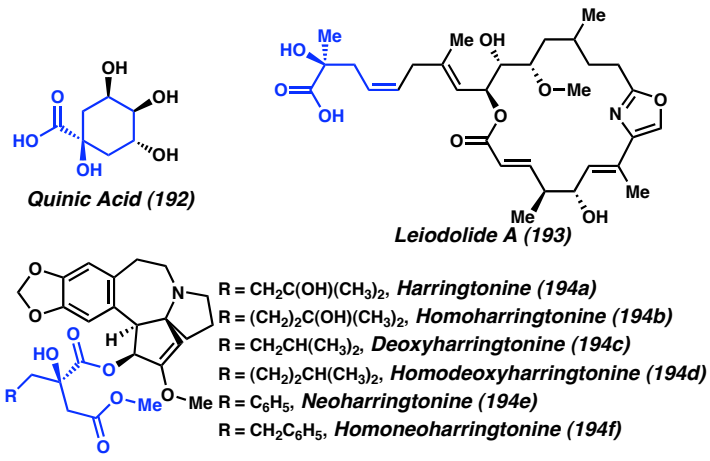
CHAPTER FOUR

Catalytic Enantioselective Alkylation of Substituted Dioxanone Enol Ethers

4.1 Methods to Form Tertiary Ether Stereocenters

The catalytic enantioselective formation of tetrasubstituted α-alkoxycarbonyl moieties is an ongoing challenge to synthetic chemists.[1] Fully substituted α-hydroxyesters and acids comprise essential components of, and building blocks for, many bioactive natural products. These include quinic acid (**192**), cytotoxic leiodolide A (**193**),[2] and the anti-cancer agents in the harringtonine series (**194a–f**), whose activities depend dramatically on the presence and composition of an α-hydroxyester side-chain.[3]

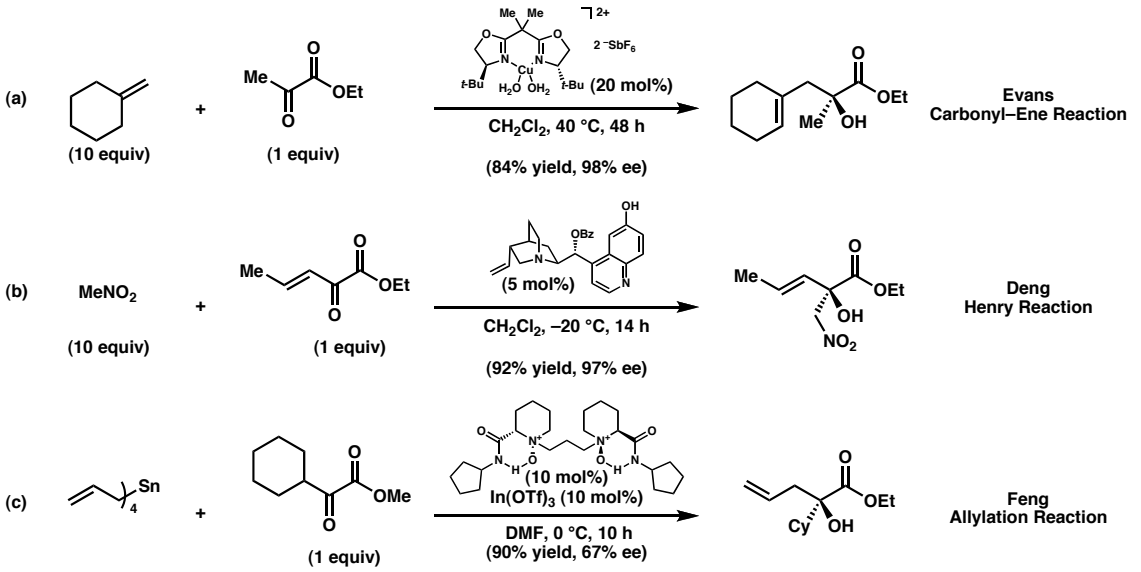
Figure 4.1.1 Fully substituted α-hydroxyesters and acids in bioactive natural products



Methods to form enantioenriched tetrasubstituted α-hydroxyesters, ketones, and acids are scarce, and are currently limited to a few, well-established, oxygen transfer processes,[4,5] selective oxidation processes,[4] and emerging methods to form C–C bonds.[4] Most C–C bond-forming strategies require the addition of carbon nucleophiles to α-

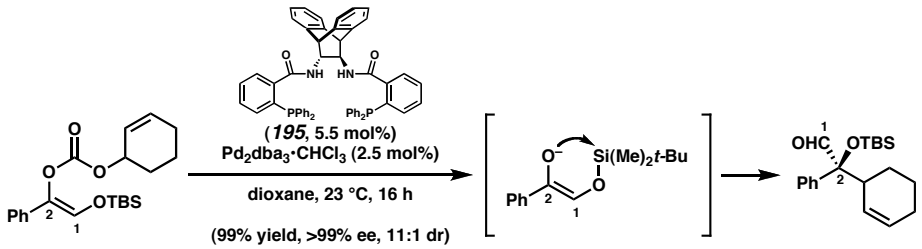
ketoesters via ene[6] Henry,[7] Aldol,[8] allylation,[9] alkylation,[10] cyclizations,[11] or Friedel–Crafts processes.[12] Simple ketone derivatives can serve as the electrophiles in cyanosilylations.[13]

Scheme 4.1.1 Benchmark methods to form enantioenriched tetrasubstituted α-hydroxycarbonyl compounds



While these studies were underway, Trost reported the use of prochiral α-oxygenated ketone or ester derivatives as nucleophiles to form enantioenriched tetrasubstituted α-hydroxycarbonyl compounds (Scheme 4.1.2).[14, 15] In most of the disclosed examples, the directly generated enolate can undergo silyl group transfer prior to product formation.

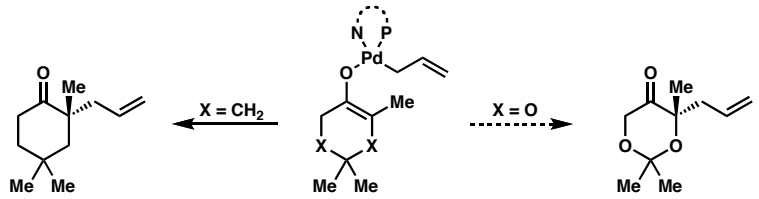
Scheme 4.1.2 Trost reported the use of prochiral oxygenated ketone nucleophiles



4.2 Introduction to Enantioselective Decarboxylative Alkylations

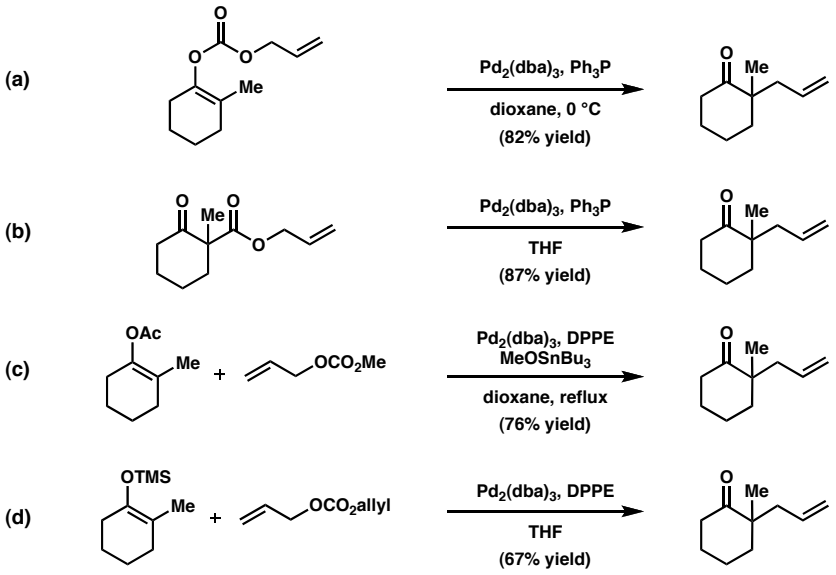
As part of a general program in the area of asymmetric catalysis, our laboratory recently reported the formation of enantioenriched all-carbon quaternary stereocenters in cyclic alkanones via palladium-catalyzed asymmetric decarboxylative alkylation of unstabilized prochiral enolate nucleophiles (Scheme 4.2.1).[16] We envisioned this technology as an ideal platform to produce asymmetric tetrasubstituted oxygenated systems (e.g., ethers and alcohols).

Scheme 4.2.1 Planned enantioselective decarboxylative alkylation to form tetrasubstituted oxygenated systems



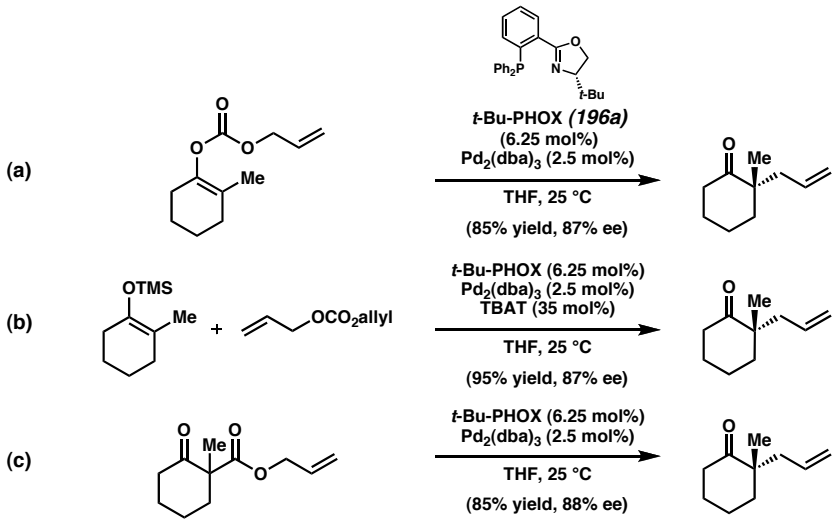
In the early 1980s, Tsuji developed a series of reactions to form α-quaternary cycloalkanone products using allyl enol carbonate,[17] allyl β-ketoester,[18] enol acetate,[19] and silyl enol ether[20] substrates as enolate precursors (Scheme 4.2.2). These transformations exhibited exquisite regiofidelity in formation of the new stereocenters, even in the presence of similarly acidic and less substituted ketone α-positions. The Stoltz group identified Tsuji's work as an important starting point for the development of asymmetric variants of these reactions.

Scheme 4.2.2 Tsuji developed position-selective alkylation reactions



Initially, Behenna and Stoltz explored the allyl enol carbonate (e.g., Scheme 4.2.3a) and silyl enol ether (e.g., Scheme 4.2.3b) substrates in the reaction. They found that both gave high yields and enantioselectivities with the catalyst generated in situ from tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$] and (*S*)-*t*-Butyl phosphinooxazoline (PHOX, **196a**) as a ligand.[21,22] Following this initial report, Stoltz, Mohr, and co-workers discovered that β-ketoesters could achieve the same levels of reactivity (e.g., Scheme 4.2.3c). Remarkably, any particular α-quaternary cycloalkanone product forms in a similar yield and enantiomeric excess regardless of which substrate class is employed.

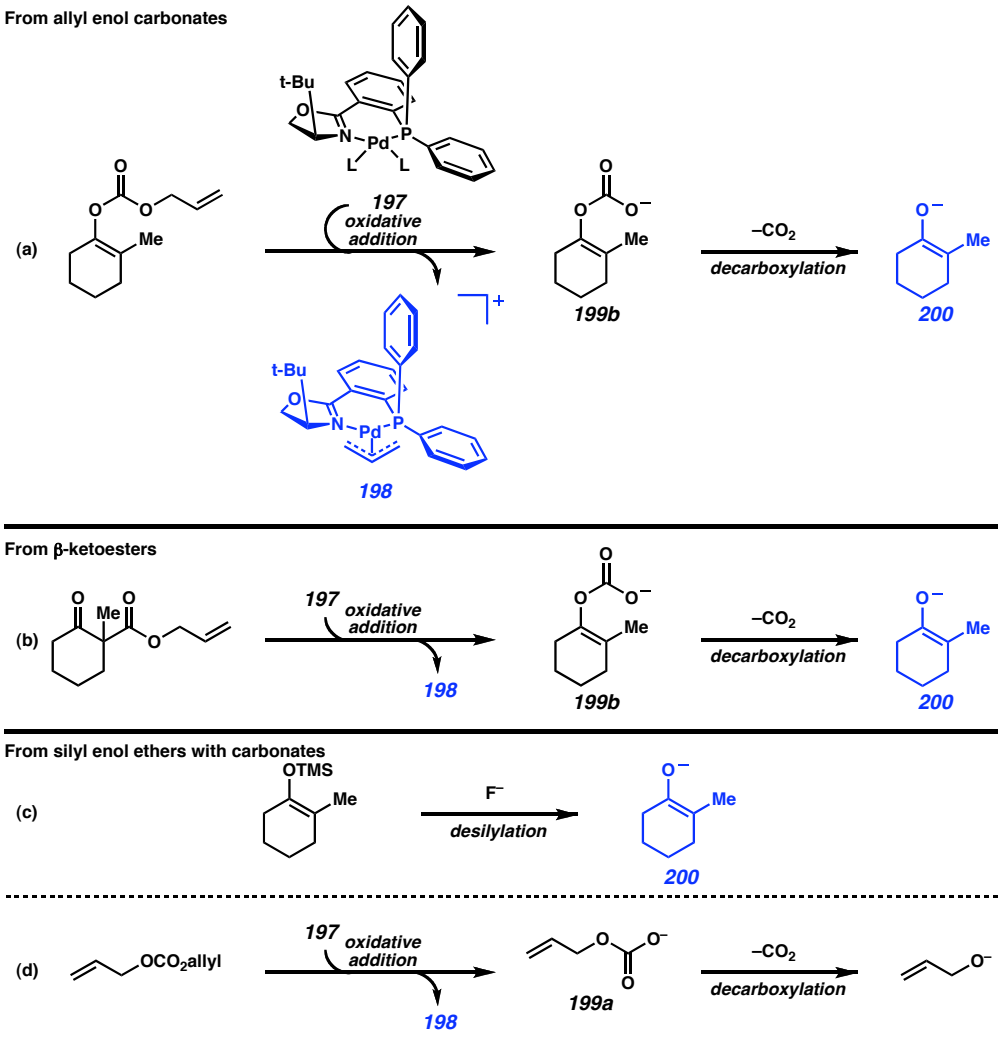
Scheme 4.2.3 Stoltz and co-workers developed asymmetric variants of this reaction



The mechanism of these reactions is an active area of research within the Stoltz group.[23] In our working model, allyl enol carbonates, silyl enol ethers, and β-ketoesters react by a common inner-sphere mechanism (Scheme 4.2.5) after generation of enolate **200** and [Pd(η^3-allyl)PHOX] complex **198** (Scheme 4.2.4).

With allyl enol carbonates and β-ketoesters, oxidative addition of Pd(0)•PHOX complex **197** leads to [Pd(η^3-allyl)PHOX] complex **198** and carboxylates **199** (Scheme 4.2.4, a and b, respectively). Subsequent loss of CO_2, furnishes enolate **200**. From silyl enol ethers, fluoride-promoted desilylation provides enolate **200** (Scheme 4.2.4c). The [Pd(η^3-allyl)PHOX] complex **198** is accessed through oxidative addition of Pd(0)•PHOX complex **197** into an allyl source, such as diallyl carbonate (Scheme 4.2.4d).

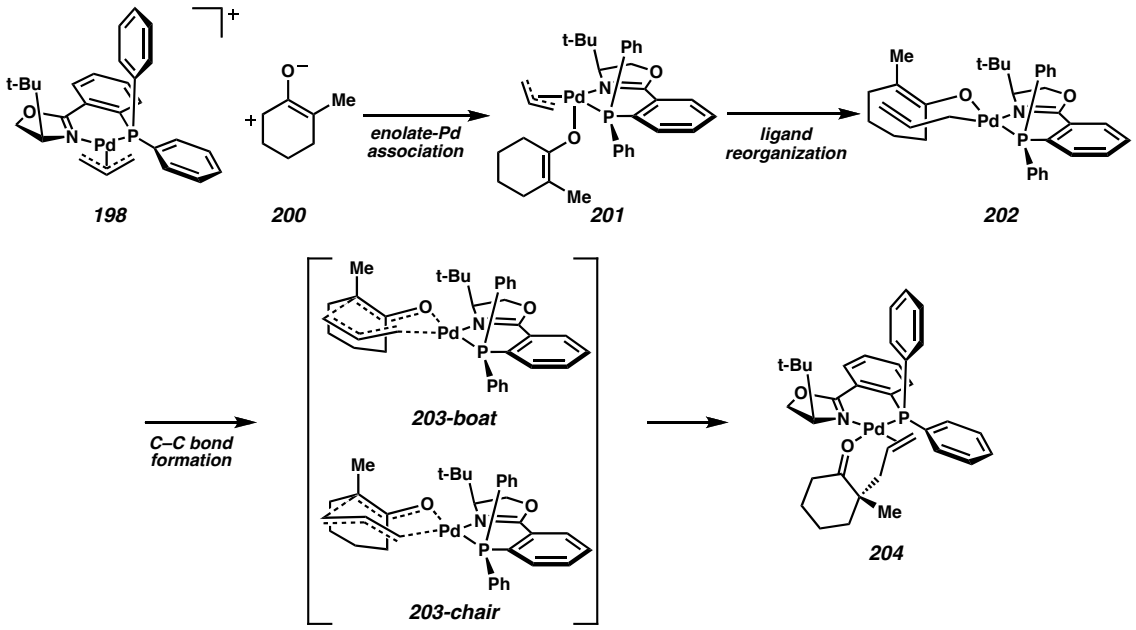
Scheme 4.2.4 Generation of enolate and [Pd(η^3-allyl)PHOX] complex



After generation of enolate **200** and [Pd(η^3-allyl)PHOX] complex **198**, all substrates are expected to proceed through a common inner-sphere mechanism (Scheme 4.2.5). Association of enolate **200** and [Pd(η^3-allyl)PHOX] complex **198** leads to 5-coordinate intermediate **201**, with the enolate bound to the sterically less-encumbered apical position of the square-planar metal. Shifting of the allyl group from an η^3- to an η^1-binding mode allows the enolate fragment to move into the square plane to form intermediate **202**. From this square-planar complex, a standard 3-centered reductive

elimination would require a shift from *O*- to *C*-bound Pd-enolate.[24] We reasoned that this isomerization would be unfavorable due to the steric demands of the resulting tertiary palladium species. As an alternative, we postulated an extended reductive elimination pathway proceeding through a cyclic 7-membered pericyclic transition state (**203-boat** or **203-chair**) similar to a sigmatropic rearrangement.[25,26] Importantly, situating the carbocyclic ring of the enolate fragment away from the bulky *t*-Bu group of the oxazoline provides a plausible predictive model for the observed absolute sense of enantiofacial selectivity.

Scheme 4.2.5 Proposed inner-sphere alkylation mechanism



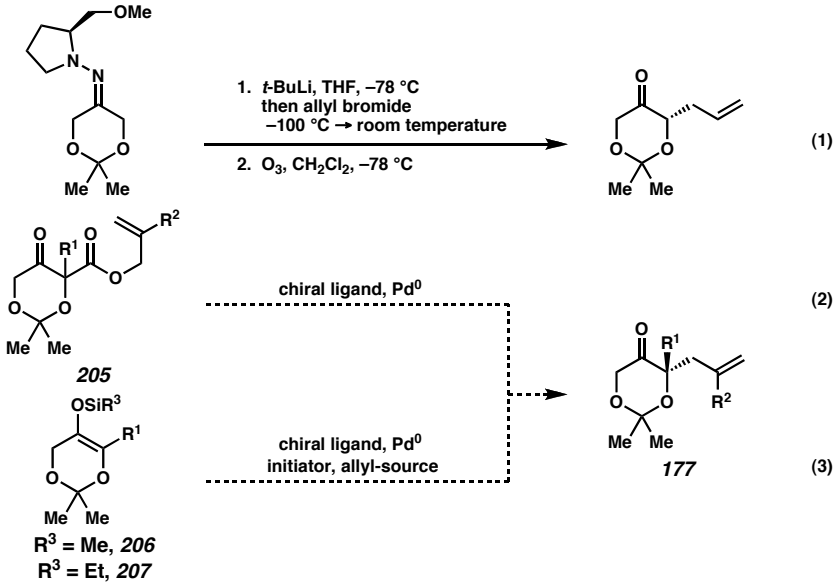
4.3 Catalytic Enantioselective Alkylation of β-ketoesters to Form Tertiary Ethers

Since inception of this program, the palladium-catalyzed enantioselective decarboxylative alkylation of cyclic alkanones had been studied in detail, but had been tested primarily for the formation of all-carbon quaternary stereocenters.[27] Our plan for

the total synthesis of ineleganolide required the extension of this method to the synthesis of enantioenriched tertiary ether stereocenters (Section 4.8).

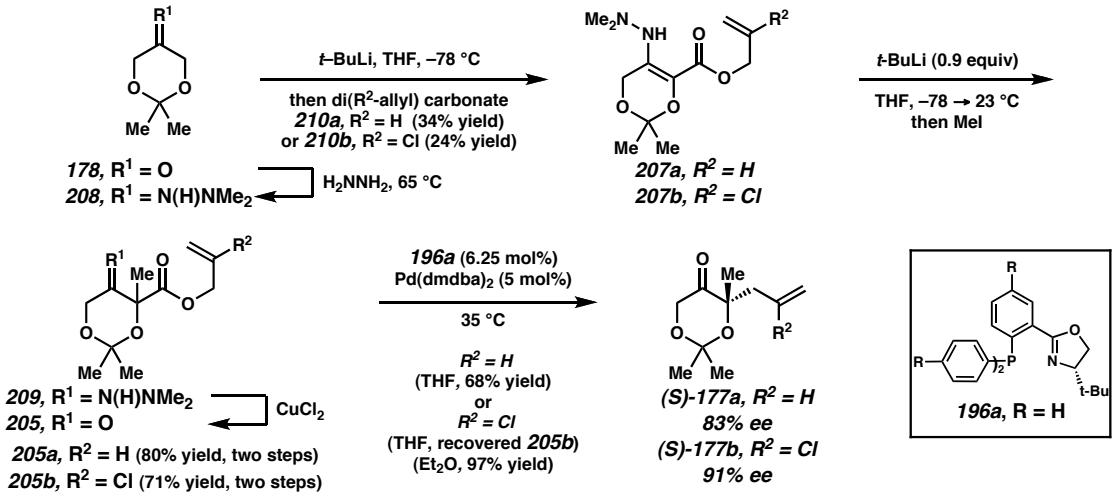
For this application, we chose to incorporate oxygenation into a cyclic motif, the 2,2-dimethyldioxanone framework,[28] and employ this strategy for the enantioselective synthesis of an α-alkylated dioxanones (e.g., **177**). Dioxanones are challenging alkylation substrates because standard conditions do not permit alkylation. Instead these conditions facilitate ketone reduction (e.g., LDA, –78 °C), or self-condensation (e.g., LHMDS), accompanied by decomposition.[29] A technology that avoids this undesirable reactivity would represent a significant advance in dioxanone chemistry. For this purpose, Enders and co-workers have developed a diastereoselective α-alkylation that relies on chirality imparted by (+)-(*S*)-1-amino-2-methoxymethylpyrrolidine hydrazones (SAMP), which can be cleaved in a subsequent step (Scheme 4.3.1, eq 1). Development of a palladium-catalyzed enantioselective decarboxylative alkylation reaction would represent a complementary advance in dioxanone chemistry (Scheme 4.3.1, eq 2 and 3).

Scheme 4.3.1 Alkylation technologies using the dioxanone framework



Due to known challenges with dioxanone alkylation, we initially targeted β-ketoester substrates for use in the palladium-catalyzed alkylation (Scheme 4.3.2). Synthesis of β-ketoester substrates begins with dioxanone **178**. Conversion of dioxanone **178** to a hydrazone enables acylation to furnish acyl hydrazone **207a** in a modest 34% yield. The targeted racemic β-ketoester **205a** for decarboxylative alkylation is accessible through thermodynamic methylation of acyl **207a**, followed by $CuCl_2$-mediated hydrazone cleavage. Upon exposure of β-ketoester **205a** to catalytic Pd^0 and (*S*)-*t*-BuPHOX (**196**), tertiary ether (*S*)-**177a** is generated in 83% ee.

Scheme 4.3.2 Formation of an enantioenriched product from α-oxygenated-β-ketoesters



Chlorinated substrate (*S*)-**177b** is accessible through an analogous sequence of transformations. Requisite β-ketoester **205b** forms from known hydrazone **208** in three steps and 17% yield. Unfortunately, chlorinated **205b** reacts less readily than simple allyl **205a**: exposure to catalytic Pd^0 and (*S*)-*t*-BuPHOX (**196a**) in THF yields primarily recovered starting material. Fortunately, chloro olefin (*S*)-**177b** is generated in 91% ee and 97% yield on exposure to catalytic Pd^0 and (*S*)-*t*-BuPHOX (**196a**) in Et_2O at slightly elevated temperatures.

4.4 Catalytic Enantioselective Alkylation of Dioxanone Silyl Enol Ethers to Form Tertiary Ethers[i]

Due to the difficult synthesis of β-ketoester starting materials **205**, we sought access to (*S*)-**177a** via trimethylsilyl enol ether precursors (Table 4.4.1). Conversion of dioxanone **178** to an imine enables methylation via a metalloenamine. On acidic work-up, imine hydrolysis furnishes alkylated **259** in good yield. The targeted silyl enol ether **206a** is available through thermodynamic silylation in 23% yield. Due to the instability of trimethylsilyl **206a**, triethylsilyl **207a** has also been prepared. Triethylsilyl **207a** is available in 55% yield over three steps.

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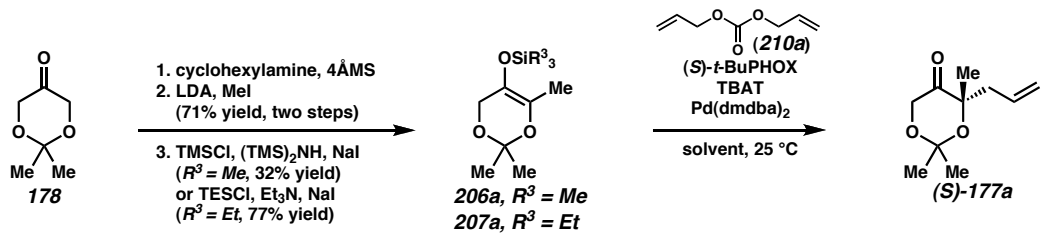
[i] This work has been carried out in collaboration with Masaki Seto, who joined this project as a postdoctoral scholar from February of 2007 to 2008. Much of this work has been reported in Seto, M.; Roizen, J. L.; Stoltz, B. M. Catalytic Enantioselective Alkylation of Substituted Dioxanone Enol Ethers: Ready Access to C(α)-Tetrasubstituted Hydroxyketones, Acids, and Esters. *Angew. Chem. Int. Ed.* **2008**, *47*, 6873–6875.

Table 4.4.1 More optimal conditions for alkylation of silyl enol ethers



Trimethylsilyl Enol Ethers (R^3 = Me)					Triethylsilyl Enol Ethers (R^3 = Et)				
Entry	TBAT [mol%]	Solvent	Yield [%][a]	*ee* [%][b]	Entry	TBAT [mol%]	Solvent	Yield [%][a]	*ee* [%][b]
1	100	THF	77	83	1	100	THF	40	81
2	100	PhMe	74	89	2	100	Et_2O	59	89
3	100	Et_2O	72	90	3	100	1,4-dioxane	65	67
4	35	Et_2O	70	89	4	100	PhH	67	84
					5	100	PhMe	74	89

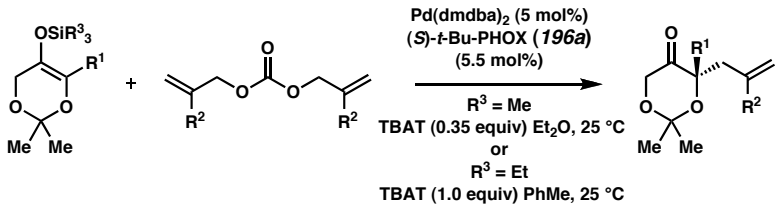
[a] Isolated yield from reaction using 0.1 mmol of substrate in solvent (0.033 M in substrate) at 25 °C with 5 mol% $Pd(dmdba)_2$, 5.5 mol% (*S*)-*t*-Bu-PHOX (**196a**), diallyl carbonate (1.05 equiv), and TBAT. Each reaction was complete in 5–7 h. [b] Enantioselectivity was measured by chiral HPLC of a derivative.

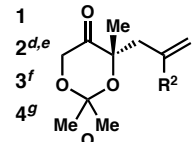
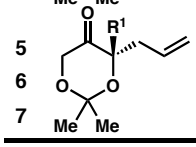
Initially, we examined the conversion of silyl enol ethers **206a**–**207a** to enantioenriched tetrasubstituted ether **177a** on exposure to $Pd(dmdba)_2$ (5 mol%), (*S*)-*t*-BuPHOX (**196**, 5.5 mol%),[21] and diallyl carbonate (1.05 equiv) at 25 °C, while varying solvent and the amount of $Bu_4NPh_3SiF_2$ (TBAT, 0.35 or 1.0 equiv). Interestingly, the choice of solvent played a significant role in the selectivity of tertiary ether formation. Within a particular solvent, selectivities were consistent for trimethylsilyl and triethylsilyl substrates. Optimal conversions and enantioselectivities were achieved from trimethylsilyl **206a** in Et_2O with lower TBAT loadings (0.35 equiv), but from triethylsilyl **207a** in PhMe with an equivalent of TBAT (Table 4.4.1).

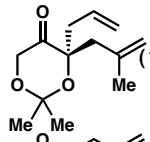
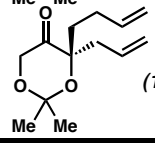
We applied these optimized conditions to silyl enol ethers with diverse α-substituents, in combination with substituted allyl carbonates (Table 4.4.2). The asymmetric alkylation tolerates a variety of substituents at the α-position, including alkyl (entries 1–5), benzyl (entry 6), and alkenyl (entries 7–9) moieties. Additionally, the

reaction proceeds when the allyl group is substituted internally by methyl, chloro, or phenyl (entries 4–7) to afford products in high yields and *ee*.

Table 4.4.2 Substrate scope for the reaction of silyl enol ethers



entry	product[a]		From R^3 = Me % yield[b]	% ee[c]	From R^3 = Et % yield[b]	% ee[c]
1		*177a*, R^2 = H	83	90	86	87
2[d,e]		*177c*, R^2 = Me	59	89	59	89
3[f]		*177b*, R^2 = Cl	28	91	59	92
4[g]		*177d*, R^2 = Ph			73	94
5		*177e*, R^1 = Et	79	93	79	93
6		*177f*, R^1 = Bn	84	85	85	86
7		*177g*, R^1 = H			13	82

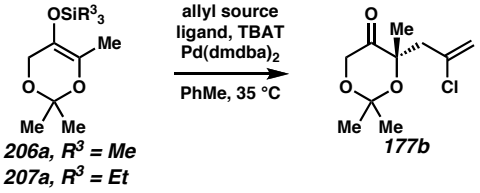
entry	product[a]		From R^3 = Me % yield[b]	% ee[c]	From R^3 = Et % yield[b]	% ee[c]
8[e]		*(177h)*	86	85	93	88
9					88	–85
10		*(177i)*			83	92

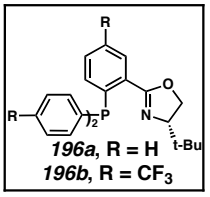
[a] Reactions were performed using 0.5 mmol of substrate at 25 °C with 5 mol% $Pd(dmdba)_2$, 5.5 mol% (*S*)-*t*-BuPHOX (**196a**), and diallyl carbonate (1.05 equiv) unless otherwise noted. If R^3 = Me, reactions were run in Et_2O (0.033 M in substrate) with TBAT (0.35 equiv). If R^3 = Et, reactions were run in PhMe (0.033 M in substrate) with TBAT (1 equiv). Each reaction was complete in 5–10 h. [b] Isolated yields. [c] Measured by chiral GC or HPLC, in some cases using a derivative. [d] Reaction performed with trimethyl silyl enol ether with 35 mol% TBAT in Et_2O (0.0167 M in substrate). [e] Reaction performed with dimethallyl carbonate (1.05 equiv). [f] Reaction performed with dichloroallyl carbonate (1.05 equiv) at 35 °C. [g] Reaction performed with diphenylallyl carbonate (1.05 equiv).

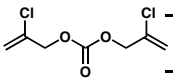
For the purposes of the synthesis of ineleganolide, the most important product has internal substitution of the allyl by a chloride. Unfortunately, triethylsilyl **207a** gives chloroalkene **177b** in only 59% yield, albeit with 92% ee on exposure to $Bu_4NPh_3SiF_2$ (TBAT, 1.0 equiv), $Pd(dmdba)_2$ (5 mol%), (*S*)-*t*-BuPHOX (**196a**, 5.5 mol%),[21] and di(2-chloroallyl) carbonate (**210b**, 1.05 equiv) at 35 °C in PhMe (Table 4.4.3, entry 2). The yield can be raised by 11%, simply by utilizing a less electron rich catalyst (e.g., **196b**, entry 3). In a final refinement, we hoped to minimize protonation of desilylated starting material by use of a π-allyl precursor that would form a π-allylpalladium species

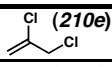
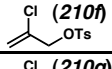
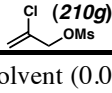
with a more weakly coordinating counteranion.[30] Yields increase from firmly to weakly coordinating counterions (e.g., from chloride to carbonate to mesylate). This trend is not sustained with use of tosylate **210f** as the allyl source, due to isolation irregularities. Fortunately, with mesylate **210g** as the allyl source enantioenriched chloroalkene **177b** forms in 82% yield and 91% ee (entry 6).

Table 4.4.3 More optimal conditions for reaction of chloroallyl silyl enol ethers





entry	allyl source	R^3	TBAT [mol%]	ligand	solvent	yield [%]	*ee* [%]
1	 (*210b*)	*206a*	35	*196a*	Et_2O	28	91
2		*207a*	100	*196a*	PhMe	59	92
3		*207a*	100	*196b*	PhMe	70	92

entry	allyl source	R^3	TBAT [mol%]	ligand	solvent	yield [%]	*ee* [%]
4	 (*210e*)	*207a*	100	*196b*	PhMe	46	91
5	 (*210f*)	*207a*	100	*196b*	PhMe	63	91
6	 (*210g*)	*207a*	100	*196b*	PhMe	82	91

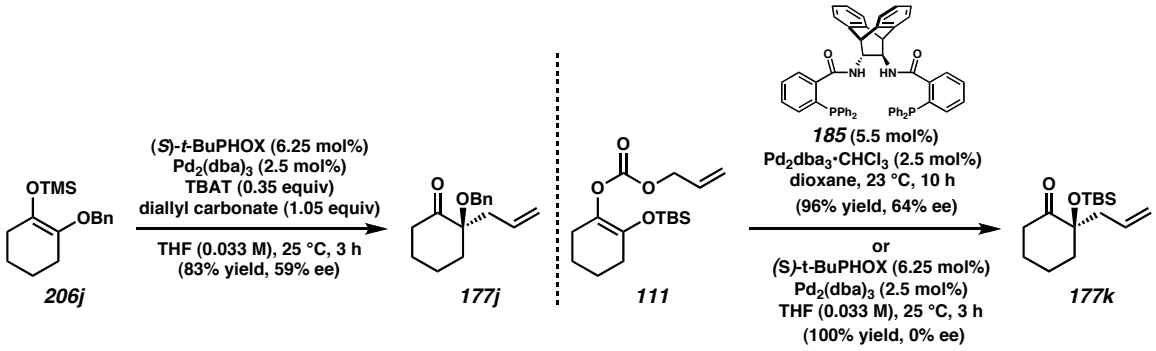
[a] Isolated yield from reaction using 0.1 mmol of substrate in solvent (0.033 M in substrate) at 25 °C with 5 mol% $Pd(dmdba)_2$, 5.5 mol% ligand, an allyl source (1.05 equiv), and TBAT. Each reaction was complete in 5–7 h. [b] Measured by chiral HPLC of a derivative.

4.5 Catalytic Enantioselective Alkylation of Carbocycles to Form Tertiary Ethers

To complement our studies of the effects of endocyclic α-oxygenation on the palladium-catalyzed asymmetric alkylation reaction, we began to explore the influence of exocyclic α-oxygenation on reaction efficiency. Preliminary experiments demonstrate that these enolate precursors rapidly undergo decarboxylative alkylation, but with variable enantioselectivity. On exposure to Pd(0) and (*S*)-*t*-BuPHOX in THF, Behenna found that benzylated **206j** forms enantioenriched **177j** in 83% yield and 59% ee. By contrast, silylated **211** furnishes racemic **177k** under similar conditions. With this same silylated **211**, Trost reported formation of silylated **177k** in 96% yield and 64% ee on

treatment with Pd(0), and Trost ligand **195** in dioxane.[15c] Studies are underway to identify the origins of these variations.

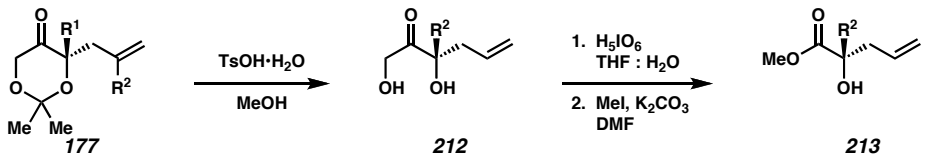
Scheme 4.5.1 Alkylation reactions of substrates with exocyclic α-oxygenation



4.6 Elaboration of Enantioenriched Dioxanones to C(α)-Tetrasubstituted Hydroxyketones, Acids, and Esters[i]

Having established a general route to enantioenriched tetrasubstituted dioxanones **177**, we have developed a straightforward sequence to transform these α-alkoxyketones into the corresponding α-hydroxyesters **213** (Table 4.6.1). To effect acetonide cleavage, enantioenriched products **177** are treated with catalytic *p*-toluenesulfonic acid in methanol or ethanol. Dihydroxyketones **212** are oxidatively cleaved in the presence of periodic acid, selectively removing the primary alcohol,[31] to generate α-hydroxyacids. Subsequent methylation furnishes tetrasubstituted enantioenriched α-hydroxyesters **213**. These operations are tolerant of a number of substitutents including alkyl (entries 1–4), chloro (entry 5), and benzyl (entries 3 and 6) groups. Furthermore, dioxanone derivatives may include enolizable α,β-unsaturated esters (entry 7), or be incorporated into cyclic structures (entries 8 and 9).

Table 4.6.1 Substrate scope for methyl ester formation



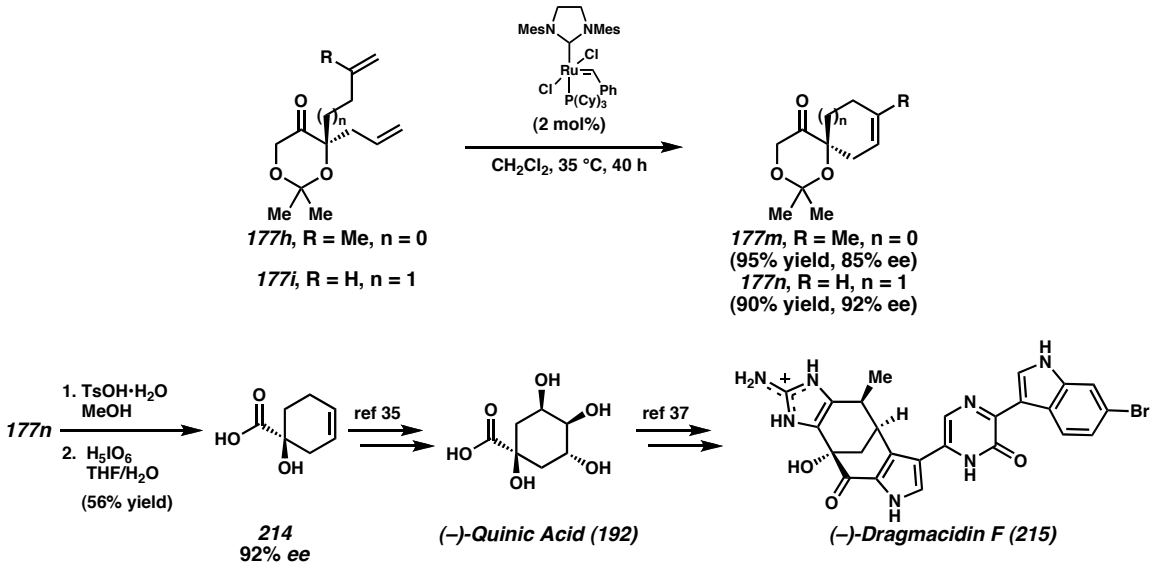
entry	substrate[a]	% yield[c,d] of *212*	% yield[c,d] of *213*
1	*177a*, R^2 = H	90	54
2[b]	*177b*, R^2 = Cl	97	76
3[d,e]	*177c*, R^2 = Me	97	84
4[h]	*177d*, R^2 = Ph	92	77
5	*177e*, R = Me	97	60
6[e]	*177f*, R = Ph	91	85
7[i]	*(177l)*	80	51
8	*(177m)*	–	48[f]
9[g]	*(177n)*	–	61[f]

[a] Acetonides **177** (1.0 equiv) were cleaved with TsOH•H_2O (0.1 equiv) in MeOH (0.1 M) over 2–3 h unless otherwise noted. Diols **212** were oxidized with H_5IO_6 (1.5 equiv) in 2:1 THF:H_2O (0.033 M) unless otherwise noted. [b] Absolute stereochemistry has been assigned by analogy, except in this case, which was assigned by conversion to (+)-(*S*)-citramalic acid dimethyl ester. [c] Isolated yields. [d] There is no measurable change of *ee* through this sequence. [e] Acetonide cleavage was performed in EtOH over 6 h. [f] Three step yield. [g] Oxidation performed with H_5IO_6 (1.0 equiv). [h] Direct treatment with H_5IO_6, and methylation provided the ester in 47% yield over two steps. [i] See the appendices for a description of the preparation of **177l** from **177a** via cross-metathesis. TsOH = *p*-toluenesulfonic acid.

Notably, assembly of acid (*S*)-**214** constitutes a catalytic enantioselective formal synthesis of (–)-quinic acid (**192**),[32] a useful chiral building block that has been employed in numerous syntheses,[33] including our recent synthesis of dragmacidin F (**215**).[34] Toward this end, we recognize that enantioenriched α,ω-dienes can be transformed into cycloalkenes with a stereocenter remote to the olefin (Scheme 4.6.1).[35] Chiral diene **177h** undergoes ring closing metathesis to generate 3-methylcyclopentene **177m** in 95% yield and 85% *ee*. Likewise, enantioenriched α,ω-diene **177i** furnishes cyclohexene **177n** in 90% yield and 92% *ee*. Cyclohexene **177n** readily undergoes acetonide cleavage and

periodic acid oxidation to provide clean, isolable carboxylic acid (*S*)-**214**, completing the formal synthesis of (–)-quinic acid (**192**).

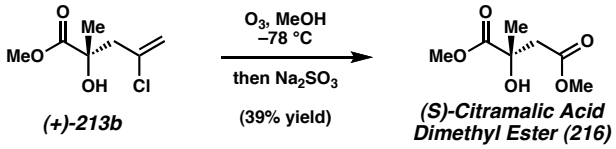
Scheme 4.6.1 Formal synthesis of (–)-quinic acid (**192**) and (–)-dragmacidin F (**215**)



4.7 Determination of the Absolute Stereochemistry of Dioxanone Products

To determine the absolute stereochemistry of products in this transformation, chlorinated **213b** has been converted to known citramalic acid dimethyl ester (**216**) by ozonolysis. The rotation of citramalic acid dimethyl ester (**216**) has been correlated with literature data to establish the absolute configuration as *S*.[36]

Scheme 4.7.1 Determination of the absolute stereochemistry of dioxanone products

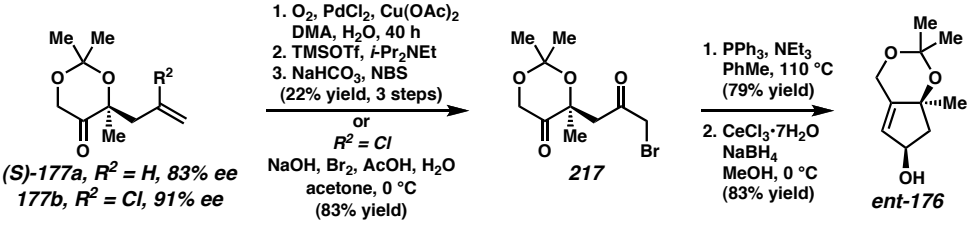


4.8 Elaboration of Enantioenriched Dioxanones toward Ineleganolide

We have converted ketone **177a** to cyclopentenol ent-**176** (Scheme 4.8.1). Low yields and decomposition plague processing of (*S*)-**177a** by Wacker oxidation and Aldol

ring closure or Wittig olefination. Thus, we have elected to use an allyl transfer unit in a higher oxidation state. Chloro olefin **177b** can be converted to alcohol ent-**176** by mild oxidation to α-bromoketone **217,** Wittig olefination, and Luche reduction.

Scheme 4.8.1 Advancing enantioenriched **177** to cyclopentenol **176**.



4.9 Concluding Remarks

In summary, we have developed a palladium-catalyzed asymmetric alkylation of simple dioxanone derivatives, and transformed the enantioenriched products into useful α-hydroxyketones, acids, and esters. This mild, straightforward sequence proceeds in high yield and enantioselectivity. This procedure has also enabled a catalytic enantioselective formal synthesis of (–)-quinic acid and the cyclopentenone precursor to ineleganolide. Research is underway to extend this chemistry to other α-oxygen- and nitrogen-containing carbonyl derivatives and to extend these methods to substrates with exocyclic heteroatoms.

4.10 Experimental Section

4.10.1 Materials and Methods

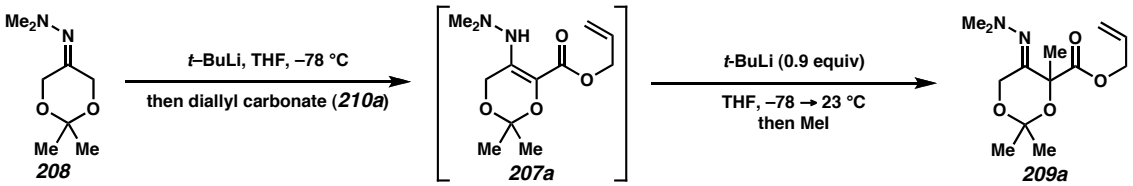
Unless otherwise stated, reactions were performed in flame-dried glassware under an argon atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Tetrabutylammonium triphenyldifluorosilicate (TBAT) was purchased from Sigma-Aldrich Chemical Company

and azeotropically dried five times from acetonitrile prior to use. Trimethylsilyl chloride (TMSCl), pyridine, and triethylamine (NEt_3) were distilled from sodium hydride immediately prior to use. Sodium iodide was dried by heating at 90 °C (2 torr) for 12 h. Bis(3,5,3',5'-dimethoxydibenzylideneacetone)palladium(0) ($Pd(dmdba)_2$) was purchased from Sigma-Aldrich Chemical Company and stored in a glove box prior to use. (*S*)-*t*-Bu-PHOX was prepared by known methods.[22] Cyclohexylamine, alkyl halides, triethylsilyl chloride, and diallyl carbonate were used without further purification. Molecular sieves were purchased from Sigma-Aldrich Chemical Company as activated 5 μm powder and stored in a 120 °C drying oven until immediately prior to use unless otherwise noted. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, anisaldehyde, or CAM staining. Florisil® (100–200 mesh) and ICN Silica gel (particle size 0.032–0.063 mm) were used for flash chromatography. Chiral HPLC analysis was performed with an Agilent 1100 Series HPLC utilizing chiralpak AD or chiralcel OD-H columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 254 nm or 220 nm. Chiral GC anaylsis was performed with an Agilent 6850 GC utilizing a G-TA (30 m x 0.25 cm) column (1.0 mL/min carrier gas flow). Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 NMR spectrometer (at 300 MHz and 75 MHz respectively), and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Data for ^{13}C NMR spectra are reported in terms of chemical shift relative to Me_4Si (δ 0.0). IR spectra

were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in wavenumbers (cm^{-1}). High resolution mass spectra were obtained from the Caltech Mass Spectrometry Facility.

4.10.2 Preparative Procedures

4.10.2. 1 Preparation of β-ketoesters



Allyl 5-(2,2-dimethylhydrazono)-2,2,4-trimethyl-1,3-dioxane-4-carboxylate (**209a**). A flask was charged with a clear solution of hydrazone **208**[37] (7.440 g, 43.2 mmol, 1 equiv) in THF (172 mL, 0.25 M) beneath N_2(g) at –78 °C (*i*PrOH, dry ice bath). The solution was treated dropwise with *t*-BuLi (1.7 M in pentane, 28 mL, 47.6 mmol, 1.1 equiv) over 40 min, and then allowed to stir for 6 min. The deep yellow mixture was treated dropwise with diallyl carbonate (5.3 mL, 36.9 mmol, 0.85 equiv) over 7 min. After stirring for an additional 46 min, the yellow solution was treated dropwise with *t*-BuLi (1.7 M in pentane, 22 mL, 37.4 mmol, 0.87 equiv) over 22 min, and then allowed to stir for 6 min. The yellow solution was treated dropwise with diallyl carbonate (4 mL, 27.9 mmol, 0.65 equiv) over 4 min. It was allowed to gradually warm to room temperature (ca. 24 °C) over several hours. Seventeen hours after diallyl carbonate addition, the reaction was

quenched by addition of phosphate buffer[ii] (ca. 120 mL) until the aqueous layer reached a pH of 8, and was then extracted with Et_2O (to 600 mL over several extractions). Each extract was sequentially rinsed with 1N HCl (28 mL, to a pH of 3), phosphate buffer (ca. 20 mL, to a pH of 7), and brine (ca. 20 mL). Extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to a yellow oil. The oil was purified through silica gel chromatography (ca. 600 mL of SiO_2 on a column with 5 cm diameter; eluent 1:5 Et_2O:hexanes). Mixed fractions were further purified by silica gel chromatography (eluent 1:7 Et_2O:hexanes) to give β-hydrazone ester **207a** as a yellow semi-solid (7.56 g, 68.3% yield).

A flask was charged with a yellow solution of β-hydrazone ester **207a** (7.56 g, 29.5 mmol, 1 equiv) in THF (118 mL, 0.25 M), and cooled to –78 °C (*i*-PrOH, dry ice bath) beneath N_2(g). The yellow solution was treated dropwise with *t*-BuLi (1.7 M in pentane, 15.6 mL, 26.5 mmol, 0.9 equiv). The reaction was allowed to gradually warm to room temperature (ca. 24 °C) over 9 h, after which point it was re-cooled to –78 °C. The cool solution was treated dropwise with MeI (9.2 mL, 147 mmol, 5.0 equiv) over 12 min, before gradually warming to room temperature (ca. 24 °C). After 5 h of stirring at this temperature, the reaction was quenched with phosphate buffer (ca. 40 mL) and saturated aq NH_4Cl (ca. 30 mL). The mixture was extracted with Et_2O (to 400 mL). Extracts were further rinsed with brine (ca. 25 mL), dried over $MgSO_4$, filtered, and concentrated under

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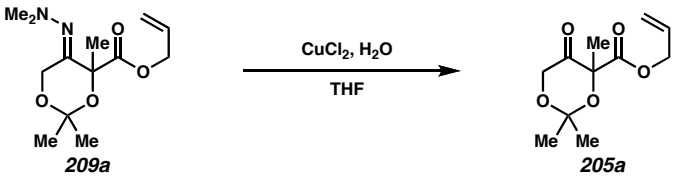
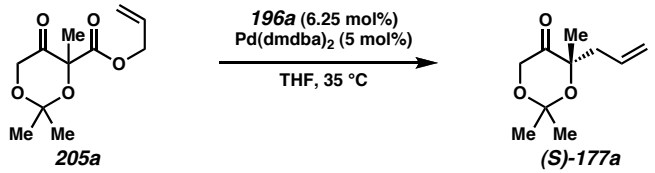
[ii] Phosphate buffer was prepared as a 500 mL solution in water through addition of sodium phosphate dibasic hydrate (87.981 g, 328.2 mmol, 1.000 equiv) and sodium phosphate monobasic hydrate (73.614 g, 533.4 mmol, 1.625 equiv).

reduced pressure to give a yellow oil. The oil was purified by silica gel chromatography silica gel chromatography (ca. 600 mL of SiO_2 on a column with 5 cm diameter; eluent 1:5 Et_2O:hexanes). Mixed fractions were further purified by silica gel chromatography (eluent 1:7 Et_2O:hexanes) to give methylated **209a** as a yellow semi-solid (6.18 g, 77.5% yield). R_f 0.57 (50% Et_2O in hexanes; visualized with anisaldehyde); ^1H NMR (300 MHz, $CDCl_3$) δ 5.90 (ddt, J = 17.2, 10.4, 5.7, 1H), 5.33 (dq, J = 17.2, 1.5, 1H), 5.22 (dq, J = 10.4, 1.3, 1H), 4.72 (d, J = 17.0, 1H), 4.62 (dtt, J = 8.5, 5.7, 1.4, 2H), 4.44 (d, J = 17.0, 1H), 2.47 (s, 6H), 1.52 (s, 3H), 1.47 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.21, 163.24, 131.80, 118.76, 101.29, 76.88, 66.13, 61.33, 47.24, 28.30, 25.14, 21.77; IR (NaCl) 2990, 2955, 2862, 2824, 2980, 1757, 1731, 1444, 1383, 1372, 1270, 1230, 1210, 1178, 1135, 1114, 1103, 1062, 996, 931, 848, 798; HRMS (EI+) *m/z* calc'd for $C_{13}H_{22}O_4N_2$ $[M+]^+$: 270.1580, found 270.1577.

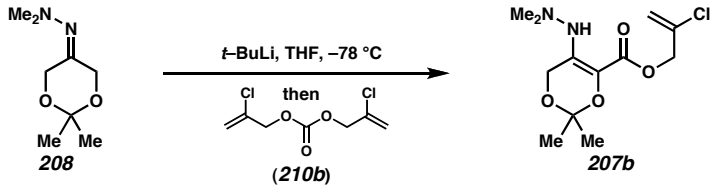


Allyl 2,2,4-trimethyl-5-oxo-1,3-dioxane-4-carboxylate (**205a**). A flask was charged with hydrazone **209a** (28.0 mg, 0.103 mmol, 1 equiv) in THF (1 mL, 0.1 M) at room temperature (ca. 24 °C). The yellow solution was treated with a 1M solution of $CuCl_2$ in H_2O (0.12 mL, 0.12 mmol, 1.2 equiv). After 7 h and 13 m, the yellow solution was treated with NH_4OH (5 drops). The resultant blue solution was extracted with Et_2O (8 mL x 3), rinsed with brine (ca. 1 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give ketone **205a** (23.6 mg, 95% yield) as a crude yellow oil. The yellow oil could be further purified through SiO_2 chromatography with Et_2O in hexanes

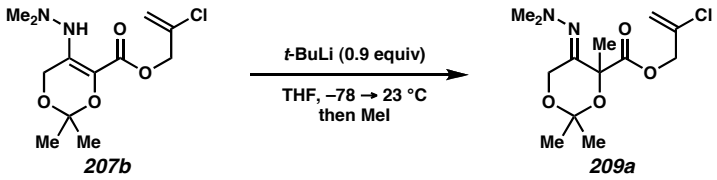
to furnish ketone **205a** as a colorless oil. R_f 0.63 (50% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.88 (ddd, J = 16.3, 11.0, 5.8, 1H), 5.32 (dd, J = 17.2, 1.5, 1H), 5.24 (dd, J = 10.4, 1.2, 1H), 4.68 (ddd, J = 7.3, 5.6, 3.6, 1H), 4.64–4.59 (m, 1H), 4.31 (d, J = 18.3, 1H), 4.26 (d, J = 18.4, 1H), 1.54 (s, 3H), 1.45 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.63, 170.28, 131.25, 119.36, 102.54, 80.21, 66.70, 66.41, 27.71, 24.60, 19.94; IR (NaCl) 2994, 2943, 1748, 1728, 1445, 1423, 1386, 1375, 1276, 1232, 1210, 1178, 1136, 1117, 1094, 1070, 996, 932, 838; HRMS (EI+) *m/z* calc'd for $C_{11}H_{16}O_5$ $[M+H]^+$: 229.1071, found 229.1071.



(*S*)-4-Allyl-2,2,4-trimethyl-1,3-dioxan-5-one (177a). A mixture of (*S*)-*t*-BuPHOX **196a** (18.5 mg, 0.048 mmol, 0.0625 equiv) and Bis(3,5,3',5'-dimethoxy-dibenzylideneacetone) palladium (0) (31 mg, 0.038 mmol, 0.05 equiv) was evacuated and backfilled with Ar(g). The mixture was solvated with freshly distilled Et_2O (23 mL, 0.033 M) and warmed for 30 minutes at 30 °C. The red/brown mixture was treated with β-ketoester **205a** (0.150 g, 0.76 mmol, 1 equiv) in Et_2O (0.2 mL x 2). After 15 hours, the reaction was concentrated under reduced pressure (>150 torr). The pale yellow solution was purified by silica gel chromatographed (SiO_2 (approx. 30 mL), 1:3 CH_2Cl_2:pentane, then 1:1 CH_2Cl_2:pentane eluent) to give enantioenriched **177a** as a colorless oil (96 mg, 68% yield, 83% ee). See below for characterization.

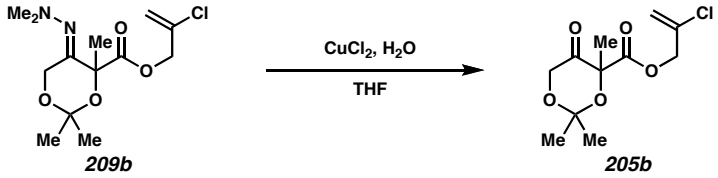


2-Chloroallyl 5-(2,2-dimethylhydrazinyl)-2,2-dimethyl-4*H*-1,3-dioxine-6-carboxylate (**207b**). For a representative procedure, see the conversion of hydrazone **208**[37] to β-hydrazone ester **207a**. 49.5% yield. Yellow solid; R_f 0.57 (50% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (s, 1H), 5.44 (dd, J = 3.2, 1.5, 1H), 5.36 (dt, J = 2.0, 1.0, 1H), 4.75–4.72 (m, 2H), 4.49 (s, 2H), 2.46 (s, 6H), 1.46 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 113.73, 65.00, 59.20, 49.02, 24.19; IR (NaCl) 2992, 2951, 2856, 2777, 1679, 1619, 1441, 1372, 1324, 1264, 1233, 1201, 1137, 1074, 1012, 958, 883, 812, 767; HRMS-MM: ESI–APCI *m/z* calc'd for $C_{12}H_{19}ClN_2O_4$ $[M+H]^+$: 290.1033, found 290.1030.

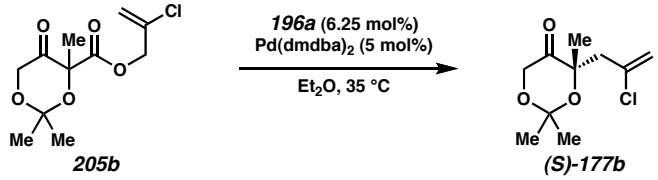


(*E*)-2-Chloroallyl 5-(2,2-dimethylhydrazono)-2,2,4-trimethyl-1,3-dioxane-4-carboxylate (**209b**). For a representative procedure, see the conversion of β-hydrazone ester **207a** to methylated **209a**. 73% yield. Yellow oil; R_f 0.65 (50% Et_2O in hexanes; stains yellow in anisaldehyde); ^1H NMR (300 MHz, C_6D_6) δ 5.08 (dd, J = 2.8, 1.2, 1H), 5.03 (d, J = 1.7, 1H), 4.77 (d, J = 16.9, 1H), 4.60 (d, J = 16.9, 1H), 4.52 (ddd, J = 13.6, 1.2, 0.6, 1H), 4.33 (ddd, J = 13.6, 1.1, 0.5, 1H), 2.35 (s, 6H), 1.82 (s, 3H), 1.61 (d, J = 0.6, 3H), 1.22 (d, J = 0.6, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 172.86, 163.45, 136.41, 115.76, 101.69, 77.53, 67.02, 61.88, 47.39, 28.78, 25.35, 22.34; IR (NaCl) 2991, 2956, 2962,

2942, 2824, 2780, 1761, 1739, 1639, 1468, 1444, 1383, 1373, 1267, 1230, 1209, 1134, 1100, 1062, 997, 930, 901, 845, 644, 530; HRMS (EI+) *m/z* calc'd for $C_{13}H_{21}ClN_2O_4$ $[M+H]^+$: 305.1263, found 305.1268.

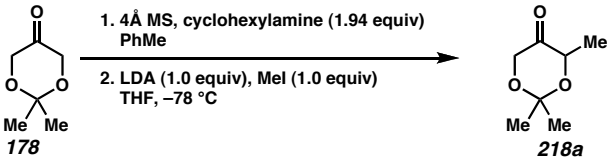


2-Chloroallyl 2,2,4-trimethyl-5-oxo-1,3-dioxane-4-carboxylate (**205b**). For a representative procedure, see the conversion of β-hydrazone ester **209a** to ketone **205a**. 94% yield. Yellow oil; R_f 0.67 (50% Et_2O in hexanes; stains blue in anisaldehyde); ^1H NMR (300 MHz, C_6D_6) δ 5.00 (d, J = 1.1, 2H), 4.41 (d, J = 13.5, 1H), 4.21 (d, J = 13.6, 1H), 4.14 (d, J = 18.3, 1H), 3.91 (dd, J = 18.3, 2.8, 1H), 1.55 (s, 6H), 1.04 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 202.75, 170.05, 135.77, 115.98, 102.80, 80.62, 66.94, 28.05, 24.52, 20.32; IR (NaCl) 2996, 2944, 1749, 1640, 1445, 1423, 1386, 1376, 1274, 1232, 1209, 1177, 1136, 1113, 1094, 1071, 998, 907, 838; HRMS (EI+) *m/z* calc'd for $C_{11}H_{15}ClO_5$ $[M+]^+$: 262.0608, found 262.0599.



(*S*)-4-(2-Chloroallyl)-2,2,4-trimethyl-1,3-dioxan-5-one (177b). For a representative procedure, see conversion of β-ketoester **205a** to enantioenriched **177a**. 97% yield, 91% ee. See below for characterization data.

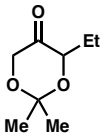
4.10.2. 2 Representative Procedure for Synthesis of 2,2-Dimethyl-1,3-dioxan-5-ones.



2,2,4-Trimethyl-1,3-dioxan-5-one (218a).[38] To a solution of 2,2-dimethyl-1,3-dioxan-5-one (**178**, 5.0 g, 38.4 mmol, 1.0 equiv)[39] in toluene (125 mL, 0.3 M) were added 4Å molecular sieves (5.0 g) and cyclohexylamine (8.50 mL, 74.3 mmol, 1.94 equiv) at room temperature (ca. 25 °C). The mixture was stirred for 14 h, before the molecular sieves were removed by filtration. The filtrate was concentrated under reduced pressure to give crude imine (7.95 g).

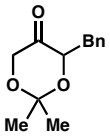
Lithium diisopropylamine was prepared in a separate flask by dropwise addition of *n*-BuLi (2.50 M in hexanes, 15.4 mL, 38.5 mmol, 1.0 equiv) via syringe to a solution of diisopropylamine (5.40 mL, 38.5 mmol, 1.0 equiv) in THF (60 mL, 0.64 M) at 0 °C. The solution was stirred at 0 °C for 10 min, and then cooled to –78 °C. A solution of the imine (7.95 g) in THF (40.0 mL) was added dropwise via syringe to the resulting LDA solution at –78 °C. The reaction mixture was warmed to –35 °C, and stirred for 2 h, after which it was re-cooled to –78 °C, and MeI (2.39 mL, 38.4 mmol, 1.0 equiv) was added. The reaction was warmed to room temperature (ca. 25 °C) over 3 h. Saturated aq NH_4Cl (60 mL) was added to the reaction mixture, and the mixture was stirred at room temperature overnight. The mixture was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and filtered. Solvent was removed under reduced pressure, and the residue was purified by flash chromatography (20% Et_2O in pentane on silica gel) to give 2,2,4-trimethyl-1,3-dioxane-

5-one (**218a**, 3.93 g, 71% yield) as a pale orange oil. R_f 0.72 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.37 (qd, *J* = 6.9, 1.5 Hz, 1H), 4.28 (dd, *J* = 17.1, 1.5 Hz, 1H), 4.01 (d, *J* = 17.1 Hz, 1 H), 1.47 (s, 3H), 1.43 (s, 3H), 1.31 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.2, 101.0, 71.1, 66.6, 24.1, 23.9, 14.3; IR (Neat Film NaCl) 2994, 2944, 1745, 1376, 1227, 1101 cm^{-1}; HRMS (EI+) *m*/*z* calc'd for $C_7H_{12}O_3$ $[M]^+$: 144.0786, found 144.0786.



218e

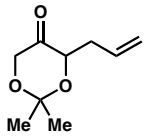
4-Ethyl-2,2-dimethyl-1,3-dioxan-5-one (**218e**).[38] 72% yield. Colorless oil; R_f 0.58 (20% Et_2O in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27 (dd, *J* = 17.0, 1.5 Hz, 1H), 4.17–4.13 (m, 1H), 3.98 (d, *J* = 17.0 Hz, 1H), 1.97–1.83 (m, 1H), 1.66–1.51 (m, 1H), 1.46 (s, 3H), 1.44 (s, 3H), 0.98 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.9, 100.9, 76.0, 66.9, 24.2, 23.7, 22.0, 9.7; IR (Neat Film NaCl) 2986, 2940, 2881, 1749, 1376, 1225, 1165, 1115, 1077, 1011, 867 cm^{-1}; HRMS (EI+) *m*/*z* calc'd for $C_8H_{14}O_3$ $[M]^+$: 158.0943, found 158.0939.



218f

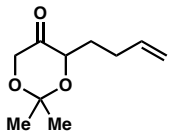
4-Benzyl-2,2-dimethyl-1,3-dioxan-5-one (**218f**).[40] 73% yield. Yellow oil; R_f 0.54 (20% Et_2O in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.16 (m, 5H), 4.46 (ddd, *J* = 9.3, 3.3, 1.8 Hz, 1H), 4.26 (dd, *J* = 17.1, 1.8 Hz, 1H), 4.01 (d, *J* = 17.1 Hz, 1H), 3.24 (dd, *J* = 15.0, 3.3 Hz, 1H), 2.79 (dd, *J* = 15.0, 9.3 Hz, 1H), 1.43 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.1, 137.9, 129.4, 128.4, 126.6, 101.2, 75.8, 66.8, 34.6, 24.1, 23.7;

IR (Neat Film NaCl) 3030, 2988, 2938, 2884, 1747, 1498, 1454, 1375, 1252, 1223, 1173, 1101, 1062, 748, 700 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{16}O_3$ $[M]^+$: 220.1100, found 220.1092.



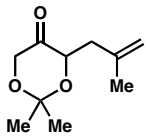
(±)-177g

4-Allyl-2,2-dimethyl-1,3-dioxan-5-one ((±)-**177g**).[28d, 41] 65% yield. Colorless oil; R_f 0.43 (10% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.92–5.78 (m, 1H), 5.20–5.08 (m, 2H), 4.33–4.24 (m, 2H), 4.01 (d, *J* = 16.8 Hz, 1H), 2.69–2.60 (m, 1H), 2.38-2.27 (m, 1H), 1.47 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.2, 133.6, 117.7, 101.1, 74.6, 66.8, 32.9, 24.1, 23.8; IR (Neat Film NaCl) 2989, 1749, 1376, 1254, 1224, 1177, 1162, 1103 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_9H_{14}O_3$ $[M]^+$: 170.0943, found 170.0951.



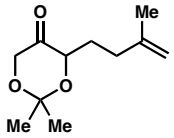
218i

4-(But-3-enyl)-2,2-dimethyl-1,3-dioxan-5-one (**218i**).[42] 53% yield. Colorless oil; R_f 0.38 (20% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.85–5.72 (m, 1H), 5.09–4.98 (m, 2H), 4.29–4.21 (m, 2H), 3.98 (d, *J* = 16.8 Hz, 1H), 2.30–2.08 (m, 2H), 2.03–1.92 (m, 1H), 1.70–1.58 (m, 1H), 1.45 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.0, 137.7, 115.8, 101.0, 73.8, 66.8, 29.3, 27.6, 24.1, 23.9; IR (Neat Film NaCl) 2988, 2938, 2884, 1748, 1642, 1434, 1376, 1251, 1225, 1175, 1103, 1071, 916, 864 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{10}H_{16}O_3$ $[M]^+$: 184.1100, found 184.1131.



218l

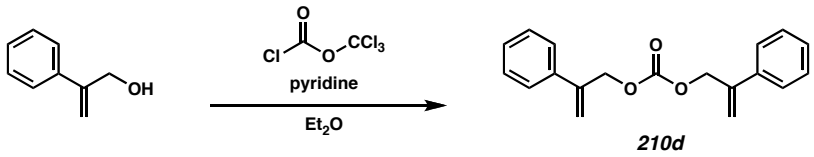
2,2-Dimethyl-4-(2-methylallyl)-1,3-dioxan-5-one (**218l**). 66% yield. Pale orange oil; R_f 0.56 (20% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 4.83 (s, 1H), 4.81 (s, 1H), 4.42 (ddd, *J* = 9.6, 3.0, 1.2 Hz, 1H), 4.29 (dd, *J* = 17.1, 1.8 Hz, 1H), 4.01 (d, *J* = 17.1 Hz, 1H), 2.69 (app. dd, *J* = 15.6, 3.0 Hz, 1H), 2.20 (dd, *J* = 15.8, 9.6 Hz, 1H), 1.77 (s, 3H), 1.48 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.5, 141.6, 112.5, 101.1, 73.8, 66.7, 36.2, 24.1, 23.8, 23.0; IR (Neat Film NaCl) 3079, 2988, 2940, 1748, 1650, 1426, 1374, 1223, 1175, 1106, 1076, 1048, 1016, 899, 833 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{10}H_{16}O_3$ $[M]^+$: 184.1100, found 184.1101.



218o

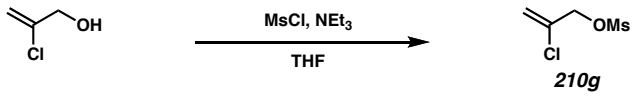
2,2-Dimethyl-4-(3-methylbut-3-enyl)-1,3-dioxan-5-one (218o). 52.6% yield. colorless oil; R_f 0.41 (20% Et_2O in hexanes); ^1H NMR (300 MHz, C_6D_6) δ 4.66–4.63 (m, 1H), 4.61 (dd, J = 2.1, 0.9, 1H), 4.16 (dd, J = 17.0, 1.4, 1H), 4.13–4.09 (m, 1H), 3.87 (d, J = 16.9, 1H), 2.08–1.93 (m, 2H), 1.92 (ddd, J = 9.2, 7.0, 3.6, 1H), 1.62 (s, 3H), 1.61–1.47 (m, 1H), 1.34 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.09, 144.79, 111.12, 101.02, 74.03, 66.82, 33.15, 26.41, 24.15, 23.88, 22.41; IR (NaCl) 3076, 2988, 2938, 1748, 1650, 1445, 1375, 1324, 1225, 1174, 1106, 1058, 1010, 890, 774; HRMS (EI+) *m/z* calc'd for $C_{11}H_{18}O_3$ $[M+H]^+$: 198.1256, found 198.1257.

4.10.2. 3 Syntheses of Allyl Sources



210d

Bis(2-phenylallyl) carbonate (**210d**). To a solution of 2-phenylallyl alcohol[43] (2.0 g, 14.9 mmol, 1.0 equiv) and pyridine (1.2 mL, 14.9 mmol, 1.0 equiv) in Et_2O (11 mL, 1.35 M) was added dropwise diphosgene (0.45 mL, 3.73 mmol, 0.25 equiv) via syringe at 0 °C over 20 min. The mixture was stirred at room temperature (ca. 25 °C) for 20 h. The white solid was removed by filtration, and the filter cake was washed with Et_2O. The filtrate was washed with aqueous $CuSO_4$ (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (10% EtOAc in hexanes on silica gel) to give carbonate (1.26 g, 57% yield) as a colorless oil. R_f 0.61 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.23 (m, 10H), 5.55 (s, 2H), 5.38 (s, 2H), 5.04 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 142.2, 138.0, 128.7, 128.4, 126.2, 115.9, 69.4; IR (Neat Film NaCl) 3058, 1747, 1496, 1448, 1395, 1254, 970, 912, 778, 706 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{19}H_{18}O_3$ $[M]^+$: 294.1256, found 294.1250.



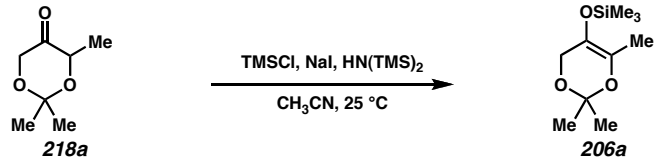
210g

2-Chloroallyl mesylate (**210g**). A flask was charged with 2-chloroallyl alcohol (1.0 g, 10.8 mmol, 1 equiv), THF (20 mL, 0.54 M), and NEt_3 (3.0 mL, 21.5 mmol, 2 equiv) at 0 °C (ice water bath). The solution was treated dropwise with mesyl chloride (1.26 mL, 16.2 mmol, 1.5 equiv). After 2 h at 0 °C, the reaction was quenched by addition of $NaHCO_3$, and the mixture was extracted with Et_2O. The organic layer was washed

successively with 1N HCl (20 mL), aq $NaHCO_3$ (20 mL), and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2 (ca. 50 g) with 1:4 EtOAc:hexanes as the eluent) to provide a colorless oil (1.716 g, 93% yield). R_f 0.34 (1:2 EtOAc:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (d, 1H, J = 0.5 Hz), 5.55 (d, 1H, J = 0.5 Hz), 4.77 (s, 2H), 3.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.27, 117.94, 77.65, 77.23, 76.81, 71.08, 38.61; IR (thin film/NaCl) 3652, 3570, 3267, 3119, 3033, 2943, 2523, 2310, 2089, 1832, 1639, 1454, 1415, 1360, 1175, 1010, 595, 923, 830, 757 cm^{-1}; HRMS–EI *m/z* calc'd for $C_4H_7O_3SCl$ $[M+\bullet]^+$: 169.9804, found 169.9811.

4.10.2. 4 Synthesis of Silyl Enol Ethers

Representative Procedure for the Synthesis of Trimethylsilyl Enol Ethers.

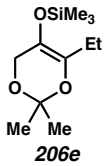


218a *206a*

2,2,4-Trimethyl-5-trimethylsilyloxy-1,3-diox-4-ene (**206a**).

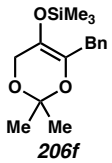
To a solution of 2,2,2-trimethyl-1,3-dioxan-5-one (**218a**, 1.0 g, 6.94 mmol, 1.0 equiv), hexamethyldisilazane (1.75 mL, 13.4 mmol, 1.9 equiv), and sodium iodide (1.17 g, 7.81 mmol, 1.1 equiv) in acetonitrile (10.0 mL, 0.7 M) was added TMSCl (1.0 mL, 7.82 mmol, 1.1 equiv) at room temperature (ca. 25 °C). After the mixture was stirred at room temperature for 16 h, it was diluted with pentane (20 mL). The mixture was stirred at room temperature for 2 min, and then the pentane was decanted. After additional pentane extractions (5 x 10 mL), the combined pentane extracts were washed with water (3 x 30

mL) and brine (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (2% Et_2O in pentane on Florisil®) to give 2,2,4-Trimethyl-5-trimethylsilyloxy-1,3-diox-4-ene (**206a**, 0.481 g, 32% yield) as a colorless oil. R_f 0.25 (10% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 4.04 (q, J = 1.8 Hz, 2H), 1.76 (t, J = 1.8 Hz, 3H), 1.45 (s, 6H), 0.20 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.9, 125.5, 98.3, 61.1, 24.2, 14.2, 0.8; IR (Neat Film NaCl) 2995, 2958, 2939, 1384, 1370, 1276, 1254, 1224, 1151, 1120, 1072, 893, 846 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_7H_{11}O_3$ $[M\text{-}C_3H_9Si]^+$: 143.0708, found 143.0718.



206e

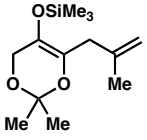
2,2-Dimethyl-4-ethyl-5-trimethylsilyloxy-1,3-diox-4-ene (**206e**). 35% yield. Colorless oil; R_f 0.52 (20% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 4.03 (app. t, J = 1.2 Hz, 2H), 2.16 (q, J = 7.4 Hz, 2H), 1.43 (s, 6H), 1.00 (t, J = 7.4 Hz, 3H), 0.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.5, 124.7, 98.1, 61.1, 24.2, 20.8, 11.1, 0.7; IR (Neat Film NaCl) 2964, 1384, 1369, 1276, 1254, 1223, 1199, 1148, 1122, 1079, 1035, 894, 867, 844, 752 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_8H_{13}O_3$ $[M\text{-}C_3H_9Si]^+$: 157.0865, found 157.0749.



206f

2,2-Dimethyl-4-benzyl-5-trimethylsilyloxy-1,3-diox-4-ene (**206f**). 16% yield. Colorless oil; R_f 0.44 (10% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.12 (m, 5H), 4.09 (t, J = 1.2 Hz, 2H), 3.47 (app. s, 2H), 1.35 (s, 6H), 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 136.9, 128.9, 128.3, 126.4, 126.2, 98.4, 61.1, 34.0, 24.1, 0.9; IR (Neat

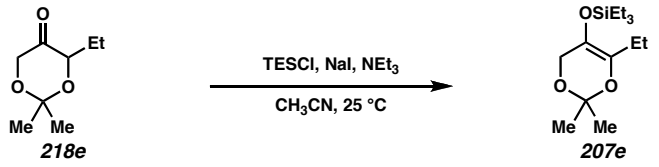
Film NaCl) 3029, 2994, 2957, 2837, 1748, 1603, 1495, 1454, 1382, 1370, 1276, 1253, 1230, 1199, 1144, 1093, 888, 845 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{16}H_{24}O_3Si$ $[M]^+$: 292.1495, found 292.1482.



206h

2,2-Dimethyl-4-(2-methylallyl)-5-trimethylsilyloxy-1,3-diox-4-ene (**206h**). 32% yield. Colorless oil; R_f 0.46 (50% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 4.78 (s, 1H), 4.78 (s, 1H), 4.07 (t, *J* = 1.1 Hz, 2H), 2.86 (s, 2H), 1.73 (s, 3H), 1.44 (s, 6H), 0.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.5, 136.0, 126.6, 111.7, 98.3, 61.1, 36.2, 24.2, 22.7, 0.8; IR (Neat Film NaCl) 3077, 2994, 2902, 2838, 1749, 1653, 1454, 1382, 1370, 1276, 1253, 1229, 1198, 1146, 1096, 891, 846 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{24}O_3Si$ $[M]^+$: 256.1495, found 256.1500.

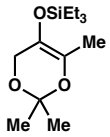
Representative Procedure for the Synthesis of Triethylsilyl Enol Ethers.



218e *207e*

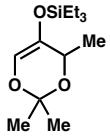
4-Ethyl-2,2-dimethyl-5-triethylsilyloxy-1,3-diox-4-ene (**207e**). To a solution of 4-ethyl-2,2-dimethyl-1,3-dioxane-5-one (0.50 g, 3.16 mmol, 1.0 equiv), Et_3N (0.71 mL, 5.09 mmol, 1.6 equiv) and sodium iodide (0.62 g, 4.14 mmol, 1.3 equiv) in acetonitrile (5.0 mL, 0.63 M) was added triethylsilyl chloride (0.69 mL, 4.11 mmol, 1.3 equiv) at room temperature (ca. 25 °C). After the mixture was stirred for 20 h, pentane (10 mL) was added. The mixture was stirred at room temperature for 2 min, before the pentane was decanted. After additional pentane extractions (5 x 10 mL), the combined pentane

extracts were washed with water (20 mL) and then with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (1% Et_2O in petroleum ether on silica gel) to give triethylsilyl enol ether **207e** (0.659 g, 77% yield) and 4-ethyl-2,2-dimethyl-5-triethylsilyloxy-1,3-diox-5-ene (70.6 mg, 8% yield).



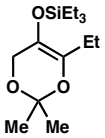
207a

4-Methyl-2,2-dimethyl-5-triethylsilyloxy-1,3-diox-4-ene (**207a**). 77% yield. Colorless oil; R_f 0.50 (10% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 4.04 (q, *J* = 1.9 Hz, 2H), 1.77 (t, *J* = 1.9 Hz, 3H), 1.43 (s, 6H), 0.98 (t, *J* = 8.1 Hz, 9H), 0.65 (q, *J* = 8.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.4, 125.6, 98.2, 61.2, 24.3, 14.0, 6.9, 5.5; IR (Neat Film NaCl) 2995, 2956, 2915, 2878, 1459, 1383, 1369, 1276, 1221, 1198, 1150, 1120, 1071, 1002, 873, 850, 729 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{26}O_3Si$ $[M]^+$: 258.1651, found 258.1642.



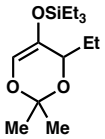
219a

Triethyl(2,2,4-trimethyl-4*H*-1,3-dioxin-5-yloxy)silane (219a). 6% yield. Colorless oil; R_f 0.55 (10% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 6.10 (d, *J* = 1.5 Hz), 4.23 (qd, *J* = 6.6, 1.5 Hz), 1.47 (s, 3H), 1.44 (s, 3H), 1.32 (d, *J* = 6.6 Hz, 3H), 0.98 (t, *J* = 7.8 Hz, 9H), 0.71-0.63 (m, 6H).



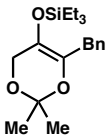
207e

4-Ethyl-2,2-dimethyl-5-triethylsilyloxy-1,3-diox-4-ene (207e). 77% yield. Colorless oil; R_f 0.53 (5% Et_2O in toluene); ^1H NMR (300 MHz, $CDCl_3$) δ 4.04 (t, *J* = 1.2 Hz, 2H), 2.19 (qt, *J* = 7.5, 1.2 Hz, 2H), 1.43 (s, 6H), 1.02–0.96 (m, 12H), 0.65 (q, *J* =7.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 124.8, 98.0, 61.1, 24.3, 20.7, 11.1, 6.9, 5.5; IR (Neat Film NaCl) 2958, 2878, 1383, 1369, 1276, 1221, 1198, 1147, 1121, 1079, 1012, 857, 745, 730 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_8H_{13}O_3Si$ $[M-C_6H_{15}]^+$: 185.0634, found 185.0639.



219e

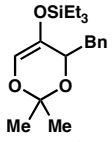
4-Ethyl-2,2-dimethyl-5-triethylsilyloxy-1,3-diox-5-ene (219e). 8% yield. Colorless oil; R_f 0.57 (5% Et_2O in toluene); ^1H NMR (300 MHz, $CDCl_3$) δ 6.14 (d, *J* = 1.5 Hz, 1H), 4.08 (ddd, *J* = 6.6, 3.6, 1.5 Hz, 1H), 1.87–1.72 (m, 1H), 1.69–1.55 (m, 1H), 1.46 (s, 3H), 1.43 (s, 3H), 1.01–0.92 (m, 12H), 0.70–0.62 (m, 6H).



207f

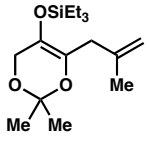
4-Benzyl-2,2-dimethyl-5-triethylsilyloxy-1,3-diox-4-ene (207f). 78% yield. Colorless oil; R_f 0.41 (10% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.31–7.12 (m, 5H), 4.10 (t, *J* = 1.2 Hz, 2H), 3.49 (s, 2H), 1.33 (s, 6H), 0.98 (t, *J* = 8.1 Hz, 9H), 0.66 (q, *J* = 8.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 136.5, 128.9, 128.3, 126.5, 126.1, 98.3,

61.2, 33.8, 24.1, 6.9, 5.7; IR (Neat Film NaCl) 2956, 2877, 1454, 1382, 1370, 1276, 1226, 1198, 1145, 1093, 1016, 867, 746, 729, 731, 696 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{19}H_{30}O_3Si$ $[M]^+$: 334.1964, found 334.1978.



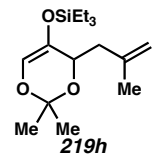
219f

Triethyl(4-benzyl-2,2-dimethyl-4*H*-1,3-dioxin-5-yloxy)silane (219f). 10% yield. Pale yellow oil; R_f 0.50 (10% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.15 (m, 5H), 6.13 (d, *J* = 1.2Hz, 1H), 4.31 (ddd, *J* = 8.4, 3.0, 1.2 Hz, 1H), 3.16 (dd, *J* = 14.4, 3.0 Hz, 1H), 2.80 (dd, *J* = 14.3, 8.4 Hz, 1H), 1.43 (s, 3H), 1.42 (s, 3H), 1.01 (t, *J* = 7.8 Hz, 9H), 0.69 (q, *J* = 7.8 Hz, 6H).



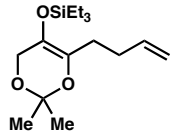
207h

2,2-Dimethyl-6-(2-methylallyl)-4*H*-1,3-dioxin-5-yloxy)triethylsilane (207h). 46% yield. Colorless oil; R_f 0.19 (10% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 4.78 (s, 2H), 4.08 (t, *J* = 1.1 Hz, 2H), 2.89 (s, 2H), 1.74 (s, 3H), 1.43 (s, 6H), 0.98 (t, *J* = 8.1 Hz, 9H), 0.65 (q, *J* = 8.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.5, 135.6, 126.7, 111.7, 98.3, 61.1, 36.0, 24.3, 22.7, 6.9, 5.6; IR (Neat Film NaCl) 2956, 2913, 2878, 1382, 1369, 1276, 1225, 1198, 1146, 1095, 1010, 851, 730 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{26}O_3Si$ $[M-H_2]^+$ 297.1886, found 297.1851.



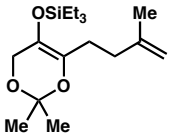
219h

(2,2-Dimethyl-4-(2-methylallyl)-4*H*-1,3-dioxin-5-yloxy)triethylsilane (219h). 15% yield. Colorless oil; R_f 0.27 (10% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 6.13 (d, *J* = 1.5 Hz, 1H), 4.82 (s, 1H), 4.80 (s, 1H), 4.25 (ddd, *J* = 9.0, 2.7, 1.5 Hz, 1H), 2.61–2.53 (m, 1H), 2.20 (dd, *J* = 14.7, 9.0 Hz, 1H), 1.79 (s, 3H), 1.46 (s, 3H), 1.43 (s, 3H), 0.98 (t, *J* = 7.8 Hz, 9H), 0.67 (q, *J* = 7.8 Hz, 6H).



207i

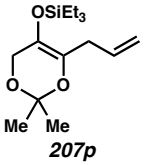
(6-(But-3-enyl)-2,2-dimethyl-4*H*-1,3-dioxin-5-yloxy)triethylsilane (207i). 66% yield. Colorless oil; R_f 0.58 (10% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.90–5.77 (m, 1H), 5.07–5.0 (m, 1H), 5.0–4.93 (m, 1H), 4.05 (s, 2H), 2.30–2.13 (m, 4H), 1.43 (s, 6H), 0.98 (t, *J* = 7.8 Hz, 9H), 0.65 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 137.2, 125.7, 114.8, 98.2, 61.1, 30.9, 27.0, 24.3, 6.9, 5.6; IR (Neat Film NaCl) 2995, 2957, 2914, 2878, 2838, 1383, 1369, 1277, 1223, 1198, 1147, 1085, 1006, 857, 745, 730 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{16}H_{30}O_3Si$ $[M]^+$: 298.1964, found 298.1967.



207o

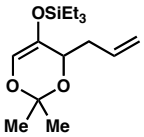
(2,2-Dimethyl-6-(3-methylbut-3-enyl)-4*H*-1,3-dioxin-5-yloxy)triethylsilane (207o). 65.4% yield. Colorless oil; R_f 0.69 (20% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 4.68 (d, J = 0.9, 2H), 4.03 (s, 2H), 2.28 (dd, J = 9.6, 6.4, 2H), 2.12 (dd, J = 9.7, 6.4, 2H), 1.72 (s, 3H), 1.40 (s, 6H), 0.96 (t, J = 7.9, 9H), 0.63 (q, J = 8.0, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.73, 137.43, 125.49, 110.04, 98.13, 61.13, 34.58, 26.03, 24.34, 22.72, 6.89, 5.57; IR (NaCl) 3075, 2994, 2958, 2914, 2879, 2837, 1650, 1458, 1383, 1370,

1277, 1223, 1199, 1146, 1100, 1069, 1016, 977, 949, 886, 858, 746, 730; HRMS (EI+) *m/z* calc'd for $C_{17}H_{33}O_3Si$ [M+H]$^+$: 313.2199, found 313.2198.



207p

4-Allyl-2,2-dimethyl-5-triethylsilyloxy-1,3-diox-4-ene (**207p**). 69% yield. Colorless oil; R_f 0.58 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87–5.73 (m, 1H), 5.15–5.01 (m, 2H), 4.06 (t, *J* = 1.2 Hz, 2H), 2.96–2.91 (m, 2H), 1.44 (s, 6H), 0.99 (t, *J* = 8.1 Hz, 9H), 0.66 (q, *J* = 8.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.8, 134.4, 126.0, 116.2, 98.3, 61.1, 32.1, 24.3, 6.9, 5.6; IR (Neat Film NaCl) 2995, 2957, 2913, 2879, 1639, 1458, 1414, 1382, 1370, 1278, 1241, 1196, 1147, 1084, 1016, 970, 909, 871, 851, 746, 731 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{15}H_{28}O_3Si$ [M]$^+$: 284.1808, found 284.1836.

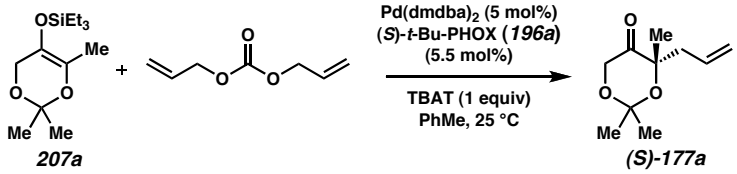


219p

(4-Allyl-2,2-dimethyl-4*H*-1,3-dioxin-5-yloxy)triethylsilane (219p). 10% yield. Pale yellow oil; R_f 0.65 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.14 (d, *J* = 1.2 Hz, 1H), 5.97–5.83 (m, 1H), 5.16–5.04 (m, 2H), 4.16 (ddd, *J* = 7.2, 3.3, 1.2 Hz, 1H), 2.61–2.49 (m, 1H), 2.40–2.27 (m, 1H), 1.46 (s, 3H), 1.43 (s, 3H), 0.98 (t, *J* = 7.8 Hz, 9H), 0.67 (q, *J* = 7.8 Hz, 6H).

4.10.2. 5 Asymmetric Alkylation Reaction

Representative Procedure for the Asymmetric Alkylation Reaction of Triethylsilyl Enol Ethers.

