PALLADIUM(II)-CATALYZED OXIDATION REACTIONS IN NATURAL PRODUCT SYNTHESIS: EFFORTS TOWARD BIELSCHOWSKYSIN AND PHALARINE

Thesis by

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To My Parents

Acknowledgements

"One must learn by doing the thing, for though you think you know it, you have no certainty until you try."

Aristotle

During my time in the Stoltz laboratory, these words have been echoed by my boss, professor Brian Stoltz, countless times when discussing organic chemistry. It amazes me how Brian stays on top of all his research projects and still finds time to follow the Red Sox season and play with his i-phone! In all seriousness, Brian has been a terrific mentor and advisor for me. His support during the difficult times, which was the vast majority of time here, never wavered. I thank Brian for his expertise, advice, friendship, support, and most of all, his patience. Brian's passion and enthusiasm toward organic chemistry has been a constant pillar of support, and he has always been open to my ideas and allowed the freedom for me to try my ideas in the laboratory. Although it's taken longer than expected, the degree and experience that I have gained from the Stoltz laboratory will no doubt allow me to continue to pursue my various passions in science, as well as live a life of more comfort than I am currently used to.

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talk with about movies, pharmaceuticals, and a whole lot more. Then there's Joe, a guy who has become a good friend throughout the years. Joe is very good at his job, golf, and being a family man. I owe you 18 holes.

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continued happiness. For the most part, Jeff and I enjoyed our time working next to each other, and I thank him for the support and friendship. Fourth, I need to thank Dr. John Phillips, my second partner on bielschowskysin. John made an immediate impact on our project by improving the cyclopropanation reaction, and making improvements in the scale-up process. John is a good friend, very knowledgeable, and also provided a positive outlook almost every day he was at Caltech. Although we were unable to achieve the results we strived for, the friendship and experience working with John was completely worth it. Finally, I'd like to thank Raissa Trend for proofreading various documents, she has a degree in English, and for having lots of entertaining conversations. I wish her success in her future endeavors.

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Abstract

Two types of oxidative transformations, an oxidative kinetic resolution and an oxidative heterocyclization, have been developed by several laboratories using palladium(II)-catalysis to provide enantioenriched products. The main drawback of these asymmetric transformations is the limited substrate scope for each set of conditions. To address this, the Stoltz laboratory developed a unique platform utilizing palladium(II)-catalysis that provides a highly effective oxidative kinetic resolution of secondary alcohols and an asymmetric oxidative heterocyclization of phenols. Key to this platform is the use of (–)-sparteine as the chiral ligand and O_2 as the stoichiometric oxidant. Both of these methodologies will be featured in this thesis as they were applied toward the total synthesis of complex natural products.

Our palladium(II)-catalyzed oxidative kinetic resolution was used to access an enantioenriched intermediate in our efforts toward the synthesis of bielschowskysin, a polycyclic diterpenoid. A key disconnection in our strategy was formation of the cyclobutane core of bielschowskysin from a cyclopropane intermediate. After considerable experimentation, we were able to synthesize a cyclopropane intermediate that could be used for future research.

In separate work, we hoped to use two palladium(II)-catalyzed oxidative heterocyclization reactions to provide the core of phalarine, a polycyclic alkaloid. The synthesis of a key intermediate relied on a Stille coupling reaction of a complex 4,5,7-substituted indole and a nitro-arene. Model cyclization studies on an aniline substrate gave inconclusive results, while a model of a phenolic substrate has shown that cyclization onto styrenyl olefins is possible.

Table of Contents

List of Figures

Chapter 1

Chapter 2

Chapter 2 Appendices

Appendix 2.2

Chapter 3 Appendices

Appendix 3.1

List of Schemes

List of Tables

List of Abbreviations

Å	Angstrom
$[\alpha]_D$	specific rotation at wavelength of Na D-line
Ac	acetyl
Acac	acetylacetonate
AIBN	2,2'-azobisisobutyronitrile
Anal.	Analysis
app.	apparent
aq.	aqueous
Ar	aryl
atm	atmosphere
BBN	borabicyclo[3.3.1]nonane
Bn	benzyl
BQ	benzoquinone
br	broad, broadened
Bu	butyl
i-Bu	isobutyl
n-Bu	*n*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl
c	concentration for specific rotation measurements
°C	degrees Celsius

calc'd	calculated
cat.	catalytic
CDI	carbonyldiimidazole
comp	complex
conv	conversion
Cy	cyclohexyl
δ	chemical shift
d	doublet, day(s)
dt	doublet of triplets
dba	dibenzylideneacetone
DIBAL	diisobutylaluminum hydride
DHP	dihydropyran
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMP	Dess-Martin periodinane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dppb	1,2-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppp	1,2-bis(diphenylphosphino)propane
dr	diastereomeric ratio
ee	enantiomeric excess
EI	electrospray ionization
elim.	Elimination

equiv	equivalents
er	enantiomeric ratio
esd	ellipsoid
Et	ethyl
FAB	fast atom bombardment
g	gram
GC	gas chromatography
[H]	reduction
h	hour(s)
HMDS	hexamethyldisilazane or hexamethyldisilazide
hν	light
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
IR	infrared
J	coupling constant
kcal	kilocalories
L	liter or neutral ligand
LAH	lithium aluminum hydride
MMPP	mono magnesium perphthalate
M	metal, molar
m	milli, multiplet, meter
m/z	mass to charge ratio

μ	micro
Me	methyl
Mes	mesityl
MHz	megahertz
min	minute(s)
mol	moles
mp	melting point
MS	molecular sieves
Ms	methanesulfonyl
N	normal
nbd	norbornadiene
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
nuc	nucleophile
[O]	oxidation
o	ortho
OKR	oxidative kinetic resolution
P	para
Ph	phenyl
PhH	benzene

PhMe	toluene
pH	hydrogen ion concentration in aqueous solution
pK_a	acidity constant
PIFA	phenyliodine(III)bis(trifluoroacetate)
ppm	part(s) per million
PPTS	pyridinium *p*-toluenesulfonate
i-Pr	isopropyl
py	pyridine
q	quartet
ref	reference
R_F	retention factor
s	singlet, selectivity factor
sat.	saturated
sp	(–)-sparteine
stoich.	stoichiometric
Sub	substrate
t	triplet
td	triplet of doublets
TBAF	tetrabutylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TBSal	*tert*-butyl salicimine
TBDPS	*tert*-butyldiphenylsilyl

TEA	triethylamine
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid or trifluoroacetate
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMPDA	*N*,*N*,*N*',*N*'-tetramethylpropylenediamine
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl
TsOH	*p*-toluenesulfonic acid
UV	ultraviolet
v/v	volume to volume
w/v	weight to volume
X	anionic ligand, halide

CHAPTER 1

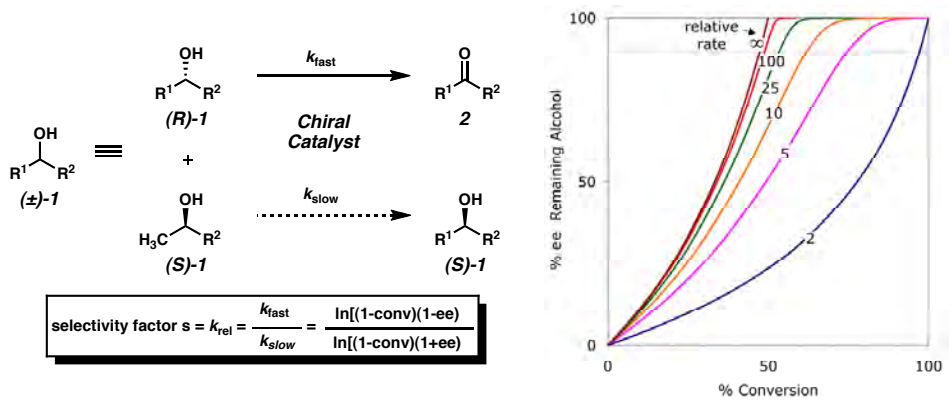
1.1 An Introduction to Oxidative Kinetic Resolution

1.1.1 Introduction

Enantiopure secondary alcohols are invaluable in organic synthesis as they are found in natural products and medicinal drugs. Furthermore, enantiopure secondary alcohols can also lead to carbon-carbon bond formation while transferring the chirality (e.g., allylic alkylation) to afford various types of complex products. One method to access enantioenriched secondary alcohols is via a kinetic resolution, which allows for the isolation of one enantioenriched alcohol from a racemic mixture via a chemical transformation, not the separation of both enantiomers.[1] In an oxidative kinetic resolution of secondary alcohols, one enantiomer (e.g., (*R*)-**1**) reacts faster with the enantiopure catalyst, at a rate of k_{fast}, to provide oxidized product **2**, while the other enantiomer (e.g., (*S*)-**1**) reacts much more slowly (k_{slow}) than its counterpart (Figure 1.1.1). Ideally, the reaction is terminated when all or most of the faster-reacting

enantiomer has been converted to product **2**. The remaining enantioenriched alcohol ((*S*)-**1**) and ketone **2** can then be separated by standard techniques. In an efficient oxidative kinetic resolution, the selectivity factor (s), which is determined by measuring the relative rate (k_{rel}) of reaction of the two enantiomers ($k_{rel} = k_{fast} / k_{slow}$), will be high (s > 15). In practice, the selectivity factor is usually determined by measuring the total conversion of starting material to product and the enantiomeric excess of the recovered starting material.[2] To achieve optimum selectivity, the chiral reagent or catalyst should maintain the same relative enantiomeric preference throughout the reaction; hence, the selectivity factor remains constant. The enantiomeric excess of the starting material will always increase with increasing conversion for any kinetic resolution with a selectivity factor greater than 1 (Figure 1.1.1). Thus, kinetic resolutions have the capacity to provide compounds with high enantioenrichment for even modestly selective processes at higher levels of conversion.

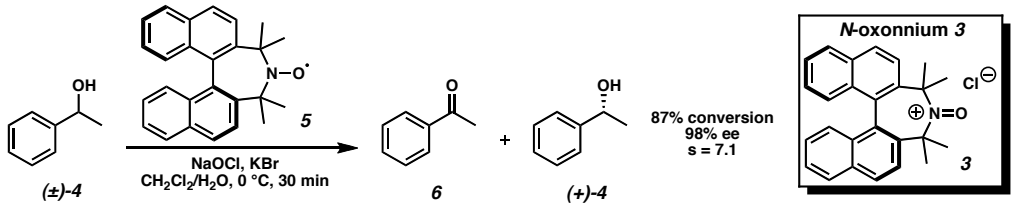
Figure 1.1.1 Kinetic Resolution Overview.



1.1.2 Nitroxyl Radicals in an Oxidative Kinetic Resolution of Secondary Alcohols

The first approach toward a kinetic resolution via alcohol oxidation involved the catalytic use of a nitroxyl radical, which formed an active *N*-oxoammonium species (**3**) under the reaction conditions. Rychnovsky reported the oxidative kinetic resolution of secondary alcohol **4** using chiral nitroxyl radical **5** and sodium hypochlorite as the oxidizing agent (Scheme 1.1.1).[3] Although modest selectivities were achieved (s = 1.5–7.1), this system represented the first example of a nonenzymatic catalytic enantioselective oxidation of secondary alcohols.

Scheme 1.1.1



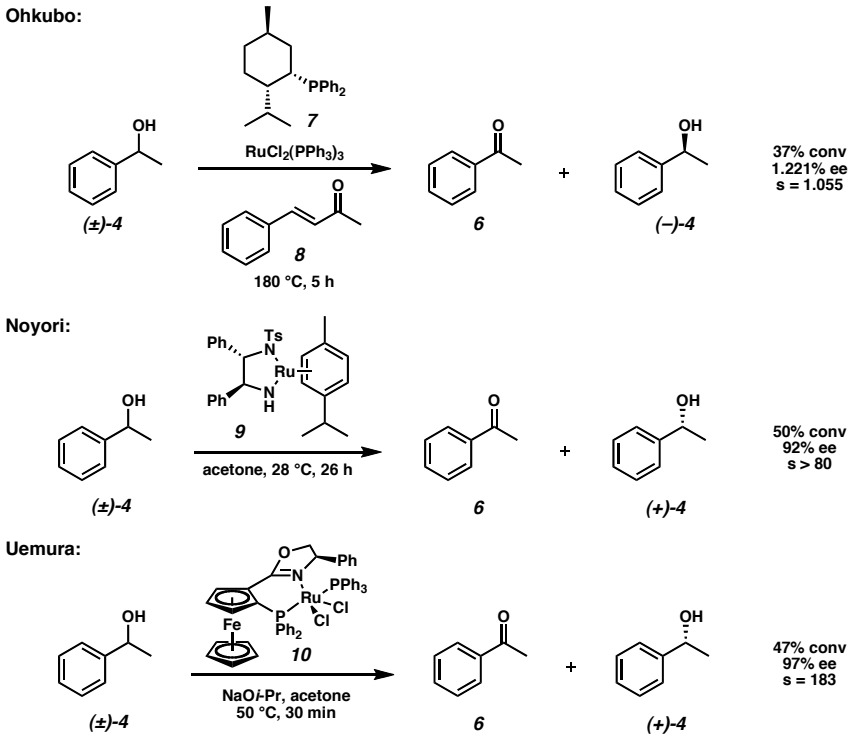
Even though improvements in enantioselectivity using this approach have been realized,[4] this methodology has not been used in the context of total synthesis.

1.1.3 Transition Metals in Oxidative Kinetic Resolutions of Secondary Alcohols

The other general approach to the oxidative kinetic resolution of secondary alcohols employs transition metal catalysis. The first report by Ohkubo et al.[5] validated the catalytic use of a transition metal in an oxidative kinetic resolution. The reaction proceeded by transfer hydrogenation using a menthol-derived phosphine (**7**) ligand to

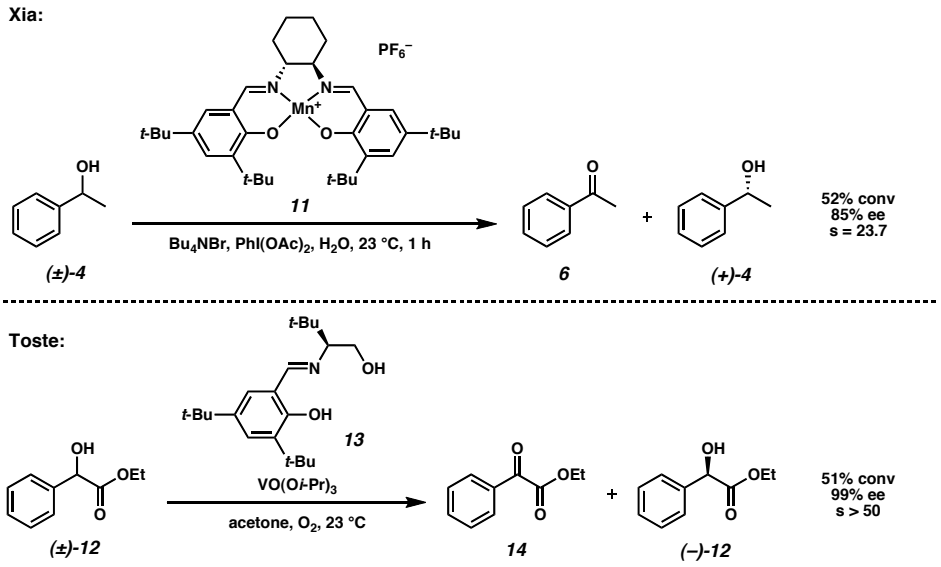
provide *sec*-phenethyl alcohol in 1.2% ee, and a selectivity factor (s) of 1.055 (Scheme 1.1.2). Since then, Noyori and Uemura have developed highly enantioselective variants of a ruthenium-catalyzed kinetic resolution of secondary alcohols. Noyori demonstrated the use of ruthenium-diamine catalyst **9** to resolve secondary alcohols with acetone as the hydrogen acceptor.[6] Uemura later reported a similar system using a ruthenium-ferrocenyloxazoline complex (**10**).[7] In both of these cases, a plethora of benzylic secondary alcohols were resolved to high enantiopurity with very high selectivity (s > 100). Furthermore, Ikariya has shown that iridium and rhodium are viable metal catalysts for the oxidative kinetic resolution of secondary alcohols. Using O_2 as the stoichiometric oxidant and Noyori's diamine ligand motif, Ikariya was able to access highly enantioenriched secondary benzylic alcohols with good selectivity factors (s > 10).[8]

Scheme 1.1.2



More recently, Xia initially reported an oxidative kinetic resolution of benzylic alcohols using a manganese-salen catalyst (**11**) and iodobenzene diacetate as the stoichiometric oxidant (Scheme 1.1.3).[9] It was later reported by Xia that changes in solvent and catalyst allowed for better selectivities for some substrates.[7b] In addition, Toste has described a vanadium catalyst using chiral salicylaldimine ligand **13** for the asymmetric oxidation of α-hydroxy esters.[10,11] High selectivities for an array of α-hydroxy esters were realized, although less-activated alcohols, such as benzylic alcohols, reacted poorly when exposed to this system.[12]

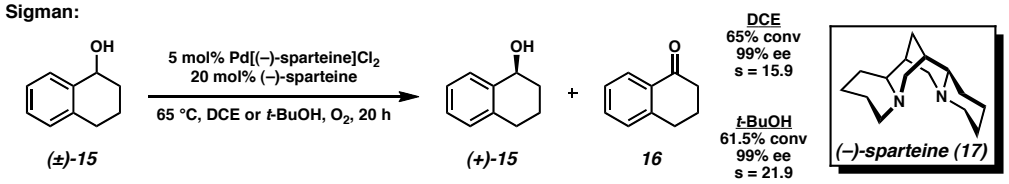
Scheme 1.1.3



In addition, Sigman published a system using (–)-sparteine (**17**) as the chiral ligand with $Pd(OAc)_2$ or $PdCl_2$,[13] and O_2 as the stoichiometric oxidant (Scheme 1.1.4). This system was optimized to use either dichloroethane (DCE) or *t*-butanol (*t*-BuOH) as solvent to obtain modest selectivities (generally s = 5–15) for a wide range of secondary alcohols.[14] Sigman has also shown that at lower catalyst loadings of (–)-sparteine (**17**), the rate-determining step is deprotonation of the alcohol. However, when 20 mol% of

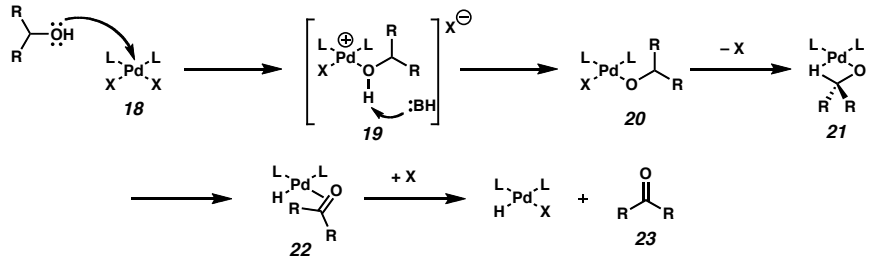
(–)-sparteine is used in the optimized conditions (Scheme 1.1.4), the rate-determining step is β-hydride elimination.[9c] Since β-hydride elimination is directly involved in enantioselectivity, slowing this step enhances the selectivity.

Scheme 1.1.4



In general, the oxidation of secondary alcohols to ketones by palladium(II) most likely involves associative alcohol substitution at the palladium(II) center (**18**), followed by deprotonation of the resulting palladium alcohol complex (**19**) by base to form palladium alkoxide **20** (Figure 1.1.2). At this stage, β-hydride elimination (**20**→**22**) and subsequent dissociation from palladium provides product **23**.

Figure 1.1.2 Proposed Mechanism for Alcohol Oxidation by Palladium.

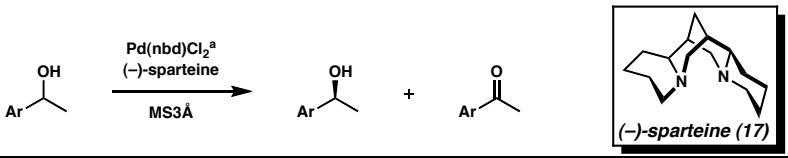


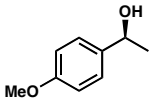
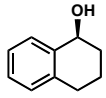
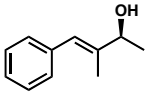
1.1.4 A Pd(II)-catalyzed Oxidative Kinetic Resolution Developed by the Stoltz Laboratory

In 2001, based on early work by Uemura,[15] the Stoltz laboratory developed a palladium(II)-catalyzed oxidative kinetic resolution utilizing (–)-sparteine as the chiral ligand and O_2 as the stoichiometric oxidant.

Since the initial development of the palladium(II)-catalyzed oxidative kinetic resolution of secondary alcohols using (–)-sparteine (**17**),[16] several improvements and further optimization to the catalytic system were accomplished. The palladium(II)-catalyzed oxidative kinetic resolutions can now be performed on a number of activated secondary alcohols to efficiently provide optically enriched secondary alcohols (Table 1.1.1).

Table 1.1.1 Oxidative Kinetic Resolution of Secondary Alcohols.



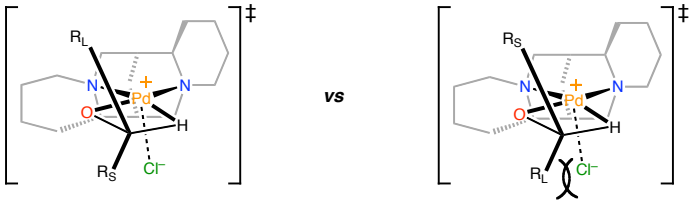
	Original [b] O_2, PhMe 80 °C	*Rate Accelerated* [c] O_2, PhMe, 60 °C Cs_2CO_3, *t*-BuOH	*Chloroform/O_2* [d] O_2, $CHCl_3$, 23 °C Cs_2CO_3	*Chloroform/Air* [e] Air, $CHCl_3$, 23 °C Cs_2CO_3
 *24*	96 h 67% conv 98% ee s = 12	9.5 h 67% conv 99.5% ee s = 15	48 h 63% conv 99.9% ee s = 27	24 h 62% conv 99.8% ee s = 25
 *25*	40 h 69% conv 98% ee s = 16	12 h 62% conv 99% ee s = 21	24 h 58% conv 98% ee s = 28	16 h 60% conv 99.6% ee s = 28
 *26*	120 h 70% conv 92% ee s = 6.6	12 h 65% conv 88% ee s = 7.5	48 h 63% conv 98.7% ee s = 18	44 h 65% conv 98.9% ee s = 16

[a] nbd = norbornadiene, s = selectivity factor, 500 mg, 3ÅMS/mmol substrate were used for all four sets of conditions. [b] 5 mol% palladium catalyst, 0.20 equiv (–)-sparteine (**17**), 0.10 M in PhMe. [c] 5 mol% palladium catalyst, 0.20 equiv (–)-sparteine (**17**), 0.50 equiv Cs_2CO_3, 1.5 equiv *t*-BuOH, 0.25 M in PhMe. [d] 5 mol% palladium catalyst, 0.12 equiv (–)-sparteine (**17**), 0.40 equiv Cs_2CO_3, 0.25 M in $CHCl_3$. Reactions were run open to air through a short drying tube of Drierite.

A model for selectivity in the palladium(II)-catalyzed oxidative kinetic resolution of secondary alcohols was developed by Dr. Raissa Trend, in collaboration with the Goddard laboratory, and is thoroughly discussed within her thesis.[17] The key conclusions from Trend's results are that (–)-sparteine is not behaving as a pseudo C_2 symmetric ligand; rather, it acts as a C_1 ligand allowing for selective displacement of a single

chloride from palladium. Furthermore, her results show that the displaced chloride ion, which has been calculated to be closely associated with palladium in an apical position under the square plane,[18] affects selectivity by clashing with one of the enantiomers of the substrate bound to palladium (Figure 1.1.3). It is thought that this is the main interaction that inhibits β-hydride elimination of one of the enantiomers.

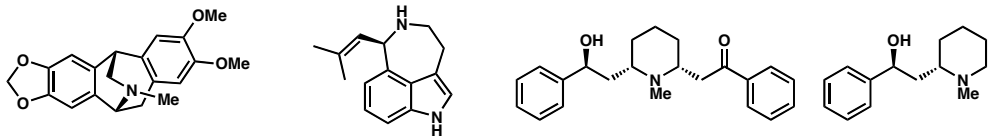
Figure 1.1.3 Proposed β-Hydride Elimination Transition State for Each Enantiomer.



fast-reacting enantiomer ***slow-reacting enantiomer***

To demonstrate the utility of this methodology, the Stoltz laboratory has completed the syntheses of (–)-amurensinine (**27**), (–)-aurantioclavine (**28**), (–)-lobeline (**29**), and (–)-sedamine (**30**) (Figure 1.1.4).[19] Each synthesis relied upon a palladium(II)-catalyzed oxidative kinetic resolution to establish a benzylic stereocenter in high enantioselectivity.

Figure 1.1.4 Natural Products Synthesized via Palladium(II)-catalyzed OKR.

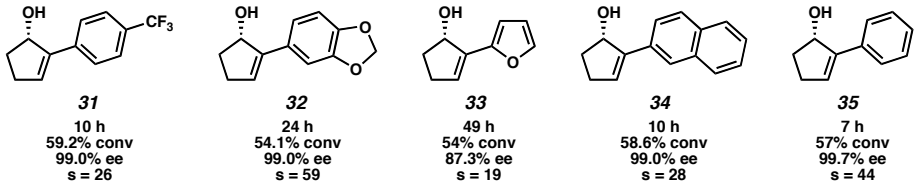


(+)-amurensinine (27) ***(–)-aurantioclavine (28)*** ***(–)-lobeline (29)*** ***(–)-sedamine (30)***

The scope of secondary alcohols used in the palladium(II)-catalyzed oxidative kinetic resolution currently includes activated alcohols bearing benzylic, allylic, or cyclopropyl substituents. One class of exceptional substrates for the palladium(II)-catalyzed oxidative kinetic resolution are 2-aryl cyclopentenols (Figure 1.1.5). Exposure

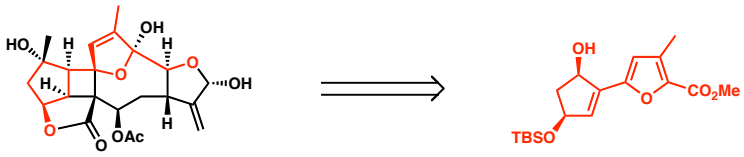
of these racemic alcohols to the original conditions (cf. Table 1.1.1) in the palladium(II)-catalyzed oxidative kinetic resolution provides cyclopentenols **31**–**35** with excellent enantioselectivity and selectivity factors (s).[20]

Figure 1.1.5 Enantioenriched 2-Aryl Cyclopentenols using the Original Conditions.



These substrates led us to examine several natural products bearing an allylic secondary alcohol for the application of this methodology toward further total syntheses. One such molecule was bielschowskysin (**36**) (Figure 1.1.6). We envisioned using the palladium(II)-catalyzed oxidative kinetic resolution to access a key alcohol intermediate (**37**) in high enantioselectivity.

Figure 1.1.6 Substrate for the Palladium(II)-catalyzed Ox. Kinetic Resolution.

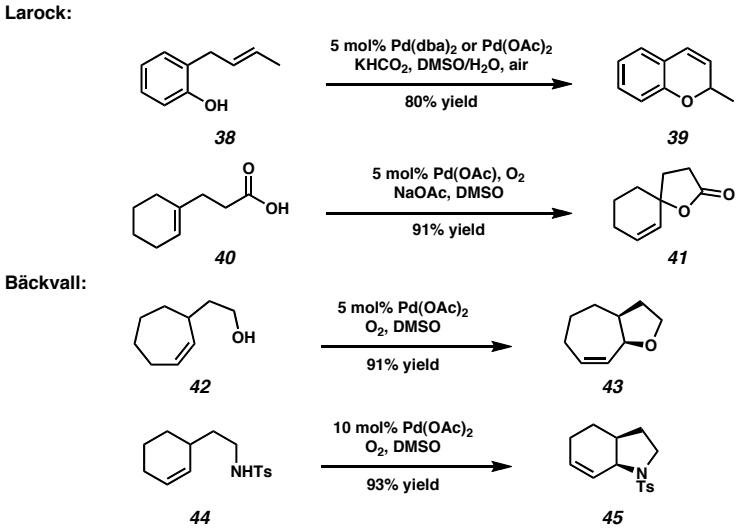


1.2 Introduction to Palladium(II)-Catalyzed Oxidative Heterocyclizations

1.2.1 Racemic and Enantioselective Pd(II)-catalyzed Oxidative Heterocyclizations

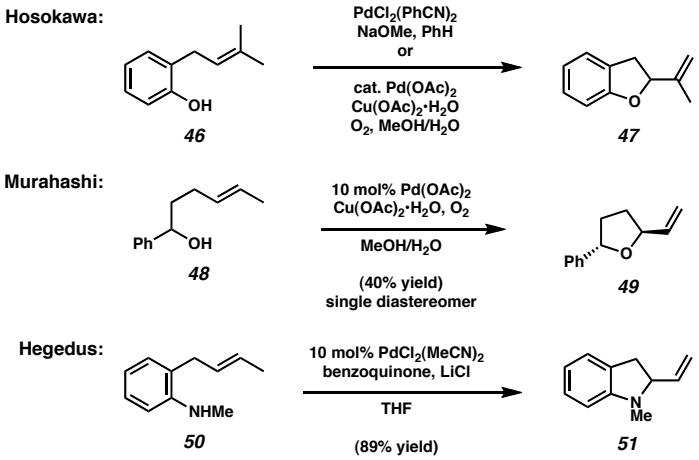
In the well-known Wacker process, $PdCl_2$ in the presence of O_2 and a copper cocatalyst oxidizes ethylene to acetaldehyde.[21] Although the Wacker process has been studied extensively, various aspects of its mechanism, such as the role of the chloride ion, are still disputed.[22] For over several decades now, it has been known that using palladium(II) complexes along with a variety of oxidants can catalyze simple Wacker-type cyclizations to provide racemic mixtures of products. Larock, Bäckvall, and others have demonstrated that palladium(II)-catalyzed oxidative heterocyclizations of olefin-appended nucleophiles provided racemic products using O_2 as the stoichiometric oxidant and DMSO as the solvent (Scheme 1.2.1).[23]

Scheme 1.2.1



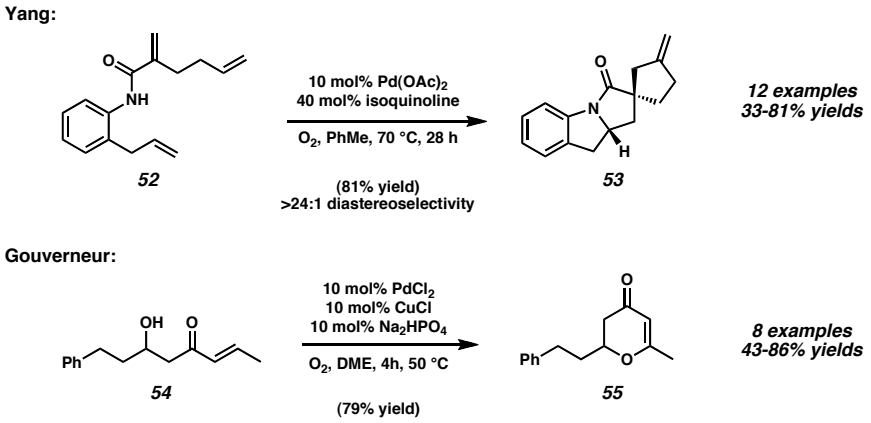
Furthermore, palladium(II)-catalyzed cyclizations have also been developed that use copper/O_2 and benzoquinone as the stoichiometric oxidants. In an early example, Hosokawa showed that stoichiometric palladium(II) could be used to cyclize olefin-appended phenols (Scheme 1.2.2), and that this methodology could be made catalytic in the presence of copper and O_2.[24] Other substrates, such as alcohols and amides, have been cyclized under similar conditions as demonstrated by Murahashi, Hegedus, and others.[25]

Scheme 1.2.2



More recent examples by Yang and Gouverneur highlight recent advances in palladium(II)-catalyzed oxidative heterocyclizations. Yang has reported an oxidative cascade cyclization using *N*-acyl anilines (**52**) to afford spirocycles (**53**) in high diastereoselectivity and good yield (Scheme 1.2.3).[26] In addition, Gouverneur has developed a palladium(II)-catalyzed oxidative cyclization of secondary alcohols (**54**) onto α,β-unsaturated olefins to provide 2,3-dihydro-4*H*-pyran-4-ones (**55**) in good yield.[27]

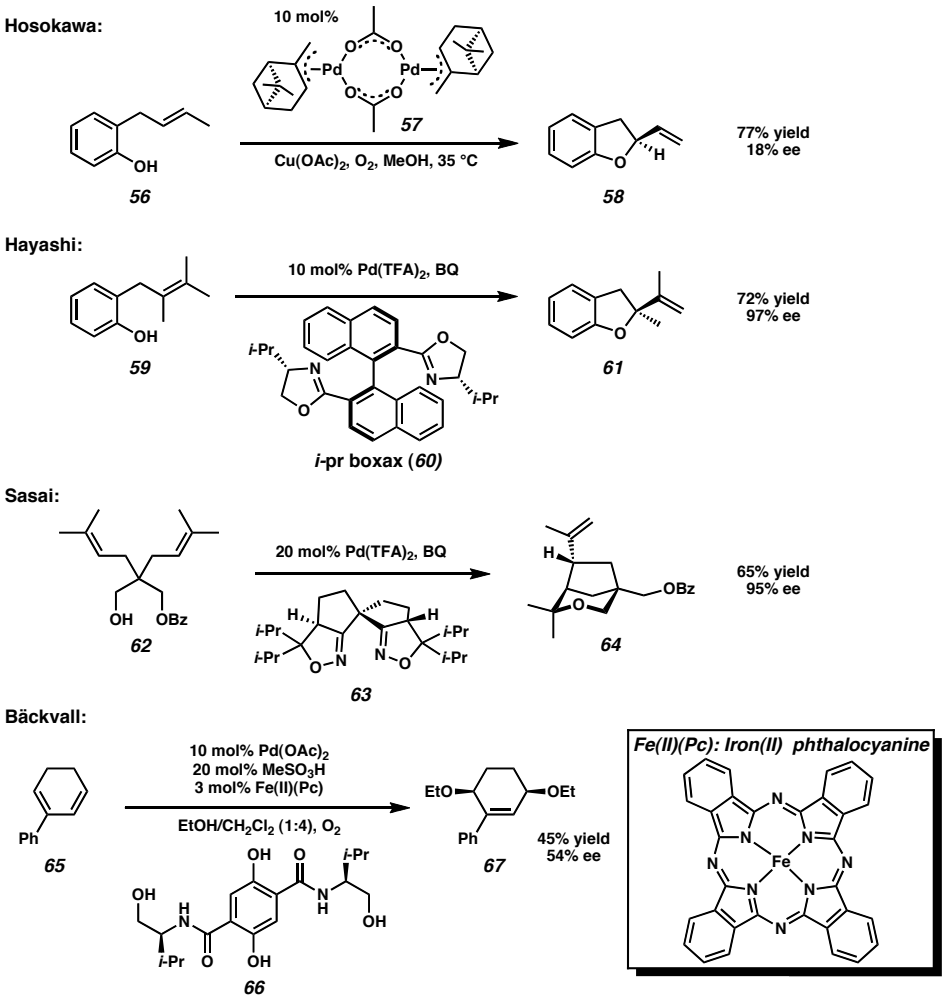
Scheme 1.2.3



Although all of these examples constitute significant advances in palladium(II)-catalyzed oxidative cyclization reactions, the conditions vary for different substrate types, and many do not meet the ideal conditions for asymmetric reactions. For example, the use of additives and co-oxidants such as $Cu(OAc)_2$ can create complex reaction conditions making optimization difficult. Furthermore, the use of highly coordinating solvents such as DMSO inhibits coordination of chiral ligands and thereby prevents the formation of any chiral palladium species necessary for an asymmetric process.

Despite these obstacles, several examples of asymmetric palladium(II)-catalyzed oxidative heterocyclizations have been reported (Scheme 1.2.4). In 1981, Hosokawa described an asymmetric oxidative cyclization with a pinene-derived palladium(II) complex (**57**).[28] More recently, Hayashi and Sasai have employed novel ligand frameworks (ligands **60** and **63**, respectively) and benzoquinone (BQ) as an oxidant to obtain cyclized products with high enantioselectivity.[29,30] In a proof-of-principle experiment by Bäckvall, a chiral benzoquinone generated in situ from arene **66** acted as a ligand in the enantioselective dialkoxylation of diene **65**.[31]

Scheme 1.2.4



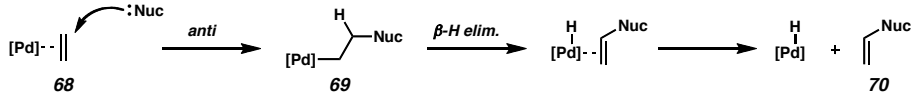
These examples established the potential for enantioselective palladium(II)-catalyzed oxidative heterocyclizations and dialkoxylations using benzoquinone oxidation systems. While these examples are limited in substrate scope, the examples by Sasai and Hayashi represent significant advances toward a general palladium(II)-catalyzed oxidative heterocyclization system.

1.2.2 Possible Mechanisms for the Pd(II)-catalyzed Oxidative Heterocyclization

Palladium(II)-catalyzed nucleophilic attack onto an olefin by a heteroatom can proceed by a variety of mechanisms. One key distinction to be made among them is whether attack occurs with the metal and nucleophile on the same face (syn, internal), or on opposite faces (anti, external) of the olefin. Another subtlety is whether π-allyl palladium(II) species are involved. This section will discuss some of the evidence that has been obtained for each mechanism.

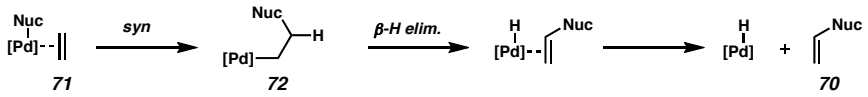
A commonly employed mechanism for palladium(II)-catalyzed oxidative heterocyclization initiates with activation of olefin **68** by palladium, followed by anti-nucleophilic attack (e.g., anti oxypalladation, Figure 1.2.1). The resulting palladium(II) alkyl intermediate (**69**) then undergoes β-hydride elimination to provide product **70**.

Figure 1.2.1 A Generic Heteroatom anti Palladation.



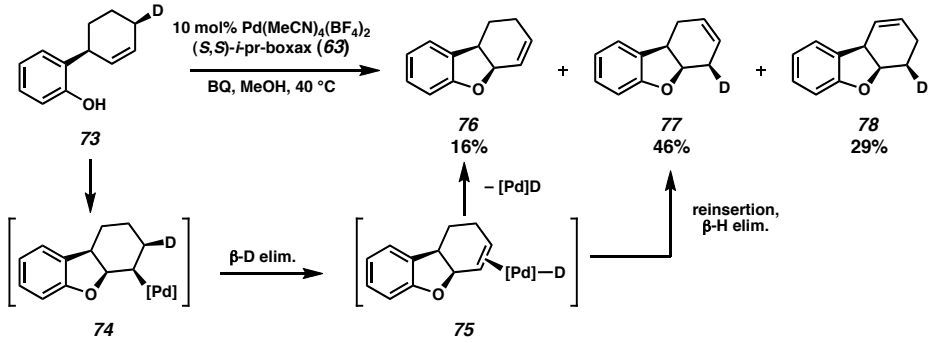
A second possible mechanism is heteroatom syn palladation (e.g., syn oxypalladation), which initially involves a nucleophile bound directly to palladium (**71**, Figure 1.2.2). The bond formed between nucleophile and olefin occurs internally via a migratory insertion, as well as on the same olefin face as the newly formed alkyl-palladium bond (**72**). At this stage, β-hydride elimination and ligand dissociation provides product **70**.

Figure 1.2.2 A Generic Heteroatom syn Palladation.



