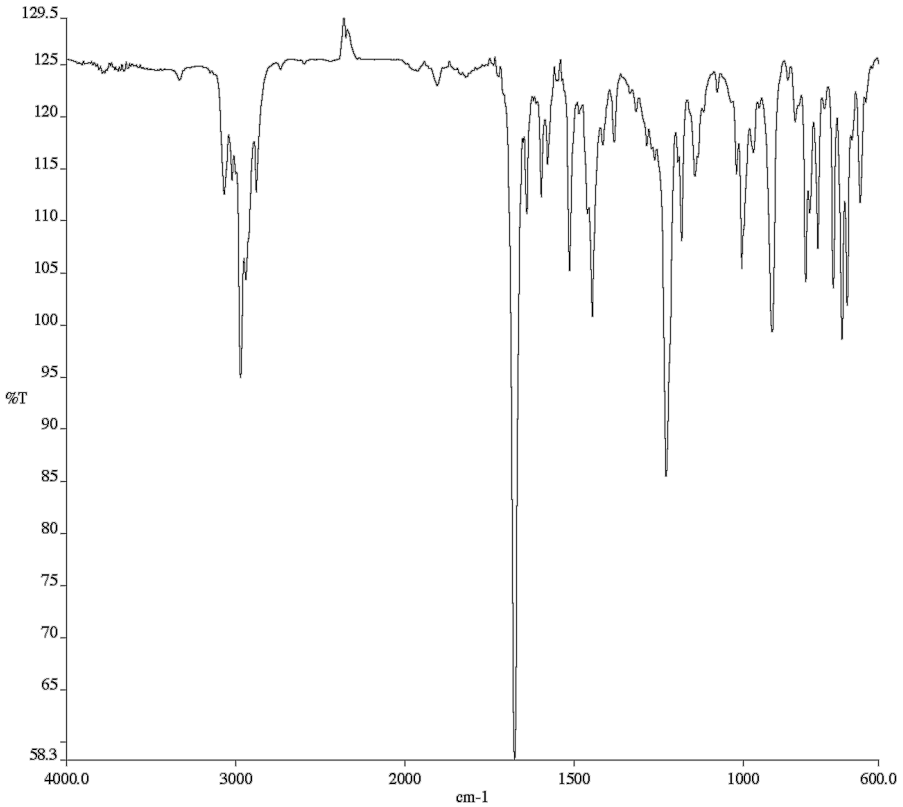



***Figure A4.47*** *Infrared spectrum (Thin Film, NaCl) of compound* ***21o***.

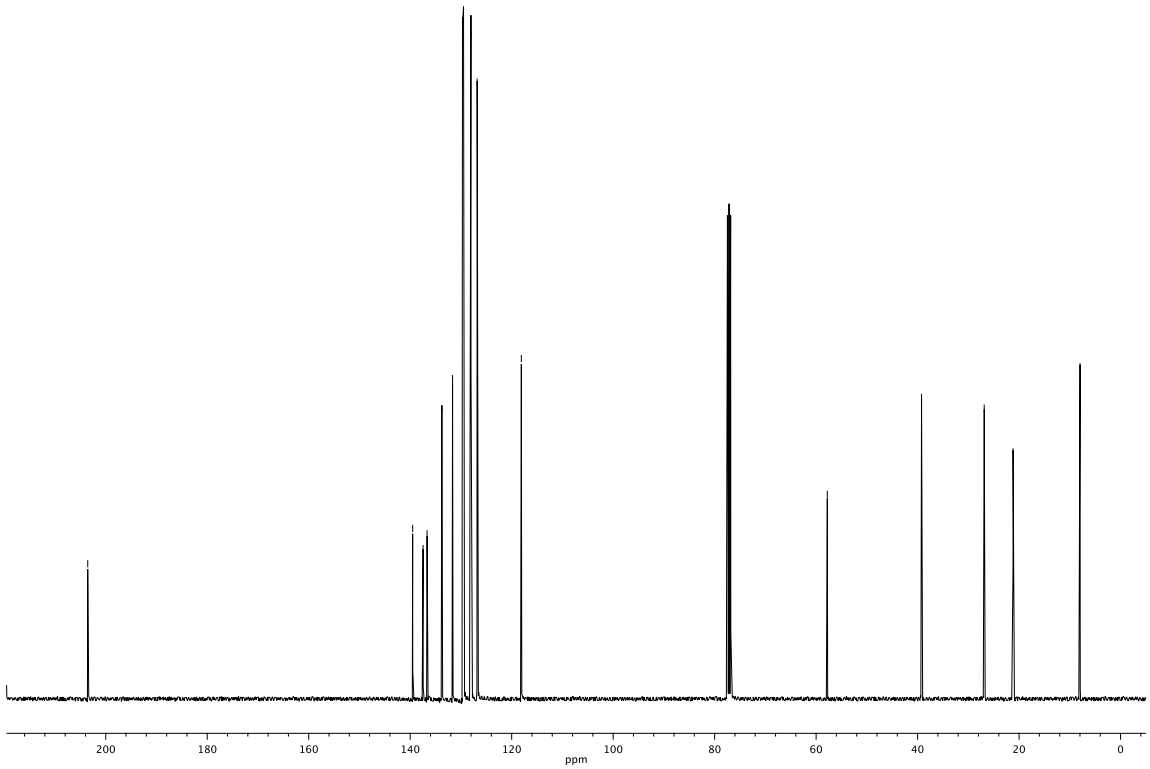



***Figure A4.48*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***21o***.

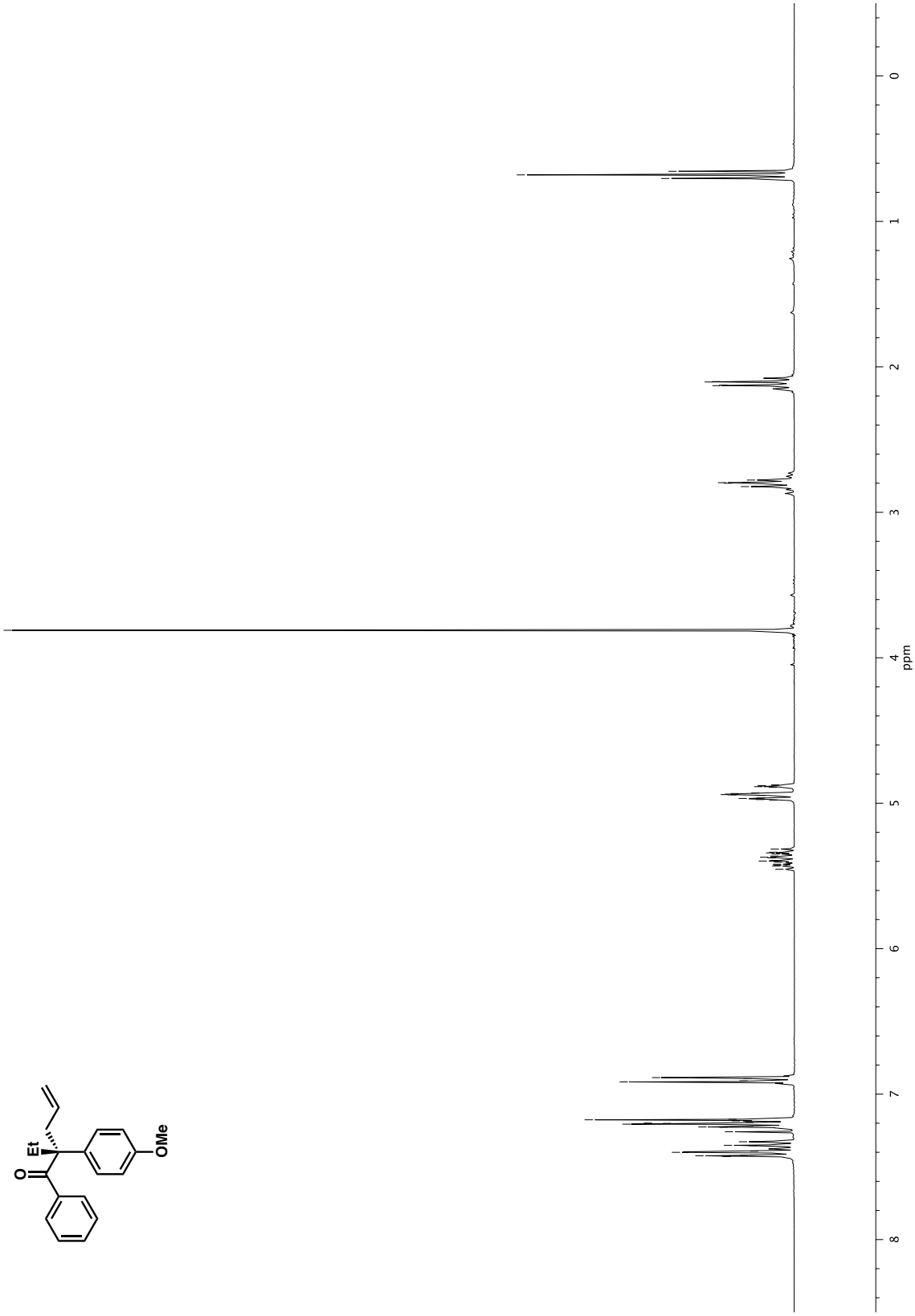



***Figure A4.49*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***21p***.

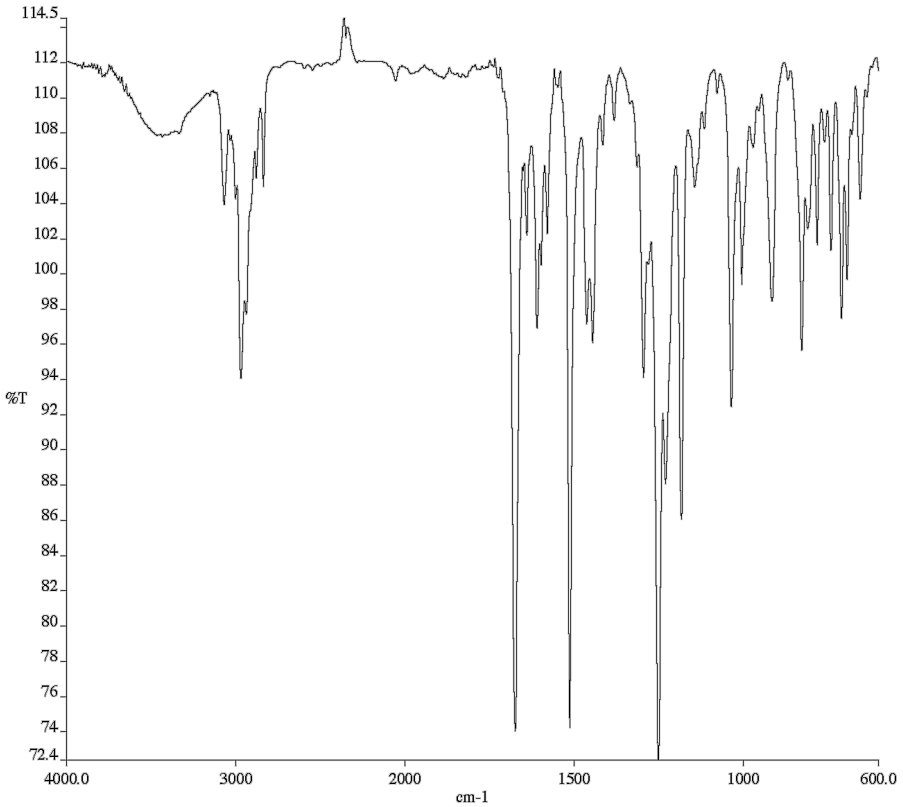



***Figure A4.50*** *Infrared spectrum (Thin Film, NaCl) of compound* ***21p***.

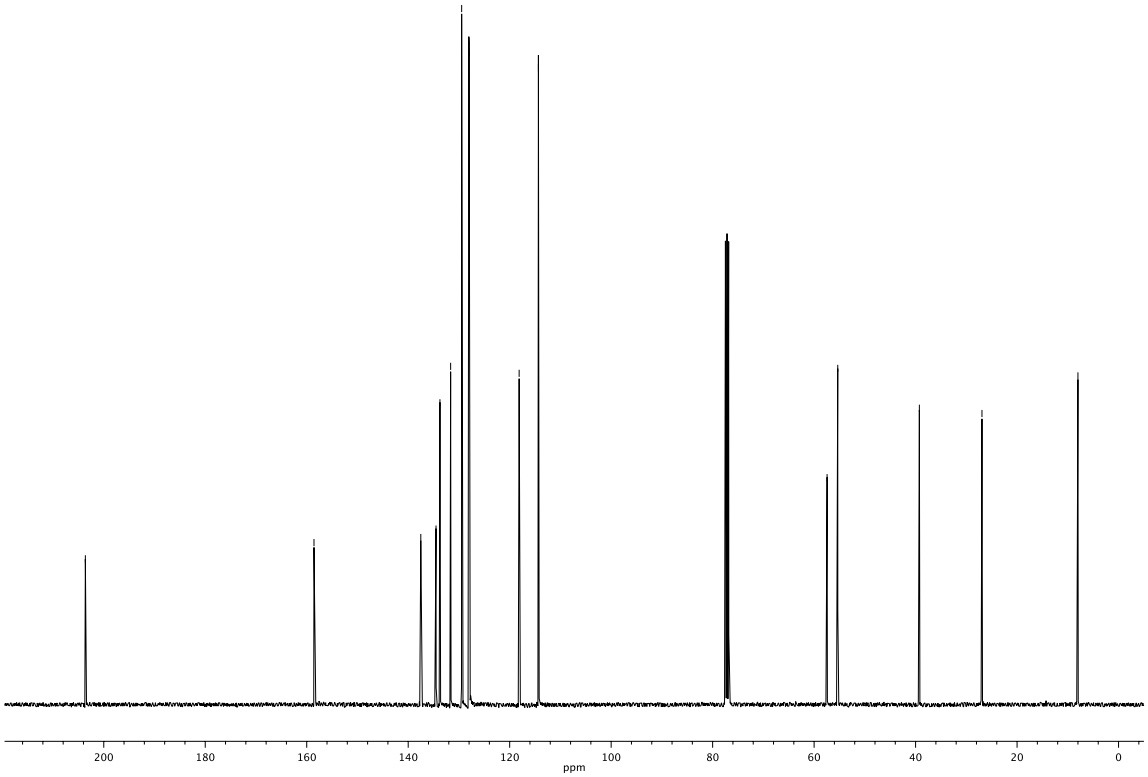



***Figure A4.51*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***21p***.

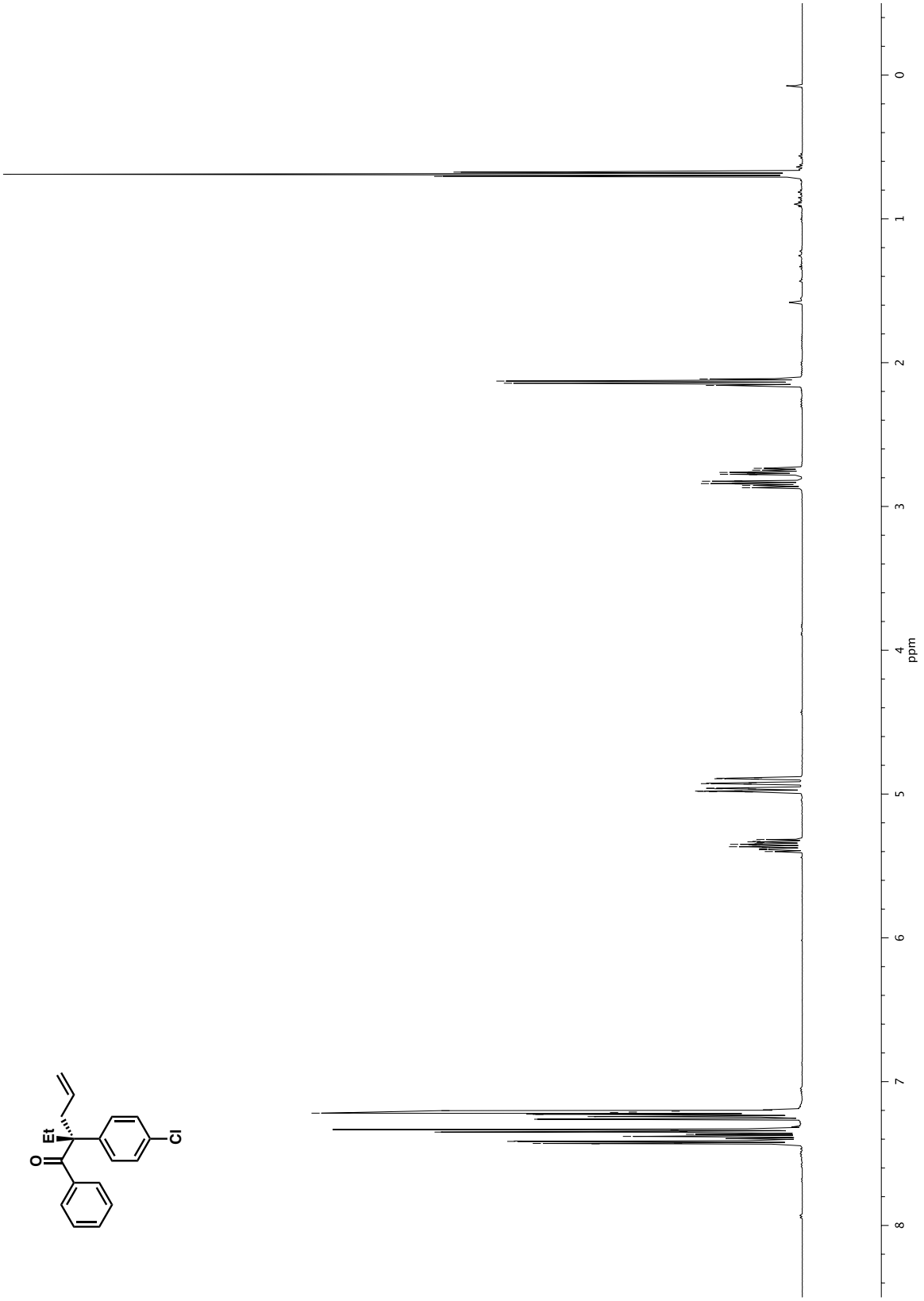



***Figure A4.52*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***21q***.

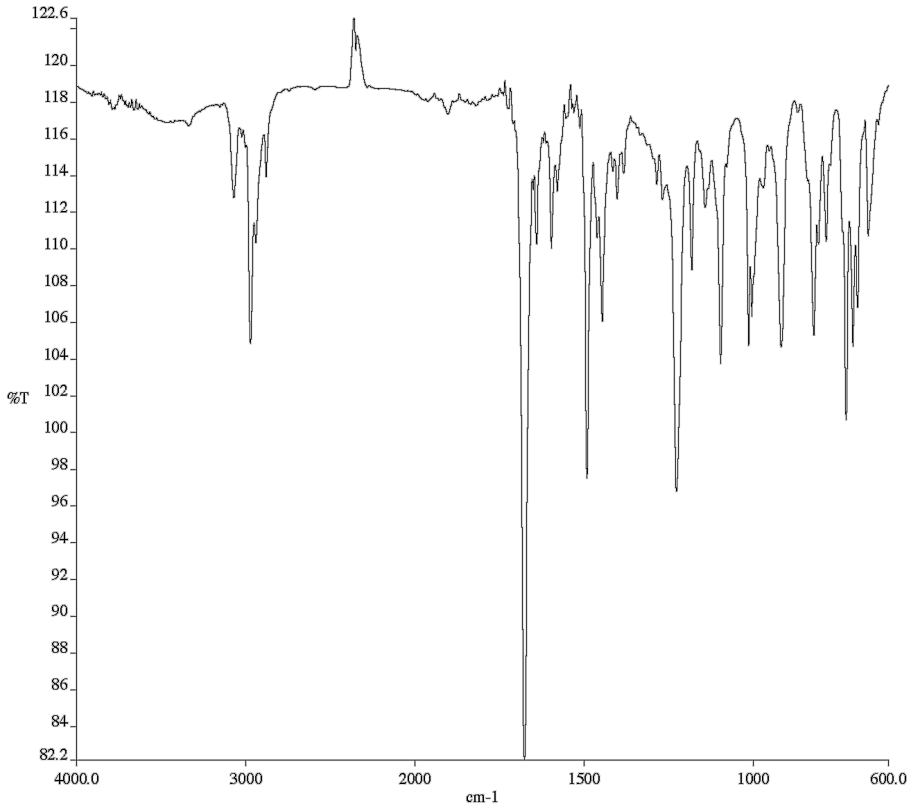



***Figure A4.53*** *Infrared spectrum (Thin Film, NaCl) of compound* ***21q***.

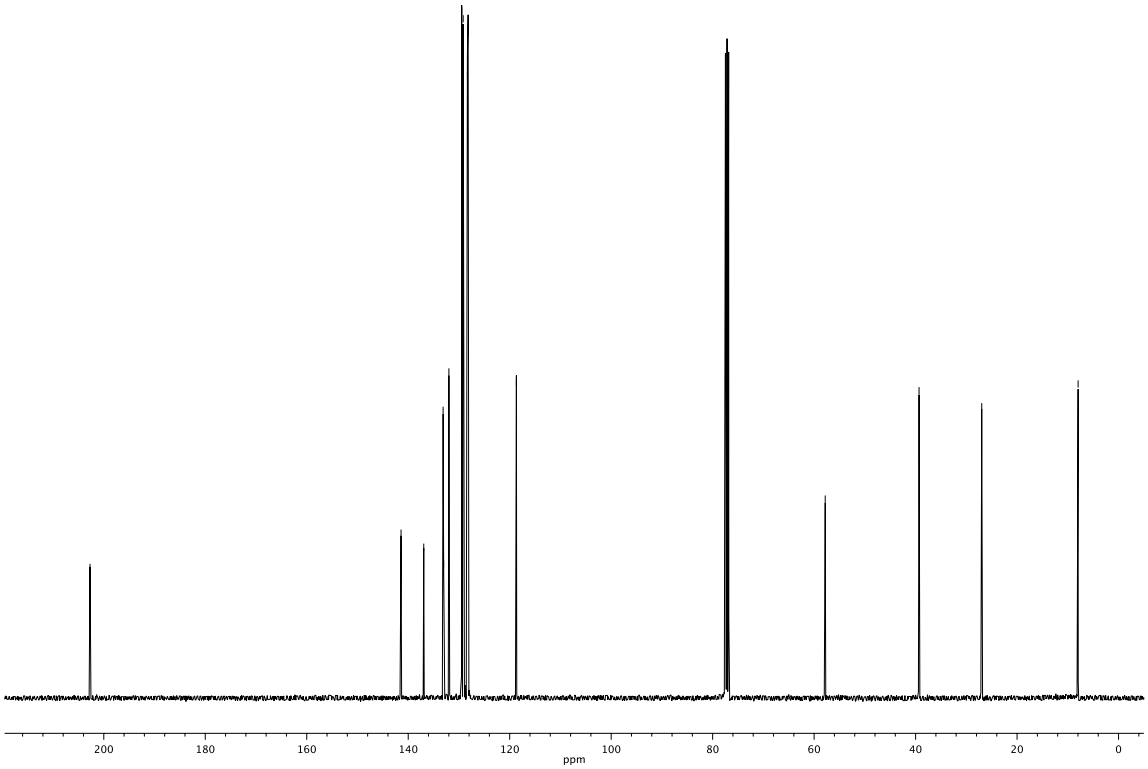



***Figure A4.54*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***21q***.

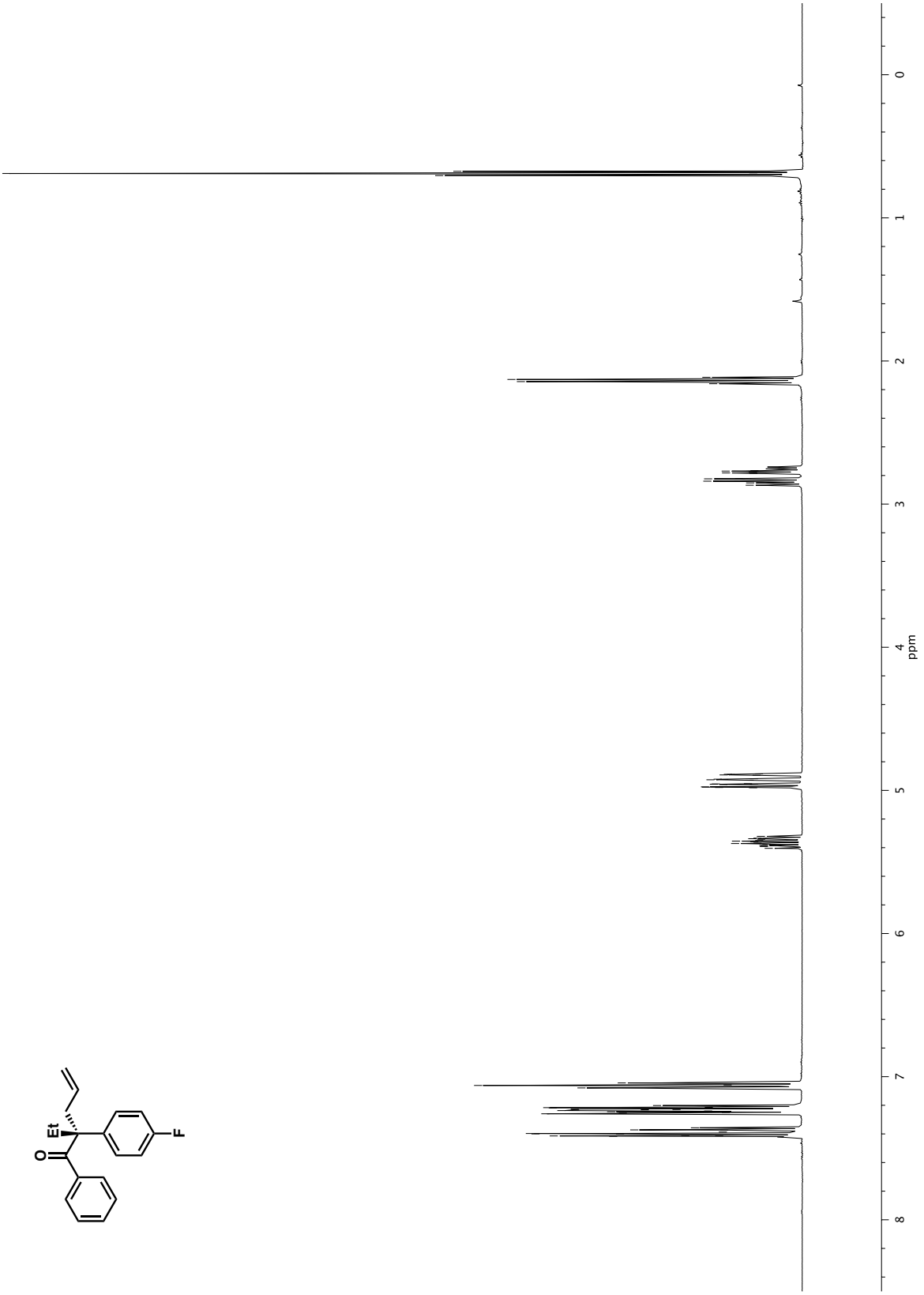



***Figure A4.55*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***21r****.*

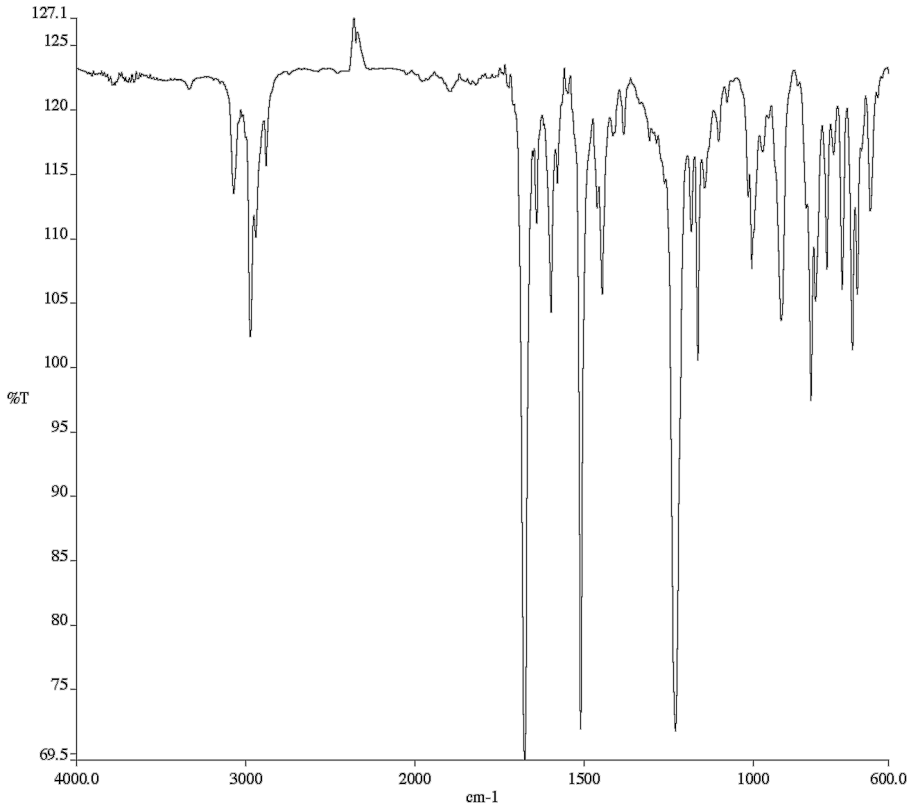



***Figure A4.56*** *Infrared spectrum (Thin Film, NaCl) of compound* ***21r****.*

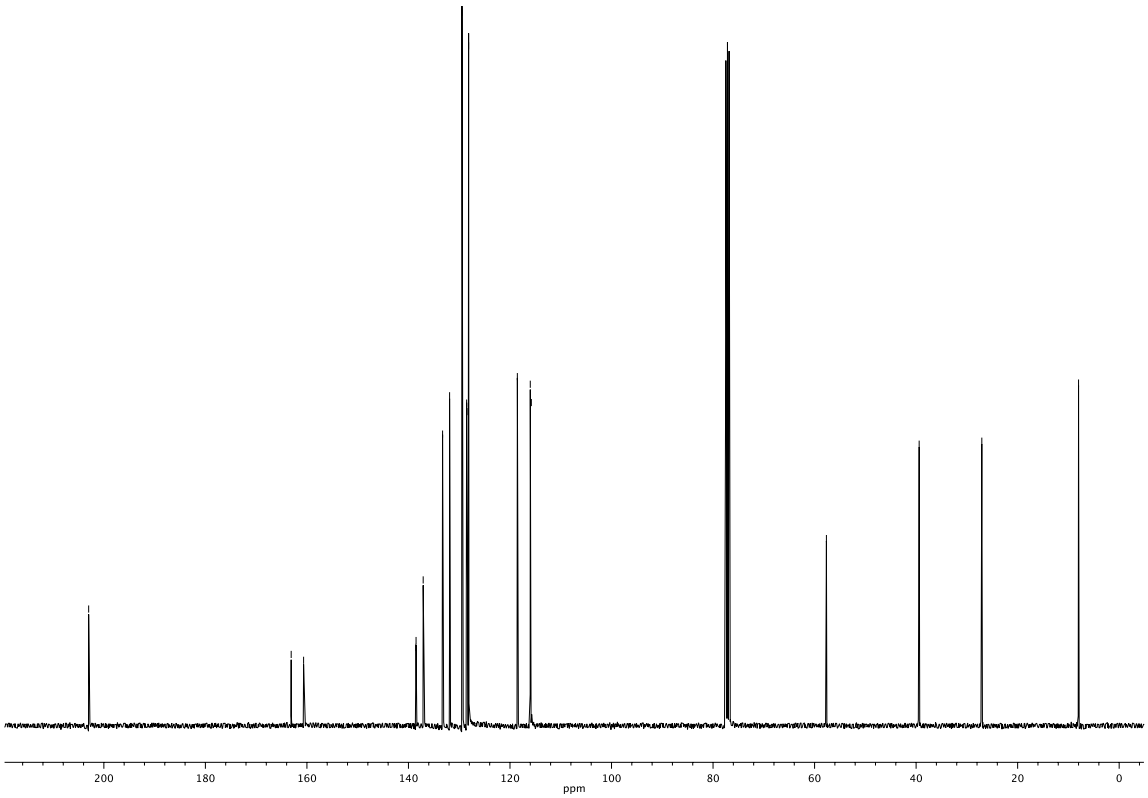



***Figure A4.57*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***21r****.*

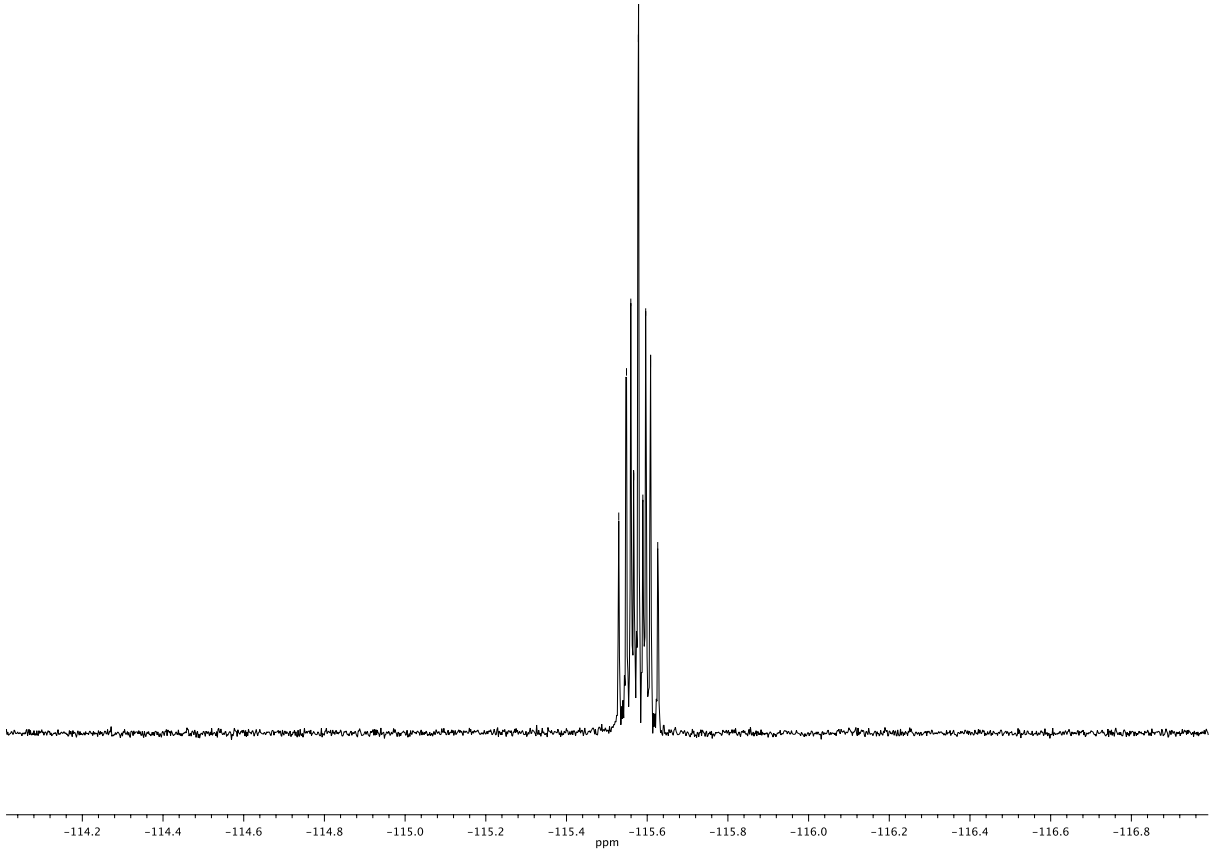



***Figure A4.58*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***21r***.

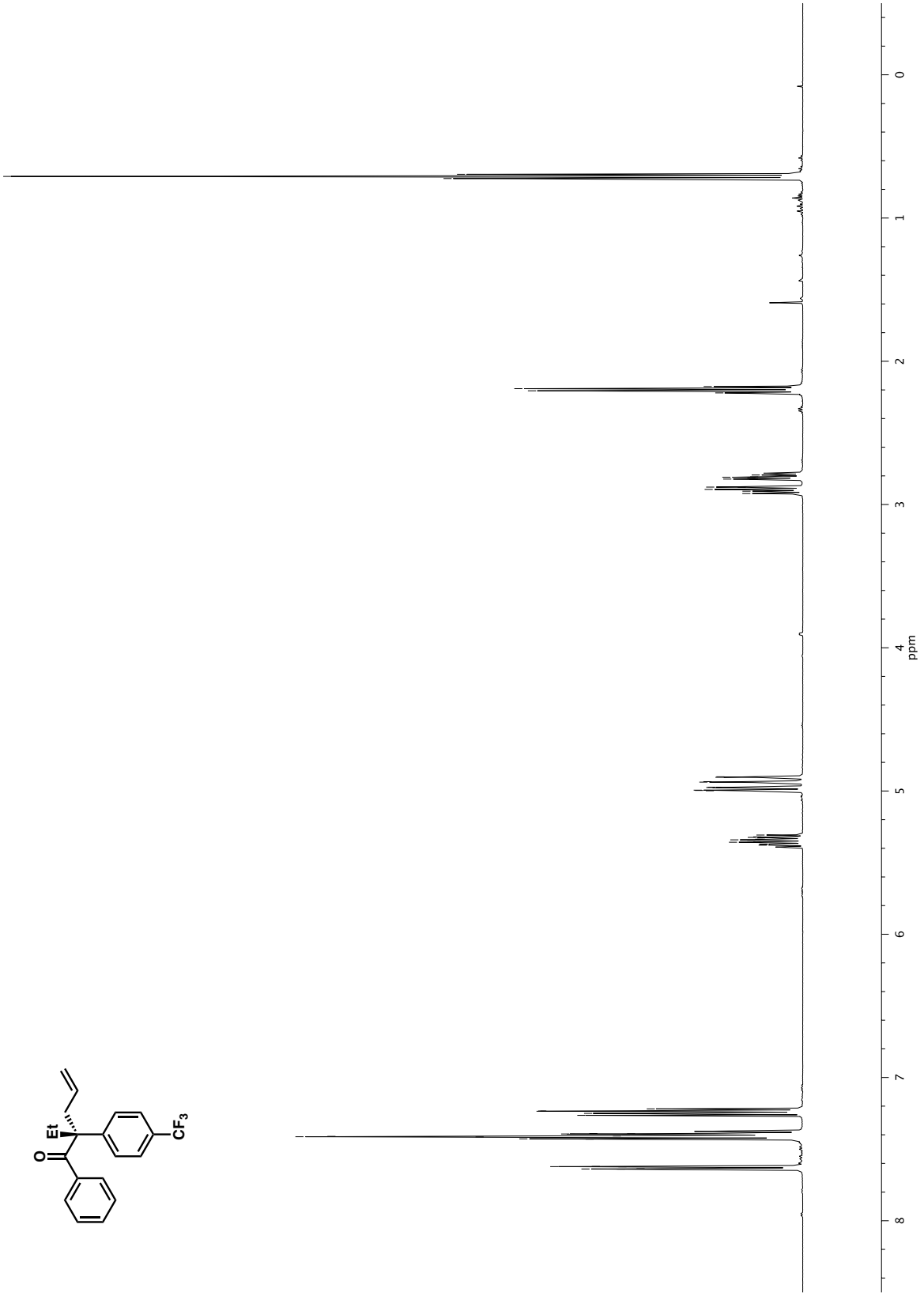



***Figure A4.59*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***21s****.*

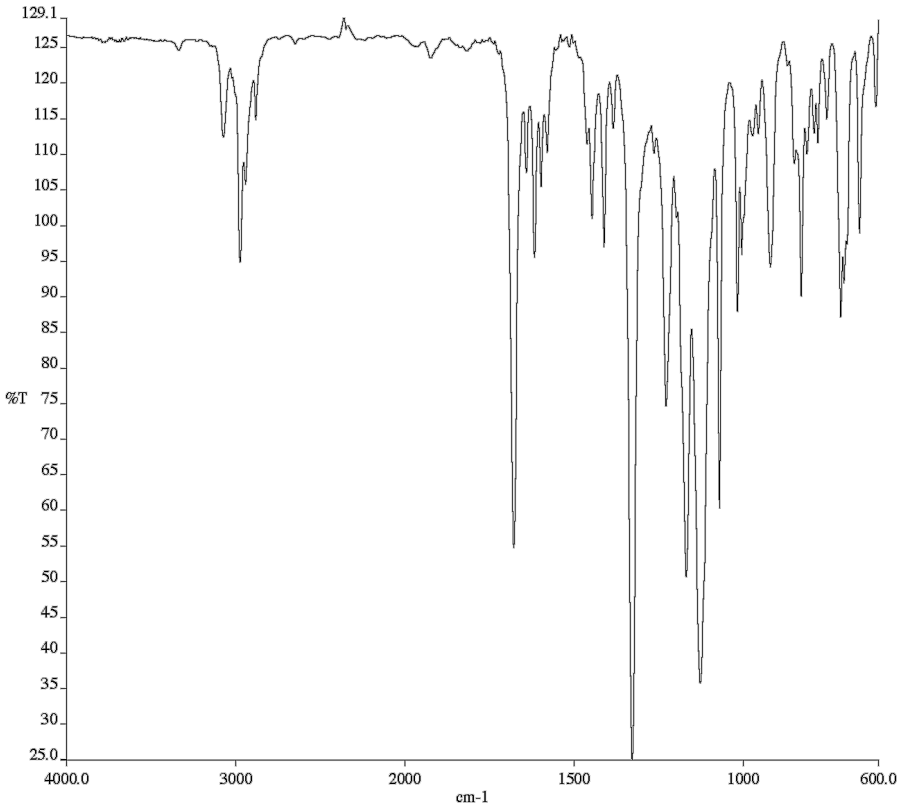



***Figure A4.60*** *Infrared spectrum (Thin Film, NaCl) of compound* ***21s****.*

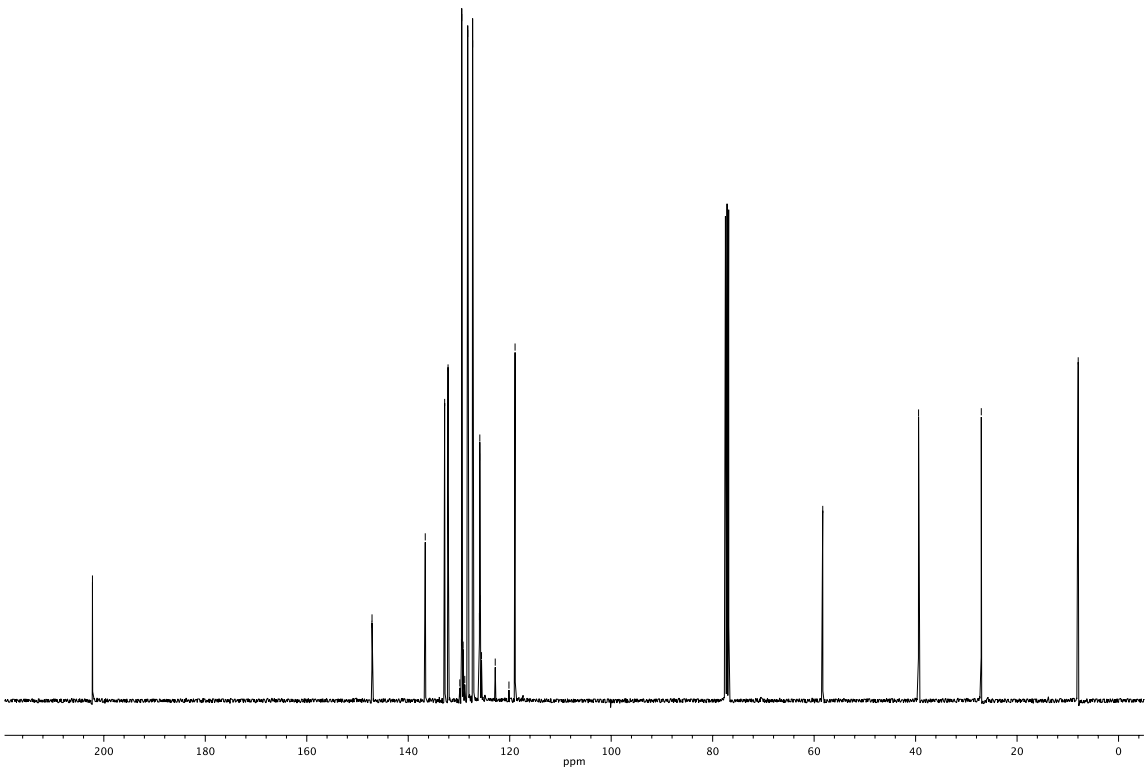



***Figure A4.61*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***21s****.*

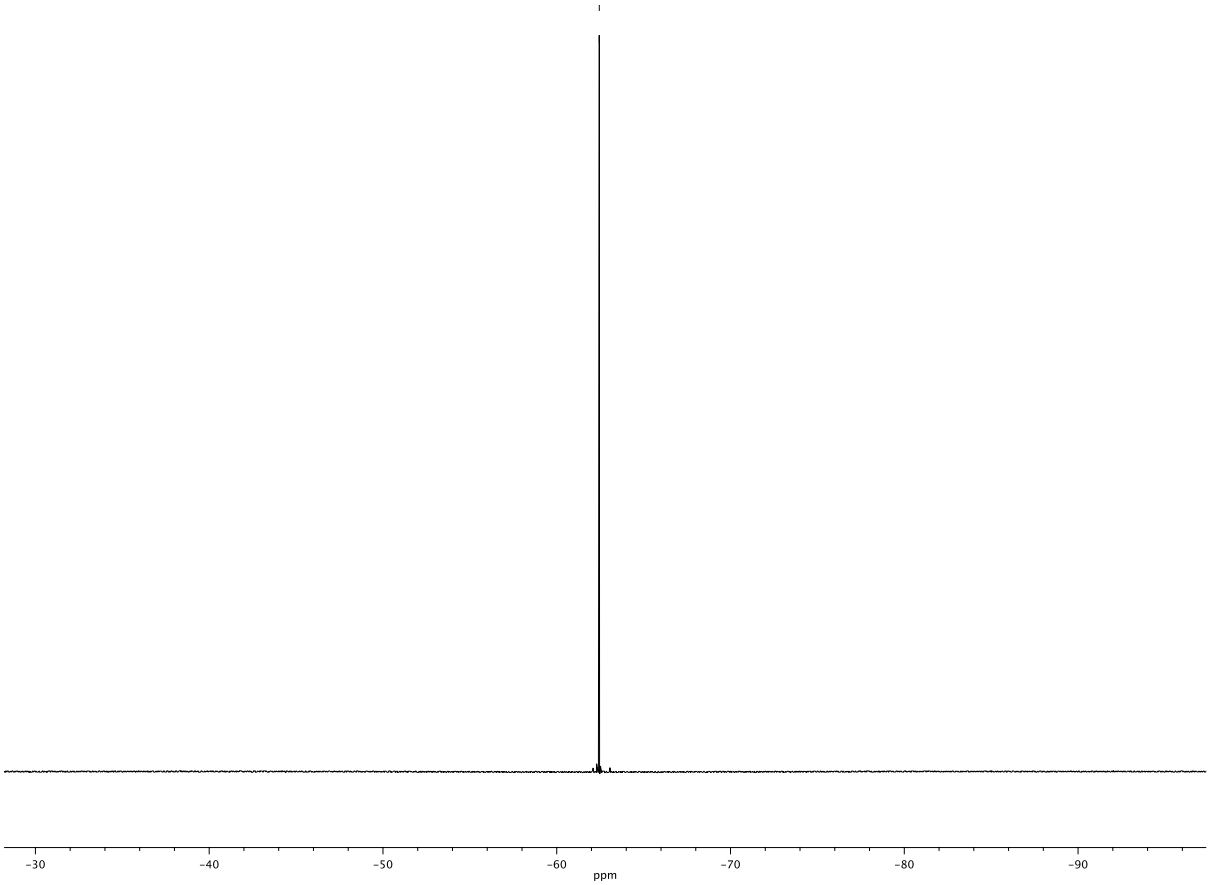



***Figure A4.62*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***21s****.*

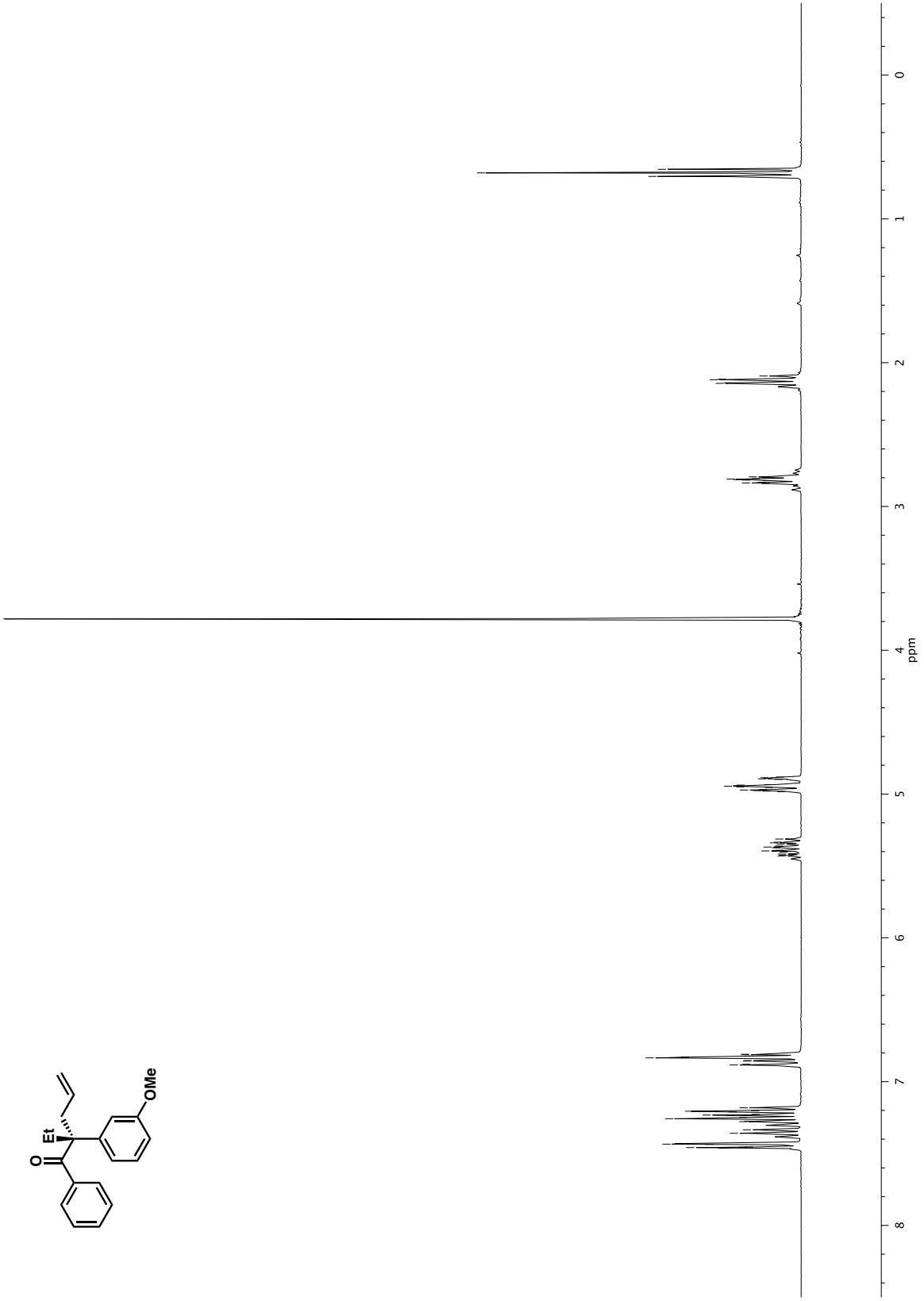



***Figure A4.63*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***21t****.*

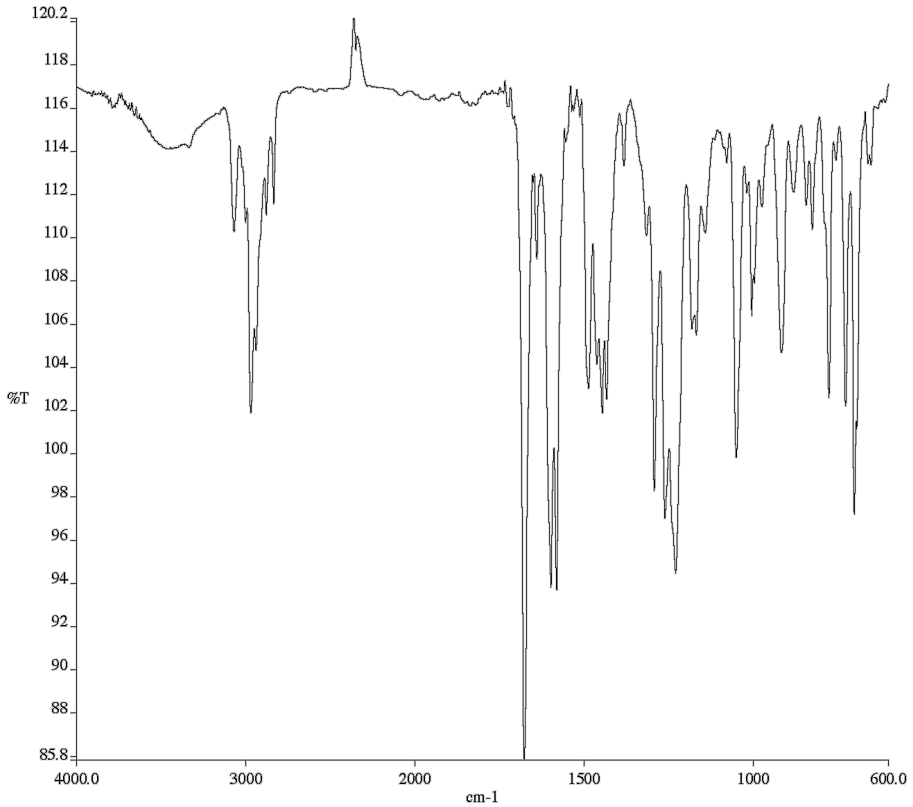



***Figure A4.64*** *Infrared spectrum (Thin Film, NaCl) of compound* ***21t****.*

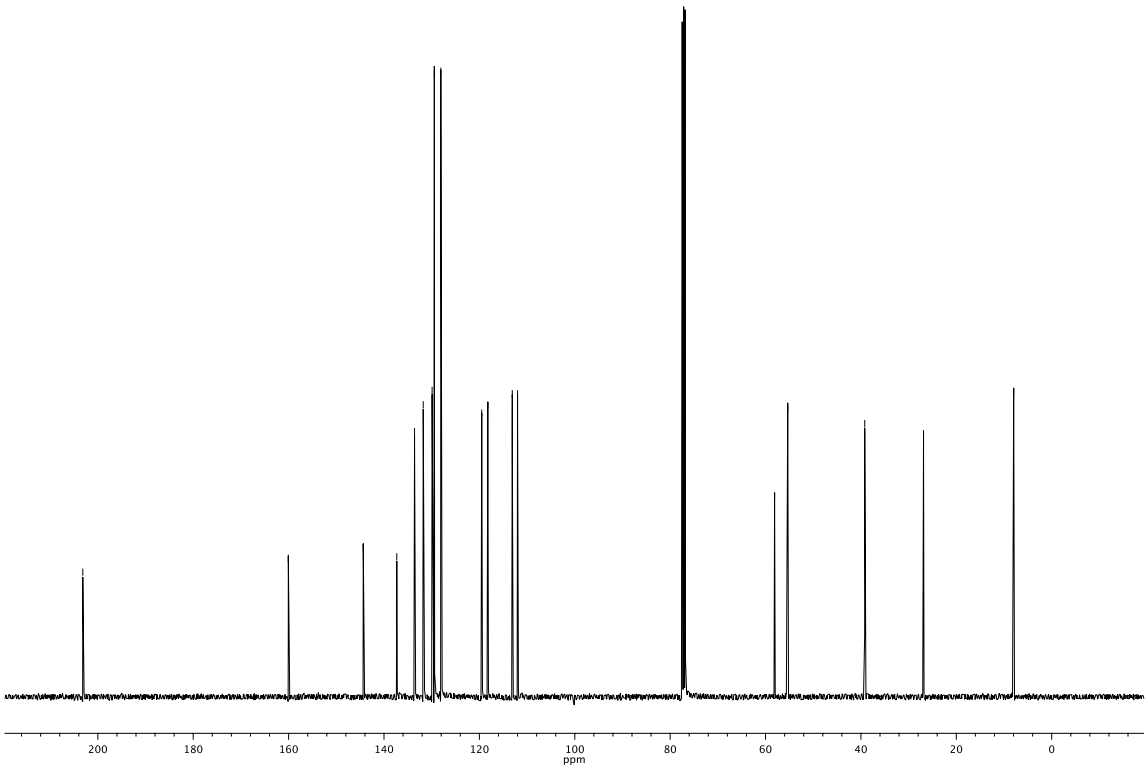



***Figure A4.65*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***21t****.*

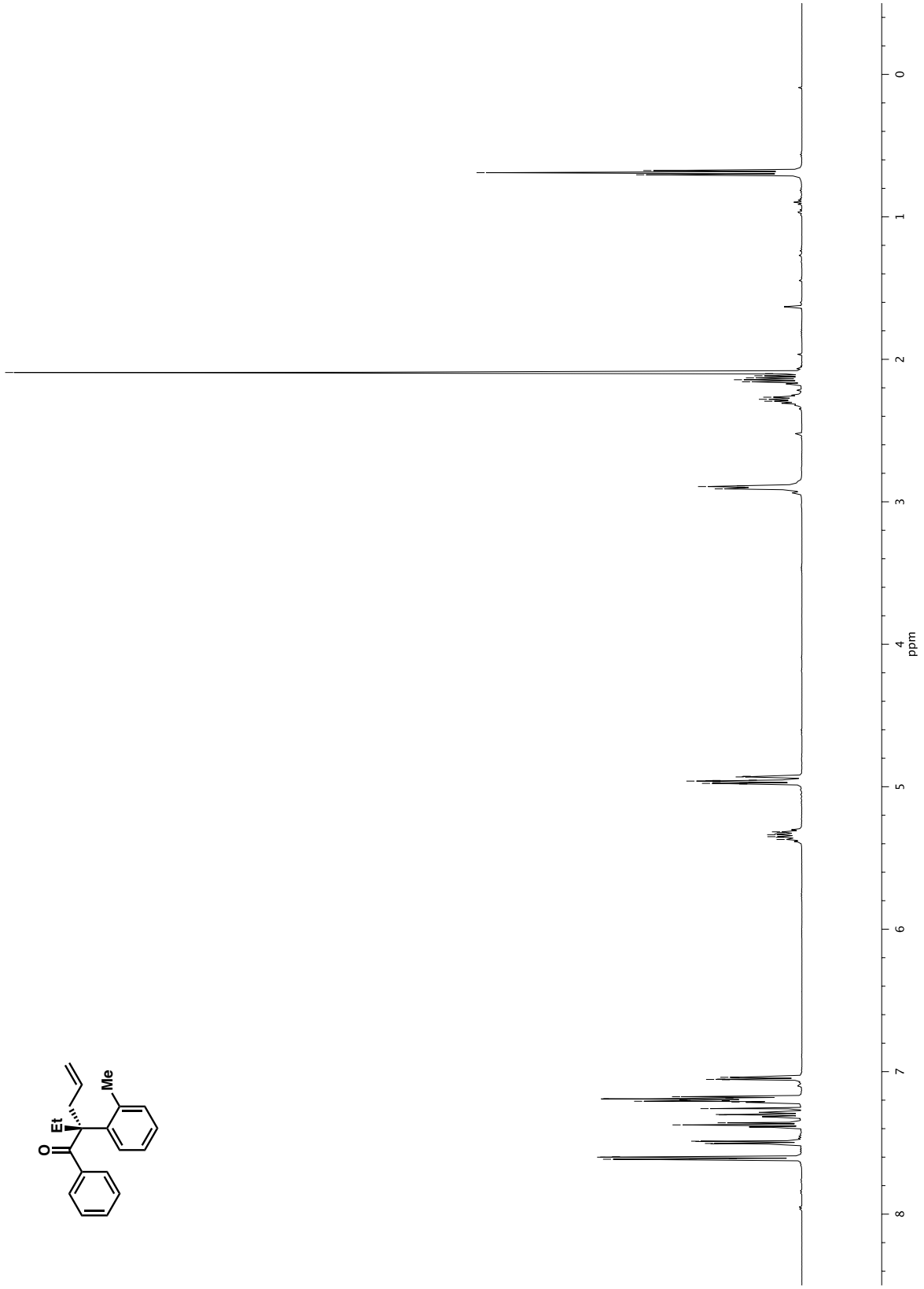



***Figure A4.66*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***21u***.

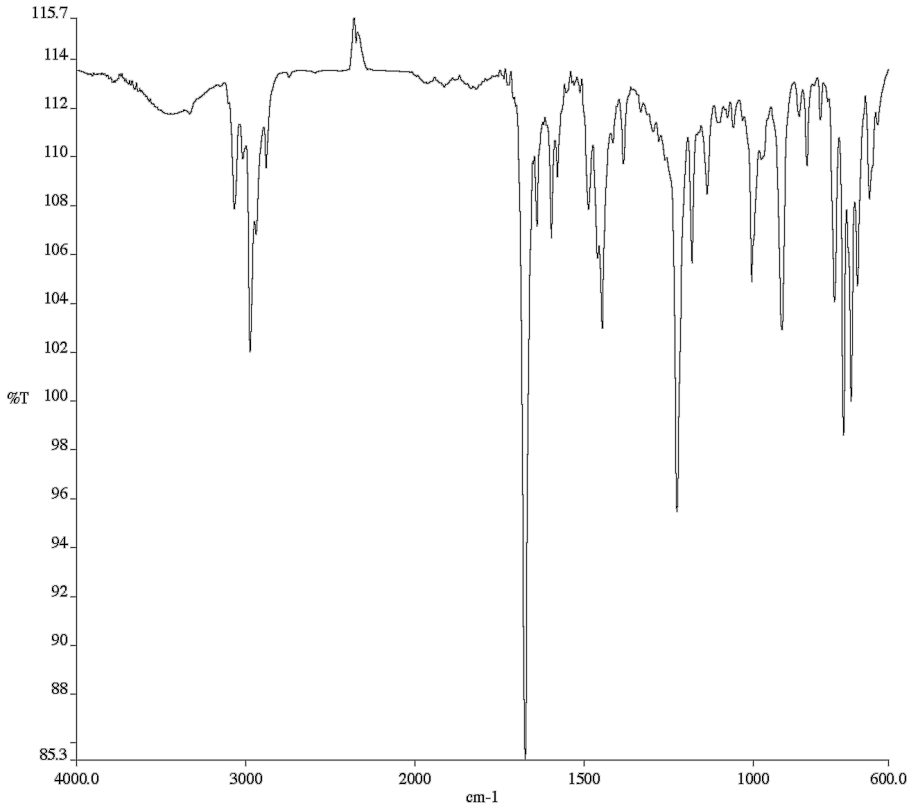



***Figure A4.67*** *Infrared spectrum (Thin Film, NaCl) of compound* ***21u***.

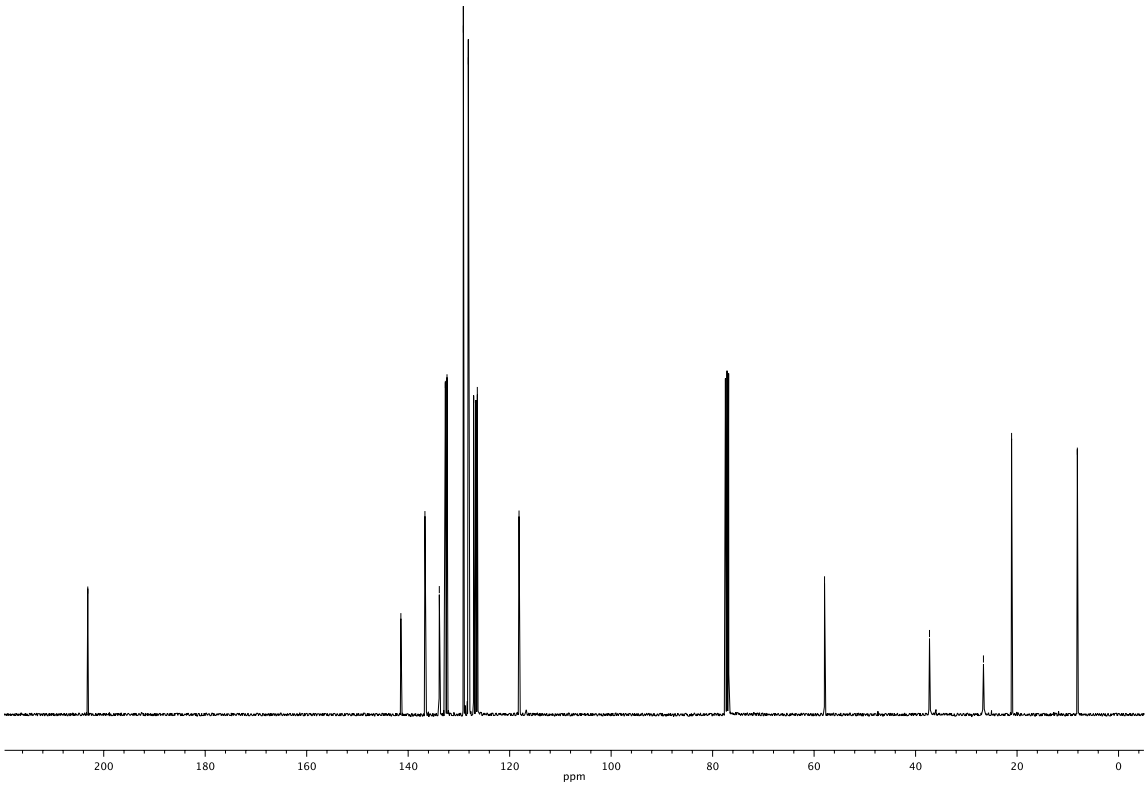



***Figure A4.68*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***21u***.

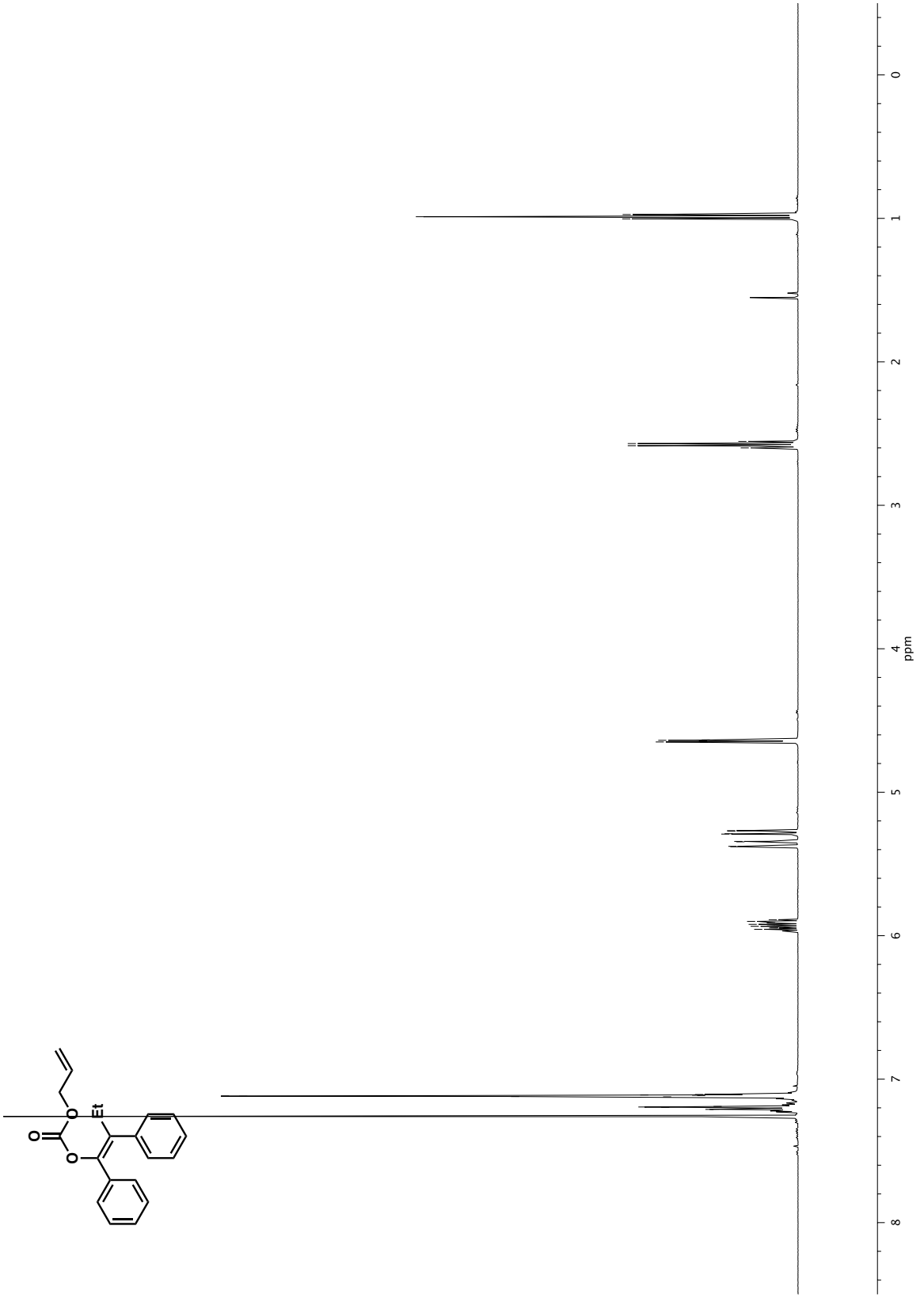



***Figure A4.69*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***20a***.

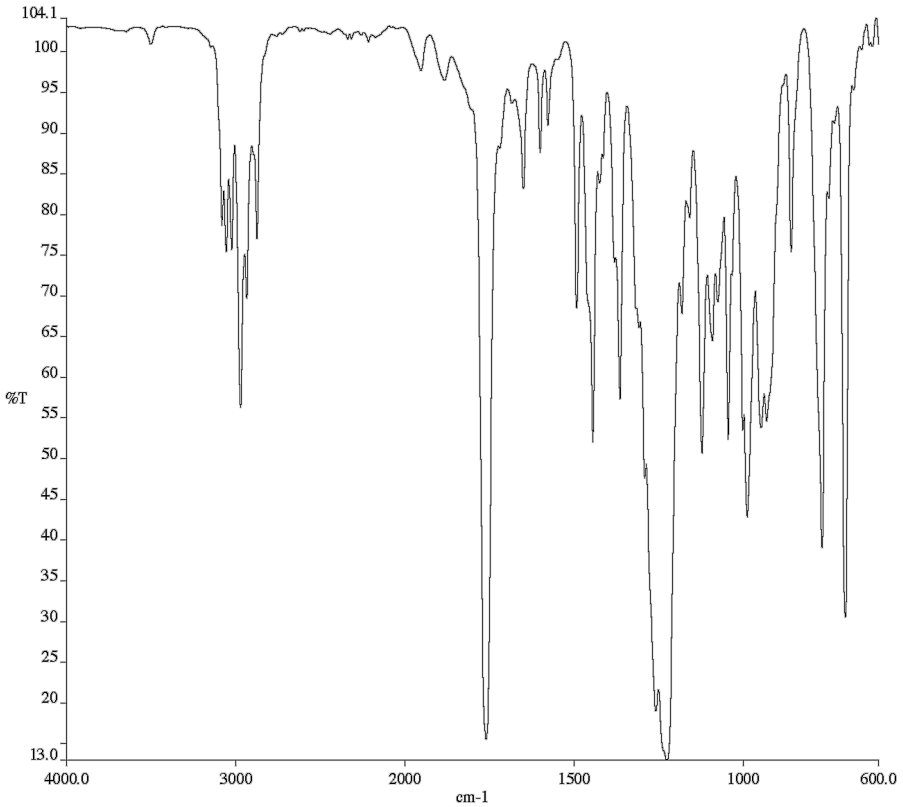



***Figure A4.70*** *Infrared spectrum (Thin Film, NaCl) of compound* ***20a****.*

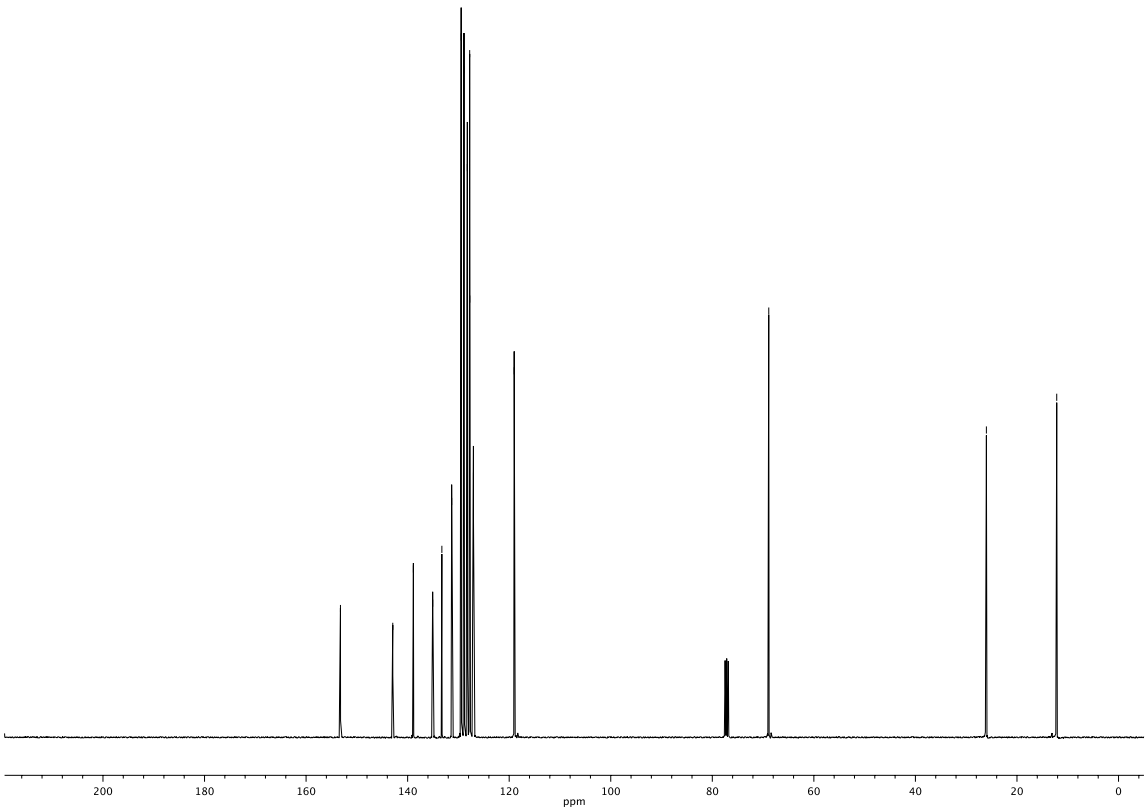



***Figure A4.71*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***20a****.*

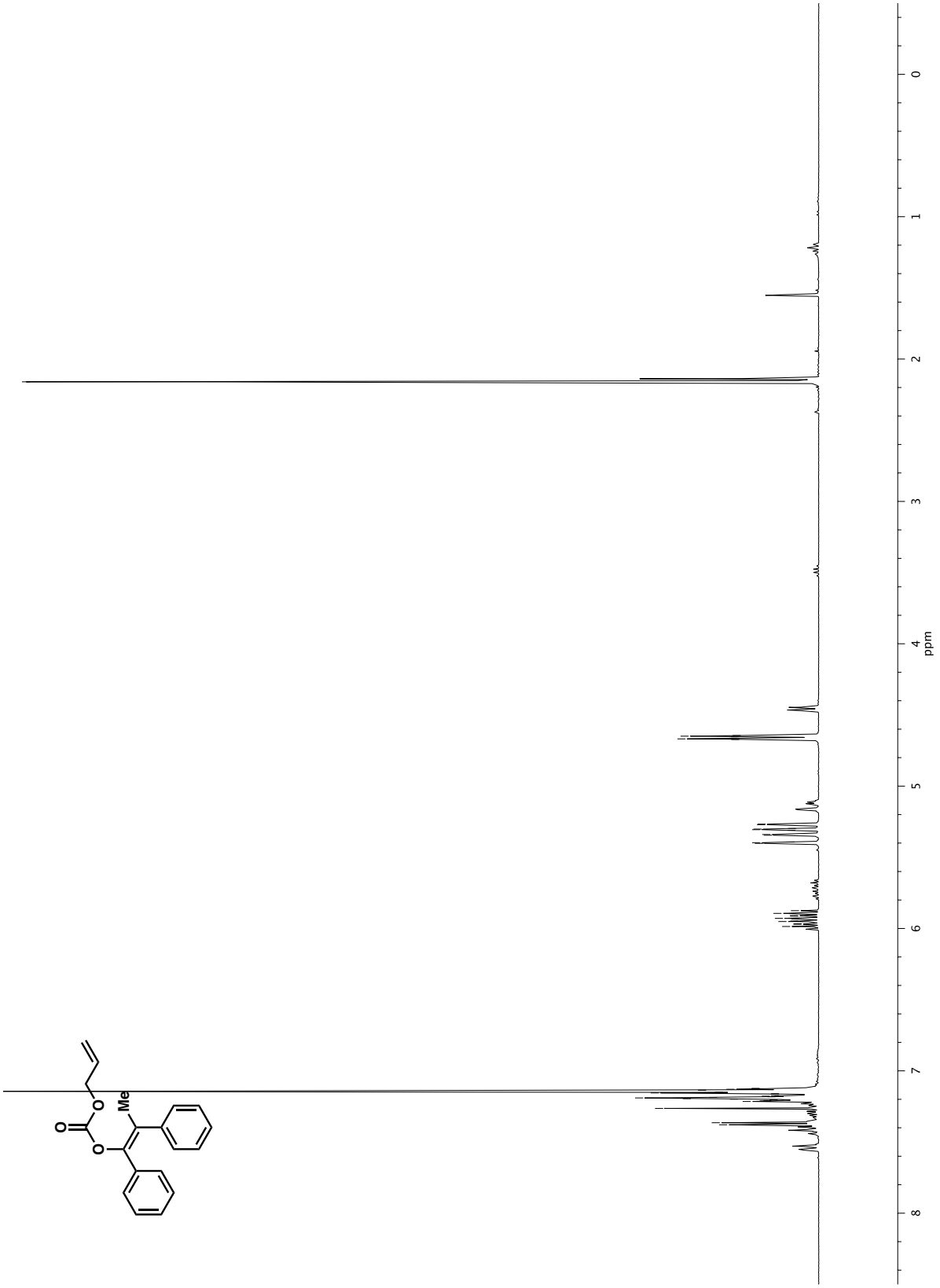



***Figure A4.72*** *$^1H$ NMR (300 MHz, $CDCl_3$) of compound* ***20b***.

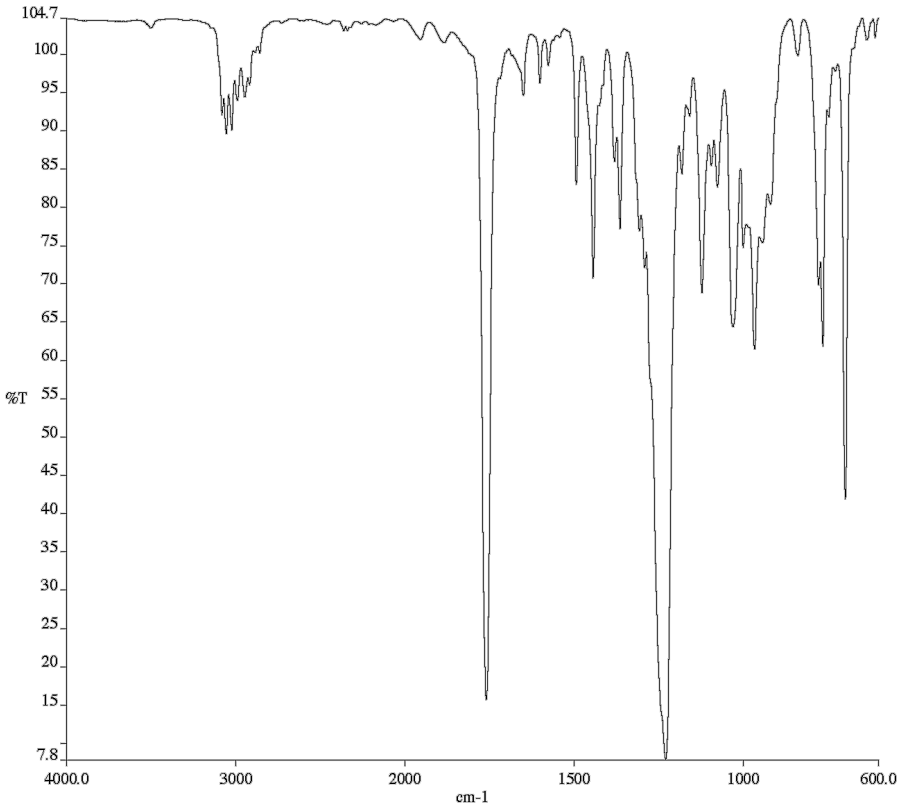



***Figure A4.73*** *Infrared spectrum (Thin Film, NaCl) of compound* ***20b***.

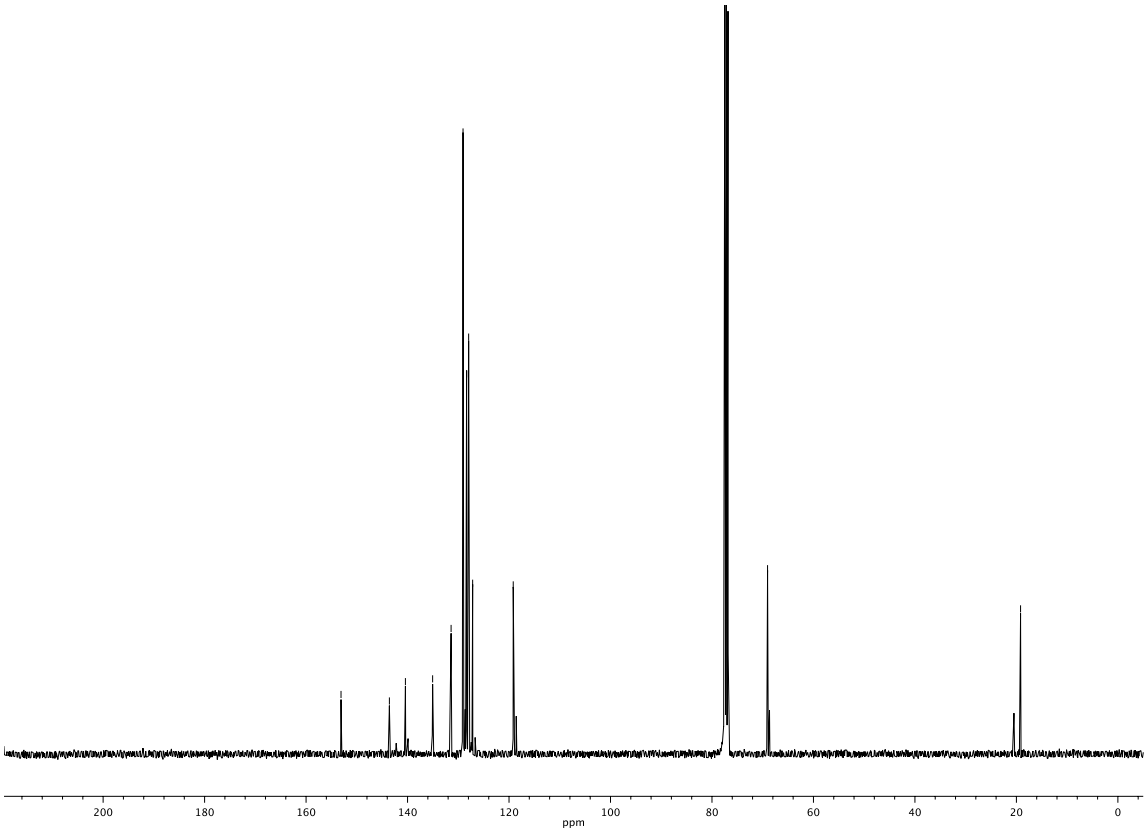



***Figure A4.74*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***20b***.

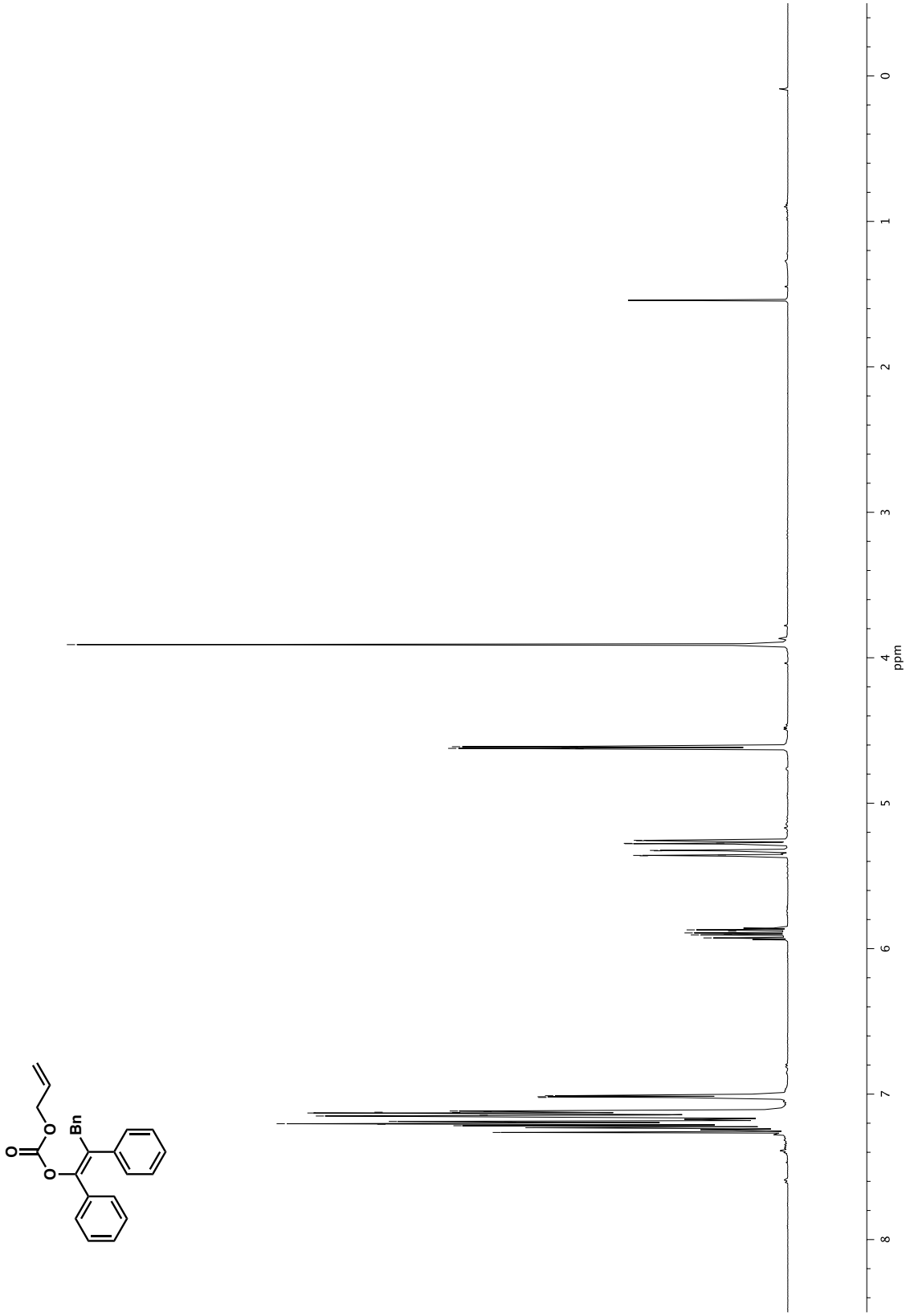



***Figure A4.75*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***20c****.*

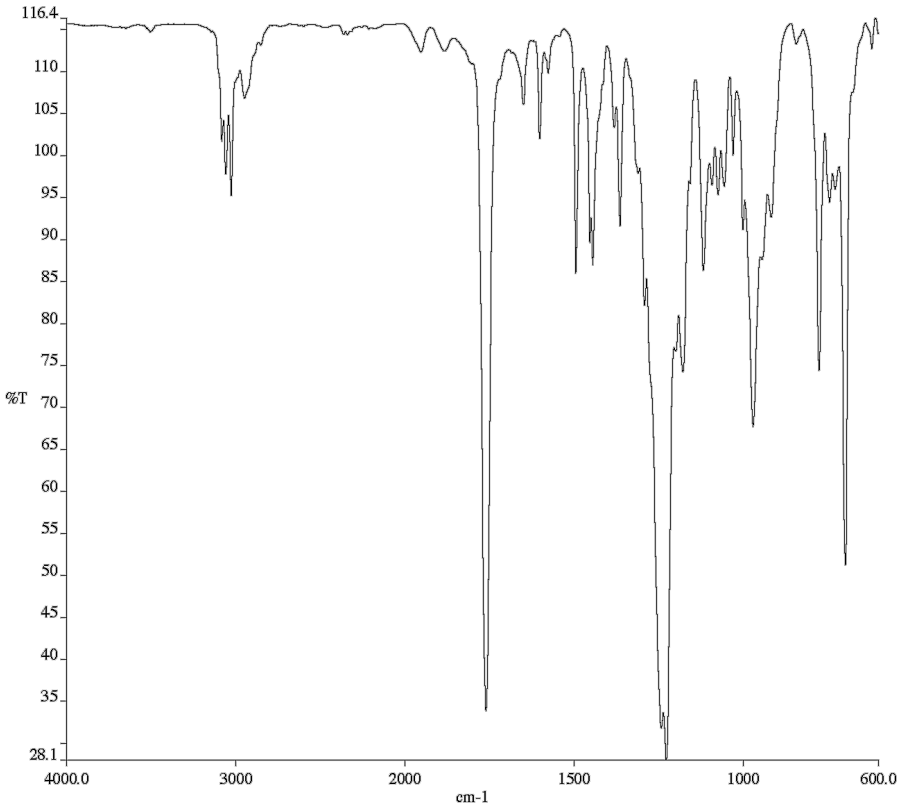



***Figure A4.76*** *Infrared spectrum (Thin Film, NaCl) of compound* ***20c****.*

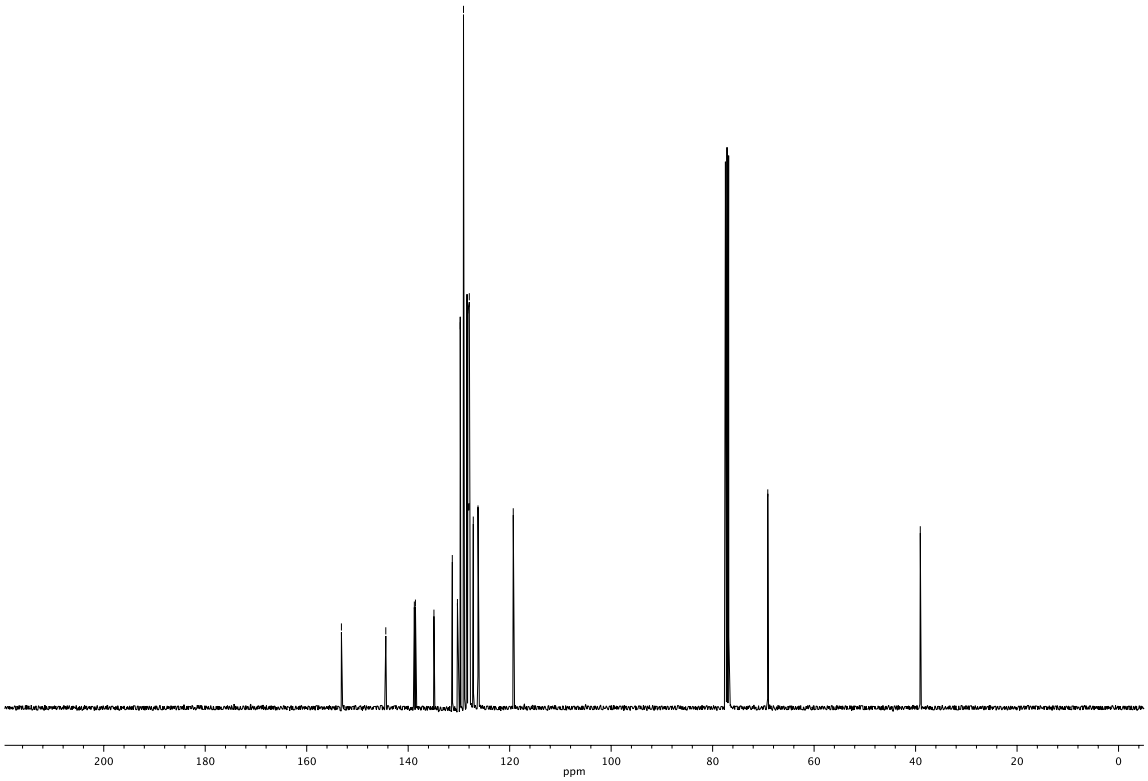



***Figure A4.77*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***20c****.*

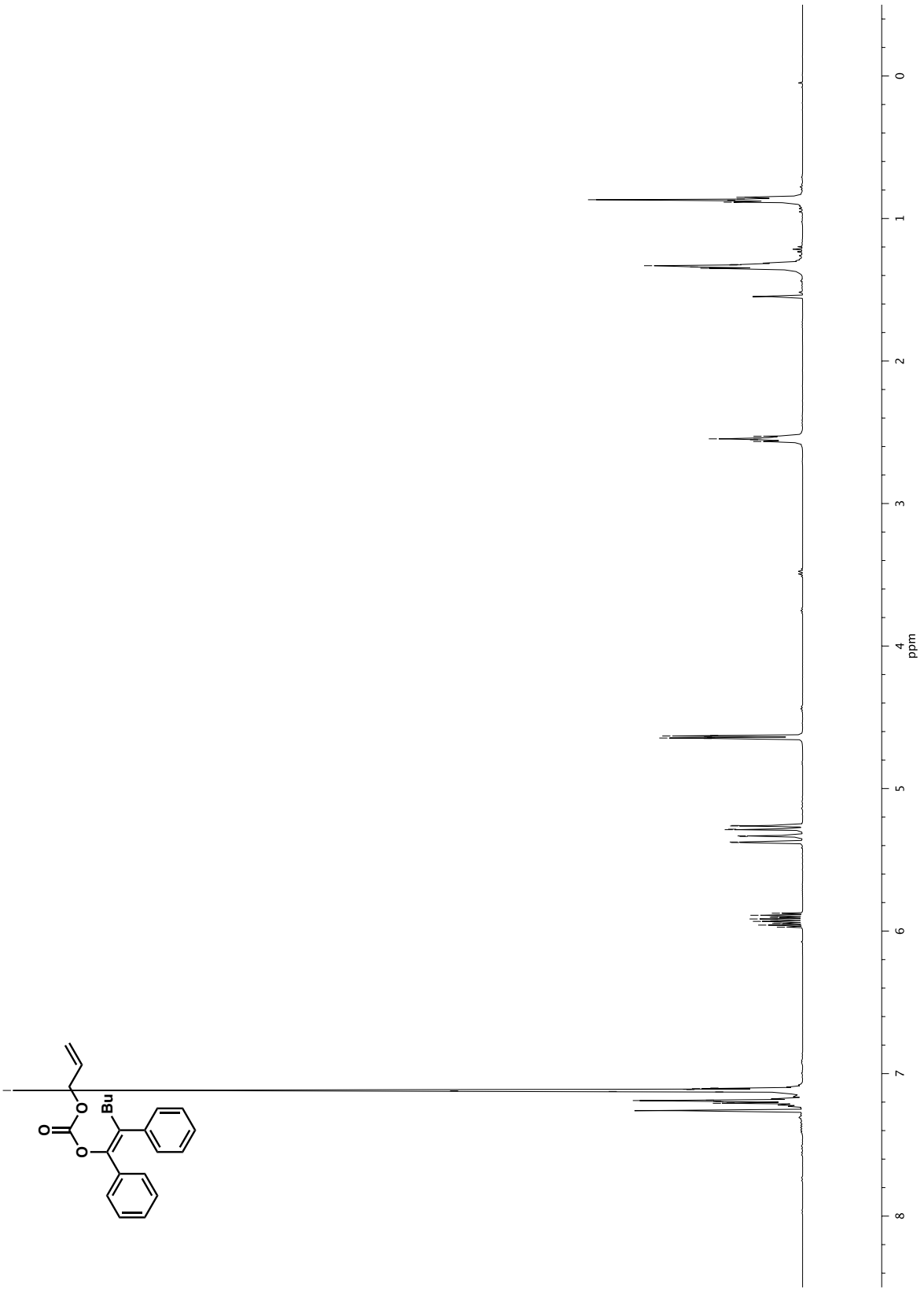



***Figure A4.78*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***20d***.

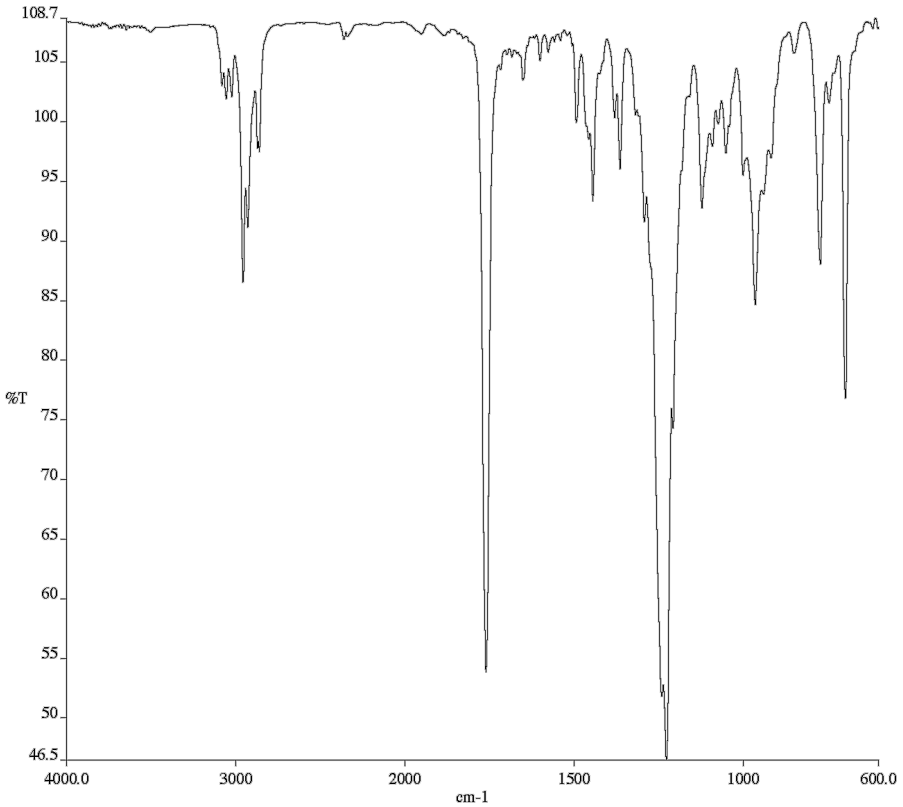



***Figure A4.79*** *Infrared spectrum (Thin Film, NaCl) of compound* ***20d****.*

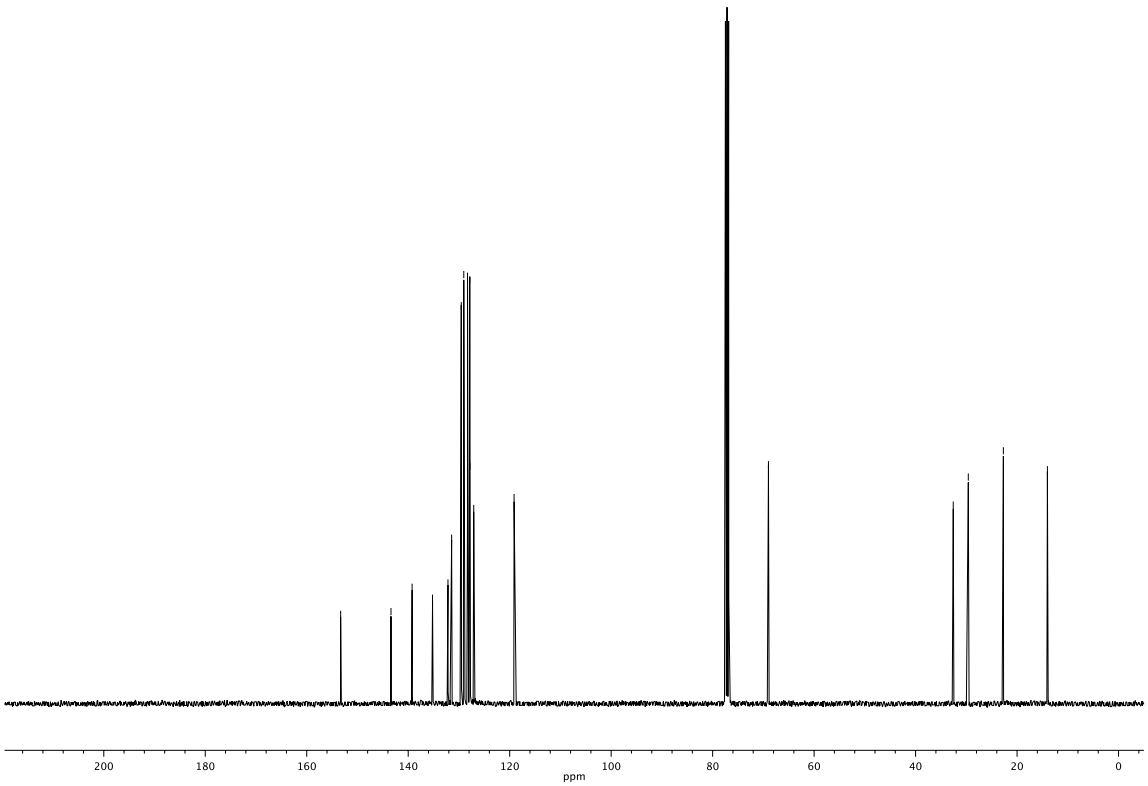



***Figure A4.80*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***20d****.*

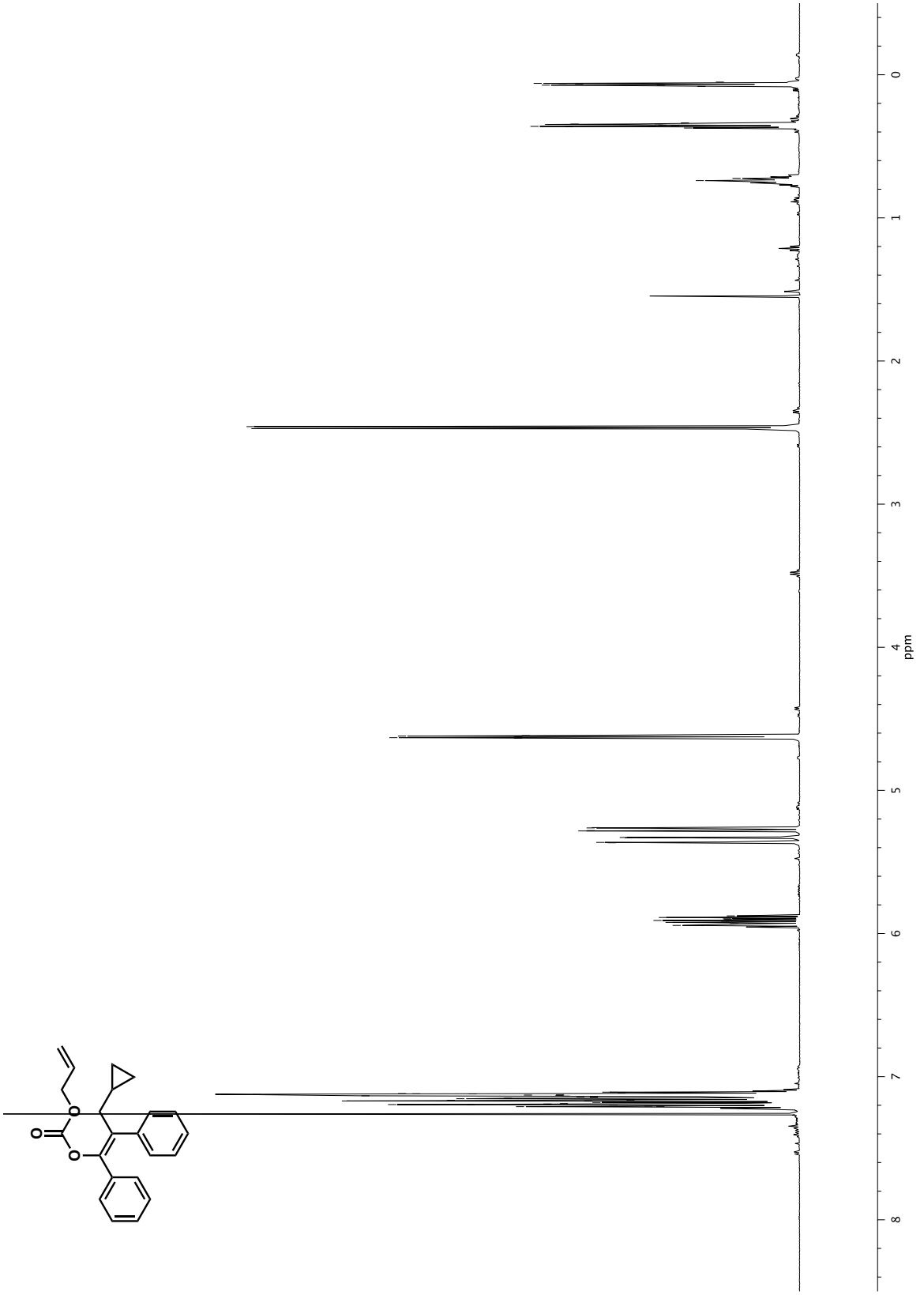



***Figure A4.81*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***20e***.

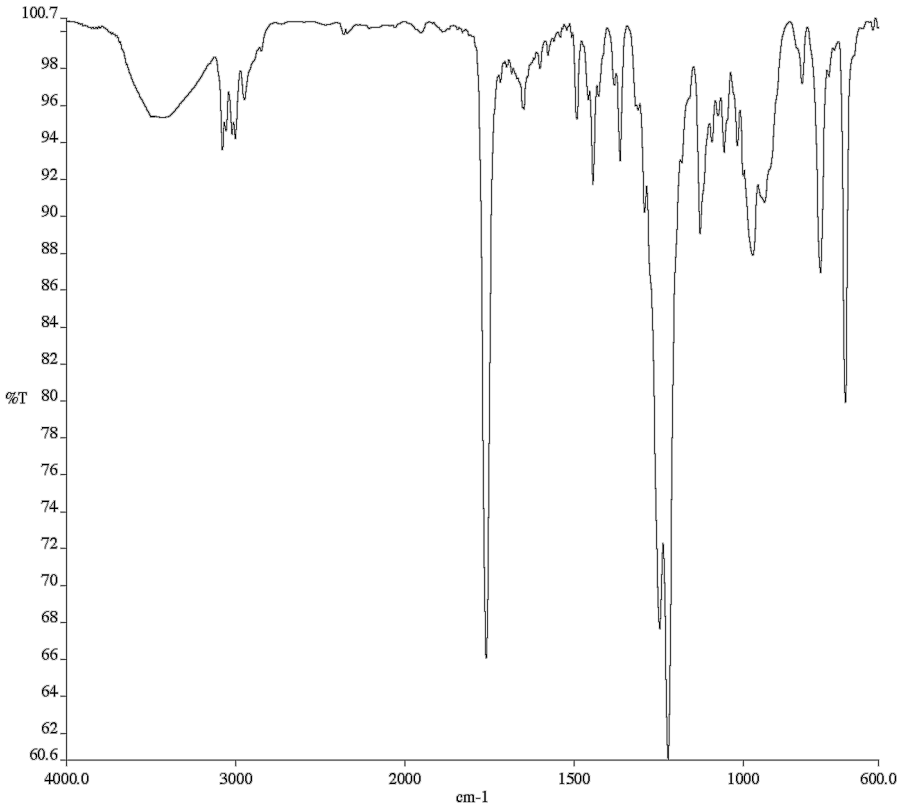



***Figure A4.82*** *Infrared spectrum (Thin Film, NaCl) of compound* ***20e****.*

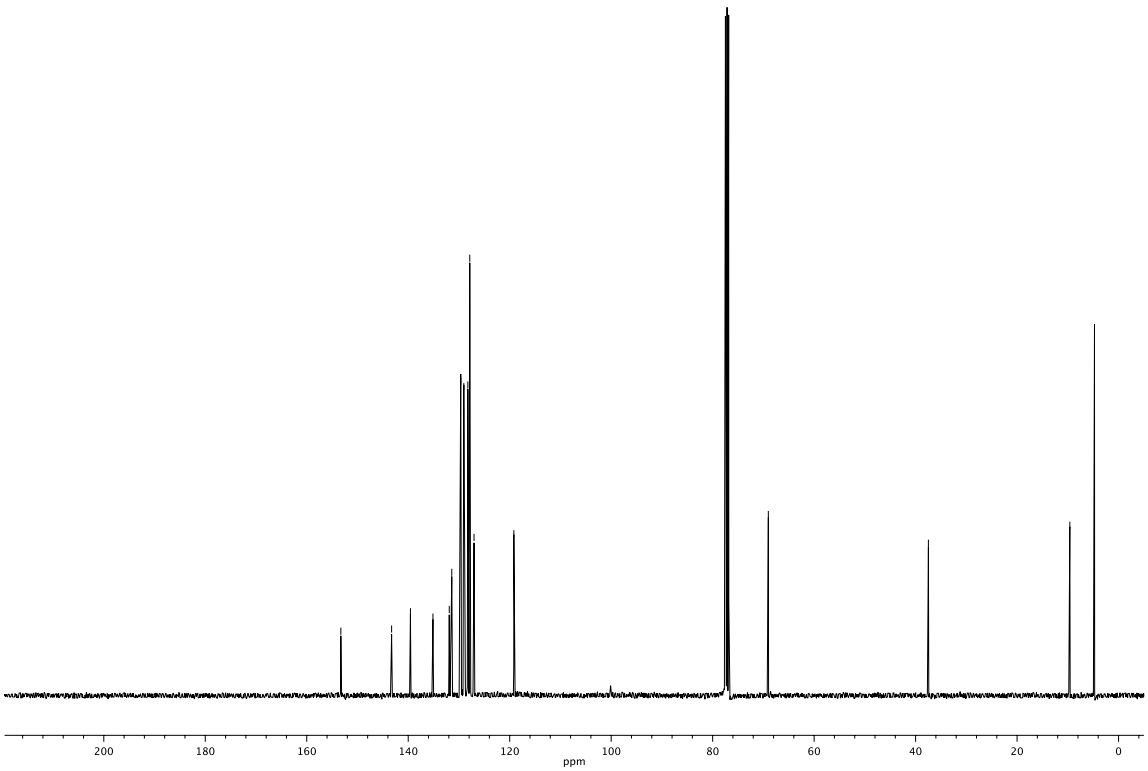



***Figure A4.83*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***20e****.*

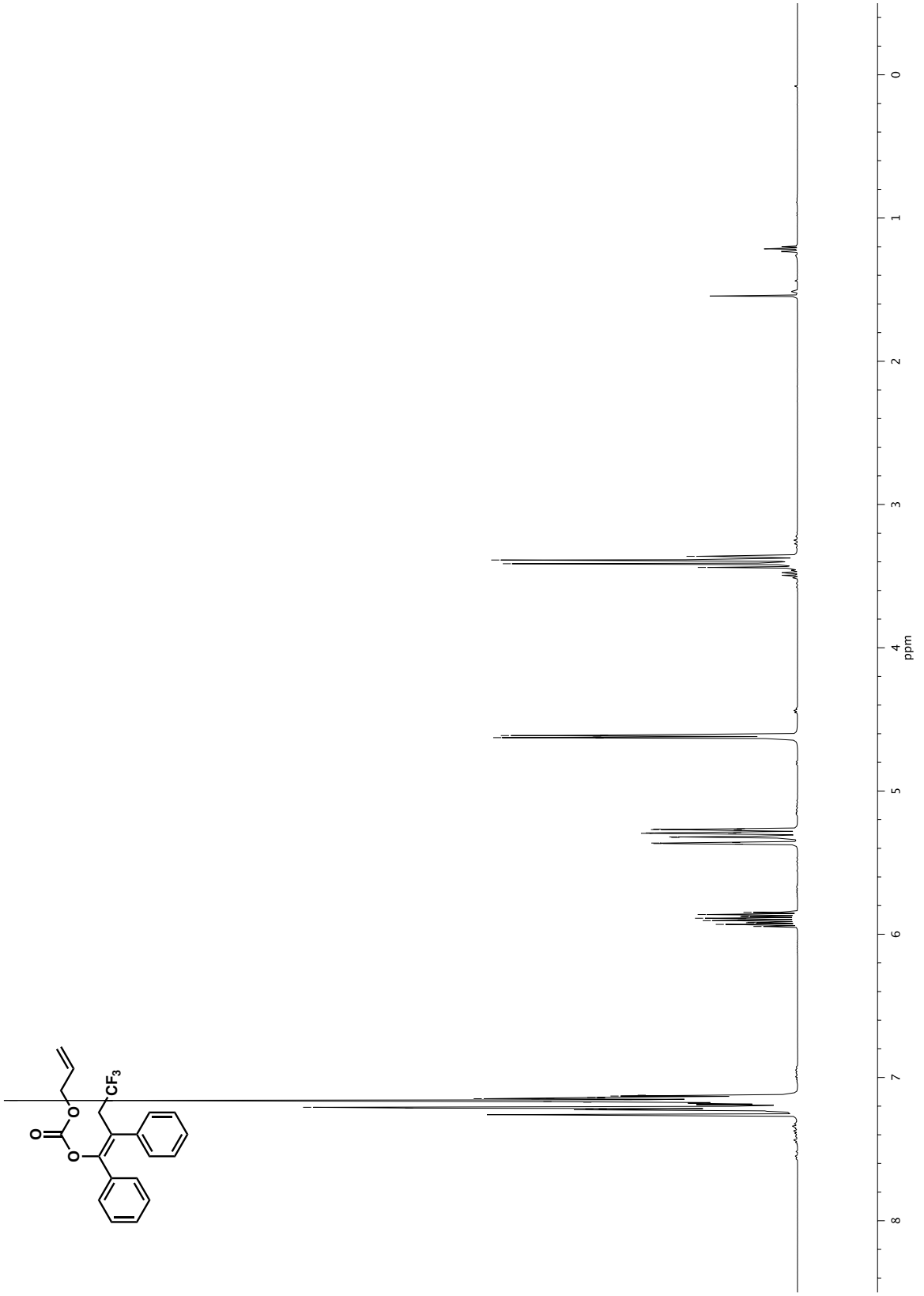



***Figure A4.84*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***20f****.*

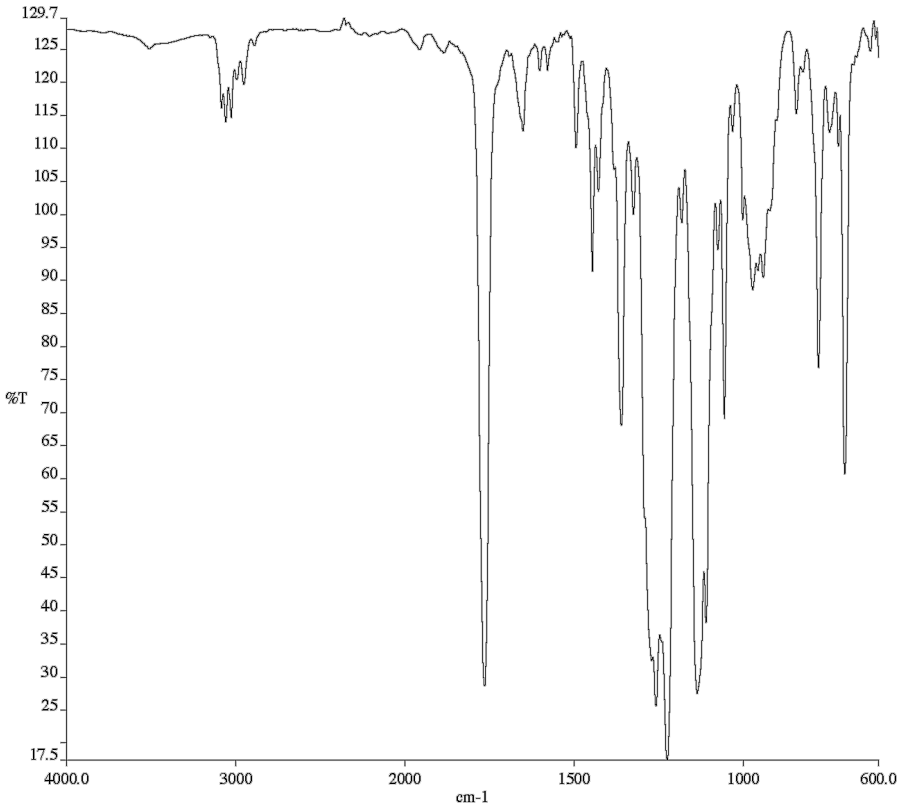



***Figure A4.85*** *Infrared spectrum (Thin Film, NaCl) of compound* ***20f****.*

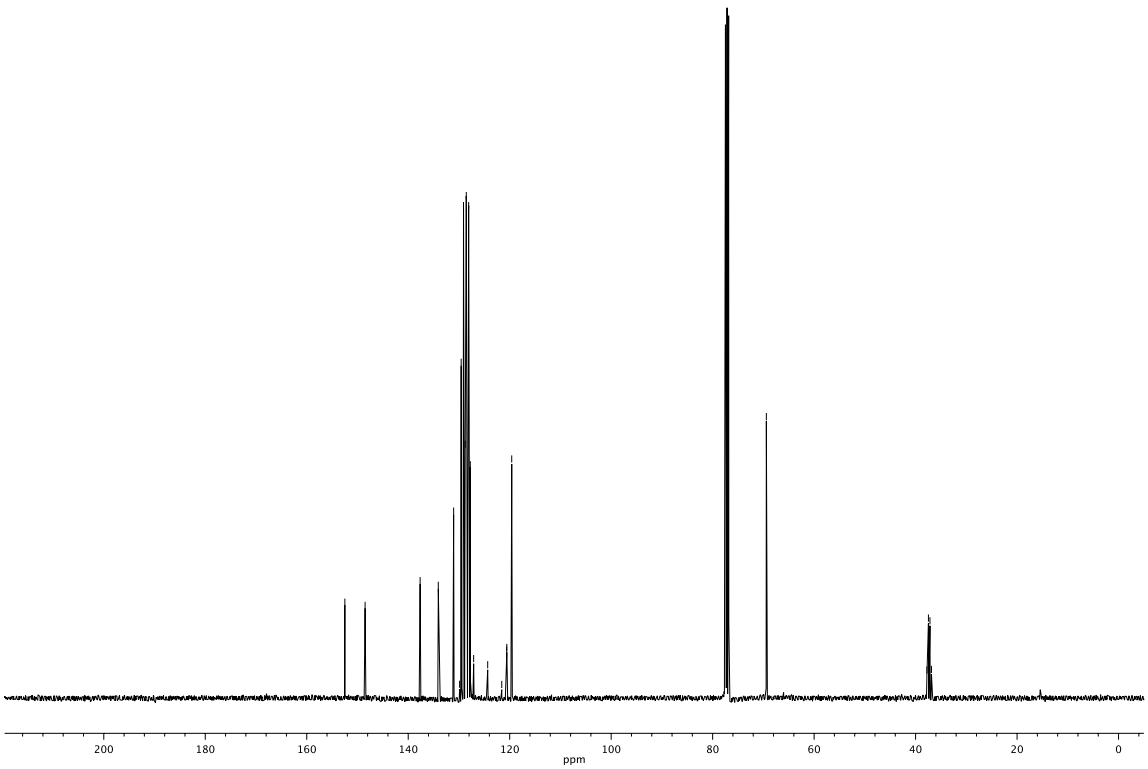



***Figure A4.86*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***20f****.*

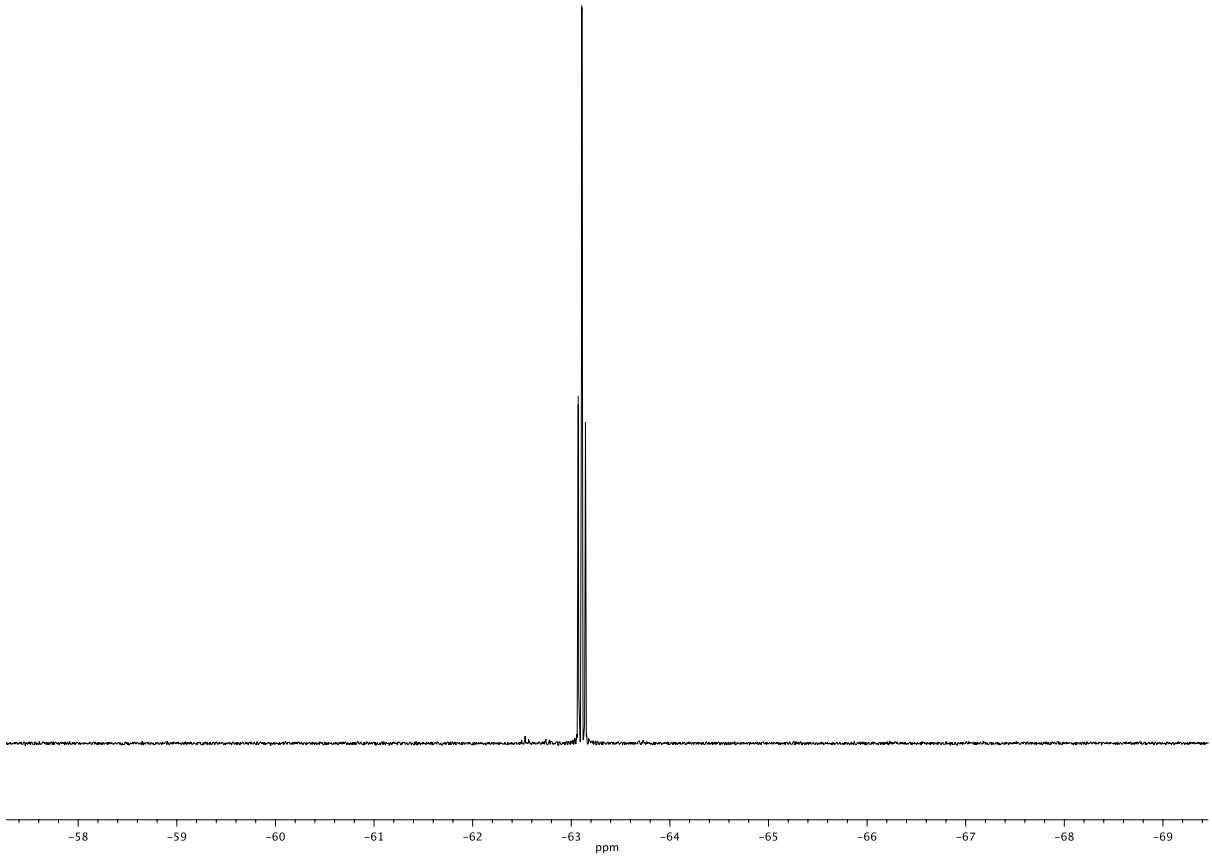



***Figure A4.87*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***20f***.

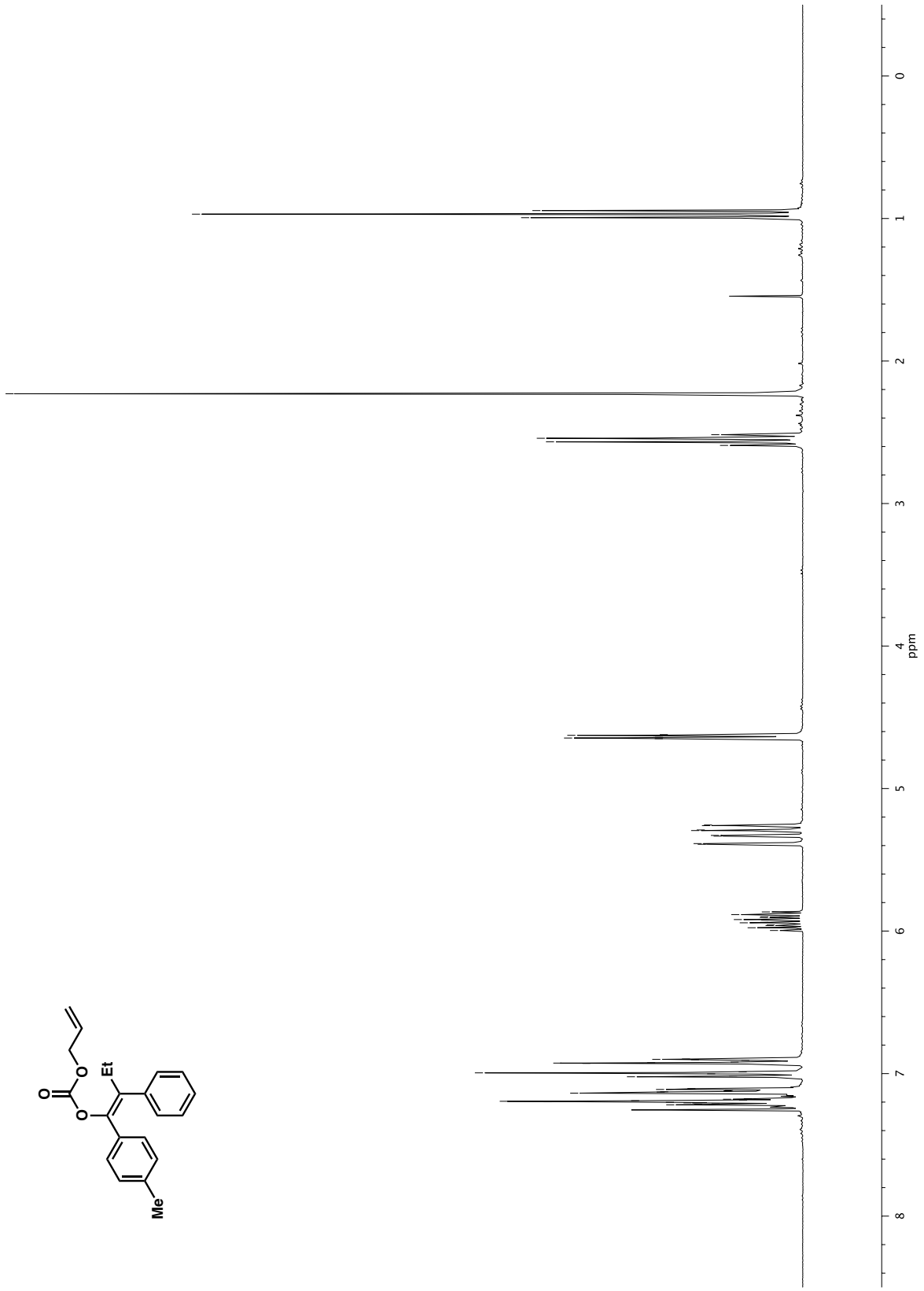



***Figure A4.88*** *$^1H$ NMR (300 MHz, $CDCl_3$) of compound* ***20g***.

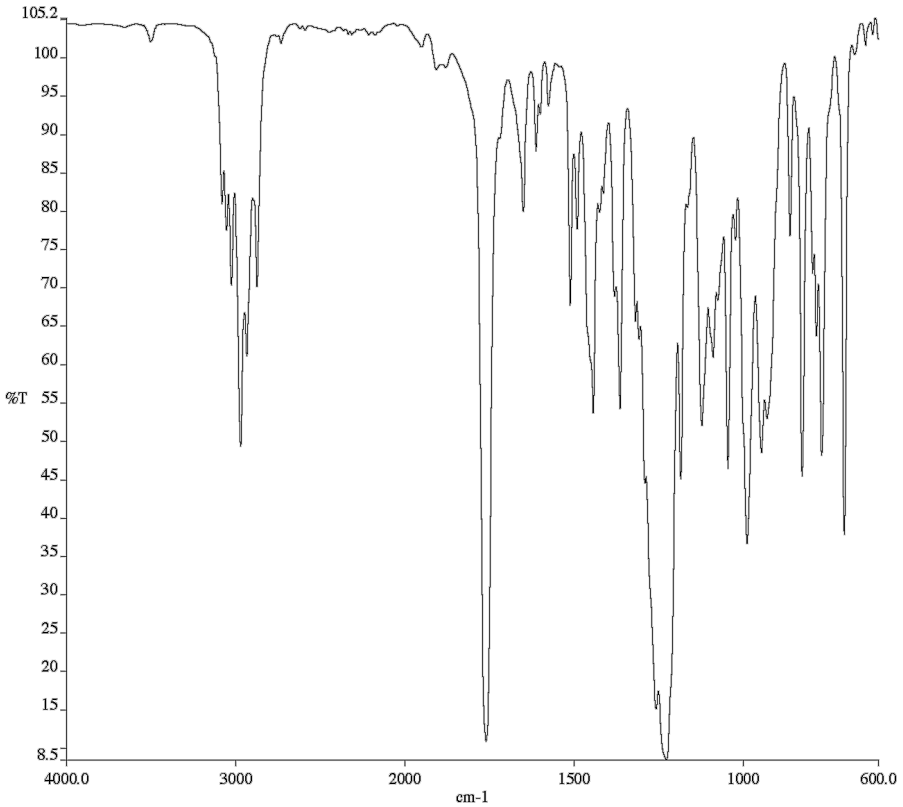



***Figure A4.89*** *Infrared spectrum (Thin Film, NaCl) of compound* ***20g****.*

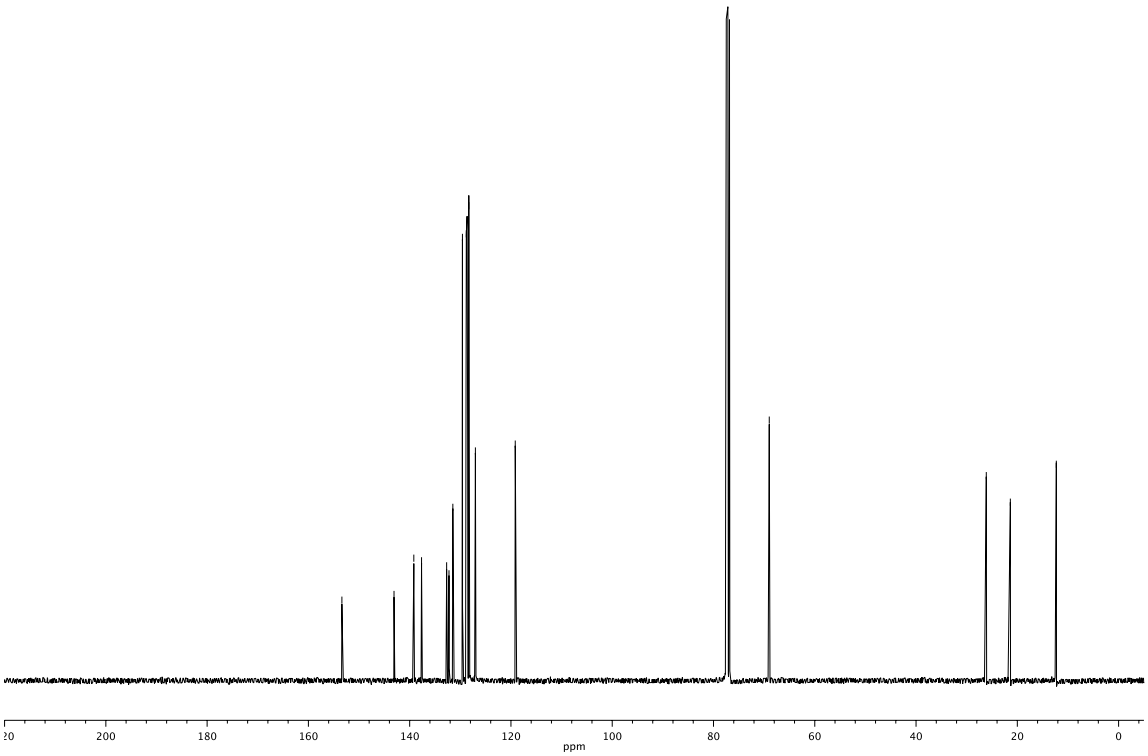



***Figure A4.90*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***20g****.*

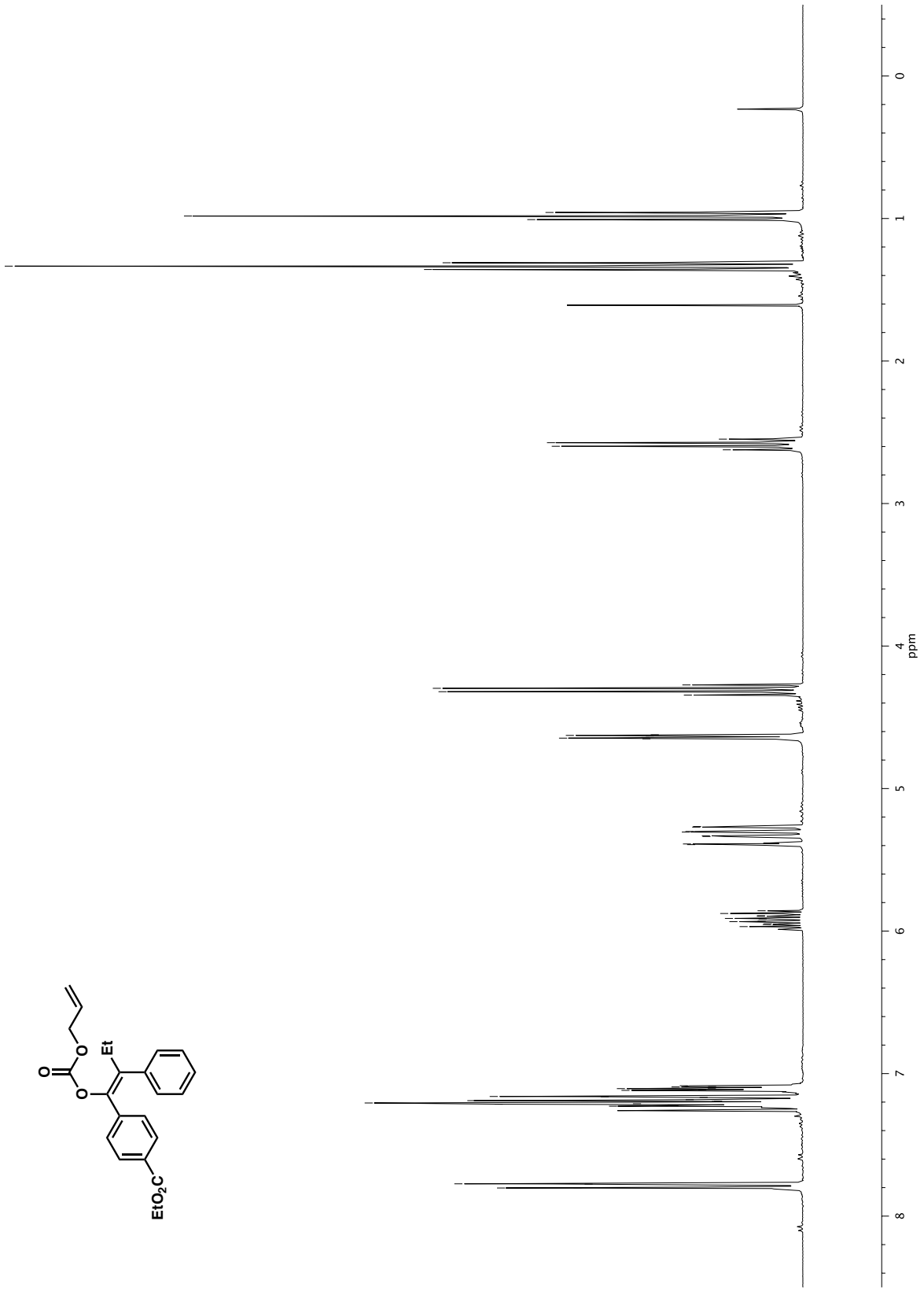



***Figure A4.91*** *$^1H$ NMR (300 MHz, $CDCl_3$) of compound* ***20h***.

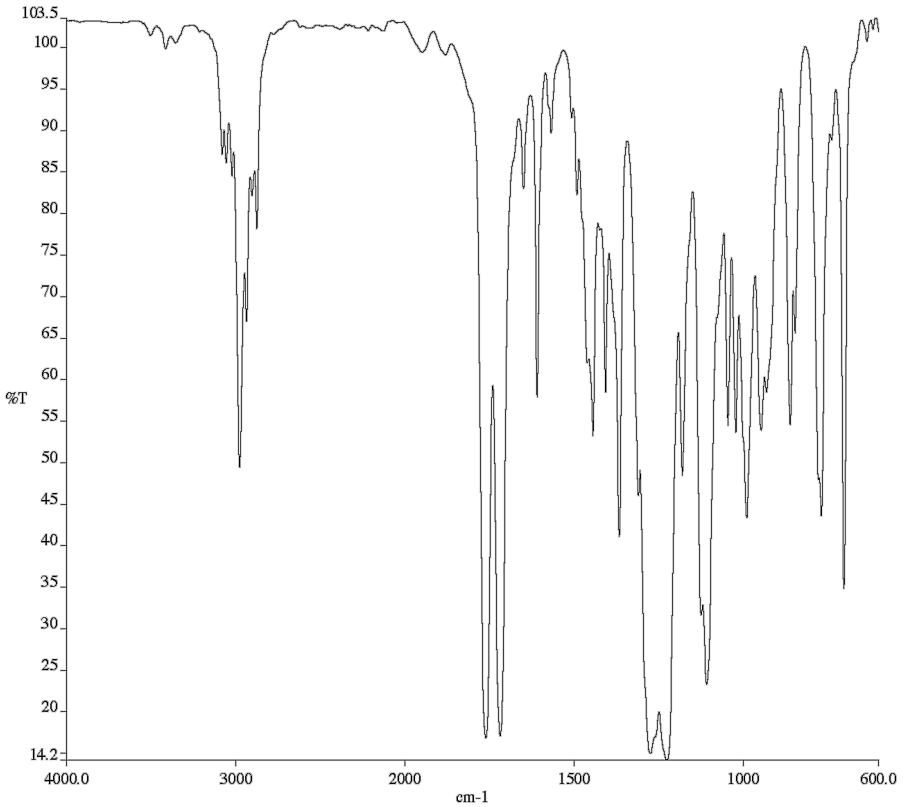



***Figure A4.92*** *Infrared spectrum (Thin Film, NaCl) of compound* ***20h***.

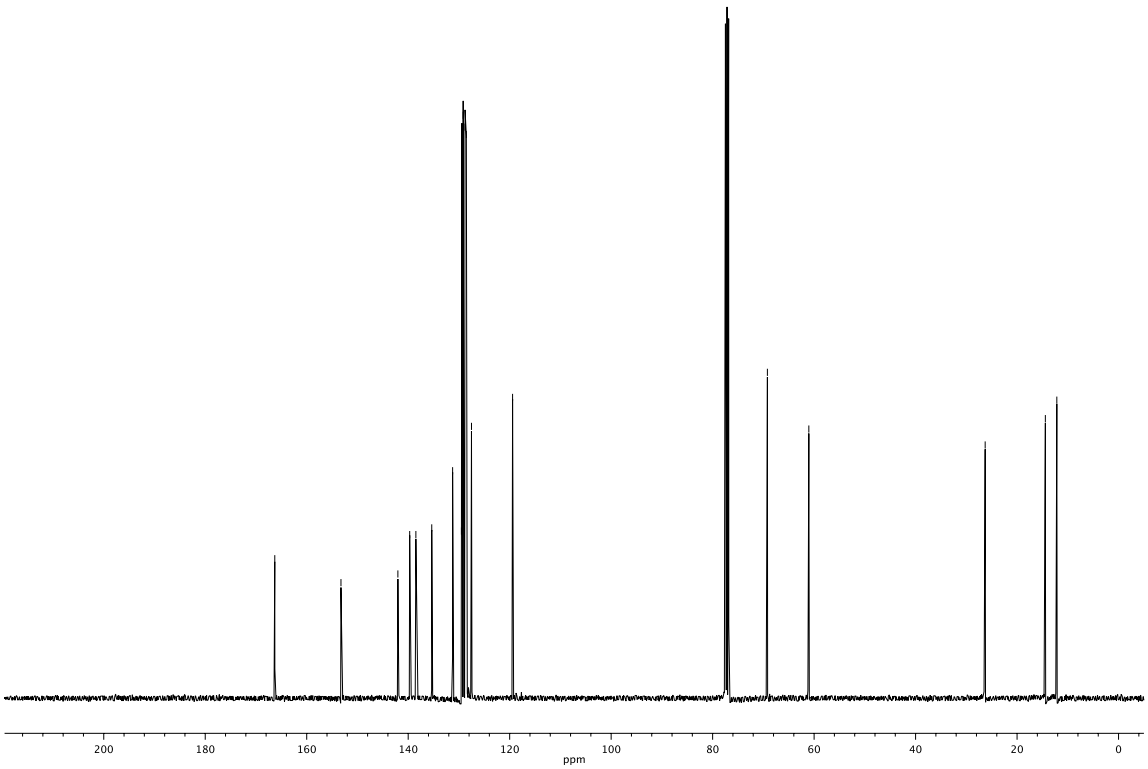



***Figure A4.93*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***20h***.

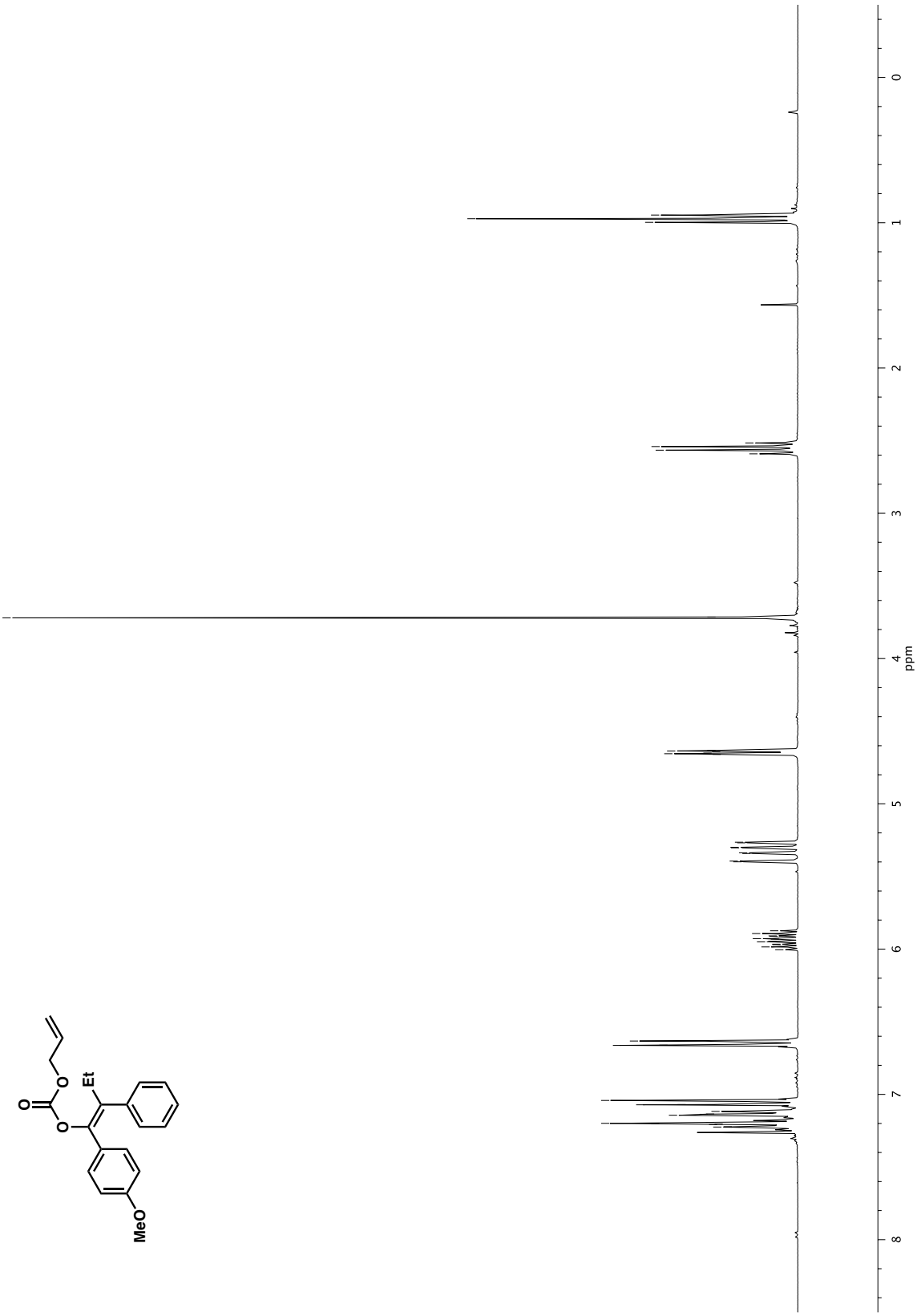



***Figure A4.94*** *$^1H$ NMR (300 MHz, $CDCl_3$) of compound* ***20i****.*

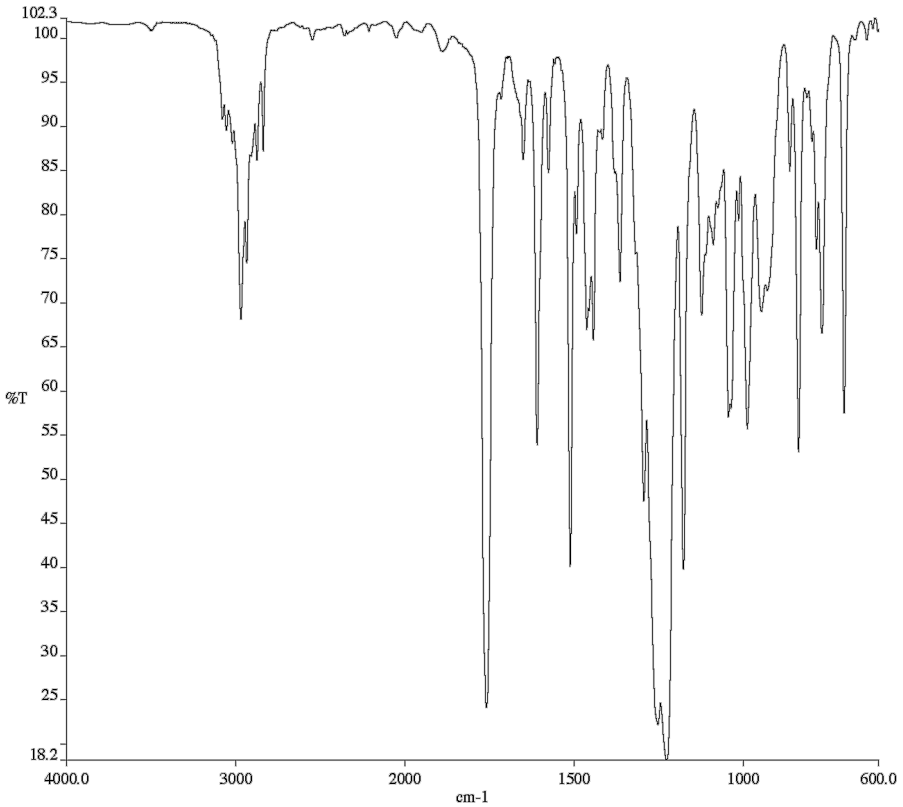



***Figure A4.95*** *Infrared spectrum (Thin Film, NaCl) of compound* ***20i****.*

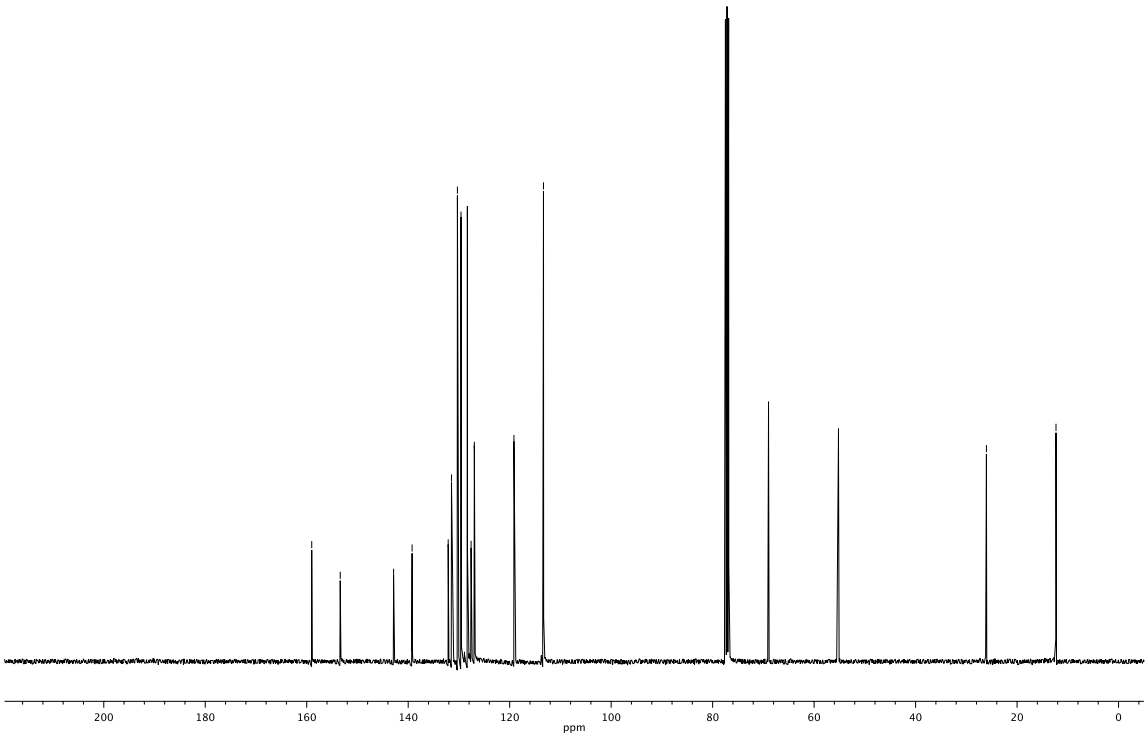



***Figure A4.96*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***20i****.*

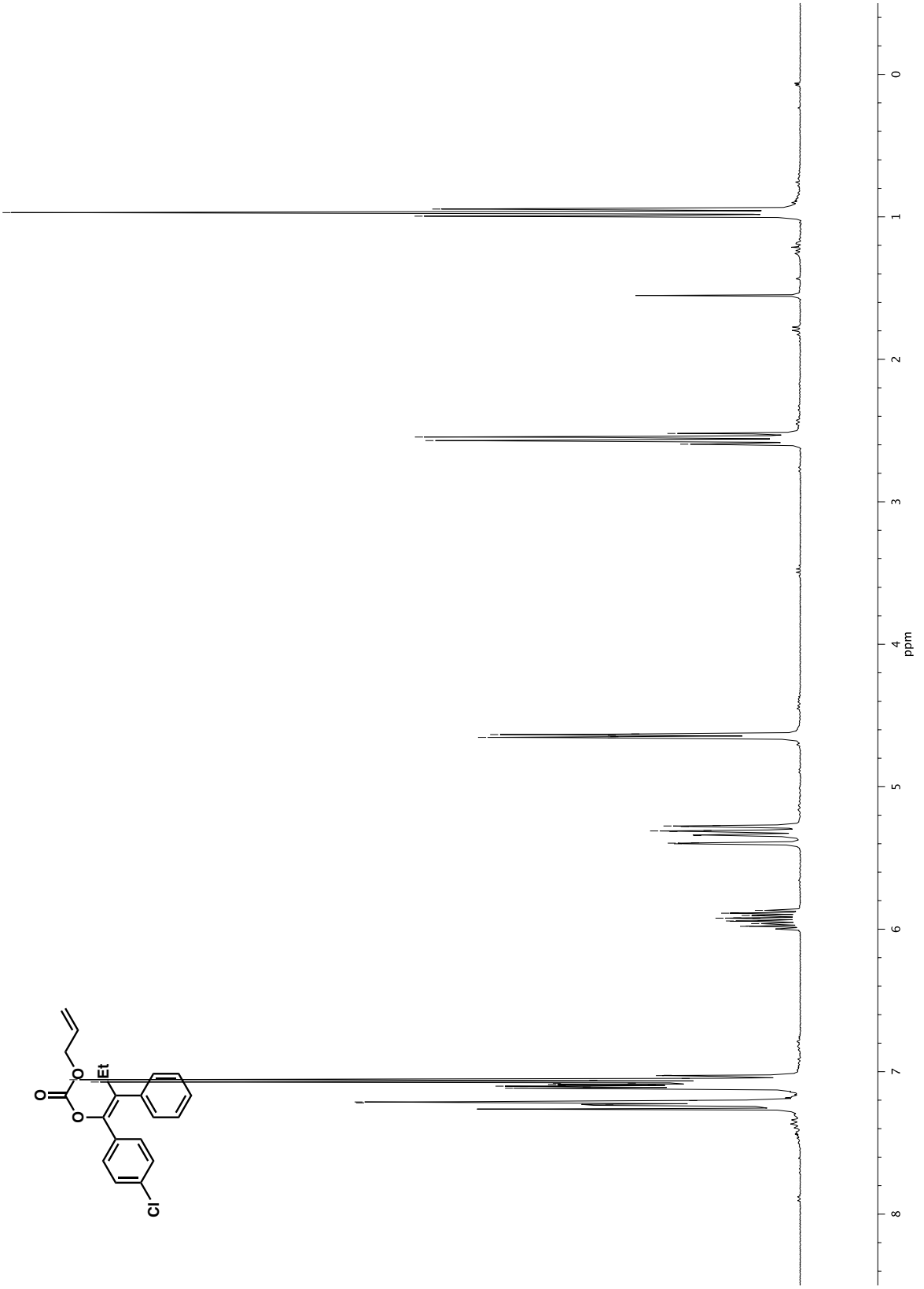



***Figure A4.97*** *$^1H$ NMR (300 MHz, $CDCl_3$) of compound* ***20j****.*

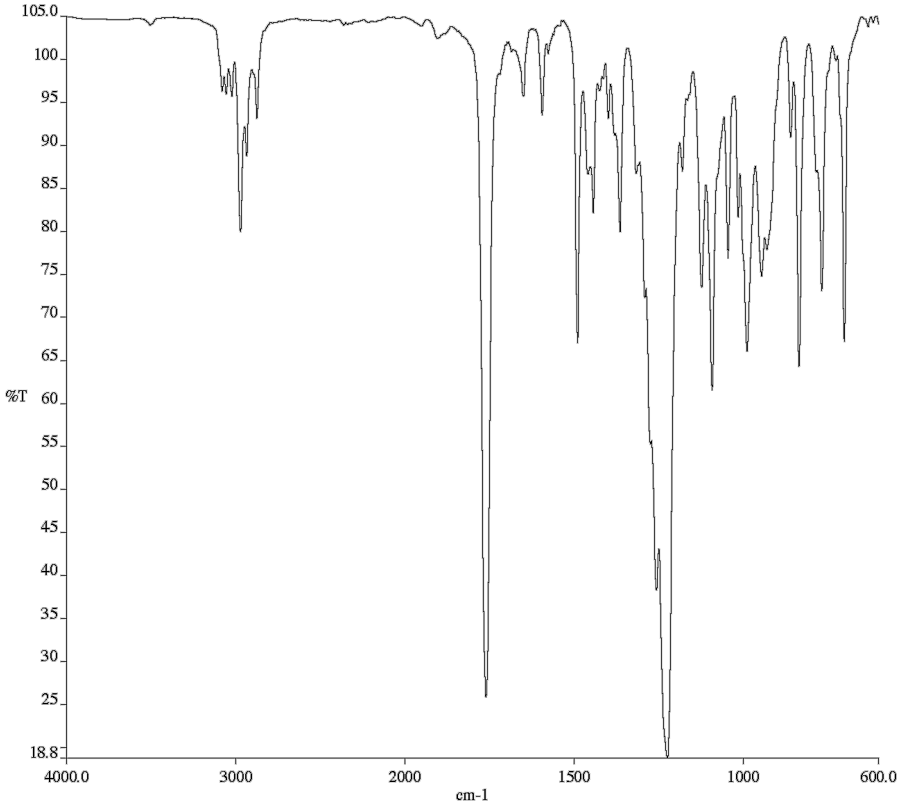



***Figure A4.98*** *Infrared spectrum (Thin Film, NaCl) of compound* ***20j****.*

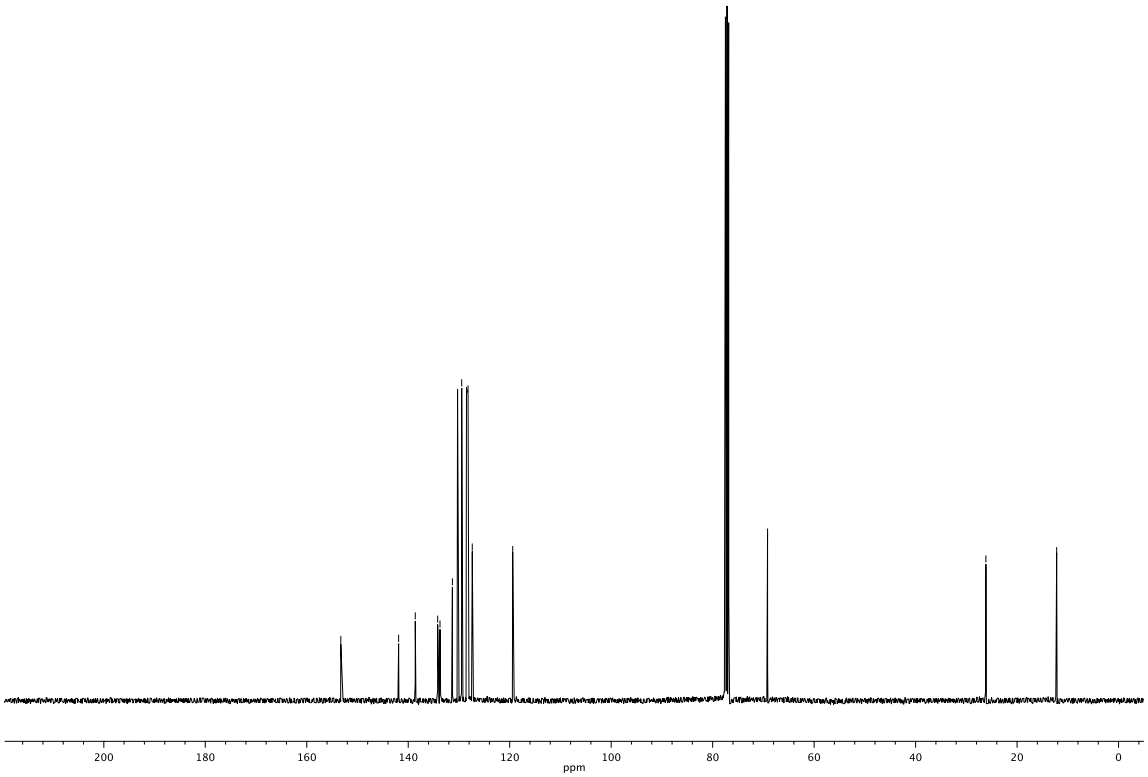



***Figure A4.99*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***20j****.*

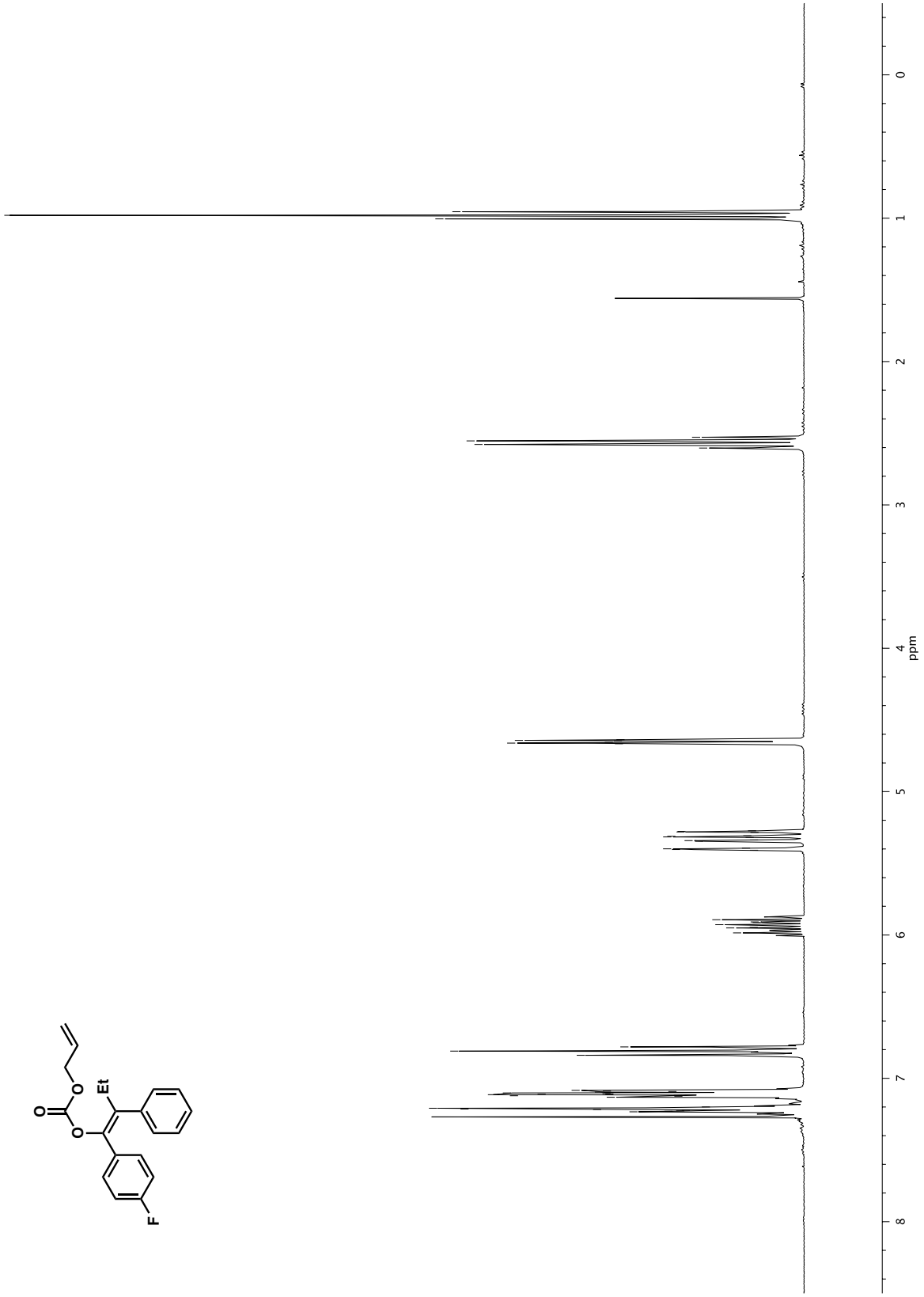



***Figure A4.100*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***20k****.*

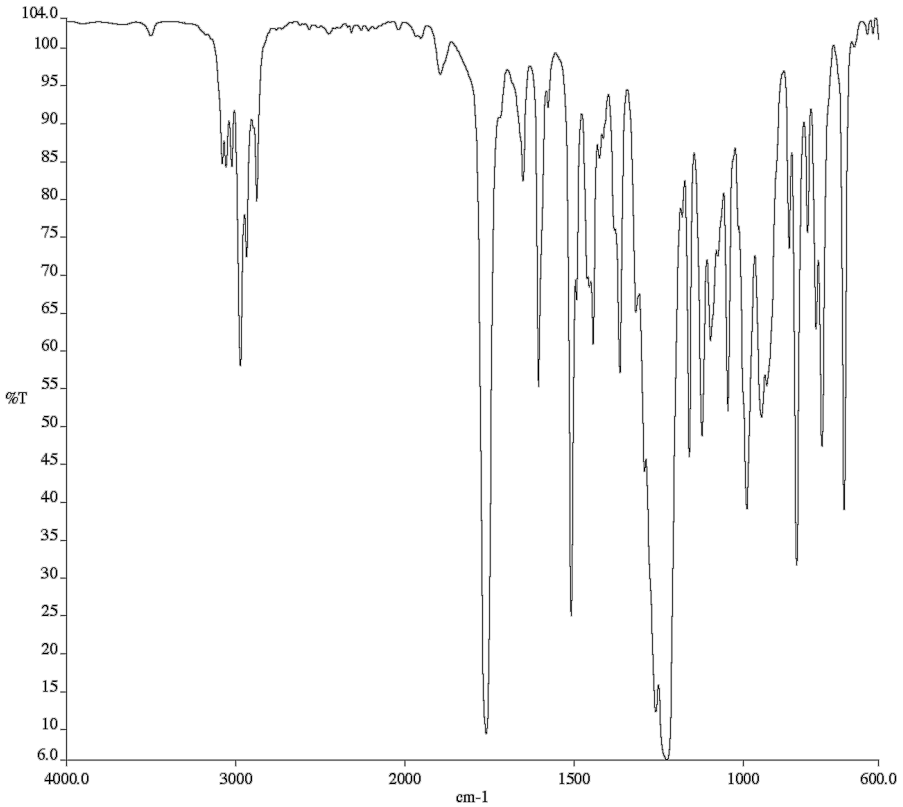



***Figure A4.101*** *Infrared spectrum (Thin Film, NaCl) of compound* ***20k****.*

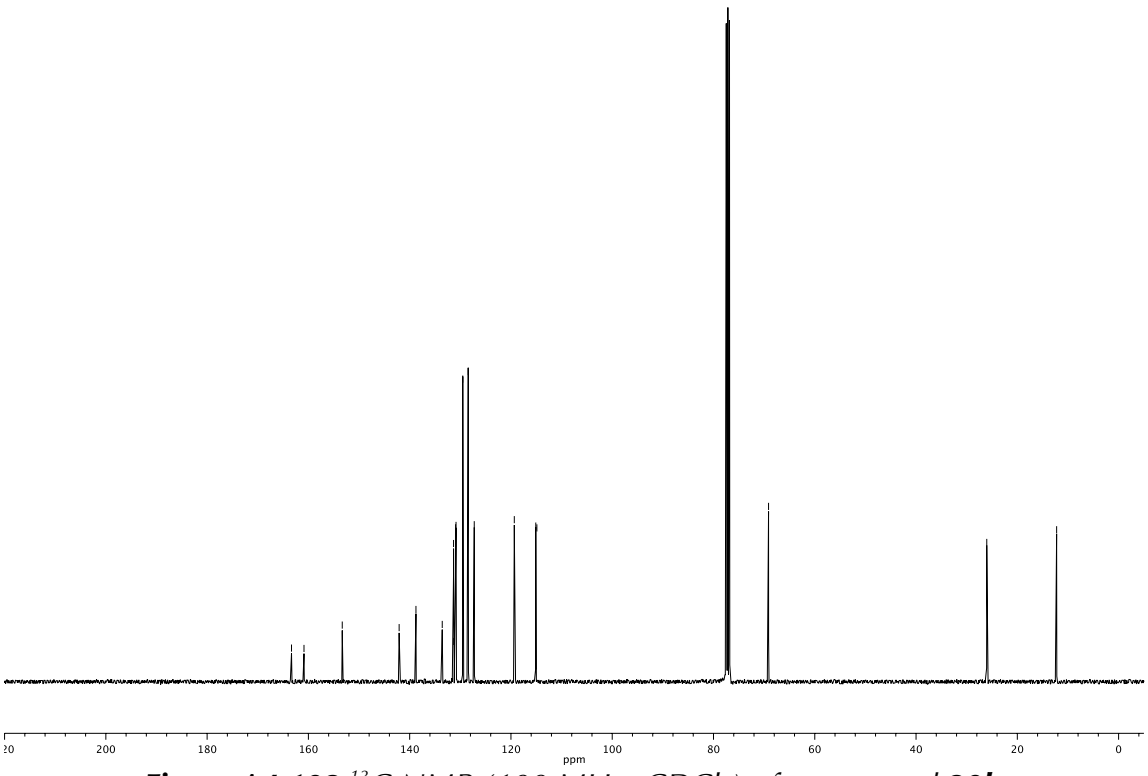



***Figure A4.102*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***20k****.*

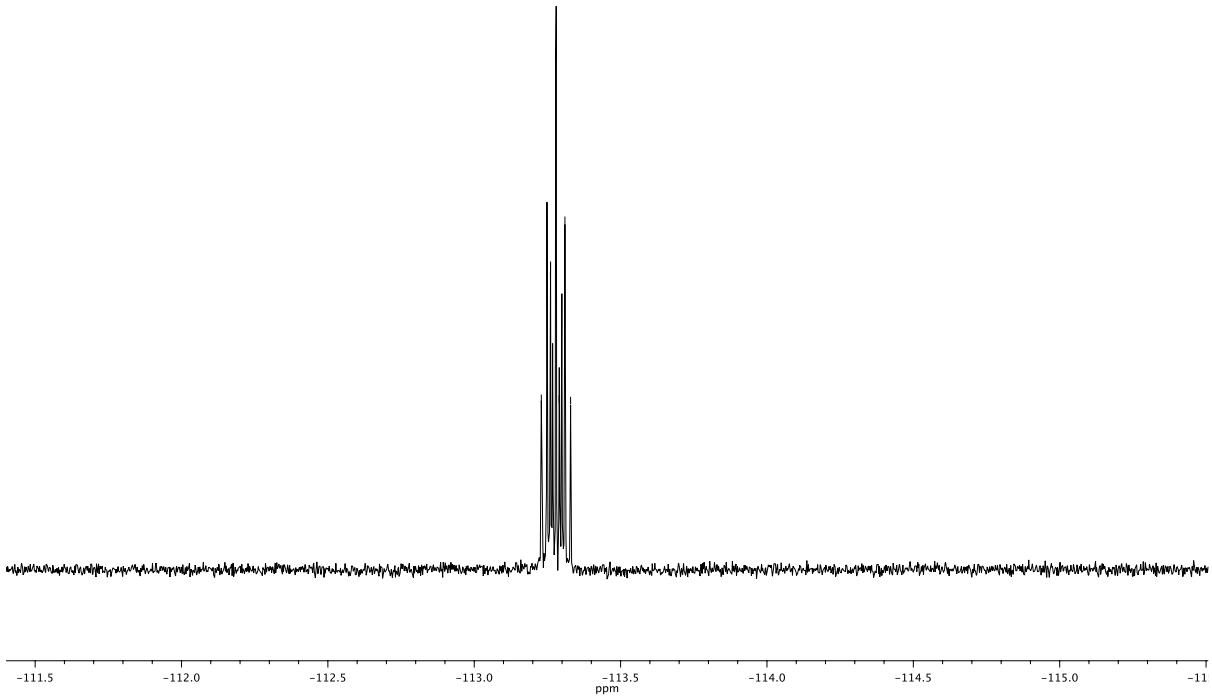



***Figure A4.103*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***20k****.*

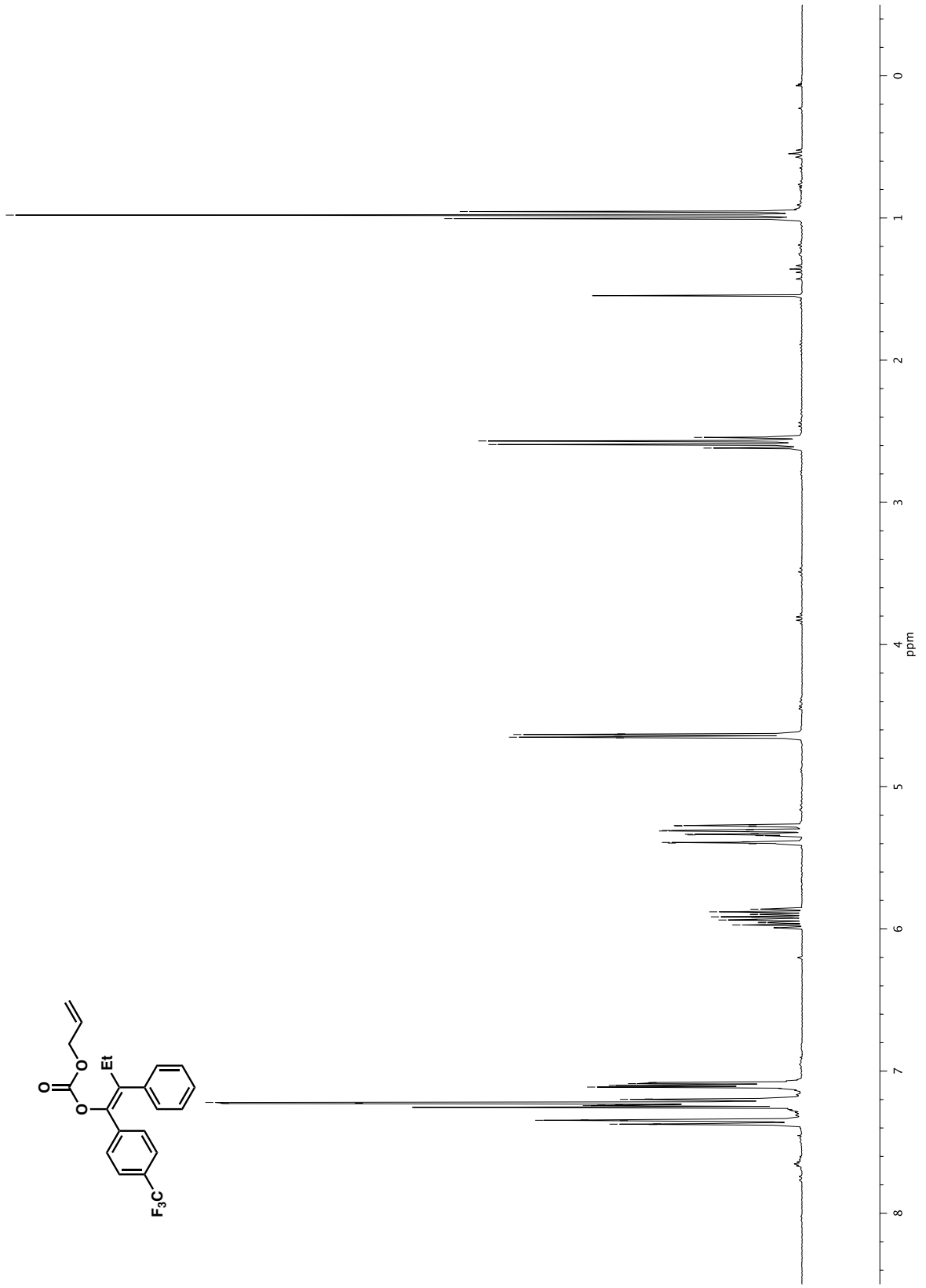



***Figure A4.104*** *$^1$H NMR (300 MHz, $CDCl_3$) of compound* ***20l****.*

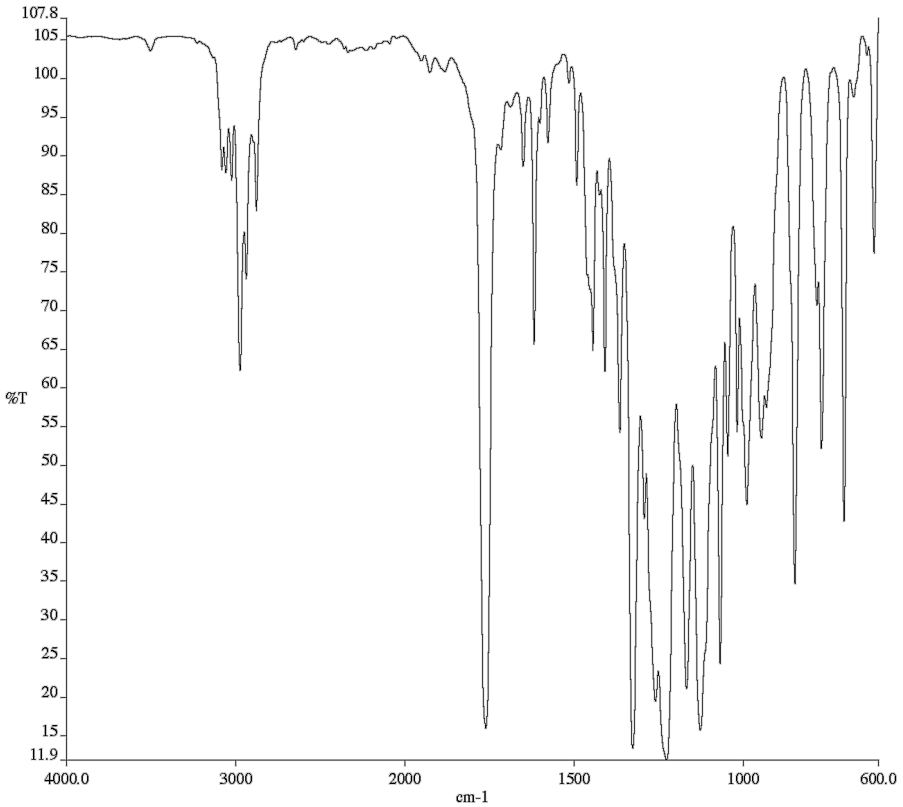



***Figure A4.105*** *Infrared spectrum (Thin Film, NaCl) of compound* ***20l****.*

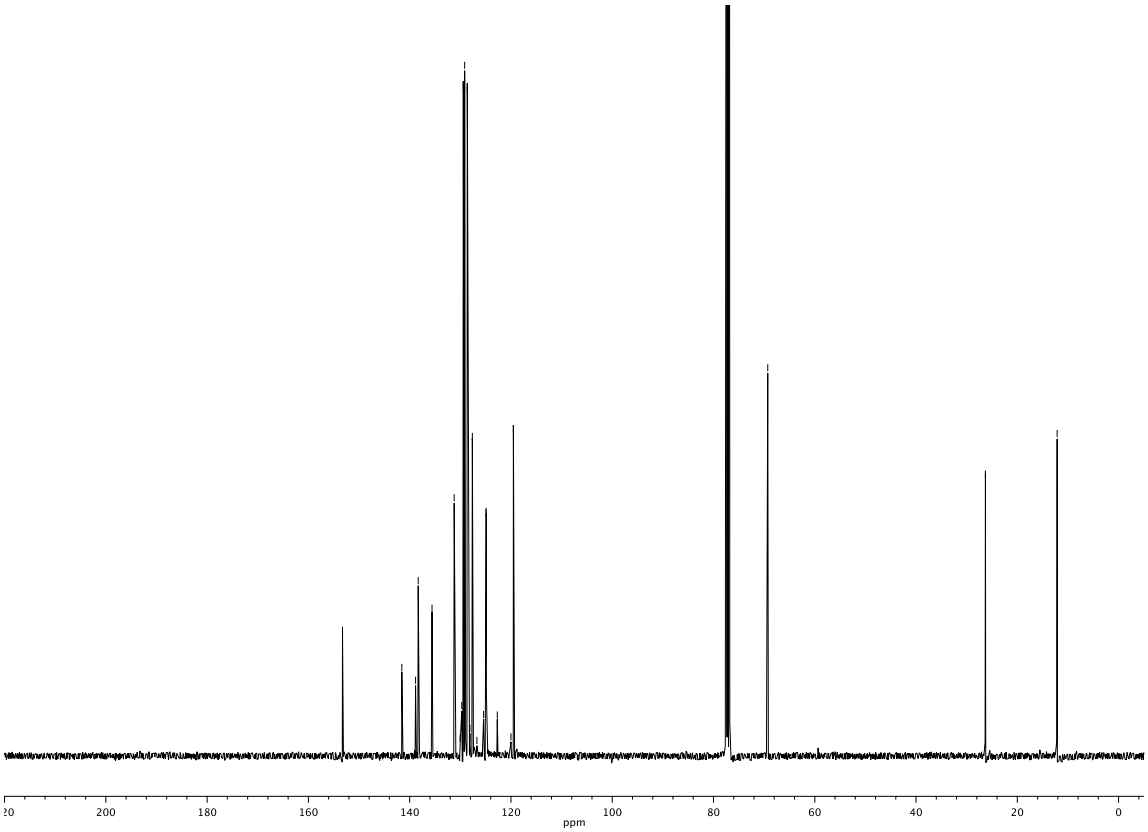



***Figure A4.106*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***20l****.*

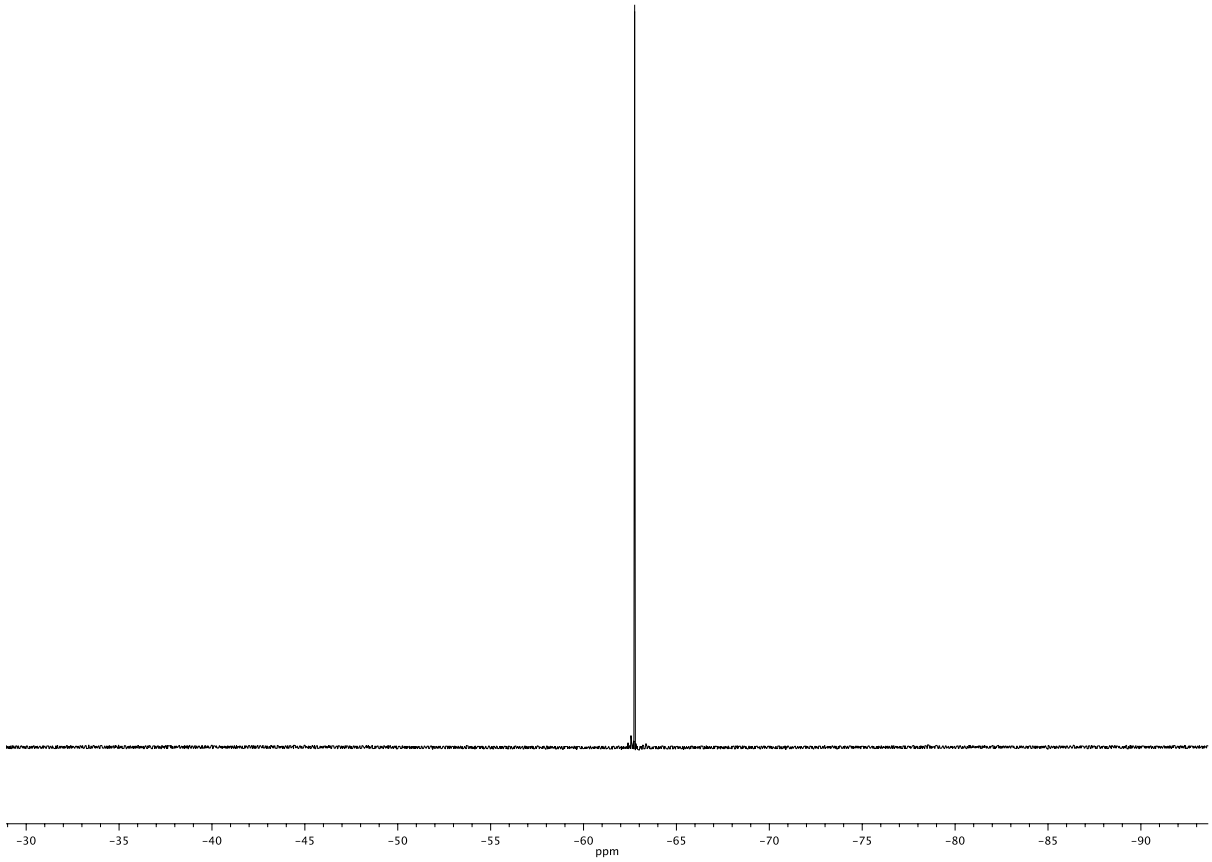



***Figure A4.107*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***20l****.*

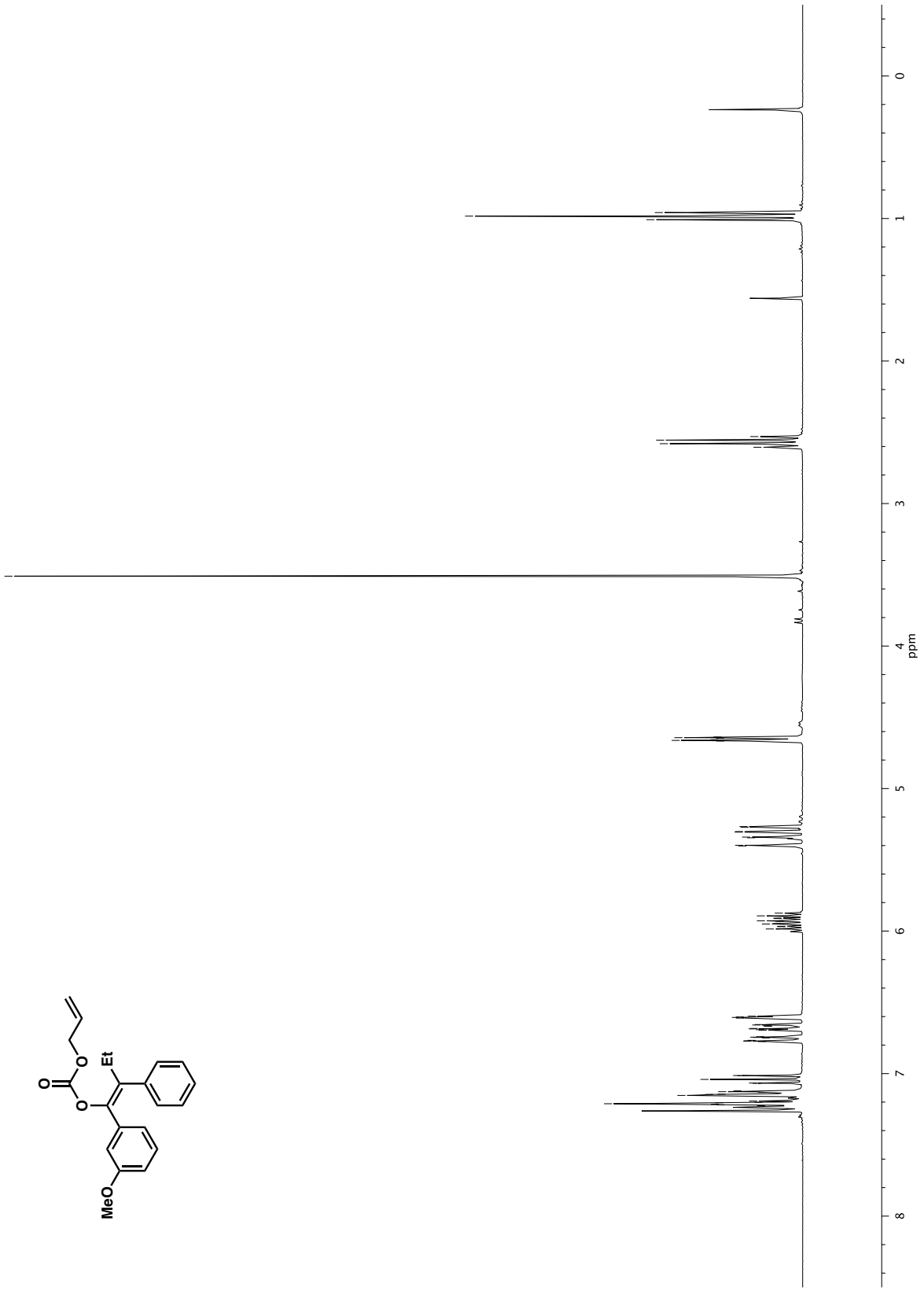



***Figure A4.108*** *$^1H$ NMR (300 MHz, $CDCl_3$) of compound* ***20m***.

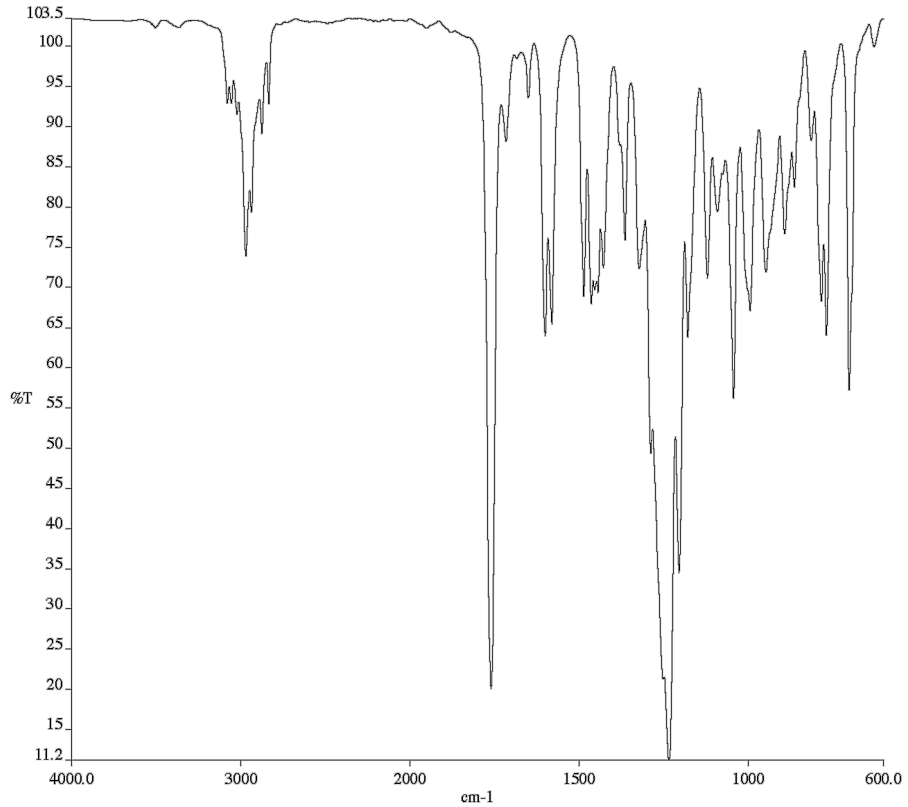



***Figure A4.109*** *Infrared spectrum (Thin Film, NaCl) of compound* ***20m****.*

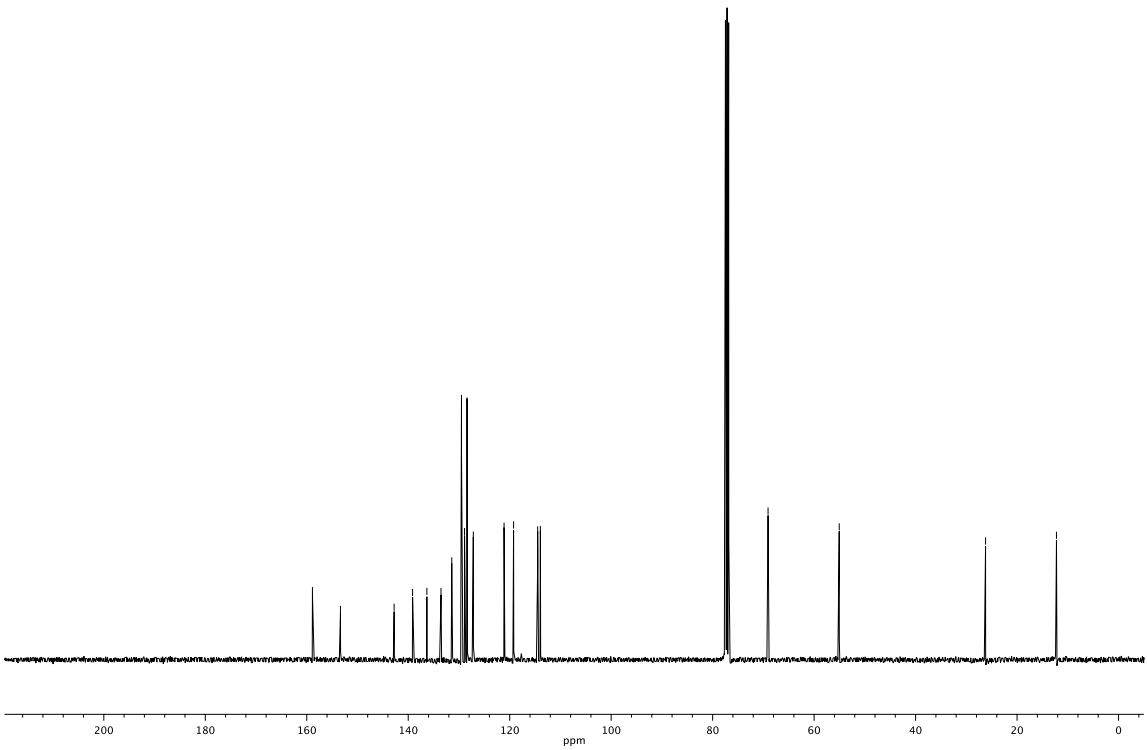



***Figure A4.110*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***20m****.*

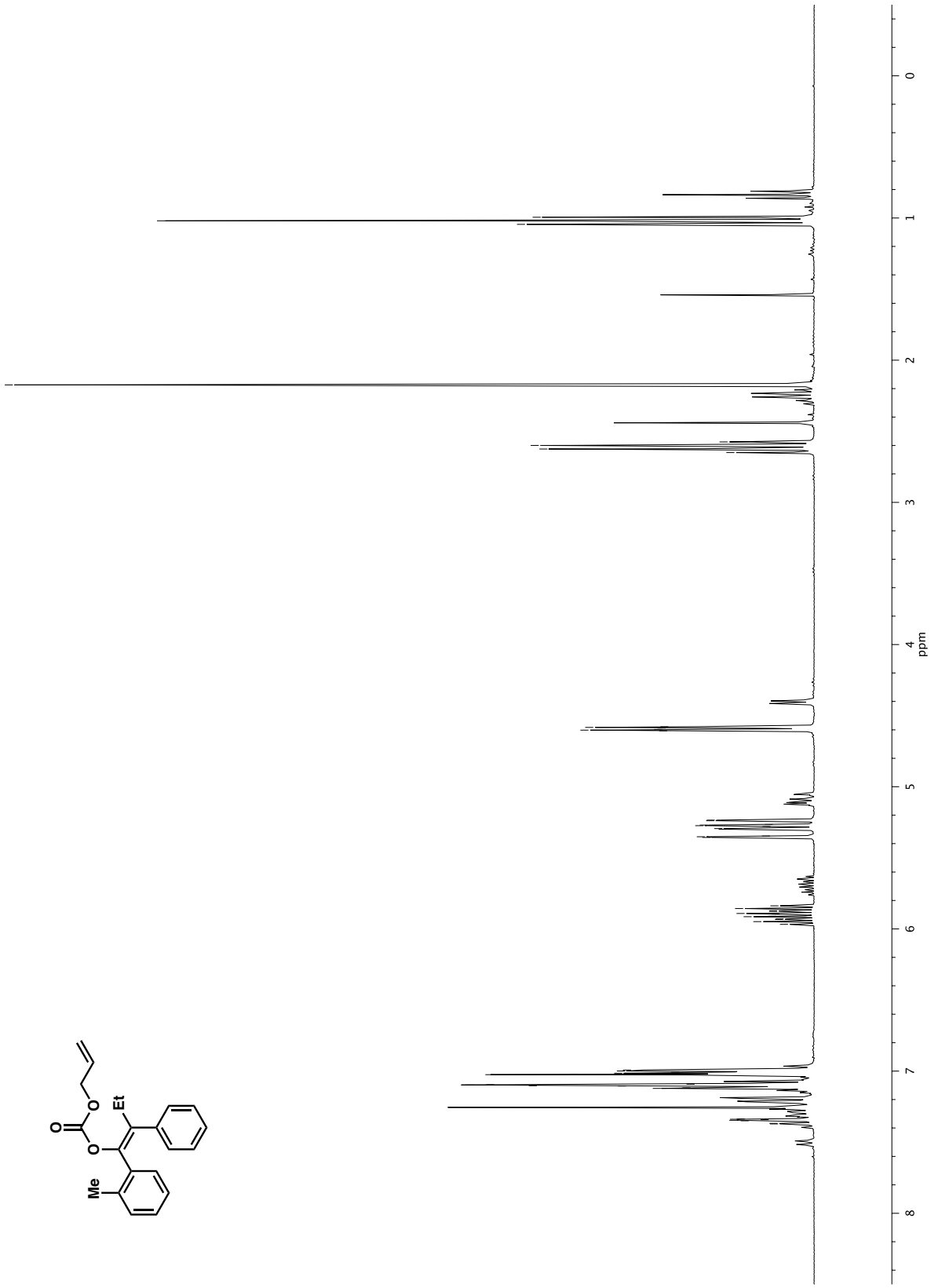



***Figure A4.111*** *$^1$H NMR (300 MHz, $CDCl_3$) of compound* ***20n***.

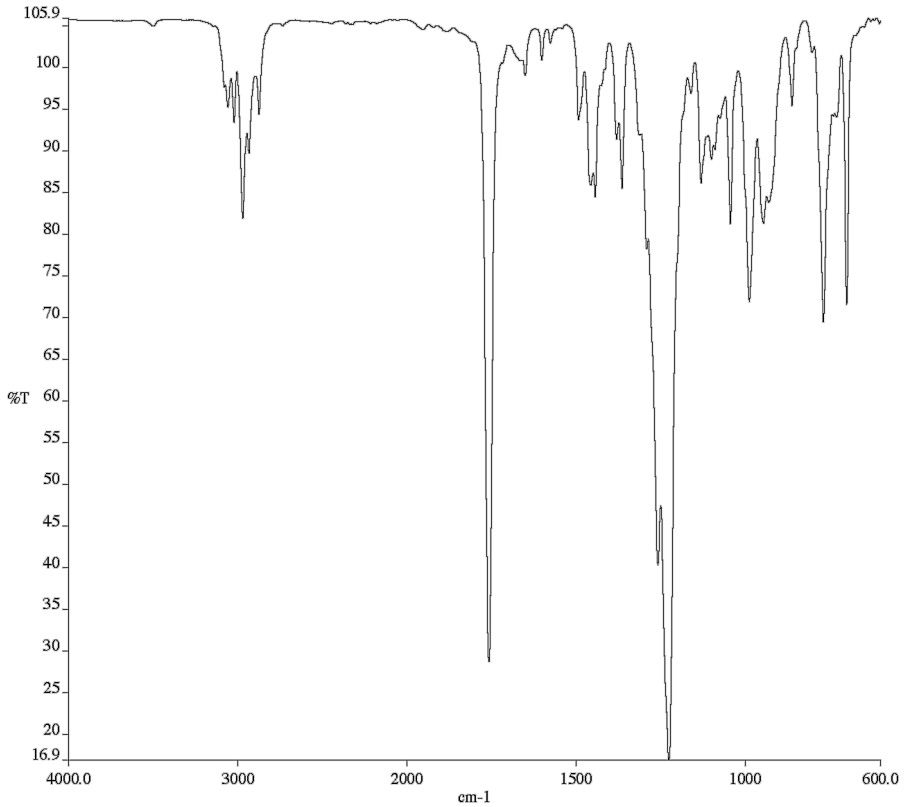



***Figure A4.112*** *Infrared spectrum (Thin Film, NaCl) of compound* ***20n***.

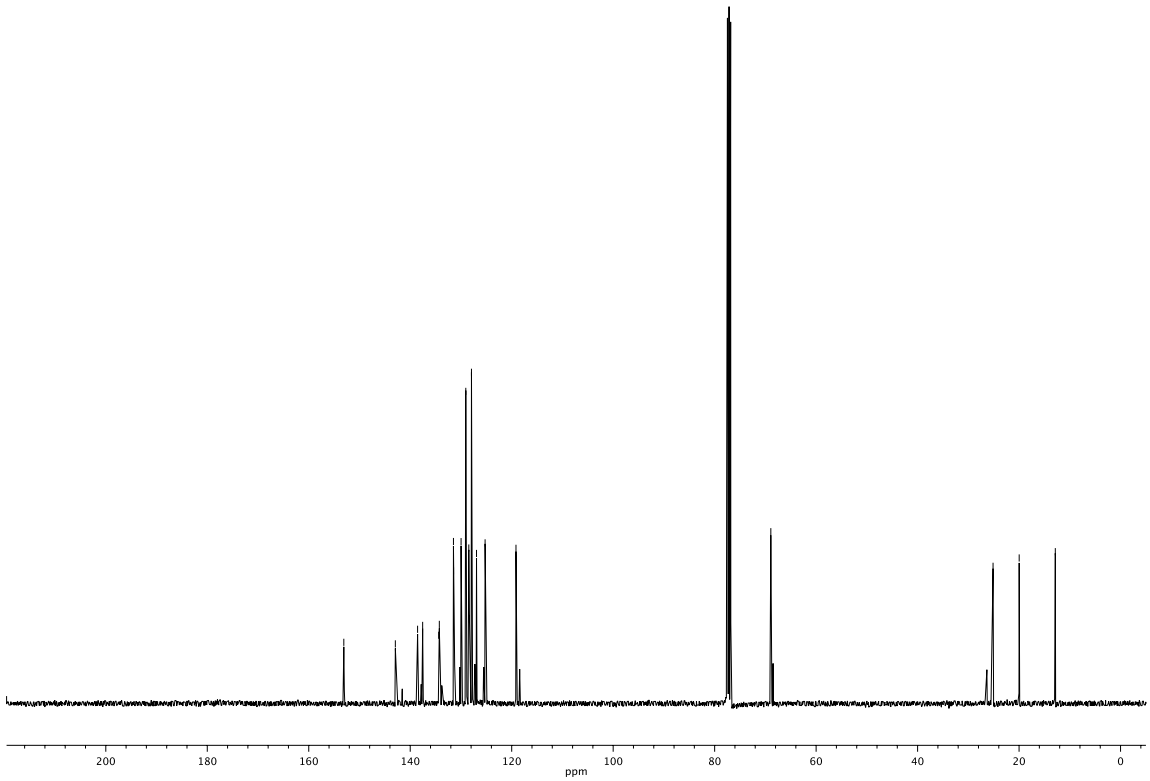



***Figure A4.113*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***20n***.

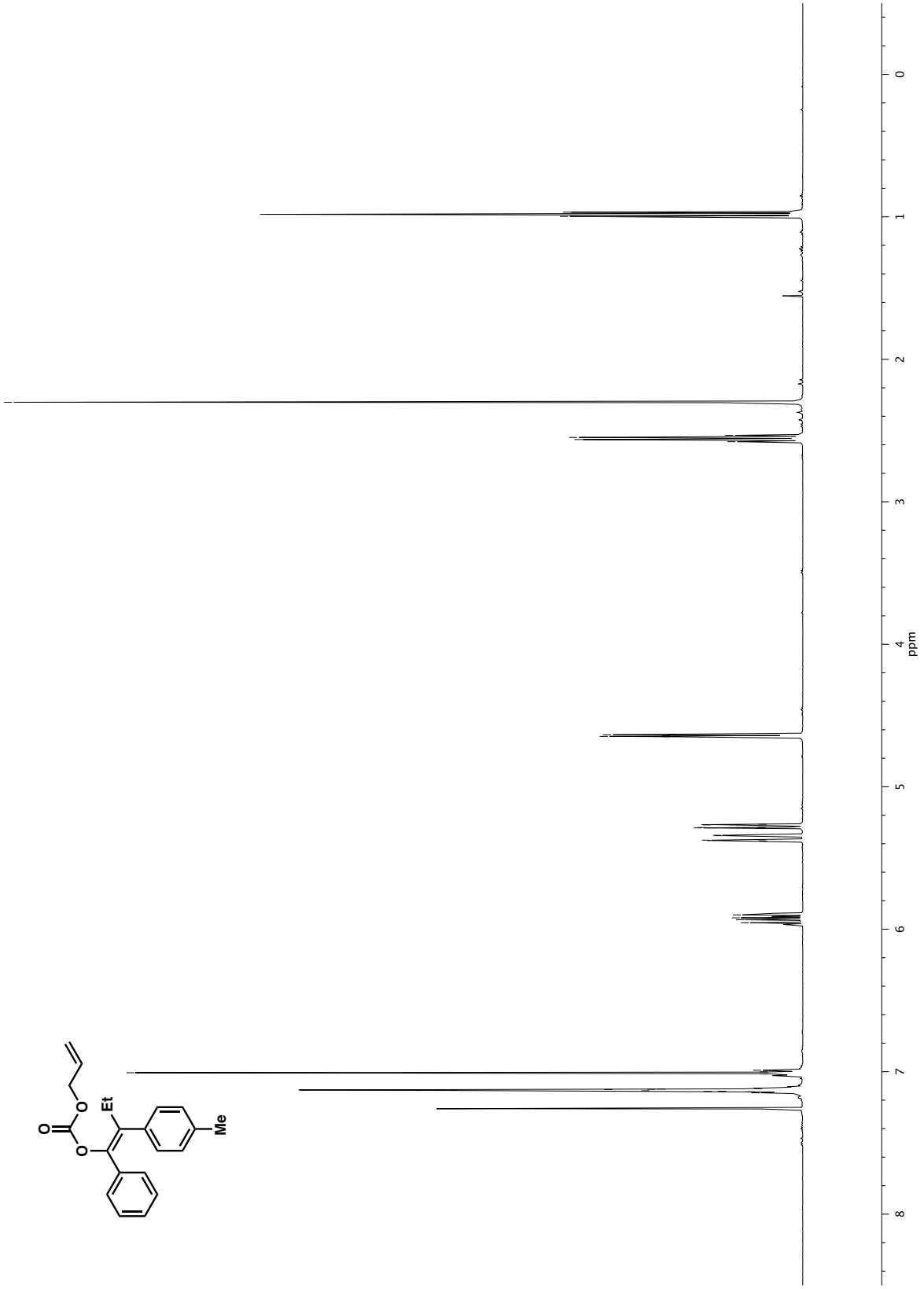



***Figure A4.114*** *$^1$H NMR (300 MHz, $CDCl_3$) of compound* ***20o***.

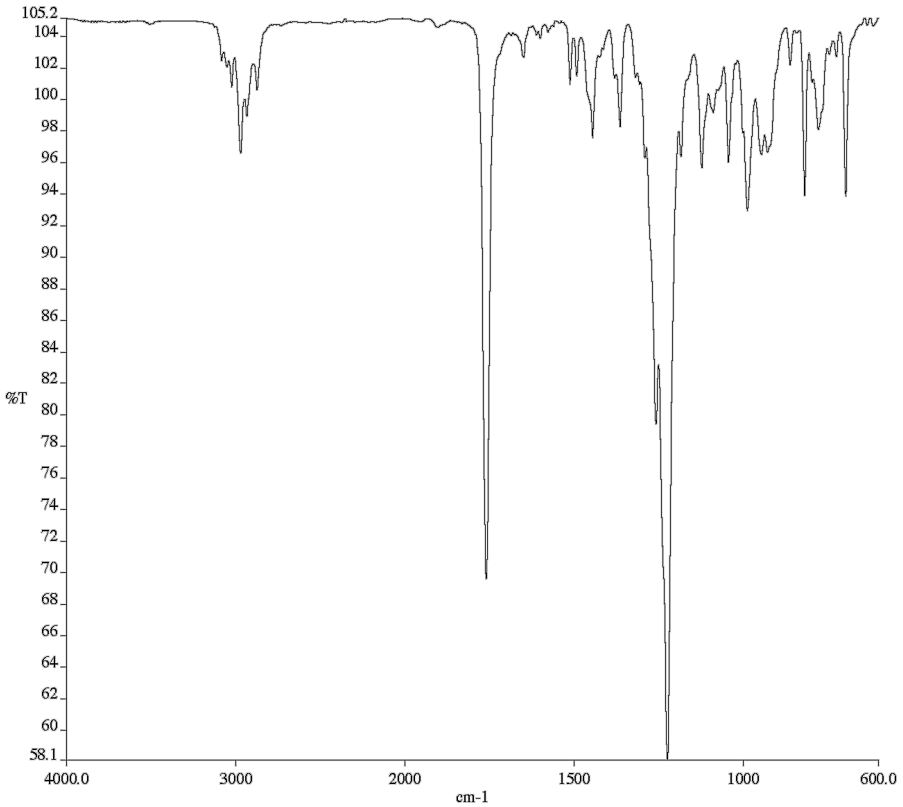



***Figure A4.115*** *Infrared spectrum (Thin Film, NaCl) of compound* ***20o****.*

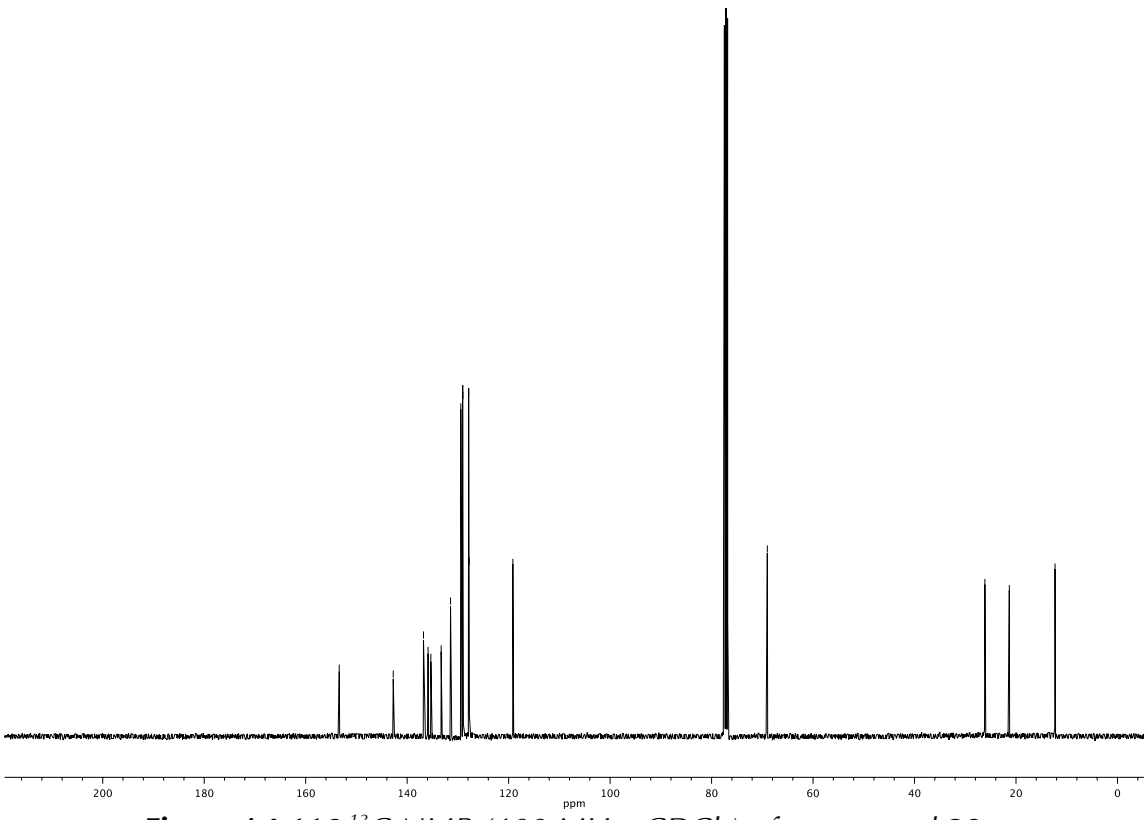



***Figure A4.116*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***20o****.*

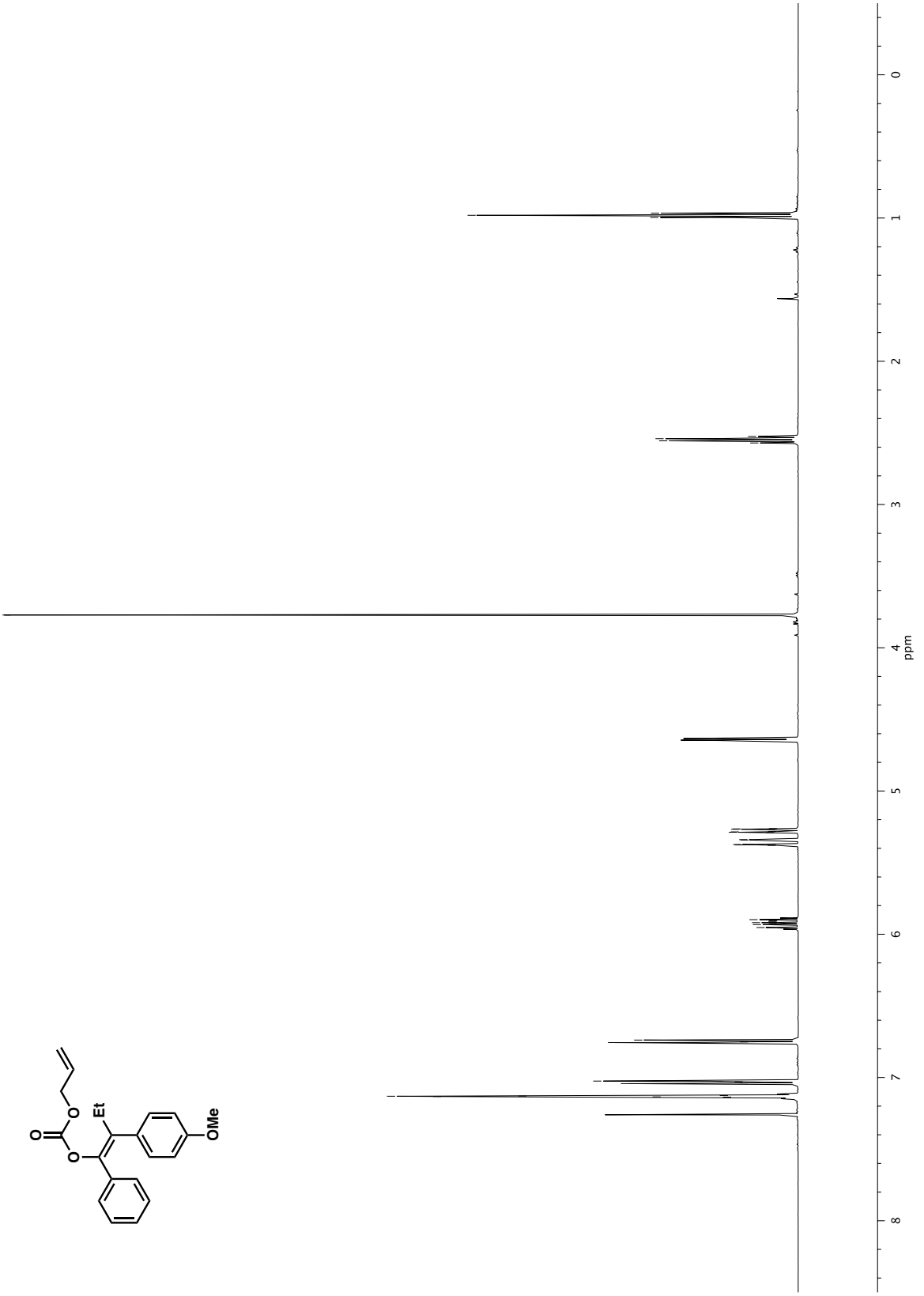



***Figure A4.117*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***20p***.

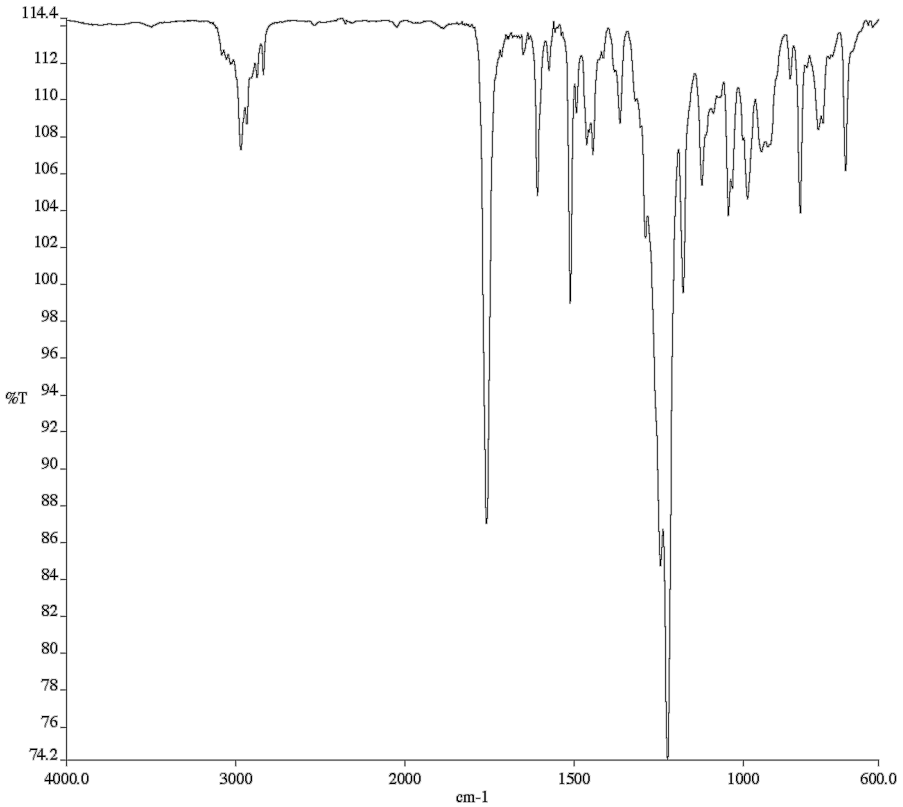



***Figure A4.118*** *Infrared spectrum (Thin Film, NaCl) of compound* ***20p***.

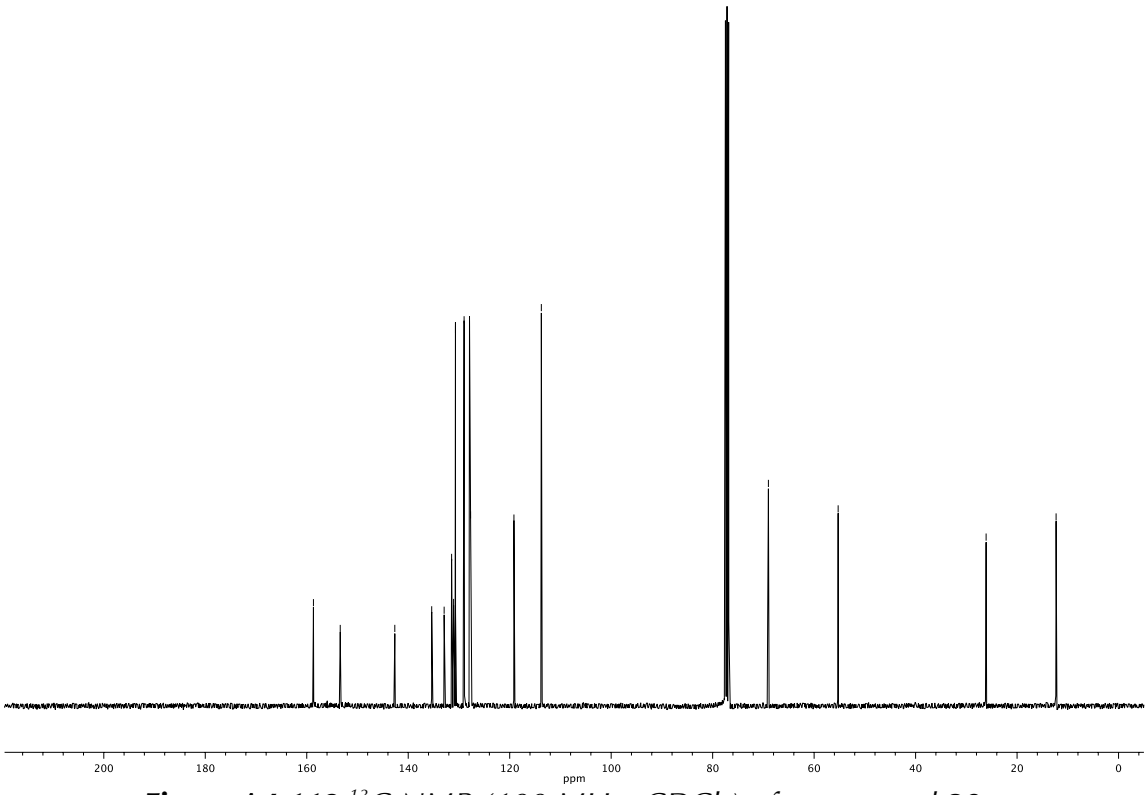



***Figure A4.119*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***20p***.

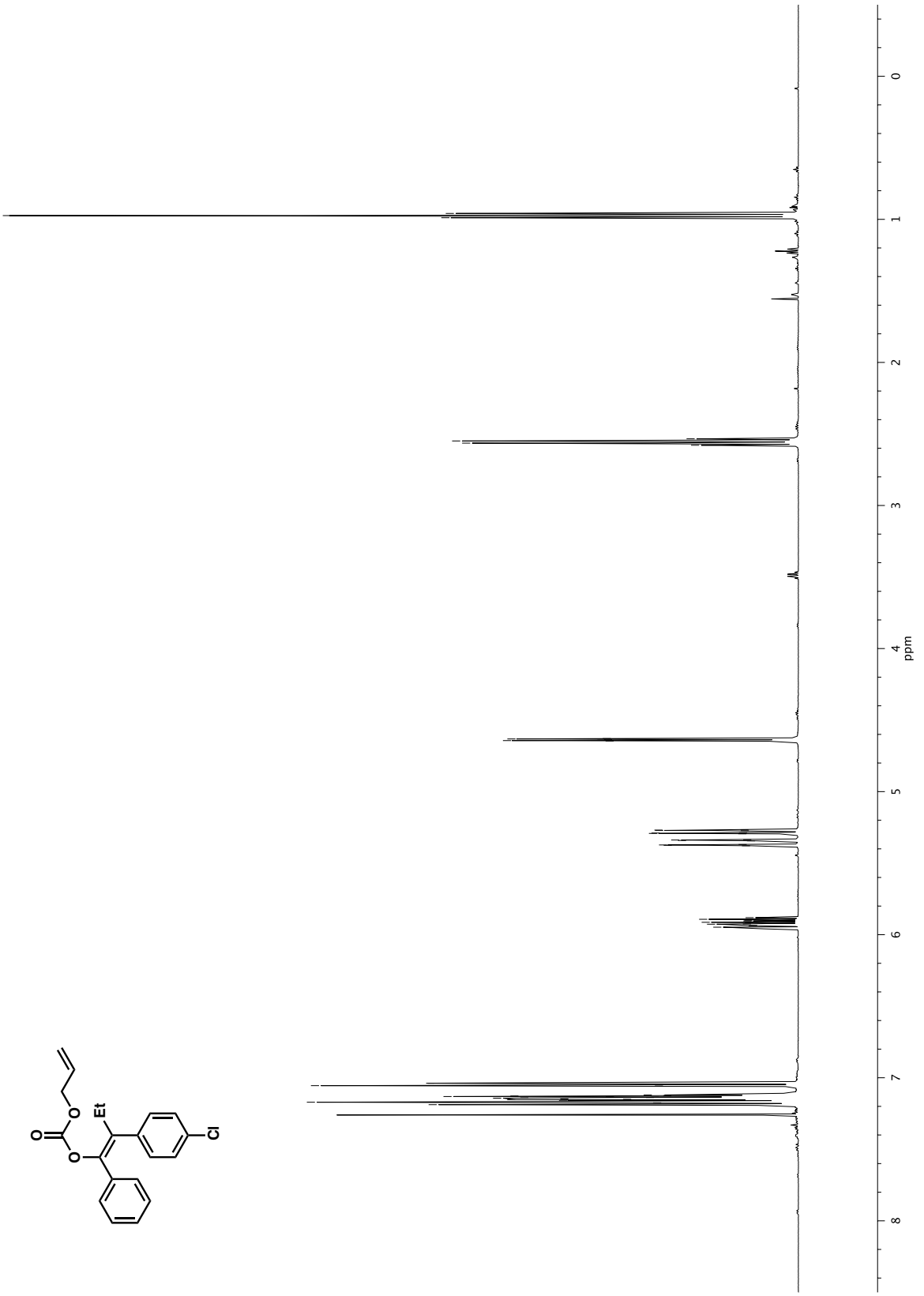



***Figure A4.120*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***20q***.

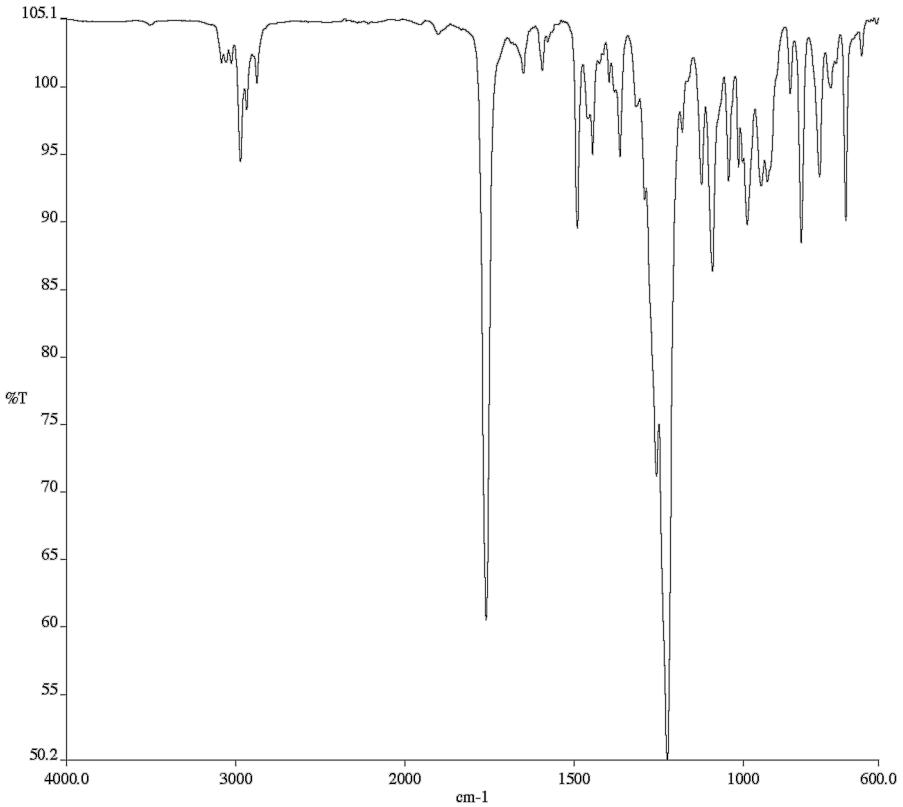



***Figure A4.121*** *Infrared spectrum (Thin Film, NaCl) of compound* ***20q***.

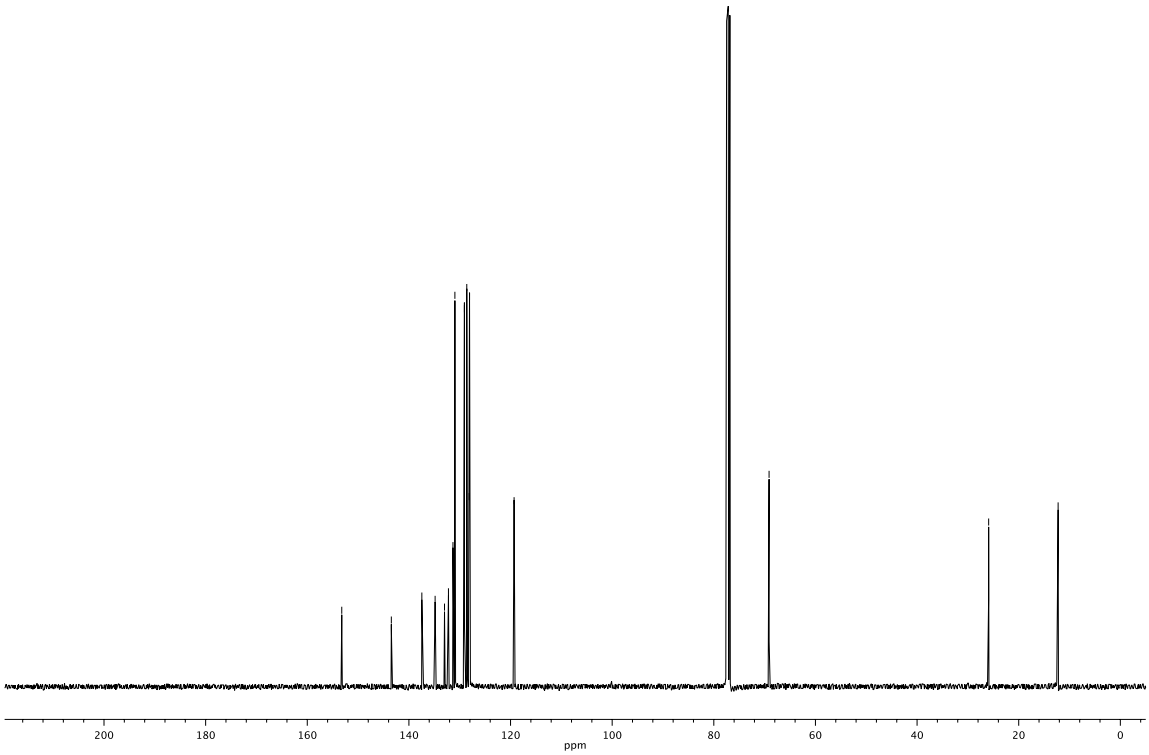



***Figure A4.122*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***20q***.

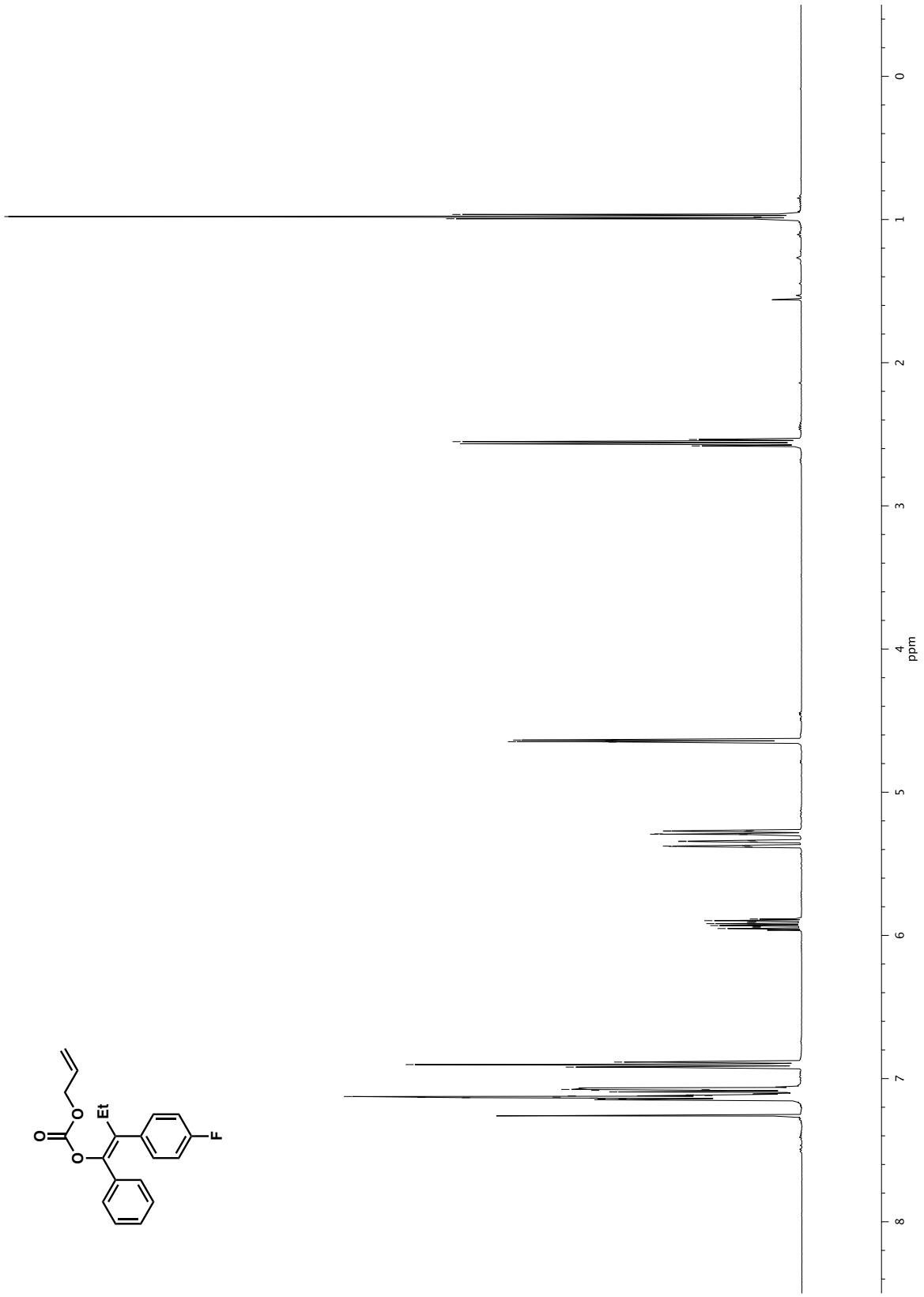



***Figure A4.123*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***20r****.*

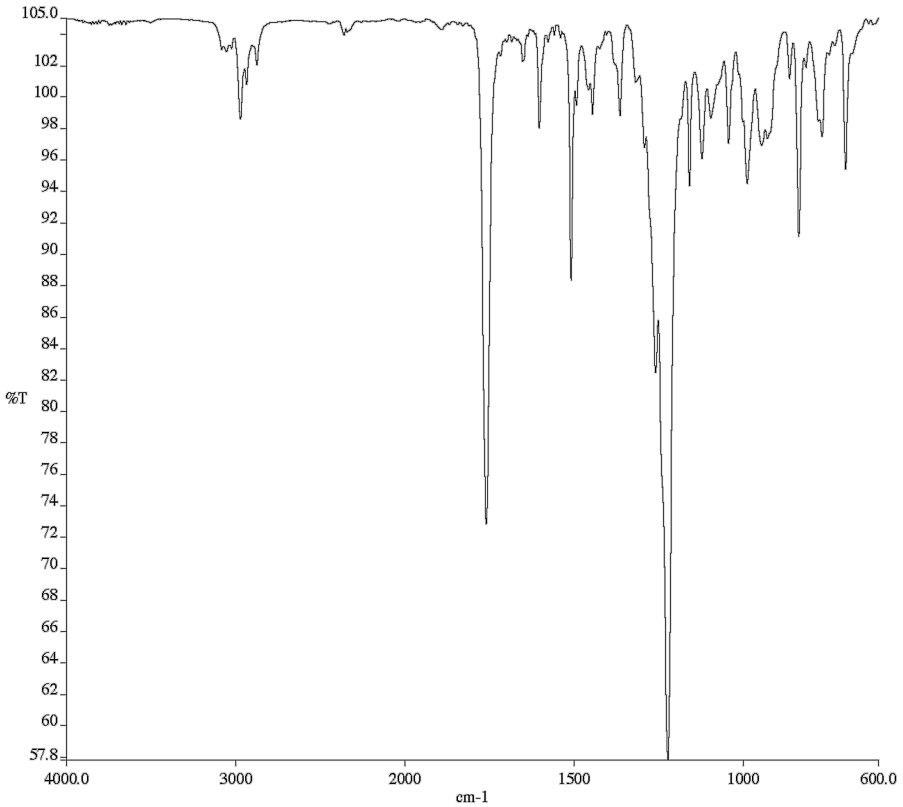



***Figure A4.124*** *Infrared spectrum (Thin Film, NaCl) of compound* ***20r****.*

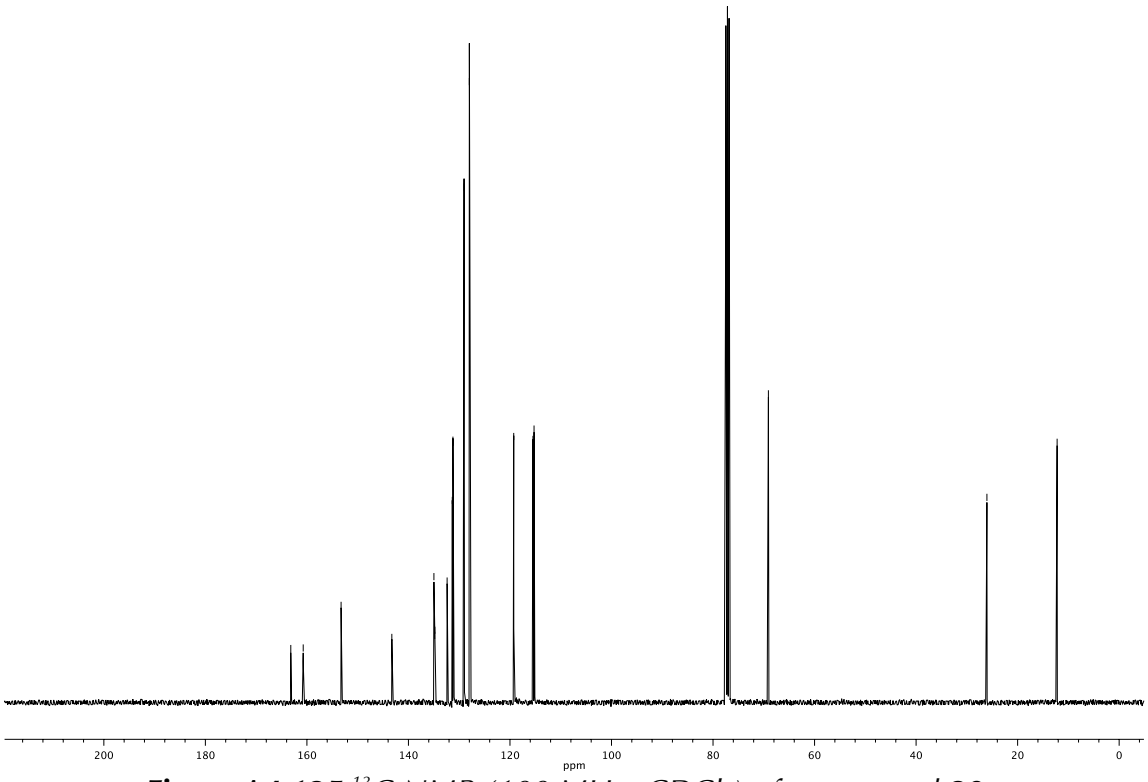



***Figure A4.125*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***20r****.*

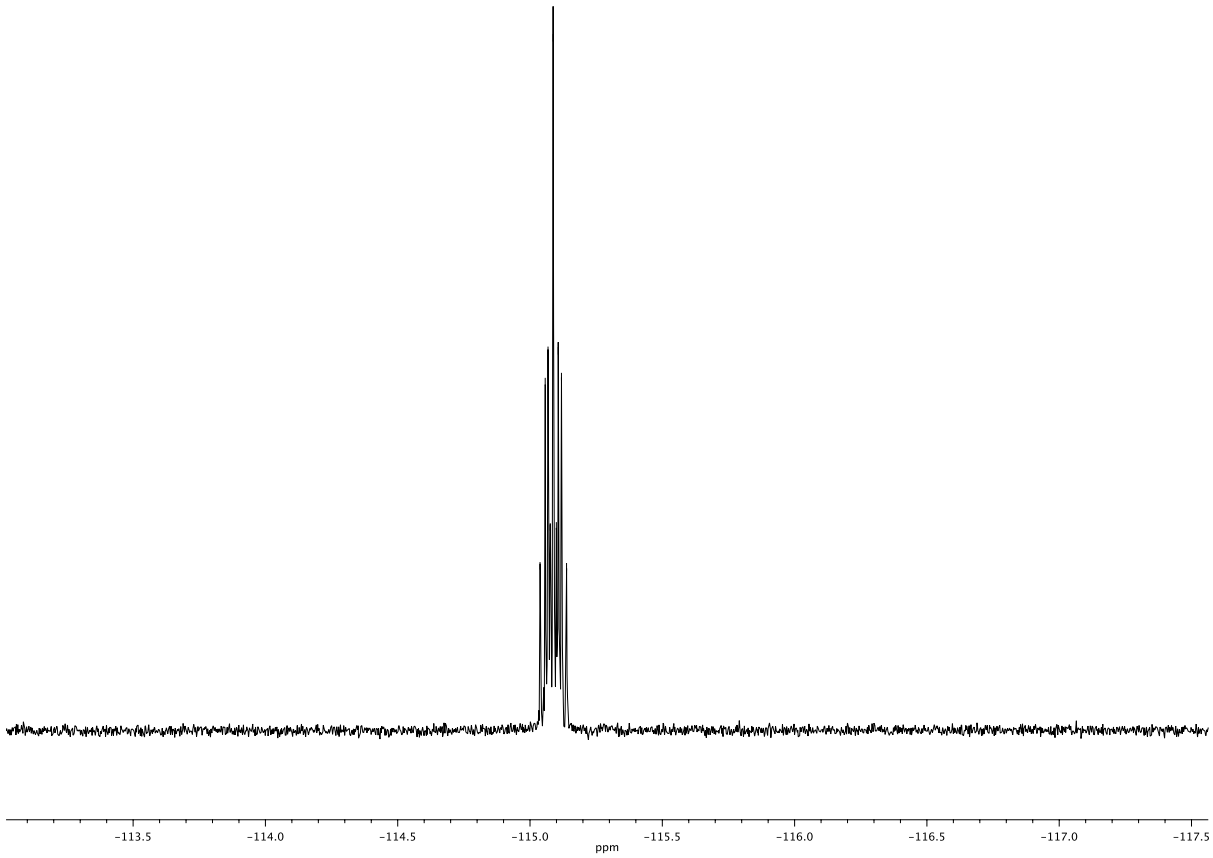



***Figure A4.126*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***20r***.

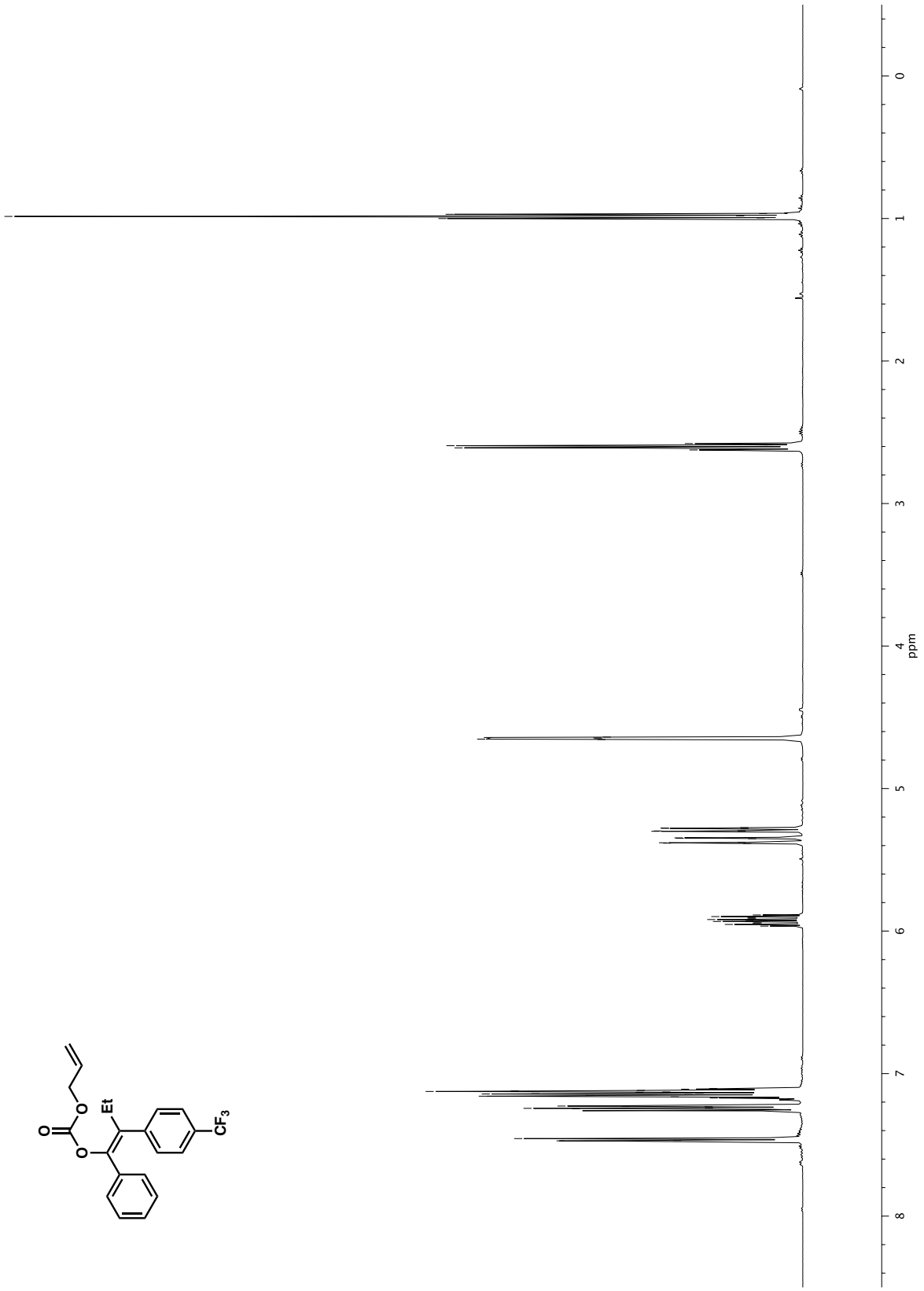



***Figure A4.127*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***20s***.

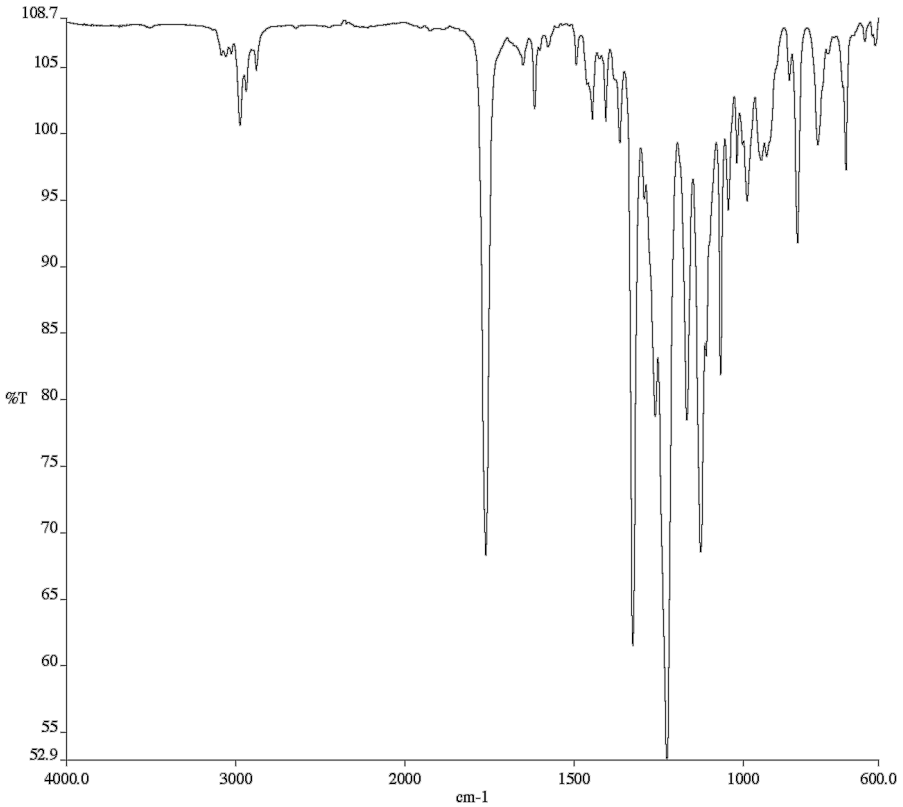



***Figure A4.128*** *Infrared spectrum (Thin Film, NaCl) of compound* ***20s****.*

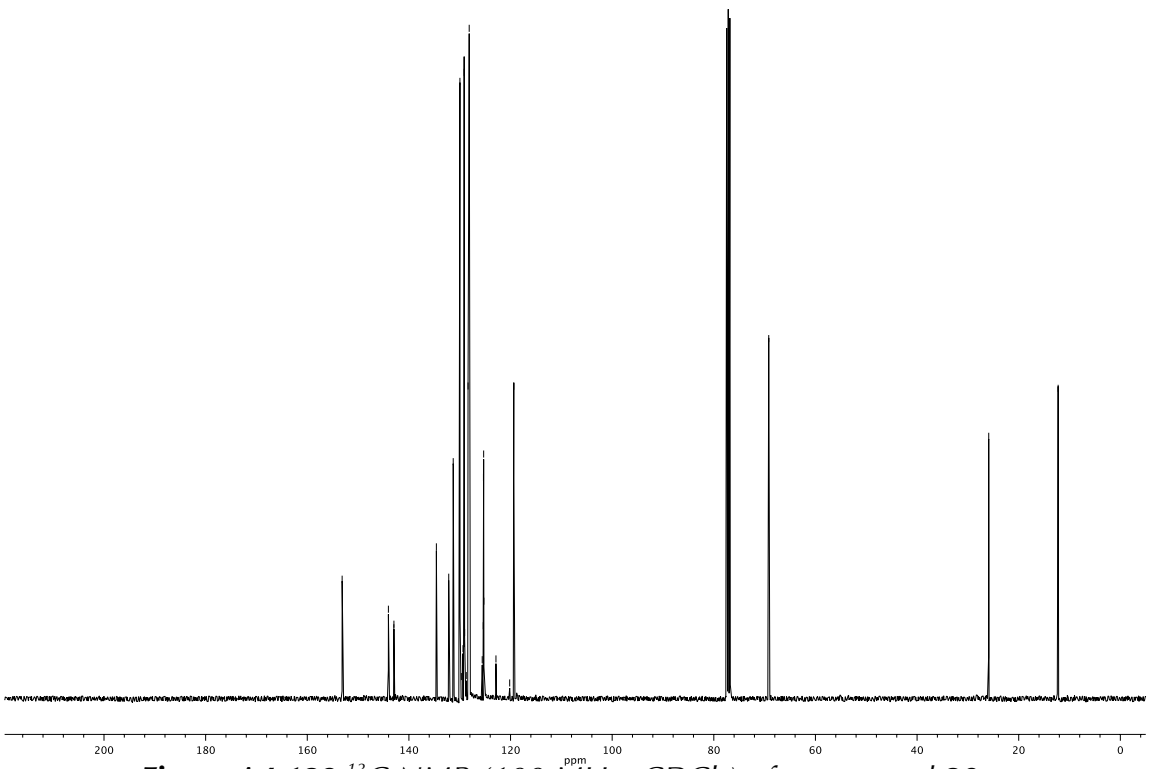



***Figure A4.129*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***20s****.*

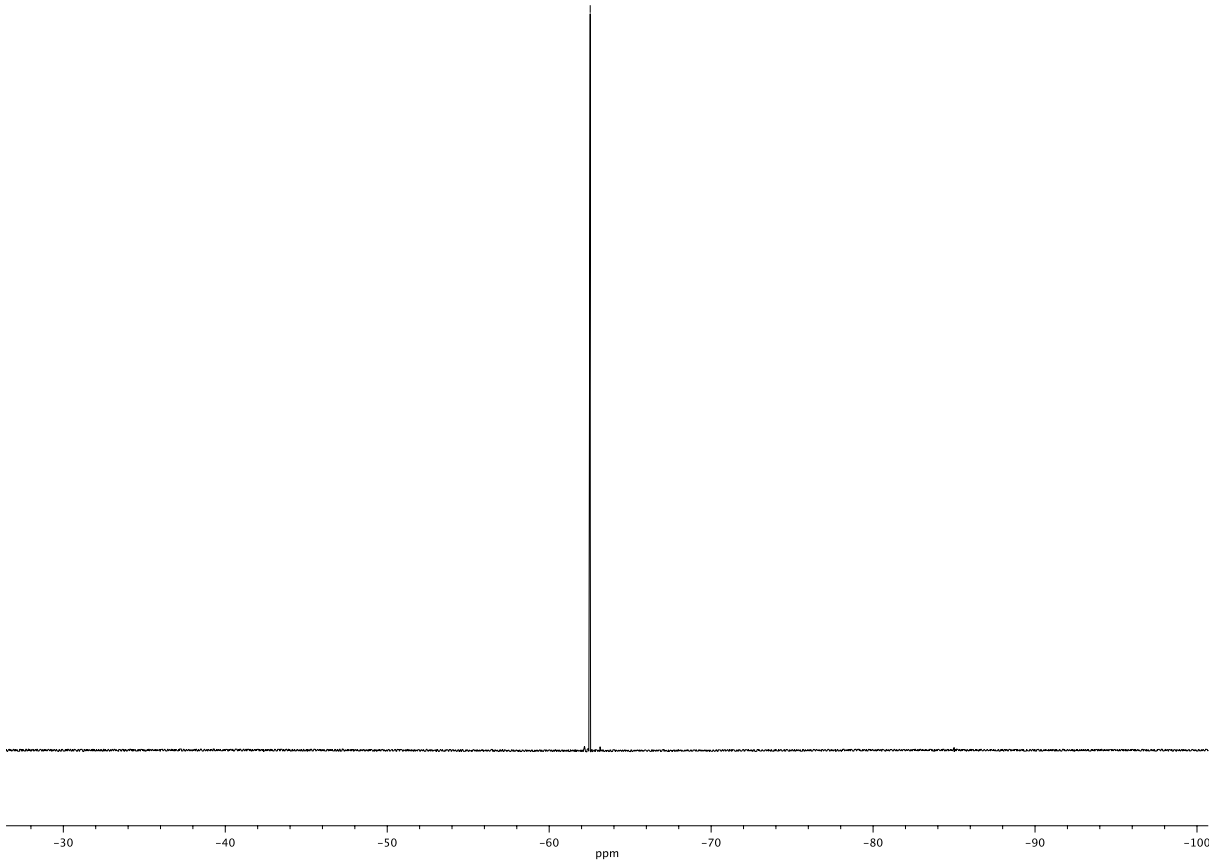



***Figure A4.130*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***20s***.

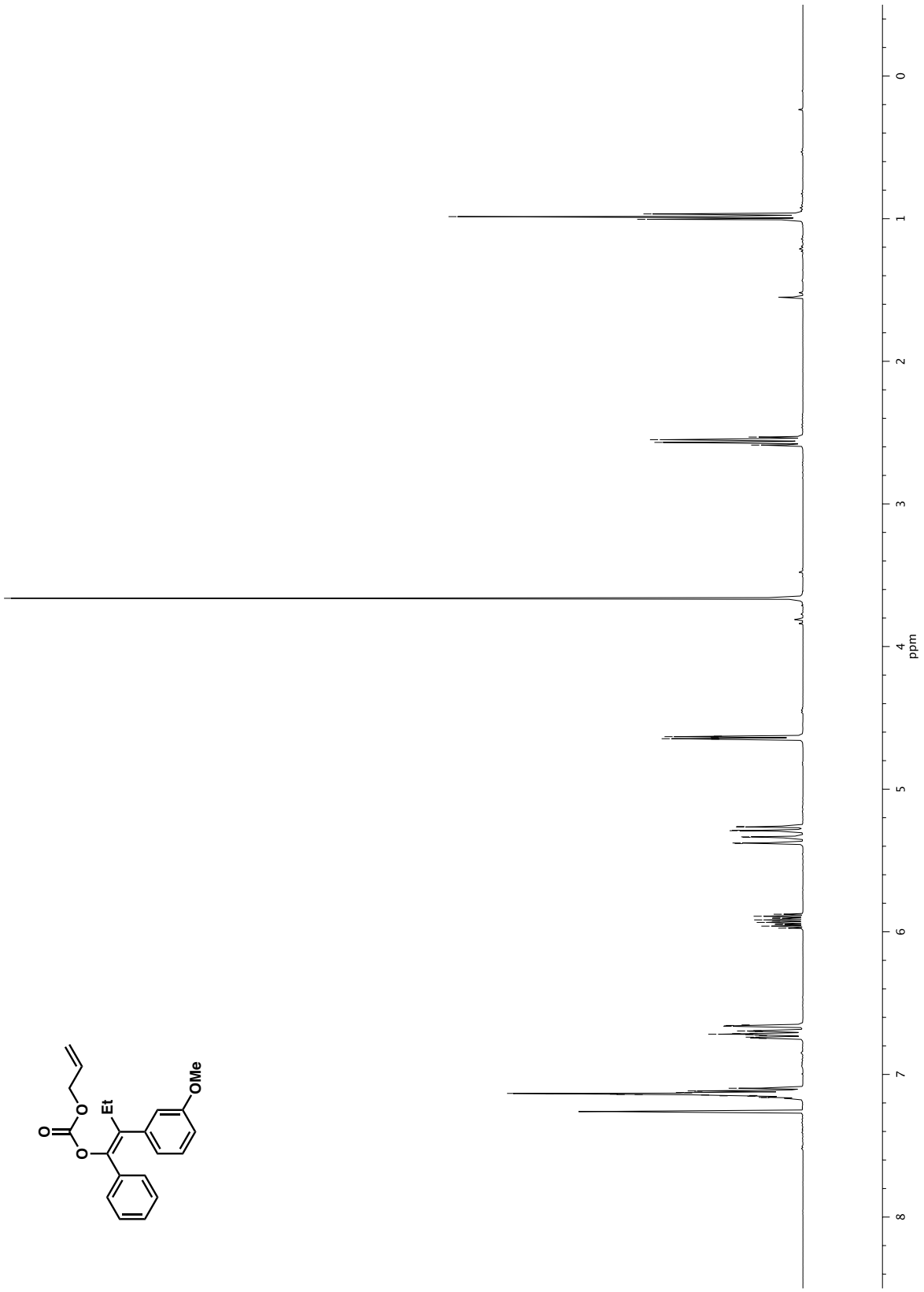



***Figure A4.131*** *$^1$H NMR (400 MHz, $CDCl_3$) of compound* ***20t****.*

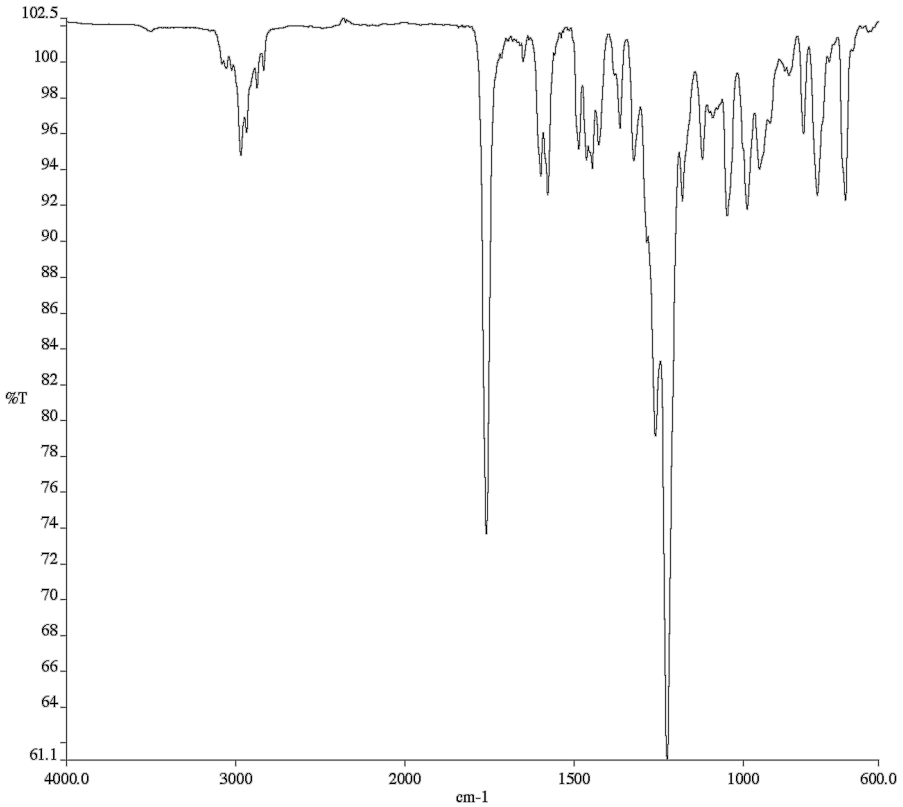



***Figure A4.132*** *Infrared spectrum (Thin Film, NaCl) of compound* ***20t****.*

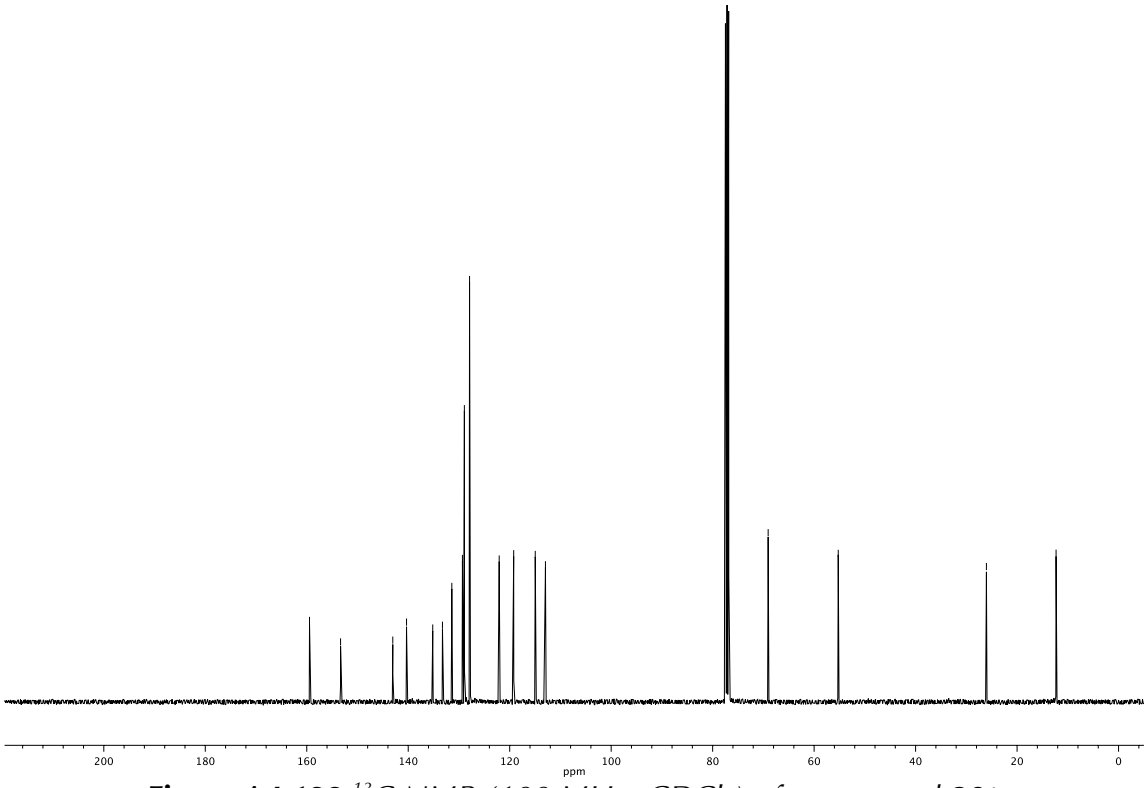



***Figure A4.133*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***20t****.*

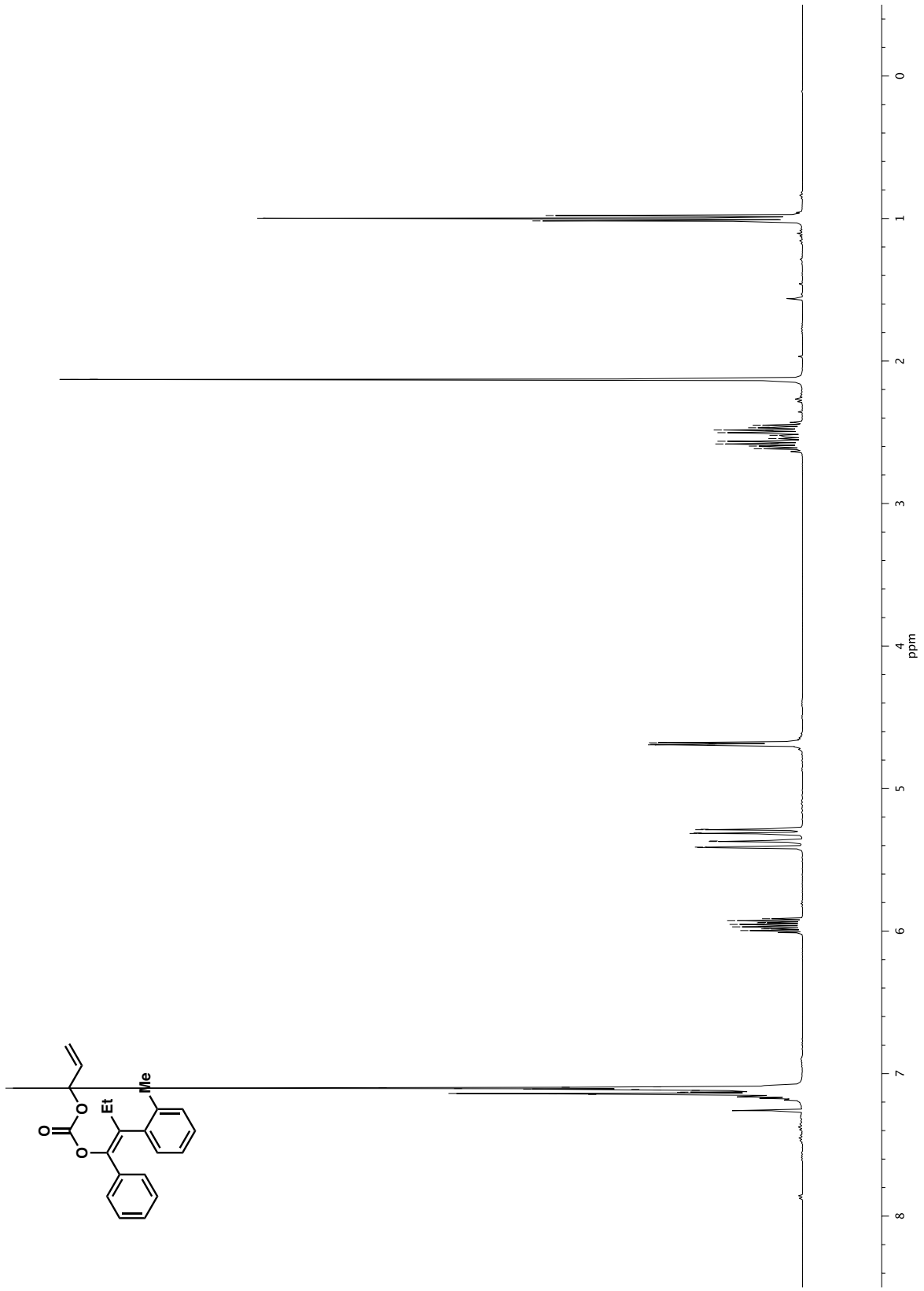



***Figure A4.134*** *$^1$H NMR (400 MHz, $CDCl_3$) of compound* ***20u***.

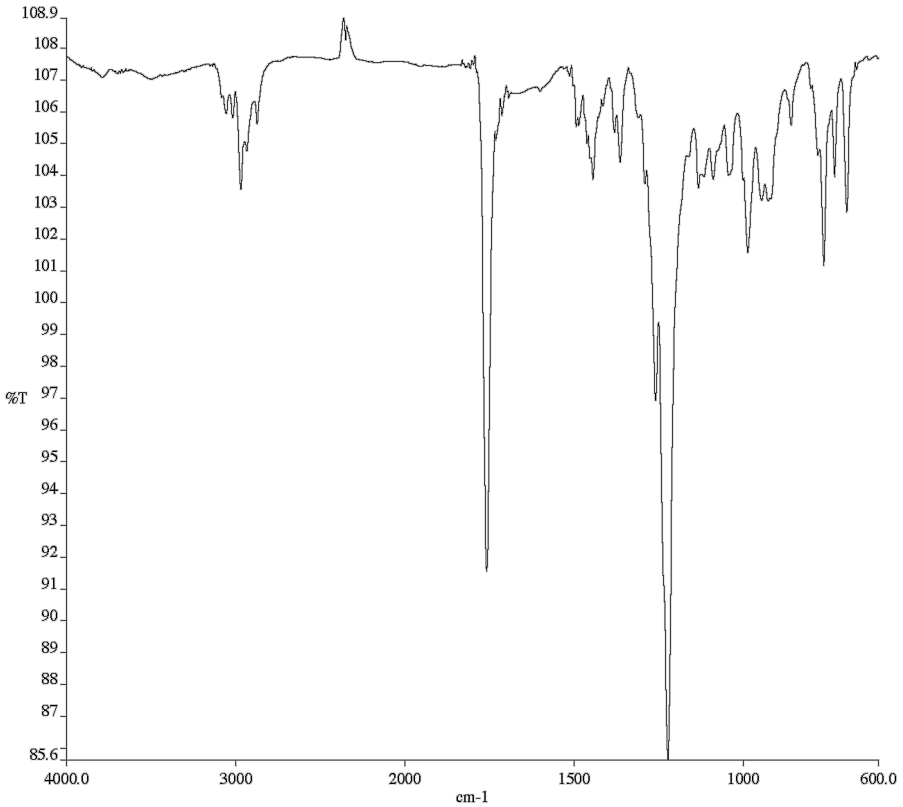



***Figure A4.135*** *Infrared spectrum (Thin Film, NaCl) of compound* ***20u****.*

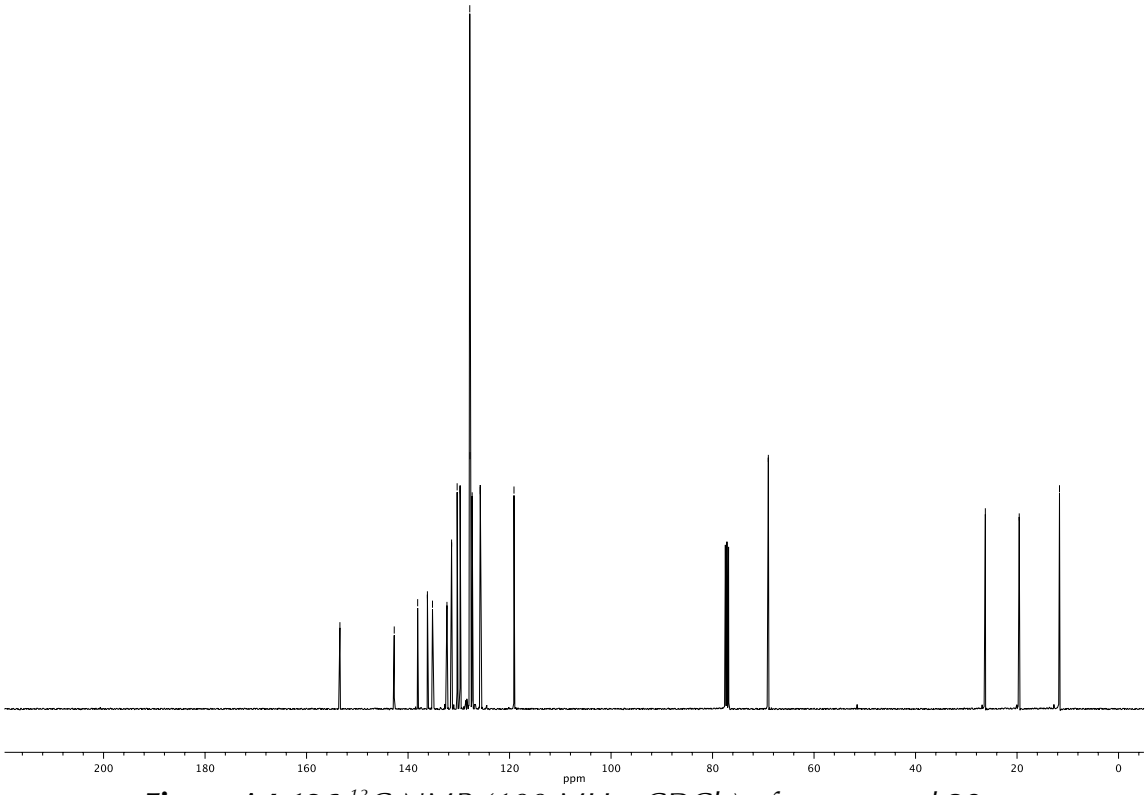



***Figure A4.136*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***20u****.*

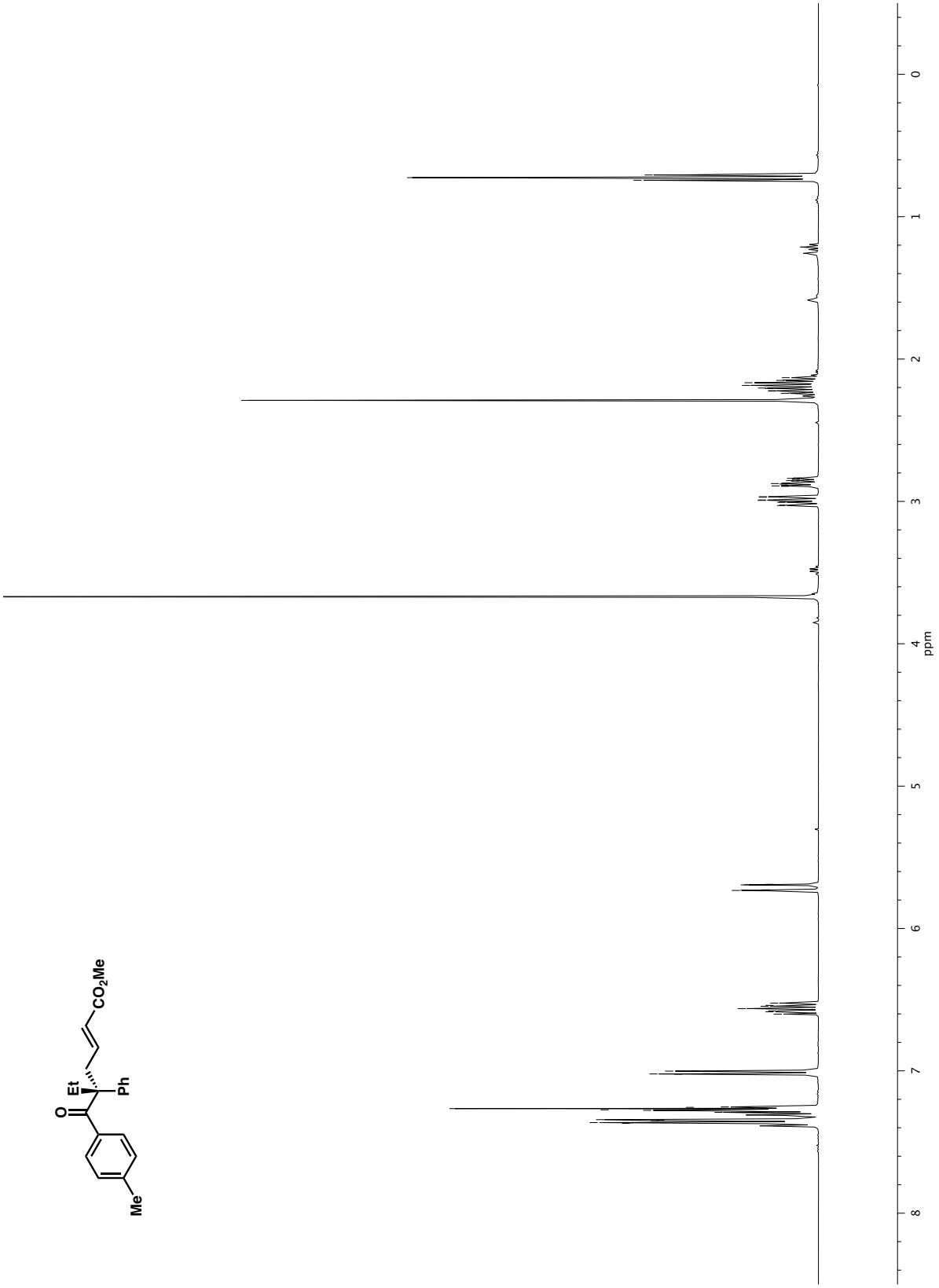



***Figure A4.137*** *$^1$H NMR (400 MHz, $CDCl_3$) of compound* ***26****.*

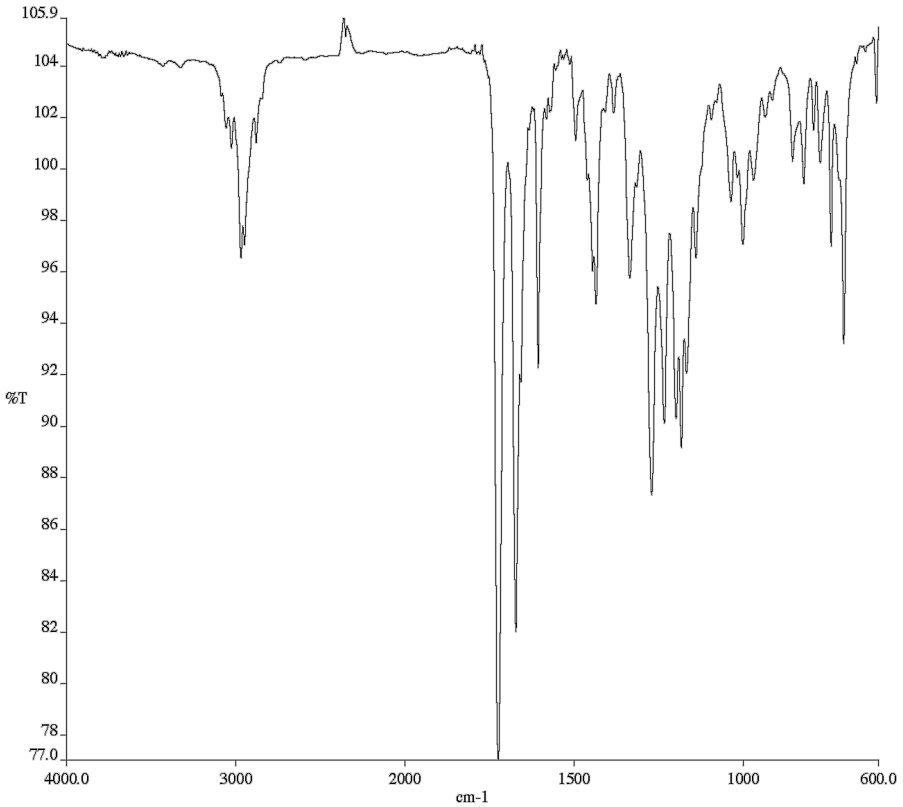



***Figure A4.138*** *Infrared spectrum (Thin Film, NaCl) of compound* ***26***.

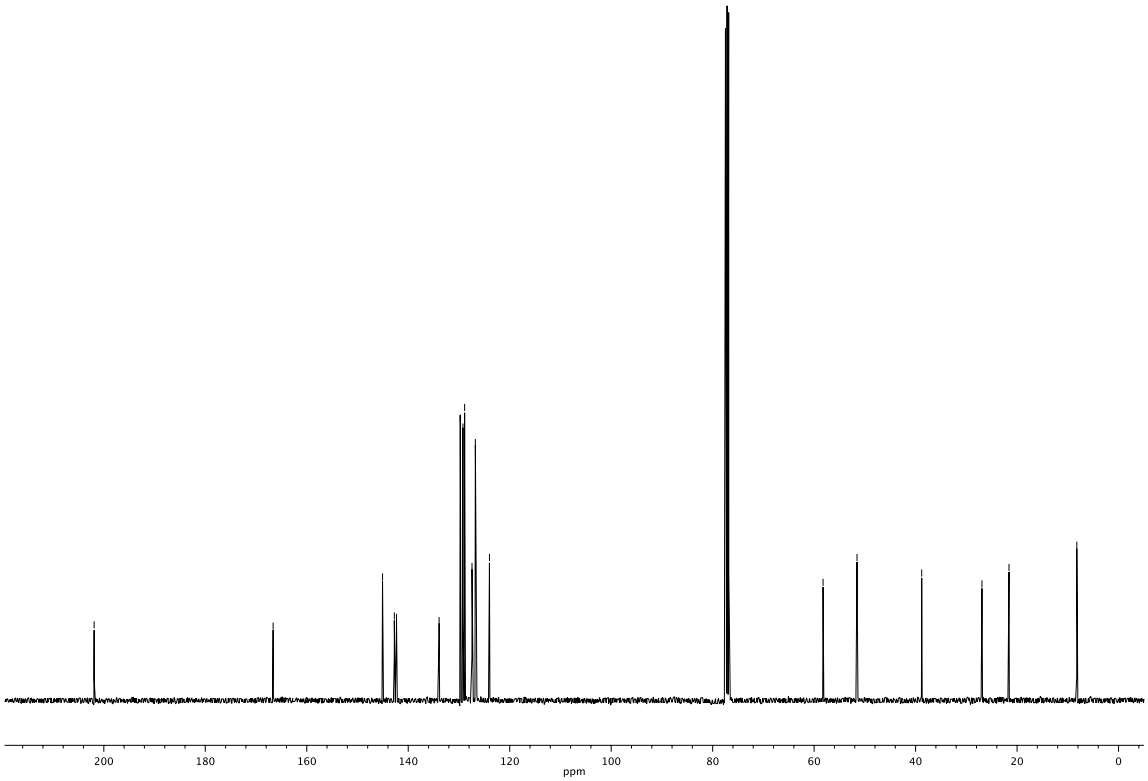



***Figure A4.139*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***26***.

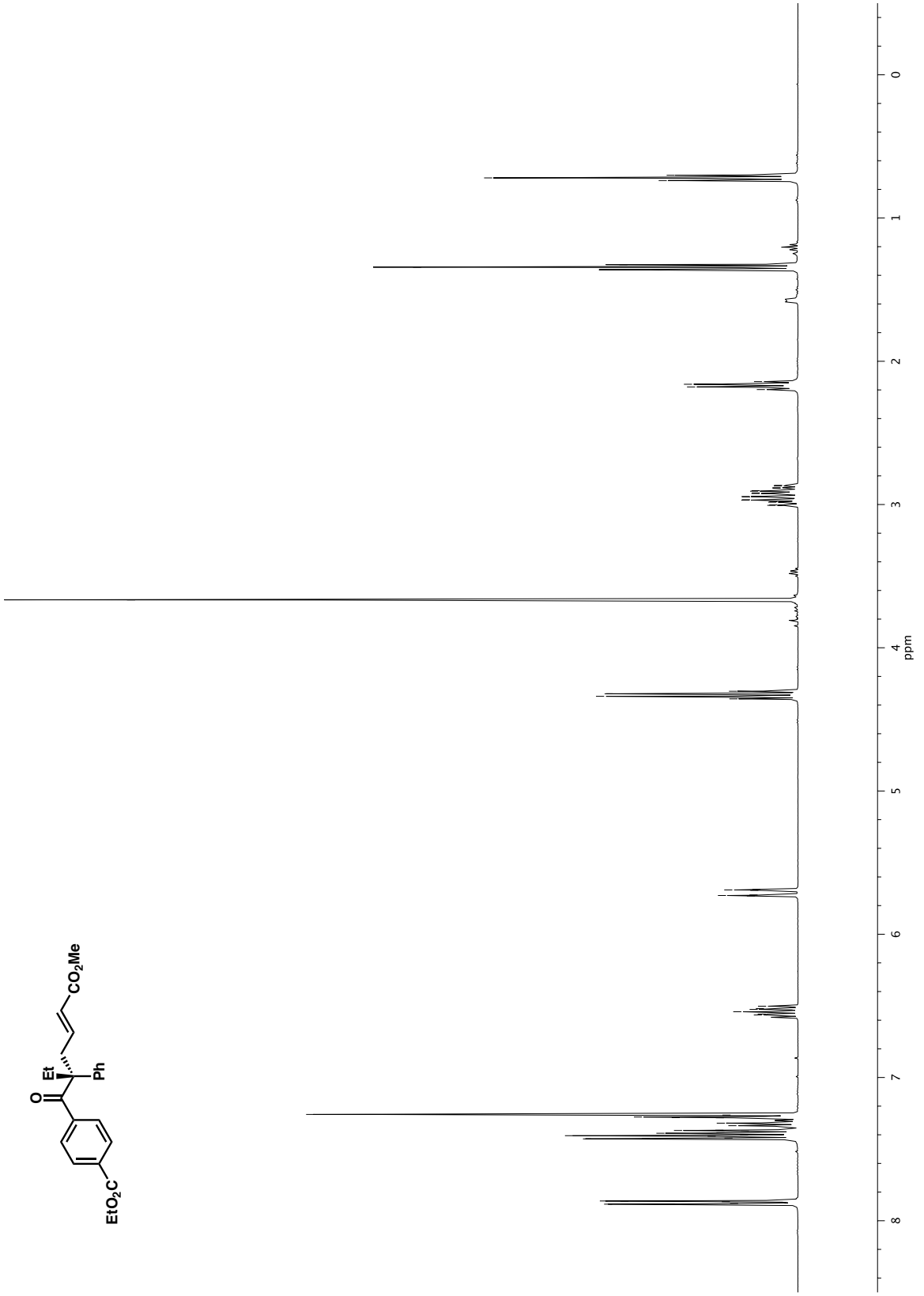



***Figure A4.140*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***25****.*

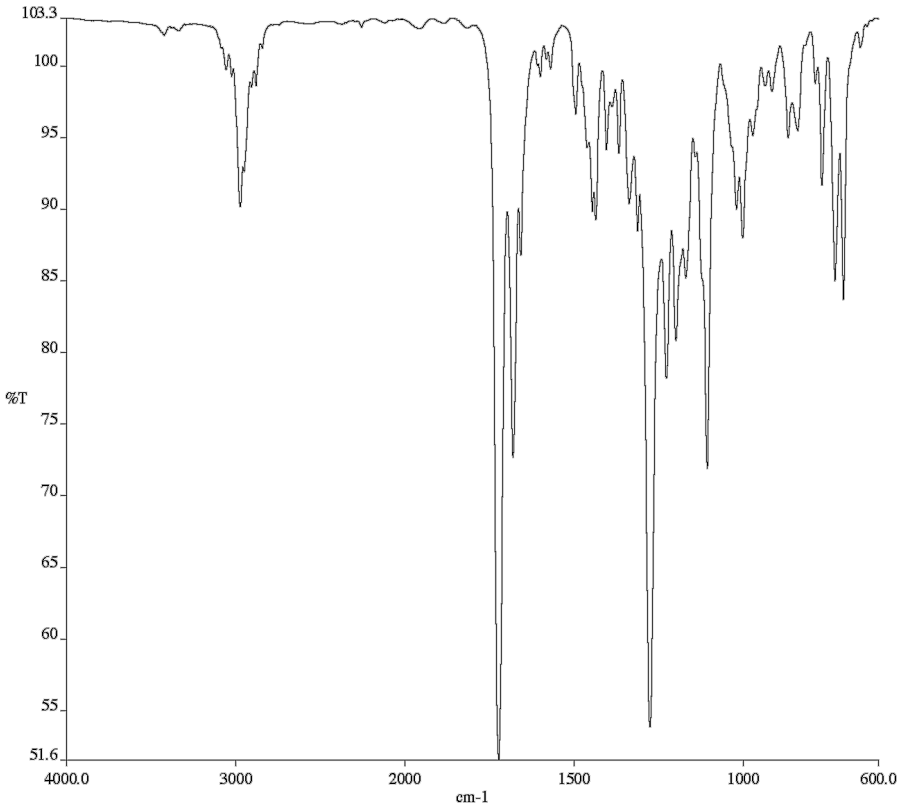



***Figure A4.141*** *Infrared spectrum (Thin Film, NaCl) of compound* ***25***.

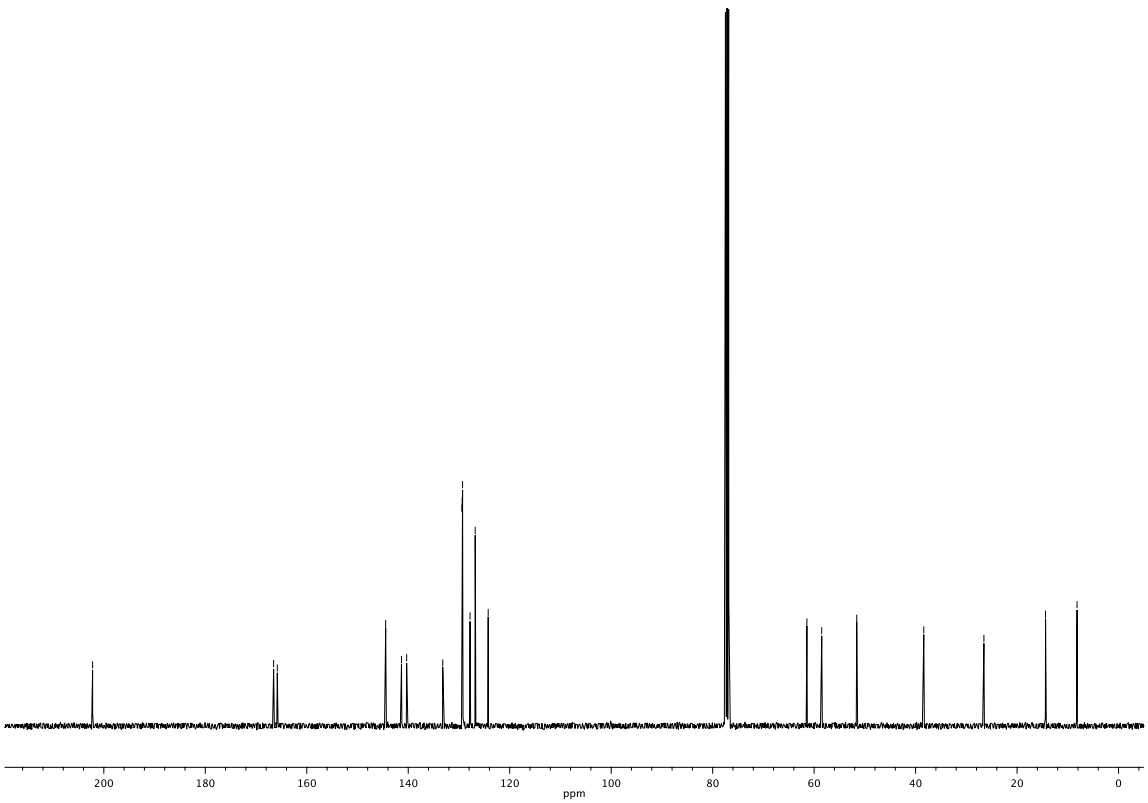



***Figure A4.142*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***25***.

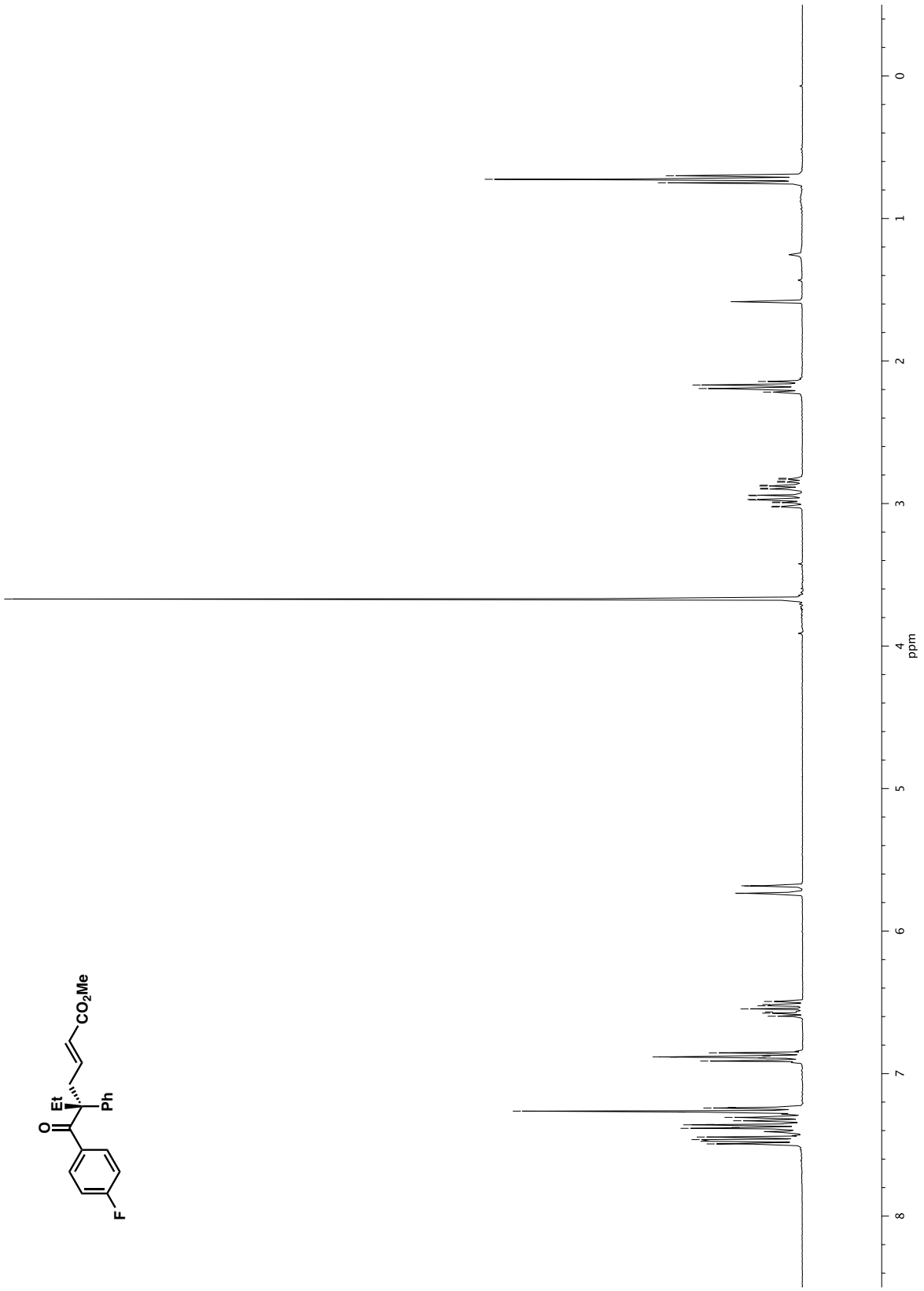



***Figure A4.143*** *$^1$H NMR (300 MHz, $CDCl_3$) of compound* ***27****.*

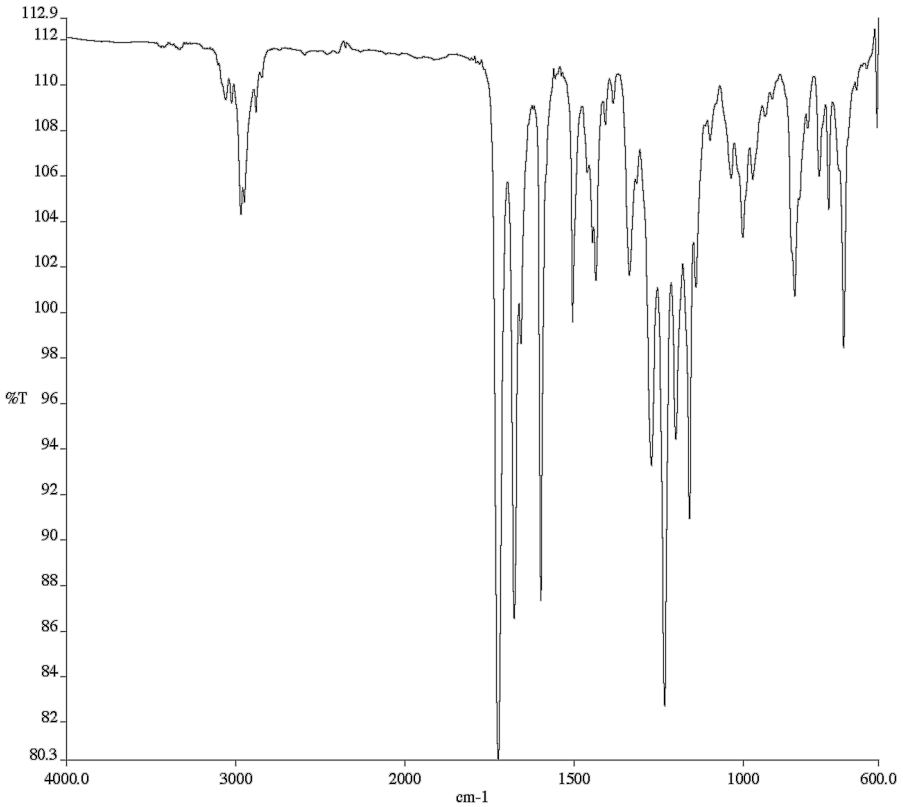



***Figure A4.144*** *Infrared spectrum (Thin Film, NaCl) of compound* ***27****.*

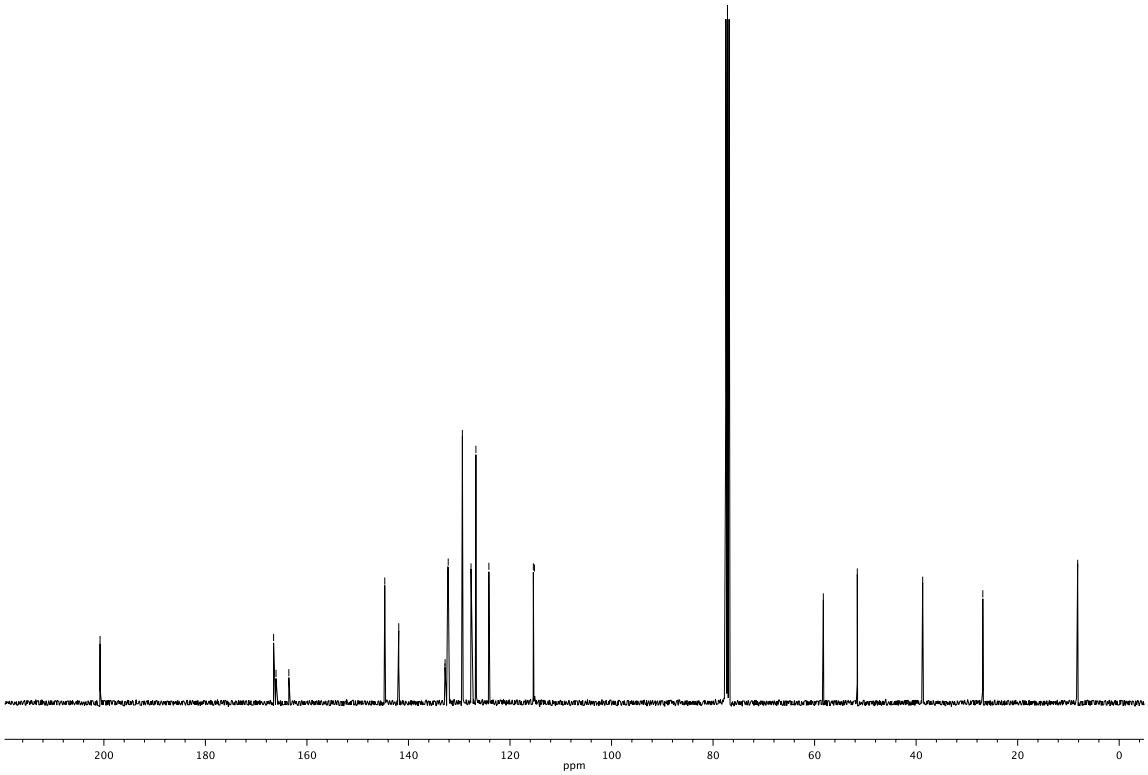



***Figure A4.145*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***27****.*

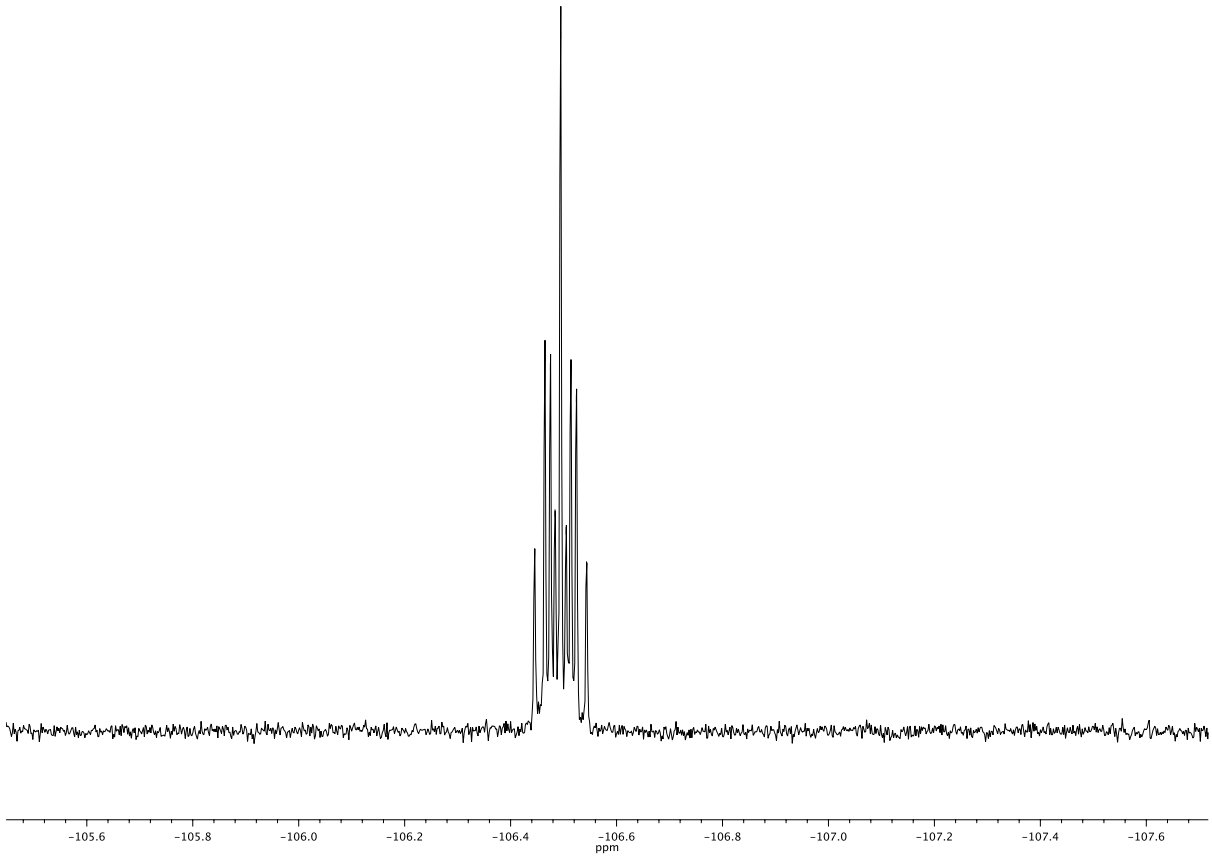



***Figure A4.146*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound **27**.*

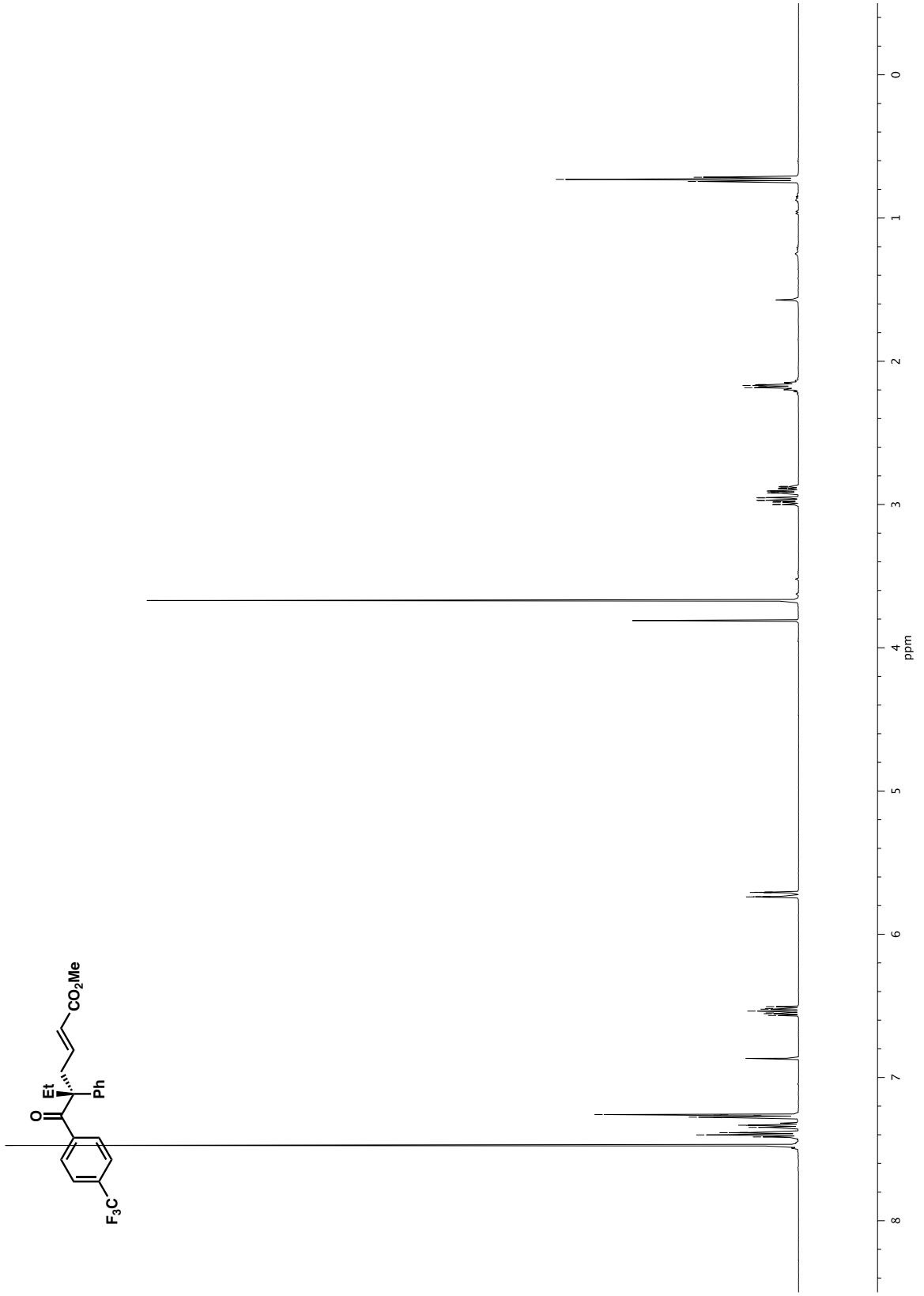



***Figure A4.147*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***28****.*

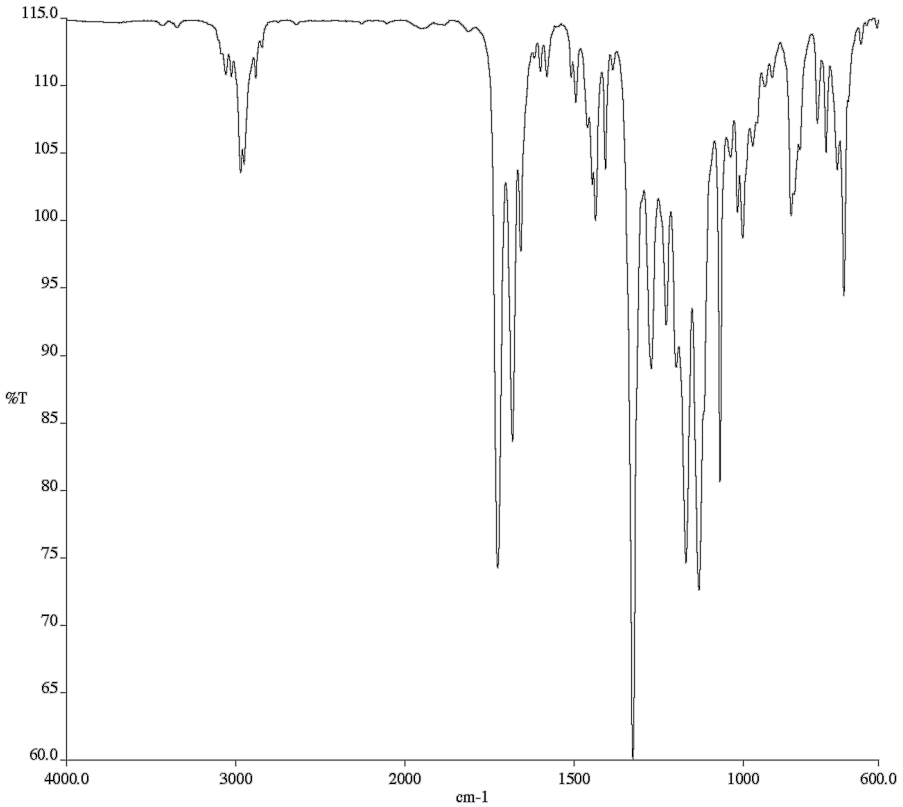



***Figure A4.148*** *Infrared spectrum (Thin Film, NaCl) of compound* ***28****.*

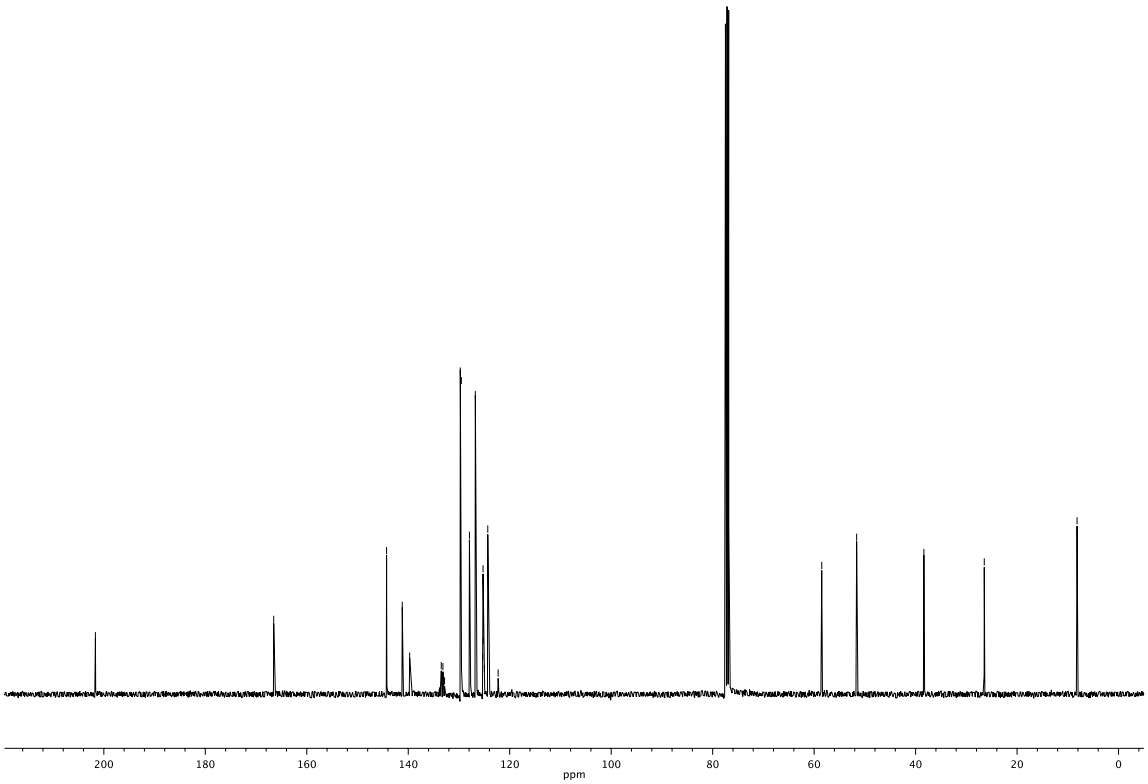



***Figure A4.149*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***28****.*

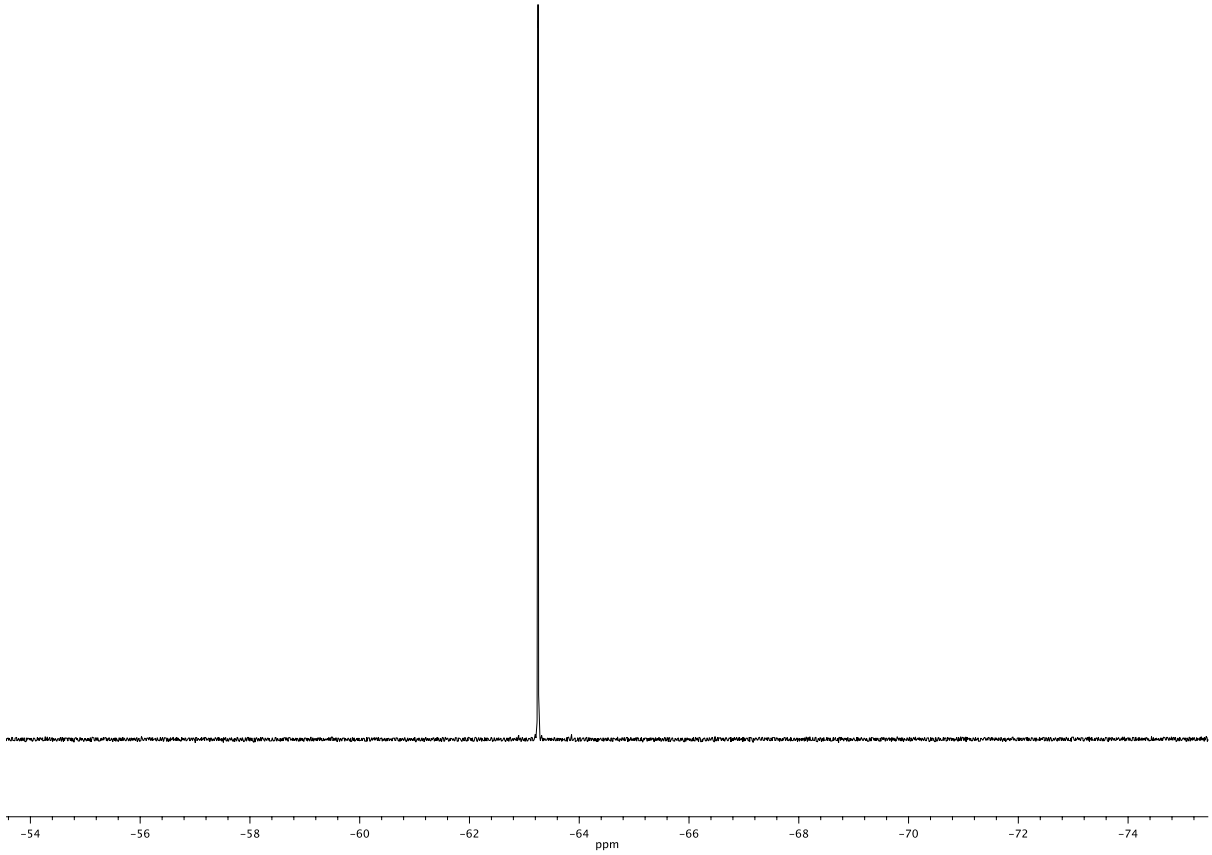



***Figure A4.150*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***28****.*

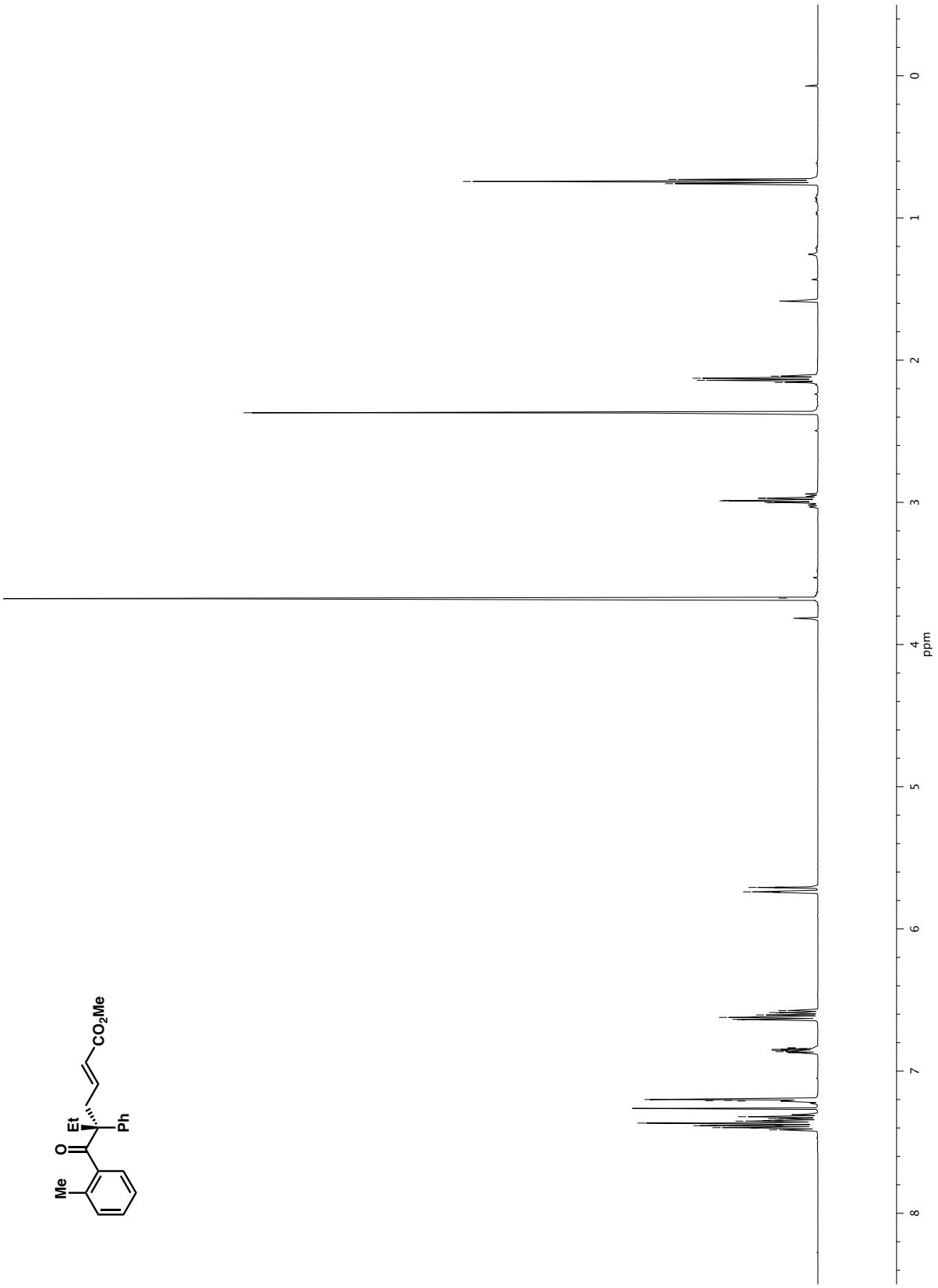



***Figure A4.151*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***29***.

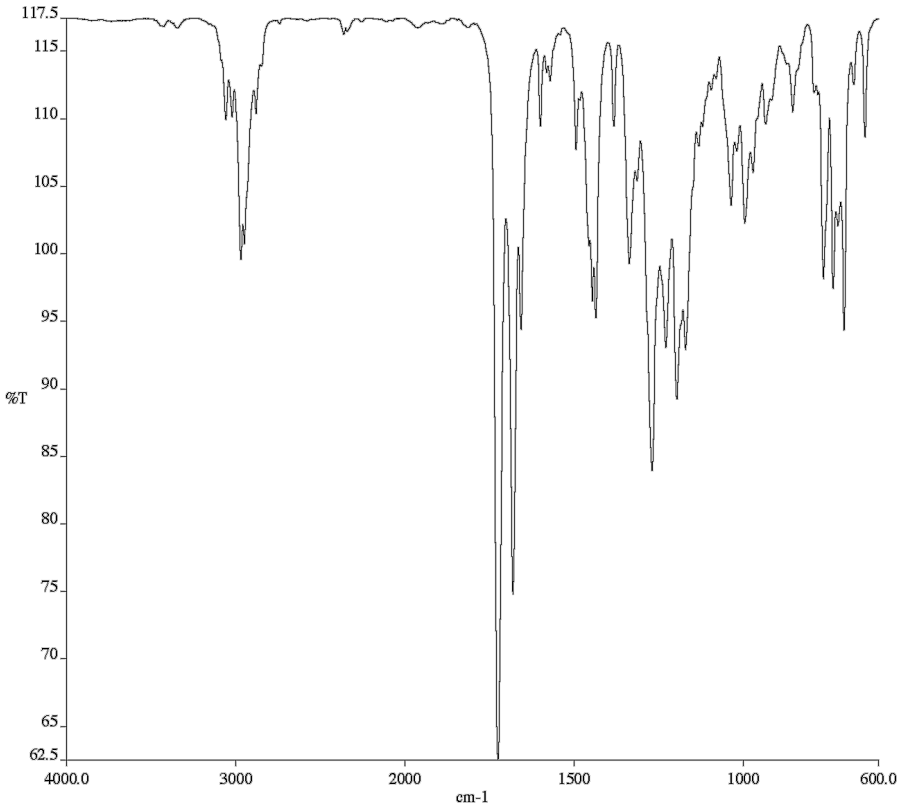



***Figure A4.152*** *Infrared spectrum (Thin Film, NaCl) of compound* ***29***.

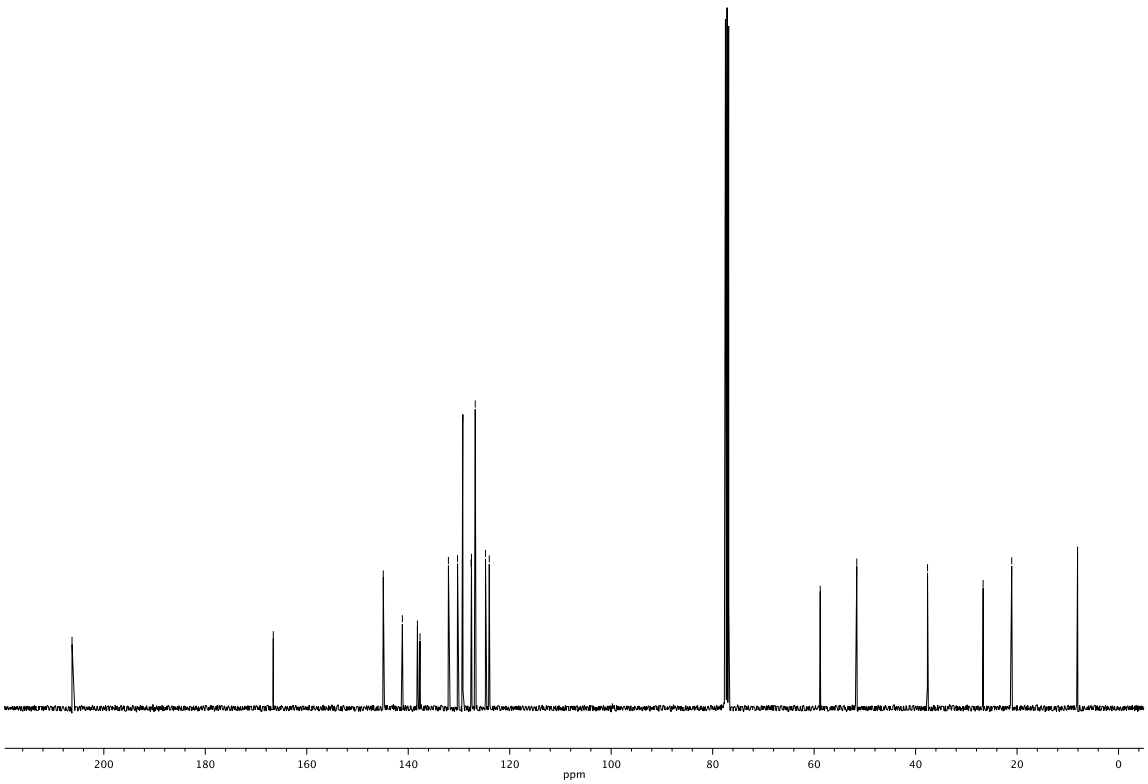



***Figure A4.153*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***29***.

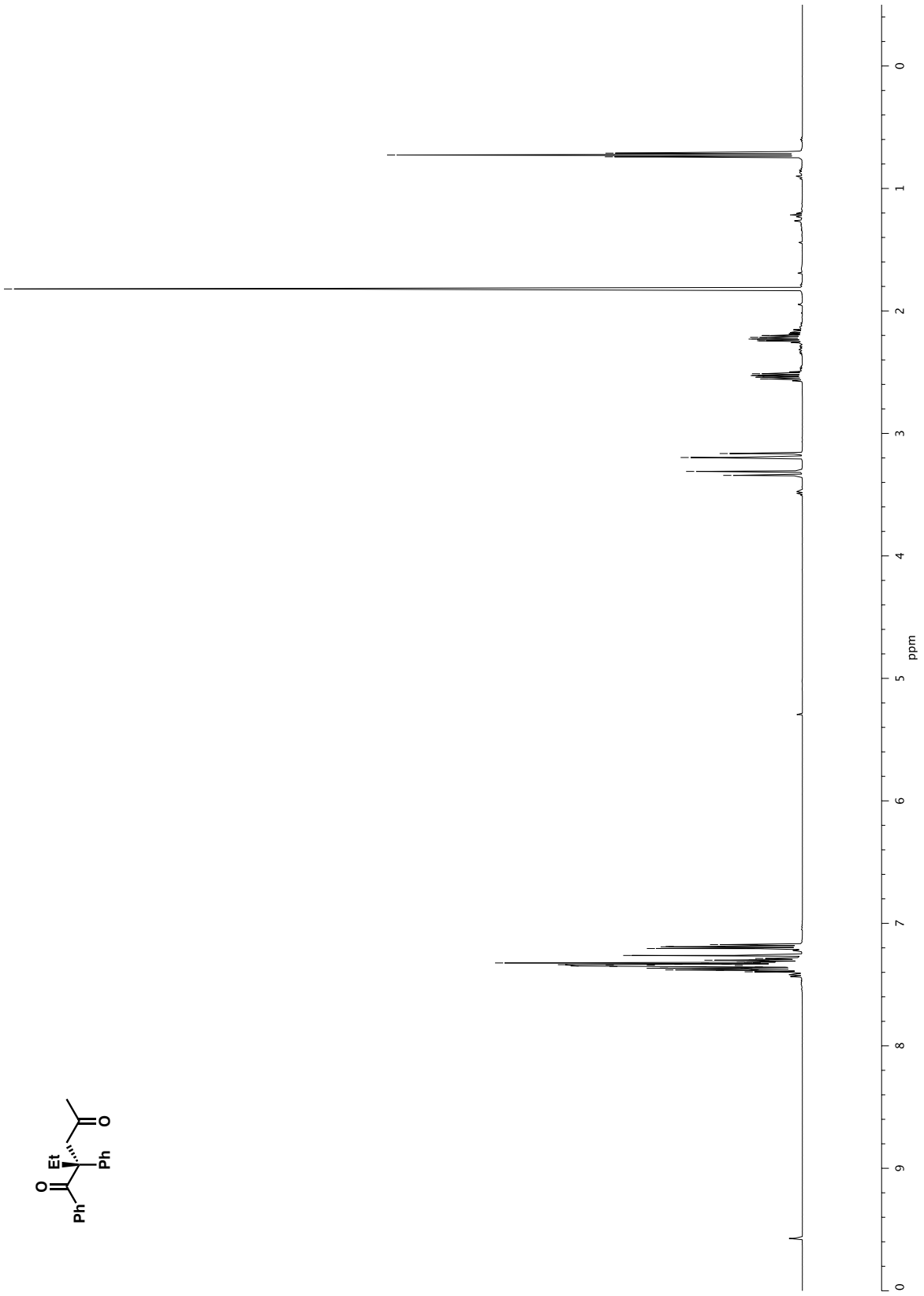



***Figure A4.154*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***22****.*

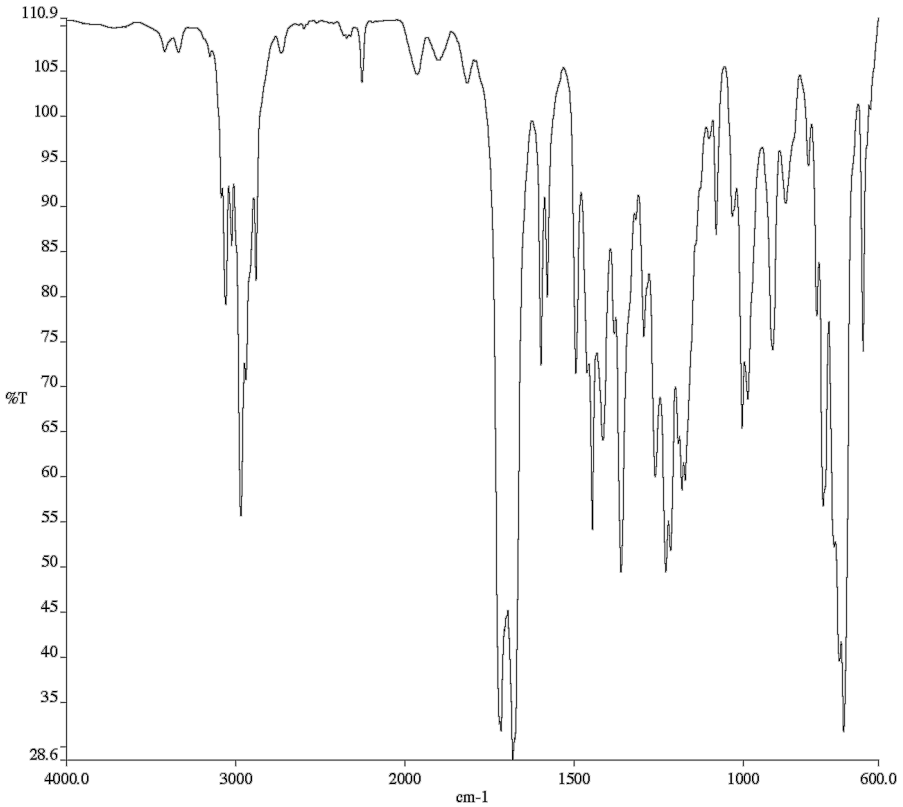



***Figure A4.155*** *Infrared spectrum (Thin Film, NaCl) of compound* ***22***.

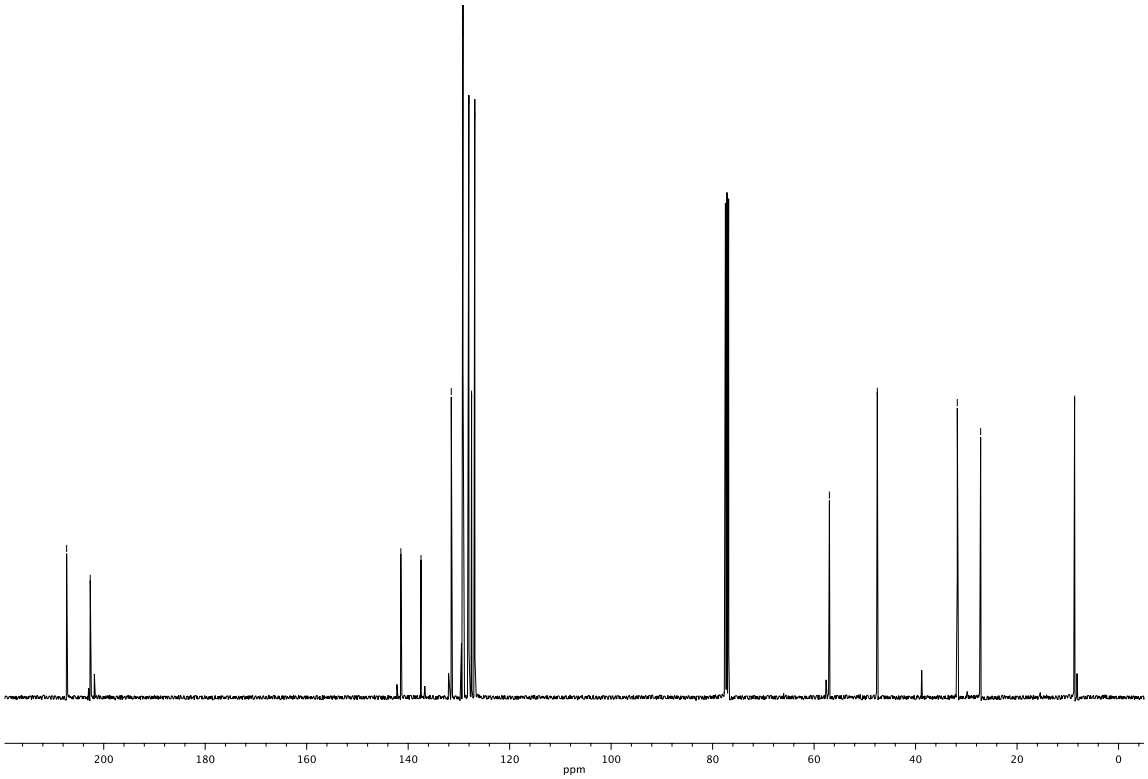



***Figure A4.156*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***22***.

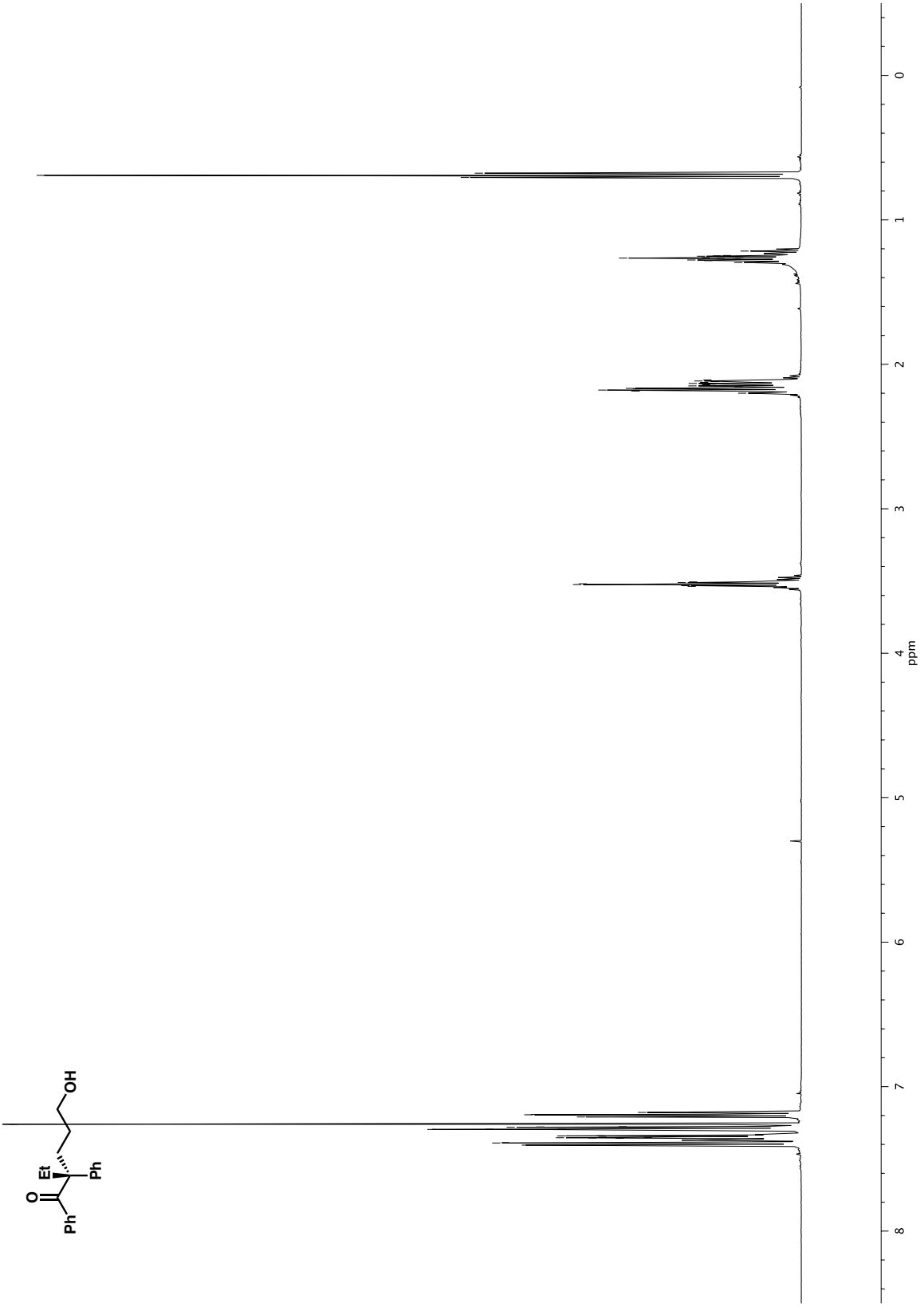



***Figure A4.157*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***23***.

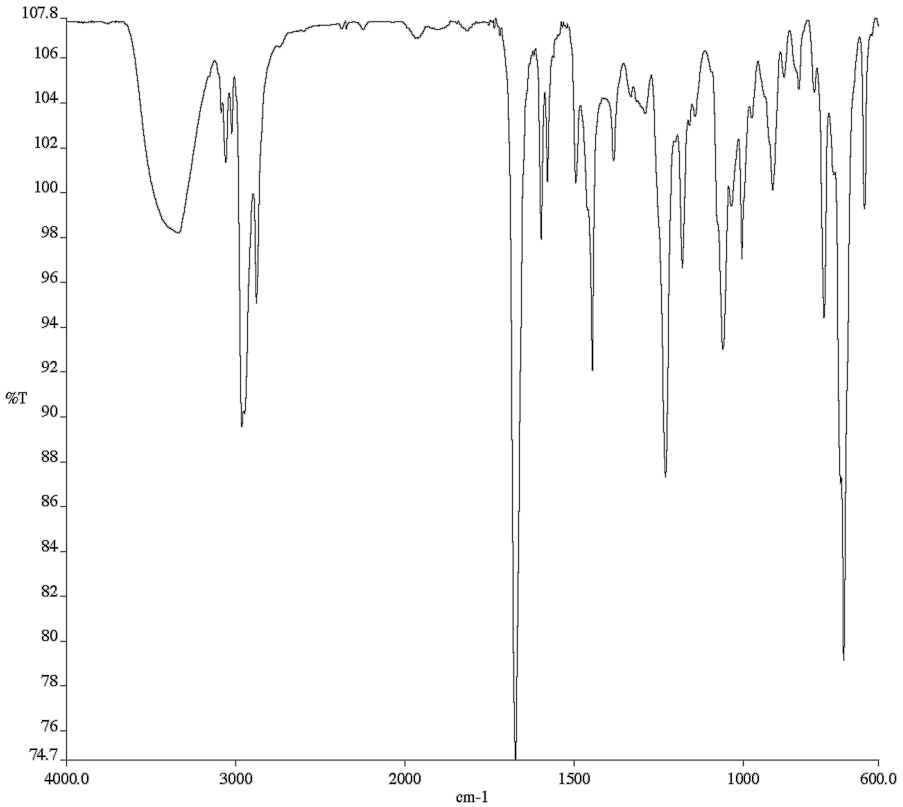



***Figure A4.158*** *Infrared spectrum (Thin Film, NaCl) of compound* ***23***.

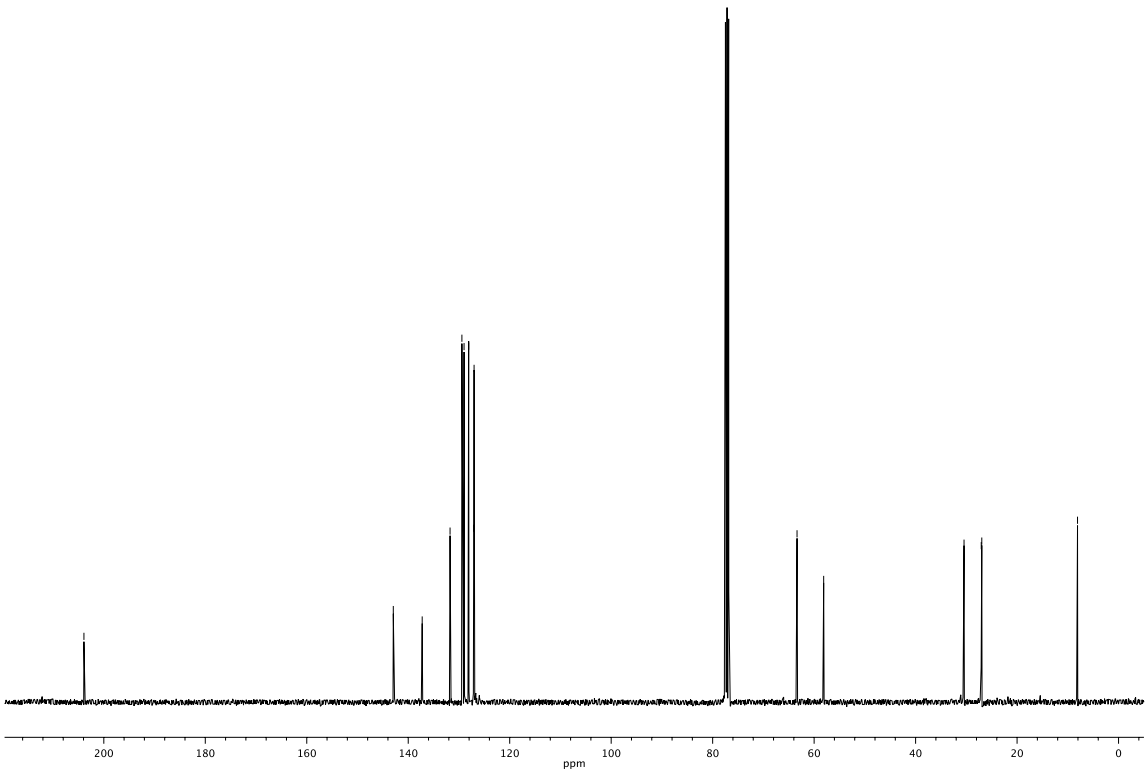



***Figure A4.159*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***23***.

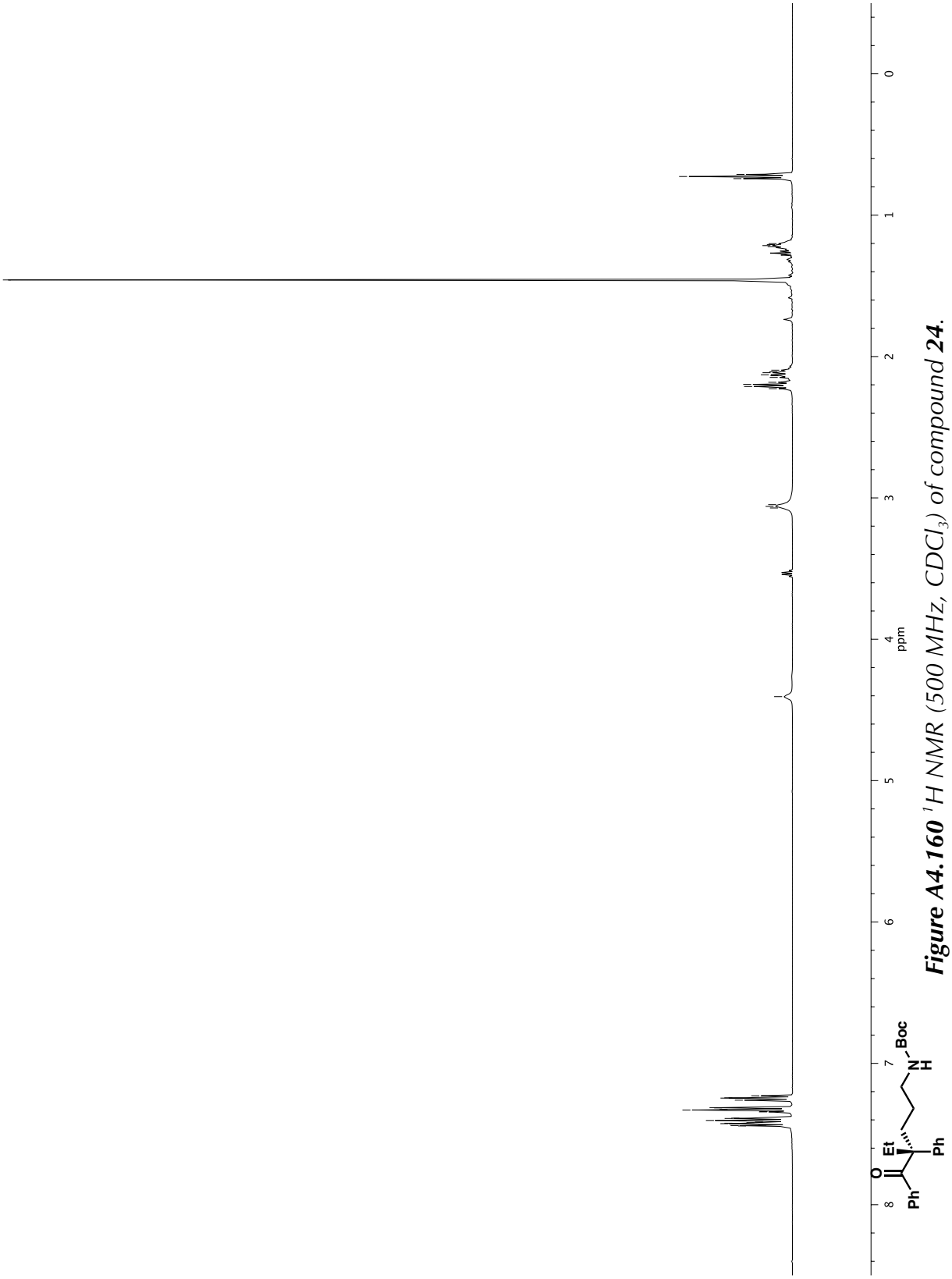



***Figure A4.160*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***24****.*

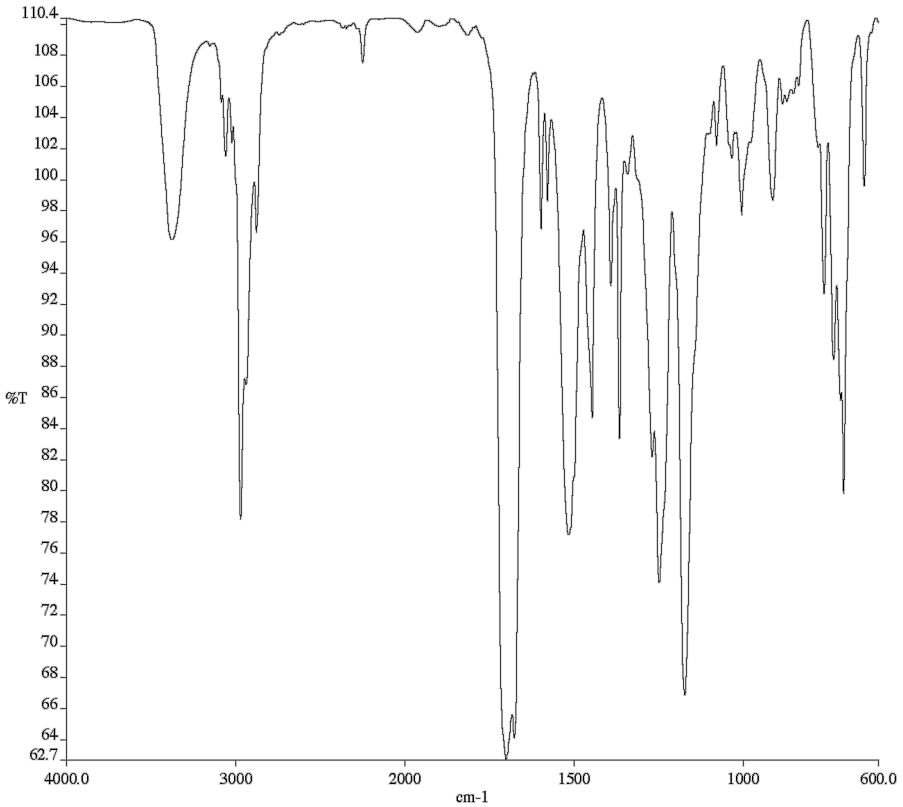



***Figure A4.161*** *Infrared spectrum (Thin Film, NaCl) of compound* ***24****.*

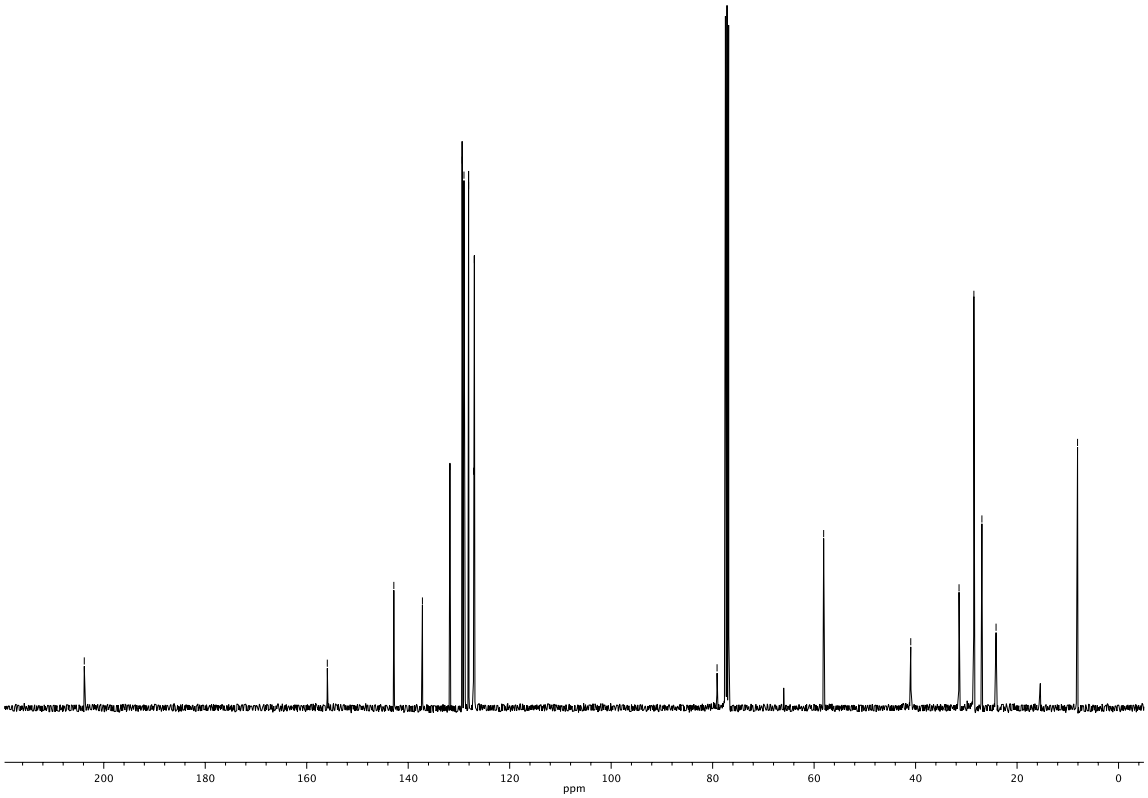



***Figure A4.162*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***24****.*

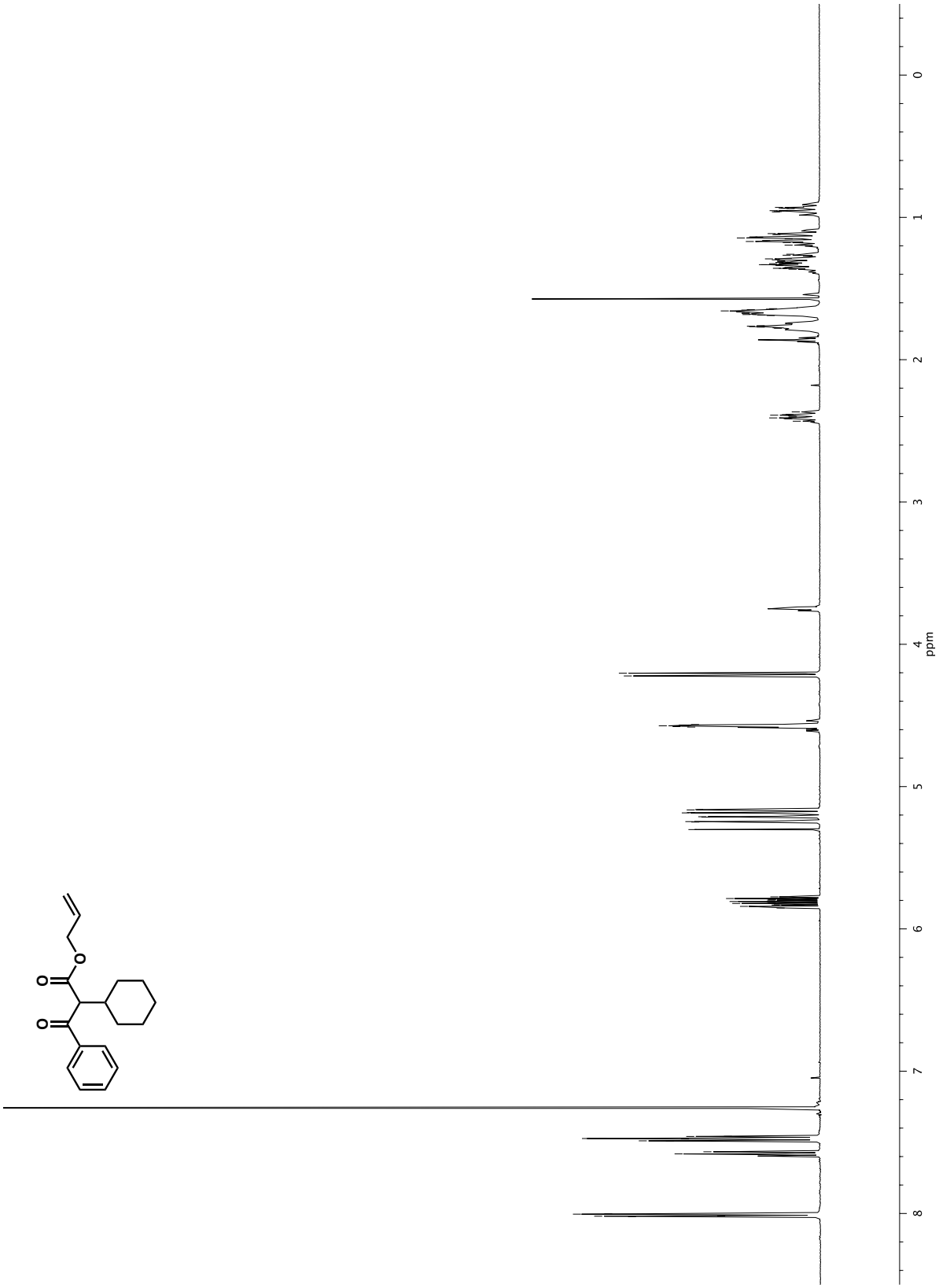



***Figure A4.163*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound **30**.*

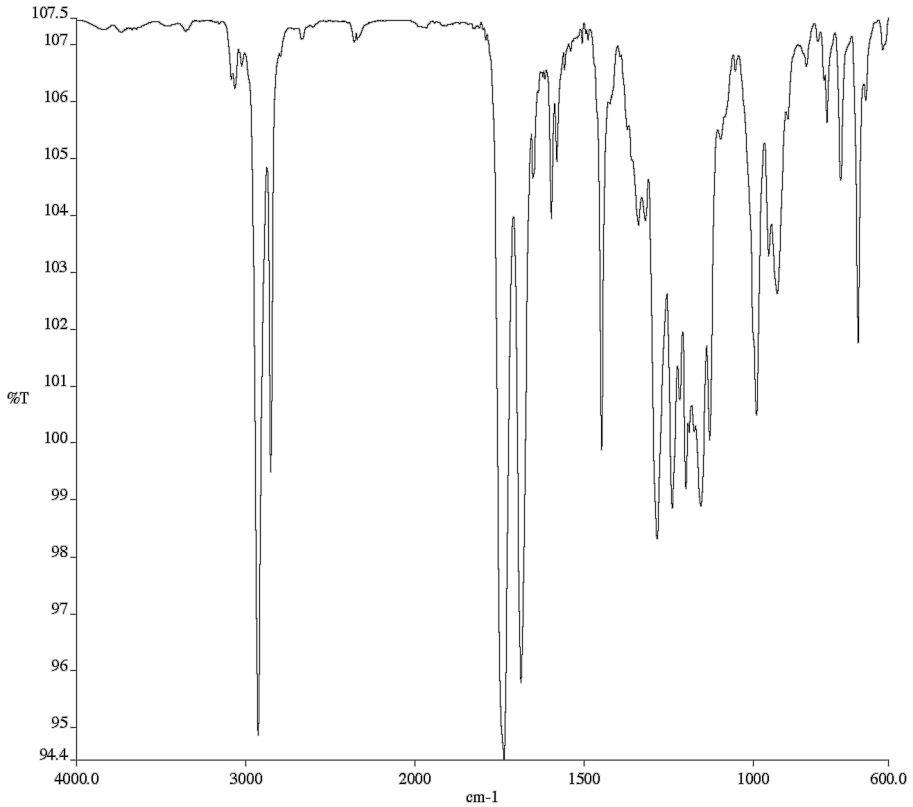



***Figure A4.164*** *Infrared spectrum (Thin Film, NaCl) of compound* ***30***.

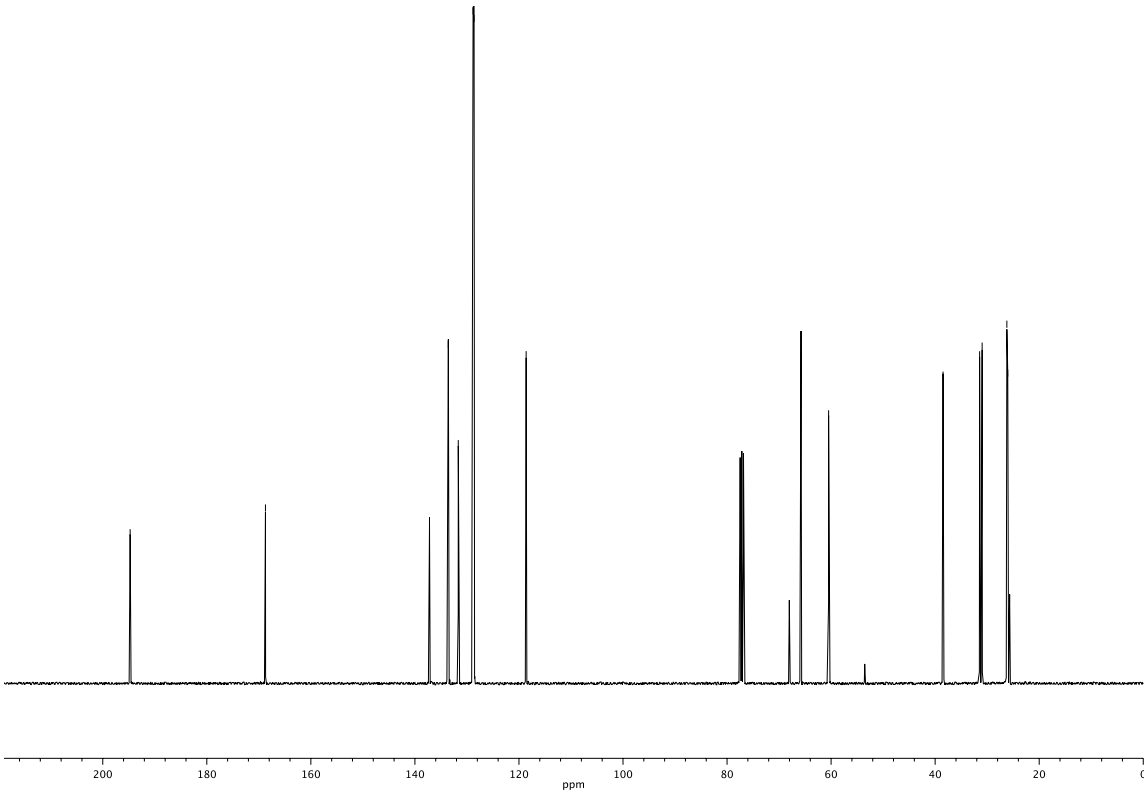



***Figure A4.165*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***30***.

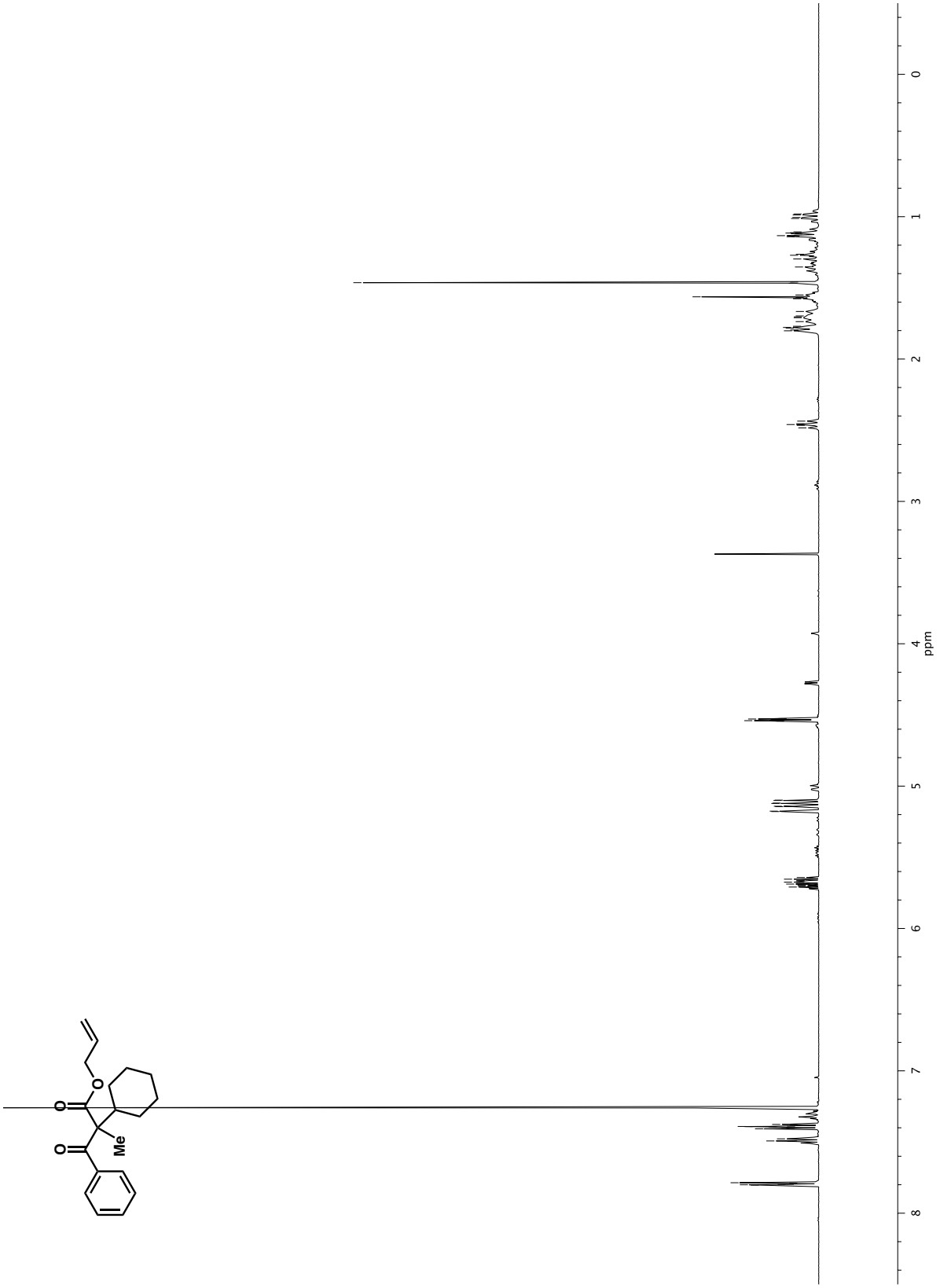



***Figure A4.166*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound **31**.*

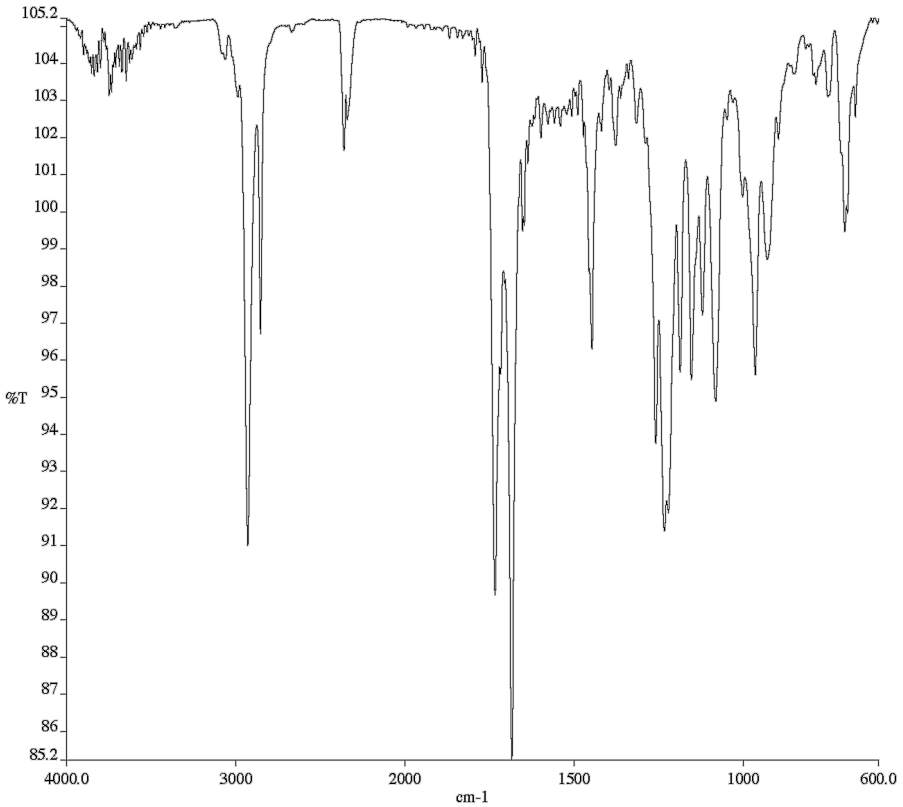



***Figure A4.167*** *Infrared spectrum (Thin Film, NaCl) of compound* ***31***.

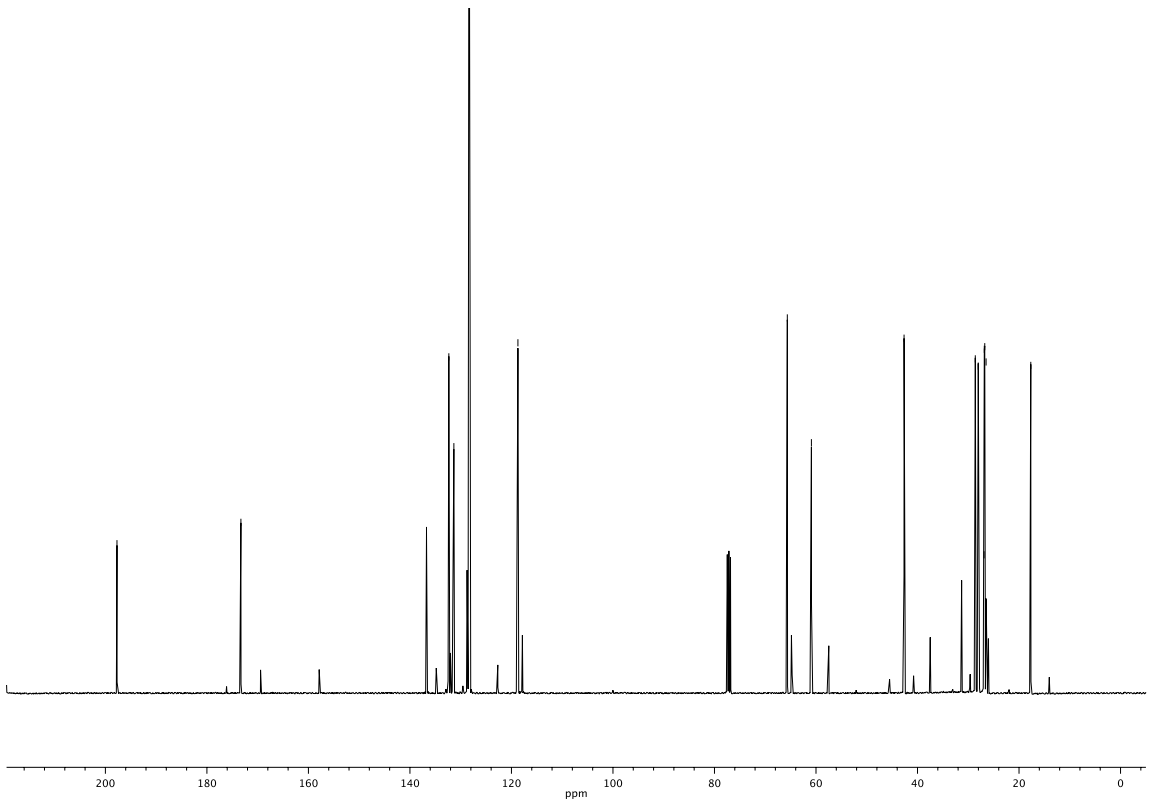



***Figure A4.168*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***31***.

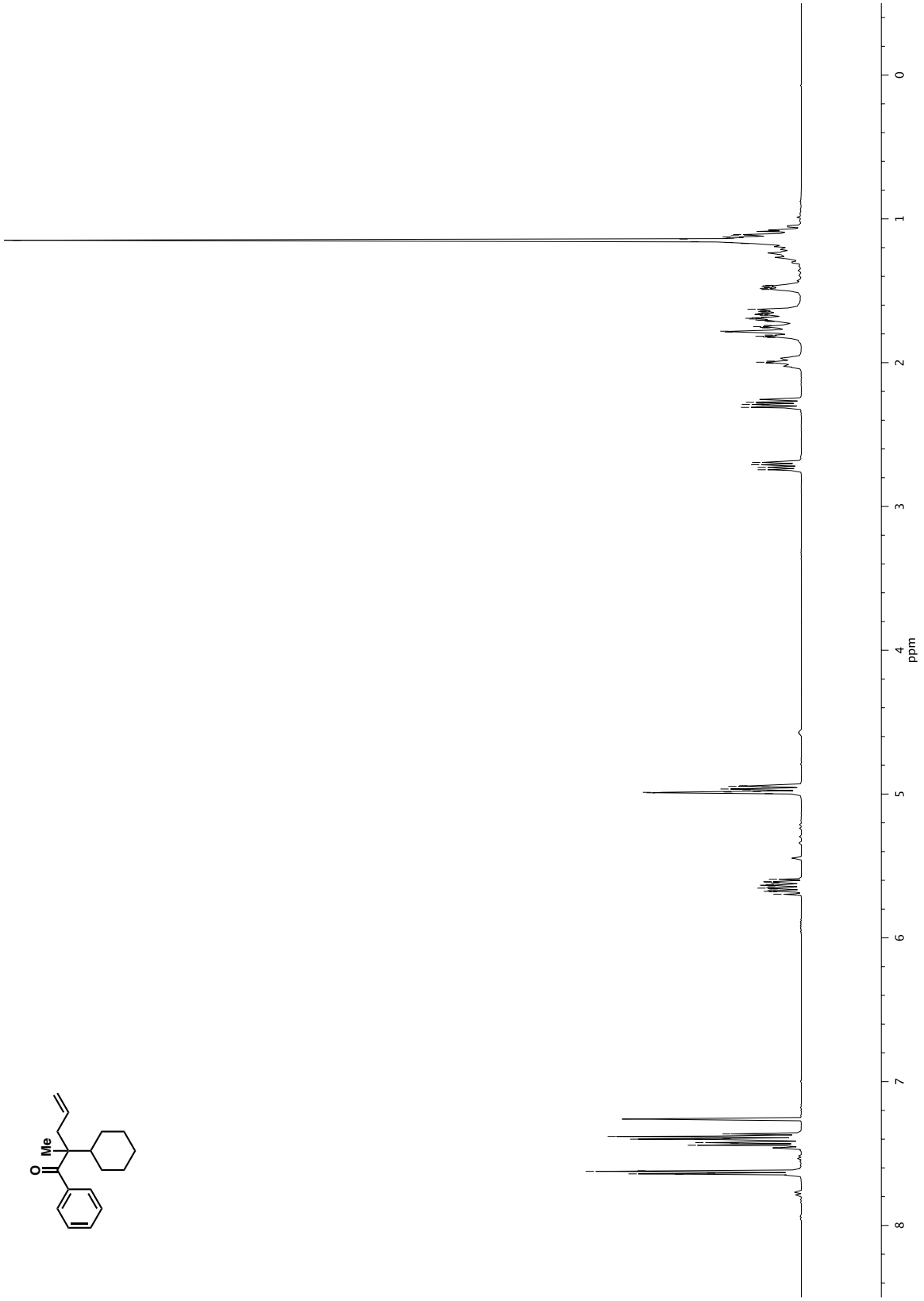



***Figure A4.169*** *$^1$H NMR (400 MHz, $CDCl_3$) of compound* ***32***.

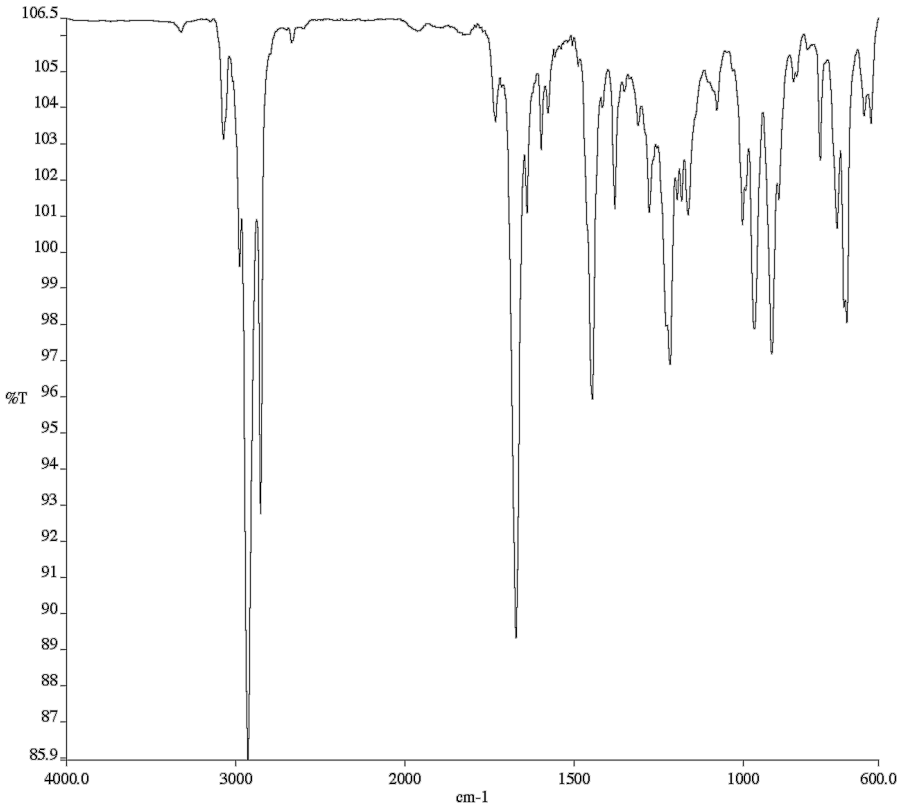



***Figure A4.170*** *Infrared spectrum (Thin Film, NaCl) of compound* ***32***.

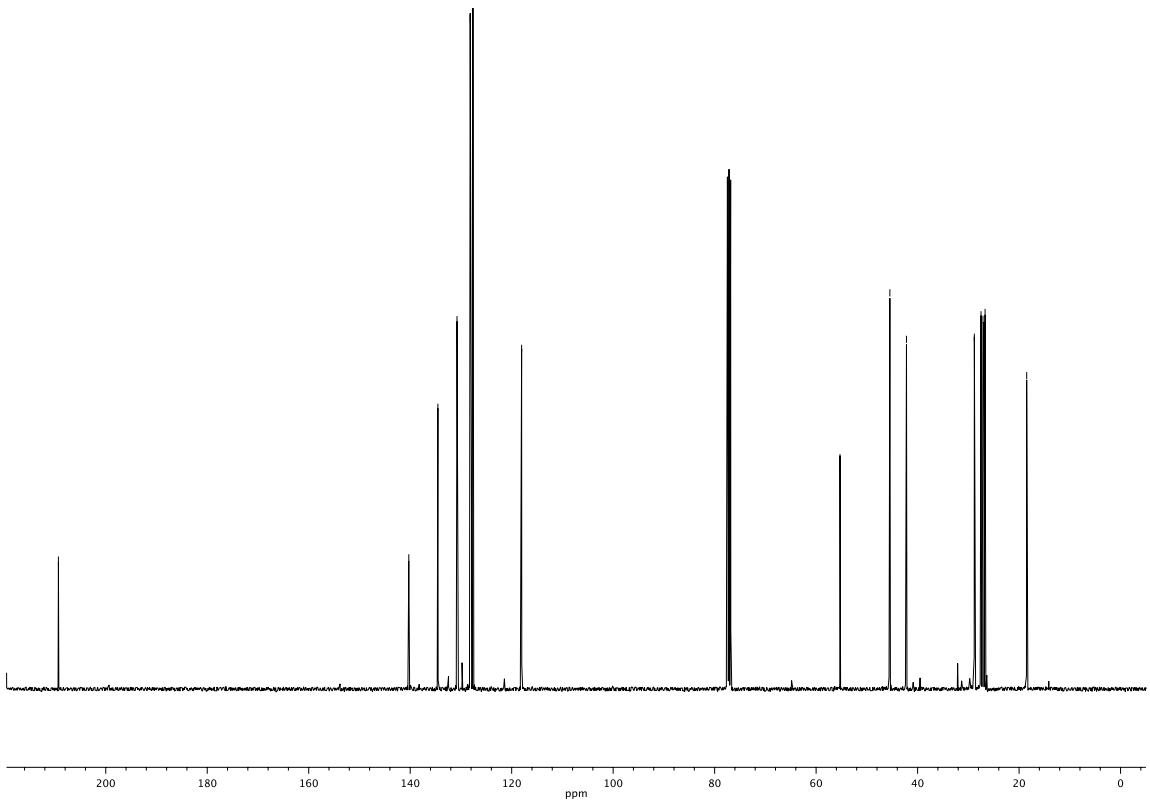



***Figure A4.171*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***32***.

# *CHAPTER 4*

## *Palladium-Catalyzed Decarboxylative Allylic Alkylation of Fully-Substituted N-Acyl Indole-Derived Enol Carbonates*[†]

### 4.1 INTRODUCTION

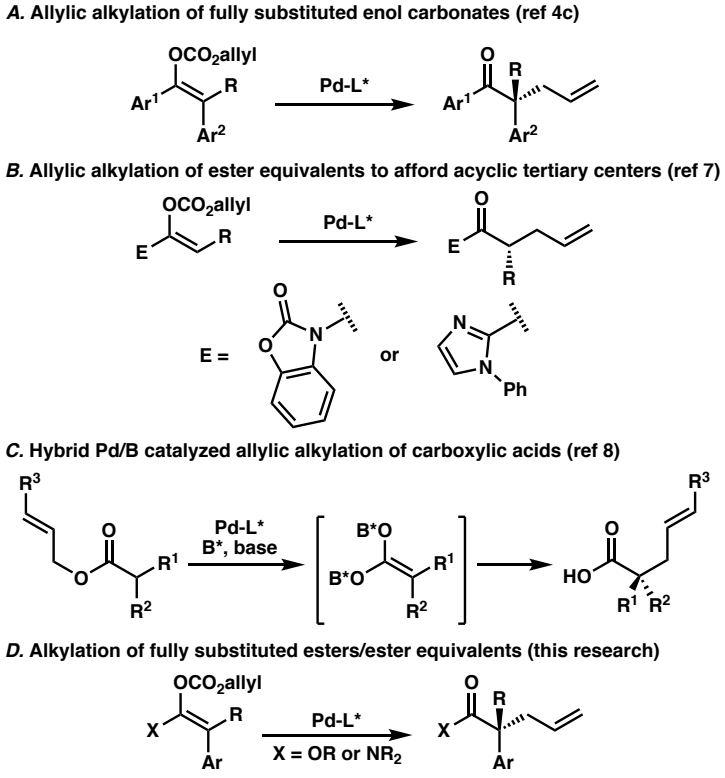
The catalytic enantioselective preparation of all-carbon quaternary stereocenters has become an important area of research owing to the prominence of such structures in natural products and their potential utility in medicinal chemistry.[1] Toward this end, numerous strategies have been developed for the synthesis of this challenging motif in cyclic systems.[1,2] Meanwhile, approaches to quaternary stereocenters in acyclic systems have proven more challenging, largely due to the need for stereodefined olefins and enolates typically necessary for high selectivities.[3] Recently, our lab has investigated the utility of palladium-catalyzed decarboxylative allylic alkylation for preparing acyclic all-carbon quaternary stereocenters.[4] In particular, we identified a unique transformation of fully-substituted acyclic enol carbonates to afford the corresponding α-quaternary ketones in an enantioselective fashion (Figure 4.1A).[4c] While the enol carbonates could be prepared with high stereochemical fidelity utilizing recently reported

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[†]This research was performed in collaboration with Tyler Fulton and Dr. Haiming Zhang. Portions of this chapter have been reproduced with permission from Alexy, E. J.; Fulton, T. J.; Zhang, H.; Stoltz, B. M. *Chem. Sci.* **2019**, *10*, 5996–6000. © 2019 Royal Society of Chemistry.

conditions,[5] we were surprised to find that the enolate geometry of the substrate was inconsequential, with the same enantiomer of product obtained in the same enantioselectivity regardless of the ratio of starting enolates. This result runs contrary to reports in the literature highlighting the central importance of controlling enolate geometry in acyclic palladium-catalyzed allylic alkylation.[4a,6]

***Figure 4.1*** *Enantioselective Pd-Catalyzed Allylic Alkylation of Acyclic Substrates.*



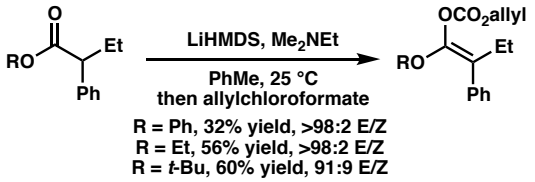

To extend the scope of the transformation, we sought to examine ester enolates as possible substrates, allowing for the synthetically more versatile α-quaternary carboxylic acid derivatives to be accessed. As background, the Trost group has previously reported the enantioselective palladium-catalyzed allylic alkylation of two different ester enolate equivalents; 2-acylimidazoles[7a] and *N*-acyl oxazolidinones (Figure 4.1B).[7b] However, both of these reports were limited to

trisubstituted enolates, highlighting the difficulty of forming acyclic quaternary stereocenters via enolate chemistry. Unique strategies have emerged as a means of bypassing this issue. For example, Shimizu and Kanai reported a dual boron-palladium catalytic system, which allowed access to α-quaternary carboxylic acids through a symmetrical, chiral carboxylic acid dianion (Figure 4.1C).[8] Additionally, both rhodium[9] and iridium-catalyzed[10] allylic alkylation have previously been shown to provide acyclic quaternary stereocenters. With this in mind, additional general methods addressing the synthesis of this challenging and useful structural motif warrant further investigation. Toward this end, we sought to prepare stereodefined acyclic ester enolates, or enolate equivalents, investigate the E/Z selectivity of their synthesis, and determine the importance of this geometry by demonstration of their application in enantioselective palladium-catalyzed allylic alkylation (Figure 4.1D).

## 4.2 ENOLIZATION AND ALKYLATION OF ACYCLIC ESTERS

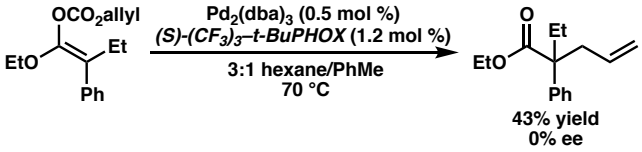
We began by investigating the selective enolization of sterically varied α-alkyl/aryl substituted esters and were intrigued to find that treatment with LiHMDS and dimethylethylamine at 25 °C,[5] followed by enolate trapping with allyl chloroformate, provides the desired ester-derived enol carbonates in high E/Z selectivity, albeit in modest yield (Scheme 4.1). Given that previous examples of enolization with this protocol had been performed on aryl ketones, this unexpected selectivity was highly exciting.

***Scheme 4.1*** *Selective Enolization of Esters.*




Our excitement was quickly tempered however, as the resulting allyl carboxy ketene acetals demonstrated surprisingly poor reactivity under standard palladium-catalyzed allylic alkylation conditions, requiring elevated temperatures to reach appreciable levels of conversion. Despite optimization efforts, the best result obtained utilized the ethyl ester-derived substrate and provided the alkylation product in only 43% yield as a racemate using (*S*)-$CF_3$-*t*-BuPHOX (**L8**) as the ligand (Scheme 4.2). Both phenyl and *t*-Bu ester-derived substrates failed to provide significant levels of the alkylation product.

***Scheme 4.2*** *Pd-Catalyzed Alkylation of Ester-Derived Enol Carbonates.*

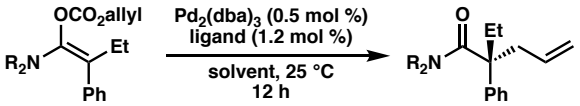


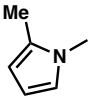
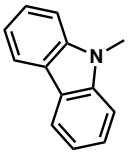
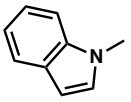
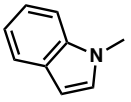

## 4.3 ENOLIZATION AND ALKYLATION OF ESTER EQUIVALENTS

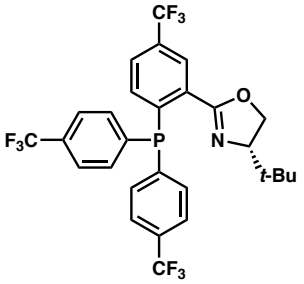
To circumvent the issues with ester-derived enol carbonates, we turned instead toward ester enolate equivalents. Based on prior precedent and our own recent findings in the area of cyclic enolate derivatives,[6b,11] we investigated *N*-acyl hetereocycles as potential substrates. We were pleased to find that a variety of *N*-acyl-heterocycle derived enol carbonates can be prepared in good to excellent E/Z selectivity under analogous selective-enolization conditions, and provided more promising reactivity in a subsequent enantioselective alkylation (Table 4.1).

Utilizing conditions our group identified for the enantioselective allylic alkylation of acyclic ketones as a starting point, we found that the *N*-acyl pyrrole-derived enol carbonate affords the desired allylic alkylation product in a high 92% yield and a moderate 73% ee with electron-deficient phosphinoxazoline **L8** as the ligand (Table 4.1, entry 1). The ee was improved to 83% by switching to a 3:1 methylcyclohexane/PhMe solvent mixture (entry 2), however, further experimentation led to no additional increase in selectivity for this substrate. By increasing the steric bulk on the pyrrole through the inclusion of an *ortho*-methyl group (entry 3), the high enolization selectivity is retained, however, the resultant alkylation product is obtained in only 65% ee. An *N*-methylimidazole-derived substrate (entry 4) was found to give no conversion under the alkylation conditions. Further increasing the steric bulk by moving to carbazole (entry 5) results in a drop in enolization selectivity, and again, no reaction is observed in the allylic alkylation. The optimal substrate was found to be an *N*-acyl indole (entry 6), which both enolizes selectively and affords the desired alkylation product in an excellent 95% yield and 90% ee. After additional experimentation, we found that the use of a novel electron-deficient PHOX ligand *(S)*-Ty-PHOX (**L12**) provides the desired product in an improved 99% yield and 95% ee when a slightly modified 3:1 hexane/toluene solvent mixture is used. Notably, the reaction is performed using only 0.5 mol % $Pd_2(dba)_3$ and 1.2 mol % ligand and is complete in 12 h at 25 °C.

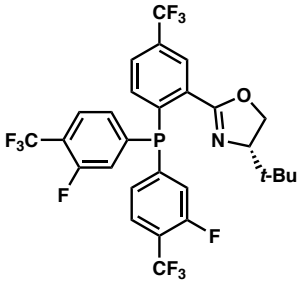
***Table 4.1*** *Optimization of decarboxylative allylic alkylation of ester equivalents*




| entry | $R_2N$– | ligand | solvent | ee[b] (yield[c]) |
|---|---|---|---|---|
| 1 |  >98:2 E/Z | *L8* | 3:1 hexane/PhMe | 73 (92) |
| 2 |  >98:2 E/Z | *L8* | 3:1 MeCy[d]/PhMe | 83 (97) |
| 3 |  >98:2 E/Z | *L8* | 3:1 MeCy/PhMe | 65 (ND) |
| 4 |  95:5 E/Z | *L8* | 3:1 MeCy/PhMe | NR |
| 5 |  83:17 E/Z | *L8* | 3:1 MeCy/PhMe | NR |
| 6 |  >98:2 E/Z | *L8* | 3:1 MeCy/PhMe | 90 (95) |
| 7 |  >98:2 E/Z | *L12* | 3:1 hexane/PhMe | 95 (99) |




***L8*: *(S)-(CF$_3$)$_3$–t-BuPHOX***



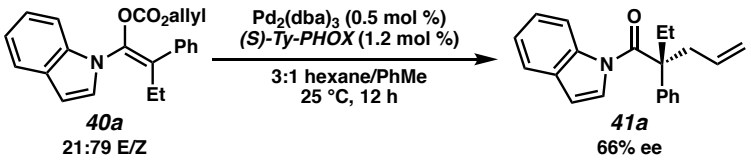

***L12*: *(S)-Ty-PHOX***

[a] Conditions: 0.1 mmol substrate, 0.5 mol % Pd(dba), 1.2 mol % ligand, 1.0 mL solvent, 25 °C. [b] Determined by chiral SFC analysis. [c] Yield of isolated product. [d] MeCy = methylcyclohexane.

## 4.4 IMPORTANCE OF ENOLATE GEOMETRY

With optimal reaction conditions identified, we sought to examine the impact of substrate enolate geometry. Contrary to our prior report on ketone enolates,[4c] in which the starting material enolate ratio was found to be inconsequential to reaction selectivity, we found that the geometry of the N-acyl indole-derived enol carbonate (**40aa**) has a significant impact on the selectivity of the reaction (Scheme 4.3). Specifically, the use of a 21:79 E/Z mixture of enol carbonates provides the alkylation product (**41a**) in a significantly diminished 66% ee with **L12** as the ligand, albeit favoring the same enantiomer of product that is observed using a 98:2 E/Z mixture. This result hints at some degree of enolate geometry equilibration in the catalytic process, but to a lesser degree than our ketone system.[4c] An analogous effect was observed with **L8**, as well as with the other N-acyl substrates examined during optimization.

***Scheme 4.3*** *Importance of starting material enolate geometry.*

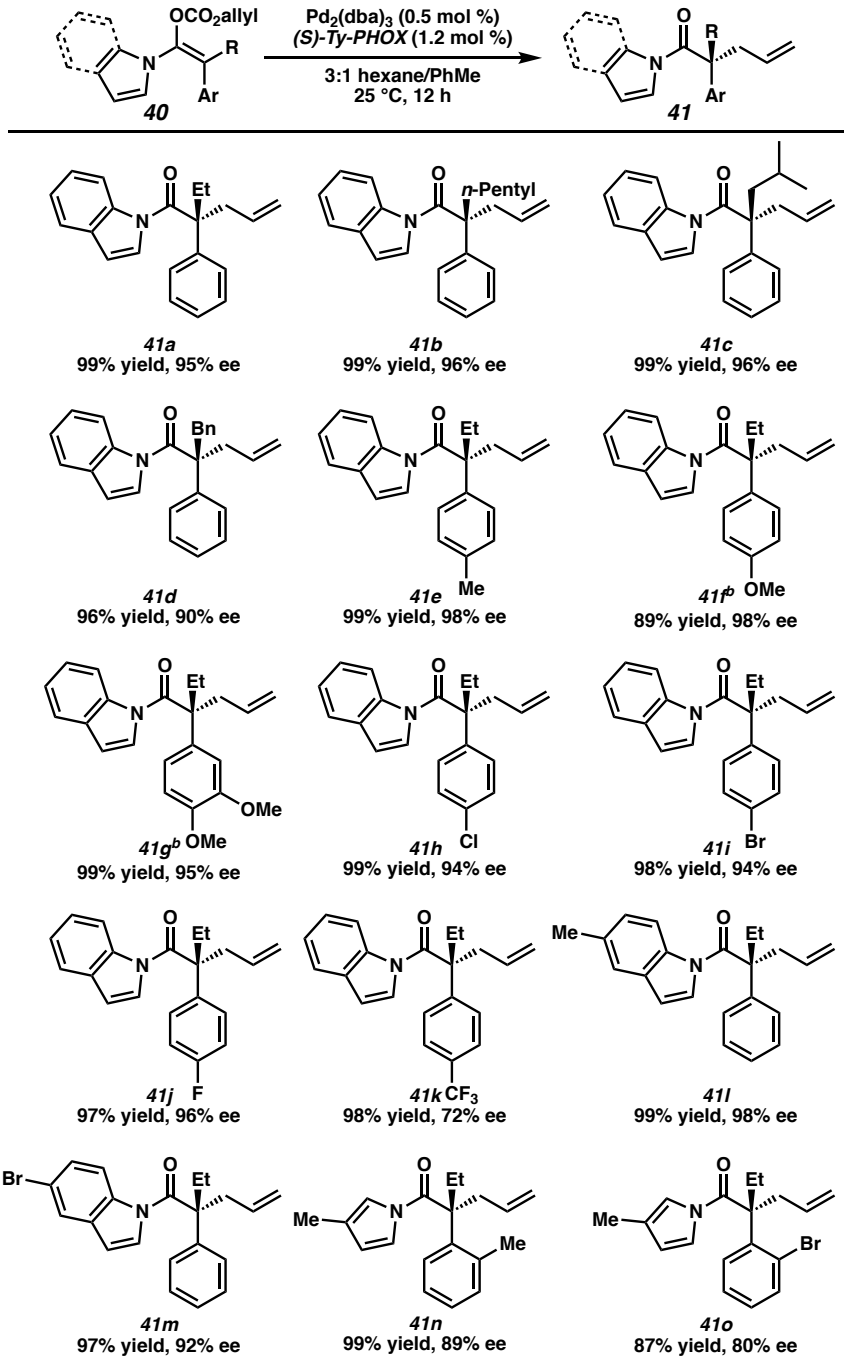



## 4.5 INVESTIGATION OF SUBSTRATE SCOPE

Having optimized conditions in hand, and now understanding the critical importance of olefin geometry in this allylic alkylation, we examined the scope of the transformation for accessing various acyclic all-carbon quaternary stereocenters (Table 4.2). All enol carbonates were prepared in excellent E/Z ratios (see Experimental Section for details) and the corresponding alkylation products were obtained in high yields. Longer alkyl chains at the α-position such as *n*-pentyl (**41b**) and those with branching (**41c**) provide the alkylation products in

excellent enantioselectivity (96% ee). Benzyl-containing substrate **41d** was also well tolerated, albeit with a slightly lower ee (90%). The presence of electron-rich aryl groups resulted in a slight increase in selectivity, with both *p*-Me (**41e**) and *p*-OMe (**41f**) substrates yielding the desired products in 98% ee each, and the bis-OMe substrate (**41g**) in 95% ee. Notably, both methoxy-containing substrates **41f** and **41g** required longer reaction times to reach full conversion (i.e., 24 h). An examination of electron-poor aryl groups demonstrated that, while *p*-Cl (**41h**), *p*-Br (**41i**), and *p*-F (**41j**) groups were well tolerated (94–96% ee), a *p*-$CF_3$ (**41k**) containing substrate provided the product in a diminished 72% ee, believed to result from increased stabilization of the resultant enolate.[2f] Additionally, substitution on the indole was tolerated, with methyl-containing substrate (**41l**) providing the product in 98% ee and the bromo substrate (**41m**) in 93% ee. While *ortho* substitutions on the α-aryl ring provided low selectivities with *N*-acyl indole-derived substrates, employing the smaller *N*-acyl 3-methyl pyrrole allowed *o*-Me (**41n**) and *o*-Br (**41o**) alkylation products to be obtained in moderate 89% and 80% ee respectively, allowing formation of an exceedingly hindered quaternary stereocenter. The use of a more electron-rich *N*-acyl heterocycle (i.e. 3-methyl pyrrole vs. pyrrole) provides a slight boost in enantioselectivity.[12]

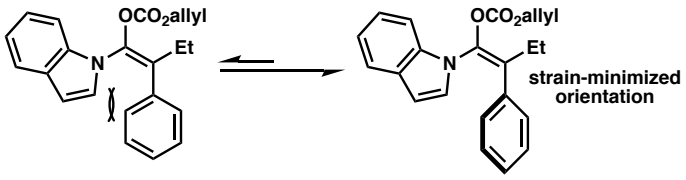
***Table 4.2*** *N-Acyl indole allylic alkylation substrate scope*




[a] Conditions: 0.2 mmol substrate, 0.5 mol % Pd(dba), 1.2 mol % ***L12***, 2.0 mL solvent. Yields of isolated products are given. The ee values were determined by chiral SFC analysis. [b] Reaction run for 24 h. [c] Absolute configuration of ***41d*** was determined by single crystal X-ray diffraction.

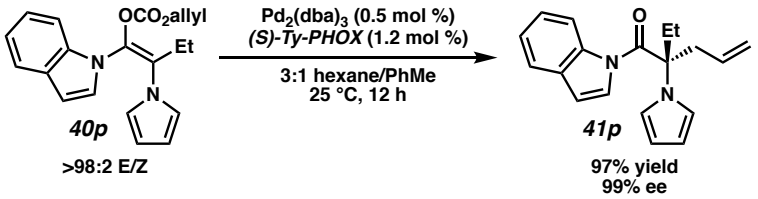
The broad scope of α-aryl substituents tolerated in this transformation (and the related ketone allylation) is surprising given that previous examples of α-aryl stabilized and other weakly basic enolates had demonstrated them to be poor substrates for enantioselective allylic alkylation using PHOX ligands, with near racemic alkylation products.[2f] To rationalize this new observation, as well as explain the necessity for a flat aromatic western portion of the substrate, we propose that the α-aryl group is likely rotated out of plane with respect to the enolate and that the indole is planar and in coordination with the enolate to avoid steric clashing between both aromatic groups (Figure 4.2). An attractive edge-to-face interaction between the two aromatic substituents may also play a role. As a result, no significant resonance stabilization is afforded to the enolate from the α-aryl substituent and high enantioselectivities can be achieved, although inductive stabilization through electron-withdrawing functionality may still result in lower enantioselectivities (e.g. **41k**).

***Figure 4.2*** *Proposed rationale for tolerance of α-aryl substituents.*




To further understand our hypothesis, we prepared α-pyrrolo substrate **40p** and subjected it to the optimized palladium-catalyzed conditions (Scheme 4.4). We reasoned that an α-pyrrole would mimic an α-phenyl substituent in the same way that the acyl-indole mimics a phenyl ketone. This is indeed the case, with alkylation product **41p** being obtained in an excellent 97% yield and 99% enantioselectivity, providing acess to an interesting amino-acid derivative.

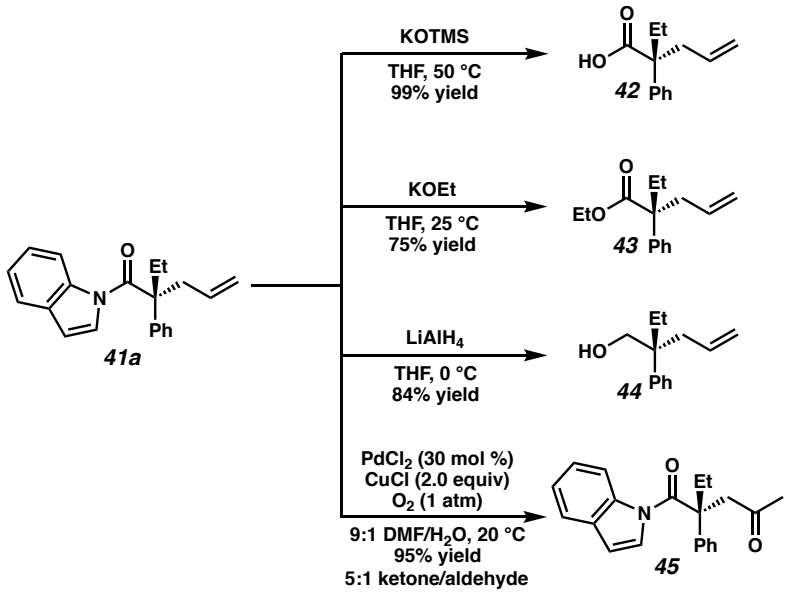
***Scheme 4.4*** *Investigation of an α-pyrrole substituted N-acyl indole substrate.*




## 4.6 DERIVATIZATION OF N-ACYL INDOLE PRODUCTS

To highlight the utility of the prepared α-quaternary *N*-acyl indoles we next turned toward examining derivatizations (Scheme 4.5). First, treatment of alkylation product **41a** with KOTMS smoothly affords the carboxylic acid **42**, which can be isolated in 99% yield following a chromatography-free procedure utilizing an acid-base extraction. Ethyl ester **43** was obtained in 75% yield by the addition of KOEt at 25 °C. Full reduction of **41a** to the corresponding primary alcohol **44** could be achieved with $LiAlH_4$ in 84% yield. Lastly, Wacker oxidation conditions affords 1,4-dicarbonyl compound **45** in 95% yield as a 5:1 mixture of ketone/aldehyde. Surprisingly, **41a** was found to be unreactive to Grignard reagents as well as direct amidation conditions, even at elevated temperatures, suggesting the potential to employ this moiety as a robust and orthogonal carboxylic acid masking group in synthesis.

***Scheme 4.5*** *Derivatization of α-quaternary N-acyl indole alkylation products.*




## 4.7 CONCLUSIONS

In summary, the first enantioselective palladium-catalyzed allylic alkylation of *N*-acyl indole-derived enol carbonates furnishing acyclic all-carbon quaternary stereocenters has been developed. Crucial to the excellent selectivities obtained is the preparation of the enol carbonates as single geometrical enolate isomers as well as the use of a new electron-deficient PHOX ligand, *(S)-Ty-PHOX* (**L12**). Additional studies addressing the scope and applications of this transformation as well as the subtle mechanistic distinctions associated with this and other recently described acyclic systems are currently underway.

## 4.8 EXPERIMENTAL SECTION

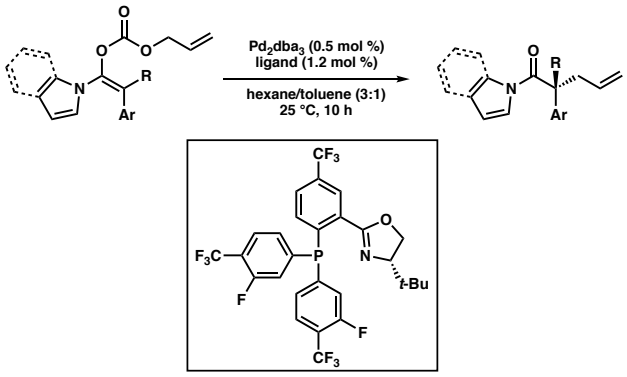
### 4.8.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 μm) was used for flash chromatography. $^1$H NMR spectra were recorded on Varian Inova 500 MHz and Bruker 400 MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm). $^{13}$C NMR spectra were recorded on a Varian Inova 500 MHz spectrometer (125 MHz) and Bruker 400 MHz spectrometers (100 MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm). Data for $^1$H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet, app = apparent. Data for $^{13}$C NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer or Nicolet 6700 FTIR spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption ($cm^{-1}$). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell and are reported as: $[\alpha]_D^T$ (concentration in 10 mg/1 mL, solvent). Analytical SFC was performed with a Mettler SFC supercritical $CO_2$ analytical

chromatography system utilizing Chiralpak (AD-H, AS-H or IC) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+), or obtained from Caltech mass spectrometry laboratory. Ligands were prepared by known methods.

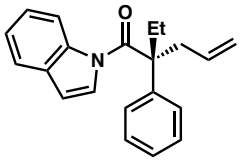
## 4.8.2 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

### 4.8.2.1 General Procedure for Pd-Catalyzed Allylic Alkylation Reactions



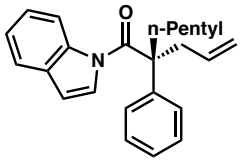

In a nitrogen-filled glovebox, a solution of $Pd_2(dba)_3$ (1.8 mg/mL) and **L12** (2.8 mg/mL) in toluene was stirred for 30 min at 25 °C, then 0.5 mL of the resulting catalyst solution was added to a one dram vial containing allyl enol carbonate substrate (0.2 mmol) dissolved in hexane (1.5 mL). The vial was sealed with a Teflon-lined cap, removed from the glovebox, and stirred at 25 °C for 12 h unless noted otherwise. The crude reaction mixture was concentrated then purified by silica gel flash chromatography to provide the desired alkylation product.

### 4.8.2.2 Spectroscopic Data for the Allylic Alkylation Products




**(*R*)-2-ethyl-1-(1*H*-indol-1-yl)-2-phenylpent-4-en-1-one (41a)**

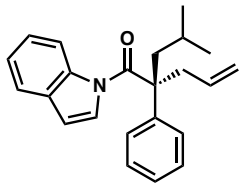
Purified by column chromatography (5% $Et_2O$ in hexanes) to provide an amorphous white solid (64.8 mg, 99% yield); 95% ee, $[\alpha]_D^{25}$ –111.4 (*c* 1.0, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 8.58 (dt, *J* = 8.3, 0.8 Hz, 1H), 7.48–7.44 (m, 1H), 7.39–7.32 (m, 3H), 7.32–7.22 (m, 4H), 6.84 (d, *J* = 3.9 Hz, 1H), 6.26 (d, *J* = 3.8 Hz, 1H), 5.45 (dddd, *J* = 16.6, 10.2, 8.5, 6.2 Hz, 1H), 5.03–4.92 (m, 2H), 2.99 (dd, *J* = 14.0, 8.5 Hz, 1H), 2.88 (dd, *J* = 14.0, 6.2 Hz, 1H), 2.25 (qd, *J* = 7.4, 1.5 Hz, 2H), 0.81 (t, *J* = 7.4 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 174.3, 143.0, 136.5, 133.0, 129.5, 129.2, 127.3, 126.5, 126.1, 125.1, 123.7, 120.6, 119.0, 117.2, 108.2, 56.8, 40.5, 28.0, 8.4.; IR (Neat Film, NaCl) 3154, 3071, 2974, 2880, 1694, 1643, 1600, 1584, 1538, 1495, 1471, 1463, 1446, 1380, 1303, 1206, 1225, 1149, 1077, 1019, 1000, 920, 891, 820, 767, 701 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{21}H_{22}NO$ $[M+H]^+$: 304.1696, found 304.1691; SFC Conditions: 10% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 6.41, major = 6.95.




**(*R*)-2-allyl-1-(1*H*-indol-1-yl)-2-phenylheptan-1-one (41b)**

Purified by column chromatography (5% $Et_2O$ in hexanes) to provide an amorphous white solid (68.4 mg, 99% yield); 96% ee, $[\alpha]_D^{25}$ –81.8 (*c* 1.0, $CHCl_3$); $^1H$ NMR (500

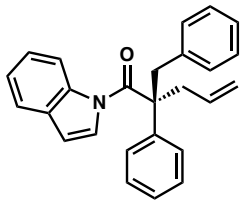
MHz, $CDCl_3$) δ 8.58 (dq, *J* = 8.4, 0.8 Hz, 1H), 7.46 (dt, *J* = 7.6, 1.1 Hz, 1H), 7.35 (ddt, *J* = 8.3, 5.3, 1.7 Hz, 3H), 7.30–7.22 (m, 4H), 6.85 (d, *J* = 3.9 Hz, 1H), 6.26 (dd, *J* = 3.8, 0.7 Hz, 1H), 5.44 (dddd, *J* = 16.6, 10.1, 8.5, 6.1 Hz, 1H), 5.03–4.90 (m, 2H), 3.00 (dd, *J* = 14.0, 8.6 Hz, 1H), 2.88 (dd, *J* = 14.0, 6.1 Hz, 1H), 2.25–2.11 (m, 2H), 1.35–1.24 (m, 1H), 1.21 (qd, *J* = 6.5, 6.0, 3.1 Hz, 4H), 1.10–0.98 (m, 1H), 0.81–0.75 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.4, 143.2, 136.5, 133.2, 129.5, 129.2, 127.3, 126.4, 126.1, 125.1, 123.7, 120.6, 119.0, 117.3, 108.2, 56.4, 41.3, 35.0, 32.2, 23.4, 22.4, 14.0; IR (Neat Film, NaCl) 3071, 2954, 2928, 2859, 1696, 1449, 1304, 1204, 1078, 919, 750, 702 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{24}H_{28}NO$ $[M+H]^+$: 346.2165, found 346.2156; SFC Conditions: 10% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 4.87, major = 5.84.




**(*R*)-1-(1*H*-indol-1-yl)-2-isobutyl-2-phenylpent-4-en-1-one (41c)**

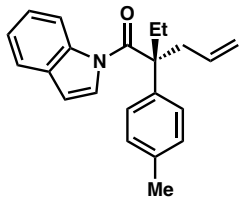
Purified by column chromatography (5% $Et_2O$ in hexanes) to provide an amorphous white solid (66.1 mg, 99% yield); 96% ee, $[\alpha]_D^{25}$ –109.1 (*c* 1.0, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 8.62–8.52 (m, 1H), 7.49–7.43 (m, 1H), 7.39–7.32 (m, 3H), 7.30–7.21 (m, 4H), 6.87 (d, *J* = 3.8 Hz, 1H), 6.27 (d, *J* = 3.8 Hz, 1H), 5.42 (dddd, *J* = 16.5, 9.9, 8.7, 5.9 Hz, 1H), 5.04–4.89 (m, 2H), 3.13–3.01 (m, 1H), 2.91 (ddd, *J* = 14.2, 5.9, 1.5 Hz, 1H), 2.26 (dd, *J* = 14.1, 4.4 Hz, 1H), 2.10 (ddd, *J* = 14.1, 6.5, 1.1 Hz, 1H), 1.74 (ddt, *J* = 13.2, 11.0, 6.5 Hz, 1H), 0.84 (d, *J* = 6.6 Hz, 3H), 0.62 (d, *J* = 6.6 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.8, 143.3, 136.5, 133.3, 129.6, 129.2, 127.3, 126.4, 126.1, 125.2,

123.8, 120.6, 119.2, 117.3, 108.2, 56.1, 43.5, 42.2, 25.2, 24.1, 23.5; IR (Neat Film, NaCl) 3164, 3071, 3026, 2957, 2868, 1693, 1639, 1600, 1584, 1537, 1472, 1449, 1306, 1222, 1206, 1149, 1079, 919, 890, 767, 750, 702 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{23}H_{26}NO$ $[M+H]^+$: 332.2009, found 332.1998; SFC Conditions: 10% IPA, 2.5 mL/min, Chiralpak AD-H column, $\lambda$ = 210 nm, $t_R$ (min): minor = 4.86, major = 5.20.



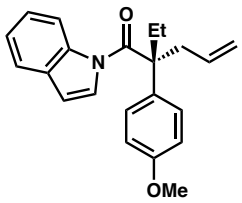
**(*S*)-2-benzyl-1-(1*H*-indol-1-yl)-2-phenylpent-4-en-1-one (41d)**

Purified by column chromatography (5% $Et_2O$ in hexanes) to provide an amorphous white solid (70.5 mg, 96% yield); 90% ee, $[\alpha]_D^{25}$ +50.9 (*c* 0.65, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 8.54–8.50 (m, 1H), 7.48 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.38–7.29 (m, 4H), 7.29–7.23 (m, 1H), 7.18–7.11 (m, 3H), 7.06 (dd, *J* = 8.2, 6.9 Hz, 2H), 6.92 (d, *J* = 3.8 Hz, 1H), 6.60 (dd, *J* = 7.6, 1.5 Hz, 2H), 6.32 (d, *J* = 3.9 Hz, 1H), 5.82–5.69 (m, 1H), 5.11–5.05 (m, 1H), 5.00–4.93 (m, 1H), 3.56 (d, *J* = 13.5 Hz, 1H), 3.42 (d, *J* = 13.5 Hz, 1H), 2.89 (d, *J* = 7.1 Hz, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 173.7, 142.4, 136.6, 136.3, 132.8, 130.8, 129.5, 129.1, 127.8, 127.6, 126.8, 126.7, 126.0, 125.2, 123.8, 120.6, 119.8, 117.3, 108.5, 57.8, 42.4, 39.0; IR (Neat Film, NaCl) 3062, 3028, 2926, 1694, 1601, 1584, 1537, 1495, 1449, 1328, 1305, 1203, 1078, 1019, 894, 751, 720, 702 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{26}H_{24}NO$ $[M+H]^+$: 366.1852, found 366.1855; SFC Conditions: 10% IPA, 2.5 mL/min, Chiralpak AD-H column, $\lambda$ = 235 nm, $t_R$ (min): minor = 17.49, major = 18.37.




**(*R*)-2-ethyl-1-(1*H*-indol-1-yl)-2-(*p*-tolyl)pent-4-en-1-one (41e)**

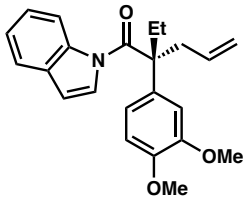
Purified by column chromatography (5% $Et_2O$ in hexanes) to provide a colorless oil (62.9 mg, 99% yield); 98% ee, $[\alpha]_D^{25}$ –112.1 (*c* 1.0, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 8.57 (dq, *J* = 8.4, 1.0 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.35 (ddt, *J* = 8.4, 7.1, 1.3 Hz, 1H), 7.26–7.21 (m, 1H), 7.15 (d, *J* = 1.0 Hz, 4H), 6.88 (dd, *J* = 3.9, 1.2 Hz, 1H), 6.27 (d, *J* = 3.8 Hz, 1H), 5.44 (dddd, *J* = 17.6, 10.9, 9.3, 6.6 Hz, 1H), 5.03–4.91 (m, 2H), 3.00–2.81 (m, 2H), 2.35 (s, 3H), 2.22 (q, *J* = 7.4 Hz, 2H), 0.80 (td, *J* = 7.4, 1.2 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 174.5, 139.9, 137.0, 136.5, 133.2, 129.9, 129.5, 126.3, 126.3, 125.0, 123.7, 120.5, 118.9, 117.2, 108.1, 56.4, 40.5, 28.0, 21.2, 8.4; IR (Neat Film, NaCl) 2973, 1695, 1640, 1585, 1537, 1514, 1472, 1450, 1380, 1321, 1304, 1224, 1206, 1105, 1077, 1020, 918, 893, 813, 768, 750 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{22}H_{24}NO$ $[M+H]^+$: 318.1852, found 318.1848; SFC Conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 4.21, major = 4.75.




**(*R*)-2-ethyl-1-(1*H*-indol-1-yl)-2-(4-methoxyphenyl)pent-4-en-1-one (41f)**

Purified by column chromatography (10% $Et_2O$ in hexanes) to provide an amorphous white solid (59.2mg, 89% yield); 98% ee, $[\alpha]_D^{25}$ –118.8 (*c* 1.0, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 8.58 (dq, *J* = 8.3, 0.8 Hz, 1H), 7.47 (ddd, *J* = 7.7, 1.4, 0.7 Hz, 1H), 7.35

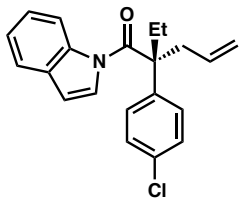
(ddd, *J* = 8.3, 7.1, 1.3 Hz, 1H), 7.30–7.21 (m, 1H), 7.21–7.15 (m, 2H), 6.93–6.85 (m, 3H), 6.28 (dd, *J* = 3.9, 0.7 Hz, 1H), 5.45 (dddd, *J* = 16.6, 10.2, 8.5, 6.1 Hz, 1H), 5.04–4.90 (m, 2H), 3.81 (s, 3H), 2.96 (dd, *J* = 13.9, 8.5 Hz, 1H), 2.85 (dd, *J* = 14.0, 6.1 Hz, 1H), 2.21 (q, *J* = 7.4 Hz, 2H), 0.80 (t, *J* = 7.4 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.6, 158.6, 136.5, 134.9, 133.2, 129.5, 127.5, 126.3, 125.1, 123.7, 120.5, 118.9, 117.2, 114.5, 108.1, 56.1, 55.3, 40.5, 28.1, 8.4; IR (Neat Film, NaCl) 3163, 3073, 2973, 2837, 1694, 1640, 1609, 153, 1538, 1514, 1450, 1380, 1304, 1250, 1206, 1184, 1076, 1034, 919, 890, 819, 768, 750 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{22}H_{24}NO_2$ $[M+H]^+$: 334.1802 found 334.1816; SFC Conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 5.09, major = 5.73.




**(*R*)-2-(3,4-dimethoxyphenyl)-2-ethyl-1-(1*H*-indol-1-yl)pent-4-en-1-one (41g)**

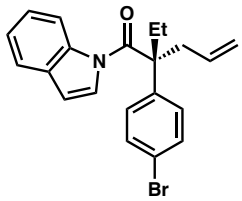
Purified by column chromatography (20% $Et_2O$ in hexanes) to provide an amorphous white solid (72.6 mg, 99% yield); 95% ee, $[\alpha]_D^{25}$ –96.6 (*c* 1.0, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 8.61 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.53 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.40 (ddd, *J* = 8.2, 7.2, 1.3 Hz, 1H), 7.33–7.28 (m, 1H), 6.98 (d, *J* = 3.8 Hz, 1H), 6.96–6.87 (m, 2H), 6.78 (d, *J* = 1.7 Hz, 1H), 6.34 (dt, *J* = 3.8, 0.8 Hz, 1H), 5.56–5.43 (m, 1H), 5.09–4.97 (m, 2H), 3.95 (s, 3H), 3.86 (s, 3H), 3.01 (dd, *J* = 14.0, 8.5 Hz, 1H), 2.91 (dd, *J* = 14.0, 6.2 Hz, 1H), 2.26 (q, *J* = 7.5 Hz, 2H), 0.91–0.78 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.5, 149.5, 148.1, 136.4, 135.3, 133.1, 129.5, 126.1, 125.0, 123.7, 120.5, 118.9, 118.5, 117.0, 111.3, 109.6, 108.1, 56.3, 56.0, 55.9, 40.4, 28.0, 8.3. IR (Neat Film, NaCl) 3072, 2967,

2835, 1694, 1640, 1587, 1518, 1449, 1412, 1306, 1260, 1206, 1150, 1077, 1027, 917, 893, 803, 768, 751 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{23}H_{26}NO_3$ $[M+H]^+$: 364.1907 found 364.1892; SFC Conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, $\lambda$ = 210 nm, $t_R$ (min): minor = 4.14, major = 4.92.



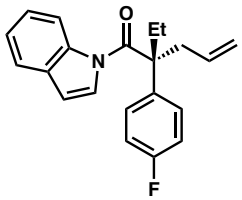

**(*R*)-2-(4-chlorophenyl)-2-ethyl-1-(1*H*-indol-1-yl)pent-4-en-1-one (41h)**

Purified by column chromatography (5% $Et_2O$ in hexanes) to provide a colorless oil (68.2 mg, 99% yield); 94% ee, $[\alpha]_D^{25}$ –103.2 (*c* 1.0, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 8.57 (d, *J* = 8.3 Hz, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.39–7.32 (m, 3H), 7.30–7.23 (m, 1H), 7.23–7.18 (m, 2H), 6.81 (dd, *J* = 3.9, 0.8 Hz, 1H), 6.31 (dd, *J* = 3.9, 0.7 Hz, 1H), 5.48–5.38 (m, 1H), 5.05–4.92 (m, 2H), 2.97 (ddt, *J* = 14.1, 8.4, 0.9 Hz, 1H), 2.84 (ddt, *J* = 13.9, 6.1, 1.3 Hz, 1H), 2.23 (q, *J* = 7.4 Hz, 2H), 0.82 (t, *J* = 7.4 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 173.7, 141.6, 136.5, 133.3, 132.6, 129.5, 129.4, 127.9, 125.8, 125.3, 123.9, 120.7, 119.4, 117.2, 108.6, 56.5, 40.6, 28.1, 8.4; IR (Neat Film, NaCl) 3074, 2974, 2880, 1695, 1639, 1539, 1493, 1450, 1304, 1224, 1206, 1150, 1097, 1077, 1014, 920, 890, 815, 768, 752 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{21}H_{21}ClNO$ $[M+H]^+$: 338.1306 found 338.1291; SFC Conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, $\lambda$ = 210 nm, $t_R$ (min): minor = 4.31, major = 4.78.




**(*R*)-2-(4-bromophenyl)-2-ethyl-1-(1*H*-indol-1-yl)pent-4-en-1-one (41i)**

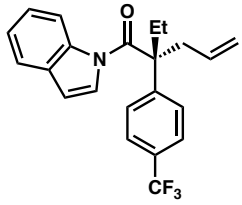
Purified by column chromatography (5% $Et_2O$ in hexanes) to provide as a white foam (75.2 mg, 98% yield); 94% ee, $[\alpha]_D^{25}$ –83.1 (*c* 1.0, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 8.45 (d, *J* = 9.6 Hz, 1H), 7.59 (d, *J* = 2.0 Hz, 1H), 7.44 (dd, *J* = 8.9, 2.0 Hz, 1H), 7.37 (dd, *J* = 8.1, 6.8 Hz, 2H), 7.33–7.26 (m, 1H), 7.29–7.23 (m, 2H), 6.84 (d, *J* = 3.8 Hz, 1H), 6.20 (dd, *J* = 3.9, 0.7 Hz, 1H), 5.44 (dddd, *J* = 16.6, 10.0, 8.5, 6.1 Hz, 1H), 5.05–4.89 (m, 2H), 3.02–2.91 (m, 1H), 2.87 (dd, *J* = 14.1, 6.2 Hz, 1H), 2.33–2.14 (m, 2H), 0.80 (t, *J* = 7.4 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 174.3, 142.7, 135.2, 132.8, 131.3, 129.3, 127.9, 127.5, 127.2, 126.4, 123.2, 119.2, 118.5, 117.0, 107.3, 56.8, 40.3, 28.0, 8.3; IR (Neat Film, NaCl) 3162, 3065, 2974, 2879, 1698, 1639, 1598, 1574, 1534, 1496, 1443, 1364, 1304, 1266, 1218, 1199, 1080, 1032, 1000, 947, 920, 887, 822, 811, 762, 734, 718, 702 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{21}H_{21}BrNO$ $[M+H]^+$: 382.0801 found 382.0785; SFC Conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 6.60, major = 7.38.




**(*R*)-2-ethyl-2-(4-fluorophenyl)-1-(1*H*-indol-1-yl)pent-4-en-1-one (41j)**

Purified by column chromatography (5% $Et_2O$ in hexanes) to provide an amorphous white solid (62.1mg, 97% yield); 96% ee, $[\alpha]_D^{25}$ –97.3 (*c* 1.0, $CHCl_3$); $^1H$ NMR (500

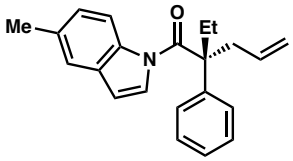
MHz, $CDCl_3$) δ 8.57 (d, *J* = 8.4 Hz, 1H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.27–7.19 (m, 3H), 7.05 (t, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 3.9 Hz, 1H), 6.29 (d, *J* = 3.8 Hz, 1H), 5.42 (dtd, *J* = 16.8, 9.0, 6.3 Hz, 1H), 5.02–4.89 (m, 2H), 2.95 (dd, *J* = 14.0, 8.4 Hz, 1H), 2.83 (dd, *J* = 14.0, 6.2 Hz, 1H), 2.21 (q, *J* = 7.4 Hz, 2H), 0.79 (t, *J* = 7.4 Hz, 3H); $^{19}$F NMR (282 MHz, $CDCl_3$) δ –114.82 (tt, *J* = 9.1, 4.7 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.0, 162.0 (d, $J_{C–F}$ = 246.9 Hz), 138.9 (d, $J_{C–F}$ = 3.4 Hz), 136.5, 132.8, 129.5, 128.10 (d, $J_{C–F}$ = 7.9 Hz), 125.9, 125.2, 123.9, 120.7, 119.3, 117.3, 116.1 (d, $J_{C–F}$ = 21.4 Hz), 108.4, 56.3, 40.7, 28.2, 8.4; IR (Neat Film, NaCl) 3073, 2973, 1694, 1602, 1539, 1510, 1450, 1305, 1226, 1206, 1164, 1102, 1077, 1016, 920, 890, 822, 810, 768, 751 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{21}H_{21}FNO$ $[M+H]^+$: 322.1602 found 322.1607; SFC Conditions: 10% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 4.57, major = 5.07.




**(*R*)-2-ethyl-1-(1*H*-indol-1-yl)-2-(4-(trifluoromethyl)phenyl)pent-4-en-1-one (41k)**

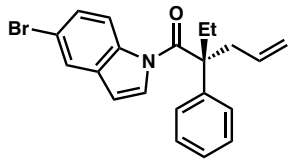
Purified by column chromatography (5% $Et_2O$ in hexanes) to provide an amorphous white solid (73.0 mg, 98% yield); 70% ee, $[\alpha]_D^{25}$ –75.6 (*c* 1.0, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 8.58 (dt, *J* = 8.3, 0.8 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.48 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.42–7.35 (m, 3H), 7.29–7.24 (m, 1H), 6.73 (d, *J* = 3.9 Hz, 1H), 6.31 (d, *J* = 3.9 Hz, 1H), 5.42 (dddd, *J* = 16.6, 10.2, 8.4, 6.2 Hz, 1H), 5.06–4.92 (m, 2H), 3.01 (dd, *J* = 14.0, 8.4 Hz, 1H), 2.88 (dd, *J* = 14.1, 6.3 Hz, 1H), 2.28 (qd, *J* = 7.3, 2.2 Hz, 2H), 0.83 (t, *J* = 7.4 Hz, 3H); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -62.67; $^{13}$C NMR (100 MHz, $CDCl_3$) δ

173.3, 147.2 (overlapping), 136.5, 132.3, 129.6 (q, $J$ = 32.7 Hz), 129.5, 127.0, 126.1 (q, $J$ = 3.8 Hz), 125.5, 125.4, 124.1, 124.1 (q, $J$ = 272.2 Hz), 120.7, 119.7, 117.3, 108.8, 56.9, 40.6, 28.1, 8.4. IR (Neat Film, NaCl) 3076, 2977, 2882, 1697, 1618, 1549, 1450, 1412, 1328, 1307, 1225, 1207, 1169, 1126, 1070, 1017, 922, 890, 843, 819, 768, 751 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{22}H_{21}F_3NO$ $[M+H]^+$: 372.1570 found 372.1555; SFC Conditions: 5% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 4.48, major = 4.97.



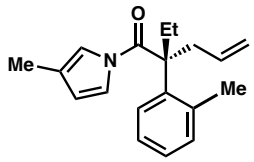

**(*R*)-2-ethyl-1-(5-methyl-1*H*-indol-1-yl)-2-phenylpent-4-en-1-one (41l)**

Purified by column chromatography (5% $Et_2O$ in hexanes) to provide a colorless oil (63.4mg, 99% yield); 98% ee, $[\alpha]_D^{25}$ –111.7 (*c* 1.0, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 8.45 (d, $J$ = 8.5 Hz, 1H), 7.37–7.32 (m, 2H), 7.31–7.23 (m, 4H), 7.18 (dd, $J$ = 8.5, 1.7 Hz, 1H), 6.80 (d, $J$ = 3.9 Hz, 1H), 6.19 (d, $J$ = 3.8 Hz, 1H), 5.44 (dddd, $J$ = 16.7, 10.3, 8.5, 6.2 Hz, 1H), 5.02–4.93 (m, 2H), 2.98 (dd, $J$ = 14.0, 8.5 Hz, 1H), 2.90–2.83 (m, 1H), 2.43 (s, 3H), 2.24 (qd, $J$ = 7.4, 1.5 Hz, 2H), 0.80 (t, $J$ = 7.4 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 174.1, 143.1, 134.7, 133.3, 133.1, 129.8, 129.1, 127.3, 126.5, 126.4, 126.1, 120.5, 118.9, 116.9, 108.0, 56.7, 40.5, 28.0, 21.4, 8.4; IR (Neat Film, NaCl) 3024, 2974, 2879, 1694, 1640, 1542, 1494, 1466, 1365, 1305, 1245, 1207, 1142, 1079, 1000, 919, 889, 830, 810, 766, 734, 716, 702 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{22}H_{24}NO$ $[M+H]^+$: 318.1852 found 318.1846; SFC Conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 5.21, major = 5.92.




**(*R*)-1-(5-bromo-1*H*-indol-1-yl)-2-ethyl-2-phenylpent-4-en-1-one (41m)**

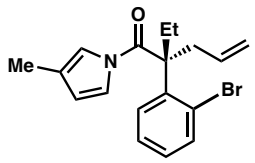
Purified by column chromatography (5% $Et_2O$ in hexanes) to provide an amorphous white foam (74.0 mg, 97% yield); 92% ee, $[\alpha]_D^{25}$ –112.5 (*c* 1.0, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 8.57 (dq, *J* = 8.4, 0.9 Hz, 1H), 7.51–7.45 (m, 3H), 7.36 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.28–7.24 (m, 1H), 7.17–7.11 (m, 2H), 6.81 (d, *J* = 3.9 Hz, 1H), 6.31 (dd, *J* = 3.9, 0.8 Hz, 1H), 5.43 (dddd, *J* = 16.6, 10.1, 8.4, 6.2 Hz, 1H), 5.03–4.92 (m, 2H), 2.96 (ddt, *J* = 14.0, 8.4, 1.0 Hz, 1H), 2.86–2.80 (m, 1H), 2.22 (q, *J* = 7.4 Hz, 2H), 0.81 (t, *J* = 7.5 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 173.6, 142.1, 136.5, 132.6, 132.3, 129.5, 128.2, 125.8, 125.3, 123.9, 121.4, 120.7, 119.4, 117.2, 108.6, 56.5, 40.5, 28.0, 8.4; IR (Neat Film, NaCl) 3073, 2974, 1694, 1586, 1537, 1492, 1450, 1305, 1224, 1206, 1149, 1076, 1010, 920, 890, 814, 768, 752 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{21}H_{21}BrNO$ $[M+H]^+$: 382.0801 found 382.0811; SFC Conditions: 15% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 5.28, major = 5.91.




**(*R*)-2-ethyl-1-(3-methyl-1*H*-pyrrol-1-yl)-2-(*o*-tolyl)pent-4-en-1-one (41n)**

Purified by column chromatography (5% $Et_2O$ in hexanes) to provide a colorless oil (56.1 mg, 99% yield); 89% ee, $[\alpha]_D^{25}$ –87.4 (*c* 1.0, $CHCl_3$); Note: Rotameric species were observed for this compound, thus the $^1H$ NMR spectrum was recorded at elevated temperature (50 ºC): $^1H$ NMR (400 MHz, $CDCl_3$, 50 ºC) δ 7.37 (dt, *J* = 8.0, 1.5 Hz, 1H),

7.30–7.21 (m, 1H), 7.18 (tt, *J* = 7.2, 1.4 Hz, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.77 (d, *J* = 10.9 Hz, 2H), 5.84 (dt, *J* = 3.2, 1.5 Hz, 1H), 5.39 (s, 1H), 5.05–4.90 (m, 2H), 2.90 (d, *J* = 7.3 Hz, 2H), 2.26 (dd, *J* = 13.1, 6.6 Hz, 1H), 2.14 (d, *J* = 11.3 Hz, 2H), 2.13 (s, 2H), 1.91 (d, *J* = 1.3 Hz, 3H), 0.77 (s, 3H); Note: Rotameric species were observed for this compound, thus the $^{13}$C NMR spectrum contains broad peaks: $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.5, 140.8, 136.8, 133.3, 132.7, 127.3, 126.4, 126.1, 122.5, 120.4, 118.8, 117.4, 114.4, 54.6, 37.8, 28.0, 20.3, 12.0, 8.4; IR (Neat Film, NaCl) 3143, 3073, 2976, 2880, 1699, 1639, 1490, 1459, 1490, 1459, 1389, 1337, 1309, 1199, 1134, 1080, 1068,990, 918, 893, 827, 773, 740 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{24}NO$ $[M+H]^+$: 282.1852 found 282.1843; SFC Conditions: 3% IPA, 2.5 mL/min, Chiralcel OD-H column, λ = 210 nm, $t_R$ (min): minor = 4.99, major = 5.37.

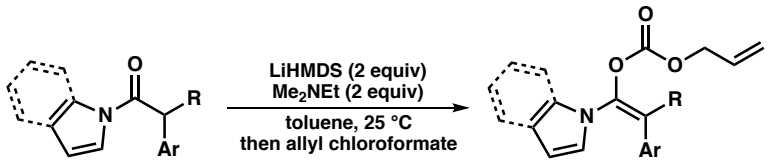



**(*R*)-2-(2-bromophenyl)-2-ethyl-1-(3-methyl-1*H*-pyrrol-1-yl)pent-4-en-1-one (41o)**

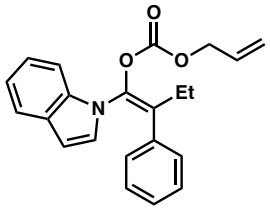
Purified by column chromatography (5% $Et_2O$ in hexanes) to provide an amorphous white solid (60.1 mg, 87% yield); 80% ee, $[\alpha]_D^{25}$ –80.9 (*c* 1.0, $CHCl_3$); Note: Rotameric species were observed for this compound, thus the $^1$H NMR spectrum was recorded at elevated temperature (50 ºC): $^1$H NMR (400 MHz, $CDCl_3$) δ 7.55 (dt, *J* = 8.0, 1.4 Hz, 1H), 7.45 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.43–7.36 (m, 1H), 7.16 (td, *J* = 7.5, 1.6 Hz, 1H), 6.74 (d, *J* = 9.1 Hz, 2H), 5.86 (dd, *J* = 3.4, 1.7 Hz, 1H), 5.46–5.24 (m, 1H), 5.04–4.92 (m, 2H), 3.14 (dd, *J* = 14.4, 6.3 Hz, 1H), 3.01–2.85 (m, 1H), 2.46–2.33 (m, 1H), 2.19–2.05 (m, 1H), 1.92 (s, 3H), 0.80 (s, 3H); Note: Rotameric species were observed for this compound, thus the $^{13}$C NMR spectrum contains broad peaks: $^{13}$C NMR (100 MHz,

$CDCl_3$) δ 171.5, 141.8, 135.3, 132.9, 129.0, 128.5, 127.8, 124.2, 122.5, 120.2, 119.1, 117.4, 114.4, 55.8, 36.5, 28.0, 12.1, 8.8; IR (Neat Film, NaCl) 2977, 1704, 1485, 1470, 1390, 1309, 1201, 1134, 1068, 1025, 919, 828, 769, 741 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{18}H_{21}BrNO$ $[M+H]^+$: 346.0801 found 346.0790; SFC Conditions: 3% IPA, 2.5 mL/min, Chiralpak OD-H column, λ = 210 nm, $t_R$ (min): minor = 9.10, major = 9.72.

#### 4.8.2.3 Selective Enolization of *N*-Acyl Substrates

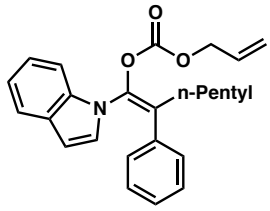



To a flame-dried flask was added LiHMDS (335 mg, 2 mmol) followed by toluene (3.0 mL) and *N,N*-dimethylethylamine (0.213 mL, 2 mmol), and the resulting mixture stirred at 25 °C for 5 min. A solution of *N*-acyl indole (1 mmol) in toluene (2.0 mL) was then added, and the reaction stirred at 25 °C for an additional 2 hours. The flask was then submerged in a room temperature water bath, and allyl chloroformate (0.217 mL, 2 mmol) was added neat, and the reaction continued until no starting material remained by TLC (typically less than 30 min). The crude reaction mixture was diluted with $Et_2O$ and quenched with water. The layers were separated, and the aqueous layer was extracted with $Et_2O$ twice. The combined organic layers were dried over $Na_2SO_4$ and concentrated. The crude product was purified by silica gel flash chromatography to afford the desired enol carbonate. The *E/Z* ratio of enol carbonates was determined by $^1H$ NMR and is >95:5 unless stated otherwise.




**(*E*)-1-(1*H*-indol-1-yl)-2-phenylbut-1-en-1-yl allyl carbonate (40a)**

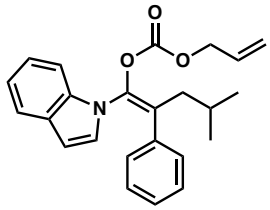
Purified by column chromatography (5% $Et_2O$ in hexanes) to provide the desired product as a colorless oil (2.08 g, 75% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.55–7.43 (m, 2H), 7.24–7.18 (m, 1H), 7.15–7.06 (m, 4H), 7.02–6.94 (m, 2H), 6.89 (d, *J* = 3.3 Hz, 1H), 6.35 (dd, *J* = 0.9, 3.4 Hz, 1H), 5.88 (ddt, *J* = 5.8, 10.4, 17.1 Hz, 1H), 5.37–5.23 (m, 2H), 4.61 (dt, *J* = 1.4, 5.8 Hz, 2H), 2.68 (q, *J* = 7.5 Hz, 2H), 1.09 (t, *J* = 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 152.7, 136.2, 135.0, 130.8, 130.2, 129.0, 128.4, 128.2, 127.5, 127.5, 122.6, 120.7, 119.4, 111.2, 103.9, 69.3, 24.9, 12.6; IR (Neat Film, NaCl) 3056, 2974, 1766, 1682, 1519, 1456, 1333, 1259, 1238, 1209, 1143, 1119, 1094, 1042, 968, 946, 913, 765, 743, 699 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{22}H_{22}NO_3$ $[M+H]^+$: 348.1594, found 348.1588.




**(*E*)-1-(1*H*-indol-1-yl)-2-phenylhept-1-en-1-yl allyl carbonate (40b)**

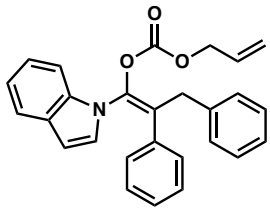
Purified by column chromatography (5% $Et_2O$ in hexanes) to provide the desired product as a colorless oil (337.6 mg, 87% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.51–7.45 (m, 2H), 7.23–7.16 (m, 1H), 7.14–7.05 (m, 4H), 6.98–6.91 (m, 2H), 6.89–6.84 (m, 1H), 6.36–6.30 (m, 1H), 5.94–5.81 (m, 1H), 5.36–5.22 (m, 2H), 4.60 (dq, *J* = 5.8, 1.4 Hz, 2H), 2.70–2.60 (m, 2H), 1.49–1.26 (m, 6H), 0.89 (td, *J* = 7.1, 1.6 Hz, 3H); $^{13}$C NMR (100

MHz, $CDCl_3$) δ 152.7, 136.4, 136.3, 135.4, 130.9, 129.1, 129.0, 128.4, 128.2, 127.5, 127.5, 122.6, 120.7, 120.7, 119.4, 111.2, 103.9, 69.3, 31.5, 31.4, 27.3, 22.4, 14.1; IR (Neat Film, NaCl) 3055, 2956, 2929, 2860, 2363, 2340, 1765, 1684, 1457, 1332, 1242, 1211, 1142, 1118, 948, 764, 742, 699 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{25}H_{28}NO_3$ $[M+H]^+$: 390.2064, found 390.2078.



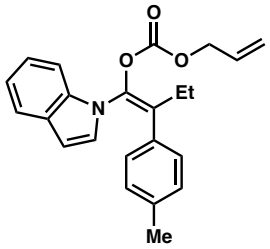