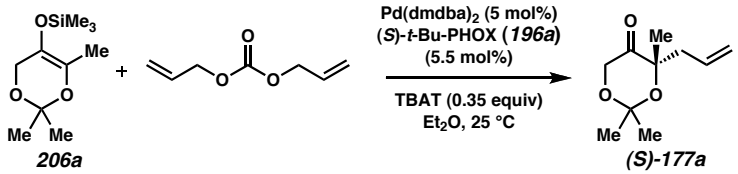


207a *(S)-177a*

(*S*)-4-Allyl-2,2,4-trimethyl-1,3-dioxan-5-one (177a). A 100 mL round-bottom flask was flame dried under vacuum and back-filled with argon. $Pd(dmdba)_2$ (20.3 mg, 0.025 mmol, 0.05 equiv), (*S*)-*t*-Bu-PHOX (10.6 mg, 0.027 mmol, 0.055 equiv), and TBAT (270 mg, 0.50 mmol, 1.0 equiv) were added to the flask. The system was evacuated under vacuum and backfilled with argon (3 x). Toluene (15 mL, 0.033 M) was added by syringe and the mixture was stirred at room temperature (ca. 25 °C) for 30 min. Diallyl carbonate (75.2 μL, 0.52 mmol, 1.05 equiv) and silyl ether **207a** (108 mg, 0.50 mmol, 1.0 equiv) were added sequentially. When the reaction was complete by TLC (after ca. 9 h),

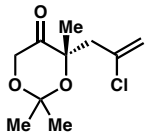
the reaction mixture was loaded onto a silica gel column and eluted with 2% Et_2O in petroleum ether to give tetrasubstituted **177a** (78.8 mg, 86% yield, 87% ee).

Representative Procedure for the Asymmetric Alkylation Reaction of Trimethylsilyl Enol Ethers.



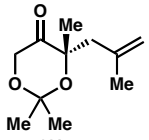
(*S*)-4-Allyl-2,2,4-trimethyl-1,3-dioxan-5-one (177a). A 100 mL round-bottom flask was flame-dried under vacuum and backfilled with argon. $Pd(dmdba)_2$ (20.3 mg, 0.025 mmol, 0.05 equiv), (*S*)-*t*-Bu-PHOX (10.6 mg, 0.027 mmol, 0.055 equiv), and TBAT (94.3 mg, 0.18 mmol, 0.35 equiv) were added to the flask. The system was evacuated under vacuum and backfilled with argon (x 3). Et_2O (30 mL) was added by syringe, and the mixture was stirred at room temperature (ca. 28 °C) for 30 min. Diallyl carbonate (75.2 μL, 0.52 mmol, 1.05 equiv) and silyl ether **206a** (108 mg, 0.50 mmol, 1.0 equiv) were added sequentially. When the reaction was complete by TLC (after ca. 5 h), the reaction mixture was filtered through silica gel, and eluted with 100% Et_2O. The filtrate was evaporated under reduced pressure (~60 mmHg), the residue was purified by flash chromatography (2% Et_2O in petroleum ether on silica gel) to give tetrasubstituted **177a** (76.2 mg, 83% yield, 90% ee) as a colorless oil. R_f 0.22 (20% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.90–5.76 (m, 1H), 5.13–5.04 (m, 2H), 4.21 (s, 2H), 2.57–2.50 (m, 1H), 2.45–2.37 (m, 1H), 1.49 (s, 3H), 1.48 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.9, 132.6, 119.0, 100.1, 82.2, 67.1, 43.6, 26.9, 26.7, 24.4; IR (Neat Film NaCl) 3079, 2989, 2942, 1742, 1641, 1429, 1382, 1373, 1229, 1203, 1180, 1161, 1143,

1080, 1007, 919 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{10}H_{18}O_3$ $[M]^+$: 184.1100, found 184.1096; $[\alpha]_D^{23.0}$ –68.6° (*c* 0.510, CH_2Cl_2, 90% ee); $[\alpha]_D^{27.5}$ –60.3° (*c* 0.845, CH_2Cl_2, 87% ee).



(S)-177b

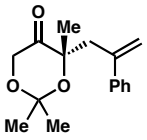
(*S*)-4-(2-Chloroallyl)-2,2,4-trimethyl-1,3-dioxan-5-one (177b). Colorless oil; R_f 0.50 (20% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.30 (d, *J* = 1.2 Hz, 1H), 5.22 (d, *J* = 0.6 Hz, 1H), 4.37 (d, *J* = 17.7 Hz, 1H), 4.21 (d, *J* = 17.9 Hz, 1H), 2.91 (d, *J* = 14.4 Hz, 1H), 2.73 (d, *J* = 14.4 Hz, 1H), 1.55 (s, 3H), 1.51 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.9, 137.1, 117.0, 100.5, 81.3, 67.1, 48.1, 27.4, 26.2, 25.1; IR (Neat Film NaCl) 2991, 2941, 2897, 1744, 1633, 1425, 1383, 1374, 1229, 1203, 1182, 1158, 1106, 1060, 1011, 891 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{16}H_{20}O_3$ $[M–CH_3]^+$: 203.0475, found 203.0484; $[\alpha]_D^{20.7}$ –89.7° (*c* 1.030, $CHCl_3$, 93% ee).



(S)-177c

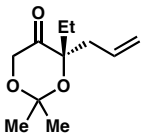
(*S*)-2,2,4-Trimethyl-4-(2-methylallyl)-1,3-dioxan-5-one (177c). Colorless oil; R_f 0.46 (20% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 4.88 (s, 1H), 4.72 (s, 1H), 4.27 (d, *J* = 17.9 Hz, 1H), 4.19 (d, *J* = 17.9 Hz, 1H), 2.50 (d, *J* = 13.7 Hz, 1H), 2.39 (d, *J* = 13.7 Hz, 1H), 1.81 (s, 3H), 1.51 (s, 3H), 1.48 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.1, 141.5, 115.4, 100.0, 83.0, 67.3, 46.8, 27.0, 26.6, 25.0, 24.6; IR (Neat Film NaCl) 2987, 2943, 2919, 1742, 1645, 1440, 1382, 1373, 1230, 1200, 1159, 1106, 1010, 896

cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{11}H_{18}O_3$ $[M]^+$: 198.1256, found 198.1263; $[\alpha]_D^{26.5}$ –87.7° (*c* 0.735, CH_2Cl_2, 89% ee).



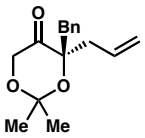
(S)-177d

(*S*)-2,2,4-Trimethyl-4-(2-phenylallyl)-1,3-dioxan-5-one (177d). Colorless oil; R_f 0.23 (5% Et_2O in toluene); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.19 (m, 5H), 5.33 (d, *J* = 1.5 Hz, 1H), 5.13 (s, 1H), 4.08 (d, *J* = 17.7 Hz, 1H), 3.95 (d, *J* = 17.7 Hz, 1H), 2.98 (s, 2H), 1.39 (s, 3H), 1.38 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.8, 144.5, 142.3, 128.1, 127.4, 127.0, 117.9, 99.9, 82.7, 67.3, 44.9, 26.5, 25.5; IR (Neat Film NaCl) 2988, 2940, 1742, 1626, 1495, 1444, 1382, 1372, 1229, 1198, 1158, 1117, 1010, 905, 778, 699 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{16}H_{20}O_3$ $[M]^+$: 260.1412, found 260.1417; $[\alpha]_D^{23.1}$ –45.9° (*c* 0.940, CH_2Cl_2, 94% ee).



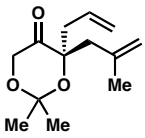
(S)-177e

(*S*)-4-Allyl-4-ethyl-2,2-dimethyl-1,3-dioxan-5-one (**177e**). Colorless oil; R_f 0.48 (20% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.89–5.70 (m, 1H), 5.14–5.02 (m, 2H), 4.17 (s, 2H), 2.60–2.39 (m, 2H), 1.91–1.64 (m, 2H), 1.49 (s, 3H), 1.48 (s, 3H), 0.88 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.8, 132.6, 118.9, 100.0, 85.2, 67.5, 41.4, 29.9, 27.0, 26.7, 7.7; IR (Neat Film NaCl) 3079, 2984, 2941, 2884, 1737, 1428, 1382, 1372, 1231, 1200, 1172, 1150, 1086, 1009, 918 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{11}H_{18}O_3$ $[M]^+$: 198.1256, found 198.1258; $[\alpha]_D^{24.4}$ –0.20° (*c* 0.575, CH_2Cl_2, 93% ee).



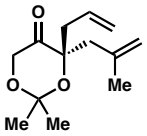
(R)-177f

(*R*)-4-Allyl-4-benzyl-2,2-dimethyl-1,3-dioxan-5-one (177f). Colorless oil; R_f 0.44 (20% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.29–7.18 (m, 5H), 5.97–5.83 (m, 1H), 5.17–5.10 (m, 2H), 4.05 (d, *J* = 18.0 Hz, 1H), 3.87 (d, *J* = 18.0 Hz, 1H), 3.08 (d, *J* = 13.5 Hz, 1H), 2.93 (d, *J* = 13.5 Hz, 1H), 2.63–2.45 (m, 2H), 1.50 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.0, 136.2, 132.4, 131.3, 128.0, 126.8, 119.3, 99.9, 85.5, 67.7, 43.2, 43.1, 27.7, 25.6; IR (Neat Film NaCl) 3077, 3031, 2990, 2939, 1736, 1496, 1454, 1426, 1382, 1372, 1231, 1196, 1102, 1052, 918 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{16}H_{20}O_3$ $[M]^+$: 260.1412, found 260.1417; $[\alpha]_D^{23.3}$ +21.4° (*c* 0.825, CH_2Cl_2, 86% ee); $[\alpha]_D^{24.2}$ +22.2° (*c* 1.055, CH_2Cl_2, 85% ee).



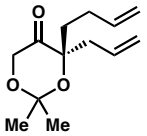
(R)-177h

(*R*)-4-Allyl-2,2-dimethyl-4-(2-methylallyl)-1,3-dioxan-5-one (177h). Colorless oil; R_f 0.55 (20% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.84 (dddd, *J* = 17.2, 10.2, 7.1, 7.1 Hz, 1H), 5.16–5.05 (m, 2H), 4.89 (ddd, *J* = 3.6, 1.5, 1.5 Hz, 1H), 4.74 (dd, *J* = 2.4, 0.9 Hz, 1H), 4.23 (d, *J* = 17.9 Hz, 1H), 4.15 (d, *J* = 17.9 Hz, 1H), 2.56–2.52 (m, 1H), 2.48–2.46 (dd, *J* = 4.8, 0.9 Hz, 2H), 1.81 (t, *J* = 1.2 Hz, 3H), 1.51 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.2, 141.4, 132.6, 119.1, 115.7, 99.9, 85.5, 67.9, 44.8, 42.5, 27.3, 26.3, 24.9; IR (Neat Film NaCl) 3078, 2986, 2944, 2919, 1740, 1642, 1427, 1383, 1372, 1231, 1197, 1159, 1001, 901 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{20}O_3$ $[M]^+$: 224.1412, found 224.1410; $[\alpha]_D^{23.3}$ +20.5° (*c* 0.515, CH_2Cl_2, 85% ee).



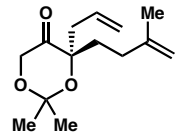
(S)-177h

(*S*)-4-Allyl-2,2-dimethyl-4-(2-methylallyl)-1,3-dioxan-5-one (*ent*-177h). Colorless oil; R_f 0.55 (20% Et_2O in hexanes); $[\alpha]_D^{26.6}$ –21.9° (*c* 0.620, CH_2Cl_2, 88% ee).



(S)-177i

(*S*)-4-Allyl-4-(but-3-enyl)-2,2-dimethyl-1,3-dioxan-5-one (177i). Colorless oil; R_f 0.33 (10% Et_2O in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86–5.70 (m, 2H), 5.11–4.92 (m, 4H), 4.19 (d, *J* = 18.0 Hz, 2H), 4.15 (d, *J* = 18.0 Hz, 2H), 2.60–2.45 (m, 2H), 2.27–1.95 (m, 2H), 1.93–1.69 (m, 2H), 1.51 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.5, 138.2, 132.4, 119.1, 115.0, 100.1, 84.5, 67.4, 41.9, 36.1, 27.7, 27.3, 26.5; IR (Neat Film NaCl) 3079, 2987, 2941, 1738 1642, 1427, 1382 1372, 1232, 1209, 1168, 1148, 1098, 998, 915 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{20}O_3$ $[M]^+$: 224.1412, found 224.1416; $[\alpha]_D^{20.2}$ +7.04° (*c* 1.030, CH_2Cl_2, 92% ee).



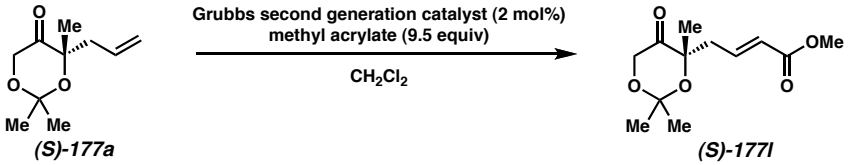
(S)-177o

(*S*)-4-Allyl-2,2-dimethyl-4-(3-methylbut-3-enyl)-1,3-dioxan-5-one (177o). Determination of ee was not carried out. 43.5% yield. Colorless oil; R_f 0.46 (10% Et_2O in PhH; stains brown in anisaldehyde); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (dddd, J = 17.6, 10.5, 7.2, 7.2, 1H), 5.12–5.09 (m, 1H), 5.08–5.02 (m, 1H), 4.67 (dd, J = 1.3, 0.7, 1H), 4.66–4.63 (m, 1H), 4.20 (d, J = 17.9, 1H), 4.13 (d, J = 17.9, 1H), 2.59–2.41 (m, 2H),

2.13–2.01 (m, 1H), 2.01–1.92 (m, 1H), 1.94–1.85 (m, 1H), 1.77 (ddd, J = 13.5, 11.8, 5.2, 1H), 1.69 (s, 3H), 1.48 (s, 3H), 1.47 (d, J = 0.4, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.52, 145.51, 132.46, 119.06, 110.27, 100.06, 84.58, 67.41, 41.81, 35.19, 31.30, 27.17, 26.62, 22.79; IR (NaCl) 3078, 2986, 2940, 1739, 1649, 1446, 1382, 1373, 1231, 1202, 1159, 1106, 1066, 1018, 999, 919, 890, 789; HRMS (EI+) *m/z* calc'd for $C_{14}H_{22}O_3$ $[M+H]^+$: 238.1569, found 238.1569.

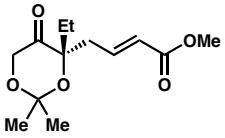
4.10.2. 6 Synthesis of of α,β-Unsaturated Esters by Cross Metathesis.

Representative Procedure for the Synthesis of α,β-Unsaturated Esters.



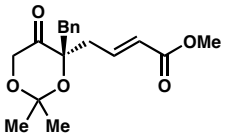
(*S,E*)-Methyl-4-(2,2,4-trimethyl-5-oxo-1,3-dioxan-4-yl)but-2-enoate (177l). To a solution of terminal olefin (***S***)-**177a** (30.0 mg, 0.163 mmol, 1 equiv) and methyl acrylate (0.14 mL, 1.55 mmol, 9.5 equiv) in CH_2Cl_2 (1.6 mL, 0.1 M) was added Grubbs second-generation catalyst (2.8 mg, 0.0033 mmol, 0.02 equiv) at room temperature (ca. 25°C). The mixture was stirred at 37 °C for 40 h. Ethyl vinyl ether (0.5 mL) was added, and it was stirred at 37 °C for 10 min. The mixture was filtered through silica gel with Et_2O/petroleum ether (1:2). After the filtrate was evaporated under reduced pressure (~60 mmHg), the residue was purified by flash column chromatography (10% Et_2O in petroleum ether on silica gel) to give α,β-unsaturated (***S***)-**177l** (32.8 mg, 83% yield) as a colorless oil. R_f 0.23 (20% Et_2O in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (ddd, *J* = 15.6, 7.8, 7.8 Hz, 1H), 5.87 (ddd, *J* = 15.6, 1.3, 1.3 Hz, 1H), 4.23 (s, 2H), 3.73 (s, 3H), 2.71–2.63 (m, 1H), 2.54–2.47 (m, 1H), 1.50 (s, 3H), 1.45 (s, 3H), 1.43 (s, 3H); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 210.1, 166.7, 143.1, 124.7, 100.5, 81.5, 66.8, 51.7, 41.3, 27.5, 26.2, 24.5; IR (Neat Film NaCl) 2992, 2951, 1727, 1659, 1437, 1374, 1338, 1274, 1231, 1197, 1180, 1155, 1117, 1008, 990 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{12}H_{19}O_5$ $[M+H]^+$: 243.1232, found 243.1224; $[\alpha]_D^{24.8}$ –49.7° (*c* 0.715, CH_2Cl_2, 90% ee).



(S)-177r

(*S,E*)-Methyl 4-(4-ethyl-2,2-dimethyl-5-oxo-1,3-dioxan-4-yl)but-2-enoate (177r). 89% yield. Colorless oil; R_f 0.19 (20% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 6.92 (ddd, *J* = 15.6, 7.6, 7.6 Hz, 1H), 5.88 (ddd, *J* = 15.6, 1.5, 1.5 Hz, 1H), 4.21 (s, 2H), 3.74 (s, 3H), 2.71–2.53 (m, 2H), 1.92–1.78 (m, 2H), 1.51 (s, 3H), 1.49 (s, 3H), 0.90 (t, *J* = 7.4 H, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.0, 166.7, 143.3, 124.6, 100.2, 84.6, 67.3, 51.7, 39.2, 30.4, 27.3, 26.4, 7.8; IR (Neat Film NaCl) 2985, 1726, 1658, 1435, 1383, 1373, 1271, 1232, 1196, 1177, 1084, 1033, 1013 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{21}O_5$ $[M+H]^+$: 257.1389, found 257.1385; $[\alpha]_D^{24.9}$ –3.14° (*c* 0.655, CH_2Cl_2, 94% ee).



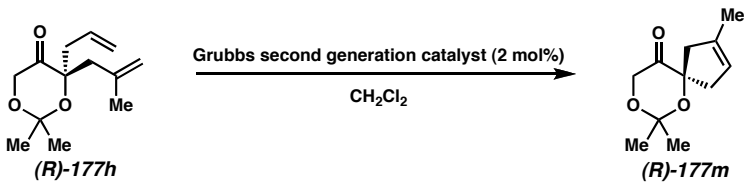
(R)-177s

(*R,E*)-Methyl 4-(4-benzyl-2,2-dimethyl-5-oxo-1,3-dioxan-4-yl)but-2-enoate (177s). 75% yield. Colorless oil; R_f 0.19 (20% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.31-7.13 (m, 5H), 7.00 (ddd, *J* = 15.6, 8.1, 7.2 Hz, 1H), 5.89 (ddd, *J* = 15.9, 1.5, 1.5 Hz, 1H), 4.06 (d, *J* = 18.0 Hz, 1H), 3.86 (d, *J* = 18.0 Hz, 1H), 3.74 (s, 3H), 3.06 (d, *J* = 13.5 Hz, 1H), 2.94 (d, *J* = 13.5 Hz, 1H), 2.72 (ddd, *J*= 14.4, 6.9, 1.2 Hz, 1H), 2.58 (ddd, *J* = 14.4, 8.1, 1.2 Hz, 1H), 1.48 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.3,

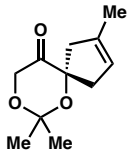
166.7, 142.9, 135.5, 131.1, 128.1, 127.1, 124.9, 100.3, 84.8, 67.5, 51.8, 43.8, 40.8, 27.0, 26.3; IR (Neat Film NaCl) 2992, 2950, 1725, 1658, 1435, 1385, 1374, 1271, 1234, 1198, 1171, 1114, 1098, 1054, 988, 702 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{18}H_{22}O_5$ $[M]^+$: 318.1467, found 318.1469; $[\alpha]_D^{27.1}$ +14.9° (*c* 0.550, CH_2Cl_2, 85% ee).

4.10.2. 7 Synthesis of Spiro Compounds by Ring-Closing Metathesis.

Representative Procedure for the Synthesis of Spiro Compounds 177m, n and q.

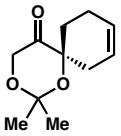


(*R*)-2,7,7-Trimethyl-6,8-dioxaspiro[4.5]dec-2-en-10-one (177m). To a solution of diene (***R***)-**177h** (60 mg, 0.268 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added Grubbs second generation catalyst (4.6 mg, 0.0054 mmol, 0.02 equiv) at room temperature. After the mixture was stirred at 35 °C for 40 h, it was concentrated under reduced pressure. The residue was purified by flash chromatography (2% Et_2O in petroleum ether on silica gel) to give the cyclopentene **177m** (51.4 mg, 98% yield) as a colorless oil. R_f 0.37 (20% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.22–5.20 (m, 1H), 4.31 (s, 2H), 2.91–2.52 (m, 4H), 1.73–1.71 (m, 3H), 1.49 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.1, 137.1, 120.8, 100.2, 88.3, 66.8, 48.5, 45.0, 27.0, 26.8, 16.5; IR (Neat Film NaCl) 2991, 2941, 1740, 1426, 1382, 1372, 1231, 1199, 1152, 1098, 1058, 988, 846 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{11}H_{16}O_3$ $[M]^+$: 196.1100, found 196.1095; $[\alpha]_D^{23.1}$ +19.2° (*c* 0.725, CH_2Cl_2, 85% ee).



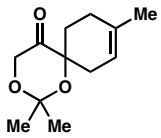
(S)-177m

(*S*)-2,7,7-Trimethyl-6,8-dioxaspiro[4.5]dec-2-en-10-one (177m). 87% yield. Colorless oil; R_f 0.37 (20% Et_2O in hexanes); $[\alpha]_D^{24.0}$ –20.4° (*c* 0.885, CH_2Cl_2, 88% ee).



(S)-177n

(*S*)-2,2-Dimethyl-1,3-dioxaspiro[5.5]undec-8-en-5-one (177n). 90% yield. Colorless oil; R_f 0.24 (10% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.80–5.70 (m, 1H), 5.67–5.58 (m, 1H), 4.27 (s, 2H), 2.60–2.47 (m, 1H), 2.38–2.18 (m, 2H), 2.17–1.81 (m, 3H), 1.51 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.1, 126.4, 122.8, 100.5, 79.9, 66.6, 33.5, 29.9, 27.7, 26.3, 21.8; IR (Neat Film NaCl) 3030, 2991, 2938, 2911, 1739, 1429, 1382, 1372, 1259, 1230, 1200, 1155, 1099, 1062, 999, 886, 836, 778, 651 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{11}H_{16}O_3$ $[M]^+$: 196.1100, found 196.1139; $[\alpha]_D^{20.2}$ –20.9° (*c* 1.045, CH_2Cl_2, 92% ee).

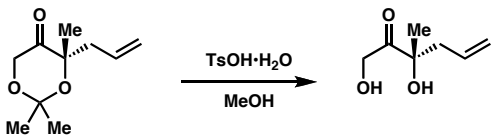


(±)-177q

(±)-2,2,9-Trimethyl-1,3-dioxaspiro[5.5]undec-8-en-5-one (177q). Prepared from racemic **177o**. 92% yield. Colorless oil; R_f 0.42 (20% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.31–5.23 (m, 1H), 4.27 (d, J = 17.9, 1H), 4.20 (d, J = 17.9, 1H), 2.56–2.43 (m, 1H), 2.21 (app. dt, J = 4.5, 2.8, 1H), 2.16 (dd, J = 4.3, 1.4, 1H), 2.02–1.93 (m, 2H), 1.83 (ddd, J = 14.1, 10.0, 6.3, 1H), 1.66 (d, J = 0.7, 3H), 1.48 (d, J = 0.6, 3H), 1.43

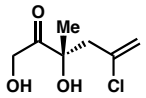
(d, J = 0.6, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.38, 133.44, 116.78, 100.53, 79.90, 66.64, 33.75, 30.28, 27.76, 26.55, 26.28, 23.53; IR (NaCl) 2990, 2967, 2931, 2912, 2857, 2836, 1739, 1430, 1382, 1372, 1261, 1229, 1201, 1159, 1101, 1069, 1029, 991, 844 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{12}H_{18}O_3$ $[M]^+$: 210.1256, found 210.1250.

4.10.2. 8 Acetonide Cleavage: Representative Procedure for the Synthesis of Diols 212.



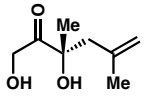
(S)-177a *(S)-212a*

(*S*)-1,3-Dihydroxy-3-methylhex-5-en-2-one (212a). To a solution of acetonide **177a** (80.5 mg, 0.44 mmol, 1.0 equiv) in MeOH (4.4 mL, 0.1 M) was added *p*-toluenesulfonic acid monohydrate (8.3 mg, 0.044 mmol, 0.1 equiv) at room temperature (ca. 25 °C). After the mixture was stirred for 3.5 h, Et_3N (0.2 mL) was added. The mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (30% EtOAc in hexanes on silica gel) to give diol **212a** (57.4 mg, 90% yield) as a colorless oil. R_f 0.21 (33% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79–5.65 (m, 1H), 5.23–5.14 (m, 2H), 4.55 (dd, *J* = 20.0, 5.1 Hz, 1H), 4.46 (dd, *J* = 20.0, 5.1 Hz, 1H), 2.92 (t, *J* = 5.1 Hz, 1H), 2.74 (s, 1H), 2.57–2.50 (m, 1H), 2.42–2.35 (m, 1H), 1.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.1, 131.5, 120.8, 78.2, 65.3, 44.5, 25.6; IR (Neat Film NaCl) 3413, 2980, 1721, 1641, 1414, 1370, 1169, 1019, 923 cm^{-1}; HRMS (ES+) *m/z* calc'd for $C_7H_{13}O_3$ $[M+H]^+$: 145.0865, found 145.0850; $[\alpha]_D^{23.5}$ –14.2° (*c* 0.810, CH_2Cl_2, 90% ee).



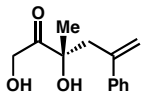
(S)-212b

(*S*)-5-Chloro-1,3-dihydroxy-3-methylhex-5-en-2-one (212b). 97% yield. Colorless oil; R_f 0.30 (33% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.38 (d, *J* = 0.9 Hz, 1H), 5.28 (d, *J* = 0.9 Hz, 1H), 4.65 (dd, *J* = 19.8, 5.1 Hz, 1H), 4.54 (dd, *J* = 19.8, 4.8 Hz, 1H), 2.96–2.91 (m, 3H), 2.74 (d, *J* = 14.7 Hz, 1H), 1.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.5, 136.0, 118.4, 78.0, 65.6, 49.2, 26.3; IR (Neat Film NaCl) 3422, 2981, 2922, 1722, 1633, 1452, 1416, 1371, 1267, 1167, 1087, 1021, 981, 895 cm^{-1}; HRMS (EI+) *m*/*z* calc'd for $C_7H_9ClO_2$ $[M-H_2O]^+$: 160.0291, found 160.0298; $[\alpha]_D^{21.2}$ –16.7° (*c* 1.000, CH_2Cl_2, 91% ee).



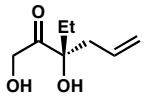
(S)-212c

(*S*)-1,3-Dihydroxy-3,5-dimethylhex-5-en-2-one (212c). 97% yield. Colorless oil; R_f 0.36 (33% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.98–4.97 (m, 1H), 4.79 (d, *J* = 0.9 Hz, 1H), 4.59 (dd, *J* = 20.0, 4.8 Hz, 1H), 4.46 (dd, *J* = 20.0, 4.8 Hz, 1H), 2.96 (t, *J* = 4.8 Hz, 1H), 2.74 (s, 1H), 2.62 (d, *J* = 14.0 Hz, 1H), 2.35 (d, *J* = 14.0 Hz, 1H), 1.70 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.8, 140.8, 116.6, 78.1, 65.5, 47.9, 26.6, 24.2; IR (Neat Film NaCl) 3429, 3078, 2976, 2917, 1720, 1644, 1452, 1373, 1229, 1135, 1101, 1024, 898 cm^{-1}; HRMS (EI+) *m*/*z* calc'd for $C_8H_{14}O_3$ $[M]^+$: 158.0943, found 158.0943; $[\alpha]_D^{23.3}$ –24.2° (*c* 0.420 CH_2Cl_2, 89% ee).



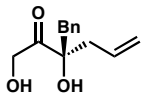
(S)-212d

(*S*)-1,3-Dihydroxy-3-methyl-phenylhex-5-en-2-one (212d). 92% yield. Colorless oil; R_f 0.27 (33% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.26 (m, 5H), 5.41 (d, *J* = 1.2 Hz, 1H), 5.17 (d, *J* = 0.9 Hz, 1H), 4.41 (dd, *J* = 20.3, 5.0 Hz, 1H), 4.18 (dd, *J* = 20.3, 5.0 Hz, 1H), 3.12 (d, *J* = 14.0 Hz, 1H), 2.86 (d, *J* = 14.0 Hz, 1H), 2.66 (t, *J* = 5.0 Hz, 1H), 2.46 (s, 1H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.5, 143.7, 140.8, 128.9, 128.4, 126.8, 118.8, 78.7, 65.7, 45.6, 26.4; IR (Neat Film NaCl) 3431, 2977, 2931, 1719, 1625, 1494, 1445, 1406, 1369, 1142, 1021, 908, 780, 700 cm^{-1}; HRMS (EI+) *m*/*z* calc'd for $C_{13}H_{16}O_3$ $[M]^+$: 220.1100, found 220.1116; $[\alpha]_D^{20.6}$ –9.82° (*c* 0.355, CH_2Cl_2, 94% ee).



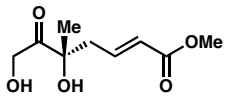
(S)-212e

(*S*)-1,3-Dihydroxy-3-ethylhex-5-en-2-one (212e). 97% yield. Colorless oil; R_f 0.32 (33% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76–5.62 (m, 1H), 5.20–5.12 (m, 2H), 4.47 (dd, *J* = 19.8, 4.8 Hz, 1H), 4.40 (dd, *J* = 19.8, 4.8 Hz, 1H), 2.94 (t, *J* = 4.8 Hz, 1H), 2.84 (s, 1H), 2.53–2.38 (m, 2H), 1.86–1.64 (m, 2H), 0.86 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.1, 131.6, 120.5, 81.1, 66.2, 43.6, 32.2, 7.7; IR (Neat Film NaCl) 3436, 2976, 1717, 1641, 1414, 1272, 1158, 1111, 1042, 922 cm^{-1}; HRMS (EI+) *m*/*z* calc'd for $C_8H_{14}O_3$ $[M]^+$: 158.0943, found 158.0948; $[\alpha]_D^{24.0}$ –0.37° (*c* 0.715, CH_2Cl_2, 93% ee).



(R)-212f

(*R*)-1,3-Dihydroxy-3-benzylhex-5-en-2-one (212f). 91% yield. Colorless oil; R_f 0.50 (33% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.24 (m, 3H), 7.13 (dd, *J* = 7.4, 1.9 Hz, 2H), 5.81–5.67 (m, 1H), 5.23–5.14 (m, 2H), 4.41 (dd, *J* = 20.1, 4.8 Hz, 1H), 4.07 (dd, *J* = 20.1, 4.8 Hz, 1H), 3.14 (d, *J* = 13.8 Hz, 1H), 2.92–2.86 (m, 2H), 2.65 (dd, *J* = 13.8, 7.4 Hz, 1H), 2.51 (s, 1H), 2.45–2.38 (dd, *J* = 14.1, 7.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.5, 134.8, 131.5, 130.3, 128.9, 127.6, 120.8, 81.4, 67.2, 45.2, 43.7; IR (Neat Film NaCl) 3436, 3079, 3030, 2917, 1717, 1640, 1496, 1454, 1429, 1412, 1259, 1098, 1043, 978, 924, 759, 703 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{16}O_3$ $[M]^+$: 220.1100, found 220.1069; $[\alpha]_D^{23.3}$ +16.1° (*c* 0.690 CH_2Cl_2, 86% ee).

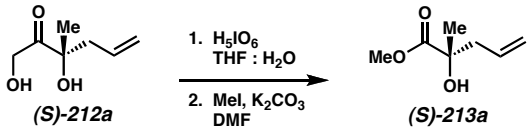


(S)-212l

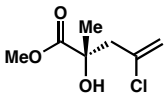
(*S*,*E*)-Methyl 5,7-dihydroxy-5-methyl-6-oxohept-2-enoate (212l). 80% yield. Colorless oil; R_f 0.58 (50% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (m, 1H), 5.94–5.88 (m, 1H), 4.52 (d, *J* = 5.1 Hz, 2H), 3.73 (s, 3H), 2.99–2.90 (m, 2H), 2.69–2.50 (m, 2H), 1.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.5, 166.6, 142.1, 125.5, 78.2, 65.1, 51.9, 42.4, 25.7; IR (Neat Film NaCl) 3436, 2954, 1721, 1658, 1439, 1339, 1280, 1204, 1021 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_9H_{15}O_5$ $[M+H]^+$: 203.0919, found 203.0918; $[\alpha]_D^{18.5}$ –8.35° (*c* 0.695, CH_2Cl_2, 92% ee).

4.10.2. 9 Synthesis of Hydroxyesters by Oxidation and Methylation.

Representative Procedure for the Synthesis of α-Hydroxy Esters 213.

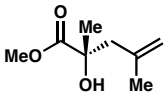


(2*R*)-Hydroxy-2-methyl-4-pentanoate (213a).[44] To a solution of diol **212a** (53.4 mg, 0.37 mmol, 1 equiv) in THF and water (THF/H_2O, 2:1, 11.1 mL, 0.033 M) was added H_5IO_6 (127 mg, 0.50 mmol, 1.5 equiv) at room temperature. After the mixture was stirred at room temperature (ca. 25 °C) for 24 h, the mixture was extracted with Et_2O (3 x 30 mL). The organic layer was washed with water (3 mL) and brine (3 mL), dried over Na_2SO_4 and concentrated under reduced pressure. To a suspension of the residue and K_2CO_3 (27.6 mg, 0.44 mmol, 1.2 equiv) in DMF (3.7 mL, 0.1 M) was added MeI (27.6 μL, 0.44 mmol, 1.2 equiv) at room temperature (ca. 25 °C). After stirring for 1 h, water (5 mL) was added, and the reaction was extracted with Et_2O (3 x 30 mL). The organic layer was washed with water (3 mL) and brine (3 mL), dried over Na_2SO_4 and concentrated under reduced pressure (~80 mmHg). The residue was purified by flash chromatography (10% Et_2O in petroleum ether on silica gel) to give methyl ester **213a** (28.9 mg, 54% yield, 90% ee) as a colorless oil. R_f 0.48 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84–5.70 (m, 1H), 5.15 (s, 1H), 5.12–5.07 (m, 1H), 3.77 (s, 3H), 3.10 (s, 1H), 2.35–2.54 (m, 2H), 1.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 132.6, 119.3, 74.7, 52.9, 44.9, 25.7; IR (Neat Film NaCl) 3504, 2982, 2955, 1736, 1642, 1455, 1437, 1372, 1271, 1227, 1170, 1143, 1069, 1000, 980, 920 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_7H_{13}O_3$ $[M+H]^+$: 145.0865, found 145.0867; $[\alpha]_D^{22.7}$ +25.6° (*c* 0.365, CH_2Cl_2, 90% ee).



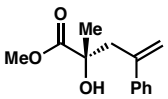
(S)-213b

2-(2-Chloroallyl)-2-hydroxymalonic acid dimethyl ester (**213b**).[45] 76% yield. Colorless oil; R_f 0.48 (33% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.33 (d, *J* = 0.9 Hz, 1H), 5.26 (d, *J* = 0.9 Hz, 1H), 3.80 (s, 3H), 3.32 (s, 1H), 2.86 (d, *J* = 14.3 Hz, 1H), 2.72 (d, *J* = 14.3 Hz, 1H), 1.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 136.6, 117.2, 73.6, 53.1, 49.6, 26.4; IR (Neat Film NaCl) 3507, 2987, 2955, 1738, 1633, 1454, 1436, 1278, 1230, 1167, 887 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_7H_{11}ClO_3$ $[M]^+$: 178.0397, found 178.0399; $[\alpha]_D^{19.0}$ +0.79° (*c* 1.190, CH_2Cl_2, 91% ee).



(S)-213c

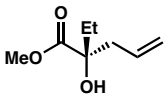
Methyl (*S*)-2-hydroxy-2,4-dimethyl-pent-4-enoic acid methyl ester (**213c**).[6a] 84% yield. Colorless oil; R_f 0.38 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.89–4.88 (m, 1H), 4.75 (s, 1H), 3.77 (s, 3H), 3.12 (s, 1H), 2.53 (d, *J* = 13.8 Hz, 1H), 2.37 (d, *J* = 13.8 Hz, 1H), 1.74 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 141.4, 115.2, 74.9, 52.8, 48.2, 26.6, 24.0; IR (Neat Film NaCl) 3514, 2954, 1736, 1644, 1452, 1375, 1266, 1212, 1156, 1114, 896 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_8H_{14}O_3$ $[M]^+$: 158.0943, found 158.0946; $[\alpha]_D^{22.0}$ +11.4° (*c* 0.220, CH_2Cl_2, 89% ee).



(S)-213d

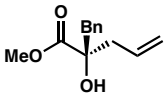
Methyl (*S*)-2-hydroxy-2-methyl-4-phenyl-4-pentanoate (**213d**)[6a,46] 77% yield. Colorless oil; R_f 0.52 (33% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.24

(m, 5H), 5.34 (d, J = 1.5 Hz, 1H), 5.17 (s, 1H), 3.18 (s, 3H), 3.07 (d, J = 13.5 Hz, 2H), 2.80 (d, J = 13.5 Hz, 1H), 1.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 144.1, 141.4, 128.3, 127.7, 126.9, 118.1, 74.3, 52.3, 46.4, 26.1; IR (Neat Film NaCl) 3514, 2981, 2952, 1736, 1626, 1494, 1447, 1269, 1214, 1129, 980, 906, 778, 709 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{16}O_3$ $[M]^+$: 220.1100, found 220.1108; $[\alpha]_D^{19.9}$ –4.09° (*c* 0.610, CH_2Cl_2, 94% ee).



(S)-213e

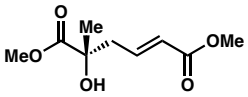
(**2*S*)-Hydroxy-2-ethyl-4-pentanoate** (**213e**). 60% yield. Colorless oil; R_f 0.59 (33% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84–5.70 (m, 1H), 5.13–5.06 (m, 2H), 3.77 (s, 3H), 3.16 (s, 1H), 2.51–2.37 (m, 2H), 1.85–1.63 (m, 2H), 0.86 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 132.7, 119.0, 78.2, 52.8, 43.8, 32.0, 8.1; IR (Neat Film NaCl) 3524, 2956, 1735, 1641, 1446, 1246, 1225, 1163, 1028, 999, 974, 919 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_8H_{15}O_3$ $[M+H]^+$: 159.1021, found 159.1026; $[\alpha]_D^{20.4}$ +24.3° (*c* 0.350, CH_2Cl_2, 93% ee).



(R)-213f

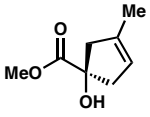
(**2*R*)-Hydroxy-2-benzyl-4-pentanoate** (**213f**). 85% yield. Colorless oil; R_f 0.52 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.11 (m, 5H), 5.88–5.74 (m, 1H), 5.16–5.11 (m, 2H), 3.72 (s, 3H), 3.07 (d, J = 13.5 Hz, 1H), 3.07 (s, 1H), 2.95 (d, J = 13.5 Hz, 1H), 2.65–2.46 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 135.9, 132.5, 130.3, 128.4, 127.2, 119.2, 78.4, 52.7, 45.3, 43.8; IR (Neat Film NaCl) 3522, 3030, 2954,

1736, 1640, 1495, 1455, 1442, 1272, 1229, 1142, 1093, 920, 701 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{16}O_3$ $[M]^+$: 220.1100, found 220.1105; $[\alpha]_D^{23.4}$ +41.8° (*c* 0.890, CH_2Cl_2, 86% ee).



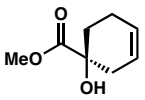
(S)-213l

(5*S*)-Hydroxy-5-methyl-hex-2-endioic acid dimethyl ester (213l).[47] 51% yield. Colorless oil; R_f 0.44 (50% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 6.89 (dt, *J* = 15.6, 7.7 Hz, 1H), 5.89 (dt, *J* = 15.6, 1.5 Hz, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 3.19 (s, 1H), 2.67–2.52 (m, 2H), 1.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 166.6, 142.9, 124.9, 74.3, 53.3, 51.7, 42.8, 26.2; IR (Neat Film NaCl) 3485, 2955, 1725, 1659, 1438, 1336, 1271, 1198, 1179, 1123, 1059, 1038, 983 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_9H_{15}O_5$ $[M+H]^+$: 203.0919, found 203.0911; $[\alpha]_D^{20.2}$ –1.06° (*c* 0.220, CH_2Cl_2, 92% ee).



(R)-213m

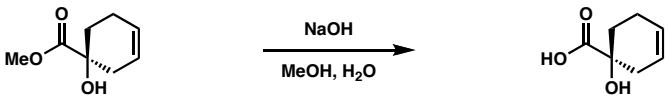
(*R*)-Methyl 1-hydroxy-3-methylcyclopent-3-enecarboxylate (213m). 48% yield. Colorless oil; R_f 0.52 (33% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.30–5.25 (m, 1H), 3.81 (s, 3H), 3.24 (s, 1H), 2.94–2.89 (m, 2H), 2.54–2.46 (m, 1H), 2.42 (d, *J* = 16.8 Hz, 1H), 1.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 137.4, 121.1, 80.8, 53.1, 50.9, 47.5, 16.5; IR (Neat Film NaCl) 3469, 2916, 1735, 1437, 1285, 1211, 1090, 1018, 960, 901 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_8H_{12}O_3$ $[M]^+$: 156.0786, found 156.0786; $[\alpha]_D^{21.1}$ +2.51° (*c* 0.360, CH_2Cl_2, 86% ee).



(S)-213n

(1*S*)-Hydroxy-cyclohex-3-ene carboxylic acid methyl ester (**213n**).[32] 61% yield. Colorless oil; R_f 0.56 (33% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86–5.74 (m, 1H), 5.70–5.58 (m, 1H), 3.80 (s, 1H), 2.98 (s, 1H), 2.65–2.54 (m, 1H), 2.40–2.24 (m, 1H), 2.17–2.05 (m, 2H), 2.00–1.89 (m, 1H), 1.84–1.71 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.5, 126.6, 123.0, 72.5, 53.0, 35.2, 30.9, 21.6; IR (Neat Film NaCl) 3471, 3029, 2954, 2915, 1732, 1437, 1278, 1258, 1223, 1096, 1058, 887 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_8H_{12}O_3$ $[M]^+$: 156.0786, found 156.0794; $[\alpha]_D^{20.9}$ +32.7° (*c* 0.660, CH_2Cl_2, 92% ee).

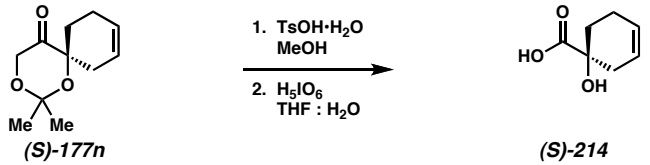
4.10.2. 10 Synthesis of Hydroxyacid.



(S)-213n *(S)-214*

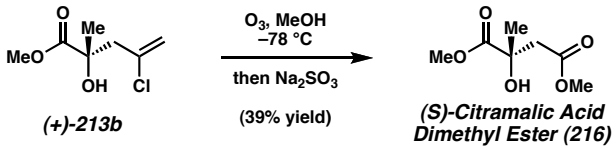
(1*S*)-Hydroxy-cyclohex-3-ene carboxylic acid ((*S*)-**214**).[32] To a solution of methyl ester **213b** (48.0 mg, 0.307 mmol, 1 equiv) in MeOH (3.0 mL, 0.1 M) was added 1N NaOH (0.37 mL, 0.37 mmol, 1.2 equiv) at room temperature (ca. 25 °C). After stirring for 18 h, the mixture was concentrated under reduced pressure. To the residue was added 1N HCl (1.0 mL) and the mixture was extracted with Et_2O (3 x 20 mL). The organic layer was washed with brine (5.0 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give carboxylic acid (***S***)-**214** (41.5 mg, 95% yield, 92% ee) as a white solid: mp 79–81 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88–5.79 (m, 1H), 5.72–5.61 (m, 1H), 2.79–2.62 (m, 1H), 2.37–2.11 (m, 4H), 1.95–1.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.5, 126.6,

122.6, 72.6, 34.9, 30.6, 21.4; IR (Neat Film NaCl) 3432, 3032, 2929, 2624, 1736, 1443, 1370, 1356, 1318, 1253, 1216, 1092, 1064, 982, 939, 886, 773, 746, 650, 736 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_8H_{12}O_3$ $[M]^+$: 143.0708, found 143.0708; $[\alpha]_D^{20.7}$ +31.7° (*c* 0.310, CH_2Cl_2, 92% ee).



(1*S*)-Hydroxy-cyclohex-3-ene carboxylic acid ((*S*)-**214**).[32] To a solution of acetonide **177n** (40 mg, 0.20 mmol, 1.0 equiv) in MeOH (4 mL, 0.05 M) was added *p*-toluenesulfonic acid monohydrate (3.9 mg, 0.02 mmol, 0.1 equiv) at room temperature (24 °C). After the mixture was stirred for 3 h, Et_3N (0.1 mL) was added. The mixture was concentrated under reduced pressure to give a yellow oil. The oil was diluted with EtOAc (10 mL), filtered through SiO_2 (1 mL), and concentrated under reduced pressure to furnish a white solid (35 mg). The solid was dissolved in THF (0.4 mL) and water (0.2 mL), and the colorless solution was cooled to 0 °C (ice water bath). H_5IO_6 (46 mg, 0.20 mmol, 1 equiv) was added to the solution. The mixture was allowed to warm to room temperature (26 °C) over 10 minutes, and then stirred for 2 h. The reaction was diluted with water (0.5 mL), and extracted with EtOAc (4 x 15 mL). Extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The white solid was purified by column chromatography over silica gel (ca. 9 mL) with 2:1 Hexanes:EtOAc to give carboxylic acid (*S*)-**214** (16.3 mg, 56% yield, 92% ee) as a white solid.

4.10.2. 11 Determination of Absolute Stereochemistry.



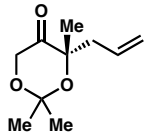
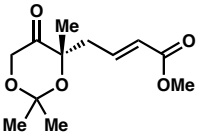
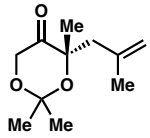
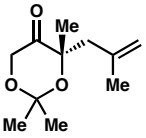
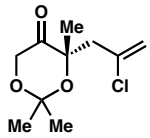
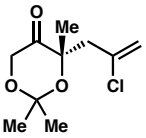
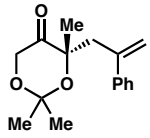
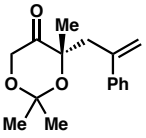
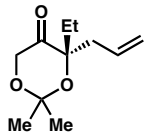
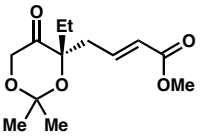
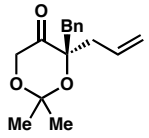
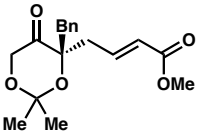
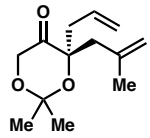
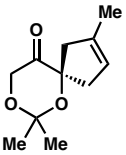
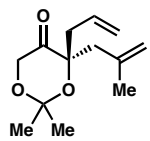
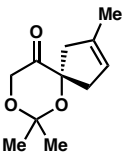
(+)-213b

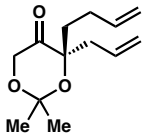
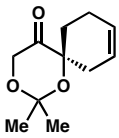
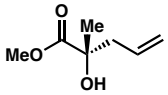
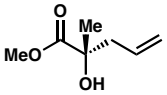
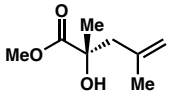
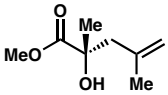
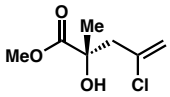
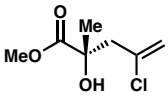
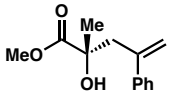
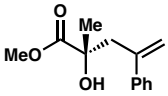
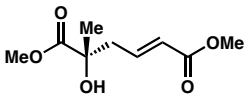
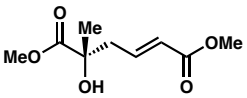
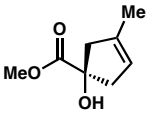
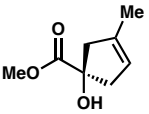
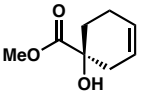
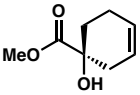
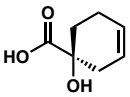
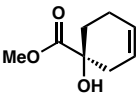
(S)-Citramalic Acid Dimethyl Ester (216)

(*S*)-Dimethyl citramalate (216).[36] Ozone was bubbled through a colorless solution of alkene (25 mg, 0.14 mmol, 1 equiv) in MeOH (0.52 mL, 0.27 M) at –78 °C until the solution turned blue (50 minutes). The blue solution was flushed with nitrogen gas until it turned colorless, at which point it was treated with sodium sulfite (79 mg, 4.5 equiv). The mixture was allowed to warm to room temperature overnight (ca. 25 °C), at which point it was diluted with Et_2O (to 30 mL), filtered, and concentrated under vacuum to a colorless oil (9.7 mg, 39% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.81 (s, 3H), 3.80 (s, 3H), 2.97 (d, *J*=16.5 Hz, 1H), 2.67 (d, *J*=16.5 Hz, 1H), 1.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 171.7, 72.8, 53.2, 52.2, 44.2, 26.5; IR (Neat Film NaCl) 3500, 2988, 2957, 2851, 1740, 1439, 1356, 1292, 1207, 1120, 1012, 983 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_8H_{12}O_3$ $[M]^+$: 170.0763, found 170.0750; $[\alpha]_D^{23.6}$ +13.4° (*c* 0.485, $CHCl_3$).

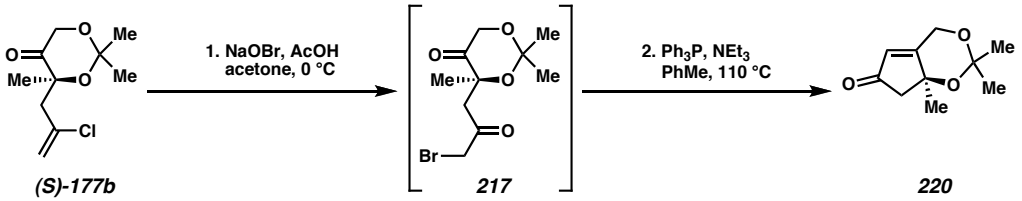
4.10.2. 12 Methods for the Determination of Enantiomeric Excess

Table 4.10.1 Methods for the determination of enantiomeric excess

entry	product[a]	compound assayed	assay conditions	Retention Time of major isomer [min]	Retention Time of minor isomer [min]	% ee
1			HPLC Chiralcel OD-H 5% EtOH in hexanes isocratic, 1.0 mL/min	7.283	9.200	90
2			GC, G-TA 65 °C isotherm	71.824	67.568	89
3			GC, G-TA 100 °C isotherm	23.425	21.998	91
4			HPLC Chiralcel OD-H 1% IPA in hexanes isocratic, 1.0 mL/min	7.256	6.818	94
5			HPLC Chiralcel OD-H 5% EtOH in hexanes isocratic, 1.0 mL/min	6.332	7.197	93
6			HPLC Chiralcel OD-H 5% EtOH in hexanes isocratic, 1.0 mL/min	9.846	12.111	85
7			GC, G-TA 80 °C isotherm	69.974	62.451	85
8			GC, G-TA 80 °C isotherm	62.170	71.087	88

entry	product	compound assayed	assay conditions	Retention Time of major isomer [min]	Retention Time of minor isomer [min]	% ee
9			HPLC CHIRALPAK AD Hexanes (220nm) isocratic, 1.0 mL/min	11.462	10.307	92
10			GC, G-TA 100 °C isotherm	5.184	4.959	90
11			GC, G-TA 100 °C isotherm	6.321	6.064	89
12			GC, G-TA 100 °C isotherm	14.338	13.530	91
13			HPLC CHIRALPAK AD 3% EtOH in hexanes isocratic, 1.0 mL/min	10.652	9.773	94
14			GC, G-TA 100 °C isotherm	84.186	92.457	92
15			GC, G-TA 110 °C isotherm	8.300	10.900	86
16			GC, G-TA 85°C isotherm	59.568	58.072	92
17			GC, G-TA 85°C isotherm	59.995	58.135	92

4.10.2.13 Elaboration of Enantioenriched Dioxanones Toward Ineleganolide



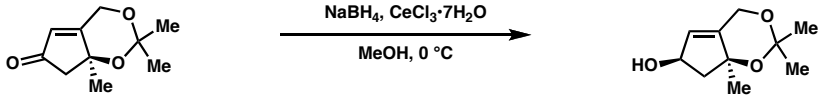
(*S*)-2,2,7α-Trimethyl-7,7a-dihydrocyclopenta[*d*][1,3]dioxin-6(4*H*)-one (**220**). A yellow solution of NaOBr was prepared at 0 °C (ice water bath) through dropwise addition of Br_2 (0.40 mL, 7.9 mmol, 1 equiv) by plastic syringe (NO METAL) to a colorless solution of NaOH (0.942 g, 24 mmol, 3 equiv) in de-ionized H_2O (11.9 mL, 0.664 M). The solution was allowed to stir for 30 min at 0 °C.

A flask was charged with a solution of chloride **177b** (0.300 g, 1.37 mmol, 1 equiv), reagent-grade acetone (12.1 mL, 0.113 M), and acetic acid (7.1 mL, 124 mmol, 90.5 equiv). The colorless solution was cooled to 0 °C (ice water bath). The reaction was treated dropwise with NaOBr (8.2 mL of 0.664 M solution, 5.44 mmol, 4.0 equiv) over 1 h. This dropwise addition was carried out with a plastic syringe (NO METAL) by hand. Care was taken to avoid contact between the syringe and the flask. The syringe was removed from above the flask between drops. At this point, the reaction was judged complete by TLC. Had the reaction been incomplete, further addition of NaOBr (up to 1 mL) would have been carried out at the same rate. To the completed reaction was added CH_2Cl_2 (10 mL) and H_2O (5 mL), followed by dropwise addition of a solution of K_2CO_3 (5.000 g) and $Na_2S_2O_3$ (2.084 g) in H_2O (10 mL). THIS AMOUNT OF K_2CO_3 SHOULD BE CONSIDERED A MAXIMUM. Addition of a greater amount of K_2CO_3 resulted in diminished yields on several occasions. Following dropwise addition, two colorless phases formed. The aqueous layer was further diluted with H_2O (15 mL), and extracted

quickly with CH_2Cl_2 (to 250 mL). Extracts were dried *quickly* over $MgSO_4$, filtered, and carefully concentrated under reduced pressure until around 2 mL of solution remained. The solution was diluted with heptanes (ca. 10 mL), and the reaction was concentrated under reduced pressure until around 0.6 mL of solution remained. The reaction was *quickly* partially purified by silica gel chromatography (SiO_2 (ca. 16 mL)) with 9:1 hexanes:Et_2O and partially concentrated under reduced pressure to give the desired α-bromoketone as a yellow solution, which was promptly diluted with anhydrous PhMe (1 mL) and *quickly* employed.

A 250 mL schlenk flask beneath Ar (g) was charged with PPh_3 (powdered, 0.893 g, 3.4 mmol, 2.5 equiv). The solid was dissolved in PhMe (10 mL) at room temperature (ca. 24 °C). The colorless solution was treated dropwise with the solution of α-bromoketone. The transfer was chased with PhMe (4 mL). The colorless solution was *quickly* treated dropwise with NEt_3 (0.29 mL, 2.1 mmol, 1.5 equiv). The flask was sealed and immediately heated at 110 °C (oil bath temperature) for 5 h, at which point, regardless of its degree of completion, it was allowed to cool to room temperature. Without concentration, the mixture was directly loaded onto a column of SiO_2 (ca. 30 mL) and purified with 3:1 to 1:1 pentane:Et_2O to furnish the volatile cyclopentenone **220** (0.180 g, 72% yield) as a yellow oil. This oil was stored as a solution in Et_2O. Repetition of this procedure provided cyclopentenone **220** in yields ranging from 0 to 85%. R_f 0.29 (50% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 5.91 (t, J = 1.7, 1H), 4.95–4.81 (m, 2H), 2.60 (d, J = 17.7, 1H), 2.47 (d, J = 17.7, 1H), 1.62 (s, 3H), 1.42 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.43, 175.89, 125.37, 100.82, 77.78, 60.94, 53.49, 30.18, 28.62, 25.40; IR (NaCl) 3072, 2991, 2937, 2861, 1723, 1639, 1445, 1408, 1382, 1372,

1349, 1316, 1267, 1226, 1200, 1169, 1139, 1094, 1060, 1010, 983, 952, 920, 903, 848, 831, 772, 752 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{10}H_{14}O_3$ $[M+]^+$: 182.0943, found 182.0941; $[\alpha]_D^{23.6}$ –19.8° (*c* 1.525, $CHCl_3$, 92% ee).



220 ***ent-176***

(6*R*,7α*S*)-2,2,7α-Trimethyl-4,6,7,7α-tetrahydrocyclopenta[*d*][1,3]dioxin-6-ol (*ent*-**176**). A flask was charged with a colorless solution of ketone **220** (0.110 g, 0.60 mmol, 1 equiv), MeOH (7.4 mL, 0.082 M) and $CeCl_3 \bullet 7H_2O$ (0.292 g, 0.78 mmol, 1.3 equiv). The solution was cooled to 0 °C (ice water bath), and treated with $NaBH_4$ (55 mg). Bubbles evolved. The solution was treated with a 1.5 M NaOH solution, extracted with EtOAc (to 150 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure, and immediately diluted with CH_2Cl_2. Alcohol **176** was purified by silica gel chromatography (SiO_2 (ca. 16 mL)) with 1:1 pentane:Et_2O as the eluent to give pure alcohol **176** as a colorless oil (75 mg, 78% yield). The alcohol was immediately diluted in Et_2O. R_f 0.11 (50% Et_2O in hexanes; visualized with anisaldehyde); ^1H NMR (300 MHz, $CDCl_3$) δ 5.54 (s, 1H), 4.68 (s, 1H), 4.63 (s, 2H), 2.54 (dd, J = 12.4, 6.5, 1H), 1.79 (dd, J = 12.4, 6.7, 1H), 1.61 (d, J = 8.9, 1H), 1.45 (s, 3H), 1.38 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.69, 125.70, 104.98, 100.18, 81.09, 74.00, 60.37, 53.54, 30.04, 28.32, 26.00; IR (NaCl) 3400 (b), 2990, 2939, 2863, 1451, 1380, 1370, 1356, 1324, 1264, 1197, 1156, 1107, 1088, 1061, 1037, 995, 983, 847; (EI+) *m/z* calc'd for $C_9H_{13}O_3$ $[M–Me]^+$: 169.0865, found 169.0858; $[\alpha]_D^{21.6}$ –2.7° (*c* 0.235, $CHCl_3$, 91% ee).

4.11 Notes and References

(1) Coppola, G. M.; Schuster, H. F. *α-Hydroxy Acids in Enantioselective Syntheses*, WILEY-VCH, Weinheim, **1997**.

(2) Sandler, J. S.; Colin, P. L.; Kelly, M.; Fenical, W. Cytotoxic Macrolides from a New Species of the Deep-Water Marine Sponge *Leiodermatium*. *J. Org. Chem.* **2006**, *71*, 7245–7251.

(3) (a) Takano, I.; Yasuda, I.; Nishijima, M.; Hitotsuyanagi, Y.; Takeya, K.; Itokawa, H. Drupangtonine, A Novel Antileukemic Alkaloid from *Cephalotaxus Harringtonia* var. *Drupacea*. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1689–1690; (b) Takano, I.; Yasuda, I.; Nishijima, M.; Yanagi, Y.; Takeya, K.; Itokawa, H. Ester-type Cephalotaxus Alkaloids from *Cephalotaxus Harringtonia* var. *Drupacea*. *Phytochemistry* **1997**, *44*, 735–738; (c) Morita, H.; Arisaka, M.; Yoshida, N.; Kobayashi, J. Cephalexomines A–F, Potent Cytotoxic Alkaloids from *Cephalotaxus harringtonia* var. *nana*. *Tetrahedron* **2000**, *56*, 2929–2934; (d) Liu, Q.; Ferreira, E. M.; Stoltz, B. M. Convergency and Divergency as Strategic Elements in Total Synthesis: The Total Synthesis of (–)-Drupacine and the Formal Total Synthesis of (±)-Cephalotaxine, (–)-Cephalotaxine, and (+)-Cephalotaxine. *J. Org. Chem.* **2007**, *72*, 7352–7358.

(4) Relevant reviews include: (a) Corey, E. J.; Guzmán-Pérez, A. The Catalytic Enantioselective Construction of Molecules with Quaternary Carbon Stereocenters. *Angew. Chem. Int. Ed.* **1998**, *37*, 388–401; (b) Ramón, D. J.; Yus, M. Chiral Tertiary Alcohols Made By Catalytic Enantioselective Addition of Unreactive Zinc

Reagents to Poorly Electrophilic Ketones? *Angew. Chem. Int. Ed.* **2004**, *43*, 284–287; (c) Ramón, D. J.; Yus, M. Enantioselective Synthesis of Oxygen-, Nitrogen-, and Halogen-Substituted Quaternary Carbon Centers. *Curr. Org. Chem.* **2004**, *8*, 149–183; (d) Garcia, C.; Martin, V. S. Asymmetric Addition to Ketones: Enantioselective Formation of Tertiary Alcohols. *Curr. Org. Chem.* **2006**, *10*, 1849–1889.

(5) For recent asymmetric α-hydroxylations, see: Smith, A. M. R.; Billen, D.; Hii, K. K. (M.) Palladium-catalysed enantioselective α-hydroxylation of β-ketoesters. *Chem. Commun.* **2009**, 3925–3927 and references therein.

(6) Catalytic enantioselective methods include: (a) Evans, D.A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T. C_2-Symmetric Copper(II) Complexes as Chiral Lewis Acids. Catalytic Enantioselective Carbonyl–Ene Reactions with Glyoxylate and Pyruvate Esters. *J. Am. Chem. Soc.* **2000**, *122*, 7936–7943; (b) Aikawa, K.; Kainuma, S.; Hatano, M.; Mikami, K. Asymmetric catalysis of ene reactions with trifluoropyruvate catalyzed by dicationic palladium(II) complexes. *Tetrahedron Lett.* **2004**, *45*, 183–185; (c) Mikami, K.; Kawakami, Y.; Akiyama, K.; Aikawa, K. Enantioselective Catalysis of Ketoester-ene Reaction of Silyl Enol Ether to Construct Quaternary Carbons by Chiral Dicationic Palladium(II) Complexes. *J. Am. Chem. Soc.* **2007**, *129*, 12950–12951.

(7) For catalytic enantioselective methods employing copper bis(oxazoline) or bis(thiazoline) complexes, see: (a) Christensen, C.; Juhl, K.; Jørgensen, K. A. Catalytic asymmetric Henry reactions–a simple approach to optically active β-nitro

α-hydroxy esters. *Chem. Commun.* **2001**, 2222–2223; (b) Christensen, C.; Juhl, K.; Jørgensen, K. A. Copper-Catalyzed Enantioselective Henry Reactions of α-Keto Ester: An Easy Entry to Optically Active β-Nitro-α-hydroxy Esters and β-Amino-α -hydroxy Esters. *J. Org. Chem.* **2002**, *67*, 4875–4881; (c) Lu, S.-F.; Du, D.-M.; Zhang, S. W.; Xu, J. Facile synthesis of C_2-symmetric tridentate bis(thiazoline) and bis(oxazoline) ligands and their application in the enantioselective Henry reaction. *Tetrahedron: Asymmetry* **2004**, *15*, 3433–3441; (d) Du, D.-M.; Lu, S.-F.; Fang, T.; Xu, J. Asymmetric Henry Reaction Catalyzed by C_2-Symmetric Tridentate Bis(oxazoline) and Bis(thiazoline) Complexes: Metal-Controlled Reversal of Enantioselectivity *J. Org. Chem.* **2005**, *70*, 3712–3715. For a heterogeneous catalytic enantioselective method based on MgO and binol, see: (e) Choudary, B. M.; Ranganath, K. V. S.; Pal, U.; Kantam, M. L.; Sreedhar, B. J. Nanocrystalline MgO for Asymmetric Henry and Michael Reactions. *J. Am. Chem. Soc.* **2005**, *127*, 13167–13171. For organocatalytic methods, see: (f) Li, H.; Wang, B.; Deng, L. Enantioselective Nitroaldol Reaction of α-Ketoesters Catalyzed by Cinchona Alkaloids. *J. Am. Chem. Soc.* **2006**, *128*, 732–733; (g) Takada, K.; Takemura, N.; Cho, K.; Sohtome, Y.; Nagasawa, K. Asymmetric organocatalytic nitroaldol reaction of α-ketoesters: stereoselective construction of chiral tertiary alcohols at subzero temperature. *Tetrahedron Lett.* **2008**, *49*, 1623–1626. For a catalytic enantioselective method employing copper(I) with an *N,N'*-dioxide ligand, see: (h) Qin, B.; Xiao, X.; Liu, X.; Huang, J.; Wen, Y.; Feng, X. Highly Enantioselective Henry (Nitroaldol) Reaction of Aldehydes and α-Ketoesters

Catalyzed by *N,N'*-Dioxide-Copper(I) Complexes. *J. Org. Chem.* **2007**, *72*, 9323–9328.

(8) For an enantioselective catalytic method employing tin-mediated catalysis, see: (a) Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. C_2-Symmetric Tin(II) Complexes as Chiral Lewis Acids. Catalytic Enantioselective *Anti* Aldol Additions of Enolsilanes to Glyoxylate and Pyruvate Esters. *J. Am. Chem. Soc.* **1997**, *119*, 10859–10860. For enantioselective catalytic methods employing copper catalysts, see: (b) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. C_2-Symmetric Copper(II) Complexes as Chiral Lewis Acids. Scope and Mechanism of the Catalytic Enantioselective Aldol Additions of Enolsilanes to Pyruvate Esters. *J. Am. Chem. Soc.* **1999**, *121*, 686–699; (c) Rémy, P.; Langner, M.; Bolm, C. Sulfoximines as Ligands in Copper-Catalyzed Asymmetric Vinylogous Mukaiyama-Type Aldol Reactions *Org. Lett.* **2006**, *8*, 1209–1211. Enantioselective methods involving α-ketoacids include: (d) Xu, X.-Y.; Tang, Z.; Wang, Y. Z.; Luo, S.-W.; Cun, L.-F.; Gong, L.-Z. Asymmetric Organocatalytic Direct Aldol Reactions of Ketones with α-Keto Acids and Their Application to the Synthesis of 2-Hydroxy-γ-butyrolactones. *J. Org. Chem.* **2007**, *72*, 9905–9913. Examples of diastereoselective methods include: (e) Basavaiah, D.; Bharathi, T. K. Enantioselective synthesis of α- and β-hydroxy acids using *trans*-2-phenylcyclohexan-1-ol-as chiral auxiliary. *Tetrahedron Lett.* **1991**, *32*, 3417–3420; (f) Tamai, Y.; Nakano, T.; Miyano, S. An Investigation of the Inherent Chiral Induction Ability of Axially Chiral 1,1'-Binaphthalene Framework in the Prelog's

Atrolactic Acid Synthesis. *Chem. Lett.* **1992**, 807–808; (g) Tamai, Y.; Nakano, T.; Miyano, S. Investigation of the Diastereoselectivity in the Addition of Organometallics to the α-Keto Esters of Axially Chiral 1,1'-Binaphthalen-2-ol Derivatives *J. Chem. Soc. Perkin Trans. 1* **1994**, 439–445; (h) Akiyama, T.; Ishikawa, K.; Ozaki, S. Asymmetric Synthesis of Functionalized Tertiary Alcohols by Diastereoselective Aldol Reaction of Silyl Enol Ether and Ketene Silyl Acetal with α-Keto Esters Bearing an Optically Active Cyclitol as a Chiral Auxiliary. *Synlett* **1994**, *4*, 275–276; (i) Basavaiah, D.; Pandiaraju, S.; Bathados, M.; Mathukumaran, K. (*1R*, *2R*)-2-nitroxycyclohexan-1-ol: First example of a cyclohexyl based chiral auxiliary with nitroxy function as diastereoface discriminating group. *Tetrahedron: Asymmetry* **1996**, *7*, 997–1000; (j) García Ruano, J. L.; Barros, D.; Carmen Maestro, M.; Alcudia, A.; Fernández, I. Synthesis of enantiomerically pure (*R*)- and (*S*)-2-ethoxycarbonylmethyl-2-hydroxy-cyclohexanones. *Tetrahedron: Asymmetry* **1998**, *9*, 3445–3453; (k) Senanayake, C. H.; Fang, K.; Grover, P.; Bakale, R. P.; Vandenbossche, C. P.; Wald, S. A. Rigid Aminoalcohol Backbone as a Highly Defined Chiral Template for the Preparation of Optically Active Tertiary α-Hydroxyl Acids. *Tetrahedron Lett.* **1999**, *40*, 819–822; (l) García Ruano, J. L.; Barros, D.; Maestro, M. C.; Slawin, A. M. Z.; Bulman Page, P. C. High Stereocontrol in Aldol Reaction with Ketones: Enantioselective Synthesis of β-Hydroxy γ-Ketoesters by Ester Enolate Aldol Reactions with 2-Acyl-2-alkyl-1,3-dithiane 1-Oxides. *J. Org. Chem.* **2000**, *65*, 6027–6034; (m) Kamino, T.; Murata, Y.; Kawai, N.; Hosokawa, S.; Kobayashi, S. Stereochemical

control of tertiary alcohol: aldol condensation of lactate derivatives. *Tetrahedron Lett*. **2001**, *42*, 5249–5252; (n) Loupy, A.; Monteux, D. A. Isomannide and isosorbide as new chiral auxiliaries for the stereoselective synthesis of tertiary α-hydroxy acids. *Tetrahedron* **2002**, *58*, 1541–1549; (o) Wipf, P.; Stephenson, C. R. J. Dimethylzinc-Mediated Addition of Alkenylzirconocenes to α-Keto and α-Imino Esters. *Org*. *Lett*. **2003**, *5*, 2449–2452.

(9) For an enantioselective method that employs superstoichiometric chiral Sn, see: (a) Yamad, K.; Tozawa, T.; Nishida, M.; Mukaiyama, T. Asymmetric Allylation of Carbonyl Compounds with Tartrate-Modified Chiral Allylic Tin Reagents. *Bull*. *Chem*. *Soc*. *Jpn*. **1997**, *70*, 2301–2308. For an enantioselective method that employs catalytic *N,N'*-dioxide-In(III), with superstoichiometric tetraallylstannane as an allyl source, see: (b) Zheng, K.; Qin, B.; Liu, X.; Feng, X. Highly Enantioselective Allylation of α-Ketoesters Catalyzed by *N,N'*-Dioxide–In(III) Complexes. *J*. *Org*. *Chem*. **2007**, *72*, 8478–8483. Diastereoselective methods include: (c) Soai, K.; Ishizaki, M. Asymmetric Synthesis of Functionalized Tertiary Homoallyl Alcohols by Diastereoselective Allylation of Chiral α-Keto Amides Derived from (*S*)-Proline Esters. Control of Stereochemistry Based on Saturated Coordination of Lewis Acid. *J*. *Org*. *Chem*. **1986**, *51*, 3290–3295; (d) Kim, Y. H.; Kim, S. H. Highly Stereoselective Allylation to Chiral α-Keto Amides Derived from (*S*)-Indoline-2-carboxylic Acid. Asymmetric Synthesis of Functionalized Tertiary Homoallyl Alcohols. *Tetrahedron Lett*. **1995**, *36*, 6895–6898.

(10) For catalytic enantioselective methods that involve either Me_2Zn, or Et_2Zn as an alkyl source, see: (a) DiMauro, E. F.; Kozlowski, M. C. Development of Bifunctional Salen Catalysts: Rapid, Chemoselective Alkylations of α-Ketoesters. *J. Am. Chem. Soc.* **2002**, *124*, 12668–12669; (b) DiMauro, E. F.; Kozlowski, M. C. The First Catalytic Asymmetric Addition of Dialkylzincs to α-Ketoesters. *Org. Lett.* **2002**, *4*, 3781–3784; (c) Funabashi, K.; Jachmann, M.; Kanai, M.; Shibasaki, M. Multicenter Strategy for the Development of Catalytic Enantioselective Nucleophilic Alkylation of Ketones: Me_2Zn Addition to α-Ketoesters. *Angew. Chem. Int. Ed.* **2003**, *42*, 5489–5492; (d) Fennie, M. W.; DiMauro, E. F.; O'Brien, E. M.; Annamalai, V.; Kozlowski, M. C. Mechanism and scope of salen bifunctional catalysts in asymmetric aldehyde and α-ketoester alkylation. *Tetrahedron* **2005**, *61*, 6249–6265; (e) Wieland, L. C.; Deng, H.; Snapper, M. L.; Hoveyda, A. H. Al-Catalyzed Enantioselective Alkylation of α-Ketoesters by Dialkylzinc Reagents. Enhancement of Enantioselectivity and Reactivity by an Achiral Lewis Base Additive. *J. Am. Chem. Soc.* **2005**, *127*, 15453–15456; (f) Blay, G.; Fernández, I.; Marco-Aleixandre, A.; Pedro, J. R. Catalytic Asymmetric Addition of Dimethylzinc to α-Ketoesters, Using Mandelamides as Ligands. *Org. Lett.* **2006**, *8*, 1287–1290; (g) Blay, G.; Fernández, I.; Marco-Aleixandre, A.; Pedro, J. R. Enantioselective Addition of Dimethylzinc to α-Keto Esters. *Synthesis* **2007**, 3754–3757. A catalytic enantioselective method to form propargylic α-hydroxyesters has been reported, see: (h) Jiang, B.; Chen, Z.; Tang, X. Highly Enantioselective Alkynylation of α-Keto Ester: An Efficient Method for

Constructing a Chiral Tertiary Carbon Center. *Org. Lett.* **2002**, *4*, 3451–3453. Diastereoselective methods include: (i) Song, J. J.; Tan, Z.; Xu, J.; Reeves, J. T.; Yee, N. K.; Ramdas, R.; Gallou, F.; Kuzmich, K.; DeLattre, L.; Lee, H.; Feng, X.; Senanayake, C. H. Practical Stereoselective Synthesis of an α-Trifluoromethyl-α-alkyl Epoxide via a Diastereoselective Trifluoromethylation Reaction. *J. Org. Chem.* **2007**, *72*, 292–294.

(11) An enantioselective copper-bis(oxazoline)-catalyzed hetero-Diels-Alder has been reported: (a) Johannsen, M.; Yao, S.; Jørgensen, K. A. The first highly enantioselective catalytic hetero-Diels–Alder reaction of ketones. *Chem. Commun.* **1997**, 2169–2170. For asymmetric rhodium-catalyzed intramolecular cycloadditions employing α-diazocarbonyl compounds, see: (b) Pierson, N.; Fernández-García, C.; McKervey, M. A. Catalytic asymmetric oxonium ylide – [2,3] sigmatropic rearrangement with diazocarbonyl compounds: First use of C_2-symmetry in Rh(II) carboxylates. *Tetrahedron Lett.* **1997**, *38*, 4705–4708; (c) Hodgson, D. M.; Petroliagi, M. Rh(II)-binaphthol phosphate catalyst in the enantioselective intramolecular oxonium ylide formation–[3,2] sigmatropic rearrangement of α-diazo-β-ketoesters. *Tetrahedron: Asymmetry* **2001**, *12*, 877–881; (d) Suga, H.; Inoue, K.; Inoue, S.; Kakehi, A. Highly Enantioselective 1,3-Dipolar Cycloaddition Reactions of 2-Benzopyrylium-4-olate Catalyzed by Chiral Lewis Acids. *J. Am. Chem. Soc.* **2002**, *124*, 14836–14837. For a palladium-catalyzed Wacker cyclization, see: (e) Uozumi, Y.; Kyota, H.; Kato, K.; Ogasawara, M.; Hayashi, T. Design and Preparation of 3,3'-Disubstituted 2,2'-

Bis(oxazolyl)-1,1'-binaphthyls (boxax): New Chiral Bis(oxazoline) Ligands for Catalytic Asymmetric Wacker-Type Cyclization. *J. Org. Chem.* **1999**, *64*, 1620–1625. For an enantioselective copper-catalyzed Claissen/ene rearrangement, see: (f) Kaden, S.; Hiersemann, M. The First Catalytic Asymmetric Domino Claisen Rearrangement/Intramolecular Carbonyl Ene Reaction. *Synlett* **2002**, 1999–2002. For an enantioselective copper-catalyzed ketene cycloaddition, see: (g) Evans, D. A.; Janey, J. M. C_2–Symmetric Cu(II) Complexes as Chiral Lewis Acids. Catalytic, Enantioselective Cycloadditions of Silyl Ketenes. *Org. Lett.* **2001**, *3*, 2125–2128.

(12) For enantioselective examples employing copper bis(oxazoline)-derived catalysts, see: (a) Zhuang, W.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A. Catalytic, Highly Enantioselective Friedel–Crafts Reactions of Aromatic and Heteroaromatic Compounds to Trifluoropyruvate. A Simple Approach for the Formation of Optically Active Aromatic and Heteroaromatic Hydroxy Trifluoromethyl Esters. *J. Org. Chem.* **2001**, *66*, 1009–1013; (b) Corma, A.; García, H.; Moussaif, A.; Sabater, M. J.; Zniber, R.; Redouane, A. Chiral copper(II) bisoxazoline covalently anchored to silica and mesoporous MCM-41 as a heterogeneous catalyst for the enantioselective Friedel–Craffts hydroxyalkylation. *Chem. Comm.* **2002**, 1058–1059.

(13) Catalytic enantioselective methods follow. For methods employing titanium, see: (a) Belokon, Y. N.; Green, B.; Ikonnikov, N. S.; North, M. The asymmetric addition of trimethylsilyl cyanide to ketones catalysed by a bimetallic, chiral (salen)titanium complex. *Tetrahedron Lett.* **1999**, *40*, 8147–8150; (b) Hamashima,

Y.; Kanai, M.; Shibasaki, M. Catalytic enantioselective cyanosilylation of ketones: improvement of enantioselectivity and catalyst turn-over by ligand tuning. *Tetrahedron Lett*. **2001**, *42*, 691–694; (c) Chen, F.; Feng, X.; Qin, B.; Zhang, G.; Jiang, Y. Enantioselective Cyanosilylation of Ketones by a Catalytic Double-Activation Method Employing Chiral Lewis Acid and Achiral *N*-Oxide Catalysts. *Org*. *Lett*. **2003**, *5*, 949–952; (d) Chen, F.-X.; Qin, B.; Feng, X.; Zhang, G.; Jiang, Y. Enantioselective cyanosilylation of ketones catalyzed by double-activation catalysts with *N*-oxides. *Tetrahedron* **2004**, *60*, 10449–10460; (e) He, B.; Chen, F.-X.; Li, Y.; Feng, X.; Zhang, G. Achiral phenolic *N*-oxides as additives: an alternative strategy for asymmetric cyanosilylation of ketones. *Tetrahedron Lett*. **2004**, *45*, 5465–5467; (f) Shen, Y.; Feng, X.; Li, Y.; Zhang, G.; Jiang, Y. Asymmetric Cyanosilylation of Ketones Catalyzed by Bifunctional Chiral *N*-Oxide Titanium Complex Catalysts. *Eur*. *J*. *Org*. *Chem*. **2004**, 129–137; (g) He, B.; Chen, F.-X.; Feng, X.; Zhang, G. Effective Activation of the Chiral Salen/Ti(O*i*Pr)$_4$ Catalyst with Achiral Phenolic *N*-Oxides as Additives in the Enantioselective Cyanosilylation of Ketones. *Eur*. *J*. *Org*. *Chem*. **2004**, 4657–4666. For methods involving aluminum, see: (h) Deng, H.; Isler, M. P.; Snapper, M. L.; Hoveyda, A. H. Aluminum-Catalyzed Asymmetric Addition of TMSCN to Aromatic and Aliphatic Ketones Promoted by an Easily Accessible and Recyclable Peptide Ligand. *Angew*. *Chem*. *Int*. *Ed*. **2002**, *41*, 1009–1012; (i) Chen, F.-X.; Zhou, H.; Liu, X.; Qin, B.; Feng, X.; Zhang, G.; Jiang, Y. Enantioselective Cyanosilylation of Ketones by a Catalytic Double-Activation Method with an Aluminium Complex

and an *N*-Oxide. *Chem. Eur. J.* **2004**, *10*, 4790–4797; (j) Kim, S. S.; Kwak, J. M. Asymmetric addition of trimethylsilyl cyanide to ketones catalyzed by Al(salen)/triphenylphosphine oxide. *Tetrahedron* **2006**, *62*, 49–53. For methods involving organocatalysis, see: (k) Tian, S. K.; Deng, L. A Highly Enantioselective Chiral Lewis Base-Catalyzed Asymmetric Cyanation of Ketones. *J. Am. Chem. Soc.* **2001**, *123*, 6195–6196; (l) Tian, S. K.; Hong, R.; Deng, L. Catalytic Asymmetric Cyanosilylation of Ketones with Chiral Lewis Base. *J. Am. Chem. Soc.* **2003**, *125*, 9900–9901; (m) Ryu, D. H.; Corey, E. J. Enantioselective Cyanosilylation of Ketones Catalyzed by a Chiral Oxazaborolidinium Ion. *J. Am. Chem. Soc.* **2005**, *127*, 5384–5387; (n) Fuerst, D. E.; Jacobsen, E. N. Thiourea-Catalyzed Enantioselective Cyanosilylation of Ketones. *J. Am. Chem. Soc.* **2005**, *127*, 8964–8965; (o) Liu, X.; Qin, B.; Zhou, X.; He, B.; Feng, X. Catalytic Asymmetric Cyanosilylation of Ketones by a Chiral Amino Acid Salt. *J. Am. Chem. Soc.* **2005**, *127*, 12224–12225; (p) Zuend, S. J.; Jacobsen, E. N. Cooperative Catalysis by Tertiary Amino-Thioureas: Mechanism and Basis for Enantioselectivity of Ketone Cyanosilylation. *J. Am. Chem. Soc.* **2007**, *129*, 15872–15883. For methods employing Mn(salen), see: (q) Kim, S. S.; Lee, S. H.; Kwak, J. M. Enantioselective cyanosilylation of ketones catalyzed by Mn(salen)/Ph_3PO. *Tetrahedron: Asymmetry* **2006**, *17*, 1165–1169; (r) Kim, S. S. Asymmetric cyanohydrin synthesis from aldehydes and ketones using chiral metal (salen) complex as catalyst. *Pure Appl. Chem.* **2006**, *78*, 977–983. For methods employing Sm-catalysts, see: (s) Yabu, K.; Masumoto, S.; Yamasaki, S.; Hamashima, Y.; Kanai, M.; Du, W.; Curran, D. P.;

Shibasaki, M. Switching Enantiofacial Selectivities Using One Chiral Source: Catalytic Enantioselective Synthesis of the Key Intermediate for (20*S*)-Camptothecin Family by (*S*)-Selective Cyanosilylation of Ketones. *J. Am. Chem. Soc*. **2001**, *123*, 9908–9909; (t) Yabu, K.; Masumoto, S.; Kanai, M.; Curran, D. P.; Shibasaki, M. Studies toward practical synthesis of (20*S*)-camptothecin family through catalytic enantioselective cyanosilylation of ketones: improved catalyst efficiency by ligand-tuning. *Tetrahedron Lett*. **2002**, *43*, 2923–2926; (u) Masumoto, S.; Suzuki, M.; Kanai, M.; Shibasaki, M. A practical synthesis of (*S*)-oxybutynin. *Tetrahedron Lett*. **2002**, *43*, 8647–8651. For an asymmetric example of cyanocarbonylation, see: (v) Tian, S.-K.; Deng, L. Enantioselective cyanocarbonylation of ketones with chiral base. *Tetrahedron* **2006**, *62*, 11320–11330.

(14) Selected diastereoselective examples include: (a) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. Alkylation of Amino Acids without Loss of the Optical Activity: Preparation of α-Substituted Proline Derivatives. A Case of Self-Reproduction of Chirality. *J. Am. Chem. Soc*. **1983**, *105*, 5390–5402; (b) Seebach, D.; Naef, R.; Calderari, G. Selective 1,4-addition of methoxyallylcopper to enone. *Tetrahedron* **1984**, *40*, 1313–1324; (c) Calderari, C.; Seebach, D. Asymmetrische Michael-Additionen. Stereoselektive Alkylierung chiraler, nicht racemischer Enolate durch Nitroolefine. Herstellung enantiomerenreiner gamma-Aminobuttersäure- und Bernsteinsäure-Derivate. *Helv. Chim. Acta* **1985**, *68*, 1592–1604; (d) Tamura, Y.;

Kondo, H.; Annoura, H.; Takeuchi, R.; Fujioka, H. Diastereoselective addition of grignard reagents to chiral α-ketoacetals. *Tetrahedron Lett*. **1986**, *27*, 81–82.

(15) For enantioselective methods, see: (a) Trost, B. M.; Dogra, K.; Franzini, M. 5*H*-Oxazol-4-ones as Building Blocks for Asymmetric Synthesis of α-Hydroxycarboxylic Acid Derivatives. *J. Am. Chem. Soc*. **2004**, *126*, 1944–1945; (b) Ooi, T.; Fukumoto, K.; Maruoka, K. Construction of Enantiomerically Enriched Tertiary α-Hydroxycarboxylic Acid Derivatives by Phase-Transfer-Catalyzed Asymmetric Alkylation of Diaryloxazolidin-2,4-diones. *Angew. Chem. Int. Ed*. **2006**, *45*, 3839–3842; (c) Trost, B. M.; Xu, J.; Reichle, M. Enantioselective Synthesis of α-Tertiary Hydroxyaldehydes by Palladium-Catalyzed Asymmetric Allylic Alkylation of Enolates. *J. Am. Chem. Soc*. **2007**, *129*, 282–283.

(16) (a) Mohr, J. T.; Stoltz, B. M. Enantioselective Tsuji Allylations. *Chem. Asian J*. **2007**, *2*, 1476–1491; (b) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. Deracemization of Quaternary Stereocenters by Pd-Catalyzed Enantioconvergent Decarboxylative Allylation of Racemic β-Ketoesters. *Angew. Chem. Int. Ed*. **2005**, *44*, 6924–6927; (c) Behenna, D. C.; Stoltz, B. M. The Enantioselective Tsuji Allylation. *J. Am. Chem. Soc*. **2004**, *126*, 15044–15045.

(17) Tsuji, J.; Minami, I.; Shimizu, I. Palladium-catalyzed allylation of ketones and aldehydes via allyl enol carbonates. *Tetrahedron Lett*. **1983**, *24*, 1793–1796.

(18) (a) Shimizu, I.; Yamada, T.; Tsuji, J. Palladium-catalyzed rearrangement of allylic esters of acetoacetic acid to give α,β-unsaturated methyl ketones. *Tetrahedron Lett*. **1980**, *21*, 3199–3202; (b) Tsuji, J.; Minami, I. New Synthetic

Reactions of Allyl Alkyl Carbonates, Allyl β-Keto Carboxylates, and Allyl Vinylic Carbonates Catalyzed by Palladium Complexes. *Acc. Chem. Res.* **1987**, *20*, 140–145; (c) Saegusa simultaneously reported work with allyl ester substrates, see: Tsuda, T.; Chujo, Y.; Nishi, S.-i.; Tawara, K; Saegusa, T. Facile Generation of a Reactive Palladium(II) Enolate Intermediate by the Decarboxylation of Palladium(II) β-Ketocarboxylate and Its Utilization in Allylic Acylation. *J. Am. Chem. Soc.* **1980**, *102*, 6381–6384.

(19) Tsuji, J.; Minami, I.; Shimizu, I. Allylation of ketones via their enol acetates catalyzed by palladium-phosphine complexes and organotin compounds. *Tetrahedron Lett.* **1983**, *24*, 4713–4714.

(20) (a) Tsuji, J.; Minami, I.; Shimizu, I. Palladium-Catalyzed Allylation of Ketones and Aldehydes with Allylic Carbonates via Silyl Enol Ethers Under Neutral Conditions. *Chem. Lett.* **1983**, 1325–1326; (b) Tsuji, J. New general synthetic methods involving π-allylpalladium complexes as intermediates and neutral reaction conditions. *Tetrahedron* **1986**, *42*, 4361–4401.

(21) For the development of the PHOX ligands, see: (a) Helmchen, G.; Pfaltz, A. Phosphinooxazolines—A New Class of Versatile, Modular P,N-Ligands for Asymmetric Catalysis. *Acc. Chem. Res.* **2000,** *33*, 336–345; (b) Williams, J. M. J. The Ups and Downs of Allylpalladium Complexes in Catalysis. *Synlett* **1996**, 705–710, and references therein.

(22) We have developed a convenient, scaleable procedure for the preparation of a variety of PHOX ligands via a Cu-catalyzed C–P coupling reaction, see: (a) Tani,

K.; Behenna, D. C.; McFadden, R. M.; Stoltz, B. M. A Facile and Modular Synthesis of Phosphinooxazoline Ligands. *Org. Lett.* **2007**, *9*, 2529–2531; (b) Krout, M. R.; Mohr, J. T.; Stoltz, B. M. Preparation of (S)-*tert*-ButylPHOX. *Org. Synth.* **2009**, *86*, 181–193.

(23) (a) Sherden, N.; Behenna, D. C.; Virgil, S. C.; Stoltz, B. M. Unusual Allylpalladium Carboxylate Complexes: Identification of the Resting State of Catalytic Enantioselective Decarboxylative Allylic Alkylation Reactions of Ketones. *Angew. Chem. Int. Ed.* **2009**, *48*, 6840–6843; (b) Keith, J. A.; Behenna, D. C.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Oxgaard, J.; Stoltz, B. M.; Goddard, W. A., III. The Inner-Sphere Process in the Enantioselective Tsuji Allylation Reaction with (*S*)-*t*-Bu-phosphinooxazoline Ligands. *J. Am. Chem. Soc.* **2007**, *129*, 11876–11877.