For evidence of syn oxypalladation, Hayashi and coworkers described the reaction of a stereospecifically deuterium-labeled phenol substrate (**73**) under their enantioselective conditions.[32] As shown in Scheme 1.2.5, after the oxypalladation step, the newly formed C-O bond, palladium, and deuterium are all syn to each other (**74**). Subsequent syn β-deuterium elimination (**74**→**75**) led to the initial product **76**. Compound **77** and olefin isomer **78** are also formed in the reaction as a result of olefin isomerization of product **76**. Nevertheless, all three products are consistent with syn oxypalladation. Interestingly, in the presence of excess chloride ion, anti oxypalladation predominated, which suggests that subtle changes in reaction conditions can have dramatic effects on the mechanism.

Scheme 1.2.5

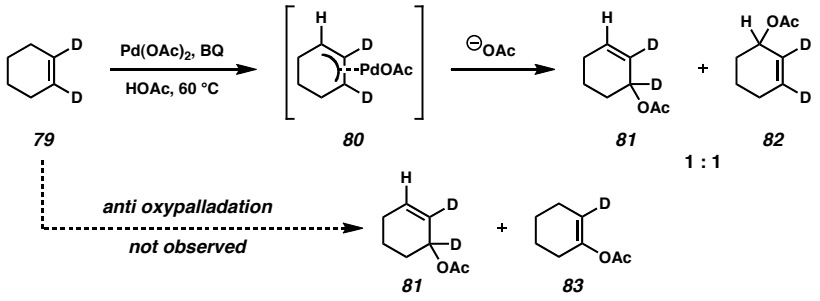


Further evidence of syn oxypalladation by Wolfe and coworkers shows that both oxygen and nitrogen nucleophiles can operate under this mechanism.[33]

Another potential reaction pathway for palladium-olefin cyclizations entails allylic C–H activation by palladium(II) to form an intermediate π-allyl species that would

then undergo reductive elimination with a heteroatom nucleophile. Trost has shown that $Pd(TFA)_2$ will form π-allyl complexes by C-H activation of olefins in acetone.[34] Experimental evidence for this pathway was shown in an intermolecular oxidative acetylation reaction of deuterium-labeled cyclohexene **79** (Scheme 1.2.6).[35] Bäckvall reported that the reaction yielded a 1:1 mixture of products **81** and **82**. This supports the intermediacy of π-allyl complex **80**, whereas anti oxypalladation would produce compound **81** and **83**.

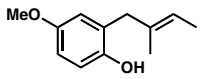
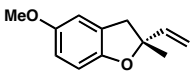
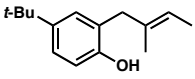
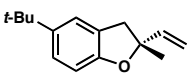
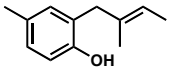
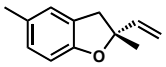
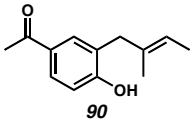
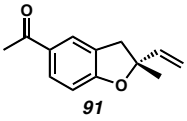
Scheme 1.2.6



1.2.3 A Pd(II)-catalyzed Oxidative Heterocyclization Developed by the Stoltz Laboratory

The Stoltz laboratory has developed an enantioselective palladium(II)-catalyzed oxidative phenol cyclization using palladium(II) catalysis with (–)-sparteine as the chiral ligand, to provide electron-rich dihydrobenzofurans in modest yield and good enantioselectivity (Table 1.2.1).[17c] Unfortunately, other substrates examined such as amines, anilines, and acids cyclize with only moderate enantioselectivity.

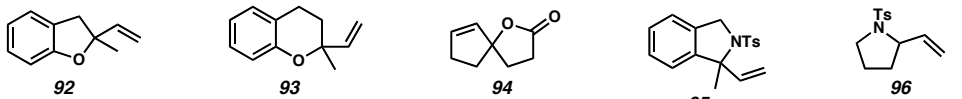
Table 1.2.1 Enantioselective Cyclization of Olefin-Appended Phenols.[a]

entry	substrate	product	time	yield[b]	ee[c]
1.	 **84**	 **85**	24 h 60 h @ 55 °C	64% 57%	88% 90%
2.	 **86**	 **87**	36 h	47%	83%
3.	 **88**	 **89**	36 h	47%	86%
4.	 **90**	 **91**	24 h	60%	20%

[a] 10 mol% (sp)Pd(TFA)$_2$, 100 mol% (–)-sparteine (**17**), 2.0 equiv Ca(OH)$_2$, 500 mg 3ÅMS/mmol substrate, 1 atm O_2, PhMe (0.10 M), 80 °C. [b] Isolated yield. [c] Measured by GC.

Accordingly, using a Pd(TFA)$_2$/pyridine/O_2 catalyst system, 3ÅMS in toluene at 80 °C, along with an exogenous base such as Na_2CO_3, a variety of heteroatom substrates cyclize to provide the desired products (**92**-**96**) in good yield (Figure 1.2.3). For some substrates, it was found that omitting Na_2CO_3 allowed for better conversion, probably due to variations of substrate pKa.

Figure 1.2.3 Heterocycles Accessed via a Pd(II)-catalyzed Oxidative Heterocyclization.



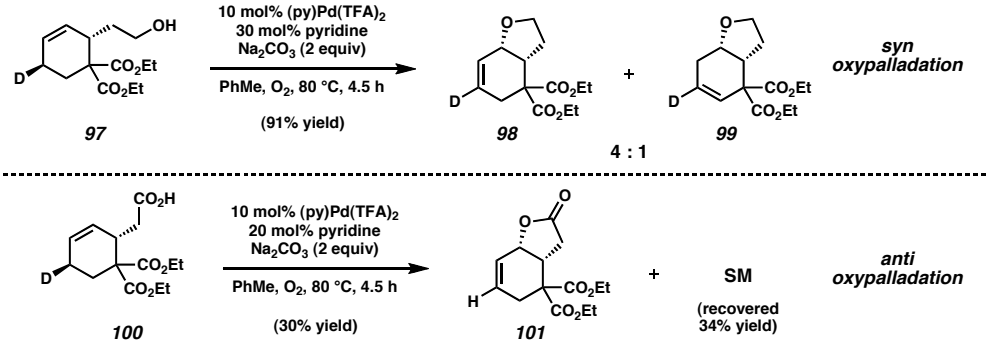
92 95% yield[a] **93** 85% yield[a] **94** 62% yield[c] **95** 88% yield[b] **96** 90% yield[b]

[a] mol% Pd(TFA)$_2$, 20 mol% pyridine, 2 equiv Na_2CO_3, 3ÅMS, 1 atm O_2, 0.10 M in PhMe, 80 °C. [b] 5 mol% Pd(TFA)$_2$, 20 mol% pyridine, 3ÅMS, 1 atm O_2, 0.10 M in PhMe, 80 °C. [c] 10 mol% Pd(TFA)$_2$, 40 mol% pyridine, 3ÅMS, 1 atm O_2, 0.10 M in PhMe, 80 °C.

In addition, further studies found that the mechanism for the palladium(II)-catalyzed oxidative heterocyclization changes between syn and anti heteroatom palladation depending on the substrate. Using deuterium-labeled substrates, it was found

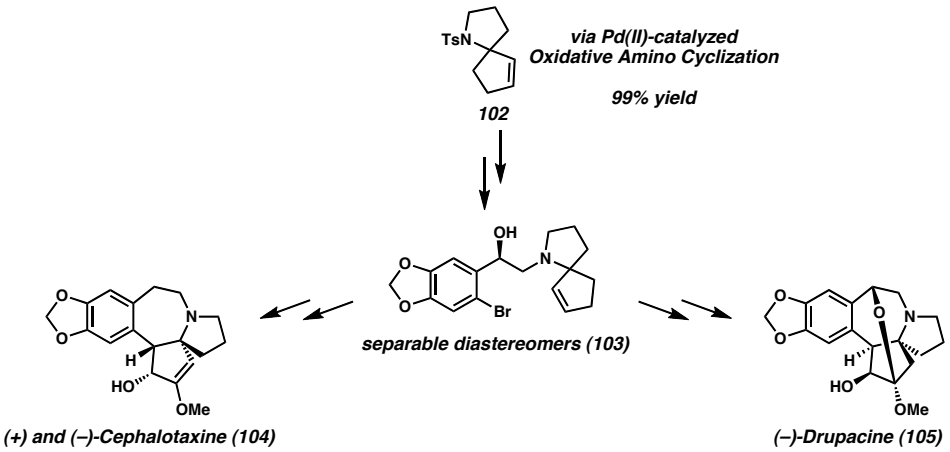
that alcohol **97** reacted via syn oxypalladation to provide tetrahydrofurans **98** and **99** in a 4:1 ratio, whereas acid **100** cyclized via anti oxypalladation to provide γ-lactone **101** (Scheme 1.2.7).[36] These changes in mechanism might be attributed to differences in the pKa of the two substrates (**97** and **100**); however, the exact reasons for the switch in mechanism has not been fully elucidated.[37]

Scheme 1.2.7



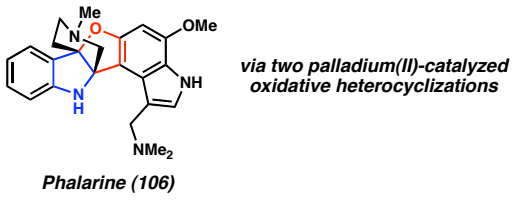
To demonstrate the application of this methodology in natural product synthesis, the Stoltz laboratory has completed the formal total synthesis of both enantiomers of cephalotaxine (**104**), as well as the asymmetric total synthesis of (–)-drupacine (**105**). All three were derived from intermediate **103**, which was accessed in excellent yield via a palladium(II)-catalyzed oxidative heterocyclization to form the spirocyclic amine moiety in intermediate **102** (Figure 1.2.4).[38]

Figure 1.2.4 Natural Products Synthesized via a Pd(II)-catalyzed Oxidative Heterocyclization.



The Stoltz laboratory is always searching for biologically active natural products that could be efficiently synthesized using developed group methodologies. For one such molecule, phalarine (**106**), we envisioned using two palladium(II)-catalyzed oxidative heterocyclizations to form the dihydrofuran (red) and dihydropyrrole (blue) rings respectively (Figure 1.2.5).

Figure 1.2.5 Structure of (–)-Phalarine.



This thesis will describe efforts toward an enantioselective total synthesis of bielschowskysin using a palladium(II)-catalyzed oxidative kinetic resolution to provide an enantioenriched early intermediate. Moreover, attempts toward the synthesis of phalarine using two palladium(II)-catalyzed oxidative heterocyclizations to construct the core of the natural product will also be discussed.

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[37] It was also shown that anilines can react via syn or anti aminopalladation depending on the ligand used. In one case, use of a bisoxazoline ligand resulted in product formation via syn aminopalladation, while use of pyridine as the ligand led to a 1:1 product mixture resulting from both syn and anti aminopalladation. See ref. 33b for further details.

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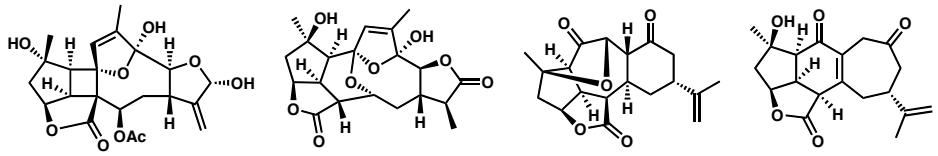
CHAPTER 2

Synthetic Efforts Toward Bielschowskysin Using a Palladium(II)-catalyzed Oxidative Kinetic Resolution

2.1 Introduction and Biosynthesis

In 2003, several novel natural products were isolated from the Caribbean gorgonian octocoral *Pseudopterogorgia kallos*. The structure of one of these compounds, bielschowskysin (**36**), eluded characterization until an X-ray crystal structure was obtained approximately one year later.[1] Bielschowskysin belongs to a sub-class of molecules called *pseudopteranes*, and is one of several structurally and biosynthetically related diterpenes (Figure 2.1.1).[2] Furthermore, bielschowskysin has been identified as a potent inhibitor of EKVX lung cancer cells (GI_{50} = 10 nM).

Figure 2.1.1 Bielschowskysin and Related Natural Products.



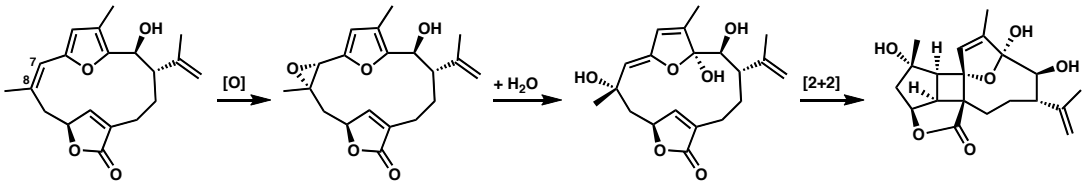
bielschowskysin ***verrillin*** ***ineleganolide*** ***scabrolide A***

36 ***107*** ***108*** ***109***

A characteristic feature of these molecules is a *cis*-fused [5,5] oxa-bicycle, as well as a dihydrofuran unit that is sometimes disguised as a 1,4 diketone moiety.[3] Bielschowskysin is arguably the most structurally complex member of this group due to its polycyclic ring system bearing eleven stereocenters, one of which is a quaternary stereocenter contained in a tetrasubstituted cyclobutane ring that is also fused to a substituted oxocane ring, resulting in a highly strained cage-like structure.[4]

Although the biosynthetic pathway of bielschowskysin has not been confirmed, Trauner has hypothesized that bielschowskysin is obtained from bipinnatin J (**110**) via a stereo- and chemoselective epoxidation of the $\Delta^{7,8}$ olefin (**110**), followed by the addition of water furan **111**, and subsequent [2+2] cycloaddition of intermediate **112** provides the cyclobutane core (**113**) (Scheme 2.1.1).[5]

Scheme 2.1.1

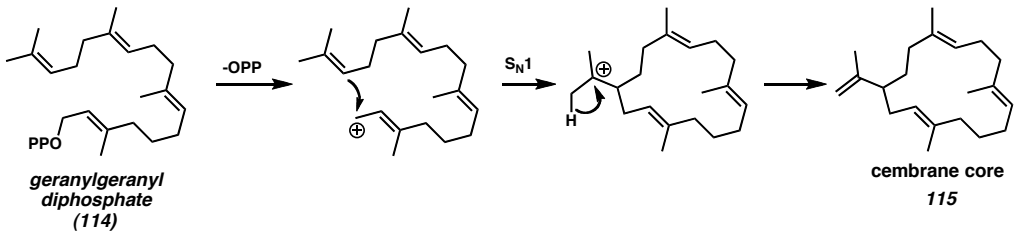


bipinnatin J (110) ***111*** ***112*** ***113***

Along with all of the molecules in Figure 2.1.1, bipinnatin J is also a member of the larger *cembranoid* class of natural products, which are biosynthesized by intramolecular S_N1 attack of geranylgeranyldiphosphate (**114**) and quenching of the

resultant tertiary carbocation to form the cembrane core (**115**) (Scheme 2.1.2). The cembrane core can undergo various enzymatic oxidations and transformations to provide an array of natural products.[6]

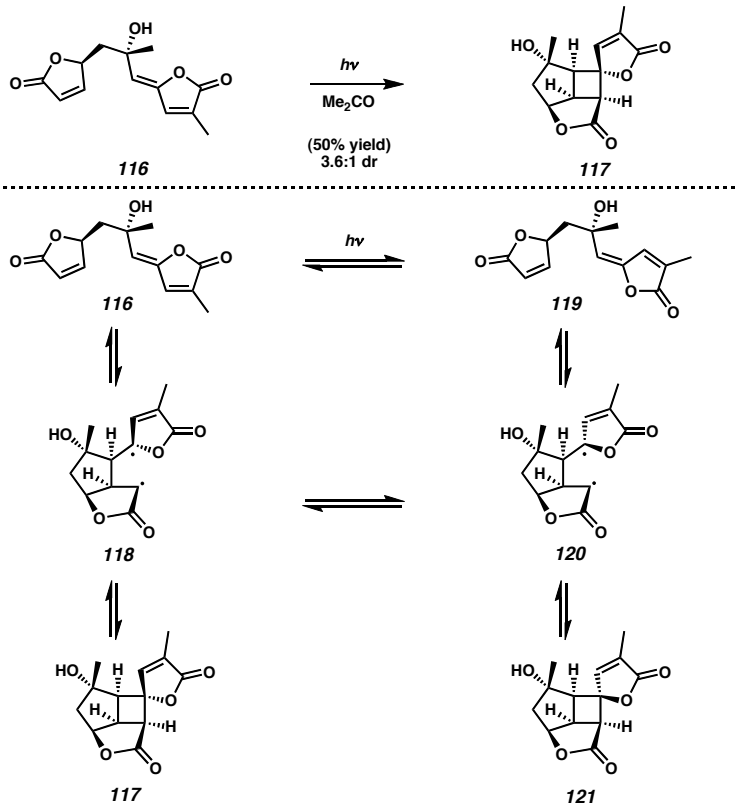
Scheme 2.1.2



2.2 Outside Efforts Toward the Total Synthesis of Bielschowskysin

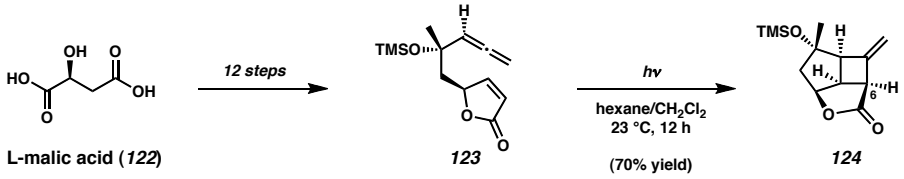
Although there are no reported total syntheses of bielschowskysin, there are two reported partial syntheses of the cyclobutane core found in the natural product. First, Doroh and Sulikowski subject alcohol **116** to a [2+2] photocycloaddition providing cyclobutane **117** in 50% yield with a 3.6:1 diastereomeric ratio (Scheme 2.2.1).[7] It is thought that this reaction occurs through an unobserved diradical intermediate **118**, which then proceeds to form cyclobutane **117**. The diastereoselectivity of this reaction is notable in consideration of the observed isomerization of alcohol **116** to isomer **119** under the reaction conditions. Additionally, possible σ-bond rotation of diradical intermediate **118** to its diasterotopic isomer **120**, which could also be formed from allylic alcohol **119**, could lead to the undesired diastereomer **121**.[8]

Scheme 2.2.1



A second approach, reported by Lear and coworkers, uses a similar method to form the core cyclobutane via photocylcoaddition of allene **123** (Scheme 2.2.2).[9] The synthesis of allene **123** is accomplished in twelve steps beginning with commercially available L-malic acid (**122**). Treatment of allene **123** with UV light in a nonpolar co-solvent provides the desired *exo*-cyclobutene **124** in 70% yield.

Scheme 2.2.2



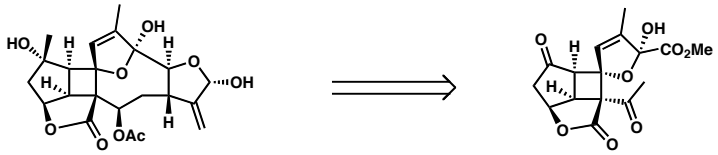
Although these partial syntheses provide access to the strained cyclobutane found in bielschowskysin, they do not address the formation of either the critical C(6)

quaternary stereocenter or the pendant oxocane ring. As such, a [2+2] cycloaddition to form the quaternary stereocenter on a larger system bearing these components would not be without significant challenges. While a well-organized transition state might be feasible via an enzymatic pathway, practical synthetic limitations encouraged us to envision forming bielschowskysin by other methods such as an aldol condensation or Michael addition.

2.3 Retrosynthesis: Use of a Cyclopropane to Access the Cyclobutane Core

While planning an initial synthetic route to bielschowskysin (**36**), a suitable model system was designed to investigate the key formation of the cyclobutane core and the quaternary stereocenter. Hence, our first synthetic target was cyclobutane **125** (Figure 2.3.1). Unlike the previous partial syntheses, this model system includes the quaternary stereocenter found in the natural product.

Figure 2.3.1 Model System for Studies Toward Bielshowskysin's Cyclobutane Core.

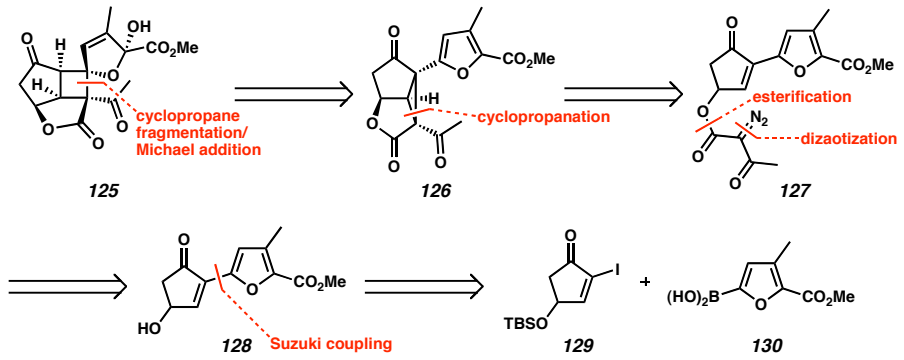


bielschowskysin (36) ***125***

Thus, we predicated our synthetic strategy upon the formation of cyclobutane **125** via a Lewis acid–mediated cyclopropane fragmentation of ketone **126**, followed by a 1,4 Michael addition (Scheme 2.3.1). We envisioned cyclopropane **126** arising from α-diazo-β-ketoester **127** by a cyclopropanation reaction using either a copper or rhodium

catalyst. In turn, α-diazo-β-ketoester **127** can be obtained from allylic alcohol **128** via esterification and diazotization. The latter compound, alcohol **128**, can be prepared via Suzuki coupling between iodide **129** and boronic acid **130**. Moreover, we postulated that allylic alcohol **128** could lead to a suitable substrate for a palladium(II)-catalyzed oxidative kinetic resolution to provide a secondary alcohol in high enantioselectivity, thus, providing access to an enantioselective synthesis of bielschowskysin.

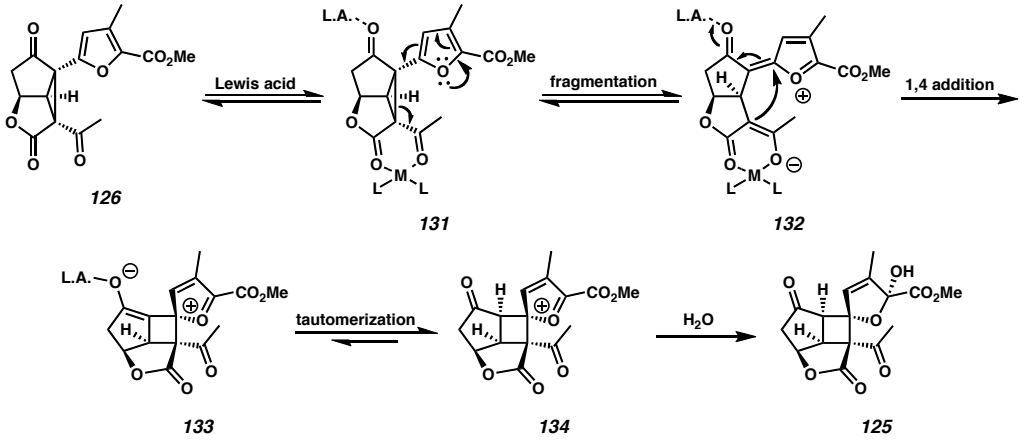
Scheme 2.3.1



The proposed key step in our synthesis of cyclobutane **125** is a Lewis acid–mediated cyclopropane fragmentation resulting in an enolate and an enone. We envision that these species will react via a Michael addition to provide the cyclobutane moiety (Figure 2.3.2). Complexation of the Lewis acid to the β-ketoester in compound **126** will lead to weakening of the bridging σ-bond of the cyclopropane ring shown in intermediate **131**. Lone pair donation by the furan will result in fragmentation to form a stabilized enolate **132**. The latter bond cleavage is preferred for two reasons: first, fragmentation of the most strained bond will relieve ring strain and lower the overall energy of the molecule; second, the π^* orbitals of the β-ketoester moiety have good overlap with the breaking C–C σ-bond, leading to favorable enolate generation. Following fragmentation, 1,4-addition produces cyclobutane **133**, which can undergo

rapid tautomerization to provide charged species **134**, followed by the addition of water to furnish dihydrofuran **125**.[10]

*Figure 2.3.2 Proposed Mechanism for the Formation of Cyclobutane **125**.*

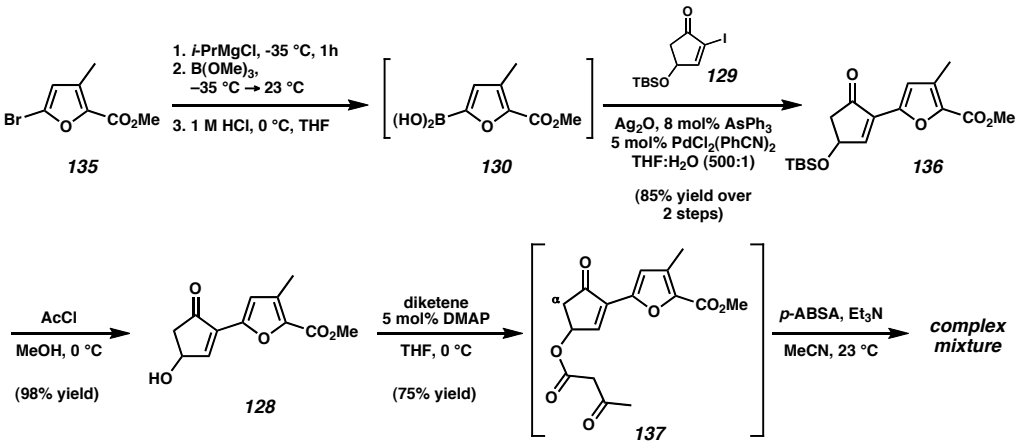


2.4 Initial Synthetic Efforts

The synthesis began with furan **135**,[11] which underwent magnesium-halogen exchange using conditions developed by Knochel,[12] followed by a sequential quench of trimethyl borate and 1 M HCl to furnish boronic acid **130** in 85% yield (Scheme 2.4.1). Coupling of enone **129** with boronic acid **130** under similar conditions reported by Johnson provided compound **136** in excellent yield.[13,14] At this stage, cleavage of the TBS group under acidic conditions provided allylic alcohol **128** in 98% yield. Exposure of allylic alcohol **118** to diketene and a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) afforded unstable β-ketoester **137**. Unfortunately, immediate treatment of β-ketoester **137** with *p*-ABSA and Et_3N did not yield the desired diazo product; instead, a complex mixture of byproducts was obtained. This mixture of byproducts is the likely result of a Michael addition by the β-ketoester moiety, as well as

subsequent deprotonation at C(α) followed by β-elimination of the carboxylate functionality.

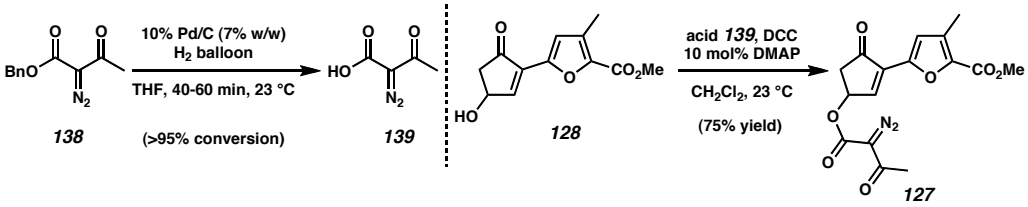
Scheme 2.4.1



To circumvent this problem, we postulated that the diazotization of β-ketoester **137** should be examined under neutral conditions. Moreover, we realized that the previous step, the synthesis of β-ketoester **137**, is accomplished in a neutral environment. These observations led us to consider 2-diazoacetoacetic acid as an amenable partner in a DCC coupling reaction with allylic alcohol **128**.[15]

The synthesis of 2-diazoacetoacetic acid (**139**) was carried out from α-diazobenzylacetoacetate (**138**)[16] by facile hydrogenolysis of the benzyl group, which provided the desired product along with a minor amount of acetoacetic acid in >95% conversion and purity.[17] To our delight, the planned DCC coupling reaction between 2-diazoacetoacetic acid (**139**) and alcohol **128** occurred in a straightforward manner to furnish targeted enone **127** in 75% yield (Scheme 2.4.2).

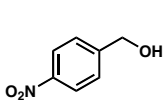
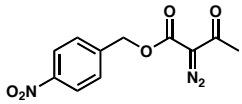
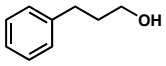
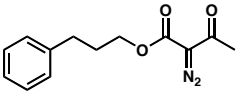
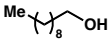
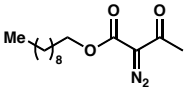
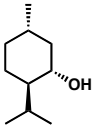
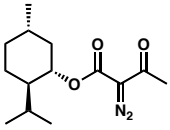
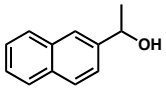
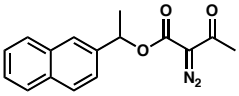
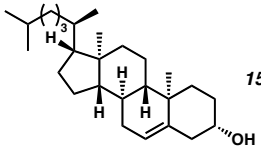
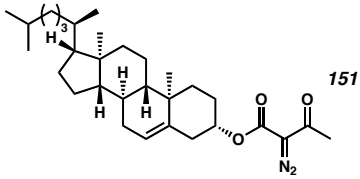
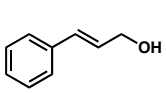
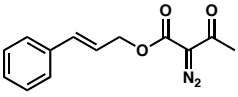
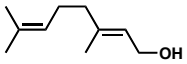
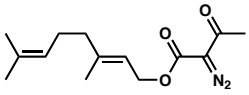
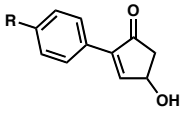
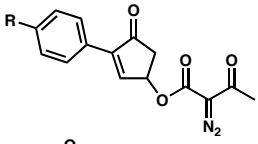
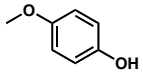
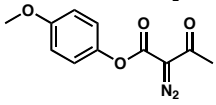
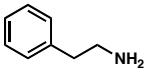
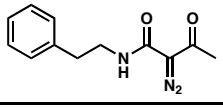
Scheme 2.4.2



The generation and coupling of 2-diazoacetoacetic acid (**139**) with allylic alcohol **128** was crucial for the synthesis of enone **127**, as these conditions minimized the risk of side reactions, and simplified the standard two-step procedure. With this more efficient route to enone **127**, we next investigated the esterification of 2-diazoacetoacetic acid (**139**) with a number of heteroatom nucleophiles to test the generality of this reaction and compare it with the two-step standard method.

Gratifyingly, esterification of 2-diazoacetoacetic acid occurs efficiently for a variety of alcohols (Table 2.4.1). Primary and secondary alcohols couple with acid **139** in good to excellent yields (entries 1-6). Allylic alcohols are also competent substrates, and lead to their respective α-diazo-β-ketoesters in good yields (entries 7-10).[18] As shown in entry 11, phenols are also viable substrates in the coupling reaction. Furthermore, the coupling of acid **139** with phenethylamine (**162**) to produce the α-diazo-β-ketoamide **163** in 95% yield illustrates that amines are also tolerated under these conditions (entry 12).[19]

*Table 2.4.1 Esterification of 2-diazoacetoacetic acid (**139**) with Heteroatom Nucleophiles.*

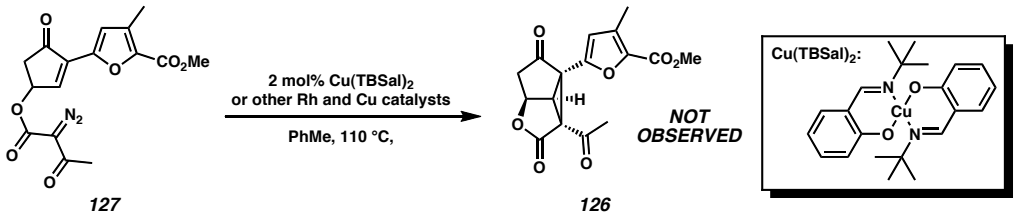
Entry	Substrate[a]		Product		Yield[b]
1		*140*		*141*	92
2		*142*		*143*	85
3		*144*		*145*	80
4[d]		*146*		*147*	77
5[d]		*148*		*149*	81
6[d]		*150*		*151*	87
7		*152*		*153*	82
8		*154*		*155*	77
9[c,d]		*R = H* *156*		*R = H* *157*	95
10		*R = NO₂* *158*		*R = NO₂* *159*	77
11[d]		*160*		*161*	75
12		*162*		*163*	95

[a] Standard conditions: 0.50 mmol substrate, 2-diazoacetic acid (**139**, 2.2 equiv), DCC (2.0 equiv), DMAP (0.10 equiv), 3.30 mL CH_2Cl_2, 23 °C, 60–90 min. [b] Isolated yield. [c] 0.30 mmol substrate. [d] Reaction at 40 °C, 60–90 min.

With our study of 2-diazoacetoacetic acid couplings complete, our attention returned to enone **127**, and we began to investigate its ability to undergo

cyclopropanation. We initiated our studies with $Cu(TBSal)_2$ as the catalyst because it has proven to be a robust catalyst system for cyclopropanation in similar systems.[20] Unfortunately, when enone **127** was treated with a variety of rhodium and copper catalysts, including $Cu(TBSal)_2$, cyclopropane **126** was never observed (Scheme 2.4.3).[21] In searching the literature, no examples of an α-diazo-β-ketoester undergoing cyclopropanation with an enone were found. Therefore, we hypothesized that the enone functionality contributed to a withdrawal of electron density from the olefin, and thus inhibited cyclopropanation.

Scheme 2.4.3

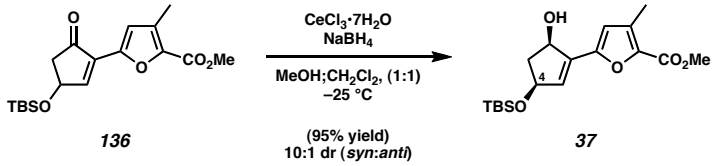


127 *126*

Following these initial cyclopropanation studies, we elected to modify the synthesis by reducing the ketone functionality in compound **136** (Scheme 2.4.1). We hypothesized that this would increase the electron density and the corresponding nucleophilicity of the olefin to facilitate cyclopropanation. Furthermore, 1,2-reduction of the enone functionality in compound **136** would provide the necessary substrate (**37**) with which to explore the palladium(II)-catalyzed oxidative kinetic resolution.

The synthesis of alcohol **37** is accomplished from enone **136** via a Luche reduction in high yield and excellent diastereoselectivity (Scheme 2.4.4).[22] The observed diastereoselectivity in this reduction is attributed to the bulky siloxy moiety at C(4), that likely prevents the approach of the hydride species from the β-face.[23]

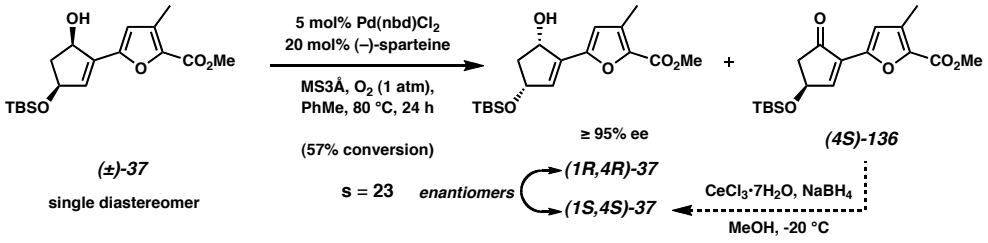
Scheme 2.4.4



2.5 The Palladium(II)-catalyzed Oxidative Kinetic Resolution

As stated previously, we envisioned using the palladium(II)-catalyzed oxidative kinetic resolution as a method to establish the absolute stereochemistry of the C(4) stereocenter that is present in alcohol **37**. Thus, with allylic alcohol **37** in hand, we examined the palladium(II)-catalyzed oxidative kinetic resolution. To our delight, treatment of racemic alcohol **37** under the original conditions developed for the palladium(II)-catalyzed oxidative kinetic resolution furnished ketone **136** in 57% conversion, and more importantly, afforded enantioenriched alcohol **37** in ≥ 95% ee and high selectivity for the overall process (s = 23, Scheme 2.5.1).[24]

Scheme 2.5.1

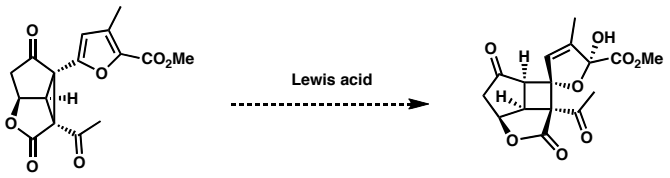


Furthermore, the opposite enantiomer of alcohol can be obtained by treating (4*S*)-enone **136** under the previously optimized Luche conditions to provide (1*S*, 4*S*)-alcohol **37** (Scheme 2.5.1).[25] Since the absolute configuration of bielschowskysin is unknown, accessing both enantiomers of alcohol **37** in this fashion is important as it provides a route to potentially synthesize either enantiomer of the natural product.

2.6 Further Investigations into the Model System

Given the success of the critical palladium(II)-catalyzed oxidative kinetic resolution, our efforts were now solely focused on the synthesis of intermediate **126** and subsequent investigation into the formation of cyclobutane **127** (Scheme 2.6.1).

Scheme 2.6.1

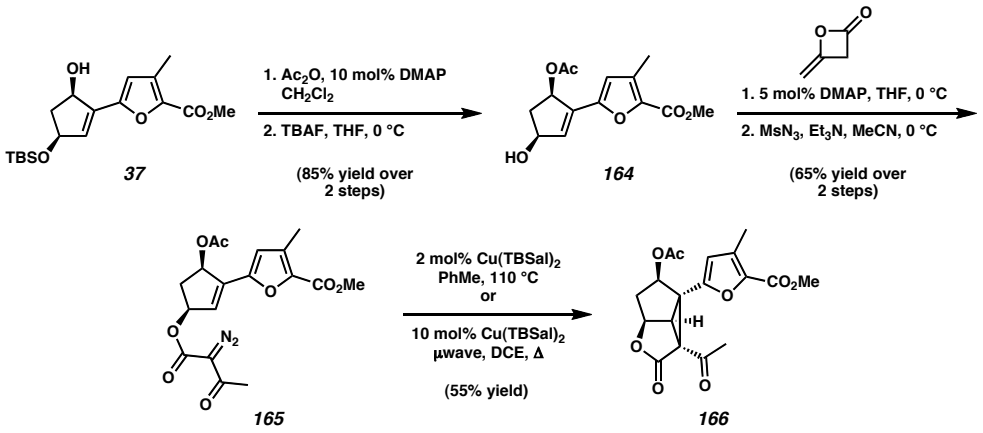


126 ***125***

Beginning with furan **37**, acetate protection of the alcohol and subsequent cleavage of the silyl ether unveiled allylic alcohol **164** in 85% overall yield (Scheme 2.6.2). The latter compound underwent esterification with diketene and subsequent diazotization to furnish α-diazo-β-ketoester **165** in good overall yield. Although the synthesis of compound **165** could be accomplished by coupling of alcohol **37** with 2-diazoacetoacetic acid (**139**), the traditional two-step procedure ultimately proceeded in overall higher yield in this case. Initially, attempts to form the cyclopropane ring using rhodium catalysts, such as $Rh_2(oct)_4$, did not provide any of the desired product. Furthermore, the use of various copper sources, such as copper bronze or $Cu(acac)_2$, led only to trace amounts of the desired product. Gratifyingly, formation of the cyclopropane was accomplished using 2 mol% $Cu(TBSal)_2$ in either refluxing toluene or heating in a microwave using 1,2-dichloroethane as solvent to provide cyclopropane **166** in 55% yield. In general, the microwave conditions furnished cleaner reactions and more consistent yields during the scale-up process. In obtaining cyclopropane **166**, we verified

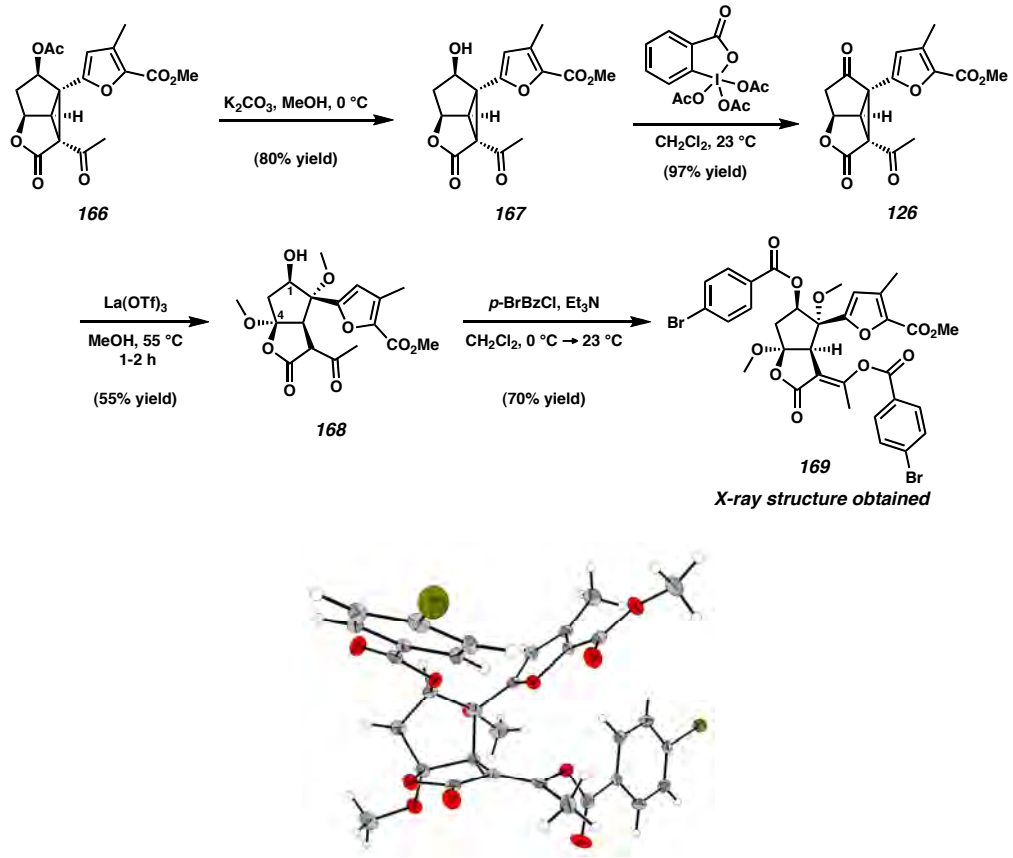
our hypothesis that the olefin in enone **136** was simply too electron deficient to undergo cyclopropanation.