**(*E*)-1-(1*H*-indol-1-yl)-4-methyl-2-phenylpent-1-en-1-yl allyl carbonate (40c)**

Purified by column chromatography (5% $Et_2O$ in hexanes) to provide the desired product as a white solid (327.6 mg, 87% yield); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.50 (ddd, *J* = 7.4, 5.8, 1.0 Hz, 2H), 7.21 (ddd, *J* = 8.3, 7.1, 1.1 Hz, 1H), 7.15–7.08 (m, 4H), 6.99–6.91 (m, 2H), 6.84 (d, *J* = 3.3 Hz, 1H), 6.33 (d, *J* = 3.3 Hz, 1H), 5.88 (ddt, *J* = 17.3, 10.5, 5.8 Hz, 1H), 5.32 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.26 (dq, *J* = 10.3, 1.3 Hz, 1H), 4.60 (dt, *J* = 5.8, 1.4 Hz, 2H), 2.56 (d, *J* = 7.3 Hz, 2H), 1.62 (hept, *J* = 6.8 Hz, 1H), 1.00 (d, *J* = 6.6 Hz, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 152.6, 136.5, 136.3, 136.1, 130.9, 129.2, 128.4, 128.2, 128.0, 127.5, 127.4, 122.6, 120.7, 120.7, 119.4, 111.2, 103.8, 69.3, 40.2, 26.5, 22.4; IR (Neat Film, NaCl) 3057, 3031, 2957, 2869, 1766, 1682, 1519, 1456, 1331, 1246, 1331, 1246, 1209, 1144, 1118, 1046, 960, 767, 743, 699 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{24}H_{26}NO_3$ $[M+H]^+$: 376.1907, found 376.1902.



**(*E*)-1-(1*H*-indol-1-yl)-2,3-diphenylprop-1-en-1-yl allyl carbonate (40d)**

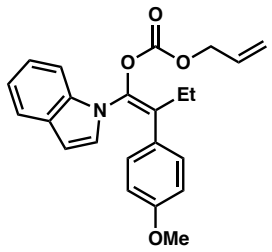
Purified by column chromatography (5% $Et_2O$ in hexanes) to provide the desired product as a yellow oil (377.6 mg, 92% yield); $^1$H NMR (500 MHz, $CHCl_3$) δ 7.58–7.49 (m, 2H), 7.34–7.25 (m, 4H), 7.26–7.18 (m, 2H), 7.14 (tt, *J* = 7.1, 0.9 Hz, 1H), 7.07–6.99 (m, 3H), 6.95 (m, 1H), 6.94–6.87 (m, 2H), 6.39 (dt, *J* = 3.4, 0.8 Hz, 1H), 5.91–5.79 (m, 1H), 5.35–5.22 (m, 2H), 4.58 (dt, *J* = 5.9, 1.3 Hz, 2H), 4.03 (s, 2H); $^{13}$C NMR (100 MHz, $CHCl_3$) δ 152.4, 138.0, 136.5, 136.1, 136.1, 130.7, 128.9, 128.8, 128.5, 128.4, 128.1, 127.7, 127.5, 126.6, 126.4, 122.7, 120.9, 120.8, 119.4, 111.3, 104.2, 69.4, 37.7; IR (Neat Film, NaCl) 3059, 3028, 1766, 1678, 1602, 1519, 1495, 1456, 1384, 1364, 1333, 1243, 1214, 1142, 1117, 967, 945 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{27}H_{24}NO_3$ $[M+H]^+$: 410.1751, found 410.1749.



**(*E*)-1-(1*H*-indol-1-yl)-2-(*p*-tolyl)but-1-en-1-yl allyl carbonate (40e)**

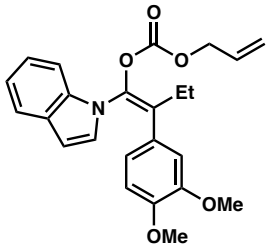
Purified by column chromatography (6% $Et_2O$ in hexanes) to provide the desired product as a yellow oil (268.7 mg, 74% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.54–7.42 (m, 2H), 7.19 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 1H), 7.10 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.92–6.80 (m, 5H), 6.35 (dd, *J* = 3.3, 0.9 Hz, 1H), 5.87 (ddt, *J* = 17.2, 10.5, 5.8 Hz, 1H), 5.41–5.18 (m,

2H), 4.59 (dt, *J* = 5.8, 1.4 Hz, 2H), 2.64 (q, *J* = 7.5 Hz, 2H), 2.19 (s, 3H), 1.07 (t, *J* = 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 152.8, 137.2, 136.3, 134.8, 133.2, 130.9, 130.3, 129.2, 129.0, 128.5, 127.5, 122.6, 120.8, 120.7, 119.6, 111.4, 103.8, 69.4, 25.0, 21.2, 12.7; IR (Neat Film, NaCl) 1764, 1457, 1333, 1258, 1238, 1209, 1143, 1120, 945, 818, 743 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{23}H_{24}NO_3$ $[M+H]^+$: 362.1751, found 362.1741.



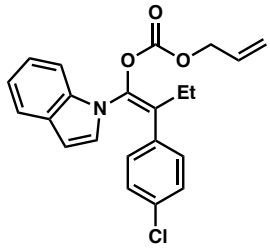

**(*E*)-1-(1*H*-indol-1-yl)-2-(4-methoxyphenyl)but-1-en-1-yl allyl carbonate (40f)**

Purified by column chromatography (10% $Et_2O$ in hexanes) to provide the desired product as a yellow oil (245.6 mg, 65% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.51 (ddd, *J* = 7.8, 1.2, 0.8 Hz, 1H), 7.45 (dq, *J* = 8.2, 0.9 Hz, 1H), 7.19 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.10 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.92–6.82 (m, 3H), 6.67– 6.57 (m, 2H), 6.36 (dd, *J* = 3.3, 0.9 Hz, 1H), 5.87 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.37–5.19 (m, 2H), 4.59 (d, *J* = 5.8 Hz, 2H), 3.68 (s, 3H), 2.63 (q, *J* = 7.5 Hz, 2H), 1.07 (t, *J* = 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 158.9, 152.9, 136.3, 134.6, 131.0, 129.9, 129.2, 128.8, 128.5, 128.3, 122.7, 120.8, 120.8, 119.6, 113.7, 111.4, 103.9, 69.5, 55.2, 25.0, 12.8; IR (Neat Film, NaCl) 1764, 1609, 1513, 1456, 1293, 1247, 1209, 1142, 1121, 1038, 831, 744 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{23}H_{24}NO_4$ $[M+H]^+$: 378.1700, found 378.1690.




**(*E*)-allyl (2-(3,4-dimethoxyphenyl)-1-(1*H*-indol-1-yl)but-1-en-1-yl) carbonate (40g)**

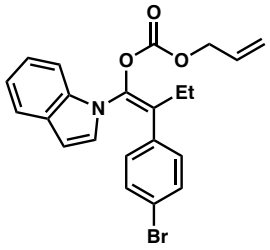
Purified by column chromatography (20% $Et_2O$ in hexanes) to provide the desired product as a colorless oil (262.1 mg, 64% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.54–7.48 (m, 2H), 7.21 (ddd, *J* = 1.3, 7.1, 8.3 Hz, 1H), 7.11 (td, *J* = 1.1, 7.5 Hz, 1H), 6.92 (t, *J* = 2.2 Hz, 1H), 6.71 (dt, *J* = 1.9, 8.3 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 6.38 (dt, *J* = 1.2, 3.5 Hz, 1H), 6.17 (t, *J* = 1.8 Hz, 1H), 5.89 (ddt, *J* = 5.8, 10.3, 17.1 Hz, 1H), 5.41–5.19 (m, 2H), 4.62 (dt, *J* = 1.4, 5.8 Hz, 2H), 3.77 (s, 3H), 3.23 (s, 3H), 2.68 (qd, *J* = 2.4, 7.6 Hz, 2H), 1.12 (td, *J* = 2.2, 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 152.9, 148.4, 148.3, 136.6, 134.5, 130.9, 130.6, 129.2, 128.4, 128.4, 122.7, 120.8, 120.8, 119.7, 119.6, 111.1, 110.7, 110.6, 104.0, 69.4, 55.7, 55.2, 24.7, 12.9; IR (Neat Film, NaCl) 1763, 1518, 1456, 1262, 1242, 1208, 1139, 1116, 1026, 946, 766, 744 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{24}H_{26}NO_5$ $[M+H]^+$: 408.1805, found 408.1817.




**(*E*)-allyl (2-(4-chlorophenyl)-1-(1*H*-indol-1-yl)but-1-en-1-yl) carbonate (40h)**

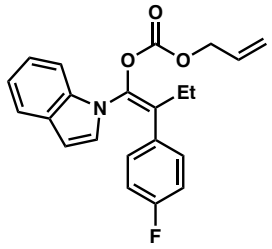
Purified by column chromatography (8% $Et_2O$ in hexanes) to provide the desired product as a light yellow oil (356.3 mg, 93% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.53–7.48 (m, 1H), 7.43 (dq, *J* = 0.9, 8.2 Hz, 1H), 7.19 (ddd, *J* = 1.2, 7.1, 8.2 Hz, 1H), 7.11 (ddd, *J* =

1.0, 7.1, 8.0 Hz, 1H), 7.09–7.03 (m, 2H), 6.92–6.82 (m, 3H), 6.37 (dd, *J* = 0.9, 3.4 Hz, 1H), 5.86 (ddt, *J* = 5.8, 10.5, 17.2 Hz, 1H), 5.36–5.23 (m, 2H), 4.59 (dt, *J* = 1.3, 5.8 Hz, 2H), 2.64 (q, *J* = 7.5 Hz, 2H), 1.06 (t, *J* = 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 152.6, 136.2, 135.4, 134.8, 133.4, 130.8, 129.2, 129.0, 128.9, 128.6, 128.5, 122.9, 121.0, 120.9, 119.8, 111.2, 104.4, 69.6, 24.9, 12.7; IR (Neat Film, NaCl) 1765, 1679, 1456, 1333, 1256, 1238, 1209, 1144, 1120, 1096, 945, 827, 743 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{22}H_{21}ClNO_3$ $[M+H]^+$: 382.1204, found 382.1201.



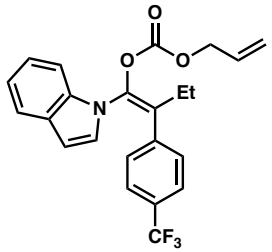

**(*E*)-allyl (2-(4-bromophenyl)-1-(1*H*-indol-1-yl)but-1-en-1-yl) carbonate (40i)**

Purified by column chromatography (5% $Et_2O$ in hexanes) to provide the desired product as an amorphous white solid (341.0 mg, 80% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.53–7.49 (m, 1H), 7.43 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.24–7.17 (m, 3H), 7.14–7.09 (m, 1H), 6.86 (d, *J* = 3.4 Hz, 1H), 6.86–6.78 (m, 2H), 6.37 (d, *J* = 3.1 Hz, 1H), 5.86 (ddt, *J* = 17.3, 10.4, 5.8 Hz, 1H), 5.36–5.23 (m, 2H), 4.59 (dt, *J* = 5.8, 1.4 Hz, 2H), 2.64 (q, *J* = 7.5 Hz, 2H), 1.06 (t, *J* = 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 152.6, 136.1, 135.3, 135.2, 131.5, 130.8, 129.3, 129.2, 128.8, 128.5, 122.8, 121.6, 121.0, 120.9, 119.7, 111.2, 104.4, 69.5, 24.8, 12.7; IR (Neat Film, NaCl) 3053, 3032, 2974, 2937, 2876, 2248, 1899, 1766, 1681, 1588, 1519, 1488, 1455, 1385, 1364, 1333, 1238, 1209, 1144, 1120, 945, 824, 766, 743 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{22}H_{21}BrNO_3$ $[M+H]^+$: 426.0699, found 426.0696.




**(*E*)-allyl (2-(4-fluorophenyl)-1-(1*H*-indol-1-yl)but-1-en-1-yl) carbonate (40j)**

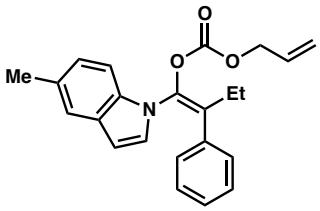
Purified by column chromatography (5% $Et_2O$ in hexanes) to provide the desired product as a colorless oil (312.6 mg, 86% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 37.4, 8.0 Hz, 2H), 7.15 (dt, *J* = 41.2, 7.4 Hz, 2H), 6.97–6.86 (m, 3H), 6.82–6.74 (m, 2H), 6.38 (d, *J* = 3.3 Hz, 1H), 5.88 (ddt, *J* = 16.7, 11.2, 5.8 Hz, 1H), 5.36–5.24 (m, 2H), 4.65–4.55 (m, 2H), 2.66 (q, *J* = 7.5 Hz, 2H), 1.08 (t, *J* = 7.5 Hz, 3H); $^{19}$F NMR (282 MHz, $CDCl_3$) δ –114.05 – –114.17 (m); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 162.0 (d, *J* = 247.1 Hz), 152.7, 136.2, 135.2, 132.1 (d, $J_{C–F}$ = 4.0 Hz), 130.8, 129.4, 129.3 (d, $J_{C–F}$ = 8.2 Hz), 128.8, 128.4, 122.7, 120.9, 120.8, 119.6, 115.3 (d, $J_{C–F}$ = 21.6 Hz), 111.2, 104.2, 69.5, 25.0, 12.6; IR (Neat Film, NaCl) 2974, 1766, 1681, 1604, 1510, 1456, 1333, 1238, 1208, 1144, 1119, 945, 835, 765, 743 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{22}H_{21}FNO_3$ $[M+H]^+$: 366.1500, found 366.1502.




**(*E*)-1-(1*H*-indol-1-yl)-2-(4-(trifluoromethyl)phenyl)but-1-en-1-yl allyl carbonate (40k)**

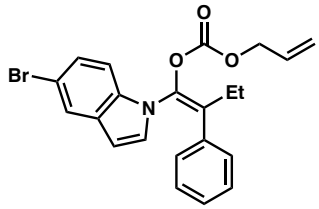
Purified by column chromatography (5% $Et_2O$ in hexanes) to provide the desired product as a white solid (375.1 mg, 90% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.54 (dt, *J* = 1.0,

7.8 Hz, 1H), 7.49 (dq, *J* = 1.0, 8.2 Hz, 1H), 7.41–7.34 (m, 2H), 7.28–7.21 (m, 1H), 7.19–7.08 (m, 3H), 6.87 (d, *J* = 3.3 Hz, 1H), 6.40 (dd, *J* = 0.9, 3.4 Hz, 1H), 5.89 (ddt, *J* = 5.9, 10.5, 17.2 Hz, 1H), 5.38–5.25 (m, 2H), 4.63 (dt, *J* = 1.4, 5.8 Hz, 2H), 2.72 (q, *J* = 7.5 Hz, 2H), 1.11 (t, *J* = 7.5 Hz, 3H); $^{19}$F NMR (282 MHz, $CDCl_3$) δ –62.73; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 152.6, 140.2, 136.2, 136.0, 130.8, 129.5 (q, *J* = 32.5 Hz), 129.0, 128.8, 128.5, 128.1, 125.4 (q, *J* = 272 Hz), 125.4–125.2 (m), 123.0, 121.1, 121.0, 119.8, 111.2, 104.6, 69.7, 24.9, 12.6; IR (Neat Film, NaCl) 1766, 1681, 1617, 1456, 1325, 1260, 1239, 1211, 1167, 1123, 1067, 946, 834, 744 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{23}H_{21}F_3NO_3$ $[M+H]^+$: 416.1468, found 416.1456.



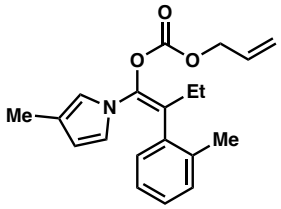

**(*E*)-allyl (1-(5-methyl-1*H*-indol-1-yl)-2-phenylbut-1-en-1-yl) carbonate (40l)**

Purified by column chromatography (hexanes → 5% $Et_2O$ in hexanes) to provide the desired product as a yellow oil (336.3 mg, 93% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.3 Hz, 1H), 7.30–7.28 (m, 1H), 7.12–7.08 (m, 3H), 7.02 (d, *J* = 8.3 Hz, 1H), 6.97 (dd, *J* = 6.4, 2.9 Hz, 2H), 6.83 (d, *J* = 3.3 Hz, 1H), 6.30–6.18 (m, 1H), 5.94–5.82 (m, 1H), 5.37–5.24 (m, 2H), 4.63–4.55 (m, 2H), 2.67 (q, *J* = 7.5 Hz, 2H), 2.42 (s, 3H), 1.09 (t, *J* = 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 152.7, 136.3, 135.3, 134.6, 130.9, 130.0, 129.8, 129.1, 128.7, 128.3, 127.7, 127.5, 124.2, 120.6 119.5, 111.0, 103.6, 69.4, 25.0, 21.5, 12.7; IR (Neat Film, NaCl) 3023, 2974, 2875, 1766, 1682, 1470, 1377, 1330, 1260, 1230, 1209, 1163, 1125, 1095, 1042, 967, 946, 843, 796, 763, 718, 699 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{23}H_{24}NO_3$ $[M+H]^+$: 362.1751, found 362.1751.




**(*E*)-allyl (1-(5-bromo-1*H*-indol-1-yl)-2-phenylbut-1-en-1-yl) carbonate (40m)**

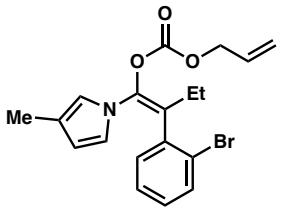
Purified by column chromatography (5% $Et_2O$ in hexanes) to provide the desired product as an amorphous white solid (352.3 mg, 83% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 1.9 Hz, 1H), 7.29 (d, *J* = 8.6 Hz, 1H), 7.24 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.12–7.08 (m, 3H), 6.94 (dd, *J* = 6.7, 3.0 Hz, 2H), 6.91 (d, *J* = 3.4 Hz, 1H), 6.29 (d, *J* = 3.3 Hz, 1H), 5.92–5.82 (m, 1H), 5.36–5.24 (m, 2H), 4.61 (dt, *J* = 5.8, 1.4 Hz, 2H), 2.66 (q, *J* = 7.5 Hz, 2H), 1.07 (t, *J* = 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 152.7, 136.0, 134.9, 134.5, 131.0, 130.8, 130.2, 130.1, 128.4, 127.8, 127.5, 125.5, 123.3, 119.8, 114.1, 112.8, 103.5, 69.6, 25.0, 12.6; IR (Neat Film, NaCl) 2973, 2934, 2873, 1764, 1679, 1452, 1375, 1236, 1208, 1128, 945, 758, 698 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{22}H_{21}BrNO_3$ $[M+H]^+$: 426.0699, found 426.0696.




**(*E*)-allyl (1-(3-methyl-1*H*-pyrrol-1-yl)-2-(*o*-tolyl)but-1-en-1-yl) carbonate (40n)**

Purified by column chromatography (2.5% $Et_2O$ in hexanes) to provide the desired product as a colorless oil (533.2 mg, 75% yield) Note: compound darkens in color overtime under argon at –20 °C; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.17–7.07 (m, 4H), 6.34 (dd, *J* = 2.9, 2.2 Hz, 1H), 6.29 (ddd, *J* = 2.2, 1.7, 1.0 Hz, 1H), 5.95 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.76 (ddd, *J* = 2.9, 1.7, 0.5 Hz, 1H), 5.44–5.28 (m, 2H), 4.70 (dq, *J* = 5.8,

1.4 Hz, 2H), 2.44 (dq, $J$ = 14.9, 7.3 Hz, 2H), 2.11 (d, $J$ = 0.5 Hz, 3H), 1.91 (d, $J$ = 1.0 Hz, 3H), 0.96 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 152.9, 136.5, 136.3, 136.3, 131.0, 130.2, 129.2, 127.5, 125.7, 122.8, 121.2, 119.6, 119.6, 118.2, 110.9, 69.5, 25.7, 19.4, 11.9, 11.8; IR (Neat Film, NaCl) 3061, 3019, 2972, 2936, 2874, 1769, 1688, 1487, 1456, 1350, 1258, 1234, 1185, 1139, 1118, 1070, 1047, 1022, 995, 958, 946, 915, 837, 761, 729, 694 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{20}H_{24}NO_3$ $[M+H]^+$: 326.1751, found 326.1733.

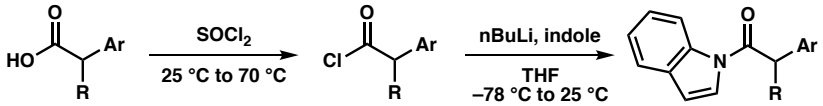



**(*E*)-allyl (2-(2-bromophenyl)-1-(3-methyl-1*H*-pyrrol-1-yl)but-1-en-1-yl) carbonate (40o)**

Purified by column chromatography (3% $Et_2O$ in hexanes) to provide the desired product as a colorless oil (410 mg, 70% yield) Note: compound darkens in color overtime under argon at –20 °C; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.53 (dd, $J$ = 8.0, 1.2 Hz, 1H), 7.18 (td, $J$ = 7.5, 1.3 Hz, 1H), 7.13–7.03 (m, 2H), 6.50 (dd, $J$ = 2.8, 2.2 Hz, 1H), 6.40 (m, 1H), 5.95 (ddt, $J$ = 17.2, 10.5, 5.8 Hz, 1H), 5.77 (dd, $J$ = 3.0, 1.7 Hz, 1H), 5.43–5.27 (m, 2H), 4.70 (dt, $J$ = 5.8, 1.3 Hz, 2H), 2.51 (ddq, $J$ = 36.7, 14.5, 7.3 Hz, 2H), 1.92 (d, $J$ = 1.0 Hz, 3H), 0.98 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 152.5, 137.7, 137.4, 132.9, 131.0, 130.9, 129.1, 127.3, 125.0, 123.7, 121.4, 119.8, 119.6, 118.6, 111.0, 69.6, 24.5, 11.9, 11.8; IR (Neat Film, NaCl) 2972, 2936, 1770, 1692, 1488, 1470, 1392, 1364, 1350, 1292, 1251, 1231, 1187, 1133, 1070, 1024, 959, 947, 758 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{21}BrNO_3$ $[M+H]^+$: 390.0699, found 390.0688.

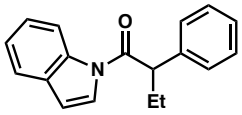
### 4.8.2.4 Preparation of *N*-Acyl Indoles

**General Procedure 1**




To an oven-dried vial containing α-aryl carboxylic acid (1.2 equiv) was added $SOCl_2$ neat (2.4 equiv) and the resulting mixture stirred at 25 °C for 20 min then 70 °C for 2 h (note: effluent gas flow is bubbled through a glass tube packed with powdered NaOH). The reaction was then concentrated in vacuo to afford the crude acid chloride, which was used in the next step without further purification.

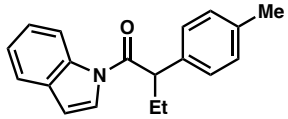
A flame-dried flask containing indole (1.0 equiv) in THF (500 mM) was cooled to 0 °C in an ice bath and n-BuLi (1.05 equiv) was added dropwise. The mixture was stirred at 0 °C for 15 min then cooled to –78 °C in a dry-ice acetone bath. The crude acid chloride dissolved in THF is then added quickly, and the resulting mixture allowed to slowly warm to room temperature. Then reaction was then quenched with water and extracted with $Et_2O$. The combined organic layers were dried over $Na_2SO_4$ and the desired *N*-acyl indole isolated by silica gel flash chromatography.




**1-(1*H*-indol-1-yl)-2-phenylbutan-1-one (46)**

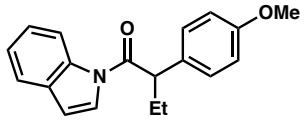
Prepared according to general procedure 1. Purified by column chromatography (3% $Et_2O$ in hexanes) to provide the desired product as a white solid (428.2 mg, 81% yield); $^1$H NMR (300 MHz, $CDCl_3$): δ 8.54 (d, $J$ = 8.3, 1H), 7.51–7.42 (m, 2H), 7.38–7.13 (m, 7H), 6.48 (d, $J$ = 3.8 Hz, 1H), 4.10 (t, $J$ = 7.2 Hz, 1H), 2.35–2.18 (m, 1H), 1.89 (dt, $J$ =

13.7, 7.2 Hz, 1H), 0.93 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 171.9, 139.1, 136.0, 130.3, 129.1, 127.7, 127.5, 125.2, 124.9, 123.8, 120.8, 117.0, 109.1, 53.7, 27.9, 12.3; IR (Neat Film, NaCl) 3063, 2967, 2943, 2874, 1704, 1602, 1584, 1539, 1472, 1451, 1384, 1355, 1328, 1304, 1222, 1208, 1181, 1154, 1082, 1017, 903, 880, 825, 807, 766, 749, 700 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{18}H_{18}NO$ $[M+H]^+$: 264.1383, found 264.1377.



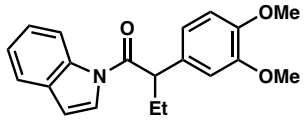

**1-(1*H*-indol-1-yl)-2-(*p*-tolyl)butan-1-one (47)**

Prepared according to general procedure 1. Purified by column chromatography (3% $Et_2O$ in hexanes) to provide the desired product as a yellow oil (901.0 mg, 76% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 8.57 (dd, $J$ = 8.4, 0.9 Hz, 1H), 7.53–7.46 (m, 2H), 7.35 (ddd, $J$ = 8.5, 7.3, 1.3 Hz, 1H), 7.27–7.22 (m, 3H), 7.16–7.09 (m, 2H), 6.52 (dd, $J$ = 3.8, 0.8 Hz, 1H), 4.11 (t, $J$ = 7.2 Hz, 1H), 2.36–2.21 (m, 4H), 1.91 (dp, $J$ = 13.7, 7.4 Hz, 1H), 0.97 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 172.0, 137.0, 136.1, 136.0, 130.3, 129.8, 127.5, 125.0, 124.9, 123.7, 120.7, 116.9, 108.9, 53.3, 27.8, 21.0, 12.2; IR (Neat Film, NaCl) 3051, 3024, 2966, 2931, 2874, 1704, 1584, 1539, 1514, 1472, 1451, 1384, 1355, 1325, 1304, 1223, 1208, 1187, 1155, 1084, 904, 808, 785, 767, 751, 715 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{20}NO$ $[M+H]^+$: 278.1539, found 278.1531.




**1-(1*H*-indol-1-yl)-2-(4-methoxyphenyl)butan-1-one (48)**

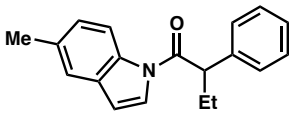
Prepared according to general procedure 1. Purified by column chromatography (3% $Et_2O$ in hexanes) to provide the desired product as a yellow oil containing minor impurities (1.2439 g, 85% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 8.56 (dq, *J* = 8.3, 0.9 Hz, 1H), 7.53–7.48 (m, 2H), 7.35 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.30–7.22 (m, 3H), 6.89–6.82 (m, 2H), 6.53 (dd, *J* = 3.8, 0.7 Hz, 1H), 4.10 (t, *J* = 7.3 Hz, 1H), 3.76 (s, 3H), 2.37–2.20 (m, 1H), 1.90 (m, 1H), 0.97 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 172.2, 158.9, 135.9, 131.1, 130.3, 128.7, 125.1, 124.9, 123.7, 120.7, 116.9, 114.4, 108.9, 55.1, 52.8, 27.8, 12.2; IR (Neat Film, NaCl) 2964, 2933, 1702, 1610, 1540, 1511, 1450, 1384, 1354, 1324, 1302, 1252, 1222, 1207, 1179, 1154, 1033, 904, 820, 788, 766, 752 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{20}NO_2$ $[M+H]^+$: 294.1489, found 294.1494.




**2-(3,4-dimethoxyphenyl)-1-(1*H*-indol-1-yl)butan-1-one (49)**

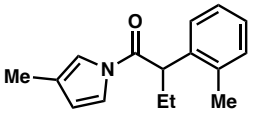
Prepared according to general procedure 1. Purified by column chromatography (20 → 30% $Et_2O$ in hexanes) to provide the desired product as a yellow oil (838.3 mg, 62% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 8.56 (dq, *J* = 8.3, 0.9 Hz, 1H), 7.54–7.49 (m, 2H), 7.35 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.29–7.22 (m, 1H), 6.92–6.85 (m, 2H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.54 (dd, *J* = 3.8, 0.8 Hz, 1H), 4.08 (t, *J* = 7.3 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 2.28 (dt, *J* = 13.7, 7.3 Hz, 1H), 1.92 (dt, *J* = 13.8, 7.3 Hz, 1H), 0.97 (t, *J* = 7.3 Hz,

3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 172.1, 149.5, 148.4, 136.0, 131.6, 130.3, 125.2, 124.9, 123.8, 120.8, 120.2, 116.9, 111.5, 110.3, 109.1, 56.0, 55.9, 53.4, 27.9, 12.3; IR (Neat Film, NaCl) 2964, 2934, 1699, 1591, 1516, 1451, 1355, 1326, 1302, 1262, 1242, 1206, 1152, 1027, 790, 766, 752 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{20}H_{22}NO_3$ $[M+H]^+$: 324.1594, found 324.1588.




**1-(5-methyl-1*H*-indol-1-yl)-2-phenylbutan-1-one (50)**

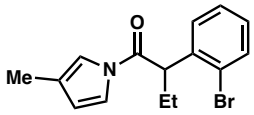
Prepared according to general procedure 1. Purified by column chromatography (5% $Et_2O$ in hexanes) to provide the desired product as a cream-colored solid (567.3 mg, 82% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 8.43 (d, *J* = 8.4 Hz, 1H), 7.45 (d, *J* = 3.7 Hz, 1H), 7.38–7.27 (m, 5H), 7.28–7.20 (m, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 6.45 (d, *J* = 3.7 Hz, 1H), 4.14 (t, *J* = 7.2 Hz, 1H), 2.43 (s, 3H), 2.31 (dtd, *J* = 14.7, 7.3, 1.0 Hz, 1H), 1.99–1.89 (m, 1H), 0.99 (td, *J* = 7.4, 0.9 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 171.7, 139.3, 134.2, 133.4, 130.6, 129.2, 127.8, 127.5, 126.5, 124.9, 120.7, 116.6, 109.0, 53.7, 27.9, 21.5, 12.4; IR (Neat Film, NaCl) 3027, 2967, 2931, 2874, 1703, 1582, 1541, 1468, 1382, 1328, 1304, 1208, 1182, 1089, 903, 833, 823, 811, 740, 700 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{20}NO$ $[M+H]^+$: 278.1539, found 278.1534.




**1-(3-methyl-1*H*-pyrrol-1-yl)-2-(*o*-tolyl)butan-1-one (51)**

Prepared according to general procedure 1. Purified by column chromatography (5% $Et_2O$ in hexanes) to provide the desired product as a light yellow oil (539.3 mg, 54%

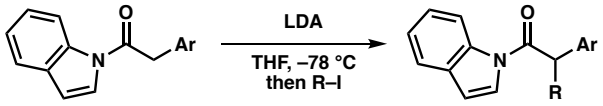
yield) Note: compound darkens in color overtime under argon at –20 °C; $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.27–6.92 (m, 6H), 6.03 (dd, *J* = 3.3, 1.6 Hz, 1H), 4.24 (dd, *J* = 8.5, 5.7 Hz, 1H), 2.47 (s, 3H), 2.20 (ddq, *J* = 14.5, 8.5, 7.3 Hz, 1H), 2.00 (d, *J* = 1.2 Hz, 3H), 1.84–1.64 (m, 1H), 0.98 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.9, 137.9, 134.6, 131.0, 127.3, 127.0, 126.8, 123.8, 119.3, 116.5, 115.4, 48.5, 27.4, 19.8, 12.7, 12.1; IR (Neat Film, NaCl) 3021, 2964, 2928, 2874, 1708, 1488, 1459, 1396, 1355, 1327, 1306, 1192, 1171, 1082, 1066, 952, 905, 834, 820, 780, 756, 730 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{16}H_{20}NO$ $[M+H]^+$: 242.1539, found 242.1532.



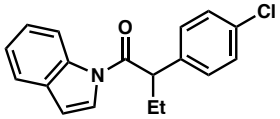

**2-(2-bromophenyl)-1-(3-methyl-1*H*-pyrrol-1-yl)butan-1-one (52)**

Prepared according to general procedure 1. Purified by column chromatography (3% $Et_2O$ in hexanes) to provide the desired product as a yellow oil (1.56 g, 72% yield) Note: compound darkens in color overtime under argon at –20 °C; $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.36 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.28–7.22 (m, 2H), 7.11 (ddd, *J* = 8.0, 7.3, 1.7 Hz, 2H), 6.07 (dd, *J* = 3.3, 1.6 Hz, 1H), 4.62 (dd, *J* = 8.2, 6.1 Hz, 1H), 2.16 (ddq, *J* = 13.7, 8.2, 7.3 Hz, 1H), 2.03 (d, *J* = 1.2 Hz, 3H), 1.83 (dqd, *J* = 13.6, 7.4, 6.2 Hz, 1H), 1.00 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.2, 138.7, 133.2, 129.0, 128.4, 128.4, 124.1, 124.1, 119.5, 116.6, 115.7, 50.7, 27.6, 12.3, 12.1; IR (Neat Film, NaCl) 2967, 2930, 2875, 1709, 1489, 1471, 1440, 1398, 1356, 1328, 1306, 1200, 1180, 1067, 1020, 908, 830, 810, 749 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{15}H_{17}BrNO$ $[M+H]^+$: 306.0488, found 306.0477.

**General Procedure 2**



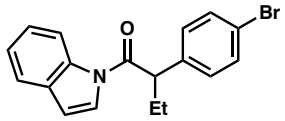

A flame-dried round bottom flask was charged with *i*-$Pr_2NH$ (367 μL, 2.60 mmol, 1.3 equiv) and THF (18.0 mL). The solution was then cooled in a 0 ºC ice bath for 10 min and a 2.40 M solution of *n*-BuLi (996 μL, 2.40 mmol, 1.2 equiv) was added dropwise. After stirring for 15 min, the solution was cooled in a –78 ºC acetone/dry ice bath for 15 min, after which time a solution of acyl indole (498.6 mg, 2.00 mmol, 1.0 equiv) in THF (4.0 mL) was added dropwise over 5 min. After stirring at –78 ºC for 1 h, neat ethyl iodide (193 μL, 2.40 mmol, 1.2 equiv) was then added dropwise. The reaction mixture was allowed to slowly warm to 20 ºC, and then heated to 65 ºC and stirred for 16 h, after which time the reaction was quenched with the slow addition of 10 mL $H_2O$. The mixture was then transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted 3 x 10 mL $Et_2O$ and the combined organics were dried over $Na_2SO_4$, filtered, and concentrated. The desired *N*-acyl indole was isolated by silica gel flash chromatography.




**2-(4-chlorophenyl)-1-(1*H*-indol-1-yl)butan-1-one (53)**

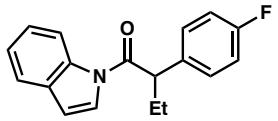
Prepared according to General Procedure 2 with (539.5 mg, 2.00 mmol, 1.0 equiv) of acyl indole. Purified by column chromatography (5% $Et_2O$ in hexanes) to provide the desired product as a light yellow oil (373.8 mg, 63% yield); $^1H$ NMR (500 MHz, $CDCl_3$) δ 8.54 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.52 (dt, *J* = 7.7, 1.1 Hz, 1H), 7.44 (d, *J* = 3.8 Hz, 1H),

7.36 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.30 (s, 4H), 7.28–7.24 (m, 1H), 6.56 (dd, *J* = 3.9, 0.8 Hz, 1H), 4.13 (t, *J* = 7.3 Hz, 1H), 2.29 (dt, *J* = 13.8, 7.3 Hz, 1H), 2.03–1.76 (m, 1H), 0.97 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 171.5, 137.6, 136.0, 133.5, 130.4, 129.4, 129.2, 125.4, 124.6, 124.0, 120.9, 117.0, 109.5, 53.1, 27.9, 12.3; IR (Neat Film, NaCl) 2967, 2361, 1700, 1540, 1491, 1451, 1384, 1354, 1328, 1302, 1221, 1207, 1094, 1015, 904, 814, 794, 752 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{18}H_{17}ClNO$ $[M+H]^+$: 298.0993, found 298.0984.



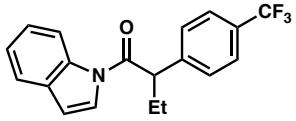

**2-(4-bromophenyl)-1-(1*H*-indol-1-yl)butan-1-one (54)**

Prepared according to General Procedure 2 with (628.4 mg, 2.00 mmol, 1.0 equiv) of acyl indole. Purified by column chromatography (5% $Et_2O$ in hexanes) to provide the desired product as a white solid (451.0 mg, 66% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 8.54 (d, *J* = 8.3 Hz, 1H), 7.52 (d, *J* = 7.7 Hz, 1H), 7.48–7.41 (m, 3H), 7.38–7.32 (m, 1H), 7.30–7.20 (m, 3H), 6.56 (d, *J* = 3.8 Hz, 1H), 4.12 (t, *J* = 7.2 Hz, 1H), 2.29 (dp, *J* = 14.6, 7.3 Hz, 1H), 1.92 (dp, *J* = 14.6, 7.3 Hz, 1H), 0.98 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 171.5, 138.1, 136.0, 132.3, 130.4, 129.6, 125.4, 124.6, 124.0, 121.6, 120.9, 117.0, 109.5, 53.2, 27.9, 12.3; IR (Neat Film, NaCl) 3052, 2967, 2931, 2874, 1703, 1486, 1451, 1383, 1354, 1327, 1301, 1207, 1154, 1074, 1011, 904, 880, 812, 792, 755, 751, 713 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{18}H_{17}BrNO$ $[M+H]^+$: 342.0488, found 342.0497.




**2-(4-fluorophenyl)-1-(1*H*-indol-1-yl)butan-1-one (55)**

Prepared according to General Procedure 2 with (506.6 mg, 2.00 mmol, 1.0 equiv) of acyl indole. Purified by column chromatography (5% $Et_2O$ in hexanes) to provide the desired product as a white solid (360.4 mg, 64% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 8.55 (d, *J* = 8.3 Hz, 1H), 7.52 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.46 (d, *J* = 3.8 Hz, 1H), 7.39–7.29 (m, 3H), 7.30–7.22 (m, 1H), 7.07–6.97 (m, 2H), 6.56 (dd, *J* = 3.8, 0.6 Hz, 1H), 4.15 (t, *J* = 7.3 Hz, 1H), 2.30 (dt, *J* = 13.8, 7.3 Hz, 1H), 1.92 (dq, *J* = 14.1, 7.3 Hz, 1H), 0.98 (t, *J* = 7.3 Hz, 3H); $^{19}$F NMR (282 MHz, $CDCl_3$) δ –114.9 (tt, *J* = 8.5, 5.2 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 171.8, 162.1 (d, $J_{C–F}$ = 246.2 Hz), 136.0, 134.8 (d, $J_{C–F}$ = 3.3 Hz), 130.3, 129.4 (d, $J_{C–F}$ = 8.0 Hz), 125.3, 124.7, 123.9, 120.9, 117.0, 116.0 (d, $J_{C–F}$ = 21.5 Hz), 109.3, 52.8, 27.9, 12.2; IR (Neat Film, NaCl) 3074, 2967, 2934, 2873, 1702, 1603, 1508, 1450, 1384, 1354, 1327, 1301, 1222, 1207, 1158, 818, 792, 752, 714 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{18}H_{17}FNO$ $[M+H]^+$: 282.1289, found 282.1286.

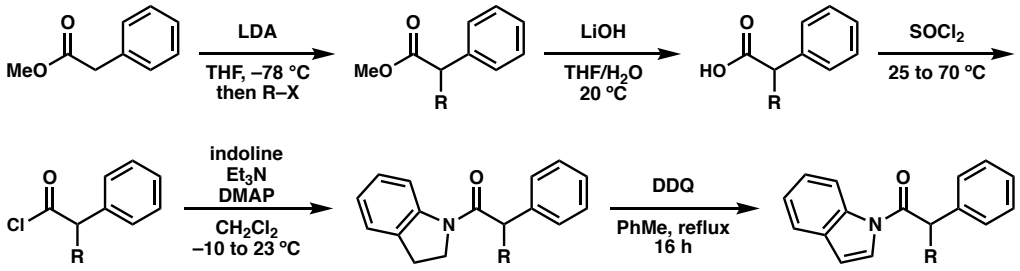



**1-(1*H*-indol-1-yl)-2-(4-(trifluoromethyl)phenyl)butan-1-one (56)**

Prepared according to General Procedure 2. Purified by column chromatography (6% $Et_2O$ in hexanes) to provide the desired product as a white solid (190.8 mg, 58% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 8.55 (dd, *J* = 8.3, 0.9 Hz, 1H), 7.62–7.58 (m, 2H), 7.55–7.48 (m, 3H), 7.44 (d, *J* = 3.9 Hz, 1H), 7.37 (ddd, *J* = 8.5, 7.2, 1.3 Hz, 1H), 7.30–7.25 (m, 1H), 6.57 (dd, *J* = 3.8, 0.7 Hz, 1H), 4.23 (t, *J* = 7.3 Hz, 1H), 2.41–2.26 (m, 1H), 1.95 (dt,

$J$ = 13.8, 7.3 Hz, 1H), 0.99 (t, $J$ = 7.4 Hz, 3H); $^{19}$F NMR (282 MHz, $CDCl_3$) δ –62.6; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 171.2, 143.0 (d, $J$ = 1.5 Hz), 136.0, 130.4, 129.9 (q, $J$ = 32.6 Hz), 128.3, 126.1 (q, $J$ = 3.8 Hz), 125.5, 125.4 (q, $J$ = 272.4 Hz), 124.5, 124.1, 121.0, 117.0, 109.7, 53.5, 28.0, 12.3; IR (Neat Film, NaCl) 1702, 1451, 1384, 1354, 1324, 1304, 1208, 1166, 1123, 1068, 1068, 1018, 831, 800, 766, 752 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{17}F_3NO$ $[M+H]^+$: 332.1257, found 332.1248.

**General Procedure 3**




A flame-dried round bottom flask was charged with *i*-$Pr_2NH$ (1.82 mL, 13.0 mmol, 1.3 equiv) and THF (15 mL). The solution was then cooled in a 0 ºC ice bath for 10 min and a 2.40 M solution of *n*-BuLi (5.0 mL, 12.0 mmol, 1.2 equiv) was added dropwise. After stirring for 15 min, the solution was cooled in a –78 ºC acetone/dry ice bath for 15 min, after which time a solution of methyl phenyl acetate (1.41 mL, 10.0 mmol, 1.0 equiv) in THF (29 mL) was added dropwise over 10 min. After stirring at –78 ºC for 1 h, the appropriate electrophile (1.5 equiv) was then added neat dropwise. The reaction mixture was allowed to slowly warm to 20 ºC and stirred for 16 h after which time the reaction was quenched with the slow addition of 30 mL of sat. aq. $NH_4Cl$. The mixture was then transferred to a separatory funnel and the layers were separated. The

aqueous layer was extracted 3 x 20 mL EtOAc and the combined organics were dried over $Na_2SO_4$, filtered, and concentrated.

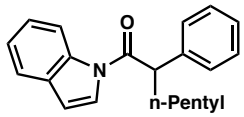
The crude material was then transferred to a round bottom flask and dissolved in THF (28 mL) and $H_2O$ (20 mL). To the solution was then added LiOH (479.0 mg, 20.0 mmol, 2.0 equiv) and the resulting reaction mixture was stirred at 20 ºC for 16 h. The mixture was then transferred to a separatory funnel and washed with 2 x 5 mL $Et_2O$. The aqueous layer was then slowly acidified to pH 1 with 2.0 N HCl and extracted 2 x 10 mL $Et_2O$. The combined organics were dried over $Na_2SO_4$, filtered, and concentrated. The crude acid was used in the next step without further purification.

To an oven-dried flask containing α-aryl carboxylic acid (5.0 mmol, 1.0 equiv) was added $SOCl_2$ neat (620 μL, 1.7 equiv) and the resulting mixture stirred at 25 °C for 20 min then 70 °C for 2 h (note: effluent gas flow is bubbled through a glass tube packed with powdered NaOH). The reaction was then concentrated in vacuo to afford the crude acid chloride, which was used in the next step without further purification.

A separate flame-dried flask containing freshly distilled indoline (4.20 mmol, 1.0 equiv), $Et_3N$ (1.17 mL, 8.40 mmol, 2.0 equiv), and DMAP (25.7 mg, 0.21 mmol, 0.05 equiv) in $CH_2Cl_2$ (42 mL) was cooled to –10 °C in an acetone/ice bath and the crude acid chloride (5.0 mmol, 1.2 equiv) dissolved in $CH_2Cl_2$ (21 mL) was added dropwise via cannula transfer. The mixture was stirred at –10 °C for 15 min then warmed to 23 ºC and stirred for 18 h. The reaction mixture was quenched with saturated $NaHCO_3$ (20 mL) and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted twice with $CH_2Cl_2$ (20 mL). The combined organics were washed with brine

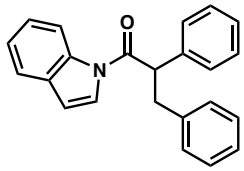
(10 mL), dried over $Na_2SO_4$, filtered, and concentrated to afford the crude amide which was used in the next step without further purification.

The crude amide prepared above was transferred to a round bottom flask affixed with a reflux condenser. Dry toluene (42 mL) and DDQ (2,3-Dichloro-5,6-dicyano-1,4-benzoquinone) (1.14 g, 5.0 mmol, 1.2 equiv) were then added and the resulting dark red reaction solution was heated to reflux for 16 h. The crude reaction mixture was then filtered through a pad of celite with toluene, concentrated, and purified via flash column chromatography to afford the desired acyl indole.



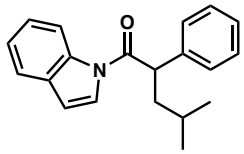

**1-(1*H*-indol-1-yl)-2-phenylheptan-1-one (57)**

Prepared according to General Procedure 3 with *n*-pentyl iodide (1.96 mL, 15.0 mmol, 1.5 equiv). Purified by column chromatography (5% $Et_2O$ in hexanes) to provide the desired product as a colorless oil (319.5 mg, 25% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 8.58 (dq, *J* = 8.4, 0.9 Hz, 1H), 7.54–7.48 (m, 2H), 7.39–7.30 (m, 5H), 7.30–7.21 (m, 2H), 6.54 (dd, *J* = 3.8, 0.8 Hz, 1H), 4.25 (t, *J* = 7.2 Hz, 1H), 2.34–2.25 (m, 1H), 1.90 (tdd, *J* = 12.9, 8.5, 5.7 Hz, 1H), 1.46–1.25 (m, 6H), 0.91–0.84 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 172.0, 139.4, 136.0, 130.3, 129.2, 127.7, 127.5, 125.2, 124.8, 123.8, 120.7, 117.0, 109.1, 52.1, 34.7, 31.8, 27.4, 22.6, 14.1; IR (Neat Film, NaCl) 3063, 3029, 2954, 2928, 2858, 1704, 1602, 1584, 1539, 1451, 1384, 1353, 1311, 1207, 1154, 1102, 941, 919, 880, 766, 749, 700 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{21}H_{24}NO$ $[M+H]^+$: 306.1846, found 306.1846.



**1-(1*H*-indol-1-yl)-2,3-diphenylpropan-1-one (58)**

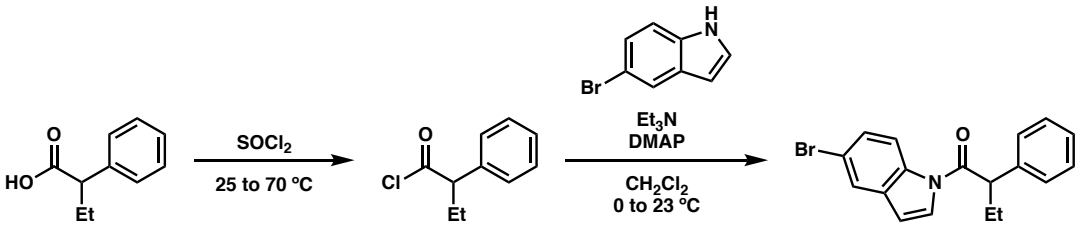
Prepared according to General Procedure 3 with BnBr (1.78 mL, 15.0 mmol, 1.5 equiv). Purified by column chromatography (5% $Et_2O$ in hexanes) to provide the desired product as a white solid (830.7 mg, 61% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 8.56 (dd, *J* = 8.3, 0.9 Hz, 1H), 7.48 (dt, *J* = 7.5, 0.9 Hz, 1H), 7.39 (d, *J* = 3.8 Hz, 1H), 7.34 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.32 – 7.27 (m, 4H), 7.26 – 7.10 (m, 7H), 6.48 (dd, *J* = 3.9, 0.7 Hz, 1H), 4.51 (t, *J* = 7.2 Hz, 1H), 3.67 (dd, *J* = 13.7, 7.6 Hz, 1H), 3.14 (dd, *J* = 13.8, 6.9 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 171.2, 139.1, 138.7, 136.0, 130.3, 129.3, 129.2, 128.5, 127.8, 127.7, 126.6, 125.3, 124.8, 123.9, 120.8, 117.0, 109.3, 54.4, 40.8; IR (Neat Film, NaCl) 3155, 3062, 3029, 2927, 1950, 1805, 1698, 1601, 1585, 1539, 1495, 1472, 1453, 1385, 1354, 1319, 1300, 1221, 1207, 1108, 1074, 911, 898, 766, 749, 699 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{23}H_{20}NO$ $[M+H]^+$: 326.1539, found 326.1536.



**1-(1*H*-indol-1-yl)-4-methyl-2-phenylpentan-1-one (59)**

Prepared according to General Procedure 3 with *i*-butyl iodide (1.73 mL, 15.0 mmol, 1.5 equiv). Purified by column chromatography (5% $Et_2O$ in hexanes) to provide the desired product as a white solid (1.2177 g, 99% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, *J* = 8.3 Hz, 1H), 7.54 (d, *J* = 3.8 Hz, 1H), 7.52–7.50 (m, 1H), 7.39–7.29 (m, 5H), 7.27–7.22 (m, 2H), 6.55 (dd, *J* = 3.8, 0.7 Hz, 1H), 4.37 (t, *J* = 7.3 Hz, 1H), 2.22 (dt, *J* = 13.6 Hz, 7.4

Hz, 1H), 1.79 (dt, *J* = 13.7, 6.9 Hz, 1H), 1.61 (dp, *J* = 13.5, 6.8 Hz, 1H), 0.97 (dd, *J* = 27.5, 6.6 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 172.0, 139.5, 136.1, 130.4, 129.3, 127.8, 127.5, 125.3, 124.8, 123.9, 120.9, 117.1, 109.3, 49.8, 43.8, 25.9, 22.9, 22.7; IR (Neat Film, NaCl) 3386, 3154, 3063, 3029, 2956, 2868, 1703, 1602, 1585 1538, 1493, 1471, 1451, 1385, 1344, 1332, 1308, 1295, 1222, 1207, 1103, 1084, 1018, 943, 886, 766, 748, 670 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{20}H_{22}NO$ $[M+H]^+$: 292.1696, found 292.1696.



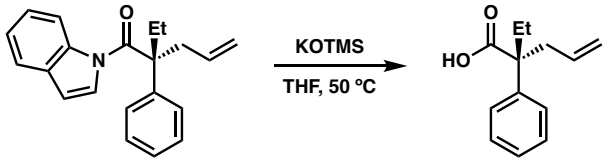

**1-(5-bromo-1*H*-indol-1-yl)-2-phenylbutan-1-one (60)**

To a flame-dried conical flask containing α-aryl carboxylic acid (1 equiv) was added $SOCl_2$ neat (2 equiv) and the resulting mixture stirred at 25 °C for 20 min and then 70 °C for 2 h (note: effluent gas flow is bubbled through a glass tube packed with powdered NaOH). The reaction was then concentrated in vacuo to afford the crude acid chloride, which was used in the next step without further purification.

To a flame-dried 25 mL round bottom flask was added 5-bromoindole (588.1 mg, 3.00 mmol, 1.0 equiv), DMAP (36.7 mg, 0.30 mmol, 0.10 equiv), $CH_2Cl_2$ (5.0 mL), and $Et_3N$ (627 μL, 4.50 mmol, 1.5 equiv). The resulting clear, colorless solution was then cooled in a 0 ºC ice bath for 10 min before a solution of the above crude acid chloride in $CH_2Cl_2$ (3.0 mL) was added dropwise via cannula. The resulting bright yellow solution was stirred at 23 ºC for 18 h then concentrated under reduced pressure. The crude yellow oil was then dissolved in $Et_2O$ (10 mL), transferred to a separatory funnel, and washed with

$H_2O$ (20 mL). The aqueous layer was then extracted with $Et_2O$ (3 x 10 mL). The combined organics were then washed with brine (10 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure to afford an orange oil which was purified by column chromatography (3% $Et_2O$ in hexanes) to provide the desired product as an off white solid with minor impurities (654.3 mg, 64% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 8.8 Hz, 1H), 7.63 (d, *J* = 1.9 Hz, 1H), 7.49 (d, *J* = 3.8 Hz, 1H), 7.44 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.38–7.30 (m, 4H), 7.30–7.22 (m, 1H), 6.46 (d, *J* = 3.8 Hz, 1H), 4.12 (t, *J* = 7.2 Hz, 1H), 2.30 (dt, *J* = 14.1, 7.3 Hz, 1H), 1.95 (dt, *J* = 14.1, 7.01 Hz, 1H), 0.98 (t, *J* = 7.3, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 171.8, 138.8, 134.6, 132.0, 129.2, 127.9, 127.7, 127.6, 125.9, 123.4, 118.3, 117.0, 108.2, 53.7, 27.8, 12.3; IR (Neat Film, NaCl) 3063, 3028, 2967, 2932, 2874, 1704, 1575, 1534, 1444, 1377, 1325, 1304, 1217, 1199, 1181, 1088, 896, 826, 810, 699 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{18}H_{17}BrNO$ $[M+H]^+$: 342.0488, found 342.0478.

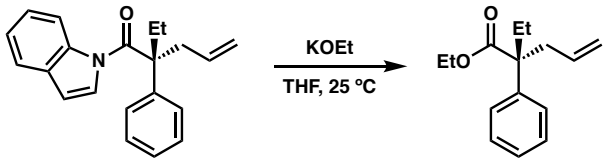
### 4.8.2.5 Derivatization of Alkylation Products




**(*R*)-2-ethyl-2-phenylpent-4-enoic acid (42)**

To a flame-dried round bottom flask containing a stirred suspension of KOTMS (162 mg, 1.26 mmol) in THF (1.5 mL) was added a solution of acyl indole ***40a*** (38.2 mg, 0.126 mmol) in THF (1.5 mL). The resulting mixture was placed in a 60 °C oil bath and stirred for 16 h. The crude reaction was diluted with $Et_2O$ and 5 M NaOH, and the layers separated. The aqueous layer was washed with $Et_2O$ and acidified with 4 M HCl to pH 1. The aqueous layer was extracted with $Et_2O$ three times and the combined organic layers

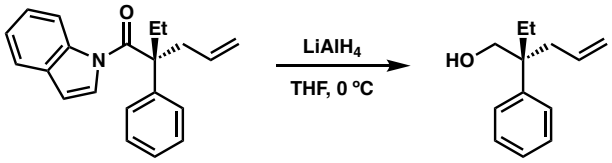
washed with water, dried over $MgSO_4$, and concentrated to a light yellow solid (25.6 mg, 99% yield), $[\alpha]_D^{25}$ –30.9 (*c* 1.0, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.45–7.17 (m, 5H), 5.54 (dddd, *J* = 17.0, 10.1, 7.6, 6.8 Hz, 1H), 5.16–4.96 (m, 2H), 2.81 (qdt, *J* = 14.1, 6.8, 1.2 Hz, 2H), 2.22–1.90 (m, 2H), 0.81 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 181.9, 141.5, 133.5, 128.5, 127.1, 126.8, 118.5, 54.0, 38.4, 26.9, 8.5; IR (Neat Film, NaCl) 3064, 2975, 1699, 1498, 1447, 1401, 1252, 918, 698 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{13}H_{17}O_2$ $[M+H]^+$: 205.1223, found 205.1213.




**ethyl (*R*)-2-ethyl-2-phenylpent-4-enoate (43)**

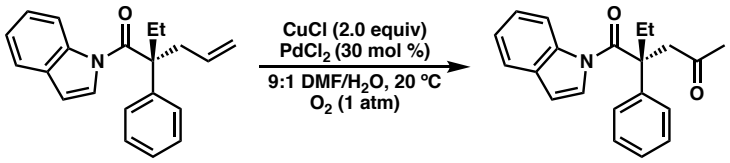
To a flame-dried round bottom flask containing a stirred solution of KOEt (32.2 mg, 0.383 mmol) in THF (1.5 mL) was added a solution of acyl indole ***40a*** (38.7 mg, 0.128 mmol) and the resulting mixture stirred at 25 °C for 15 h. The crude reaction was diluted with $Et_2O$ and quenched with saturated $NH_4Cl$, and the layers separated. The aqueous layer was extracted with $Et_2O$ and the combined organic fractions dried over $Na_2SO_4$ and concentrated. The crude product was purified by silica gel flash chromatography (5% $Et_2O$ in hexanes) to provide the desired product as a colorless oil (22.3 mg, 75% yield), $[\alpha]_D^{25}$ –4.7 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.33–7.07 (m, 5H), 5.46 (dddd, *J* = 16.9, 10.1, 7.8, 6.7 Hz, 1H), 5.07–4.87 (m, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 2.87–2.58 (m, 2H), 2.13–1.87 (m, 2H), 1.12 (t, *J* = 7.1 Hz, 3H), 0.71 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 175.6, 142.4, 133.8, 128.3, 126.7, 126.6, 118.2, 60.8, 54.1, 38.7,

27.1, 14.2, 8.5; IR (Neat Film, NaCl) 2976, 2360, 1728, 1220, 1135, 1030, 916, 700 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{15}H_{21}O_2$ $[M+H]^+$: 233.1536, found 233.1531.




**(*R*)-2-ethyl-2-phenylpent-4-en-1-ol (44)**

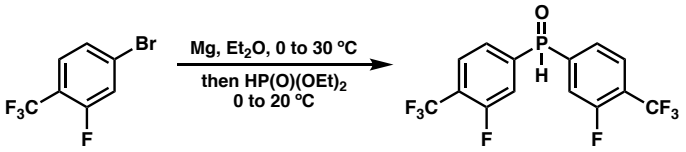
To a flame-dried round bottom flask was added acyl indole ***40a*** (32.6 mg, 0.107 mmol, 1.0 equiv) and THF (2.1 mL). The resulting solution was cooled to 0 ºC for 5 min and then a 1.0 M solution of $LiAlH_4$ (320 mL, 0.320 mmol, 3.0 equiv) was added dropwise. The resulting solution was stirred at 0 ºC for 5 min, then diluted with $Et_2O$ (2.1 mL) and quenched with the addition of $H_2O$ (12 μL) followed by 15% w/v $NaOH/H_2O$ (12 μL), and an additional portion of $H_2O$ (36 μL). The resulting gray suspension was warmed to 20 ºC and stirred vigorously for 15 min. $MgSO_4$ (50 mg) was added and the resulting suspension was stirred for 15 min and filtered through a plug of celite with $Et_2O$. The crude product was purified by silica gel flash chromatography (10% $Et_2O$ in hexanes) to provide the desired product as a colorless oil (17.2 mg, 84% yield); $[\alpha]_D^{25}$ +12.9 (*c* 0.65, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.38–7.31 (m, 4H), 7.23 (td, *J* = 6.4, 2.3 Hz, 1H), 5.70 (ddt, *J* = 17.3, 10.1, 7.3 Hz, 1H), 5.18–5.01 (m, 2H), 3.82–3.70 (m, 2H), 2.55 (ddd, *J* = 61.6, 13.9, 7.2 Hz, 2H), 1.73 (q, *J* = 7.4 Hz, 2H), 1.34 (s, 1H), 0.74 (t, *J* = 7.4 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 143.9, 134.9, 128.6, 127.0, 126.3, 117.8, 67.9, 46.3, 38.6, 27.5, 8.0; IR (Neat Film, NaCl) 3399 (br), 3060, 3024, 3004, 2966, 2934, 2880, 2361, 1638, 1497, 1459, 1456, 1379, 1045, 1001, 914, 760, 699 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{13}H_{22}NO$ $[M+NH_4]^+$: 208.1696, found 208.1692.




**(*R*)-2-ethyl-1-(1*H*-indol-1-yl)-2-phenylpentane-1,4-dione (45)**

To a round bottom flask containing acyl indole ***40a*** (33.1 mg, 0.109 mmol, 1.0 equiv) dissolved in 2.5 mL of 9:1 DMF/$H_2O$ was added $PdCl_2$ (5.8 mg, 0.033 mmol, 0.30 equiv) and CuCl (21.6 mg, 0.218 mmol, 2.0 equiv). The flask was then quickly evacuated and backfilled three times with a balloon of $O_2$, and then stirred at 20 ºC under a balloon of $O_2$ for 48 h. The crude reaction was then diluted with EtOAc (2 mL) followed by brine (2 mL). The layers were separated and the aqueous layer was extracted with EtOAc (5 mL) twice. The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated. The crude product was purified by silica gel flash chromatography (10% $Et_2O$ in hexanes) to afford the desired product as a white foam in a 5:1 ketone/aldehyde ratio (33.2 mg, 0.104 mmol, 95% yield); $[\alpha]_D^{25}$ –194.5 (*c* 0.58, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 7.7 Hz, 1H), 7.31–7.23 (m , 5H), 7.23–7.12 (m, 2H), 6.70 (d, *J* = 3.9 Hz, 1H), 6.18 (d, *J* = 3.8 Hz, 1H), 3.26 (d, *J* = 15.4 Hz, 1H), 3.14 (d, *J* = 15.5 Hz, 1H), 2.64 (dq, *J* = 14.9, 7.5 Hz, 1H), 2.32–2.15 (m, 1H), 1.68 (s, 3H), 0.78 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 207.1, 173.5, 142.1, 136.5, 129.3, 127.7, 126.5, 125.7, 125.2, 123.8, 120.5, 117.1, 108.4, 108.4, 55.8, 48.5, 32.1, 27.5, 8.9; IR (Neat Film, NaCl) 3163, 3056, 3056, 2972, 1721, 1697, 1537, 1450, 1308, 1206, 1076, 882, 768, 752, 702 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{21}H_{22}NO_2$ $[M+H]^+$: 320.1645, found 320.1630.

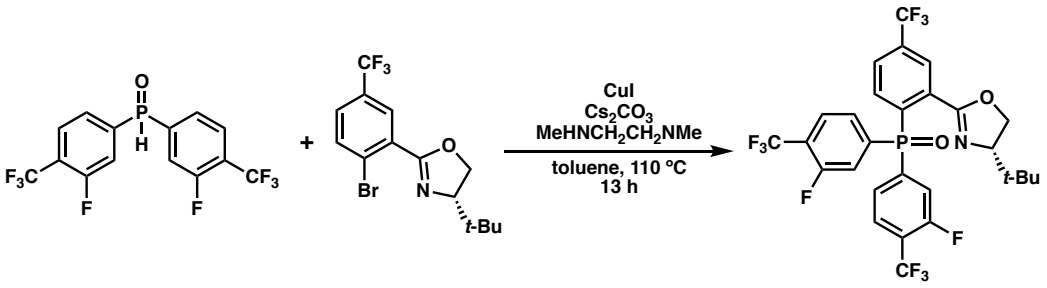
### 4.8.2.6 Synthesis of New Ligand




**Bis(3-fluoro-4-(trifluoromethyl)phenyl)phosphine oxide (61)**

According to the procedure of Stoltz[2]; A flame-dried 50 mL round bottomed flask was charged with magnesium turnings (804.7 mg, 33.1 mmol, 3.1 equiv) and $Et_2O$ (17.8 mL). The mixture was cooled to 0 ºC and 4-bromo-2-fluoro-1-(trifluoromethyl)benzene (4.52 mL, 32.0 mmol, 3.0 equiv) was added dropwise over 15 min during which the reaction mixture turned from colorless to brown to black. A reflux condenser was then attached to the flask, and the mixture was warmed to 30 ºC in a water bath and stirred for 1 h. The resulting black solution was then canula transferred to a second 50 mL flame-dried round bottom flask to remove residual magnesium turnings. The resulting solution was then cooled to 0 ºC and neat diethyl phosphite (1.38 mL, 10.7 mmol, 1.0 equiv) was added dropwise over 10 min. The black reaction mixture was then allowed to warm to 20 ºC over 1 h and stirred for 24 h. The reaction mixture was then cooled to 0 ºC and 2.0 N HCl (20 mL) was added dropwise with vigorous stirring, leading to the precipitation of a brown solid. The mixture was then allowed to warm to 20 ºC and extracted with EtOAc (3 x 10 mL). The combined organic layers were then washed with brine (10 mL), dried over $Na_2SO_4$, filtered, and concentrated to an orange oil. Purification by silica gel chromatography (30% EtOAc in hexanes → 60% EtOAc in hexanes) provided the desired product as a yellow solid (2.6803 g, 7.72 mmol, 72% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 7.80 (td, $J$ = 7.2, 3.2 Hz, 2H), 7.59 (ddd, $J$ = 19.8, 13.7, 8.6 Hz, 4H); $^{19}$F NMR (282 MHz, $CDCl_3$) δ –62.02 (d, $J$ = 12.7 Hz), –110.40 – –110.63 (m); $^{31}$P

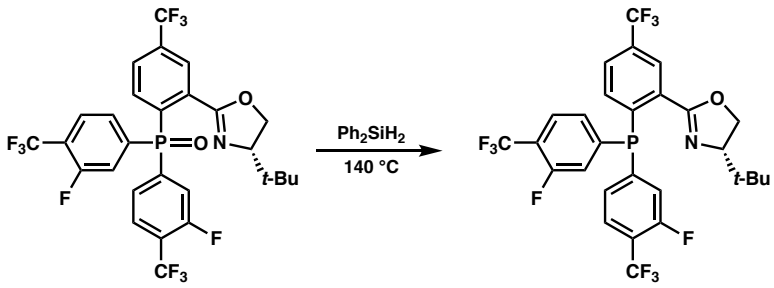
NMR (162 MHz, $CDCl_3$) δ 14.77; $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 159.9 (dd, J = 262.9, 17.6 Hz), 137.2 (dd, J = 98.7, 6.0 Hz), 128.7 (dq, J = 14.0, 4.4 Hz), 126.3 (dd, J = 11.1, 4.4 Hz), 123.7–122.4 (m), 121.8 (q, J = 273.2 Hz), 119.2 (dd, J = 22.0, 12.5 Hz); IR (Neat Film, NaCl) 3040, 2368, 1622, 1576, 1498, 1409, 1323, 1239, 1178, 1134, 1043, 951, 901, 833, 696, 632 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{14}H_8F_8OP$ $[M+H]^+$: 375.0180, found 375.0172.




**(*S*)-(2-(4-(*tert*-butyl)-4,5-dihydrooxazol-2-yl)-4-(trifluoromethyl)phenyl)bis(3-fluoro-4-(trifluoromethyl)phenyl)phosphine oxide (62)**

To a flame-dried 100 mL two-necked round bottom flask equipped with a reflux condenser and glass stopper was added phosphine oxide **61** (2.4321 g, 6.50 mmol, 1.3 equiv), CuI (952.3 mg, 5.00 mmol, 1.0 equiv), and toluene (11.4 mL) followed by *N*,*N*'-dimethylethylenediamine (1.61 mL, 15.0 mmol, 3.0 equiv). The resulting green solution was stirred at 20 ºC for 20 min after which time oxazoline (1.75 g, 5.00 mmol, 1.0 equiv), $Cs_2CO_3$ (6.03 g, 18.5 mmol, 3.7 equiv), and toluene (4.9 mL) were added. The flask was then immersed in a 110 ºC oil bath and the reaction suspension gradually turned blue and then orange. After 13 h, the reaction was cooled to 20 ºC and the orange reaction mixture was loaded directly onto a silica gel column (hexanes → 25% EtOAc in hexanes) to provide a white foam (841.9 mg, 26% yield); $[\alpha]_D^{25}$ –47.5 (*c* 1.0, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 8.24 (dd, *J* = 3.9, 1.8 Hz, 1H), 8.13–8.01 (m, 1H), 7.91–7.87 (m, 1H),

7.80–7.60 (m, 4H), 7.50–7.39 (m, 2H), 4.03 – 3.93 (m, 2H), 3.42 (dd, $J$ = 10.2, 9.4 Hz, 1H), 0.72 (s, 9H); $^{31}$P NMR (121 MHz, $CDCl_3$) δ 26.10; $^{19}$F NMR (282 MHz, $CDCl_3$) δ –61.90 (dd, $J$ = 15.3, 12.6 Hz), –63.48, –111.76 – –112.14 (m); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 160.8 (d, $J$ = 17.3 Hz), 160.4 (d, $J$ = 2.1 Hz), 158.2 (d, $J$ = 17.3 Hz), 140.7 (d, $J$ = 5.7 Hz), 139.8 – 139.2 (m), 138.4 (d, $J$ = 6.1 Hz), 136.2 (d, $J$ = 10.3 Hz), 135.8 – 134.4 (m), 134.0, 133.0, 132.8 (d, $J$ = 6.6 Hz), 127.7 (ddt, $J$ = 20.1, 9.0, 4.2 Hz), 126.8 (dd, $J$ = 9.5, 4.2 Hz), 124.4, 123.4, 122.4 – 121.3 (m), 120.9 – 120.3 (m), 119.9 (dd, $J$ = 22.1, 11.1 Hz), 69.3, 33.6, 25.8s; IR (Neat Film, NaCl) 2963, 2907, 2873, 1664, 1621, 1574, 1497, 1479, 1664, 1621, 1574, 1497, 1479, 1407, 1322, 1235, 1178, 1136, 1178, 1083, 1042, 964, 915, 833, 720, 699, 629 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{28}H_{22}F_{11}NO_2P$ $[M+H]^+$: 644.1207, found 644.1184.




**(*S*)-2-(2-(bis(3-fluoro-4-(trifluoromethyl)phenyl)phosphaneyl)-5-(trifluoromethyl)phenyl)-4-(*tert*-butyl)-4,5-dihydrooxazole (*L12,* Ty–PHOX)**

To an oven-dried 25 mL schlenk tube was added phosphine oxide **61** and $Ph_2SiH_2$ (1.49 mL, 8.05 mmol, 7.0 equiv) . The schlenk tube was then sealed and heated in a 140 ºC oil bath behind a blast shield. After 16 h, the reaction was cooled to 20 ºC and slowly opened to a nitrogen atmosphere. The colorless reaction mixture was then loaded directly onto a silica gel column (hexanes → 25% $CH_2Cl_2$ in hexanes) to provide a white foam (610 mg, 85% yield); $[\alpha]_D^{25}$ –12.5 (*c* 1.0, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 8.31–8.25 (m,

1H), 7.67–7.54 (m, 3H), 7.10 (dt, $J$ = 19.3, 7.4 Hz, 2H), 7.03–6.95 (m, 3H), 4.33 (dd, $J$ = 10.1, 8.7 Hz, 1H), 4.16 (t, $J$ = 8.6 Hz, 1H), 3.99 (dd, $J$ = 10.1, 8.5 Hz, 1H), 0.74 (s, 9H); $^{19}$F NMR (282 Hz, $CDCl_3$) δ –61.51 (dd, $J$ = 21.1, 12.4 Hz), –63.10, –113.31 – –113.52 (m), –113.57 – –113.78 (m); $^{31}$P NMR (121 MHz, $CDCl_3$) δ –7.38; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 161.05 – 160.82 (m), 160.49 (d, $J$ = 4.0 Hz), 158.46 – 158.25 (m), 145.63 (t, $J$ = 4.2 Hz), 145.46 (d, $J$ = 5.6 Hz), 140.49 (d, $J$ = 28.6 Hz), 134.94, 134.74 – 134.58 (m), 134.47 – 134.20 (m), 132.38 (d, $J$ = 20.4 Hz), 131.64 (q, $J$ = 33.3 Hz), 129.24 (ddd, $J$ = 34.0, 22.2, 3.7 Hz), 128.00 – 127.58 (m), 127.33 (dq, $J$ = 12.2, 4.1 Hz), 126.65 (p, $J$ = 3.4 Hz), 126.43, 124.79, 123.73, 122.44 – 120.79 (m), 119.75 – 118.09 (m), 68.83, 33.59, 25.60; IR (Neat Film, NaCl) 3071, 2960, 2871, 2138, 1655, 1617, 1570, 1491, 1430, 1403, 1323, 1176, 1133, 1083, 1042, 967, 830, 735, 714, 698, 684, 624 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{28}H_{22}F_{11}NOP$ $[M+H]^+$: 628.1258, found 628.1271.

### 4.8.3 Determination of Enantiomeric Excess

***Table 4.3*** *Determination of Enantiomeric Excess.*

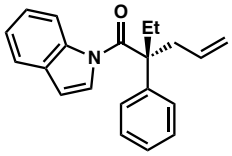
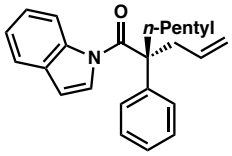
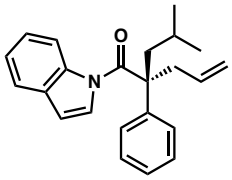
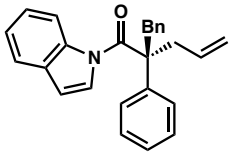
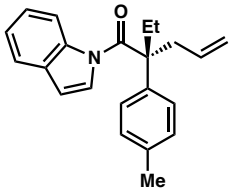
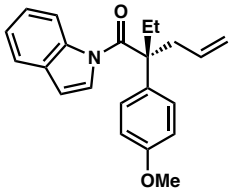
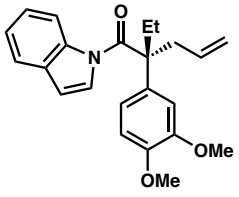
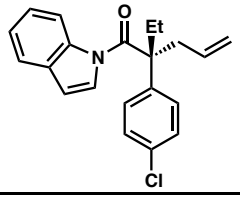
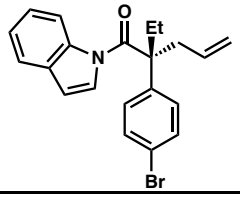
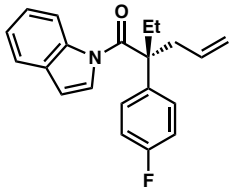
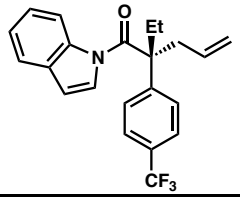
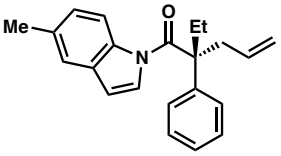
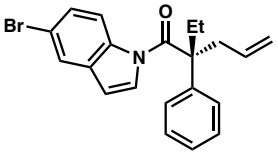
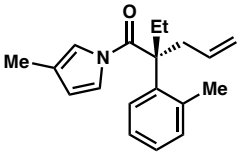
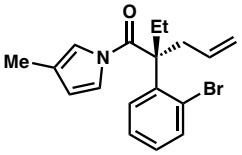
| Entry | Compound | Assay Conditions | $t_R$ of major isomer (min) | $t_R$ of minor isomer (min) | %ee |
|---|---|---|---|---|---|
| 1 |  | SFC<br>Chiralpak AD-H<br>10% IPA<br>isocratic, 2.5 mL/min | 6.95 | 6.41 | 91 |
| 2 |  | SFC<br>Chiralpak AD-H<br>10% IPA<br>isocratic, 2.5 mL/min | 5.84 | 4.87 | 96 |
| 3 |  | SFC<br>Chiralpak AD-H<br>10% IPA<br>isocratic, 2.5 mL/min | 5.20 | 4.86 | 96 |
| 4 |  | SFC<br>Chiralpak AD-H<br>10% IPA<br>isocratic, 2.5 mL/min | 18.37 | 17.49 | 96 |
| 5 |  | SFC<br>Chiralpak AD-H<br>15% IPA<br>isocratic, 2.5 mL/min | 4.75 | 4.21 | 98 |
| 6 |  | SFC<br>Chiralpak AD-H<br>15% IPA<br>isocratic, 2.5 mL/min | 5.73 | 5.09 | 98 |
| 7 |  | SFC<br>Chiralpak AD-H<br>15% IPA<br>isocratic, 2.5 mL/min | 4.92 | 4.14 | 95 |

***Table 4.3*** *Determination of Enantiomeric Excess (continued)*

| Entry | Compound | Assay Conditions | $t_R$ of major isomer (min) | $t_R$ of minor isomer (min) | %ee |
|---|---|---|---|---|---|
| 8 |  | SFC<br>Chiralpak AD-H<br>15% IPA<br>isocratic, 2.5 mL/min | 4.78 | 4.31 | 94 |
| 9 |  | SFC<br>Chiralpak AD-H<br>15% IPA<br>isocratic, 2.5 mL/min | 7.38 | 6.60 | 94 |
| 10 |  | SFC<br>Chiralpak AD-H<br>10% IPA<br>isocratic, 2.5 mL/min | 5.07 | 4.57 | 96 |
| 11 |  | SFC<br>Chiralpak AD-H<br>5% IPA<br>isocratic, 2.5 mL/min | 4.97 | 4.48 | 70 |
| 12 |  | SFC<br>Chiralpak AD-H<br>15% IPA<br>isocratic, 2.5 mL/min | 5.92 | 5.21 | 98 |
| 13 |  | SFC<br>Chiralpak AD-H<br>15% IPA<br>isocratic, 2.5 mL/min | 5.91 | 5.28 | 92 |
| 14 |  | SFC<br>Chiralcel OD-H<br>3% IPA<br>isocratic, 2.5 mL/min | 5.37 | 4.99 | 89 |
| 15 |  | SFC<br>Chiralcel OD-H<br>3% IPA<br>isocratic, 2.5 mL/min | 9.72 | 9.10 | 80 |

## 4.9 REFERENCES AND NOTES

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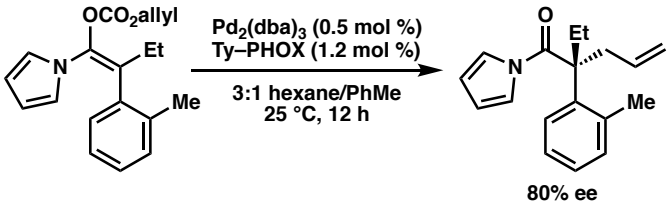
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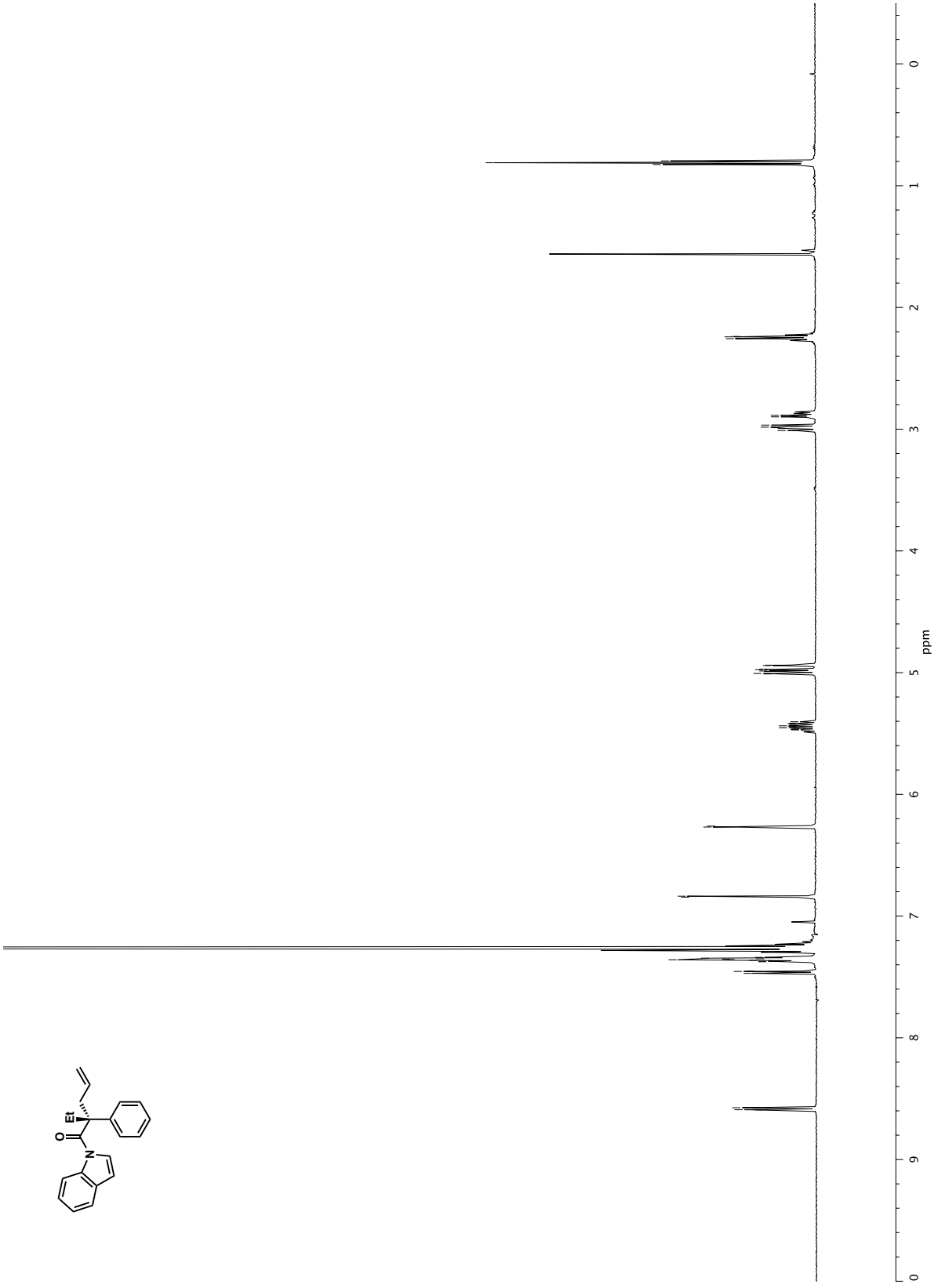
12 The standard *N*-acyl pyrrole substrate provides the *o*-Me product in 80% ee.



# *APPENDIX 5*

*Spectra Relevant to Chapter 4:*

*Palladium-Catalyzed Decarboxylative Allylic Alkylation of Fully-Substituted N-Acyl Indole-Derived Enol Carbonates*




***A5.1*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***41a***.

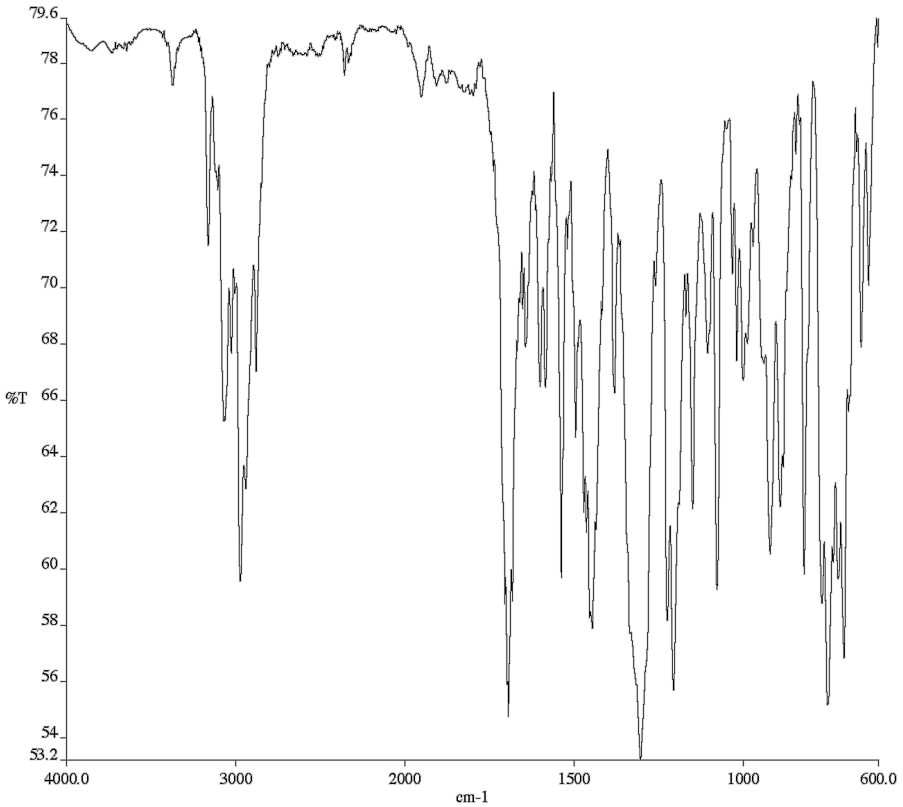



***Figure A5.2*** *Infrared spectrum (Thin Film, NaCl) of compound* ***41a****.*

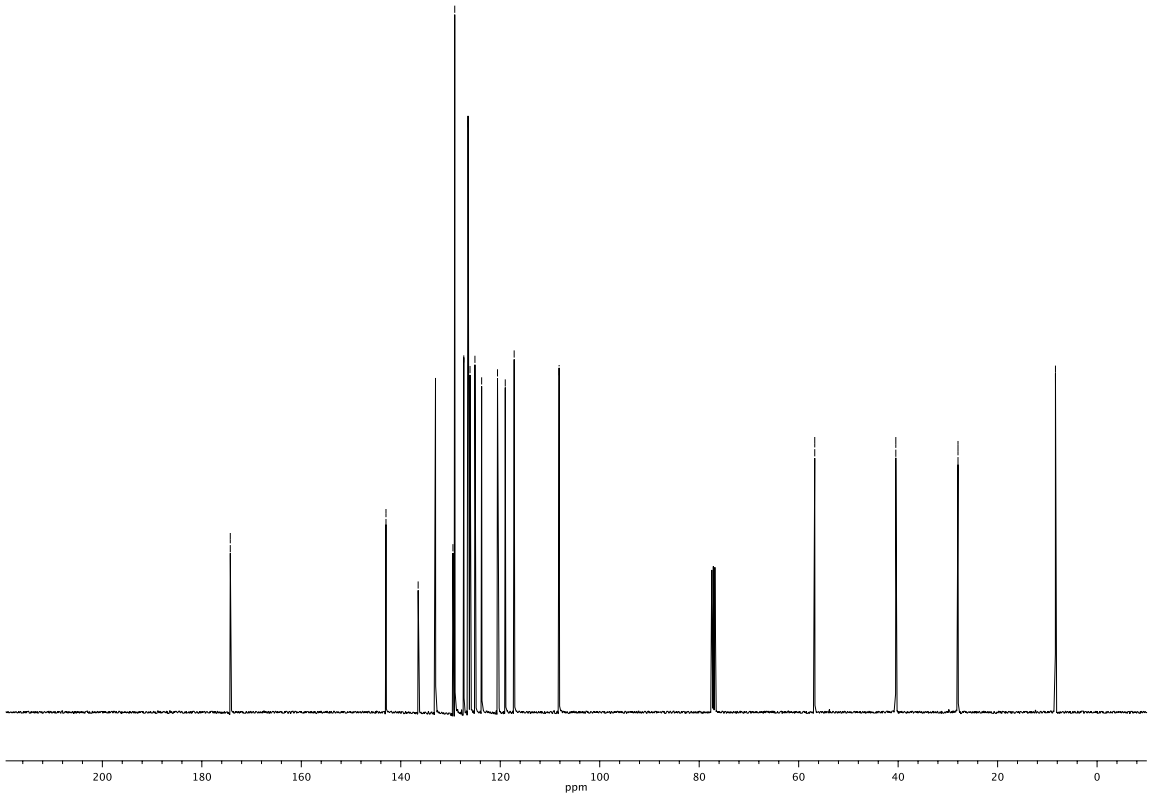
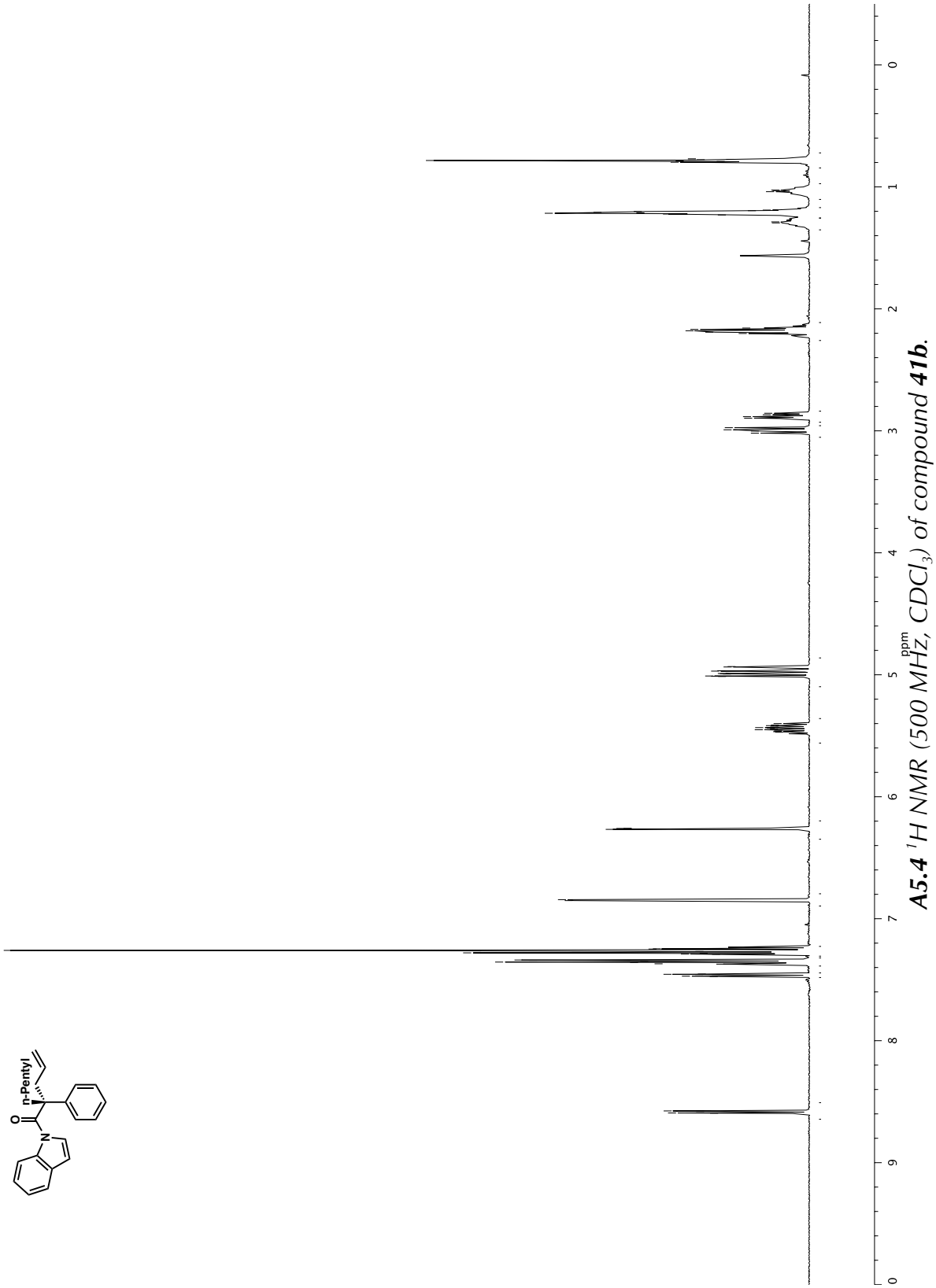



***Figure A5.3*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***41a****.*




***A5.4*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***41b***.

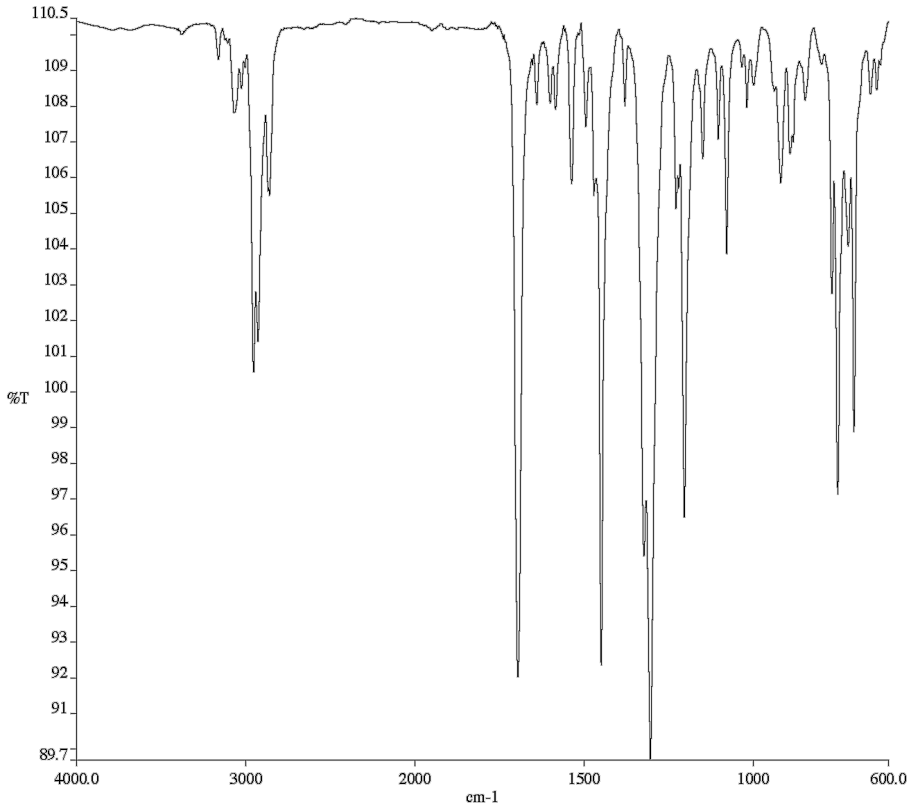



***Figure A5.5*** *Infrared spectrum (Thin Film, NaCl) of compound* ***41b****.*

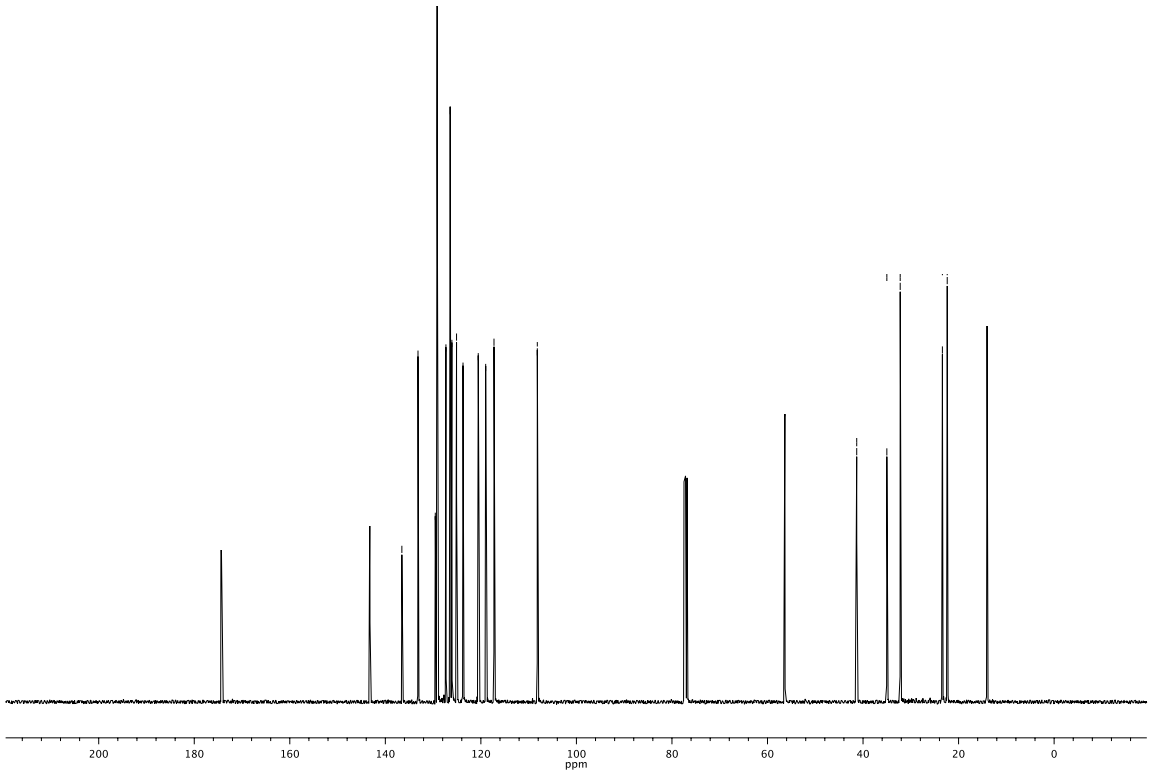
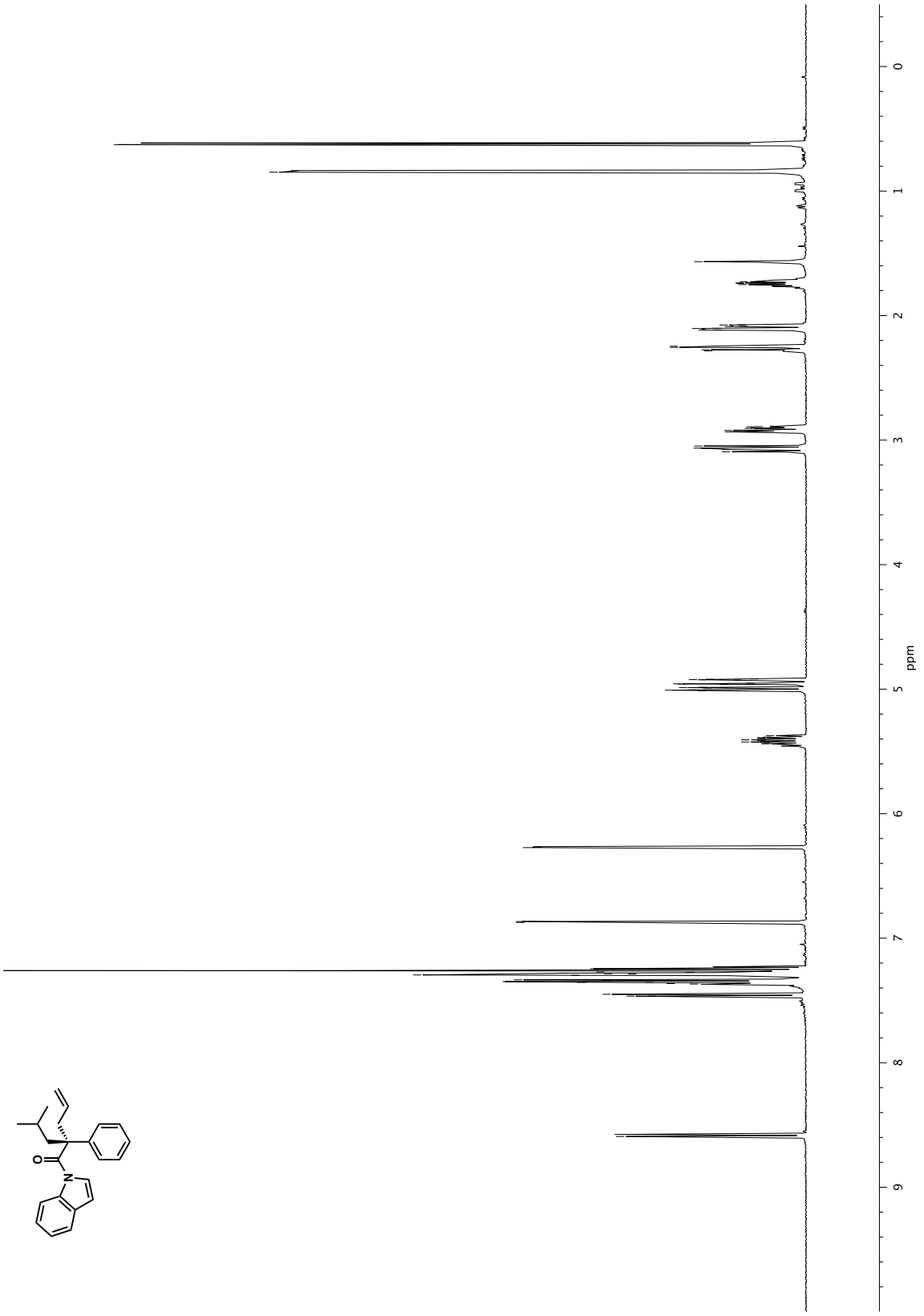



***Figure A5.6*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***41b****.*




***A5.7*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***41c****.*

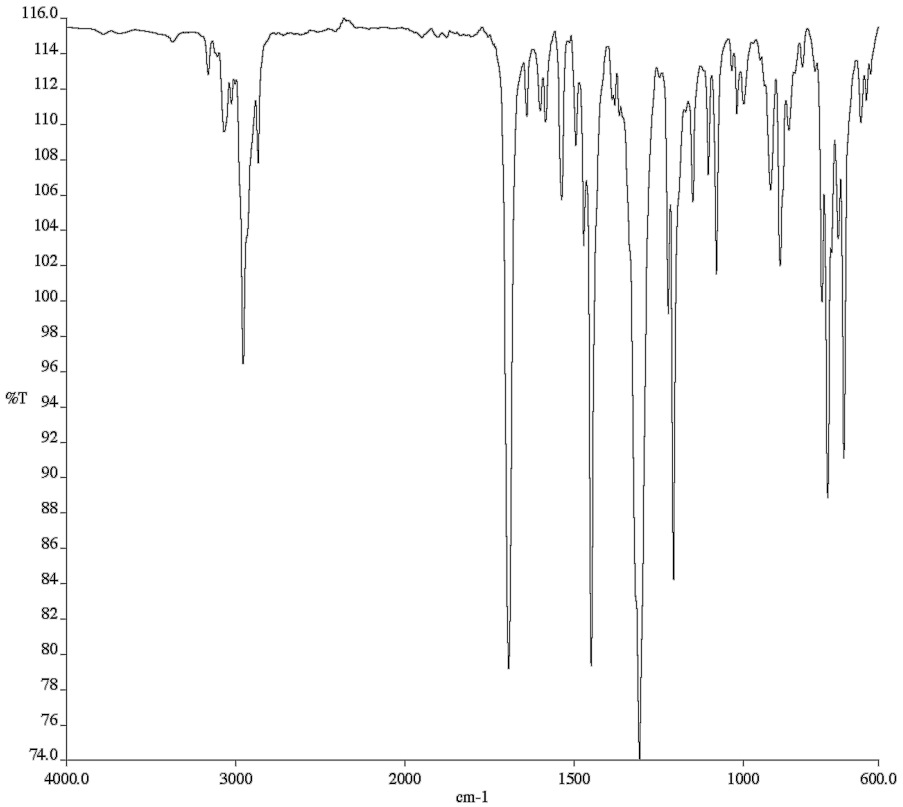



***Figure A5.8*** *Infrared spectrum (Thin Film, NaCl) of compound* ***41c****.*

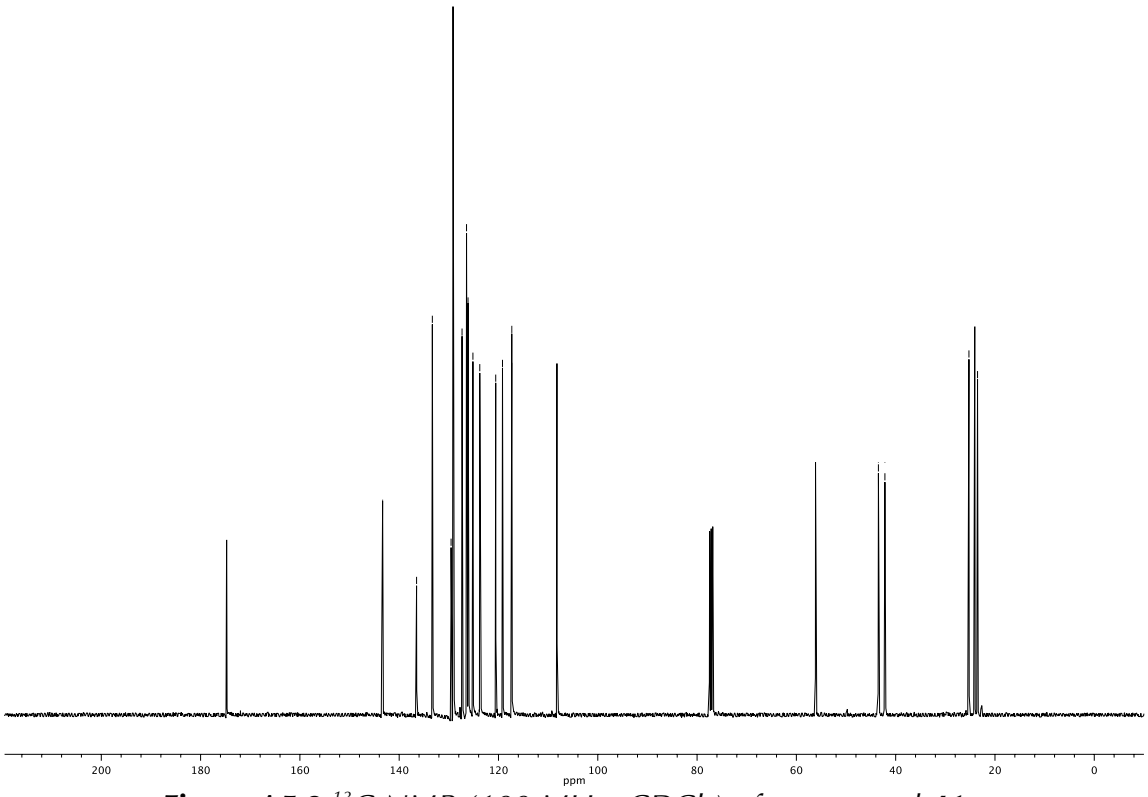
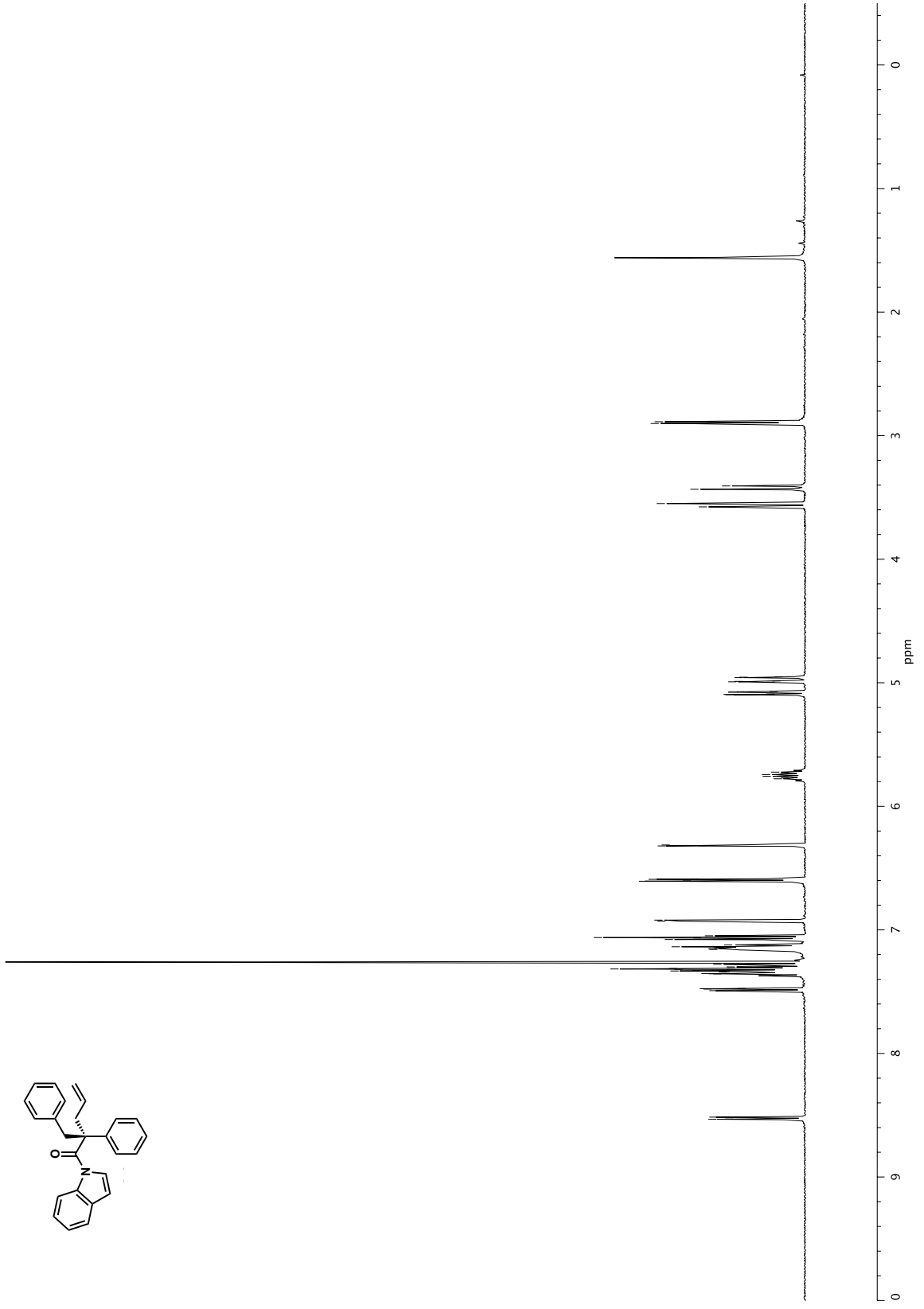



***Figure A5.9*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***41c****.*




***A5.10*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***41d****.*

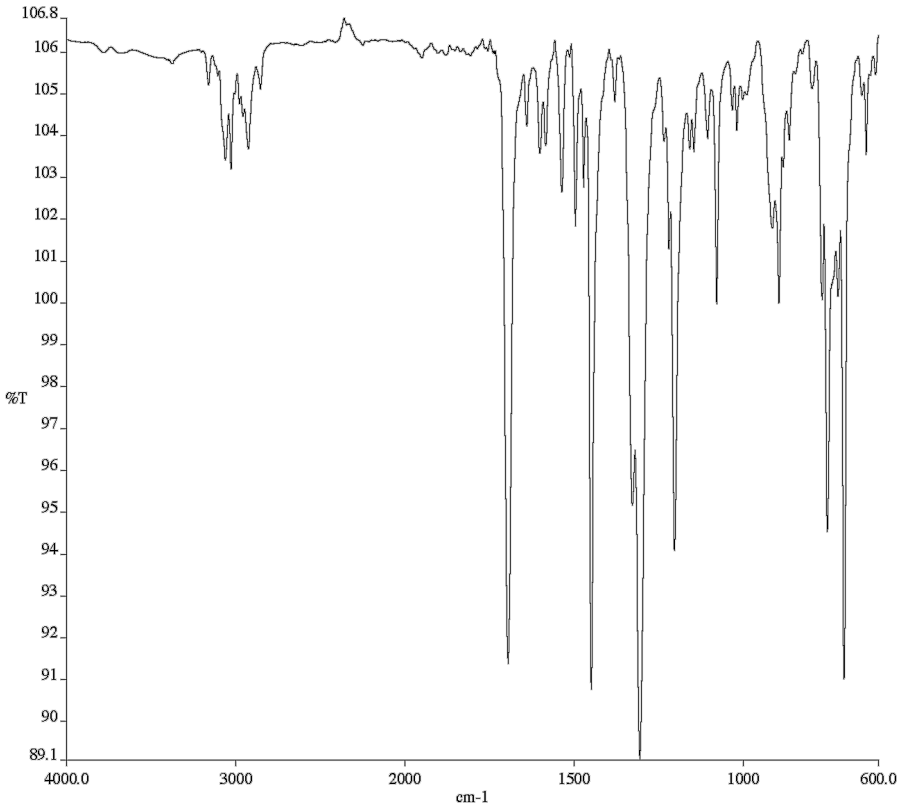



***Figure A5.11*** *Infrared spectrum (Thin Film, NaCl) of compound* ***41d***.

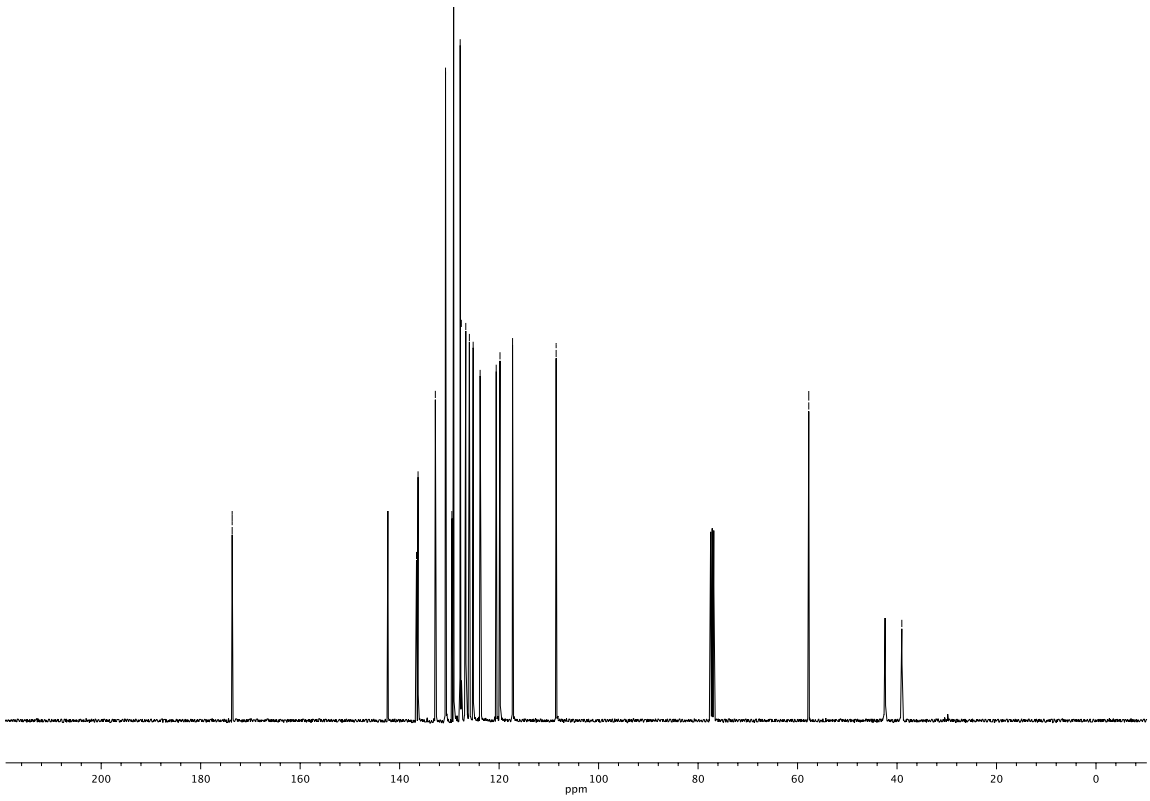
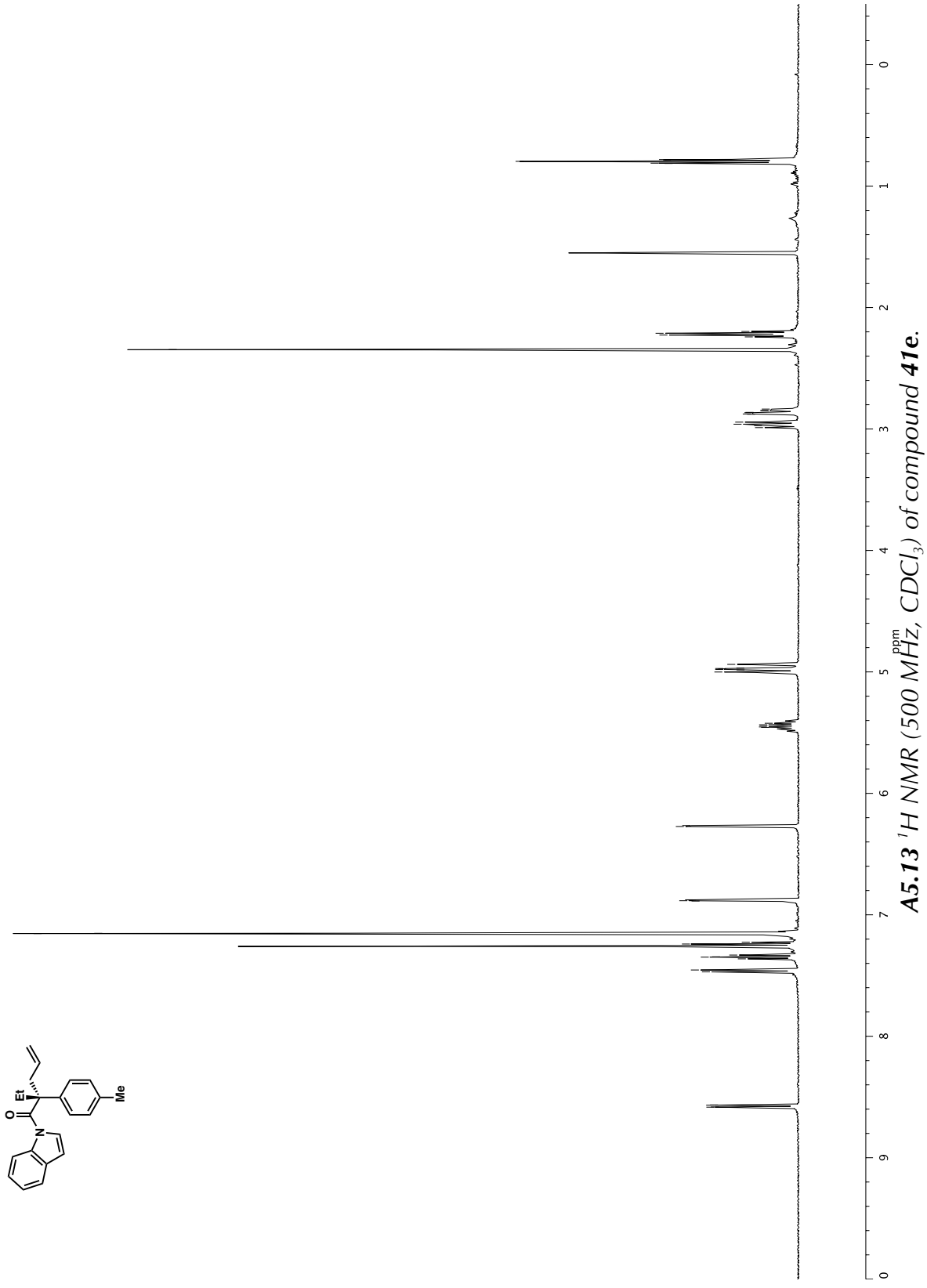



***Figure A5.12*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***41d***.




***A5.13*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***41e***.

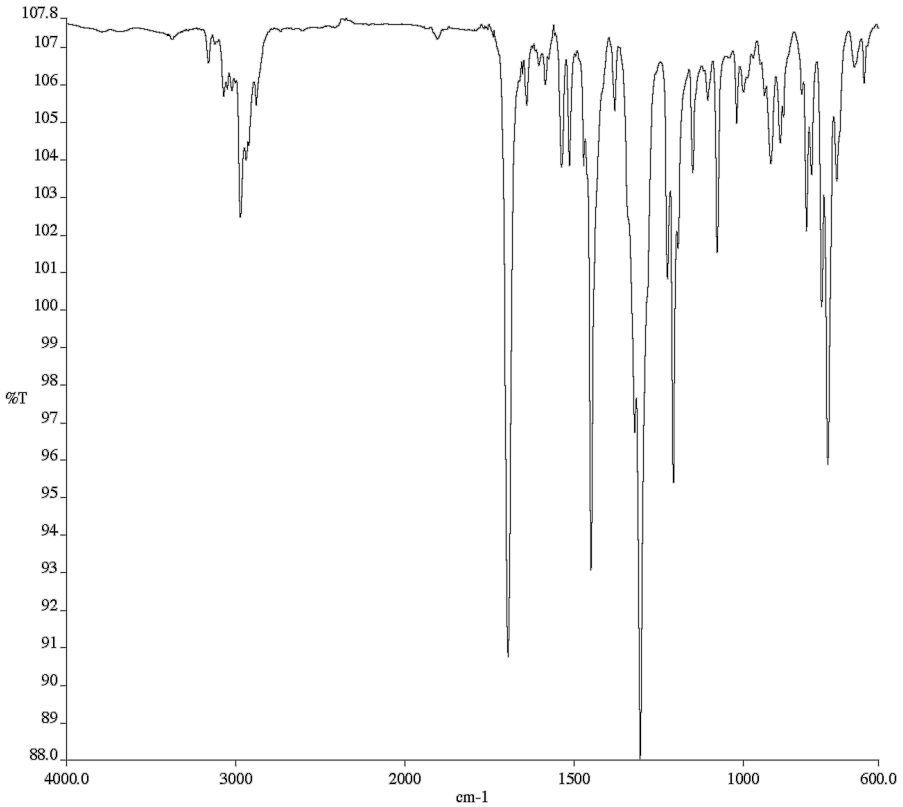



***Figure A5.14*** *Infrared spectrum (Thin Film, NaCl) of compound* ***41e****.*

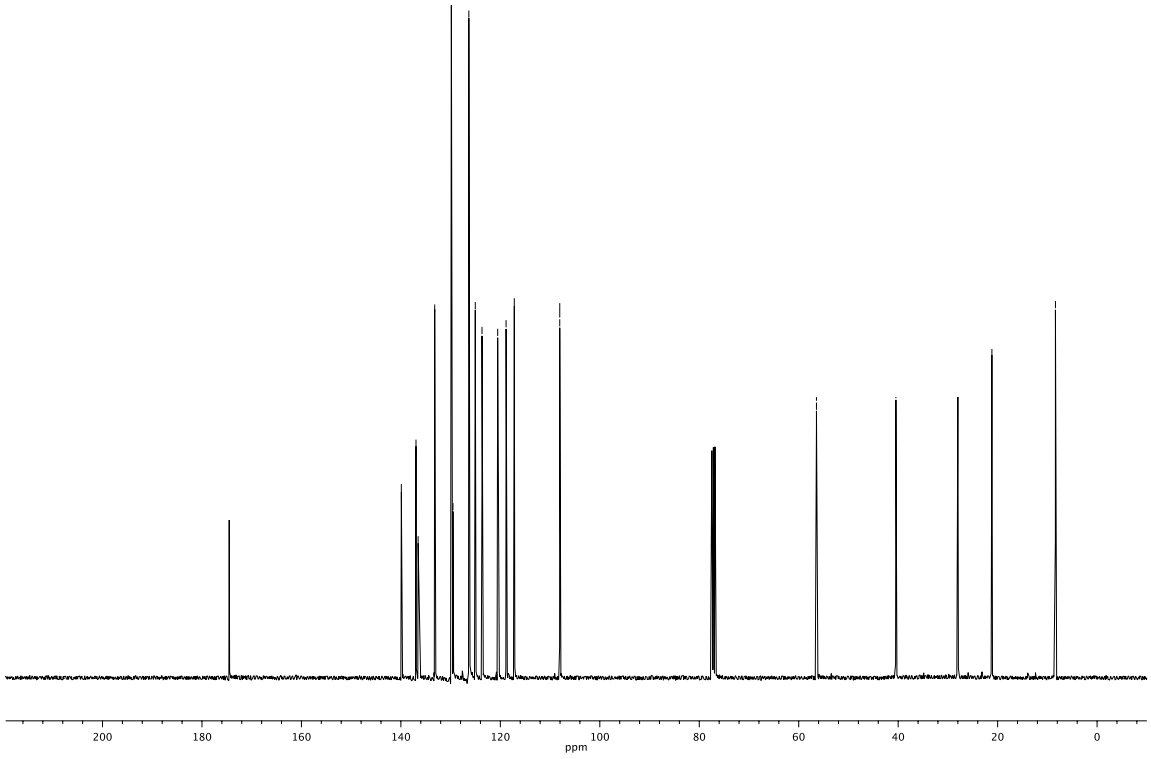
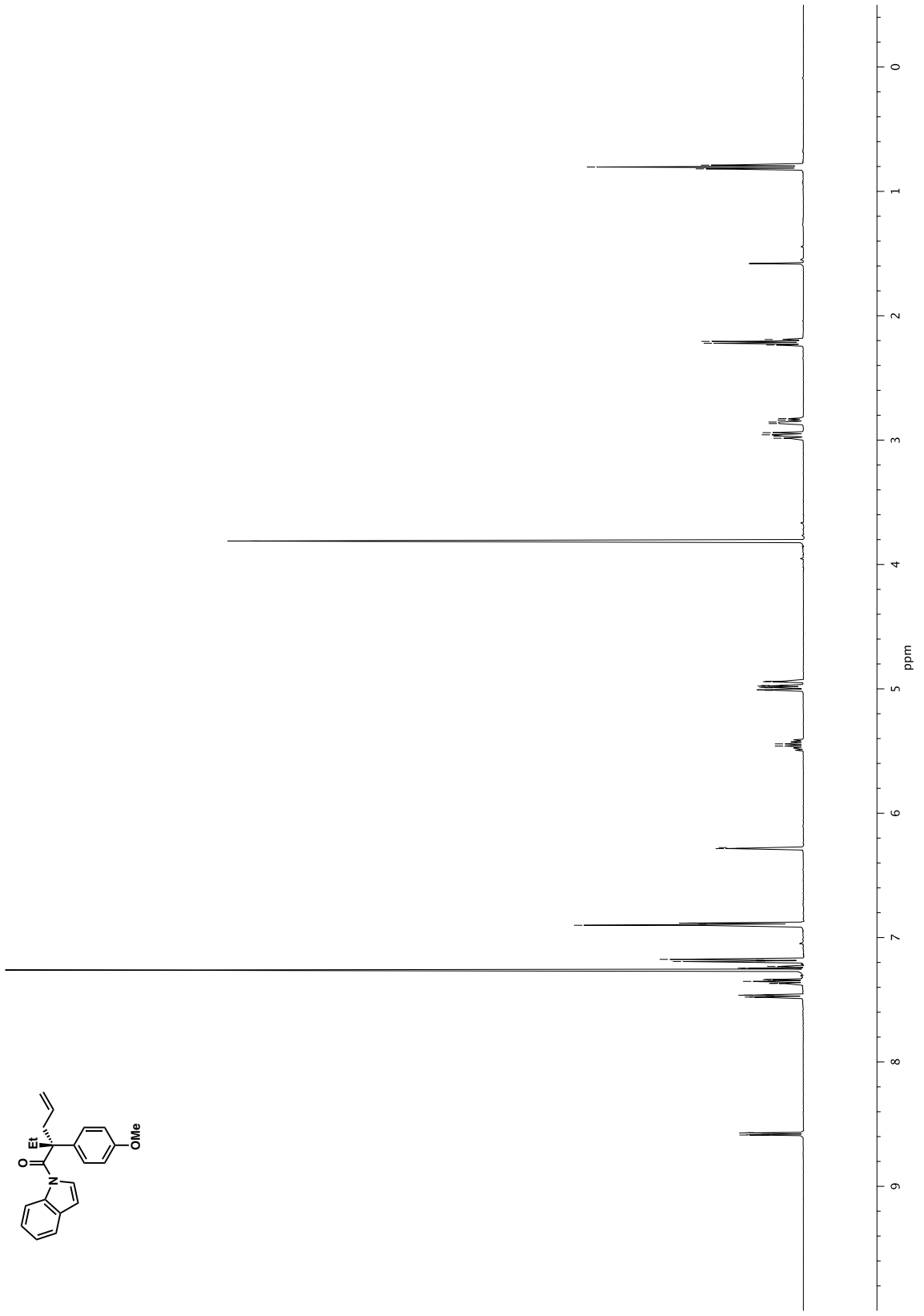



***Figure A5.15*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***41e****.*




***A5.16*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***41f****.*

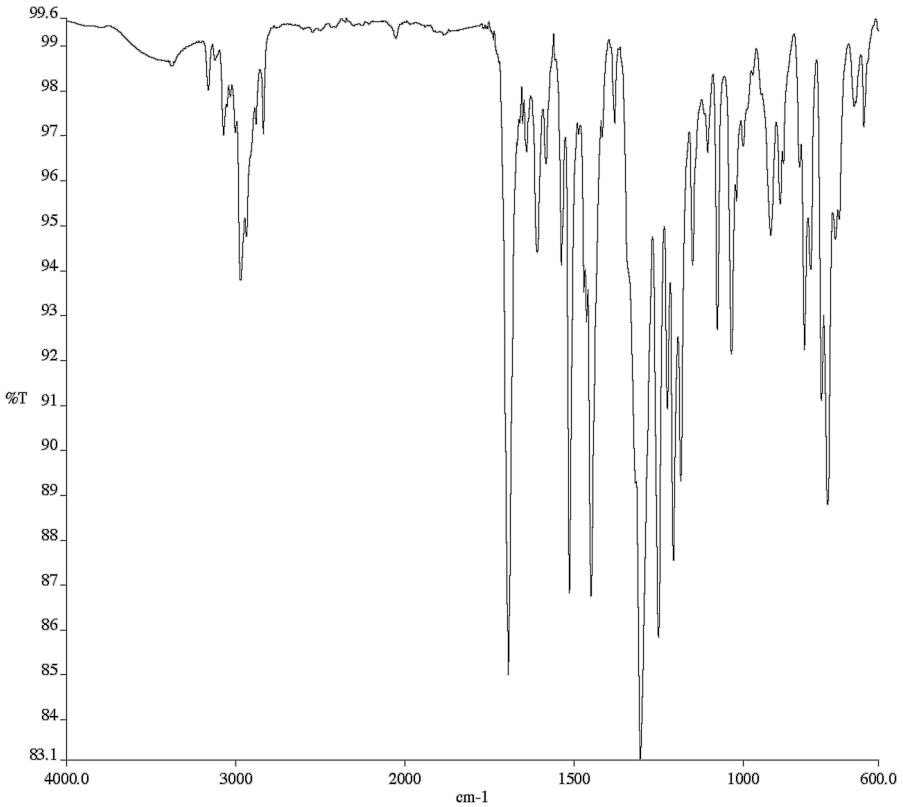



***Figure A5.17*** *Infrared spectrum (Thin Film, NaCl) of compound* ***41f****.*

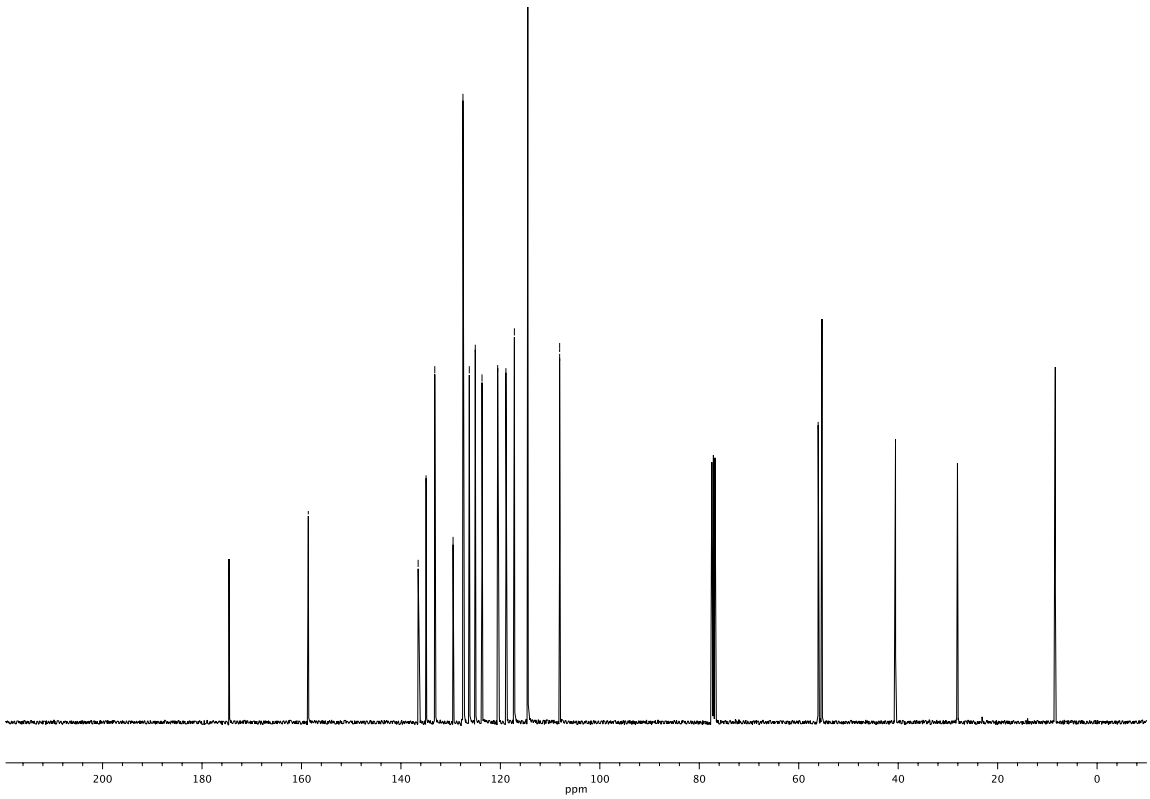
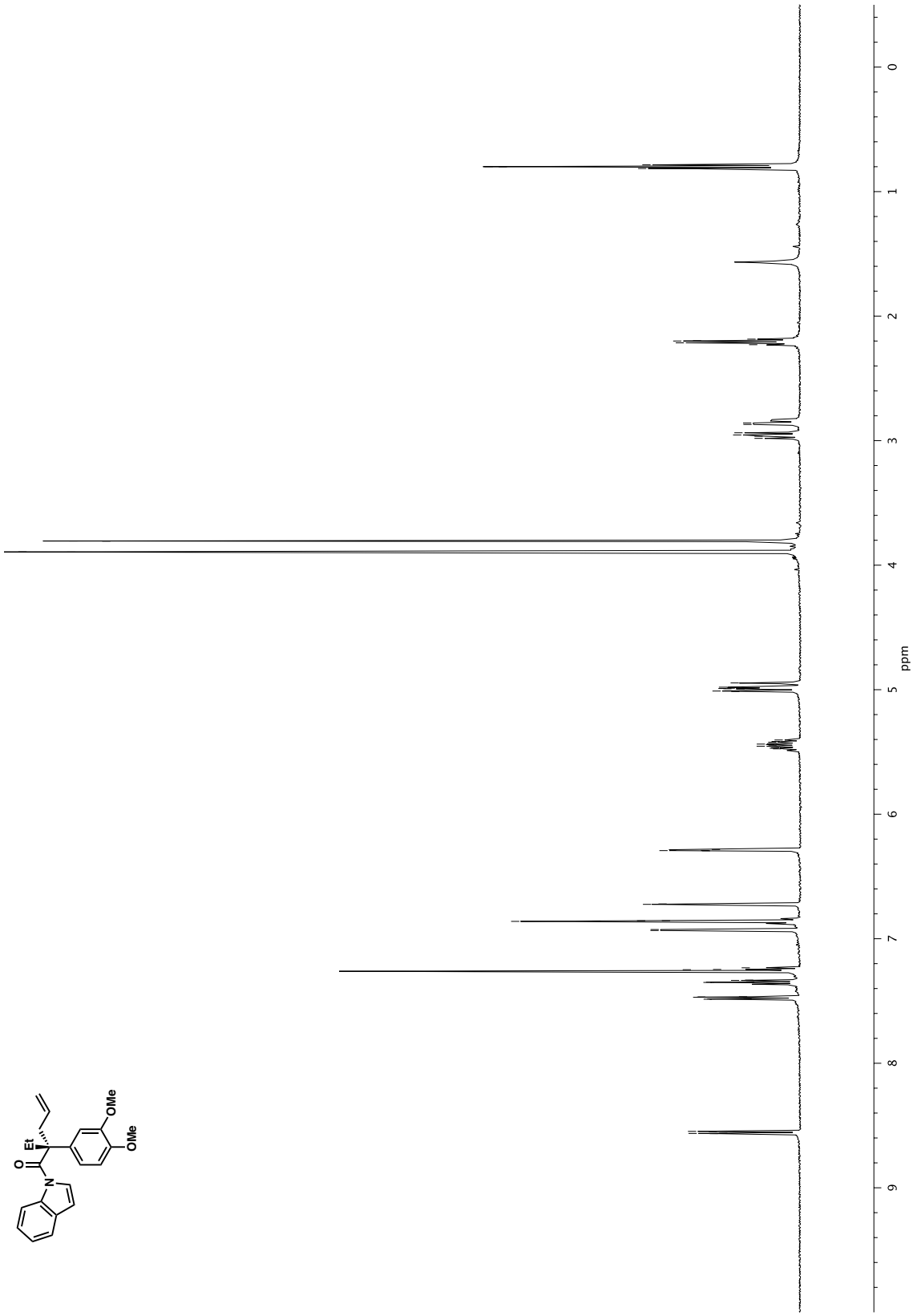



***Figure A5.18*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***41f****.*




***A5.19*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***41g***.

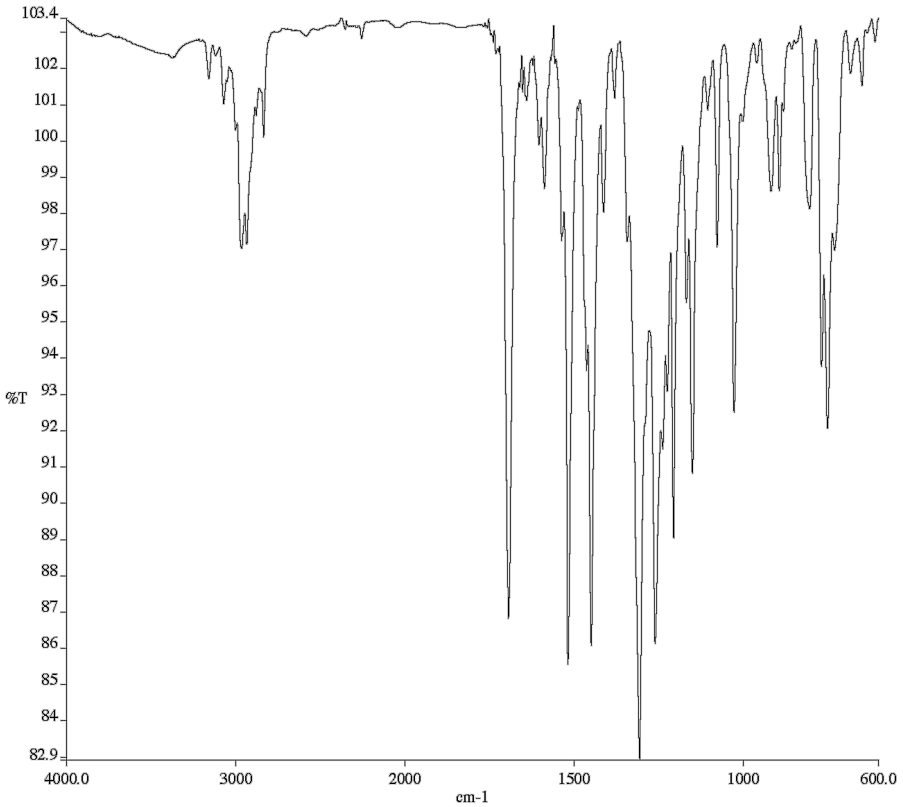



***Figure A5.20*** *Infrared spectrum (Thin Film, NaCl) of compound* ***41g****.*

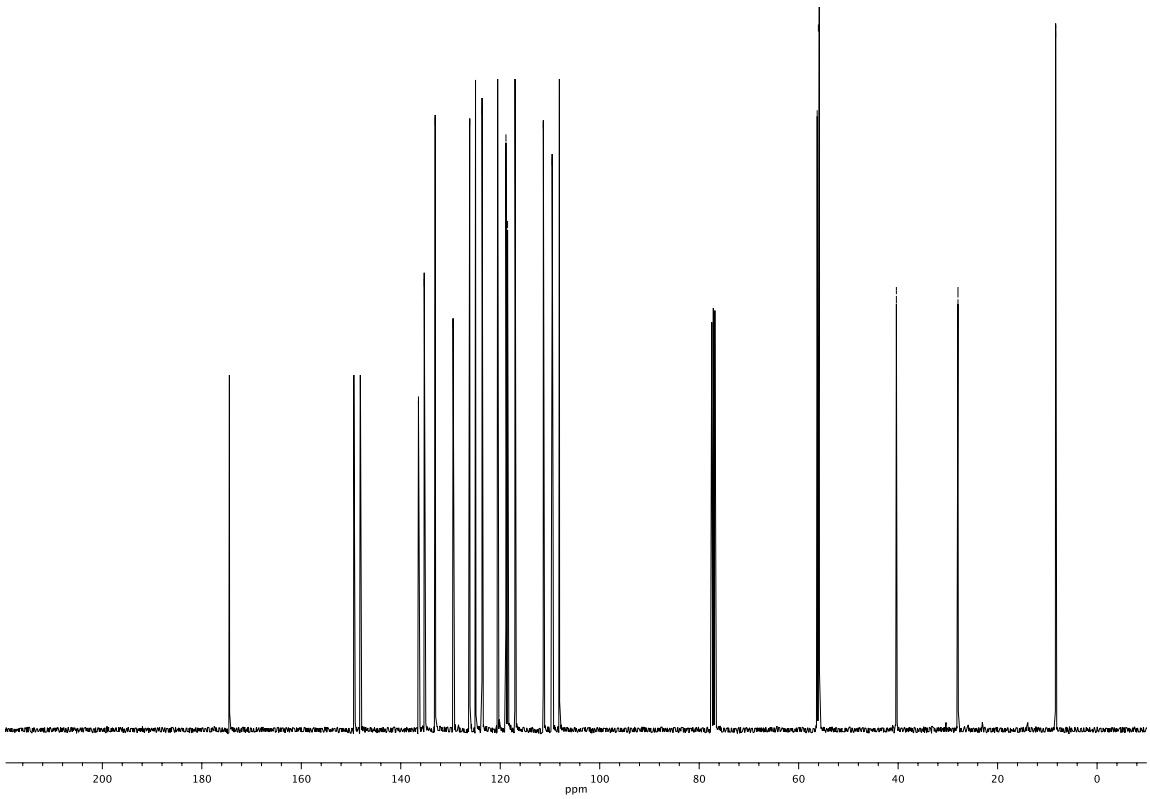
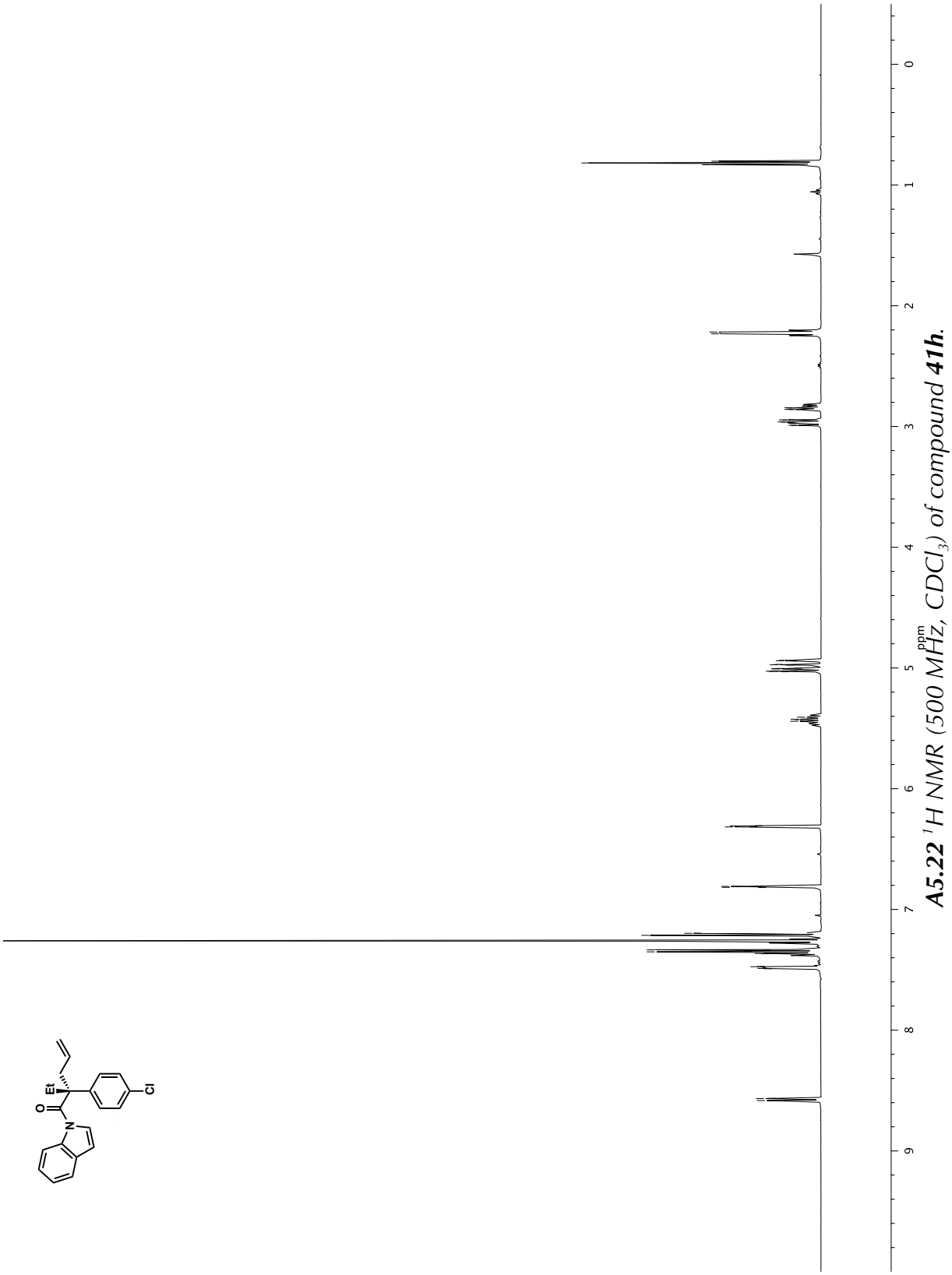



***Figure A5.21*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***41g****.*




***A5.22*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***41h***.

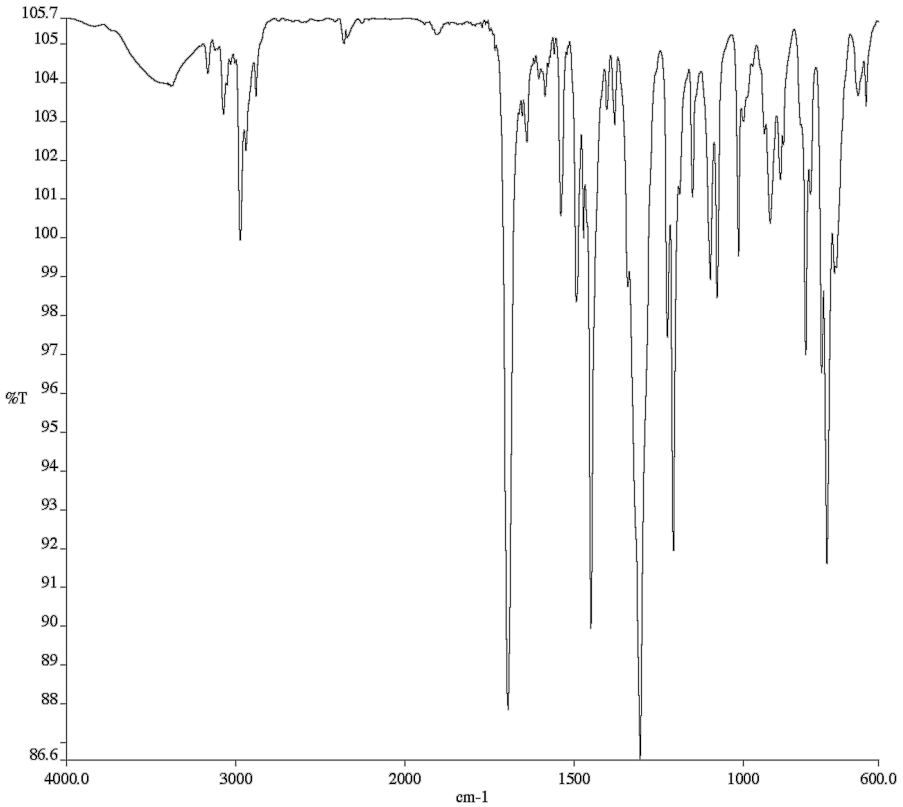



***Figure A5.23*** *Infrared spectrum (Thin Film, NaCl) of compound* ***41h***.

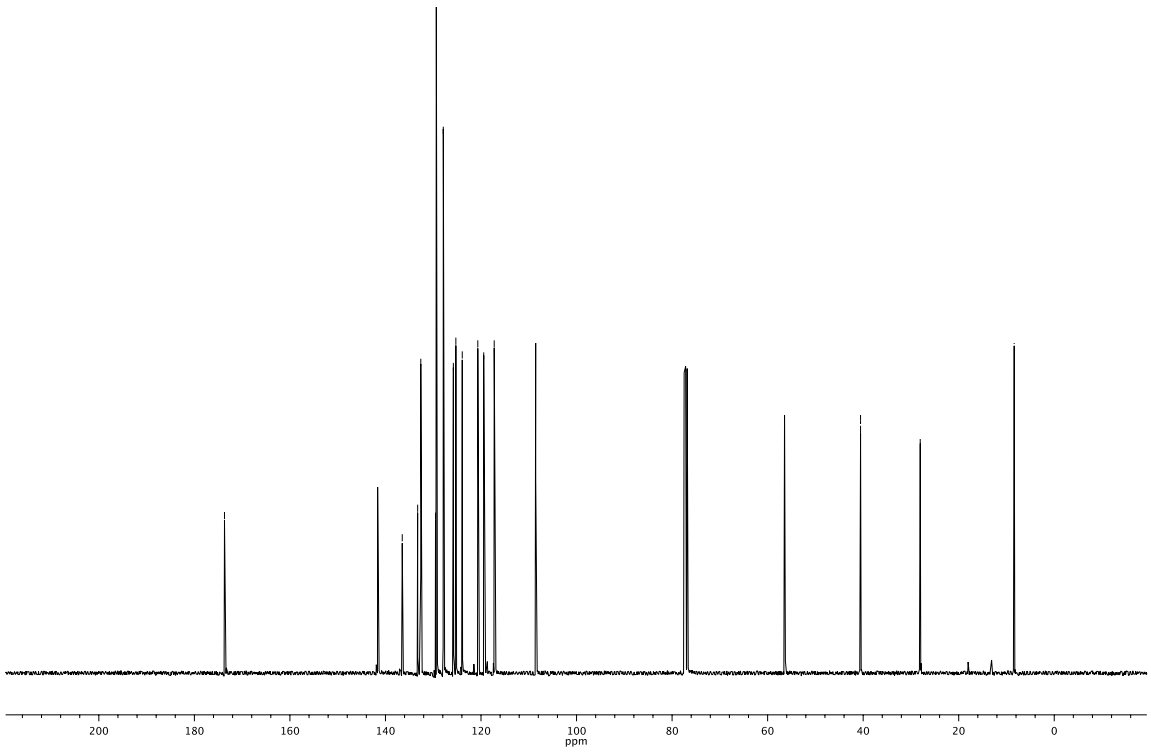
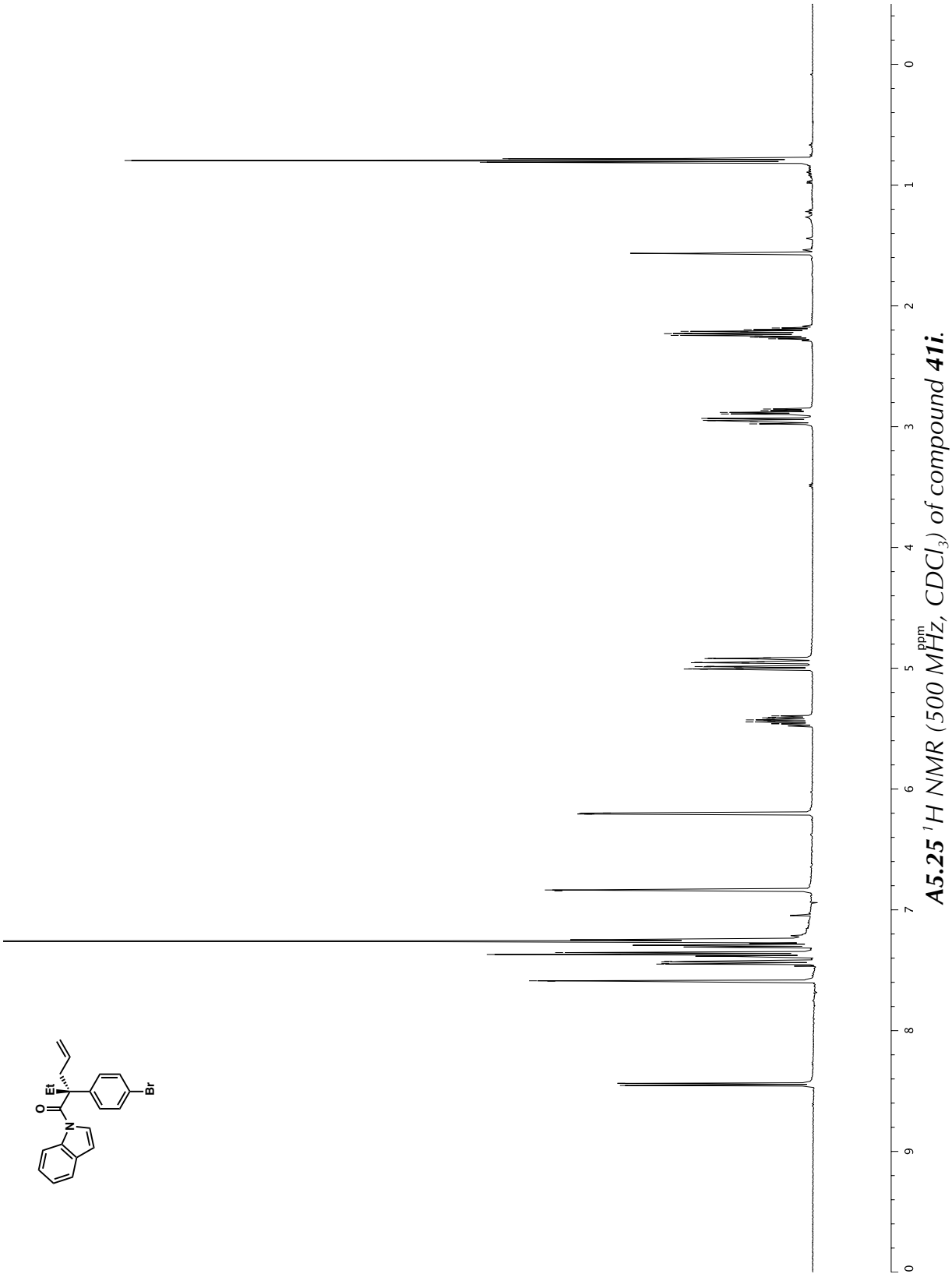



***Figure A5.24*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***41h***.




***A5.25*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***41i****.*

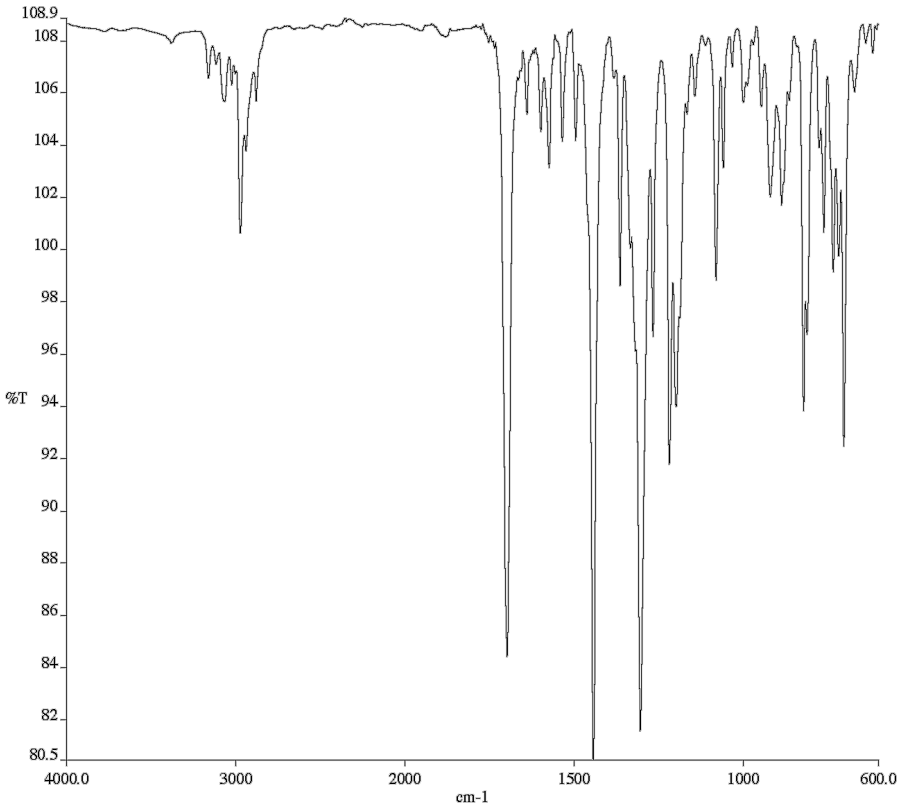



***Figure A5.26*** *Infrared spectrum (Thin Film, NaCl) of compound* ***41i****.*

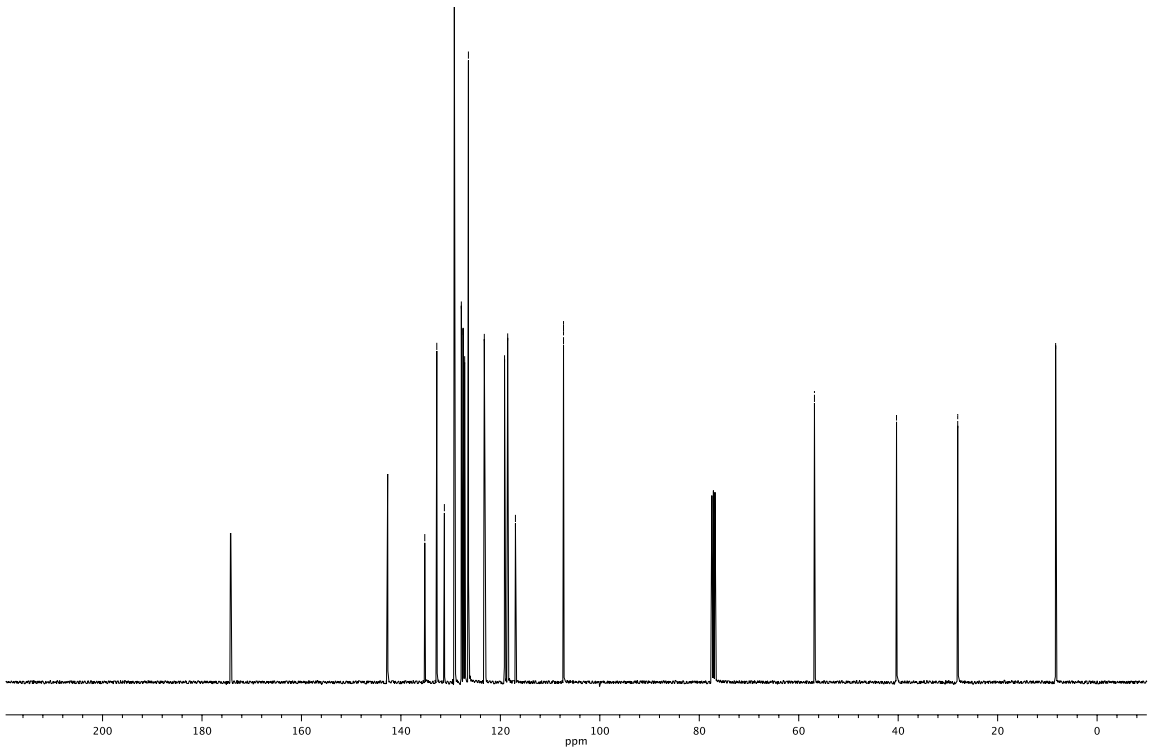
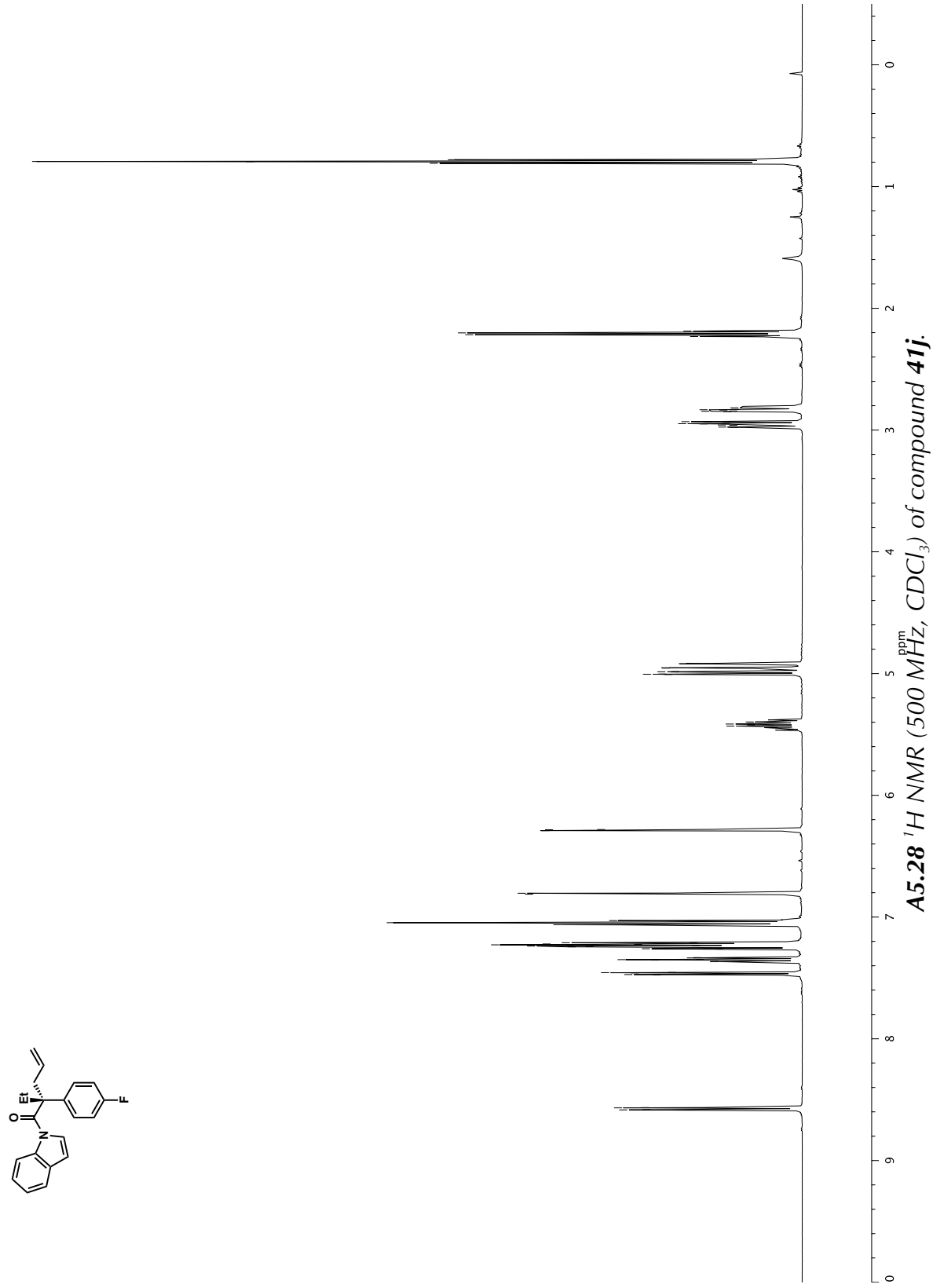



***Figure A5.27*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***41i****.*




***A5.28*** *$^{1}H$ NMR (500 MHz, $CDCl_3$) of compound* ***41j****.*

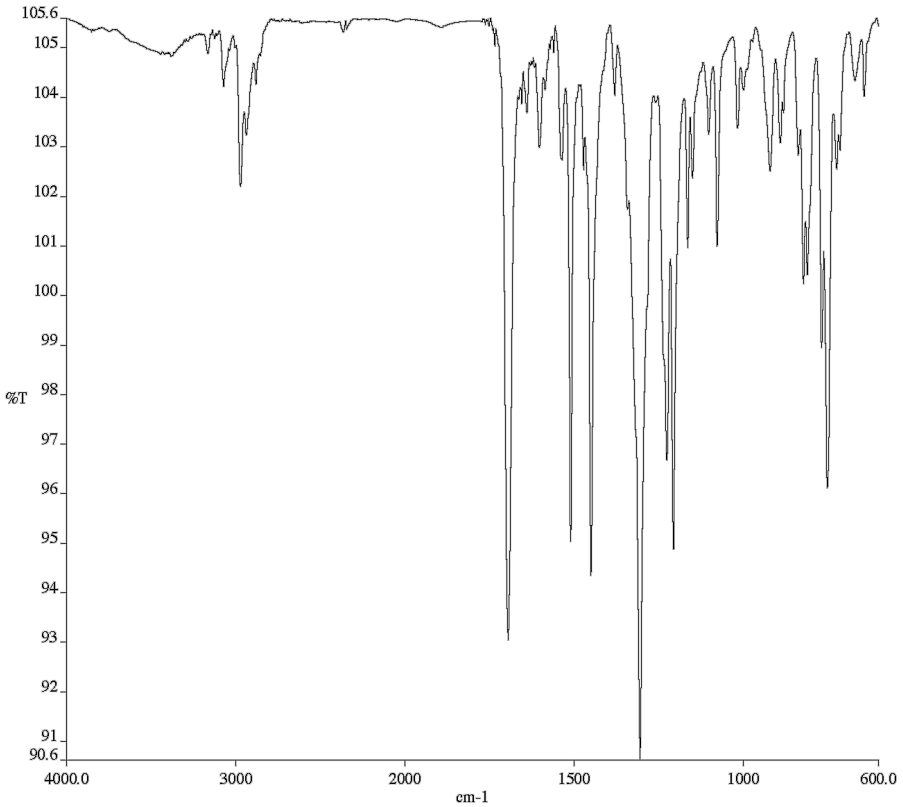



***Figure A5.29*** *Infrared spectrum (Thin Film, NaCl) of compound* ***41j****.*

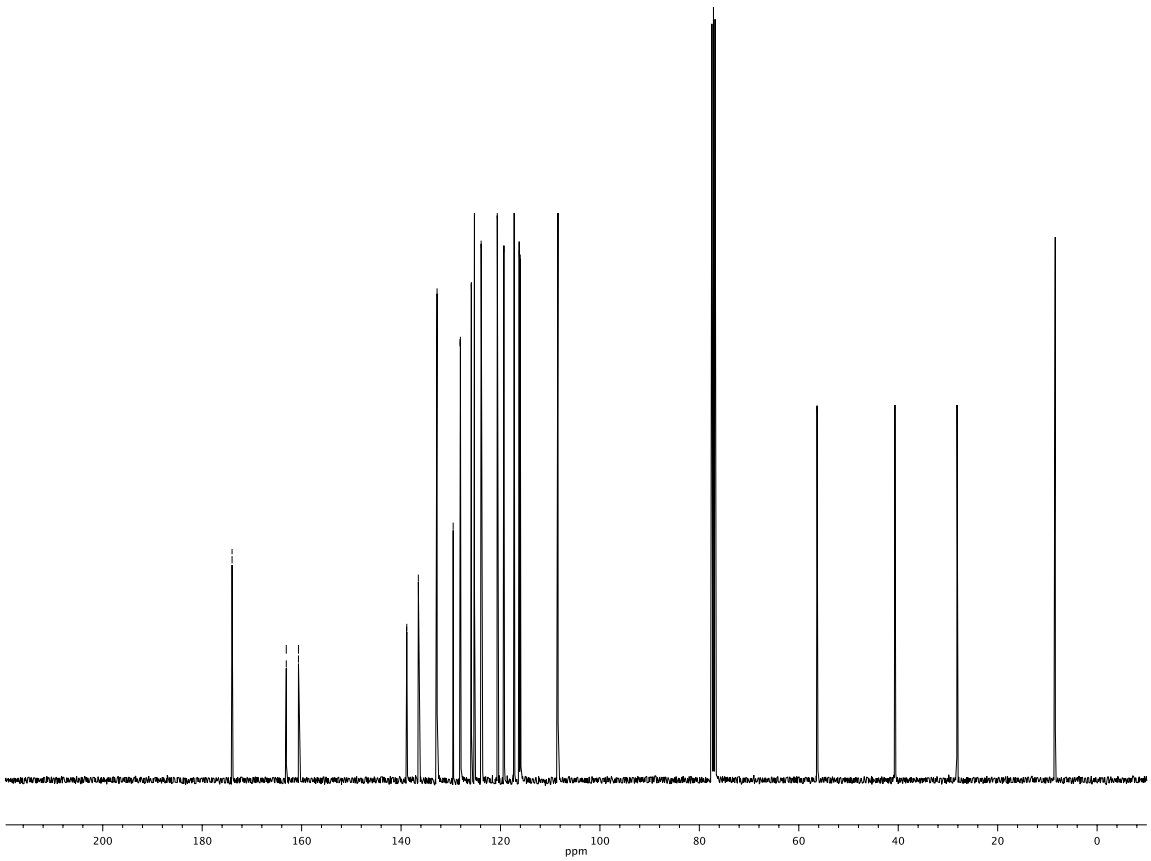



***Figure A5.30*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***41j****.*

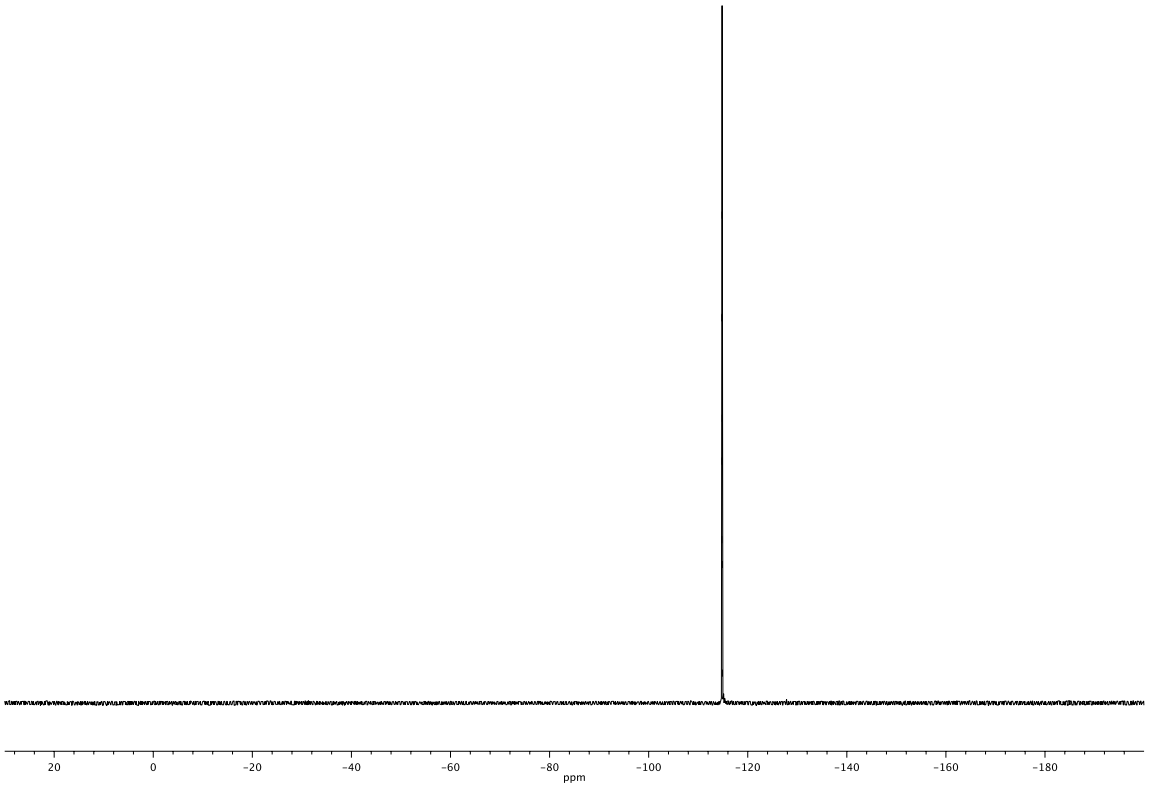
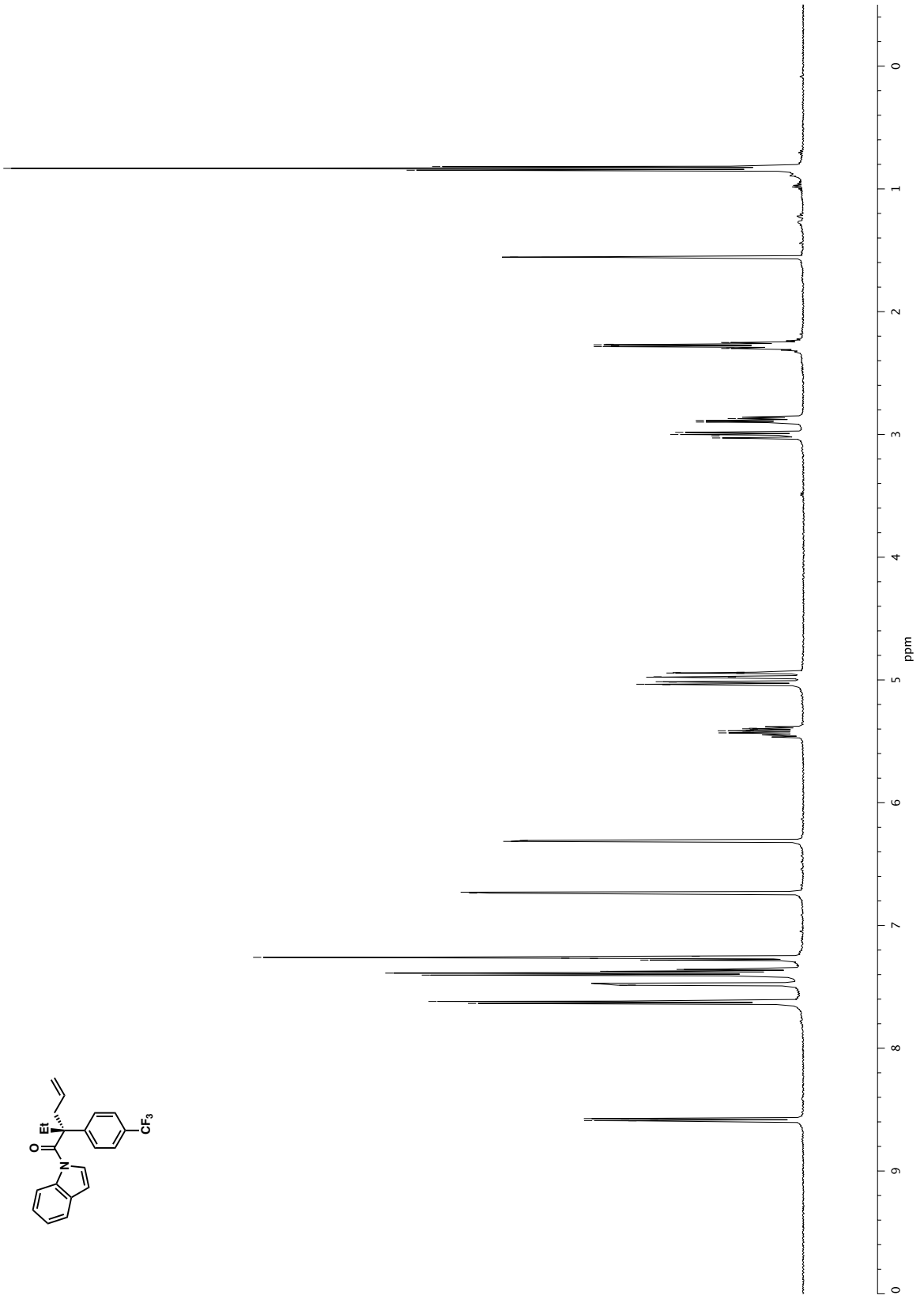



***Figure A5.31*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***41j****.*




***A5.32*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***41k****.*

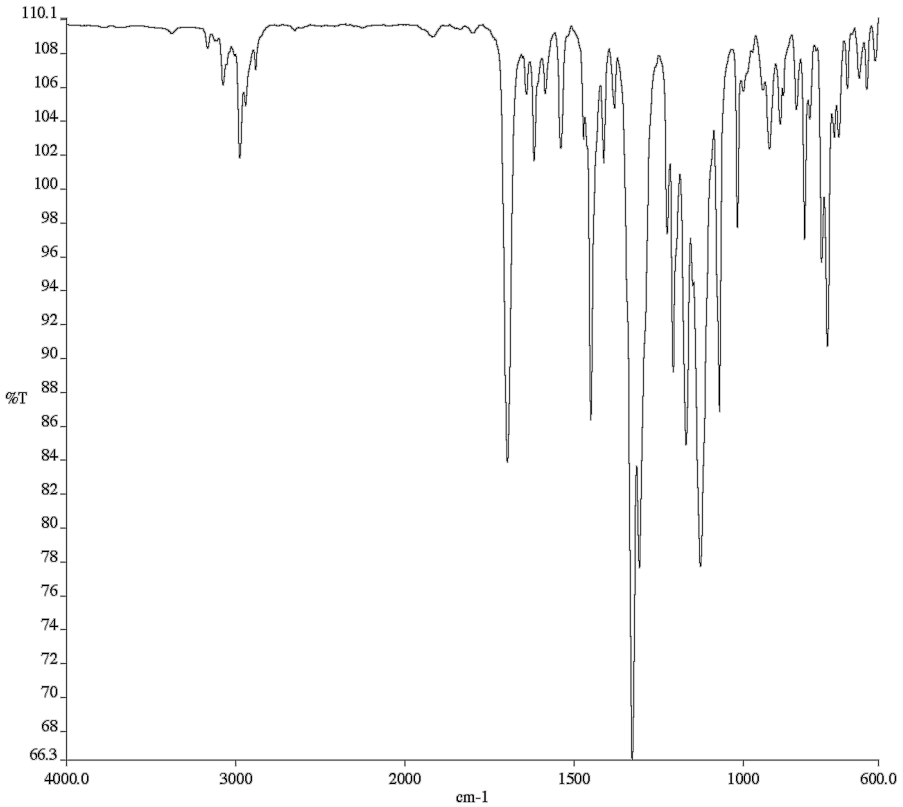



***Figure A5.33*** *Infrared spectrum (Thin Film, NaCl) of compound* ***41k***.

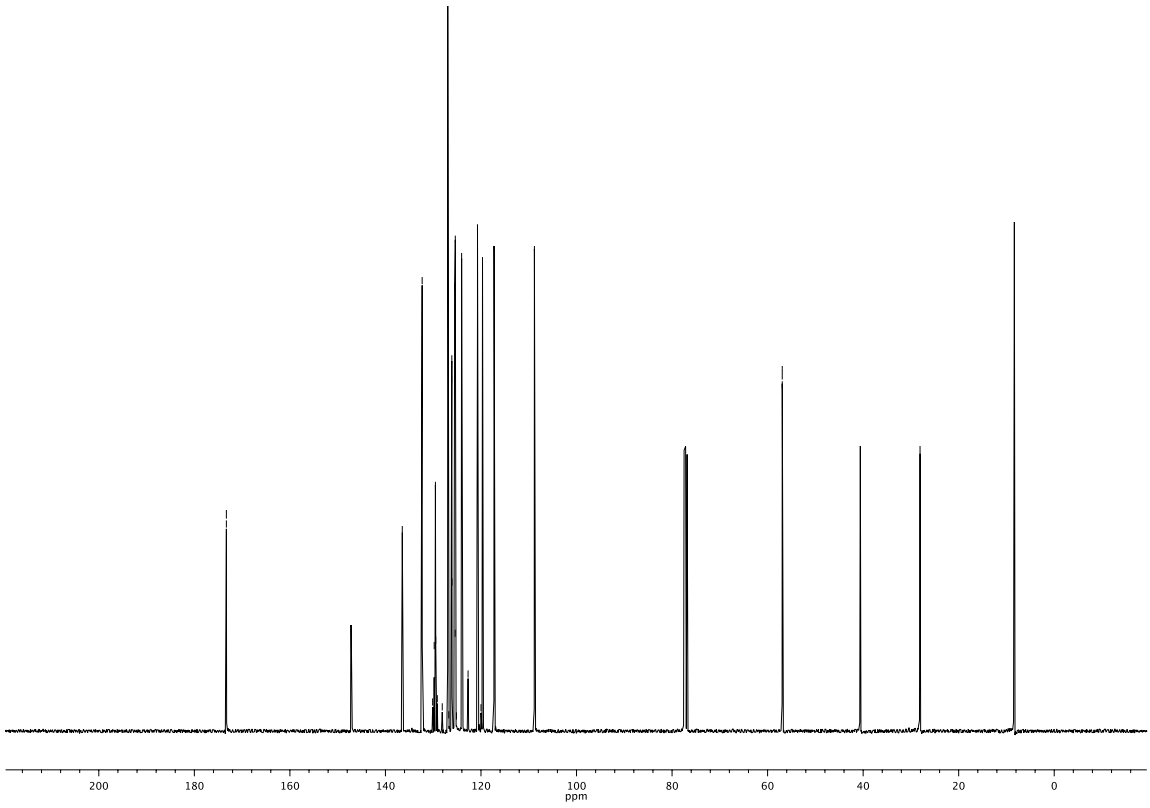



***Figure A5.34*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***41k***.

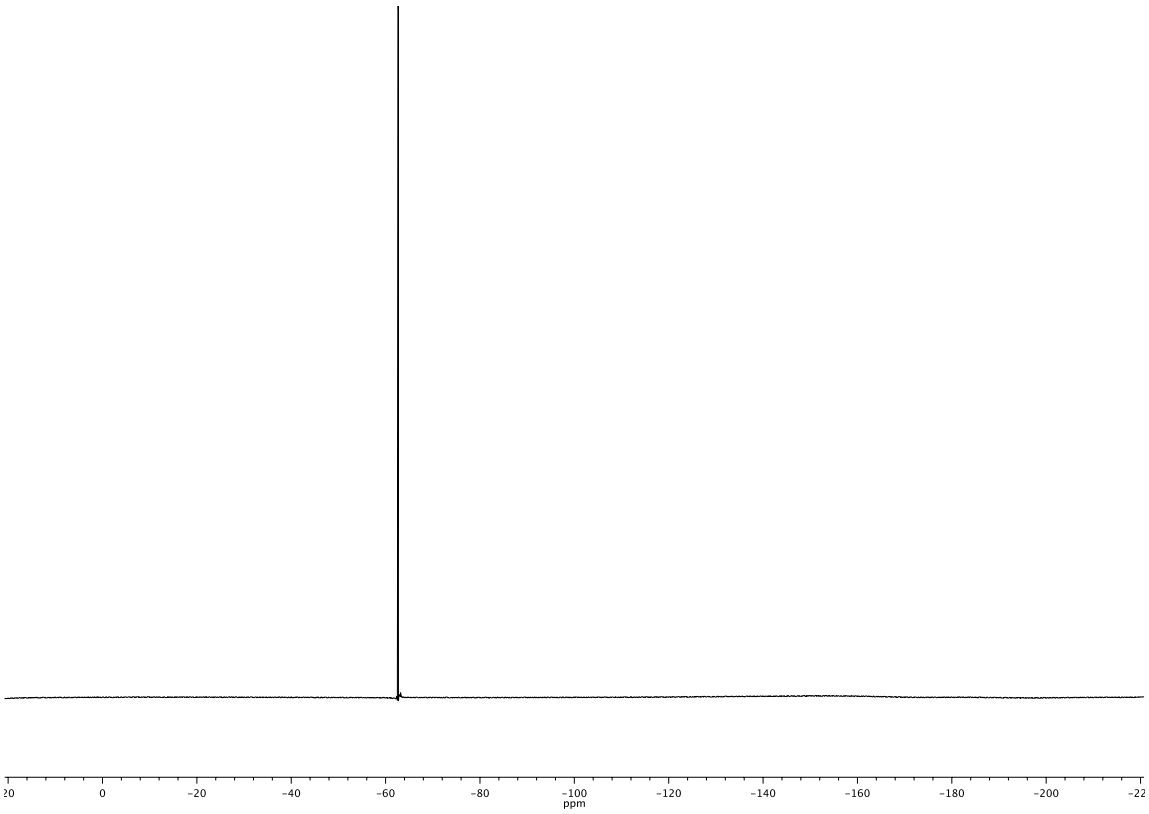
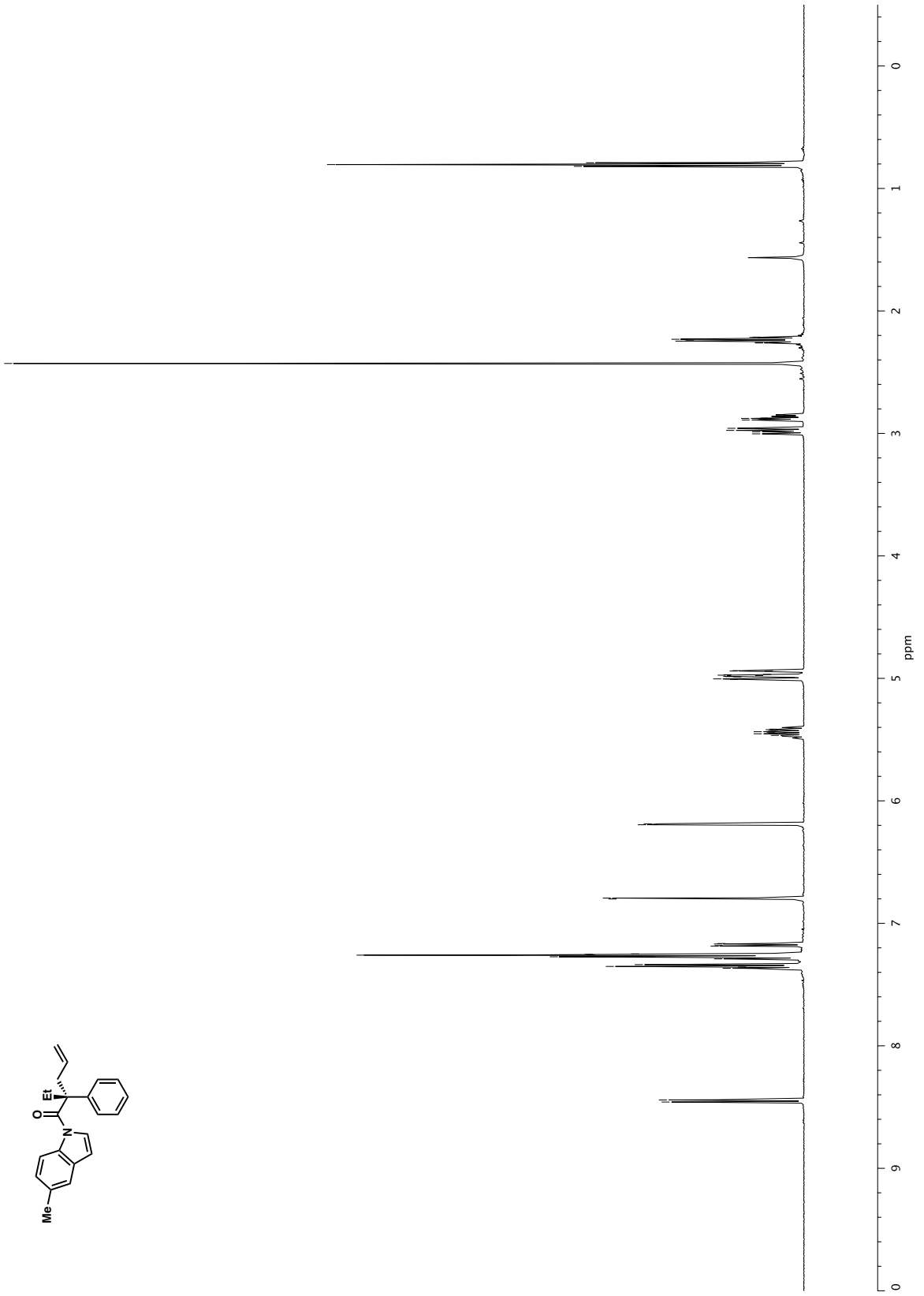



***Figure A5.35*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***41k****.*




***A5.36*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***41l****.*

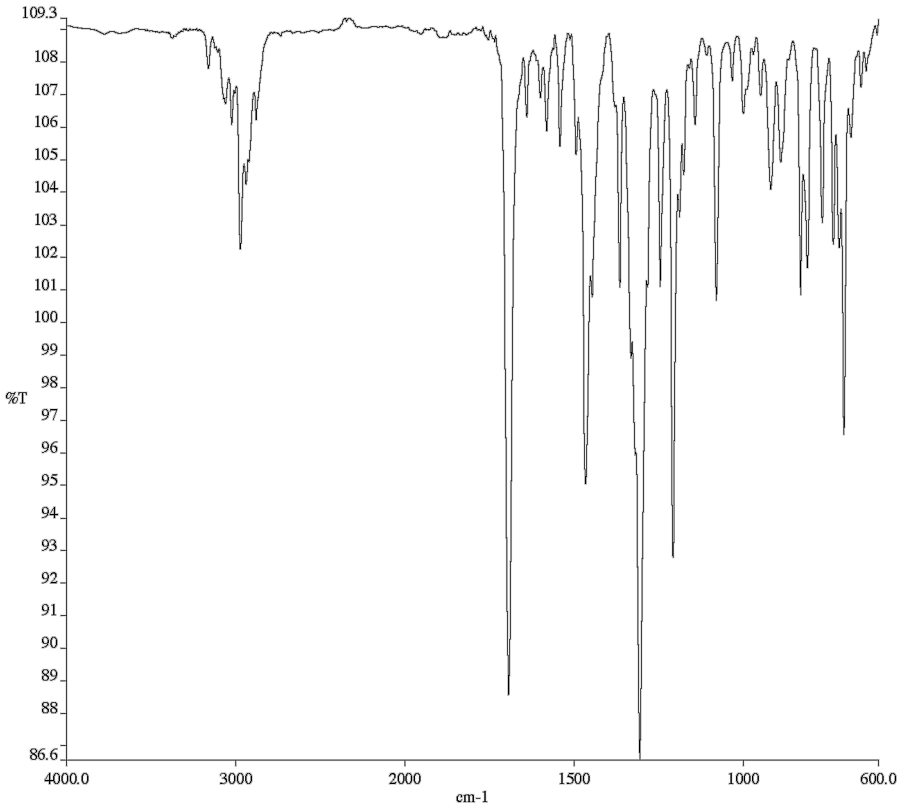



***Figure A5.37*** *Infrared spectrum (Thin Film, NaCl) of compound* ***41l****.*

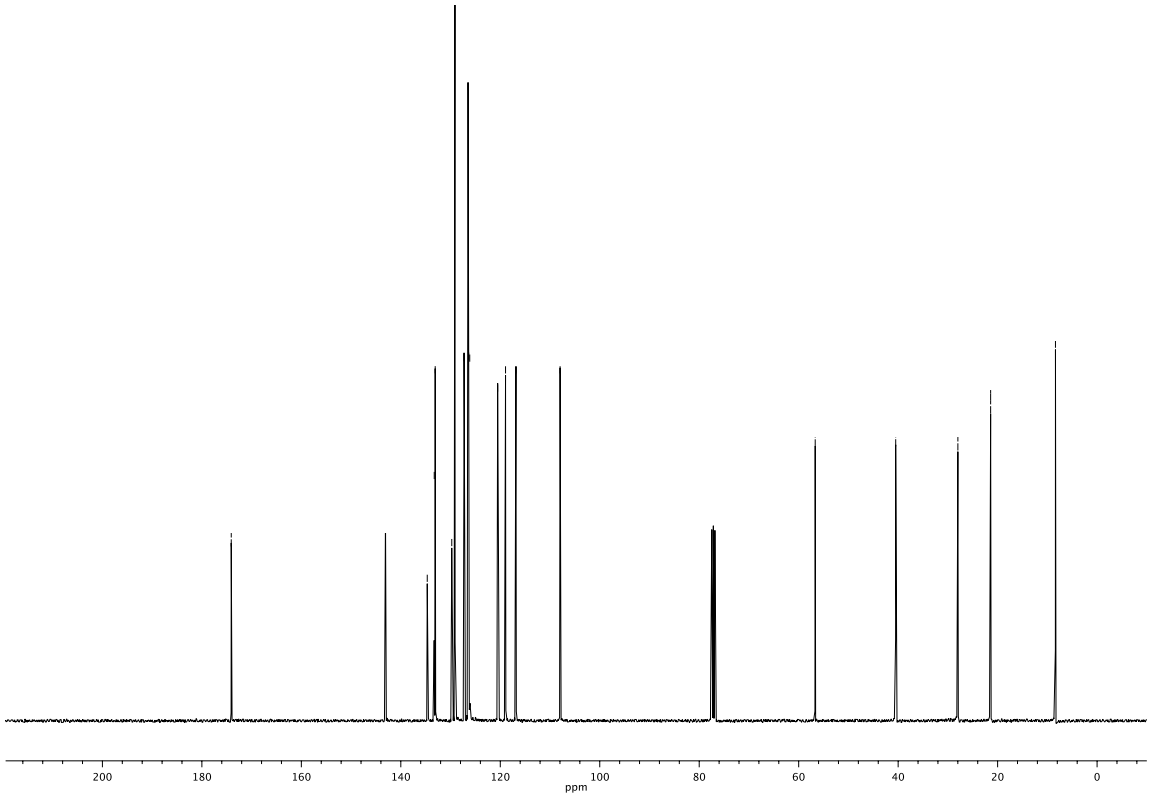
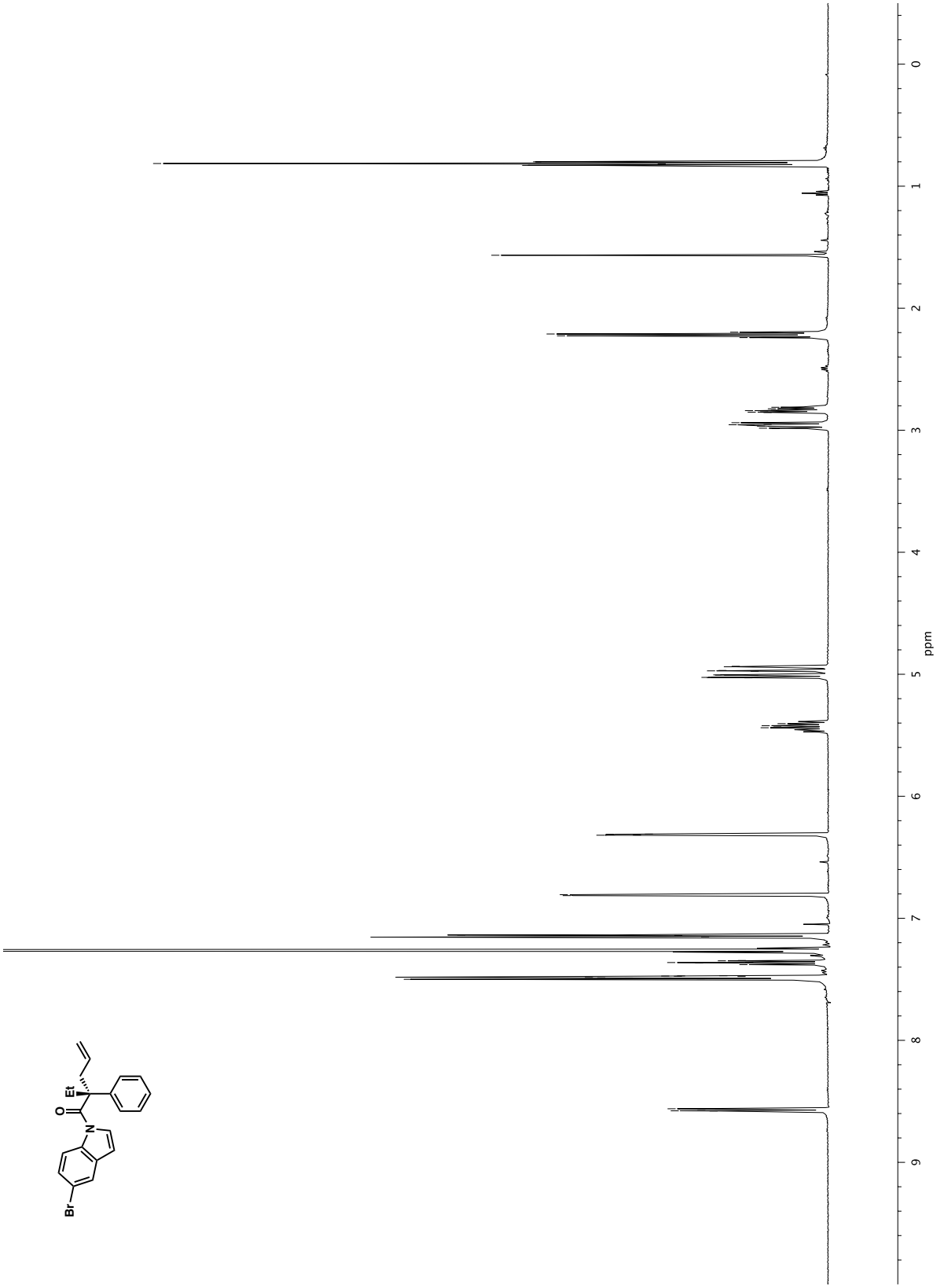