(24) For representative examples of *O*- and *C*-bound Pd-enolates, see: (a) Burkhardt, E. R.; Bergman, R. G.; Heathcock, C. H. Synthesis and Reactions of Nickel and Palladium Carbon-Bound Enolate Complexes. *Organometallics* **1990**, *9*, 30–44; (b) Balegroune, F.; Grandjean, D.; Lakkisb, D.; Matt, D. Transition Metal Enolate Chemistry. Formation of a Palladium Alkyl Complex from a Highly Reactive Enolato Palladium Complex. *J. Chem. Soc., Chem. Commun.* **1992**, 1084–1085; (c) Byers, P. K.; Canty, A. J.; Skelton, B. W.; Traill, P. R.; Watson, A. A.; White, A. H. ^{1}H NMR Detection of Cationic Organopalladium(IV) Intermediates in Oxidative-Addition Reactions and the Structure of *fac*-$PdBrMe_2(CH_2COPh)(bpy)$. *Organometallics* **1992**, *11*, 3085–3088; (d) Veya, P.; Floriani, C.; Chiesi-Villa, A.;

Rizzoli, C. Terminal and Bridging Bonding Modes of the Acetophenone Enolate to Palladium(II): The Structural Evidence and the Insertion of Isocyanides. *Organometallics* **1993**, *12*, 4899–4901; (e) Sodeoka, M.; Tokunoh, R.; Miyazaki, F.; Hagiwara, E.; Shibasaki, M. Stable Diaqua Palladium(II) Complexes of BINAP and Tol-BINAP as Highly Efficient Catalysts for Asymmetric Aldol Reactions. *Synlett* **1997**, 463–466; (f) Kawatsura, M.; Hartwig, J. F. Simple, Highly Active Palladium Catalysts for Ketone and Malonate Arylation: Dissecting the Importance of Chelation and Steric Hindrance. *J. Am. Chem. Soc.* **1999**, *121,* 1473–1478; (g) Albéniz, A. C.; Catalina, N. M.; Espinet, P.; Redón, R. Bonding Modes in Palladium(II) Enolates: Consequences for Dynamic Behavior and Reactivity. *Organometallics* **1999**, *18*, 5571–5576; (h) Vicente, J.; Arcas, A.; Fernández-Hernández, J. M.; Bautista, D. $[Pd\{CH_2C(O)Me\}Cl]_n$, a Key Product for the Synthesis of Acetonylpalladium(II) Complexes. *Organometallics* **2001**, *20*, 2767–2774; (i) Culkin, D. A.; Hartwig, J. F. C–C Bond-Forming Reductive Elimination of Ketones, Esters, and Amides from Isolated Arylpalladium(II) Enolates. *J. Am. Chem. Soc.* **2001**, *123*, 5816–5817; (j) Tian, G.; Boyle, P. D.; Novak, B. M. Synthesis and Crystal Structure of a Dinuclear Palladium Complex Containig C,O-Bridging Ester–Enolato Moieties. *Organometallics* **2002**, *21*, 1462–1465; (k) Culkin, D. A.; Hartwig, J. F. Carbon–Carbon Bond-Forming Reductive Elimination from Arylpalladium Complexes Containing Functionalized Alkyl Groups. Influence of Ligand Steric and Electronic Properties on Structure, Stability, and Reactivity. *Organometallics* **2004**, *23*, 3398–3416.

(25) Similar transition states have been proposed previously for C–C bond formation, see: (a) Kitching, W.; Sakakiyama, T.; Rappoport, Z.; Sleezer, P. D.; Winstein, S.; Young, W. G. Metal Acetate Promoted Reactions of σ and π Allylic Organometallics. *J. Am. Chem. Soc.* **1972**, *94*, 2329–2335; (b) Méndez, M.; Cuerva, J. M.; Gómez-Bengoa, E.; Cárdenas, D. J.; Echavarren, A. M. Intramolecular Coupling of Allyl Carboxylates with Allyl Stannanes and Allyl Silanes: A New Type of Reductive Elimination Reaction? *Chem. Eur. J.* **2002**, *8*, 3620–3628.

(26) Similar transition states have been proposed previously for C–O bond formation, see: (a) Bäckvall, J.-E.; Nordberg, R. E.; Björkman, E. E.; Moberg, C. Stereochemistry of Nucleophilic Attack on π-Allylpalladium Complexes. Evidence for *cis*-Migration of Acetate from Palladium to Carbon. *J. Chem. Soc., Chem. Commun.* **1980**, 943–944; (b) Bäckvall, J.-E.; Nordberg, R. E.; Wilhelm, D. Dual Stereoselectivity in the Nucleophilic Attack on (π-Allyl)palladium Complexes. *J. Am. Chem. Soc.* **1985**, *107*, 6892–6898; (c) Grennberg, H.; Langer, V.; Bäckvall, J.-E. Structure and Reactivity of *cis*- and *trans*-Bis-[{5-carbomethoxy-(1,2,3-η)-cyclohexenyl}palladium]. Evidence for a (σ-Allyl) palladium Inetermediate in the *cis*-Migration of Acetate from Palladium to Coordinated π-Allyl. *J. Chem. Soc., Chem. Commun.* **1991**, 1190–1192.

(27) Notable exceptions include α-fluorination chemistry that has been reported in (a) Reference 16; (b) Nakamura, M.; Hajra, A.; Endo, K.; Nakamura, E. Synthesis of Chiral α-Fluoroketones through Catalytic Enantioselective Decarboxylation.

Angew Chem. Int. Ed. **2005**, *44*, 7248–7251; (c) Burger, E. C.; Barron, B. R.; Tunge, J. A. Catalytic Asymmetric Synthesis of Cyclic α-Allylated α-Fluoroketones. *Synlett* **2006**, 2824–2826; (d) Bélanger, É.; Cantin, K.; Messe, O.; Tremblay, M.; Paquin, J.-F. Enantioselective Pd-Catalyzed Allylation Reaction of Fluorinated Silyl Enol Ethers. *J. Am. Chem. Soc.* **2007**, *129*, 1034–1035.

(28) For the use of dioxanones as a template for the synthesis of stereochemically rich substrances, see: (a) Enders, D.; Bettray, W. in *Asymmetric Synthesis with Chemical and Biological Methods* (Eds: D. Enders, K.-E. Jaeger), WILEY-VCH, Weinheim, **2007**, pp. 38–75; (b) Enders, D.; Breuer, I.; Drosdow, E. Asymmetric Synthesis of 4'-epi-Trachycladines A and B. *Synthesis* **2005**, 3239–3244; (c) Enders, D.; Grondal, C. Direct Organocatalytic De Novo Synthesis of Carbohydrates. *Angew. Chem. Int. Ed.* **2005**, *44*, 1210–1212; (d) Enders, D.; Bockstiegel, B. Enantioselective Alkylation of 2,2-Dimethyl-1,3-dioxan-5-one Using the SAMP-/RAMP-Hydrazone Method. *Synthesis*, **1989**, 493–496.

(29) Majewski, M.; Gleave, D. M.; Nowak, P. 1,3-Dioxan-5-ones: synthesis, deprotonation, and reactions of their lithium enolates. *Can. J. Chem.* **1995**, *73*, 1616–1626.

(30) Tsukada, N.; Sugawara, S.; Inoue, Y. Benzannulation from Alkynes and Allyl Tosylates via a π-Allylpalladium Intermediate. *Org. Lett.* **2000**, *2*, 655–657.

(31) Phillips, G. H.; Bailey, E. J.; Bain, B. M.; Borella, R. A.; Buckton, J. B.; Clark, J. C.; Doherty, A. E.; English, A. F.; Fazakerley, H.; Laing, S. B.; Lane-Allman, E.; Robinson, J. D.; Sandford, P. E.; Sharratt, P. J.; Steeples, I. P.; Stonehouse, R. D.;

Williamson, C. Synthesis and Structure—Activity Relationships in a Series of Antiinflammatory Corticosteroid Analogues, Halomethyl Androstane-17β-carbothiolates and -17β-carboselenoates. *J. Med. Chem.* **1994**, *37*, 3717–3729.

(32) (a) Rapado, L. P.; Bulugahapitiya, V.; Renauld, P. Synthesis of Non-Racemic 1-Hydroxycycloalkene-1-carboxylic-Acid Derivatives by Metathesis of α,α-Dialkylated Glycolate Derivatives. *Helv. Chim. Acta* **2000**, *83*, 1625–1623; (b) Wolinsky, J.; Novak, R.; Vasilev, R. A Stereospecific Synthesis of (±)-Quinic Acid. *J. Org. Chem.* **1964**, *29*, 3596–3598.

(33) For a review, see: Barco, A.; Benetti, S.; De Risi, C.; Marchetti, P.; Pollini, G. P.; Zanirato, V. D-(–)-Quinic acid: a chiron store for natural product synthesis. *Tetrahedron: Asymmetry* **1997**, *8*, 3515–3545.

(34) (a) Garg, N. K.; Caspi, D. D.; Stoltz, B. M. The Total Synthesis of (+)-Dragmacidin F. *J. Am. Chem. Soc.* **2004**, *126*, 9552–9553; (b) Garg, N. K.; Caspi, D. D.; Stoltz, B. M. Development of an Enantiodivergent Strategy for the Total Synthesis of (+)- and (–)-Dragmacidin F from a Single Enantiomer of Quinic Acid. *J. Am. Chem. Soc.* **2005**, *127*, 5970–5978; (c) Garg, N. K.; Stoltz, B. M. A unified synthetic approach to the pyrazinone dragmacidins. *Chem. Commun.* **2006**, 3769–3779; (d) Garg, N. K.; Caspi, D. D.; Stoltz, B. M. The Utility of the Classical and Oxidative Heck Reactions in Natural Product Synthesis: Studies Directed toward the Total Synthesis of Dragmacidin F. *Synlett* **2006**, 3081–3087.

(35) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. Synthesis and Activity of a New Generation of Ruthenium-Based Olefin Metathesis Catalysts Coordinated with 1,3-Dimesityl-4,5-dihydroimidazol-2-ylidene Ligands. *Org. Lett.* **1999**, *1*, 953–956.

(36) Baldwin, J. E.; Adlington, R. M.; Marquess, D. G.; Pitt, A. R.; Porter, M. J.; Russell, A. T. Evidence for an Insertion-Homolysis Mechanism for Carbon-Sulphur Bond Formation in Penicillin Biosynthesis; 1. Synthesis of Tripeptide Probes. *Tetrahedron* **1996**, *52*, 2515–2536.

(37) Enders, D.; Jegelka, U.; Dücker, B. Diastereo- and Enantioselective Synthesis of C_2-Symmetrical HIV-1 Protease Inhibitors. *Angew. Chem. Int. Ed.* **1993**, *32*, 423–425.

(38) Previous preparations include: (a) reference 28d; (b) Enders, D.; Herriger, C. Asymmetric Synthesis of 2-Trifluoromethyl-1,2,3-triols. *Eur. J. Org. Chem.* **2007**, *7*, 1085–1090.

(39) Forbes, D. C.; Ene, D. G.; Doyle, M. P. Stereoselective Synthesis of Substituted 5-Hydroxy-1,3-dioxanes. *Synthesis* **1998**, *6*, 879–882.

(40) Previous preparations include: (a) Enders, D.; Voith, M. Asymmetric Synthesis of Monoprotected Double Allylic Alcohols. *Synthesis* **2002**, *11*, 1571–1577; (b) Enders, D.; Muller-Huwen, A. Asymmetric Synthesis of 2-Amino-1,3-diols and D-*erythro*-Sphinganine. *Eur. J. Org. Chem.* **2004**, *8*, 1732–1739.

(41) Previous preparations include: (a) Ibrahem, I.; Córdova, A. Direct Catalytic Intermolecular α-Allylic Alkylation of Aldehydes by Combination of Transition-Metal and Organocatalysis. *Angew. Chem. Int. Ed.* **2006**, *45*, 1952–1956;

(b) Enders, D.; Voith, M.; Ince, S. J. Preparation and Reactions of 2,2-Dimethyl-1,3-dioxan-5-one-SAMP-Hydrazone: A Versatile Chiral Dihydroxyacetone Equivalent. *Synthesis* **2002**, *12*, 1775–1779.

(42) Previous preparations include: Enders, D.; Hundertmark, T.; Lazny, R. Copper(II) Chloride Mediated Racemization-Free Hydrolysis of α-Alkylated Ketone SAMP-Hydrazones. *Synth. Commun.* **1999**, *29*, 27–34.

(43) Eames, J.; Mitchell, H. J.; Nelson, A.; O'Brien, P.; Warren, S.; Wyatt, P. An efficient protocol for Sharpless-style racemic dihydroxylation. *J. Chem. Soc. Perkin Trans. 1* **1999**, *8*, 1095–1103.

(44) Previous preparations of the racemate include: (a) Uneyama, K.; Matsuda, H.; Torii, S. Grignard-type allylation of carbonyl compounds in methanol by the electrochemically recycled allyltin reagent. *Tetrahedron Lett.* **1984**, *25*, 6017–6020; (b) Ojima, I.; Miyazawa, Y.; Kumagai, M. Asymmetric Addition of Allyltrimethylsilane to (–)-Menthyl Pyruvate and Phenylglyoxylate. *J. Chem. Soc. Chem. Commun.* **1976**, 927–928.

(45) Previous preparations of the racemate have been reported: Achmatowitz, O.; Cieplak, P.; Rozwadowski, J. The Ene Reaction of Dimethyl Mesoxalate with Electron Deficient Olefins. *Pol. J. Chem.* **1989**, *63*, 531–539.

(46) Previous enantioenriched preparations include: Langner, M.; Remy, P.; Bolm, C. C_1-Symmetric Aminosulfoximines as Ligands in Copper-Catalyzed Carbonyl-Ene Reactions. *Synlett* **2005**, *5*, 781–784.

(47) Previous preparations of the racemate have been reported: Naruta, Y.; Uno, H.; Maruyama, K. New Synthesis of Methyl 2-Triorganosilyl-3-butenoates as a new synthon of 3-Methoxycarbonylallyl Anion. *Chem. Lett.* **1982**, 961–964.