Scheme 2.6.2



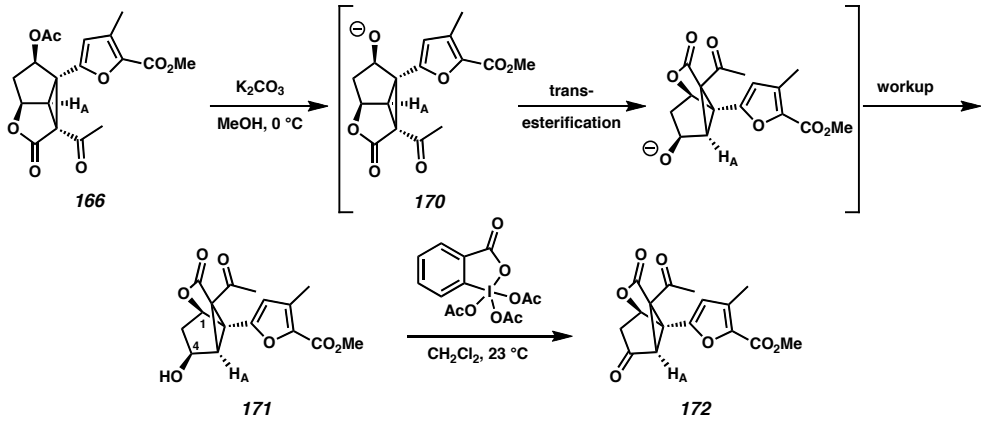
Although the synthesis of cyclopropane **166** was a significant accomplishment, this intermediate still needed to be elaborated to ketone **126**. Initially, it was thought that cyclopropane **166** would undergo acetate cleavage to provide alcohol **167**, followed by Dess-Martin periodinane oxidation to arrive at ketone **126** (Scheme 2.6.3).[26] Gratifyingly, when cyclopropane **166** was subjected to these conditions, the desired ketone (**126**) appeared to be obtained in high overall yield. We next investigated the Lewis acid–mediated cyclopropane fragmentation and subsequent Michael addition en route to cyclobutane **125**. Initial screening with several lanthanide Lewis acids found that treatment of ketone **126** with $La(OTf)_3$ in methanol at 55 °C provided one product (**168**) as a single diastereomer in a 55% yield (unoptimized). Unfortunately, we were unable to confirm the structure of compound **168** by NMR; thus, we chose to esterify compound **168** to yield compound **169** in 79% yield. This enabled us to grow crystals of compound **169** suitable for analysis by X-ray crystallography. To our dismay, the X-ray data showed the structure of an unexpected product, β-ketoester **168**.

Scheme 2.6.3



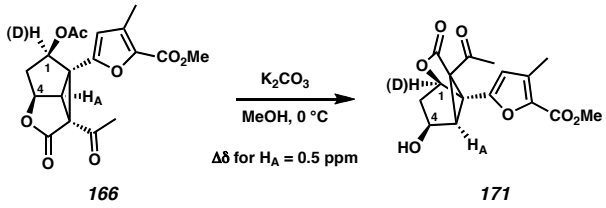
Upon examination of the connectivity of β-ketoester **169**, we noticed that the oxidation states of C(1) and C(4) were opposite to those of desired ketone **126**. This is the likely result of an undesired trans-esterification reaction that occurs when cyclopropane **166** undergoes acetate cleavage (Scheme 2.6.4). Treatment of cyclopropane **166** with K_2CO_3 in methanol presumably provided alkoxide **170**. This alkoxide could potentially undergo a trans-esterification reaction and protonation to form alcohol **171**. Finally, treatment of alcohol **171** with Dess-Martin periodinane provided α-cyclopropyl ketone **172**, which was originally misassigned as ketone **126**.

Scheme 2.6.4



To confirm this undesired rearrangement, we partially incorporated deuterium at C(1), allowing us to follow the chemical shifts of the protons on both C(1) and C(4) during the course of acetate removal (Scheme 2.6.5). As hypothesized, the C(1) proton of intermediate **166** underwent a downfield shift in the ^{1}H NMR, while the C(4) proton exhibited a slight upfield shift. Furthermore, cyclopropyl proton H_A exhibits a 0.50 ppm shift that we have attributed to conformational changes that result from trans-esterification.[27] These results confirmed that the trans-lactonization reaction did in fact occur during acetate removal.

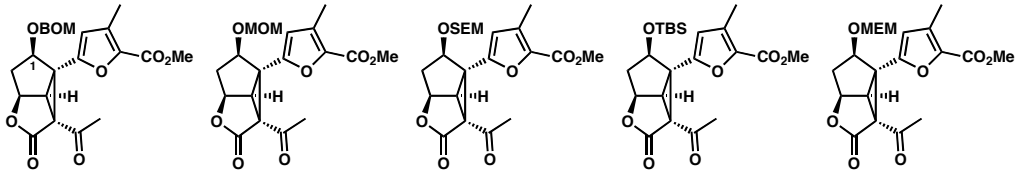
Scheme 2.6.5



In an effort to circumvent the trans-lactonization reaction, we synthesized a variety of compounds similar to cyclopropane **166** that differed only in the hydroxyl protecting group at C(1) (Figure 2.6.2).[28] We postulated that these protecting groups may be removed under conditions that suppress the formation of alcohol **171**. Unfortunately,

all attempts to deprotect compounds **173–177** in Figure 2.7.2 led solely to undesired alcohol **171**. This result led us to conclude that the undesired lactone (**171**) is likely the thermodynamic product.[29]

Figure 2.6.2 Various Cyclopropane Derivatives.

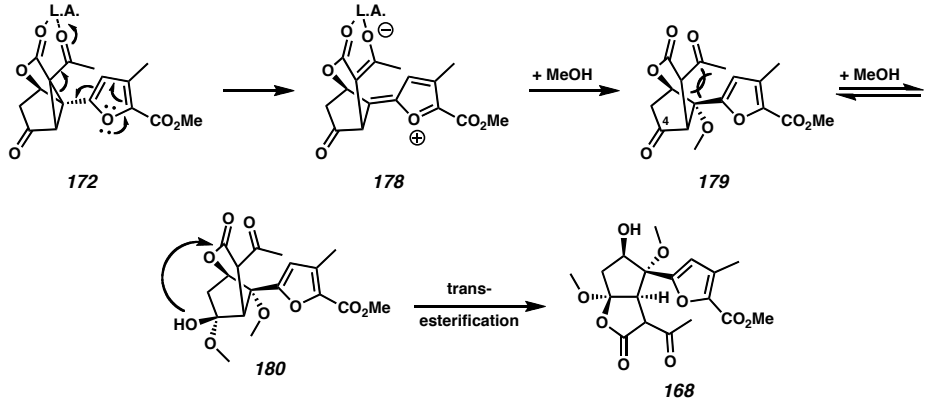


173 ***174*** ***175*** ***176*** ***177***

Other interesting observations can be made from the Lewis acid–mediated fragmentation reaction of cyclopropyl ketone **172** to provide unexpected alcohol **168** (Scheme 2.6.3). Beginning with ketone **172** in Scheme 2.6.6, we believe that Lewis acidic activation weakens the cyclopropane ring to allow the furan ring to assist in fragmentation to form an enolate and extended oxocarbenium ion in intermediate **178**, both of which are quenched respectively by the overall addition of methanol to provide ketone **179**.[30] Thus, fragmentation of the cyclopropane ring occurred as anticipated; however, the addition of methanol preserved the aromaticity in the furan ring rather than undergoing a 1,2-addition into the oxocarbenium ion. We hypothesized that the driving force for the observed chemoselectivity in the methanol addition is due to rearomatization. Furthermore, under these conditions, an additional molecule of methanol can add into ketone **179** from the less-hindered α-face to form a hemiketal at C(4), which in turn, can undergo trans-esterification to produce alcohol **168**. Notably, formation of the hemiketal at C(4) can occur at any point in the reaction; however, *trans-esterification to generate the fused lactone is not favorable until the cyclopropane ring undergoes fragmentation.* Another possible reason for the trans-esterification in Scheme

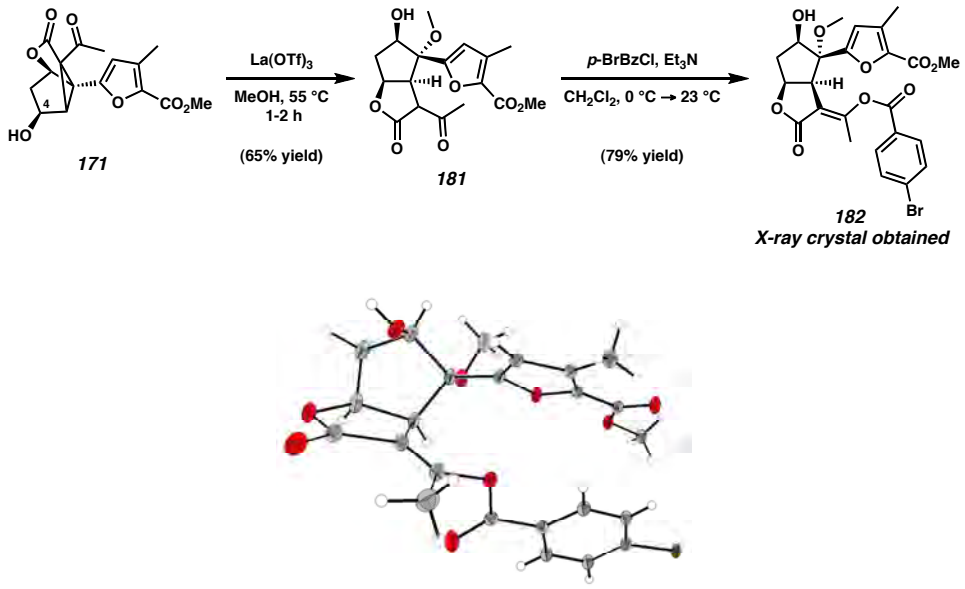
2.6.6 is the increased steric interaction that the bridged lactone in compound **179** would sustain with the furan moiety, compared to the fused lactone in alcohol **168**.

Scheme 2.6.6



To examine our hypothesis of trans-esterification, we subjected compound **171** to identical Lewis acidic conditions that resulted in the formation of alcohol **181** in 65% yield as a single diastereomer (Scheme 2.6.7). Alcohol **181** can undergo subsequent functionalization to provide compound **182**, allowing for suitable X-ray analysis (Figure 2.6.3). We initially believed that the hemiketal in intermediate **180** might force the alcohol into a pseudo-axial position and promote trans-esterification. However, by forming alcohol **181** without the ability for ketalization, we have shown that trans-esterification is facile once the cyclopropane ring has fragmented, regardless of the C(4) oxidation state.

Scheme 2.6.7



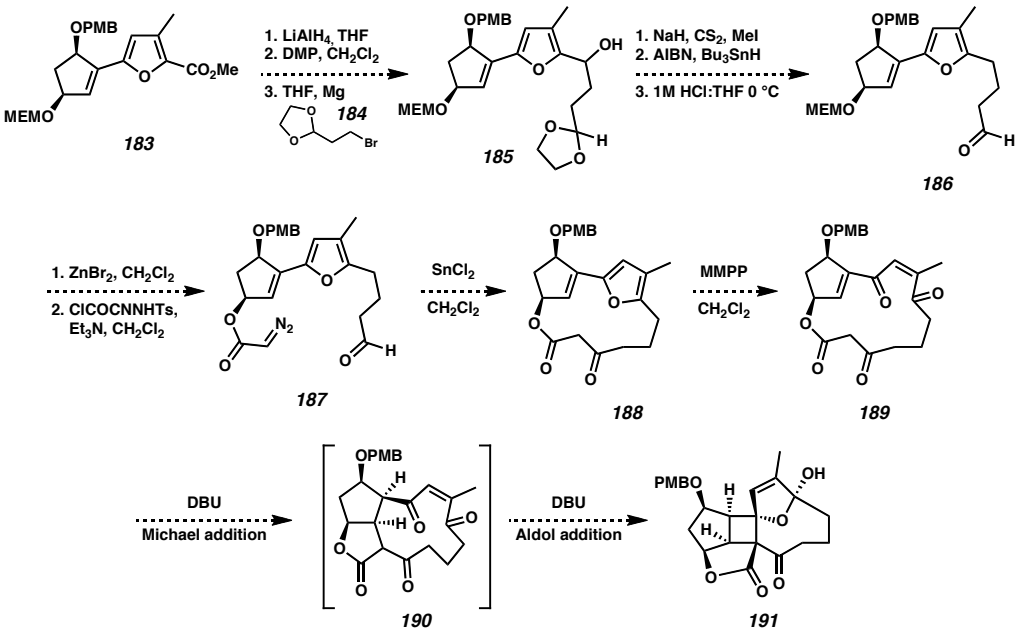
2.7 Future Directions

Since the formation of alcohol **171** could not be averted, we decided to evaluate an alternative synthetic strategy focusing on initial construction of a macrocyclic intermediate.[31] By beginning with macrocycle **188** (Scheme 2.8.1), we can reinforce chemo- and diastereoselectivity later in the synthesis. We believe there are at least two possible routes that could provide the cyclobutane core and the substituted oxocane ring found in bielschowskysin. The first route relies on a Michael addition and subsequent aldol reaction to provide the cyclobutane core, while the second route employs a reduction of an intermediate cyclopropane ring followed by a similar aldol addition to arrive at the highly strained core.[32]

We believe that ester **183** in Scheme 2.7.1 would serve as an excellent starting point since the enantio- and diastereoselective syntheses of similar compounds has been disclosed previously. Conversion of ester **183** to furan **185** could be accomplished in

three transformations: $LiAlH_4$ reduction of the ester to the primary alcohol, Dess-Martin periodinane oxidation, followed by Grignard addition of reagent **184** into the newly formed aldehyde. With furan **185** in hand, deoxygenation of the secondary alcohol followed by acidic hydrolysis of the ketal will provide aldehyde **186**. At this stage, removal of the MEM protecting group, followed by formation of the α-diazoacetate moiety would provide intermediate **187**. It is thought that exposure of compound **187** to $SnCl_2$ would effect the key intramolecular Roskamp reaction to provide macrocycle **188**.[33] Once formed, treating macrocycle **188** with monomagnesium peroxyphthalate (MMPP),[34] a mild oxidizing agent, would oxidize the furan to provide enedione **189**. This compound is now ready to undergo critical, sequential enolate additions to furnish the cyclobutane core. Hence, treatment of enedione **189** with DBU would first deprotonate the β-ketoester moiety resulting in a 1,4 Michael addition to form lactone **190**. It is thought that protonation of the resulting enolate from the Michael addition will occur from the less-hindered α-face to provide the desired diastereomer needed for the Aldol addition. Once lactone **190** has formed, another equivalent of DBU could again deprotonate the β-ketoester moiety to promote an aldol addition and subsequent hemiketalization to afford cyclobutane **191**.

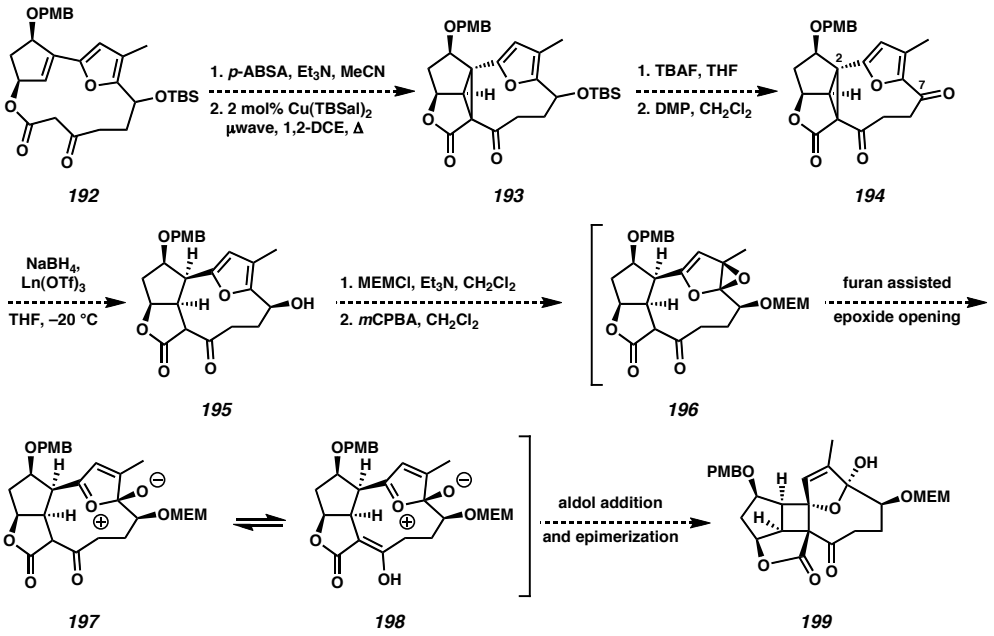
Scheme 2.7.1



A second approach, although not as rapid as above, utilizes our knowledge of the cyclopropane system to build the γ-lactone moiety and subsequently set the relative stereochemistry at C(2) by reduction of the cyclopropane ring. Starting with macrocycle **192** (Scheme 2.7.1), standard diazotization of the β-ketoester moiety followed by copper catalyzed cyclopropanation would afford cyclopropane **193**. At this stage, removal of the TBS group followed by a Dess-Martin periodinane oxidation would provide ketone **194**. Treating this product with $La(OTf)_3$ and $NaBH_4$ is expected to reduce the cyclopropane ring at C(2) as well as the C(7) ketone to provide alcohol **195** in high diastereoselectivity. We believe that the desired diastereoselectivity in the cyclopropane reduction is favored as a result of the observed selectivity that methanol showed in the model system in Scheme 2.6.6. Furthermore, with the macrocycle in place, hydride addition into the C(7) ketone should occur from the accessible α-face to provide the correct diastereomer. Protection of the alcohol in compound **195** as a MEM ether preserves the C(7)-oxygen's

ability to direct. Hence, treating this compound with *m*CPBA should result in a regio- and diastereoselective epoxidation of the furan to produce epoxide **196**. At this stage, electron donation by the furan should be facile and lead to epoxide opening and the formation of oxocarbenium ion **197**. This intermediate is in equilibrium with enol **198**, which could undergo an aldol addition into the oxocarbenium ion followed by epimerization of the hemiketal to provide cyclobutane **199**.

Scheme 2.7.2



Both routes discussed above use similar macrocycles as key intermediates in the synthesis of compounds **191** and **199** respectively. The macrocycle is vital in both of these routes as it controls the diastereoselectivity at several stereocenters. Thus, future studies toward bielschowskysin should focus on the formation of either macrocycle **188** or macrocycle **192** prior to any investigations into the cyclobutane core.

2.8 Concluding Remarks

Although the cyclopropane route did not achieve its ultimate goal in synthesizing the cyclobutane ring, several successful aspects of our research can be extracted. Foremost, we have successfully implemented the palladium(II)-catalyzed oxidative kinetic resolution early in the synthesis to provide alcohol **37** in ≥95% ee and 43% yield. Moreover, this methodology could allow for rapid access to either enantiomer of allylic alcohol **37**, an important intermediate in synthesizing advanced compounds within our synthetic efforts. Secondly, we have effectively developed a general method for obtaining α-diazo-β-ketoesters using 2-diazoacetoacetic acid (**139**). The latter reagent is readily generated, and has been synthesized on reasonable scale (*ca*. 5.0 mmol) in a straightforward manner from commercially available starting materials. The coupling of 2-diazoacetoacetic acid (**139**) using DCC under neutral conditions provided the desired products in high yields and tolerated a variety of alcohols. In addition, amines can be used as substrates for the amidation with 2-diazoacetoacetic acid, thus providing access to α-diazo-β-ketamides. Although our synthetic endeavors did not yield the cyclobutane core found in bielschowskysin, we did discover an important trans-esterification process that was later observed during synthetic efforts toward ineleganolide (**108**, Figure 2.1.1).[35] Finally, an understanding of the reactivity of these molecules has been gained, thus allowing for efficient synthetic revisions and paving the way for further research.

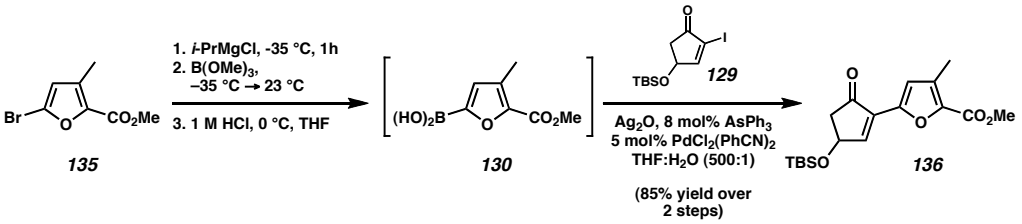
2.9 Experimental Procedures

2.9.1 *Materials and Methods*

Unless otherwise stated, reactions were performed at ambient temperature (typically 20–22 ºC) in flame-dried glassware under an argon or nitrogen atmosphere using dry solvents. Solvents were dried by passage through an activated alumina column under argon. Et_3N, $i Pr_2NH$, $i Pr_2NEt$, and pyridine were freshly distilled from CaH_2. Trifluoroacetic acid (99%) was purchased from Aldrich. Tf_2O was freshly distilled from P_2O_5. All other commercially obtained reagents were used as received. 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, $KMnO_4$, or CAM staining. ICN silica gel (particle size 0.032–0.063 mm) was used for flash chromatography. Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz respectively), or a Varian Inova 500 (at 500 MHz and 125 MHz respectively) and are reported relative to solvent for ^1H NMR ($CHCl_3$ = 7.27 ppm, C_6H_6 = 7.16 ppm, CH_2Cl_2 = 5.30 ppm, DMSO = 2.51 ppm) and ^{13}C NMR ($CDCl_3$ = 77.0 ppm, C_6D_6 = 128.4 ppm). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicitiy, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, dt = doublet of triplets, td = triplet of doublets, dd = doublet of doublets, m = multiplet, comp. m = complex multiplet, app. = apparent, bs = broad singlet. IR spectra were recorded on a Perkin Elmer BX-11 FT-IR spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass

spectra were obtained from the California Institute of Technology Mass Spectral Facility. Crystallographic analyses were performed at the California Institute of Technology Beckman Institute X-Ray Crystallography Laboratory. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, from the CCDC by quoting the publication citation and the deposition number (see Appendix 3 for deposition numbers).

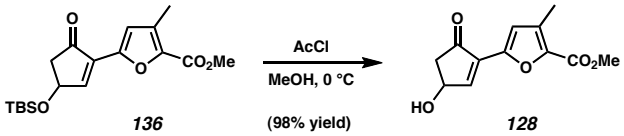
2.9.2 *Preparation of Compounds*



Enone 136. To a solution of furan **135** (609 mg, 2.78 mmol, 1.00 equiv) in THF (15 mL) at –35 °C, was added a 1.84 M solution (THF) of *i*PrMgCl (1.96 mL, 3.61 mmol, 1.30 equiv) to the reaction. The reaction stirred for 45 minutes and the temperature was maintained between -40 and -30 °C. At this stage, trimethylborate (1.24 mL, 11.1 mmol, 4.00 equiv) was added rapidly at -30 °C, and the reaction was allowed to warm to ambient temperature and stir overnight. The reaction was cooled to 0 °C, 1 M HCl was added, and the mixture stirred for 30 minutes. The reaction was diluted with EtOAc and H_2O, and the layers were separated. The aqueous layer was then washed 2x with EtOAc. The organic layers were combined, and washed with saturated K_2CO_3 (aq.) until the aqueous layer was basic. The basic aqueous layer was then acidified using 1 M HCl, and then washed 5x with EtOAc. The latter batch of EtOAc was washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo to afford boronic acid **130** (375 mg,

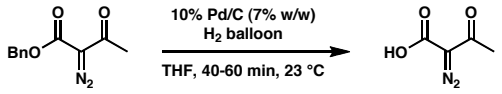
73%) as a light-brown solid. This compound was used directly in the following Suzuki coupling reaction.

To a solution of vinyl iodide **129** (87.0 mg, 0.260 mmol, 1.00 equiv), boronic acid **130** (71.0 mg, 0.390 mmol, 1.50 equiv), Ag_2O (180 mg, 0.770 mmol, 3.00 equiv), and Ph_3As (8.00 mg, 0.0260 mmol, 0.100 equiv) in THF (1.30 mL) was added $PdCl_2(PhCN)_2$ (5.00 mg, 0.0130 mmol, 0.0500 equiv) and H_2O (50.0 μL). The reaction was stirred until consumption of vinyl iodide **129** as indicated by TLC (ca. 1.5 h) and filtered through a pad of celite. The solvent was concentrated in vacuo, and the residue was purified by flash chromatography using 3:97→5:95 EtOAc:hexanes to afford furan **136** as a white solid (74 mg, 80%). R_F 0.15 (90:10 hexanes:EtOAc, UV); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 2.7 Hz, 1H), 7.03 (s, 1H), 5.03 (m, 1H), 3.90 (s, 3H), 2.88 (dd, *J* = 5.9, 18.3 Hz, 1H), 2.42 (dd, *J* = 2.2, 18.6 Hz, 1H), 2.34 (s, 3H), 0.91 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.8, 160.1, 156.0, 147.4, 140.0, 133.7, 132.6, 116.1, 68.9, 51.8, 45.9, 25.8, 18.3, 11.5, -4.8; IR (film) 3133, 2949, 2928, 2891, 2857, 1721, 1703, 1594, 1509, 1448 cm^{-1}; HRMS (FAB$^+$) calc'd for $[C_{18}H_{26}SiO_5]^+$: *m/z* 350.1550, found 350.1542.



Alcohol 128. To a solution of acetyl chloride (50.5 μL, 0.710 mmol, 5.00 equiv) in MeOH (570 μL) at 0 °C, was added enone **136** (52.5 mg, 0.150 mmol, 1.00 equiv) in one portion. Enone **136** dissolved slowly over 20–30 minutes at 0 °C, and once completely in solution, the reaction stirred for 45 minutes at 0 °C. The reaction was then diluted with

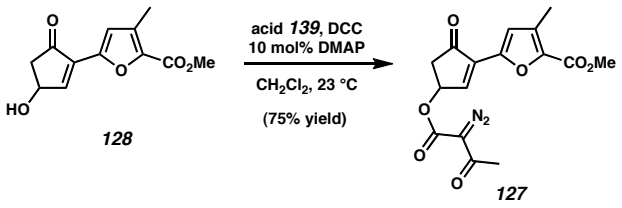
brine and EtOAc. These layers were separated, and the aqueous layer was washed 2x with EtOAc. The organic layers were combined, washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. This semi-solid was diluted with toluene, and then reconcentrated under vacuum (repeated 3x). Upon final concentration in vacuo, alcohol **128** was obtained as a white solid (35.3 mg, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 2.9 Hz, 1H), 7.02 (s, 1H), 5.21 (br, 1H), 3.90 (s, 3H), 2.96 (dd, *J* = 6.1, 18.8 Hz, 1H), 2.71 (d, *J* = 5.40 Hz, 1H), 2.49 (dd, *J* = 2.2, 18.8 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.8, 160.0, 154.9, 147.1, 139.9, 134.1, 132.4, 116.1, 68.3, 51.7, 45.2, 11.6; IR (film) 3447, 2920, 2850, 1716, 1506, 1440, 1405, 1295, 1167, 1102 cm^{-1}; HRMS (FAB$^+$) calc'd for $[C_{12}H_{13}O_5]^+$: *m/z* 237.0763, found 237.0763.



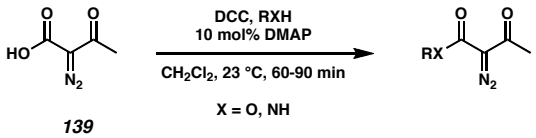
138 *139*

Acid 139. 10% Pd/C (17.5 mg, 7% w/w) was added to a solution of benzyl ester **138** (250 mg, 1.15 mmol, 1.00 equiv) in THF (11.5 mL) at 23 °C. The N_2 atmosphere was evacuated and backfilled with H_2 (balloon), this was repeated three additional times. The reaction was complete within 40–60 minutes as monitored by TLC (4:6 EtOAc:Hexanes). Once finished, the reaction mixture was passed through a short pad of celite (Et_2O eluent), and the solvent was concentrated in vacuo to obtain 2-diazoacetoacetic acid (**139**) as a pale-yellow solid that was used directly in the esterification step. Compound **139** was ca. 95% pure by ^{1}H NMR. *Note:* A pure (98%) sample of acid **139** was obtained by crystallization using Et_2O/Heptane and cooling at -20 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ

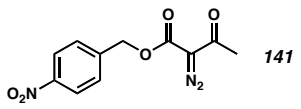
2.46 (s, 3H); IR (film) 2932, 2150, 1722, 1601, 1302 cm^{-1}; HRMS (EI^+) calc'd for $[C_4H_4N_2O_3]^+$: *m/z* 128.0222; found, 128.0227.



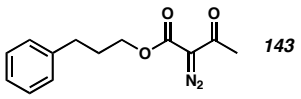
Enone 127. To a solution of alcohol **128** (71.0 mg, 0.300 mmol, 1.00 equiv), acid **139** (92.1 mg, 0.720 mmol, 2.40 equiv), and DMAP (3.67 mg, 0.0300 mmol, 0.100 equiv) in CH_2Cl_2 (2.00 mL) at 23 °C, was added DCC (206 mg, 1.00 mmol, 2.0 equiv) in one portion. After the addition of DCC, the reaction was heated to 40 °C for 90 minutes. The reaction was allowed to cool to ambient temperature, filtered through a plug of celite (Et_2O eluent), and the resulting filtrate was partitioned between H_2O and Et_2O. The aqueous layer was extracted 2x with Et_2O. The organic extracts were combined, washed once with H_2O, and then once with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by flash chromatography using 25:75 EtOAc:Hexanes to afford compound **127** as a light-yellow solid (78 mg, 75% yield). ^1H NMR (500 MHz, C_6D_6) δ 7.30 (s, 1H), 7.23 (s, 1H), 5.24 (m, 1H), 3.46 (s, 3H), 2.33 (dd, *J* = 6.6, 18.6 Hz, 1H), 2.24 (s, 3H), 2.18 (s, 3H), 1.90 (d, *J* = 18.6 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 199.3, 188.6, 160.8, 159.9, 149.1, 147.3, 141.4, 136.4, 132.7, 117.5, 71.2, 51.5, 42.0, 28.4, 11.8; IR (film) 2954, 2145, 1715, 1660, 1366, 1312, 1155, 1062; HRMS (FAB^+) calc'd for $[C_{16}H_{14}N_2O_7]^+$: *m/z* 346.0801; found, 346.0817.



General Procedure for the Esterification of Acid 139 (Table 2.4.1). To a solution of substrate (0.500 mmol, 1 equiv), acid **139** (1.20 mmol, 2.4 equiv), and DMAP (0.0500 mmol, 0.10 equiv) in CH_2Cl_2 (3.30 mL) at 23 °C, was added DCC (1.00 mmol, 2.0 equiv) in one portion. *Note: For 1° alcohols, the reaction remained at 23 °C. However, for 2° alcohols, the reaction was heated to 40 °C after the addition of DCC.* The reaction was monitored by TLC, and the reaction was complete in 60–90 minutes. The reaction was filtered through a plug of celite (Et_2O eluent), and the resulting filtrate was partitioned between H_2O and Et_2O. The aqueous layer was extracted 2x with Et_2O. The organic extracts were combined, washed with $NaHCO_3$ (saturated), and then with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The products were purified by flash chromatography.

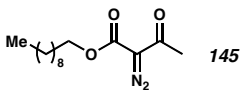


Substrate 141.[36] See General Procedure for the Esterification of Acid **139** (92% yield). Product was purified by flash chromatography (20:80 EtOAc:Hexanes). R_F = 0.40 (30:70 EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 8.7 Hz, 2H), 5.35 (s, 2H), 2.47 (s, 2H); IR (film) 2148, 1711, 1344 cm^{-1}.



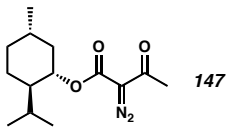
143

Substrate 143. See General Procedure for the Esterification of Acid **139** (85% yield). Product was purified by flash chromatography (17:83 EtOAc:Hexanes). R_F = 0.45 (30:70 EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.27 (m, 2H), 7.23-7.16 (m, 2H), 4.27 (t, *J* = 6.3 Hz, 2H), 2.71 (t, *J* = 7.2 Hz, 2H), 2.47 (s, 3H), 2.08-2.01 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.0, 161.2, 140.6, 128.4, 128.2, 126.1, 64.6, 32.0, 30.0, 28.1; IR (film) 2141, 1716, 1660, 1314 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{13}H_{15}N_2O_3]^+$: *m/z* 247.1083; found, 247.1089.



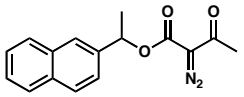
145

Substrate 145. See General Procedure for the Esterification of Acid **139** (80% yield). Product was purified by flash chromatography (5:95 EtOAc:Hexanes). R_F = 0.50 (20:80 EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.24 (t, *J* = 6.6 Hz, 2H), 2.49 (s, 3H), 1.71-1.66 (m, 2H), 1.33-1.27 (m, 14H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.2, 161.5, 65.5, 31.8, 29.4, 29.4, 29.2, 29.1, 28.6, 28.2, 25.7, 22.6, 14.1; IR (film) 2927, 2856, 2138, 1721, 1663, 1313 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{14}H_{25}N_2O_3]^+$: *m/z* 269.1865; found, 269.1864.



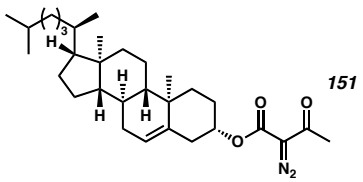
147

Substrate 147. See General Procedure for the Esterification of Acid **139** (77% yield). Product was purified by flash chromatography (10:90 EtOAc:Hexanes). All spectroscopic data is identical to that reported by Doyle.[37]



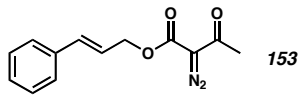
149

Substrate 149. See General Procedure for the Esterification of Acid **139** (81% yield). Product was purified by flash chromatography (10:90 EtOAc:Hexanes). R_F = 0.20 (10:90 EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90-7.83 (m, 4H), 7.55-7.50 (m, 3H), 6.21 (q, *J* = 6.6 Hz, 1H), 2.49 (s, 3H), 1.72 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.0, 160.7, 138.0, 133.1, 133.0, 128.6, 128.0, 127.6, 126.4, 126.3, 125.2, 123.6, 73.8, 28.2, 22.1; IR (film) 2140, 1715, 1658, 1305 cm^{-1}; HRMS (FAB$^+$) calc'd for $[C_{16}H_{15}N_2O_3]^+$: *m/z* 283.1083; found, 283.1079.



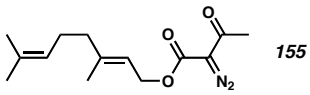
151

Substrate 151. See General Procedure for the Esterification of Acid **139** (87% yield). Product was purified by flash chromatography (5:95 EtOAc:Hexanes). ^{1}H NMR ($CDCl_3$) is identical to that reported by Doyle.[38]



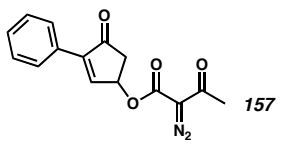
153

Substrate 153. See General Procedure for the Esterification of Acid **139** (82% yield). Product was purified by flash chromatography (15:85 EtOAc:Hexanes). R_F = 0.50 (20:80 EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.28 (m, 5H), 6.70 (d, *J* = 15.6 Hz, 1H), 6.31 (dt, *J* = 6.6, 15.6 Hz, 1H), 4.90 (dd, *J* = 1.5, 6.6 Hz, 2H), 2.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.0, 161.1, 135.7, 135.3, 128.6, 128.3, 126.6, 122.2, 65.8, 28.2; IR (film) 2140, 1716, 1659, 1316 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{13}H_{12}N_2O_3]^+$: *m/z* 244.0848; found, 244.0839.



155

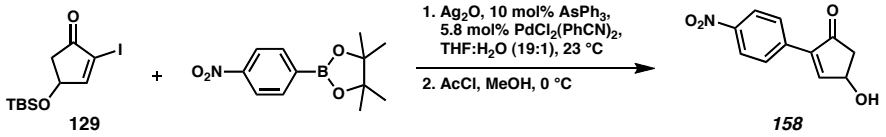
Substrate 155. See General Procedure for the Esterification of Acid **139** (77% yield). Product was purified by flash chromatography (10:90 EtOAc:Hexanes). R_F = 0.50 (20:80 EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.37 (dt, *J* = 1.2, 3.6 Hz, 1H), 5.10-5.04 (m, 1H), 4.75 (d, *J* = 7.2 Hz, 2H), 2.49 (s, 3H), 2.13-2.05 (m, 4H), 1.74 (s, 3H), 1.68 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.1, 161.4, 143.4, 131.9, 123.5, 117.6, 62.1, 39.4, 28.1, 26.1, 25.6, 17.6, 16.4; IR (film) 2138, 1717, 1662, 1309 cm^{-1}; HRMS (FAB$^+$) calc'd for $[C_{14}H_{21}N_2O_3]^+$, *m/z* 265.1552; found, 265.1548.