***Figure A5.38*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***41l****.*




***A5.39*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***41m***.

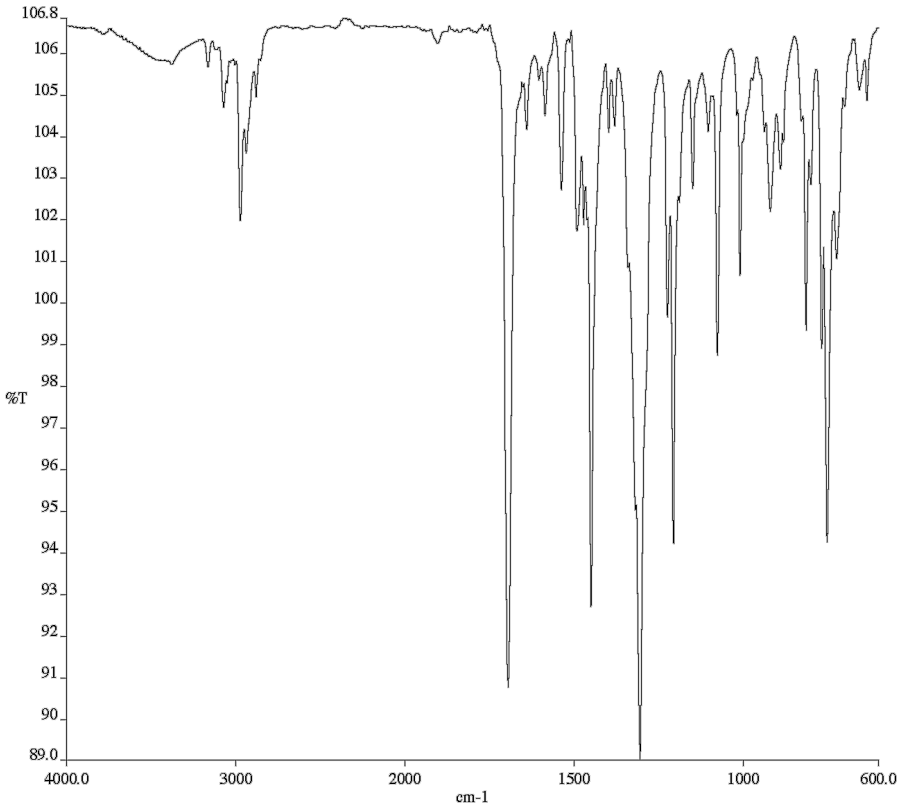



***Figure A5.40*** *Infrared spectrum (Thin Film, NaCl) of compound* ***41m****.*

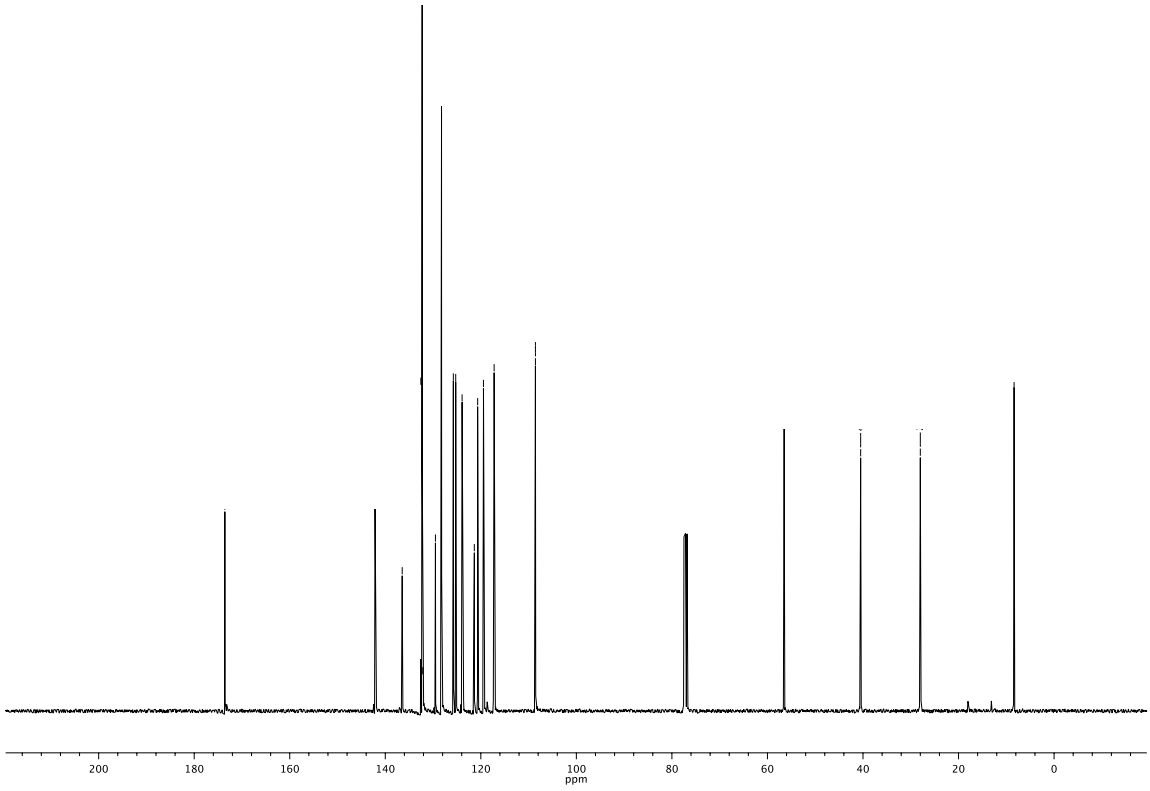
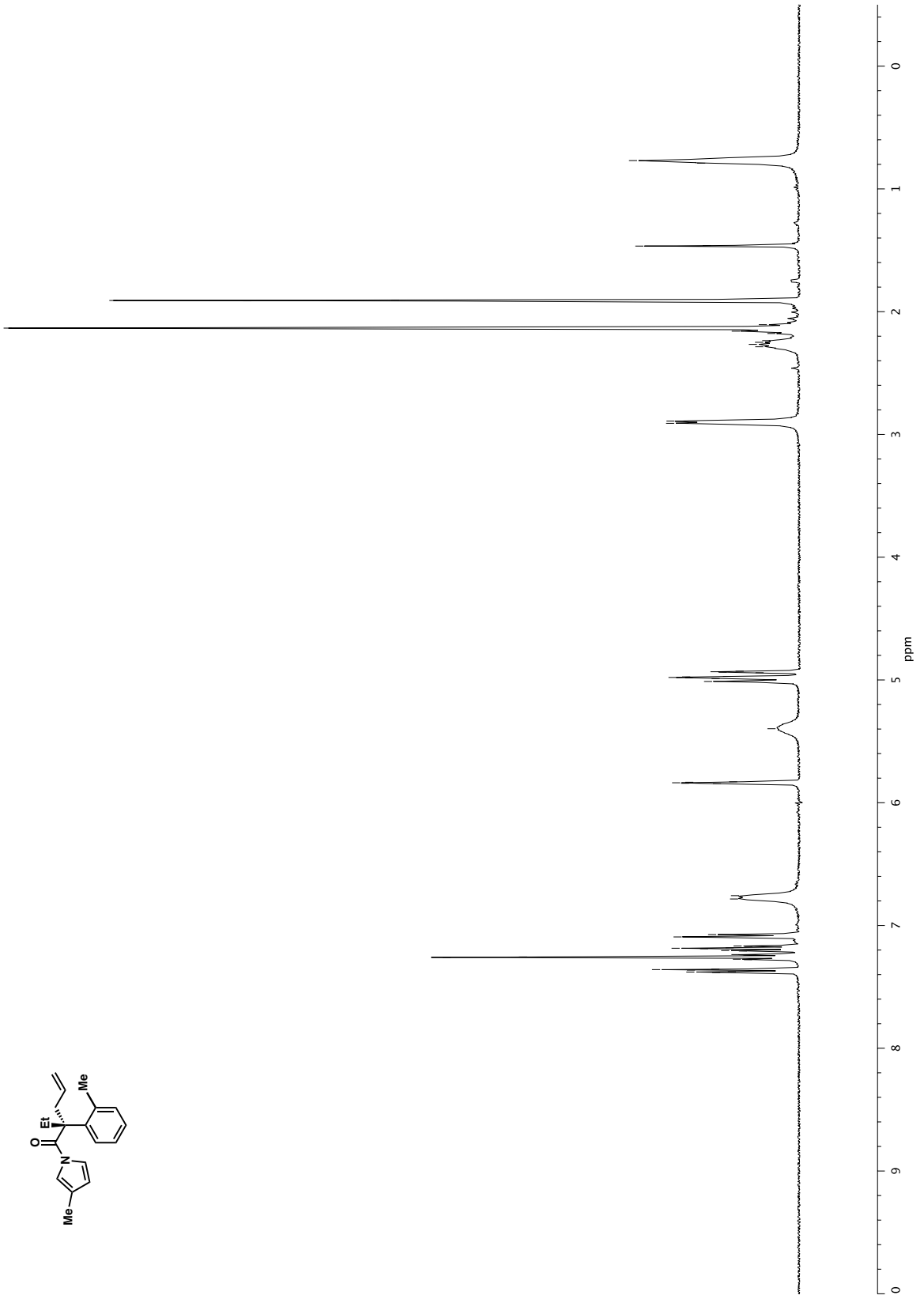



***Figure A5.41*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***41m****.*




***A5.42*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***41n***.

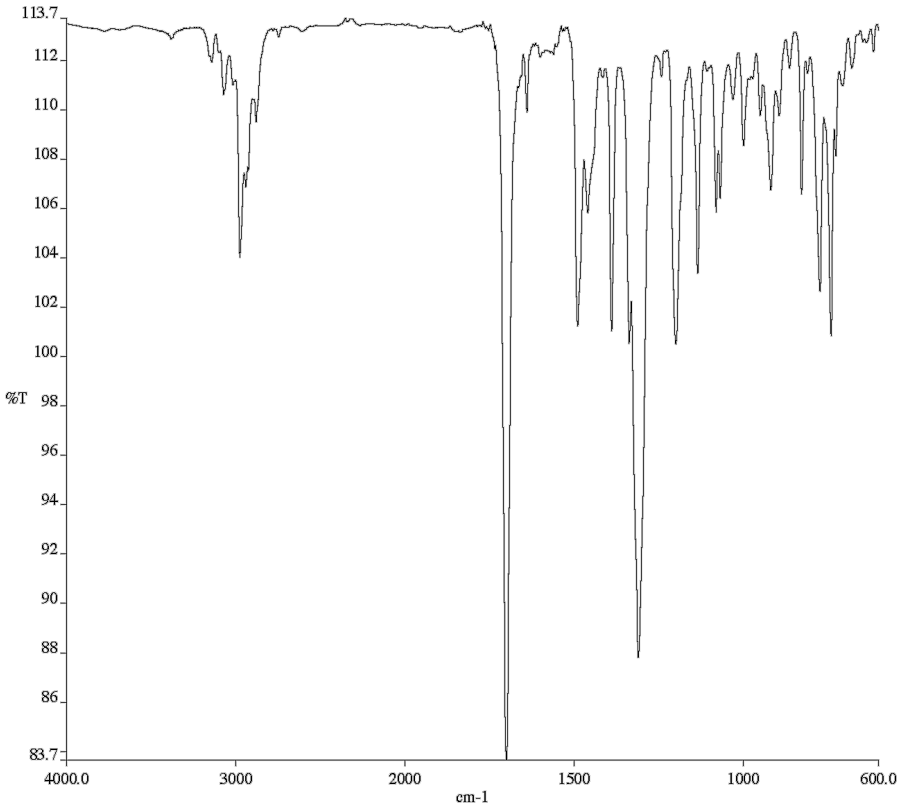



***Figure A5.43*** *Infrared spectrum (Thin Film, NaCl) of compound* ***41n***.

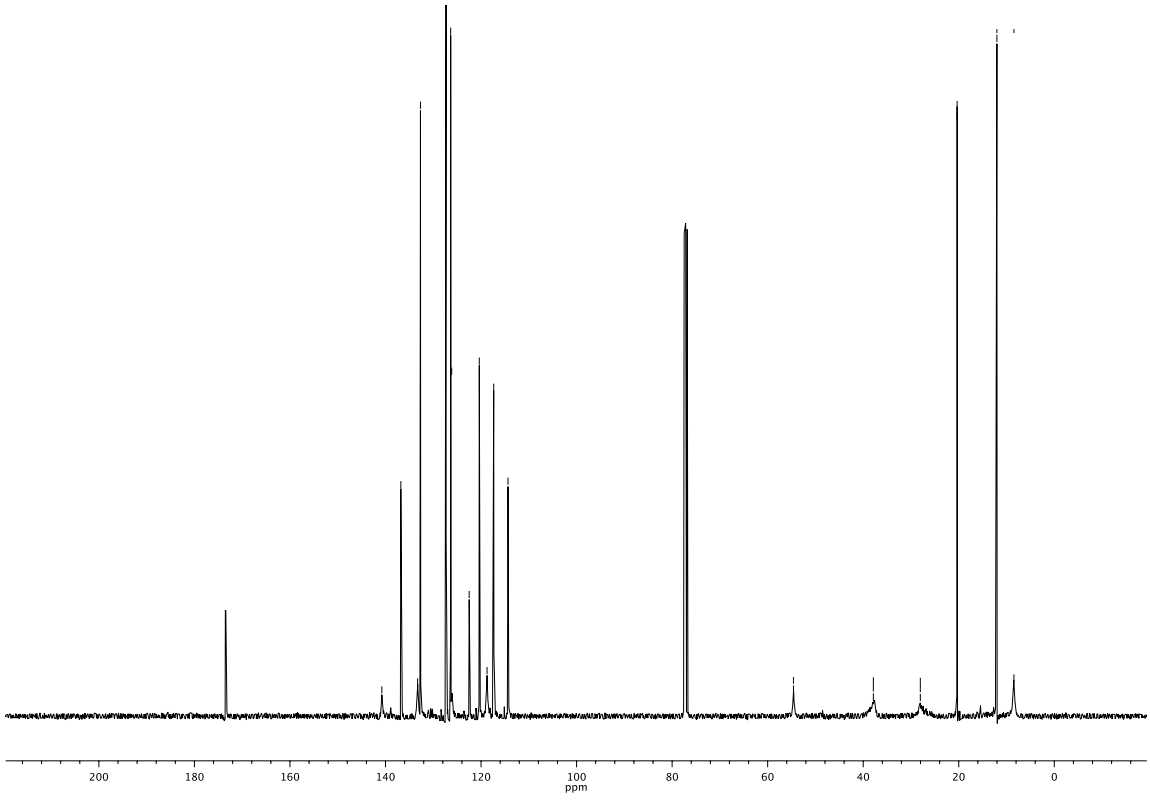
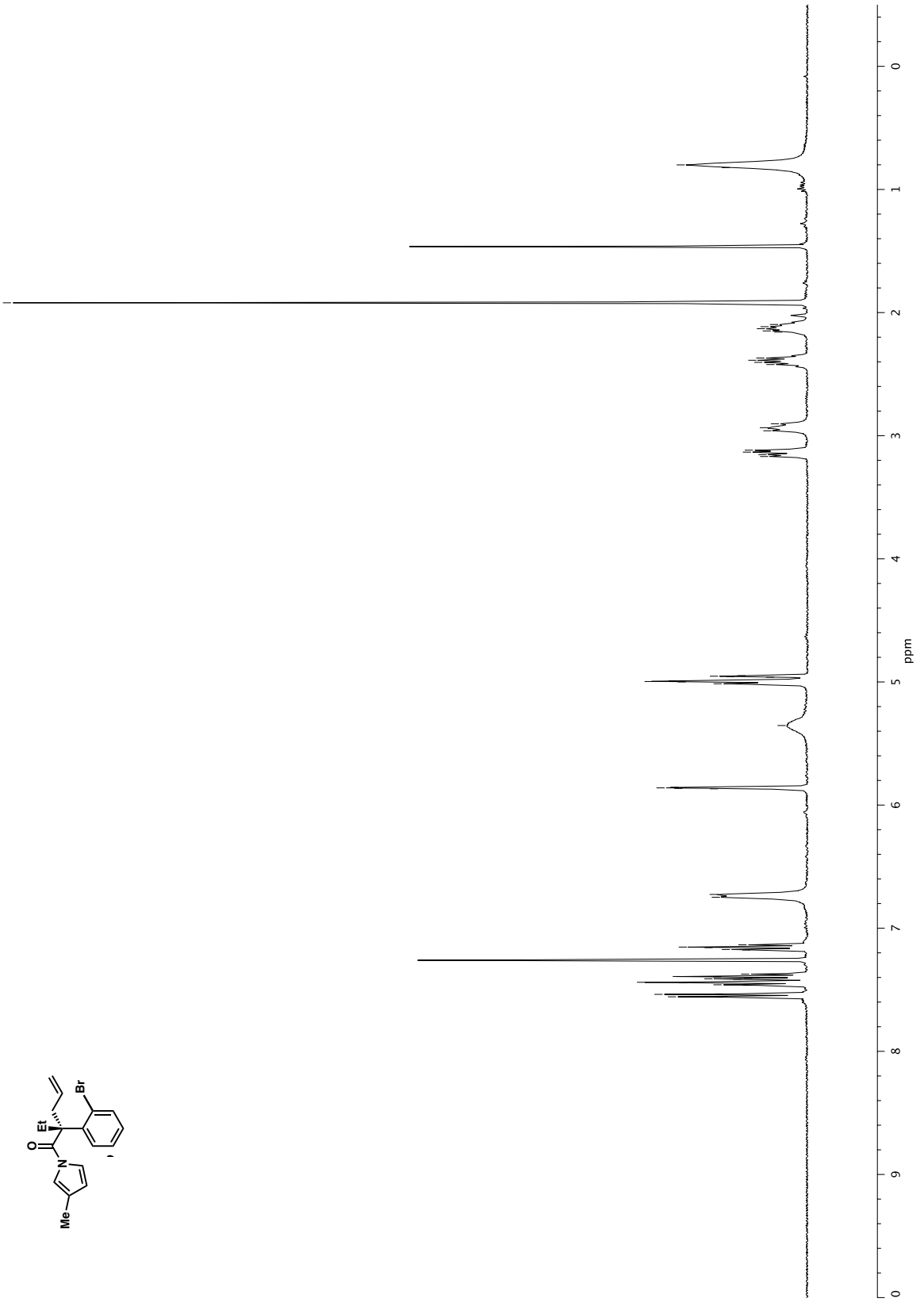



***Figure A5.44*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***41n***.




***A5.45*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***41o*** *at 50 °C.*

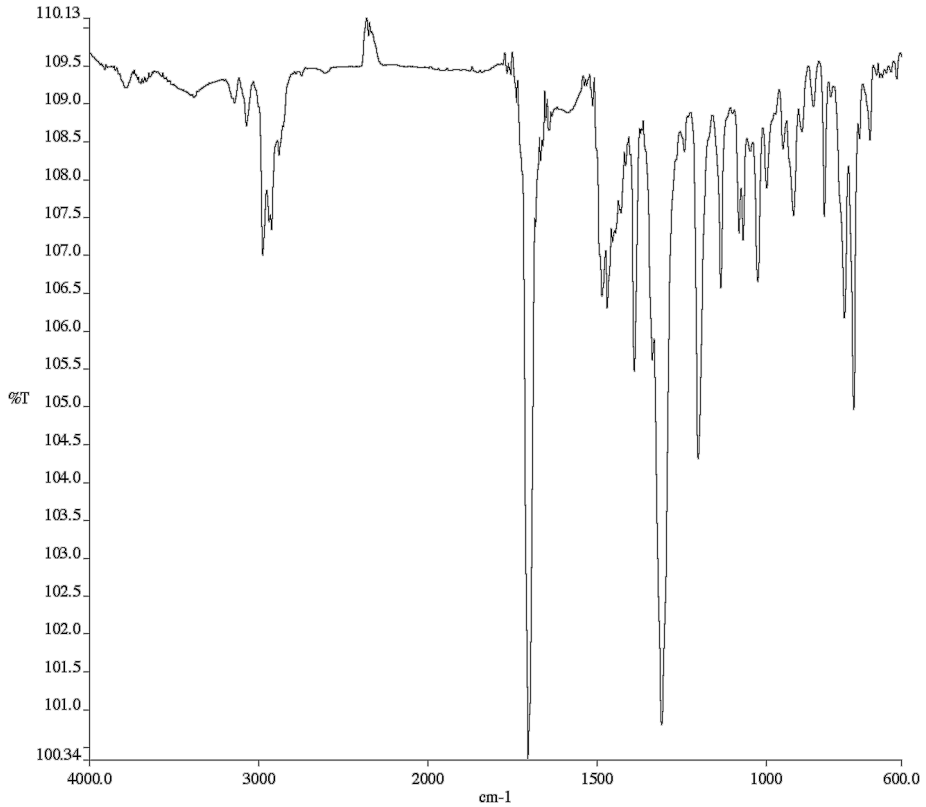



***Figure A5.46*** *Infrared spectrum (Thin Film, NaCl) of compound* ***41o****.*

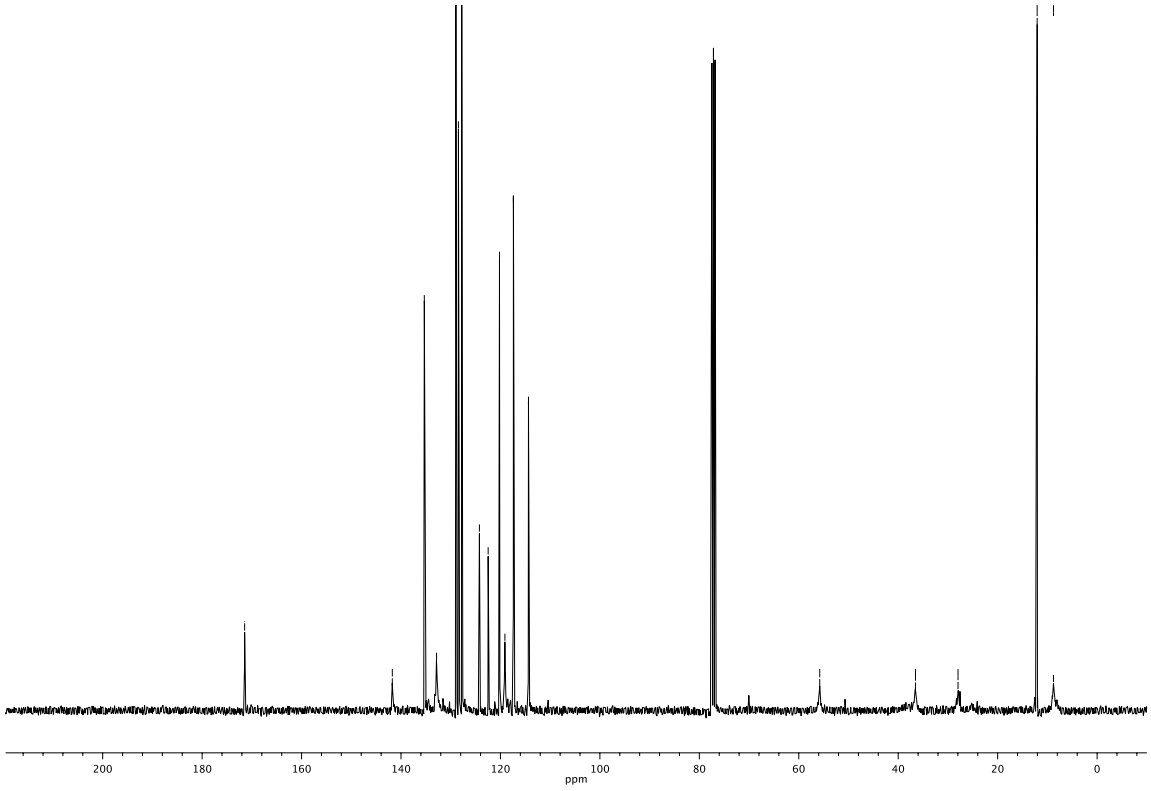
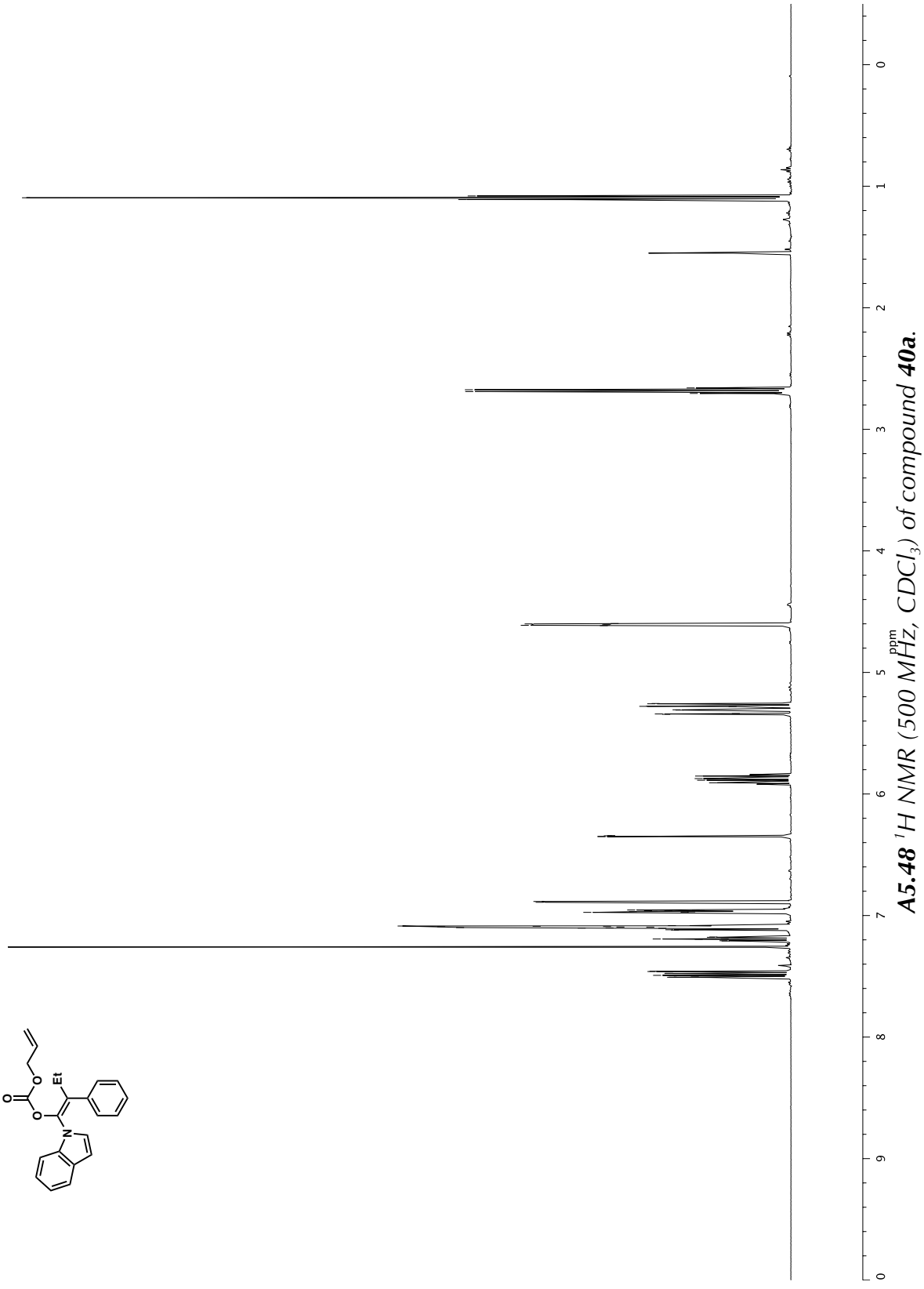



***Figure A5.47*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***41o****.*




***A5.48*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***40a***.

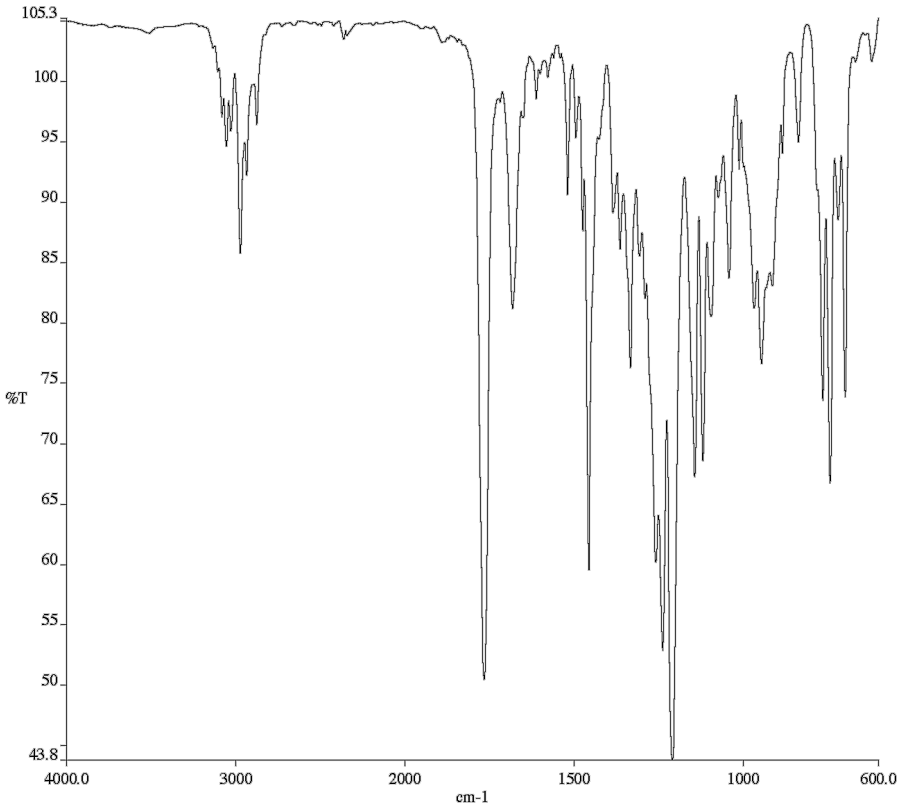



***Figure A5.49*** *Infrared spectrum (Thin Film, NaCl) of compound* ***40a***.

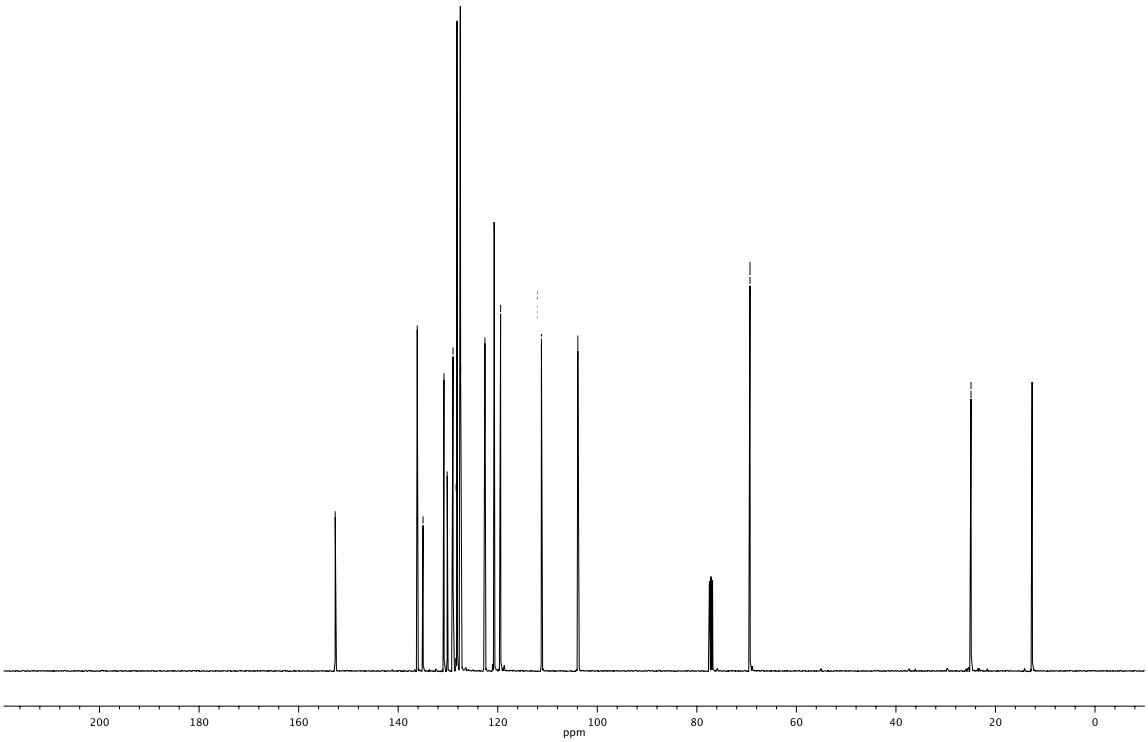
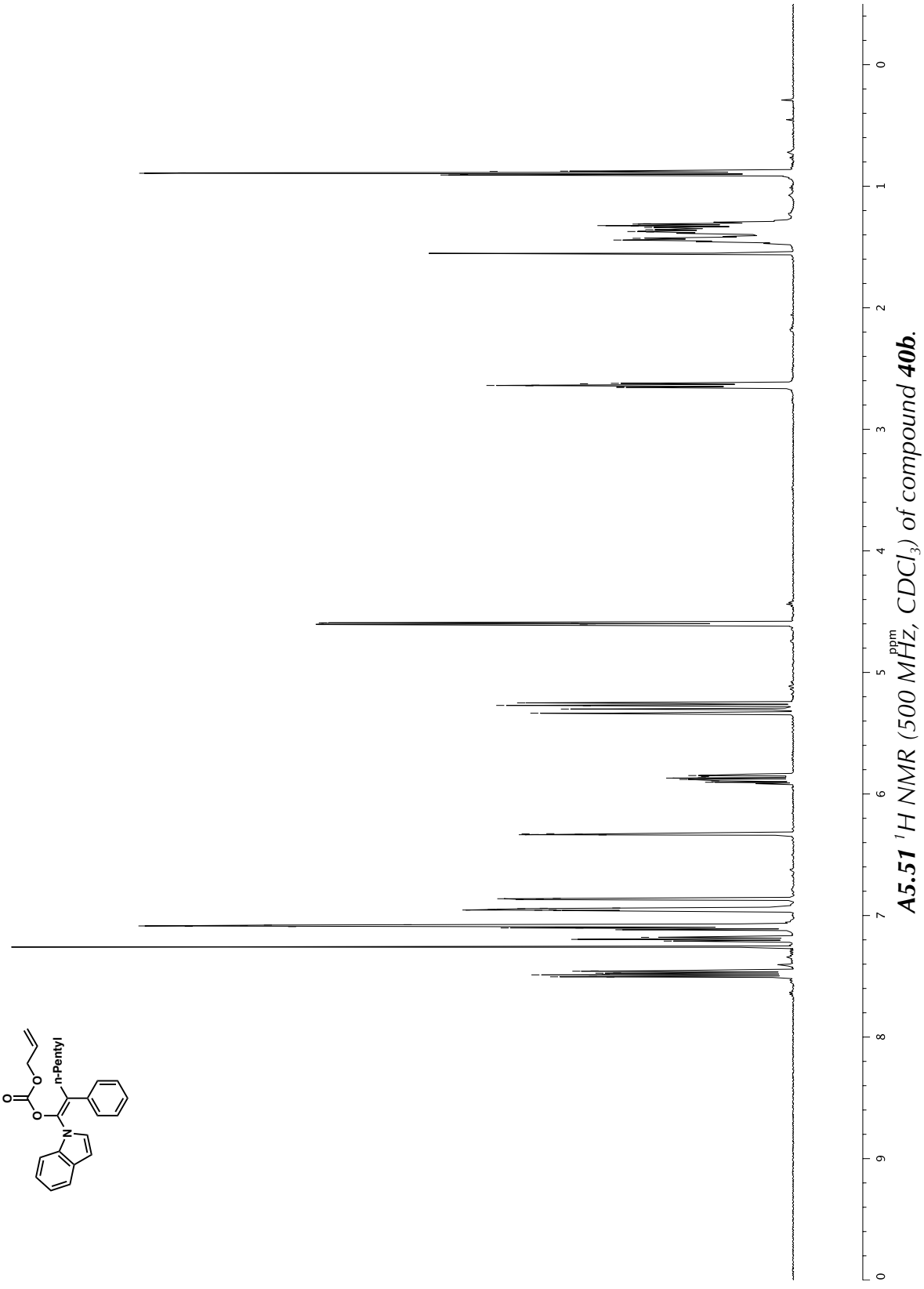



***Figure A5.50*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***40a***.




***A5.51*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***40b***.

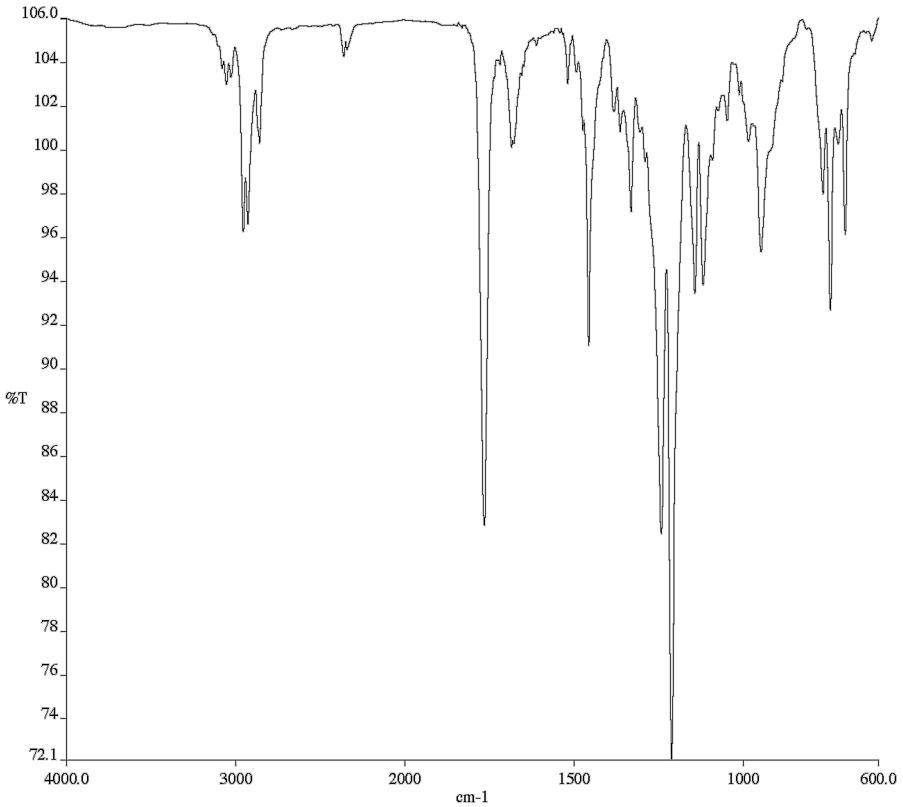



***Figure A5.52*** *Infrared spectrum (Thin Film, NaCl) of compound* ***40b****.*

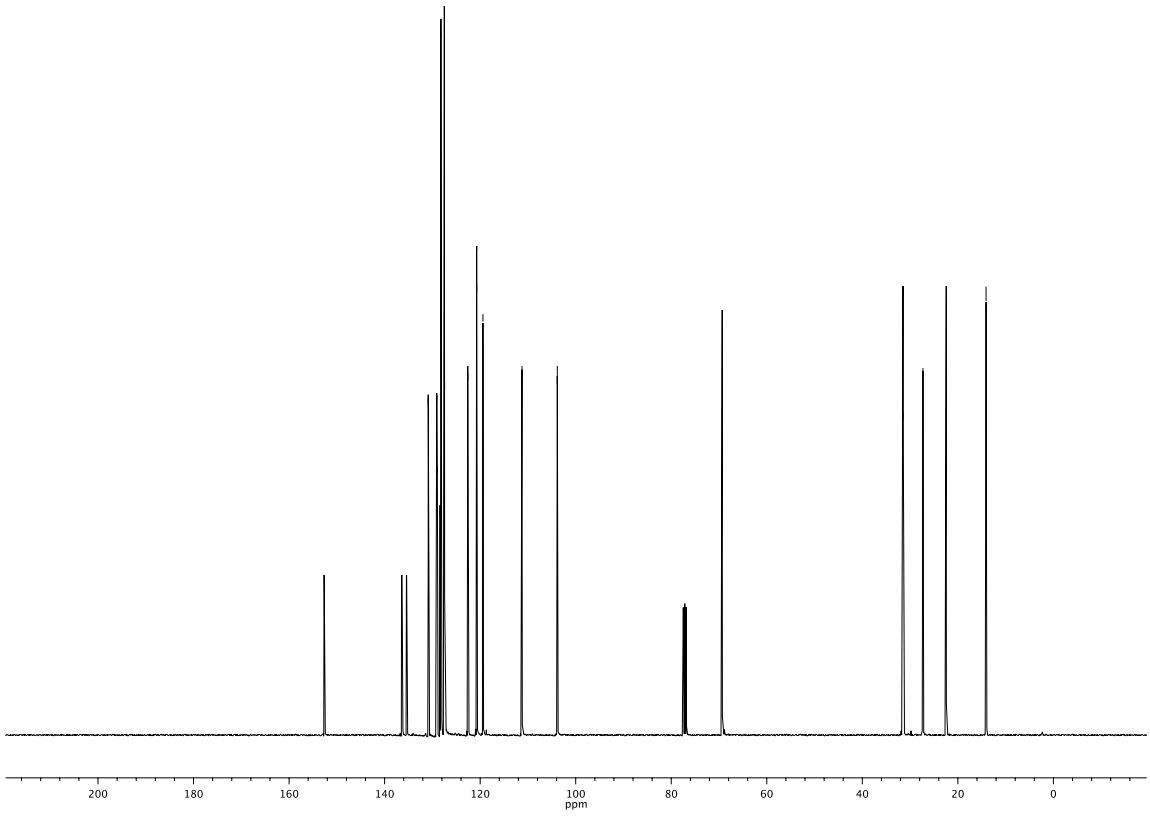
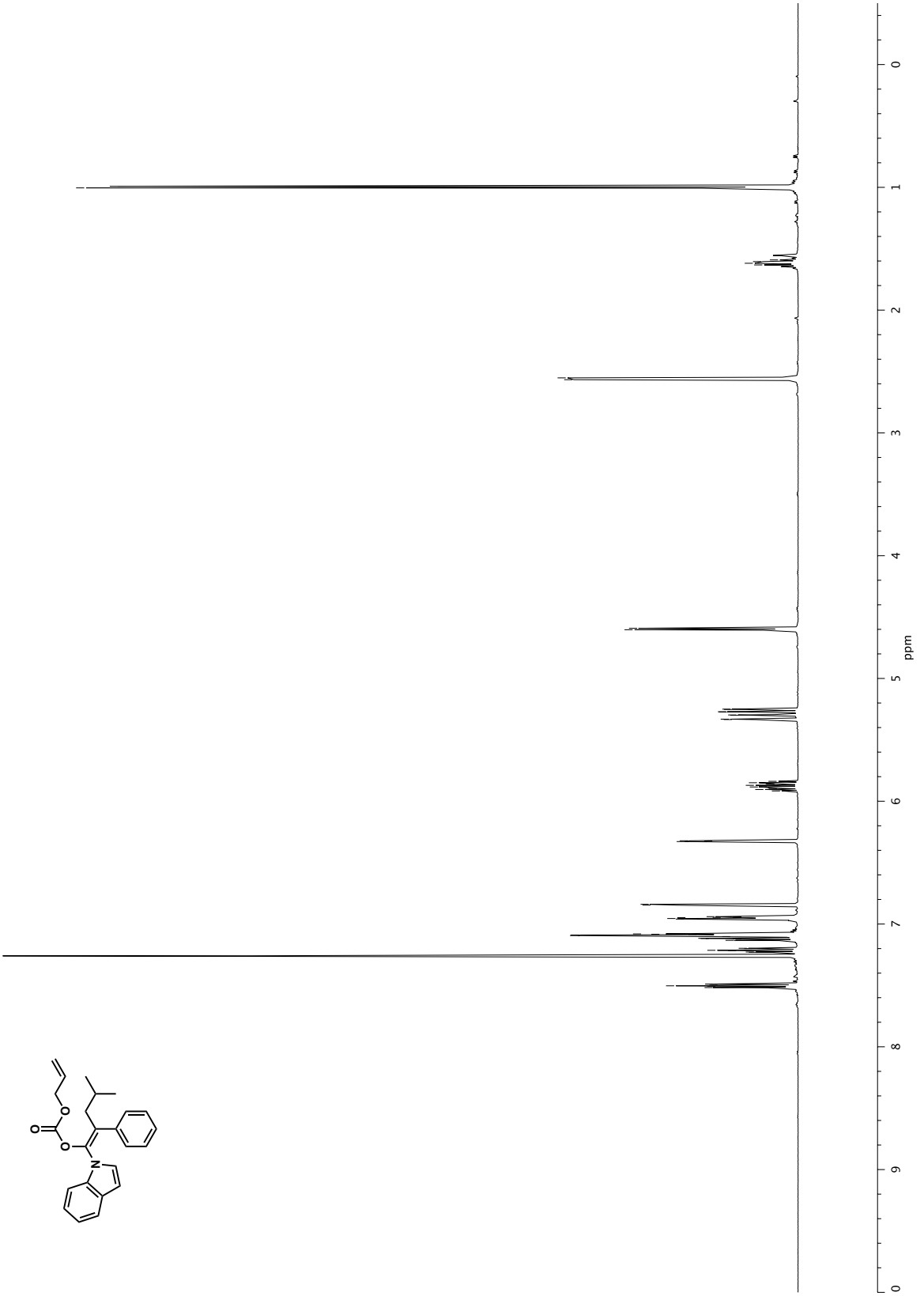



***Figure A5.53*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***40b****.*




***A5.54*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***40c****.*

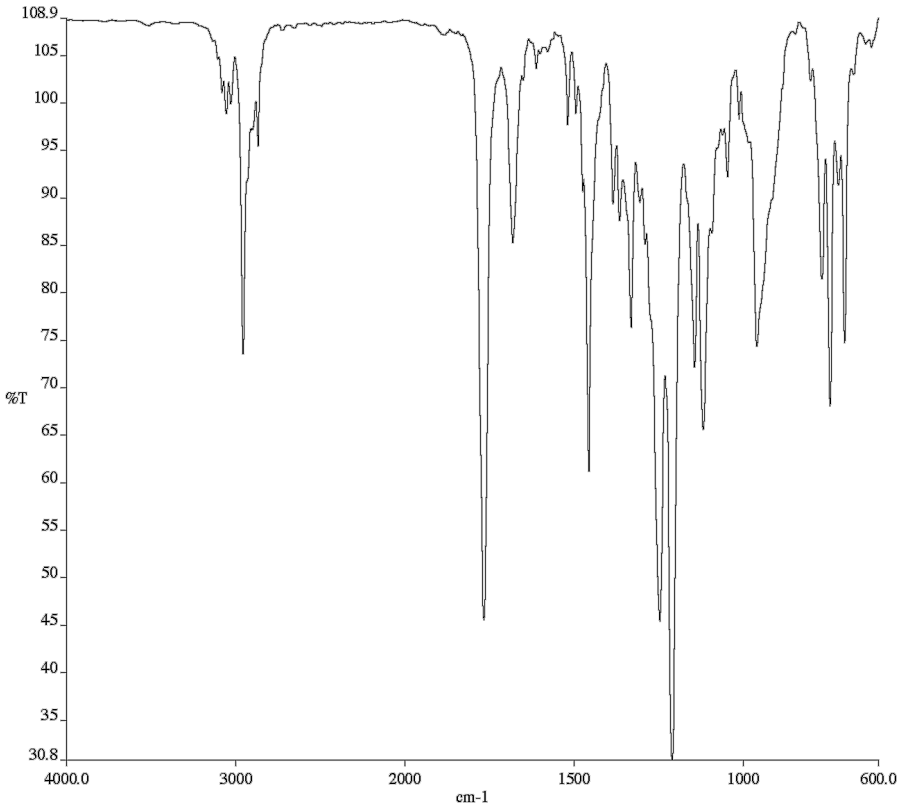



***Figure A5.55*** *Infrared spectrum (Thin Film, NaCl) of compound* ***40c****.*

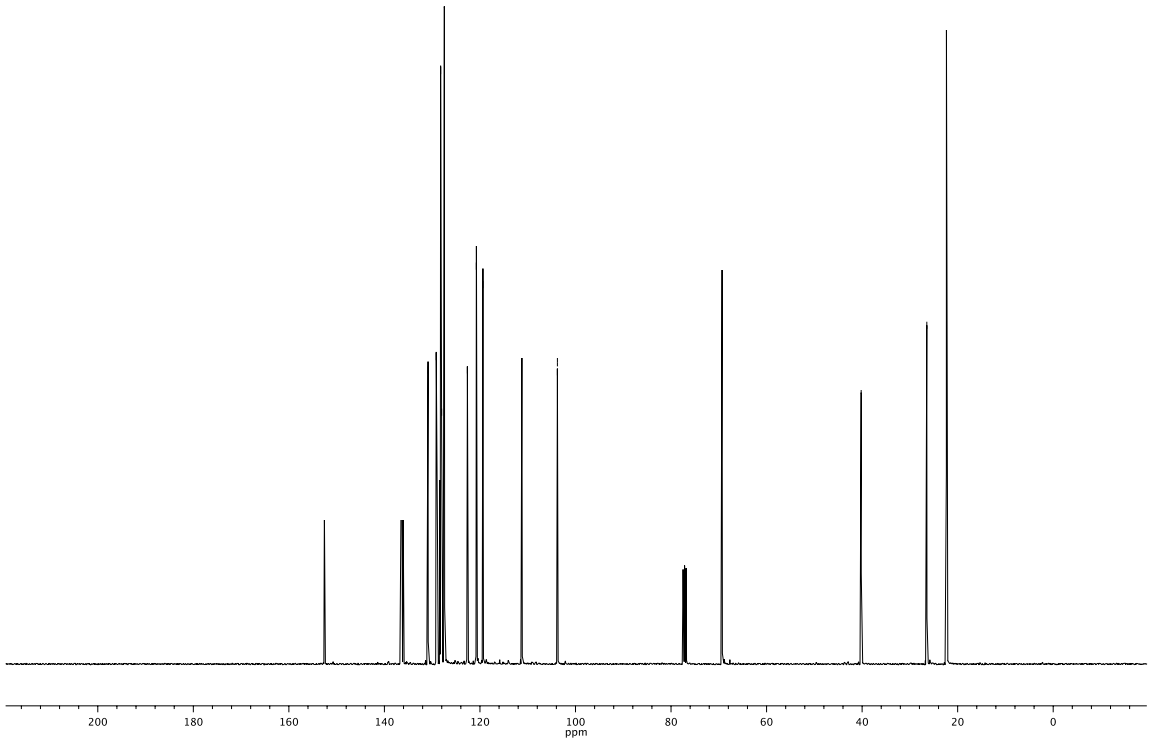
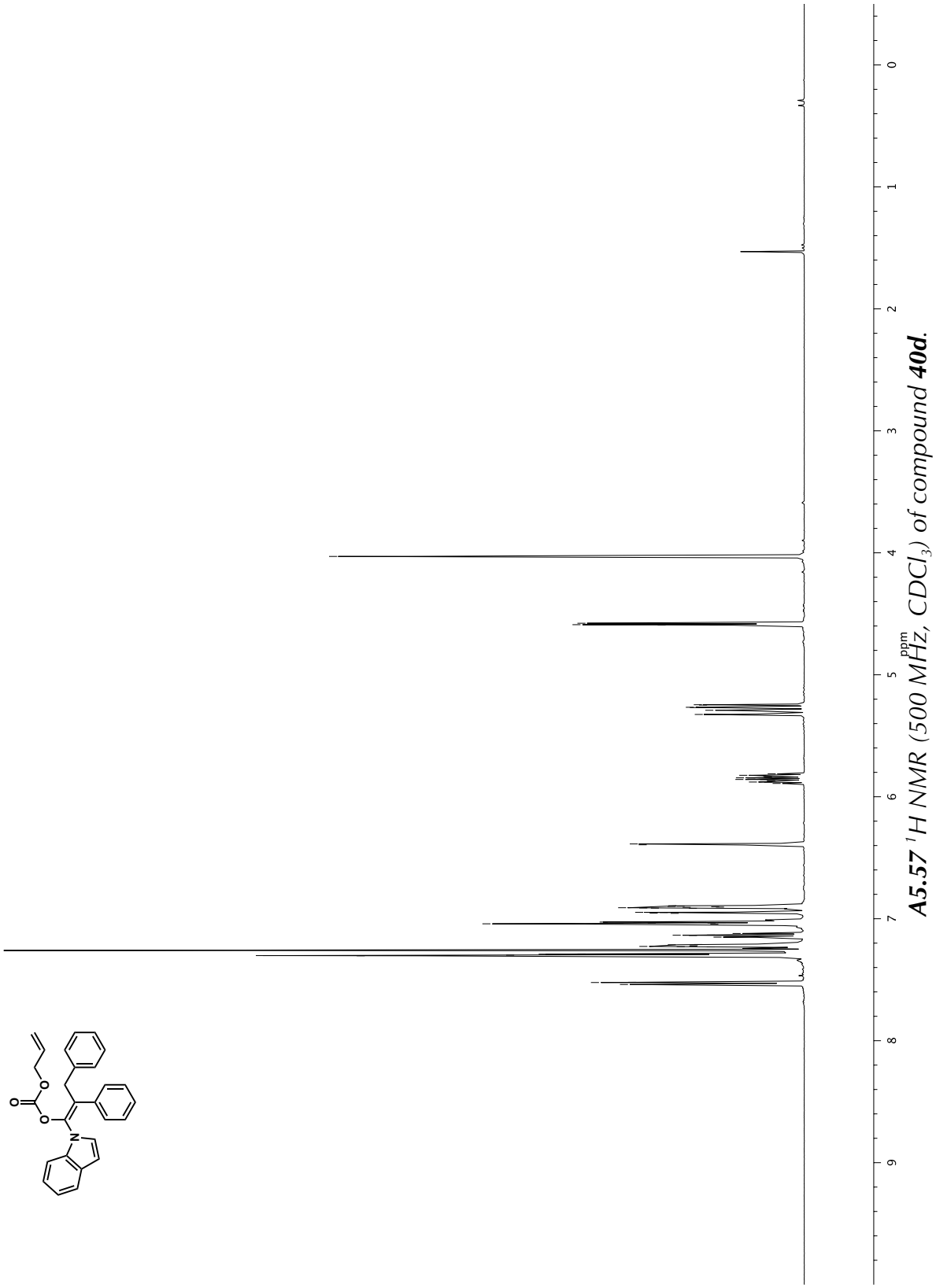



***Figure A5.56*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***40c****.*




***A5.57*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***40d***.

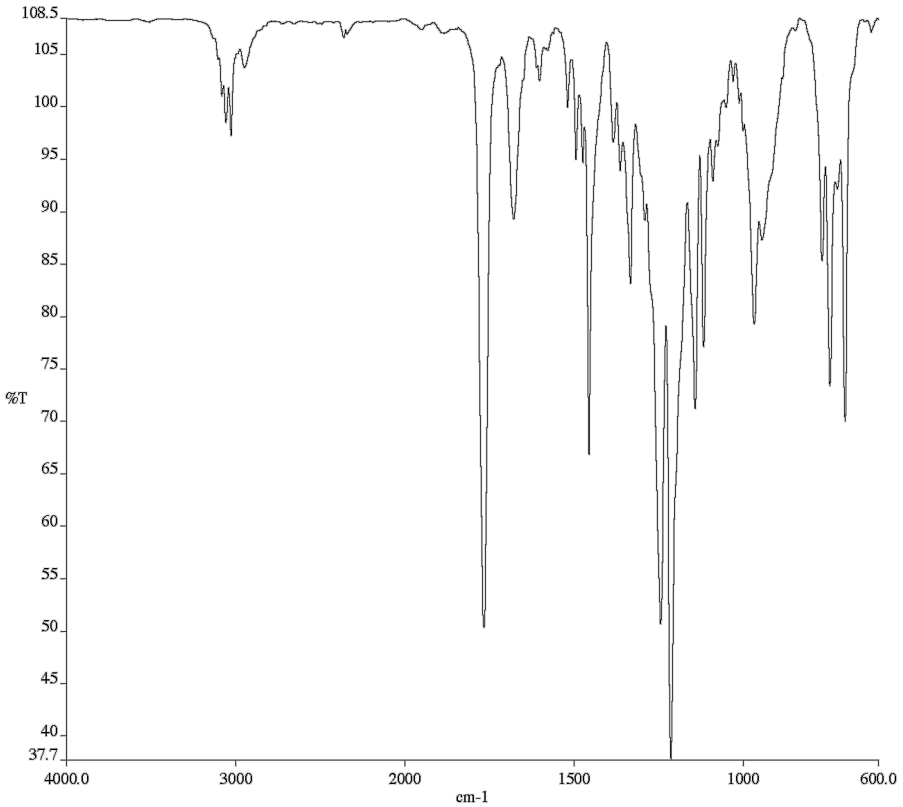



***Figure A5.58*** *Infrared spectrum (Thin Film, NaCl) of compound* ***40d****.*

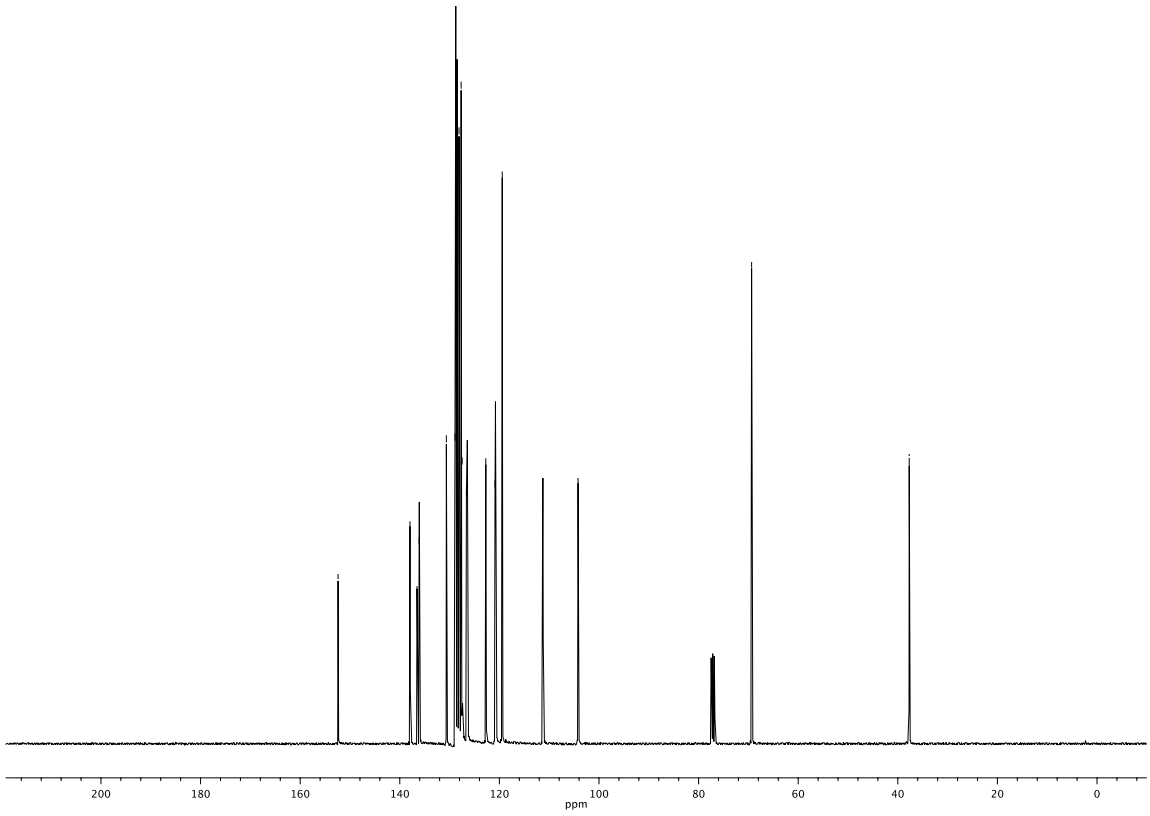
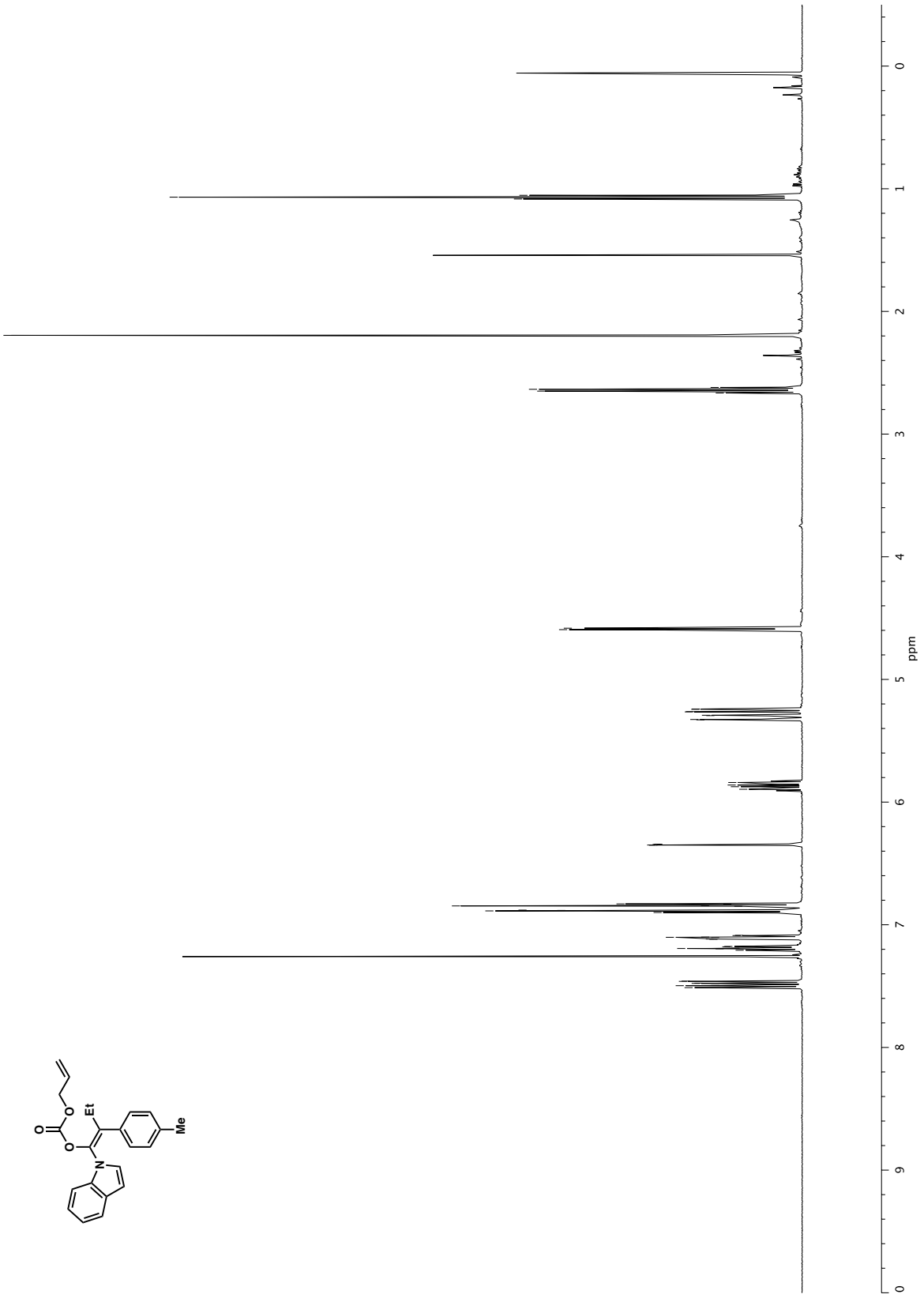



***Figure A5.59*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***40d****.*




***A5.60*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***40e***.

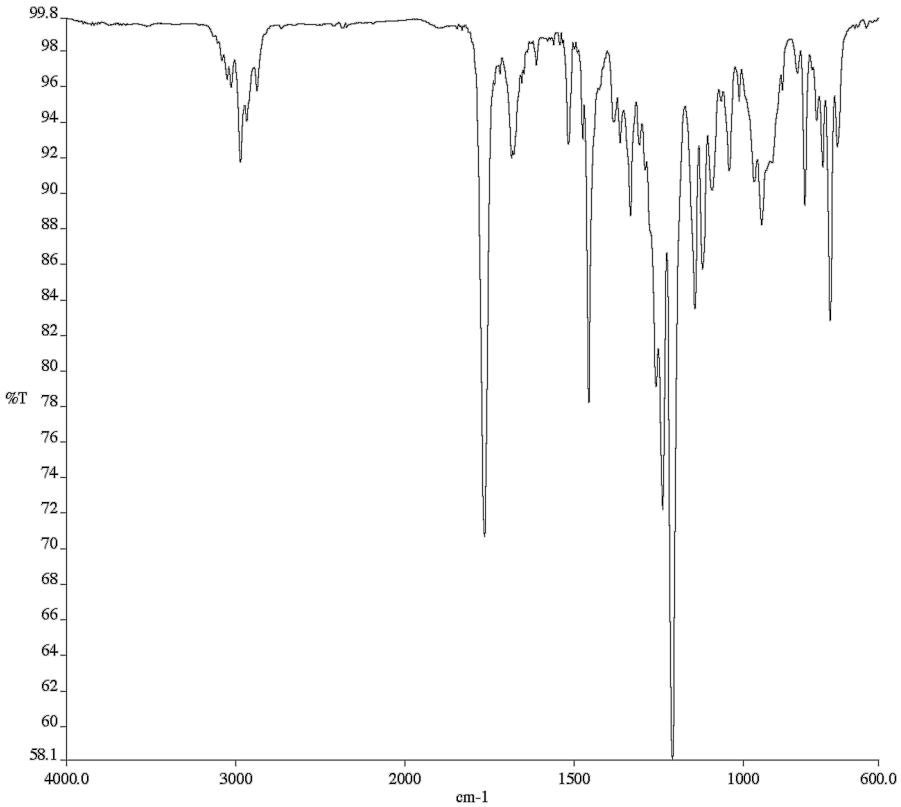



***Figure A5.61*** *Infrared spectrum (Thin Film, NaCl) of compound* ***40e***.

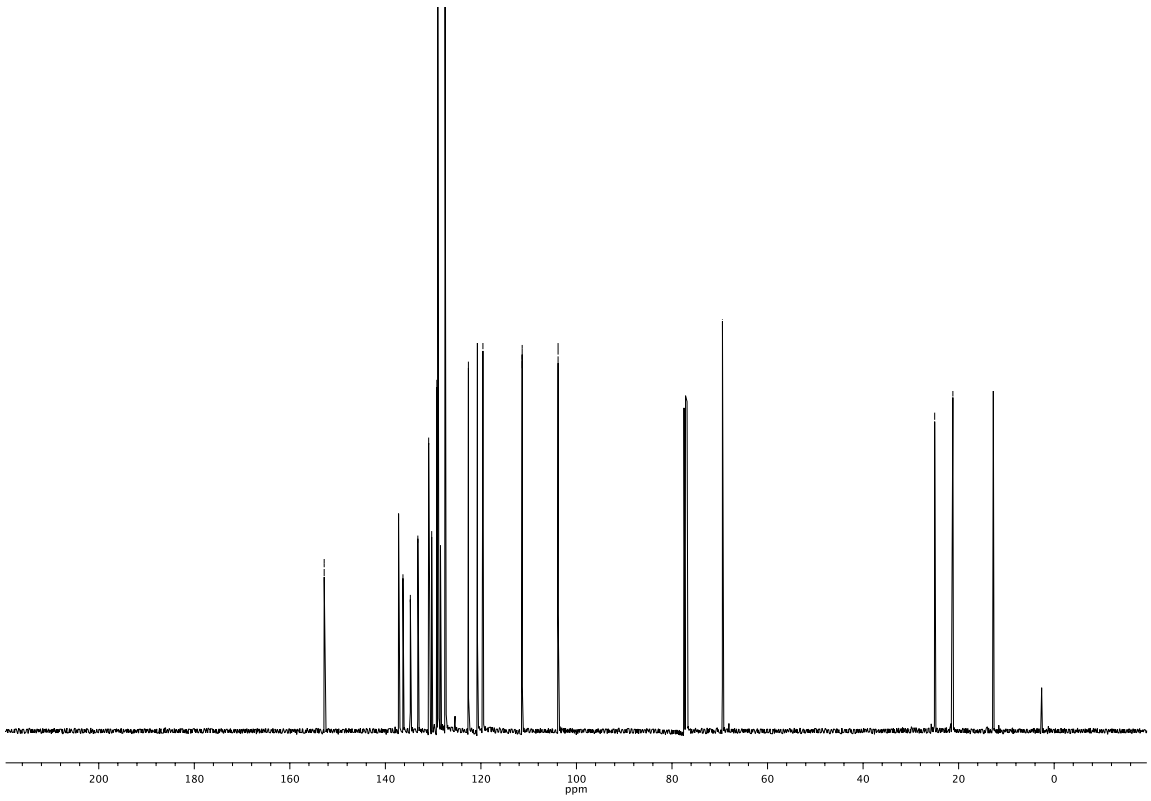
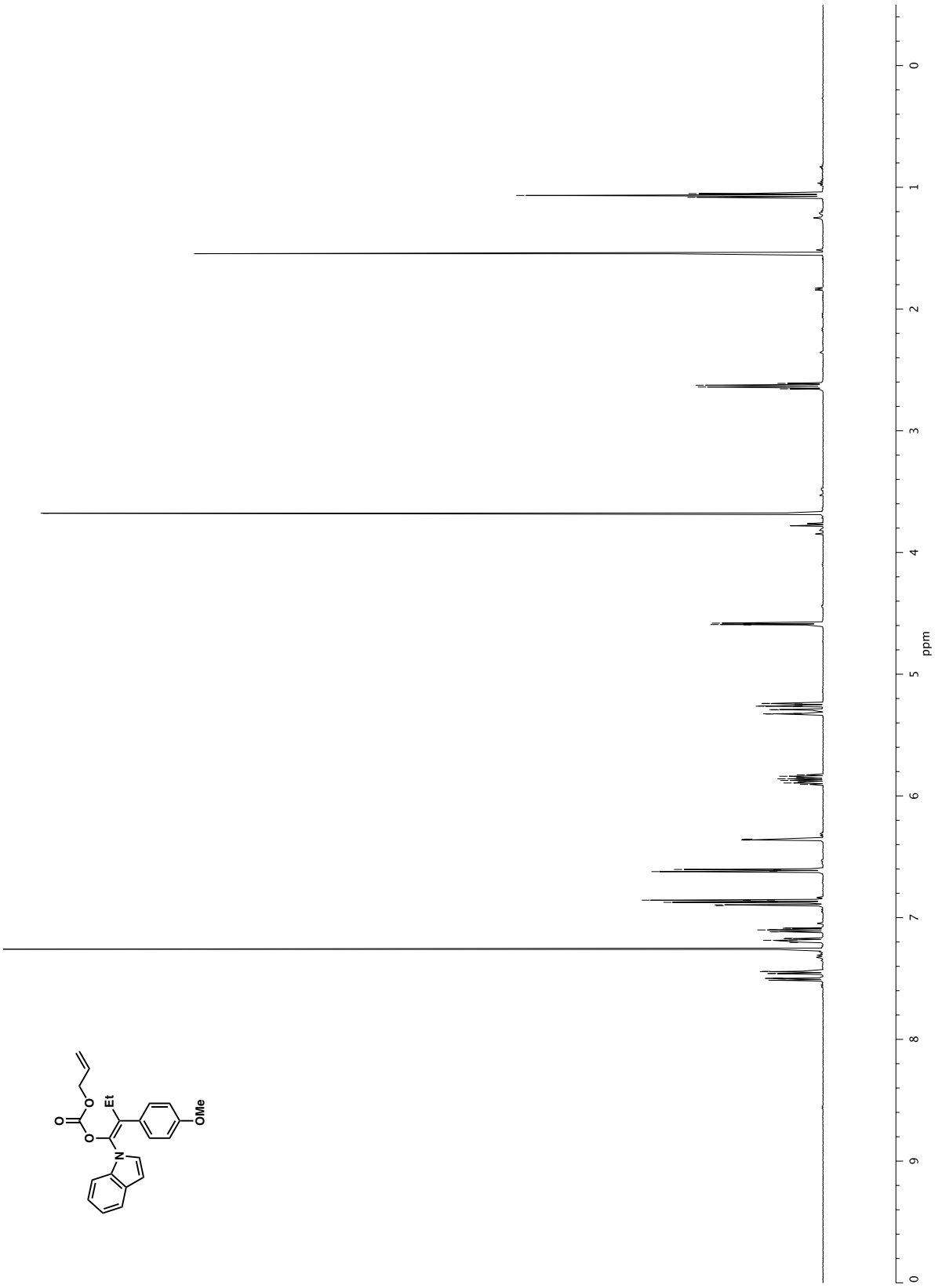



***Figure A5.62*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***40e***.




***A5.63*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***40f****.*

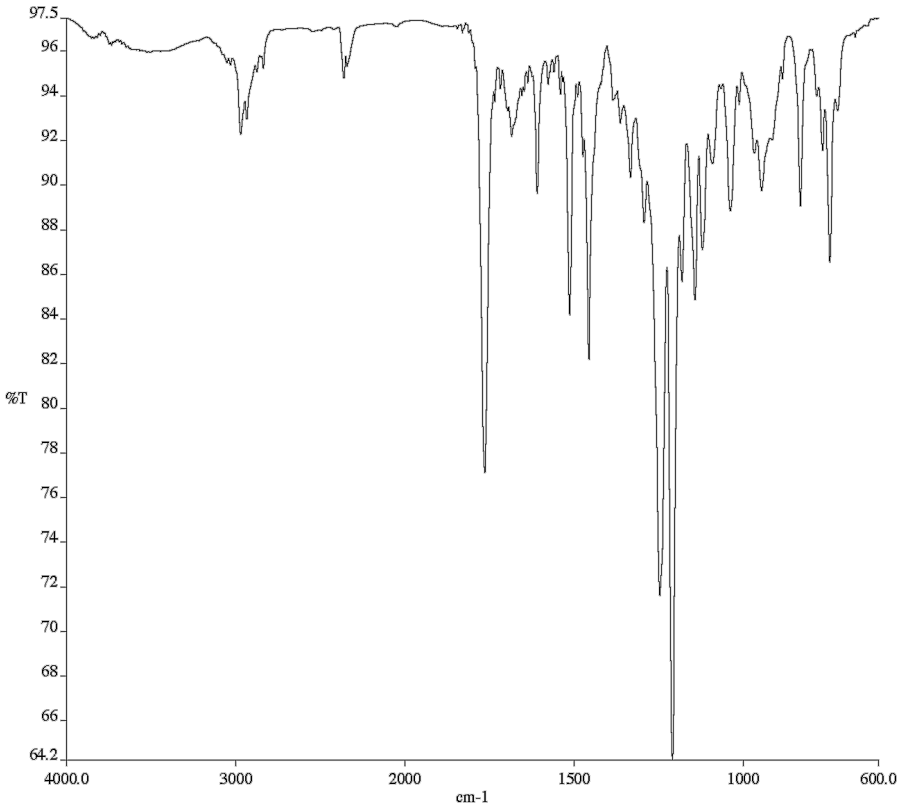



***Figure A5.64*** *Infrared spectrum (Thin Film, NaCl) of compound* ***40f****.*

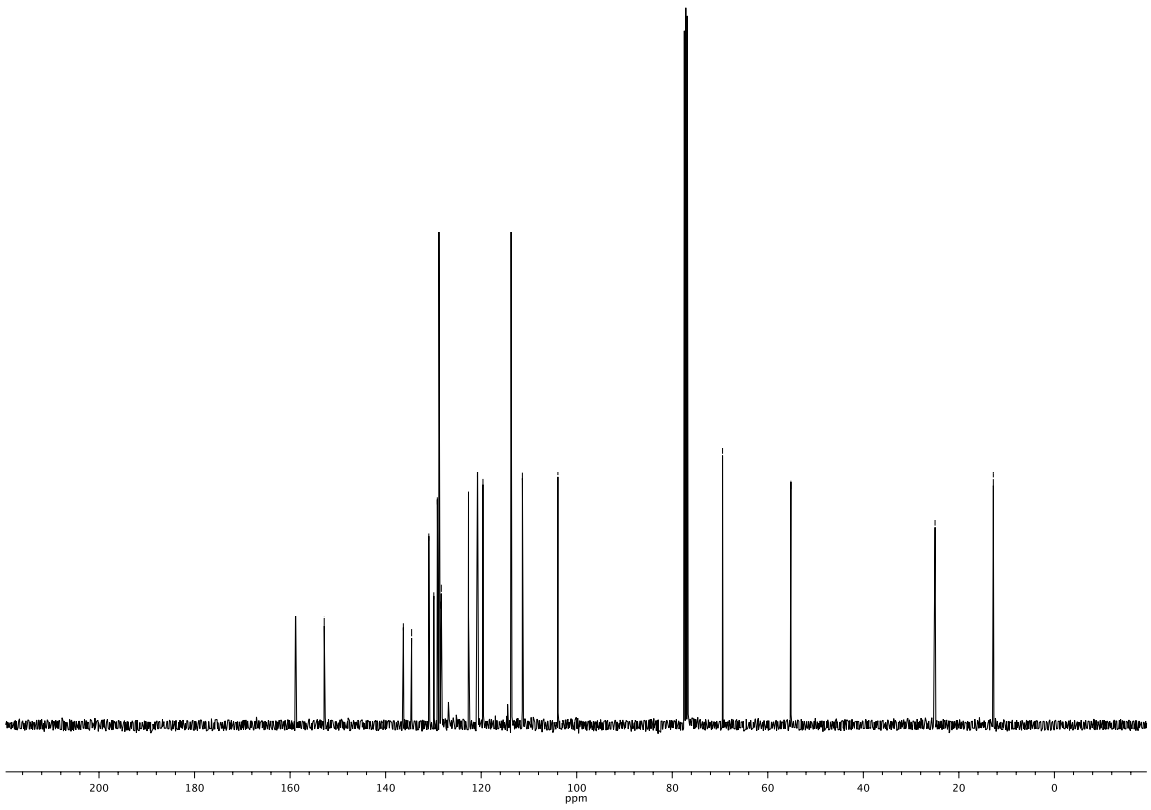
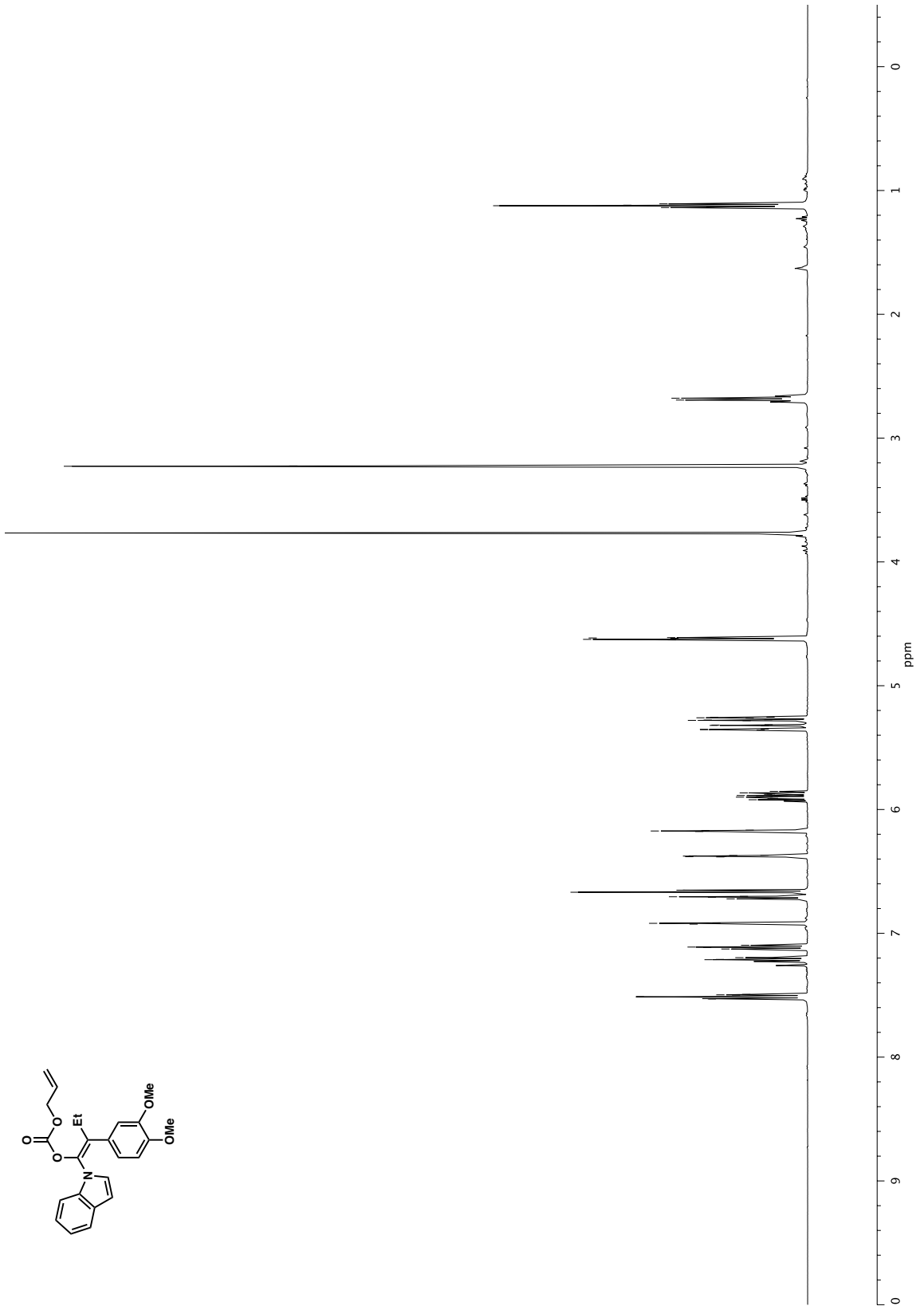



***Figure A5.65*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***40f****.*




***A5.66*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***40g***.

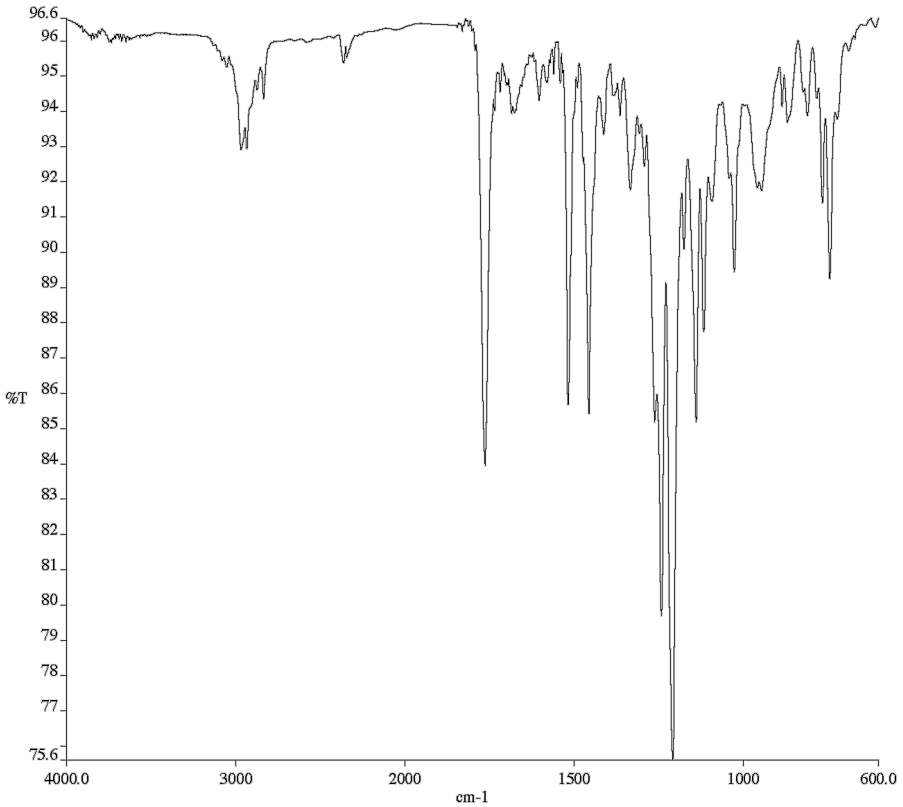



***Figure A5.67*** *Infrared spectrum (Thin Film, NaCl) of compound* ***40g****.*

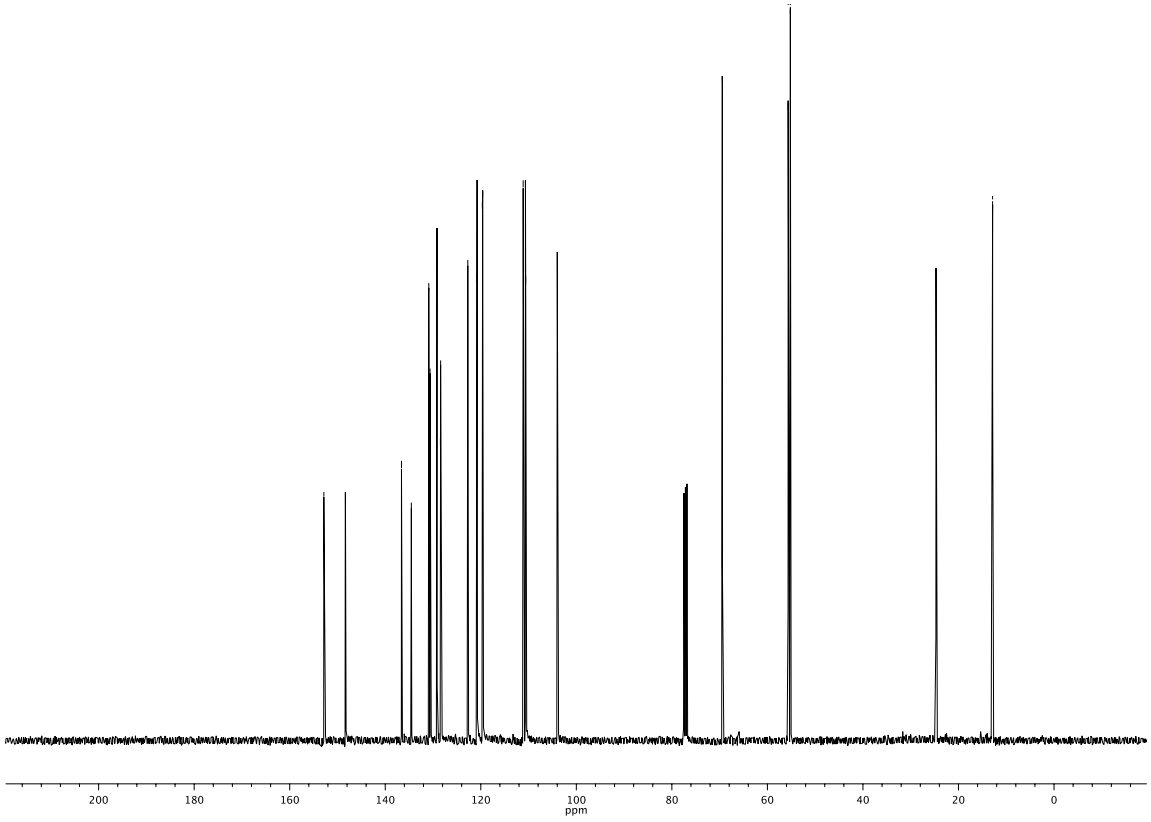
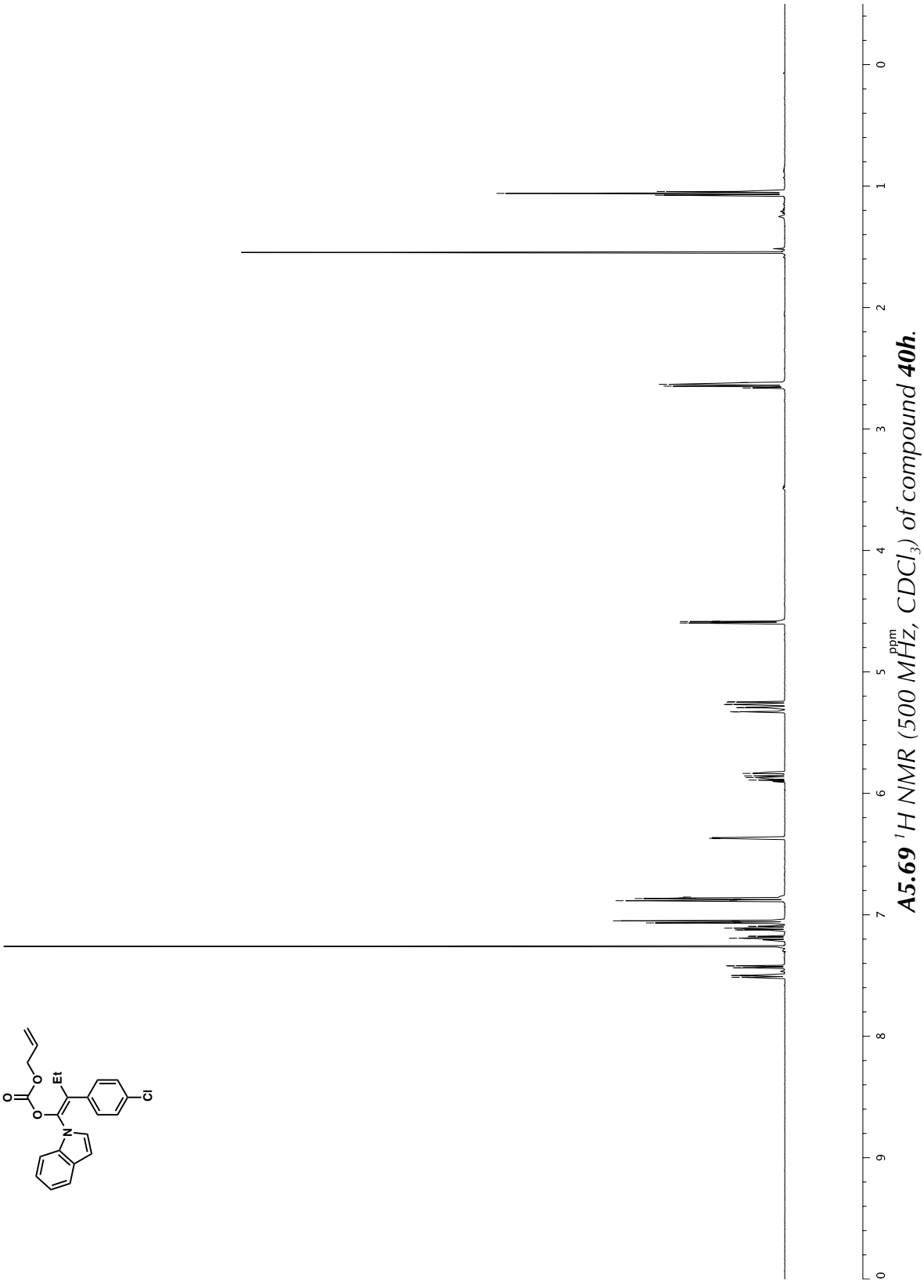



***Figure A5.68*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***40g****.*




***A5.69*** *$^{1}H$ NMR (500 MHz, $CDCl_3$) of compound* ***40h***.

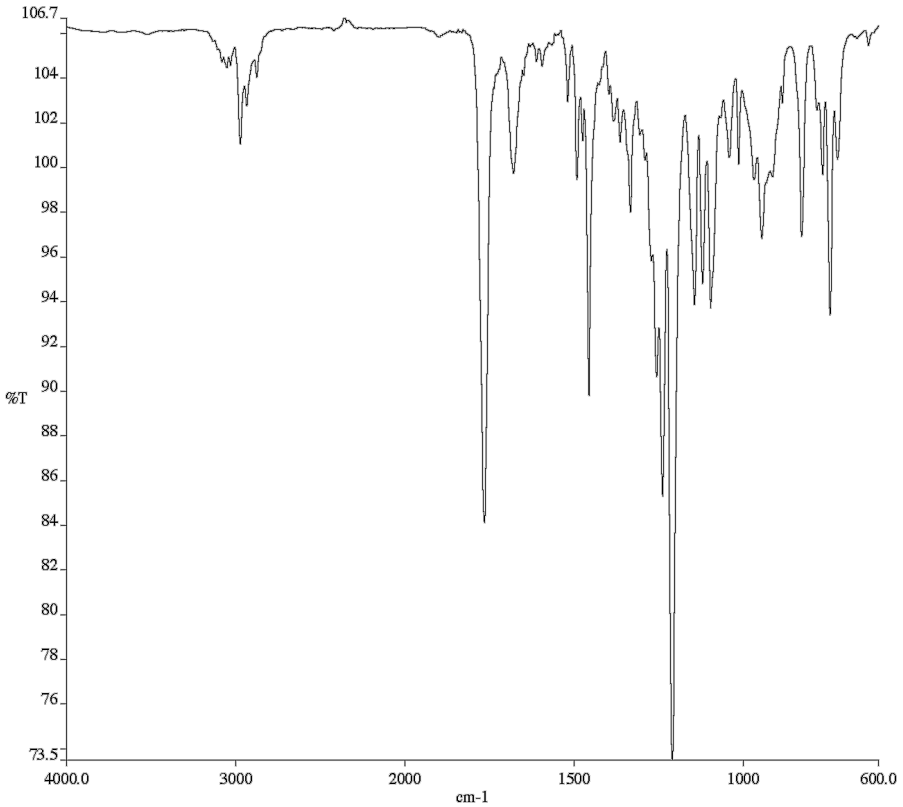



***Figure A5.70*** *Infrared spectrum (Thin Film, NaCl) of compound* ***40h***.

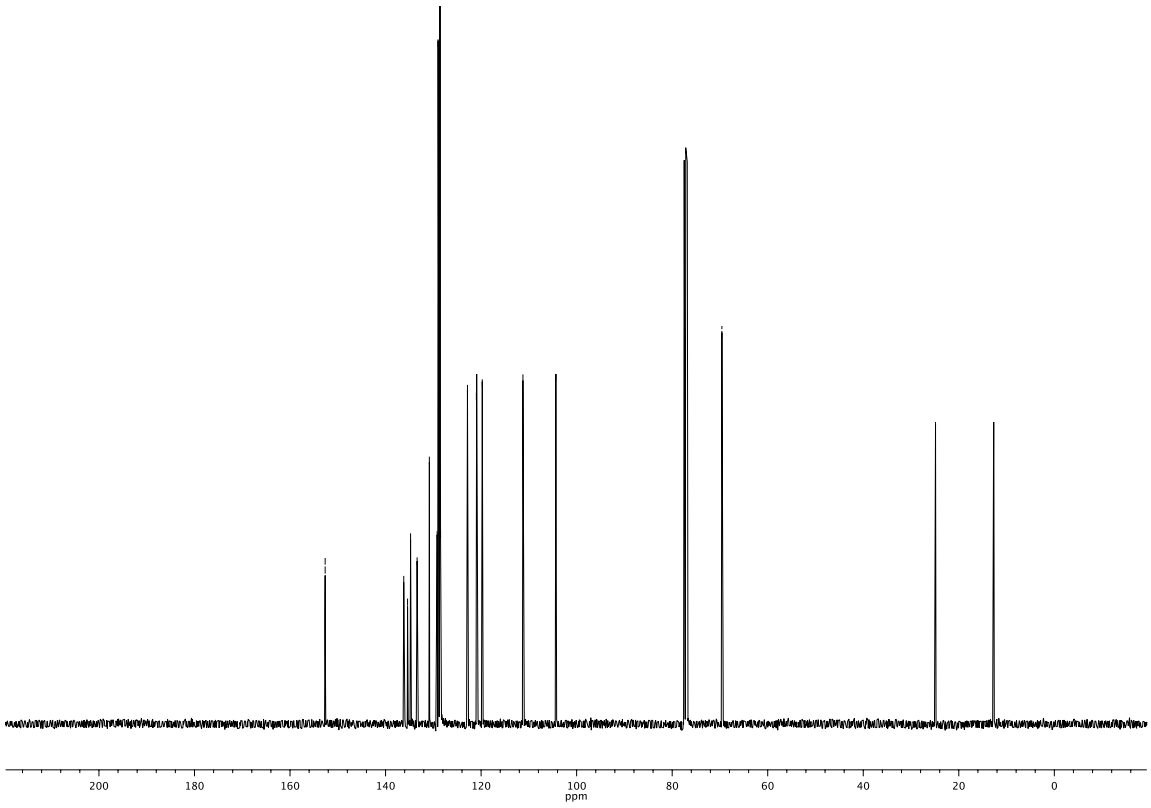
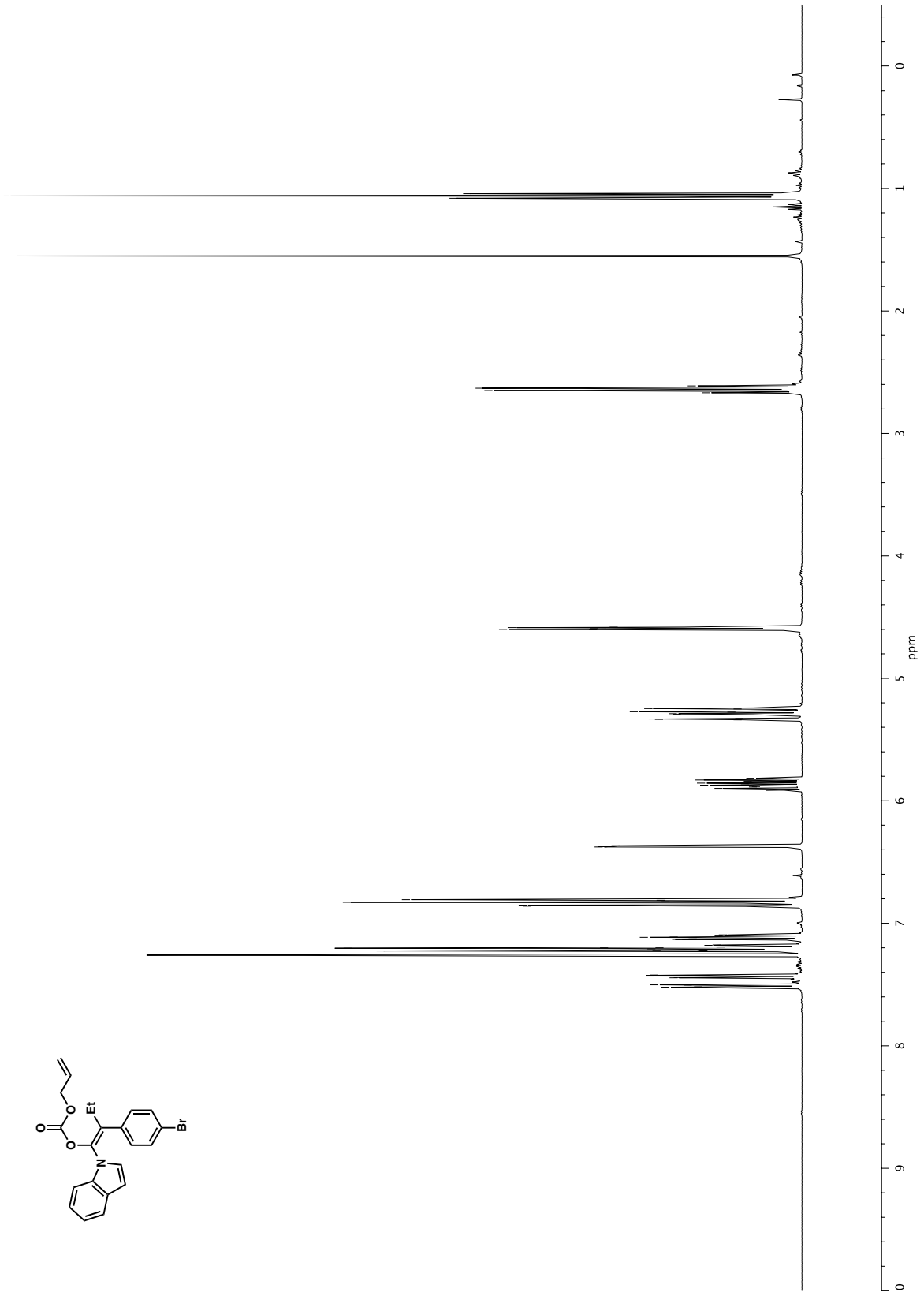



***Figure A5.71*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***40h***.




***A5.72*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***40i***.

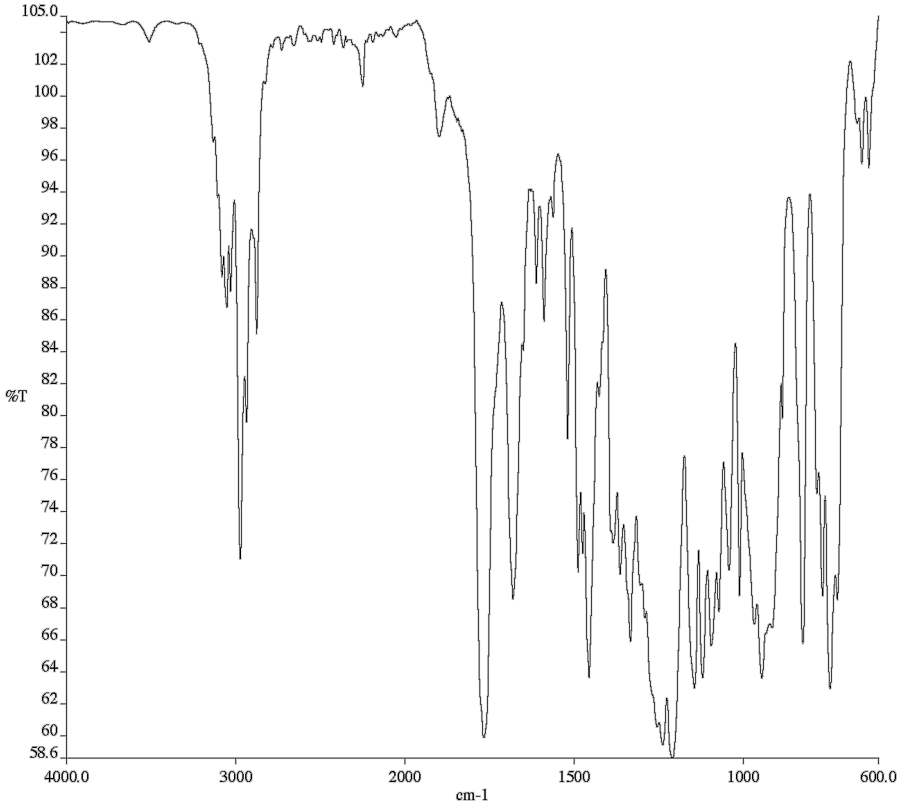



***Figure A5.73*** *Infrared spectrum (Thin Film, NaCl) of compound* ***40i***.

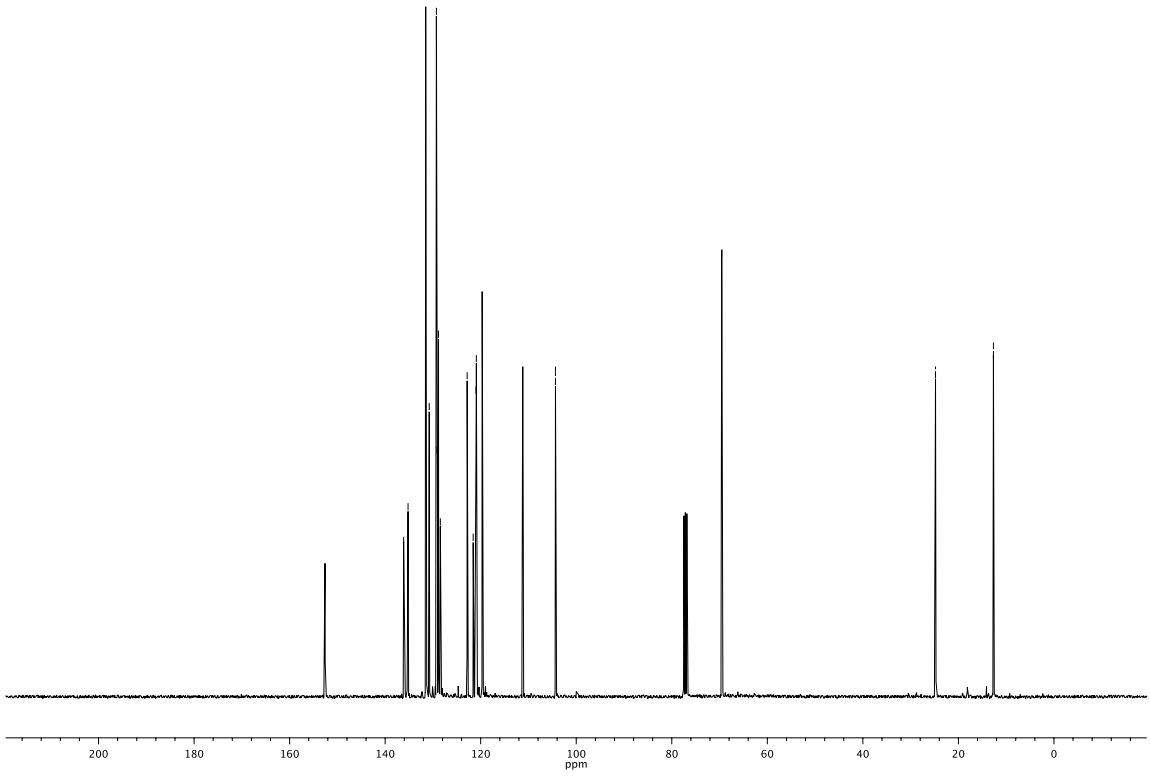
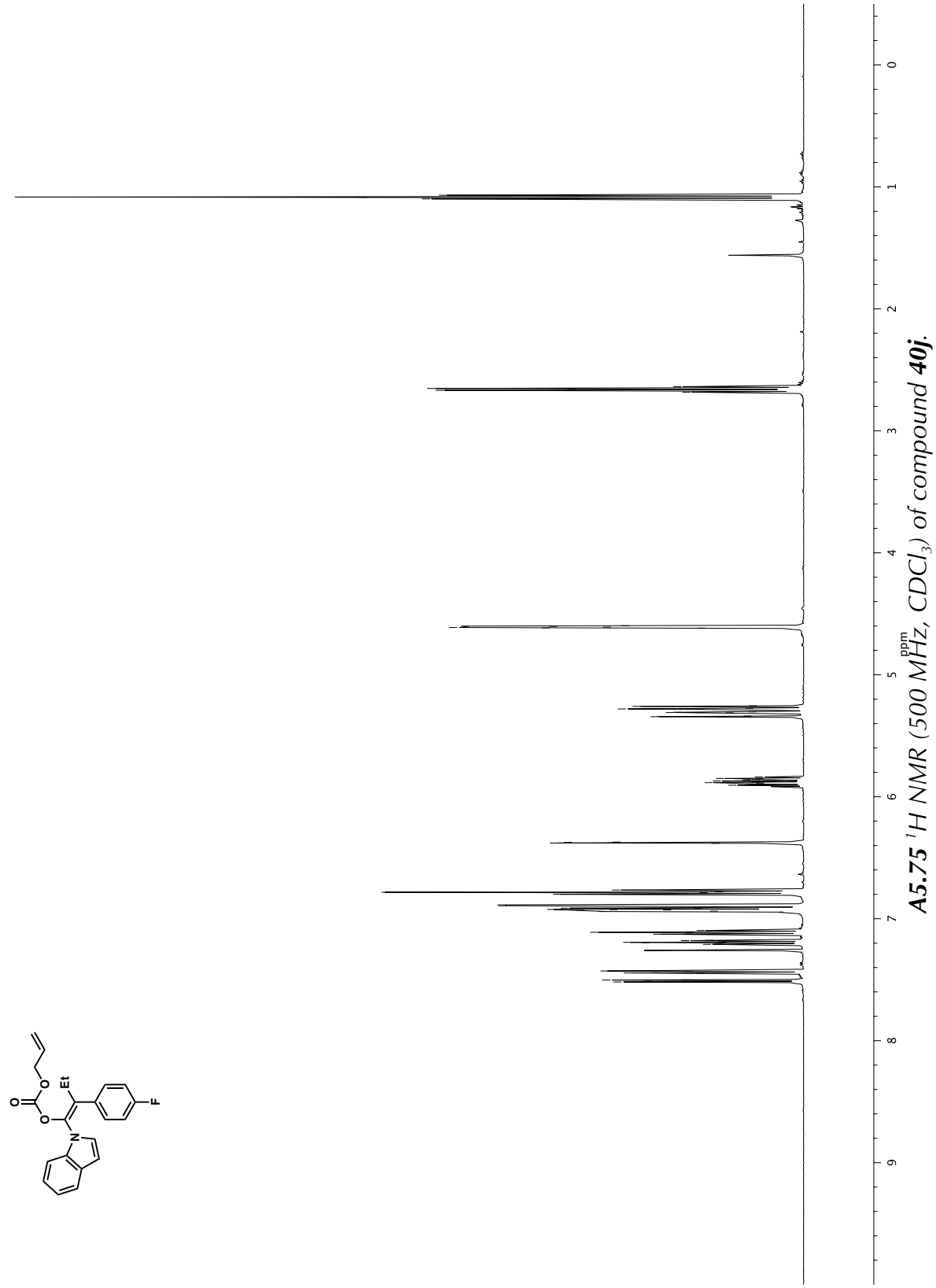



***Figure A5.74*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***40i***.




***A5.75*** *$^{1}H$ NMR (500 MHz, $CDCl_3$) of compound* ***40j***.

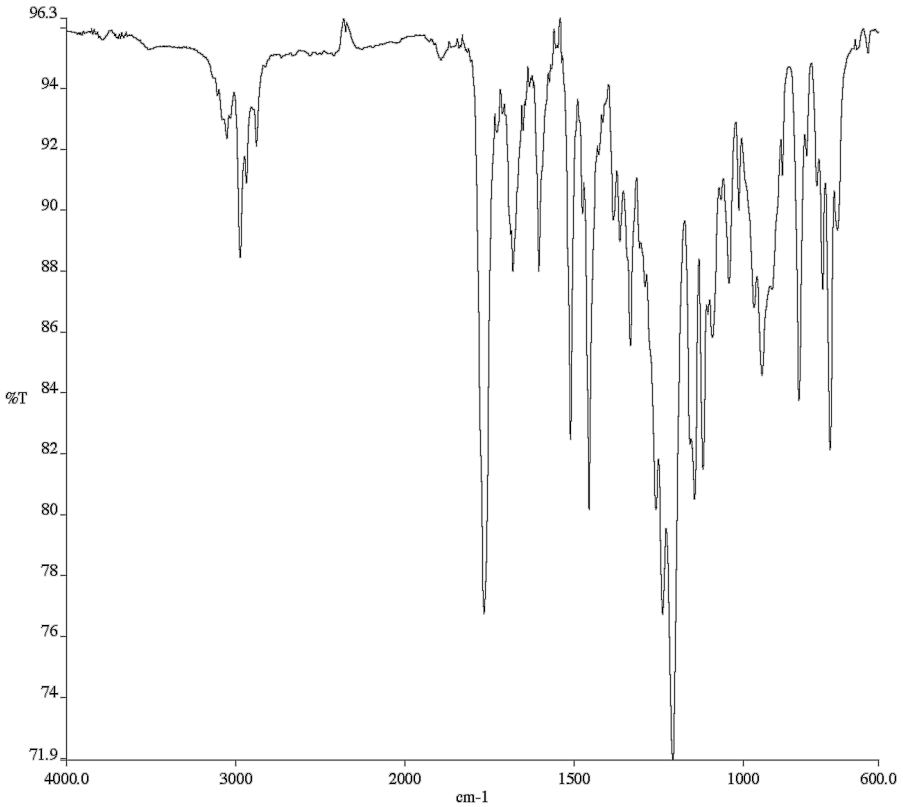



***Figure A5.76*** *Infrared spectrum (Thin Film, NaCl) of compound* ***40j****.*

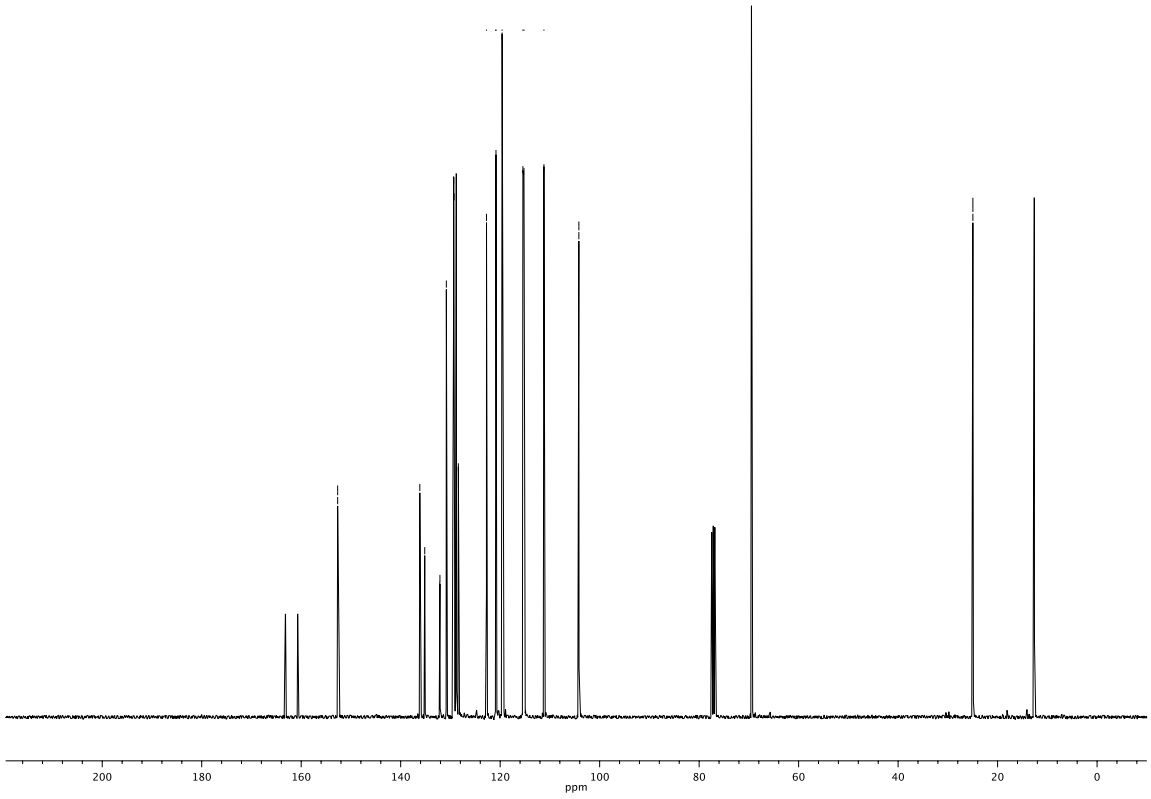



***Figure A5.77*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***40j****.*

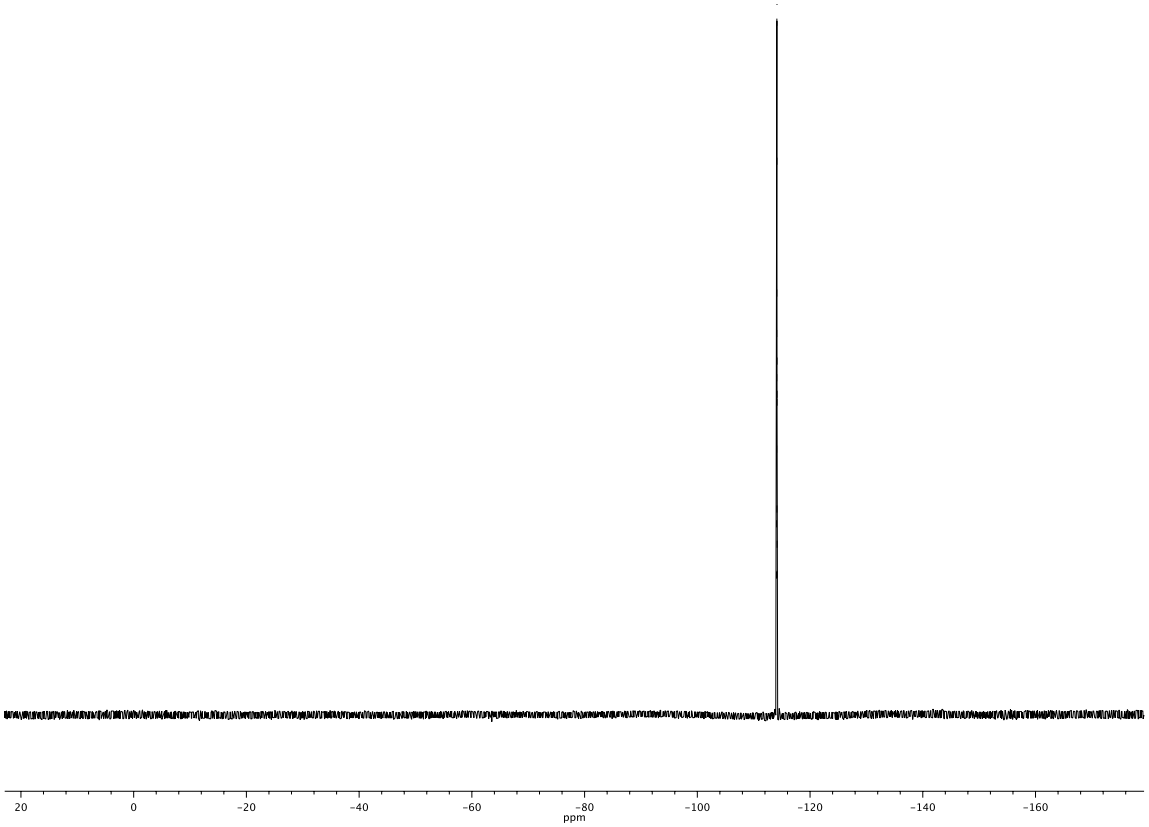
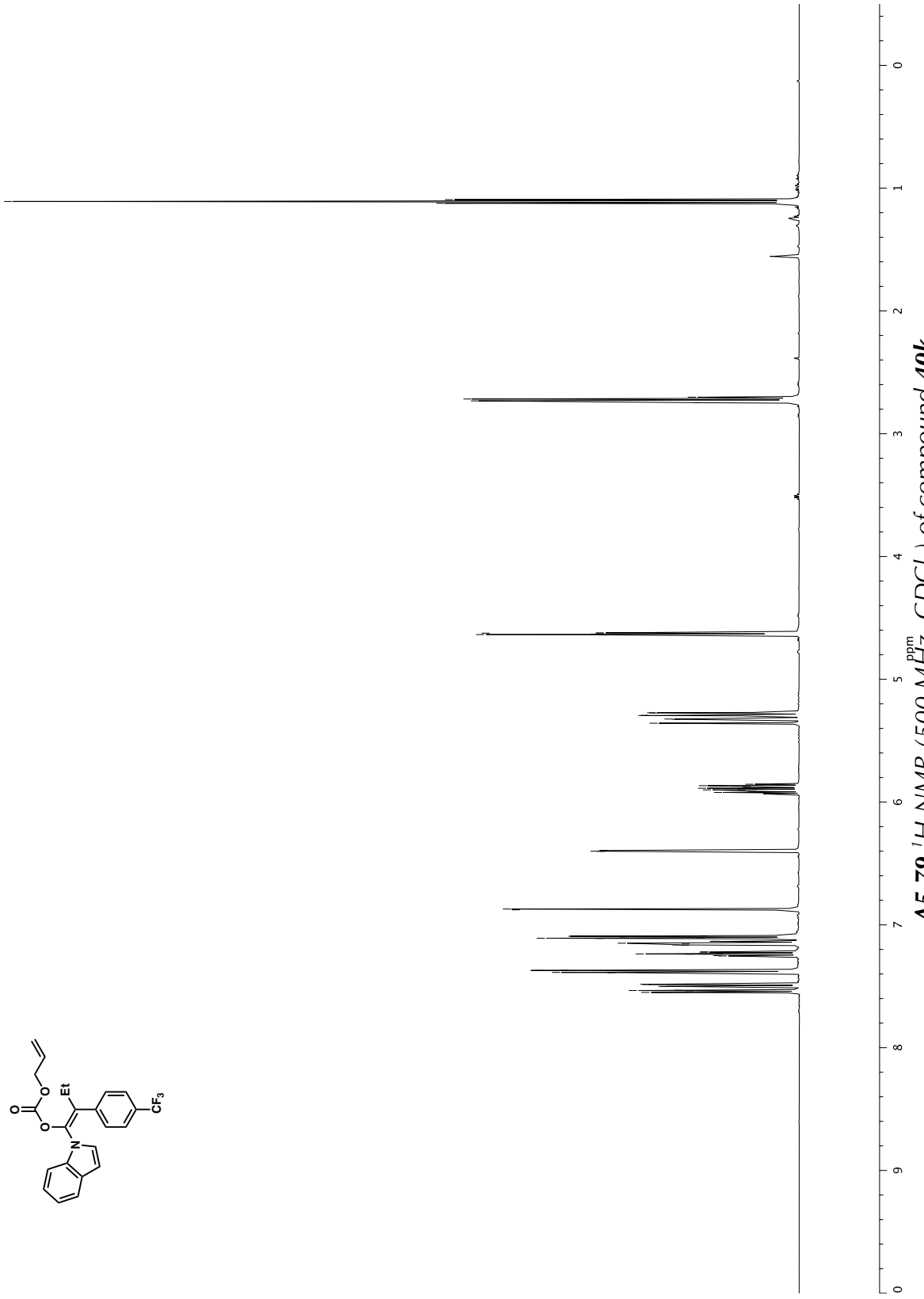



***Figure A5.78*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***40j****.*




***A5.79*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***40k***.

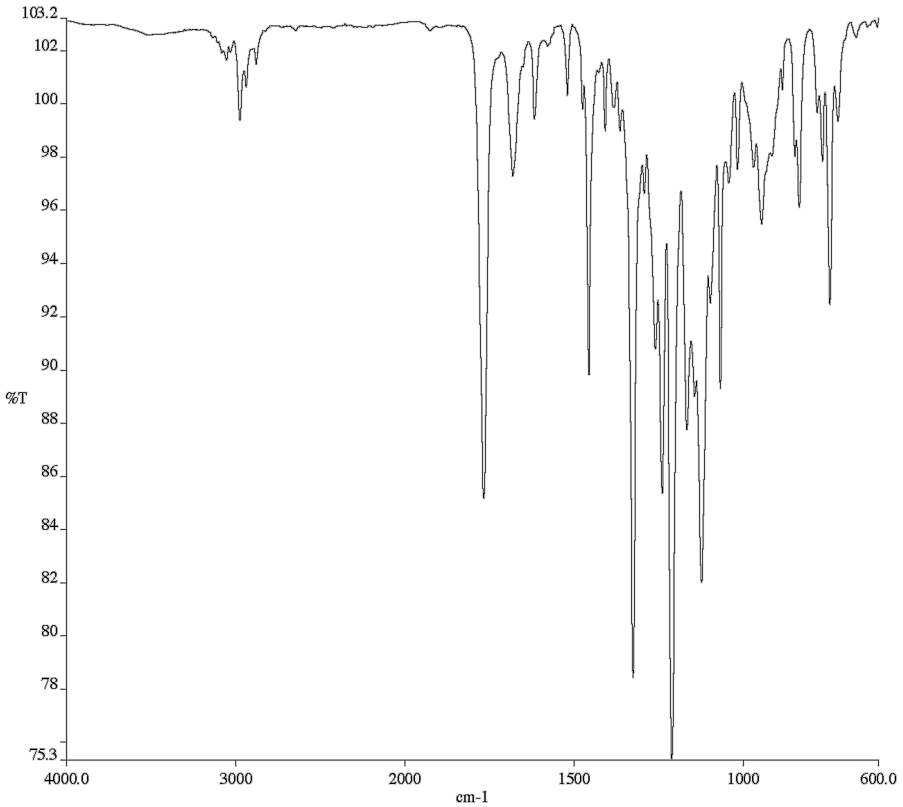



***Figure A5.80*** *Infrared spectrum (Thin Film, NaCl) of compound* ***40k****.*

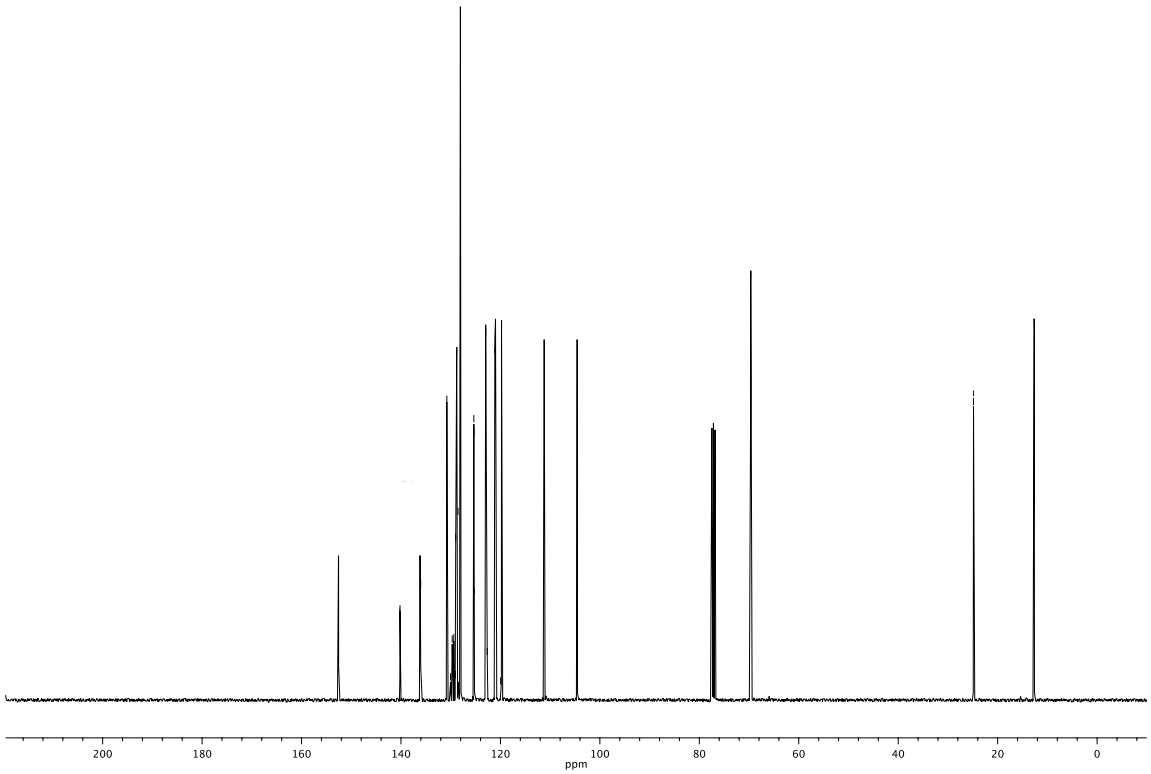



***Figure A5.81*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***40k****.*

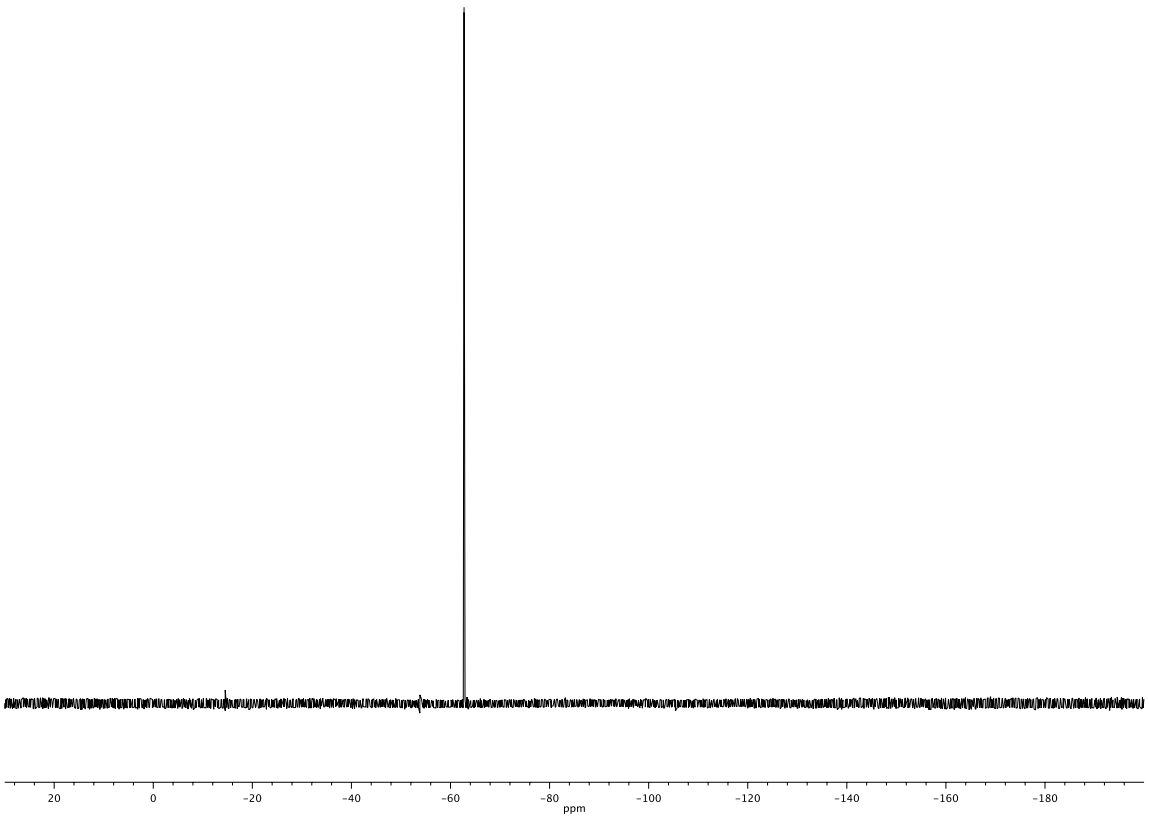
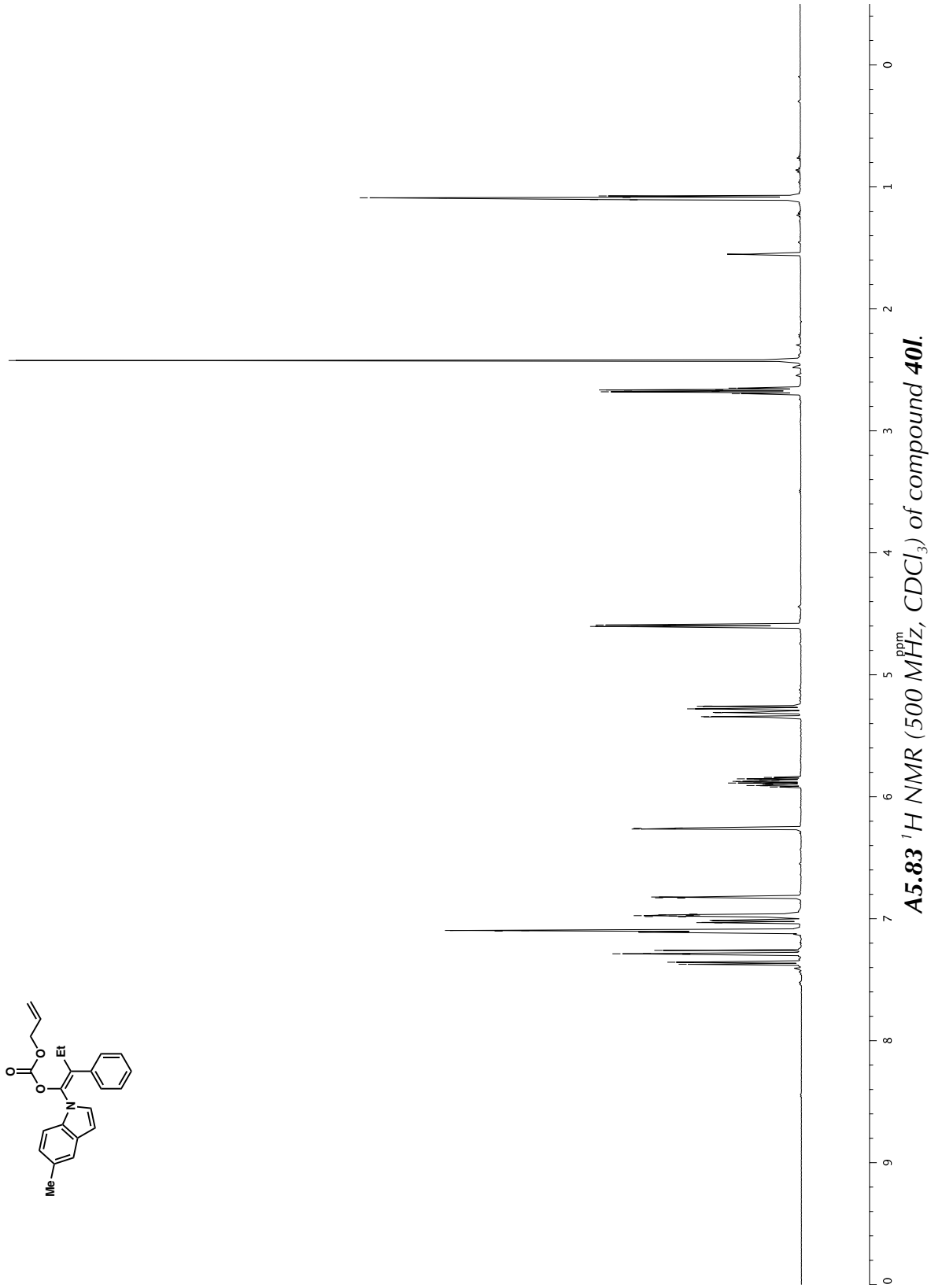



***Figure A5.82*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***40k****.*




***A5.83*** *$^{1}H$ NMR (500 MHz, $CDCl_3$) of compound* ***40l***.

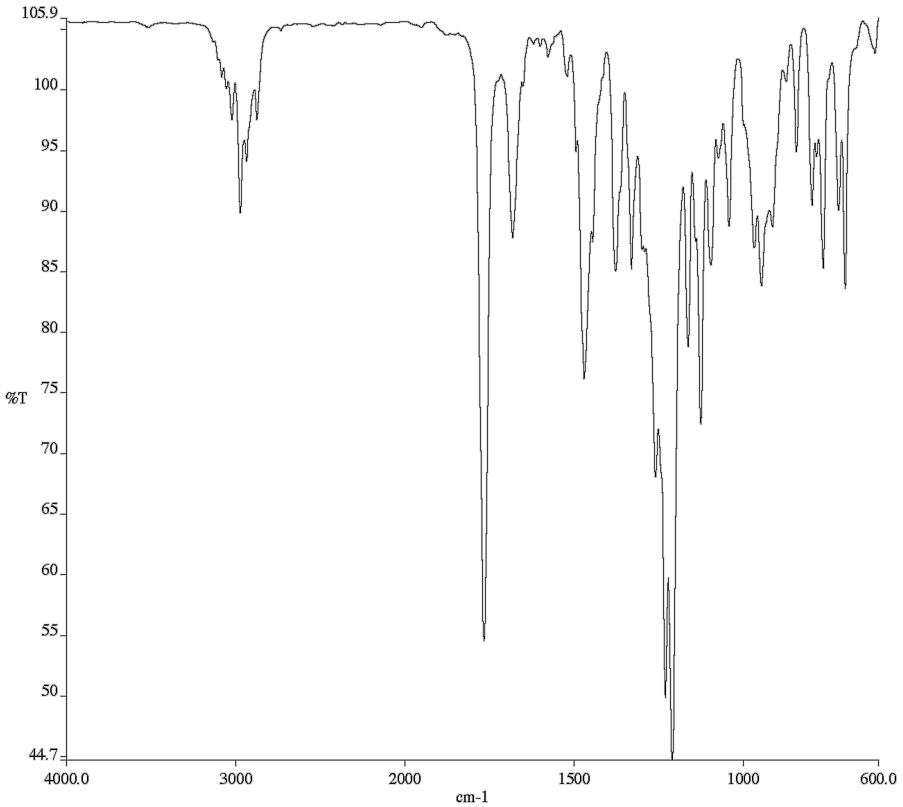



***Figure A5.84*** *Infrared spectrum (Thin Film, NaCl) of compound* ***40l****.*

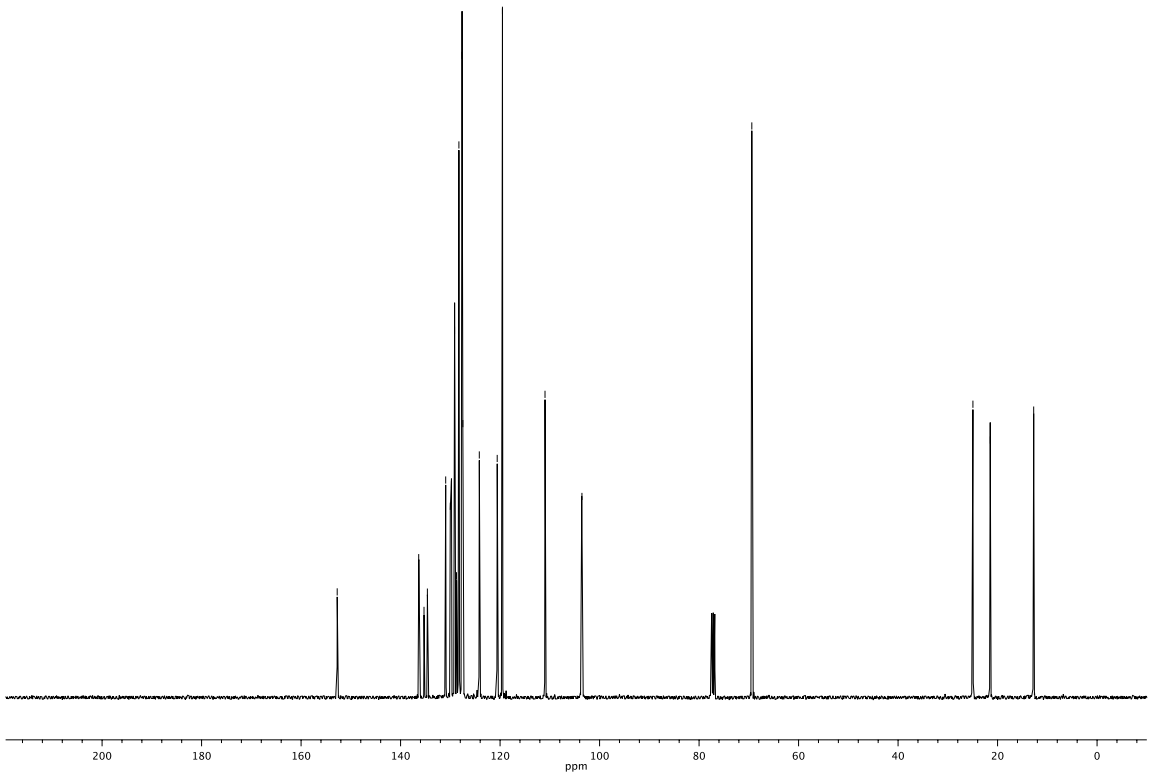
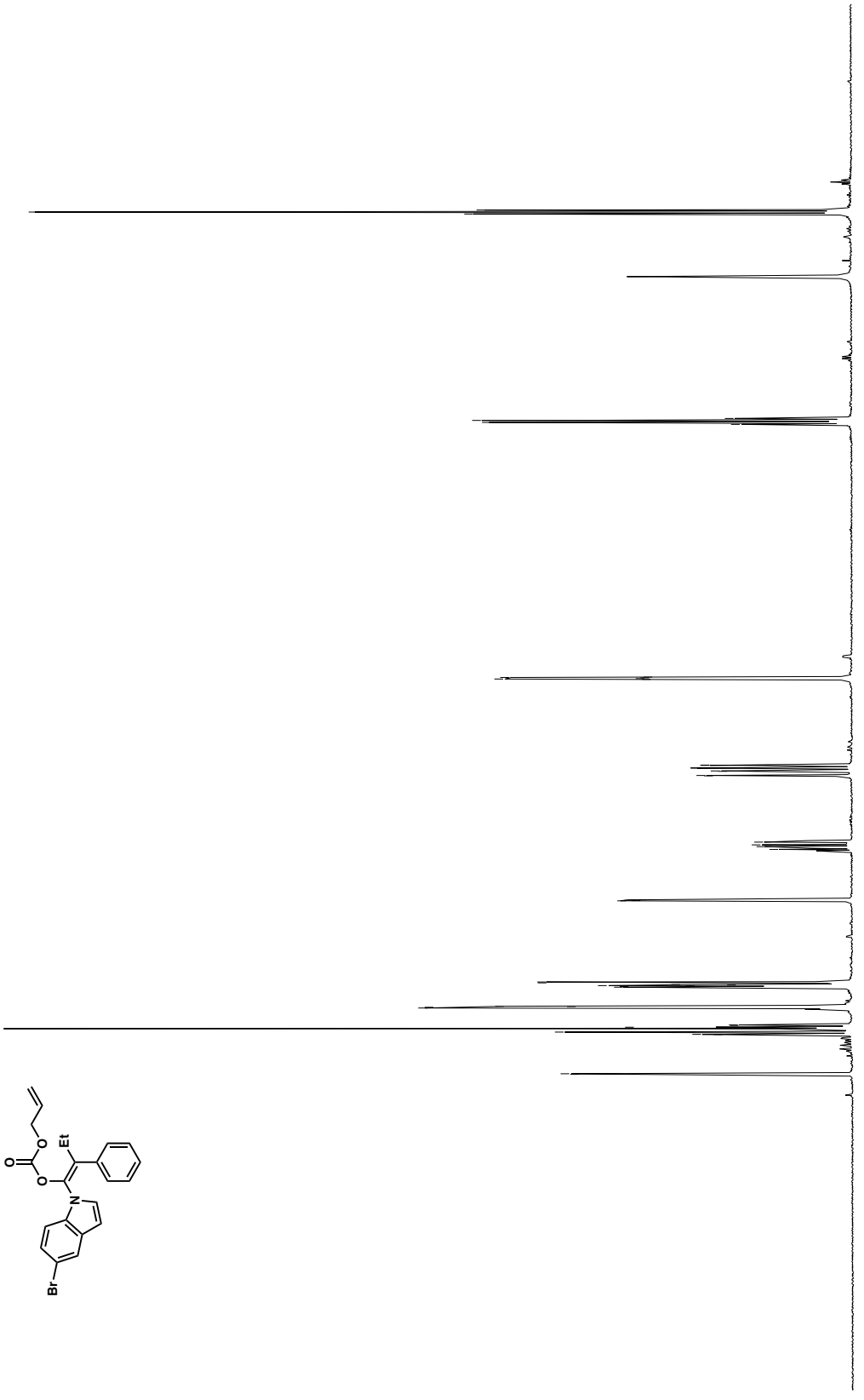



***Figure A5.85*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***40l****.*




***A5.86*** *$^{1}$H NMR (500 MHz, $CDCl_3$) of compound* ***40m***.

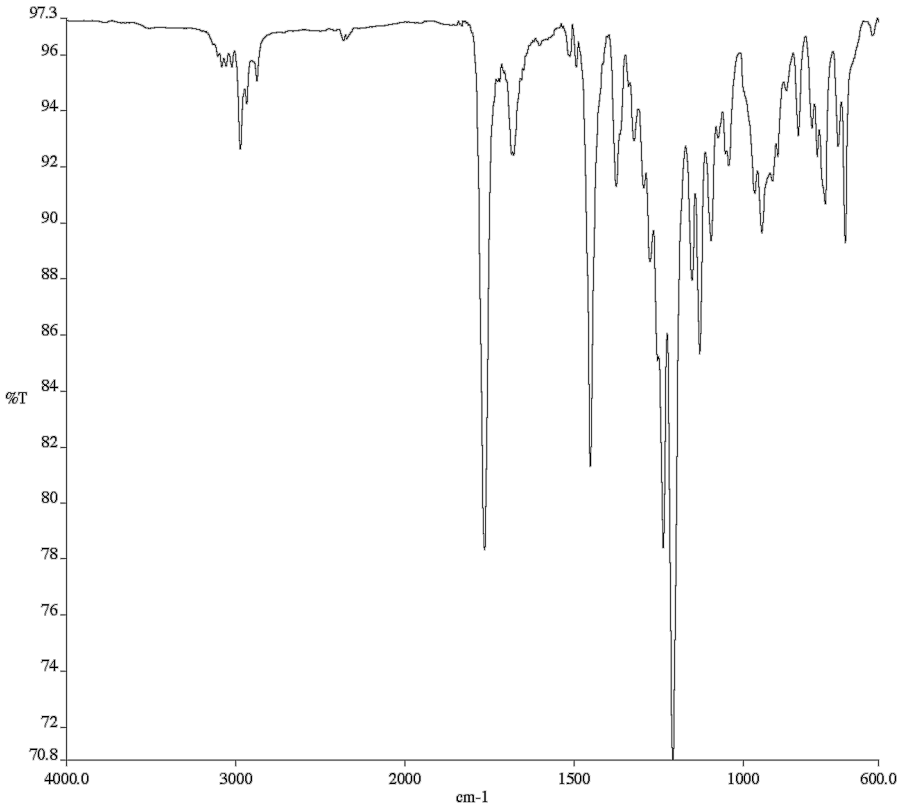



***Figure A5.87*** *Infrared spectrum (Thin Film, NaCl) of compound* ***40m****.*

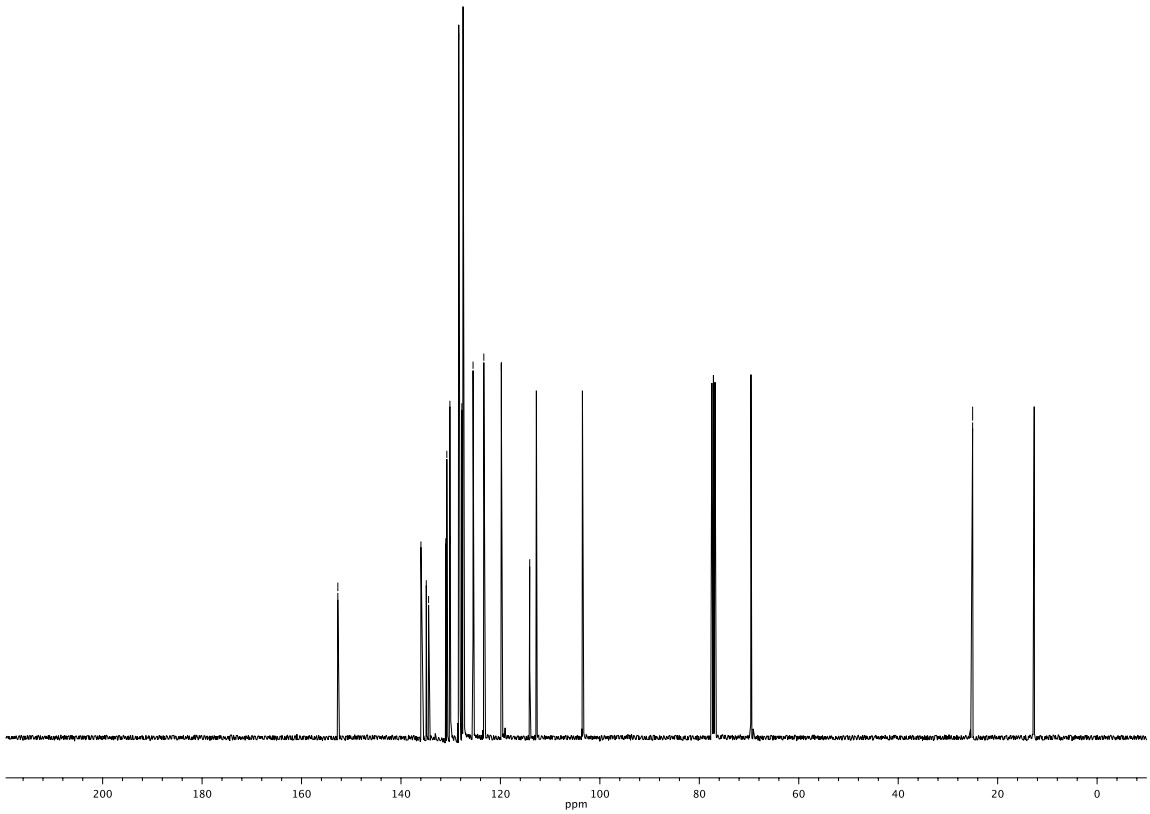
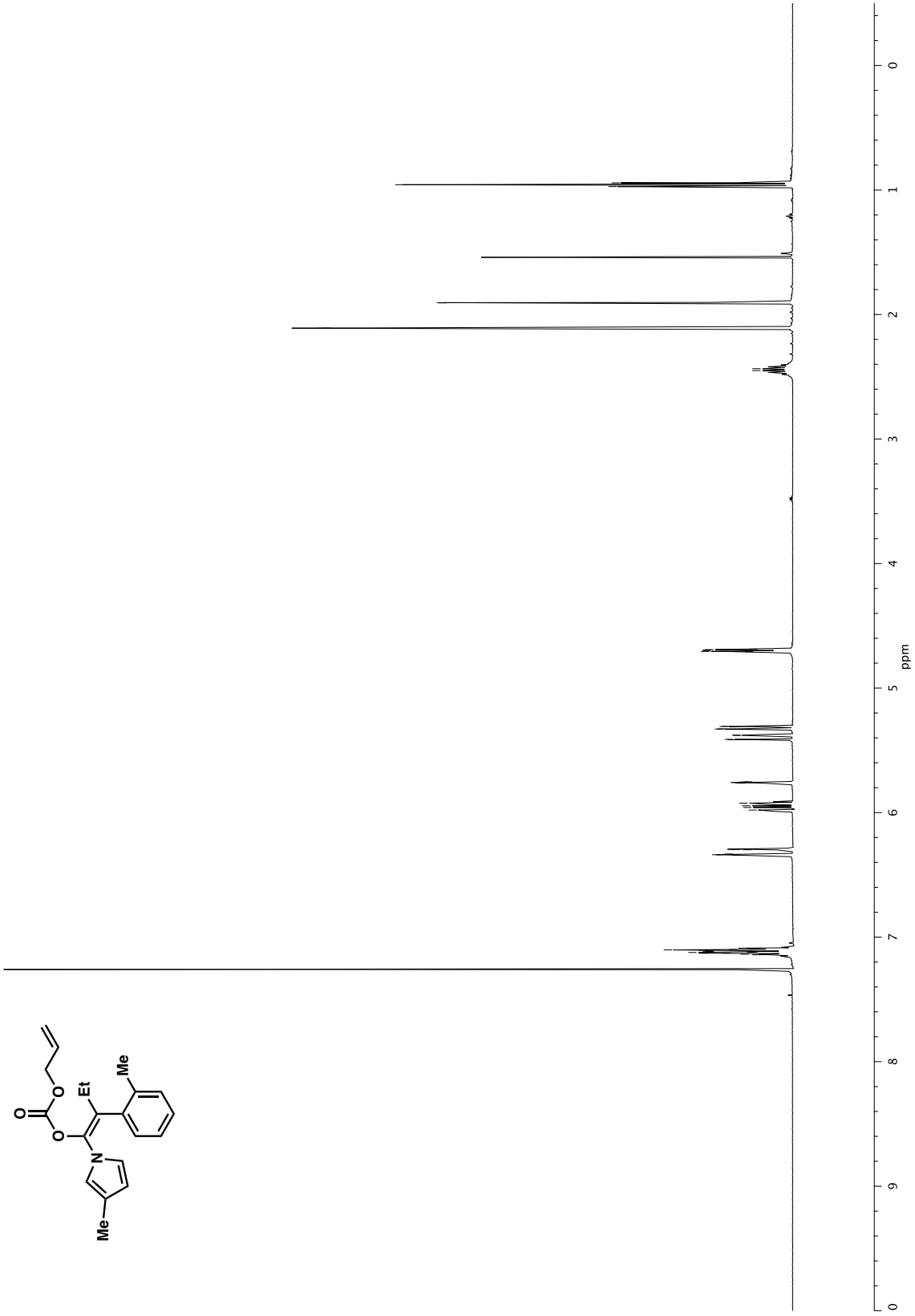



***Figure A5.88*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***40m****.*




***A5.89*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***40n***.

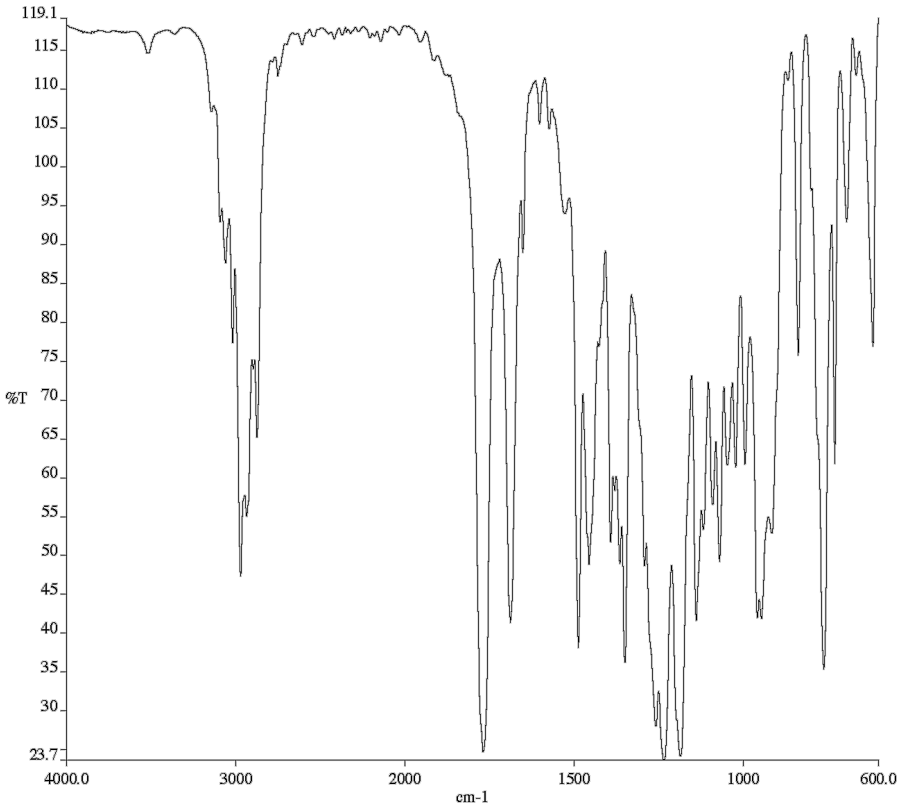



***Figure A5.90*** *Infrared spectrum (Thin Film, NaCl) of compound* ***40n***.

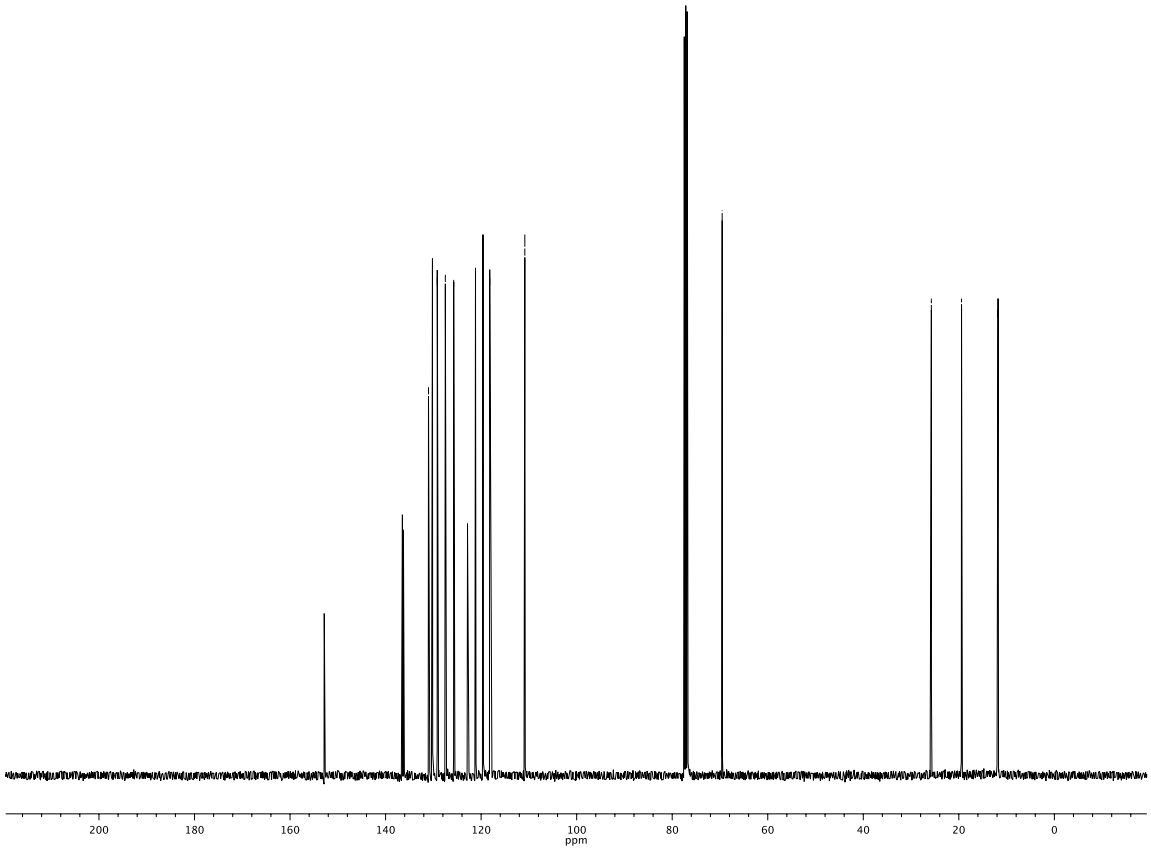
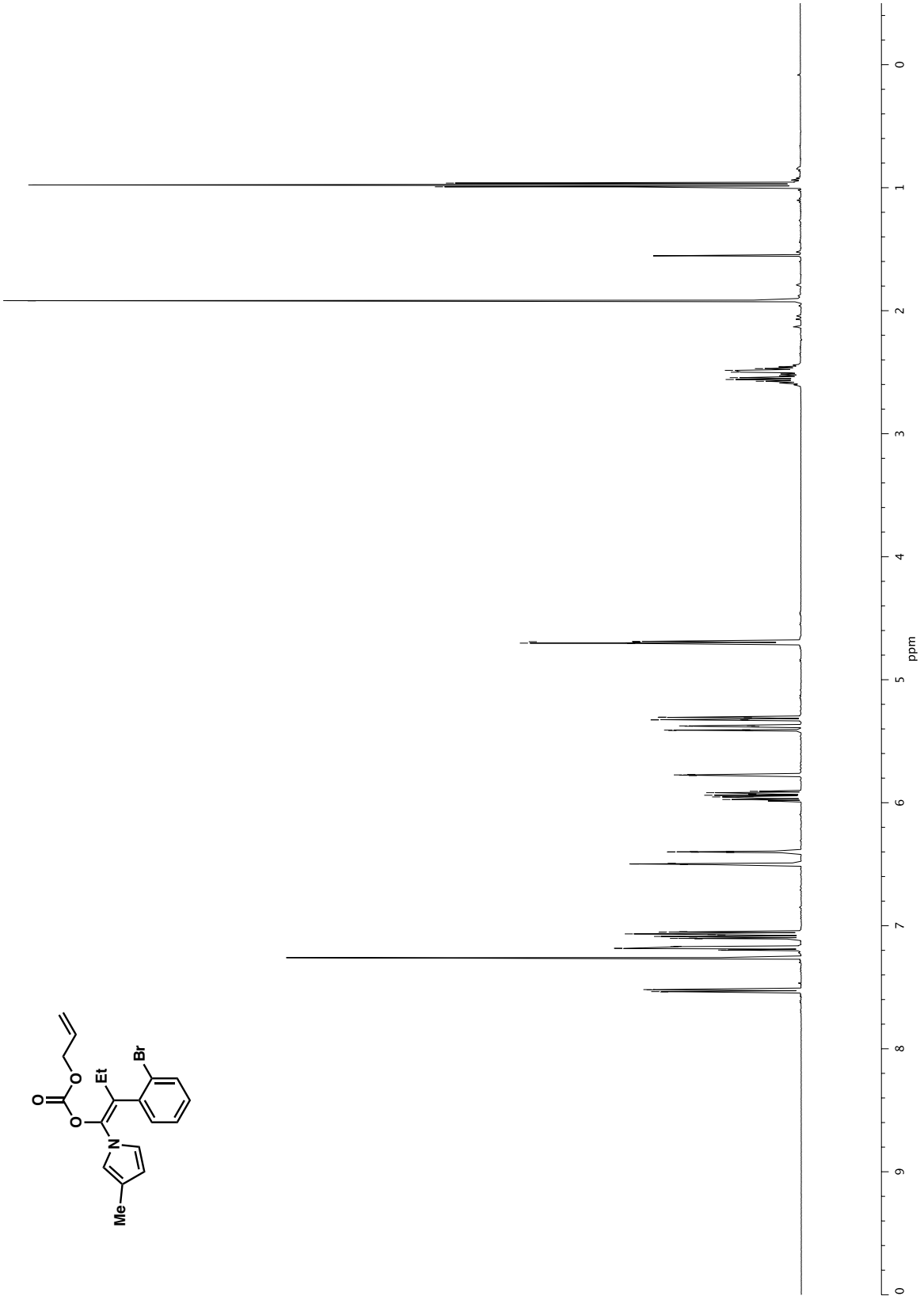



***Figure A5.91*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***40n***.




***A5.92*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***40o***.

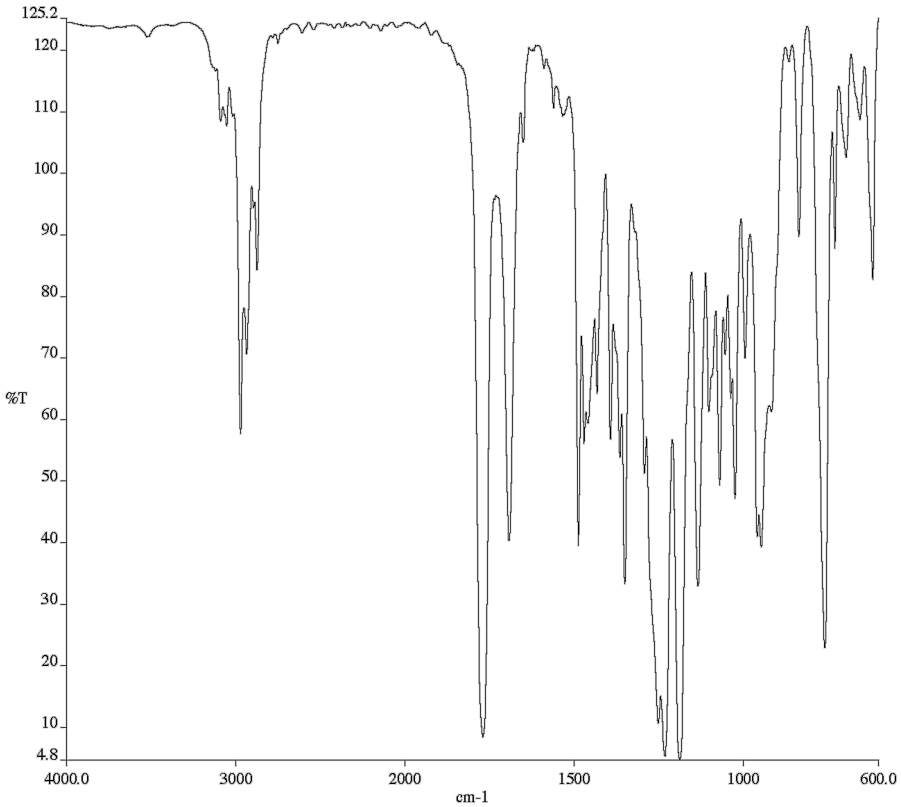



***Figure A5.93*** *Infrared spectrum (Thin Film, NaCl) of compound* ***40o****.*

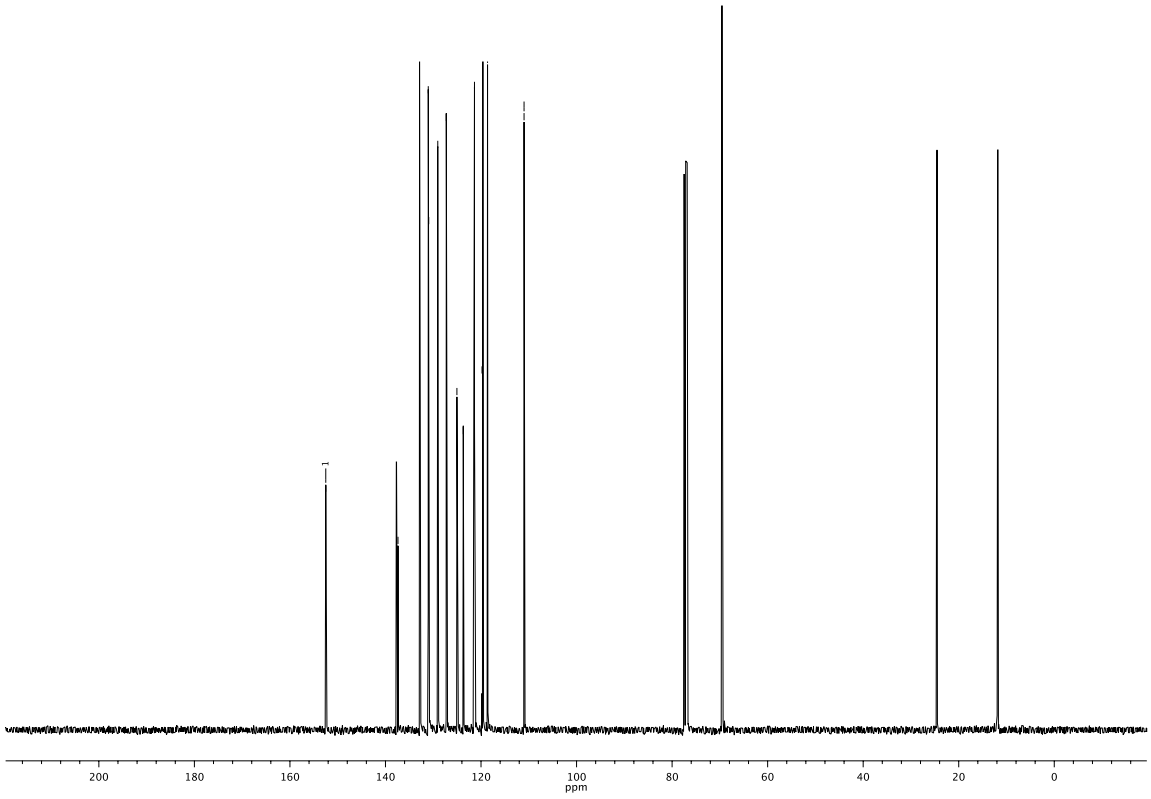
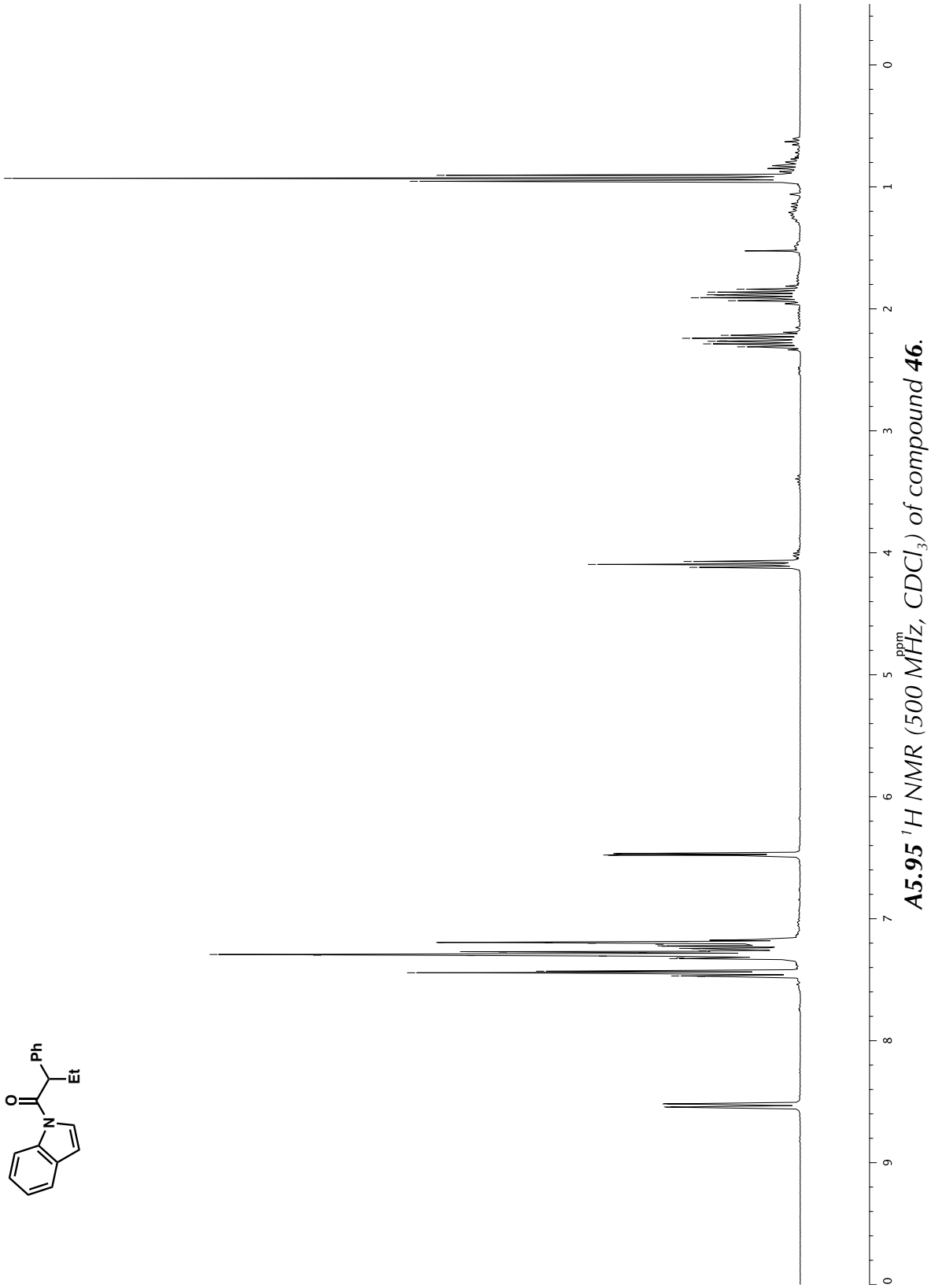



***Figure A5.94*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***40o****.*




***A5.95*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***46***.

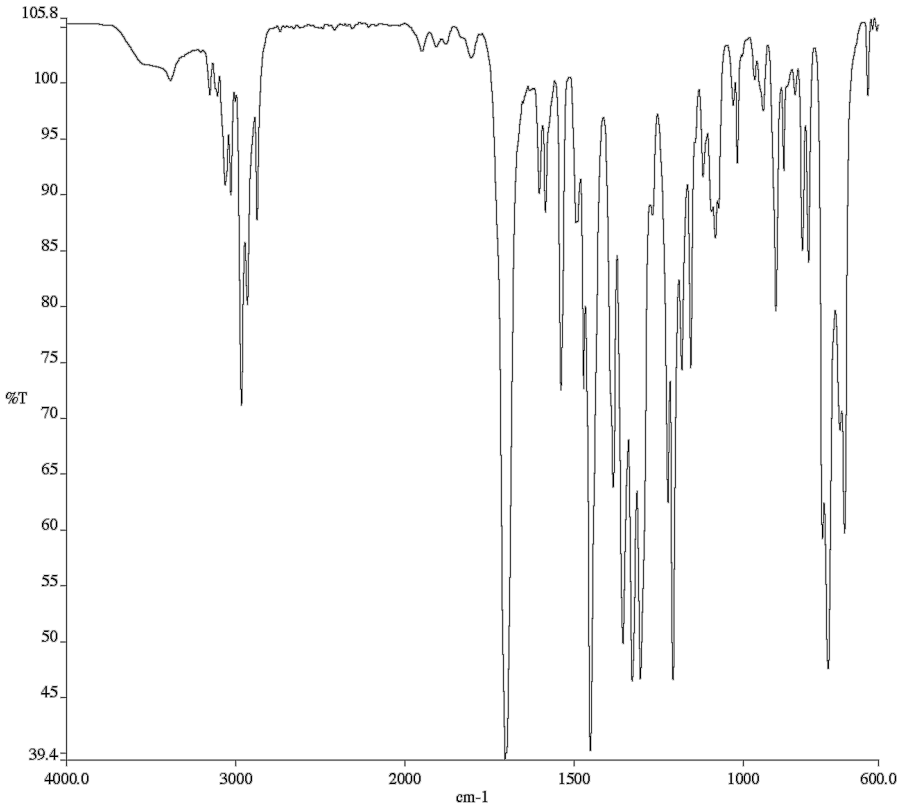



***Figure A5.96*** *Infrared spectrum (Thin Film, NaCl) of compound* ***46***.

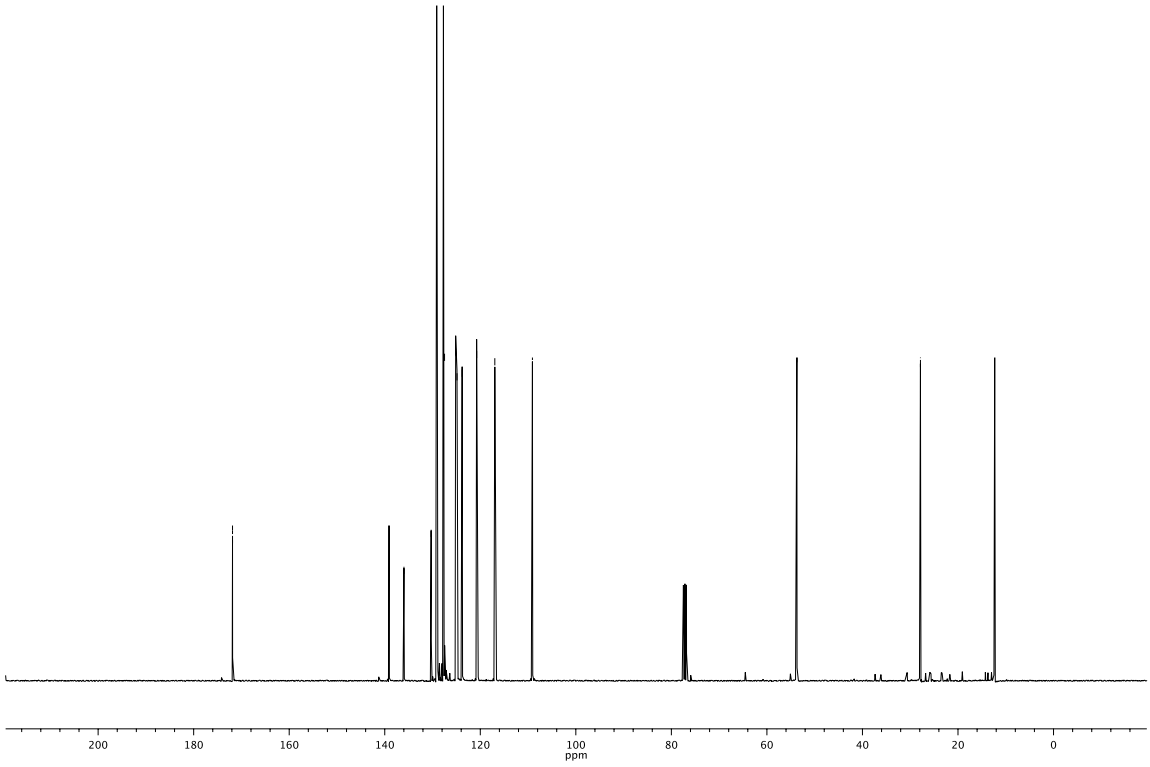
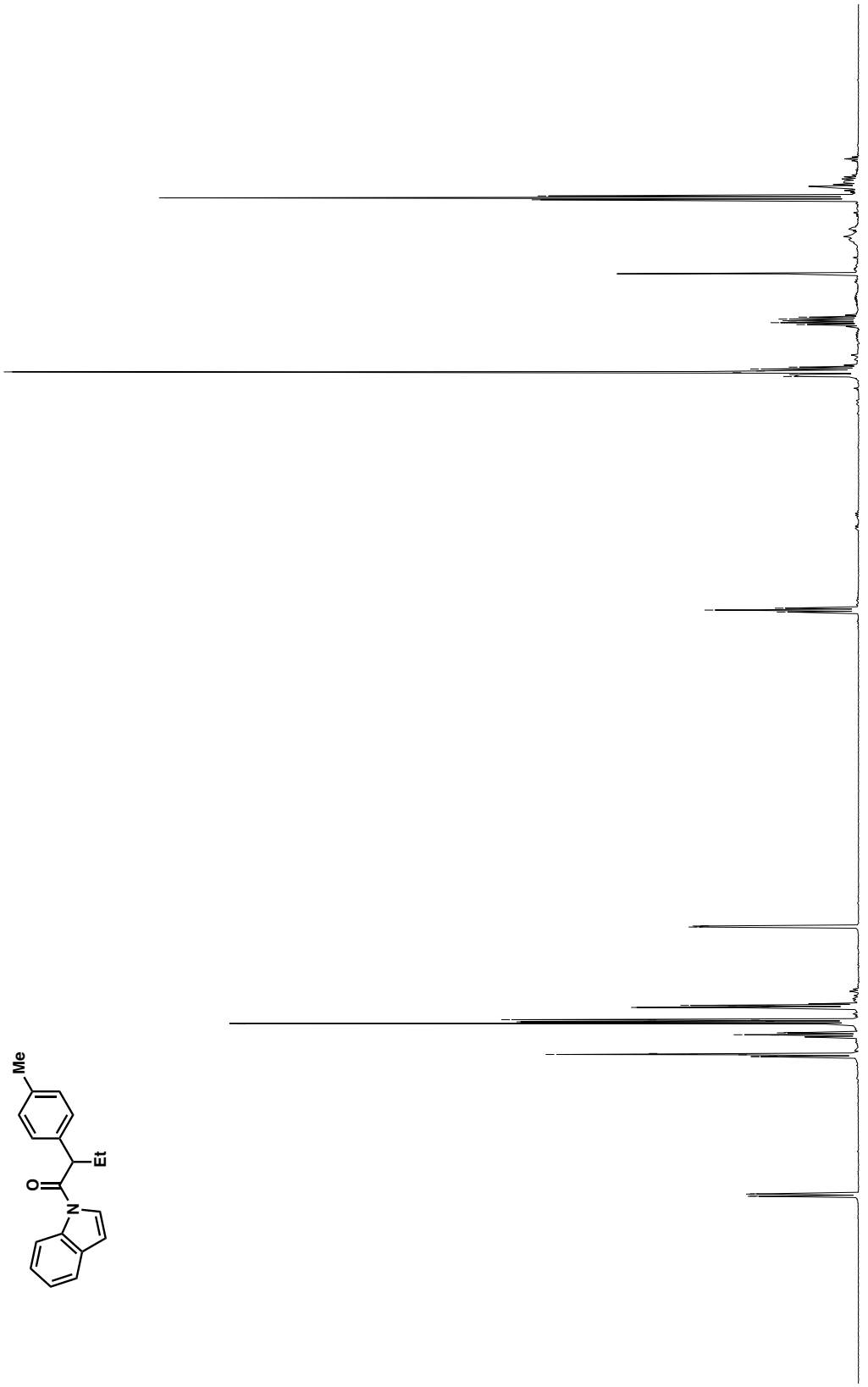



***Figure A5.97*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***46***.




***A5.98*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***47****.*

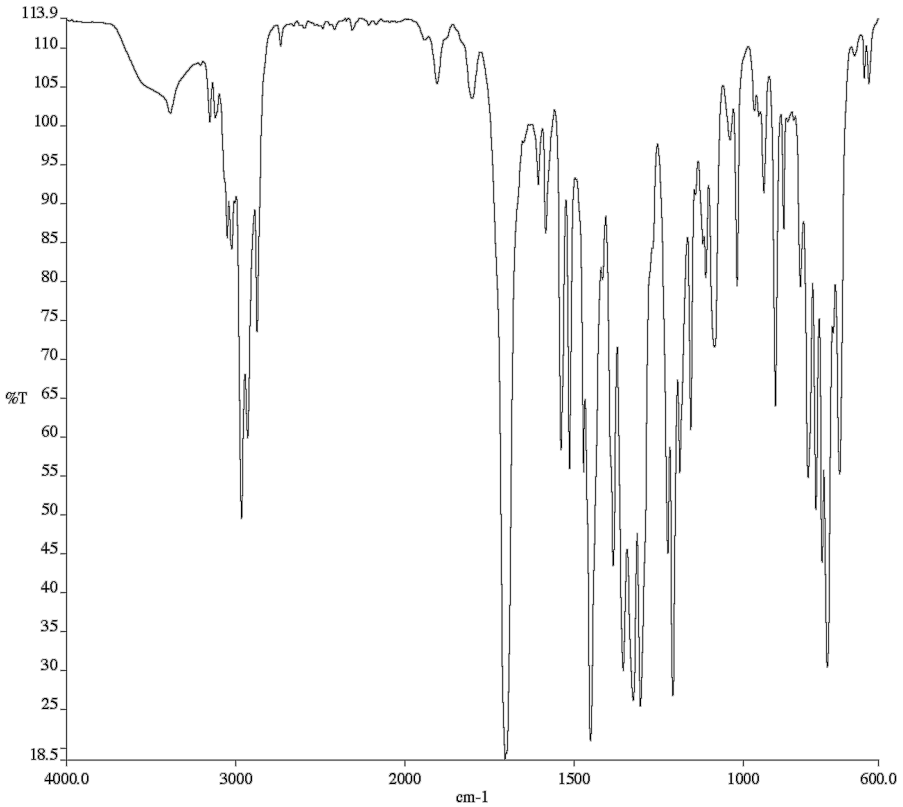



***Figure A5.99*** *Infrared spectrum (Thin Film, NaCl) of compound* ***47****.*

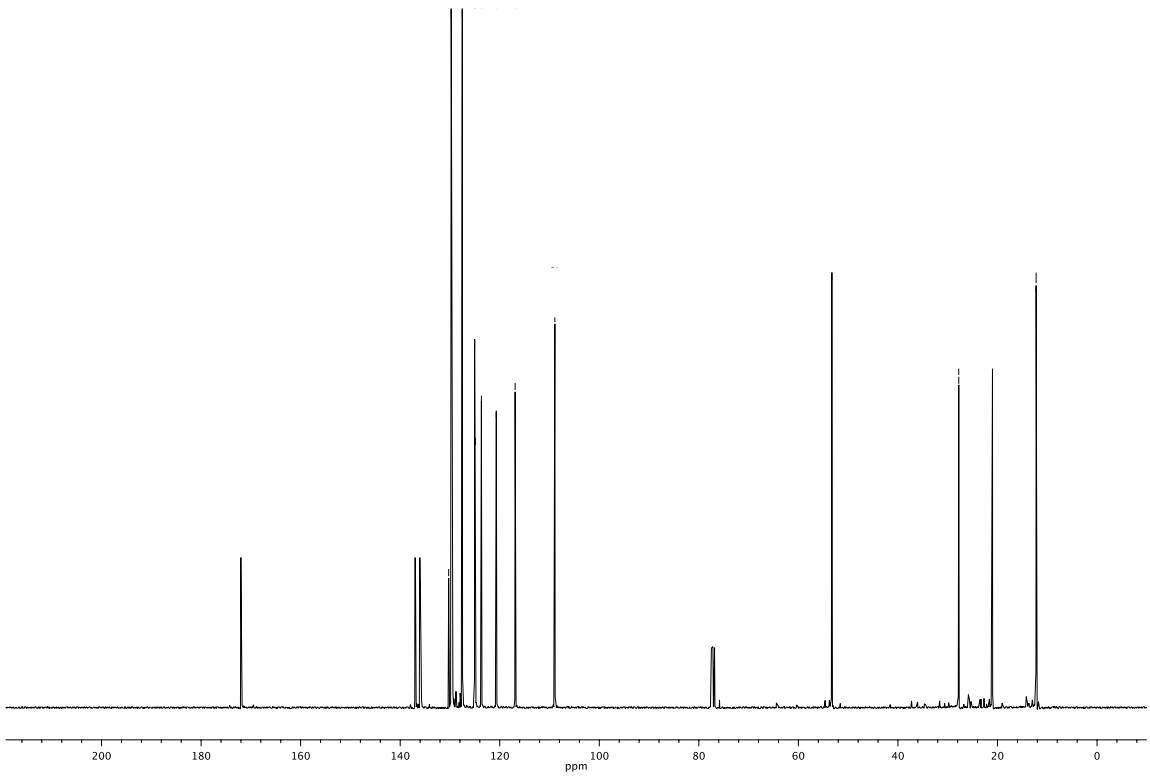
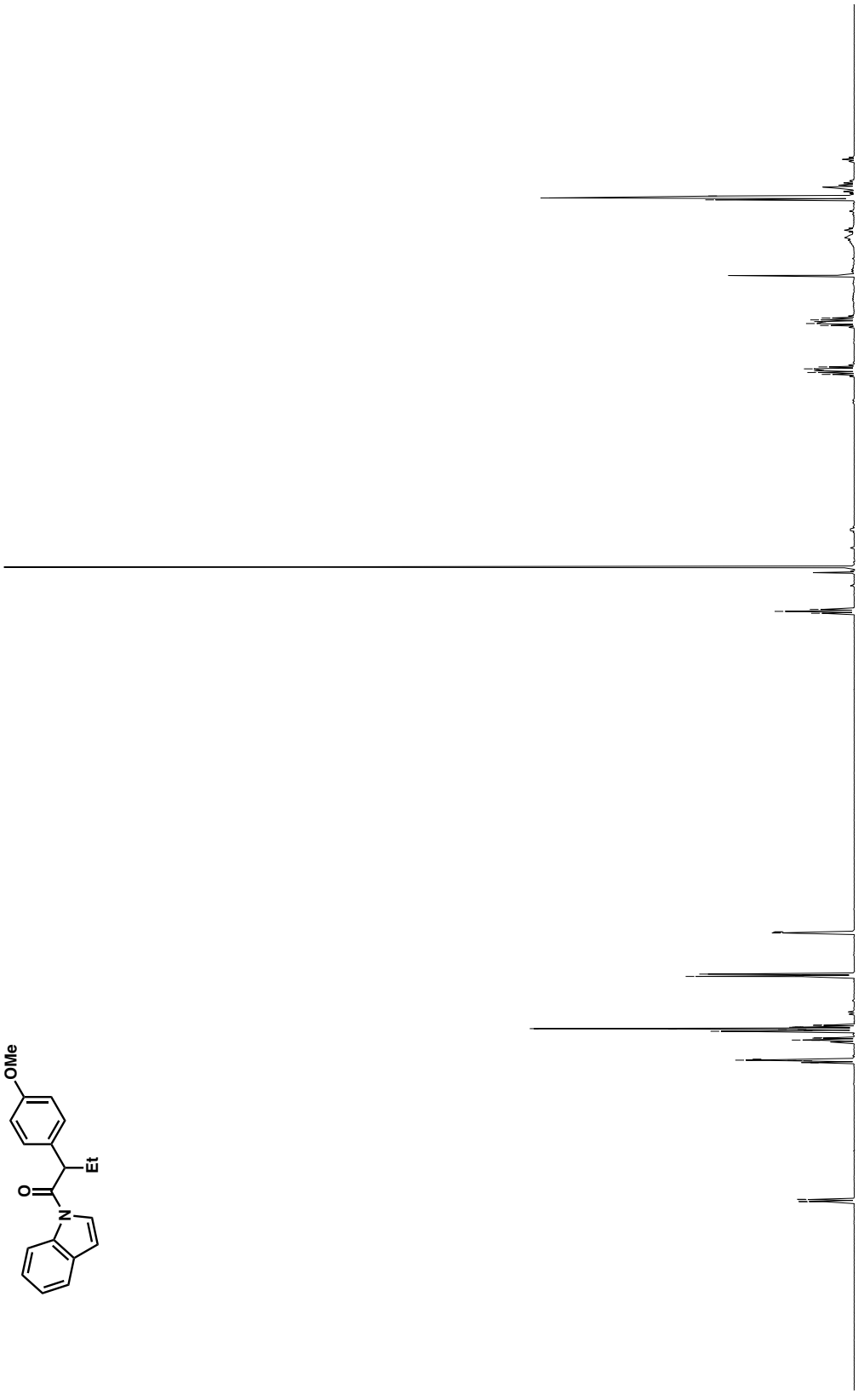



***Figure A5.100*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***47****.*




***A5.101*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***48****.*

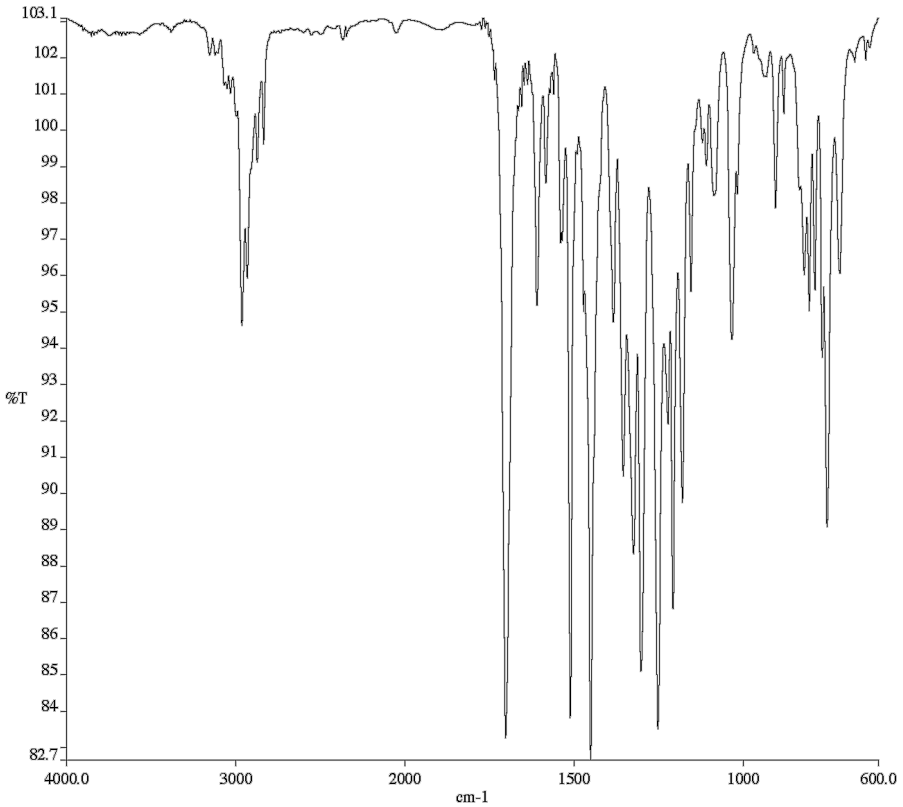



***Figure A5.102*** *Infrared spectrum (Thin Film, NaCl) of compound* ***48****.*

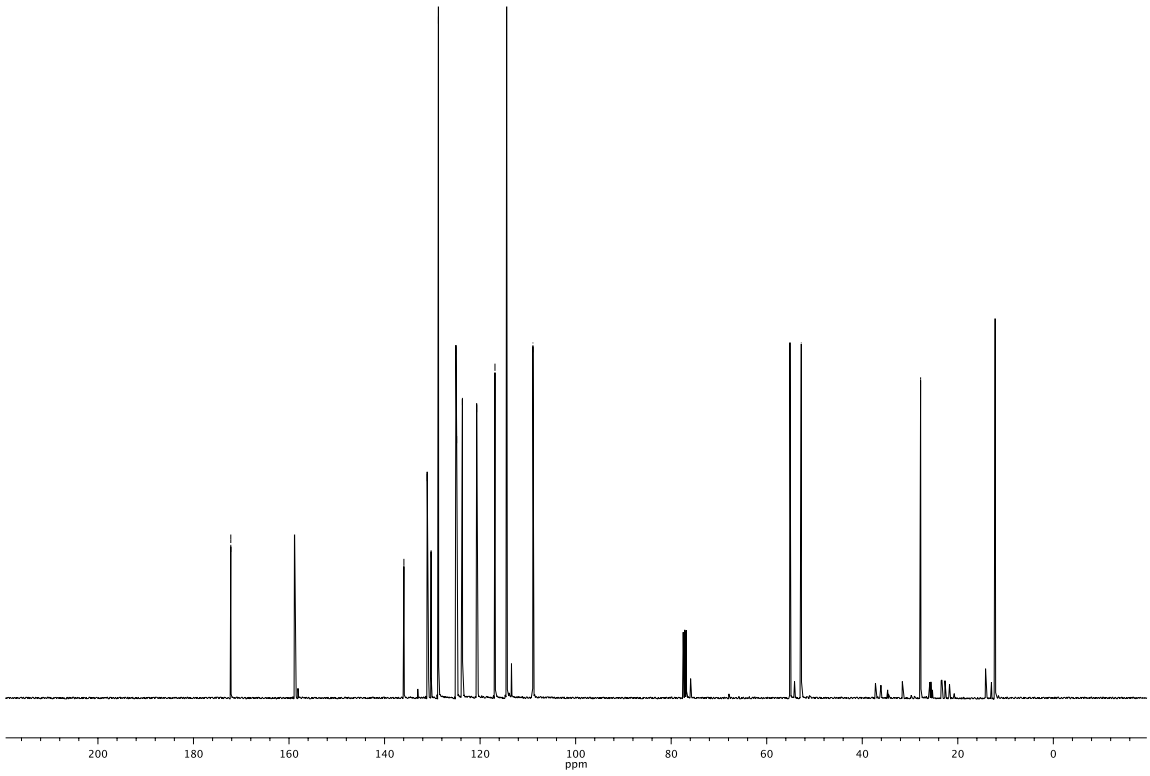
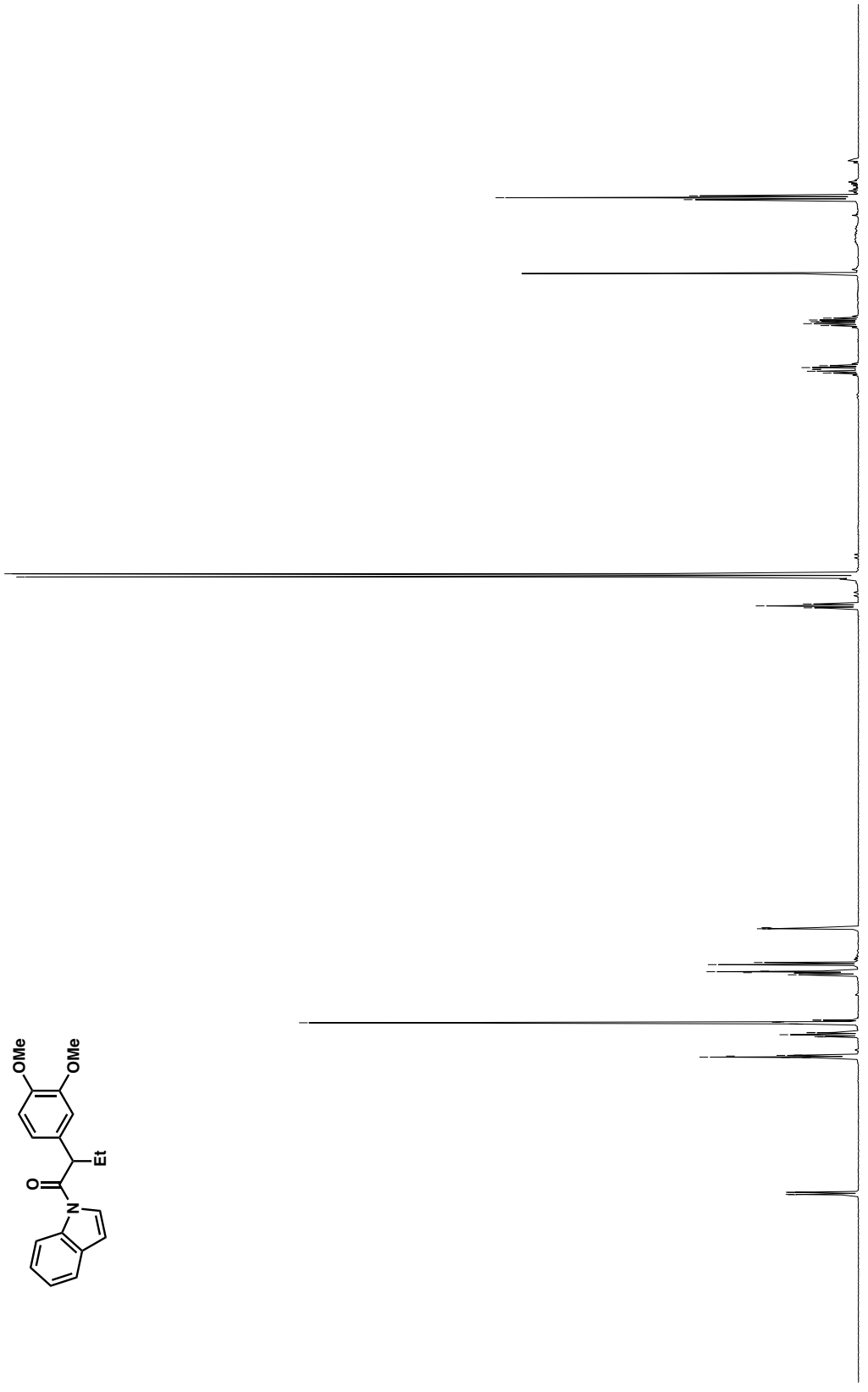



***Figure A5.103*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***48****.*




***A5.104*** *$^{1}H$ NMR (500 MHz, $CDCl_3$) of compound* ***49****.*

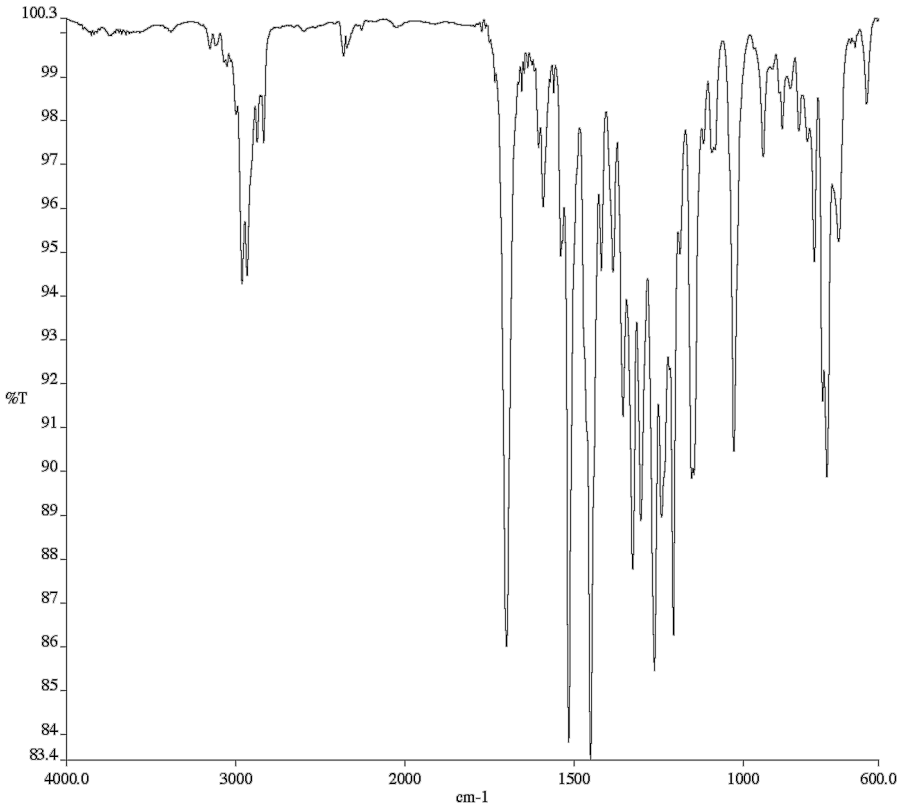



***Figure A5.105*** *Infrared spectrum (Thin Film, NaCl) of compound* ***49***.

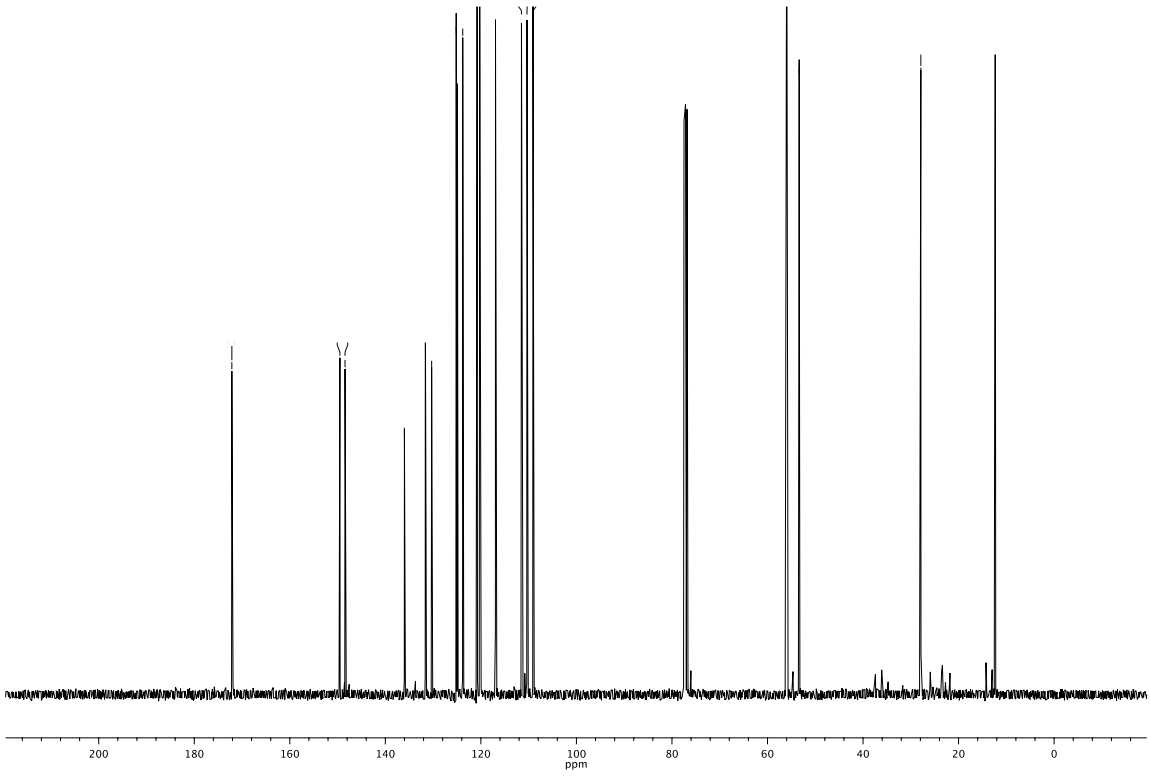
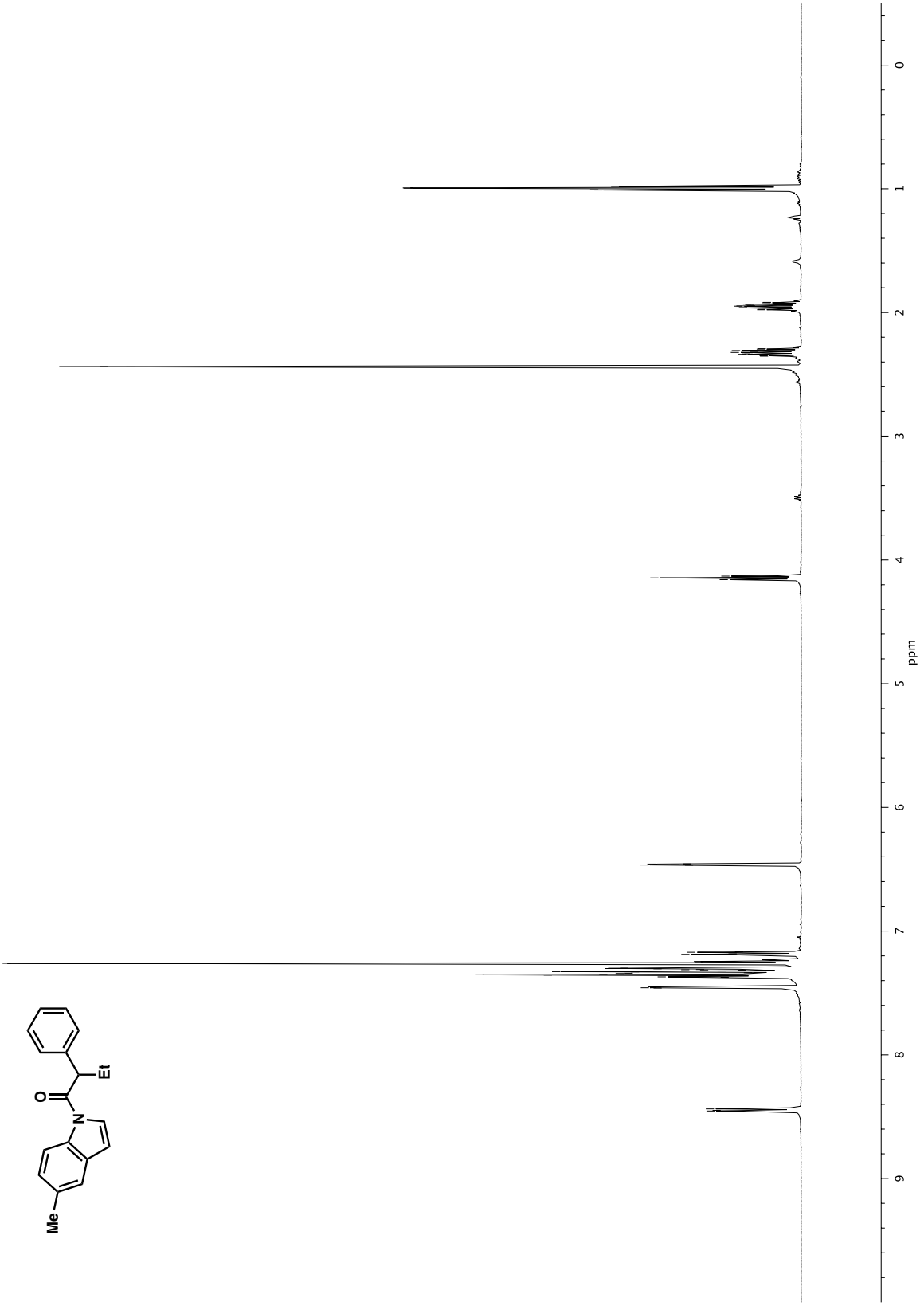



***Figure A5.106*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***49***.




***A5.107*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***50****.*

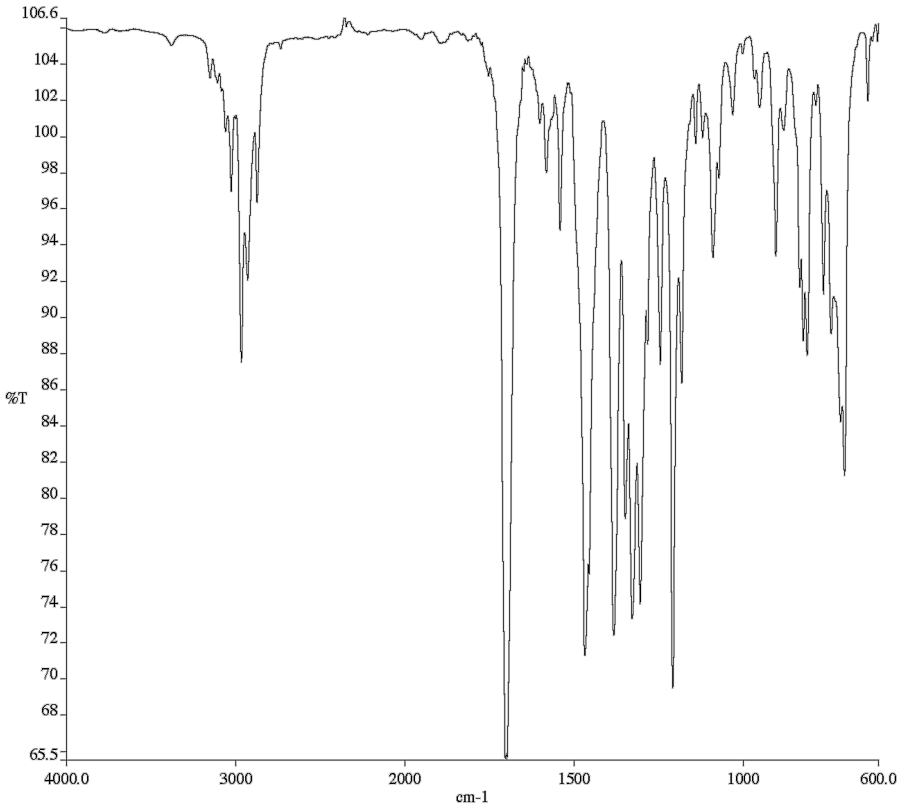



***Figure A5.108*** *Infrared spectrum (Thin Film, NaCl) of compound* ***50****.*

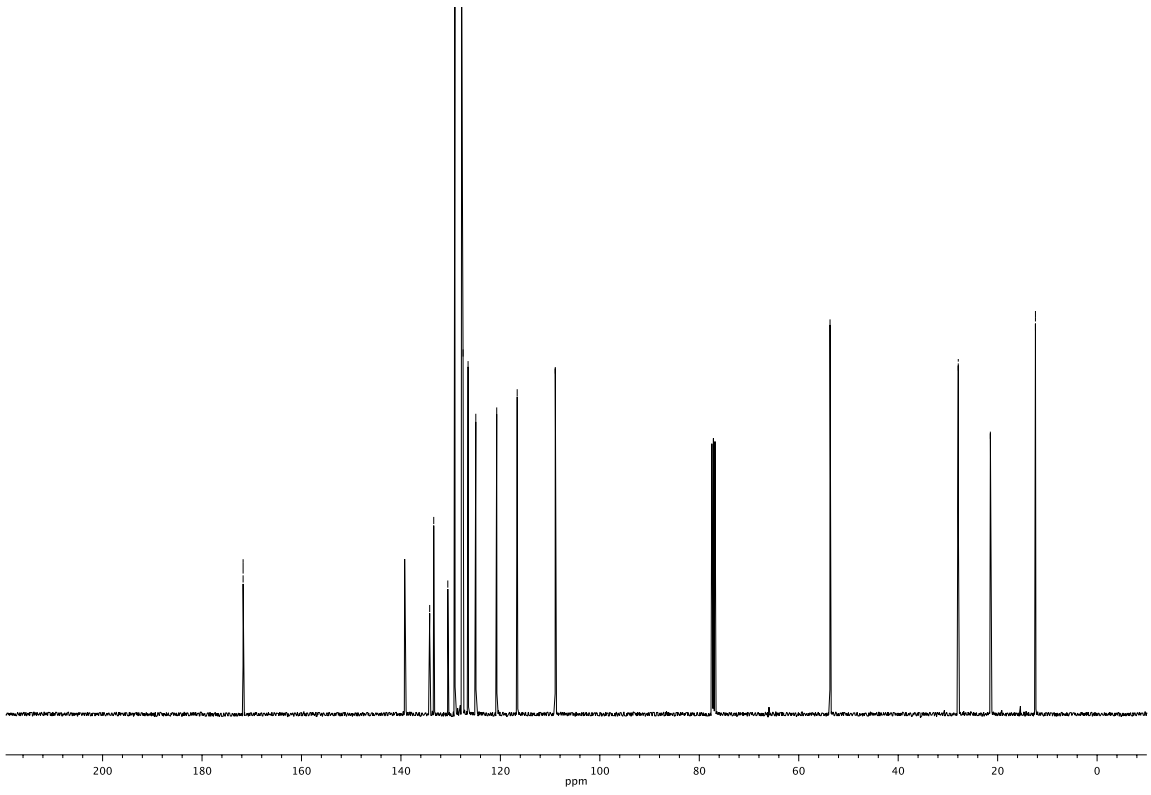
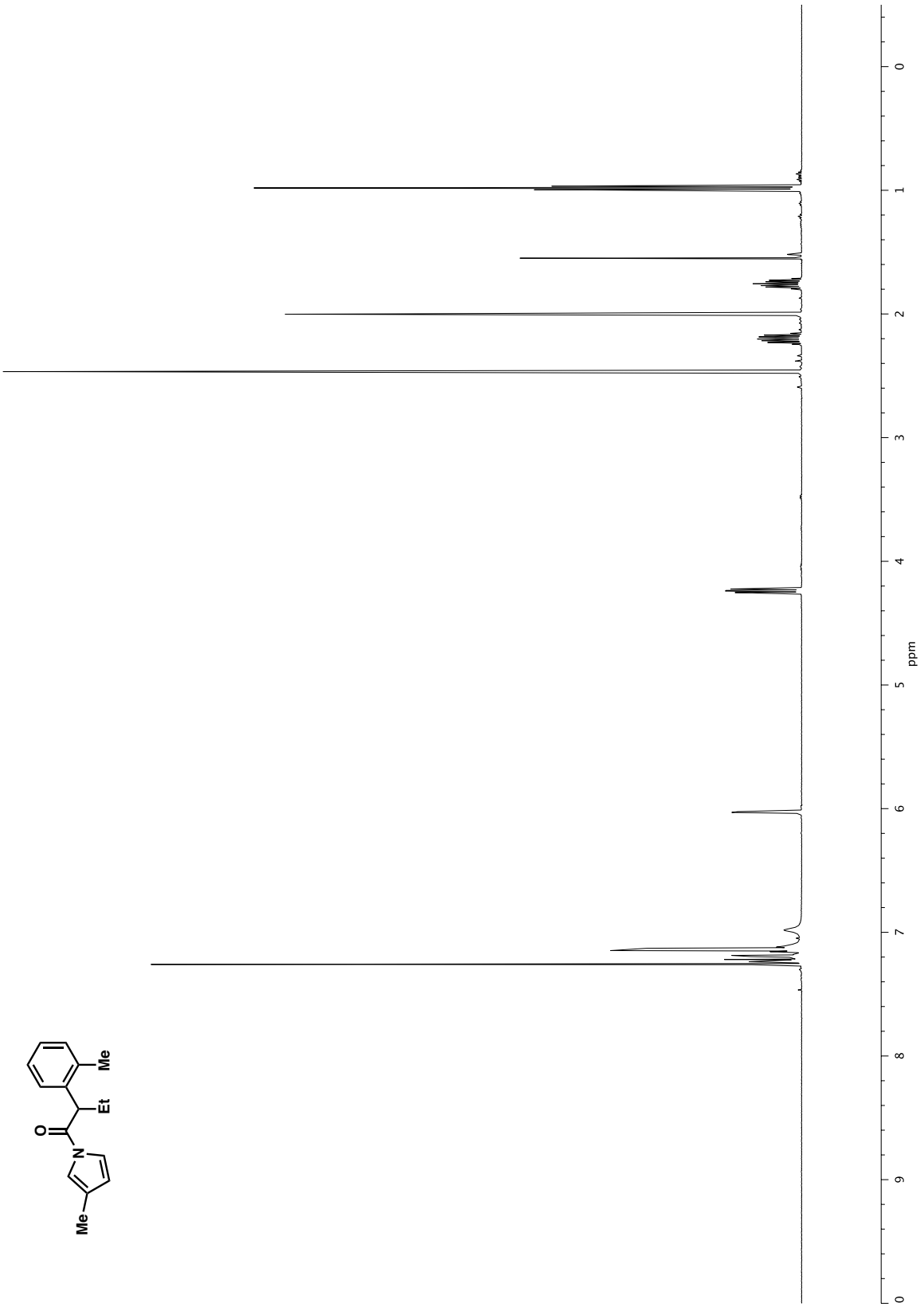



***Figure A5.109*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***50****.*




***A5.110*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***51****.*

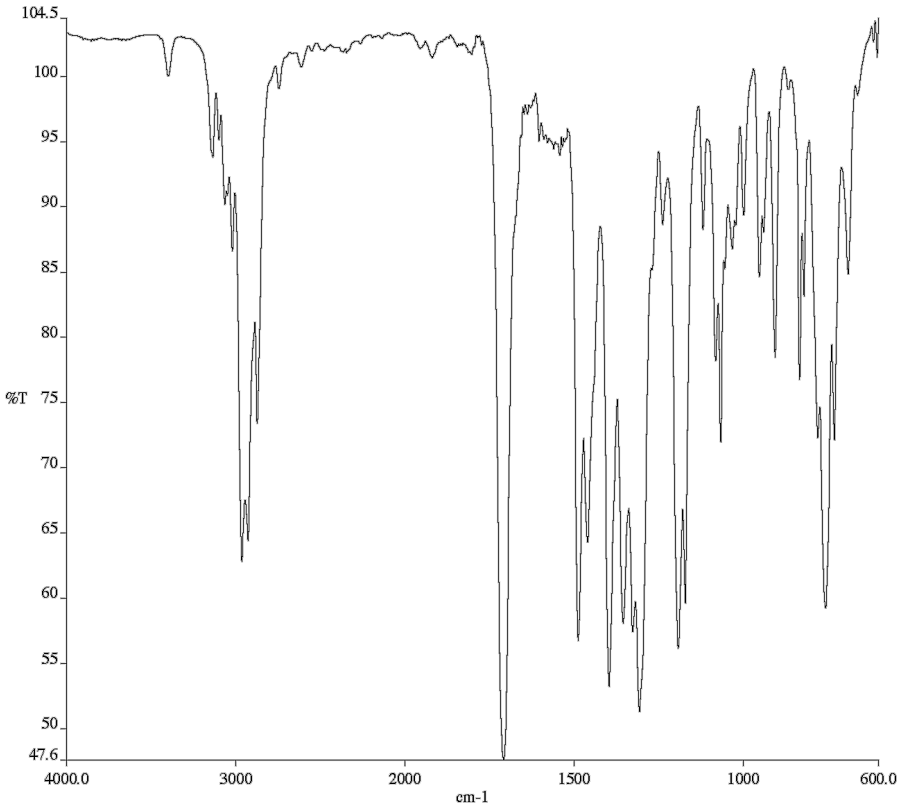



***Figure A5.111*** *Infrared spectrum (Thin Film, NaCl) of compound* ***51***.

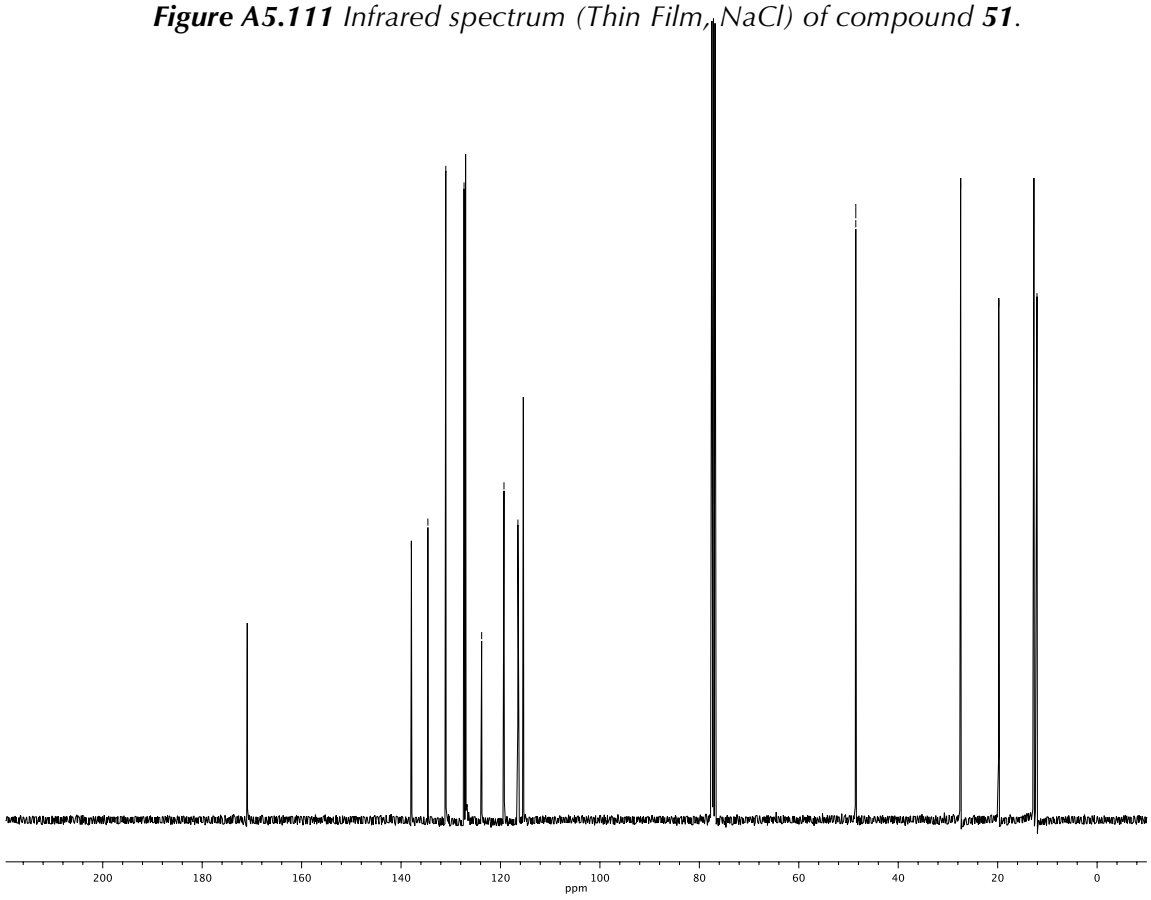
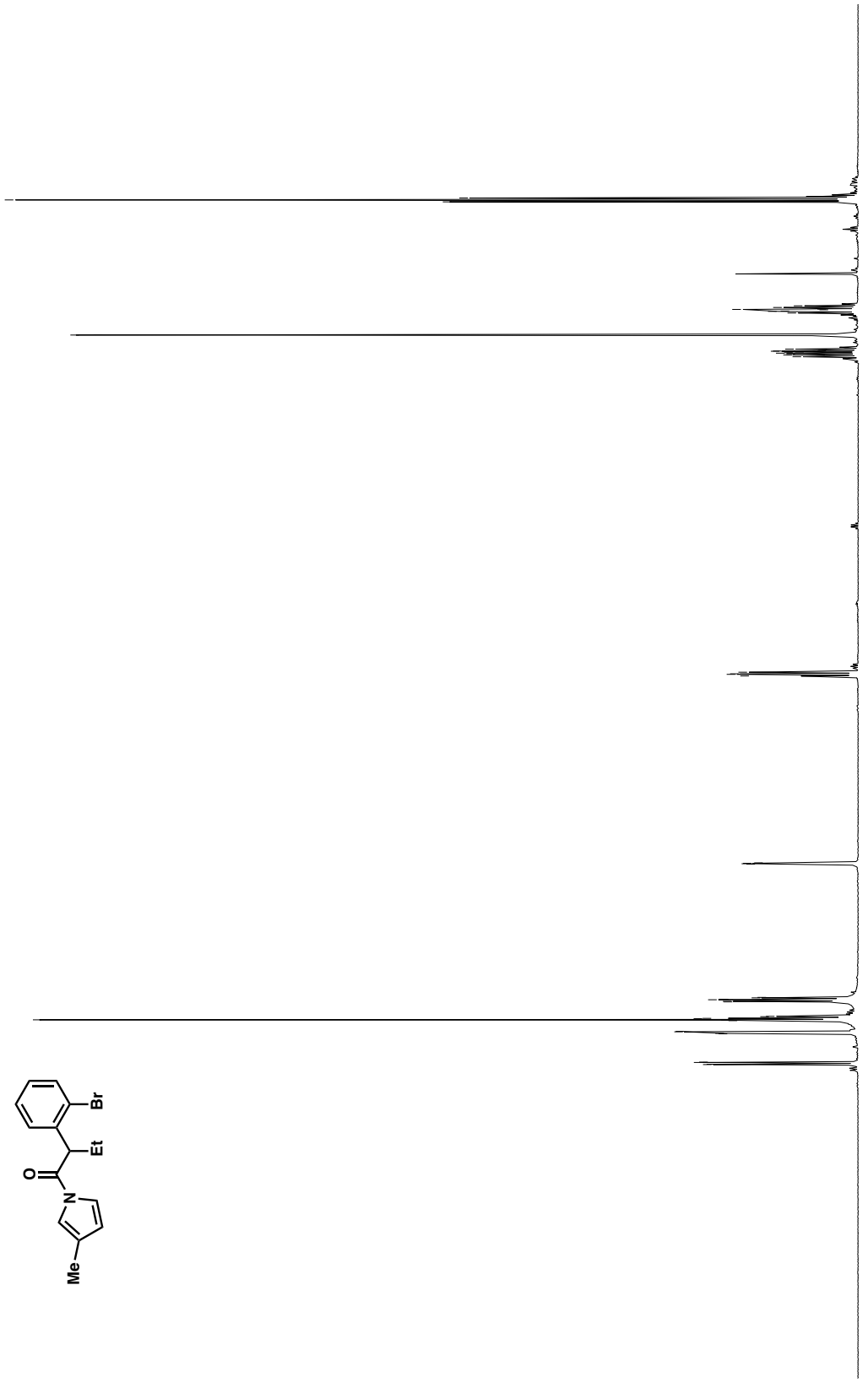



***Figure A5.112*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***51***.




***A5.113*** *$^{1}H$ NMR (500 MHz, $CDCl_3$) of compound* ***52****.*

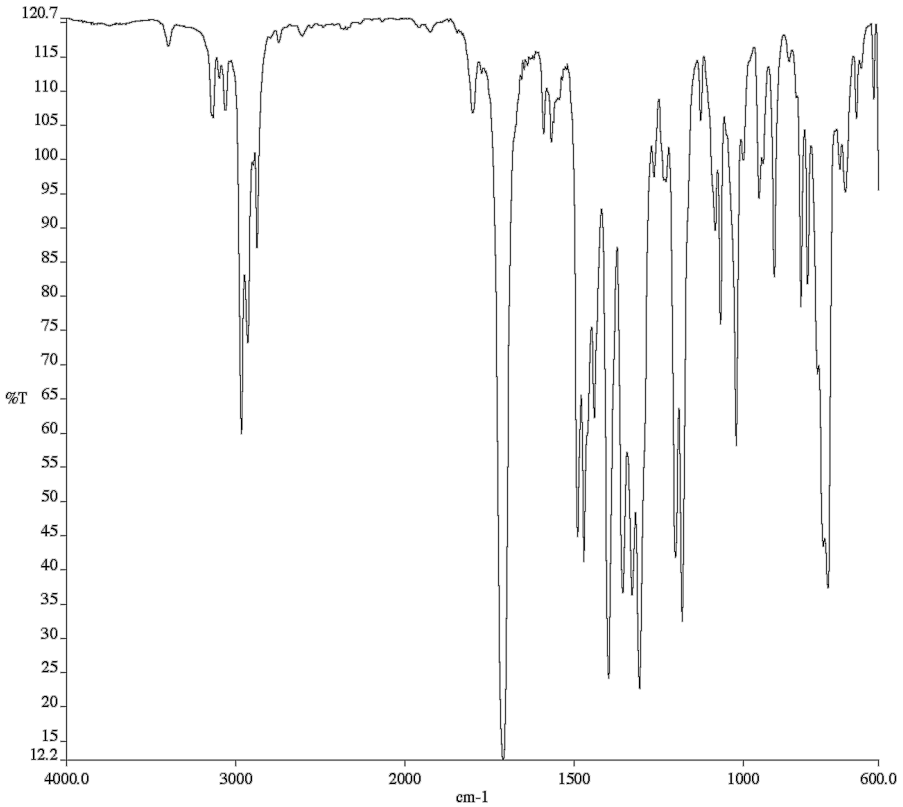



***Figure A5.114*** *Infrared spectrum (Thin Film, NaCl) of compound* ***52****.*

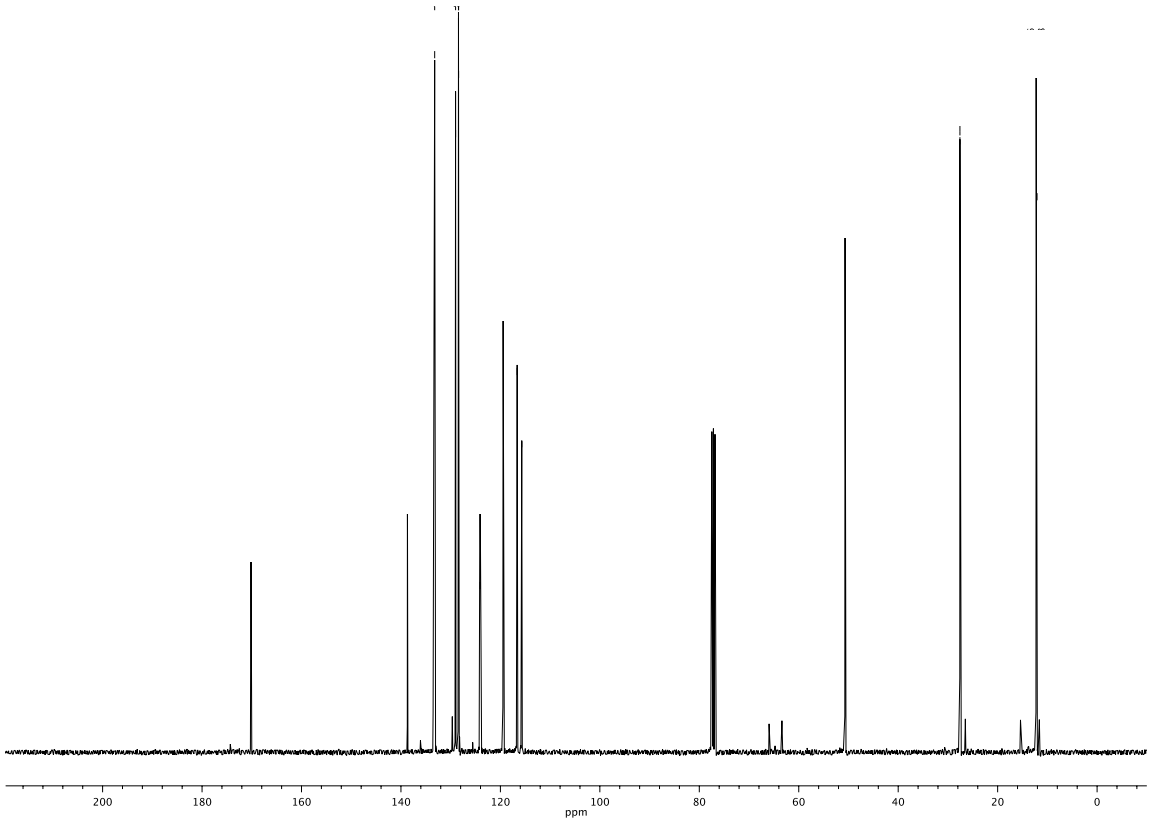
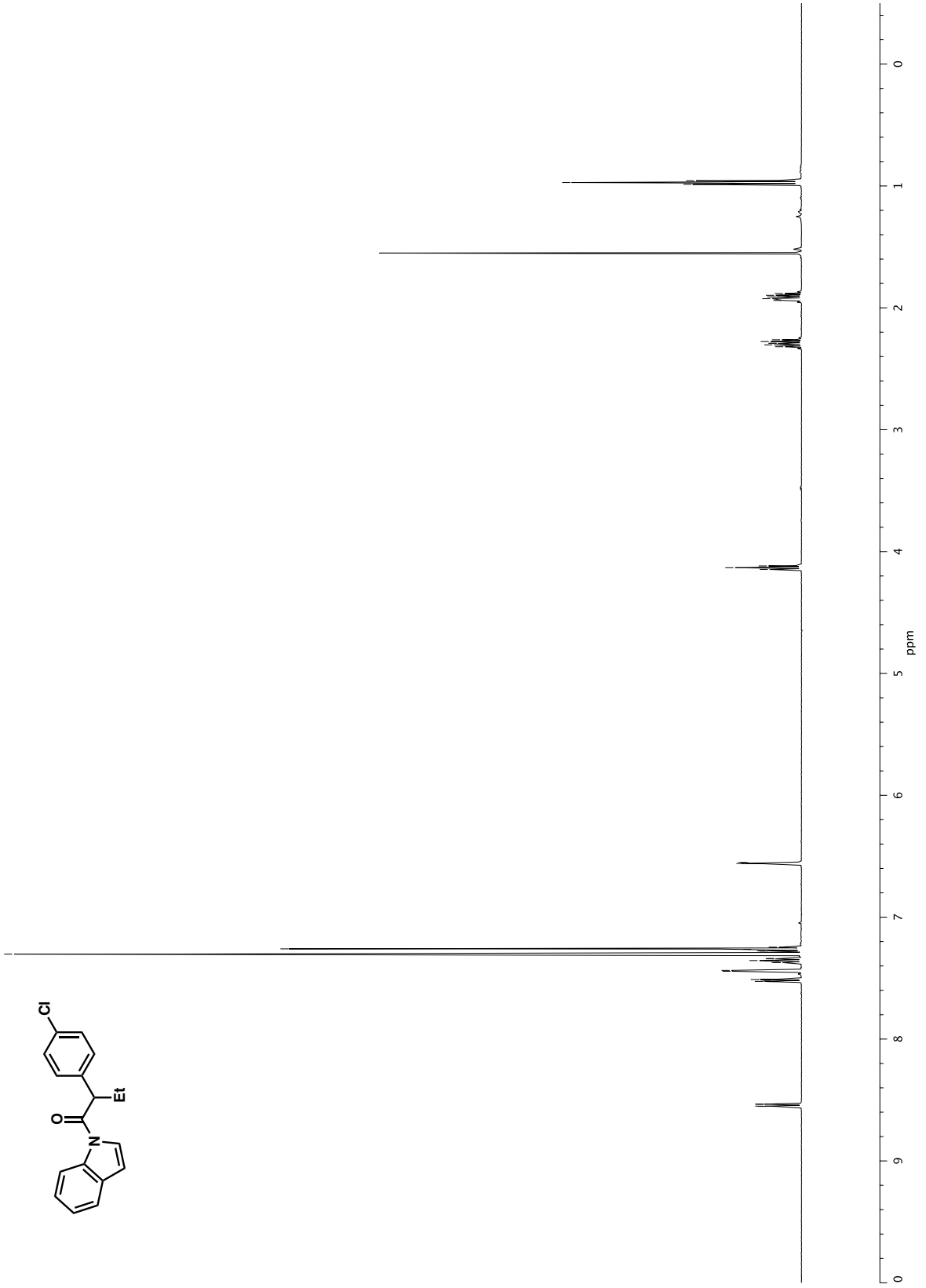



***Figure A5.115*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***52****.*




***A5.116*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***53****.*

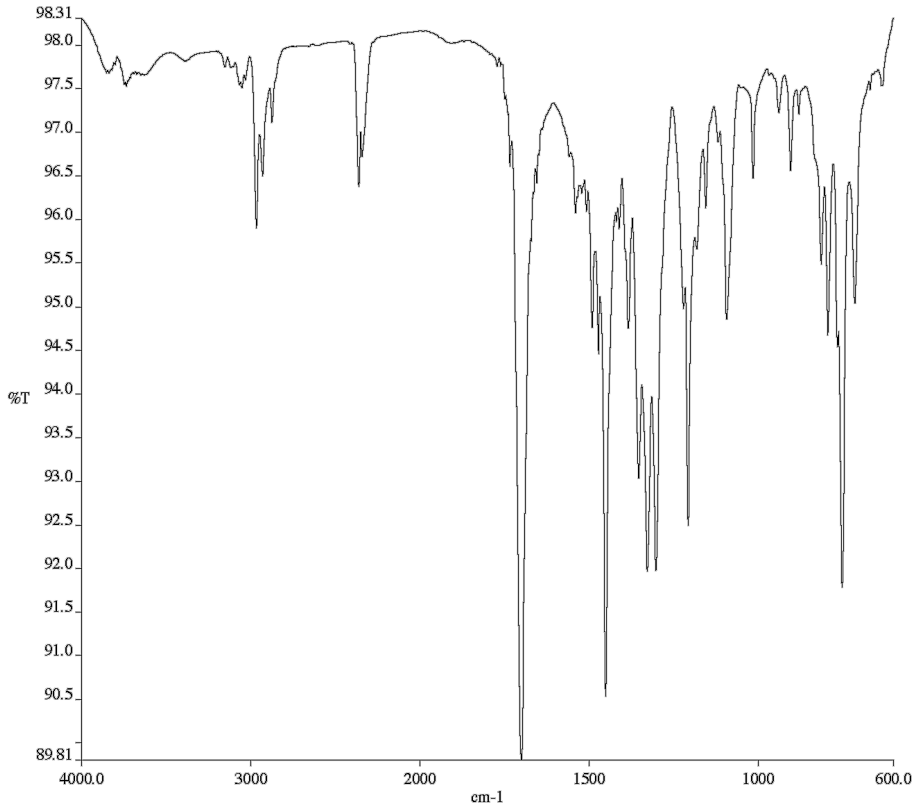



***Figure A5.117*** *Infrared spectrum (Thin Film, NaCl) of compound* ***53***.

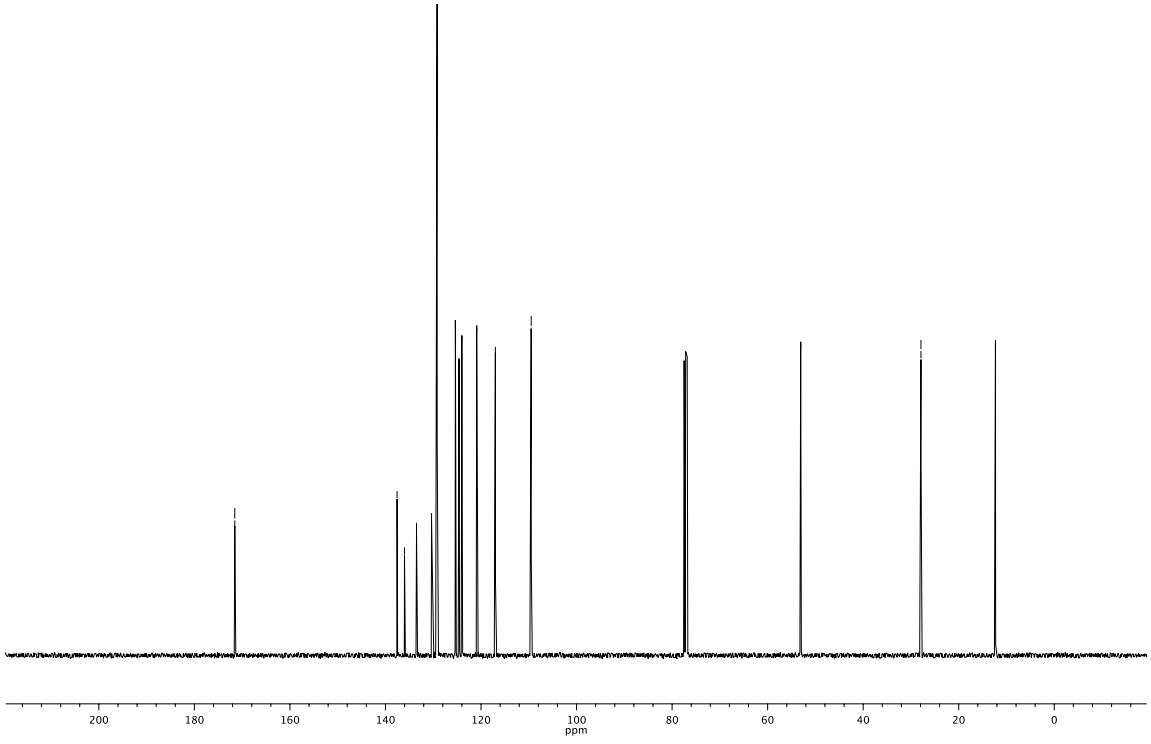
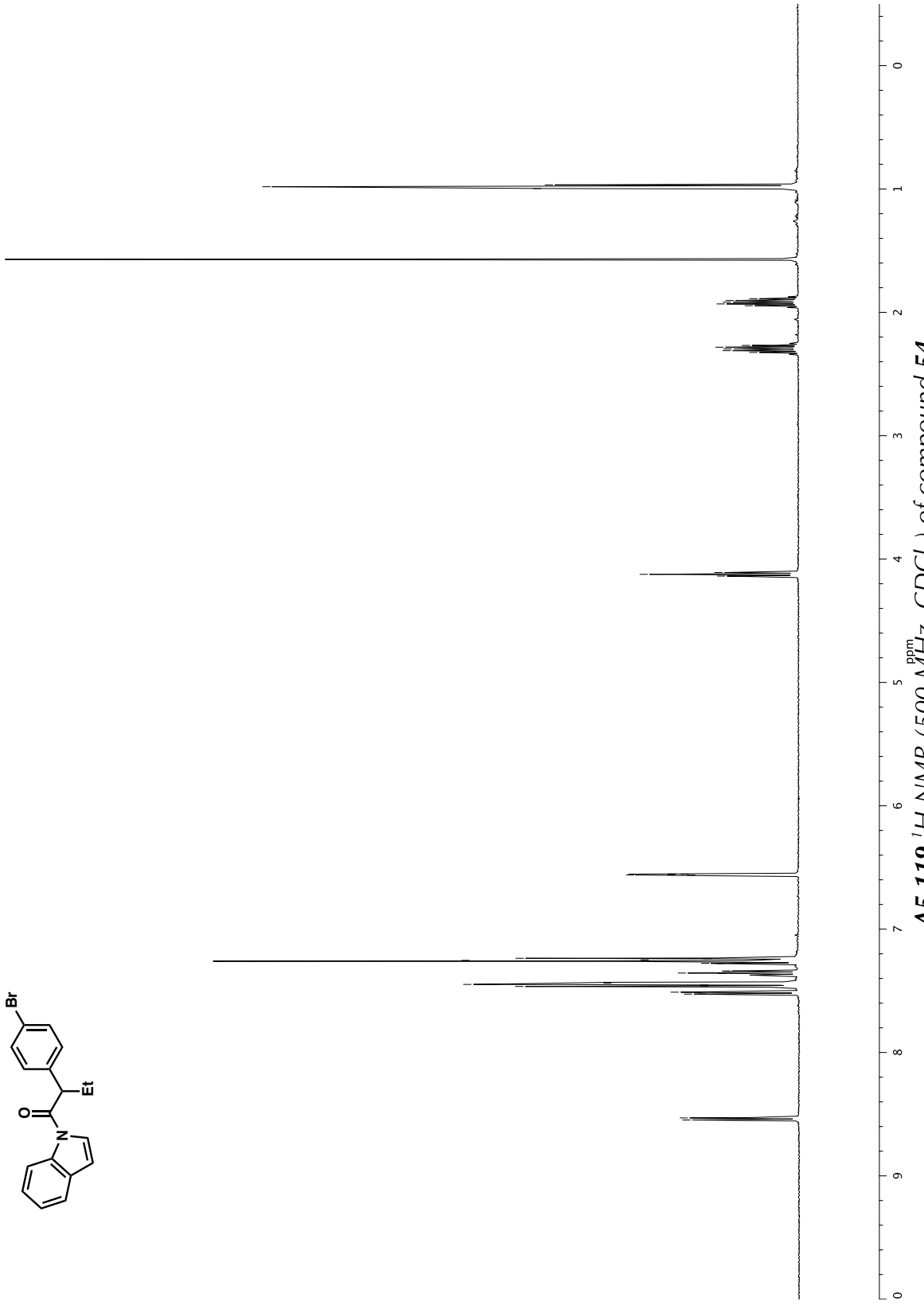



***Figure A5.118*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***53***.




***A5.119*** *$^{1}H$ NMR (500 MHz, $CDCl_3$) of compound* ***54****.*

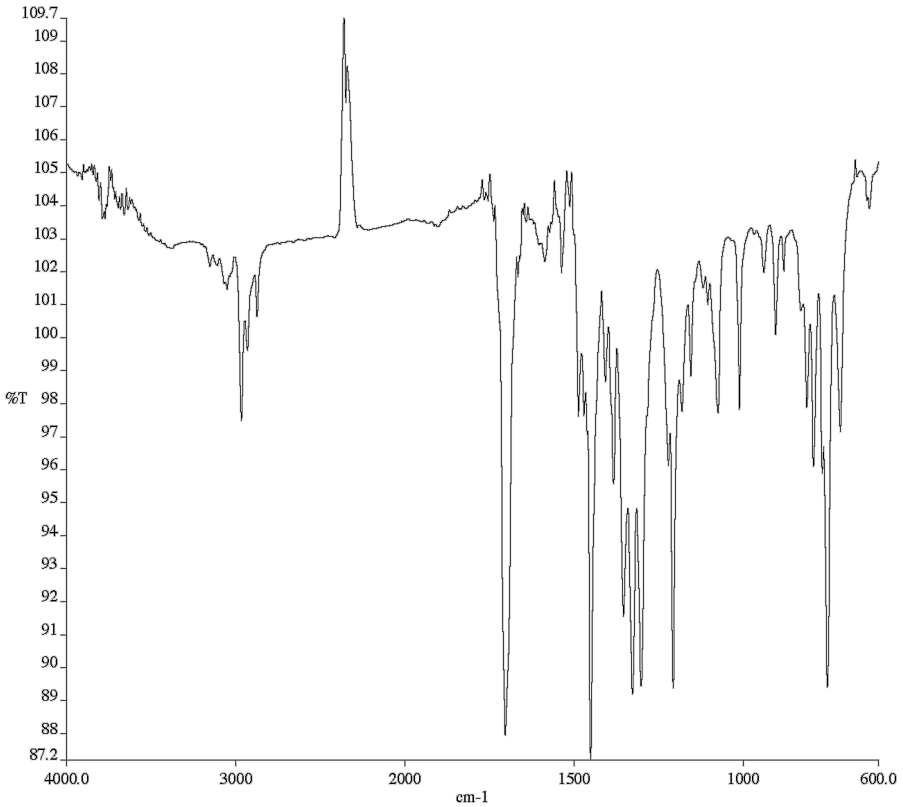



***Figure A5.120*** *Infrared spectrum (Thin Film, NaCl) of compound* ***54****.*

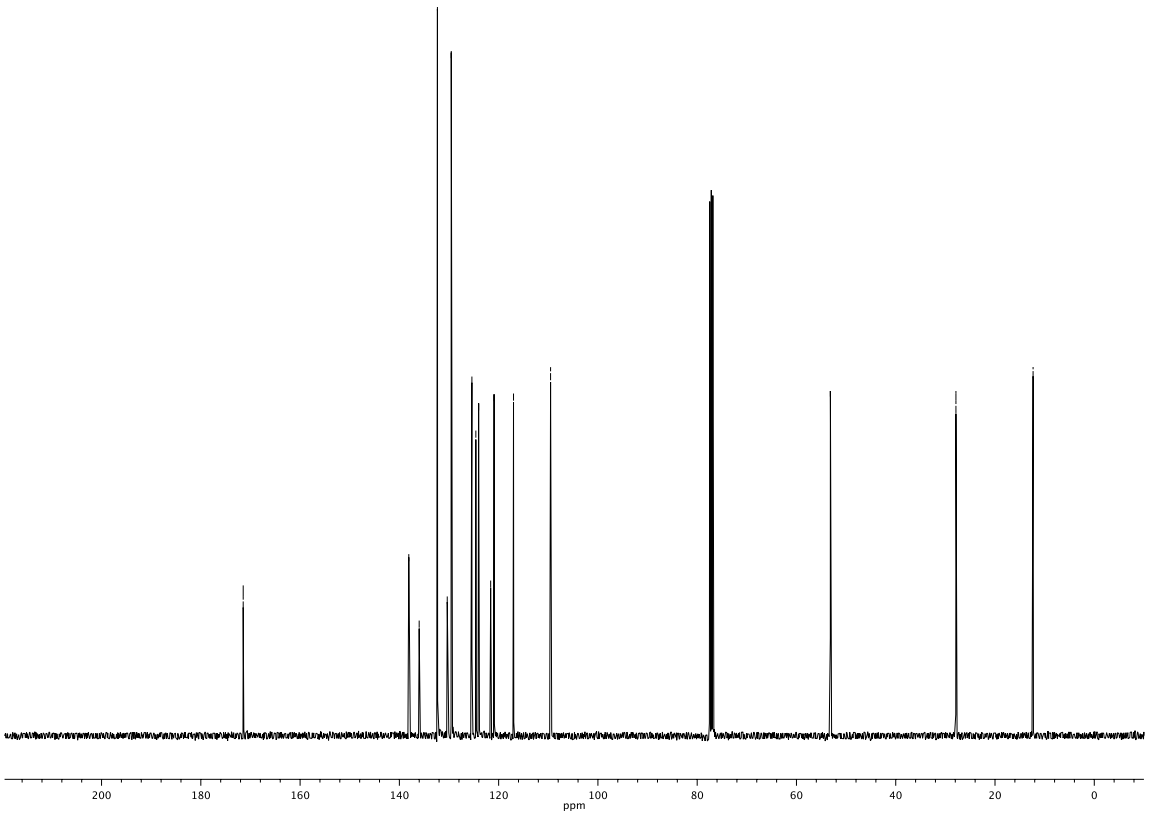
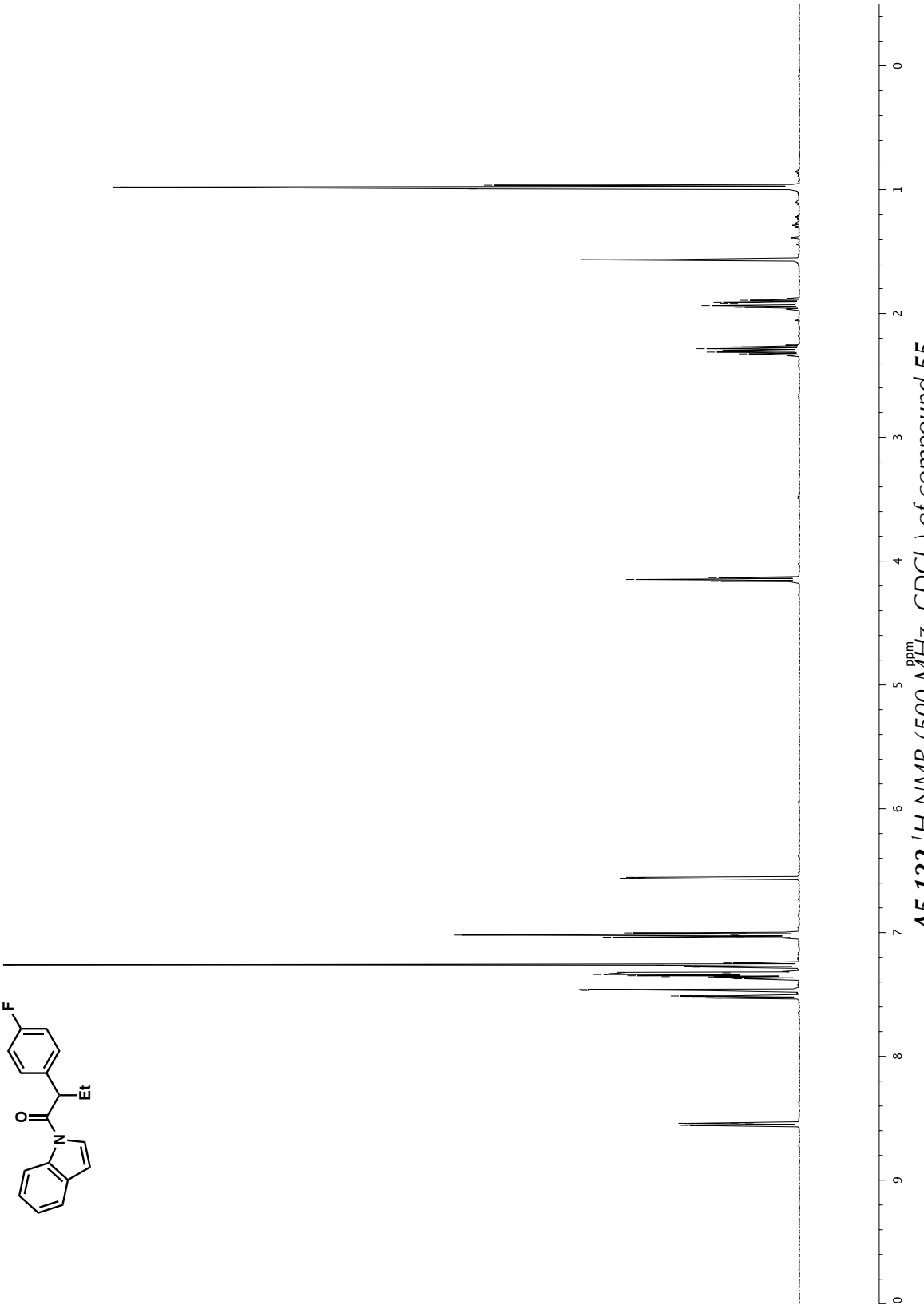



***Figure A5.121*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***54****.*




***A5.122*** *$^{1}H$ NMR (500 MHz, $CDCl_3$) of compound* ***55****.*

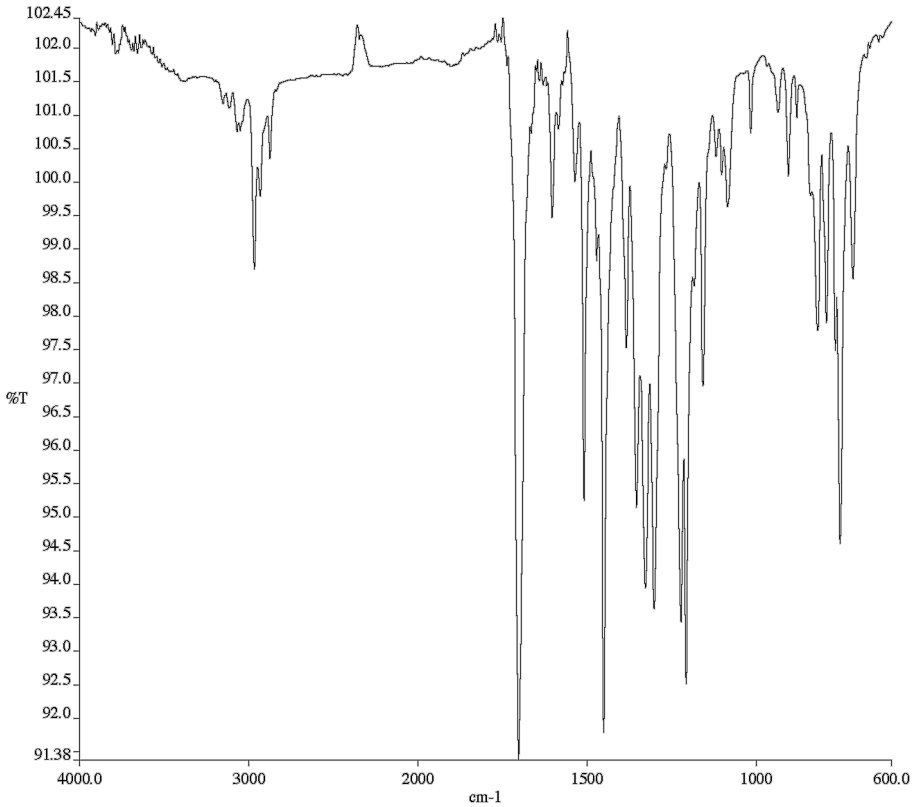



***Figure A5.123*** *Infrared spectrum (Thin Film, NaCl) of compound* ***55***.

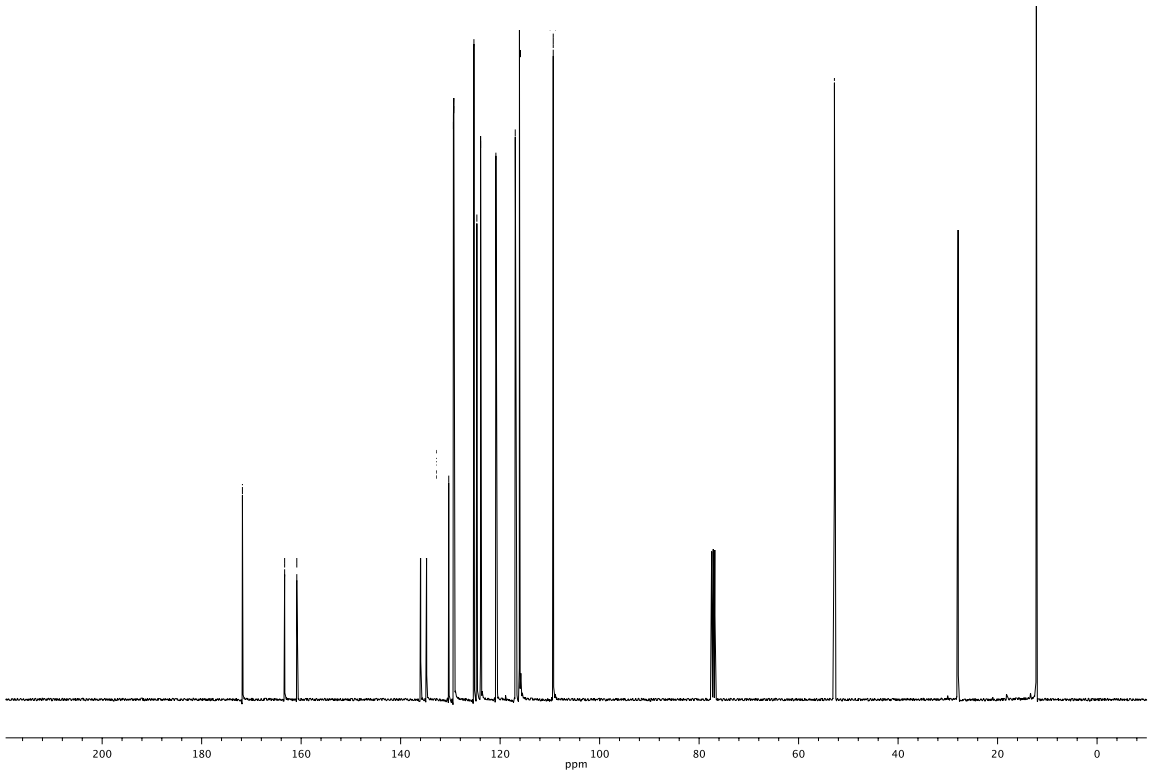



***Figure A5.124*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***55***.

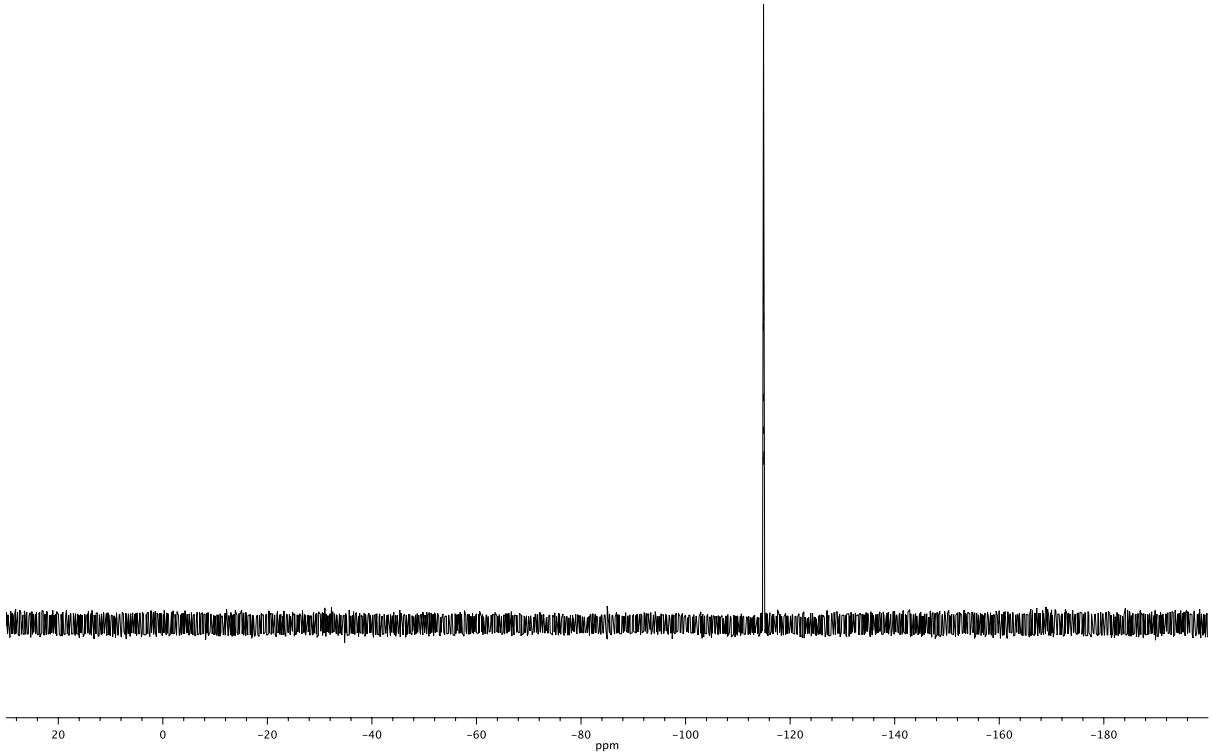
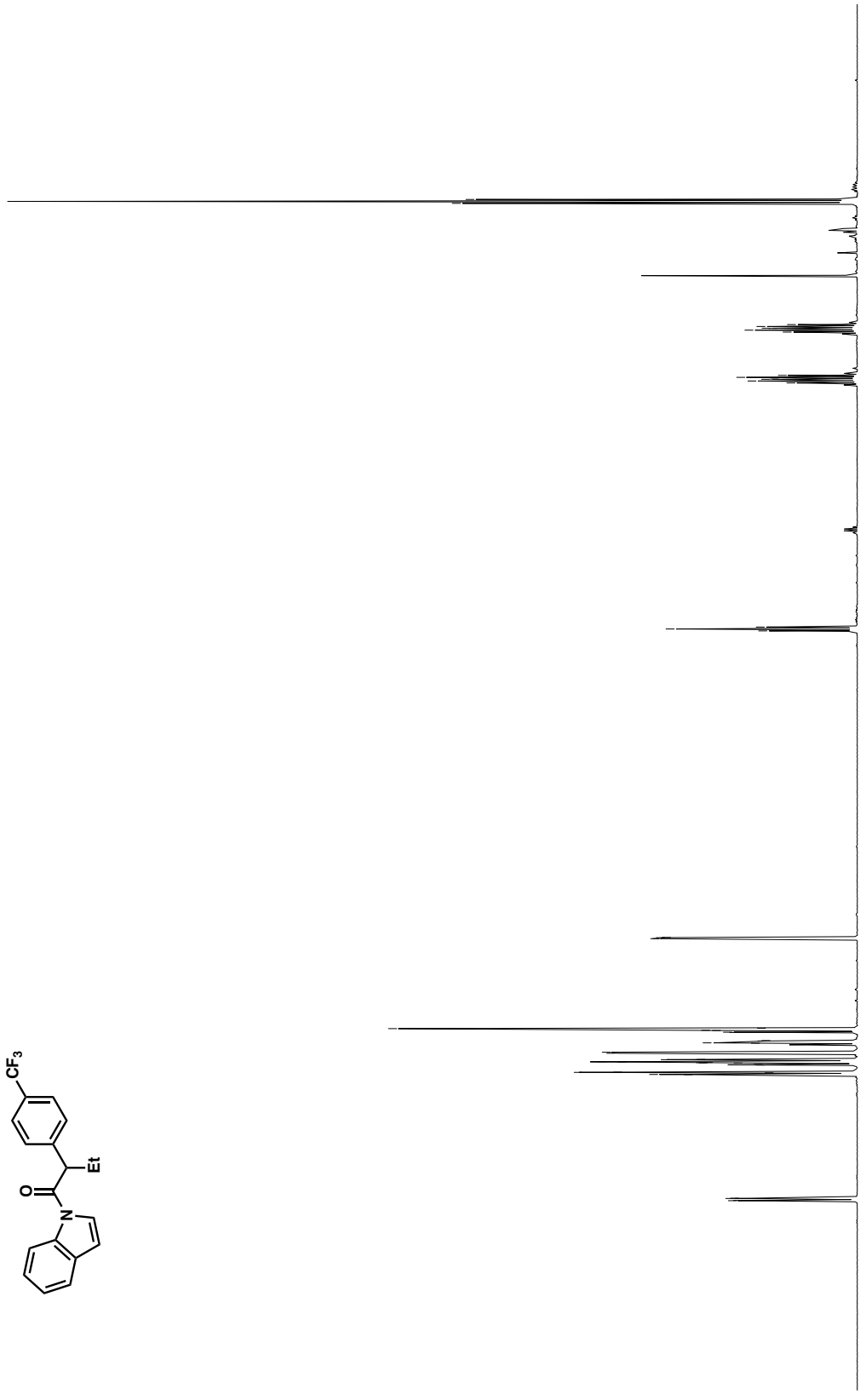



***Figure A5.125*** *$^{19}F$ NMR (282 MHz, $CDCl_3$) of compound* ***55****.*




***A5.126*** *$^{1}H$ NMR (500 MHz, $CDCl_3$) of compound* ***56****.*

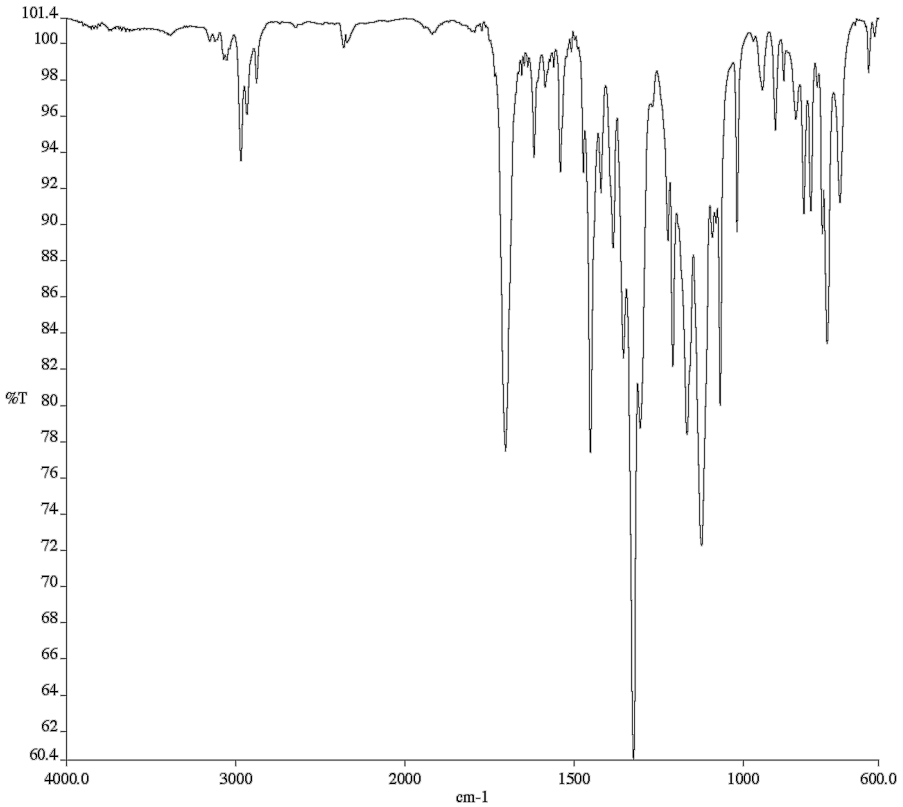



***Figure A5.127*** *Infrared spectrum (Thin Film, NaCl) of compound* ***56***.

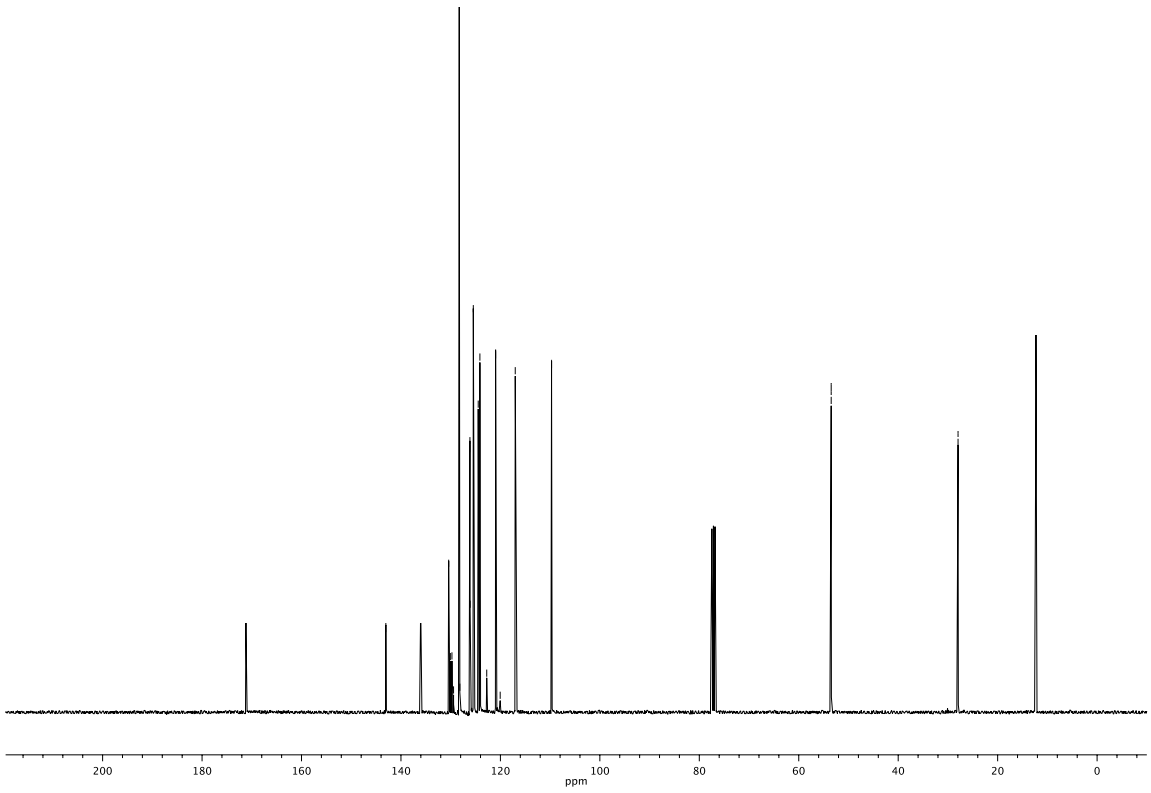



***Figure A5.128*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***56***.

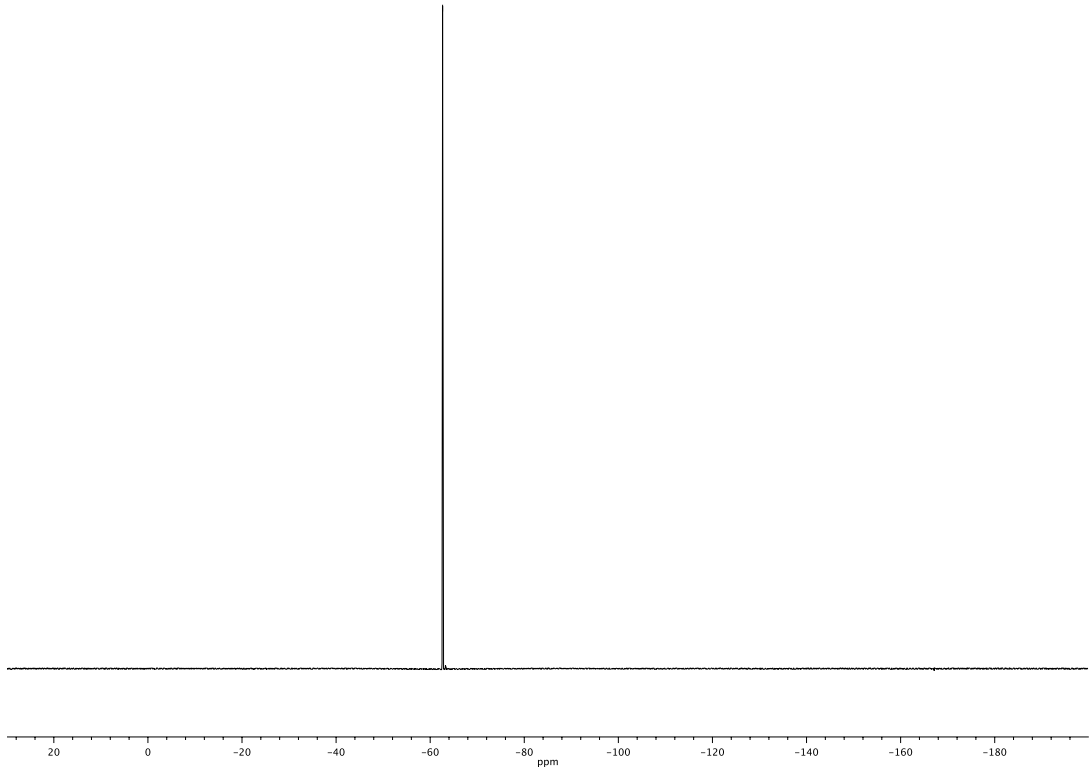
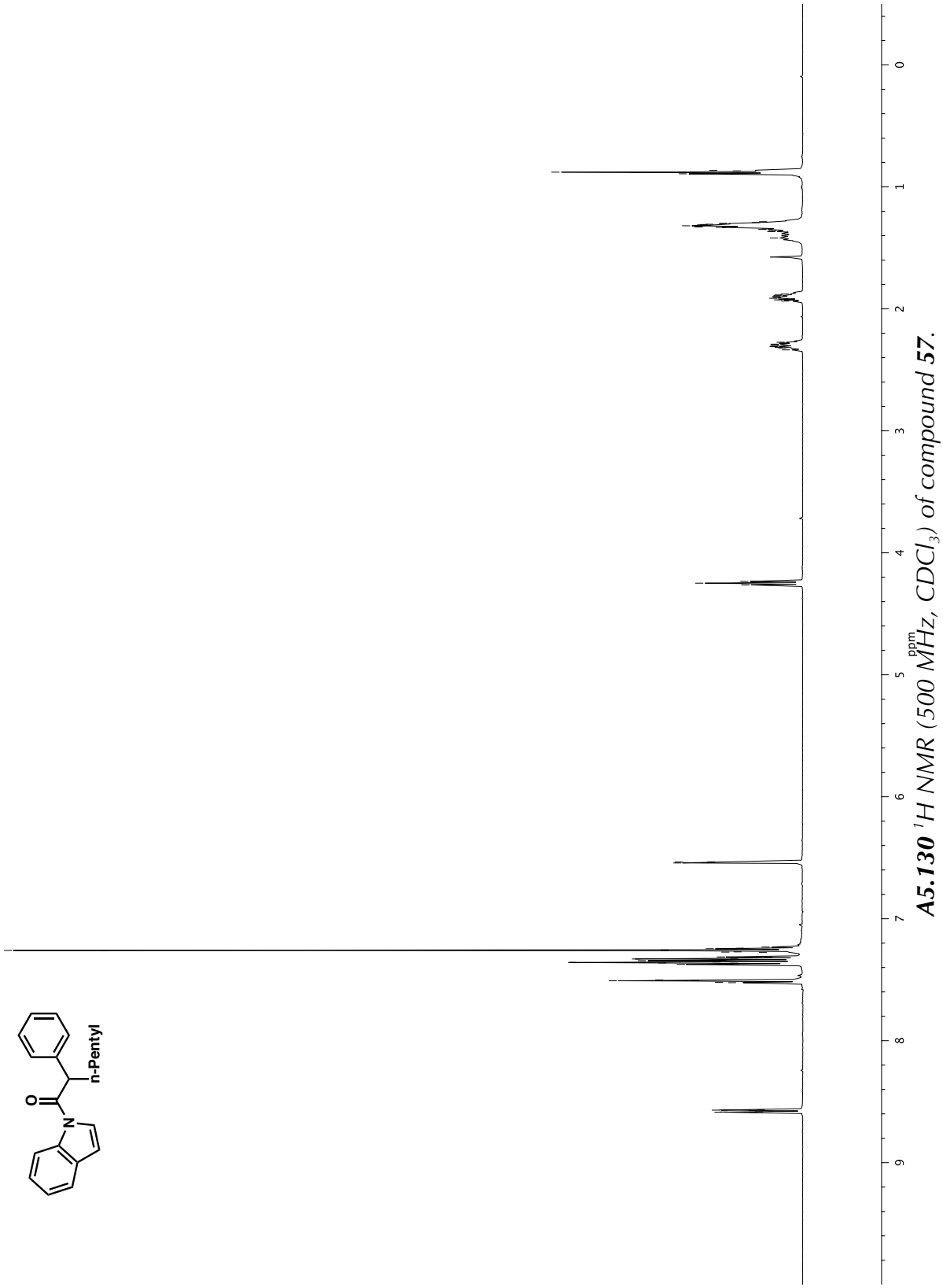



***Figure A5.129*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***56***.




***A5.130*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***57****.*

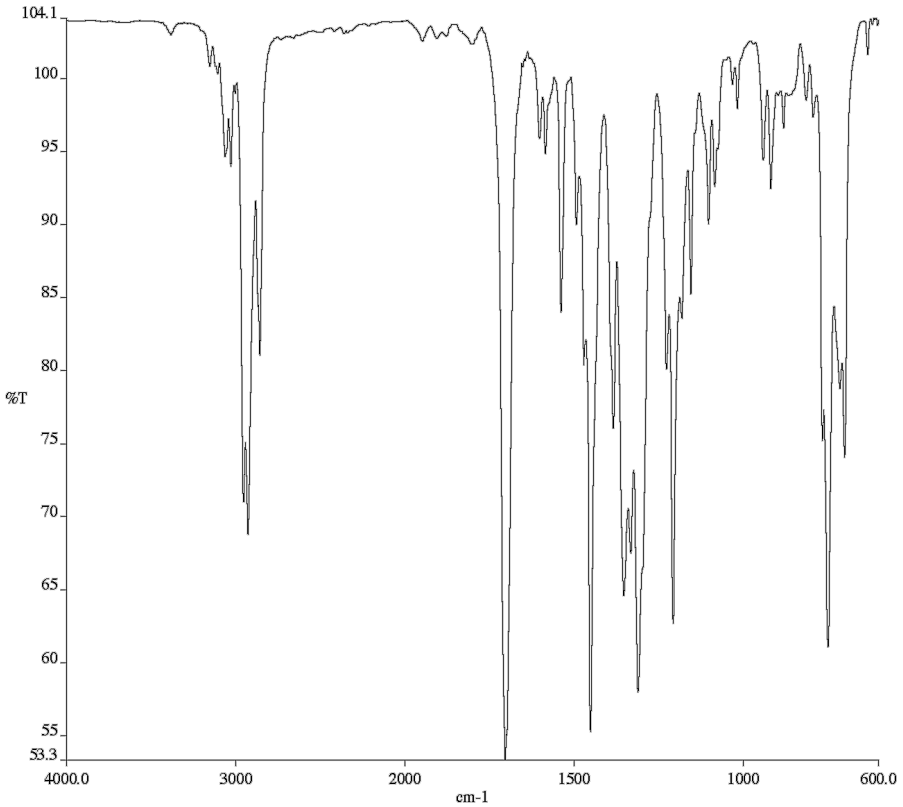



***Figure A5.131*** *Infrared spectrum (Thin Film, NaCl) of compound* ***57****.*

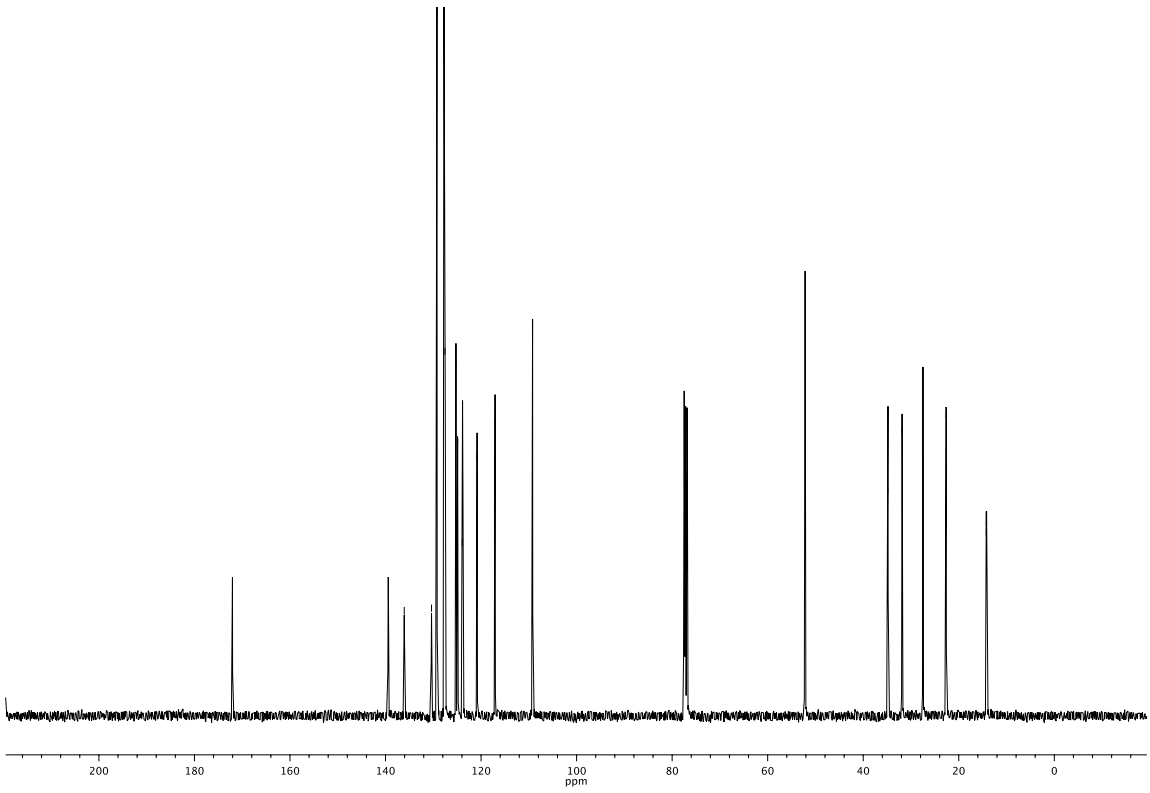
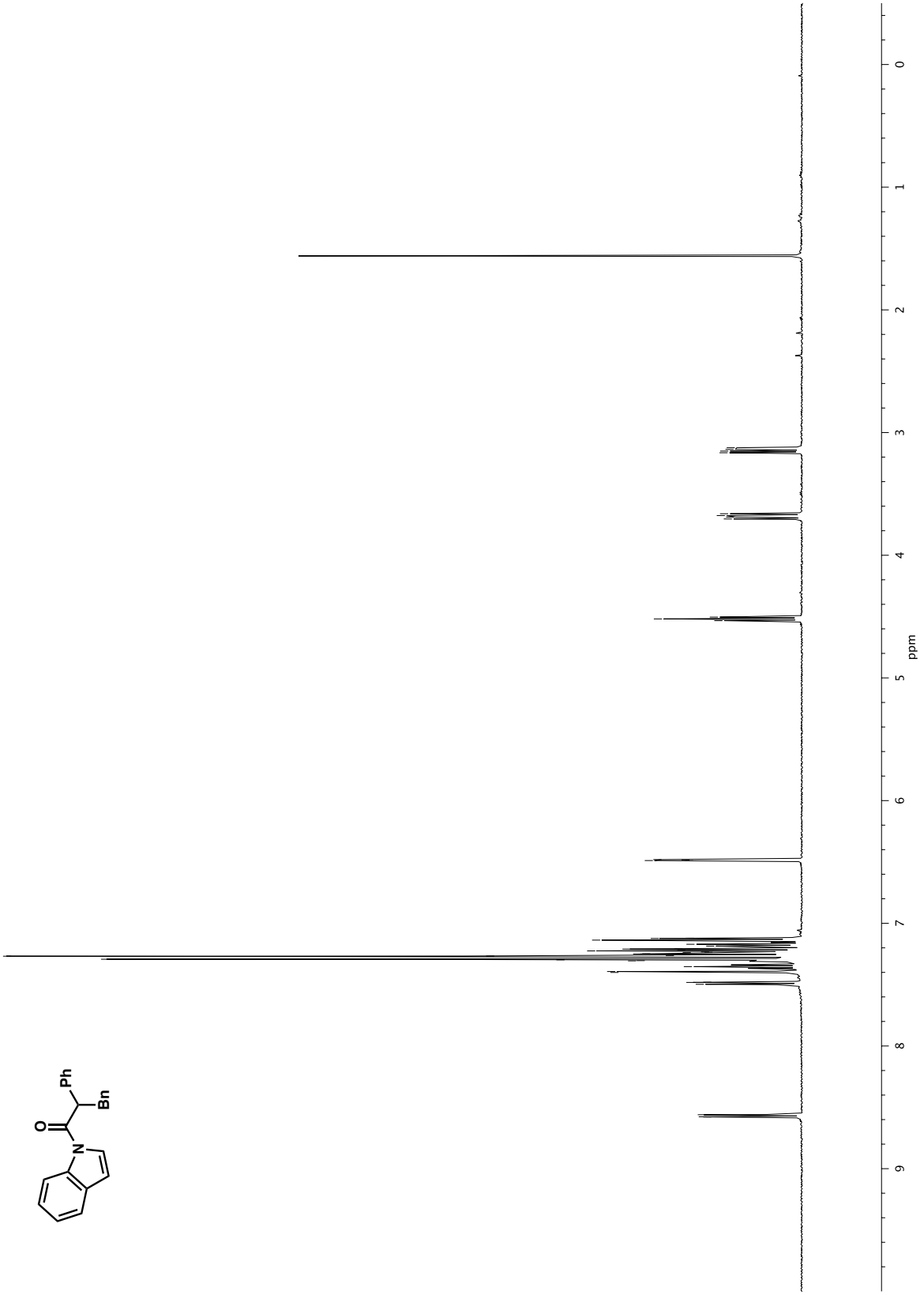



***Figure A5.132*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***57****.*




***A5.133*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***58****.*

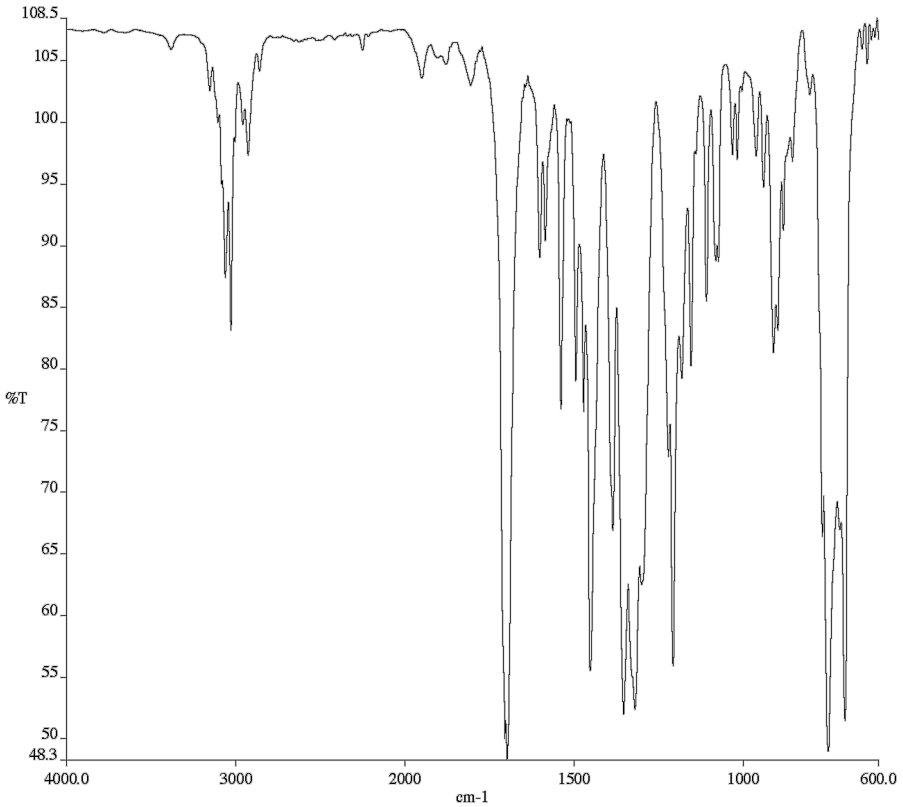



***Figure A5.134*** *Infrared spectrum (Thin Film, NaCl) of compound* ***58****.*

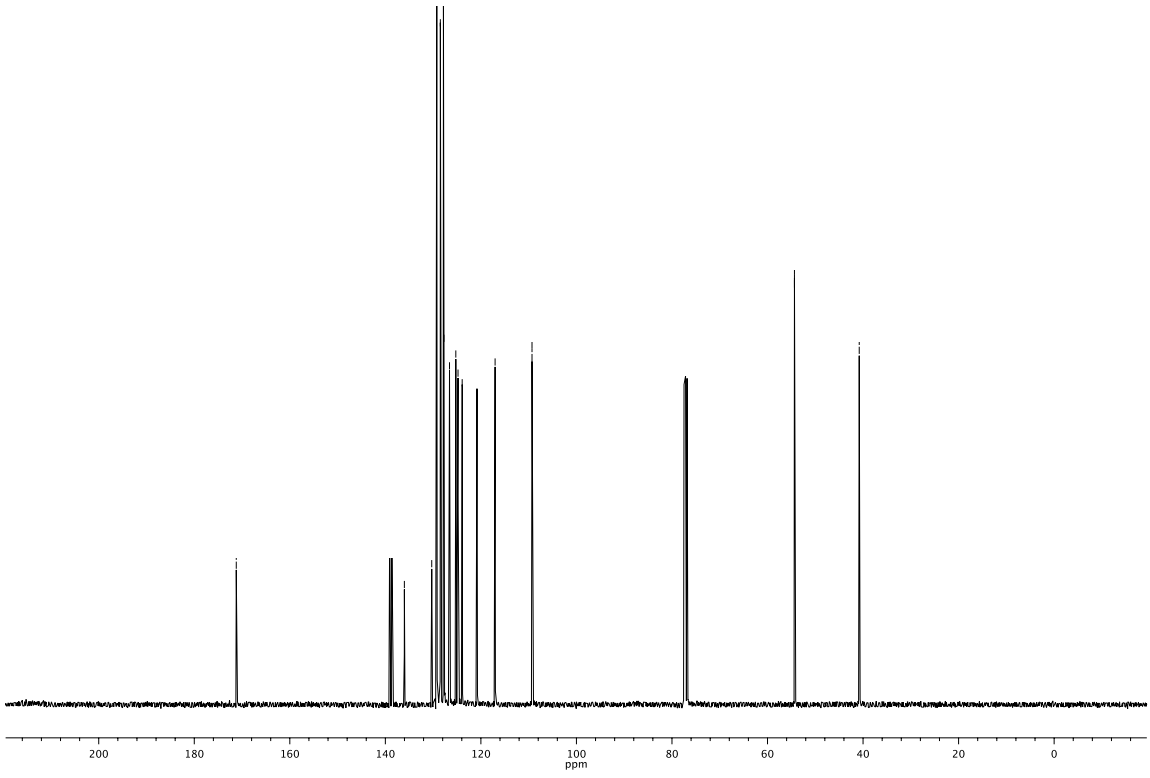
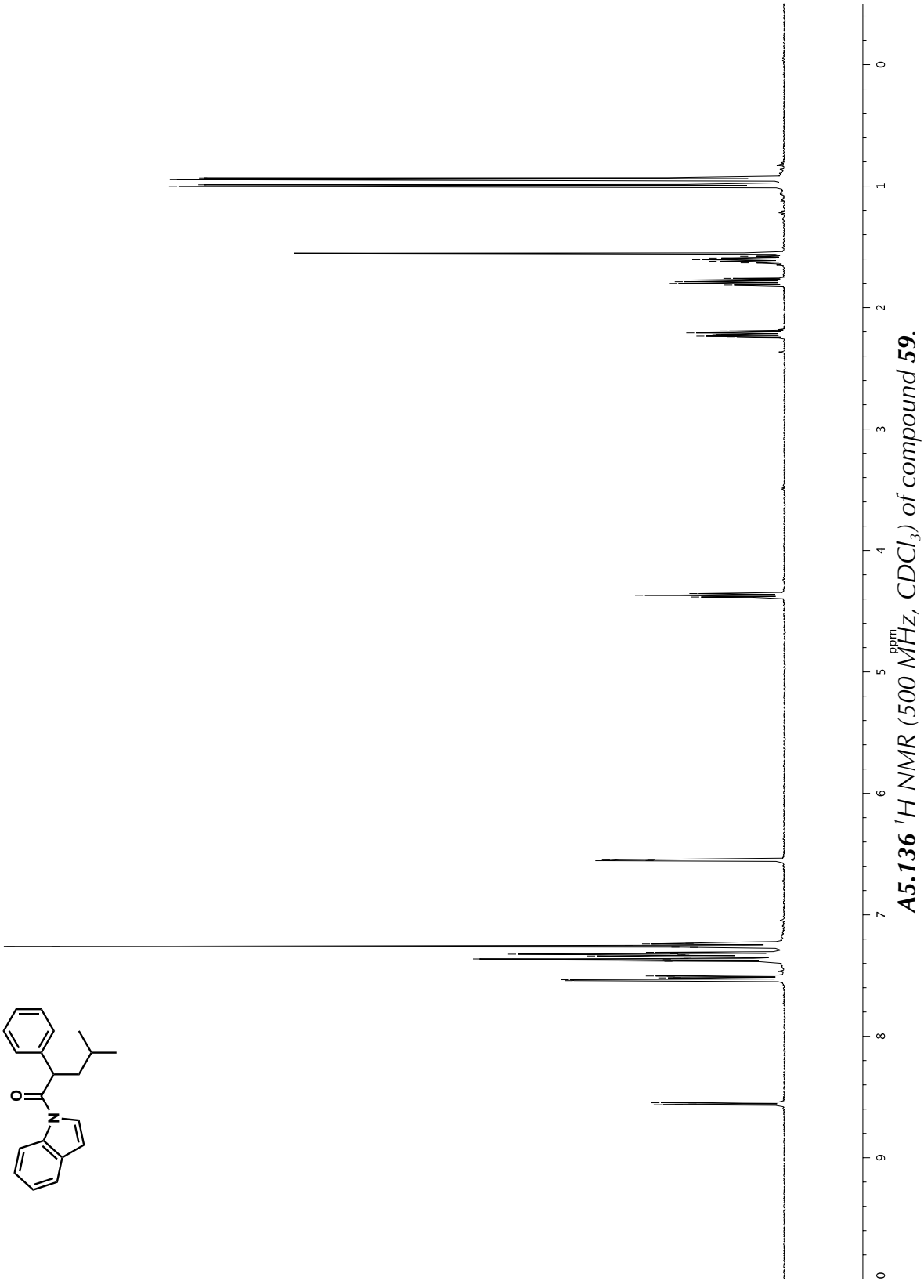



***Figure A5.135*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***58****.*




***A5.136*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***59***.

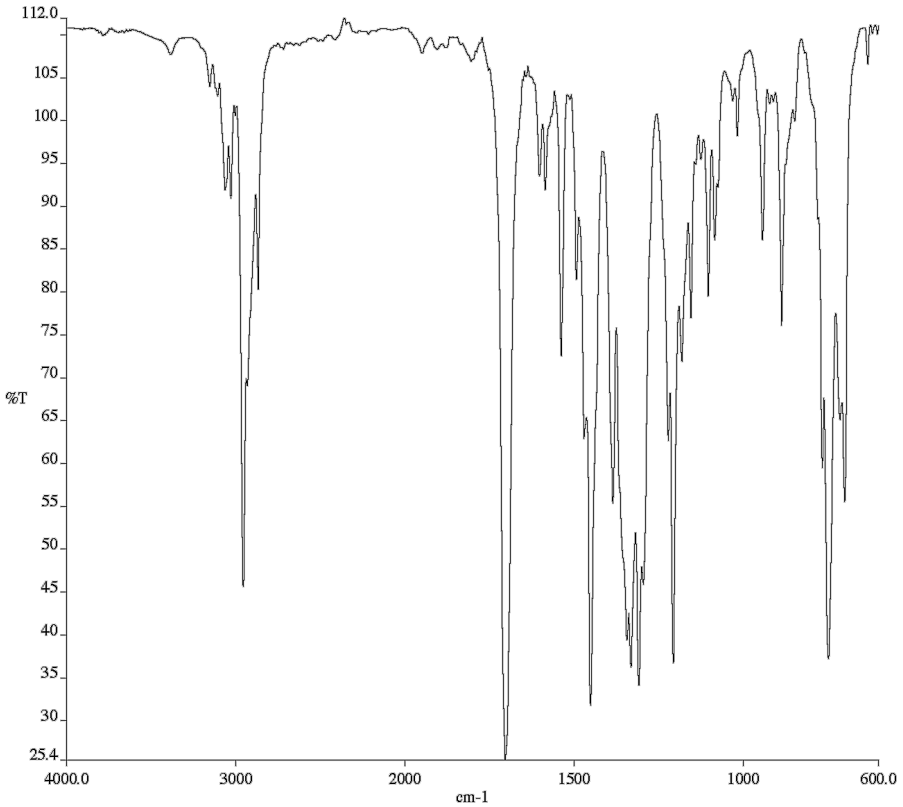



***Figure A5.137*** *Infrared spectrum (Thin Film, NaCl) of compound* ***59****.*

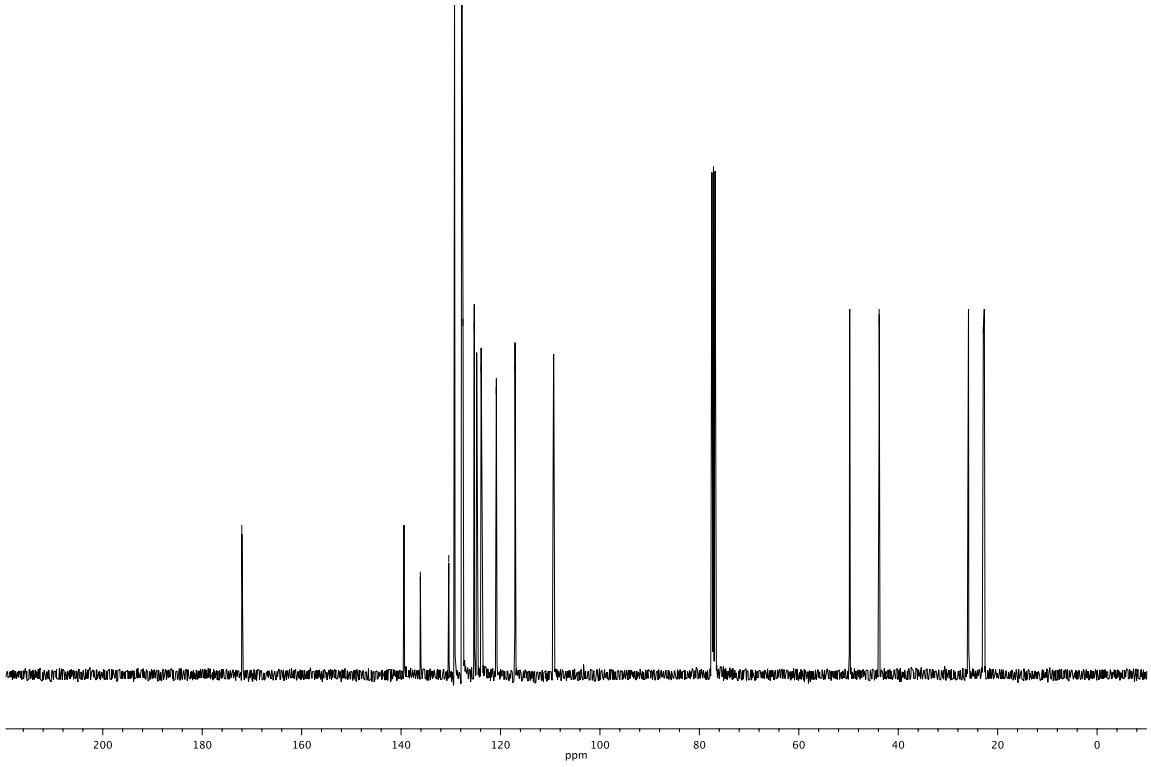
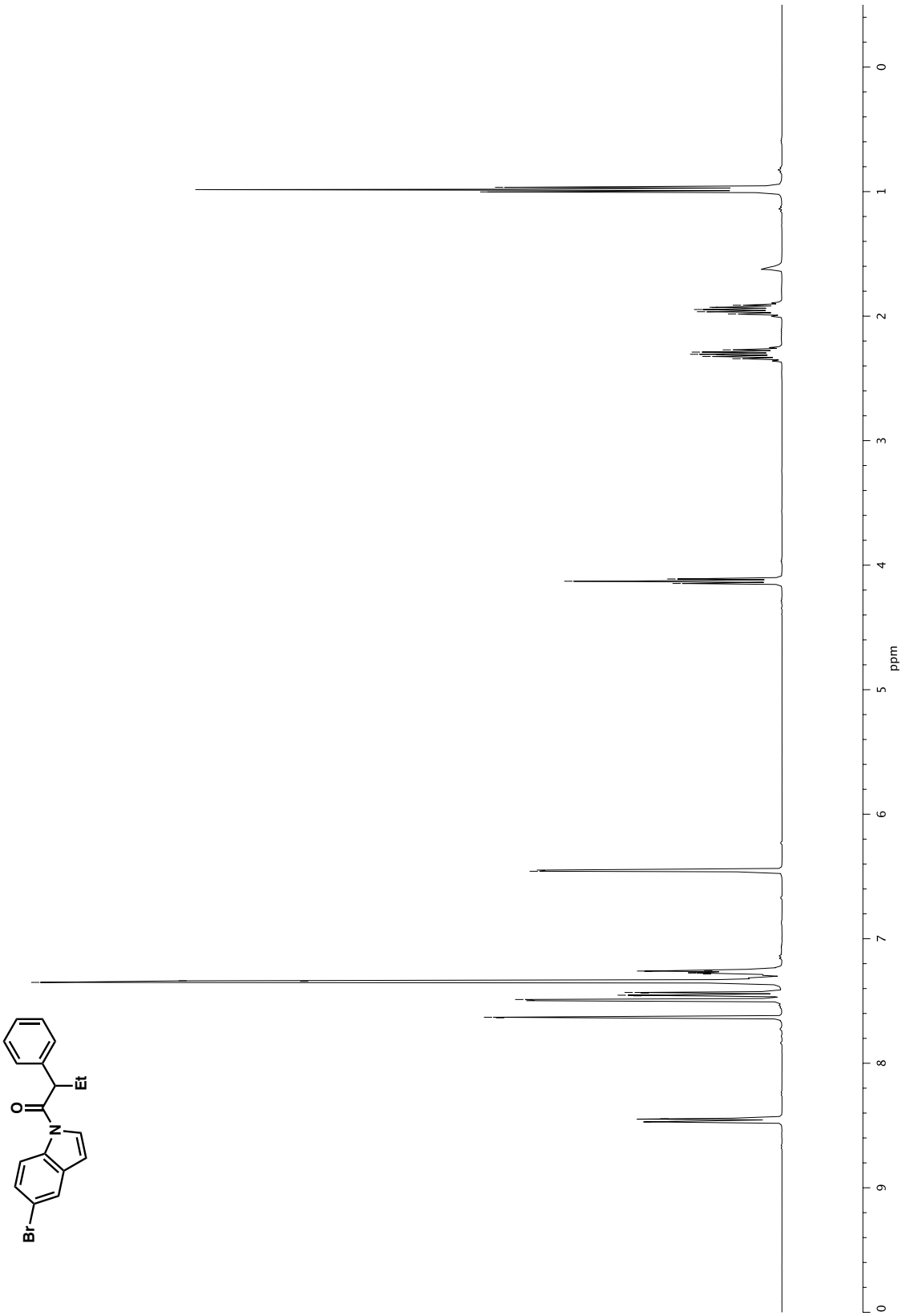



***Figure A5.138*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***59****.*




***A5.139*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***60****.*

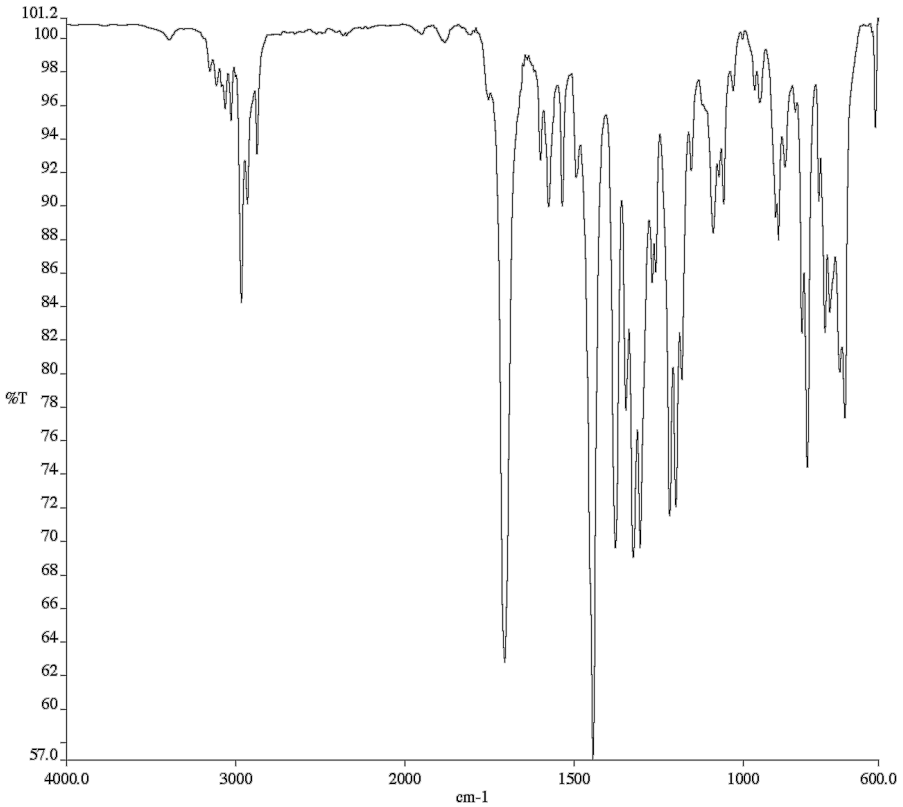



***Figure A5.140*** *Infrared spectrum (Thin Film, NaCl) of compound* ***60****.*

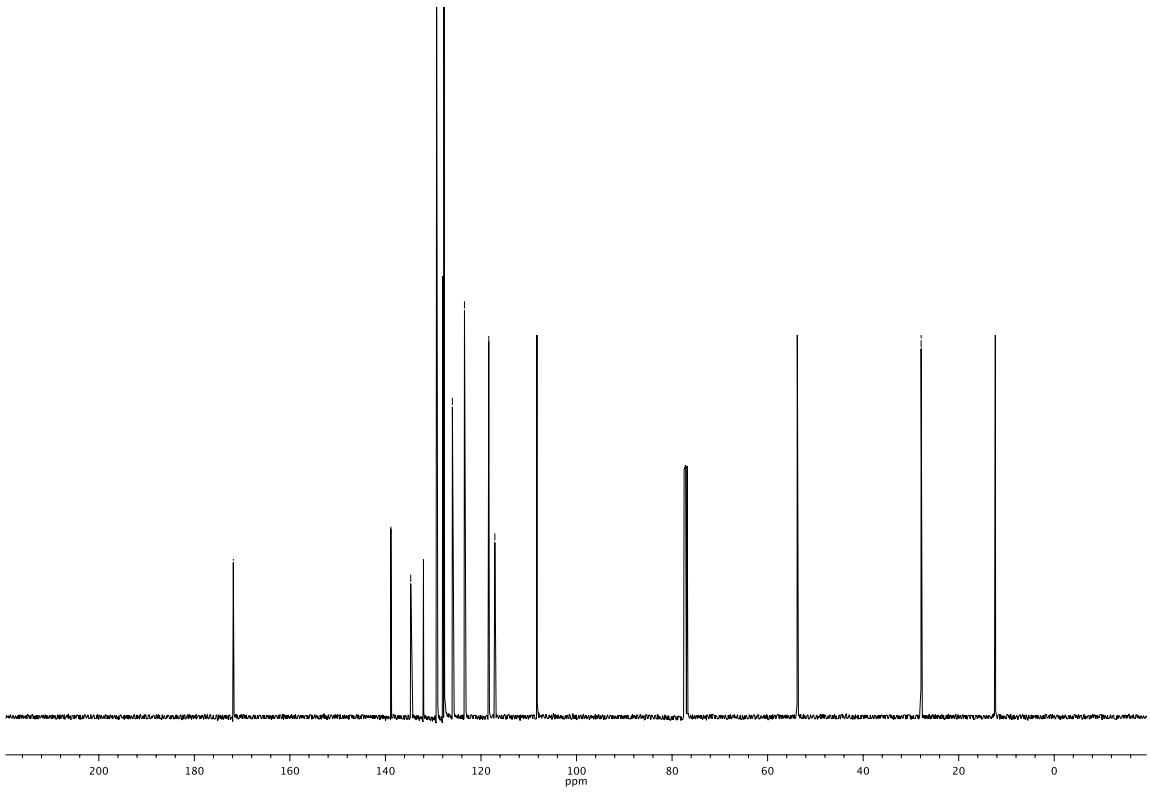
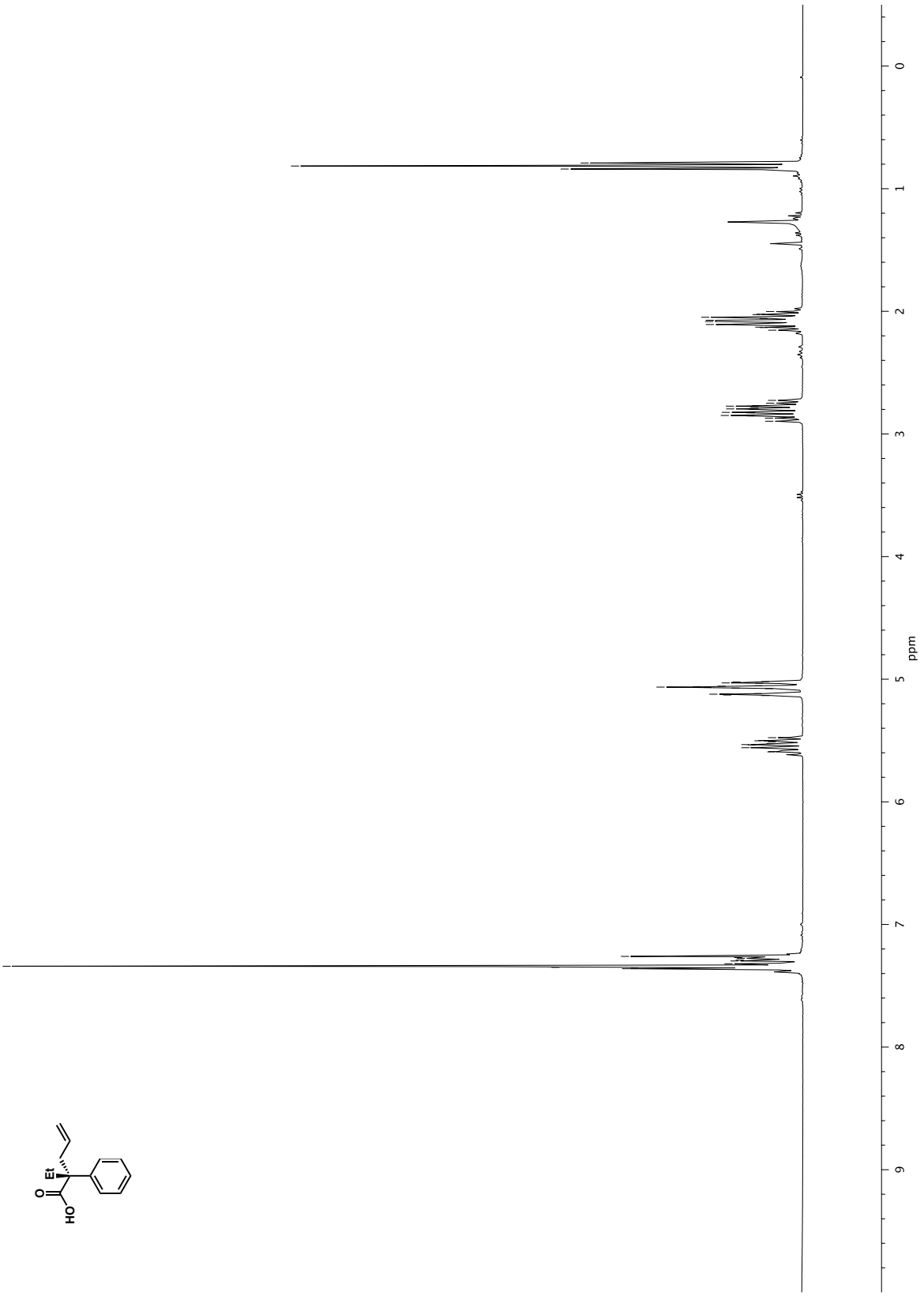