APPENDIX FOUR

Spectra of Compounds Relevant to Chapter Four

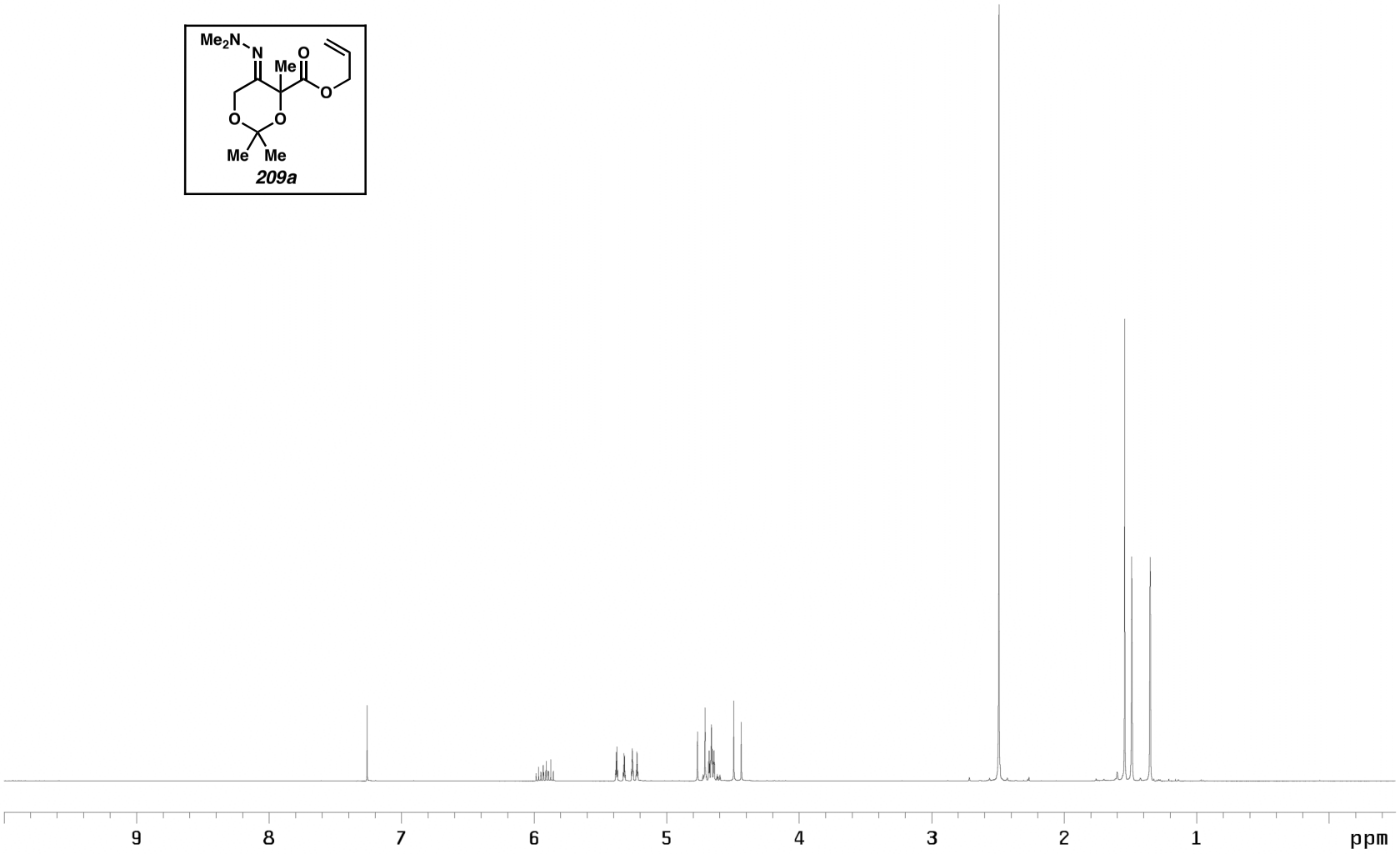


Figure A4.1 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **209a**

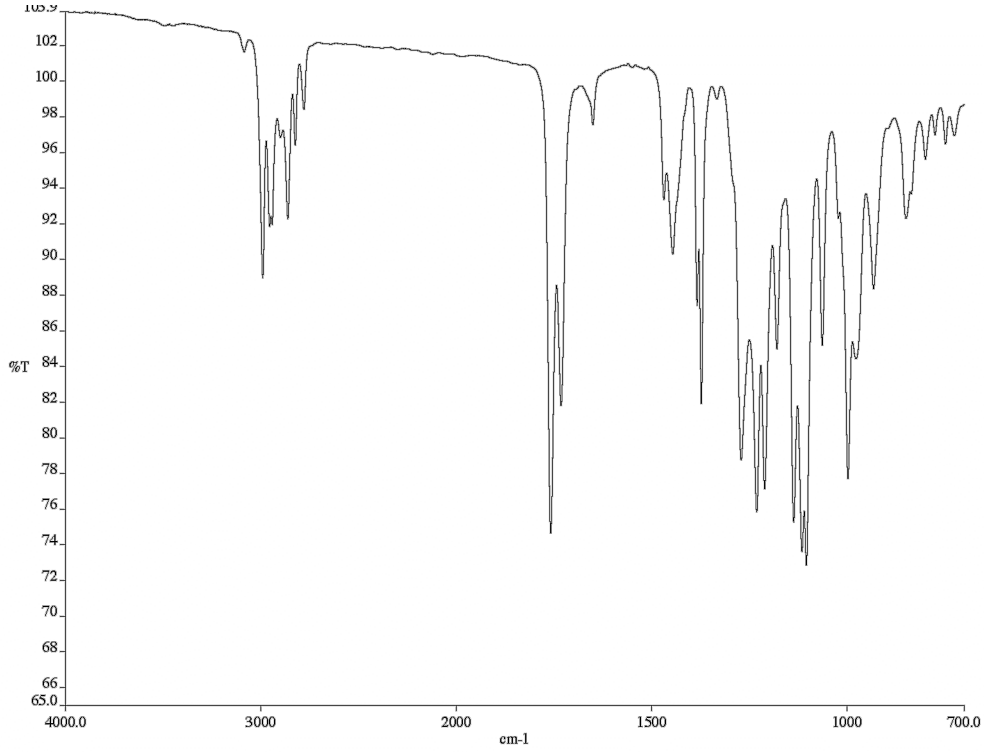


Figure A4.2 Infrared spectrum (thin film/NaCl) of compound **209a**

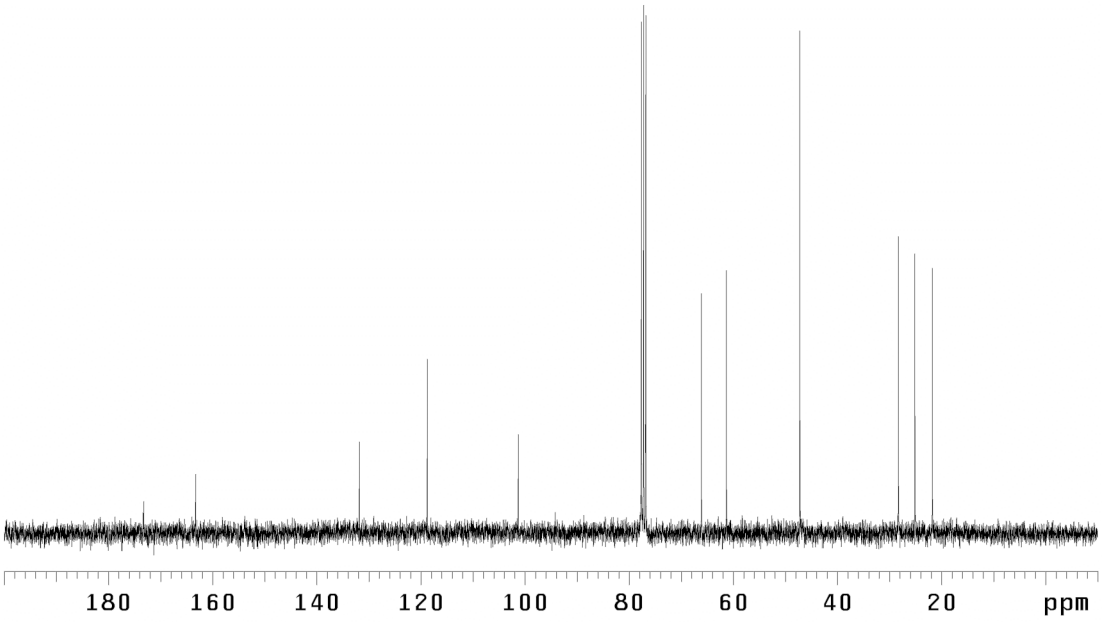


Figure A4.3 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **209a**

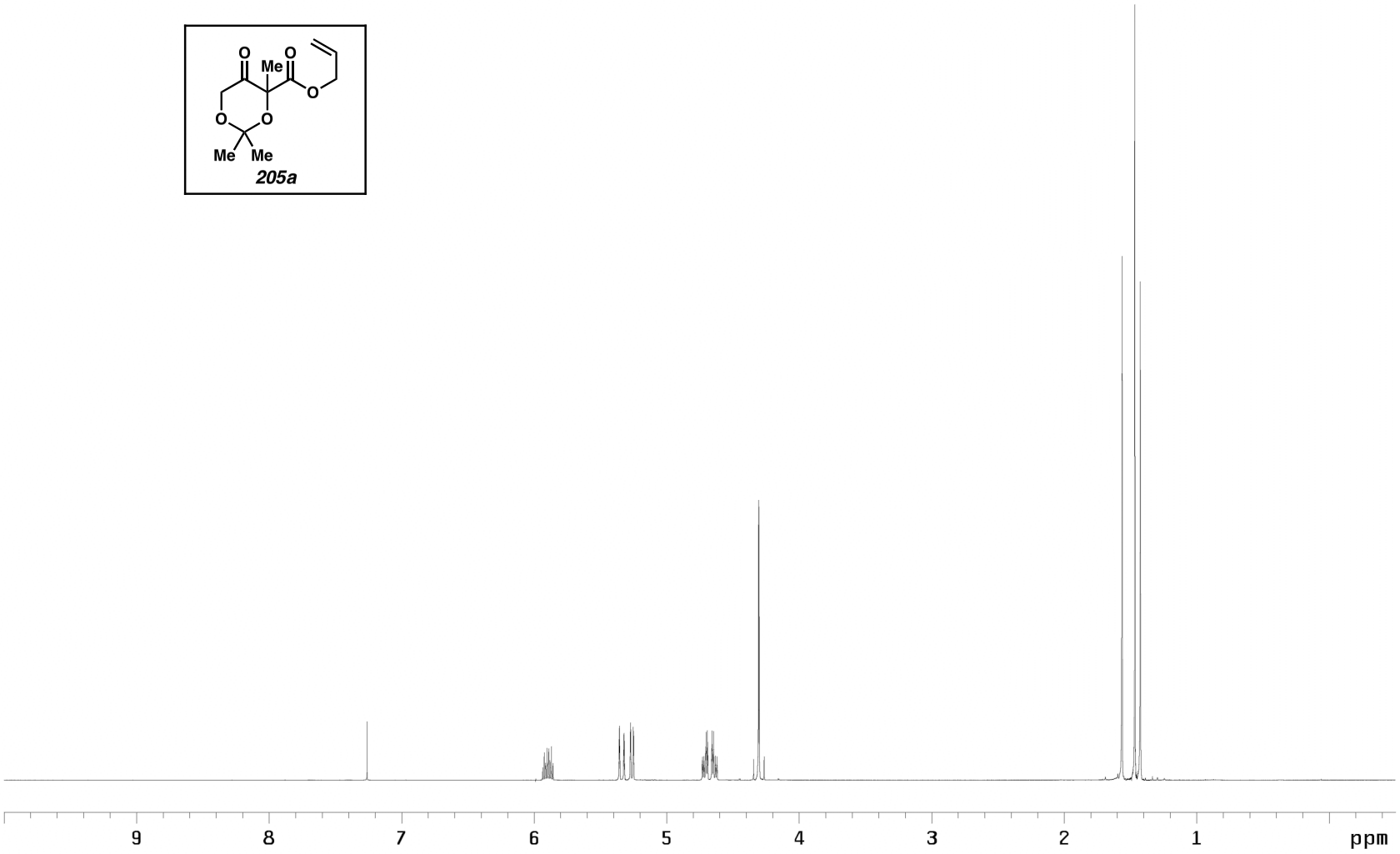


Figure A4.4 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **205a**

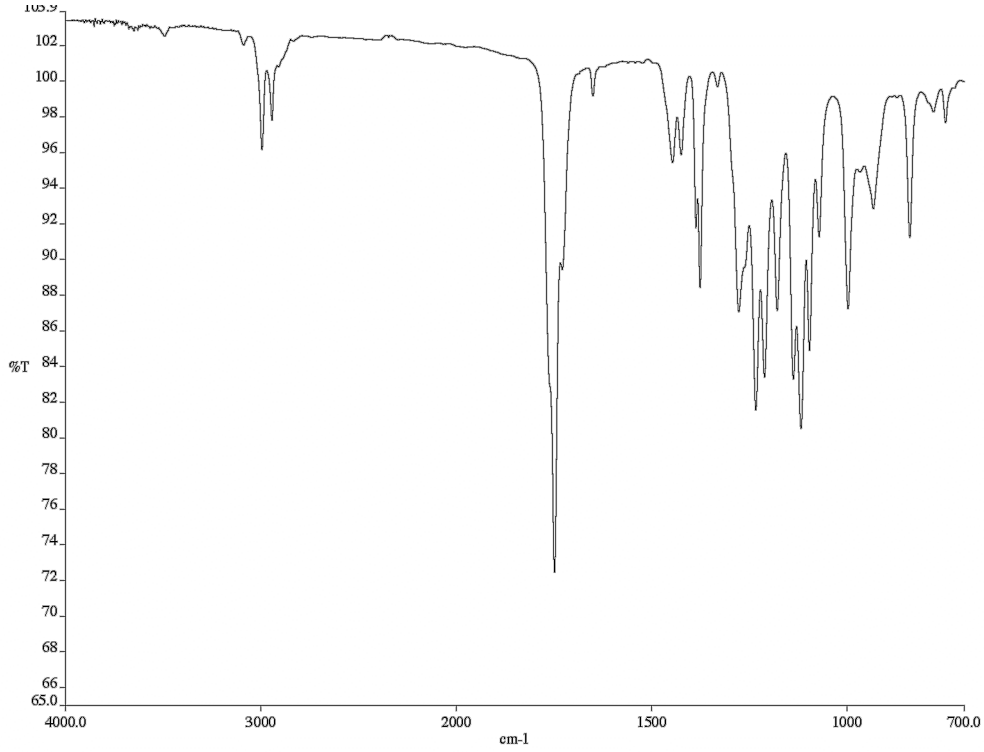


Figure A4.5 Infrared spectrum (thin film/NaCl) of compound **205a**

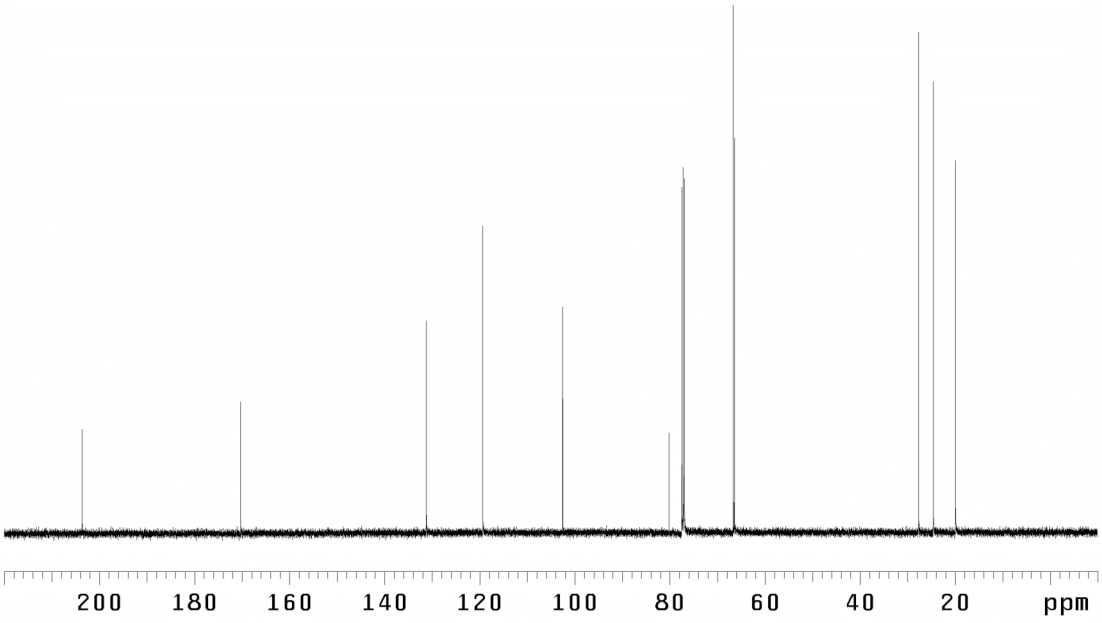


Figure A4.6 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **205a**

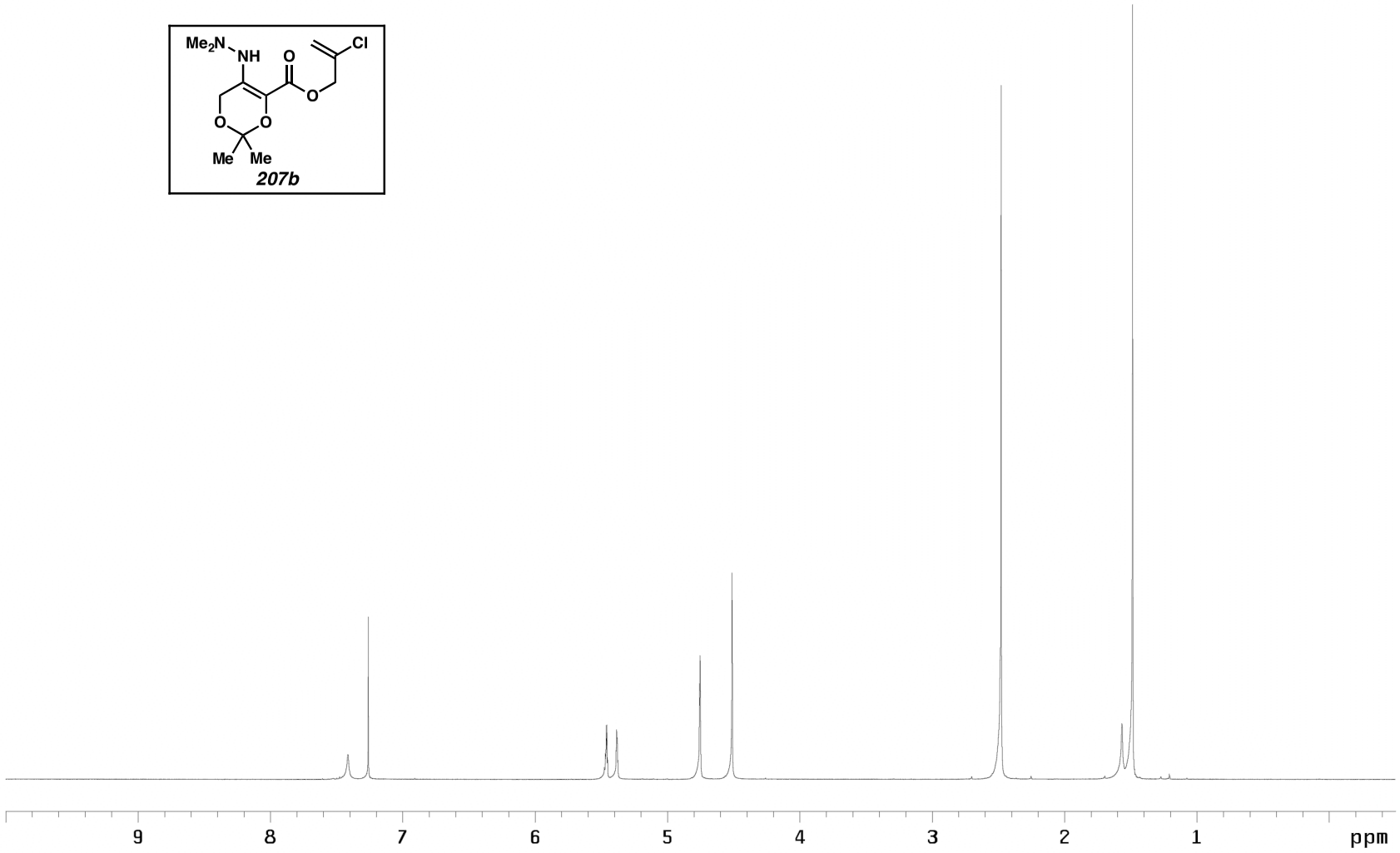


Figure A4.7 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **207b**

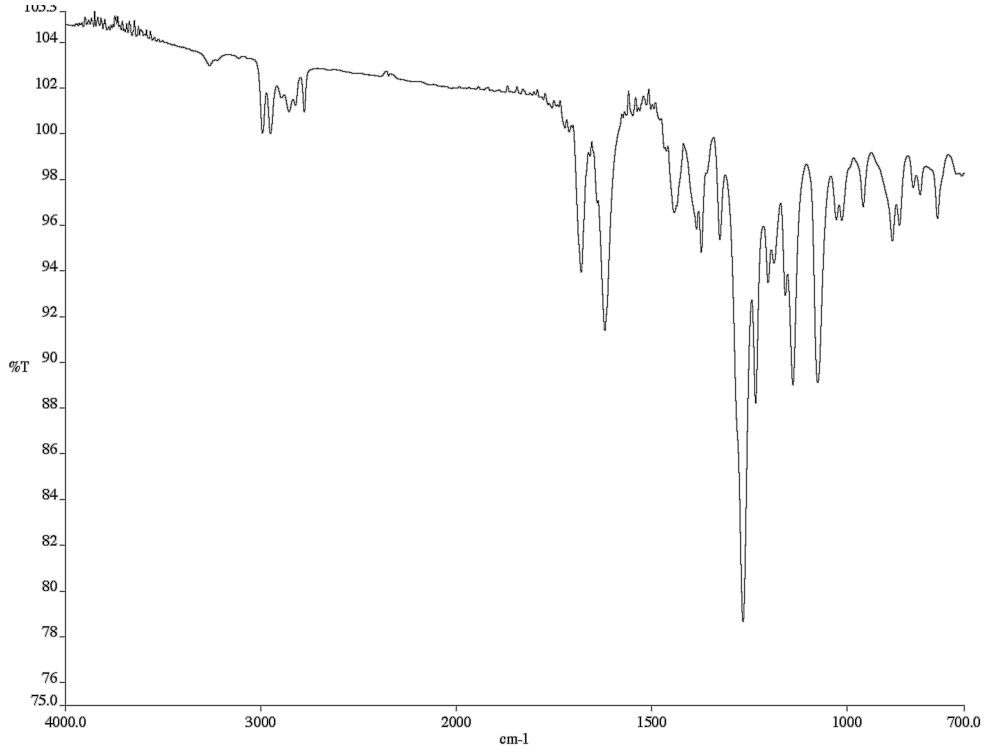


Figure A4.8 Infrared spectrum (thin film/NaCl) of compound **207b**

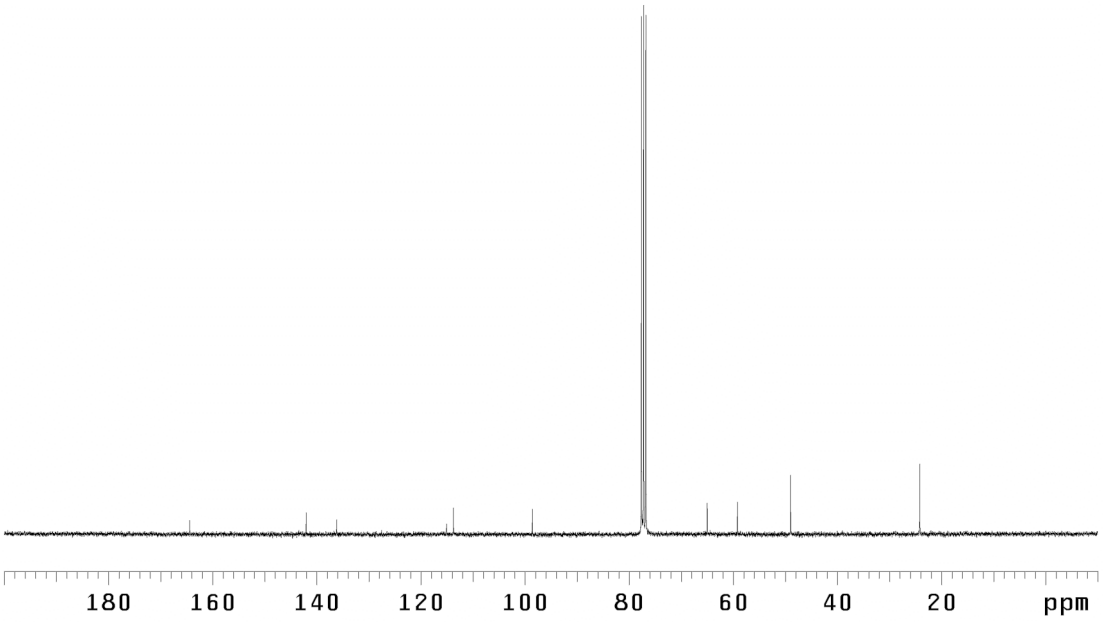


Figure A4.9 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **207b**

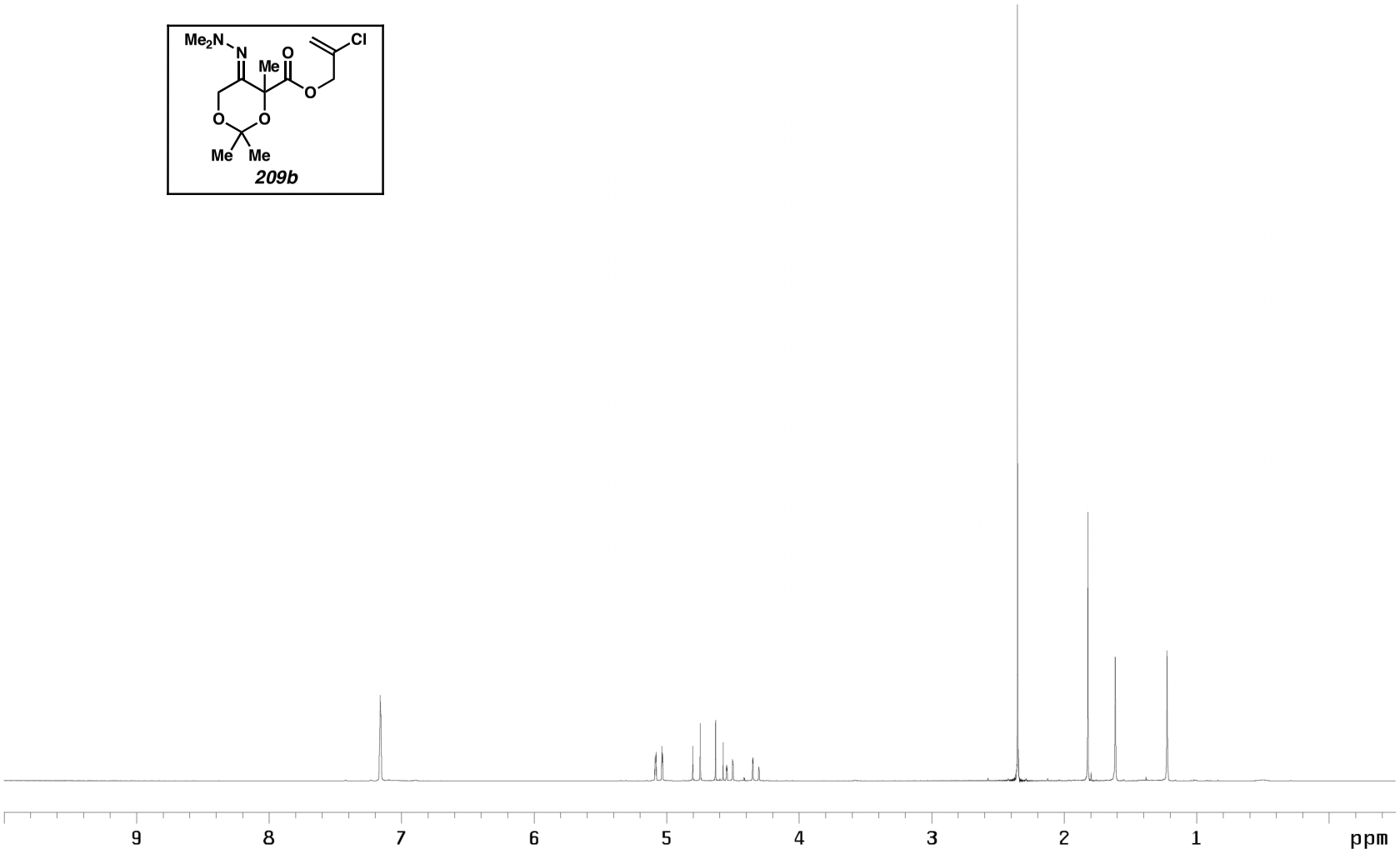


Figure A4.10 ^{1}H NMR (300 MHz, C_6D_6) of compound **209b**

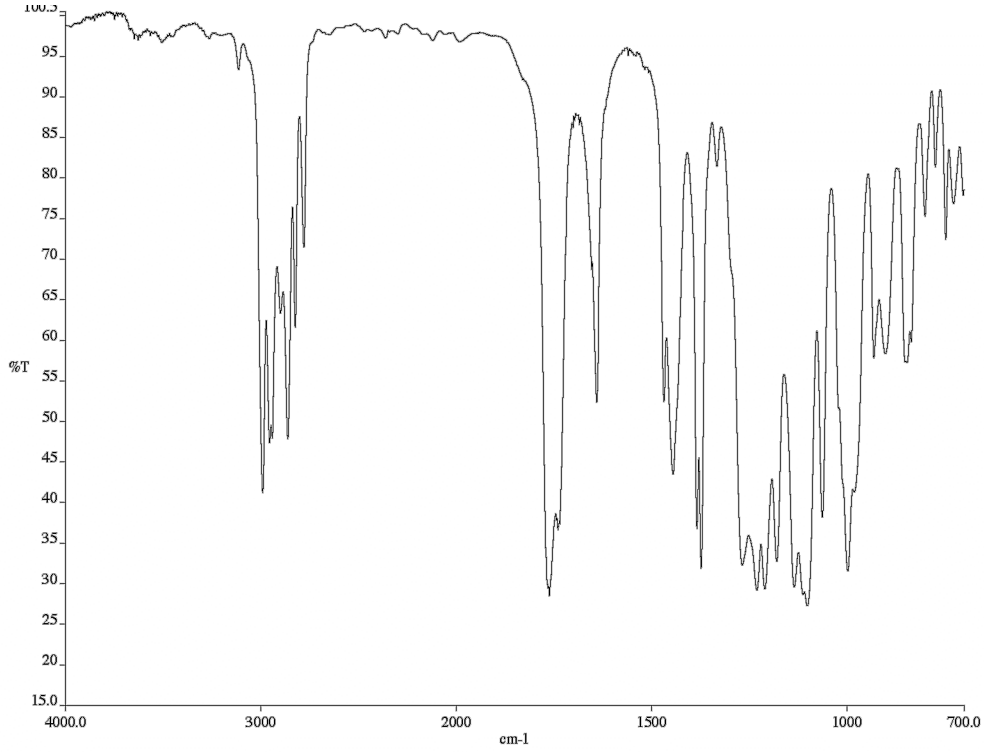


Figure A4.11 Infrared spectrum (thin film/NaCl) of compound **209b**

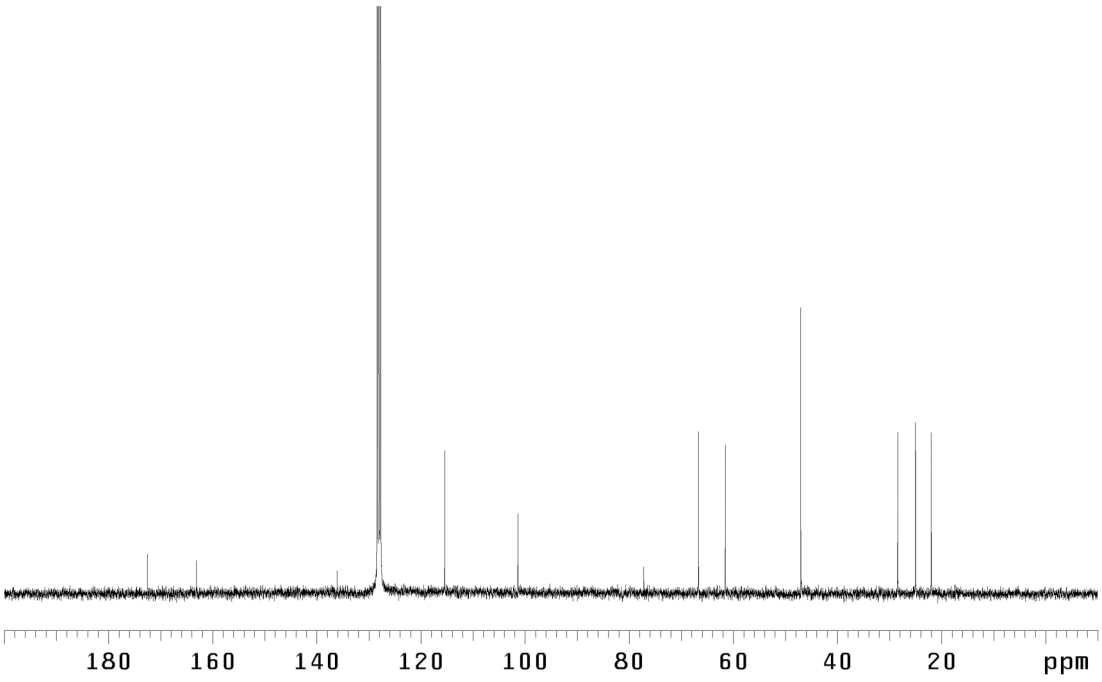


Figure A4.12 ^{13}C NMR (75 MHz, C_6D_6) of compound **209b**

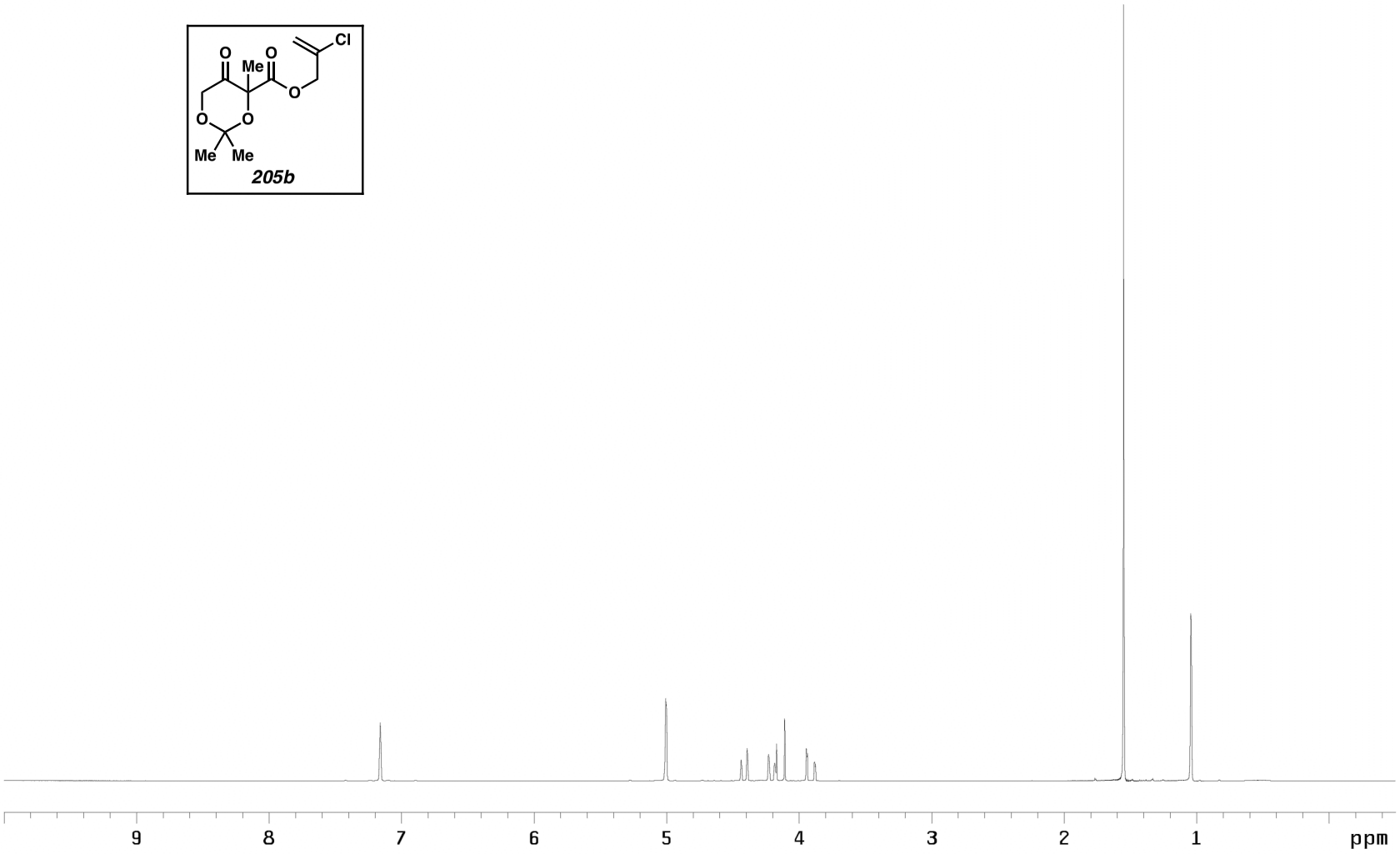


Figure A4.13 ^{1}H NMR (300 MHz, C_6D_6) of compound **205b**

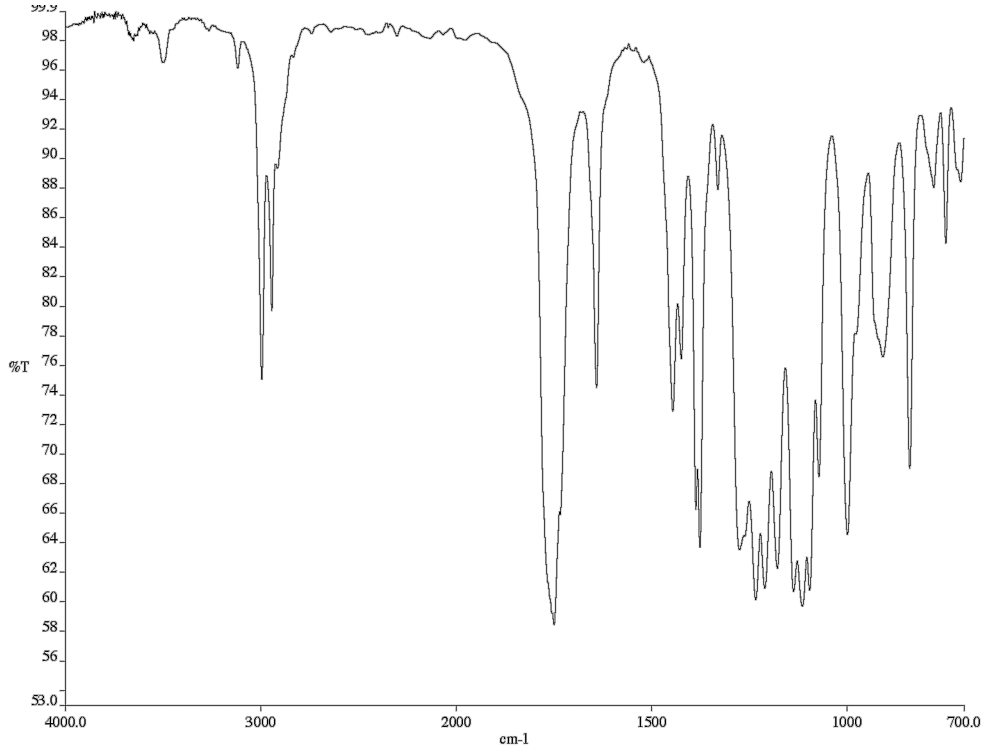


Figure A4.14 Infrared spectrum (thin film/NaCl) of compound **205b**

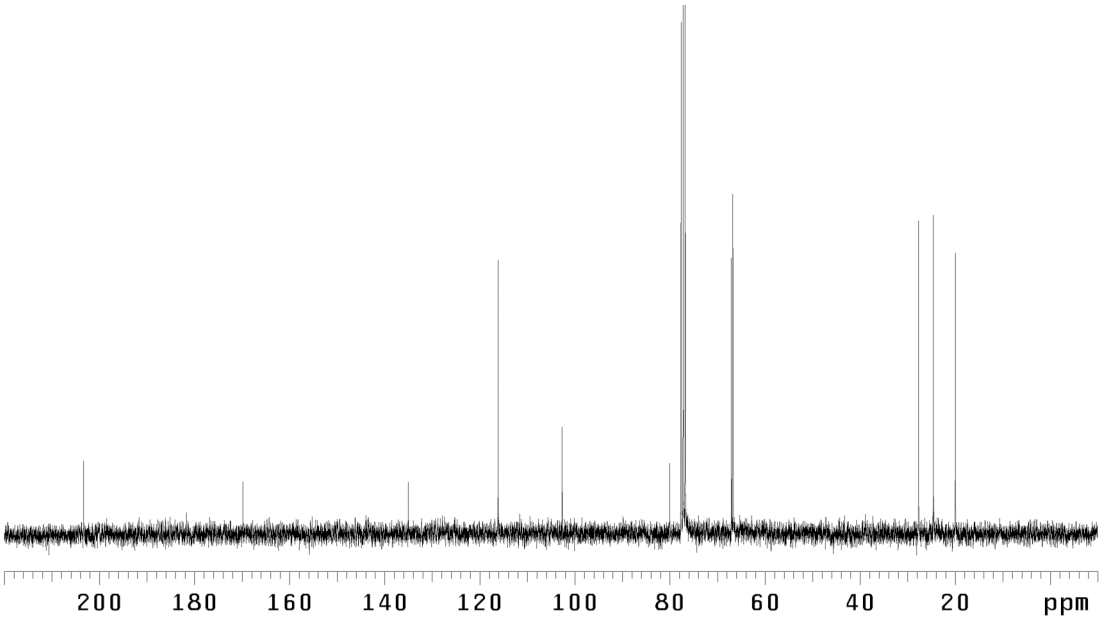


Figure A4.15 ^{13}C NMR (75 MHz, C_6D_6) of compound **205b**

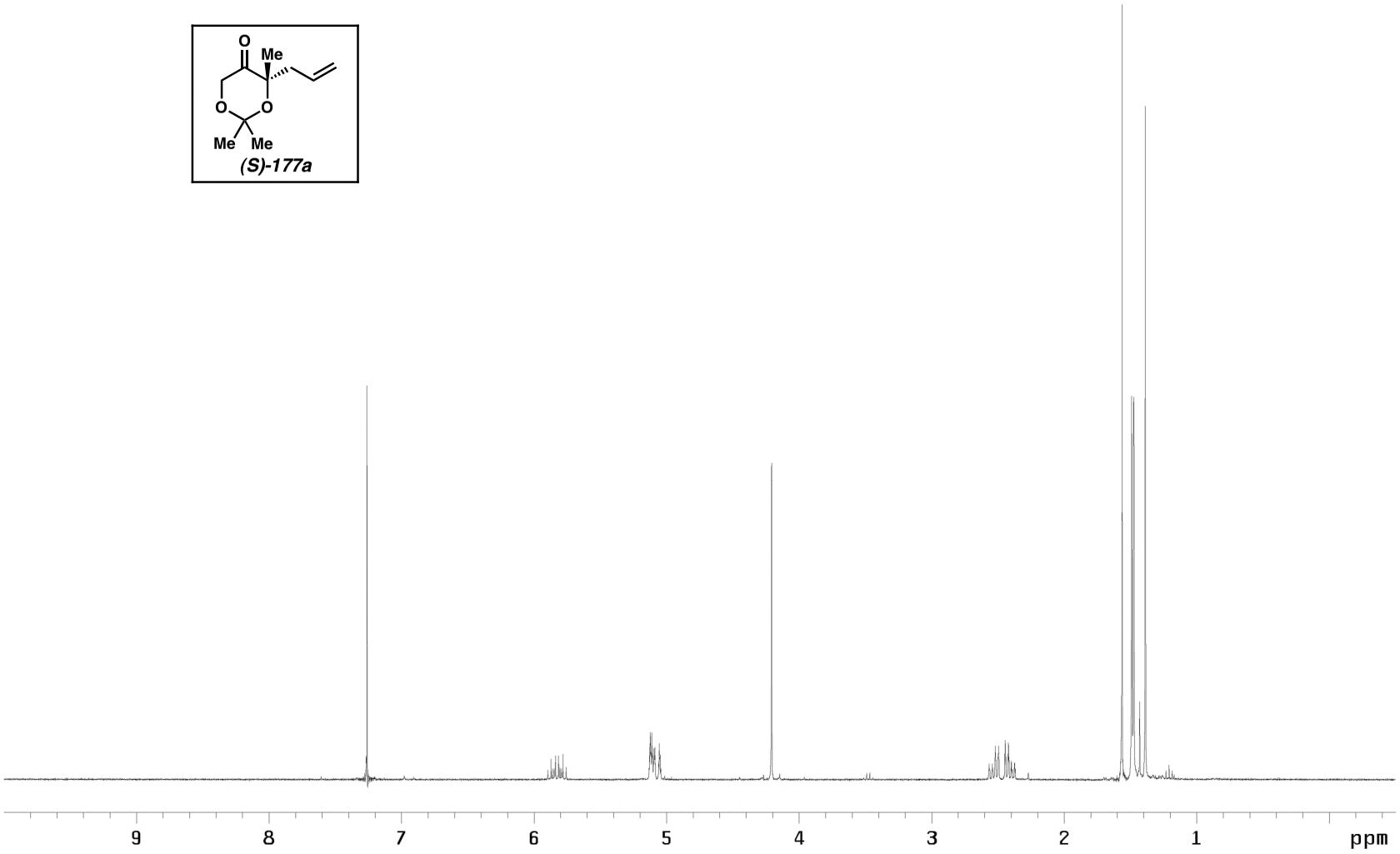


Figure A4.16 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **177a**

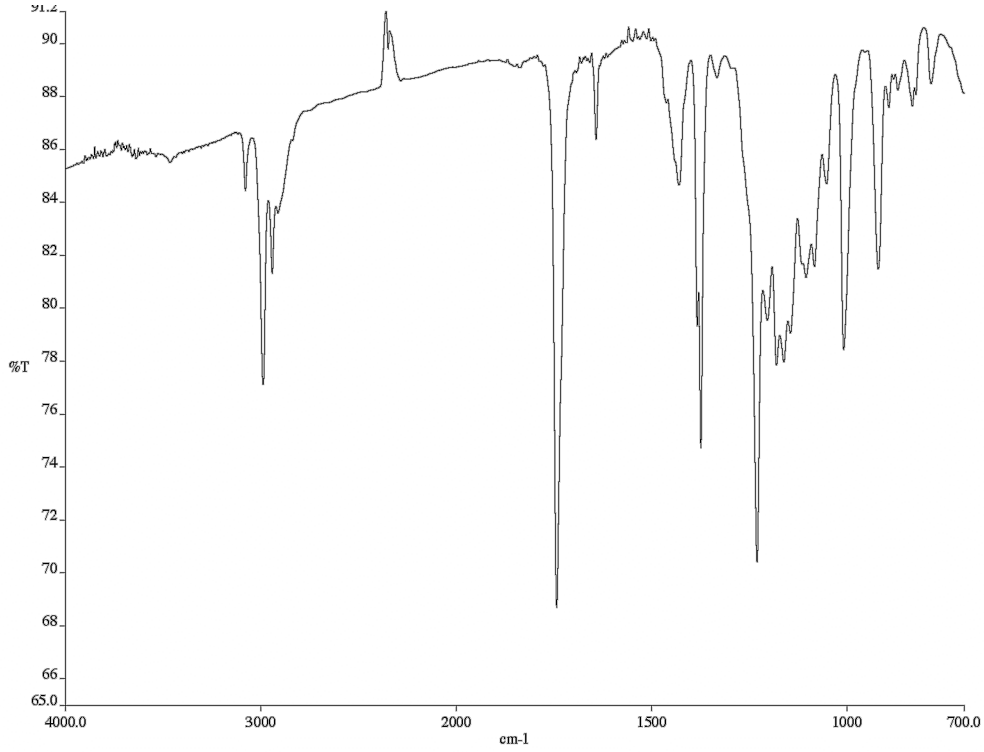


Figure A4.17 Infrared spectrum (thin film/NaCl) of compound **177a**

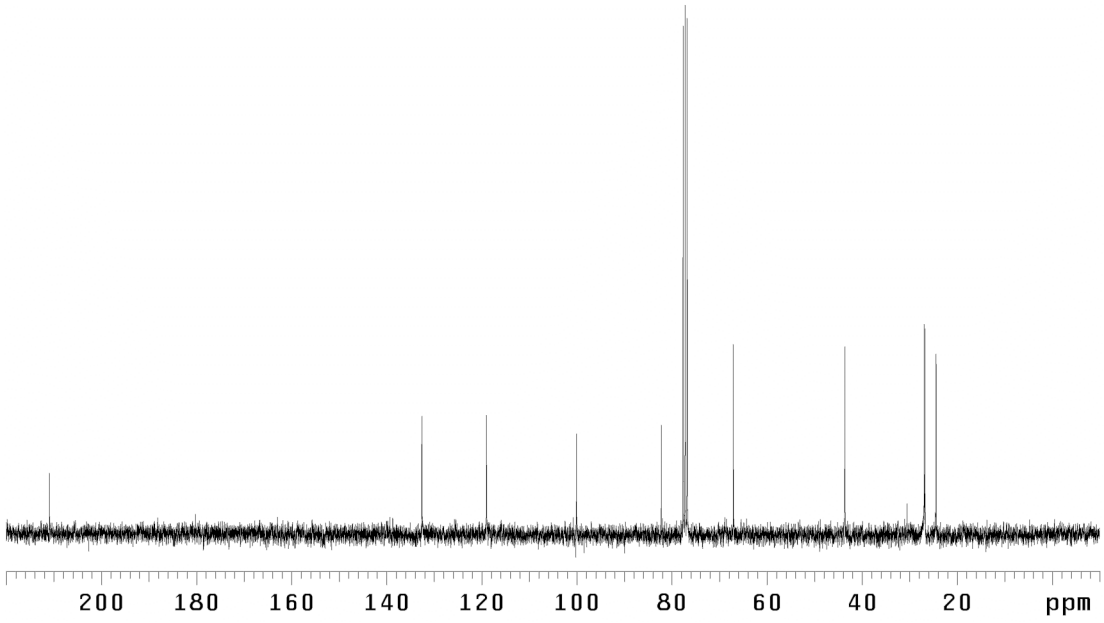


Figure A4.18 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **177a**

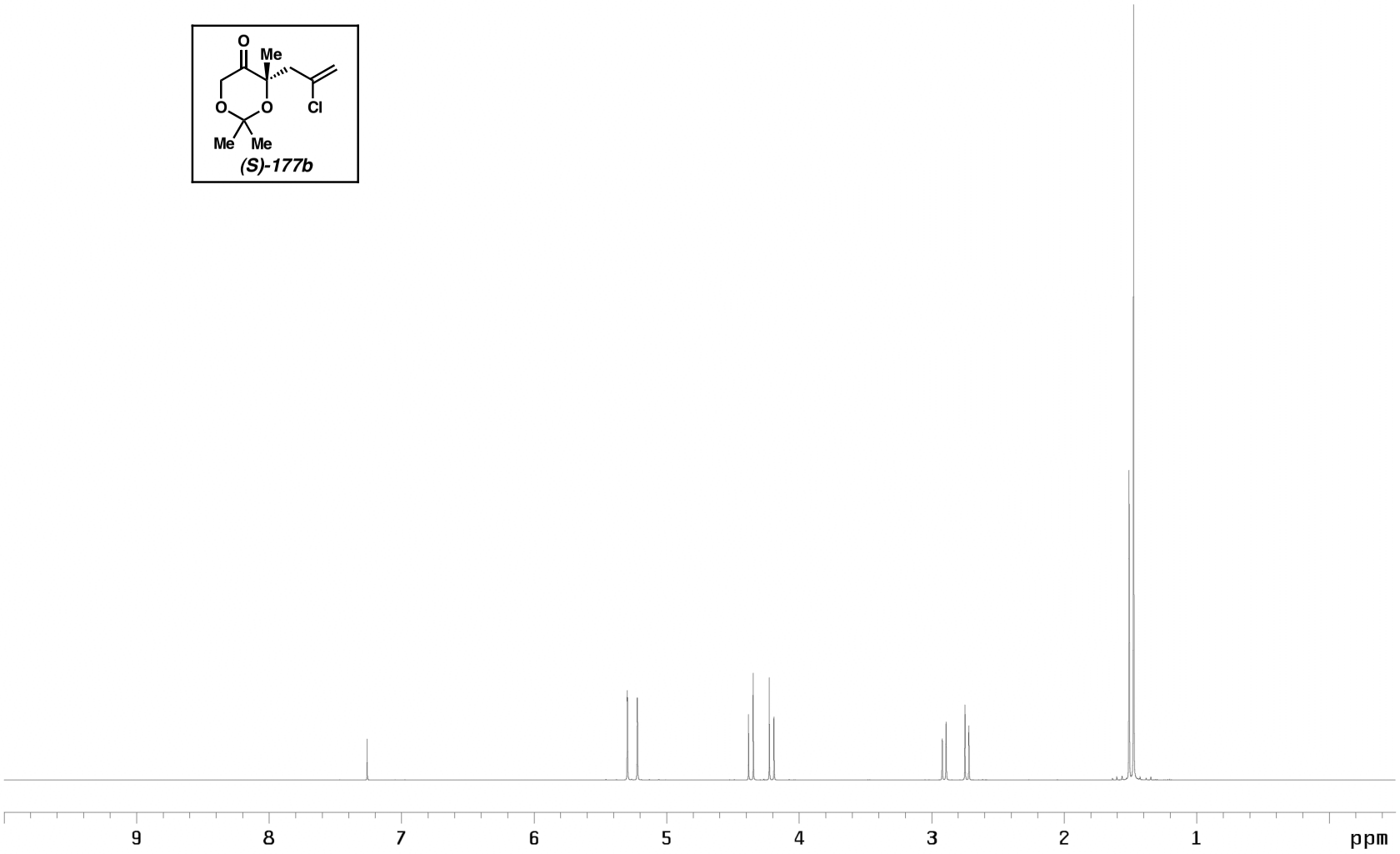


Figure A4.19 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **177b**

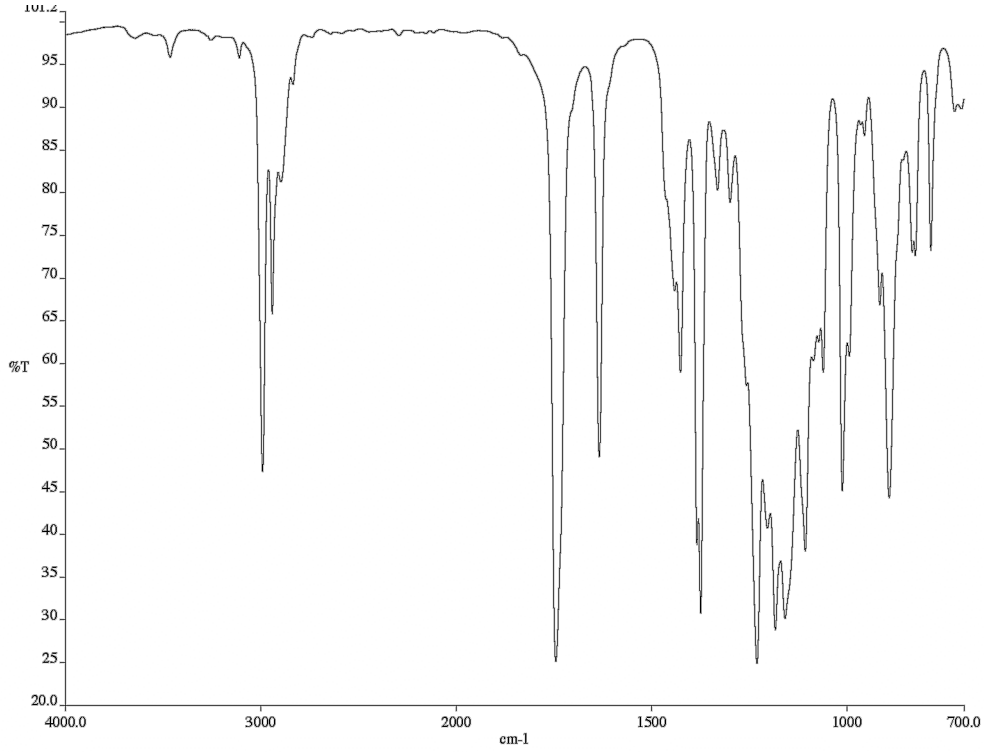


Figure A4.20 Infrared spectrum (thin film/NaCl) of compound **177b**

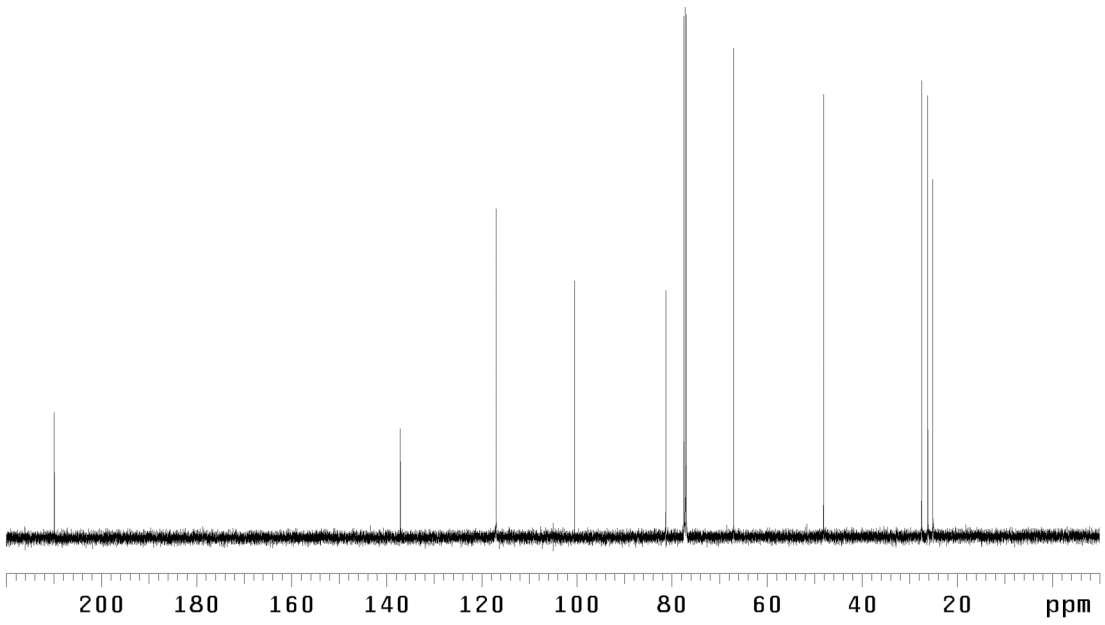


Figure A4.21 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **177b**

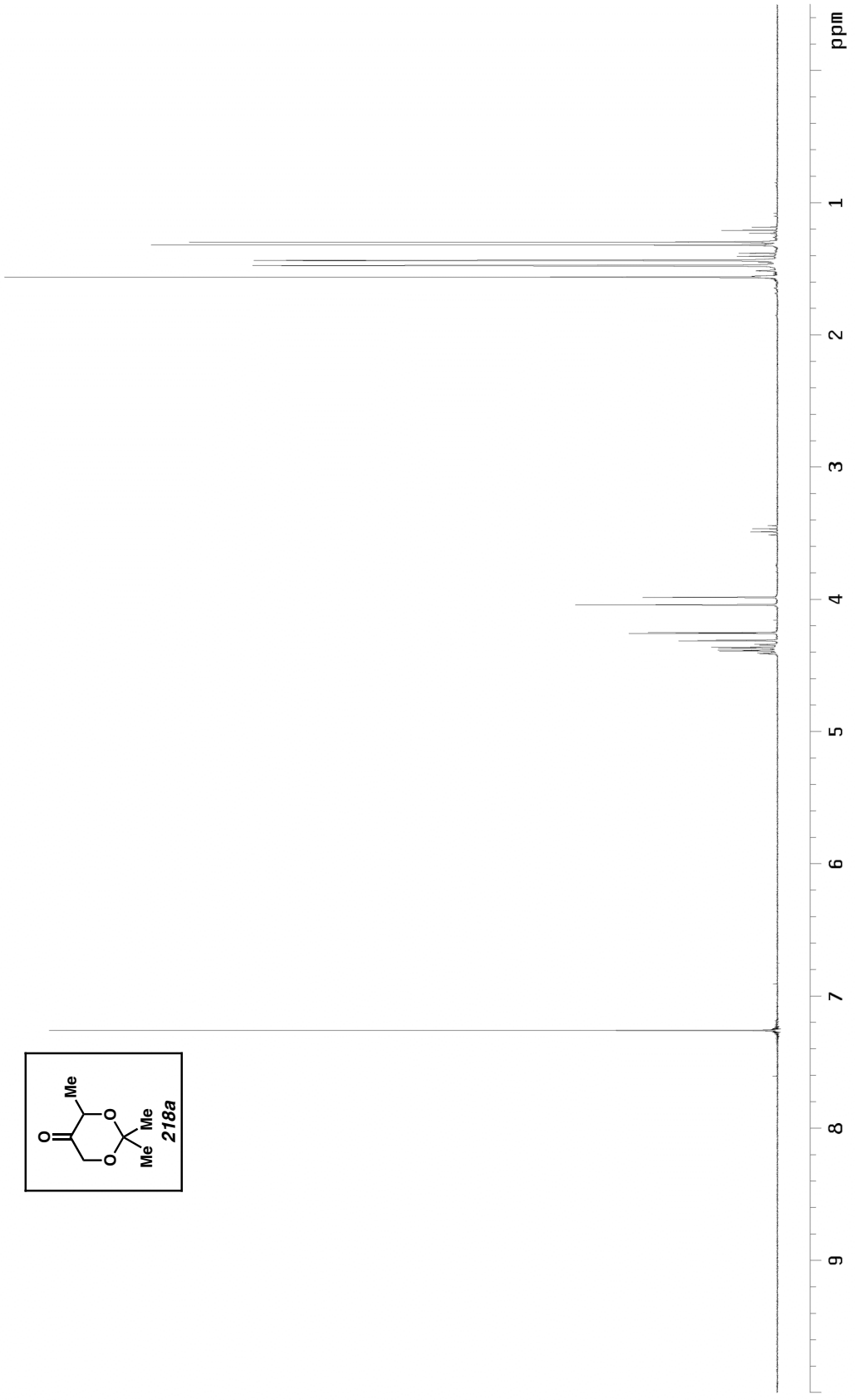


Figure A4.22 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **218a**

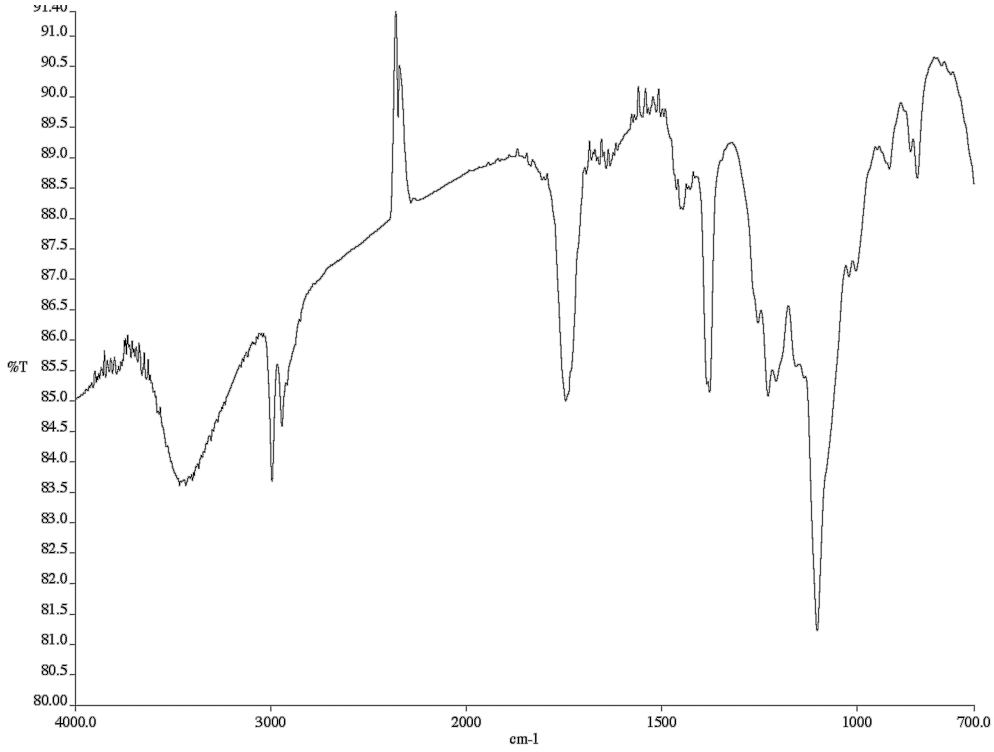


Figure A4.23 Infrared spectrum (thin film/NaCl) of compound **218a**

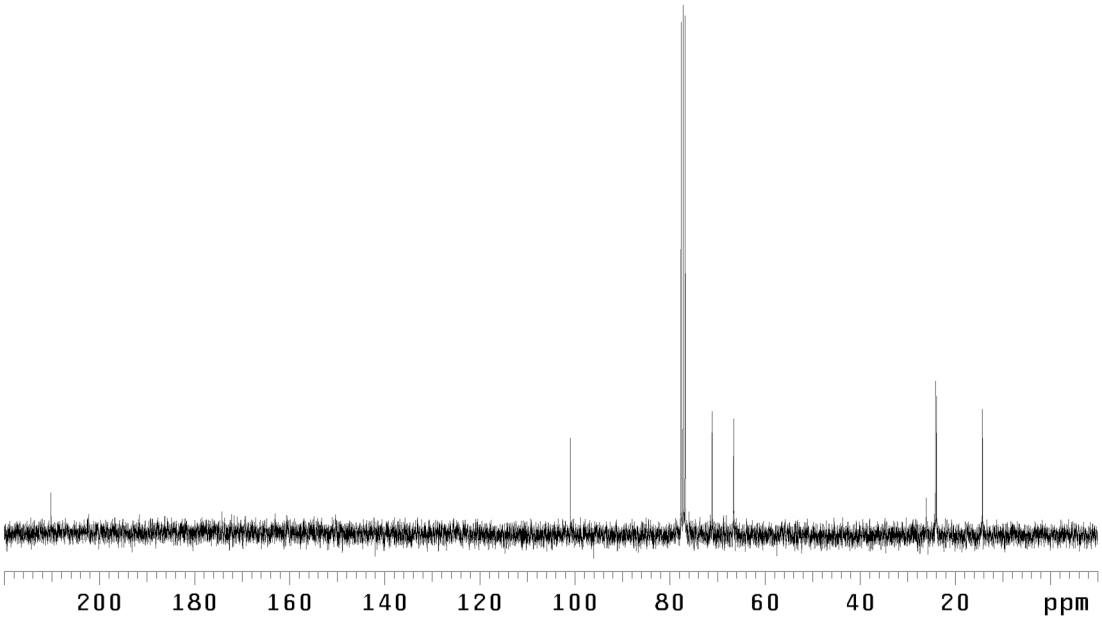


Figure A4.24 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **218a**

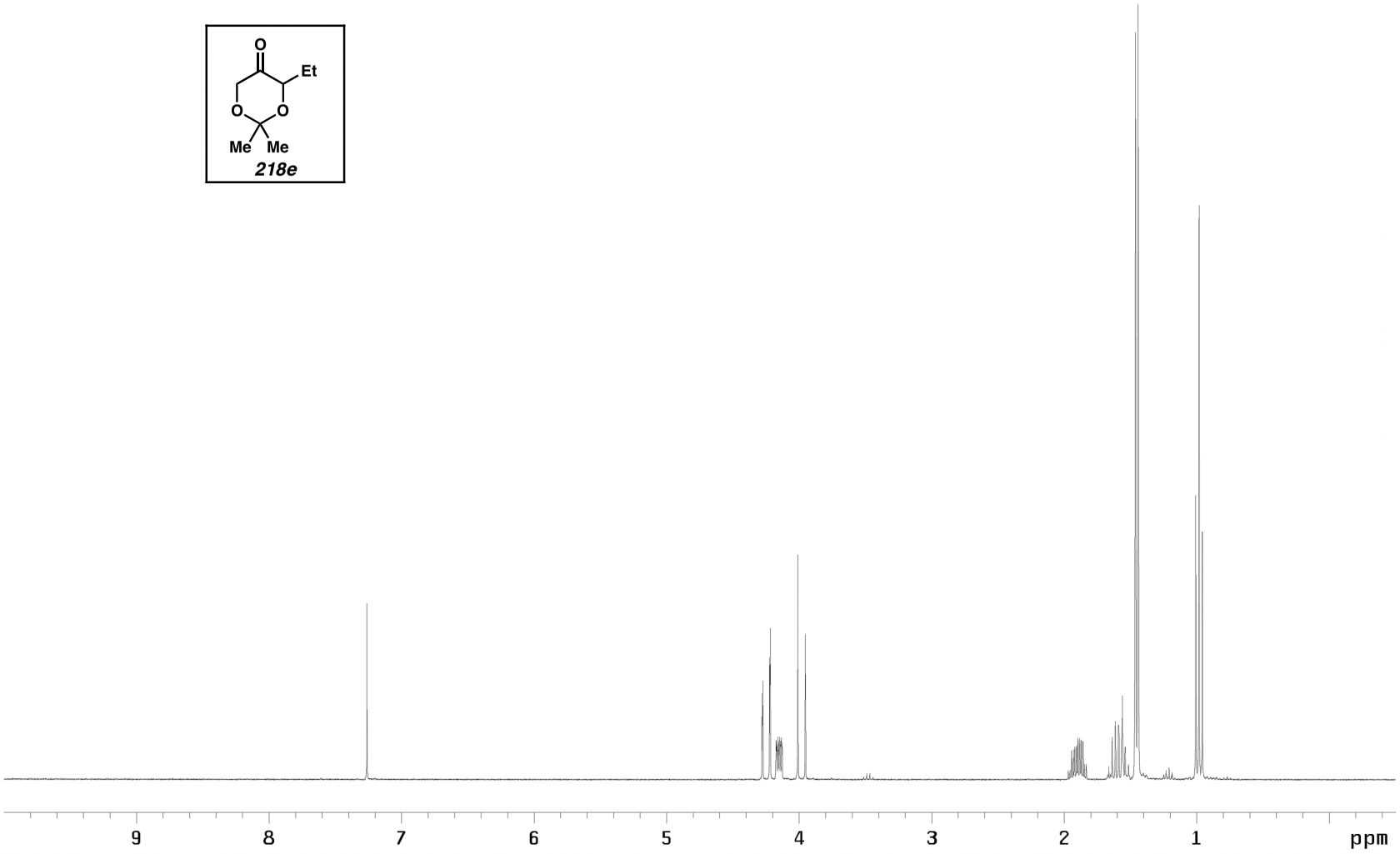


Figure A4.25 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **218e**

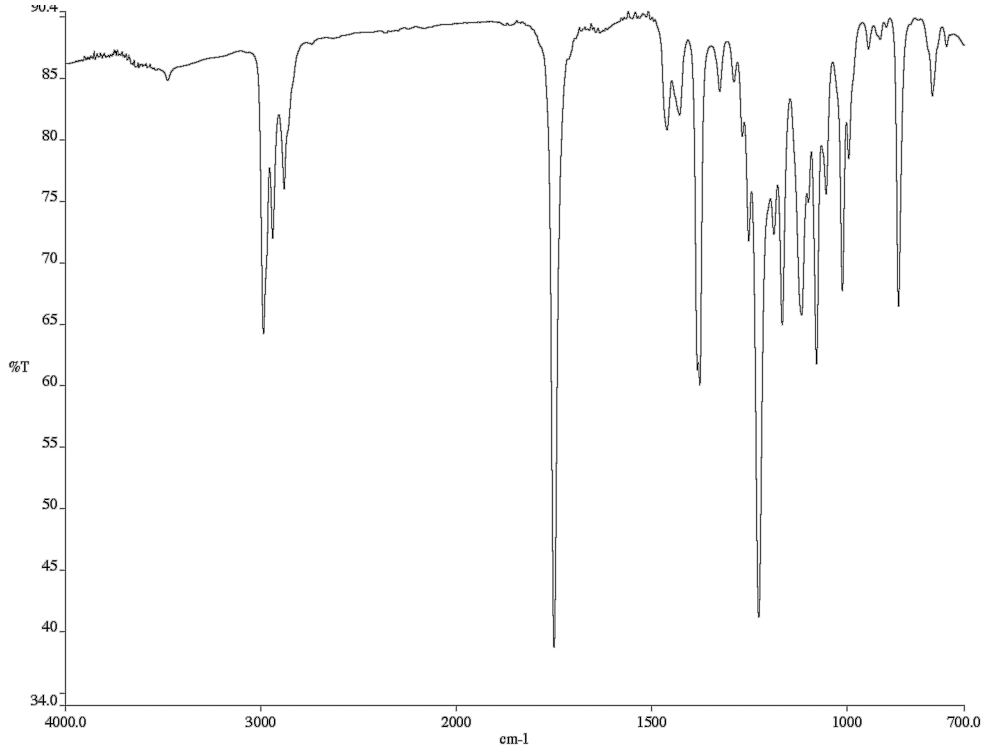


Figure A4.26 Infrared spectrum (thin film/NaCl) of compound **218e**

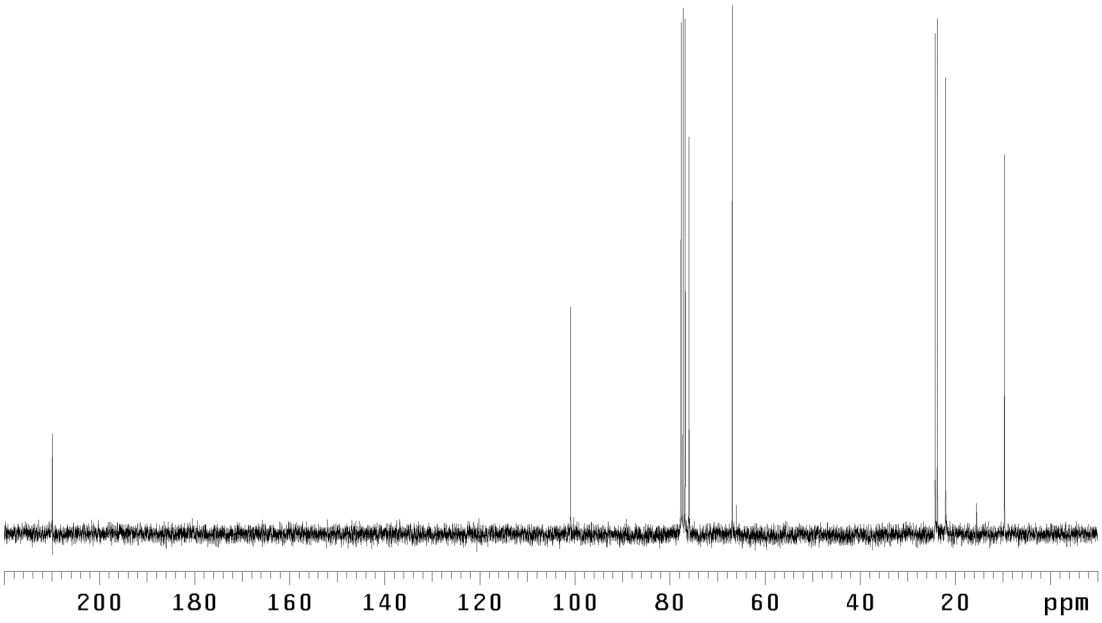


Figure A4.27 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **218e**

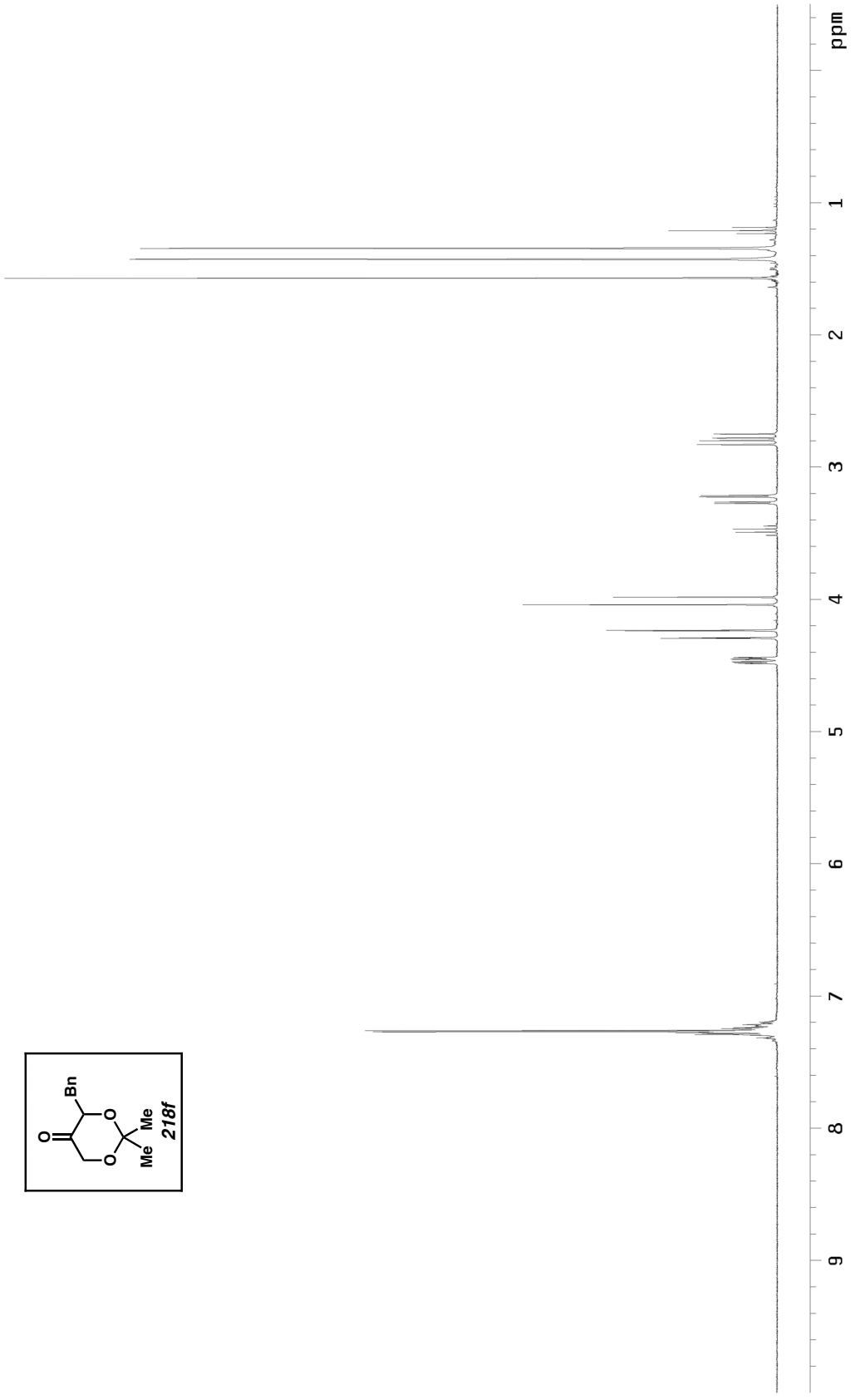


Figure A4.28 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **218f**

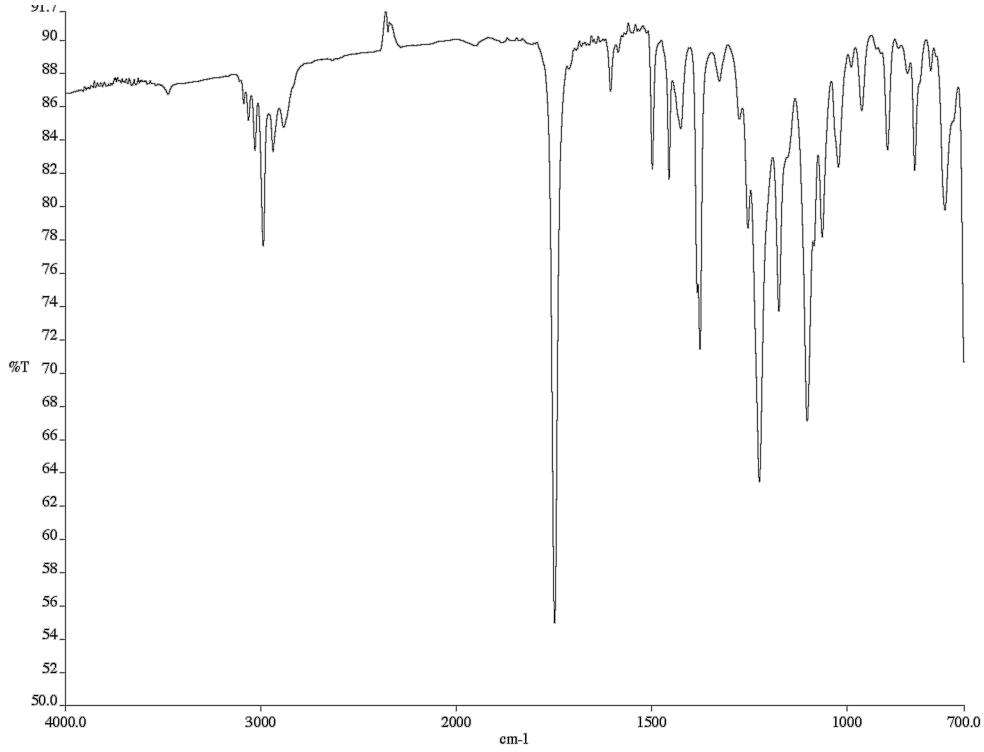


Figure A4.29 Infrared spectrum (thin film/NaCl) of compound **218f**

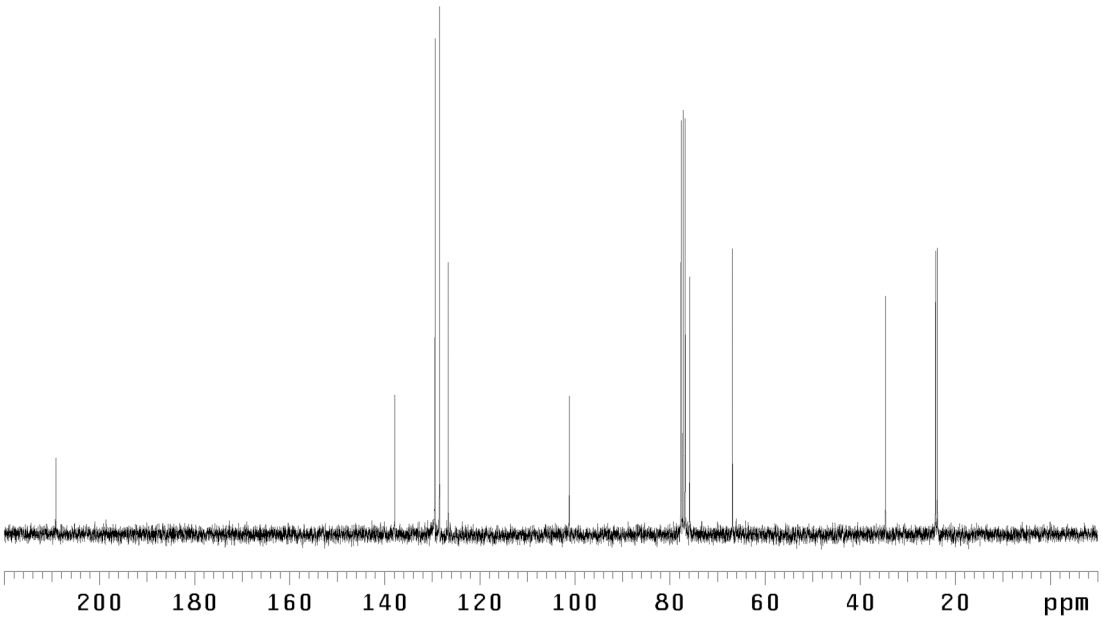


Figure A4.30 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **218f**

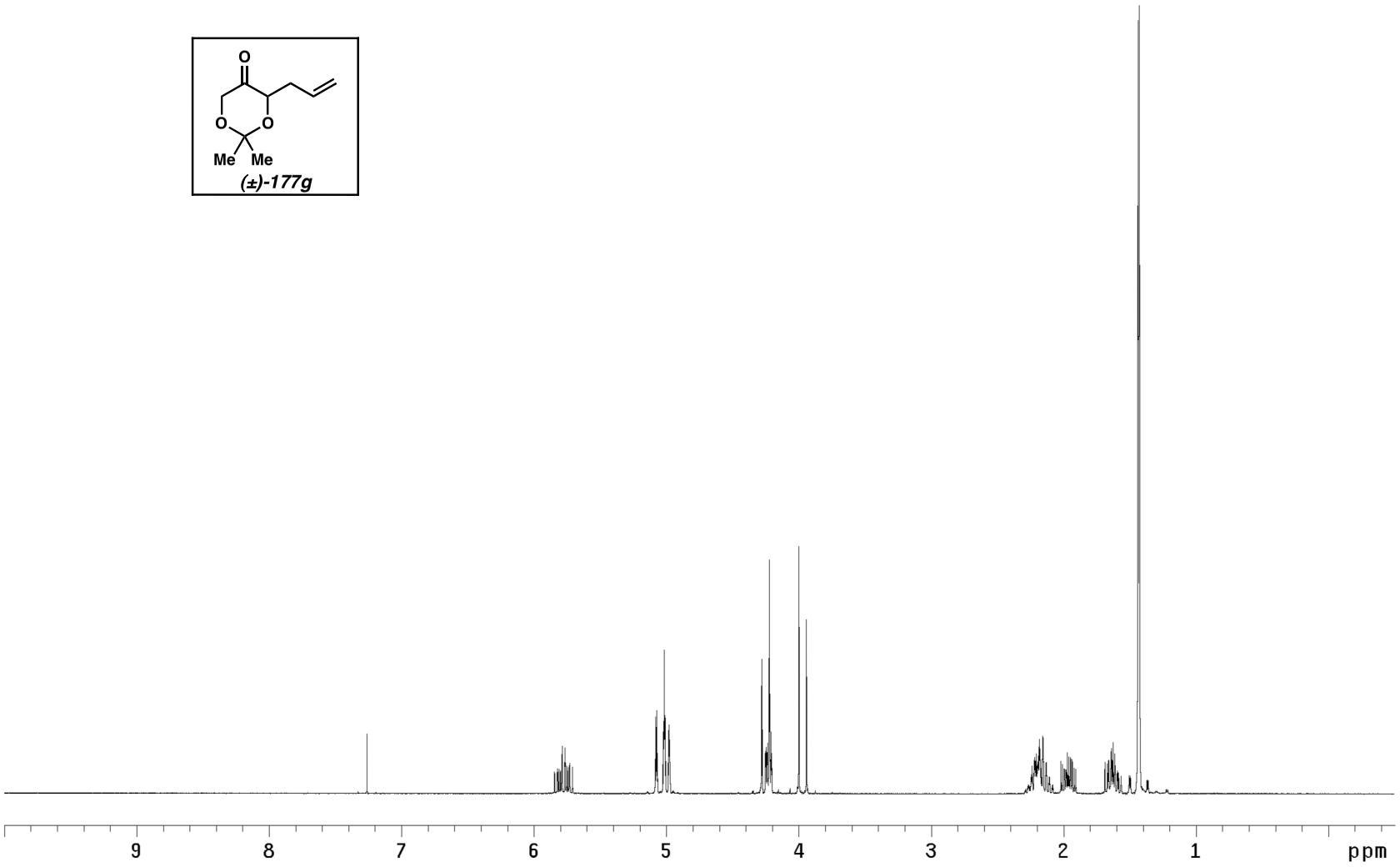


Figure A4.31 ^{1}H NMR (300 MHz, $CDCl_3$) of compound (±)-**177g**

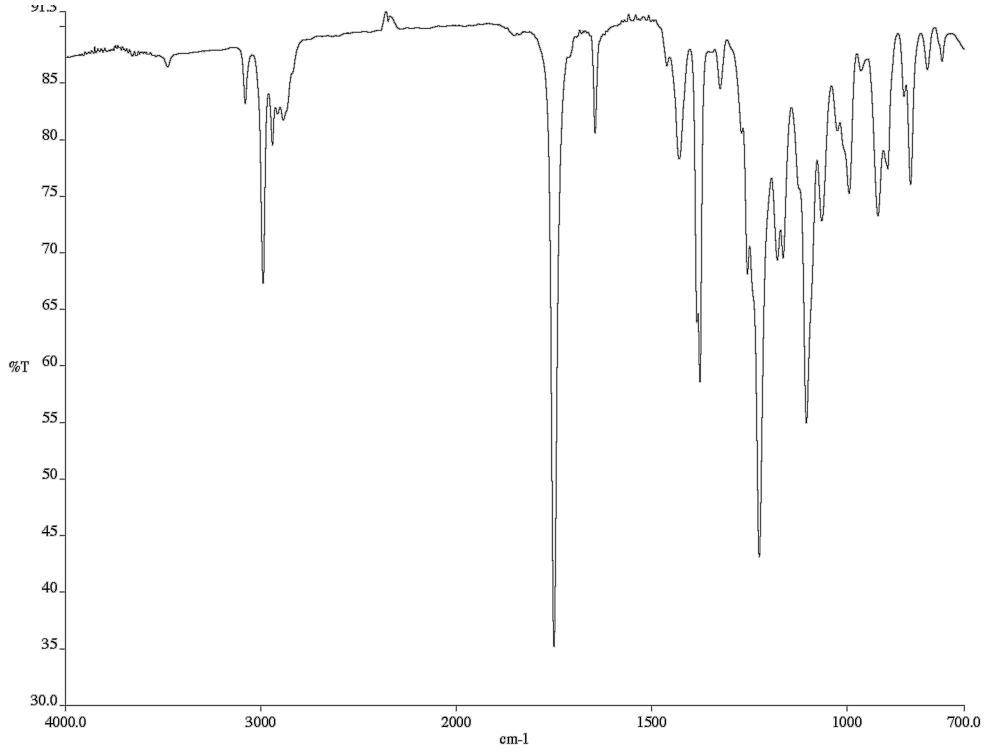


Figure A4.32 Infrared spectrum (thin film/NaCl) of allyl (±)-**177g**

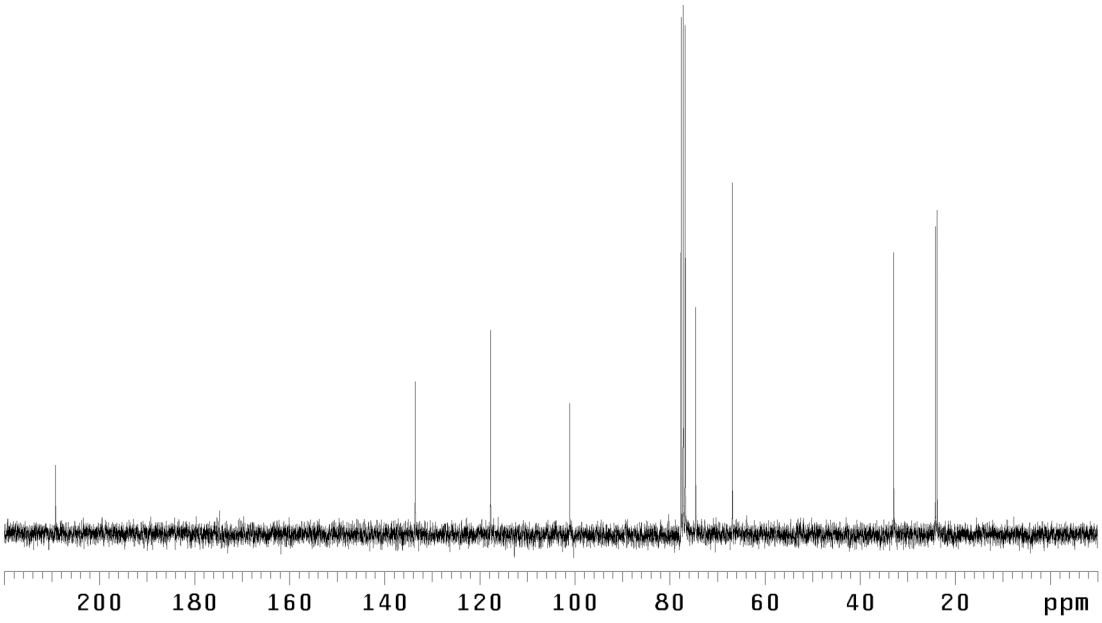


Figure A4.33 ^{13}C NMR (75 MHz, $CDCl_3$) of allyl (±)-**177g**

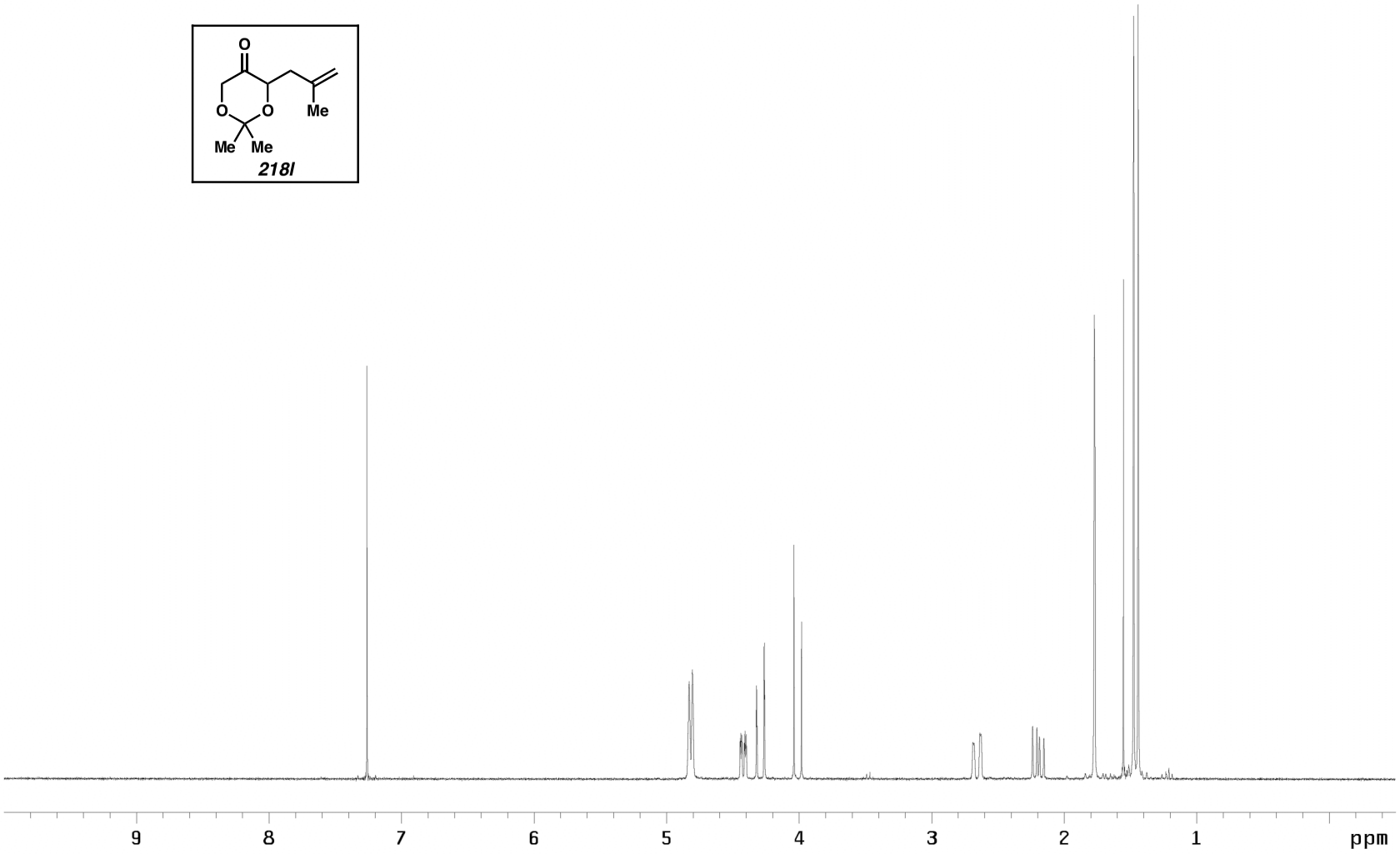


Figure A4.34 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **218l**

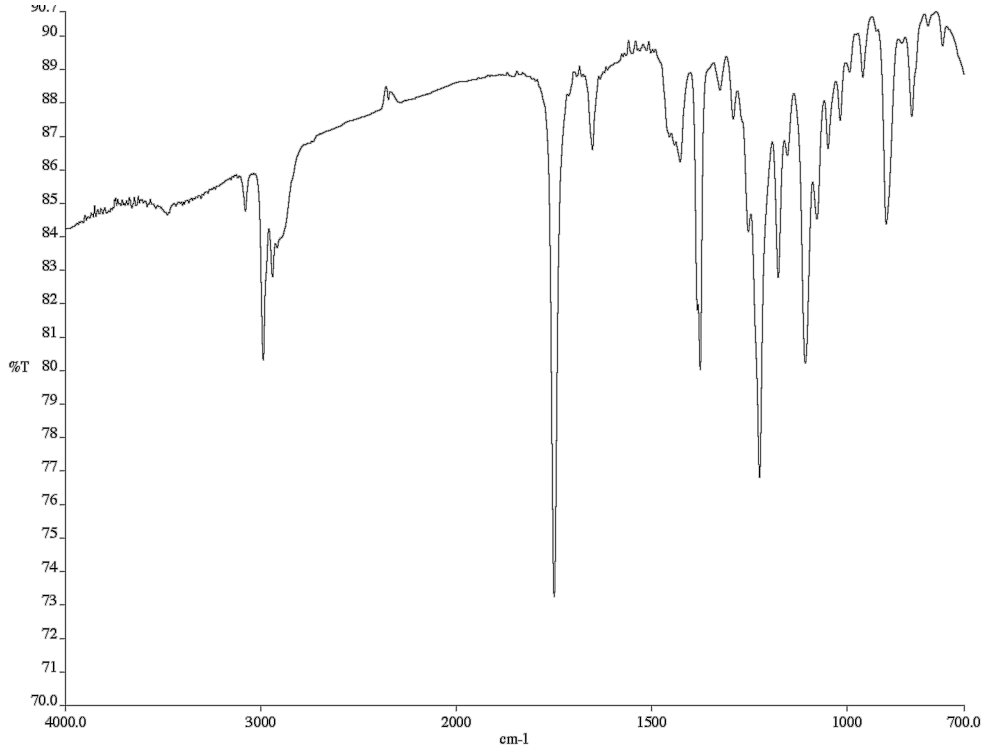


Figure A4.35 Infrared spectrum (thin film/NaCl) of compound **218l**

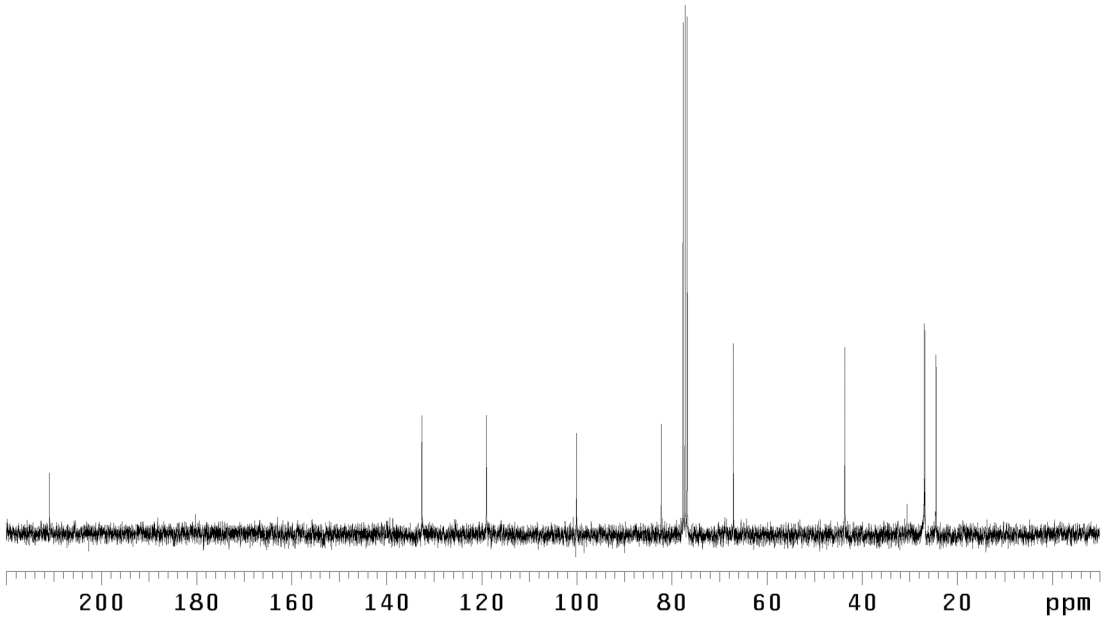


Figure A4.36 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **218l**

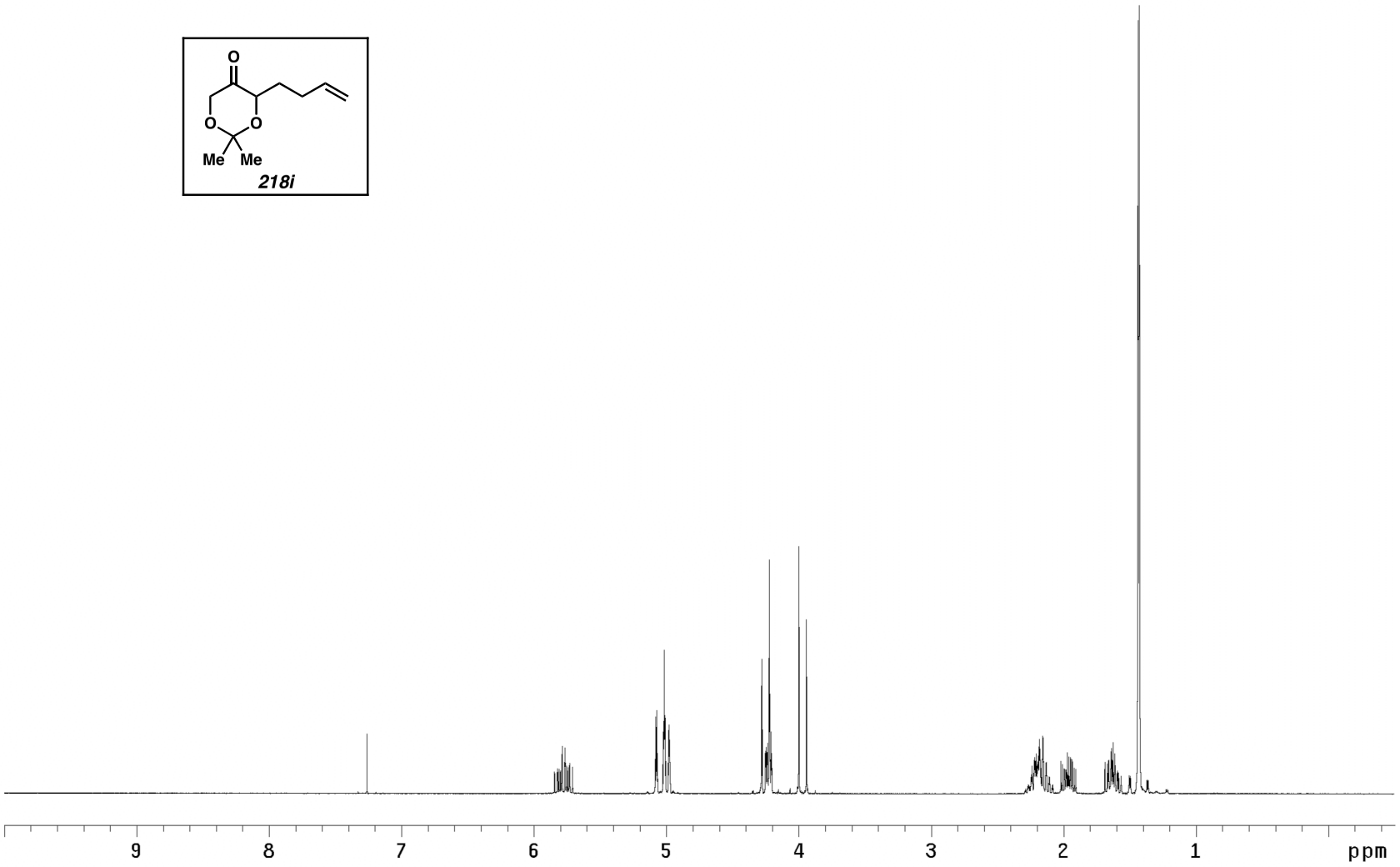


Figure A4.37 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **218i**

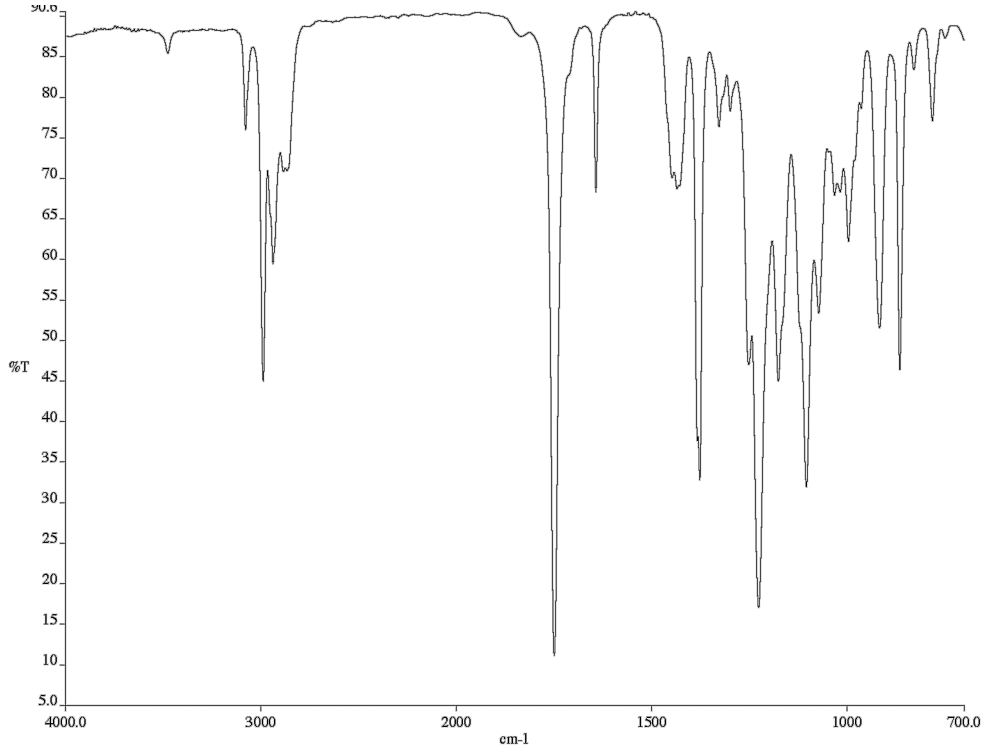


Figure A4.38 Infrared spectrum (thin film/NaCl) of compound **218i**

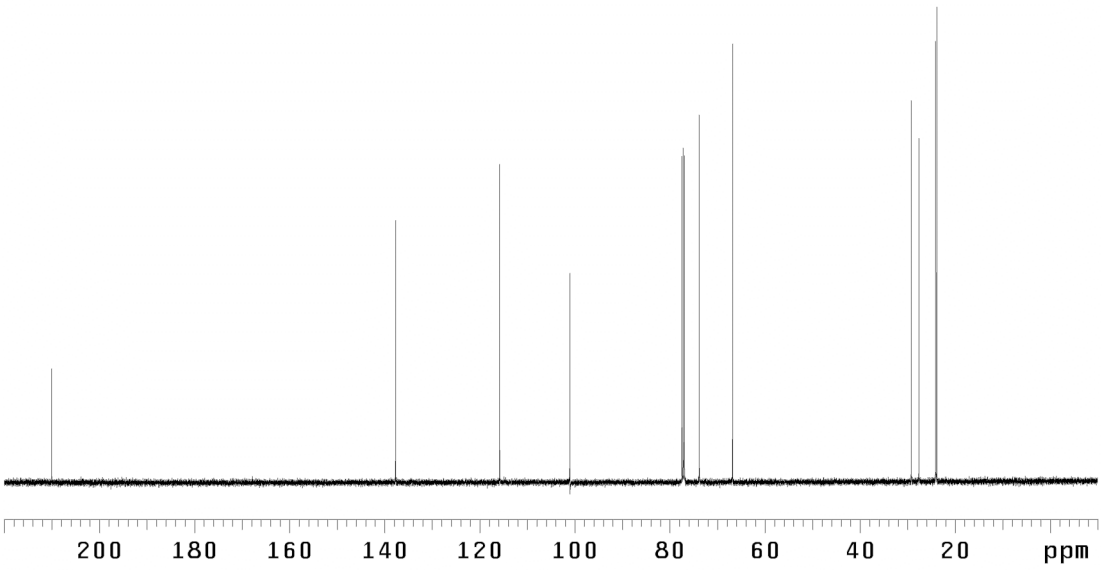