157

Substrate 157.[39] See General Procedure for the Esterification of Acid **139** (95% yield). Product was purified by flash chromatography (15:85 EtOAc:Hexanes). R_F = 0.40 (30:70

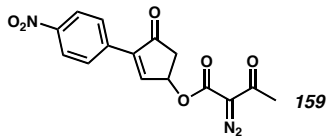
EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76-7.73 (m, 2H), 7.68 (d, *J* = 2.7 Hz, 1H), 7.42-7.40 (m, 2H), 6.05 (dt, *J* = 2.4, 6.6 Hz, 1H), 3.10 (dd, *J* = 6.6, 18.6 Hz, 1H), 2.66 (dd, *J* = 1.8, 18.6 Hz, 1H), 2.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 189.6, 160.9, 150.8, 146.3, 129.7, 129.6, 128.5, 127.6, 70.7, 42.4, 28.3; IR (film) 2144, 1716, 1654, 1313 cm^{-1}; HRMS (FAB^+) calc'd for $[C_{15}H_{13}N_2O_4]^+$: *m/z* 285.0875; found, 285.0869.



Hydroxy Enone 158. A flask containing 4-(*tert*-butyldimethylsilyloxy)-2-iodocyclopent-2-enone[40] (400 mg, 1.60 mmol, 1.40 equiv) was charged with *p*-nitrophenyl pinacolato borate (388 mg, 1.15 mmol, 1.00 equiv),[41] silver(I) oxide (800 mg, 3.45 mmol, 3.00 equiv), and Ph_3As (35.2 mg, 0.120 mmol, 0.100 equiv) at 23 °C. THF (5.5 mL) and H_2O (290 μL) were added, followed by addition of $PdCl_2(PhCN)_2$ (22.1 mg, 0.0580 mmol). The reaction mixture was stirred for 15 minutes at 23 °C, at which point TLC (5:95 EtOAc:Hexanes) indicated the reaction was complete. The reaction was passed through a pad of celite (EtOAc eluent), and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (7:93 EtOAc:Hexanes) to afford the Suzuki product as an oil (405 mg, 95% yield).

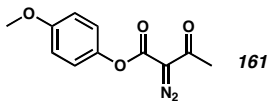
This product (125 mg, 0.370 mmol, 1.00 equiv) was then added to a solution of AcCl (130 μL, 1.90 mmol, 5.10 equiv) in MeOH (7.5 mL) at 0 °C. The reaction was allowed to stir for 20 minutes, upon which TLC (40:60 EtOAc:Hexanes) showed consumption of the Suzuki product. The reaction was diluted with brine and EtOAc.

The layers were separated, and the aqueous layer was washed 2x with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. TBSOH was removed azeotropically with toluene to afford alcohol **158** (80 mg, 99% yield). R_F = 0.20 (50:50 EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25-8.20 (m, 2H), 7.91-7.87 (m, 2H), 7.82 (d, *J* = 2.4 Hz, 1H), 5.15 (m, 1H), 3.05 (dd, *J* = 6.6, 18.9 Hz, 1H), 2.60 (dd, *J* = 2.1, 18.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2, 159.3, 147.8, 142.1, 136.7, 128.4, 123.7, 67.7, 45.7; IR (film) 3415, 1711, 1516, 1348 cm^{-1}; HRMS (EI$^+$): calc'd for $[C_{11}H_9NO_4]^+$: *m/z* 219.0532; found, 219.0506.



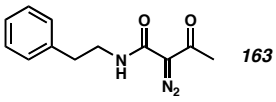
159

Substrate 159. See General Procedure for the Esterification of Acid **139** (77% yield). Product was purified by flash chromatography (50:50 EtOAc:Hexanes). R_F = 0.30 (30:70 EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (m, 2H), 7.97-7.93 (m, 2H), 7.87 (d, *J* = 2.7 Hz, 1H), 6.09 (dt, *J* = 2.7, 6.6 Hz, 1H), 3.18 (dd, *J* = 6.6, 18.9 Hz, 1H), 2.70 (dd, *J* = 2.1, 18.9 Hz, 1H), 2.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 189.4, 160.9, 153.8, 148.3, 144.4, 135.9, 128.6, 124.0, 70.4, 42.3, 28.3; IR (film) 2145, 1717, 1519, 1350, 1317 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{15}H_{11}N_3O_6]^+$: *m/z* 329.0648; found, 329.0647.



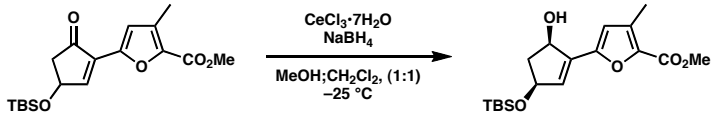
161

Substrate 161. See General Procedure for the Esterification of Acid **139** (75% yield). Product was purified by flash chromatography (15:85 EtOAc:Hexanes). R_F = 0.20 (20:80 EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.23 (m, 2H), 7.13-7.08 (m, 2H), 4.00 (s, 3H), 2.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.9, 160.4, 157.6, 143.0, 122.3, 114.5, 55.6, 28.3; IR (film) 2142, 1732, 1507, 1324, 1191 cm^{-1}; HRMS (FAB$^+$) calc'd for $[C_{11}H_{11}N_2O_4]^+$: *m/z* 235.0179; found, 235.0174.



163

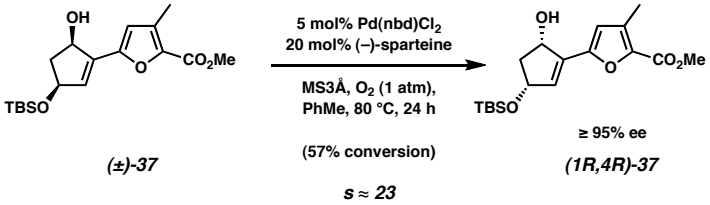
Substrate 163. See General Procedure for the Esterification of Acid **139** (95% yield). Product was purified by flash chromatography (40:60 EtOAc:Hexanes). R_F = 0.25 (40:60 EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (br, 1H), 7.32-7.19 (m, 5H), 3.60 (q, *J* = 6.9 Hz, 2H), 2.84 (t, *J* = 7.4 Hz, 2H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.8, 160.5, 138.9, 129.0, 128.8, 126.8, 41.4, 36.1, 26.9; IR (film) 3309, 2124, 1667, 1538, 1312 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{12}H_{13}N_3O_2]^+$: *m/z* 231.1008; found, 231.1007.



136 (95% yield) 10:1 dr (*syn*:*anti*) ***37***

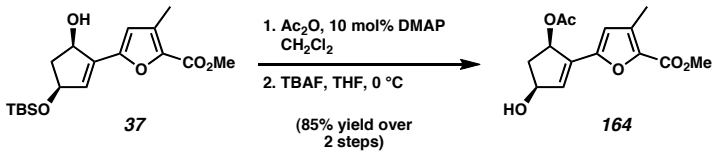
Alcohol 37. To a solution of furan **136** (100 mg, 0.290 mmol, 1.00 equiv) and $CeCl_3$•$7H_2O$ (430 mg, 1.10 mmol, 4.00 equiv) in MeOH:CH_2Cl_2 (4.90 mL, 1:1) at -25 °C, was added sodium borohydride (43.0 mg, 1.10 mmol, 4.00 equiv) portionwise while

maintaining the reaction between -25 and -20 °C. Upon consumption of the ketone as visualized by TLC (ca. 30 min.), the reaction was diluted with EtOAc and H_2O. The solution was allowed to warm to ambient temperature and the layers were separated. The aqueous layer was extracted 3x with EtOAc, and the organic layers were combined and washed with brine. The EtOAc layer was dried with Na_2SO_4, filtered, and concentrated in vacuo to provide allylic alcohol **137** as a yellow oil (96 mg, 95%). R_F = 0.20 (20:80 EtOAc:hexanes, UV); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 (s, 1H), 6.39 (s, 1H), 4.84 (m, 1H), 4.79 (m, 1H), 3.91 (s, 3H), 2.76 (dt, *J* = 6.9, 14.2 Hz, 1H), 2.36 (s, 3H), 1.98 (d, *J* = 9.3 Hz, 1H), 1.77 (d, *J* = 14.2 Hz, 1H), 0.92 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 151.7, 139.5, 136.2, 133.0, 132.6, 113.7, 74.8, 74.2, 51.5, 44.7, 25.8, 18.1, 11.6, -4.6, -4.7; IR (film) 3420, 2954, 2930, 2857, 1711, 1440, 1298, 1101 cm^{-1}; HRMS (FAB$^+$) calc'd for $[C_{18}H_{27}O_5Si]^+$: *m/z* 351.1628; found 351.1632.



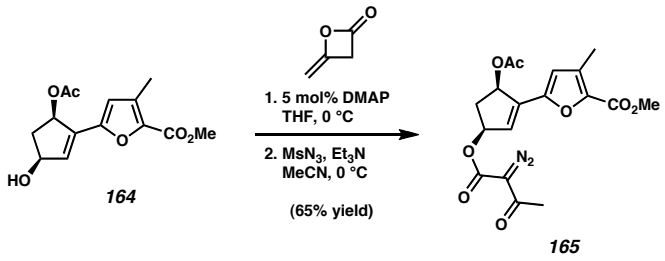
(*1R,4R*)-Alcohol 37. A 10 mL Schlenk tube equipped with a magnetic stir bar was charged with powdered molecular sieves (3ÅMS, 150 mg) and flame-dried under vacuum. After cooling under dry N_2, $Pd(nbd)Cl_2$ (0.380 mg, 1.42 μmol, 0.0500 equiv) was added, followed by toluene (285 μL). To this yellow suspension was added (–)-sparteine (1.33 mg, 5.67 μmol, 0.200 equiv), and the top of the Schlenk tube was then fitted with an O_2 balloon. The reaction was purged under vacuum and replaced with O_2, and this process was repeated 4x's. The light yellow suspension was stirred at ambient

temperature for 10 minutes, then heated to 80 °C for an additional 10 minutes. The reaction mixture darkened to an orange suspension. Upon completion of the 10 minutes, racemic alcohol **37** (10.0 mg, 28.4 μmol, 1.00 equiv, in 100μL of PhMe) was added to the reaction mixture. The suspension was then heated to 80 °C for 24 hours. The reaction was allowed to cool to ambient temperature, and was then filtered through a small pad of celite using toluene as eluent. The filtrate was concentrated in vacuo, and the ^{1}H NMR of this material indicated a 43% yield of (*1R,4R*)-alcohol **37** (4.3 mg, 43% yield, 95% ee). $[\alpha]_D^{24.98}$ +26.4 (*c* = 0.15, EtOAc).[42]



Allylic Alcohol 164. To a solution of alcohol **37** (96.0 mg, 0.270 mmol, 1.00 equiv) in pyridine (2.70 mL, 0.100 M) was added acetic anhydride (0.270 mL, 2.50 mmol, 9.00 equiv) and DMAP (3.30 mg, 0.0270, 0.100 equiv) at ambient temperature. The reaction was stirred until consumption of allylic alcohol **37** as monitored by TLC (ca. 30 min). The solution was cooled to 0 °C and diluted with EtOAc:brine (1:1). The aqueous solution was extracted 2x with EtOAc. The combined organic layer was successively washed with sat. $CuSO_4$ (aq.), H_2O, sat. $NaHCO_3$ (aq.), and brine. The organic layer was then dried with Na_2SO_4, filtered, and concentrated in vacuo to yield an allylic acetate (101 mg, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.49 (dd, *J* = 0.9, 2.1 Hz, 1H), 6.26 (s, 1H), 5.85 (dd, *J* = 4.2, 7.5 Hz, 1H), 4.84 (m, 1H), 3.90 (s, 3H), 2.96 (dt, *J* = 7.5, 14.4 Hz, 1H), 2.33 (s, 3H), 2.10 (s, 3H), 1.73 (m, 1H), 0.91 (s, 9H), 0.11 (s, 3H), 0.11 (s, 3H).

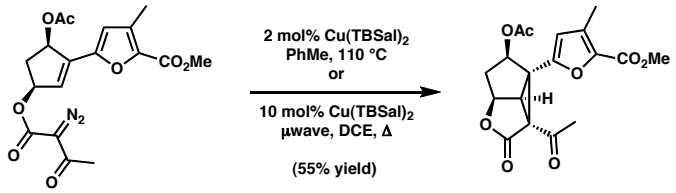
A solution of TBAF (0.290 mL of 1M solution in THF, 0.289 mmol, 1.20 equiv) was added to the crude silyl ether (95 mg, 0.241 mmol, 1.00 equiv) in THF (4.8 mL) at 0 °C and under N_2. The reaction was allowed to warm to ambient temperature and monitored by TLC. Once complete, the reaction was diluted with H_2O, and the reaction was extracted 3x with EtOAc. The combined organic extracts were washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude solid was purified by flash chromatography (50:50, EtOAc:hexanes) to provide allylic alcohol **164** as a white solid (64 mg, 85% from alcohol **37**).: R_F 0.2 (40:60, EtOAc:hexanes, UV); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.60 (d, *J* = 2.4 Hz, 1H), 6.29 (s, 1H), 5.88 (dd, *J* = 2.9, 7.3 Hz, 1H), 4.83 (m, 1H), 3.88 (s, ,3H), 2.88 (app dt, *J* = 14.7, 7.1, 1H), 2.32 (s, 3H), 2.07 (s, 3H), 1.81 (app dt, *J* = 12.2, 2.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 160.0, 150.6, 140.1, 134.6, 133.6, 132.6, 113.8, 75.7, 74.4, 51.7, 41.5, 21.3, 11.7; IR (film) 3424, 2953, 1712, 1598, 1511, 1440, 1374, 1297, 1240, 1197, 1104, 1035 cm^{-1}; HRMS (EI^+) calc'd for $[C_{14}H_{16}O_6]^+$: *m/z* 280.2804, found 280.2800.



Ester 165. A solution of allylic alcohol **164** (15.0 mg, 0.0540 mmol, 1.00 equiv) and diketene (8.00 μL, 0.110 mmol, 2.00 equiv) in THF (1.10 mL) was cooled to 0 °C, and DMAP (0.350 mg, 0.00270 mmol, 0.0500 equiv) was added. The reaction was stirred at 0 °C for 10 minutes, and was then allowed to warm to ambient temperature. Once

complete by TLC (ca. 30 min), the reaction was concentrated in vacuo and carried on directly. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (d, *J* = 1.8 Hz, 1H), 6.34 (s, 1H), 5.99 (dd, *J* = 2.7, 7.2 Hz, 1H), 5.73 (m, 1H), 3.90 (s, 3H), 3.48 (s, 2H), 3.00 (dt, *J* = 7.8, 15.6 Hz, 1H), 2.34 (s, 3H), 2.10 (s, 3H), 1.94 (dt, *J* = 7.8, 15.6 Hz, 1H).

The crude β-ketoester (380 mg, 1.0 mmol, 1.0 equiv) was dissolved in MeCN (10.4 mL), and MsN_3 (630 mg, 5.20 mmol, 5.00 equiv) followed by Et_3N (0.870 mL, 6.20 mmol, 6.00 equiv) was added to the reaction. The resulting solution was stirred at ambient temperature until complete by TLC (ca. 6 h). The reaction was concentrated in vacuo, and the resulting crude oil was purified by silica gel chromatography (80:20→75:25, hexanes:EtOAc) to yield ester **165** as a light-yellow solid (338 mg, 65% average). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.60 (d, *J* = 2.2 Hz, 1H), 6.30 (s, 1H), 6.19 (m, 1H), 6.07 (m, 1H), 3.88 (s, 3H), 2.47 (s, 3H), 2.44 (m, 2H), 2.33 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.0, 170.8, 161.2, 159.8, 149.9, 140.5, 136.2, 132.5, 130.5, 114.7, 79.0, 76.2, 51.8, 39.1, 28.4, 21.2, 11.7; IR (film) 2142, 1713, 1657, 1295, 1237 cm^{-1}; HRMS (EI^+) calc'd for $[C_{18}H_{18}N_2O_8]^+$: *m/z* 390.1063, found 390.1061.

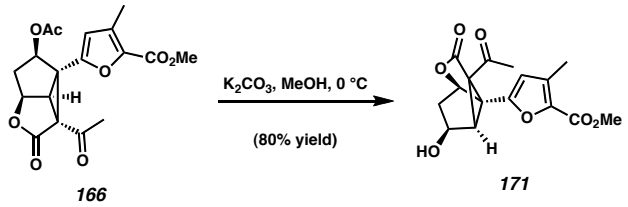


165 ***166***

Cyclopropane 166. ***µwave conditions:*** The microwave is pre-warmed by undergoing an actual run with just DCE in the reaction tube. A solution of compound **165** (45.0 mg, 0.120 mmol, 1.00 equiv) and $Cu(TBSal)_2$ (5.00 mg, 0.0120 mmol, 0.100 equiv) in DCE (3.00 mL) was heated for 20 min at 105 °C in the microwave. The following parameters

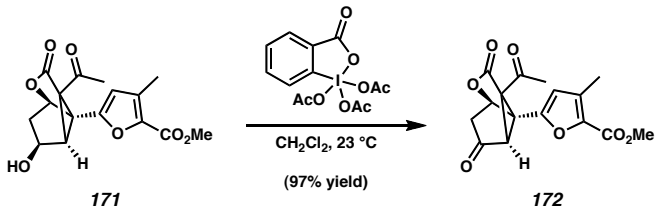
for the μwave are as follows: Power = 150 W, Temperature = 105 °C, Pressure = 200 atm, Ramp = 1 minute, Run Time = 20 minutes. The reaction was concentrated in vacuo, and the resulting crude oil was purified by silica gel chromatography (40:60 EtOAc:hexanes) to yield cyclopropane **166** as a white solid (21 mg, 55%). ^{1}H NMR (500 MHz, C_6D_6) δ 6.20 (s, 1H), 5.47 (dd, *J* = 1.7, 7.3 Hz, 1H), 4.01 (m, 1H), 3.53 (d, *J* = 4.6 Hz, 1H), 3.39 (s, 3H), 2.39 (s, 3H), 2.13 (s, 3H), 1.73 (d, *J* = 14.4 Hz, 1H), 1.71 (s, 3H), 1.29 (ddd, *J* = 3.4, 7.6, 14.6 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 195.7, 170.8, 170.5, 160.0, 150.8, 141.5, 132.8, 116.2, 81.6, 78.4, 52.8, 51.9, 50.4, 46.0, 45.8, 29.7, 20.8, 12.0; IR (film) 2954, 1770, 1747, 1714, 1230 cm^{-1}; HRMS (EI^{+}) calc'd for $[C_{18}H_{19}O_8]^{+}$: *m/z* 363.1080, found 363.1085.

Thermal conditions: A solution of $Cu(TBSal)_2$ (1.30 mg, 0.00300 mmol, 0.0200 equiv) in toluene (2.40 mL) was heated, under Ar, to 108 °C. A warm solution of diazo **165** (62.0 mg, 0.150 mmol, 1.00 equiv) in toluene (0.400 mL) was added dropwise over 6 minutes. The reaction was heated to 112 °C, and monitored by TLC (40:60 EtOAc:hexanes). After 100 minutes, the reaction was complete, and allowed to cool to ambient temperature. The solvent was removed in vacuo, and the dark residue was purified by flash chromatography (40:60 EtOAc:hexanes) to provide cyclopropane **166** (35 mg, 56%).



166 *171*

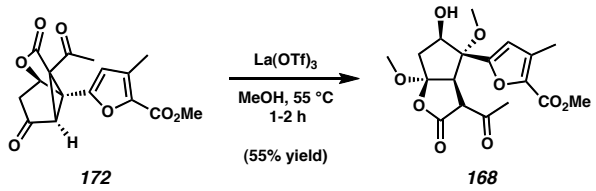
Alcohol 171. K_2CO_3 (32.0 mg, 0.240 mmol, 2.00 equiv) was added to a solution of cyclopropane **166** (43.0 mg, 0.120 mmol, 1.00 equiv) in MeOH (2.30 mL) at 0 °C. The reaction was stirred at 0 °C and monitored by TLC. Once complete, the reaction was diluted with saturated NH_4Cl (aq.) and EtOAc, the layers were then separated, and the aqueous layer was further extracted 2x with EtOAc. The organic layers were combined, washed with H_2O and brine, dried with Na_2SO_4, filtered, and concentrated in vacuo to afford a crude oil. The latter was purified by silica gel chromatography (50:50 EtOAc:Hexanes) to provide alcohol **171** as a glue (30 mg, 80%). ^{1}H NMR (500 MHz, C_6D_6) δ 5.66 (s, 1H), 4.69 (m, 1H), 4.03 (app. q, J = 1.7, 5.6 Hz, 1H), 3.42 (s, 3H), 3.34 (d, J = 5.6 Hz, 1H), 2.28 (s, 3H), 2.12 (s, 3H), 1.53 (d, J = 14.4 Hz, 1H), 1.13 (ddd, J = 3.4, 7.3, 14.4 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 209.4, 196.2, 171.1, 159.6, 148.7, 141.6, 132.3, 114.6, 84.0, 71.5, 58.4, 51.4, 46.8, 45.9, 29.8, 11.8; IR (film) 3469, 1770, 1706, 1299, 1081 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{16}H_{16}O_7Na]^+$: m/z 343.0794, found 343.0811.



171 *172*

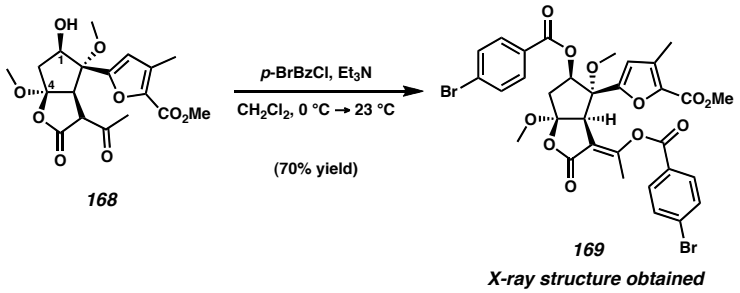
Ketone 172. To a solution of alcohol **171** (62.0 mg, 0.190 mmol, 1.00 equiv) in CH_2Cl_2 (3.90 mL) was added Dess-Martin periodinane (160 mg, 0.390 mmol, 2.00 equiv), and

the resulting slurry stirred until consumption of starting material (ca. 1 h). The reaction was diluted with EtOAc and a 1:1 ratio of saturated $Na_2S_2O_4$ (aq.) to saturated $NaHCO_3$(aq.), and stirred vigorously for 5 minutes. The layers were separated and the organic layer was washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo to yield crude ketone **172** as a colorless oil (60 mg, 97%). The ketone was carried on crude as attempts toward further purification resulted in decomposition. ^{1}H NMR (500 MHz, C_6D_6) δ 5.53 (s, 1H), 4.59 (dd, *J* = 1.2, 4.4 Hz, 1H), 3.49 (d, *J* = 1.2 Hz, 1H), 3.43 (s, 3H), 2.07 (s, 3H), 2.00 (s, 3H), 1.90 (d, *J* = 17.6 Hz, 1H), 1.66 (dd, *J* = 4.6, 17.6 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 202.0, 193.2, 168.7, 159.6, 146.2, 140.0, 142.4, 132.3, 115.9, 78.4, 54.4, 52.6, 51.6, 49.9, 45.3, 29.5, 11.8; IR (film) 2924, 2854, 1180, 1750, 1715, 1559, 1438, 1294, 1102 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{16}H_{14}O_7]^+$: *m/z* 318.0740, found 318.0732.



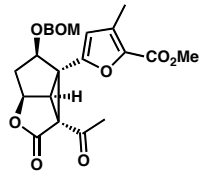
Alcohol 168. Crude ketone **172** (11.0 mg, 0.0340 mmol, 1.00 equiv) and $La(OTf)_3$ (20.0 mg, 0.0340 mmol, 1.00 equiv) were dissolved in MeOH (0.670 mL) at ambient temperature, then heated to 55 °C and stirred until the majority of starting material appeared consumed by TLC. The reaction was diluted with EtOAc and H_2O and the aqueous layer was extracted 3x with EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography using 66:34 EtOAc:Hexanes to afford alcohol **168** as an oil (8.0 mg, 55%).; ^{1}H NMR (500 MHz, C_6D_6) δ 5.90 (s, 1H), 4.26 (dd, *J* = 1.7, 5.6

Hz, 1H), 4.24 (m, 1H), 4.04 (d, J = 5.8 Hz, 1H), 3.38 (s, 3H), 3.20 (s, 3H), 2.80 (s, 3H), 2.56 (dd, J = 4.2, 14.2 Hz, 1H), 2.26 (s, 3H), 2.20 (d, J = 14.2 Hz, 1H), 2.15 (s, 3H), 1.84 (d, J = 2.7 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 199.3, 170.6, 159.8, 154.1, 140.9, 132.0, 119.4, 115.9, 87.4, 76.9, 60.5, 52.0, 51.5, 51.4, 48.0, 43.7, 29.5, 11.8; IR (film) 3465, 2955, 1771, 1722, 1441, 1297, 1197, 1102 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{18}H_{22}O_9]^+$: m/z 382.1264, found 382.1259.



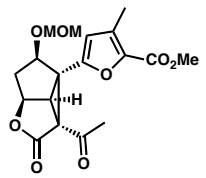
Furan 169. Triethylamine (19.0 mL, 0.140 mmol, 2.40 equiv) was added at ambient temperature to a solution of alcohol **168** (22.0 mg, 0.0580 mmol, 1.00 equiv) in CH_2Cl_2 (310 mL). DMAP (0.700 mg, 0.00580 mmol, 0.100 equiv) and *p*-bromobenzoyl bromide (28.0 mg, 0.130 mmol, 2.20 equiv) were then added, and the reaction stirred for 1 hour at ambient temperature. The reaction was diluted with EtOAc and H_2O, the layers were separated, and the aqueous layer was washed once with EtOAc. The EtOAc layers were combined, washed with saturated $NaHCO_3$ (aq.), washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. Crystals suitable for X-ray analysis were obtained by crystallization of crude furan **169** (30 mg, yield 70%) from EtOAc:heptane. ^{1}H NMR (500 MHz, C_6D_6) δ 7.97 (m, 2H), 7.39 (m, 2H), 7.25 (m, 2H), 7.10 (m, 2H), 5.99 (s, 1H), 5.73 (m, 1H), 3.93 (s, 1H), 3.24 (s, 3H), 3.13 (s, 3H), 2.88 (s, 3H), 2.54 (s, 3H), 2.49 (m, 2H), 2.15 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 168.1, 164.6, 161.9, 161.6, 159.2, 152.9,

141.0, 132.1, 132.0, 132.0, 131.8, 131.4, 129.3, 128.8, 128.6, 127.7, 114.9, 114.7, 114.2, 87.4, 78.1, 55.5, 52.3, 51.6, 50.1, 39.3, 17.4, 11.4; IR (film) 2948, 1762, 1725, 1589, 1227, 1101, 1070, 1010 cm^{-1}; HRMS (FAB^+) calc'd for $[C_{32}H_{30}O_{11}Br^{81}Br]^+$: *m/z* 750.0135, found 750.0159. mp = 175-177 °C (heptane/EtOAc).



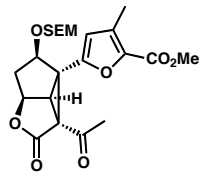
173

Cyclopropane 173. Cyclopropane **173** was obtained from allylic alcohol **37** using the same route employed to obtain cyclopropane **166** (Scheme 2.6.2). For the cyclopropanation reaction, cyclopropane **173** was obtained as an oil (3.5 mg, 74 %). ^1H NMR (500 MHz, C_6D_6) δ 7.30 (d, *J* = 8.3 Hz, 2H), 7.13 (d, *J* = 7.6 Hz, 1H), 7.06 (t, *J* = 7.3 Hz, 2H), 5.93 (s, 1H), 4.93 (d, *J* = 7.1 Hz, 1H), 4.63 (d, *J* = 7.1 Hz, 1H), 4.60 (s, 2H), 4.11 (m, 1H), 3.42 (d, *J* = 4.6 Hz, 1H), 3.39 (s, 3H), 2.42 (s, 3H), 2.12 (s, 3H), 1.86 (d, *J* = 14.2 Hz, 1H), 1.20 (dd, *J* = 3.2, 14.2 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 195.0, 169.4, 158.9, 150.4, 140.4, 138.0, 131.4, 128.2, 114.2, 93.3, 80.7, 69.7, 51.4, 50.6, 50.3, 44.8, 28.6, 11.1; IR (film) 2952, 1769, 1713, 1297, 1102, 1037 cm^{-1}; HRMS (EI^+) calc'd for $[C_{24}H_{23}DO_8]^+$: *m/z* 441.1534, found 441.1523.



174

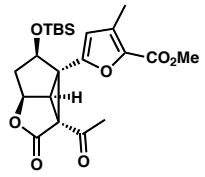
Cyclopropane 174. Cyclopropane **174** was obtained from allylic alcohol **37** using the same route employed to obtain cyclopropane **166** (Scheme 2.6.2). For the cyclopropanation reaction, cyclopropane **174** was obtained as an oil (2.3 mg, 62%). ^{1}H NMR (500 MHz, C_6D_6) δ 5.95 (s, 1H), 4.78 (d, *J* = 7.1 Hz, 1H), 4.48 (d, *J* = 7.1 Hz), 4.09 (m, 1H), 3.43 (d, *J* = 4.9, 1H), 3.39 (s, 3H), 3.23 (s, 3H), 2.43 (s, 3H), 2.13 (s, 3H), 1.82 (d, *J* = 14.2, 1H), 1.20 (dd, *J* = 3.4, 14.2 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 196.0, 170.3, 159.8, 151.3, 141.2, 132.3, 115.0, 96.1, 81.5, 56.3, 52.3, 51.5, 51.1, 45.8, 45.7, 29.4, 12.0; IR (film) 2926, 1767, 1711, 1402, 1297, 1100 cm^{-1}; HRMS (EI^{+}) calc'd for $[C_{18}H_{19}DO_8]^{+}$: *m/z* 365.1221, found 365.1216.



175

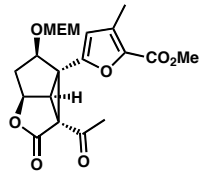
Cyclopropane 175. Cyclopropane **175** was obtained from allylic alcohol **37** using the same route employed to obtain cyclopropane **166** (Scheme 2.6.2). For the cyclopropanation reaction, cyclopropane **175** was obtained as an oil (2.9 mg, 62%). ^{1}H NMR (500 MHz, C_6D_6) δ 6.02 (s, 1H), 4.94 (d, *J* = 7.1Hz, 1H), 4.65 (d, *J* = 7.1 Hz, 1H), 4.13-4.11 (m, 1H), 3.78-3.73 (m, 1H), 3.46 (d, *J* = 4.6Hz, 1H), 3.42 (s, 3H), 2.44 (s, 3H), 2.15 (s, 3H), 1.93 (d, *J* = 14.2 Hz, 1H), 1.27 (dd, *J* = 3.2, 13.9 Hz, 1H), 0.94-0.90 (m), 0.01 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 196.0, 170.3, 159.8, 151.5, 141.2, 132.4,

115.2, 94.3, 81.6, 66.5, 56.2, 51.6, 51.1, 45.9, 46.0, 29.5, 18.6, 12.0, -0.80; IR (film) 2953, 1770, 1713, 1440, 1297 cm^{-1}; HRMS (FAB^+) calc'd for $[C_{22}H_{29}DO_8SiNa]^+$: *m/z* 474.1773, found 474.1675.



176

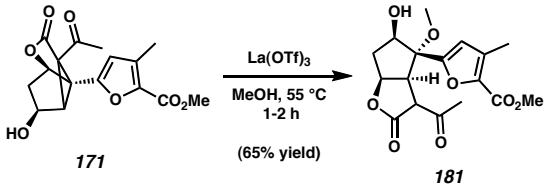
Cyclopropane 176. Cyclopropane **176** was obtained from allylic alcohol **37** using the same route employed to obtain cyclopropane **166** (Scheme 2.6.2). For the cyclopropanation reaction, cyclopropane **176** was obtained as an oil (6.5 mg, 71%). ^1H NMR (500 MHz, C_6D_6) δ 5.71 (s, 1H), 4.15-4.13 (m, 1H), 3.42 (s, 3H), 3.33 (d, *J* = 4.6 Hz, 1H), 2.45 (s, 3H), 2.13 (s, 3H), 1.63 (d, *J* = 13.7 Hz, 1H), 1.21 (dd, *J* = 3.4, 13.7 Hz, 1H), 1.09 (s, 9H), 0.29 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 196.3, 170.2, 159.7, 151.2, 141.4, 132.0, 114.4, 81.6, 53.6, 52.6, 51.4, 48.2, 45.3, 29.4, 26.3, 18.8, 11.9, -4.5, -4.6; IR (film) 2953, 2930, 2857, 1770, 1714, 1297, 1113 cm^{-1}; HRMS (FAB^+) calc'd for $[C_{22}H_{29}DO_7SiNa]^+$: *m/z* 459.1800, found 458.1749.



177

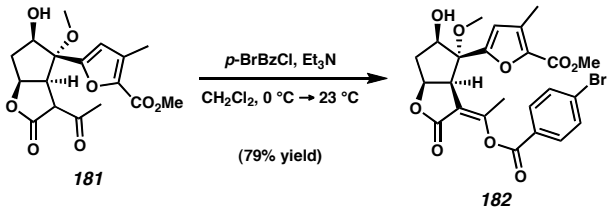
Cyclopropane 177. Cyclopropane **177** was obtained from allylic alcohol **37** using the same route employed to obtain cyclopropane **166** (Scheme 2.6.2). For the cyclopropanation reaction, thermal conditions were used, and cyclopropane **177** was

obtained as an oil (9.1 mg, 42%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.23 (s, 1H), 5.11 (m, 1H), 5.02 (d, *J* = 7.1 Hz, 1H), 4.92 (d, *J* = 7.1 Hz, 1H), 3.99 (d, *J* = 4.9 Hz, 1H), 3.86 (s, 3H), 3.83 (q, *J* = 4.4 Hz, 2H), 3.58 (t, *J* = 4.4 Hz, 2H), 3.39 (s, 3H), 2.46 (s, 3H), 2.34 (d, *J* = 14.2 Hz, 1H), 2.29 (s, 3H), 2.20 (dd, *J* = 3.2, 14.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.2, 170.1, 159.4, 149.8, 140.2, 131.9, 114.7, 94.3, 81.5, 71.6, 67.4, 59.0, 51.6, 51.4, 50.9, 45.4, 45.2, 29.1, 11.6; IR (film) 2925, 1767, 1711, 1613, 1548, 1440, 1297, 1198, 1099, 1037 cm^{-1}; HRMS (EI^{+}) calc'd for $[C_{20}H_{23}DNaO_9]^{+}$: *m*/*z* 432.1381, found 432.1365.



Alcohol 181. Furan **171** (49.0 mg, 0.153 mmol, 1.00 equiv) and La(OTf)$_3$ (89.5 mg, 0.153 mmol, 1.00 equiv) were dissolved in MeOH (3.00 mL) at ambient temperature, and then heated to 55 °C and stirred for 1–2 hours. The reaction was diluted with EtOAc and H_2O and the aqueous layer was extracted 3x with EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography using 60:40 EtOAc:Hexanes to afford alcohol **181** as an oil (35 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.34 (s, 1H), 5.30 (br, 1H), 5.17 (t, *J* = 7.3 Hz, 1H), 4.64 (d, *J* = 3.8 Hz, 1H), 4.10 (t, *J* = 6.7 Hz, 1H), 3.91 (d, *J* = 5.5 Hz, 1H), 3.89 (s, 3H), 3.03 (s, 3H) 2.50 (ddd, *J* = 4.1, 7.1, 15.4 Hz, 1H), 2.43 (s, 3H), 2.47 (s, 3H), 2.20 (d, *J* = 15.4 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 200.0, 172.4, 159.9, 154.3, 140.9, 132.1, 116.2, 88.5, 83.5, 77.0, 58.6, 51.4, 51.4, 45.9, 40.0, 29.6,

11.8; IR (film) 3474, 2952, 1769, 1717, 1297, 1195, 1098 cm^{-1}; HRMS (EI^+) calc'd for $[C_{17}H_{21}O_8Na]^+$: *m/z* 353.1236, found 353.1246.



Furan 182. Triethylamine (43.0 μL , 306 μmol, 4.00 equiv) was added at 0 °C and under N_2, to a solution of alcohol **181** (27.0 mg, 76.6 μmol, 1.00 equiv) in CH_2Cl_2 (955 μL). After 1 minute, *p*-bromobenzoyl bromide (42.0 mg, 192 μmol, 2.50 equiv) was added, and the reaction was stirred for 30 minutes at 0 °C. The reaction was allowed to warm to ambient temperature and stir for an additional 1 hour. The reaction was then diluted with Et_2O and H_2O, the layers were separated, and the aqueous layer was washed once with Et_2O. The Et_2O layers were combined, washed with saturated $NaHCO_3$ (aq.), washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. Crystals suitable for X-ray analysis were obtained by crystallization of crude furan **182** (54 mg, 98% yield) from EtOAc:heptane. ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 2H), 6.38 (s, 1H)5.06 (t, *J* = 6.4 Hz, 1H), 4.46 (q, *J* = 7.2, 3.5 Hz, 1H), 3.80 (m, 4H), 3.18 (s, 3H), 2.45 (s, 3H), 2.37 (m, 1H), 2.33 (s, 3H), 2.28 (d, *J* = 3.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 162.0, 159.9, 153.5, 139.9, 132.0, 131.9, 131.6, 129.2, 129.0, 127.6, 115.8, 115.3, 88.7, 79.8, 52.6, 52.3, 51.5, 38.5, 17.1, 11.6; IR (film) 3445, 2950, 1749, 1705, 1589, 1439, 1399, 1300, 1231, 1070, 1010 cm^{-1}; HRMS (EI^+) calc'd for $[C_{24}H_{23}BrO_9]^+$: *m/z* 557.0423, found 557.0427. mp = 158-159 °C (EtOAc:Heptane).

2.10 Notes and References

[1] Marrero, J.; Rodriguez, A. D.; Baran, P.; Raptis, R. G.; Sanchez, J. A.; Ortega-Barria, E.; Capson, T. L. *Org. Lett.* **2004**, *6*, 1661–1664.

[2] For verrillin, see: Rodriguez, A. D.; Shi, Y. P. *J. Org. Chem.* **2000**, *65*, 5839–5842.; For ineleganolide, see: Duh, C. Y.; Wang, S. K.; Chiang, M. Y. *Tetrahedron Lett.* **1999**, *40*, 6033–6035.; For scabrolide A, see; Sheu, J. H.; Ahmed, A. F.; Shiue, R. T.; Dai, C. F.; Kuo Y. H. *J. Nat. Prod.* **2002**, *65*, 1904–1908.

[3] The dihydrofuran unit actually disguises a 1,4 enedione moiety. However, as in ineleganolide (**108**) and scabrolide A (**109**), the olefin may further undergo various reactions such as 1,4-hetero-Michael addition or an olefin migration, respectively.

[4] An oxocane is an 8-membered ethereal ring that is fully saturated.

[5] (a) Roethle, P. A.; Trauner, D. *Org. Lett.* **2006**, *8*, 345–347. (b) Roethle, P. A.; Hernandez, P. T.; Trauner, D. *Org. Lett.* **2006**, *8*, 5901–5904.

[6] For example, bipinnatin A can undergo two different cycloisomerization reactions to provide two known natural products. For examples, see: (a) Rodriguez, A. D.; Shi, J.-G. *J. Org. Chem.* **1998**, *63*, 420–421. (b) Rodriguez, A. D.; Shi, J.-G.; Huang, S. D. *J. Org. Chem.* **1998**, *63*, 4425–4432.

[7] Doroh, B.; Sulikowski, G. A. *Org. Lett.* **2006**, *8*, 903–906.

[8] Although this is possible, it is also feasible that the undesired diradical intermediate **120** is higher in energy and undergoes σ-bond rotation to the desired diradical intermediate **118**. Since neither diradical intermediate **118** or **120** has been observed,

one can only speculate as to how prevalent σ-bond rotation is, as well as its impact on the diastereoselectivity.

[9] Miao, R.; Subramanian, G. G.; Lear, M. L. *Tetrahedron Lett.* **2009**, *50*, 1731–1733.

[10] Although the addition of water into the oxocarbenium ion is shown as the last step of the mechanism, it is possible that this may occur at any point after cyclopropane fragmentation.

[11] Khatuya, J. *Tetrahedron Lett.* **2001**, *42*, 2643–2644.

[12] (a) Knochel, P.; Cahiez, G.; Rottlander, M.; Boymond, L. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1701–1703. (b) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 3333–3336.