***Figure A5.141*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***60****.*




***A5.142*** *$^1H$ NMR (300 MHz, $CDCl_3$) of compound* ***42****.*

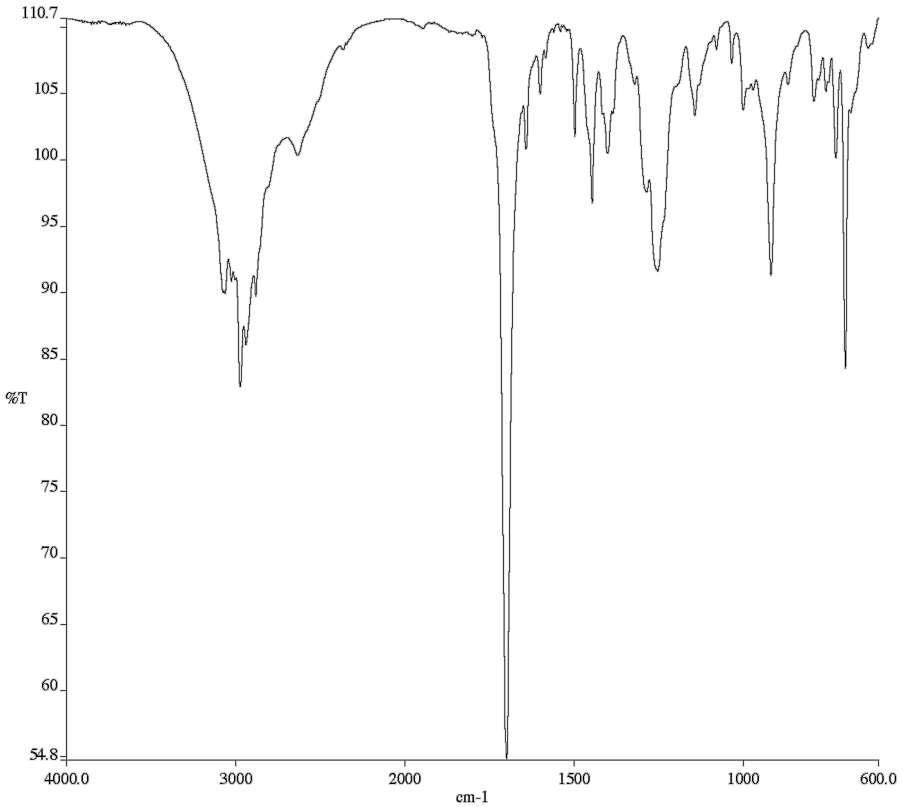



***Figure A5.143*** *Infrared spectrum (Thin Film, NaCl) of compound* ***42***.

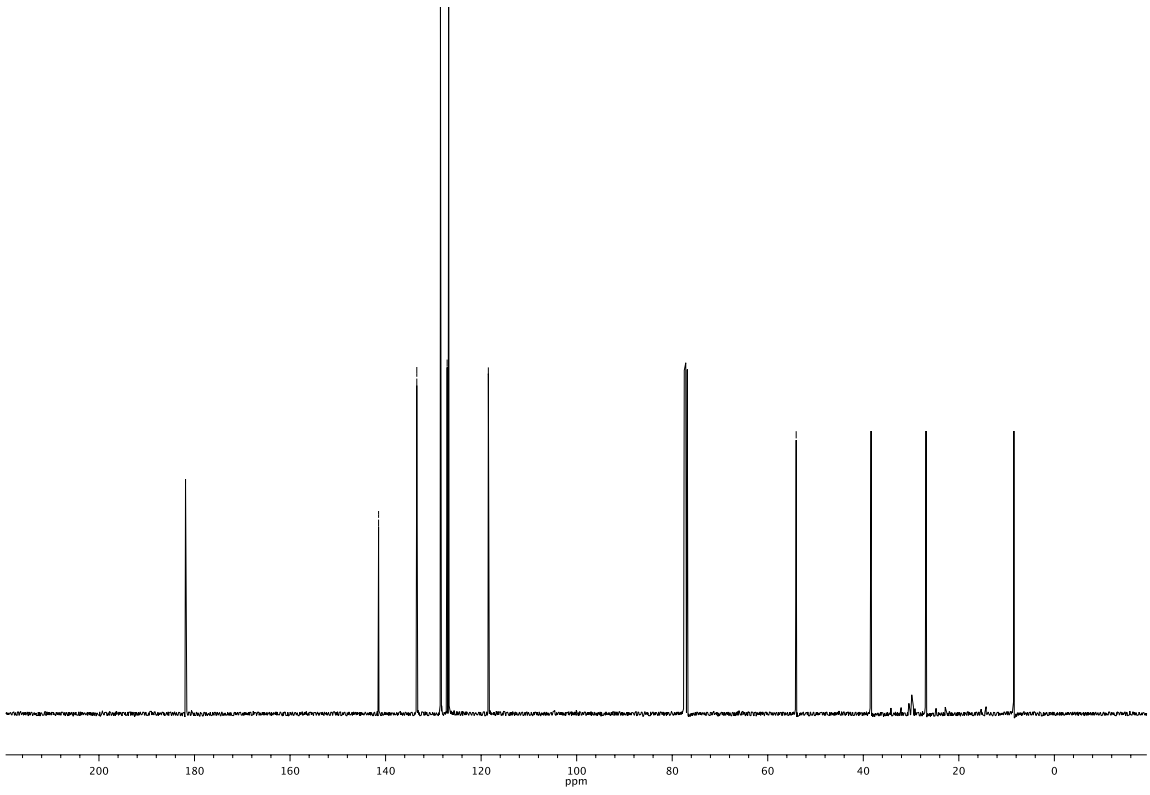
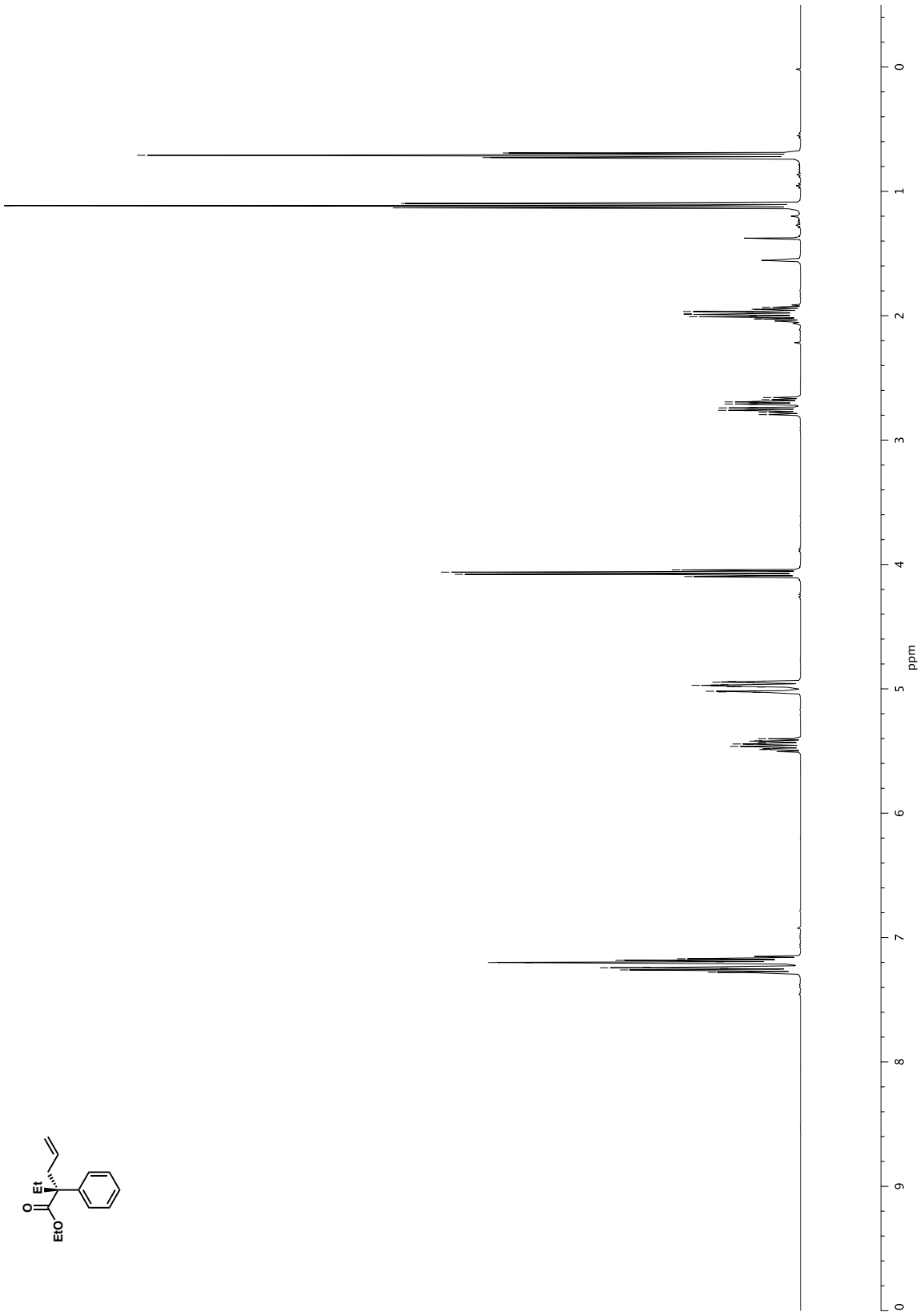



***Figure A5.144*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***42***.




***A5.145*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***43****.*

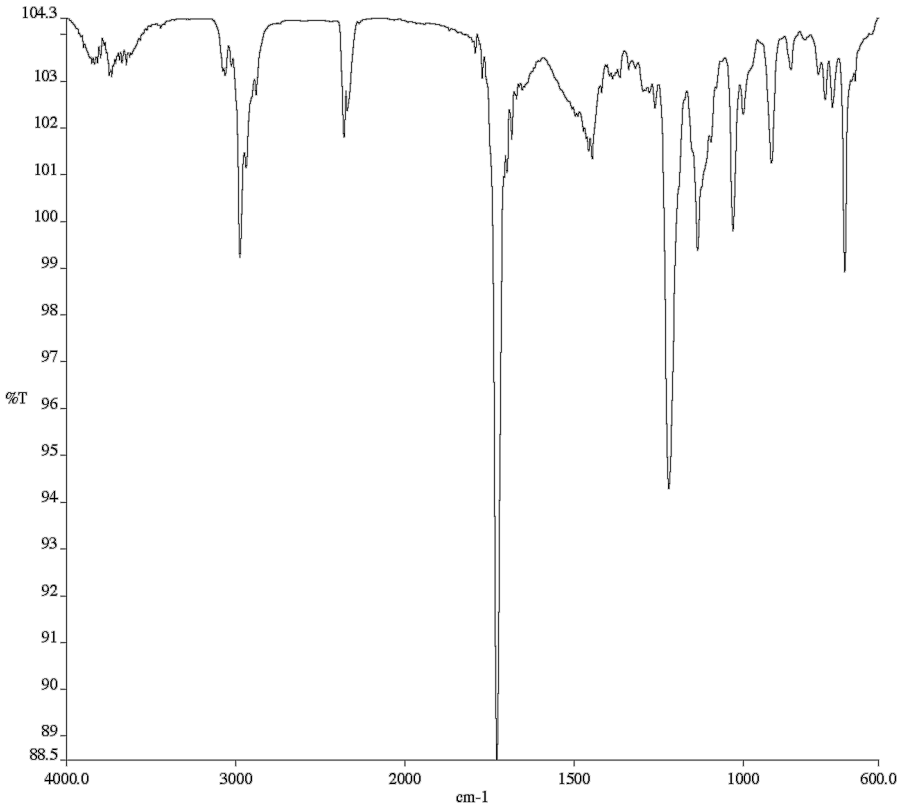



***Figure A5.146*** *Infrared spectrum (Thin Film, NaCl) of compound* ***43***.

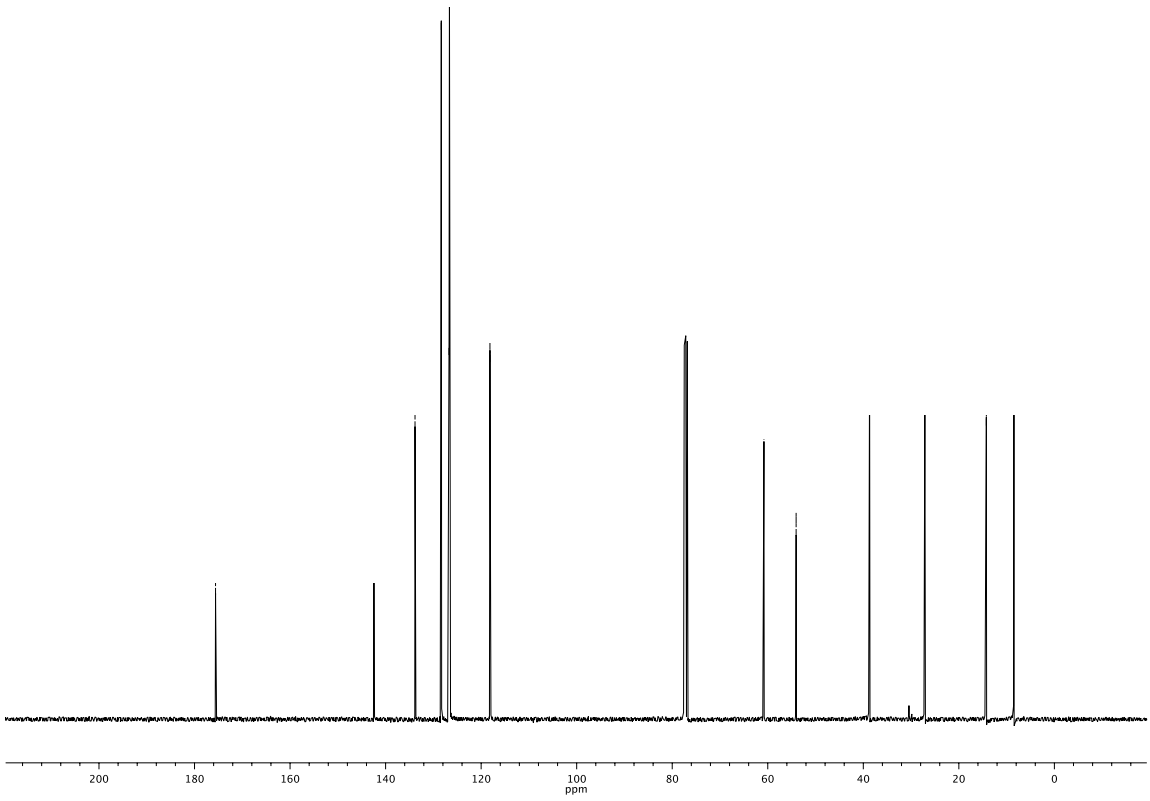
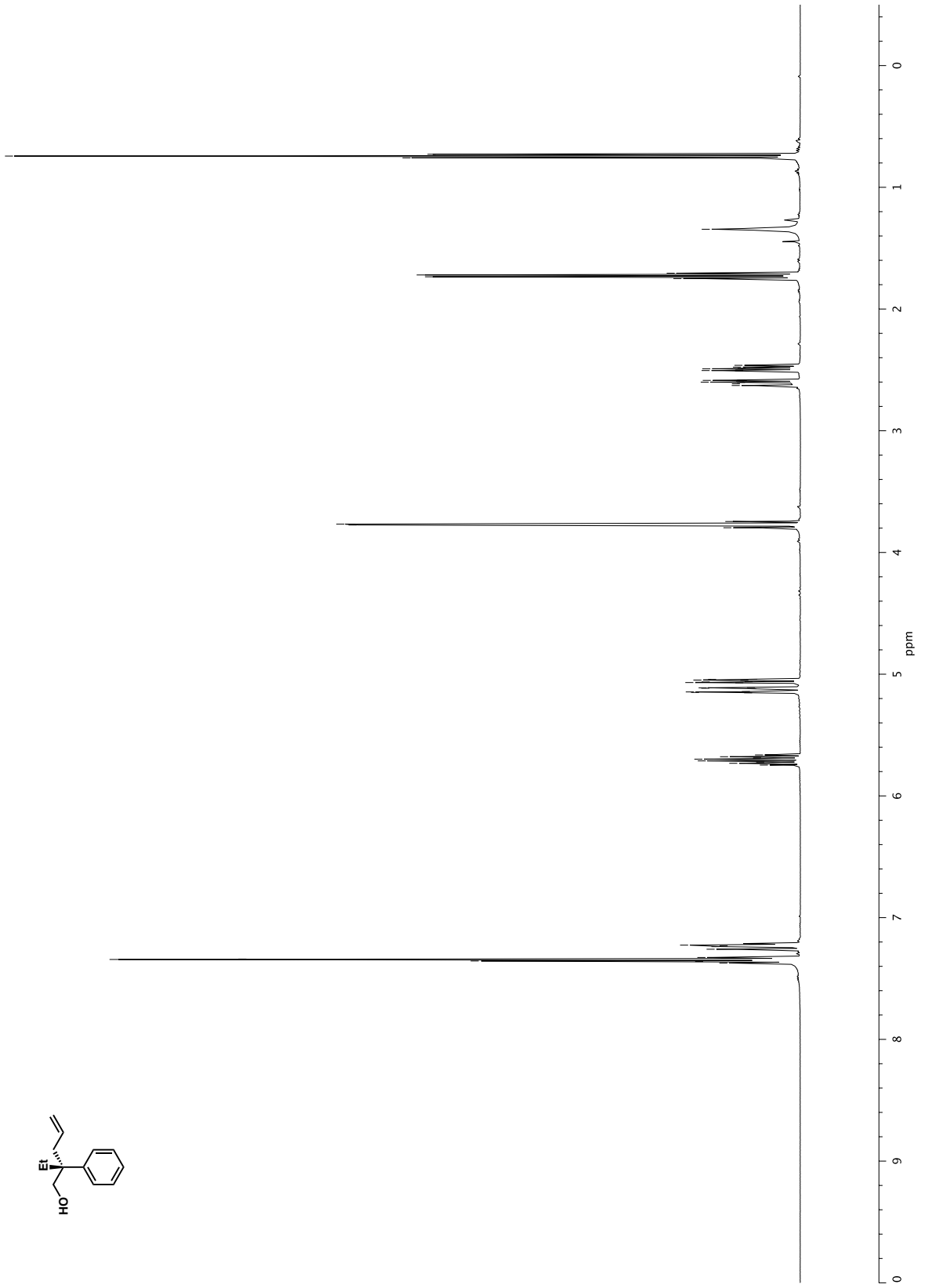



***Figure A5.147*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***43***.




***A5.148*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***44****.*

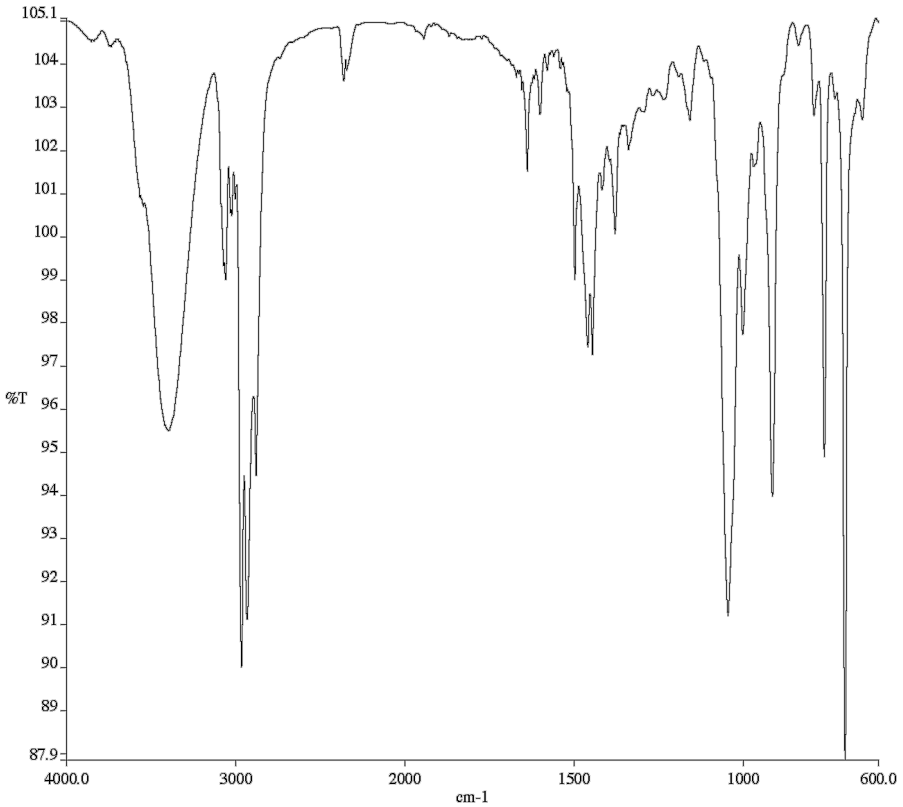



***Figure A5.149*** *Infrared spectrum (Thin Film, NaCl) of compound* ***44****.*

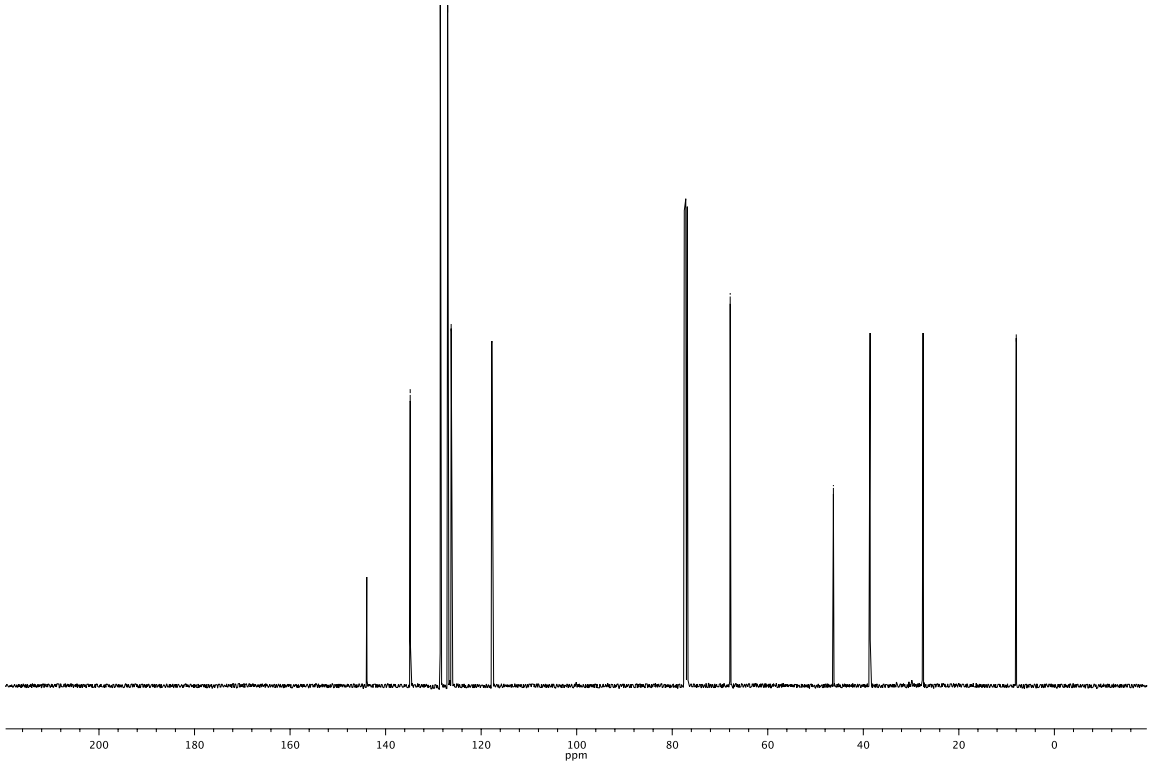
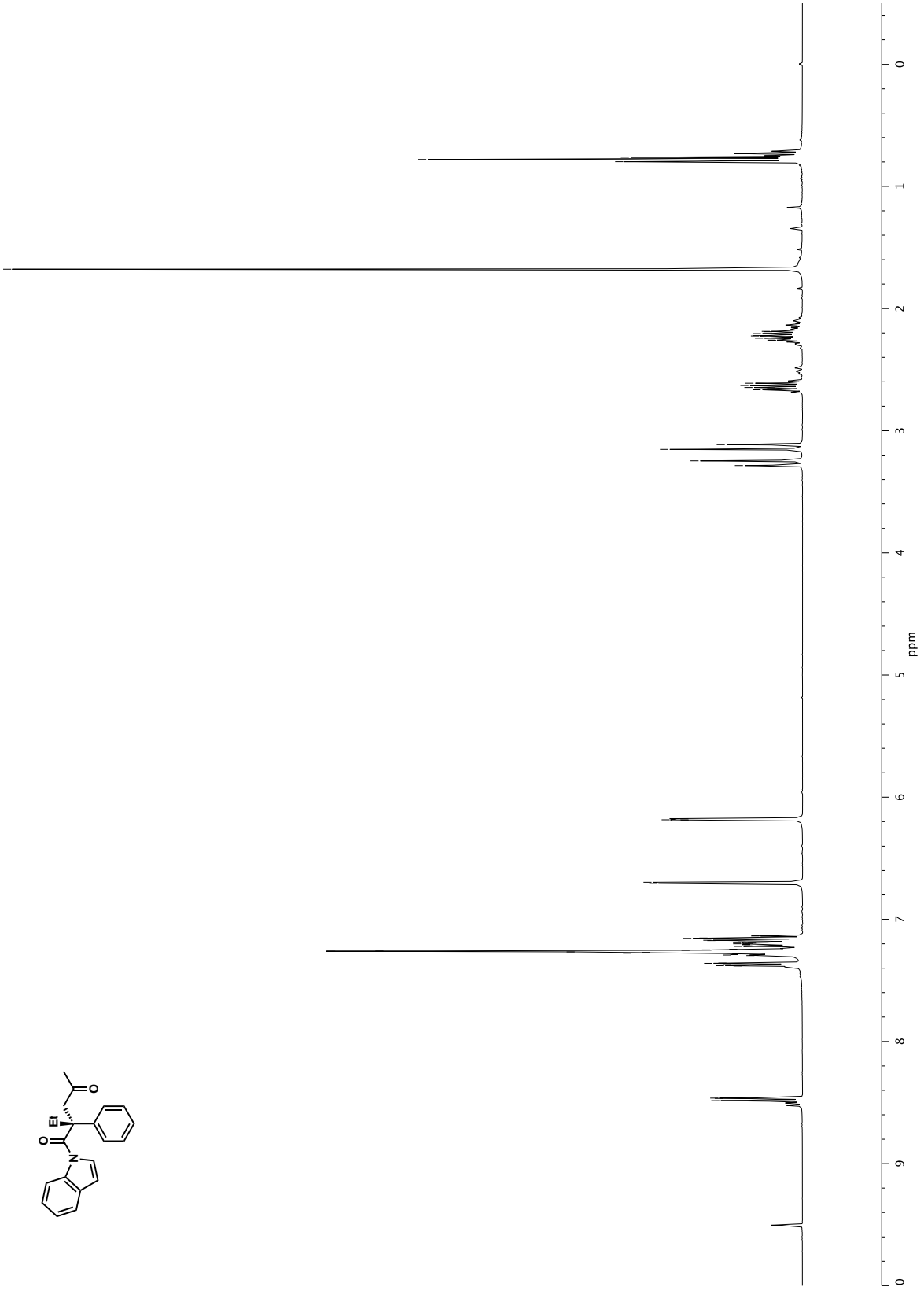



***Figure A5.150*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***44****.*




***A5.151*** *$^1$H NMR (400 MHz, $CDCl_3$) of compound* ***45****.*

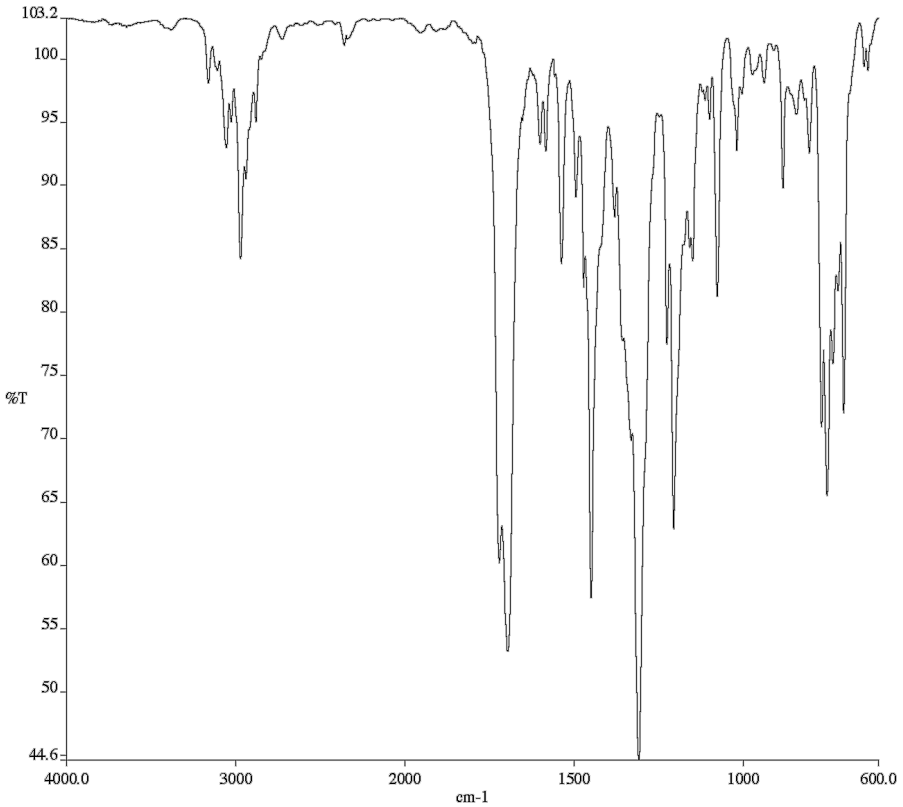



***Figure A5.152*** *Infrared spectrum (Thin Film, NaCl) of compound* ***45***.

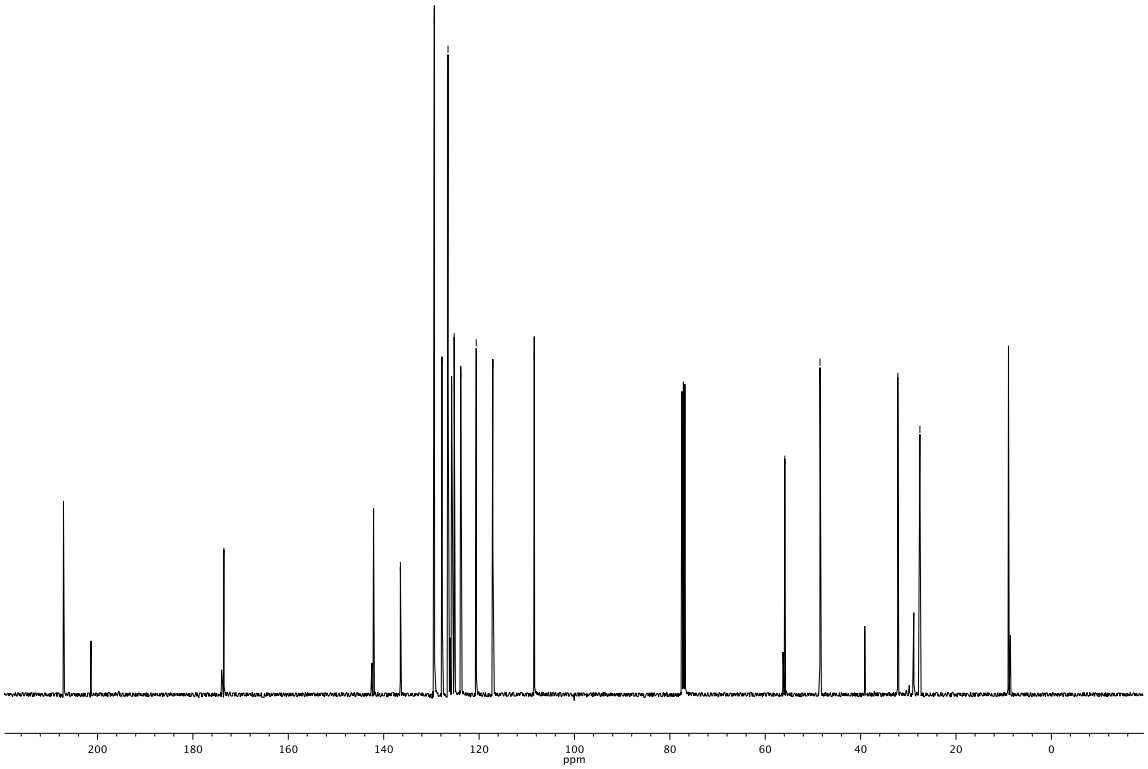
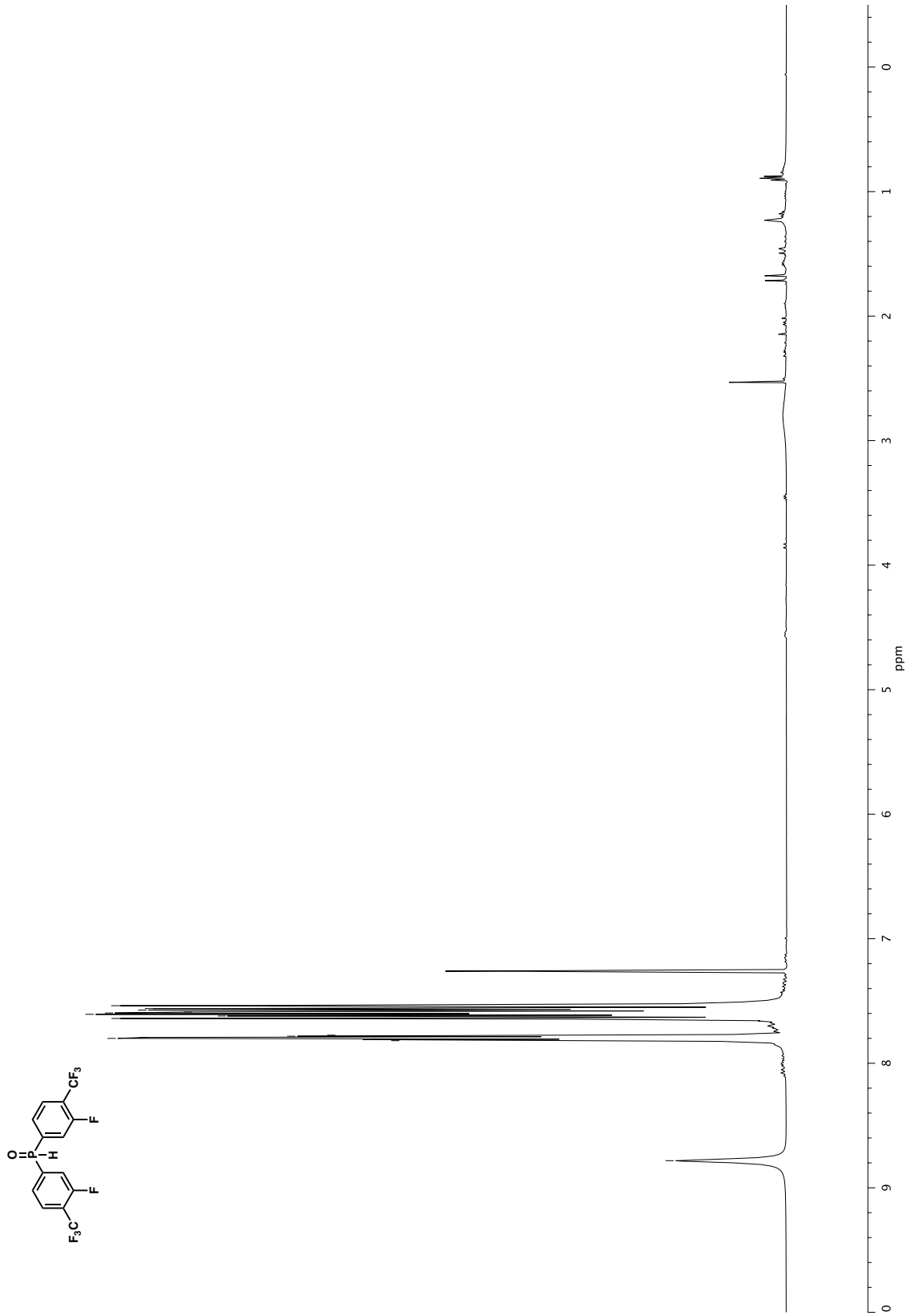



***Figure A5.153*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***45***.




***A5.154*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***61****.*

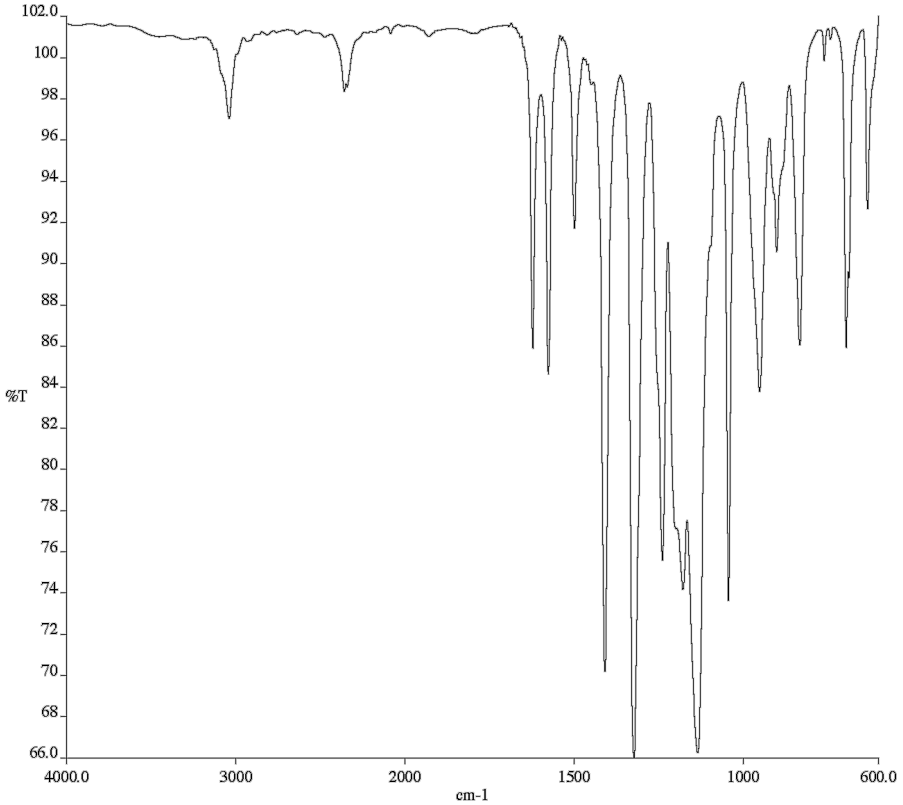



***Figure A5.155*** *Infrared spectrum (Thin Film, NaCl) of compound* ***61****.*

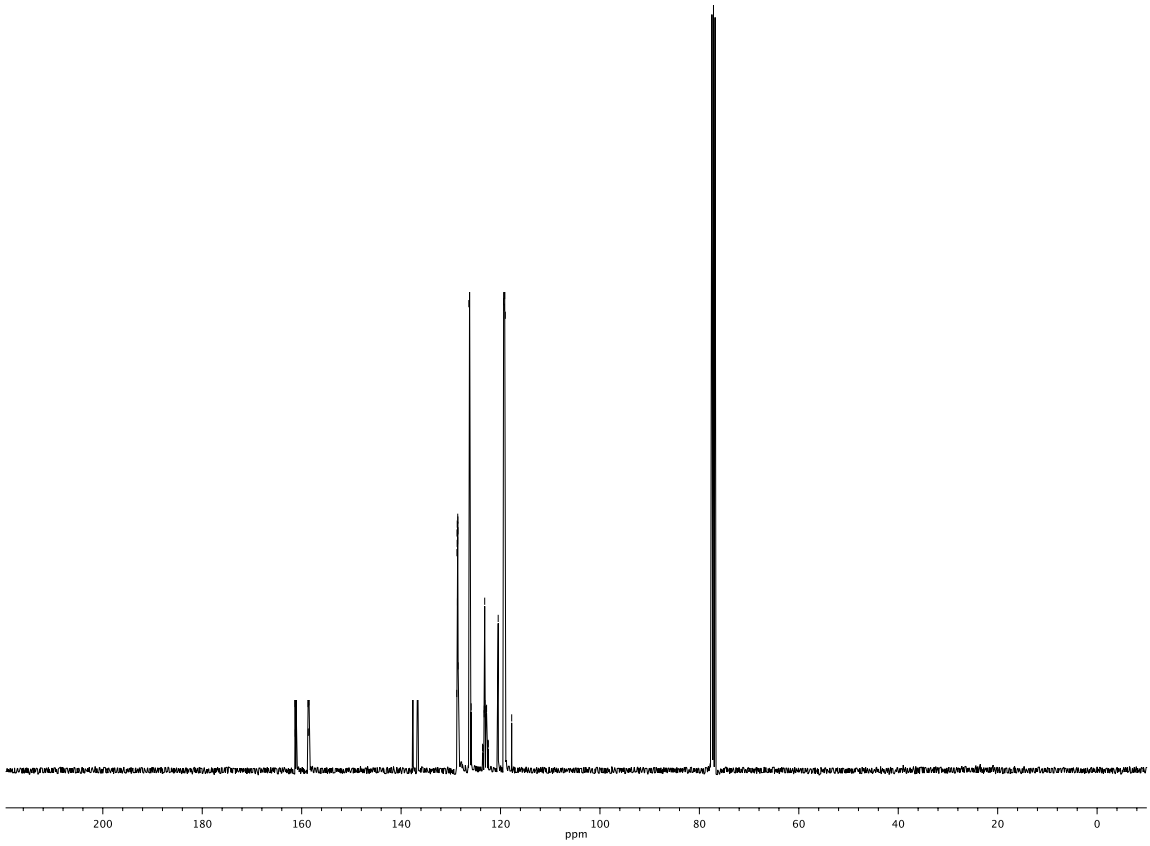



***Figure A5.156*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***61****.*

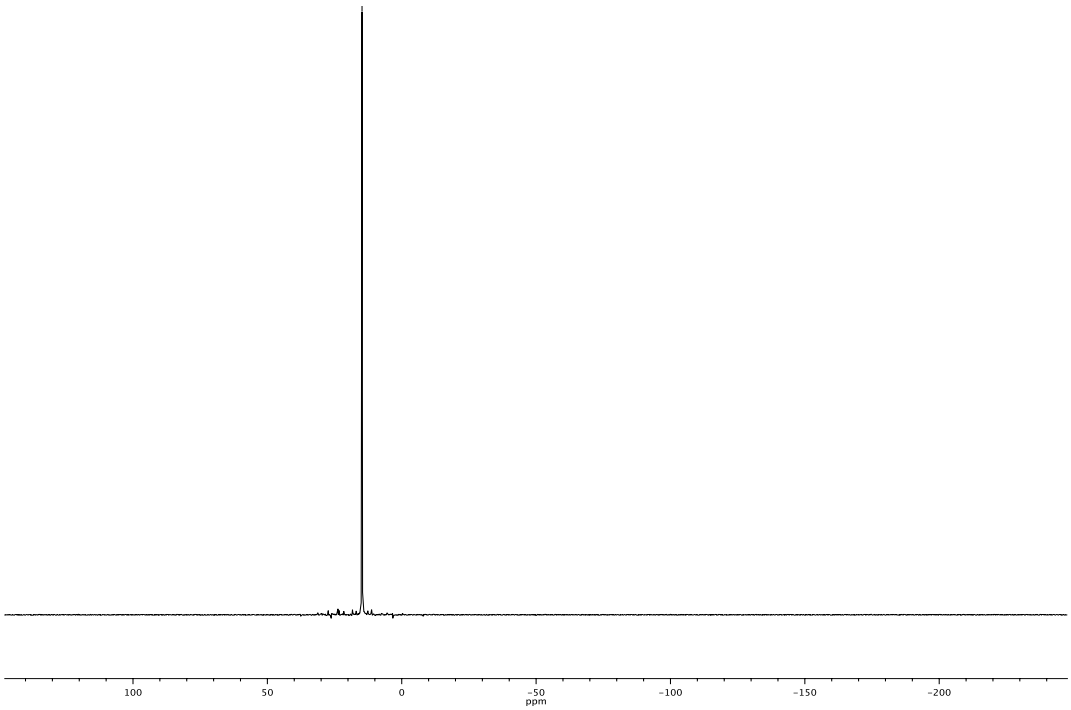



***Figure A5.157*** *$^{31}P$ NMR (162 MHz, $CDCl_3$) of compound **61**.*

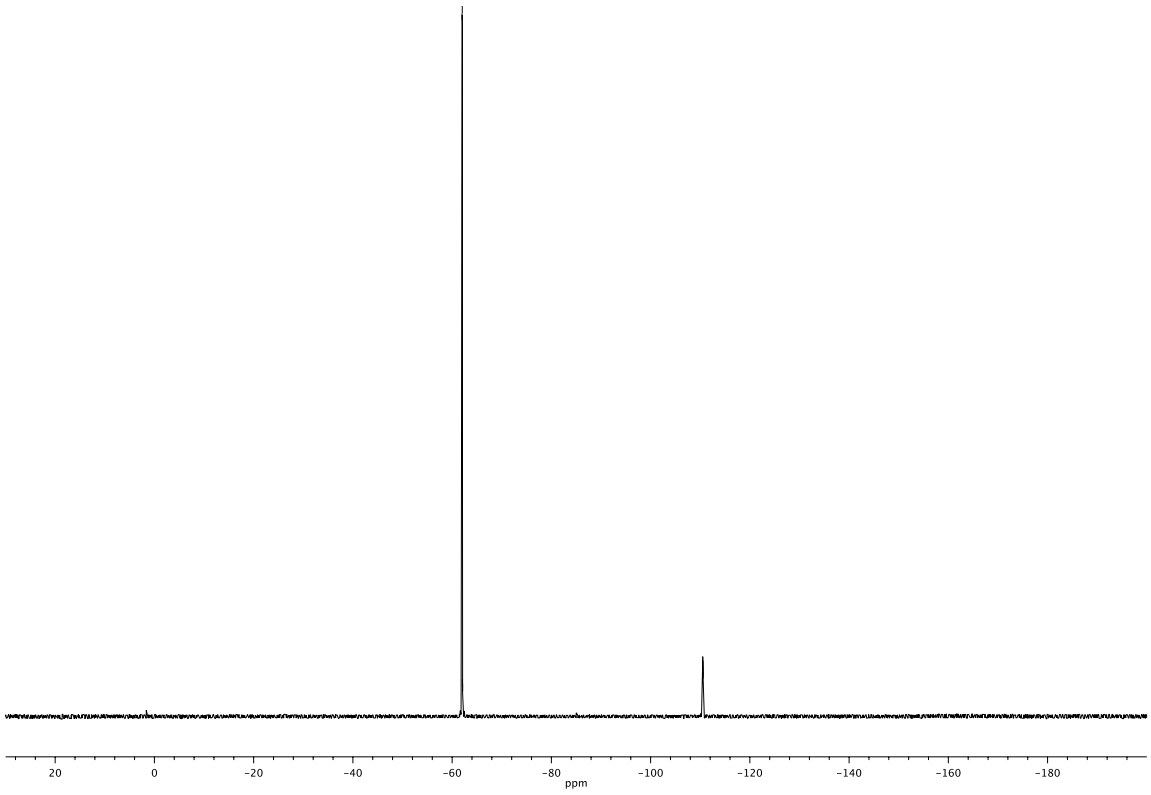
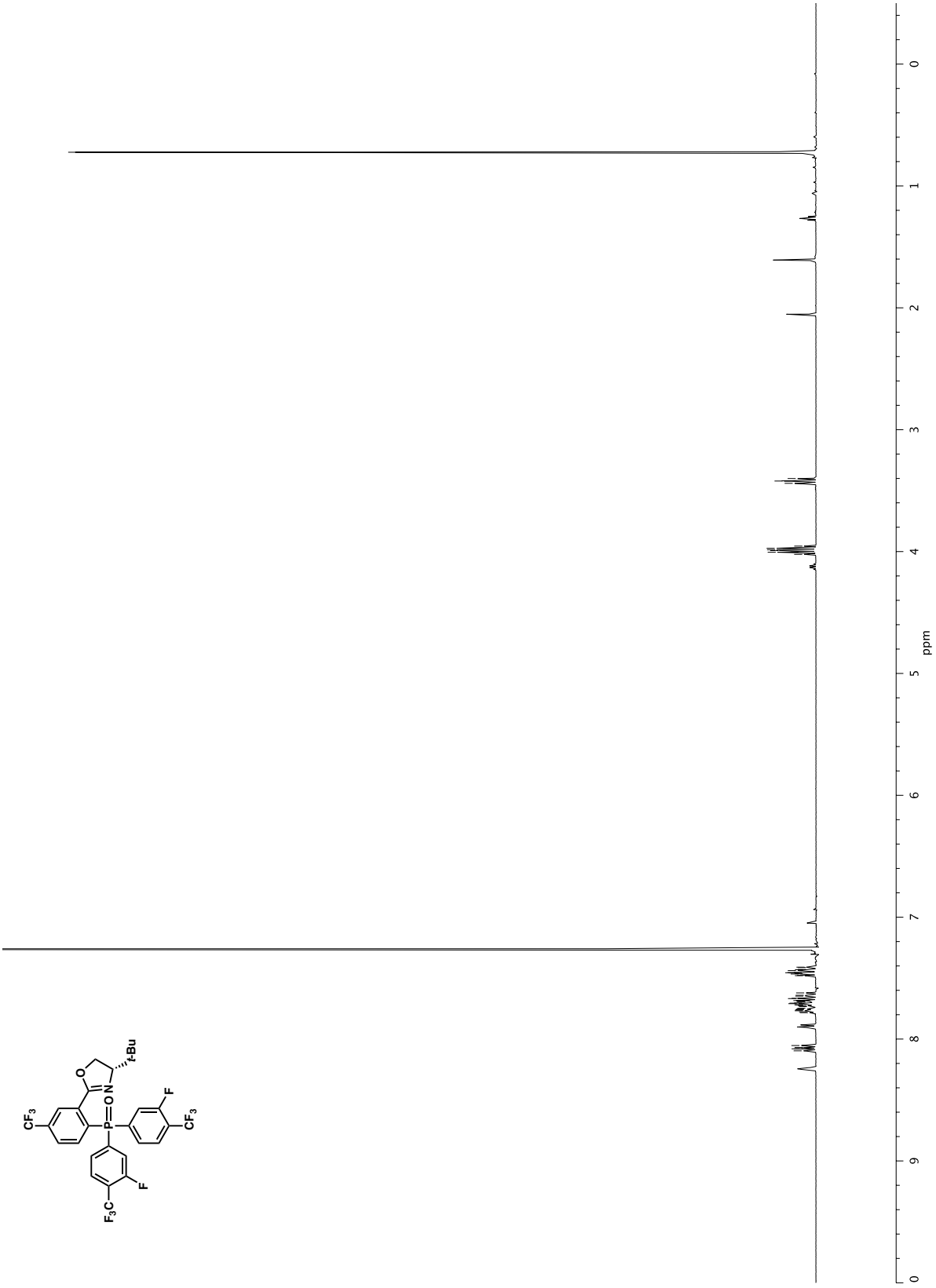



***Figure A5.158*** *$^{19}F$ NMR (282 MHz, $CDCl_3$) of compound **61**.*




***A5.159*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***62****.*

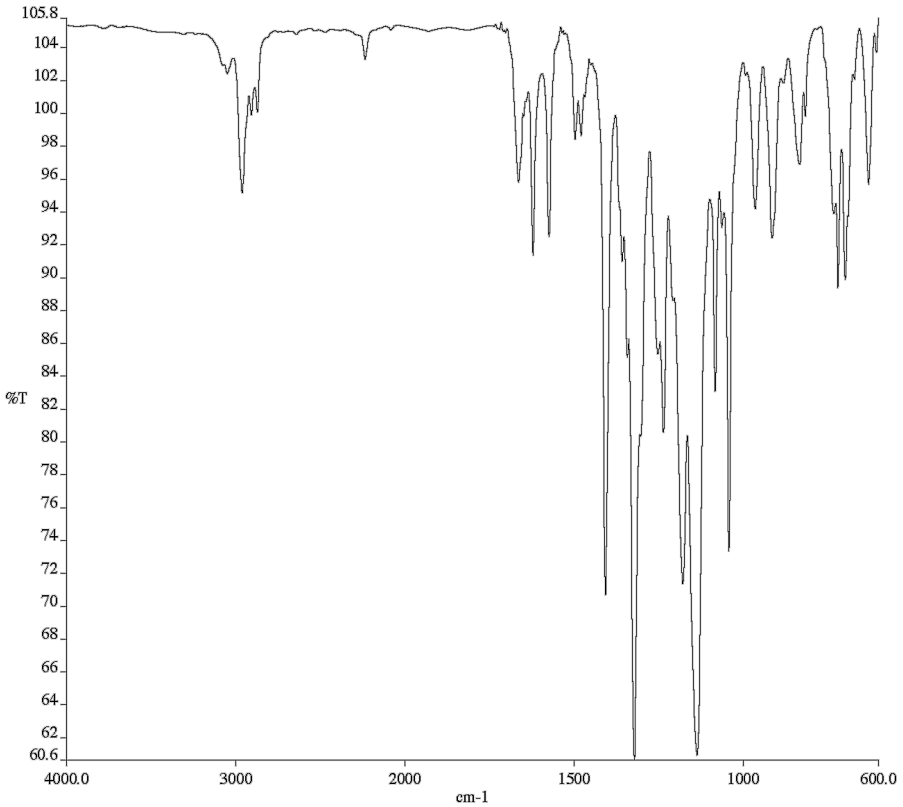



***Figure A5.160*** *Infrared spectrum (Thin Film, NaCl) of compound* ***62****.*

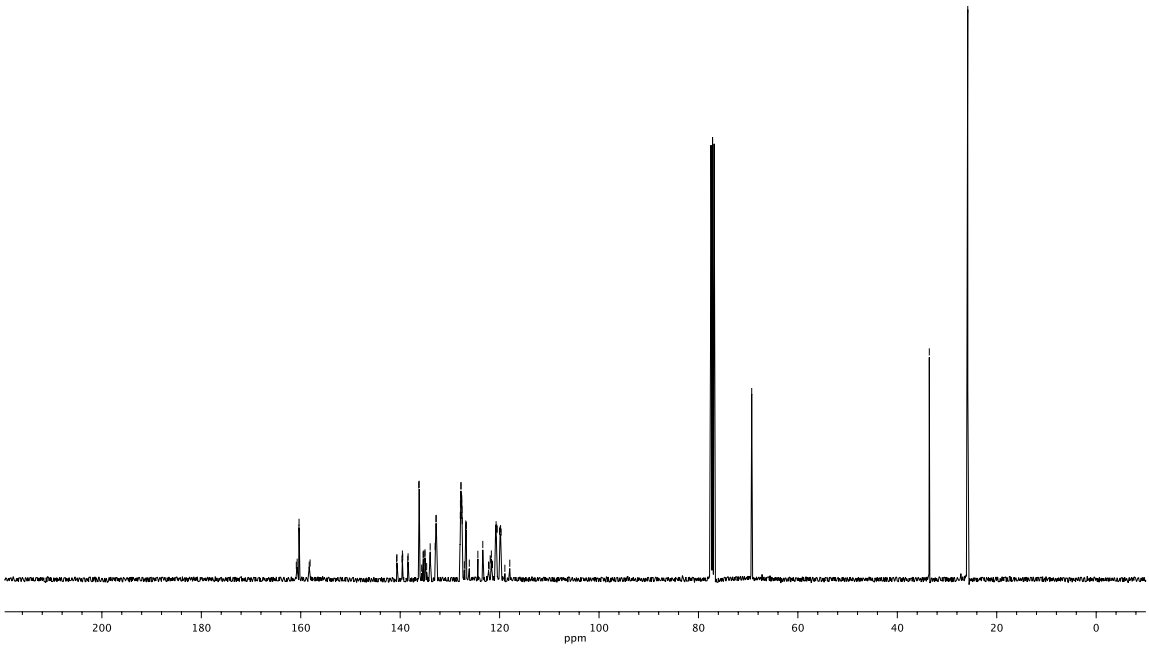



***Figure A5.161*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***62****.*

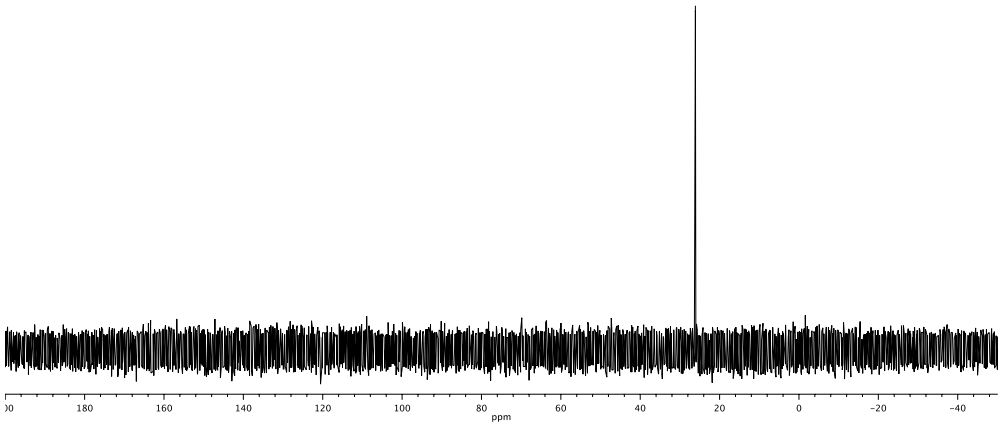



***Figure A5.162*** *$^{31}$P NMR (162 MHz, $CDCl_3$) of compound* ***62***.

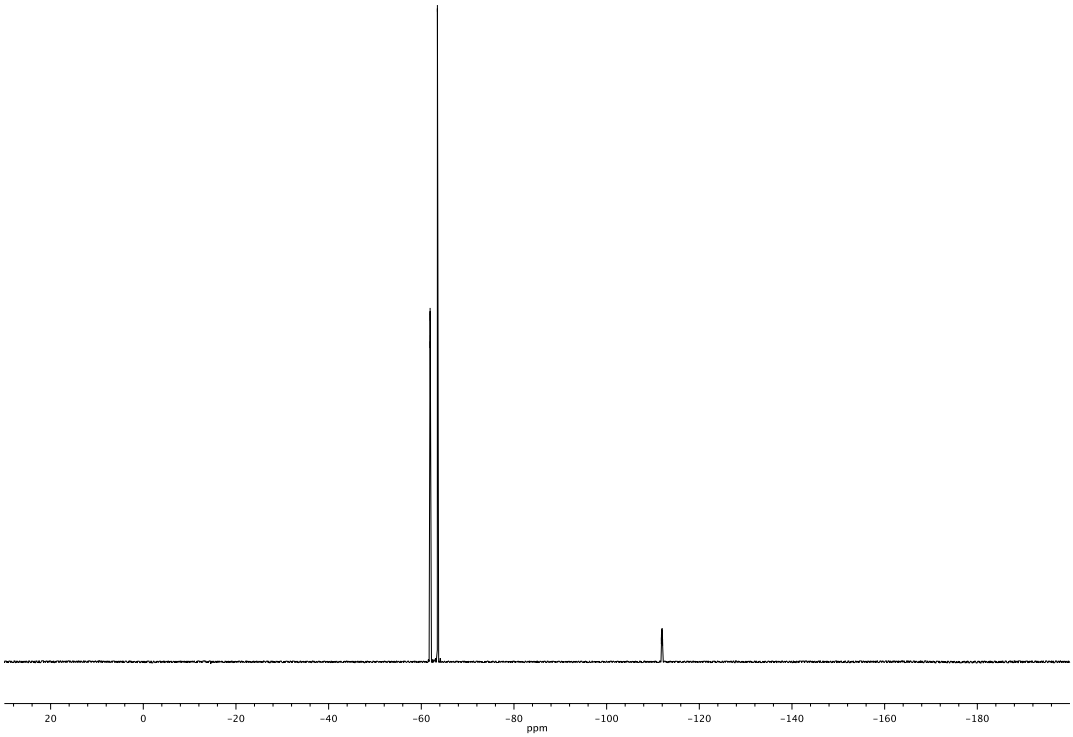
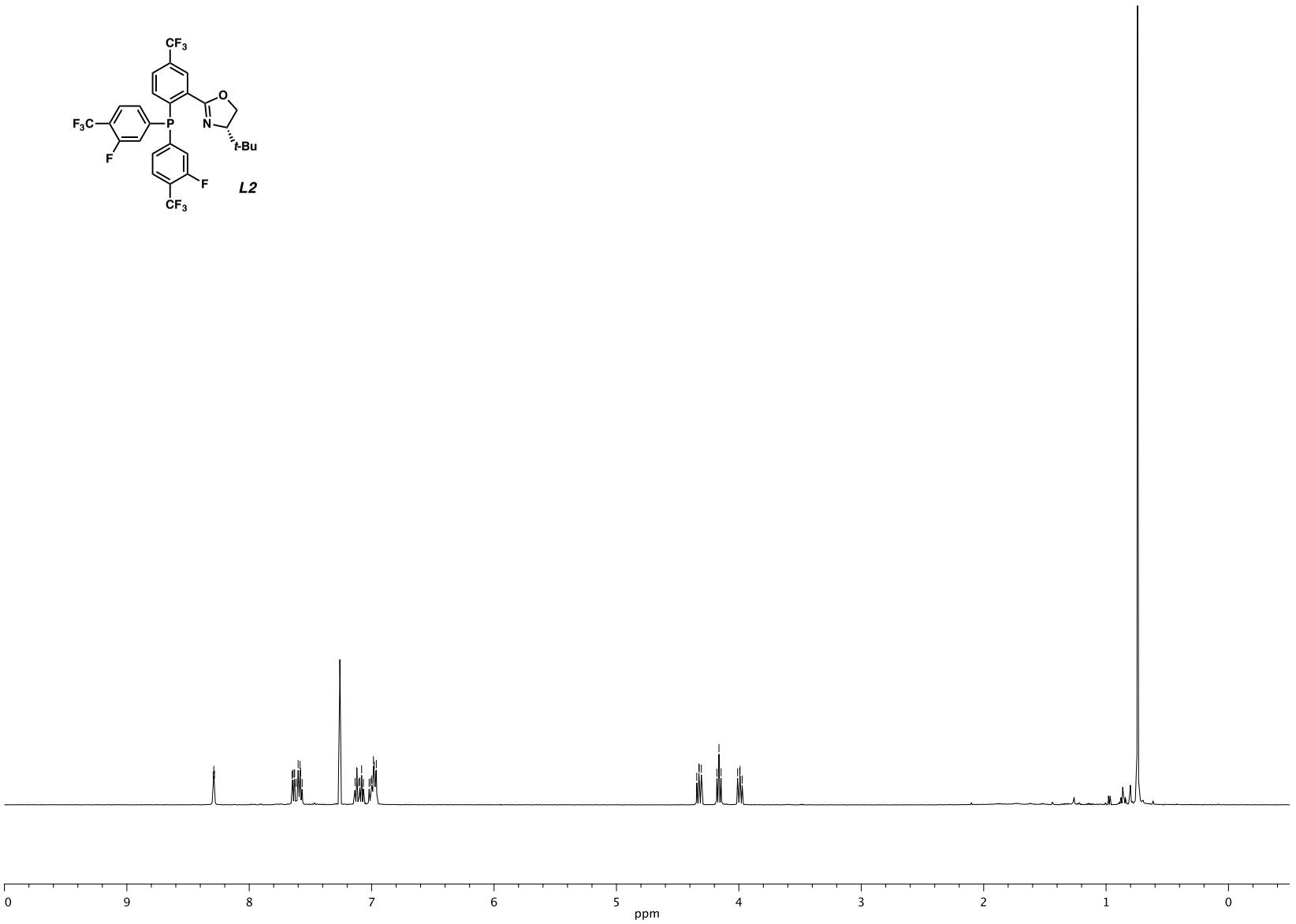



***Figure A5.163*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***62***.




***A5.164*** *$^{1}$H NMR (500 MHz, $CDCl_3$) of compound* ***L12***.

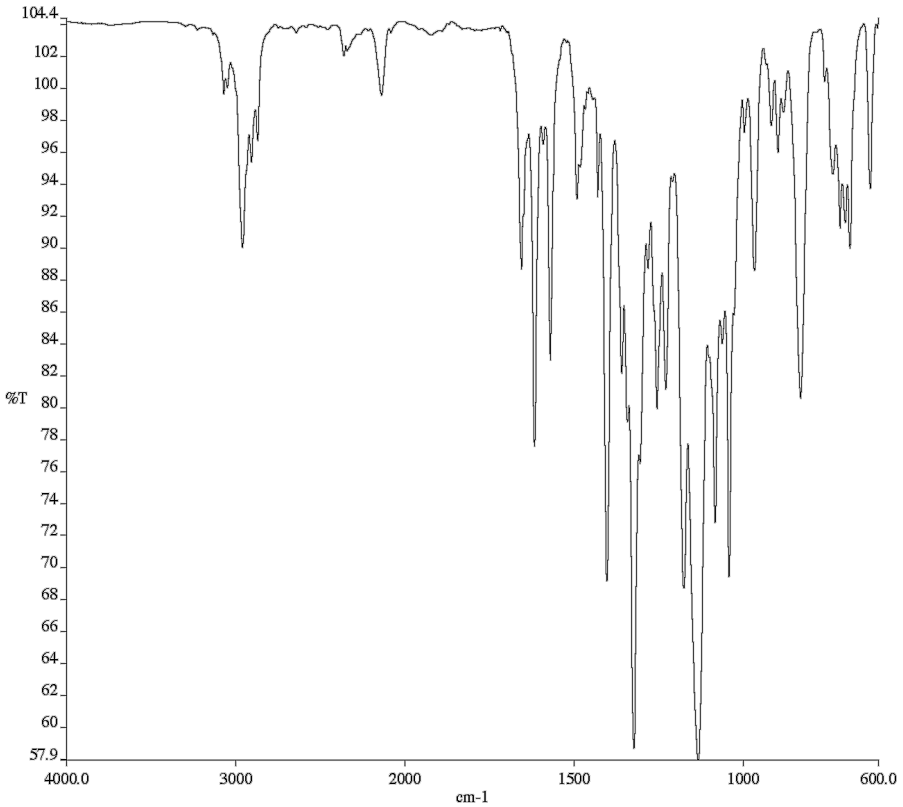



***Figure A5.165*** *Infrared spectrum (Thin Film, NaCl) of compound* ***L12****.*

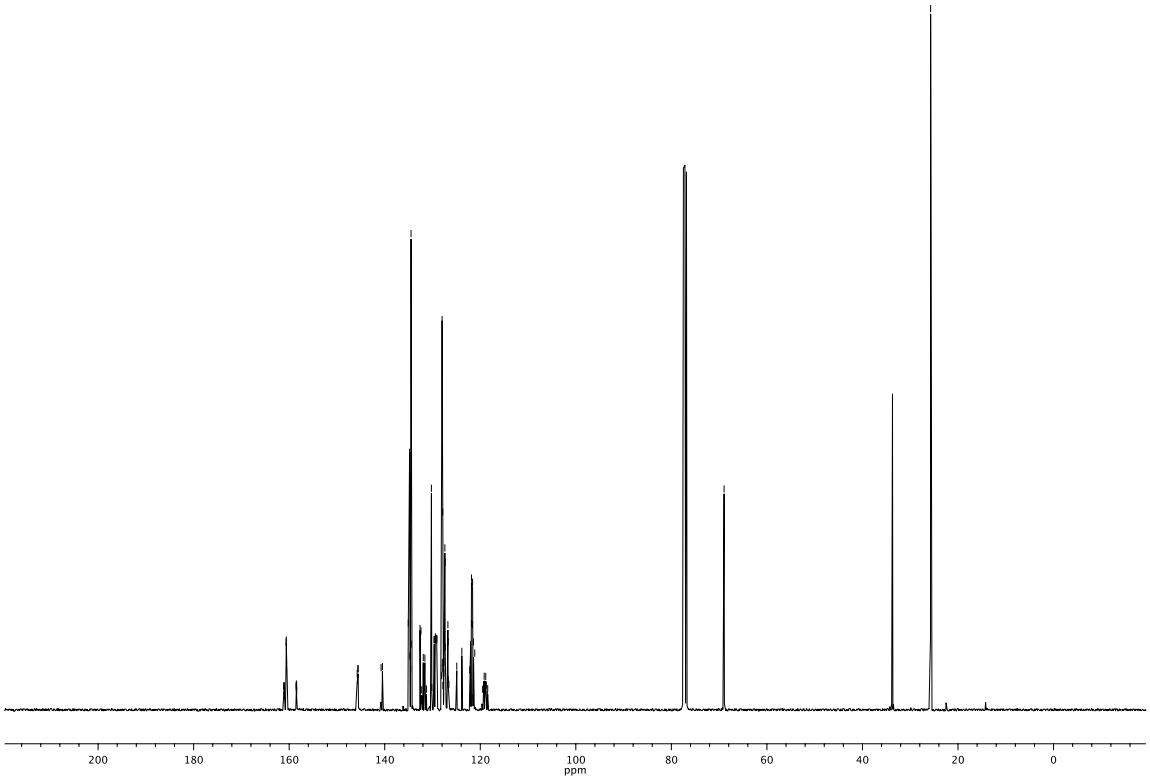



***Figure A5.166*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***L12****.*

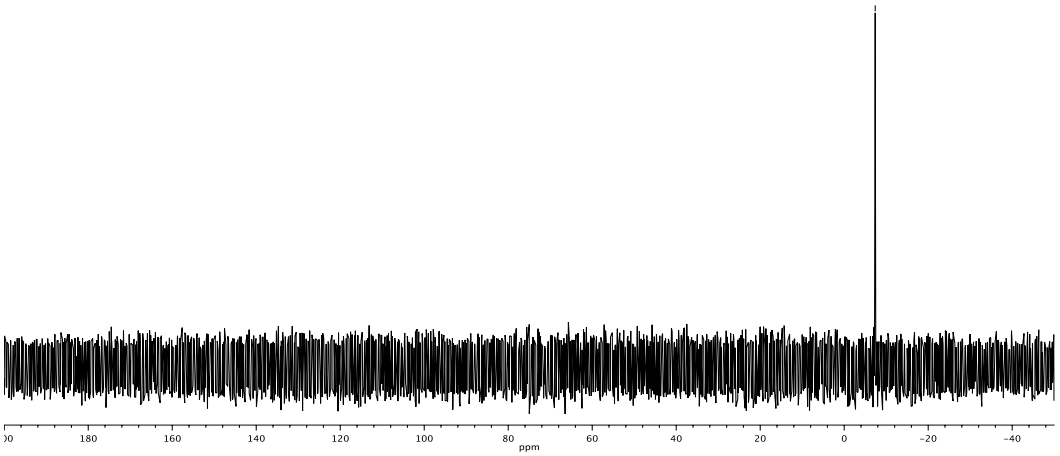



***Figure A5.167*** *$^{31}$P NMR (162 MHz, $CDCl_3$) of compound* ***L12***.

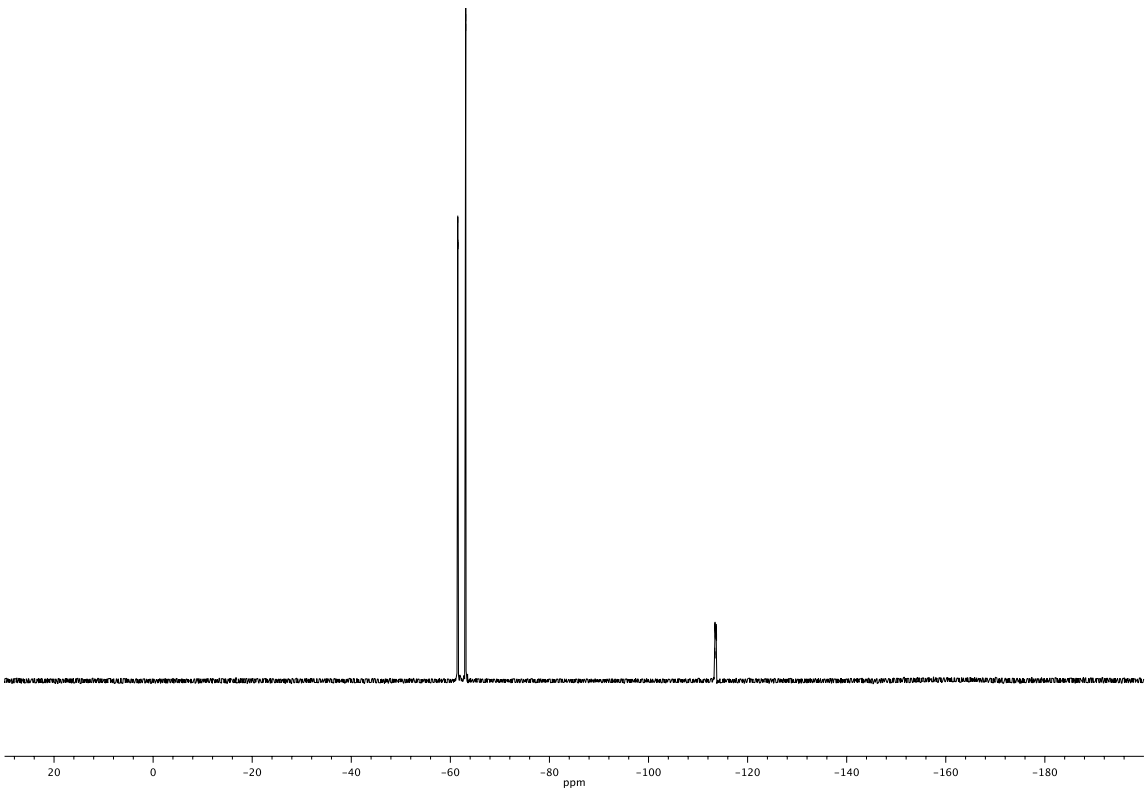



***Figure A5.168*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***L12***.

# *APPENDIX 6*

*X-Ray Crystallography Reports Relevant to Chapter 4:*

*Palladium-Catalyzed Decarboxylative Allylic Alkylation of Fully-*

*Substitued N-Acyl Indole-Derived Enol Carbonates*

## A6.1 GENERAL EXPERIMENTAL

X-ray crystallographic analysis was obtained from the Caltech X-Ray Crystallography Facility using a Bruker D8 Venture Kappa Duo Photon 100 CMOS diffractometer.

### A6.1.1 X-RAY CRYSTAL STRUCTURE ANALYSIS OF ALLYLIC ALKYLATION PRODUCT 41d

***Figure A6.1*** *X-Ray Coordinate of Allylation Product* ***41d***.

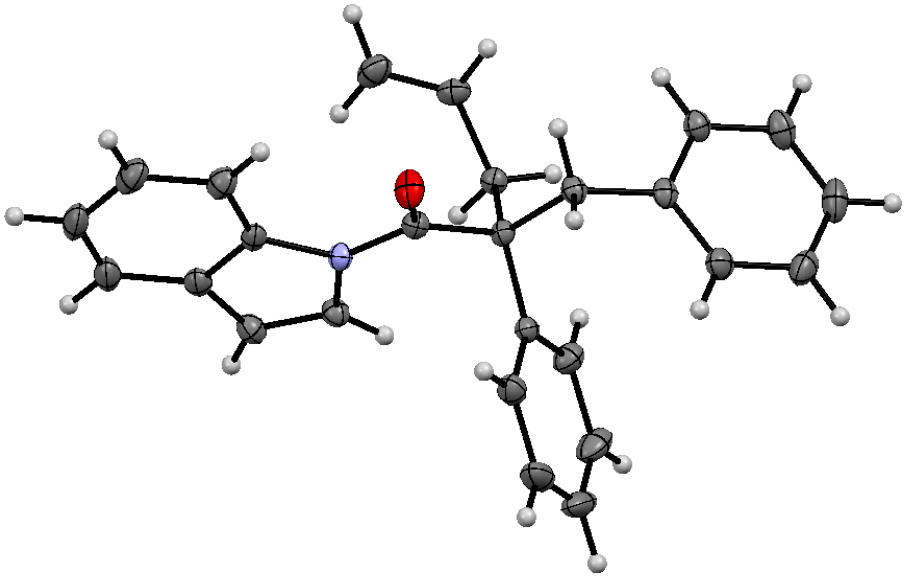


***Table A6.1*** *Crystal data and structure refinement for* ***41d***.

| | | |
|---|---|---|
| Empirical formula | C26 H23 N O | |
| Formula weight | 365.45 | |
| Temperature | 100(2) K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Monoclinic | |
| Space group | $P2_1$ | |
| Unit cell dimensions | a = 11.2225(10) Å | a= 90°. |
| | b = 6.4382(6) Å | b= 99.6595(18)°. |

| | |
|---|---|
| | c = 14.0893(13) Å g = 90°. |
| Volume | 1003.56(16) $Å^3$ |
| Z | 2 |
| Density (calculated) | 1.209 $Mg/m^3$ |
| Absorption coefficient | 0.564 $mm^{-1}$ |
| F(000) | 388 |
| Crystal size | 0.500 x 0.500 x 0.300 $mm^3$ |
| Theta range for data collection | 3.182 to 80.104°. |
| Index ranges | -14<=h<=14, -7<=k<=7, -17<=l<=17 |
| Reflections collected | 34321 |
| Independent reflections | 4134 [R(int) = 0.0282] |
| Completeness to theta = 67.679° | 99.0 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 1.0000 and 0.8766 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 4134 / 1 / 253 |
| Goodness-of-fit on $F^2$ | 1.038 |
| Final R indices [I>2sigma(I)] | R1 = 0.0265, wR2 = 0.0681 |
| R indices (all data) | R1 = 0.0265, wR2 = 0.0682 |
| Absolute structure parameter | 0.05(4) |
| Extinction coefficient | n/a |
| Largest diff. peak and hole | 0.201 and -0.133 $e.Å^{-3}$ |

***Table A6.2*** *Atomic coordinates (x$10^5$) and equivalent isotropic displacement parameters (Å$^2$x $10^4$) for* ***41d****. U(eq) is defined as one third of the trace of the orthogonalized U$^{ij}$ tensor.*

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(1) | 5786(1) | 1813(2) | 7273(1) | 26(1) |
| C(1) | 5783(1) | 3638(2) | 7476(1) | 17(1) |
| C(2) | 4688(1) | 5066(2) | 7141(1) | 15(1) |
| C(11) | 4200(1) | 5966(2) | 8006(1) | 17(1) |
| C(12) | 4150(1) | 4711(3) | 8806(1) | 24(1) |
| C(13) | 3652(2) | 5458(3) | 9579(1) | 35(1) |
| C(14) | 3193(2) | 7449(3) | 9561(1) | 37(1) |
| C(15) | 3241(2) | 8701(3) | 8777(1) | 34(1) |
| C(16) | 3742(1) | 7973(2) | 8000(1) | 24(1) |
| C(3) | 3683(1) | 3670(2) | 6559(1) | 18(1) |
| C(21) | 2520(1) | 4803(2) | 6183(1) | 18(1) |
| C(22) | 1602(1) | 4907(3) | 6737(1) | 24(1) |
| C(23) | 530(1) | 5950(3) | 6403(1) | 29(1) |
| C(24) | 351(1) | 6888(3) | 5504(1) | 30(1) |
| C(25) | 1252(1) | 6781(3) | 4941(1) | 27(1) |
| C(26) | 2327(1) | 5746(2) | 5278(1) | 21(1) |
| C(4) | 5090(1) | 6761(2) | 6474(1) | 17(1) |
| C(5) | 5781(1) | 5882(2) | 5740(1) | 22(1) |
| C(6) | 6953(2) | 6153(3) | 5768(1) | 29(1) |
| N(1) | 6826(1) | 4548(2) | 7998(1) | 17(1) |
| C(31) | 6936(1) | 6510(2) | 8438(1) | 20(1) |
| C(32) | 8087(1) | 6829(3) | 8874(1) | 23(1) |
| C(33) | 8774(1) | 5024(2) | 8712(1) | 21(1) |
| C(34) | 9996(1) | 4507(3) | 8984(1) | 27(1) |
| C(35) | 10389(1) | 2616(3) | 8694(1) | 31(1) |
| C(36) | 9598(1) | 1254(3) | 8132(1) | 31(1) |
| C(37) | 8379(1) | 1719(3) | 7857(1) | 24(1) |
| C(38) | 7982(1) | 3609(2) | 8164(1) | 18(1) |

***Table A6.3*** *Bond lengths [Å] and angles [°] for* ***41d***

| | |
|---|---|
| O(1)-C(1) | 1.2093(19) |
| C(1)-N(1) | 1.4021(17) |
| C(1)-C(2) | 1.5434(18) |
| C(2)-C(11) | 1.5317(17) |
| C(2)-C(4) | 1.5553(17) |
| C(2)-C(3) | 1.5630(18) |
| C(11)-C(16) | 1.390(2) |
| C(11)-C(12) | 1.3950(19) |
| C(12)-C(13) | 1.391(2) |
| C(12)-H(12) | 0.9500 |
| C(13)-C(14) | 1.380(3) |
| C(13)-H(13) | 0.9500 |
| C(14)-C(15) | 1.375(3) |
| C(14)-H(14) | 0.9500 |
| C(15)-C(16) | 1.393(2) |
| C(15)-H(15) | 0.9500 |
| C(16)-H(16) | 0.9500 |
| C(3)-C(21) | 1.5111(18) |
| C(3)-H(3A) | 0.9900 |
| C(3)-H(3B) | 0.9900 |
| C(21)-C(22) | 1.3949(19) |
| C(21)-C(26) | 1.3967(19) |
| C(22)-C(23) | 1.388(2) |
| C(22)-H(22) | 0.9500 |
| C(23)-C(24) | 1.387(2) |
| C(23)-H(23) | 0.9500 |
| C(24)-C(25) | 1.388(2) |
| C(24)-H(24) | 0.9500 |
| C(25)-C(26) | 1.390(2) |
| C(25)-H(25) | 0.9500 |
| C(26)-H(26) | 0.9500 |
| C(4)-C(5) | 1.5041(18) |
| C(4)-H(4A) | 0.9900 |
| C(4)-H(4B) | 0.9900 |

| | |
|---|---|
| C(5)-C(6) | 1.320(2) |
| C(5)-H(5) | 0.9500 |
| C(6)-H(6A) | 0.9500 |
| C(6)-H(6B) | 0.9500 |
| N(1)-C(31) | 1.4035(18) |
| N(1)-C(38) | 1.4145(17) |
| C(31)-C(32) | 1.3505(19) |
| C(31)-H(31) | 0.9500 |
| C(32)-C(33) | 1.433(2) |
| C(32)-H(32) | 0.9500 |
| C(33)-C(34) | 1.4006(19) |
| C(33)-C(38) | 1.410(2) |
| C(34)-C(35) | 1.380(3) |
| C(34)-H(34) | 0.9500 |
| C(35)-C(36) | 1.395(3) |
| C(35)-H(35) | 0.9500 |
| C(36)-C(37) | 1.391(2) |
| C(36)-H(36) | 0.9500 |
| C(37)-C(38) | 1.390(2) |
| C(37)-H(37) | 0.9500 |

| | |
|---|---|
| O(1)-C(1)-N(1) | 119.69(12) |
| O(1)-C(1)-C(2) | 122.66(12) |
| N(1)-C(1)-C(2) | 117.58(12) |
| C(11)-C(2)-C(1) | 110.77(10) |
| C(11)-C(2)-C(4) | 113.19(11) |
| C(1)-C(2)-C(4) | 107.86(10) |
| C(11)-C(2)-C(3) | 108.16(10) |
| C(1)-C(2)-C(3) | 106.58(11) |
| C(4)-C(2)-C(3) | 110.09(10) |
| C(16)-C(11)-C(12) | 118.57(13) |
| C(16)-C(11)-C(2) | 121.87(12) |
| C(12)-C(11)-C(2) | 119.46(13) |
| C(13)-C(12)-C(11) | 120.54(16) |
| C(13)-C(12)-H(12) | 119.7 |
| C(11)-C(12)-H(12) | 119.7 |

| | |
|---|---|
| C(14)-C(13)-C(12) | 120.31(16) |
| C(14)-C(13)-H(13) | 119.8 |
| C(12)-C(13)-H(13) | 119.8 |
| C(15)-C(14)-C(13) | 119.60(15) |
| C(15)-C(14)-H(14) | 120.2 |
| C(13)-C(14)-H(14) | 120.2 |
| C(14)-C(15)-C(16) | 120.62(17) |
| C(14)-C(15)-H(15) | 119.7 |
| C(16)-C(15)-H(15) | 119.7 |
| C(11)-C(16)-C(15) | 120.36(15) |
| C(11)-C(16)-H(16) | 119.8 |
| C(15)-C(16)-H(16) | 119.8 |
| C(21)-C(3)-C(2) | 114.28(11) |
| C(21)-C(3)-H(3A) | 108.7 |
| C(2)-C(3)-H(3A) | 108.7 |
| C(21)-C(3)-H(3B) | 108.7 |
| C(2)-C(3)-H(3B) | 108.7 |
| H(3A)-C(3)-H(3B) | 107.6 |
| C(22)-C(21)-C(26) | 118.29(13) |
| C(22)-C(21)-C(3) | 120.20(12) |
| C(26)-C(21)-C(3) | 121.50(12) |
| C(23)-C(22)-C(21) | 120.85(14) |
| C(23)-C(22)-H(22) | 119.6 |
| C(21)-C(22)-H(22) | 119.6 |
| C(24)-C(23)-C(22) | 120.35(14) |
| C(24)-C(23)-H(23) | 119.8 |
| C(22)-C(23)-H(23) | 119.8 |
| C(23)-C(24)-C(25) | 119.44(14) |
| C(23)-C(24)-H(24) | 120.3 |
| C(25)-C(24)-H(24) | 120.3 |
| C(24)-C(25)-C(26) | 120.22(14) |
| C(24)-C(25)-H(25) | 119.9 |
| C(26)-C(25)-H(25) | 119.9 |
| C(25)-C(26)-C(21) | 120.85(13) |
| C(25)-C(26)-H(26) | 119.6 |
| C(21)-C(26)-H(26) | 119.6 |

| | |
|---|---|
| C(5)-C(4)-C(2) | 112.72(12) |
| C(5)-C(4)-H(4A) | 109.0 |
| C(2)-C(4)-H(4A) | 109.0 |
| C(5)-C(4)-H(4B) | 109.0 |
| C(2)-C(4)-H(4B) | 109.0 |
| H(4A)-C(4)-H(4B) | 107.8 |
| C(6)-C(5)-C(4) | 123.74(14) |
| C(6)-C(5)-H(5) | 118.1 |
| C(4)-C(5)-H(5) | 118.1 |
| C(5)-C(6)-H(6A) | 120.0 |
| C(5)-C(6)-H(6B) | 120.0 |
| H(6A)-C(6)-H(6B) | 120.0 |
| C(1)-N(1)-C(31) | 127.69(12) |
| C(1)-N(1)-C(38) | 124.72(12) |
| C(31)-N(1)-C(38) | 107.59(11) |
| C(32)-C(31)-N(1) | 110.11(13) |
| C(32)-C(31)-H(31) | 124.9 |
| N(1)-C(31)-H(31) | 124.9 |
| C(31)-C(32)-C(33) | 107.67(13) |
| C(31)-C(32)-H(32) | 126.2 |
| C(33)-C(32)-H(32) | 126.2 |
| C(34)-C(33)-C(38) | 119.61(15) |
| C(34)-C(33)-C(32) | 132.62(15) |
| C(38)-C(33)-C(32) | 107.76(12) |
| C(35)-C(34)-C(33) | 118.44(15) |
| C(35)-C(34)-H(34) | 120.8 |
| C(33)-C(34)-H(34) | 120.8 |
| C(34)-C(35)-C(36) | 121.20(14) |
| C(34)-C(35)-H(35) | 119.4 |
| C(36)-C(35)-H(35) | 119.4 |
| C(37)-C(36)-C(35) | 121.68(16) |
| C(37)-C(36)-H(36) | 119.2 |
| C(35)-C(36)-H(36) | 119.2 |
| C(38)-C(37)-C(36) | 116.98(15) |
| C(38)-C(37)-H(37) | 121.5 |
| C(36)-C(37)-H(37) | 121.5 |

| | |
|---|---|
| C(37)-C(38)-C(33) | 122.06(13) |
| C(37)-C(38)-N(1) | 131.03(13) |
| C(33)-C(38)-N(1) | 106.87(12) |

***Table A6.4*** *Anisotropic displacement parameters (Åx10$^3$) for* ***41d****. The anisotropic displacement factor exponent takes the form* $-2\pi^2[h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*U^{12}]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| O(1) | 23(1) | 15(1) | 39(1) | -3(1) | -1(1) | 2(1) |
| C(1) | 18(1) | 16(1) | 18(1) | 1(1) | 3(1) | -1(1) |
| C(2) | 16(1) | 14(1) | 16(1) | 0(1) | 2(1) | 1(1) |
| C(11) | 14(1) | 20(1) | 16(1) | -2(1) | 2(1) | -3(1) |
| C(12) | 21(1) | 31(1) | 21(1) | 4(1) | 3(1) | -2(1) |
| C(13) | 27(1) | 59(1) | 19(1) | 1(1) | 6(1) | -9(1) |
| C(14) | 26(1) | 60(1) | 27(1) | -19(1) | 13(1) | -9(1) |
| C(15) | 28(1) | 34(1) | 43(1) | -17(1) | 15(1) | -2(1) |
| C(16) | 24(1) | 23(1) | 28(1) | -4(1) | 8(1) | 0(1) |
| C(3) | 18(1) | 17(1) | 20(1) | -1(1) | 1(1) | -1(1) |
| C(21) | 16(1) | 15(1) | 22(1) | -2(1) | 1(1) | -2(1) |
| C(22) | 20(1) | 28(1) | 24(1) | -2(1) | 2(1) | -5(1) |
| C(23) | 18(1) | 32(1) | 37(1) | -7(1) | 7(1) | -2(1) |
| C(24) | 17(1) | 25(1) | 46(1) | -1(1) | -2(1) | 2(1) |
| C(25) | 23(1) | 23(1) | 32(1) | 6(1) | -3(1) | -2(1) |
| C(26) | 18(1) | 22(1) | 24(1) | 0(1) | 1(1) | -3(1) |
| C(4) | 18(1) | 16(1) | 17(1) | 2(1) | 3(1) | 0(1) |
| C(5) | 28(1) | 22(1) | 19(1) | 1(1) | 7(1) | 0(1) |
| C(6) | 30(1) | 33(1) | 28(1) | 8(1) | 13(1) | 7(1) |
| N(1) | 16(1) | 15(1) | 19(1) | 1(1) | 2(1) | 1(1) |
| C(31) | 20(1) | 18(1) | 20(1) | -2(1) | 1(1) | 0(1) |
| C(32) | 22(1) | 24(1) | 21(1) | -1(1) | 0(1) | -3(1) |
| C(33) | 19(1) | 27(1) | 17(1) | 4(1) | 3(1) | -2(1) |
| C(34) | 17(1) | 40(1) | 24(1) | 6(1) | 1(1) | 0(1) |
| C(35) | 17(1) | 44(1) | 31(1) | 10(1) | 5(1) | 7(1) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C(36) | 26(1) | 33(1) | 34(1) | 7(1) | 10(1) | 11(1) |
| C(37) | 23(1) | 24(1) | 27(1) | 3(1) | 6(1) | 4(1) |
| C(38) | 15(1) | 22(1) | 17(1) | 6(1) | 4(1) | 1(1) |

***Table A2.5*** *Hydrogen coordinates (x $10^4$) and isotropic displacement parameters ($Å^2$ x$10^3$) for* ***41d****.*

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(12) | 4458 | 3335 | 8822 | 29 |
| H(13) | 3627 | 4594 | 10122 | 42 |
| H(14) | 2846 | 7953 | 10087 | 45 |
| H(15) | 2929 | 10074 | 8765 | 41 |
| H(16) | 3771 | 8853 | 7463 | 29 |
| H(3A) | 3999 | 3053 | 6008 | 22 |
| H(3B) | 3503 | 2516 | 6978 | 22 |
| H(22) | 1710 | 4257 | 7351 | 29 |
| H(23) | -83 | 6021 | 6792 | 34 |
| H(24) | -384 | 7599 | 5275 | 36 |
| H(25) | 1134 | 7416 | 4324 | 32 |
| H(26) | 2939 | 5680 | 4887 | 26 |
| H(4A) | 4365 | 7493 | 6137 | 20 |
| H(4B) | 5602 | 7793 | 6874 | 20 |
| H(5) | 5351 | 5085 | 5227 | 27 |
| H(6A) | 7407 | 6943 | 6273 | 35 |
| H(6B) | 7341 | 5559 | 5284 | 35 |
| H(31) | 6293 | 7474 | 8431 | 24 |
| H(32) | 8389 | 8032 | 9225 | 27 |
| H(34) | 10541 | 5436 | 9358 | 33 |
| H(35) | 11213 | 2235 | 8880 | 37 |
| H(36) | 9901 | -24 | 7933 | 37 |
| H(37) | 7842 | 786 | 7476 | 29 |

# *CHAPTER 5*

## *Palladium-Catalyzed Enantioselective Decarboxylative Allylic Alkylation of Protected Benzoin-Derived Enol Carbonates*[†]

### 5.1 INTRODUCTION

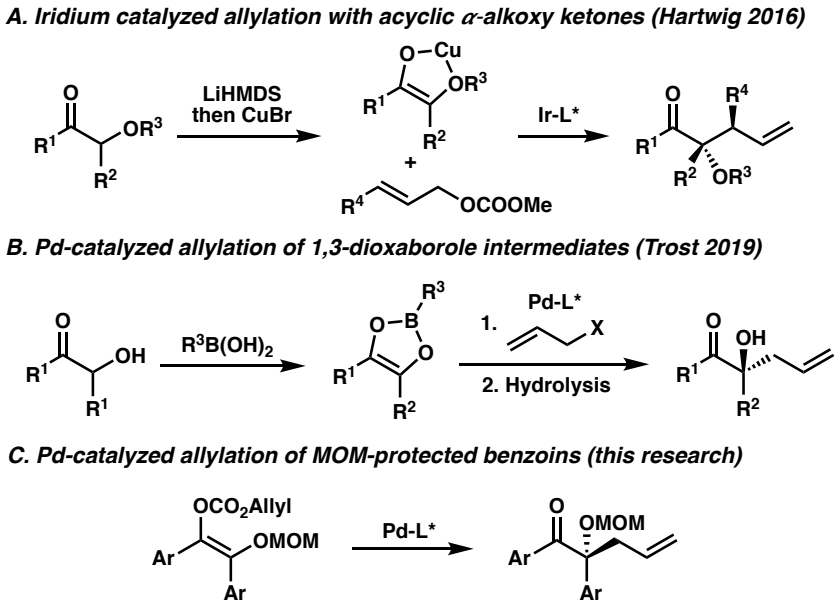
Benzoins are a preeminent motif in organic chemistry that are used as synthetic intermediates to access a variety of useful structures.[1] As a result, extensive efforts toward the asymmetric synthesis of benzoin derivatives have been reported, including enantioselective benzoin condensations,[2] reductions of α-diketones,[3] and enzyme-catalyzed kinetic resolutions.[4] However, the direct synthesis of a fully-substituted α-carbonyl stereocenter in an enantioselective manner has only recently been developed. In 2008, the Glorius group reported the palladium-catalyzed direct C-allylation of benzoins, as well as a tandem benzoin-allylation process.[5] They note, however, that performing the transformation in an asymmetric fashion proved to be challenging, likely due to nonselective formation of a mixture of enolates. Several years later, the Hartwig group reported the use of iridium-catalysis for the diastereo- and enantioselective synthesis of branched α-alkoxy ketones via a stereodefined enolate, formed by enolization in the presence

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[†]This research was performed in collaboration with Remi Lavernhe and Dr. Haiming Zhang. Portions of this chapter have been reproduced with permission from Lavernhe, R.; Alexy, E. J.; Zhang, H.; Stoltz, B. M. *Adv. Synth. Catal* **2020**, *362*, 344–347. © 2019 Wiley-VCH.

of a copper additive (Figure 5.1A).[6] Recently, the Trost group has reported a unique strategy toward the asymmetric alkylation of benzoins via a 1,3-dioxaborole intermediate (Figure 5.1B).[7] Due to the importance of this structural motif, and in continuation of recent research from our group regarding the synthesis and utility of fully-substituted acyclic enolates for palladium-catalyzed allylic alkylation,[8] we hypothesized that preformation of a benzoin-derived enolate precursor as a single geometric isomer would allow for an enantioselective alkylation process. (Figure 5.1C).

**Figure 5.1** Asymmetric Strategies Toward Tertiary α-Hydroxy Ketones.

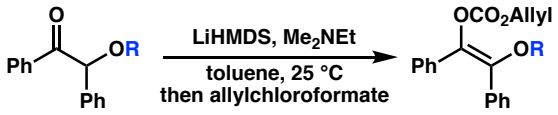



## 5.2 INVESTIGATION OF BENZOIN ENOLIZATION

We began our investigations by examining the enolization selectivities obtained from various protected benzoins when treated with recently reported selective enolization conditions (Table 5.1).[9] While a 2,2,2-trichloroethoxycarbonyl (Troc) carbonate protecting group (entry 1) decomposes under the reaction conditions, a variety of alternative groups were found to be stable. When benzoin is protected with a TBS group,

enolization selectivity is poor providing the enol carbonate in only a 56:44 ratio (entry 2). This could be improved slightly to 75:25 by switching to a benzoyl (Bz) group (entry 3). The use of methoxyacetal protecting group variants provided an additional boost to enolization selectivity with a benzyloxymethyl (BOM) group resulting in a 86:14 ratio (entry 4) and a MOM group (entry 5) providing access to a >98:2 isomeric ratio. While certain chelating protecting groups provide higher levels of enolization selectivity, we note that deviation from the standard selective enolization conditions (i.e. omission of $Me_2NEt$) results in decreased enolization selectivity.

**Table 5.1** Impact of Protecting Group on Enolization Selectivity.[a]




| entry | R | Z/E ratio |
|---|---|---|
| 1 | Troc | – |
| 2 | TBS | 56:44 |
| 3 | Bz | 75:25 |
| 4 | BOM | 86:14 |
| 5 | MOM | >98:2 |

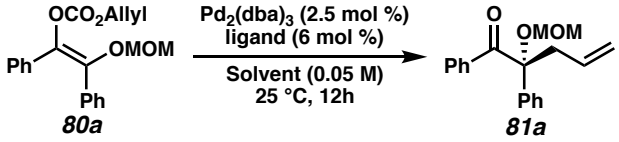
[a] Conditions: ketone (2.0 mmol), LiHMDS (2 equiv), $Me_2NEt$ (2.0 equiv), PhMe (5.0 mL), 23 °C; then allyl chloroformate (2.0 equiv), 25 °C. E/Z ratio and assignment of olefin stereochemistry was determined by NMR analysis.

## 5.3 INVESTIGATION OF BENZOIN ALLYLIC ALKYLATION

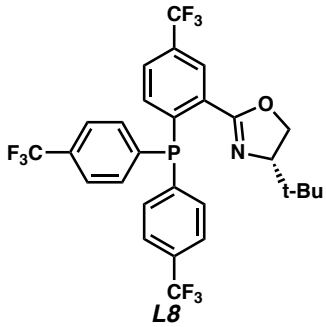
With ready access to a stereodefined benzoin enolate precursor established, we next examined conditions for performing an enantioselective palladium-catalyzed allylic alkylation (Table 5.2). We began our investigations by examining a variety of ligands commonly used in the literature for this transformation. The electron deficient phosphinooxazoline ligand (*S*)-$(CF_3)_3$-*t*-BuPHOX (***L8***) was found to provide the desired product in a low 25% ee (entry 1). Switching to

bisphosphine ligands developed by Trost and coworkers, product ee could be improved. Both the (*R*,*R*)-DACH-Ph (***L9***, entry 2) and (*R*,*R*)-DPEN-Ph (***L10***, entry 3) ligands provided the desired product in promising levels of ee (64% and 67% respectively). Switching to the (*R*,*R*)-ANDEN-Ph ligand (***L11***, entry 4) resulted in an increase to 80% ee, and was carried forward as the optimal ligand. A screen of solvents revealed that methylcyclohexane (entry 7) was the optimal solvent for the transformation, affording the desired product in a good 88% ee and an excellent 99% isolated yield. Notably, the catalyst loading could be lowered to 1 mol % of $Pd_2(dba)_3$ and 2.4 mol % of ligand with no deleterious results.

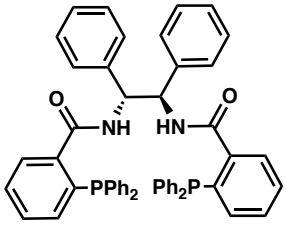
**Table 5.2** Optimization of acyclic, decarboxylative allylic alkylation of benzoin-derived enol carbonates.[a]



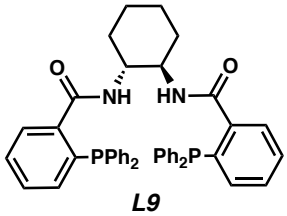

| entry | ligand | solvent | %ee (yield)[b] |
|---|---|---|---|
| 1 | L8 | 3:1 hexane/PhMe | 25 |
| 2 | L9 | 3:1 hexane/PhMe | 64 |
| 3 | L10 | 3:1 hexane/PhMe | 67 |
| 4 | L11 | 3:1 hexane/PhMe | 80 |
| 5 | L11 | PhMe | 79 |
| 6 | L11 | $Et_2O$ | 82 (97) |
| 7 | L11 | methylcyclohexane | 88 (99) |



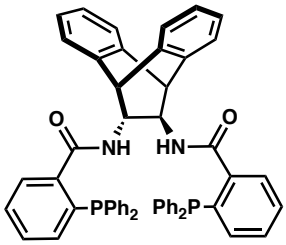

*L8*




*L10*




*L9*




*L11*

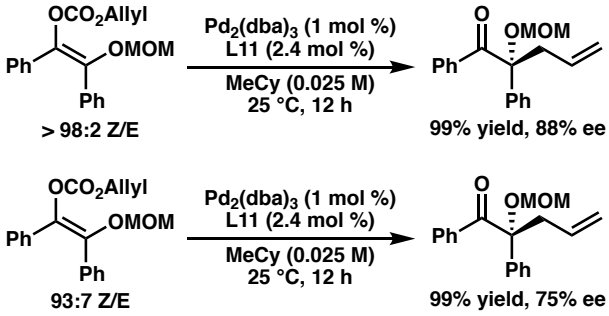
[a] Conditions: 0.1 mmol **80a**, 2.5 mol % $Pd_2(dba)_3$, 6 mol % ligand, 2.0 mL solvent. [b] Determined by chiral supercritical fluid chromatography (SFC) analysis. [c] Conversion over 95% if no yield from isolated product stated. [d] Reaction performed with 0.2 mmol of 1 mol % $Pd_2(dba)_3$, 2.4 mol % ligand, and 4.0 mL solvent.

## 5.4 IMPORTANCE OF ENOLATE GEOMETRY

With optimal conditions identified, we next sought to examine the importance of enolate geometry on the transformation (Scheme 5.1). Under the standard conditions, the desired product is obtained in a 99% isolated yield and 88% ee favoring the *R*-absolute stereochemistry when the starting material consists of a >98:2 Z/E ratio of enolates.

Even when a relatively high 93:7 Z/E mixture of enolates is used, the alkylation product is obtained in a significantly decreased 75% ee, highlighting the importance of forming the starting enol carbonate in as high geometric purity as possible.

**Scheme 5.1** Importance of substrate enolate geometry.

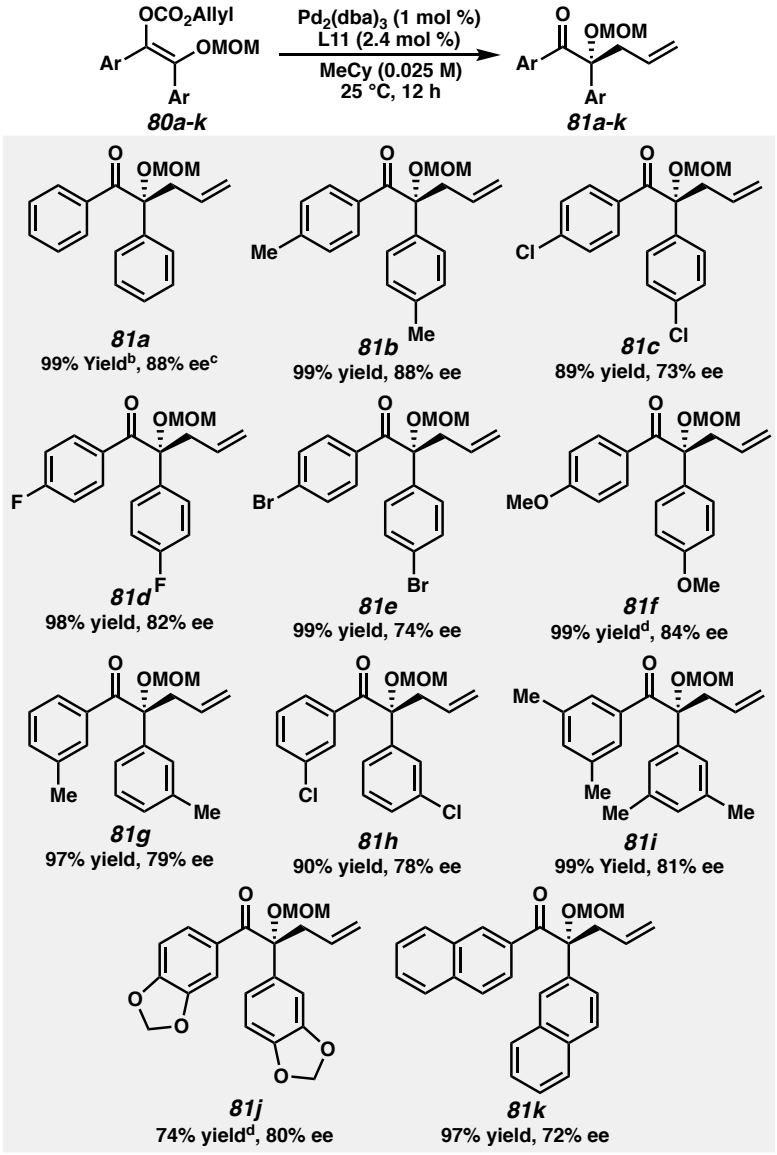



## 5.5 INVESTIGATION OF REACTION SCOPE

Having identified optimized reaction conditions, we examined the scope of the transformation for accessing various benzoin derivatives (Table 5.3). In all cases, the starting enol carbonate is prepared as a single enolate isomer. A variety of substrates were examined showing that both electronic and steric changes were tolerated leading to excellent yield and good enantioselectivity. Substitution at the *para*-position showed that both electron rich and electron deficient rings performed well, with *para*-Me (**81b**), *para*-OMe (**81f**), and *para*-fluoro (**81d**) substrates yielding the products in 98-99% yield and 82-88% ee. The presence of other halides at the *para*-position lead to a decrease in enantioselectivity down to 71% ee for *para*-chloro (**81c**) and 73% ee for a *para*-bromo substituent (**81e**). Substitution at the *meta*-position led to consistent results, proceeding with excellent yield and modest enantioselectivity for *meta*-Me (**81g**) and *meta*-chloro (**81h**) alkylation products obtained in 79% and 78% ee respectively. More hindered substrates such as the bis-Me substrate (**81i**), and (**81j**) derived from piperonal showed promising results, providing the products in 80% ee and 81% ee, respectively. However,

a naphthyl ring (**81k**) showed the limit of steric hindrance on this system with a diminished 72% ee. Notably, both electron rich substrates (**81f**) and (**81j**) required longer reaction times to reach full conversion (i.e., 48 h).

**Table 5.3** Substrate scope of asymmetric, decarboxylative allylic alkylation of benzoin derivatives.[a]

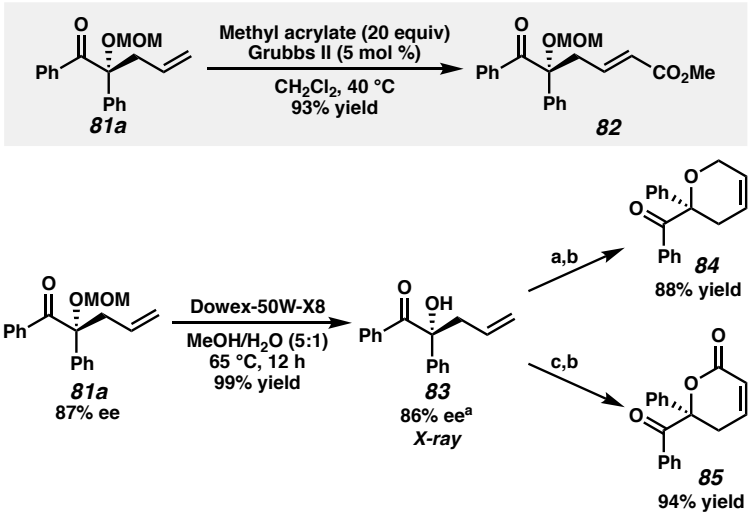



[a] Reactions performed on 0.2 mmol scale [b]Yield of isolated product. [c] Determined by chiral SFC analysis. [d] Reaction performed for 48 h.

## 5.6 DERIVATIZATION OF ALKYLATION PRODUCTS

With a scope of the transformation examined, we next sought to demonstrate the utility of the produced α-tetrasubstituted benzoins toward further functionalizations (Scheme 5.2). Direct treatment of the standard alkylation product **81a** to cross metathesis conditions using methyl acrylate provided ester **3** in 93% isolated yield. Deprotection of the MOM group to afford the corresponding enantioenriched tertiary alcohol **4**[10] was achieved using acidic Dowex-50W-X8 resin[11] in quantitative yield. Notably, no erosion of enantiomeric excess of **4** was observed, a process that might theoretically occur via an α-ketol rearrangement. Alcohol **4** could be further derivatized via alkylation with allyl bromide and subsequent ring-closing metathesis using Grubbs' second generation catalyst, yielding dihydropyran **5** in 88% yield over two steps. Alternatively, acylation with acryloyl chloride followed by ring-closing metathesis yields α,β-unsaturated lactone **6** in 94% yield over two steps.

**Scheme 5.2** Derivatization of alkylation products.[a]




[a] Absolute configuration of **83** was determined by single crystal X-ray diffraction, all other compounds are assigned by analogy. Conditions: a) NaH then allyl bromide, DMF, 0 °C. b) Grubbs II (1 mol %), $CH_2Cl_2$, 40 °C. c) *n*-BuLi then acryloyl chloride, THF, –78 °C.

## 5.7 CONCLUSIONS

In conclusion, we have developed an asymmetric palladium-catalyzed decarboxylative allylic alkylation of enol carbonates derived from protected benzoins. Both the use of the hindered bisphosphine (*R*,*R*)-ANDEN-Ph ligand and the preparation of the starting enol carbonate in high isomeric purity are necessary for obtaining high enantioselectivity. The obtained tetrasubstituted benzoin products can be derivatized to afford chiral building blocks containing several differentiated reactive sites poised to undergo additional transformations.

## 5.8 EXPERIMENTAL SECTION

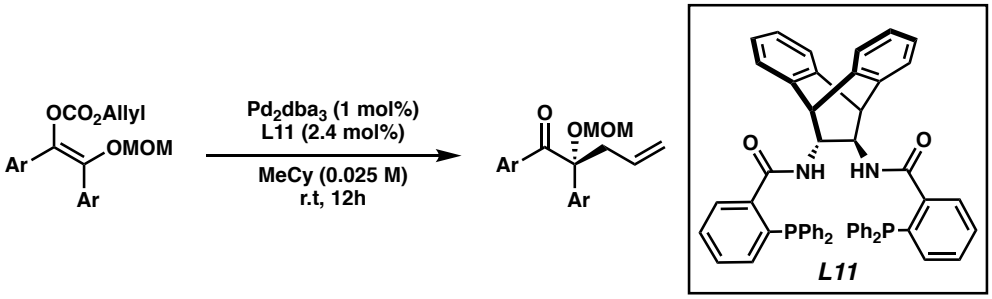
### 5.8.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 μm) was used for flash chromatography. $^1$H NMR spectra were recorded on Varian Inova 500 MHz and Bruker 400 MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm). $^{13}$C NMR spectra were recorded on a Varian Inova 500 MHz spectrometer (125 MHz) and Bruker 400 MHz spectrometers (100 MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm). Data for $^1$H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet, app = apparent. Data for $^{13}$C NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer or Nicolet 6700 FTIR spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption ($cm^{-1}$). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell and are reported as: $[\alpha]_D^T$ (concentration in 10 mg/1 mL, solvent). Analytical SFC was performed with a Mettler SFC supercritical $CO_2$ analytical

chromatography system utilizing Chiralpak (AD-H, AS-H or IC) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+), or obtained from Caltech mass spectrometry laboratory. Ligands and MOM-protected benzoins were prepared by known methods unless otherwise described below.

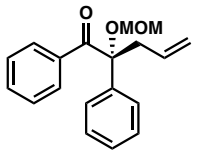
## 5.8.2 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

### 5.8.2.1 General Procedure for Pd-Catalyzed Allylic Alkylation Reactions



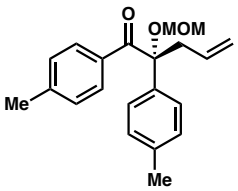

In a nitrogen-filled glovebox, a solution of $Pd_2(dba)_3$ (1.8 mg) and **L4** (3.9 mg) in MeCy (4 mL) was stirred for 30 minutes at 25 °C, then the resulting catalyst solution was added to a vial containing allyl enol carbonate substrate (0.2 mmol) in MeCy (4 mL). The vial was sealed with a Teflon-lined cap, removed from the glovebox, and stirred at 25 °C for 12 h. The crude reaction mixture was concentrated then purified by silica gel flash chromatography to provide the desired alkylation product.

### 5.8.2.2 Spectroscopic Data for the Allylic Alkylation Products




**(*S*)-2-(methoxymethoxy)-1,2-diphenylpent-4-en-1-one (81a)**

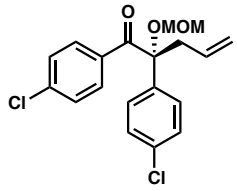
Purified by column chromatography (10% $Et_2O$ in hexanes) to provide a white solid (58.7 mg, 99% yield); 88% ee, $[\alpha]_D^{25}$ +198.4 (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.84–7.78 (m, 2H), 7.40 – 7.35 (m, 2H), 7.34–7.23 (m, 3H), 7.21–7.15 (m, 3H), 5.46 (dddd, *J* = 16.9, 10.6, 7.6, 6.3 Hz, 1H), 4.92 – 4.89 (m, 1H), 4.89 – 4.84 (m, 1H), 4.72 (d, *J* = 6.9 Hz, 1H), 4.66 (d, *J* = 6.9 Hz, 1H), 3.10 (ddt, *J* = 15.5, 7.7, 1.2 Hz, 1H), 3.02 (s, 3H), 2.91 (ddt, *J* = 15.5, 6.4, 1.6 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 199.6, 140.7, 135.0, 132.5, 132.4, 130.6, 128.6, 128.0, 127.6, 125.4, 118.5, 93.2, 87.0, 57.1, 40.6; IR (Neat Film, NaCl) 3070, 2926, 1683, 1640, 1597, 1578, 1491, 1446, 1414, 1239, 1182, 1152, 1103, 1078, 1028, 1019, 920, 759, 720, 701, 664 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{24}NO_3$ $[M+NH_4]^+$: 314.1751, found 314.1753; SFC Conditions: 5% IPA, 2.5 mL/min, Chiralpak IC column, λ = 254 nm, $t_R$ (min): major = 4.62, minor = 5.37.




**(*S*)-2-(methoxymethoxy)-1,2-di-*p*-tolylpent-4-en-1-one (81b)**

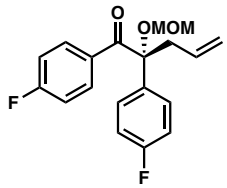
Purified by column chromatography (8% $Et_2O$ in hexanes) to provide a colorless oil (64.3 mg, 99% yield); 88% ee, $[\alpha]_D^{25}$ +154.6 (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.79 (m, 2H), 7.36 – 7.28 (m, 2H), 7.18 – 7.10 (m, 2H), 7.10 – 7.00 (m, 2H), 5.63

– 5.47 (m, 1H), 4.99 – 4.91 (m, 2H), 4.76 (d, *J* = 6.8 Hz, 1H), 4.72 (d, *J* = 6.8 Hz, 1H), 3.19 – 3.09 (m, 4H), 2.97 (ddt, *J* = 15.4, 6.3, 1.6 Hz, 1H), 2.31 (s, 3H), 2.29 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.3, 143.1, 137.9, 137.1, 132.8, 132.4, 130.8, 129.3, 128.7, 125.3, 118.3, 93.2, 87.0, 57.1, 40.6, 21.7, 21.2; IR (Neat Film, NaCl) 3075, 2922, 2824, 1677, 1640, 1606, 1570, 1511, 1445, 1409, 1242, 1183, 1153, 1101, 1029, 1017, 921, 849, 815, 776, 750 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{21}H_{28}NO_3$ $[M+NH_4]^+$: 342.2064, found 342.2062; SFC Conditions: 5% IPA, 2.5 mL/min, Chiralpak IC column, λ = 254 nm, $t_R$ (min): major = 6.77, minor = 8.03.



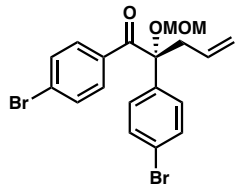

**(*S*)-1,2-bis(4-chlorophenyl)-2-(methoxymethoxy)pent-4-en-1-one (81c)**

Purified by column chromatography (7% $Et_2O$ in hexanes) to provide a colorless oil (64.7 mg, 89% yield); 73% ee, $[\alpha]_D^{25}$ +112.9 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.78 (m, 2H), 7.34 – 7.26 (m, 4H), 7.26 – 7.19 (m, 2H), 5.46 (dddd, *J* = 17.0, 10.3, 7.4, 6.5 Hz, 1H), 4.99 – 4.87 (m, 2H), 4.80 (d, *J* = 7.0 Hz, 1H), 4.69 (d, *J* = 7.1 Hz, 1H), 3.13 (ddt, *J* = 15.5, 7.5, 1.2 Hz, 1H), 3.08 (s, 3H), 2.88 (ddt, *J* = 15.5, 6.5, 1.6 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.8, 139.1, 139.0, 133.7, 132.9, 132.1, 131.8, 128.9, 128.5, 126.7, 119.1, 93.3, 86.6, 57.3, 40.2; IR (Neat Film, NaCl) 3077, 2926 (br), 1684, 1639, 1588, 1489, 1400, 1244, 1178, 1154, 1092, 1025, 1012, 922, 849, 815, 757, 748 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{22}Cl_2NO_3$ $[M+NH_4]^+$: 382.0971, found 382.0981; SFC Conditions: 5% IPA, 2.5 mL/min, Chiralpak IC column, λ = 210 nm, $t_R$ (min): major = 4.46, minor = 5.41.



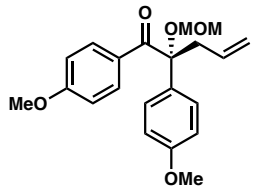

**(*S*)-1,2-bis(4-fluorophenyl)-2-(methoxymethoxy)pent-4-en-1-one (81d)**

Purified by column chromatography (10% $Et_2O$ in hexanes) to provide a white solid (65.1 mg, 98% yield); 82% ee, $[\alpha]_D^{25}$ +155.1 (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.89 (m, 2H), 7.44 – 7.32 (m, 2H), 7.07 – 6.99 (m, 2H), 6.99 – 6.90 (m, 2H), 5.50 (dddd, *J* = 17.0, 10.4, 7.5, 6.5 Hz, 1H), 5.01 – 4.89 (m, 2H), 4.81 (d, *J* = 7.0 Hz, 1H), 4.72 (d, *J* = 7.0 Hz, 1H), 3.15 (ddt, 15.5, 7.5, 1.3Hz, 1H), 3.11 (s, 3H), 2.92 (ddt, *J* = 15.5, 6.5, 1.6 Hz, 1H); $^{19}F$ NMR (282 MHz, $CDCl_3$) δ -105.5 (tt, *J* = 8.4, 5.5 Hz), -114.7 (tt, *J* = 8.5, 5.1 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 197.7, 165.1 (d, *J* = 255.0 Hz), 162.2 (d, *J* = 246.7 Hz), 136.4 (d, *J* = 3.2 Hz), 133.4 (d, *J* = 9.1 Hz), 132.0, 131.0 (d, *J* = 3.1 Hz), 127.1 (d, *J* = 8.1 Hz), 118.9, 115.6 (d, *J* = 21.5 Hz), 115.2 (d, *J* = 21.5 Hz), 93.3, 86.6, 57.2, 40.4; IR (Neat Film, NaCl) 3077, 2929 (br), 2848, 2826, 1685, 1640, 1598, 1508, 1445, 1409, 1300, 1237, 1157, 1098, 1024, 1013, 976, 922, 854, 835, 814, 792, 760, 620 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{22}F_2NO_3$ $[M+NH_4]^+$: 350.1562, found 350.1558; SFC Conditions: 5% IPA, 2.5 mL/min, Chiralpak IC column, λ = 254 nm, $t_R$ (min): major = 2.22, minor = 2.69.




**(S)-1,2-bis(4-bromophenyl)-2-(methoxymethoxy)pent-4-en-1-one (81e)**

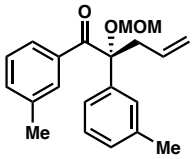
Purified by column chromatography (8% $Et_2O$ in hexanes) to provide a colorless oil (91.6 mg, 99% yield); 74% ee, $[\alpha]_D^{25}$ +73.9 (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.71 (m, 2H), 7.51 – 7.37 (m, 4H), 7.31 – 7.22 (m, 2H), 5.47 (dddd, *J* = 17.0, 10.4, 7.5, 6.5 Hz, 1H), 5.03 – 4.89 (m, 2H), 4.81 (d, *J* = 7.0 Hz, 1H), 4.70 (d, *J* = 7.0 Hz, 1H), 3.14 (ddt, *J* = 15.7, 7.5, 1.2 Hz, 1H), 3.09 (s, 3H), 2.88 (ddt, *J* = 15.5, 6.5, 1.5 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 198.0, 139.6, 133.3, 132.2, 131.9, 131.7, 131.5, 127.9, 127.1, 121.9, 119.1, 93.3, 86.6, 57.3, 40.2; IR (Neat Film, NaCl) 3076, 2928, 1682, 1641, 1583, 1565, 1486, 1445, 1395, 1244, 1178, 1154, 1100, 1072, 1024, 1008, 921, 845, 810, 754, 737 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{22}Cl_2NO_3$ $[M+NH_4]^+$: 469.9961, found 469.9943; SFC Conditions: 5% IPA, 2.5 mL/min, Chiralpak IC column, λ = 210 nm, $t_R$ (min): major = 6.38, minor = 8.03.




**(*S*)-2-(methoxymethoxy)-1,2-bis(4-methoxyphenyl)pent-4-en-1-one (81f)**

Reaction carried out 48h instead of 12h. Purified by column chromatography (30% $Et_2O$ in hexanes) to provide a colorless oil (71.2 mg, 99% yield); 84% ee, $[\alpha]_D^{25}$ +129.7 (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.88 (m, 2H), 7.37 – 7.29 (m, 2H), 6.91 – 6.80 (m, 2H), 6.80 – 6.70 (m, 2H), 5.55 (dddd, *J* = 16.9, 10.6, 7.5, 6.3 Hz, 1H), 5.00 –

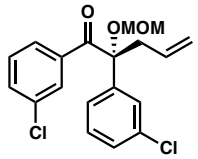
4.90 (m, 2H), 4.75 (d, $J$ = 6.8 Hz, 1H), 4.72 (d, $J$ = 6.8 Hz, 1H), 3.78 (s, 6H), 3.16 (s, 3H), 3.12 (ddt, $J$ = 15.4, 7.6, 1.2 Hz, 1H), 2.94 (ddt, $J$ = 15.4, 6.3, 1.6 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 198.2, 162.8, 158.9, 133.1, 133.1, 132.8, 127.8, 126.6, 118.3, 113.9, 113.2, 93.2, 86.8, 57.1, 55.4, 55.3, 40.7; IR (Neat Film, NaCl) 3073, 2935br, 2838, 1671, 1640, 1600, 1574, 1510, 1462, 1443, 1419, 1307, 1249, 1172, 1152, 1101, 1027, 1009, 922, 828, 798, 782, 760, 622 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{21}H_{24}NaO_5$ $[M+Na]^+$: 379.1516, found 379.1525; SFC Conditions: 15% IPA, 2.5 mL/min, Chiralpak IC column, λ = 254 nm, $t_R$ (min): major = 3.47, major = 3.98.




**(*S*)-2-(methoxymethoxy)-1,2-di-*m*-tolylpent-4-en-1-one (81g)**

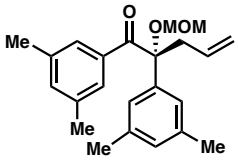
Purified by column chromatography (7% $Et_2O$ in hexanes) to provide a colorless oil (63.4 mg, 97% yield); 79% ee, $[\alpha]_D^{25}$ +168.0 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.74 (td, $J$ = 1.8, 1.0 Hz, 1H), 7.65 (dq, $J$ = 8.0, 1.2 Hz, 1H), 7.30 – 7.17 (m, 4H), 7.12 (t, $J$ = 7.7 Hz, 1H), 7.09 – 7.02 (m, 1H), 5.61 – 5.46 (m, 1H), 4.98 (d, $J$ = 1.4 Hz, 1H), 4.97 – 4.92 (m, 1H), 4.76 (d, $J$ = 6.8 Hz, 1H), 4.71 (d, $J$ = 6.9 Hz, 1H), 3.18 – 3.11 (m, 1H), 3.10 (s, 3H), 2.99 (ddt, $J$ = 15.5, 6.2, 1.7 Hz, 1H), 2.33 (s, 3H), 2.29 (d, $J$ = 0.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.7, 165.1 (d, $J$ = 255.0 Hz), 162.2 (d, $J$ = 246.7 Hz), 136.4 (d, $J$ = 3.2 Hz), 133.4 (d, $J$ = 9.1 Hz), 132.0, 131.0 (d, $J$ = 3.1 Hz), 127.1 (d, $J$ = 8.1 Hz), 118.9, 115.6 (d, $J$ = 21.5 Hz), 115.2 (d, $J$ = 21.5 Hz), 93.3, 86.6, 57.2, 40.4; IR (Neat Film, NaCl) 3077, 2929 (br), 2848, 2826, 1685, 1640, 1598, 1508, 1445, 1409, 1300, 1237, 1157, 1098, 1024, 1013, 976, 922, 854, 835, 814, 792, 760, 620 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{22}F_2NO_3$ $[M+NH_4]^+$: 350.1562, found 350.1558;

SFC Conditions: 5% IPA, 2.5 mL/min, Chiralcel OD-H column, λ = 210 nm, $t_R$ (min): minor = 4.22, major = 4.64.



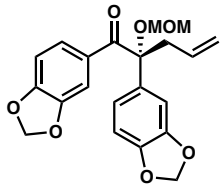

**(*S*)-1,2-bis(3-chlorophenyl)-2-(methoxymethoxy)pent-4-en-1-one (81h)**

Purified by column chromatography (8% Et2O in hexanes) to provide a colorless oil (64.9 mg, 78% yield); 78% ee, $[\alpha]_D^{25}$ +158.0 (*c* 1.0, CHCl3); 1H NMR (400 MHz, $CDCl_3$) δ 7.90 (ddd, J = 2.1, 1.6, 0.4 Hz, 1H), 7.74 (ddd, J = 7.9, 1.6, 1.0 Hz, 1H), 7.50 (td, J = 1.7, 0.8 Hz, 1H), 7.38 (ddd, J = 8.0, 2.2, 1.1 Hz, 1H), 7.27 – 7.19 (m, 4H), 5.48 (dddd, J = 16.9, 10.4, 7.5, 6.4 Hz, 1H), 5.05 – 4.91 (m, 2H), 4.84 (d, J = 7.1 Hz, 1H), 4.71 (d, J = 7.1 Hz, 1H), 3.16 (ddt, J = 15.6, 7.5, 1.2 Hz, 1H), 3.09 (s, 3H), 2.92 (ddt, J = 15.6, 6.4, 1.6 Hz, 1H); 13C NMR (100 MHz, $CDCl_3$) δ 197.6, 142.5, 136.2, 134.9, 134.4, 132.6, 131.6, 130.5, 130.0, 129.4, 128.8, 128.1, 125.5, 123.5, 119.2, 93.3, 86.6, 57.3, 40.2; IR (Neat Film, NaCl) 3074, 2925, 1686, 1640, 1594, 1570, 1474, 1418, 1278, 1234, 1154, 1079, 1027, 997, 921, 863, 790, 750, 734, 716, 691 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{22}Cl_2NO_3$ $[M+NH_4]^+$: 382.0971, found 382.0967; SFC Conditions: 3% IPA, 2.5 mL/min, Chiralpak IC column, λ = 254 nm, $t_R$ (min): major = 5.42, minor = 6.31.




**(S)-1,2-bis(3,5-dimethylphenyl)-2-(methoxymethoxy)pent-4-en-1-one (81i)**

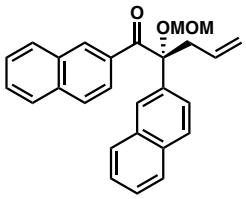
Purified by column chromatography (10% $Et_2O$ in hexanes) to provide a white solid (70.6 mg, 99% yield); 81% ee, $[\alpha]_D^{25}$ +168.4 (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.30 – 7.17 (m, 4H), 7.12 (t, *J* = 7.7 Hz, 1H), 7.06 (d, 1H), 5.61 – 5.46 (m, 1H), 5.01 – 4.92 (m, 2H), 4.76 (d, *J* = 6.8 Hz, 1H), 4.71 (d, *J* = 6.9 Hz, 1H), 3.14 (ddt, *J* = 15.5, 7.7, 1.3 Hz, 1H), 3.10 (s, 3H), 2.99 (ddt, *J* = 15.5, 6.2, 1.7 Hz, 1H), 2.33 (s, 3H), 2.29 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 200.0, 140.6, 138.2, 137.7, 135.1, 133.2, 132.7, 130.9, 128.4, 128.4, 128.1, 127.8, 125.9, 122.5, 118.3, 93.2, 87.1, 57.0, 40.7, 21.8, 21.5; IR (Neat Film, NaCl) 2921 (br), 1680, 1639, 1602, 1585, 1484, 1444, 1258, 1215, 1182, 1150, 1090, 1030, 921, 766, 741, 708 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{21}H_8NO_3$ $[M+NH_4]^+$: 325.1798, found 325.1792; SFC Conditions: 5% IPA, 2.5 mL/min, Chiralpak IC column, λ = 254 nm, $t_R$ (min): minor = 4.38, major = 5.02.




**(*S*)-1,2-bis(benzo[*d*][1,3]dioxol-5-yl)-2-(methoxymethoxy)pent-4-en-1-one (81j)**

Reaction carried out 48h instead of 12h. Purified by column chromatography (25% $Et_2O$ in hexanes) to provide a colorless oil (56.5 mg, 74% yield); 80% ee, $[\alpha]_D^{25}$ +104.1 (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.45 (d, *J* = 1.7 Hz, 1H), 6.96 (d, *J* = 1.8 Hz, 1H), 6.82 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.74 (d, *J* = 8.2 Hz, 1H),

6.70 (d, $J$ = 8.3 Hz, 1H), 5.99 – 5.92 (m, 4H), 5.54 (dddd, $J$ = 16.9, 10.5, 7.5, 6.4 Hz, 1H), 5.02 – 4.92 (m, 2H), 4.75 (d, $J$ = 6.8 Hz, 1H), 4.71 (d, $J$ = 6.8 Hz, 1H), 3.20 (s, 3H), 3.09 (ddt, $J$ = 15.5, 7.5, 1.2 Hz, 1H), 2.90 (ddt, $J$ = 15.5, 6.5, 1.6 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.4, 151.1, 148.0, 147.4, 146.9, 135.0, 132.6, 129.2, 127.2, 118.7, 118.4, 110.5, 108.4, 107.7, 106.1, 101.7, 101.3, 93.3, 86.8, 57.2, 40.8; IR (Neat Film, NaCl) 3075, 2898 (br), 2784, 1673, 1640, 1604, 1504, 1487, 1437, 1350, 1254, 1157, 1105, 1039, 934, 814, 793, 756 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{21}H_{20}NaO_7$ $[M+Na]^+$: 407.1101, found 407.1105; SFC Conditions: 20% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 254 nm, $t_R$ (min): major = 3.35, minor = 4.10.

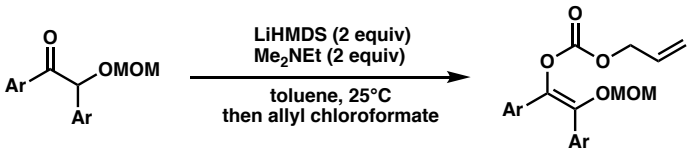



**(*S*)-2-(methoxymethoxy)-1,2-di(naphthalen-2-yl)pent-4-en-1-one (81k)**

Purified by column chromatography (12% $Et_2O$ in hexanes) to provide a white amorphous solid (79.2 mg, 97% yield); 72% ee, $[\alpha]_D^{25}$ +127.4 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.06 (s, 1H), 8.00 (dd, $J$ = 8.7, 1.8 Hz, 1H), 7.89 – 7.84 (m, 1H), 7.84 – 7.78 (m, 2H), 7.77 – 7.70 (m, 2H), 7.67 (d, $J$ = 8.7 Hz, 1H), 7.58 (dd, $J$ = 8.6, 1.9 Hz, 1H), 7.51 – 7.45 (m, 3H), 7.41 (ddd, $J$ = 8.2, 6.8, 1.4 Hz, 1H), 5.59 (dddd, $J$ = 16.8, 10.4, 7.6, 6.3 Hz, 1H), 5.02 – 4.93 (m, 2H), 4.91 (d, $J$ = 7.0 Hz, 1H), 4.84 (d, $J$ = 7.0 Hz, 1H), 3.32 (ddt, $J$ = 15.5, 7.6, 1.1 Hz, 1H), 3.15 (ddt, $J$ = 15.5, 6.3, 1.6 Hz, 1H), 3.10 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.4, 138.4, 135.1, 133.3, 132.8, 132.7, 132.4, 132.3, 132.3, 129.9, 128.5, 128.4, 127.8, 127.7, 127.6, 126.4, 126.4, 126.3, 126.2, 124.5, 123.3, 118.6, 93.4, 87.4, 57.3, 40.6; IR (Neat Film, NaCl) 3059, 2932 (br), 1679,

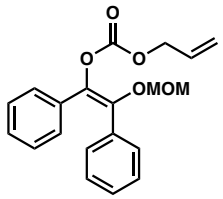
1640, 1625, 1596, 1507, 1464, 1436, 1353, 1274, 1220, 1190, 1152, 1130, 1099, 1075, 1027, 999, 921, 859, 821, 774, 757 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{27}H_{24}NaO_3$ $[M+Na]^+$: 419.1618, found 419.1623; SFC Conditions: 2% IPA, 2.5 mL/min, Chiralcel OJ-H column, $\lambda = 254$ nm, $t_R$ (min): major = 5.14, minor = 6.46.

### 5.8.2.3 General Procedure for Preparation of Allyl Enol Carbonates



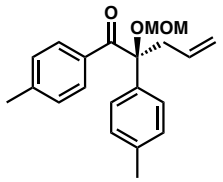

To a flame-dried flask was added LiHMDS (335 mg, 2 mmol) followed by toluene (3.0 mL) and N,N-dimethylethylamine (0.213 mL) and the resulting mixture stirred at 25 °C for 5 minutes. A solution of ketone (1 mmol) in toluene (2.0 mL) was then added, and the reaction stirred at 25 °C for an additional 30 minutes. The flask was then submerged in a room temperature water bath, and allyl chloroformate (0.217 mL, 2 mmol) was added neat, and the reaction continued until no starting material remained by TLC (typically less than 30 minutes). The crude reaction mixture was diluted with $Et_2O$ and quenched with water. The layers were separated, and the aqueous layer was extracted with $Et_2O$ twice. The combined organic layers were dried over $Na_2SO_4$ and concentrated. The crude product was purified by silica gel flash chromatography to afford the desired enol carbonate. After purification, the major isomer is obtained with a ratio >98:2 (determined by $^1H$ NMR) unless stated otherwise.

### 5.8.2.4 Spectroscopic Data for the Allyl Enol Carbonates




**(*Z*)-allyl (2-(methoxymethoxy)-1,2-diphenylvinyl) carbonate (80a)**

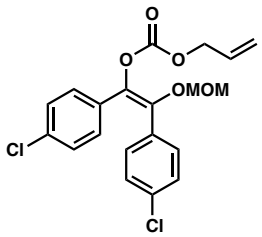
Run on 5.85 mmol scale. Purified by column chromatography (20% $Et_2O$ in hexanes) to provide a white solid (1.588 g, 80% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 5H), 7.21 – 7.12 (m, 5H), 5.95 (ddt, *J* = 17.2, 10.5, 5.7 Hz, 1H), 5.37 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.27 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.77 (s, 2H), 4.69 (dt, *J* = 5.6, 1.4 Hz, 2H), 3.56 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.3, 144.2, 135.8, 133.8, 132.1, 131.5, 130.4, 129.1, 128.7, 128.6, 128.1, 128.0, 118.9, 94.3, 69.0, 57.0; IR (Neat Film, NaCl) 2954, 1761, 1445, 1364, 1233, 1156, 1130, 1049, 1006, 956, 778, 698 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{20}H_{20}NaO_5$ $[M+Na]^+$: 363.1203, found 363.1203.




**(*Z*)-allyl (2-(methoxymethoxy)-1,2-di-*p*-tolylvinyl) carbonate (80b)**

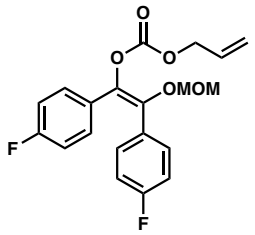
Run on 1.19 mmol scale. Purified by column chromatography (18% $Et_2O$ in hexanes) to provide a colorless oil (389.0 mg, 89% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.16 (m, 2H), 7.11 – 7.03 (m, 4H), 7.00 – 6.92 (m, 2H), 5.94 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.37 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.26 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.75 (s, 2H), 4.68 (dt, *J* = 5.6, 1.5 Hz, 2H), 3.54 (s, 3H), 2.32 (s, 3H), 2.26 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 153.4, 143.8, 139.0, 137.7, 135.6, 131.6, 131.0, 130.2, 129.3, 129.2, 128.9, 128.5, 118.8,

94.3, 69.0, 57.0, 21.5, 21.4; IR (Neat Film, NaCl) 2922 (br), 1762, 1652, 1609, 1558, 1513, 1448 (br), 1364, 1319, 1302, 1235, 1183, 1156, 1131, 1107, 1048, 1026, 1006, 961, 877, 824, 786 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{22}H_{28}NO_5$ $[M+NH4]^+$: 386.1962, found 386.1970.



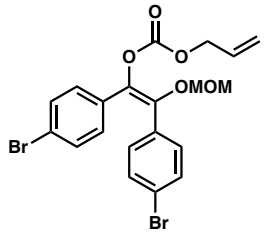

**(*Z*)-allyl (1,2-bis(4-chlorophenyl)-2-(methoxymethoxy)vinyl) carbonate (80c)**

Run on 0.573 mmol scale. Purified by column chromatography (20% $Et_2O$ in hexanes) to provide a colorless oil (198.3 mg, 85% yield); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.21 (m, 4H), 7.18 – 7.13 (m, 2H), 7.12 – 7.07 (m, 2H), 5.94 (ddt, *J* = 17.3, 10.9, 5.7 Hz, 1H), 5.38 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.29 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.76 (s, 2H), 4.68 (dt, *J* = 5.8, 1.5 Hz, 2H), 3.55 (d, *J* = 0.5 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 153.1, 143.7, 135.4, 135.3, 134.2, 132.1, 131.6, 131.3, 130.4, 130.0, 129.1, 128.6, 119.2, 94.5, 69.3, 57.1; IR (Neat Film, NaCl) 3088, 2956, 2900, 1763, 1648, 1593, 1490, 1398, 1364, 1317, 1297, 1236, 1157, 1133, 1091, 1049, 1004, 958, 925, 874, 835, 782 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{20}H_{22}Cl_2NO_5$ $[M+NH4]^+$: 426.0870, found 426.0854.




**(*Z*)-allyl (1,2-bis(4-fluorophenyl)-2-(methoxymethoxy)vinyl) carbonate (80d)**

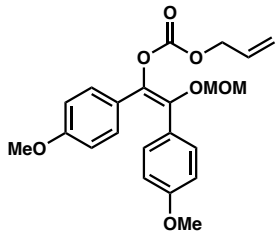
Run on 1.25 mmol scale. Purified by column chromatography (20% $Et_2O$ in hexanes) to provide a white solid (323.1 mg, 69% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.25 (m, 2H), 7.18 – 7.12 (m, 2H), 7.01 – 6.93 (m, 2H), 6.90 – 6.83 (m, 2H), 5.94 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.37 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.28 (dq, *J* = 10.5, 1.2 Hz, 1H), 4.76 (s, 2H), 4.68 (dt, *J* = 5.7, 1.4 Hz, 2H), 3.54 (s, 3H); $^{19}$F NMR (282 MHz, $CDCl_3$) δ -111.1 (dddd, *J* = 13.8, 8.7, 5.4, 1.2 Hz), -112.7 (dddd, *J* = 13.9, 8.7, 5.3, 1.3 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 163.1 (d, *J* = 250.0 Hz), 162.4 (d, *J* = 248.5 Hz), 153.2, 143.3, 135.1, 132.3 (d, *J* = 8.3 Hz), 131.4, 130.7 (d, *J* = 8.3 Hz), 129.8 (d, *J* = 3.4 Hz), 128.0 (d, *J* = 3.4 Hz), 119.1, 115.9 (d, *J* = 21.7 Hz), 115.4 (d, *J* = 21.8 Hz), 94.4, 69.2, 57.0; IR (Neat Film, NaCl) 2952, 1762, 1648, 1602, 1508, 1364, 1318, 1298, 1233, 1157, 1131, 1096, 1048, 1006, 959, 880, 841, 817, 780 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{20}H_{22}F_2NO_5$ $[M+NH4]^+$: 394.1461, found 394.1450.




**(*Z*)-allyl (1,2-bis(4-bromophenyl)-2-(methoxymethoxy)vinyl) carbonate (80e)**

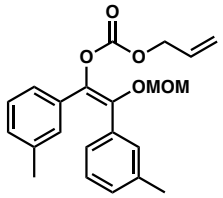
Run on 0.853 mmol scale. Purified by column chromatography (20% $Et_2O$ in hexanes) to provide a white solid (316.2 mg, 74% yield); $^1$H NMR (400 MHz $CDCl_3$) δ 7.45 – 7.39

(m, 2H), 7.34 – 7.28 (m, 2H), 7.21 – 7.14 (m, 2H), 7.07 – 7.01 (m, 2H), 5.94 (ddt, *J* = 17.2, 10.5, 5.7 Hz, 1H), 5.37 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.28 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.76 (s, 2H), 4.68 (dt, *J* = 5.7, 1.4 Hz, 2H), 3.54 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 153.1, 143.8, 135.4, 132.6, 132.1, 131.9, 131.6, 131.3, 130.9, 130.3, 123.8, 122.5, 119.2, 94.6, 69.3, 57.1; IR (Neat Film, NaCl) 2953 (br), 1762, 1651, 1586, 1488, 1384, 1363, 1316, 1297, 1234, 1156, 1132, 1100, 1070, 1047, 1001, 958, 872, 830, 778 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{20}H_{22}Br_2NO_5$ $[M+NH4]^+$: 513.9859, found 513.9860.



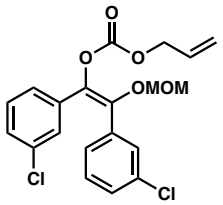

**(*Z*)-allyl (2-(methoxymethoxy)-1,2-bis(4-methoxyphenyl)vinyl) carbonate (80f)**

Run on 1.08 mmol scale. Purified by column chromatography (40% $Et_2O$ in hexanes) to provide a slightly yellow oil (327.3 mg, 76% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.21 (m, 2H), 7.15 – 7.09 (m, 2H), 6.82 – 6.76 (m, 2H), 6.72 – 6.67 (m, 2H), 5.94 (ddt, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.37 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.27 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.76 (s, 2H), 4.68 (dt, *J* = 5.6, 1.4 Hz, 2H), 3.79 (s, 3H), 3.75 (s, 3H), 3.55 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 160.0, 159.1, 153.4, 143.0, 135.1, 131.7, 131.6, 130.0, 126.4, 124.4, 118.8, 114.0, 113.6, 94.2, 68.9, 56.9, 55.3, 55.2; IR (Neat Film, NaCl) 2952 (br), 2838, 1761, 1608, 1511, 1458, 1364, 1319, 1292, 1237, 1175, 1156, 1130, 1107, 1049, 1017, 999, 960, 836 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{22}H_{28}NO_7$ $[M+NH4]^+$: 418.1860, found 418.1843.




**(*Z*)-allyl (2-(methoxymethoxy)-1,2-di-*m*-tolylvinyl) carbonate (80g)**

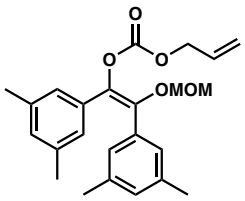
Run on 1.18 mmol scale. Purified by column chromatography (20% $Et_2O$ in hexanes) to provide a colorless oil (250.5 mg, 58% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.17 – 6.90 (m, 8H), 5.95 (ddt, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.38 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.28 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.77 (s, 2H), 4.69 (dt, *J* = 5.6, 1.4 Hz, 2H), 3.56 (s, 3H), 2.27 (s, 2H), 2.20 (s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.3, 144.2, 138.2, 137.6, 135.8, 133.7, 132.0, 131.6, 130.8, 129.9, 129.0, 128.7, 128.4, 127.9, 127.6, 125.9, 118.9, 94.3, 69.0, 57.0, 21.4, 21.4; IR (Neat Film, NaCl) 2950, 2921, 1763, 1651, 1604, 1584, 1488, 1449, 1381, 1363, 1320, 1239, 1192, 1156, 1127, 1053, 1031, 991, 969, 926, 851, 791, 714, 695 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{22}H_{28}NO_5$ $[M+NH4]^+$: 386.1962, found 386.1973.




**(*Z*)-allyl (1,2-bis(3-chlorophenyl)-2-(methoxymethoxy)vinyl) carbonate (80h)**

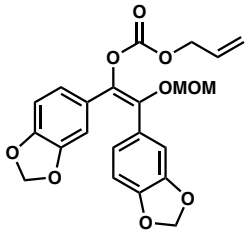
Run on 0.397 mmol scale. Purified by column chromatography (15% $Et_2O$ in hexanes) to provide a slightly yellow oil (101.9 mg, 63% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.34 (ddd, *J* = 2.0, 1.5, 0.5 Hz, 1H), 7.30 (ddd, *J* = 7.9, 2.1, 1.2 Hz, 1H), 7.24 – 7.19 (m, 2H), 7.16 (dddd, *J* = 5.6, 4.5, 2.3, 1.3 Hz, 2H), 7.08 (td, *J* = 7.9, 0.5 Hz, 1H), 6.99 (ddd, *J* = 7.8, 1.7, 1.1 Hz, 1H), 5.95 (ddt, *J* = 17.1, 10.4, 5.7 Hz, 1H), 5.39 (dq, *J* = 17.2, 1.5 Hz,

1H), 5.30 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.78 (s, 2H), 4.70 (dt, *J* = 5.7, 1.4 Hz, 2H), 3.55 (s, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 153.0, 143.9, 135.3, 135.3, 134.7, 134.2, 133.7, 131.3, 130.1, 130.0, 129.7, 129.5, 128.7, 128.5, 127.1, 119.2, 94.6, 69.3; IR (Neat Film, NaCl) 2958 (br), 1762, 1594, 1566, 1474, 1418, 1363, 1234, 1157, 1136, 1080, 1052, 1018, 966, 792, 682 (br) cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{20}H_{22}Cl_2NO_5$ $[M+NH4]^+$: 426.0870, found 426.0859.



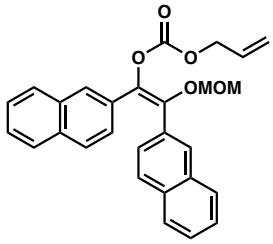

**(*Z*)-allyl (1,2-bis(3,5-dimethylphenyl)-2-(methoxymethoxy)vinyl) carbonate (80i)**

Run on 1.09 mmol scale. Purified by column chromatography (15% $Et_2O$ in hexanes) to provide a white solid (290.7 mg, 67% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.00 – 6.87 (m, 3H), 6.87 – 6.69 (m, 3H), 5.96 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.38 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.27 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.76 (s, 2H), 4.69 (dt, *J* = 5.6, 1.5 Hz, 2H), 3.55 (s, 3H), 2.21 (s, 6H), 2.13 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.4, 144.1, 137.9, 137.3, 135.8, 133.6, 131.9, 131.7, 130.7, 129.6, 128.0, 126.2, 118.8, 94.3, 69.0, 56.9, 21.3, 21.3; IR (Neat Film, NaCl) 2950, 2920, 1763, 1648, 1601, 1449, 1379, 1363, 1336, 1307, 1291, 1245, 1222, 1203, 1157, 1129, 1054, 1014, 987, 952, 926, 855, 783, 682 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{24}H_{30}NO_5$ $[M+NH4]^+$: 414.2275, found 414.2260.




**(*Z*)-allyl (1,2-bis(benzo[*d*][1,3]dioxol-5-yl)-2-(methoxymethoxy)vinyl) carbonate (80j)**

Run on 0.44 mmol scale. Purified by column chromatography (35% $Et_2O$ in hexanes) to provide a colorless oil (188.2 mg, 99% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.83 – 6.60 (m, 6H), 6.01 – 5.87 (m, 5H), 5.37 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.27 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.76 (s, 2H), 4.68 (dt, *J* = 5.7, 1.4 Hz, 2H), 3.54 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.3, 148.3, 147.9, 147.4, 143.2, 135.2, 131.5, 127.8, 125.8, 124.7, 123.0, 119.0, 110.2, 109.1, 108.6, 108.2, 101.4, 101.2, 94.3, 69.1, 57.0; IR (Neat Film, NaCl) 2897, 1759, 1503, 1489, 1439, 1364, 1341, 1300, 1239, 1225, 1154, 1101, 1082, 1039, 1008, 968, 932, 884, 870, 812 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{22}H_{24}NO_9$ $[M+NH4]^+$: 446.1446, found 446.1452.

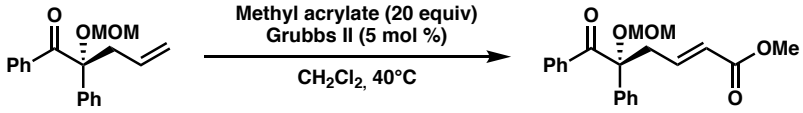



**(*Z*)-allyl (2-(methoxymethoxy)-1,2-di(naphthalen-2-yl)vinyl) carbonate (80k)**

Run on 0.988 mmol scale. Purified by column chromatography (20% $Et_2O$ in hexanes) to provide a beige oil (345.8 mg, 79% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.87 (m, 1H), 7.86 – 7.83 (m, 1H), 7.81 – 7.76 (m, 1H), 7.74 – 7.63 (m, 4H), 7.52 – 7.36 (m, 6H), 7.15 (dd, *J* = 8.6, 1.8 Hz, 1H), 5.96 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.39 (dq, *J* = 17.2,

1.5 Hz, 1H), 5.28 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.85 (s, 2H), 4.71 (dt, *J* = 5.7, 1.4 Hz, 2H), 3.62 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.4, 144.6, 136.5, 133.5, 133.2, 133.1, 132.9, 131.5, 131.4, 130.2, 129.7, 128.5, 128.4, 128.4, 127.8, 127.8, 127.7, 127.6, 127.4, 127.0, 126.5, 126.5, 126.2, 119.0, 94.7, 69.2, 57.2; IR (Neat Film, NaCl) 3058, 2952, 1761, 1648, 1506, 1457, 1362, 1298, 1244, 1224, 1192, 1156, 1118, 1049, 1012, 974, 948, 862, 823, 752 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{28}H_{28}NO_5$ $[M+NH4]^+$: 458.1962, found 458.1980.

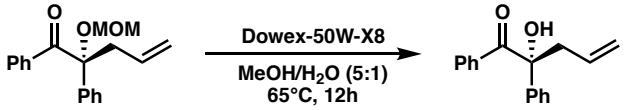
### 5.8.2.5 Derivatization of Alkylation Products




**methyl (*R*,*E*)-5-(methoxymethoxy)-6-oxo-5,6-diphenylhex-2-enoate (82)**

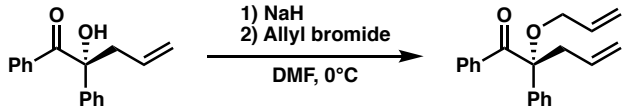
To an oven dried vial was added the alpha-tertiary benzoin (0.1 mmol) followed by $CH_2Cl_2$ (1 mL) and methyl acrylate (2.0 mmol, 180 μL). The resulting solution was stirred for five minutes at ambient temperature then treated with a solution of Grubbs' second generation catalyst (4.2 mg) in 500 μL $CH_2Cl_2$. The reaction was then heated to 40 °C and stirred overnight. The crude reaction mixture was directly concentrated and then purified by silica gel flash chromatography (10% EtOAc in hexanes) to provide a colorless oil (32.0 mg, 93% yield; $[\alpha]_D^{25}$ +164.54 (*c* 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.81 (m, 2H), 7.46 – 7.31 (m, 5H), 7.30 – 7.22 (m, 3H), 6.71 (ddd, *J* = 15.8, 7.8, 6.8 Hz, 1H), 5.72 (dt, *J* = 15.7, 1.5 Hz, 1H), 4.73 (s, 2H), 3.66 (s, 3H), 3.30 (ddd, *J* = 15.7, 7.7, 1.4 Hz, 1H), 3.15 (s, 3H), 3.14 – 3.08 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.0, 166.7, 143.7, 139.9, 134.5, 132.7, 130.7, 128.9, 128.2, 128.0, 125.1, 124.3, 93.6, 87.3, 57.1, 51.5, 39.7; IR (Neat Film, NaCl) 2949 (br), 1723, 1681, 1597,

1463, 1447, 1272, 1238, 1199, 1153, 1079, 1025, 926, 734, 702, 682 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{21}H_{26}NO_5$ $[M+NH_4]^+$: 372.1805, found 372.1796.



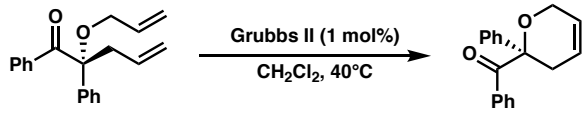

**(*S*)-2-hydroxy-1,2-diphenylpent-4-en-1-one (83)**

Dowex-50W-X8 resin (H+ form, 170 mg) and the corresponding ketone **81a** (0.111 mmol) were added to a 1-dram vial containing 1.6 mL of MeOH and 0.32 ml of $H_2O$. The vial was sealed with a cap containing a PTFE-lined silicone-septum. The solution was heated and stirred at 65 °C for 12 h. The crude mixture was filtered through a short Celite plug to remove the solids (eluting with 1:1 hexanes:EtOAc). The resulting solution was concentrated under reduced pressure and the residue was purified by column chromatography (20% $Et_2O$ in hexanes) to provide a white solid (27.8 mg, 99% yield); 86% ee, $[\alpha]_D^{25}$ +54.5 (*c* 1.00, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.75 – 7.70 (m, 2H), 7.53 – 7.48 (m, 2H), 7.46 – 7.42 (m, 1H), 7.41 – 7.36 (m, 2H), 7.34 – 7.27 (m, 3H), 5.74 (dddd, *J* = 17.1, 10.2, 7.5, 6.9 Hz, 1H), 5.12 (ddt, *J* = 10.2, 1.9, 0.9 Hz, 1H), 5.02 (ddt, *J* = 17.2, 2.0, 1.3 Hz, 1H), 4.19 (s, 1H), 3.15 (ddt, *J* = 13.8, 7.5, 1.0 Hz, 1H), 2.98 (ddt, *J* = 13.7, 6.9, 1.2 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 200.9, 141.9, 134.6, 132.9, 132.4, 130.3, 129.0, 128.3, 128.2, 125.8, 120.5, 81.5, 44.1; IR (Neat Film, NaCl) 3459 (Br), 3062, 2924, 1674, 1597, 1578, 1491, 1447, 1364, 1230, 1181, 1140, 1096, 1068, 1035, 1001, 976, 922, 762, 724, 699, 678, 632 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{17}H_{15}O$ $[M-OH]^+$: 235.1117, found 235.1118; SFC Conditions: 10% IPA, 2.5 mL/min, Chiralcel OD-H column, λ = 210 nm, $t_R$ (min): major = 4.11, minor = 5.01.



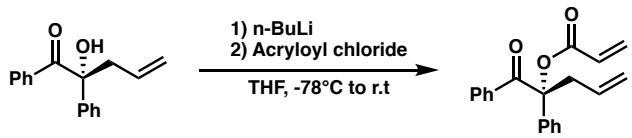

**(*R*)-2-(allyloxy)-1,2-diphenylpent-4-en-1-one (86)**

To a solution of **83** in DMF (3 mL) was added NaH (0.6 mmol) at 0 °C. The mixture was stirred for 30 min at 0 °C then allyl bromide (0.39 mmol) was added dropwise and the reaction was allowed to warm-up to room temperature. After completion of the reaction showed by TLC, $NH_4Cl$ (aq) was added and the mixture was extracted with EtOAc three times. The combined organic layers were washed with water, brine, dried over $Na_2SO_4$, filtered, and concentrated. The crude product was purified by silica gel flash chromatography (2% EtOAc in hexanes) to afford the desired product as a colorless oil (77.2 mg, 88% yield); $[\alpha]_D^{25}$ +52.3 (*c* 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.94 (m, 2H), 7.52 – 7.45 (m, 2H), 7.44 – 7.37 (m, 1H), 7.36 – 7.30 (m, 2H), 7.29 – 7.21 (m, 3H), 5.75 (dddd, *J* = 17.2, 10.5, 5.6, 5.0 Hz, 1H), 5.60 – 5.47 (m, 1H), 5.22 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.08 (dq, *J* = 10.4, 1.5 Hz, 1H), 5.01 – 4.98 (m, 1H), 4.98 – 4.91 (m, 1H), 4.16 (ddt, *J* = 11.9, 5.6, 1.5 Hz, 1H), 3.72 (ddt, *J* = 11.9, 5.0, 1.6 Hz, 1H), 3.16 (ddt, *J* = 15.4, 7.6, 1.2 Hz, 1H), 2.91 (ddt, *J* = 15.4, 6.4, 1.6 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 200.9, 140.7, 135.0, 134.1, 132.8, 132.4, 130.3, 128.5, 128.1, 127.6, 125.5, 118.3, 116.8, 87.6, 65.4, 40.0; IR (Neat Film, NaCl) 3072, 2935, 1681, 1647, 1596, 1447, 1238, 1120, 1072, 1028, 994, 918, 827, 730, 701, 681, 667 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{20}H_{20}O_2Na$ $[M+Na]^+$: 315.1356, found 315.1343.




**(*R*)-phenyl(2-phenyl-3,6-dihydro-2*H*-pyran-2-yl)methanone (84)**

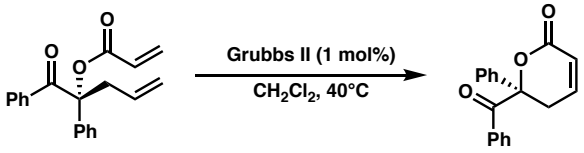
To an oven dried vial was added **86** (0.24 mmol) followed by $CH_2Cl_2$ (3 mL). The resulting solution was treated with a solution of Grubbs' second-generation catalyst (2 mg) in $CH_2Cl_2$ (1.5 mL). The reaction was then heated to 40 °C and stirred overnight. The crude reaction mixture was directly concentrated and then purified by silica gel flash chromatography (3% EtOAc in hexanes) to provide a colorless oil (64.2 mg, 99% yield); $[\alpha]_D^{25}$ +222.8 (*c* 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.97 (m, 2H), 7.55 – 7.49 (m, 2H), 7.47 – 7.40 (m, 1H), 7.39 – 7.33 (m, 2H), 7.33 – 7.26 (m, 3H), 5.92 (ddq, *J* = 10.2, 5.7, 2.2 Hz, 1H), 5.70 – 5.59 (m, 1H), 4.33 (dtdd, *J* = 17.2, 3.2, 2.2, 1.0 Hz, 1H), 4.05 (dddt, *J* = 17.2, 4.1, 3.0, 2.1 Hz, 1H), 3.27 – 3.15 (m, 1H), 2.23 (ddtd, *J* = 17.3, 4.1, 3.0, 2.2 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 199.6, 142.4, 135.1, 132.8, 130.0, 128.9, 128.2, 127.6, 124.5, 124.4, 124.2, 84.2, 63.7, 35.0; IR (Neat Film, NaCl) 3059, 3037, 2931, 2900, 2840, 1682, 1597, 1579, 1492, 1447, 1417, 1386, 1327, 1258, 1226, 1210, 1180, 1089, 1024, 978, 960, 942, 793, 754, 700, 657 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{18}H_{17}O_2$ $[M+H]^+$: 265.1223, found 265.1224.




**(*R*)-1-oxo-1,2-diphenylpent-4-en-2-yl acrylate (87)**

To a solution of **83** (0.147 mmol) in THF (1.5 mL) was added dropwise *n*-BuLi (0.127 mL, 2.3M solution in hexane, 0.294 mmol, 2 equiv) at –78 °C. The resulting yellow solution was stirred for 30 min at -78 °C. Acryloyl chloride (0.735 mmol) was then

added dropwise and the reaction was allowed to warm-up to room temperature overnight. Water was added and the reaction was extracted three times with EtOAc. The combined organic layers were washed with 1N NaOH (aq), brine, dried over $Na_2SO_4$, filtered, and concentrated. The crude product was purified by silica gel flash chromatography (5% EtOAc in hexanes) to afford the desired product as a colorless oil (42.2 mg, 94% yield); $[\alpha]_D^{25}$ +140.6 (*c* 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.69 (m, 2H), 7.60 – 7.54 (m, 2H), 7.45 – 7.38 (m, 2H), 7.38 – 7.29 (m, 2H), 7.23 (ddt, *J* = 8.0, 6.7, 1.2 Hz, 2H), 6.40 (dd, *J* = 17.3, 1.3 Hz, 1H), 6.12 (dd, *J* = 17.3, 10.5 Hz, 1H), 5.83 (dd, *J* = 10.4, 1.3 Hz, 1H), 5.46 (dddd, *J* = 17.0, 10.3, 8.8, 5.9 Hz, 1H), 5.02 – 4.87 (m, 2H), 3.60 – 3.41 (m, 1H), 3.13 (ddt, *J* = 14.8, 5.9, 1.5 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 196.4, 164.2, 137.8, 135.1, 132.3, 132.0, 131.6, 129.2, 129.0, 128.2, 128.2, 128.0, 125.0, 119.4, 88.3, 41.9; IR (Neat Film, NaCl) 3060, 2929, 1727, 1687, 1634, 1598, 1491, 1447, 1404, 1295, 1243, 1173, 1121, 1061, 1028, 986, 919, 828, 809, 760, 736, 701, 688, 681 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{20}H_{22}NO_3$ $[M+NH_4]^+$: 324.1594, found 324.1597.

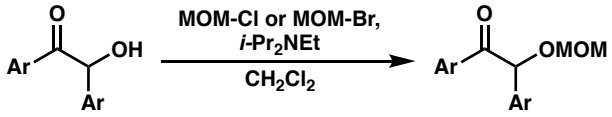



**(*R*)-6-benzoyl-6-phenyl-5,6-dihydro-2*H*-pyran-2-one (85)**

In an oven dried vial, a solution of **87** (0.078 mmol) in $CH_2Cl_2$ (1.1 mL) was treated with a solution of Grubbs' second-generation catalyst (0.6 mg) in $CH_2Cl_2$ (0.5 mL). The reaction was then heated to 40 °C and stirred overnight. The crude reaction mixture was directly concentrated and then purified by silica gel flash chromatography (10% EtOAc in hexanes) to provide a colorless oil (21.5 mg, 99% yield); $[\alpha]_D^{25}$ +344.7 (*c* 1.00,

$CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.87 (m, 2H), 7.61 – 7.56 (m, 2H), 7.48 – 7.38 (m, 3H), 7.38 – 7.28 (m, 3H), 6.95 (ddd, *J* = 9.9, 5.9, 2.5 Hz, 1H), 5.97 (ddd, *J* = 9.9, 2.7, 0.9 Hz, 1H), 3.65 (ddd, *J* = 18.2, 5.9, 1.0 Hz, 1H), 2.70 (dt, *J* = 18.2, 2.6 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 196.9, 162.3, 146.3, 138.4, 134.0, 133.5, 130.7, 129.3, 128.8, 128.5, 124.4, 120.9, 90.4, 34.9; IR (Neat Film, NaCl) 3061, 2924, 2854, 1744, 1682, 1596, 1579, 1491, 1448, 1409, 1378, 1319, 1244, 1222, 1184, 1158, 1100, 1056, 1002, 951, 909, 868, 815, 784, 755, 736, 699 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{18}H_{18}NO_3$ $[M+NH_4]^+$: 296.1281, found 296.1280.

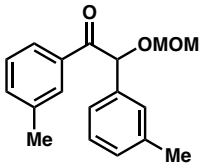
### 5.8.2.6 Synthesis of MOM-Protected Benzoins




**Method A:** At room temperature, MOM-Br (4 equiv) was added to a solution of corresponding benzoin (1 equiv) and *i*-$Pr_2NEt$ (5 equiv) in $CH_2Cl_2$ (0.25 mol/L). The reaction was stirred overnight at 40 °C. The crude reaction mixture was quenched with the addition of a 2 M NaOH solution. The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ twice. The combined organic layers were washed with a 1 M HCl solution, dried over $Na_2SO_4$, and concentrated. The crude product was purified by silica gel flash chromatography to afford the desired Mom protected benzoin.

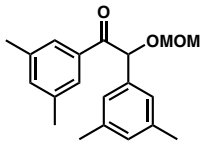
**Method B:** At 0 °C, MOM-Cl (4 equiv) was added to a solution of corresponding benzoin (1 equiv) and *i*-$Pr_2NEt$ (5 equiv) in $CH_2Cl_2$ (0.25 mol/L). The reaction was stirred overnight at room temperature. The crude reaction mixture was quenched with the addition of a 2 M NaOH solution. The layers were separated, and the aqueous layer was

extracted with $CH_2Cl_2$ twice. The combined organic layers were washed with a 1 M HCl solution, dried over $Na_2SO_4$, and concentrated. The crude product was purified by silica gel flash chromatography to afford the desired Mom protected benzoin.




**2-(methoxymethoxy)-1,2-di-*m*-tolylethan-1-one (88)**

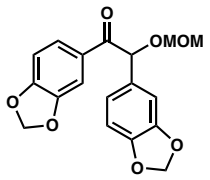
Method A. Run on 2.31 mmol scale. Purified by column chromatography (20% $Et_2O$ in hexanes) to provide a colorless oil (415.3 mg, 75% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.32 – 7.19 (m, 5H), 7.08 (d, *J* = 7.4 Hz, 1H), 5.97 (s, 1H), 4.74 (s, 2H), 3.36 (s, 3H), 2.34 (s, 3H), 2.31 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 196.8, 138.9, 138.5, 135.9, 135.3, 134.2, 129.6, 129.6, 128.9, 128.7, 128.5, 126.4, 125.4, 95.1, 79.9, 56.1, 21.5, 21.5; IR (Neat Film, NaCl) 2926 (br), 1694, 1604, 1586, 1487, 1457, 1254, 1213, 1167, 1149, 1108, 1034, 964, 918, 773, 700 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{18}H_{21}O_3$ $[M+H]^+$: 285.1485, found 285.1484.




**1,2-bis(3,5-dimethylphenyl)-2-(methoxymethoxy)ethan-1-one (89)**

Method A. Run on 1.49 mmol scale. Purified by column chromatography (20% $Et_2O$ in hexanes) to provide a colorless oil (411.1 mg, 88% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.58 (s, 2H), 7.13 (s, 1H), 7.07 (s, 2H), 6.92 (s, 1H), 5.96 (s, 1H), 4.76 – 4.72 (m, 2H), 3.39 (s, 3H), 2.32 (s, 6H), 2.28 (s, 6H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 196.9, 138.6, 138.2, 135.8, 135.4, 135.0, 130.5, 126.8, 126.0, 95.0, 79.6, 56.1, 21.4, 21.3; IR (Neat

Film, NaCl) 2920 (br), 1691, 1606, 1457 br, 1305, 1184, 1149, 1107, 1043, 1017, 918, 848, 792 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{20}H_{25}O_3$ $[M+H]^+$: 313.1798, found 313.1804.




**1,2-bis(benzo[*d*][1,3]dioxol-5-yl)-2-(methoxymethoxy)ethan-1-one (90)**

Method B. Run on 1.73 mmol scale. Purified by column chromatography (50% $Et_2O$ in hexanes) to provide a beige amorphous solid (571.3 mg, 96% yield); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.59 (ddd, *J* = 8.2, 1.8, 0.6 Hz, 1H), 7.44 (d, *J* = 1.7 Hz, 1H), 6.94 – 6.89 (m, 2H), 6.82 – 6.73 (m, 2H), 6.00 (s, 2H), 5.94 – 5.92 (m, 2H), 5.83 (s, 1H), 4.72 (s, 2H), 3.36 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 194.4, 152.0, 148.3, 148.2, 148.1, 130.0, 129.8, 125.5, 122.1, 108.9, 108.7, 108.3, 108.1, 102.0, 101.4, 94.9, 79.3, 56.1; IR (Neat Film, NaCl) 2896, 1684, 1604, 1503, 1489, 1443, 1358, 1251, 1150, 1099, 1037, 931, 798 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{18}H_{17}O_7$ $[M+H]^+$: 345.0969, found 345.0963.

### 5.8.3 Determination of Enantiomeric Excess

***Table 5.4*** *Determination of Enantiomeric Excess.*

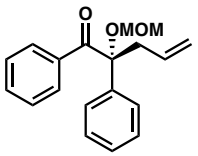
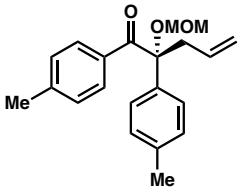
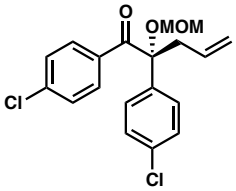
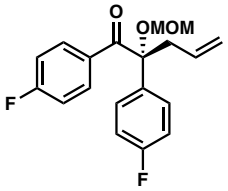
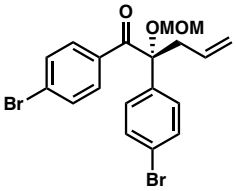
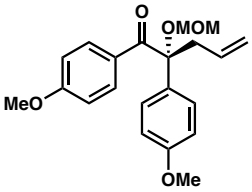
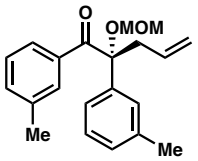
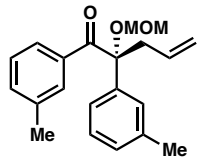
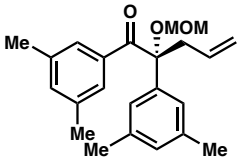
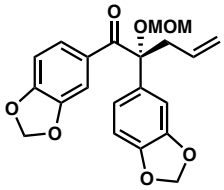
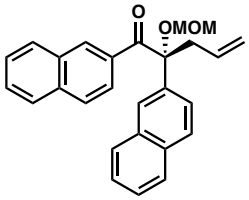
| Entry | Compound | Assay Conditions | $t_R$ of major isomer (min) | $t_R$ of minor isomer (min) | %ee |
|---|---|---|---|---|---|
| 1 |  | SFC<br>Chiralpak IC<br>5% IPA<br>isocratic, 2.5 mL/min | 4.62 | 5.37 | 88 |
| 2 |  | SFC<br>Chiralpak IC<br>5% IPA<br>isocratic, 2.5 mL/min | 6.77 | 8.03 | 88 |
| 3 |  | SFC<br>Chiralpak IC<br>5% IPA<br>isocratic, 2.5 mL/min | 4.46 | 5.41 | 73 |
| 4 |  | SFC<br>Chiralpak IC<br>5% IPA<br>isocratic, 2.5 mL/min | 2.22 | 2.69 | 82 |
| 5 |  | SFC<br>Chiralpak AD-H<br>5% IPA<br>isocratic, 2.5 mL/min | 6.38 | 8.03 | 74 |
| 6 |  | SFC<br>Chiralpak IC<br>15% IPA<br>isocratic, 2.5 mL/min | 3.98 | 3.47 | 84 |
| 7 |  | SFC<br>Chiralcel OD-H<br>5% IPA<br>isocratic, 2.5 mL/min | 4.64 | 4.22 | 79 |

***Table 5.4*** *Determination of Enantiomeric Excess (continued)*

| Entry | Compound | Assay Conditions | $t_R$ of major isomer (min) | $t_R$ of minor isomer (min) | %ee |
|---|---|---|---|---|---|
| 8 |  | SFC<br>Chiralpak IC<br>3% IPA<br>isocratic, 2.5 mL/min | 5.42 | 6.31 | 78 |
| 9 |  | SFC<br>Chiralpak IC<br>5% IPA<br>isocratic, 2.5 mL/min | 5.02 | 4.38 | 81 |
| 10 |  | SFC<br>Chiralpak AD-H<br>20% IPA<br>isocratic, 2.5 mL/min | 3.35 | 4.10 | 80 |
| 11 |  | SFC<br>Chiralcel OJ-H<br>2% IPA<br>isocratic, 2.5 mL/min | 5.14 | 6.46 | 72 |

## 5.9 REFERENCES AND NOTES

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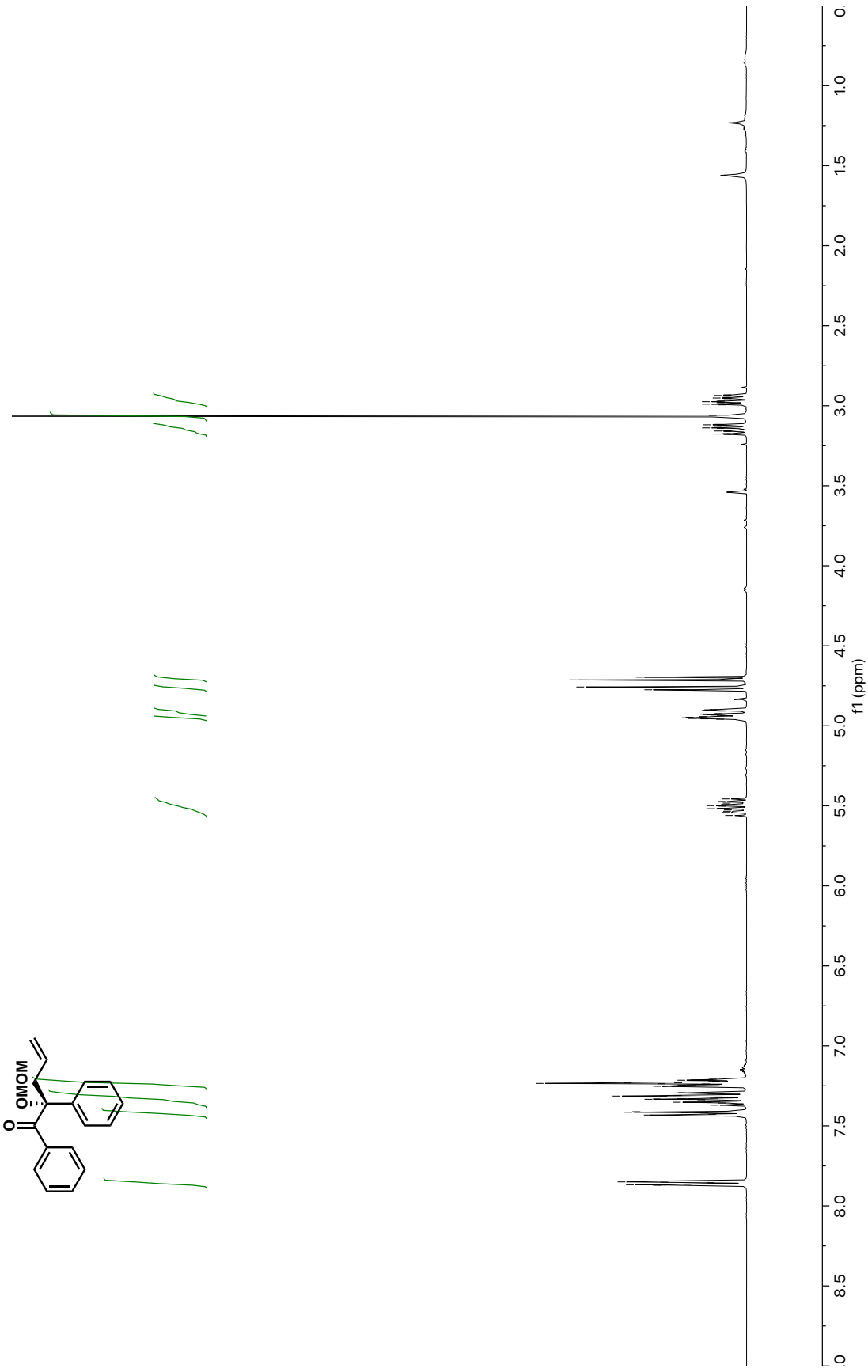
(10) CCDC-1955415 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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# *APPENDIX 7*

*Spectra Relevant to Chapter 5:*

*Palladium-Catalyzed Enantioselective Decarboxylative Allylic Alkylation of Protected Benzoin-Derived Enol Carbonates*




***A7.1*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***81a***.

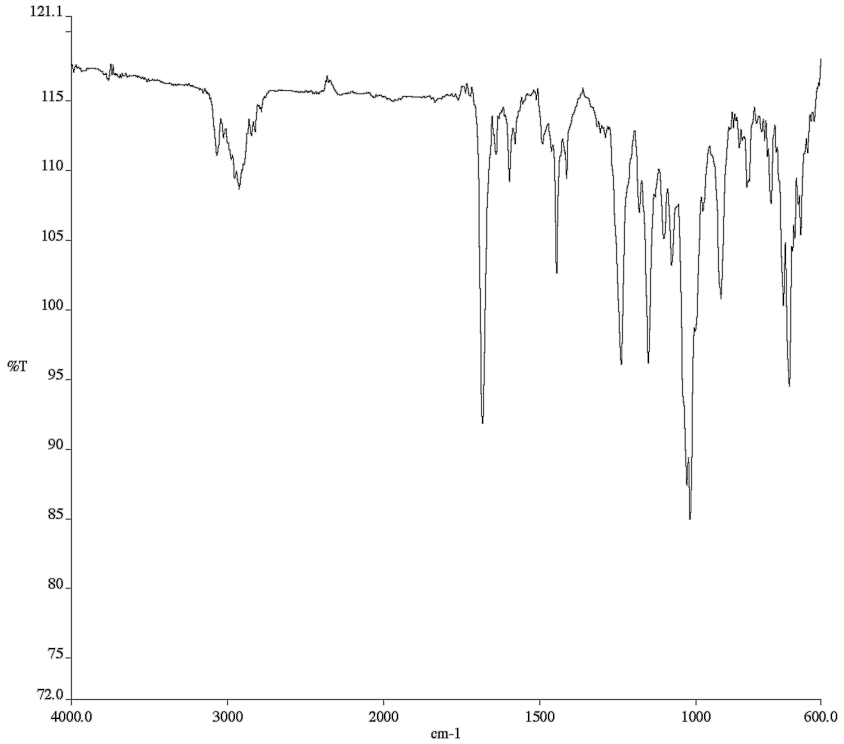



***Figure A7.2*** *Infrared spectrum (Thin Film, NaCl) of compound* ***81a****.*

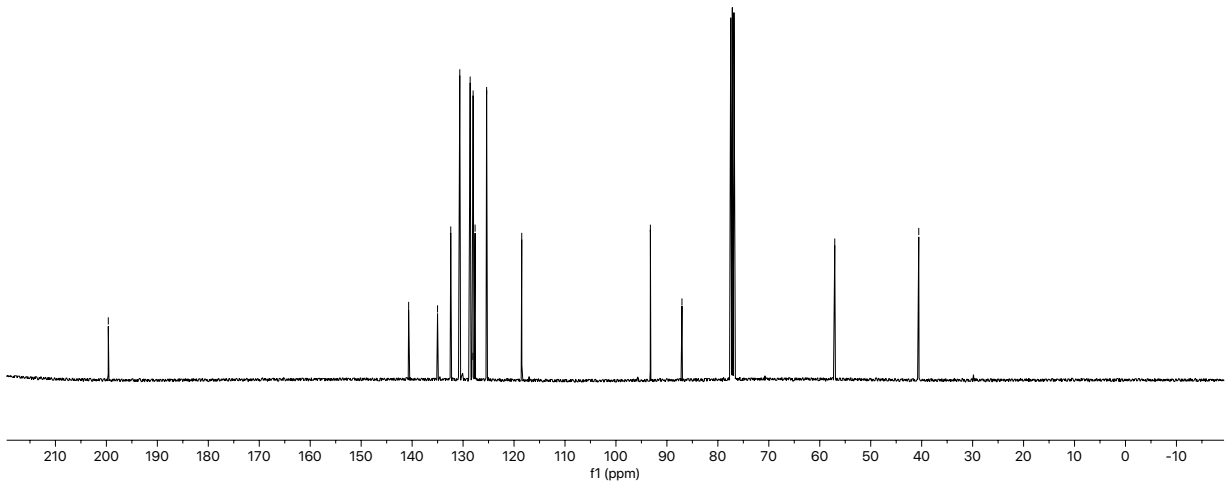
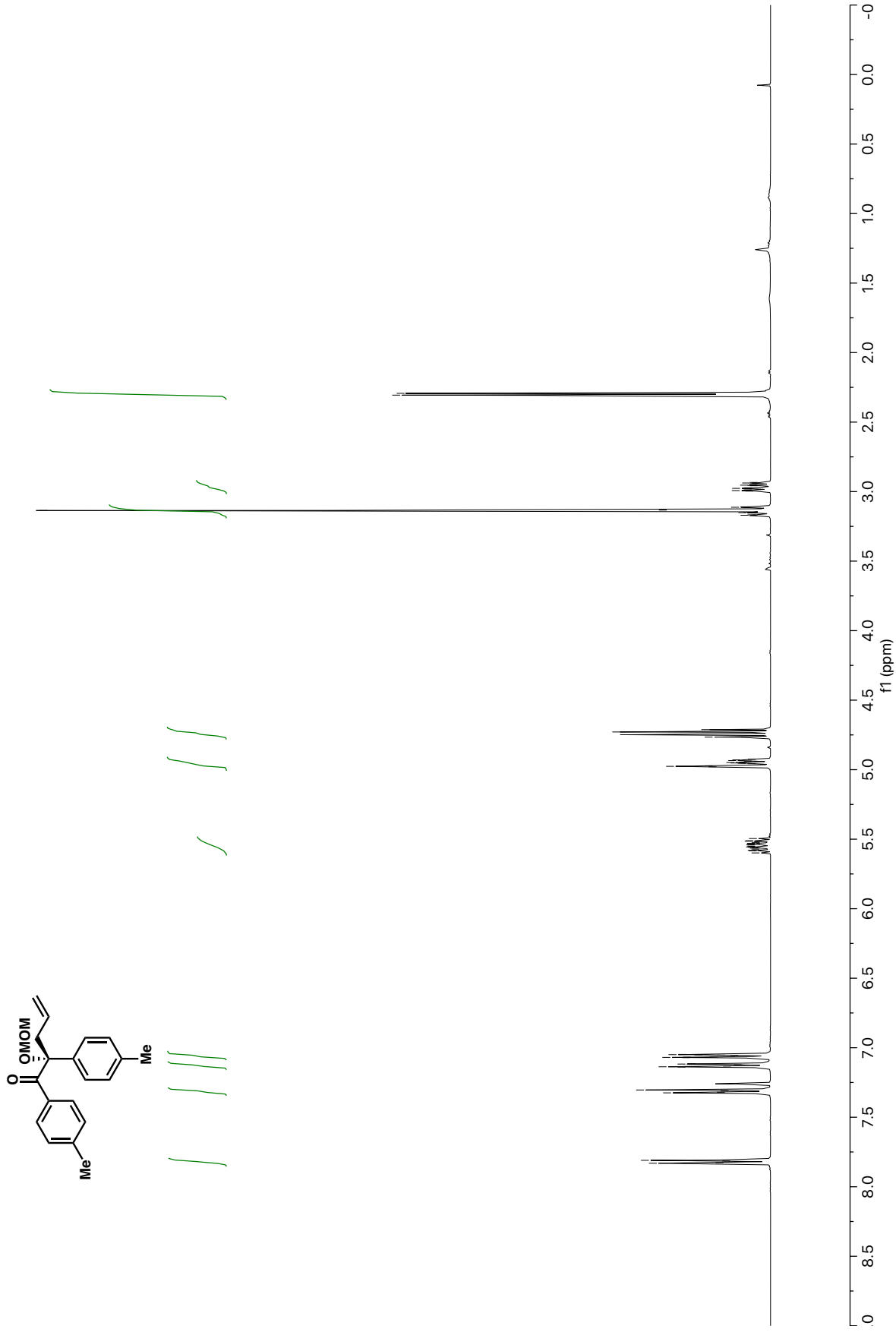



***Figure A7.3*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***81a****.*




***A7.4*** *$^1$H NMR (400 MHz, $CDCl_3$) of compound* ***81b***.

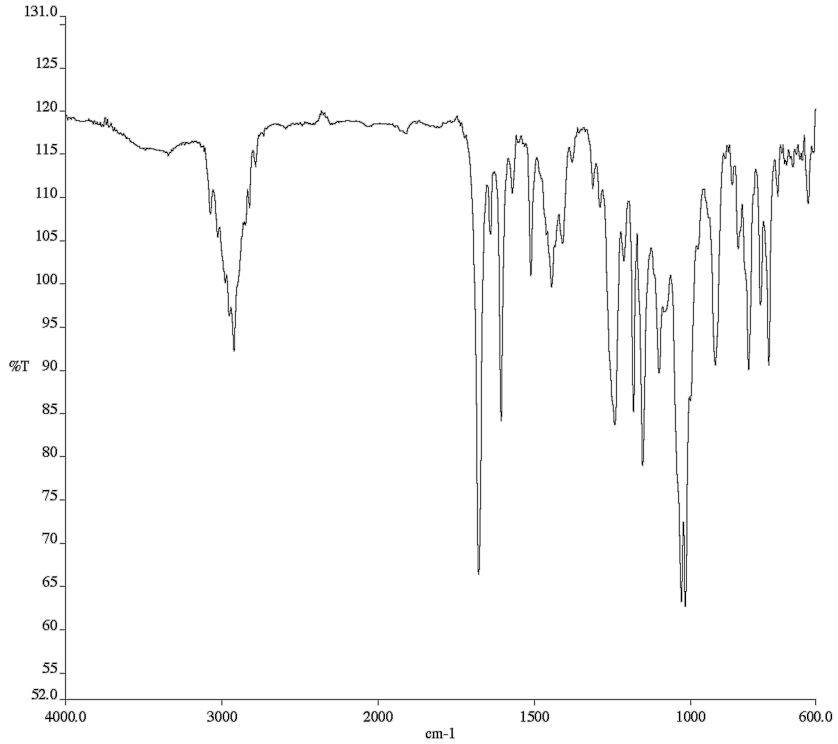



***Figure A7.5*** *Infrared spectrum (Thin Film, NaCl) of compound* ***81b****.*

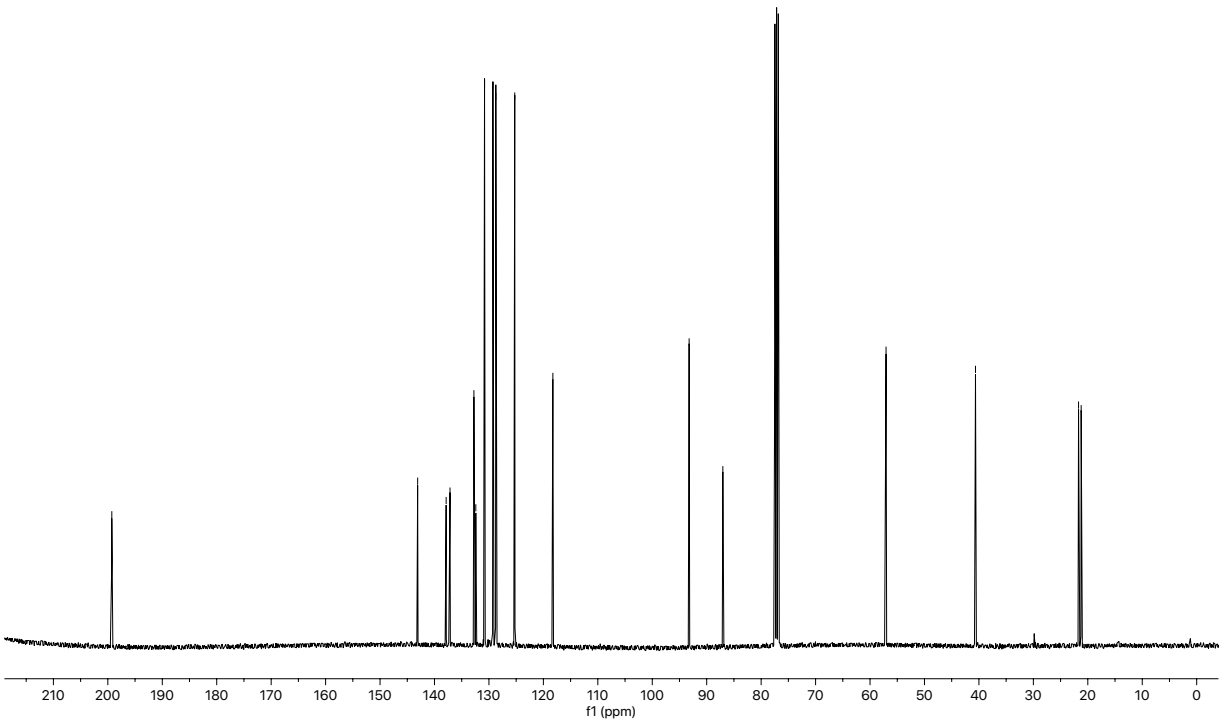
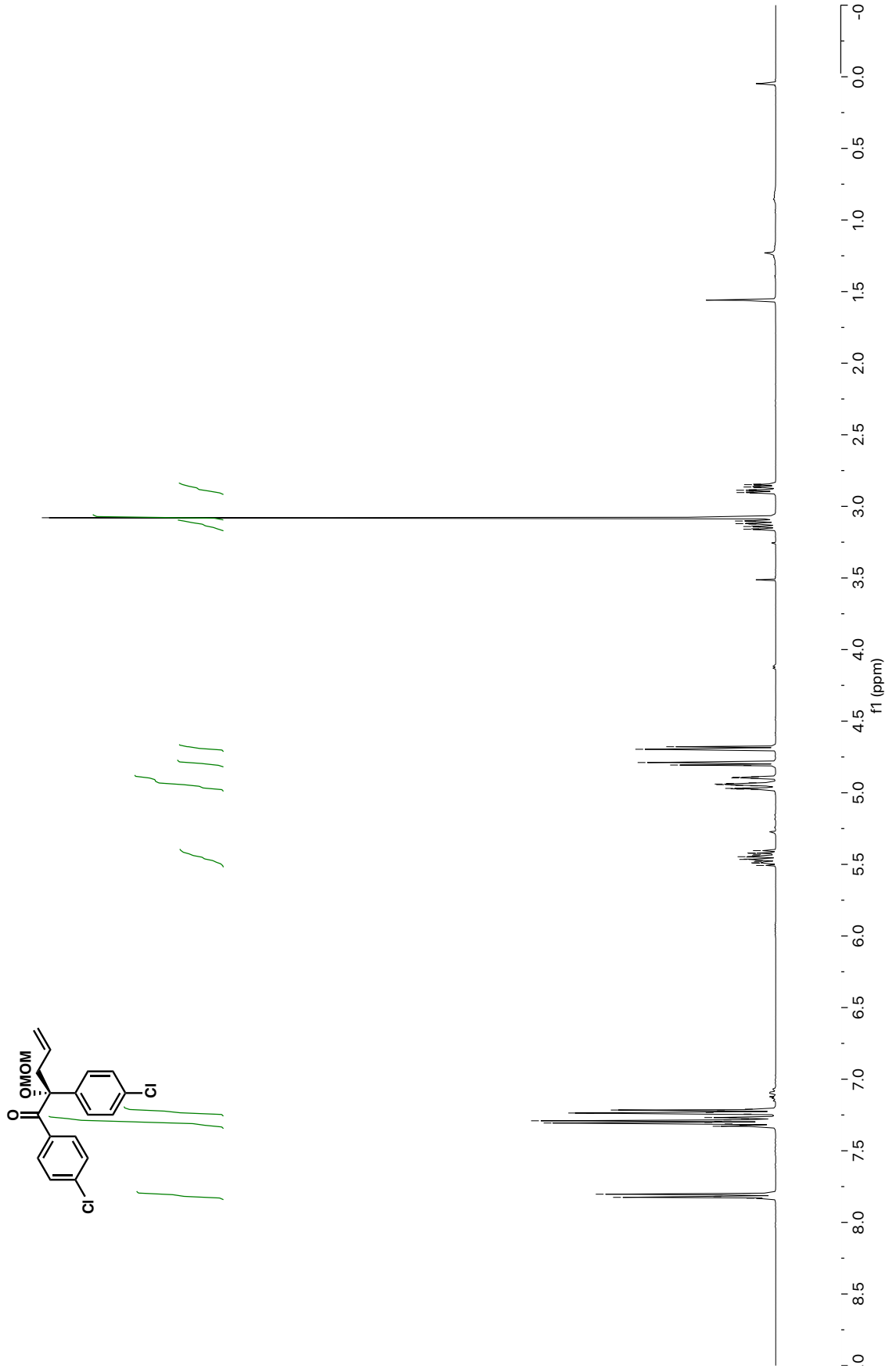



***Figure A7.6*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***81b****.*




***A7.7*** *$^1$H NMR (400 MHz, $CDCl_3$) of compound* ***81c***.

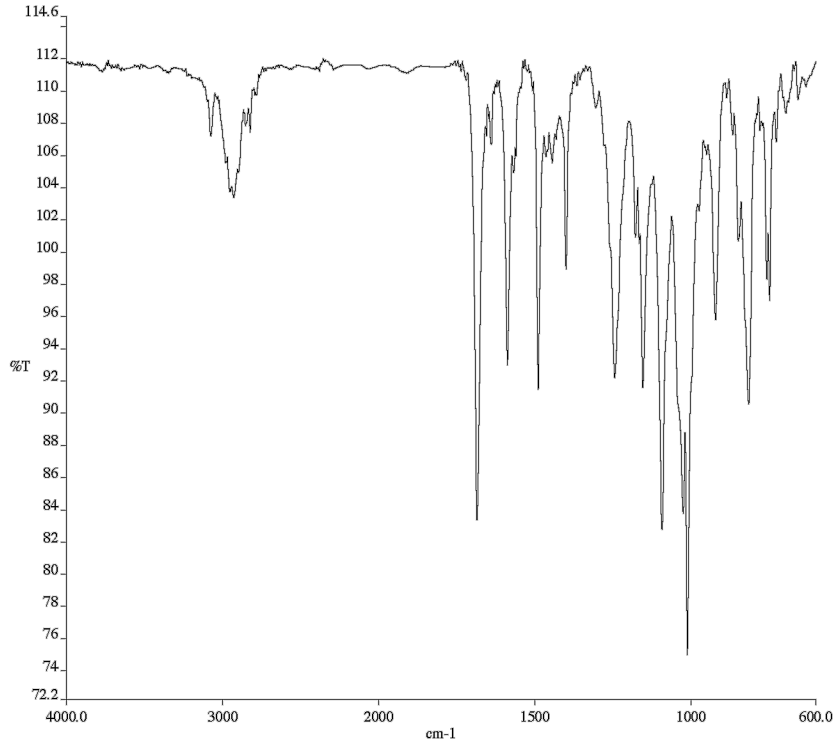



***Figure A7.8*** *Infrared spectrum (Thin Film, NaCl) of compound* ***81c****.*

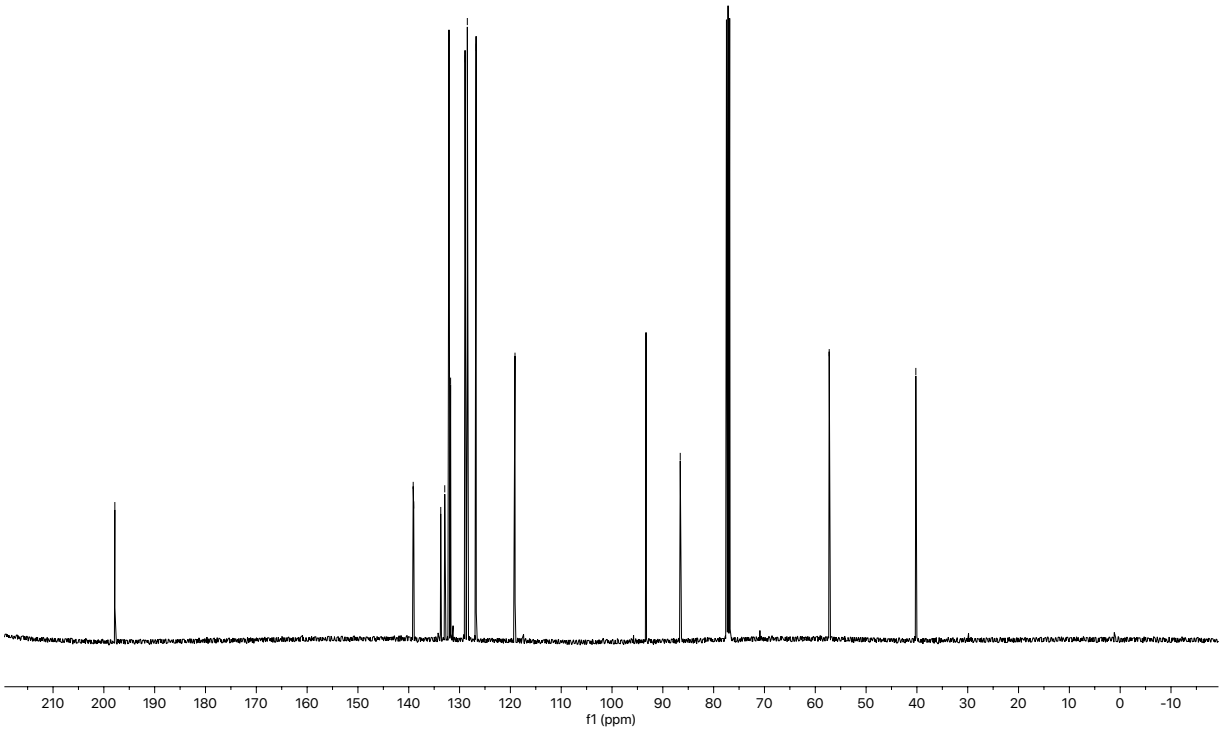
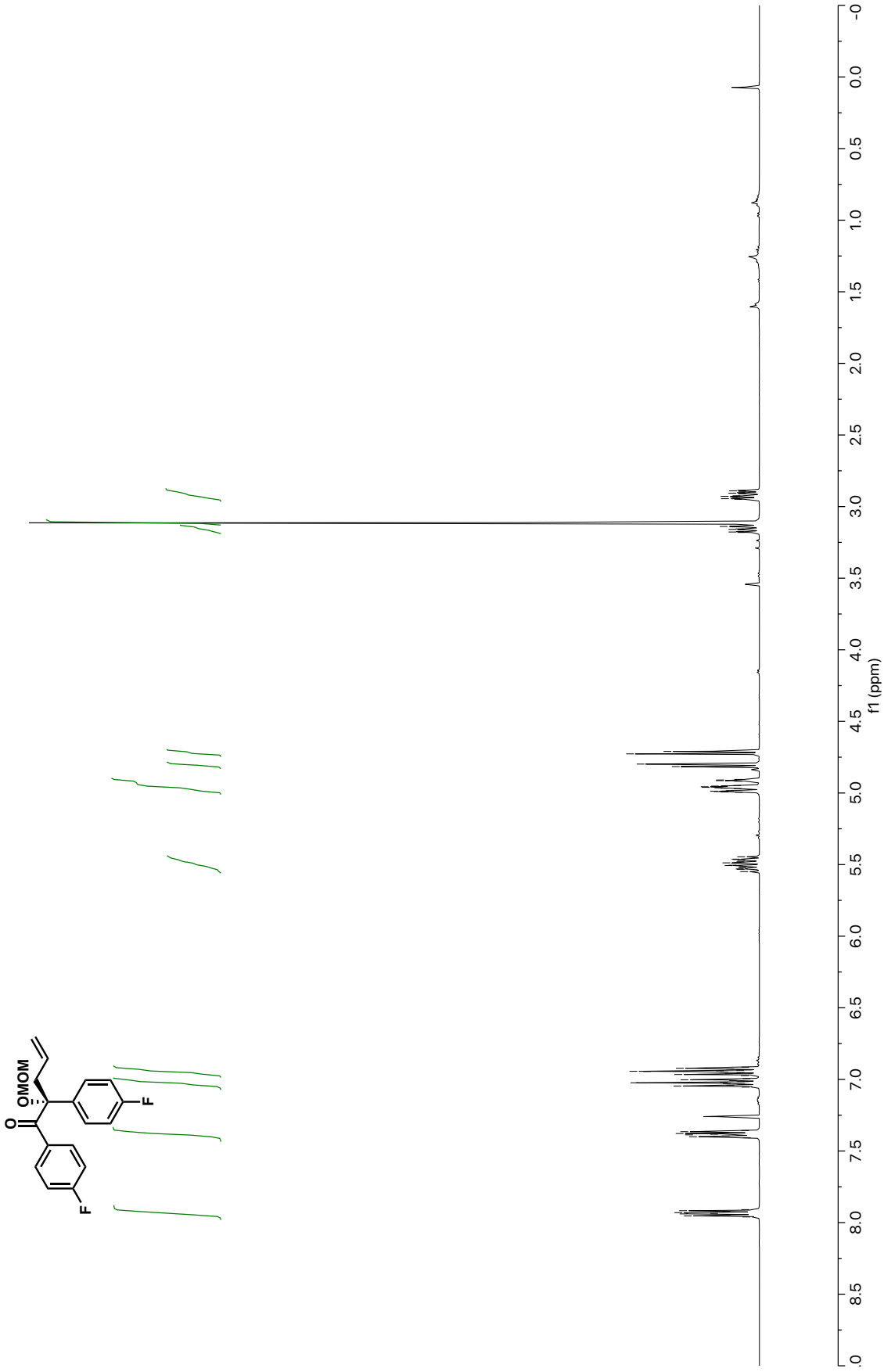



***Figure A7.9*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***81c****.*




***A7.10*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***81d****.*

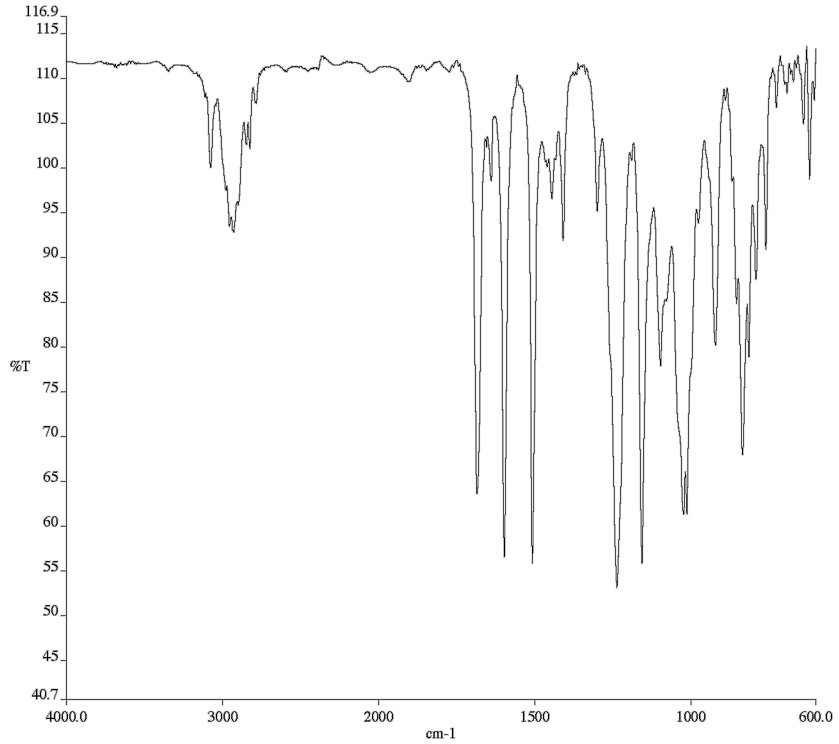



***Figure A7.11*** *Infrared spectrum (Thin Film, NaCl) of compound* ***81d****.*

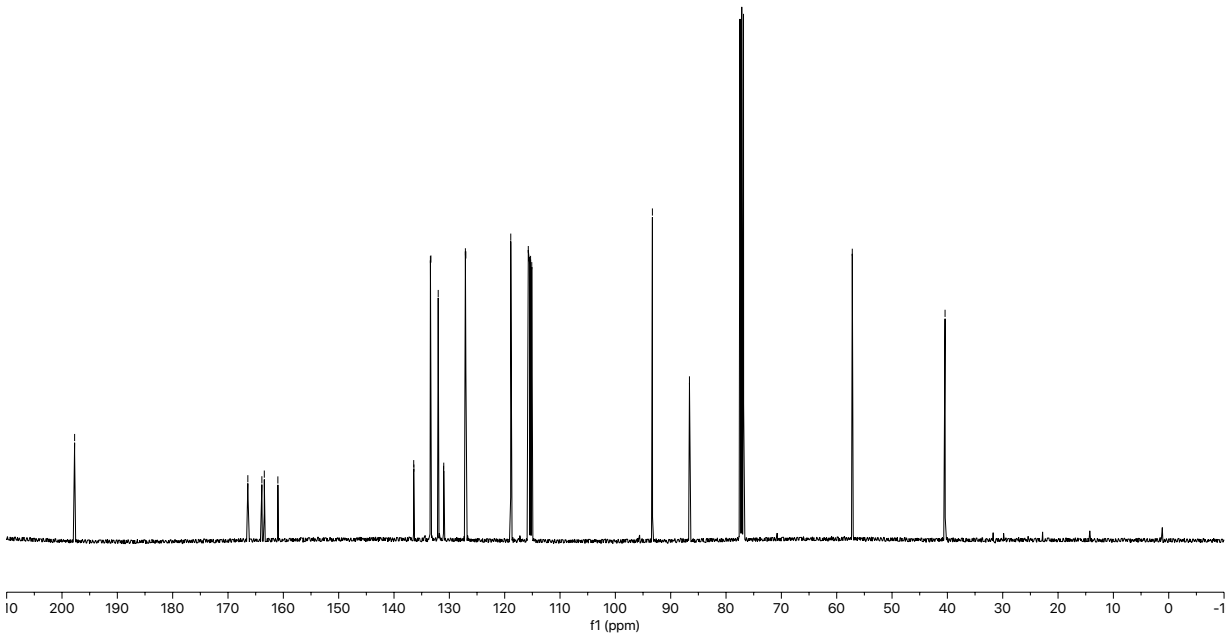



***Figure A7.12*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***81d****.*

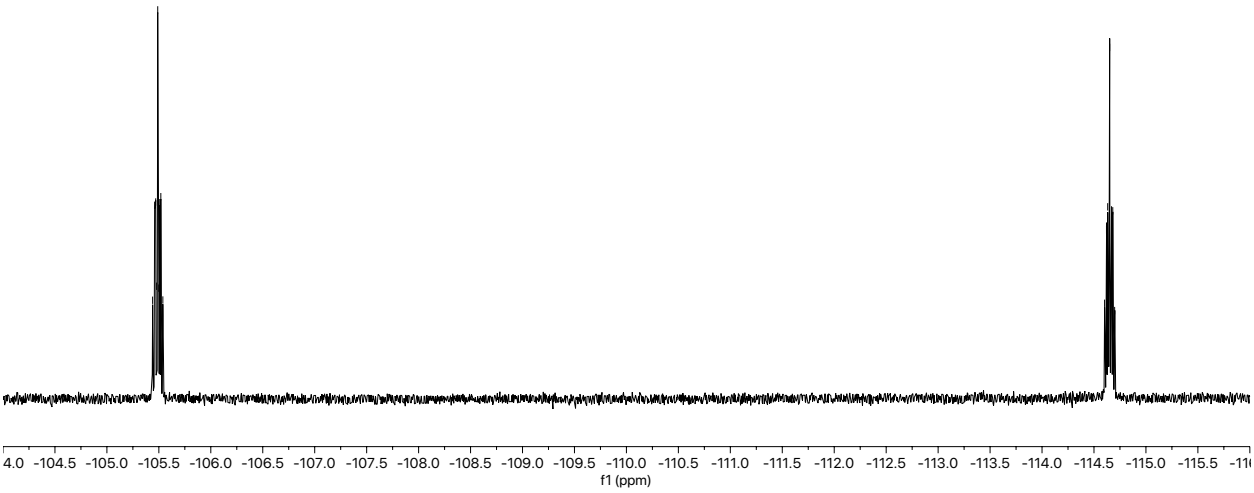
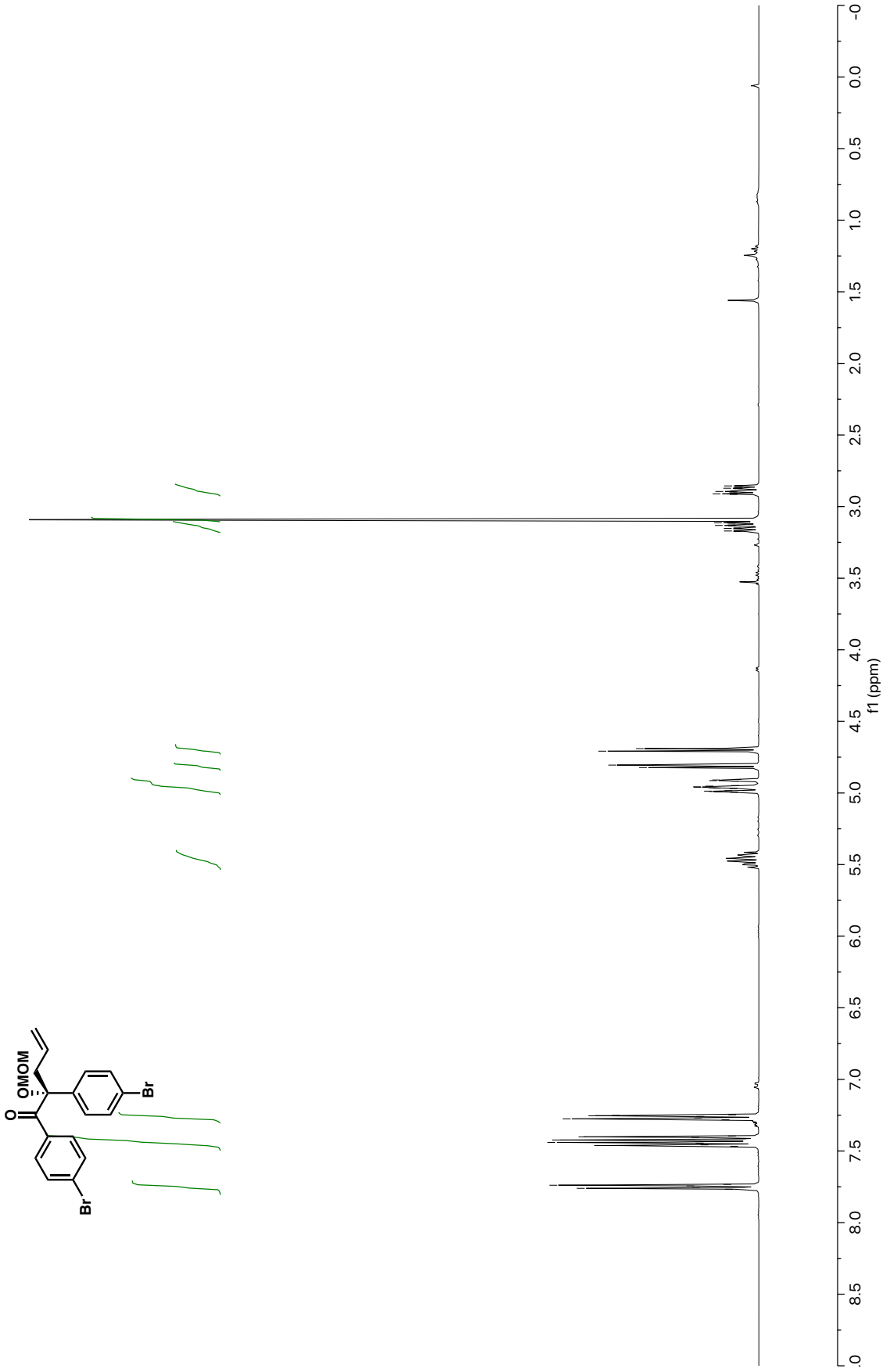



***Figure A7.13*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***81d***.




***A7.14*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***81e***.

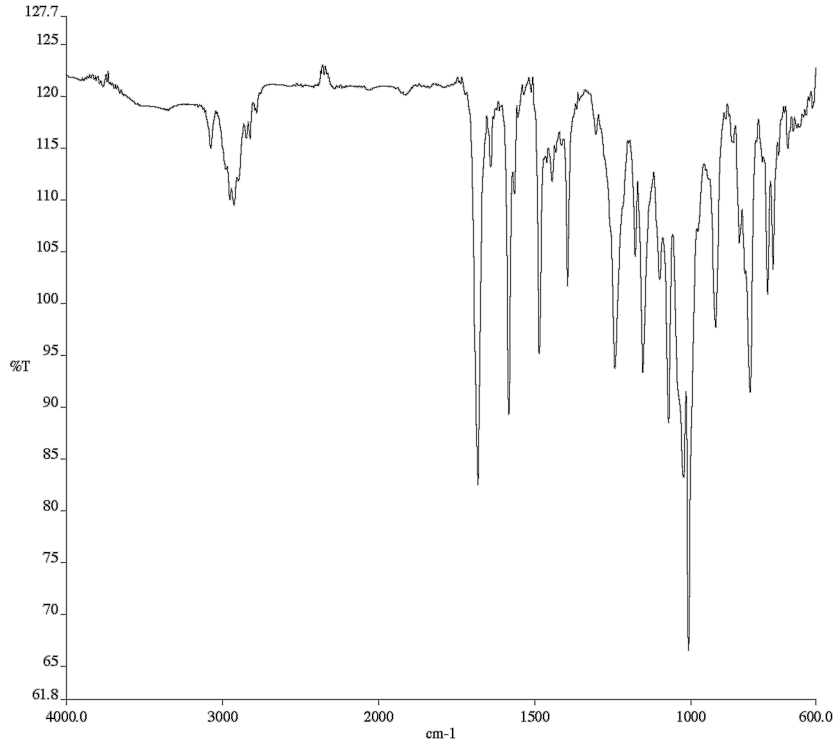



***Figure A7.15*** *Infrared spectrum (Thin Film, NaCl) of compound* ***81e****.*

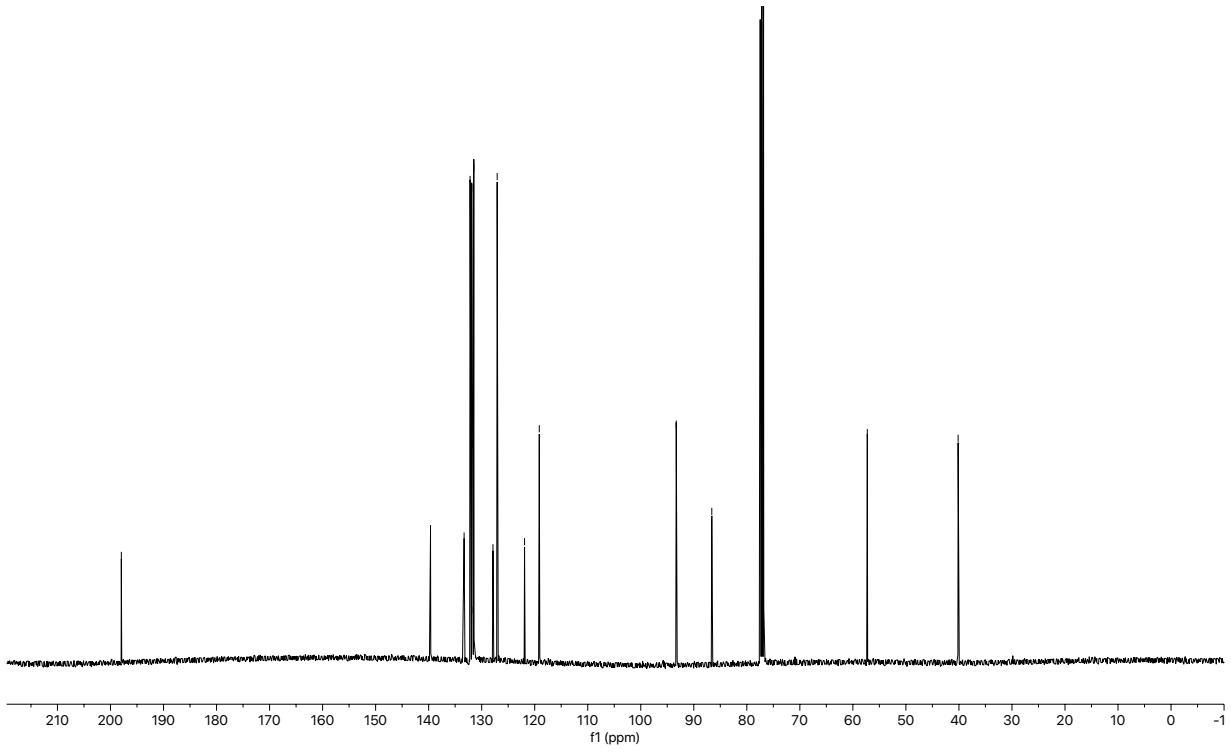
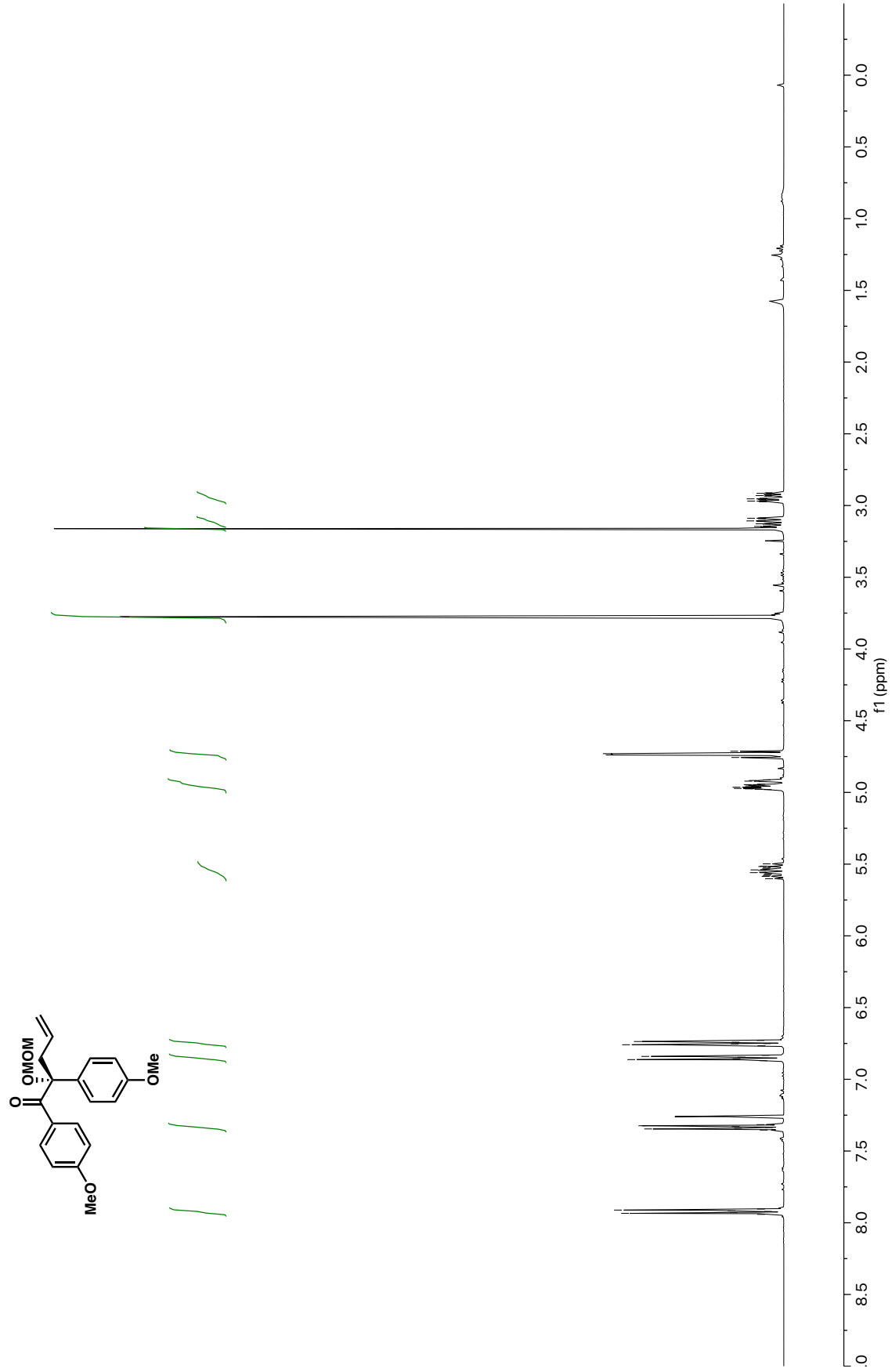



***Figure A7.16*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***81e****.*




***A7.17*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***81f****.*

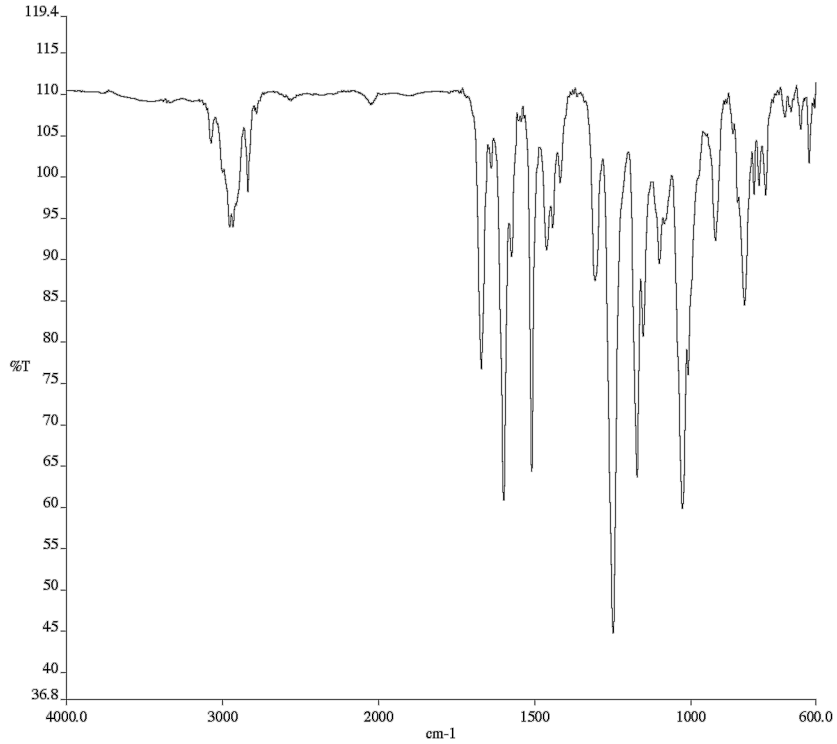



***Figure A7.18*** *Infrared spectrum (Thin Film, NaCl) of compound* ***81f****.*

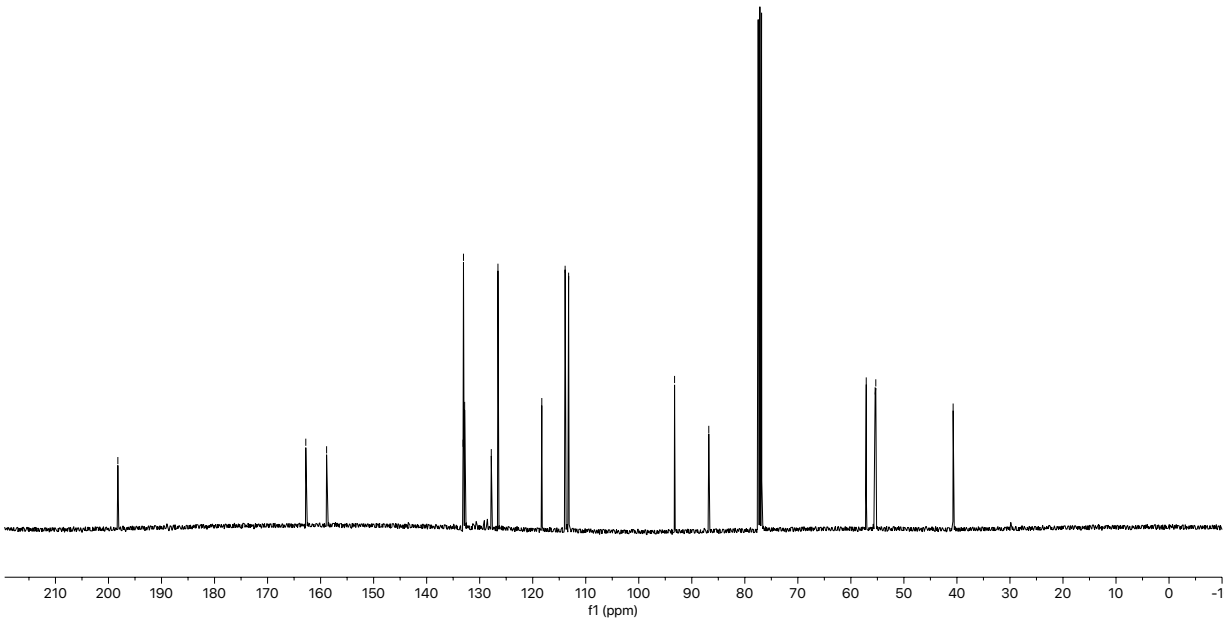
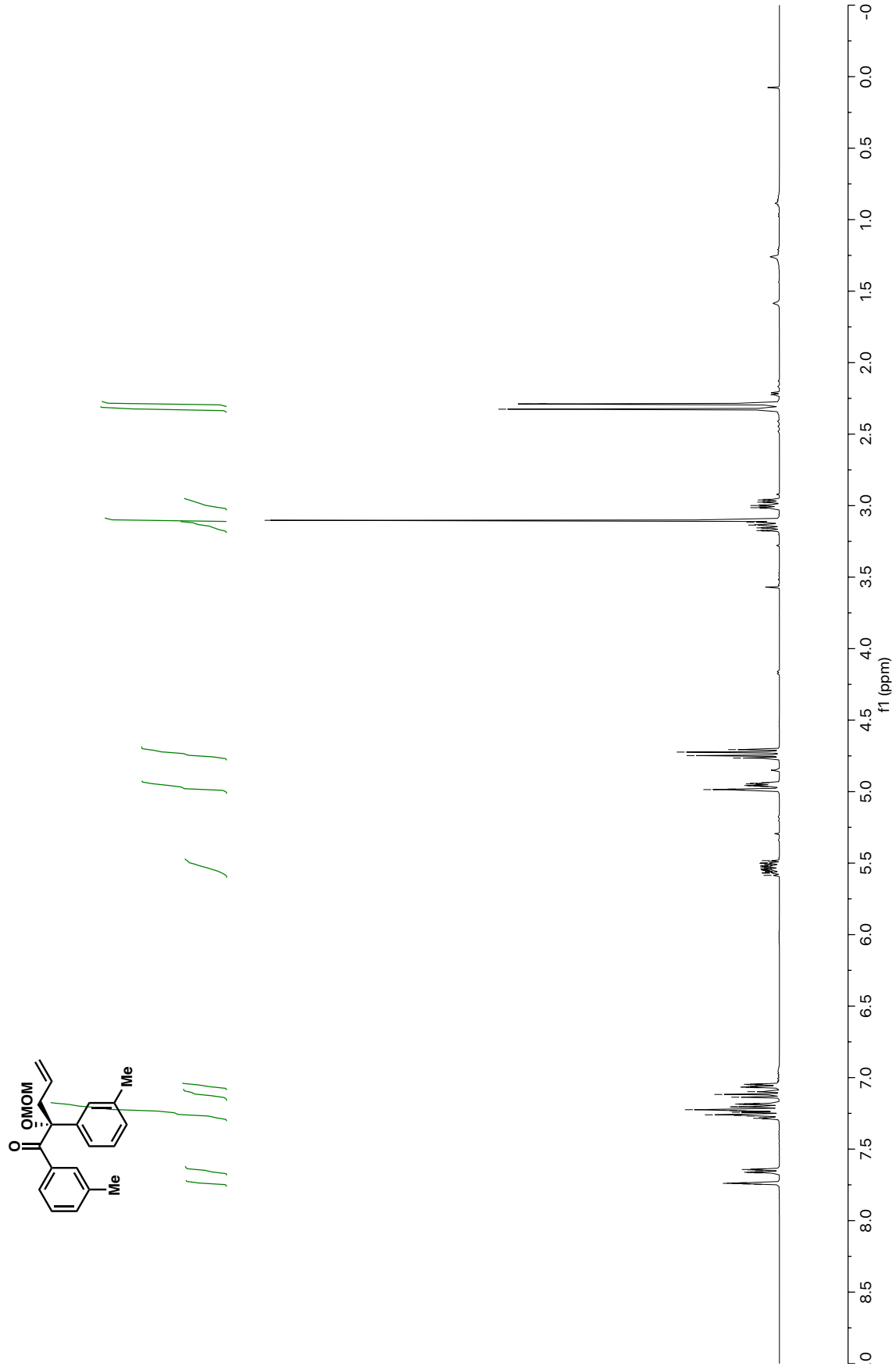



***Figure A7.19*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***81f****.*




***A7.20*** *$^1$H NMR (400 MHz, $CDCl_3$) of compound* ***81g****.*

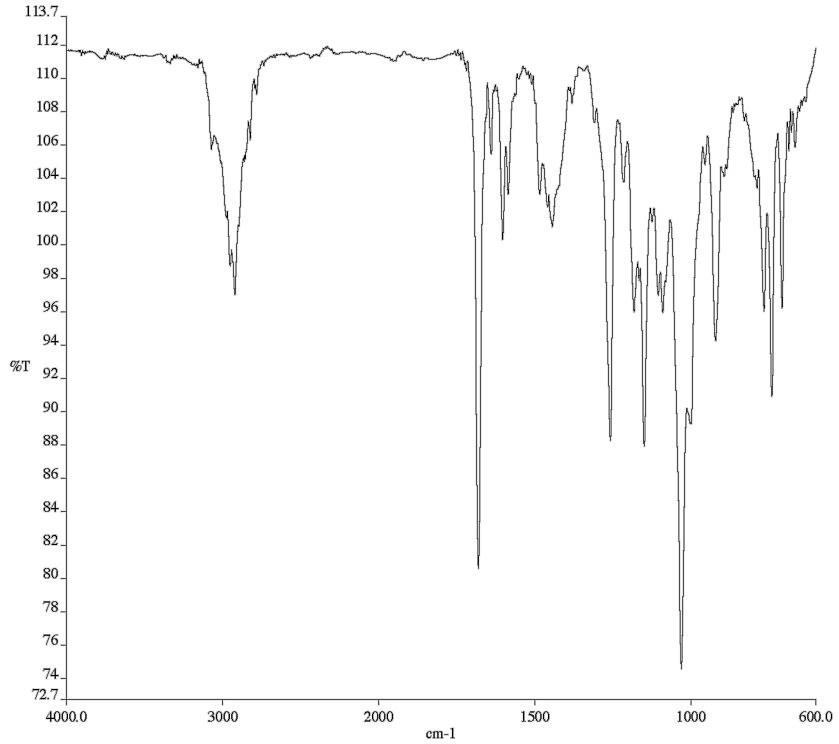



***Figure A7.21*** *Infrared spectrum (Thin Film, NaCl) of compound* ***81g****.*

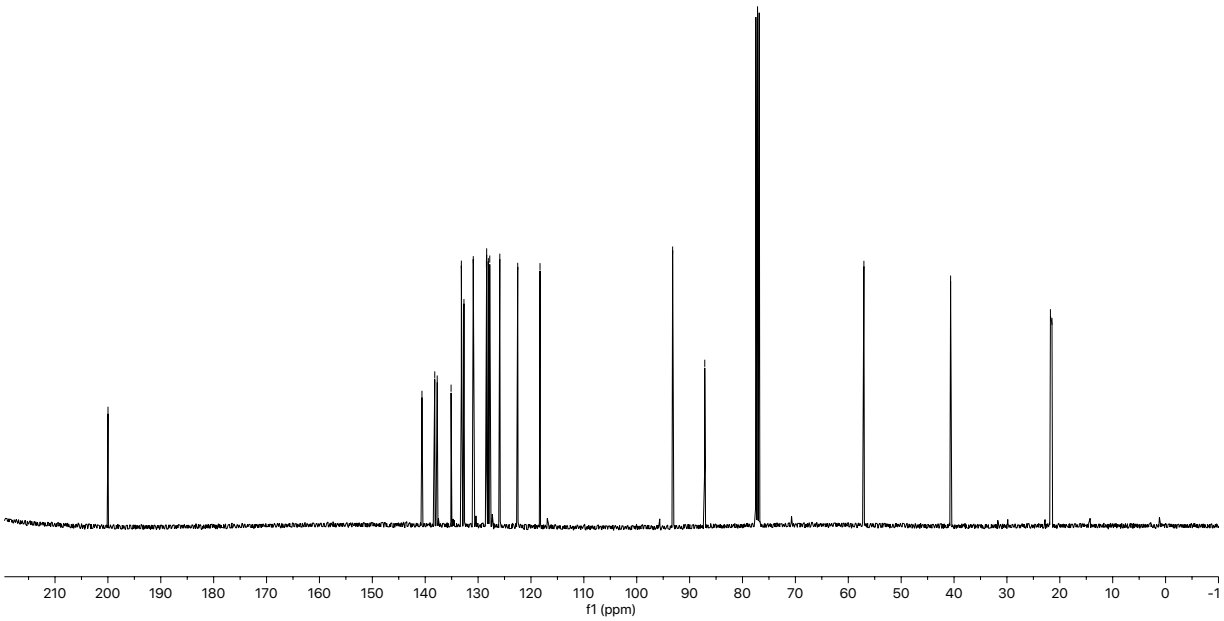
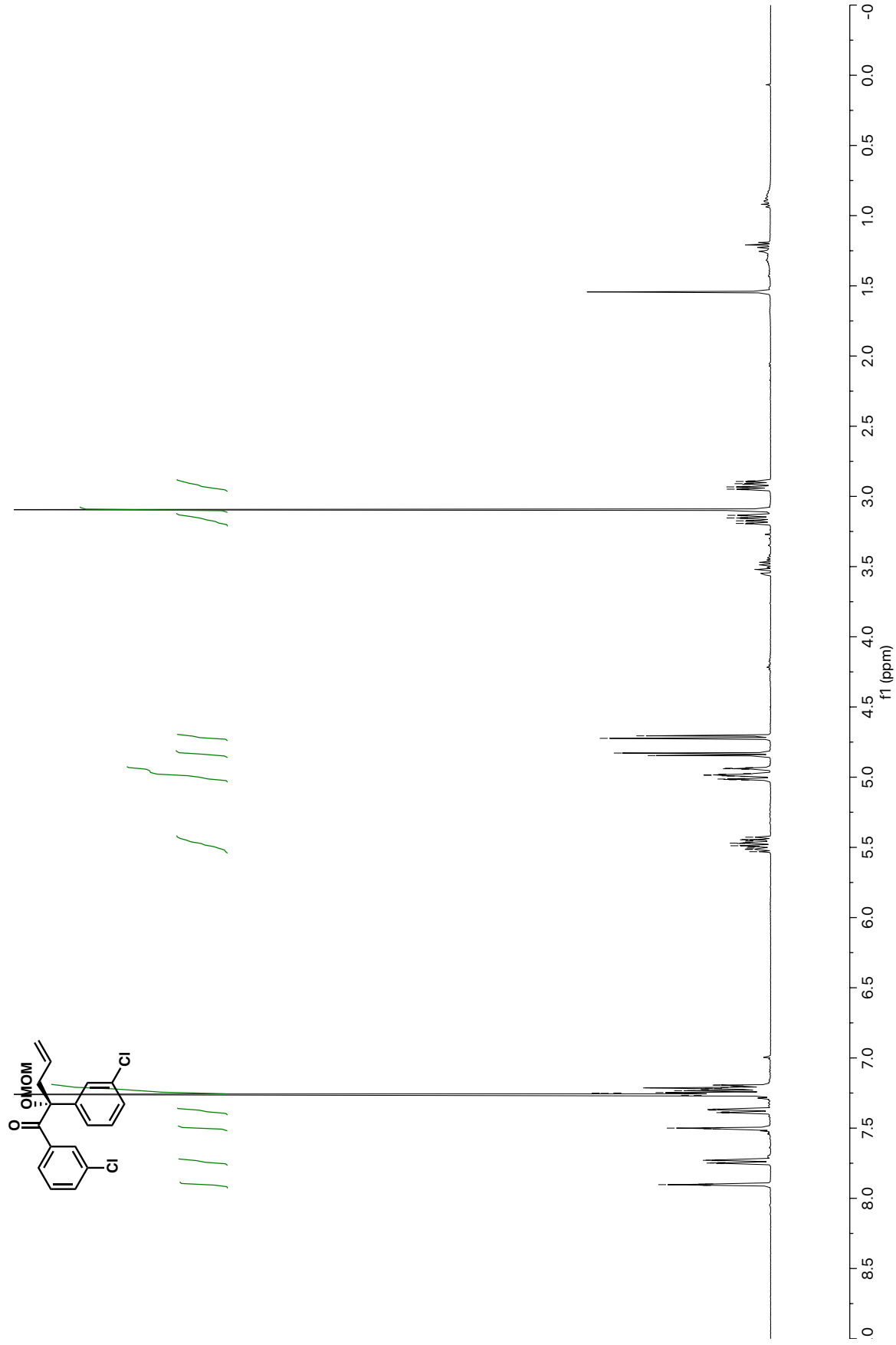



***Figure A7.22*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***81g****.*




***A7.23*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***81h***.

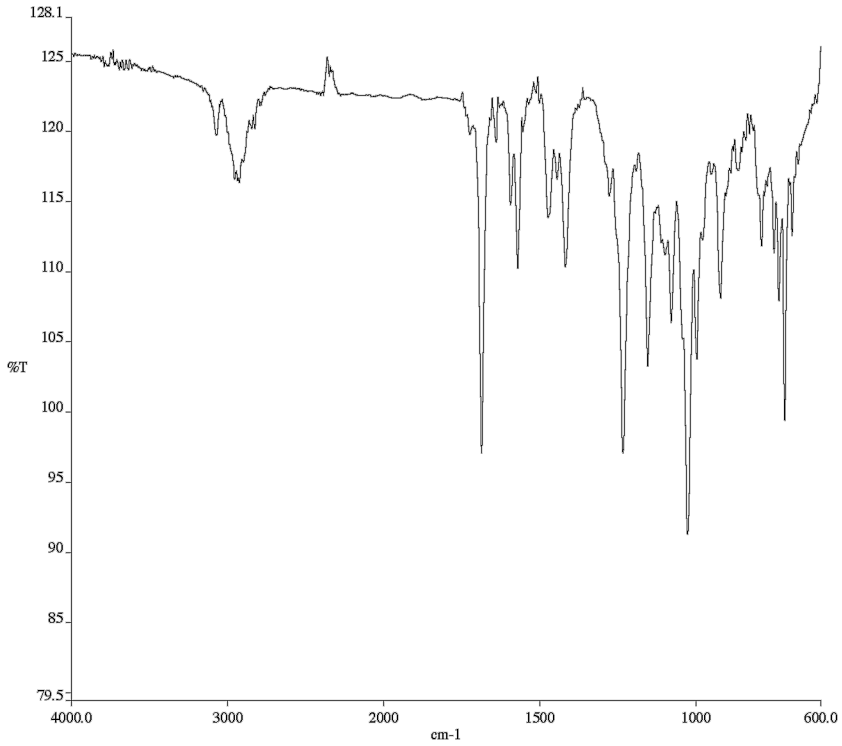



***Figure A7.24*** *Infrared spectrum (Thin Film, NaCl) of compound* ***81h***.

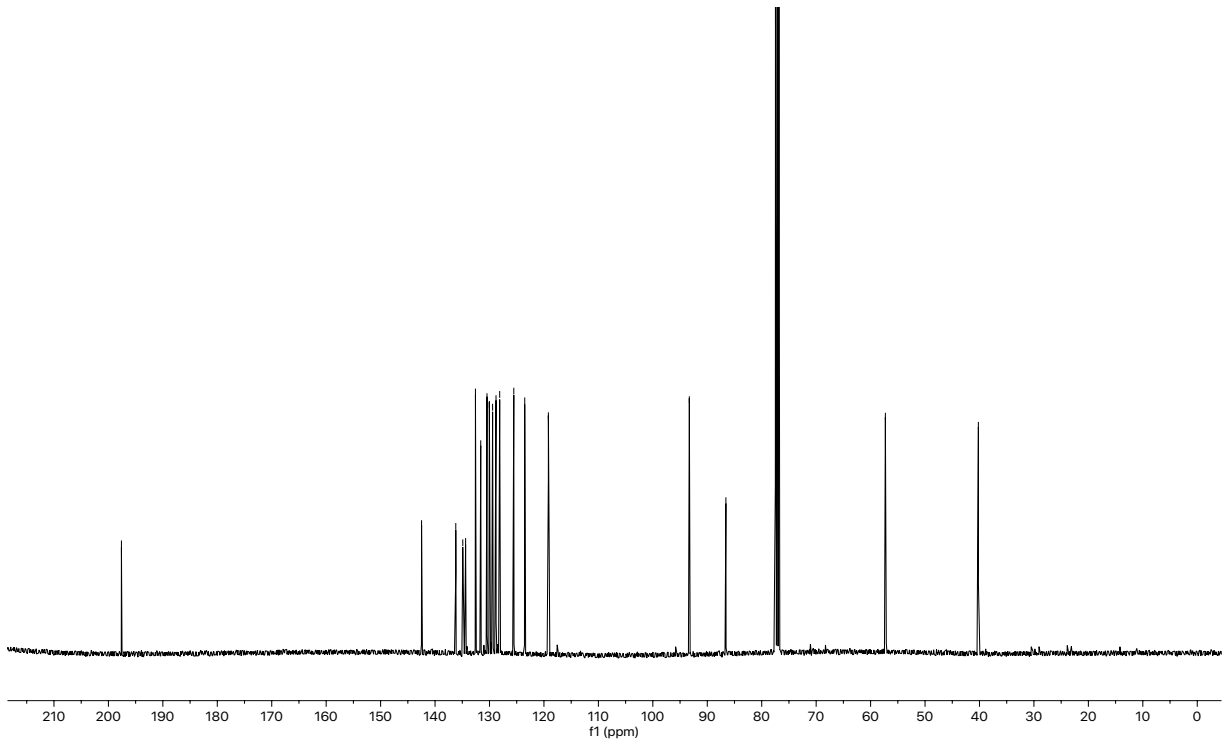
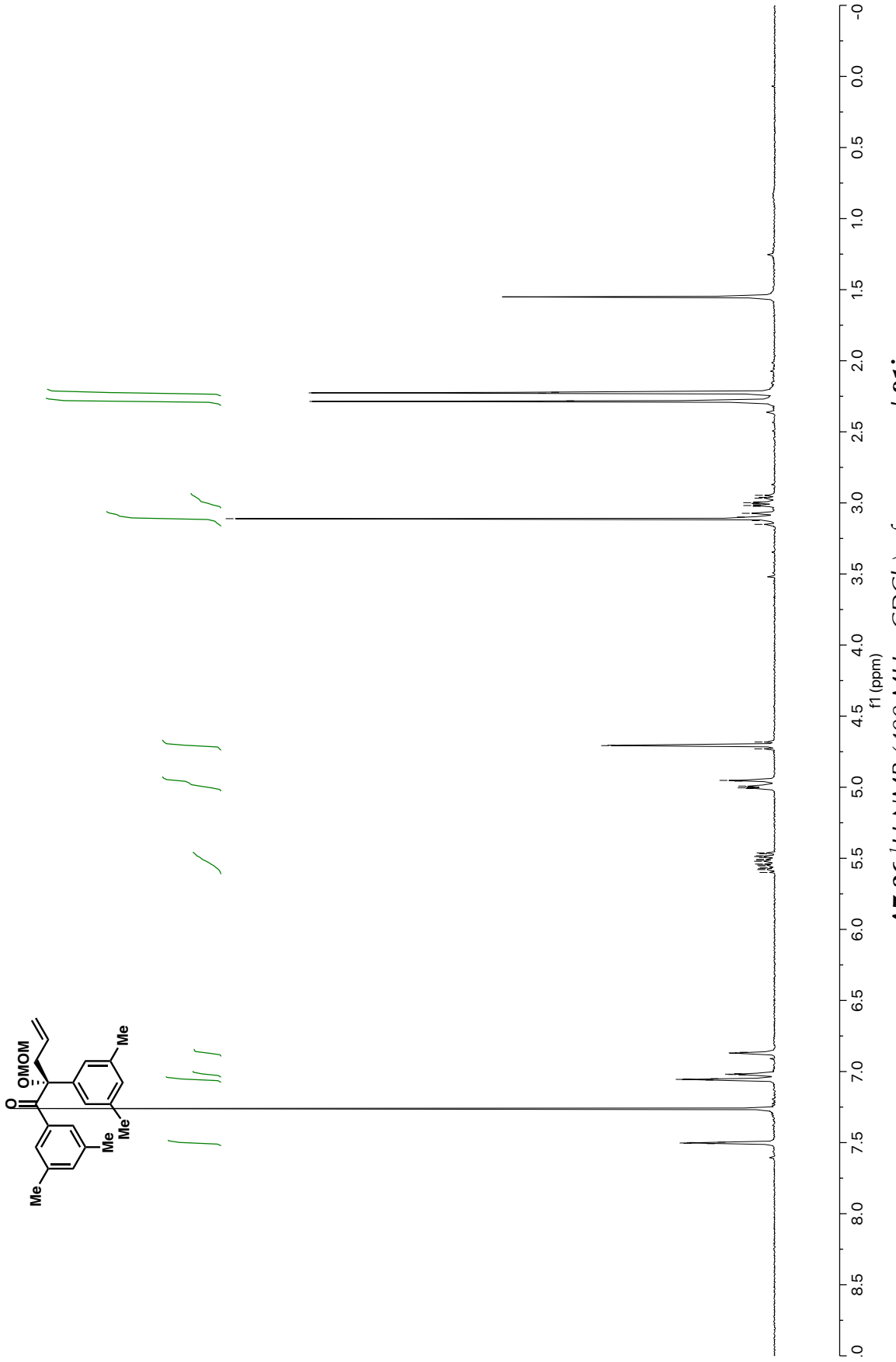



***Figure A7.25*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***81h***.




***A7.26*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***81i****.*

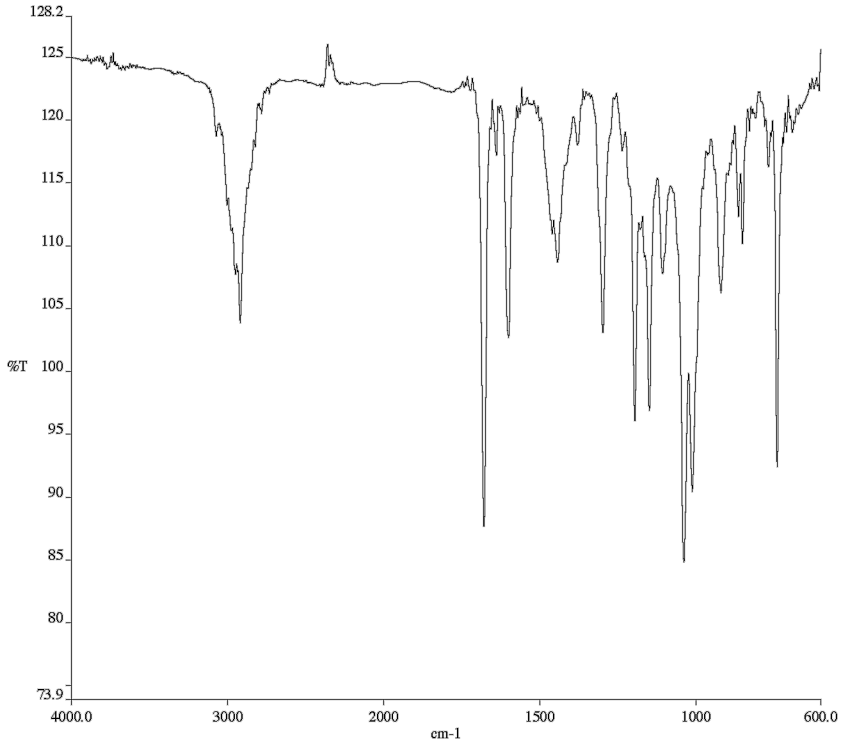



***Figure A7.27*** *Infrared spectrum (Thin Film, NaCl) of compound* ***81i****.*

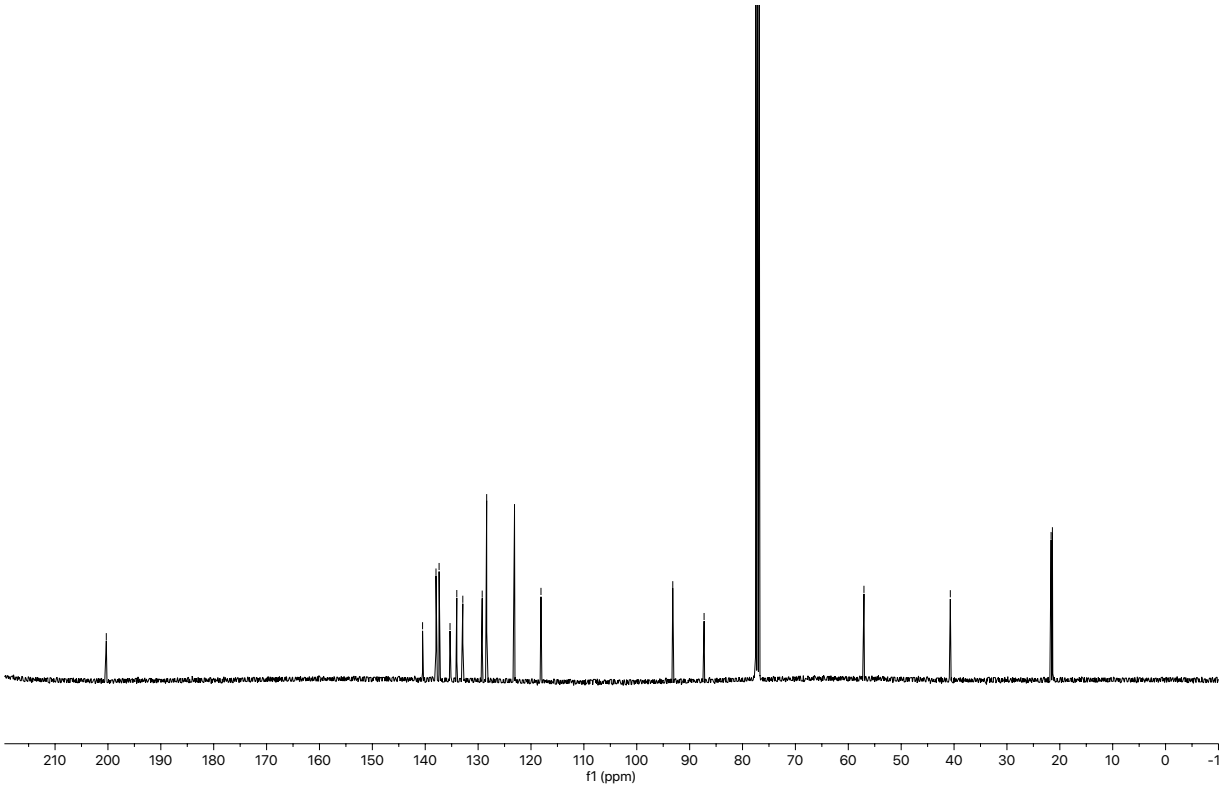
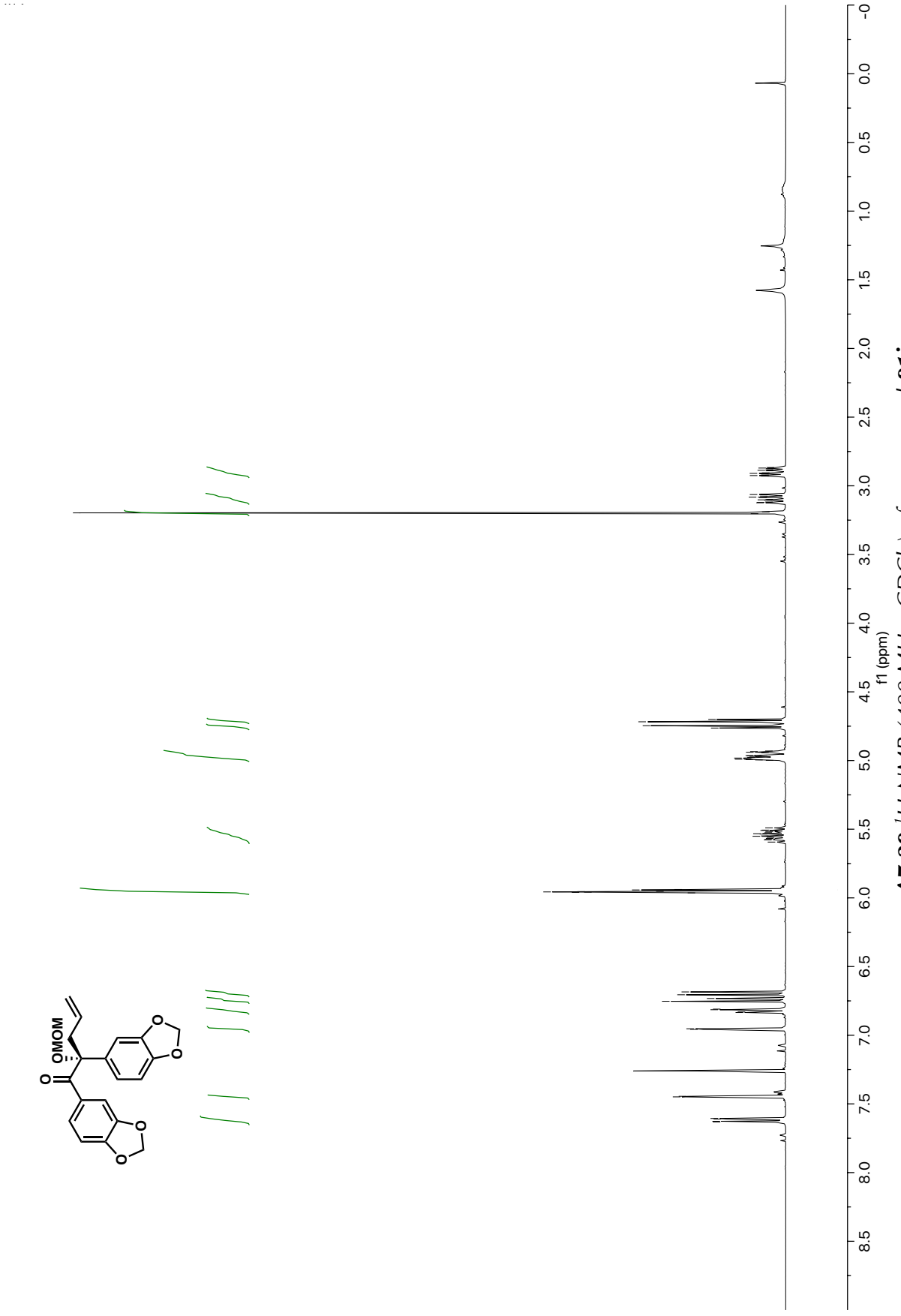



***Figure A7.28*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***81i****.*




***A7.29*** *$^{1}H$ NMR (400 MHz, $CDCl_3$) of compound* ***81j****.*

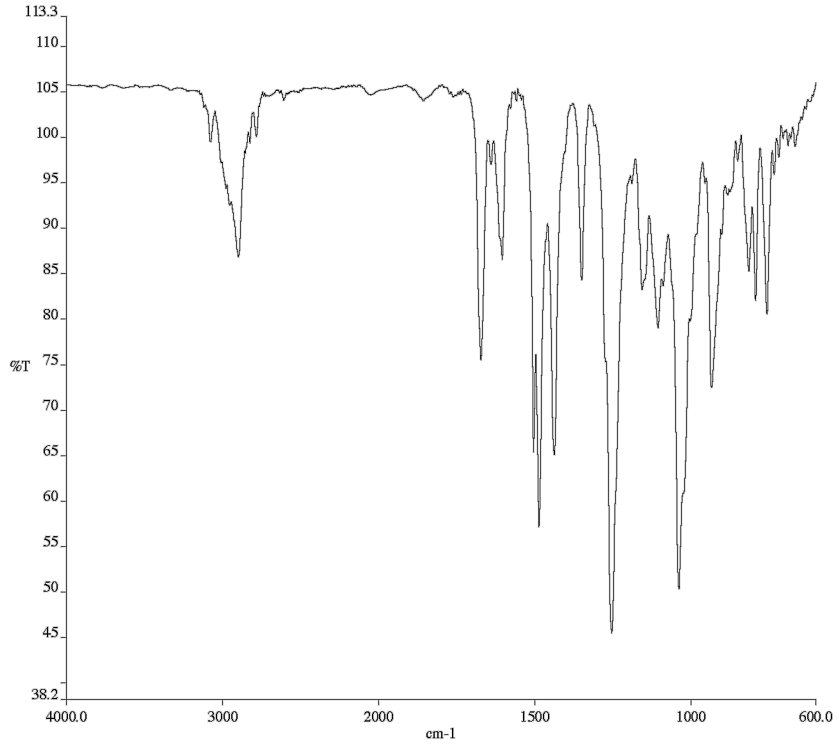



***Figure A7.30*** *Infrared spectrum (Thin Film, NaCl) of compound* ***81j****.*

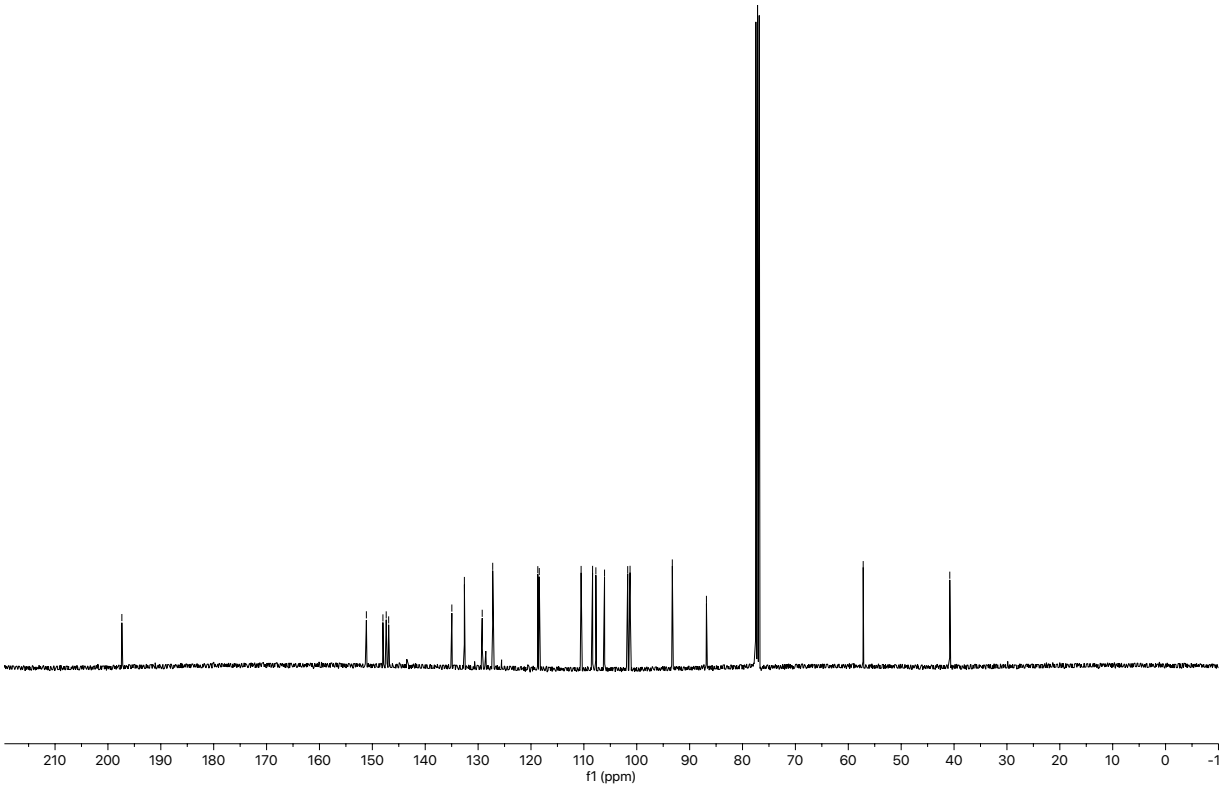
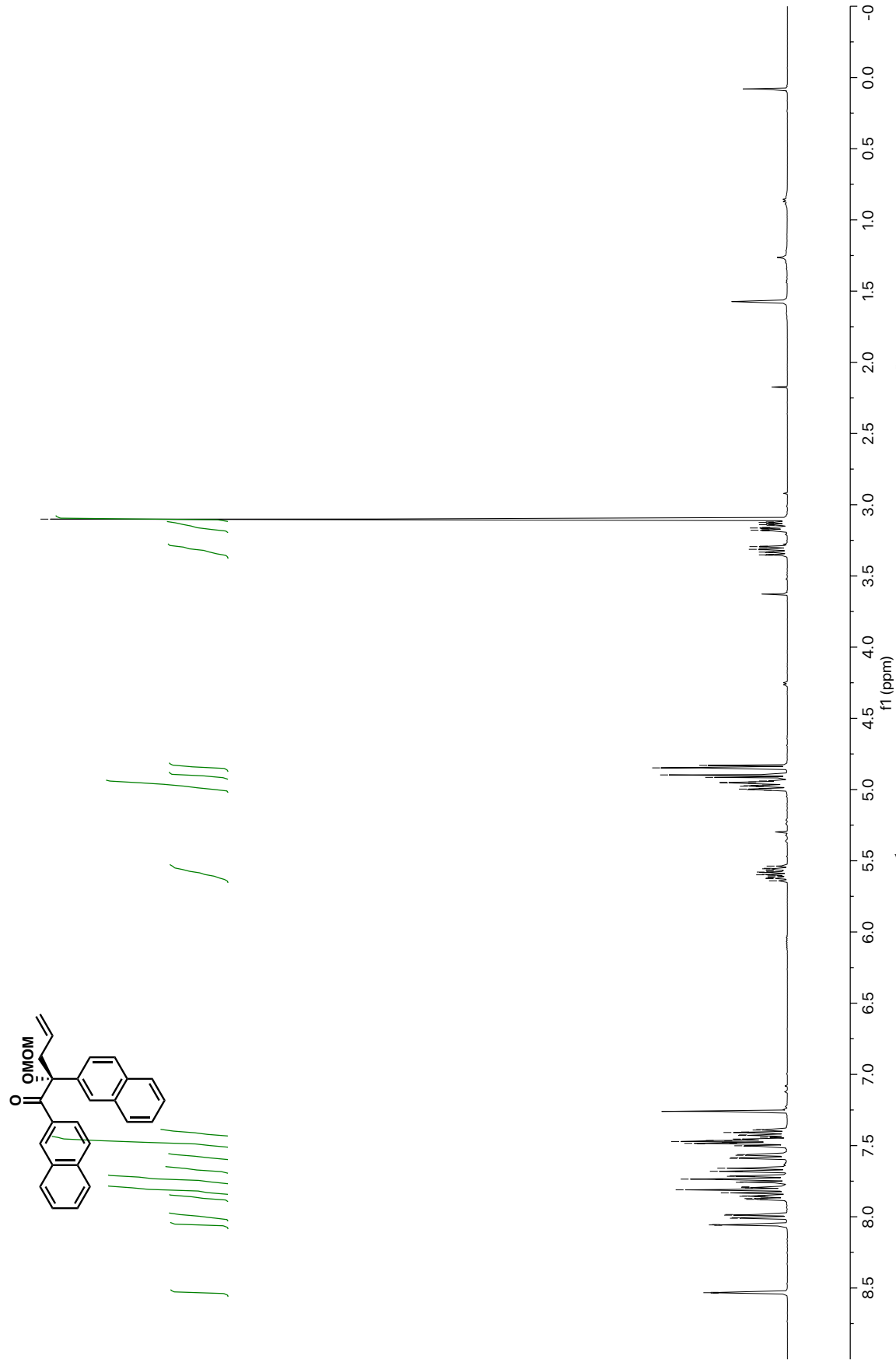



***Figure A7.31*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***81j****.*




***A7.32*** *$^1$H NMR (400 MHz, $CDCl_3$) of compound* ***81k.***

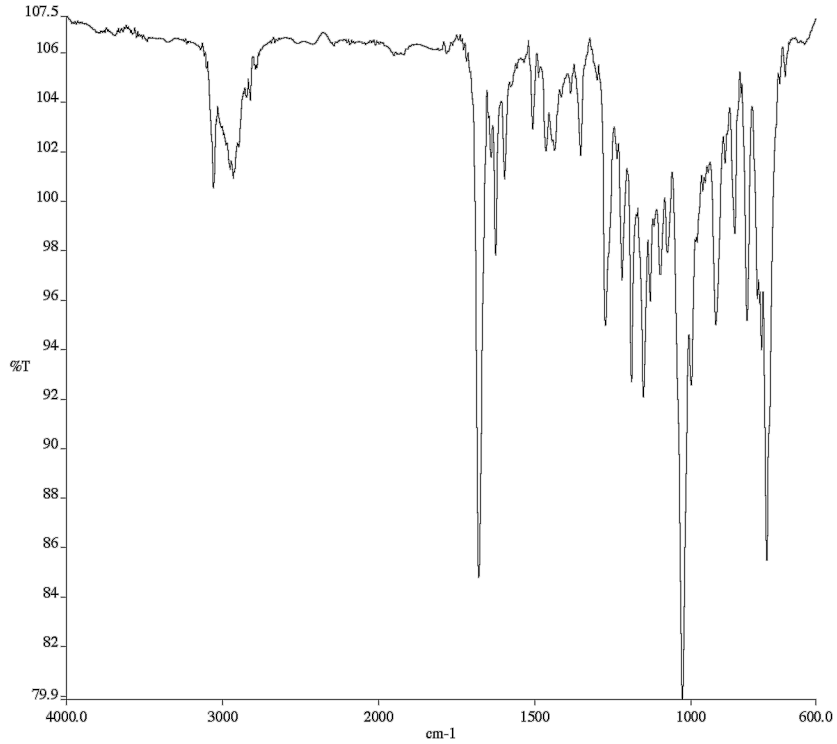



***Figure A7.33*** *Infrared spectrum (Thin Film, NaCl) of compound* ***81k****.*

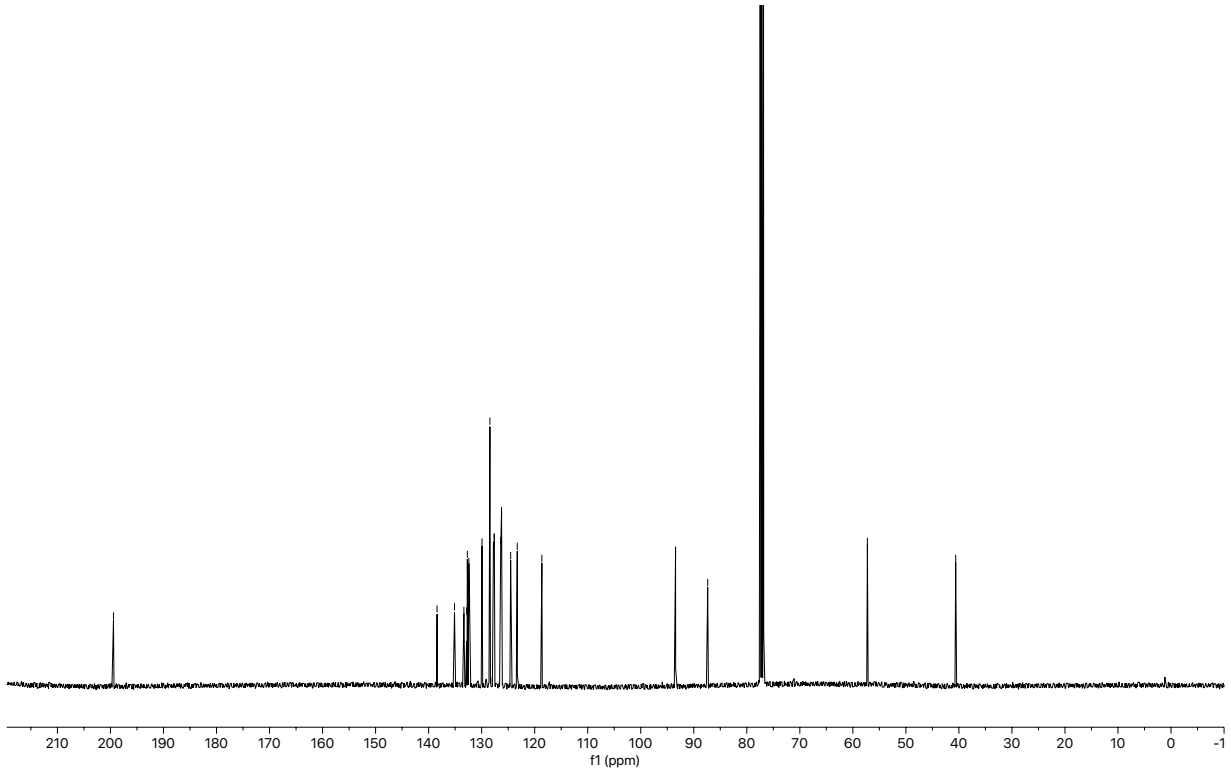
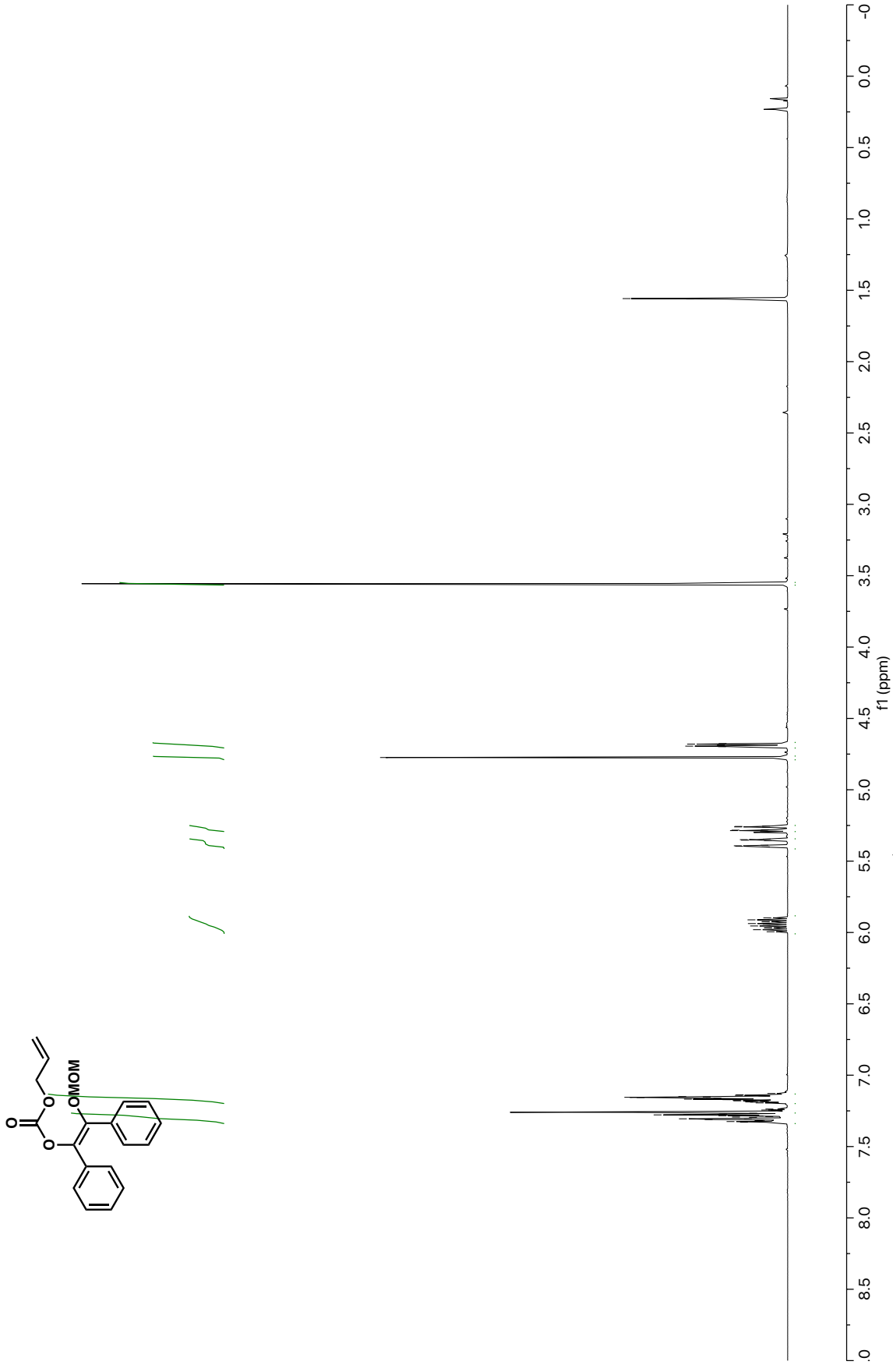



***Figure A7.34*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***81k****.*




***A7.35*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***80a.***

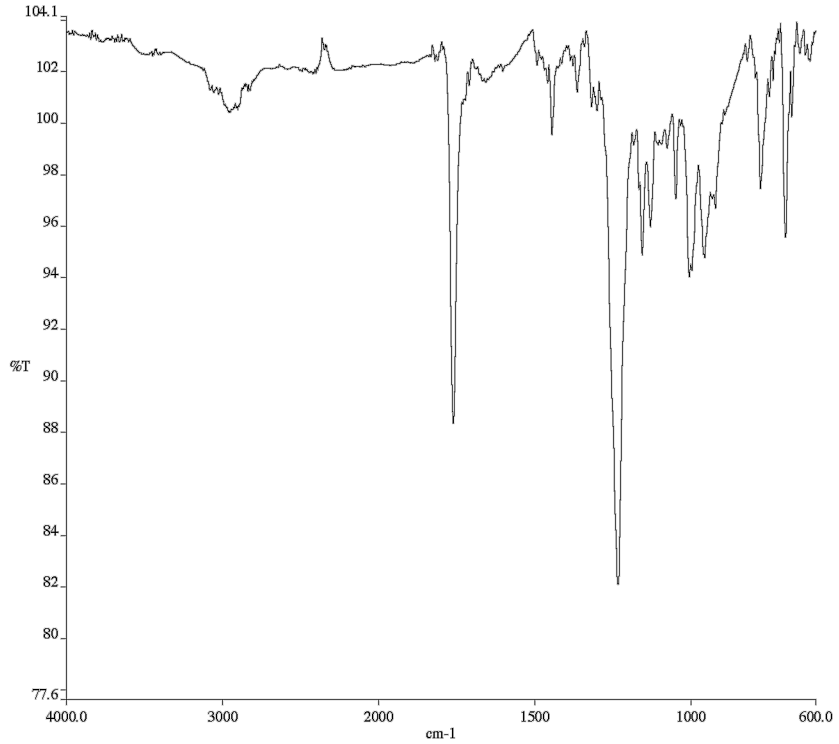



***Figure A7.36*** *Infrared spectrum (Thin Film, NaCl) of compound* ***80a****.*

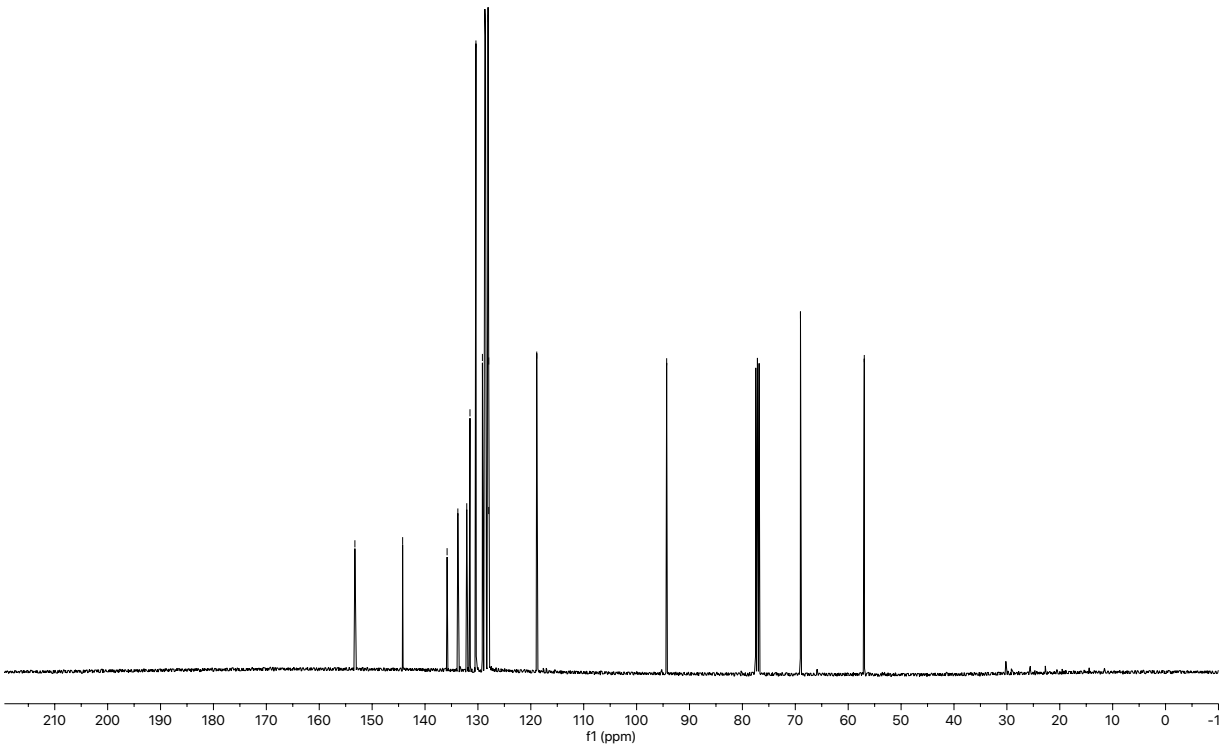
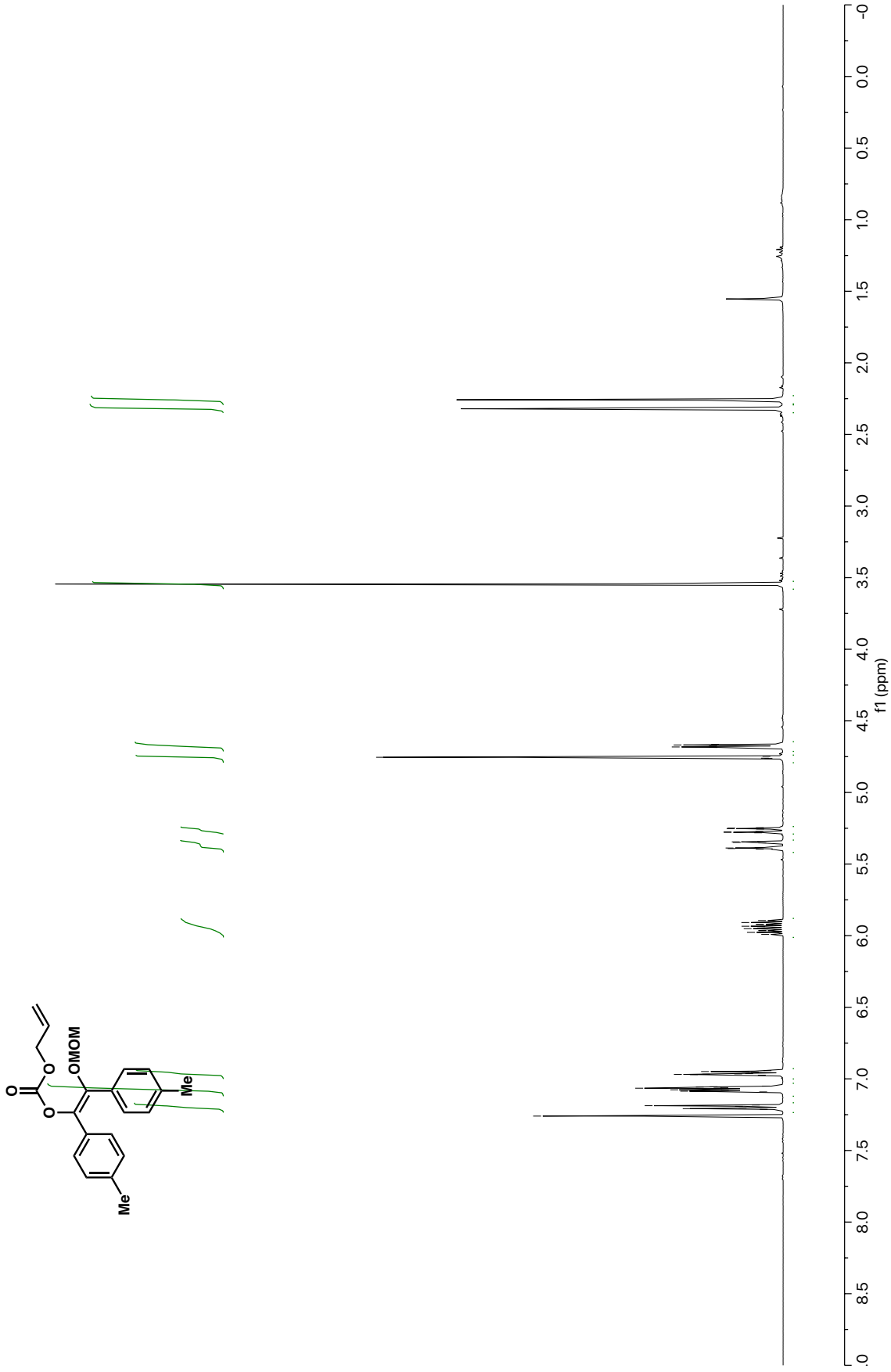



***Figure A7.37*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***80a****.*




***A7.38*** *$^1$H NMR (400 MHz, $CDCl_3$) of compound* ***80b.***

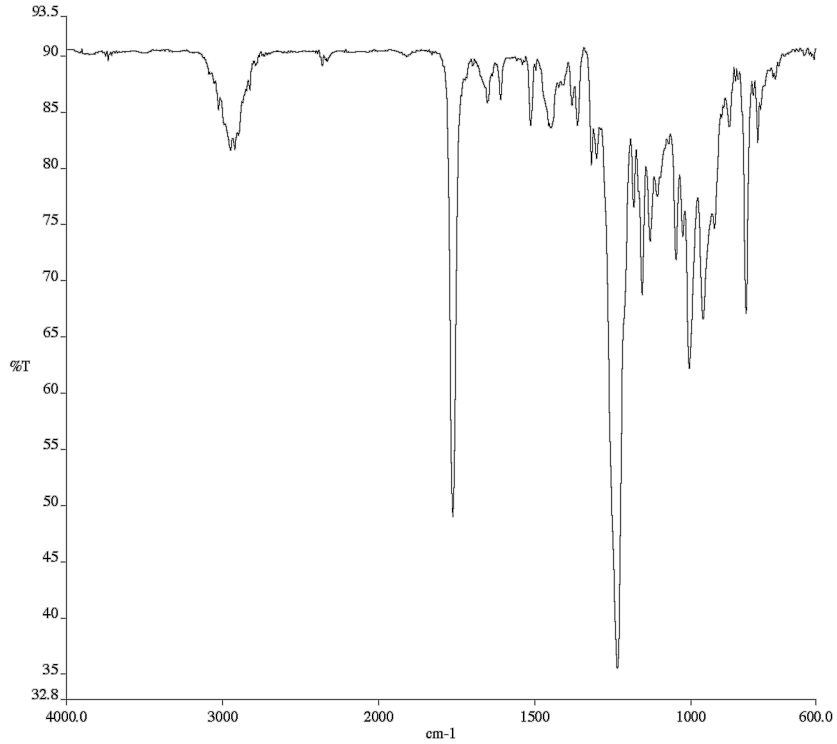



***Figure A7.39*** *Infrared spectrum (Thin Film, NaCl) of compound* ***80b****.*

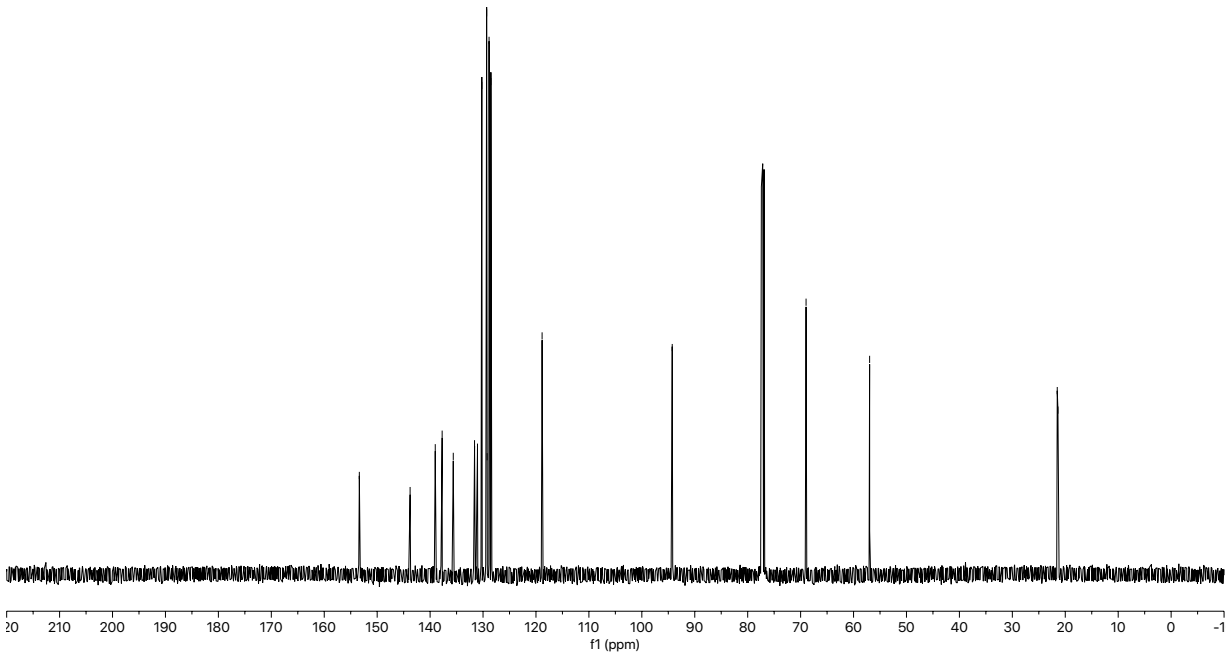
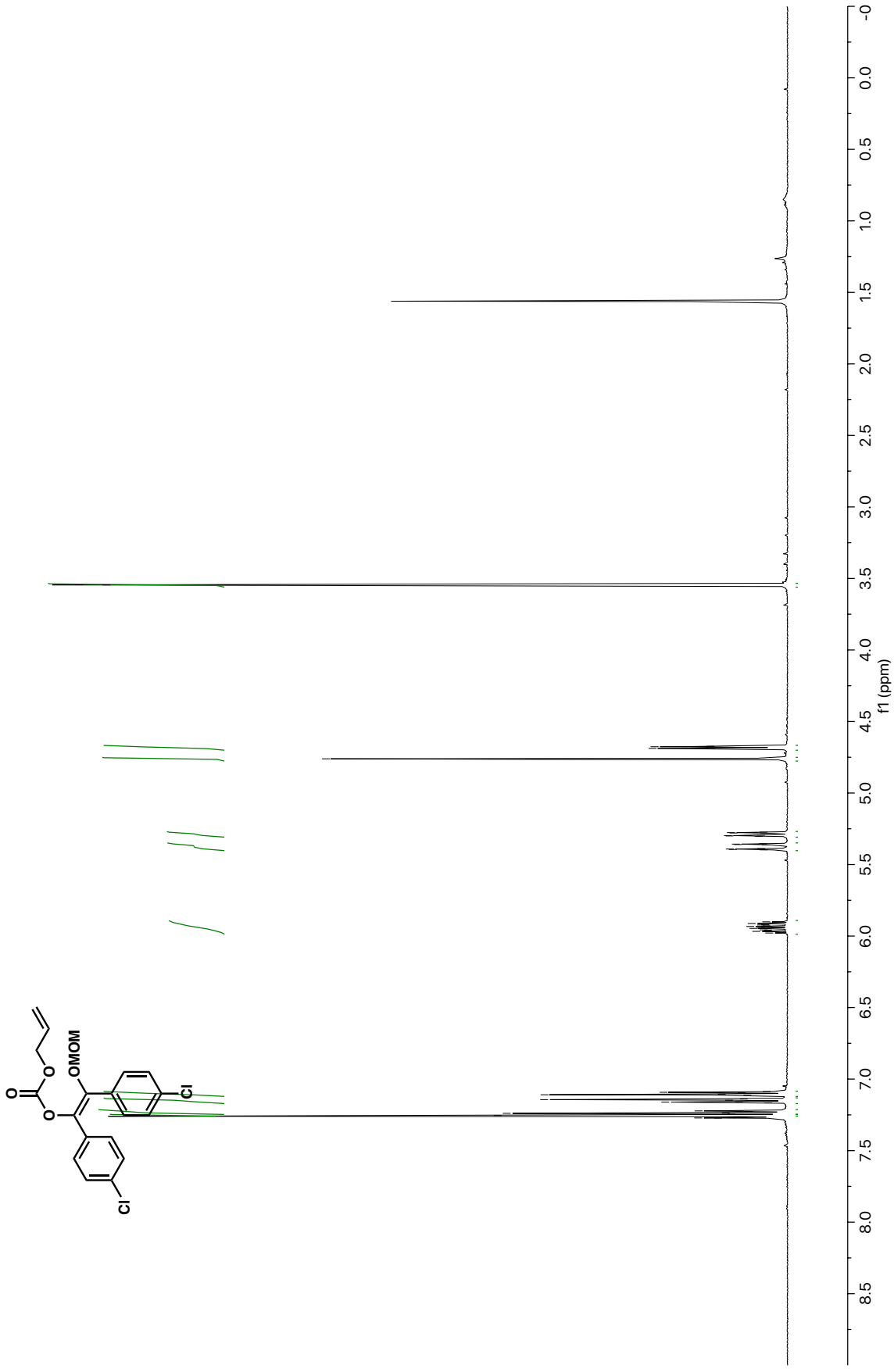



***Figure A7.40*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***80b****.*




***A7.41*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***80c.***

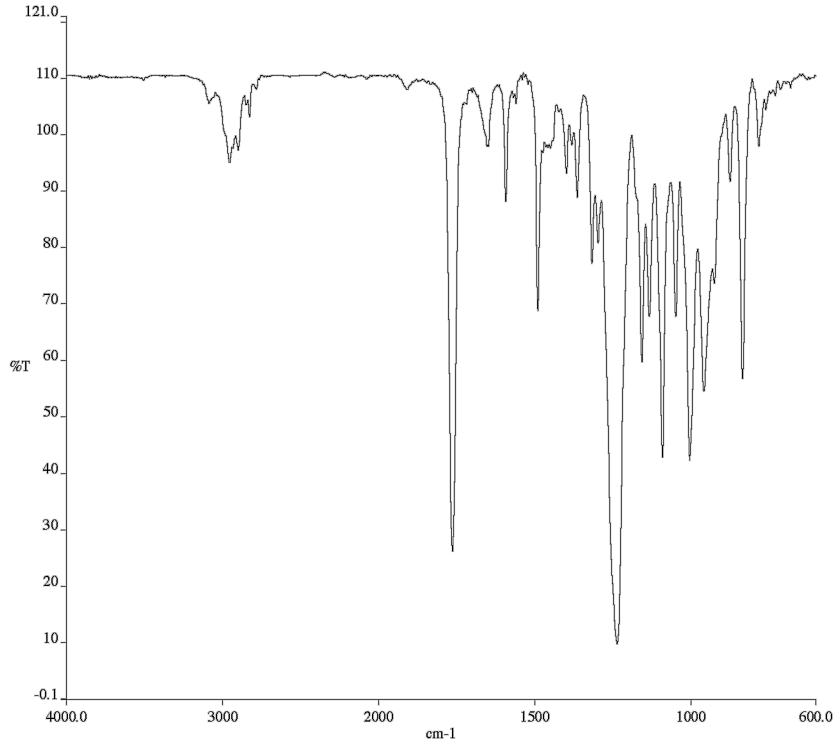



***Figure A7.42*** *Infrared spectrum (Thin Film, NaCl) of compound* ***80c****.*

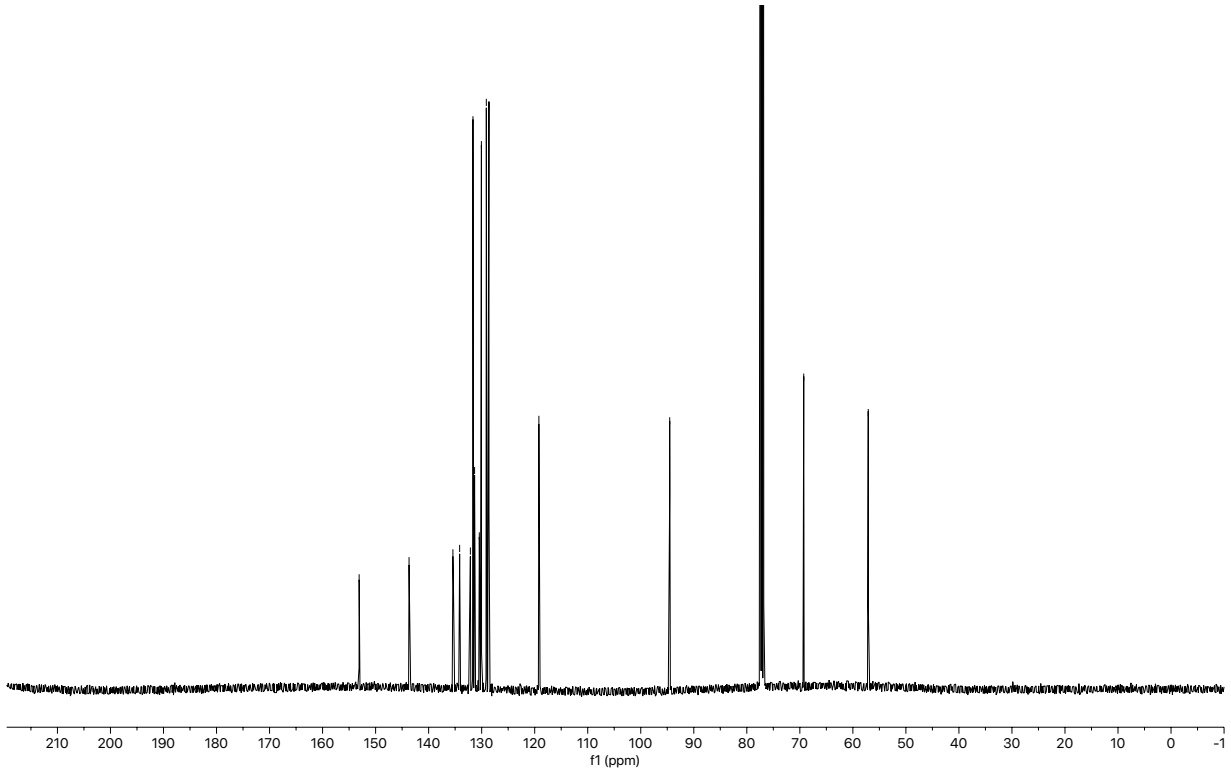
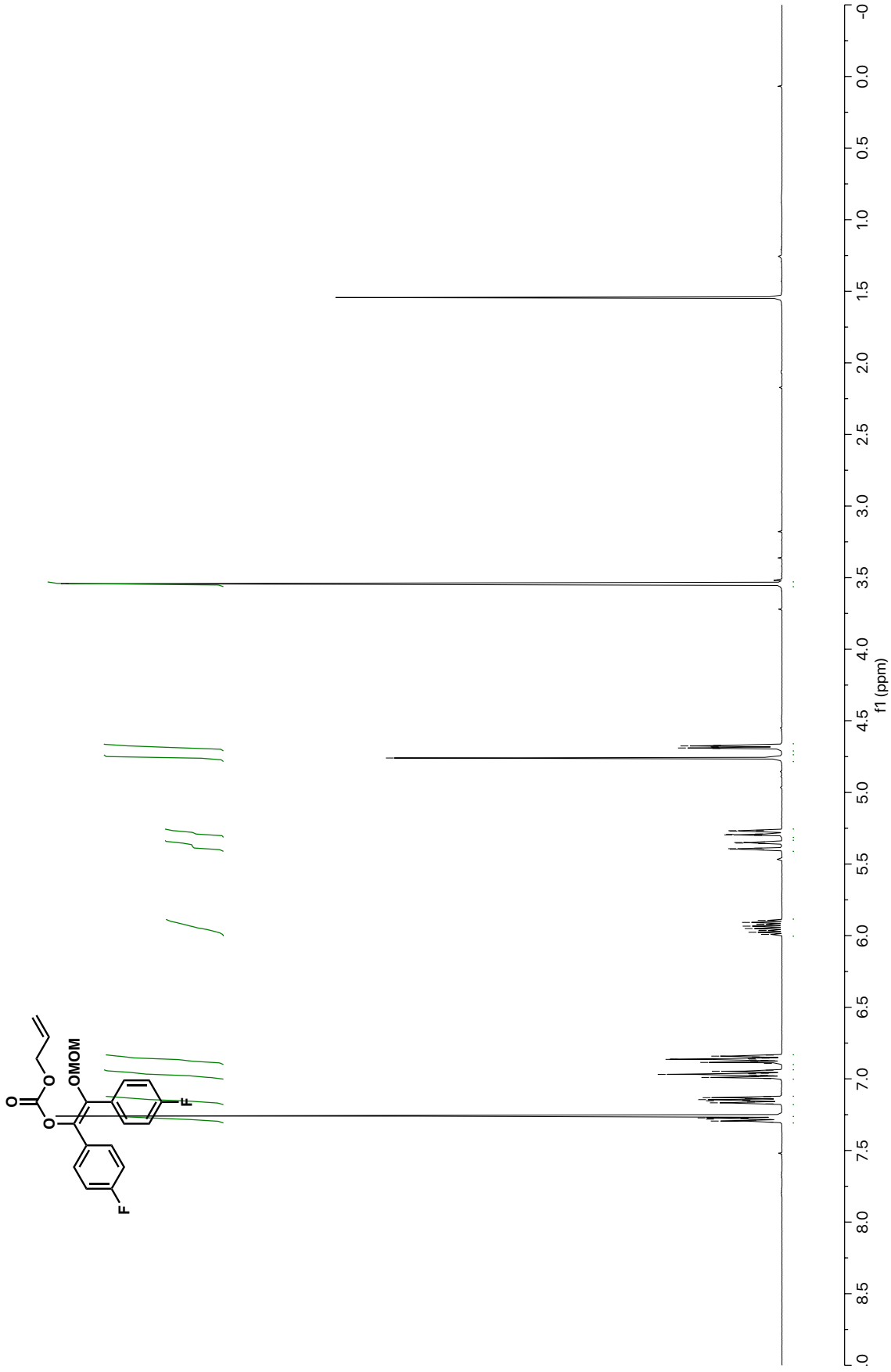



***Figure A7.43*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***80c****.*




***A7.44*** *$^1$H NMR (400 MHz, $CDCl_3$) of compound* ***80d.***

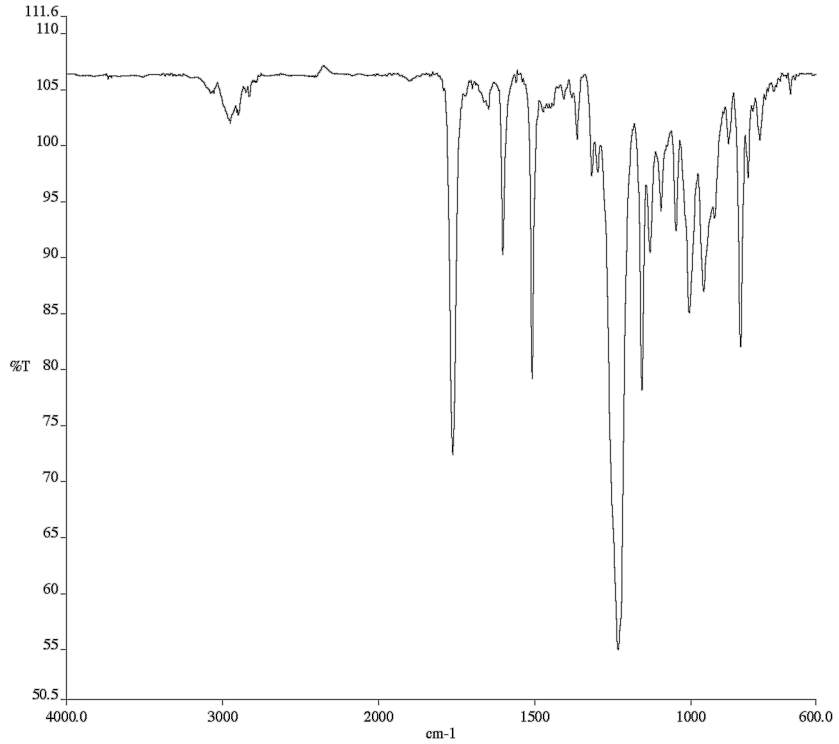



***Figure A7.45*** *Infrared spectrum (Thin Film, NaCl) of compound* ***80d****.*

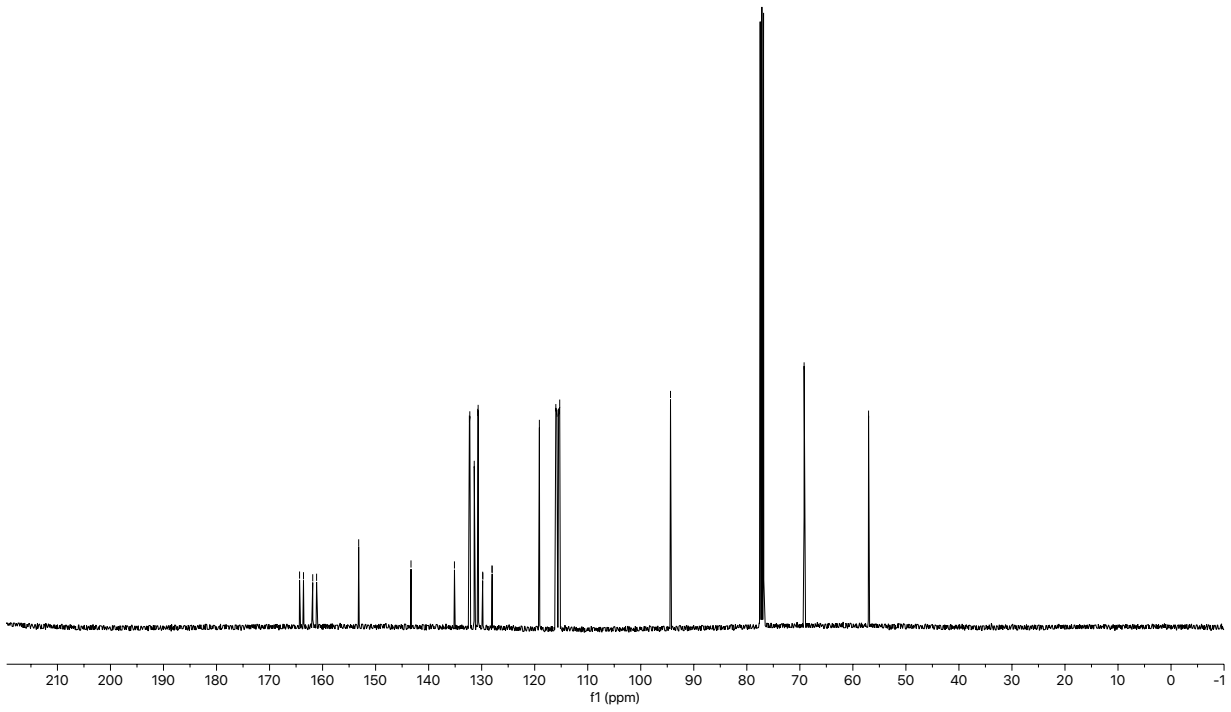



***Figure A7.46*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***80d****.*

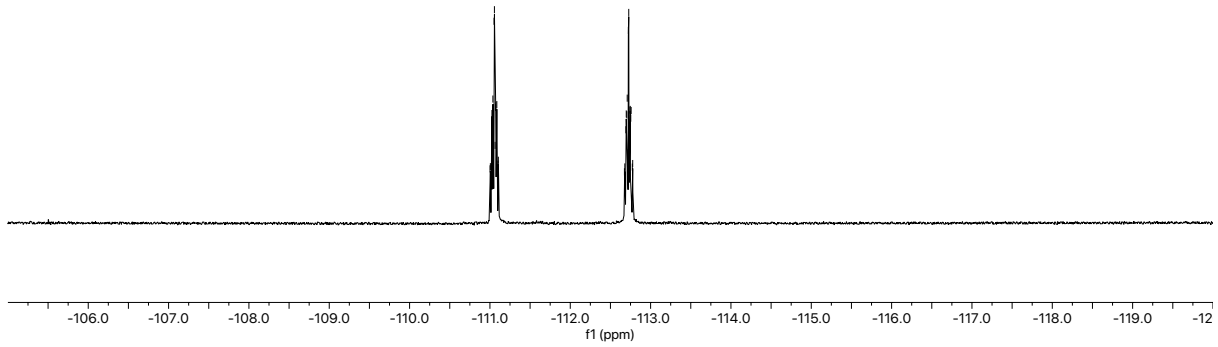
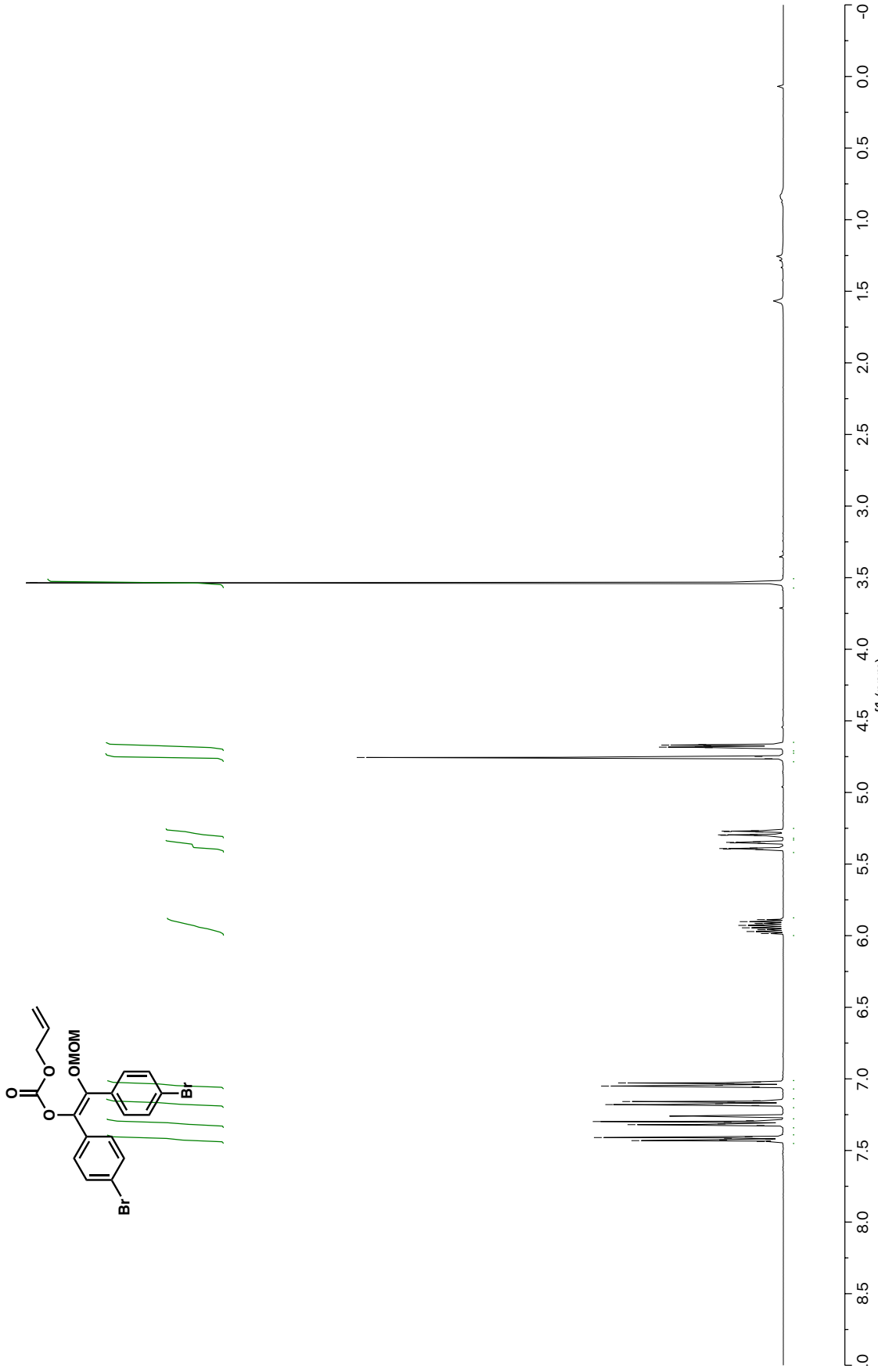



***Figure A7.47*** *$^{19}F$ NMR (282 MHz, $CDCl_3$) of compound* ***80d****.*




***A7.48*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***80e.***

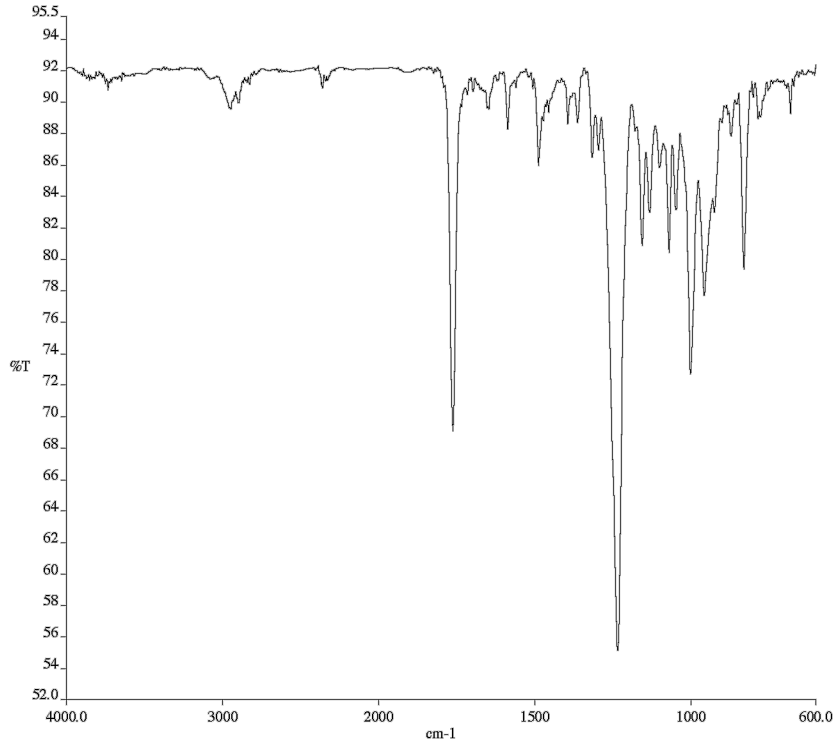



***Figure A7.49*** *Infrared spectrum (Thin Film, NaCl) of compound* ***80e****.*

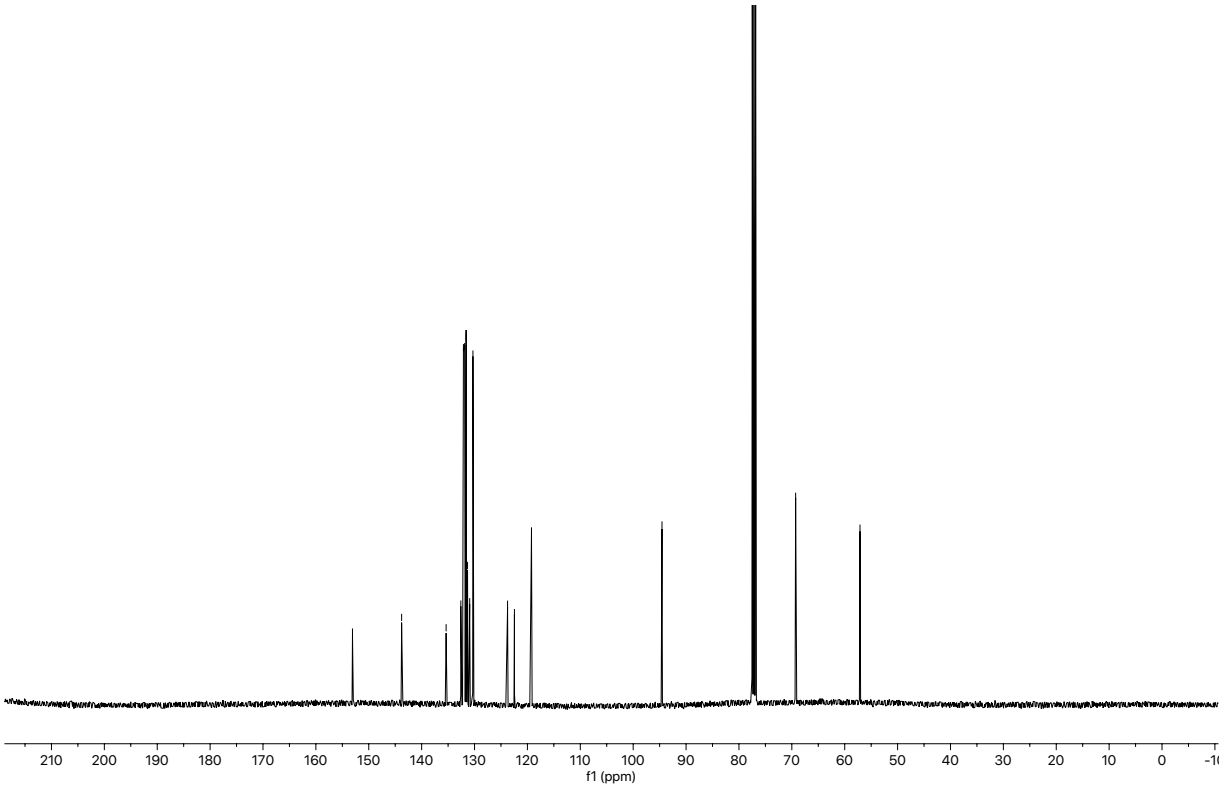
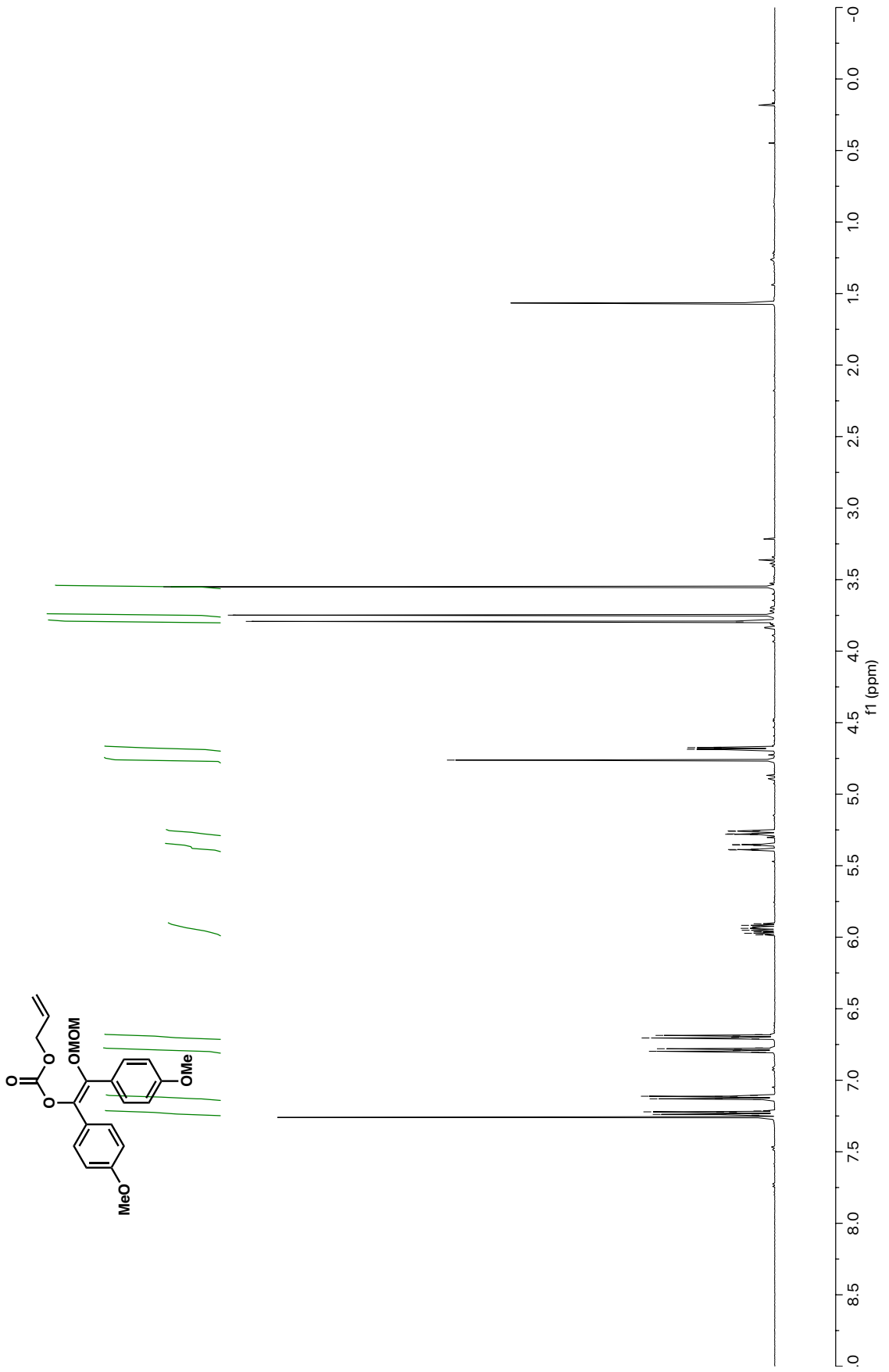