Figure A4.39 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **218i**

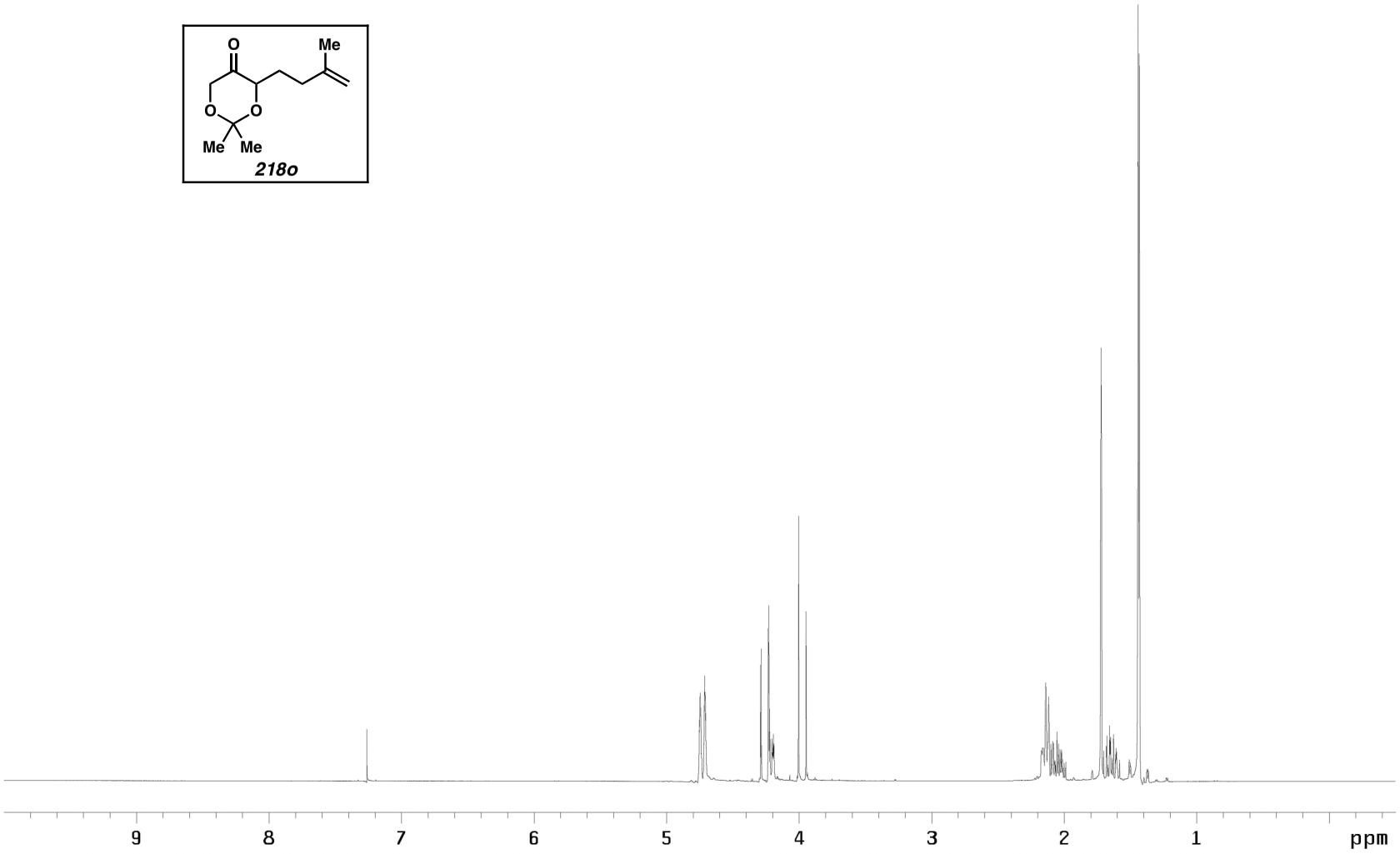


Figure A4.40 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **218o**

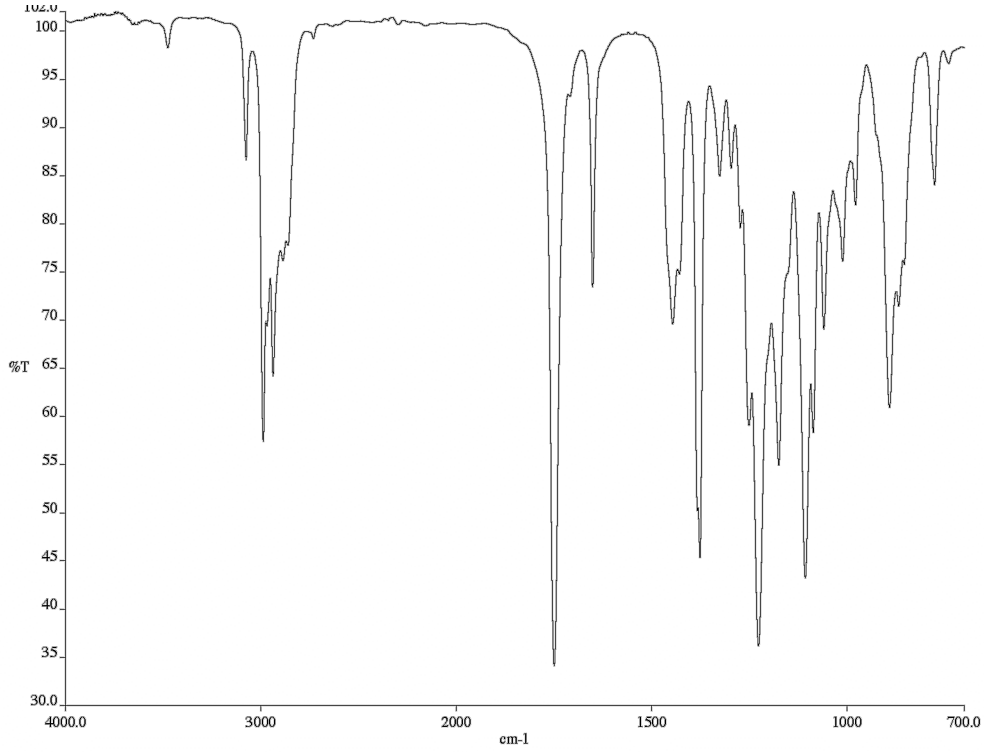


Figure A4.41 Infrared spectrum (thin film/NaCl) of compound **218o**

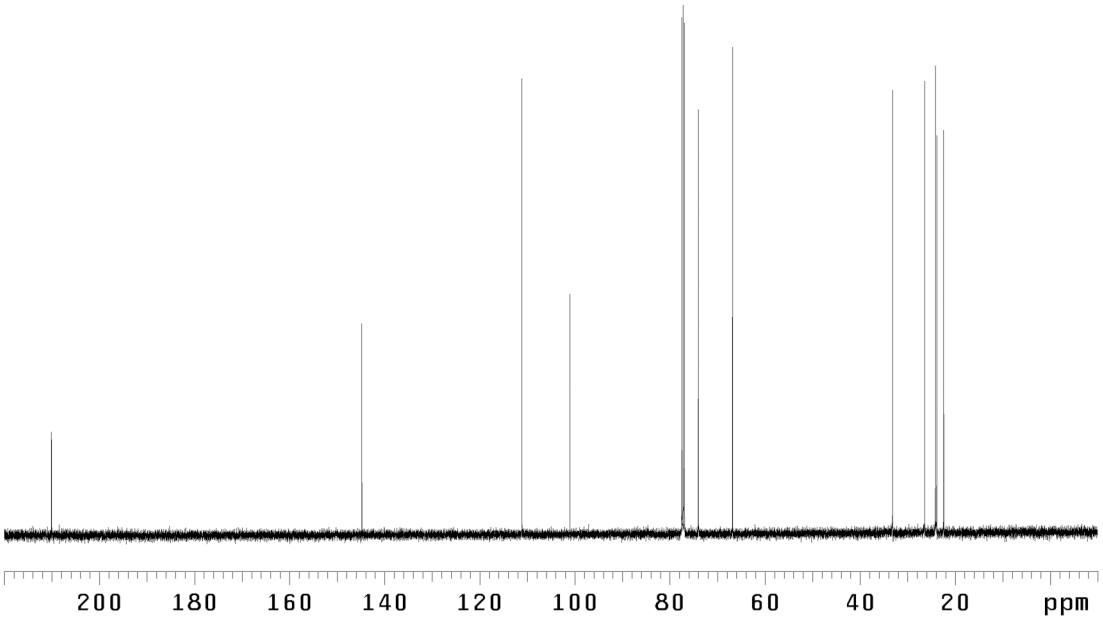


Figure A4.42 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **218o**

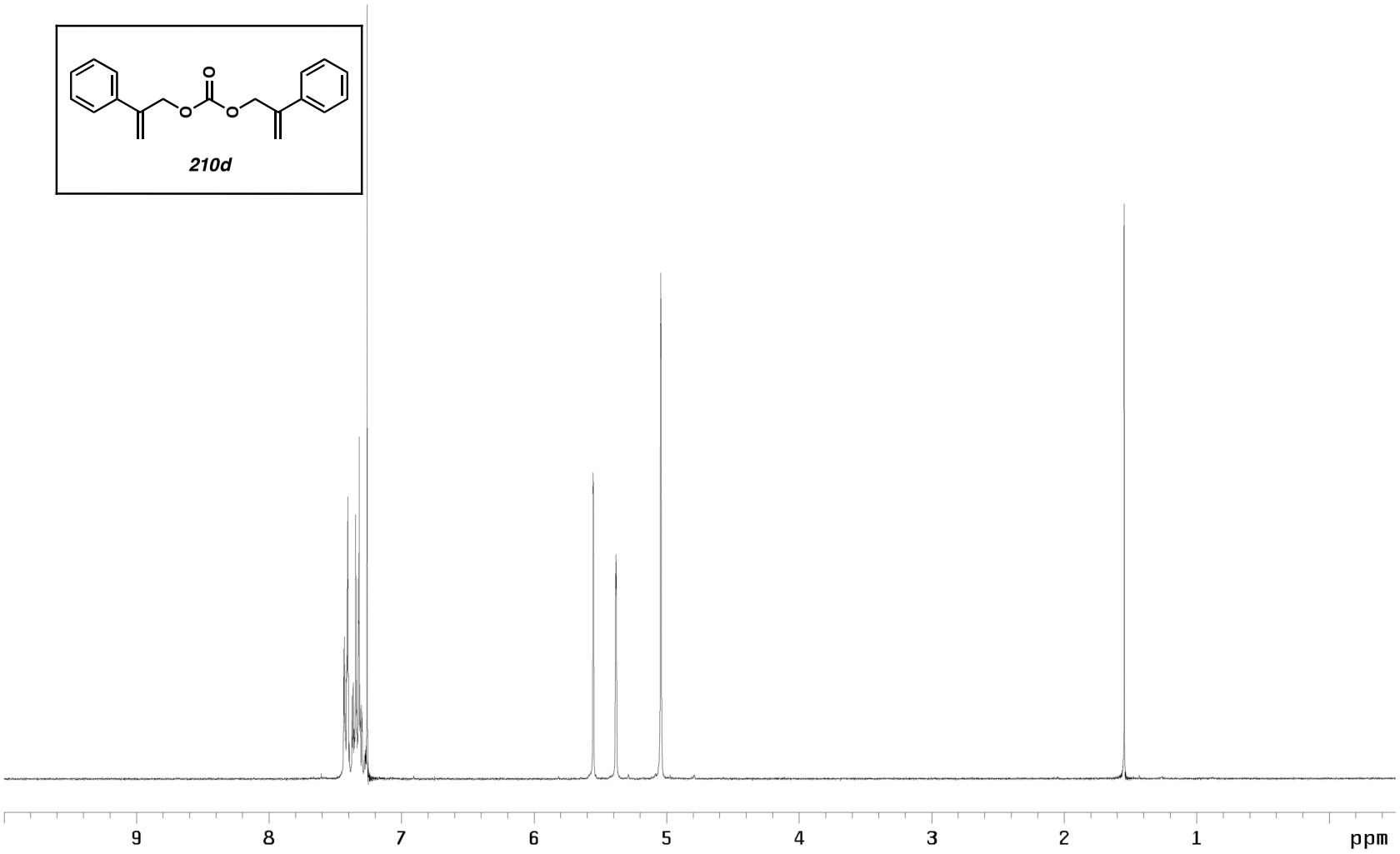


Figure A4.43 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **210d**

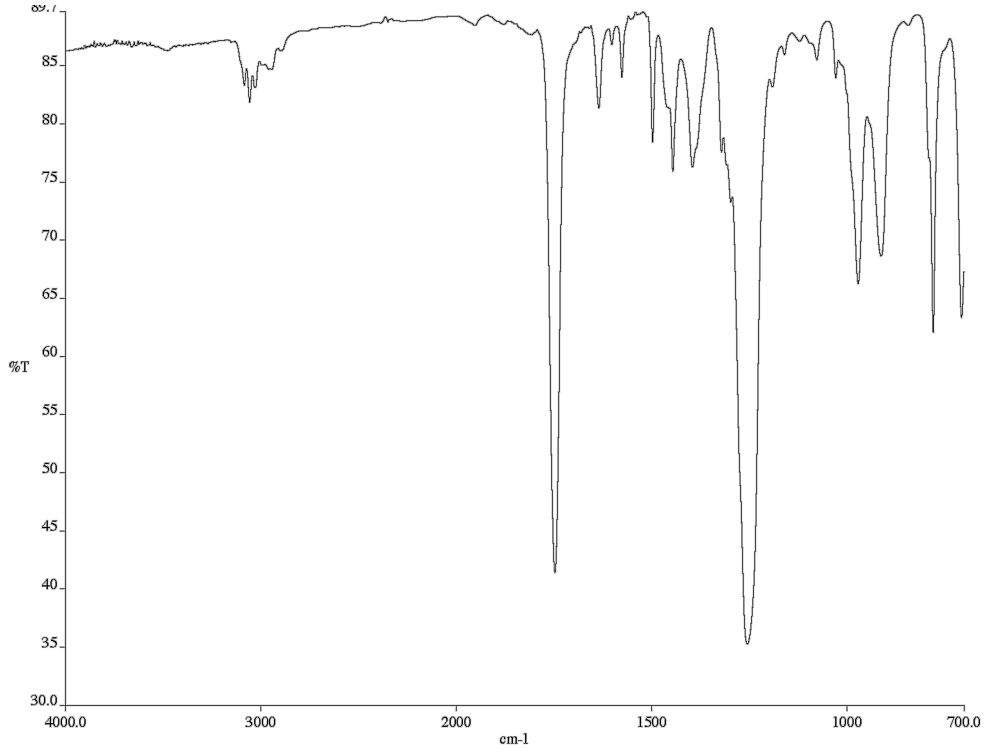


Figure A4.44 Infrared spectrum (thin film/NaCl) of compound **210d**

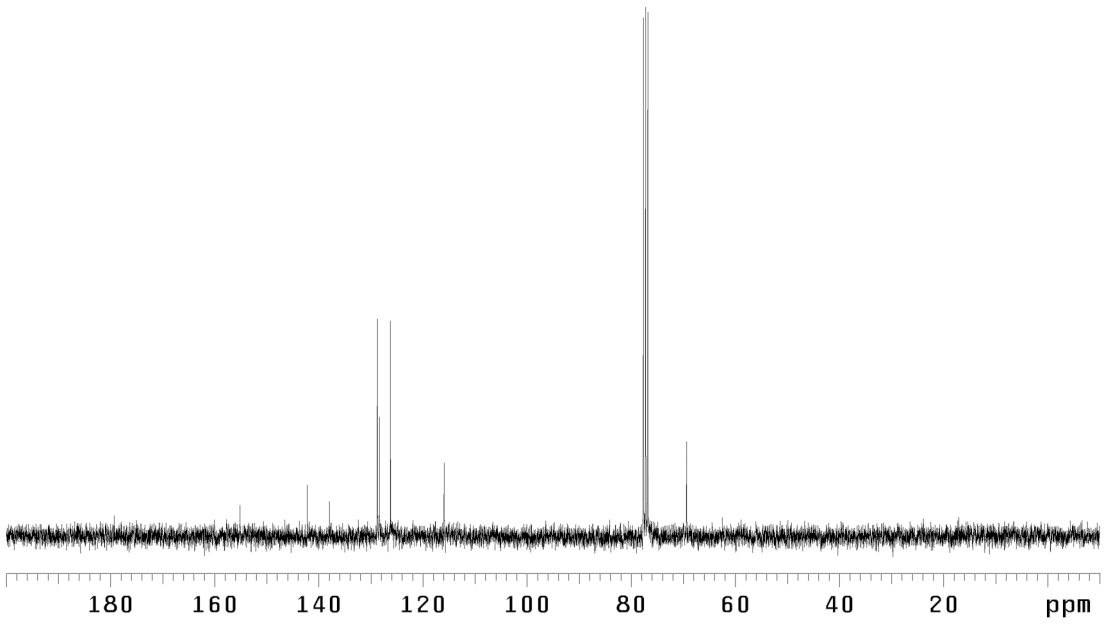


Figure A4.45 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **210d**

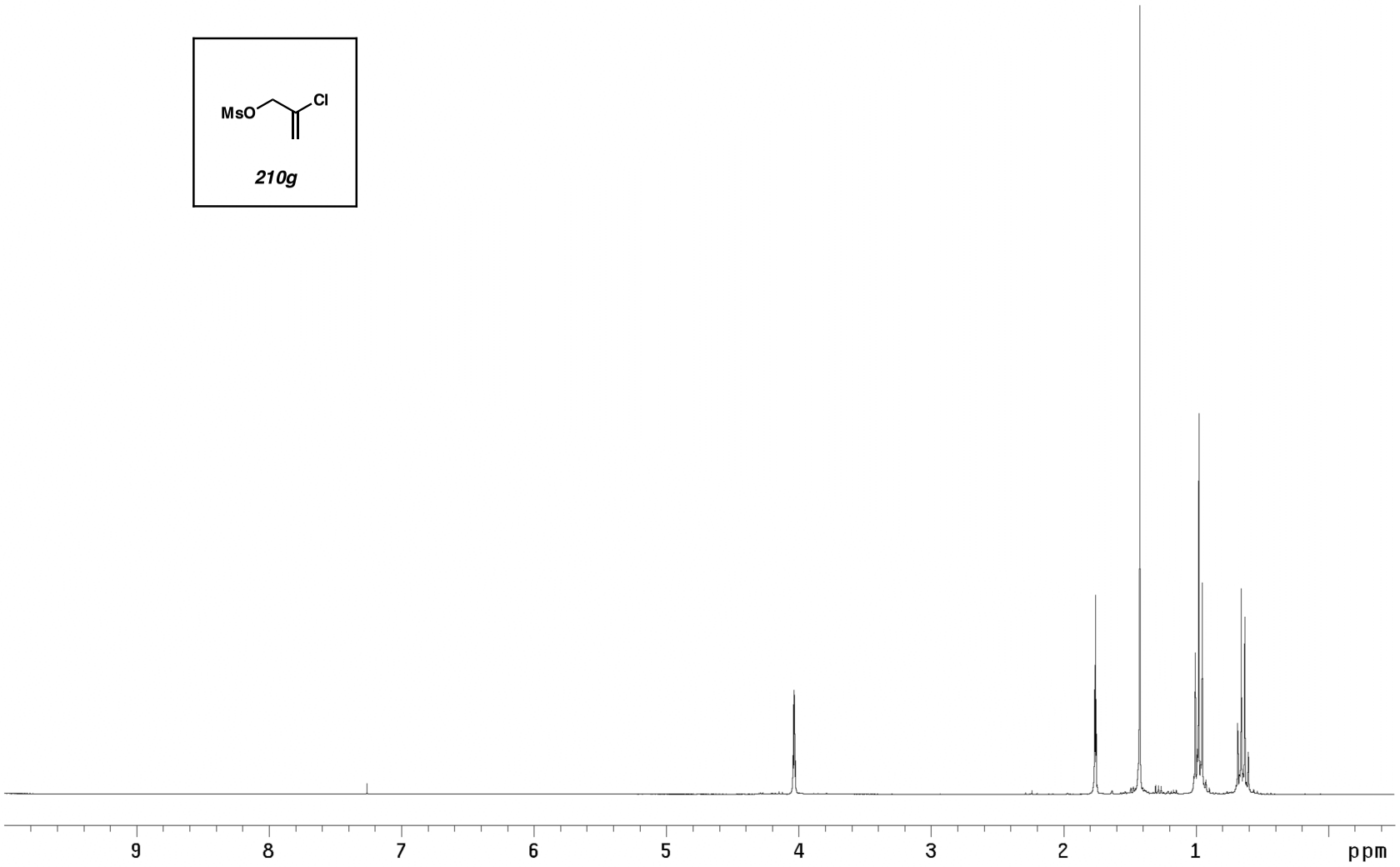


Figure A4.46 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **210g**

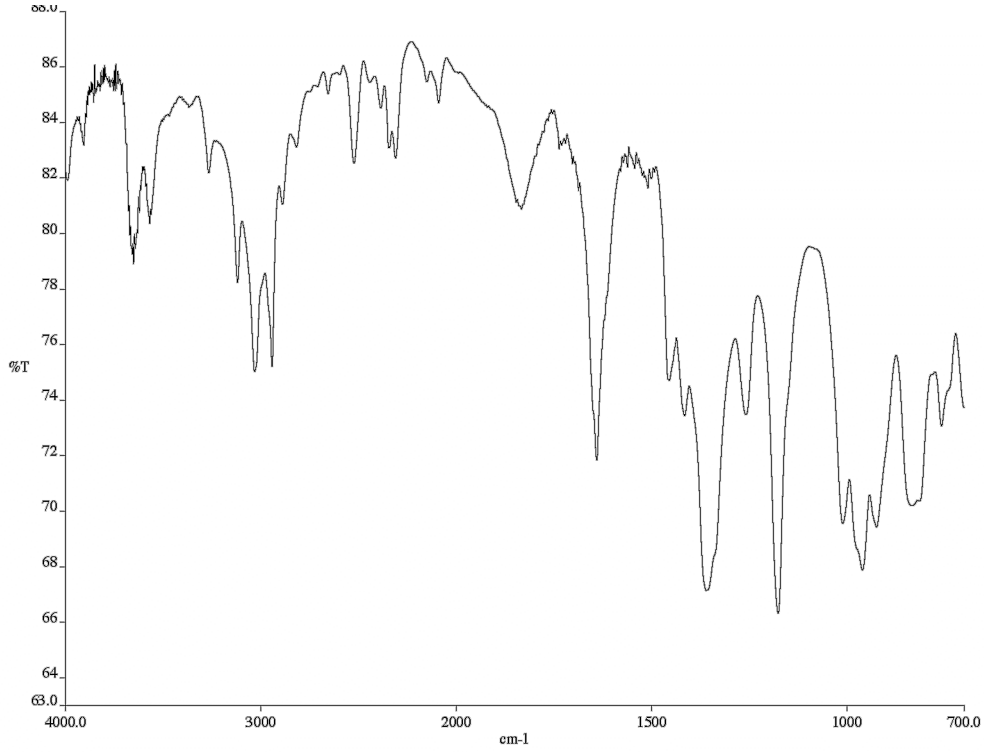


Figure A4.47 Infrared spectrum (thin film/NaCl) of compound **210g**

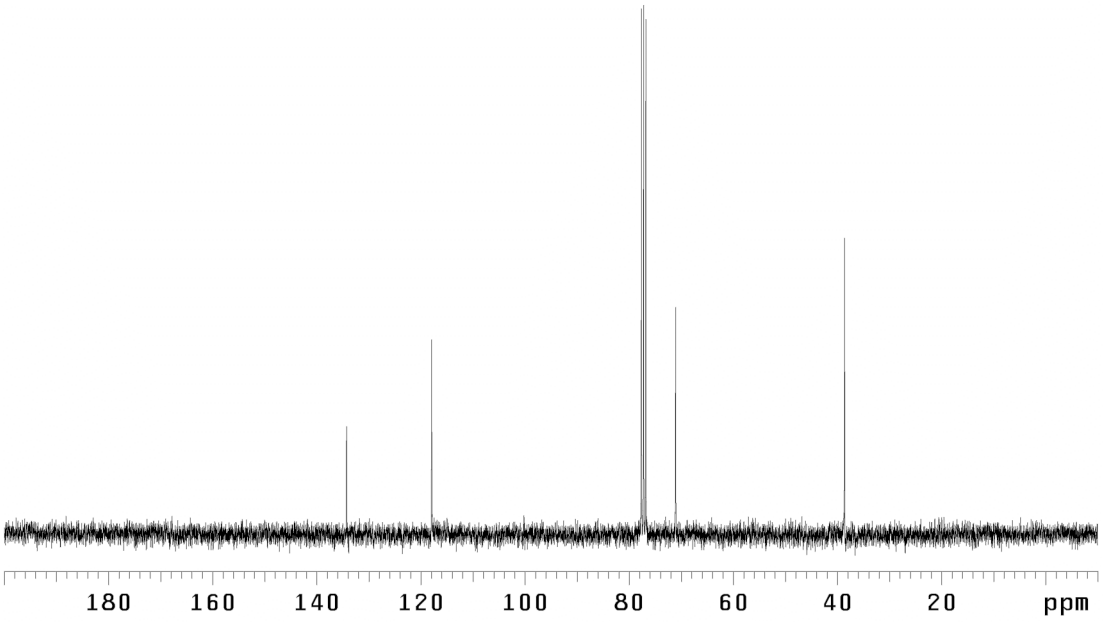


Figure A4.48 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **210g**

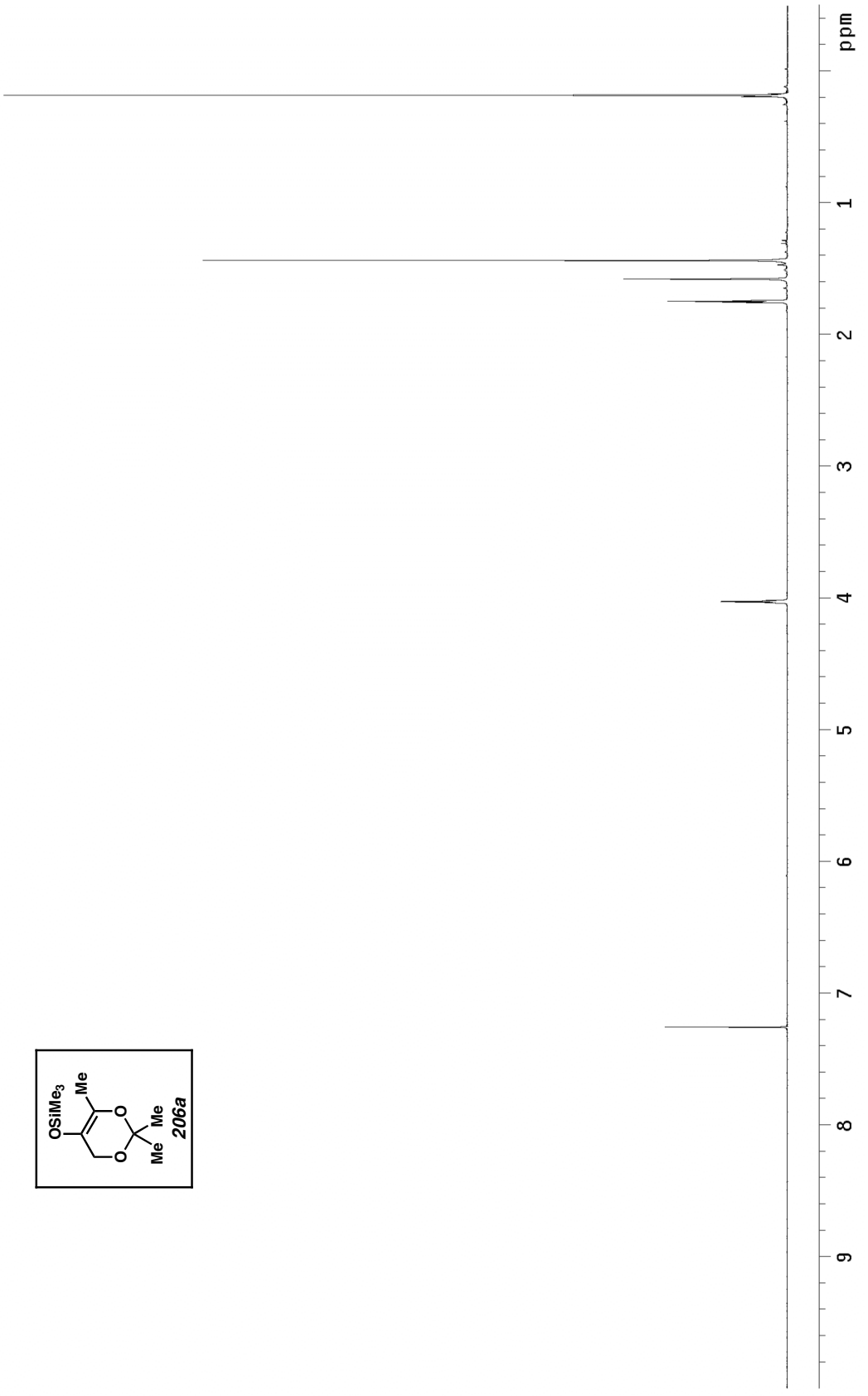


Figure A4.49 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **206a**

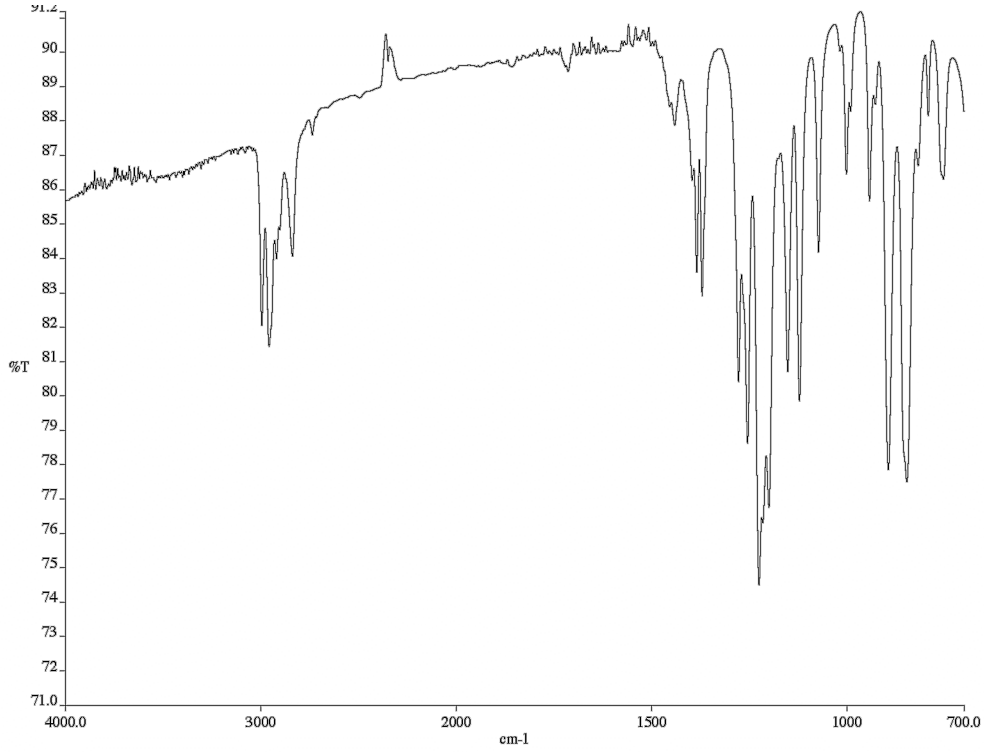


Figure A4.50 Infrared spectrum (thin film/NaCl) of compound **206a**

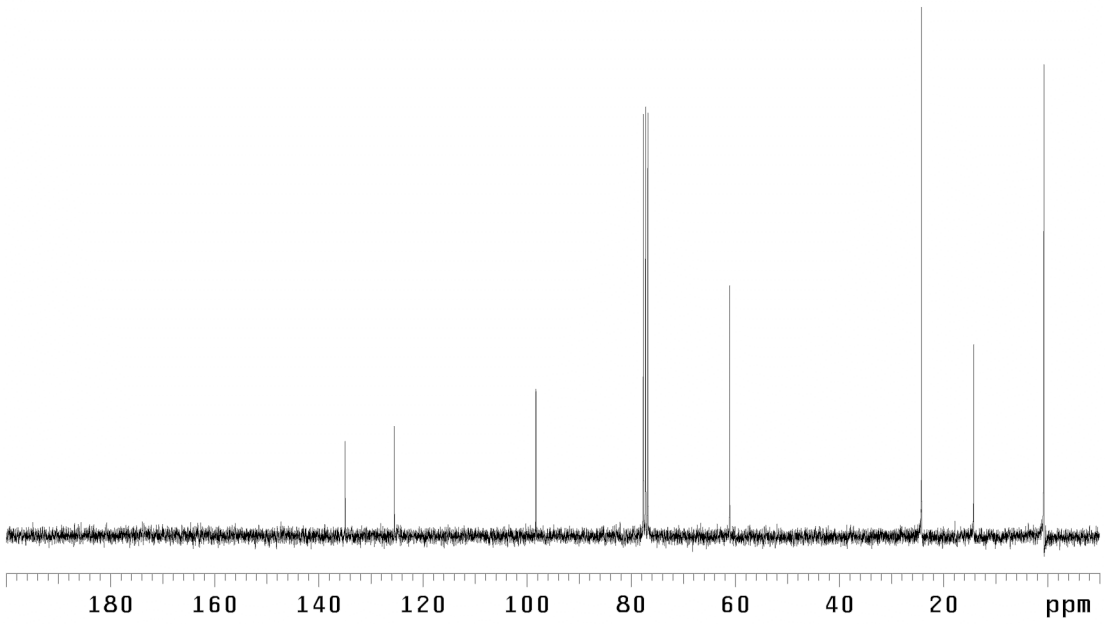


Figure A4.51 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **206a**

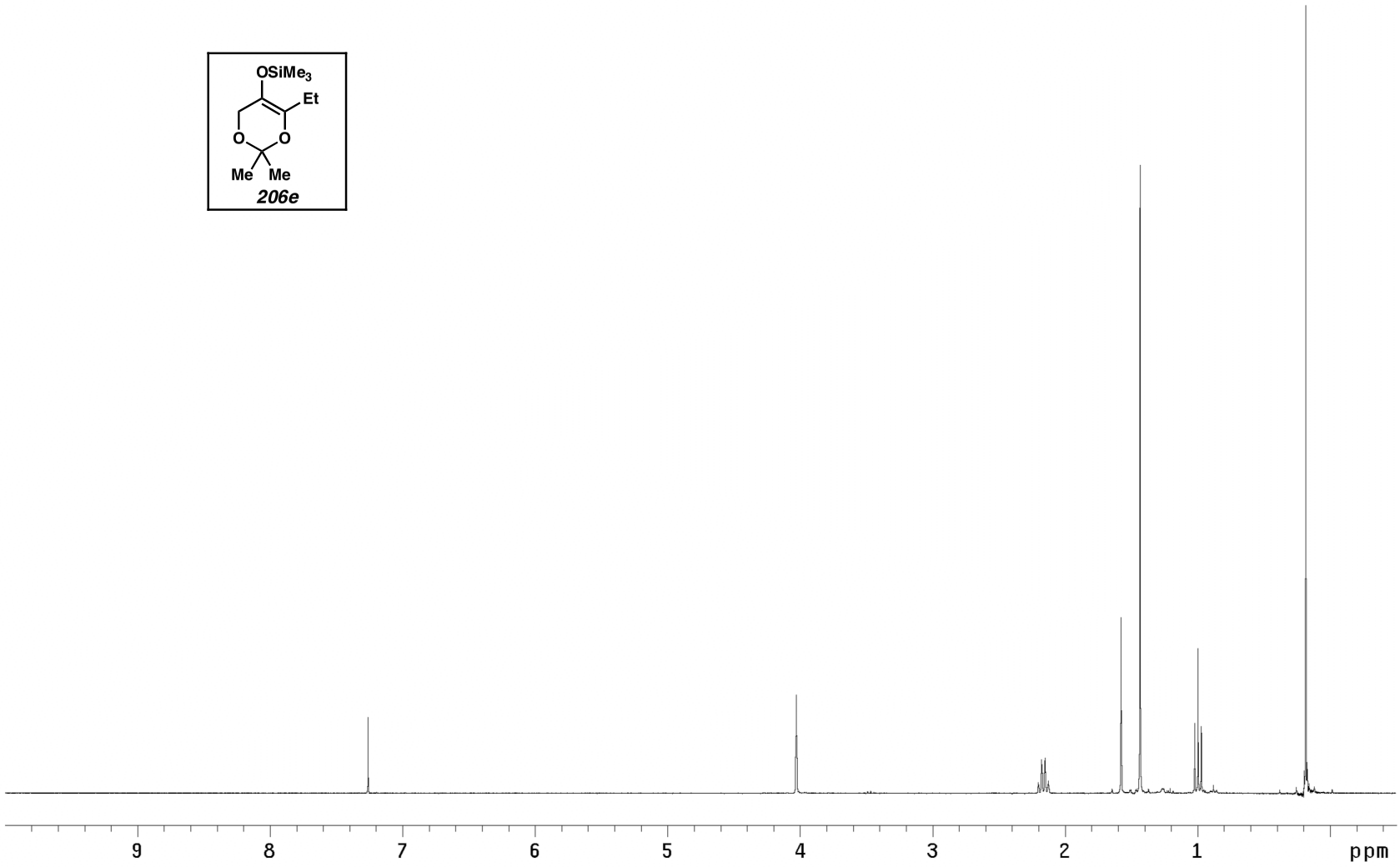


Figure A4.52 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **206e**

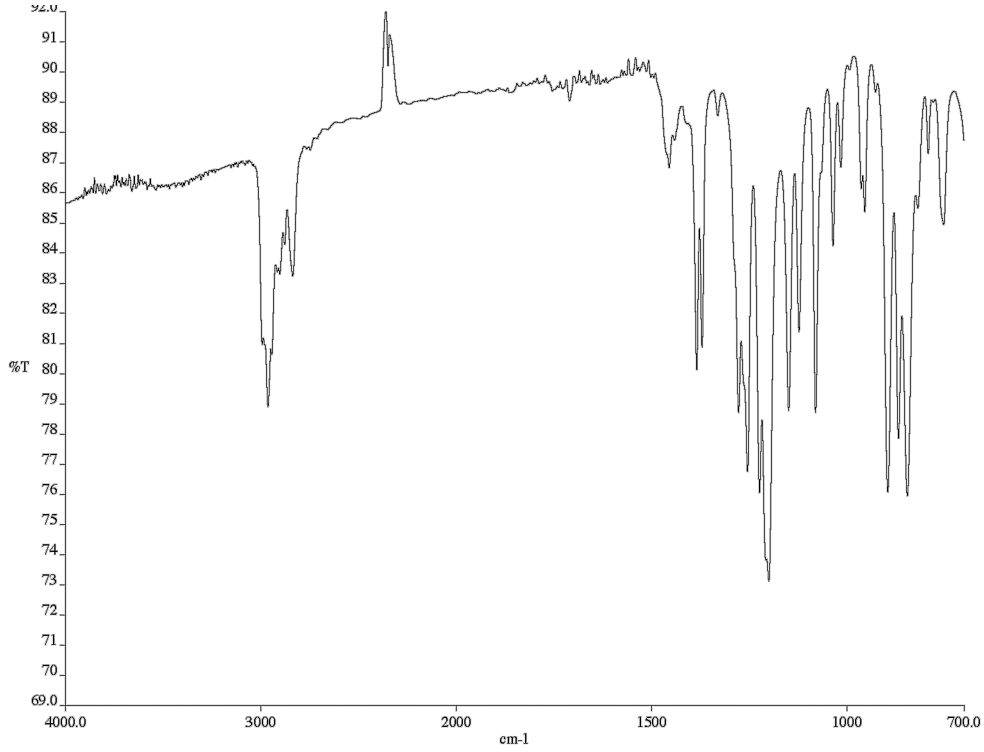


Figure A4.53 Infrared spectrum (thin film/NaCl) of compound **206e**

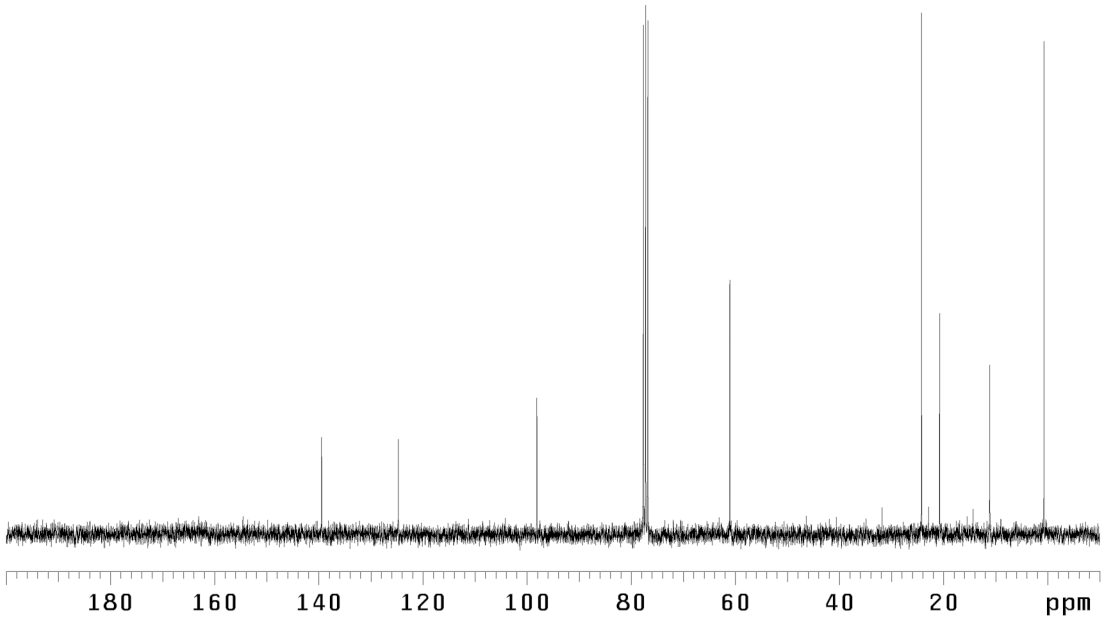


Figure A4.54 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **206e**

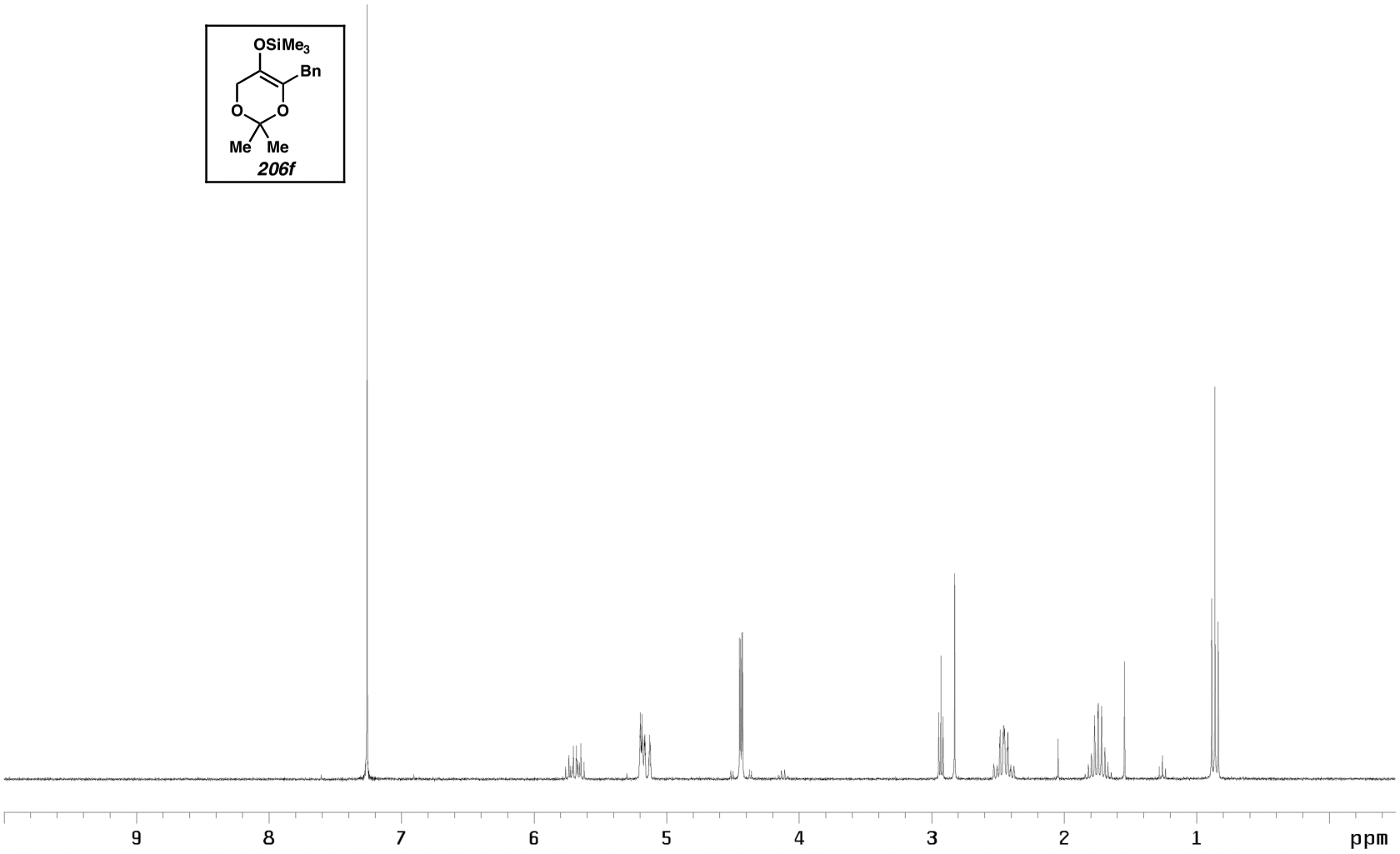


Figure A4.55 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **206f**

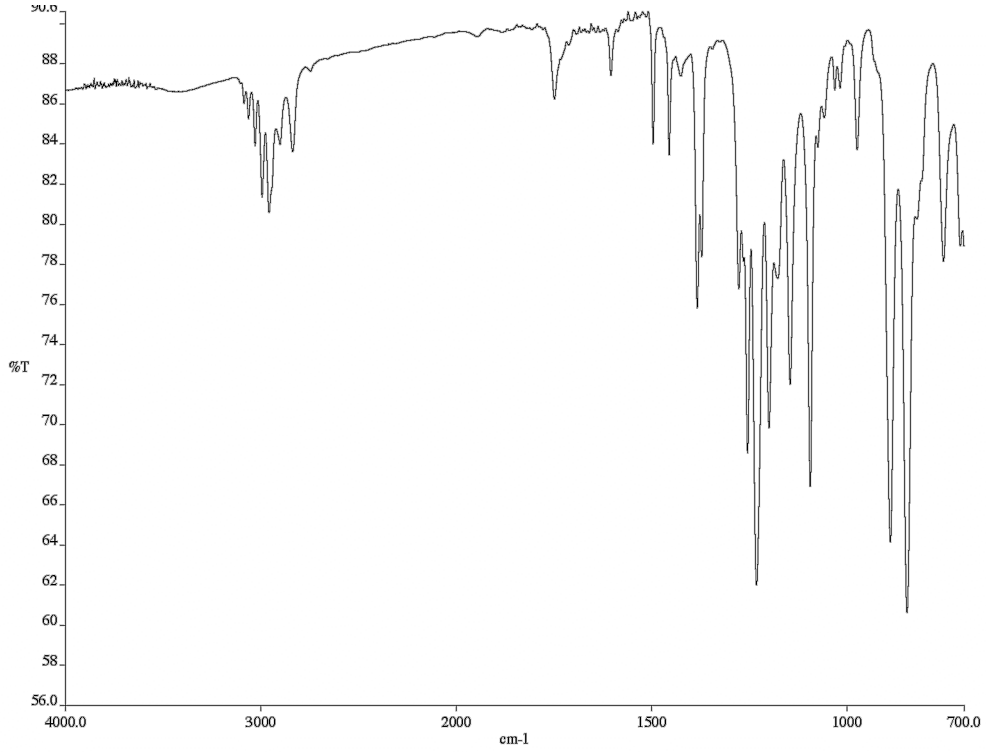


Figure A4.56 Infrared spectrum (thin film/NaCl) of compound **206f**

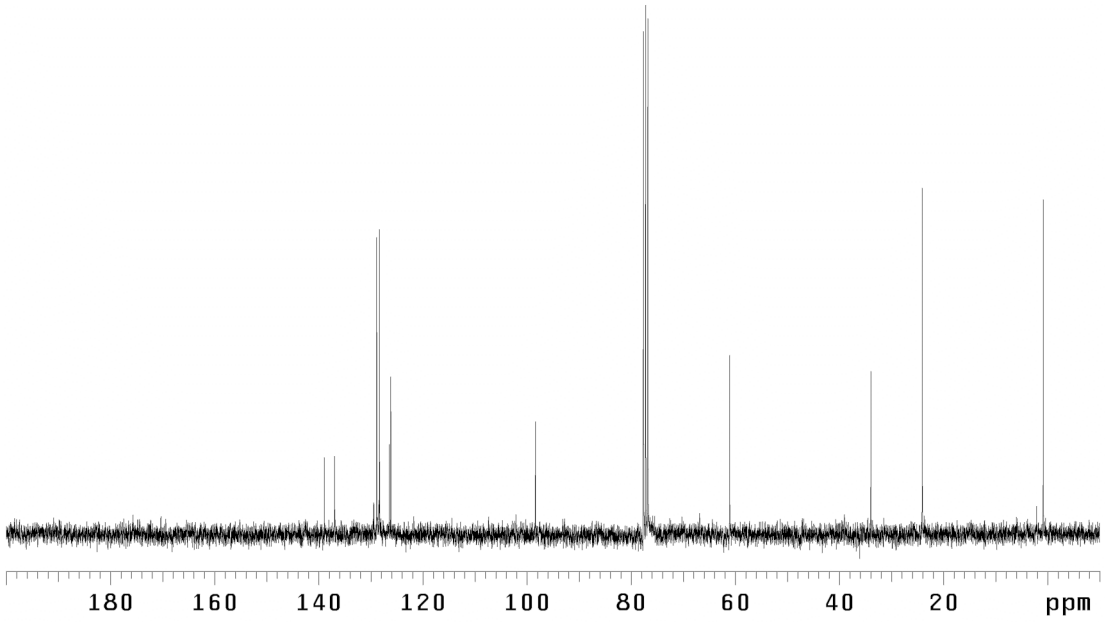


Figure A4.57 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **206f**

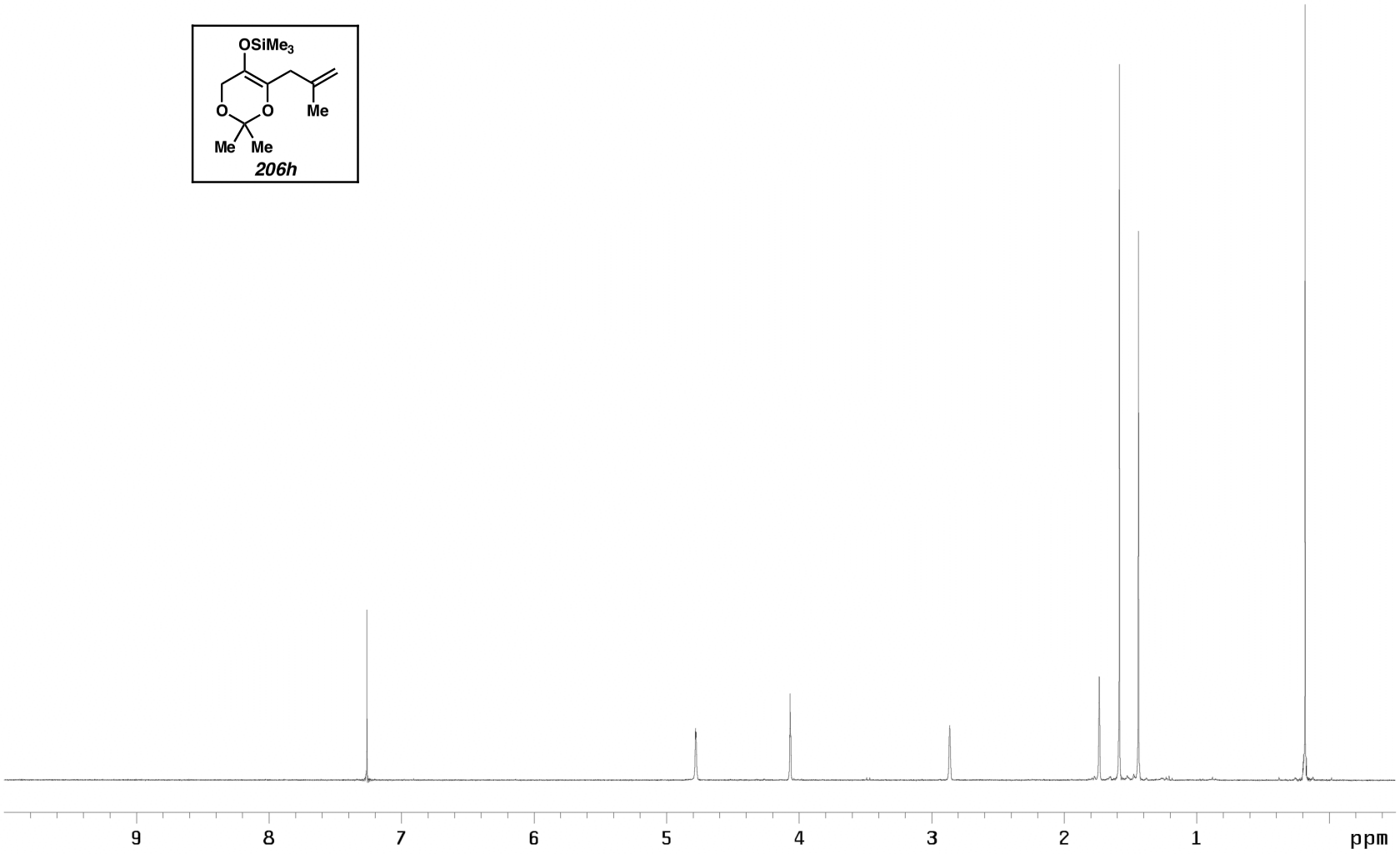


Figure A4.58 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **206h**

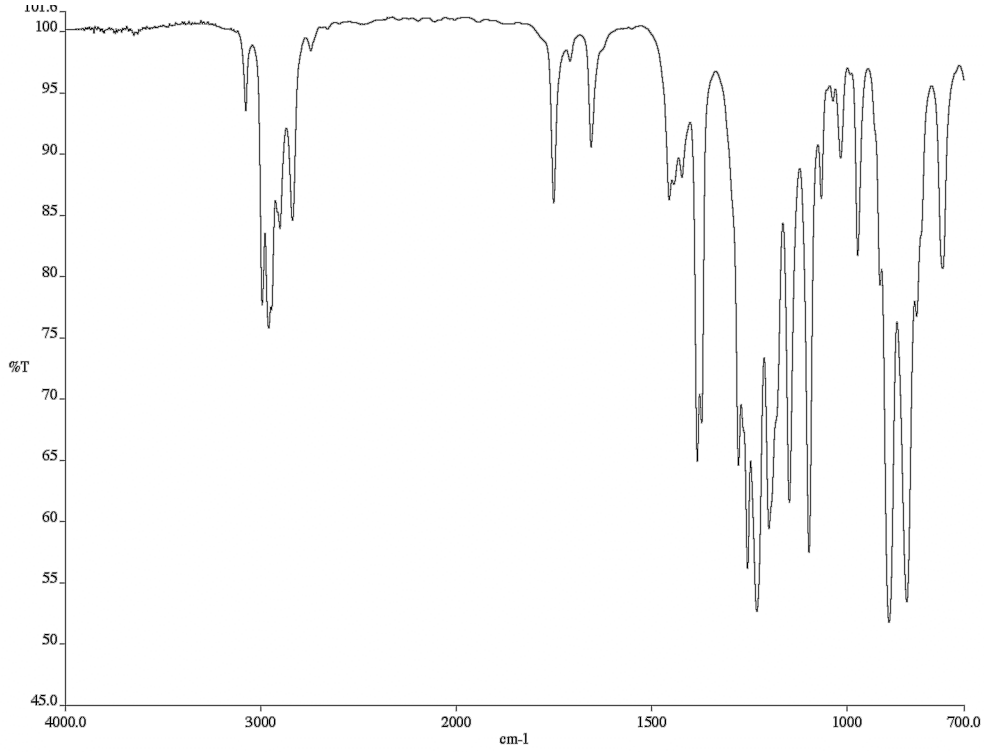


Figure A4.59 Infrared spectrum (thin film/NaCl) of compound **206h**

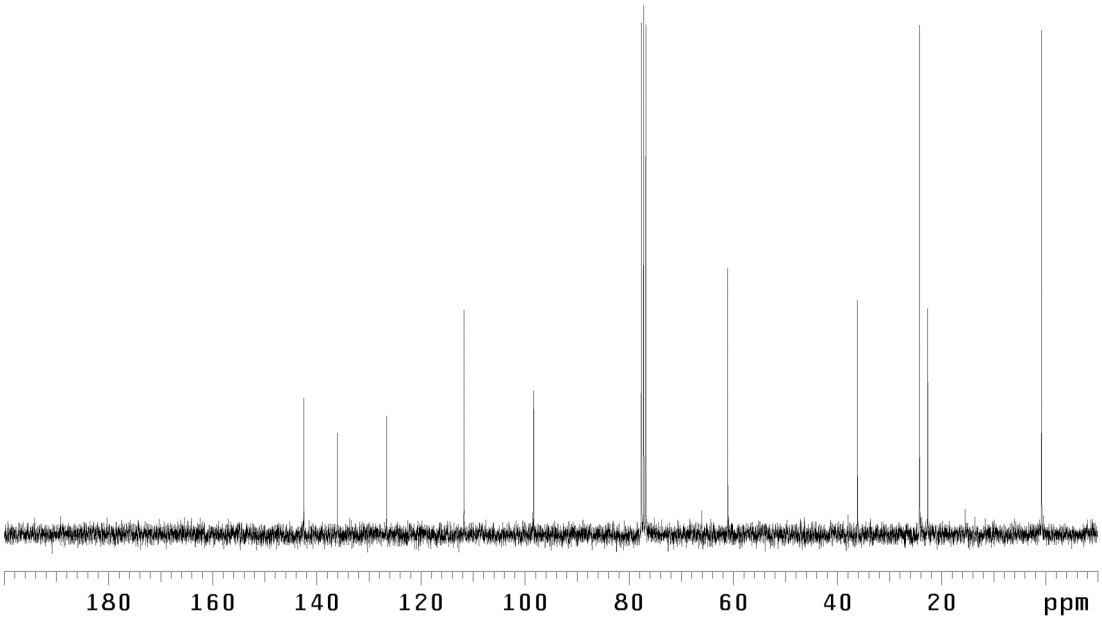


Figure A4.60 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **206h**

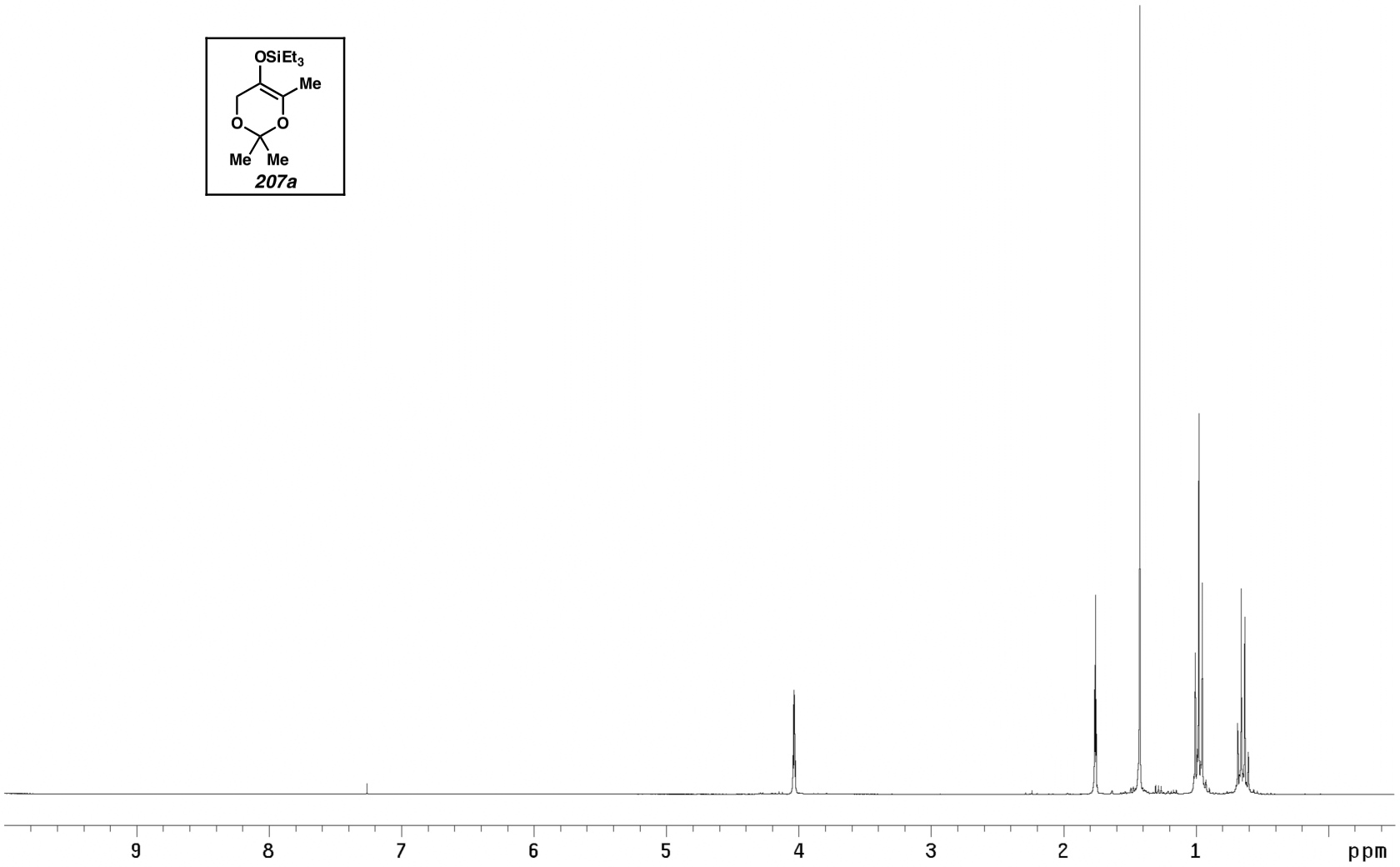


Figure A4.61 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **207a**

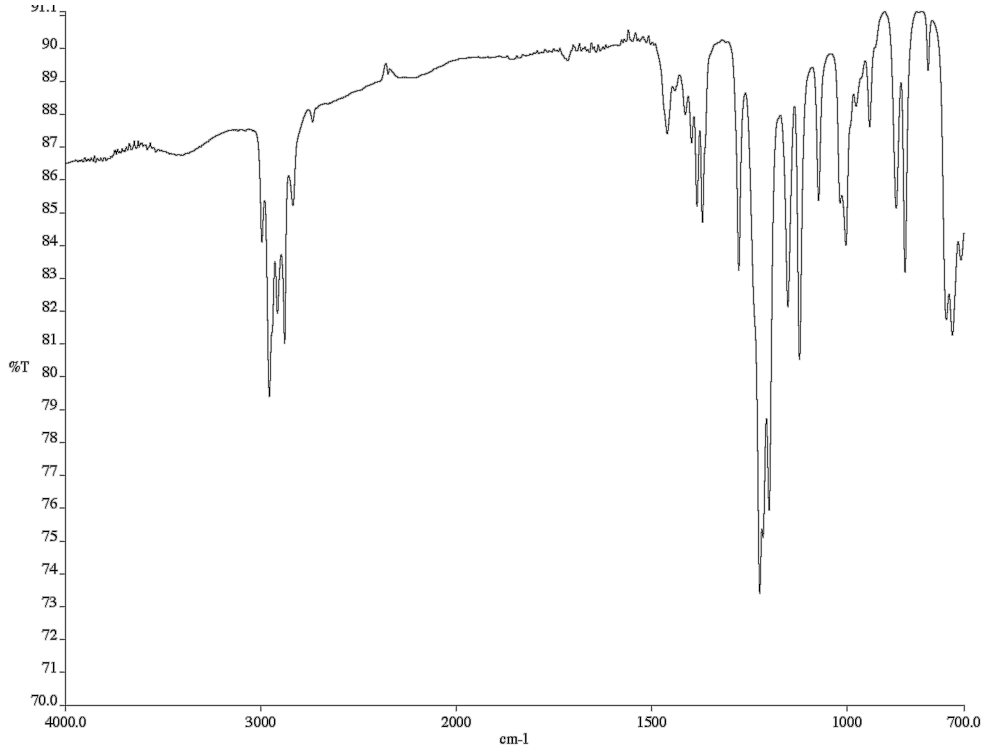


Figure A4.62 Infrared spectrum (thin film/NaCl) of compound **207a**

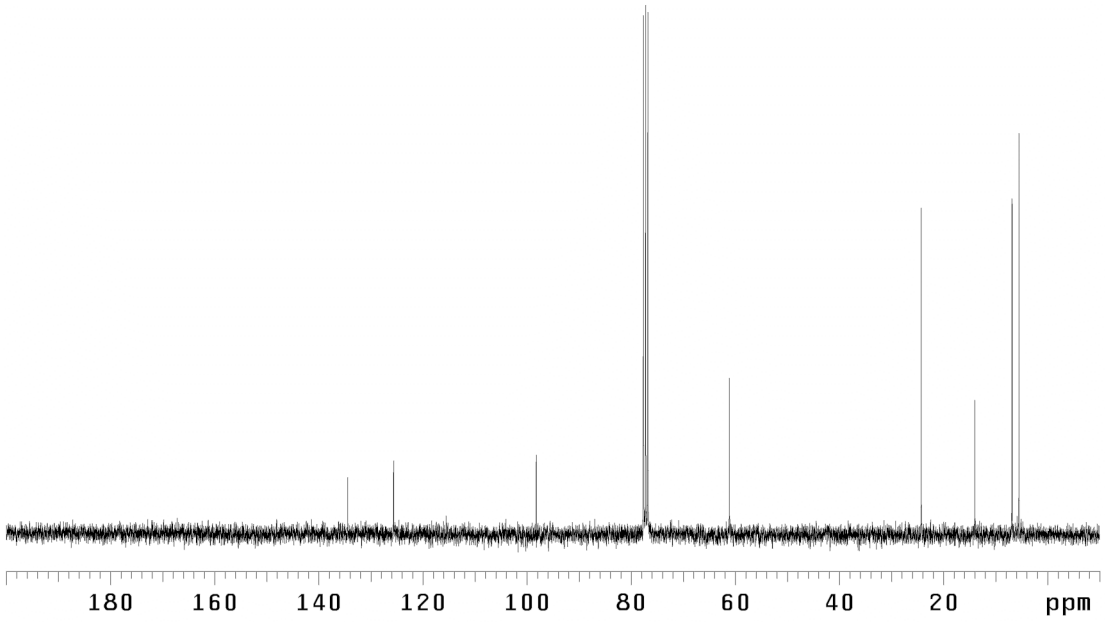


Figure A4.63 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **207a**

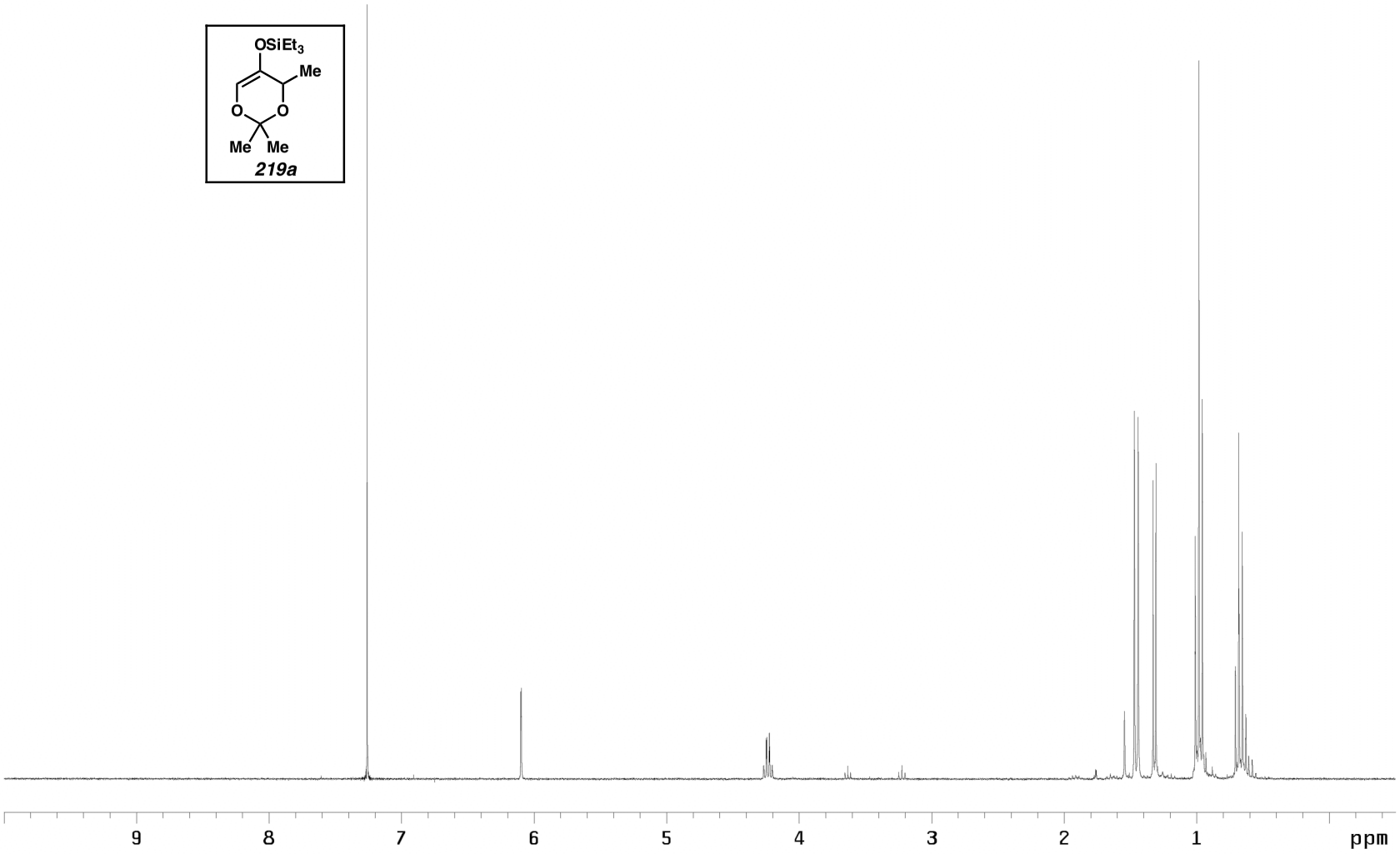


Figure A4.64 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **219a**

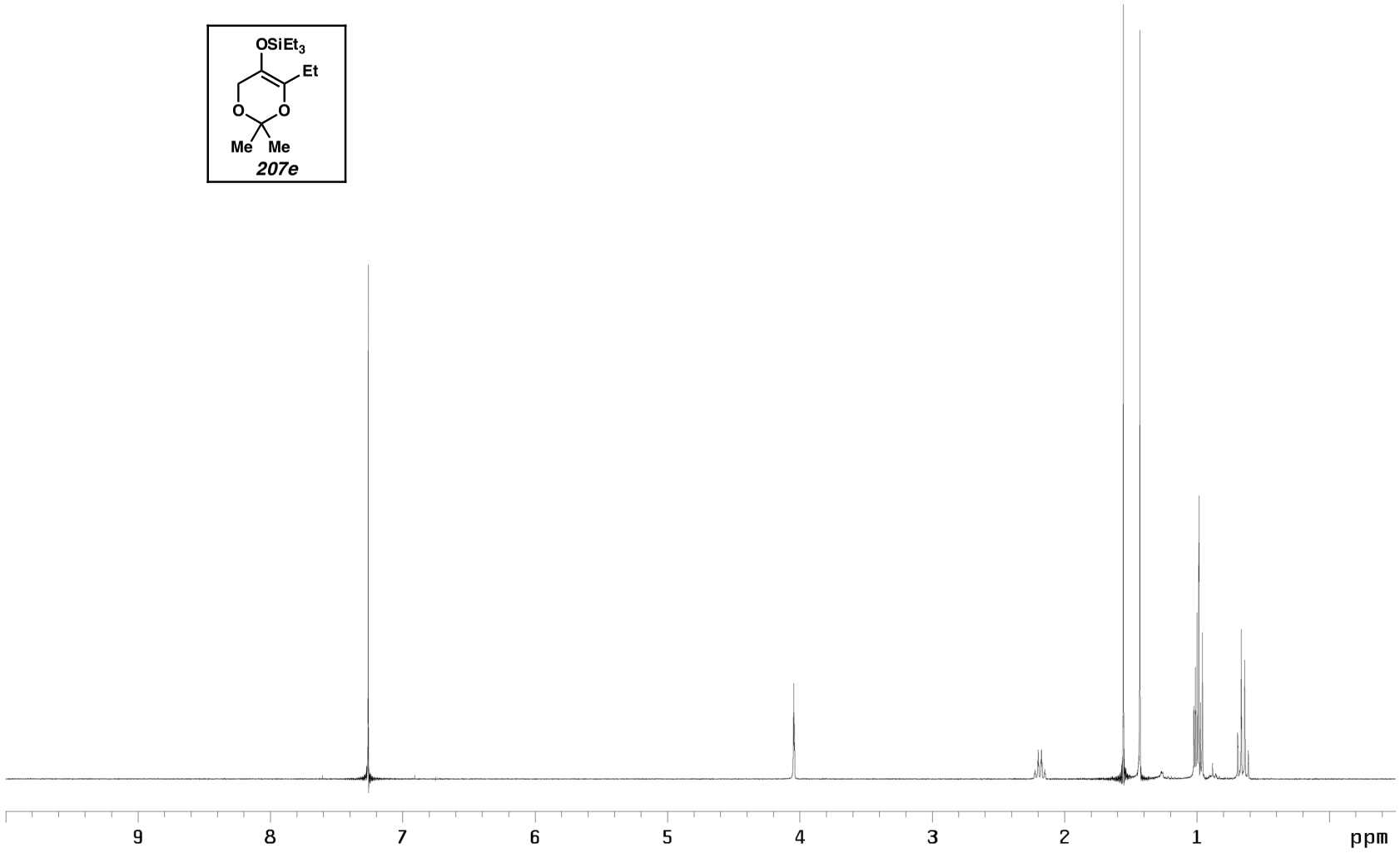


Figure A4.65 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **207e**

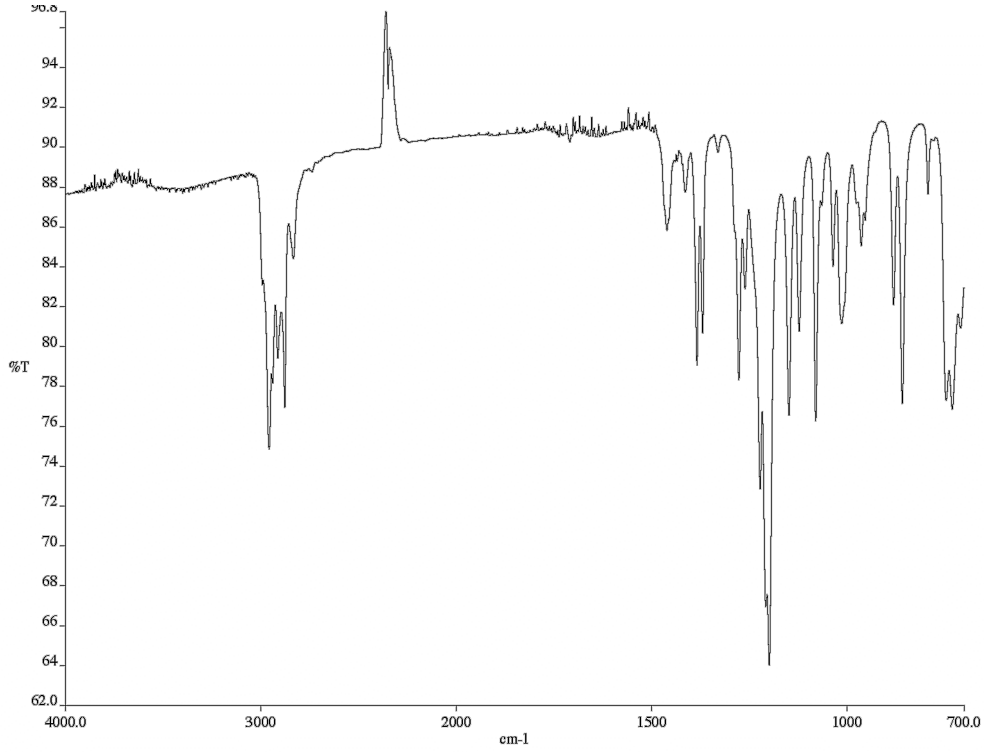


Figure A4.66 Infrared spectrum (thin film/NaCl) of compound **207e**

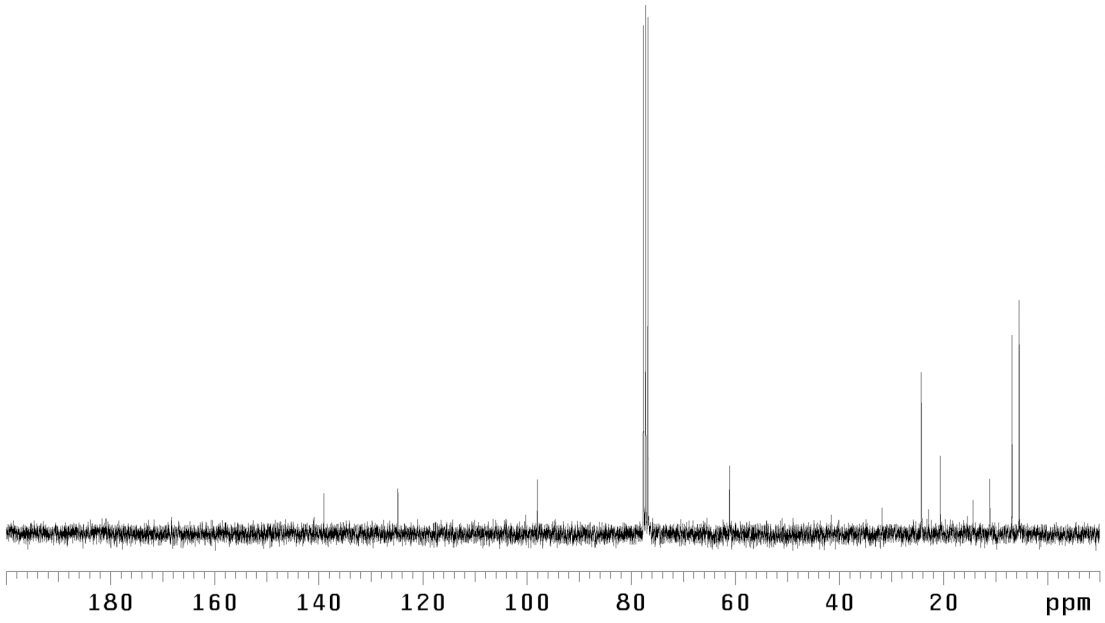


Figure A4.67 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **207e**

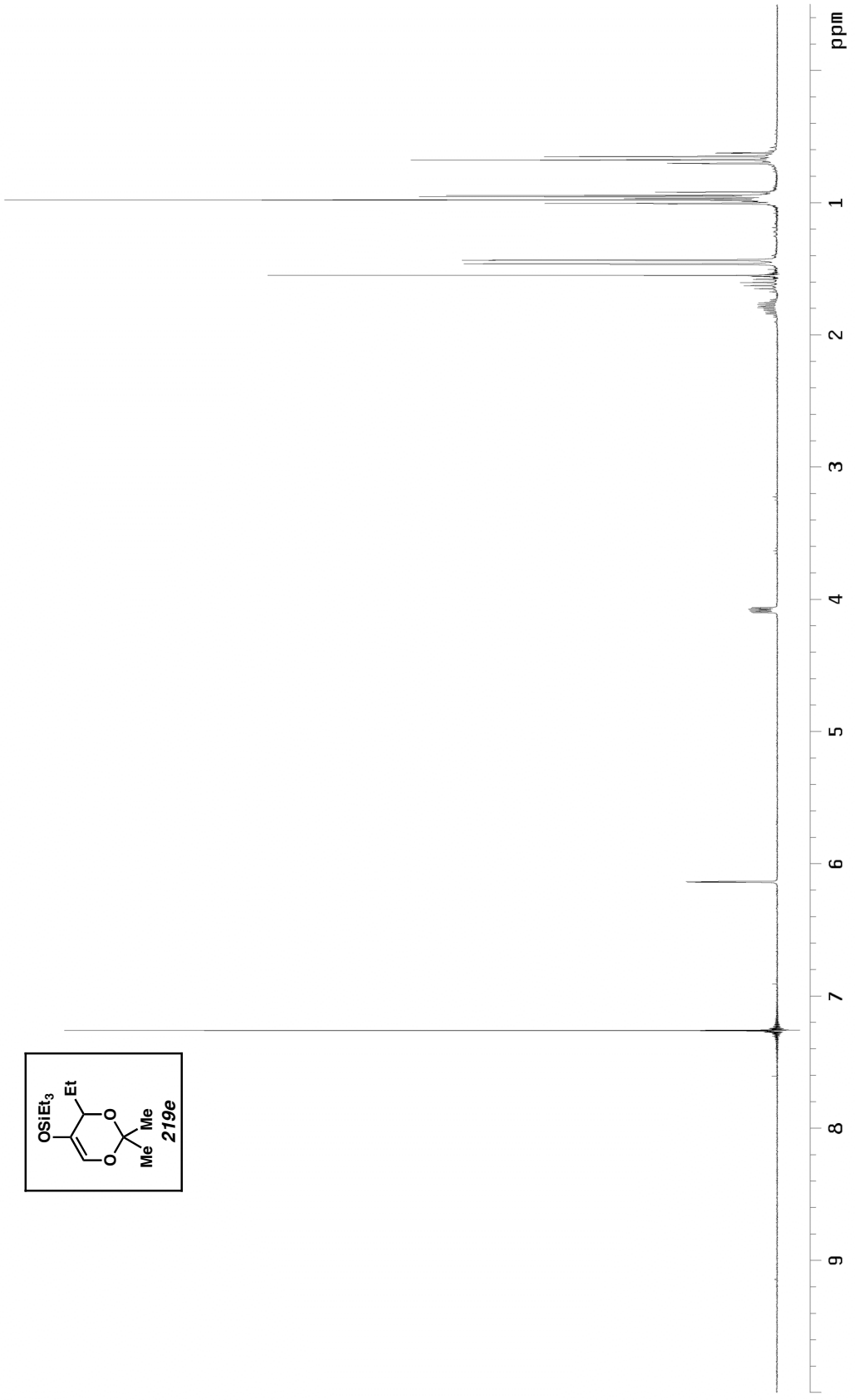


Figure A4.68 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **219e**

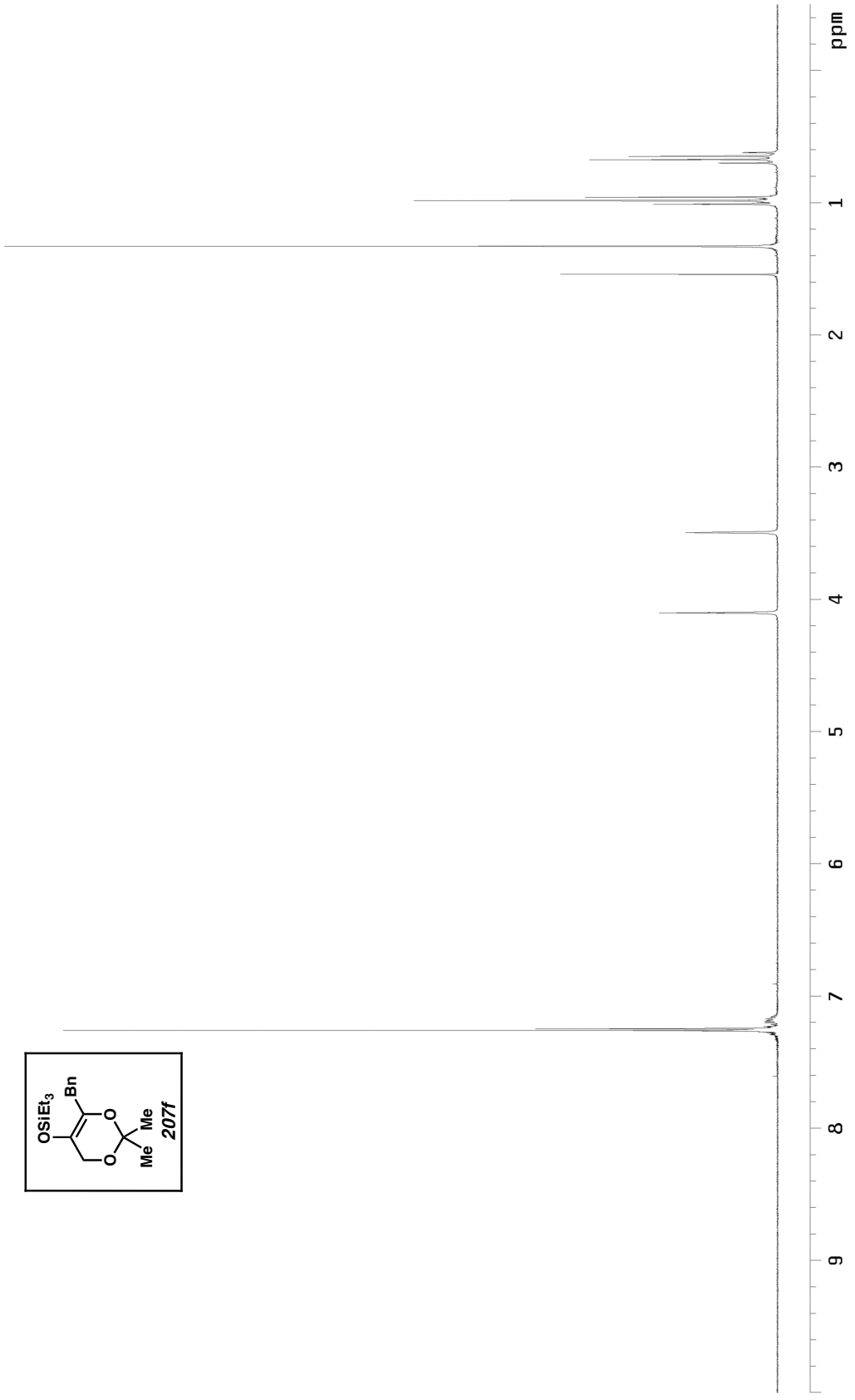


Figure A4.69 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **207f**

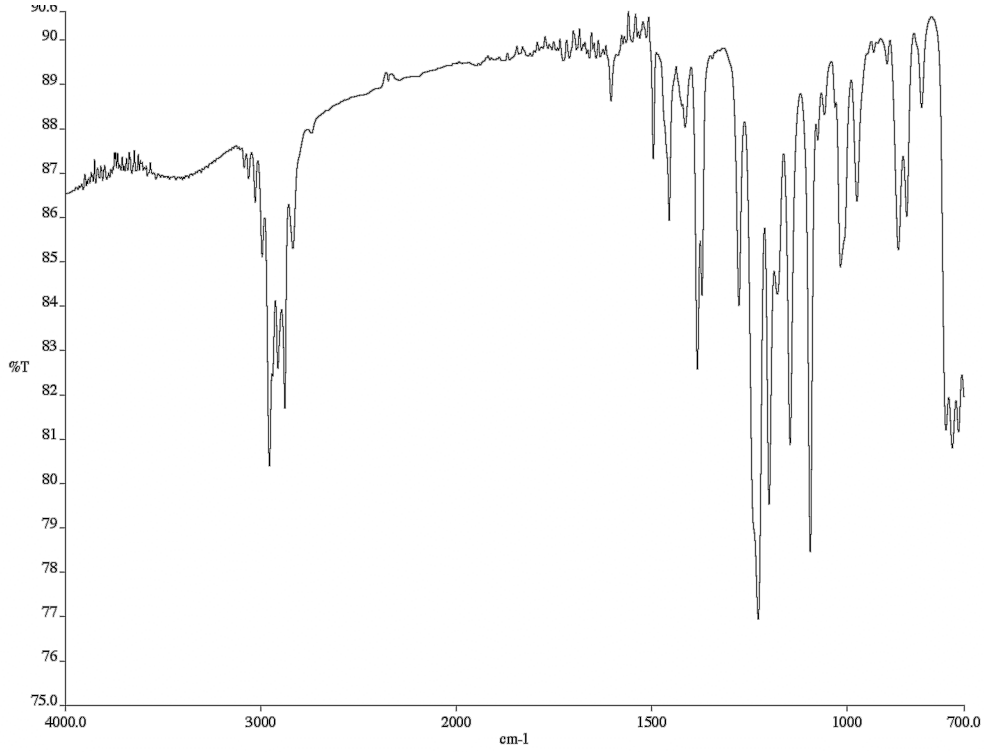


Figure A4.70 Infrared spectrum (thin film/NaCl) of compound **207f**

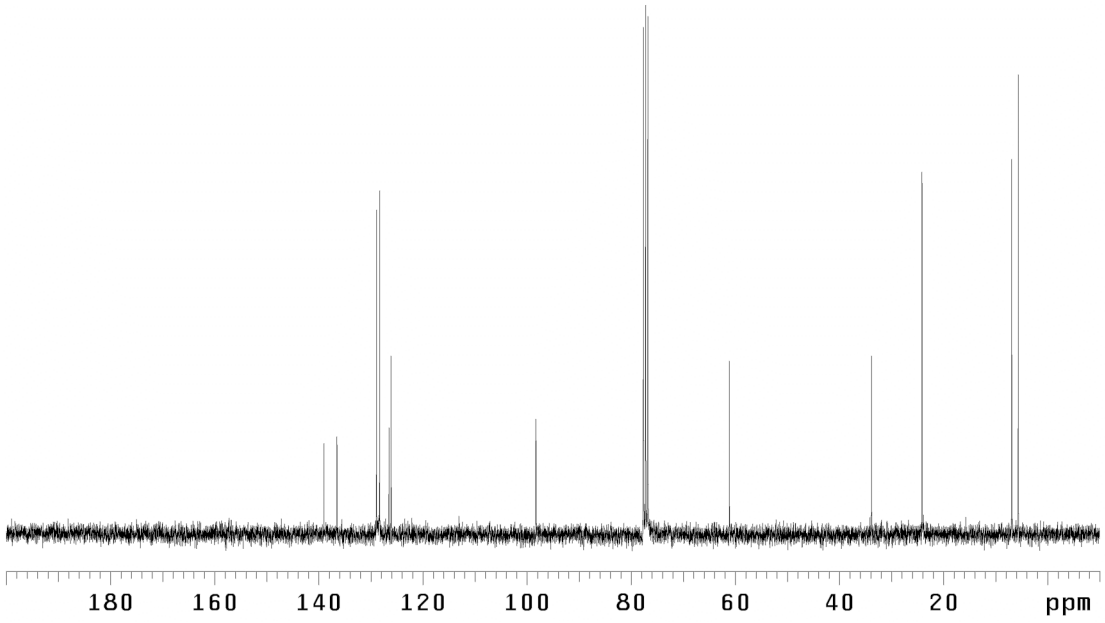


Figure A4.71 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **207f**

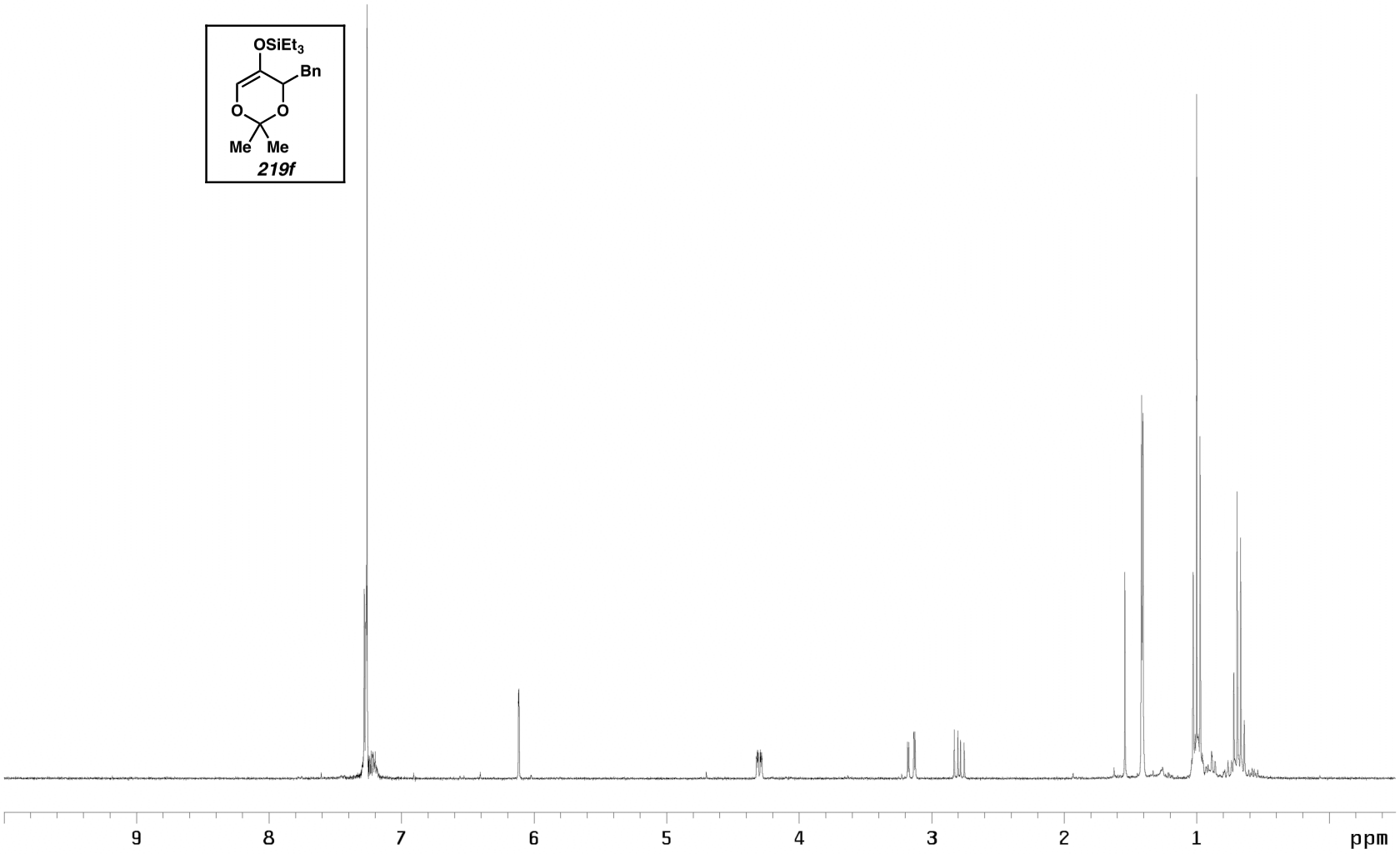


Figure A4.72 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **219f**

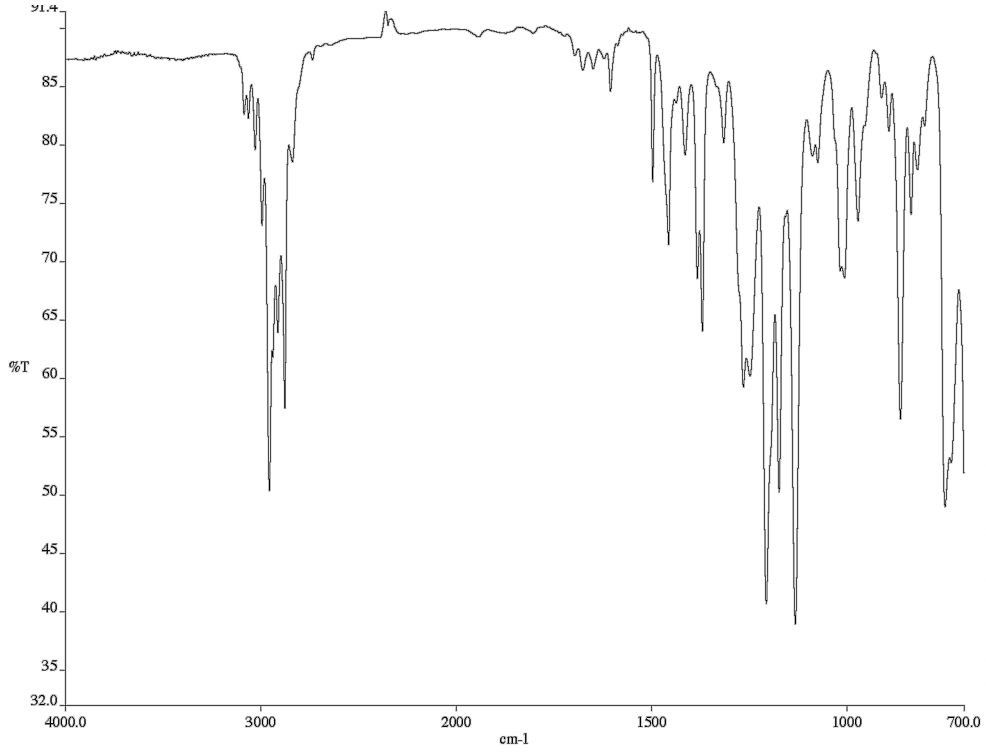


Figure A4.73 Infrared spectrum (thin film/NaCl) of compound **219f**

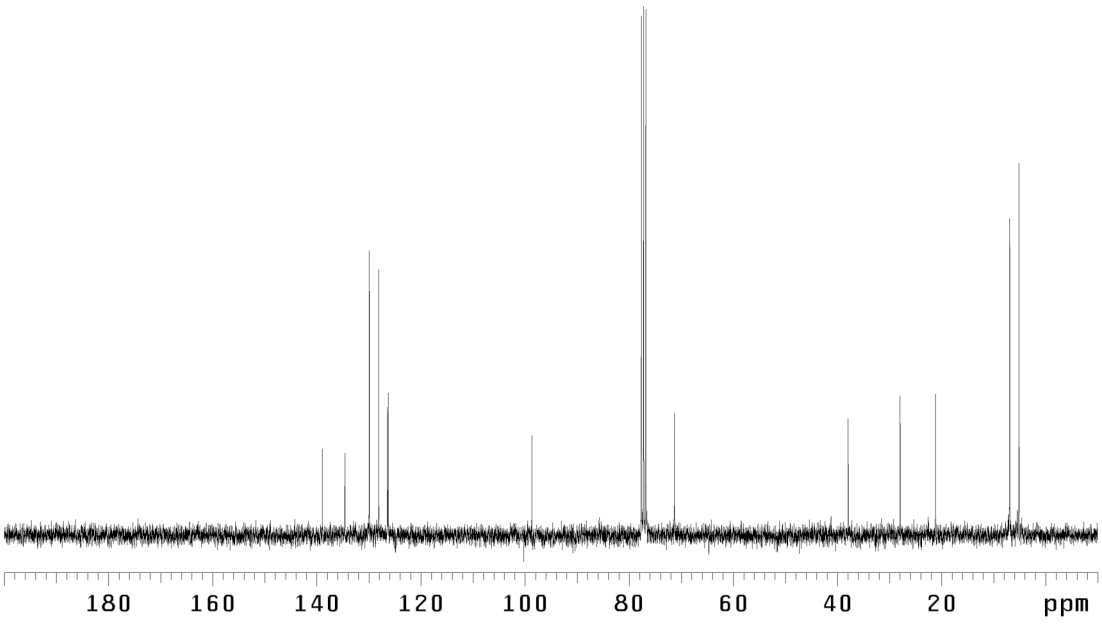


Figure A4.74 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **219f**

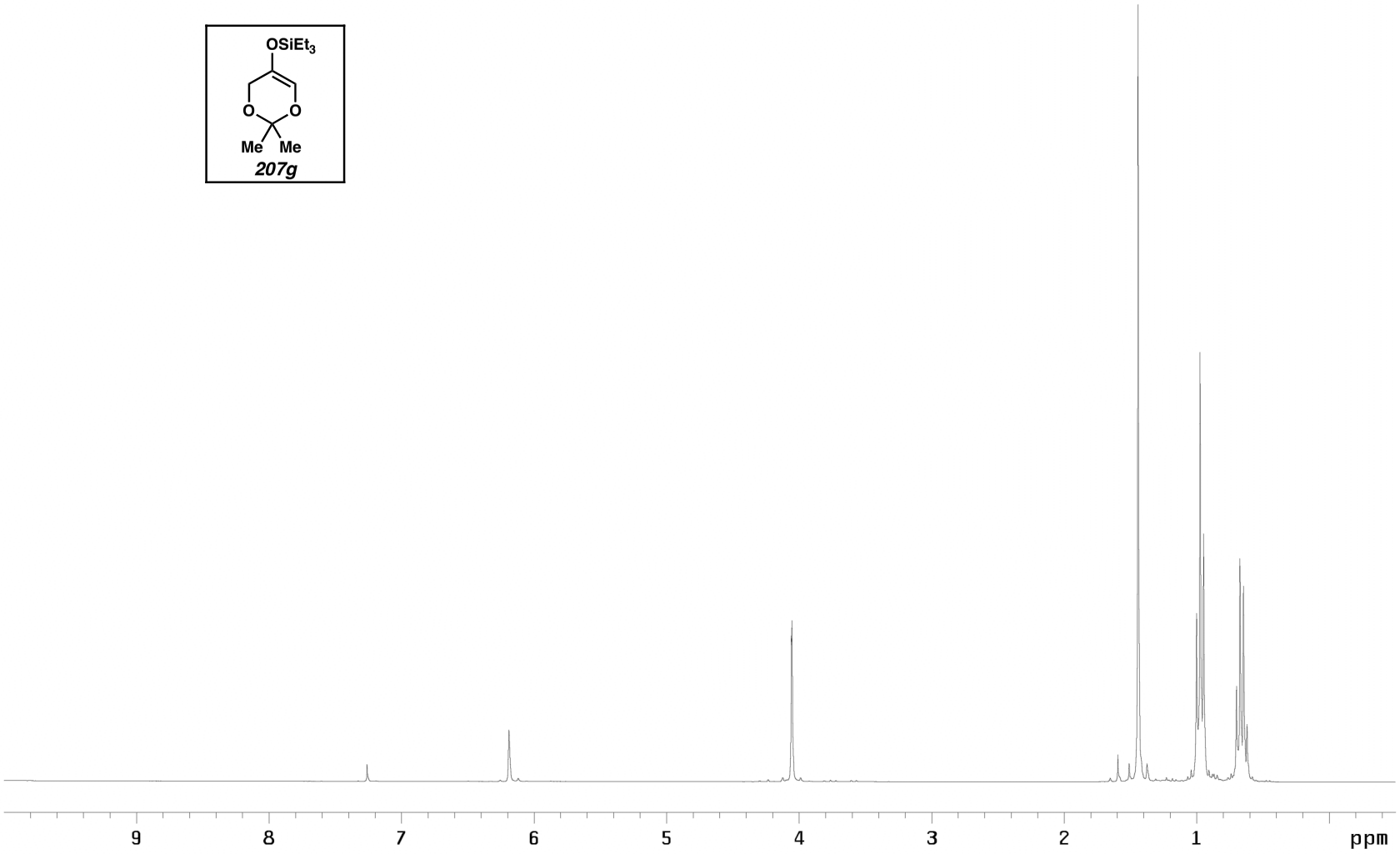


Figure A4.75 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **207g**

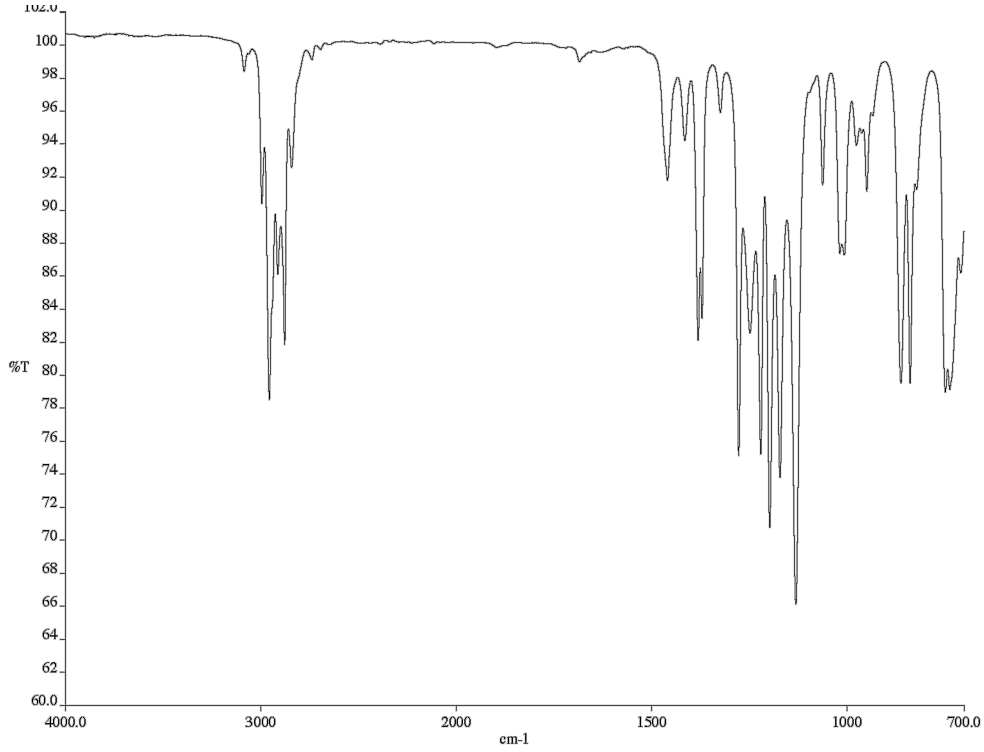


Figure A4.76 Infrared spectrum (thin film/NaCl) of compound **207g**

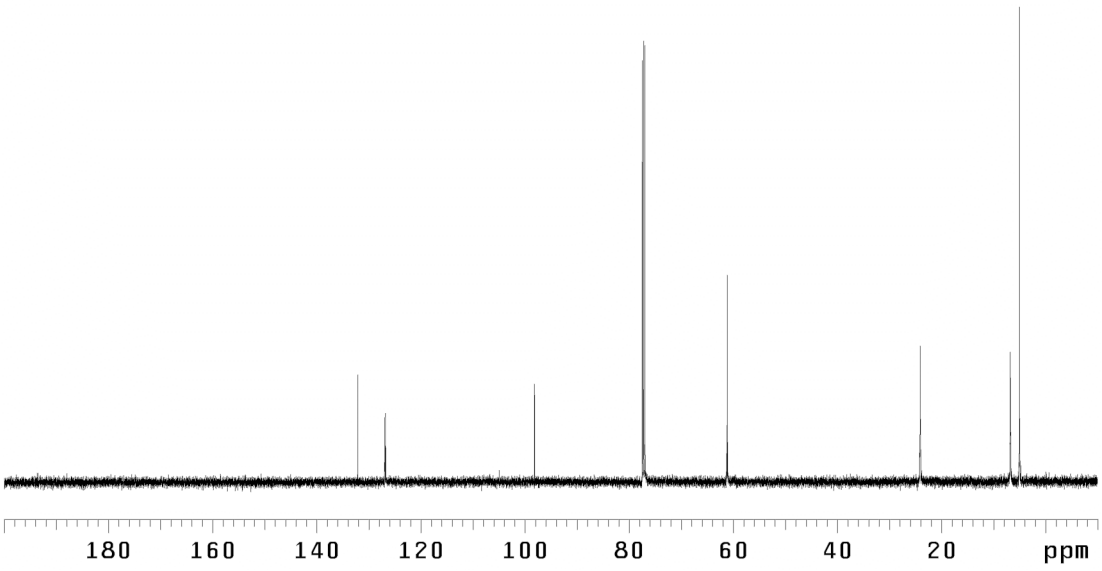


Figure A4.77 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **207g**