[13] Myers, A.; Dragovich, P. S. *J. Am. Chem. Soc.* **1993**, *115*, 7021–7022.

[14] Johnson, C. R.; Braun, M. P.; Ruel, F. S. *Org. Synth.* **1996**, *75*, 69–72.

[15] For a related system that provides nonsymmetrical α-diazomalonates, see: Kido, F.; Yamaji, K.; Abiko, T.; Kato, M. *J. Chem. Res.* **1993**, 18–19.

[16] Prepared using standard diazotization conditions (see S.I.).

[17] Although the crude product could be crystallized to higher purity using 95% EtOH at –20 °C overnight, the crude solid was used in the coupling reaction and still provided acceptable yields.

[18] Meyer, M. E.; Ferreira, E. M.; Stoltz, B. M. *Chem. Commun.* **2006**, 1316–1318.

[19] For examples of α-diazo-β-ketoamides, see: (a) Jeganathan, A.; Richardson, S. K.; Mani, R. S.; Haley, E. B.; Watt, D. S. *J. Org. Chem.* **1986**, *51*, 5362–5367. (b) Padwa,

A.; Zhi, L. *J. Am. Chem. Soc*. **1990**, *112*, 2037–2038. (c) Padwa, A.; Dean, D. C.; Fairfax, D. J.; Xu, S. L. *J. Org. Chem*. **1993**, *58*, 4646–4655.

[20] For examples of $Cu(TBSal)_2$ being used in total synthesis, see: (a) Corey, E. J.; Myers, A. G. *Tetrahedron Lett*. **1984**, *25*, 3559–3562. (b) Corey, E. J.; Wess, G.; Xiang, Y. B.; Singh, A. K. *J. Am. Chem. Soc*. **1987**, *109*, 4717–4718. (c) Singh, A. K.; Bakshi, R. K.; Corey, E. J. *J. Am. Chem. Soc*. **1987**, *109*, 6187–6189. (d) Fukuyama, T.; Chen, X. *J. Am. Chem. Soc*. **1994**, *116*, 3125–3126. (e) Fernandez, M. A.; Barba, L. *J. Org. Chem*. **1995**, *60*, 3580–3585.

[21] The only isolated product from this reaction other than starting material was an α-hydroxy-β-ketoester that resulted from the overall addition of water to the "carbene".

[22] Germal, A. L.; Luche, J. L. *J. Am. Chem. Soc*. **1981**, *103*, 5454–5459.

[23] For a study of reduction conditions for a similar enone, see: Curran, T. T.; Hay, D. A.; Koegel, C. P. *Tetrahedron* **1997**, *53*, 1983–2004.

[24] Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc*. **2001**, 123, 7725–7726.

[25] In a separate run, ketone **136** was obtained in 40% yield and 93% ee after 18 hours.

[26] Dess, D. B.; Martin, J. C. *J. Org. Chem*. **1991**, 113, 7277–7287.

[27] Deuterium labeling may not be needed if the ^1H NMR spectra of cyclopropane **166**, alcohol **171**, and ketone **172**, are attained in C_6D_6, and each spectrum is analyzed and compared. The spectra, in C_6D_6, for these three compounds are in Appendix 2.2 (Spectra of Compounds Relevant to Chapter 2).

[28] All compounds in Figure 2.6.2 had partial deuterium incorporation at C(1) similar to cyclopropane **166** in Scheme 2.6.5.

[29] Spartan calculations (semi-empirical, AM1) show that undesired alcohol **171** is 4.3 kcal lower in energy than desired alcohol **167**.

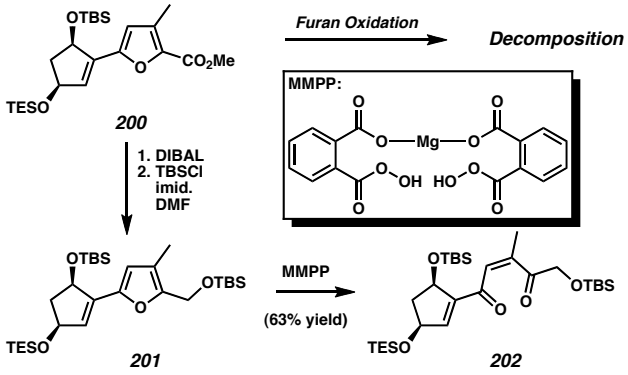
[30] For examples of nucleophilic addition into a cyclopropane ring, see: (a) Danishefsky, S.; Dynak, J. *J. Org. Chem.* **1974**, *39*, 1979–1980. (b) Isobe, M.; Lio, H.; Kawai, T.; Goto, T. *J. Am. Chem. Soc.* **1978**, *100*, 1940–1942. (c) Callant, P.; Wilde, H. D.; Vaderwalle, M. *Tetrahedron* **1981**, *37*, 2079–2084.

[31] See Appendix 2.1 for our attempts to form a macrocycle.

[32] For an example of a domino Michael addition followed by an aldol addition to provide a fused cyclobutane ring, see: (a) Ihara, M.; Toyota, M.; Fukumoto, K. *J. Chem. Soc. Perkin Trans. I* **1986**, 2151–2161. (b) Ihara, M.; Ohnishi, M.; Takano, M. *J. Am. Chem. Soc.* **1992**, *114*, 4408–4410. (c) Ihara, M.; Taniguchi, T.; Makita, K.; Takano, M.; Ohnishi, M.; Taniguchi, N.; Fukumoto, K.; Kabuto, C. *J. Am. Chem. Soc.* **1993**, *115*, 8107–8115. (d) Takasu, K.; Misawa, K.; Ihara, M. *Tetrahedron Lett.* **2001**, *42*, 8489–8491. (e) Stelmakh, A.; Stellfeld, T.; Kalesse, M. *Org. Lett.* **2006**, *8*, 3485–3488.

[33] (a) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258–3260. (b) Holmquist, C. R.; Roskamp, E. J. *Tetrahedron Lett.* **1992**, *33*, 1131–1134. (c) Kanemasa, S.; Kanai, T.; Araki, T.; Wada, E. *Tetrahedron Lett.* **1999**, *40*, 5055–5058.

[34] Furan **200** can be treated with MMPP to provide enedione **202** in an unoptomized 63% yield:



[35] Roizen, J. L.; Progress Toward an Enantioselective Total Synthesis of Ineleganolide. Ph.D. Thesis, California Institute of Technology, Pasadena, CA, 2009.

[36] Ueda, Y.; Roberge, G.; Vinet, V. *Can. J. Chem.* **1984**, *62*, 2936–2939.

[37] Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958–964.

[38] Doyle, M. P.; Davies, S. B.; May, E. J. *J. Org. Chem.* **2001**, *66*, 8112–8119.

[39] This starting alcohol (**156**) was prepared in the same manner as compound **158**, using phenyl boronic acid as the coupling partner. It was also made via a known route, see: D'Auria, M. *Heterocycles* **2000**, *52*, 185–194.

[40] Reul, F. S.; Braun, M. P.; Johnson, C. R. *Org. Synth.* **1996**, *75*, 69–72.

[41] Zhu, L.; Duquette, J.; Zhang, M. *J. Org. Chem.* **2003**, *68*, 3729–3732.

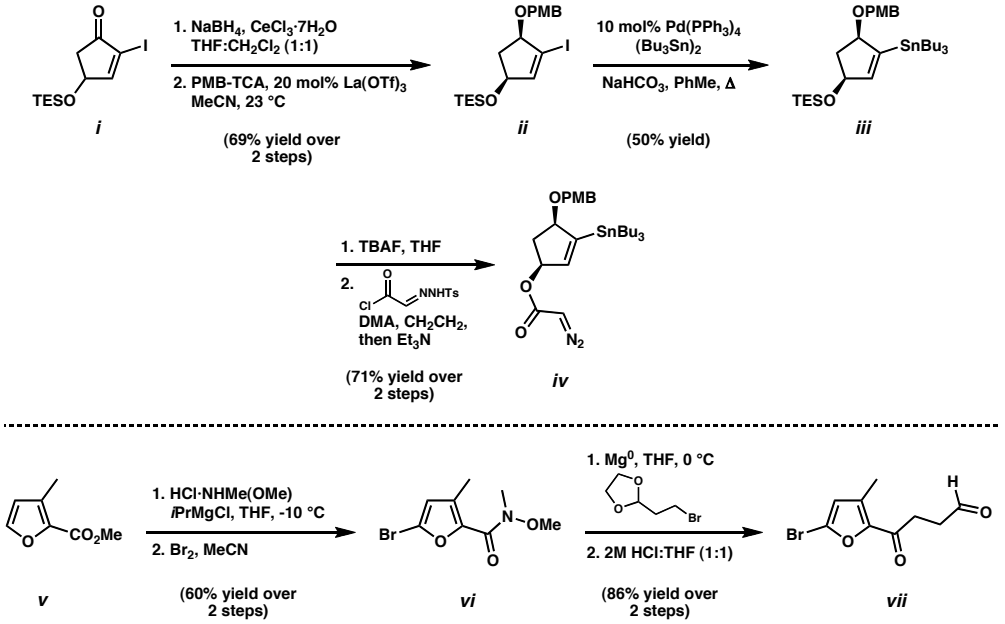
[42] For a separate sample, alcohol **37** at 70% ee, gave an $[\alpha]_D^{24.9}$ +16.9.

Appendix 2.1

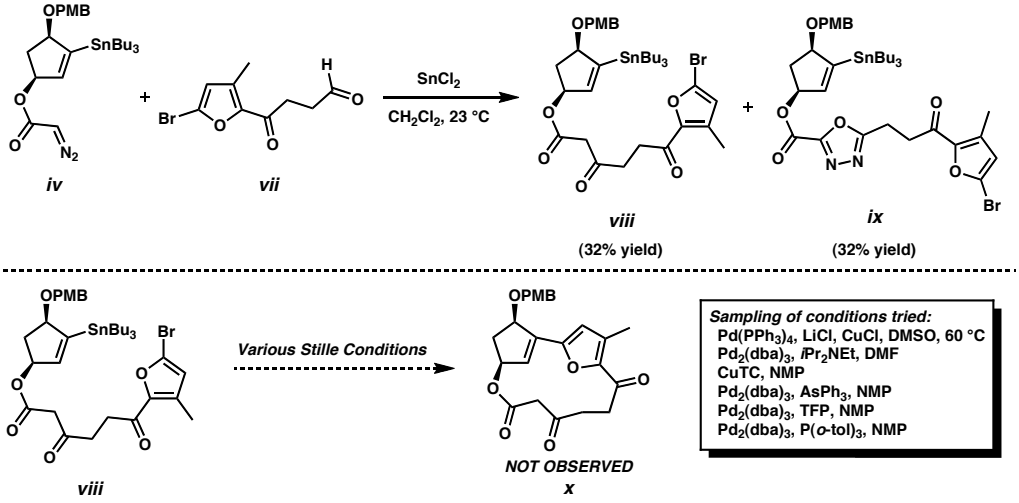
Failed Synthetic Approaches Toward a Macrocyclic Intermediate

(All Characterization Data Obtained for Compounds **i–xx** in Appendix 2.1 can be found in "JHP Characterized Compounds" binder)

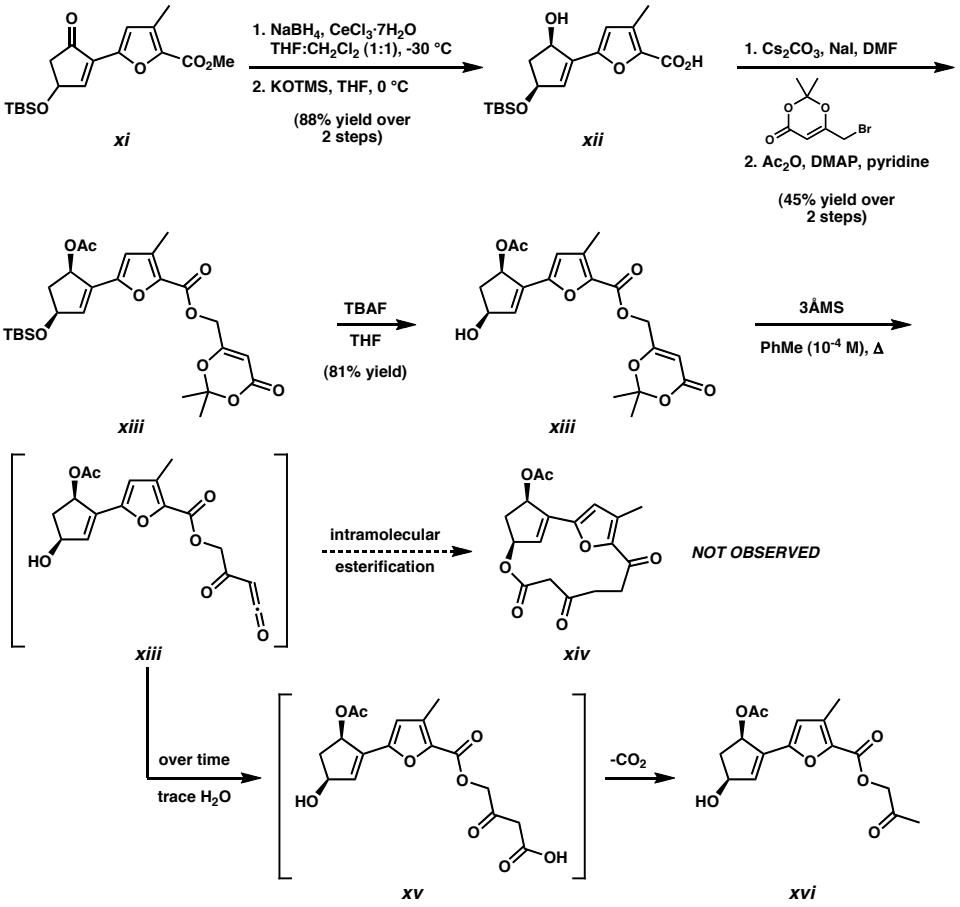
Scheme A2.1.1 Stille coupling route: formation of vinyl halide and vinyl stannane.



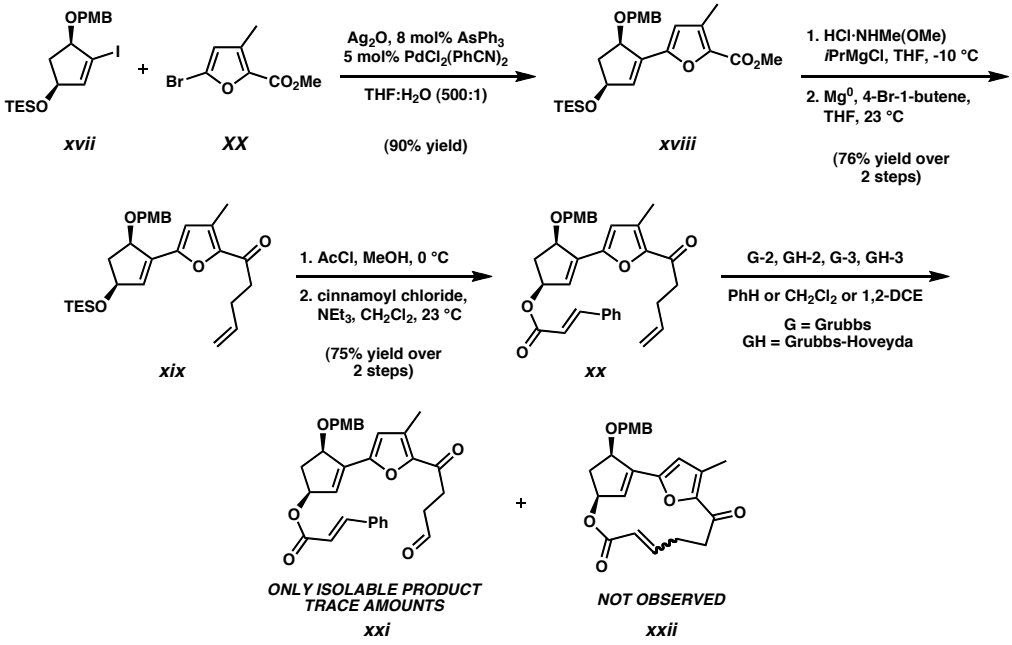
Scheme A2.1.2 Stille coupling route: Attempts at macrocyclization.



Scheme A2.1.3 Intramolecular esterification route.



Scheme A2.1.4 Ring closing metathesis route.