***Figure A7.50*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***80e****.*




***A7.51*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***80f.***

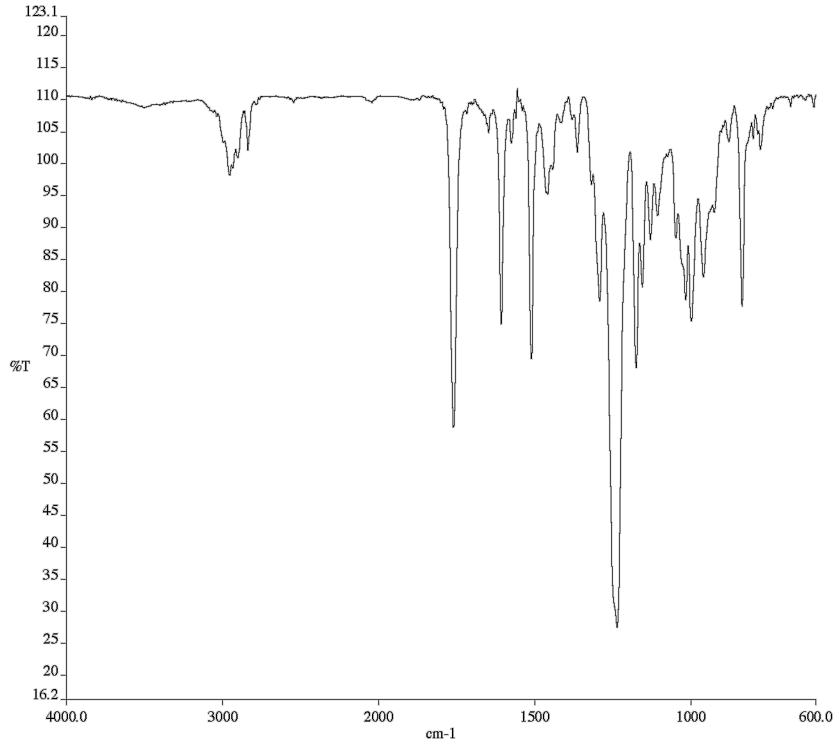



***Figure A7.52*** *Infrared spectrum (Thin Film, NaCl) of compound* ***80f****.*

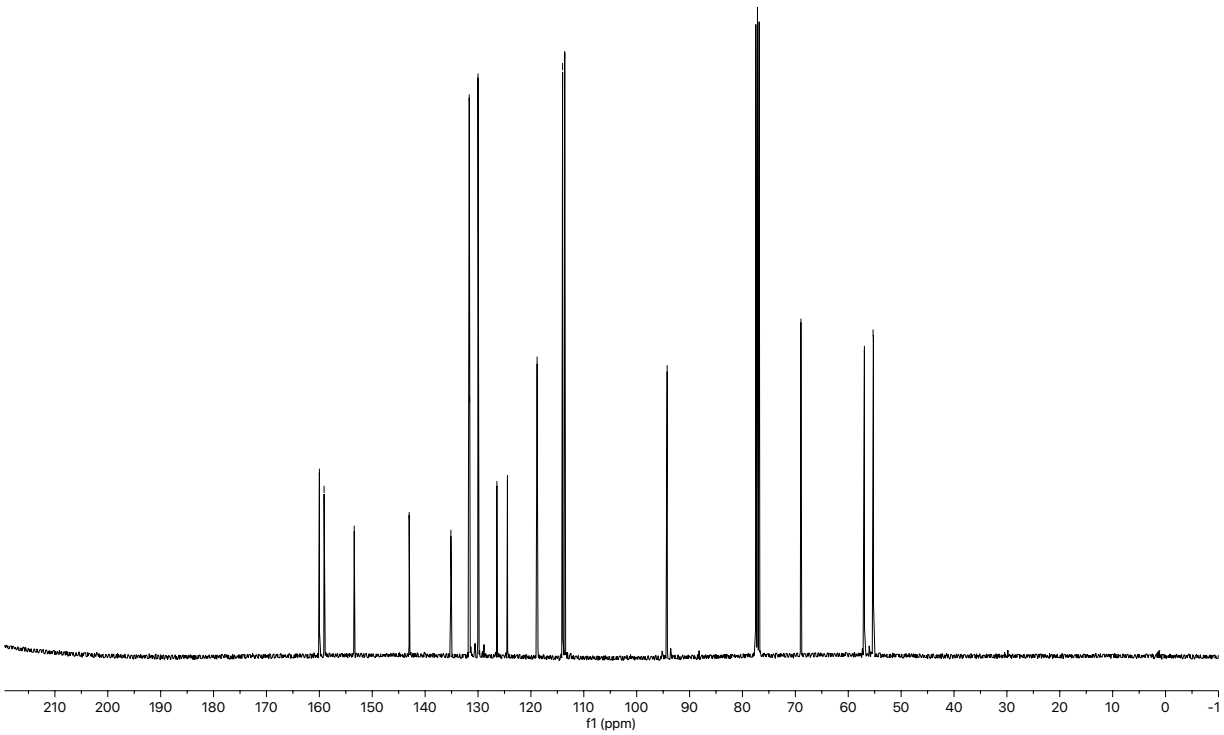
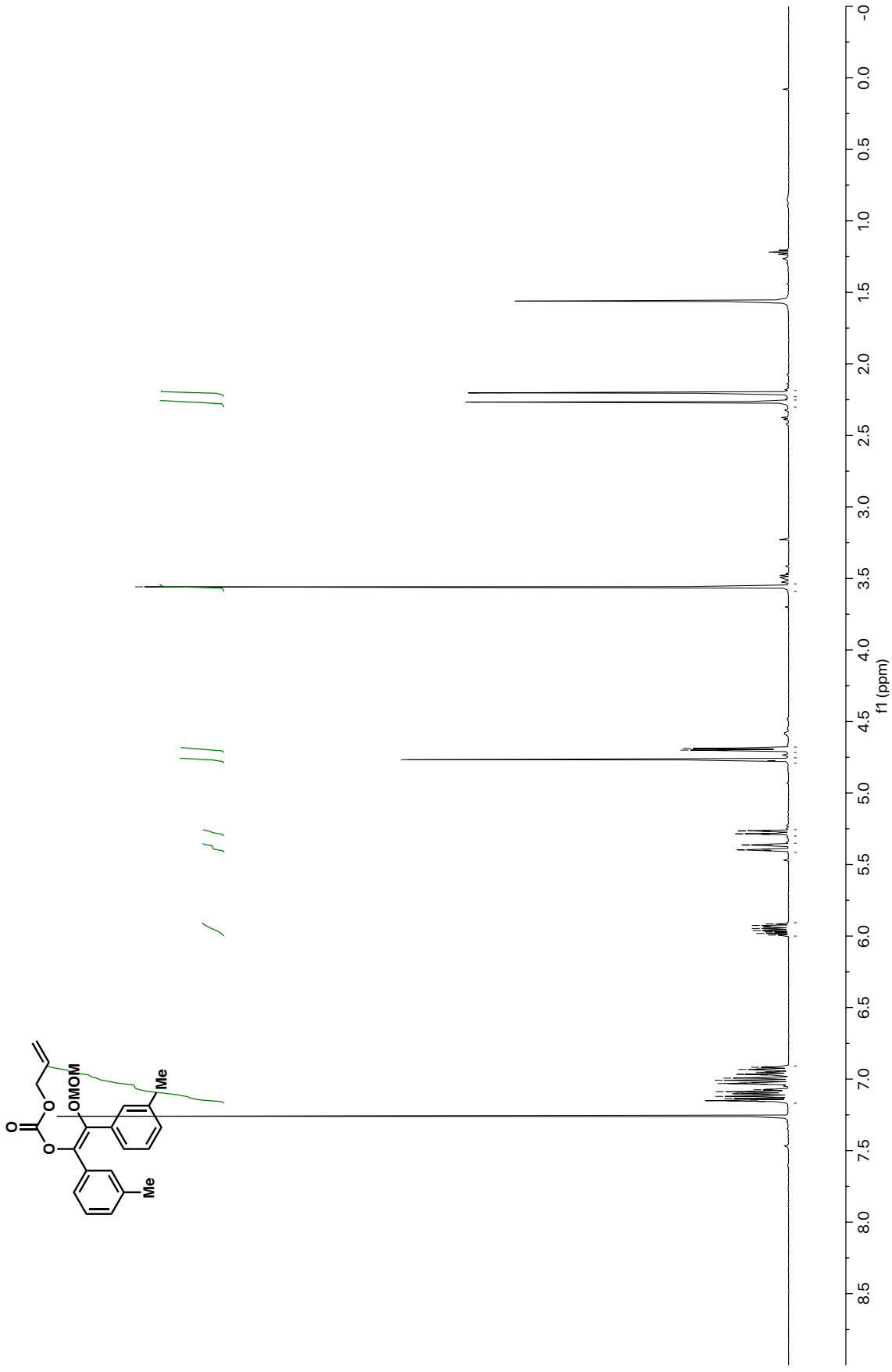



***Figure A7.53*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***80f****.*




***A7.54*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***80g.***

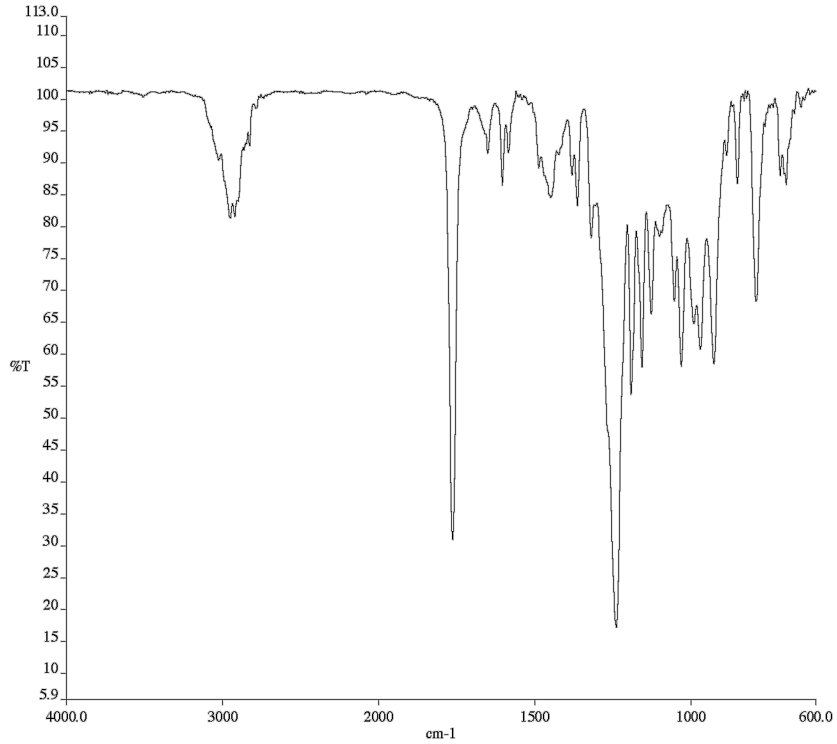



***Figure A7.55*** *Infrared spectrum (Thin Film, NaCl) of compound* ***80g***.

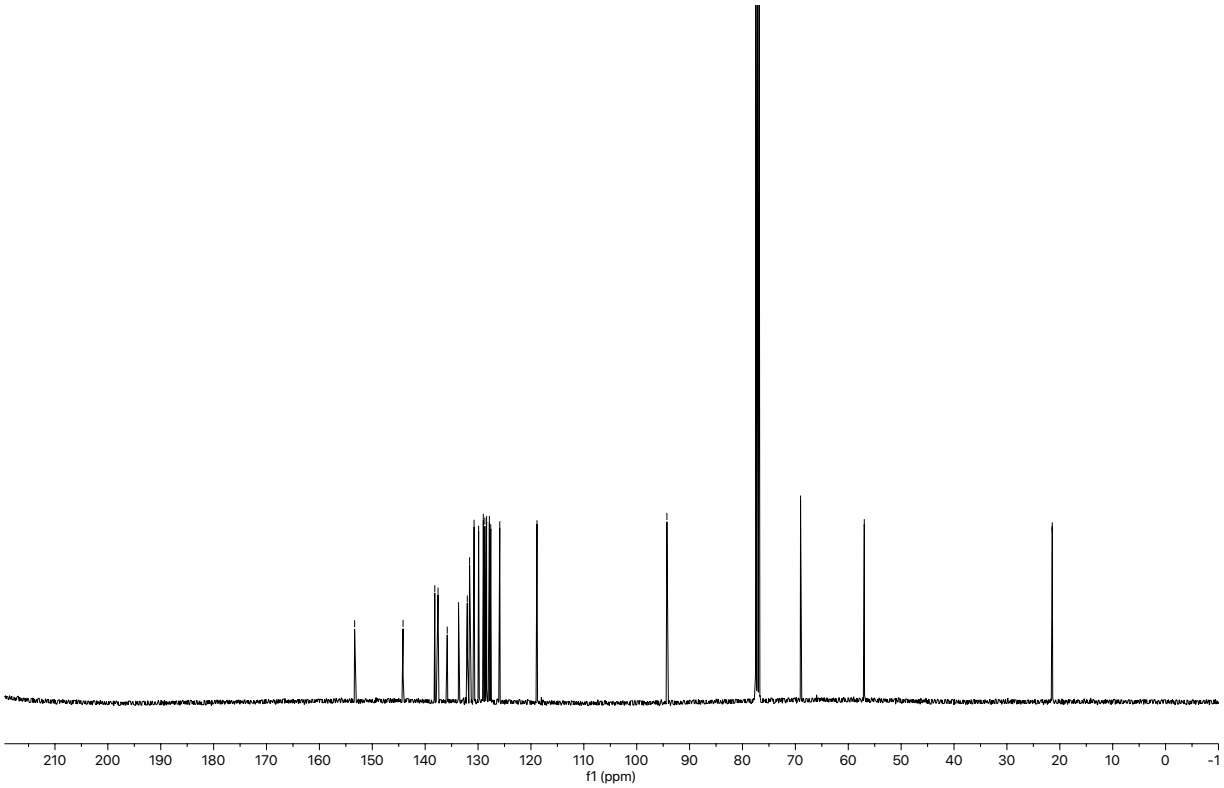
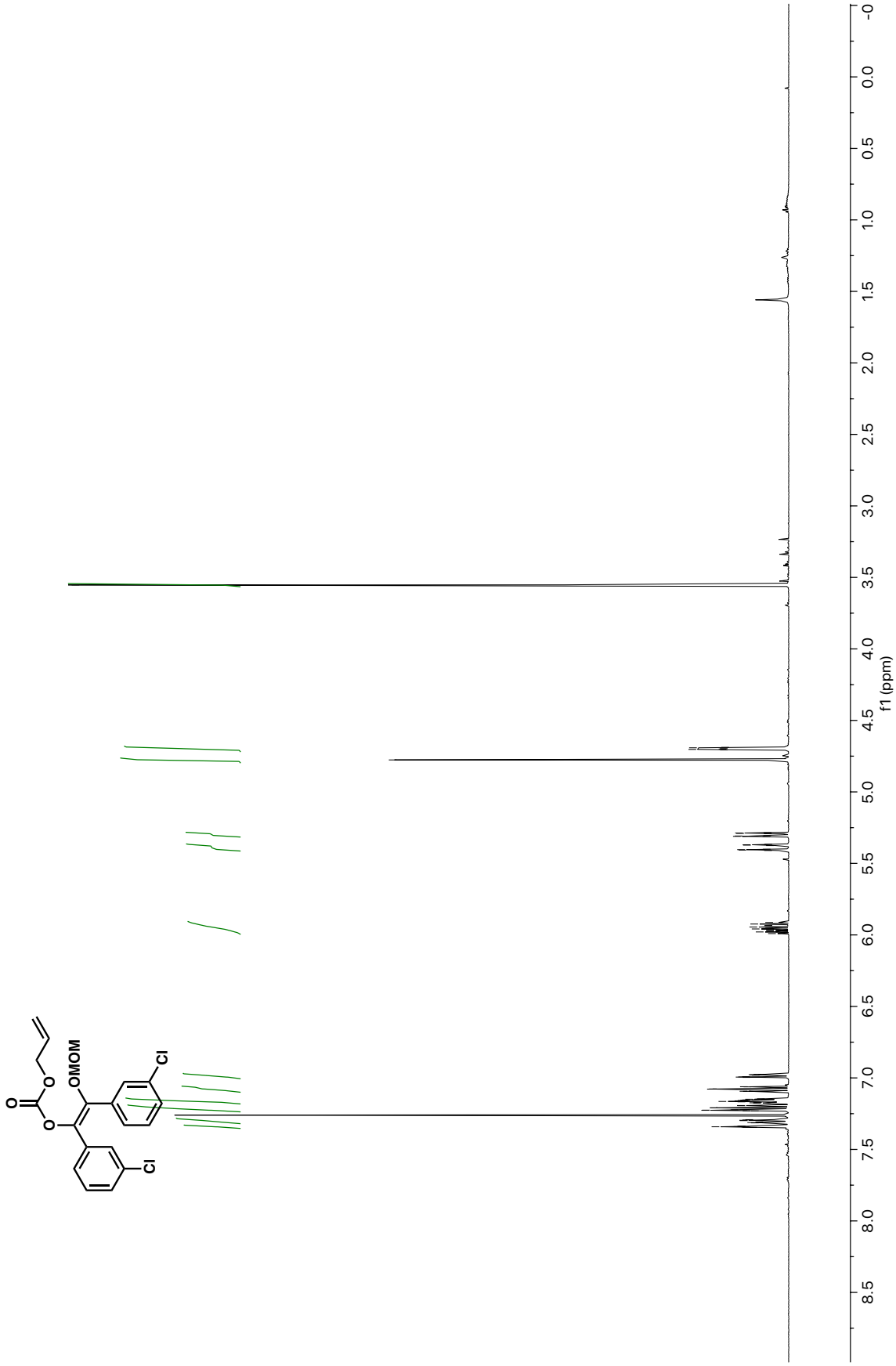



***Figure A7.56*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***80g***.




***A7.57*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***80h.***

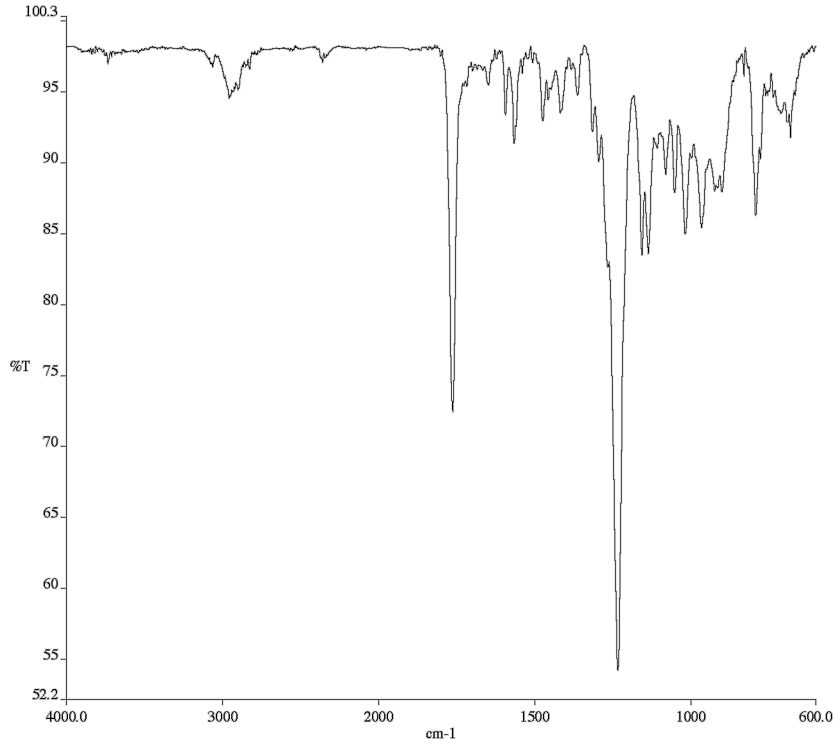



***Figure A7.58*** *Infrared spectrum (Thin Film, NaCl) of compound* ***80h***.

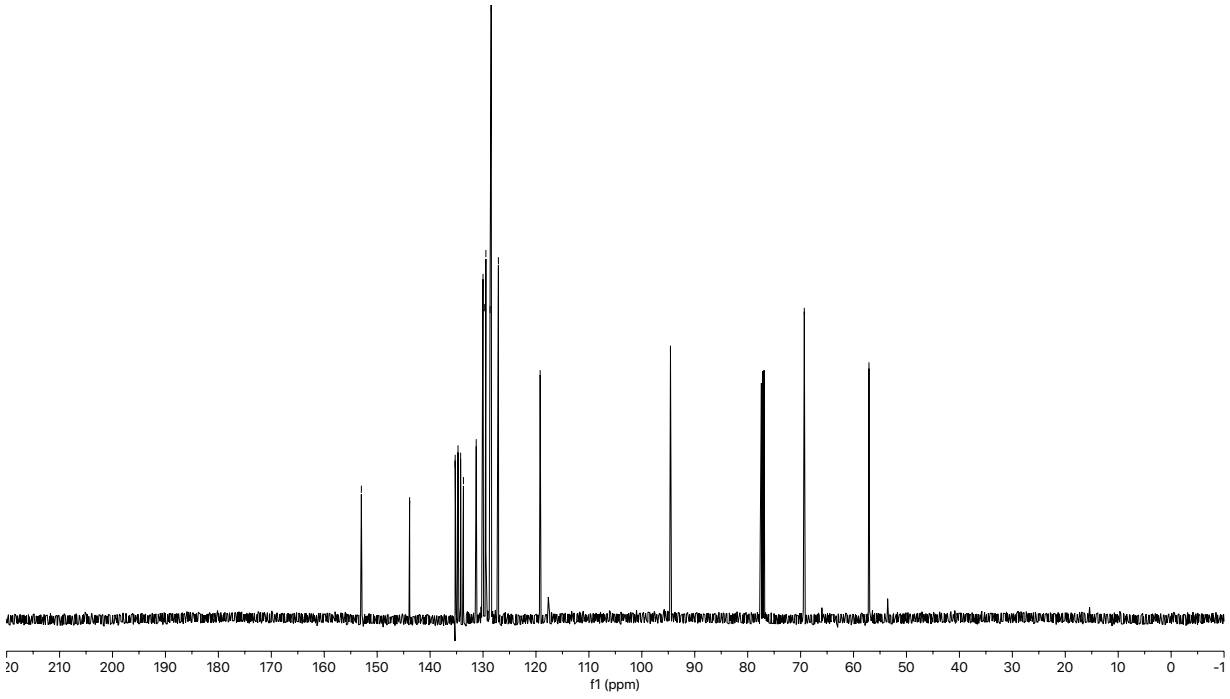
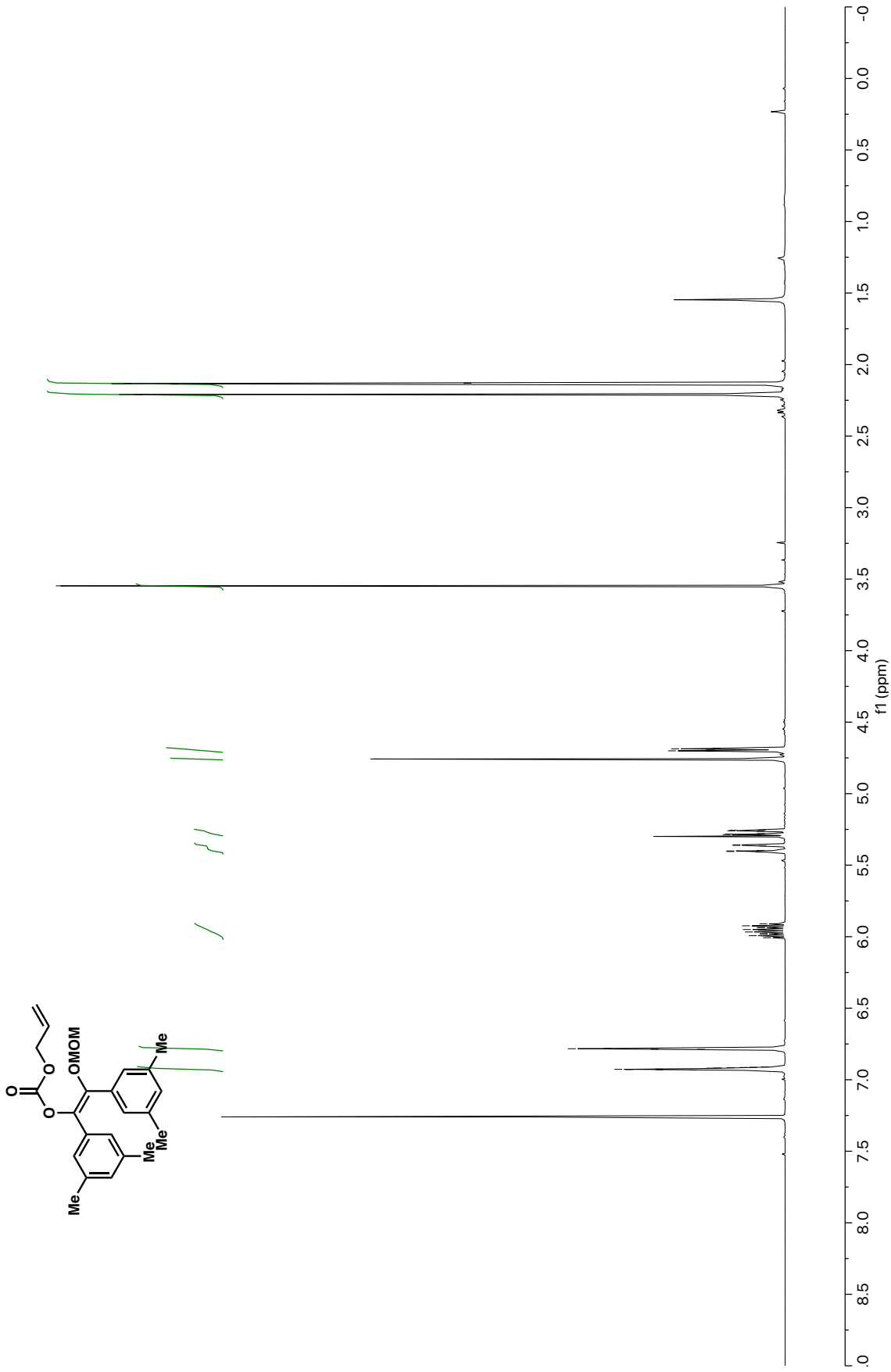



***Figure A7.59*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***80h***.




***A7.60*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***80i.***

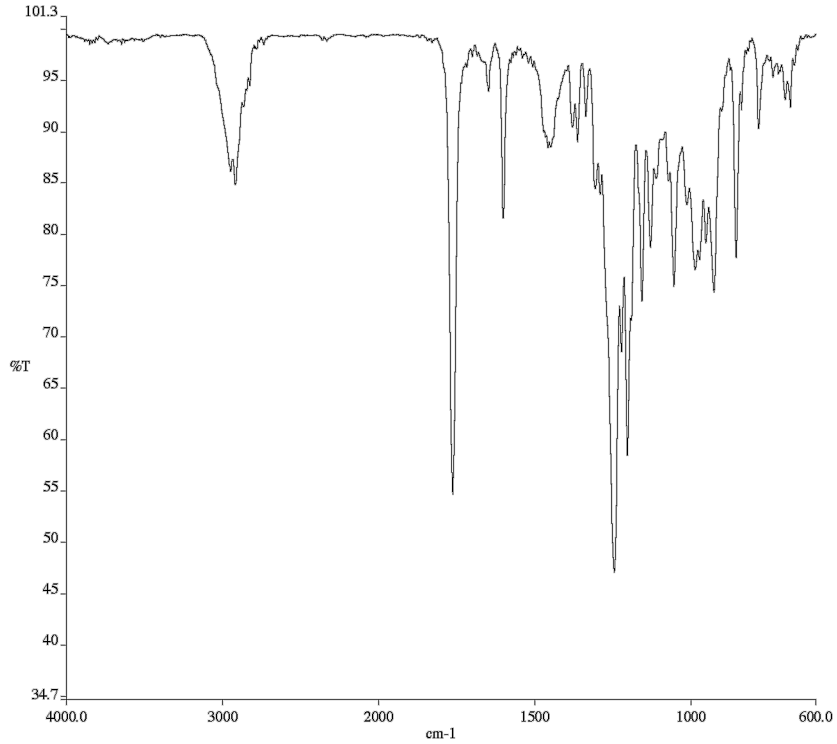



***Figure A7.61*** *Infrared spectrum (Thin Film, NaCl) of compound* ***80i****.*

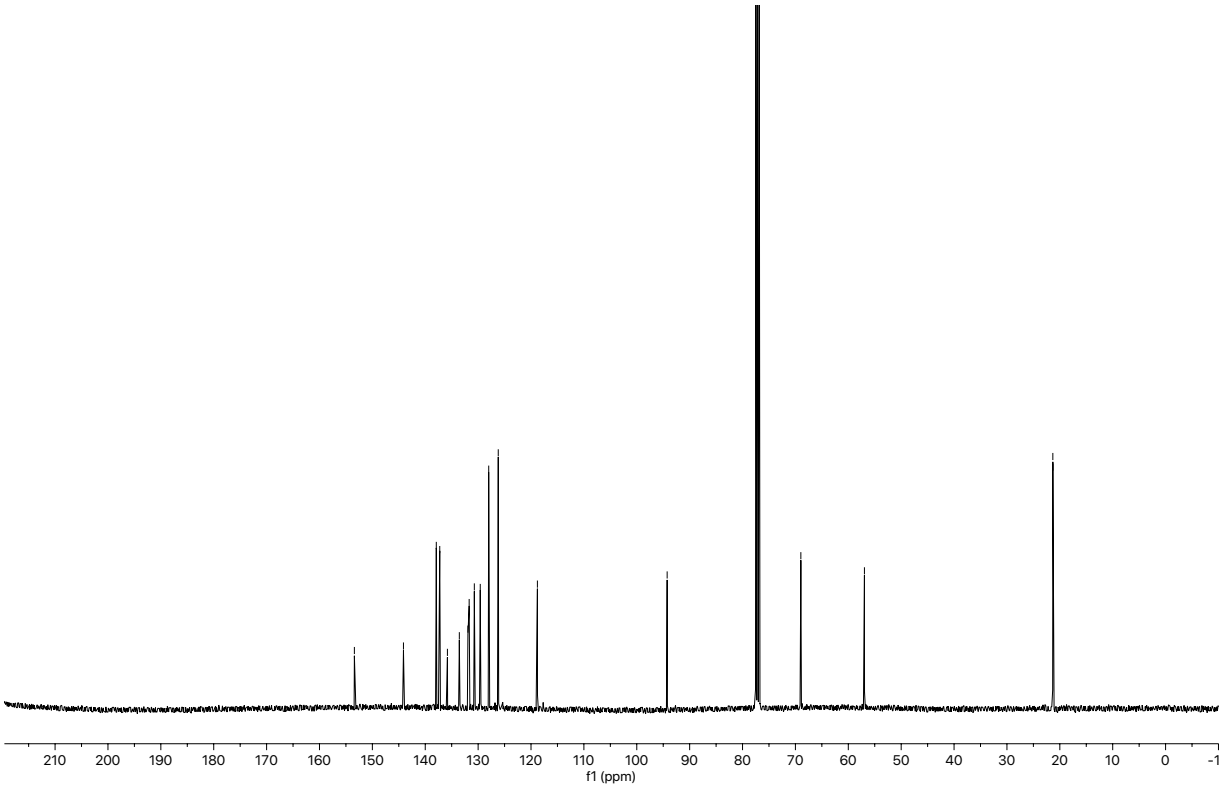
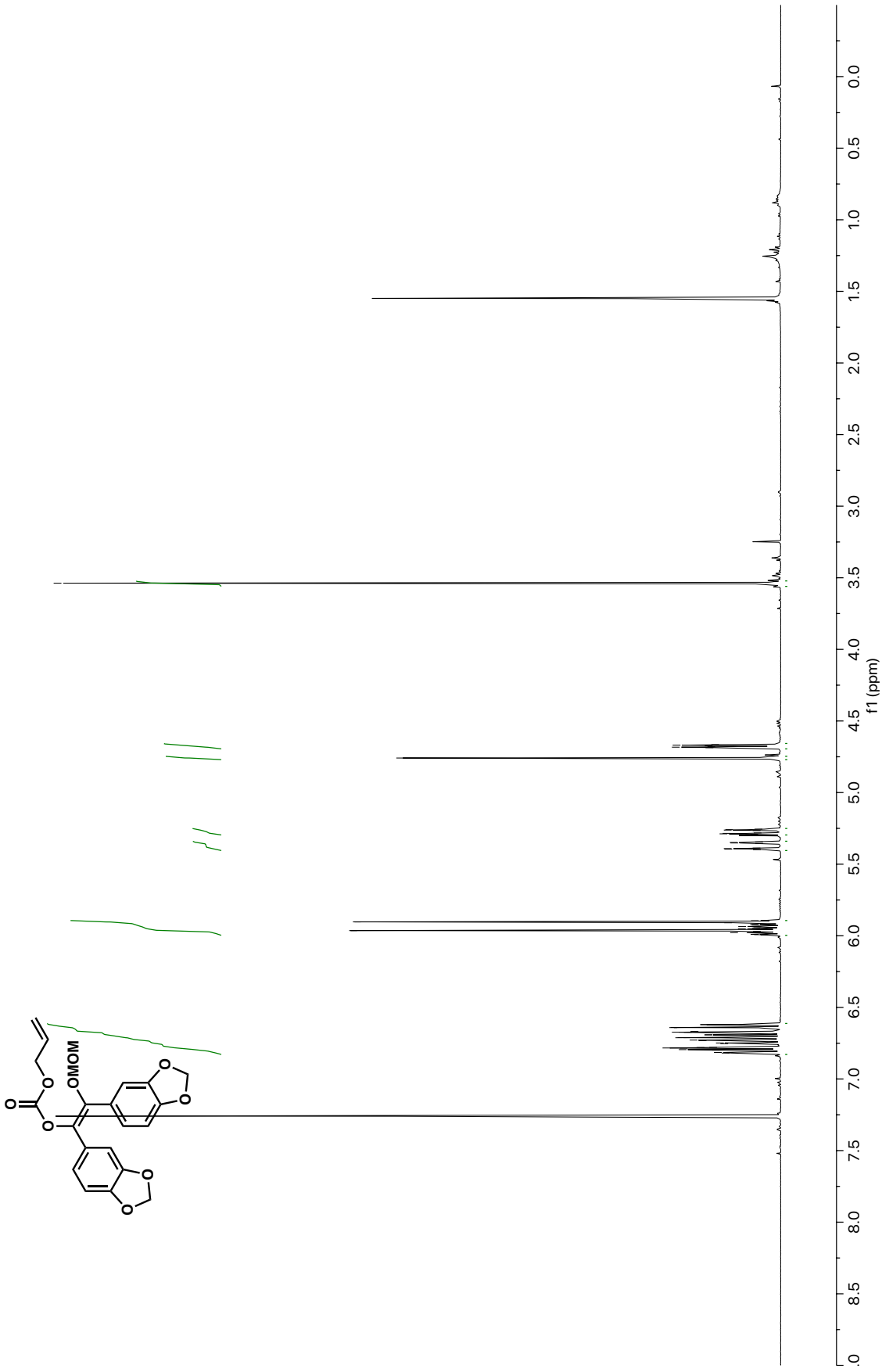



***Figure A7.62*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***80i****.*




***A7.63*** *$^{1}H$ NMR (400 MHz, $CDCl_3$) of compound* ***80j.***

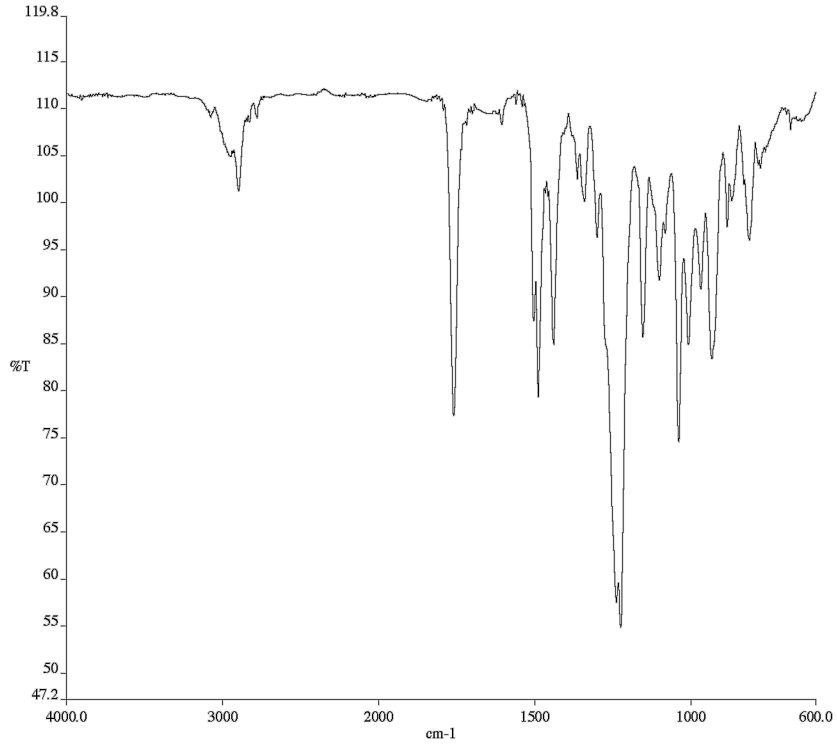



***Figure A7.64*** *Infrared spectrum (Thin Film, NaCl) of compound* ***80j****.*

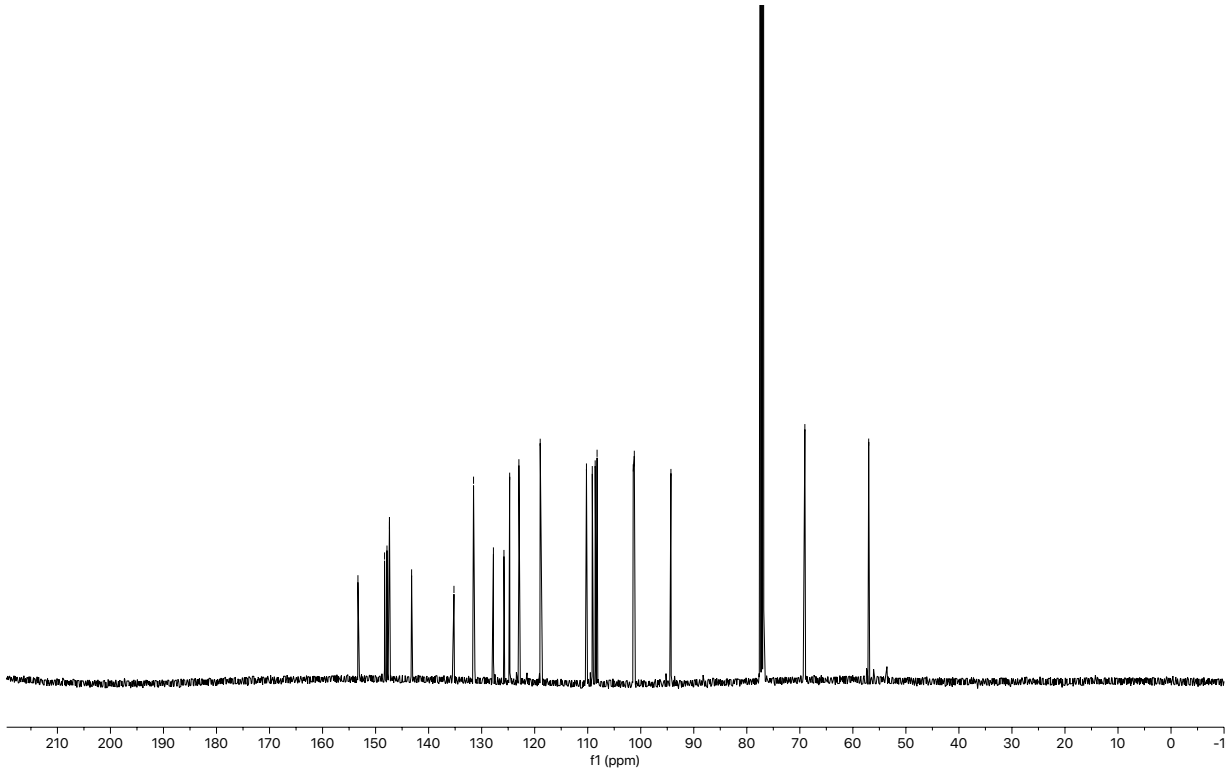
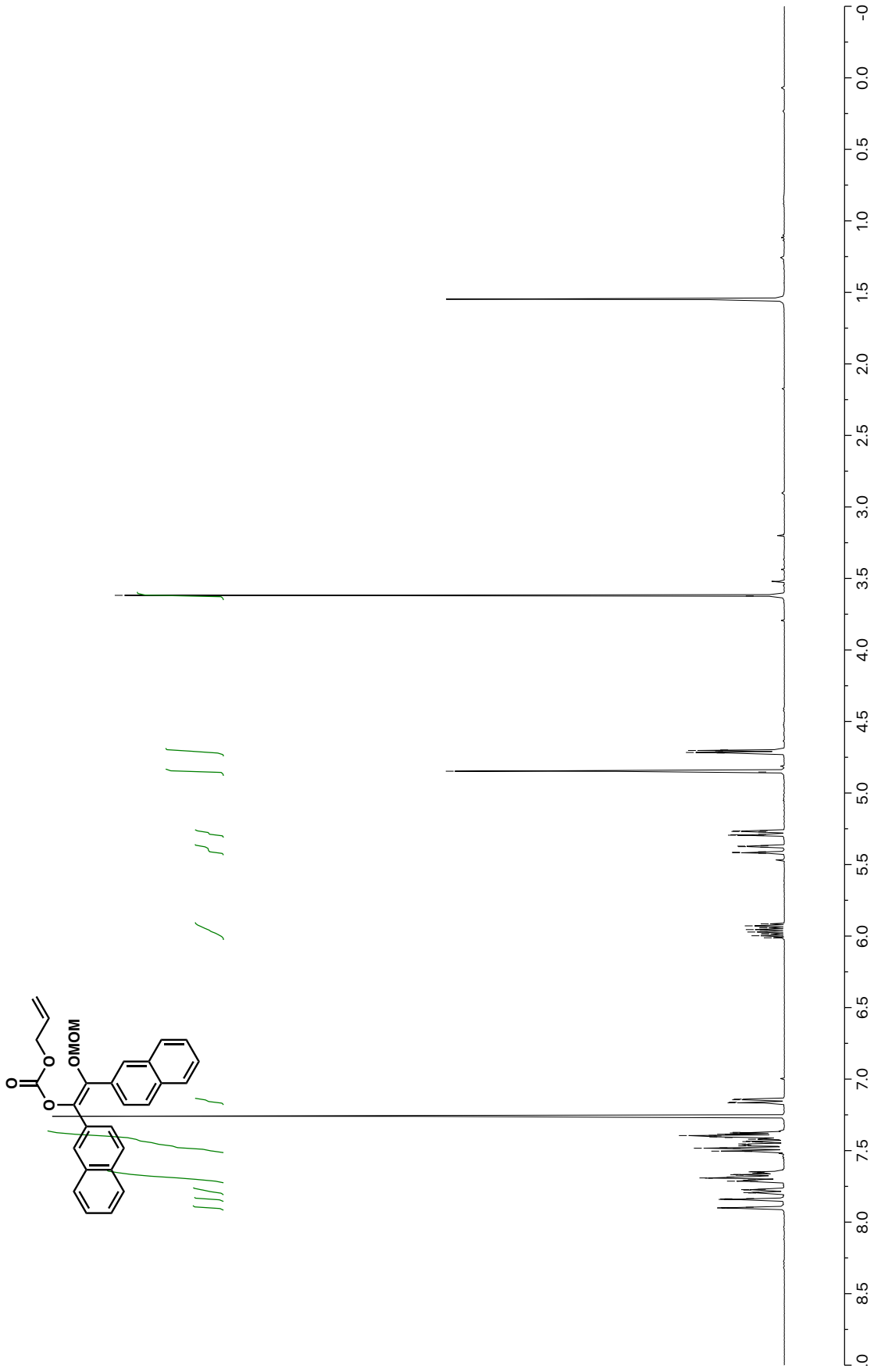



***Figure A7.65*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***80j****.*




***A7.66*** *$^1$H NMR (400 MHz, $CDCl_3$) of compound* ***80k.***

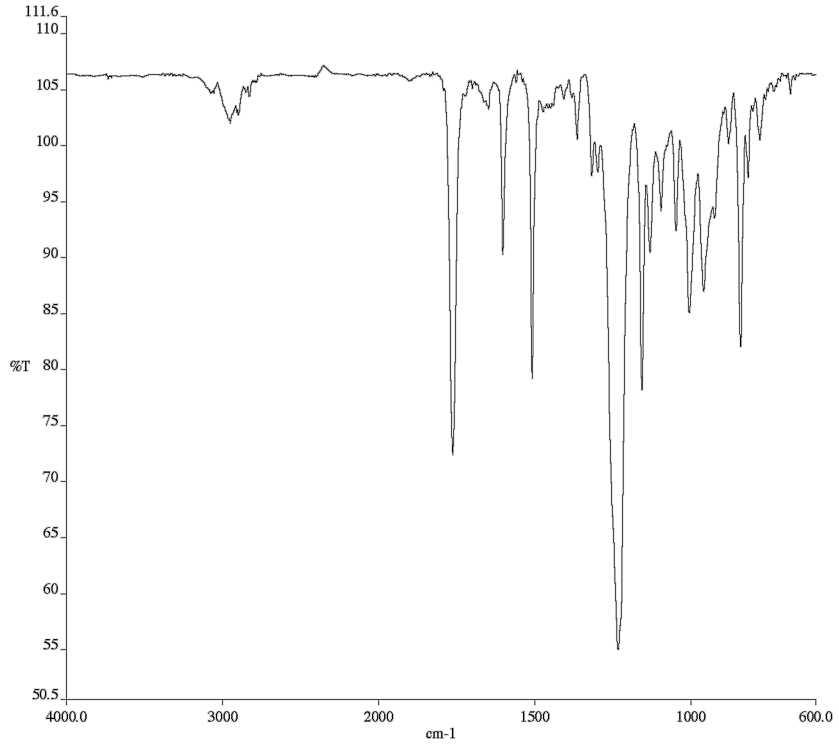



***Figure A7.67*** *Infrared spectrum (Thin Film, NaCl) of compound* ***80k****.*

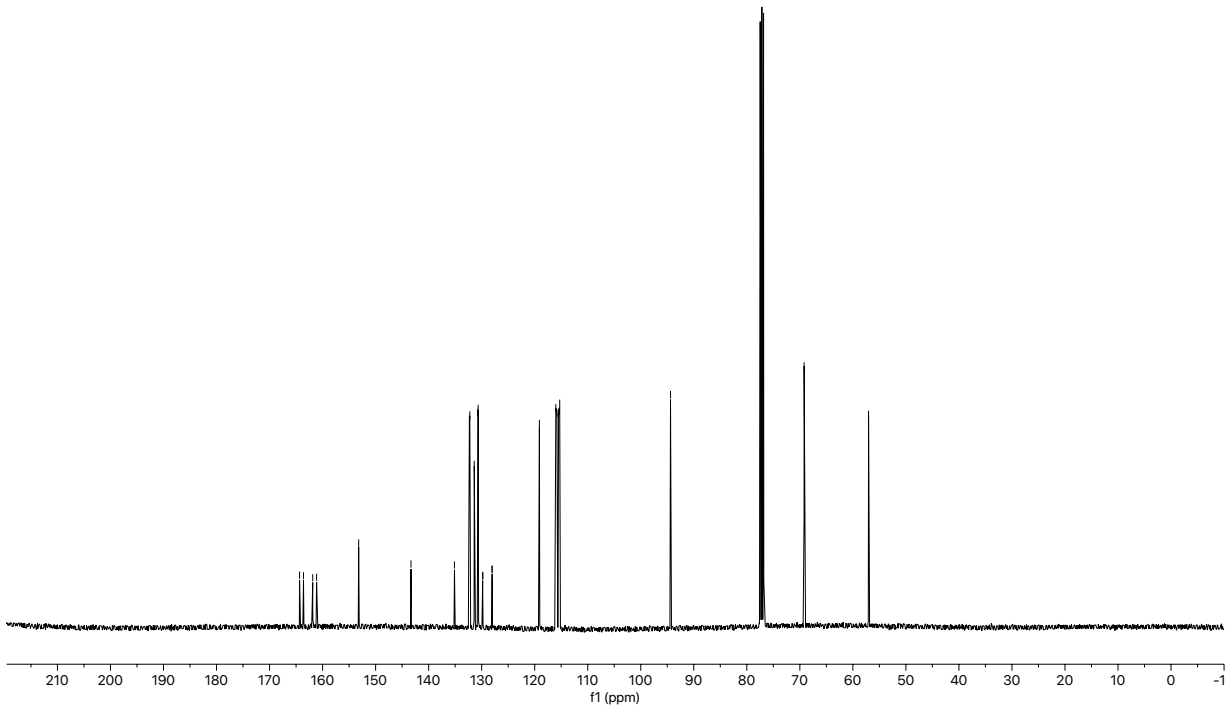
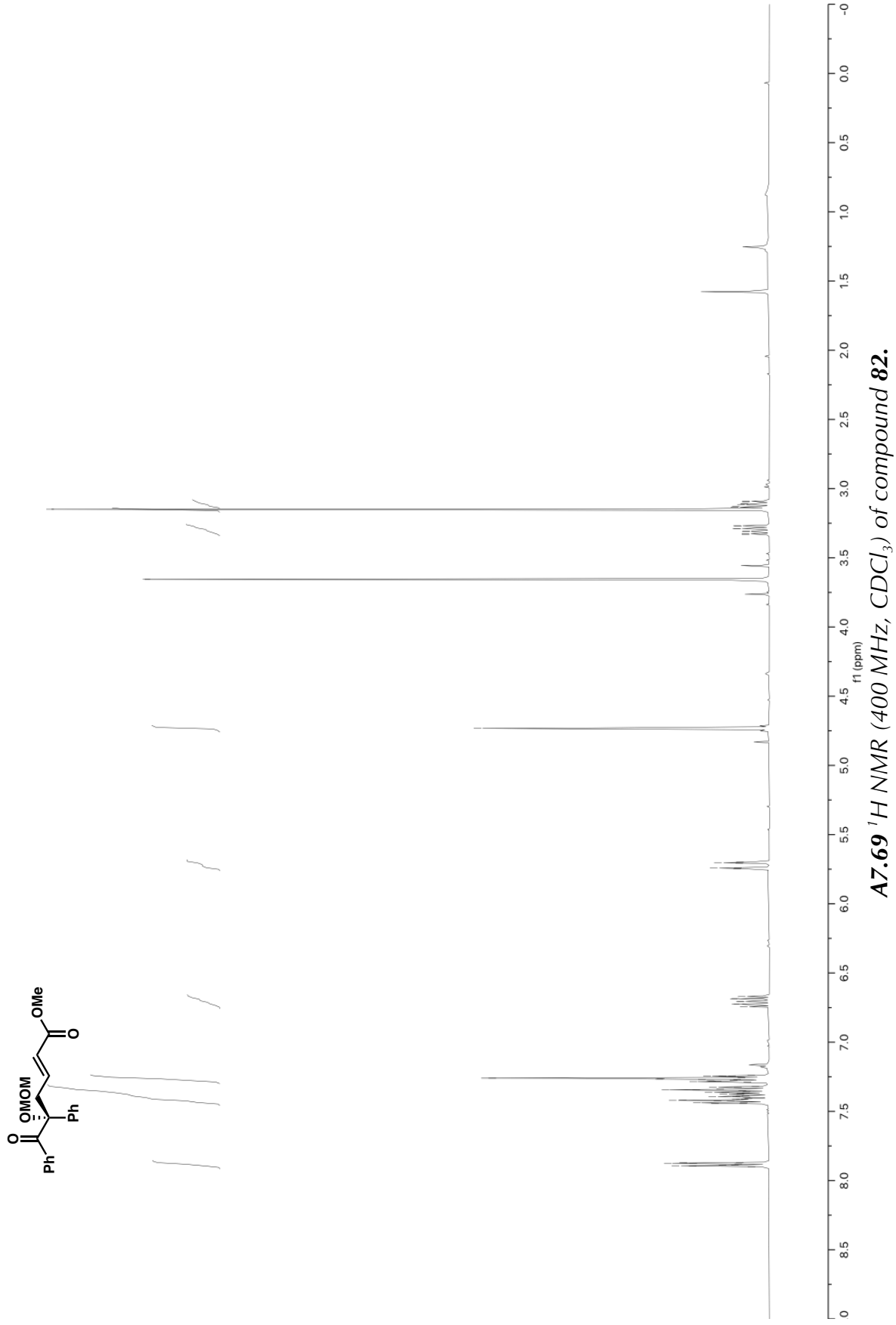



***Figure A7.68*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***80k****.*




***A7.69*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***82.***

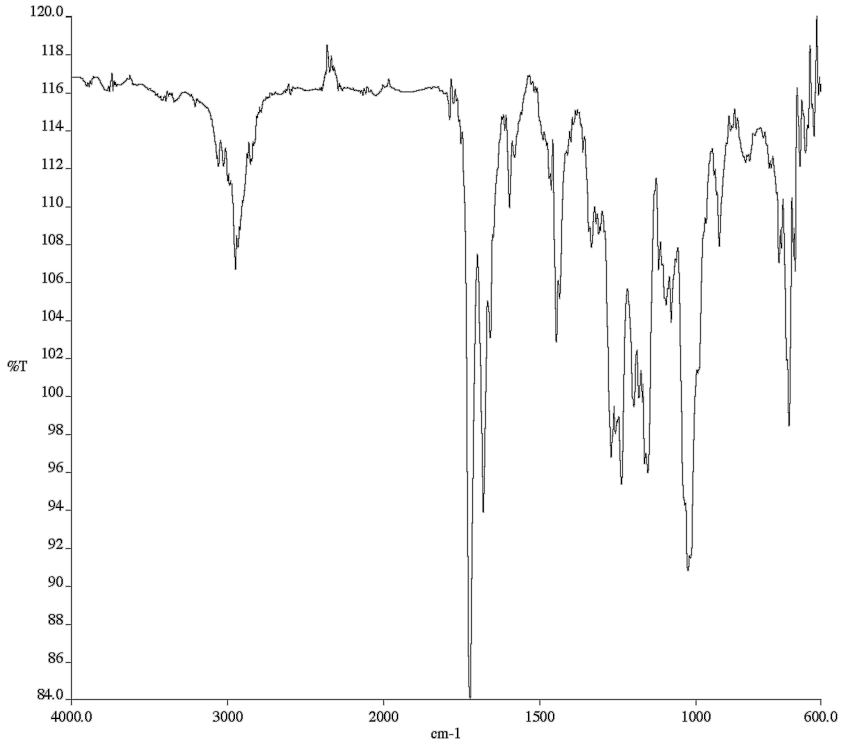



***Figure A7.70*** *Infrared spectrum (Thin Film, NaCl) of compound* ***82***.

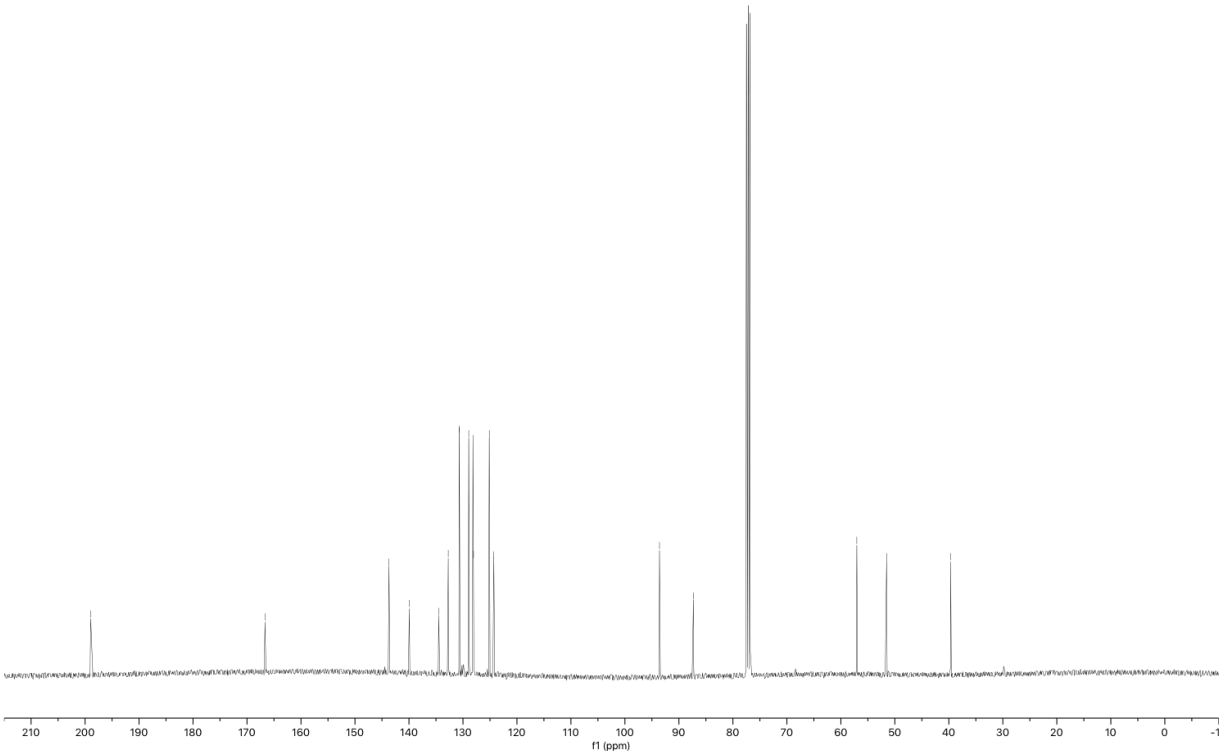
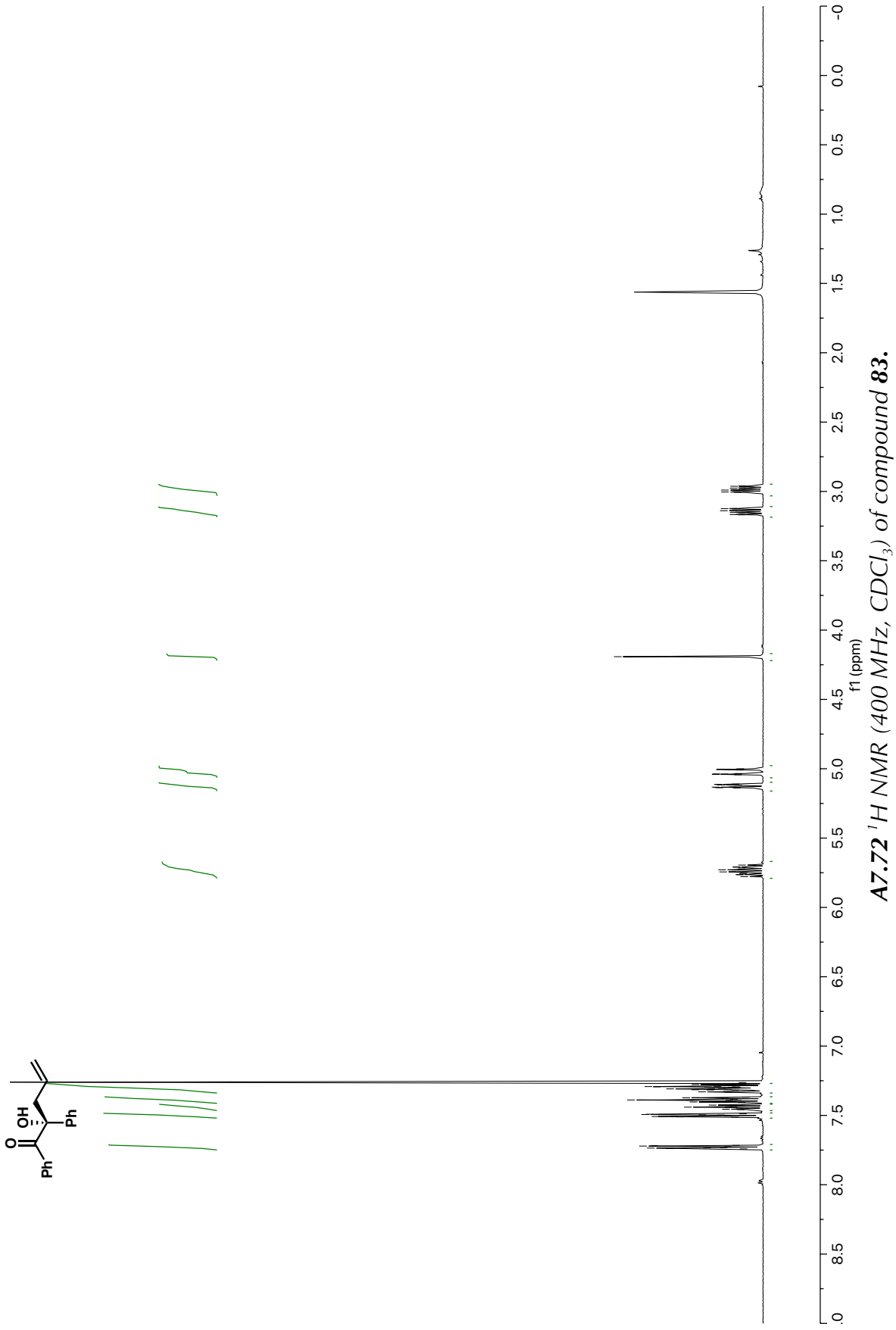



***Figure A7.71*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***82***.




***A7.72*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***83.***

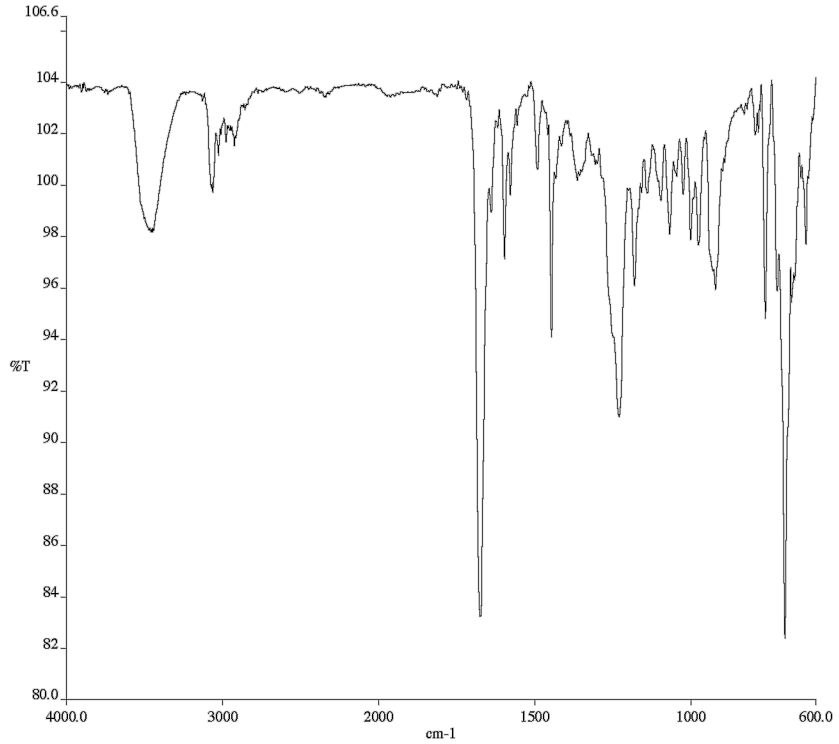



***Figure A7.73*** *Infrared spectrum (Thin Film, NaCl) of compound* ***83***.

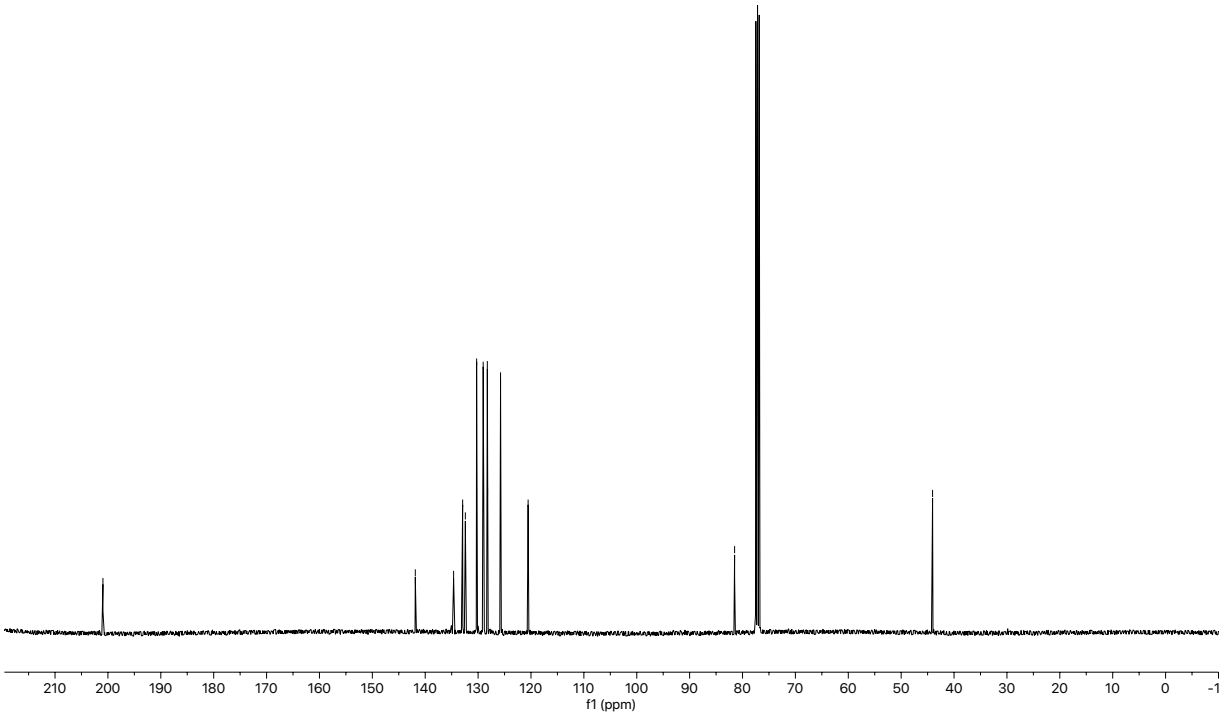
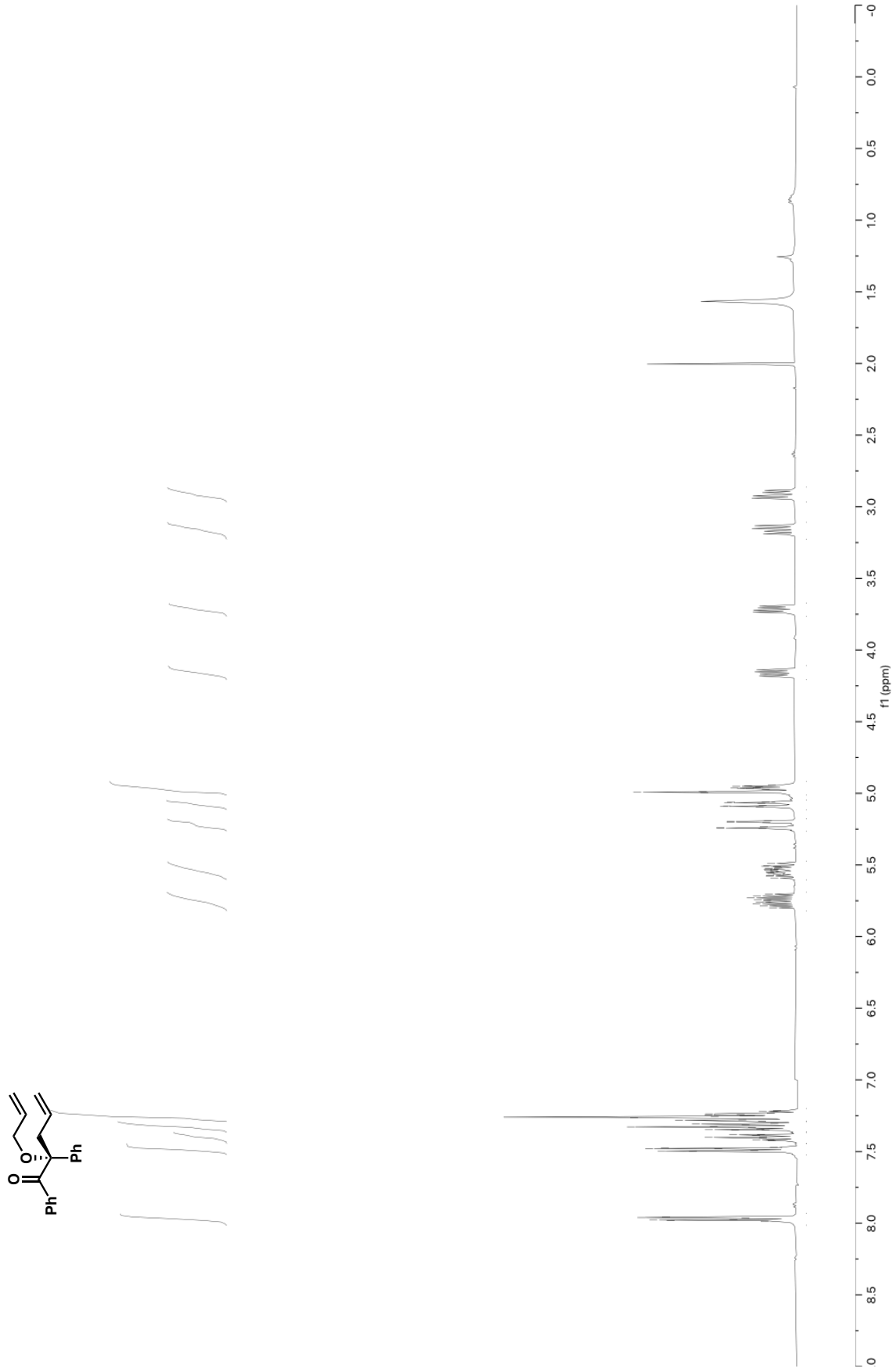



***Figure A7.74*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***83***.




***A7.75*** *$^{1}H$ NMR (400 MHz, $CDCl_3$) of compound* ***86.***

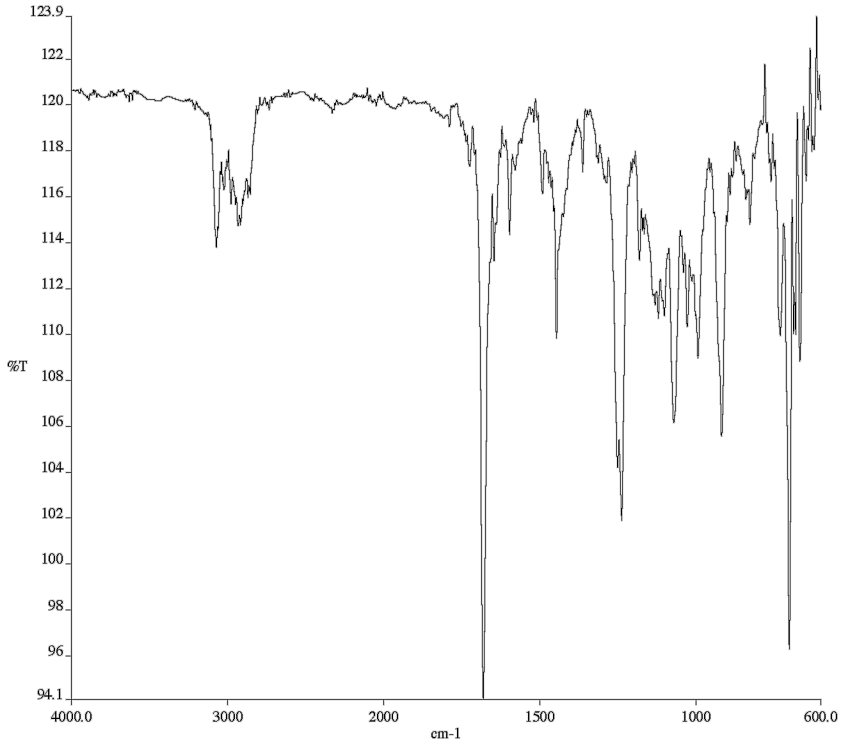



***Figure A7.76*** *Infrared spectrum (Thin Film, NaCl) of compound* ***86***.

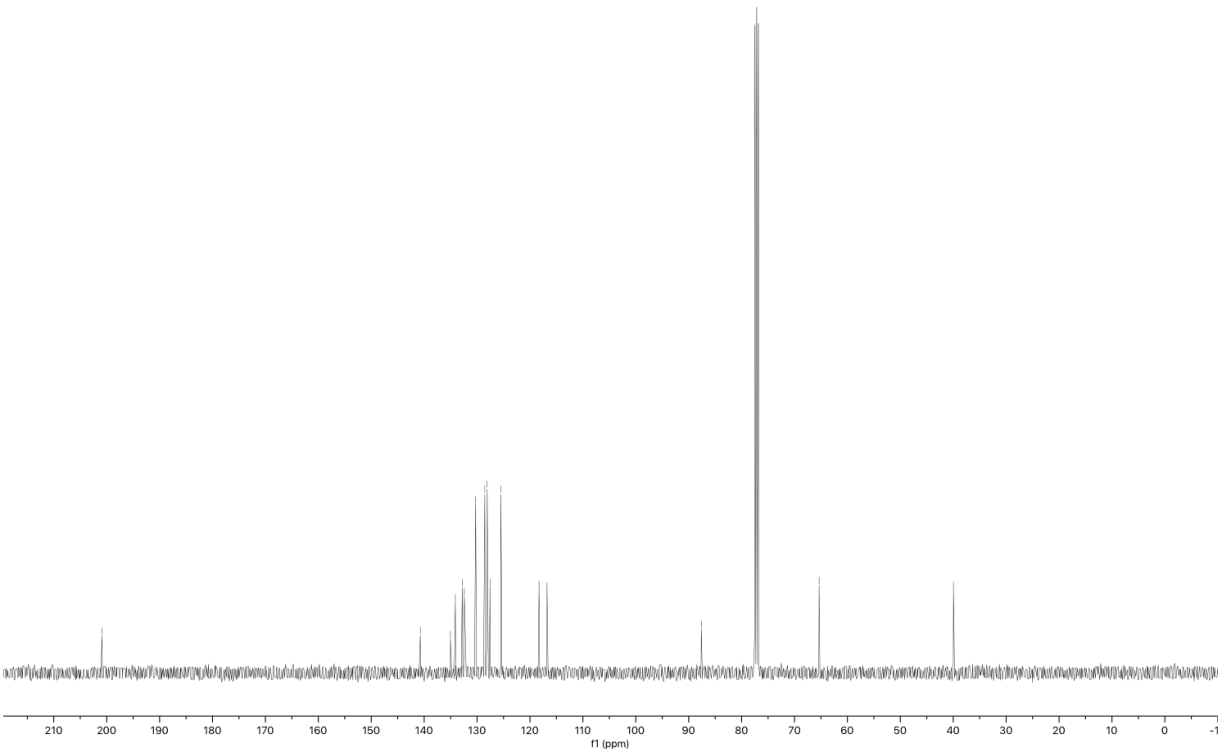
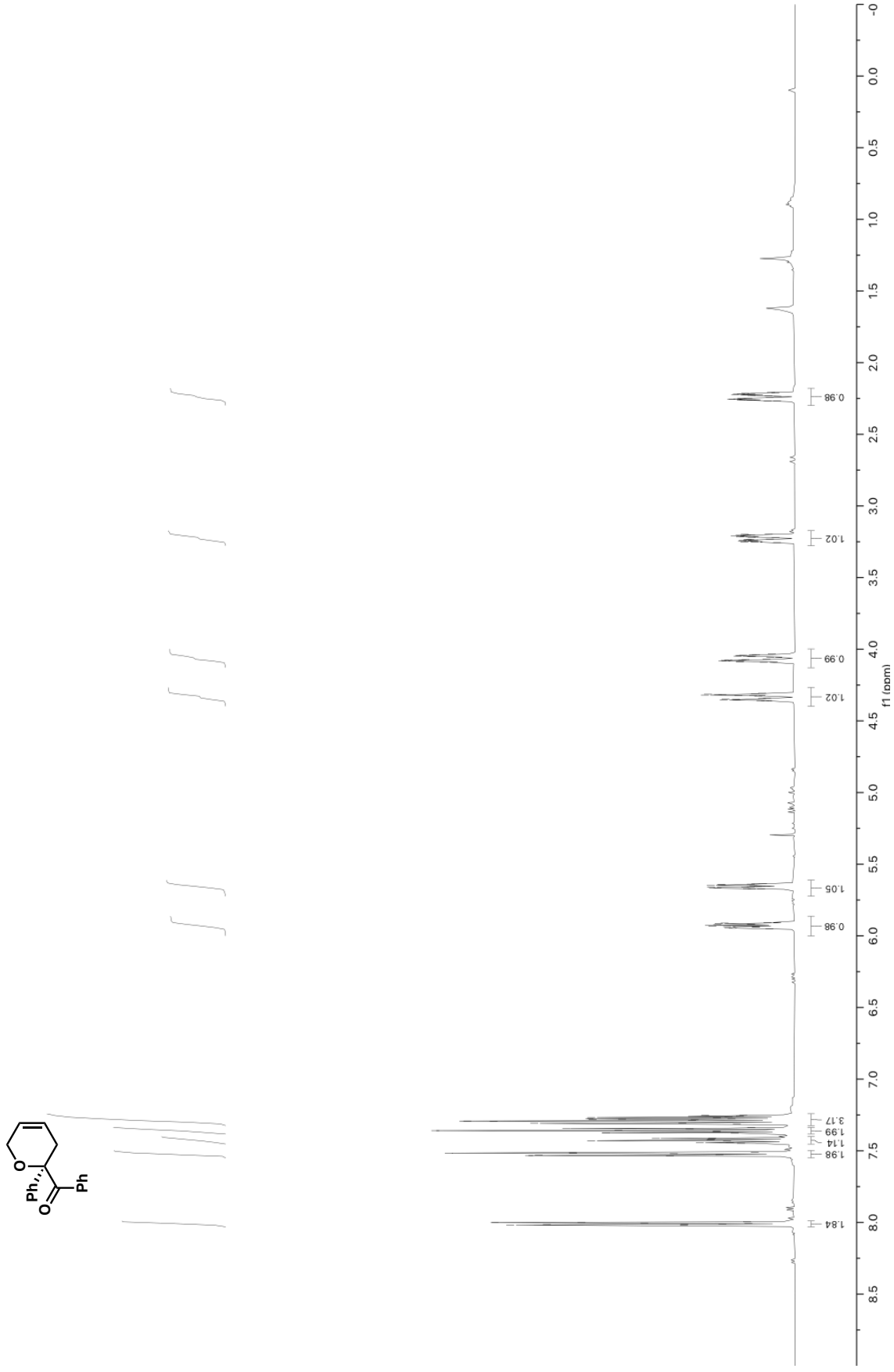



***Figure A7.77*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***86***.


O
Ph
O
Ph
0.98
1.02
0.99
1.02
1.05
0.98
3.17
1.99
1.14
1.98
1.84
f1 (ppm)

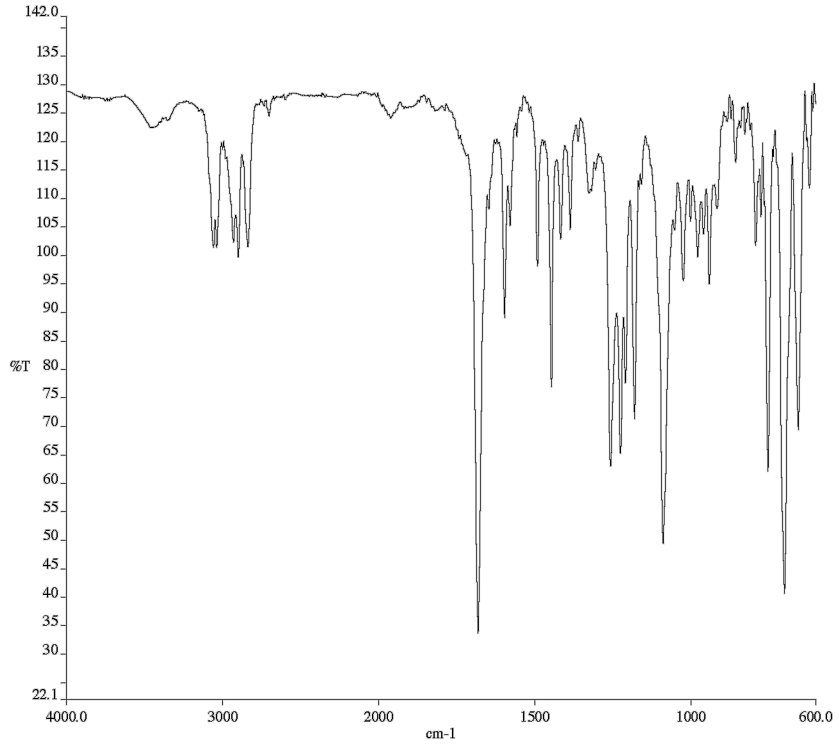



***Figure A7.79*** *Infrared spectrum (Thin Film, NaCl) of compound* ***84****.*

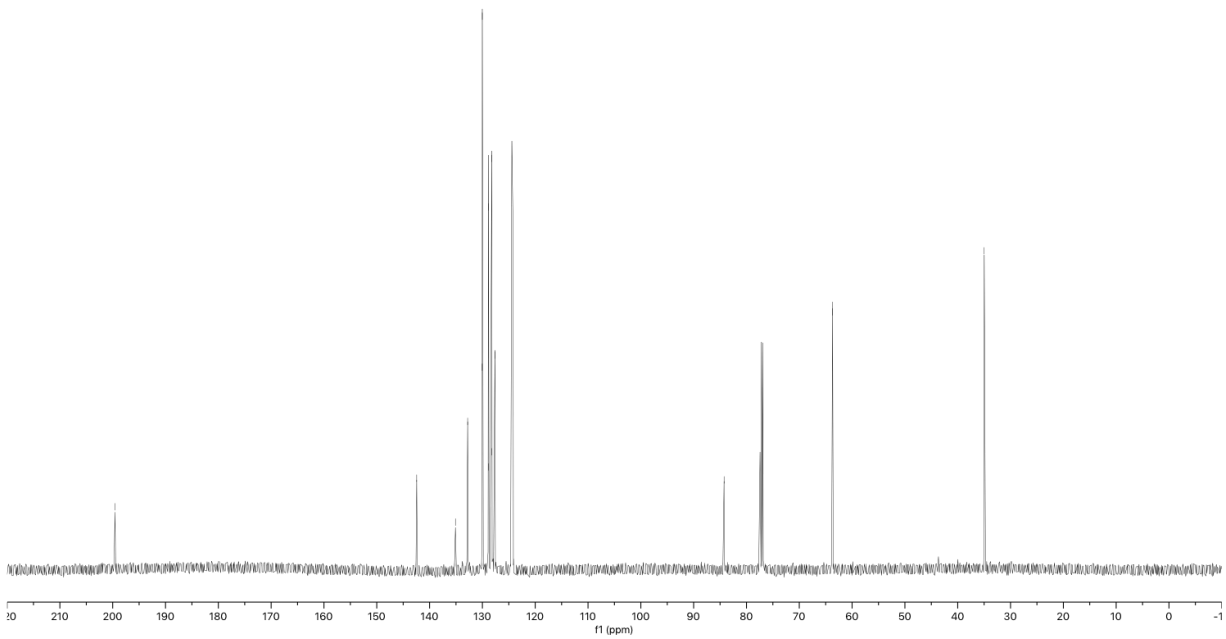
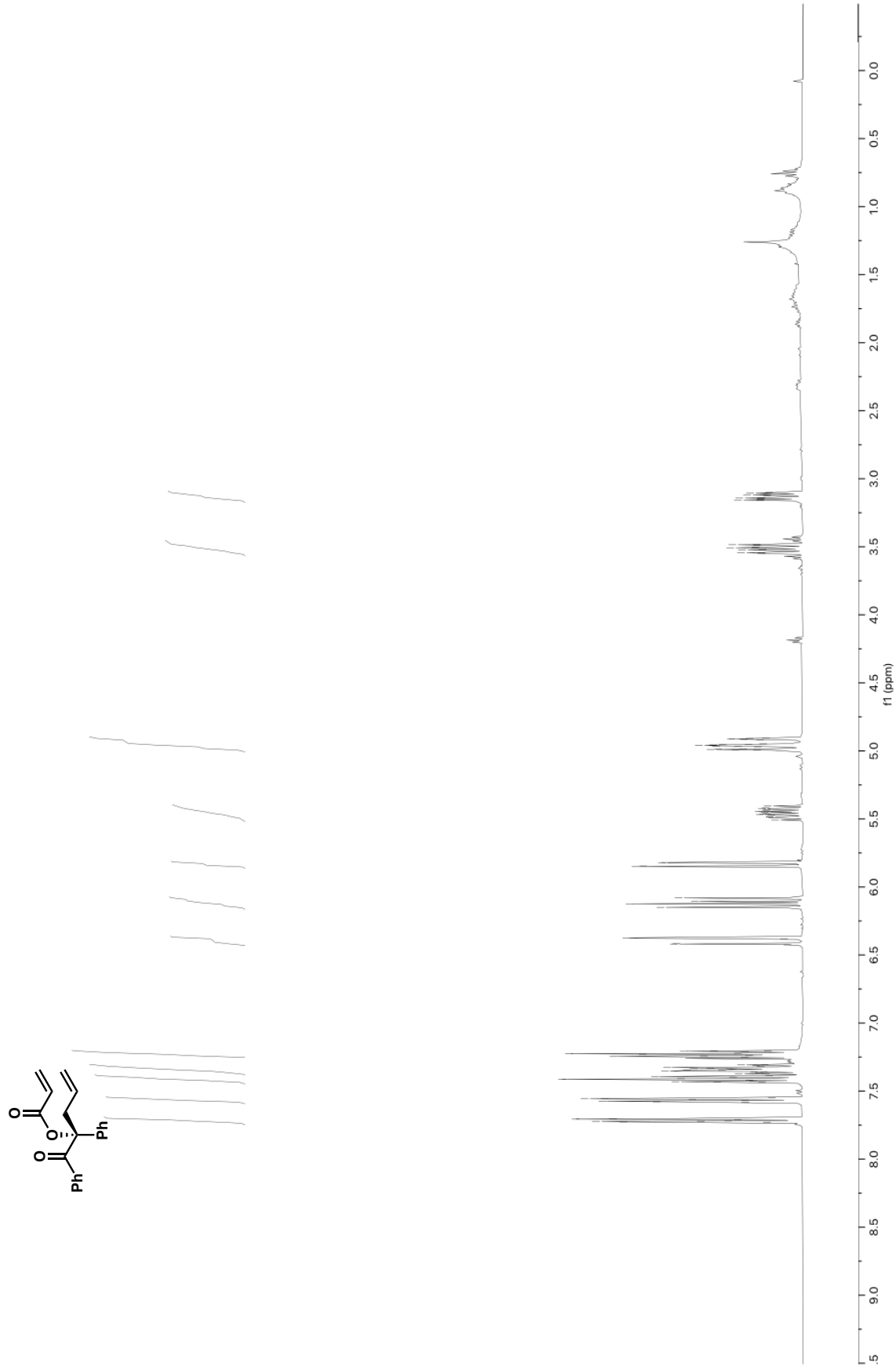



***Figure A7.80*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***84****.*




***A7.81*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***87.***

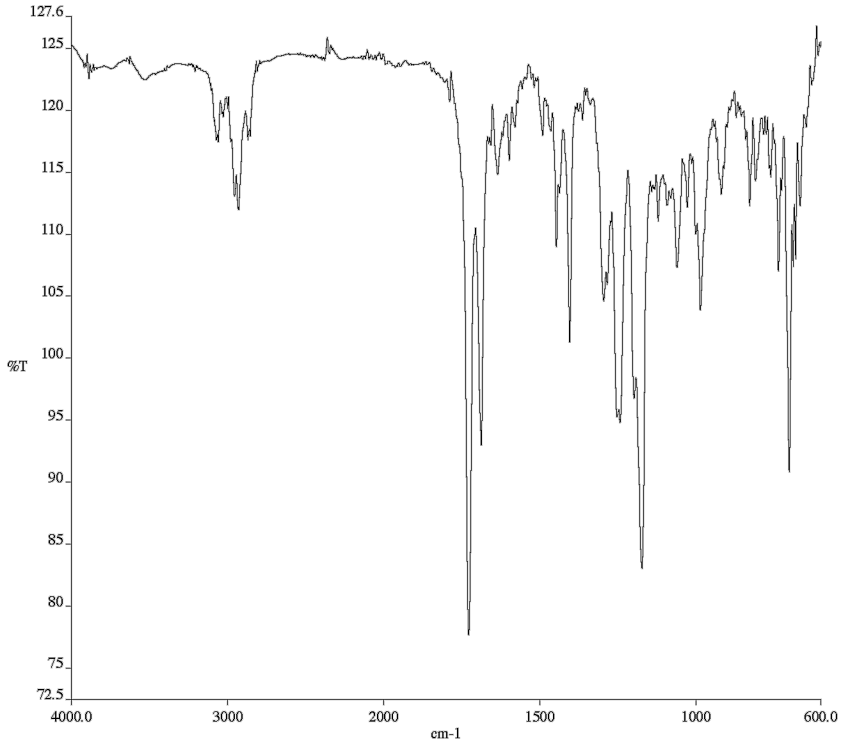



***Figure A7.82*** *Infrared spectrum (Thin Film, NaCl) of compound* ***87****.*

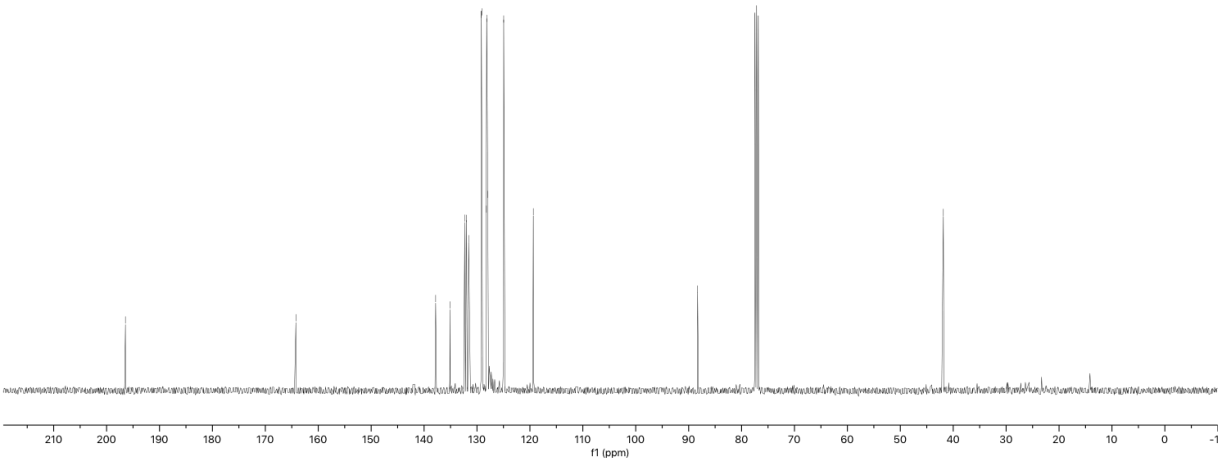
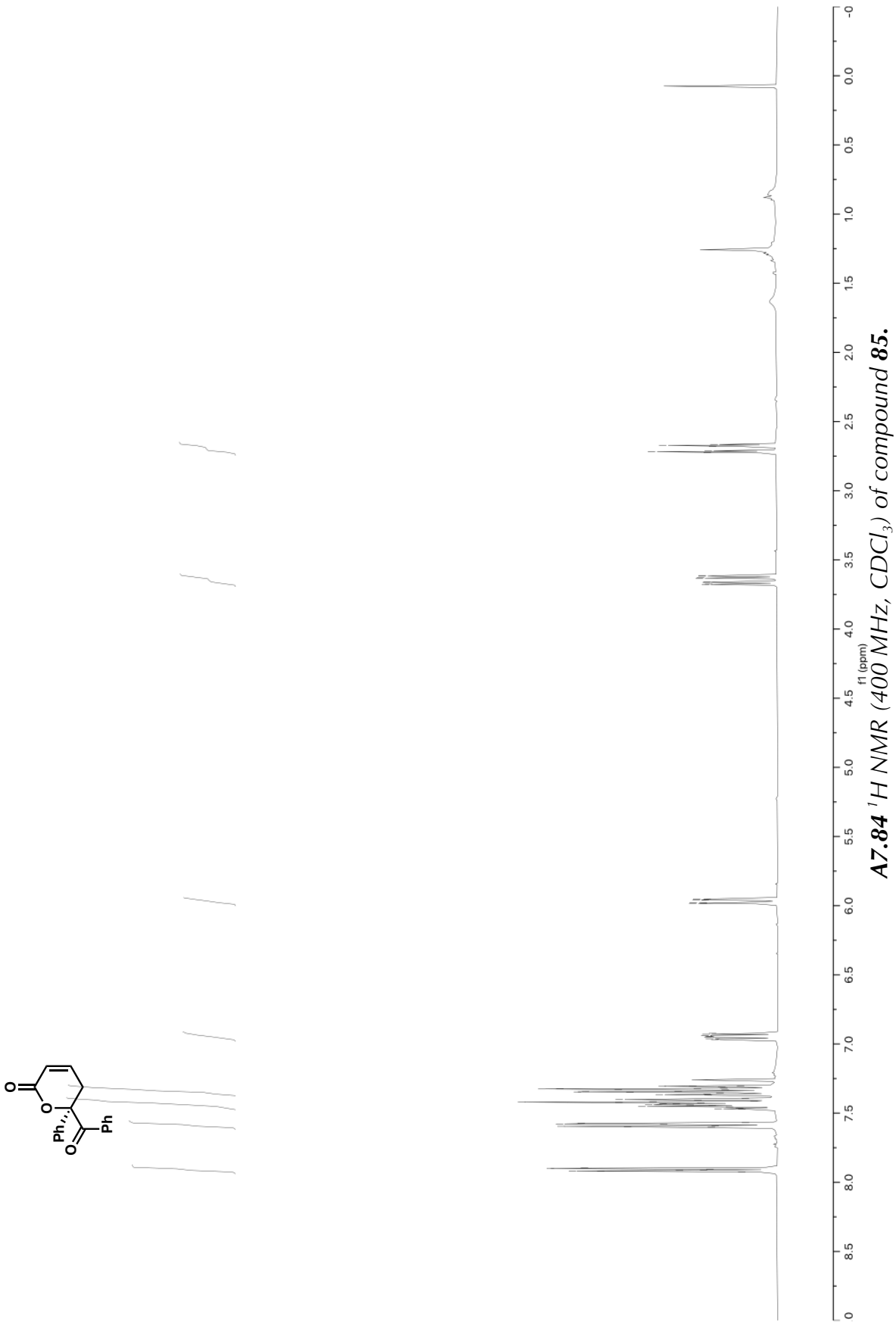



***Figure A7.83*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***87****.*




***A7.84*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***85.***

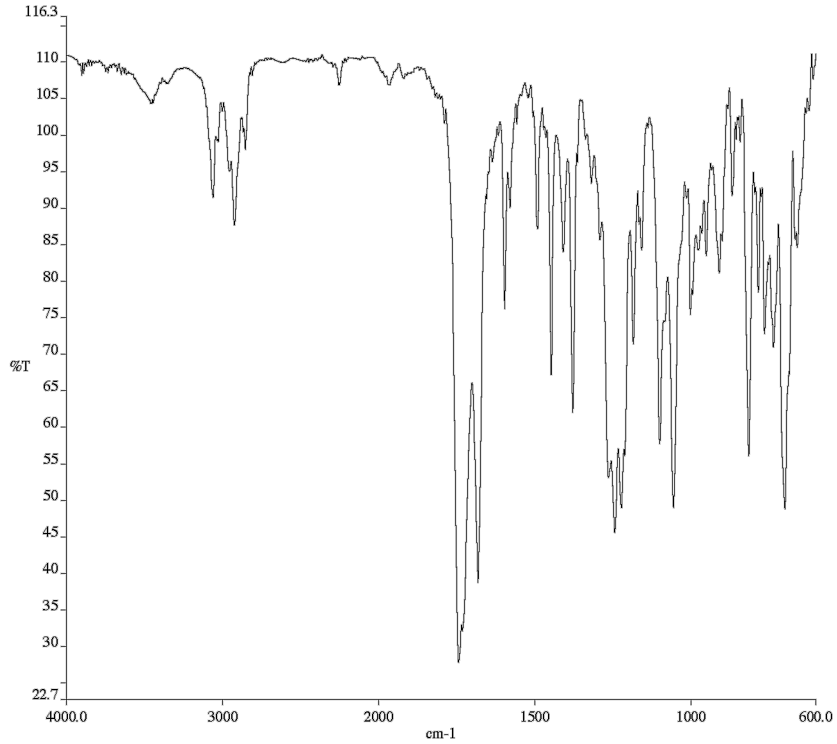



***Figure A7.85*** *Infrared spectrum (Thin Film, NaCl) of compound* ***85***.

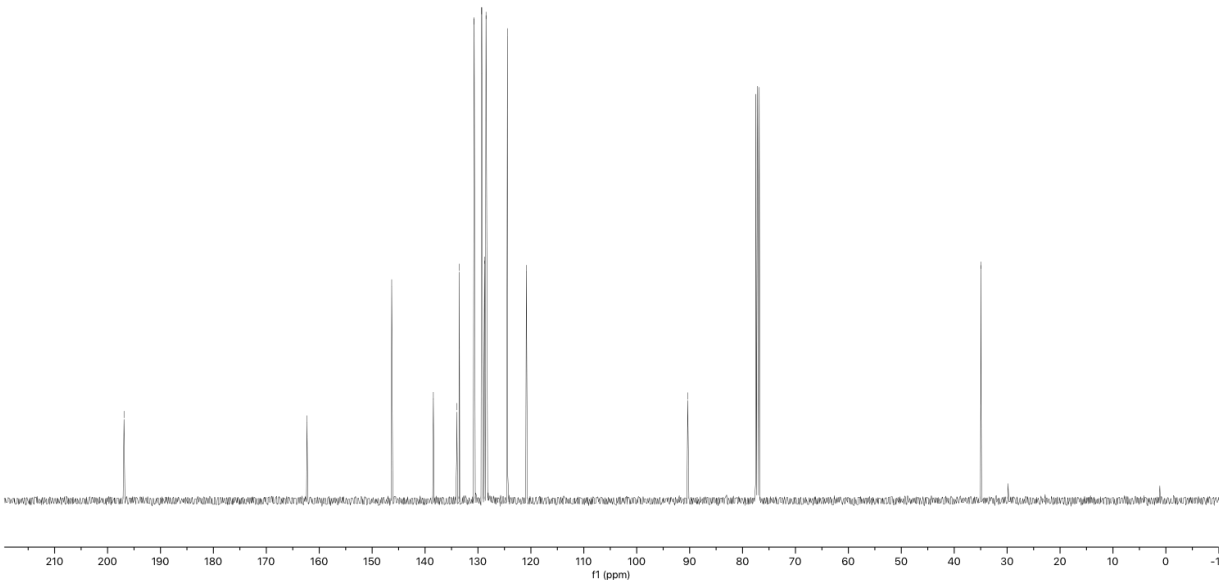
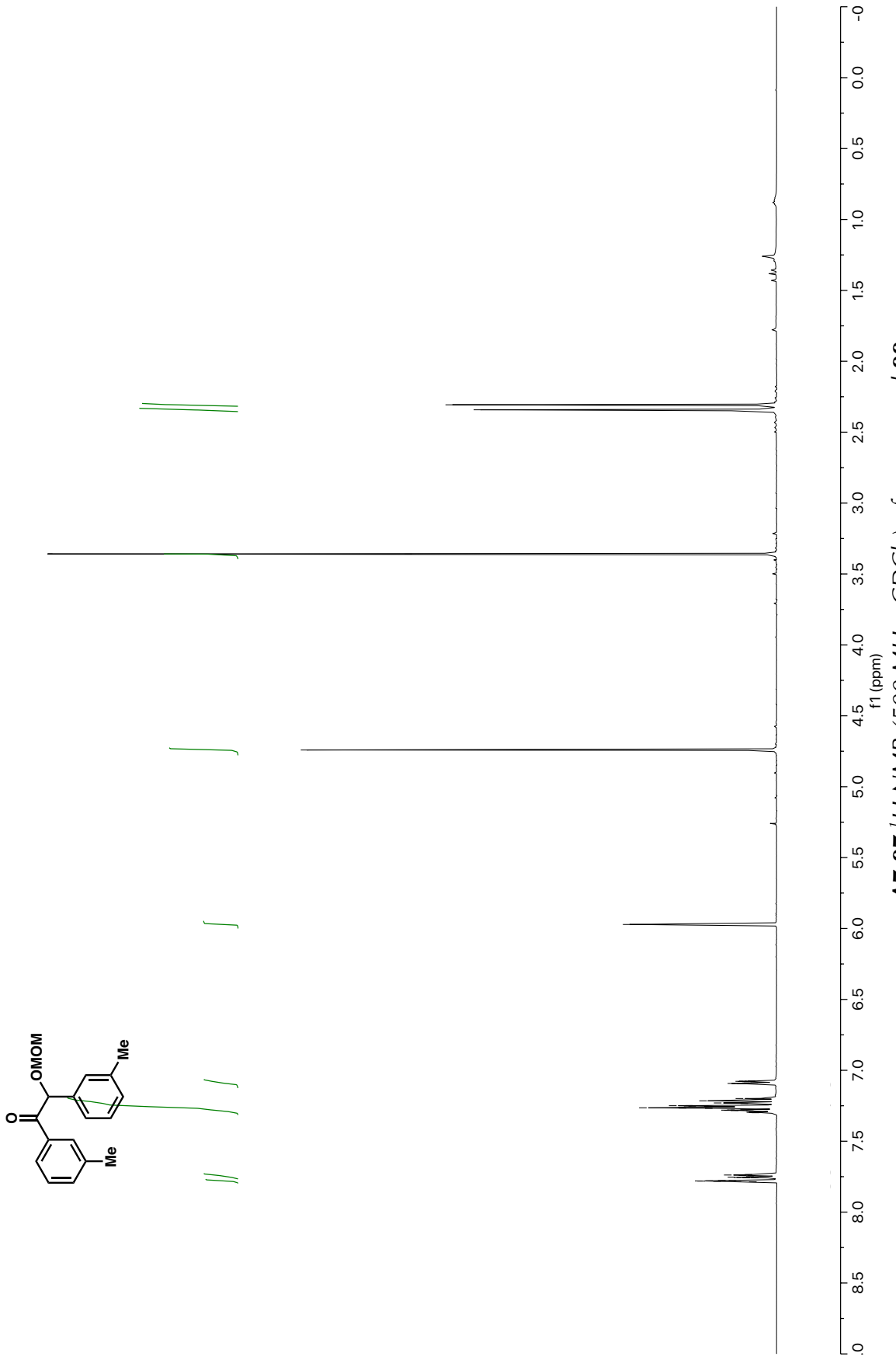



***Figure A7.86*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***85***.




***A7.87*** *$^{1}H$ NMR (500 MHz, $CDCl_3$) of compound* ***88.***

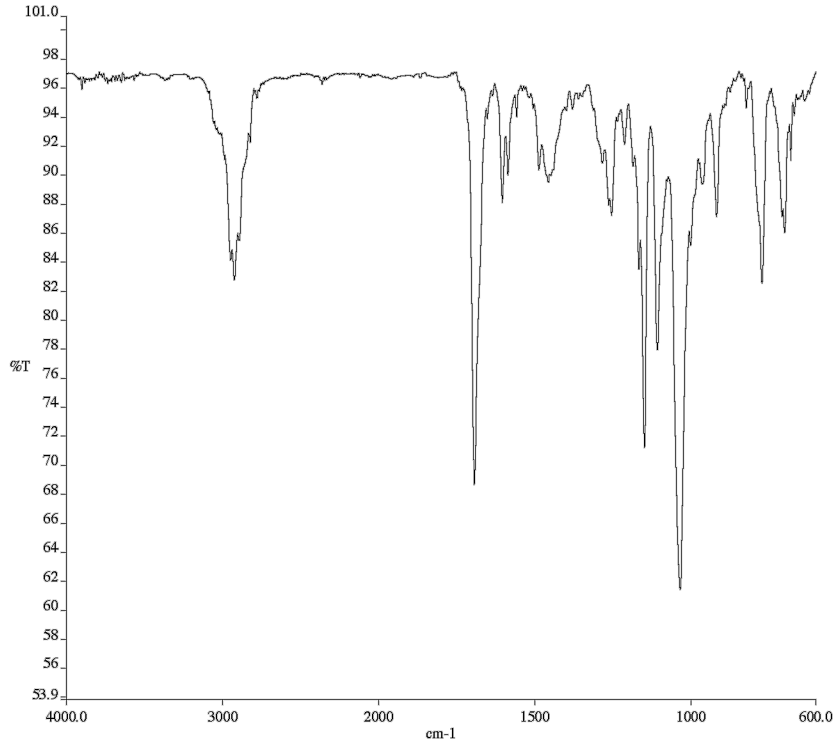



***Figure A7.88*** *Infrared spectrum (Thin Film, NaCl) of compound* ***88****.*

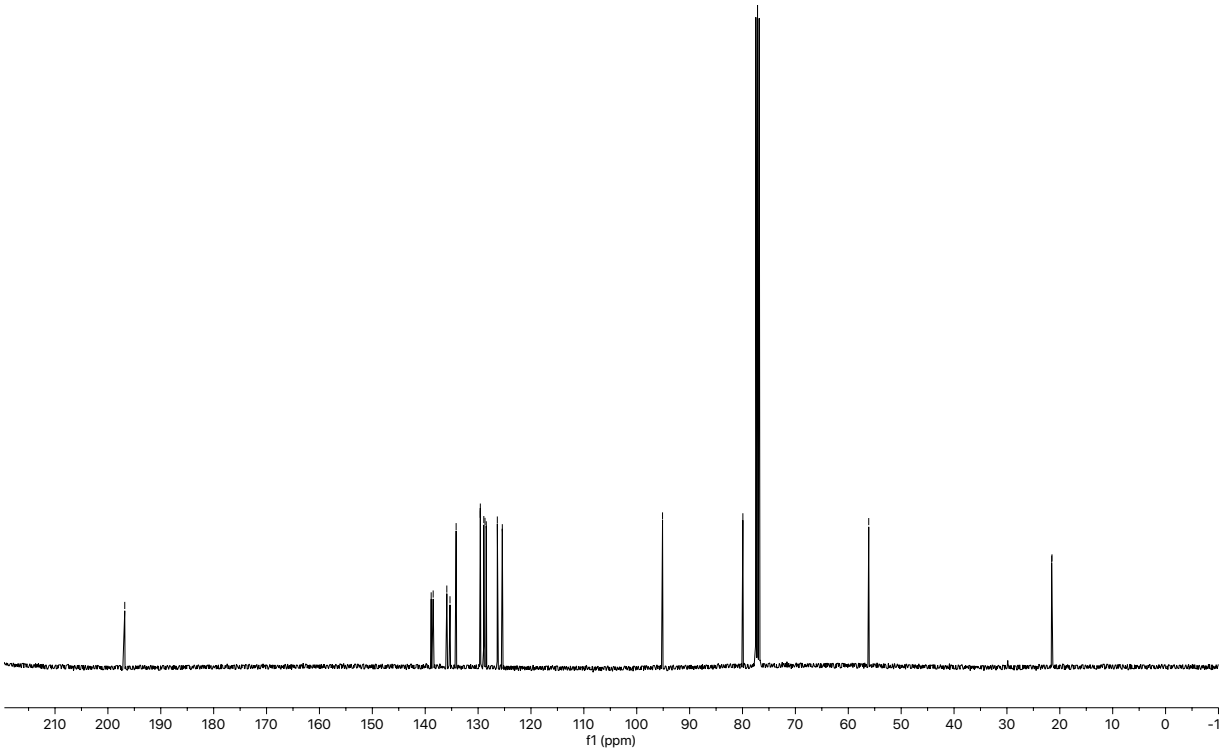
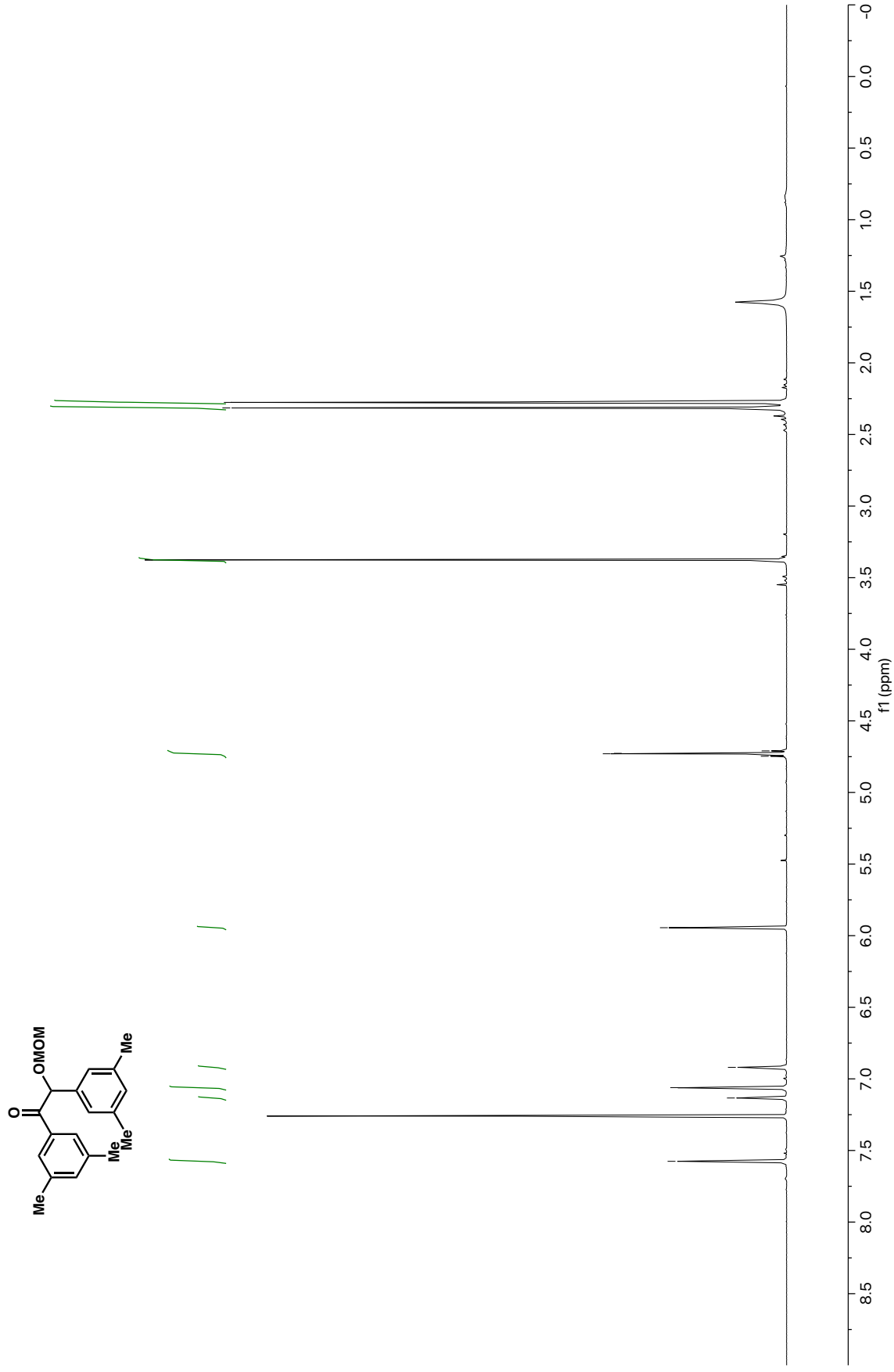



***Figure A7.89*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***88****.*




***A7.90*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***89.***

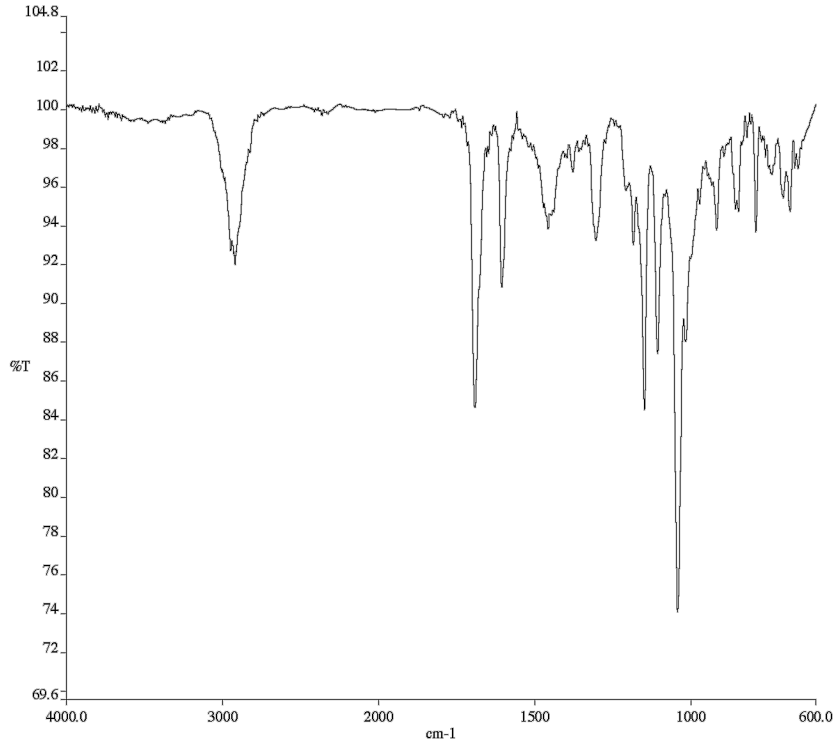



***Figure A7.91*** *Infrared spectrum (Thin Film, NaCl) of compound* ***89***.

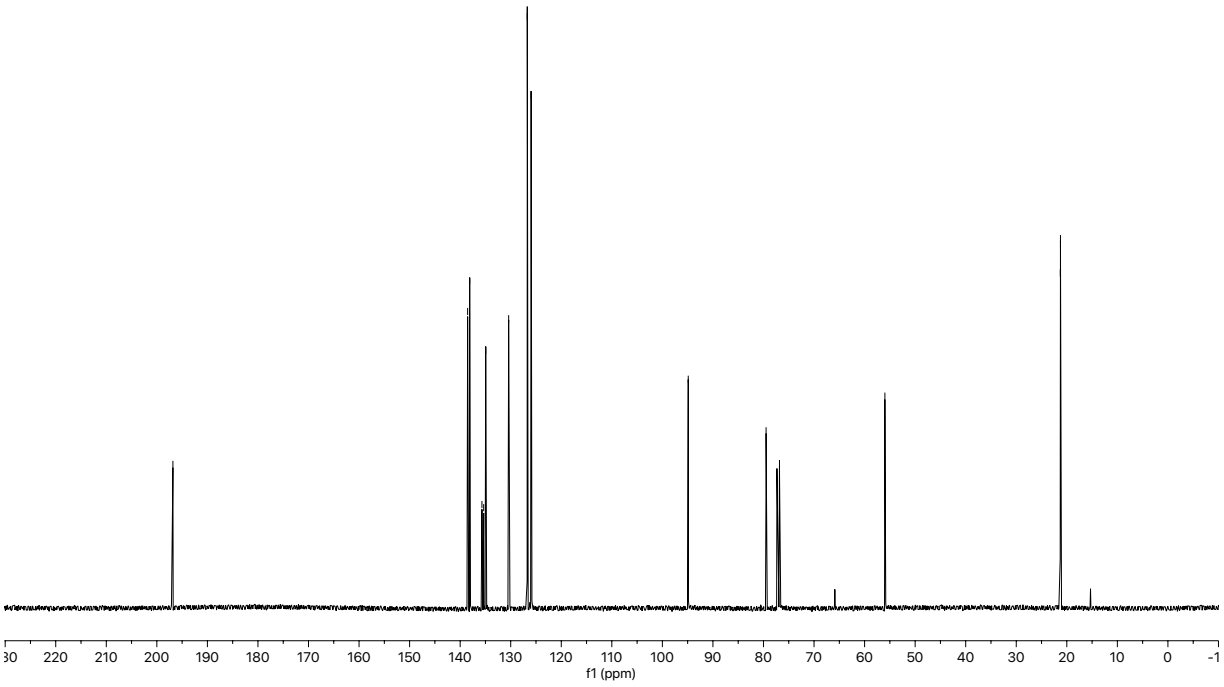
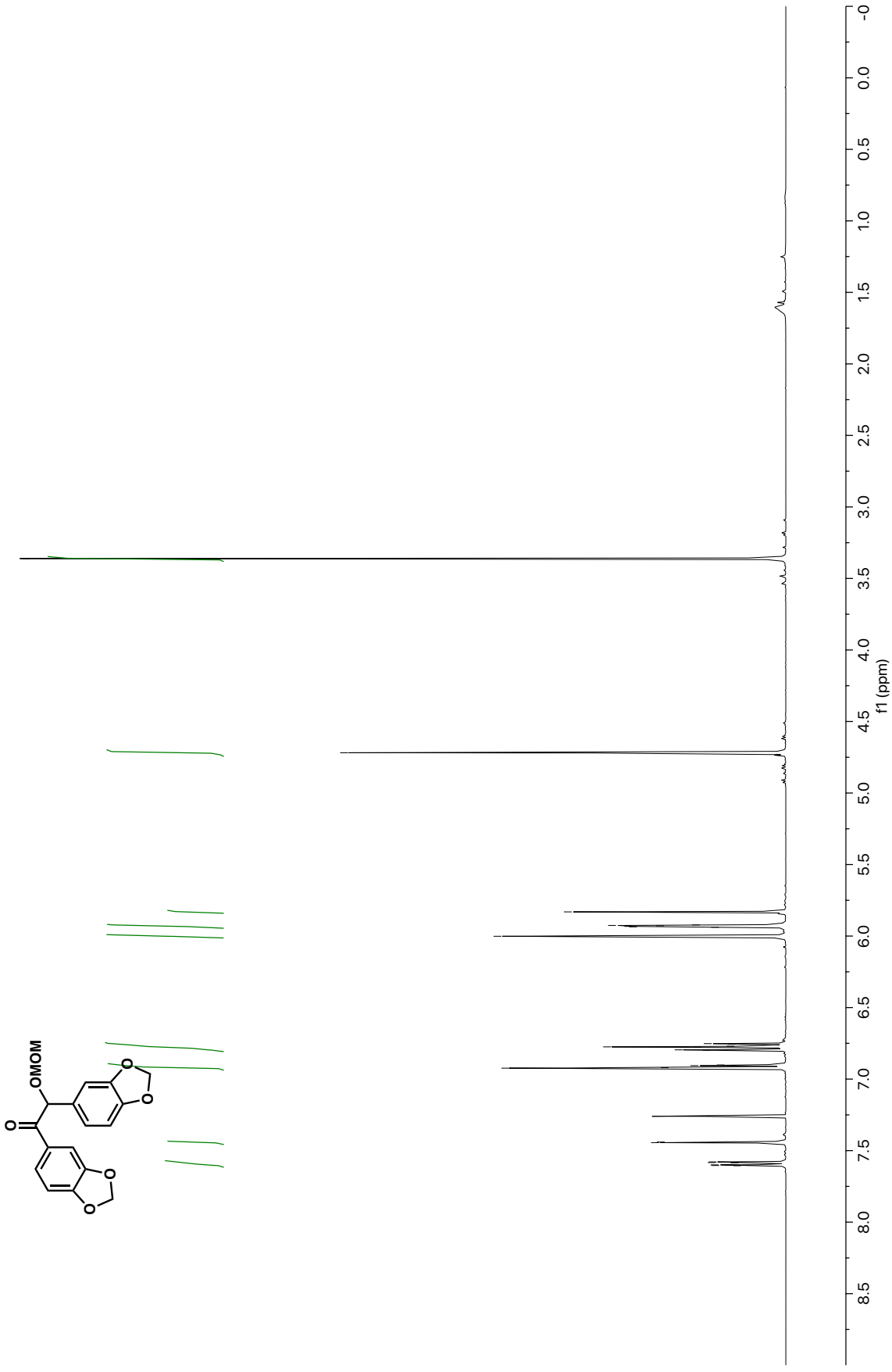



***Figure A7.92*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***89***.




***A7.93*** *$^{1}H$ NMR (500 MHz, $CDCl_3$) of compound* ***90.***

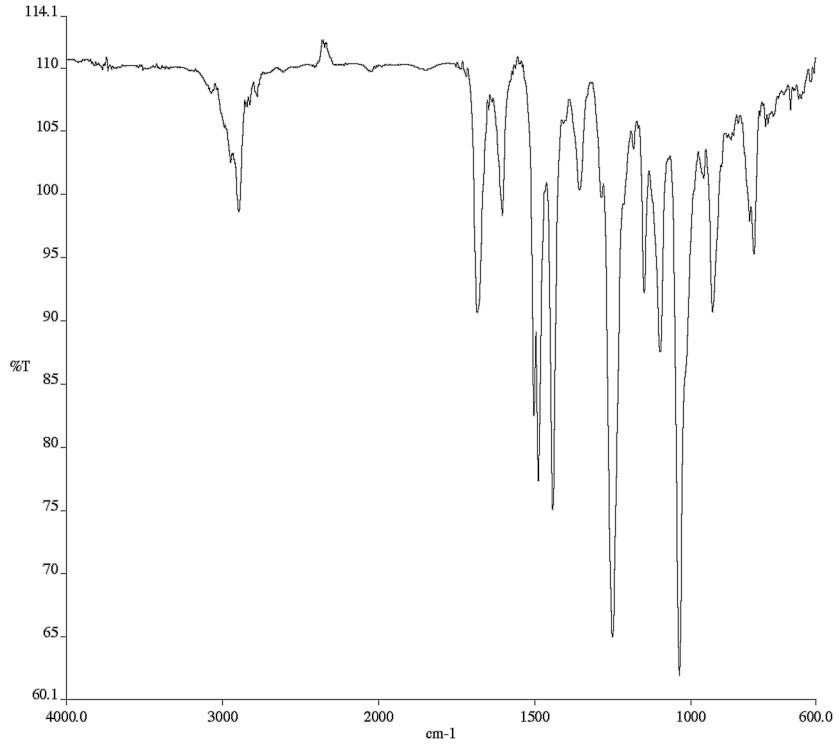



***Figure A7.94*** *Infrared spectrum (Thin Film, NaCl) of compound* ***90****.*

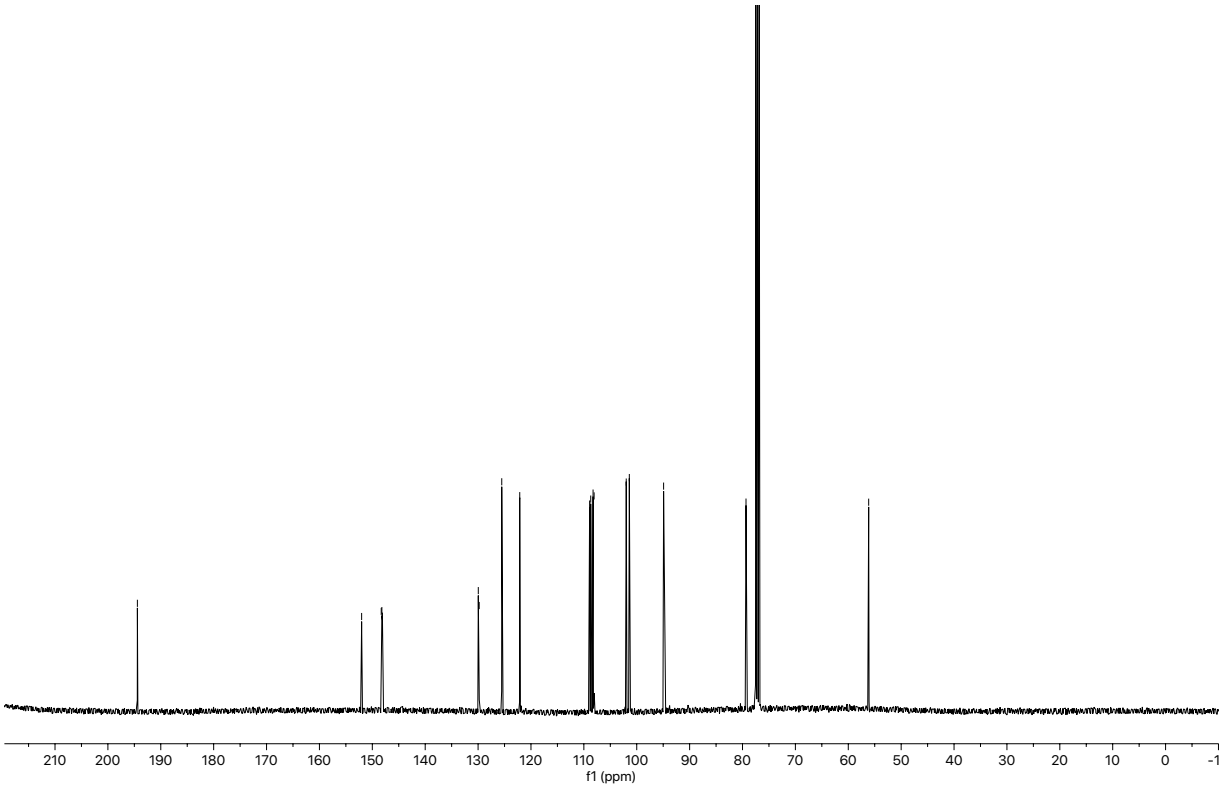



***Figure A7.95*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***90****.*

# *APPENDIX 8*

*X-Ray Crystallography Reports Relevant to Chapter 5:*

*Palladium-Catalyzed Enantioselective Decarboxylative Allylic Alkylation*

*of Protected Benzoin-Derived Enol Carbonates*

## A8.1 GENERAL EXPERIMENTAL

X-ray crystallographic analysis was obtained from the Caltech X-Ray Crystallography Facility using a Bruker D8 Venture Kappa Duo Photon 100 CMOS diffractometer. Crystal sample was prepared via slow evaporation from EtOAc/hexanes.

### A8.1.1 X-RAY CRYSTAL STRUCTURE ANALYSIS OF ACYCLIC ALCOHOL 83

***Figure A8.1*** *X-Ray Coordinate of Acyclic Alcohol* ***83***.

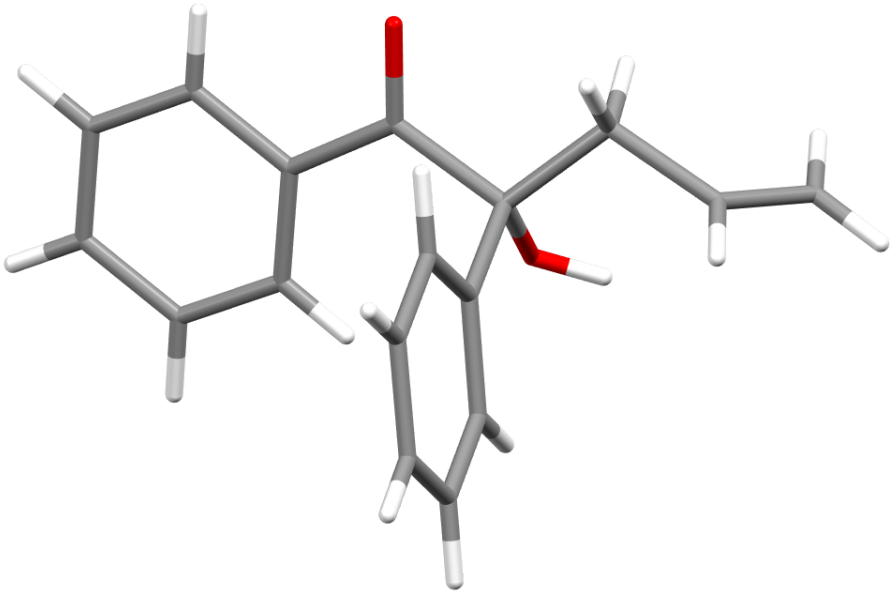


***Table A8.1*** *Crystal data and structure refinement for* ***83***.

| | | |
|---|---|---|
| Empirical formula | C17 H16 O2 | |
| Formula weight | 252.30 | |
| Temperature | 100 K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Triclinic | |
| Space group | P1 | |
| Unit cell dimensions | a = 6.0838(9) Å | a= 104.527(6)° |
| | b = 7.2384(11) Å | b= 95.732(7)° |

| | |
|---|---|
| | c = 8.3465(12) Å g = 105.236(7)° |
| Volume | 337.85(9) $Å^3$ |
| Z | 1 |
| Density (calculated) | 1.240 $g/cm^3$ |
| Absorption coefficient | 0.635 $mm^{-1}$ |
| F(000) | 134 |
| Crystal size | 0.23 x 0.22 x 0.09 $mm^3$ |
| Theta range for data collection | 5.564 to 79.408°. |
| Index ranges | -7<=h<=7,-9<=k<=9,-10<=l<=10 |
| Reflections collected | 15392 |
| Independent reflections | 2730 [R(int) = 0.0394] |
| Completeness to theta = 67.679° | 100.0 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 1.0000 and 0.8971 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 2730 / 3 / 173 |
| Goodness-of-fit on $F^2$ | 1.124 |
| Final R indices [I>2sigma(I)] | R1 = 0.0347, wR2 = 0.1003 |
| R indices (all data) | R1 = 0.0350, wR2 = 0.1008 |
| Absolute structure parameter [Flack] | -0.08(12) |
| Extinction coefficient | n/a |
| Largest diff. peak and hole | 0.237 and -0.195 $e.Å^{-3}$ |

***Table A8.2*** *Atomic coordinates (x$10^4$) and equivalent isotropic displacement parameters (Å$^2$x $10^3$) for* ***83****. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.*

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(1) | 1929(3) | 6639(2) | 3788(2) | 28(1) |
| O(2) | 7109(2) | 5729(2) | 3722(2) | 18(1) |
| C(1) | 3498(4) | 2012(3) | 2629(3) | 19(1) |
| C(2) | 2477(4) | 21(3) | 1703(3) | 23(1) |
| C(3) | 196(4) | -625(4) | 867(3) | 25(1) |
| C(4) | -1054(4) | 738(4) | 941(3) | 26(1) |
| C(5) | -46(4) | 2728(3) | 1848(3) | 21(1) |
| C(6) | 2246(4) | 3391(3) | 2708(3) | 18(1) |
| C(7) | 3157(4) | 5550(3) | 3727(3) | 17(1) |
| C(8) | 5633(3) | 6424(3) | 4782(3) | 16(1) |
| C(9) | 5597(4) | 5646(3) | 6333(3) | 17(1) |
| C(10) | 7086(4) | 4584(3) | 6704(3) | 18(1) |
| C(11) | 7052(4) | 3930(3) | 8137(3) | 22(1) |
| C(12) | 5520(4) | 4327(4) | 9212(3) | 25(1) |
| C(13) | 4017(4) | 5365(4) | 8842(3) | 24(1) |
| C(14) | 4053(4) | 6033(3) | 7417(3) | 20(1) |
| C(15) | 6325(4) | 8725(3) | 5307(3) | 20(1) |
| C(16) | 8745(4) | 9622(3) | 6294(3) | 20(1) |
| C(17) | 10493(4) | 10636(4) | 5752(3) | 27(1) |

***Table A8.3*** *Bond lengths [Å] and angles [°] for* ***83***

| | |
|---|---|
| O(1)-C(7) | 1.216(3) |
| O(2)-H(2W) | 0.8400 |
| O(2)-C(8) | 1.420(3) |
| C(1)-H(1) | 0.9500 |
| C(1)-C(2) | 1.391(3) |
| C(1)-C(6) | 1.399(3) |
| C(2)-H(2) | 0.9500 |
| C(2)-C(3) | 1.390(3) |
| C(3)-H(3) | 0.9500 |
| C(3)-C(4) | 1.389(4) |
| C(4)-H(4) | 0.9500 |
| C(4)-C(5) | 1.386(3) |
| C(5)-H(5) | 0.9500 |
| C(5)-C(6) | 1.402(3) |
| C(6)-C(7) | 1.502(3) |
| C(7)-C(8) | 1.549(3) |
| C(8)-C(9) | 1.535(3) |
| C(8)-C(15) | 1.540(3) |
| C(9)-C(10) | 1.392(3) |
| C(9)-C(14) | 1.401(3) |
| C(10)-H(10) | 0.9500 |
| C(10)-C(11) | 1.393(3) |
| C(11)-H(11) | 0.9500 |
| C(11)-C(12) | 1.391(4) |
| C(12)-H(12) | 0.9500 |
| C(12)-C(13) | 1.384(4) |
| C(13)-H(13) | 0.9500 |
| C(13)-C(14) | 1.392(3) |
| C(14)-H(14) | 0.9500 |
| C(15)-H(15A) | 0.9900 |
| C(15)-H(15B) | 0.9900 |
| C(15)-C(16) | 1.502(3) |
| C(16)-H(16) | 0.9500 |
| C(16)-C(17) | 1.314(3) |

| | |
|---|---|
| C(17)-H(17A) | 0.9500 |
| C(17)-H(17B) | 0.9500 |

| | |
|---|---|
| C(8)-O(2)-H(2W) | 109.5 |
| C(2)-C(1)-H(1) | 119.9 |
| C(2)-C(1)-C(6) | 120.2(2) |
| C(6)-C(1)-H(1) | 119.9 |
| C(1)-C(2)-H(2) | 119.8 |
| C(3)-C(2)-C(1) | 120.5(2) |
| C(3)-C(2)-H(2) | 119.8 |
| C(2)-C(3)-H(3) | 120.2 |
| C(4)-C(3)-C(2) | 119.5(2) |
| C(4)-C(3)-H(3) | 120.2 |
| C(3)-C(4)-H(4) | 119.8 |
| C(5)-C(4)-C(3) | 120.4(2) |
| C(5)-C(4)-H(4) | 119.8 |
| C(4)-C(5)-H(5) | 119.8 |
| C(4)-C(5)-C(6) | 120.5(2) |
| C(6)-C(5)-H(5) | 119.8 |
| C(1)-C(6)-C(5) | 118.9(2) |
| C(1)-C(6)-C(7) | 124.26(18) |
| C(5)-C(6)-C(7) | 116.77(19) |
| O(1)-C(7)-C(6) | 120.41(19) |
| O(1)-C(7)-C(8) | 118.4(2) |
| C(6)-C(7)-C(8) | 121.18(17) |
| O(2)-C(8)-C(7) | 106.12(16) |
| O(2)-C(8)-C(9) | 112.43(17) |
| O(2)-C(8)-C(15) | 110.40(17) |
| C(9)-C(8)-C(7) | 107.21(17) |
| C(9)-C(8)-C(15) | 110.82(17) |
| C(15)-C(8)-C(7) | 109.68(16) |
| C(10)-C(9)-C(8) | 121.64(19) |
| C(10)-C(9)-C(14) | 118.92(19) |
| C(14)-C(9)-C(8) | 119.43(19) |
| C(9)-C(10)-H(10) | 119.7 |
| C(9)-C(10)-C(11) | 120.5(2) |

| | |
|---|---|
| C(11)-C(10)-H(10) | 119.7 |
| C(10)-C(11)-H(11) | 119.9 |
| C(12)-C(11)-C(10) | 120.3(2) |
| C(12)-C(11)-H(11) | 119.9 |
| C(11)-C(12)-H(12) | 120.2 |
| C(13)-C(12)-C(11) | 119.6(2) |
| C(13)-C(12)-H(12) | 120.2 |
| C(12)-C(13)-H(13) | 119.8 |
| C(12)-C(13)-C(14) | 120.4(2) |
| C(14)-C(13)-H(13) | 119.8 |
| C(9)-C(14)-H(14) | 119.9 |
| C(13)-C(14)-C(9) | 120.3(2) |
| C(13)-C(14)-H(14) | 119.9 |
| C(8)-C(15)-H(15A) | 109.4 |
| C(8)-C(15)-H(15B) | 109.4 |
| H(15A)-C(15)-H(15B) | 108.0 |
| C(16)-C(15)-C(8) | 111.06(18) |
| C(16)-C(15)-H(15A) | 109.4 |
| C(16)-C(15)-H(15B) | 109.4 |
| C(15)-C(16)-H(16) | 118.0 |
| C(17)-C(16)-C(15) | 124.1(2) |
| C(17)-C(16)-H(16) | 118.0 |
| C(16)-C(17)-H(17A) | 120.0 |
| C(16)-C(17)-H(17B) | 120.0 |
| H(17A)-C(17)-H(17B) | 120.0 |

---

***Table A8.4*** *Anisotropic displacement parameters ($Å^2x10^3$) for* ***83****. The anisotropic displacement factor exponent takes the form* $-2\pi^2[h^2a^{*2}U^{11} + ... +2\ h\ k\ a^*\ b^*U^{12}]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| O(1) | 16(1) | 22(1) | 44(1) | 7(1) | 1(1) | 8(1) |
| O(2) | 13(1) | 22(1) | 19(1) | 4(1) | 6(1) | 4(1) |
| C(1) | 18(1) | 18(1) | 18(1) | 6(1) | 3(1) | 4(1) |
| C(2) | 26(1) | 21(1) | 22(1) | 6(1) | 5(1) | 9(1) |
| C(3) | 28(1) | 21(1) | 21(1) | 0(1) | 4(1) | 3(1) |
| C(4) | 18(1) | 31(1) | 21(1) | 1(1) | -1(1) | 3(1) |
| C(5) | 18(1) | 26(1) | 20(1) | 4(1) | 2(1) | 8(1) |
| C(6) | 16(1) | 22(1) | 15(1) | 7(1) | 4(1) | 5(1) |
| C(7) | 14(1) | 18(1) | 22(1) | 10(1) | 5(1) | 4(1) |
| C(8) | 14(1) | 17(1) | 19(1) | 6(1) | 6(1) | 6(1) |
| C(9) | 16(1) | 15(1) | 18(1) | 3(1) | 3(1) | 2(1) |
| C(10) | 18(1) | 19(1) | 19(1) | 4(1) | 3(1) | 7(1) |
| C(11) | 24(1) | 18(1) | 21(1) | 4(1) | -1(1) | 6(1) |
| C(12) | 28(1) | 25(1) | 16(1) | 5(1) | 1(1) | 2(1) |
| C(13) | 25(1) | 23(1) | 19(1) | 2(1) | 9(1) | 3(1) |
| C(14) | 20(1) | 19(1) | 22(1) | 4(1) | 5(1) | 6(1) |
| C(15) | 18(1) | 17(1) | 25(1) | 7(1) | 4(1) | 5(1) |
| C(16) | 23(1) | 18(1) | 18(1) | 4(1) | 3(1) | 6(1) |
| C(17) | 21(1) | 24(1) | 27(1) | 1(1) | 4(1) | 1(1) |

***Table A8.5*** *Hydrogen coordinates (x $10^4$) and isotropic displacement parameters ($Å^2$ x$10^3$) for* ***83***.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(2W) | 8466 | 6502 | 4056 | 28 |
| H(1) | 5051 | 2437 | 3210 | 22 |
| H(2) | 3344 | -903 | 1642 | 27 |
| H(3) | -502 | -1990 | 248 | 31 |
| H(4) | -2611 | 303 | 366 | 31 |
| H(5) | -913 | 3650 | 1887 | 26 |
| H(10) | 8134 | 4303 | 5974 | 22 |
| H(11) | 8078 | 3209 | 8381 | 26 |
| H(12) | 5506 | 3889 | 10194 | 30 |
| H(13) | 2955 | 5622 | 9566 | 28 |
| H(14) | 3025 | 6755 | 7179 | 24 |
| H(15A) | 6221 | 9189 | 4291 | 23 |
| H(15B) | 5234 | 9184 | 5999 | 23 |
| H(16) | 9030 | 9446 | 7378 | 24 |
| H(17A) | 10264 | 10838 | 4674 | 32 |
| H(17B) | 11985 | 11166 | 6438 | 32 |

***Table A8.6*** *Torsion Anlges [°] for* ***83***.

| | |
|---|---|
| O(1)-C(7)-C(8)-O(2) | -136.5(2) |
| O(1)-C(7)-C(8)-C(9) | 103.2(2) |
| O(1)-C(7)-C(8)-C(15) | -17.2(3) |
| O(2)-C(8)-C(9)-C(10) | 7.1(3) |
| O(2)-C(8)-C(9)-C(14) | -173.72(18) |
| O(2)-C(8)-C(15)-C(16) | -61.9(2) |
| C(1)-C(2)-C(3)-C(4) | 0.9(4) |
| C(1)-C(6)-C(7)-O(1) | -176.9(2) |
| C(1)-C(6)-C(7)-C(8) | 0.5(3) |
| C(2)-C(1)-C(6)-C(5) | 0.3(3) |
| C(2)-C(1)-C(6)-C(7) | 177.4(2) |
| C(2)-C(3)-C(4)-C(5) | -0.3(4) |
| C(3)-C(4)-C(5)-C(6) | -0.2(3) |
| C(4)-C(5)-C(6)-C(1) | 0.3(3) |
| C(4)-C(5)-C(6)-C(7) | -177.1(2) |
| C(5)-C(6)-C(7)-O(1) | 0.3(3) |
| C(5)-C(6)-C(7)-C(8) | 177.67(19) |
| C(6)-C(1)-C(2)-C(3) | -0.9(3) |
| C(6)-C(7)-C(8)-O(2) | 46.1(2) |
| C(6)-C(7)-C(8)-C(9) | -74.3(2) |
| C(6)-C(7)-C(8)-C(15) | 165.33(18) |
| C(7)-C(8)-C(9)-C(10) | 123.4(2) |
| C(7)-C(8)-C(9)-C(14) | -57.5(2) |
| C(7)-C(8)-C(15)-C(16) | -178.45(18) |
| C(8)-C(9)-C(10)-C(11) | 178.69(19) |
| C(8)-C(9)-C(14)-C(13) | -179.09(19) |
| C(8)-C(15)-C(16)-C(17) | 112.5(2) |
| C(9)-C(8)-C(15)-C(16) | 63.4(2) |
| C(9)-C(10)-C(11)-C(12) | 0.2(3) |
| C(10)-C(9)-C(14)-C(13) | 0.1(3) |
| C(10)-C(11)-C(12)-C(13) | 0.5(3) |
| C(11)-C(12)-C(13)-C(14) | -0.9(3) |
| C(12)-C(13)-C(14)-C(9) | 0.6(3) |

| | |
|---|---|
| C(14)-C(9)-C(10)-C(11) | -0.5(3) |
| C(15)-C(8)-C(9)-C(10) | -117.0(2) |
| C(15)-C(8)-C(9)-C(14) | 62.2(2) |

***Table A8.7*** *Hydrogen Bonds for* ***83*** *[Å and °].*

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| O(2)-H(2W)...O(1)#1 | 0.84 | 2.12 | 2.823(2) | 141.1 |

# CHAPTER 6

## Palladium-Catalyzed Enantioselective Decarboxylative Allylic Alkylation of Acyclic α-Pyrrolyl/Indolyl Ketones†

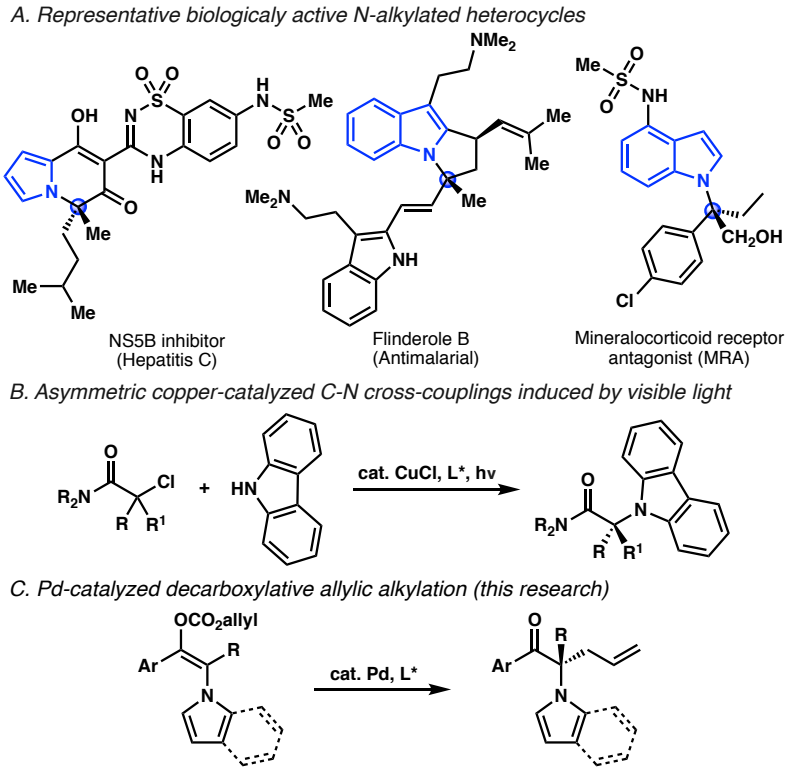
### 6.1 INTRODUCTION

Aromatic nitrogen heterocycles, such as indoles and pyrroles, are high value motifs found in a wide range of natural products, agrochemicals, and pharmaceuticals.[1] In fact, indole is one of the most common heterocycles in FDA approved drugs.[2] While extensive efforts toward the functionalization of indole (or pyrrole) C2 and C3 positions have been described in the literature,[3] functionalization of the N−H can be challenging due to the attenuated nucleophilicity of this position. This drawback led to N–H functionalization of such heterocycles being overlooked in the past. Recently, progress has been made in intermolecular enantioselective *N*-alkylation of indoles.[4] However, few methods have been reported for the enantioselective synthesis of fully substituted *N*–stereocenters, a motif which is found in a number of bioactive compounds (Figure 6.1A).[5] Furthermore, to the best of our knowledge, there is no report of the asymmetric synthesis of fully substituted α-pyrrolyl ketones, which is in sharp contrast to the wide utility of pyrrole in medicinal chemistry. In 2016, the Peters and Fu groups disclosed a

†This research was performed in collaboration with Remi Lavernhe and Dr. Haiming Zhang. Portions of this chapter have been submitted for publication, Lavernhe, R.; Alexy, E. J.; Zhang, H.; Stoltz, B. M. *submitted*.

photoinduced copper-catalyzed method for coupling readily available racemic tertiary alkyl chloride electrophiles with carbazole and C3 protected indole derivatives to generate fully substituted *N*-stereocenters in high enantioselectivity (Figure 6.1B).[6] Due to the importance of these heterocycles, and in continuation of ongoing research from our group regarding the synthesis and utility of fully substituted acyclic enolates in palladium-catalyzed allylic alkylation,[7] we sought to target this challenging structural motif by ultimate C–C bond formation, not C–N bond construction (Figure 6.1C).

**Figure 6.1** Significance and foundational research.

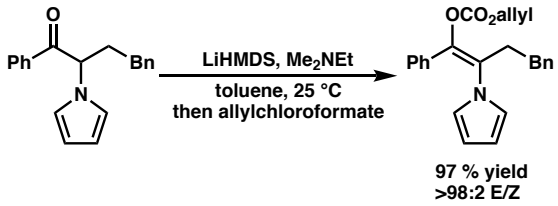



## 6.2 INVESTIGATION OF SUBSTRATE ENOLIZATION

We began by investigating the synthesis of fully-substituted acyclic ketone enolates bearing an *N*-α-pyrrole substituent. Utilizing recently reported conditions,[8] a highly selective enolization could be performed and, following enolate trapping with allyl

chloroformate, provide a fully-substituted enol carbonate poised to undergo a subsequent palladium-catalyzed allylic alkylation (Figure 6.2). This robust and operationally simple process relies on the combination of LiHMDS and dimethylethylamine (2 equiv each), and proceeds smoothly at ambient temperature.

**Figure 6.2** Enolization of an acyclic α-pyrrolyl ketone.

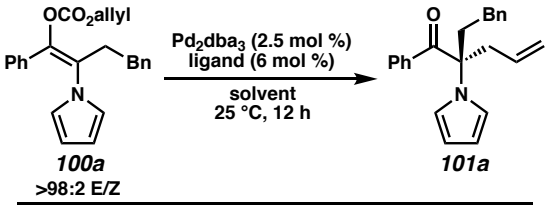



## 6.3 INVESTIGATION OF ALLYLIC ALKYLATION

With ready access to a stereodefined α-pyrrolyl enolate derivative established, we next sought to examine a subsequent palladium-catalyzed allylic alkylation to establish the desired tetrasubstituted stereocenter. Initially, a variety of ligands commonly utilized in the literature for this transformation were examined, with a representative set of these provided in Table 6.1 below. Use of the Trost type bis-phosphine ligand ***L11*** in a 2:1 hexane/toluene solvent mixture led to formation of the desired product in a promising 51% ee (entry 1). Switching to the phosphinooxazoline (PHOX) ligand ***L7***, ee decreased slightly to 34% (entry 2). We were pleased to find, however, that the use of the electron-deficient PHOX ligand ***L8*** provided the desired product in an improved 85% ee. However, no further increase in selectivity was observed through the use of even more electron-deficient ligands, such as ***L12*** (entry 4). Continuing with PHOX ligand ***L8***, a screen of solvents and conditions revealed that a 2:1 hexane/toluene mixture was indeed the optimal solvent for this transformation, and that the catalyst loading could be significantly lowered to 0.25 mol % $Pd_2(dba)_3$ and 0.6 mol % ***L8***. With these conditions,

the alkylation product is obtained in a high 86% ee and an excellent 96% isolated yield (entry 7).

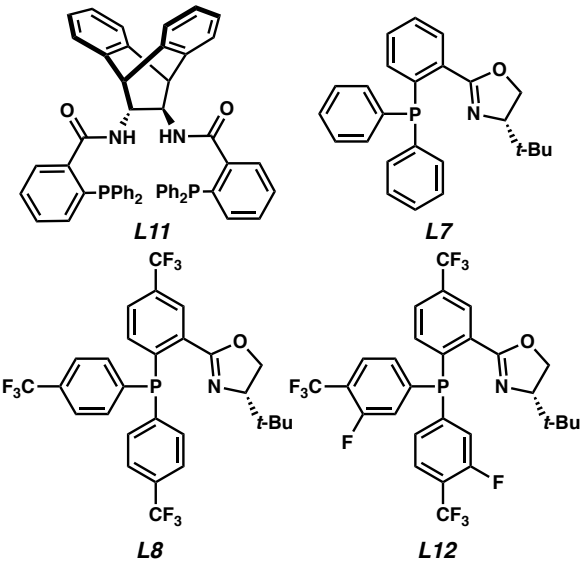
**Table 6.1** Optimization of acyclic, decarboxylative allylic alkylation.[a]




*100a*
>98:2 E/Z

*101a*

| entry | ligand | solvent | %ee[c] (yield) |
|---|---|---|---|
| 1 | *L11* | 2:1 hexane/PhMe | –51 |
| 2 | *L7* | 2:1 hexane/PhMe | 34 |
| 3 | *L8* | 2:1 hexane/PhMe | 85 |
| 4 | *L12* | 2:1 hexane/PhMe | 84 |
| 5 | *L8* | benzene | 80 |
| 6 | *L8* | methylcyclohexane | 81 |
| 7[d] | *L8* | 2:1 hexane/PhMe | 86 (96) |



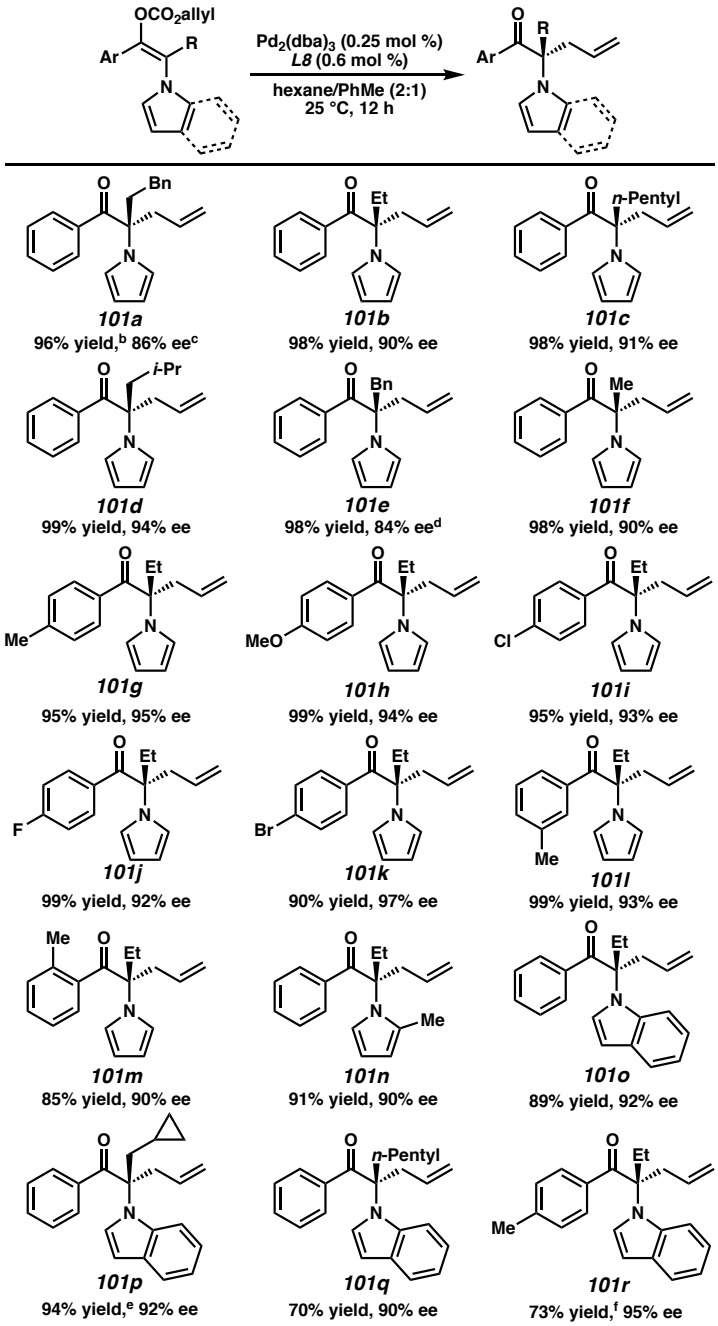

[a] Conditions: 0.1 mmol **100a**, 2.5 mol % $Pd_2(dba)_3$, 6 mol % ligand, 2.0 mL solvent. [b] Conversion over 95% if no yield from isolated product stated. [c] Determined by chiral supercritical fluid chromatography (SFC) analysis. [d] Reaction performed with 0.2 mmol of **100a**, 0.25 mol % $Pd_2(dba)_3$, 0.6 mol % ligand, and 4.0 mL solvent.

## 6.4 INVESTIGATION OF REACTION SCOPE

Having identified optimized reaction conditions, we next examined the scope of the transformation. A variety of substrates containing different α-alkyl and ketone aryl groups were synthesized and subjected to the optimized reaction conditions (Table 6.2). All enol carbonate substrates were prepared with excellent E/Z selectivity (>98:2). Substrates bearing simple α-alkyl groups such as ethyl (**101b**) and methyl (**101f**) proceeded well, providing the alkylation products in excellent 98% yield and 90% ee in both cases. Substrate **101c** bearing a *n*-pentyl chain and **101d** bearing a branching isobutyl substituent both proceeded well, with the alkylation products being afforded in 91% and 94% ee, respectively, both in excellent yields. A slightly decreased 84% ee was

obtained with α-benzyl substrate (**101e**). Examining the electronic effects of the ketone aryl substituent revealed that both donating and withdrawing groups were tolerated (**101g**–**101l**). Notably, alkylation product **101k** with a *p*-Br phenyl group was obtained in 90% yield and an excellent 97% ee, and contains multiple reactive functionality that may be utilized for subsequent synthetic manipulations. We were pleased to find that sterically demanding substrate **101m** bearing an *o*-tolyl substituent performed well in the transformation, with the product obtained in 85% yield and a high 90% ee. Additionally, substitution at the 2-position of the α-pyrrole was tolerated, forging an exceedingly hindered tetra-substituted stereocenter in a high 90% ee (i.e., **101n**). From this result, we were inspired to investigate additional, bulkier α-indole containing substrates (**101o**–**101r**), finding these to perform exceedingly well, providing the alkylation products in excellent 90–95% ee.

**Table 6.2** Substrate scope of asymmetric, decarboxylative allylic alkylation.[a]

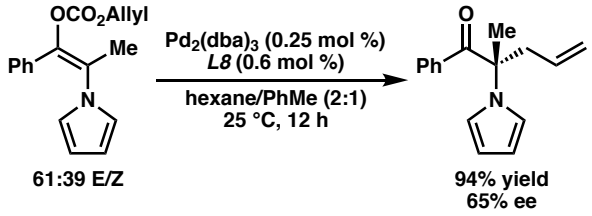



[a] Reactions performed on 0.2 mmol scale unless stated otherwise. [b] Yield of isolated product. [c] Determined by chiral SFC analysis. [d] Absolute configuration of **101e** determined by single crystal X-ray diffraction, all other compounds are assigned by analogy. [e] Reaction performed on 0.107 mmol scale.

## 6.5 IMPORTANCE OF ENOLATE GEOMETRY

With a scope of the transformation established, we next sought to examine the importance of enolate geometry on the selectivity of the transformation (Figure 6.3). Enol carbonate substrate **101f** was prepared as a 61:39 E/Z mixture via a nonselective enolization, and subjected to the optimized allylic alkylation conditions. The resultant alkylation product was obtained in an excellent 94% yield, but with a diminished 65% ee, highlighting the importance of synthesizing the starting enol carbonate as a single geometric isomer. This result runs contrary to the alkylation of acyclic ketones bearing all-carbon substituents in which we found the starting enolate geometry of acyclic ketones was inconsequential for obtaining high selectivity.[7b] This divergence in reactivity may be due to the electron-rich nature of the α-*N*-hetereocyclic substrates used herein, which may facilitate a faster reductive elimination and outcompete enolate equilibration of an intermediate Pd enolate, thereby reacting to form the C–C bond through both geometries, and with only moderate observable enantioselectivity.

**Figure 6.3** Importance of substrate enolate geometry.

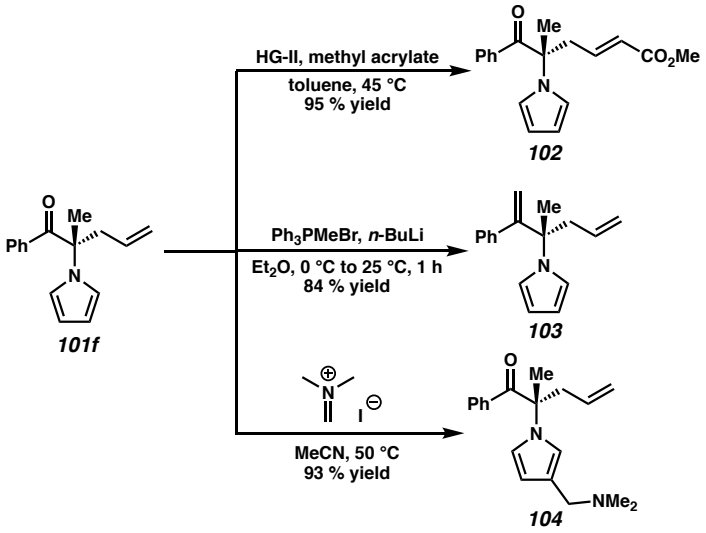



## 6.6 DERIVATIZATION OF ALKYLATION PRODUCTS

Lastly, we turned toward examining product derivatizations (Scheme 6.1). Divergent functionalization of the ketone, terminal olefin, and pyrrole are all possible. Treatment of the alkylation product **101f** to cross metathesis conditions using methyl acrylate and Hoveyda-Grubbs 2$^{nd}$ generation catalyst provided unsaturated ester **102** in an

excellent 95% isolated yield. Substituted styrene **103** could be obtained in 84% yield via a Wittig olefination. Functionalization of the pyrrole could be affected by treatment with Eschenmoser's salt, providing tertiary amine containing product **104** in an excellent 93% yield.

**Scheme 6.1** Derivatization of alkylation products.




## 6.7 CONCLUSIONS

In conclusion, we have developed a general method to access fully-substituted α-pyrrolyl and indolyl ketones. Both use of the electron-deficient phosphinooxazoline ligand ***L8***, and preparation of the starting enol carbonates as single geometric isomers, are crucial for obtaining high enantioselectivity. The transformation proceeds efficiently with only 0.25 mol % of $Pd_2(dba)_3$ and 0.6 mol % ligand, and the resulting alkylated products could be selectively functionalized at different reactive sites in high yields.

## 6.8 EXPERIMENTAL SECTION

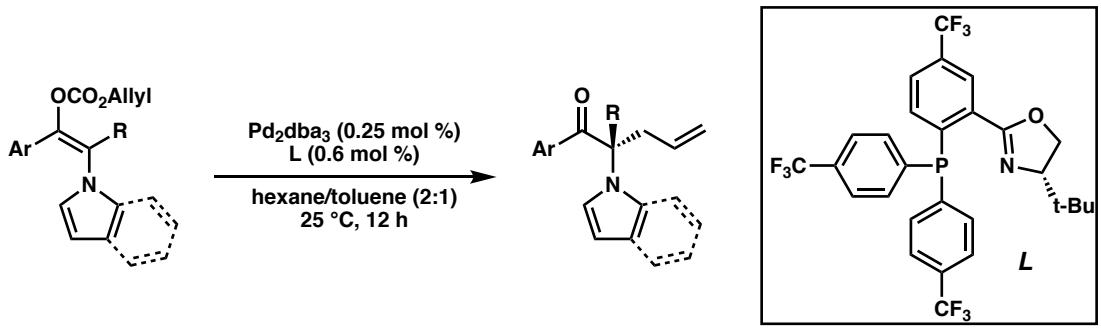
### 6.8.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 μm) was used for flash chromatography. $^1$H NMR spectra were recorded on Varian Inova 500 MHz and Bruker 400 MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm). $^{13}$C NMR spectra were recorded on a Varian Inova 500 MHz spectrometer (125 MHz) and Bruker 400 MHz spectrometers (100 MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm). Data for $^1$H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet, app = apparent. Data for $^{13}$C NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer or Nicolet 6700 FTIR spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption ($cm^{-1}$). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell and are reported as: $[\alpha]_D^T$ (concentration in 10 mg/1 mL, solvent). Analytical SFC was performed with a Mettler SFC supercritical $CO_2$ analytical

chromatography system utilizing Chiralpak (AD-H, AS-H or IC) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+), or obtained from Caltech mass spectrometry laboratory. Ligands and MOM-protected benzoins were prepared by known methods unless otherwise described below.

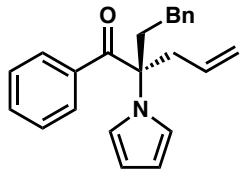
## 6.8.2 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

### 6.8.2.1 General Procedure for Pd-Catalyzed Allylic Alkylation Reactions



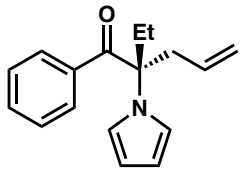

In a nitrogen-filled glovebox, a solution of $Pd_2(dba)_3$ (0.69 mg/mL) and **L** (1.06 mg/mL) in toluene was stirred for 30 minutes at 25 °C, then 0.67 mL of the resulting catalyst solution was transferred to a one dram vial containing allyl enol carbonate substrate (0.2 mmol) dissolved in hexanes (1.33 mL). The vial was sealed with a Teflon-lined cap, removed from the glovebox, and stirred at 25 °C for 12 h. The crude reaction mixture was concentrated then purified by silica gel flash chromatography to provide the desired alkylation product.

### 6.8.2.2 Spectroscopic Data for the Allylic Alkylation Products




**(*S*)-2-phenethyl-1-phenyl-2-(1*H*-pyrrol-1-yl)pent-4-en-1-one (101a)**

Purified by column chromatography (2% $Et_2O$ in hexanes) to provide a beige solid (65.8 mg, 96% yield); 86% ee, $[\alpha]_D^{25}$ –50.0 (*c* 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.43 (m, 1H), 7.32 – 7.25 (m, 2H), 7.25 – 7.13 (m, 5H), 7.00 – 6.92 (m, 2H), 6.80 (t, *J* = 2.2 Hz, 2H), 6.29 – 6.23 (m, 2H), 5.42 (dddd, *J* = 16.9, 10.3, 7.8, 6.7 Hz, 1H), 5.17 – 5.06 (m, 2H), 3.08 – 2.95 (m, 2H), 2.60 – 2.27 (m, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 198.9, 141.1, 136.0, 132.8, 131.5, 128.7, 128.7, 128.6, 128.4, 126.3, 119.9, 118.9, 109.6, 69.9, 39.7, 36.9, 29.6 ; IR (Neat Film, NaCl) 3065, 3024, 2962, 1682, 1646, 1596, 1483, 1455, 1250, 1220, 1181, 1097, 975, 923, 724, 698, 662 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{23}H_{24}NO$ $[M+H]^+$: 330.1852, found 330.1856; SFC Conditions: 5% IPA, 2.5 mL/min, Chiralpak IC column, λ = 210 nm, $t_R$ (min): major = 5.03, minor = 6.06.

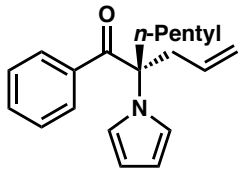



**(*S*)-2-ethyl-1-phenyl-2-(1*H*-pyrrol-1-yl)pent-4-en-1-one (101b)**

Purified by column chromatography (2% $Et_2O$ in hexanes) to provide a colorless oil (49.6 mg, 98% yield); 90% ee, $[\alpha]_D^{25}$ –97.7 (*c* 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 1H), 7.29 – 7.22 (m, 2H), 7.19 – 7.13 (m, 2H), 6.77 (t, *J* = 2.2 Hz, 2H), 6.25 (t, *J* = 2.2 Hz, 2H), 5.34 (dddd, *J* = 16.9, 10.2, 7.8, 6.7 Hz, 1H), 5.09 – 4.96 (m, 2H), 2.90 (dq, *J* = 7.7, 1.3 Hz, 2H), 2.36 – 2.10 (m, 2H), 0.75 (t, *J* = 7.5 Hz, 3H); $^{13}$C NMR

(100 MHz, $CDCl_3$) δ 199.0, 136.0, 132.6, 131.6, 128.7, 128.6, 119.6, 118.9, 109.4, 70.5, 39.0, 27.2, 7.6; IR (Neat Film, NaCl) 3070, 2976, 1683, 1641, 1596, 1484, 1464, 1446, 1266, 1228, 1186, 1048, 1093, 1075, 1003, 976, 922, 722, 692 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{17}H_{20}NO$ $[M+H]^+$: 254.1539, found 254.1540; SFC Conditions:* 10% IPA, 2.5 mL/min, Chiralpak IC column, λ = 210 nm, $t_R$ (min): major = 4.04, minor = 4.66.

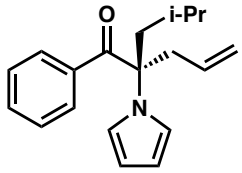
*SFC performed on cross-metathesis product of **101b** with methyl acrylate with Grubbs II.




**(*S*)-2-allyl-1-phenyl-2-(1*H*-pyrrol-1-yl)heptan-1-one (101c)**

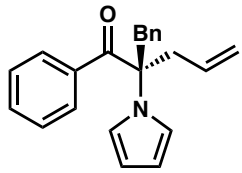
Purified by column chromatography (2% $Et_2O$ in hexanes) to provide a colorless oil (57.9 mg, 98% yield); 91% ee, $[\alpha]_D^{25}$ –96.0 (*c* 1.00, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 1H), 7.29 – 7.23 (m, 2H), 7.19 – 7.14 (m, 2H), 6.76 (t, *J* = 2.2 Hz, 2H), 6.24 (t, *J* = 2.2 Hz, 2H), 5.35 (dddd, *J* = 16.7, 10.2, 8.1, 6.4 Hz, 1H), 5.06 (ddt, *J* = 10.2, 2.0, 1.0 Hz, 1H), 5.00 (ddt, *J* = 16.9, 2.1, 1.3 Hz, 1H), 3.00 – 2.81 (m, 2H), 2.22 (ddd, *J* = 13.3, 12.2, 4.0 Hz, 1H), 2.16 – 2.04 (m, 1H), 1.24 – 1.08 (m, 5H), 1.08 – 0.95 (m, 1H), 0.78 (t, *J* = 6.8 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 199.1, 136.0, 132.6, 131.7, 128.7, 128.5, 119.6, 118.9, 109.3, 70.1, 39.8, 34.2, 32.0, 22.7, 22.3, 14.0; IR (Neat Film, NaCl) 3102, 3069, 2956, 2931, 2870, 1682, 1641, 1596, 1578, 1483, 1467, 1446, 1418, 1379, 1268, 1252, 1219, 1203, 1185, 1150, 1095, 1073, 1002, 971, 920, 867, 783, 725, 692, 665 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{20}H_{26}NO$ $[M+H]^+$: 296.2009, found

296.2022; SFC Conditions: 5% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 2.88, major = 3.23.




**(*S*)-2-isobutyl-1-phenyl-2-(1*H*-pyrrol-1-yl)pent-4-en-1-one (101d)**

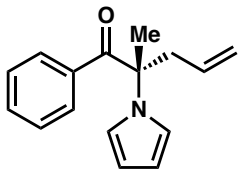
Purified by column chromatography (2% $Et_2O$ in hexanes) to provide a white solid (55.1 mg, 99% yield); 94% ee, $[\alpha]_D^{25}$ –33.1 (*c* 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.38 (m, 1H), 7.28 – 7.22 (m, 2H), 7.21 – 7.16 (m, 2H), 6.78 – 6.73 (m, 2H), 6.25 – 6.20 (m, 2H), 5.36 (dddd, *J* = 16.8, 10.2, 7.8, 6.5 Hz, 1H), 5.06 (ddt, *J* = 10.2, 2.0, 1.0 Hz, 1H), 4.97 (dq, *J* = 17.0, 1.6 Hz, 1H), 3.07 – 2.91 (m, 2H), 2.25 – 2.06 (m, 2H), 1.68 – 1.57 (m, 1H), 0.74 (d, *J* = 1.3 Hz, 3H), 0.72 (d, *J* = 1.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 198.9, 136.1, 132.5, 131.5, 128.7, 128.4, 119.8, 118.7, 109.2, 70.1, 42.8, 40.0, 24.4, 23.9, 23.6; IR (Neat Film, NaCl) 3070, 2957, 2870, 1682, 1642, 1596, 1483, 1470, 1446, 1388, 1367, 1273, 1258, 1219, 1186, 1148, 1095, 1026, 1002, 921, 900, 724, 691, 666 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{24}NO$ $[M+H]^+$: 282.1852, found 252.1857; SFC Conditions: 2% IPA, 2.5 mL/min, Chiralpak IC column, λ = 210 nm, $t_R$ (min): minor = 4.40, major = 4.93.




**(*R*)-2-benzyl-1-phenyl-2-(1*H*-pyrrol-1-yl)pent-4-en-1-one (101e)**

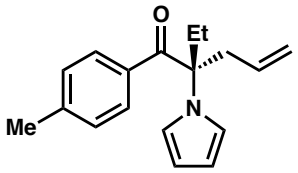
Purified by column chromatography (2% $Et_2O$ in hexanes) to provide a colorless oil (61.8 mg, 98% yield); 84% ee, $[\alpha]_D^{25}$ +82.353 (*c* 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ

7.45 (ddt, $J$ = 8.6, 6.8, 1.5 Hz, 1H), 7.31 – 7.12 (m, 7H), 6.66 (t, $J$ = 2.2 Hz, 2H), 6.63 – 6.56 (m, 2H), 6.24 (t, $J$ = 2.2 Hz, 2H), 5.61 (ddt, $J$ = 17.3, 10.2, 7.1 Hz, 1H), 5.13 (dq, $J$ = 10.2, 1.3 Hz, 1H), 4.93 (dq, $J$ = 17.0, 1.6 Hz, 1H), 3.43 (s, 2H), 2.88 – 2.75 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 198.1, 136.0, 135.5, 132.8, 130.8, 130.5, 129.0, 128.6, 128.1, 127.0, 120.7, 119.1, 109.6, 70.4, 41.7, 38.4; IR (Neat Film, NaCl) 3064, 1686, 1645, 1487, 1443, 1276, 1256, 1214, 1188, 1141, 1100, 1027, 1000, 934, 905, 808, 756, 737, 701, 692, 667, 643 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{22}H_{22}NO$ $[M+H]^+$: 316.1696, found 316.1696; SFC Conditions: 5% IPA, 2.5 mL/min, Chiralpak IC column, λ = 210 nm, $t_R$ (min): major = 5.35, minor = 6.14.



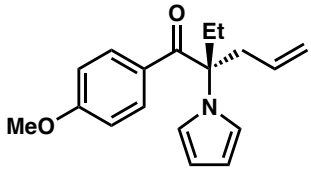

**(*S*)-2-methyl-1-phenyl-2-(1*H*-pyrrol-1-yl)pent-4-en-1-one (101f)**

Purified by column chromatography (2% $Et_2O$ in hexanes) to provide a white solid (47.0 mg, 98% yield); 90% ee, $[\alpha]_D^{25}$ –163.0 (*c* 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 1H), 7.29 – 7.19 (m, 4H), 6.74 (d, $J$ = 2.2 Hz, 2H), 6.23 (t, $J$ = 2.2 Hz, 2H), 5.40 (dddd, $J$ = 16.7, 10.3, 8.2, 6.3 Hz, 1H), 5.10 – 5.00 (m, 2H), 2.97 – 2.89 (m, 1H), 2.83 (ddt, $J$ = 13.9, 8.2, 1.0 Hz, 1H), 1.75 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.4, 135.5, 132.7, 132.1, 128.8, 128.5, 119.9, 118.8, 109.5, 67.2, 43.9, 23.4; IR (Neat Film, NaCl) 3070, 2982, 1682, 1641, 1596, 1484, 1446, 1378, 1280, 1255, 1152, 1092, 1073, 974, 951, 922, 794, 719, 693 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{16}H_{17}NONa$ $[M+Na]^+$: 262.1202, found 262.1210; SFC Conditions: 0.5% IPA, 2.5 mL/min, Chiralcel OB-H column, λ = 210 nm, $t_R$ (min): minor = 3.52, major = 3.89.




**(*S*)-2-ethyl-2-(1*H*-pyrrol-1-yl)-1-(*p*-tolyl)pent-4-en-1-one (101g)**

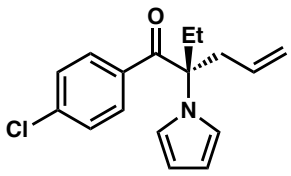
Purified by column chromatography (2% $Et_2O$ in hexanes) to provide a colorless oil (50.4 mg, 95% yield); 95% ee, $[\alpha]_D^{25}$ –90.8 (*c* 1.00, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.16 – 7.09 (m, 2H), 7.10 – 7.02 (m, 2H), 6.75 (t, *J* = 2.2 Hz, 2H), 6.23 (t, *J* = 2.2 Hz, 2H), 5.41 – 5.27 (m, 1H), 5.09 – 4.97 (m, 2H), 2.90 (dt, *J* = 7.7, 1.2 Hz, 2H), 2.31 (s, 3H), 2.30 – 2.14 (m, 2H), 0.74 (t, *J* = 7.5 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 198.4, 143.4, 133.3, 131.8, 129.3, 128.9, 119.5, 118.9, 109.2, 70.5, 39.2, 27.4, 21.6, 7.6; IR (Neat Film, NaCl) 3070, 2976, 2881, 1681, 1641, 1606, 1484, 1459, 1265, 1236, 1187, 1149, 1093, 1075, 1003, 917, 846, 827, 792, 756, 724 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{18}H_{22}NO$ $[M+H]^+$: 268.1696, found 268.1693; SFC Conditions: 2% IPA, 2.5 mL/min, Chiralcel OB-H column, λ = 210 nm, $t_R$ (min): minor = 2.80, major = 3.20.




**(*S*)-2-ethyl-1-(4-methoxyphenyl)-2-(1*H*-pyrrol-1-yl)pent-4-en-1-one (101h)**

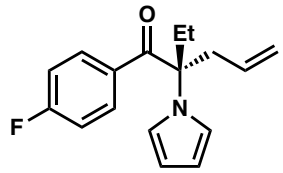
Purified by column chromatography (5% $Et_2O$ in hexanes) to provide a colorless oil (55.9 mg, 99% yield); 94% ee, $[\alpha]_D^{25}$ –80.0 (*c* 1.00, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.22 (m, 2H), 6.76 – 6.70 (m, 4H), 6.22 (t, *J* = 2.2 Hz, 2H), 5.33 (dddd, *J* = 16.8, 10.3, 7.9, 6.6 Hz, 1H), 5.08 – 4.96 (m, 2H), 3.78 (s, 3H), 2.95 – 2.81 (m, 2H), 2.35 – 2.12 (m, 2H), 0.74 (t, *J* = 7.4 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 197.2, 163.1, 131.9, 131.2, 128.6, 119.5, 118.9, 113.7, 109.2, 70.6, 55.5, 39.4, 27.7, 7.7; IR (Neat Film, NaCl)

3076, 2974, 2839, 1673, 1645, 1600, 1574, 1508, 1484, 1459, 1418, 1306, 1263, 1242, 1178, 1149, 1092, 1074, 1032, 917, 847, 726 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{18}H_{22}NO_2$ $[M+H]^+$: 284.1645, found 284.1644; SFC Conditions: 1% IPA, 2.5 mL/min, Chiralcel OB-H column, λ = 210 nm, $t_R$ (min): minor = 4.11, major = 4.62.



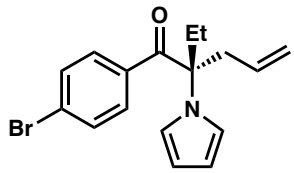

**(*S*)-1-(4-chlorophenyl)-2-ethyl-2-(1*H*-pyrrol-1-yl)pent-4-en-1-one (101i)**

Purified by column chromatography (2% $Et_2O$ in hexanes) to provide a colorless oil (54.8 mg, 95% yield); 93% ee, $[\alpha]_D^{25}$ –86.8 (*c* 1.00, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.20 (m, 2H), 7.12 – 7.06 (m, 2H), 6.74 (t, *J* = 2.2 Hz, 2H), 6.26 – 6.23 (m, 2H), 5.33 (dddd, *J* = 16.8, 10.3, 7.9, 6.5 Hz, 1H), 5.14 – 4.94 (m, 2H), 2.97 – 2.79 (m, 2H), 2.28 (dq, *J* = 13.6, 7.5 Hz, 1H), 2.14 (dqd, *J* = 13.7, 7.4, 0.8 Hz, 1H), 0.74 (t, *J* = 7.5 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 197.8, 139.1, 134.2, 131.4, 130.2, 128.9, 119.8, 118.9, 109.6, 70.6, 39.0, 27.3, 7.6; IR (Neat Film, NaCl) 3074, 2980, 1682, 1644, 1586, 1486, 1398, 1280, 1266, 1224, 1184, 1147, 1116, 1093, 1075, 1003, 926, 914, 845, 824, 750, 726, 707 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{17}H_{19}ClNO$ $[M+H]^+$: 288.1150, found 288.1150; SFC Conditions: 3% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 6.42, major = 7.10.




**(*S*)-2-ethyl-1-(4-fluorophenyl)-2-(1*H*-pyrrol-1-yl)pent-4-en-1-one (101j)**

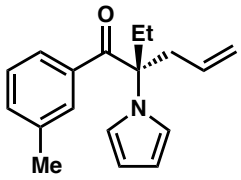
Purified by column chromatography (4% $Et_2O$ in hexanes) to provide a colorless oil (53.9 mg, 99% yield); 92% ee, $[\alpha]_D^{25}$ –93.7 (*c* 1.00, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.16 (m, 2H), 6.96 – 6.89 (m, 2H), 6.74 (t, *J* = 2.2 Hz, 2H), 6.25 (t, *J* = 2.2 Hz, 2H), 5.34 (dddd, *J* = 16.9, 10.2, 7.8, 6.6 Hz, 1H), 5.07 (ddt, *J* = 10.1, 1.9, 1.0 Hz, 1H), 5.01 (dq, *J* = 16.9, 1.5 Hz, 1H), 2.89 (ddt, *J* = 7.9, 2.3, 1.1 Hz, 2H), 2.29 (dq, *J* = 13.6, 7.5 Hz, 1H), 2.22 – 2.11 (m, 1H), 0.75 (t, *J* = 7.4 Hz, 3H); $^{19}F$ NMR (282 MHz, $CDCl_3$) δ -105.6 – -105.7 (m); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 197.4, 165.3 (d, *J* = 254.7 Hz), 132.3 (d, *J* = 3.6 Hz), 131.5 (d, *J* = 9.5 Hz), 131.5, 119.7, 118.9, 115.6 (d, *J* = 21.5 Hz), 109.5, 70.6, 39.1, 27.4, 7.6; IR (Neat Film, NaCl) 3078, 2977, 2882, 1682, 1642, 1598, 1504, 1484, 1463, 1266, 1235, 1161, 1093, 1075, 1006, 921, 853, 841, 759, 726$cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{17}H_{19}FNO$ $[M+H]^+$: 272.1445, found 272.1446; SFC Conditions: 5% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): major = 2.74, minor = 3.02




**(*S*)-1-(4-bromophenyl)-2-ethyl-2-(1*H*-pyrrol-1-yl)pent-4-en-1-one (101k)**

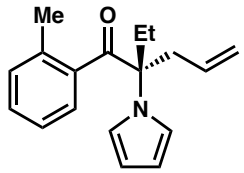
Purified by column chromatography (2% $Et_2O$ in hexanes) to provide a colorless oil (60.0 mg, 90% yield); 97% ee, $[\alpha]_D^{25}$ –73.6 (*c* 1.00, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.36 (m, 2H), 7.04 – 6.97 (m, 2H), 6.73 (t, *J* = 2.2 Hz, 2H), 6.24 (t, *J* = 2.2 Hz,

2H), 5.33 (dddd, *J* = 16.8, 10.2, 8.0, 6.5 Hz, 1H), 5.06 (ddt, *J* = 10.2, 2.0, 1.0 Hz, 1H), 5.04 – 4.98 (m, 1H), 2.95 – 2.79 (m, 2H), 2.27 (dq, *J* = 13.6, 7.6 Hz, 1H), 2.19 – 2.08 (m, 1H), 0.74 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 198.0, 134.6, 131.9, 131.3, 130.3, 127.9, 119.8, 118.9, 109.6, 70.6, 38.9, 27.2, 7.6; IR (Neat Film, NaCl) 3074, 2975, 1682, 1642, 1582, 1483, 1462, 1394, 1266, 1227, 1384, 1150, 1093, 1074, 1004, 979, 918, 844, 818, 751, 725 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{17}H_{19}BrNO$ $[M+H]^+$: 332.0645, found 332.0640; SFC Conditions: 2% IPA, 2.5 mL/min, Chiralpak IC column, λ = 210 nm, $t_R$ (min): minor = 5.80, major = 6.29.



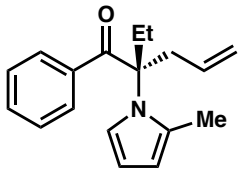

**(*S*)-2-ethyl-2-(1*H*-pyrrol-1-yl)-1-(*m*-tolyl)pent-4-en-1-one (101l)**

Purified by column chromatography (2% $Et_2O$ in hexanes) to provide a colorless oil (53.4 mg, 99% yield); 93% ee, $[\alpha]_D^{25}$ –96.6 (*c* 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.24 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.11 (t, *J* = 7.7 Hz, 1H), 7.04 (s, 1H), 6.86 (dt, *J* = 7.9, 1.3 Hz, 1H), 6.76 (t, *J* = 2.2 Hz, 2H), 6.24 (t, *J* = 2.2 Hz, 2H), 5.35 (ddt, *J* = 17.2, 10.2, 7.3 Hz, 1H), 5.11 – 4.97 (m, 2H), 2.94 – 2.84 (m, 2H), 2.26 (s, 3H), 2.32 – 2.12 (m, 2H), 0.75 (t, *J* = 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.3, 138.2, 136.0, 133.3, 131.7, 129.4, 128.4, 125.6, 119.5, 118.9, 109.3, 70.5, 39.0, 27.2, 21.4, 7.6; IR (Neat Film, NaCl) 3067, 2977, 2942, 2882, 1682, 1642, 1601, 1584, 1484, 1462, 1266, 1251, 1190, 1140, 1093, 923, 790, 724, 694 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{18}H_{22}NO$ $[M+H]^+$: 268.1696, found 268.1699; SFC Conditions: 3% IPA, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, $t_R$ (min): minor = 2.63, major = 2.84.




**(*S*)-2-ethyl-2-(1*H*-pyrrol-1-yl)-1-(*o*-tolyl)pent-4-en-1-one (101m)**

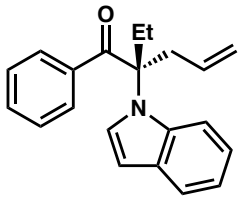
Purified by column chromatography (2% $Et_2O$ in hexanes) to provide a white solid (45.6 mg, 85% yield); 90% ee, $[\alpha]_D^{25}$ –67.5 (*c* 1.00, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.17 (m, 2H), 6.96 – 6.89 (m, 1H), 6.79 (t, *J* = 2.2 Hz, 2H), 6.23 (t, *J* = 2.2 Hz, 2H), 6.12 (dd, *J* = 7.9, 1.3 Hz, 1H), 5.44 (dddd, *J* = 16.7, 10.3, 8.0, 6.3 Hz, 1H), 5.12 – 5.00 (m, 2H), 2.98 (ddq, *J* = 14.4, 6.3, 1.3 Hz, 1H), 2.92 – 2.83 (m, 1H), 2.36 (s, 3H), 2.31 – 2.21 (m, 1H), 2.20 – 2.09 (m, 1H), 0.80 (t, *J* = 7.4 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 202.3, 138.1, 136.5, 131.8, 131.7, 130.6, 126.6, 125.5, 119.6, 118.8, 109.3, 70.4, 38.3, 26.9, 21.1, 7.4; IR (Neat Film, NaCl) 3071, 2972, 2932, 2875, 1688, 1645, 1485, 1456, 1383, 1318, 1289, 1262, 1121, 1084, 999, 965, 917, 755, 748, 723 $cm^1$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{18}H_{22}NO$ $[M+H]^+$: 268.1696, found 268.1705; SFC Conditions: 3% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): major = 4.38, minor = 4.80.




**(*S*)-2-ethyl-2-(2-methyl-1*H*-pyrrol-1-yl)-1-phenylpent-4-en-1-one (101n)**

Purified by column chromatography (2% $Et_2O$ in hexanes) to provide a colorless oil (48.7 mg, 91% yield); 90% ee, $[\alpha]_D^{25}$ –105.4 (*c* 1.00, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.40 (m, 1H), 7.30 – 7.21 (m, 4H), 6.93 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.16 (t, *J* = 3.2 Hz, 1H), 5.91 (ddq, *J* = 3.6, 1.8, 0.9 Hz, 1H), 5.30 (dddd, *J* = 16.6, 10.2, 8.3, 6.1 Hz, 1H),

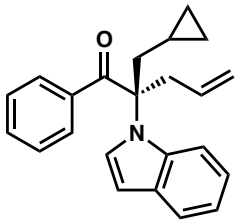
5.11 – 4.97 (m, 2H), 3.03 – 2.93 (m, 1H), 2.89 (ddt, *J* = 14.3, 8.3, 0.9 Hz, 1H), 2.39 – 2.27 (m, 1H), 2.17 (dqd, *J* = 13.5, 7.4, 1.2 Hz, 1H), 1.98 (s, 3H), 0.71 (t, *J* = 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.2, 135.7, 132.9, 131.8, 129.5, 129.2, 128.7, 119.6, 118.0, 110.4, 107.6, 70.6, 37.8, 27.2, 14.0, 7.6; IR (Neat Film, NaCl) 3070, 2977, 1683, 1596, 1446, 1417, 1268, 1228, 1146, 1085, 1006, 920, 840, 780, 724, 692 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{18}H_{21}NONa$ $[M+Na]^+$: 290.1515, found 290.1516; SFC Conditions: 2% IPA, 2.5 mL/min, Chiralcel OD-H column, λ = 210 nm, $t_R$ (min): major = 6.13, minor = 6.59.




**(*S*)-2-ethyl-2-(1*H*-indol-1-yl)-1-phenylpent-4-en-1-one (101o)**

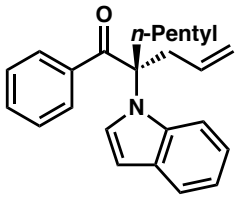
Purified by column chromatography (2% $Et_2O$ in hexanes) to provide a colorless oil (54.1 mg, 89% yield); 92% ee, $[\alpha]_D^{25}$ –115.2 (*c* 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.59 (m, 1H), 7.48 (d, *J* = 3.4 Hz, 1H), 7.33 (ddt, *J* = 8.6, 7.0, 1.3 Hz, 1H), 7.29 – 7.26 (m, 2H), 7.21 – 7.11 (m, 3H), 7.07 – 6.97 (m, 2H), 6.68 (dd, *J* = 3.3, 0.9 Hz, 1H), 5.23 (dddd, *J* = 16.5, 10.1, 8.5, 6.0 Hz, 1H), 5.02 (ddd, *J* = 10.2, 2.3, 1.1 Hz, 1H), 4.96 (ddt, *J* = 16.9, 1.9, 1.2 Hz, 1H), 3.29 (ddq, *J* = 14.3, 6.0, 1.4 Hz, 1H), 3.00 (dd, *J* = 14.3, 8.4 Hz, 1H), 2.57 (dq, *J* = 13.3, 7.5 Hz, 1H), 2.31 (dqd, *J* = 13.4, 7.4, 1.3 Hz, 1H), 0.76 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 200.3, 135.8, 135.7, 132.9, 131.5, 129.7, 128.6, 128.6, 124.5, 122.2, 121.3, 120.1, 119.8, 111.8, 102.8, 70.6, 36.7, 26.8, 7.6; IR (Neat Film, NaCl) 3069, 2980, 1681, 1596, 1512, 1457, 1311, 1296, 1226, 1185, 1142, 1005, 925, 742, 721, 691 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{21}H_{22}NO$

$[M+H]^+$: 304.1696, found 304.1706; SFC Conditions: 5% IPA, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, $t_R$ (min): minor = 5.19, major = 5.71.



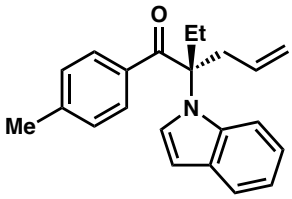

**(*R*)-2-(cyclopropylmethyl)-2-(1*H*-indol-1-yl)-1-phenylpent-4-en-1-one (101p)**

Performed on 0.1 mmol scale. Purified by column chromatography (4% $Et_2O$ in hexanes) to provide a colorless oil (33.1 mg, 94% yield); 92% ee, $[\alpha]_D^{25}$ –49.9 (*c* 1.00, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.64 – 7.58 (m, 1H), 7.47 (d, *J* = 3.4 Hz, 1H), 7.37 – 7.30 (m, 3H), 7.20 – 7.11 (m, 3H), 7.06 – 6.97 (m, 2H), 6.68 (dd, *J* = 3.3, 0.9 Hz, 1H), 5.29 (q, *J* = 9.1, 8.2 Hz, 1H), 5.10 – 4.92 (m, 2H), 3.50 (dd, *J* = 14.1, 6.0 Hz, 1H), 3.21 (dd, *J* = 14.0, 8.2 Hz, 1H), 2.54 (dd, *J* = 13.8, 6.0 Hz, 1H), 2.23 (dd, *J* = 13.8, 6.7 Hz, 1H), 0.53 – 0.27 (m, 3H), –0.10 (s, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 200.1, 135.8, 135.6, 132.9, 131.6, 129.6, 128.7, 128.5, 124.4, 122.2, 121.2, 120.1, 120.0, 111.8, 102.8, 71.0, 38.3, 38.2, 5.4, 5.0, 4.0; IR (Neat Film, NaCl) 3076, 3003, 2362, 2341, 1678, 1595, 1457, 1309, 1229, 1019, 922, 764, 743, 724, 692 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{23}H_{24}NO$ $[M+H]^+$: 330.1858, found 330.1861; SFC Conditions: 5% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 10.38, major = 11.27.




**(*S*)-2-allyl-2-(1*H*-indol-1-yl)-1-phenylheptan-1-one (101q)**

Purified by column chromatography (2% $Et_2O$ in hexanes) to provide a colorless oil (48.6 mg, 70% yield); 90% ee, $[\alpha]_D^{25}$ –94.5 (*c* 1.00, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.65 – 7.59 (m, 1H), 7.50 (d, *J* = 3.3 Hz, 1H), 7.33 (tt, *J* = 7.3, 1.3 Hz, 1H), 7.31 – 7.27 (m, 2H), 7.21 (dq, *J* = 7.1, 1.1 Hz, 1H), 7.17 – 7.12 (m, 2H), 7.03 (tt, *J* = 7.1, 5.5 Hz, 2H), 6.69 (dd, *J* = 3.4, 0.9 Hz, 1H), 5.23 (ddd, *J* = 16.3, 9.6, 4.6 Hz, 1H), 5.13 – 4.91 (m, 2H), 3.38 – 3.25 (m, 1H), 3.02 (dd, *J* = 14.2, 8.6 Hz, 1H), 2.52 (td, *J* = 13.1, 3.9 Hz, 1H), 2.33 – 2.18 (m, 1H), 1.26 – 1.02 (m, 6H), 0.89 – 0.77 (m, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 200.3, 135.7, 135.6, 132.8, 131.7, 129.7, 128.5, 124.4, 122.2, 121.2, 120.1, 119.7, 111.8, 102.8, 70.2, 37.4, 33.9, 32.0, 22.7, 22.3, 14.0; IR (Neat Film, NaCl) 2956, 2929, 2870, 1679, 1596, 1457, 1313, 1225, 922, 764, 743, 692 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{24}H_{28}NO$ $[M+H]^+$: 346.2171, found 346.2168; SFC Conditions: 5% IPA, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, $t_R$ (min): major = 3.55, minor = 4.34.

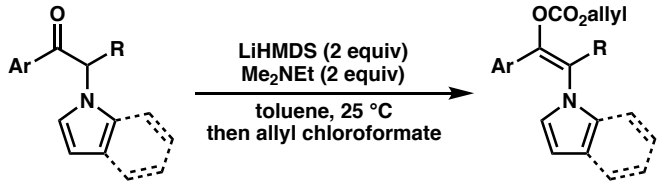



**(*S*)-2-ethyl-2-(1*H*-indol-1-yl)-1-(*p*-tolyl)pent-4-en-1-one (101r)**

Performed on 0.107 mmol scale. Purified by column chromatography (3% $Et_2O$ in hexanes) to provide a colorless oil (23.3 mg, 73% yield); 95% ee, $[\alpha]_D^{25}$ –87.8 (*c* 1.00,

$CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.64 – 7.58 (m, 1H), 7.49 (d, *J* = 3.4 Hz, 1H), 7.24 – 7.16 (m, 3H), 7.02 (tt, *J* = 7.0, 5.5 Hz, 2H), 6.95 (d, *J* = 8.1 Hz, 2H), 6.68 (dd, *J* = 3.3, 0.9 Hz, 1H), 5.23 (dq, *J* = 16.6, 8.5 Hz, 1H), 5.08 – 4.90 (m, 2H), 3.38 – 3.23 (m, 1H), 3.02 (dd, *J* = 14.2, 8.5 Hz, 1H), 2.58 (dq, *J* = 13.3, 7.5 Hz, 1H), 2.33 (dtd, *J* = 14.6, 8.6, 8.0, 6.8 Hz, 1H), 2.23 (s, 3H), 0.78 (t, *J* = 7.4 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 199.7, 143.7, 135.6, 133.1, 131.7, 129.6, 129.3, 128.7, 124.4, 122.1, 121.2, 120.0, 119.6, 111.8, 102.7, 70.6, 36.8, 27.0, 21.6, 7.7; IR (Neat Film, NaCl) 2978, 2360, 1674, 1605, 1457, 1295, 1226, 1186, 1142, 922, 742 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{22}H_{24}NO$ $[M+H]^+$: 318.1858, found 318.1845; SFC Conditions: 5% IPA, 2.5 mL/min, Chiralpak IC column, λ = 210 nm, $t_R$ (min): minor = 6.97, major = 7.61.

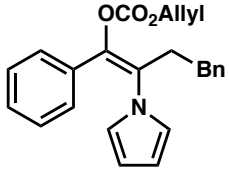
### 6.8.2.3 General Procedure for Preparation of Allyl Enol Carbonates




To a flame-dried flask was added LiHMDS (335 mg, 2 mmol) followed by toluene (3.0 mL) and N,N-dimethylethylamine (0.213 mL), and the resulting mixture stirred at 25 °C for 5 minutes. A solution of ketone (1 mmol) in toluene (2.0 mL) was then added, and the reaction continued at 25 °C for an additional 30 minutes. The flask was then submerged in a room temperature water bath and allyl chloroformate (0.217 mL, 2 mmol) was added slowly, and the reaction continued until no starting material remained by TLC (typically less than 30 minutes). The crude reaction mixture was diluted with $Et_2O$ and quenched with water. The layers were separated, and the aqueous

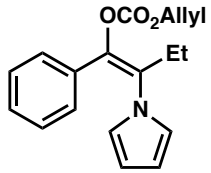
layer was extracted with $Et_2O$ twice. The combined organic layers were dried over $Na_2SO_4$ and concentrated. The crude product was purified by silica gel flash chromatography to afford the desired enol carbonate. The *E/Z* ratio of enol carbonates was determined by $^1H$ NMR and is >95:5 unless stated otherwise.

### 6.8.2.4 Spectroscopic Data for the Allyl Enol Carbonates



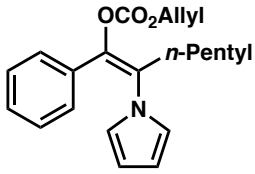

**(*E*)-allyl (1,4-diphenyl-2-(1*H*-pyrrol-1-yl)but-1-en-1-yl) carbonate (100a)**

Run on 1.0 mmol scale. Purified by column chromatography (10% $Et_2O$ in hexanes) to provide a yellow oil (363.1 mg, 97% yield); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 7.23 – 7.16 (m, 6H), 6.99 – 6.95 (m, 2H), 6.50 (t, *J* = 2.1 Hz, 2H), 6.16 (t, *J* = 2.2 Hz, 2H), 5.92 (ddt, *J* = 17.2, 10.5, 5.8 Hz, 1H), 5.36 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.29 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.65 (dt, *J* = 5.8, 1.4 Hz, 2H), 2.93 – 2.84 (m, 2H), 2.78 – 2.63 (m, 2H); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ 153.0, 142.7, 140.9, 133.0, 131.6, 131.1, 128.7, 128.5, 128.5, 128.4, 127.1, 126.3, 121.1, 119.6, 109.8, 69.4, 33.9, 32.7; IR (Neat Film, NaCl) 1762, 1482, 1348, 1228, 1138, 1080, 1040, 942, 729, 696 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{24}H_{24}NO_3$ $[M+H]^+$: 374.1751, found 374.1745.




**(*E*)-allyl (1-phenyl-2-(1*H*-pyrrol-1-yl)but-1-en-1-yl) carbonate (100b)**

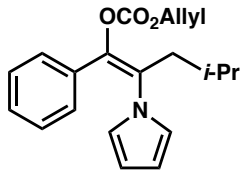
Run on a 1.47 mmol scale. Purified by column chromatography (10% $Et_2O$ in hexanes) to provide a colorless oil (380.2 mg, 87% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.15 (m, 3H), 7.04 – 6.95 (m, 2H), 6.52 (t, *J* = 2.1 Hz, 2H), 6.16 (t, *J* = 2.2 Hz, 2H), 5.94 (ddt, *J* = 17.4, 10.5, 5.8 Hz, 1H), 5.38 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.30 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.67 (dt, *J* = 5.8, 1.4 Hz, 2H), 2.61 (q, *J* = 7.5 Hz, 2H), 1.00 (t, *J* = 7.5 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 153.1, 141.9, 133.7, 133.1, 131.1, 128.6, 128.3, 127.0, 121.2, 119.6, 109.6, 69.4, 25.2, 11.1; IR (Neat Film, NaCl) 3060, 2977, 2938, 2877, 1766, 1494, 1483, 1458, 1446, 1364, 1347, 1320, 1292, 1260, 1224, 1145, 1121, 1085, 1039, 990, 946, 922, 901, 843, 775, 730, 696 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{18}H_{20}NO_3$ $[M+H]^+$: 298.1438, found 298.1442.




**(*E*)-allyl (1-phenyl-2-(1*H*-pyrrol-1-yl)hept-1-en-1-yl) carbonate (100c)**

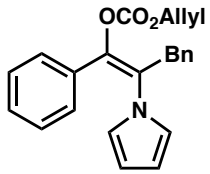
Run on a 1.31 mmol scale. Purified by column chromatography (5% $Et_2O$ in hexanes) to provide a slightly brown oil (421.4 mg, 95% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.16 (m, 3H), 7.02 – 6.94 (m, 2H), 6.51 (t, *J* = 2.1 Hz, 2H), 6.14 (t, *J* = 2.2 Hz, 2H), 5.93 (ddt, *J* = 17.2, 10.5, 5.8 Hz, 1H), 5.37 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.30 (dq, *J* = 10.5, 1.2 Hz, 1H), 4.66 (dt, *J* = 5.7, 1.4 Hz, 2H), 2.56 (dd, *J* = 8.0, 6.5 Hz, 2H), 1.44 – 1.22 (m, 5H), 0.92 – 0.83 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.1, 142.4, 133.2, 132.6,

131.2, 128.6, 128.3, 127.1, 121.1, 119.5, 109.5, 69.3, 31.8, 31.5, 26.1, 22.5, 14.1; IR (Neat Film, NaCl) 3061, 3026, 2957, 2931, 2861, 1767, 1494, 1483, 1446, 1380, 1363, 1347, 1292, 1229 (br), 1144, 1125, 1087, 1071, 1040, 988, 944, 862, 774, 729, 696 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{21}H_{26}NO_3$ $[M+H]^+$: 340.1907, found 340.1893.




**(*E*)-allyl (4-methyl-1-phenyl-2-(1*H*-pyrrol-1-yl)pent-1-en-1-yl) carbonate (100d)**

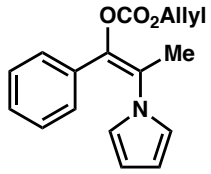
Run on a 1.22 mmol scale. Purified by column chromatography (7% $Et_2O$ in hexanes) to provide a white solid (324.2 mg, 82% yield); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.16 (m, 3H), 7.03 – 6.95 (m, 2H), 6.50 (t, *J* = 2.2 Hz, 2H), 6.12 (t, *J* = 2.1 Hz, 2H), 5.91 (ddt, *J* = 17.2, 10.5, 5.8 Hz, 1H), 5.35 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.28 (dq, *J* = 10.5, 1.2 Hz, 1H), 4.64 (dt, *J* = 5.8, 1.4 Hz, 2H), 2.46 (d, *J* = 7.2 Hz, 2H), 1.62 – 1.51 (m, 1H), 0.94 (s, 3H), 0.92 (s, 3H); $^{13}C$ NMR (101 MHz, Chloroform-*d*) δ 153.0, 143.0, 133.3, 131.7, 131.2, 128.6, 128.3, 127.1, 121.1, 119.5, 109.5, 69.3, 40.5, 26.0, 22.4; IR (Neat Film, NaCl) 2959, 2367, 1753, 1541, 1226, 1068, 1039, 785, 730 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{20}H_{23}NO_3Na$ $[M+Na]^+$: 348.1570, found 348.1564.




**(*E*)-allyl (1,3-diphenyl-2-(1*H*-pyrrol-1-yl)prop-1-en-1-yl) carbonate (100e)**

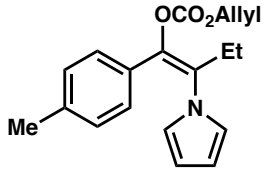
Run on a 1.58 mmol scale. Purified by column chromatography (8% $Et_2O$ in hexanes) to provide a white solid (461.7 mg, 81% yield); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.13 (m, 8H), 7.06 – 6.97 (m, 2H), 6.38 (t, *J* = 2.2 Hz, 2H), 6.05 (t, *J* = 2.2 Hz, 2H), 5.91 (ddt,

*J* = 17.2, 10.4, 5.8 Hz, 1H), 5.36 (dq, *J* = 17.2, 1.4 Hz, 1H), 5.29 (dq, *J* = 10.5, 1.2 Hz, 1H), 4.65 (dt, *J* = 5.8, 1.4 Hz, 2H), 3.89 (s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.0, 143.1, 137.0, 132.9, 131.1, 130.9, 128.9, 128.9, 128.7, 128.4, 127.1, 126.8, 121.3, 119.7, 109.6, 69.5, 38.3; IR (Neat Film, NaCl) 3028, 1763, 1481, 1454, 1346, 1230, 1136, 1070, 1038, 987, 937, 772, 729, 696 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{23}H_{22}NO_3$ $[M+H]^+$: 360.1594, found 360.1589.



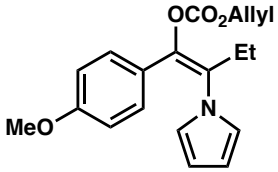

**(*E*)-allyl (1-phenyl-2-(1*H*-pyrrol-1-yl)prop-1-en-1-yl) carbonate (100f)**

Run on a 1.36 mmol scale. Purified by column chromatography (10% $Et_2O$ in hexanes) to provide a colorless oil (372.2 mg, 97% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.18 (m, 3H), 7.02 – 6.96 (m, 2H), 6.54 (t, *J* = 2.2 Hz, 2H), 6.14 (t, *J* = 2.2 Hz, 2H), 5.94 (ddt, *J* = 17.1, 10.3, 5.7 Hz, 1H), 5.38 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.34 – 5.27 (m, 1H), 4.67 (dt, *J* = 5.7, 1.4 Hz, 2H), 2.24 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 152.9, 141.9, 133.1, 131.1, 128.6, 128.4, 128.3, 127.2, 120.8, 119.5, 109.6, 69.4, 18.4; IR (Neat Film, NaCl) 3060, 2951, 1763, 1484, 1446, 1381, 1364, 1345, 1316, 1292, 1230, 1143, 1118, 1081, 1037, 998, 978, 940, 773, 729, 697, 623 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{17}H_{18}NO_3$ $[M+H]^+$: 284.1281, found 284.1285.




**(*E*)-2-(1*H*-pyrrol-1-yl)-1-(*p*-tolyl)but-1-en-1-yl allyl carbonate (100g)**

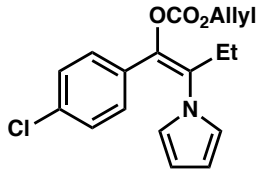
Run on a 0.736 mmol scale. Purified by column chromatography (7% EtOAc in hexanes) to provide a yellow oil (196.0 mg, 86% yield); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.02 – 6.97 (m, 2H), 6.89 – 6.83 (m, 2H), 6.53 (t, *J* = 2.2 Hz, 2H), 6.16 (t, *J* = 2.1 Hz, 2H), 5.94 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.38 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.30 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.66 (dt, *J* = 5.8, 1.4 Hz, 2H), 2.58 (q, *J* = 7.5 Hz, 2H), 2.27 (s, 3H), 0.98 (t, *J* = 7.5 Hz, 3H); $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 153.1, 142.1, 138.6, 133.0, 131.2, 130.2, 129.1, 126.9, 121.2, 119.5, 109.5, 69.3, 25.3, 21.4, 11.1; IR (Neat Film, NaCl) 3028, 2976, 2938, 2878, 1766, 1651, 1613, 1513, 1484, 1456, 1363, 1346, 1320, 1292, 1228, 1188, 1146, 1119, 1084, 1057, 1040, 990, 945, 903, 848, 824, 795, 782, 727 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{22}NO_3$ $[M+H]^+$: 312.1594, found 312.1578.




**(*E*)-allyl (1-(4-methoxyphenyl)-2-(1*H*-pyrrol-1-yl)but-1-en-1-yl) carbonate (100h)**

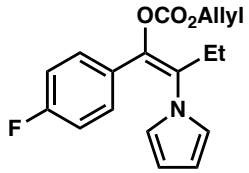
Run on a 0.955 mmol scale. Reaction washed three times with 1M HCl beforehand to remove an overlapping by-product resulting from the addition of LHMDS onto allyl chloroformate. Purified by column chromatography (10% EtOAc in hexanes) to provide a beige oil (253.8 mg, 81% yield); $^{1}$H NMR (500 MHz, $CDCl_3$) δ 6.92 – 6.86 (m, 2H), 6.75 – 6.67 (m, 2H), 6.53 (t, *J* = 2.1 Hz, 2H), 6.16 (t, *J* = 2.1 Hz, 2H), 5.94 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.38 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.30 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.66 (dt, *J* =

5.7, 1.4 Hz, 2H), 3.75 (s, 3H), 2.57 (q, $J$ = 7.4 Hz, 2H), 0.98 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 159.6, 153.1, 142.0, 132.3, 131.2, 128.4, 125.5, 121.2, 119.5, 113.8, 109.5, 69.3, 55.2, 25.2, 11.2; IR (Neat Film, NaCl) 2972, 2938, 2838, 1763, 1608, 1576, 1540, 1512, 1483, 1459, 1364, 1345, 1297, 1254, 1227, 1179, 1146, 1120, 1084, 1038, 990, 942, 836, 783, 730 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{22}NO_4$ $[M+H]^+$: 328.1543, found 328.1535.



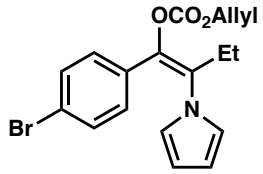

**(*E*)-allyl (1-(4-chlorophenyl)-2-(1*H*-pyrrol-1-yl)but-1-en-1-yl) carbonate (100i)**

Run on a 0.758 mmol scale. Purified by column chromatography (6% EtOAc in hexanes) to provide a yellow oil (227.8 mg, 91% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.12 (m, 2H), 6.94 – 6.84 (m, 2H), 6.50 (t, $J$ = 2.2 Hz, 2H), 6.17 (t, $J$ = 2.2 Hz, 2H), 5.93 (ddt, $J$ = 17.1, 10.4, 5.8 Hz, 1H), 5.38 (dq, $J$ = 17.2, 1.4 Hz, 1H), 5.31 (dq, $J$ = 10.4, 1.2 Hz, 1H), 4.66 (dt, $J$ = 5.8, 1.4 Hz, 2H), 2.58 (q, $J$ = 7.5 Hz, 2H), 0.98 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.0, 141.0, 134.4, 134.3, 131.7, 131.0, 128.7, 128.3, 121.0, 119.8, 109.9, 69.5, 25.2, 11.0; IR (Neat Film, NaCl) 3101, 2977, 2938, 2878, 1765, 1594, 1490, 1482, 1458, 1364, 1346, 1319, 1255, 1224, 1146, 1120, 1092, 1057, 1039, 1014, 990, 944, 903, 836, 785, 728 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{18}H_{19}ClNO_3$ $[M+H]^+$: 332.1048, found 332.1044.




**(*E*)-allyl (1-(4-fluorophenyl)-2-(1*H*-pyrrol-1-yl)but-1-en-1-yl) carbonate (100j)**

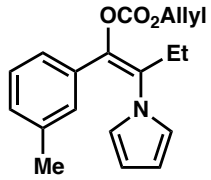
Run on a 0.902 mmol scale. Purified by column chromatography (6% EtOAc in hexanes) to provide a slightly yellow oil (258.8 mg, 91% yield); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.01 – 6.81 (m, 4H), 6.50 (t, *J* = 2.2 Hz, 2H), 6.16 (t, *J* = 2.2 Hz, 2H), 5.93 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.38 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.31 (dq, *J* = 10.5, 1.2 Hz, 1H), 4.66 (dt, *J* = 5.8, 1.3 Hz, 2H), 2.58 (q, *J* = 7.5 Hz, 2H), 0.98 (t, *J* = 7.5 Hz, 3H); $^{19}$F NMR (282 MHz, $CDCl_3$) δ -112.1 (dddd, *J* = 13.9, 8.4, 5.6, 1.6 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 162.4 (d, *J* = 249.1 Hz), 152.9, 141.0, 133.6, 130.9, 129.1 (d, *J* = 3.5 Hz), 128.9 (d, *J* = 8.2 Hz), 120.9, 119.6, 115.4 (d, *J* = 21.7 Hz), 109.7, 69.4, 25.1, 11.0; IR (Neat Film, NaCl) 2976, 1764, 1604, 1509, 1483, 1460, 1364, 1346, 1293, 1256, 1226, 1162, 1145, 1120, 1084, 1039, 990, 945, 904, 842, 780, 727 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{18}H_{19}FNO_3$ $[M+H]^+$: 316.1343, found 316.1346.




**(*E*)-allyl (1-(4-bromophenyl)-2-(1*H*-pyrrol-1-yl)but-1-en-1-yl) carbonate (100k)**

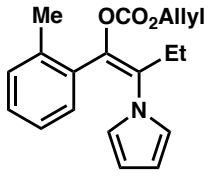
Run on a 0.669 mmol scale. Purified by column chromatography (6% EtOAc in hexanes) to provide a yellow oil (195.7 mg, 78% yield); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H), 6.86 – 6.78 (m, 2H), 6.50 (t, *J* = 2.2 Hz, 2H), 6.17 (t, *J* = 2.1 Hz, 2H), 5.93 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.38 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.31 (dq, *J* = 10.1, 1.0 Hz, 1H), 4.66 (dt, *J* = 5.8, 1.3 Hz, 2H), 2.58 (q, *J* = 7.5 Hz, 2H), 0.98 (t, *J* = 7.5 Hz, 3H); $^{13}$C

NMR (100 MHz, $CDCl_3$) δ 153.0, 141.0, 134.4, 132.1, 131.6, 131.0, 128.6, 122.8, 121.0, 119.8, 110.0, 69.5, 25.3, 11.0; IR (Neat Film, NaCl) 2977, 2937, 1765, 1588, 1483, 1460, 1364, 1346, 1254, 1225, 1145, 1120, 1084, 1072, 1039, 990, 945, 902, 831, 784, 729 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{18}H_{19}BrNO_3$ $[M+NH_4]^+$: 376.0543, found 376.0540.




**(*E*)-2-(1*H*-pyrrol-1-yl)-1-(*m*-tolyl)but-1-en-1-yl allyl carbonate (100l)**

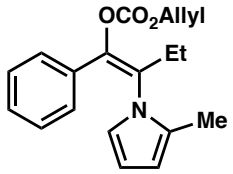
Run on a 1.0 mmol scale. Purified by column chromatography (6% EtOAc in hexanes) to provide a yellow oil (294.0 mg, 94% yield); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.12 – 6.96 (m, 2H), 6.81 – 6.75 (m, 2H), 6.51 (t, *J* = 2.2 Hz, 2H), 6.15 (t, *J* = 2.2 Hz, 2H), 5.94 (ddt, *J* = 17.2, 10.5, 5.8 Hz, 1H), 5.38 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.34 – 5.27 (m, 1H), 4.67 (dt, *J* = 5.7, 1.4 Hz, 2H), 2.59 (q, *J* = 7.5 Hz, 2H), 2.21 (s, 3H), 0.99 (t, *J* = 7.5 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 153.1, 142.1, 137.9, 133.5, 132.9, 131.2, 129.4, 128.1, 127.6, 124.1, 121.2, 119.5, 109.5, 69.3, 25.2, 21.5, 11.1; IR (Neat Film, NaCl) 2975, 1764, 1484, 1364, 1346, 1234, 1190, 1120, 1085, 1040, 988, 942, 874, 784, 727, 698 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{22}NO_3$ $[M+H]^+$: 312.1594, found 312.1593.




**(E)-2-(1*H*-pyrrol-1-yl)-1-(*o*-tolyl)but-1-en-1-yl allyl carbonate (100m)**

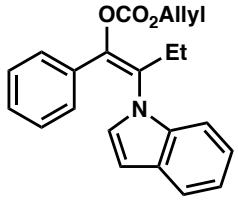
Run on a 0.546 mmol scale. Purified by column chromatography (6% EtOAc in hexanes) to provide a colorless oil (138.7 mg, 82% yield); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.25 –

7.22 (m, 1H), 7.19 – 7.14 (m, 1H), 7.12 – 7.06 (m, 2H), 6.42 (t, $J$ = 2.2 Hz, 2H), 6.01 (t, $J$ = 2.2 Hz, 2H), 5.89 (ddt, $J$ = 17.2, 10.5, 5.8 Hz, 1H), 5.33 (dq, $J$ = 17.2, 1.5 Hz, 1H), 5.27 (dq, $J$ = 10.4, 1.2 Hz, 1H), 4.60 (dt, $J$ = 5.8, 1.3 Hz, 2H), 2.66 (q, $J$ = 7.5 Hz, 2H), 2.08 (s, 3H), 1.03 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.0, 140.2, 137.9, 134.7, 132.8, 131.2, 130.1, 129.8, 129.0, 125.7, 121.0, 119.5, 109.0, 69.2, 24.3, 19.5, 11.7; IR (Neat Film, NaCl) 2974, 1761, 1482, 1458, 1346, 1292, 1254, 1225, 1147, 1122, 1084, 1038, 990, 945, 725 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{22}NO_3$ $[M+H]^+$: 312.1594, found 312.1601.



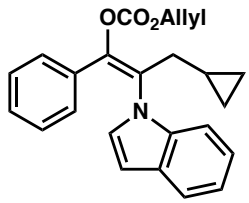

**(*E*)-allyl (2-(2-methyl-1*H*-pyrrol-1-yl)-1-phenylbut-1-en-1-yl) carbonate (100n)**

Run on a 0.532 mmol scale. Purified by column chromatography (7% EtOAc in hexanes) to provide a colorless oil (156.6 mg, 95% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.13 (m, 3H), 6.91 – 6.84 (m, 2H), 6.56 (dd, $J$ = 2.9, 1.7 Hz, 1H), 6.15 (t, $J$ = 3.1 Hz, 1H), 5.95 (ddt, $J$ = 17.2, 10.4, 5.8 Hz, 1H), 5.86 (ddq, $J$ = 3.5, 1.8, 0.9 Hz, 1H), 5.39 (dq, $J$ = 17.2, 1.5 Hz, 1H), 5.31 (dq, $J$ = 10.5, 1.2 Hz, 1H), 4.69 (dt, $J$ = 5.8, 1.4 Hz, 2H), 2.57 (q, $J$ = 7.5 Hz, 2H), 1.89 (d, $J$ = 0.9 Hz, 3H), 0.99 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.1, 144.0, 133.0, 132.1, 131.1, 129.2, 128.6, 128.4, 126.7, 119.6, 119.6, 109.1, 107.9, 69.4, 25.8, 12.1, 10.7; IR (Neat Film, NaCl) 2976, 2940, 1764, 1481, 1445, 1420, 1363, 1343, 1260, 1224, 1183, 1132, 1110, 1042, 988, 947, 776, 698 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{22}NO_3$ $[M+H]^+$: 312.1594, found 312.1597.




**(*E*)-2-(1*H*-indol-1-yl)-1-phenylbut-1-en-1-yl allyl carbonate (100o)**

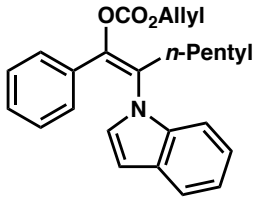
Run on a 0.647 mmol scale. Purified by column chromatography (8% EtOAc in hexanes) to provide a beige oil (213.9 mg, 95% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.59 (dt, *J* = 7.5, 0.9 Hz, 1H), 7.28 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.15 – 7.05 (m, 5H), 6.99 – 6.94 (m, 3H), 6.56 (dd, *J* = 3.3, 0.9 Hz, 1H), 5.98 (ddt, *J* = 17.1, 10.4, 5.8 Hz, 1H), 5.43 (dq, *J* = 17.1, 1.4 Hz, 1H), 5.34 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.73 (dt, *J* = 5.8, 1.4 Hz, 2H), 2.74 (q, *J* = 7.5 Hz, 2H), 0.94 (t, *J* = 7.5 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 153.2, 145.0, 136.2, 133.1, 131.8, 131.3, 128.9, 128.9, 128.4, 128.0, 126.8, 122.4, 121.0, 120.3, 119.7, 111.1, 103.9, 69.6, 24.7, 11.2; IR (Neat Film, NaCl) 3058, 2976, 2940, 1764, 1513, 1494, 1474, 1458, 1363, 1335, 1292, 1260, 1224, 1144, 1012, 988, 946, 846, 764, 743, 694 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{22}H_{22}NO_3$ $[M+H]^+$: 348.1594, found 348.1601.




**(*E*)-allyl (3-cyclopropyl-2-(1*H*-indol-1-yl)-1-phenylprop-1-en-1-yl) carbonate (100p)**

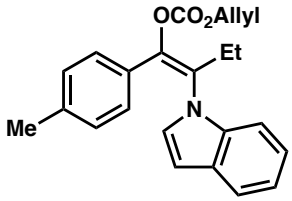
Run on a 0.514 mmol scale. Purified by column chromatography (7% EtOAc in hexanes) to provide a brown oil (164.8 mg, 86% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.58 (dt, *J* = 7.4, 0.9 Hz, 1H), 7.28 (dq, *J* = 8.4, 0.9 Hz, 1H), 7.15 – 7.04 (m, 5H), 7.03 – 6.97 (m, 3H), 6.54 (dd, *J* = 3.2, 0.9 Hz, 1H), 5.96 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.40 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.32 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.71 (dt, *J* = 5.7, 1.4 Hz, 2H), 2.57 (d, *J* =

7.0 Hz, 2H), 0.72 – 0.56 (m, 1H), 0.35 – 0.25 (m, 2H), -0.03 (dt, *J* = 6.0, 4.6 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.0, 145.3, 136.1, 132.9, 131.1, 130.5, 128.8, 128.8, 128.3, 128.1, 126.8, 122.2, 120.9, 120.1, 119.6, 111.0, 103.6, 69.5, 35.7, 8.7, 4.3; IR (Neat Film, NaCl) 3081, 3004, 2956, 1766, 1514, 1494, 1475, 1459, 1426, 1383, 1362, 1335, 1293, 1249, 1223, 1158, 1132, 1020, 966, 946, 831, 763, 743, 721, 695 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{24}H_{24}NO_3$ $[M+H]^+$: 374.1751, found 374.1748.




**(*E*)-2-(1*H*-indol-1-yl)-1-phenylhept-1-en-1-yl allyl carbonate (100q)**

Run on a 0.89 mmol scale. Purified by column chromatography (7% EtOAc in hexanes) to provide a beige oil (325.5 mg, 94% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.52 (m, 1H), 7.30 – 7.20 (m, 1H), 7.17 – 7.00 (m, 5H), 7.00 – 6.90 (m, 3H), 6.59 – 6.50 (m, 1H), 5.97 (ddt, *J* = 16.5, 11.0, 5.7 Hz, 1H), 5.41 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.33 (dt, *J* = 10.5, 1.3 Hz, 1H), 4.75 – 4.66 (m, 2H), 2.74 – 2.64 (m, 2H), 1.28 (ddt, *J* = 20.1, 13.5, 6.0 Hz, 6H), 0.83 (t, *J* = 6.9 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 153.1, 145.2, 136.0, 133.0, 131.2, 130.8, 128.8, 128.7, 128.3, 127.9, 126.8, 122.3, 120.9, 120.1, 119.5, 111.0, 103.8, 69.4, 31.6, 31.2, 26.2, 22.4, 14.0; IR (Neat Film, NaCl) 3057, 2957, 2929, 2860, 1764, 1513, 1494, 1475, 1458, 1381, 1363, 1334, 1293, 1225, 1158, 1143, 1130, 1012, 992, 958, 764, 742, 696 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{25}H_{28}NO_3$ $[M+H]^+$: 390.2064, found 390.2064.

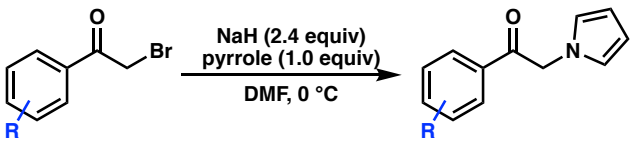



**(*E*)-2-(1*H*-indol-1-yl)-1-(*p*-tolyl)but-1-en-1-yl allyl carbonate (100r)**

Run on a 0.14 mmol scale. Purified by column chromatography (10% EtOAc in hexanes) to provide a brown oil (51.0 mg, 99% yield); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.54 (m, 1H), 7.28 (dd, J = 8.2, 1.1 Hz, 1H), 7.16 – 7.05 (m, 2H), 6.93 (d, J = 3.3 Hz, 1H), 6.90 – 6.81 (m, 4H), 6.54 (dd, J = 3.2, 0.9 Hz, 1H), 5.97 (ddt, J = 17.2, 10.4, 5.8 Hz, 1H), 5.41 (dq, J = 17.2, 1.5 Hz, 1H), 5.33 (dq, J = 10.5, 1.2 Hz, 1H), 4.71 (dt, J = 5.8, 1.4 Hz, 2H), 2.70 (q, J = 7.5 Hz, 2H), 2.17 (s, 3H), 0.90 (t, J = 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.1, 145.0, 138.8, 136.1, 131.2, 131.0, 130.0, 129.1, 128.8, 128.1, 126.6, 122.3, 120.9, 120.1, 119.6, 111.0, 103.6, 69.4, 24.6, 21.3, 11.2; IR (Neat Film, NaCl) 2976, 1764, 1610, 1512, 1475, 1459, 1381, 1361, 1335, 1293, 1259, 1226, 1187, 1145, 1013, 989, 946, 822, 764, 742 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{23}H_{24}NO_3$ $[M+H]^+$: 362.1752, found 362.1749.

### 6.8.2.5 Synthesis of alpha-Pyrrolyl Acetophenone Derivatives

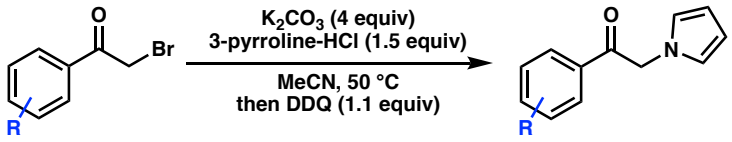
**Method A:**



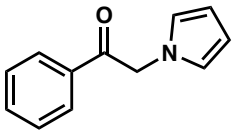

To a flame-dried flask was added freshly distilled pyrrole (2.0 mmol, 1 equiv) and DMF (8 mL), and the resulting mixture was stirred at room temperature for 5 minutes. Then, NaH (4.8 mmol, 2.4 equiv) was slowly added at 0 °C with vigorous stirring until no

hydrogen evolution was observed. Afterwards, the bromoacetophenone derivative (2.0 mmol, 1 equiv) was added and the suspension was allowed to warm to room temperature and continued overnight. The reaction was quenched with aqueous $NH_4Cl$ and extracted with $Et_2O$. The combined organic layers were washed with brine, dried with $Na_2SO_4$, and filtered. Following concentration, the crude residue was purified by silica gel column chromatography.

**Method B:**



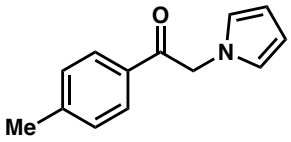

To a solution of the bromoacetophenone derivative (2.0 mmol) and $K_2CO_3$ (8.0 mmol, 4 equiv) in MeCN (16 mL) was added 3-pyrroline hydrochloride (2.4 mmol, 1.2 equiv), and the mixture was stirred at 50 °C until TLC analysis showed complete consumption of the starting material. DDQ was then added (2.2 mmol, 1.1 equiv) and the resulting mixture was stirred at the same temperature overnight. The crude reaction mixture was filtered through celite (using $CH_2Cl_2$ as eluent), concentrated, and then purified by silica gel flash chromatography to obtain the desired product.




**1-phenyl-2-(1*H*-pyrrol-1-yl)ethan-1-one (105)**

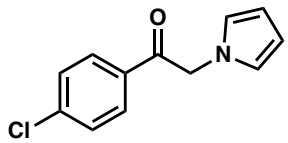
Method A run on a 20.1 mmol scale. Purified by column chromatography (30% $Et_2O$ in hexanes) to provide an orange solid (920 mg, 25% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.94 (m, 2H), 7.67 – 7.60 (m, 1H), 7.54 – 7.48 (m, 2H), 6.68 (t, J = 2.1 Hz, 2H),

6.25 (t, J = 2.1 Hz, 2H), 5.32 (s, 2H). Characterization data matched those reported in the literature.



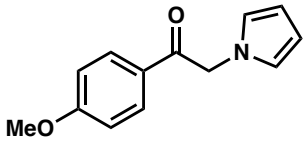

**2-(1*H*-indol-1-yl)-1-phenylethan-1-one (106)**

Method A run on a 2.35 mmol scale. Purified by column chromatography (30% $CH_2Cl_2$ in hexanes) to provide a slightly yellow solid (127.0 mg, 28% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.88 – 7.83 (m, 2H), 7.33 – 7.27 (m, 2H), 6.67 (t, *J* = 2.1 Hz, 2H), 6.25 (t, *J* = 2.1 Hz, 2H), 5.29 (s, 2H), 2.44 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 193.1, 145.1, 132.4, 129.7, 128.2, 122.1, 109.1, 55.4, 21.9; IR (Neat Film, NaCl) 3122, 3091, 1703, 1540, 1358, 1065, 815, 745, 734, 712 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{13}H_{14}NO$ $[M+H]^+$: 200.1070, found 200.1070.



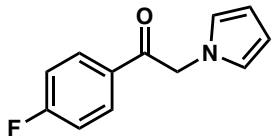

**1-(4-chlorophenyl)-2-(1*H*-pyrrol-1-yl)ethan-1-one (107)**

Method A run on a 4.92 mmol scale. Purified by column chromatography (60% $CH_2Cl_2$ in hexanes) to provide a yellow solid (248.7 mg, 23% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.85 (m, 2H), 7.52 – 7.44 (m, 2H), 6.66 (t, *J* = 2.1 Hz, 2H), 6.25 (t, *J* = 2.1 Hz, 2H), 5.28 (s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 192.5, 140.6, 133.1, 129.5, 129.4, 122.0, 109.4, 55.6; IR (Neat Film, NaCl) 1703, 1401, 1358, 1065, 816, 736, 704 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{12}H_{11}ClNO$ $[M+H]^+$: 220.0524, found 220.0520.



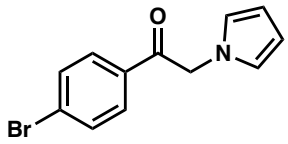

**1-(4-methoxyphenyl)-2-(1*H*-pyrrol-1-yl)ethan-1-one (108)**

Method B run on a 3.0 mmol scale. In this case, displacement by chloride counter-anion happened first and addition of $Et_3N$ (12.0 mmol) led to the correct product. Purified by column chromatography (20% EtOAc in hexanes) to provide a brown solid (325.5 mg, 50% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.89 (m, 2H), 6.99 – 6.93 (m, 2H), 6.67 (t, *J* = 2.1 Hz, 2H), 6.24 (t, *J* = 2.1 Hz, 2H), 5.26 (s, 2H), 3.89 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 192.0, 164.2, 130.5, 127.9, 122.1, 114.2, 109.1, 55.7, 55.3; IR (Neat Film, NaCl) 1685, 1601, 1574, 1500, 1420, 1356, 1318, 1293, 1266, 1234, 1186, 1167, 1116, 1092, 1020, 993, 738 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{13}H_{14}NO_2$ $[M+H]^+$: 216.1019, found 216.1028.



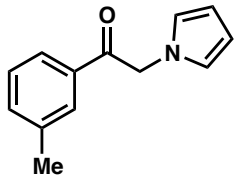

**1-(4-fluorophenyl)-2-(1*H*-pyrrol-1-yl)ethan-1-one (109)**

Method B run on a 2.0 mmol scale. Purified by column chromatography (10% to 20% EtOAc in hexanes) to provide a beige solid (196.8 mg, 46% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.93 (m, 2H), 7.23 – 7.10 (m, 2H), 6.67 (t, *J* = 2.1 Hz, 2H), 6.25 (t, *J* = 2.1 Hz, 2H), 5.28 (s, 2H); $^{19}$F NMR (282 MHz, $CDCl_3$) δ -103.3 (tt, *J* = 8.4, 5.3 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 192.0, 166.3 (d, *J* = 256.3 Hz), 131.3 (d, *J* = 3.0 Hz), 130.8 (d, *J* = 9.4 Hz), 122.0, 116.3 (d, *J* = 22.0 Hz), 109.3, 55.5; IR (Neat Film, NaCl) 3098, 1702, 1678, 1598, 1408, 1359, 1097, 1066, 832, 742, 719 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{12}H_{11}FNO$ $[M+H]^+$: 204.0819, found 204.0821.



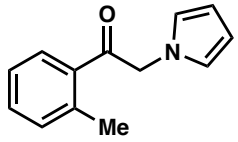

**1-(4-bromophenyl)-2-(1*H*-pyrrol-1-yl)ethan-1-one (110)**

Method B run on a 1.0 mmol scale. Purified by column chromatography (10% EtOAc in hexanes) to provide a white solid (196.8 mg, 46% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, $J$ = 8.6 Hz, 2H), 7.64 (d, $J$ = 8.5 Hz, 2H), 6.66 (t, $J$ = 2.1 Hz, 2H), 6.25 (t, $J$ = 2.1 Hz, 2H), 5.28 (s, 2H). Characterization data matched those reported in the literature.



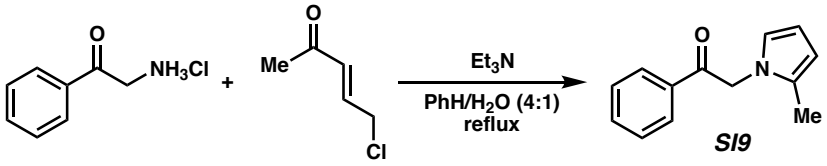

**2-(1*H*-pyrrol-1-yl)-1-(*m*-tolyl)ethan-1-one (111)**

Method B run on a 2.0 mmol scale. Purified by column chromatography (10% EtOAc in hexanes) to provide a beige solid (174.8 mg, 44% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.72 (m, 2H), 7.47 – 7.35 (m, 2H), 6.67 (t, $J$ = 2.1 Hz, 2H), 6.25 (t, $J$ = 2.1 Hz, 2H), 5.31 (s, 2H), 2.43 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 193.6, 139.0, 134.9, 134.9, 128.9, 128.6, 125.3, 122.1, 109.2, 55.6, 21.5; IR (Neat Film, NaCl) 3106, 3094, 2923, 1693, 1588, 1488, 1417, 1356, 1297, 1257, 1192, 1096, 1066, 834, 788, 733, 711, 687, 649 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{13}H_{14}NO$ $[M+H]^+$: 200.1070, found 200.1065.




**2-(1*H*-pyrrol-1-yl)-1-(*o*-tolyl)ethan-1-one (112)**

Method B run on a 2.0 mmol scale. Purified by column chromatography (10% EtOAc in hexanes) to provide a low melting point brown solid (164.0 mg, 41% yield); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.44 (td, *J* = 7.4, 1.4 Hz, 1H), 7.31 (dddt, *J* = 7.9, 7.3, 1.4, 0.7 Hz, 2H), 6.66 (t, *J* = 2.1 Hz, 2H), 6.24 (t, *J* = 2.1 Hz, 2H), 5.21 (s, 2H), 2.52 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 196.7, 139.6, 134.8, 132.6, 132.4, 128.3, 126.0, 122.0, 109.2, 57.2, 21.7; IR (Neat Film, NaCl) 3094, 2924, 1696, 1458, 1351, 1290, 1065, 758, 746, 737, 718 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{13}H_{14}NO$ $[M+H]^+$: 200.1070, found 200.1067.

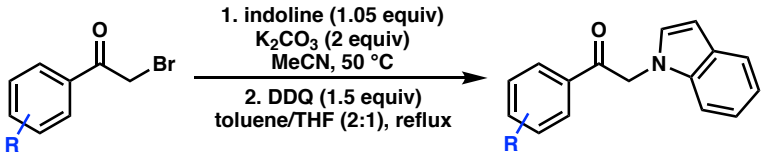



**(2-methyl-1*H*-pyrrol-1-yl)-1-phenylethan-1-one (113)**

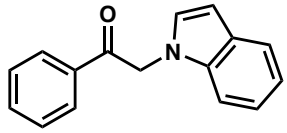
2-Aminoacetophenone hydrochloride (789.5 mg, 4.60 mmol) and $Et_3N$ (2.56 mL, 18.4 mmol) were added to a mixture of benzene (5 mL) and water (2.5 mL). A solution of 5-chloropent-3-en-2-one (4.60 mmol) in benzene (2.5 mL) was then added, and the mixture stirred at reflux for 5 h. Upon completion, the crude reaction mixture was allowed to cool to room temperature, and diluted with EtOAc and water. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with 1M HCl and brine, then dried over $Na_2SO_4$ and concentrated. The crude product was purified by column chromatography (10% EtOAc in hexanes) to provide a

light brown solid **SI** (110.0 mg, 12% yield); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.94 (m, 2H), 7.68 – 7.59 (m, 1H), 7.57 – 7.47 (m, 2H), 6.57 (dd, $J$ = 2.9, 1.8 Hz, 1H), 6.15 (t, $J$ = 3.1 Hz, 1H), 5.98 (ddq, $J$ = 3.6, 1.8, 0.9 Hz, 1H), 5.24 (s, 2H), 2.14 (d, $J$ = 0.9 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 193.6, 134.9, 134.1, 129.3, 129.1, 128.1, 121.3, 107.9, 107.6, 53.2, 12.0; IR (Neat Film, NaCl) 2914, 1698, 1596, 1489, 1450, 1425, 1354, 1303, 1223, 1078, 1016, 990, 752, 710, 624 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{13}H_{14}NO$ $[M+H]^+$: 200.1070, found 200.1063.

### 6.8.2.6 Synthesis of alpha-Indolyl Acetophenone Derivatives

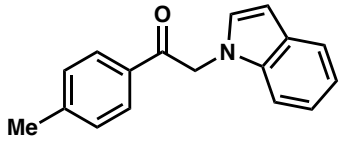



To a solution of the bromoacetophenone derivative (2.0 mmol) and $K_2CO_3$ (4.0 mmol) in MeCN (20 mL) was added indoline (2.1 mmol), and the mixture was stirred at 50 °C until TLC analysis showed complete consumption of the starting material. The mixture was filtered through celite and concentrated. The crude residue was redissolved in toluene (26 mL) and THF (14 mL) and treated with DDQ (2.2 mmol). The resulting mixture was stirred at reflux overnight. Following completion, the crude reaction was allowed to cool to room temperature and filtered through celite and concentrated. The crude residue was purified by silica gel flash chromatography to obtain the desired product.




**2-(1*H*-indol-1-yl)-1-phenylethan-1-one (114)**

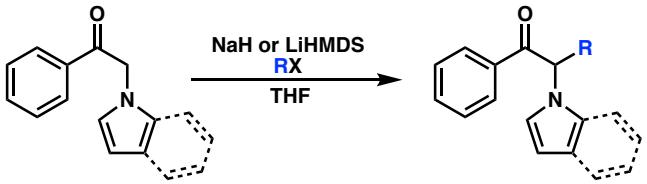
Run on a 2.0 mmol scale. Purified by column chromatography (15% EtOAc in hexanes) to provide a beige solid (144.1 mg, 31% yield); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.06 – 7.98 (m, 2H), 7.71 – 7.60 (m, 2H), 7.57 – 7.49 (m, 2H), 7.22 – 7.18 (m, 2H), 7.17 – 7.10 (m, 2H), 6.62 (d, *J* = 3.2 Hz, 1H), 5.53 (s, 1H). Characterization data matched those reported in the literature.[5]




**2-(1*H*-indol-1-yl)-1-(*p*-tolyl)ethan-1-one (115)**

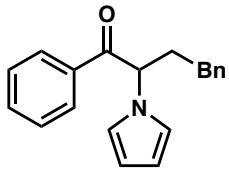
Run on a 2.0 mmol scale. Purified by column chromatography (15% EtOAc in hexanes) to provide a beige solid (90.0 mg, 18% yield); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.89 (m, 2H), 7.66 (dt, J = 7.8, 1.0 Hz, 1H), 7.34 – 7.29 (m, 2H), 7.19 (dt, J = 3.9, 1.0 Hz, 2H), 7.14 – 7.09 (m, 2H), 6.61 (dd, J = 3.2, 0.5 Hz, 1H), 5.50 (s, 2H), 2.44 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 192.8, 145.2, 136.8, 132.4, 129.8, 128.8, 128.8, 128.3, 122.1, 121.3, 119.8, 109.1, 102.6, 52.3, 21.9; IR (Neat Film, NaCl) 3054, 2968, 2934, 2877, 1682, 1607, 1574, 1514, 1459, 1307, 1260, 1200, 1183, 763, 739, 720 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{17}H_{16}NO$ $[M+H]^+$: 250.1226, found 250.1227.

### 6.8.2.7 Alkylation of alpha-pyrrolyl/indolyl acetophenone derivatives



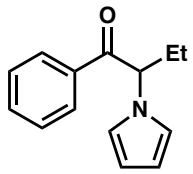

**Method A:** A flame-dried round bottom flask was charged with NaH (2.4 mmol, 1.2 equiv) and THF (7.5 mL). The suspension was then cooled in a 0 °C ice bath and a solution of ketone (2.0 mmol) in THF (2.5 mL) was added dropwise. The reaction was allowed to warm to room temperature and continued until no more $H_2$ evolution was observed. The mixture was then treated with the appropriate electrophil (2.4 mmol, 1.2 equiv) and the resulting mixture heated to 50 °C and stirred overnight. Following completion, the reaction was allowed to cool to room temperature and then quenched by slow addition of saturated aqueous $NH_4Cl$ and extracted with $CH_2Cl_2$. The combined organic layers were dried with $Na_2SO_4$ and concentrated. The crude residue was purified by silica gel flash chromatography to afford the desired alkylated product.

**Method B:** A flame-dried round bottom flask was charged with LiHMDS (2.2 mmol, 1.1 equiv) and THF (7.5 mL). The solution was then cooled in a 0 °C ice bath for 10 min and a solution of ketone (2.0 mmol) in THF (2.5 mL) was added dropwise. After stirring for 15 min, the electrophile (2.4 mmol, 1.2 equiv) was added dropwise and the reaction heated to 60 °C and continued overnight. Following completion, the reaction was allowed to cool to room temperature and then quenched with a slow addition of saturated aqueous $NH_4Cl$ and extracted with EtOAc. The combined organics were dried over $Na_2SO_4$ and concentrated. The crude residue was purified by silica gel flash chromatography to afford the alkylated product.




**1,4-diphenyl-2-(1*H*-pyrrol-1-yl)butan-1-one (116)**

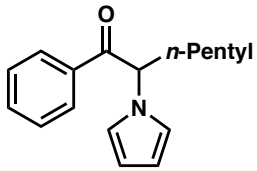
Method A run on a 2.16 mmol scale. Purified by column chromatography (10% $Et_2O$ in hexanes) to provide a yellow solid (314.7 mg, 50% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.74 (m, 2H), 7.53 (ddt, *J* = 7.9, 6.9, 1.3 Hz, 1H), 7.44 – 7.36 (m, 2H), 7.36 – 7.29 (m, 2H), 7.28 – 7.21 (m, 1H), 7.20 – 7.15 (m, 2H), 6.78 (t, *J* = 2.1 Hz, 2H), 6.21 (t, *J* = 2.1 Hz, 2H), 5.38 (dd, *J* = 9.3, 5.0 Hz, 1H), 2.73 – 2.61 (m, 1H), 2.57 – 2.35 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 195.8, 140.5, 135.2, 133.7, 128.9, 128.8, 128.7, 128.5, 126.5, 120.3, 109.1, 61.5, 34.2, 31.9; IR (Neat Film, NaCl) 3025, 2923, 1687, 1597, 1580, 1488, 1259, 1214, 1092, 1070, 788, 723, 698 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{20}H_{19}NONa$ $[M+Na]^+$: 312.1359, found 312.1357.




**1-phenyl-2-(1*H*-pyrrol-1-yl)butan-1-one (117)**

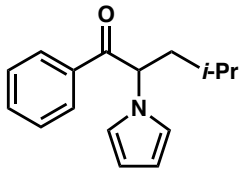
Method A run on a 2.16 mmol scale. Purified by column chromatography (10% $Et_2O$ in hexanes) to provide a yellow solid (315.6 mg, 69% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.94 – 7.88 (m, 2H), 7.55 (ddt, *J* = 7.8, 6.9, 1.3 Hz, 1H), 7.49 – 7.40 (m, 2H), 6.76 (t, *J* = 2.1 Hz, 2H), 6.17 (t, *J* = 2.2 Hz, 2H), 5.34 (dd, *J* = 9.2, 5.6 Hz, 1H), 2.25 – 2.13 (m, 1H), 2.07 (ddq, *J* = 14.6, 9.3, 7.4 Hz, 1H), 0.93 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 196.0, 135.7, 133.6, 128.9, 128.5, 120.2, 109.0, 64.3, 26.2, 10.7; IR (Neat Film, NaCl) 3100, 3061, 2970, 2934, 2876, 1688, 1597, 1579, 1488, 1458, 1448, 1273, 1263,

1208, 1183, 1095, 1082, 1068, 1002, 988, 902, 813, 725, 688 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{14}H_{16}NO$ $[M+H]^+$: 214.1226, found 214.1235.




**1-phenyl-2-(1*H*-pyrrol-1-yl)heptan-1-one (118)**

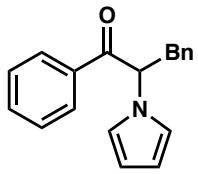
Method A run on a 2.16 mmol scale. Purified by column chromatography (10% $Et_2O$ in hexanes) to provide a brown solid (358.5 mg, 65% yield); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.93 – 7.89 (m, 2H), 7.58 – 7.53 (m, 1H), 7.47 – 7.42 (m, 2H), 6.76 (t, *J* = 2.1 Hz, 2H), 6.17 (t, *J* = 2.1 Hz, 2H), 5.44 (dd, *J* = 9.3, 5.5 Hz, 1H), 2.18 – 1.97 (m, 2H), 1.43 – 1.18 (m, 6H), 0.87 (t, *J* = 6.9 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 196.1, 135.5, 133.7, 128.9, 128.5, 120.1, 108.9, 62.8, 32.8, 31.5, 25.8, 22.5, 14.1; IR (Neat Film, NaCl) 3064, 2956, 2929, 2859, 1690, 1597, 1580, 1487, 1448, 1267, 1206, 1182, 1090, 1069, 966, 723, 688 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{17}H_{22}NO$ $[M+H]^+$: 256.1696, found 256.1705.




**4-methyl-1-phenyl-2-(1*H*-pyrrol-1-yl)pentan-1-one (119)**

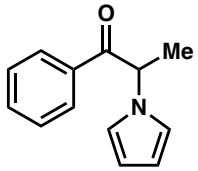
Method A run on a 2.16 mmol scale. Purified by column chromatography (10% $Et_2O$ in hexanes) to provide a brown solid (335.7 mg, 64% yield); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.95 – 7.89 (m, 2H), 7.60 – 7.53 (m, 1H), 7.49 – 7.42 (m, 2H), 6.77 (t, *J* = 2.1 Hz, 2H), 6.17 (t, *J* = 2.1 Hz, 2H), 5.57 (dd, *J* = 10.0, 5.0 Hz, 1H), 2.03 (ddd, *J* = 14.1, 10.0, 4.9 Hz, 1H), 1.91 (ddd, *J* = 14.1, 8.9, 5.0 Hz, 1H), 1.47 (dddd, *J* = 13.3, 11.5, 8.9, 6.5 Hz, 1H),

1.03 (d, $J$ = 6.6 Hz, 3H), 0.91 (d, $J$ = 6.7 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 196.2, 135.4, 133.7, 129.0, 128.5, 120.2, 108.9, 60.9, 41.6, 24.8, 23.2, 21.9; IR (Neat Film, NaCl) 2956, 2929, 2869, 1690, 1596, 1579, 1488, 1448, 1386, 1368, 1279, 1204, 1182, 1091, 1069, 1002, 861, 775, 723, 688 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{16}H_{20}NO$ $[M+H]^+$: 242.1539, found 242.1547.



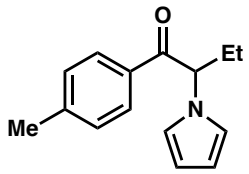

**1,3-diphenyl-2-(1*H*-pyrrol-1-yl)propan-1-one (120)**

Method A run on a 2.16 mmol scale. Reaction complete after 1 h at room temperature, no additional heating required. Purified by column chromatography (10% $Et_2O$ in hexanes) to provide a white solid (566.5 mg, 95% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.84 (m, 2H), 7.57 – 7.48 (m, 1H), 7.45 – 7.34 (m, 2H), 7.25 – 7.16 (m, 3H), 7.05 – 6.95 (m, 2H), 6.66 (t, $J$ = 2.2 Hz, 2H), 6.12 (t, $J$ = 2.2 Hz, 2H), 5.57 (dd, $J$ = 8.8, 5.7 Hz, 1H), 3.47 (dd, $J$ = 13.9, 5.7 Hz, 1H), 3.28 (dd, $J$ = 13.9, 8.8 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 195.2, 137.3, 135.4, 133.8, 129.2, 128.9, 128.6, 128.6, 126.9, 120.1, 109.3, 64.3, 39.3; IR (Neat Film, NaCl) 3027, 2922, 1687, 1596, 1487, 1448, 1271, 1202, 1090, 1070, 967, 874, 725, 700, 688, 665 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{18}NO$ $[M+H]^+$: 276.1383, found 276.1371.




**1-phenyl-2-(1*H*-pyrrol-1-yl)propan-1-one (121)**

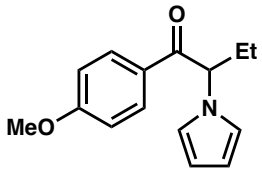
Method A run on a 2.16 mmol scale. Reaction done after 45 min at room temperature, no additional heating required. Purified by column chromatography (8% $Et_2O$ in hexanes) to provide a white solid (320.2 mg, 74% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.87 (m, 2H), 7.61 – 7.52 (m, 1H), 7.50 – 7.40 (m, 2H), 6.77 (t, *J* = 2.1 Hz, 2H), 6.19 (t, *J* = 2.2 Hz, 2H), 5.65 (q, *J* = 7.0 Hz, 1H), 1.74 (d, *J* = 7.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 196.3, 135.0, 133.7, 128.9, 128.5, 119.8, 109.1, 58.4, 18.8; IR (Neat Film, NaCl) 3097, 2988, 2937, 1693, 1596, 1488, 1449, 1374, 1275, 1250, 1214, 1183, 1093, 1070, 1000, 964, 938, 726, 687, 646 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{13}H_{14}NO$ $[M+H]^+$: 200.1070, found 200.1073.




**2-(1*H*-pyrrol-1-yl)-1-(*p*-tolyl)butan-1-one (122)**

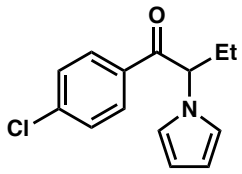
Method B run on a 1.30 mmol scale. Purified by column chromatography (8% EtOAc in hexanes) to provide a white solid (213.6 mg, 73% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.77 (m, 2H), 7.25 – 7.21 (m, 2H), 6.76 (t, *J* = 2.1 Hz, 2H), 6.16 (t, *J* = 2.1 Hz, 2H), 5.31 (dd, *J* = 9.1, 5.7 Hz, 1H), 2.39 (s, 3H), 2.23 – 1.97 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 195.6, 144.6, 133.0, 129.6, 128.7, 120.2, 108.8, 64.1, 26.2, 21.8, 10.8; IR (Neat Film, NaCl) 3097, 2969, 2931, 2876, 1684, 1606, 1573, 1488,

1459, 1406, 1263, 1205, 1183, 1096, 1068, 982, 901, 860, 779, 725 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{15}H_{18}NO$ $[M+H]^+$: 228.1383, found 228.1392.




**1-(4-methoxyphenyl)-2-(1*H*-pyrrol-1-yl)butan-1-one (123)**

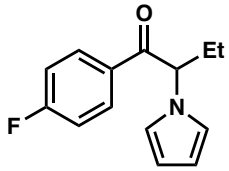
Method B run on a 1.51 mmol scale. Purified by column chromatography (10% EtOAc in hexanes) to provide a yellow oil (264.7 mg, 72% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.87 (m, 2H), 6.96 – 6.85 (m, 2H), 6.77 (t, *J* = 2.2 Hz, 2H), 6.17 (t, *J* = 2.1 Hz, 2H), 5.30 (dd, *J* = 9.0, 5.8 Hz, 1H), 3.85 (s, 3H), 2.26 – 1.94 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 194.4, 163.9, 130.9, 128.5, 120.1, 114.1, 108.8, 63.9, 55.6, 26.3, 10.8; IR (Neat Film, NaCl) 2968, 1681, 1600, 1574, 1509, 1488, 1456, 1421, 1312, 1260, 1212, 1170, 1095, 1027, 988, 860, 839, 724 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{15}H_{18}NO_2$ $[M+H]^+$: 244.1332, found 244.1331.




**1-(4-chlorophenyl)-2-(1*H*-pyrrol-1-yl)butan-1-one (124)**

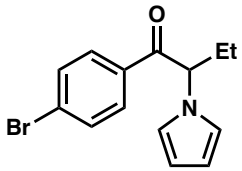
Method B run on a 1.11 mmol scale. Purified by column chromatography (5% EtOAc in hexanes) to provide a yellow oil (212.3 mg, 77% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.86 – 7.79 (m, 2H), 7.43 – 7.36 (m, 2H), 6.72 (t, *J* = 2.2 Hz, 2H), 6.17 (t, *J* = 2.1 Hz, 2H), 5.25 (dd, *J* = 9.2, 5.6 Hz, 1H), 2.22 – 1.99 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 194.8, 140.1, 133.9, 129.9, 129.2, 120.1, 109.2, 64.4, 26.0, 10.7; IR (Neat Film, NaCl) 3101, 2970, 2935, 2877, 1688, 1588, 1570, 1488, 1462, 1400,

1307, 1274, 1262, 1230, 1207, 1180, 1094, 1069, 1012, 990, 965, 902, 862, 832, 806, 726, 626 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{14}H_{15}ClNO$ $[M+H]^+$: 248.0837, found 248.0842.




**11-(4-fluorophenyl)-2-(1*H*-pyrrol-1-yl)butan-1-one (125)**

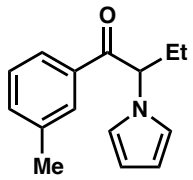
Method B run on a 1.34 mmol scale. Purified by column chromatography (5% EtOAc in hexanes) to provide a yellow oil (231.2 mg, 75% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.87 (m, 1H), 7.15 – 7.05 (m, 1H), 6.74 (t, *J* = 2.2 Hz, 1H), 6.17 (t, *J* = 2.2 Hz, 1H), 5.27 (dd, *J* = 9.1, 5.7 Hz, 1H), 2.24 – 1.98 (m, 1H), 0.92 (t, *J* = 7.4 Hz, 2H); $^{19}$F NMR (282 MHz, $CDCl_3$) δ -104.0 (ttd, *J* = 8.2, 5.4, 2.4 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 194.4, 166.0 (d, *J* = 256.0 Hz), 132.0 (d, *J* = 3.1 Hz), 131.2 (d, *J* = 9.4 Hz), 120.1, 116.1 (d, *J* = 22.0 Hz), 109.2, 64.3, 26.1, 10.7; IR (Neat Film, NaCl) 3104, 2971, 2936, 2878, 1688, 1598, 1506, 1488, 1458, 1410, 1302, 1274, 1263, 1231, 1208, 1159, 1096, 1069, 1010, 991, 964, 903, 864, 843, 792, 726 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{14}H_{15}FNO$ $[M+H]^+$: 232.1132, found 232.1144.




**1-(4-bromophenyl)-2-(1*H*-pyrrol-1-yl)butan-1-one (126)**

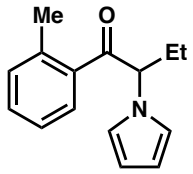
Method B run on a 0.912 mmol scale. Purified by column chromatography (7% EtOAc in hexanes) to provide an orange solid (204.6 mg, 77% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.78 – 7.71 (m, 2H), 7.61 – 7.53 (m, 2H), 6.72 (t, *J* = 2.1 Hz, 2H), 6.17 (t, *J* =

2.1 Hz, 2H), 5.24 (dd, $J$ = 9.1, 5.6 Hz, 1H), 2.23 – 1.99 (m, 2H), 0.92 (t, $J$ = 7.4 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 195.0, 134.3, 132.3, 130.0, 128.9, 120.1, 109.3, 64.4, 26.0, 10.7; IR (Neat Film, NaCl) 2971, 2936, 1693, 1584, 1553, 1485, 1462, 1396, 1263, 1206, 1180, 1095, 1071, 1007, 989, 902, 862, 806, 727 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{14}H_{15}BrNO$ $[M+H]^+$: 292.0332, found 292.0335.




**2-(1*H*-pyrrol-1-yl)-1-(*m*-tolyl)butan-1-one (127)**

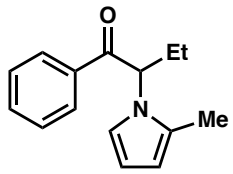
Method B run on a 1.46 mmol scale. Purified by column chromatography (5% EtOAc in hexanes) to provide a yellow oil (259.4 mg, 78% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.68 (m, 2H), 7.41 – 7.29 (m, 2H), 6.78 (t, $J$ = 2.1 Hz, 2H), 6.18 (t, $J$ = 2.1 Hz, 2H), 5.35 (dd, $J$ = 9.2, 5.7 Hz, 1H), 2.40 (s, 3H), 2.25 – 1.99 (m, 2H), 0.93 (t, $J$ = 7.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 196.2, 138.7, 135.6, 134.4, 129.1, 128.7, 125.6, 120.1, 108.8, 64.2, 26.2, 21.5, 10.7; IR (Neat Film, NaCl) 3099, 2970, 2933, 2876, 1686, 1602, 1585, 1487, 1460, 1381, 1265, 1240, 1164, 1096, 1068, 964, 773, 724, 687 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{15}H_{18}NO$ $[M+H]^+$: 228.1383, found 228.1383.




**2-(1*H*-pyrrol-1-yl)-1-(*o*-tolyl)butan-1-one (128)**

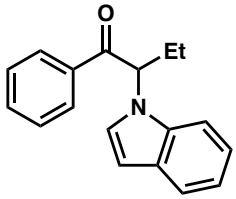
Method B run on a 0.76 mmol scale. Purified by column chromatography (5% EtOAc in hexanes) to provide a yellow oil (139.5 mg, 81% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, $J$ = 8.1, 1.4 Hz, 1H), 7.35 (td, $J$ = 7.5, 1.4 Hz, 1H), 7.25 – 7.20 (m, 2H), 6.72 (t,

*J* = 2.2 Hz, 2H), 6.16 (t, *J* = 2.2 Hz, 2H), 5.16 (dd, *J* = 9.3, 5.6 Hz, 1H), 2.40 (s, 3H), 2.18 (dqd, *J* = 14.7, 7.4, 5.6 Hz, 1H), 2.03 (ddq, *J* = 14.5, 9.3, 7.3 Hz, 1H), 0.92 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 200.3, 138.6, 136.9, 132.0, 131.6, 127.5, 125.7, 120.1, 108.9, 66.8, 25.6, 20.9, 10.8; IR (Neat Film, NaCl) 3100, 3064, 3022, 2967, 2932, 2876, 1695, 1600, 1570, 1487, 1457, 1382, 1272, 1261, 1228, 1210, 1197, 1095, 1082, 1068, 980, 965, 904, 850, 821, 780, 758, 723, 656 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{15}H_{18}NO$ $[M+H]^+$: 228.1383, found 228.1384.



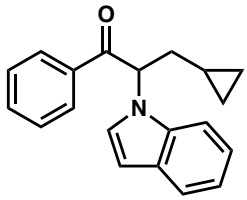

**2-(2-methyl-1*H*-pyrrol-1-yl)-1-phenylbutan-1-one (129)**

Method B run on a 0.872 mmol scale. Purified by column chromatography (5% EtOAc in hexanes) to provide a yellow oil (134.8 mg, 68% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.78 (m, 2H), 7.59 – 7.50 (m, 1H), 7.48 – 7.39 (m, 2H), 6.65 (dd, *J* = 3.0, 1.8 Hz, 1H), 6.07 (t, *J* = 3.2 Hz, 1H), 5.91 (ddq, *J* = 3.5, 1.7, 0.9 Hz, 1H), 5.32 (dd, *J* = 8.8, 5.8 Hz, 1H), 2.30 (d, *J* = 0.9 Hz, 3H), 2.28 – 2.16 (m, 1H), 2.08 – 1.95 (m, 1H), 0.95 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 196.6, 135.9, 133.5, 128.9, 128.4, 128.1, 118.5, 107.9, 107.7, 61.3, 26.0, 12.6, 10.9; IR (Neat Film, NaCl) 2970, 2936, 1689, 1597, 1486, 1448, 1418, 1291, 1211, 1182, 1147, 1068, 964, 907, 815, 773, 698 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{15}H_{18}NO$ $[M+H]^+$: 228.1383, found 228.1385.




**2-(1*H*-indol-1-yl)-1-phenylbutan-1-one (130)**

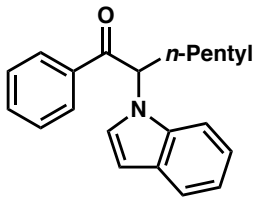
Method B run for 36h on a 0.594 mmol scale. Purified by column chromatography (6% EtOAc in hexanes) to provide a beige solid (130.3 mg, 83% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.88 (m, 2H), 7.63 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.54 – 7.49 (m, 1H), 7.46 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.39 (ddt, *J* = 7.9, 6.7, 1.2 Hz, 2H), 7.27 – 7.21 (m, 2H), 7.13 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.55 (dd, *J* = 3.3, 0.9 Hz, 1H), 5.76 (dd, *J* = 9.0, 5.7 Hz, 1H), 2.38 – 2.25 (m, 1H), 2.25 – 2.12 (m, 1H), 0.92 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 196.5, 136.2, 135.6, 133.7, 129.0, 128.9, 128.4, 126.0, 122.0, 121.4, 120.0, 109.1, 103.0, 60.8, 25.4, 11.0; IR (Neat Film, NaCl) 3052, 2969, 1685, 1596, 1512, 1475, 1458, 1307, 1202, 1014, 902, 812, 762, 741, 722 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{18}H_{18}NO$ $[M+H]^+$: 264.1383, found 264.1388.




**3-cyclopropyl-2-(1*H*-indol-1-yl)-1-phenylpropan-1-one (131)**

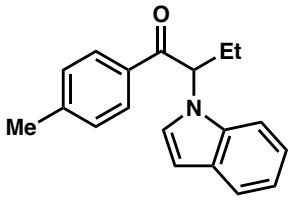
Method B run for 36 h with 1.5 equivalent of electrophile on a 1.28 mmol scale. Purified by column chromatography (5% EtOAc in hexanes) to provide a yellow oil (184.1 mg, 49% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.95 – 7.91 (m, 2H), 7.62 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.55 – 7.46 (m, 2H), 7.43 – 7.34 (m, 2H), 7.30 – 7.20 (m, 2H), 7.13 (ddd, *J* = 7.9, 7.0, 0.9 Hz, 1H), 6.55 (dd, *J* = 3.3, 0.9 Hz, 1H), 5.96 (dd, *J* = 8.7, 5.7 Hz, 1H), 2.18 (ddd,

*J* = 14.7, 8.7, 6.3 Hz, 1H), 2.03 (ddd, *J* = 14.0, 7.8, 5.7 Hz, 1H), 0.56 (qdt, *J* = 7.9, 6.3, 4.9 Hz, 1H), 0.49 – 0.39 (m, 1H), 0.36 (dddd, *J* = 9.3, 7.9, 5.4, 4.3 Hz, 1H), 0.15 (dtd, *J* = 9.2, 5.2, 4.2 Hz, 1H), 0.03 (dtd, *J* = 9.4, 5.3, 4.4 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 196.5, 136.2, 135.7, 133.7, 129.0, 128.9, 128.4, 126.0, 122.0, 121.4, 119.9, 109.2, 103.0, 59.7, 37.1, 8.2, 4.8, 4.8; IR (Neat Film, NaCl) 3056, 2999, 1686, 1596, 1513, 1476, 1458, 1308, 1275, 1249, 1210, 1163, 1015, 926, 763, 739, 691 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{20}H_{20}NO$ $[M+H]^+$: 290.1539, found 290.1529.




**2-(1*H*-indol-1-yl)-1-phenylheptan-1-one (132)**

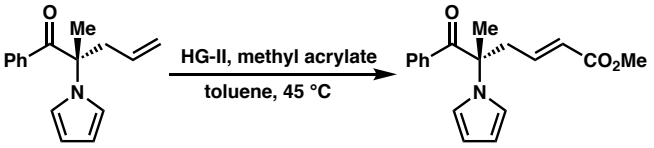
Method B run for 36h with 1.5 equivalent of electrophile on a 1.28 mmol scale. Purified by column chromatography (5% EtOAc in hexanes) to provide a beige oil (299.7 mg, 77% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.88 (m, 2H), 7.62 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.56 – 7.48 (m, 1H), 7.47 – 7.36 (m, 3H), 7.28 – 7.19 (m, 2H), 7.12 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 6.55 (dd, *J* = 3.3, 0.8 Hz, 1H), 5.85 (dd, *J* = 9.1, 5.6 Hz, 1H), 2.26 (ddt, *J* = 14.0, 11.0, 5.5 Hz, 1H), 2.20 – 2.08 (m, 1H), 1.40 – 1.18 (m, 6H), 0.83 (t, *J* = 7.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 196.6, 136.2, 135.6, 133.7, 129.0, 128.9, 128.4, 126.0, 122.0, 121.4, 119.9, 109.1, 102.9, 59.2, 32.0, 31.6, 26.0, 22.5, 14.1; IR (Neat Film, NaCl) 3054, 2955, 2929, 2860, 1688, 1596, 1513, 1478, 1460, 1309, 1227, 1198, 1014, 957, 763, 738, 718, 690 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{21}H_{24}NO$ $[M+H]^+$: 306.1852, found 306.1857.




**2-(1*H*-indol-1-yl)-1-(*p*-tolyl)butan-1-one (133)**

Run on a 0.22 mmol scale. Purified by column chromatography (8% EtOAc in hexanes) to provide a brown oil (43.0 mg, 78% yield); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.81 (m, 2H), 7.62 (dt, J = 7.8, 1.0 Hz, 1H), 7.46 (dd, J = 8.4, 1.0 Hz, 1H), 7.26 – 7.21 (m, 2H), 7.21 – 7.16 (m, 2H), 7.12 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 6.55 (dd, J = 3.3, 0.8 Hz, 1H), 5.74 (dd, J = 8.9, 5.7 Hz, 1H), 2.35 (s, 3H), 2.29 (dtd, J = 14.8, 7.3, 5.7 Hz, 1H), 2.17 (ddq, J = 14.6, 9.0, 7.3 Hz, 1H), 0.92 (t, J = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 196.0, 144.7, 136.2, 133.1, 129.6, 128.9, 128.5, 126.0, 122.0, 121.3, 119.9, 109.1, 102.8, 60.6, 25.4, 21.8, 11.0; IR (Neat Film, NaCl) 3054, 2968, 2934, 2877, 1682, 1607, 1574, 1514, 1459, 1307, 1260, 1200, 1183, 763, 739, 720 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{20}NO$ $[M+H]^+$: 278.1539, found 278.1542.

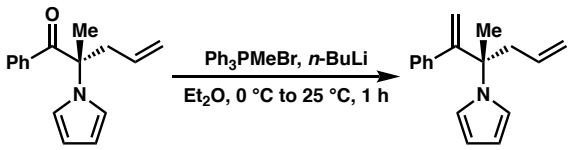
### 6.8.2.8 Derivatization of Alkylation Products




**methyl (*S*,*E*)-5-methyl-6-oxo-6-phenyl-5-(1*H*-pyrrol-1-yl)hex-2-enoate (102)**

To an oven-dried 1 dram vial was added α-pyrrolo ketone **101f** (23.9 mg, 0.1 mmol), Hoveyda-Grubbs 2$^{nd}$ generation catalyst (3.2 mg, 0.005 mmol), and toluene (1.0 mL). The resulting mixture was stirred till all solids dissolved, then trated with methyl acrylate (90 μL, 1 mmol) and heated to 45 °C in a metal heating block for 12 h. Following completion, the reaction was allowed to cool to room temperature and concentrated to a

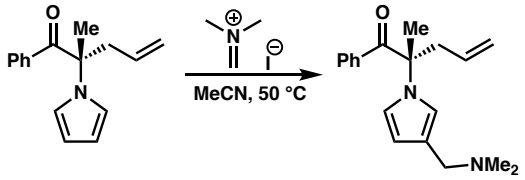
crude oil. The crude mixture was purified by column chromatogprahy (10 to 20% $Et_2O$ in hexanes) to afford the desired product as a colorless oil (28.4 mg, 95% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.44 (tt, *J* = 7.0, 1.5 Hz, 1H), 7.31 – 7.21 (m, 6H), 6.72 (t, *J* = 2.2 Hz, 2H), 6.60 (ddd, *J* = 15.4, 8.3, 6.9 Hz, 1H), 6.25 (t, *J* = 2.1 Hz, 2H), 5.80 (dt, *J* = 15.5, 1.4 Hz, 1H), 3.70 (s, 4H), 3.08 – 2.91 (m, 2H), 1.79 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 198.6, 166.4, 142.6, 134.9, 132.9, 128.9, 128.6, 125.3, 118.7, 110.0, 67.0, 51.6, 42.7, 23.2; IR (Neat Film, NaCl) 3068, 2994, 2950, 1723, 1682, 1659, 1595, 1484, 1436, 1381, 1335, 1278, 1221, 1177, 1132, 1091, 1040, 974, 726 cm $^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{18}H_{20}NO_3$ $[M+H]^+$: 298.1438, found 298.1442.




**(*S*)-1-(3-methyl-2-phenylhexa-1,5-dien-3-yl)-1*H*-pyrrole (103)**

To an oven-dried 1 dram vial was added methyltriphenylphosphonium bromide (53.6 mg, 0.15 mmol) and $Et_2O$ (0.75 mL). The resulting suspension was cooled in an ice-bath and *n*-BuLi (58 μL, 0.14 mmol, 2.4 M) added dropwise. After stirring for an additional 30 min, a solution of α-pyrrolo ketone **101f** (23.9 mg, 0.1 mmol) in $Et_2O$ (0.75 mL) was added, and the ice-bath removed. The reaction was allowed to warm to room temperature and continued for 1 h. Following completion, the reaction was diluted with $H_2O$ and extracted with $Et_2O$. The combined organics were washed with brine, dried with $MgSO_4$, and then concentrated. The crude product was purified by column chromatography (0 to 5% $Et_2O$ in hexanes) to afford the desired product as a colorless oil (20.0 mg, 84% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.15 (m, 3H), 6.85 (t, *J* = 2.2 Hz, 2H), 6.59 (dt, *J* = 7.0, 1.5 Hz, 2H), 6.22 (t, *J* = 2.2 Hz, 2H), 5.51 (ddt, *J* = 16.1, 10.9, 7.1 Hz, 1H), 5.39 (s,

1H), 5.22 (s, 1H), 5.14 – 5.02 (m, 2H), 2.89 (dd, $J$ = 13.7, 6.6 Hz, 1H), 2.66 (dd, $J$ = 13.6, 7.4 Hz, 1H), 1.57 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.8, 140.9, 133.1, 128.4, 128.0, 127.4, 119.0, 118.9, 115.4, 108.1, 61.9, 44.3, 25.2; IR (Neat Film, NaCl) 3079, 2981, 1492, 1483, 1442, 1376, 1266, 1243, 1092, 1072, 918, 778, 723, 701 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{17}H_{20}N$ $[M+H]^+$: 238.1590, found 238.1584.




**(*S*)-2-(3-((dimethylamino)methyl)-1*H*-pyrrol-1-yl)-2-methyl-1-phenylpent-4-en-1-one (104)**

To an oven-dried 1 dram vial was added α-pyrrolo ketone **101f** (23.9 mg, 0.1 mmol), Escehnmoser's salt (27.8 mg, 0.15 mmol), and MeCN (1.0 mL). The resulting mixture was heated to 55 °C in a metal heating block and stirred for 2 h. Following completion, the reaction was diluted with EtOAc and washed with saturated $NaHCO_3$ and brine. Following drying with $MgSO_4$ and concentration, the desired product was obtained as a light-yellow foam (28.1 mg, 93% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.40 (tt, $J$ = 6.8, 1.9 Hz, 1H), 7.29 – 7.20 (m, 4H), 6.68 (dt, $J$ = 15.4, 2.3 Hz, 2H), 6.19 (t, $J$ = 2.2 Hz, 1H), 5.39 (dddd, $J$ = 16.6, 10.1, 8.1, 6.2 Hz, 1H), 5.14 – 4.96 (m, 2H), 3.55 – 3.36 (m, 2H), 2.95 – 2.72 (m, 2H), 2.24 (s, 6H), 1.74 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 199.3, 135.3, 132.7, 131.9, 128.7, 128.5, 119.9, 119.4, 119.1, 119.1, 111.0, 67.3, 56.0, 44.0, 43.7, 23.2; IR (Neat Film, NaCl) 3069, 2977, 2938, 2854, 2811, 2761, 1682, 1488, 1456, 1446, 1320, 1255, 1179, 1166, 968, 924, 774, 718, 692 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{25}N_2O$ $[M+H]^+$: 297.1961, found 297.1972.