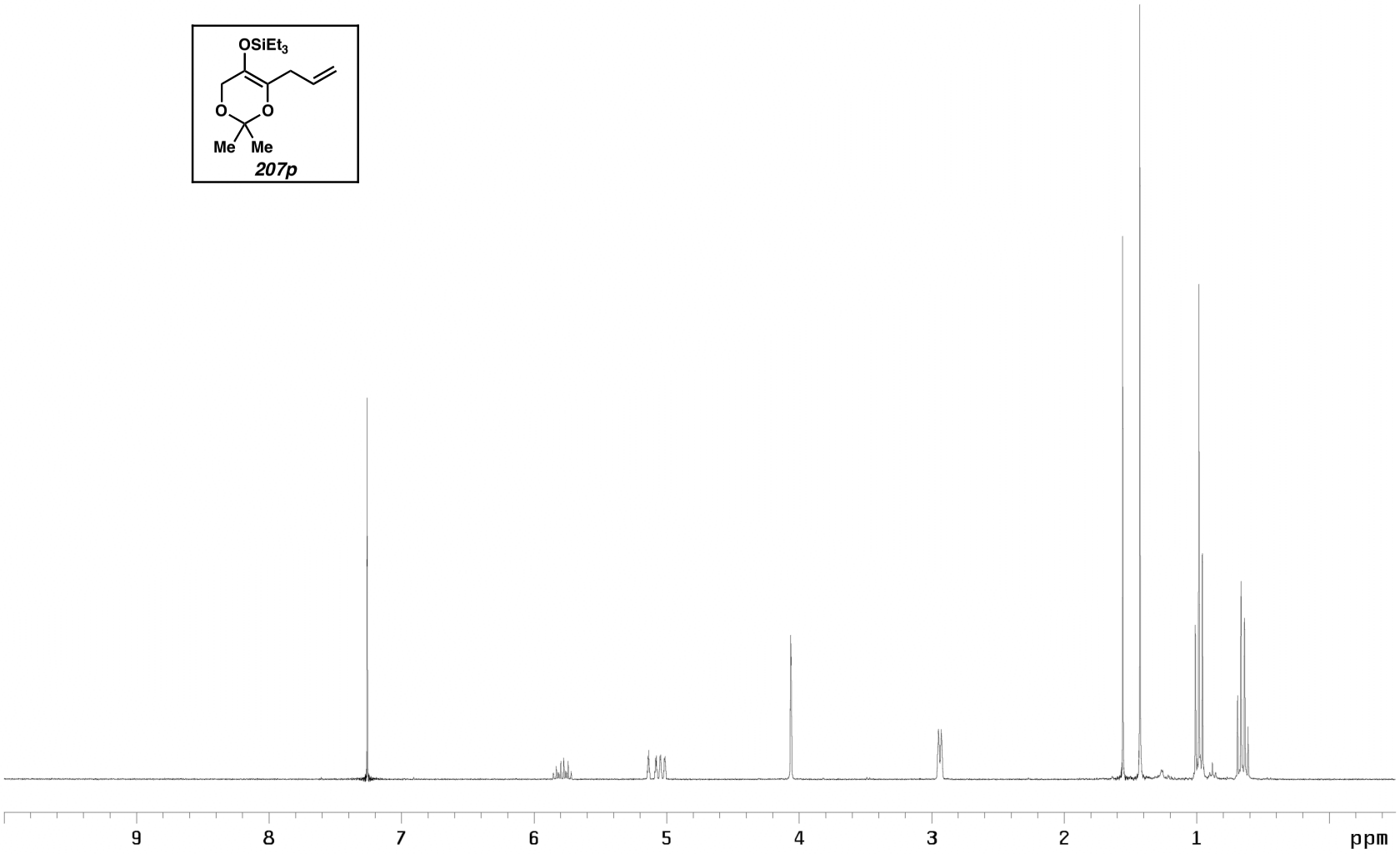


Figure A4.78 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **207p**

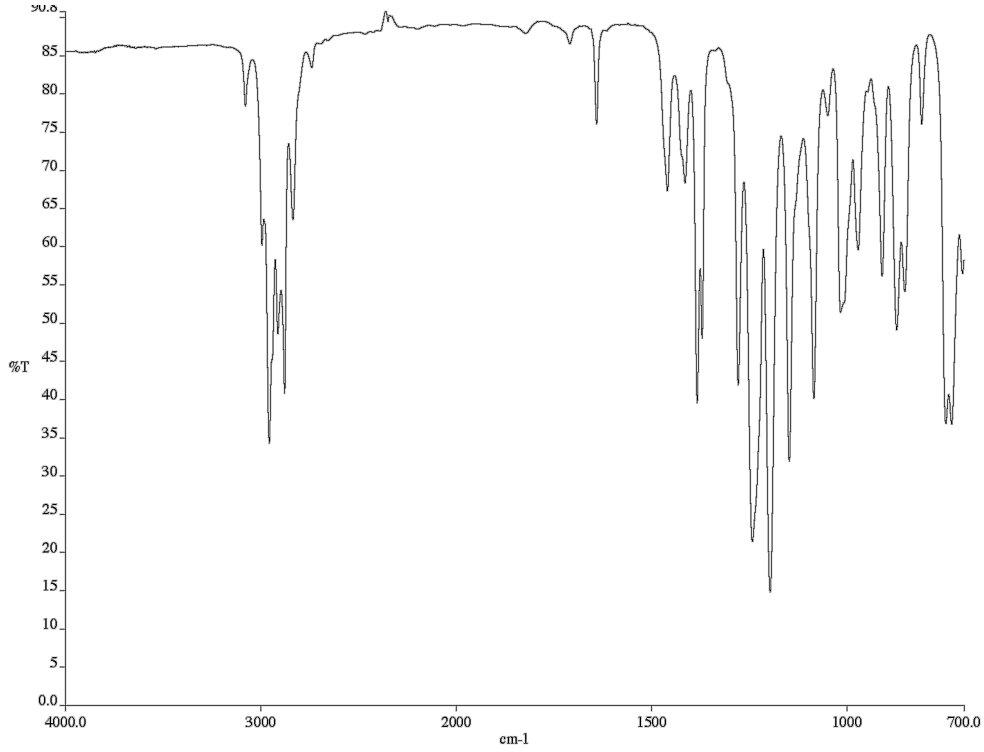


Figure A4.79 Infrared spectrum (thin film/NaCl) of compound **207p**

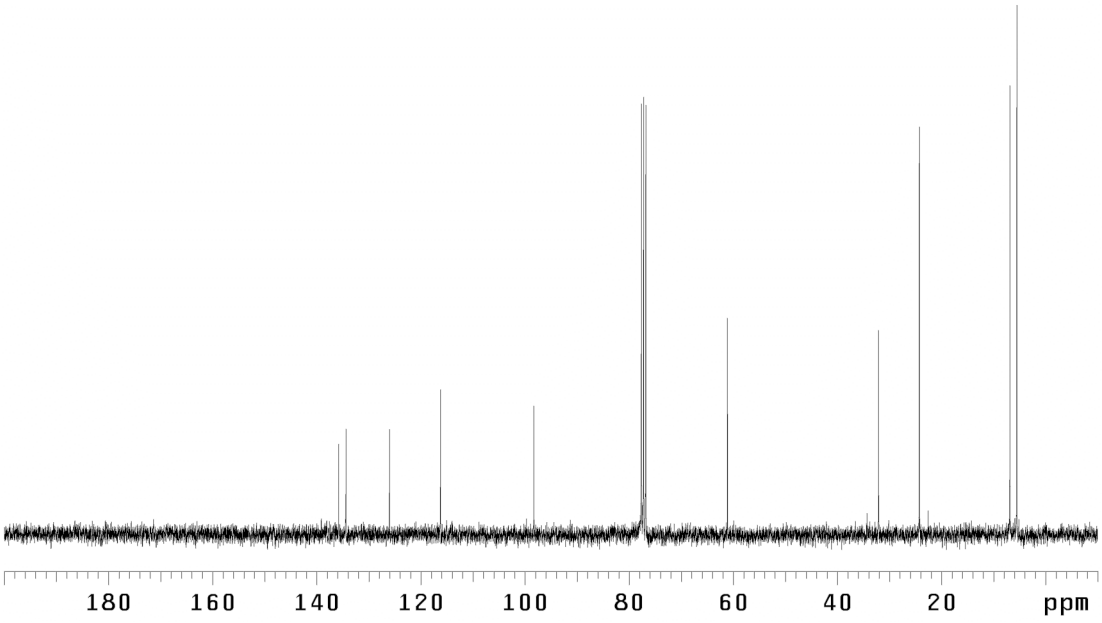


Figure A4.80 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **207p**

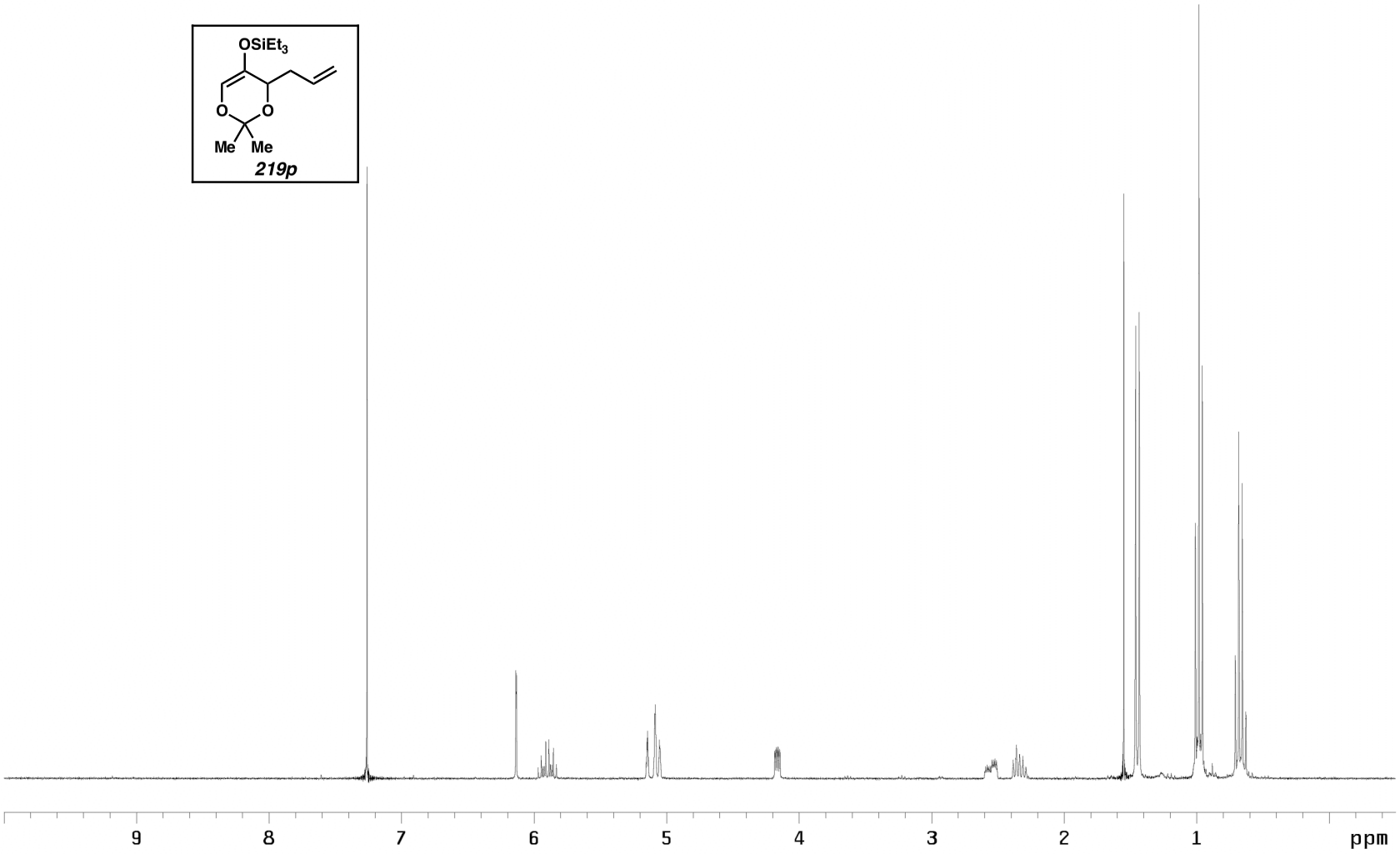


Figure A4.81 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **219p**

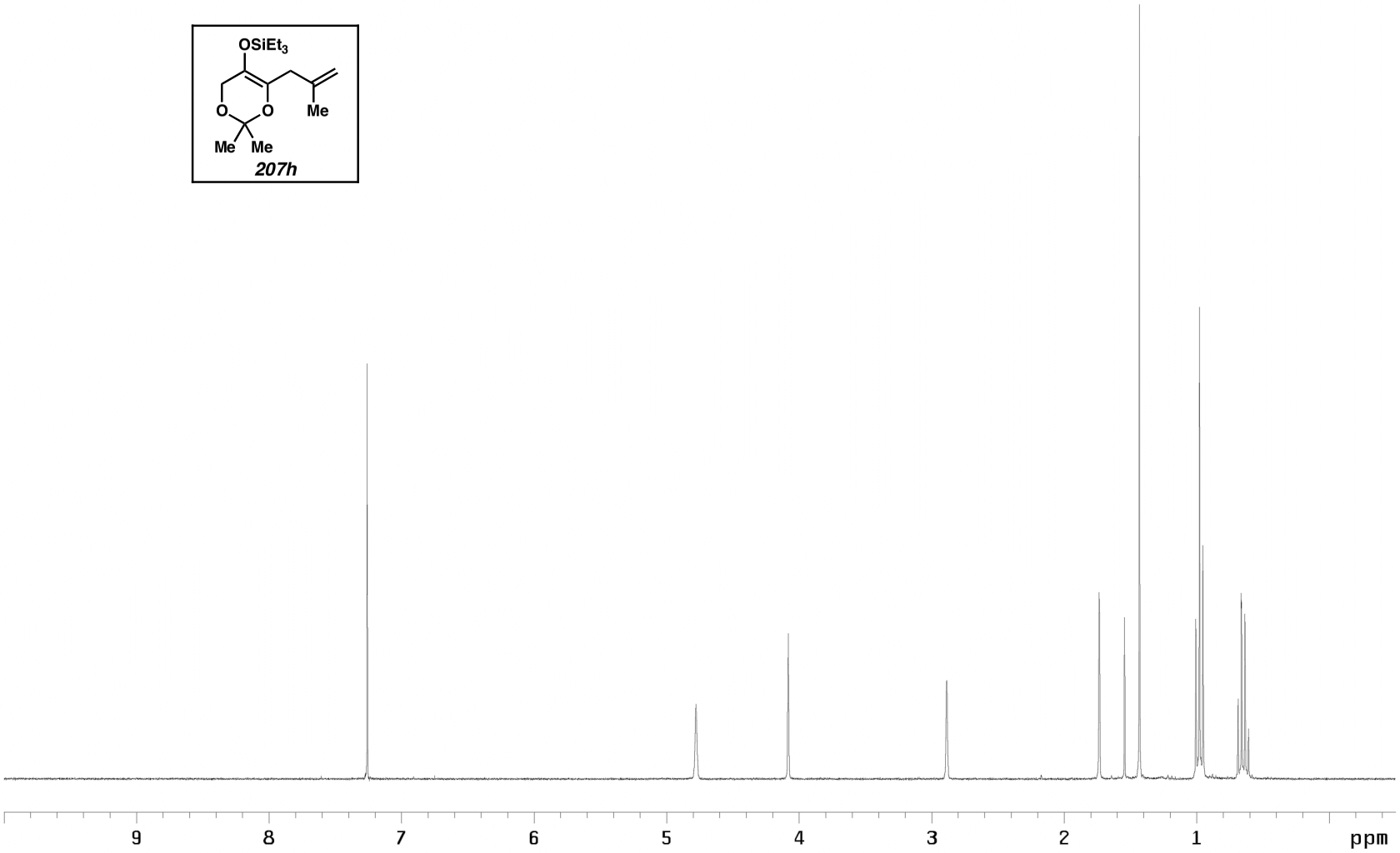


Figure A4.82 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **207h**

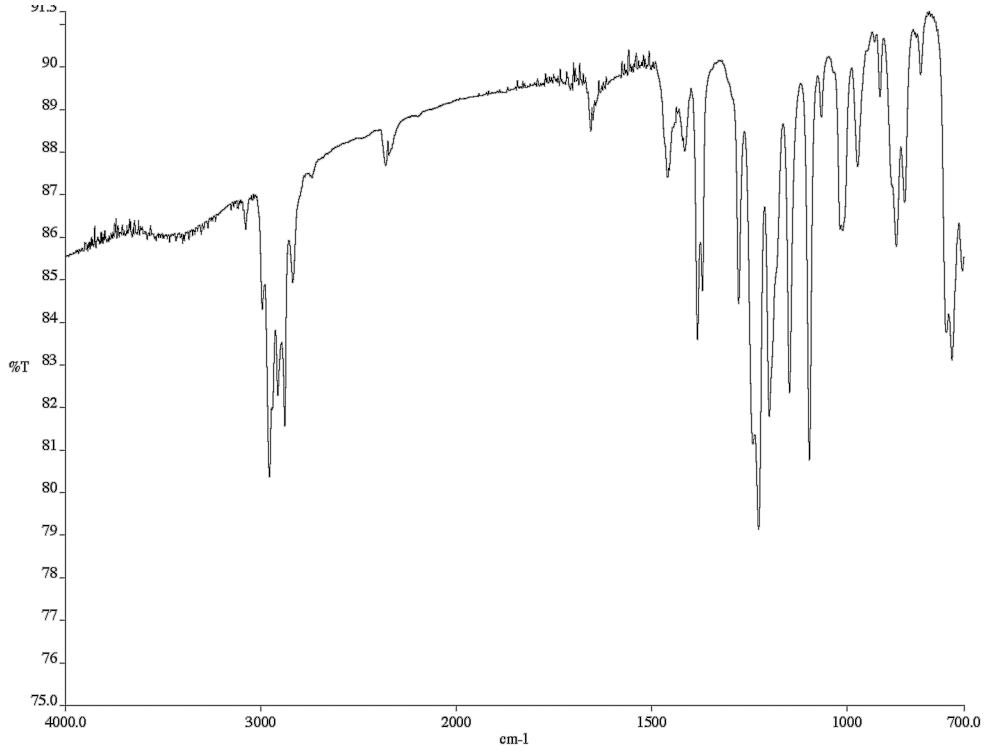


Figure A4.83 Infrared spectrum (thin film/NaCl) of compound **207h**

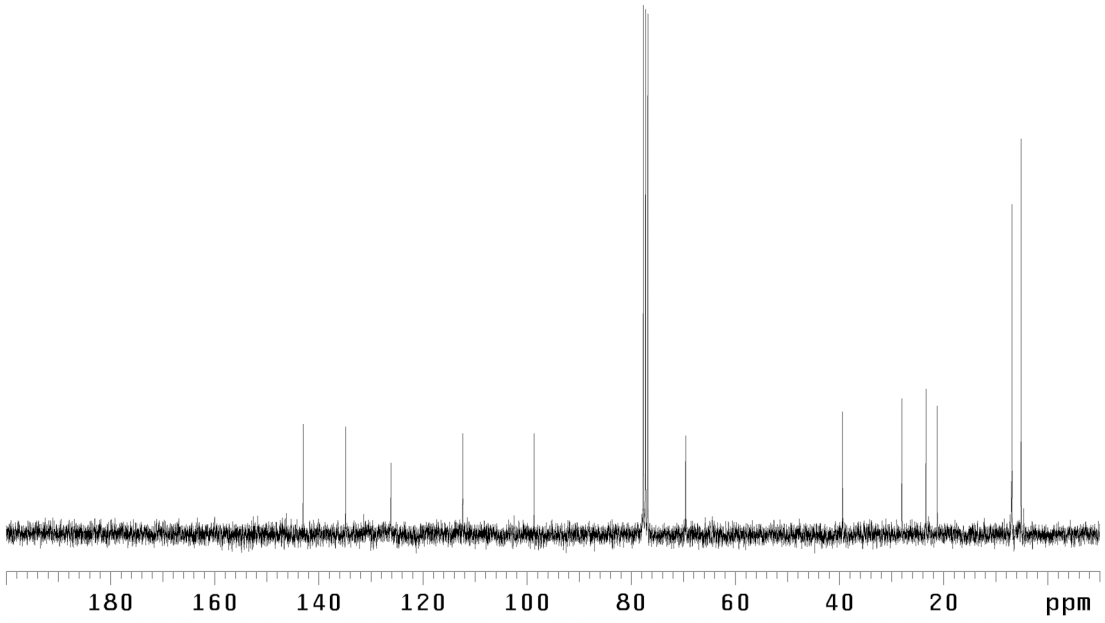


Figure A4.84 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **207h**

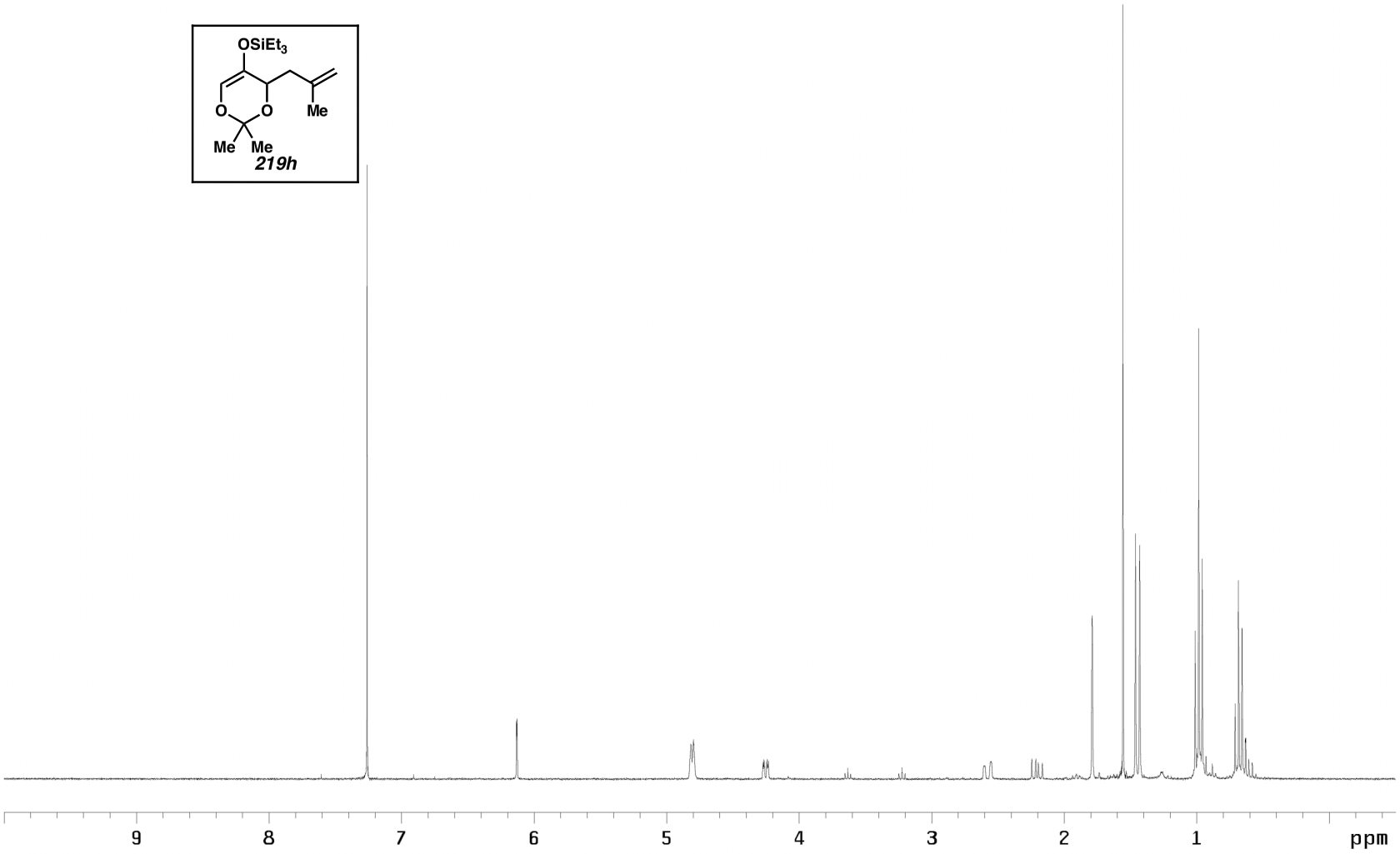


Figure A4.85 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **219h**

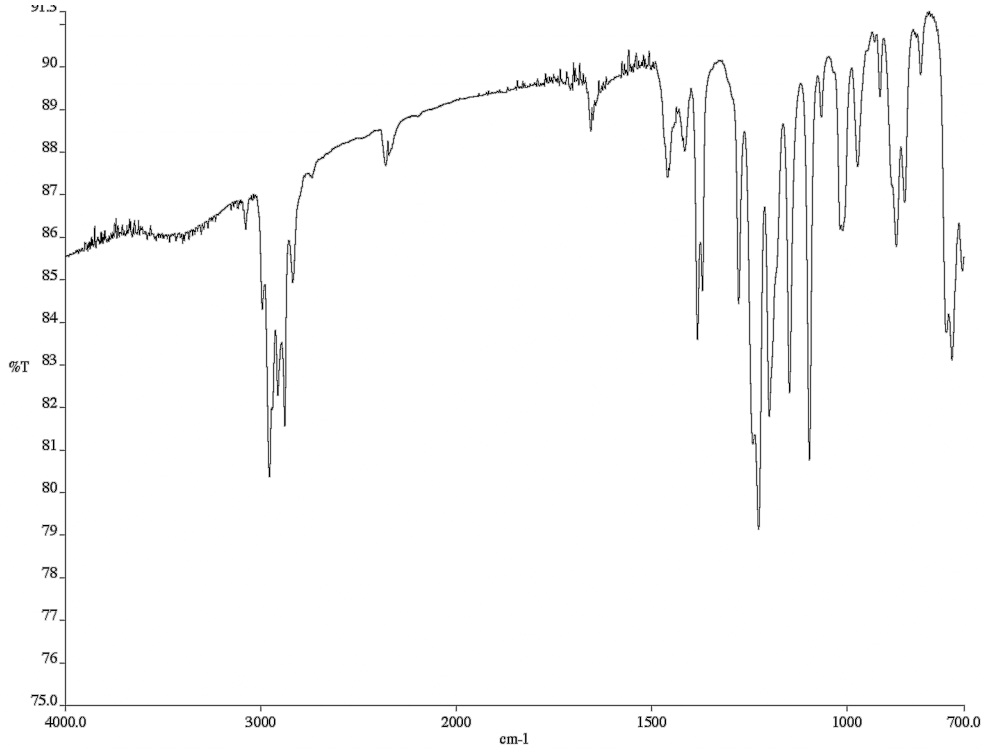


Figure A4.86 Infrared spectrum (thin film/NaCl) of compound **219h**

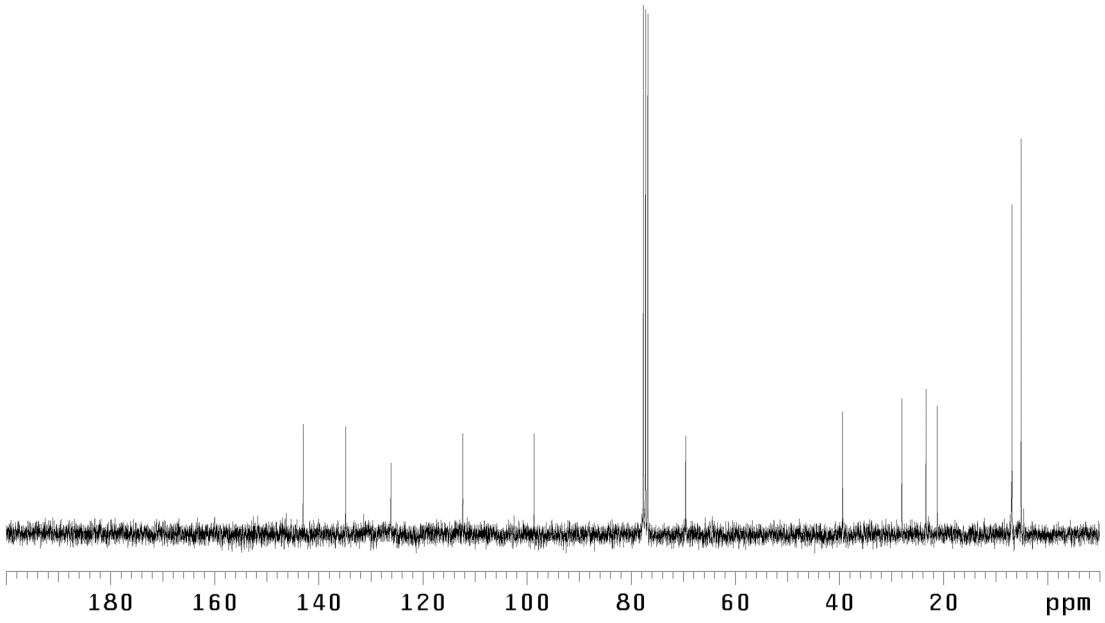


Figure A4.87 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **219h**

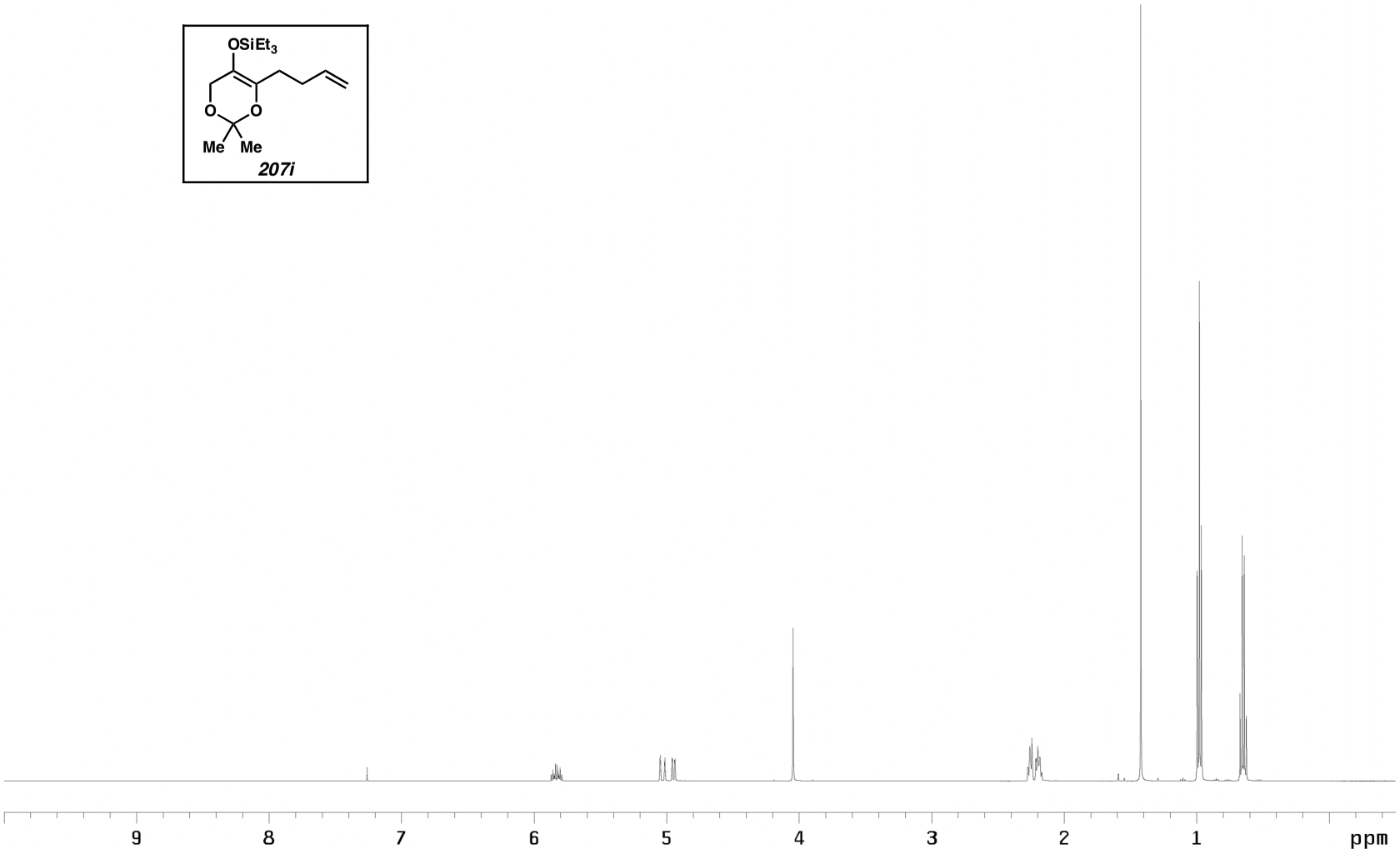


Figure A4.88 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **207i**

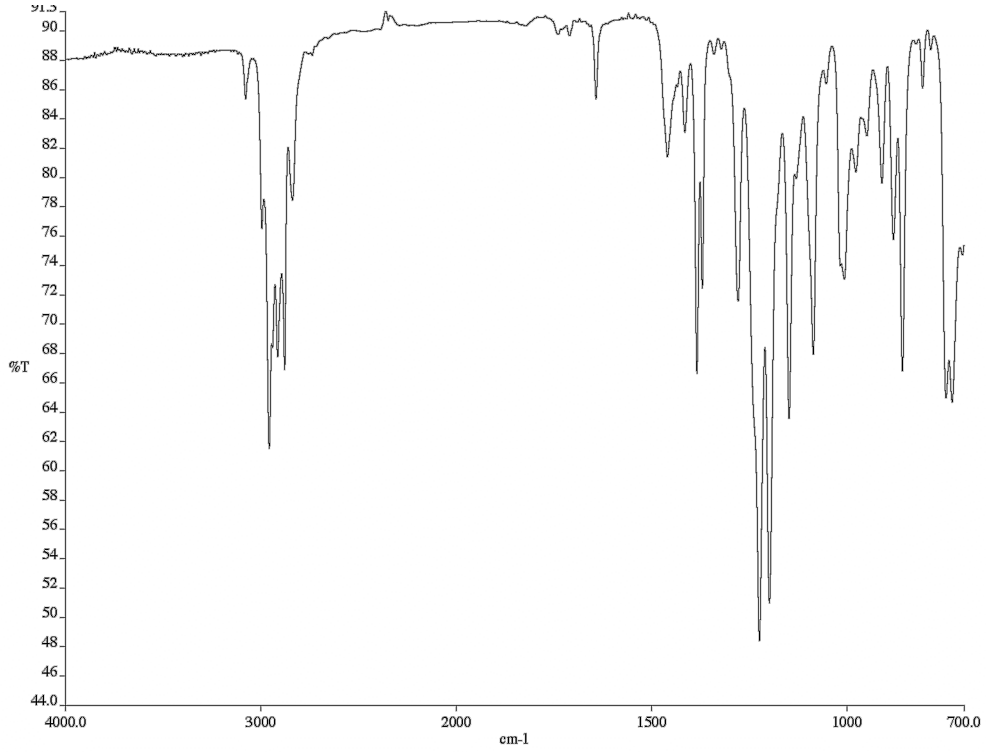


Figure A4.89 Infrared spectrum (thin film/NaCl) of compound **207i**

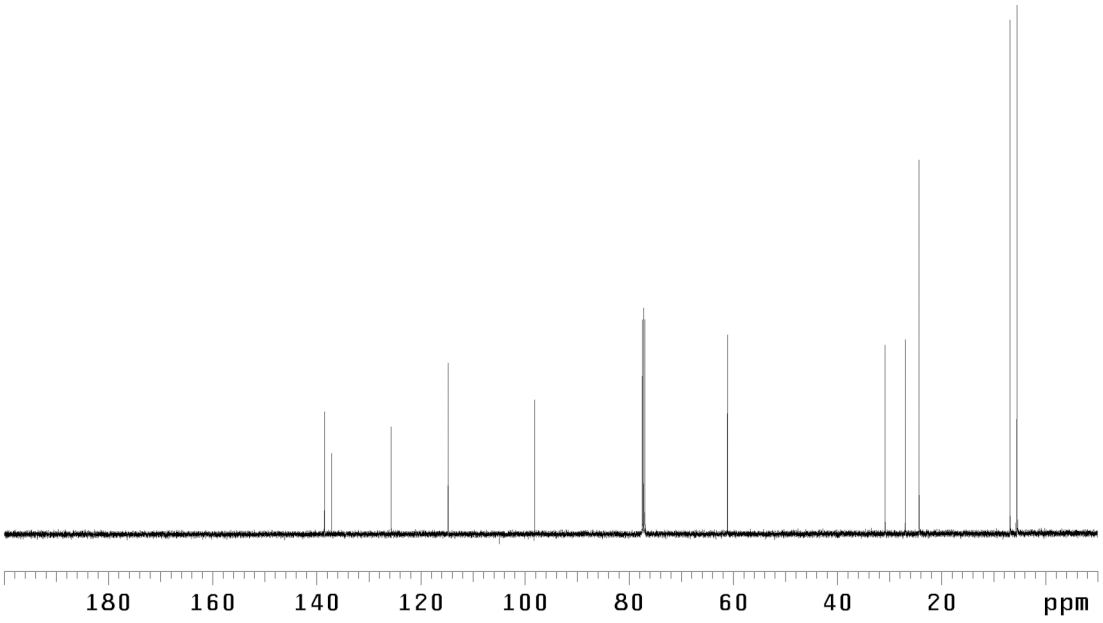


Figure A4.90 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **207i**

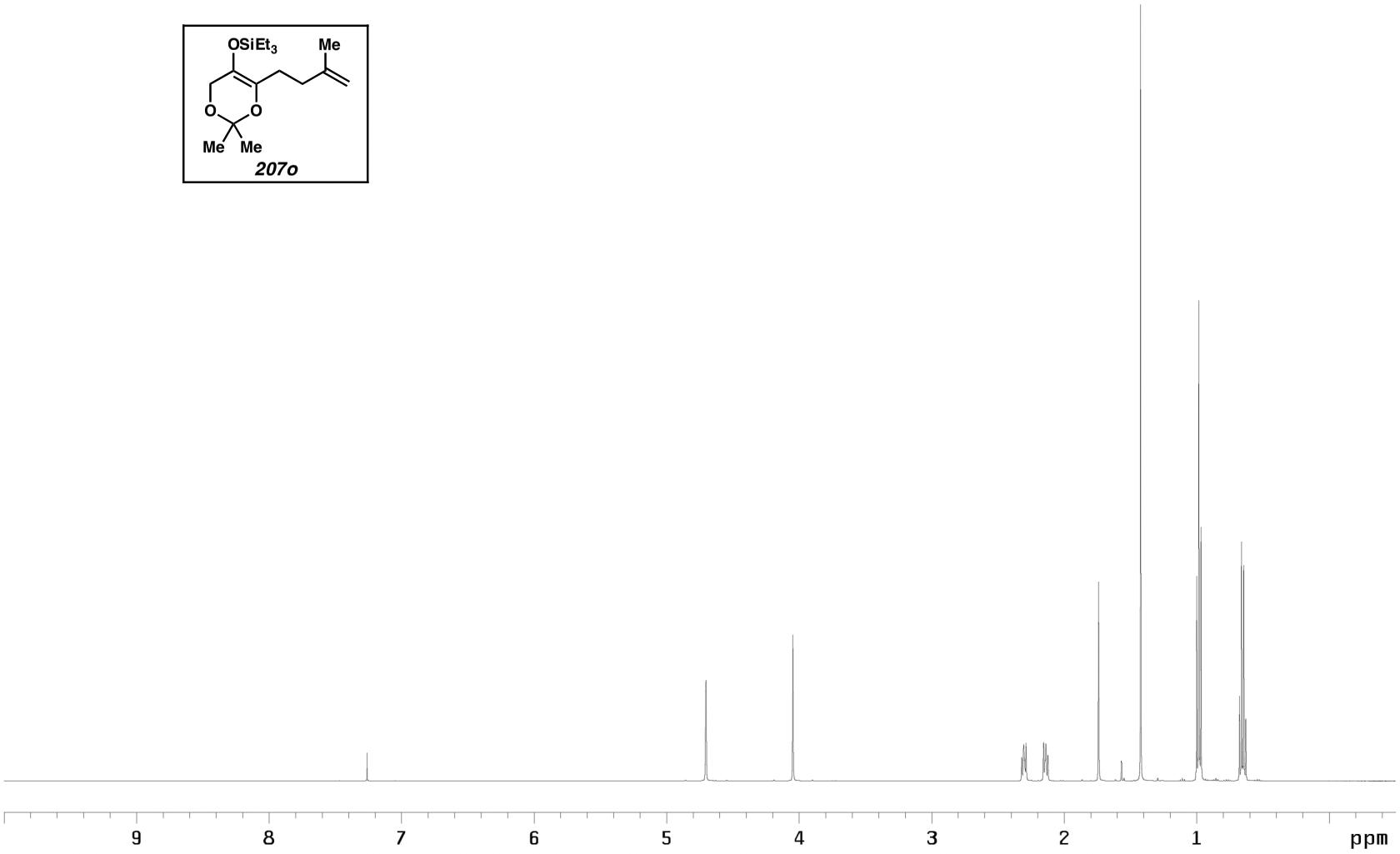


Figure A4.91 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **207o**

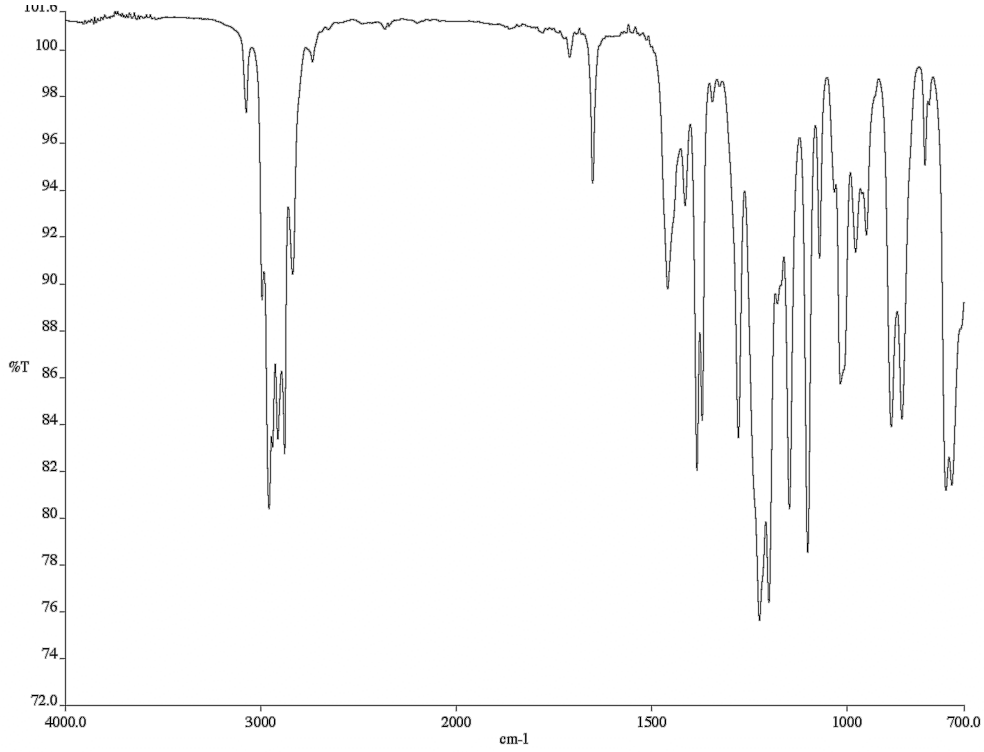


Figure A4.92 Infrared spectrum (thin film/NaCl) of compound **207o**

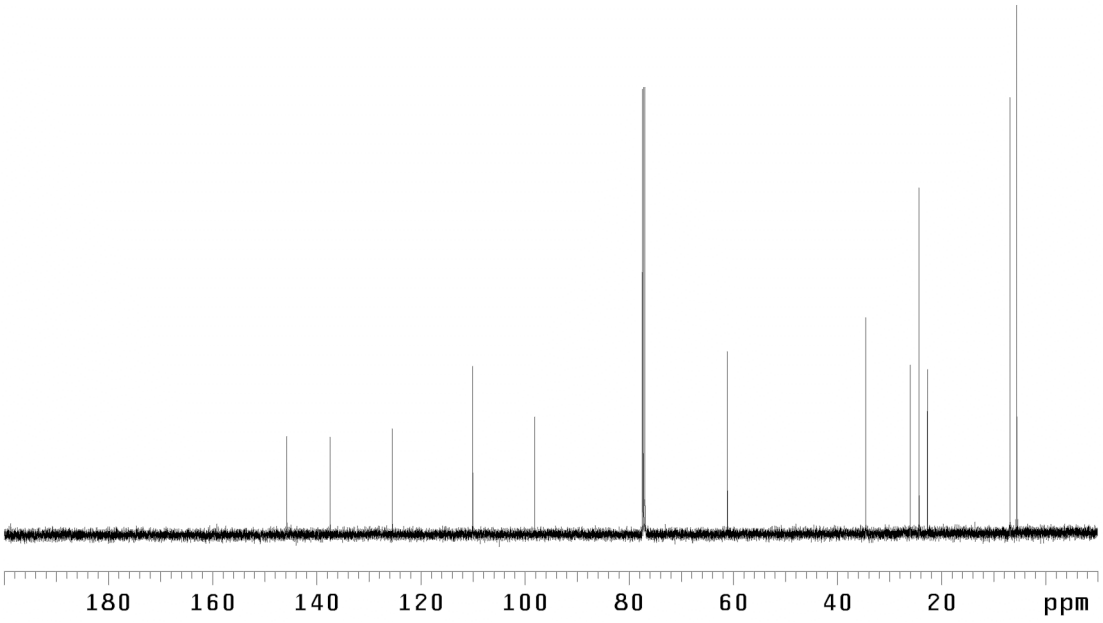


Figure A4.93 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **207o**

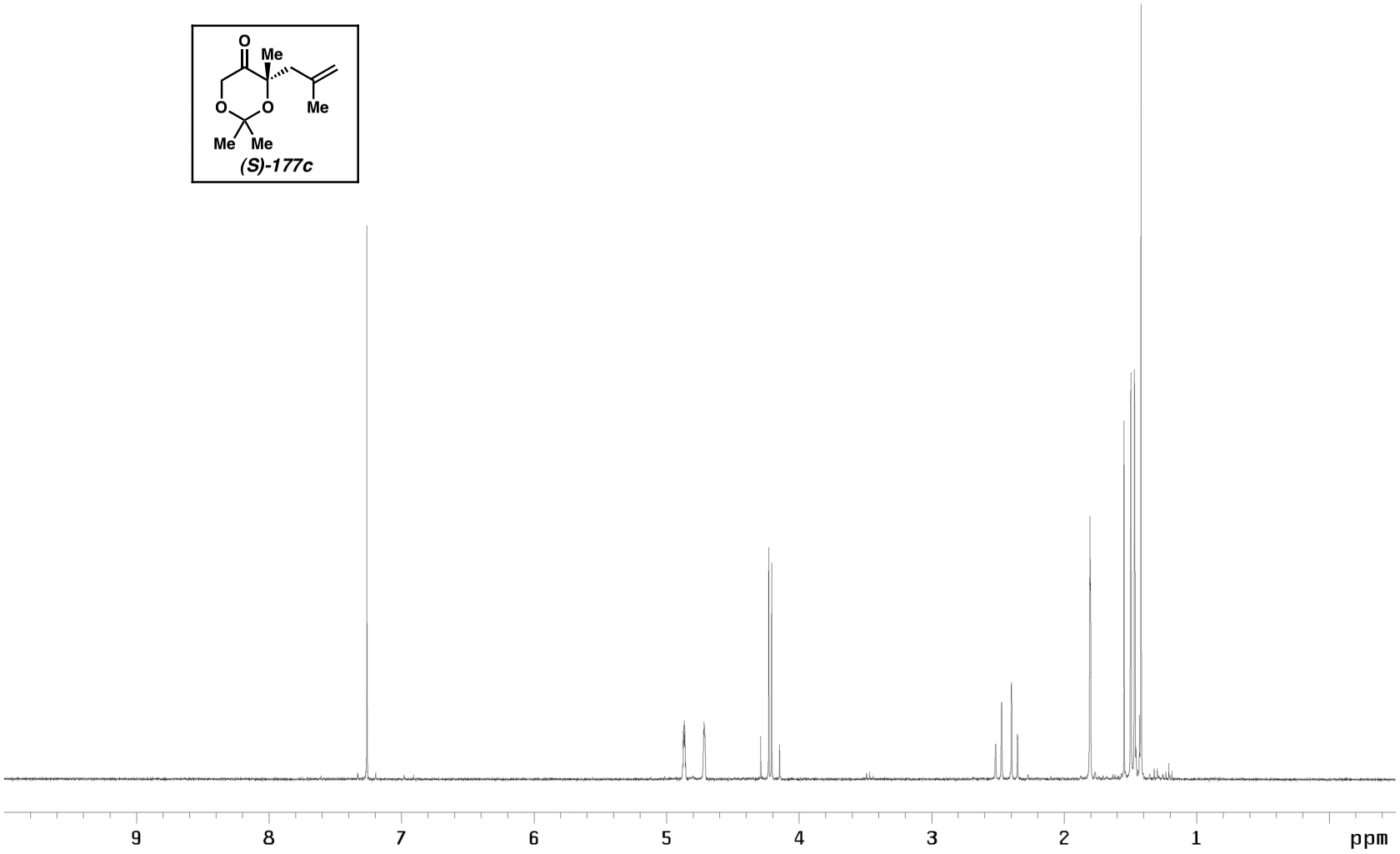


Figure A4.94 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **177c**

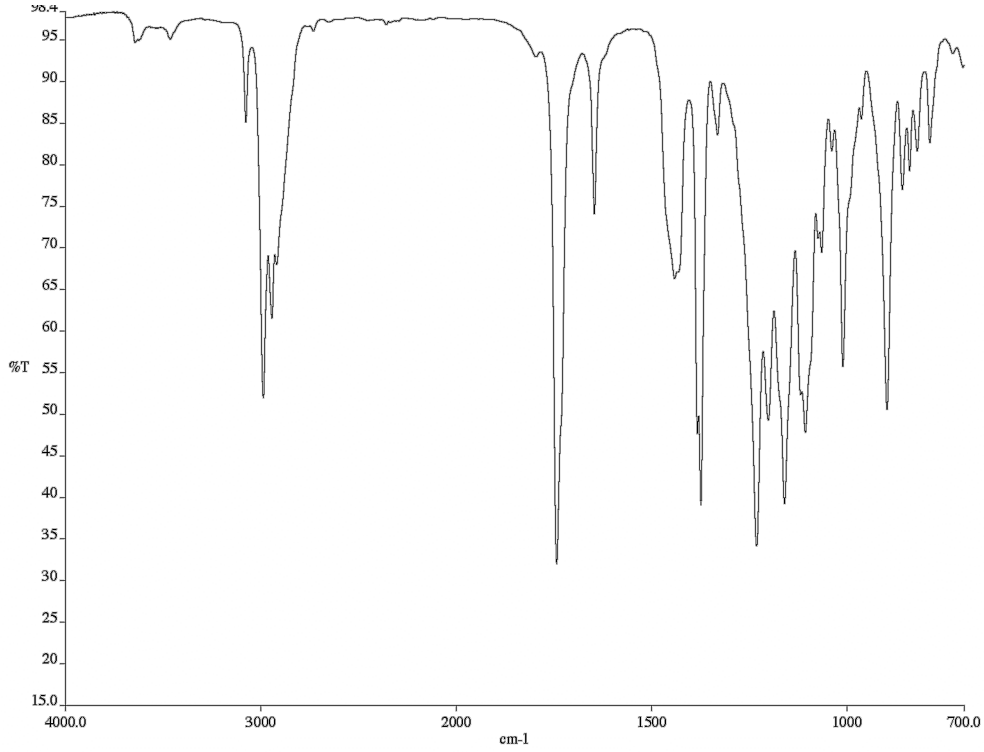


Figure A4.95 Infrared spectrum (thin film/NaCl) of compound **177c**

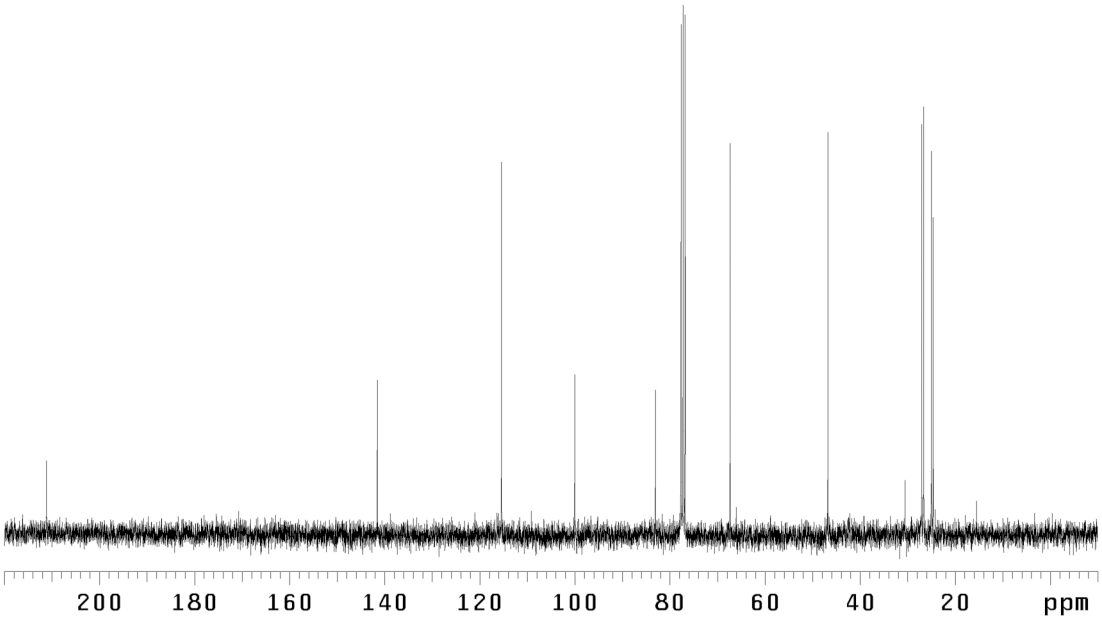


Figure A4.96 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **177c**

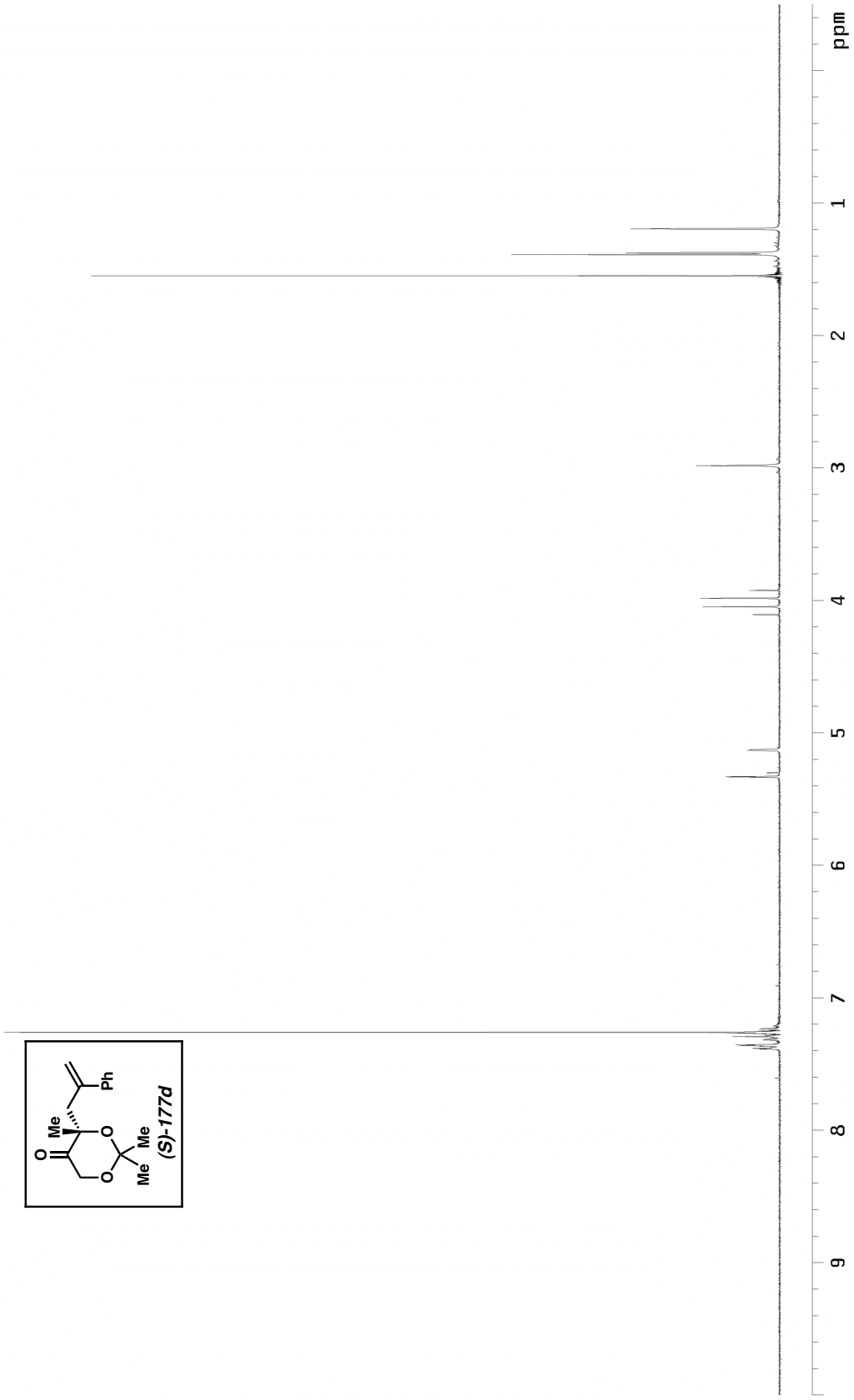


Figure A4.97 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **177d**

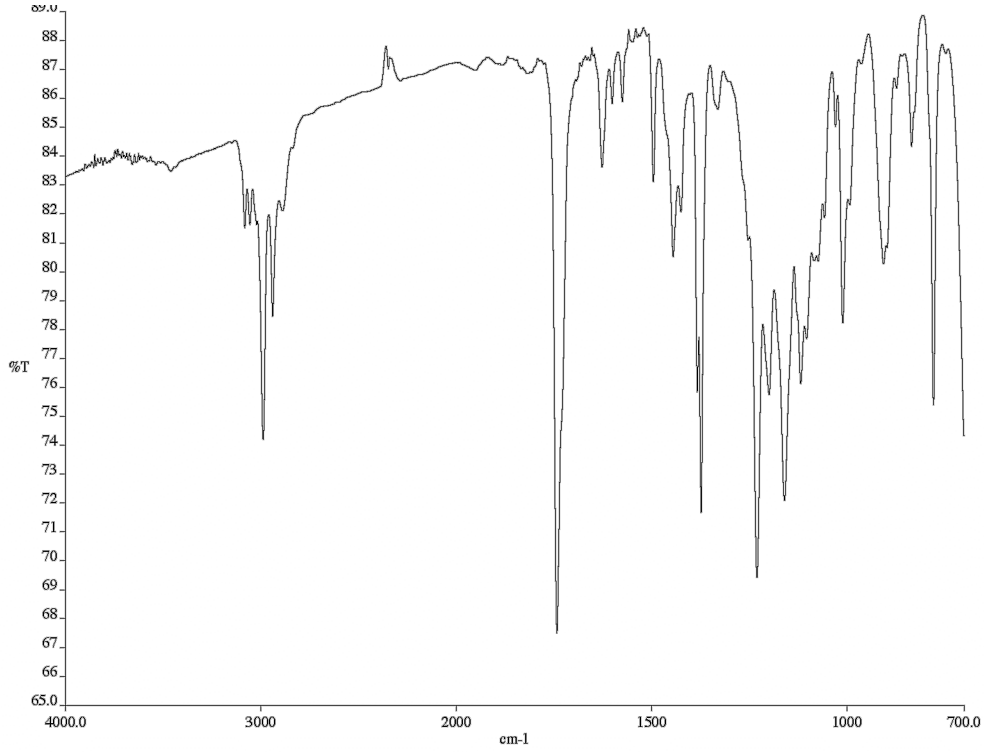


Figure A4.98 Infrared spectrum (thin film/NaCl) of compound **177d**

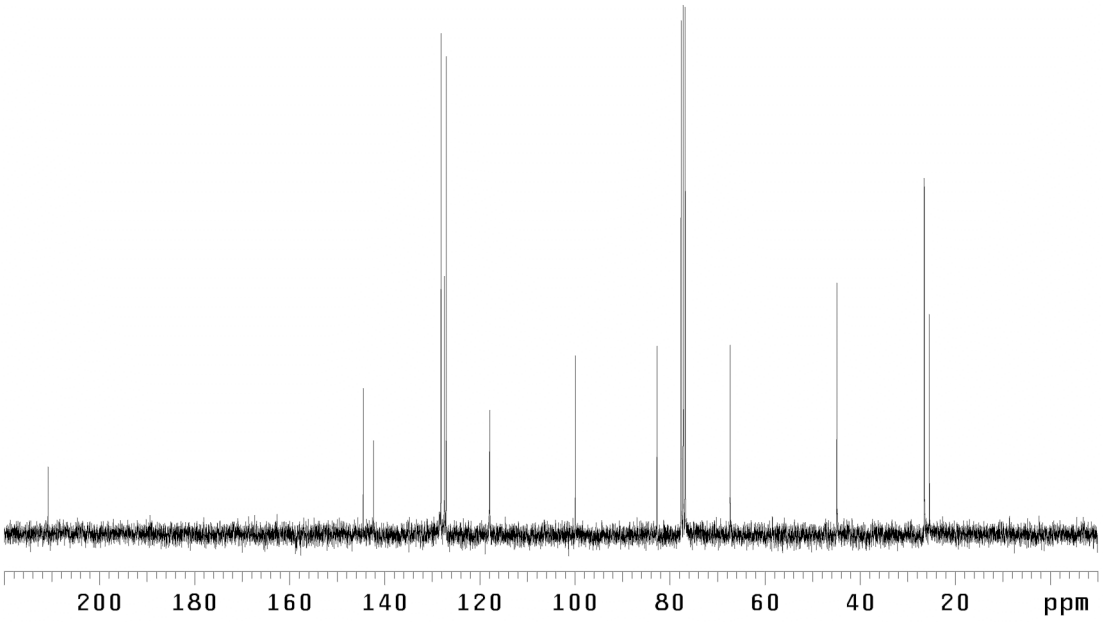


Figure A4.99 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **177d**

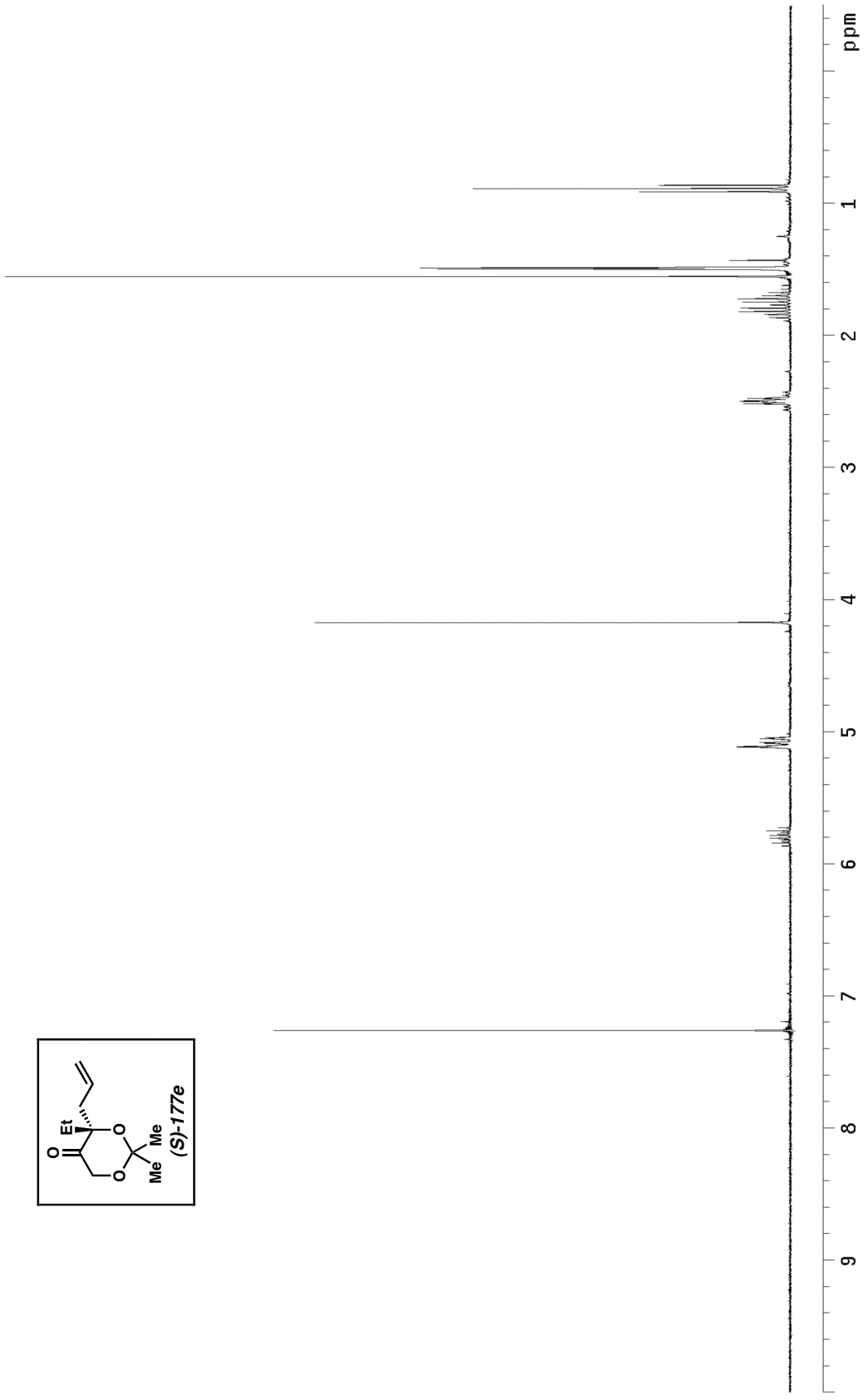


Figure A4.100 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **177e**

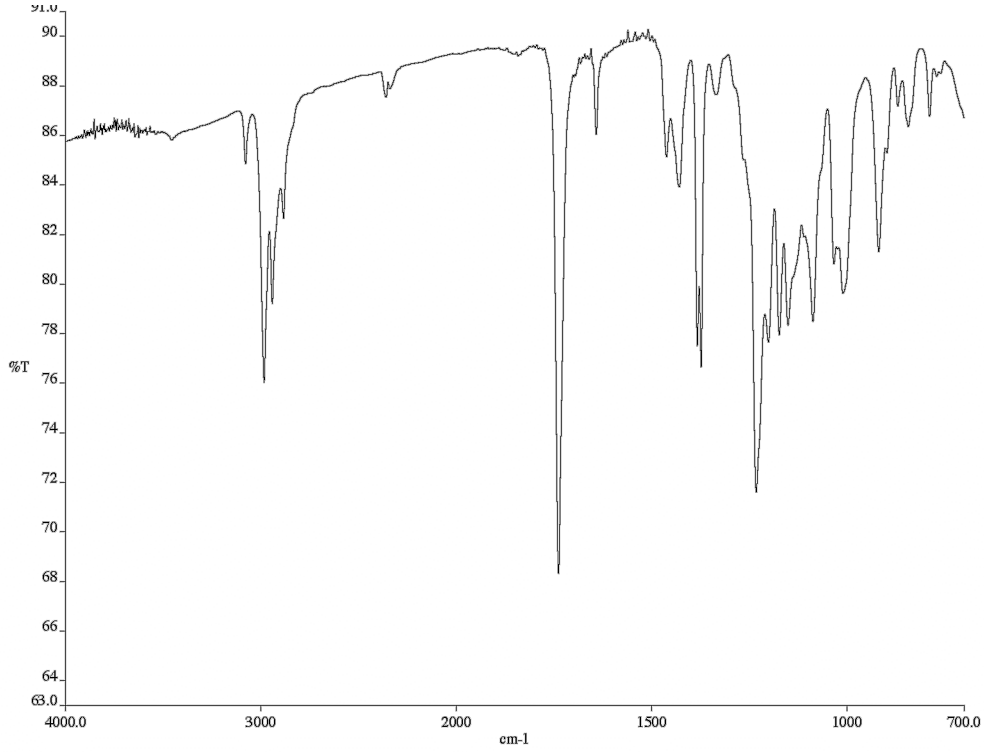


Figure A4.101 Infrared spectrum (thin film/NaCl) of compound **177e**

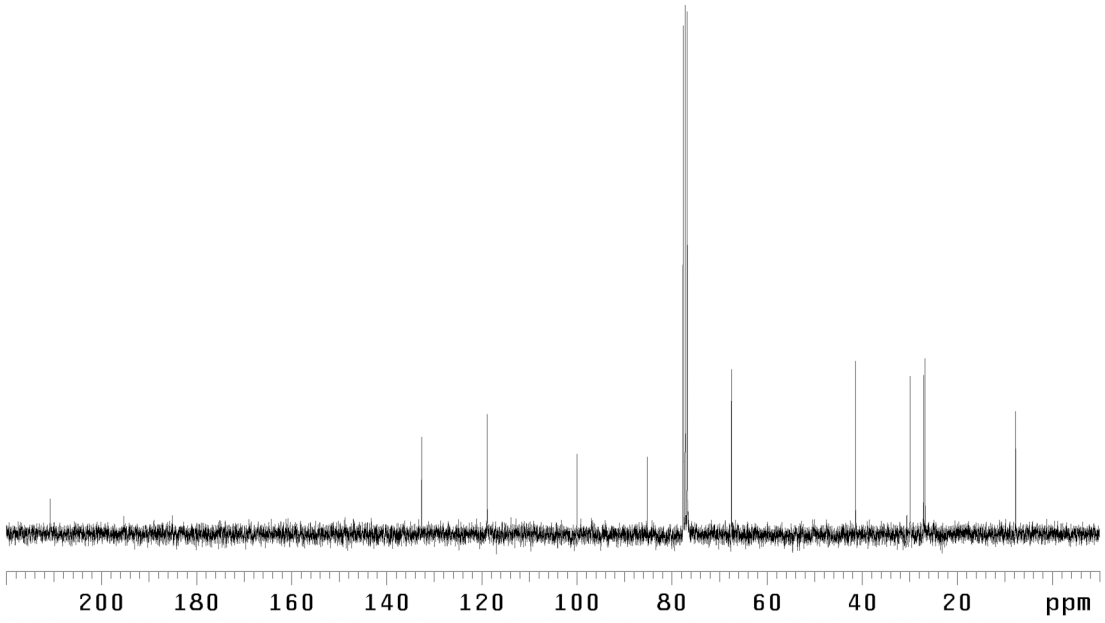


Figure A4.102 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **177e**

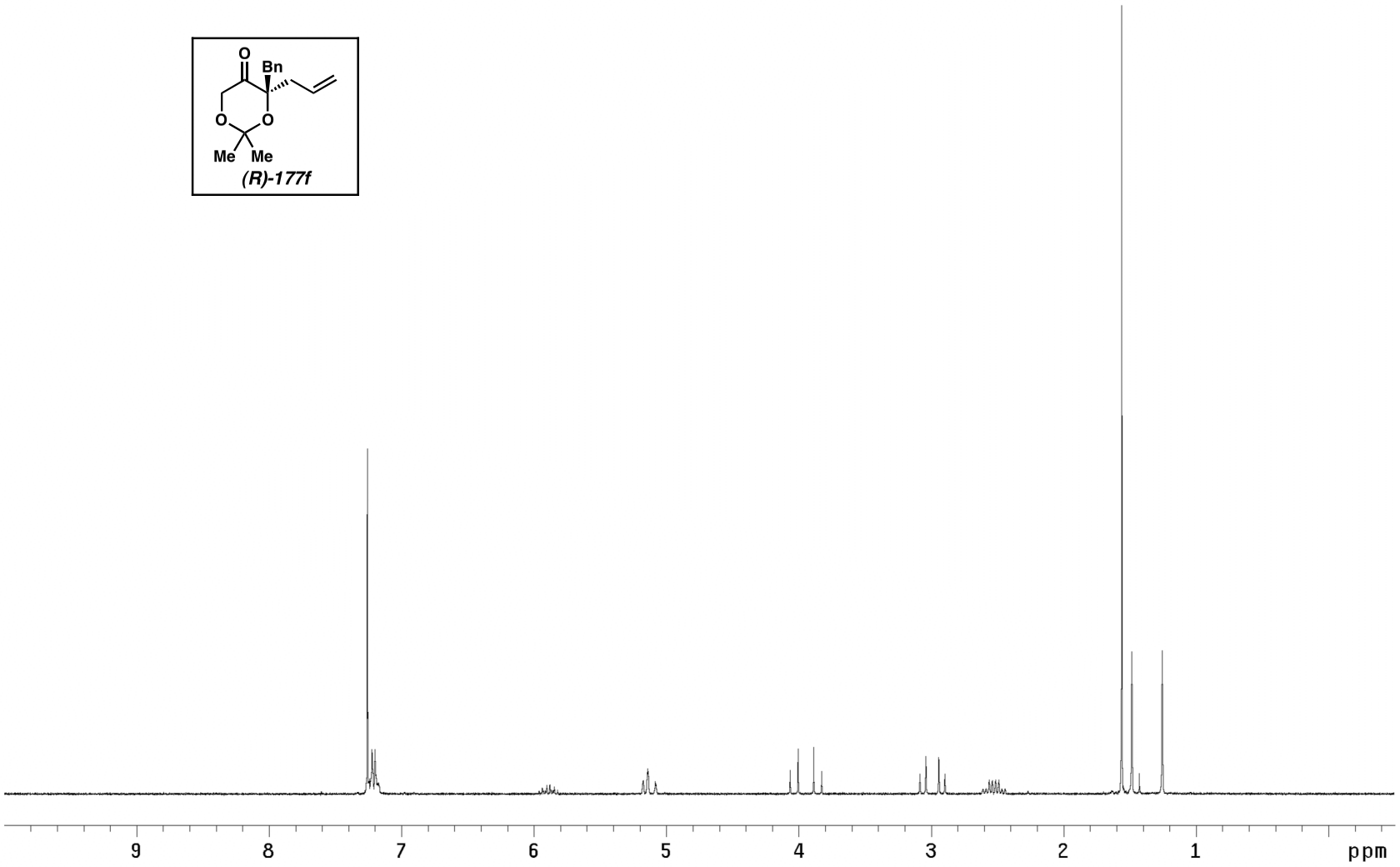


Figure A4.103 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **177f**

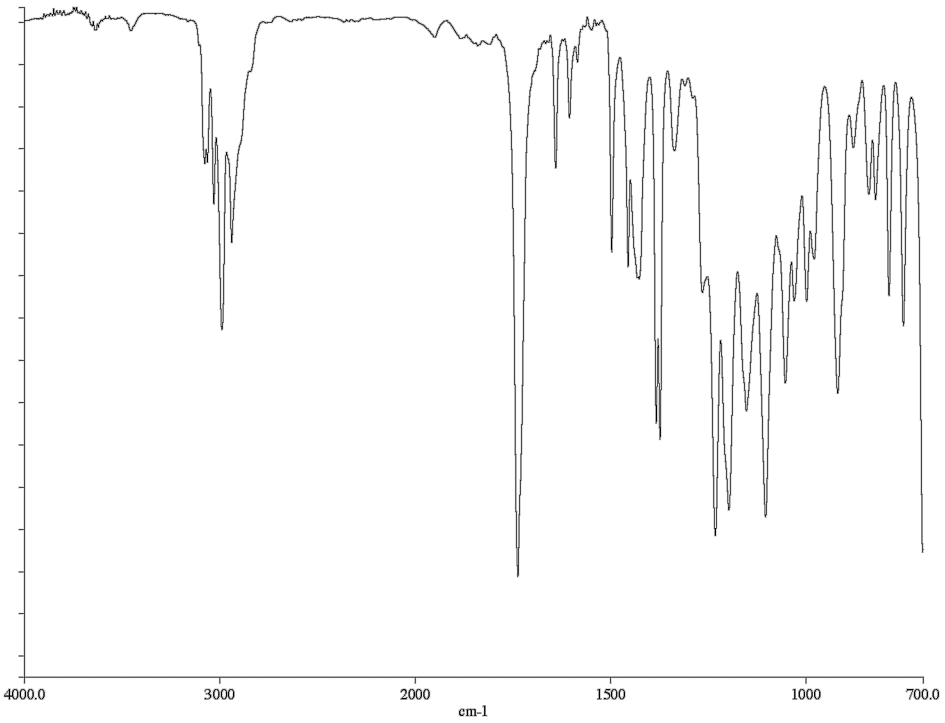


Figure A4.104 Infrared spectrum (thin film/NaCl) of compound **177f**

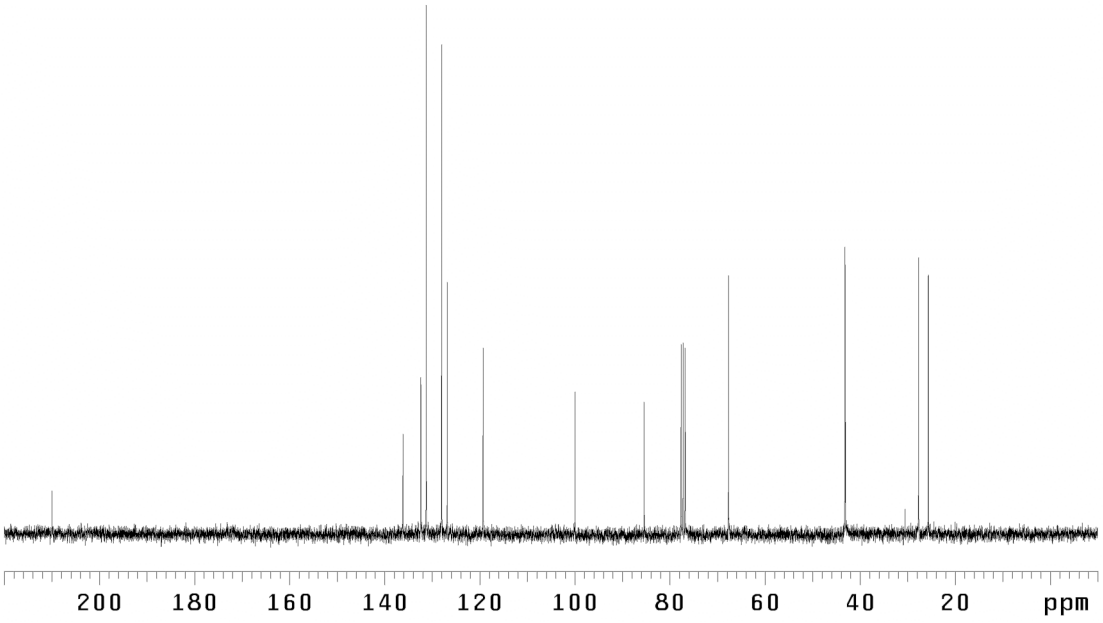


Figure A4.105 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **177f**

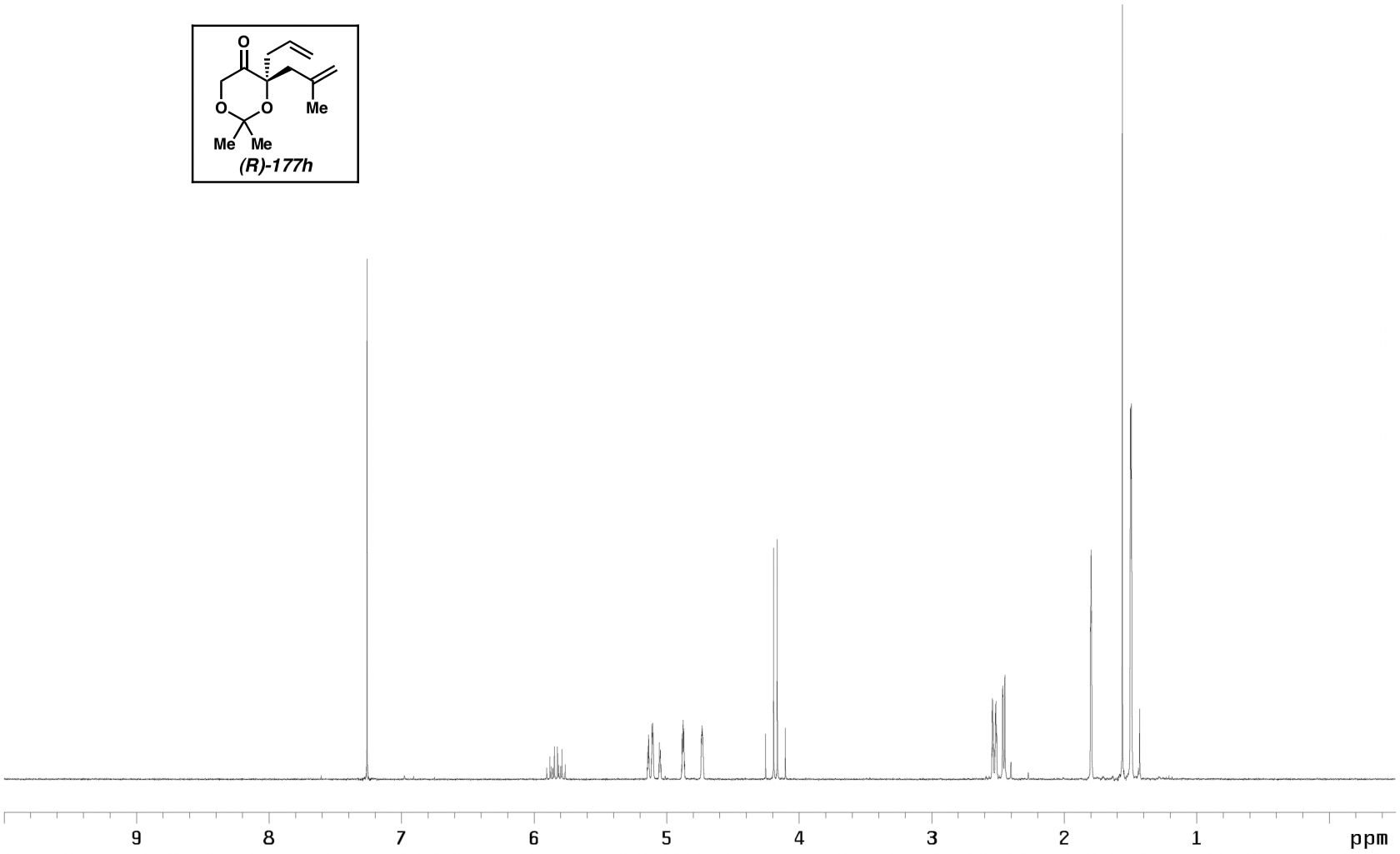


Figure A4.106 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **177h**

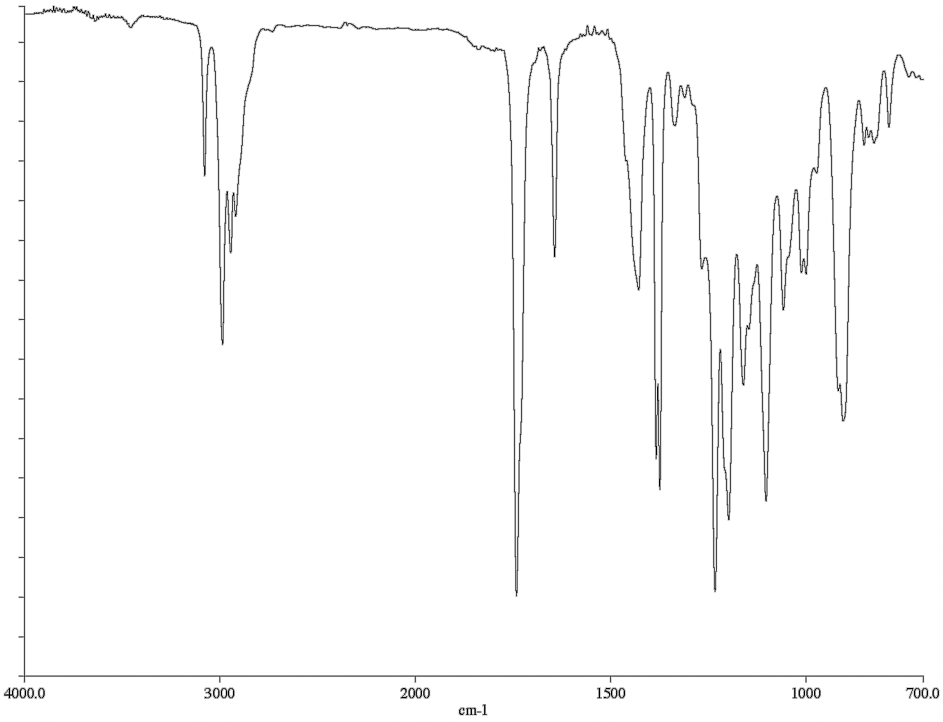


Figure A4.107 Infrared spectrum (thin film/NaCl) of ketone **177h**

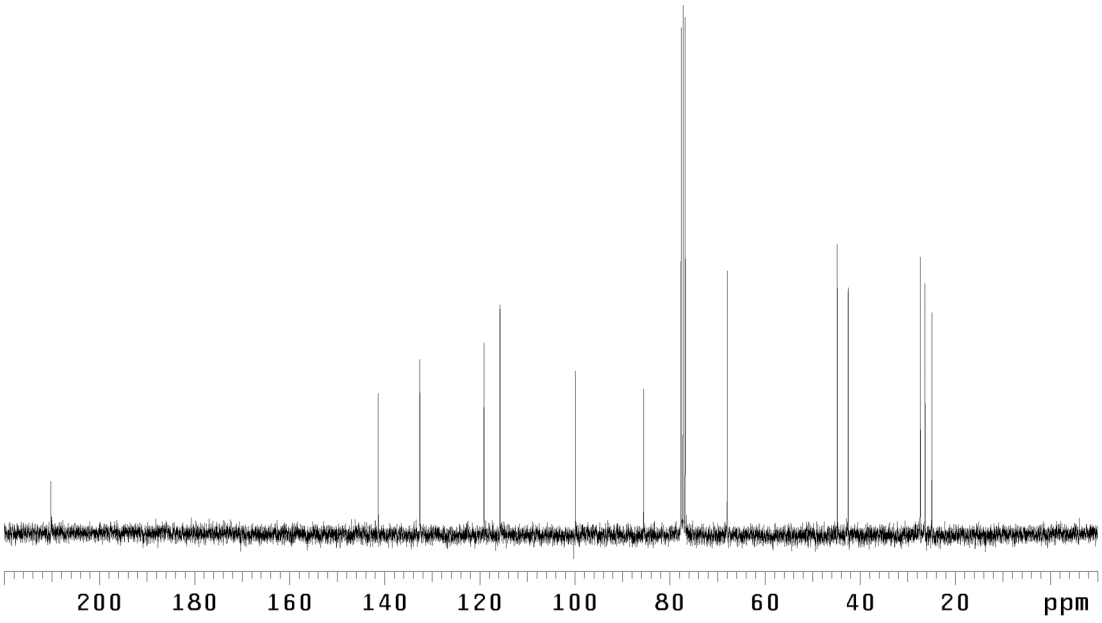


Figure A4.108 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **177h**

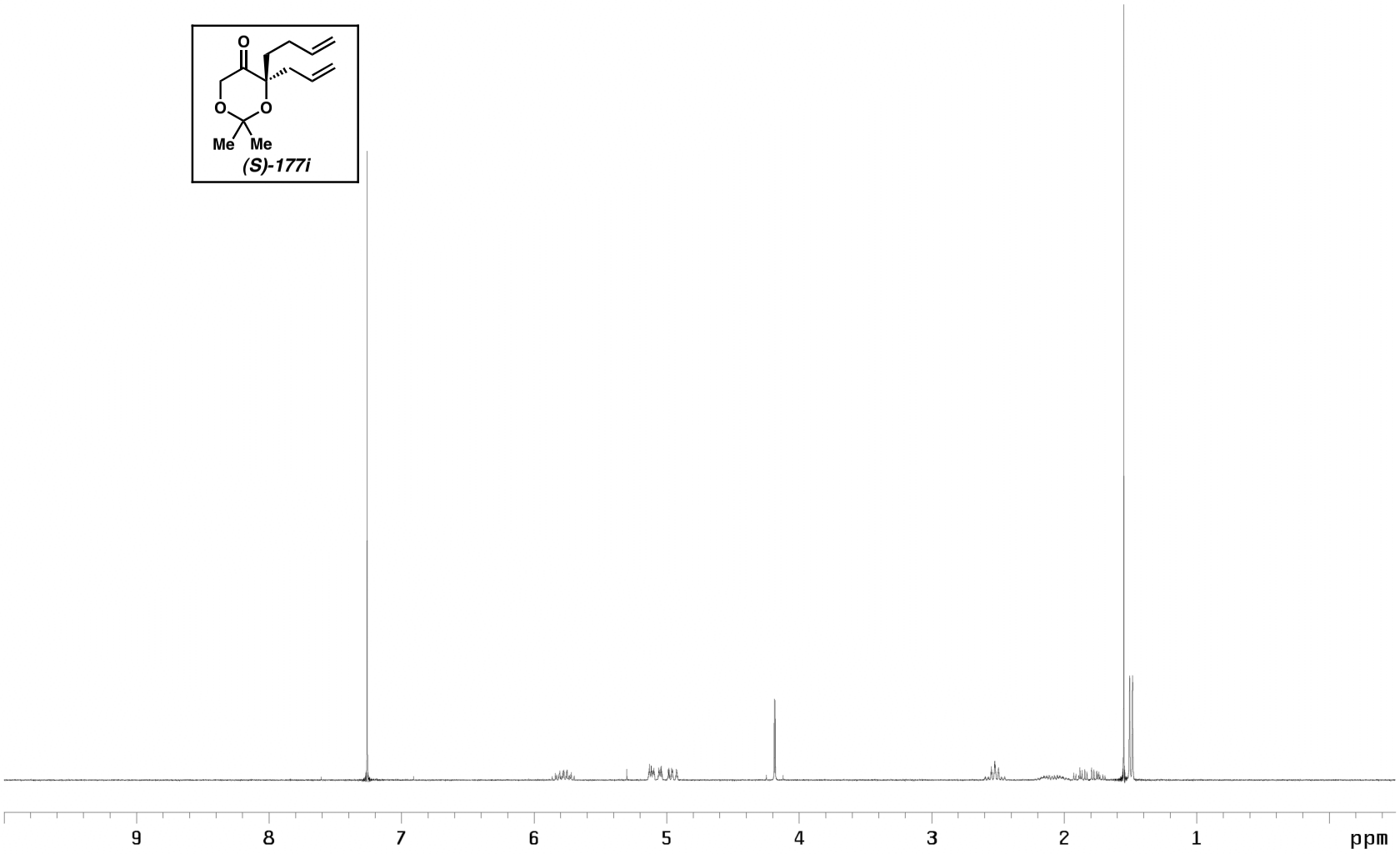


Figure A4.109 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **177i**

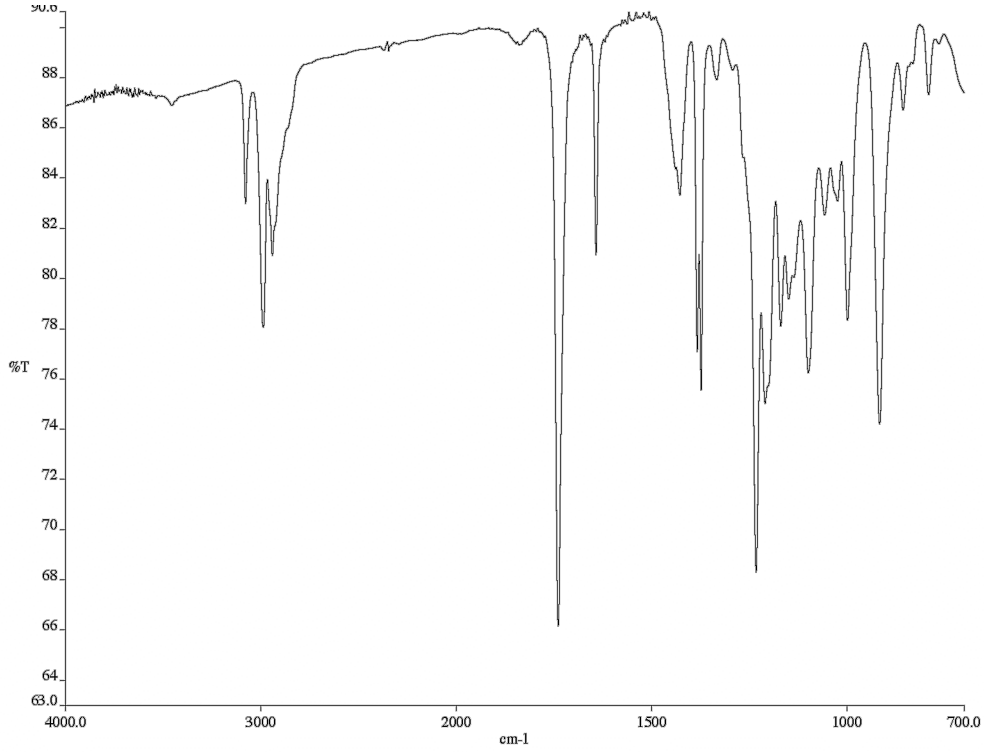


Figure A4.110 Infrared spectrum (thin film/NaCl) of compound **177i**

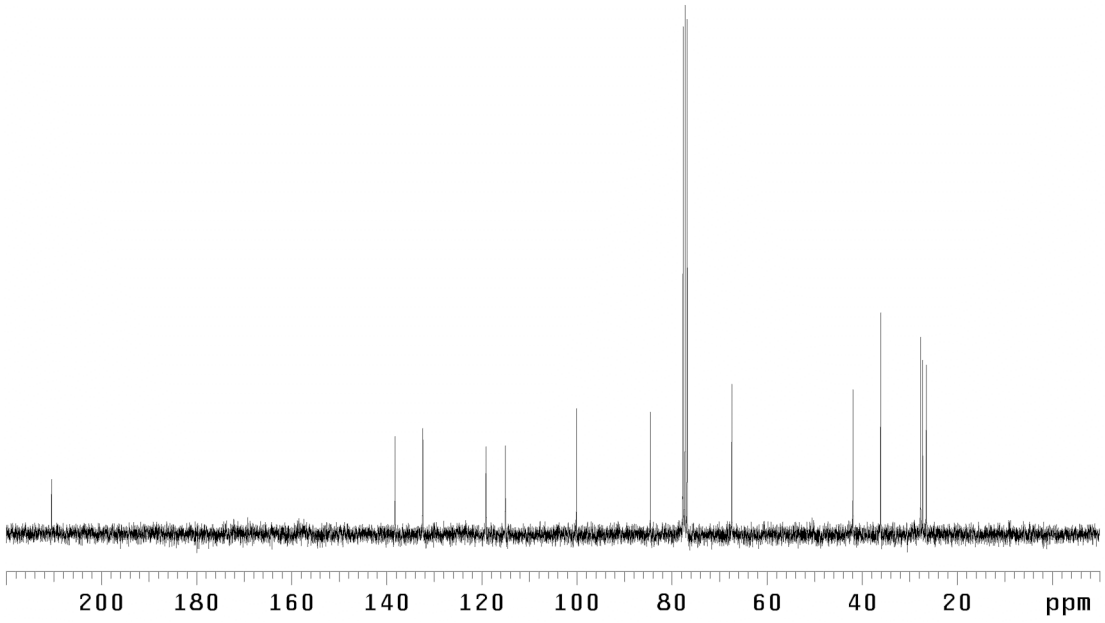


Figure A4.111 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **177i**

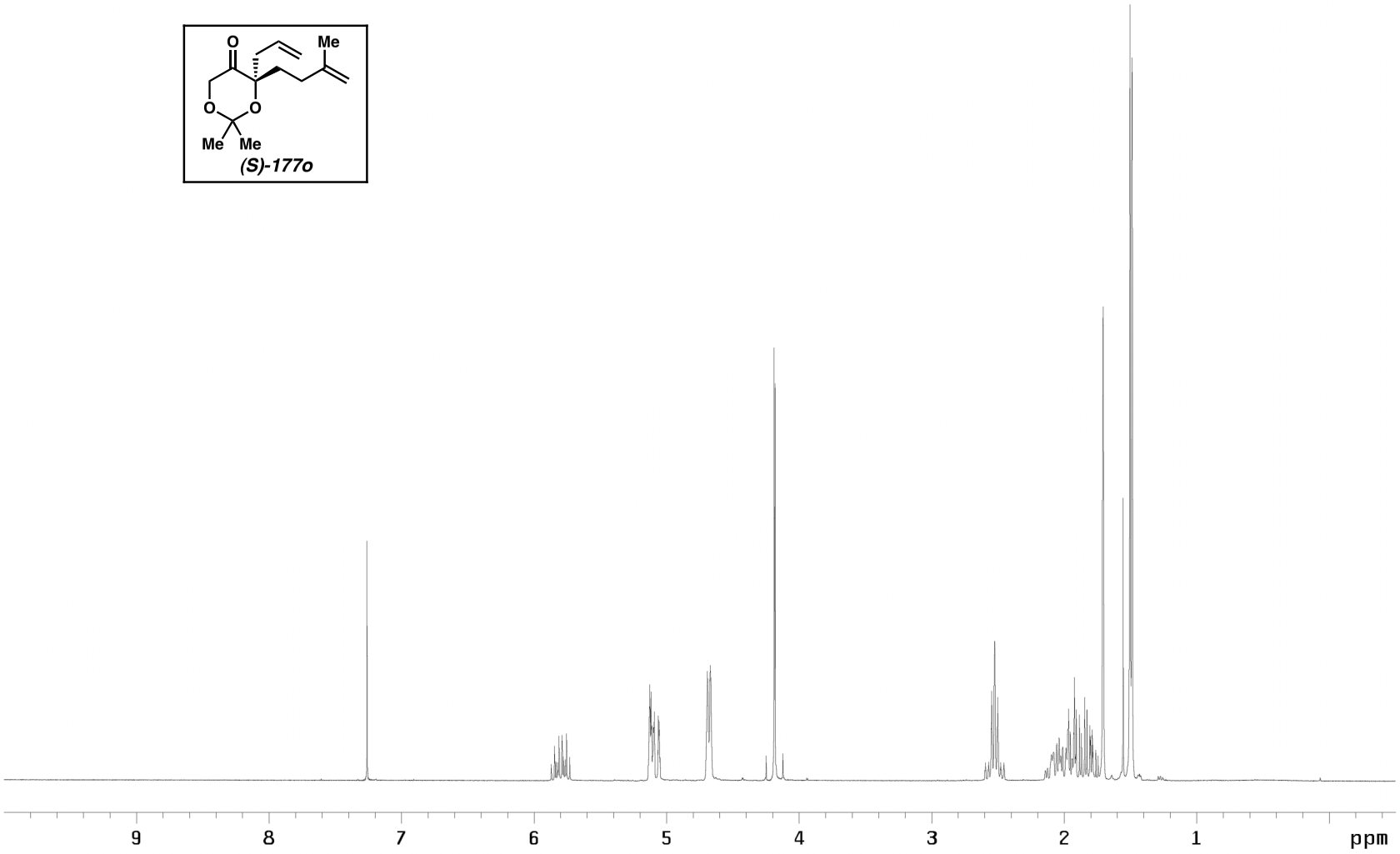


Figure A4.112 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **177o**

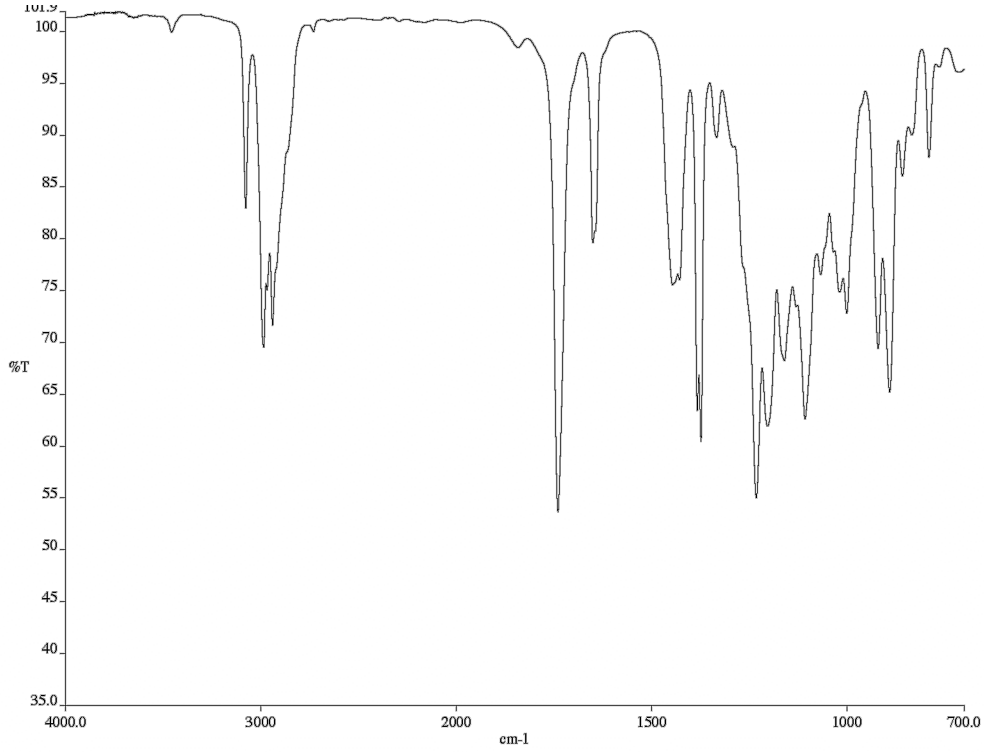


Figure A4.113 Infrared spectrum (thin film/NaCl) of compound **177o**

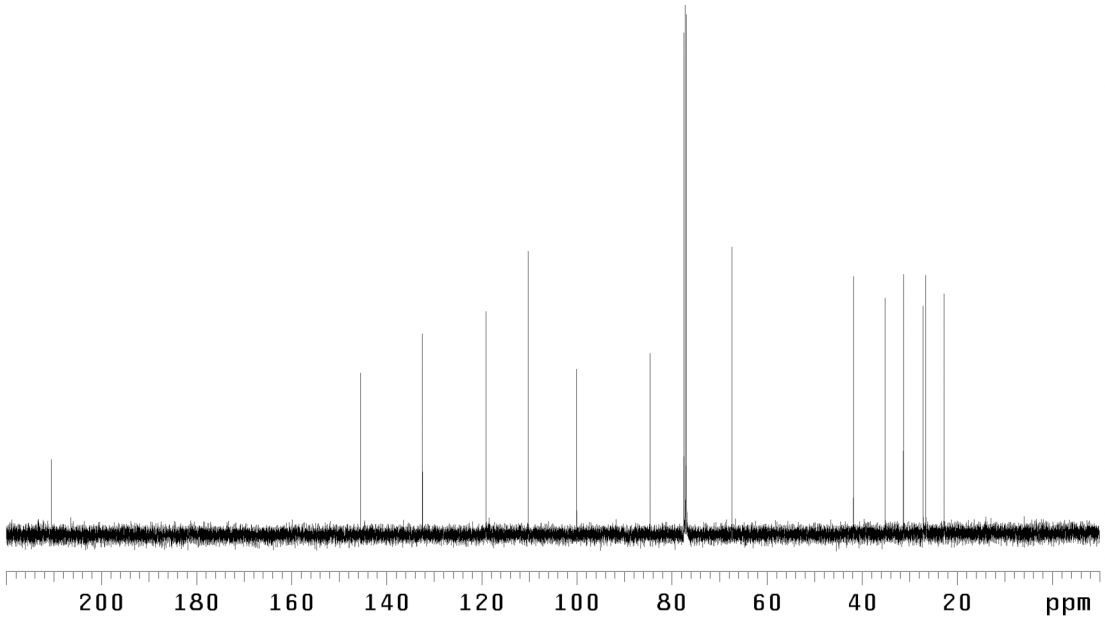


Figure A4.114 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **177o**

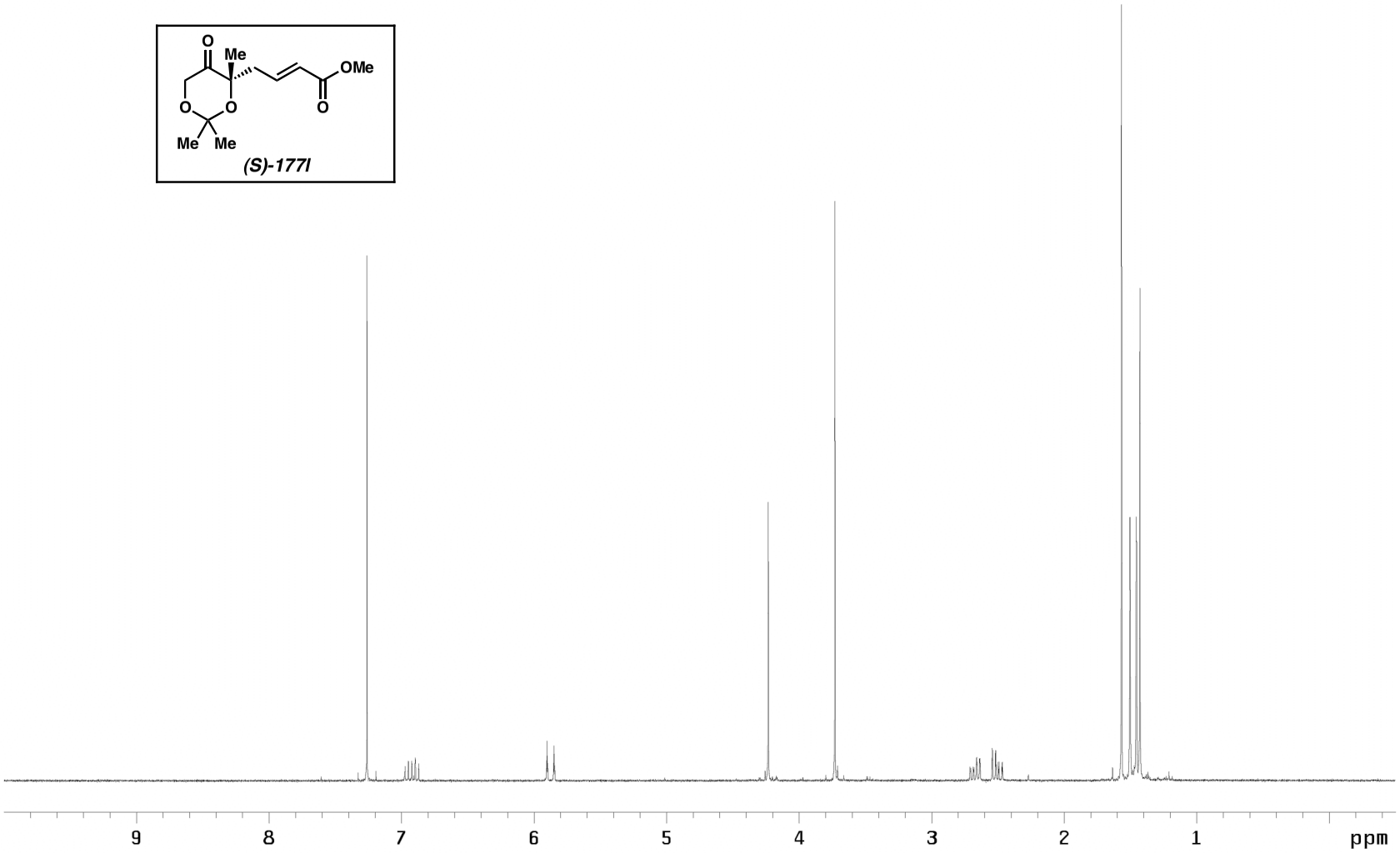


Figure A4.115 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **177l**