Appendix 2.2

Spectra of Compounds Relevant to Chapter Two

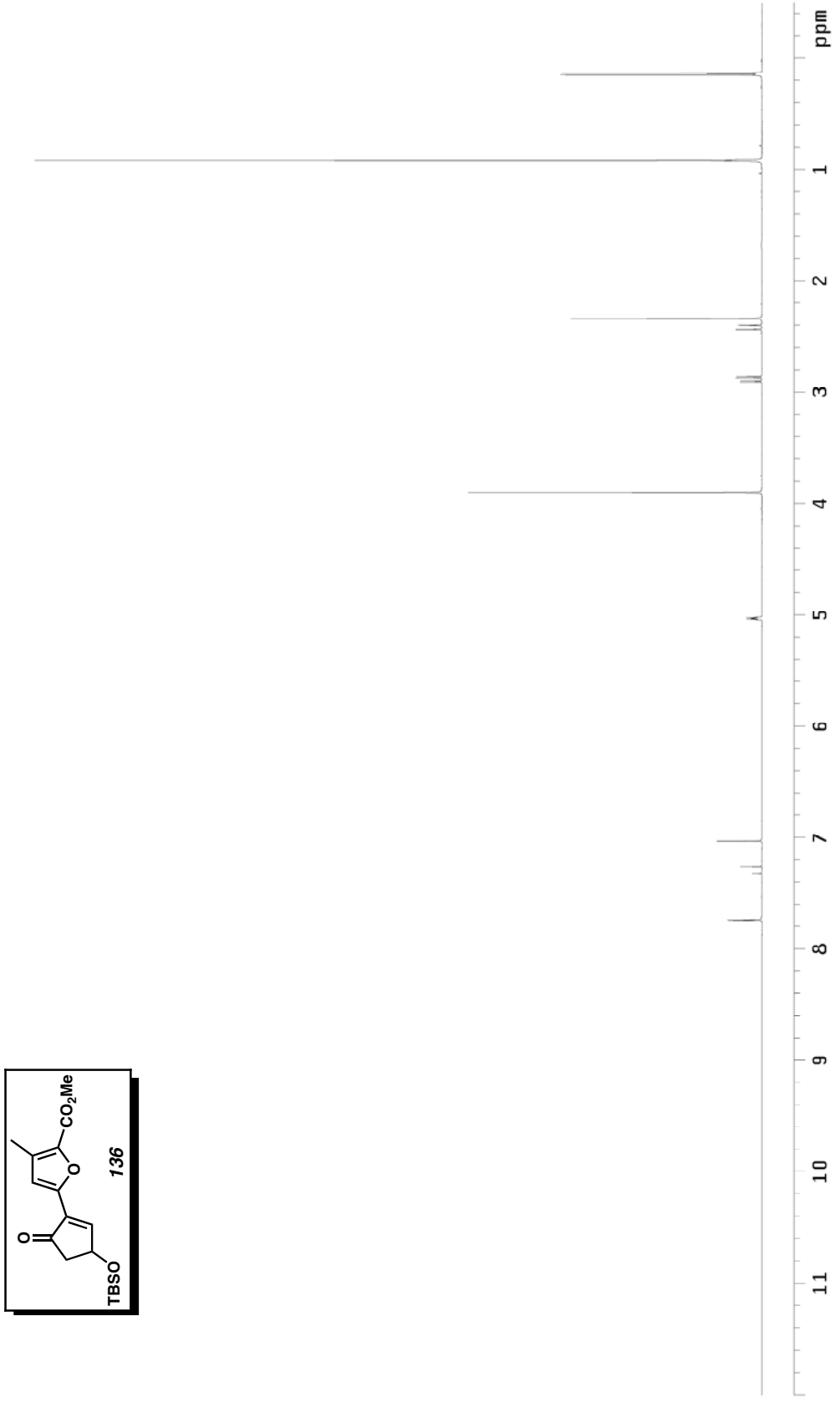


Figure A2.2.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **136**

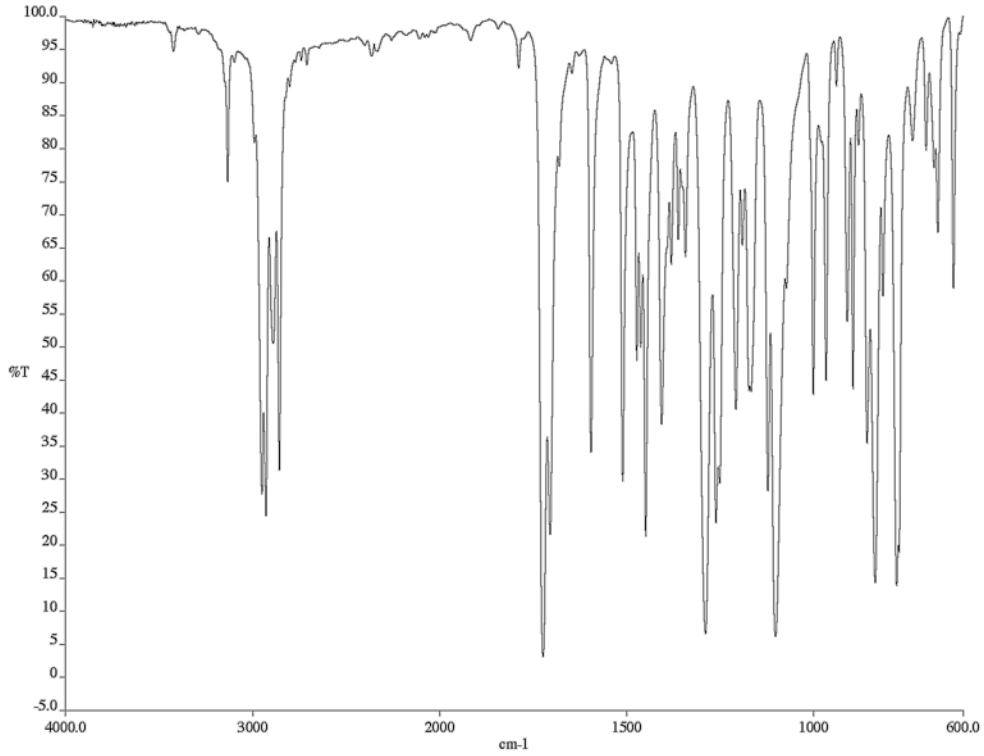


Figure A2.2.2 Infrared spectrum (film/NaCl) of compound **136**

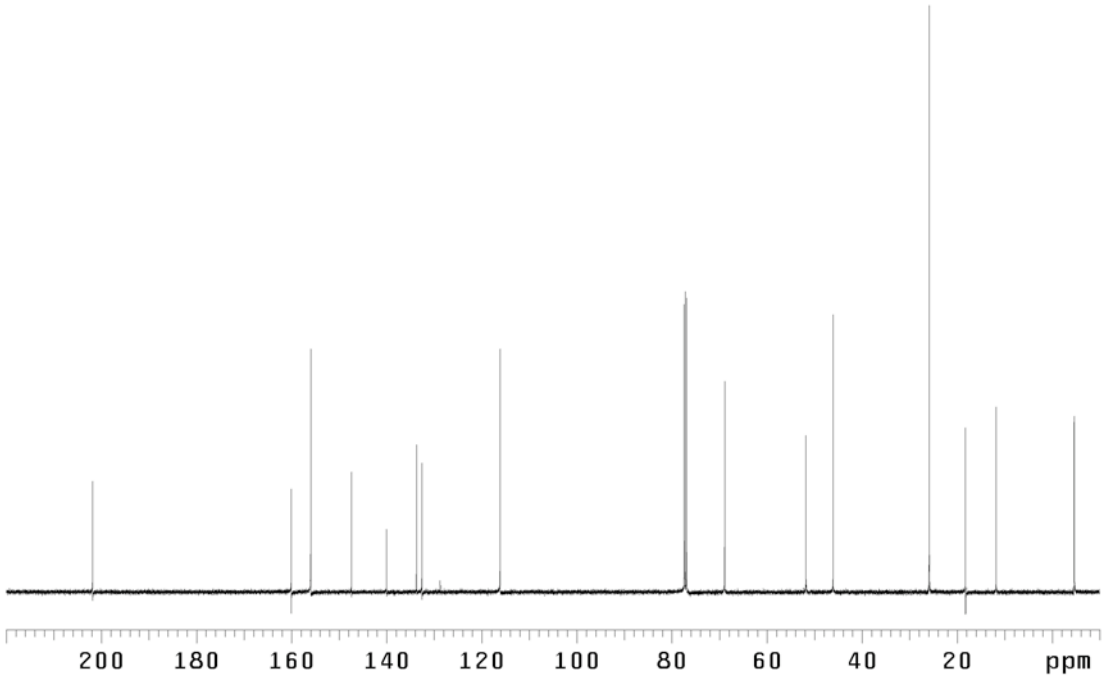


Figure A2.2.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **136**

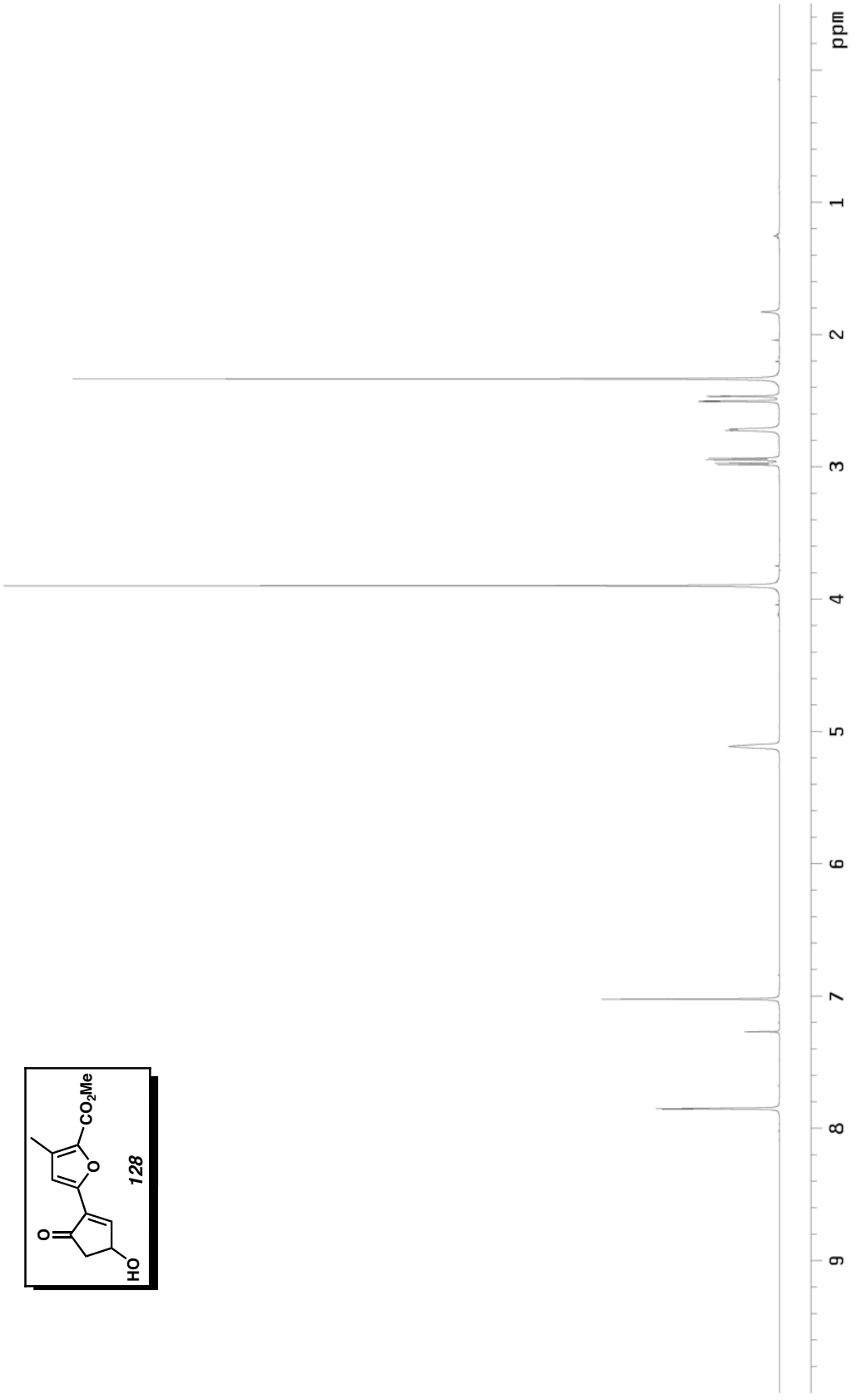


Figure A2.2.4 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **128**

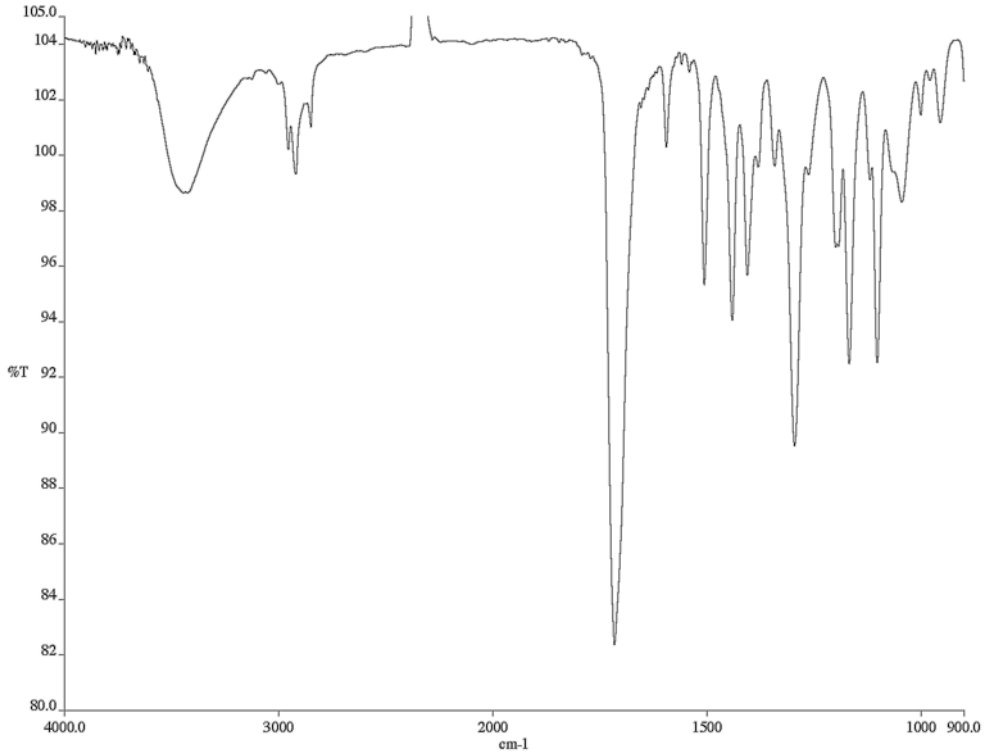


Figure A2.2.5 Infrared spectrum (film/NaCl) of compound **128**

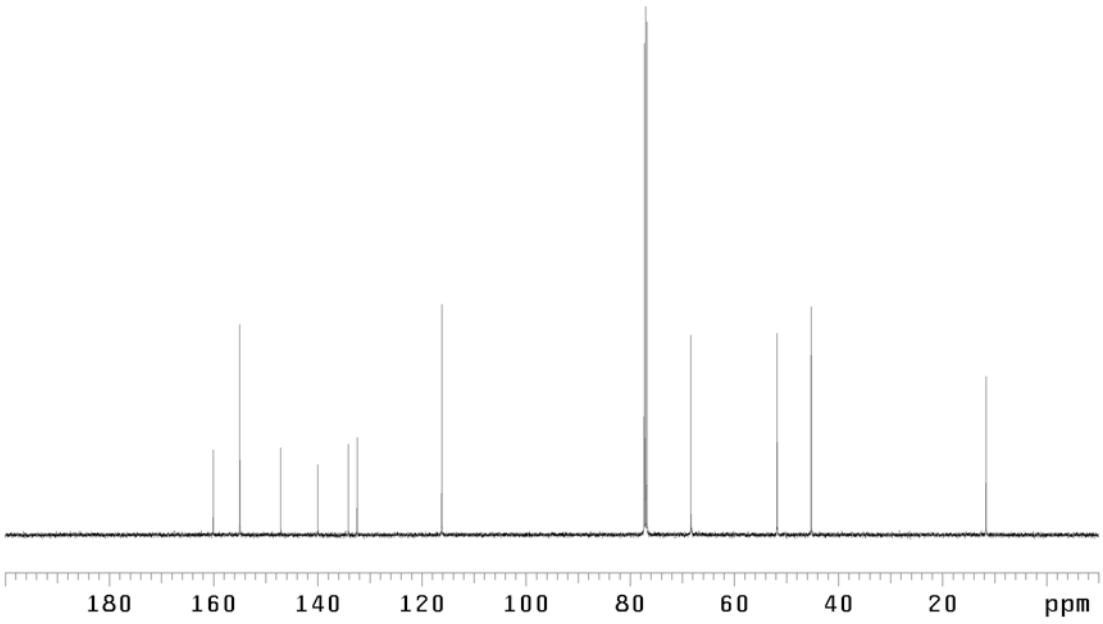


Figure A2.2.6 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **128**

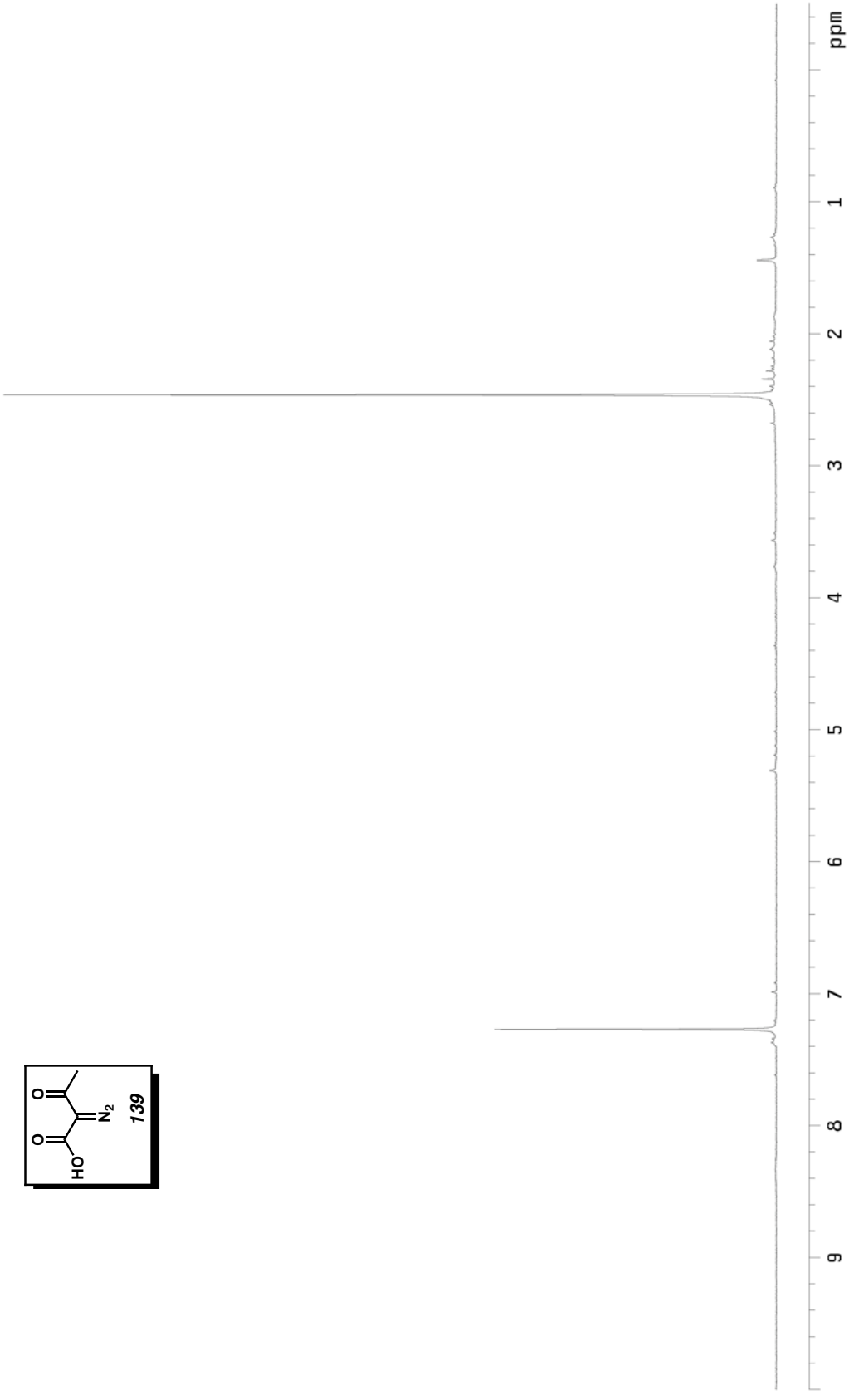


Figure A2.2.7 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **139**

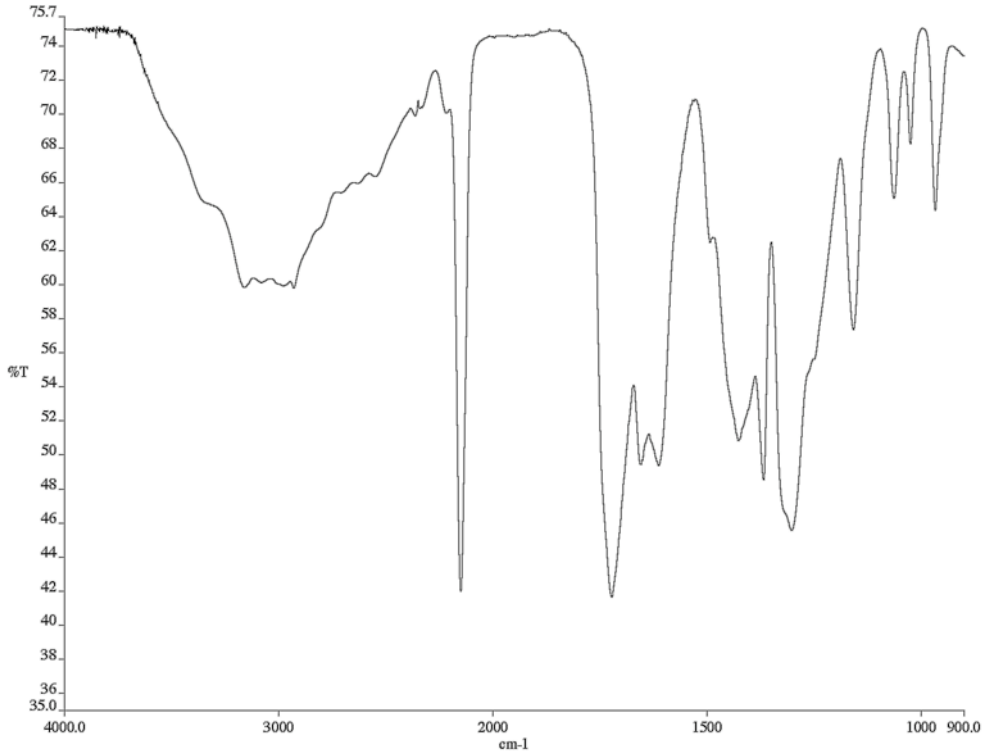


Figure A2.2.8 Infrared spectrum (film/NaCl) of compound **139**

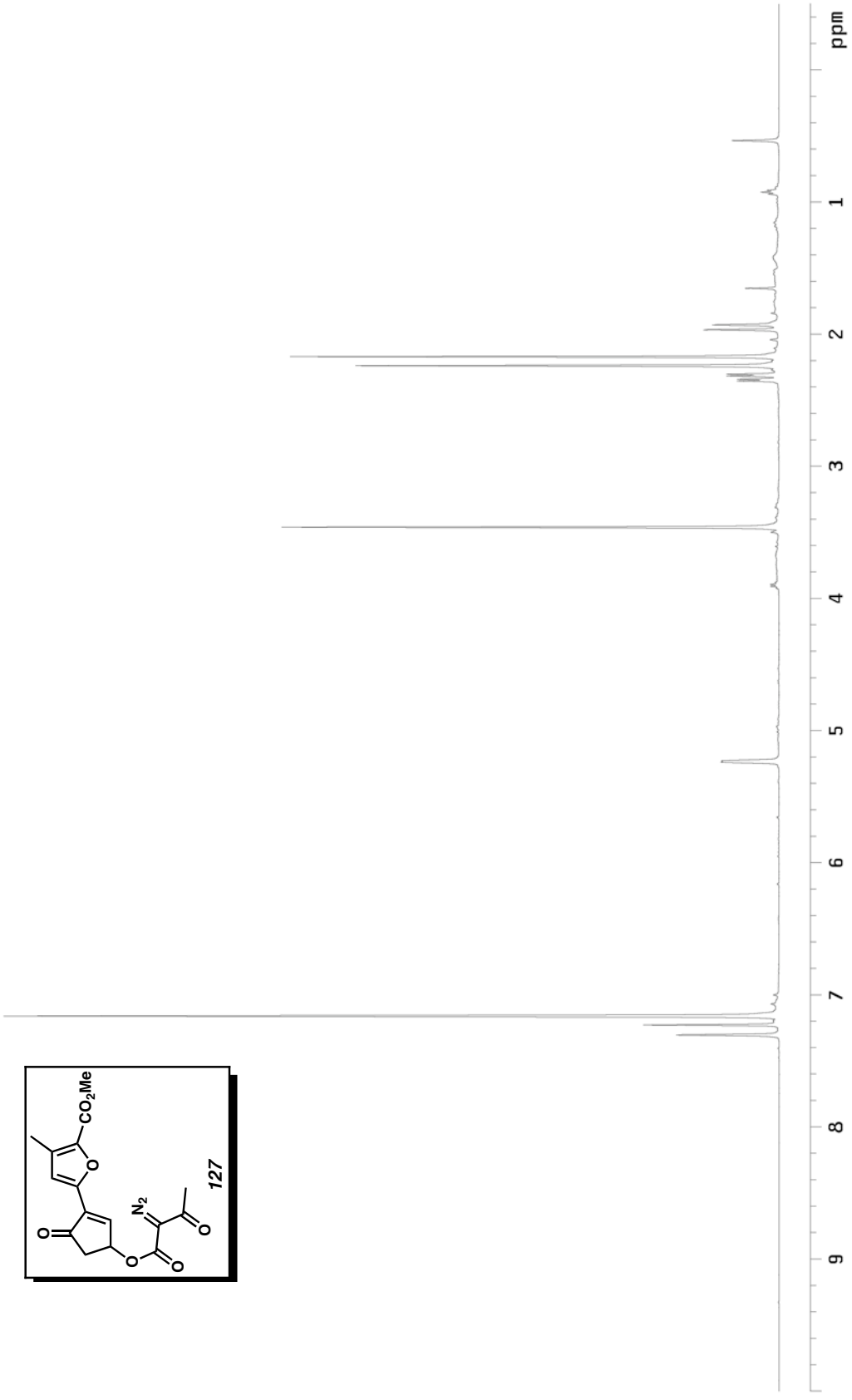


Figure A2.2.9 ^{1}H NMR (500 MHz, C_6D_6) of compound **127**

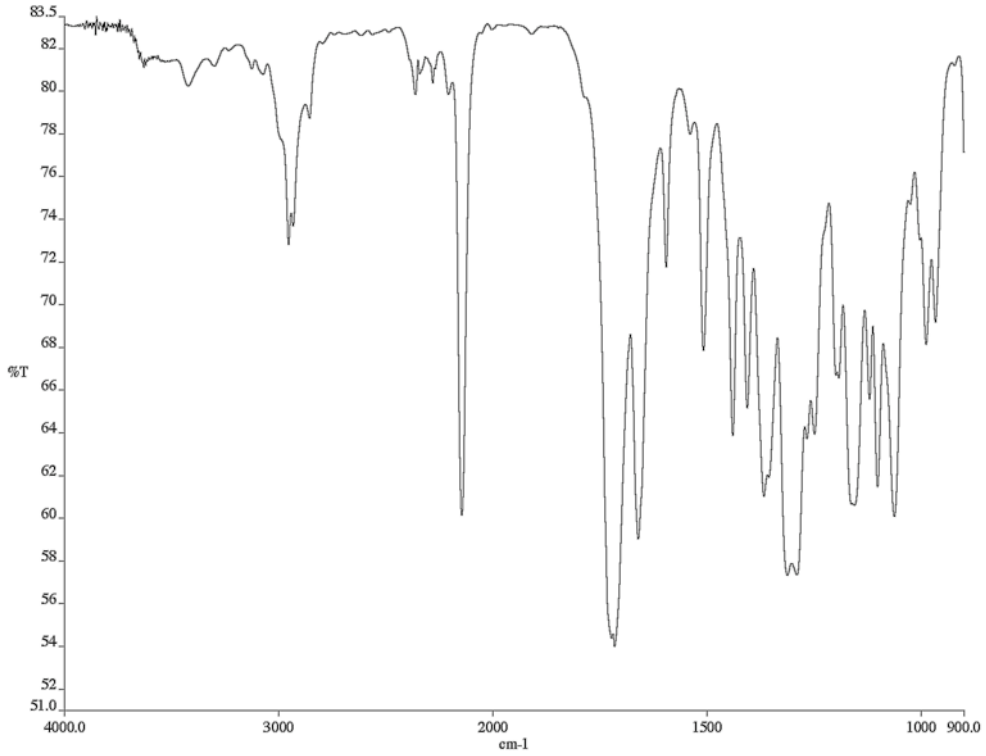


Figure A2.2.10 Infrared spectrum (film/NaCl) of compound **127**

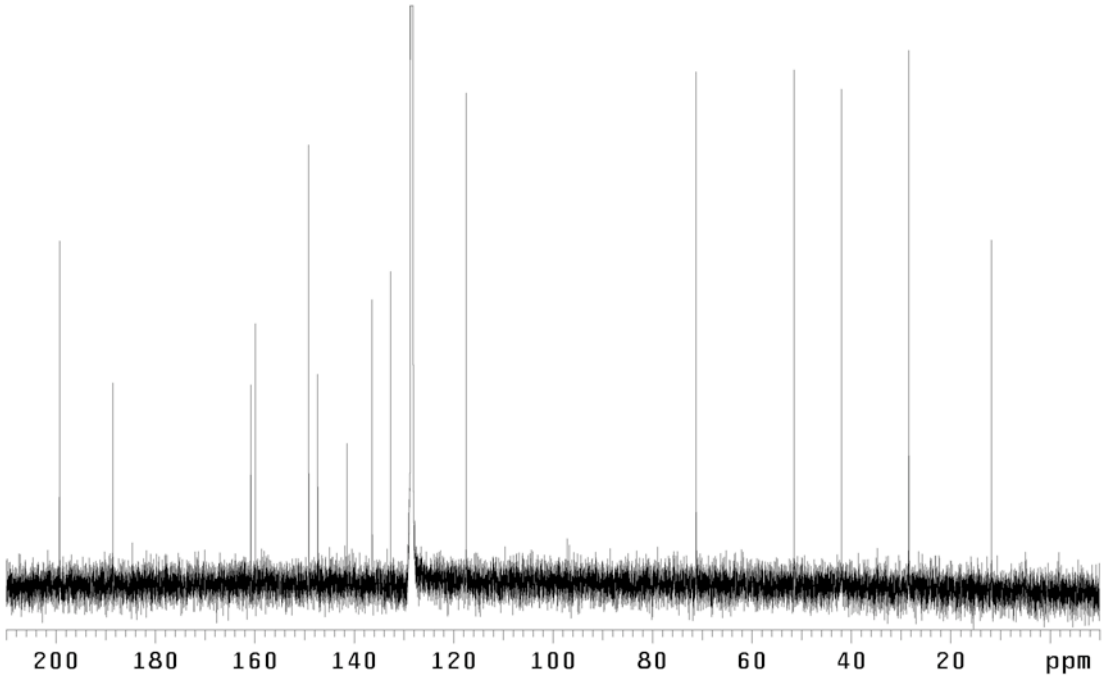


Figure A2.2.11 ^{13}C NMR (125 MHz, C_6D_6) of compound **127**

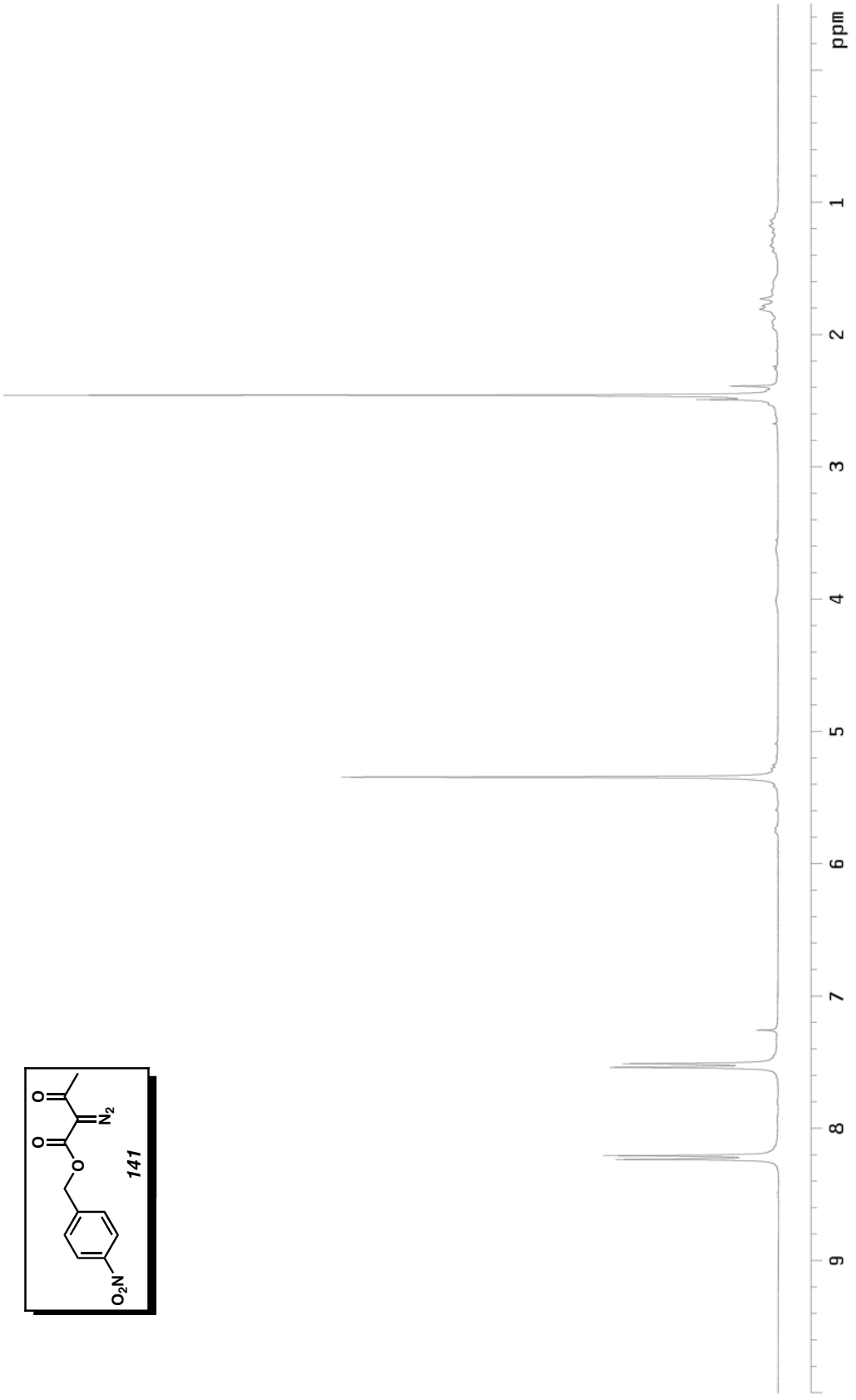


Figure A2.2.12 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **141**

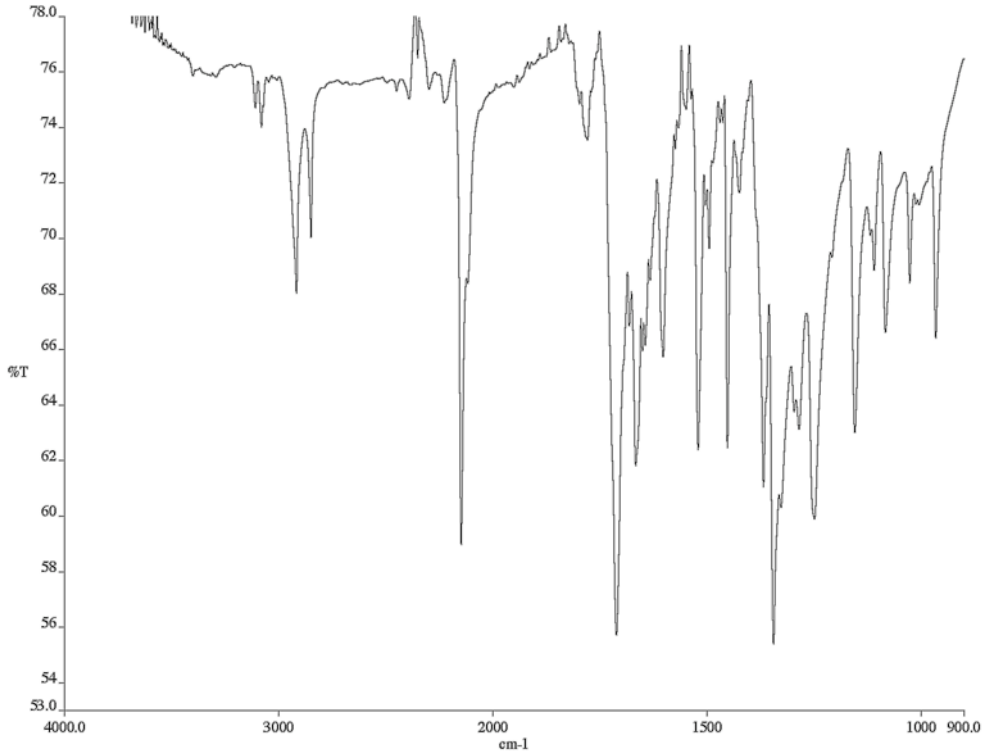


Figure A2.2.13 Infrared spectrum (film/NaCl) of compound **141**

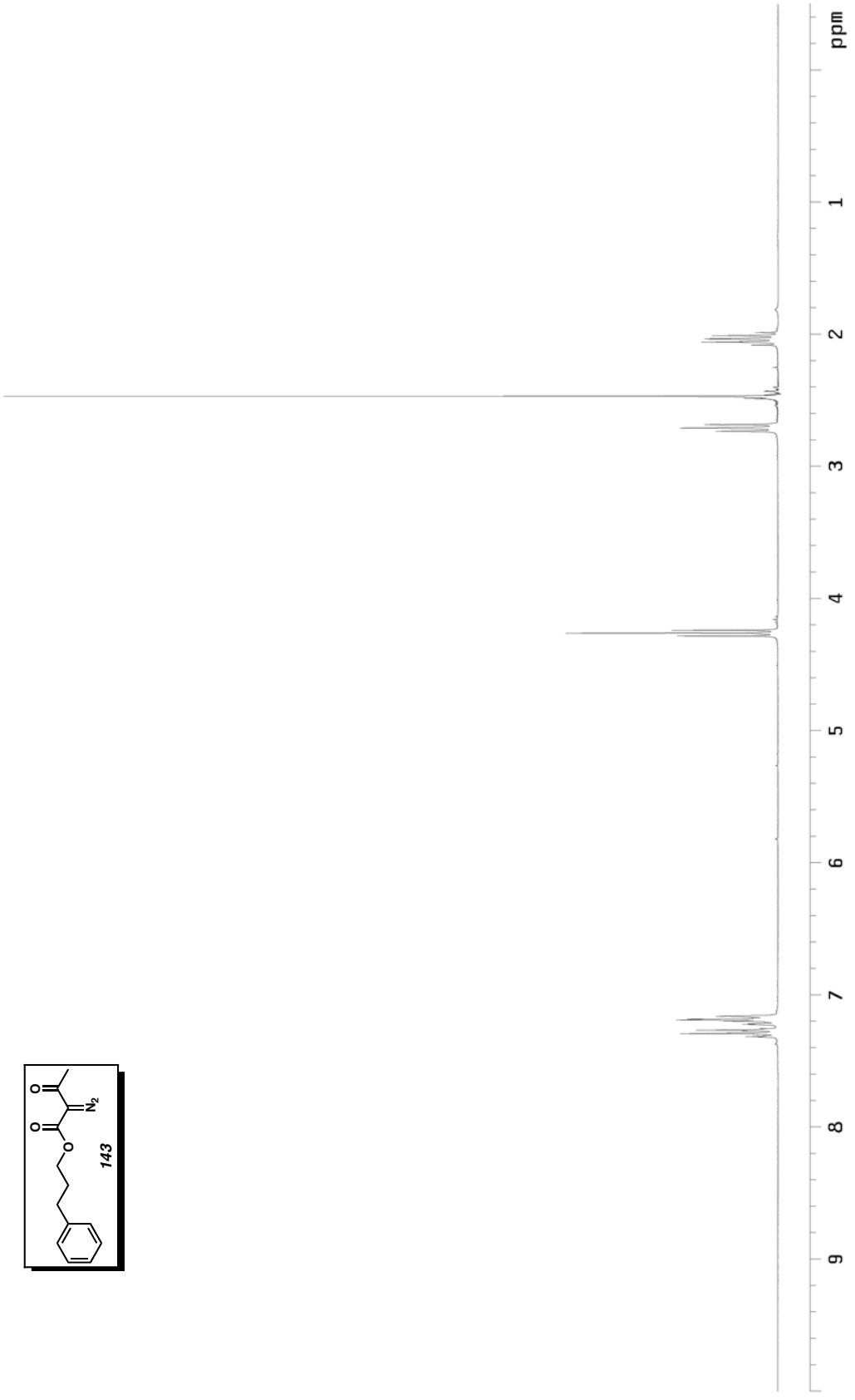


Figure A2.2.14 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **143**

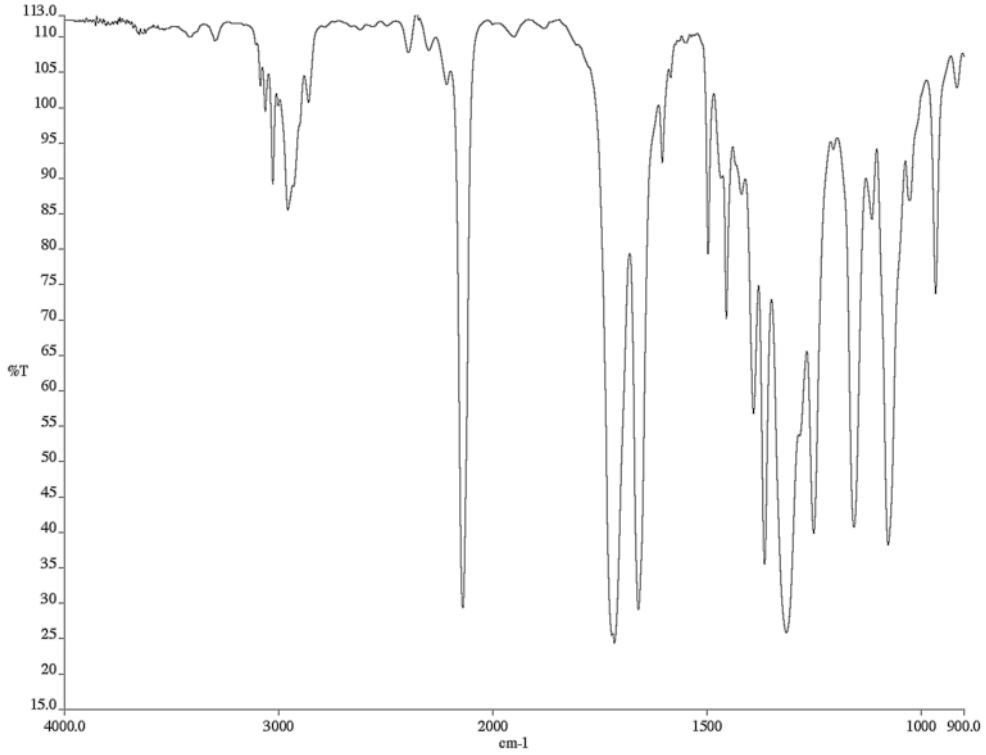


Figure A2.2.15 Infrared spectrum (film/NaCl) of compound **143**

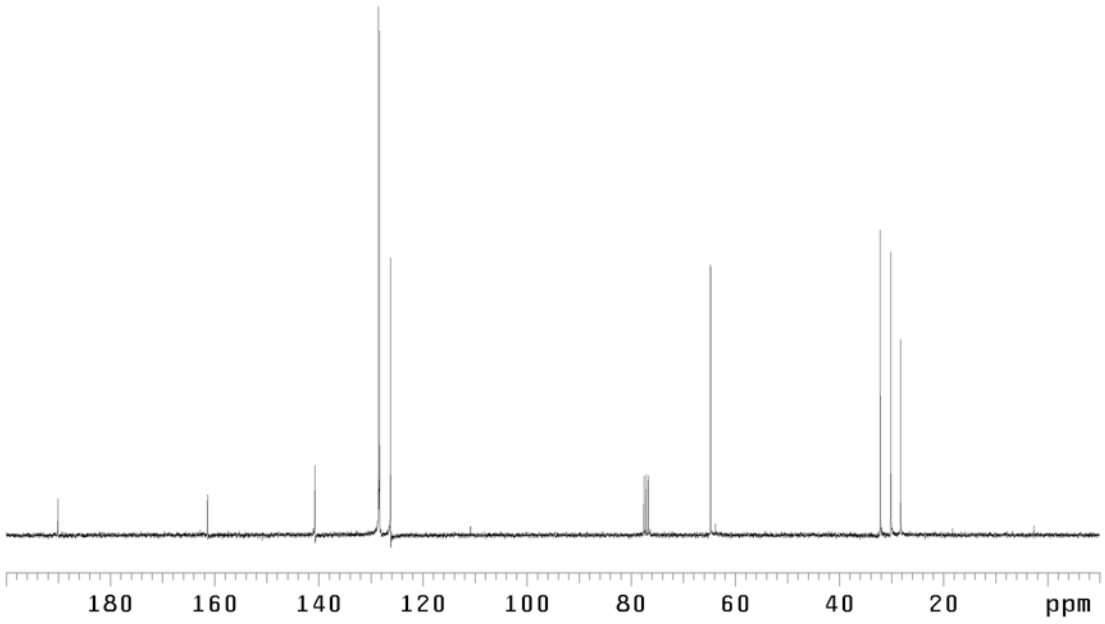


Figure A2.2.16 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **143**

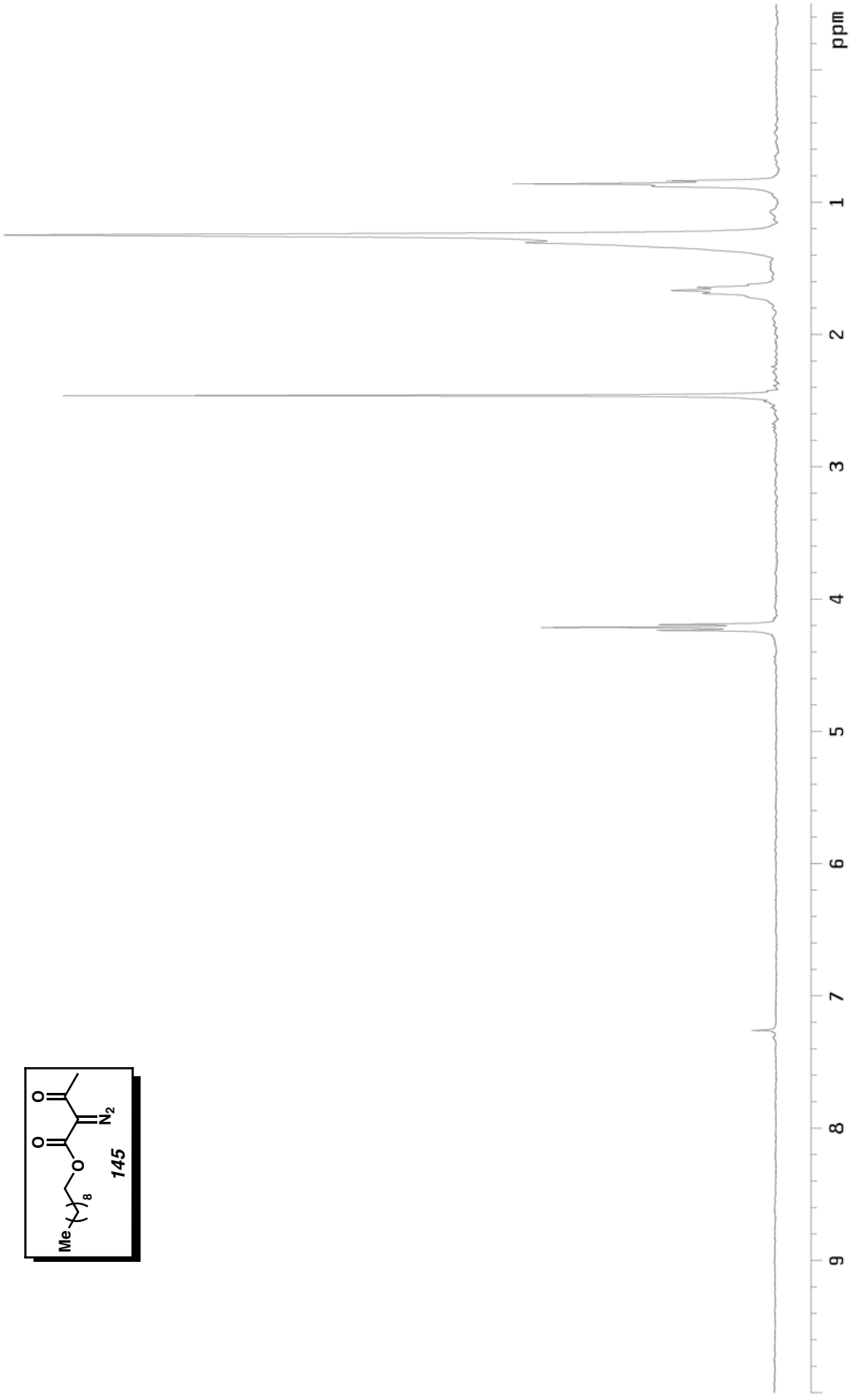