### 6.8.3 Determination of Enantiomeric Excess

***Table 6.3*** *Determination of Enantiomeric Excess.*

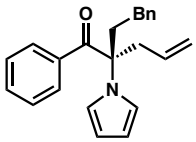
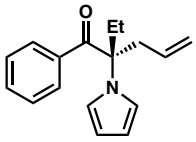
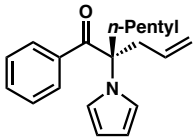
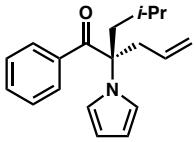
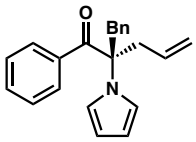
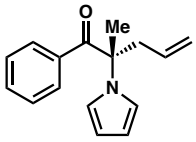
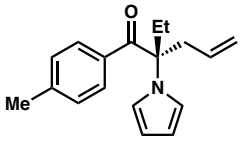
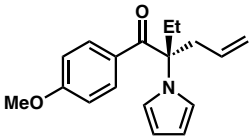
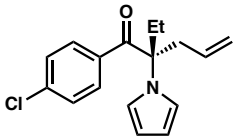
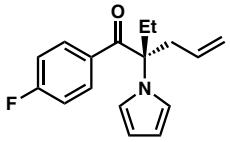
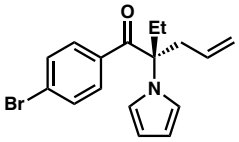
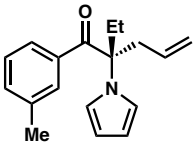
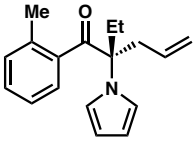
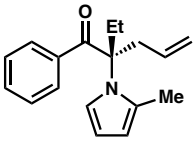
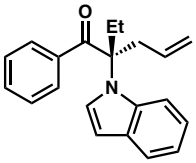
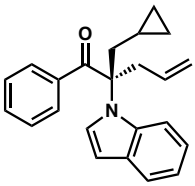
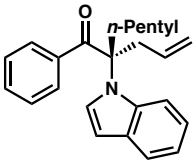
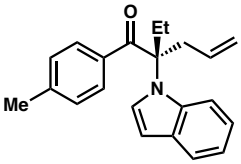
| Entry | Compound | Assay Conditions | $t_R$ of major isomer (min) | $t_R$ of minor isomer (min) | %ee |
|---|---|---|---|---|---|
| 1 |  | SFC<br>Chiralpak IC<br>5% IPA<br>isocratic, 2.5 mL/min | 5.03 | 6.06 | 86 |
| 2 |  | SFC<br>Chiralpak IC<br>10% IPA<br>isocratic, 2.5 mL/min | 4.04 | 4.66 | 90 |
| 3 |  | SFC<br>Chiralpak AD-H<br>5% IPA<br>isocratic, 2.5 mL/min | 3.23 | 2.88 | 91 |
| 4 |  | SFC<br>Chiralpak IC<br>2% IPA<br>isocratic, 2.5 mL/min | 4.93 | 4.40 | 94 |
| 5 |  | SFC<br>Chiralpak IC<br>5% IPA<br>isocratic, 2.5 mL/min | 5.35 | 6.14 | 84 |
| 6 |  | SFC<br>Chiralcel OB-H<br>0.5% IPA<br>isocratic, 2.5 mL/min | 3.89 | 3.52 | 90 |
| 7 |  | SFC<br>Chiralcel OB-H<br>2% IPA<br>isocratic, 2.5 mL/min | 3.20 | 2.80 | 95 |
| 8 |  | SFC<br>Chiralcel OB-H<br>1% IPA<br>isocratic, 2.5 mL/min | 4.62 | 4.11 | 94 |
| 9 |  | SFC<br>Chiralpak AD-H<br>3% IPA<br>isocratic, 2.5 mL/min | 7.10 | 6.42 | 93 |

***Table 6.4*** *Determination of Enantiomeric Excess (continued)*

| Entry | Compound | Assay Conditions | $t_R$ of major isomer (min) | $t_R$ of minor isomer (min) | %ee |
|---|---|---|---|---|---|
| 10 |  | SFC<br>Chiralpak AD-H<br>5% IPA<br>isocratic, 2.5 mL/min | 2.74 | 3.02 | 92 |
| 11 |  | SFC<br>Chiralpak IC<br>2% IPA<br>isocratic, 2.5 mL/min | 6.29 | 5.80 | 97 |
| 12 |  | SFC<br>Chiralcel OJ-H<br>3% IPA<br>isocratic, 2.5 mL/min | 2.84 | 2.63 | 93 |
| 13 |  | SFC<br>Chiralpak AD-H<br>3% IPA<br>isocratic, 2.5 mL/min | 4.38 | 4.80 | 90 |
| 14 |  | SFC<br>Chiralcel OD-H<br>2% IPA<br>isocratic, 2.5 mL/min | 6.13 | 6.59 | 90 |
| 15 |  | SFC<br>Chiralcel OJ-H<br>5% IPA<br>isocratic, 2.5 mL/min | 5.71 | 5.19 | 92 |
| 16 |  | SFC<br>Chiralpak AD-H<br>5% IPA<br>isocratic, 2.5 mL/min | 11.27 | 10.38 | 92 |
| 17 |  | SFC<br>Chiralcel OJ-H<br>5% IPA<br>isocratic, 2.5 mL/min | 3.55 | 4.34 | 90 |
| 18 |  | SFC<br>Chiralpak IC<br>5% IPA<br>isocratic, 2.5 mL/min | 7.61 | 6.97 | 95 |

## 6.9 REFERENCES AND NOTES

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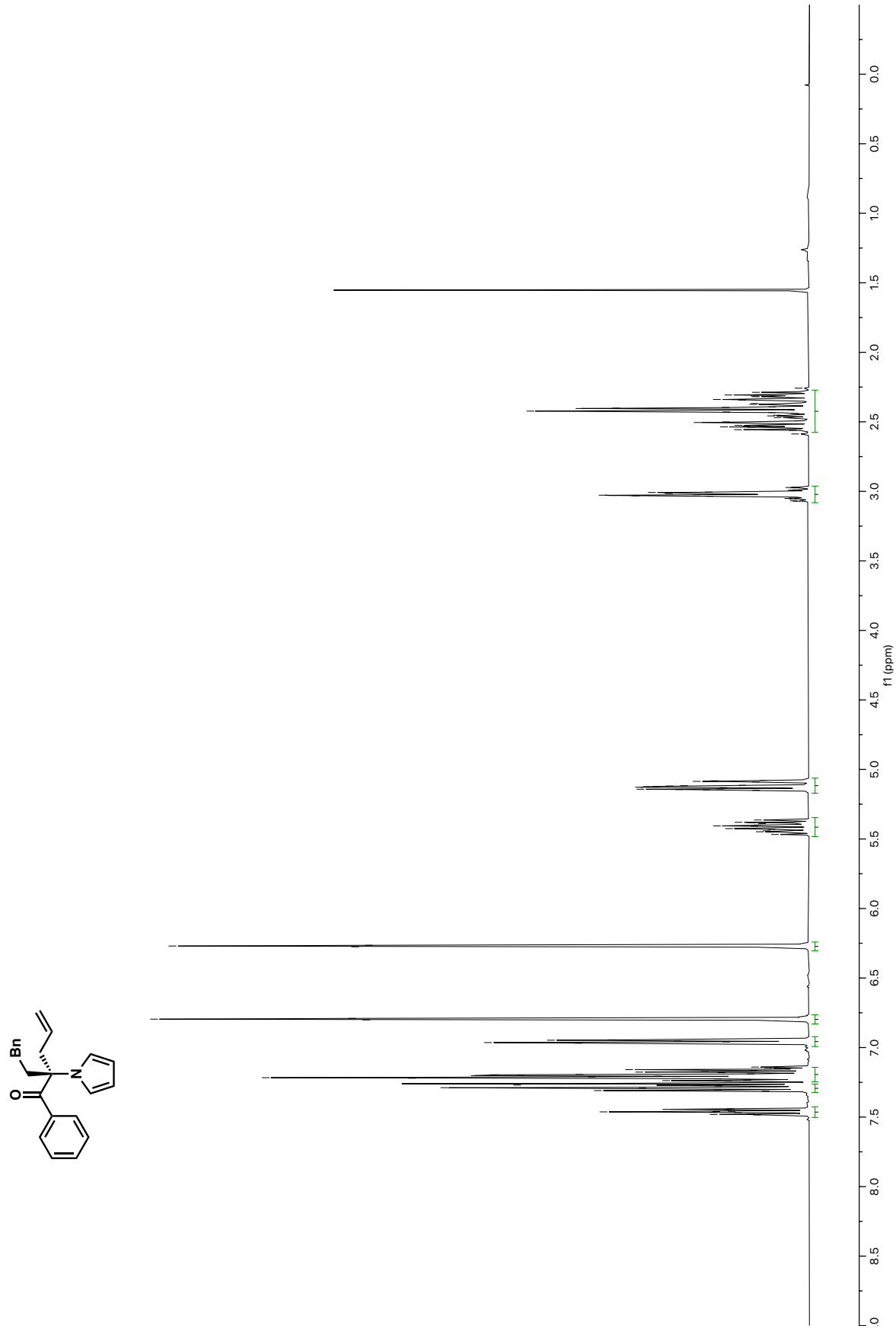
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# *APPENDIX 9*

*Spectra Relevant to Chapter 6:*

*Palladium-Catalyzed Enantioselective Decarboxylative Allylic Alkylation of Acyclic α-Pyrrolyl/Indolyl Ketones*




***A9.1*** *$^1H$ NMR (400 MHz, $CDCl_3$) of compound* ***101a***.

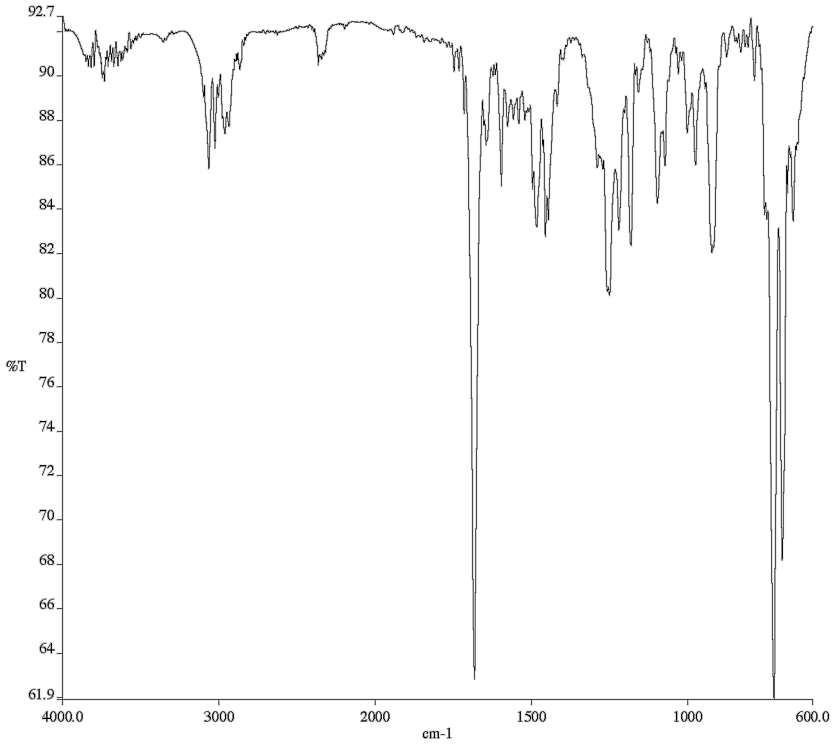



***Figure A9.2*** *Infrared spectrum (Thin Film, NaCl) of compound* ***101a****.*

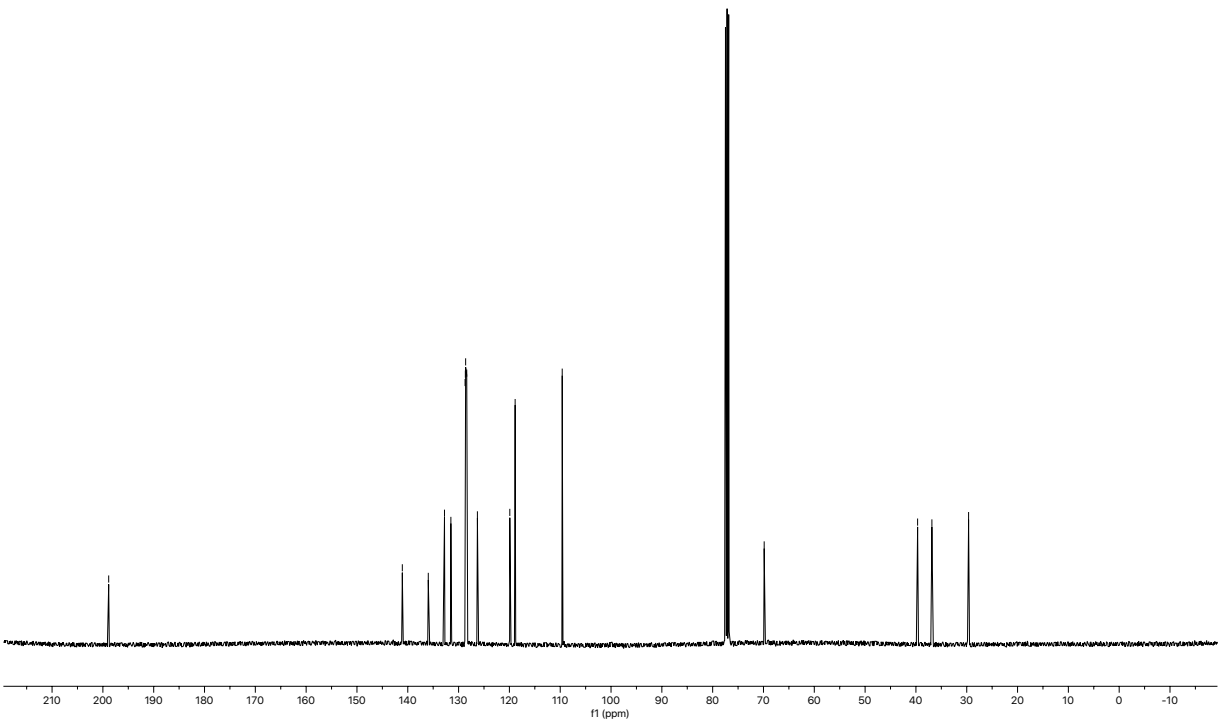
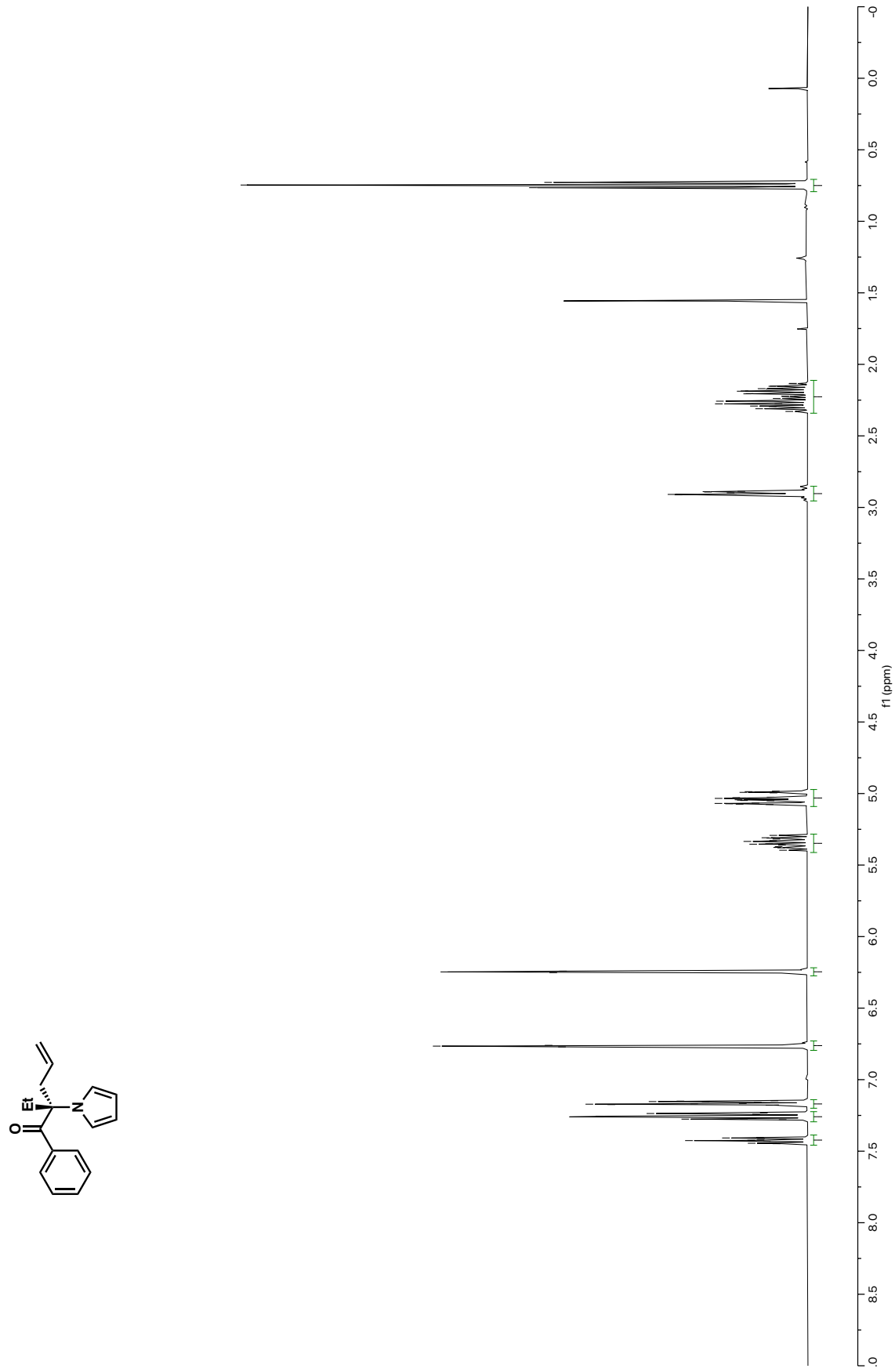



***Figure A9.3*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***101a****.*




***A9.4*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***101b***.

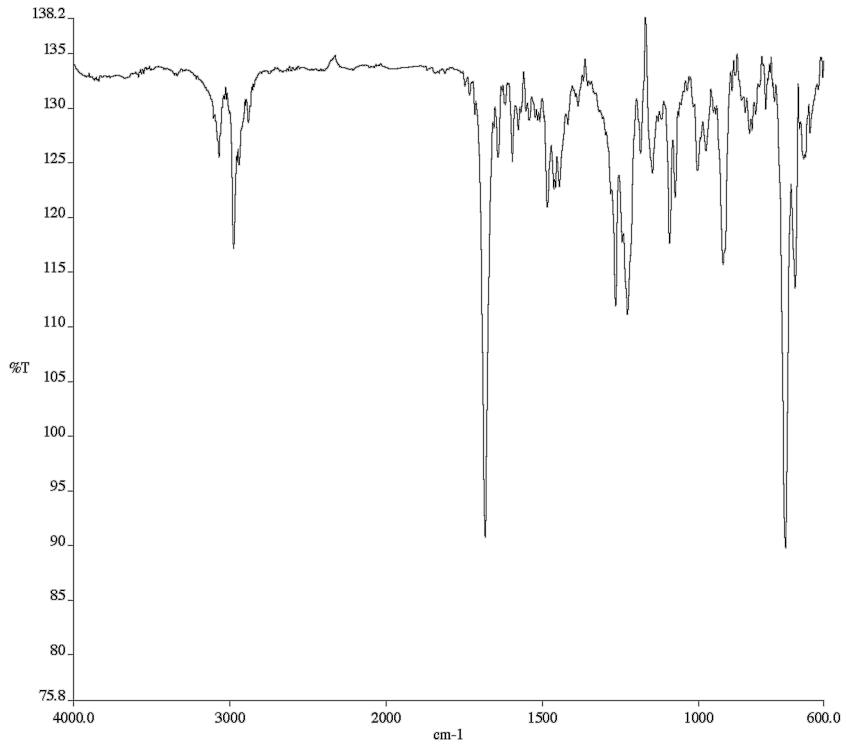



***Figure A9.5*** *Infrared spectrum (Thin Film, NaCl) of compound* ***101b****.*

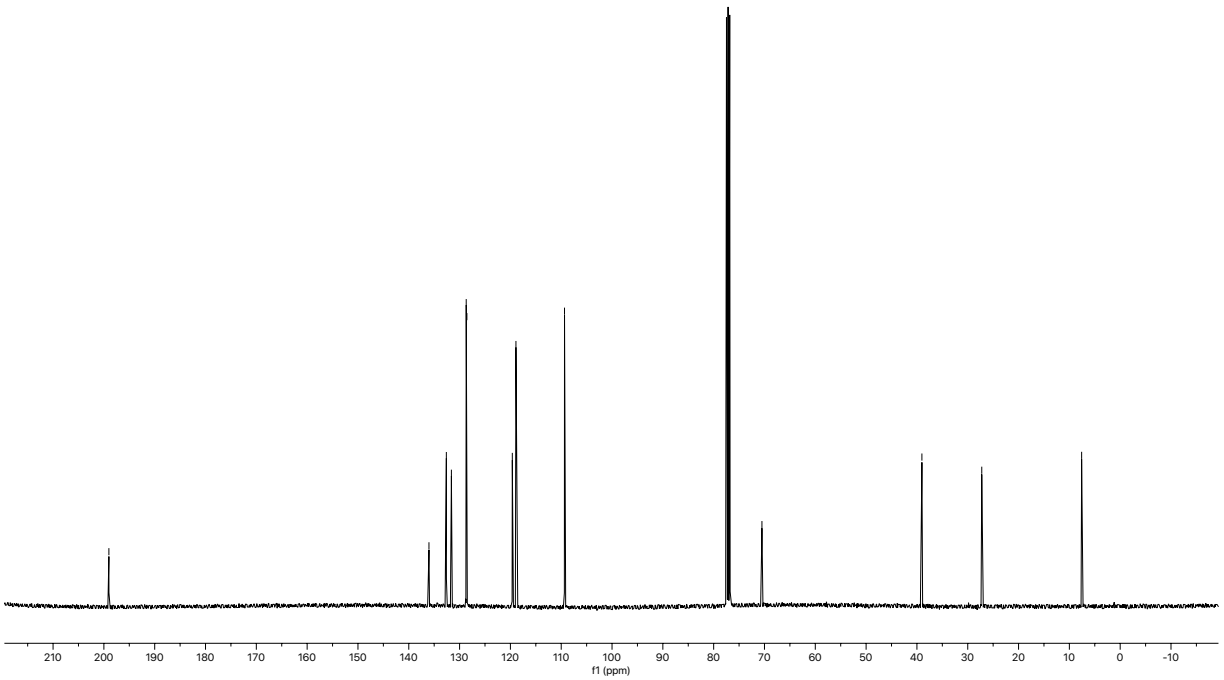
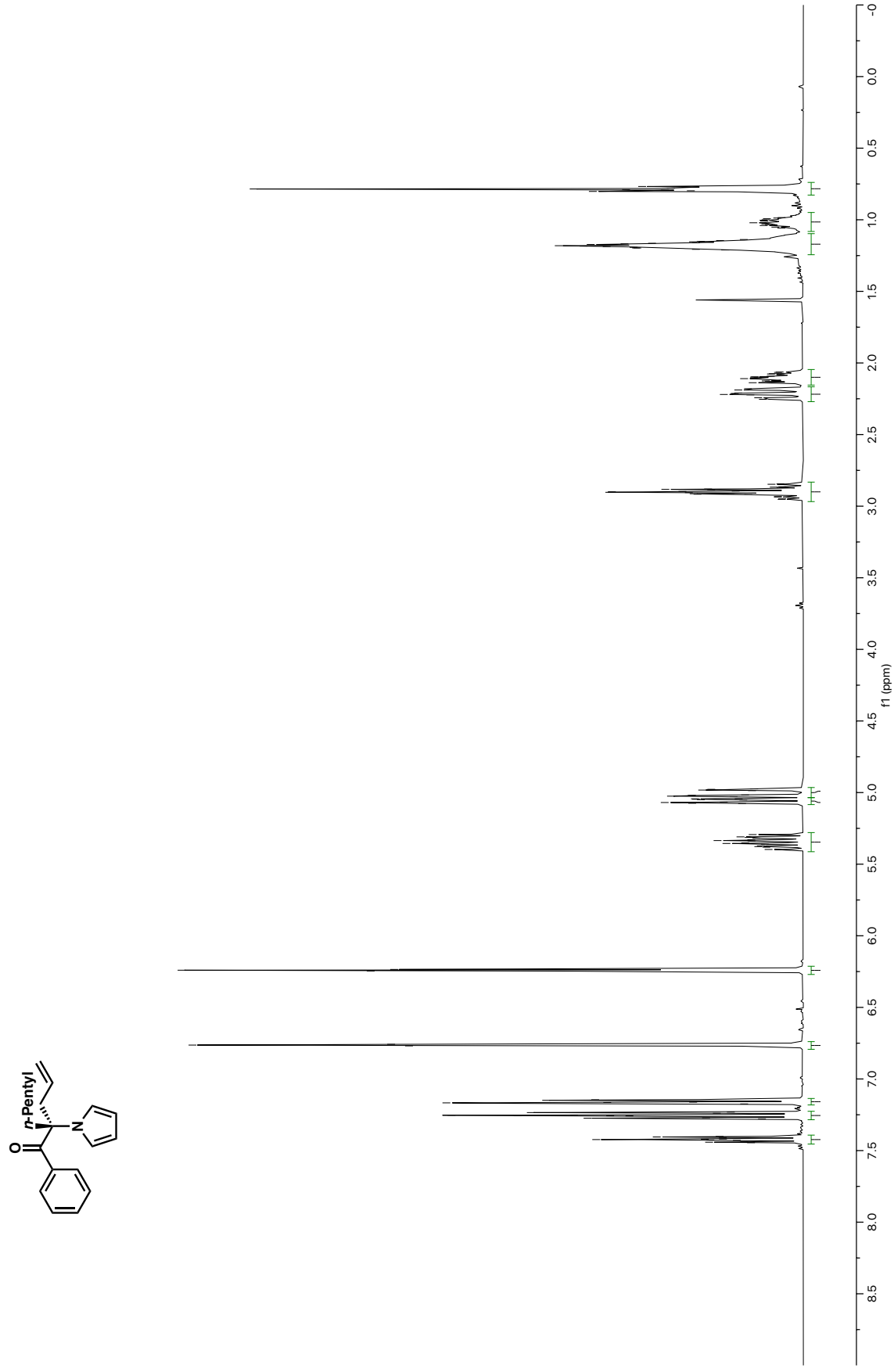



***Figure A9.6*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***101b****.*




***A9.7*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***101c****.*

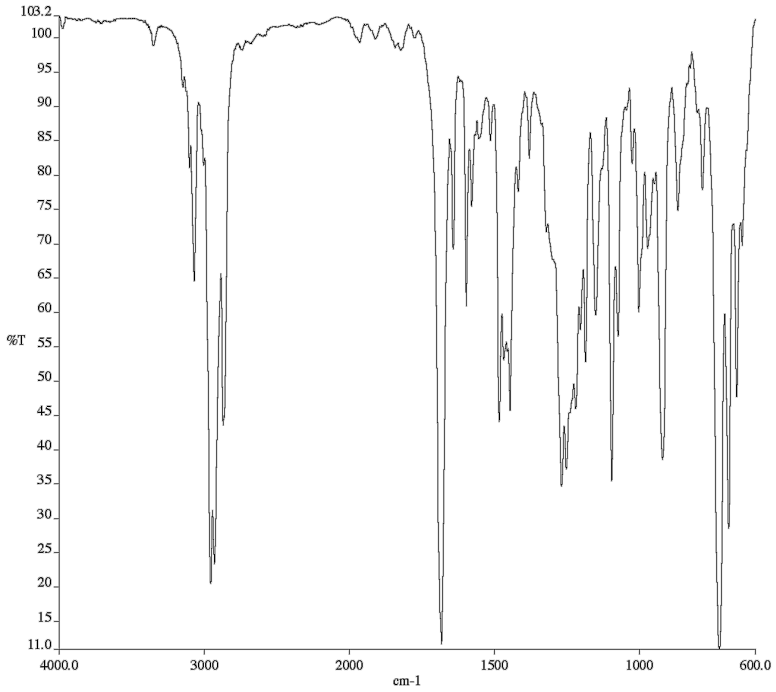



***Figure A9.8*** *Infrared spectrum (Thin Film, NaCl) of compound* ***101c****.*

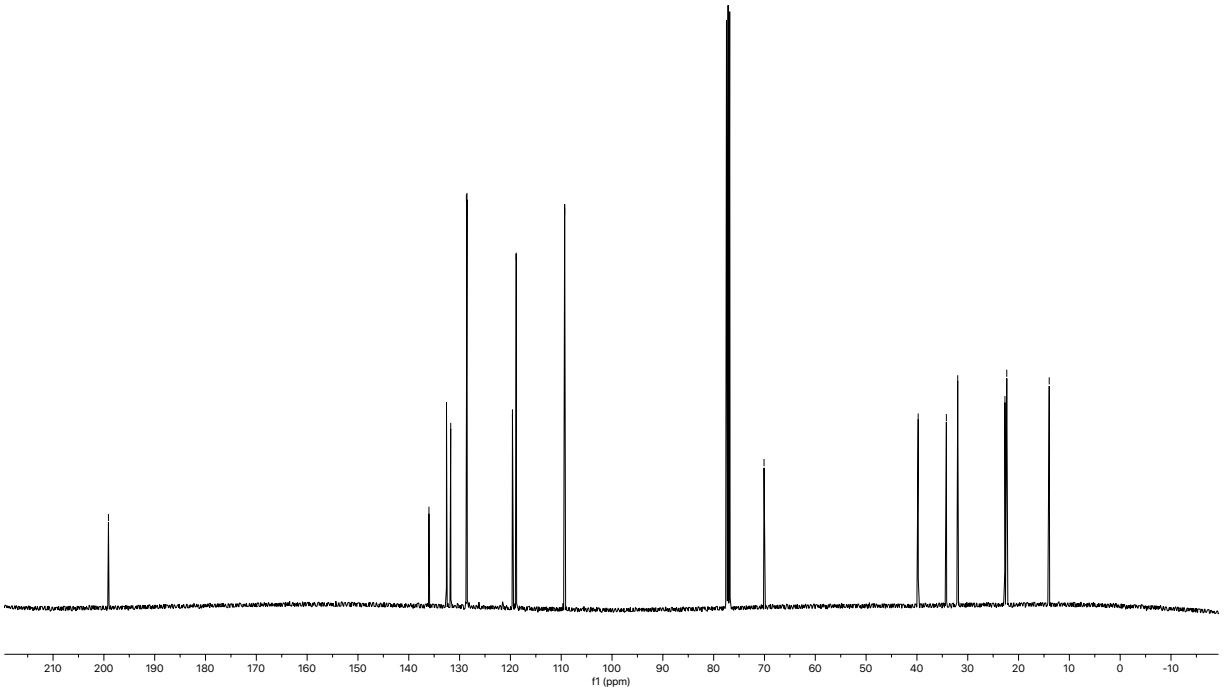
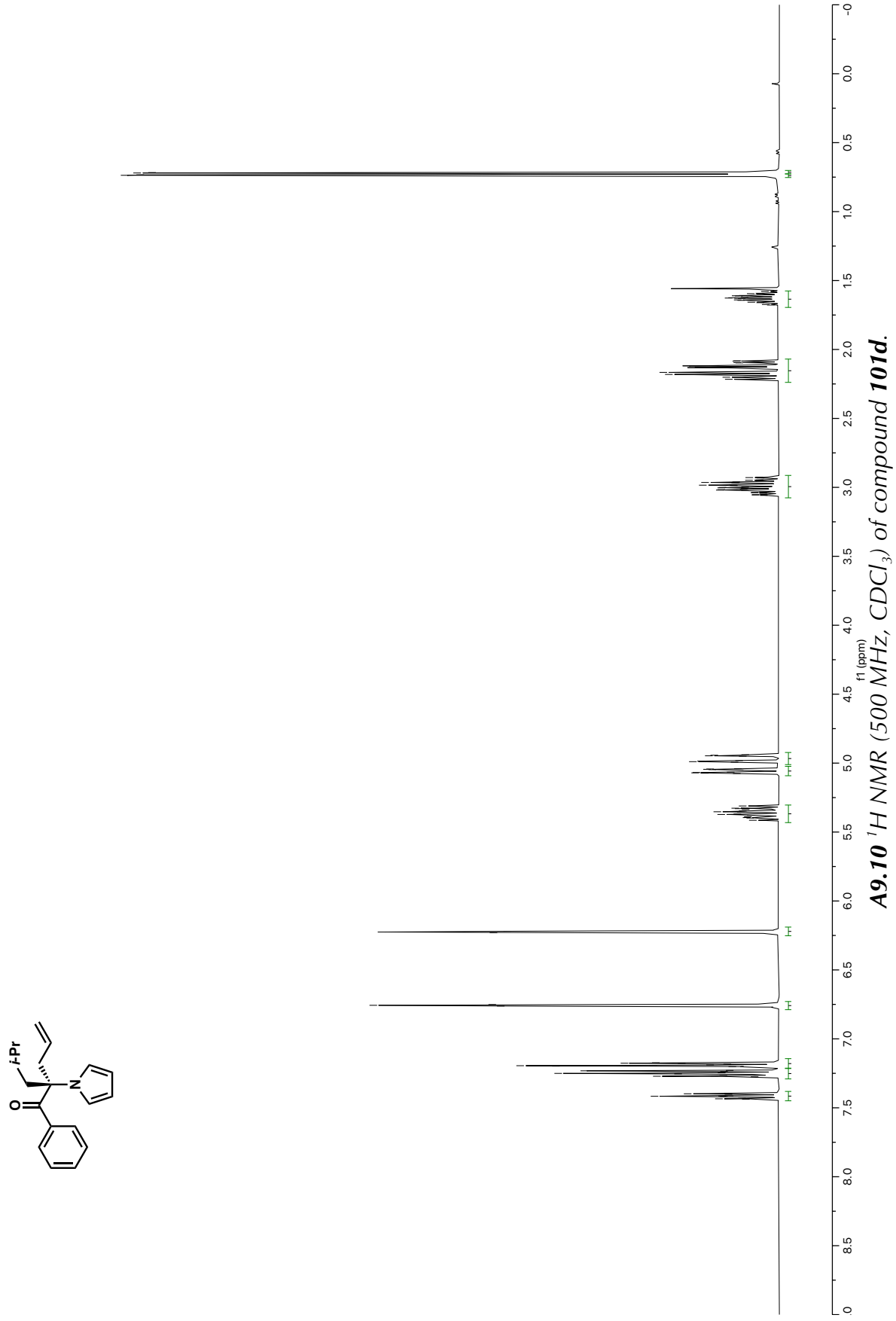



***Figure A9.9*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***101c****.*




***A9.10*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***101d***.

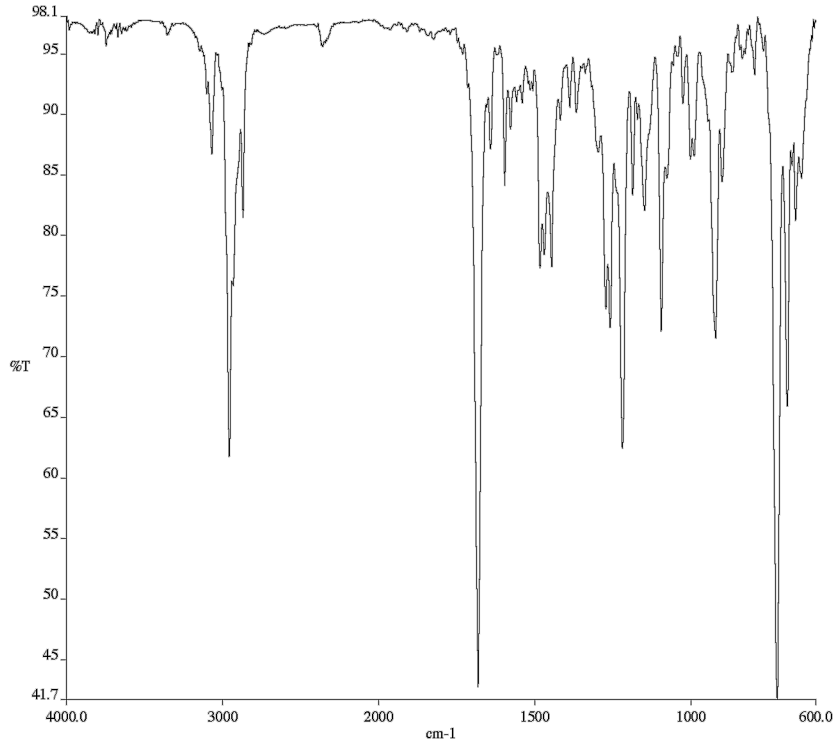



***Figure A9.11*** *Infrared spectrum (Thin Film, NaCl) of compound* ***101d****.*

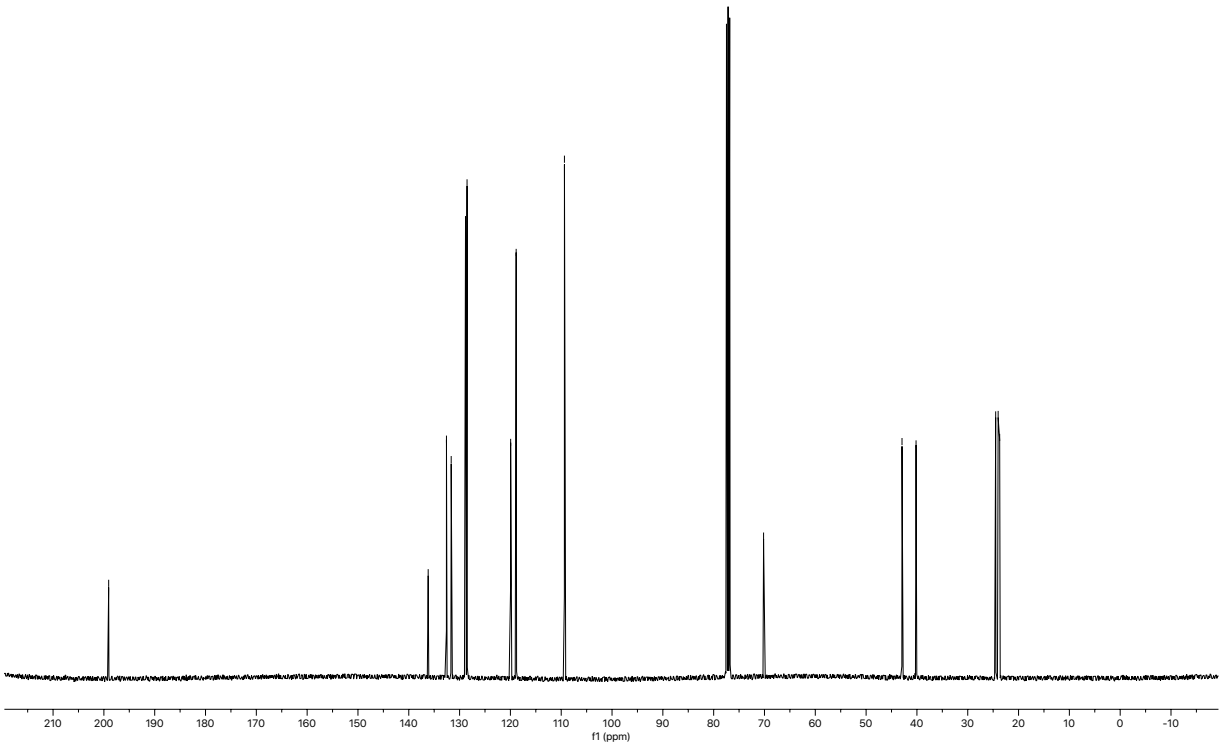
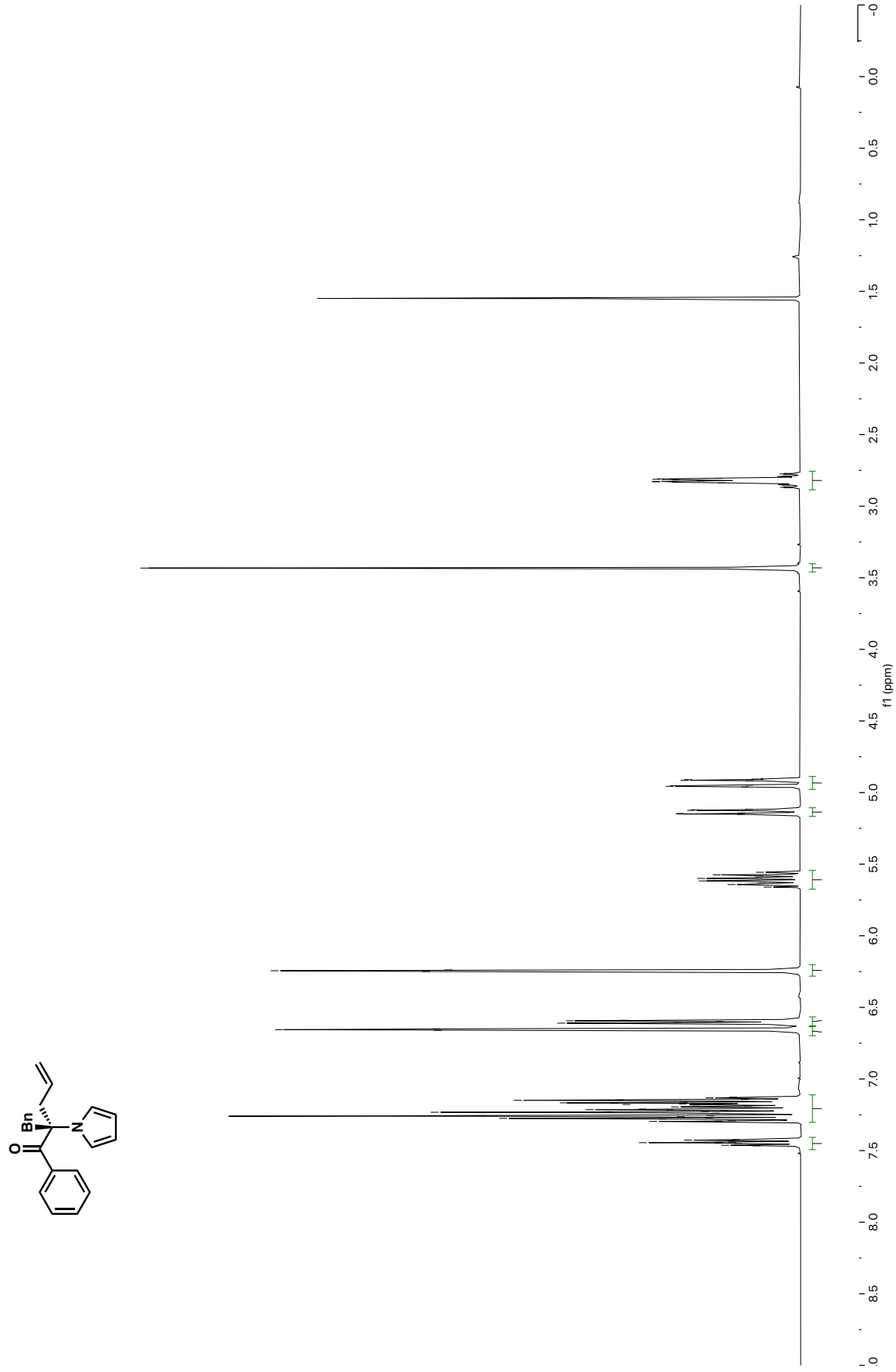



***Figure A9.12*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***101d****.*




***A9.13*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***101e***.

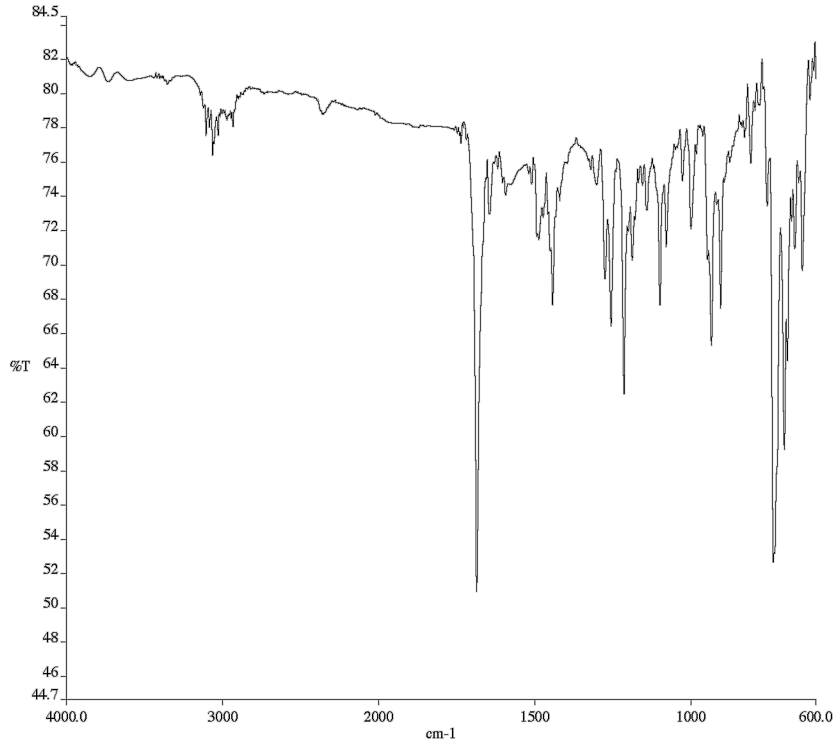



***Figure A9.14*** *Infrared spectrum (Thin Film, NaCl) of compound* ***101e****.*

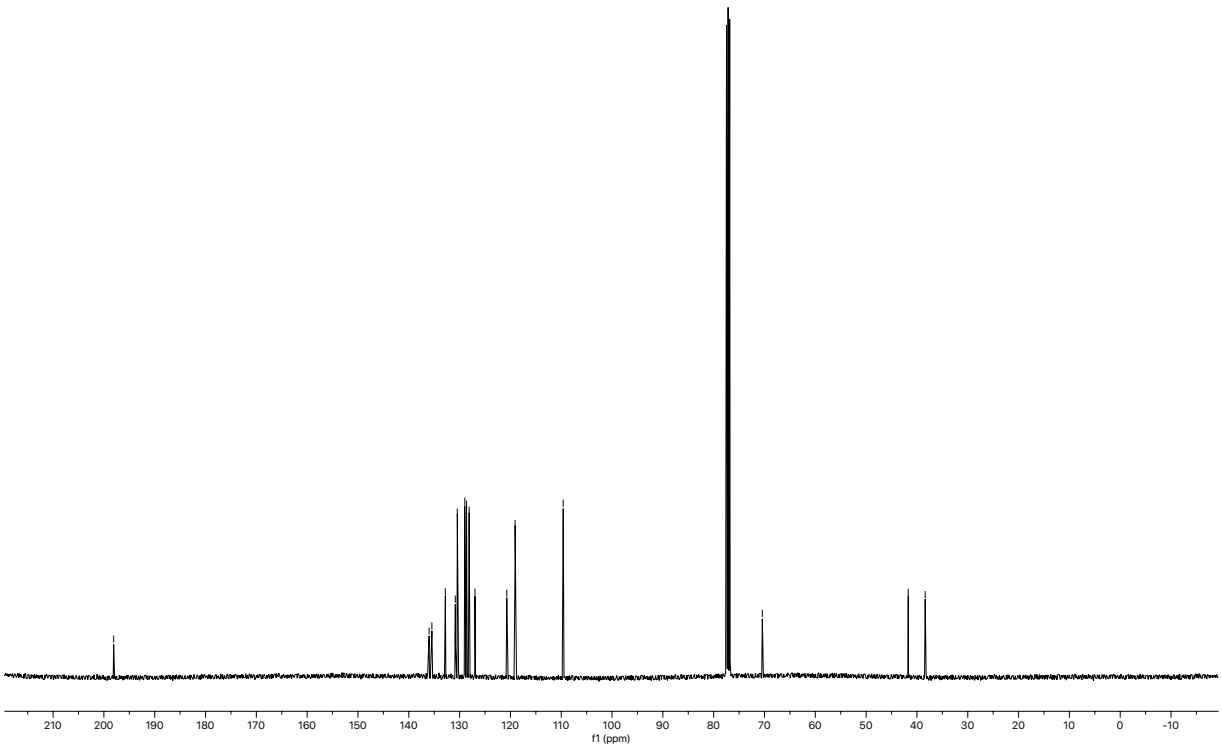
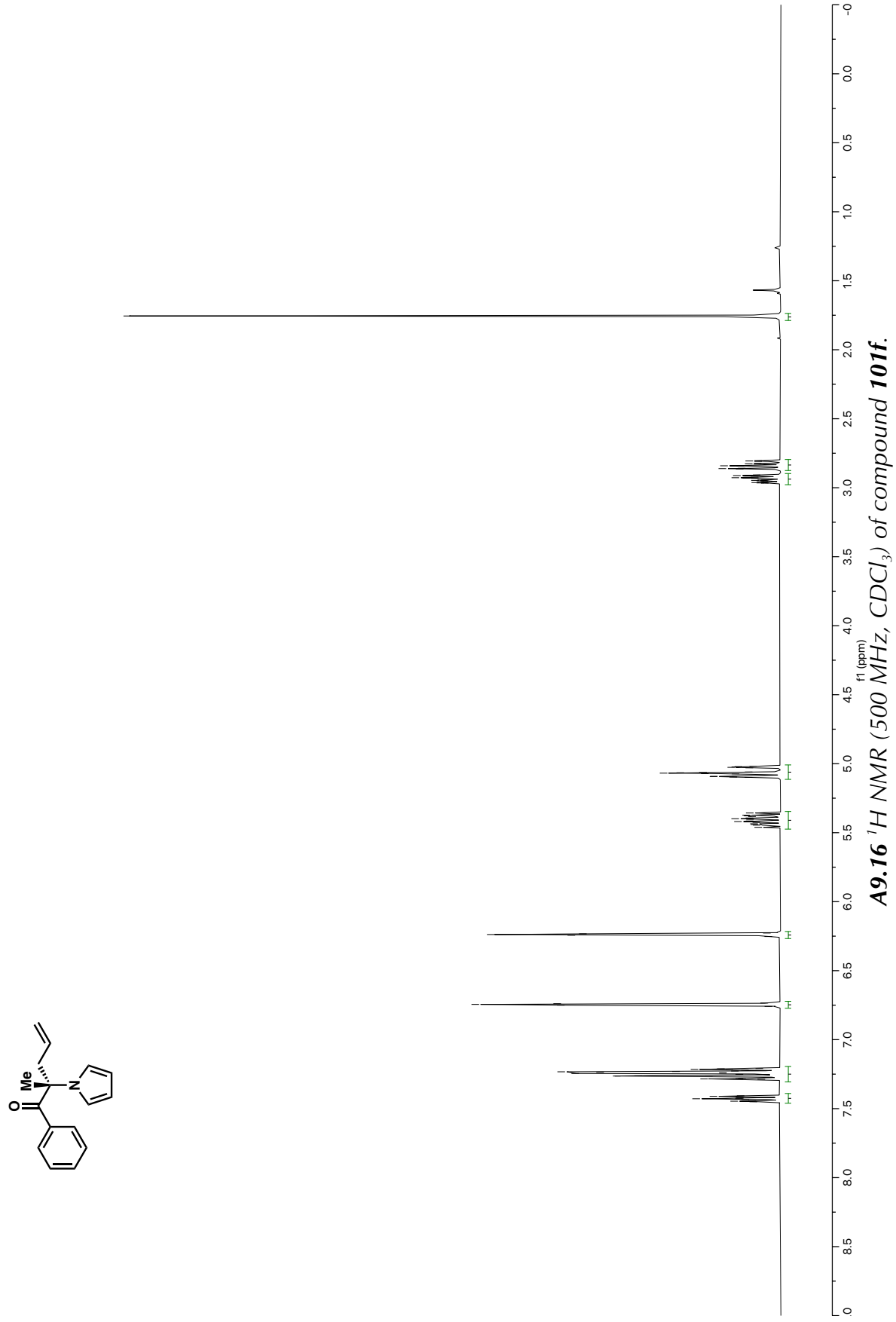



***Figure A9.15*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***101e****.*




***A9.16*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***101f****.*

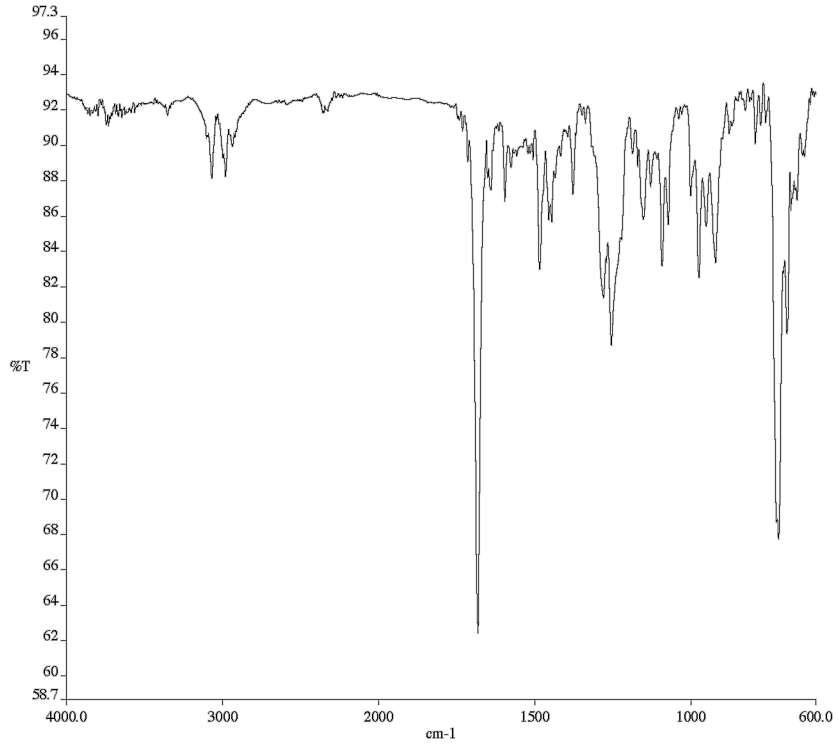



***Figure A9.17*** *Infrared spectrum (Thin Film, NaCl) of compound* ***101f****.*

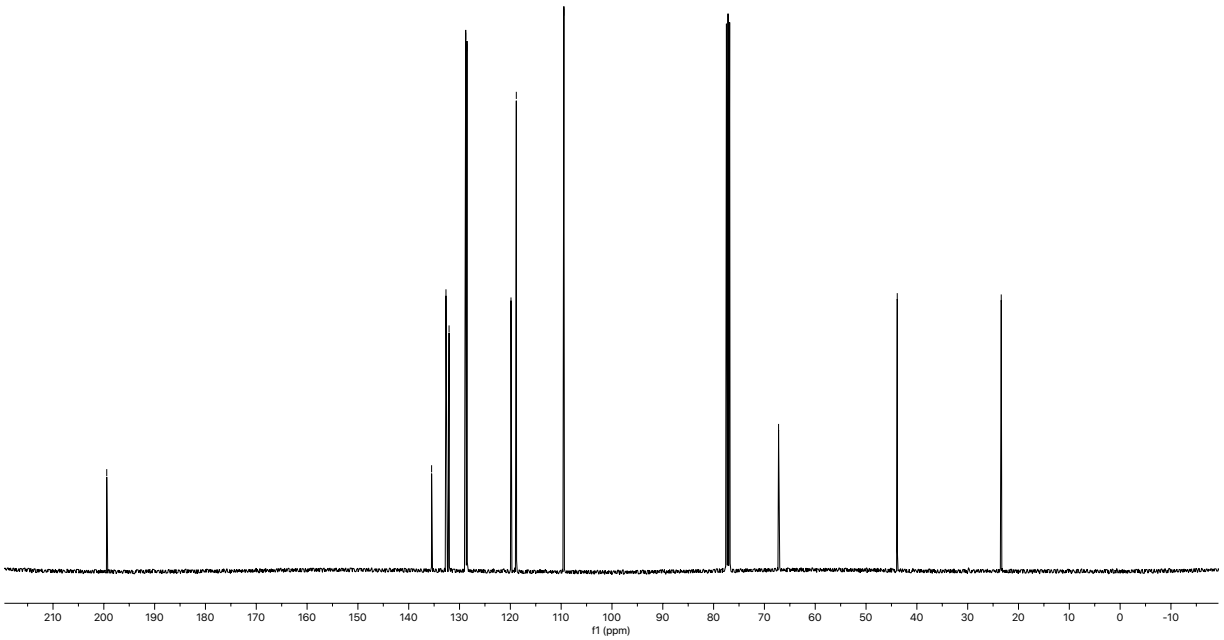
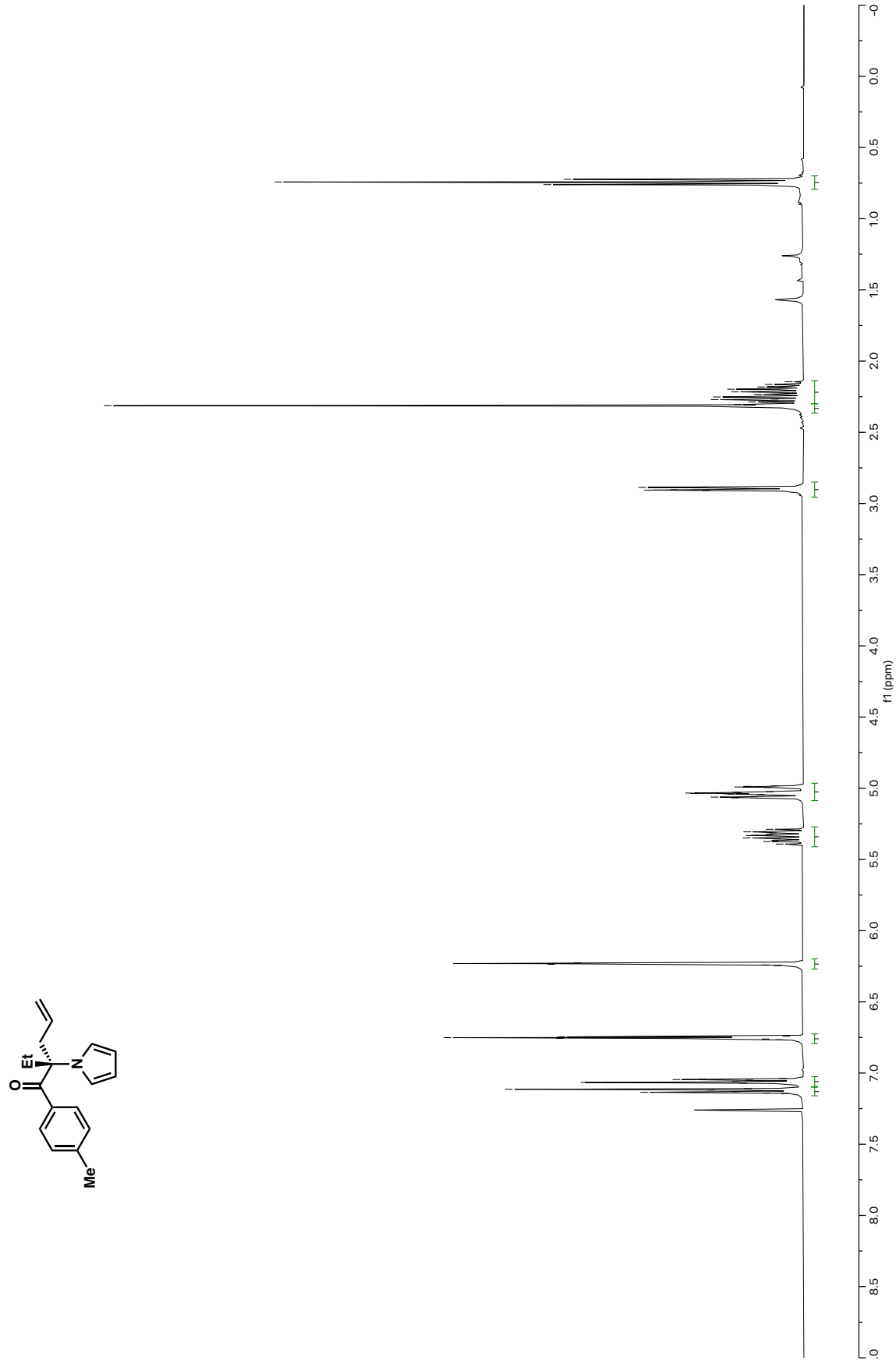



***Figure A9.18*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***101f****.*




***A9.19*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***101g***.

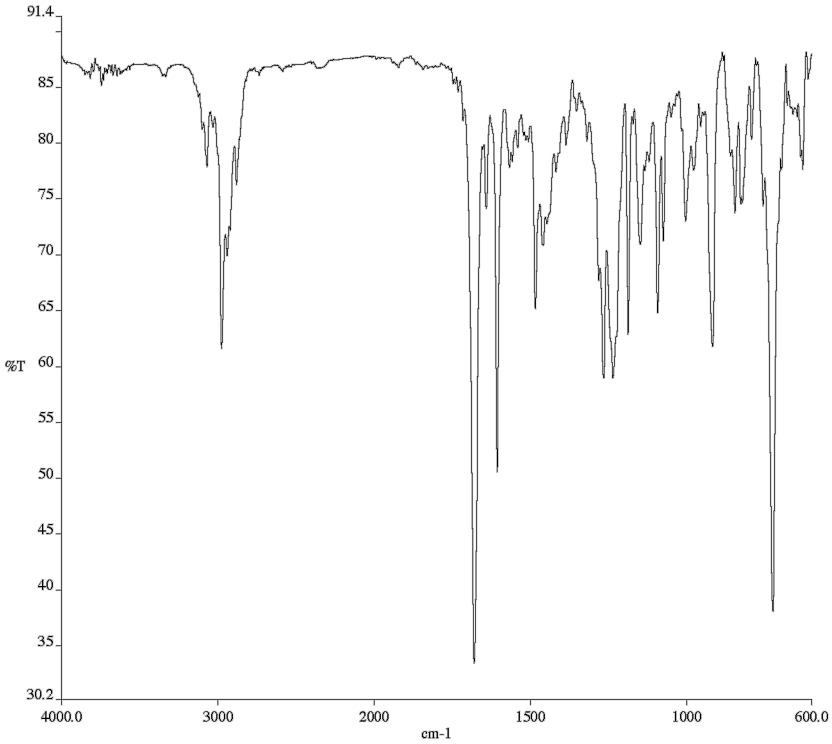



***Figure A9.20*** *Infrared spectrum (Thin Film, NaCl) of compound* ***101g***.

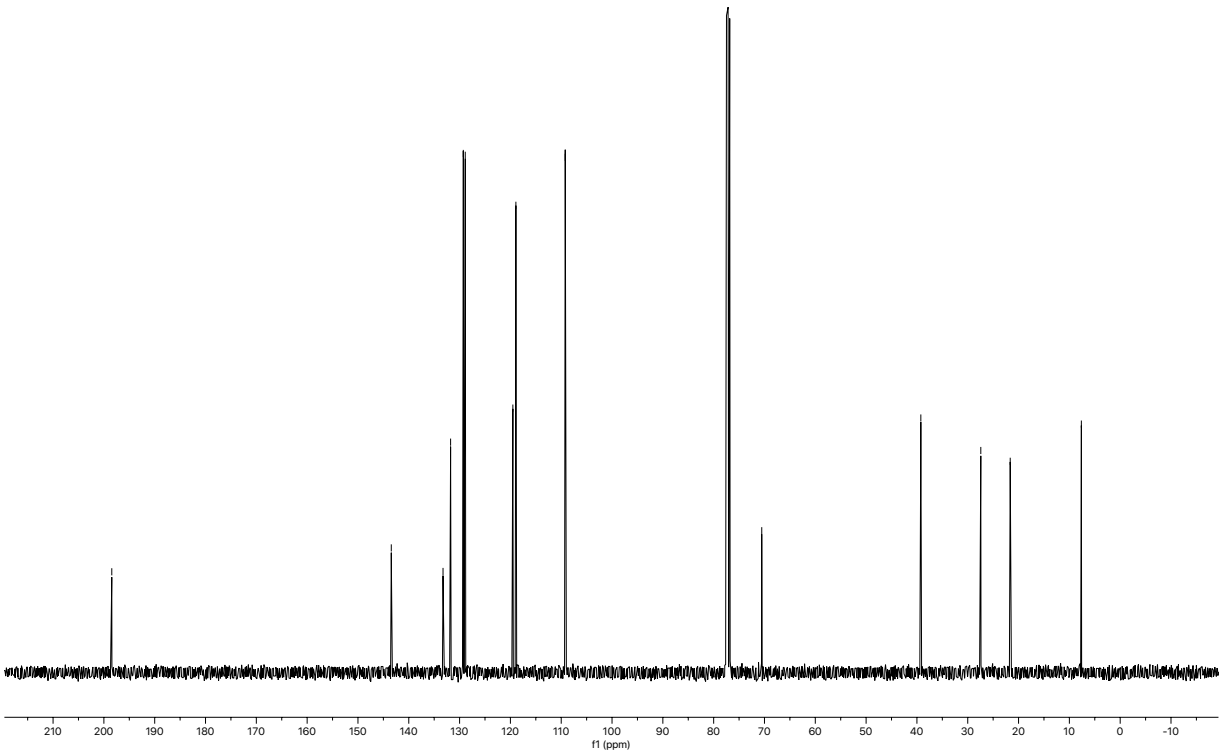
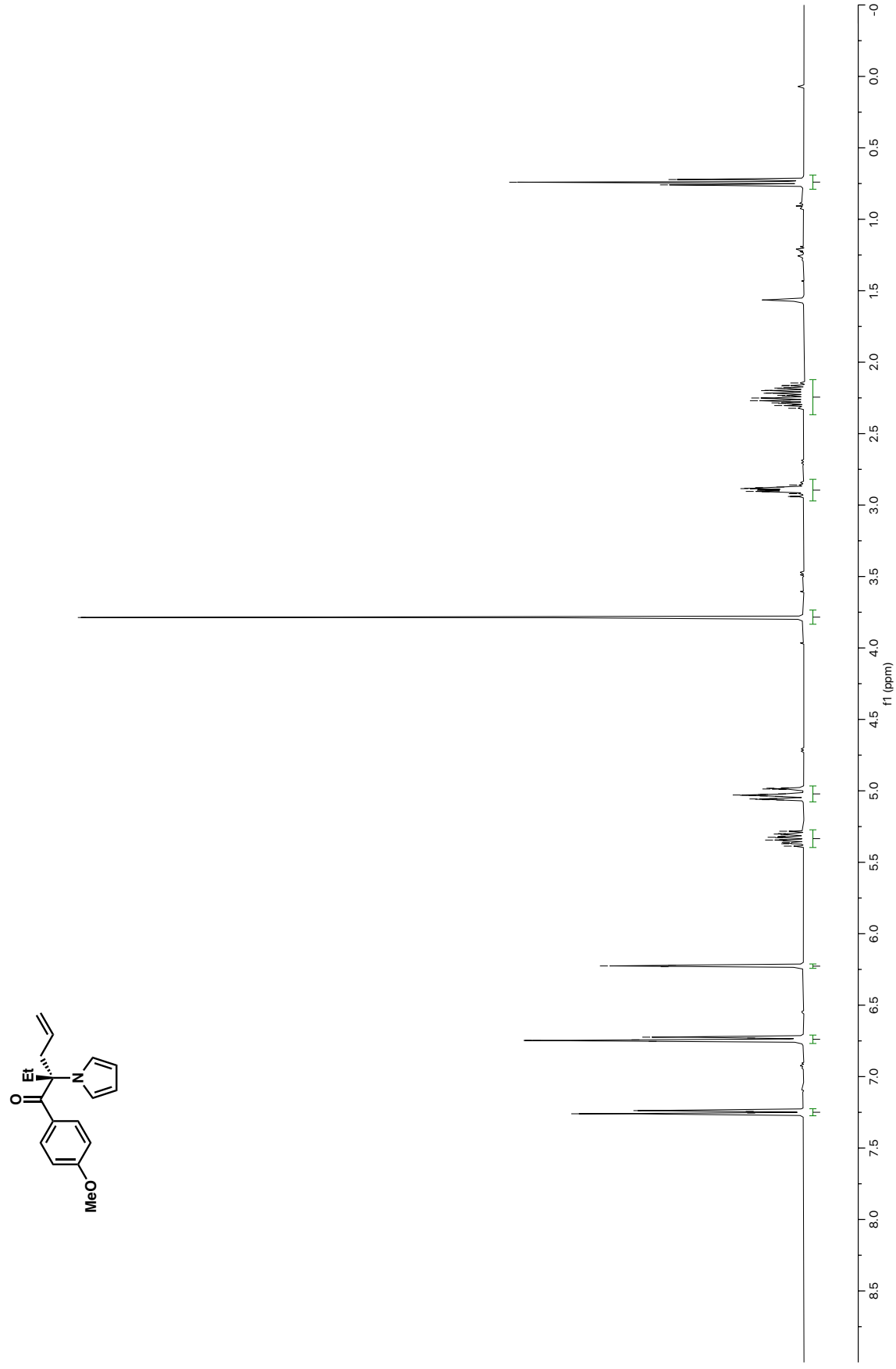



***Figure A9.21*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***101g***.




***A9.22*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***101h***.

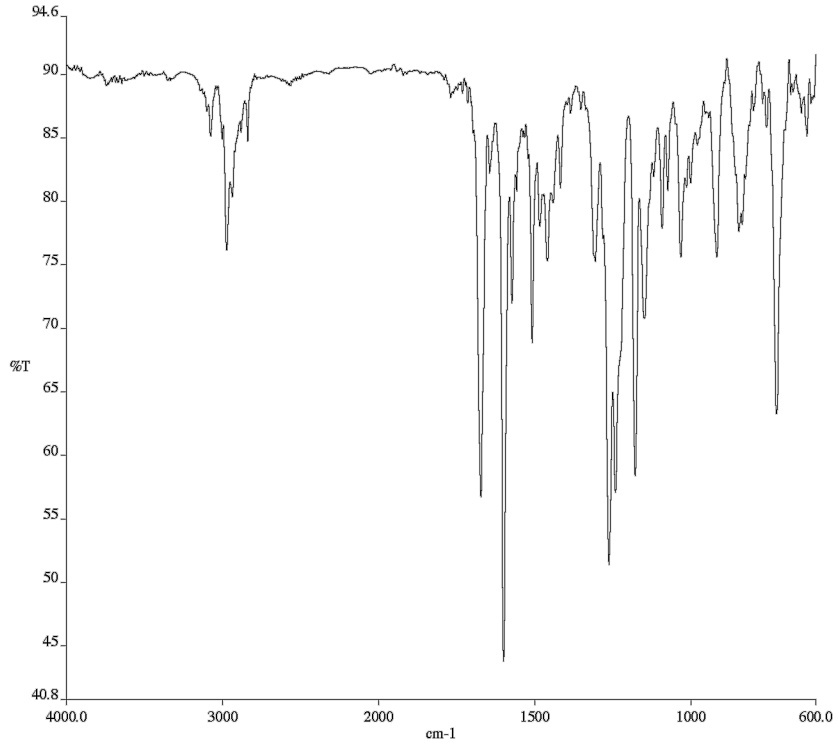



***Figure A9.23*** *Infrared spectrum (Thin Film, NaCl) of compound* ***101h***.

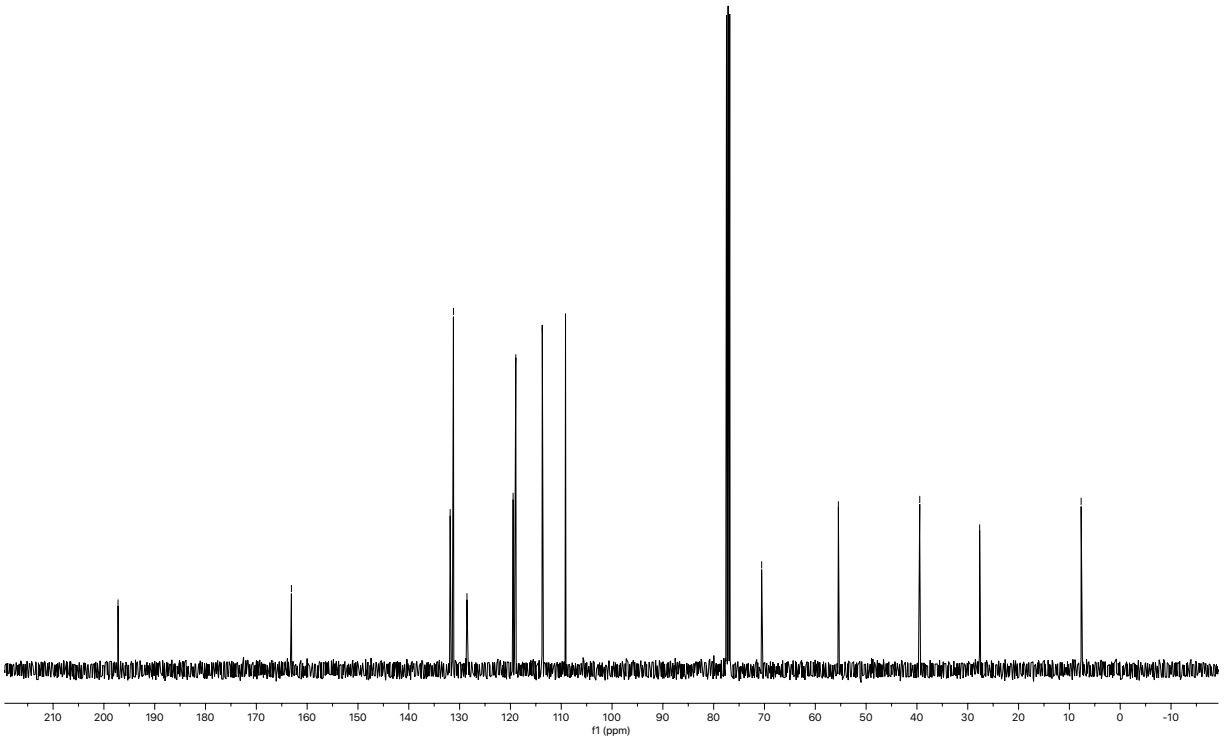
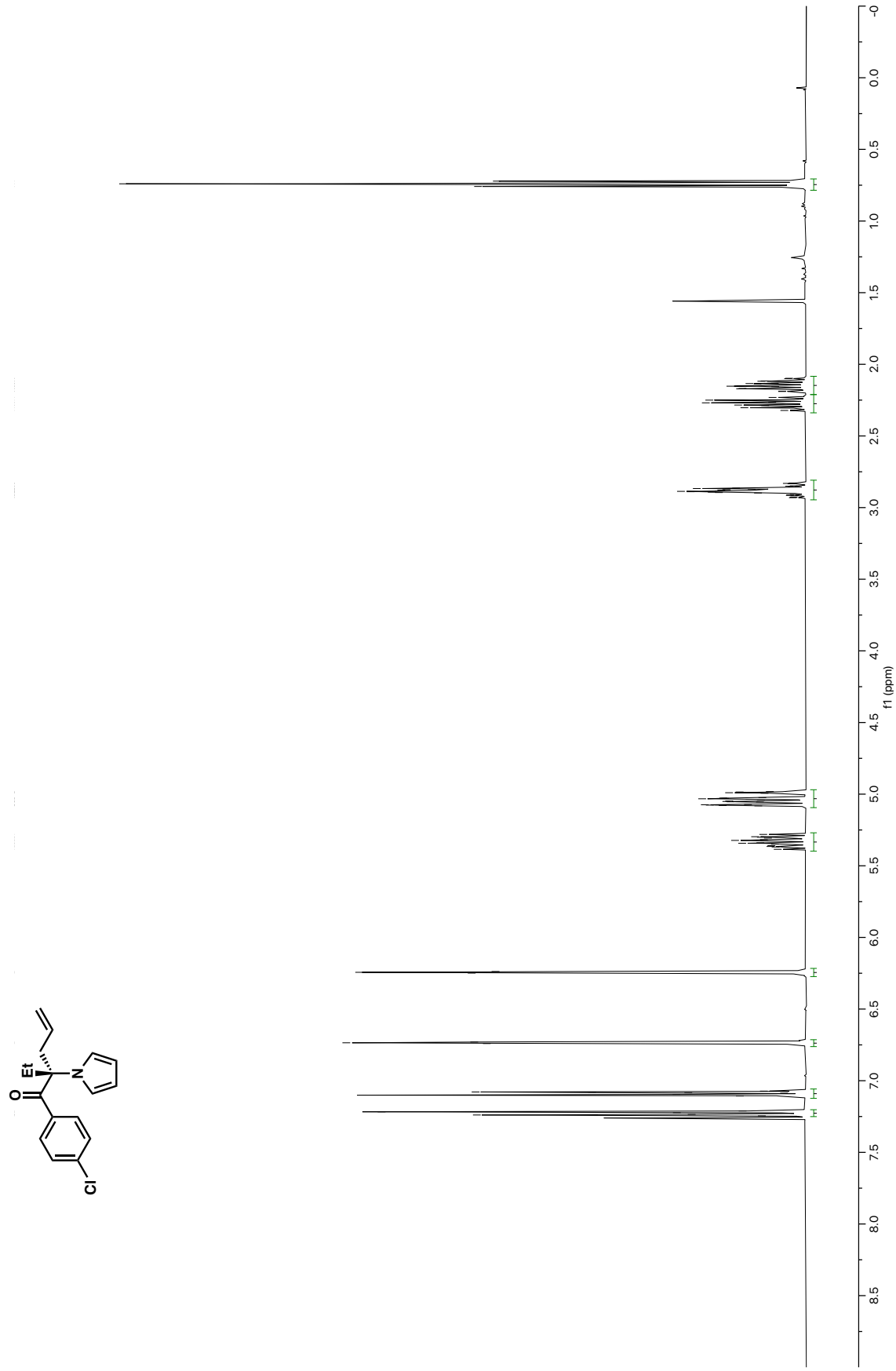



***Figure A9.24*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***101h***.




***A9.25*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***101i.***

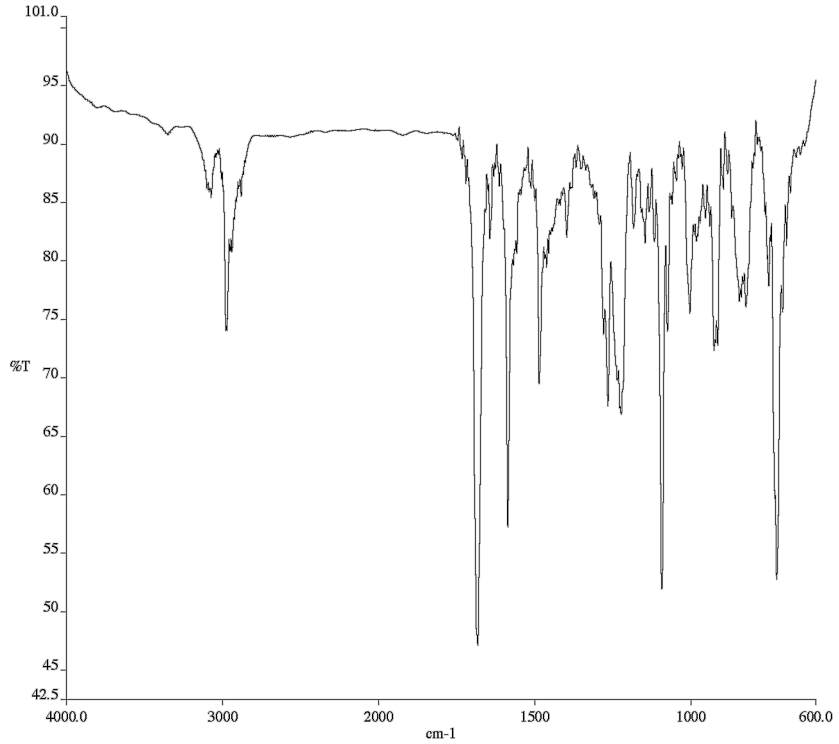



***Figure A9.26*** *Infrared spectrum (Thin Film, NaCl) of compound* ***101i***.

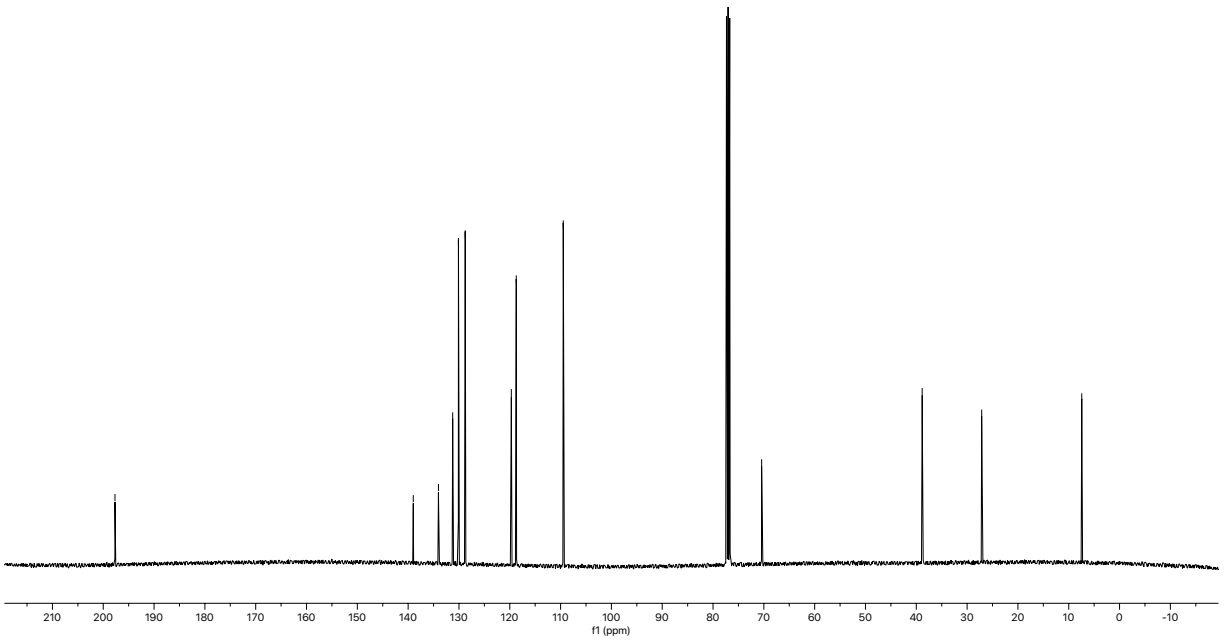
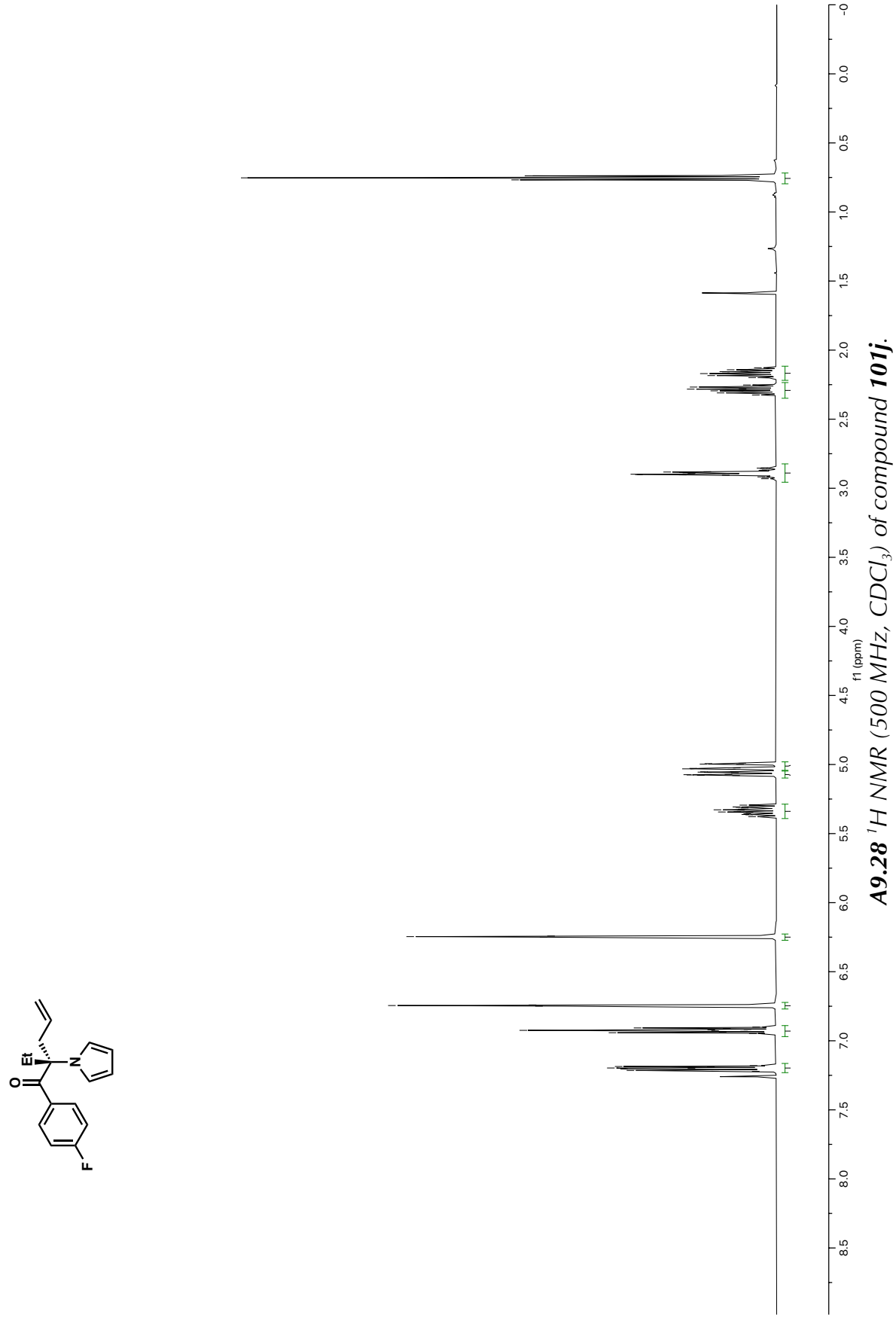



***Figure A9.27*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***101i***.




***A9.28*** *$^{1}H$ NMR (500 MHz, $CDCl_3$) of compound* ***101j****.*

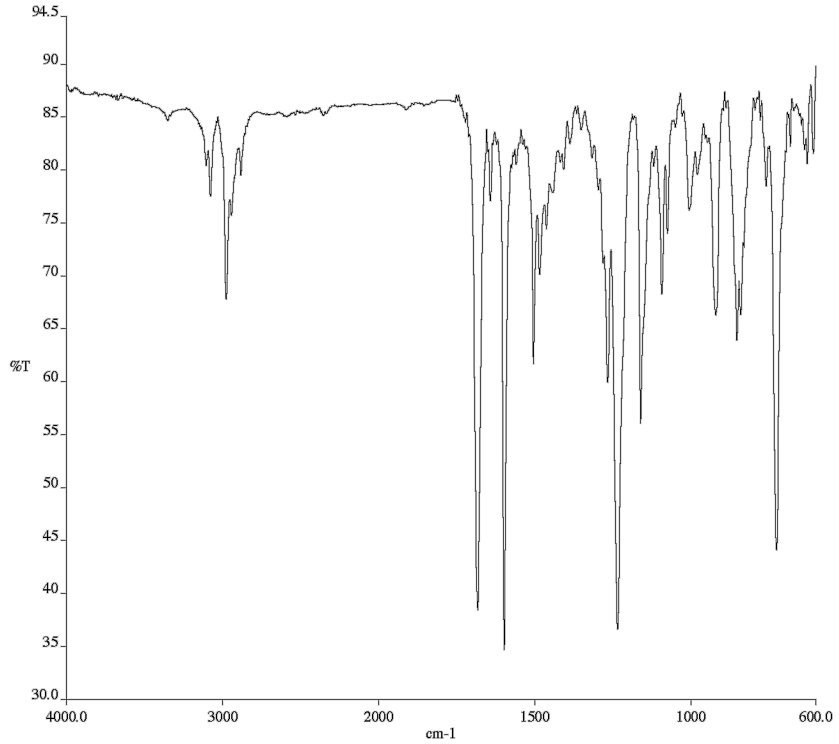



***Figure A9.29*** *Infrared spectrum (Thin Film, NaCl) of compound* ***101j****.*

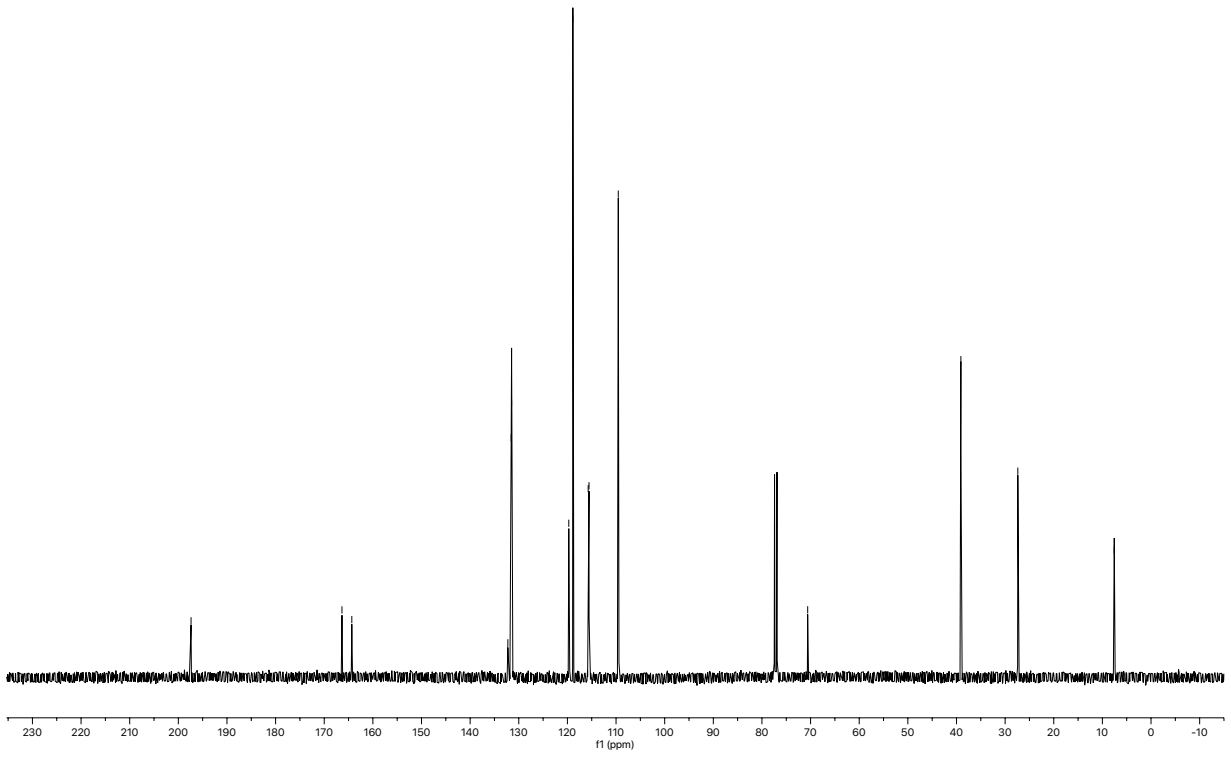



***Figure A9.30*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***101j****.*

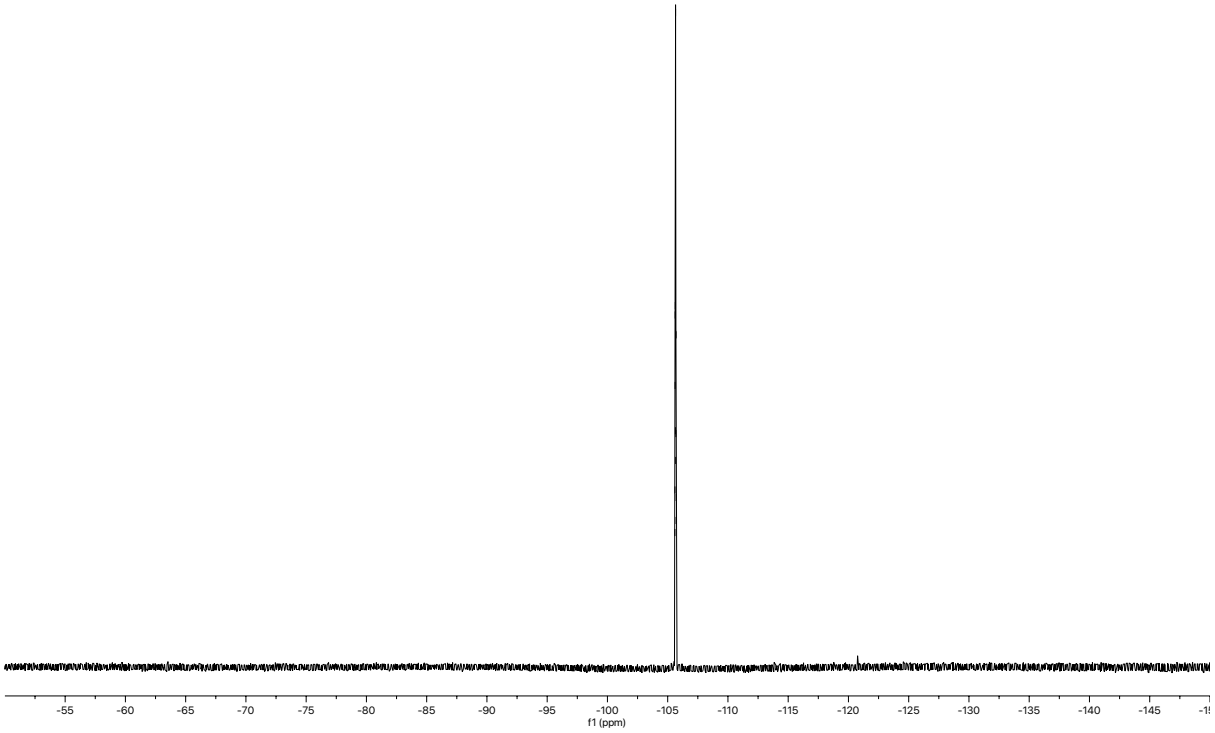
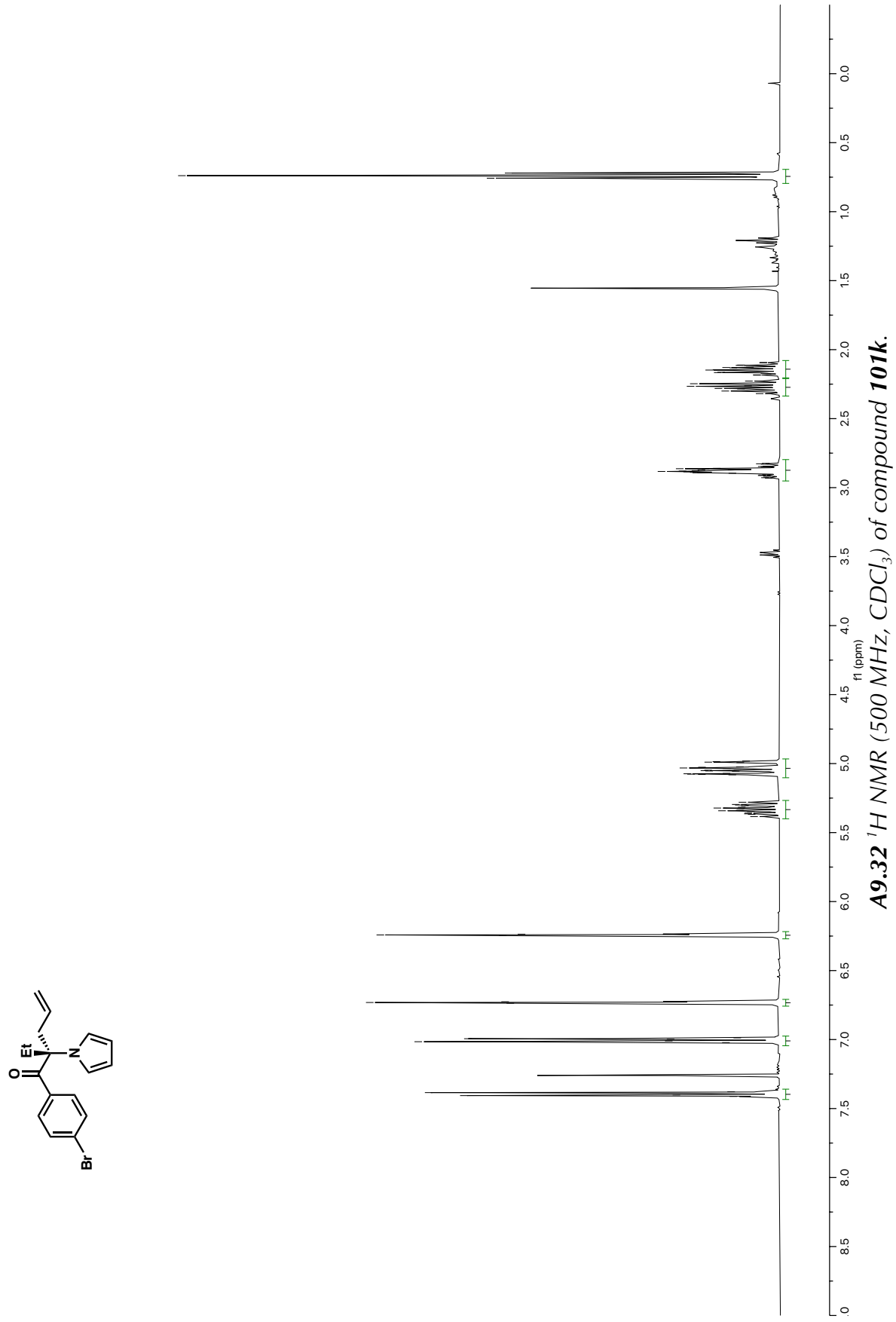



***Figure A9.31*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***101j***.




***A9.32*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***101k***.

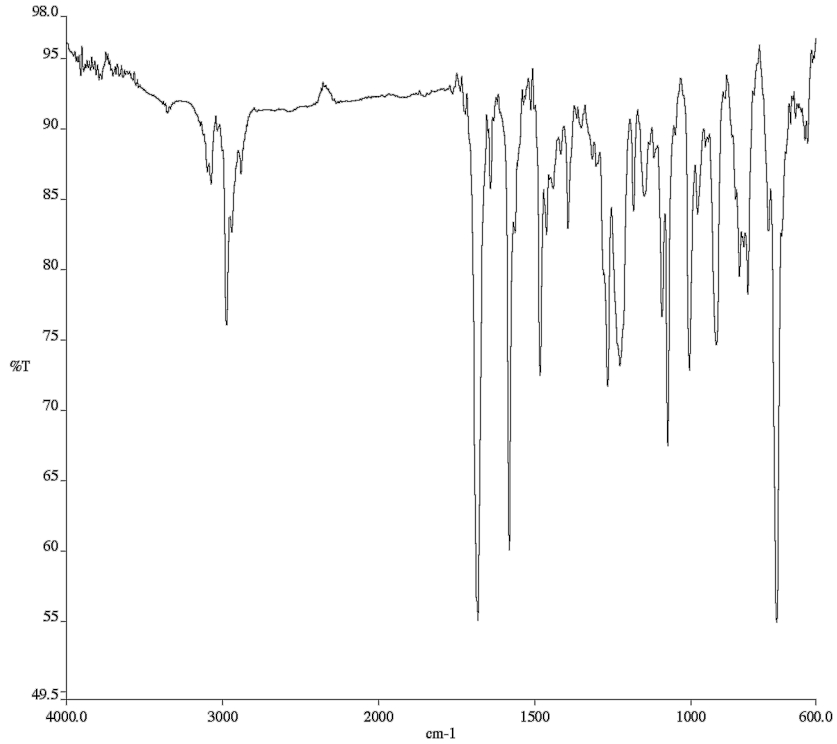



***Figure A9.33*** *Infrared spectrum (Thin Film, NaCl) of compound* ***101k****.*

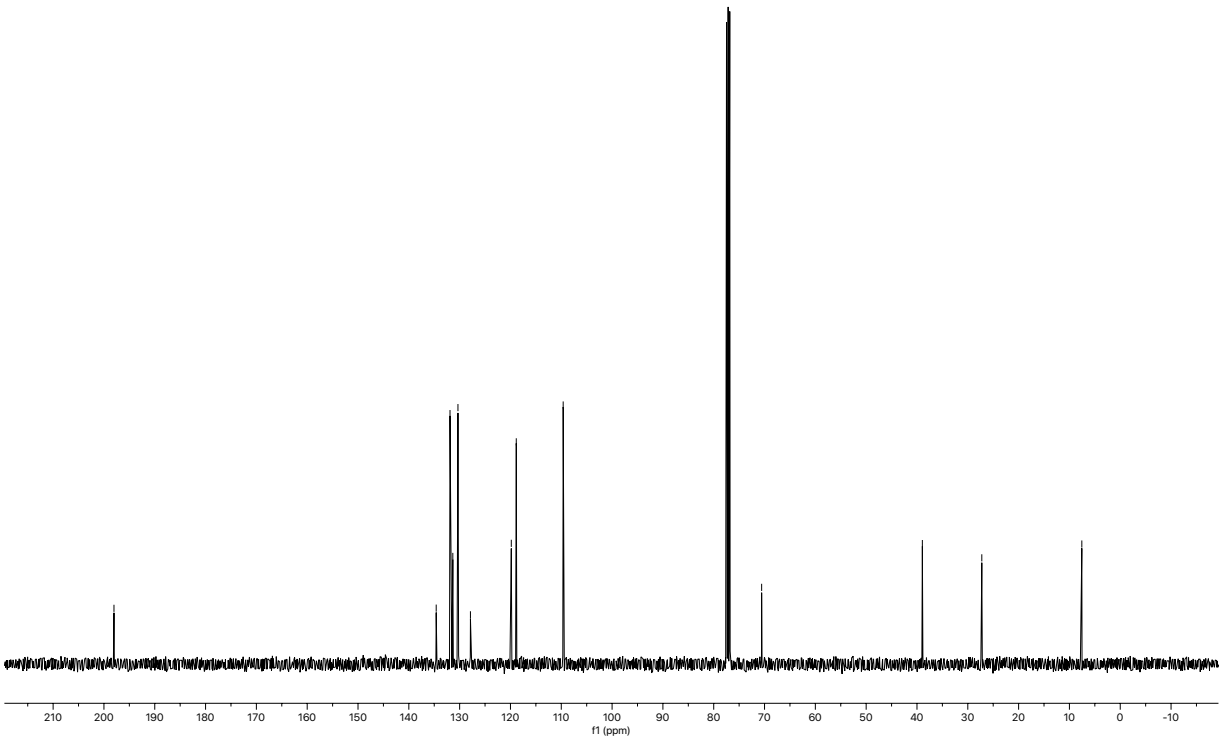
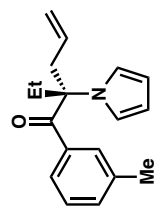
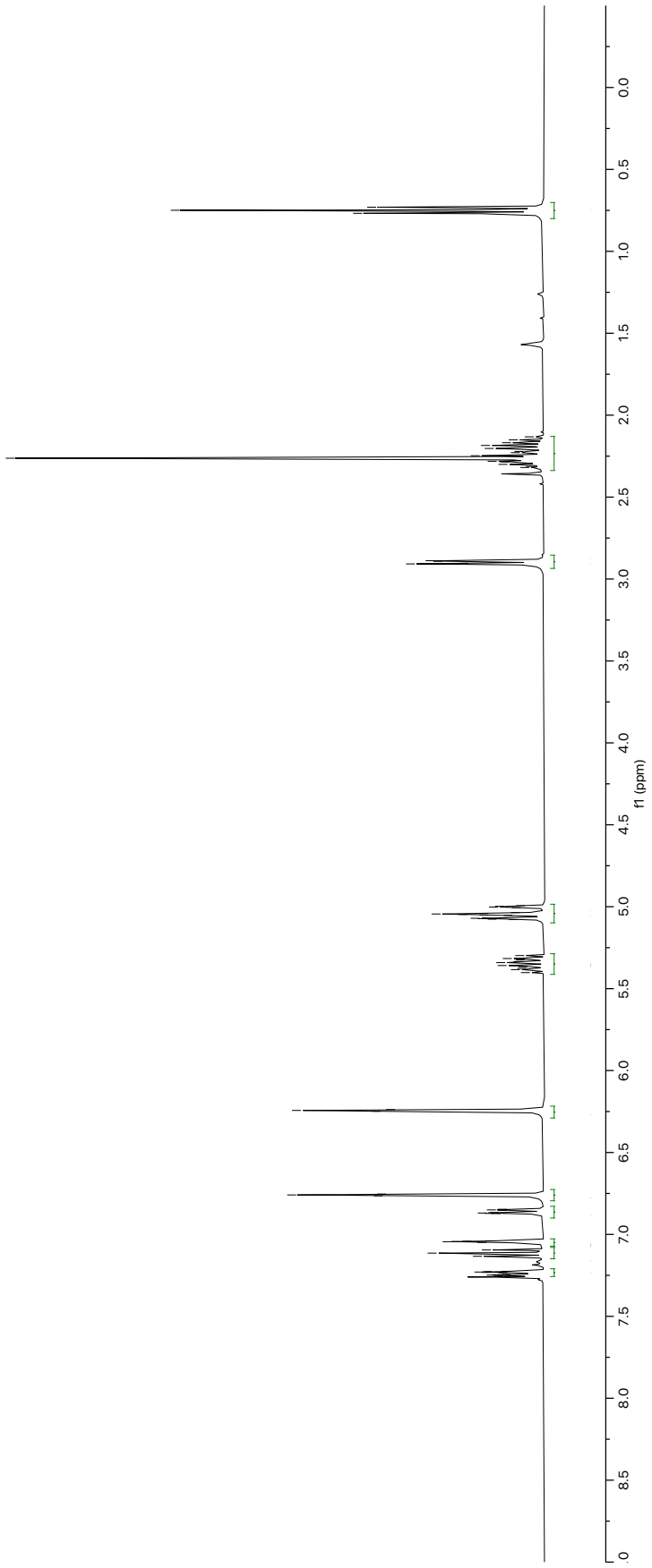



***Figure A9.34*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***101k****.*




***A9.35*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***101l****.*

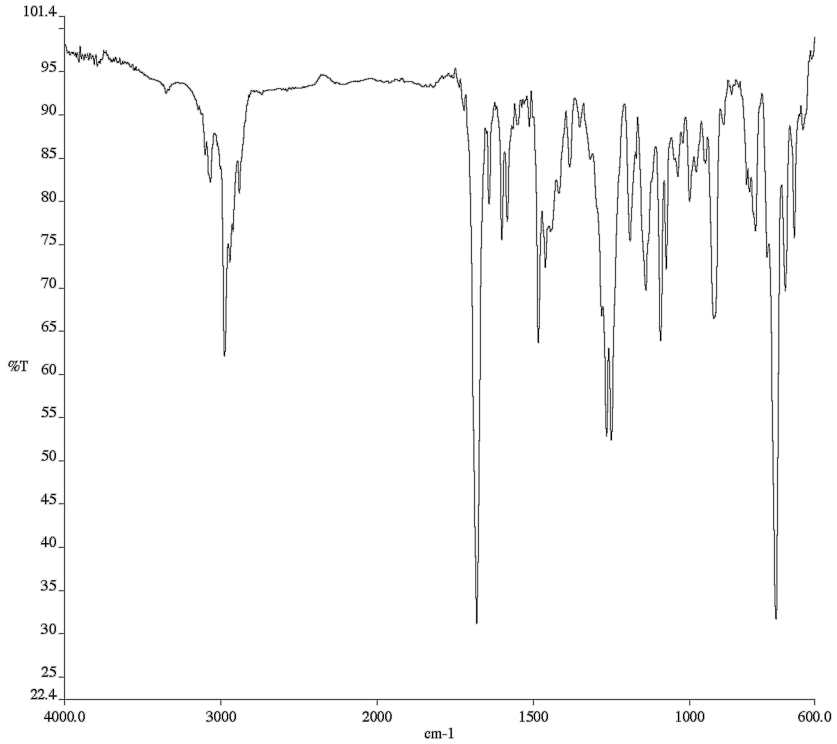



***Figure A9.36*** *Infrared spectrum (Thin Film, NaCl) of compound* ***101l****.*

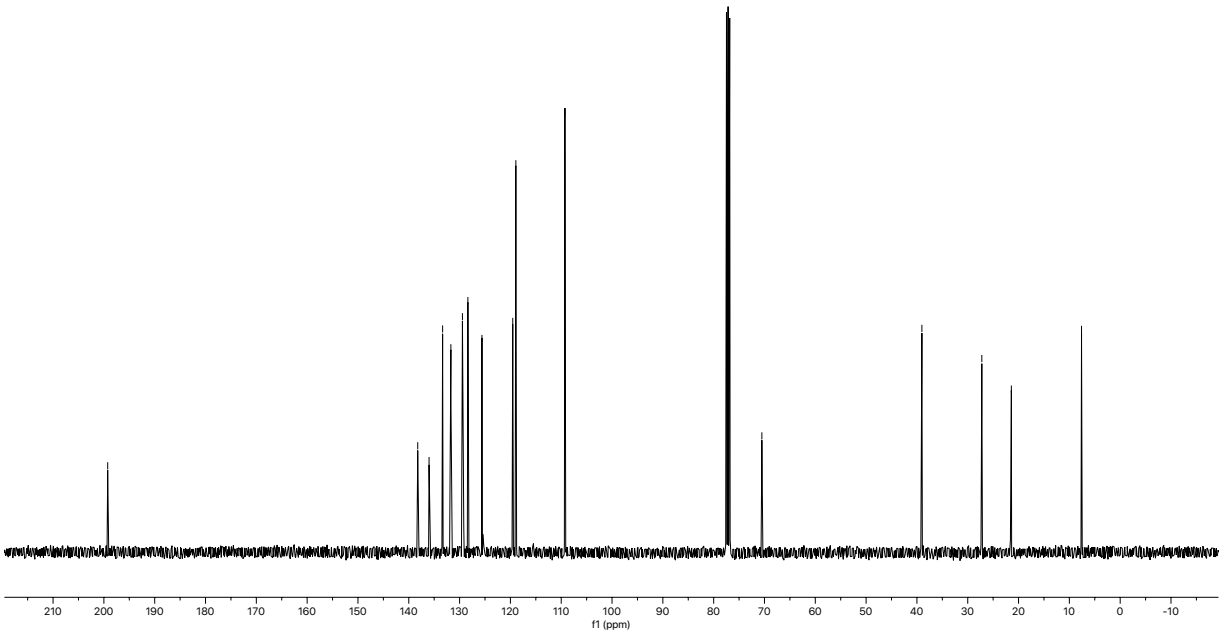
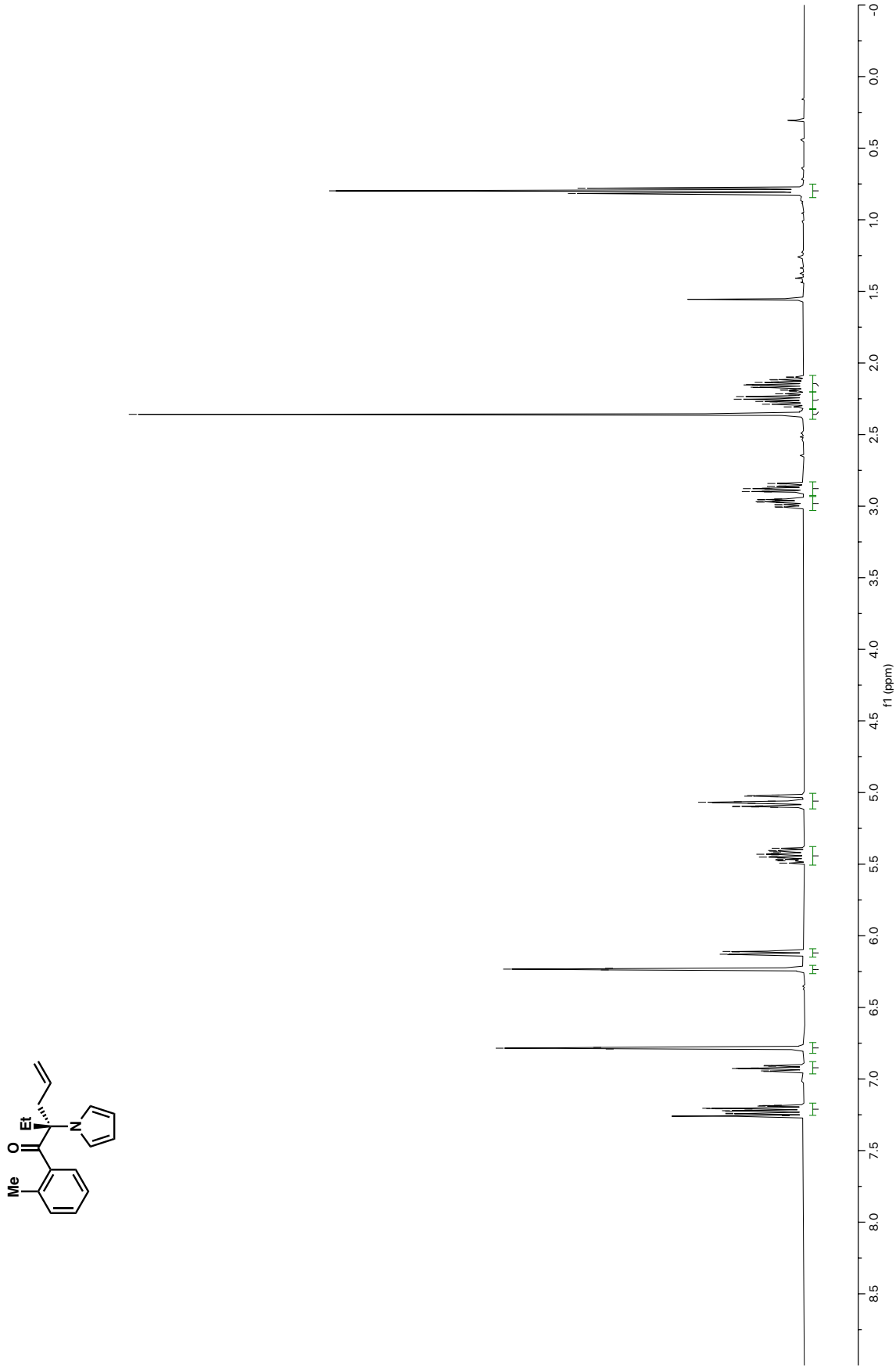



***Figure A9.37*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***101l****.*




***A9.38*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***101m****.*

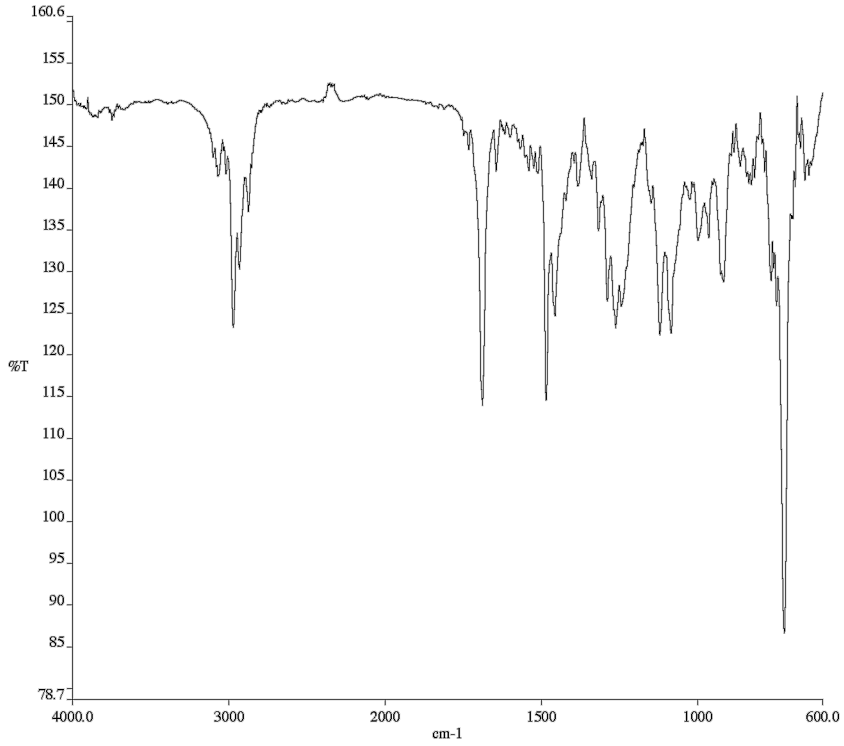



***Figure A9.39*** *Infrared spectrum (Thin Film, NaCl) of compound* ***101m***.

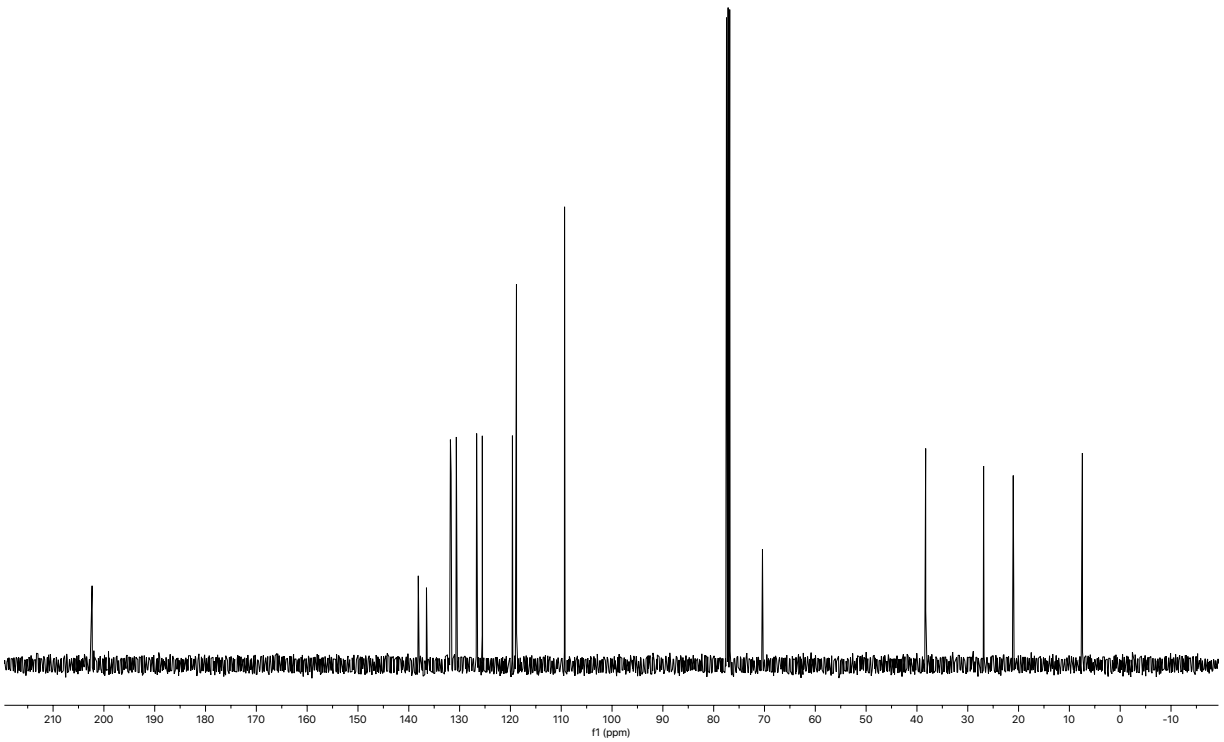
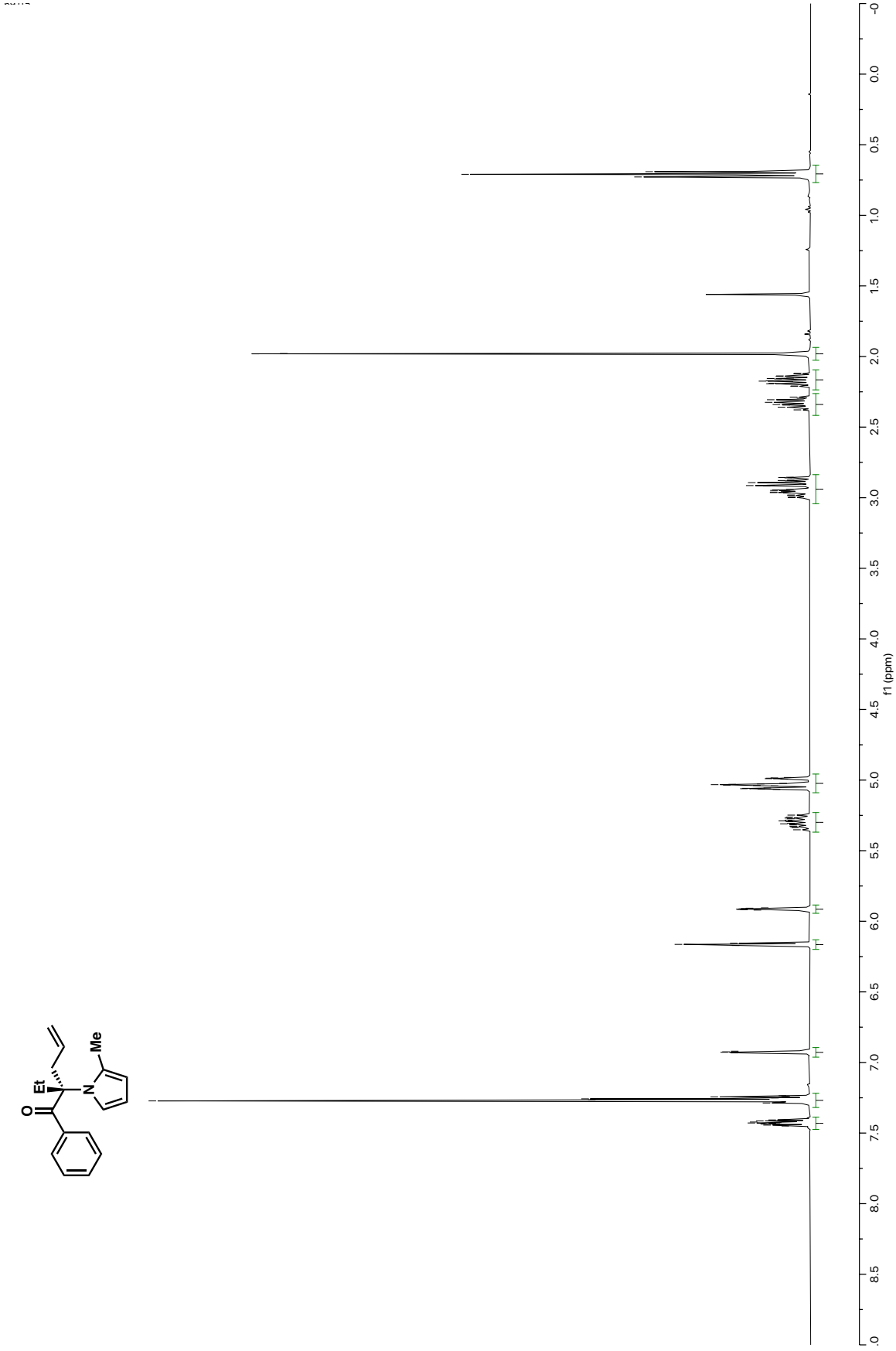



***Figure A9.40*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***101m***.




***A9.41*** *$^{1}H$ NMR (500 MHz, $CDCl_3$) of compound* ***101n***.

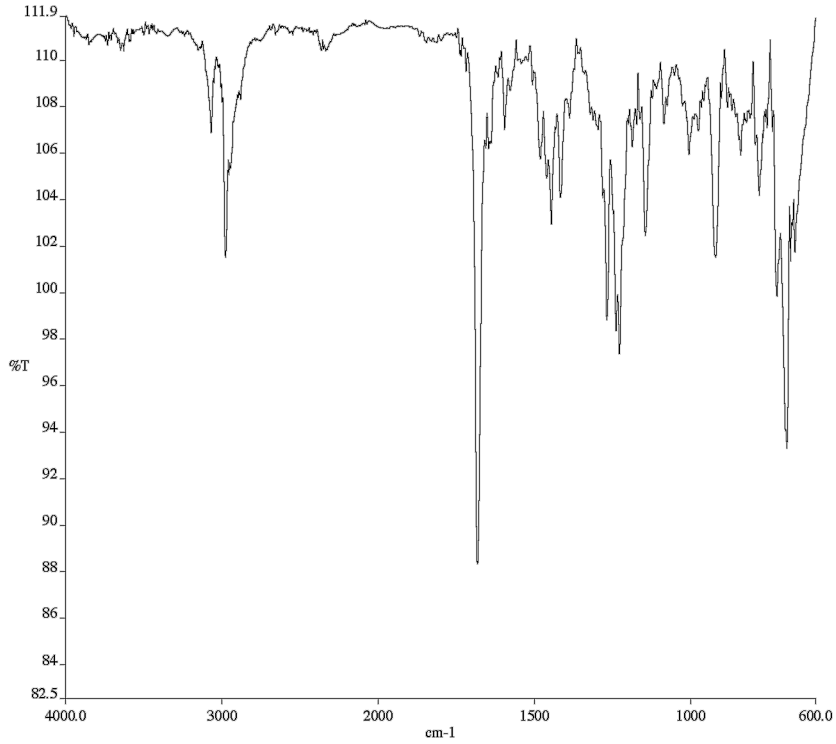



***Figure A9.42*** *Infrared spectrum (Thin Film, NaCl) of compound* ***101n***.

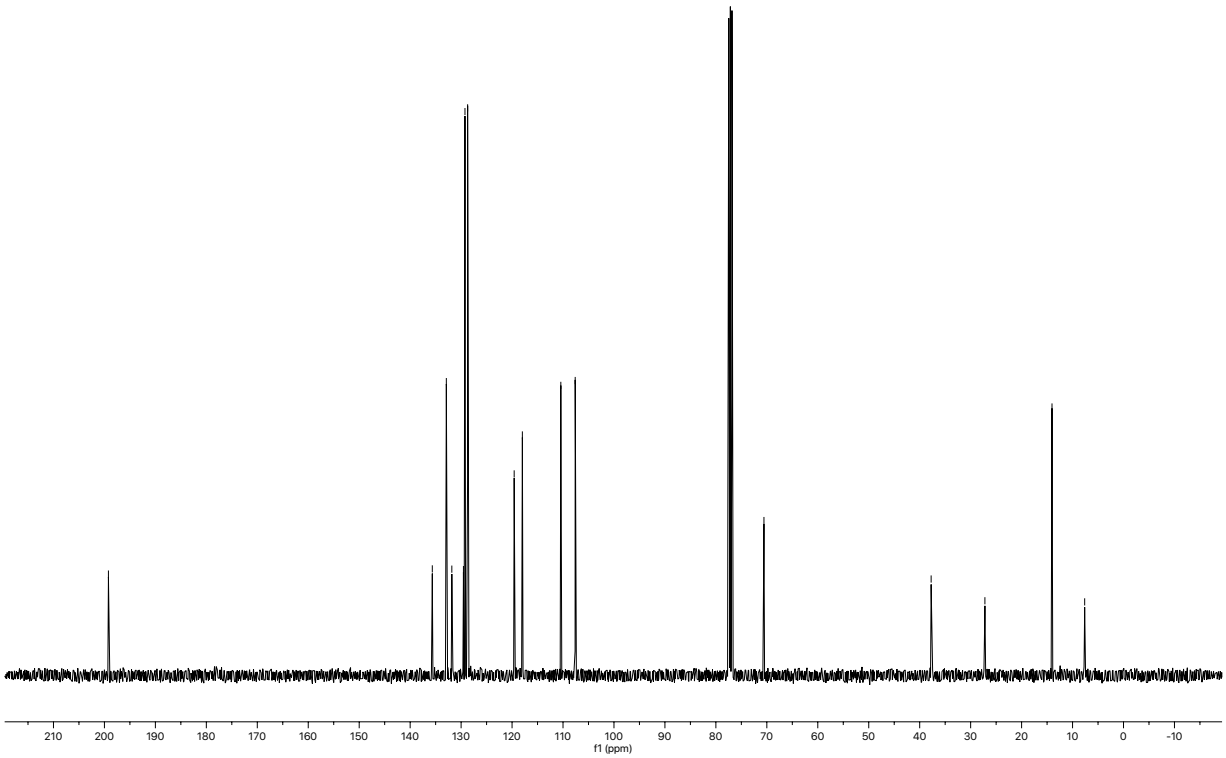
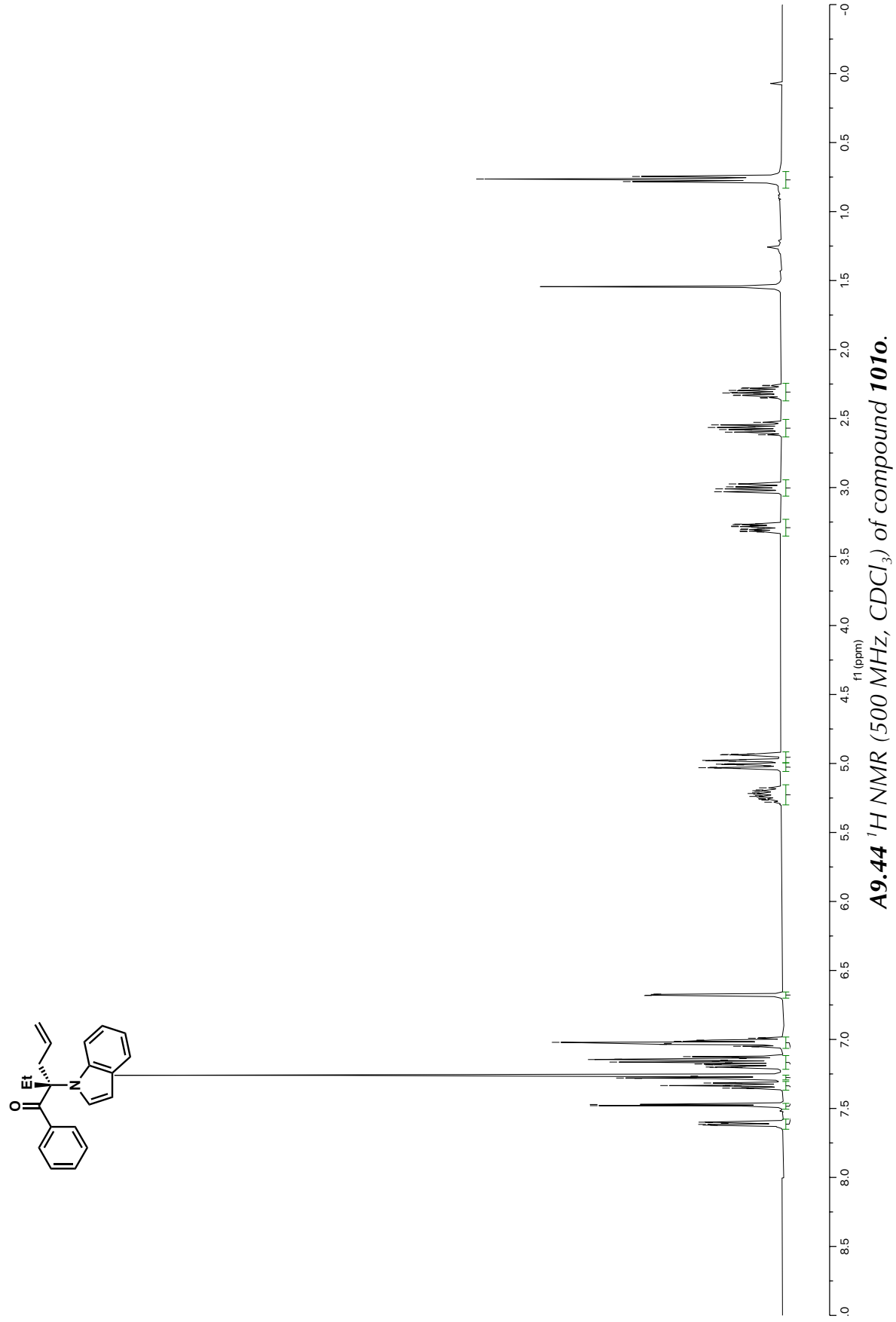



***Figure A9.43*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***101n***.




***A9.44*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***101o***.

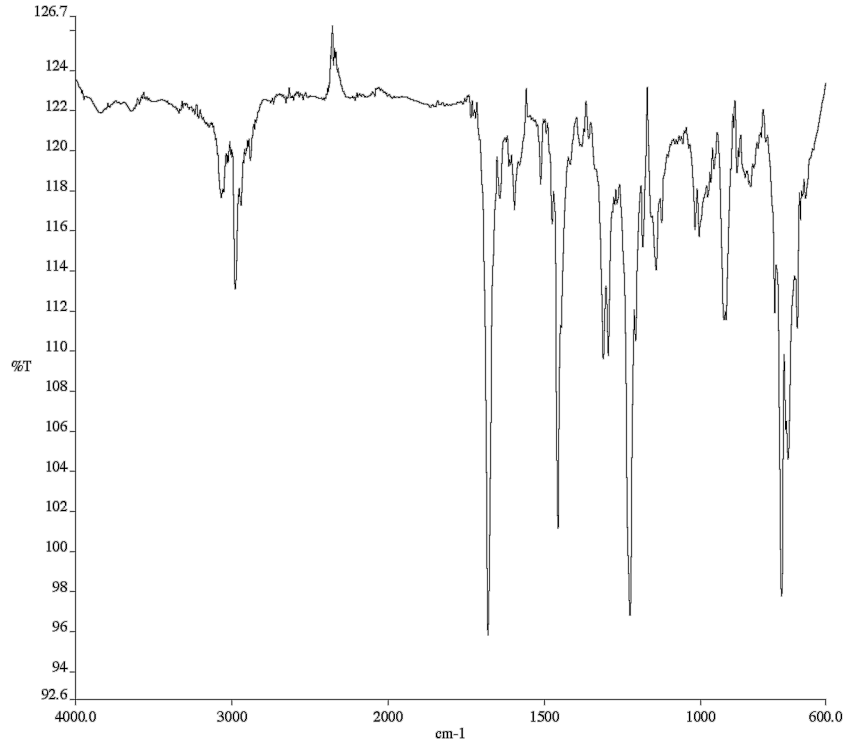



***Figure A9.45*** *Infrared spectrum (Thin Film, NaCl) of compound* ***101o***.

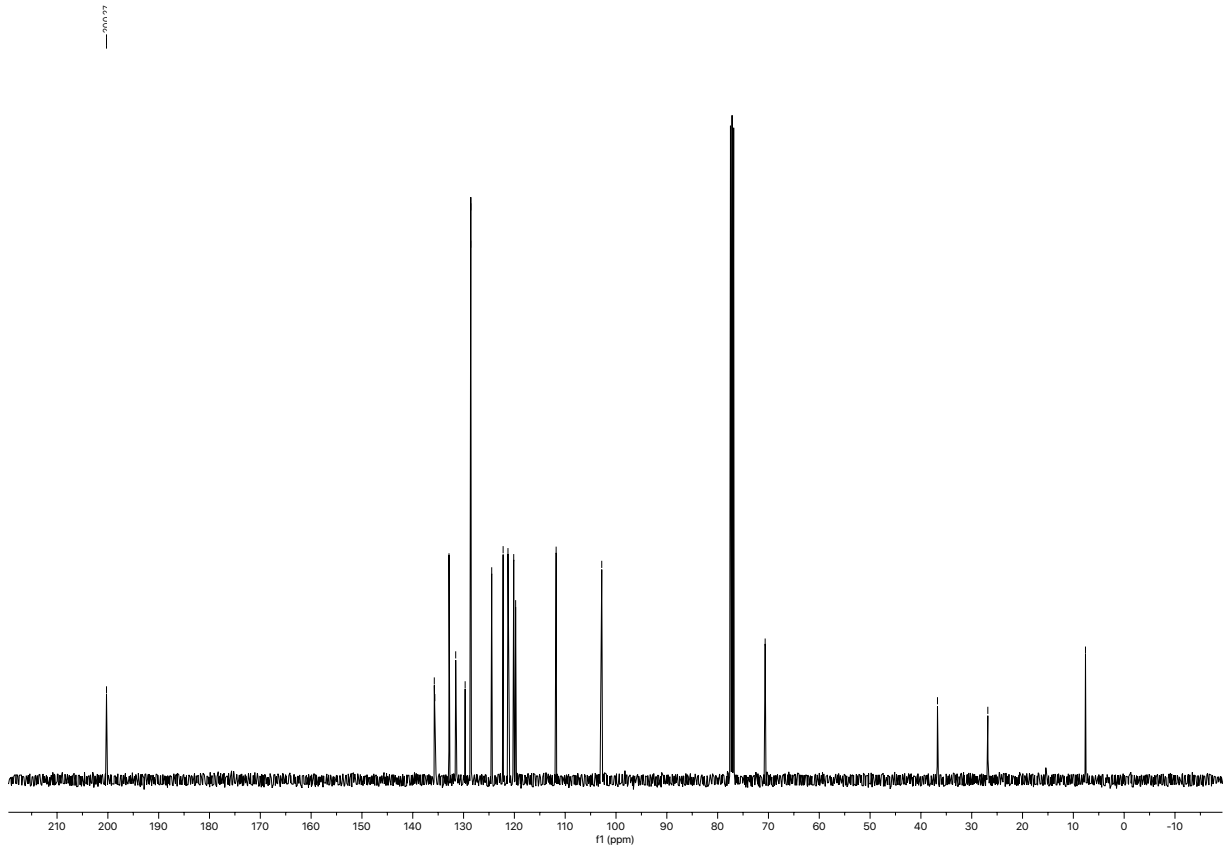
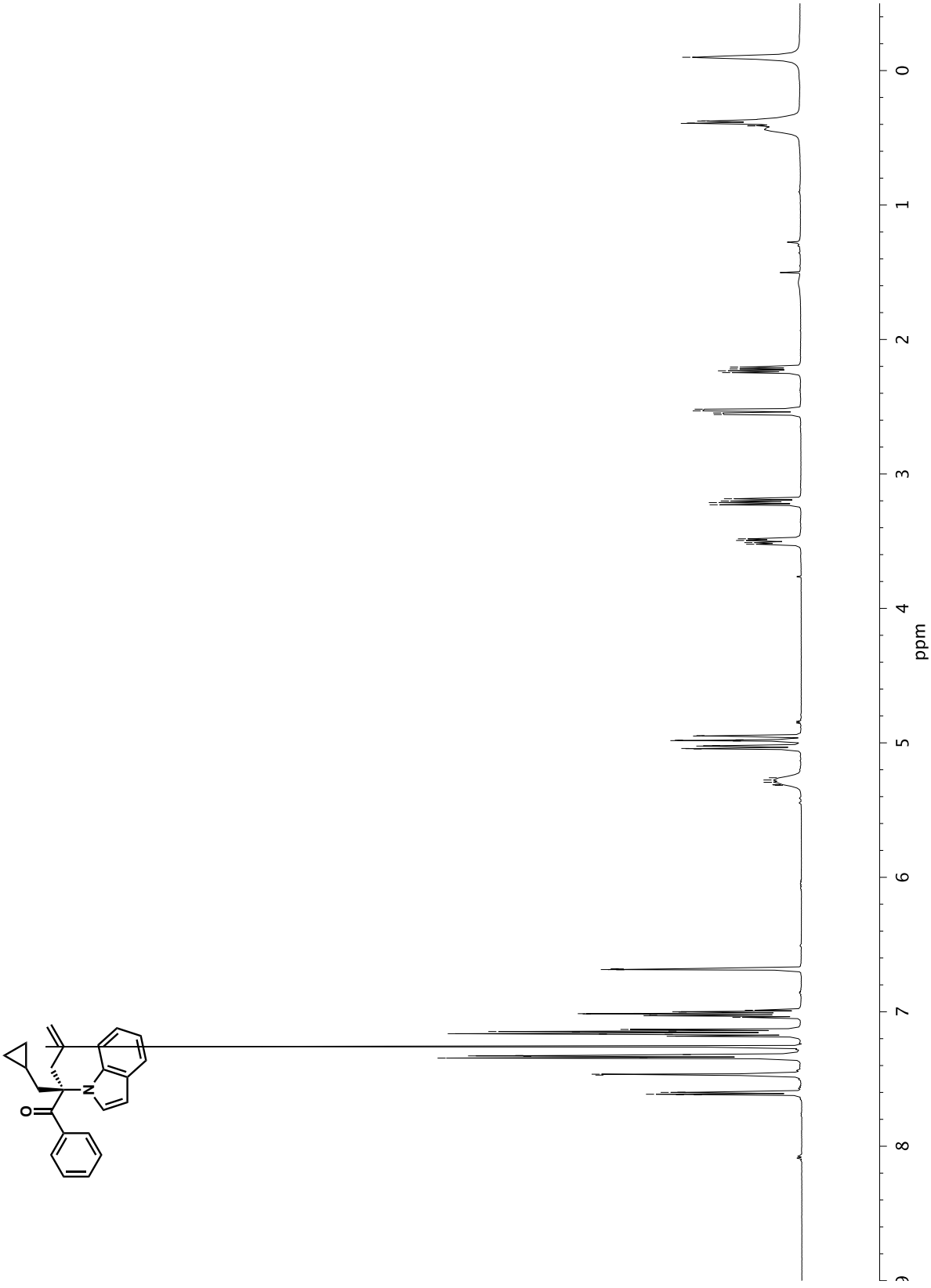



***Figure A9.46*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***101o***.




***A9.47*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***101p****.*

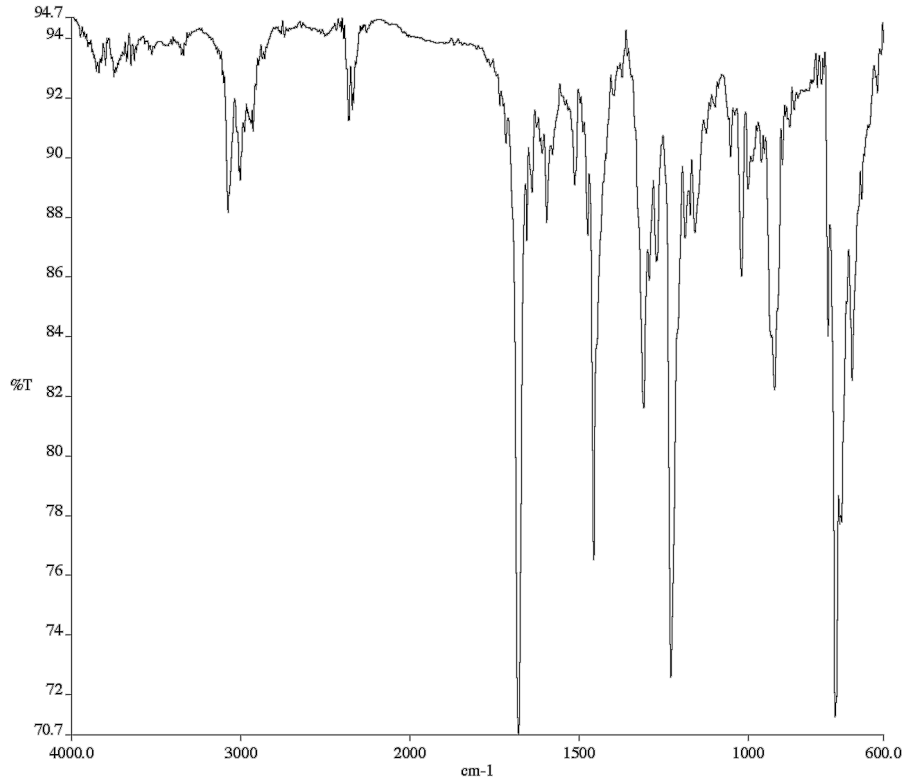



***Figure A9.48*** *Infrared spectrum (Thin Film, NaCl) of compound* ***101p***.

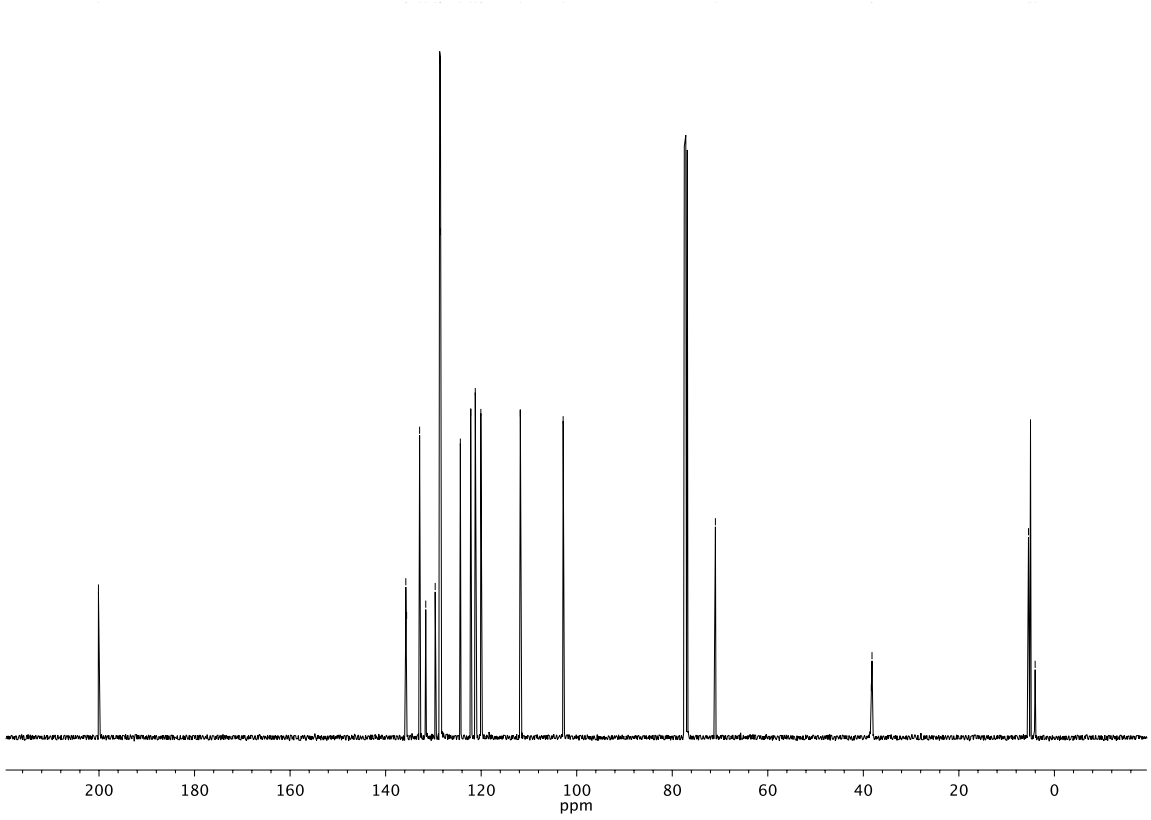
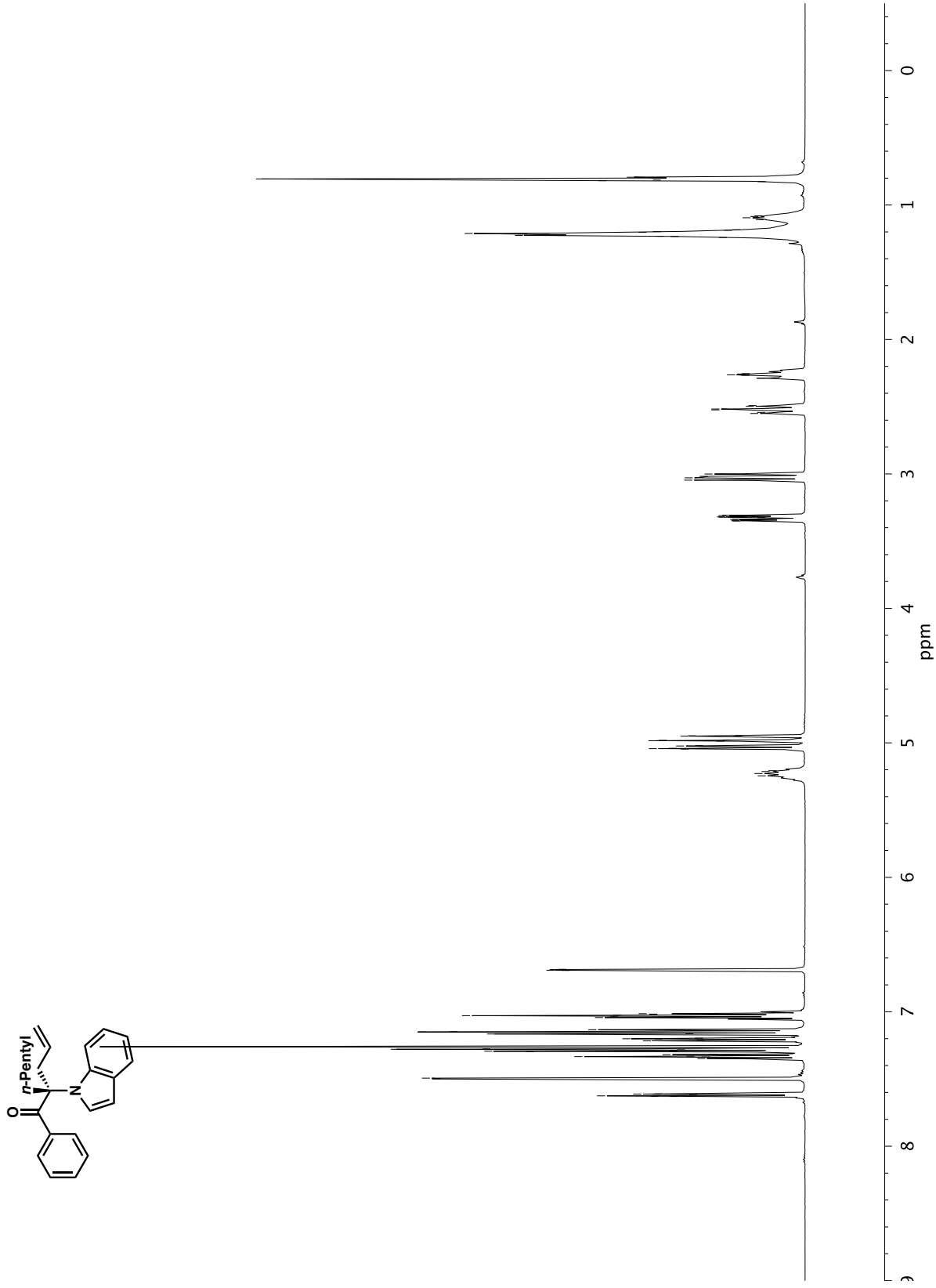



***Figure A9.49*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***101p***.




***A9.50*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***101q***.

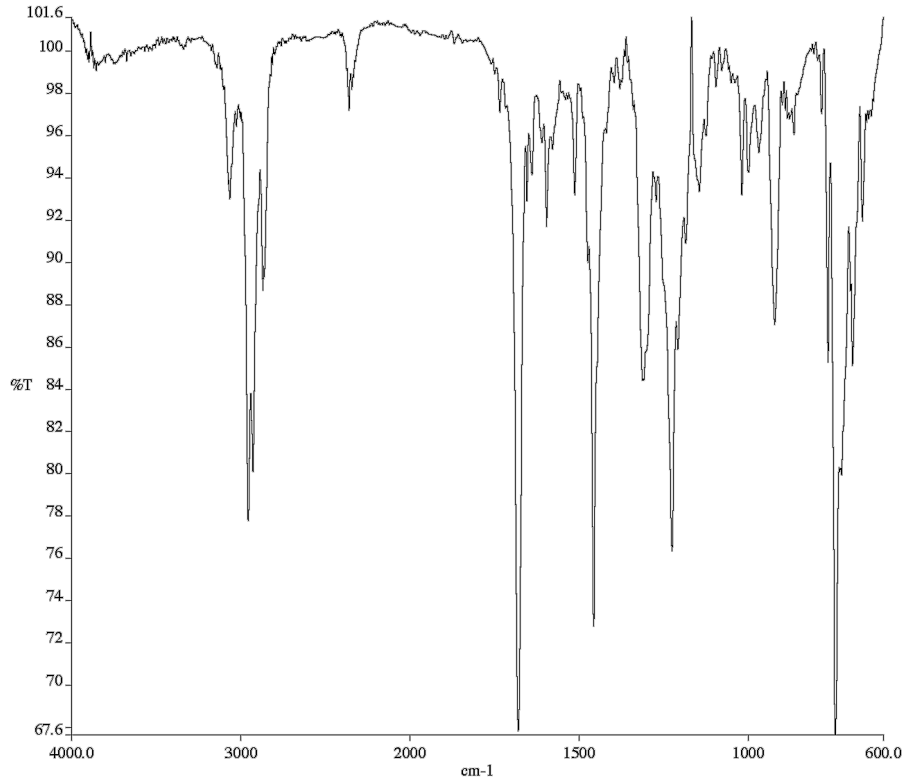



***Figure A9.51*** *Infrared spectrum (Thin Film, NaCl) of compound* ***101q***.

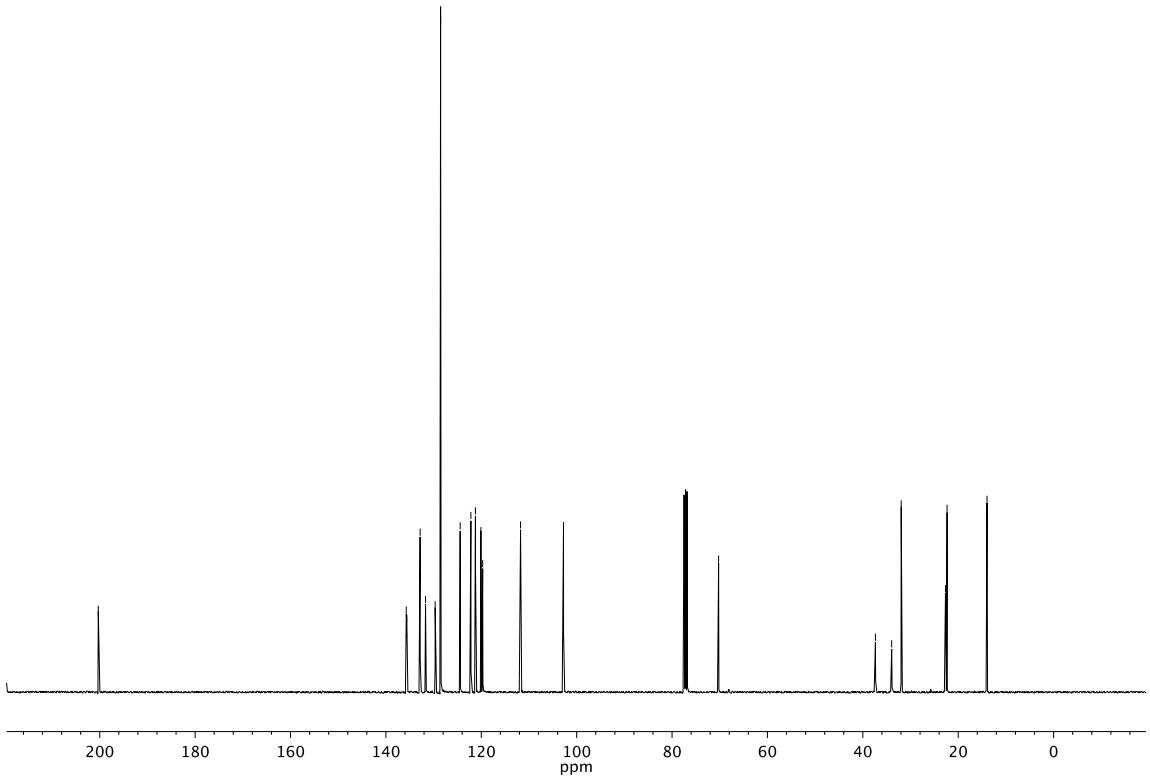
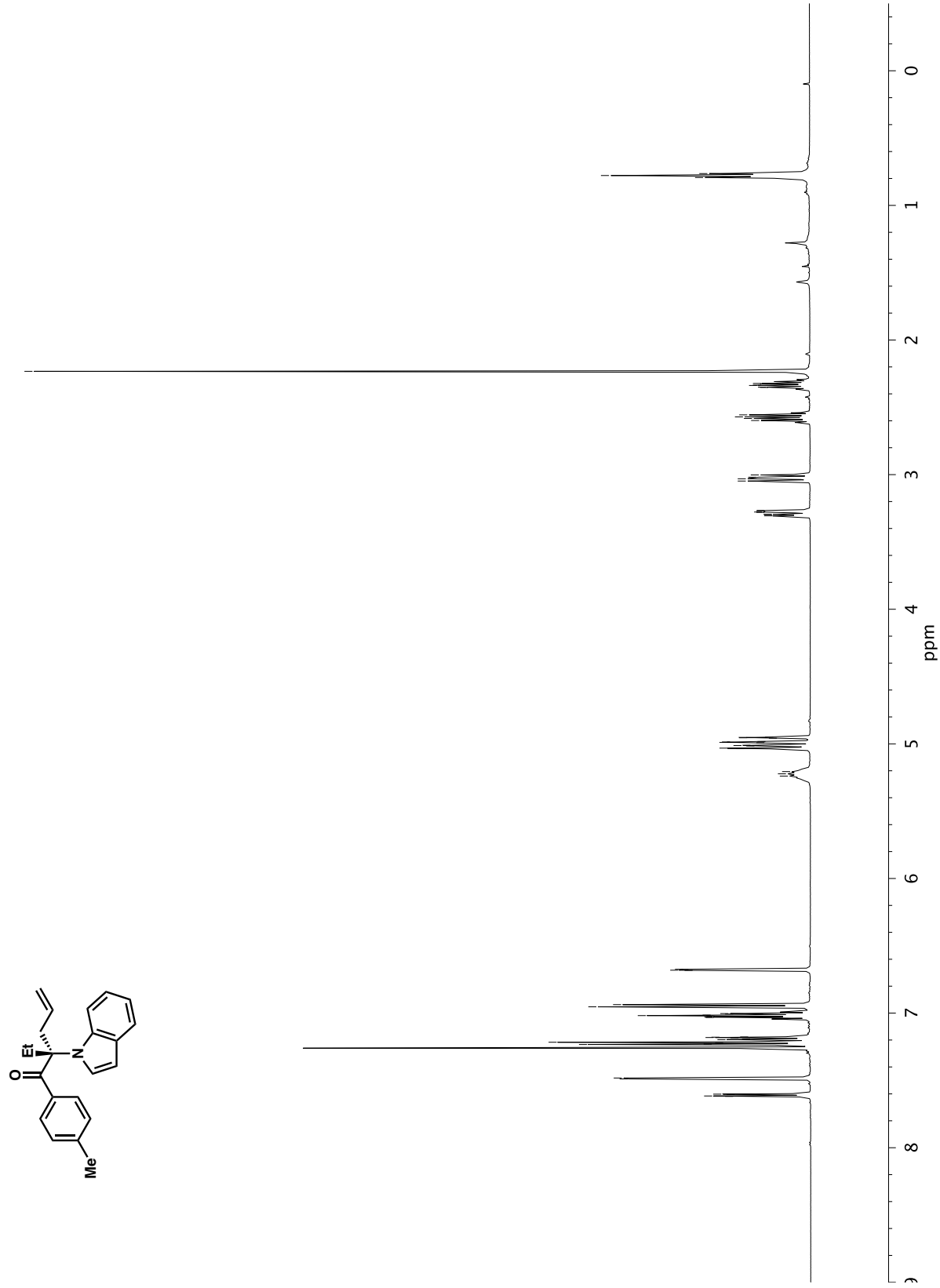



***Figure A9.52*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***101q***.




***A9.53*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***101r.***

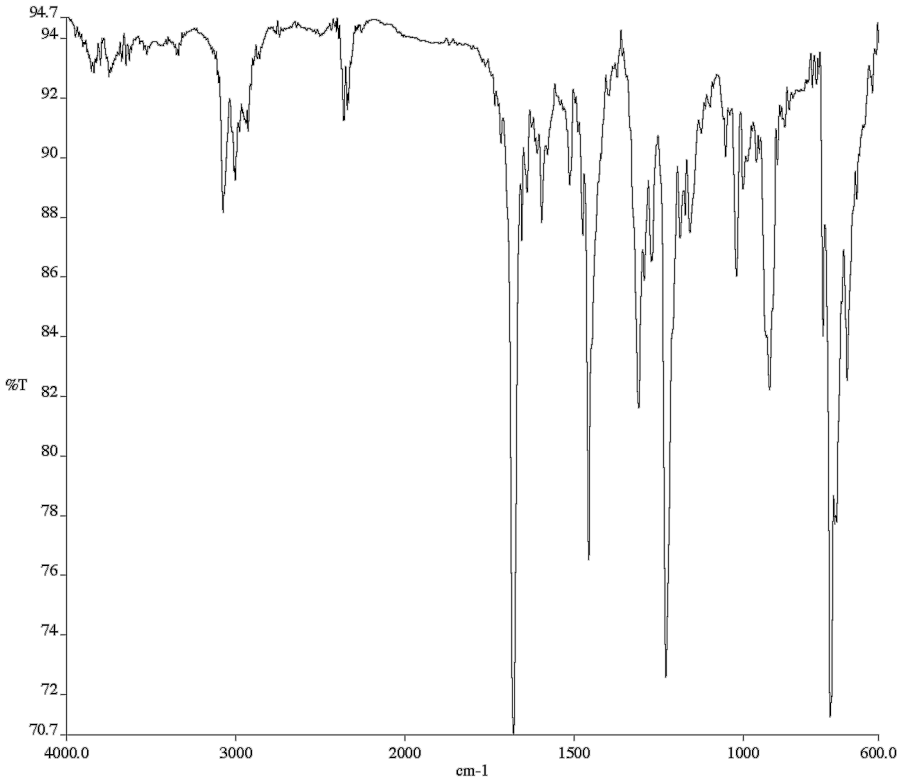



***Figure A9.54*** *Infrared spectrum (Thin Film, NaCl) of compound* ***101r****.*

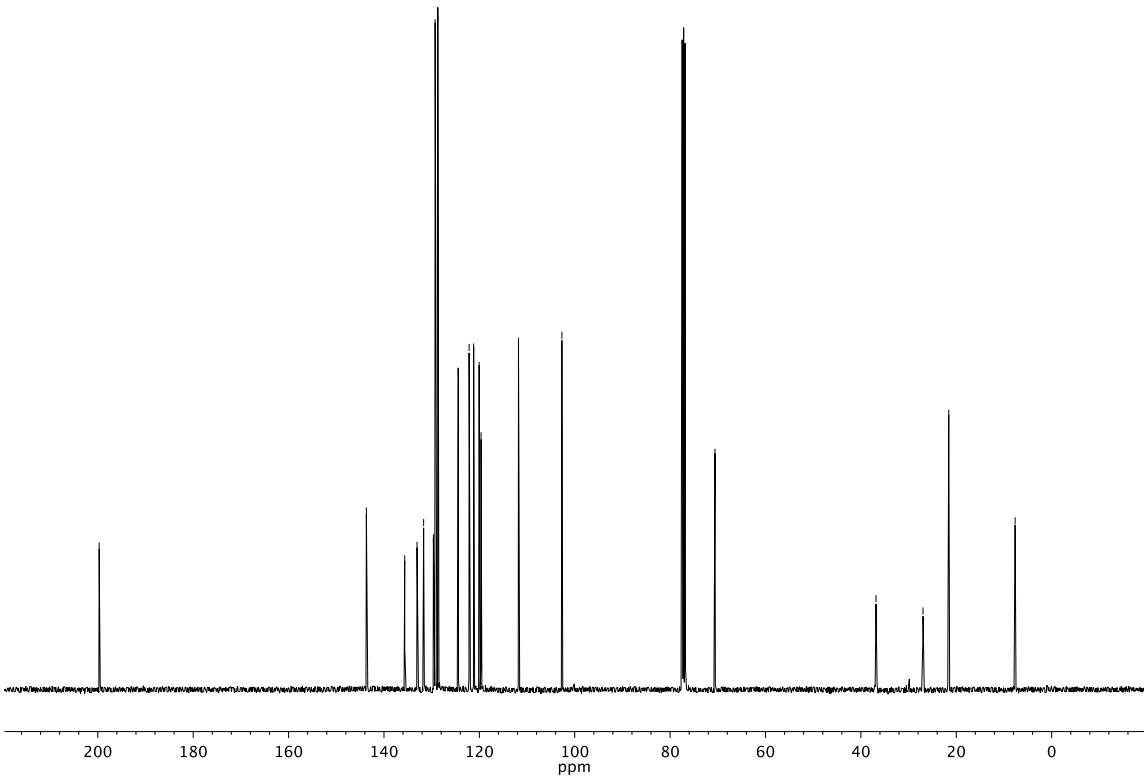



***Figure A9.55*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***101r****.*

***A9.56*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***100a***.

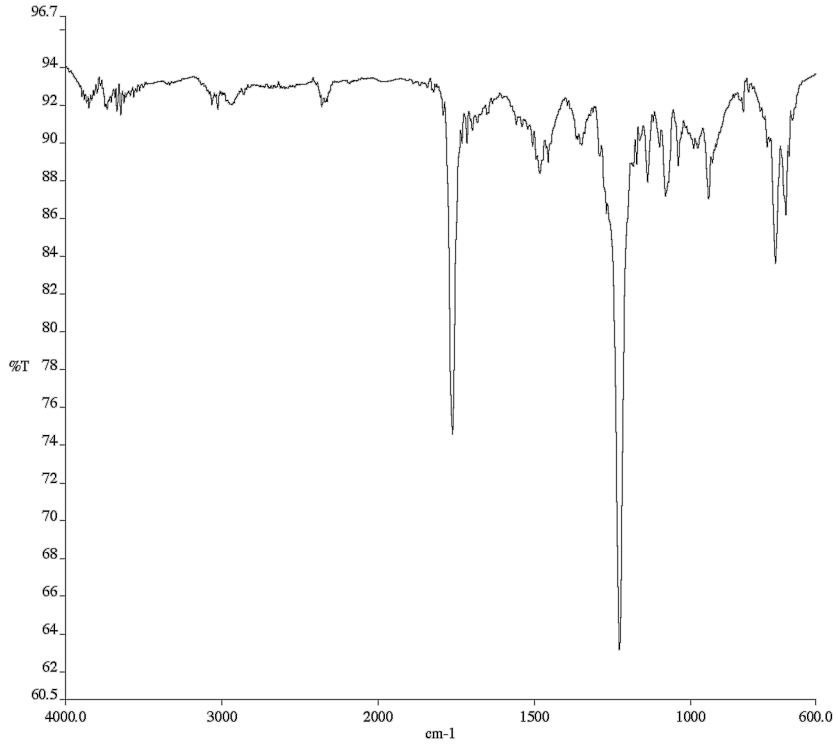



***Figure A9.57*** *Infrared spectrum (Thin Film, NaCl) of compound* ***100a****.*

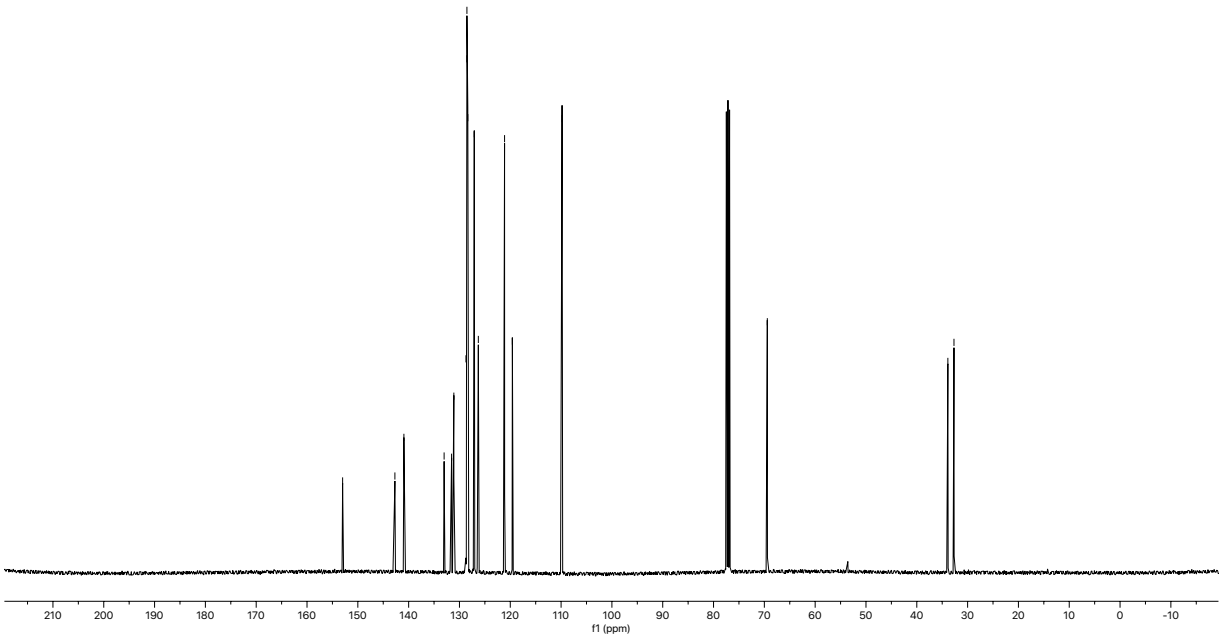
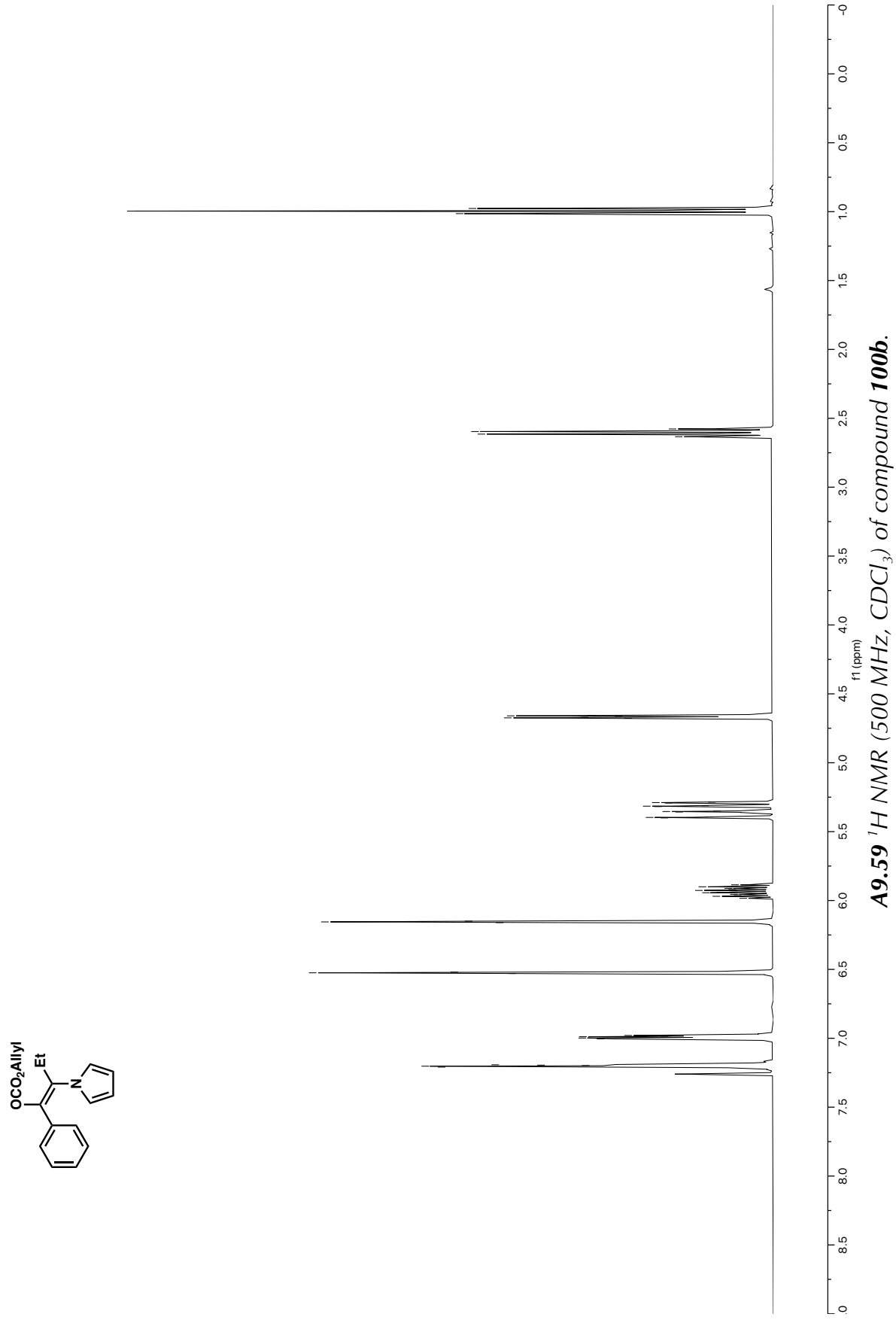



***Figure A9.58*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***100a****.*




***A9.59*** *$^{1}H$ NMR (500 MHz, $CDCl_3$) of compound* ***100b***.

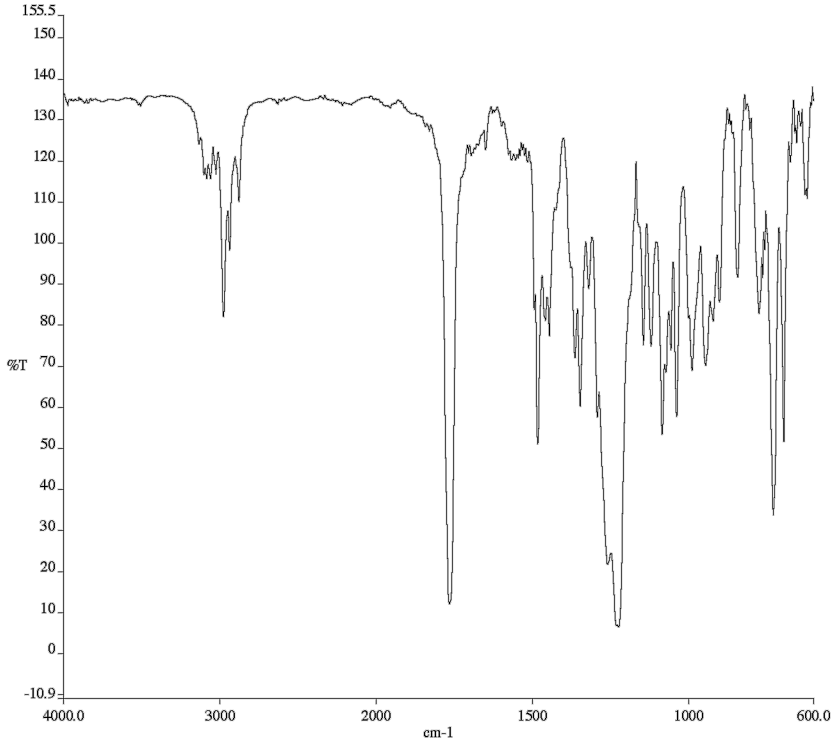



***Figure A9.60*** *Infrared spectrum (Thin Film, NaCl) of compound* ***100b***.

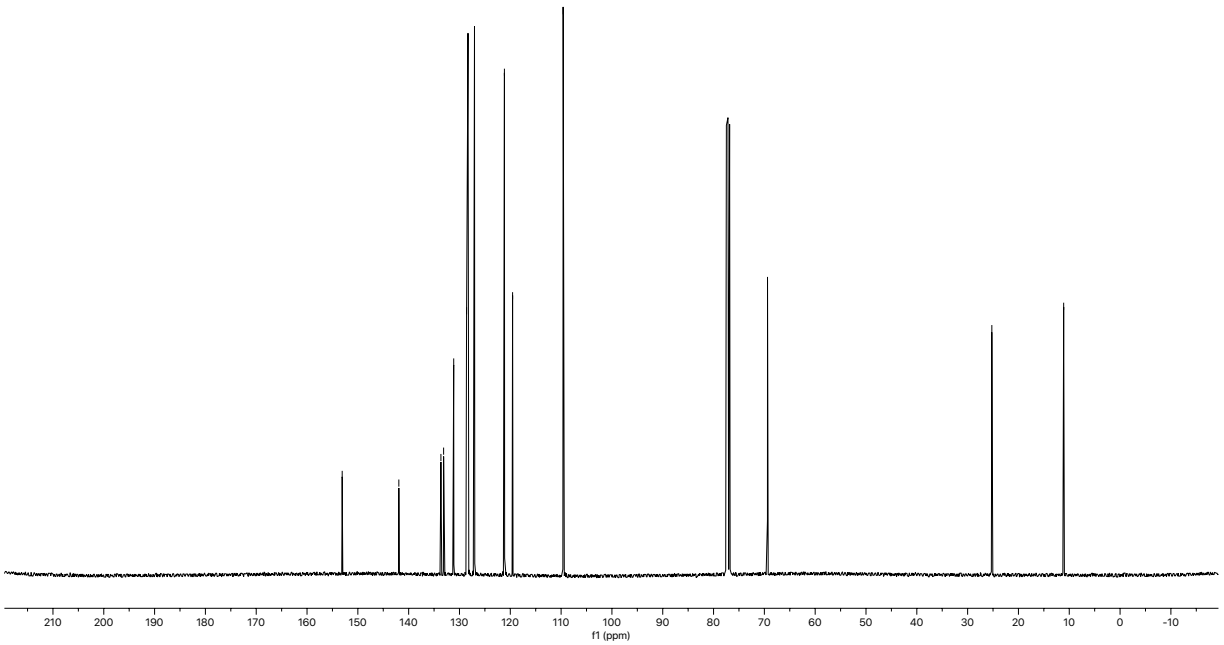



***Figure A9.61*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***100b***.

***A9.62*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***100c***.

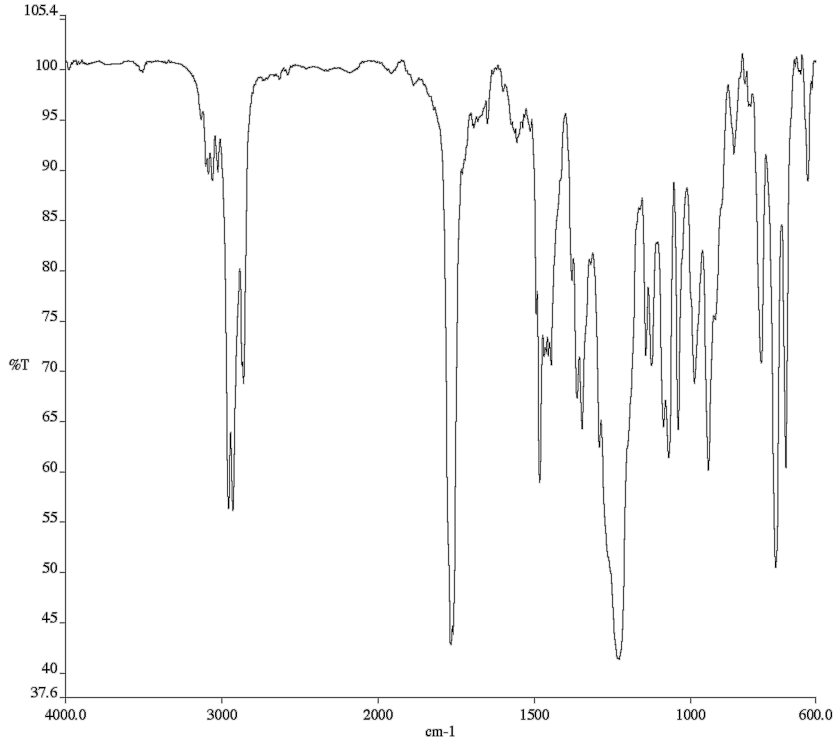



***Figure A9.63*** *Infrared spectrum (Thin Film, NaCl) of compound* ***100c****.*

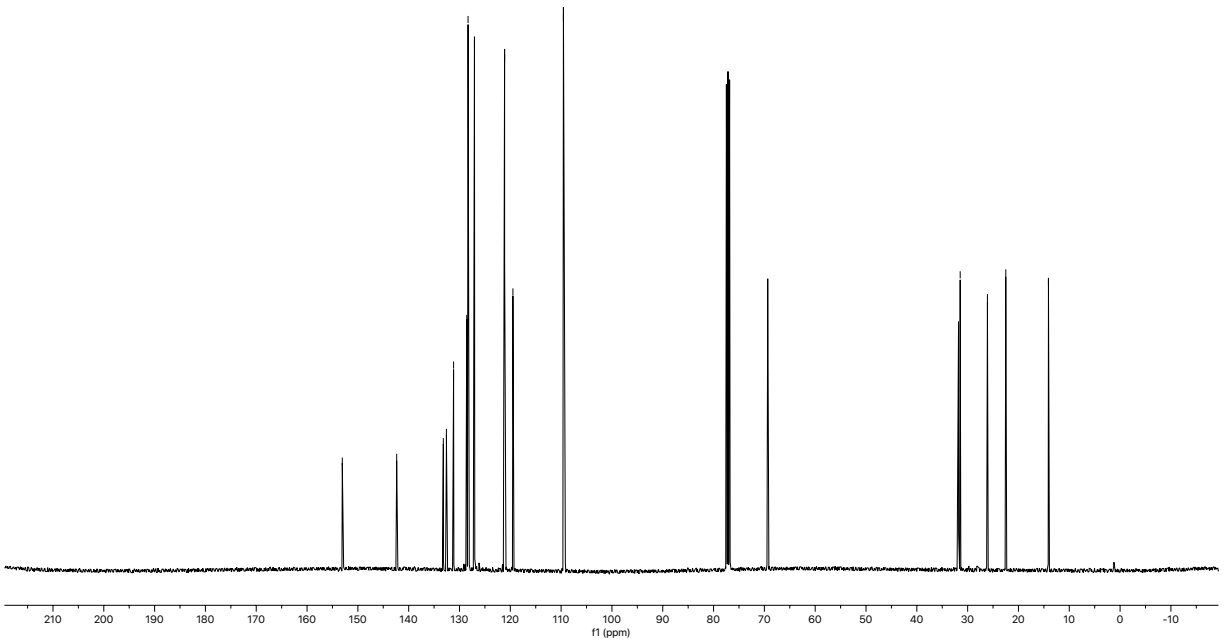



***Figure A9.64*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***100c****.*

***A9.65*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***100d***.

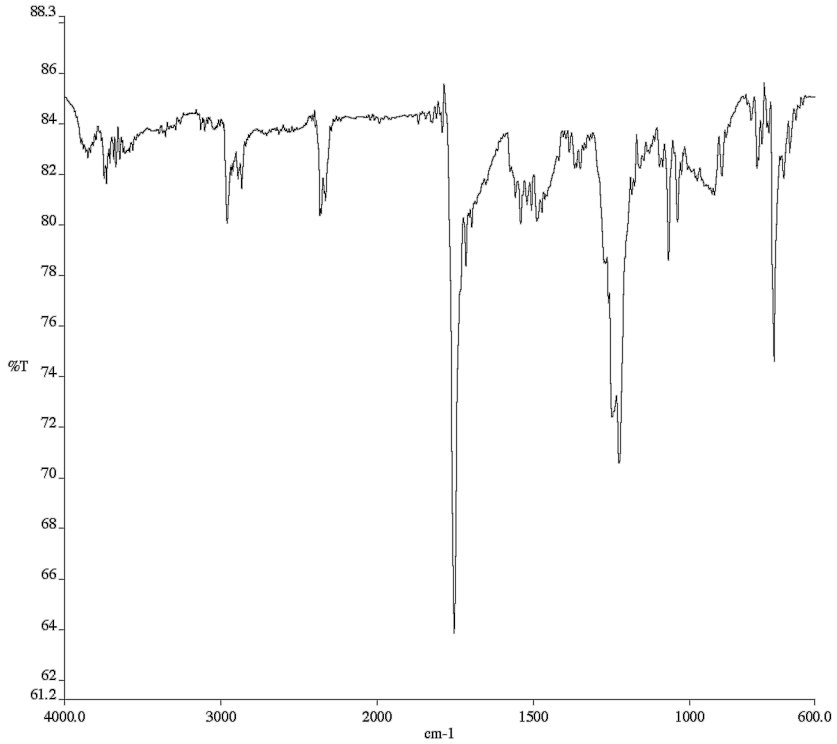



***Figure A9.66*** *Infrared spectrum (Thin Film, NaCl) of compound* ***100d***.

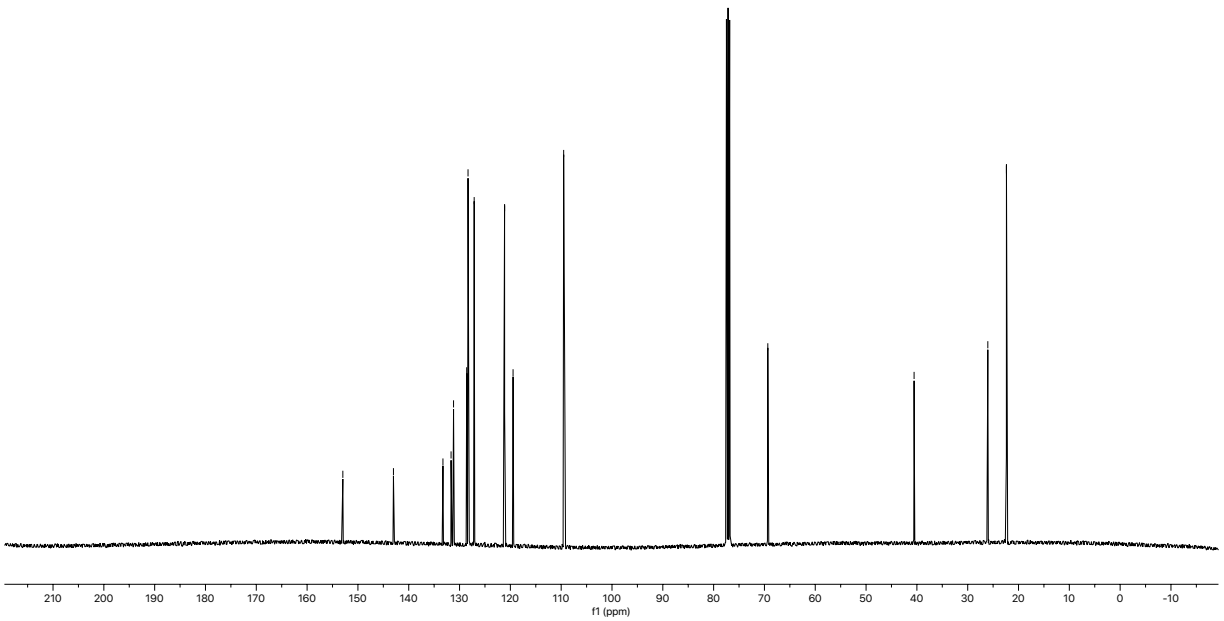
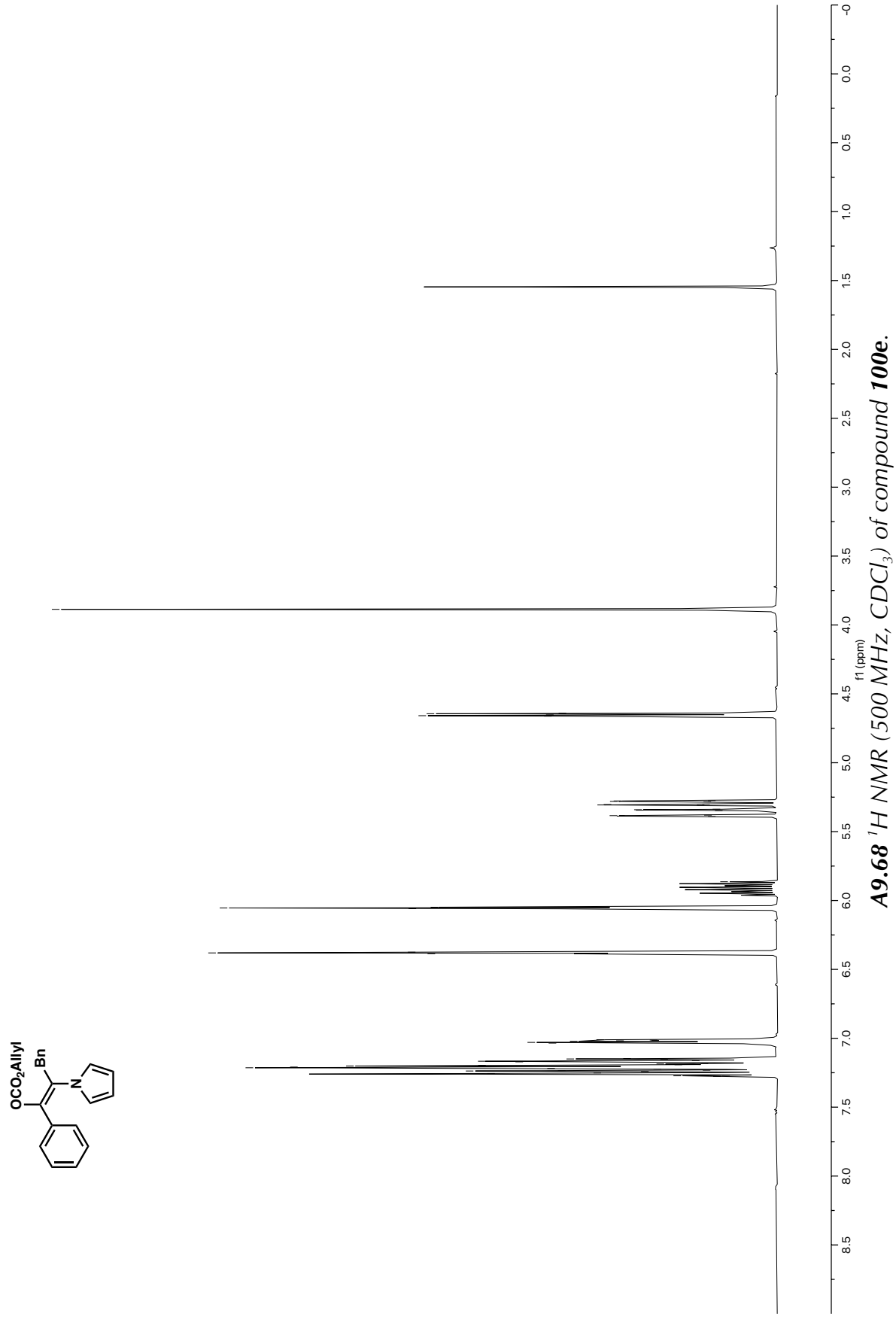



***Figure A9.67*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***100d***.




***A9.68*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***100e***.

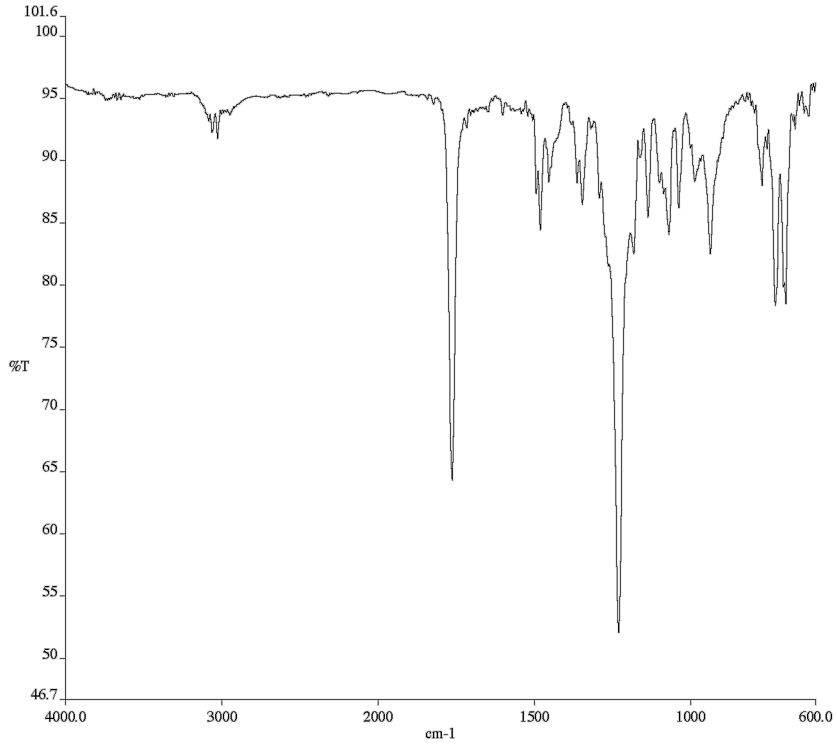



***Figure A9.69*** *Infrared spectrum (Thin Film, NaCl) of compound* ***100e****.*

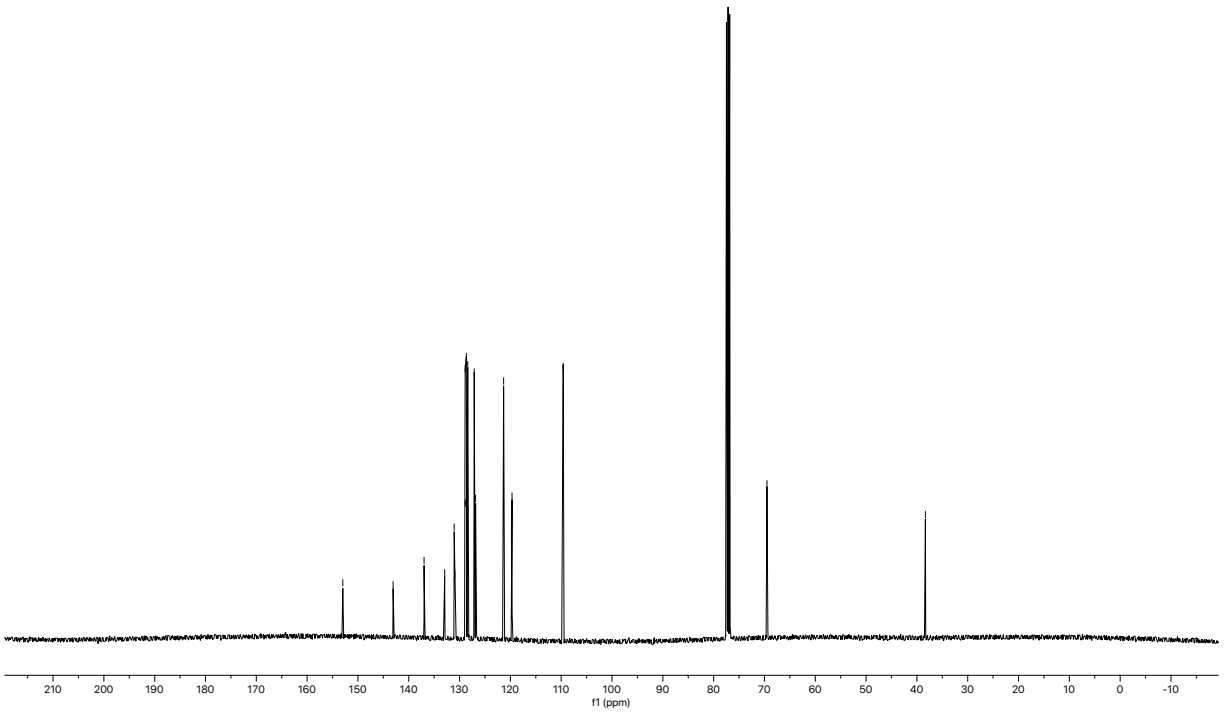
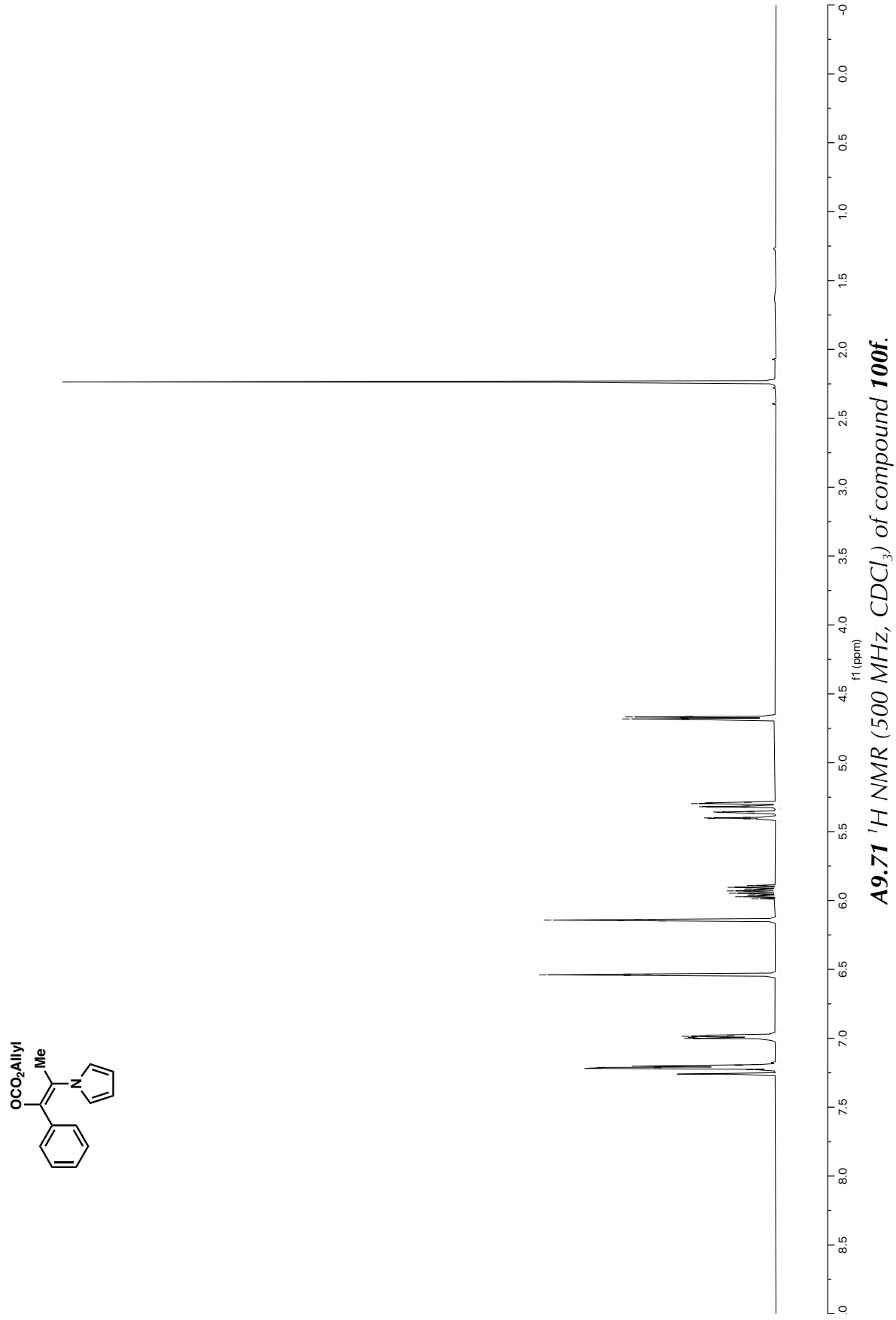



***Figure A9.70*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***100e****.*




***A9.71*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***100f****.*

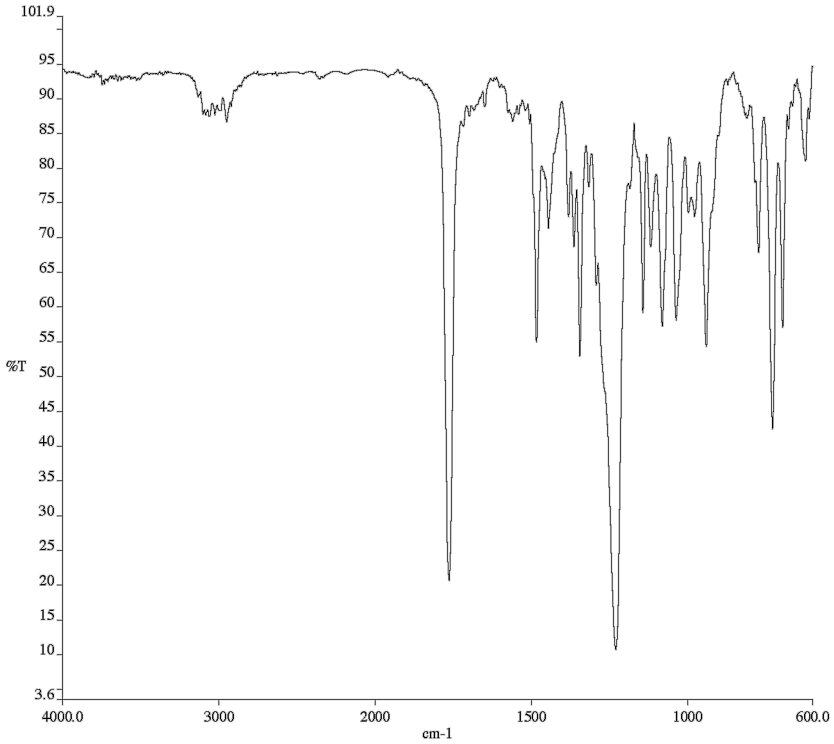



***Figure A9.72*** *Infrared spectrum (Thin Film, NaCl) of compound* ***100f****.*

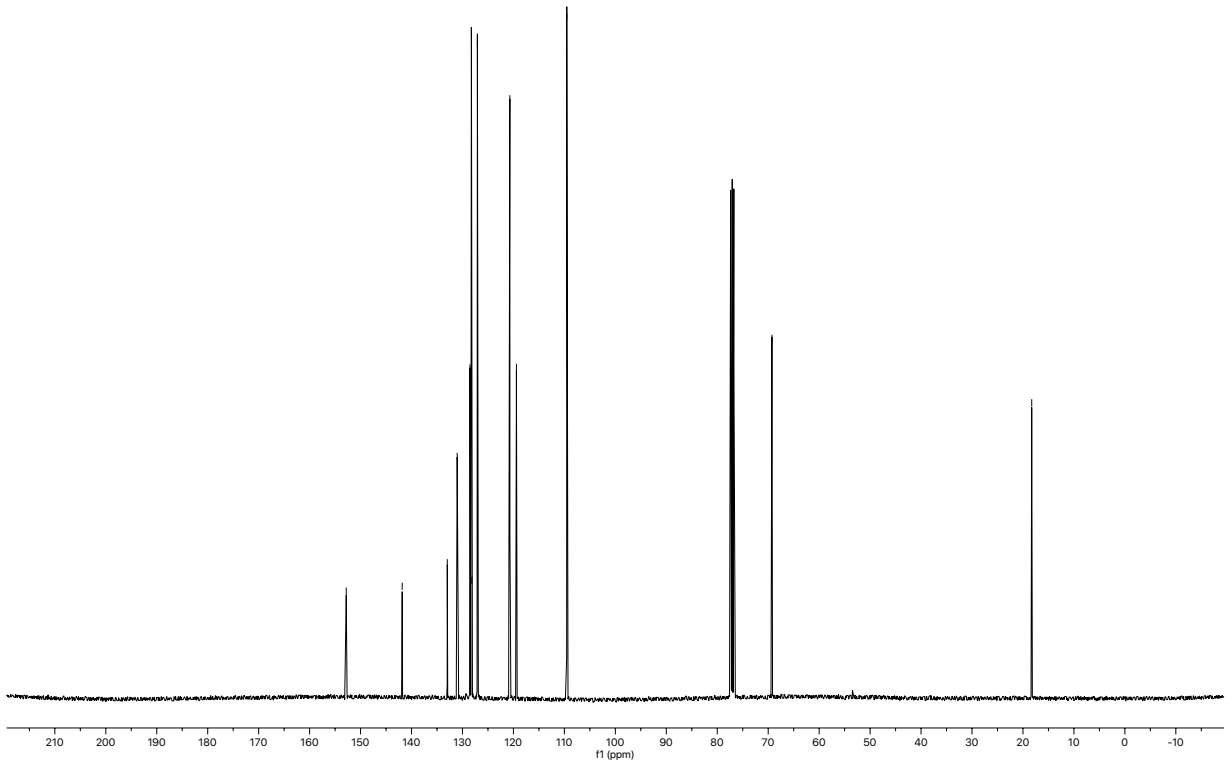
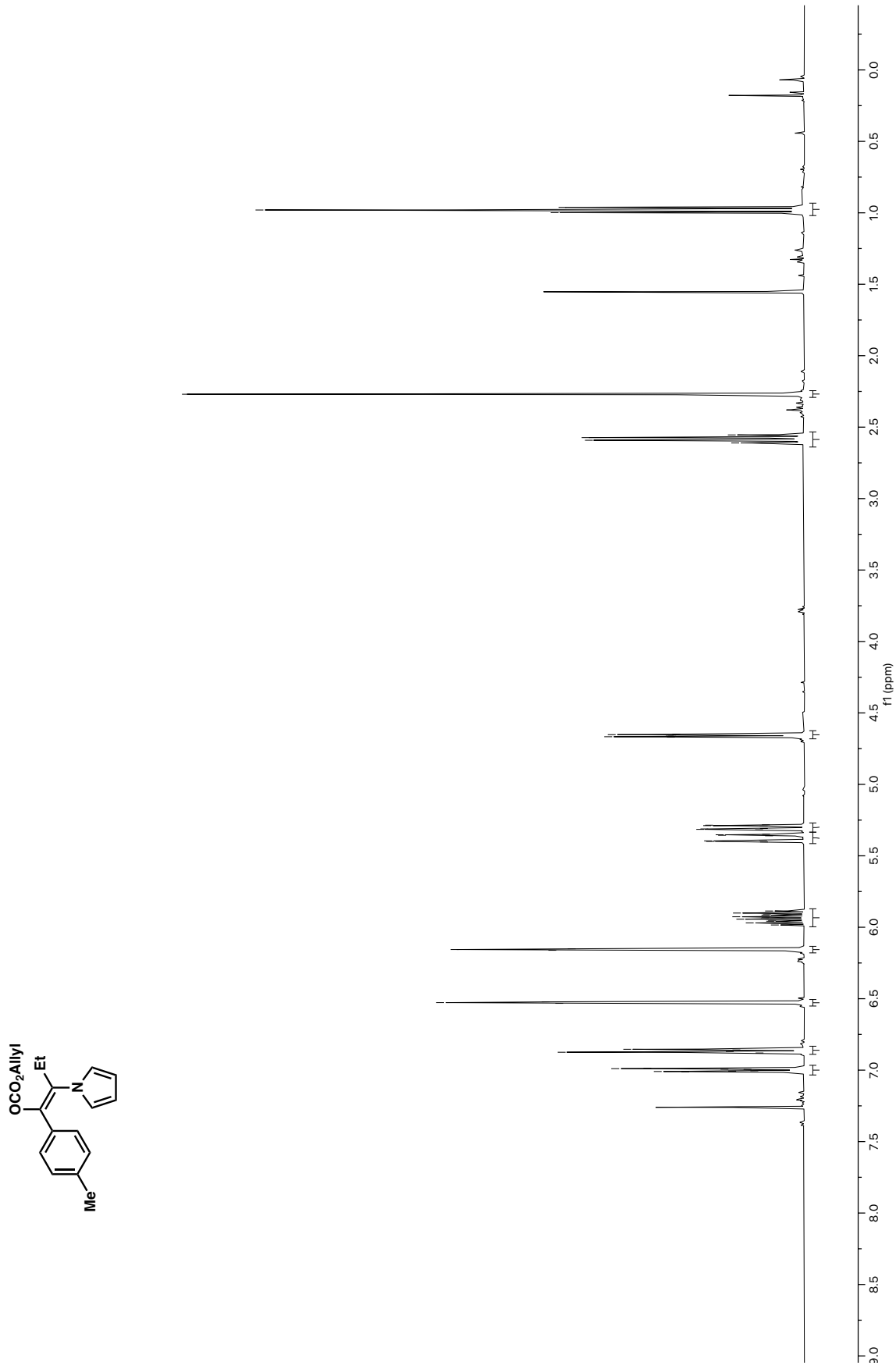



***Figure A9.73*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***100f****.*




***A9.74*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***100g***.

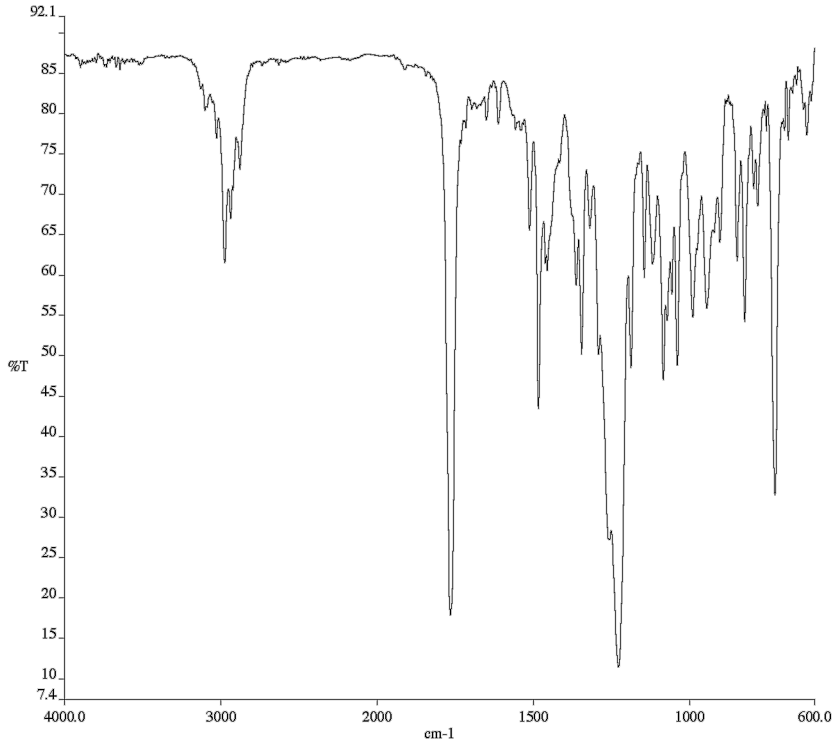



***Figure A9.75*** *Infrared spectrum (Thin Film, NaCl) of compound* ***100g***.

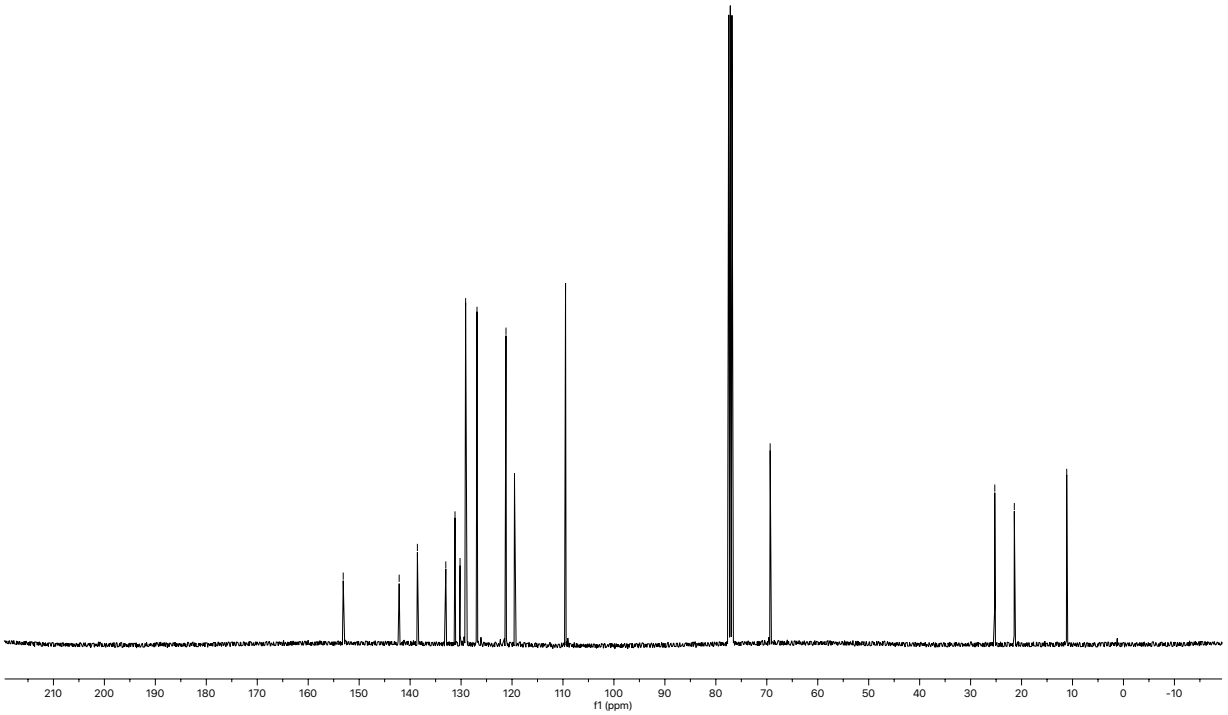
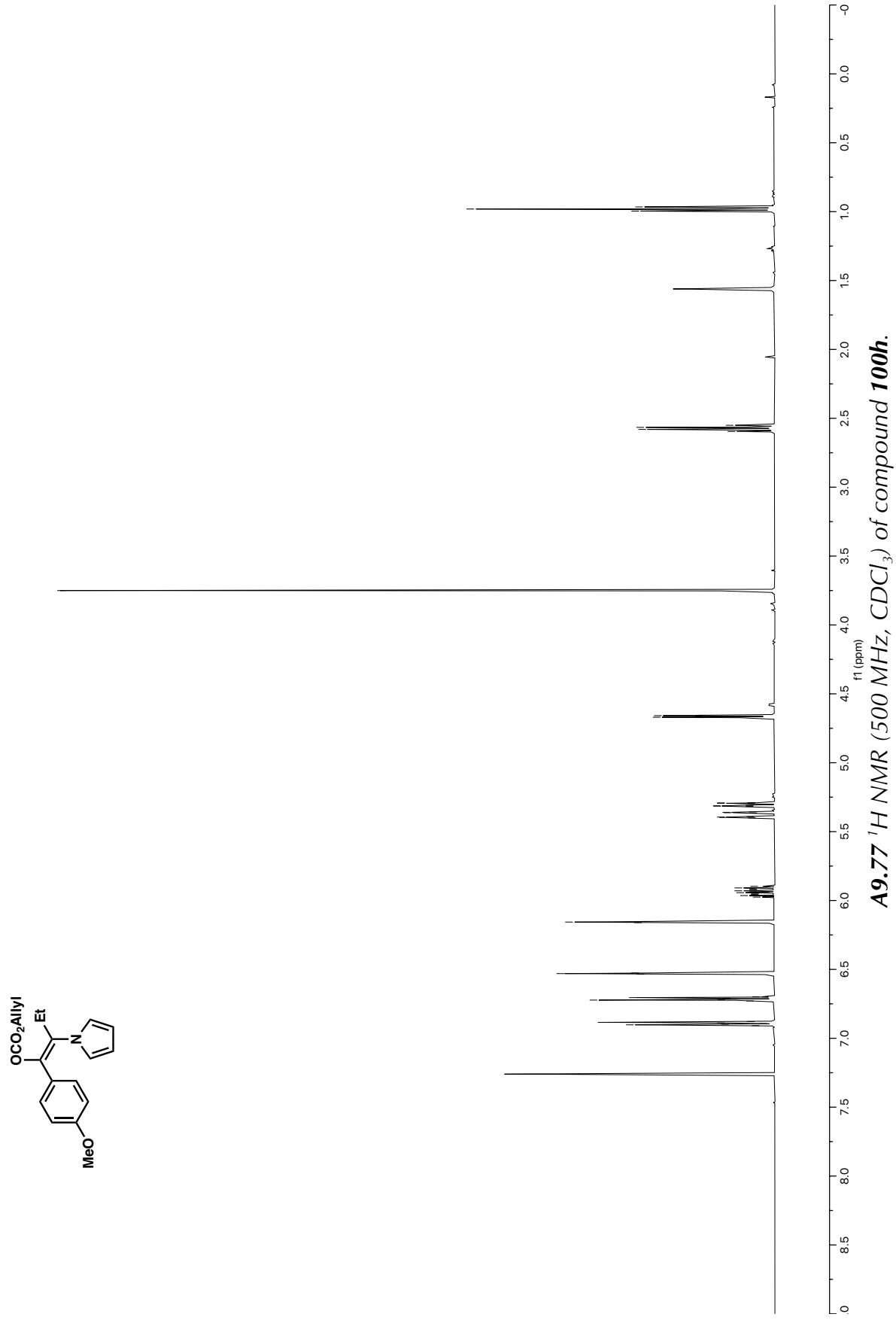



***Figure A9.76*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***100g***.




***A9.77*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***100h***.

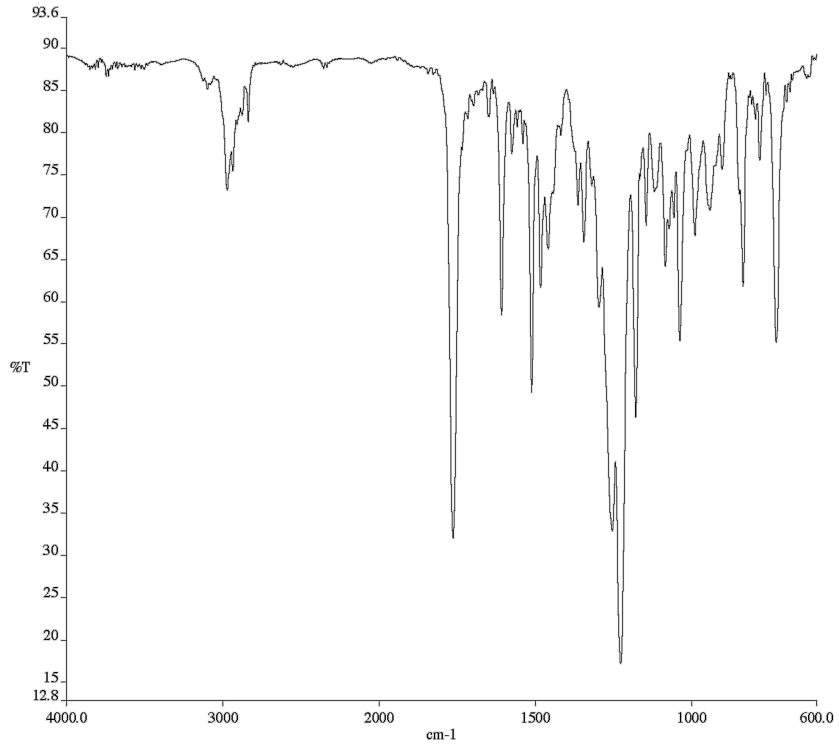



***Figure A9.78*** *Infrared spectrum (Thin Film, NaCl) of compound* ***100h***.

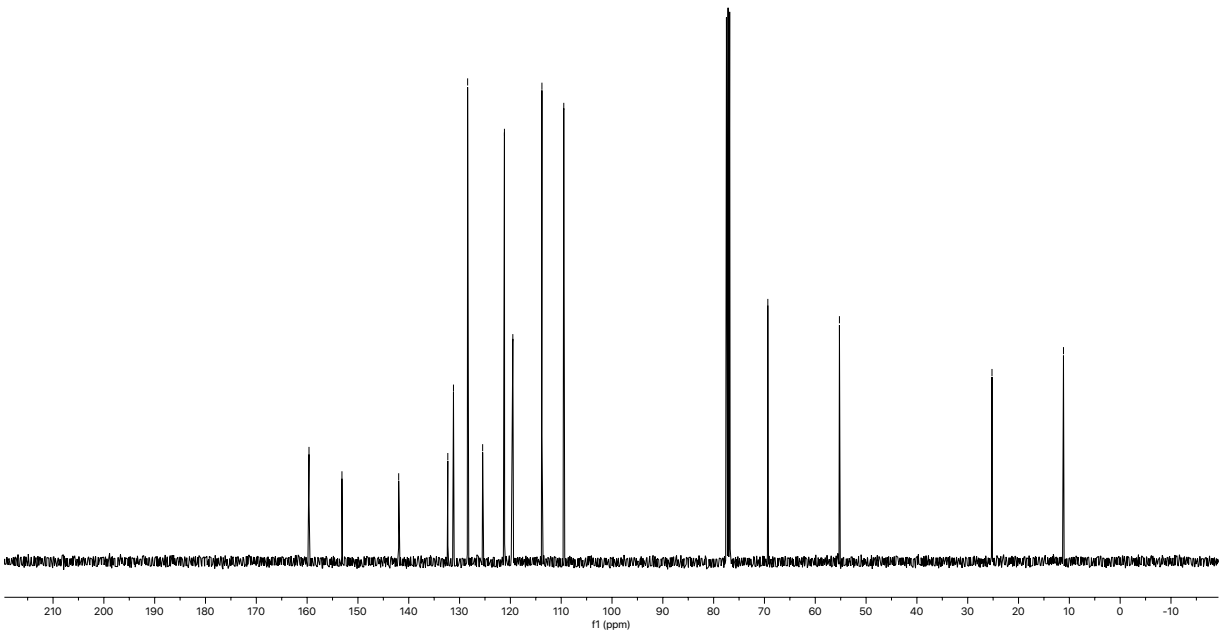
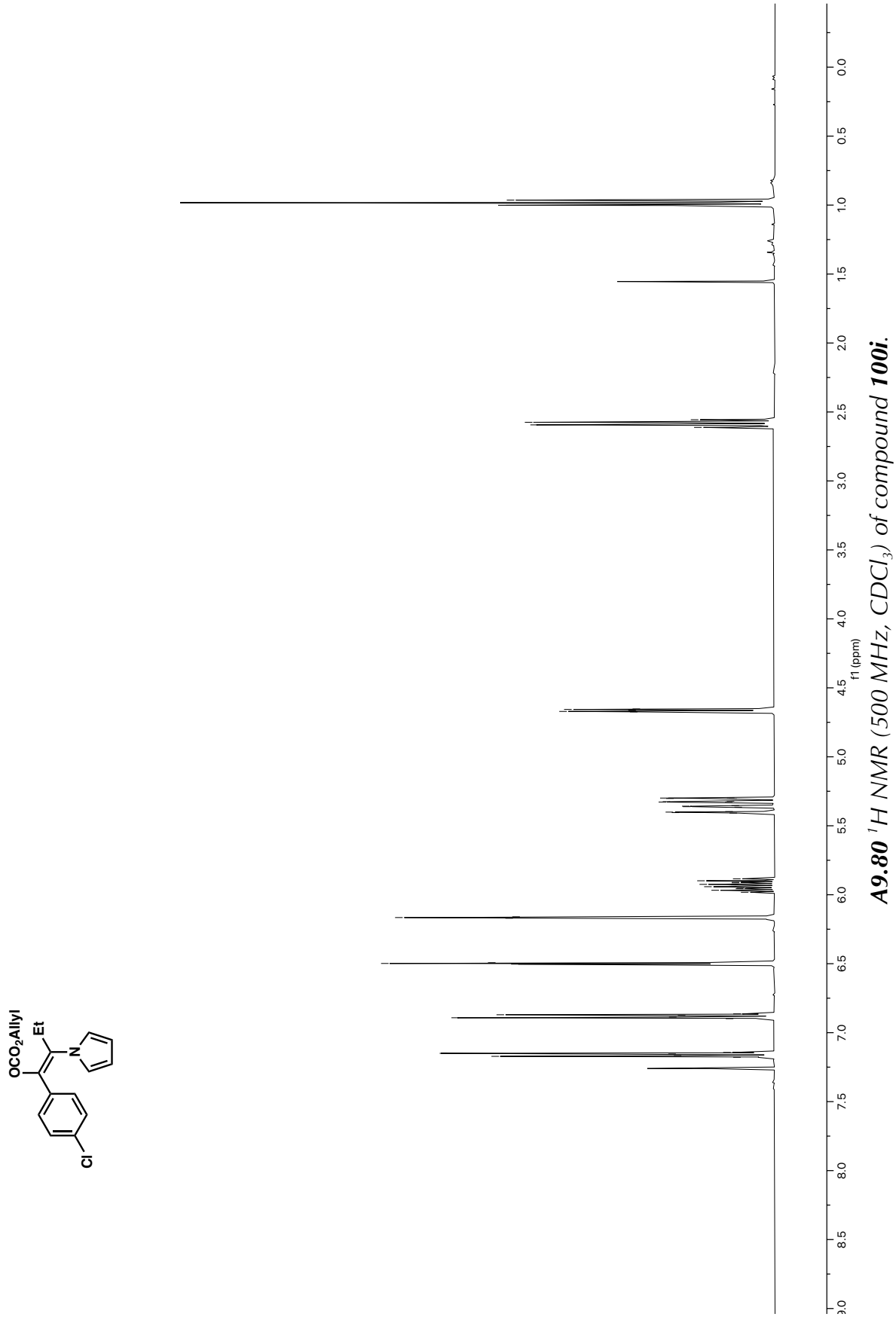



***Figure A9.79*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***100h***.




***A9.80*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***100i*****.**

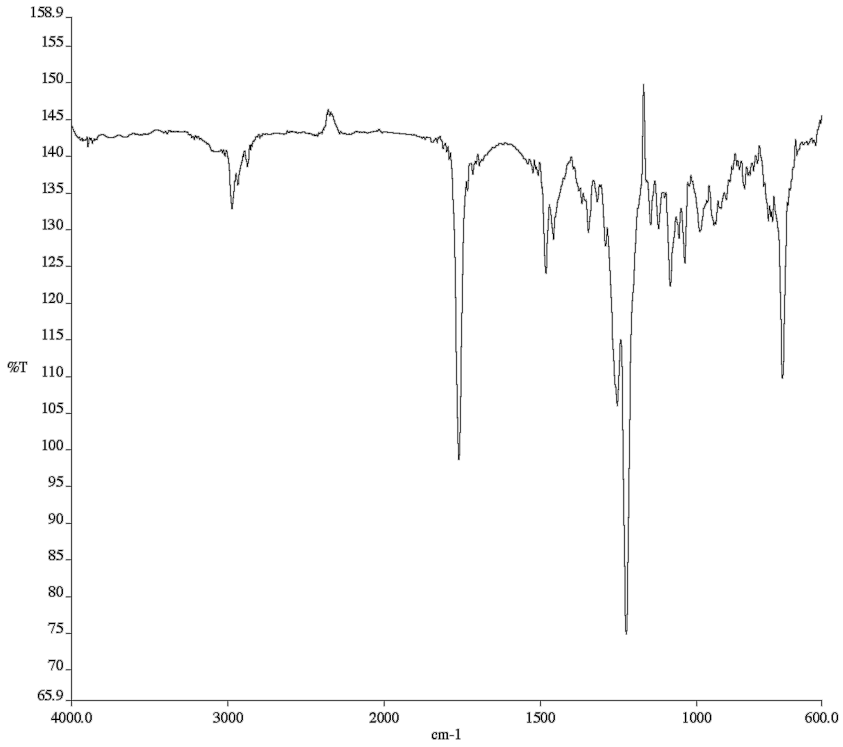



***Figure A9.81*** *Infrared spectrum (Thin Film, NaCl) of compound* ***100i***.

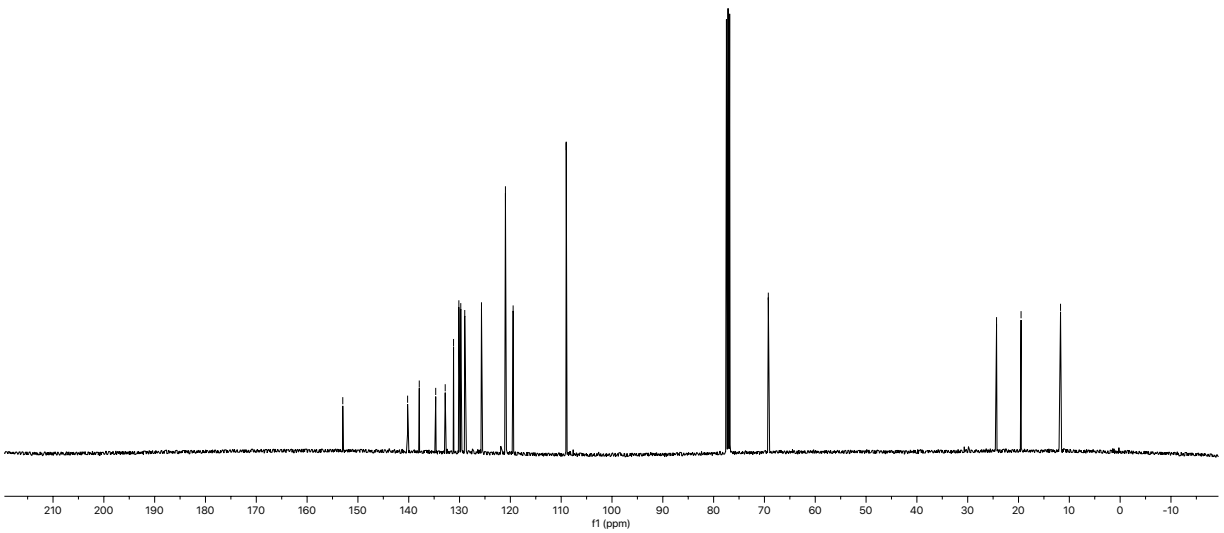
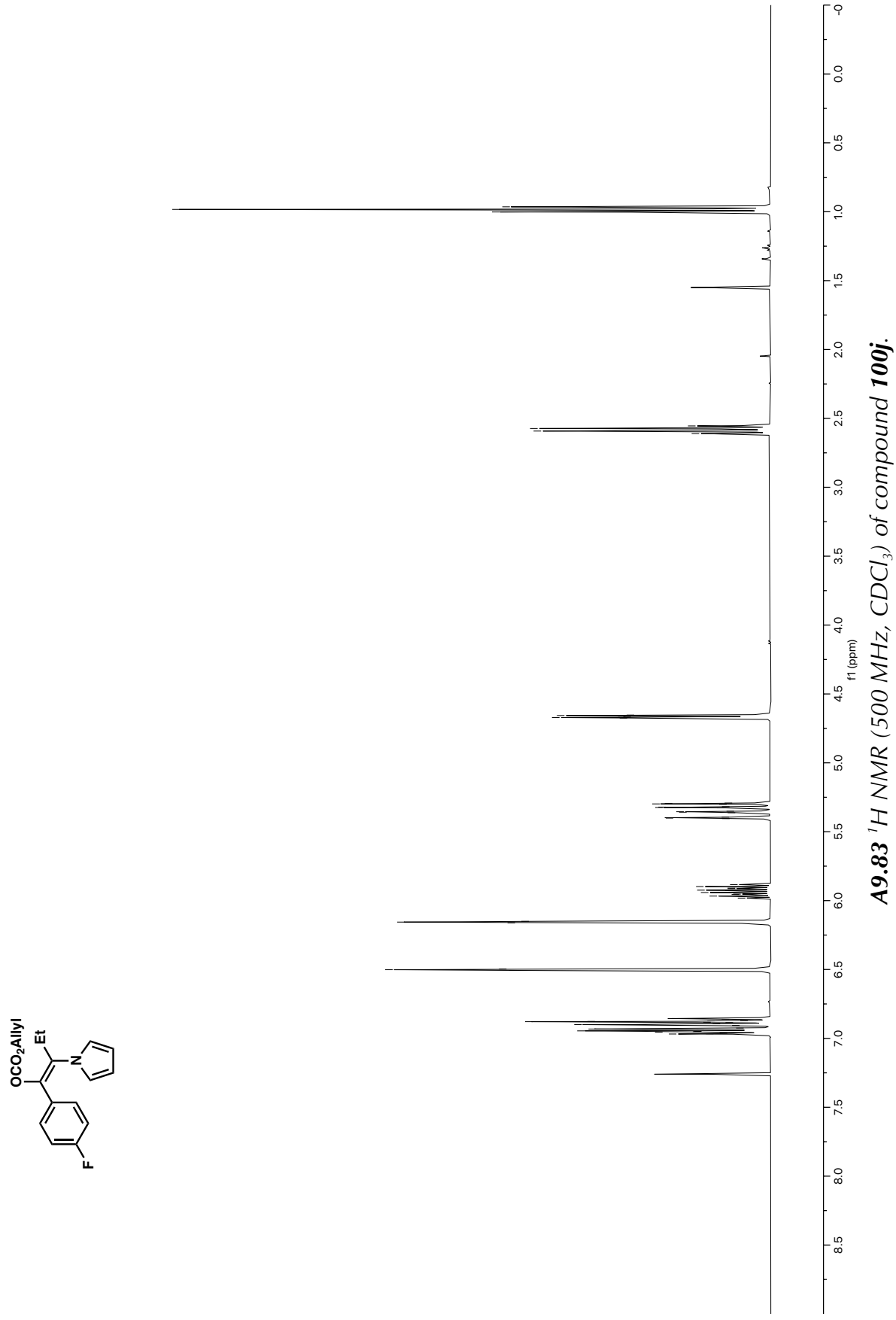



***Figure A9.82*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***100i***.




***A9.83*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***100j*****.**

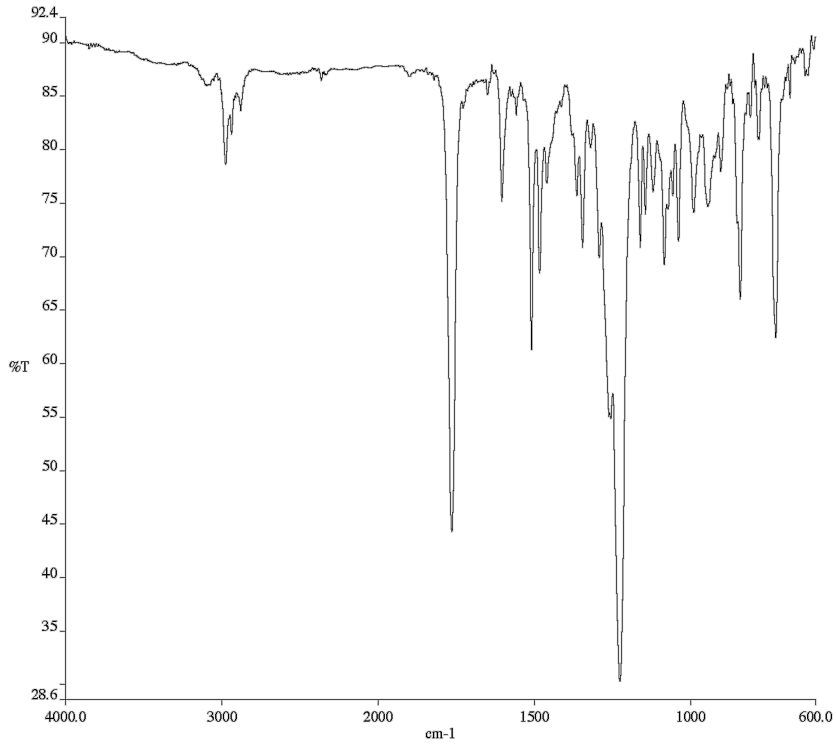



***Figure A9.84*** *Infrared spectrum (Thin Film, NaCl) of compound* ***100j****.*

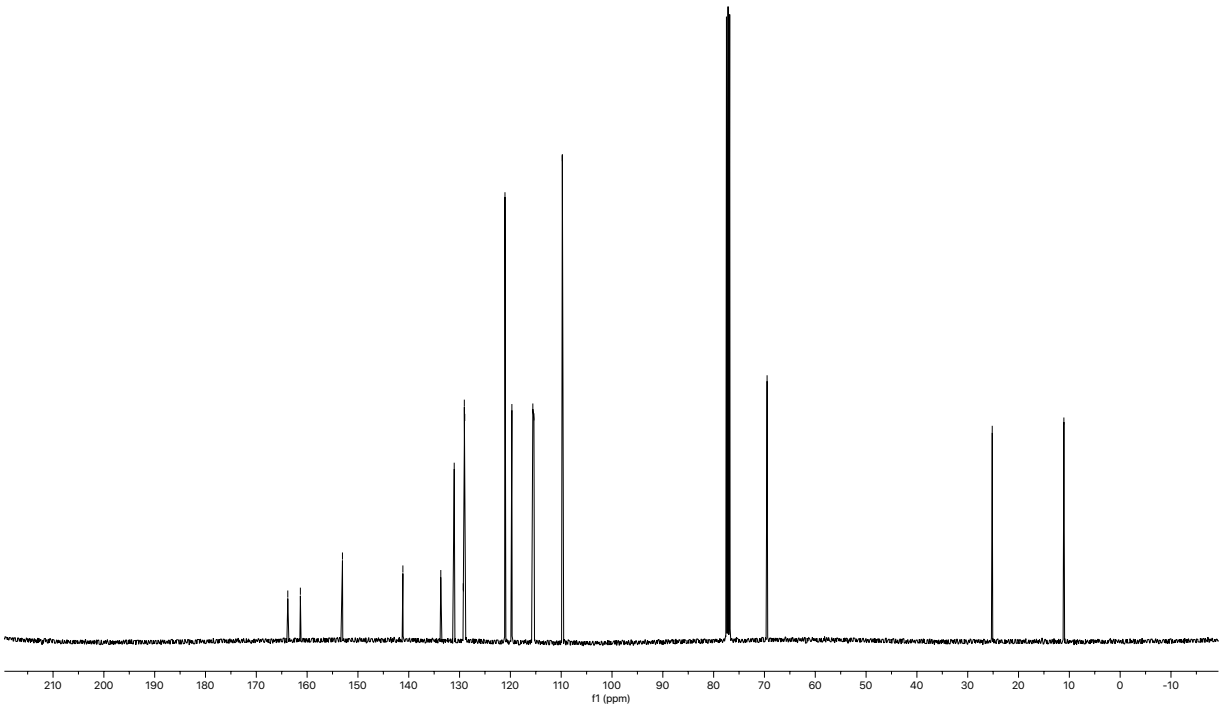



***Figure A9.85*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***100j****.*

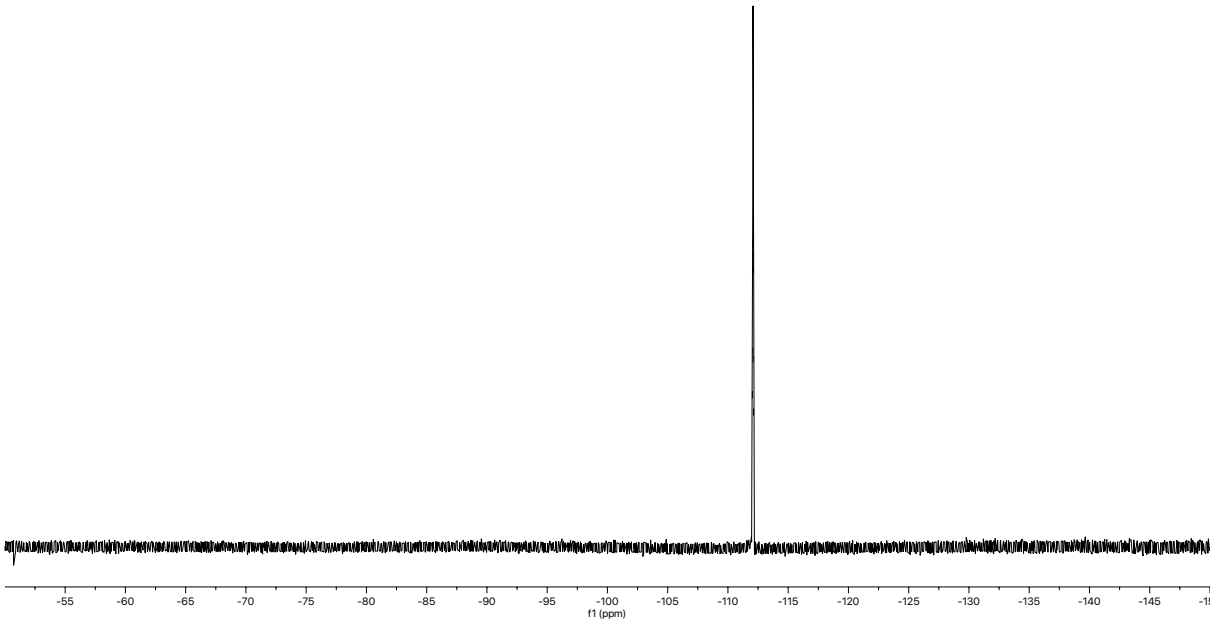
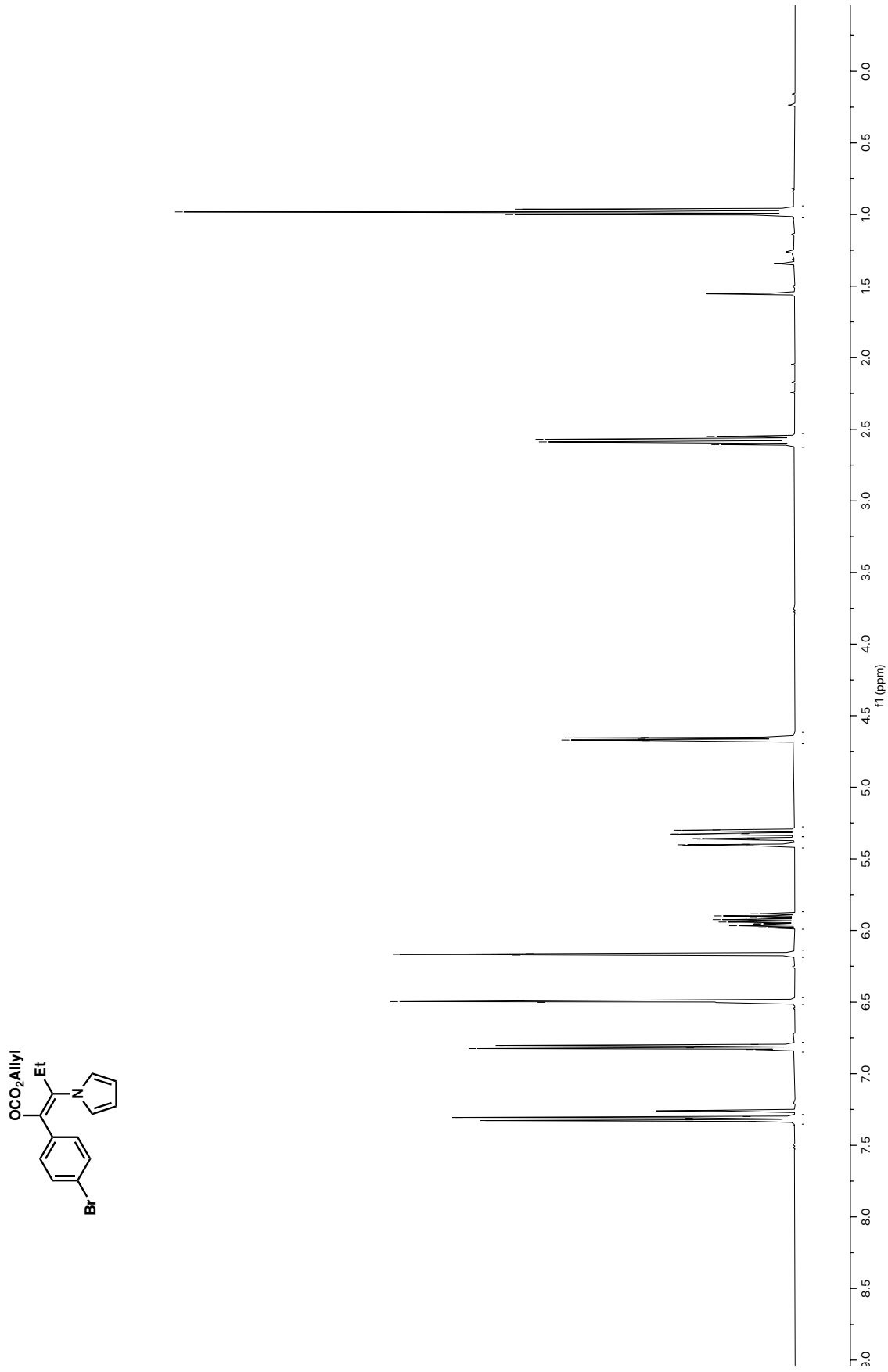



***Figure A9.86*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***100j***.




***A9.87*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***100k***.

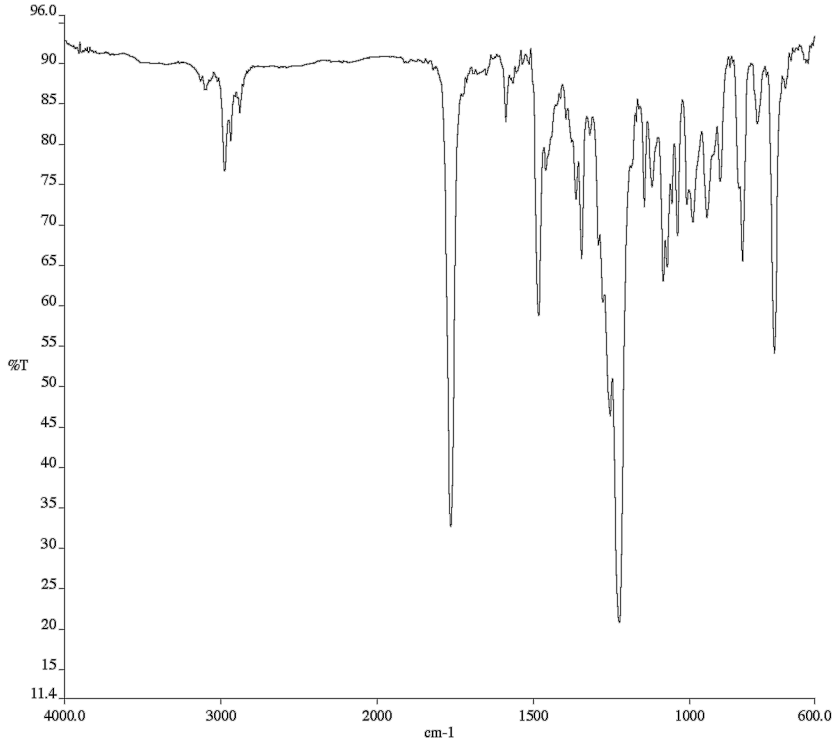



***Figure A9.88*** *Infrared spectrum (Thin Film, NaCl) of compound* ***100k****.*

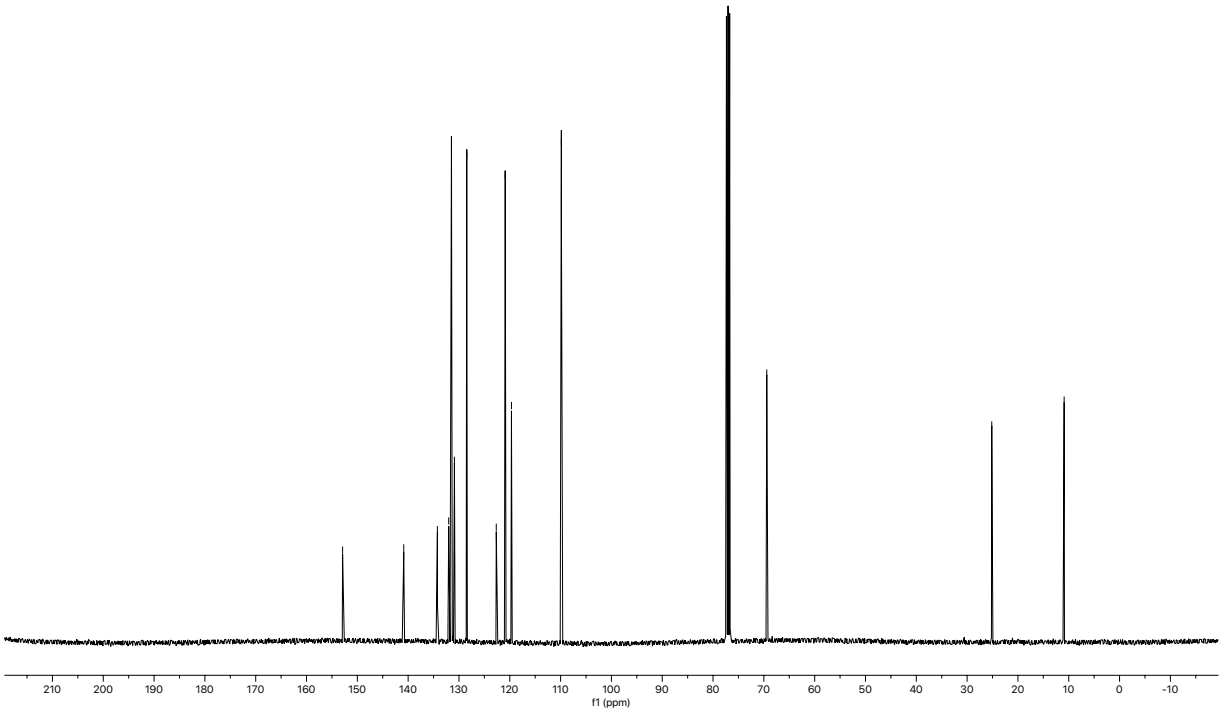
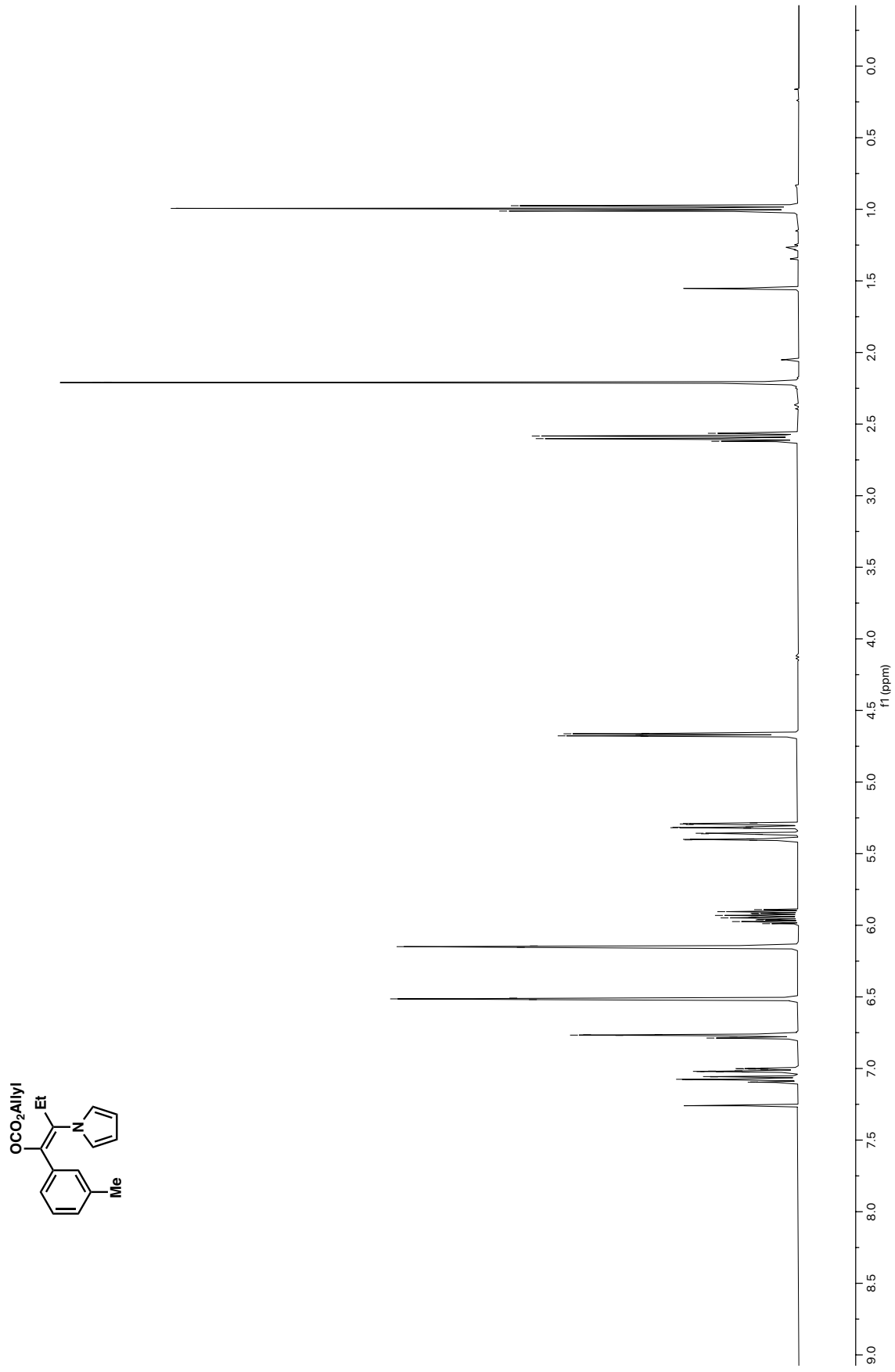



***Figure A9.89*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***100k****.*




***A9.90*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***100l***.

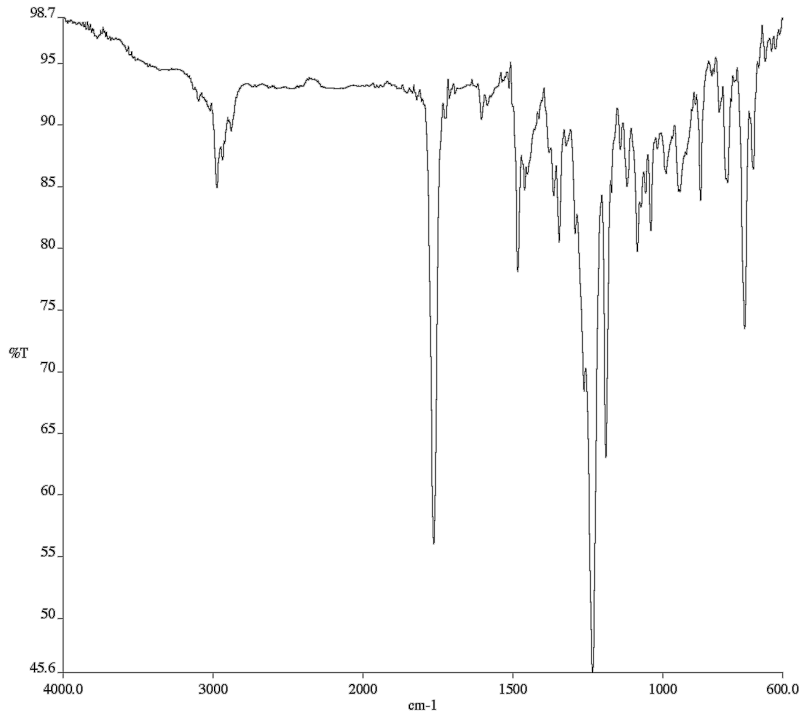



***Figure A9.91*** *Infrared spectrum (Thin Film, NaCl) of compound* ***100l***.

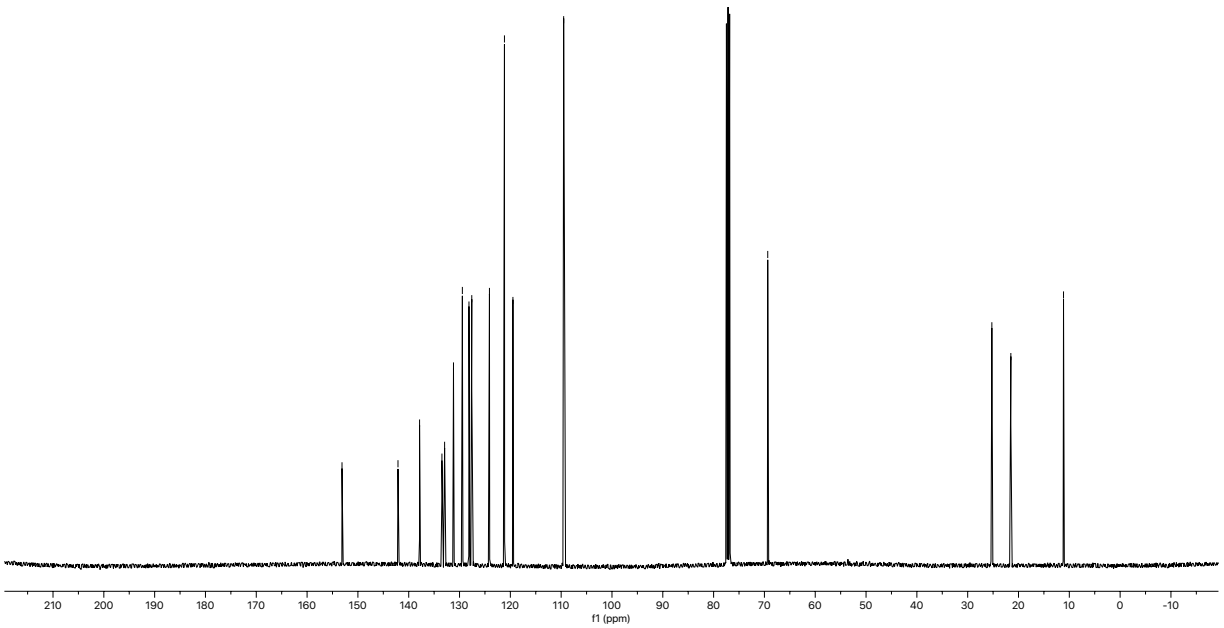
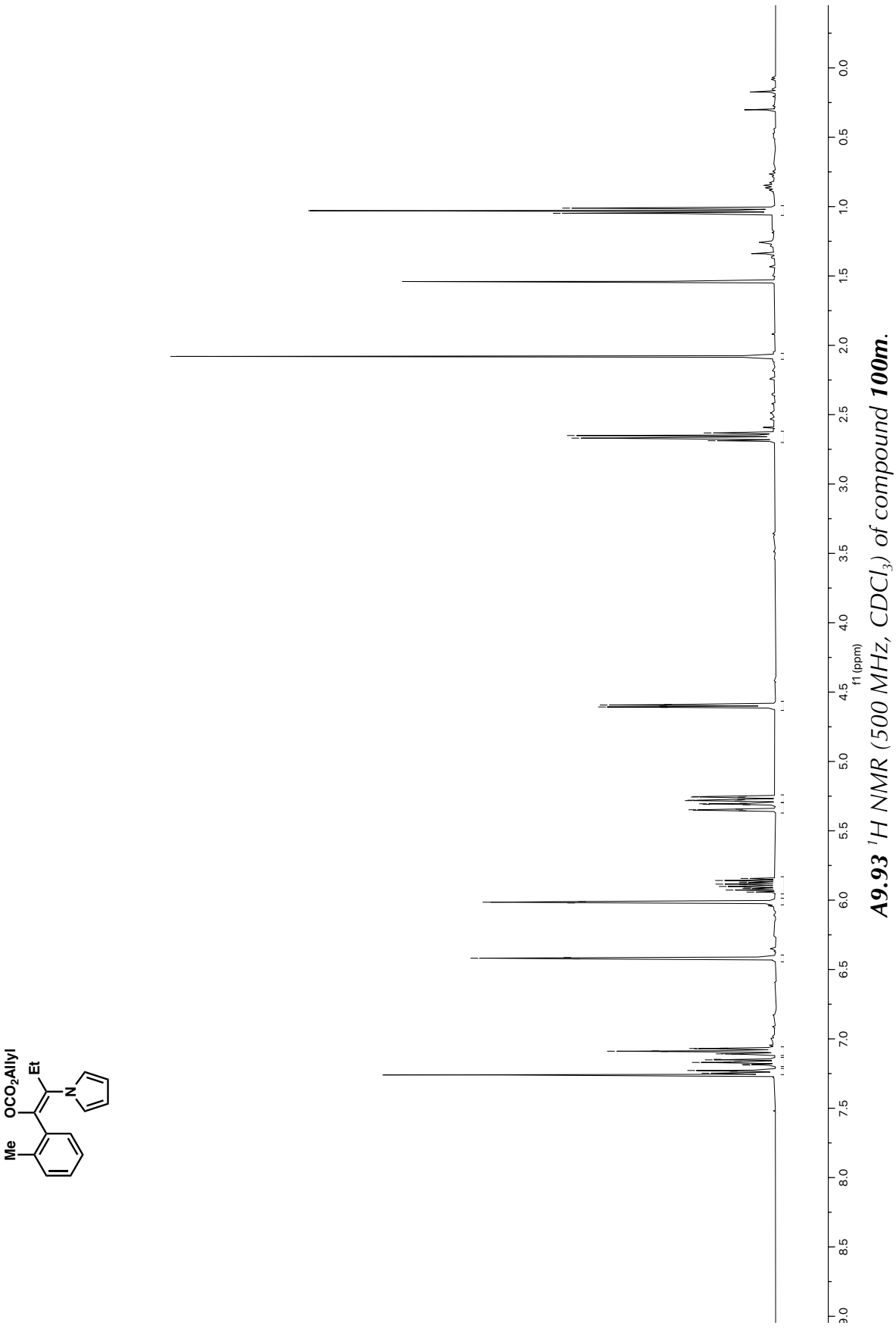



***Figure A9.92*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***100l***.




***A9.93*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***100m***.

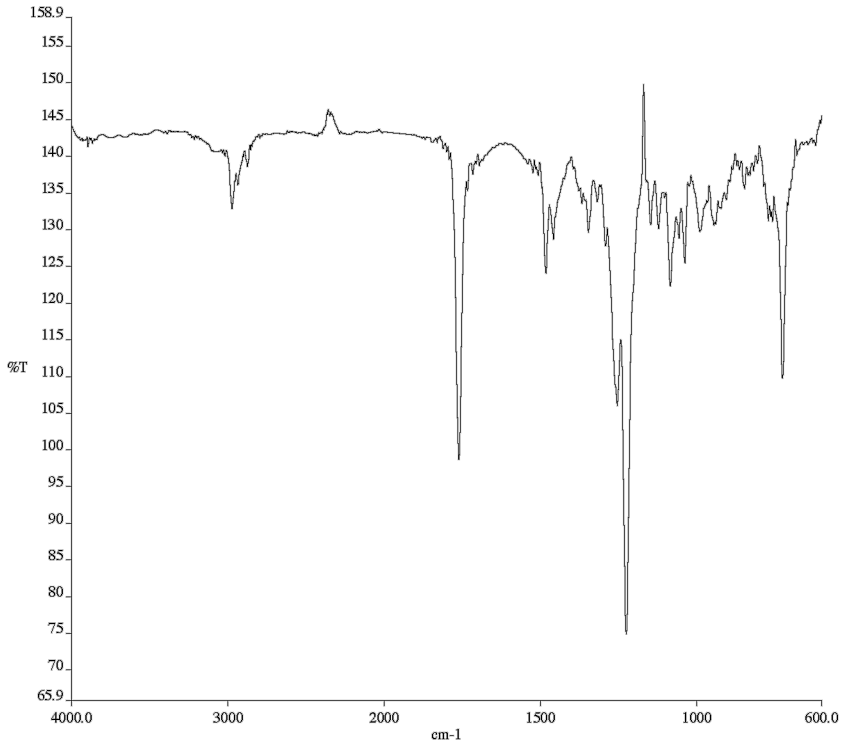



***Figure A9.94*** *Infrared spectrum (Thin Film, NaCl) of compound* ***100m***.

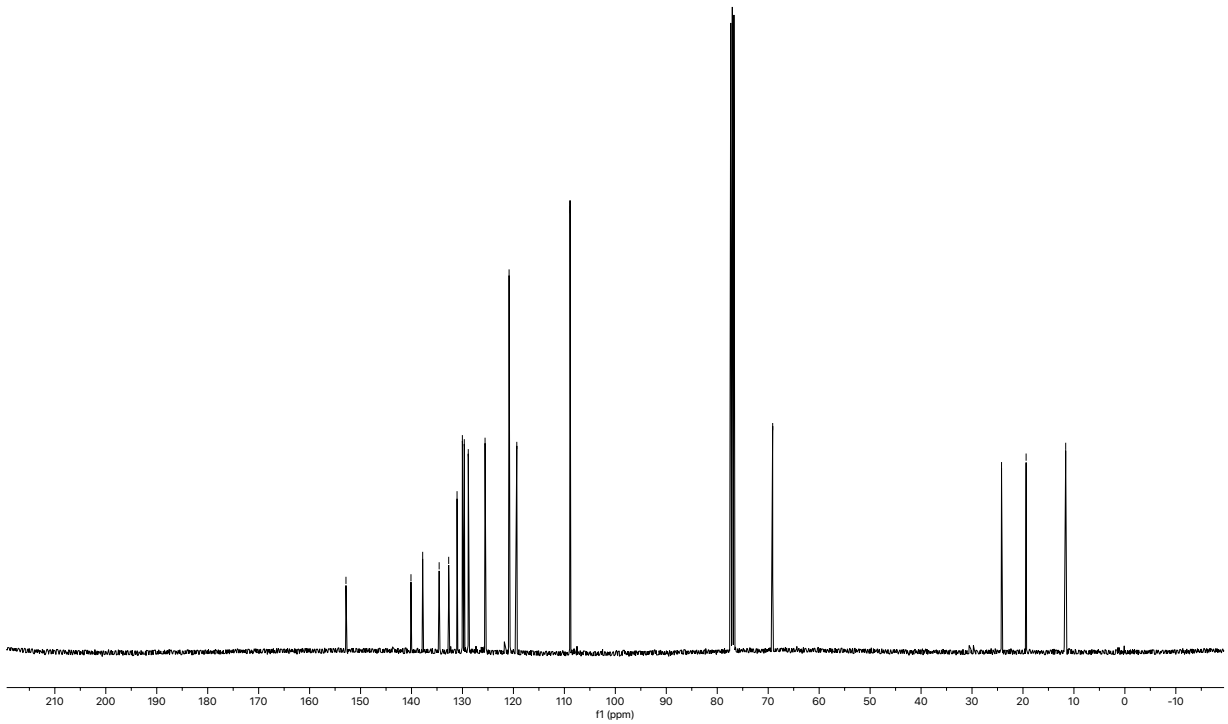
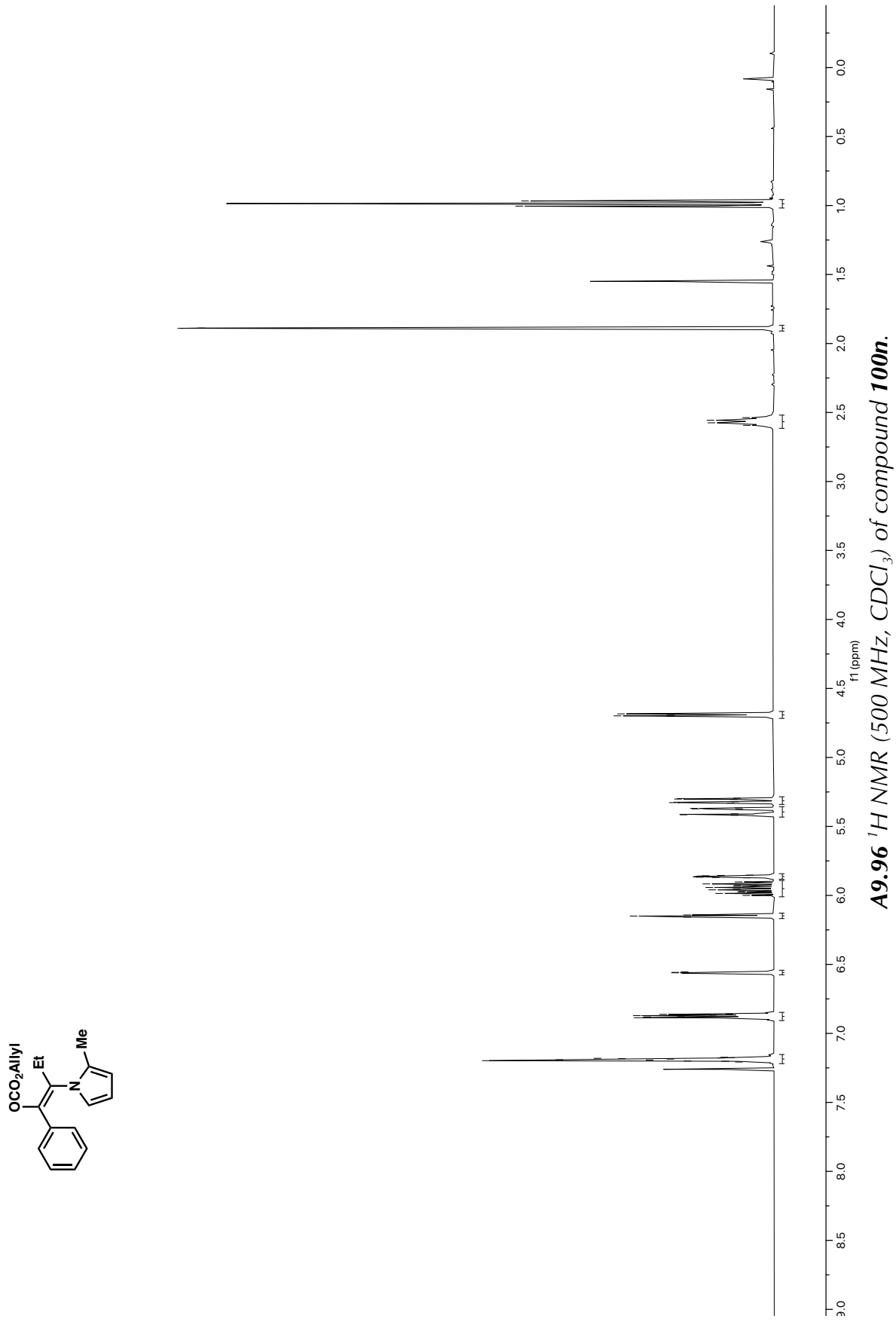



***Figure A9.95*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***100m***.




***A9.96*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***100n***.

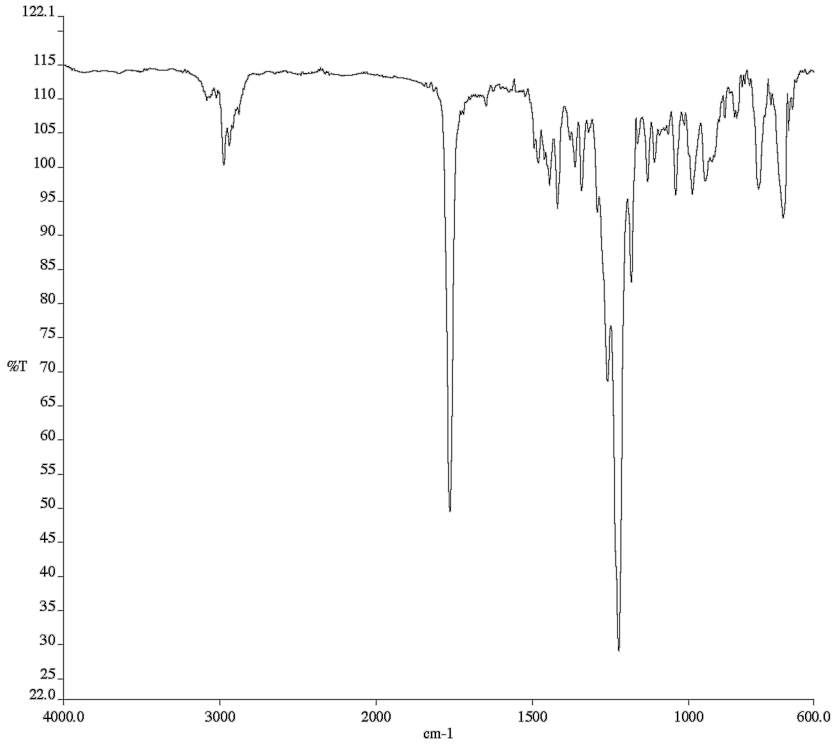



***Figure A9.97*** *Infrared spectrum (Thin Film, NaCl) of compound* ***100n***.

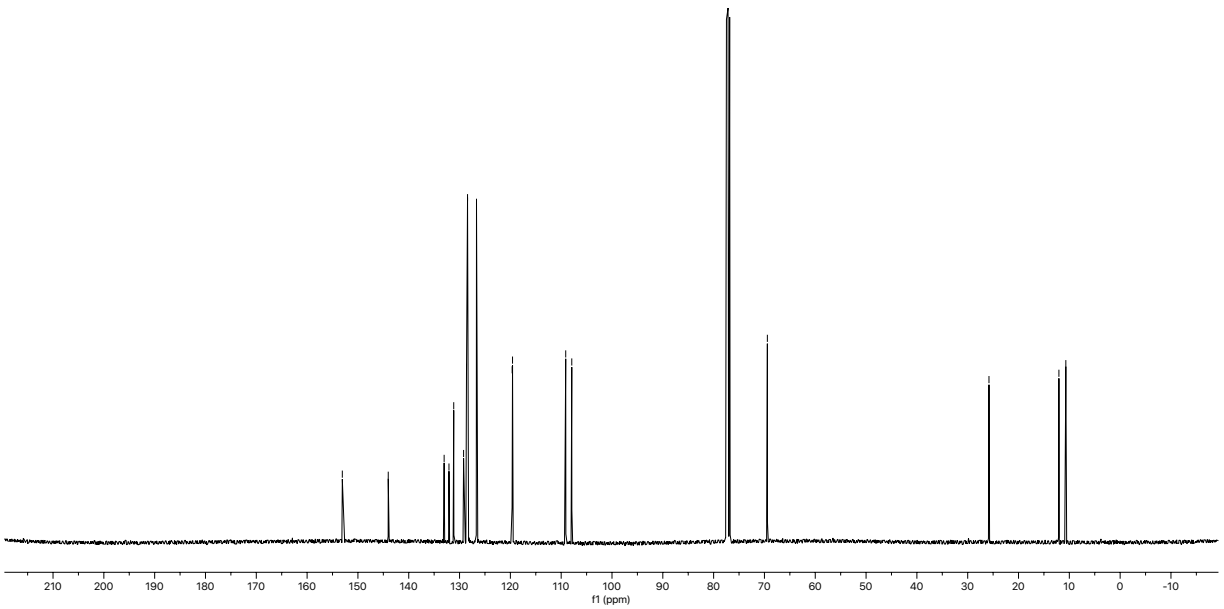
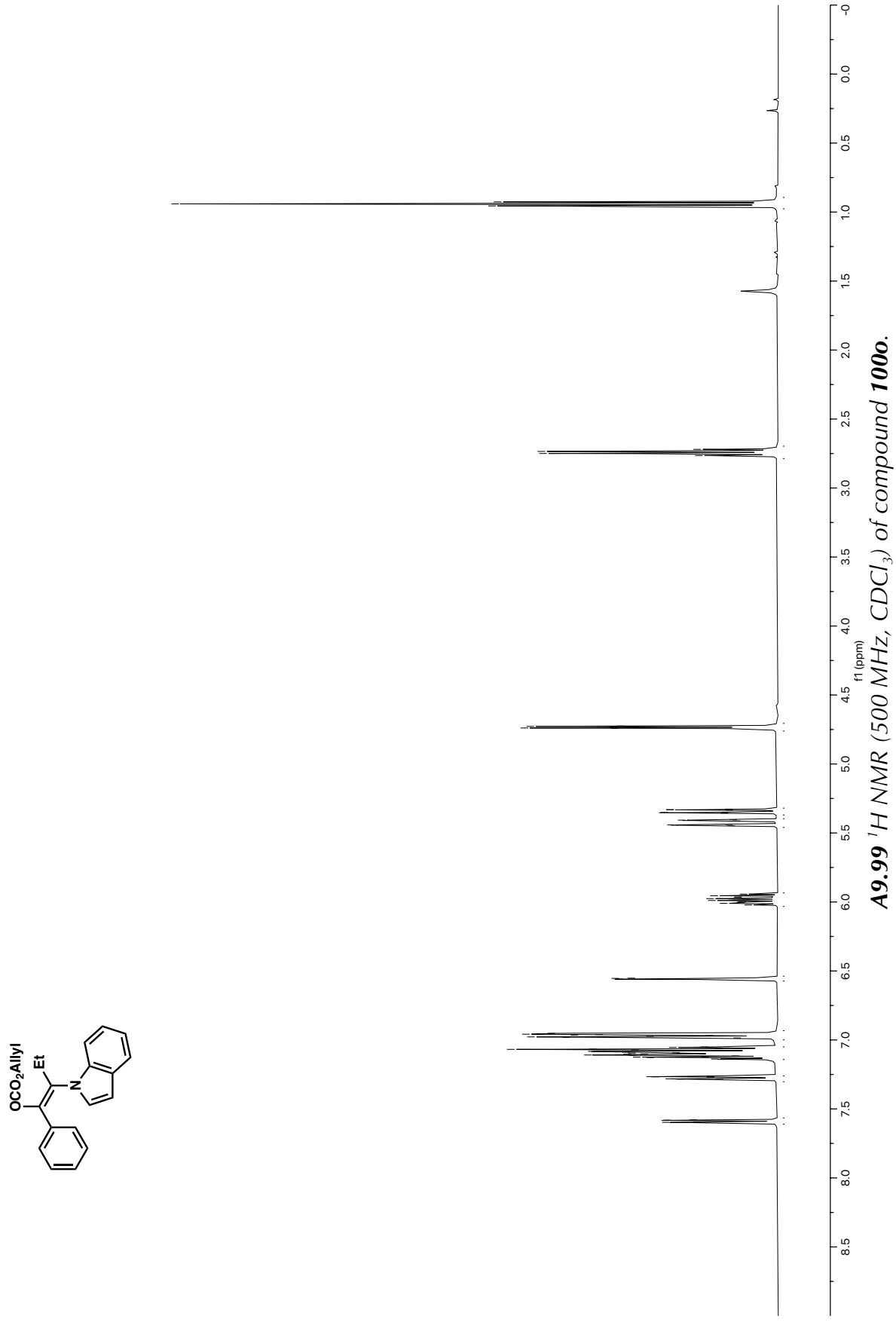



***Figure A9.98*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***100n***.




***A9.99*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***100o***.

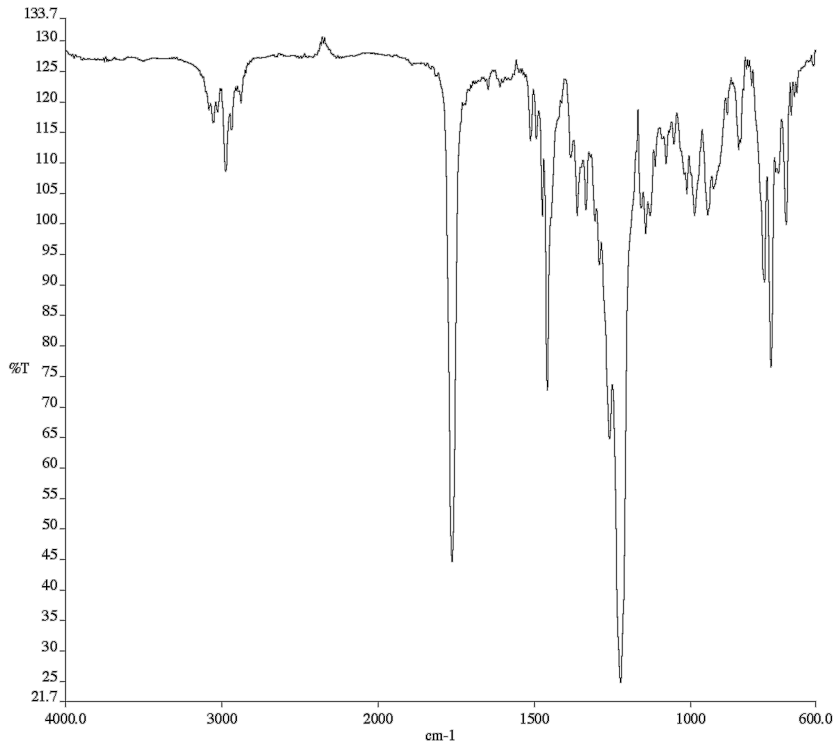



***Figure A9.100*** *Infrared spectrum (Thin Film, NaCl) of compound* ***100o***.

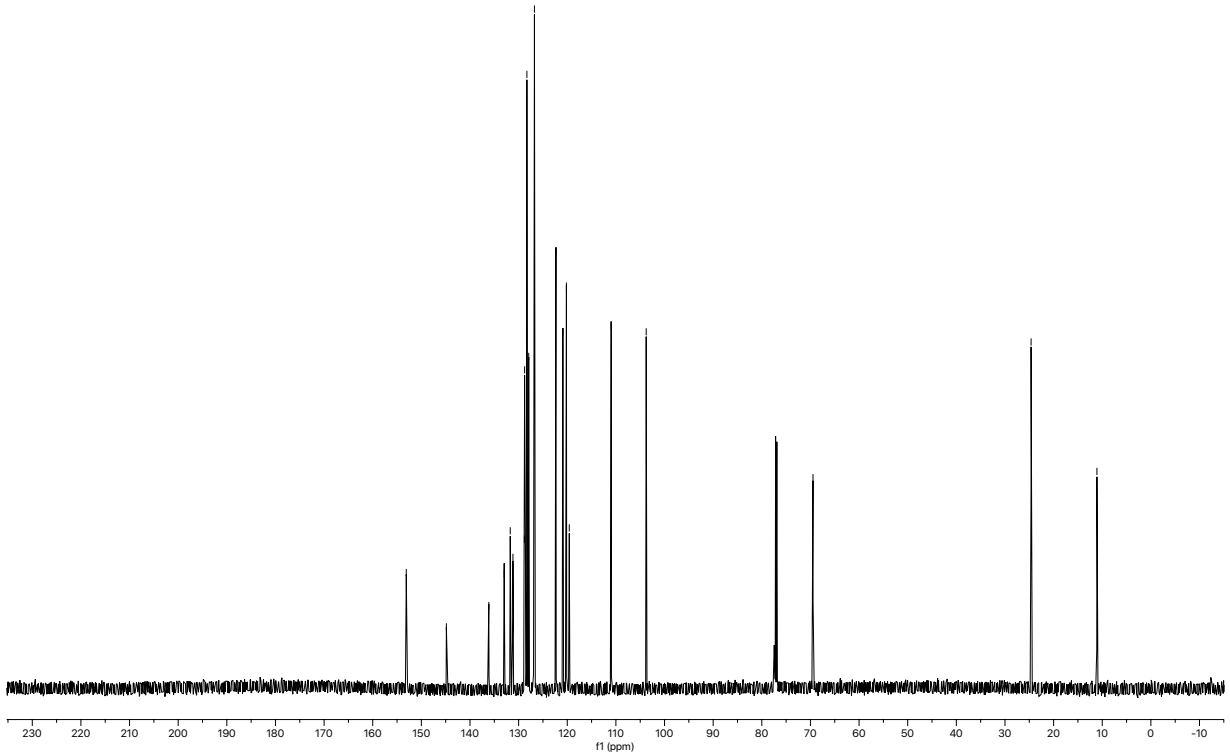
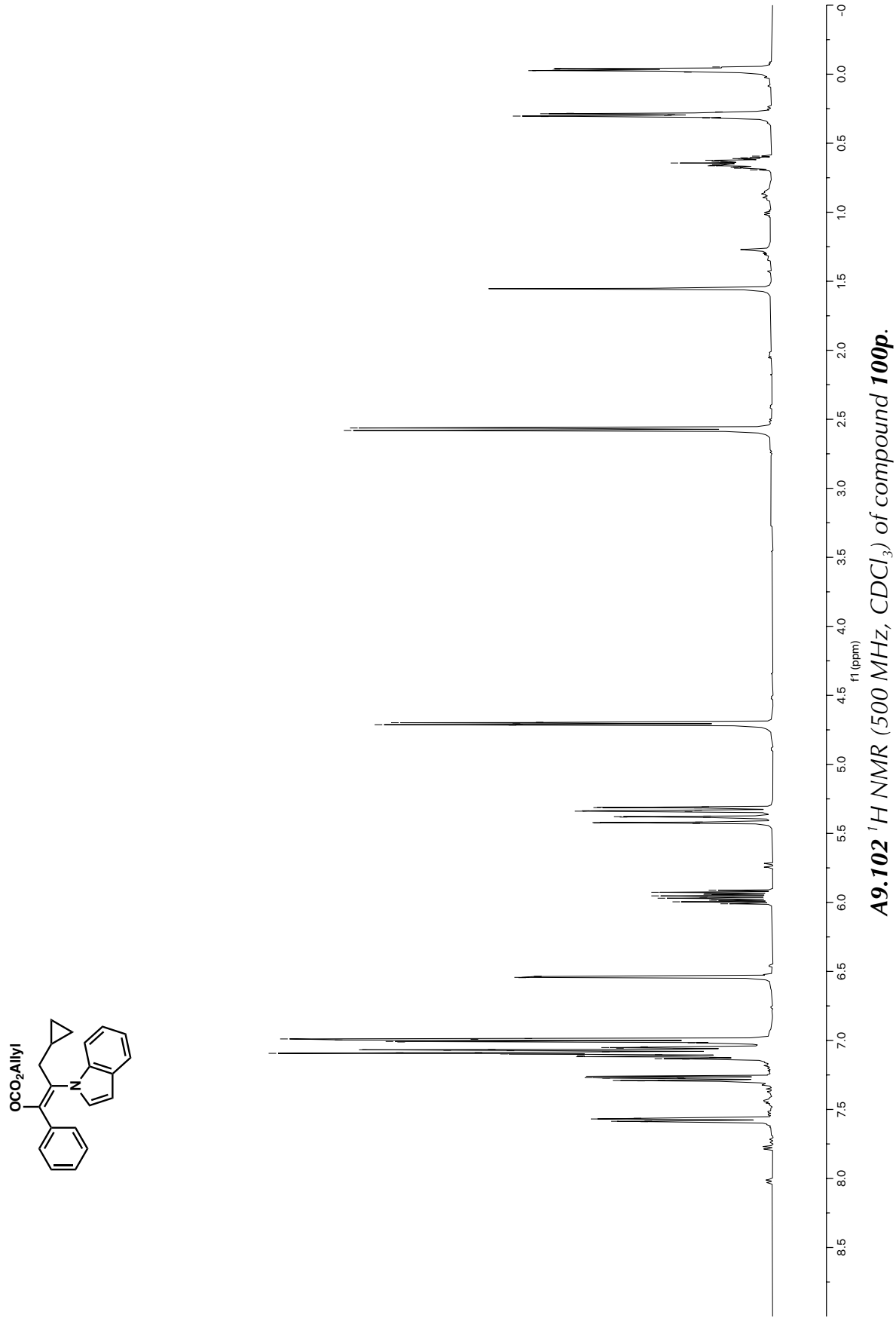



***Figure A9.101*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***100o***.




***A9.102*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***100p***.

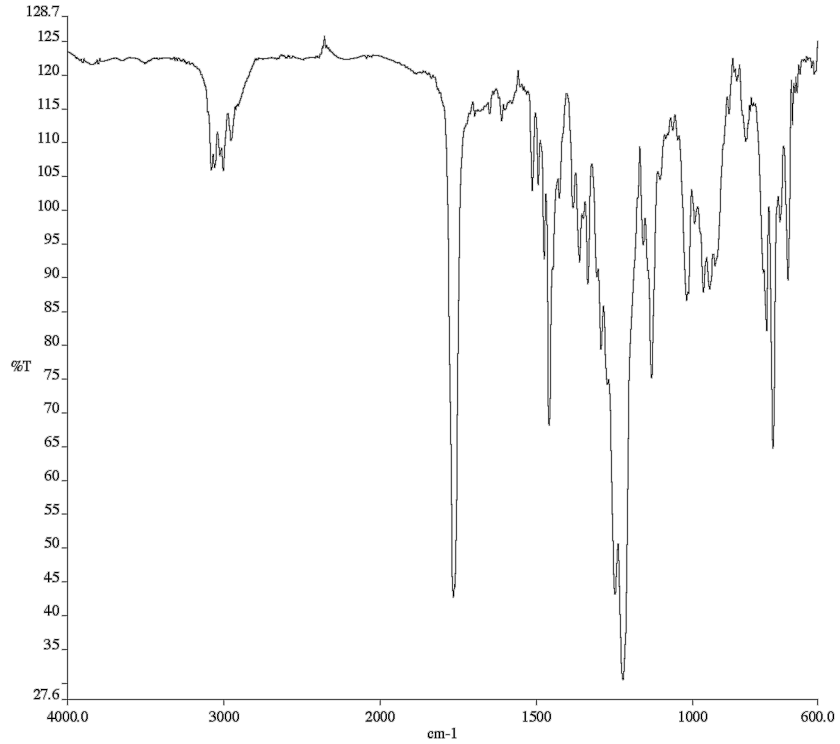



***Figure A9.103*** *Infrared spectrum (Thin Film, NaCl) of compound* ***100p***.

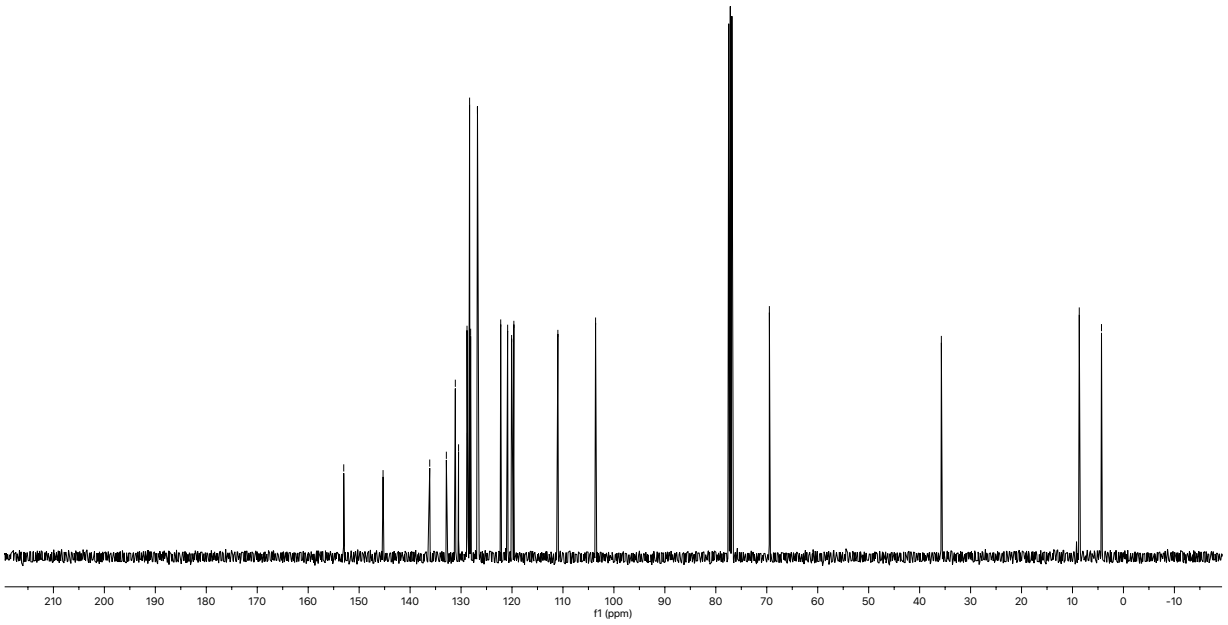



***Figure A9.104*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***100p***.

***A9.105*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***100q***.

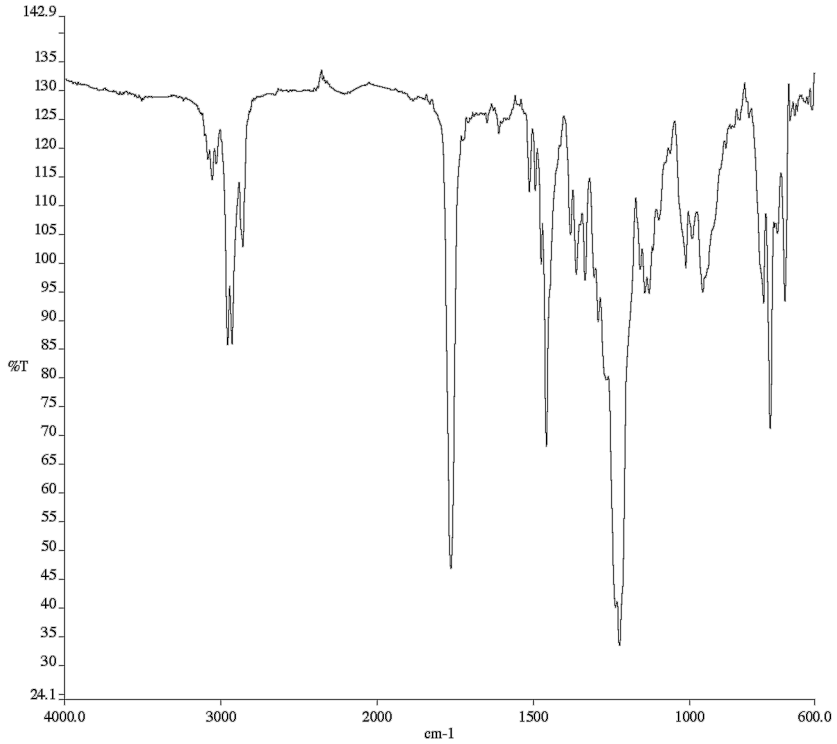



***Figure A9.106*** *Infrared spectrum (Thin Film, NaCl) of compound* ***100q***.

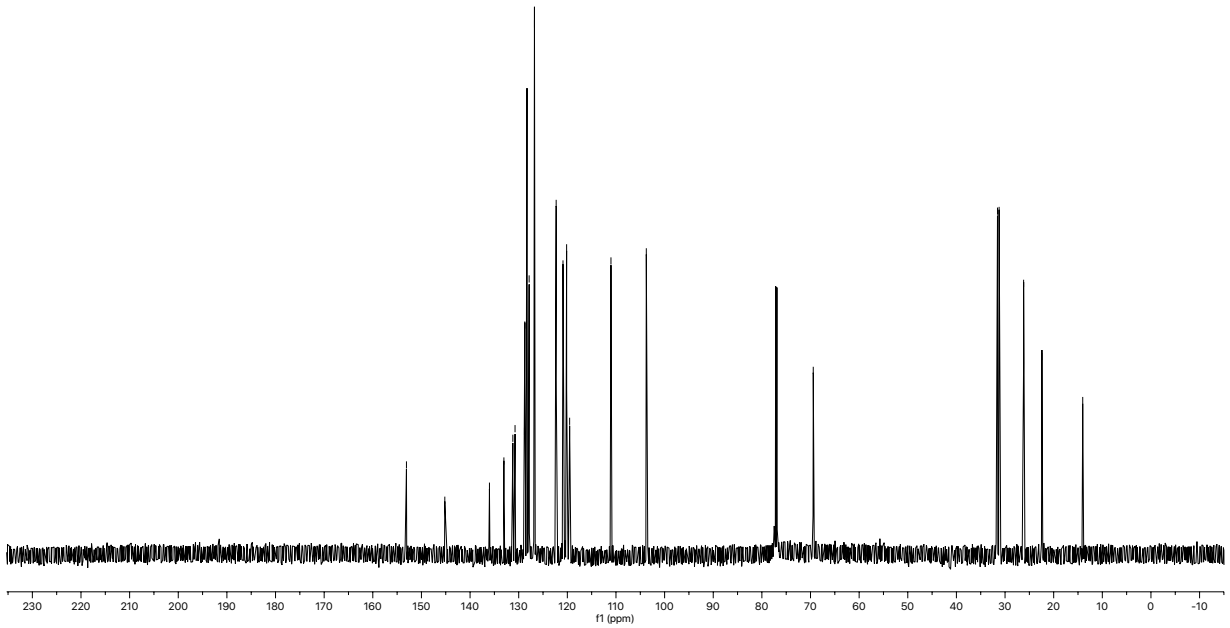
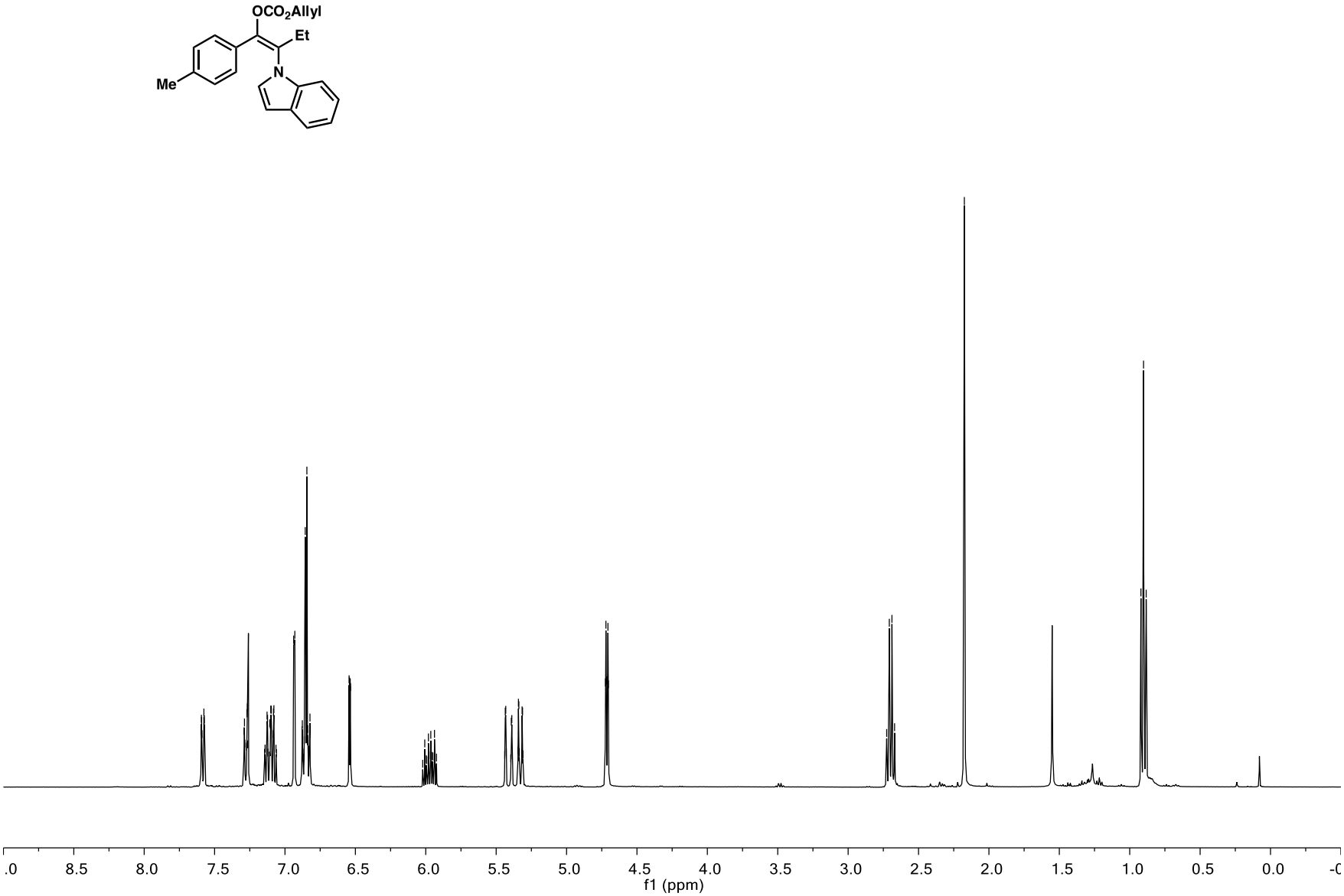



***Figure A9.107*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***100q***.




***A9.108*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***100r***.

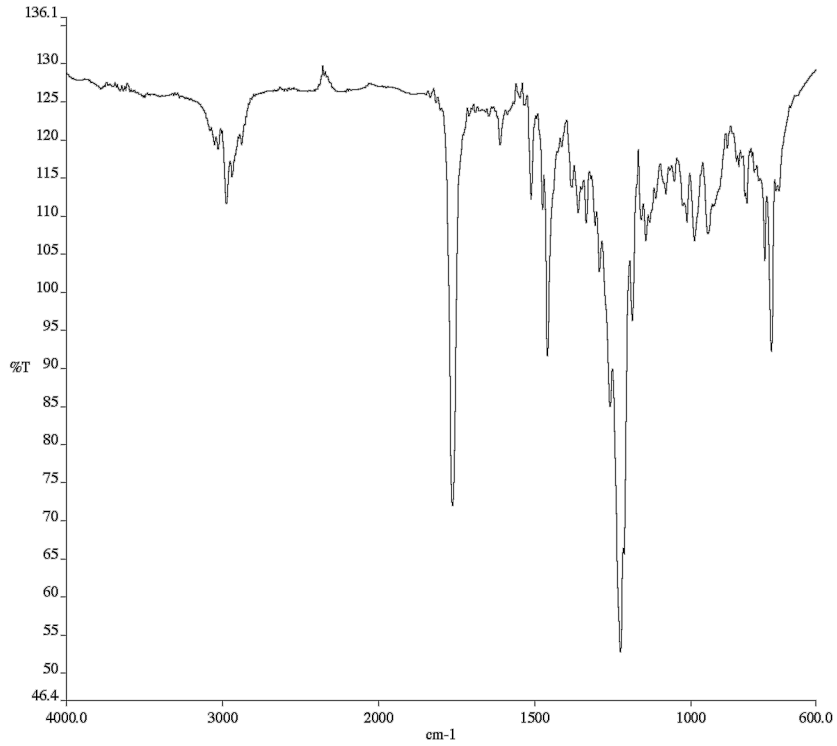



***Figure A9.109*** *Infrared spectrum (Thin Film, NaCl) of compound* ***100r****.*

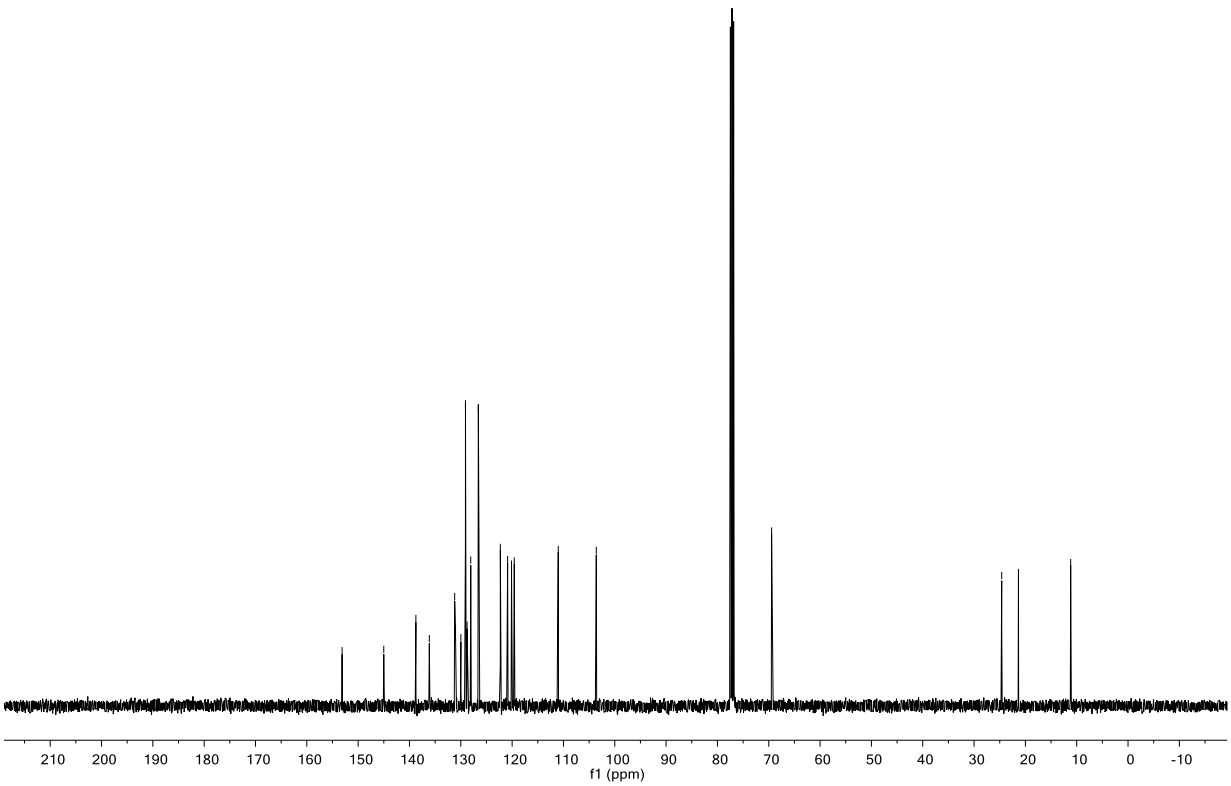
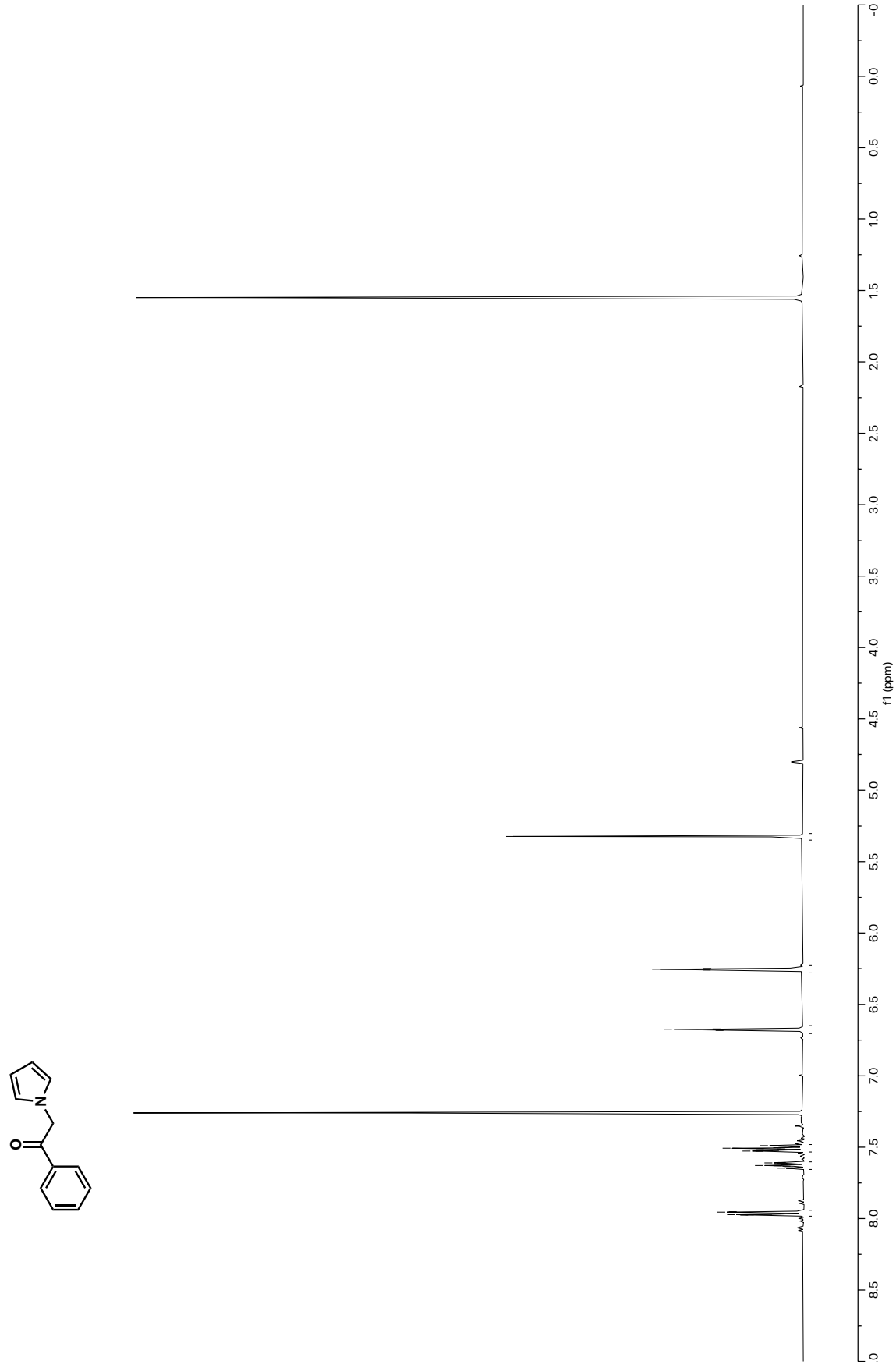
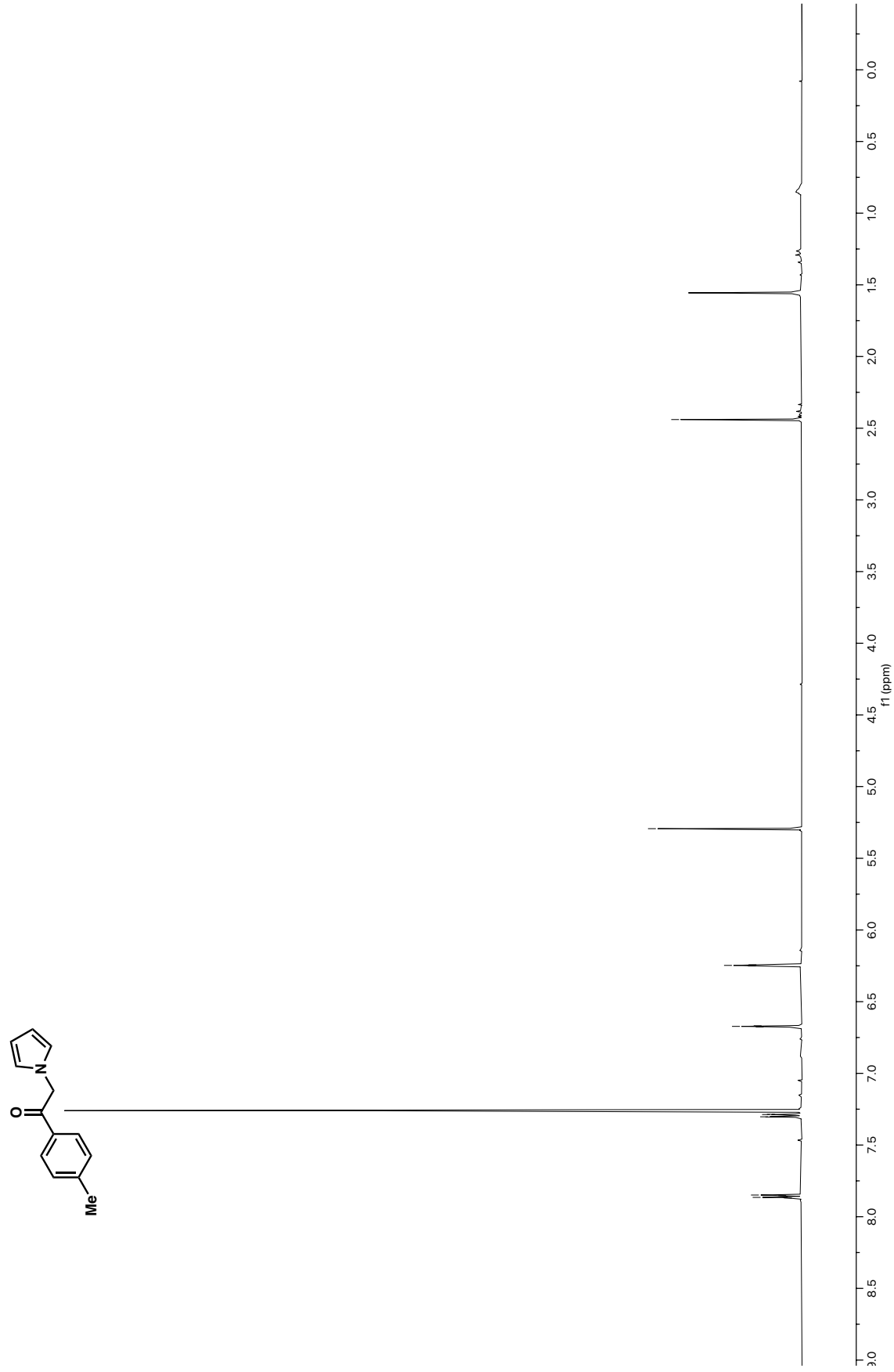



***Figure A9.110*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***100r****.*




***A9.111*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***105***.




***A9.112*** *$^{1}H$ NMR (500 MHz, $CDCl_3$) of compound* ***106****.*

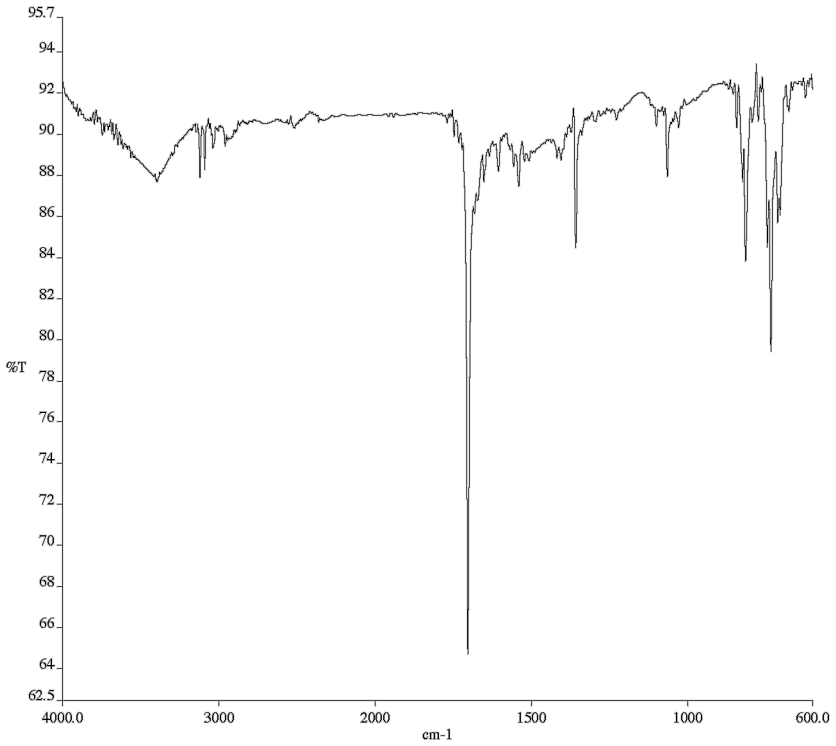



***Figure A9.113*** *Infrared spectrum (Thin Film, NaCl) of compound* ***106***.

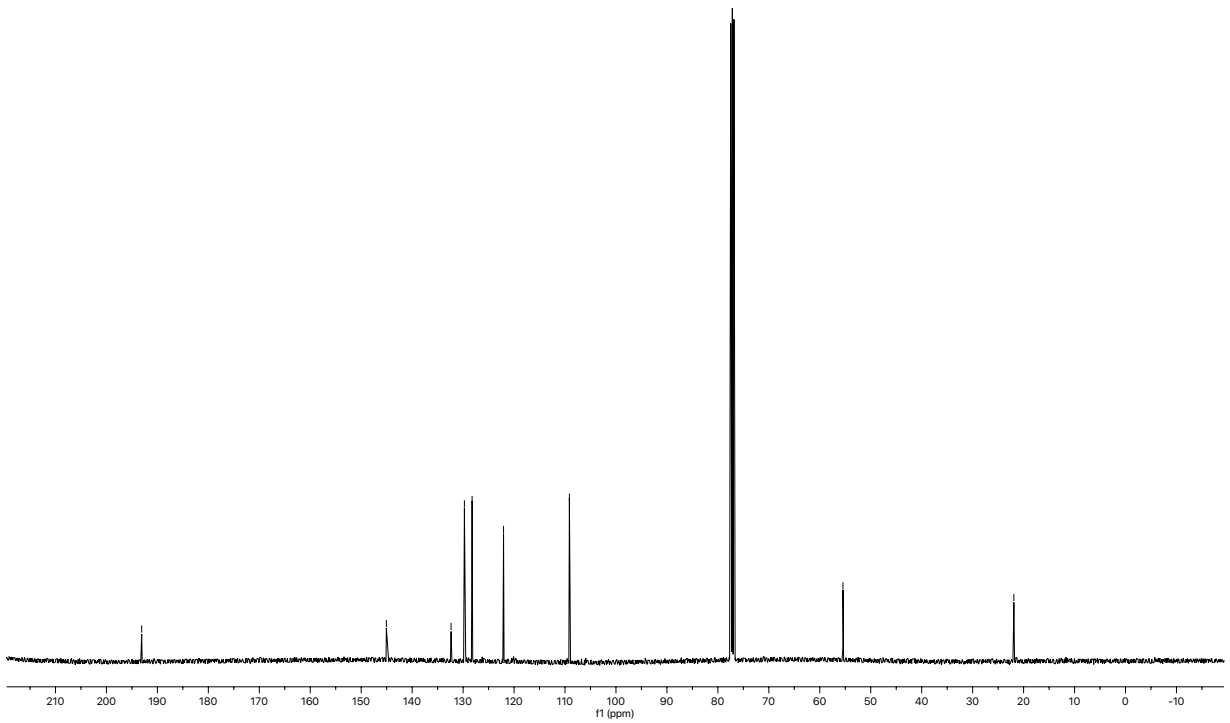
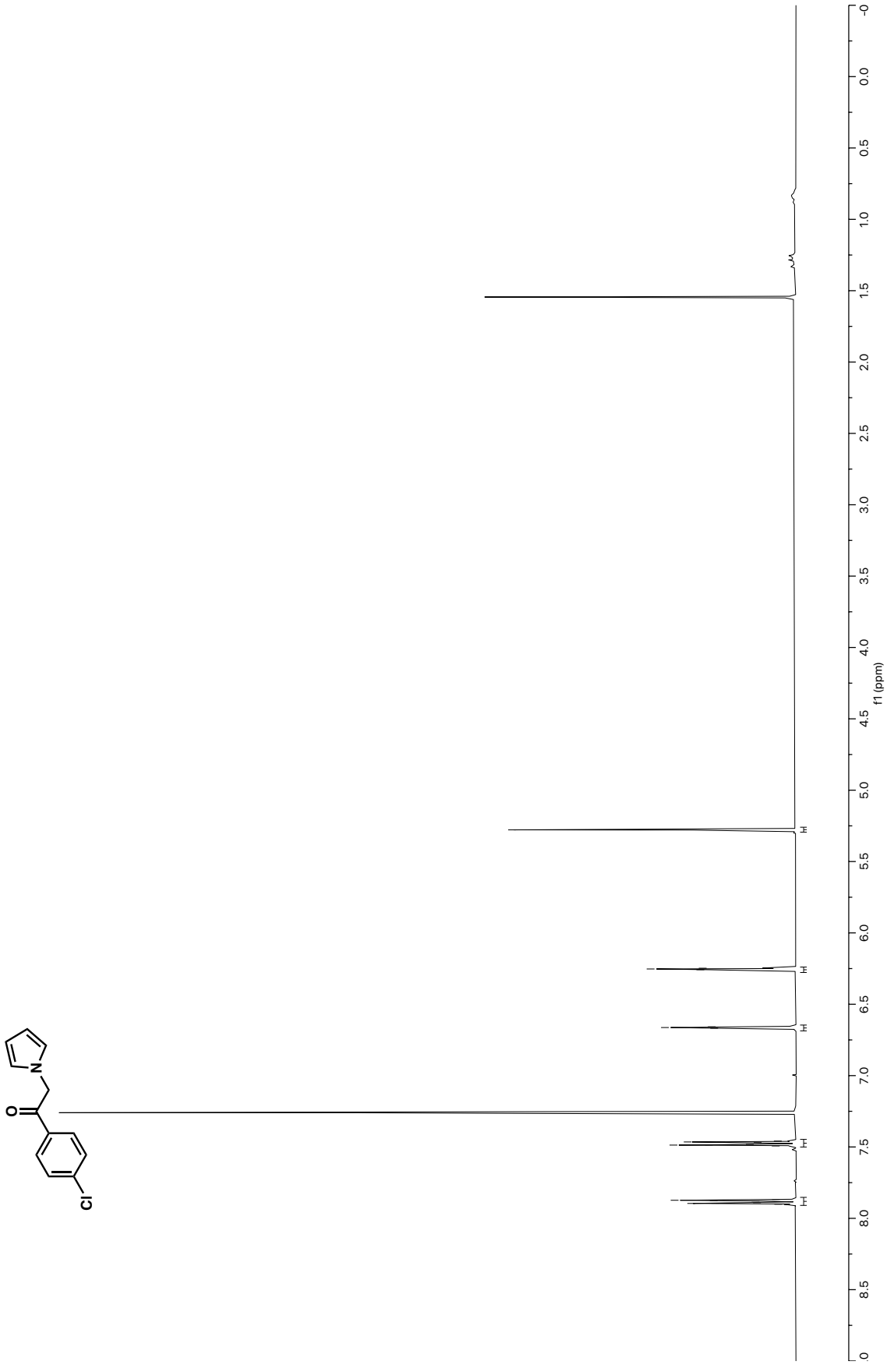



***Figure A9.114*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***106***.




***A9.115*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***107****.*

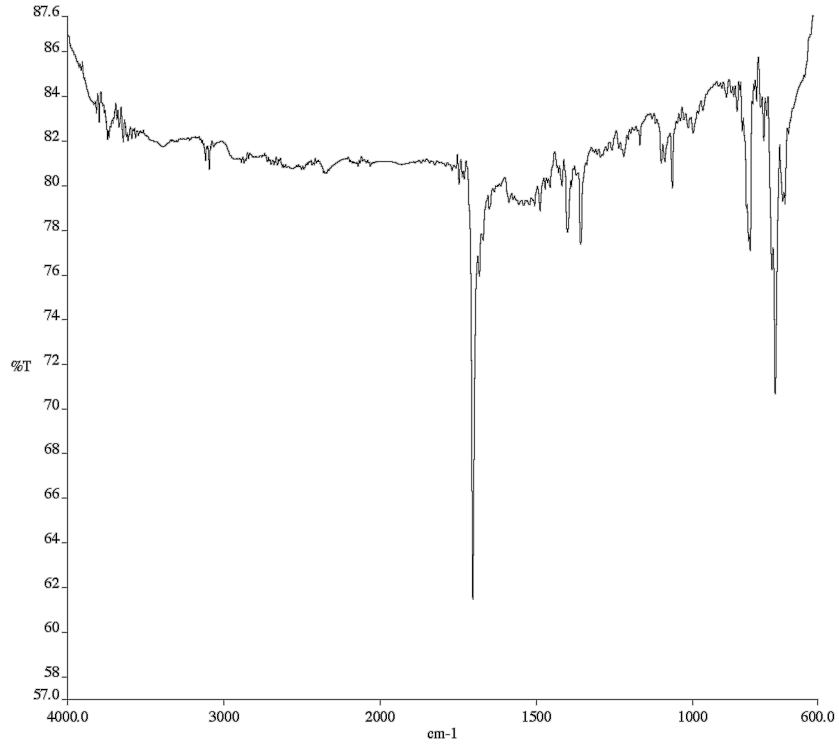



***Figure A9.116*** *Infrared spectrum (Thin Film, NaCl) of compound* ***107****.*

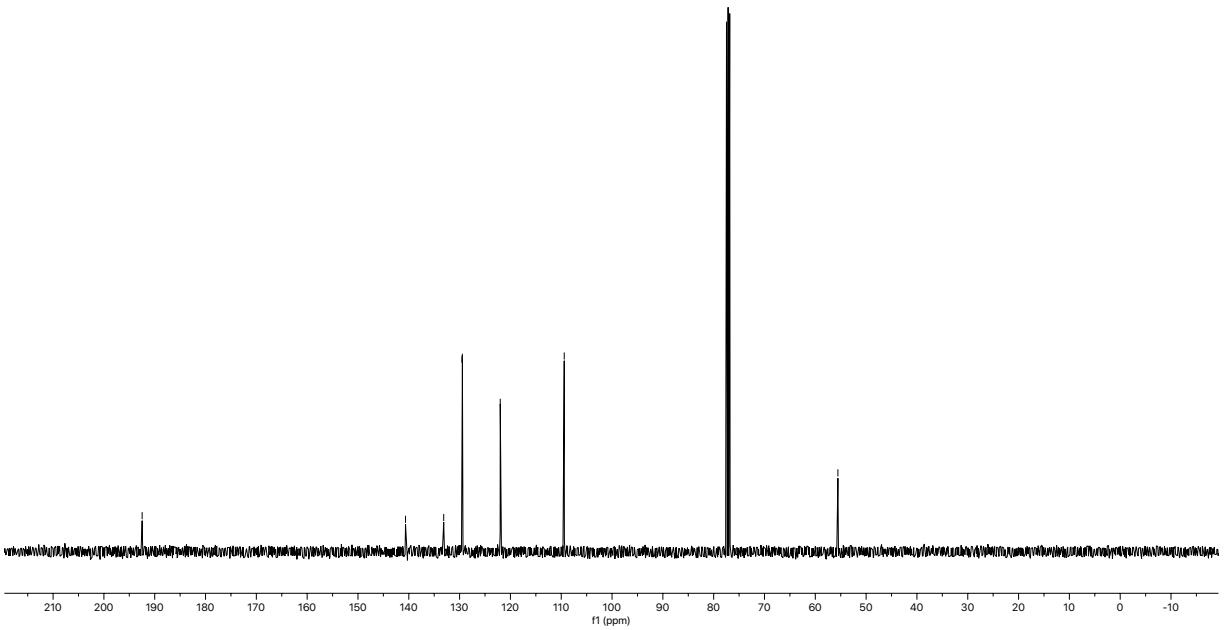
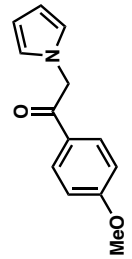
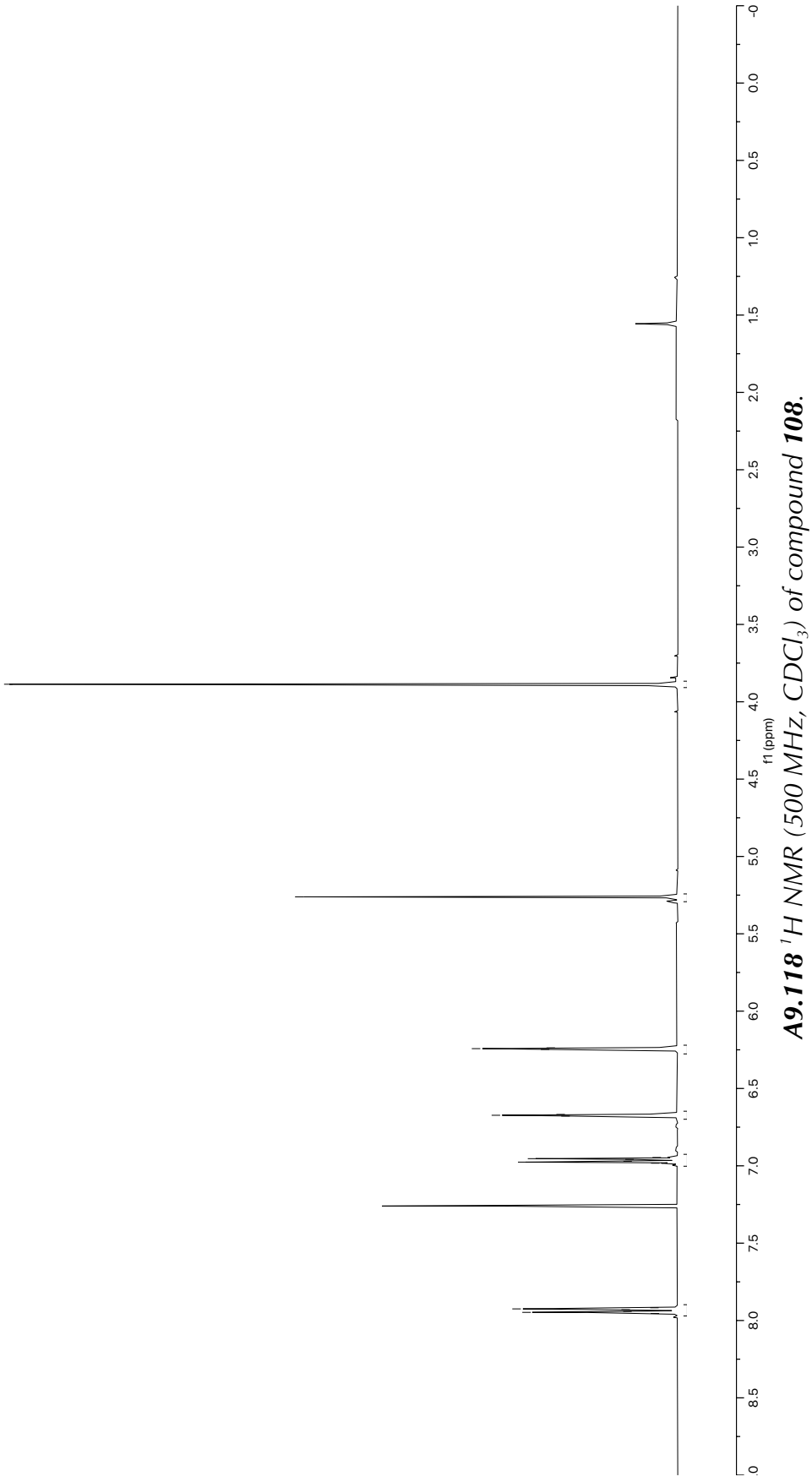



***Figure A9.117*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***107****.*




***A9.118*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***108****.*

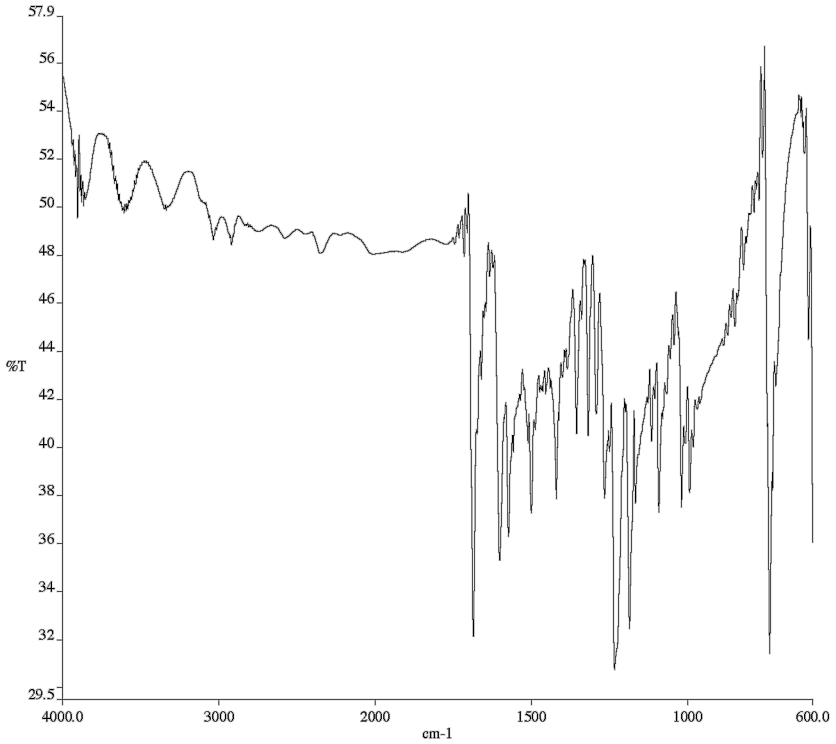



***Figure A9.119*** *Infrared spectrum (Thin Film, NaCl) of compound* ***108****.*

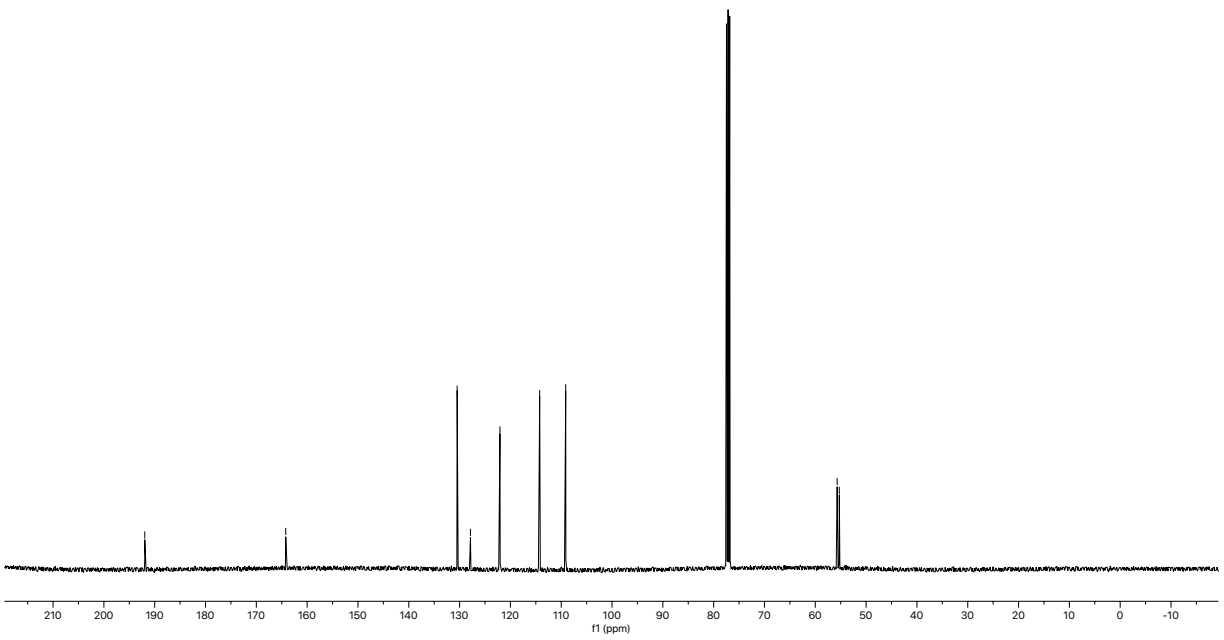
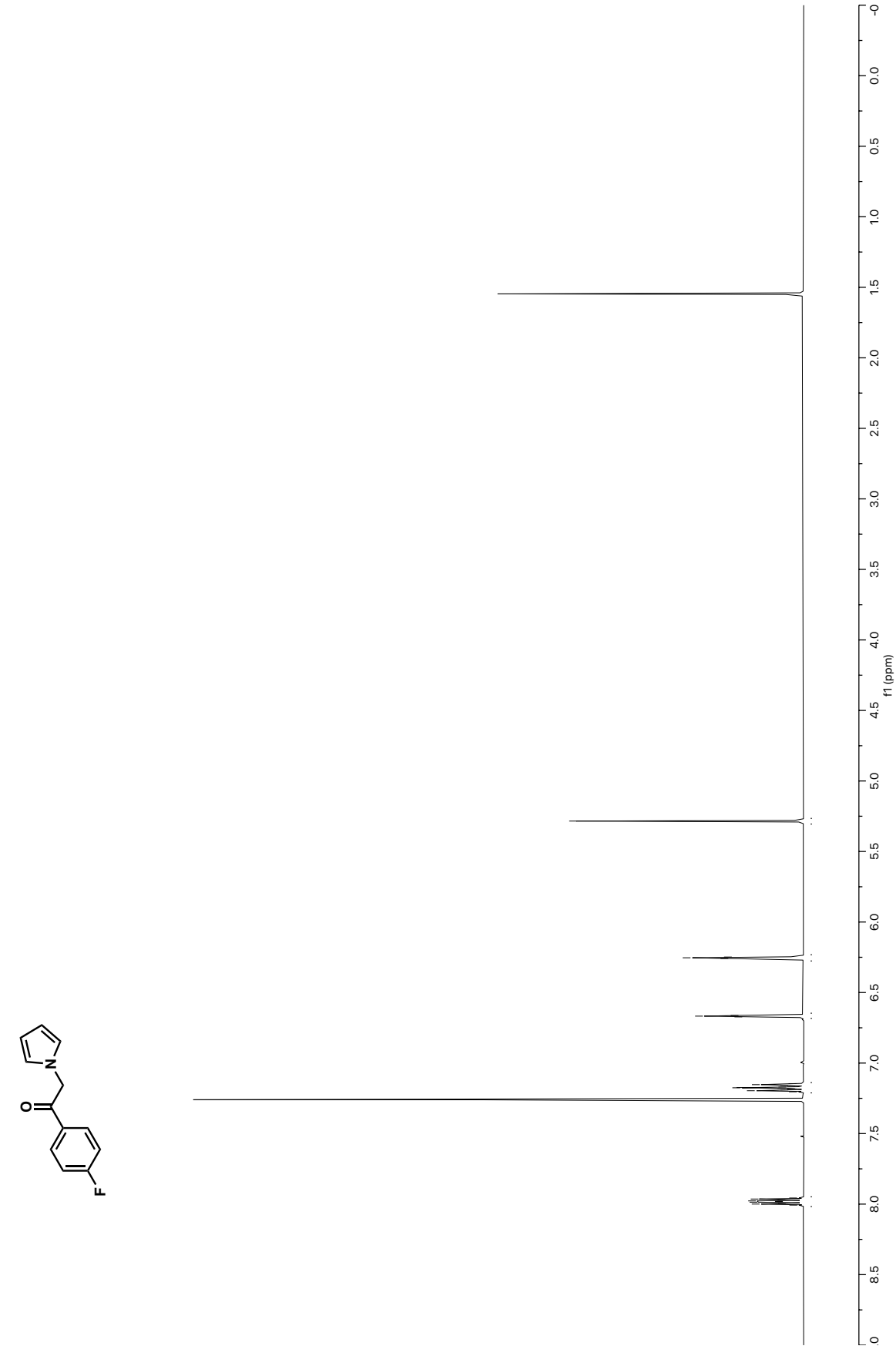



***Figure A9.120*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***108****.*




***A9.121*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***109***.

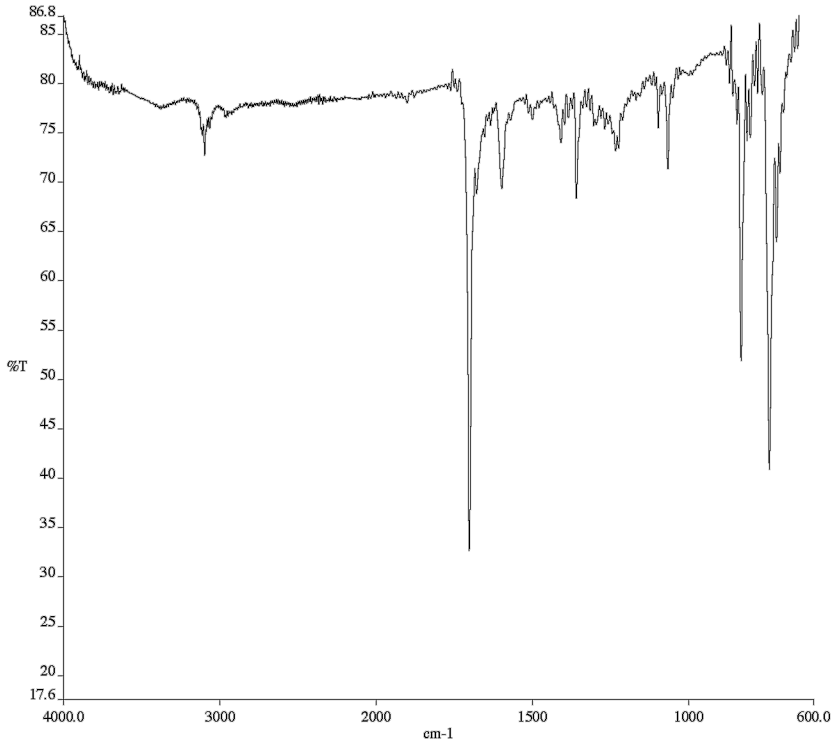



***Figure A9.122*** *Infrared spectrum (Thin Film, NaCl) of compound* ***109***.

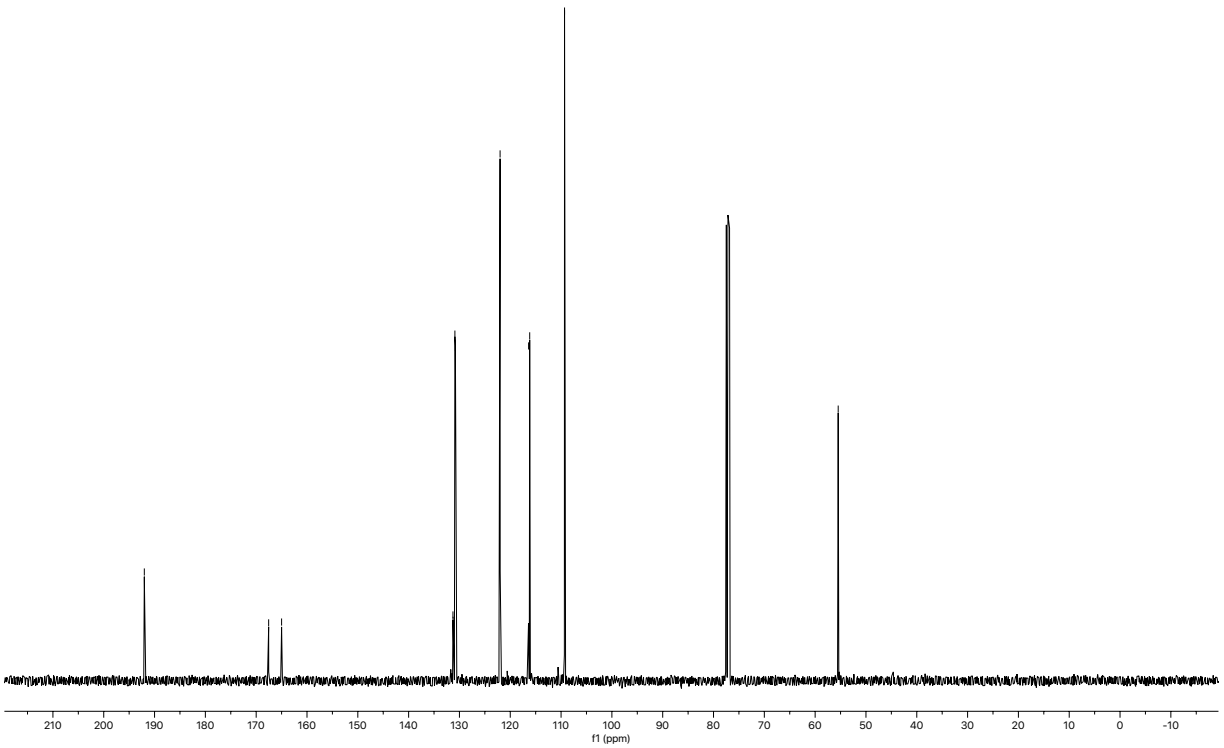



***Figure A9.123*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***109***.

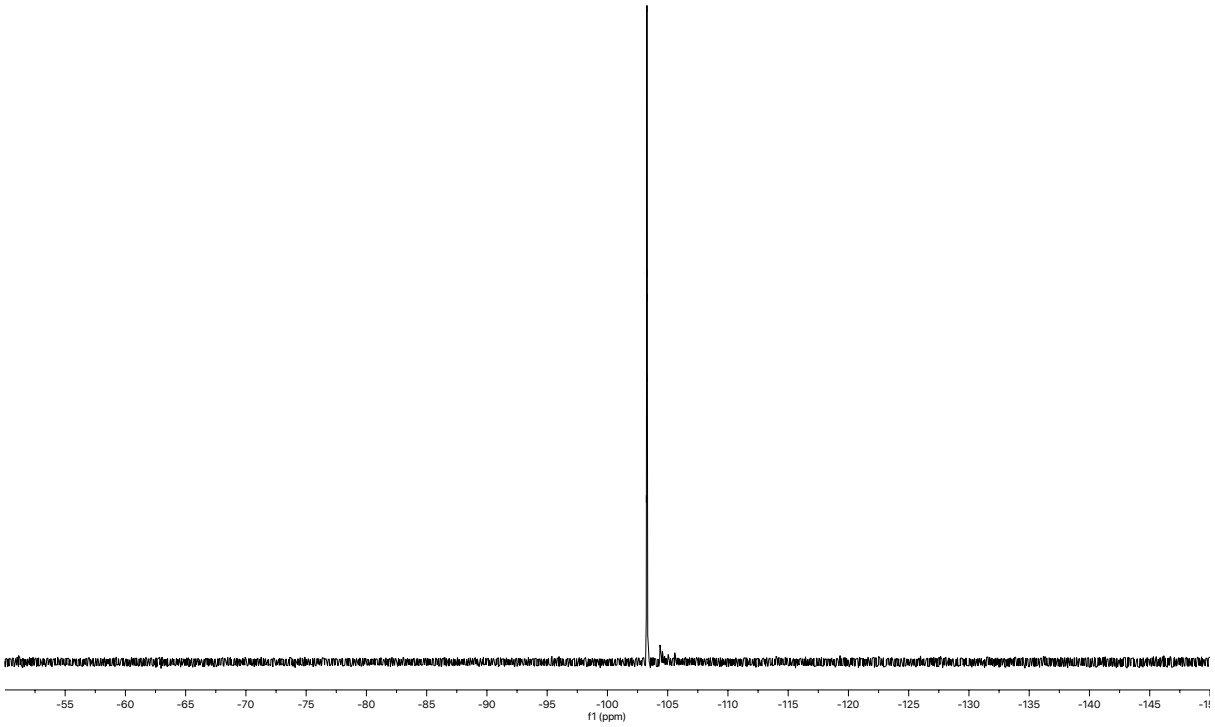
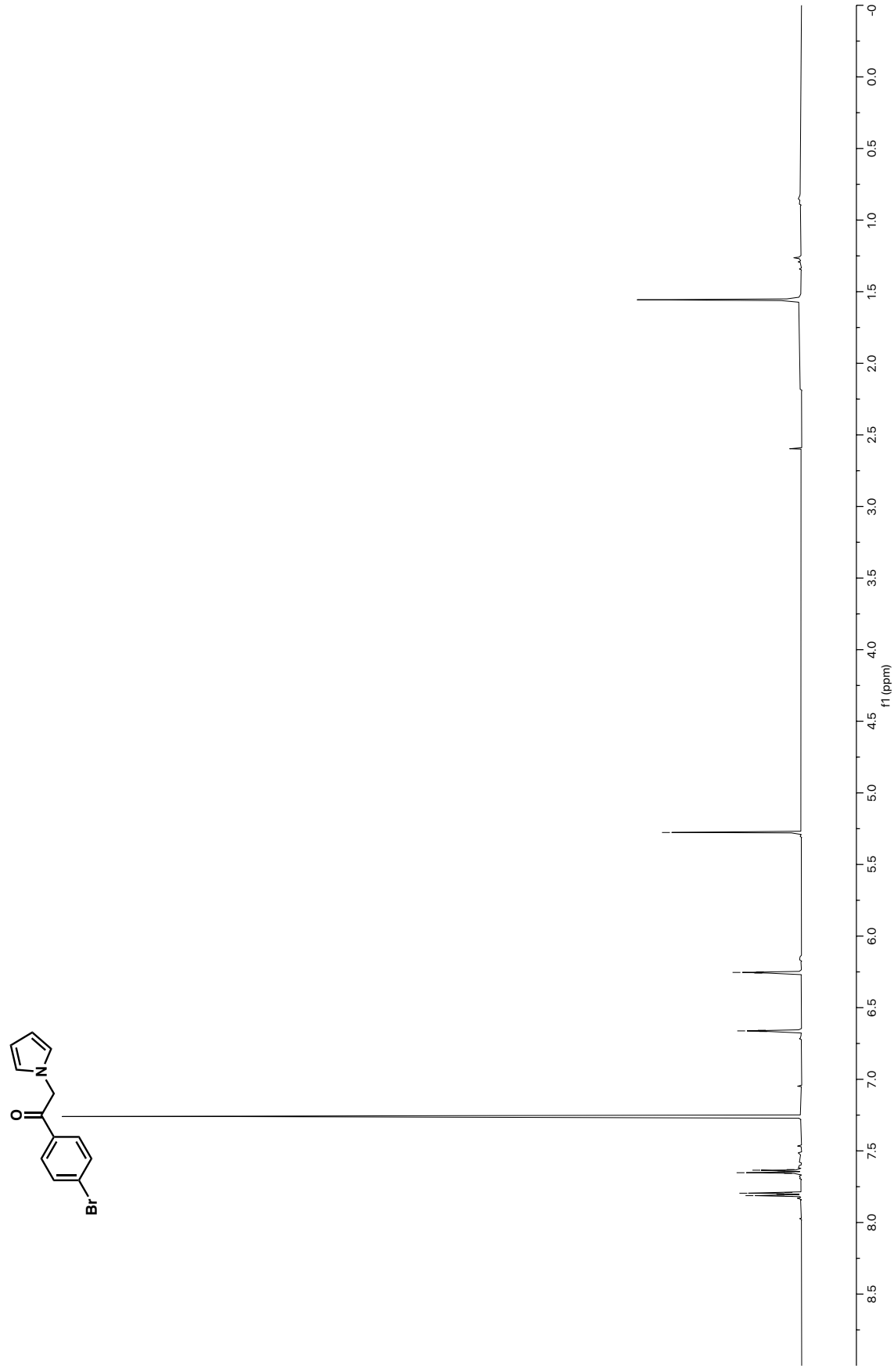
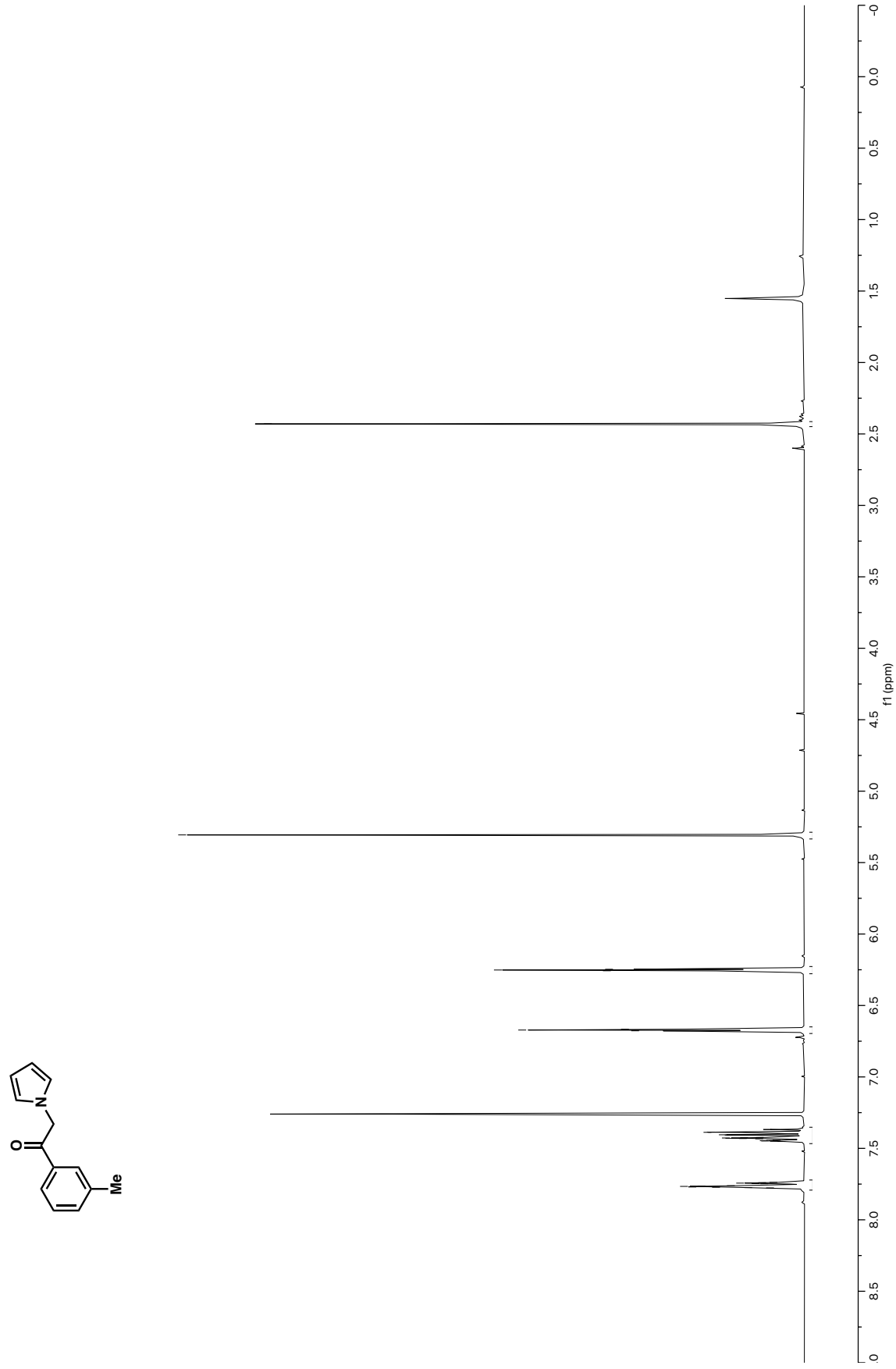