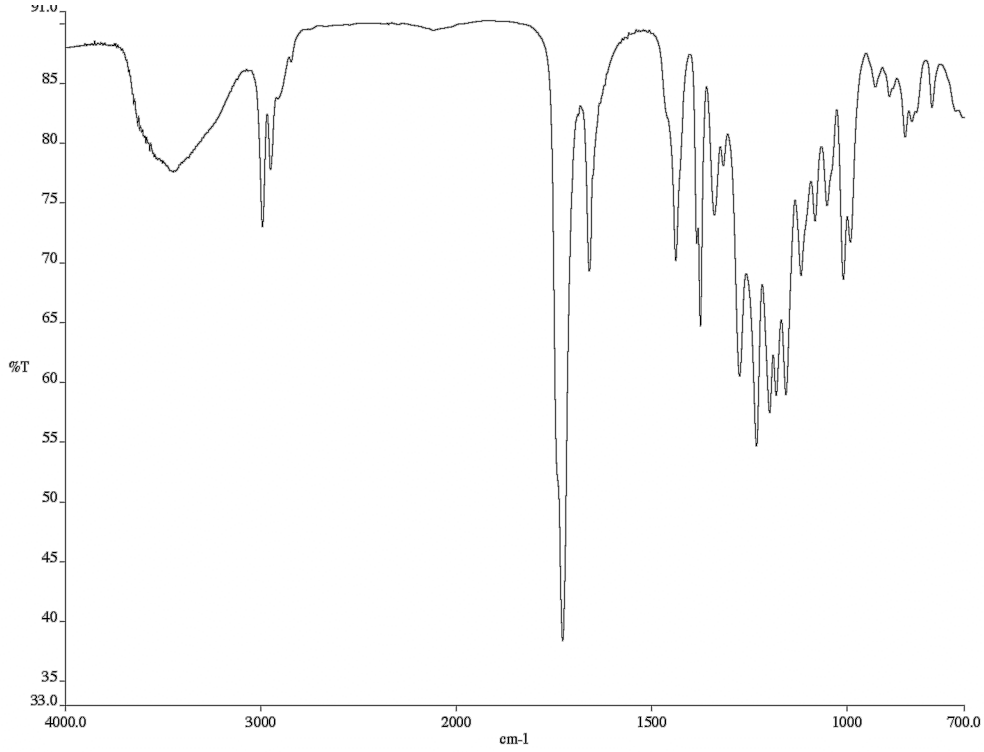


Figure A4.116 Infrared spectrum (thin film/NaCl) of compound **177l**

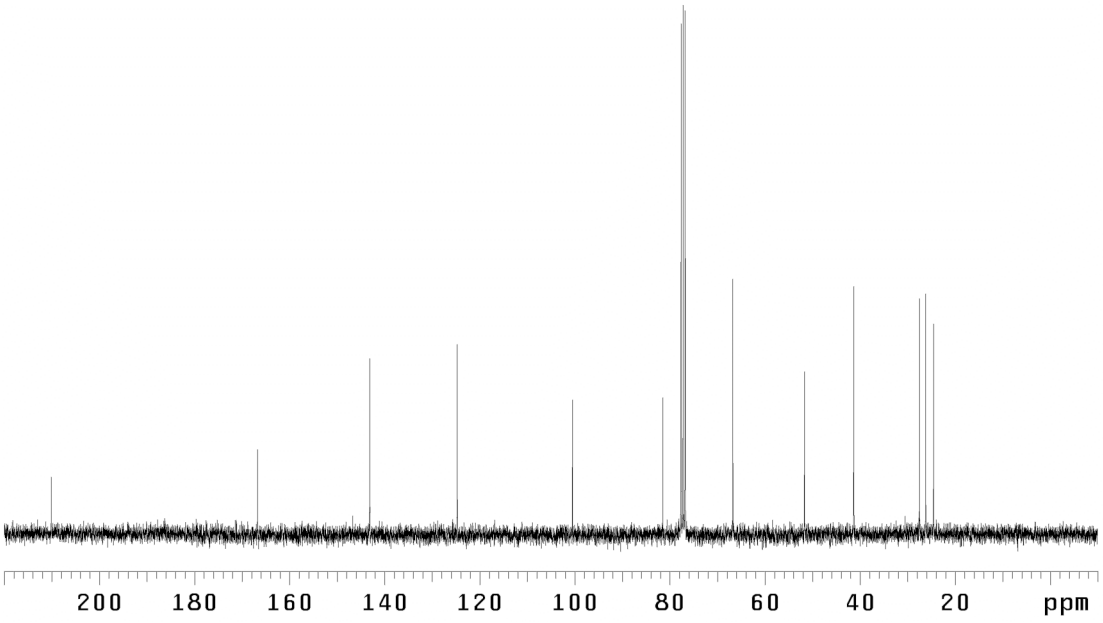


Figure A4.117 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **177l**

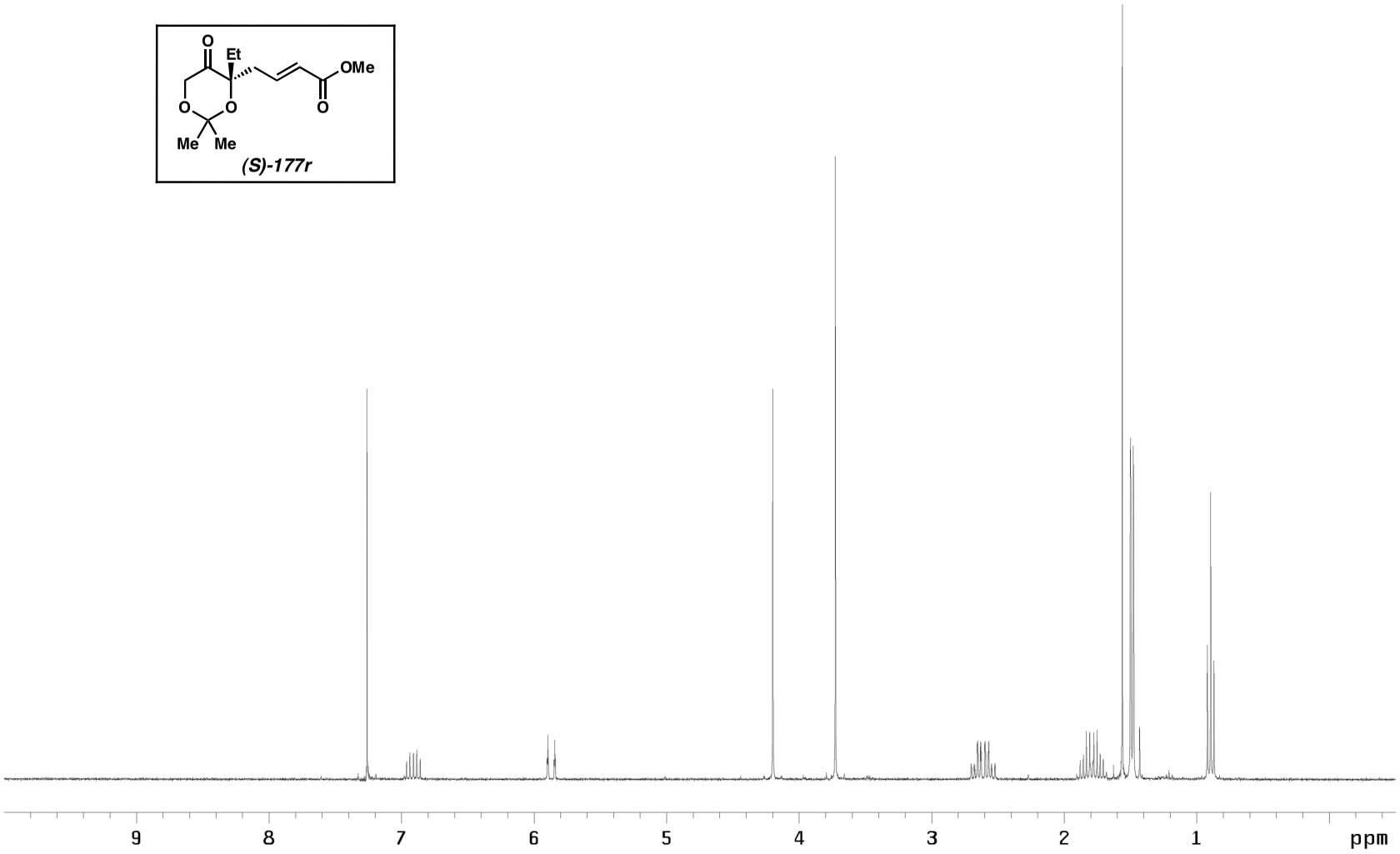


Figure A4.118 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **177r**

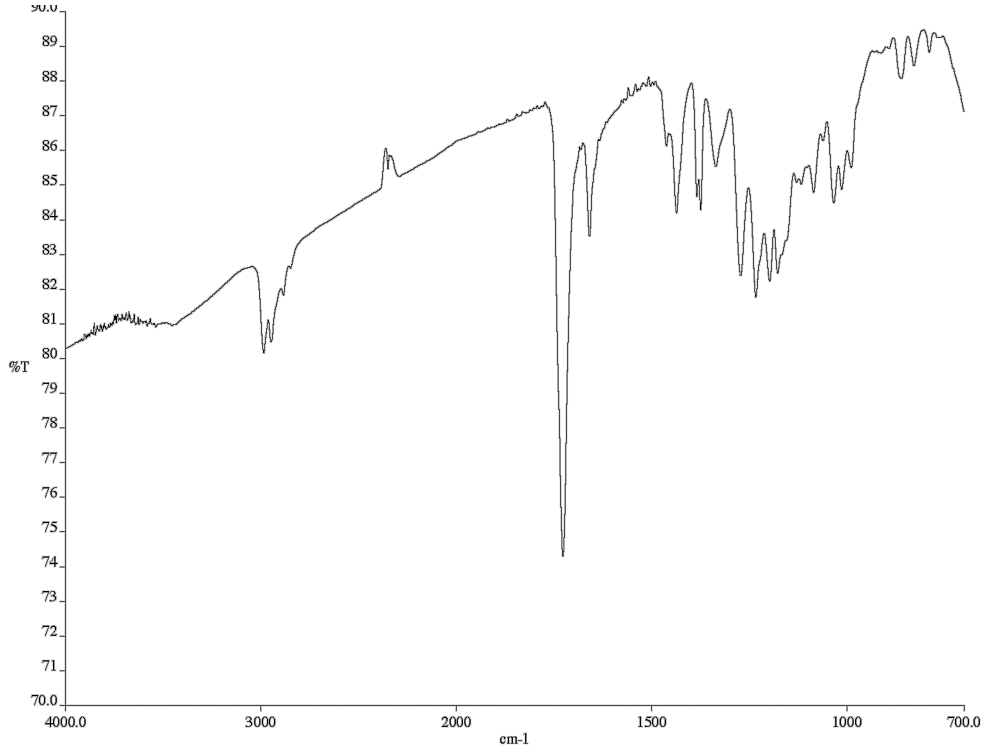


Figure A4.119 Infrared spectrum (thin film/NaCl) of compound **177r**

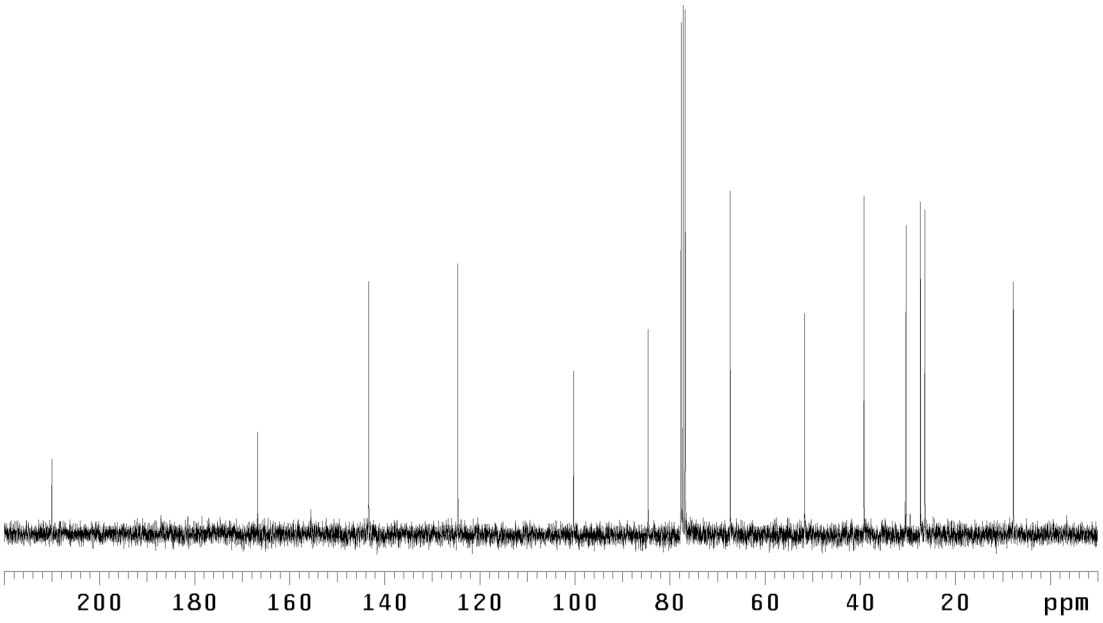


Figure A4.120 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **177r**

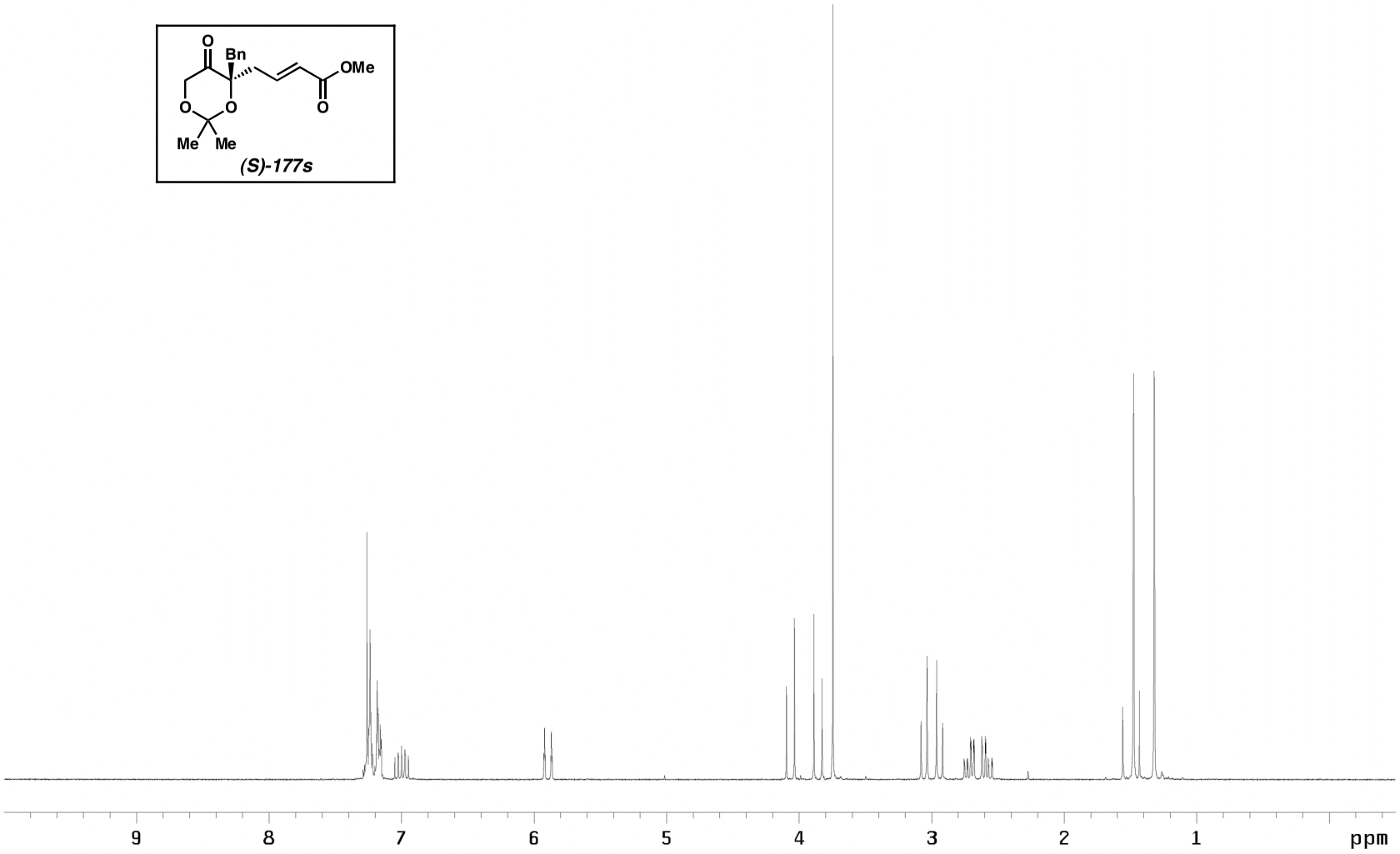


Figure A4.121 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **177s**

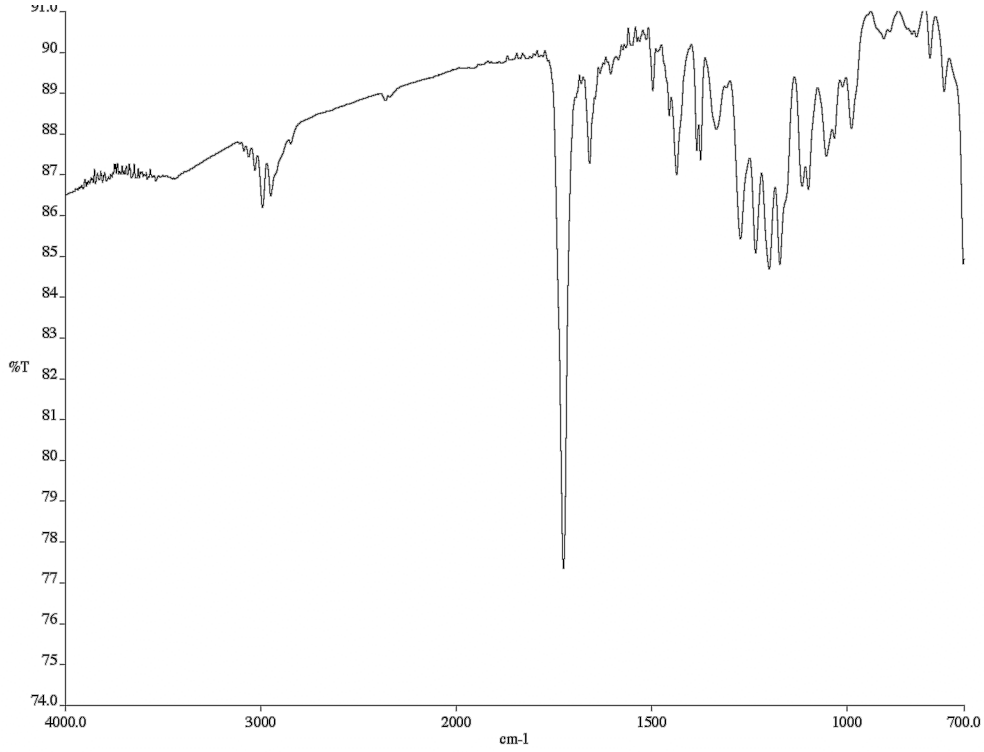


Figure A4.122 Infrared spectrum (thin film/NaCl) of compound **177s**

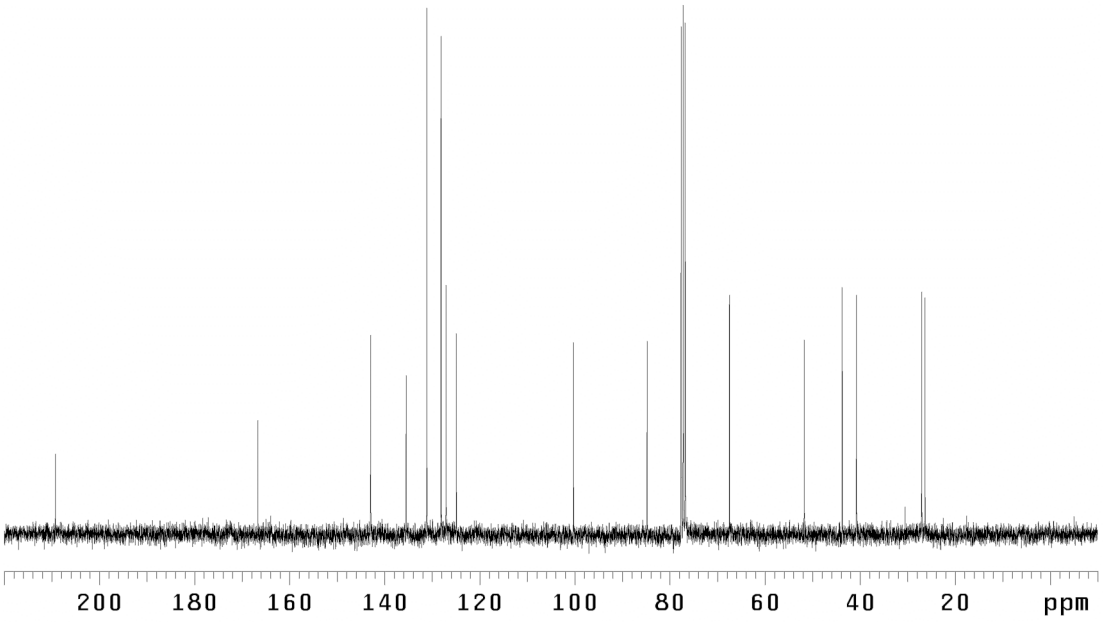


Figure A4.123 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **177s**

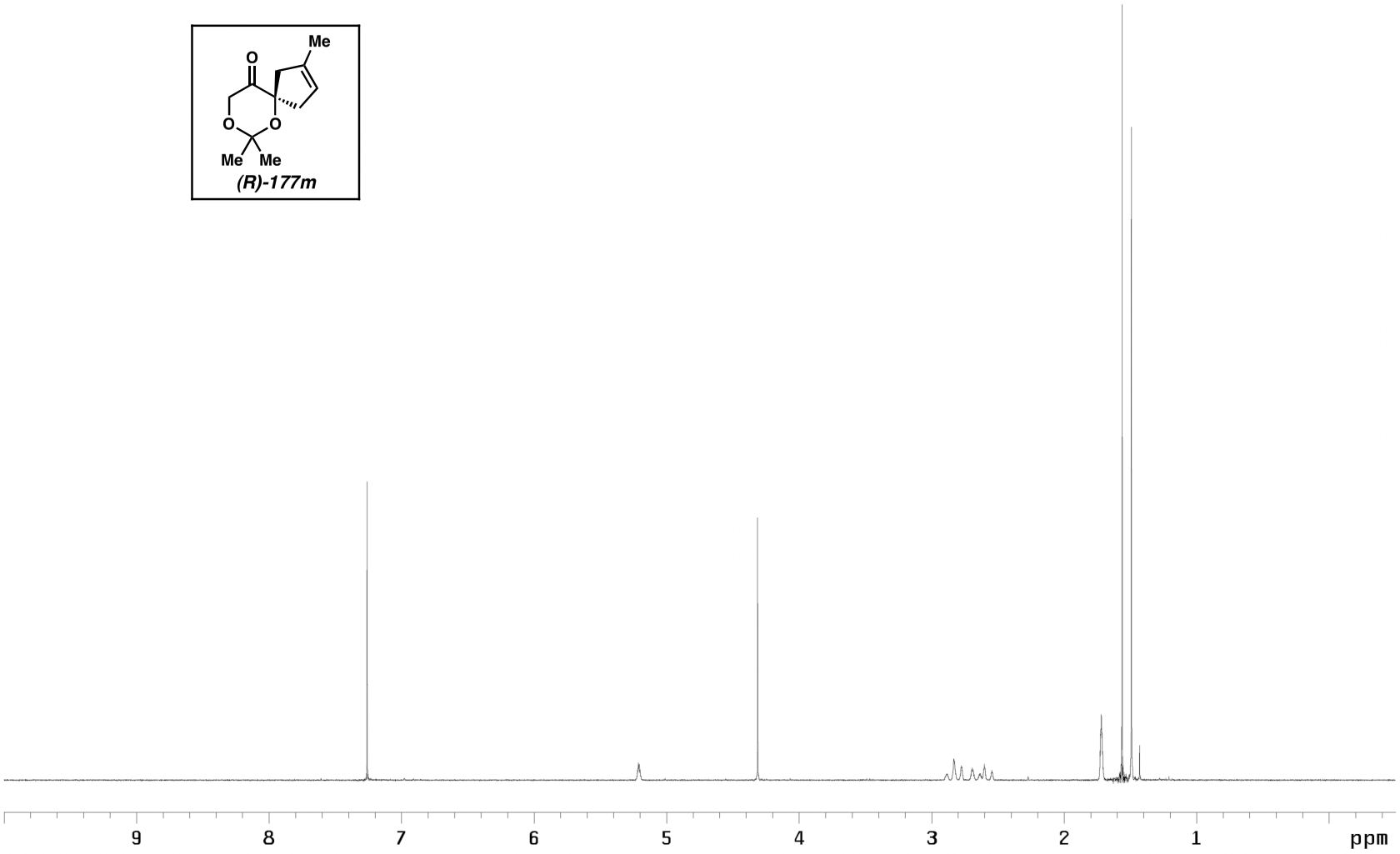


Figure A4.124 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **177m**

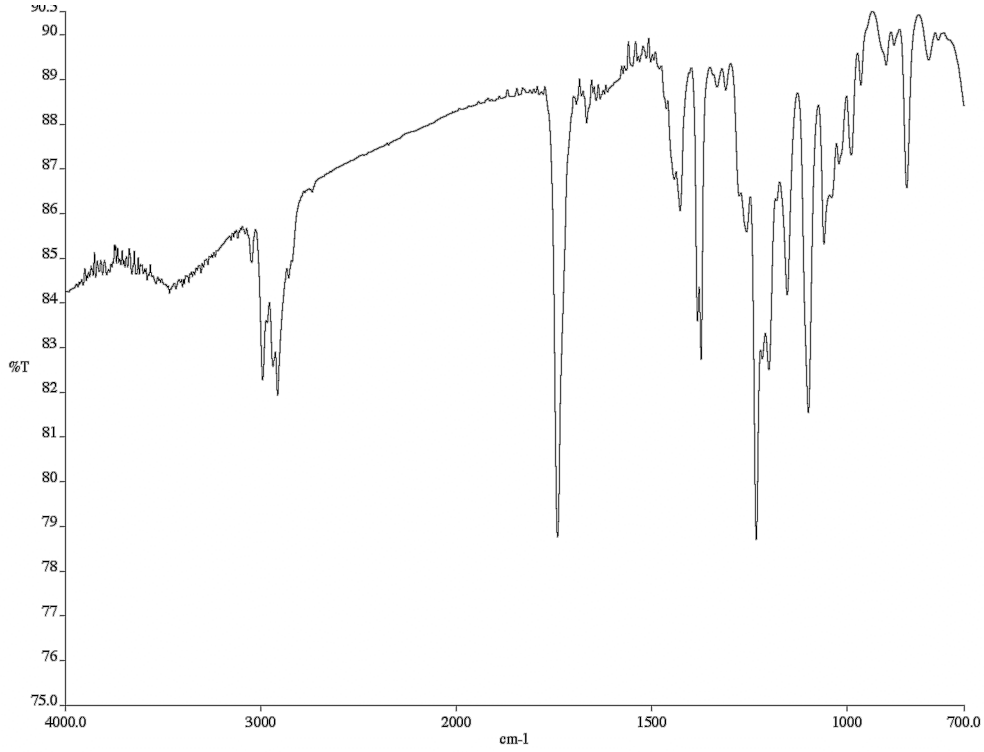


Figure A4.125 Infrared spectrum (thin film/NaCl) of ketone **177m**

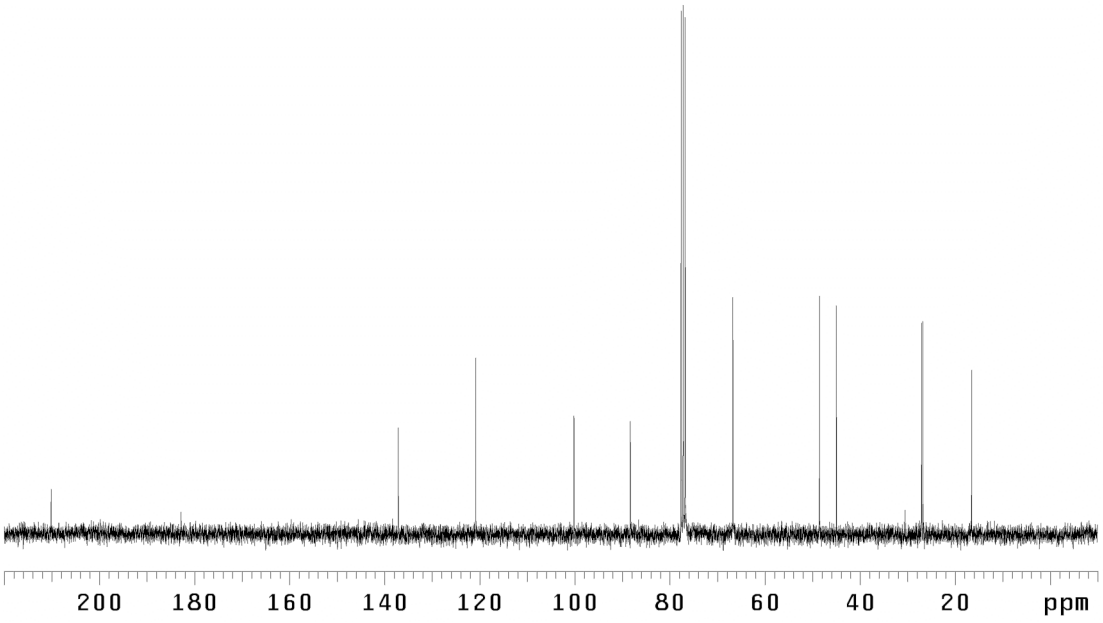


Figure A4.126 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **177m**

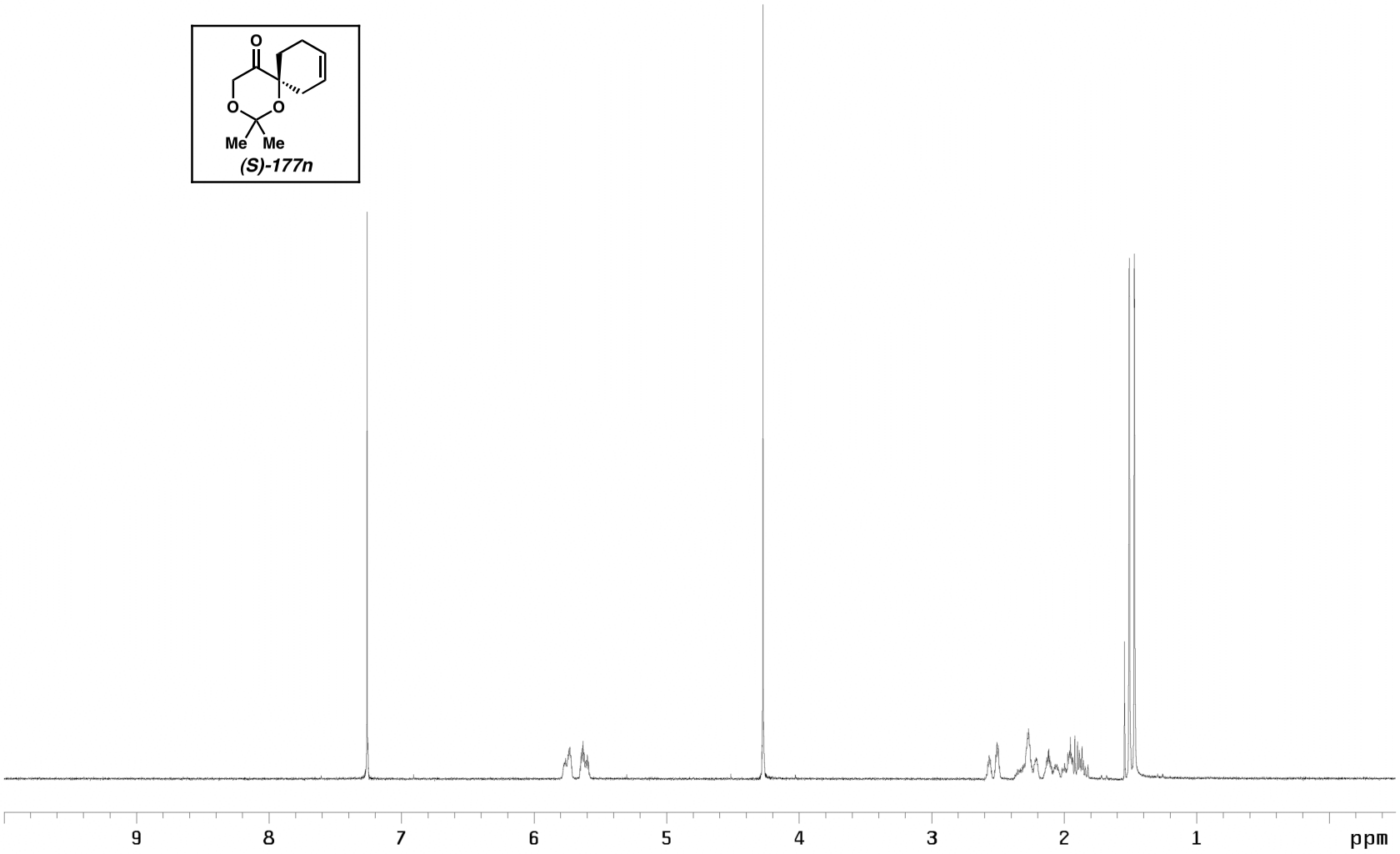


Figure A4.127 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **177n**

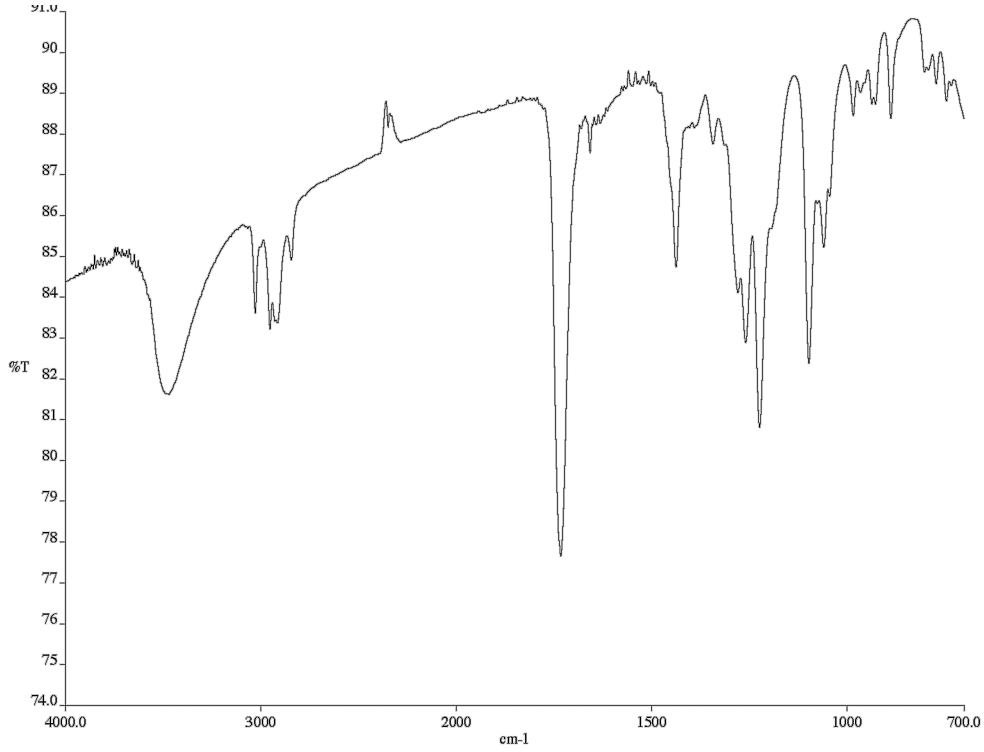


Figure A4.128 Infrared spectrum (thin film/NaCl) of ketone **177n**

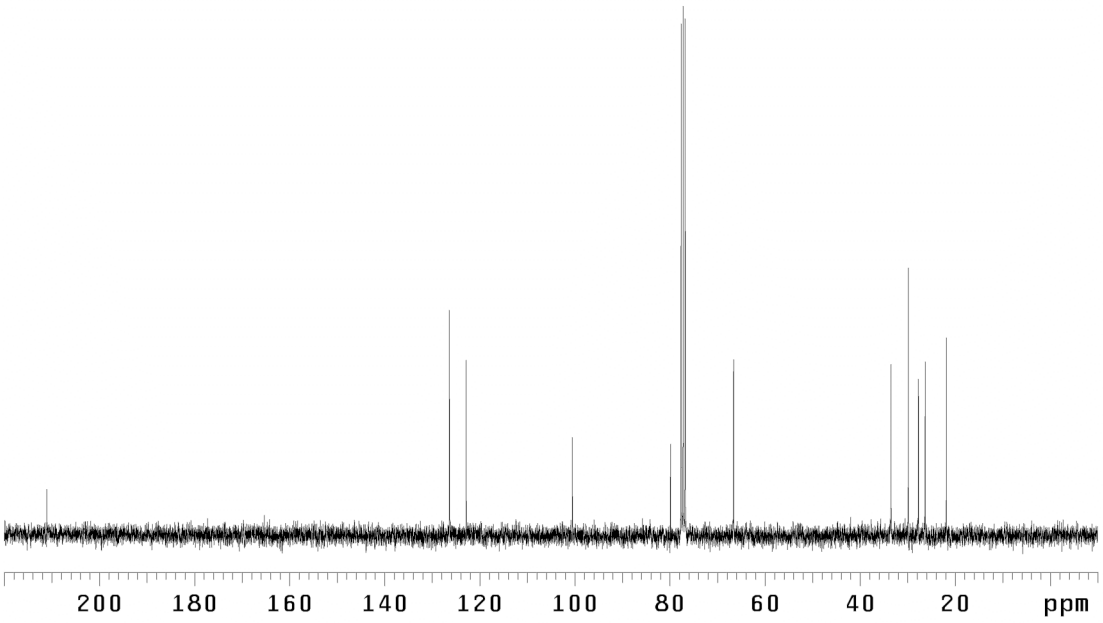


Figure A4.129 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **93n**

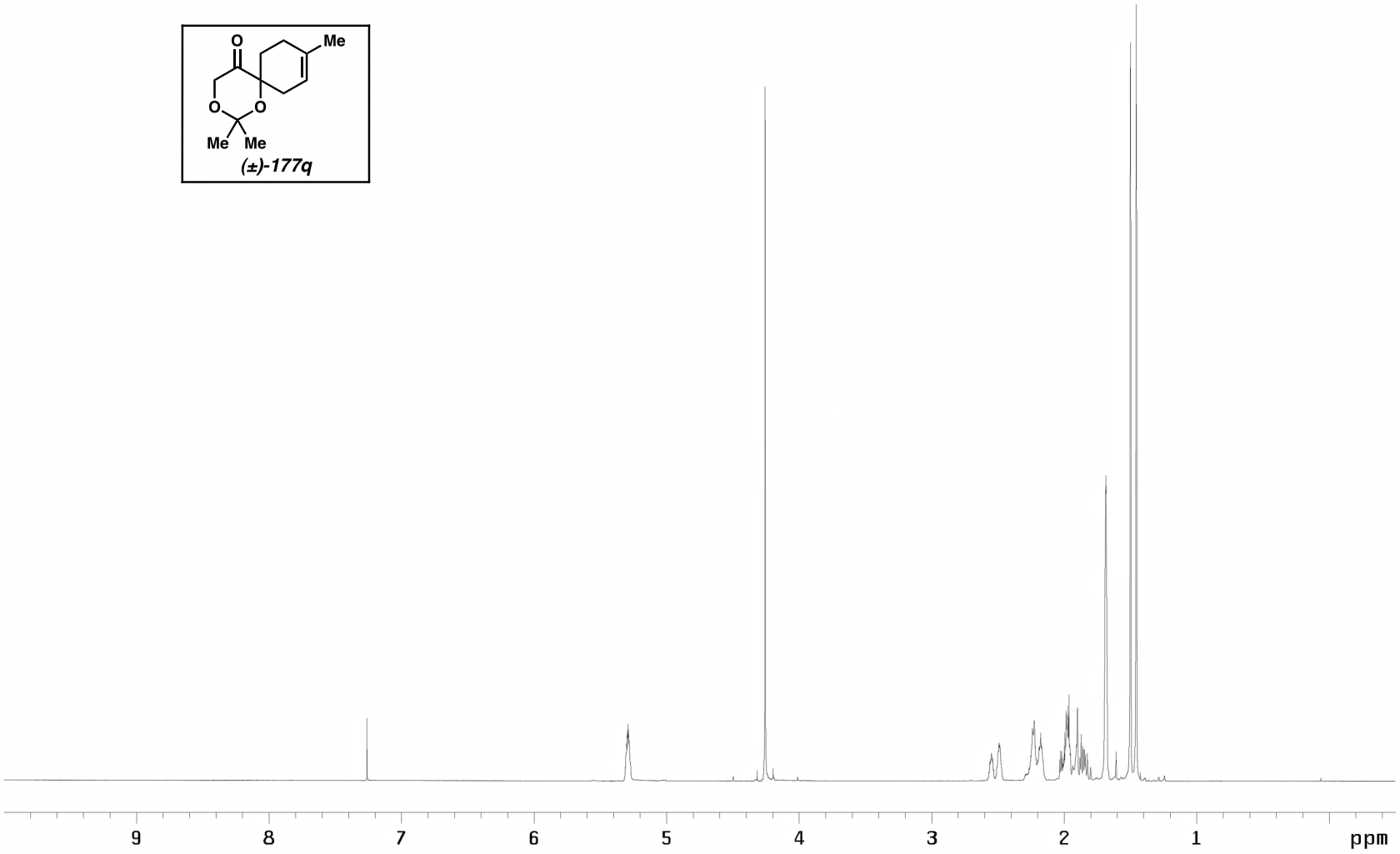


Figure A4.130 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **177q**

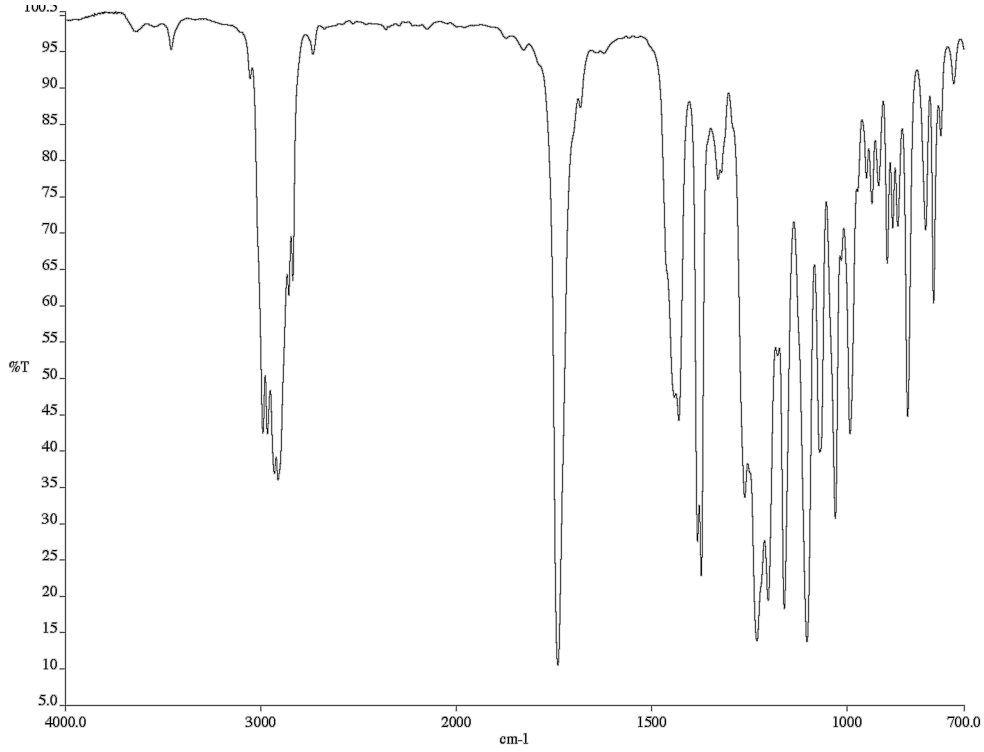


Figure A4.131 Infrared spectrum (thin film/NaCl) of ketone **177q**

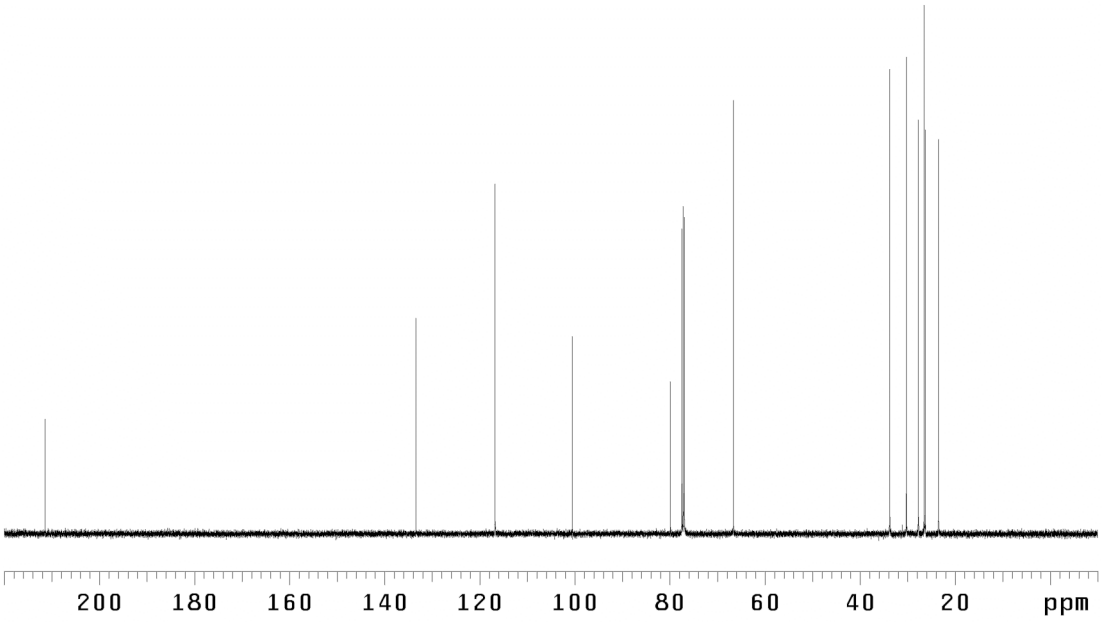


Figure A4.132 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **177q**

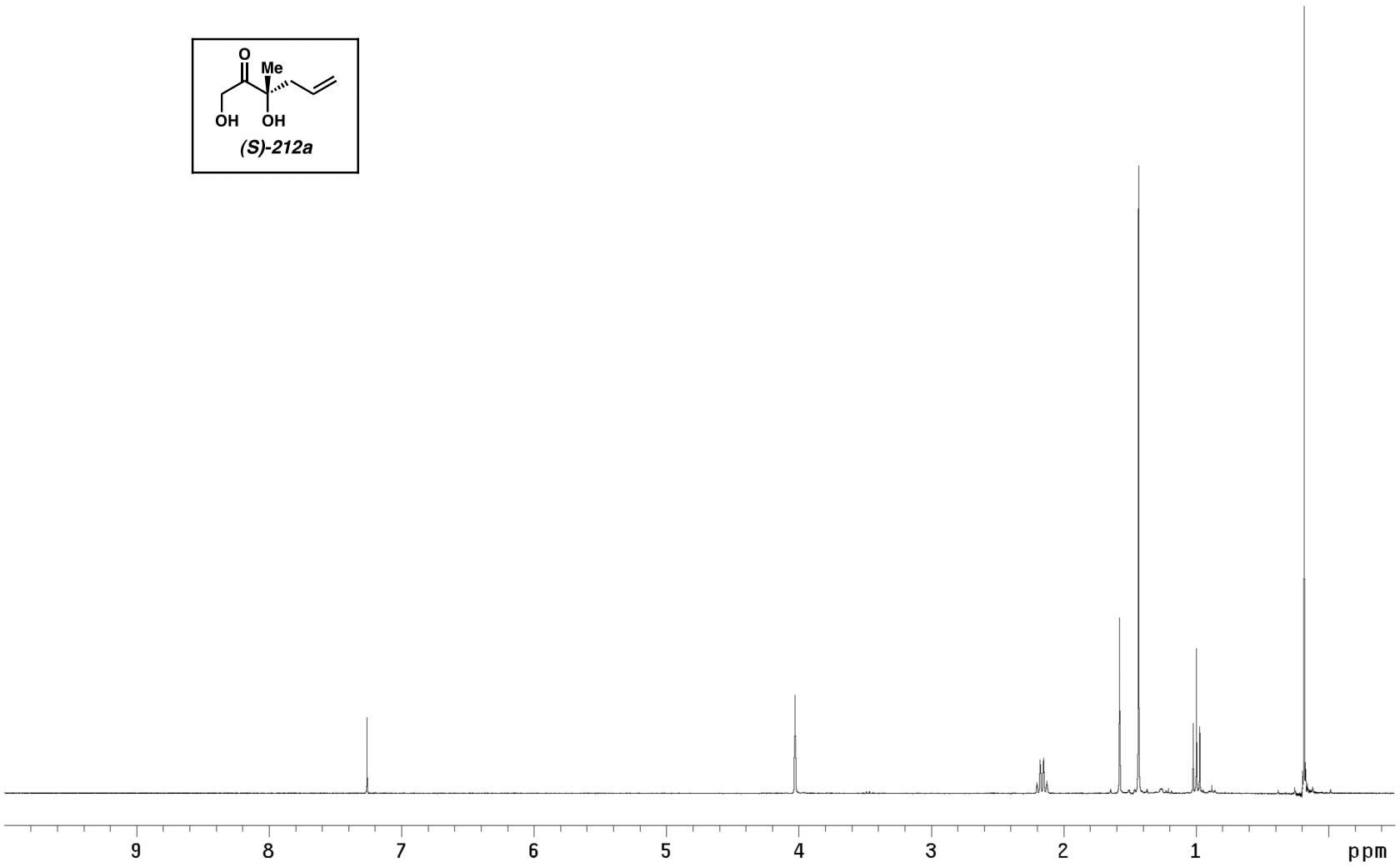


Figure A4.133 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **212a**

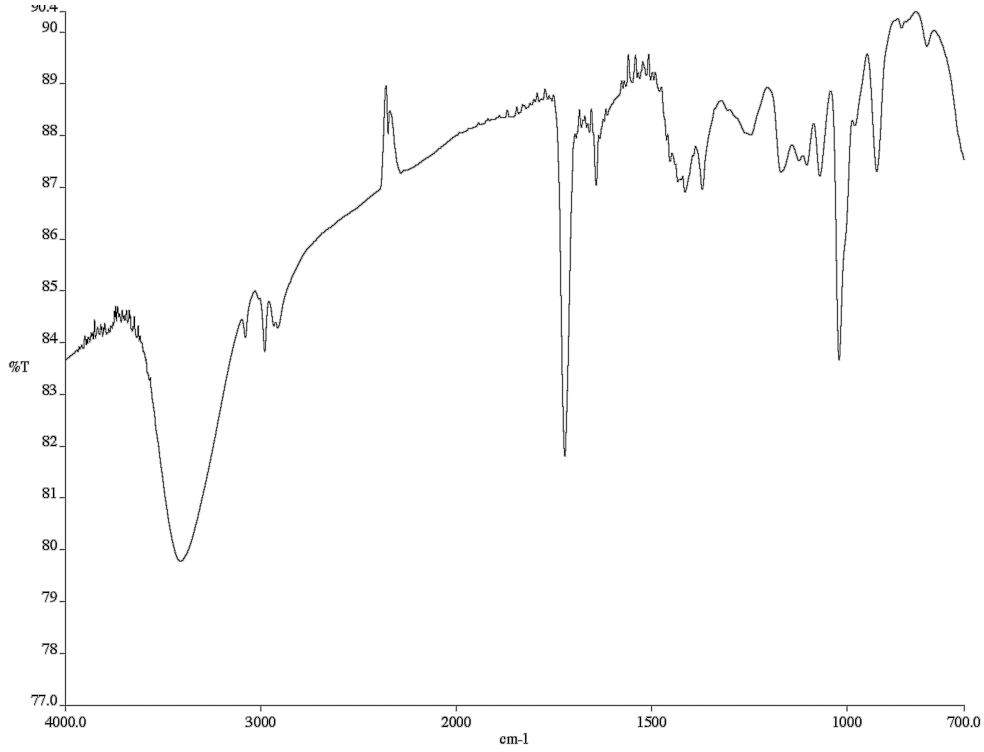


Figure A4.134 Infrared spectrum (thin film/NaCl) of compound **212a**

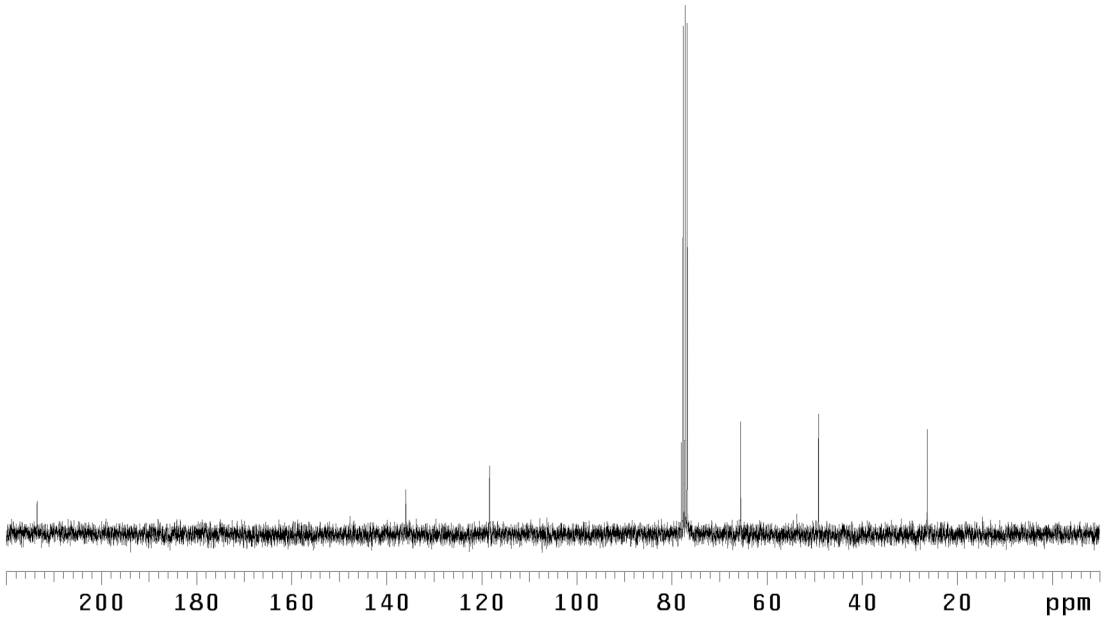


Figure A4.135 ^{13}C NMR (75 MHz, $CDCl_3$) of diol **212a**

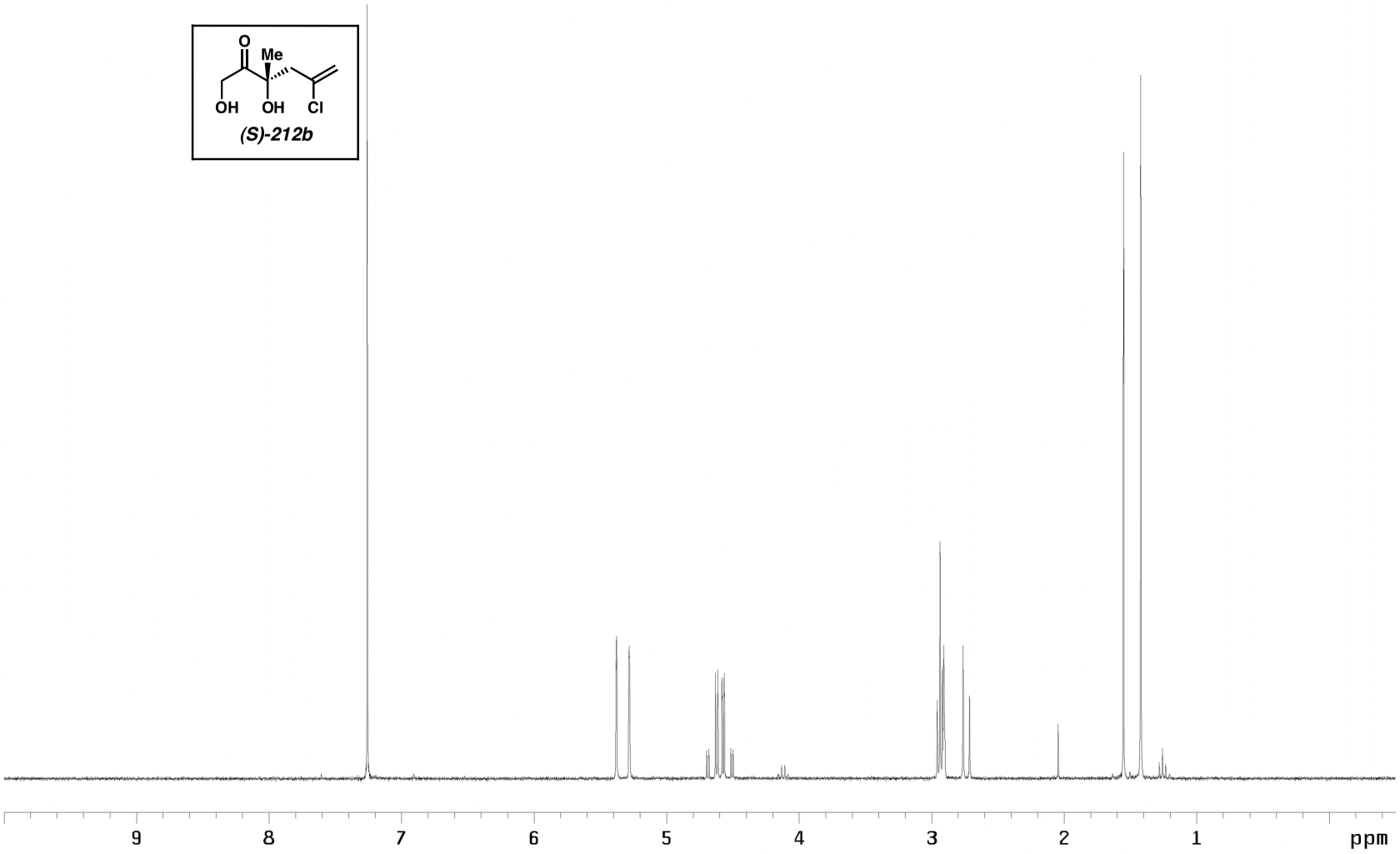


Figure A4.136 ^{1}H NMR (300 MHz, $CDCl_3$) of diol **212b**

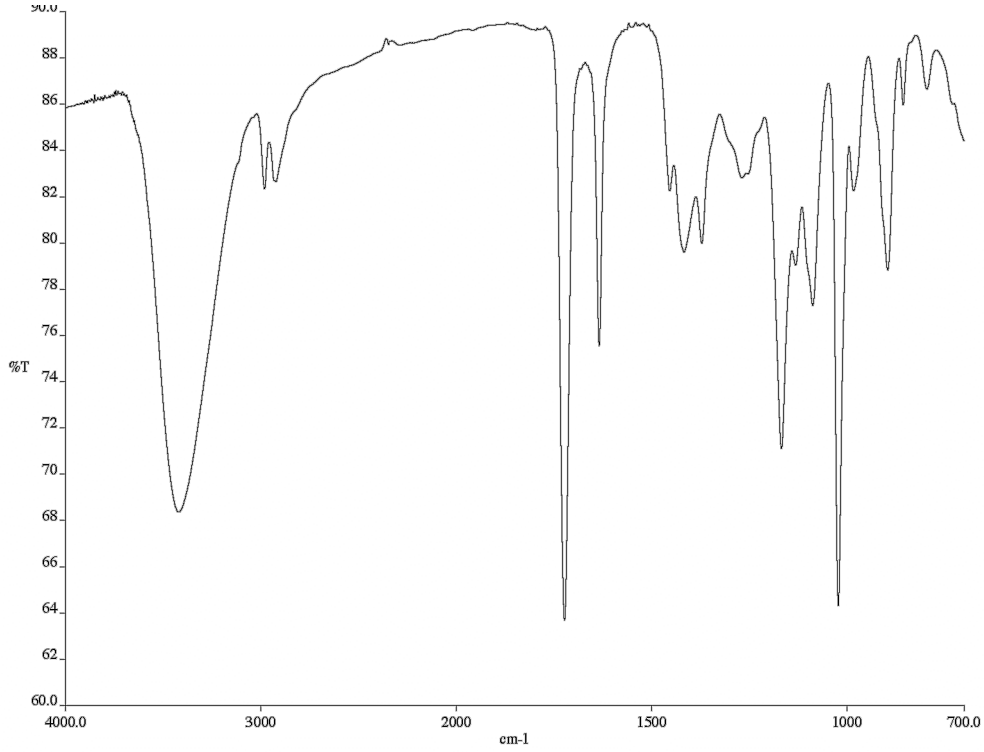


Figure A4.137 Infrared spectrum (thin film/NaCl) of diol **212b**

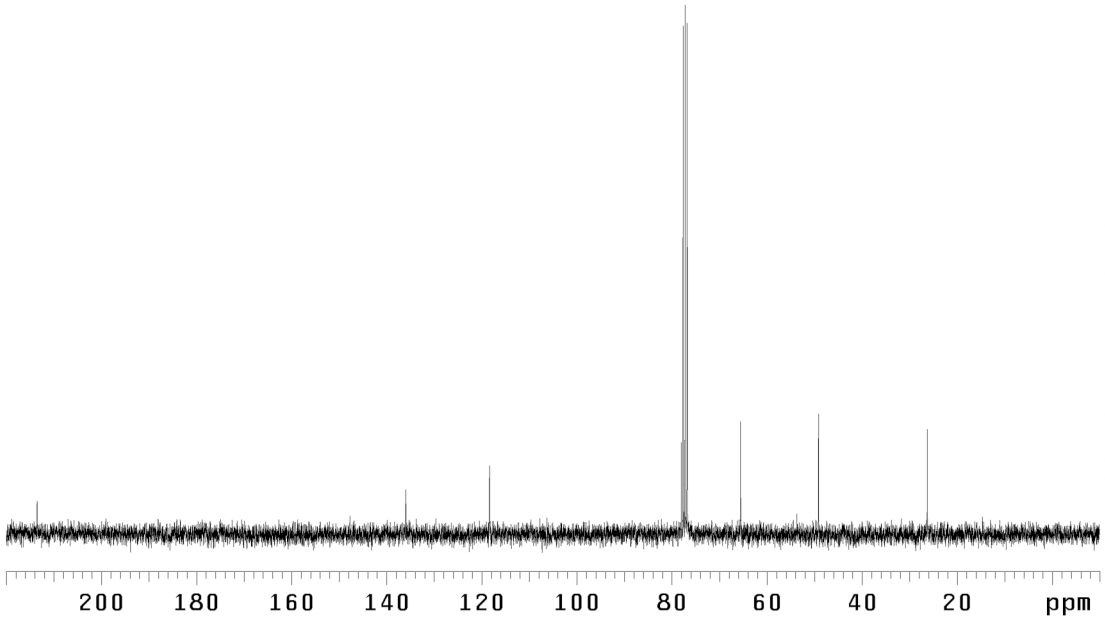


Figure A4.138 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **212b**

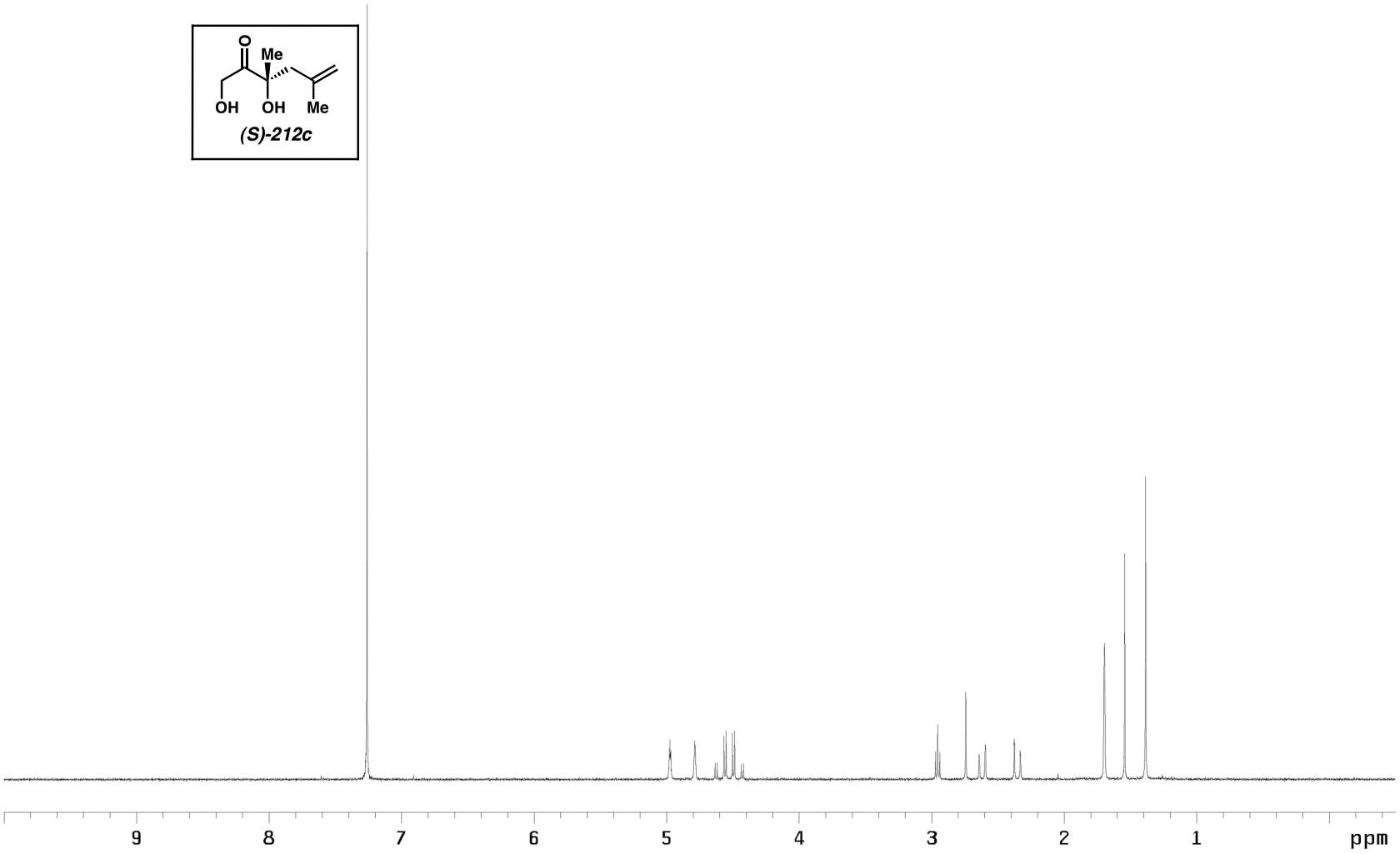


Figure A4.139 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **212c**

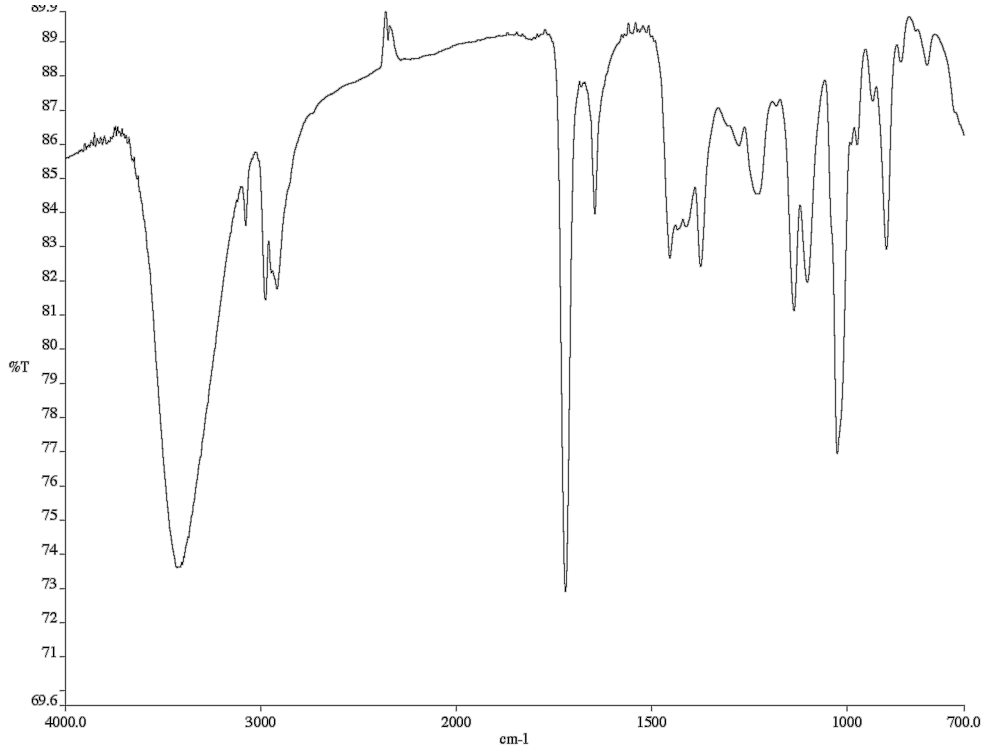


Figure A4.140 Infrared spectrum (thin film/NaCl) of compound **212c**

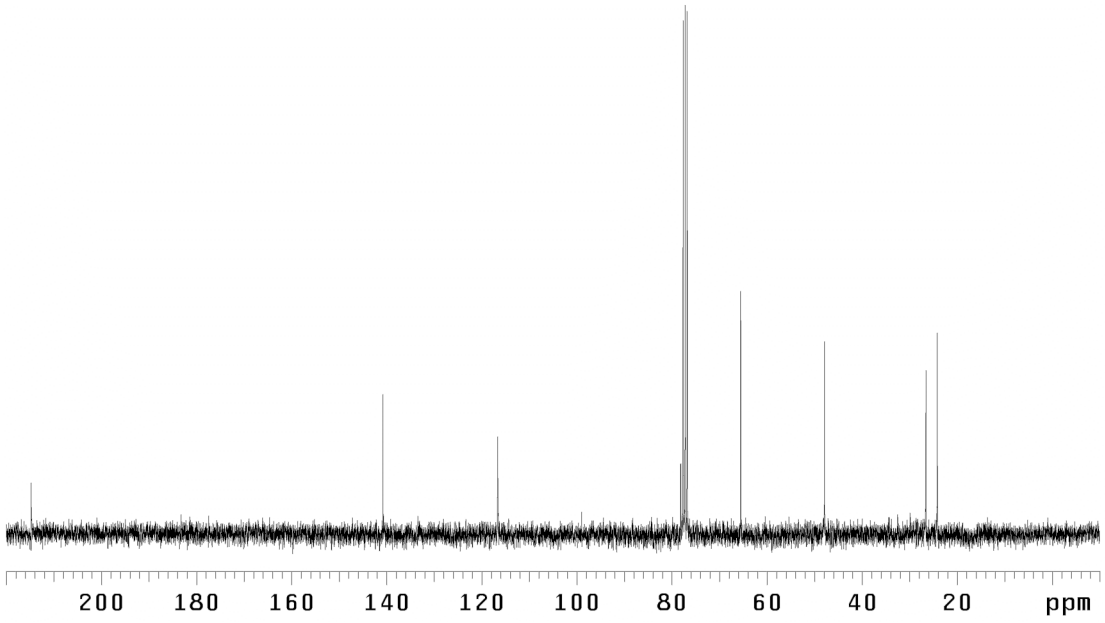


Figure A4.141 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **212c**

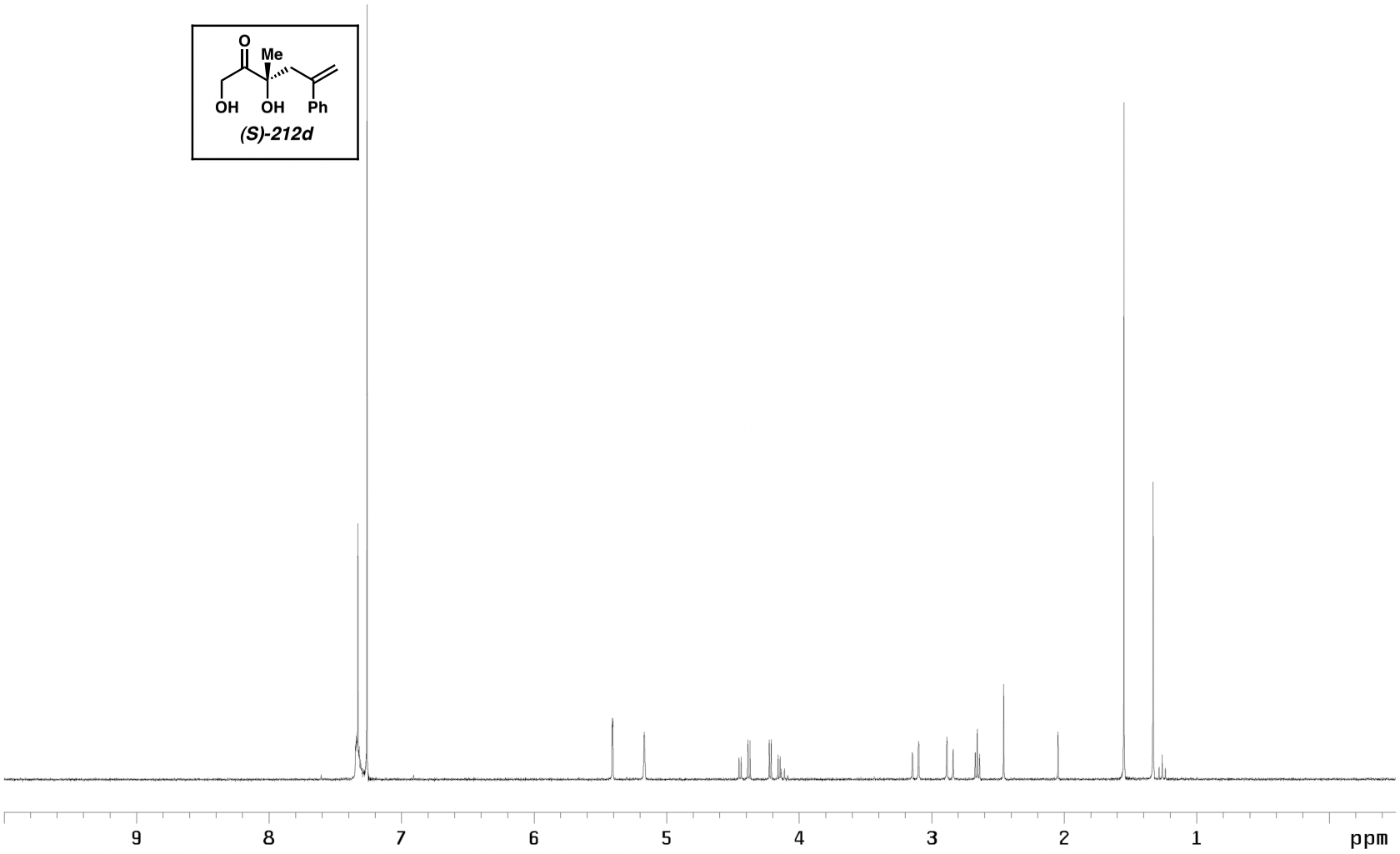


Figure A4.142 ^{1}H NMR (300 MHz, $CDCl_3$) of diol **212d**

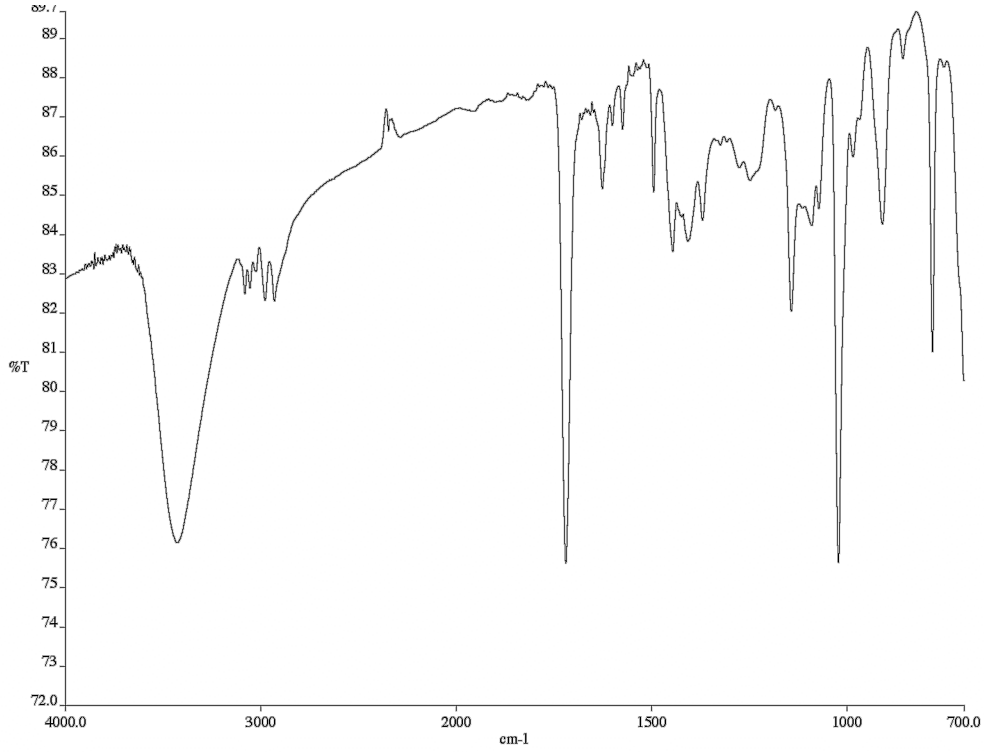


Figure A4.143 Infrared spectrum (thin film/NaCl) of diol **212d**

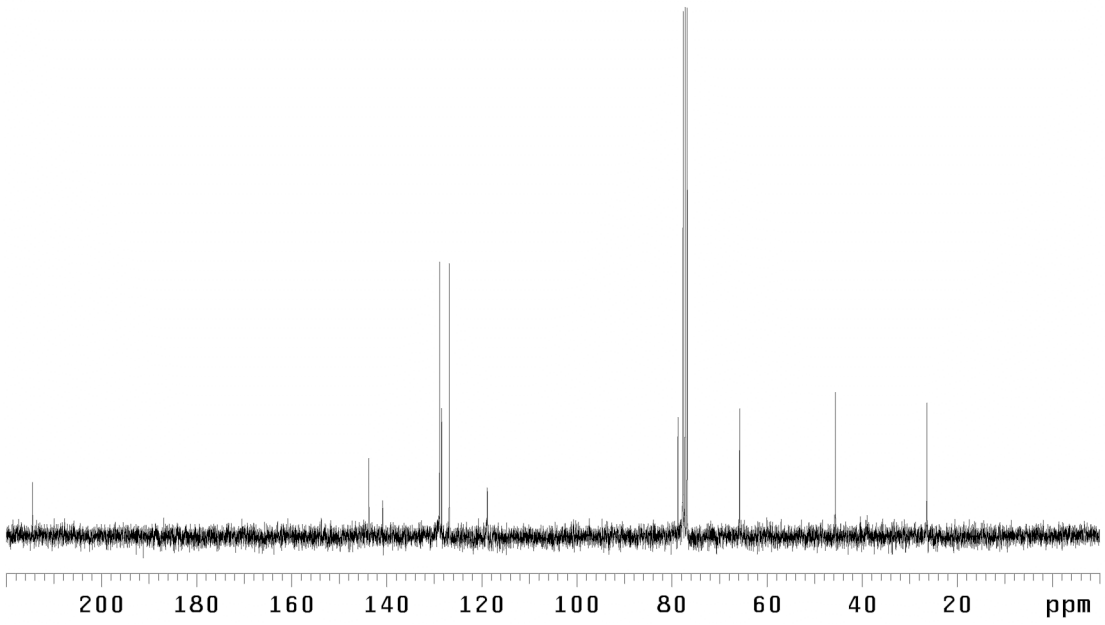


Figure A4.144 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **212d**

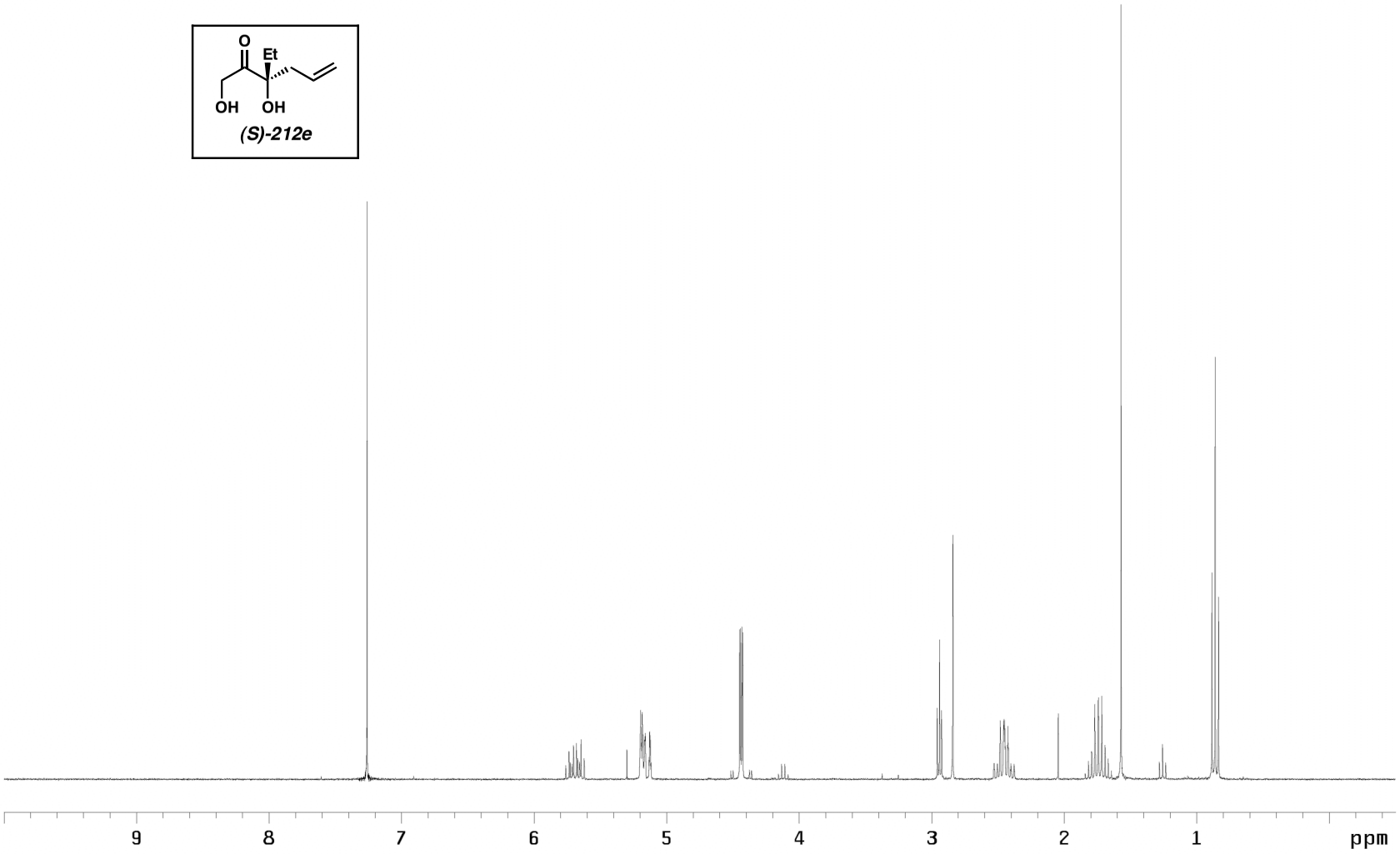


Figure A4.145 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **212e**

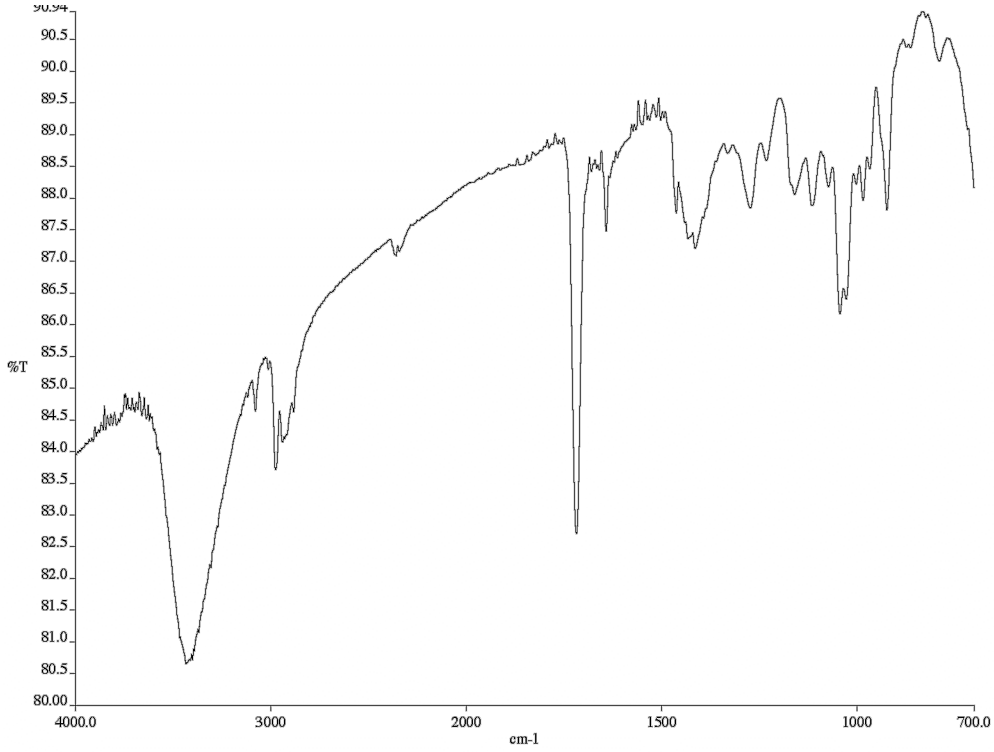


Figure A4.146 Infrared spectrum (thin film/NaCl) of compound **212e**

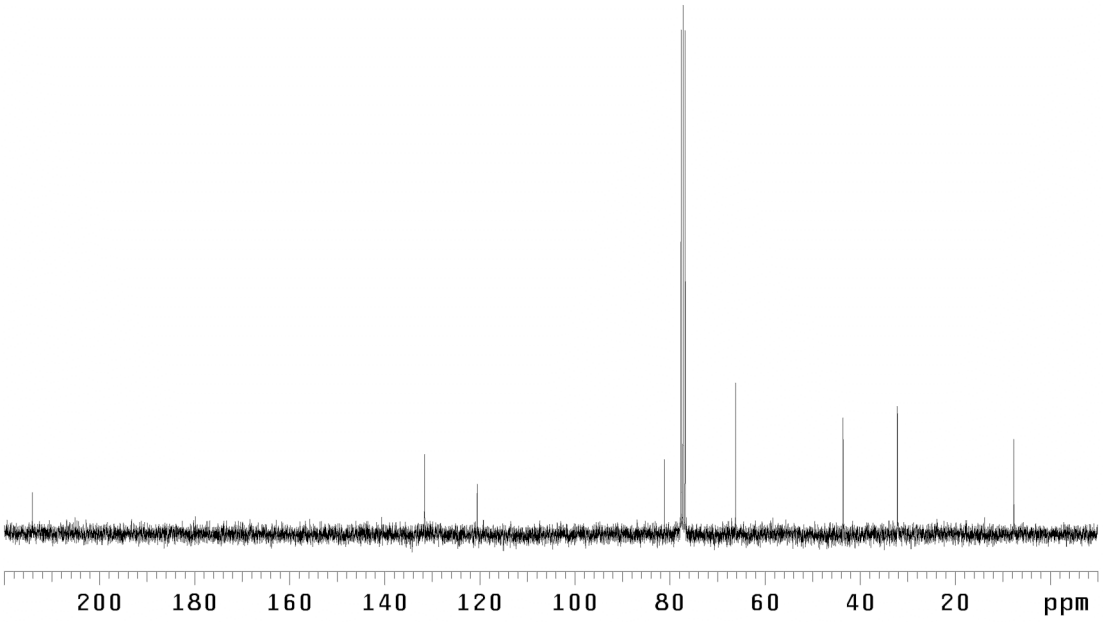


Figure A4.147 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **212e**

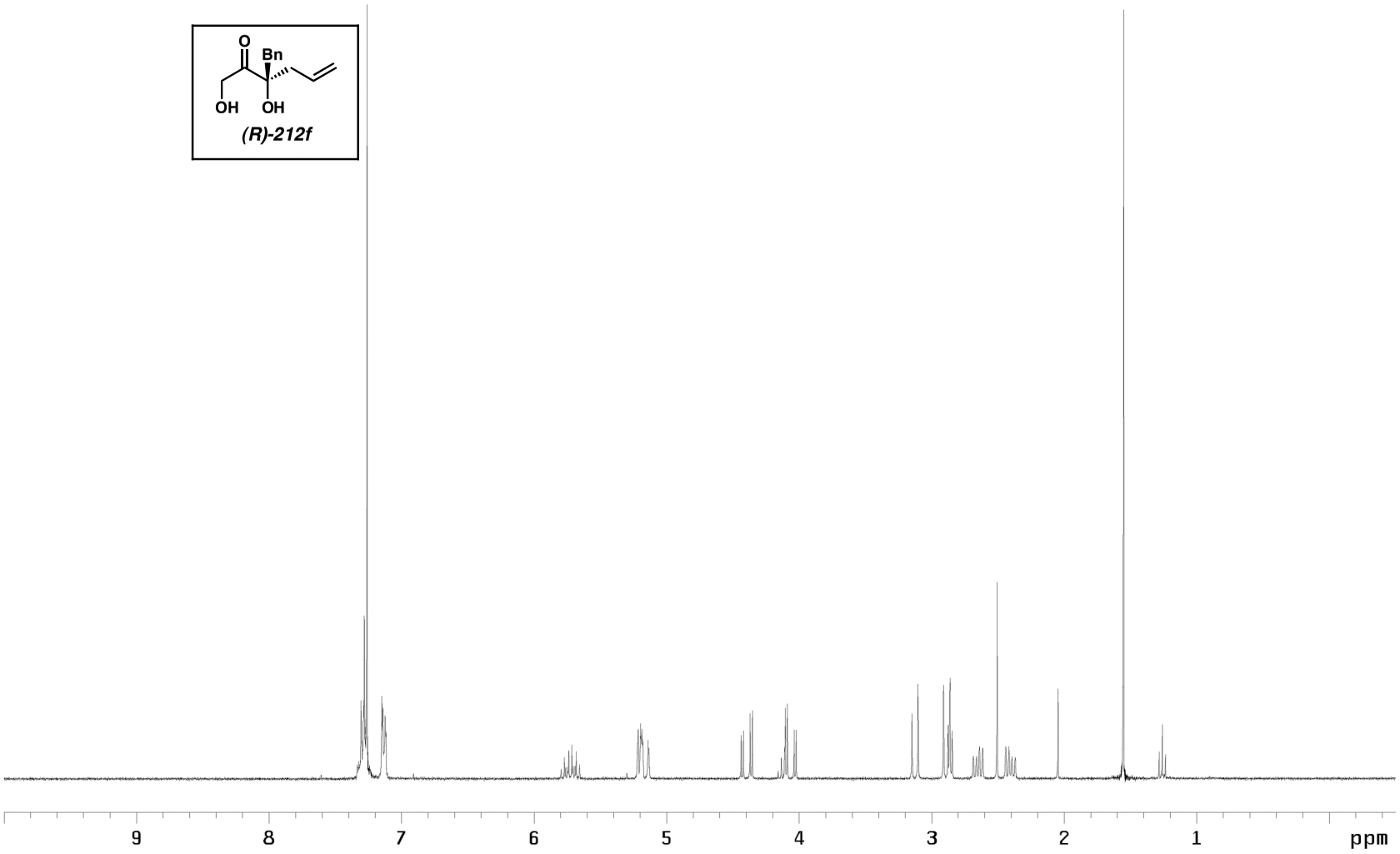


Figure A4.148 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **212f**

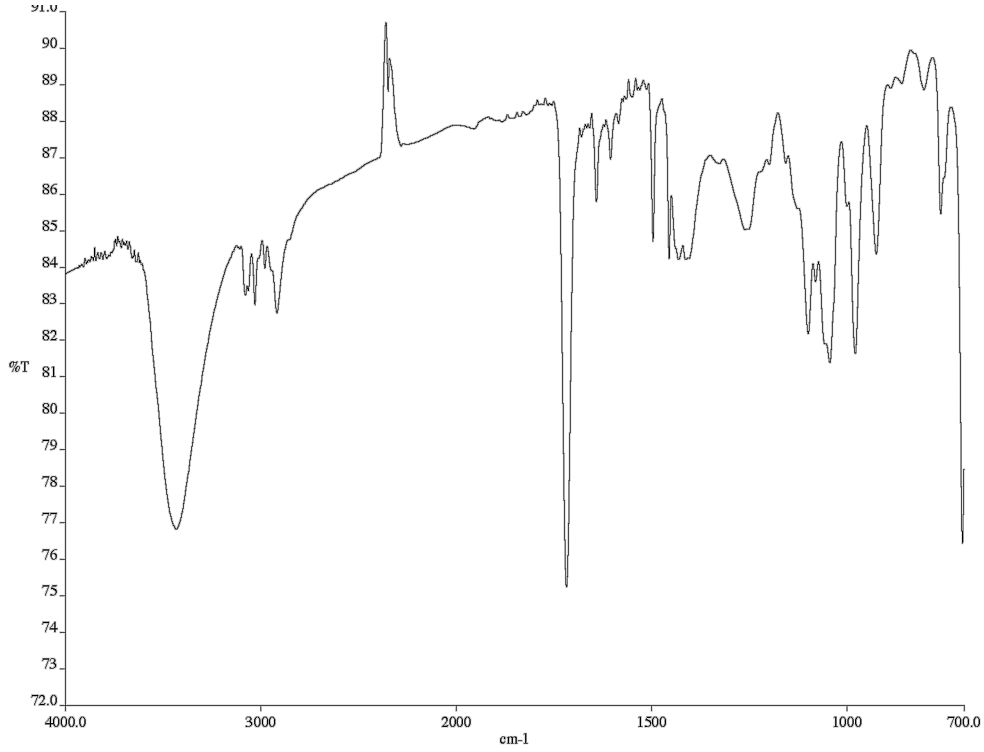


Figure A4.149 Infrared spectrum (thin film/NaCl) of compound **212f**

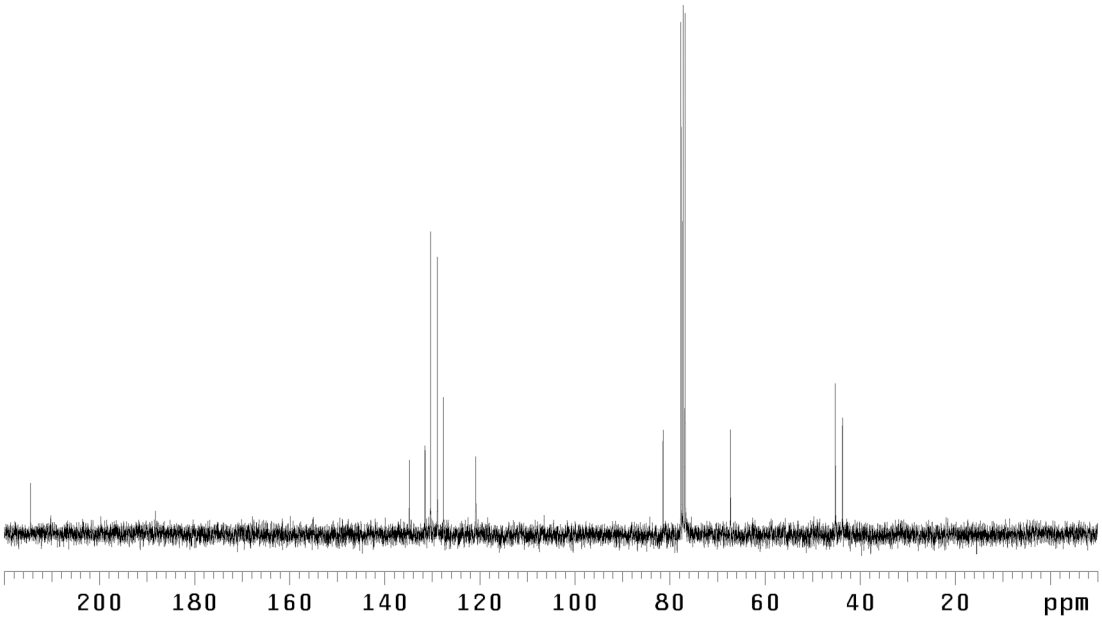


Figure A4.150 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **212f**

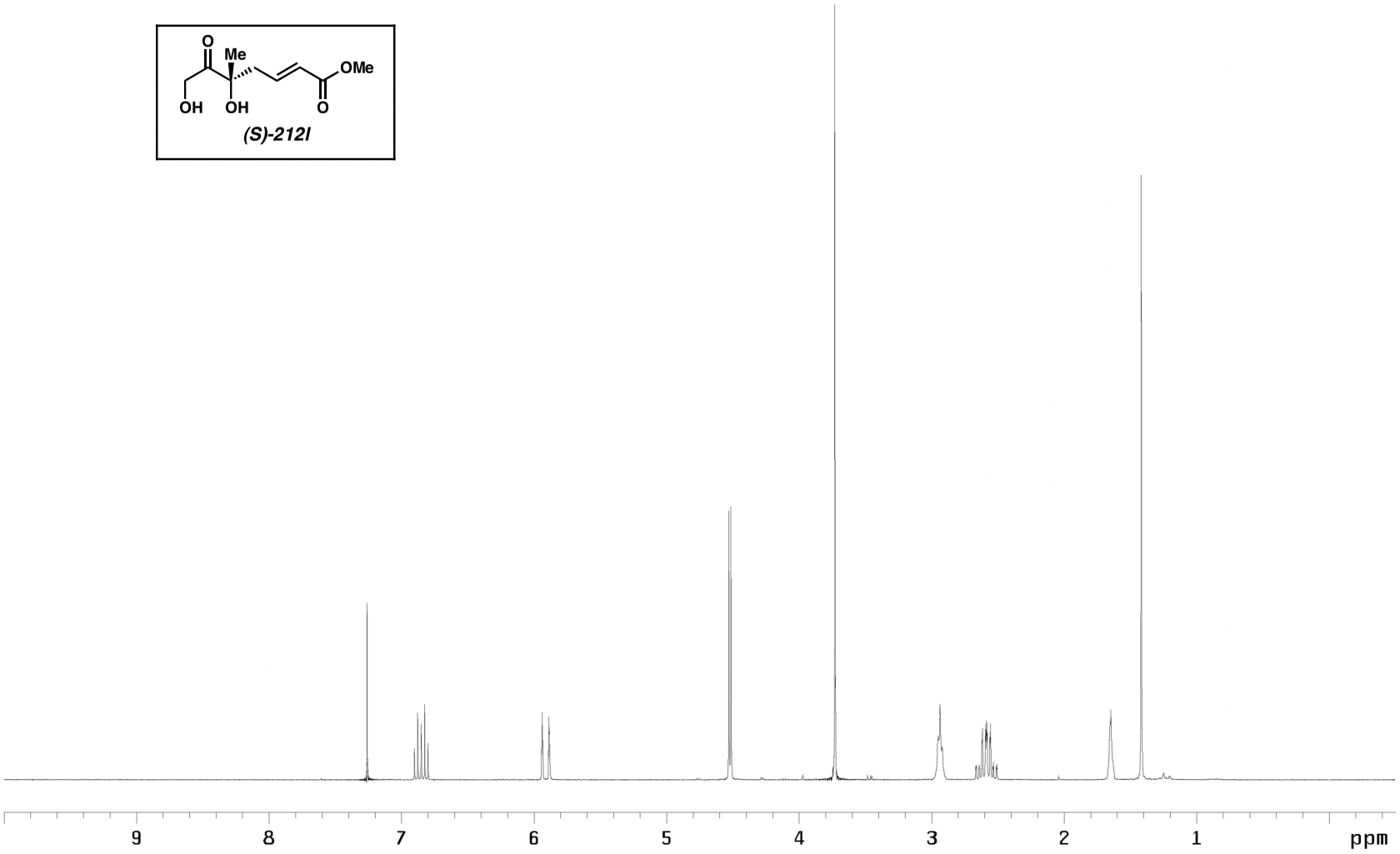


Figure A4.151 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **212l**

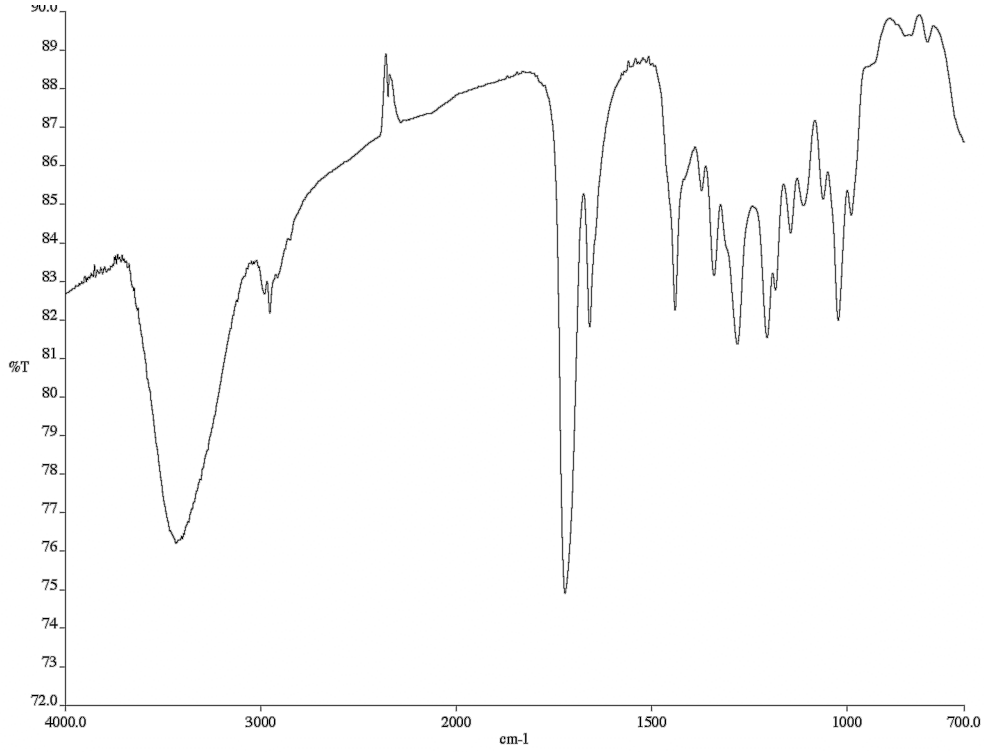


Figure A4.152 Infrared spectrum (thin film/NaCl) of compound **212l**

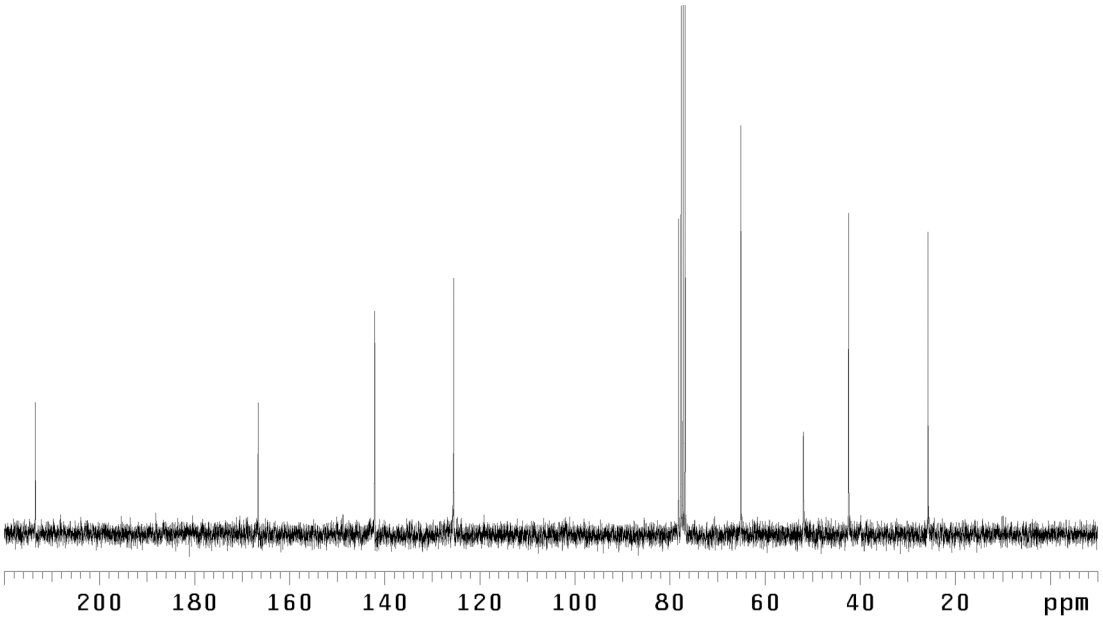


Figure A4.153 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **212l**

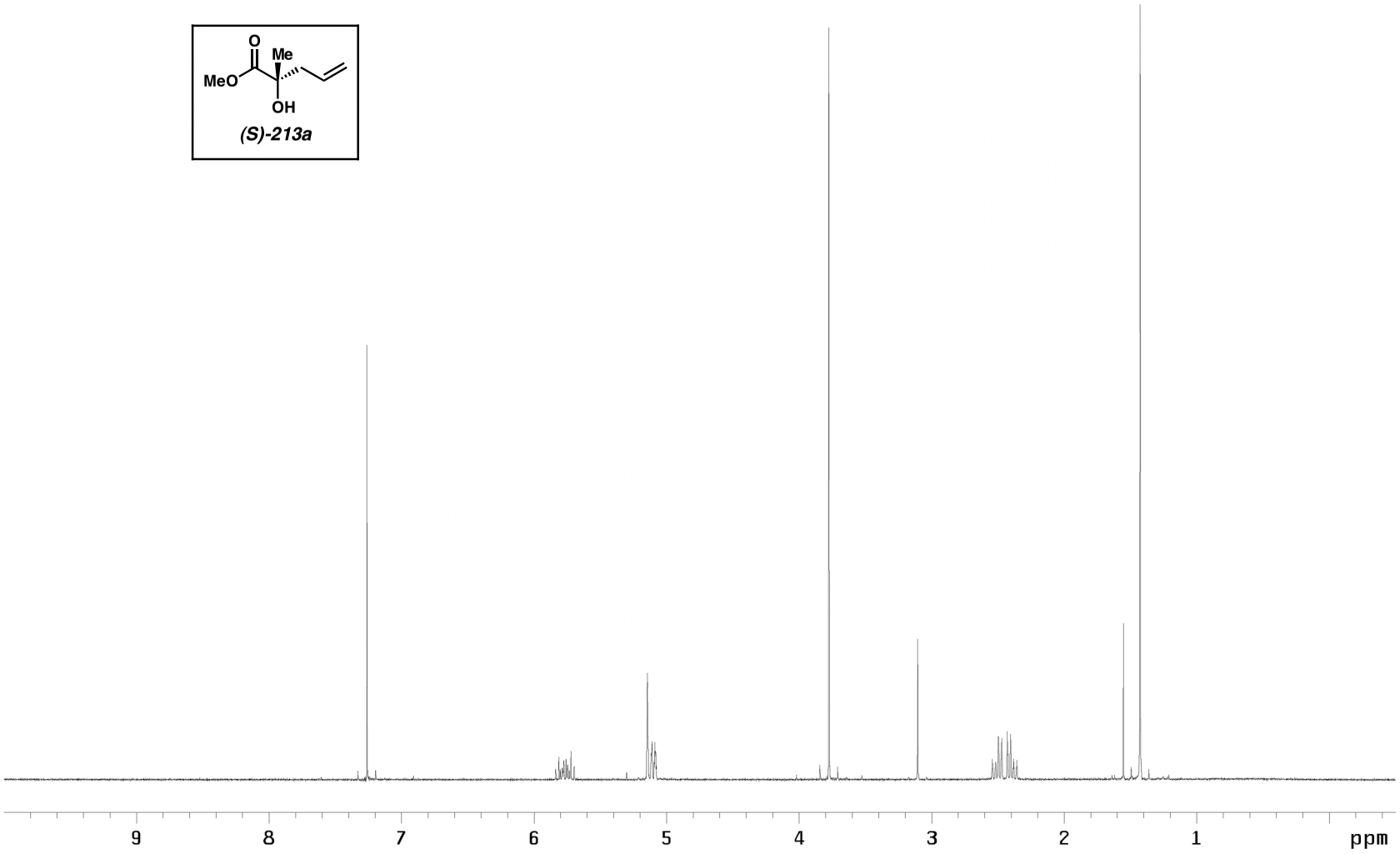