Figure A2.2.17 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **145**

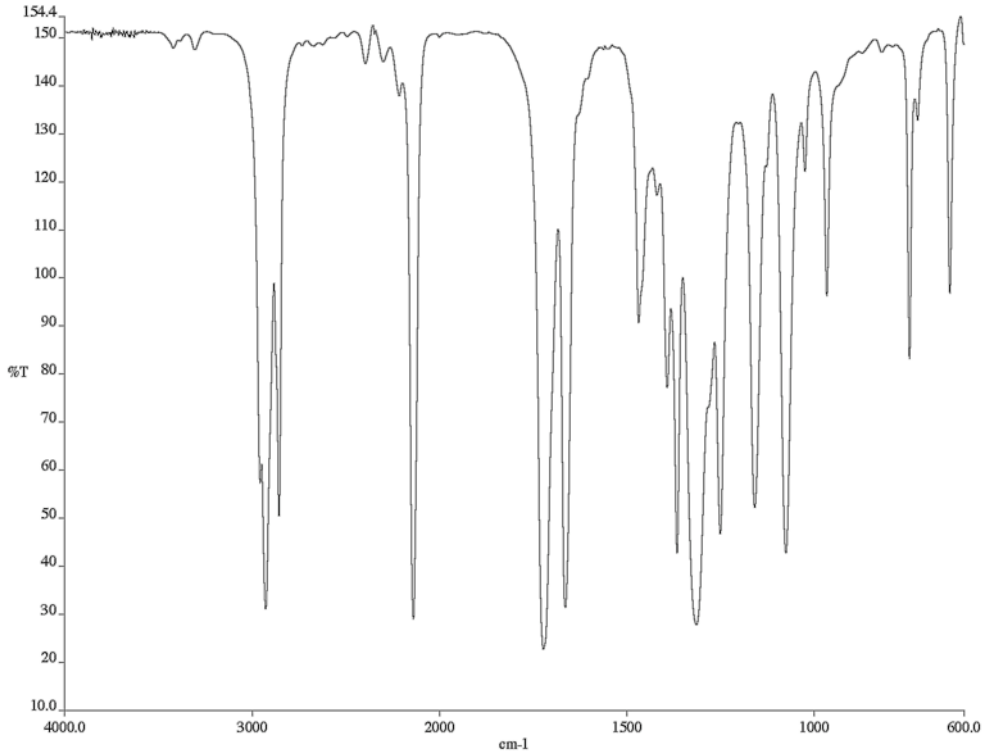


Figure A2.2.18 Infrared spectrum (film/NaCl) of compound **145**

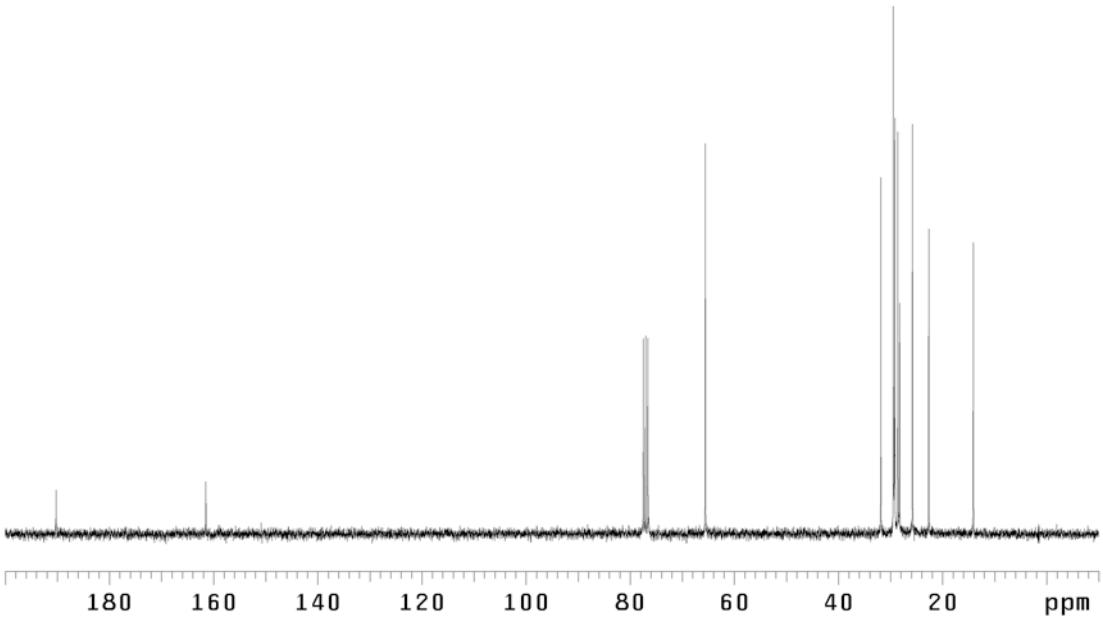


Figure A2.2.19 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **145**

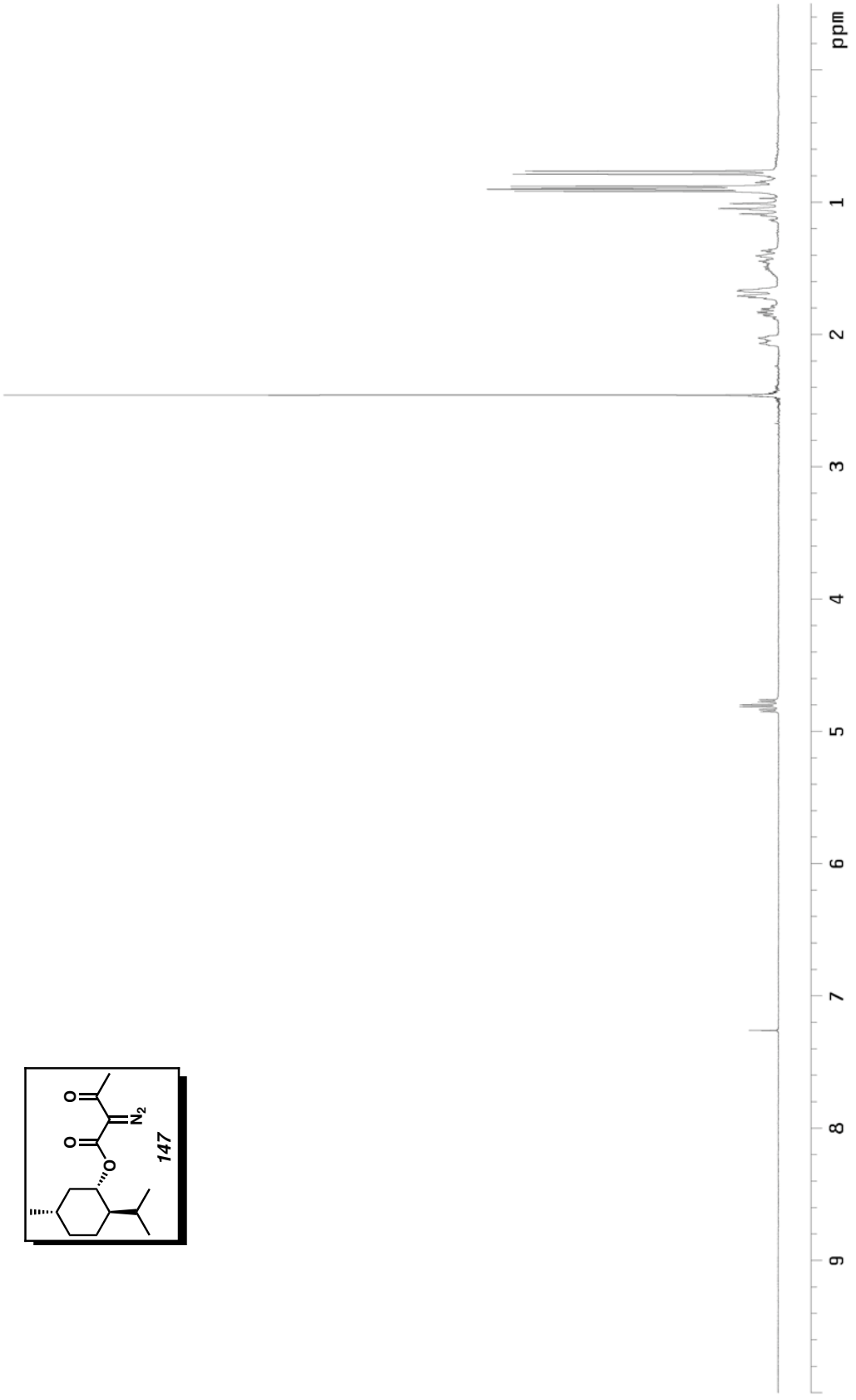


Figure A2.2.20 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **147**

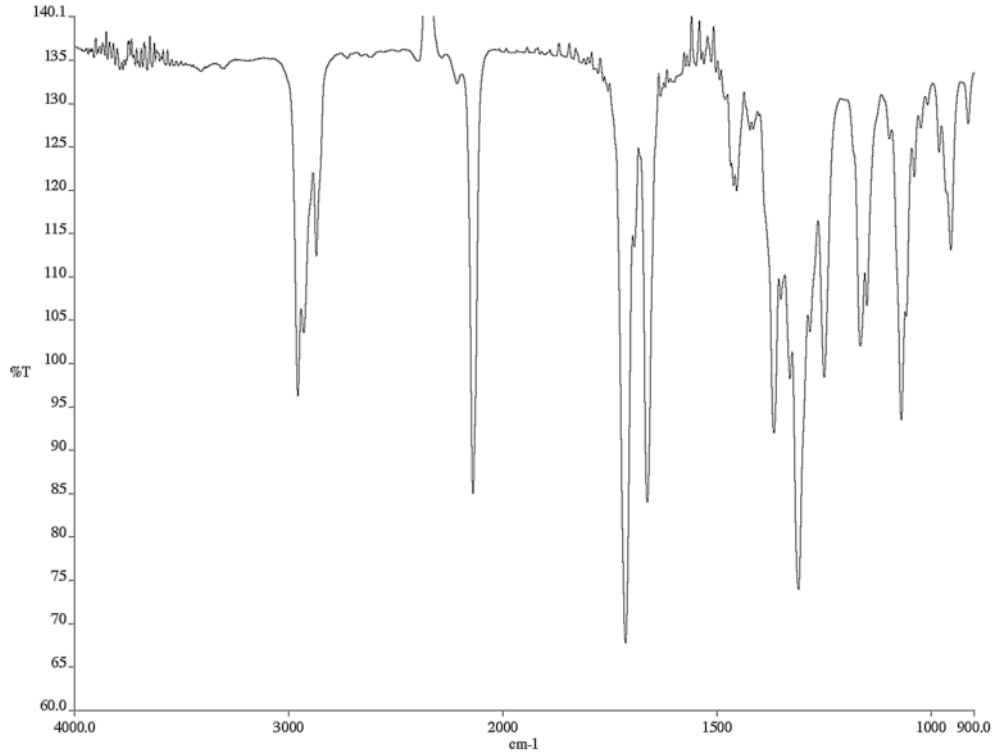


Figure A2.2.21 Infrared spectrum (film/NaCl) of compound **147**

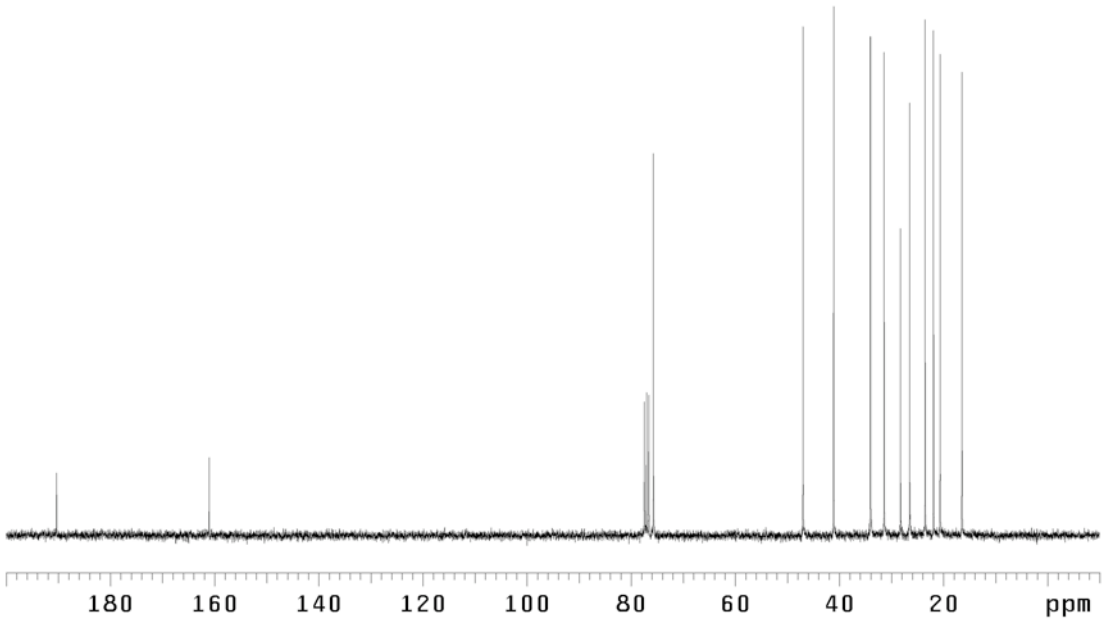


Figure A2.2.22 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **147**

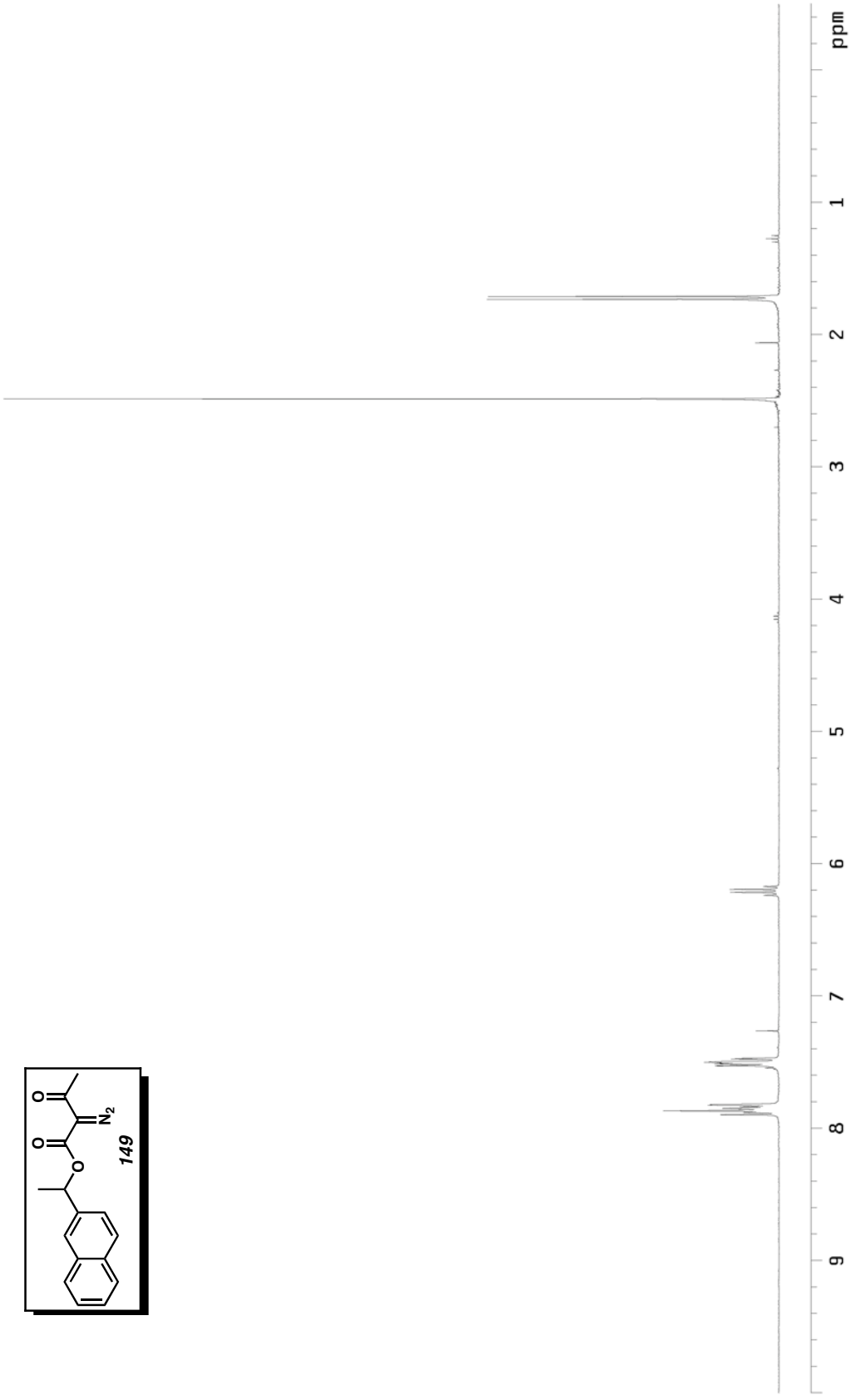


Figure A2.2.23 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **149**

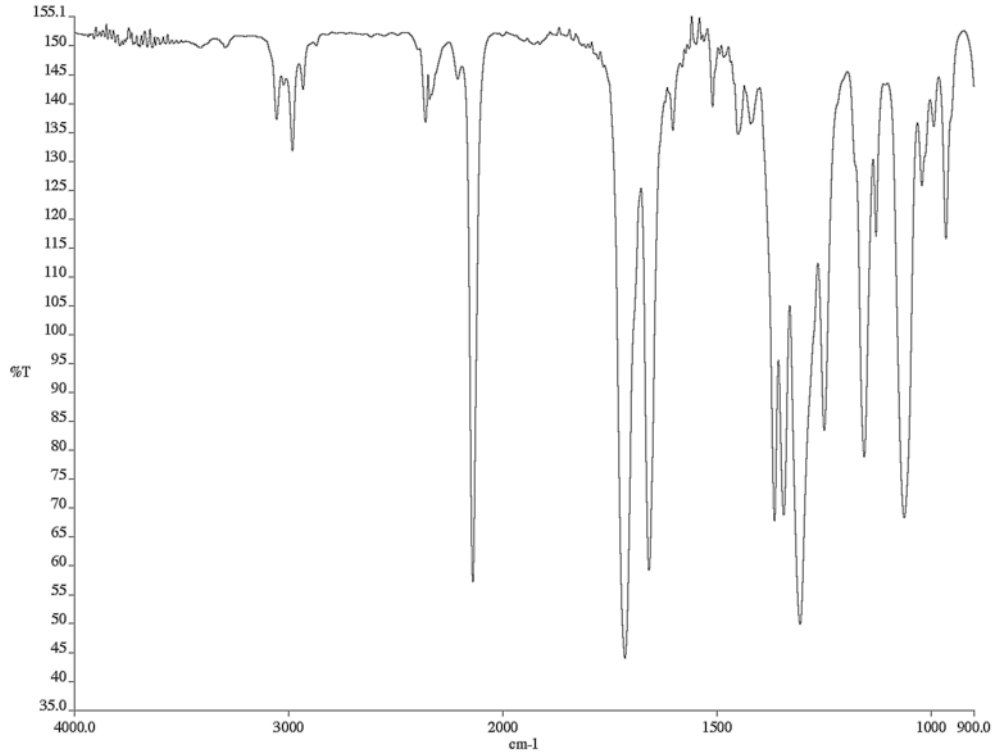


Figure A2.2.24 Infrared spectrum (film/NaCl) of compound **149**

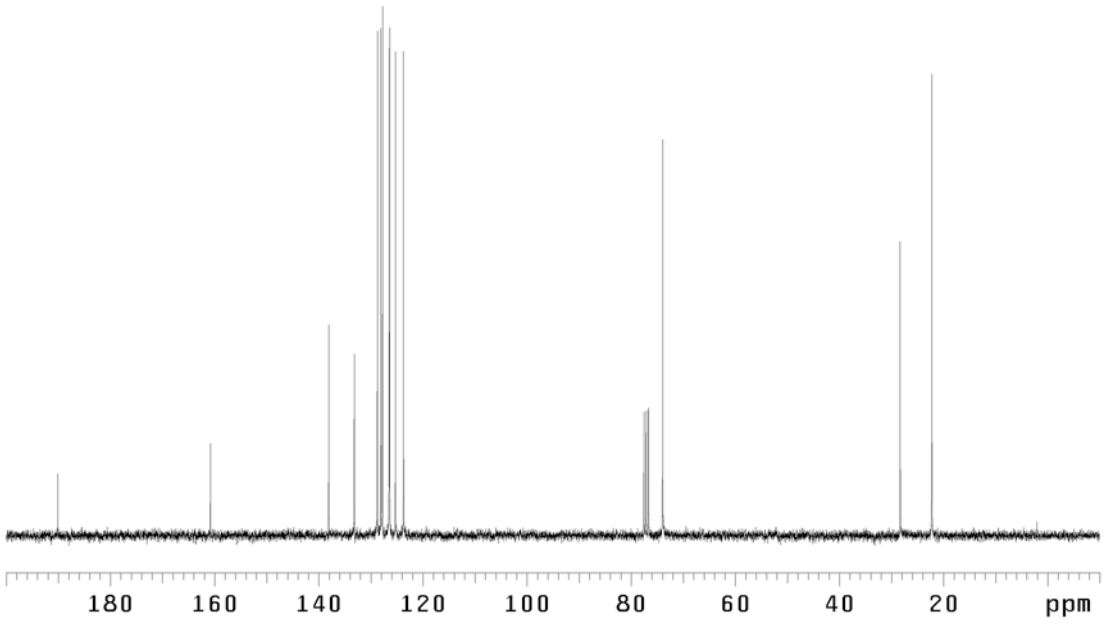


Figure A2.2.25 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **149**

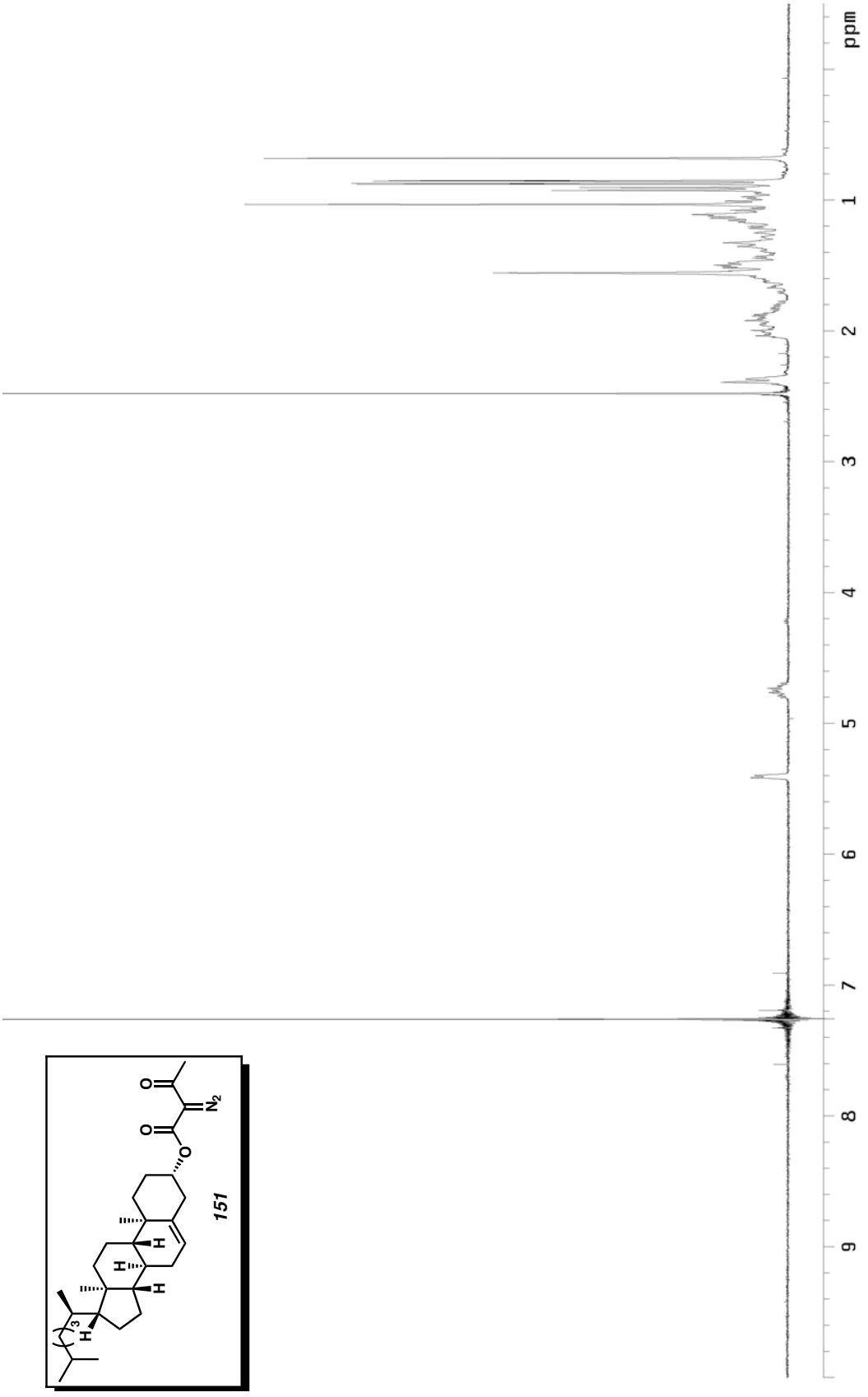


Figure A2.2.26 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **151**

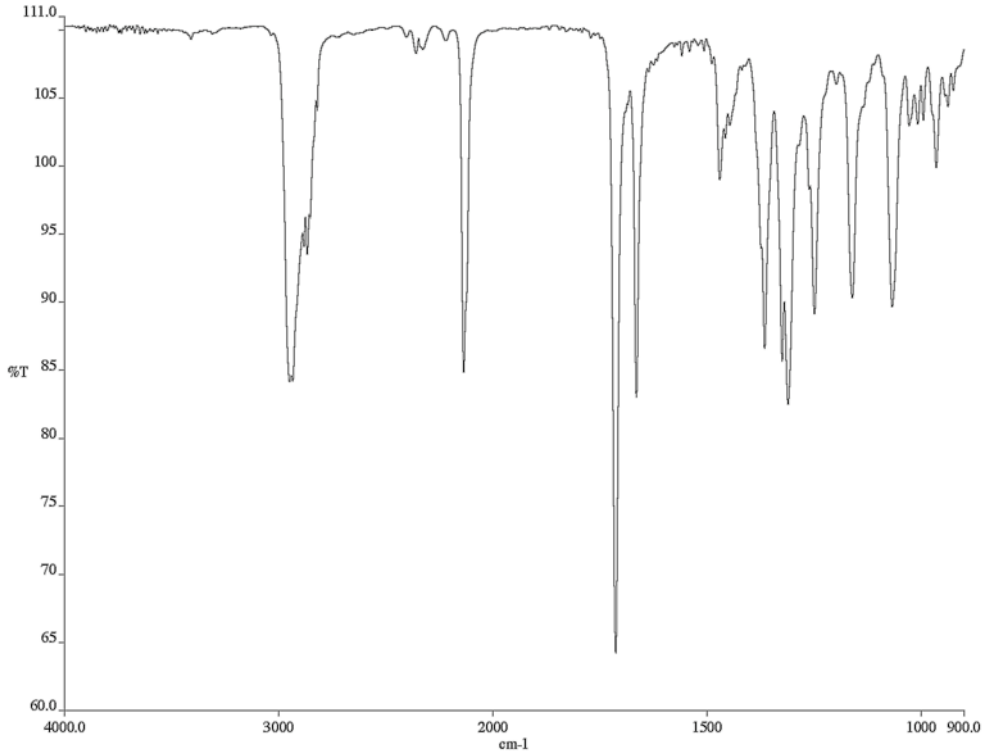


Figure A2.2.27 Infrared spectrum (film/NaCl) of compound **151**

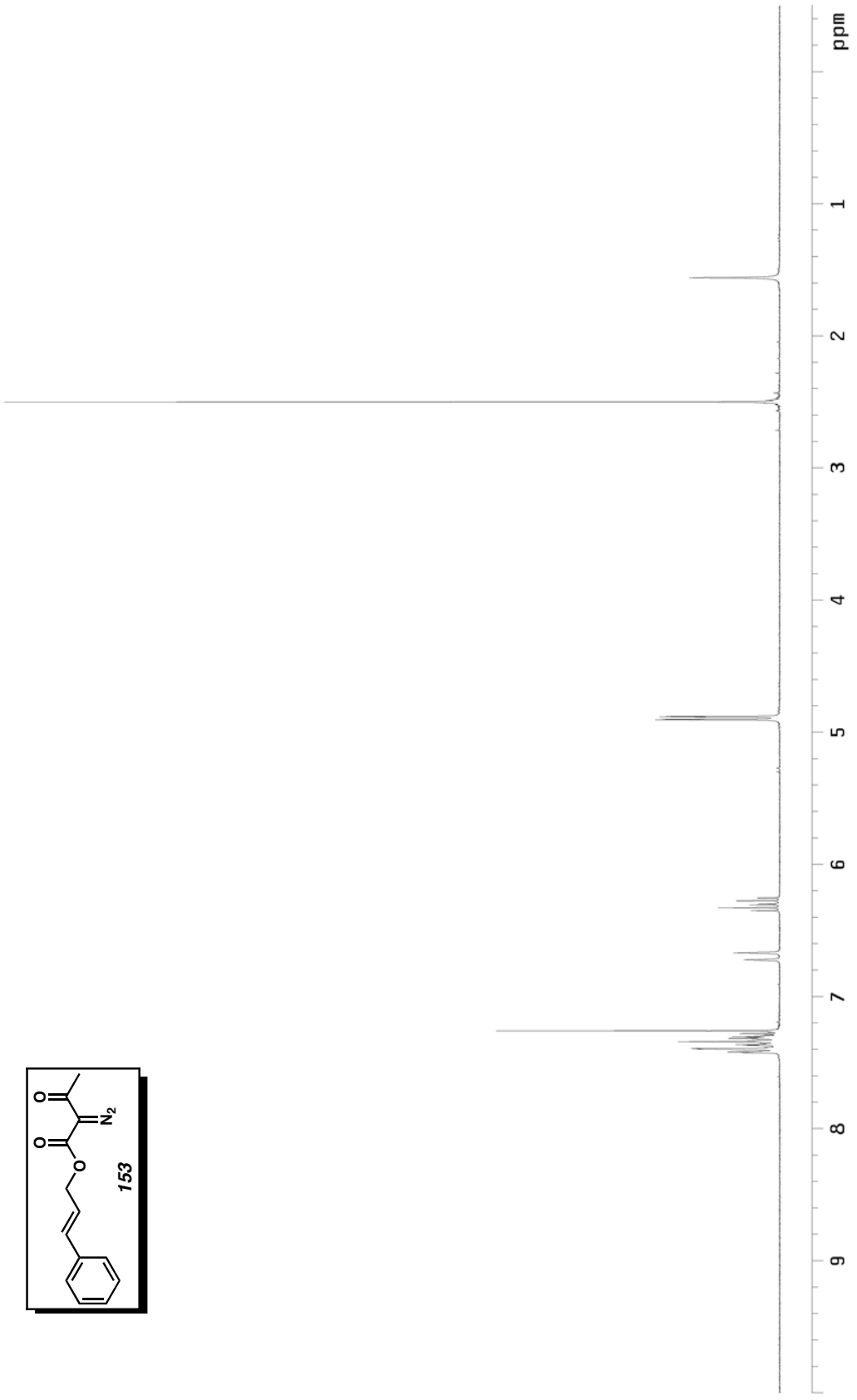


Figure A2.2.28 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **153**

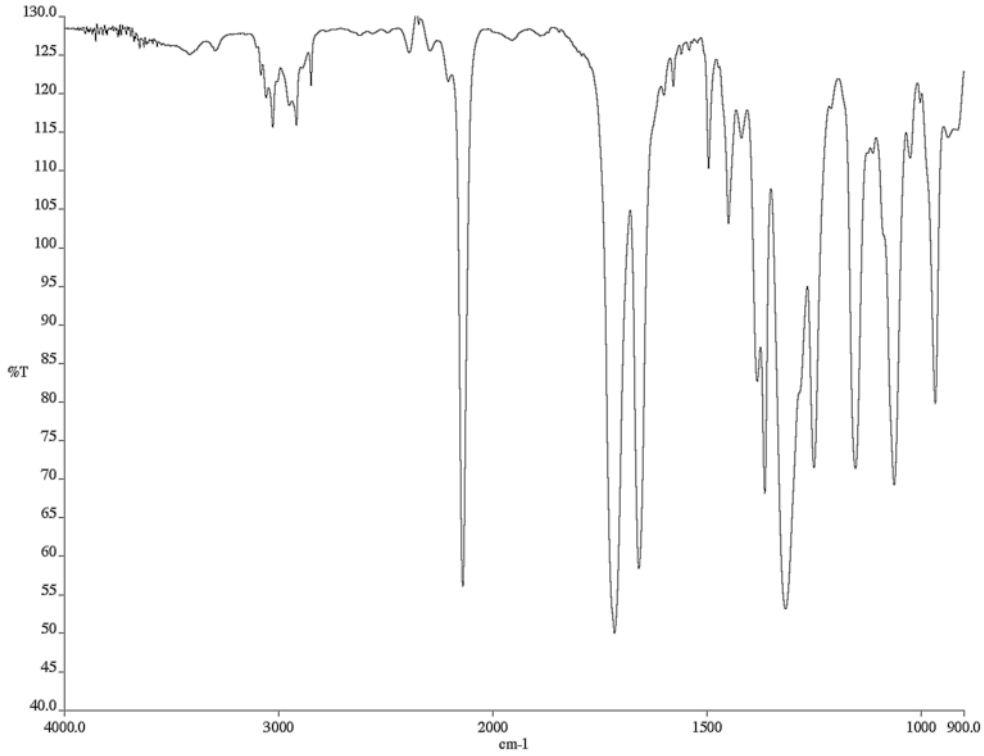


Figure A2.2.29 Infrared spectrum (film/NaCl) of compound **153**

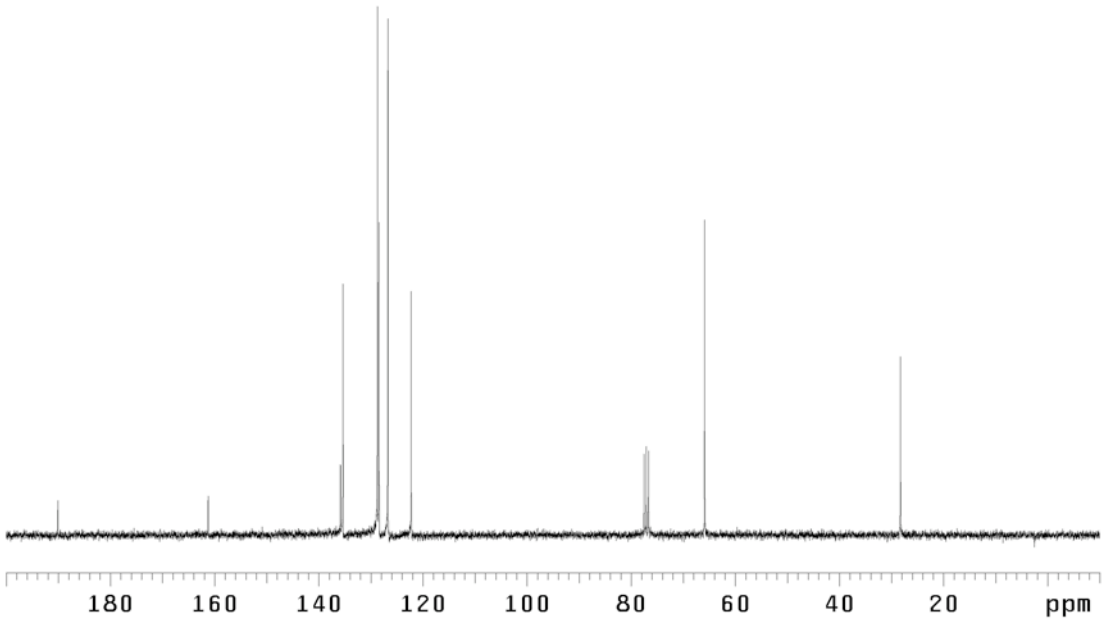


Figure A2.2.30 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **153**

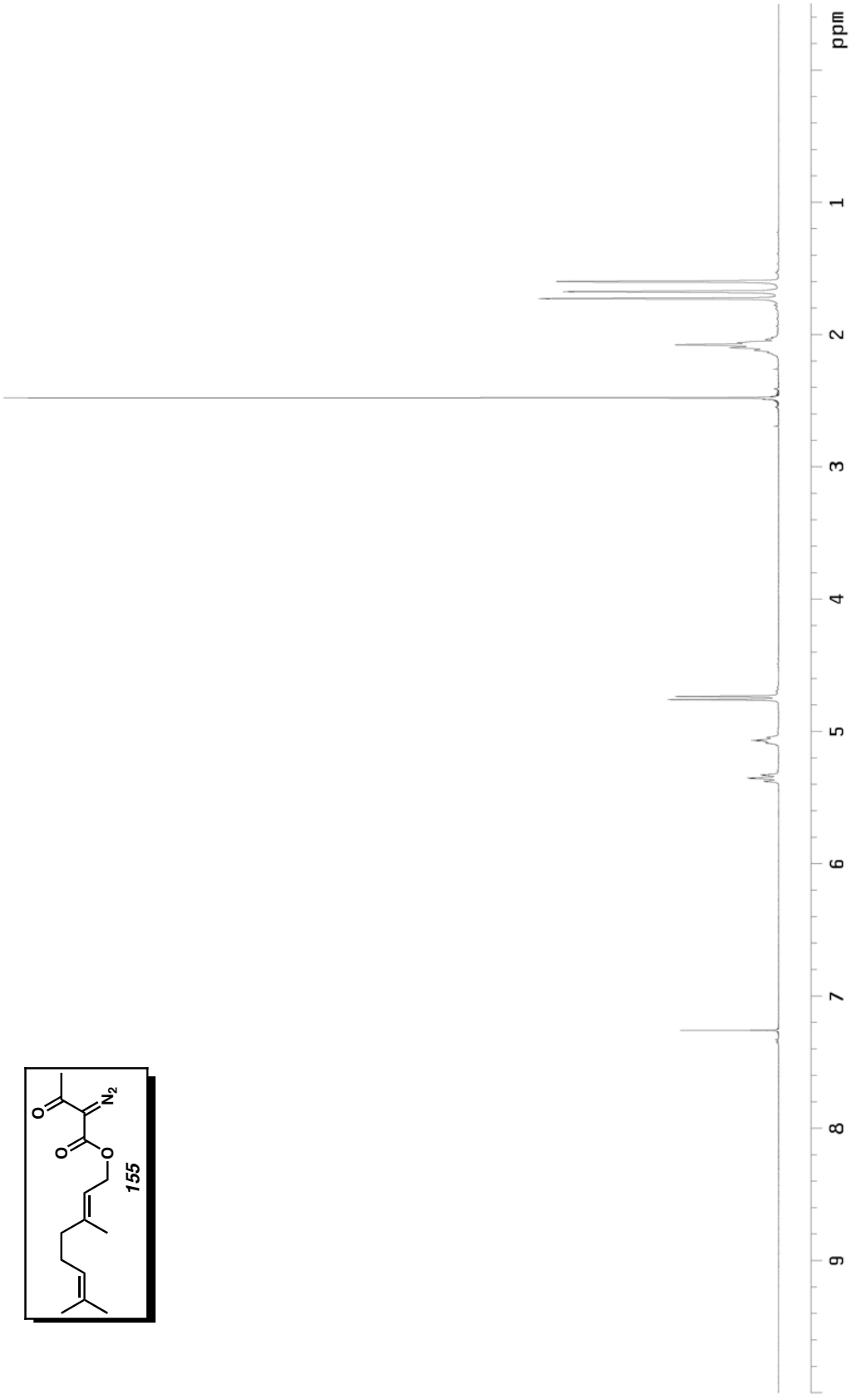


Figure A2.2.31 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **155**

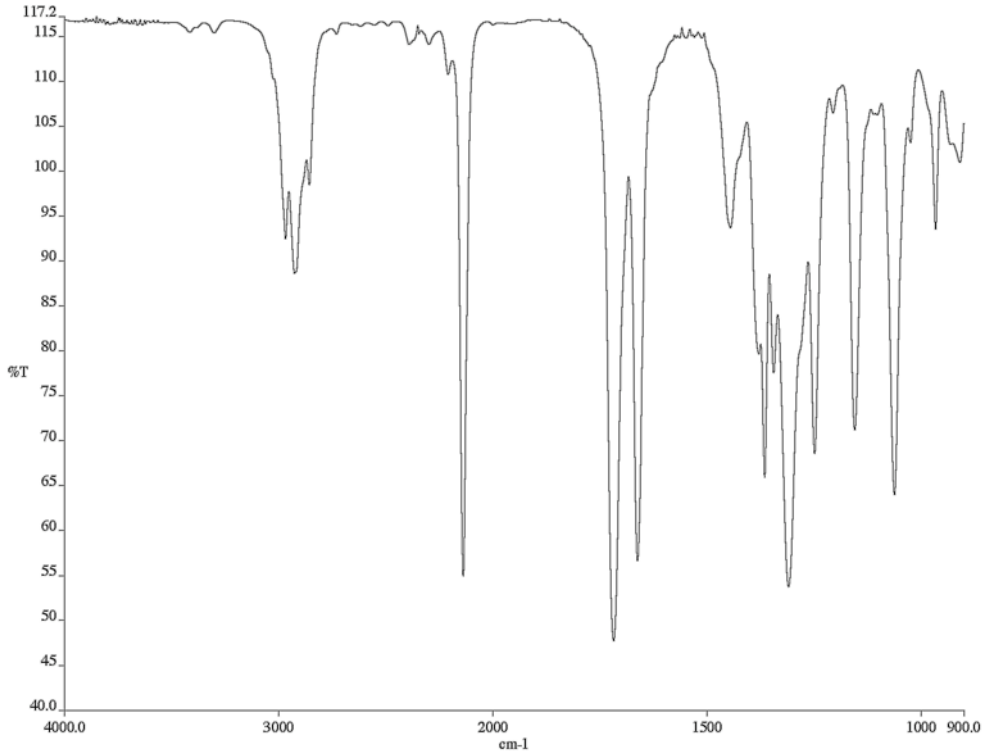


Figure A2.2.32 Infrared spectrum (film/NaCl) of compound **155**

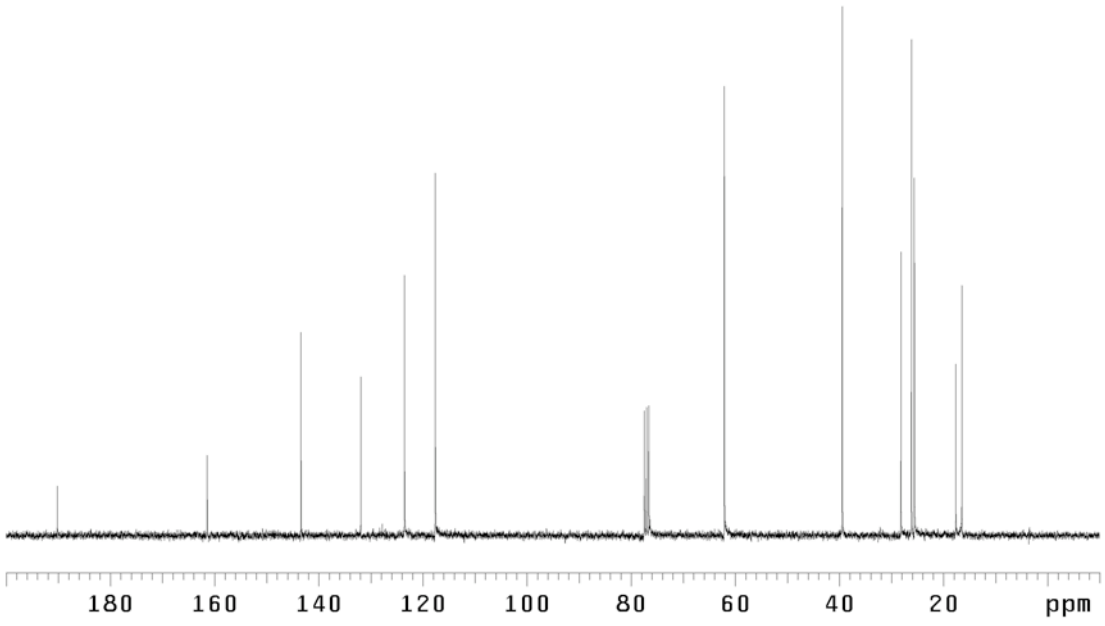


Figure A2.2.33 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **155**

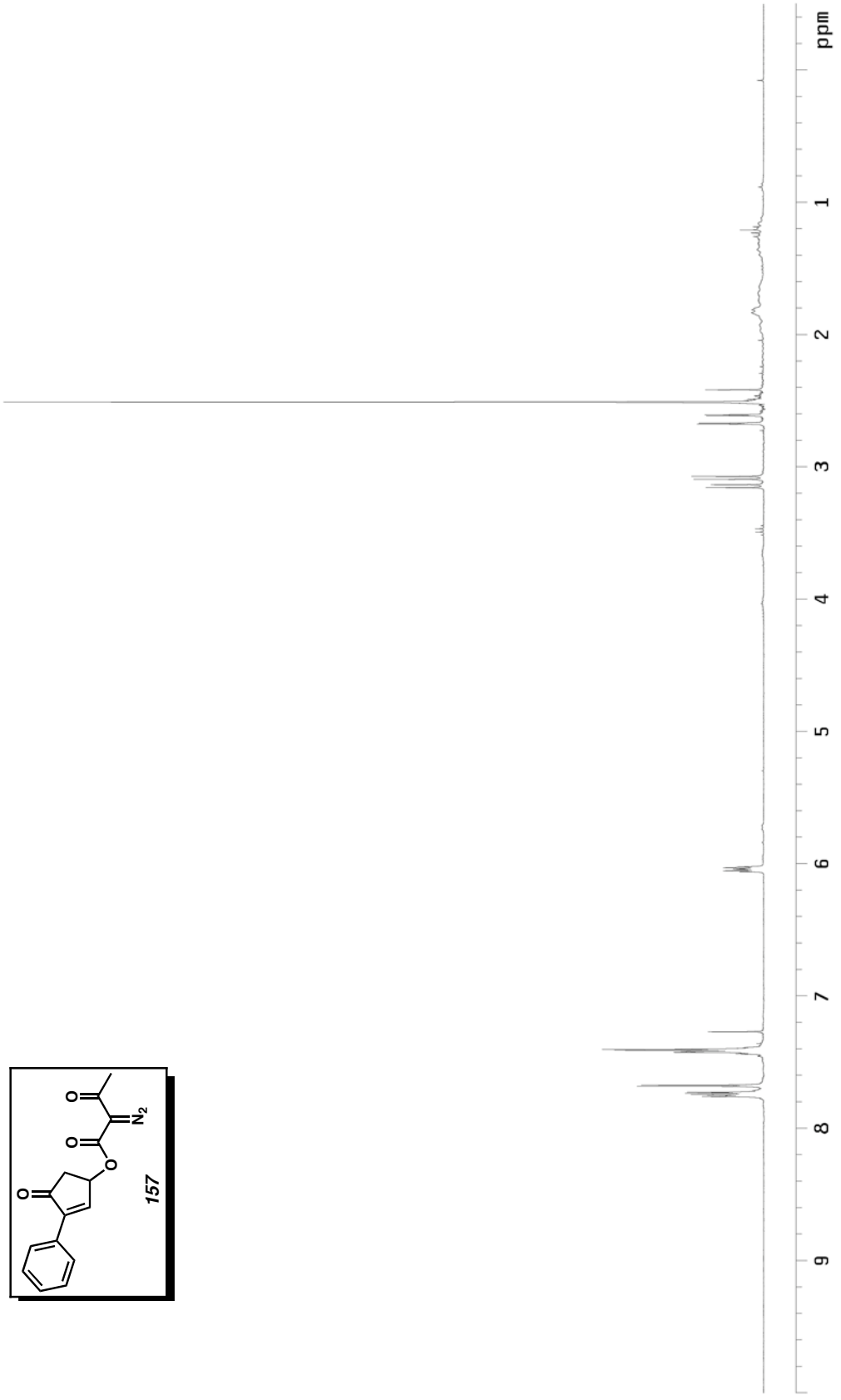