***Figure A9.124*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***109***.




***A9.125*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***110****.*




***A9.126*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***111***.

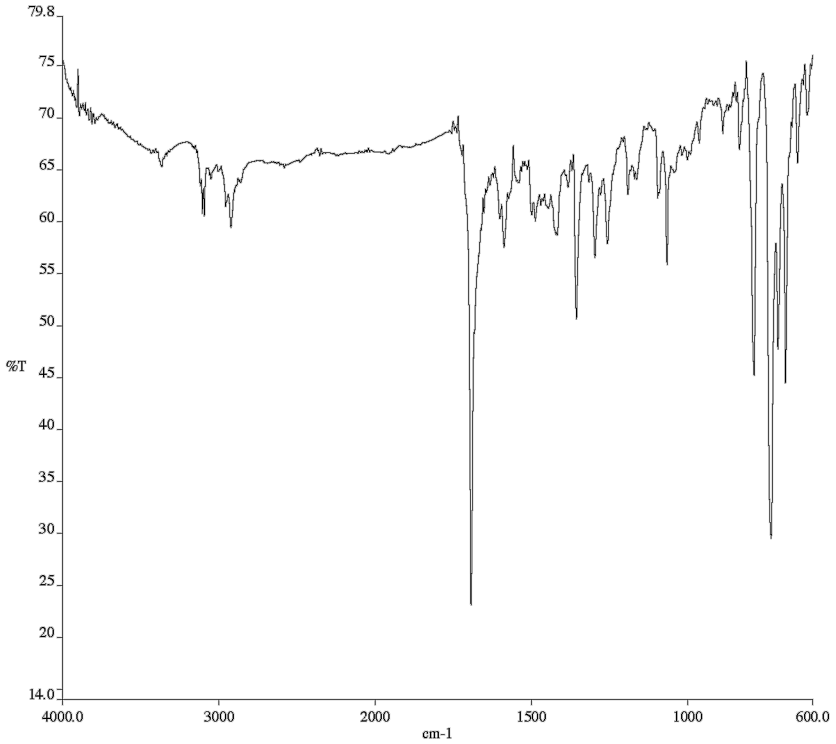



***Figure A9.127*** *Infrared spectrum (Thin Film, NaCl) of compound* ***111***.

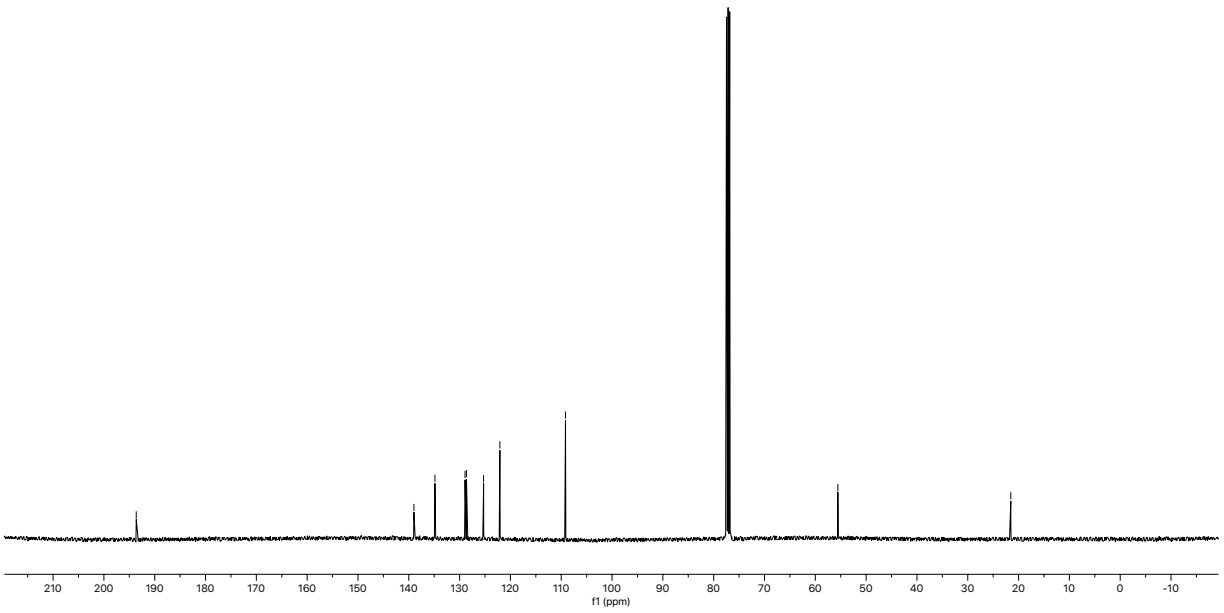
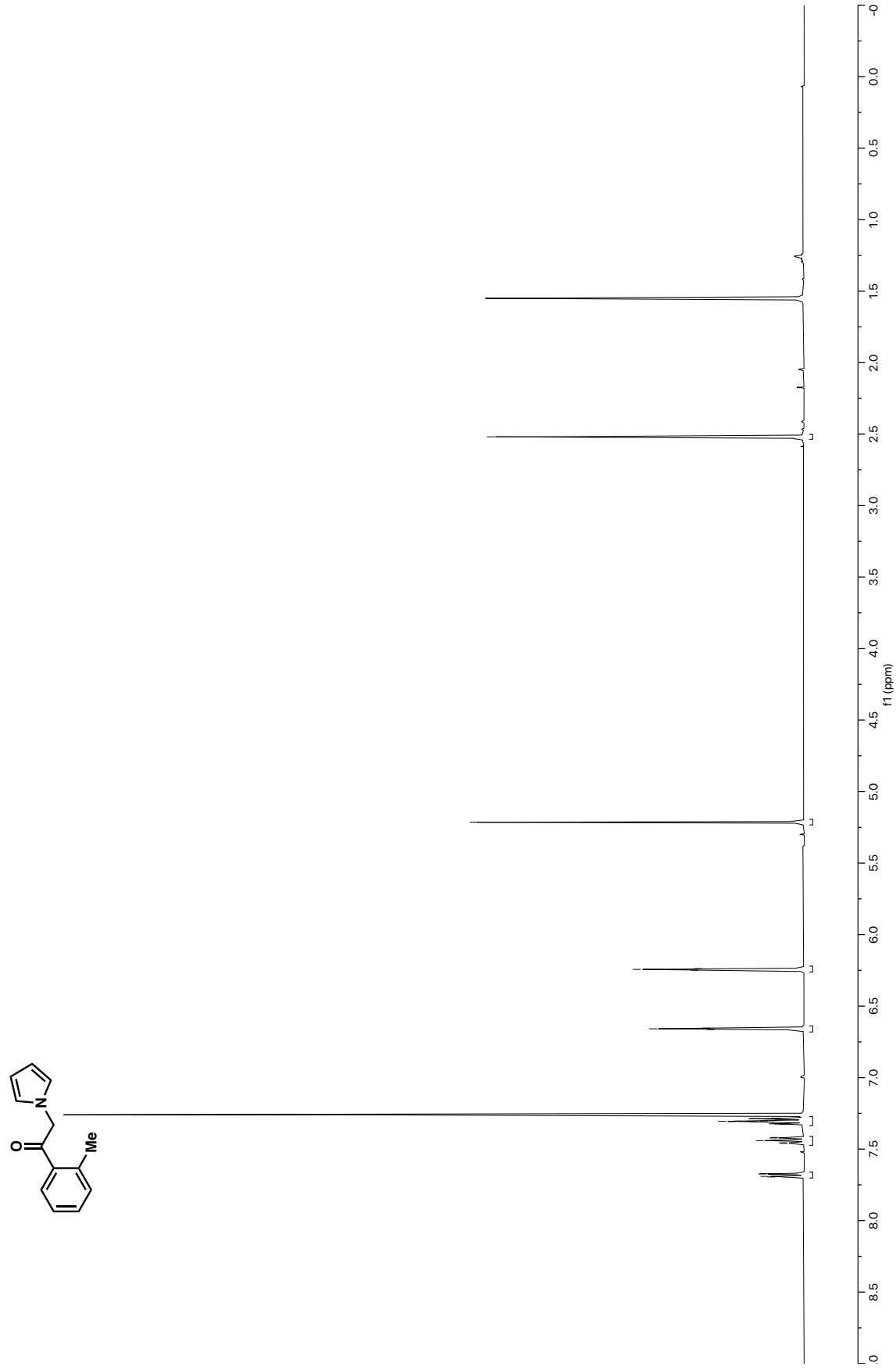



***Figure A9.128*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***111***.




***A9.129*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***112****.*

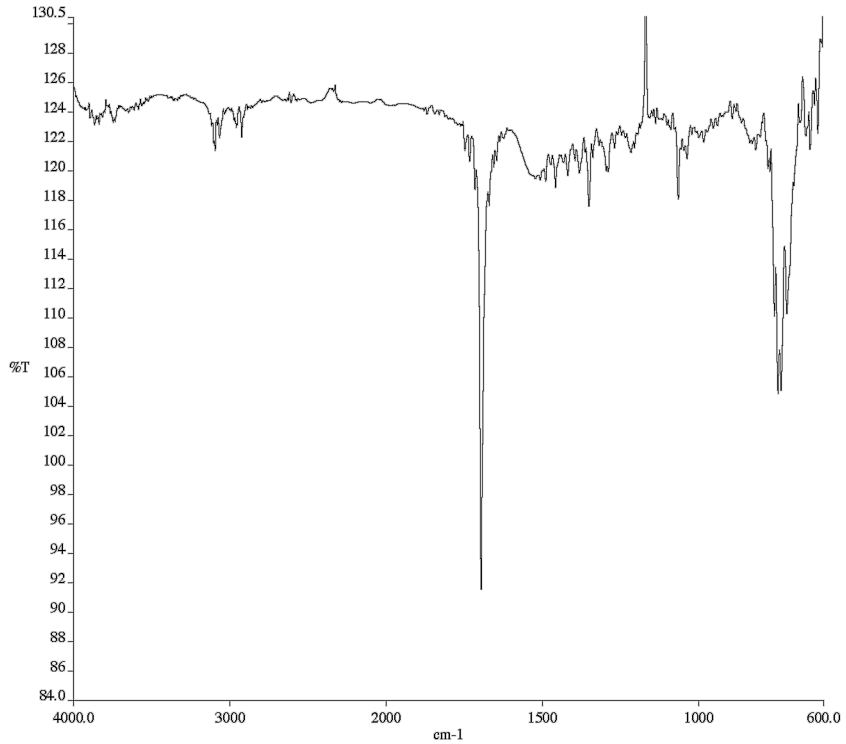



***Figure A9.130*** *Infrared spectrum (Thin Film, NaCl) of compound* ***112***.

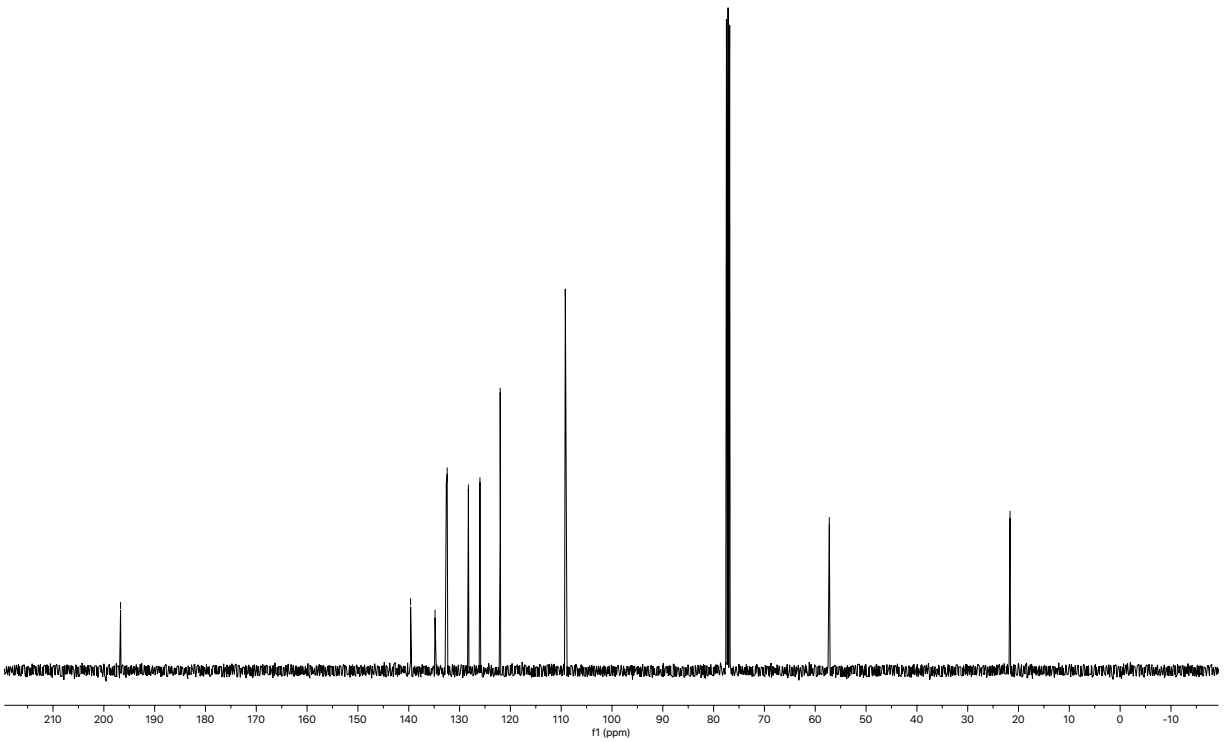
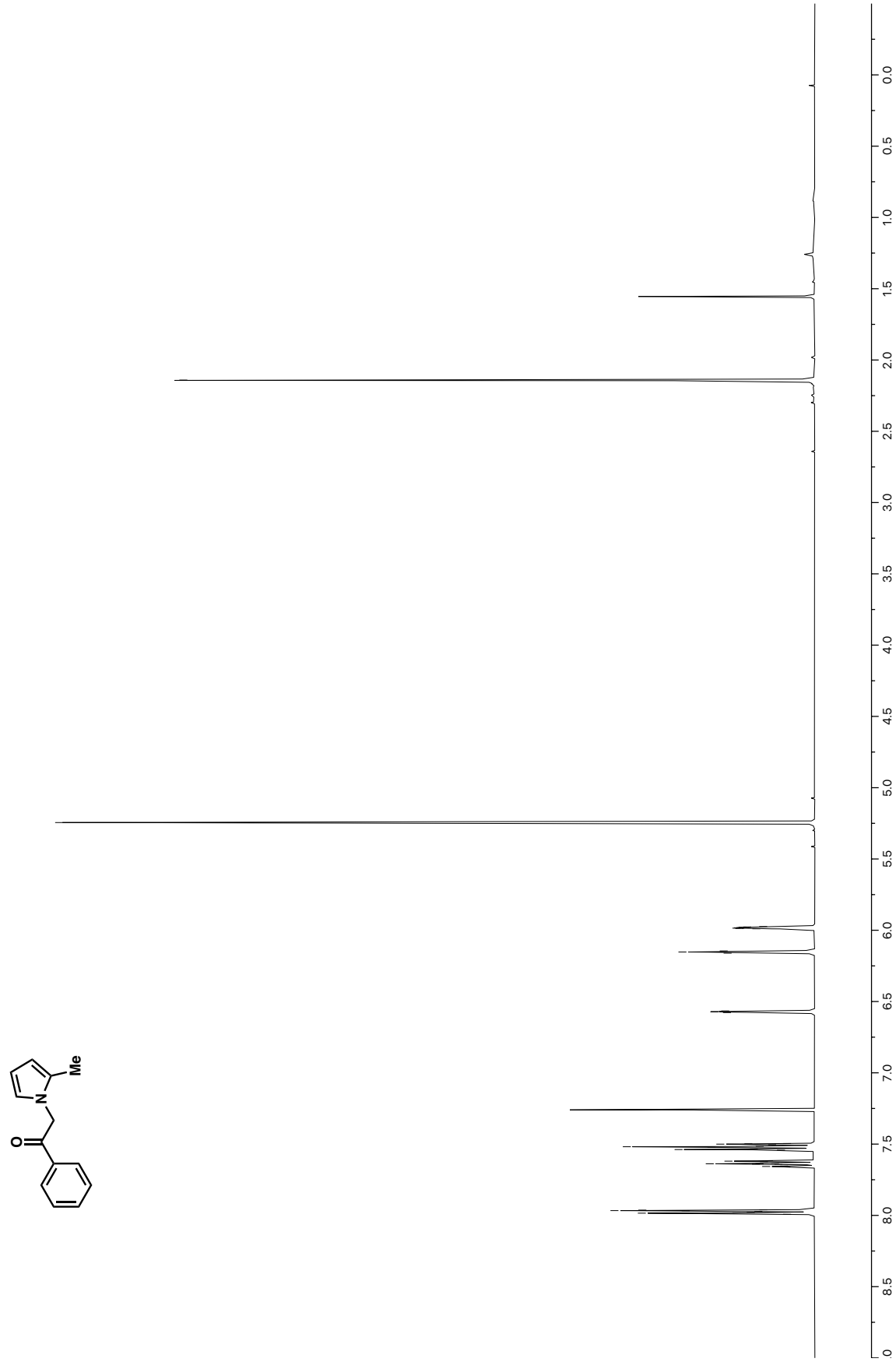



***Figure A9.131*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***112***.




***A9.132*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***113***.

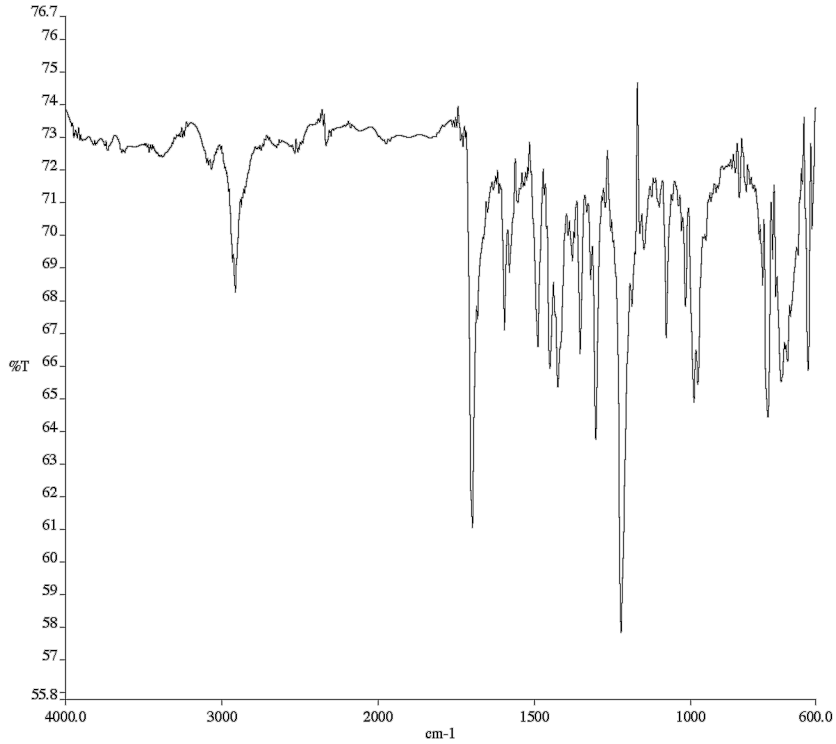



***Figure A9.133*** *Infrared spectrum (Thin Film, NaCl) of compound* ***113***.

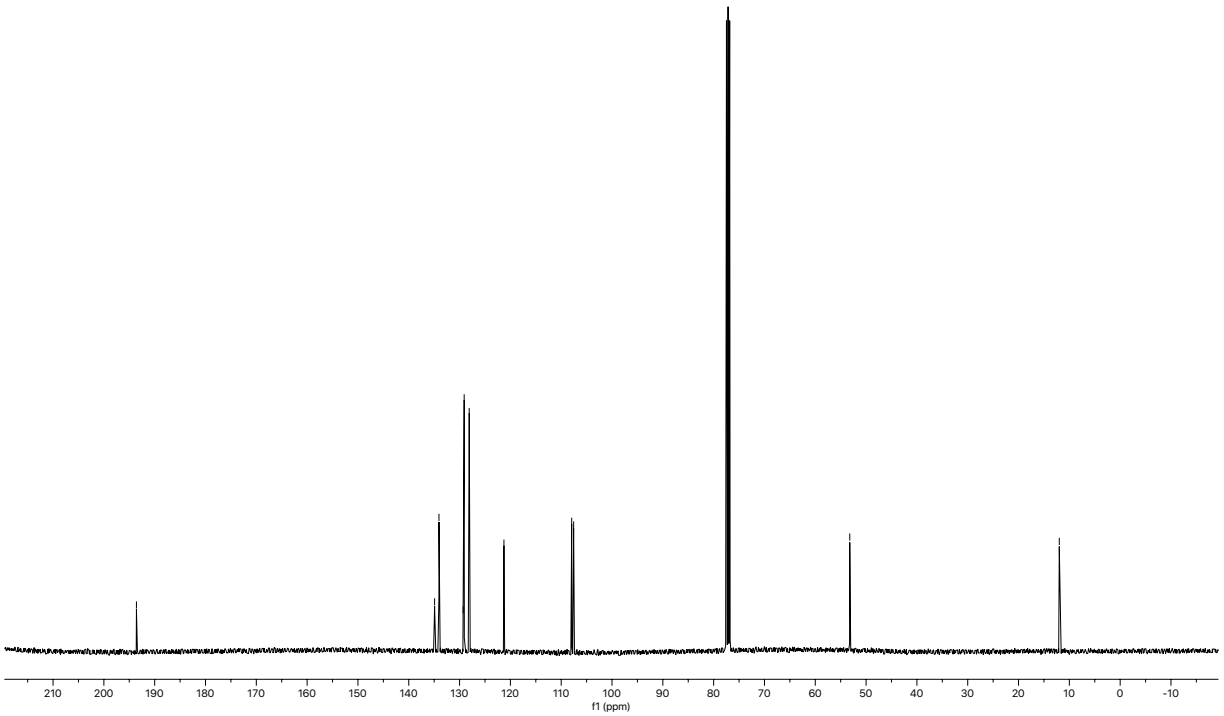
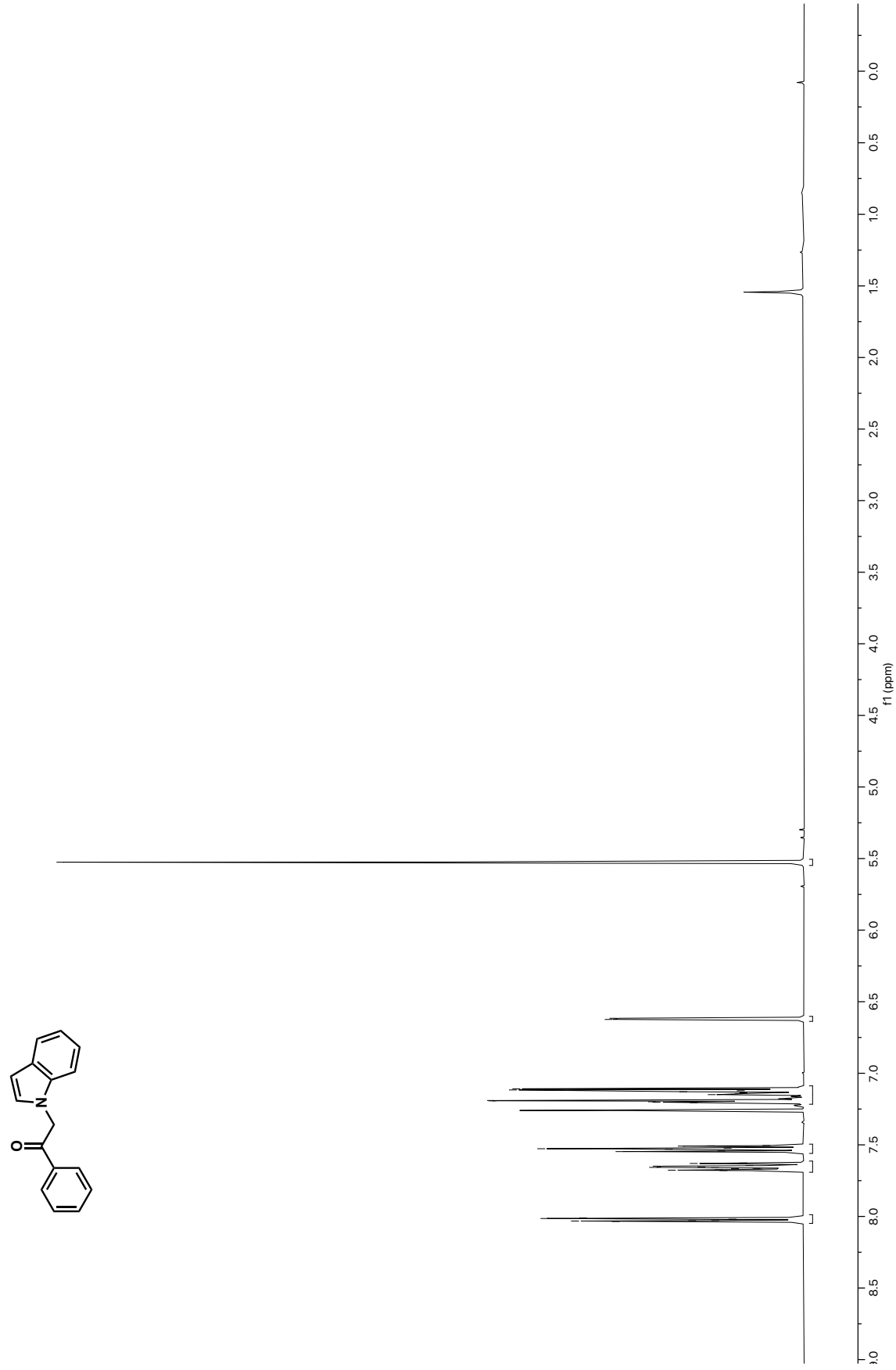
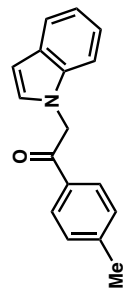
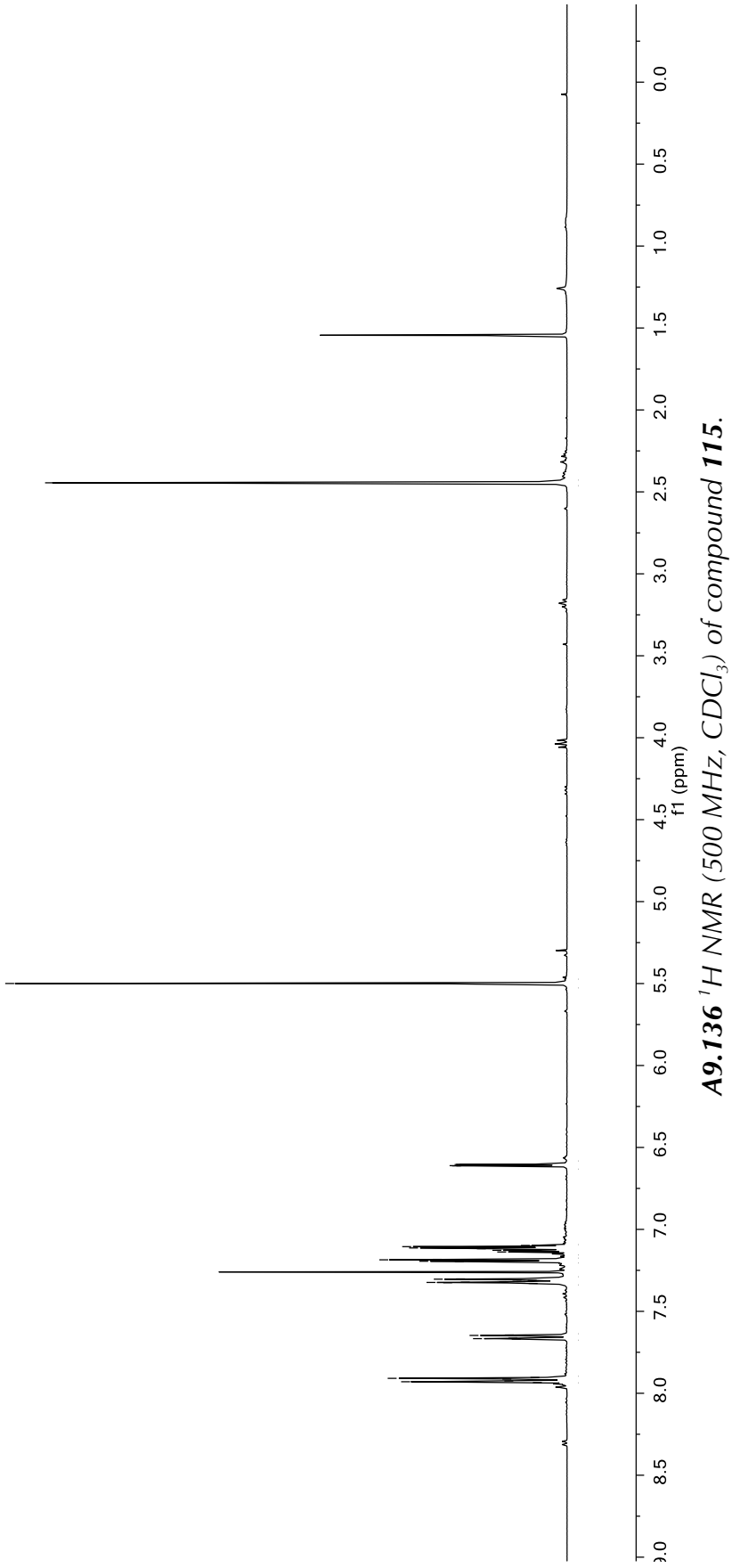



***Figure A9.134*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***113***.




***A9.135*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***114****.*




***A9.136*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***115***.

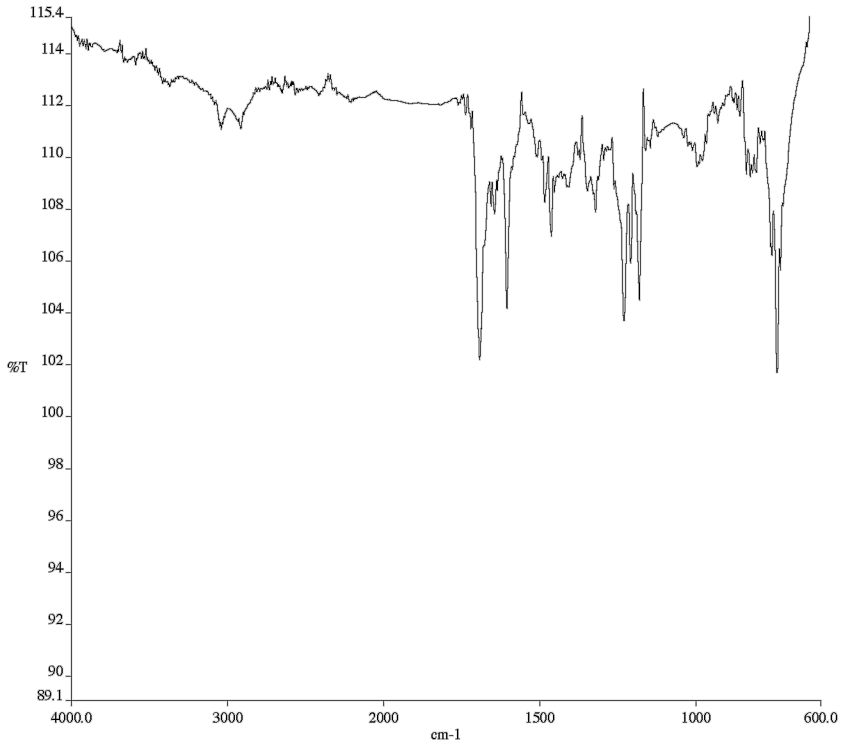



***Figure A9.137*** *Infrared spectrum (Thin Film, NaCl) of compound* ***115***.

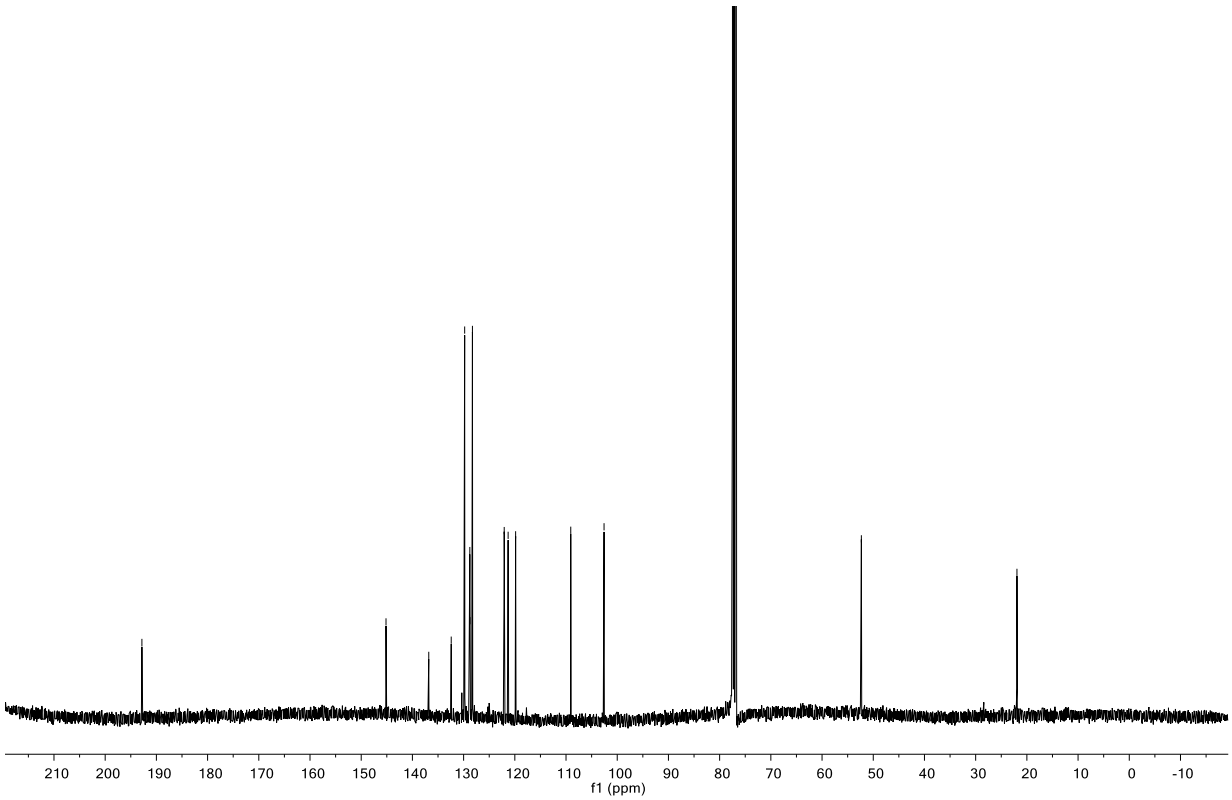
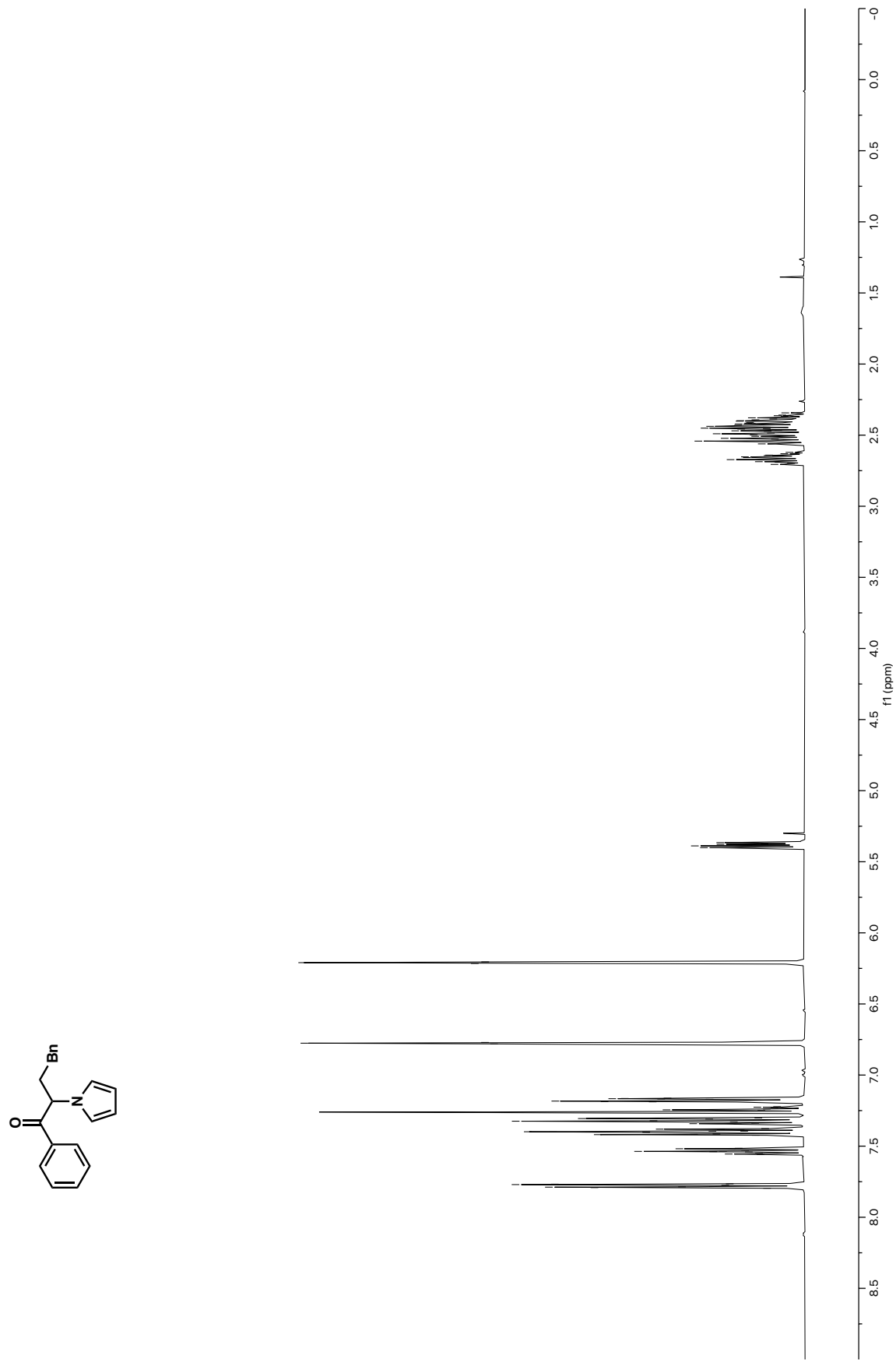



***Figure A9.138*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***115***.




***A9.139*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***116****.*

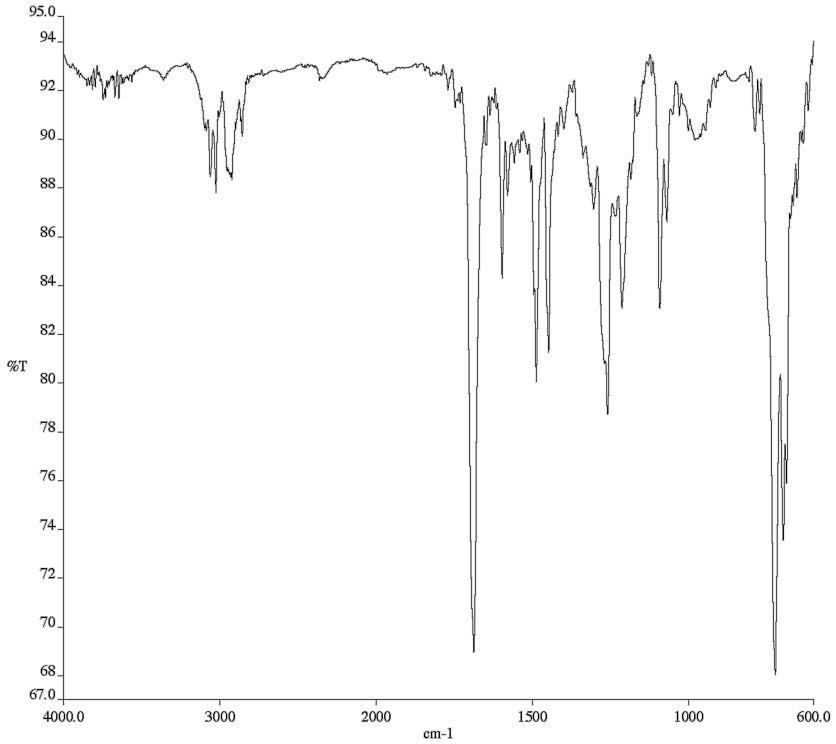



***Figure A9.140*** *Infrared spectrum (Thin Film, NaCl) of compound* ***116***.

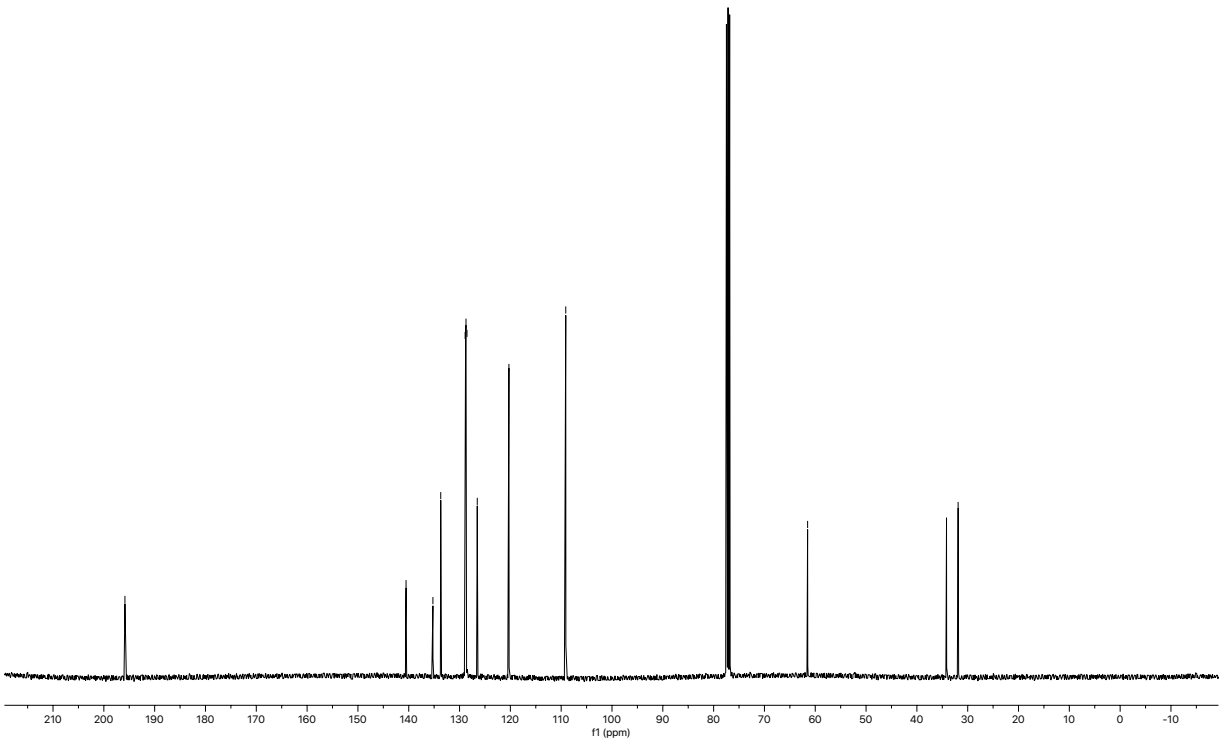
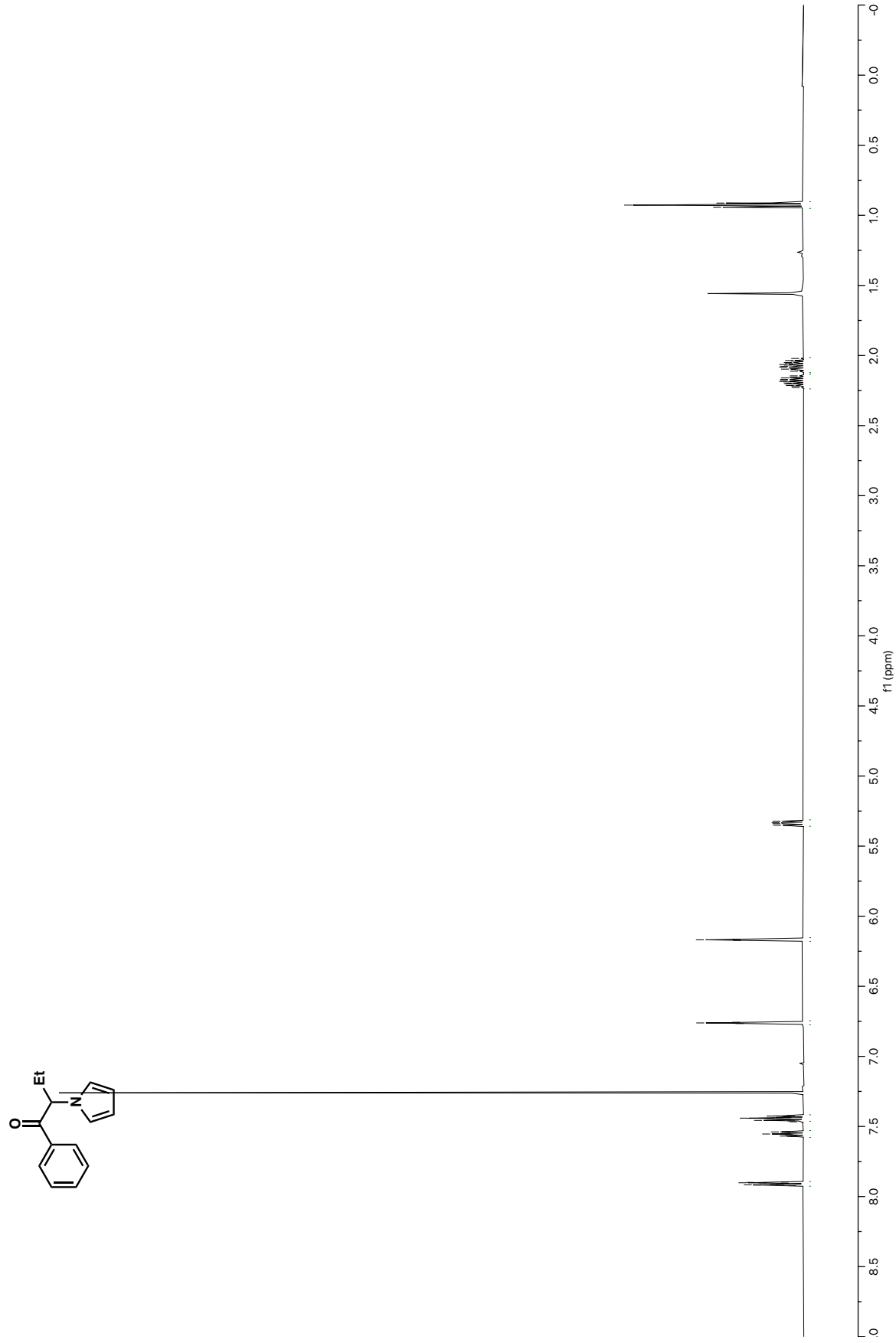



***Figure A9.141*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***116***.




***A9.142*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***117****.*

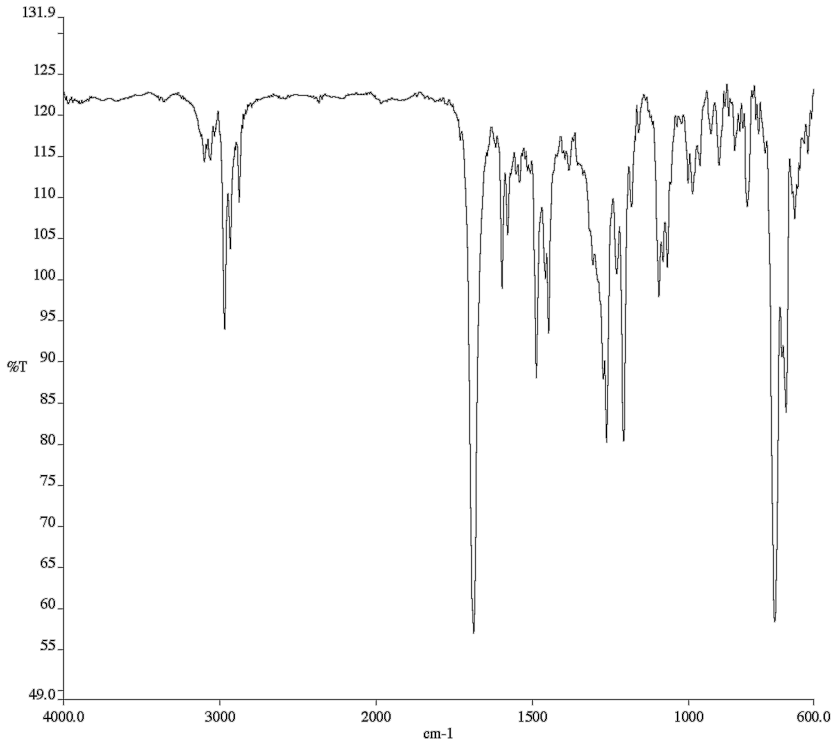



***Figure A9.143*** *Infrared spectrum (Thin Film, NaCl) of compound* ***117****.*

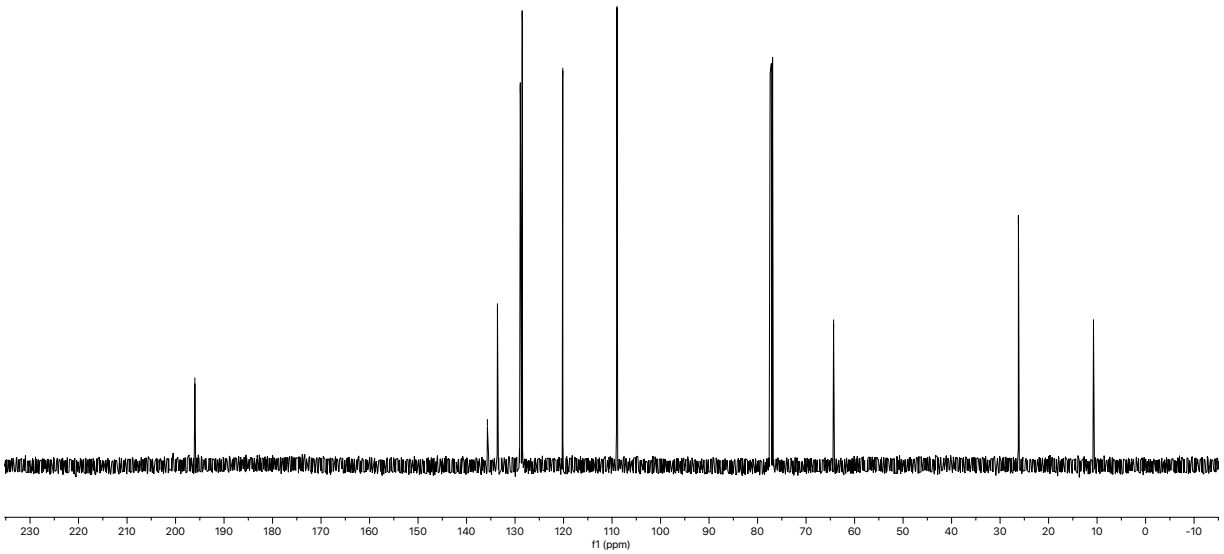



***Figure A9.144*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***117****.*

***A9.145*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***118****.*

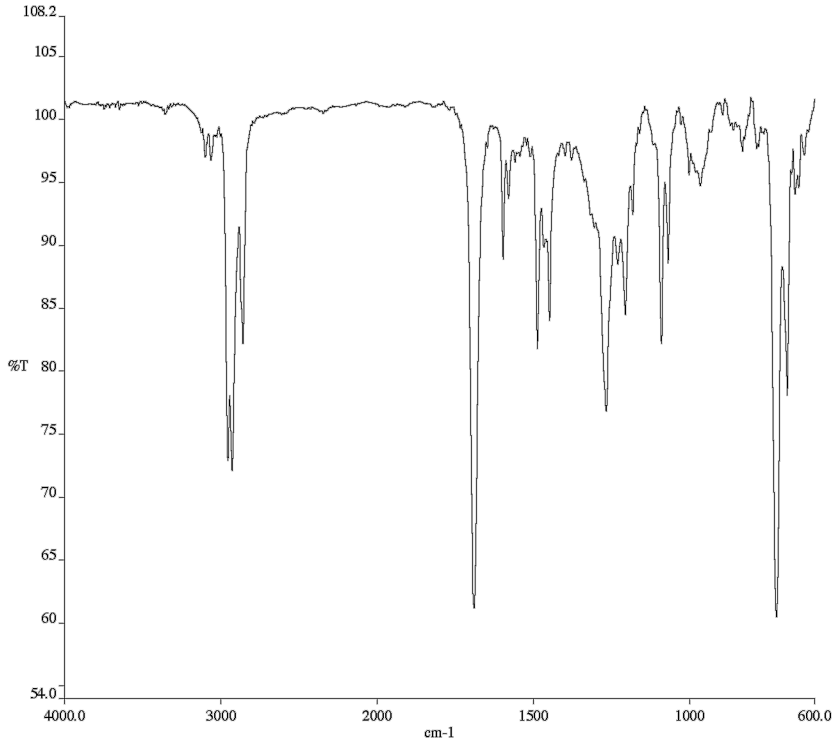



***Figure A9.146*** *Infrared spectrum (Thin Film, NaCl) of compound* ***118****.*

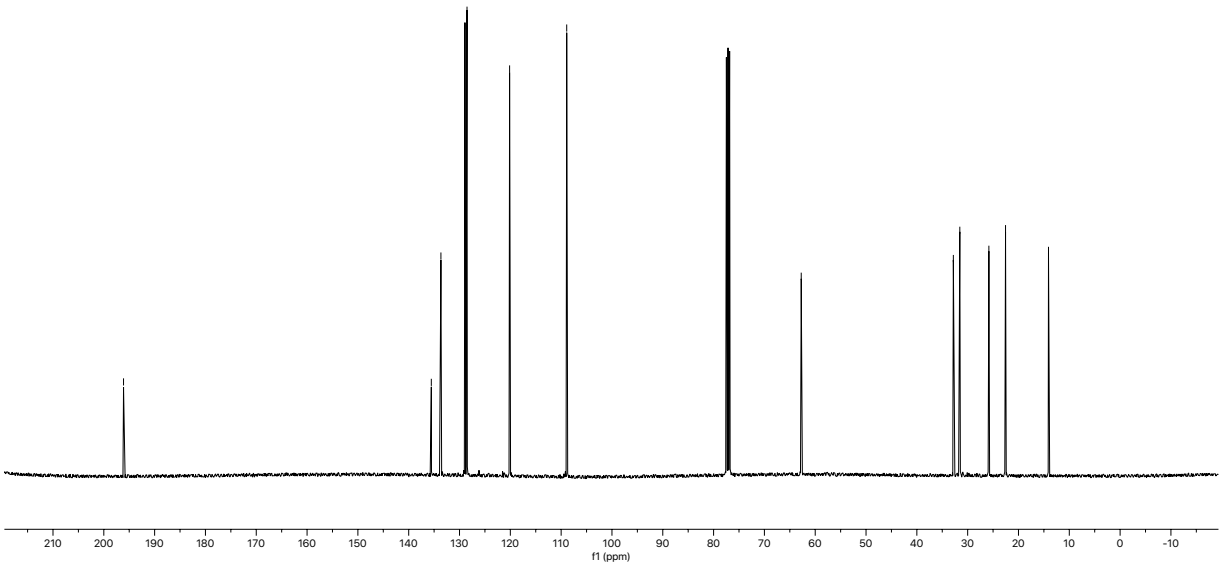
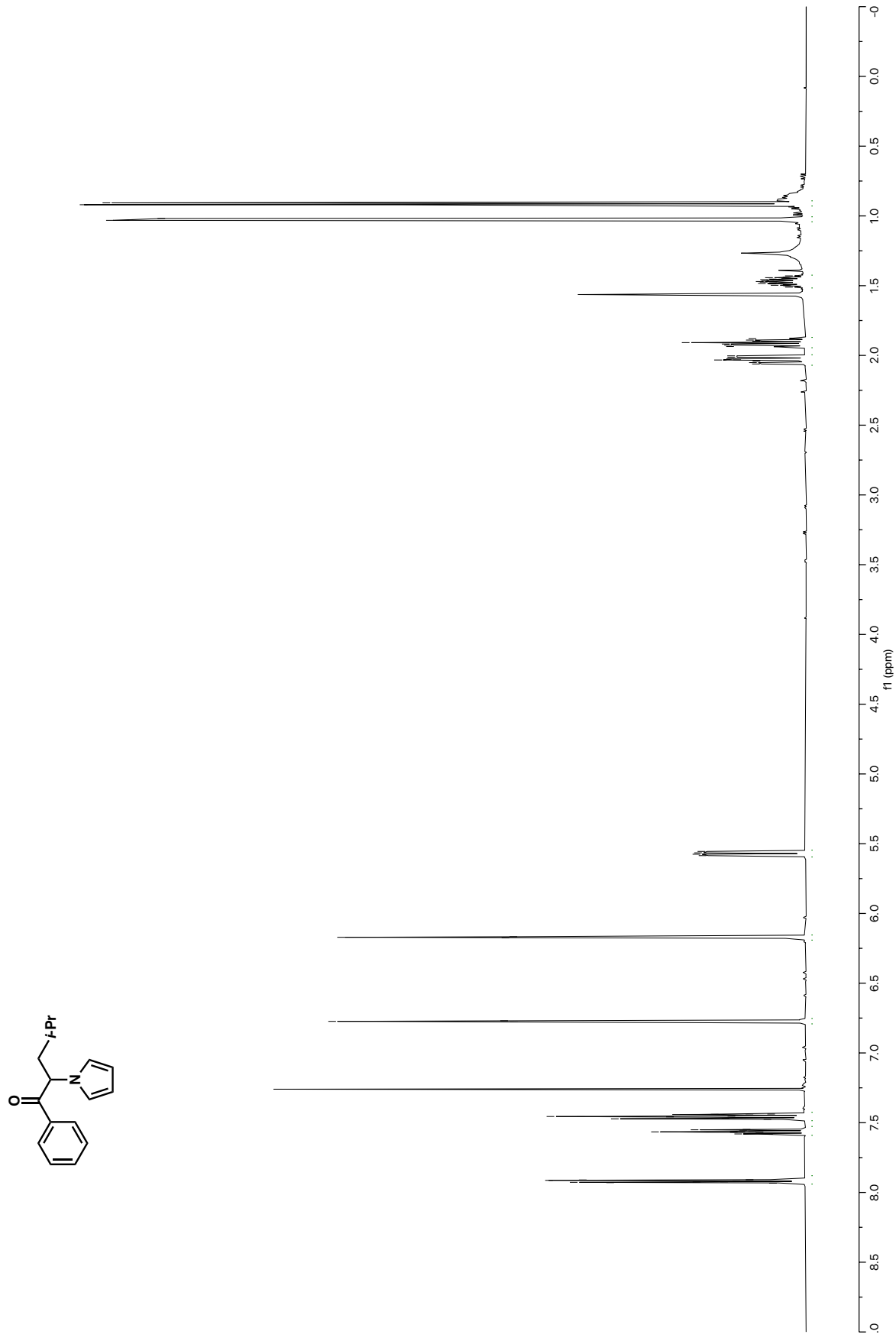



***Figure A9.147*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***118****.*




***A9.148*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***119***.

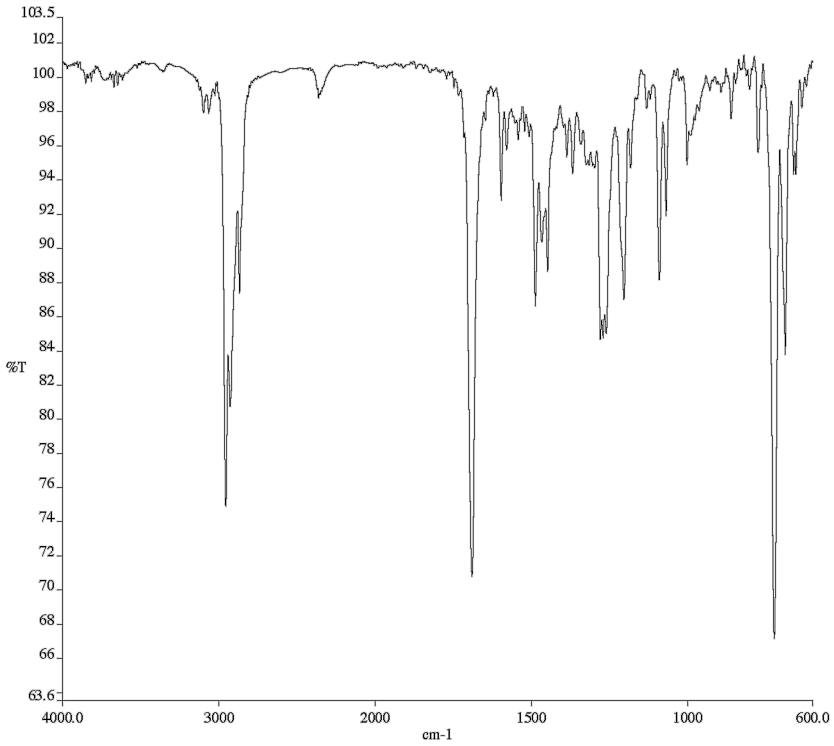



***Figure A9.149*** *Infrared spectrum (Thin Film, NaCl) of compound* ***119***.

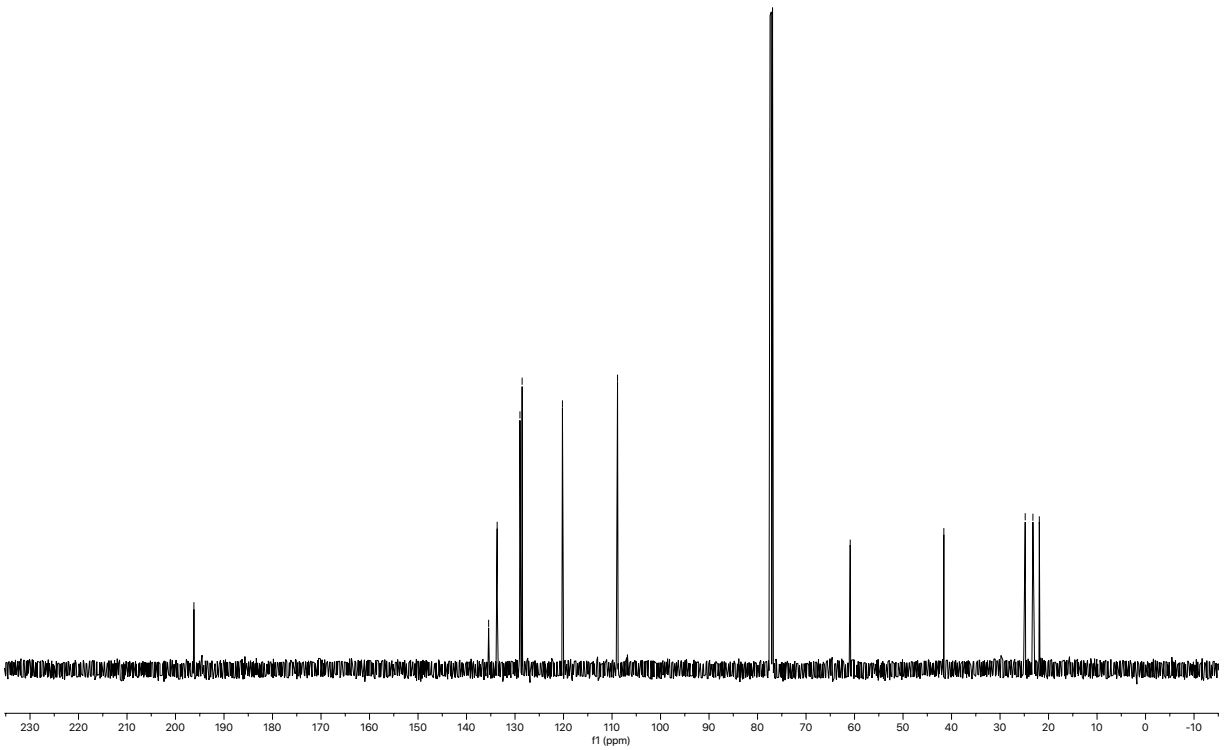
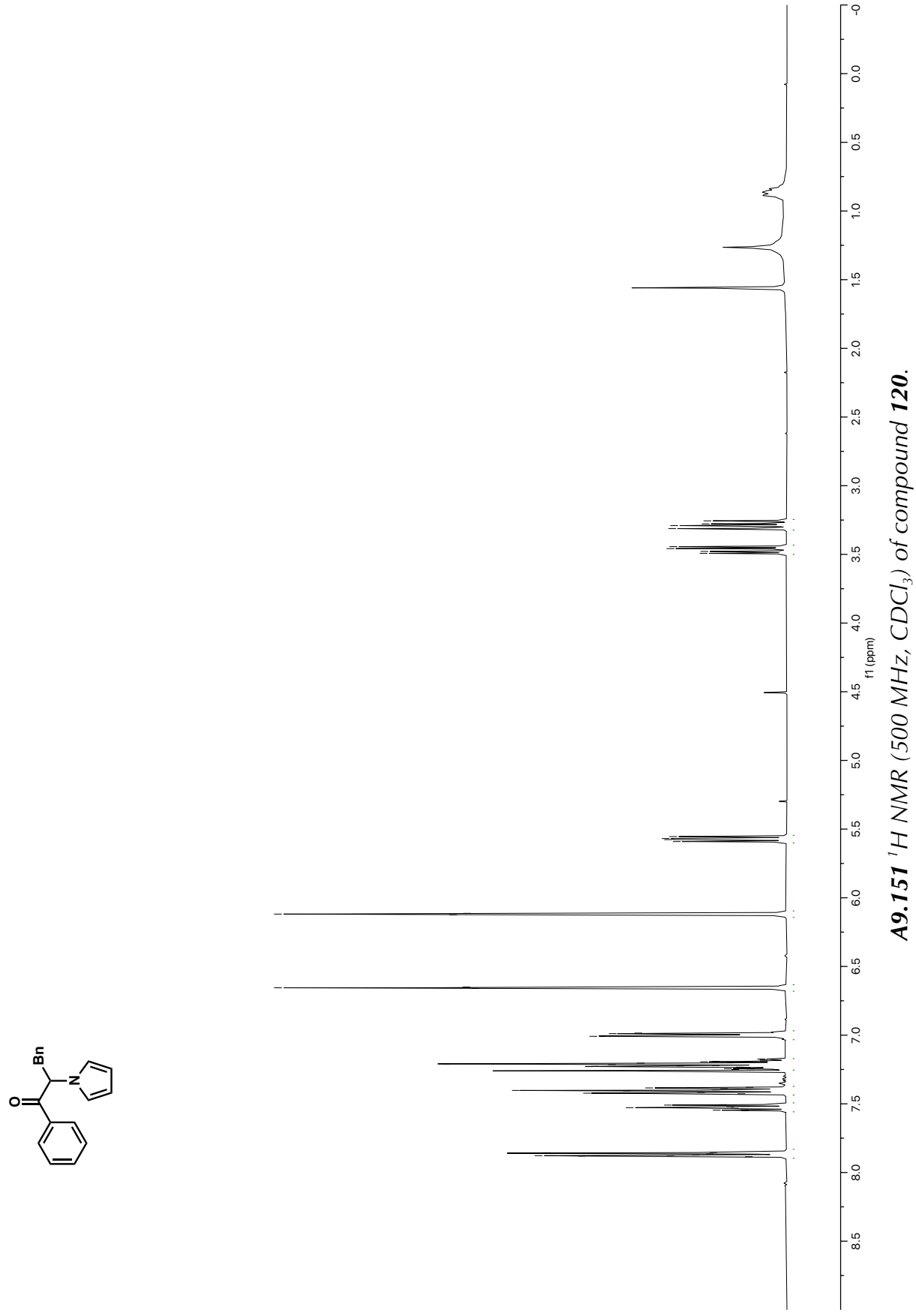



***Figure A9.150*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***119***.




***A9.151*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***120***.

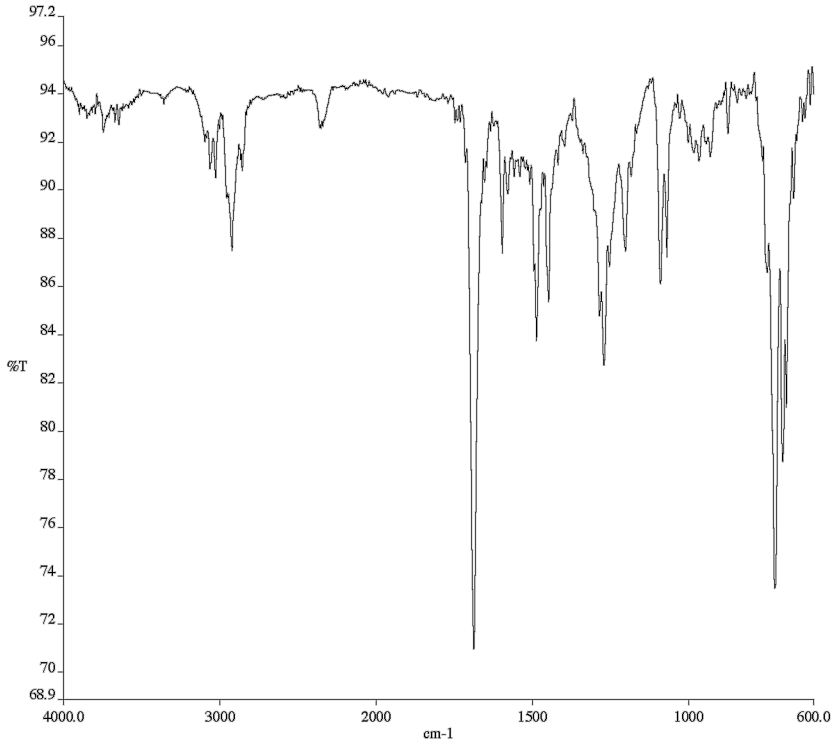



***Figure A9.152*** *Infrared spectrum (Thin Film, NaCl) of compound* ***120***.

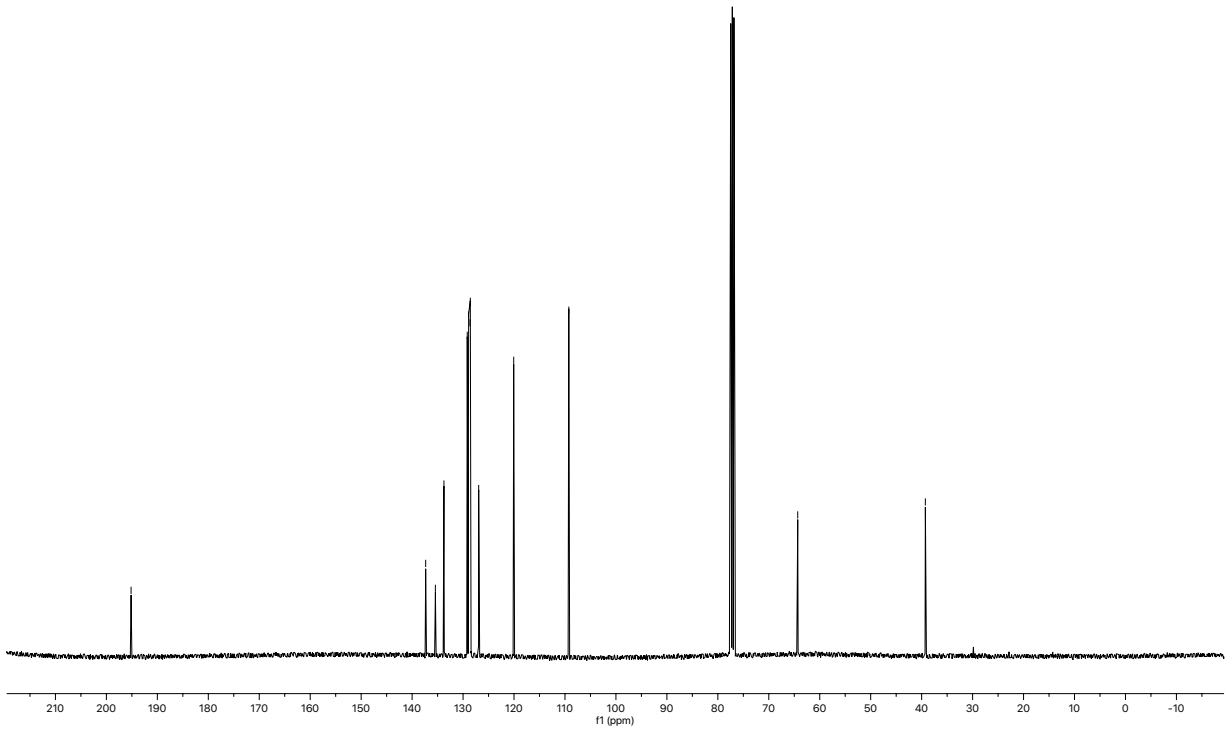
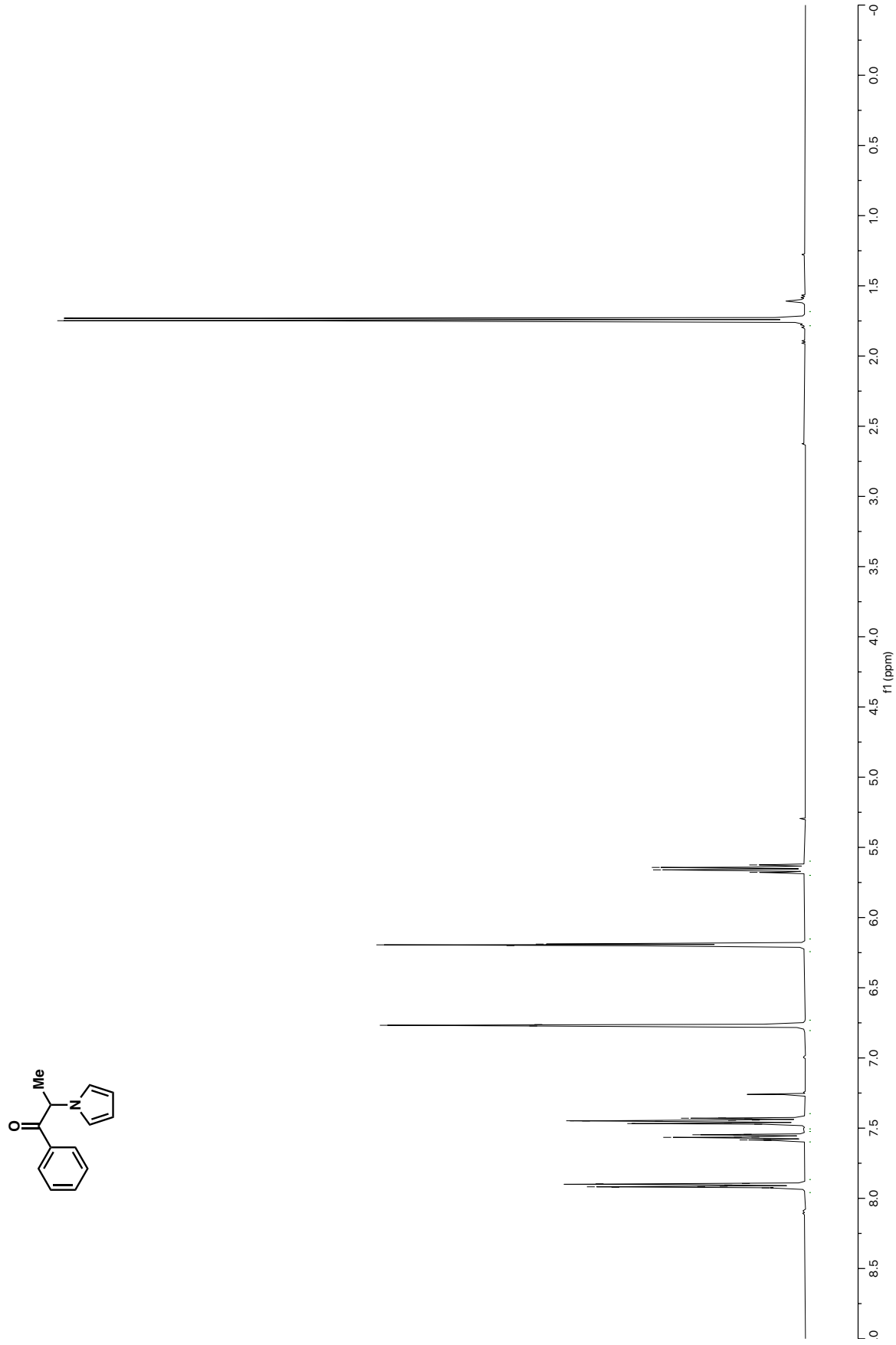



***Figure A9.153*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***120***.




***A9.154*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***121***.

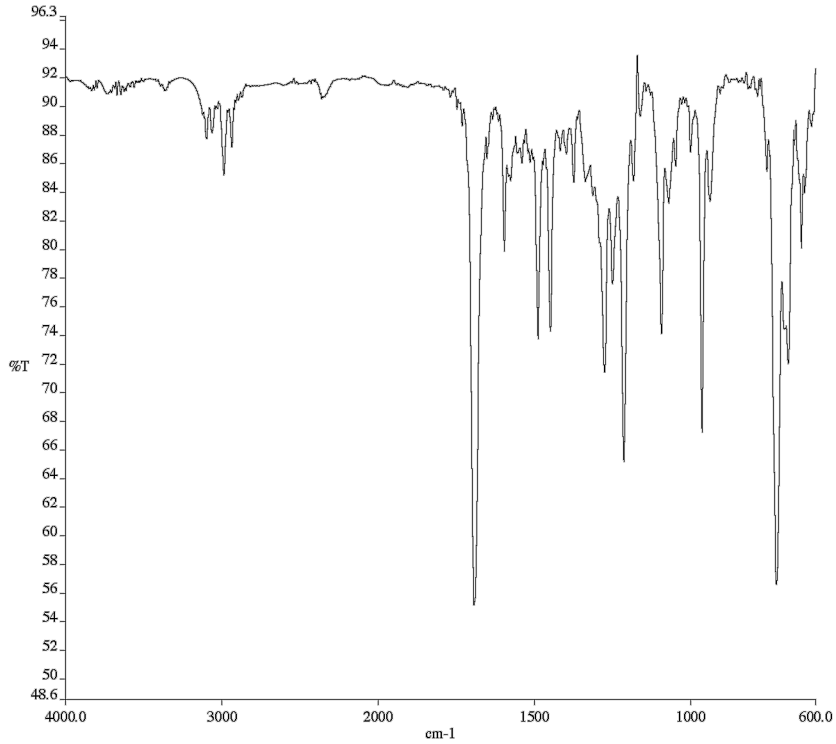



***Figure A9.155*** *Infrared spectrum (Thin Film, NaCl) of compound* ***121***.

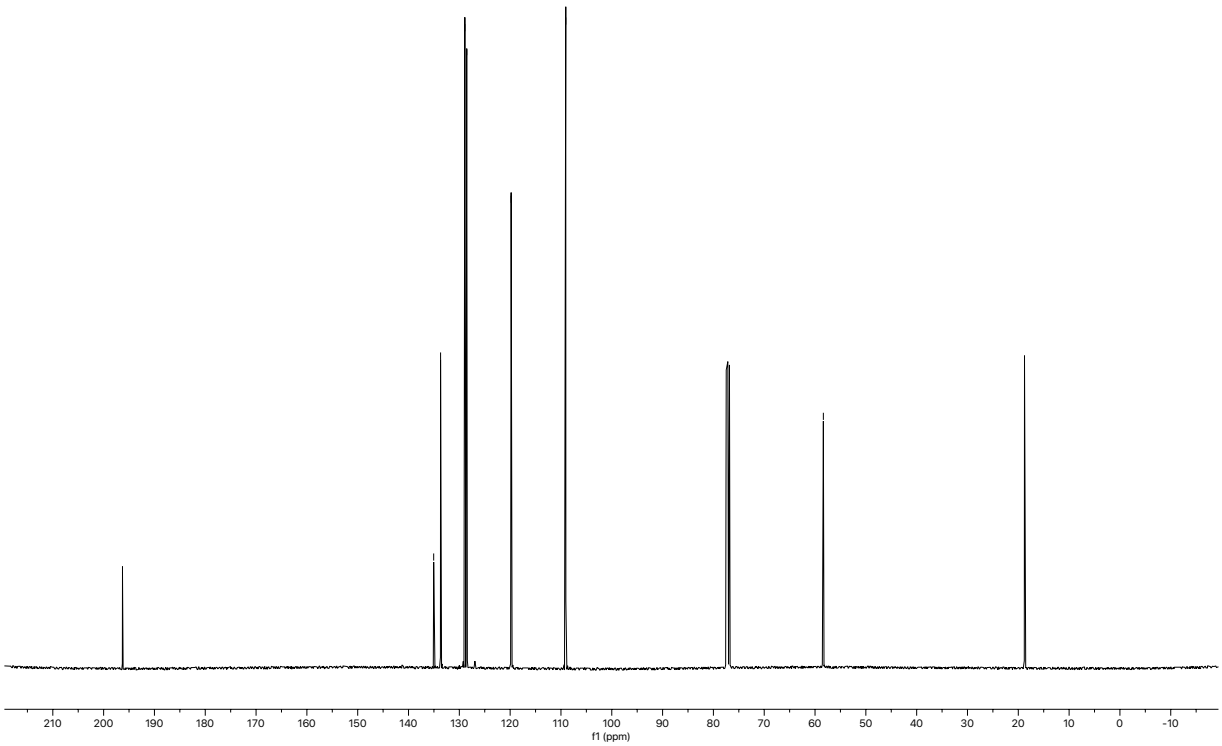
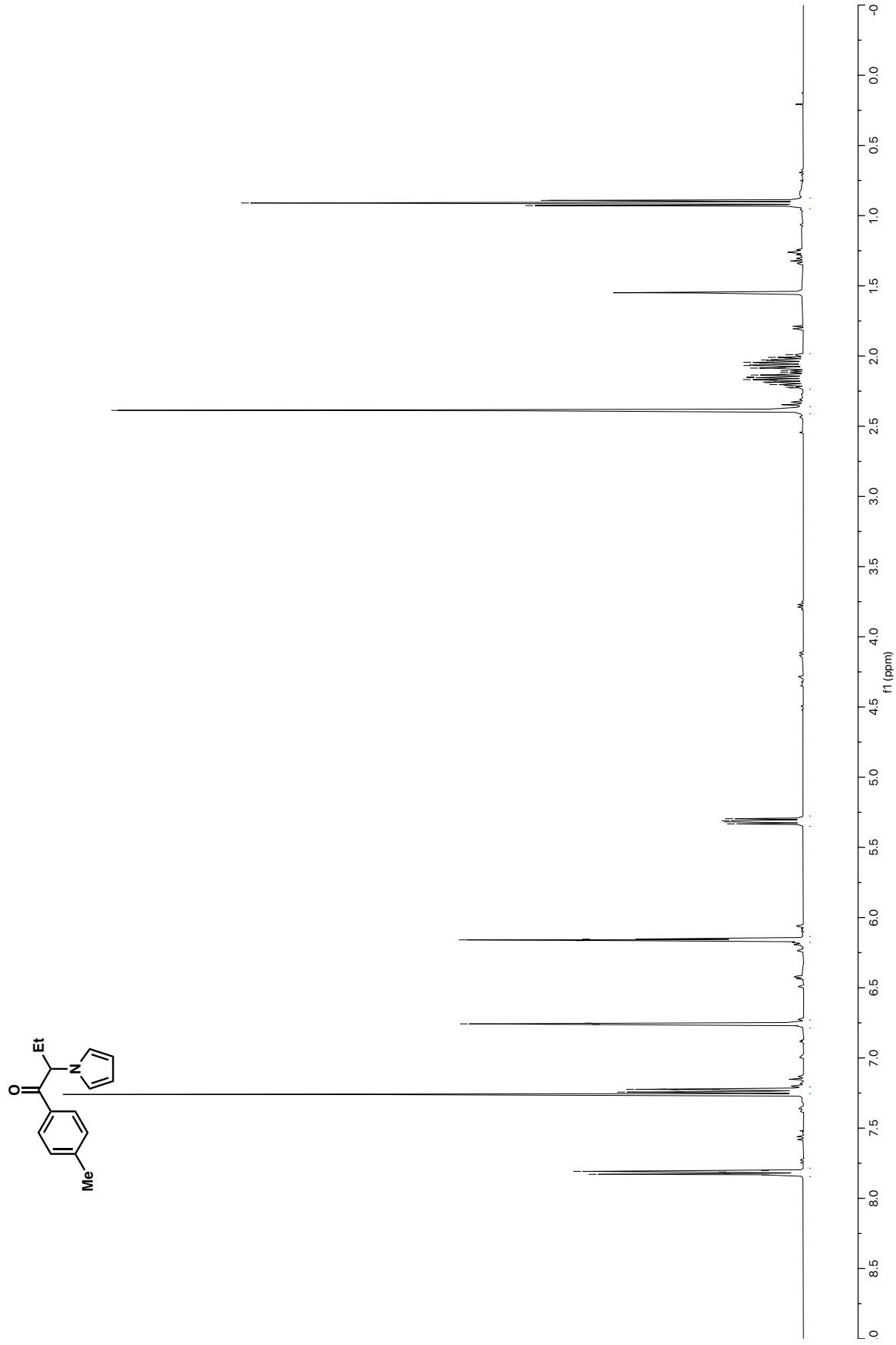



***Figure A9.156*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***121***.




***A9.157*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***122***.

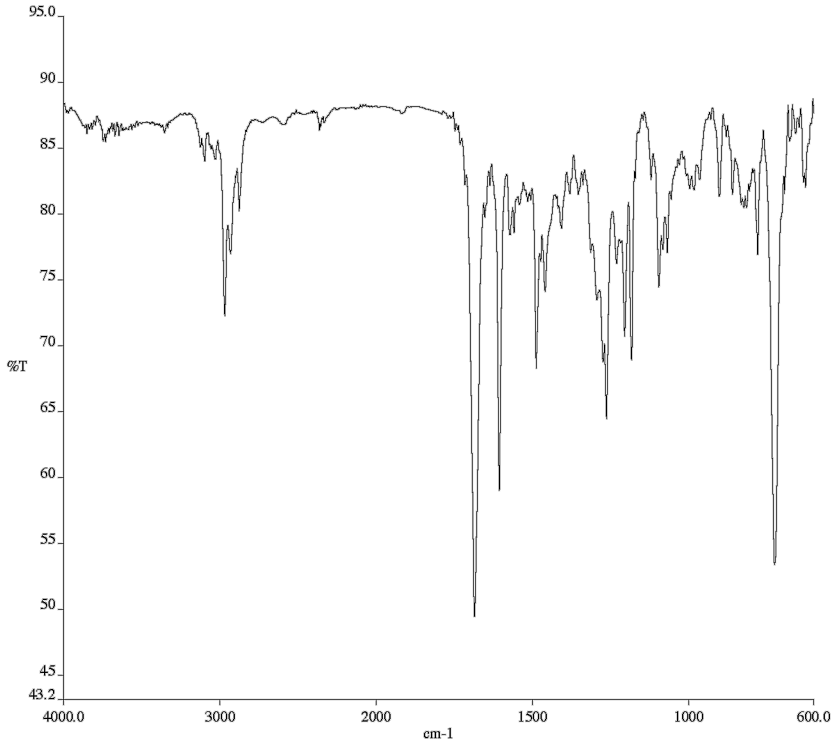



***Figure A9.158*** *Infrared spectrum (Thin Film, NaCl) of compound* ***122***.

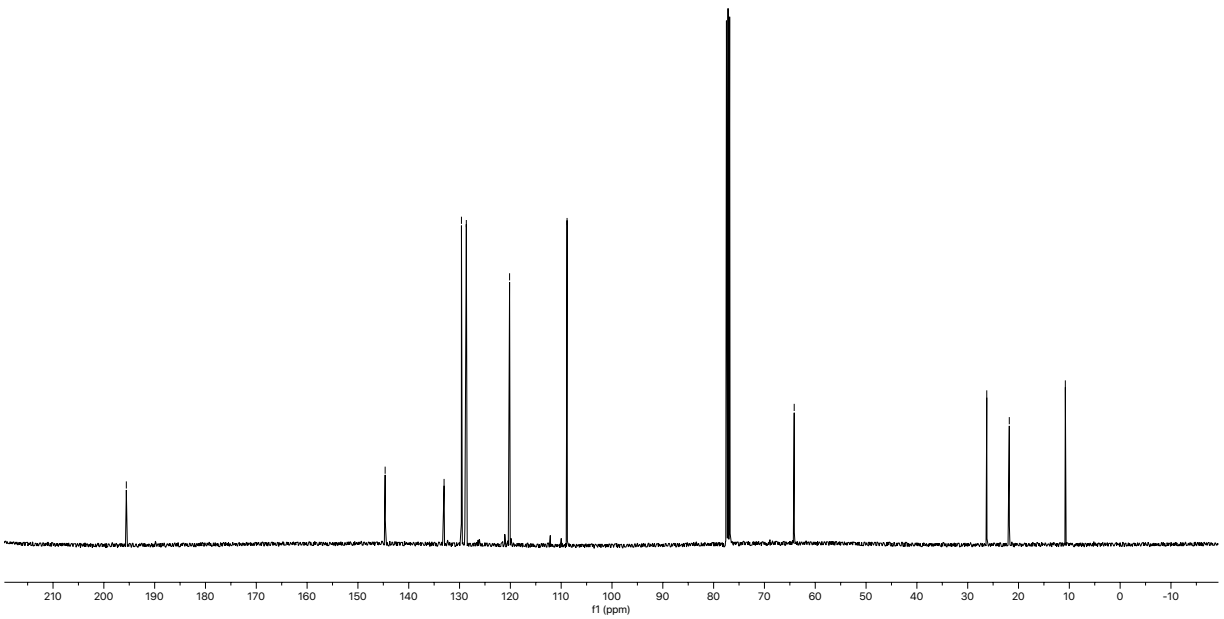
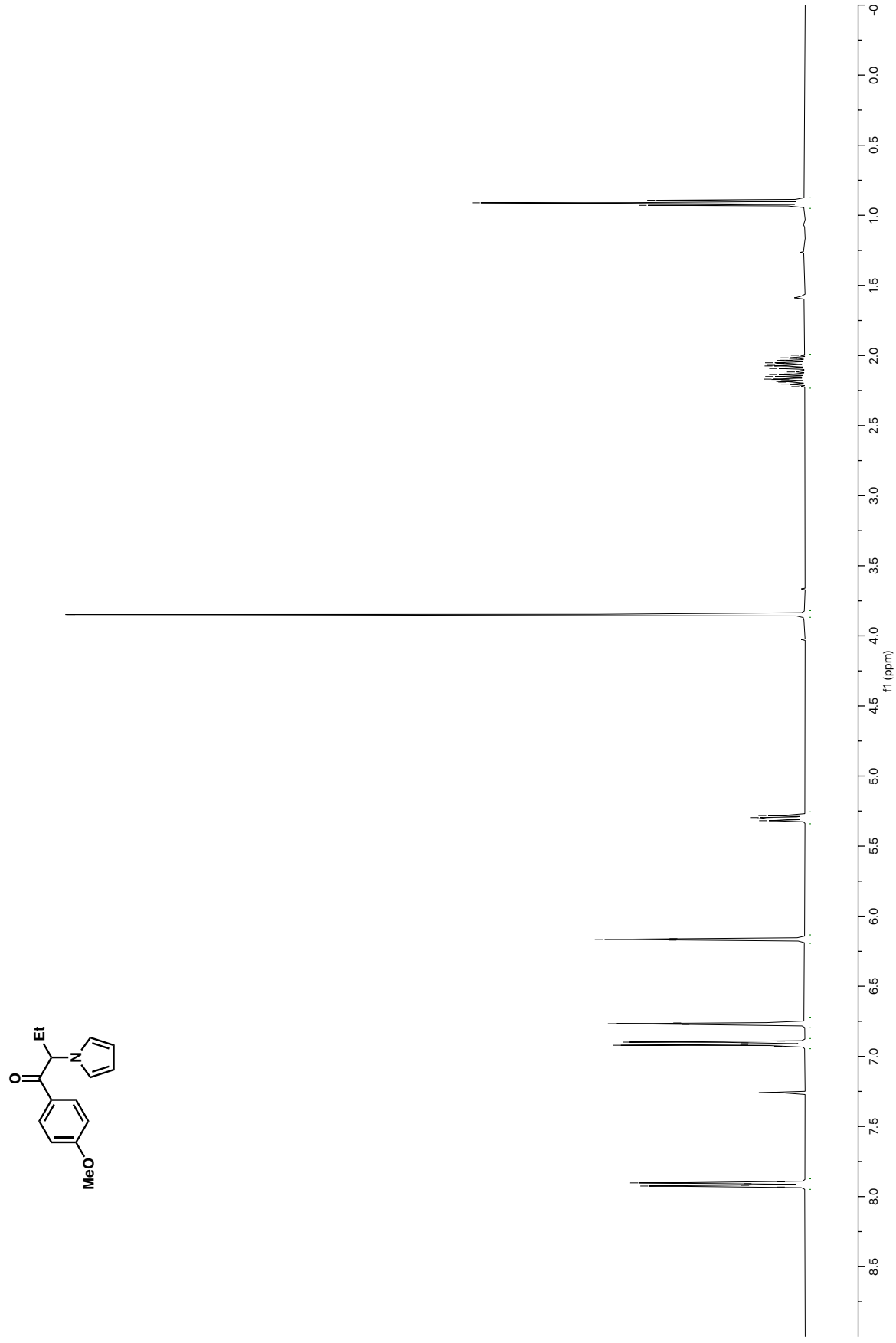



***Figure A9.159*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***122***.




***A9.160*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***123***.

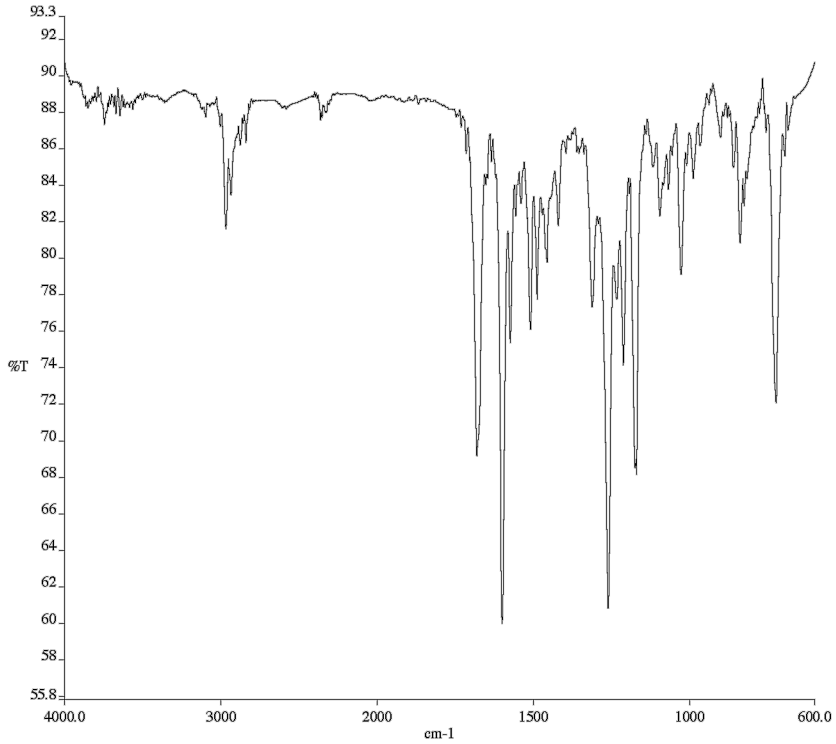



***Figure A9.161*** *Infrared spectrum (Thin Film, NaCl) of compound* ***123***.

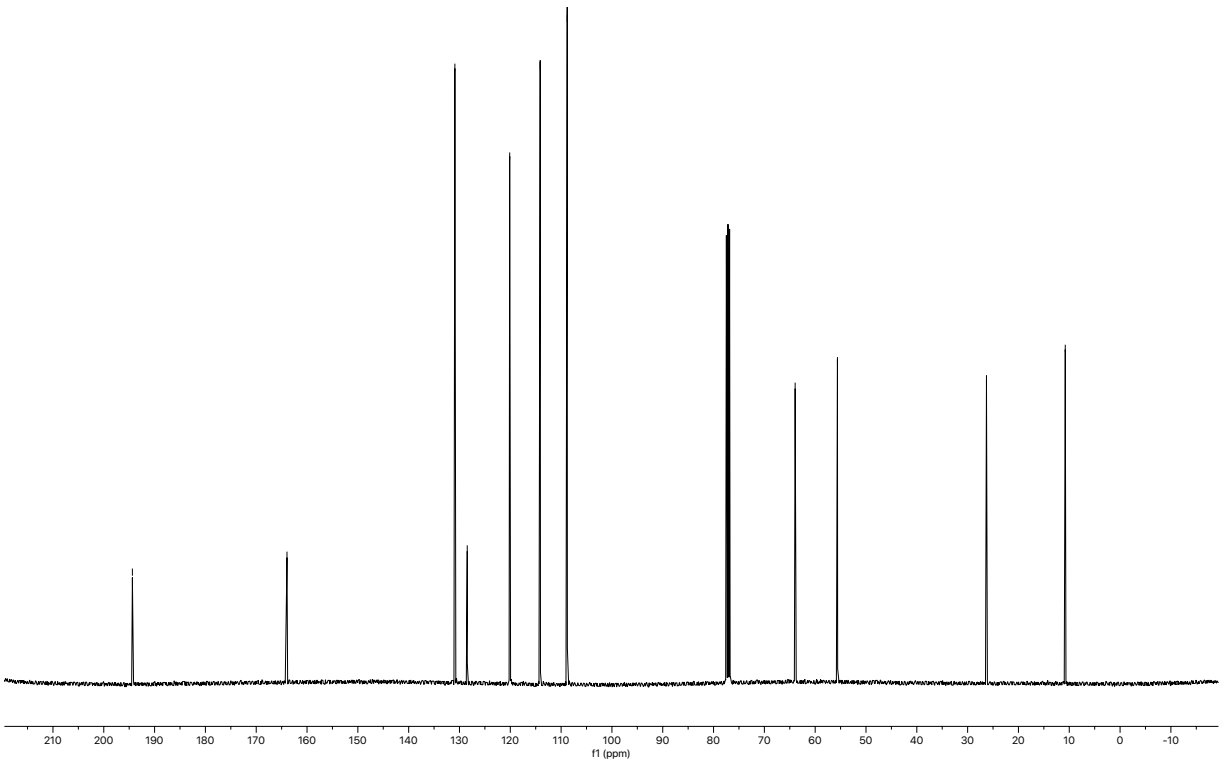
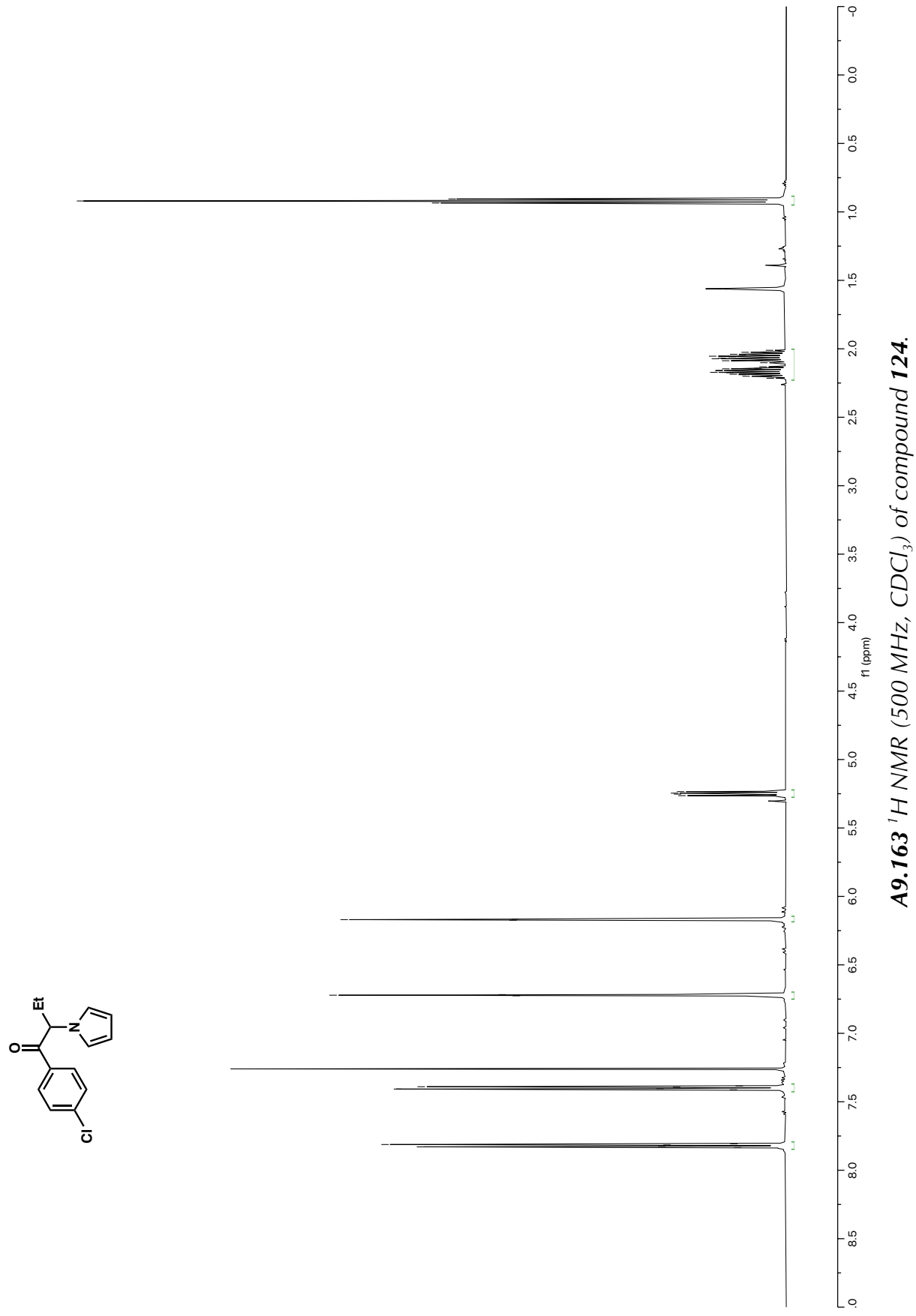



***Figure A9.162*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***123***.




***A9.163*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***124****.*

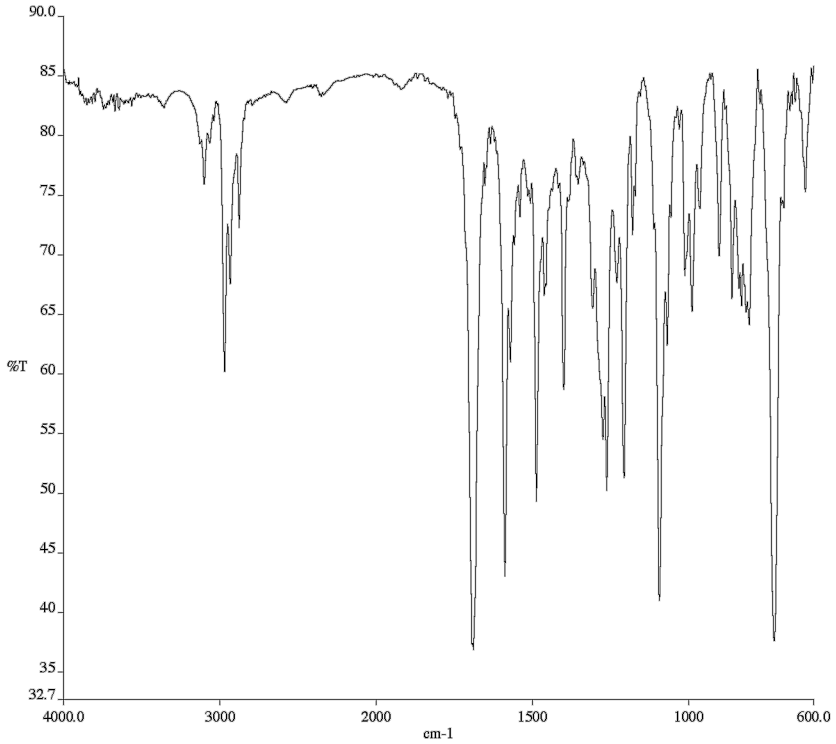



***Figure A9.164*** *Infrared spectrum (Thin Film, NaCl) of compound* ***124***.

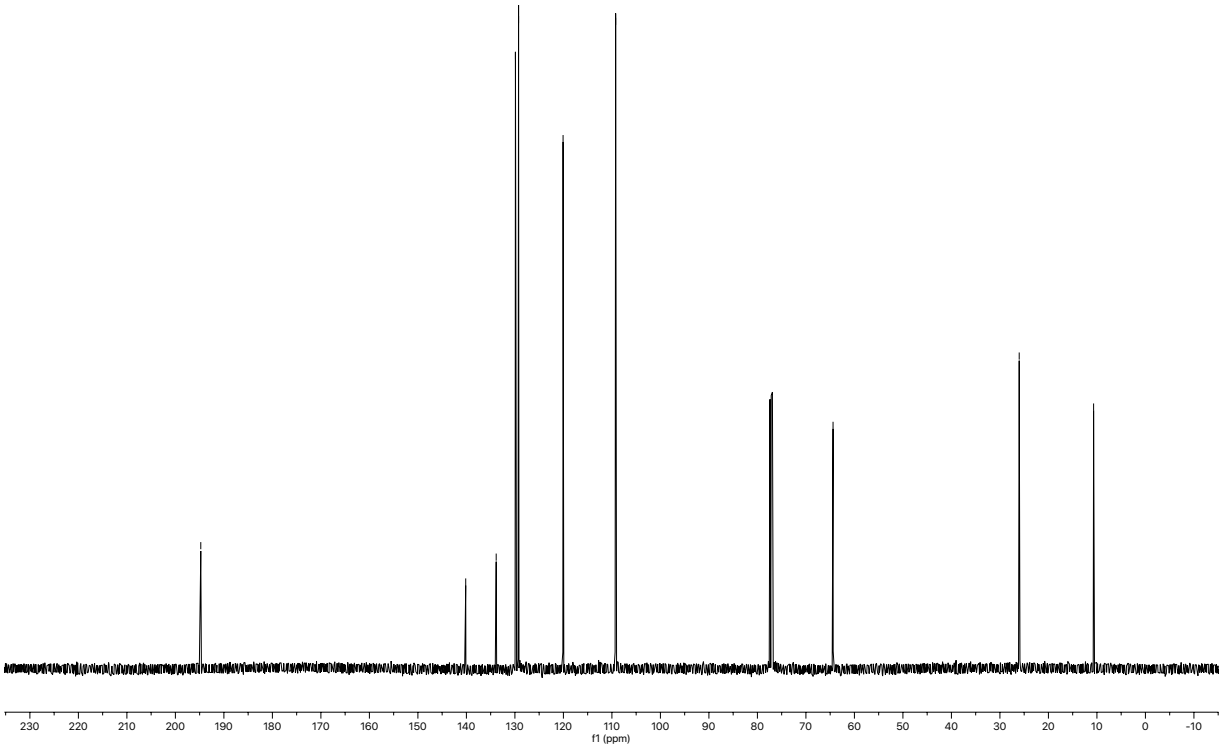
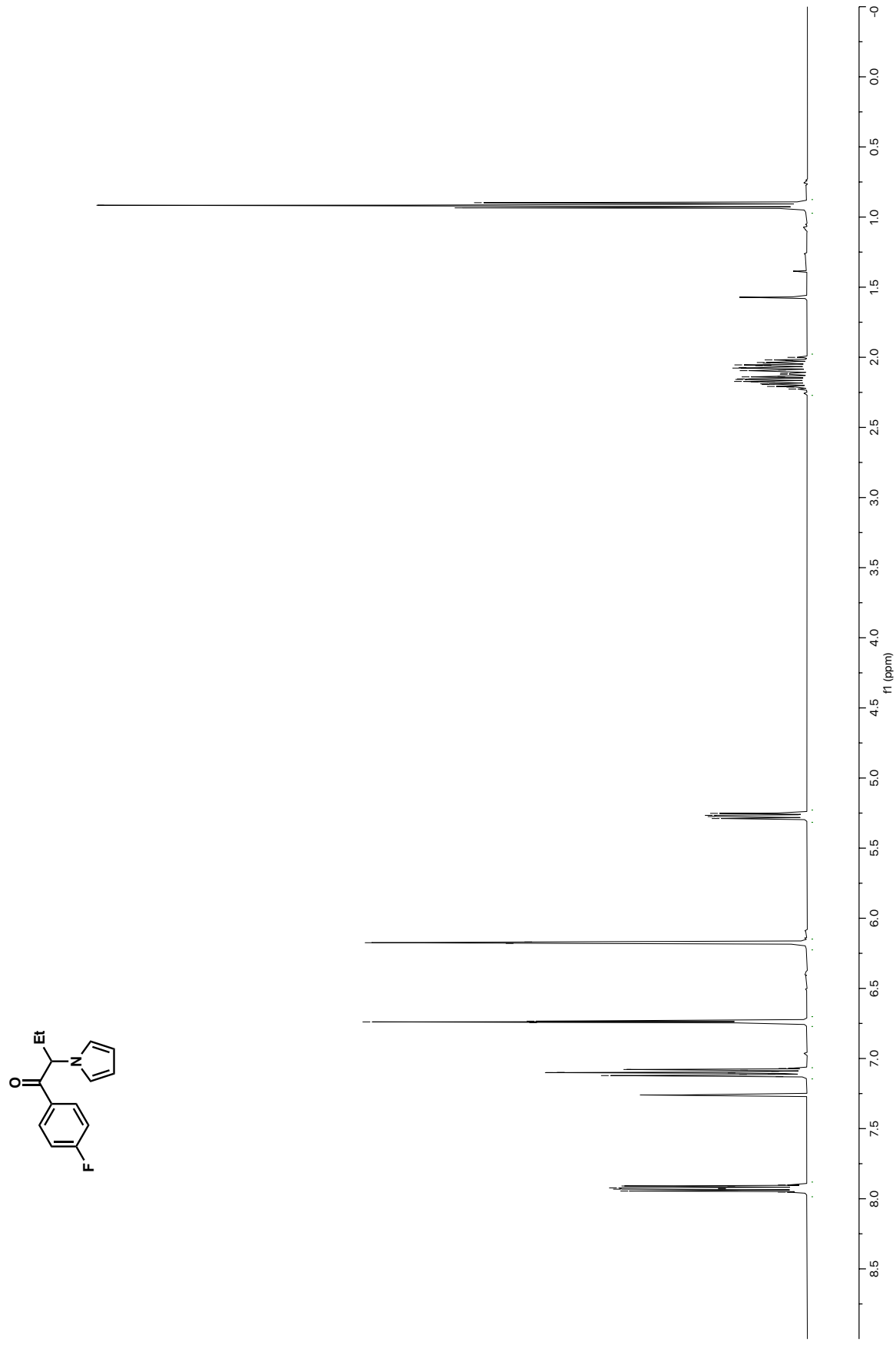



***Figure A9.165*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***124***.




***A9.166*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***125****.*

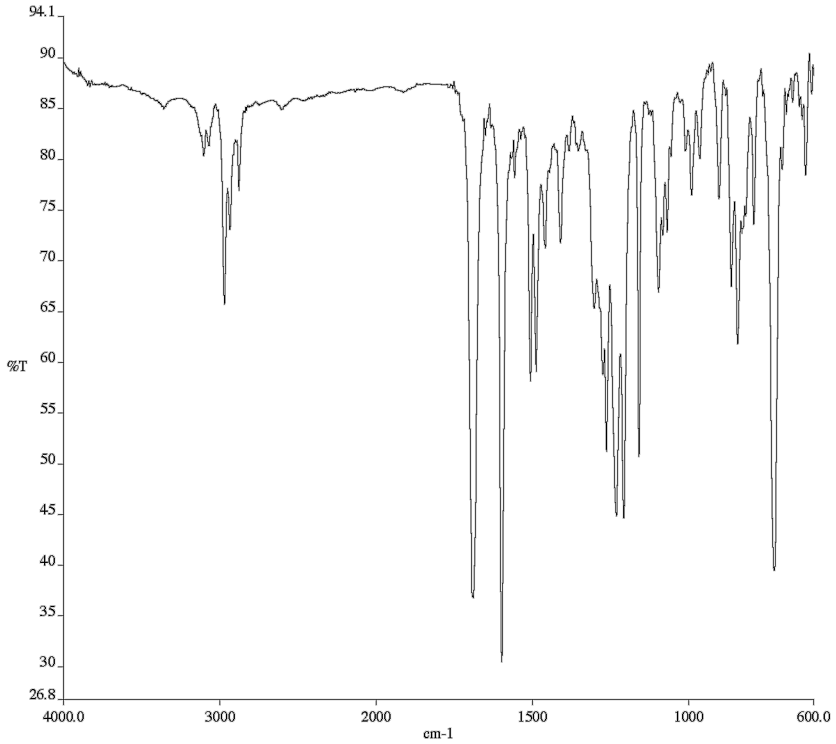



***Figure A9.167*** *Infrared spectrum (Thin Film, NaCl) of compound* ***125***.

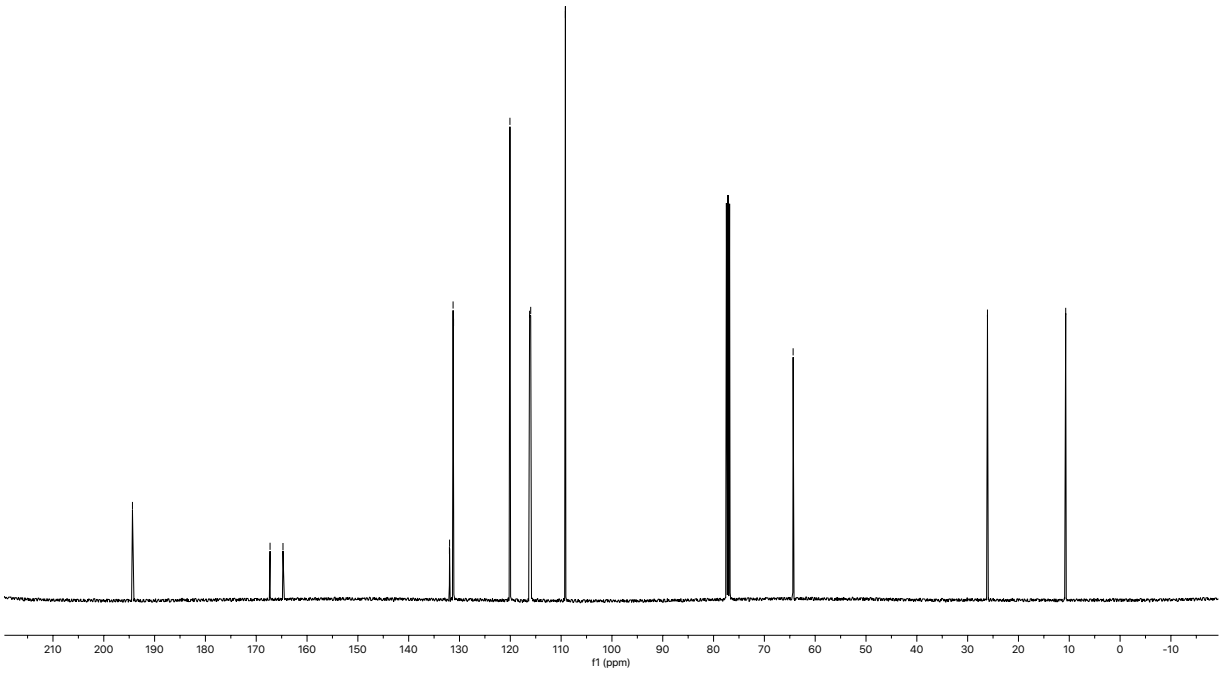



***Figure A9.168*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***125***.

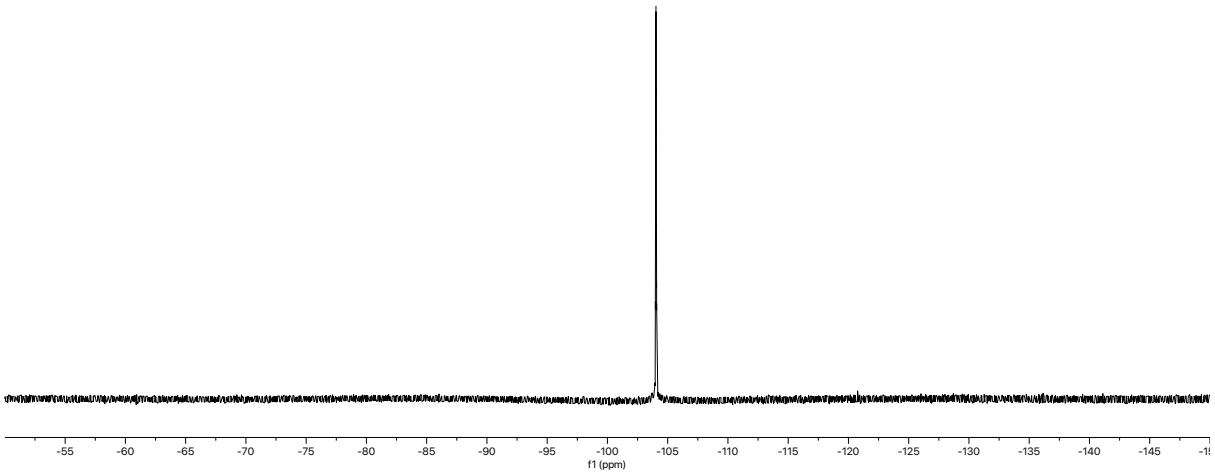
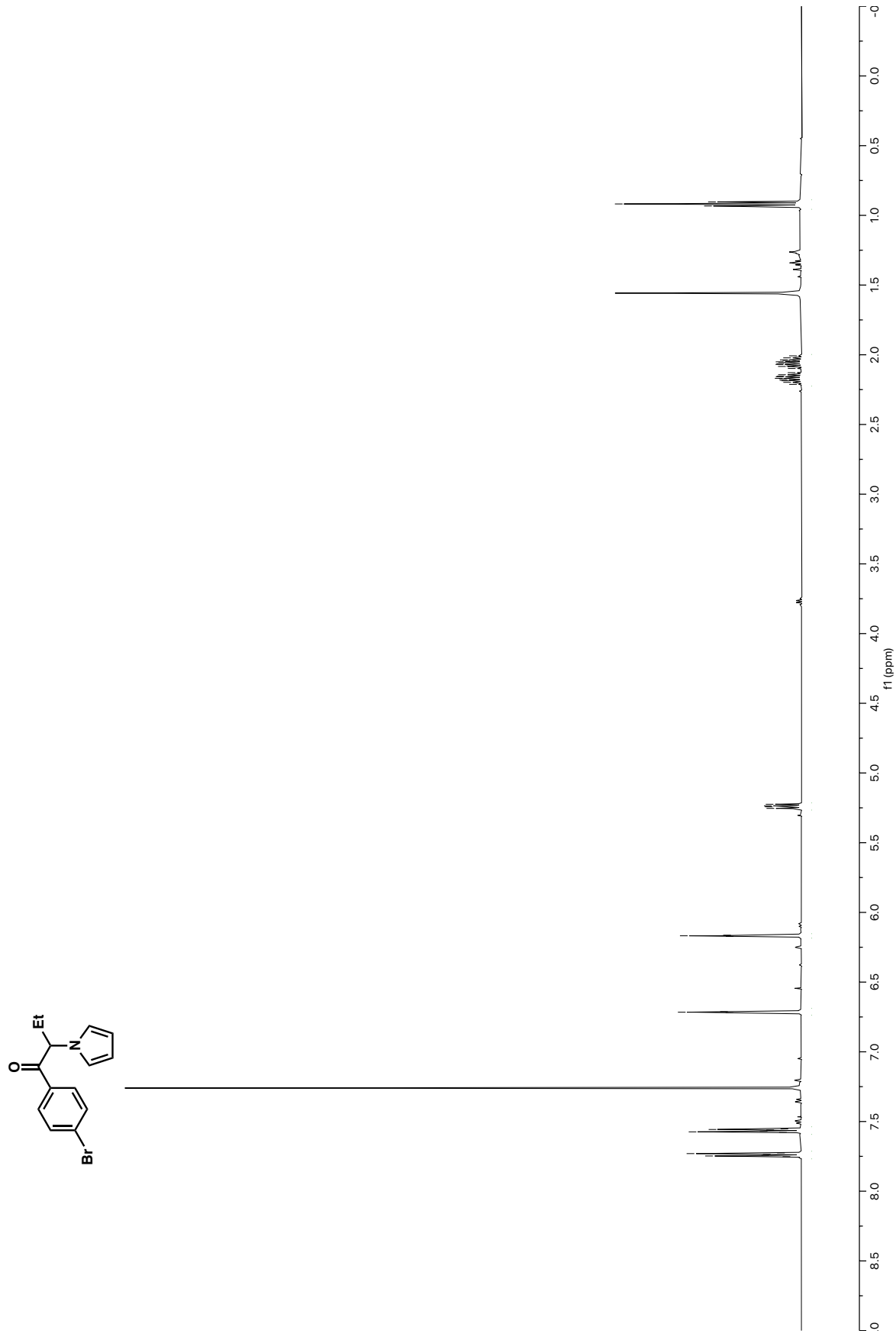



***Figure A9.169*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***125***.




***A9.170*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***126***.

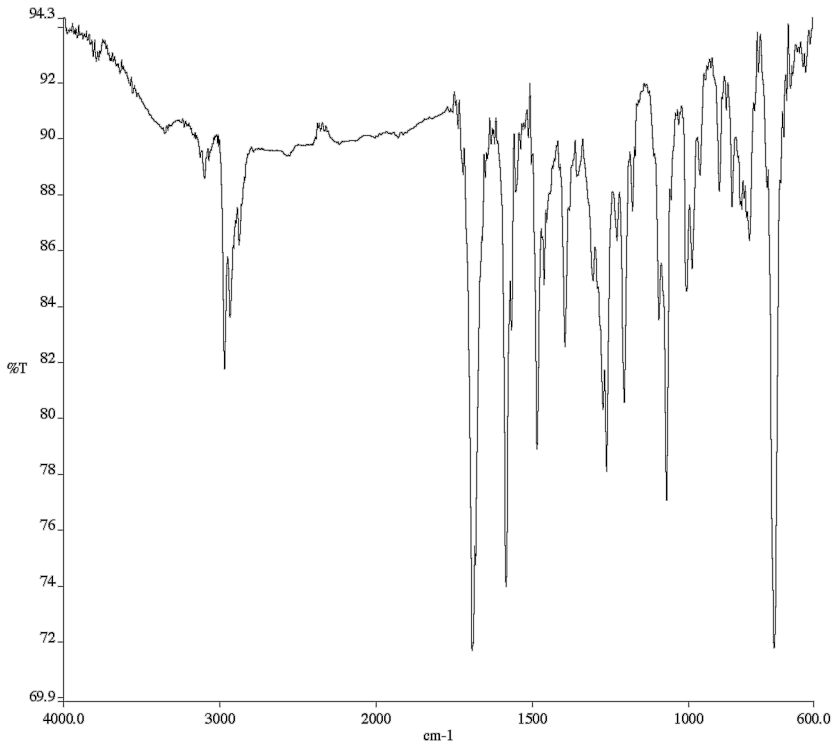



***Figure A9.171*** *Infrared spectrum (Thin Film, NaCl) of compound* ***126***.

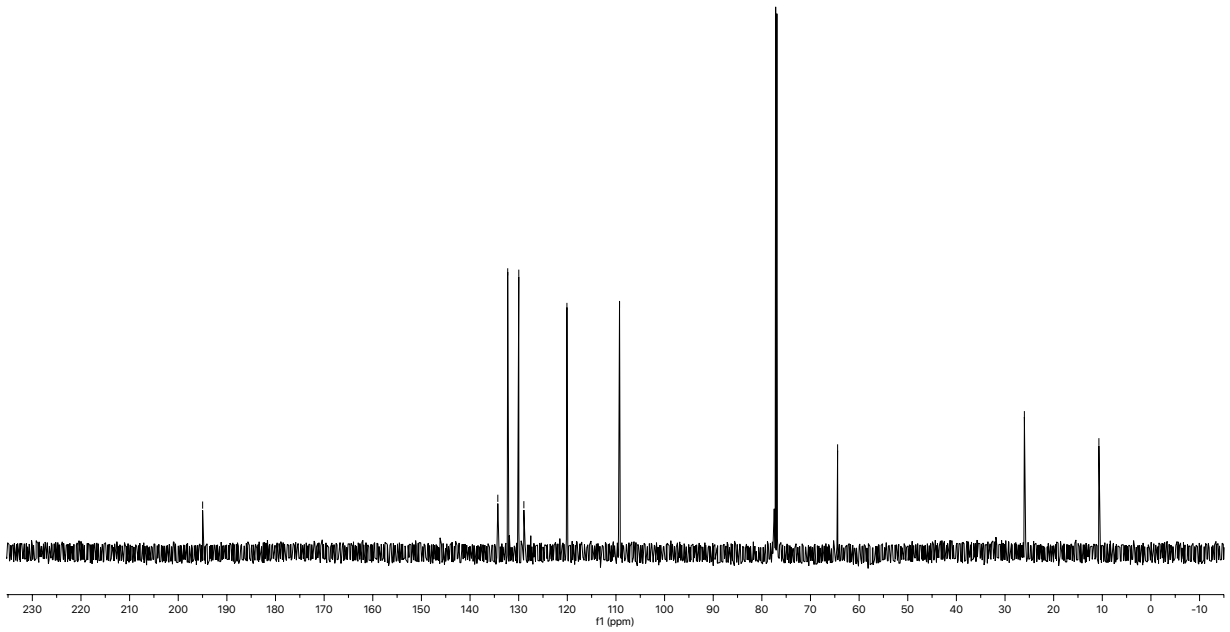
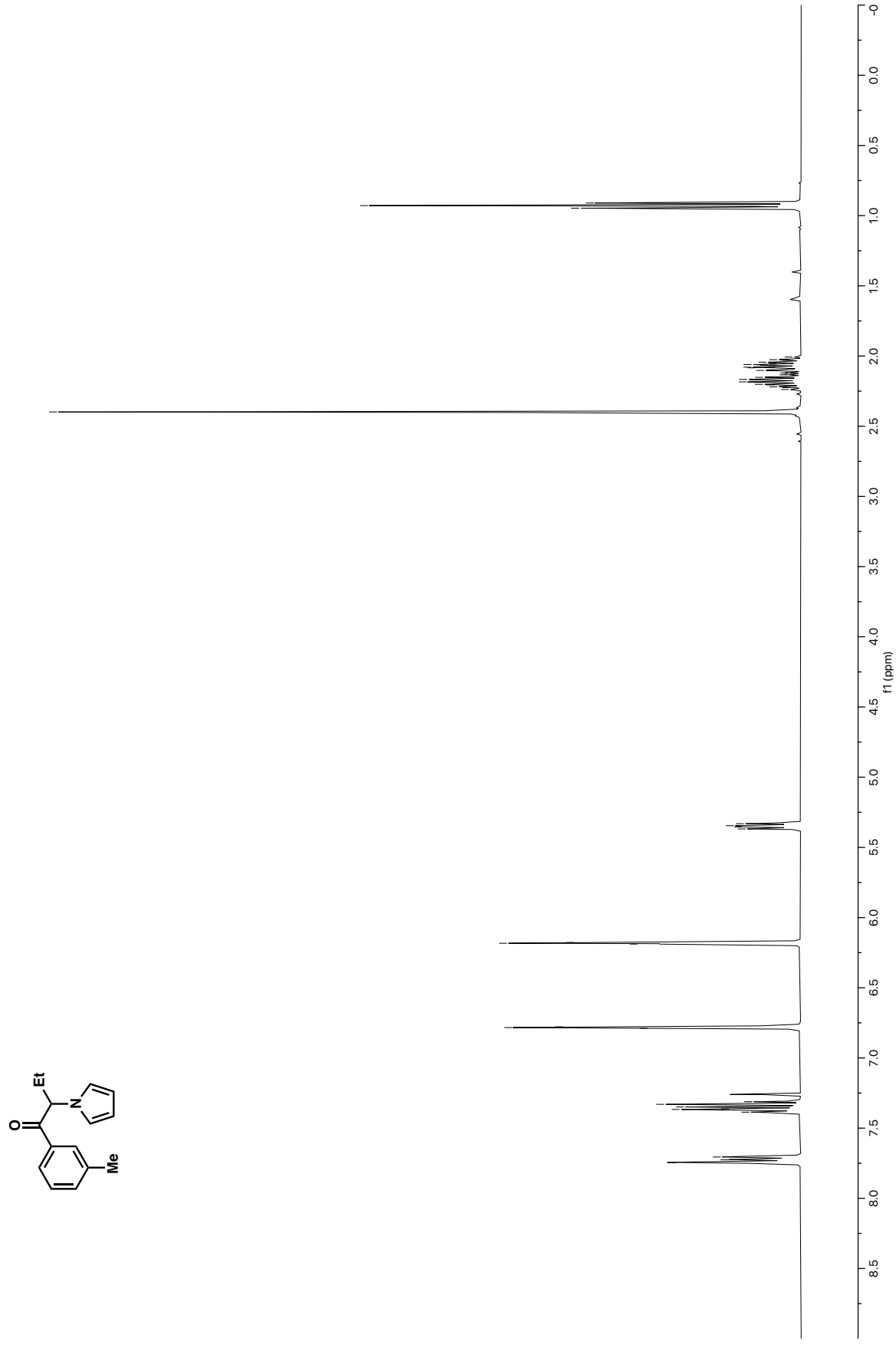



***Figure A9.172*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***126***.




***A9.173*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***127****.*

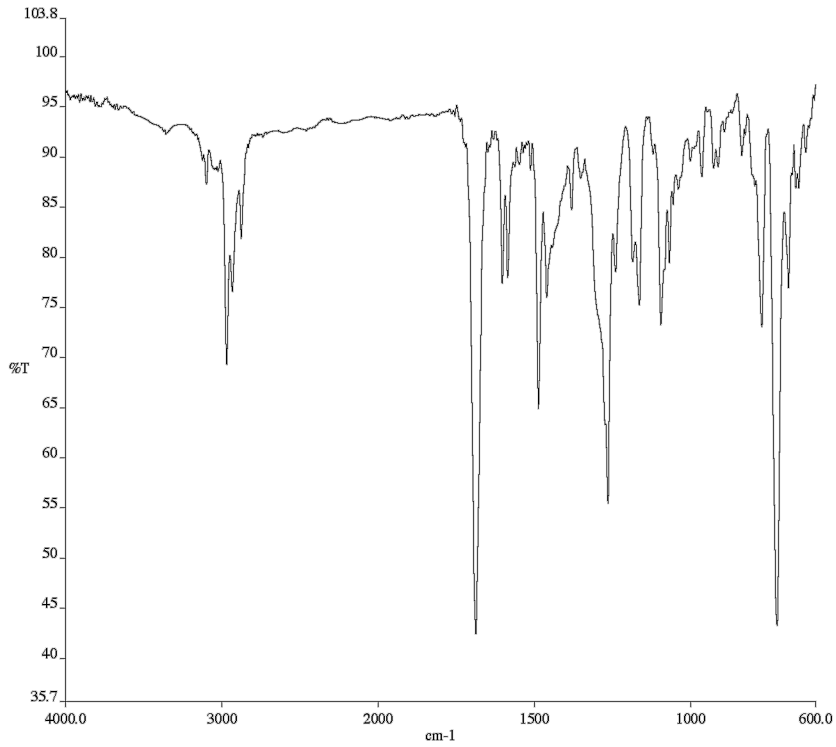



***Figure A9.174*** *Infrared spectrum (Thin Film, NaCl) of compound* ***127****.*

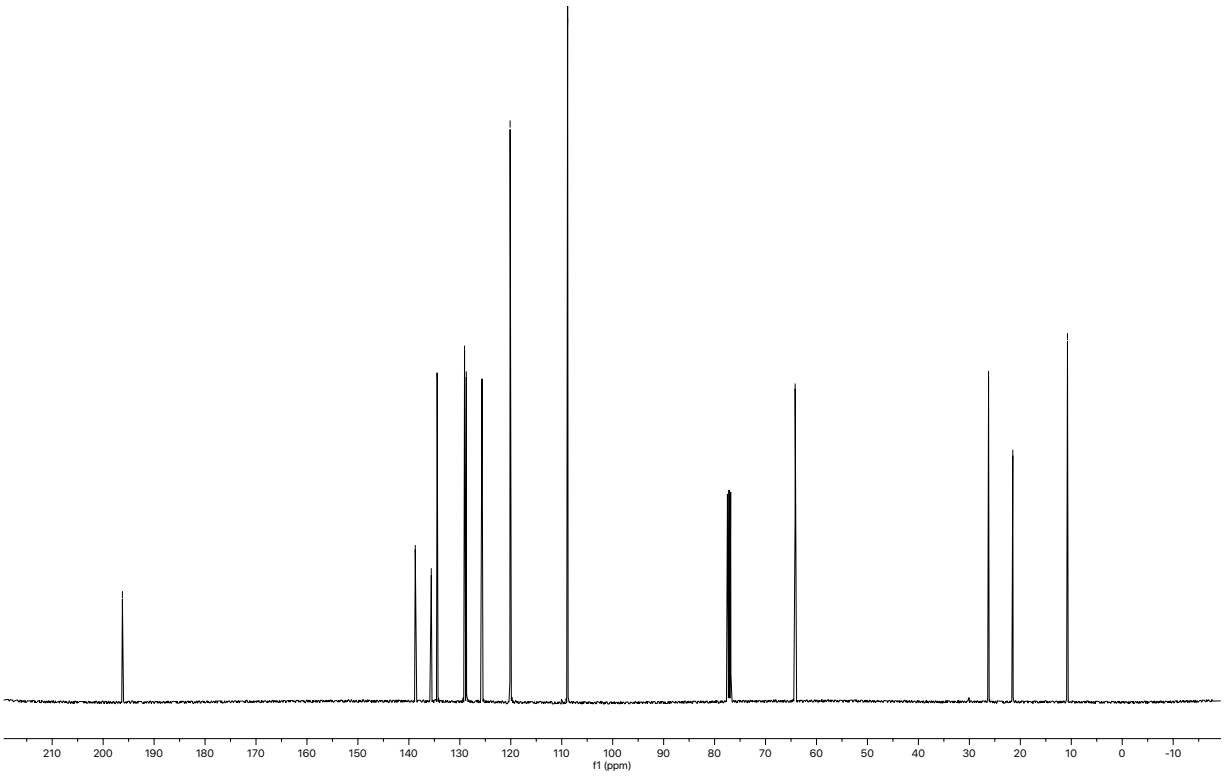
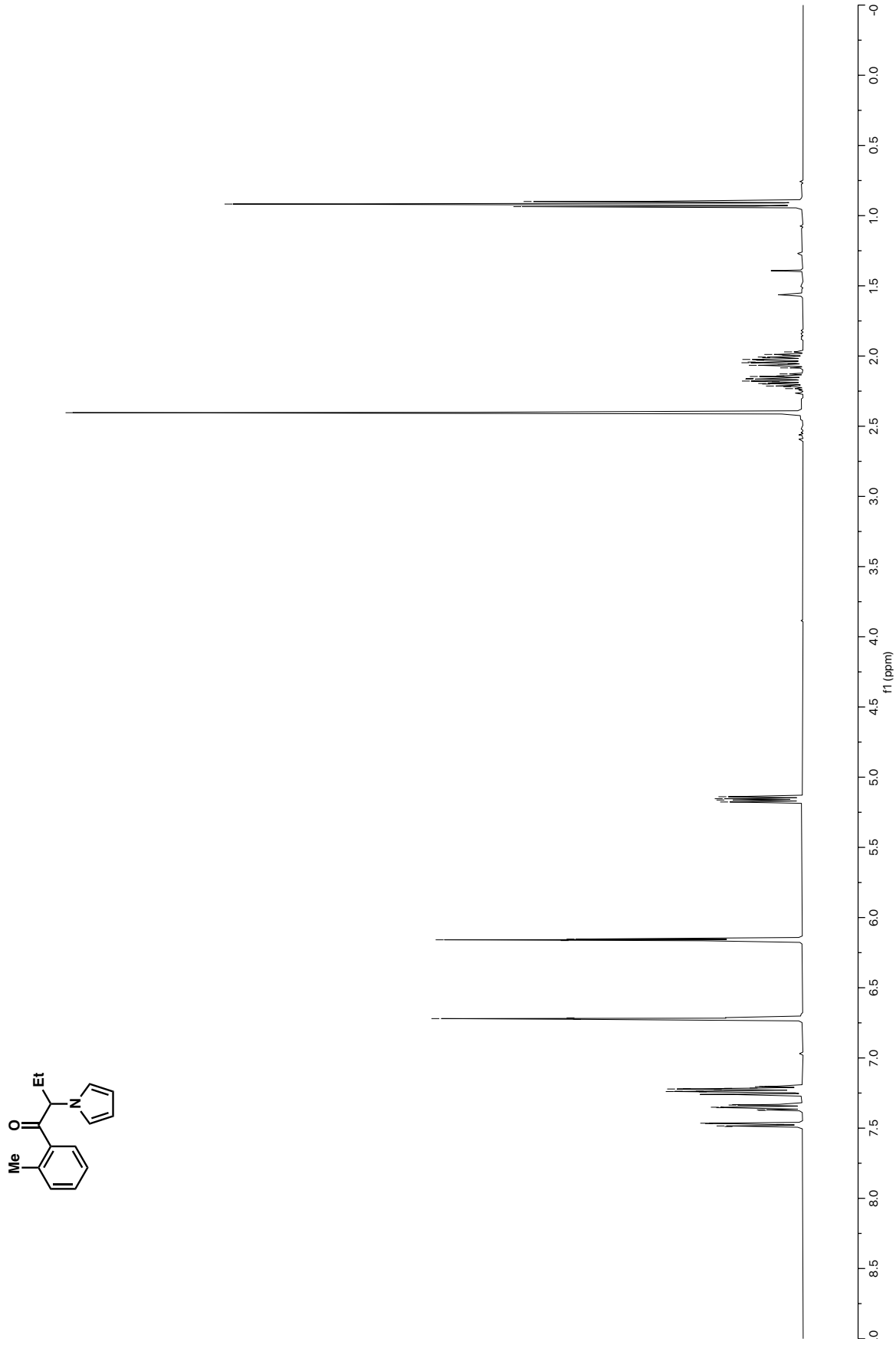



***Figure A9.175*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***127****.*




***A9.176*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***128****.*

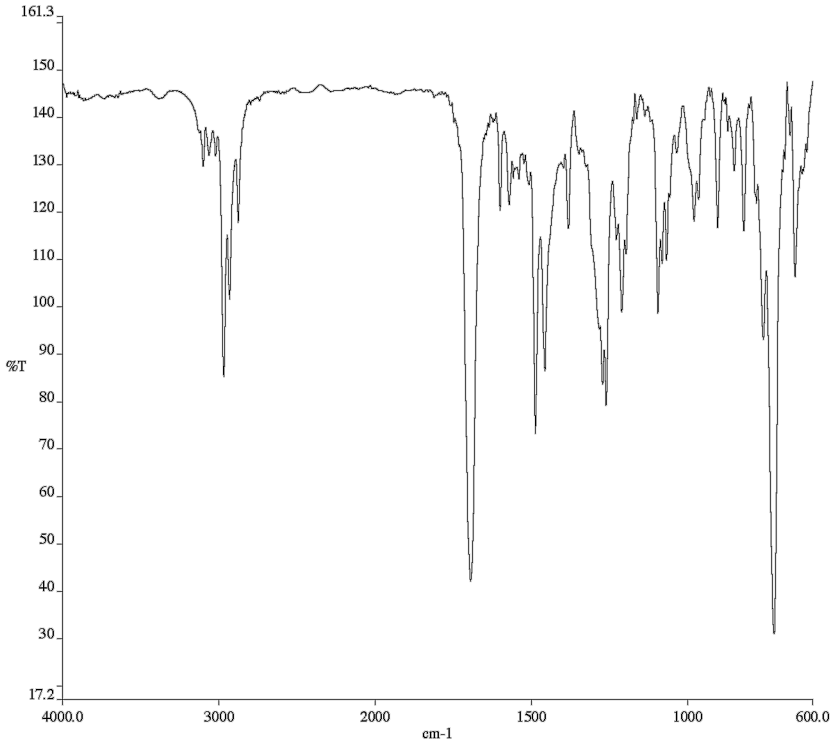



***Figure A9.177*** *Infrared spectrum (Thin Film, NaCl) of compound* ***128****.*

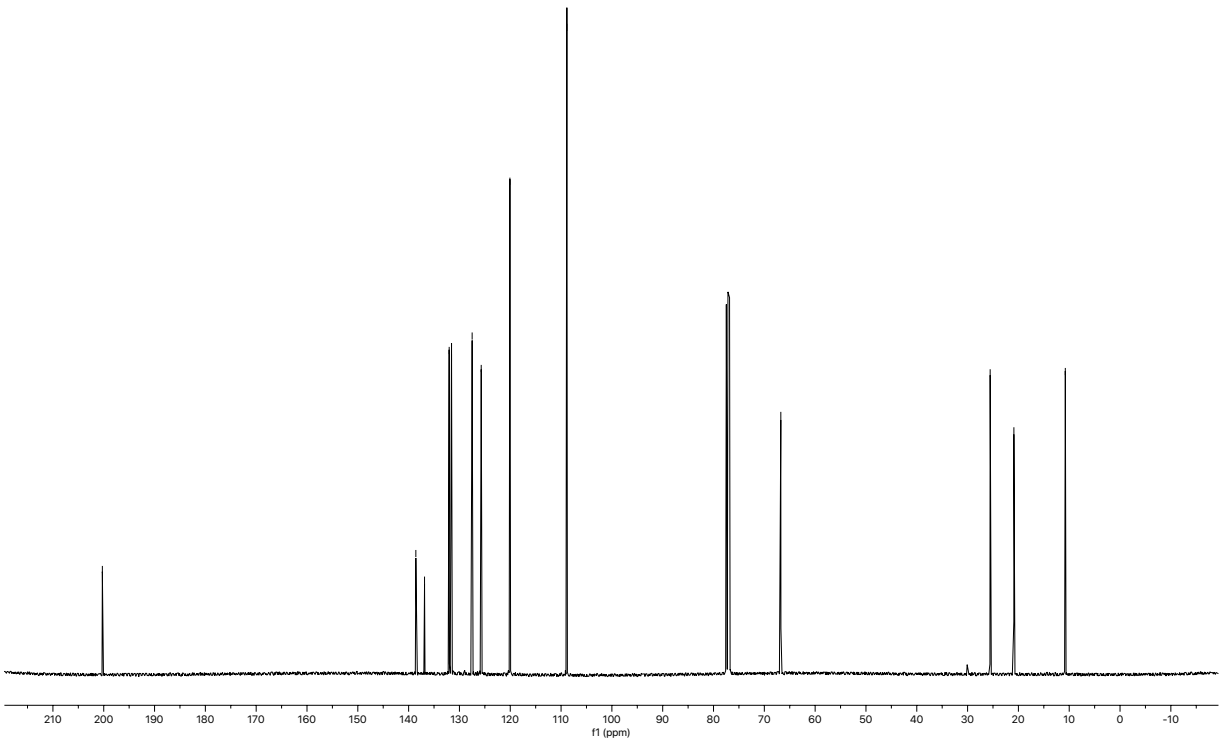
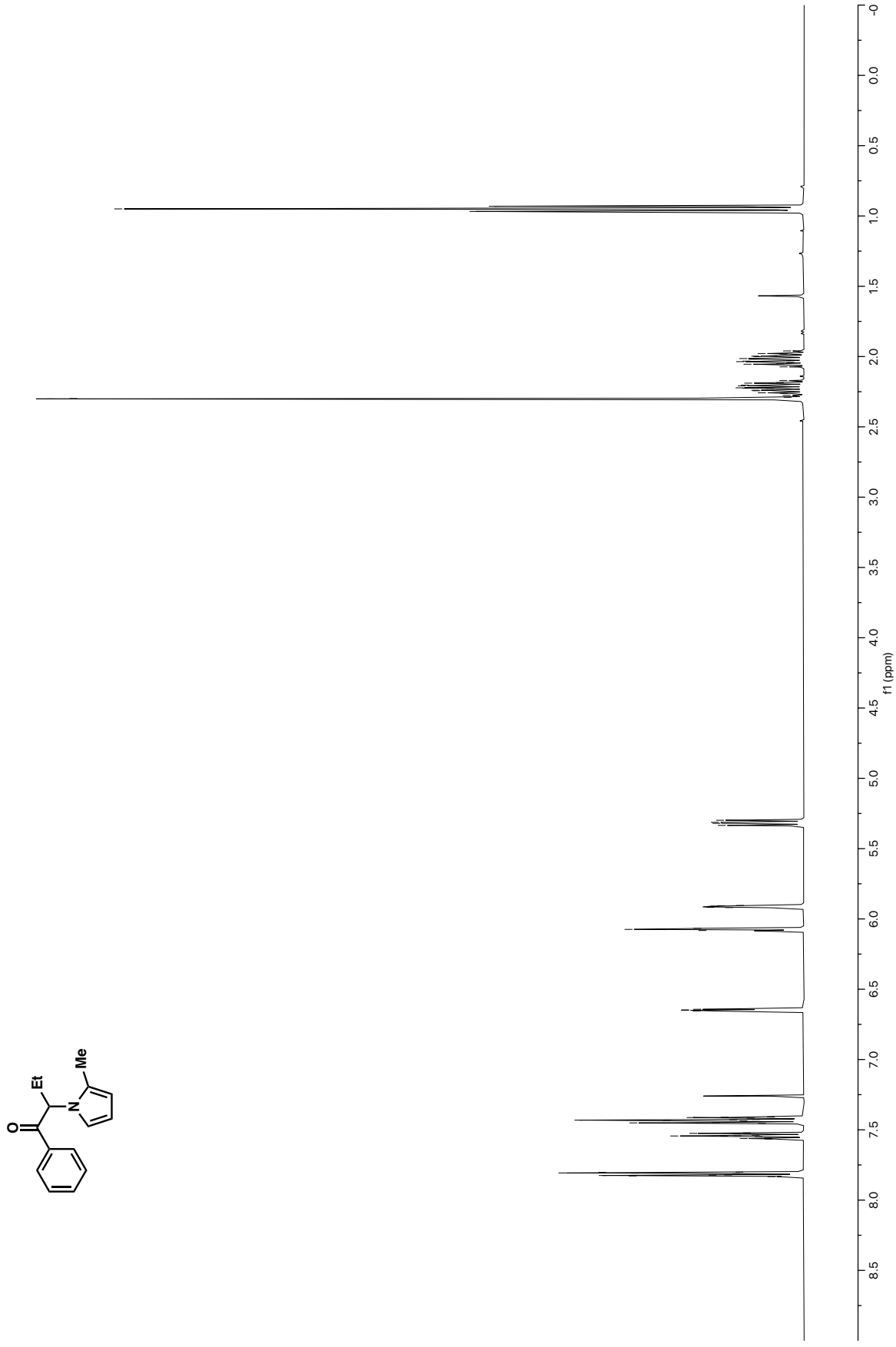



***Figure A9.178*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***128****.*




***A9.179*** *$^{1}H$ NMR (500 MHz, $CDCl_3$) of compound* ***129***.

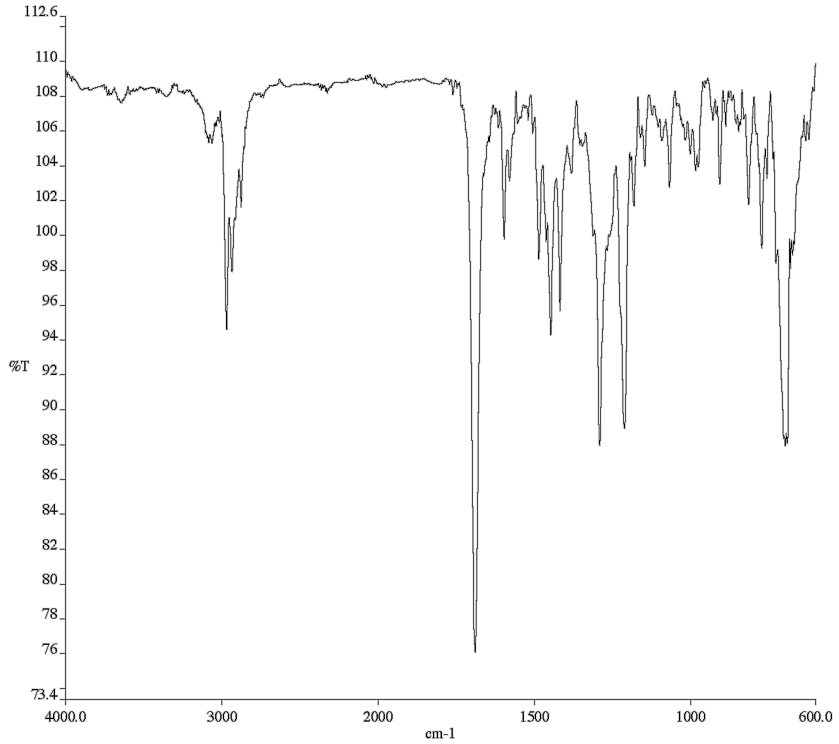



***Figure A9.180*** *Infrared spectrum (Thin Film, NaCl) of compound* ***129***.

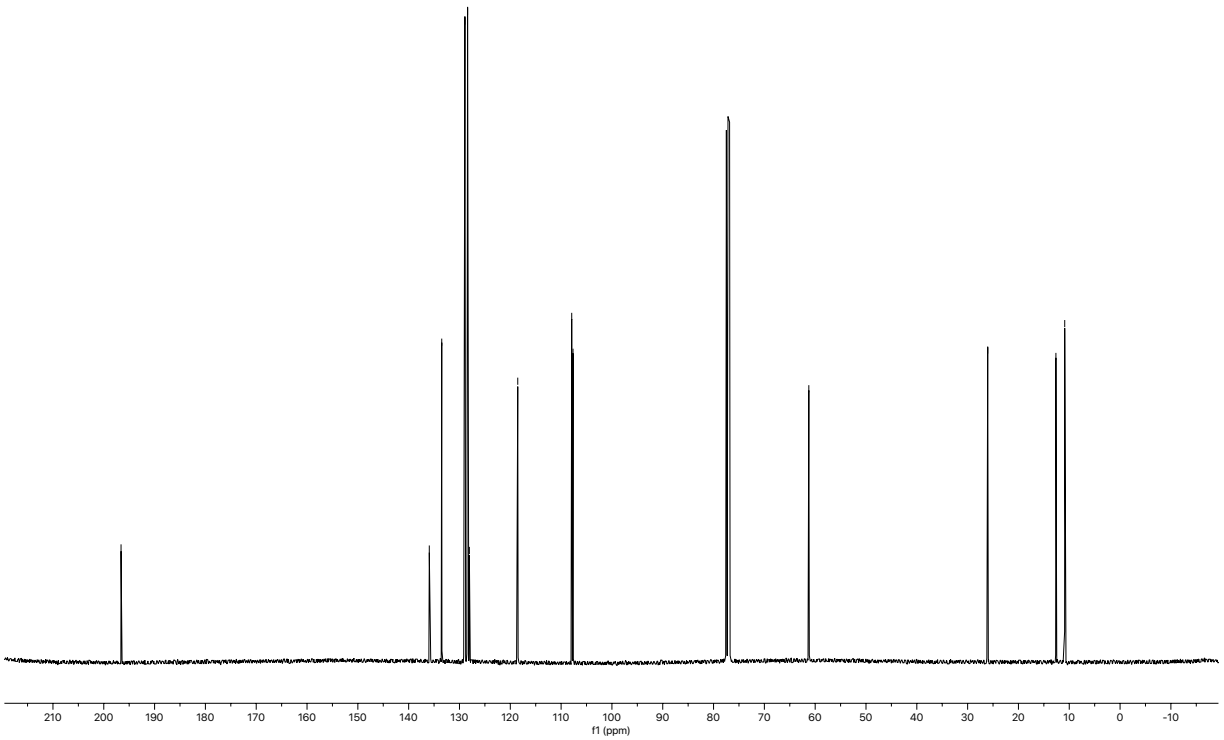
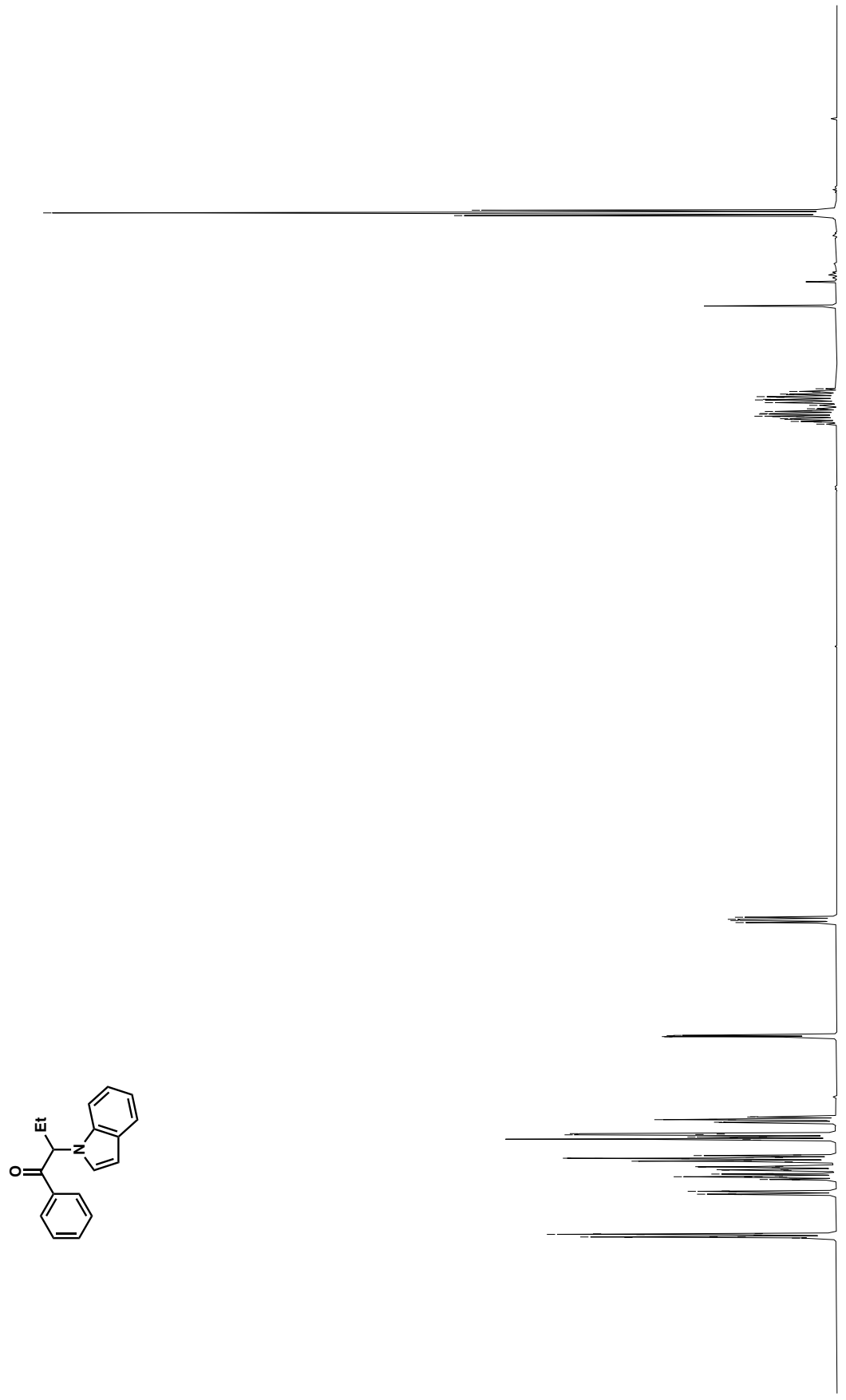



***Figure A9.181*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***129***.




***A9.182*** *$^{1}H$ NMR (500 MHz, $CDCl_3$) of compound* ***130***.

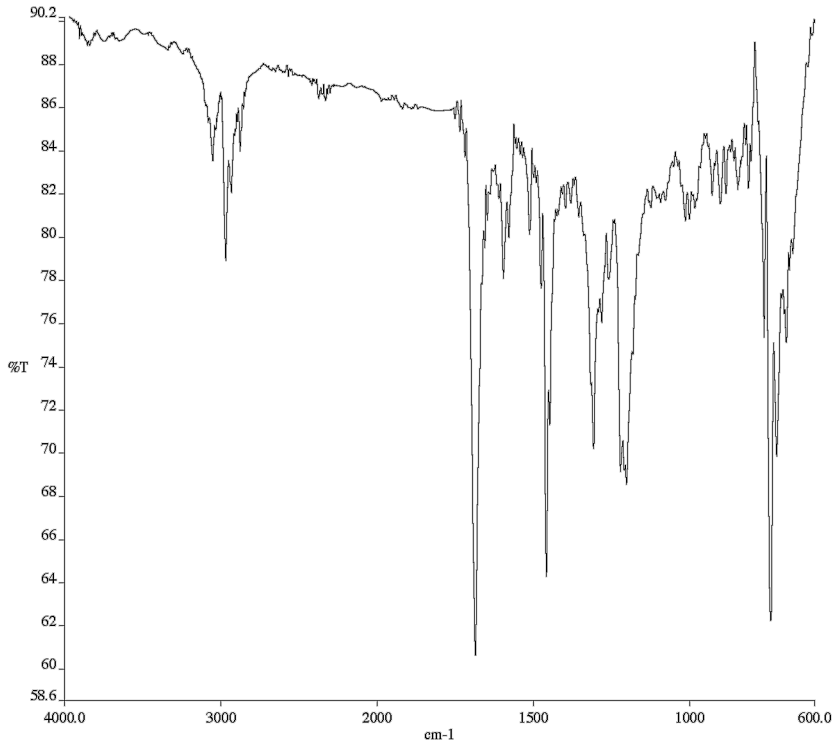



***Figure A9.183*** *Infrared spectrum (Thin Film, NaCl) of compound* ***130****.*

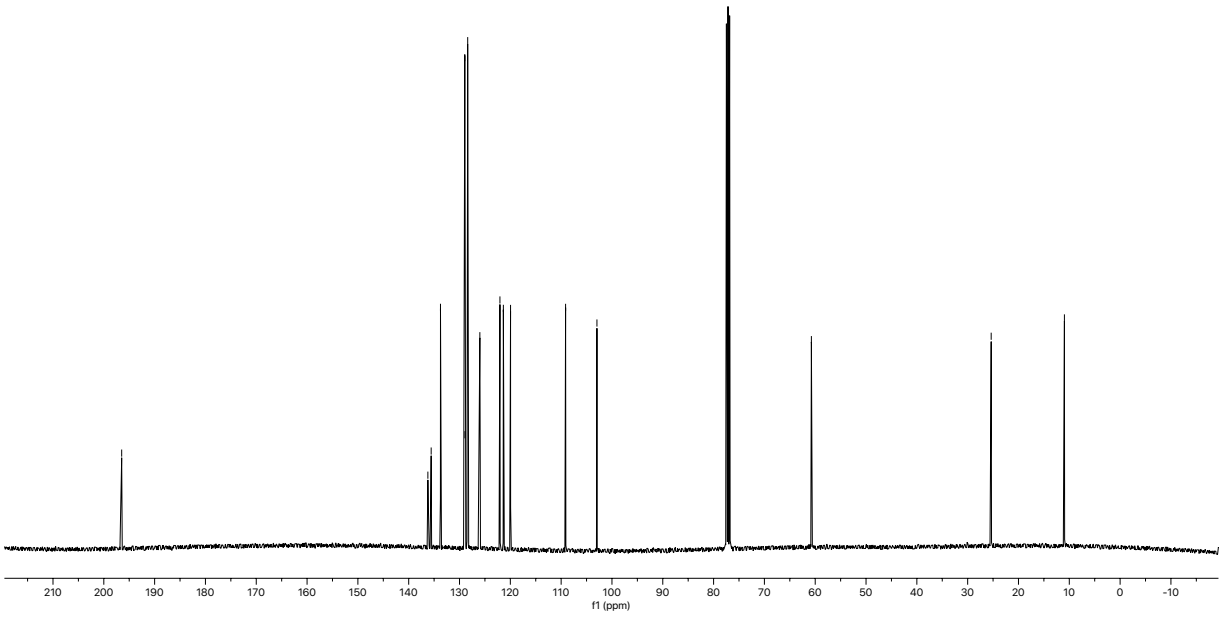
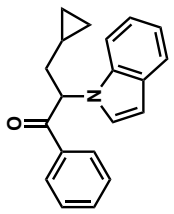
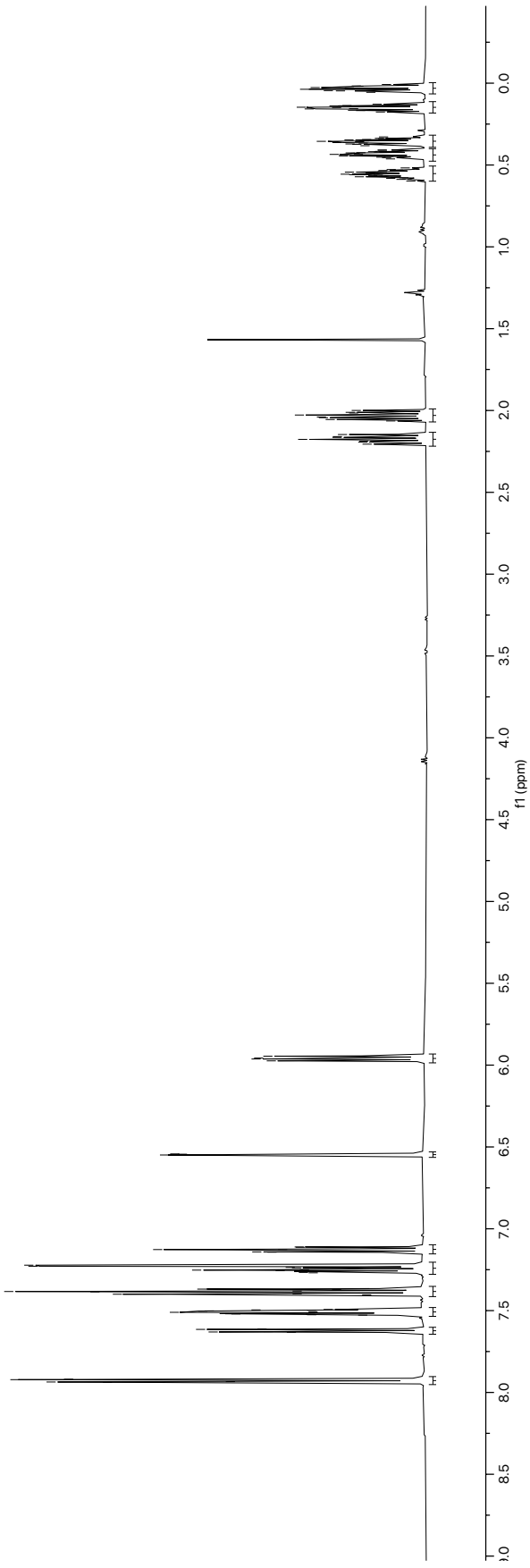



***Figure A9.184*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***130****.*




***A9.185*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***131***.

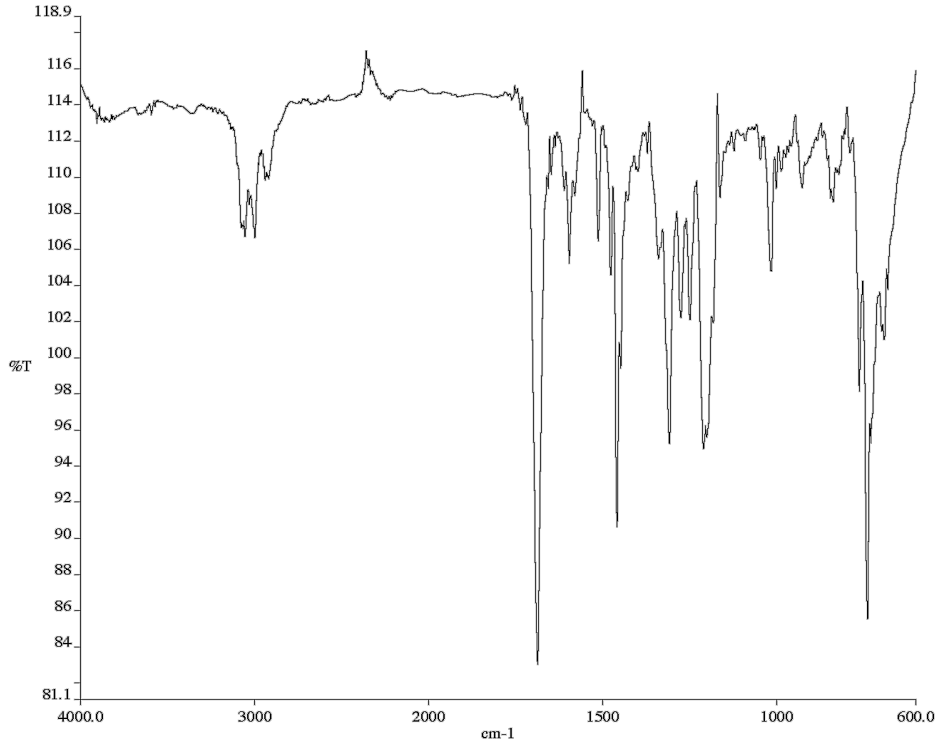



***Figure A9.186*** *Infrared spectrum (Thin Film, NaCl) of compound* ***131***.

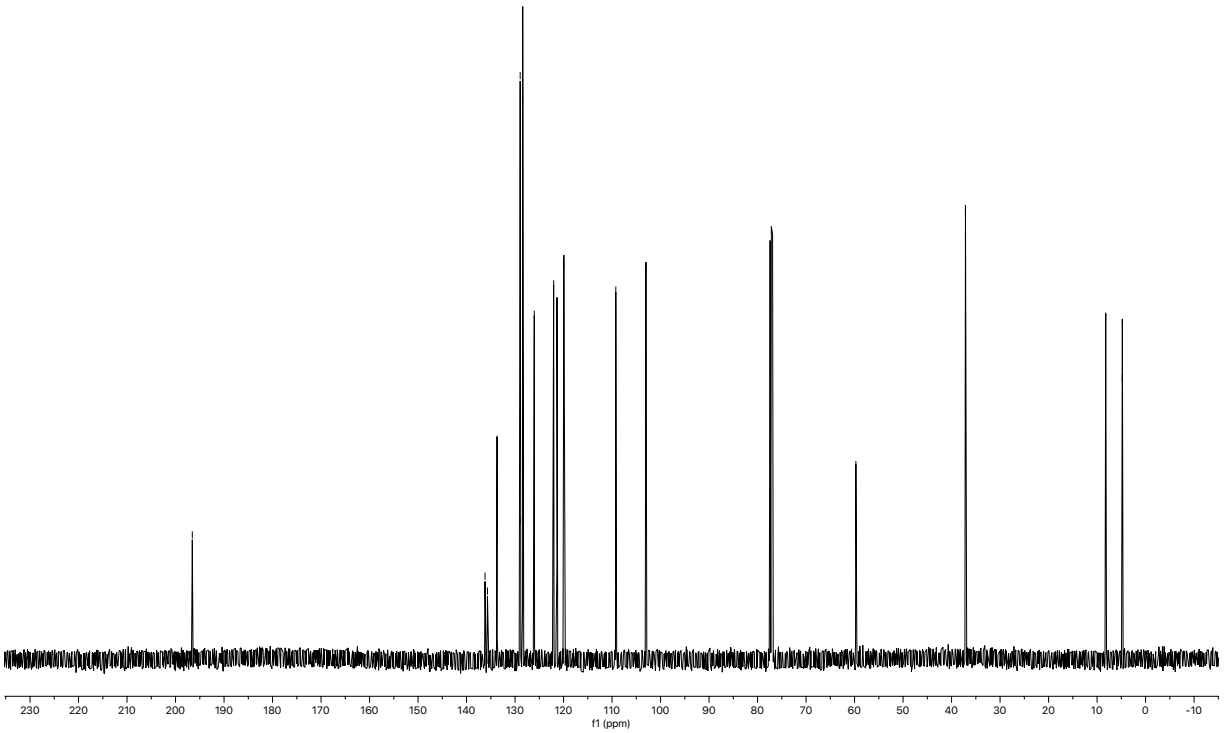



***Figure A9.187*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***131***.

***A9.188*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***132***.

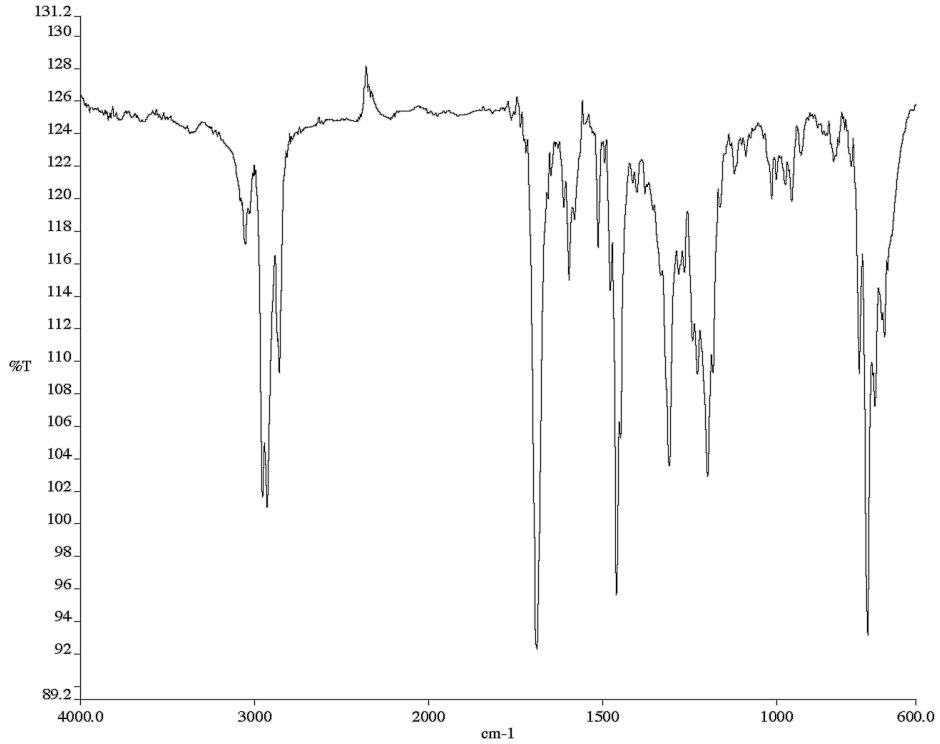



***Figure A9.189*** *Infrared spectrum (Thin Film, NaCl) of compound* ***132***.

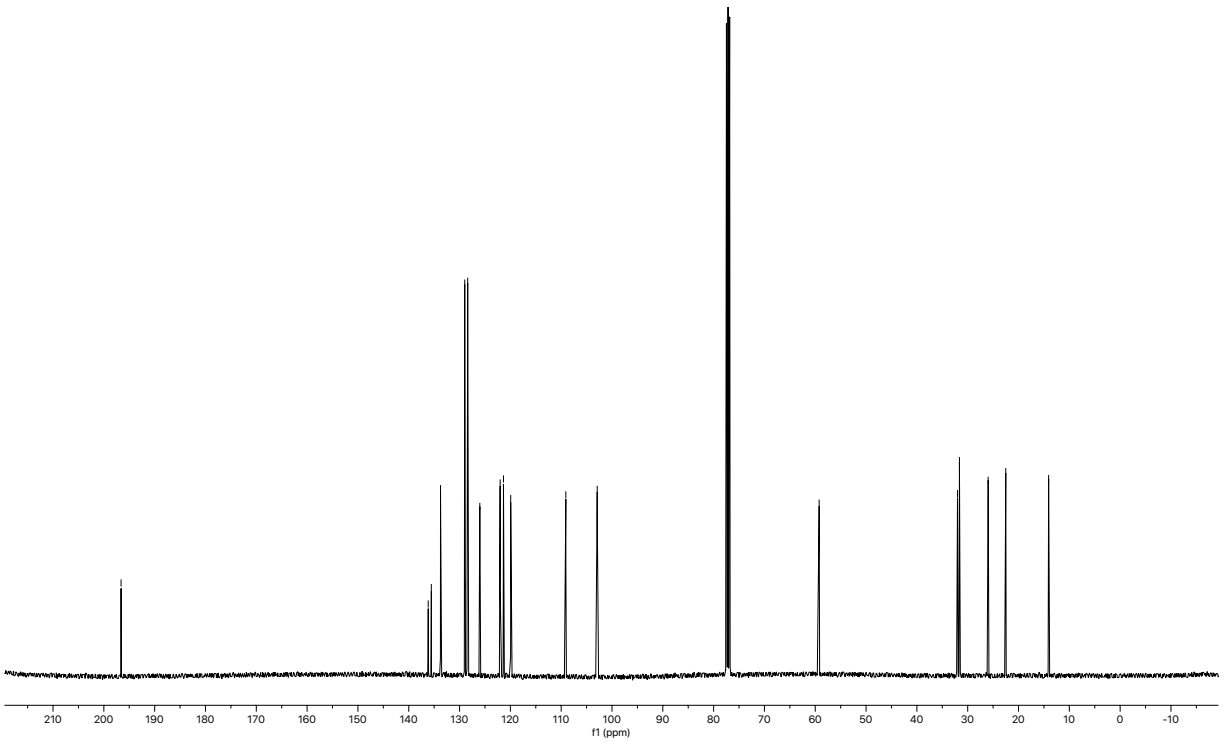
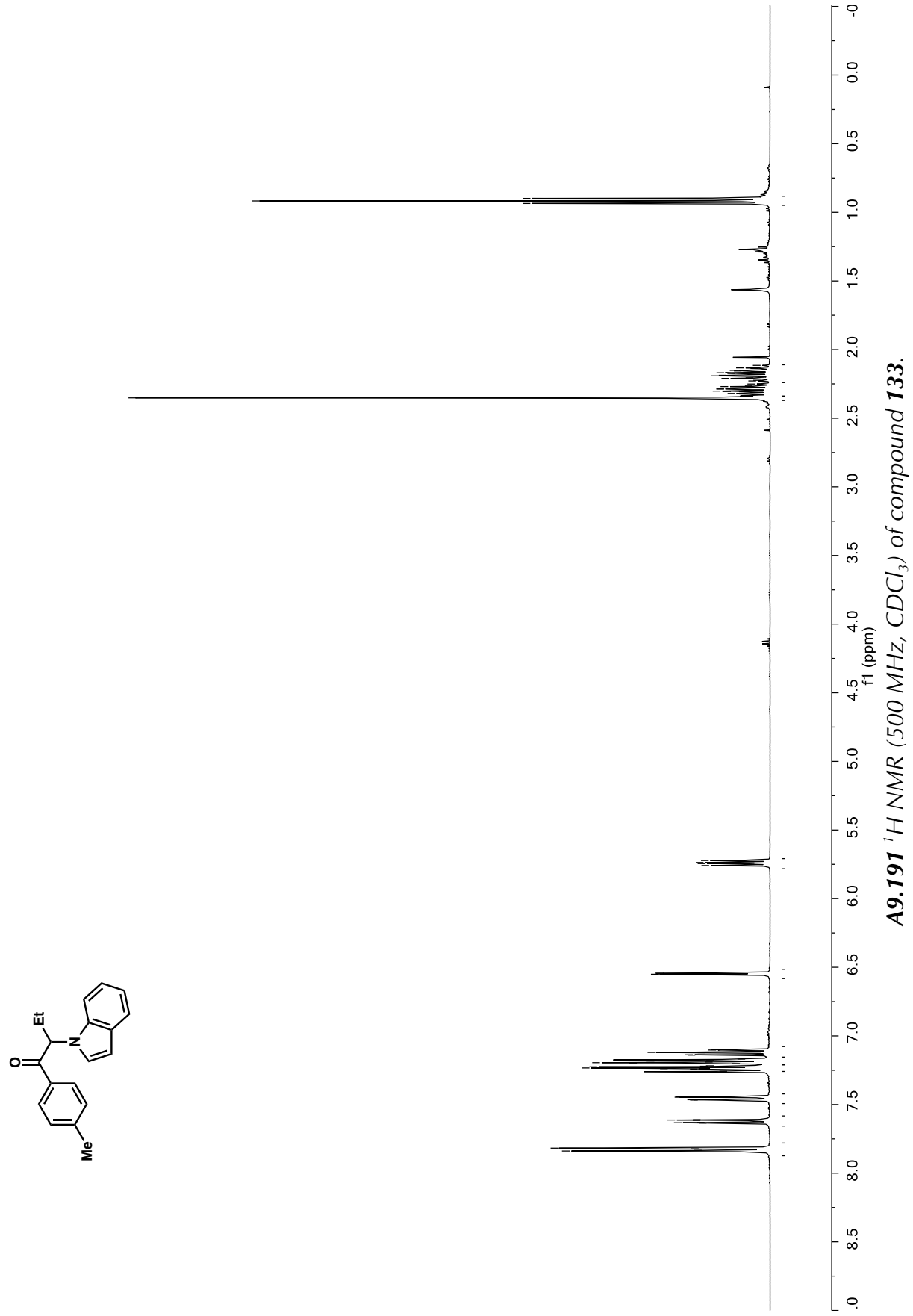



***Figure A9.190*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***132***.




***A9.191*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***133***.

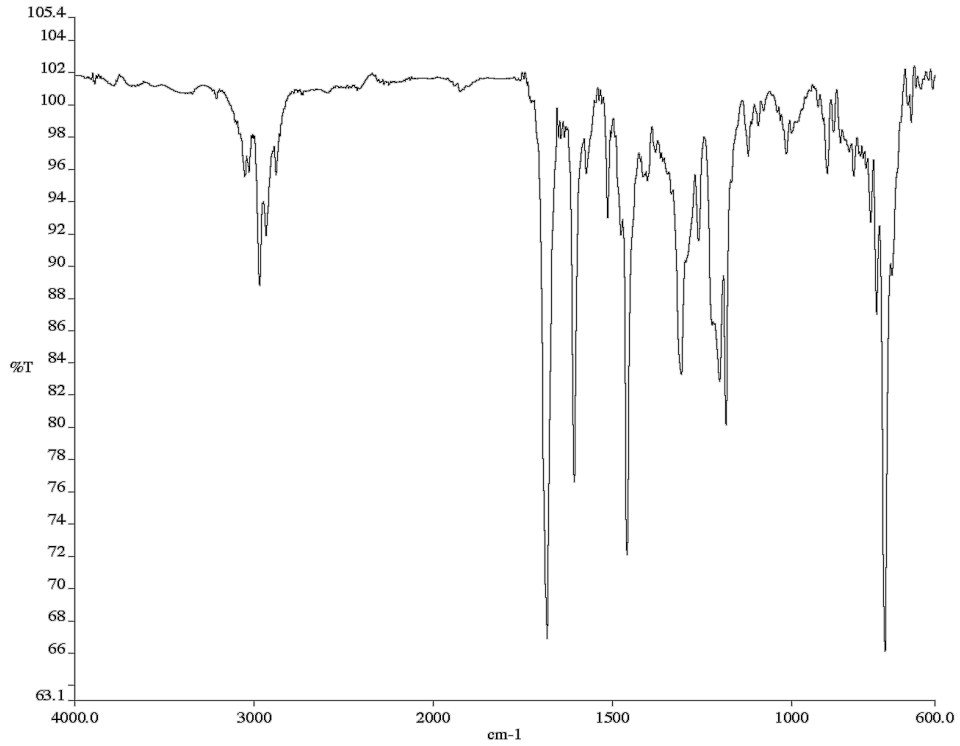



***Figure A9.192*** *Infrared spectrum (Thin Film, NaCl) of compound* ***133***.

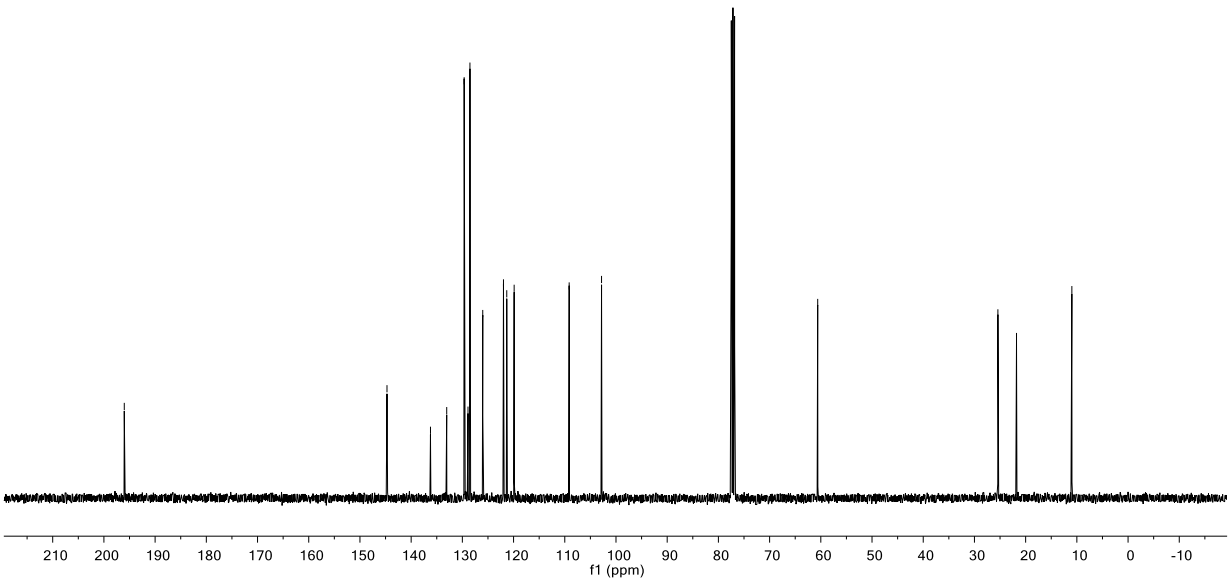
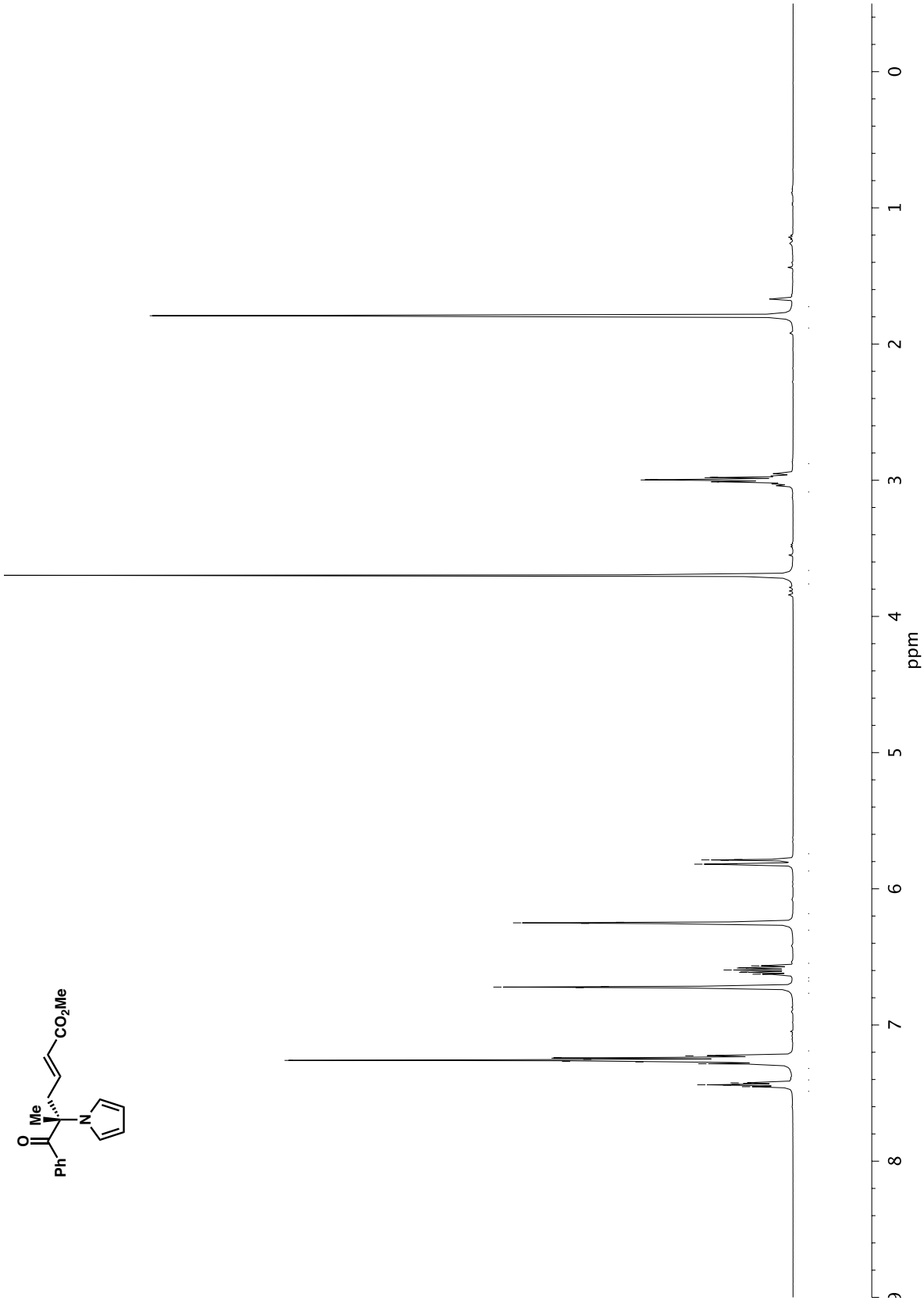



***Figure A9.193*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***133***.




***A9.194*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***102***.

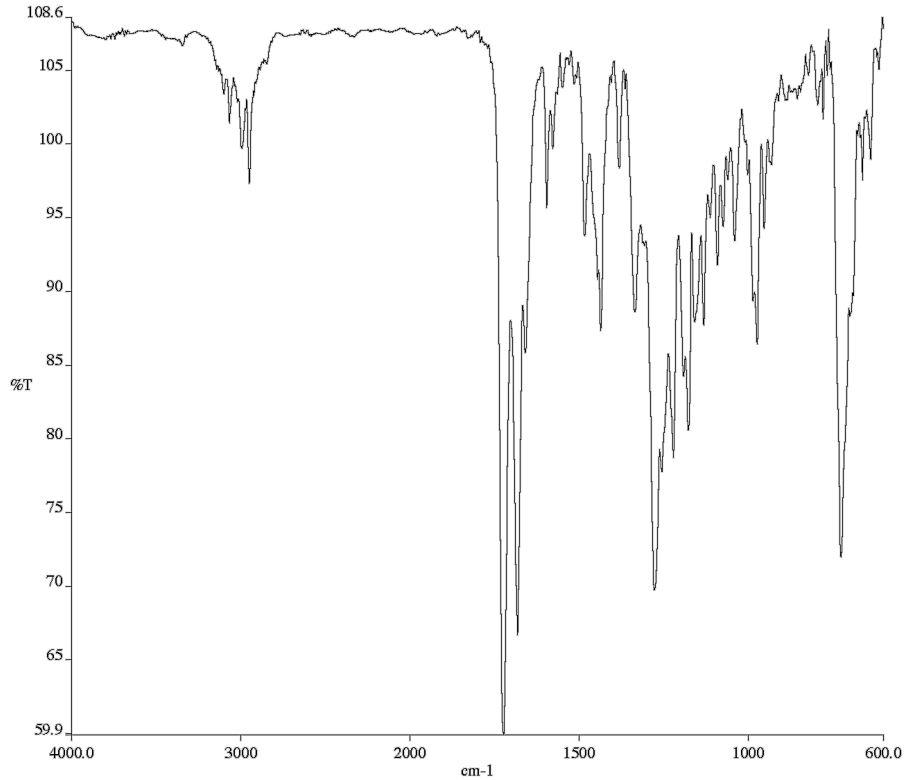



***Figure A9.195*** *Infrared spectrum (Thin Film, NaCl) of compound* ***102***.

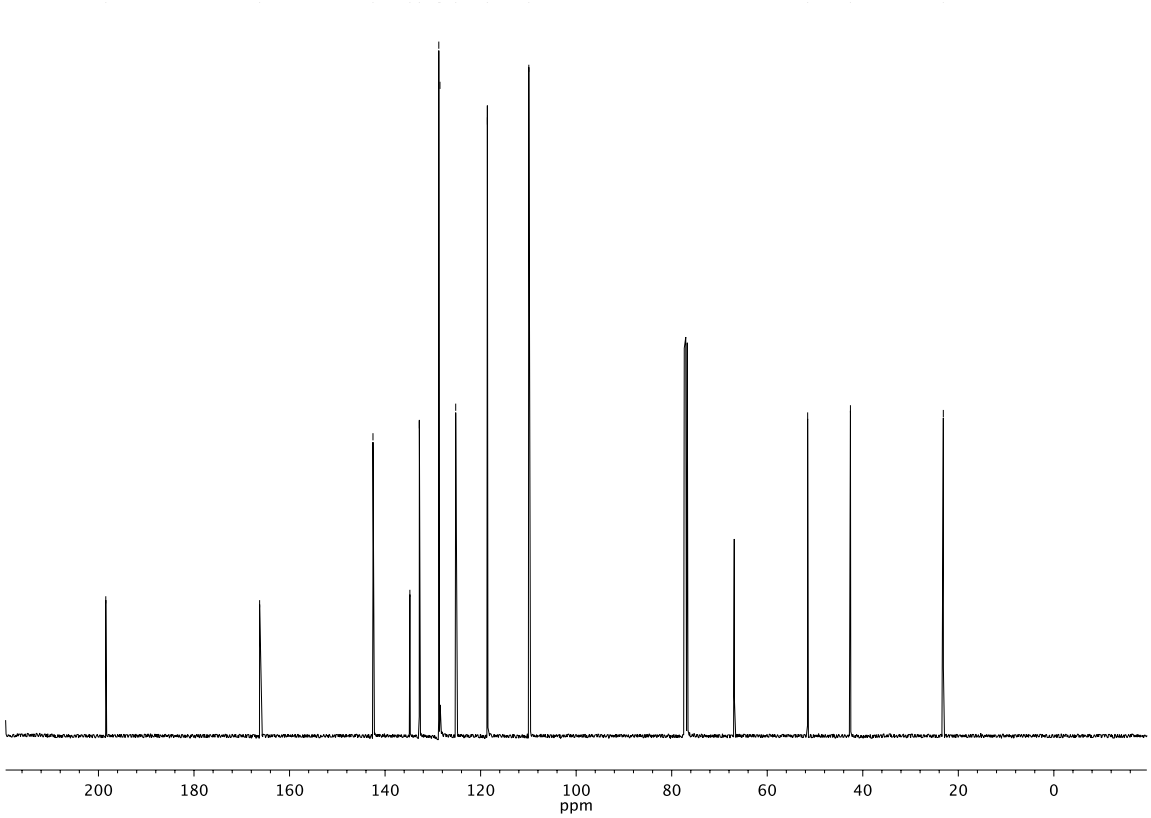
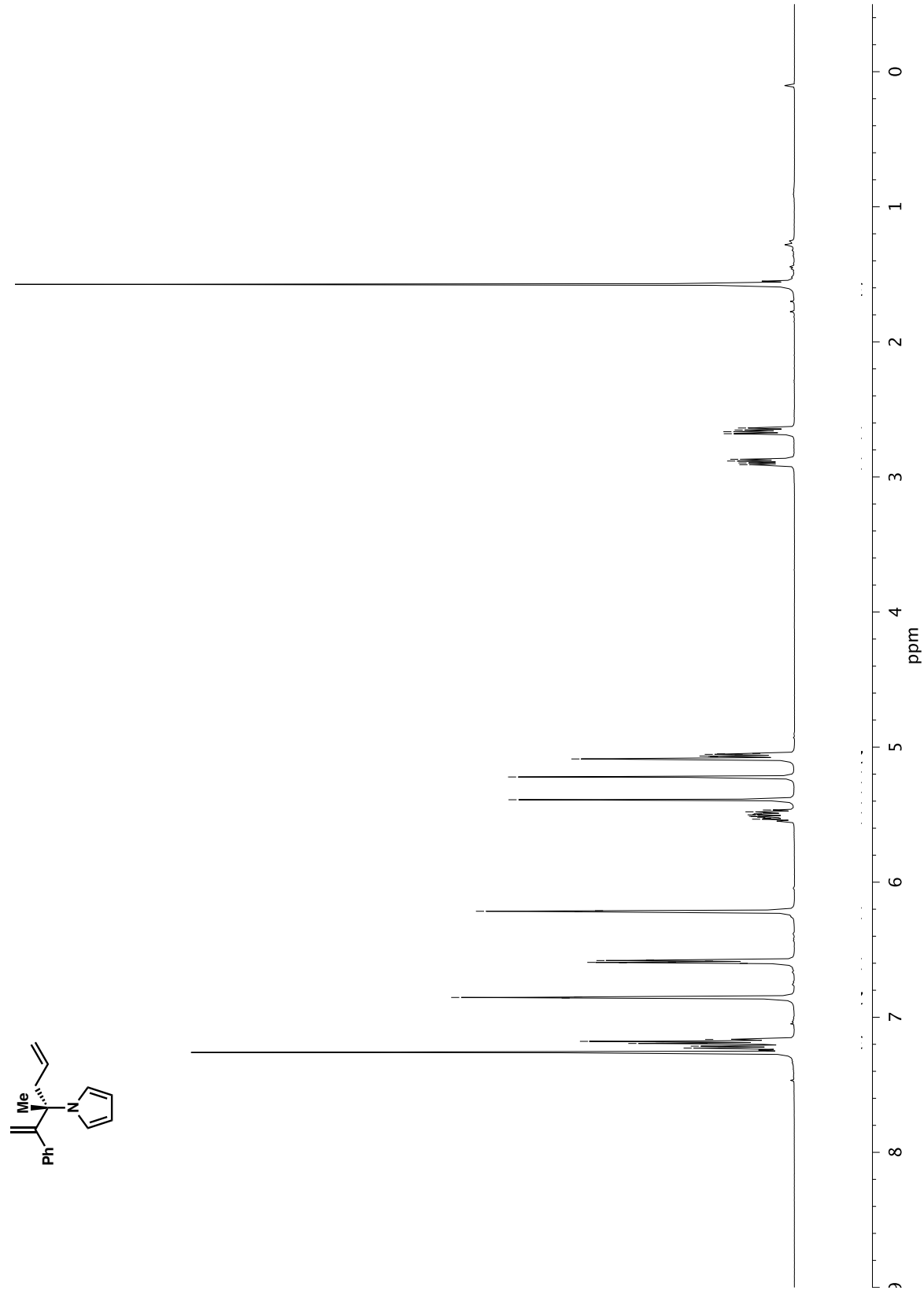



***Figure A9.196*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***102***.




***A9.197*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***103***.

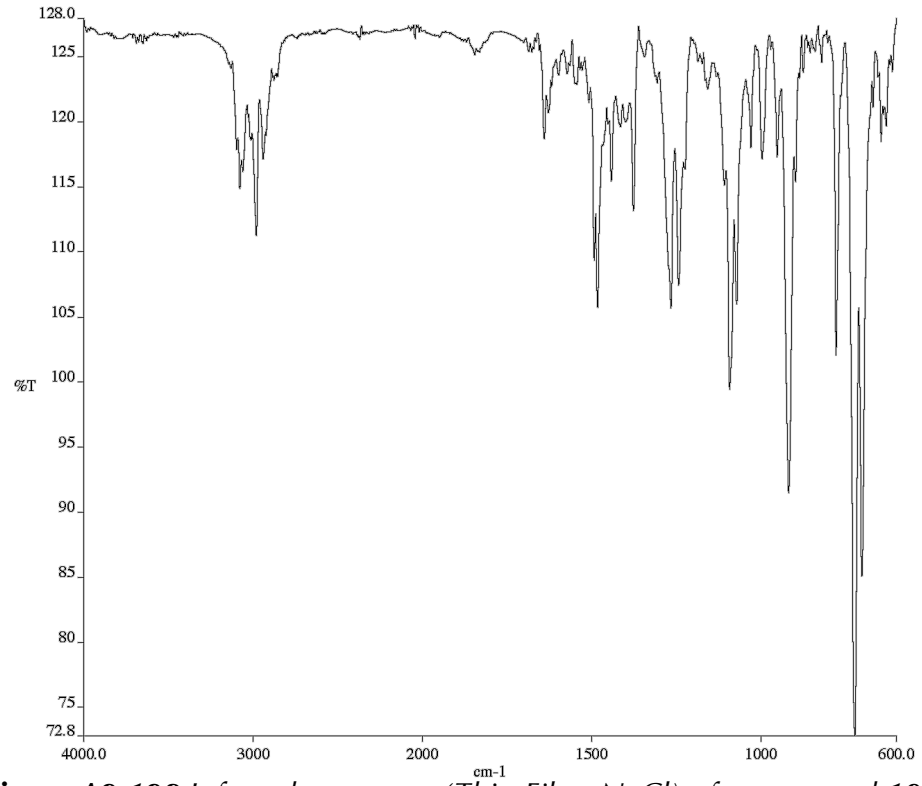



***Figure A9.198*** *Infrared spectrum (Thin Film, NaCl) of compound* ***103***.

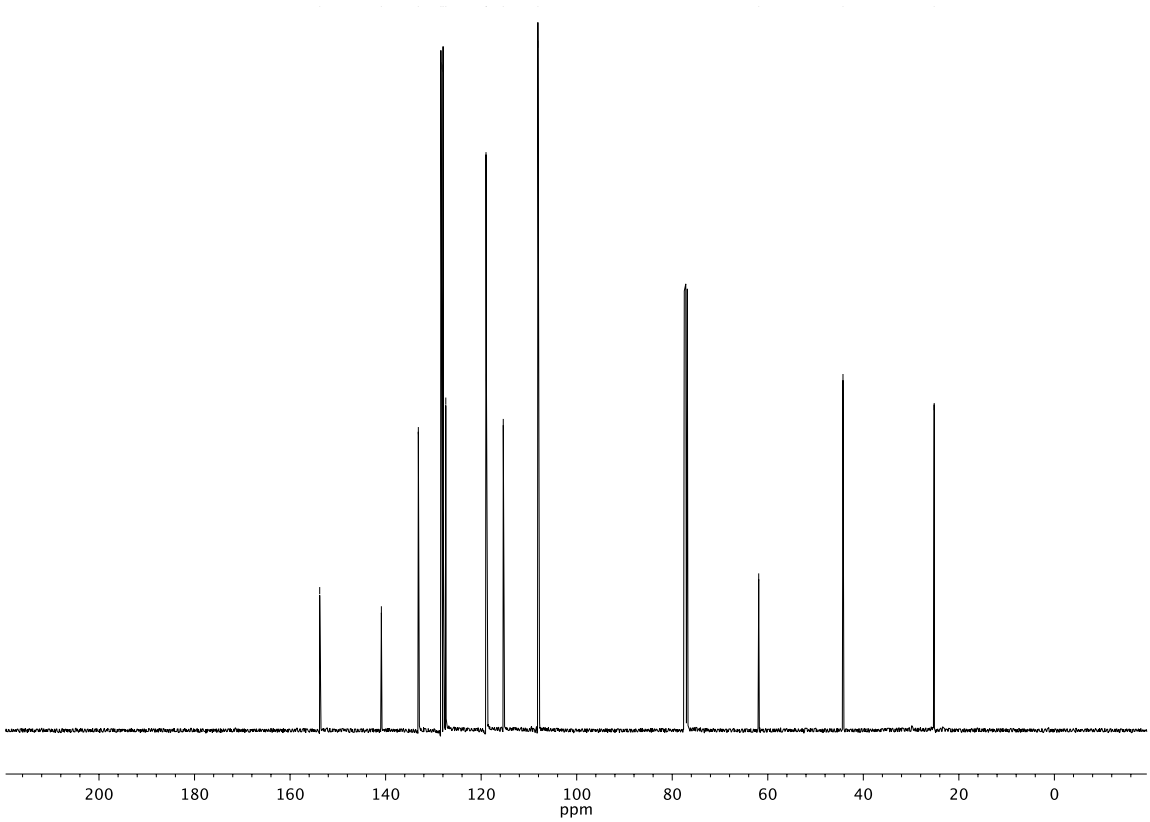
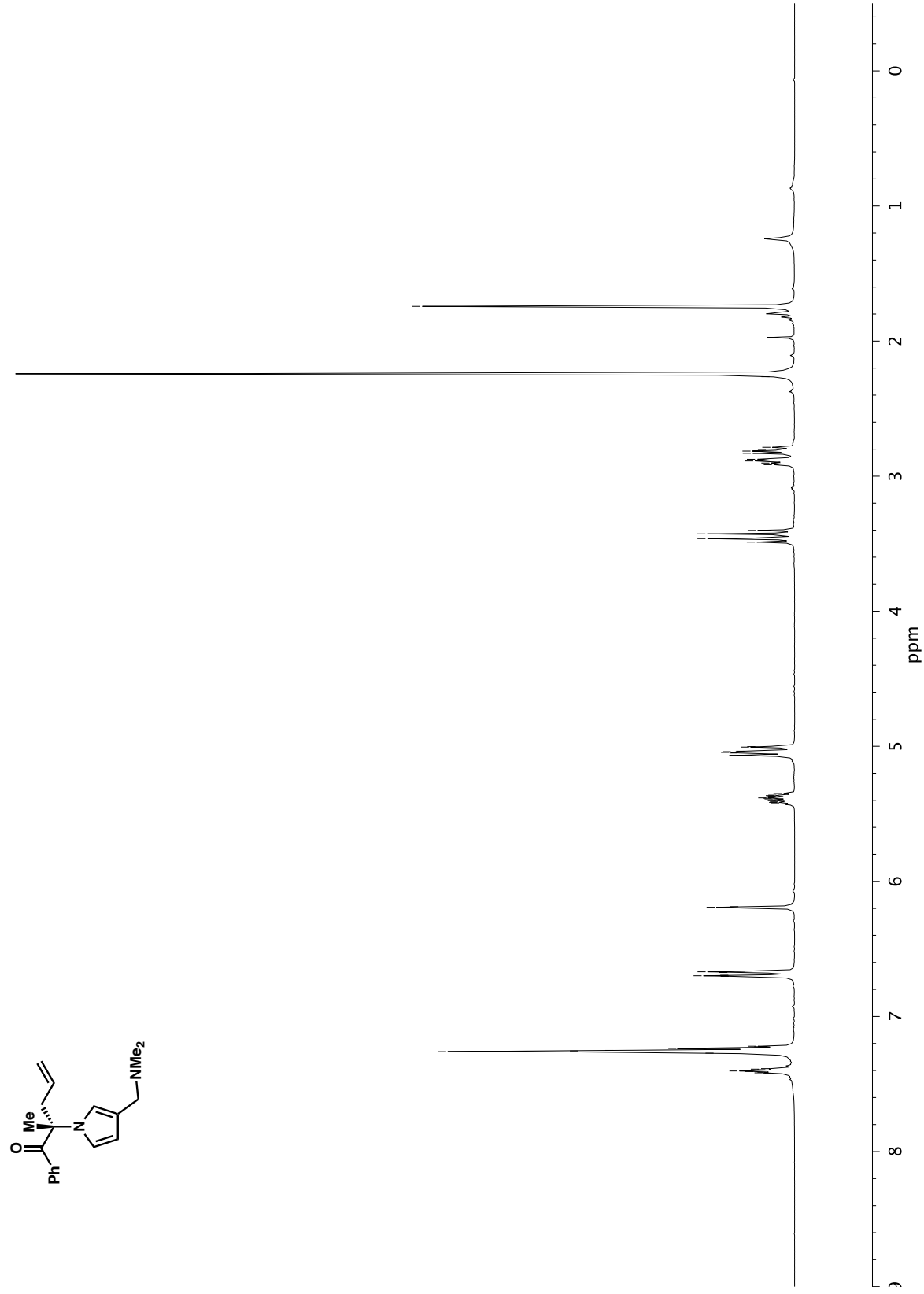



***Figure A9.199*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***103***.




***A9.200*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***104***.

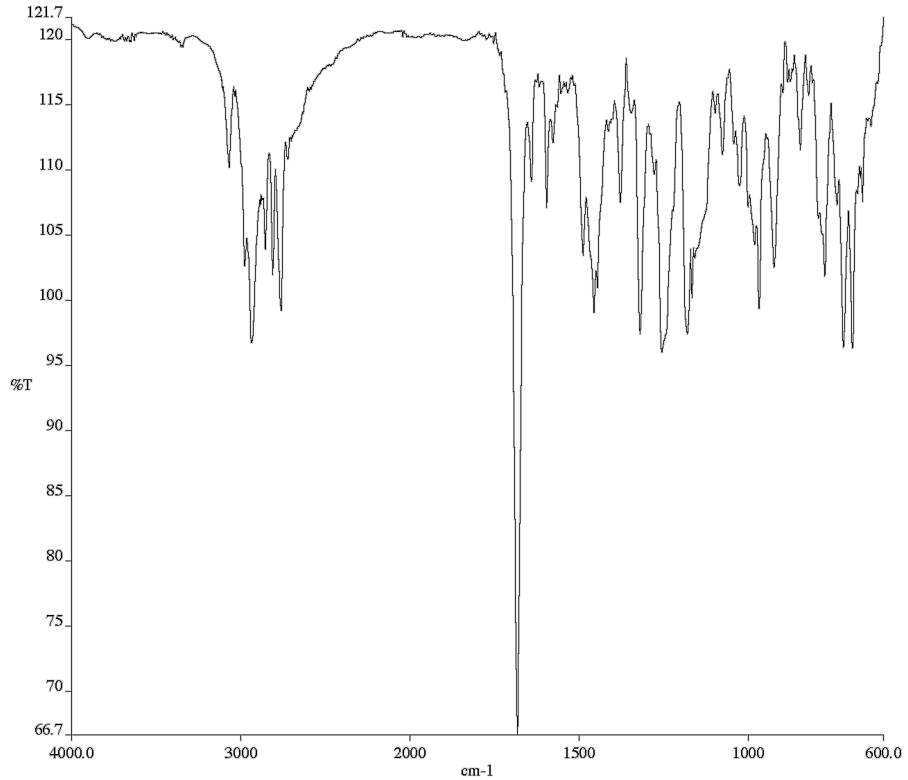



***Figure A9.201*** *Infrared spectrum (Thin Film, NaCl) of compound* ***104****.*

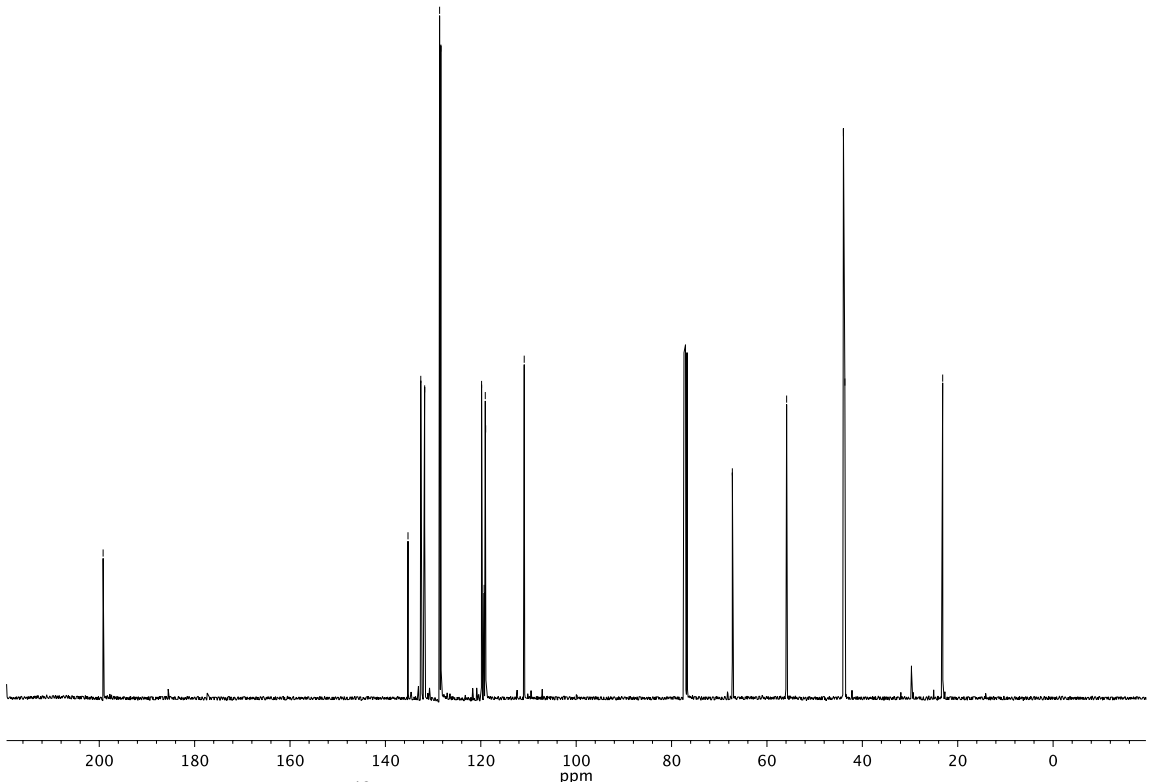



***Figure A9.202*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***104****.*

# *APPENDIX 10*

*X-Ray Crystallography Reports Relevant to Chapter 6:*

*Palladium-Catalyzed Enantioselective Decarboxylative Allylic Alkylation*

*of Acyclic α-Pyrrolyl/Indolyl Ketones*

## A10.1 GENERAL EXPERIMENTAL

X-ray crystallographic analysis was obtained from the Caltech X-Ray Crystallography Facility using a Bruker AXS D8 VENTURE KAPPA diffractometer coupled to a PHOTON II CPAD detector with Cu $K_\alpha$ radiation ($\lambda$ = 1.54178 Å) from an I$\mu$S micro-source. Crystal sample was prepared via slow evaporation from chloroform. Compound crystallizes in the hexagonal space group $P6_122$ with one molecule in the asymmetric unit.

### A10.1.1 X-RAY CRYSTAL STRUCTURE ANALYSIS OF ACYCLIC ALCOHOL 83

***Figure A10.1*** *X-Ray Coordinate of Alkylation Product* ***101f****.*

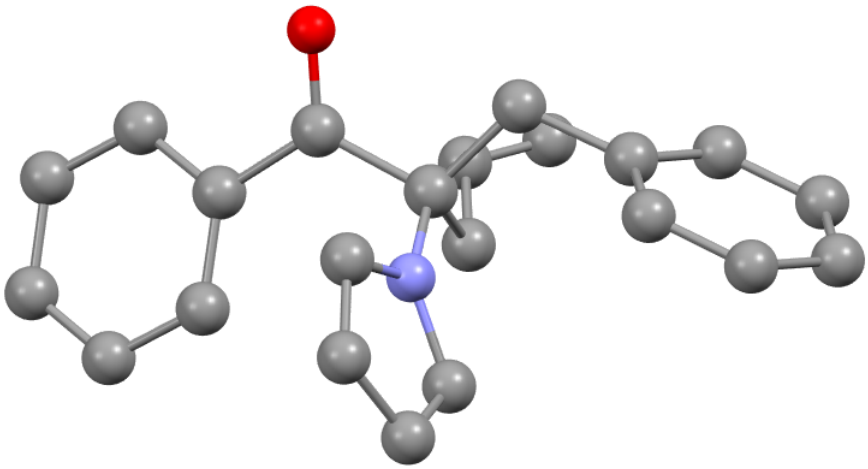


***Table A10.1*** *Crystal data and structure refinement for* ***101f****.*

| | |
|---|---|
| Empirical formula | C22 H21 N O |
| Formula weight | 315.40 |
| Temperature | 100(2) K |
| Wavelength | 1.54178 Å |
| Crystal system | Hexagonal |
| Space group | $P6_122$ |

| | | |
|---|---|---|
| Unit cell dimensions | a = 10.0004(9) Å | a= 90°. |
| | b = 10.0004(9) Å | b= 90°. |
| | c = 60.021(9) Å | g = 120°. |
| Volume | 5198.4(12) $Å^3$ | |
| Z | 12 | |
| Density (calculated) | 1.209 $Mg/m^3$ | |
| Absorption coefficient | 0.570 $mm^{-1}$ | |
| F(000) | 2016 | |
| Crystal size | 0.400 x 0.300 x 0.250 $mm^3$ | |
| Theta range for data collection | 4.420 to 74.784°. | |
| Index ranges | -12<=h<=12, -12<=k<=12, -74<=l<=74 | |
| Reflections collected | 52855 | |
| Independent reflections | 3574 [R(int) = 0.0580] | |
| Completeness to theta = 67.679° | 99.9 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.7538 and 0.6512 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3574 / 0 / 217 | |
| Goodness-of-fit on $F^2$ | 1.096 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0324, wR2 = 0.0766 | |
| R indices (all data) | R1 = 0.0336, wR2 = 0.0774 | |
| Absolute structure parameter | 0.07(9) | |
| Extinction coefficient | n/a | |
| Largest diff. peak and hole | 0.107 and -0.172 $e.Å^{-3}$ | |

***Table A10.2*** *Atomic coordinates (x$10^4$) and equivalent isotropic displacement parameters (Å$^2$x $10^3$) for* ***101f****. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.*

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(1) | 3640(1) | 3587(2) | 799(1) | 25(1) |
| C(1) | 3750(2) | 3710(2) | 597(1) | 18(1) |
| C(11) | 2319(2) | 3021(2) | 456(1) | 18(1) |
| C(12) | 962(2) | 2749(2) | 562(1) | 21(1) |
| C(13) | -416(2) | 2128(2) | 444(1) | 25(1) |
| C(14) | -453(2) | 1771(2) | 220(1) | 26(1) |
| C(15) | 883(2) | 2023(2) | 113(1) | 24(1) |
| C(16) | 2270(2) | 2652(2) | 229(1) | 20(1) |
| C(2) | 5368(2) | 4675(2) | 489(1) | 16(1) |
| N(1) | 5602(2) | 3635(2) | 343(1) | 16(1) |
| C(17) | 5208(2) | 2152(2) | 402(1) | 19(1) |
| C(18) | 5550(2) | 1500(2) | 227(1) | 22(1) |
| C(19) | 6183(2) | 2621(2) | 56(1) | 23(1) |
| C(20) | 6214(2) | 3928(2) | 132(1) | 20(1) |
| C(3) | 5384(2) | 6001(2) | 354(1) | 18(1) |
| C(4) | 4800(2) | 6877(2) | 487(1) | 23(1) |
| C(5) | 5550(2) | 8380(2) | 518(1) | 29(1) |
| C(6) | 6621(2) | 5322(2) | 674(1) | 19(1) |
| C(21) | 8244(2) | 6227(2) | 584(1) | 19(1) |
| C(22) | 9002(2) | 5484(2) | 502(1) | 26(1) |
| C(23) | 10486(2) | 6322(2) | 415(1) | 31(1) |
| C(24) | 11236(2) | 7919(2) | 410(1) | 31(1) |
| C(25) | 10506(2) | 8677(2) | 494(1) | 28(1) |
| C(26) | 9019(2) | 7834(2) | 580(1) | 23(1) |

***Table A10.3*** *Bond lengths [Å] and angles [°] for* ***101f****.*

| | |
|---|---|
| O(1)-C(1) | 1.2169(18) |
| C(1)-C(11) | 1.503(2) |
| C(1)-C(2) | 1.551(2) |
| C(11)-C(12) | 1.397(2) |
| C(11)-C(16) | 1.403(2) |
| C(12)-C(13) | 1.388(2) |
| C(12)-H(12) | 0.9500 |
| C(13)-C(14) | 1.390(2) |
| C(13)-H(13) | 0.9500 |
| C(14)-C(15) | 1.386(2) |
| C(14)-H(14) | 0.9500 |
| C(15)-C(16) | 1.390(2) |
| C(15)-H(15) | 0.9500 |
| C(16)-H(16) | 0.9500 |
| C(2)-N(1) | 1.4668(19) |
| C(2)-C(3) | 1.547(2) |
| C(2)-C(6) | 1.549(2) |
| N(1)-C(20) | 1.3745(19) |
| N(1)-C(17) | 1.377(2) |
| C(17)-C(18) | 1.369(2) |
| C(17)-H(17) | 0.9500 |
| C(18)-C(19) | 1.415(2) |
| C(18)-H(18) | 0.9500 |
| C(19)-C(20) | 1.371(2) |
| C(19)-H(19) | 0.9500 |
| C(20)-H(20) | 0.9500 |
| C(3)-C(4) | 1.504(2) |
| C(3)-H(3A) | 0.9900 |
| C(3)-H(3B) | 0.9900 |
| C(4)-C(5) | 1.314(3) |
| C(4)-H(4) | 0.9500 |
| C(5)-H(5A) | 0.9500 |
| C(5)-H(5B) | 0.9500 |
| C(6)-C(21) | 1.509(2) |

| | |
|---|---|
| C(6)-H(6A) | 0.9900 |
| C(6)-H(6B) | 0.9900 |
| C(21)-C(22) | 1.390(2) |
| C(21)-C(26) | 1.392(2) |
| C(22)-C(23) | 1.392(3) |
| C(22)-H(22) | 0.9500 |
| C(23)-C(24) | 1.384(3) |
| C(23)-H(23) | 0.9500 |
| C(24)-C(25) | 1.385(3) |
| C(24)-H(24) | 0.9500 |
| C(25)-C(26) | 1.391(2) |
| C(25)-H(25) | 0.9500 |
| C(26)-H(26) | 0.9500 |

| | |
|---|---|
| O(1)-C(1)-C(11) | 119.94(14) |
| O(1)-C(1)-C(2) | 119.47(14) |
| C(11)-C(1)-C(2) | 120.46(12) |
| C(12)-C(11)-C(16) | 119.18(15) |
| C(12)-C(11)-C(1) | 116.18(13) |
| C(16)-C(11)-C(1) | 124.64(14) |
| C(13)-C(12)-C(11) | 120.43(15) |
| C(13)-C(12)-H(12) | 119.8 |
| C(11)-C(12)-H(12) | 119.8 |
| C(12)-C(13)-C(14) | 120.01(16) |
| C(12)-C(13)-H(13) | 120.0 |
| C(14)-C(13)-H(13) | 120.0 |
| C(15)-C(14)-C(13) | 120.07(16) |
| C(15)-C(14)-H(14) | 120.0 |
| C(13)-C(14)-H(14) | 120.0 |
| C(14)-C(15)-C(16) | 120.29(15) |
| C(14)-C(15)-H(15) | 119.9 |
| C(16)-C(15)-H(15) | 119.9 |
| C(15)-C(16)-C(11) | 120.02(15) |
| C(15)-C(16)-H(16) | 120.0 |
| C(11)-C(16)-H(16) | 120.0 |
| N(1)-C(2)-C(3) | 110.92(11) |

| | |
|---|---|
| N(1)-C(2)-C(6) | 109.91(12) |
| C(3)-C(2)-C(6) | 110.88(13) |
| N(1)-C(2)-C(1) | 107.15(12) |
| C(3)-C(2)-C(1) | 108.26(12) |
| C(6)-C(2)-C(1) | 109.63(12) |
| C(20)-N(1)-C(17) | 109.05(13) |
| C(20)-N(1)-C(2) | 127.78(13) |
| C(17)-N(1)-C(2) | 123.17(12) |
| C(18)-C(17)-N(1) | 107.93(14) |
| C(18)-C(17)-H(17) | 126.0 |
| N(1)-C(17)-H(17) | 126.0 |
| C(17)-C(18)-C(19) | 107.53(15) |
| C(17)-C(18)-H(18) | 126.2 |
| C(19)-C(18)-H(18) | 126.2 |
| C(20)-C(19)-C(18) | 107.53(14) |
| C(20)-C(19)-H(19) | 126.2 |
| C(18)-C(19)-H(19) | 126.2 |
| C(19)-C(20)-N(1) | 107.95(14) |
| C(19)-C(20)-H(20) | 126.0 |
| N(1)-C(20)-H(20) | 126.0 |
| C(4)-C(3)-C(2) | 112.32(12) |
| C(4)-C(3)-H(3A) | 109.1 |
| C(2)-C(3)-H(3A) | 109.1 |
| C(4)-C(3)-H(3B) | 109.1 |
| C(2)-C(3)-H(3B) | 109.1 |
| H(3A)-C(3)-H(3B) | 107.9 |
| C(5)-C(4)-C(3) | 125.02(17) |
| C(5)-C(4)-H(4) | 117.5 |
| C(3)-C(4)-H(4) | 117.5 |
| C(4)-C(5)-H(5A) | 120.0 |
| C(4)-C(5)-H(5B) | 120.0 |
| H(5A)-C(5)-H(5B) | 120.0 |
| C(21)-C(6)-C(2) | 113.48(12) |
| C(21)-C(6)-H(6A) | 108.9 |
| C(2)-C(6)-H(6A) | 108.9 |
| C(21)-C(6)-H(6B) | 108.9 |

| | |
|---|---|
| C(2)-C(6)-H(6B) | 108.9 |
| H(6A)-C(6)-H(6B) | 107.7 |
| C(22)-C(21)-C(26) | 118.29(16) |
| C(22)-C(21)-C(6) | 121.09(15) |
| C(26)-C(21)-C(6) | 120.62(15) |
| C(21)-C(22)-C(23) | 120.91(17) |
| C(21)-C(22)-H(22) | 119.5 |
| C(23)-C(22)-H(22) | 119.5 |
| C(24)-C(23)-C(22) | 120.16(17) |
| C(24)-C(23)-H(23) | 119.9 |
| C(22)-C(23)-H(23) | 119.9 |
| C(23)-C(24)-C(25) | 119.61(16) |
| C(23)-C(24)-H(24) | 120.2 |
| C(25)-C(24)-H(24) | 120.2 |
| C(24)-C(25)-C(26) | 120.00(17) |
| C(24)-C(25)-H(25) | 120.0 |
| C(26)-C(25)-H(25) | 120.0 |
| C(25)-C(26)-C(21) | 121.01(16) |
| C(25)-C(26)-H(26) | 119.5 |
| C(21)-C(26)-H(26) | 119.5 |

***Table A10.4*** *Anisotropic displacement parameters ($Å^2x10^3$) for* ***101f****. The anisotropic displacement factor exponent takes the form* $-2\pi^2[h^2a^{*2}U^{11} + ... +2\ h\ k\ a^*\ b^*U^{12}]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| O(1) | 24(1) | 35(1) | 17(1) | 4(1) | 3(1) | 15(1) |
| C(1) | 20(1) | 18(1) | 18(1) | 2(1) | 2(1) | 11(1) |
| C(11) | 18(1) | 15(1) | 21(1) | 4(1) | 1(1) | 8(1) |
| C(12) | 20(1) | 17(1) | 25(1) | 2(1) | 4(1) | 9(1) |
| C(13) | 18(1) | 20(1) | 36(1) | 1(1) | 2(1) | 9(1) |
| C(14) | 18(1) | 22(1) | 36(1) | -2(1) | -5(1) | 9(1) |
| C(15) | 25(1) | 22(1) | 24(1) | 0(1) | -3(1) | 11(1) |
| C(16) | 18(1) | 19(1) | 22(1) | 3(1) | 1(1) | 9(1) |
| C(2) | 18(1) | 18(1) | 15(1) | 0(1) | 1(1) | 10(1) |
| N(1) | 18(1) | 16(1) | 16(1) | 1(1) | 1(1) | 9(1) |
| C(17) | 19(1) | 17(1) | 20(1) | 3(1) | 1(1) | 8(1) |
| C(18) | 23(1) | 17(1) | 27(1) | -1(1) | 2(1) | 10(1) |
| C(19) | 24(1) | 24(1) | 21(1) | -1(1) | 5(1) | 11(1) |
| C(20) | 20(1) | 19(1) | 18(1) | 2(1) | 4(1) | 8(1) |
| C(3) | 20(1) | 17(1) | 17(1) | 2(1) | 0(1) | 9(1) |
| C(4) | 30(1) | 24(1) | 20(1) | 1(1) | -1(1) | 17(1) |
| C(5) | 39(1) | 26(1) | 27(1) | -6(1) | -9(1) | 20(1) |
| C(6) | 19(1) | 21(1) | 16(1) | 0(1) | -1(1) | 11(1) |
| C(21) | 19(1) | 21(1) | 17(1) | 0(1) | -3(1) | 10(1) |
| C(22) | 21(1) | 21(1) | 34(1) | -1(1) | 0(1) | 10(1) |
| C(23) | 21(1) | 33(1) | 37(1) | -4(1) | 2(1) | 13(1) |
| C(24) | 19(1) | 34(1) | 31(1) | 4(1) | 1(1) | 6(1) |
| C(25) | 24(1) | 19(1) | 31(1) | 2(1) | -7(1) | 4(1) |
| C(26) | 24(1) | 21(1) | 23(1) | -2(1) | -6(1) | 11(1) |

***Table A10.5*** *Hydrogen coordinates (x $10^4$) and isotropic displacement parameters ($Å^2$ x$10^3$) for* ***101f****.*

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(12) | 983 | 2990 | 715 | 25 |
| H(13) | -1334 | 1947 | 517 | 30 |
| H(14) | -1396 | 1353 | 139 | 31 |
| H(15) | 851 | 1765 | -40 | 29 |
| H(16) | 3185 | 2833 | 155 | 24 |
| H(17) | 4775 | 1668 | 541 | 23 |
| H(18) | 5392 | 482 | 221 | 27 |
| H(19) | 6525 | 2490 | -86 | 28 |
| H(20) | 6591 | 4871 | 52 | 24 |
| H(3A) | 6453 | 6722 | 304 | 21 |
| H(3B) | 4734 | 5566 | 220 | 21 |
| H(4) | 3813 | 6299 | 555 | 28 |
| H(5A) | 6541 | 8997 | 453 | 35 |
| H(5B) | 5102 | 8849 | 604 | 35 |
| H(6A) | 6429 | 5997 | 773 | 23 |
| H(6B) | 6527 | 4451 | 764 | 23 |
| H(22) | 8499 | 4389 | 505 | 31 |
| H(23) | 10987 | 5797 | 358 | 37 |
| H(24) | 12245 | 8491 | 349 | 37 |
| H(25) | 11021 | 9773 | 494 | 34 |
| H(26) | 8525 | 8362 | 638 | 27 |

***Table A10.6*** *Torsion Anlges [°] for* ***101f****.*

| | |
|---|---|
| O(1)-C(1)-C(11)-C(12) | 21.4(2) |
| C(2)-C(1)-C(11)-C(12) | -154.28(14) |
| O(1)-C(1)-C(11)-C(16) | -158.82(15) |
| C(2)-C(1)-C(11)-C(16) | 25.5(2) |
| C(16)-C(11)-C(12)-C(13) | -0.3(2) |
| C(1)-C(11)-C(12)-C(13) | 179.47(14) |
| C(11)-C(12)-C(13)-C(14) | 0.1(3) |
| C(12)-C(13)-C(14)-C(15) | 0.5(3) |
| C(13)-C(14)-C(15)-C(16) | -0.8(3) |
| C(14)-C(15)-C(16)-C(11) | 0.6(3) |
| C(12)-C(11)-C(16)-C(15) | 0.0(2) |
| C(1)-C(11)-C(16)-C(15) | -179.78(15) |
| O(1)-C(1)-C(2)-N(1) | 120.14(15) |
| C(11)-C(1)-C(2)-N(1) | -64.12(17) |
| O(1)-C(1)-C(2)-C(3) | -120.17(15) |
| C(11)-C(1)-C(2)-C(3) | 55.57(17) |
| O(1)-C(1)-C(2)-C(6) | 0.9(2) |
| C(11)-C(1)-C(2)-C(6) | 176.64(13) |
| C(3)-C(2)-N(1)-C(20) | 18.9(2) |
| C(6)-C(2)-N(1)-C(20) | -104.03(17) |
| C(1)-C(2)-N(1)-C(20) | 136.92(15) |
| C(3)-C(2)-N(1)-C(17) | -160.68(14) |
| C(6)-C(2)-N(1)-C(17) | 76.34(18) |
| C(1)-C(2)-N(1)-C(17) | -42.71(18) |
| C(20)-N(1)-C(17)-C(18) | -0.91(18) |
| C(2)-N(1)-C(17)-C(18) | 178.78(14) |
| N(1)-C(17)-C(18)-C(19) | 0.46(19) |
| C(17)-C(18)-C(19)-C(20) | 0.1(2) |
| C(18)-C(19)-C(20)-N(1) | -0.70(19) |
| C(17)-N(1)-C(20)-C(19) | 1.00(18) |
| C(2)-N(1)-C(20)-C(19) | -178.67(15) |
| N(1)-C(2)-C(3)-C(4) | 167.14(13) |
| C(6)-C(2)-C(3)-C(4) | -70.45(17) |

| | |
|---|---|
| C(1)-C(2)-C(3)-C(4) | 49.85(17) |
| C(2)-C(3)-C(4)-C(5) | 126.00(17) |
| N(1)-C(2)-C(6)-C(21) | 60.14(17) |
| C(3)-C(2)-C(6)-C(21) | -62.85(17) |
| C(1)-C(2)-C(6)-C(21) | 177.66(13) |
| C(2)-C(6)-C(21)-C(22) | -79.89(18) |
| C(2)-C(6)-C(21)-C(26) | 99.92(17) |
| C(26)-C(21)-C(22)-C(23) | -1.2(2) |
| C(6)-C(21)-C(22)-C(23) | 178.60(15) |
| C(21)-C(22)-C(23)-C(24) | 0.4(3) |
| C(22)-C(23)-C(24)-C(25) | 0.7(3) |
| C(23)-C(24)-C(25)-C(26) | -1.0(3) |
| C(24)-C(25)-C(26)-C(21) | 0.2(2) |
| C(22)-C(21)-C(26)-C(25) | 0.9(2) |
| C(6)-C(21)-C(26)-C(25) | -178.88(14) |

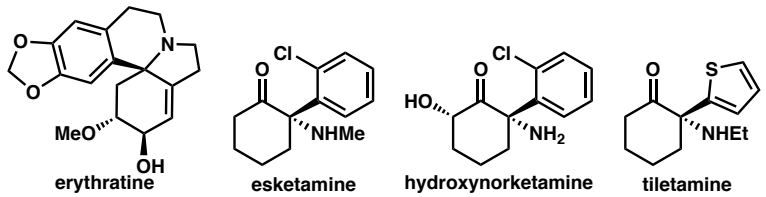
# *CHAPTER 7*

## *Stereospecific Overman Rearrangement of Substituted Cyclic Vinyl Bromides: Access to Fully-Substituted α-Amino Ketones*[†]

### 7.1 INTRODUCTION

The synthesis of amine containing stereocenters has been researched extensively owing to the presence of this moiety in a number of bioactive and synthetically useful molecules (Figure 7.1).[1] Despite this interest, the preparation of this motif in some situations remains a challenge, particularly with respect to enantioenriched fully-substituted α-amino ketones.[2] Many of the reported asymmetric strategies toward this specific motif rely on the functionalization of enolates with electrophilic amine sources, primarily nitroso[3] and azodicarboxylates[4] derivatives (Scheme 7.1). Recently, however, other unique strategies have arisen such as aza-Rubottom type reactions[5] or those based on nucleophilic amine sources.[6]

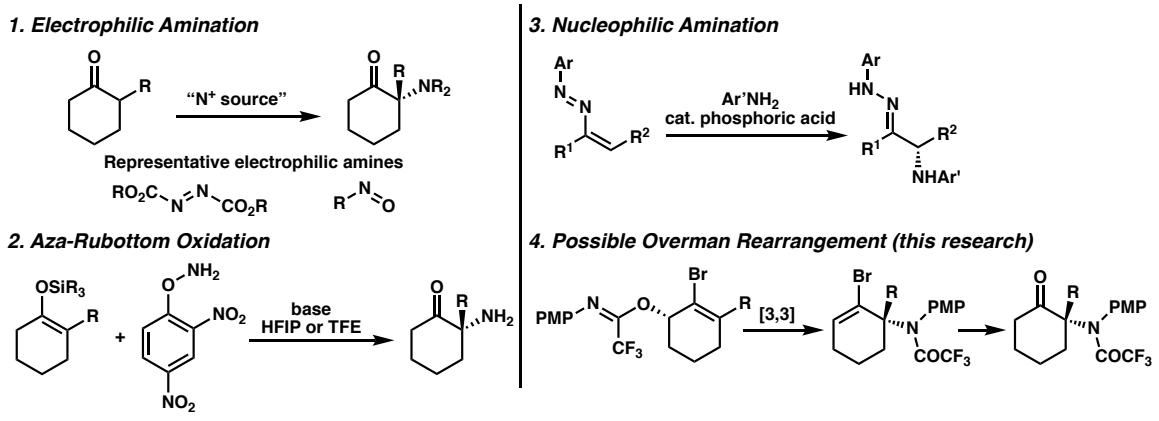
**Figure 7.1** Structures Containing Fully-Substituted Amino Stereocenters.




[†]Research in collaboration with Alvaro Velasco-Rubio, Makoto Yoritate, and Austin Wright. Portions of this chapter have been reproduced with permission from Velasco-Rubio, Á.; Alexy, E. J.; Yoritate, M.; Wright, A. C.; Stoltz, B. M. *Org. Lett.* **2019**, *21*, 8962–8965. © 2019 American Chemical Society.

In continuation of these studies, the development of new strategies would allow for more varied methods to build this important structural motif. Given our interest in fully substituted stereocenters,[7] we sought to employ a strategy that would specifically allow the synthesis of tertiary amine stereocenters in an asymmetric fashion. Sigmatropic rearrangements have proven to be among the most reliable methods for forming hindered stereocenters, with the ability to transfer starting asymmetry to the product in a stereospecific manner. Thus, we decided to target the use of an Overman rearrangement[8] of enantioenriched, substituted allylic alcohols bearing functionality that would ultimately allow the synthesis of an α-amino ketone. The asymmetric aspect of this overall transformation is therefor simplified to the preparation of an enantioenriched allylic alcohol, for which there are numerous reliable preparative procedures. Notably, a related strategy was recently reported by researchers from Janssen for the synthesis of esketamine via a cyanate sigmatropic rearrangement utilizing an asymmetric transfer hydrogenation to provide the requisite enantioenriched allylic alcohol.[9]

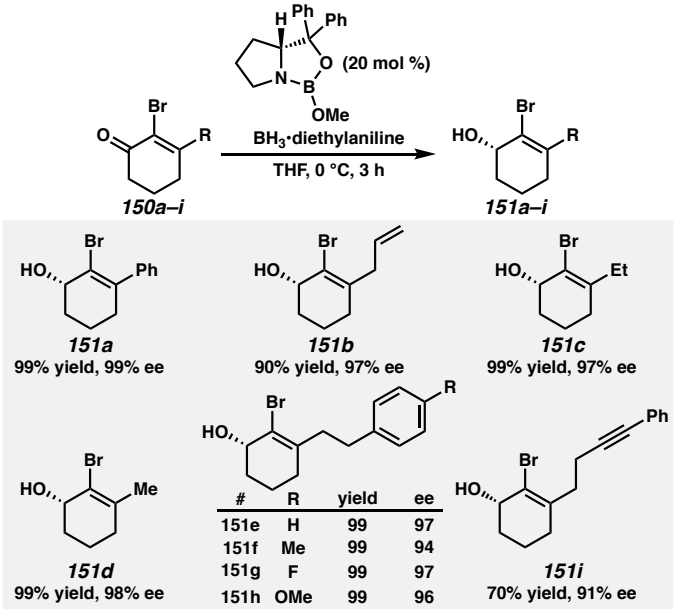
**Scheme 7.1** Synthetic Strategies Toward α-Amino Ketones.



## 7.2 INVESTIGATION OF ENANTIOSELECTIVE REDUCTION

To begin we first investigated different strategies toward the synthesis of chiral, enantioenriched allylic alcohols. Ultimately, the Corey–Bakshi–Shibata (CBS) reduction was identified as ideal for our strategy since it is known to reliably reduce substituted cyclic enones in high enantioselectivity.[10] In particular, bromo-enones are common substrates for CBS reductions, with the bromide imparting enhanced facial bias of the ketone leading to increased enantioselectivities. Often, however, the bromide is solely used as a means of obtaining increasing enantioselectivity, and is subsequently removed via a debromination step following the reduction. In this case, we wondered whether the vinyl bromide functionality could instead be further utilized as a synthetic handle toward the synthesis of additional chiral amine building blocks, in particular α-amino ketones. We were pleased to find that a number of β-substituted α-bromo-enones, containing various aryl and alkyl substituents, could be selectively reduced via the *in situ* formation of the CBS catalyst (Figure 7.2),[11] setting the stage for the subsequent stereospecific Overman rearrangement.

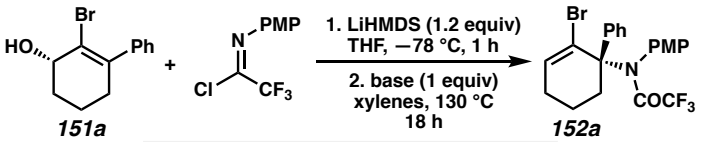
**Figure 7.2** Synthesis of Enantioenriched Alcohols via CBS Reduction.




## 7.3 INVESTIGATION OF OVERMAN REARRANGEMENT

Our initial interest in this transformation focused on aryl-substituted systems owing to their prevalence in pharmaceuticals (e.g. esketamine). Thus we chose cyclohexenol **151a** as a standard substrate for examination of the reaction conditions. While transition-metal catalyzed rearrangements[12] were not successful in our hands, standard thermal conditions affected the desired transformation (Table 7.1). Starting from the allylic alcohol, an intermediate trifluoroacetimidate could be prepared by treatment with LiHMDS and an imidoyl chloride reagent. This material could then be carried on crude through the rearrangement by heating to 130 °C in xylenes with the addition of a base to prevent material decomposition. A variety of bases for the rearrangement were examined, with inorganic bases generally proving to be superior. Potassium carbonate was identified as the optimal base providing the desired rearranged product in 45% yield and 97% ee (entry 6).

**Table 7.1** Overman Rearrangement Base Screen.[a]



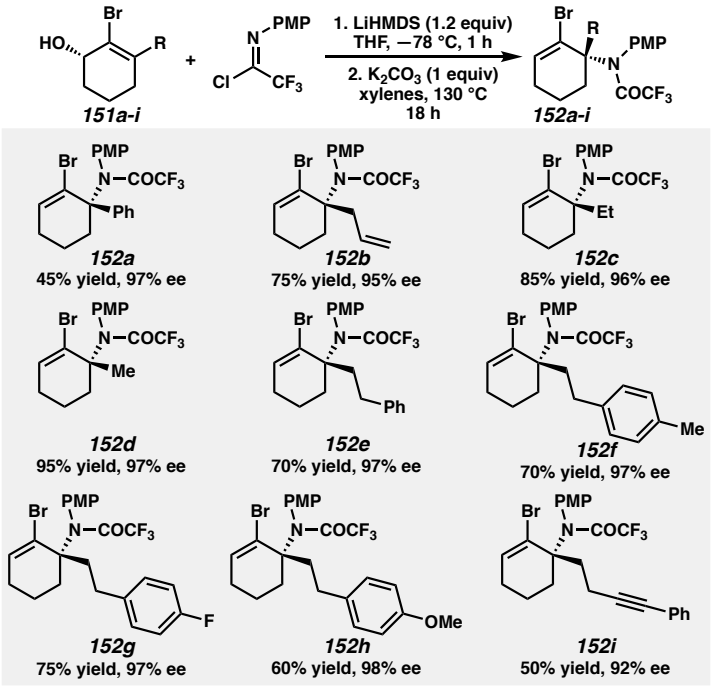

*151a* *152a*

| entry | base | yield (%)[b] | ee (%)[c] |
|---|---|---|---|
| 1 | DBU | 15 | 96 |
| 2 | $Et_3N$ | 33 | 97 |
| 3 | NaOAc | 36 | 97 |
| 4 | NaOH | 40 | 96 |
| 5 | $Li_2CO_3$ | 33 | 96 |
| 6 | $K_2CO_3$ | 45 | 97 |

[a] Conditions: 0.2 mmol **151a**, 0.2 mmol base, 2 mL solvent. [b] Yield of isolated product. [c] Determined by chiral SFC.

Unfortunately, attempts to increase the yield above this point proved to be unsuccessful. Modifying variables such as solvent/temperature combinations and amine protecting group afforded suboptimal results. Additionally, differentially substituted aromatic substituents (e.g., *para*-fluoro) as well as other substrates bearing directly connected $sp^2$ functionality (e.g., vinyl) failed to provide any of the desired product. We wondered how other substrates might perform in this transformation and decided to continue forward with examining a substrate scope (Table 7.2). We were pleased to find that the use of alkyl substituents indeed proved to be more successful. Allyl substituted **152b** was obtained in 75% yield and 95% ee. Small alkyl groups such as ethyl (**152c**) and methyl (**152d**) were also tolerated, furnishing the products in 80% and 95% yield respectively, both in high enantiopurity. The rearrangement performed well with phenylethyl groups bearing various *para*-substituents leading to products **152e**–**152h** in modest 60–75% yield. Lastly, an alkyne was also tolerated in the transformation (**152i**), albeit in a diminished 50% yield. In all cases, minimal to no erosion of allylic alcohol enantiopurity was observed following the rearrangement.[13]

**Table 7.2** Reaction Scope of Overman Rearrangement.[a]

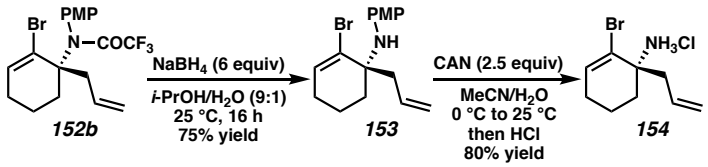



[a] Conditions: 0.2 mmol **151**, 0.2 mmol base, 2 mL solvent. [b] Yield of isolated product. [c] Determined by chiral SFC.

## 7.4 DERIVATIZATION OF REARRANGED PRODUCTS

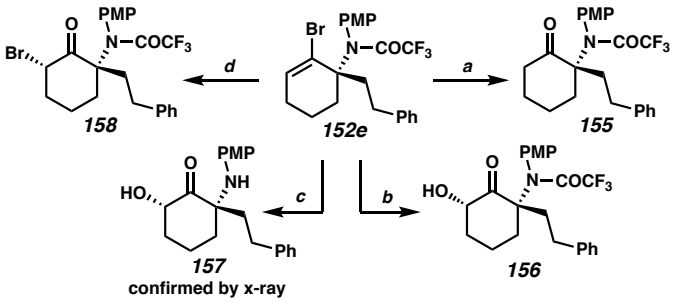
With a scope of the rearrangement examined, we next turned toward derivatizations of the obtained products. Using allyl substituted **152b** as a test substrate, sequential amine deprotections could be performed (Scheme 7.2).[10] First, removal of the trifluoroacetate group was realized under reductive conditions with sodium borohydride providing substituted aniline **153**. Next, oxidative removal of the *p*-methoxy phenyl substituent could be affected under standard oxidative conditions, furnishing the desired tertiary amine **154** as its hydrochloride salt, following treatment with HCl in ether.

**Scheme 7.2** Sequential Removal of Amine Protecting Groups.




Next, our original strategy of targeting fully-substituted α-amino ketones was realized upon exposure of vinyl bromide **152e** to a variety of conditions (Scheme 7.3). Treatment with $Co(acac)_2$ and $Et_3SiH$ under an atmosphere of oxygen affords the corresponding ketone **155** in 75% yield.[14] This transformation is proposed to occur via a Mukaiyama hydration followed by loss of bromide. Surprisingly, during attempts to oxidatively cleave the vinyl bromide under ozonolysis conditions in $CH_2Cl_2$ with pyridine, cyclic α-hydroxy ketone **156** was obtained instead as a single diastereomer in 85% yield, potentially via the intermediacy of an epoxide.[15] This compound is particularly interesting as this substituent pattern mirrors that which is believed to be the active human metabolite of esketamine (hydroxynorketamine) that is essential for the parent molecule's antidepressant activity.[16] When the ozonolysis is performed in methanol, with a dimethylsulfide quench, the α-hydroxy ketone is again obtained, however in this case concomitant removal of the trifluoroacetate protecting group occurs providing ketone **157** in 80% yield. The identity and stereochemistry of ketone **157** was confirmed by X-ray diffraction (see supporting information for details). Lastly, treatment with $RuCl_3$ and sodium periodate interestingly affords the α-bromoketone **158** as a single diastereomer. We were pleased to find that these experiments validate our original hypothesis that the vinyl bromide handle could lead to a variety of α-amino ketone derivatives through relatively straightforward transformations.

**Scheme 7.3** Derivatization of Rearrangement Product **152e**.




Conditions: (a) $Co(acac)_2$ (1 equiv), $Et_2SiH$ (5 equiv), $O_2$ (1 atm), *i*-PrOH, 50 °C, 2 h, 75% yield. (b) $O_3$, pyridine (2.5 equiv), $CH_2Cl_2$, –78 °C to 25 °C, 85% yield. (c) $O_3$, MeOH, then DMS, –78 °C to 25 °C, 80% yield. (d) $RuCl_3$ (2 mol %), $NaIO_4$, MeCN/EtOAc/$H_2O$, 25 °C, 16 h, 60% yield.

## 7.5 CONCLUSIONS

In summary, we have developed a versatile asymmetric method for the synthesis of fully-substituted allylic amines in good yields and excellent enantioselectivities via the combination of a CBS reduction and a stereospecific Overman rearrangement. Subsequent transformations allow the preparation of stereochemically rich and biologically important α-amino ketone derivatives bearing multiple reactive sites poised to undergo further functionalization.

## 7.6 EXPERIMENTAL SECTION

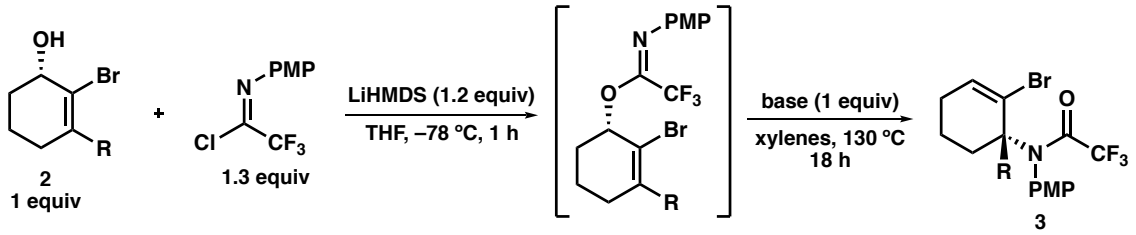
### 7.6.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 μm) was used for flash chromatography. $^1$H NMR spectra were recorded on Varian Inova 500 MHz and Bruker 400 MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm). $^{13}$C NMR spectra were recorded on a Varian Inova 500 MHz spectrometer (125 MHz) and Bruker 400 MHz spectrometers (100 MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm). Data for $^1$H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet, app = apparent. Data for $^{13}$C NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer or Nicolet 6700 FTIR spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption ($cm^{-1}$). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell and are reported as: $[\alpha]_D^T$ (concentration in 10 mg/1 mL, solvent). Analytical SFC was performed with a Mettler SFC supercritical $CO_2$ analytical

chromatography system utilizing Chiralpak (AD-H, AS-H or IC) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+), or obtained from Caltech mass spectrometry laboratory. Reagents were purchased from commercial sources and used as received unless otherwise states.

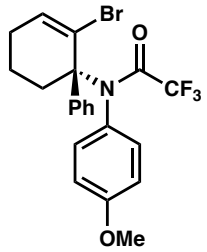
## 7.6.2 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

### 7.6.2.1 General Procedure for Overman Rearrangement



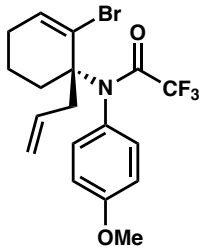

To a stirred solution of the alcohol **2** (0.2 mmol, 1.0 equiv) in THF (1 mL) at –78 ºC under a nitrogen atmosphere was added slowly a solution of LiHMDS (40 mg, 0.24 mmol, 1.2 equiv) in THF (1 mL). The mixture was stirred at –78 °C for 30 min before adding a solution of (*E*)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetimidoyl chloride[1] (62 mg, 0.26 mmol, 1.3 equiv) in THF (1 mL). The reaction was allowed to reach room temperature and stirred for 30 min. The reaction was then filtered through a silica plug (pretreated with $Et_3N$) eluting with 10% $Et_3N$ in $Et_2O$. Following solvent removal in vacuo the crude residue was dissolved in 2 mL of xylenes and $K_2CO_3$ (28 mg, 0.2 mmol, 1.0 equiv) was added. The reaction was then heated to 130 ºC for 18 h, allowed to cool to ambient temperature, and directly purified by silica gel column chromatography to provide the desired product.

### 7.6.2.2 Spectroscopic Data for the Rearranged Vinyl Bromides




**(*S*)-*N*-(6-bromo-3,4-dihydro-[1,1'-biphenyl]-1(2*H*)-yl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (152a)**

Purified by column chromatography (10% EtOAc in Hexanes) to provide the desired product as an amorphous white solid (41 mg, 45% yield); 96% ee, $[\alpha]_D^{25}$ 181.7 (c 0.70, $CHCl_3$); $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.21 (m, 6H), 7.00 (dd, J = 8.9, 2.6 Hz, 1H), 6.80 (dd, J = 8.7, 3.0 Hz, 1H), 6.60 (dd, J = 8.8, 3.0 Hz, 1H), 6.51 (dd, J = 4.9, 3.1 Hz, 1H), 3.77 (s, 3H), 2.88 (d, J = 12.0 Hz, 1H), 2.35 (d, J = 10.1 Hz, 1H), 2.28 – 2.17 (m, 1H), 2.12 – 2.01 (m, 1H), 1.66 – 1.56 (m, 1H), 1.31 – 1.18 (m, 1H); $^{13}$C NMR (100 MHz, Chloroform-*d*) δ 159.7, 156.6 (q, *J* = 34.5 Hz), 139.7, 136.0, 132.4, 132.4, 129.6, 128.3, 127.7, 127.2, 124.1, 116.3 (q, *J* = 289.8 Hz), 113.6, 112.8, 73.1, 55.4, 35.5, 27.62, 18.5; $^{19}$F NMR (282 MHz, Chloroform-*d*) δ –67.1; IR (Neat film, NaCl) 3443, 2931, 1697, 1509, 1250, 1200, 1177, 1035, 760, 732, 698 $cm^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{21}H_{20}BrF_3NO_2$ $[M+H]^+$: 454.0629, found 454.0605; SFC conditions: 10% IPA, Chiralpak OJ-H column, λ=210 nm, $t_R$ (min): minor = 4.68, major = 5.18.



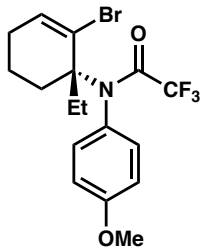

**(*S*)-*N*-(1-allyl-2-bromocyclohex-2-en-1-yl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (152b)**

Purified by column chromatography (5% $Et_2O$ in hexanes) to provide the desired product as a yellow solid (63 mg, 75% yield); 95% ee, $[\alpha]_D^{25}$ 124.0 (c 0.70, $CHCl_3$); $^1$H NMR (400 MHz, Chloroform-*d*) δ 7.47 (d, *J* = 8.8 Hz, 1H), 7.10 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.88 (ddd, *J* = 22.0, 8.7, 3.0 Hz, 2H), 6.37 (dd, *J* = 5.8, 2.9 Hz, 1H), 5.53 – 5.39 (m, 1H), 5.00 – 4.92 (m, 2H), 3.85 (s, 3H), 2.79 – 2.67 (m, 1H), 2.48 (dd, *J* = 13.7, 5.6 Hz, 1H), 2.41 – 2.25 (m, 1H), 2.19 – 2.02 (m, 2H), 1.95 – 1.74 (m, 3H); $^{13}$C NMR (100 MHz, Chloroform-*d*) δ 160.2, 156.0 (q, *J* = 34.3 Hz), 134.5, 133.0, 132.7, 132.3, 128.4, 124.9, 118.5, 116.1 (q, *J* = 289.5 Hz), 113.7, 113.5, 67.4, 55.5, 44.0, 33.0, 26.9, 20.5; $^{19}$F NMR (282 MHz, Chloroform-*d*) δ –67.4; IR (Neat film, NaCl) 3076, 2937, 3838, 1703, 1310, 1444, 1252, 1201, 1152, 1032, 922, 838, 739 $cm^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{18}H_{20}BrF_3NO_2$ $[M+H]^+$: 418.0629, found 418.0609 ; SFC conditions: 5% IPA, Chiralpak OJ-H column, λ=210 nm, $t_R$ (min): minor = 3.26, major = 3.79.

**Procedure for Preparatory Scale Preparation of 152b**

A solution of alcohol **151b** (4.62 mmol, 1.0 g) dissolved in 23 mL of THF was cooled to –78 °C in a dry-ice/acetone bath. A solution of LiHMDS (6.06 mmol, 1.440 g) in 20 mL THF was then added slowly, and the resulting mixture stirred at –78 °C for 30 min. A solution of (*E*)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetimidoyl chloride in 10 mL of

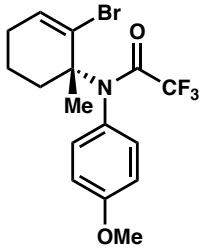
THF was then added slowly, and the reaction allowed to slowly warm to room temperature and continued for 30 min. The crude reaction mixture was then filtered through a short silica plug (pretreated with $Et_3N$) eluting 10% $Et_3N$ in $Et_2O$. Following solvent removal in vacuo, the crude residue was redissolved in 20 mL xylenes and $K_2CO_3$ (4.62 mmol, 637 mg) was added. The reaction was then heated to 130 °C for 18 h, allowed to cool to ambient temperature, and directly purified by silica gel column chromatography (5% $Et_2O$ in hexanes) to provide the desired product as a yellow solid (1.6 g, 83% yield)




**(*R*)-*N*-(2-bromo-1-ethylcyclohex-2-en-1-yl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (152c)**

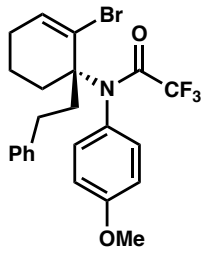
Purified by column chromatography (10% $Et_2O$ in hexanes) to provide the desired product as a brown oil (69 mg, 85% yield); 96% ee, $[\alpha]_D^{25}$ 137.3 (c 0.70, $CHCl_3$); $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.44 (ddd, *J* = 8.8, 2.6, 1.2 Hz, 1H), 7.08 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.89 (dd, *J* = 8.8, 3.0 Hz, 1H), 6.83 (dd, *J* = 8.7, 3.0 Hz, 1H), 6.40 (dd, *J* = 5.6, 3.1 Hz, 1H), 3.84 (s, 3H), 2.73 (dddd, *J* = 13.2, 11.8, 4.6, 1.2 Hz, 1H), 2.42 – 2.33 (m, 1H), 2.16 – 2.05 (m, 2H), 1.91 (dp, *J* = 14.1, 5.0 Hz, 1H), 1.81 – 1.60 (m, 2H), 1.27 – 1.17 (m, 1H), 0.75 (t, *J* = 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, Chloroform-*d*) δ 160.0, 156.1 (q, *J* = 34.2 Hz), 135.0, 132.8, 132.3, 128.5, 125.0, 116.2 (q, *J* = 289.8 Hz), 113.6, 113.2, 68.2, 55.4, 32.8, 32.5, 26.9, 21.2, 9.4; $^{19}$F NMR (282 MHz, Chloroform-*d*) δ –67.3;

IR (Neat film, NaCl) 3390, 2970, 2941, 2838, 1703, 1697, 1505, 1252, 1200, 1179, 1166, 1033, 839, 800, 736, 680, 625 $cm^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{20}BrF_3NO_2$ $[M+H]^+$: 406.0629, found 406.0632; SFC conditions: 3% IPA, Chiralpak AD-H column, λ=210 nm, $t_R$ (min): minor = 6.03, major = 6.58.



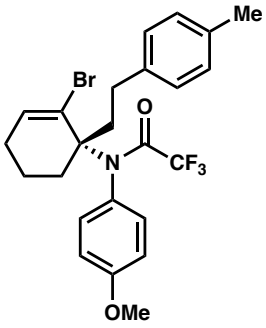

**(*R*)-*N*-(2-bromo-1-methylcyclohex-2-en-1-yl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (152d)**

Purified by column chromatography (10% $Et_2O$ in hexanes) to provide the desired product as a colorless oil (75 mg, 95% yield); 97% ee, $[\alpha]_D^{25}$ 77.1 (c 0.50, $CHCl_3$); $^1H$ NMR (500 MHz, Chloroform-*d*) δ 7.51 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.05 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.91 (dd, *J* = 8.8, 3.0 Hz, 1H), 6.85 (dd, *J* = 8.6, 3.0 Hz, 1H), 6.18 (dd, *J* = 6.5, 2.1 Hz, 1H), 3.84 (s, 3H), 2.86 – 2.75 (m, 1H), 2.34 (dddd, *J* = 17.4, 11.8, 5.6, 2.4 Hz, 1H), 2.14 – 2.06 (m, 1H), 1.97 (dtd, *J* = 12.4, 3.4, 1.6 Hz, 1H), 1.87 (dt, *J* = 10.0, 4.8 Hz, 1H), 1.80 – 1.67 (m, 1H), 1.04 (s, 3H); $^{13}C$ NMR (100 MHz, Chloroform-*d*) δ 160.0, 155.8 (q, *J* = 34.6 Hz), 132.4, 131.7, 131.1, 128.7, 127.2, 116.1 (q, *J* = 289.4 Hz), 113.7, 113.5, 66.3, 56.8, 33.5, 27.1, 26.1; $^{19}F$ NMR (282 MHz, Chloroform-*d*) δ –67.7; IR (Neat film, NaCl) 3435m 2941, 2838, 1697, 1510, 1201, 1182, 1149, 1032, 840, 738, 687 $cm^{-1}$. HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{18}BrF_3NO_2$ $[M+H]^+$: 392.0473, found 392.0450 ; SFC conditions: 10% IPA, Chiralpak OJ-H column, λ=210 nm, $t_R$ (min): minor = 3.41, major = 4.11.



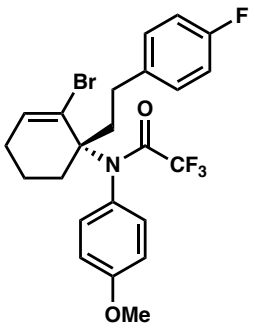

**(*S*)-*N*-(2-bromo-1-phenethylcyclohex-2-en-1-yl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (152e)**

Purified by column chromatography ($Et_2O$ 10% in hexanes) to provide the desired product as a yellow foam (68 mg, 70% yield); 97 % ee, $[\alpha]_D^{25}$ 123.2 (c 0.70, $CHCl_3$); $^1H$ NMR (500 MHz, Chloroform-*d*) δ 7.43 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.24 – 7.18 (m, 2H), 7.18 – 7.10 (m, 2H), 7.00 – 6.94 (m, 2H), 6.93 – 6.86 (m, 1H), 6.83 (dd, *J* = 8.7, 3.0 Hz, 1H), 6.41 (dd, *J* = 5.5, 3.1 Hz, 1H), 3.83 (s, 3H), 2.95 – 2.84 (m, 1H), 2.54 (td, *J* = 12.9, 3.8 Hz, 1H), 2.42 (dddd, *J* = 18.0, 9.1, 5.8, 3.1 Hz, 1H), 2.31 – 2.13 (m, 4H), 1.96 (td, *J* = 13.4, 3.9 Hz, 2H), 1.90 – 1.70 (m, 2H); $^{13}C$ NMR (100 MHz, Chloroform-*d*) δ 160.1, 156.2 (q, *J* = 34.4 Hz), 141.3, 134.9, 132.7, 132.6, 128.4, 128.3, 126.0, 125.4, 116.2 (q, *J* = 289.8 Hz), 113.8, 113.3, 68.0, 55.5, 41.2, 32.2, 31.3, 27.1, 20.8; $^{19}F$ NMR (282 MHz, Chloroform-*d*) δ –67.2; IR (Neat film, NaCl) 3437, 2937, 1697, 1667, 1643, 1509, 1454, 1251, 1201, 1178, 1165, 1149, 1031, 738, 690 $cm^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{23}H_{24}BrF_3NO_2$ $[M+H]^+$: 482.0942, found 482.0953; SFC conditions: 20% IPA, Chiralpak OJ-H column, λ=210 nm, $t_R$ (min): minor = 2.80, major = 3.64.



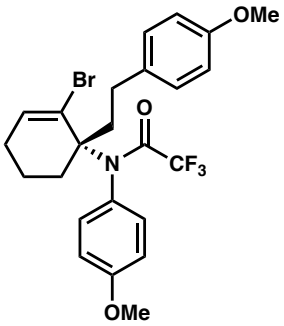

**(*S*)-*N*-(2-bromo-1-(4-methylphenethyl)cyclohex-2-en-1-yl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (152f)**

Purified by column chromatography ($Et_2O$ 10% in hexanes) to provide the desired product as a off-white solid (70 mg, 70% yield); 97% ee, $[\alpha]_D^{25}$ 222.3 (c 0.70, $CHCl_3$); $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.43 (ddd, *J* = 8.8, 2.7, 1.1 Hz, 1H), 7.13 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.02 (d, *J* = 7.7 Hz, 2H), 6.90 – 6.81 (m, 4H), 6.40 (dd, *J* = 5.5, 3.1 Hz, 1H), 3.83 (s, 3H), 2.92 – 2.84 (m, 1H), 2.54 – 2.37 (m, 2H), 2.29 (s, 3H), 2.26 – 2.14 (m, 3H), 2.01 – 1.69 (m, 4H); $^{13}$C NMR (100 MHz, Chloroform-*d*) δ 160.1, 156.2 (q, *J* = 34.3 Hz), 138.3, 135.5, 134.8, 132.8, 132.6, 129.1, 128.4, 128.2, 125.4, 116.2 (q, *J* = 289.8 Hz), 113.8, 113.3, 68.0, 55.5, 41.3, 32.2, 30.8, 27.1, 20.8; $^{19}$F NMR (282 MHz, Chloroform-*d*) δ –67.2; IR (Neat film, NaCl) 3444, 2937, 1697, 1509, 1198, 1178, 1151, 1164, 1033, 839, 736, 624 $cm^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{24}H_{26}BrF_3NO_2$ $[M+H]^+$: 496.1099, found 496.1118; SFC conditions: 10% IPA, Chiralpak OJ-H column, λ = 210 nm, $t_R$ (min): minor = 6.47, major = 6.87.



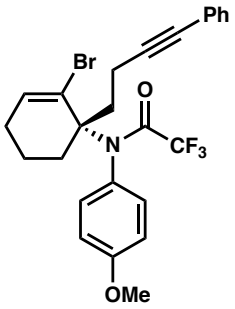

**(*S*)-*N*-(2-bromo-1-(4-fluorophenethyl)cyclohex-2-en-1-yl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (152g)**

Purified by column chromatography ($Et_2O$ 10% in hexanes) to provide the desired product as an amorphous solid (75 mg, 75% yield); 97% ee, $[\alpha]_D^{25}$ 118.3 (c 0.70, $CHCl_3$); $^1$H NMR (400 MHz, Chloroform-*d*) δ 7.42 (dd, *J* = 8.7, 1.5 Hz, 1H), 7.13 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.95 – 6.78 (m, 6H), 6.41 (dd, *J* = 5.5, 3.1 Hz, 1H), 3.82 (s, 3H), 2.89 (ddd, *J* = 13.2, 11.4, 4.2 Hz, 1H), 2.57 – 2.35 (m, 2H), 2.31 – 2.11 (m, 3H), 2.02 – 1.66 (m, 4H); $^{13}$C NMR (100 MHz, Chloroform-*d*) δ 162.5, 160.1, 160.1, 156.2 (q, *J* = 34.3 Hz), 137.0, 136.9, 135.1, 132.7, 132.6, 129.7, 129.6, 128.3, 116.2 (q, *J* = 289.7 Hz), 115.3, 115.1, 113.8, 113.3, 68.0, 55.5, 41.4, 32.2, 30.5, 27.1, 20.7; $^{19}$F NMR (282 MHz, Chloroform-*d*) δ –67.2, -116.1 – -118.8 (m); IR (Neat film, NaCl) 3443, 2936, 1698, 1509, 1252, 1201, 1179, 1154, 1032, 970, 834, 736 $cm^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{23}H_{23}BrF_4NO_2$ $[M+H]^+$: 500.0848, found 500.0846; SFC conditions: 10% IPA, Chiralpak OJ-H column, λ = 210 nm, $t_R$ (min): minor = 4.96, major = 5.98.




**(*S*)-*N*-(2-bromo-1-(4-methoxyphenethyl)cyclohex-2-en-1-yl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (152h)**

Purified by column chromatography ($CH_2Cl_2$ 50% in hexanes) to provide the desired product as a colorless oil (62mg, 60% yield); 98% ee, $[\alpha]_D^{25}$ 85.2 (c 0.70, $CHCl_3$); $^1$H NMR (400 MHz, Chloroform-*d*) δ 7.43 (dd, *J* = 8.8, 1.5 Hz, 1H), 7.12 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.94 – 6.79 (m, 4H), 6.79 – 6.70 (m, 2H), 6.40 (dd, *J* = 5.5, 3.0 Hz, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 2.94 – 2.80 (m, 1H), 2.54 – 2.34 (m, 2H), 2.25 – 2.09 (m, 3H), 2.02 – 1.77 (m, 3H), 1.70 (td, *J* = 13.2, 4.9 Hz, 1H); $^{13}$C NMR (100 MHz, Chloroform-*d*) δ 160.1, 157.9, 156.2 (q, *J* = 34.4 Hz), 134.8, 133.4, 132.8, 132.6, 129.2, 128.4, 125.4, 116.2 (q, *J* = 289.8 Hz), 113.8, 113.3, 68.0, 55.5, 41.5, 30.4, 20.8; $^{19}$F NMR (282 MHz, Chloroform-*d*) δ -67.2; IR (Neat film, NaCl) 3386, 2934, 2836, 1697, 1513, 1249, 1201, 1178, 1151, 1034, 824, 737 $cm^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{24}H_{26}BrF_3NO_3$ $[M+H]^+$: 512.1048, found 512.1056; SFC conditions: 10% IPA, Chiralpak OJ-H column, λ = 210 nm, $t_R$ (min): minor = 10.76, major = 11.37.

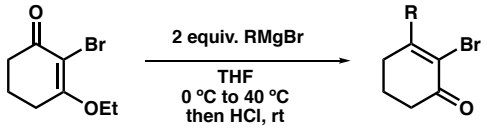



**(*S*)-*N*-(2-bromo-1-(4-phenylbut-3-yn-1-yl)cyclohex-2-en-1-yl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (152i)**

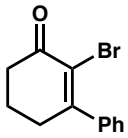
Purified by column chromatography (15% $Et_2O$ in Hexanes) to provide the desired product as a colorless oil (51 mg, 50% yield); 92% ee, $[\alpha]_D^{25}$ 181.7 (c 0.70, $CHCl_3$); $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.47 (ddd, *J* = 8.8, 3.0, 1.4 Hz, 1H), 7.36 – 7.30 (m, 2H), 7.27 (tq, *J* = 3.9, 2.1 Hz, 3H), 7.14 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.94 (dd, *J* = 8.8, 3.0 Hz, 1H), 6.87 (dd, *J* = 8.7, 3.0 Hz, 1H), 6.43 (dd, *J* = 5.5, 3.2 Hz, 1H), 3.86 (s, 3H), 2.84 (ddd, *J* = 13.4, 11.5, 4.4 Hz, 1H), 2.46 – 2.30 (m, 2H), 2.24 – 2.12 (m, 3H), 2.06 (ddd, *J* = 13.5, 10.6, 5.1 Hz, 1H), 2.02 – 1.92 (m, 1H), 1.92 – 1.70 (m, 2H); $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 160.2, 156.2 (q, *J* = 34.4 Hz), 135.5, 132.7, 132.4, 131.5, 128.2, 127.8, 124.5, 123.5, 116.2 (q, *J* = 289.7 Hz), 113.9, 113.5, 88.9, 80.8, 67.5, 55.5, 55.4, 38.1, 32.3, 27.0, 20.7, 15.3; $^{19}$F NMR (282 MHz, Chloroform-*d*) δ -67.2; IR (Neat film, NaCl) 3441, 2937, 2839, 1703, 1698, 1510, 1300, 1252, 1200, 1179, 1152, 1032, 972, 756, 690 $cm^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{25}H_{24}BrF_3NO_2$ $[M+H]^+$: 506.0942, found 506.0962; SFC conditions: 15% IPA, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 4.51, major =4.98.

### 7.6.2.3 Synthesis of 2-Bromo-Enones

**General procedure A for the synthesis of the 2-bromo-enones**

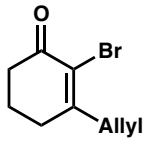



To a solution of 2-bromo-3-ethoxycyclohex-2-en-1-one[2] (1.09 g, 5 mmol, 1.0 equiv) in THF (0.1 M) at 0 ºC was added slowly the corresponding Grignard (2.0 equiv). The reaction was then heated to 40 °C and continued until no starting material remained as seen by TLC. The reaction was then quenched with 2M HCl (2.0 equiv) and stirred at room temperature for 2 hours. The reaction was diluted with water and extracted with $Et_2O$, and the combined organic phases dried over anhydrous $Na_2SO_4$ and concentrated. The crude product was purified by silica gel column chromatography to yield the desired product.



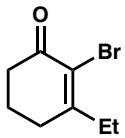

**2-bromo-5,6-dihydro-[1,1'-biphenyl]-3(4*H*)-one (150a)**

Purified by column chromatography (10% AcOEt in Hexanes) to provide a white-off solid (1 g, 80% yield); $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.46 – 7.29 (m, 5H), 2.79 (t, *J* = 6.0 Hz, 2H), 2.75 – 2.69 (m, 2H), 2.21 – 2.13 (m, 2H); $^{13}$C NMR (100 MHz, Chloroform-*d*) δ 191.7, 160.8, 140.8, 128.9, 128.4, 126.9, 122.5, 37.8, 35.1, 22.4; IR (Neat film NaCl) 3056, 2957, 2867, 1681, 1588, 1265, 1182, 1130, 983, 785, 755, 700 cm$^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{12}H_{12}BrO$ $[M+H]^+$: 251.0071, found 251.0069.



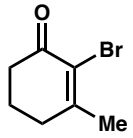

**3-allyl-2-bromocyclohex-2-en-1-one (150b)**

Purified by column chromatography (20% AcOEt in Hexanes) to provide a colorless oil (1.020 g, 95% yield); $^{1}$H NMR (500 MHz, Chloroform-*d*) δ 5.78 (td, *J* = 16.8, 16.0, 7.4 Hz, 1H), 5.22 – 5.14 (m, 2H), 3.24 (d, *J* = 6.7 Hz, 2H), 2.59 (t, *J* = 6.6 Hz, 2H), 2.50 (t, *J* = 6.0 Hz, 2H), 1.99 (p, *J* = 5.9 Hz, 2H); $^{13}$C NMR (100 MHz, Chloroform-*d*) δ 191.3, 161.0, 131.6, 123.1, 118.4, 43.4, 37.8, 32.1, 21.9; IR (Neat film NaCl) 3079, 2949, 2888, 1693, 1598, 1453, 1427, 1416, 1273, 1183, 985, 920, 794 cm$^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_9H_{12}BrO$ $[M+H]^+$: 215.0071, found 215.0059.



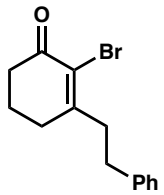

**2-bromo-3-ethylcyclohex-2-en-1-one (150c)**

Purified by column chromatography (10% AcOEt in Hexanes) to provide a red oil (707 mg, 70% yield); $^{1}$H NMR (500 MHz, Chloroform-*d*) δ 2.60 – 2.54 (m, 2H), 2.54 – 2.41 (m, 4H), 2.04 – 1.95 (m, 2H), 1.13 (t, *J* = 7.6 Hz, 3H); $^{13}$C NMR (100 MHz, Chloroform-*d*) δ 191.4, 165.3, 122.0, 37.8, 32.5, 31.9, 22.0, 11.0; IR (Neat film NaCl) 3436, 2936, 2875, 1693, 1598, 1455k 1461, 1282, 1191, 1170, 1133, 984, 886, 801 cm$^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_8H_{12}BrO$ $[M+H]^+$: 203.0071, found 203.0060.




**2-bromo-3-methylcyclohex-2-en-1-one (150d)**

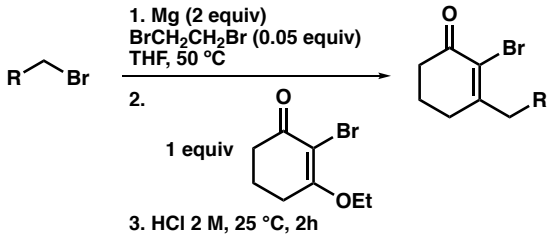
Purified by column chromatography (10% AcOEt in Hexanes) to provide the desired product a colorless oil (750 mg, 80% yield); $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 2.58 – 2.45 (m, 4H), 2.14 (t, *J* = 0.9 Hz, 3H), 2.02 – 1.90 (m, 2H); $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 191.0, 160.6, 122.7, 37.6, 34.2, 25.9, 21.8; IR (Neat film NaCl) 2946, 2869, 1681, 1605, 1452, 1426, 1371, 1269, 1194, 1172, 1269, 1194, 1172, 1134, 1039, 978, 909, 793 cm$^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_7H_{10}BrO$ $[M+H]^+$: 188.9915, found 188.9907.



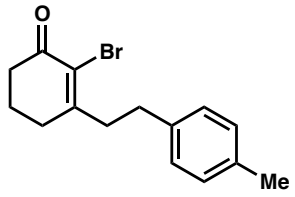

**2-bromo-3-phenethylcyclohex-2-en-1-one (150e)**

Purified by column chromatography (20% AcOEt in Hexanes) to provide the desired product as a white solid (1.110 g, 80% yield); $^{1}$H NMR (500 MHz, Chloroform-*d*) δ 7.33 – 7.28 (m, 2H), 7.25 – 7.21 (m, 3H), 2.92 – 2.85 (m, 2H), 2.83 – 2.74 (m, 2H), 2.62 – 2.53 (m, 2H), 2.39 (t, *J* = 6.1 Hz, 2H), 1.99 – 1.87 (m, 2H); $^{13}$C NMR (100 MHz, Chloroform-*d*) δ 191.3, 163.1, 140.5, 128.7, 128.5, 126.6, 123.3, 41.3, 37.8, 33.2, 32.9, 22.0; IR (Neat film NaCl) 2932, 2865, 1681, 1598, 1495, 1454, 1269, 1175, 978, 795, 749, 700 cm$^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{14}H_{16}BrO$ $[M+H]^+$: 279.0384, found 279.0370.

**General procedure B for the synthesis of the 2-bromo-enones**



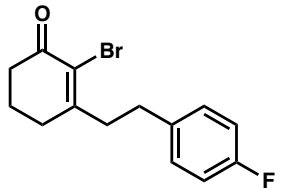

A flame-dried flask under nitrogen was charged with magnesium turnings (260 mg, 20 mmol, 2.0 equiv,), the bromo derivative (2 mmol, 0.2 equiv), dibromoethane (0.2 mmol, 0.01 equiv) and 5 mL of THF. The reaction was heated to 50 ºC to initiate the Grignard reagent formation. Then, a solution of the bromo derivative (18 mmol, 1.8 equiv) in 15 mL of THF was added to the reaction and the resulting mixture was heated for 30 min. The reaction was then cooled to room temperature and a solution of 2-bromo-3-ethoxycyclohex-2-en-1-one (2.20 g, 10 mmol, 1.0 equiv) in THF (15 mL) was added slowly. The reaction was heated at 50 ºC until no starting material remained by TLC. The reaction was allowed to cool to ambient temperature, then quenched with 2M HCl and stirred for 2 h. The reaction was diluted with water and extracted with $Et_2O$. The combined organic phases were dried over $Na_2SO_4$ and concentrated. The crude product was purified by silica gel column chromatography to provide the desired product.




**2-bromo-3-(4-methylphenethyl)cyclohex-2-en-1-one (150f)**

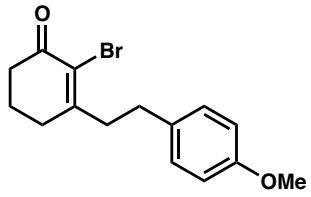
Purified by column chromatography (20% AcOEt in Hexanes) provide the desired product as a white solid (2.248 g, 77% yield); $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.11 (s, 4H), 2.87 – 2.72 (m, 4H), 2.60 – 2.54 (m, 2H), 2.40 (t, *J* = 6.0 Hz, 2H), 2.34 (s, 3H),

1.99 – 1.90 (m, 2H); $^{13}$C NMR (100 MHz, Chloroform-*d*) δ 191.2, 163.2, 137.3, 136.0, 129.3, 128.3, 123.1, 41.3, 37.8, 33.1, 32.4, 21.9, 21.1; IR (Neat film NaCl) 2925, 2866, 1681, 1596, 1514, 1454, 1425, 1269, 1174, 1127, 978, 808 cm$^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{18}BrO$ $[M+H]^+$: 293.0541, found 293.0546.




**2-bromo-3-(4-fluorophenethyl)cyclohex-2-en-1-one (150g)**

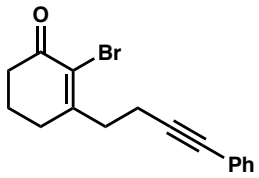
Purified by column chromatography (20% AcOEt in Hexanes) to provide the desired product as white solid (2.368 g, 80% yield); $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.22 – 7.12 (m, 2H), 7.03 – 6.93 (m, 2H), 2.85 (dd, *J* = 9.6, 6.6 Hz, 2H), 2.79 – 2.70 (m, 2H), 2.62 – 2.50 (m, 2H), 2.39 (t, *J* = 6.0 Hz, 2H), 1.98 – 1.89 (m, 2H); $^{13}$C NMR (100 MHz, Chloroform-*d*) δ 191.1, 162.6, 161.6 (d, *J* = 244.3 Hz), 136.0 (d, *J* = 3.2 Hz), 129.8 (d, *J* = 7.8 Hz), 123.3, 115.4 (d, *J* = 21.2 Hz), 41.2, 37.7, 33.1, 31.9, 21.9; $^{19}$F NMR (282 MHz, Chloroform-*d*) δ -116.56 (tt, *J* = 8.7, 5.4 Hz); IR (Neat Film NaCl) 2932, 2868, 1693, 1681, 1599, 1512, 1505, 1222, 979, 824, 805, 771 cm$^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{14}H_{15}BrFO$ $[M+H]^+$: 297.0290, found 297.0304.




**2-bromo-3-(4-methoxyphenethyl)cyclohex-2-en-1-one (150h)**

Purified by column chromatography (25% AcOEt in Hexanes) to provide the desired product as a white solid (3.0 g, 65% yield); $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.18 –

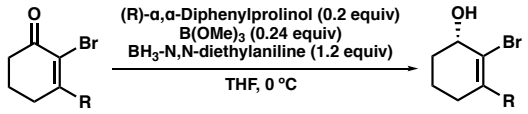
7.09 (m, 2H), 6.90 – 6.74 (m, 2H), 3.80 (s, 3H), 2.86 – 2.80 (m, 2H), 2.75 (ddd, *J* = 8.6, 6.6, 1.3 Hz, 2H), 2.60 – 2.54 (m, 2H), 2.38 (t, *J* = 6.0 Hz, 2H), 1.99 – 1.89 (m, 2H); $^{13}$C NMR (100 MHz, Chloroform-*d*) δ 191.23, 163.23, 158.22, 132.41, 129.32, 123.09, 113.97, 55.30, 41.42, 37.75, 33.12, 31.91, 21.93; IR (Neat film NaCl) 2933, 2834, 1681, 1597, 1513,1454, 1426, 1246, 1176, 1034, 978, 822, 801 cm$^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{18}BrO_2$ $[M+H]^+$: 309.0490, found 309.0500.



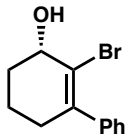

**2-bromo-3-(4-phenylbut-3-yn-1-yl)cyclohex-2-en-1-one (150i)[3]**

Purified by column chromatography (20% AcOEt in Hexanes) to provide the desired product as a colorless oil (1.5 g, 50% yield); $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.35 (qd, *J* = 3.8, 1.6 Hz, 2H), 7.29 – 7.24 (m, 3H), 2.78 (dd, *J* = 7.5, 5.7 Hz, 2H), 2.71 (td, *J* = 6.8, 1.4 Hz, 2H), 2.63 (t, *J* = 6.0 Hz, 2H), 2.58 (dd, *J* = 7.4, 6.0 Hz, 2H), 2.06 – 1.96 (m, 2H); $^{13}$C NMR (100 MHz, Chloroform-*d*) δ 191.1, 162.0, 131.5, 128.3, 128.0, 123.7, 123.3, 87.8, 81.9, 37.8, 37.8, 33.2, 21.9, 17.0; IR (Neat film NaCl) 2942, 2866, 1681, 1597, 1441, 1271, 1175, 978, 757, 689 cm$^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{16}BrO$ $[M+H]^+$: 303.0384, found 303.0387

### 7.6.2.4 CBS Reduction of Ketones

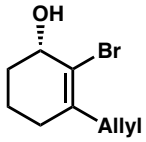



To a stirred solution of (R)-α,α-Diphenylprolinol (0.2 equiv) in THF (0.1 M) was added trimethyl borate (0.24 equiv) and the resulting mixture was stirred for 1 h at room temperature. Then, borane N,N-diethylaniline complex (1.2 equiv) was added and the reaction was cooled to 0 ºC. After 10 min of stirring at this temperature, a solution of **1** in THF (0.5 M) was added slowly over 3 hours. Following completion of the addition, the reaction was quenched with 2 M HCl and extracted with $Et_2O$. The combined organic layers were dried over $Na_2SO_4$ and concentrated. The crude mixture was purified by column chromatography to provide the desired alcohol.



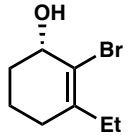

**(*S*)-2-bromo-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-ol (151a)**

Purified by column chromatography (20% EtOAc in Hexanes) to provide the desired product as a white solid (250 mg, 99% yield); 99% ee, $[\alpha]_D^{25}$ -61.8 (c 0.70, $CHCl_3$); $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.38 (tt, *J* = 7.6, 1.4 Hz, 2H), 7.34 – 7.29 (m, 1H), 7.26 – 7.22 (m, 2H), 4.44 (ddt, *J* = 4.8, 2.8, 1.5 Hz, 1H), 2.68 (s, 1H), 2.51 – 2.33 (m, 2H), 2.08 – 1.89 (m, 3H), 1.85 – 1.73 (m, 1H); $^{13}$C NMR (100 MHz, Chloroform-*d*) δ 142.3, 141.7, 128.3, 127.7, 127.5, 123.6, 71.1, 34.5, 31.8, 18.6; IR (Neat film NaCl) 3382, 2930, 1489, 1441, 1331, 1064, 990, 756, 697 $cm^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{12}H_{14}BrO$ $[M\text{-}OH]^+$: 235.0117, found 235.0125; SFC conditions: 15% IPA, Chiralpak IC column, λ = 210 nm, $t_R$ (min): minor = 3.90, major = 4.74.




**(*S*)-3-allyl-2-bromocyclohex-2-en-1-ol (151b)**

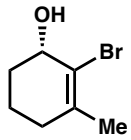
Purified by column chromatography (20% EtOAc in Hexanes) to provide the desired product as a colorless oil (195 mg, 90% yield); 97% ee, $[\alpha]_D^{25}$ -102.1 (c 0.70, $CHCl_3$); $^1H$ NMR (500 MHz, Chloroform-*d*) δ 5.75 (ddt, *J* = 16.8, 10.0, 6.7 Hz, 1H), 5.18 – 5.00 (m, 2H), 4.28 (t, *J* = 4.6 Hz, 1H), 2.96 (ddtd, *J* = 6.7, 4.7, 1.5, 0.7 Hz, 2H), 2.21 – 2.02 (m, 2H), 1.95 – 1.84 (m, 2H), 1.83 – 1.72 (m, 1H), 1.69 – 1.53 (m, 1H); $^{13}C$ NMR (100 MHz, Chloroform-*d*) δ 138.5, 133.6, 123.6, 116.7, 71.1, 41.6, 32.0, 31.3, 18.3; IR (Neat film, NaCl) 3382, 2932, 1636, 1447, 1335, 1170, 1075, 993, 971, 917, 798, 699 $cm^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_9H_{12}Br$ $[M\text{-}OH]^+$: 199.0117, found 199.0126; SFC conditions: 10% IPA, Chiralpak IC column, λ = 210 nm, $t_R$ (min): minor = 3.60, major = 4.05.




**(*S*)-2-bromo-3-ethylcyclohex-2-en-1-ol (151c)**

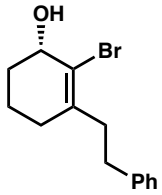
Purified by column chromatography (20% EtOAc in Hexanes) to provide the desired product as a white solid (203 mg, 99% yield); 97% ee, $[\alpha]_D^{25}$ -90.2 (c 0.70, $CHCl_3$); $^1H$ NMR (400 MHz, Chloroform-*d*) δ 4.23 (t, *J* = 4.6 Hz, 1H), 2.42 (s, 1H), 2.22 – 2.04 (m, 4H), 1.88 – 1.82 (m, 2H), 1.81 – 1.68 (m, 1H), 1.65 – 1.56 (m, 1H), 0.99 (t, *J* = 7.6 Hz, 3H); $^{13}C$ NMR (100 MHz, Chloroform-*d*) δ 142.1, 122.0, 71.1, 32.1, 30.9, 30.4, 18.4, 11.4; IR (Neat film, NaCl) 3366, 2934, 2872, 1651, 1455, 1337, 1166, 1077, 978, 914,

801, 725 $cm^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_8H_{12}Br$ $[M\text{-}OH]^+$: 187.0117, found 187.0123; Chiral GC: 120 ºC Isotherm, GTA column, FID detector, $t_R$ (min): minor = 14.52, major = 15.77.




**(*S*)-2-bromo-3-methylcyclohex-2-en-1-ol (151d)**

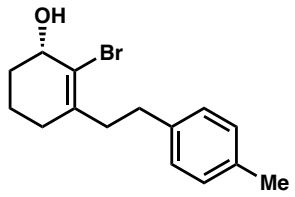
Purified by column chromatography (20% EtOAc in Hexanes) to provide the desired product as a white solid (189 mg, 99% yield); 98% ee, $[\alpha]_D^{25}$ -100.5 (c 0.70, $CHCl_3$); $^1H$ NMR (500 MHz, Chloroform-*d*) δ 4.27 (tq, *J* = 4.6, 1.3 Hz, 1H), 2.25 – 2.03 (m, 3H), 1.92 – 1.86 (m, 2H), 1.86 – 1.83 (m, 3H), 1.83 – 1.75 (m, 1H), 1.67 – 1.60 (m, 1H); $^{13}C$ NMR (100 MHz, Chloroform-*d*) δ 137.1, 122.5, 71.0, 33.3, 32.0, 23.5, 18.2; IR (Neat film, NaCl) 3334, 2936, 2864, 1654, 1438, 1337, 1166, 1078, 1010, 978, 794 $cm^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_7H_{10}Br$ $[M\text{-}OH]^+$: 172.9960, found 172.9965; Chiral GC: 120 ºC Isotherm, GTA column, FID detector, $t_R$ (min): minor = 11.10, major = 12.84.




**(*S*)-2-bromo-3-phenethylcyclohex-2-en-1-ol (151e)**

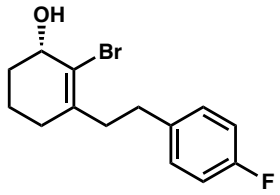
Purified by column chromatography (20% EtOAc in Hexanes) to provide the desired product as a white solid (278 mg, 99% yield); 97% ee, $[\alpha]_D^{25}$ -50.2 (c 0.70, $CHCl_3$); $^1H$ NMR (500 MHz, Chloroform-*d*) δ 7.31 (t, *J* = 7.6 Hz, 2H), 7.23 (dd, *J* = 8.0, 3.1 Hz, 3H), 4.31 – 4.26 (m, 1H), 2.80 – 2.73 (m, 2H), 2.49 (ddt, *J* = 13.6, 7.3, 3.4 Hz, 2H), 2.35 (s,

1H), 2.20 – 2.02 (m, 2H), 1.88 (dd, *J* = 7.9, 4.5 Hz, 2H), 1.83 – 1.71 (m, 1H), 1.63 (dt, *J* = 13.6, 5.1 Hz, 1H); $^{13}$C NMR (100 MHz, Chloroform-*d*) δ 141.4, 140.2, 128.4, 128.4, 126.1, 123.5, 71.1, 39.3, 33.3, 32.0, 31.9, 18.3; IR (Neat film, NaCl) 3390, 2934, 2863, 1495, 1454, 1335, 1077, 972, 748, 699cm$^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{14}H_{16}Br$ $[M\text{-}OH]^+$: 263.0430, found 263.0420; SFC conditions: 15% IPA, Chiralpak OJ-H column, λ = 210 nm, $t_R$ (min): minor = 5.03, major = 5.43.



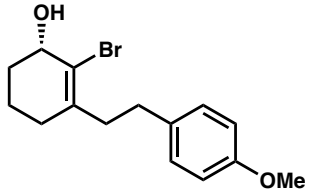

**(*S*)-2-bromo-3-(4-methylphenethyl)cyclohex-2-en-1-ol (151f)**

Purified by column chromatography (20% EtOAc in Hexanes) to provide the desired product as a white solid (292 mg, 99% yield); 94% ee, $[\alpha]_D^{25}$ -59.4 (c 0.70, $CHCl_3$); $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.19 (s, 3H), 4.35 (t, *J* = 4.6 Hz, 1H), 2.86 – 2.71 (m, 2H), 2.55 (tdq, *J* = 11.3, 7.8, 3.5 Hz, 3H), 2.41 (s, 3H), 2.30 – 2.07 (m, 2H), 2.01 – 1.89 (m, 2H), 1.84 (dddd, *J* = 14.1, 10.4, 8.5, 5.3 Hz, 1H), 1.75 – 1.65 (m, 1H); $^{13}$C NMR (100 MHz, Chloroform-*d*) δ 140.3, 138.4, 135.5, 129.1, 128.3, 123.4, 71.2, 39.5, 32.9, 32.1, 31.9, 21.1, 18.4; IR (Neat film, NaCl) 3392, 2932, 2863, 1514, 1454, 1334, 1249, 1163, 1076, 806, 610 cm$^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{18}Br$ $[M\text{-}OH]^+$: 277.0586, found 277.0574; SFC conditions: 10% IPA, Chiralpak OJ-H column, λ = 210 nm, $t_R$ (min): minor = 7.79, major = 8.70.




**(*S*)-2-bromo-3-(4-fluorophenethyl)cyclohex-2-en-1-ol (151g)**

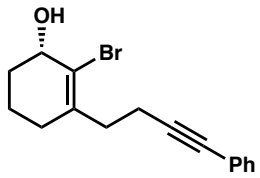
Purified by column chromatography (20% AcOEt in Hexanes) to provide the desired product as a white solid (296 mg, 99% yield); 97% ee, $[\alpha]_D^{25}$ -59.9 (c 0.70, $CHCl_3$); $^1H$ NMR (500 MHz, Chloroform-*d*) δ 7.19 – 7.13 (m, 2H), 7.00 – 6.94 (m, 2H), 4.27 (t, *J* = 4.7 Hz, 1H), 2.72 (ddd, *J* = 9.0, 6.9, 2.5 Hz, 2H), 2.53 – 2.39 (m, 2H), 2.26 (s, 1H), 2.18 – 1.99 (m, 2H), 1.92 – 1.83 (m, 2H), 1.76 (dtt, *J* = 16.7, 8.4, 5.4 Hz, 1H), 1.70 – 1.54 (m, 1H); $^{13}C$ NMR (101 MHz, Chloroform-*d*) δ 161.4 (d, *J* = 243.7 Hz), 139.9, 136.9 (d, *J* = 3.3 Hz), 129.8 (d, *J* = 7.8 Hz), 123.7, 115.1 (d, *J* = 21.2 Hz), 71.1, 39.3, 32.4, 31.9, 31.9, 18.3; $^{19}F$ NMR (282 MHz, Chloroform-*d*) δ -117.34 (tt, *J* = 8.9, 5.4 Hz); IR (Neat film, NaCl) 3392, 2932, 2864, 1600, 1509, 1221, 1157, 1076, 973, 825 $cm^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{14}H_{15}BrF$ $[M\text{-}OH]^+$: 281.0336, found 281.0327; SFC conditions: 10% IPA, Chiralpak OJ-H column, λ=210, $t_R$ (min): minor = 4.73, major = 5.63.




**(*S*)-2-bromo-3-(4-methoxyphenethyl)cyclohex-2-en-1-ol (151h)**

Purified by column chromatography (20% AcOEt in Hexanes) to provide the desired product as a white solid (308 mg, 99% yield); 96% ee, $[\alpha]_D^{25}$ -59.9 (c 0.70, $CHCl_3$); $^1H$ NMR (500 MHz, Chloroform-*d*) δ 7.19 – 7.08 (m, 2H), 6.91 – 6.67 (m, 2H), 4.27 (t, *J* =

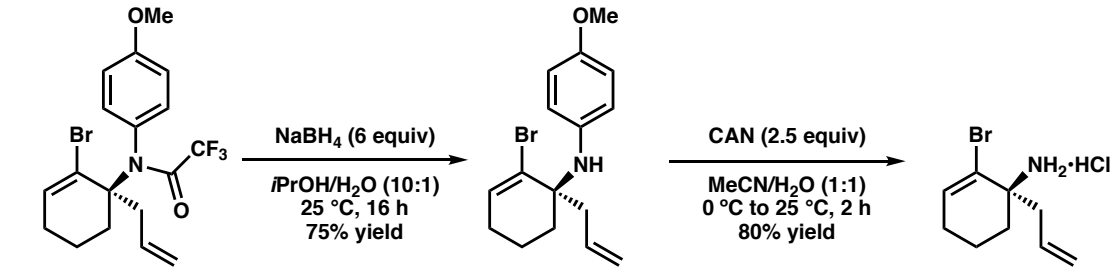
4.6 Hz, 1H), 3.80 (s, 3H), 2.75 – 2.67 (m, 2H), 2.50 – 2.40 (m, 2H), 2.35 (s, 1H), 2.19 – 2.00 (m, 2H), 1.92 – 1.84 (m, 2H), 1.76 (dtt, *J* = 19.6, 8.7, 5.3 Hz, 1H), 1.68 – 1.56 (m, 1H); $^{13}$C NMR (100 MHz, Chloroform-*d*) δ 158.0, 140.3, 133.5, 129.4, 123.5, 113.9, 71.2, 55.4, 39.6, 32.5, 32.1, 32.0, 18.4; IR (Neat film, NaCl) 3380, 2935, 2863, 1611, 1511, 1454, 1243, 1174, 1033, 972, 818, 728 cm$^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{18}BrO$ $[M\text{-}OH]^+$: 293.0535, found 293.0527; SFC conditions: 20 % IPA, Chiralpak OJ-H column, λ = 210 nm, $t_R$ (min): minor = 4.72, major = 5.45.

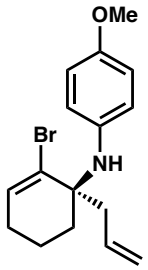



**(*S*)-2-bromo-3-(4-phenylbut-3-yn-1-yl)cyclohex-2-en-1-ol (151i)**

Purified by column chromatography (20% $Et_2O$ in Hexanes) to provide the desired product as a brown oil (213 mg, 70% yield); 91% ee, $[\alpha]_D^{25}$ -62.8 (c 0.70, $CHCl_3$); $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.42 – 7.36 (m, 2H), 7.31 – 7.26 (m, 3H), 4.29 (t, *J* = 4.7 Hz, 1H), 2.59 (ddd, *J* = 7.1, 6.3, 3.1 Hz, 2H), 2.52 (dd, *J* = 8.7, 7.0 Hz, 2H), 2.30 (dtd, *J* = 17.2, 5.1, 1.2 Hz, 2H), 2.25 – 2.19 (m, 1H), 1.91 (dt, *J* = 9.5, 4.6 Hz, 2H), 1.87 – 1.76 (m, 1H), 1.71 – 1.61 (m, 1H); $^{13}$C NMR (100 MHz, Chloroform-*d*) δ 139.3, 131.5, 128.3, 127.7, 124.2, 123.7, 89.0, 81.2, 71.1, 36.2, 32.0, 32.0, 18.3, 17.3; IR (Neat film, NaCl) 3432, 2933, 2864, 2364, 1681, 1597, 1489, 1442, 1335, 1272, 1175, 1076, 977, 757, 692 cm$^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{16}Br$ $[M\text{-}OH]^+$: 287.0430, found 287.0437; SFC conditions: 20% IPA, Chiralpak AD-H column, λ = 210 nm, $t_R$ (min): minor = 6.35, major = 7.31.

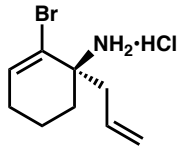
### 7.6.2.5 Rearrangement Product Derivatization



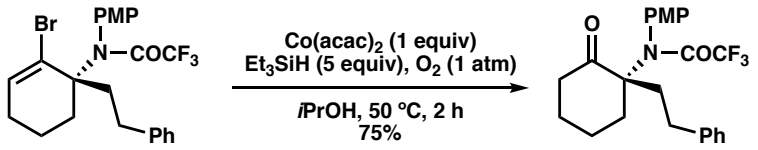

**(*S*)-*N*-(1-allyl-2-bromocyclohex-2-en-1-yl)-4-methoxyaniline (153)[4]**

To a stirred solution of **3b** (209 mg, 0.5 mmol) in 10:1 *i*PrOH/$H_2O$ (2.5 mL) was added $NaBH_4$ (115 mg, 3 mmol) and the resulting mixture stirred for 16 h at 25 °C. The crude reaction was diluted with $H_2O$ and extracted with $CH_2Cl_2$. The combined organic layers were washed with brine and dried with $MgSO_4$ and concentrated. The crude product was purified by silica gel column chromatography (2:1 $CH_2Cl_2$/hexanes) to afford the desired product as a brown oil (120 mg, 75% yield). $[\alpha]_D^{25}$ -18.1 (c 0.70, $CHCl_3$); $^1$H NMR (400 MHz, Chloroform-*d*) δ 6.81 – 6.72 (m, 4H), 6.31 (dd, *J* = 4.9, 3.5 Hz, 1H), 5.88 (dddd, *J* = 16.5, 10.2, 8.7, 6.1 Hz, 1H), 5.29 – 5.18 (m, 2H), 3.75 (s, 3H), 3.57 (d, *J* = 7.5 Hz, 1H), 2.61 – 2.42 (m, 2H), 2.26 – 1.99 (m, 3H), 1.89 – 1.51 (m, 3H); $^{13}$C NMR (100 MHz, Chloroform-*d*) δ 153.5, 138.9, 133.3, 132.9, 119.8, 119.7, 114.4, 59.5, 55.6, 44.5, 30.8, 27.6, 19.7; IR (Neat film, NaCl) 3493, 2621, 1636, 1512, 1258, 937, 738 cm$^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{21}BrNO$ $[M+H]^+$ 322.0801, found 322.0794.



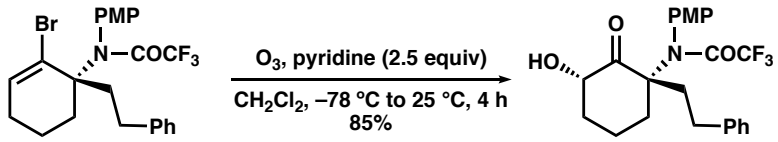

**(*S*)-1-allyl-2-bromocyclohex-2-en-1-aminium Chloride (154)[4]**

A solution of PMP-protected amine **4** (65 mg, 0.2 mmol) in 6.0 mL MeCN was cooled in an ice-bath and treated with a solution of CAN (275 mg, 0.5 mmol, 2.5 equiv) in water (6 mL) dropwise. The reaction allowed to warm to 25 °C and stirred for 3 h. The crude reaction was diluted with water, washed with $Et_2O$, and the organic layer discarded. The aqueous layer was basified to pH 10 with a saturated $Na_2CO_3$ solution and extracted with $Et_2O$. The combined organic layers were dried with $MgSO_4$ and treated with a 1 M HCl solution in $Et_2O$, and concentrated to afford the hydrochloride salt of the product as a white solid (40 mg, 80% yield). $[\alpha]_D^{25}$ 51.0 (c 0.70, $CHCl_3$); $^1$H NMR (500 MHz, Methanol-$d_4$) δ 6.51 (t, $J$ = 4.1 Hz, 1H), 5.73 (dddd, $J$ = 16.6, 10.1, 8.1, 6.3 Hz, 1H), 5.33 – 5.20 (m, 2H), 2.69 (dd, $J$ = 14.0, 6.3 Hz, 1H), 2.56 (dd, $J$ = 14.0, 8.1 Hz, 1H), 2.26 – 2.04 (m, 3H), 2.04 – 1.91 (m, 2H), 1.84 – 1.67 (m, 2H); $^{13}$C NMR (100 MHz, Methanol-$d_4$) δ 138.3, 129.9, 121.3, 120.7, 58.2, 41.6, 32.2, 27.2, 17.2; IR (Neat film, NaCl) 2933, 2863, 1603 1515, 1447, 361, 984, 925, 761, 681 cm$^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_9H_{15}BrN$ $[M\text{-}Cl]^+$ , 216.0382, found 216.0372.



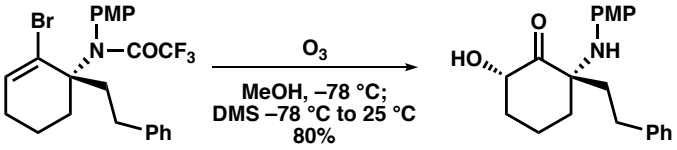

**(*S*)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)-*N*-(2-oxo-1-phenethylcyclohexyl)acetamide (155)**[5]

A vial was charged with $Co(acac)_2$ (90 mg, 0.35 mmol, 1.00 equiv) and the vial was evacuated and backfilled with oxygen three times. Isopropanol was then added (2 mL) followed by starting material **152e** (170 mg, 0.35 mmol, 1.00 equiv) and $Et_3SiH$ (280 μL, 1.75 mmol, 5 equiv). The resulting mixture was heated to 50 °C for 2 h under a balloon of oxygen. The crude reaction mixture was directly concentrated and purified by silica gel column chromatography (20% EtOAc/hexanes) to provide the desired product as a colorless oil (110 mg, 75% yield). $[\alpha]_D^{25}$ 72.1 (c 1.0, $CHCl_3$); $^1$H NMR (400 MHz, Chloroform-*d*) δ 7.50 – 7.43 (m, 1H), 7.30 – 7.09 (m, 4H), 6.95 (ddd, *J* = 13.1, 8.7, 2.9 Hz, 2H), 6.81 (dt, *J* = 6.3, 1.4 Hz, 2H), 3.86 (s, 3H), 2.73 (dtd, *J* = 15.9, 4.5, 1.8 Hz, 1H), 2.51 – 2.34 (m, 2H), 2.33 – 1.85 (m, 8H), 1.85 – 1.58 (m, 3H); $^{13}$C NMR (100 MHz, Chloroform-*d*) δ 205.0, 160.4, 157.3 (q, *J* = 35.1 Hz), 140.9, 132.4, 131.8, 128.5, 128.1, 127.7, 126.2, 122.3, 116.3 (q, *J* = 288.3 Hz), 114.0, 113.9, 72.0, 55.6, 40.1, 36.5, 36.1, 30.4, 25.1, 22.6; IR (Neat film, NaCl) 2945, 1720, 1962, 1510, 1300, 1252, 1185, 1203, 1155, 1032, 737, 703 $cm^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{23}H_{25}F_3NO_3$ $[M+H]^+$: 420.1786, found 420.1796.



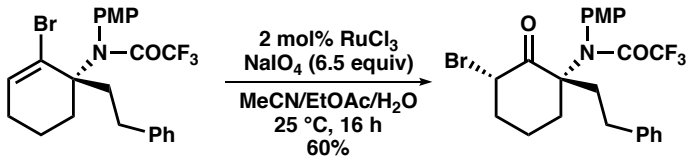

**2,2,2-trifluoro-*N*-((1*S*,3*S*)-3-hydroxy-2-oxo-1-phenethylcyclohexyl)-*N*-(4-methoxyphenyl)acetamide (156)**

To a solution of **152e** (96 mg, 0.2 mmol, 1 equiv) in wet $CH_2Cl_2$ (0.1 M) was added pyridine (40 μL, 0.5 mmol, 2.5 equiv). This solution was then cooled to –78 ºC and $O_3$ was bubbled through until no starting material remained by TLC (~ 1 h). $O_2$ was then bubbled through the solution for 10 min and the reaction was allowed to warm up to 25 °C. After 3 h at 25 °C, the product was purified by column chromatography (20% to 50% EtOAc/hexanes) to provide the desired product as a white foam (75 mg, 85% yield). $[\alpha]_D^{25}$ 88.3 (c 1, $CHCl_3$); $^1$H NMR (400 MHz, Chloroform-*d*) δ 7.44 (d, *J* = 8.6 Hz, 1H), 7.18 (dt, *J* = 14.1, 7.8 Hz, 4H), 7.02 – 6.89 (m, 2H), 6.87 – 6.67 (m, 2H), 4.23 (dd, *J* = 11.9, 6.3 Hz, 1H), 3.86 (s, 3H), 3.60 (s, 1H), 2.50 – 2.29 (m, 3H), 2.16 (d, *J* = 34.0 Hz, 2H), 2.04 (d, *J* = 12.2 Hz, 1H), 2.00 – 1.73 (m, 4H); $^{13}$C NMR (100 MHz, Chloroform-*d*) δ 205.4, 160.5, 157.2 (q, *J* = 35.1 Hz), 140.2, 132.5, 132.1, 128.5, 128.0, 126.3, 116.2 (q, *J* = 288.5 Hz), 114.1, 113.9, 74.2, 72.5, 55.5, 36.4, 35.3, 30.2, 19.7; $^{19}$F NMR (282 MHz, Chloroform-*d*) δ –67.4; IR (Neat film, NaCl) 3469, 2939, 1723, 1693, 1509, 1455, 1251, 1201, 1184, 1154, 1030, 759, 701 $cm^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{23}H_{25}F_3NO_4$ $[M+H]^+$: 436.1735, found 436.1733.




**(2*S*,6*S*)-6-hydroxy-2-((4-methoxyphenyl)amino)-2-phenethylcyclohexan-1-one (157)**

A solution of **152e** (96 mg, 0.2 mmol, 1.00 equiv) in wet MeOH (0.1 M) was cooled to –78 ºC and $O_3$ was bubbled through until no starting material remained by TLC (~30 min). $O_2$ was then bubbled through for 10 min and DMS (55 μL, 0.6 mmol, 3 equiv) was added. The reaction was allowed to warm up to 25 °C and stirred overnight. The reaction was washed with a saturated solution of $NH_4Cl$ and extracted with $CH_2Cl_2$. The crude product was purified by column chromatography (20% to 50% EtOAc/hexanes) to provide the desired product as an amorphous brown solid (55 mg, 80% yield). $[\alpha]_D^{25}$ 50.2 (c 1, $CHCl_3$); $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.25 – 7.21 (m, 2H), 7.19 – 7.14 (m, 1H), 6.98 – 6.93 (m, 2H), 6.82 – 6.74 (m, 4H), 4.47 (dd, *J* = 12.3, 6.8 Hz, 1H), 3.78 (s, 3H), 2.73 – 2.62 (m, 1H), 2.57 – 2.44 (m, 2H), 2.32 (ddd, *J* = 14.2, 12.2, 4.6 Hz, 1H), 2.25 – 2.08 (m, 2H), 1.89 – 1.77 (m, 3H), 1.55 (dddd, *J* = 12.6, 10.6, 8.7, 5.5 Hz, 1H); $^{13}$C NMR (100 MHz, Chloroform-*d*) δ 212.1, 153.5, 141.0, 138.1, 128.5, 128.3, 126.2, 120.1, 114.6, 72.9, 66.9, 55.7, 40.9, 37.1, 37.0, 29.5, 19.2; IR (Neat film, NaCl) 3374, 2948, 1711, 1510, 1454, 1237, 1035, 826, 700 $cm^{-1}$; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{21}H_{26}NO_3$ $[M+H]^+$: 340.1912, found 340.1923.




**_N_-((1_S_,3_S_)-3-bromo-2-oxo-1-phenethylcyclohexyl)-2,2,2-trifluoro-_N_-(4-methoxyphenyl)acetamide (158)**

To a solution of **152e** (96 mg, 0.2 mmol, 1.00 equiv) in $H_2O$ (0.55 mL), acetonitrile (1.25 mL), and EtOAc (1.25 mL) was added sodium periodate ($NaIO_4$, 274 mg, 1.28 mmol, 6.40 equiv) and ruthenium(III) trichloride ($RuCl_3$, 4 μL, 0.1 M solution in $H_2O$, 0.02 equiv). The reaction mixture was then stirred at room temperature for 18 h, at which time consumption of starting material was complete as determined by TLC analysis. The crude reaction mixture was washed with a saturated solution of $NaHCO_3$, and the aqueous layer extracted with EtOAc. The combined organic layers were dried over anhydrous $Na_2SO_4$ and concentrated. The crude product was purified by column chromatography (20% EtOAc/hexanes) to provide the desired product as a white foam (60 mg, 60% yield). $[\alpha]_D^{25}$ 50.2 (c 1.0, $CHCl_3$); $^1$H NMR (500 MHz, Chloroform-*d*) δ 7.55 (ddd, *J* = 8.7, 2.7, 1.1 Hz, 1H), 7.23 – 7.10 (m, 4H), 6.99 (ddd, *J* = 21.4, 8.7, 3.0 Hz, 2H), 6.85 – 6.74 (m, 2H), 4.80 (d, *J* = 1.3 Hz, 1H), 3.89 (s, 3H), 2.69 (ddq, *J* = 14.5, 10.7, 3.5 Hz, 1H), 2.49 – 2.36 (m, 2H), 2.31 – 2.16 (m, 3H), 2.02 (dtt, *J* = 13.9, 8.3, 2.8 Hz, 2H), 1.85 (s, 1H), 1.80 (ddd, *J* = 15.3, 10.8, 5.9 Hz, 1H); $^{13}$C NMR (100 MHz, Chloroform-*d*) δ 196.6, 160.6, 157.6 (q, *J* = 35.8 Hz), 141.0, 132.4, 131.4, 128.4, 128.2, 126.8, 126.1, 116.1 (q, *J* = 287.9 Hz), 114.3, 113.9, 71.3, 55.7, 51.3, 38.7, 37.2, 34.3, 30.5, 18.9; $^{19}$F NMR (282 MHz, Chloroform-*d*) δ –67.5; IR (Neat film, NaCl) 3493, 2942, 1716, 1682, 1509, 1455, 1254, 1206, 1184, 1165, 1031, 752 $cm^{-1}$; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{23}H_{24}BrF_3NO_3$ $[M+H]^+$: 498.0891, found 498.0891.