Figure A4.154 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **213a**

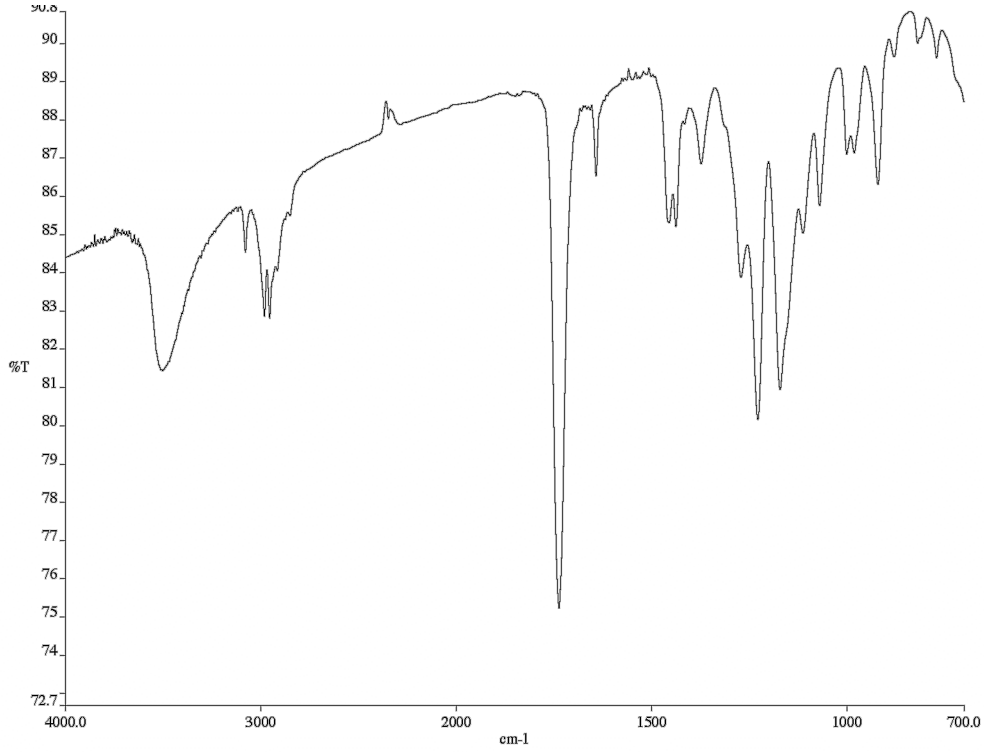


Figure A4.155 Infrared spectrum (thin film/NaCl) of compound **213a**

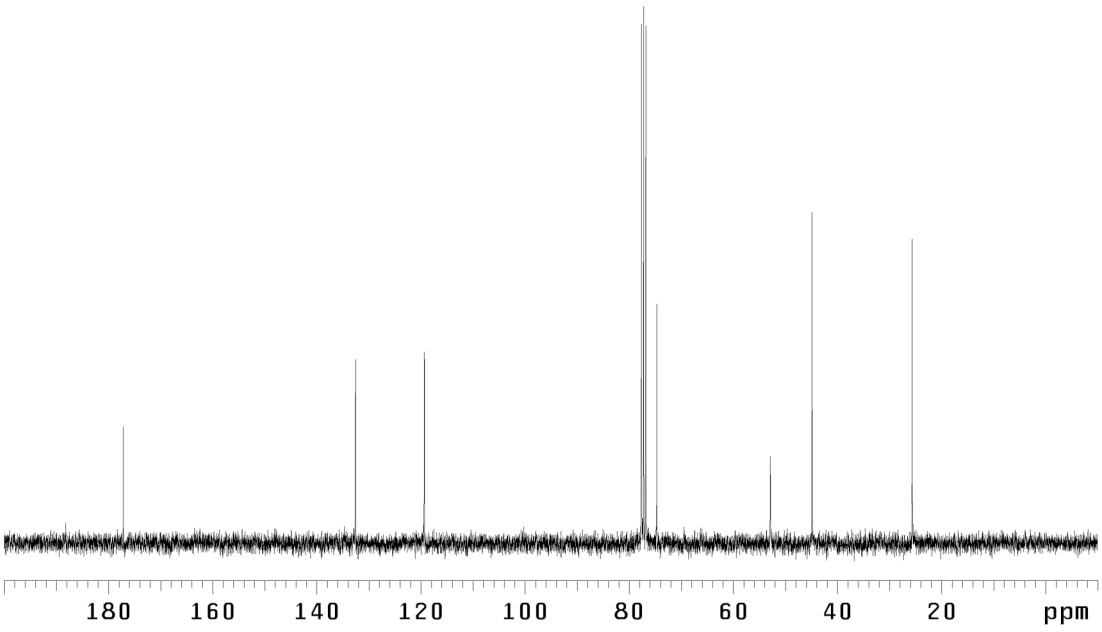


Figure A4.156 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **213a**

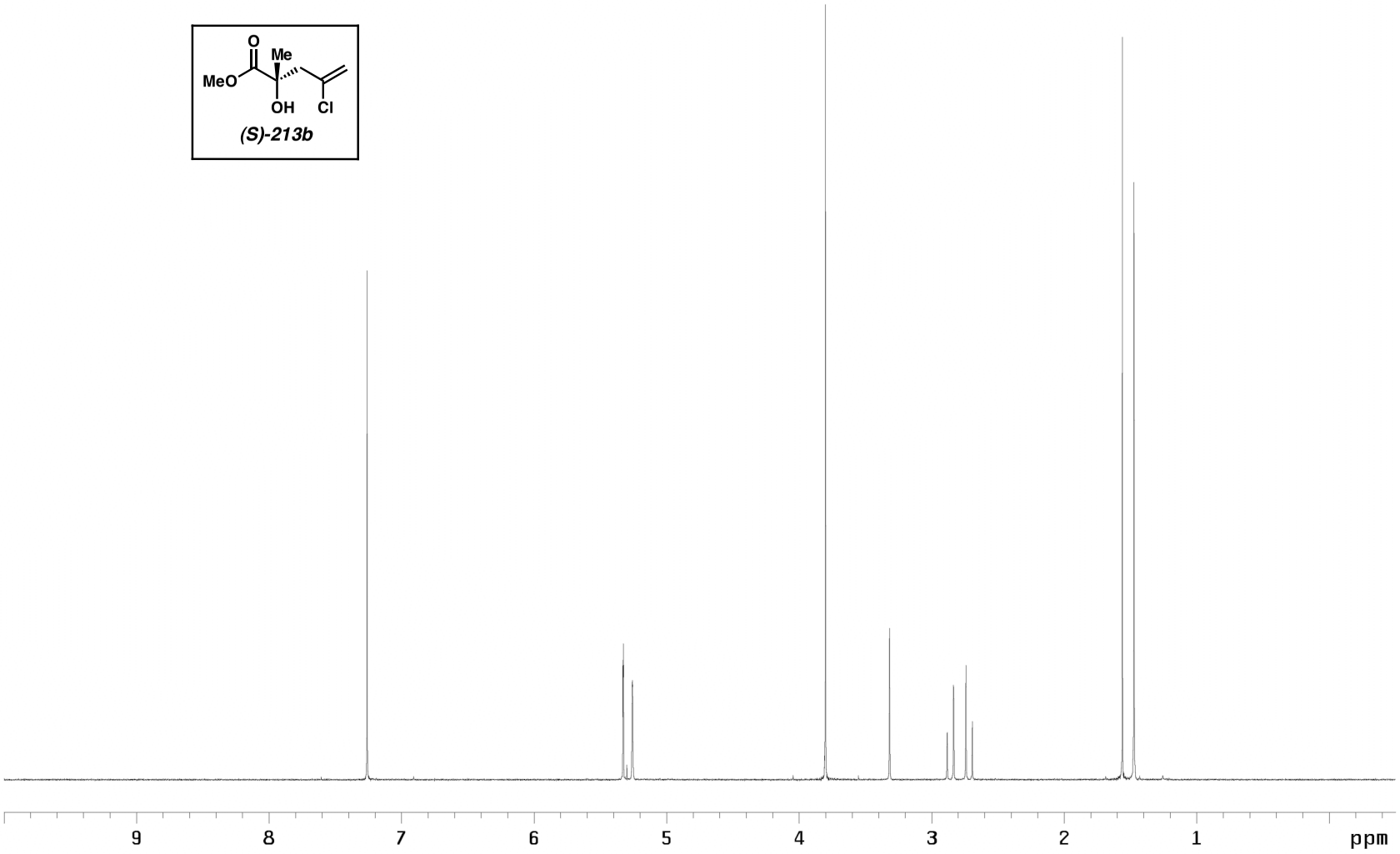


Figure A4.157 ^{1}H NMR (300 MHz, $CDCl_3$) of ester **213b**

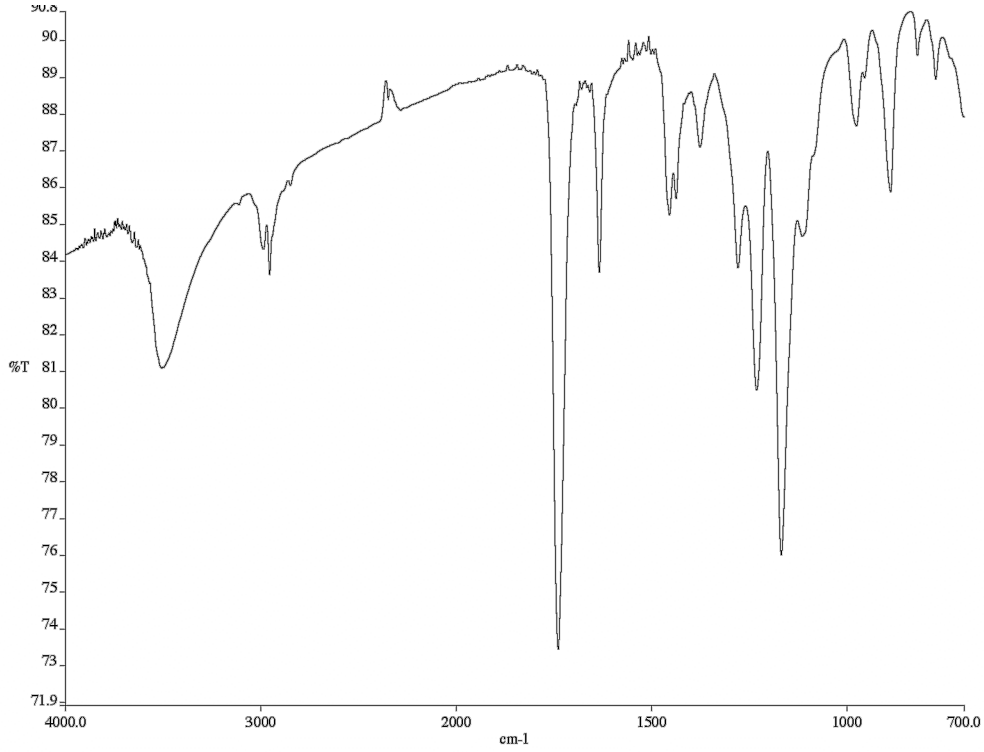


Figure A4.158 Infrared spectrum (thin film/NaCl) of ester **213b**

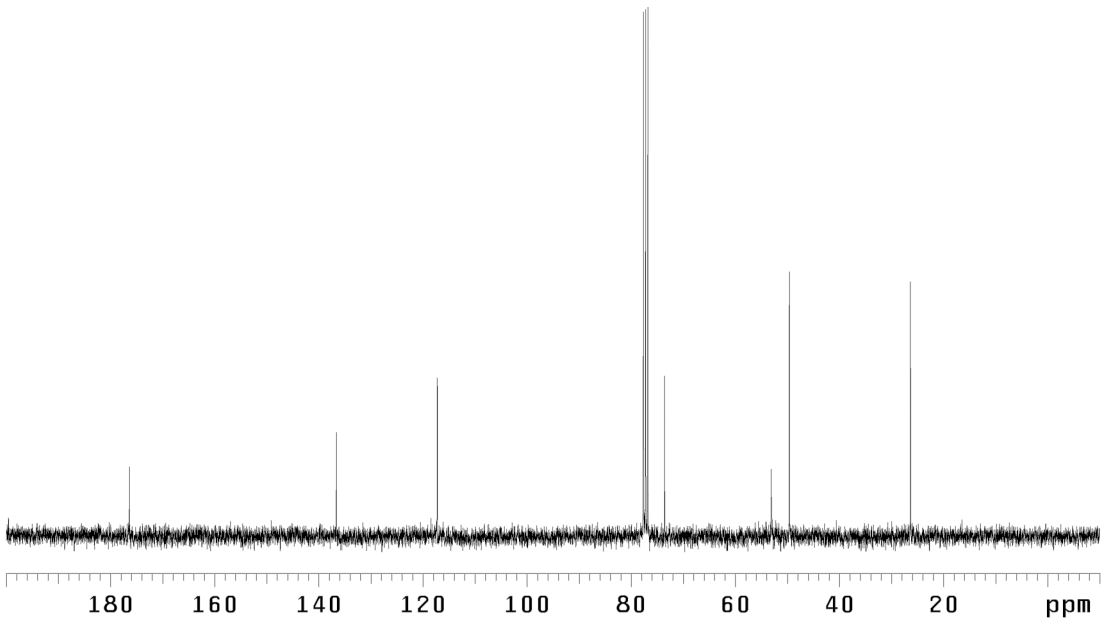


Figure A4.159 ^{13}C NMR (75 MHz, $CDCl_3$) of ester **213b**

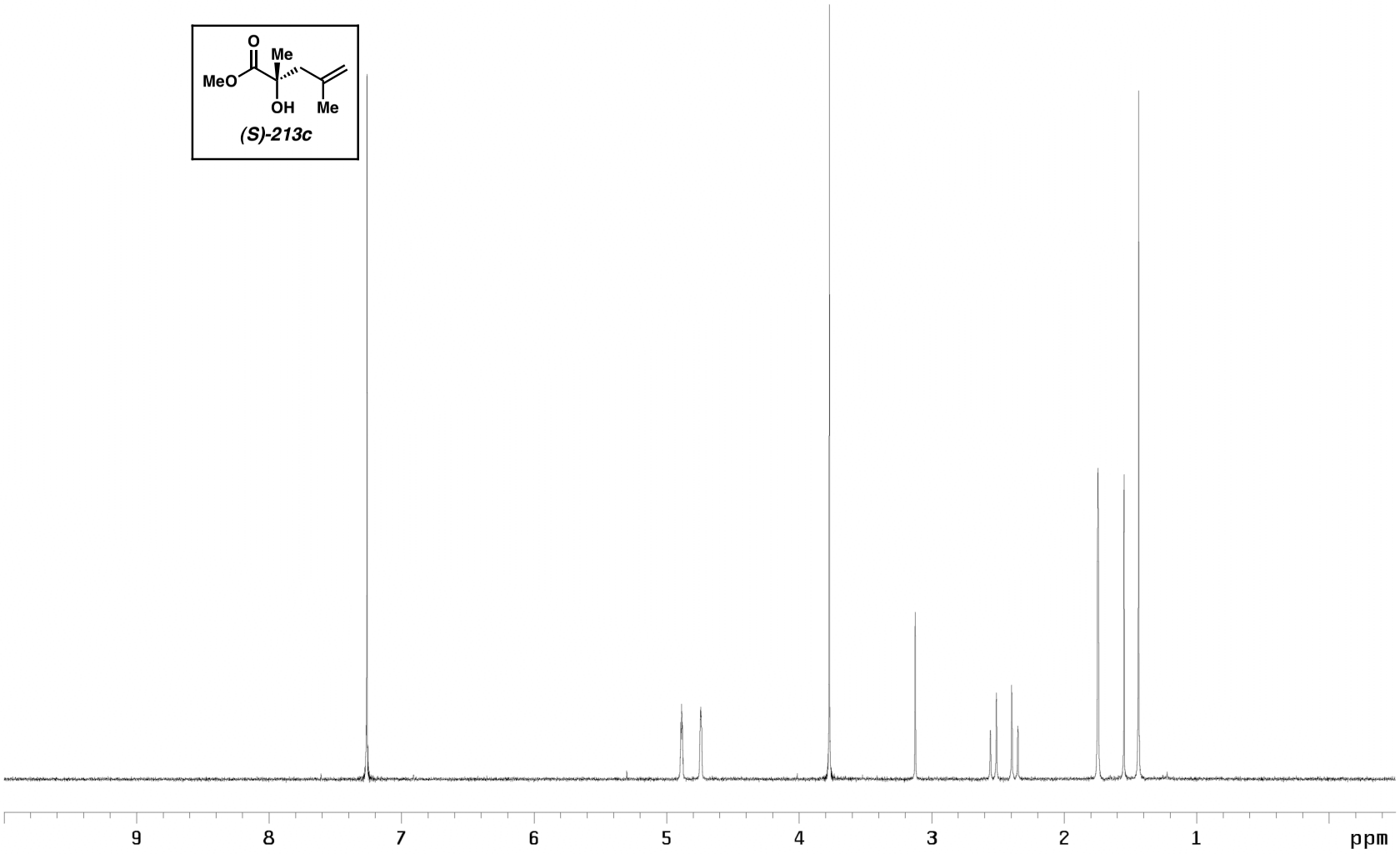


Figure A4.160 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **213c**

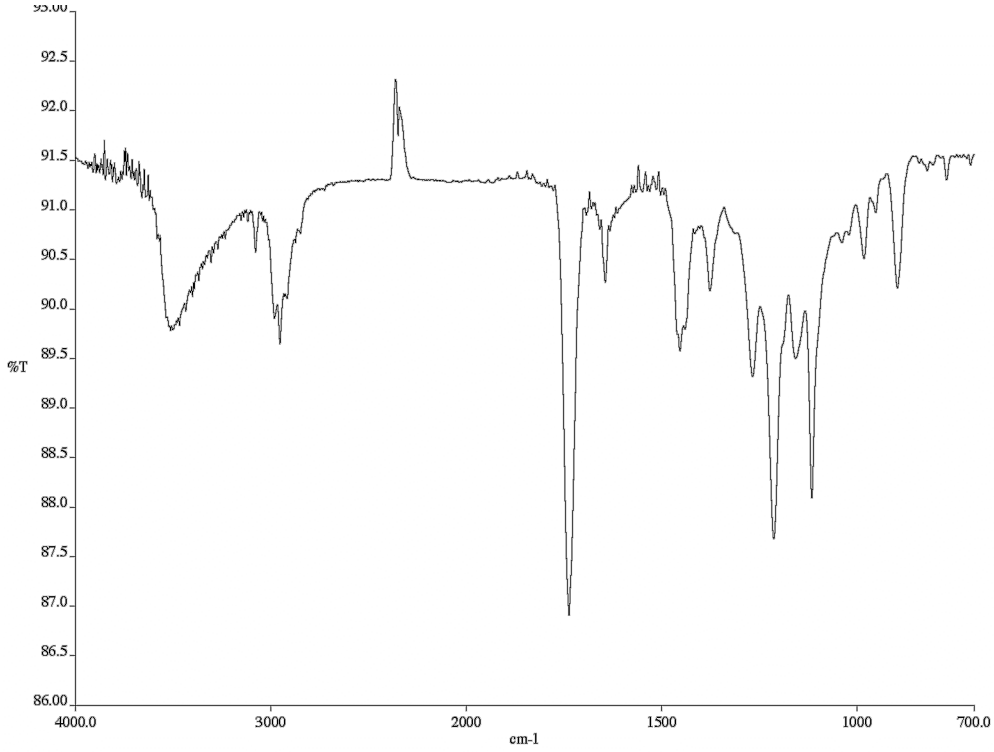


Figure A4.161 Infrared spectrum (thin film/NaCl) of compound **213c**

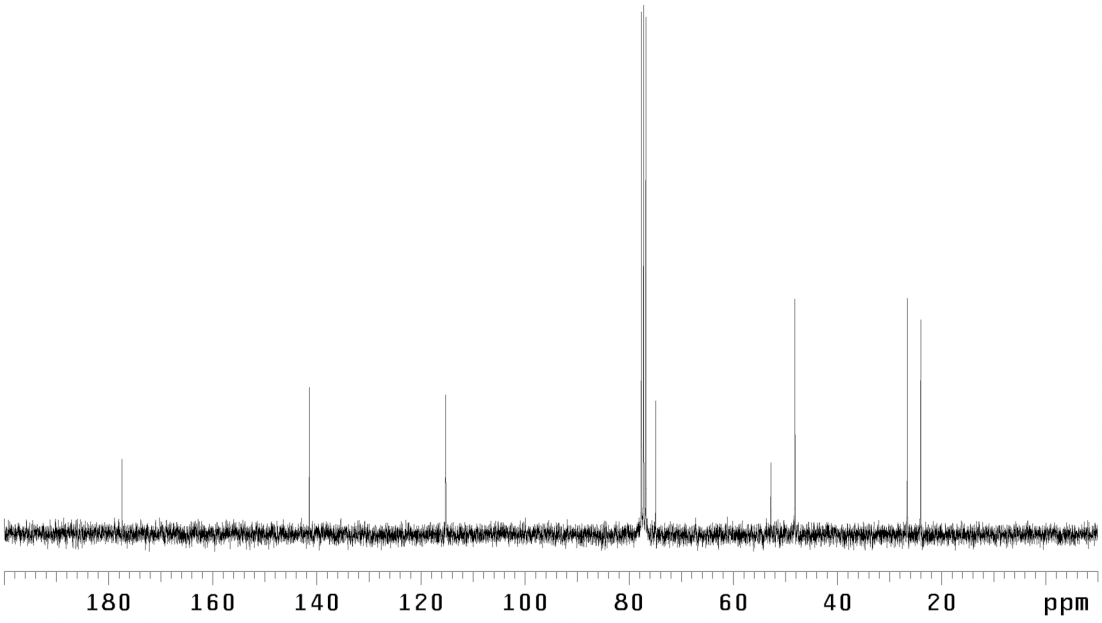


Figure A4.162 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **213c**

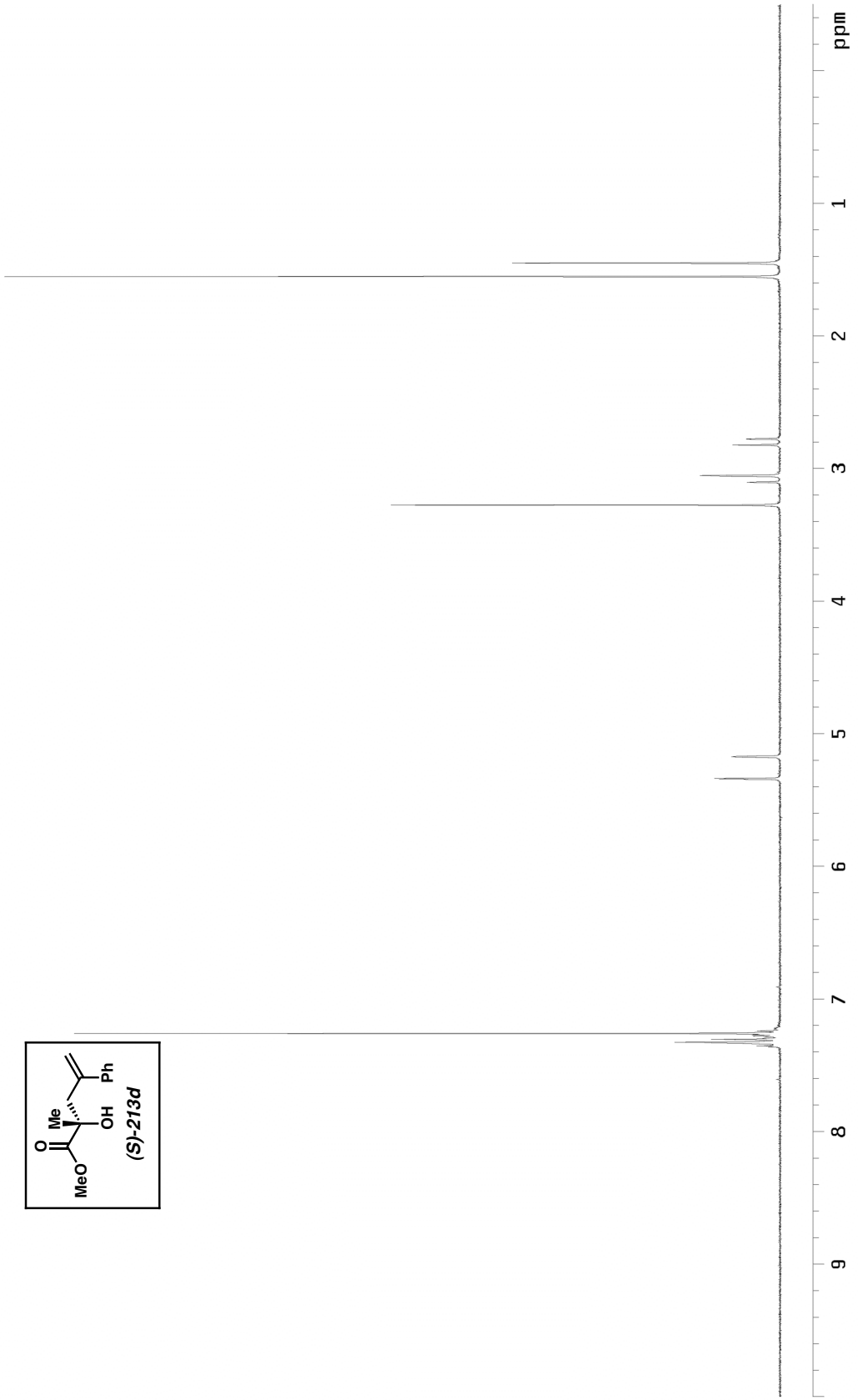


Figure A4.163 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **213d**

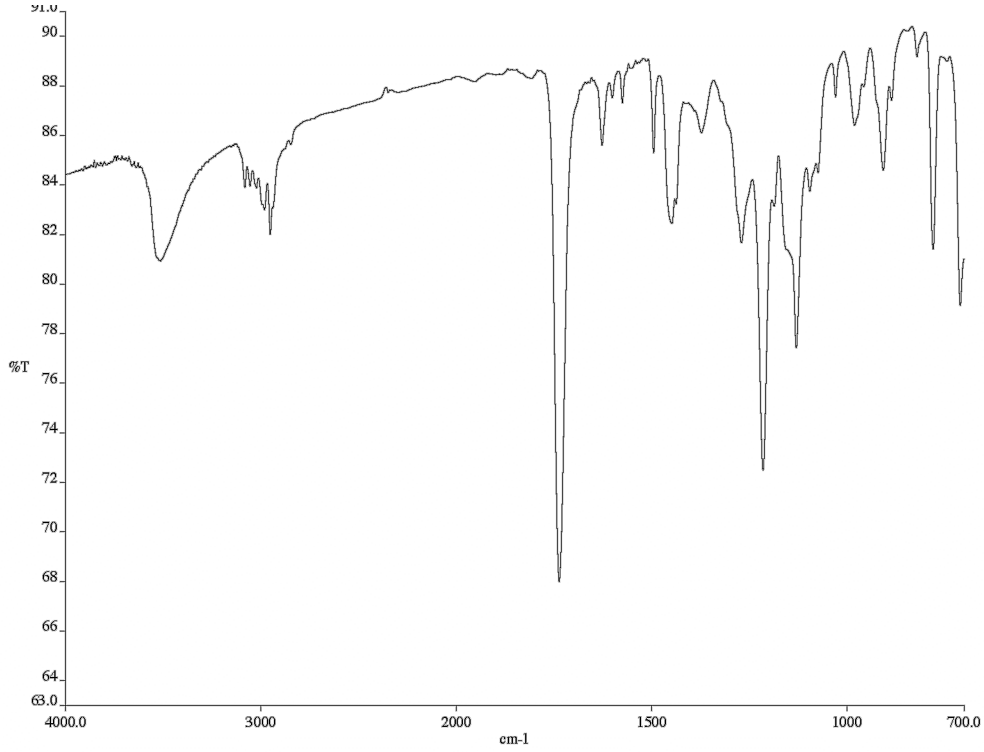


Figure A4.164 Infrared spectrum (thin film/NaCl) of ester **213d**

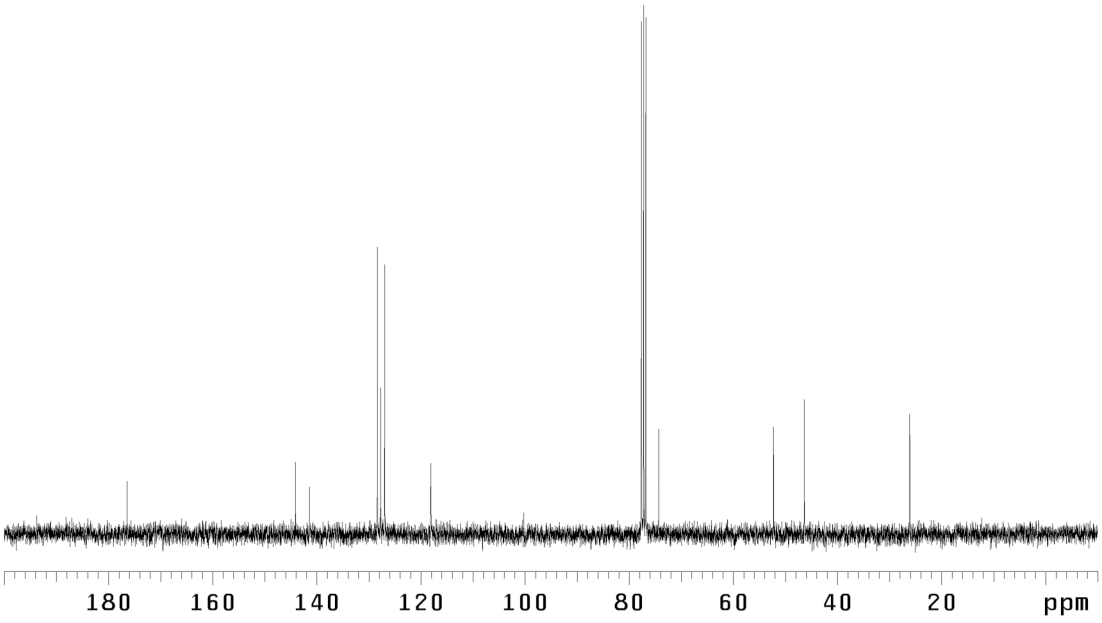


Figure A4.165 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **213d**

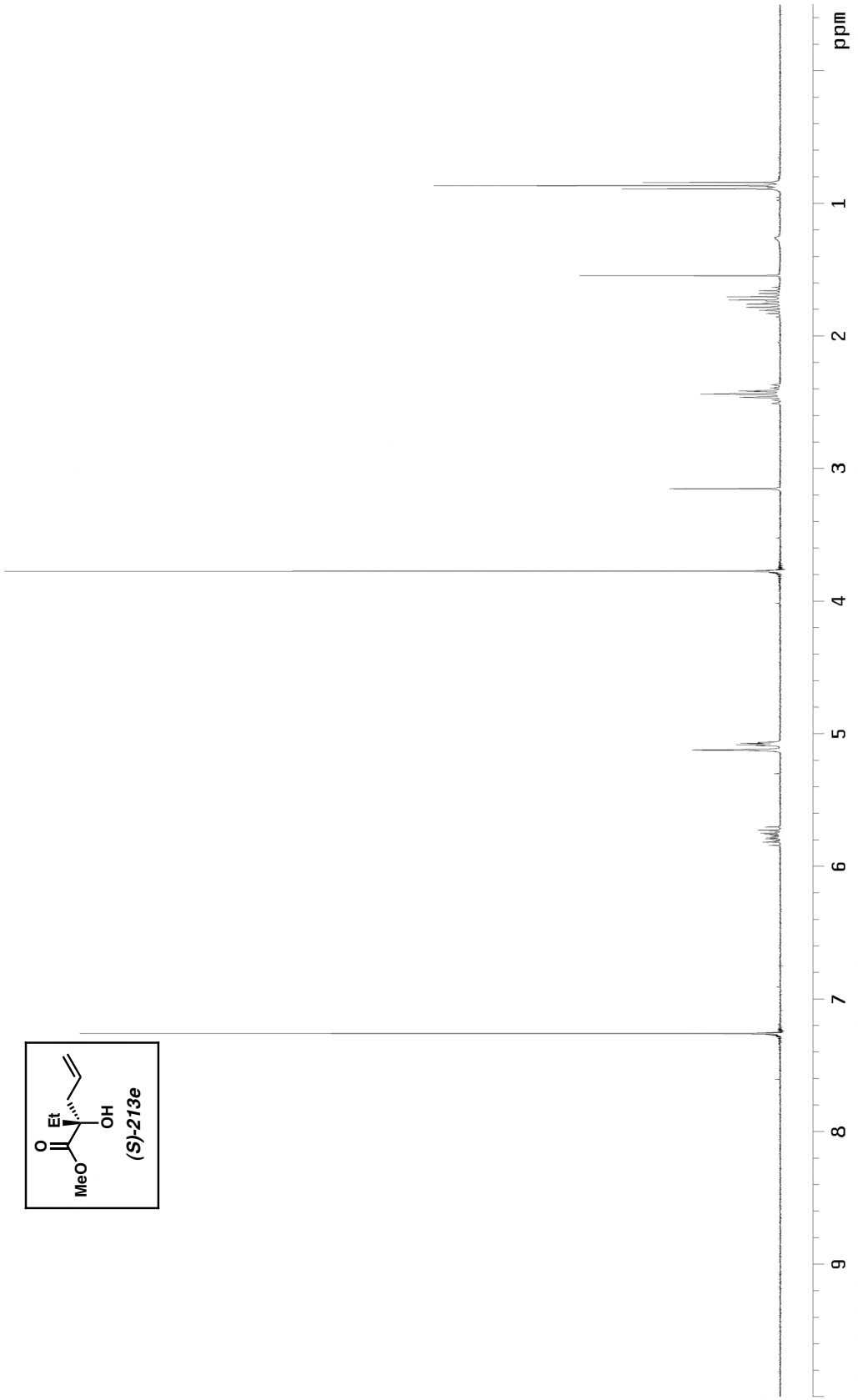


Figure A4.166 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **213e**

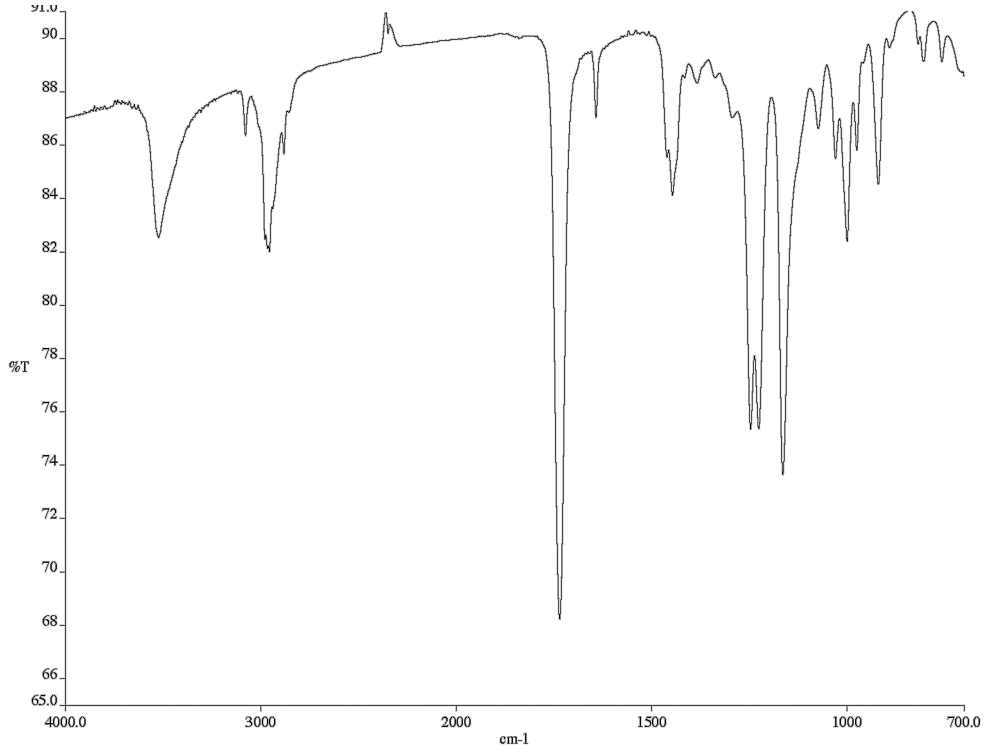


Figure A4.167 Infrared spectrum (thin film/NaCl) of compound **213e**

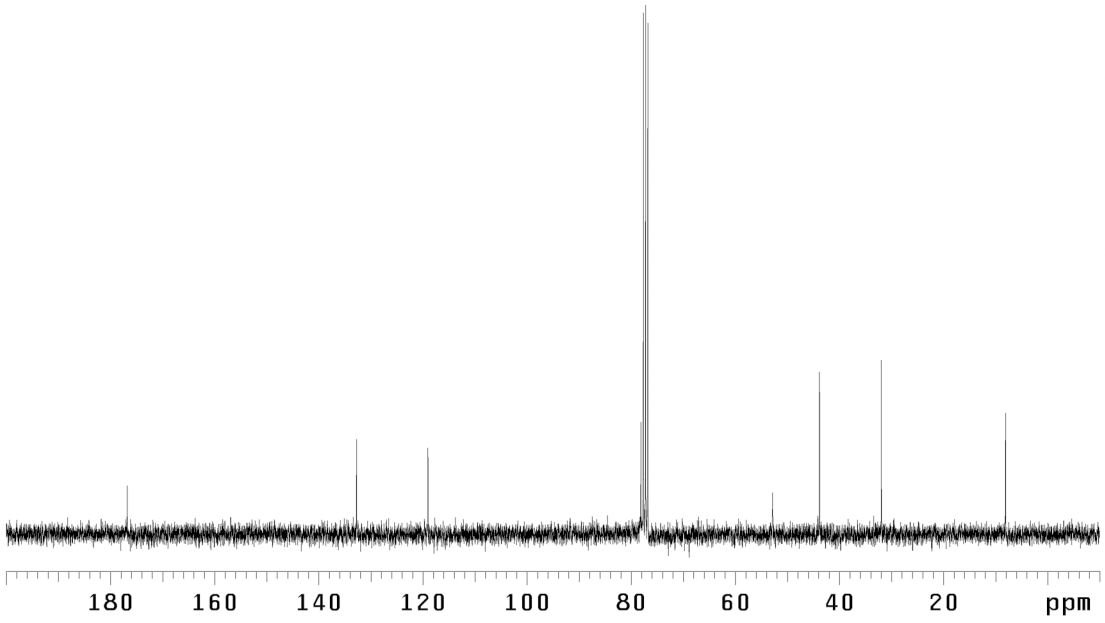


Figure A4.168 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **213e**

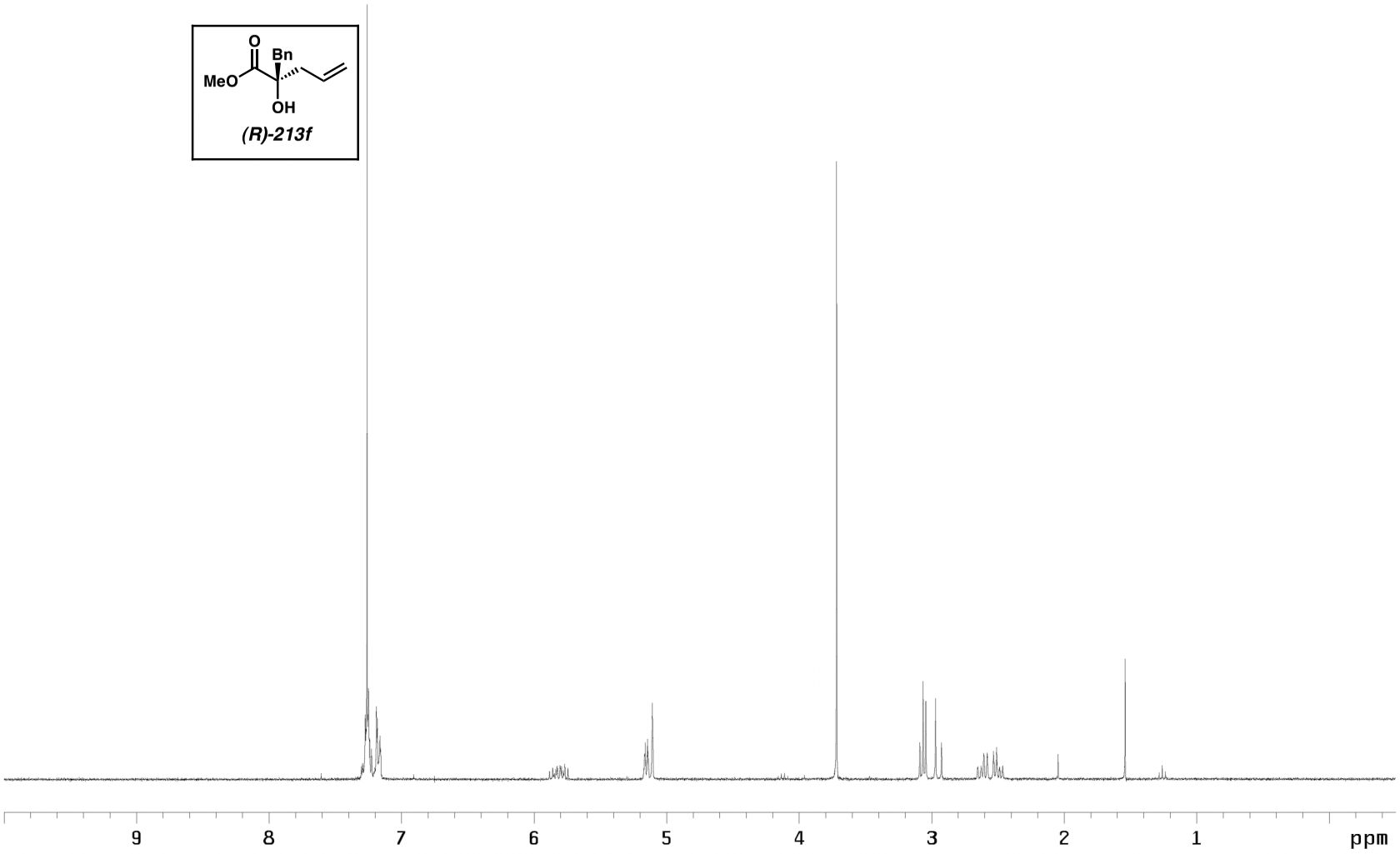


Figure A4.169 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **213f**

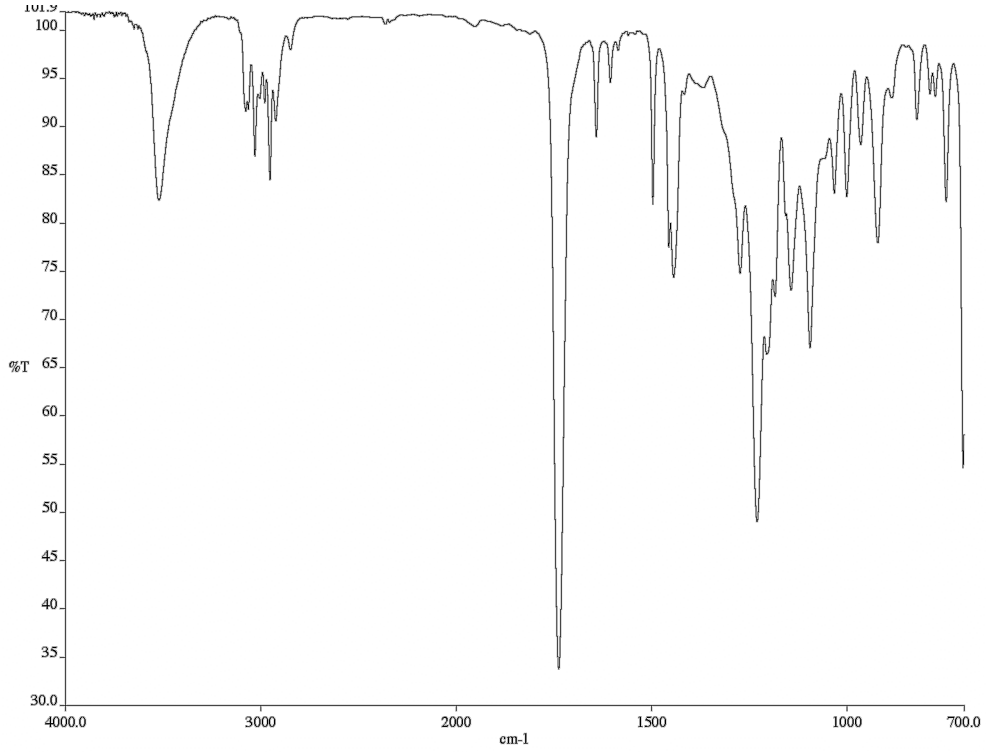


Figure A4.170 Infrared spectrum (thin film/NaCl) of compound **213f**

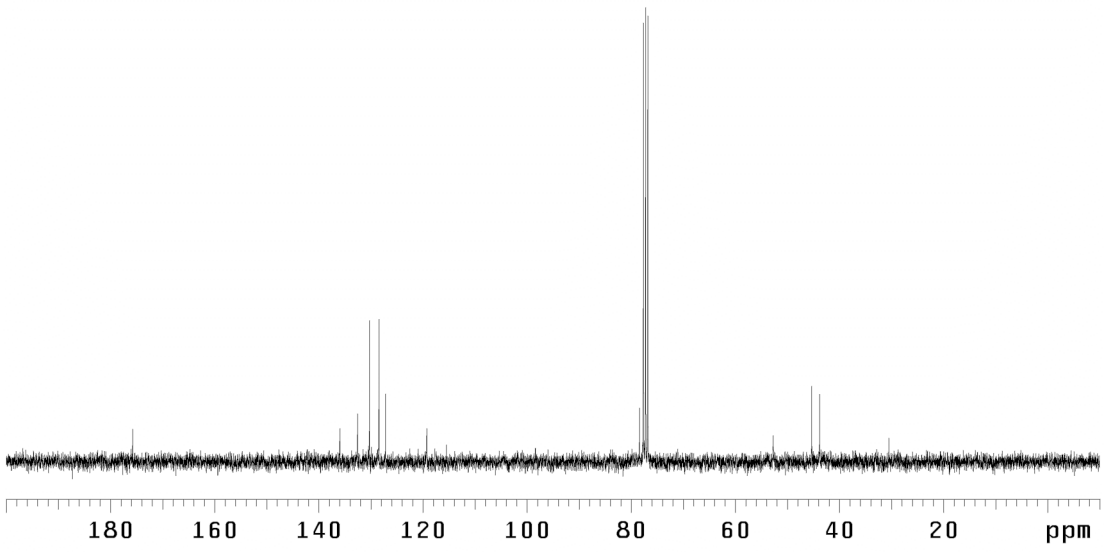


Figure A4.171 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **213f**

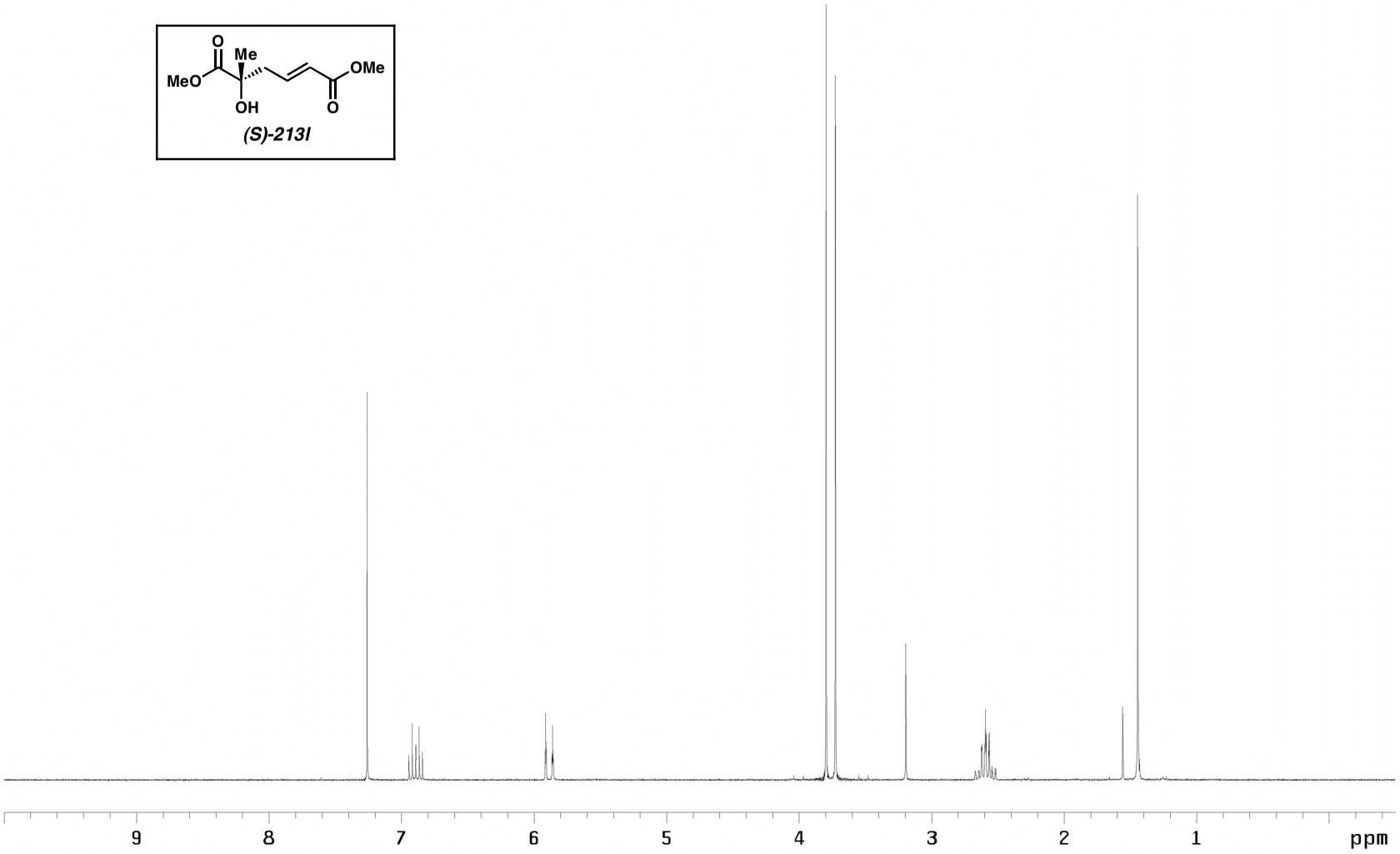


Figure A4.172 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **213l**

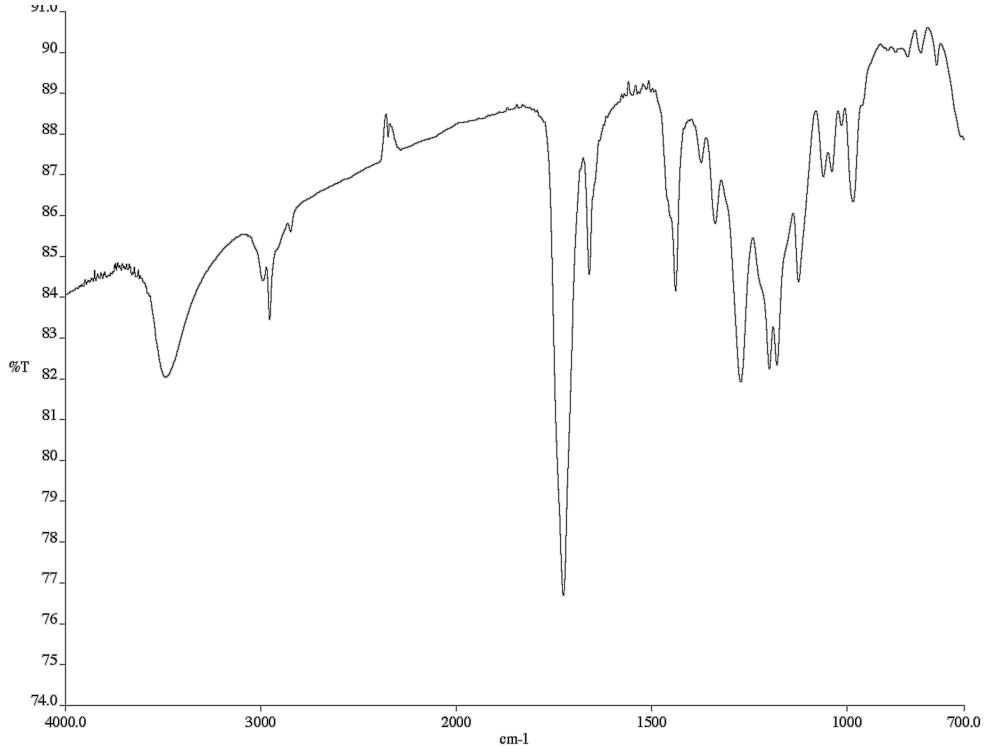


Figure A4.173 Infrared spectrum (thin film/NaCl) of compound **213l**

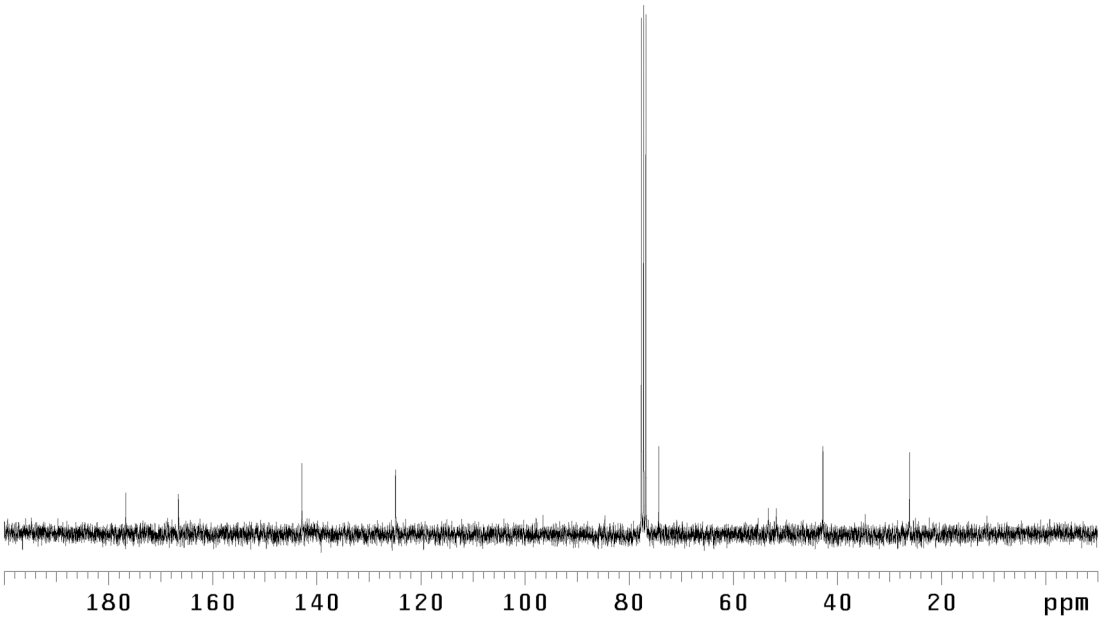


Figure A4.174 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **213l**

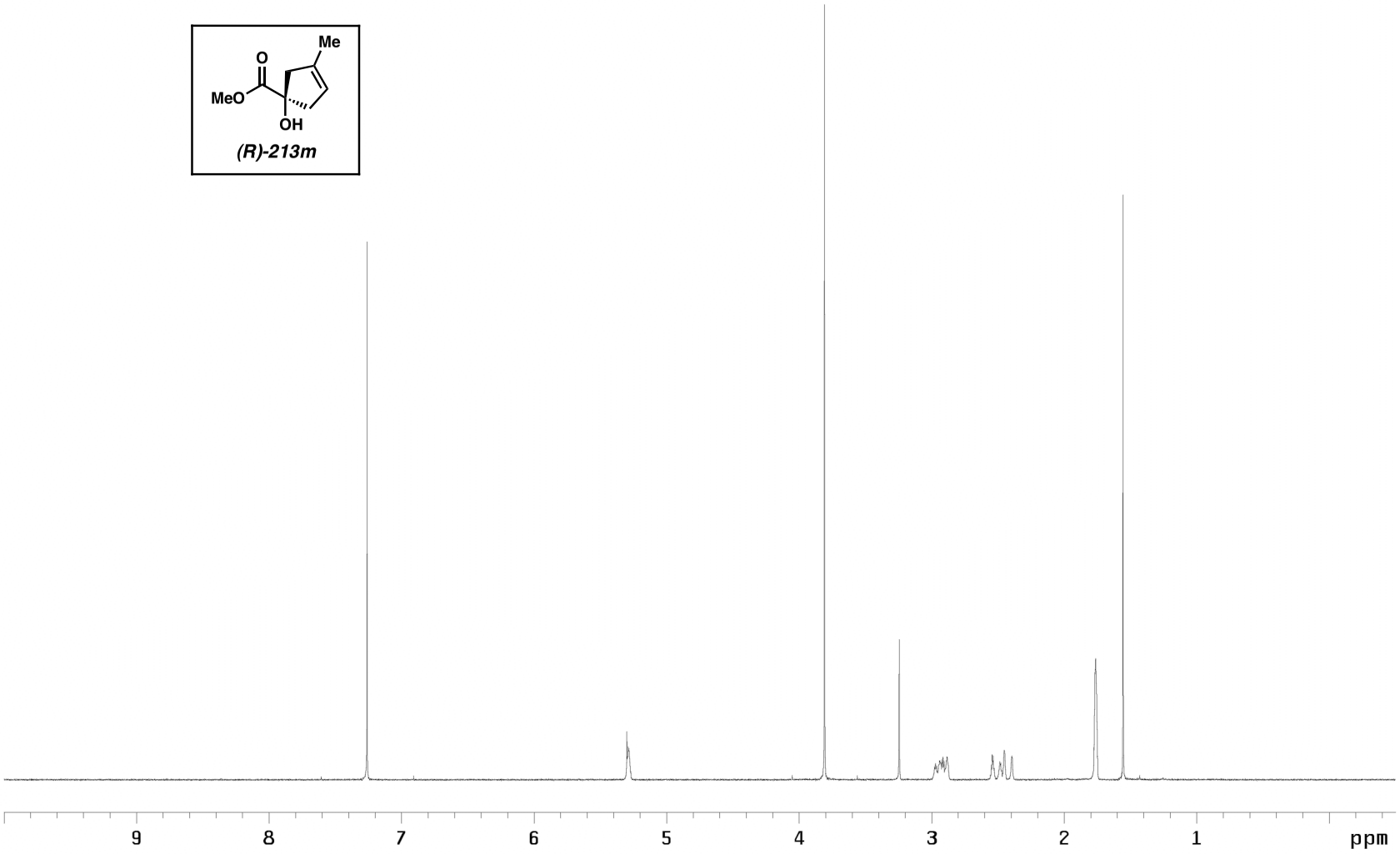


Figure A4.175 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **213m**

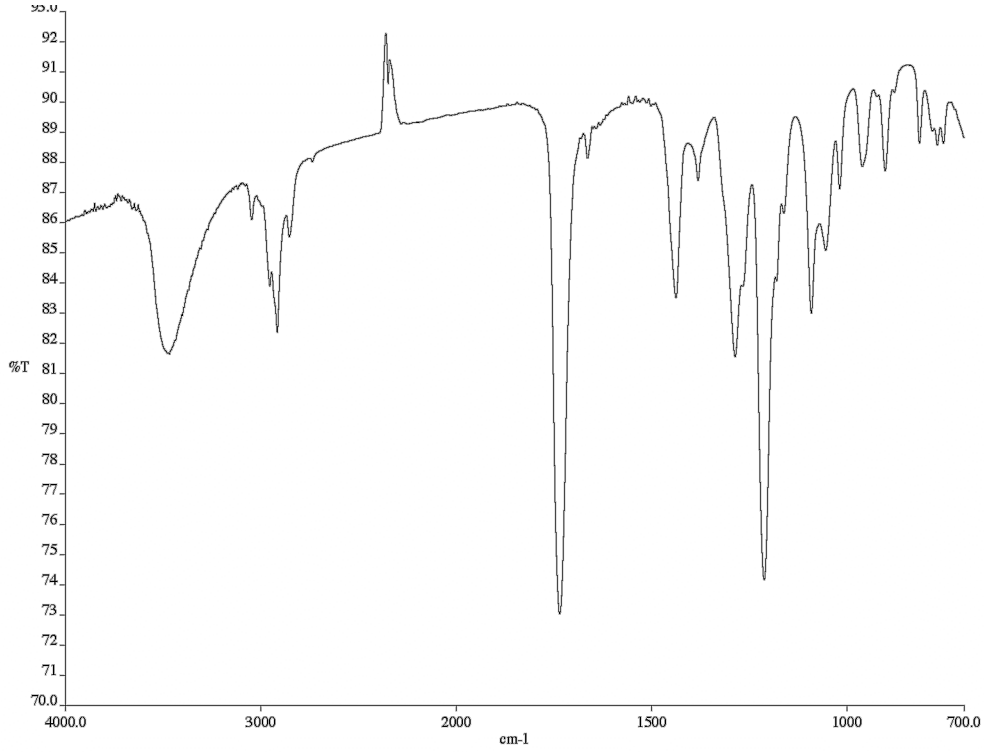


Figure A4.176 Infrared spectrum (thin film/NaCl) of ester **213m**

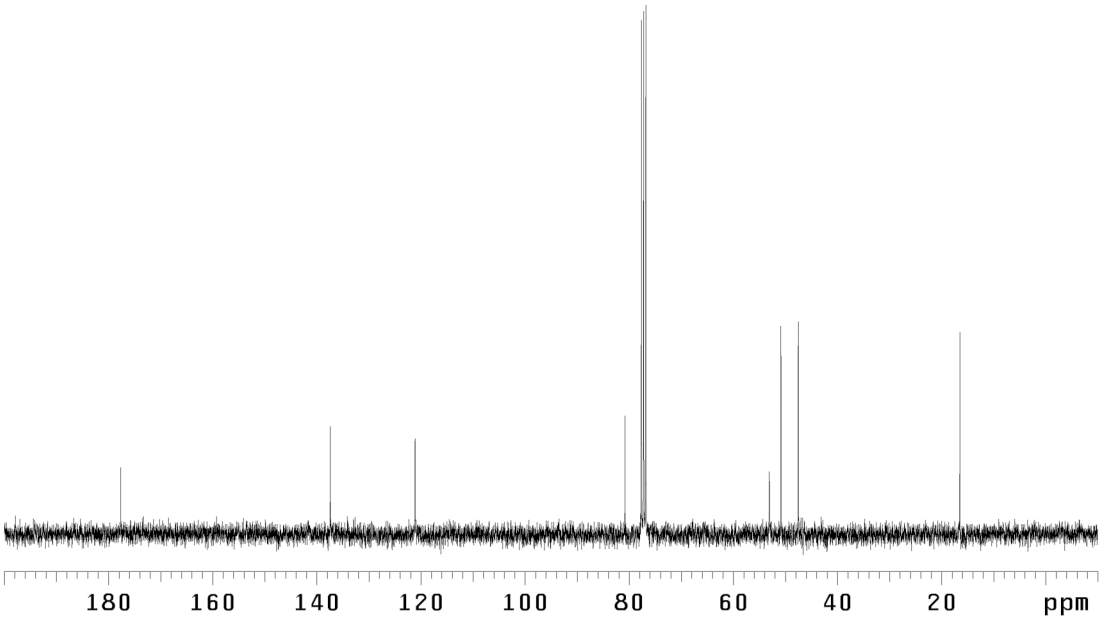


Figure A4.177 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **213m**

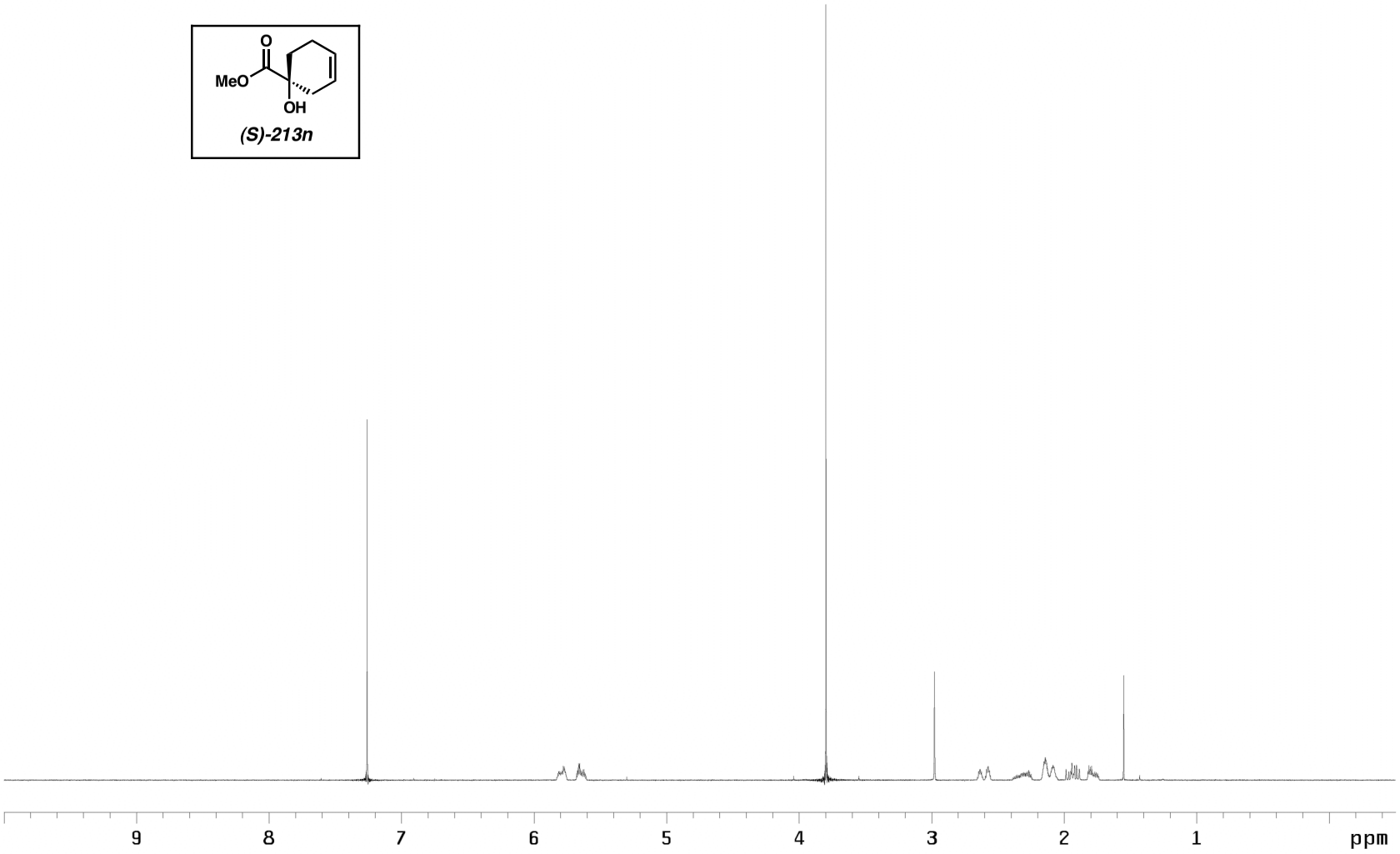


Figure A4.178 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **213n**

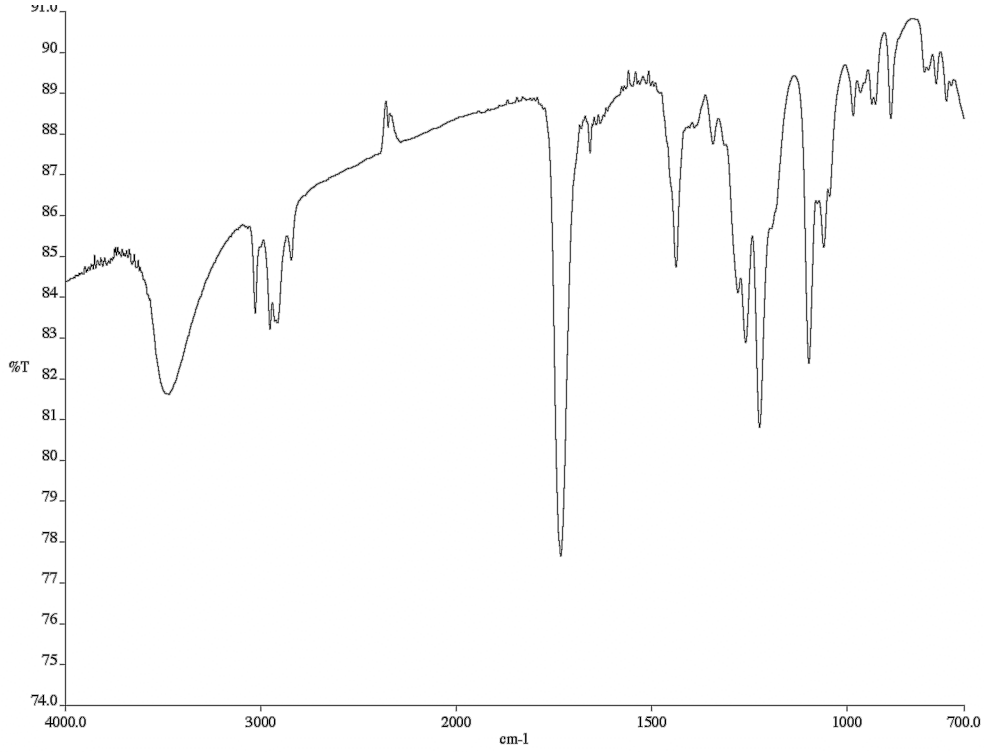


Figure A4.179 Infrared spectrum (thin film/NaCl) of ester **213n**

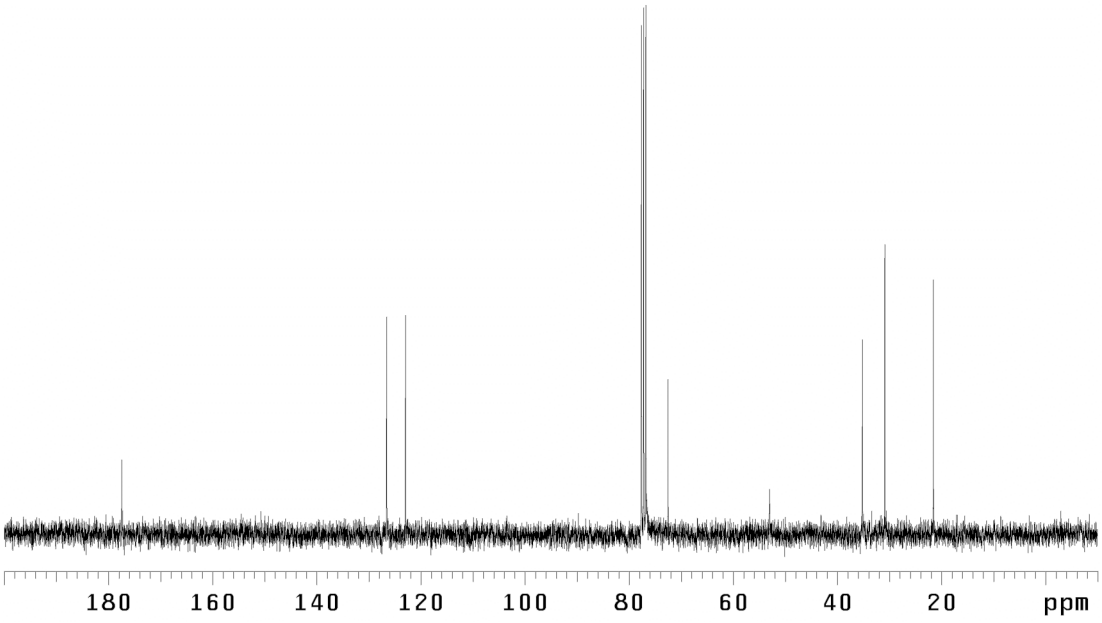


Figure A4.180 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **213n**

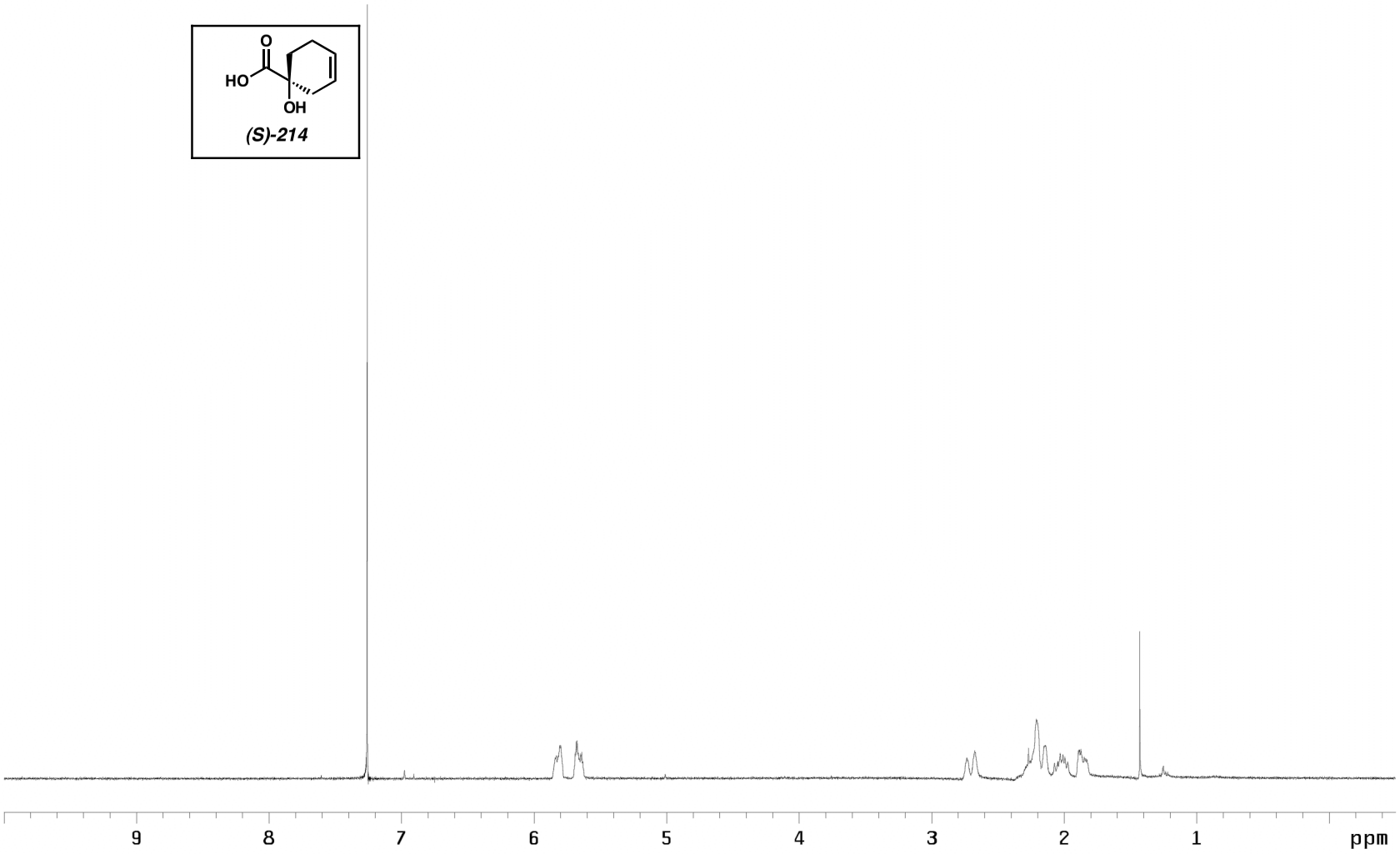


Figure A4.181 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **214**

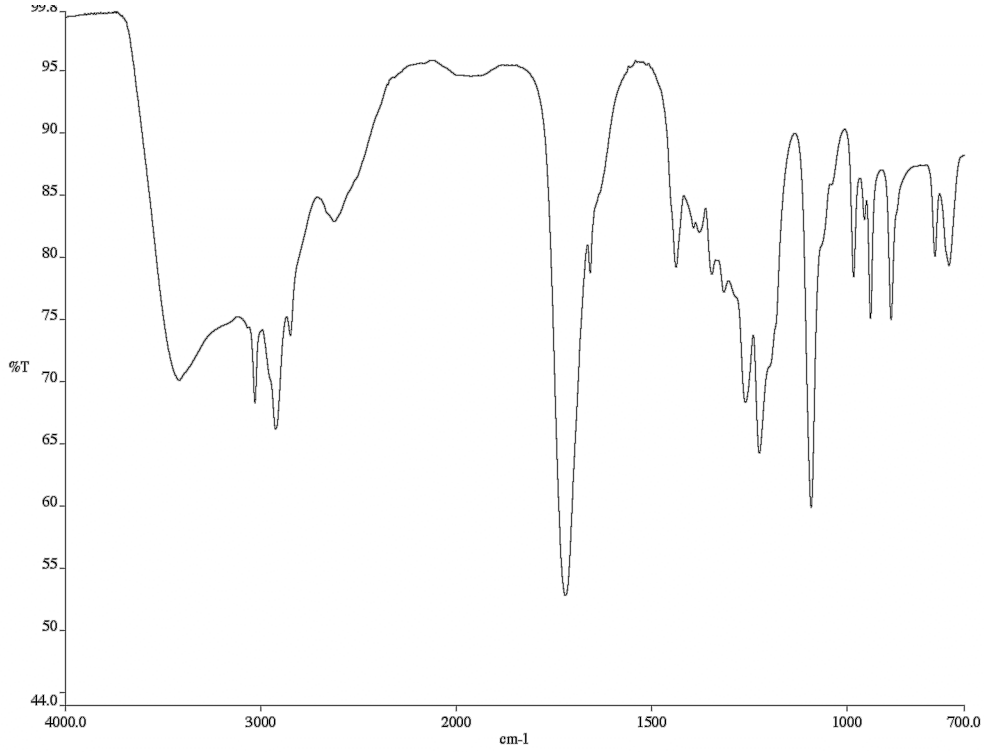


Figure A4.182 Infrared spectrum (thin film/NaCl) of compound **214**

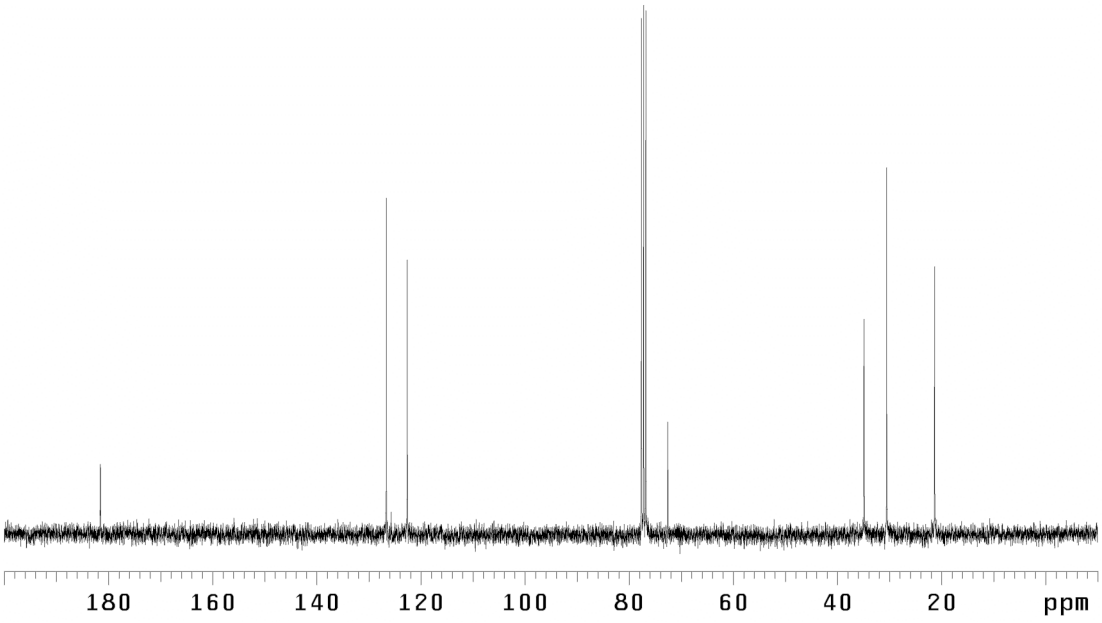


Figure A4.183 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **214**

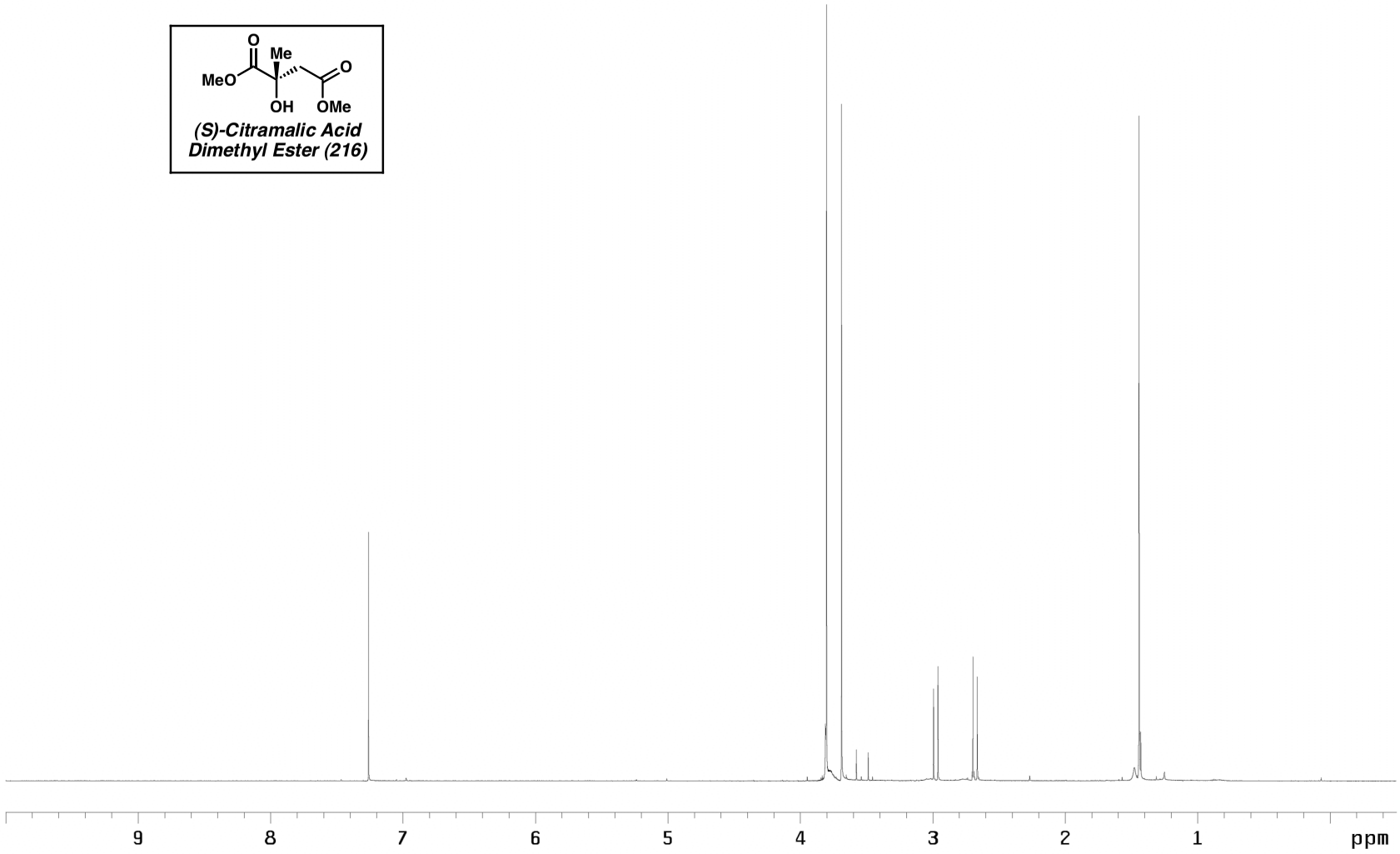


Figure A4.184 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **216**

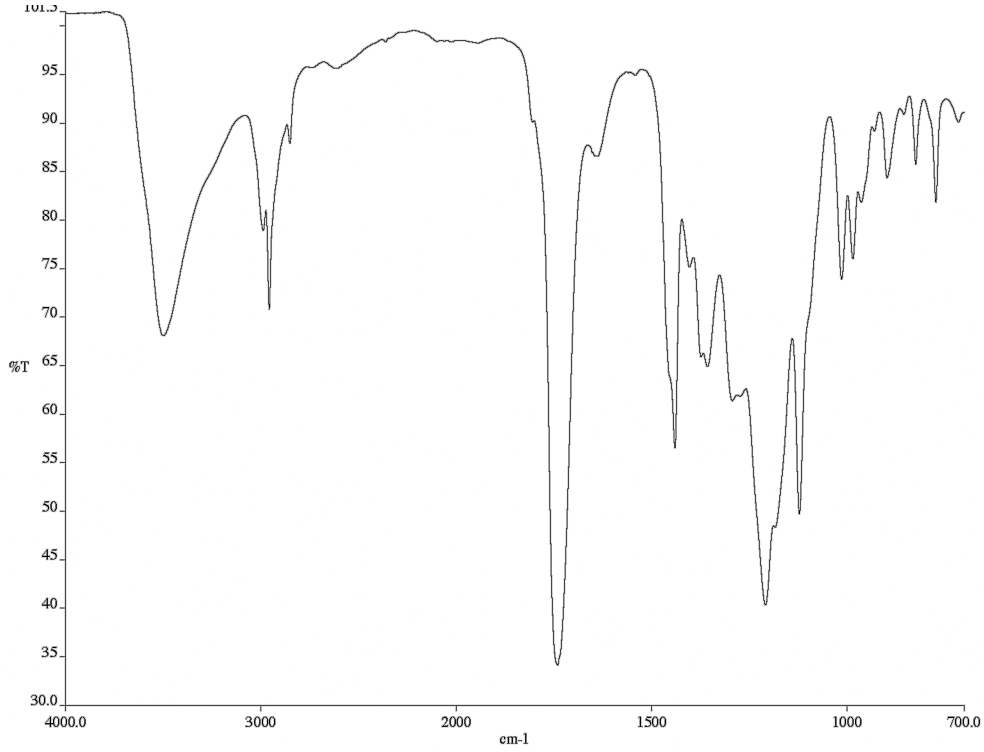


Figure A4.185 Infrared spectrum (thin film/NaCl) of compound **216**

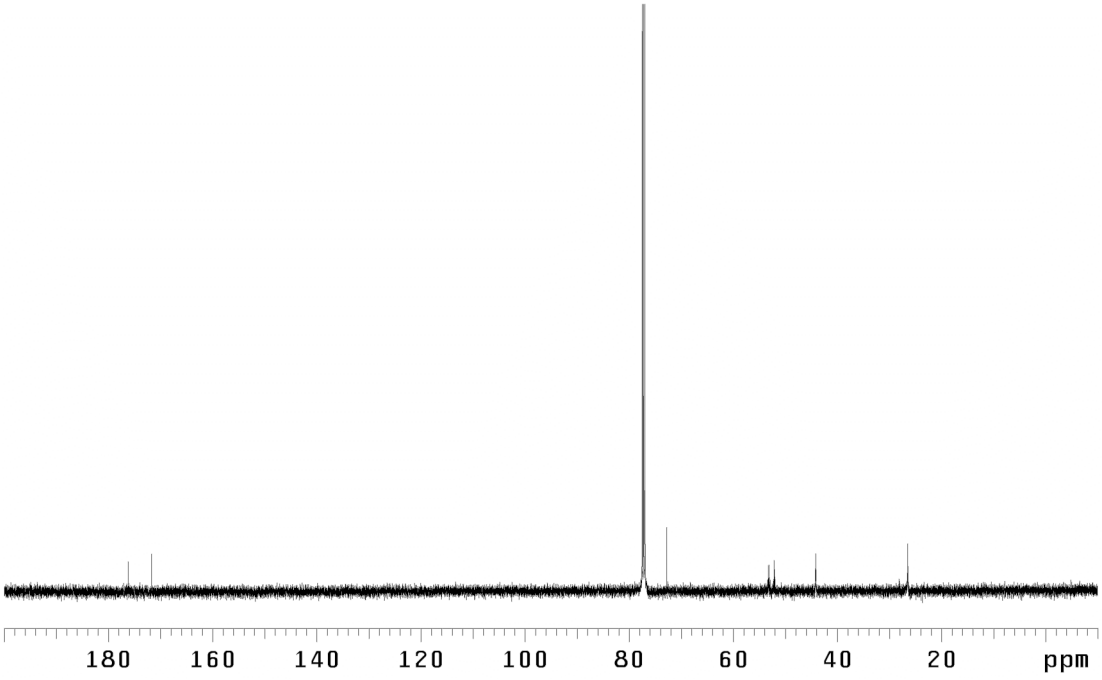


Figure A4.186 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **216**

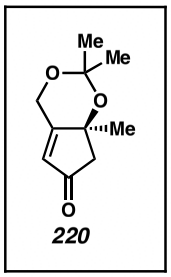


Figure A4.187 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **220**

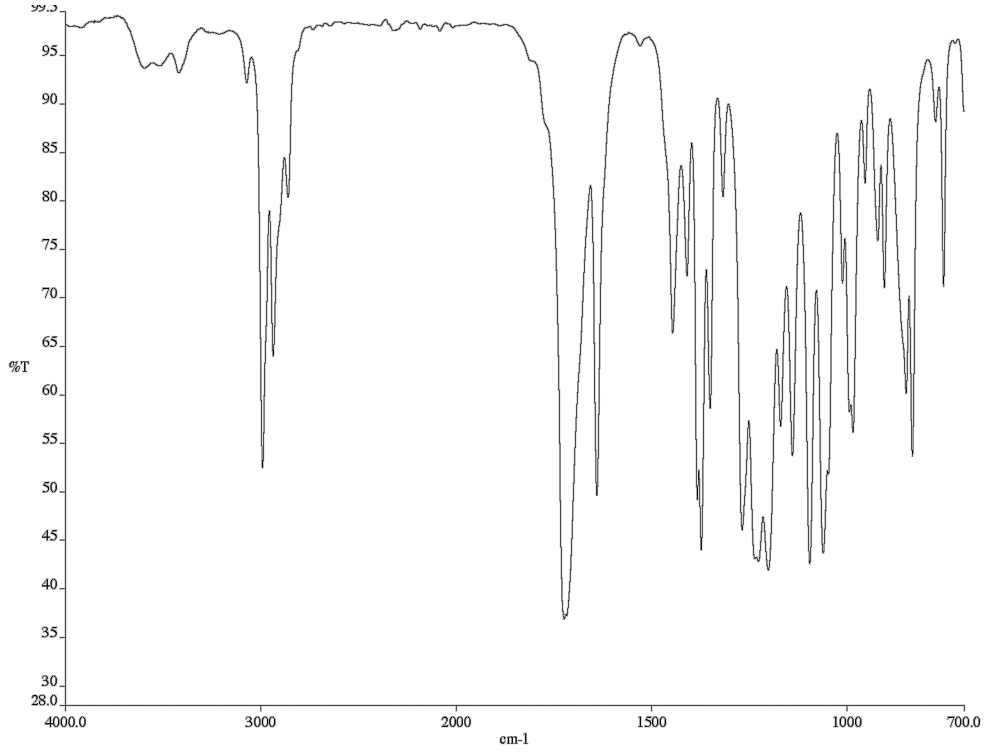


Figure A4.188 Infrared spectrum (thin film/NaCl) of compound **220**

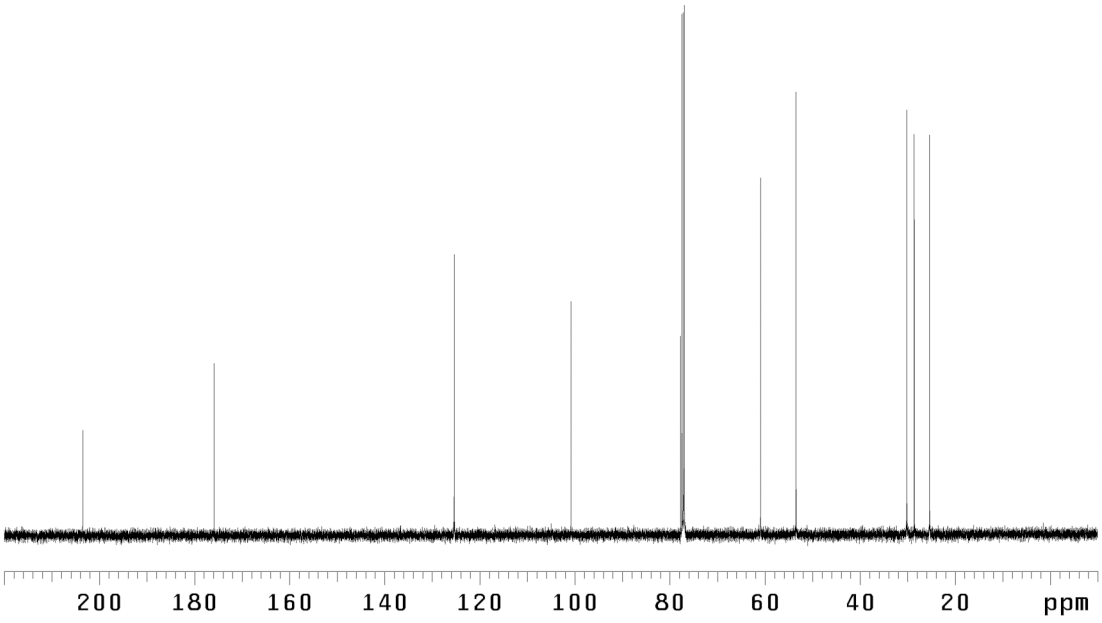
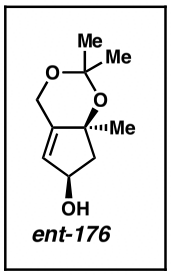


Figure A4.189 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **220**



ent-176

Figure A4.190 ^{1}H NMR (300 MHz, $CDCl_3$) of compound ent-**176**

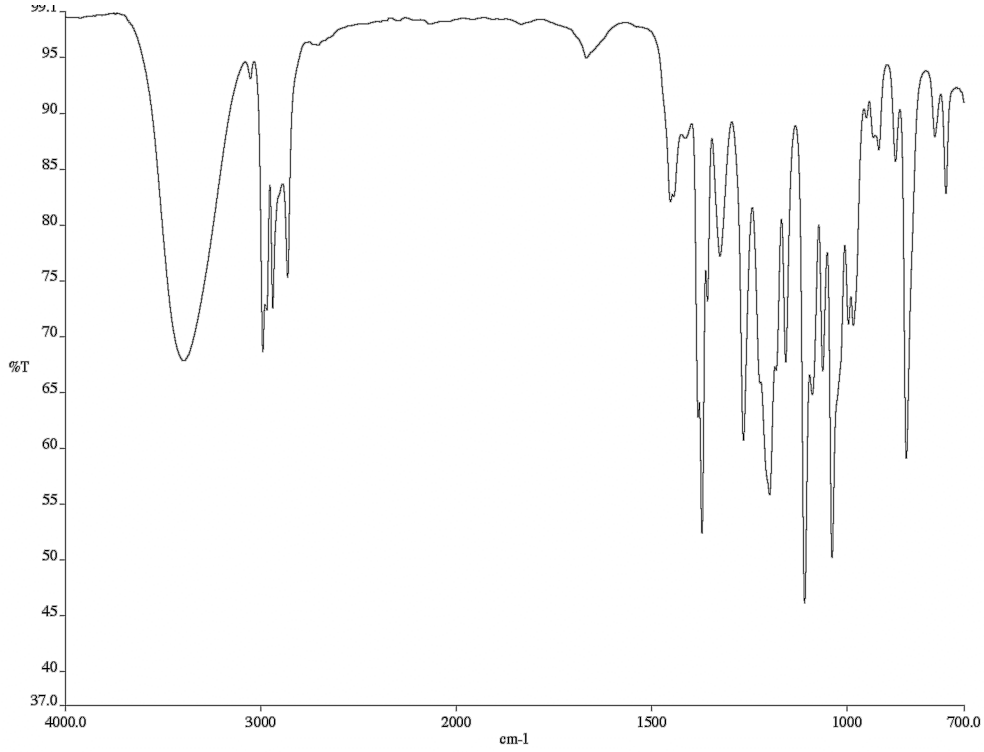


Figure A4.191 Infrared spectrum (thin film/NaCl) of alcohol ent-**176**

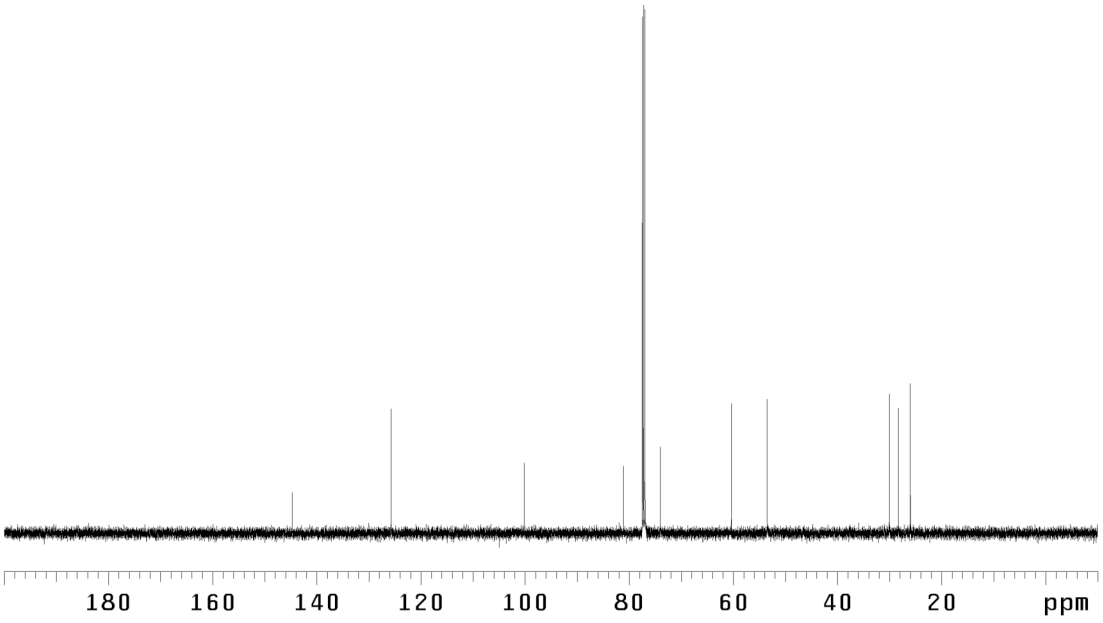


Figure A4.191 ^{13}C NMR (75 MHz, $CDCl_3$) of compound ent-**176**