## 7.6.3 Determination of Enantiomeric Excess

***Table 7.3*** *Determination of Enantiomeric Excess.*

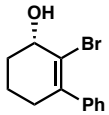
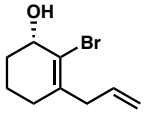
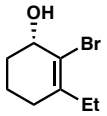
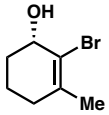
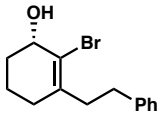
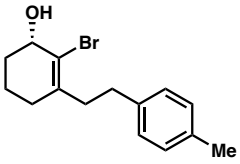
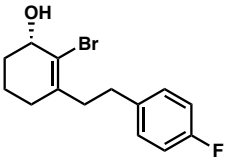
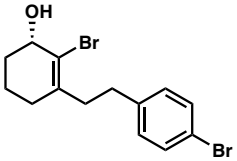
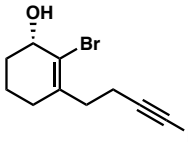
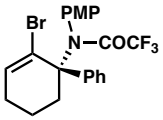
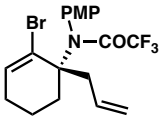
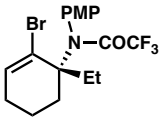
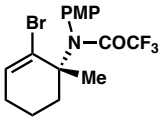
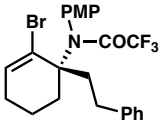
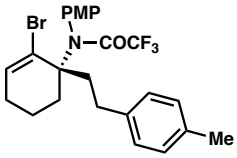
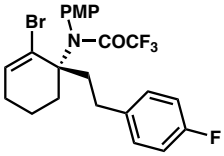
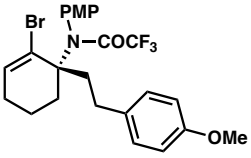
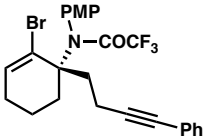
| Entry | Compound | Assay Conditions | $t_R$ of major isomer (min) | $t_R$ of minor isomer (min) | %ee |
|---|---|---|---|---|---|
| 1 |  | SFC<br>Chiralpak IC<br>15% IPA<br>isocratic, 2.5 mL/min | 4.74 | 3.90 | 99 |
| 2 |  | SFC<br>Chiralpak IC<br>10% IPA<br>isocratic, 2.5 mL/min | 4.05 | 3.60 | 97 |
| 3 |  | GC<br>GTA column<br>120 °C, isotherm | 15.77 | 14.52 | 97 |
| 4 |  | GC<br>GTA column<br>120 °C, isotherm | 12.84 | 11.10 | 98 |
| 5 |  | SFC<br>Chiralcel OJ-H<br>15% IPA<br>isocratic, 2.5 mL/min | 5.43 | 5.03 | 97 |
| 6 |  | SFC<br>Chiralcel OJ-H<br>10% IPA<br>isocratic, 2.5 mL/min | 8.70 | 7.79 | 94 |
| 7 |  | SFC<br>Chiralcel OJ-H<br>10% IPA<br>isocratic, 2.5 mL/min | 5.63 | 4.73 | 97 |
| 8 |  | SFC<br>Chiralcel OJ-H<br>20% IPA<br>isocratic, 2.5 mL/min | 5.45 | 4.72 | 96 |
| 9 |  | SFC<br>Chiralpak AD-H<br>20% IPA<br>isocratic, 2.5 mL/min | 7.31 | 6.35 | 91 |

***Table 7.3*** *Determination of Enantiomeric Excess (continued)*

| Entry | Compound | Assay Conditions | $t_R$ of major isomer (min) | $t_R$ of minor isomer (min) | %ee |
|---|---|---|---|---|---|
| 10 |  | SFC<br>Chiralcel OJ-H<br>10% IPA<br>isocratic, 2.5 mL/min | 5.18 | 4.68 | 96 |
| 11 |  | SFC<br>Chiralcel OJ-H<br>5% IPA<br>isocratic, 2.5 mL/min | 3.79 | 3.26 | 95 |
| 12 |  | SFC<br>Chiralpak AD-H<br>3% IPA<br>isocratic, 2.5 mL/min | 6.58 | 6.03 | 96 |
| 13 |  | SFC<br>Chiralcel OJ-H<br>10% IPA<br>isocratic, 2.5 mL/min | 4.11 | 3.41 | 97 |
| 14 |  | SFC<br>Chiralcel OJ-H<br>20% IPA<br>isocratic, 2.5 mL/min | 3.64 | 2.80 | 97 |
| 15 |  | SFC<br>Chiralcel OJ-H<br>10% IPA<br>isocratic, 2.5 mL/min | 6.87 | 6.47 | 97 |
| 16 |  | SFC<br>Chiralcel OJ-H<br>10% IPA<br>isocratic, 2.5 mL/min | 5.98 | 4.96 | 97 |
| 17 |  | SFC<br>Chiralcel OJ-H<br>10% IPA<br>isocratic, 2.5 mL/min | 11.37 | 10.76 | 98 |
| 18 |  | SFC<br>Chiralpak AD-H<br>15% IPA<br>isocratic, 2.5 mL/min | 4.98 | 4.51 | 92 |

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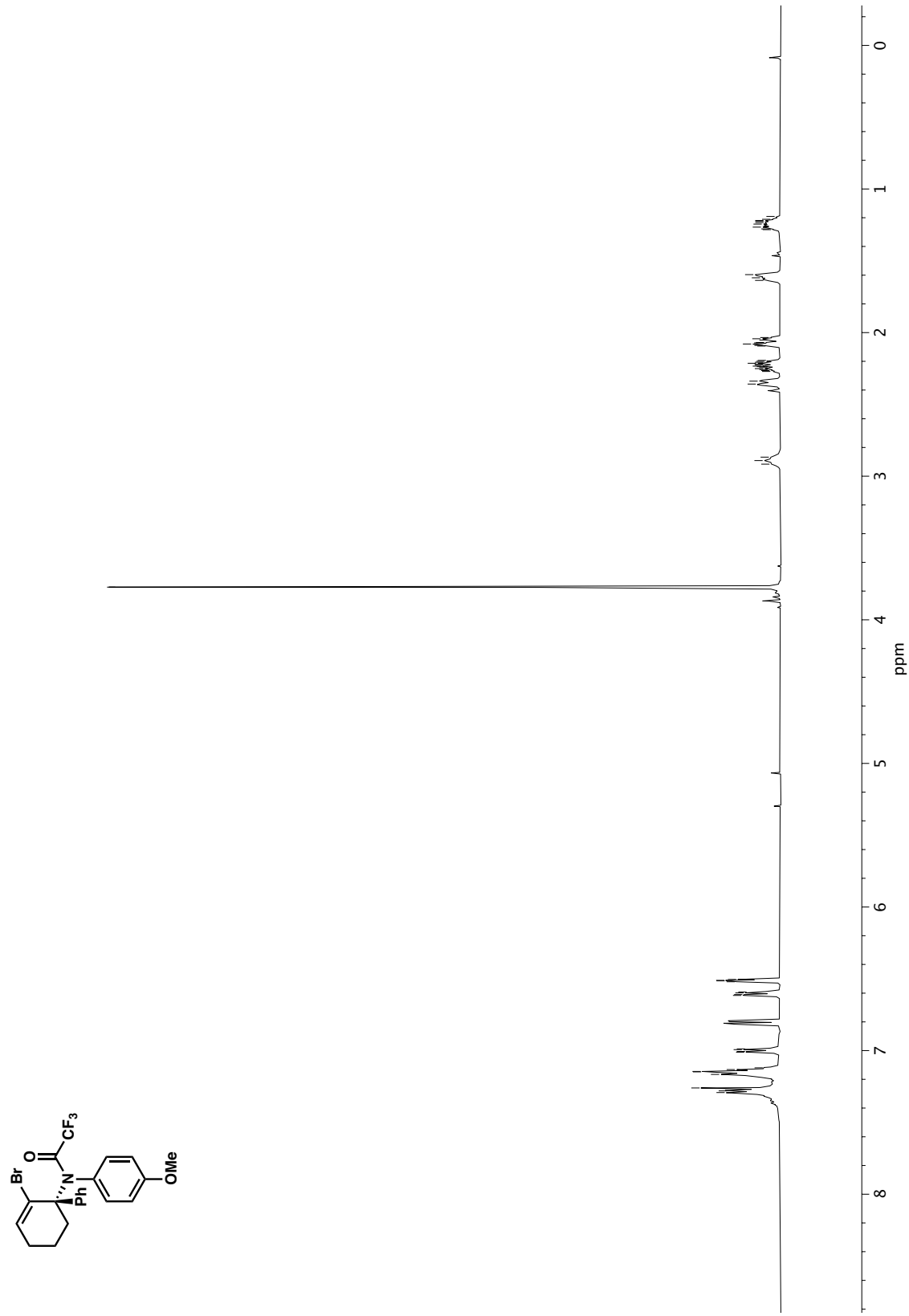
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# *APPENDIX 11*

*Spectra Relevant to Chapter 7:*

*Stereospecific Overman Rearrangement of Substituted Cyclic Vinyl Bromides: Access to Fully-Substituted α-Amino Ketones*




***A11.1*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***152a***.

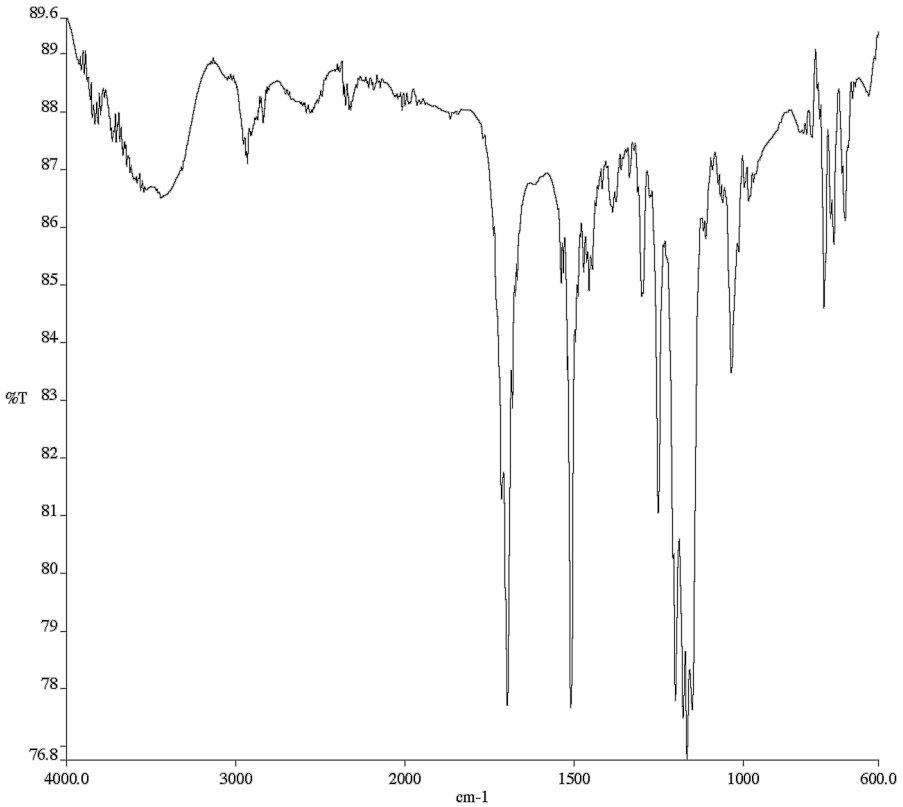



***Figure A11.2*** *Infrared spectrum (Thin Film, NaCl) of compound* ***152a****.*

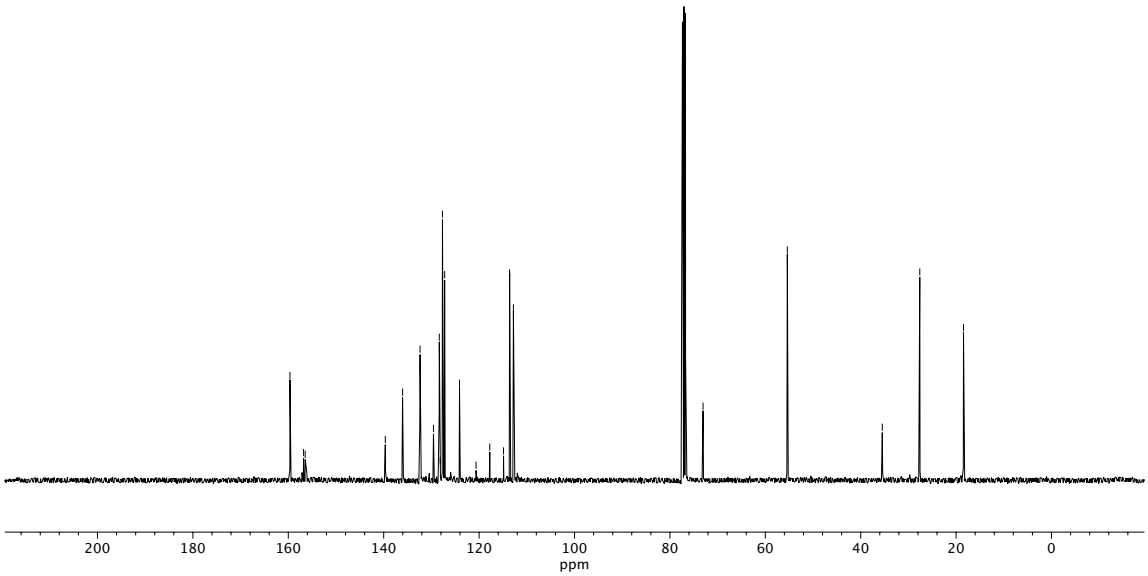



***Figure A11.3*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***152a****.*

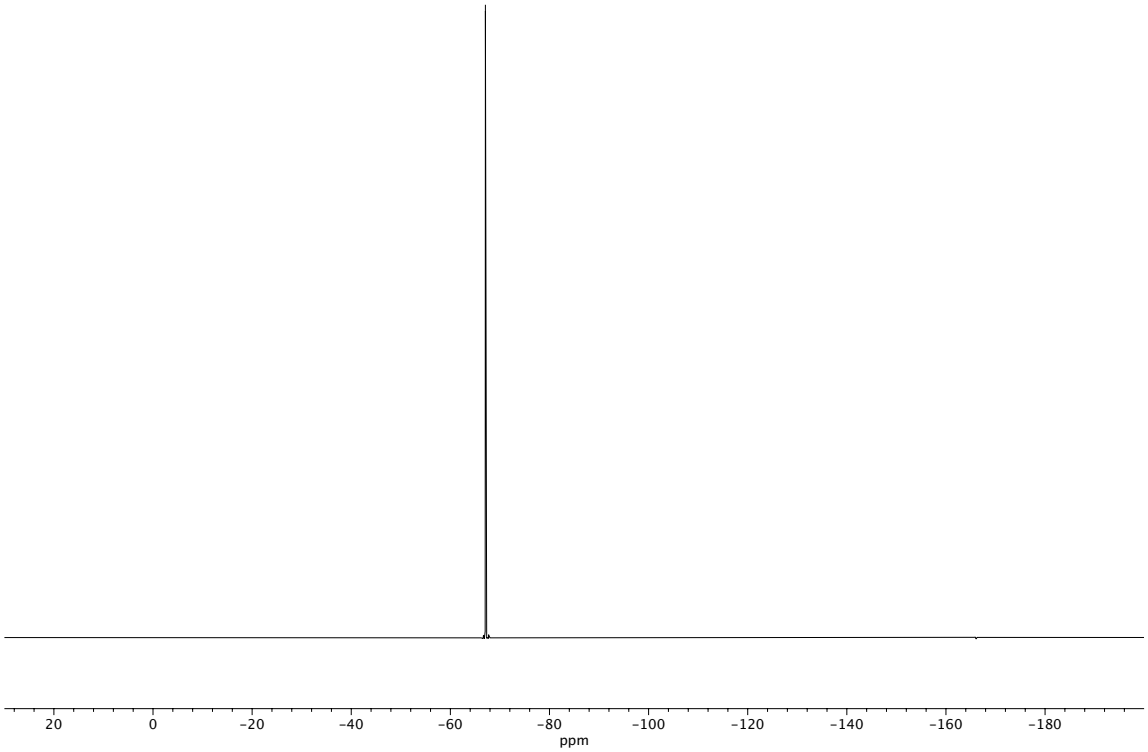
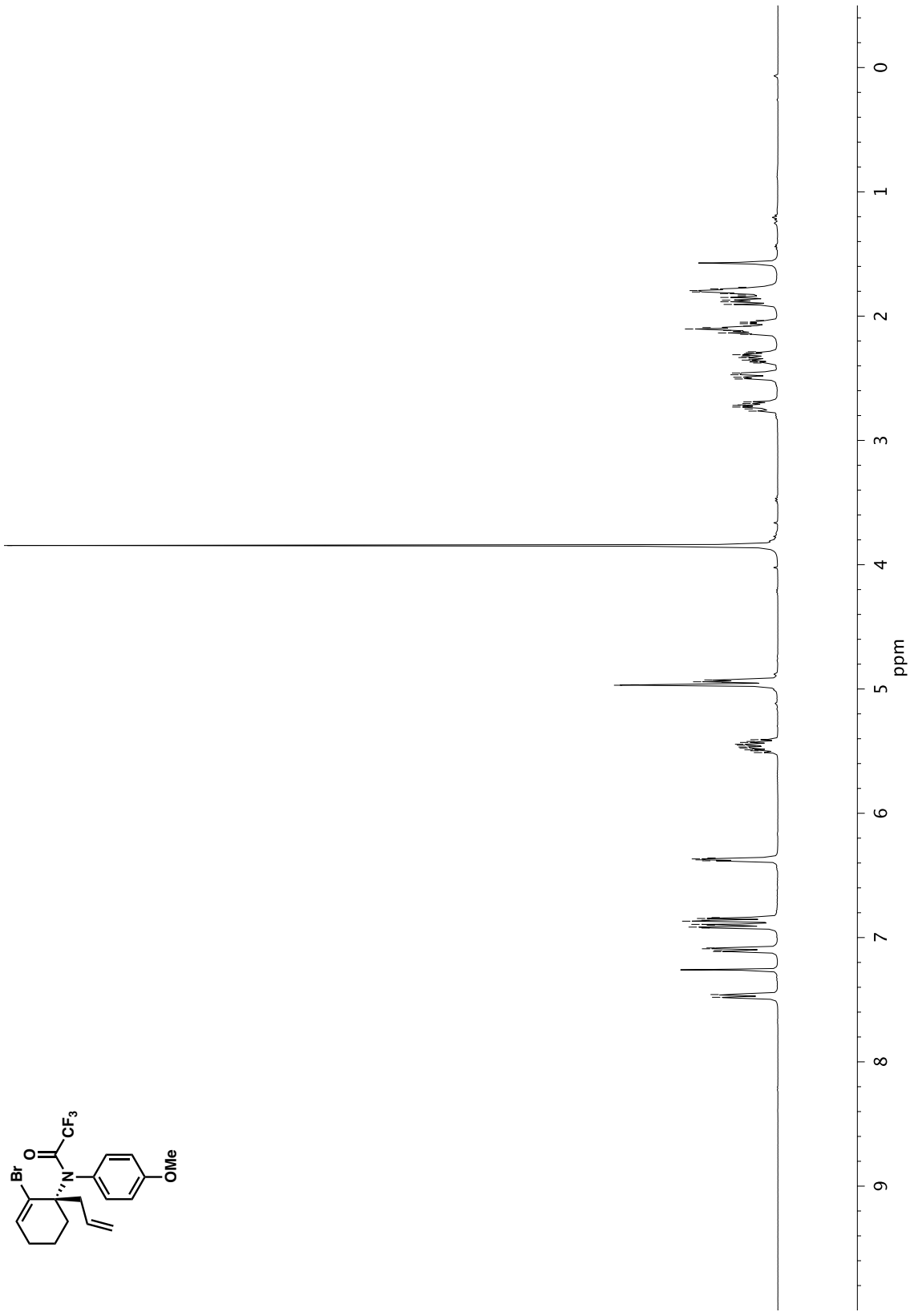



***Figure A11.4*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***152a***.




***A11.5*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***152b***.

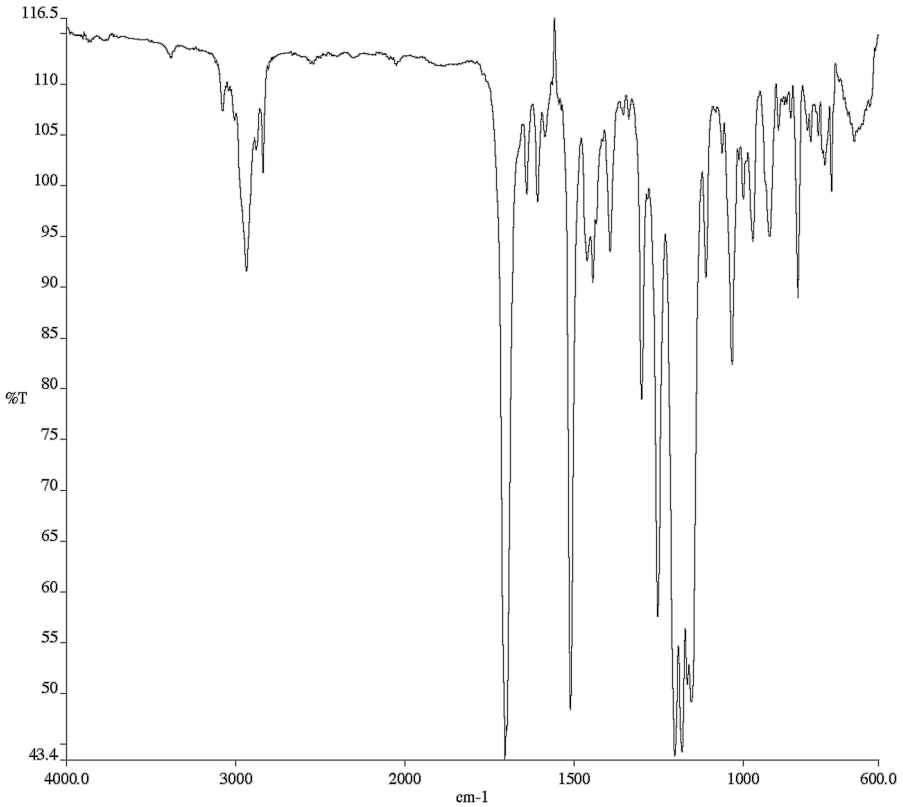



***Figure A11.6*** *Infrared spectrum (Thin Film, NaCl) of compound* ***152b***.

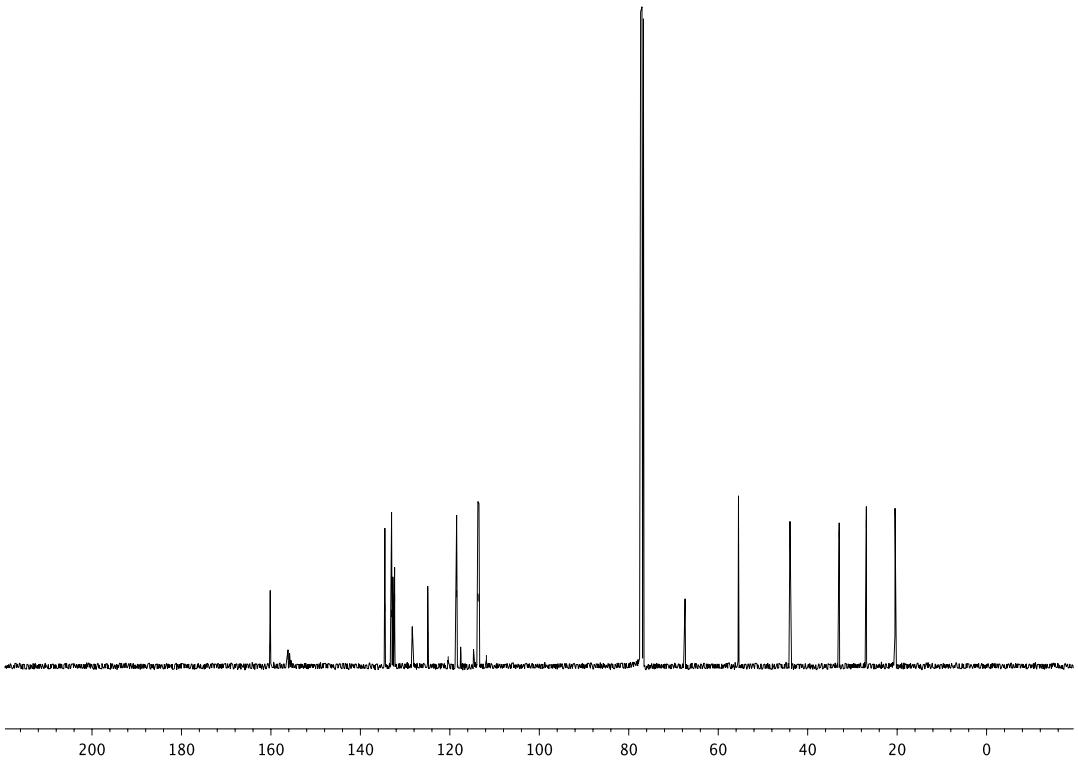



***Figure A11.7*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***152b***.

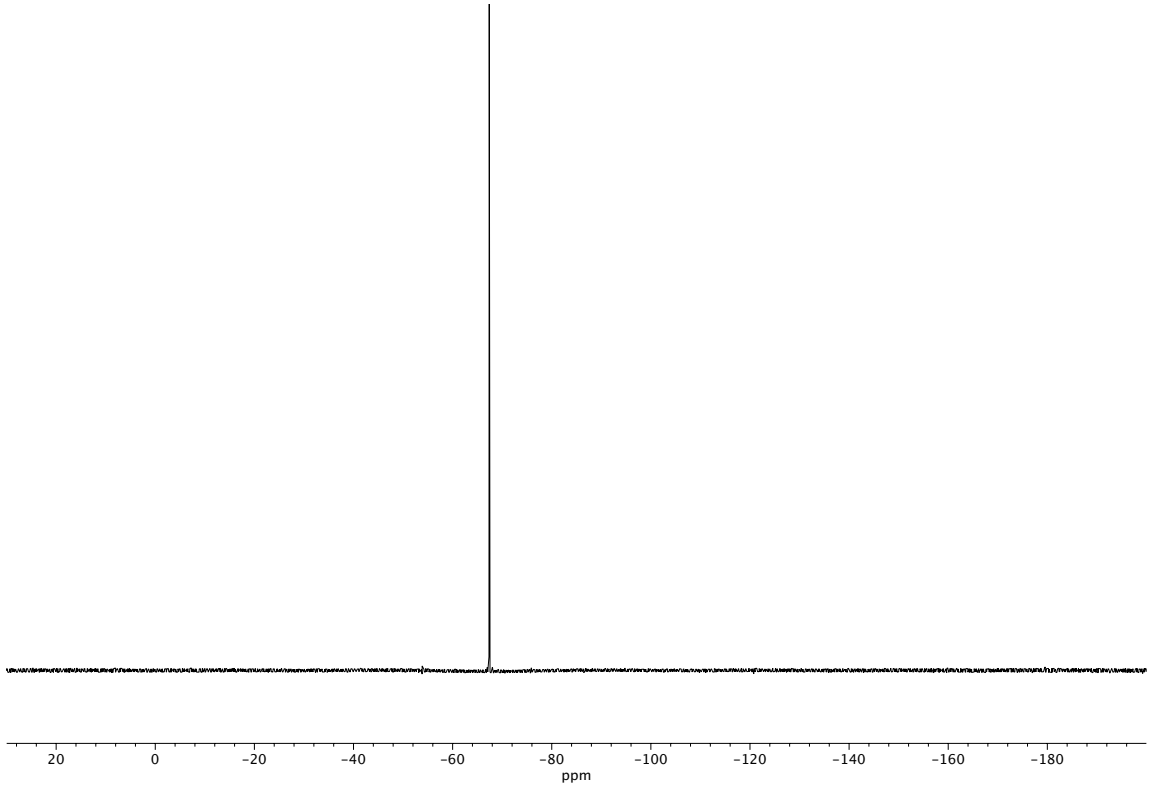
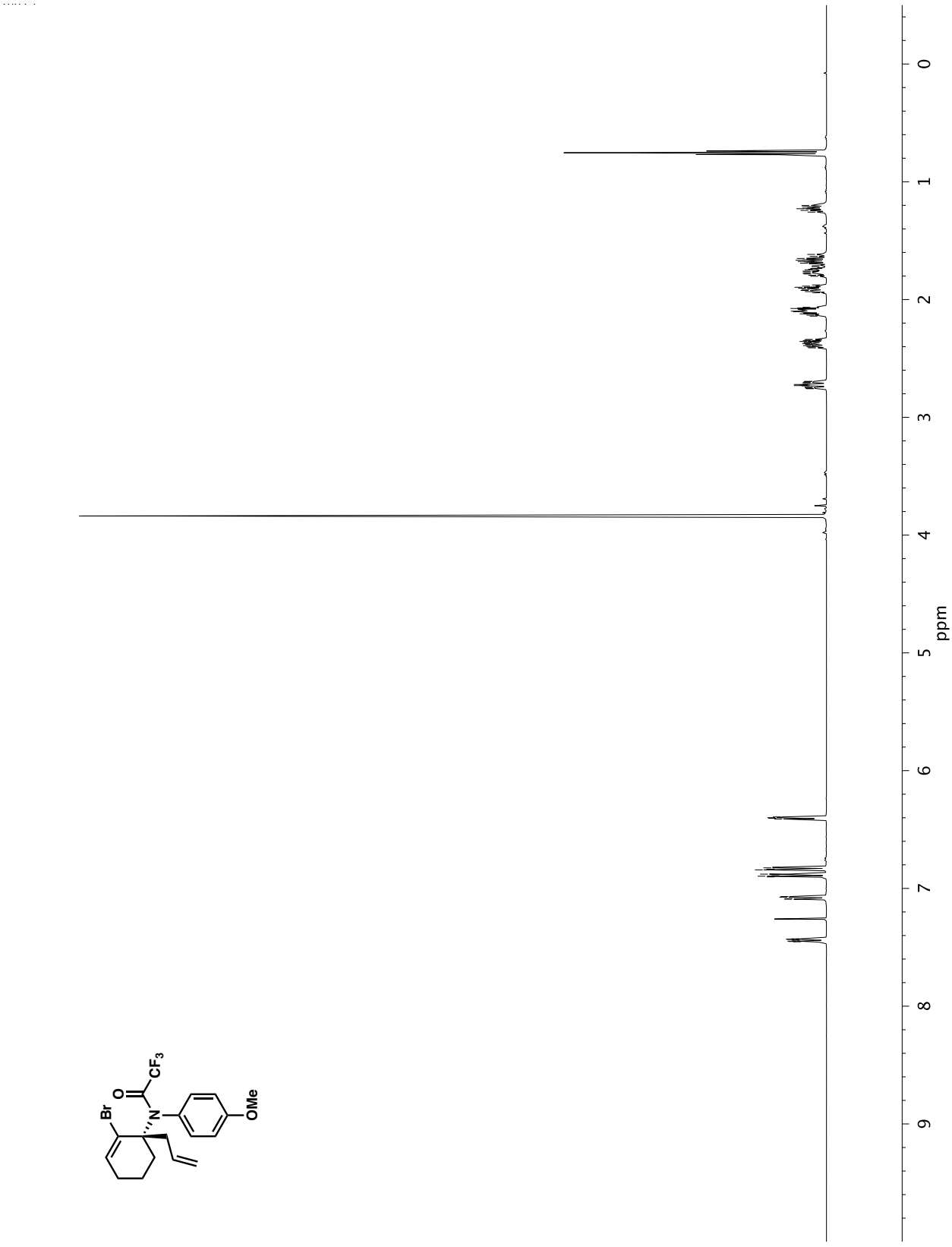



***Figure A11.8*** *$^{19}F$ NMR (282 MHz, $CDCl_3$) of compound* ***152b***.




***A11.9*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***152c****.*

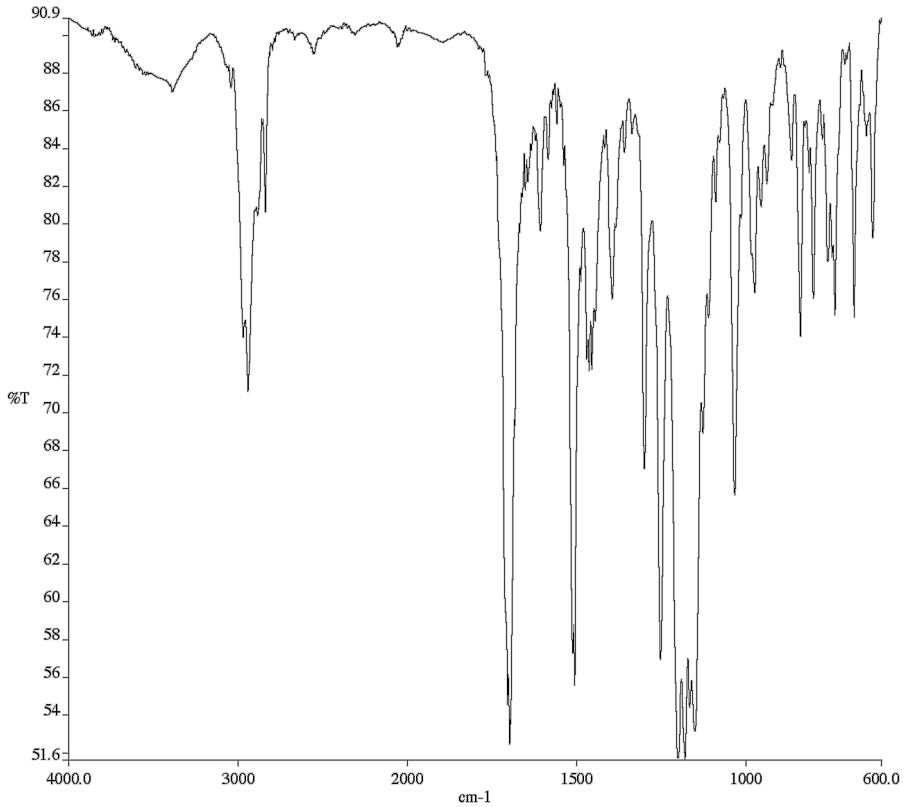



***Figure A11.10*** *Infrared spectrum (Thin Film, NaCl) of compound* ***152c****.*

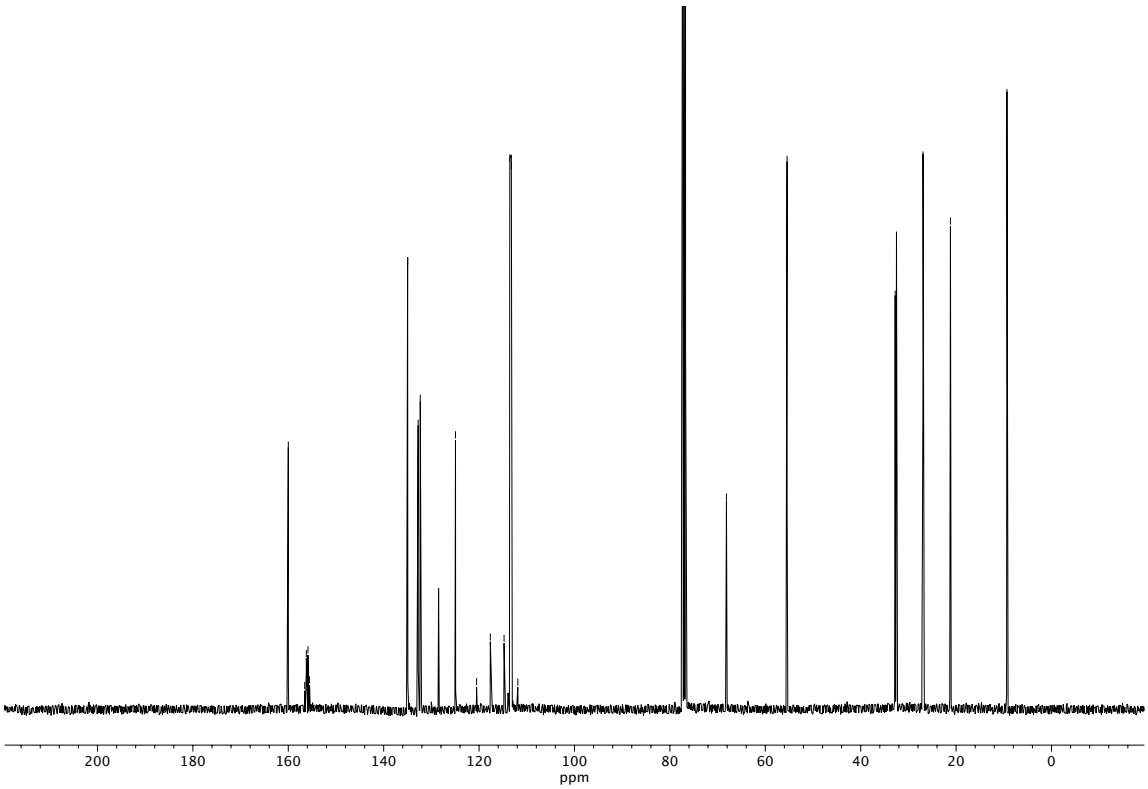



***Figure A11.11*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***152c****.*

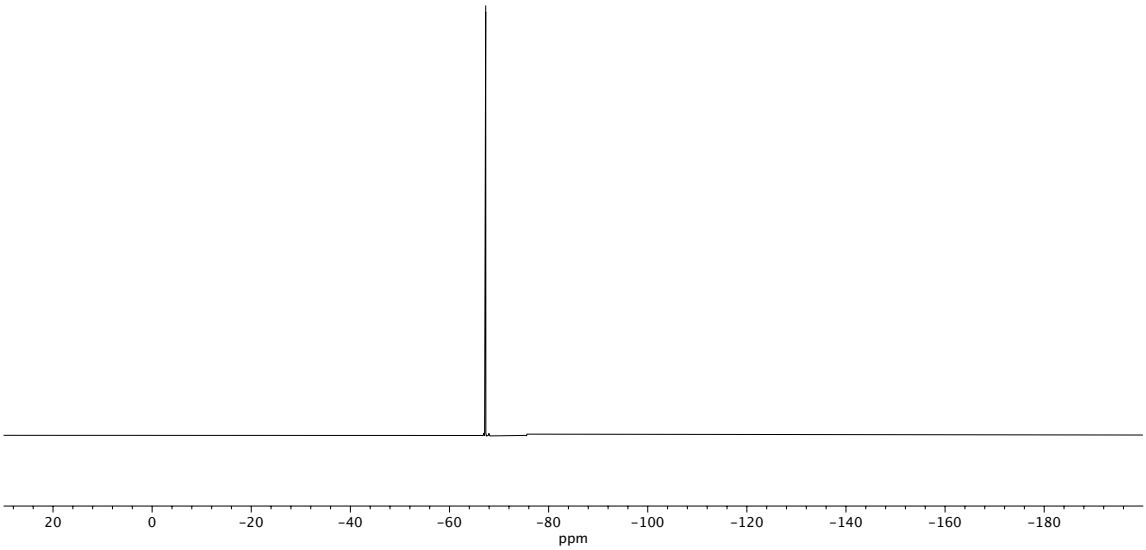



***Figure A11.12*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***152c***.

***A11.13*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***152d****.*

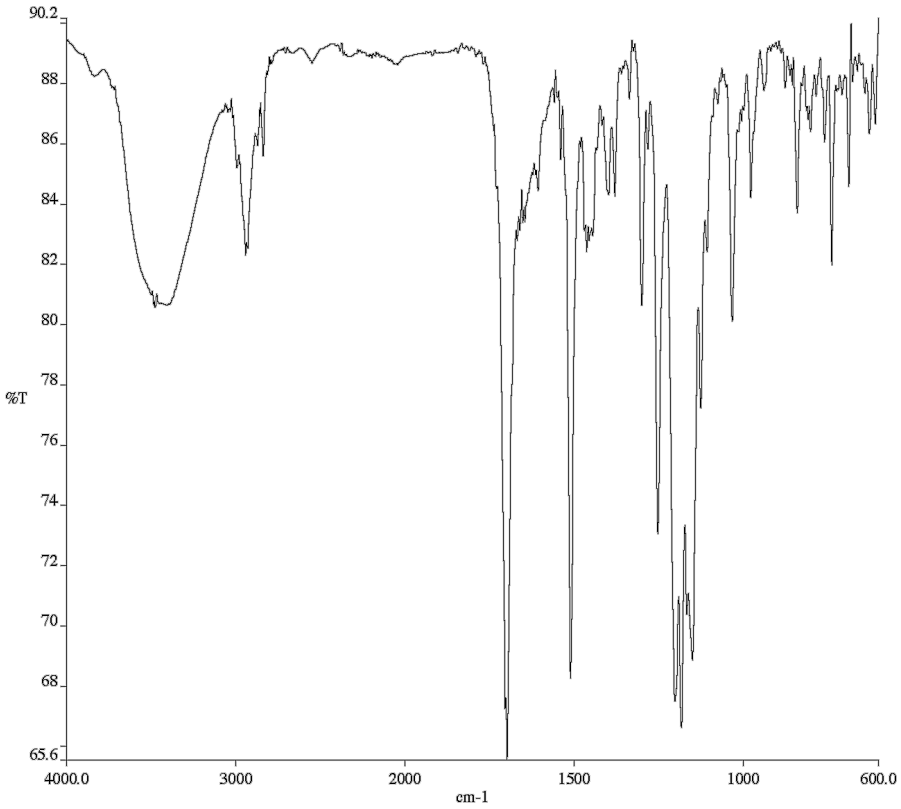



***Figure A11.14*** *Infrared spectrum (Thin Film, NaCl) of compound* ***152d****.*

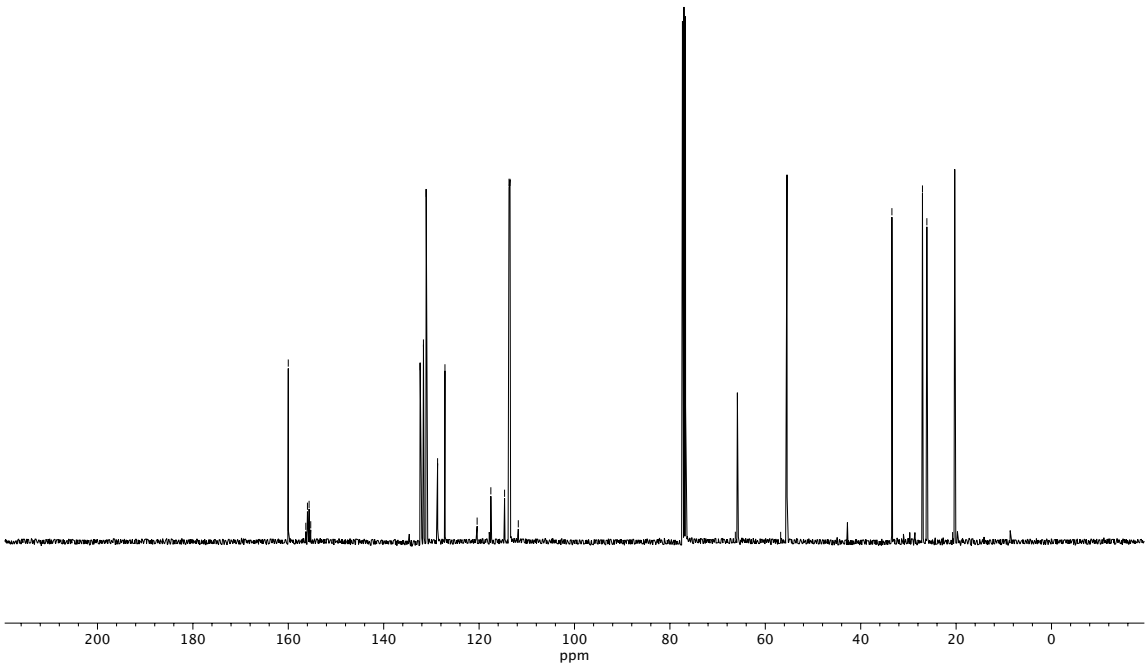



***Figure A11.15*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***152d****.*

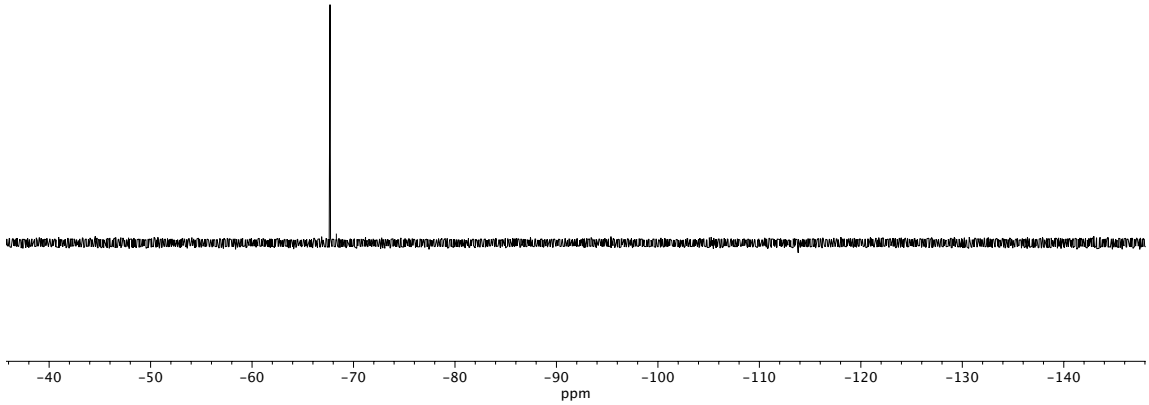
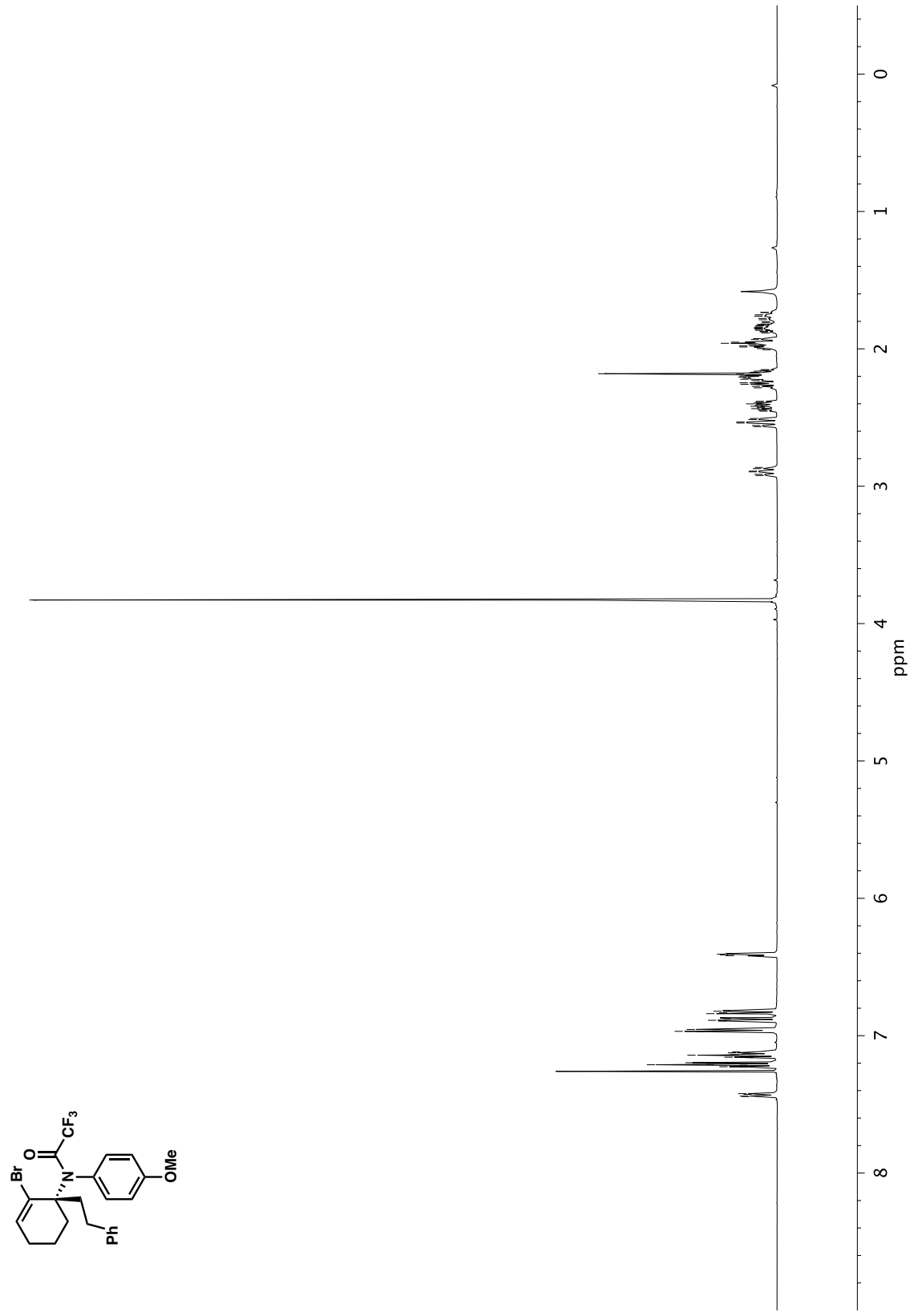



***Figure A11.16*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***152d***.




***A11.17*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***152e***.

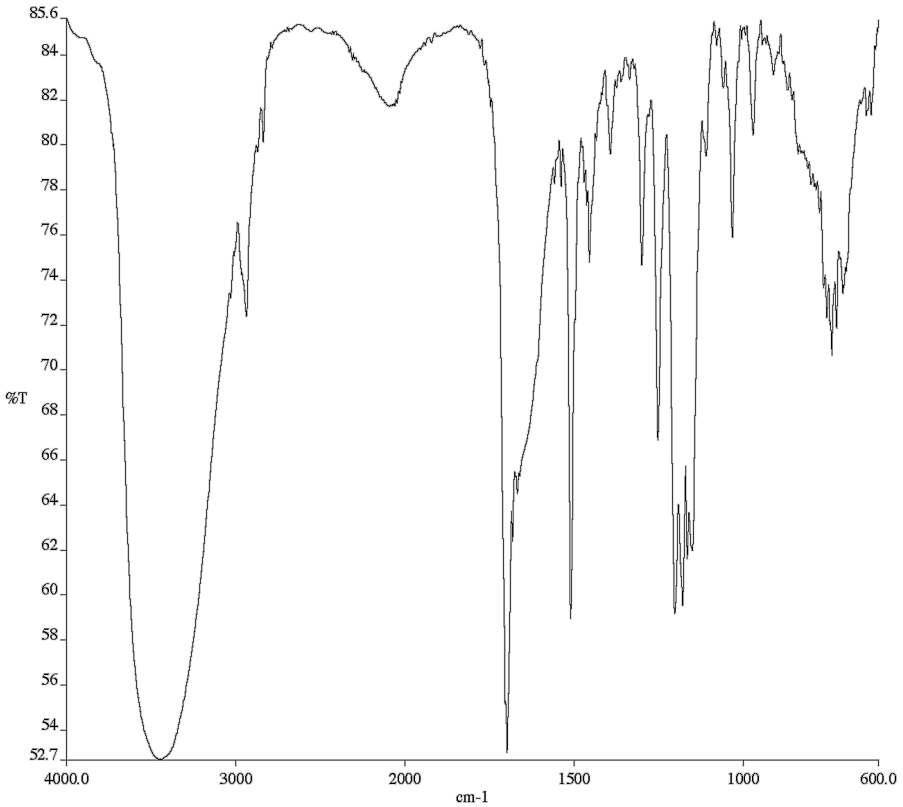



***Figure A11.18*** *Infrared spectrum (Thin Film, NaCl) of compound* ***152e****.*

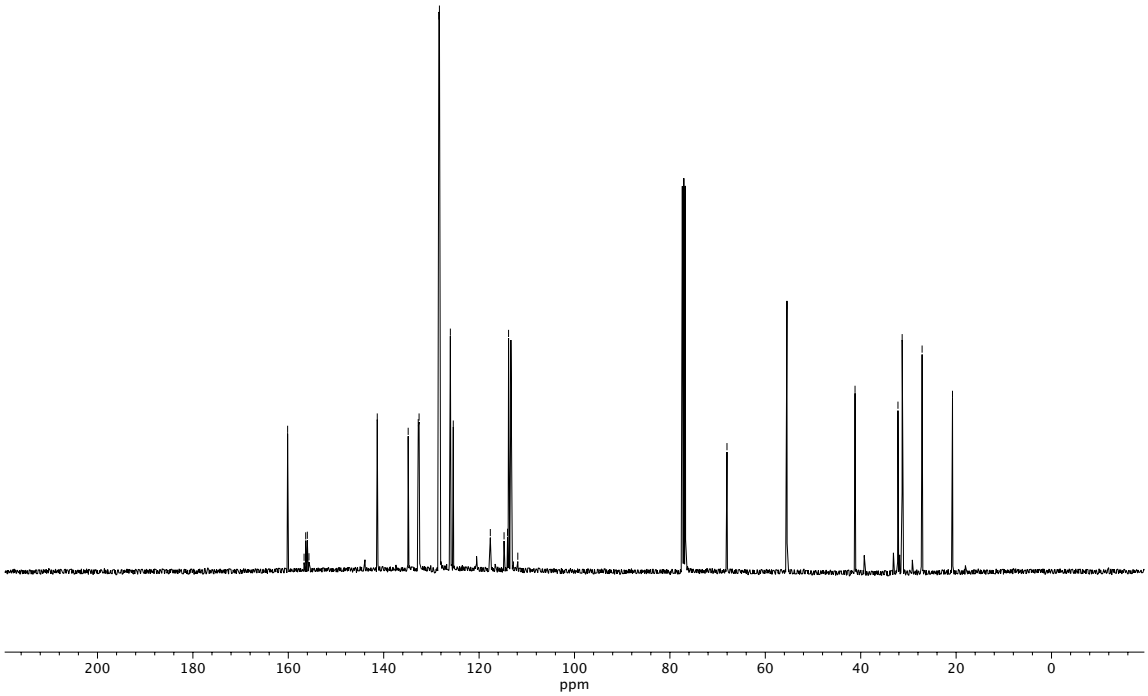



***Figure A11.19*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***152e****.*

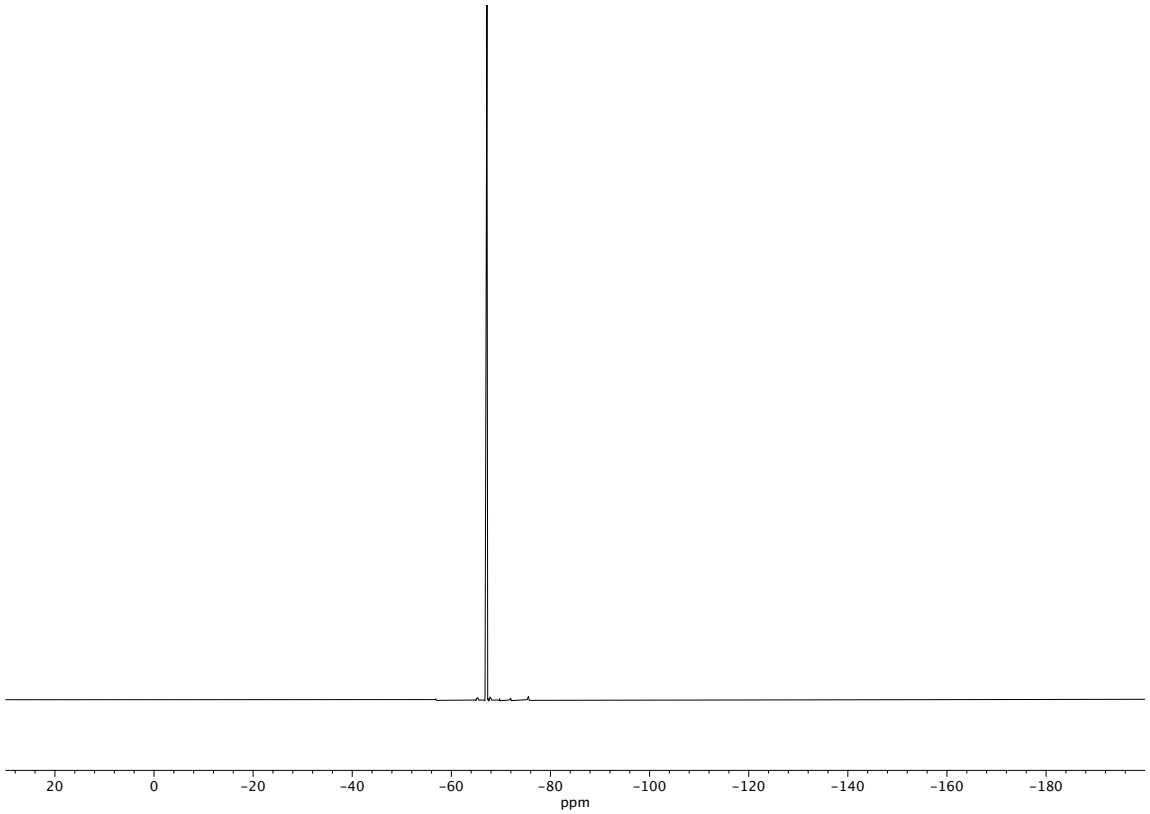



***Figure A11.20*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***152e***.

***A11.21*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***152f****.*

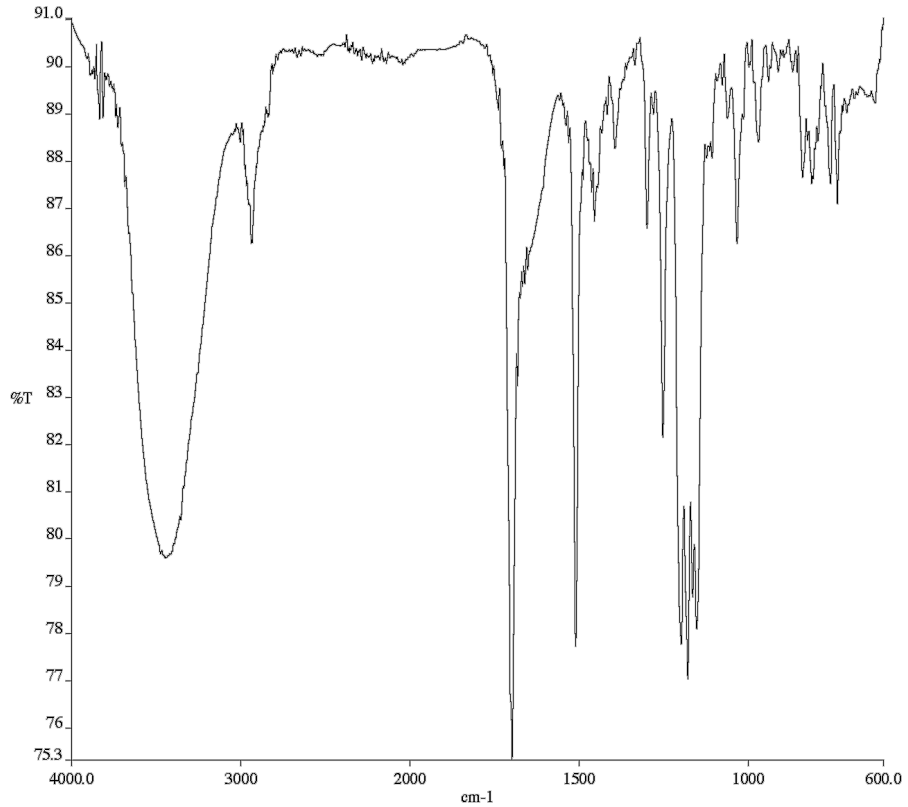



***Figure A11.22*** *Infrared spectrum (Thin Film, NaCl) of compound* ***152f****.*

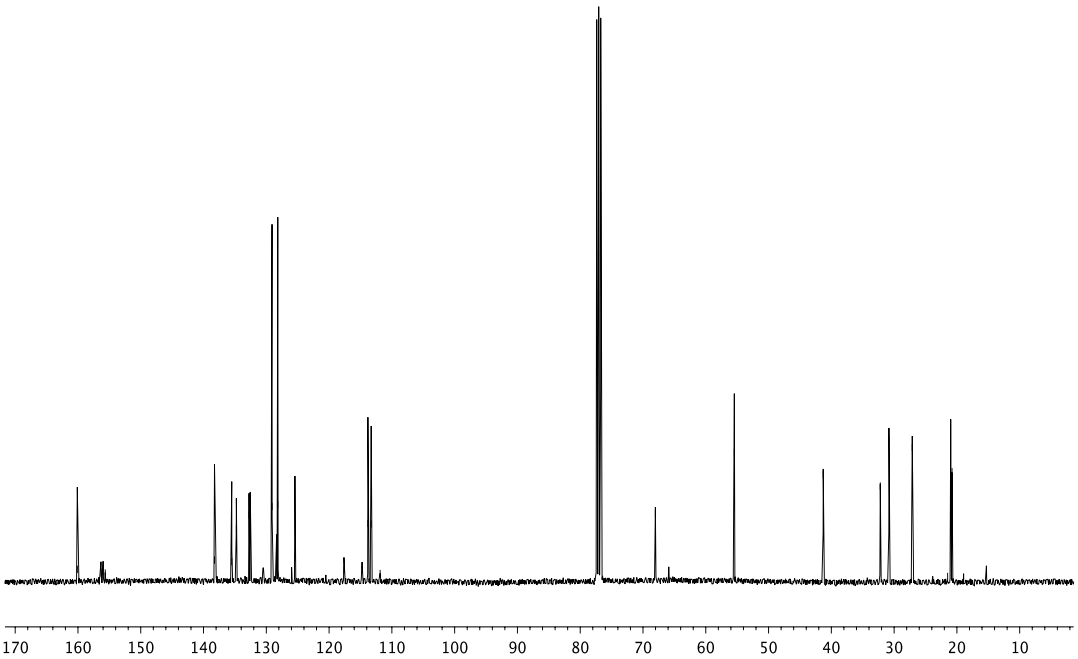



***Figure A11.23*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***152f****.*

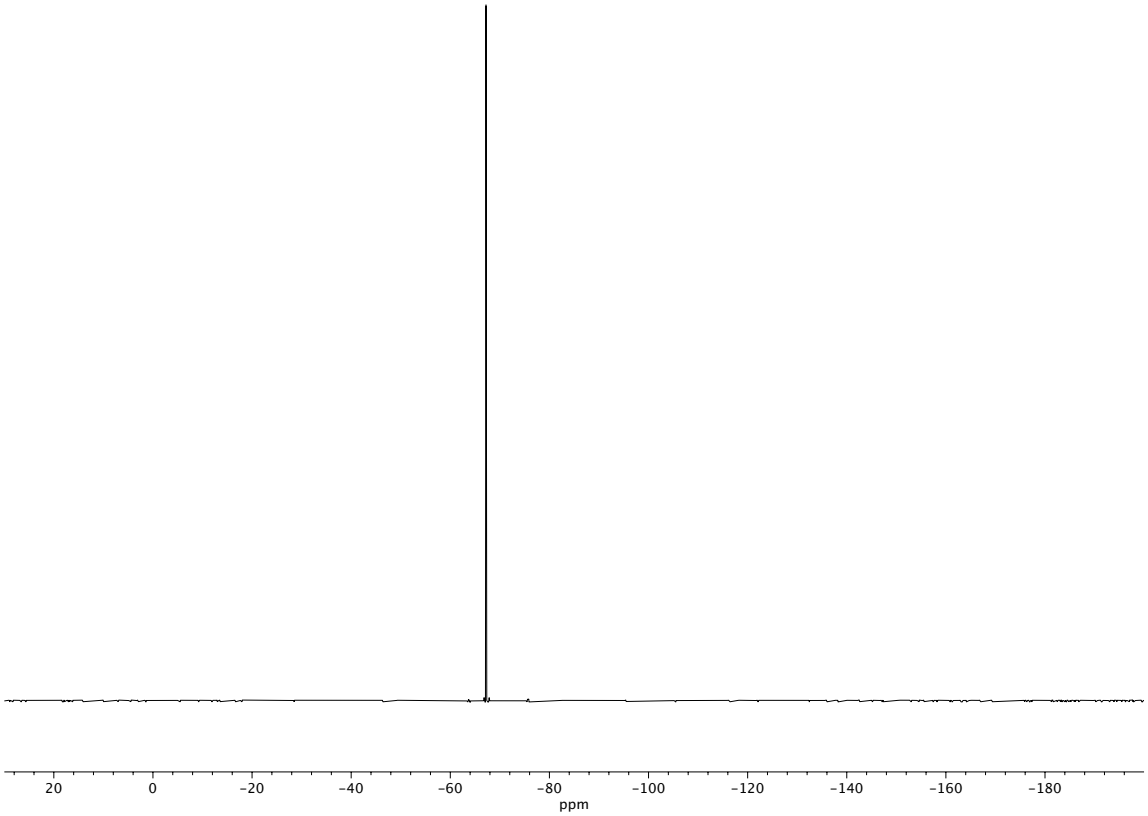



***Figure A11.24*** *$^{19}F$ NMR (282 MHz, $CDCl_3$) of compound* ***152f****.*

***A11.25*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***152g***.

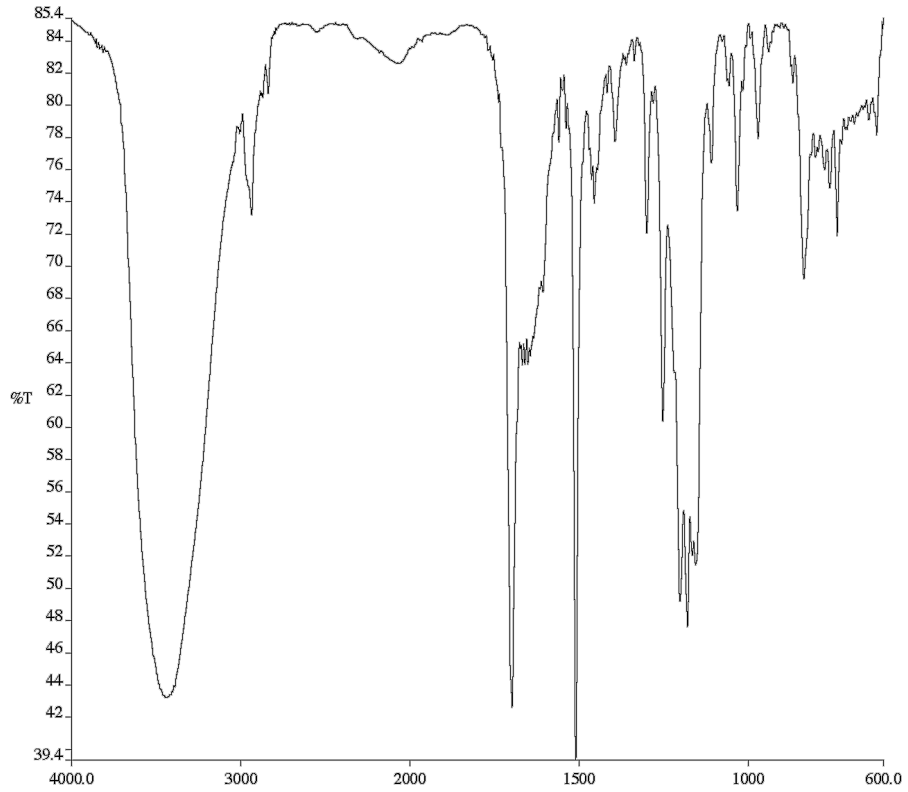



***Figure A11.26*** *Infrared spectrum (Thin Film, NaCl) of compound* ***152g***.

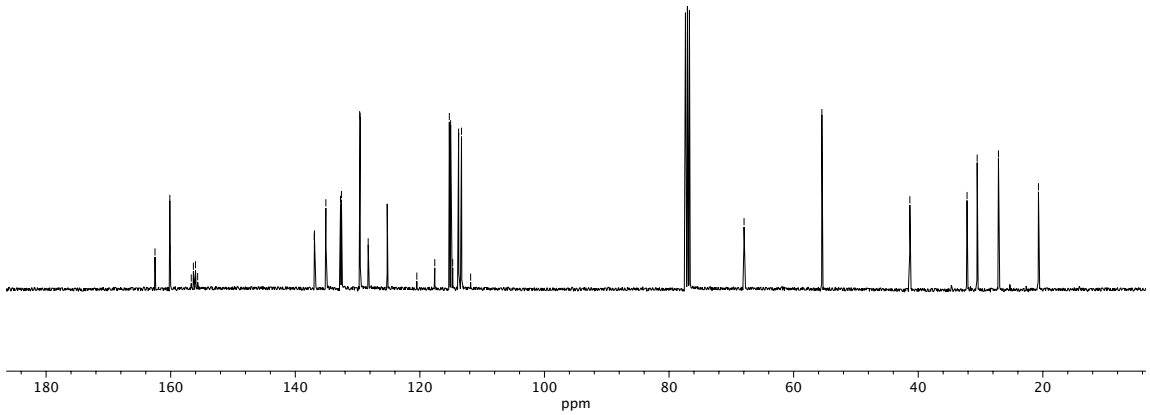



***Figure A11.27*** *$^{13}$C NMR (100 MHz, $CDCl_3$) of compound* ***152g***.

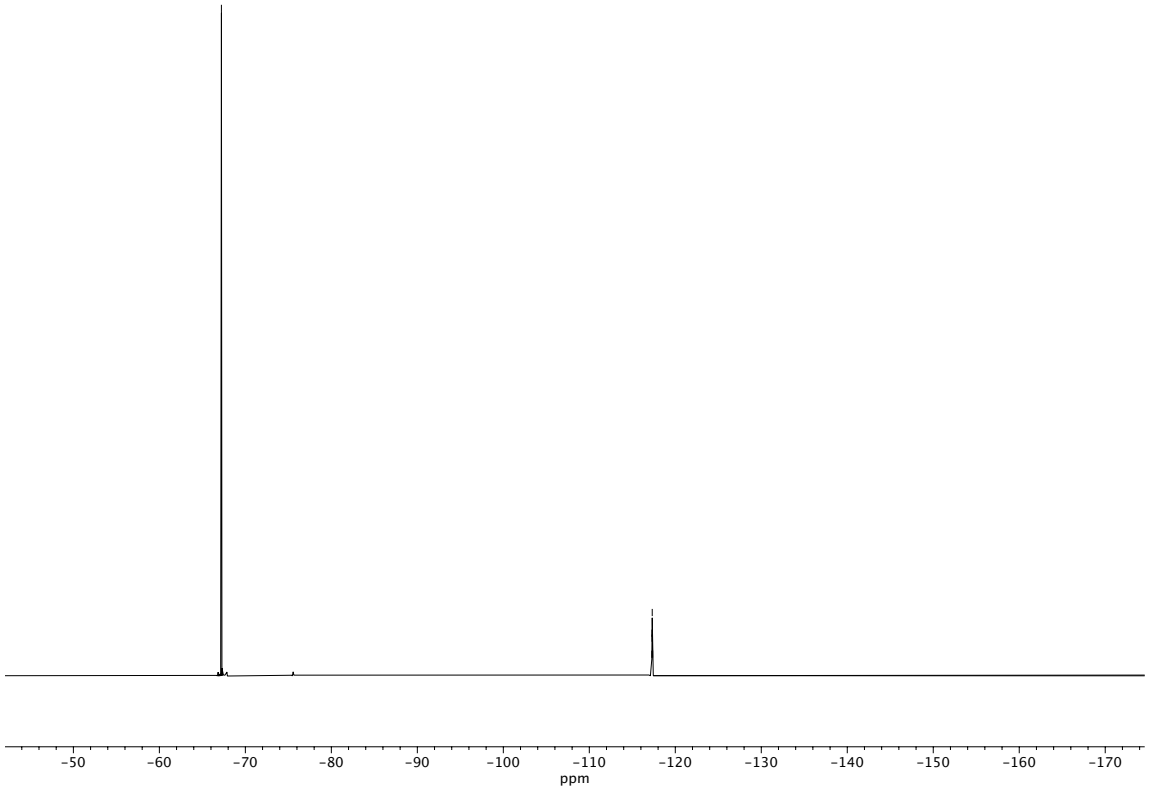



***Figure A11.28*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***152g***.

***A11.29*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***152h***.

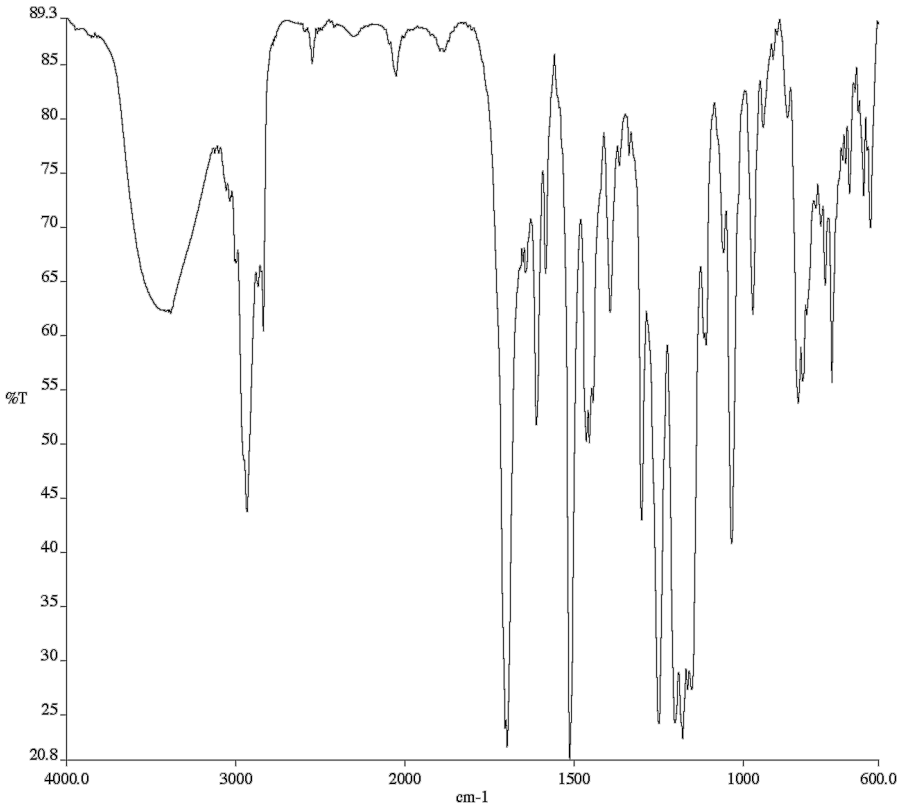



***Figure A11.30*** *Infrared spectrum (Thin Film, NaCl) of compound* ***152h***.

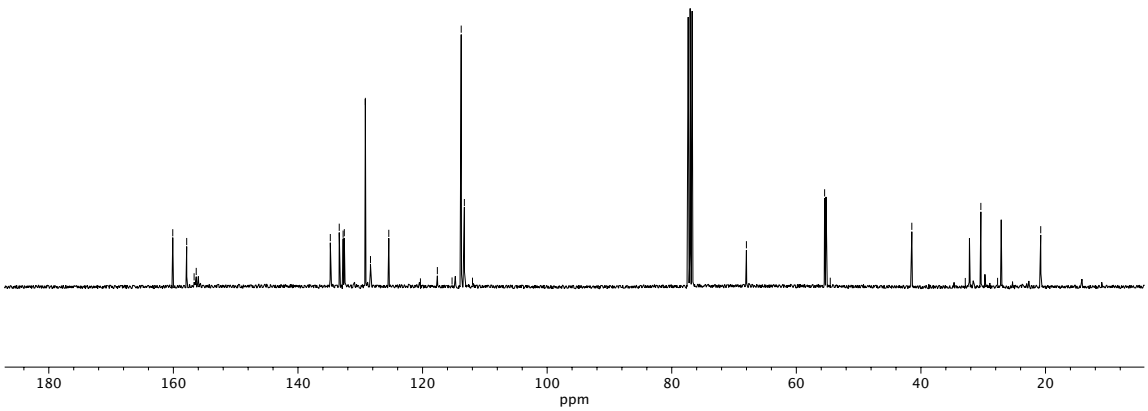



***Figure A11.31*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***152h***.

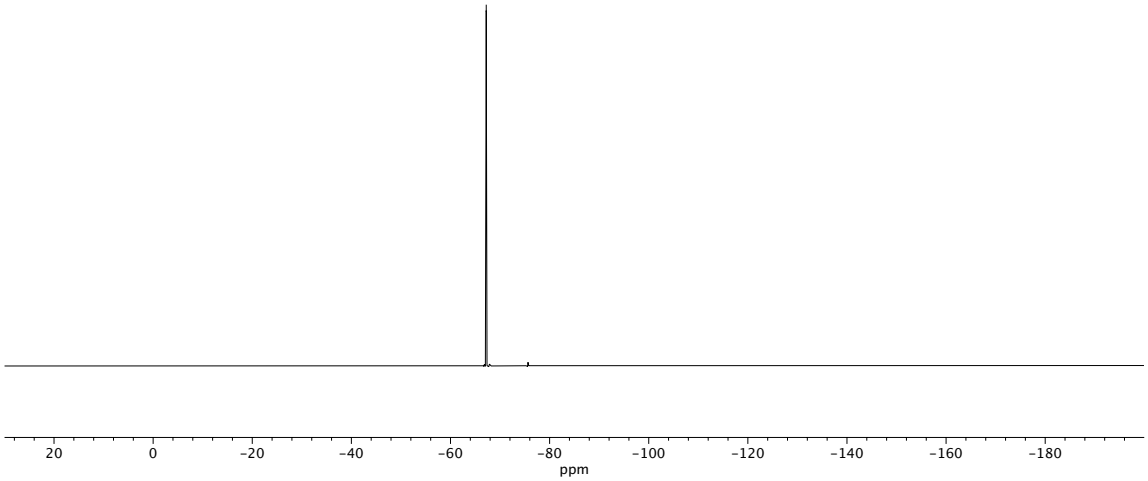



***Figure A11.32*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***152h***.

***A11.33*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***152i*****.**

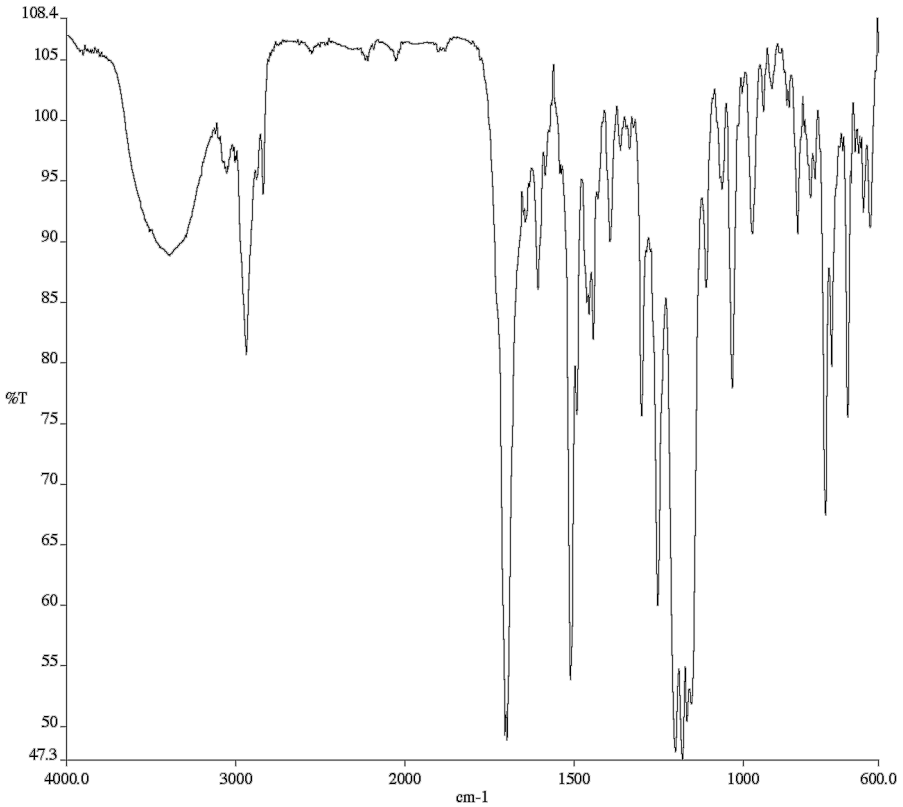



***Figure A11.34*** *Infrared spectrum (Thin Film, NaCl) of compound* ***152i****.*

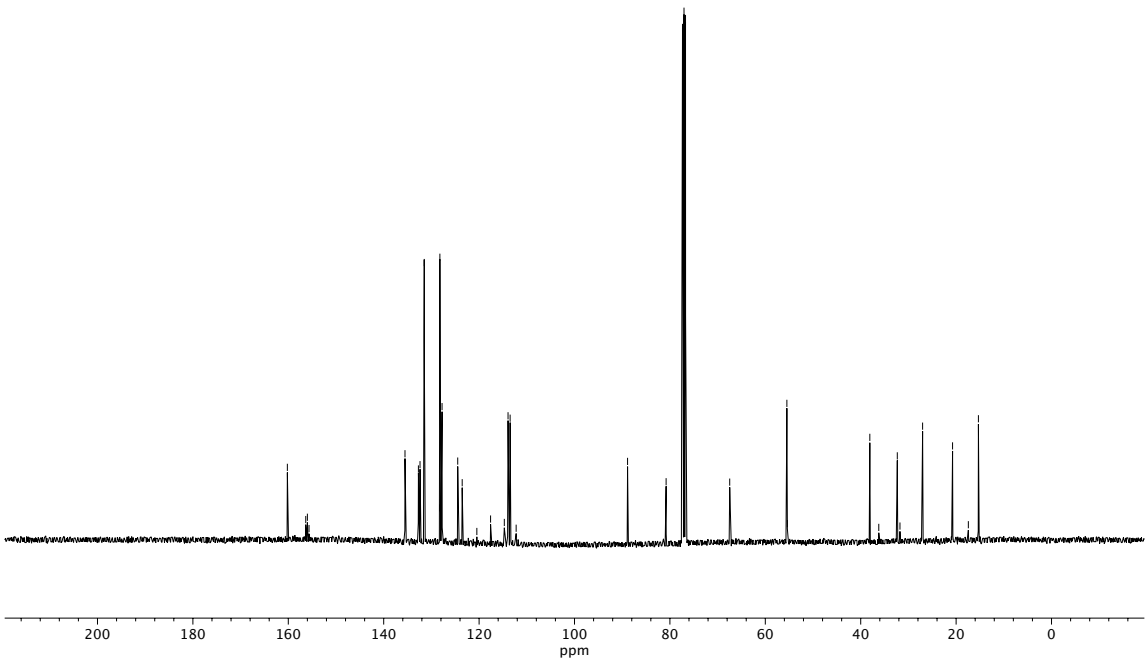



***Figure A11.35*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***152i****.*

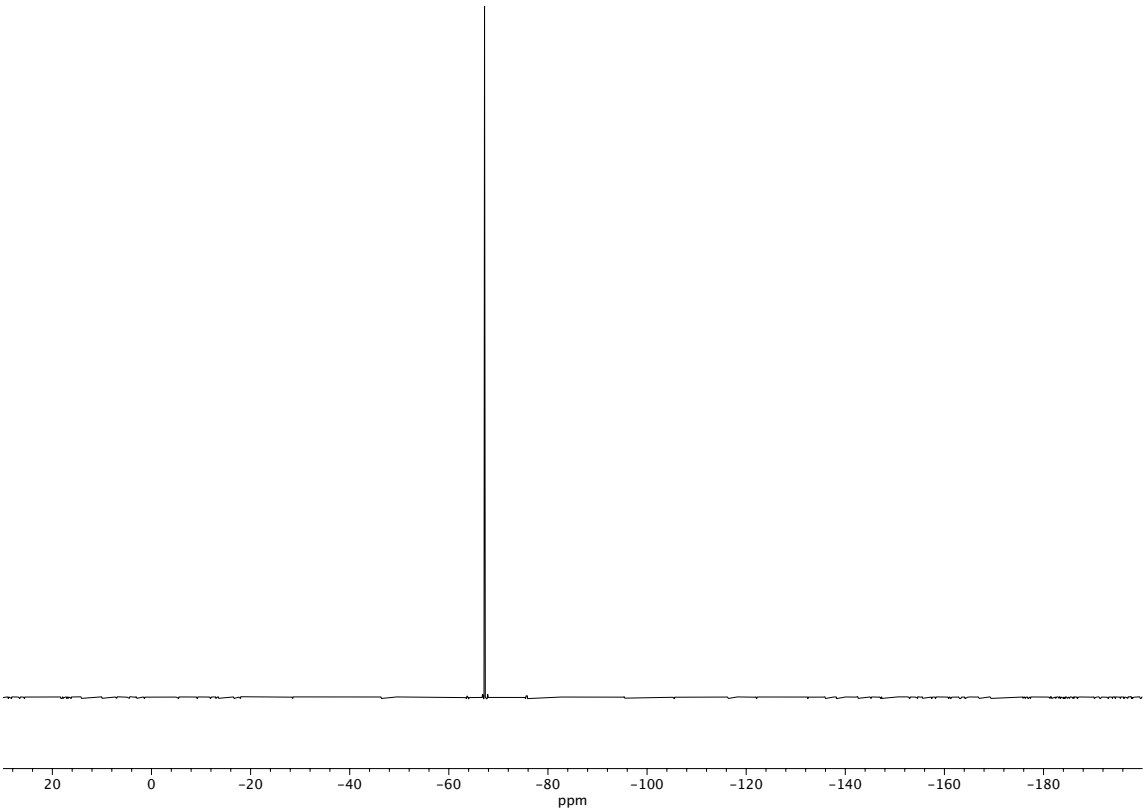
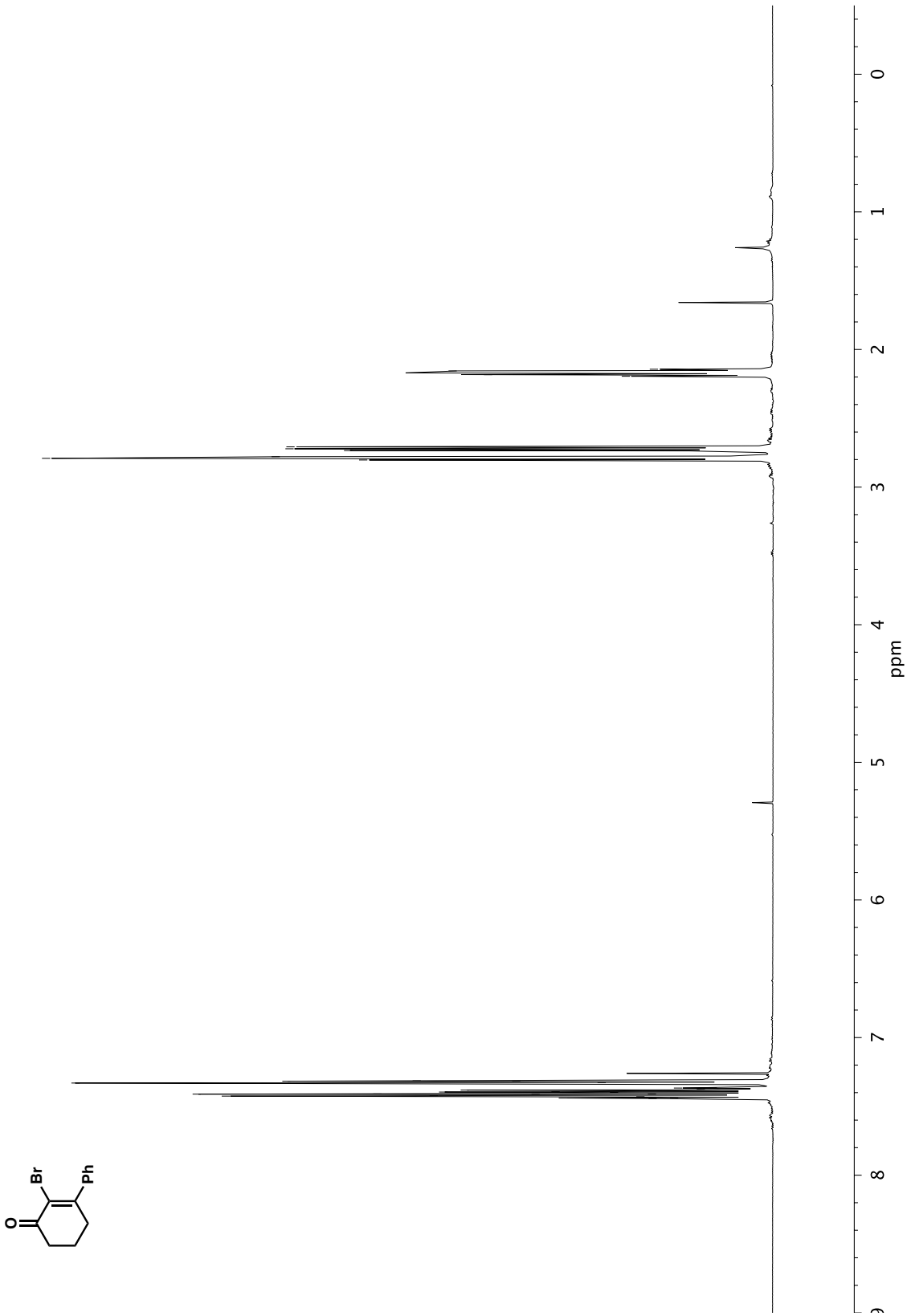



***Figure A11.36*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***152i****.*




***A11.37*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***150a***.

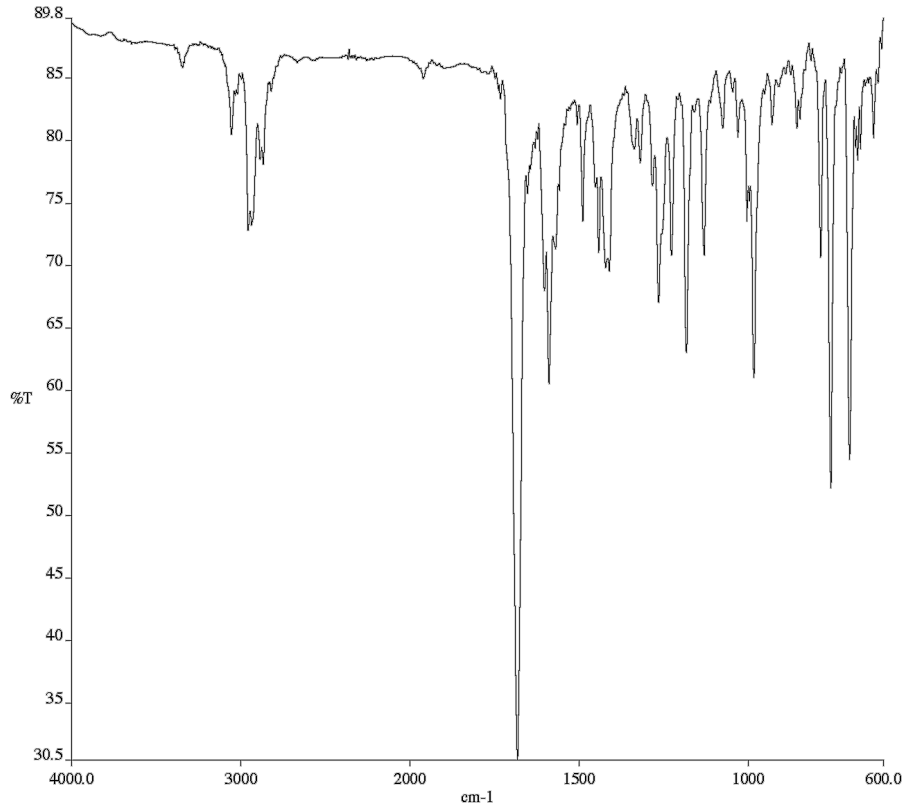



***Figure A11.38*** *Infrared spectrum (Thin Film, NaCl) of compound* ***150a***.

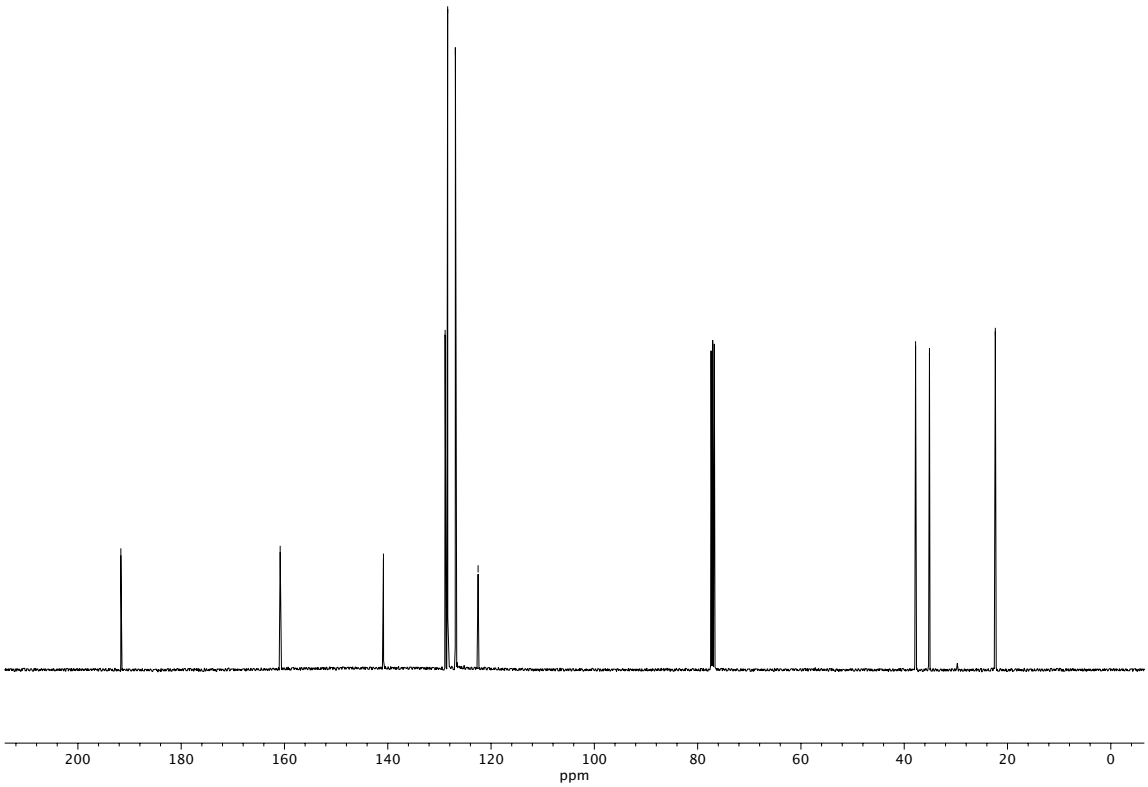
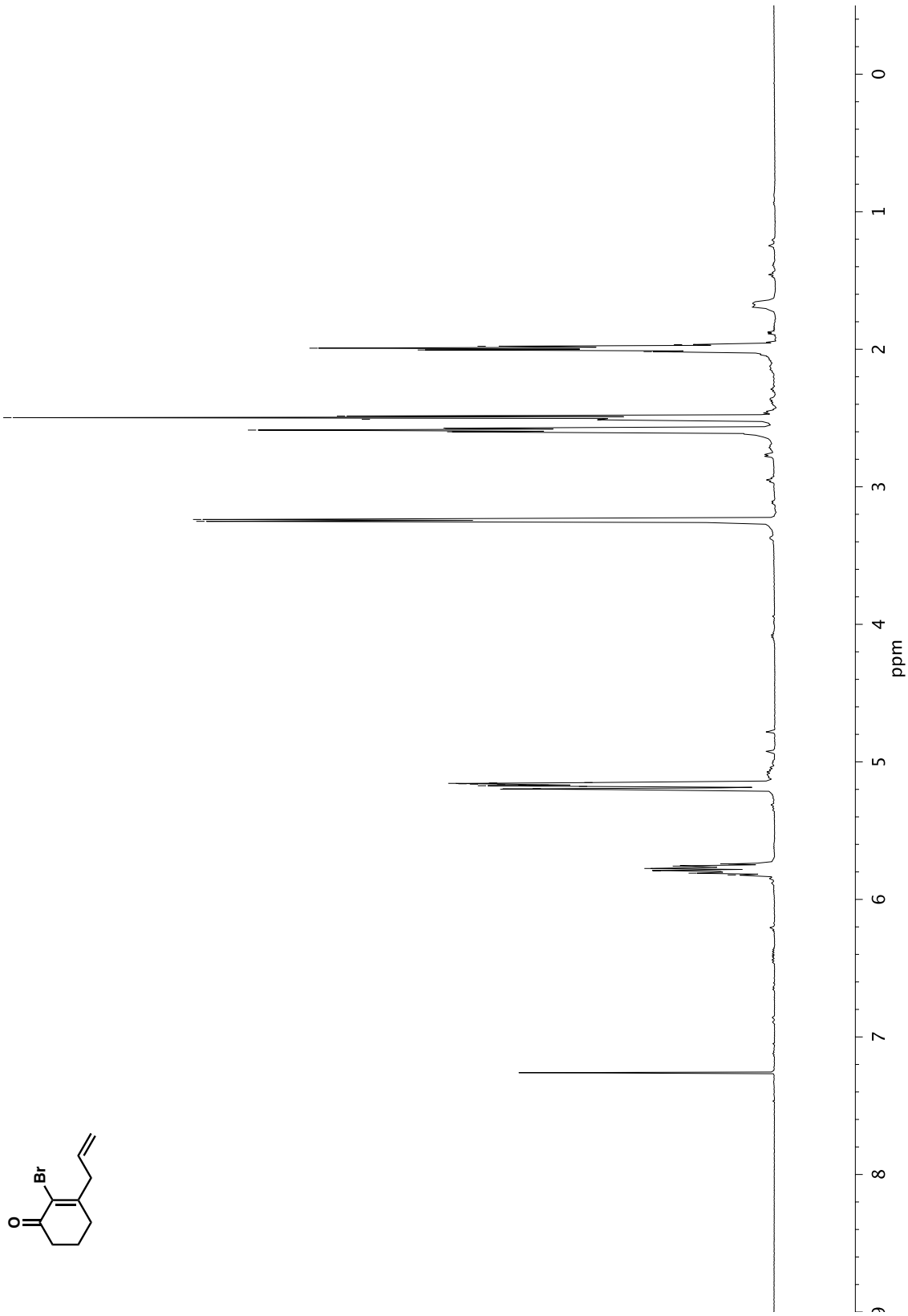



***Figure A11.39*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***150a***.




***A11.40*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***150b***.

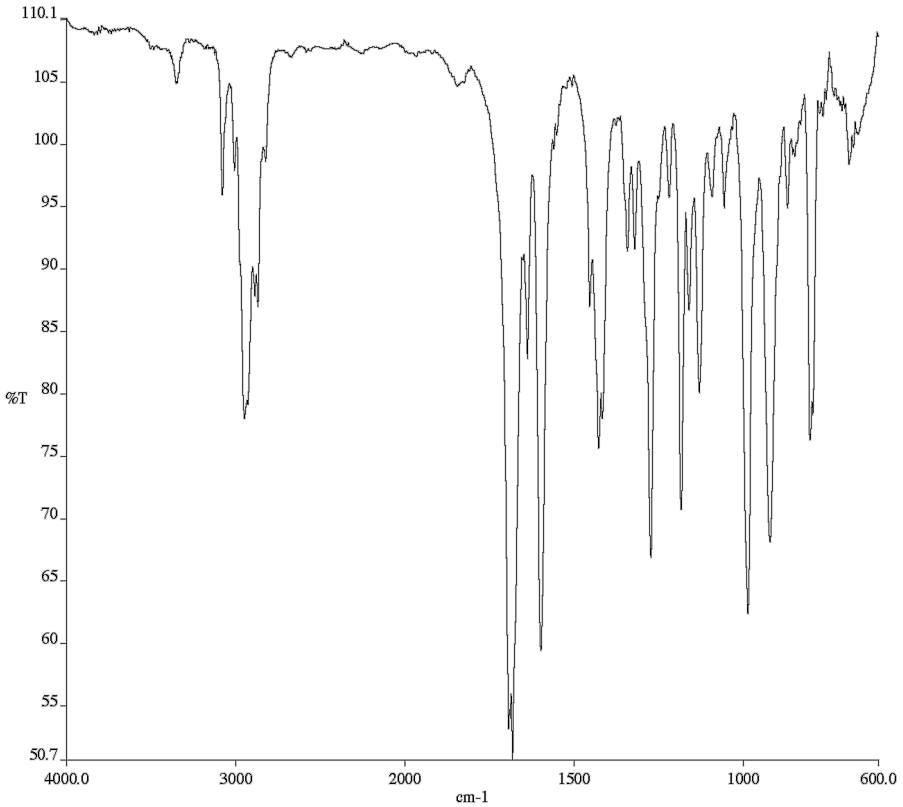



***Figure A11.41*** *Infrared spectrum (Thin Film, NaCl) of compound* ***150b***.

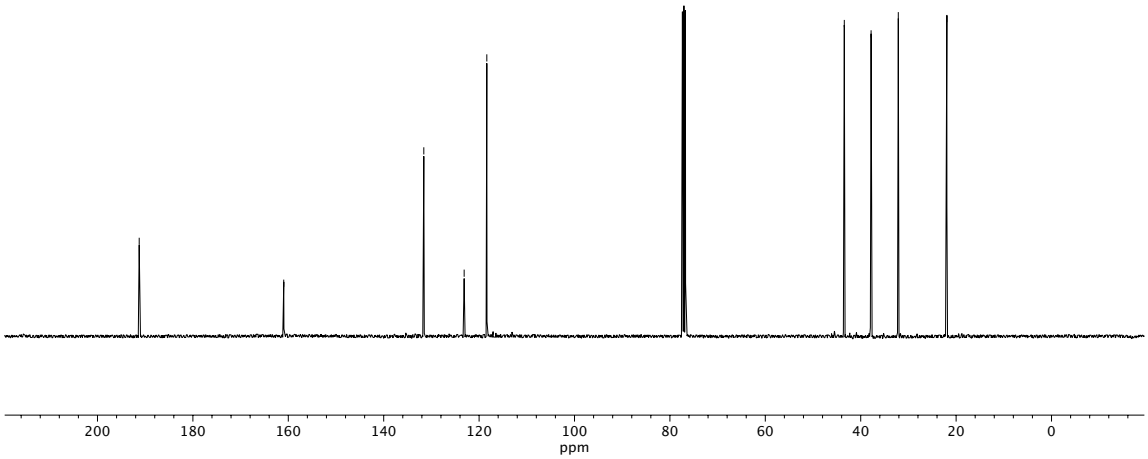
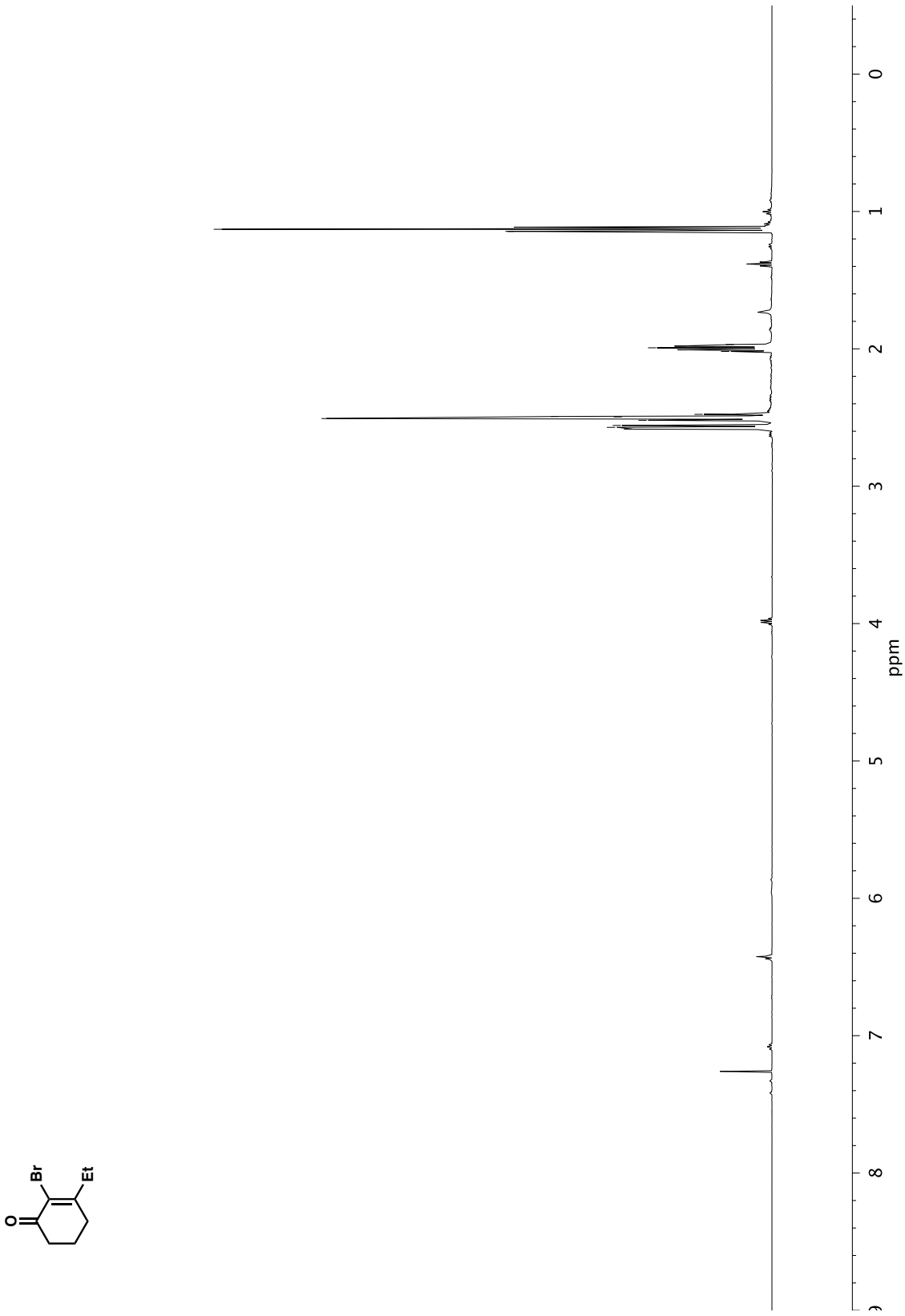



***Figure A11.42*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***150b***.




***A11.43*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***150c****.*

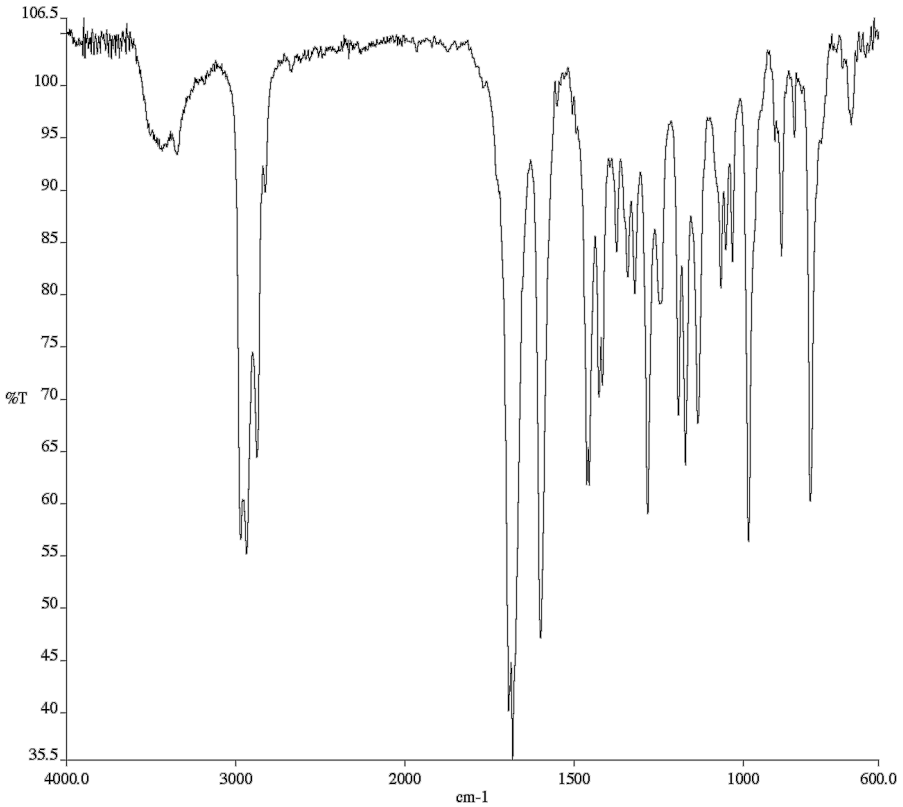



***Figure A11.44*** *Infrared spectrum (Thin Film, NaCl) of compound* ***150c****.*

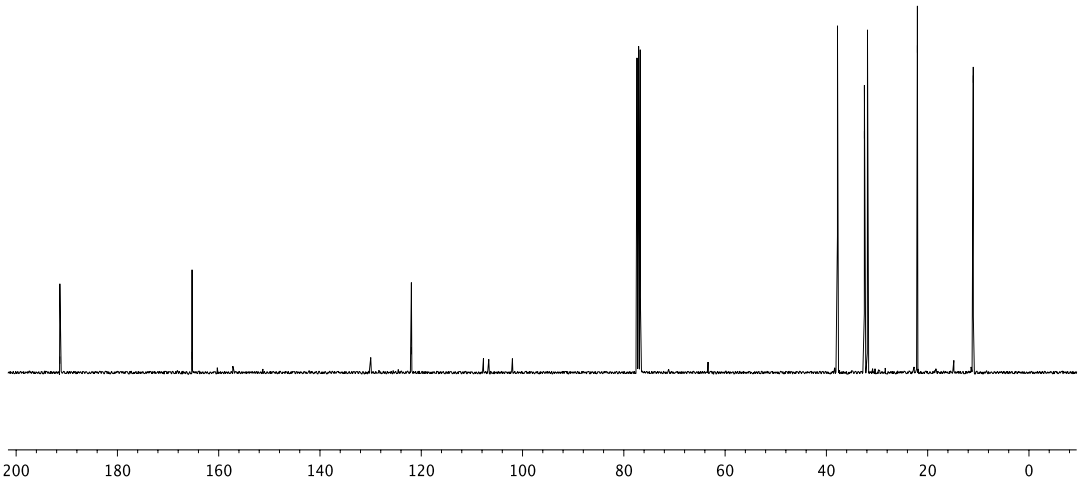
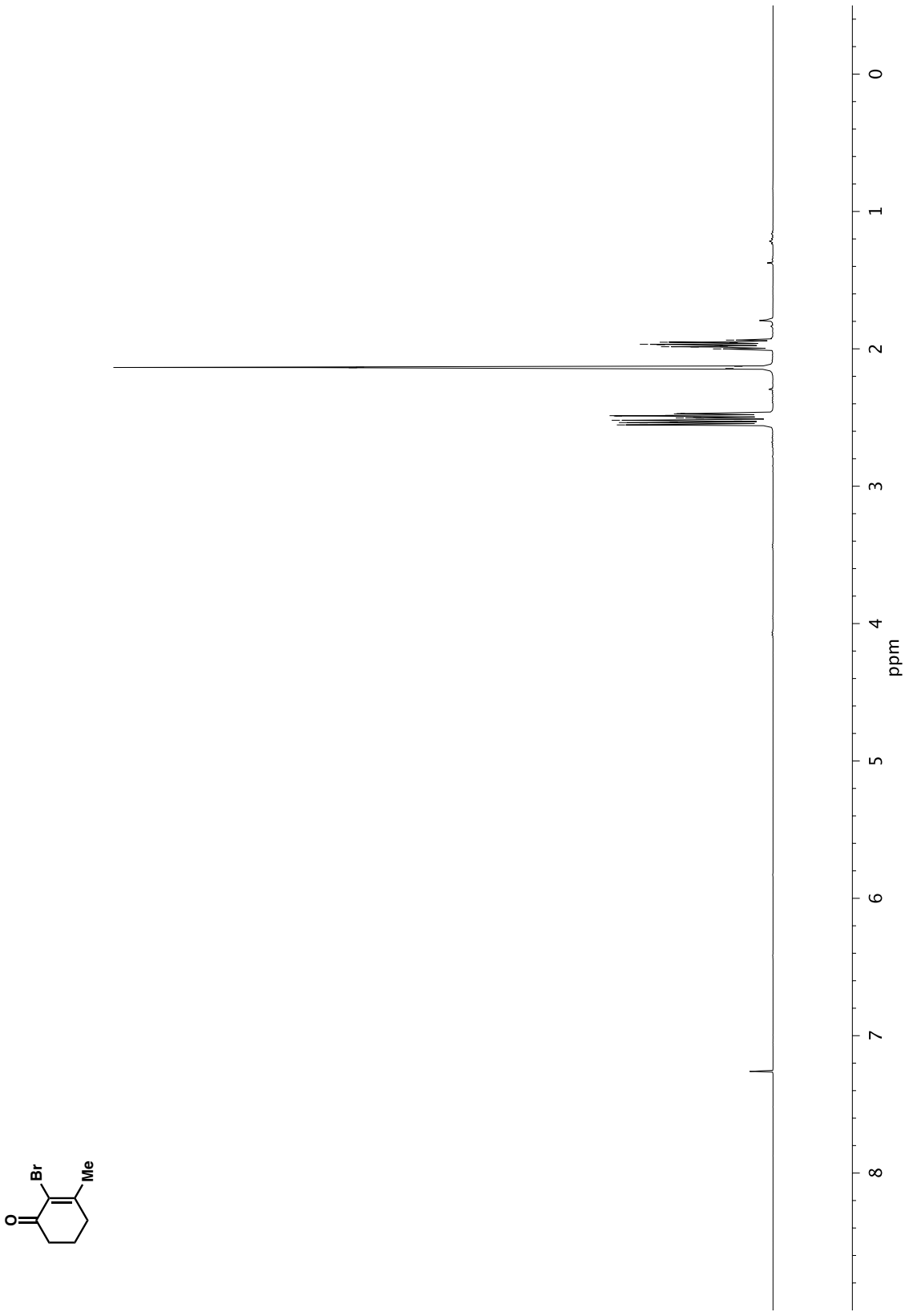



***Figure A11.45*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***150c****.*




***A11.46*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***150d***.

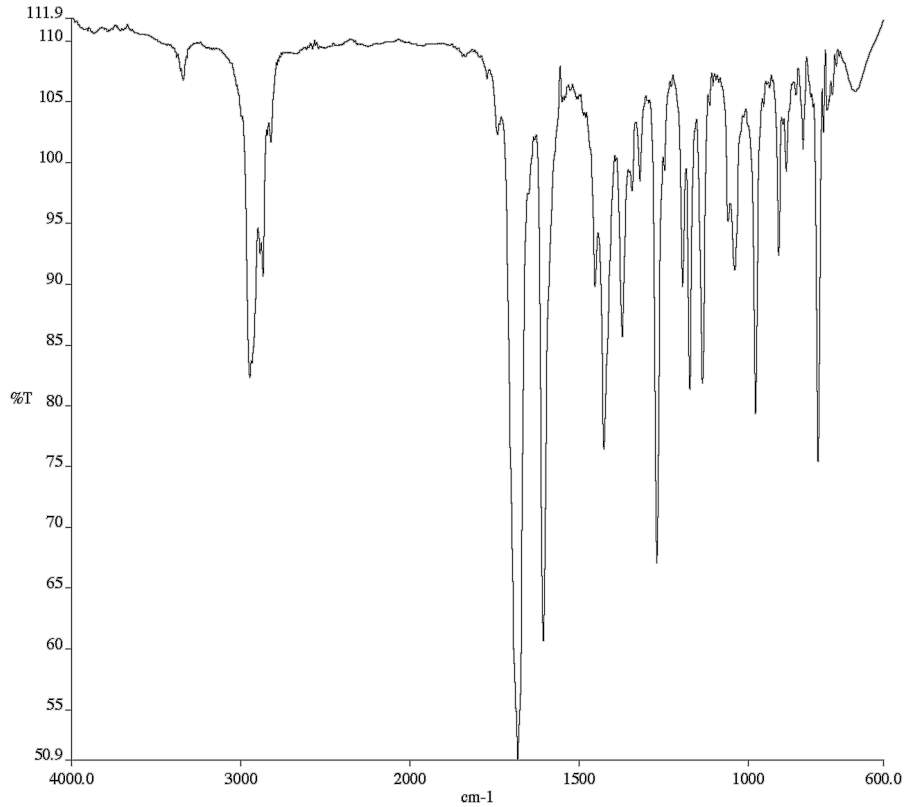



***Figure A11.47*** *Infrared spectrum (Thin Film, NaCl) of compound* ***150d****.*

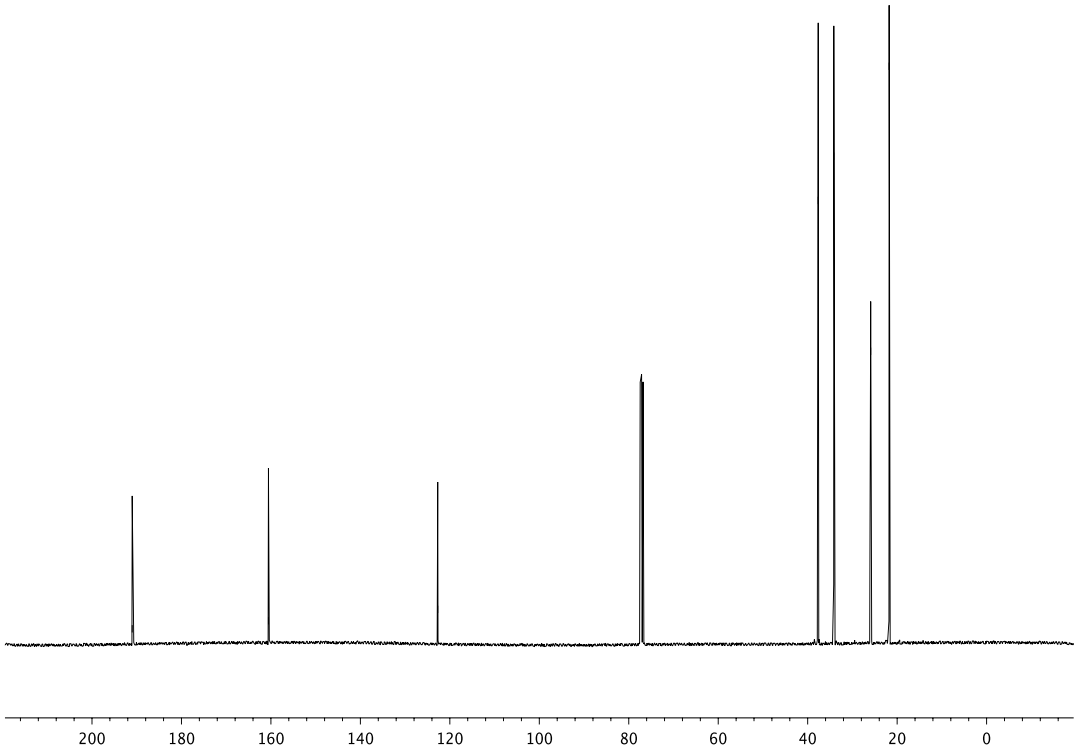
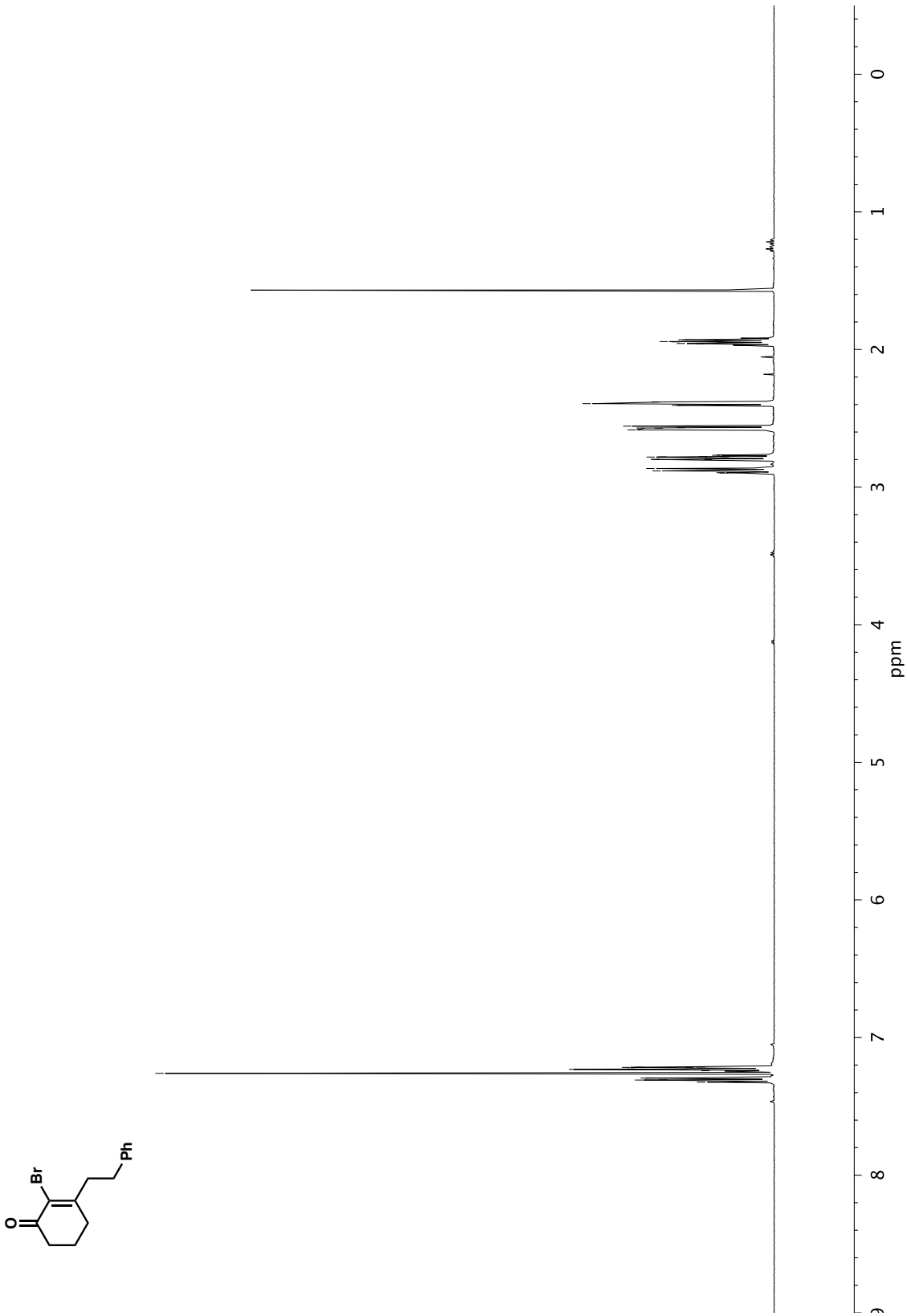



***Figure A11.48*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***150d****.*




***A11.49*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***150e***.

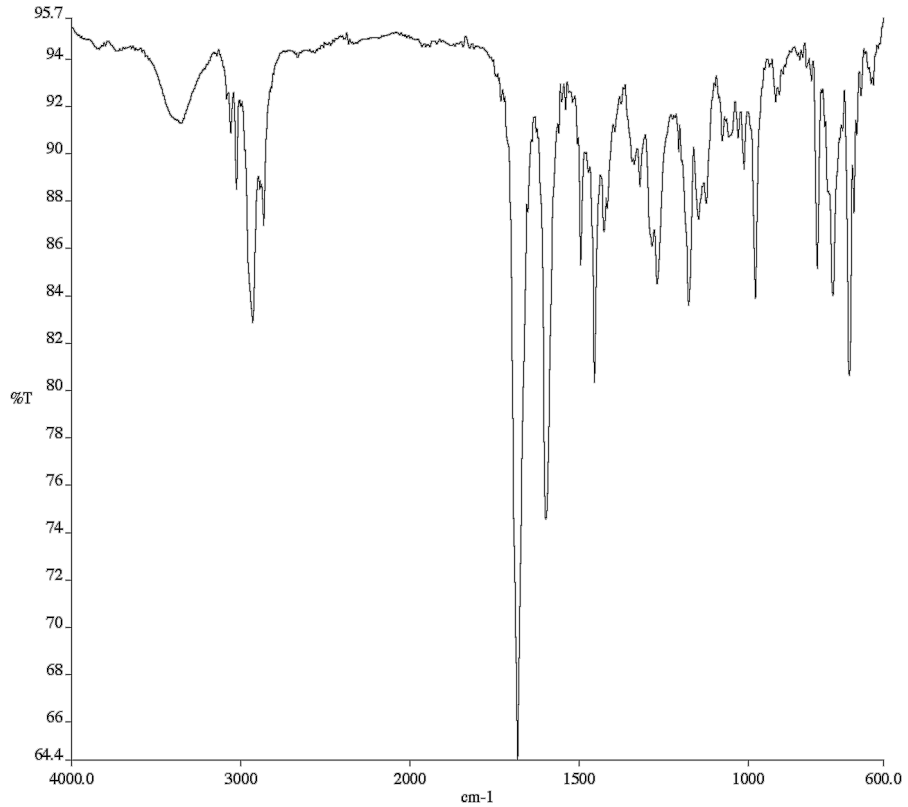



***Figure A11.50*** *Infrared spectrum (Thin Film, NaCl) of compound* ***150e****.*

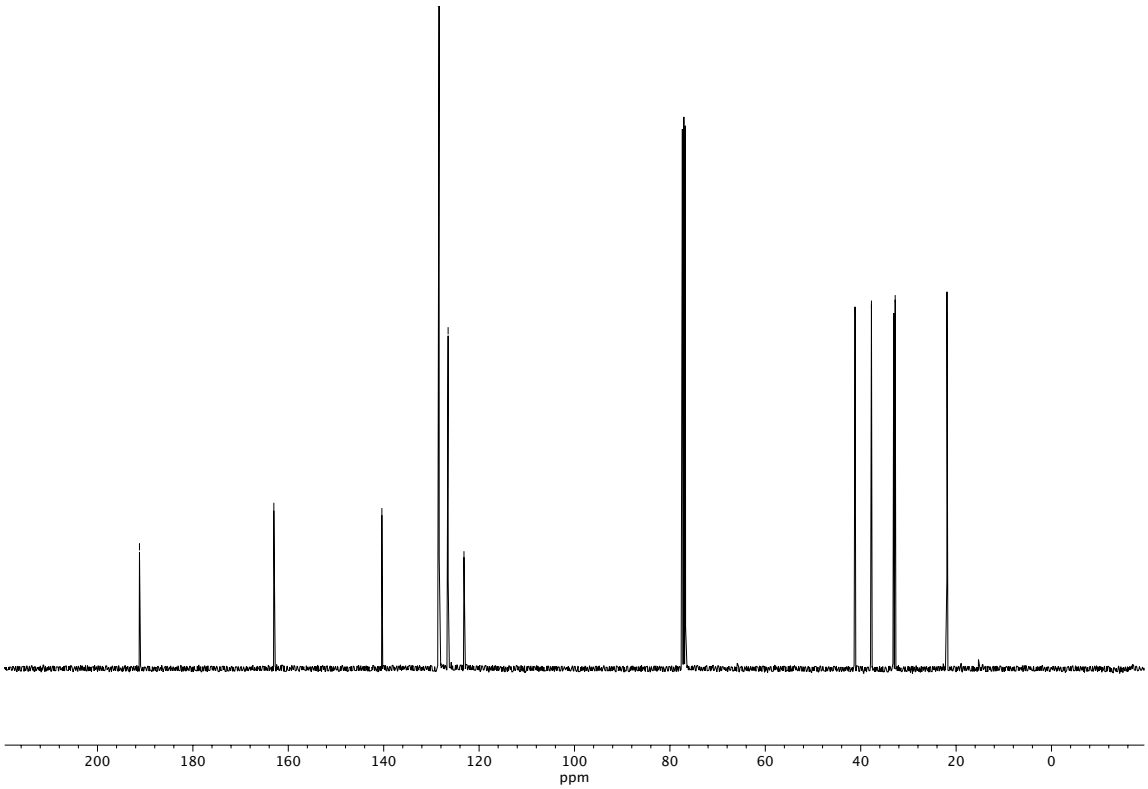
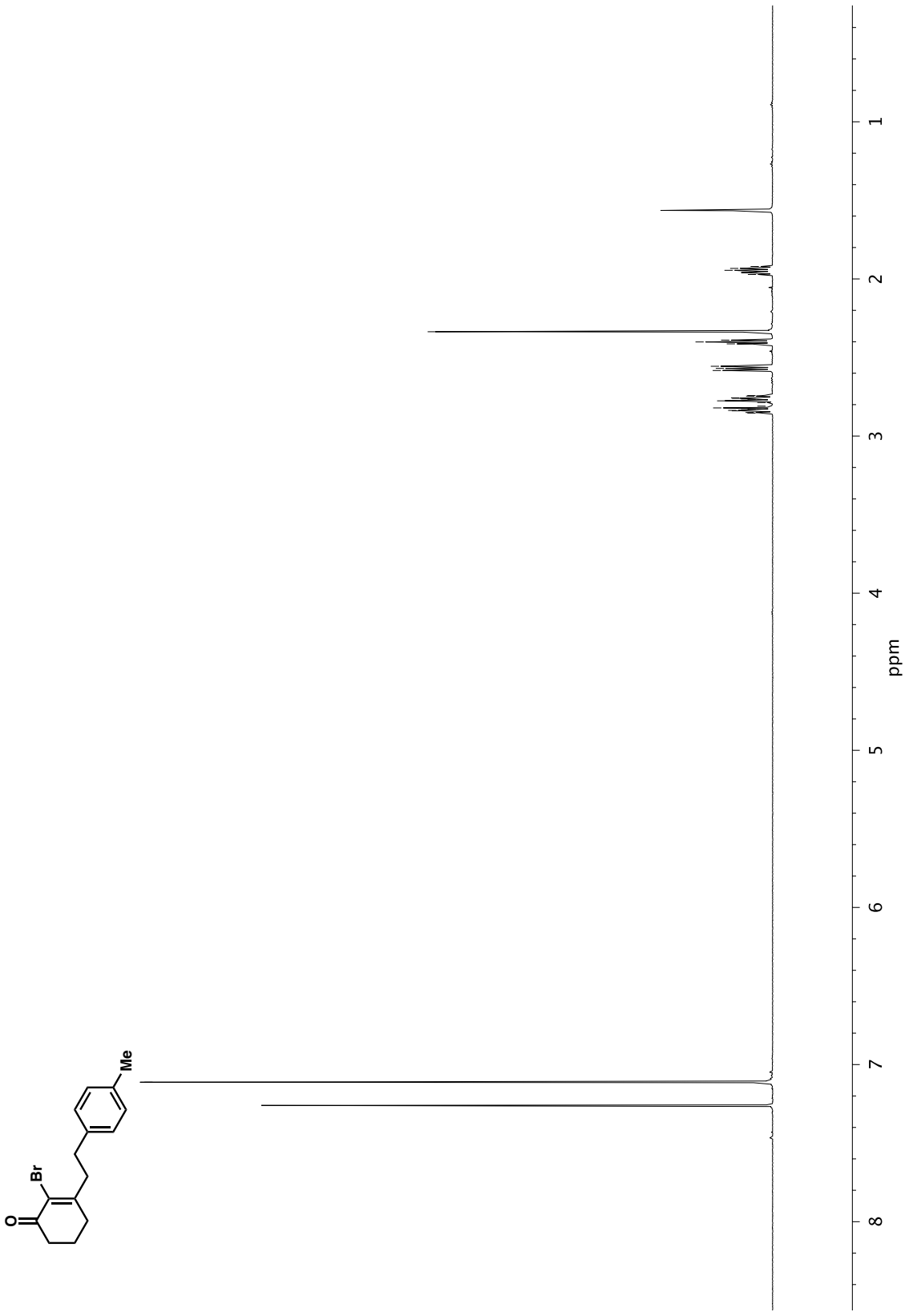



***Figure A11.51*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***150e****.*




***A11.52*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***150f****.*

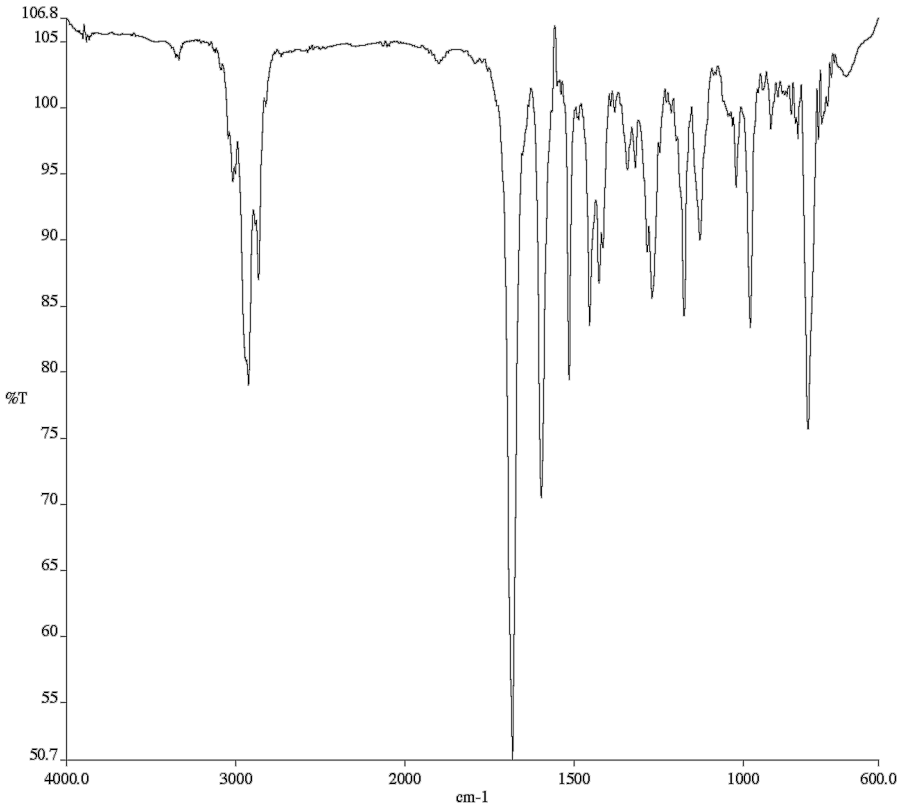



***Figure A11.53*** *Infrared spectrum (Thin Film, NaCl) of compound* ***150f****.*

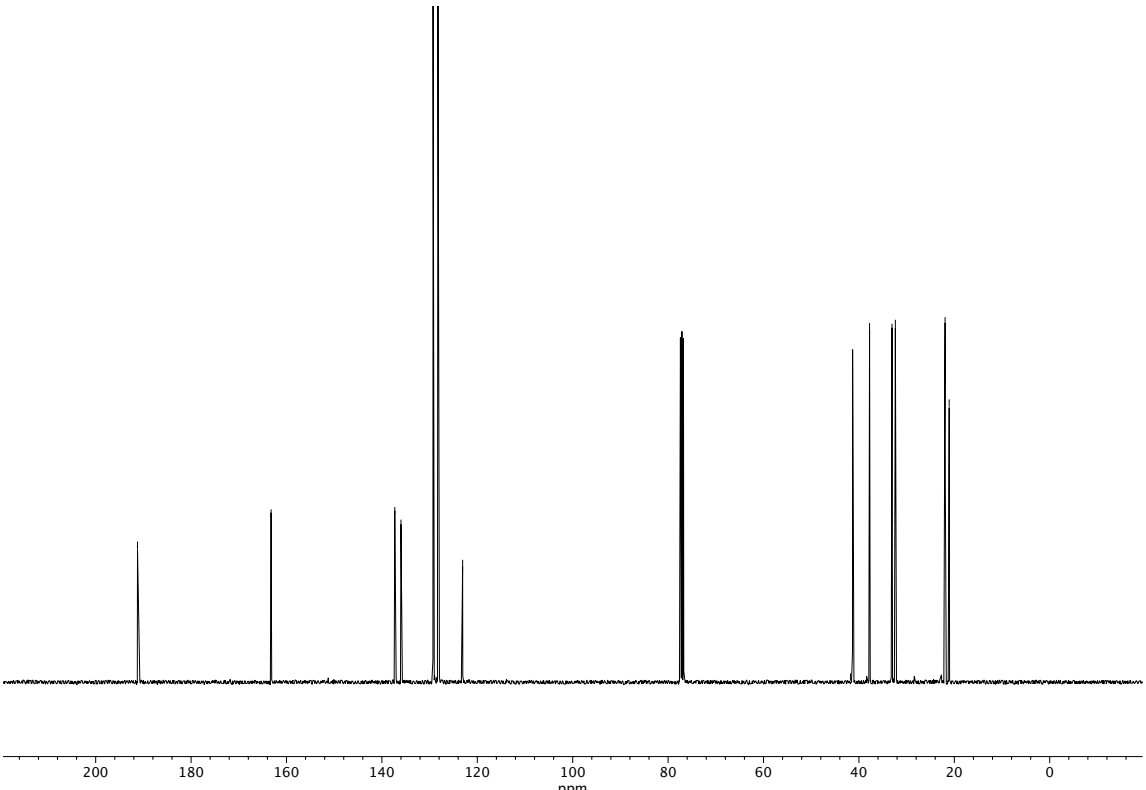
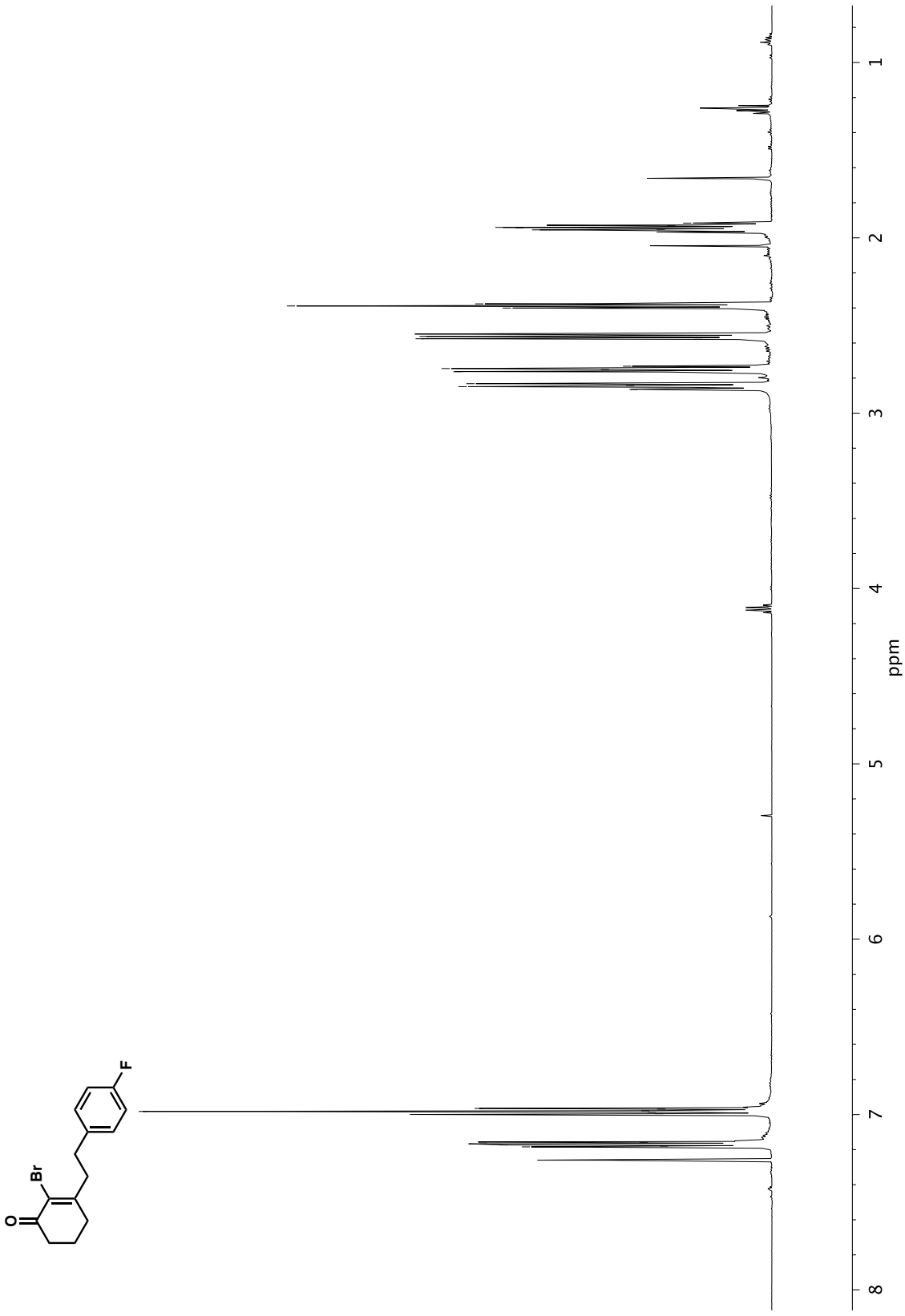



***Figure A11.54*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***150f****.*




***A11.55*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***150g***.

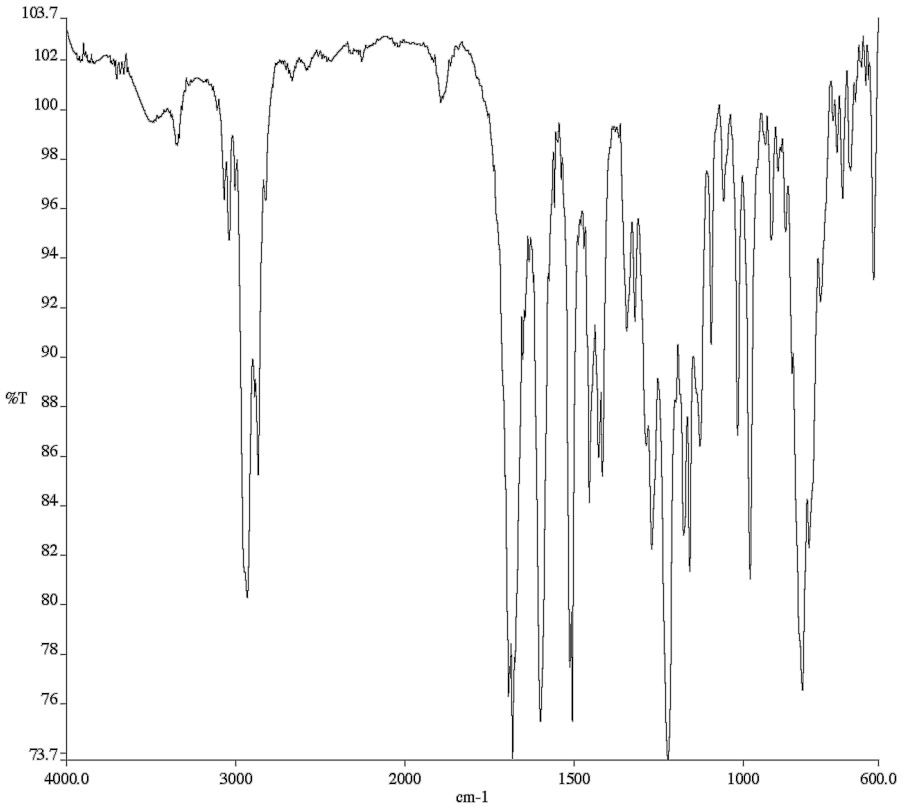



***Figure A11.56*** *Infrared spectrum (Thin Film, NaCl) of compound* ***150g***.

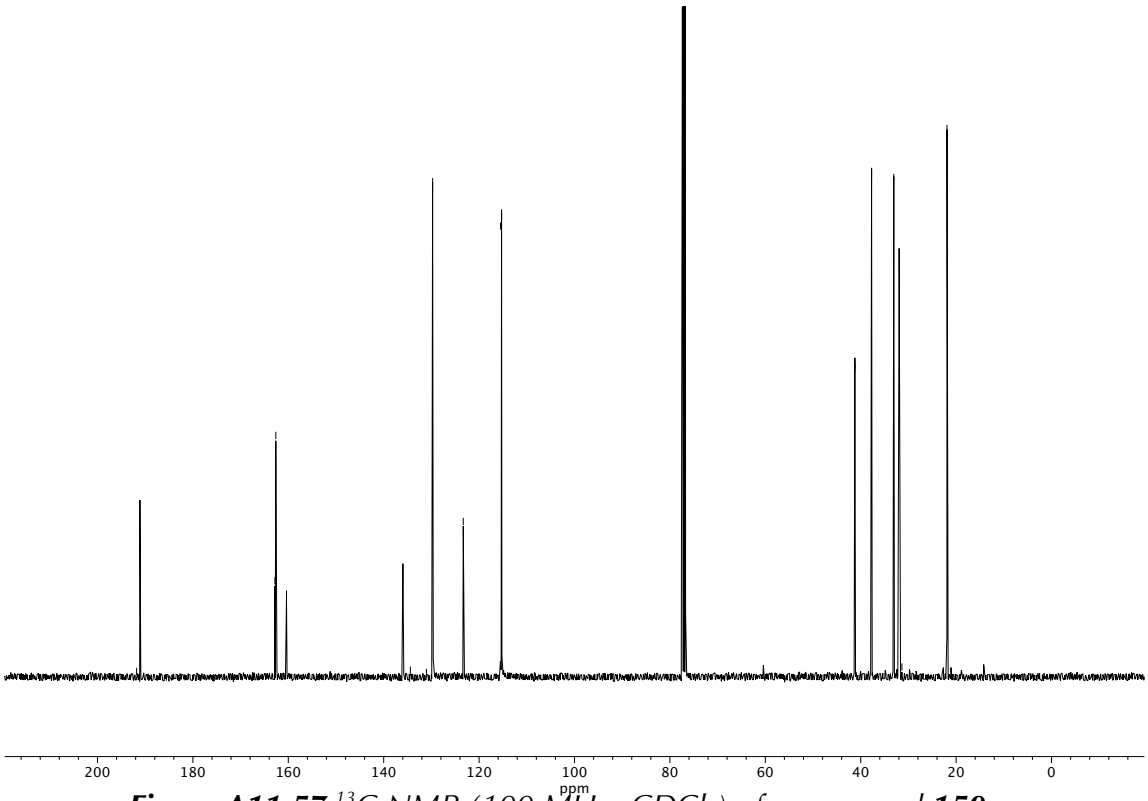



***Figure A11.57*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***150g***.

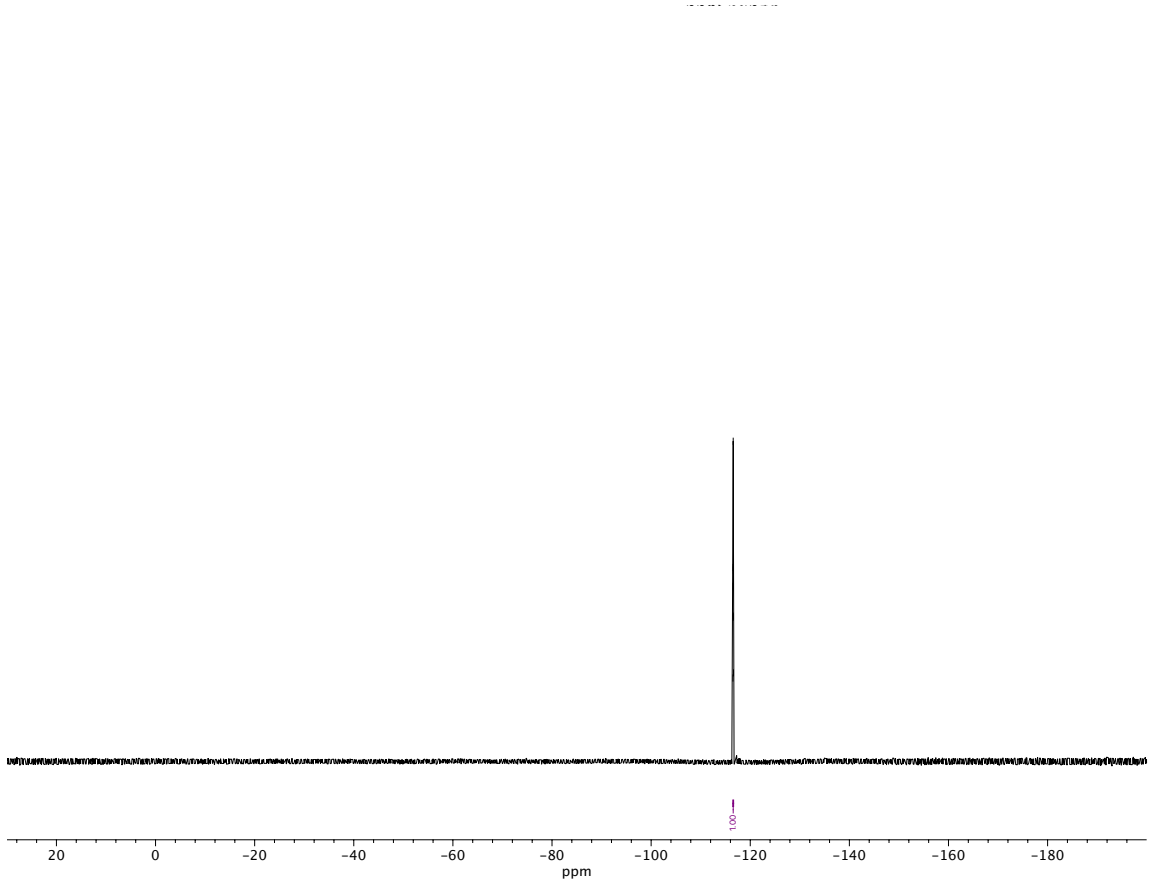
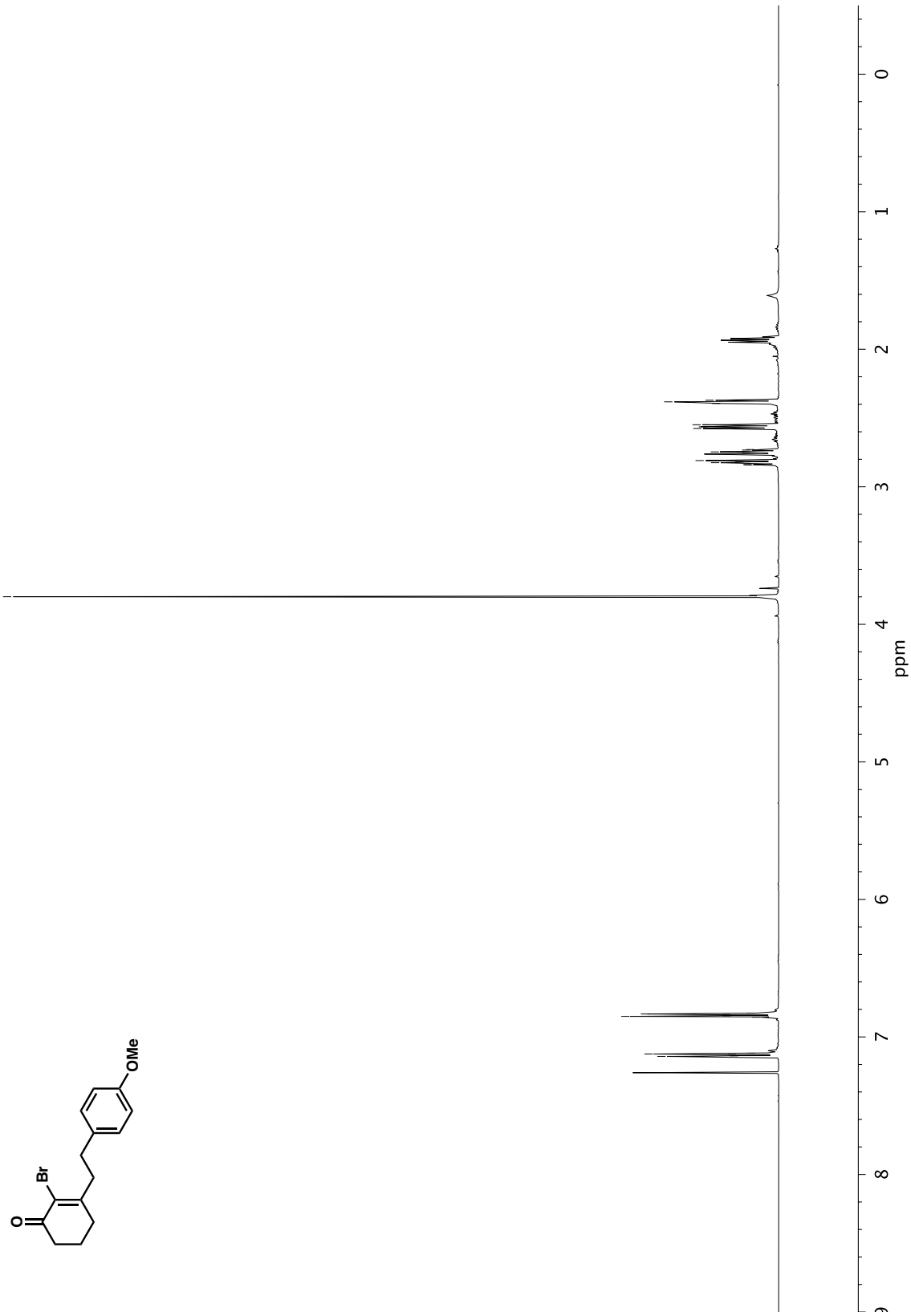



***Figure A11.58*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***150g***.




***A11.59*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***150h***.

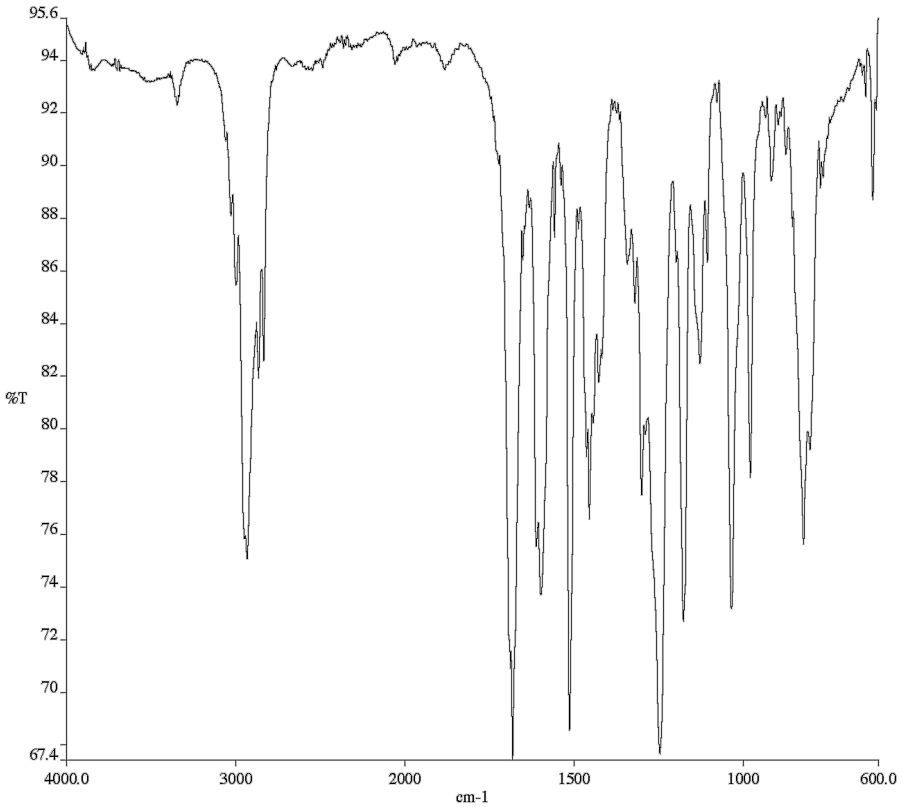



***Figure A11.60*** *Infrared spectrum (Thin Film, NaCl) of compound* ***150h***.

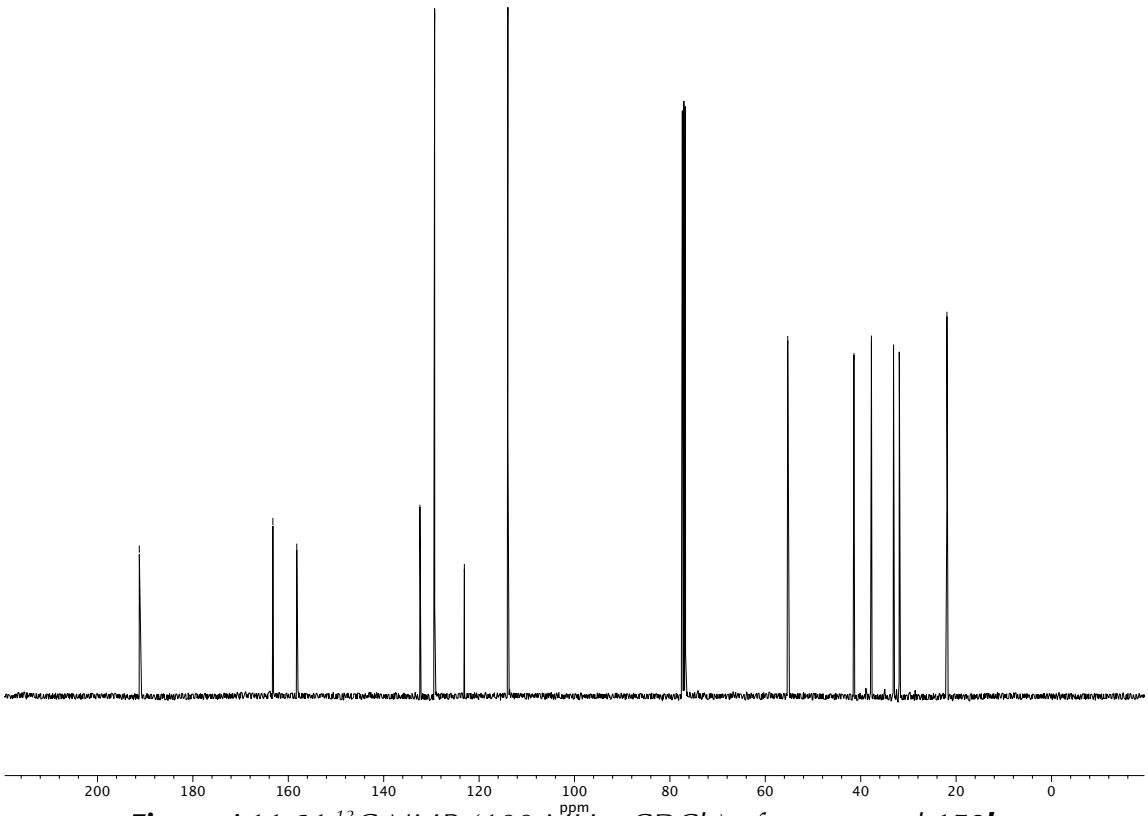
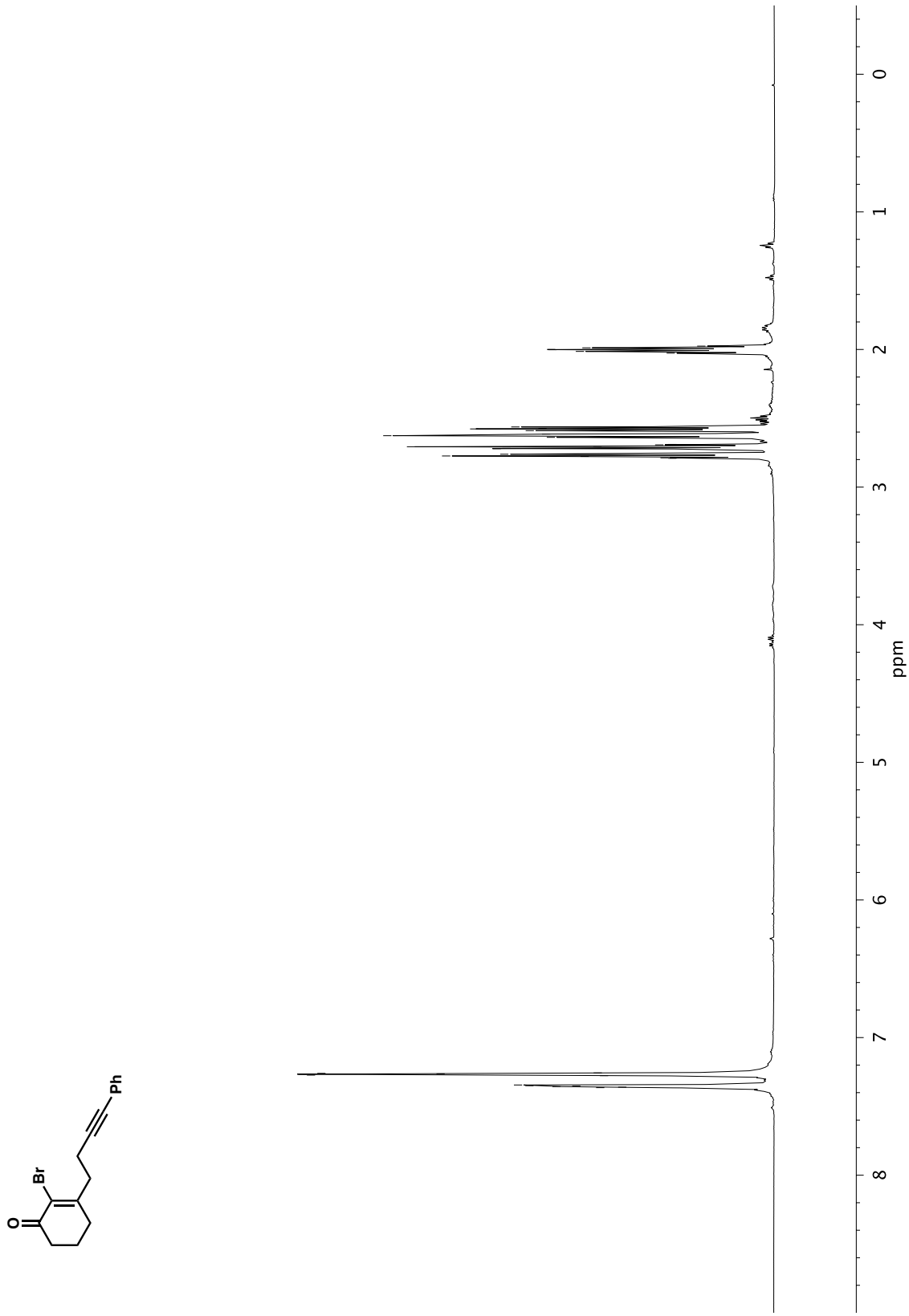



***Figure A11.61*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***150h***.




***A11.62*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***150i****.*

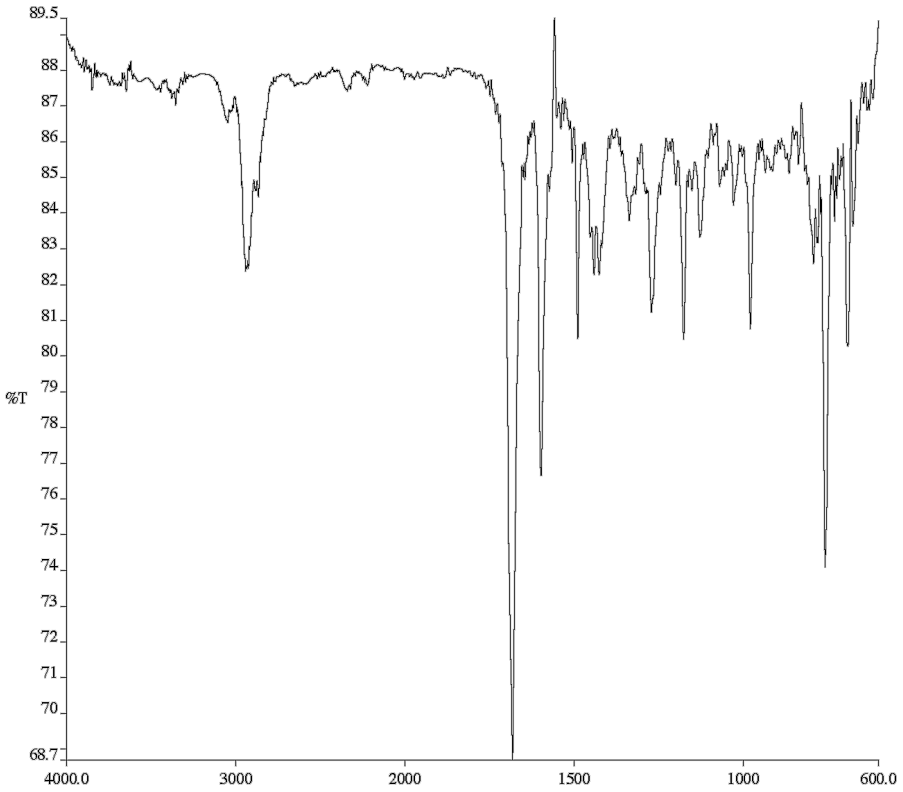



***Figure A11.63*** *Infrared spectrum (Thin Film, NaCl) of compound* ***150i****.*

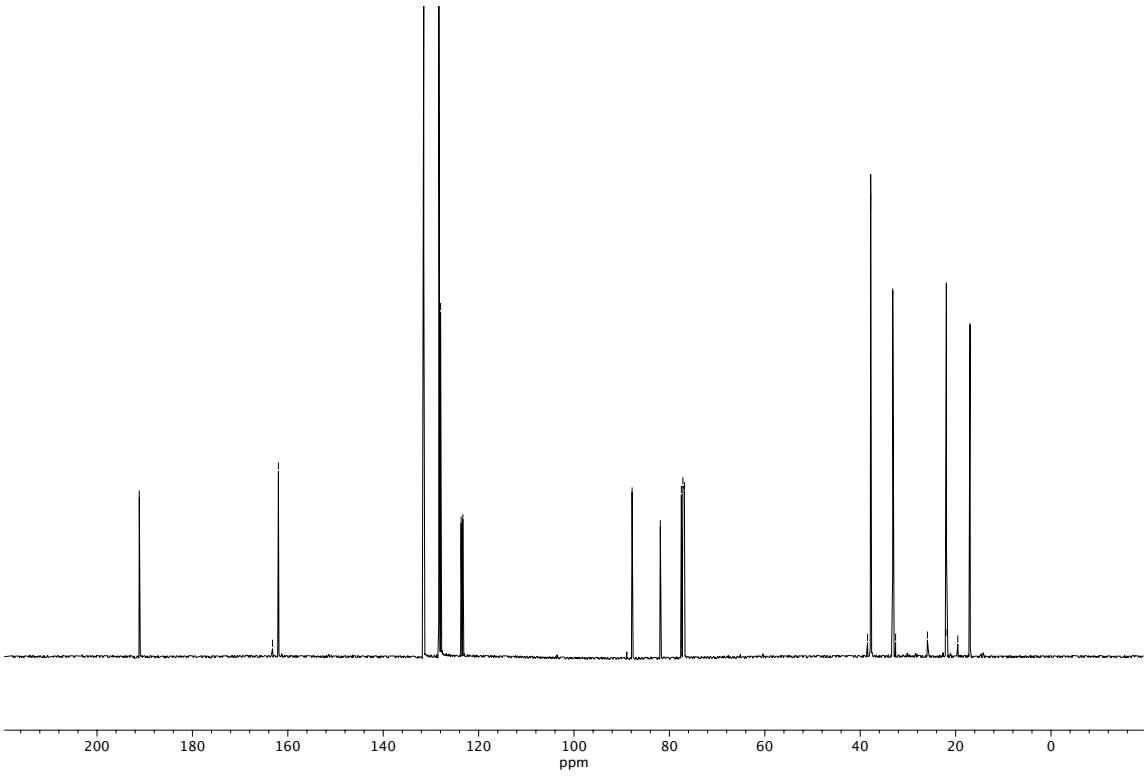
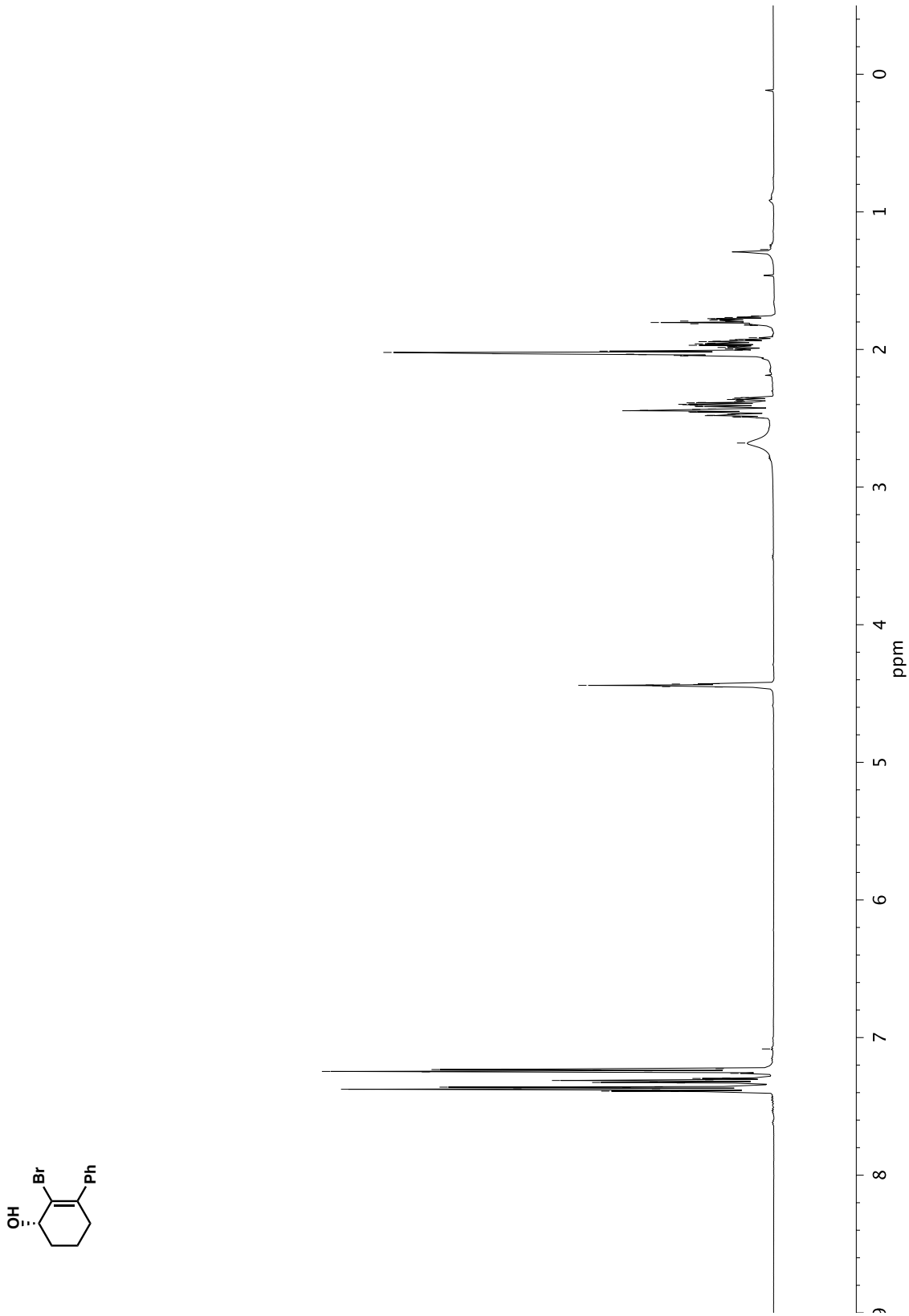



***Figure A11.64*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***150i****.*




***A11.65*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***151a***.

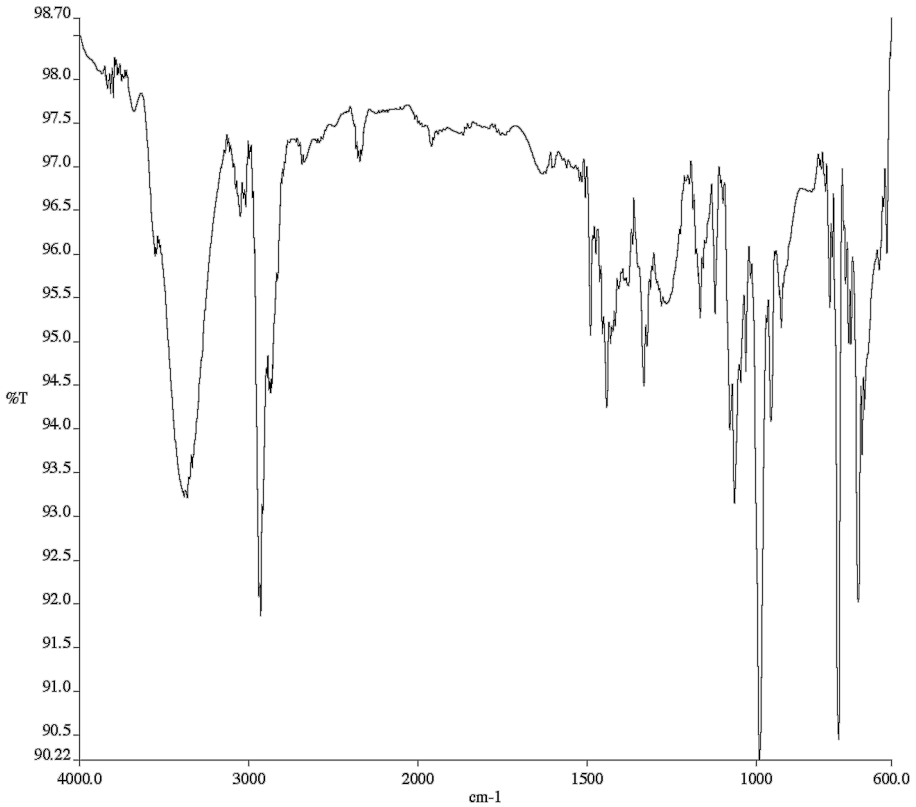



***Figure A11.66*** *Infrared spectrum (Thin Film, NaCl) of compound* ***151a***.

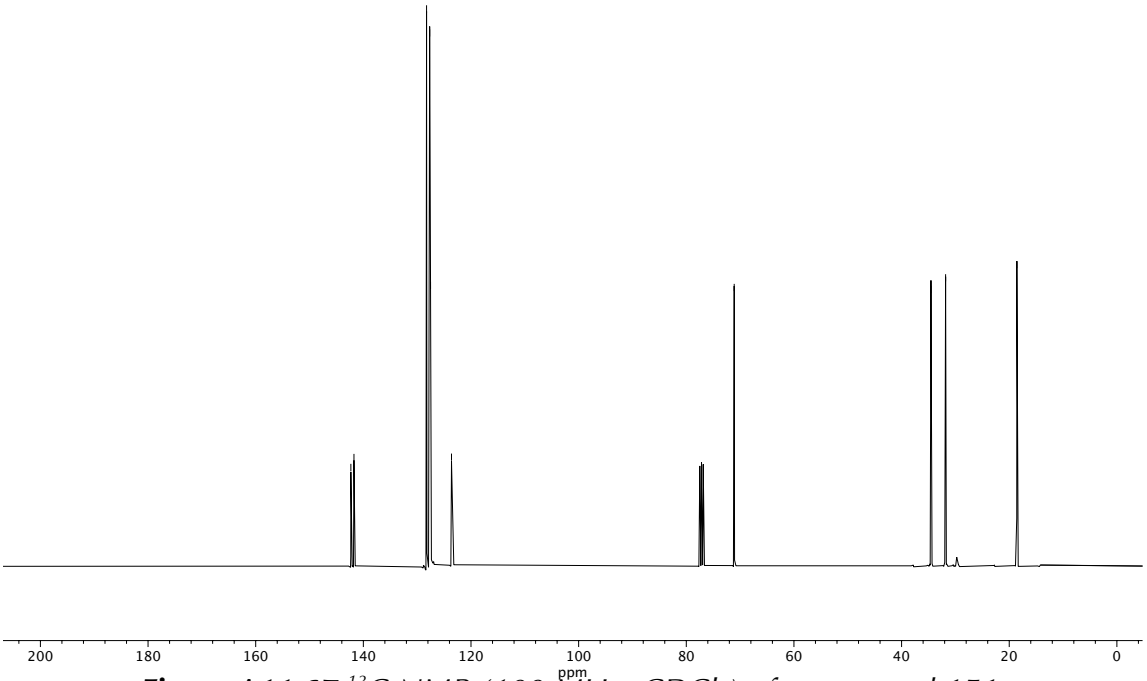
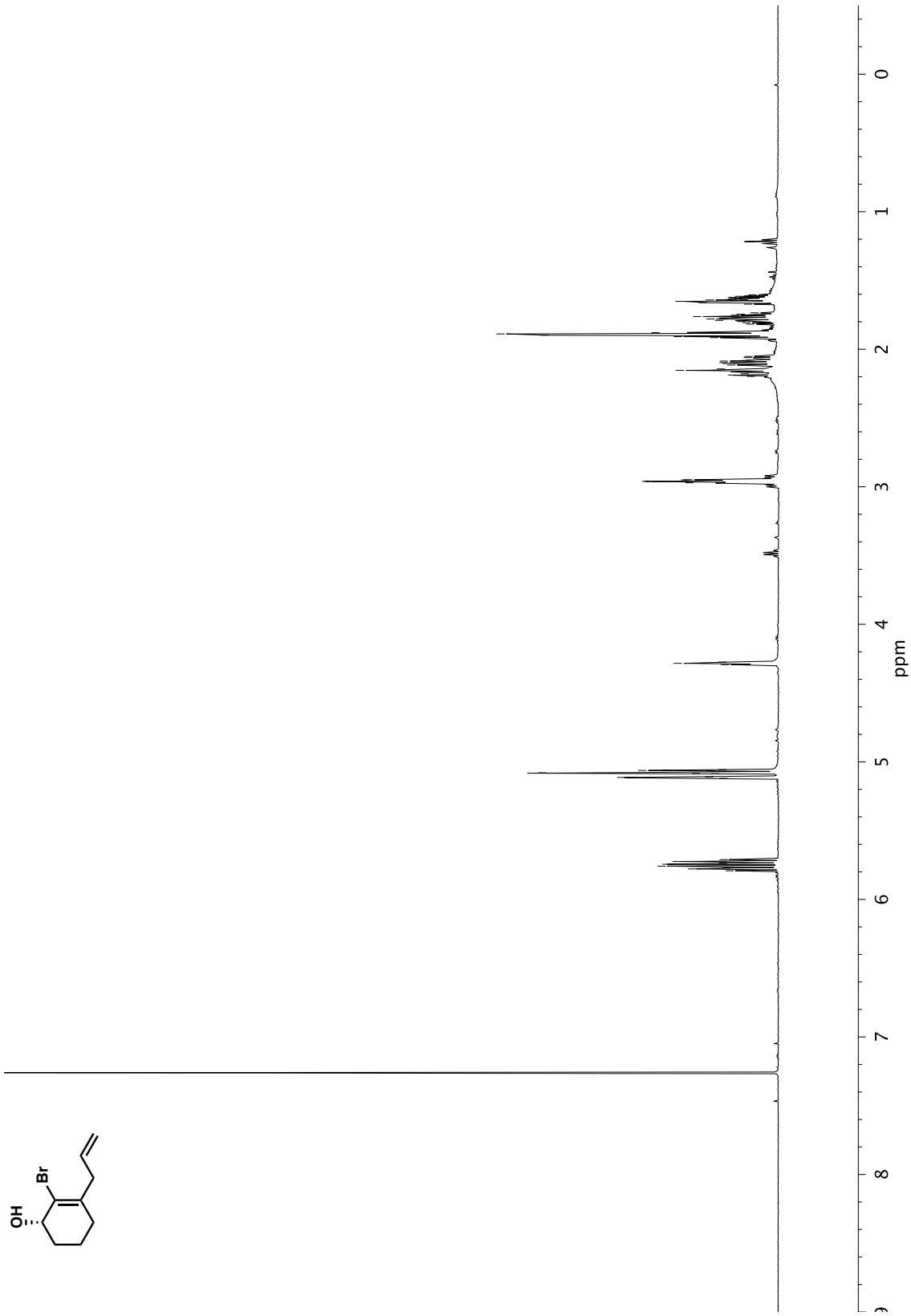



***Figure A11.67*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***151a***.




***A11.68*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***151b***.

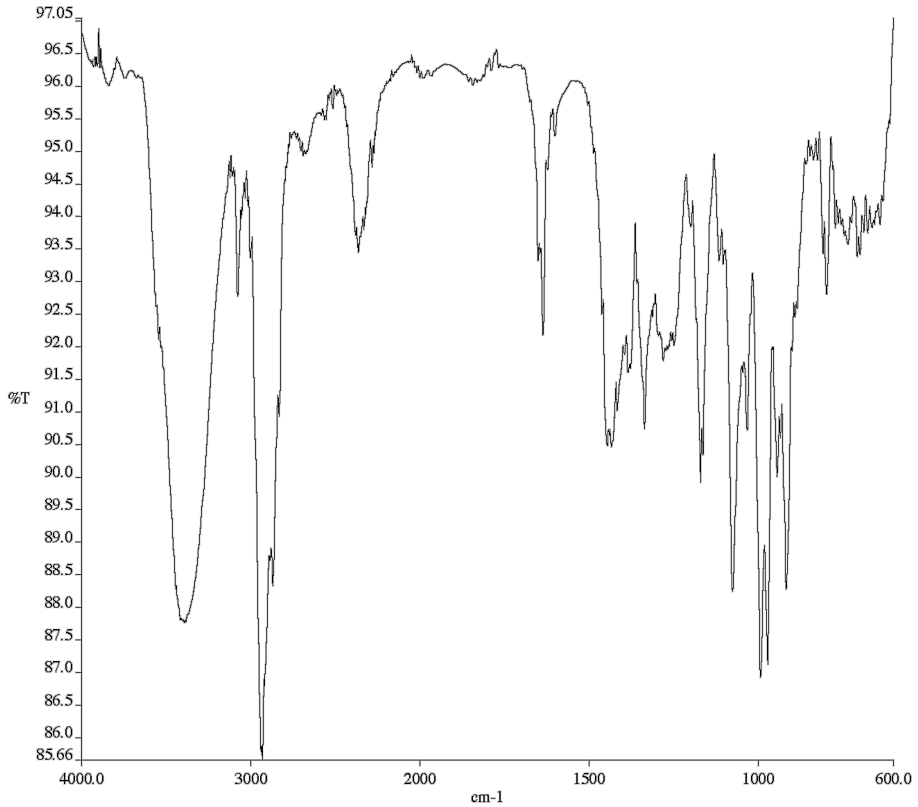



***Figure A11.69*** *Infrared spectrum (Thin Film, NaCl) of compound* ***151b***.

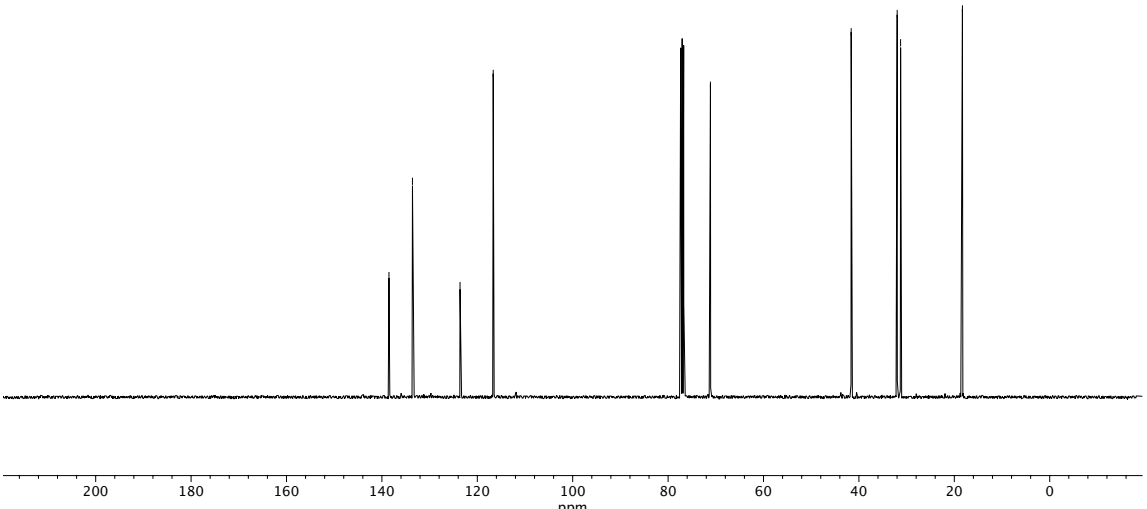
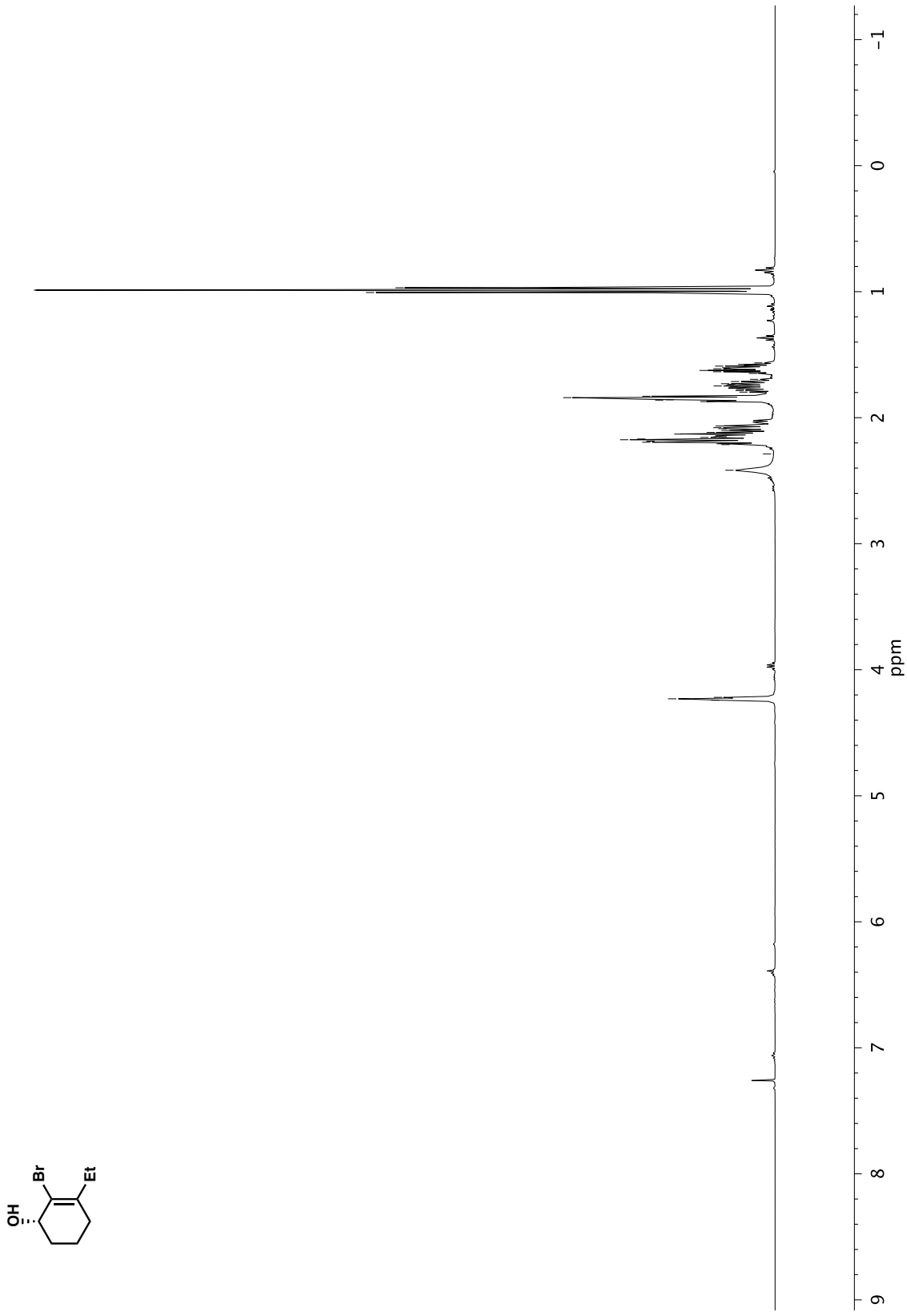



***Figure A11.70*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***151b***.




***A11.71*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***151c****.*

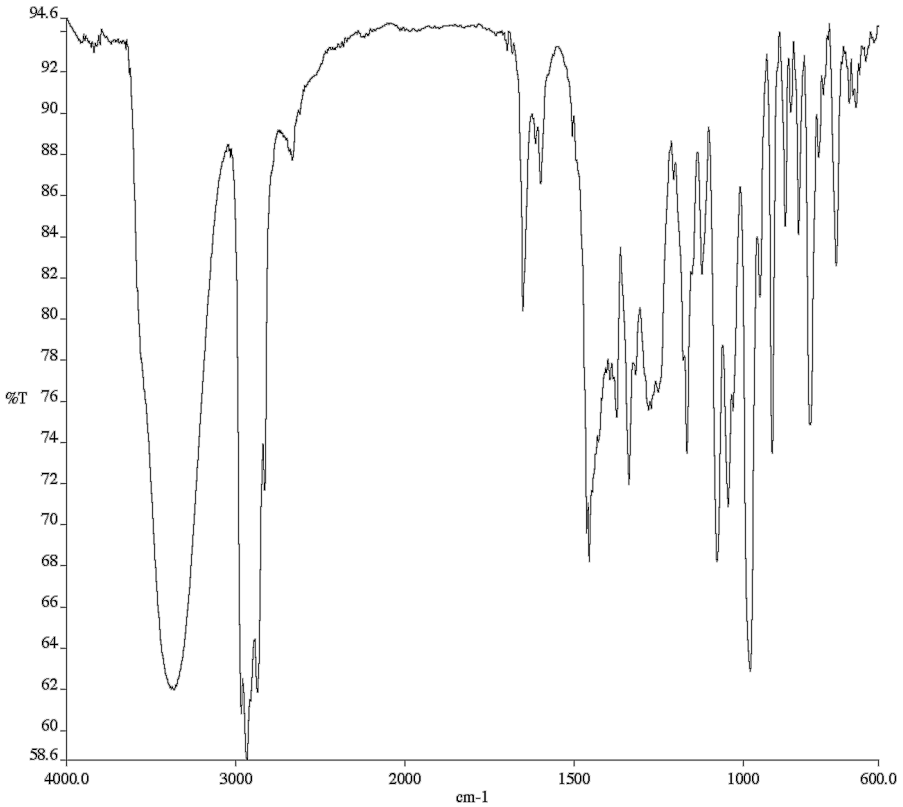



***Figure A11.72*** *Infrared spectrum (Thin Film, NaCl) of compound* ***151c****.*

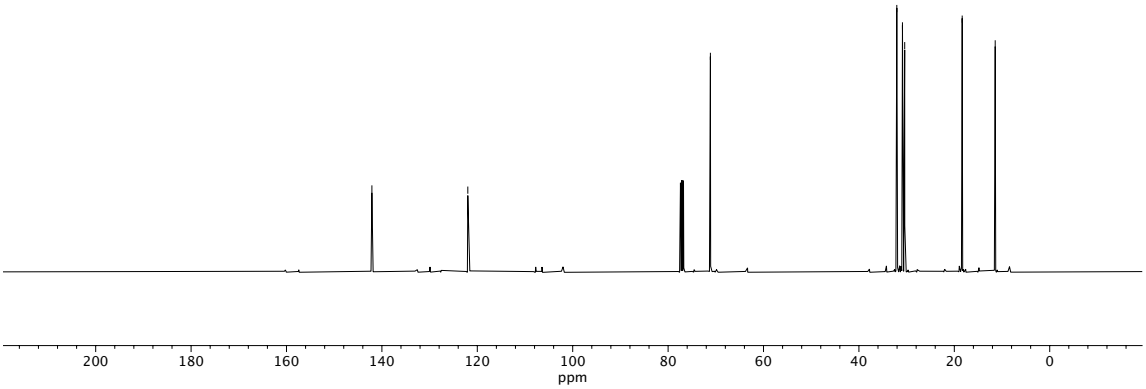
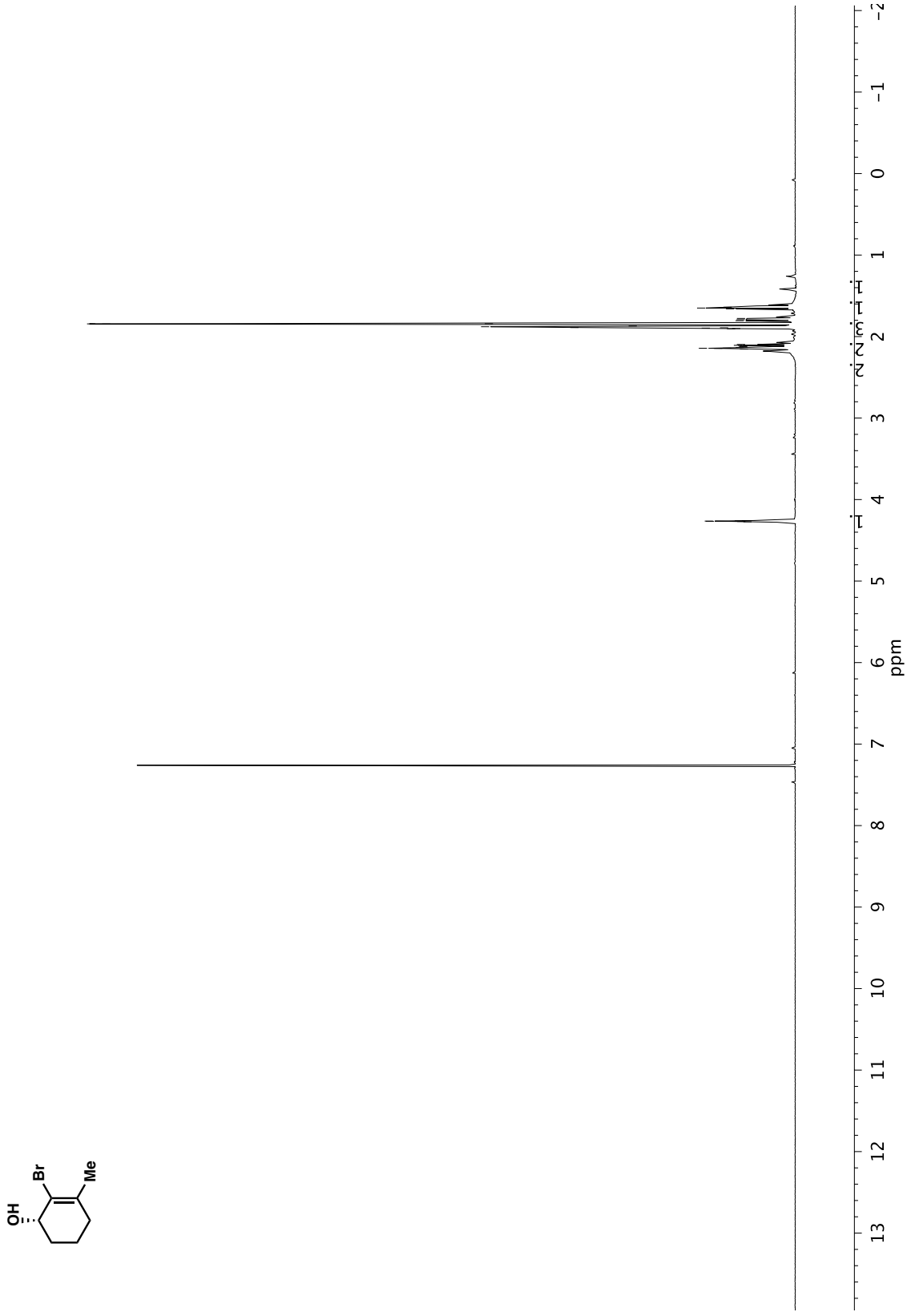



***Figure A11.73*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***151c****.*




***A11.74*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***151d***.

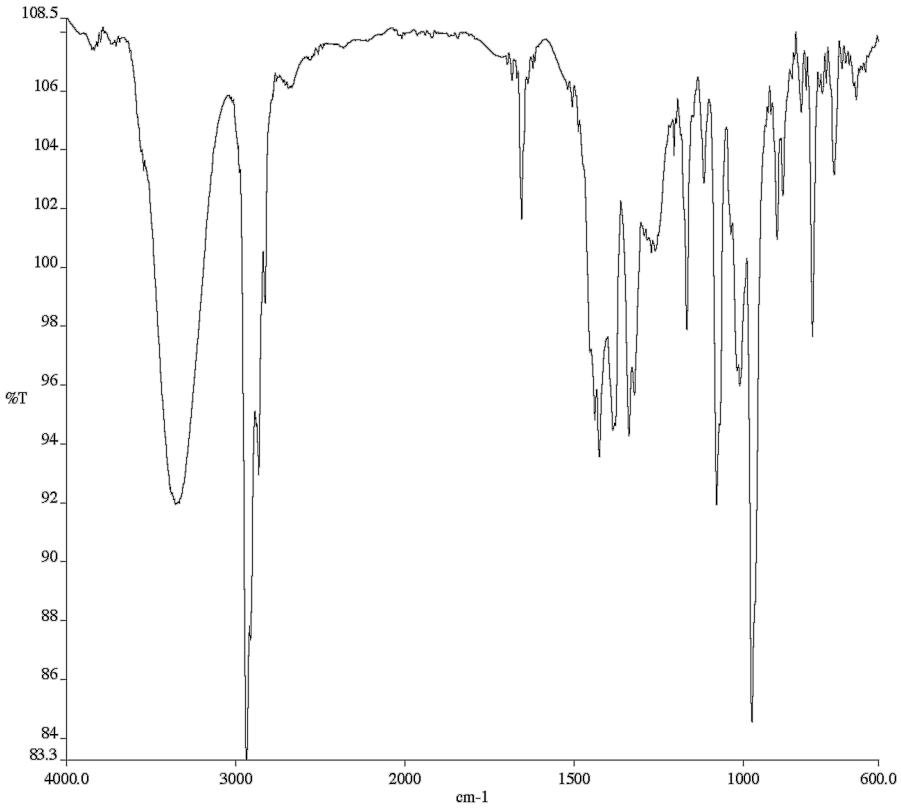



***Figure A11.75*** *Infrared spectrum (Thin Film, NaCl) of compound* ***151d****.*

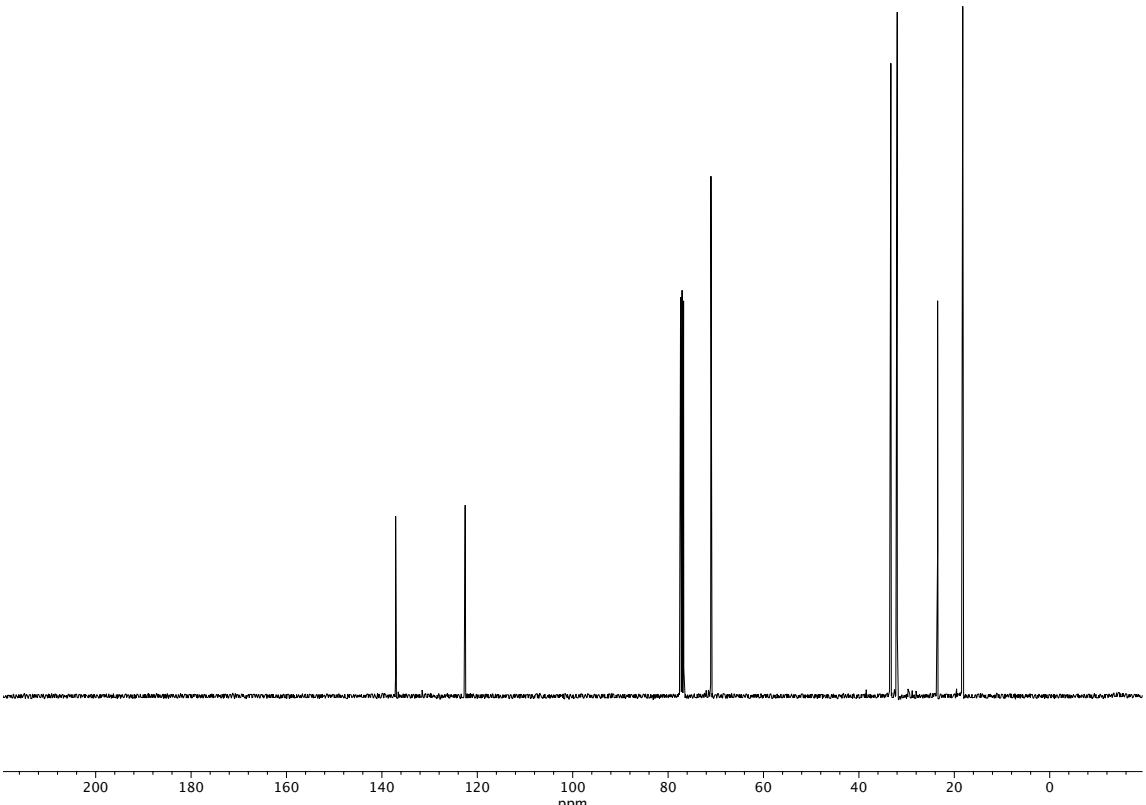
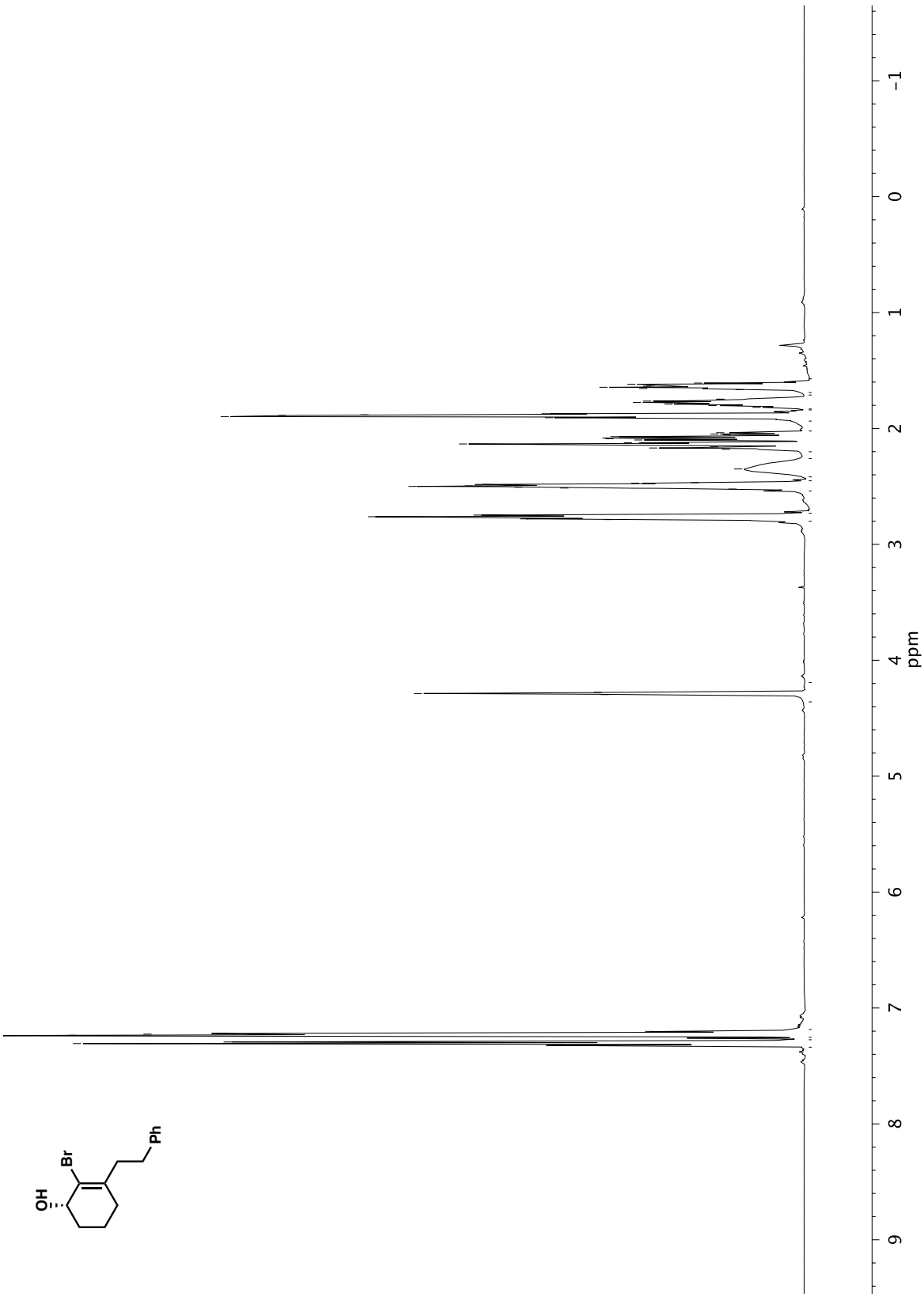



***Figure A11.76*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***151d****.*




***A11.77*** *$^1$H NMR (500 MHz, $CDCl_3$) of compound* ***151e***.

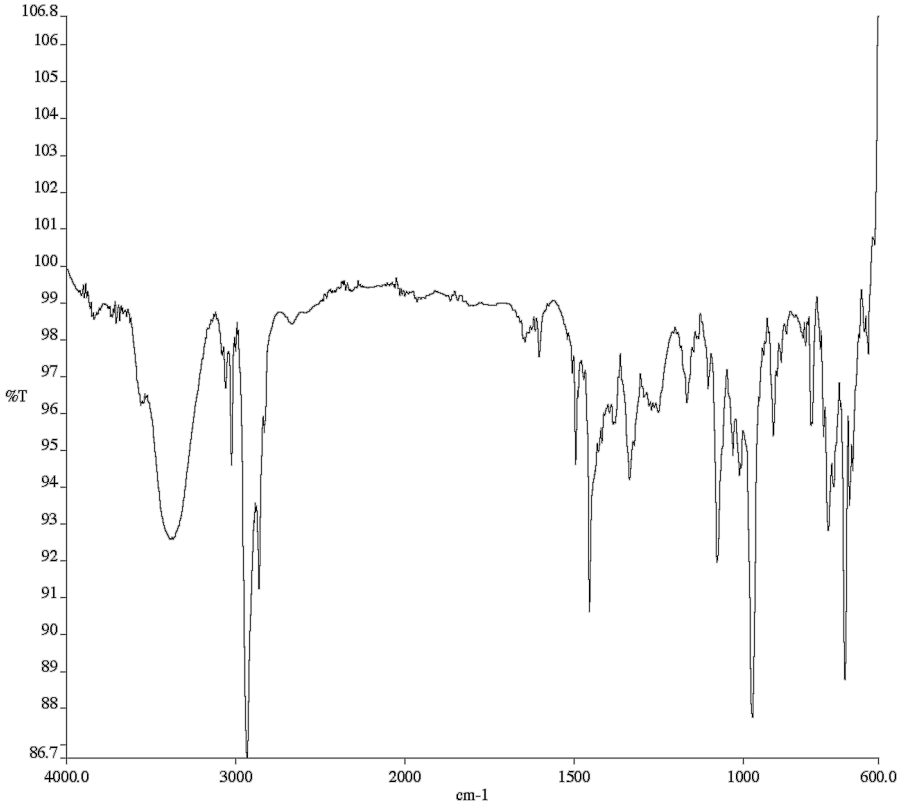



***Figure A11.78*** *Infrared spectrum (Thin Film, NaCl) of compound* ***151e****.*

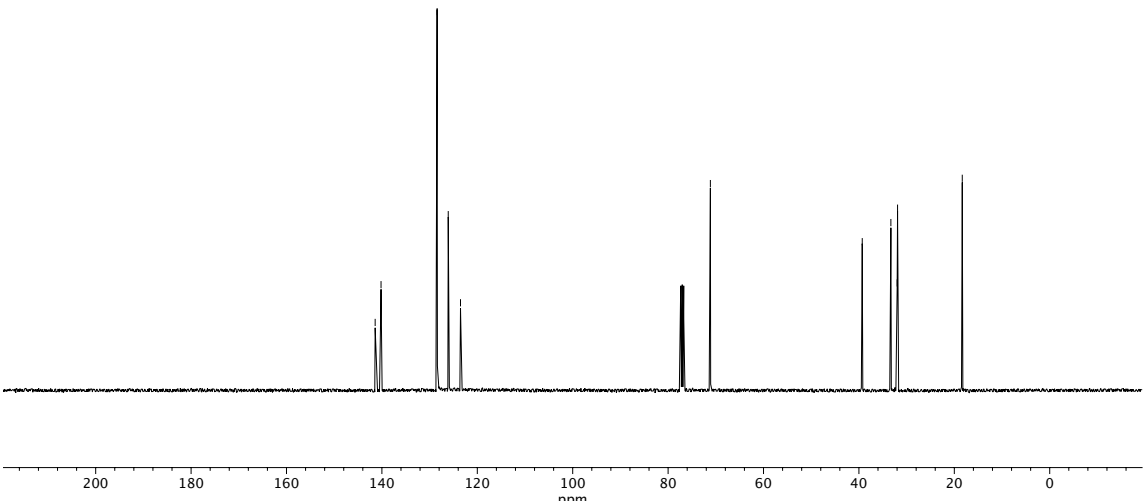
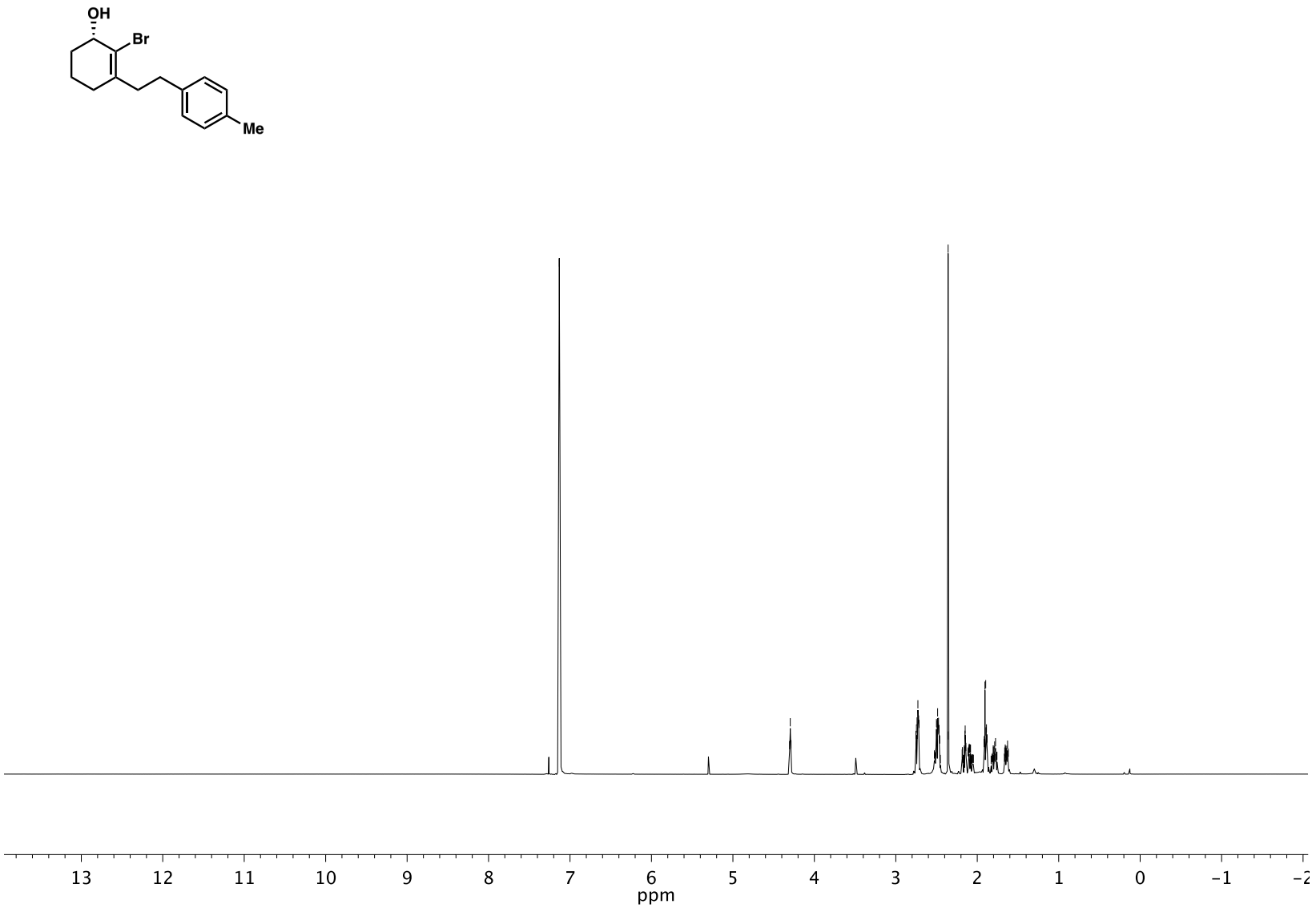



***Figure A11.79*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***151e****.*




***A11.80*** *$^{1}$H NMR (500 MHz, $CDCl_3$) of compound* ***151f****.*

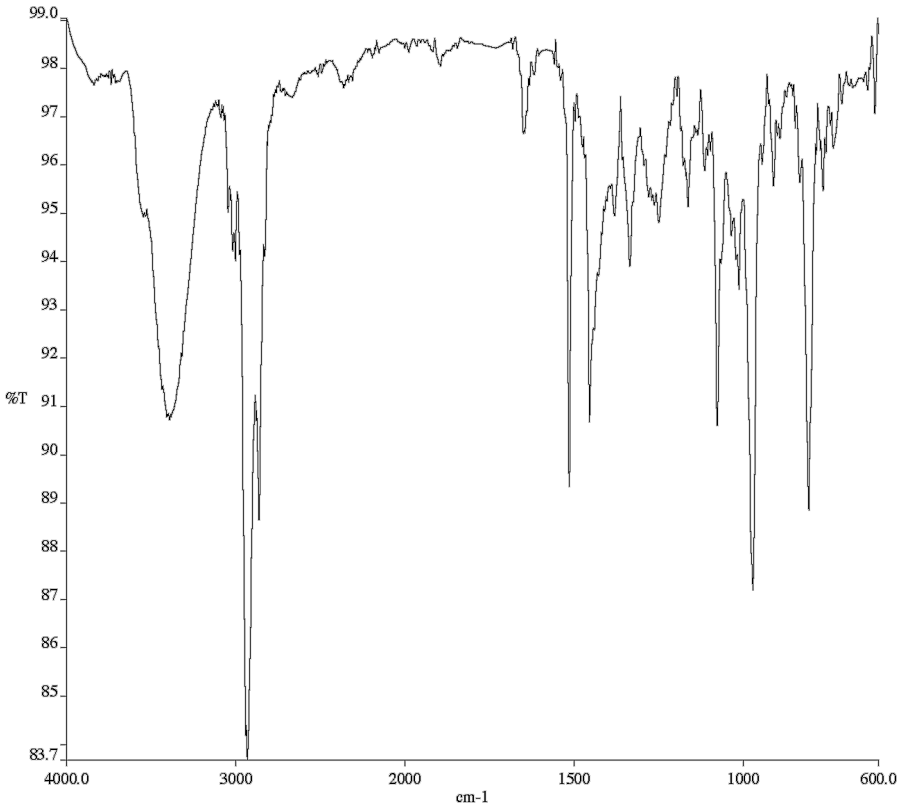



***Figure A11.81*** *Infrared spectrum (Thin Film, NaCl) of compound* ***151f****.*

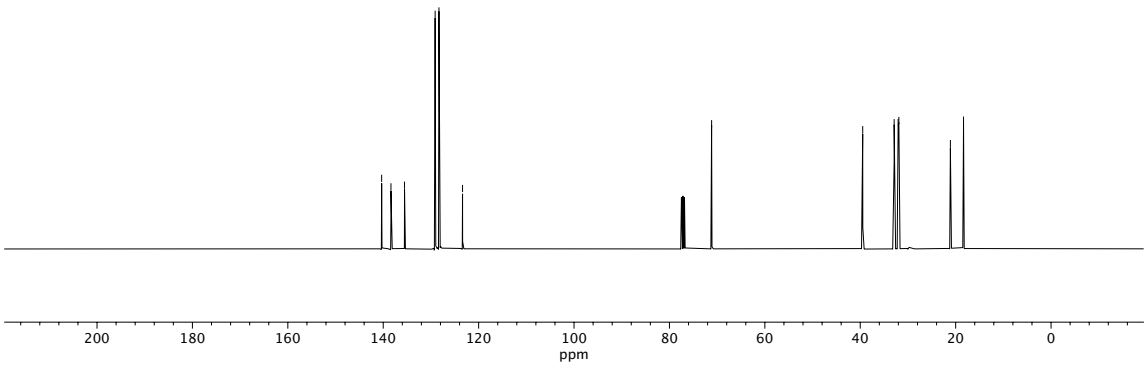
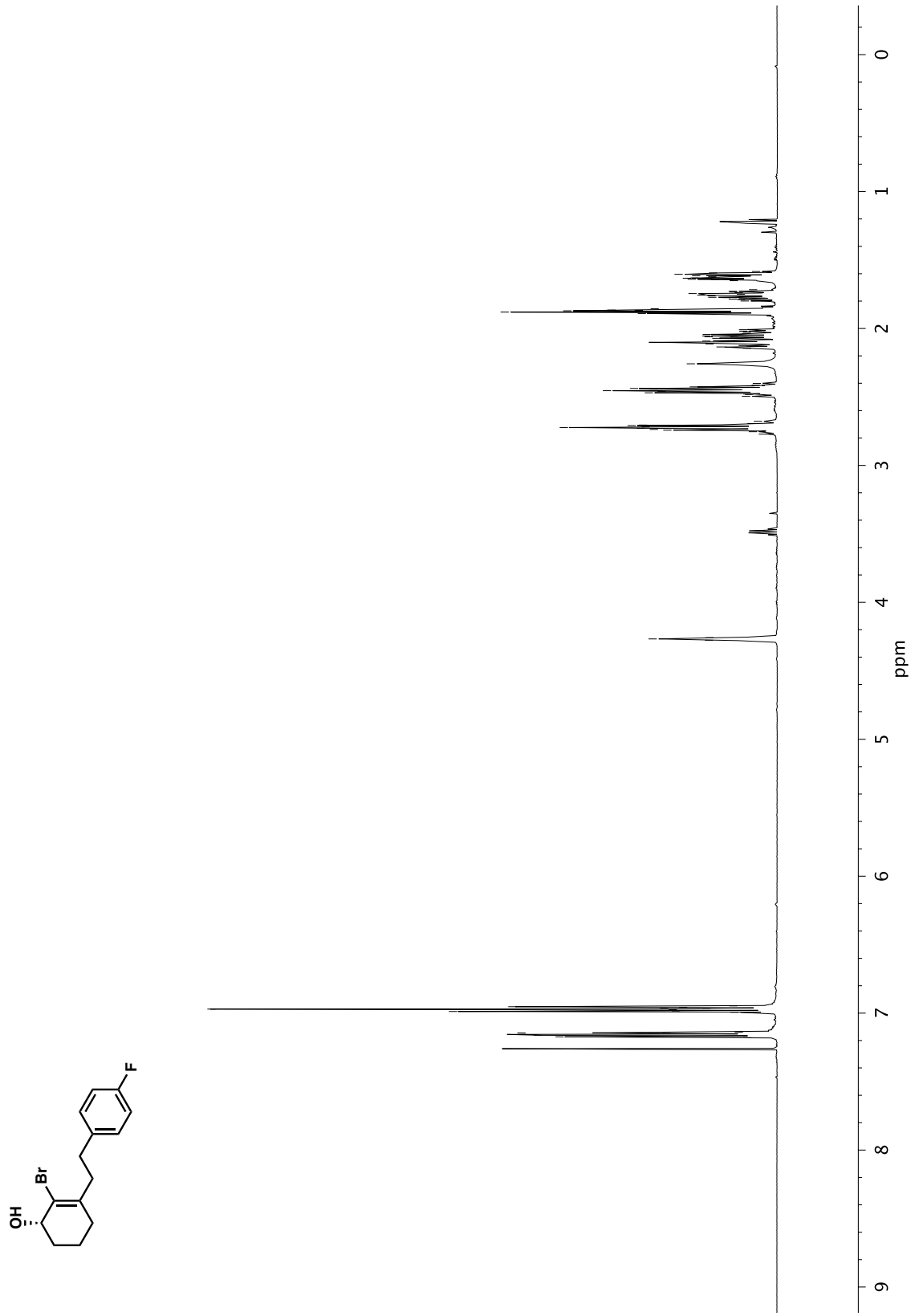



***Figure A11.82*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***151f****.*




***A11.83*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***151g***.

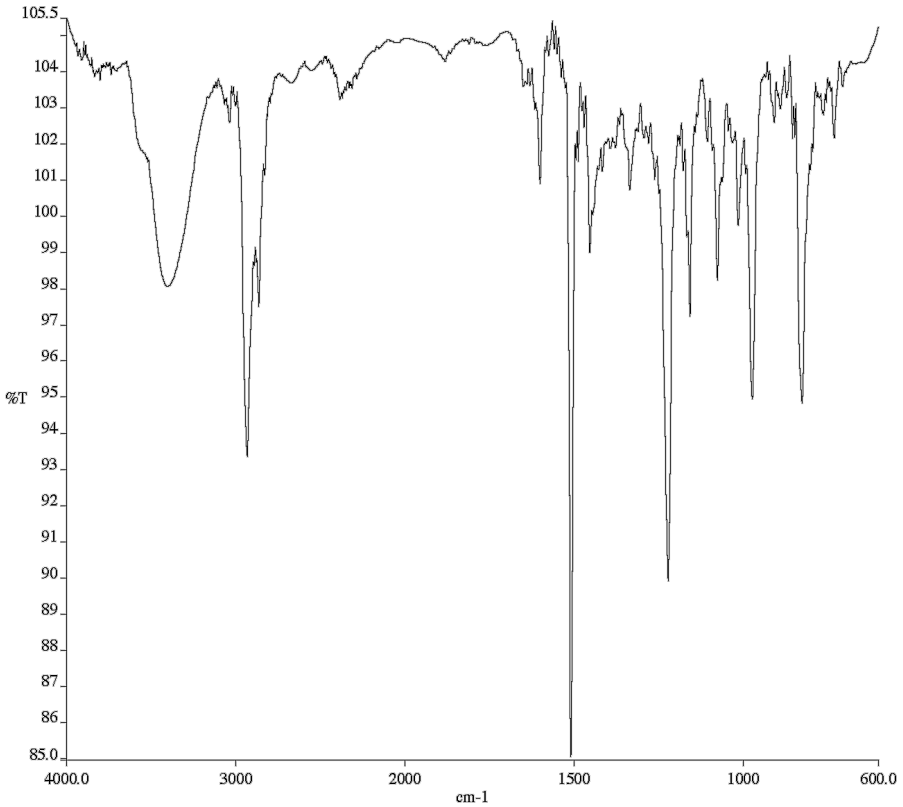



***Figure A11.84*** *Infrared spectrum (Thin Film, NaCl) of compound* ***151g****.*

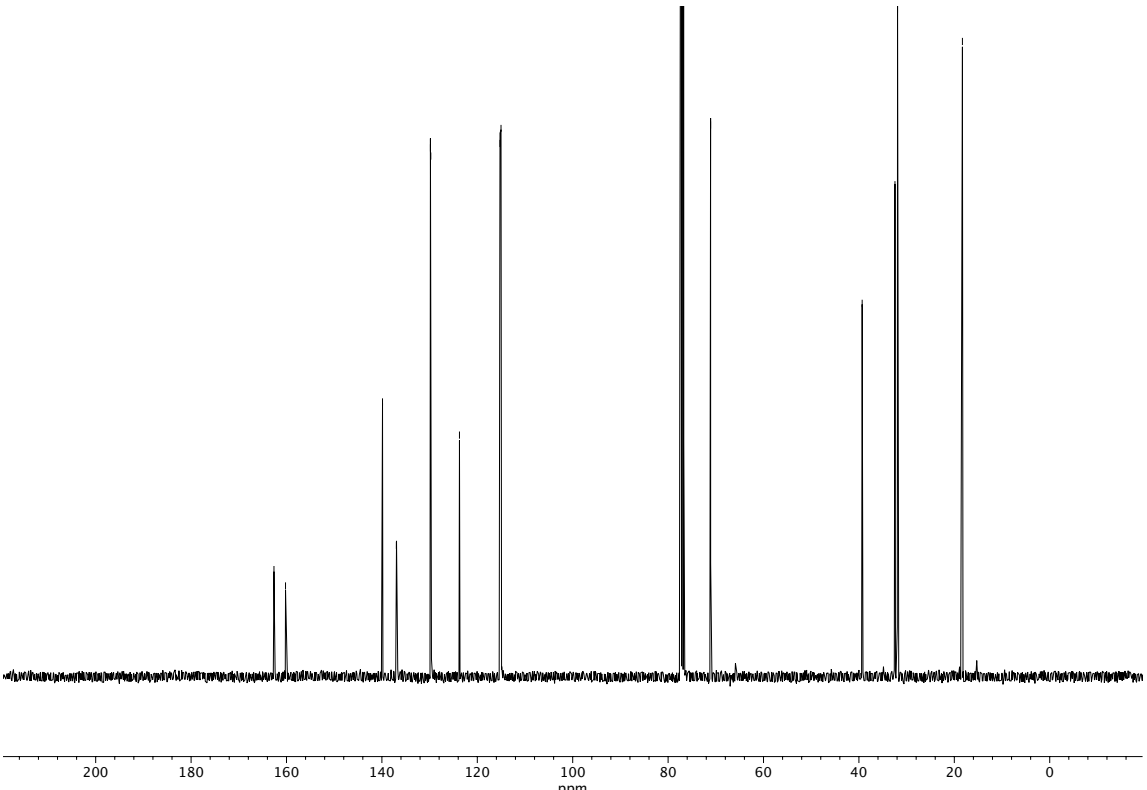



***Figure A11.85*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***151g****.*

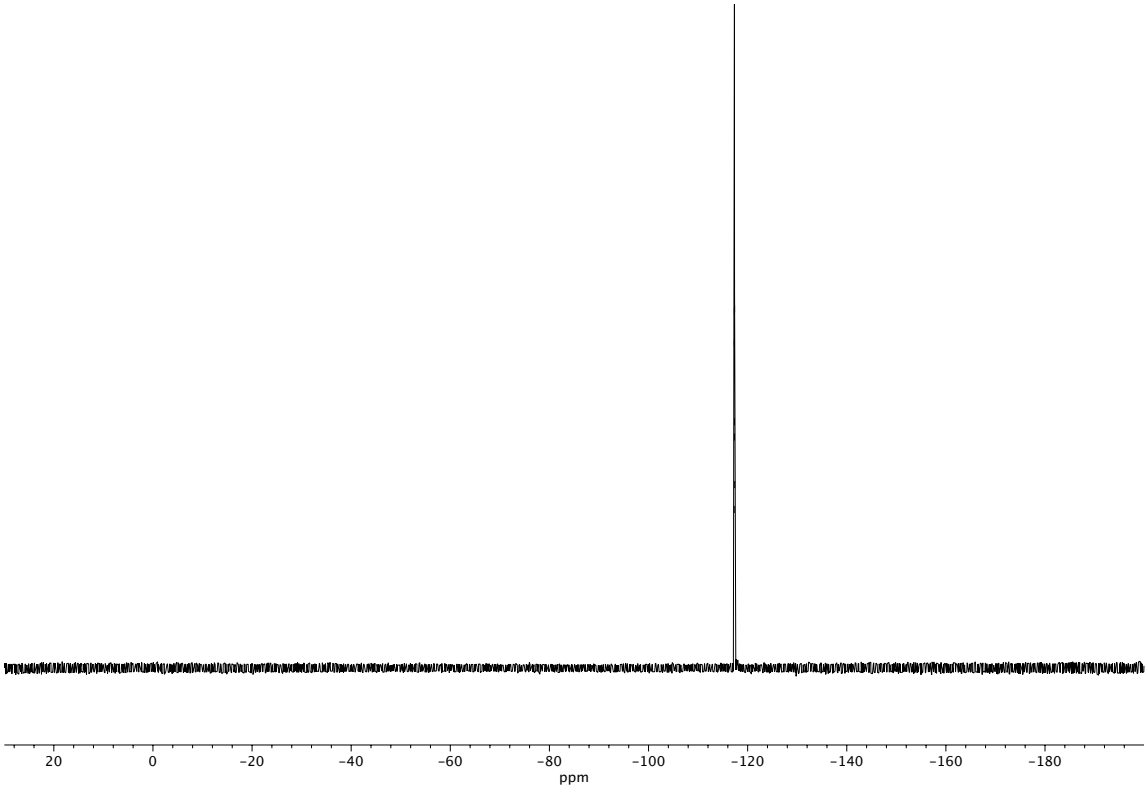
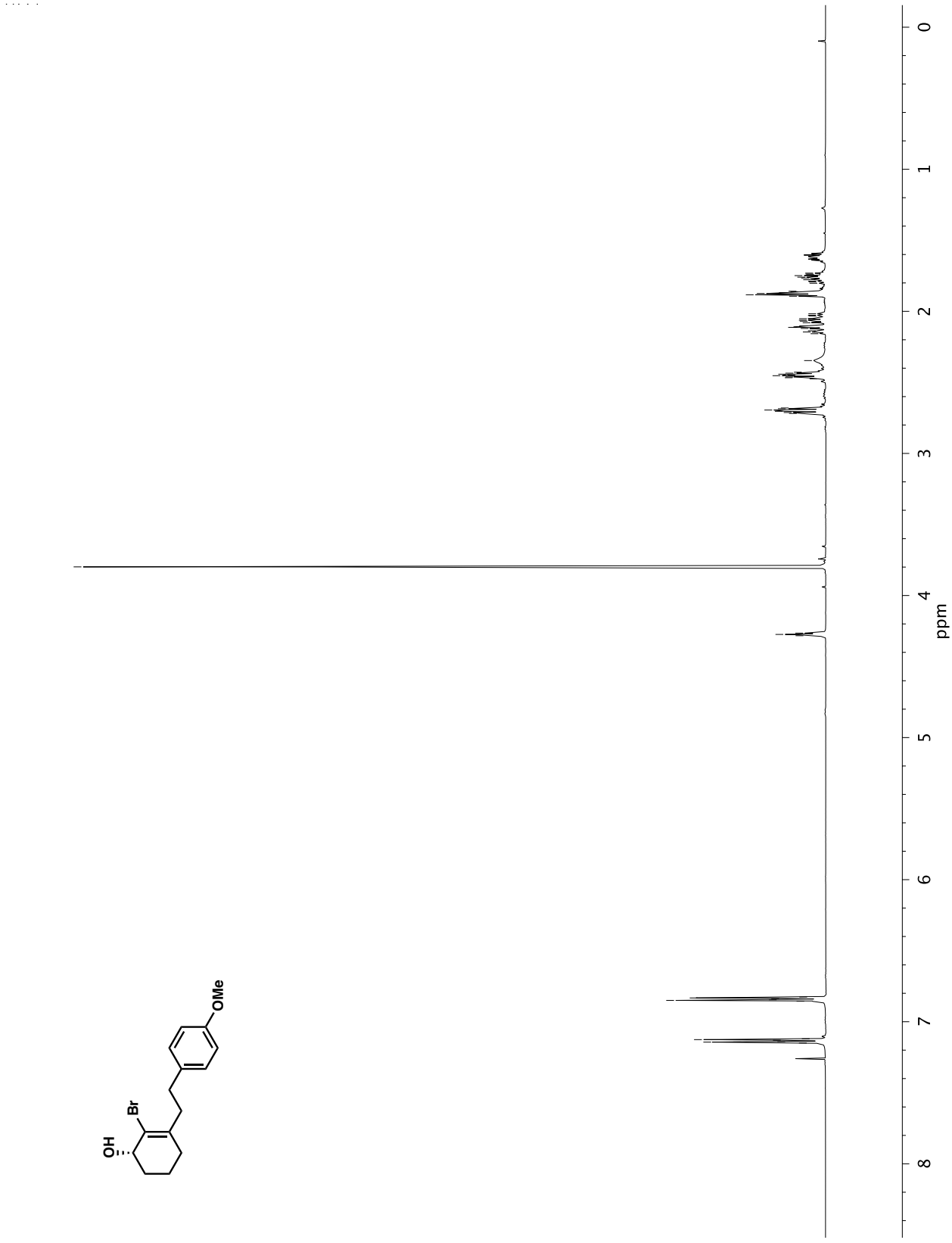



***Figure A11.86*** *$^{19}F$ NMR (282 MHz, $CDCl_3$) of compound* ***151g***.




***A11.87*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***151h***.

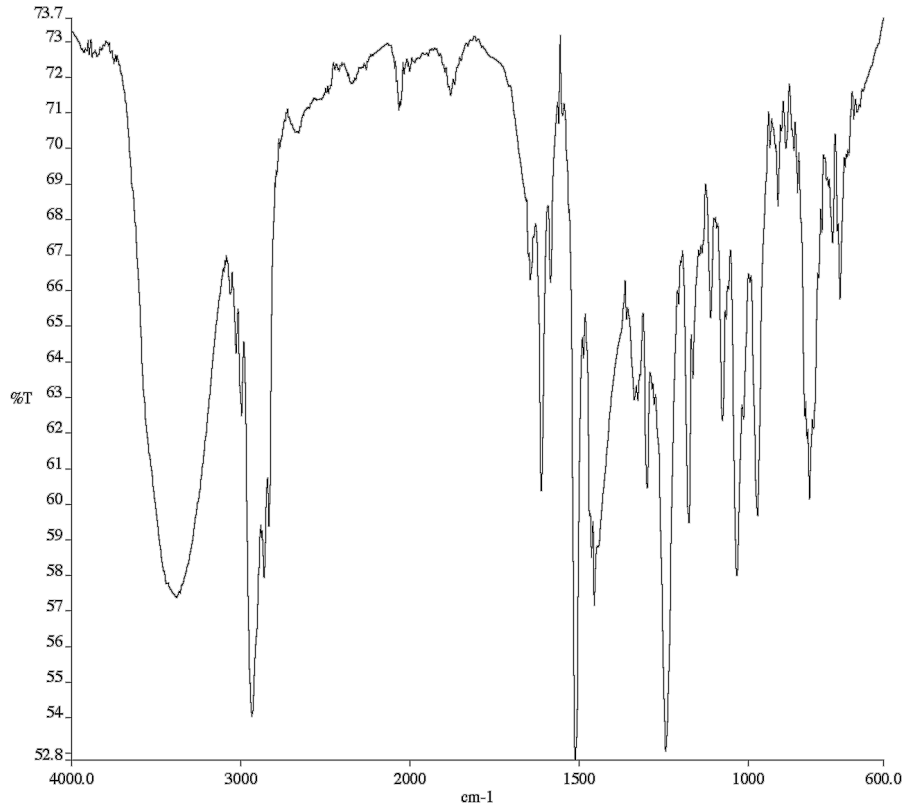



***Figure A11.88*** *Infrared spectrum (Thin Film, NaCl) of compound* ***151h***.

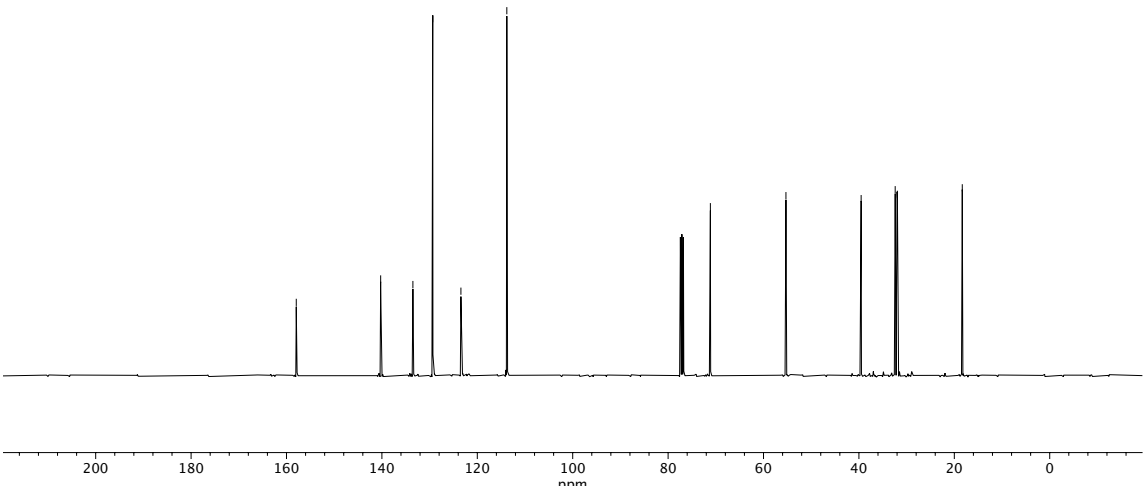
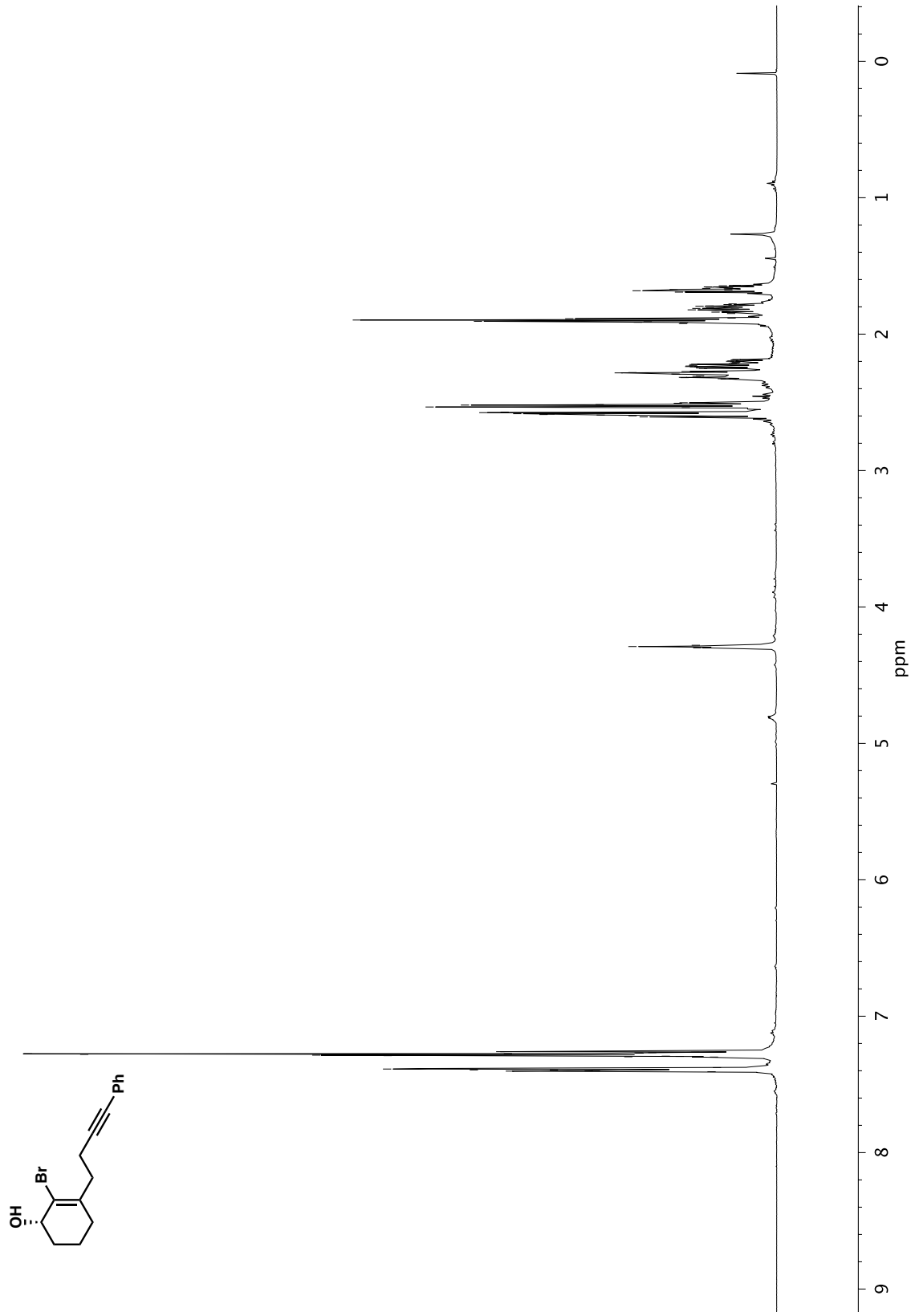



***Figure A11.89*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***151h***.




***A11.90*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***151i*****.**

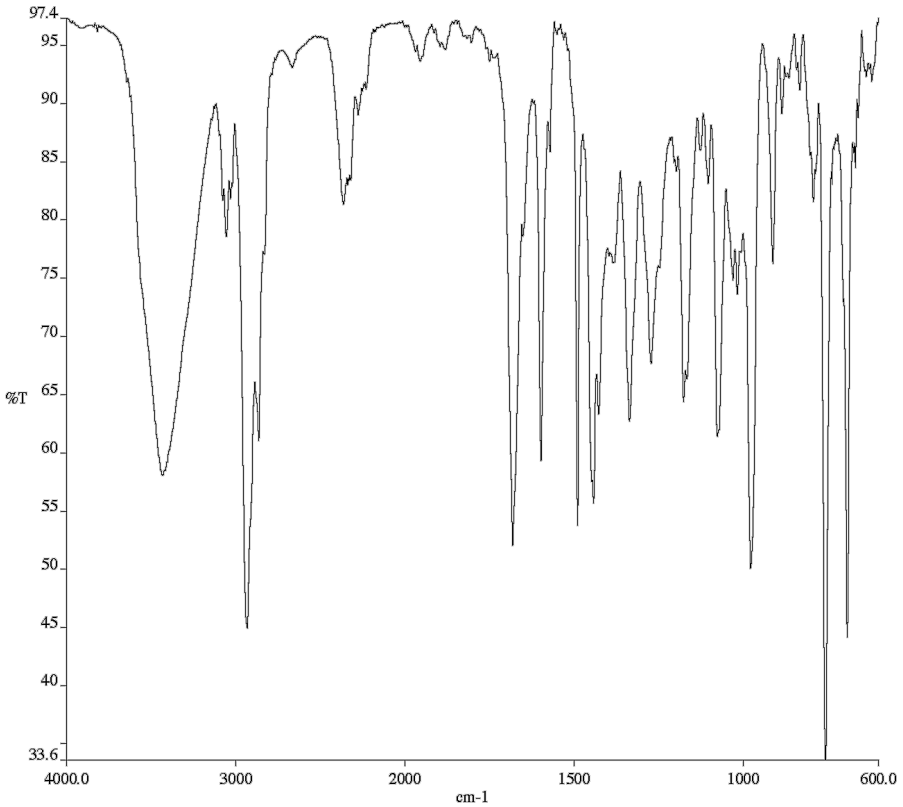



***Figure A11.91*** *Infrared spectrum (Thin Film, NaCl) of compound* ***151i****.*

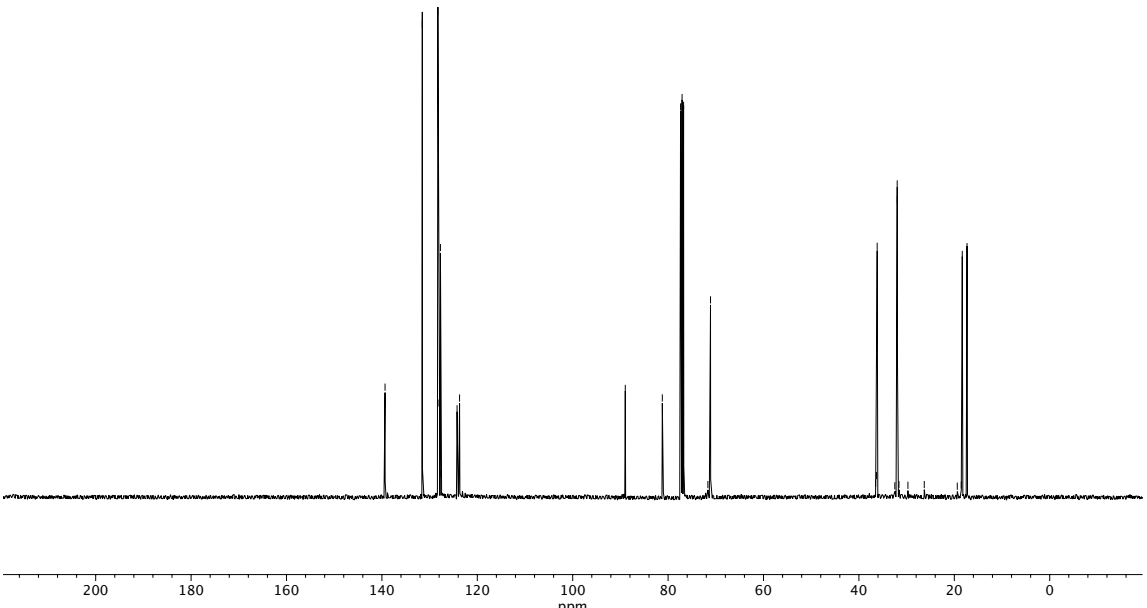
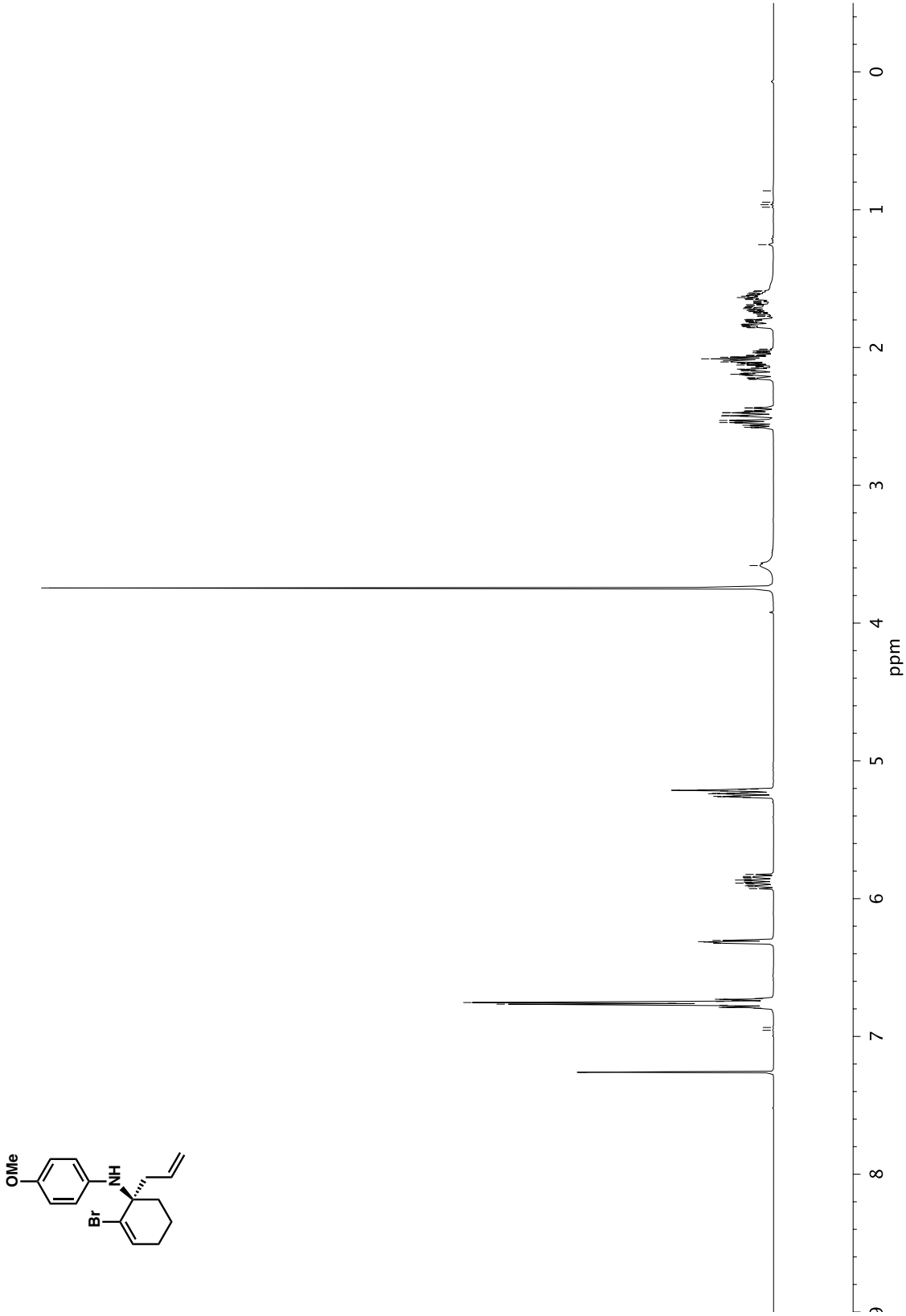



***Figure A11.92*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***151i****.*




***A11.93*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***153***.

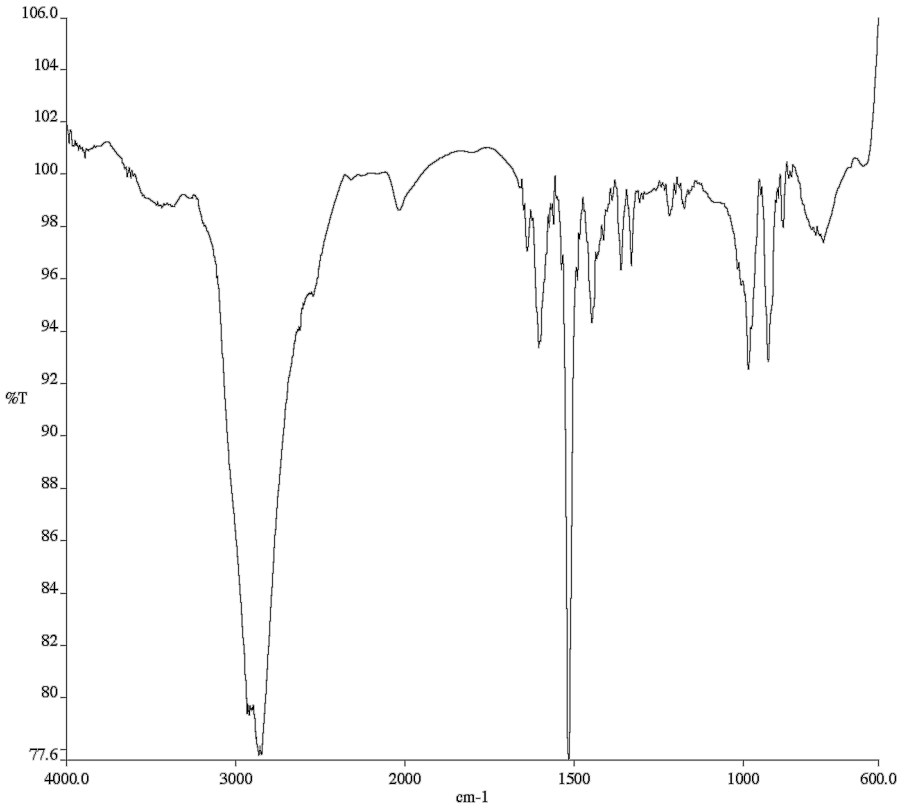



***Figure A11.94*** *Infrared spectrum (Thin Film, NaCl) of compound* ***153***.

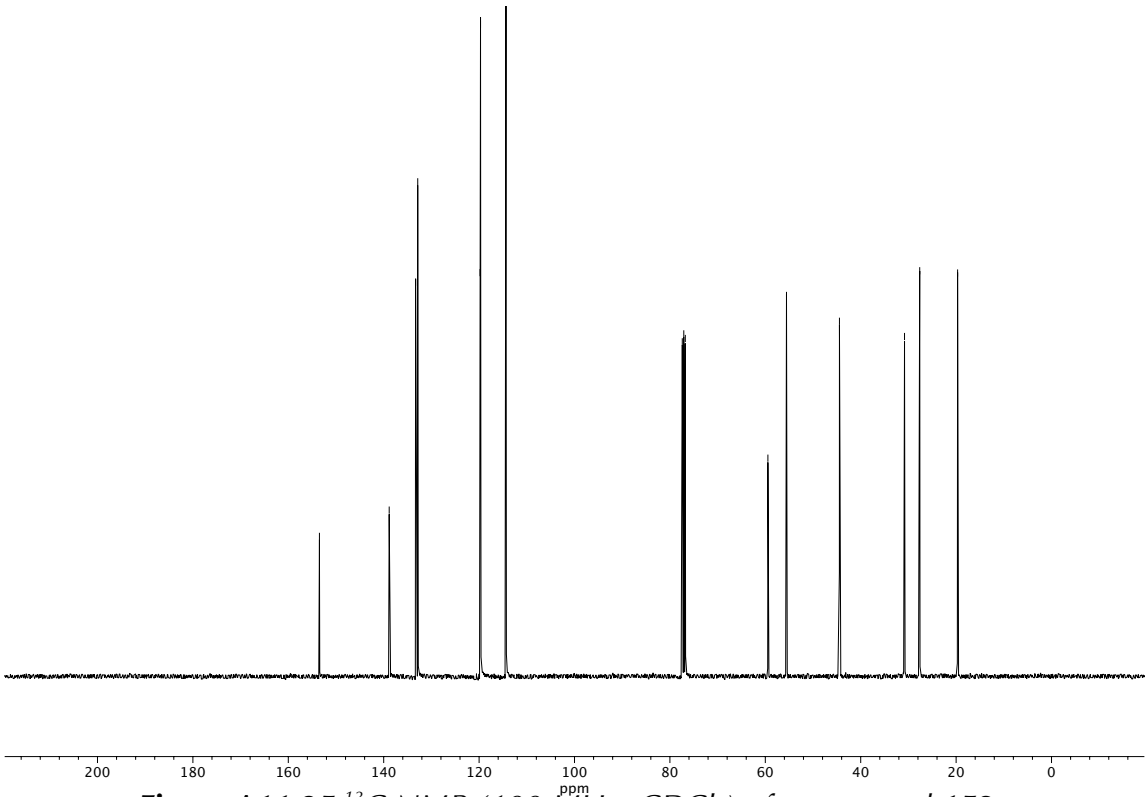
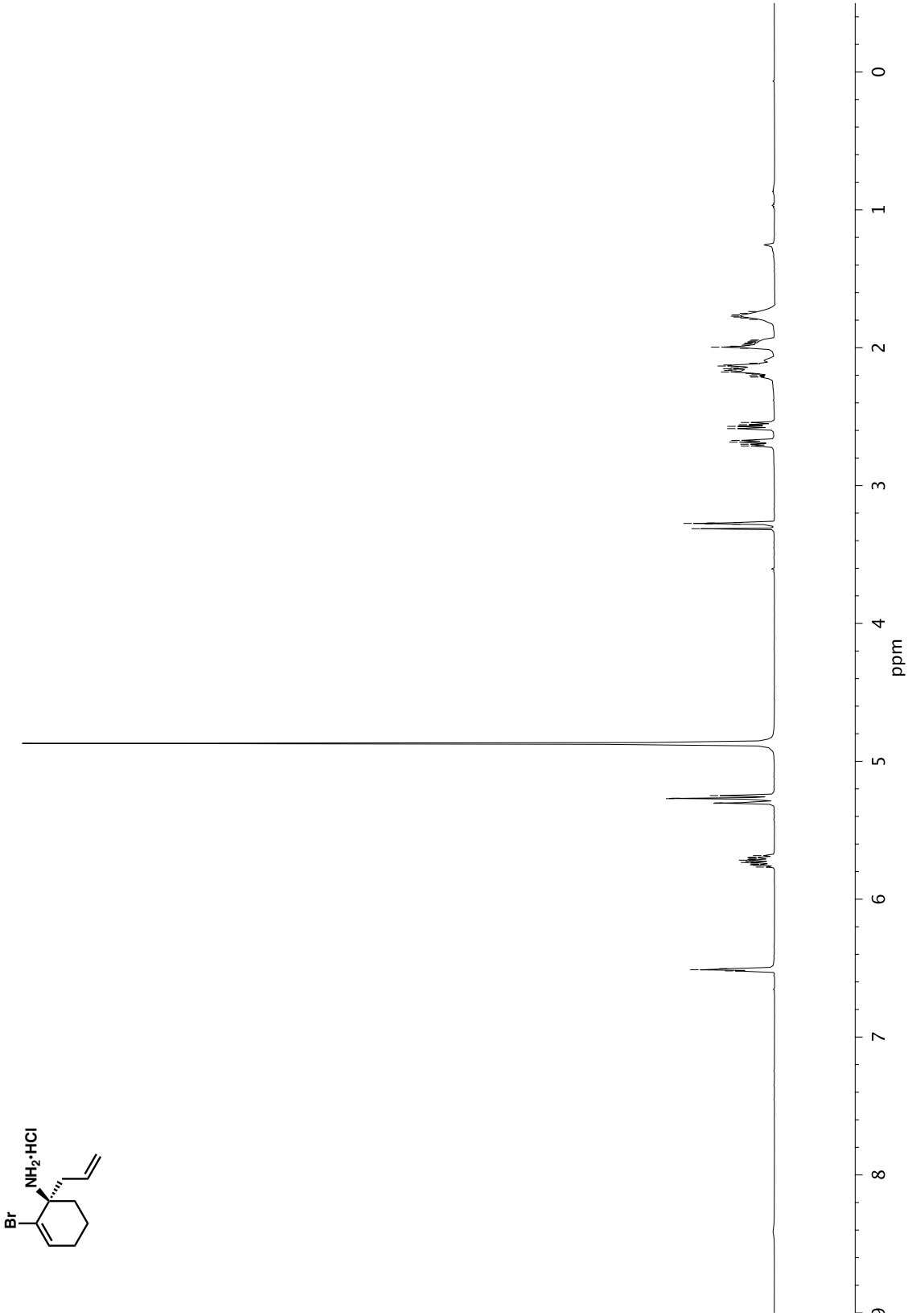



***Figure A11.95*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***153***.




***A11.96*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***154***.

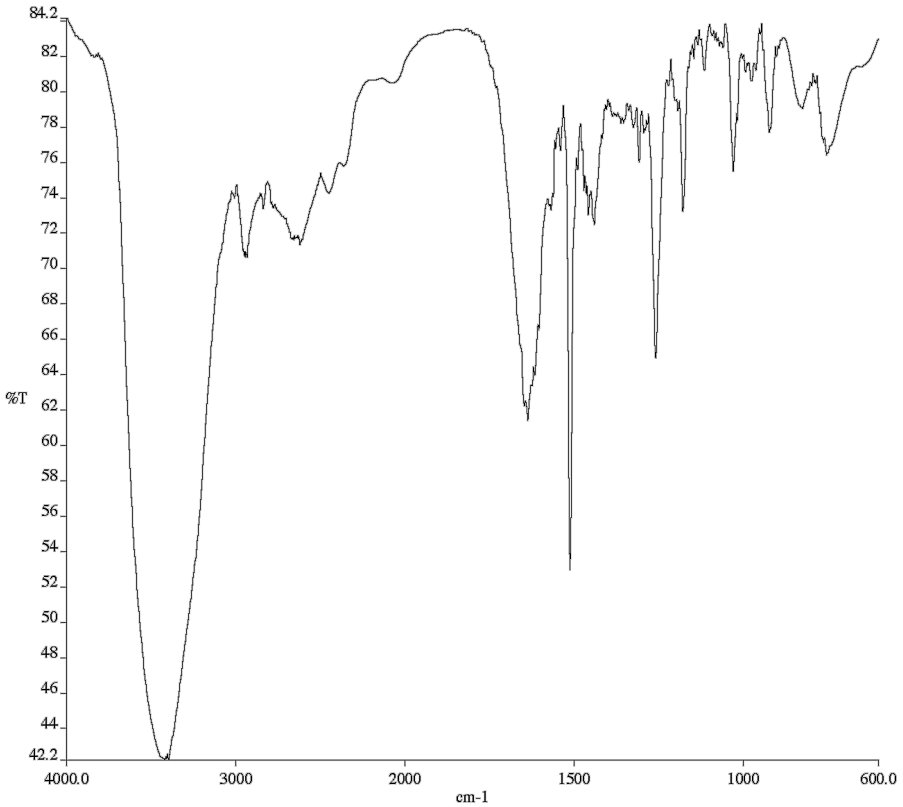



***Figure A11.97*** *Infrared spectrum (Thin Film, NaCl) of compound* ***154****.*

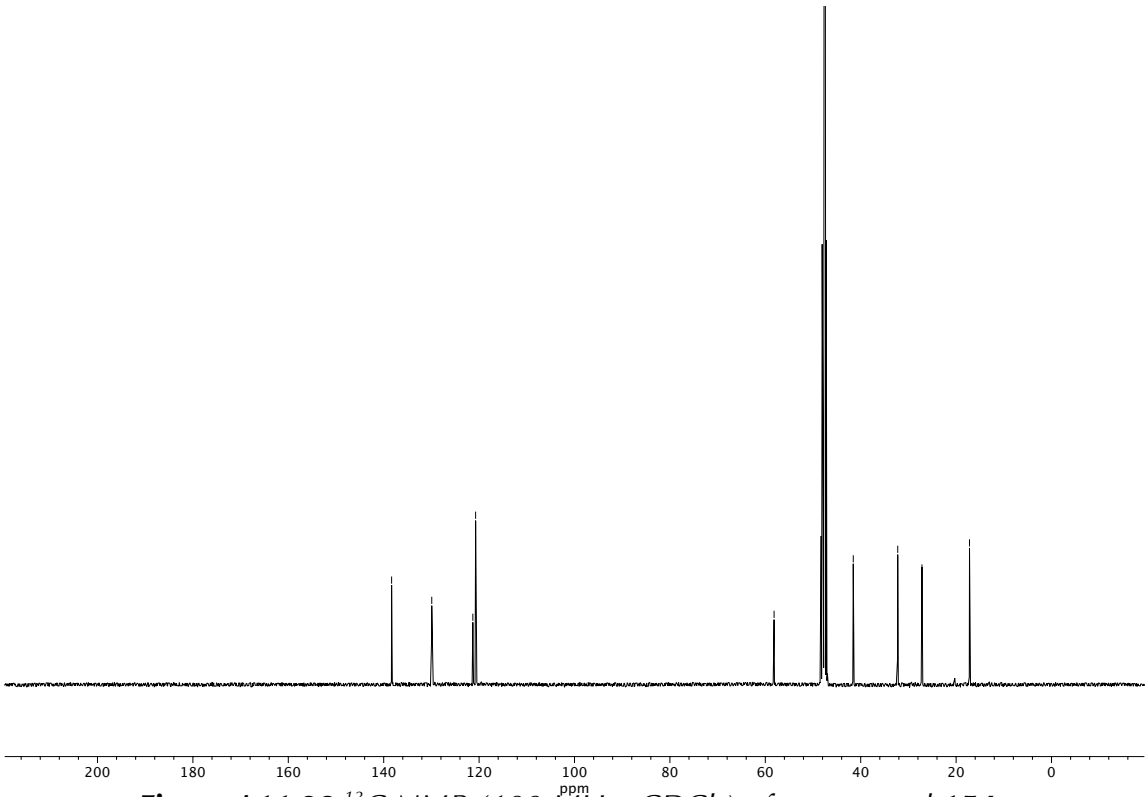
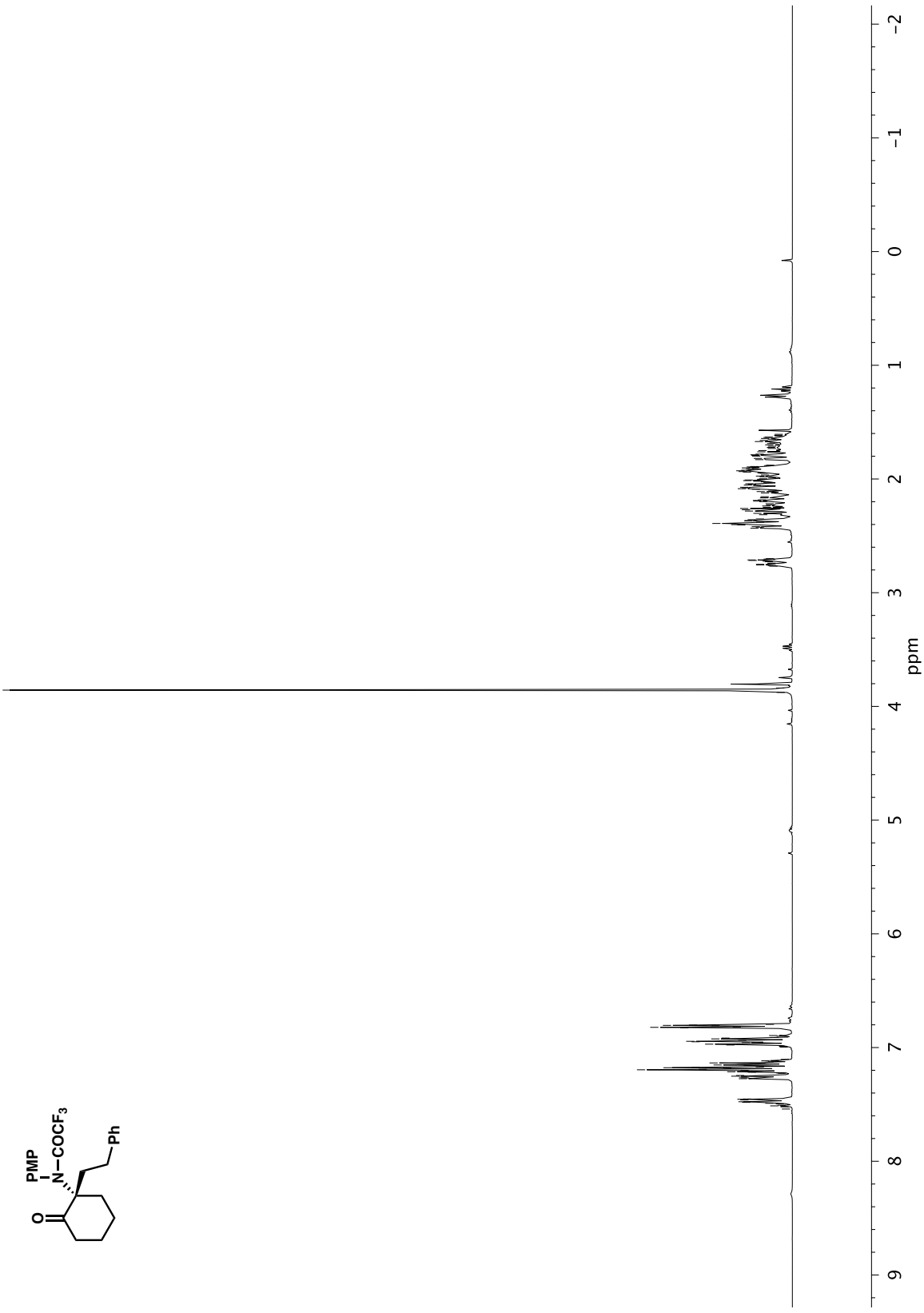



***Figure A11.98*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***154****.*




***A11.99*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***155***.

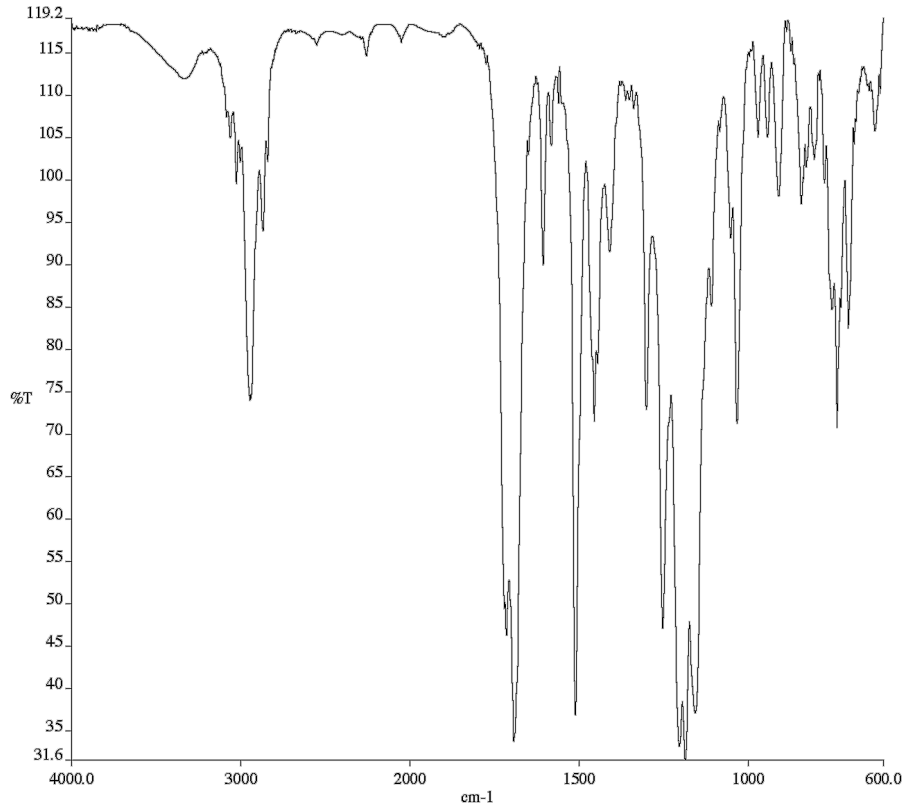



***Figure A11.100*** *Infrared spectrum (Thin Film, NaCl) of compound* ***155****.*

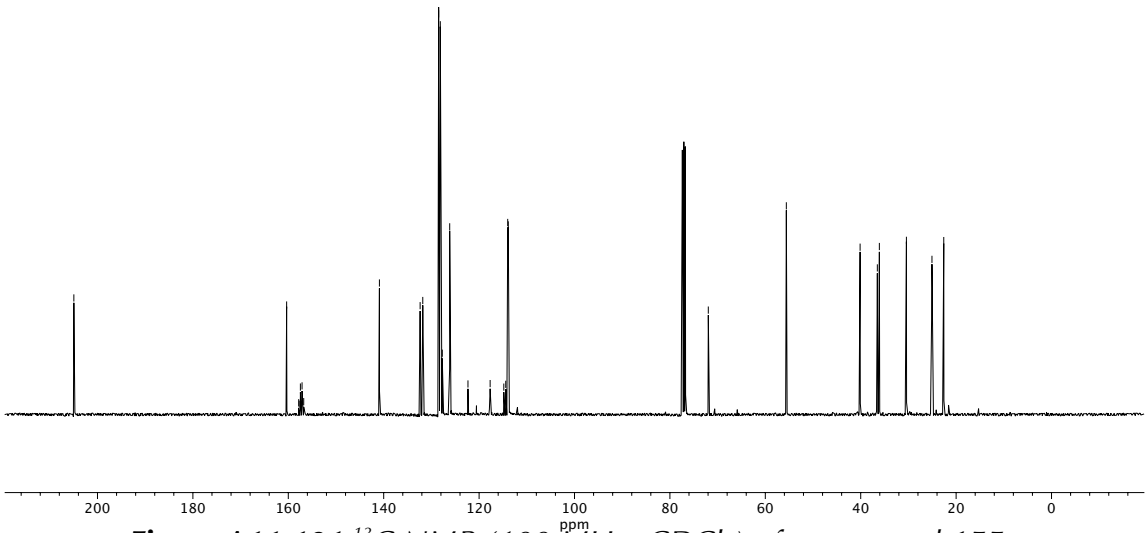
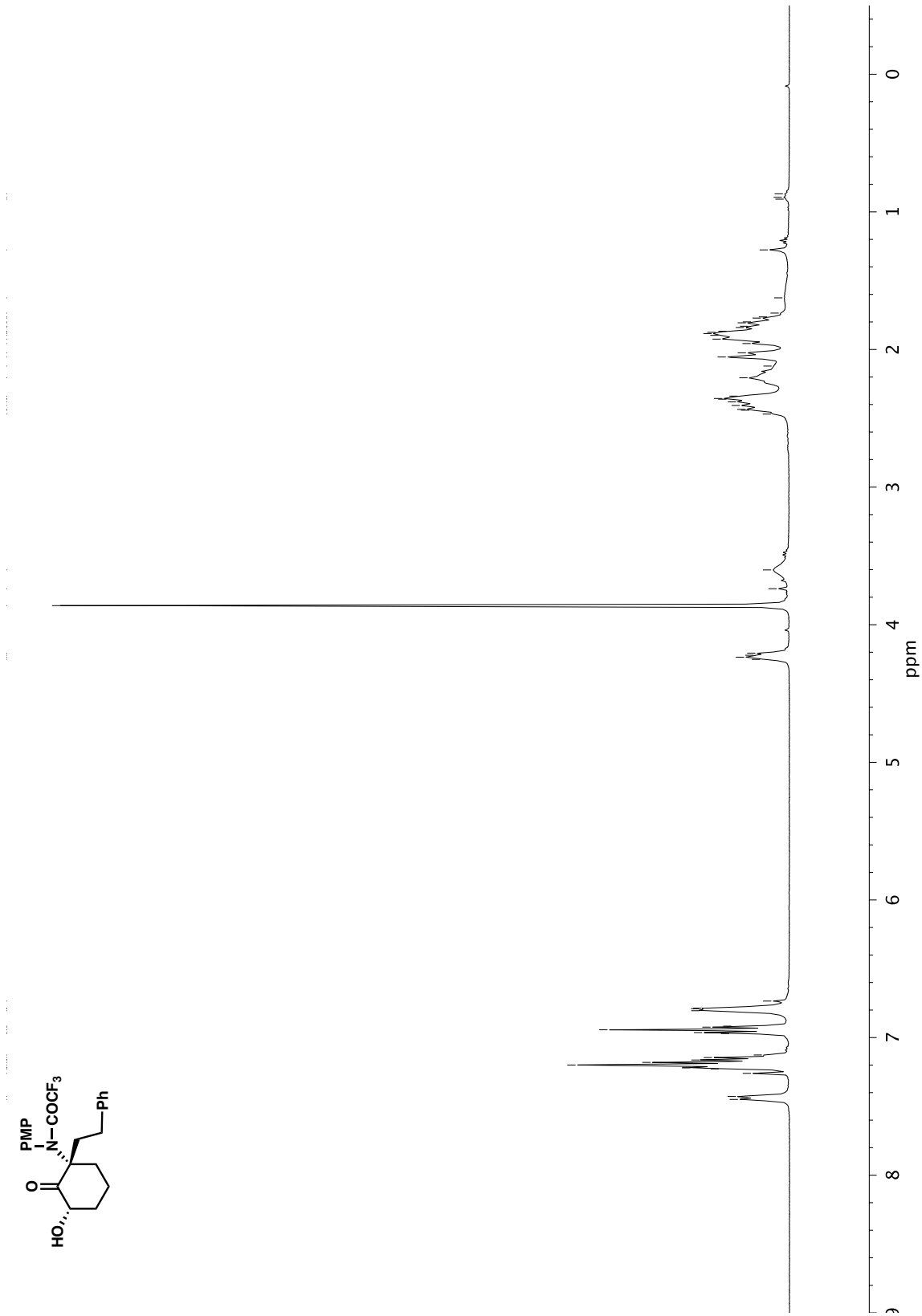



***Figure A11.101*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***155****.*




***A11.102*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***156****.*

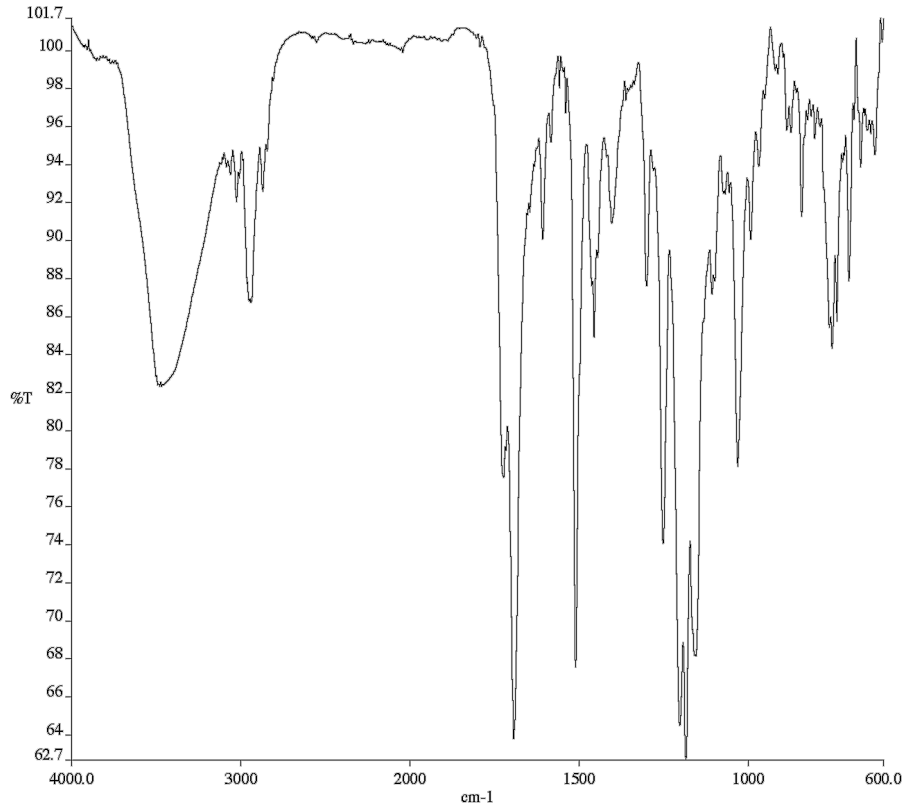



***Figure A11.103*** *Infrared spectrum (Thin Film, NaCl) of compound* ***156****.*

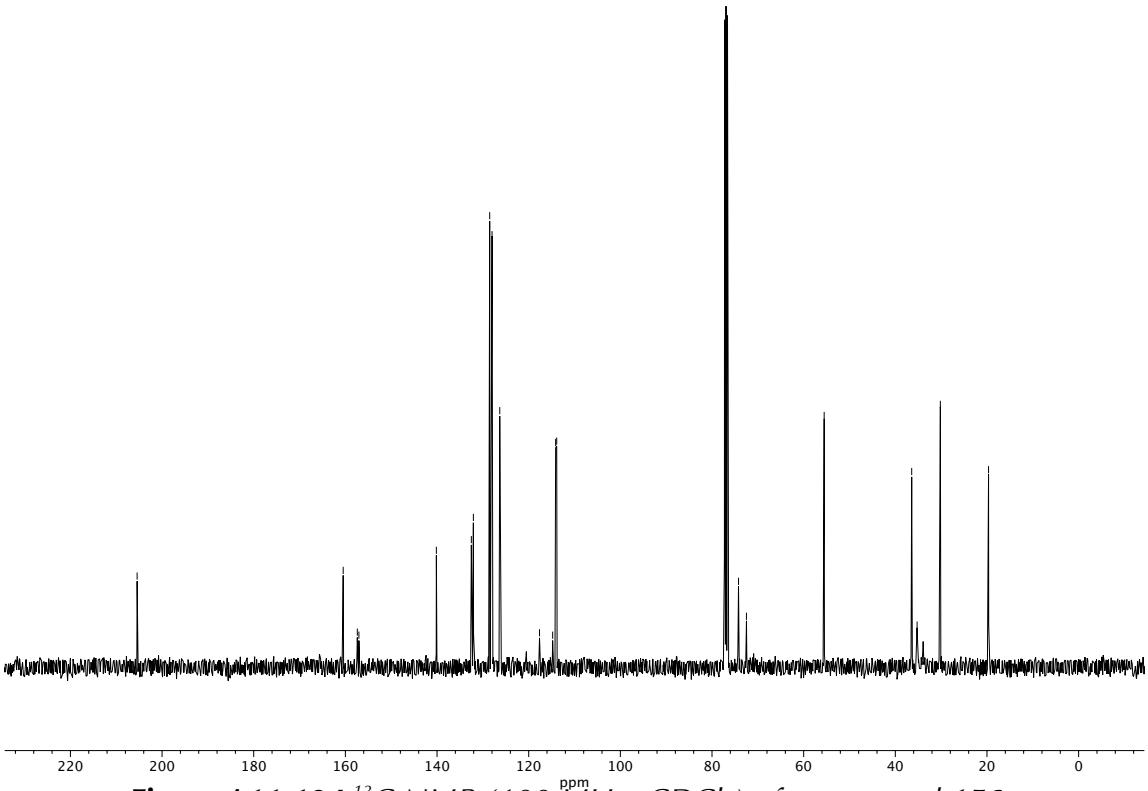
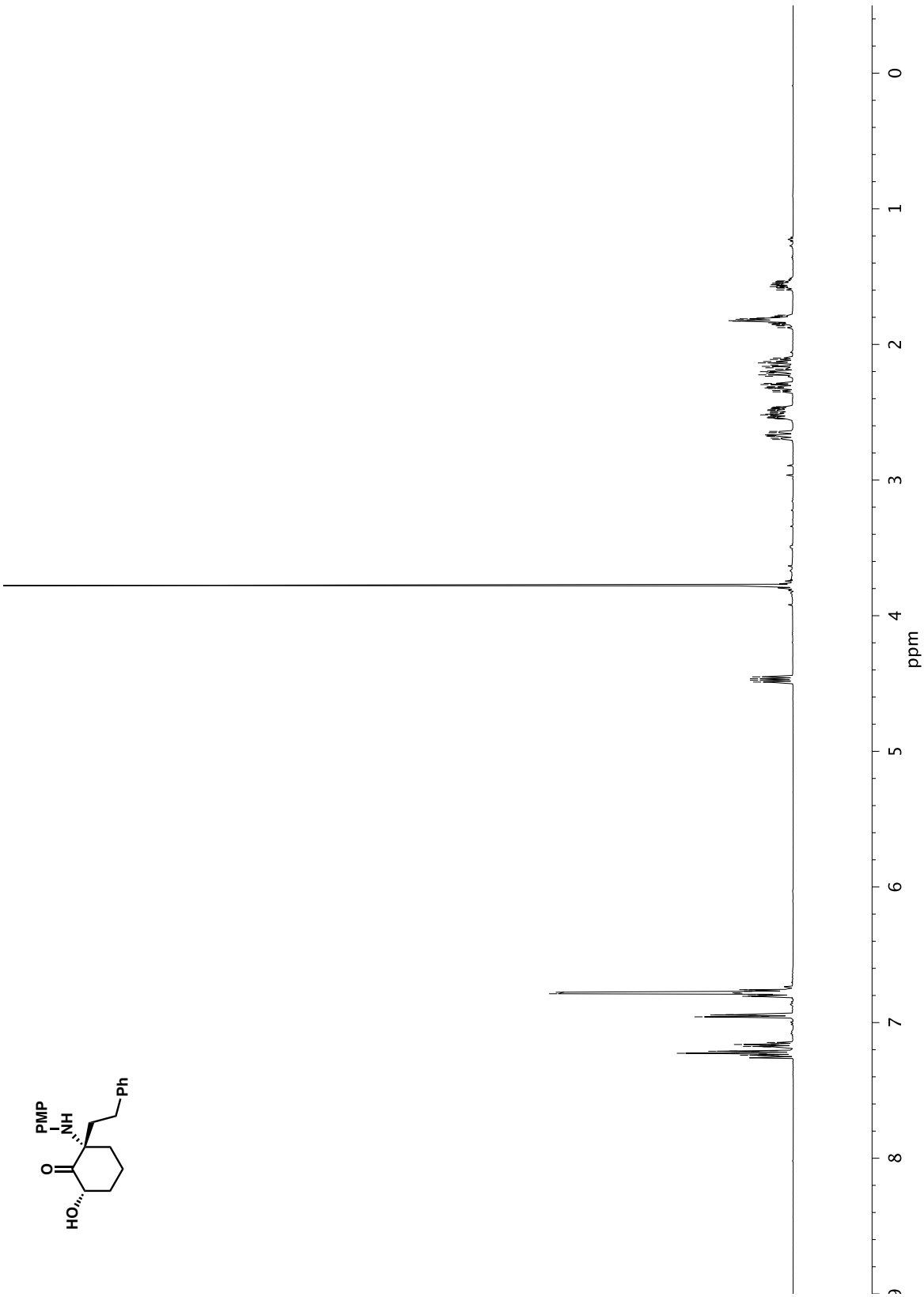



***Figure A11.104*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***156****.*




***A11.105*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***157****.*

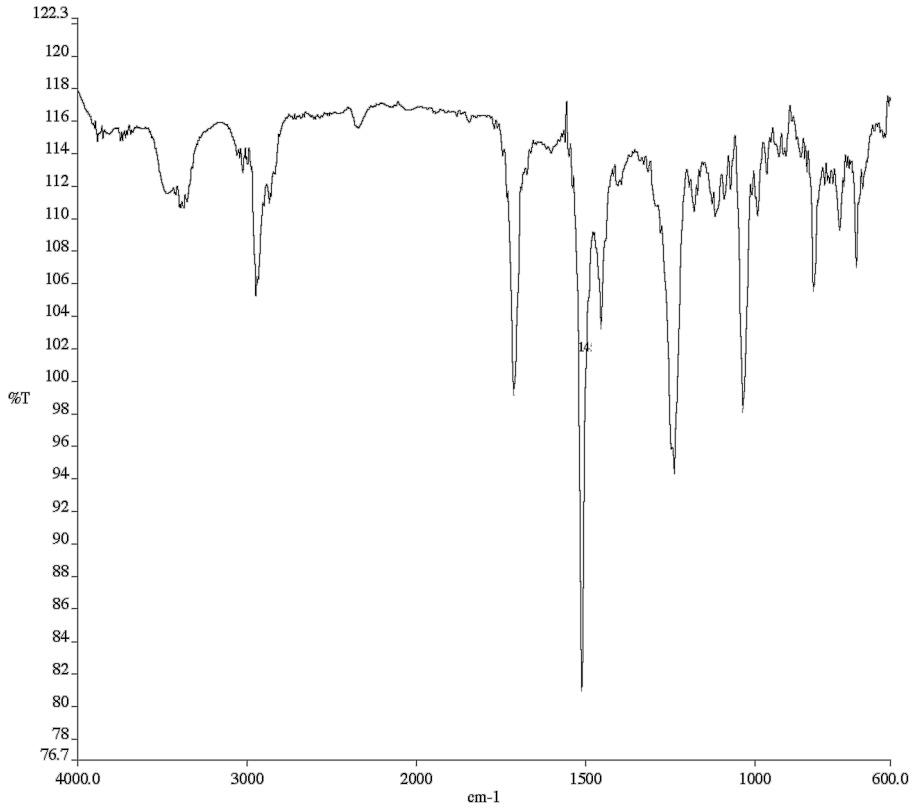



***Figure A11.106*** *Infrared spectrum (Thin Film, NaCl) of compound* ***157****.*

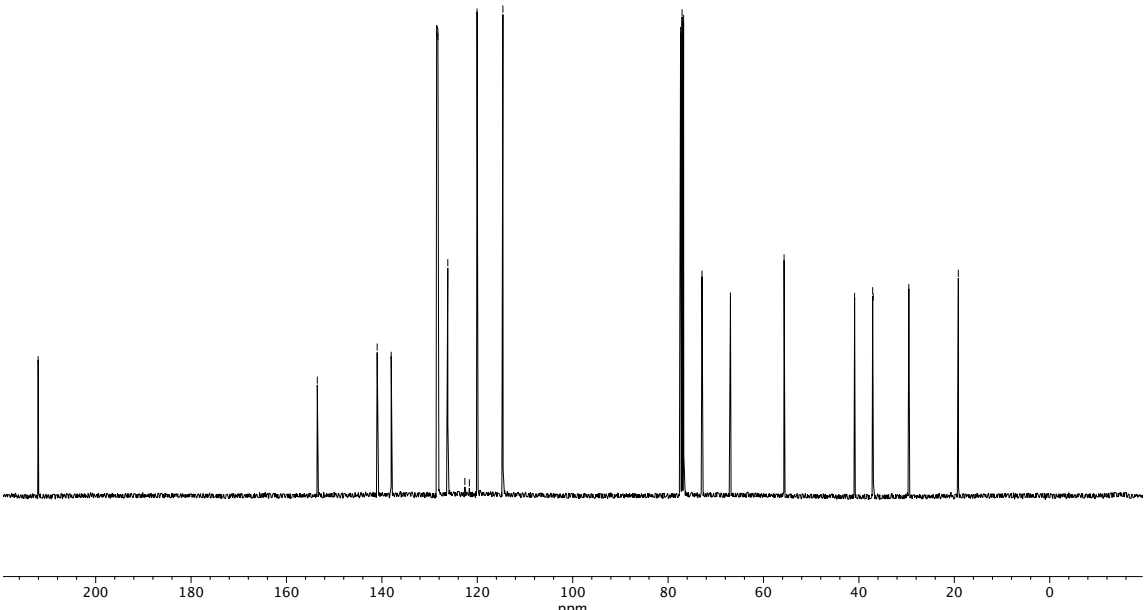
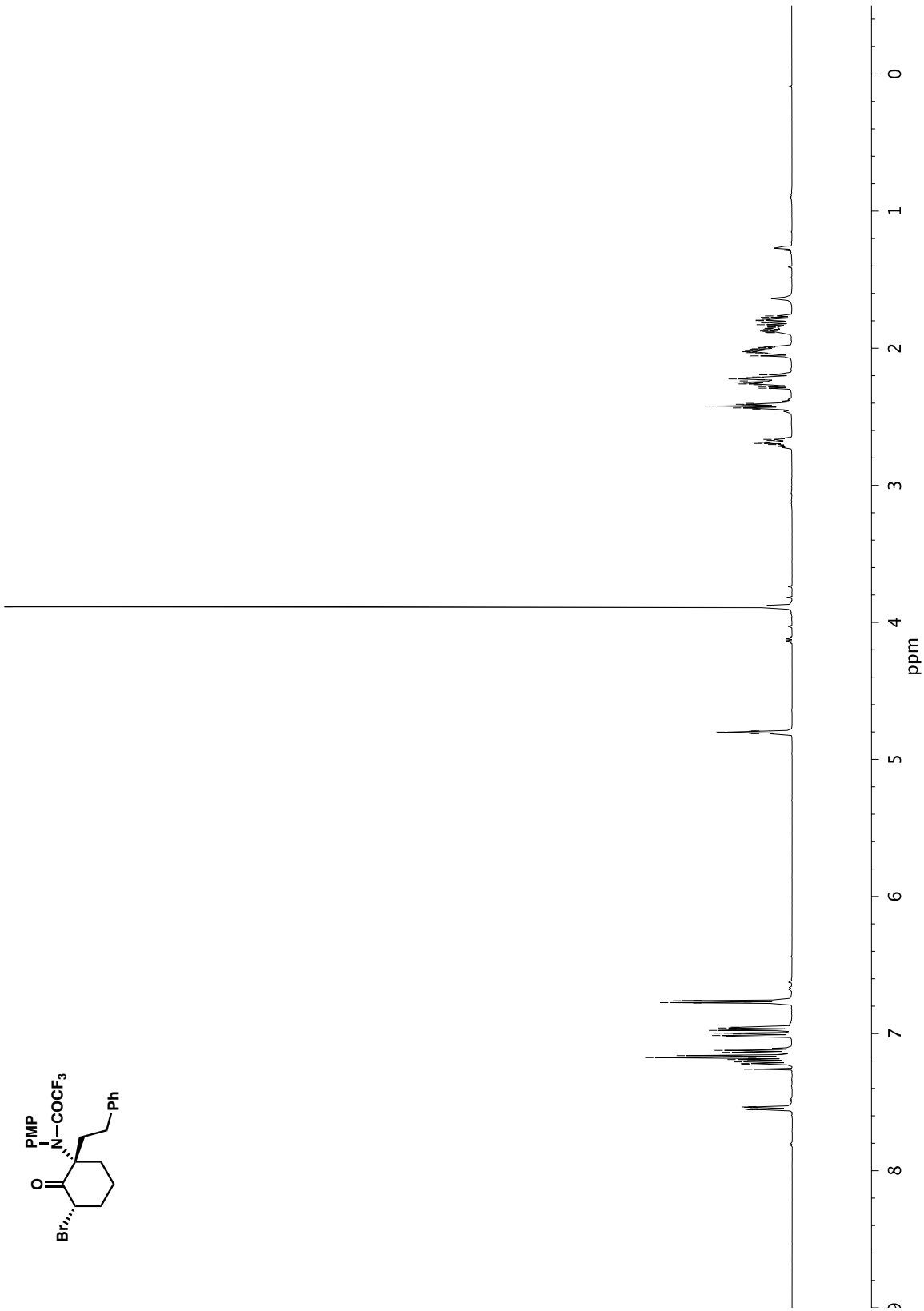



***Figure A11.107*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***157****.*




***A11.108*** *$^1H$ NMR (500 MHz, $CDCl_3$) of compound* ***158****.*

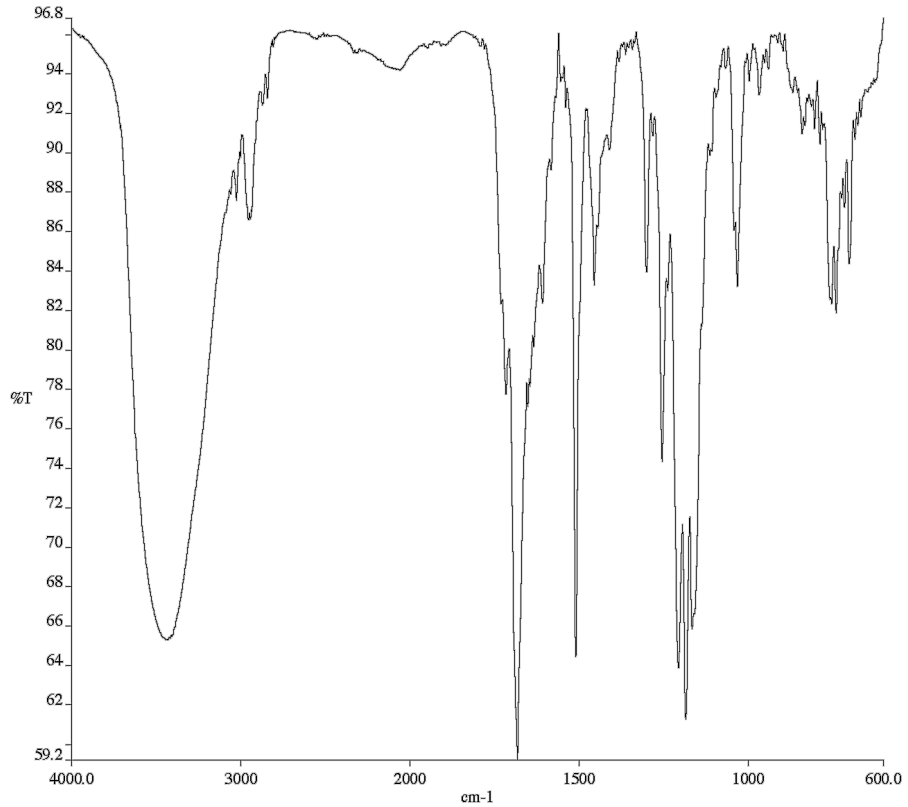



***Figure A11.109*** *Infrared spectrum (Thin Film, NaCl) of compound* ***158****.*

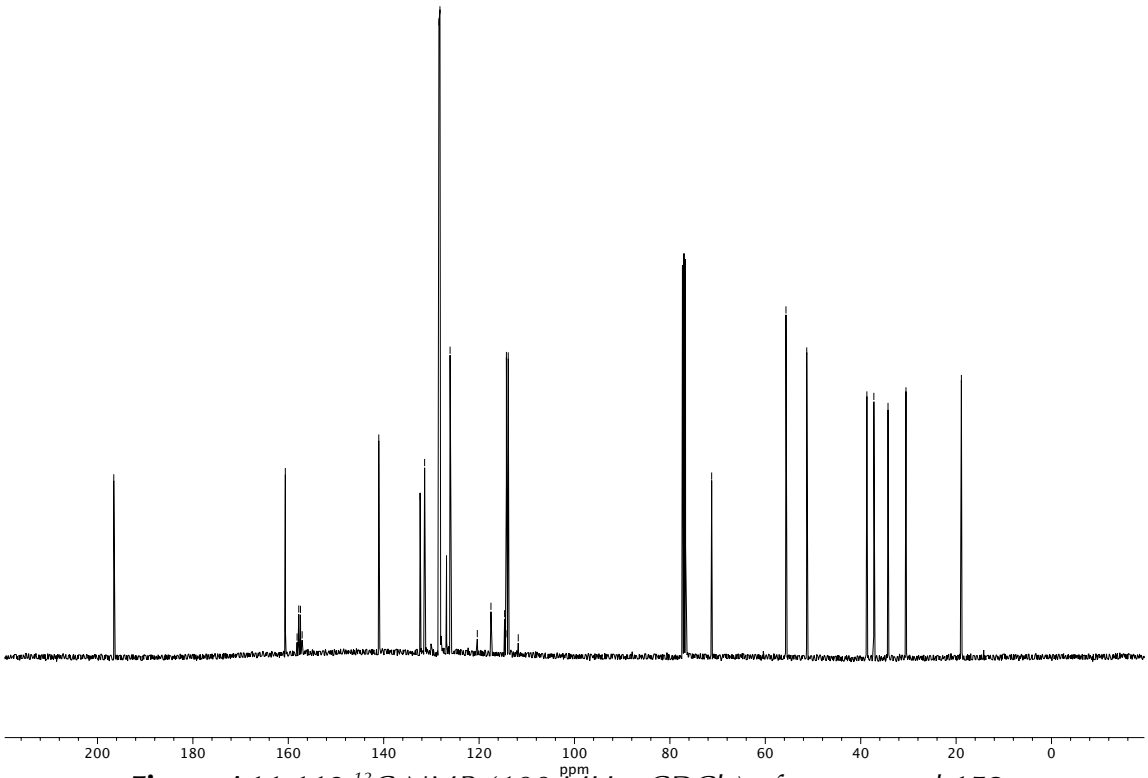



***Figure A11.110*** *$^{13}C$ NMR (100 MHz, $CDCl_3$) of compound* ***158****.*

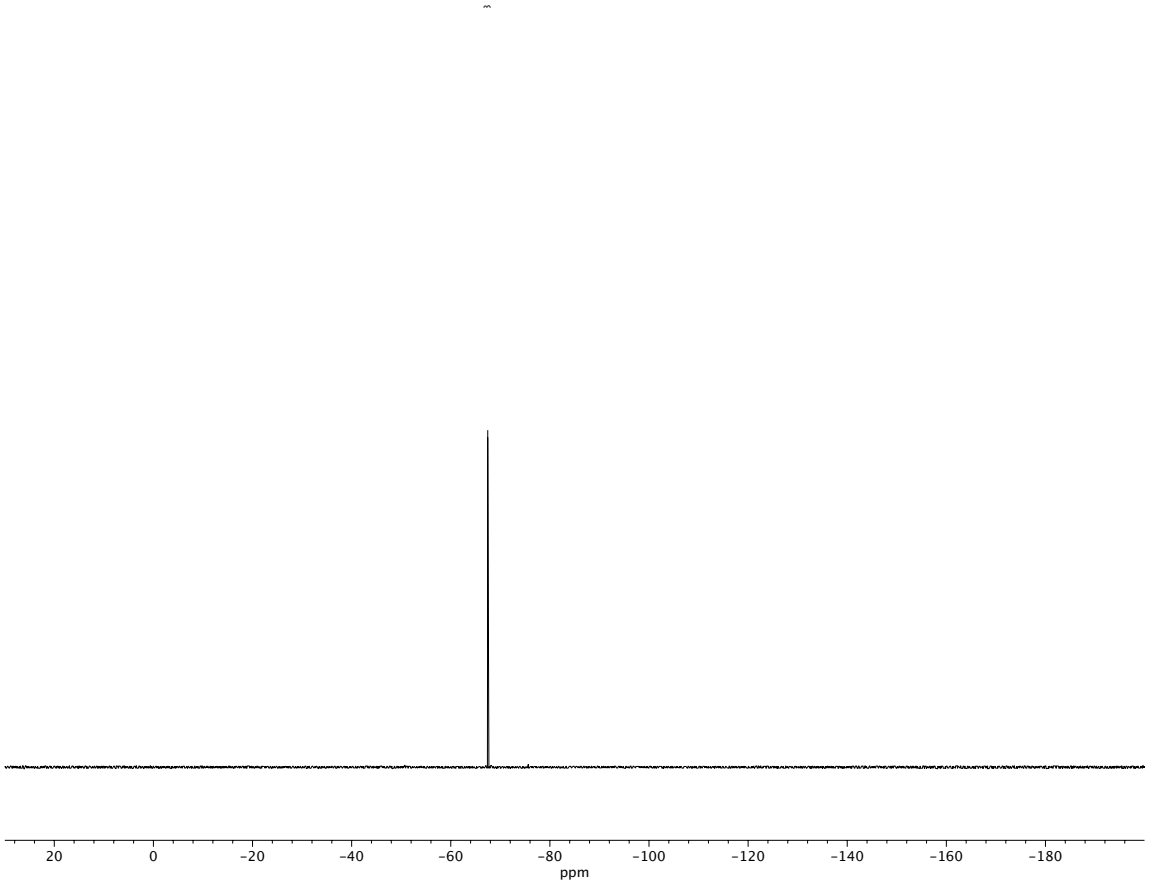



***Figure A11.111*** *$^{19}$F NMR (282 MHz, $CDCl_3$) of compound* ***158****.*

# *APPENDIX 12*

*X-Ray Crystallography Reports Relevant to Chapter 7:*

*Stereospecific Overman Rearrangement of Substituted Cyclic Vinyl Bromides: Access to Fully-Substituted α-Amino Ketones*

## A12.1 GENERAL EXPERIMENTAL

X-ray crystallographic analysis was obtained from the Caltech X-Ray Crystallography Facility using a Bruker AXS D8 VENTURE KAPPA diffractometer coupled to a PHOTON II CPAD detector with Cu $K_\alpha$ radiation ($\lambda$ = 1.54178 Å) from an I$\mu$S micro-source. Crystal sample was prepared via vapor diffusion.

### A12.1.1 X-RAY CRYSTAL STRUCTURE ANALYSIS OF ALCOHOL 157

***Figure A12.1*** *X-Ray Coordinate of Alkylation Product* ***157****.*

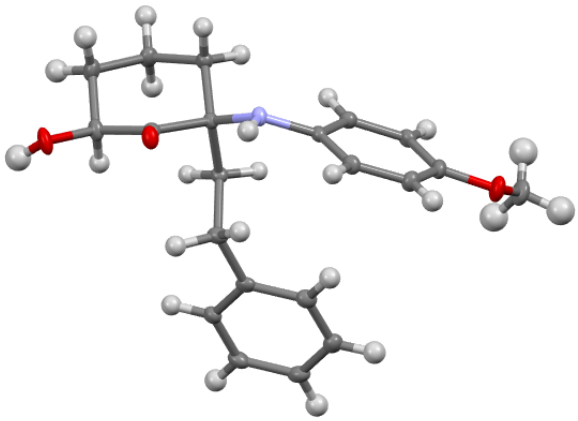


***Table A12.1*** *Crystal data and structure refinement for* ***157****.*

| | | |
|---|---|---|
| Empirical formula | C21 H25 N O3 | |
| Formula weight | 339.42 | |
| Temperature | 100(2) K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Orthorhombic | |
| Space group | $P2_12_12_1$ | |
| Unit cell dimensions | a = 5.9218(7) Å | a= 90°. |
| | b = 7.5604(10) Å | b= 90°. |
| | c = 41.115(6) Å | g = 90°. |

| | |
|---|---|
| Volume | 1840.8(4) $Å^3$ |
| Z | 4 |
| Density (calculated) | 1.225 $Mg/m^3$ |
| Absorption coefficient | 0.650 $mm^{-1}$ |
| F(000) | 728 |
| Crystal size | 0.300 x 0.100 x 0.100 $mm^3$ |
| Theta range for data collection | 4.301 to 79.710°. |
| Index ranges | -5<=h<=7, -8<=k<=9, -51<=l<=50 |
| Reflections collected | 19853 |
| Independent reflections | 3921 [R(int) = 0.0518] |
| Completeness to theta = 67.679° | 99.9 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.7451 and 0.6491 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 3921 / 2 / 233 |
| Goodness-of-fit on $F^2$ | 1.032 |
| Final R indices [I>2sigma(I)] | R1 = 0.0307, wR2 = 0.0714 |
| R indices (all data) | R1 = 0.0340, wR2 = 0.0731 |
| Absolute structure parameter | -0.02(8) |
| Extinction coefficient | n/a |
| Largest diff. peak and hole | 0.184 and -0.169 $e.Å^{-3}$ |

***Table A12.2*** *Atomic coordinates (x$10^4$) and equivalent isotropic displacement parameters (Å$^2$x $10^3$) for* ***157****. U(eq) is defined as one third of the trace of the orthogonalized U$^{ij}$ tensor.*

| | x | y | z | U(eq) |
|---|---|---|---|---|
| N(1) | 2984(2) | 4882(2) | 3921(1) | 16(1) |
| C(1) | 4851(2) | 5030(2) | 4154(1) | 14(1) |
| C(2) | 3912(3) | 5870(2) | 4466(1) | 15(1) |
| O(1) | 1984(2) | 6407(2) | 4486(1) | 20(1) |
| C(3) | 5573(3) | 5965(2) | 4746(1) | 19(1) |
| O(2) | 4536(2) | 6809(2) | 5013(1) | 24(1) |
| C(4) | 6395(3) | 4103(2) | 4829(1) | 23(1) |
| C(5) | 7396(3) | 3169(2) | 4532(1) | 21(1) |
| C(6) | 5718(3) | 3171(2) | 4249(1) | 18(1) |
| C(7) | 3311(2) | 4934(2) | 3581(1) | 15(1) |
| C(8) | 5057(3) | 4034(2) | 3423(1) | 17(1) |
| C(9) | 5305(3) | 4126(2) | 3086(1) | 18(1) |
| C(10) | 3762(3) | 5069(2) | 2900(1) | 19(1) |
| O(3) | 3866(2) | 5233(2) | 2566(1) | 26(1) |
| C(13) | 5968(3) | 4833(3) | 2416(1) | 29(1) |
| C(11) | 1965(3) | 5913(2) | 3053(1) | 20(1) |
| C(12) | 1766(3) | 5864(2) | 3389(1) | 18(1) |
| C(14) | 6760(2) | 6244(2) | 4026(1) | 15(1) |
| C(15) | 5972(3) | 8156(2) | 3974(1) | 19(1) |
| C(16) | 7559(3) | 9143(2) | 3752(1) | 17(1) |
| C(17) | 7148(3) | 9212(2) | 3419(1) | 20(1) |
| C(18) | 8634(3) | 10088(2) | 3211(1) | 22(1) |
| C(19) | 10541(3) | 10910(2) | 3336(1) | 22(1) |
| C(20) | 10992(3) | 10823(2) | 3668(1) | 22(1) |
| C(21) | 9512(3) | 9938(2) | 3874(1) | 19(1) |

***Table A12.3*** *Bond lengths [Å] and angles [°] for* ***157****.*

| | |
|---|---|
| N(1)-C(7) | 1.4128(18) |
| N(1)-C(1) | 1.4668(19) |
| N(1)-H(1N) | 0.894(18) |
| C(1)-C(2) | 1.534(2) |
| C(1)-C(6) | 1.546(2) |
| C(1)-C(14) | 1.548(2) |
| C(2)-O(1) | 1.214(2) |
| C(2)-C(3) | 1.518(2) |
| C(3)-O(2) | 1.4111(19) |
| C(3)-C(4) | 1.528(2) |
| C(3)-H(3) | 1.0000 |
| O(2)-H(2O) | 0.87(2) |
| C(4)-C(5) | 1.529(2) |
| C(4)-H(4A) | 0.9900 |
| C(4)-H(4B) | 0.9900 |
| C(5)-C(6) | 1.532(2) |
| C(5)-H(5A) | 0.9900 |
| C(5)-H(5B) | 0.9900 |
| C(6)-H(6A) | 0.9900 |
| C(6)-H(6B) | 0.9900 |
| C(7)-C(8) | 1.398(2) |
| C(7)-C(12) | 1.399(2) |
| C(8)-C(9) | 1.396(2) |
| C(8)-H(8) | 0.9500 |
| C(9)-C(10) | 1.388(2) |
| C(9)-H(9) | 0.9500 |
| C(10)-O(3) | 1.3786(18) |
| C(10)-C(11) | 1.392(2) |
| O(3)-C(13) | 1.421(2) |
| C(13)-H(13A) | 0.9800 |
| C(13)-H(13B) | 0.9800 |
| C(13)-H(13C) | 0.9800 |
| C(11)-C(12) | 1.387(2) |
| C(11)-H(11) | 0.9500 |

| | |
|---|---|
| C(12)-H(12) | 0.9500 |
| C(14)-C(15) | 1.535(2) |
| C(14)-H(14A) | 0.9900 |
| C(14)-H(14B) | 0.9900 |
| C(15)-C(16) | 1.507(2) |
| C(15)-H(15A) | 0.9900 |
| C(15)-H(15B) | 0.9900 |
| C(16)-C(17) | 1.395(2) |
| C(16)-C(21) | 1.396(2) |
| C(17)-C(18) | 1.394(2) |
| C(17)-H(17) | 0.9500 |
| C(18)-C(19) | 1.388(3) |
| C(18)-H(18) | 0.9500 |
| C(19)-C(20) | 1.389(2) |
| C(19)-H(19) | 0.9500 |
| C(20)-C(21) | 1.392(2) |
| C(20)-H(20) | 0.9500 |
| C(21)-H(21) | 0.9500 |

| | |
|---|---|
| C(7)-N(1)-C(1) | 122.78(12) |
| C(7)-N(1)-H(1N) | 110.0(13) |
| C(1)-N(1)-H(1N) | 111.4(14) |
| N(1)-C(1)-C(2) | 107.64(12) |
| N(1)-C(1)-C(6) | 110.24(12) |
| C(2)-C(1)-C(6) | 106.67(12) |
| N(1)-C(1)-C(14) | 111.97(12) |
| C(2)-C(1)-C(14) | 107.59(12) |
| C(6)-C(1)-C(14) | 112.43(12) |
| O(1)-C(2)-C(3) | 122.75(14) |
| O(1)-C(2)-C(1) | 122.50(13) |
| C(3)-C(2)-C(1) | 114.75(13) |
| O(2)-C(3)-C(2) | 109.31(13) |
| O(2)-C(3)-C(4) | 112.41(13) |
| C(2)-C(3)-C(4) | 109.45(13) |
| O(2)-C(3)-H(3) | 108.5 |
| C(2)-C(3)-H(3) | 108.5 |

| | |
|---|---|
| C(4)-C(3)-H(3) | 108.5 |
| C(3)-O(2)-H(2O) | 107.7(17) |
| C(3)-C(4)-C(5) | 111.77(13) |
| C(3)-C(4)-H(4A) | 109.3 |
| C(5)-C(4)-H(4A) | 109.3 |
| C(3)-C(4)-H(4B) | 109.3 |
| C(5)-C(4)-H(4B) | 109.3 |
| H(4A)-C(4)-H(4B) | 107.9 |
| C(4)-C(5)-C(6) | 110.78(13) |
| C(4)-C(5)-H(5A) | 109.5 |
| C(6)-C(5)-H(5A) | 109.5 |
| C(4)-C(5)-H(5B) | 109.5 |
| C(6)-C(5)-H(5B) | 109.5 |
| H(5A)-C(5)-H(5B) | 108.1 |
| C(5)-C(6)-C(1) | 114.11(13) |
| C(5)-C(6)-H(6A) | 108.7 |
| C(1)-C(6)-H(6A) | 108.7 |
| C(5)-C(6)-H(6B) | 108.7 |
| C(1)-C(6)-H(6B) | 108.7 |
| H(6A)-C(6)-H(6B) | 107.6 |
| C(8)-C(7)-C(12) | 117.76(13) |
| C(8)-C(7)-N(1) | 123.25(14) |
| C(12)-C(7)-N(1) | 118.93(13) |
| C(9)-C(8)-C(7) | 121.04(14) |
| C(9)-C(8)-H(8) | 119.5 |
| C(7)-C(8)-H(8) | 119.5 |
| C(10)-C(9)-C(8) | 120.19(14) |
| C(10)-C(9)-H(9) | 119.9 |
| C(8)-C(9)-H(9) | 119.9 |
| O(3)-C(10)-C(9) | 124.37(15) |
| O(3)-C(10)-C(11) | 116.30(14) |
| C(9)-C(10)-C(11) | 119.34(14) |
| C(10)-O(3)-C(13) | 116.80(13) |
| O(3)-C(13)-H(13A) | 109.5 |
| O(3)-C(13)-H(13B) | 109.5 |
| H(13A)-C(13)-H(13B) | 109.5 |

| | |
|---|---|
| O(3)-C(13)-H(13C) | 109.5 |
| H(13A)-C(13)-H(13C) | 109.5 |
| H(13B)-C(13)-H(13C) | 109.5 |
| C(12)-C(11)-C(10) | 120.21(15) |
| C(12)-C(11)-H(11) | 119.9 |
| C(10)-C(11)-H(11) | 119.9 |
| C(11)-C(12)-C(7) | 121.38(14) |
| C(11)-C(12)-H(12) | 119.3 |
| C(7)-C(12)-H(12) | 119.3 |
| C(15)-C(14)-C(1) | 112.59(12) |
| C(15)-C(14)-H(14A) | 109.1 |
| C(1)-C(14)-H(14A) | 109.1 |
| C(15)-C(14)-H(14B) | 109.1 |
| C(1)-C(14)-H(14B) | 109.1 |
| H(14A)-C(14)-H(14B) | 107.8 |
| C(16)-C(15)-C(14) | 111.21(12) |
| C(16)-C(15)-H(15A) | 109.4 |
| C(14)-C(15)-H(15A) | 109.4 |
| C(16)-C(15)-H(15B) | 109.4 |
| C(14)-C(15)-H(15B) | 109.4 |
| H(15A)-C(15)-H(15B) | 108.0 |
| C(17)-C(16)-C(21) | 118.79(14) |
| C(17)-C(16)-C(15) | 120.31(14) |
| C(21)-C(16)-C(15) | 120.85(14) |
| C(18)-C(17)-C(16) | 120.69(15) |
| C(18)-C(17)-H(17) | 119.7 |
| C(16)-C(17)-H(17) | 119.7 |
| C(19)-C(18)-C(17) | 119.91(15) |
| C(19)-C(18)-H(18) | 120.0 |
| C(17)-C(18)-H(18) | 120.0 |
| C(18)-C(19)-C(20) | 119.96(15) |
| C(18)-C(19)-H(19) | 120.0 |
| C(20)-C(19)-H(19) | 120.0 |
| C(19)-C(20)-C(21) | 120.02(15) |
| C(19)-C(20)-H(20) | 120.0 |
| C(21)-C(20)-H(20) | 120.0 |

| | |
|---|---|
| C(20)-C(21)-C(16) | 120.60(14) |
| C(20)-C(21)-H(21) | 119.7 |
| C(16)-C(21)-H(21) | 119.7 |

***Table A12.4*** *Anisotropic displacement parameters ($Å^2x10^3$) for* ***157****. The anisotropic displacement factor exponent takes the form* $-2\pi^2[h^2a^{*2}U^{11} + ... +2\ h\ k\ a^*\ b^*U^{12}]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| N(1) | 13(1) | 20(1) | 14(1) | -2(1) | 1(1) | -1(1) |
| C(1) | 13(1) | 15(1) | 14(1) | -1(1) | 0(1) | -1(1) |
| C(2) | 15(1) | 15(1) | 16(1) | 0(1) | 2(1) | -4(1) |
| O(1) | 14(1) | 28(1) | 17(1) | -5(1) | 1(1) | 1(1) |
| C(3) | 16(1) | 25(1) | 15(1) | -6(1) | 1(1) | 1(1) |
| O(2) | 18(1) | 36(1) | 18(1) | -14(1) | -1(1) | 0(1) |
| C(4) | 27(1) | 28(1) | 15(1) | -1(1) | -2(1) | 4(1) |
| C(5) | 24(1) | 21(1) | 18(1) | 1(1) | -3(1) | 4(1) |
| C(6) | 22(1) | 16(1) | 16(1) | -1(1) | 0(1) | 1(1) |
| C(7) | 17(1) | 15(1) | 14(1) | -1(1) | 1(1) | -2(1) |
| C(8) | 17(1) | 16(1) | 18(1) | 0(1) | 0(1) | 1(1) |
| C(9) | 20(1) | 16(1) | 18(1) | -3(1) | 3(1) | 1(1) |
| C(10) | 22(1) | 22(1) | 13(1) | -1(1) | 1(1) | -3(1) |
| O(3) | 28(1) | 37(1) | 13(1) | 0(1) | 2(1) | 4(1) |
| C(13) | 32(1) | 38(1) | 16(1) | 0(1) | 7(1) | 2(1) |
| C(11) | 20(1) | 23(1) | 18(1) | 2(1) | -1(1) | 2(1) |
| C(12) | 14(1) | 20(1) | 18(1) | -2(1) | 2(1) | 1(1) |
| C(14) | 12(1) | 15(1) | 16(1) | 0(1) | 1(1) | -2(1) |
| C(15) | 16(1) | 16(1) | 25(1) | 0(1) | 4(1) | 0(1) |
| C(16) | 18(1) | 12(1) | 22(1) | 0(1) | 4(1) | 2(1) |
| C(17) | 18(1) | 18(1) | 25(1) | 0(1) | -2(1) | 0(1) |
| C(18) | 26(1) | 20(1) | 20(1) | 2(1) | -1(1) | 3(1) |
| C(19) | 24(1) | 16(1) | 27(1) | 2(1) | 7(1) | 0(1) |
| C(20) | 21(1) | 17(1) | 28(1) | -3(1) | 1(1) | -4(1) |
| C(21) | 21(1) | 16(1) | 19(1) | -2(1) | 1(1) | -1(1) |

***Table A12.5*** *Hydrogen coordinates (x $10^4$) and isotropic displacement parameters ($Å^2$ x$10^3$) for* ***157****.*

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1N) | 1830(30) | 5580(30) | 3977(5) | 24 |
| H(3) | 6901 | 6689 | 4676 | 22 |
| H(2O) | 5590(40) | 7310(30) | 5127(6) | 36 |
| H(4A) | 5114 | 3399 | 4914 | 28 |
| H(4B) | 7554 | 4176 | 5002 | 28 |
| H(5A) | 7782 | 1934 | 4590 | 25 |
| H(5B) | 8802 | 3777 | 4466 | 25 |
| H(6A) | 4409 | 2423 | 4308 | 21 |
| H(6B) | 6454 | 2630 | 4057 | 21 |
| H(8) | 6091 | 3350 | 3547 | 20 |
| H(9) | 6533 | 3541 | 2983 | 22 |
| H(13A) | 7164 | 5541 | 2517 | 43 |
| H(13B) | 5885 | 5108 | 2184 | 43 |
| H(13C) | 6305 | 3573 | 2445 | 43 |
| H(11) | 870 | 6524 | 2927 | 24 |
| H(12) | 555 | 6475 | 3491 | 21 |
| H(14A) | 8024 | 6237 | 4184 | 18 |
| H(14B) | 7333 | 5765 | 3818 | 18 |
| H(15A) | 4439 | 8152 | 3878 | 23 |
| H(15B) | 5891 | 8770 | 4186 | 23 |
| H(17) | 5840 | 8657 | 3332 | 24 |
| H(18) | 8343 | 10122 | 2984 | 27 |
| H(19) | 11536 | 11532 | 3196 | 27 |
| H(20) | 12310 | 11368 | 3753 | 26 |
| H(21) | 9834 | 9875 | 4100 | 22 |

***Table A12.6*** *Torsion Anlges [°] for* ***157***.

| | |
|---|---|
| C(7)-N(1)-C(1)-C(2) | 150.99(14) |
| C(7)-N(1)-C(1)-C(6) | -93.03(17) |
| C(7)-N(1)-C(1)-C(14) | 32.94(19) |
| N(1)-C(1)-C(2)-O(1) | -5.1(2) |
| C(6)-C(1)-C(2)-O(1) | -123.39(16) |
| C(14)-C(1)-C(2)-O(1) | 115.76(16) |
| N(1)-C(1)-C(2)-C(3) | 174.48(13) |
| C(6)-C(1)-C(2)-C(3) | 56.17(16) |
| C(14)-C(1)-C(2)-C(3) | -64.68(16) |
| O(1)-C(2)-C(3)-O(2) | -2.2(2) |
| C(1)-C(2)-C(3)-O(2) | 178.20(13) |
| O(1)-C(2)-C(3)-C(4) | 121.28(17) |
| C(1)-C(2)-C(3)-C(4) | -58.28(17) |
| O(2)-C(3)-C(4)-C(5) | 176.86(14) |
| C(2)-C(3)-C(4)-C(5) | 55.20(17) |
| C(3)-C(4)-C(5)-C(6) | -54.08(18) |
| C(4)-C(5)-C(6)-C(1) | 54.73(18) |
| N(1)-C(1)-C(6)-C(5) | -170.37(12) |
| C(2)-C(1)-C(6)-C(5) | -53.78(16) |
| C(14)-C(1)-C(6)-C(5) | 63.92(16) |
| C(1)-N(1)-C(7)-C(8) | 43.0(2) |
| C(1)-N(1)-C(7)-C(12) | -139.76(15) |
| C(12)-C(7)-C(8)-C(9) | 2.7(2) |
| N(1)-C(7)-C(8)-C(9) | 179.92(14) |
| C(7)-C(8)-C(9)-C(10) | -2.3(2) |
| C(8)-C(9)-C(10)-O(3) | -179.95(15) |
| C(8)-C(9)-C(10)-C(11) | -0.3(2) |
| C(9)-C(10)-O(3)-C(13) | -17.7(2) |
| C(11)-C(10)-O(3)-C(13) | 162.65(16) |
| O(3)-C(10)-C(11)-C(12) | -178.00(15) |
| C(9)-C(10)-C(11)-C(12) | 2.3(3) |
| C(10)-C(11)-C(12)-C(7) | -1.9(3) |
| C(8)-C(7)-C(12)-C(11) | -0.7(2) |

| | |
|---|---|
| N(1)-C(7)-C(12)-C(11) | -178.00(15) |
| N(1)-C(1)-C(14)-C(15) | 62.65(16) |
| C(2)-C(1)-C(14)-C(15) | -55.43(16) |
| C(6)-C(1)-C(14)-C(15) | -172.59(12) |
| C(1)-C(14)-C(15)-C(16) | -161.29(12) |
| C(14)-C(15)-C(16)-C(17) | 93.17(17) |
| C(14)-C(15)-C(16)-C(21) | -84.11(18) |
| C(21)-C(16)-C(17)-C(18) | -1.2(2) |
| C(15)-C(16)-C(17)-C(18) | -178.53(15) |
| C(16)-C(17)-C(18)-C(19) | -0.4(2) |
| C(17)-C(18)-C(19)-C(20) | 1.5(3) |
| C(18)-C(19)-C(20)-C(21) | -1.1(3) |
| C(19)-C(20)-C(21)-C(16) | -0.5(2) |
| C(17)-C(16)-C(21)-C(20) | 1.6(2) |
| C(15)-C(16)-C(21)-C(20) | 178.93(15) |

***Table 12.7*** *Hydrogen bonds for* ***157*** *[Å and °].*

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| N(1)-H(1N)...O(1) | 0.894(18) | 2.19(2) | 2.6591(16) | 112.5(16) |
| C(3)-H(3)...O(2)#1 | 1.00 | 2.31 | 3.053(2) | 129.9 |
| O(2)-H(2O)...O(1)#1 | 0.87(2) | 2.04(2) | 2.8566(16) | 157(2) |
| O(2)-H(2O)...O(2)#1 | 0.87(2) | 2.50(2) | 3.1420(10) | 132(2) |
| C(13)-H(13C)...O(3)#2 | 0.98 | 2.53 | 3.480(3) | 163.8 |
| C(14)-H(14A)...O(1)#3 | 0.99 | 2.66 | 3.6265(19) | 166.6 |

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# ABOUT THE AUTHOR

Eric John Alexy was born in Raleigh, North Carolina on July 29th, 1993 to Joanna and Thomas Alexy, and grew up in Cary, North Carolina with his older sister Tiffany. His interest in chemistry began in high school, where he occasionally spent weekends working for a former neighbor, Dr. John Wasson, at his small chemical supply company. Further inspiring instruction in an AP Chemistry course in school solidified his interest, setting him down a path to study chemistry in College.

In the fall of 2011, Eric started attending North Carolina State University in Raleigh, North Carolina. During his time at NCSU, he conducted undergraduate research in the lab of Professor Jonathan Lindsey regarding the synthesis and photochemical characterization of perylene-porphyrin arrays, and investigating the prebiotic origins of porphyrins and proteins. Incredible mentorship, both in and out of the lab, from Dr. Lindsey, as well as early coursework and guidance from Dr. Feducia, focused his attention on organic chemistry, and he was inspired to continue his studies in graduate school.

Upon completion of his undergraduate studies in 2015, he moved to Pasadena, California to pursue graduate studies at the California Institute of Technology under the direction of Professor Brian Stoltz. His research interests focused on the development of asymmetric transition-metal catalysis. Following completion of his graduate studies in May 2020, Eric will begin his professional career as a Process Chemist at Gilead in Foster City, CA.