Figure A2.2.34 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **157**

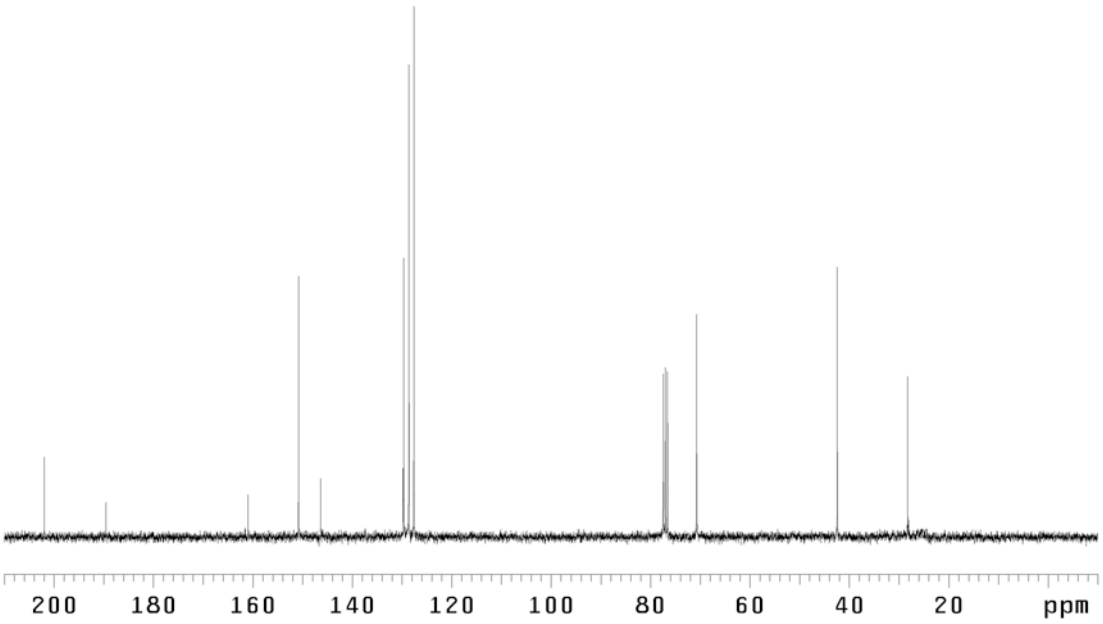


Figure A2.2.35 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **157**

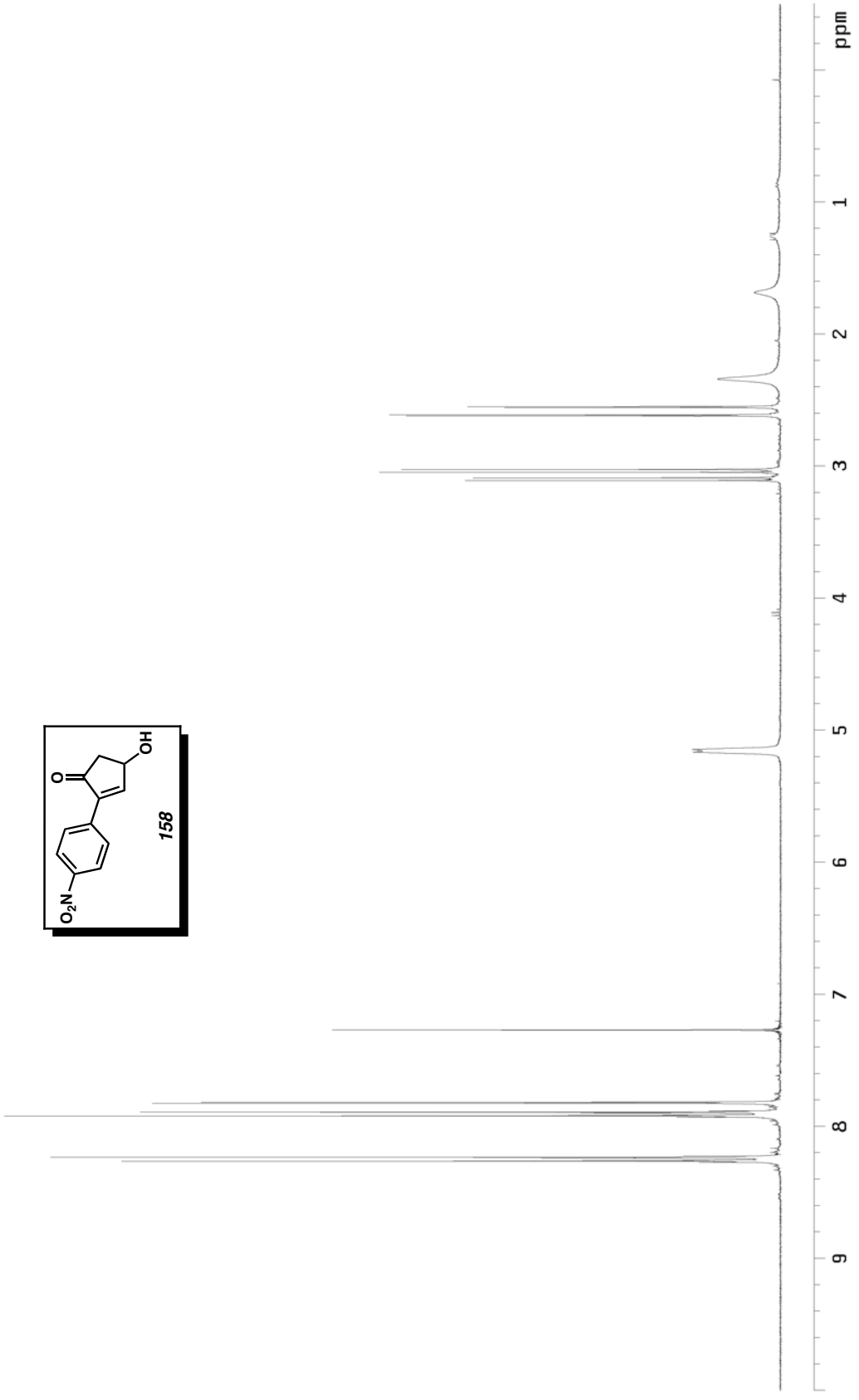


Figure A2.2.36 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **158**

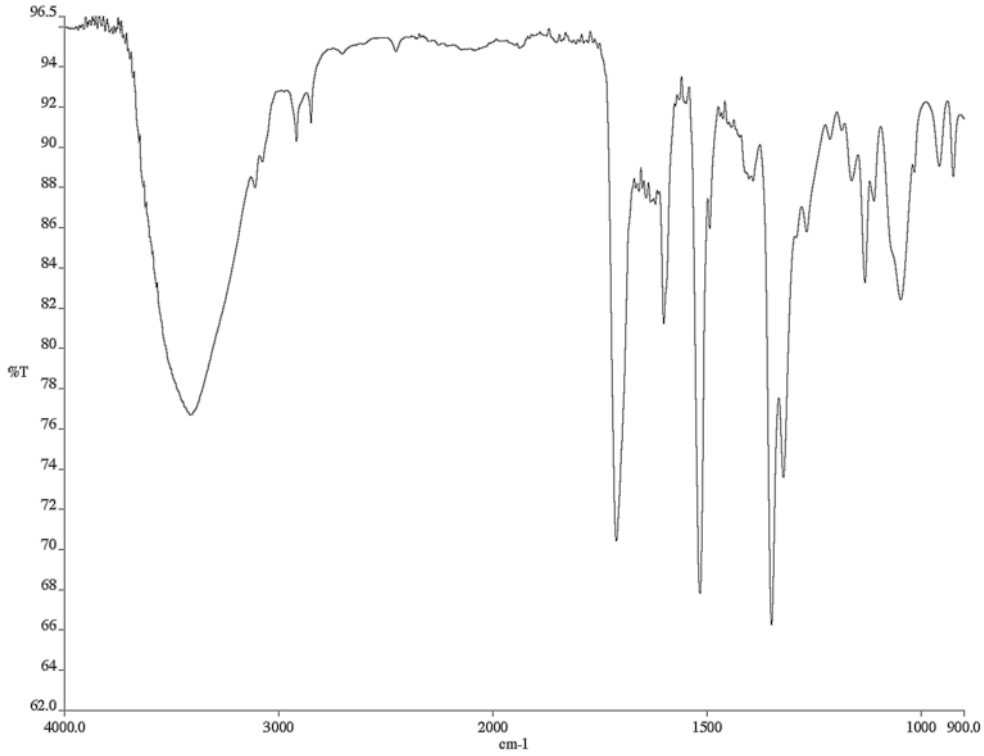


Figure A2.2.37 Infrared spectrum (film/NaCl) of compound **158**

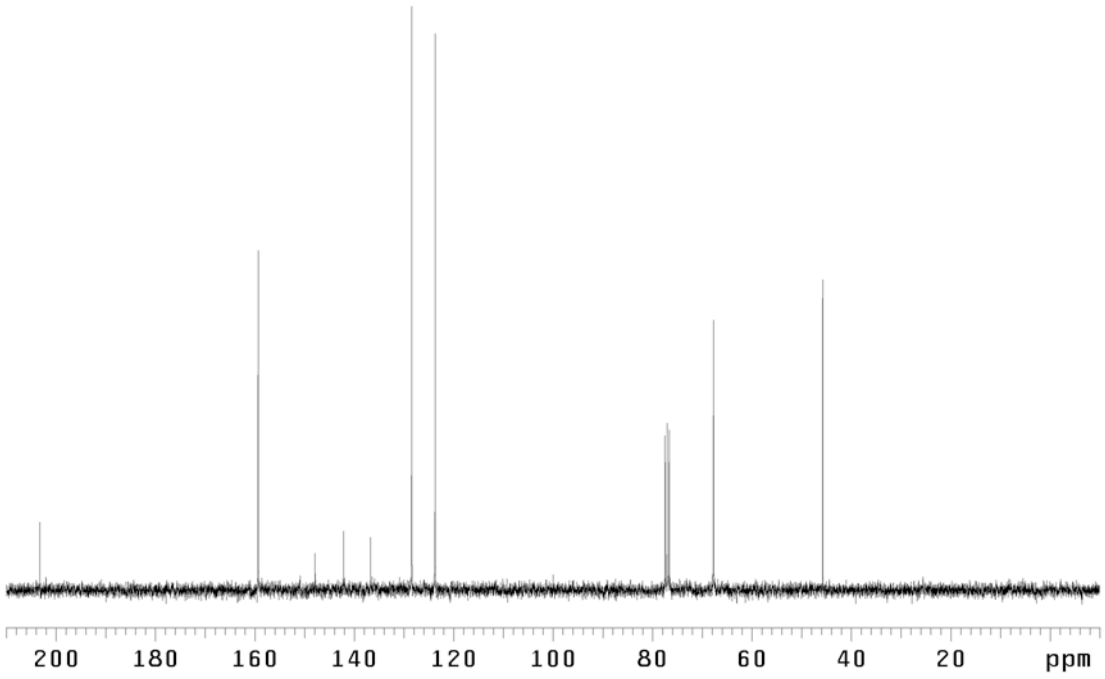


Figure A2.2.38 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **158**

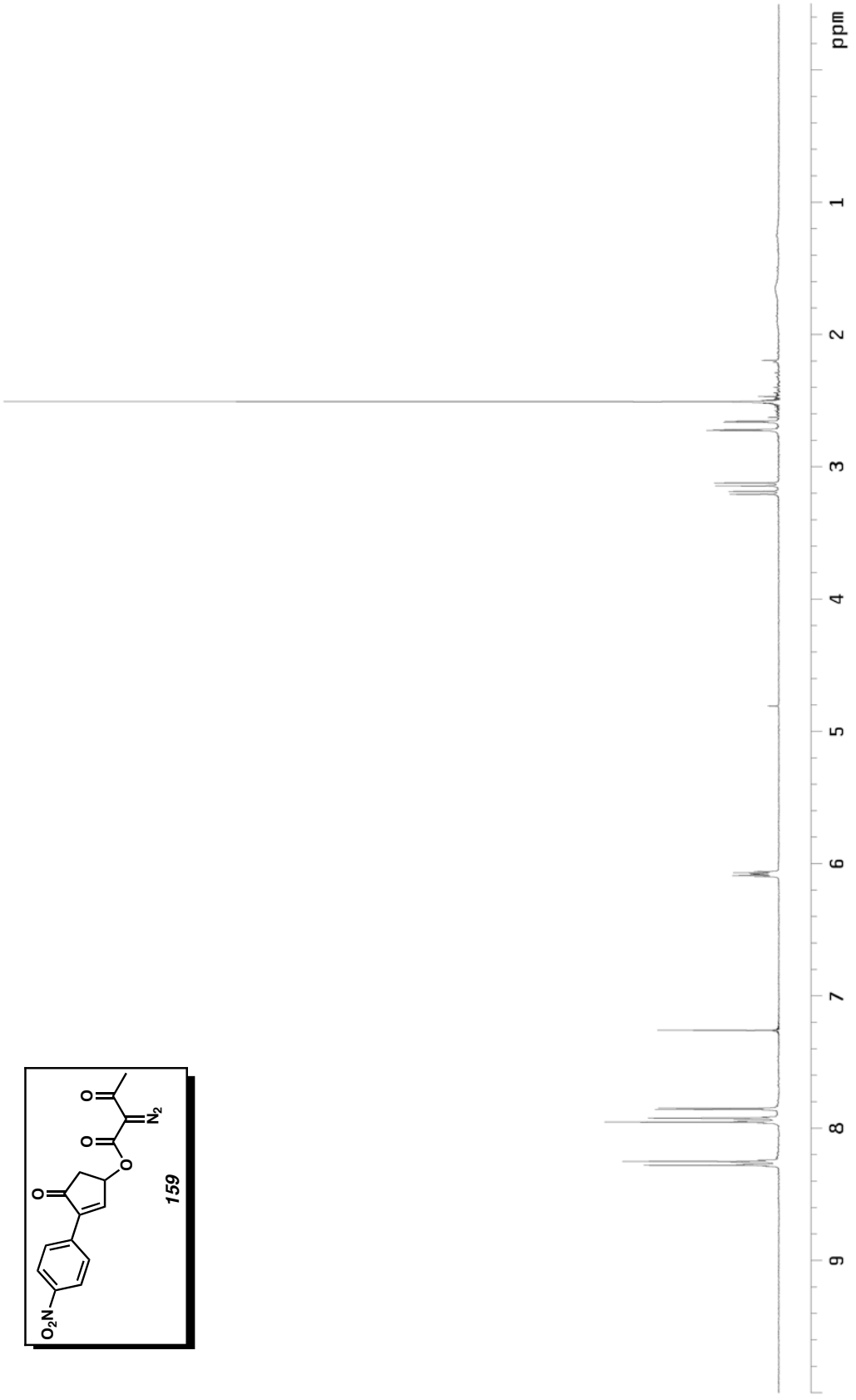


Figure A2.2.39 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **159**

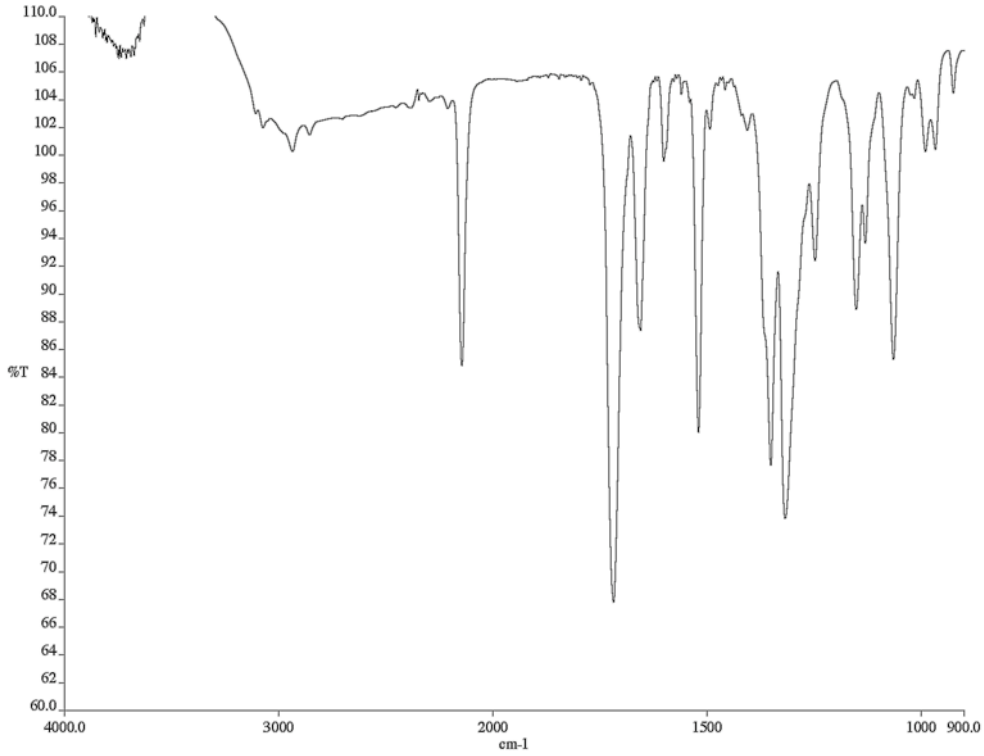


Figure A2.2.40 Infrared spectrum (film/NaCl) of compound **159**

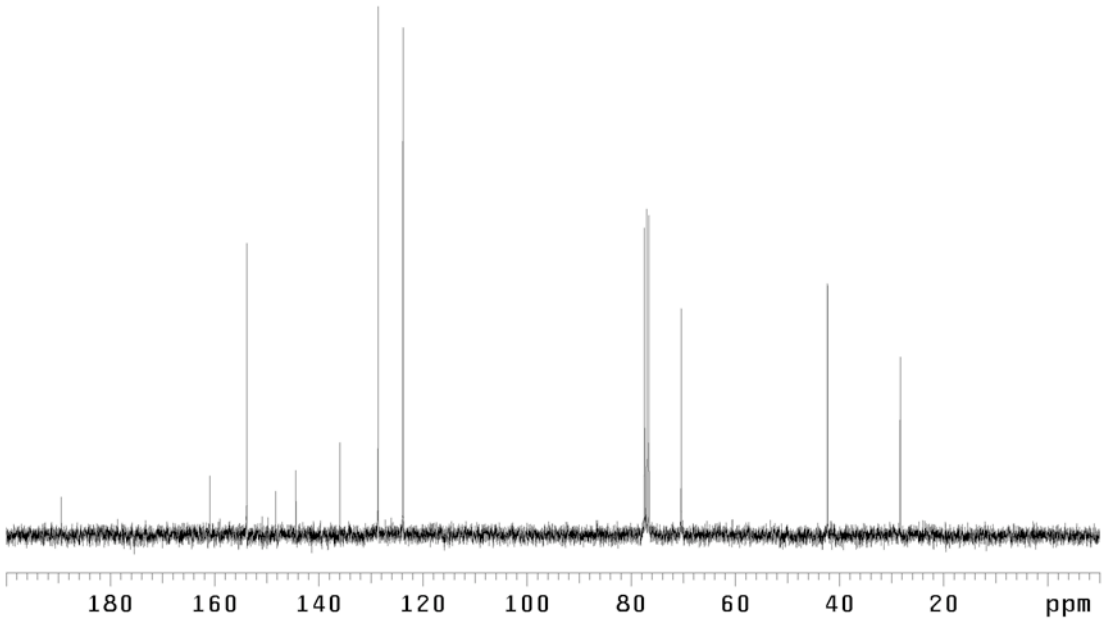


Figure A2.2.41 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **159**

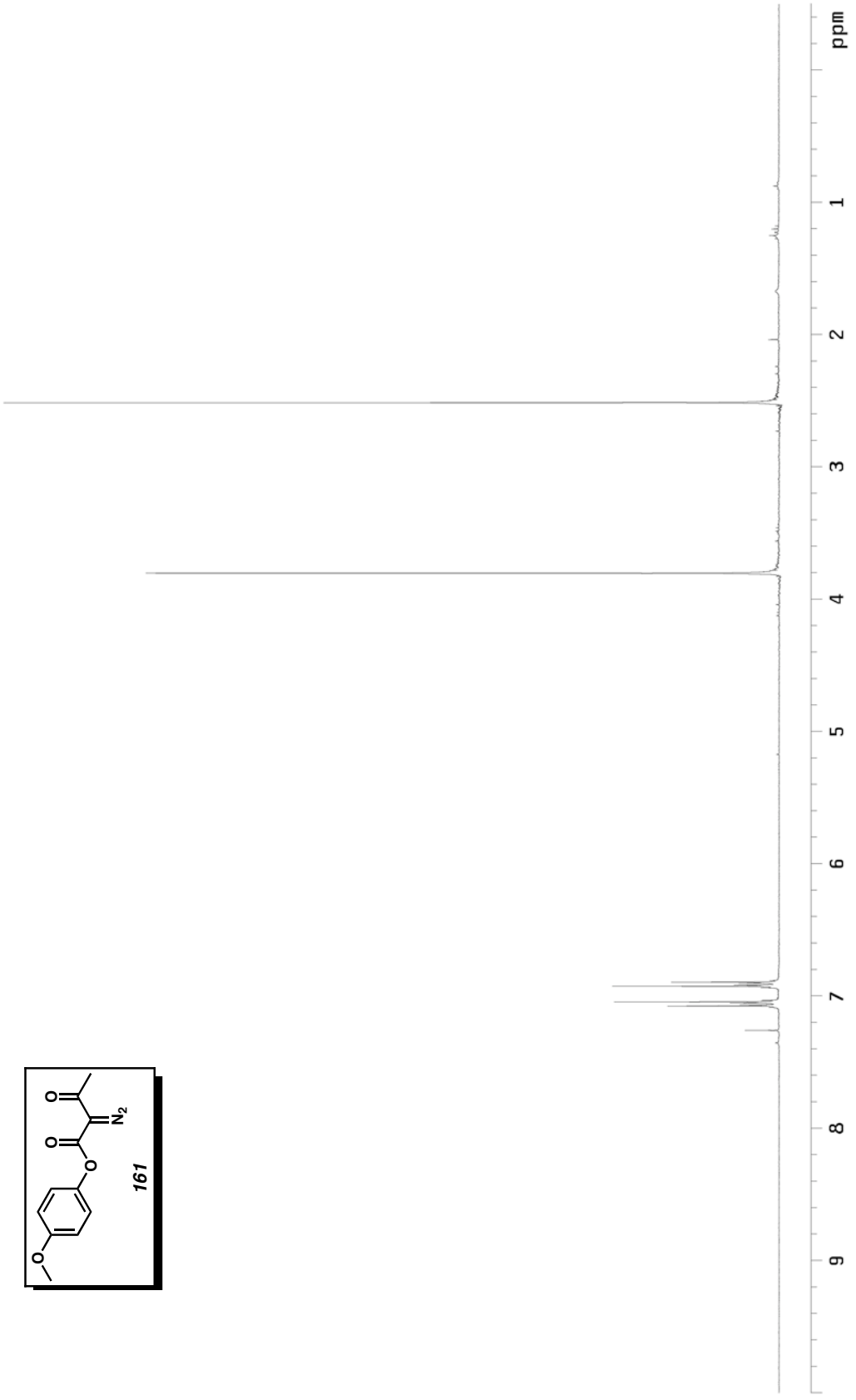


Figure A2.2.42 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **161**

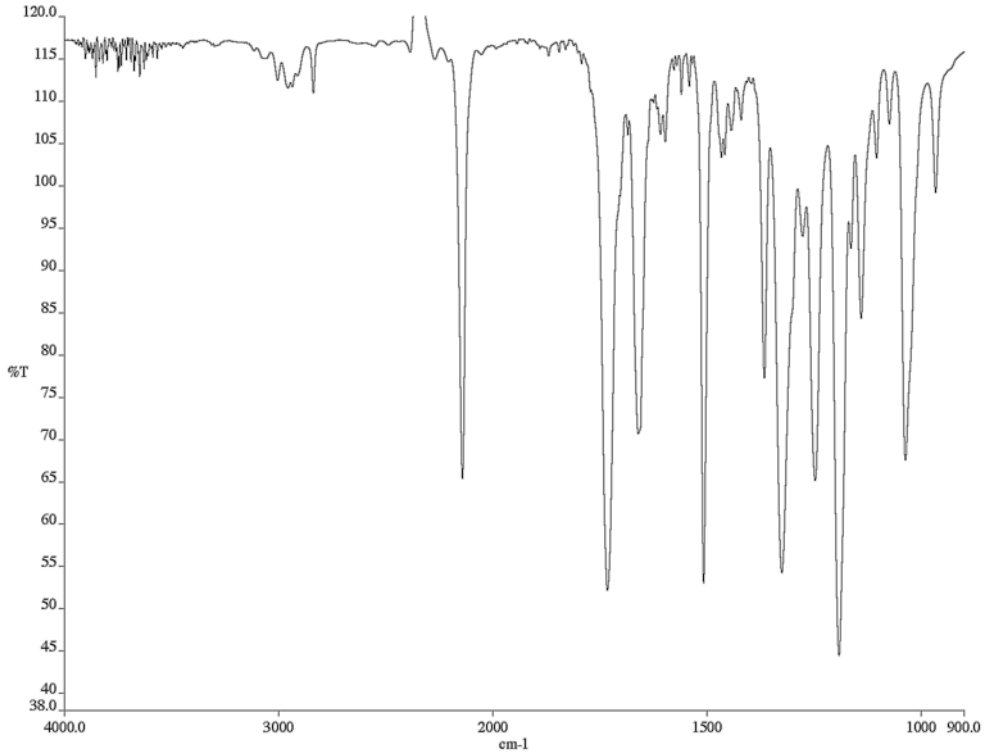


Figure A2.2.43 Infrared spectrum (film/NaCl) of compound **161**

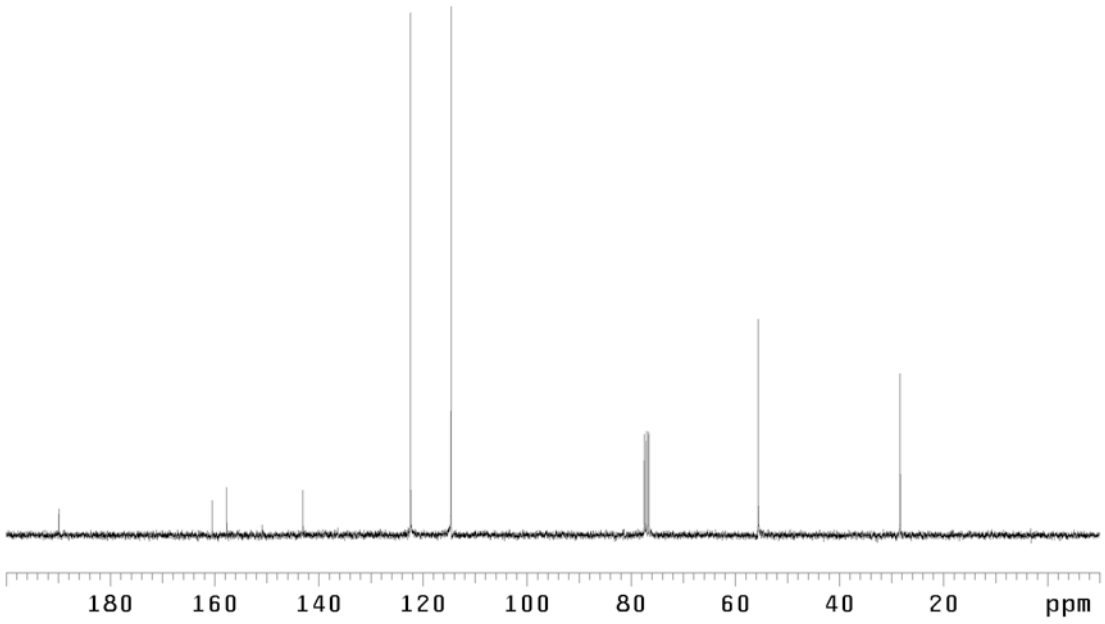


Figure A2.2.44 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **161**

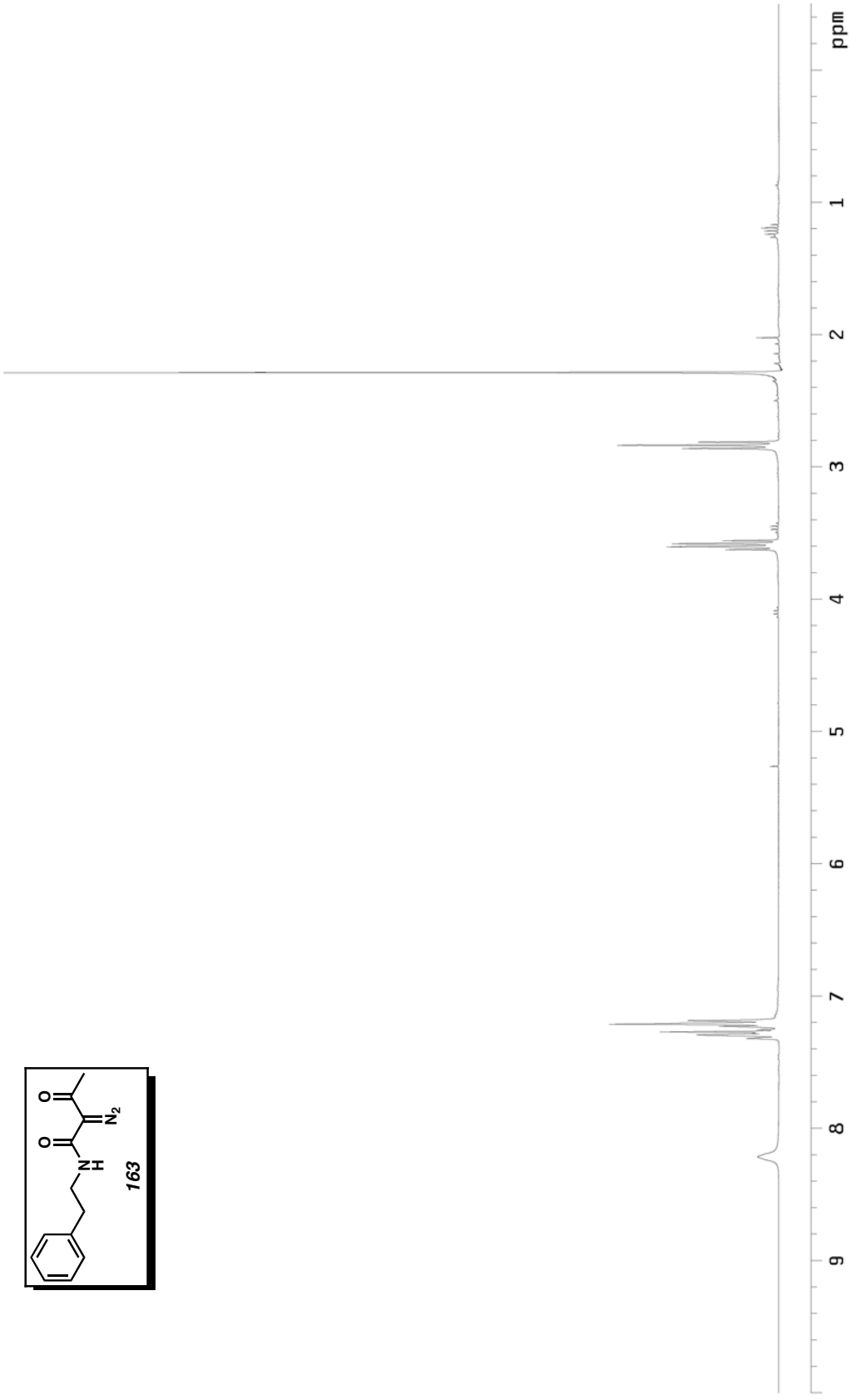


Figure A2.2.45 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **163**

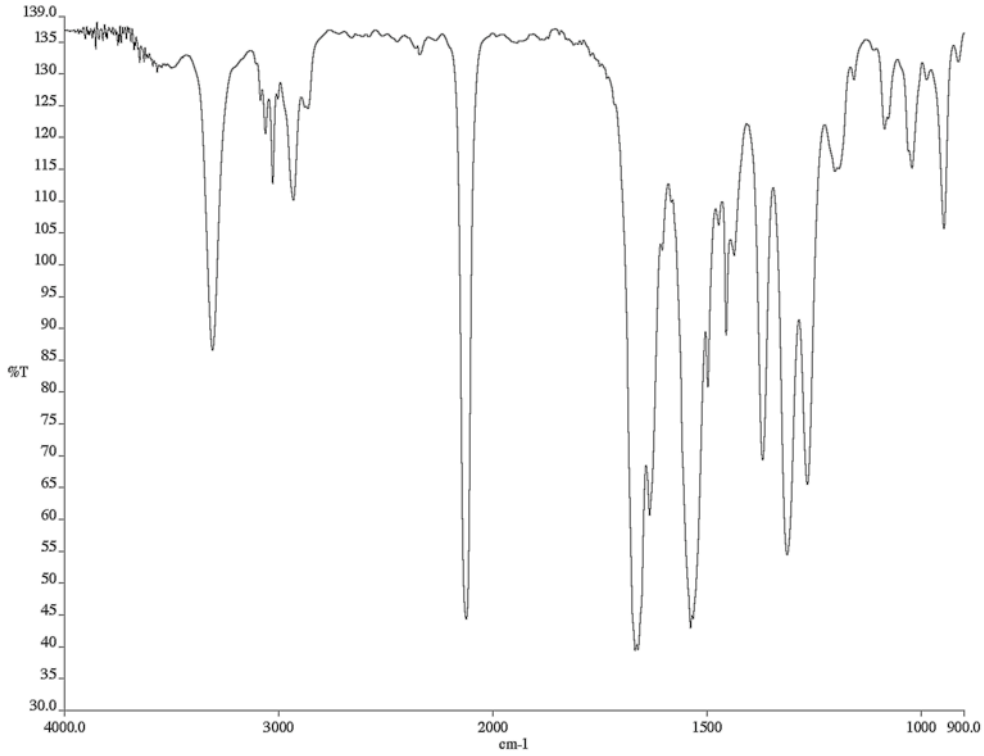


Figure A2.2.46 Infrared spectrum (film/NaCl) of compound **163**

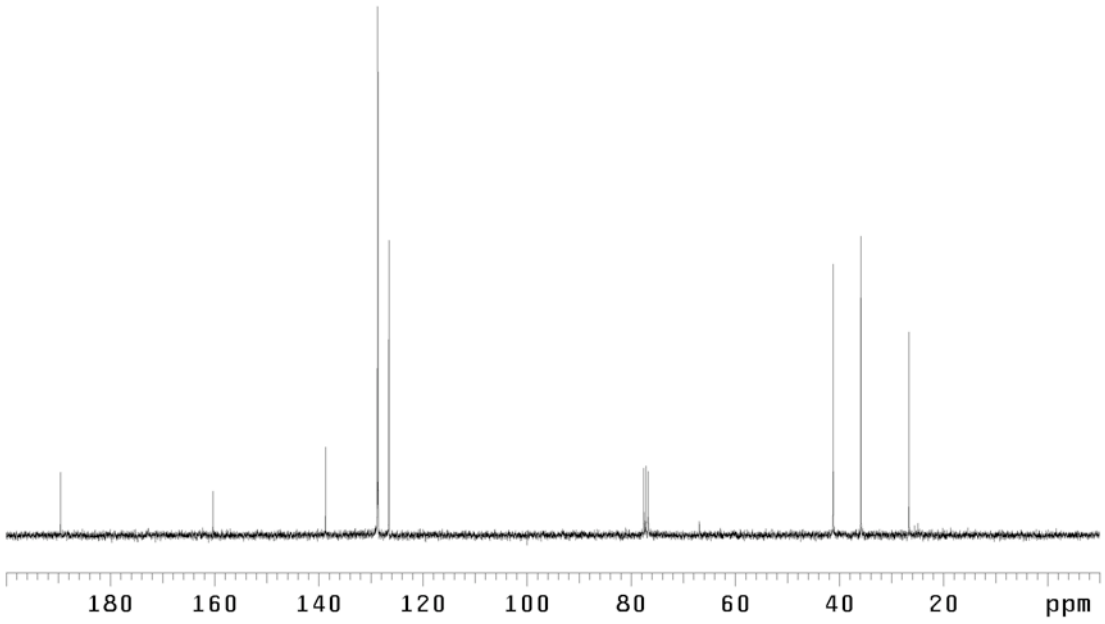


Figure A2.2.47 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **163**

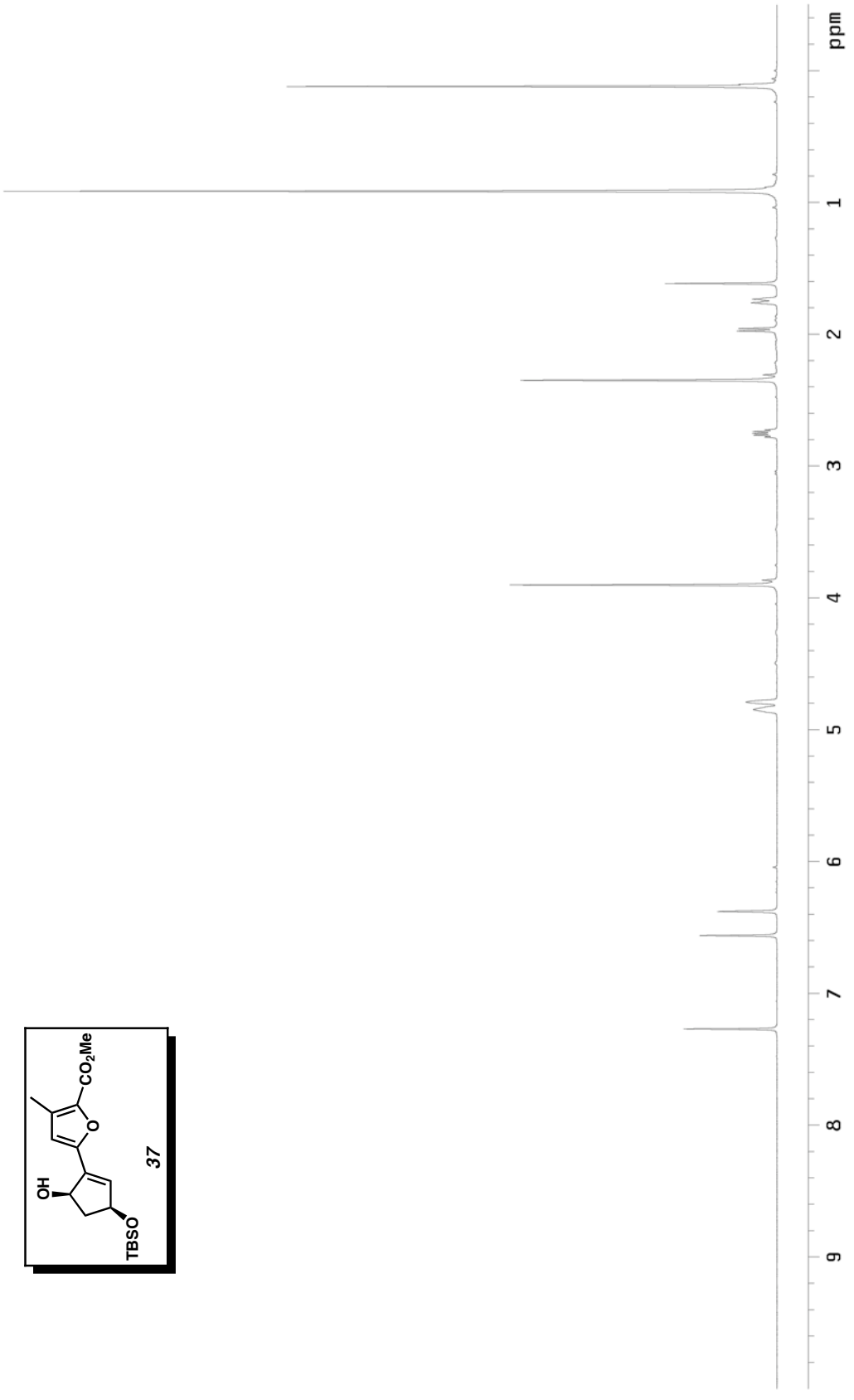


Figure A2.2.48 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **37**

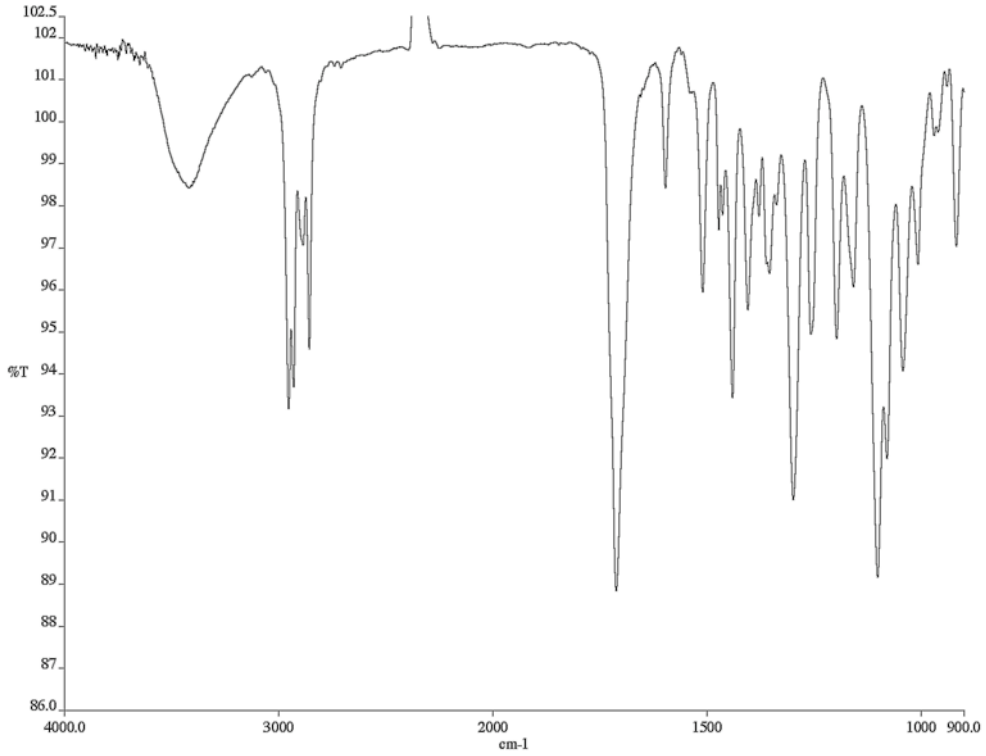


Figure A2.2.49 Infrared spectrum (film/NaCl) of compound **37**

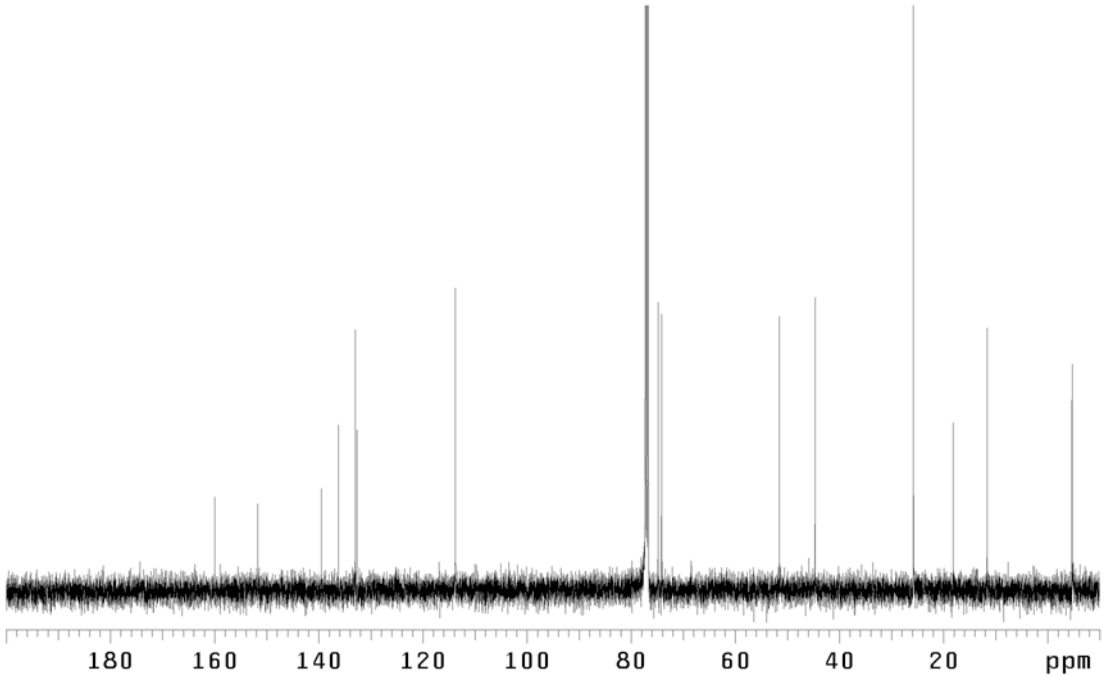


Figure A2.2.50 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **37**

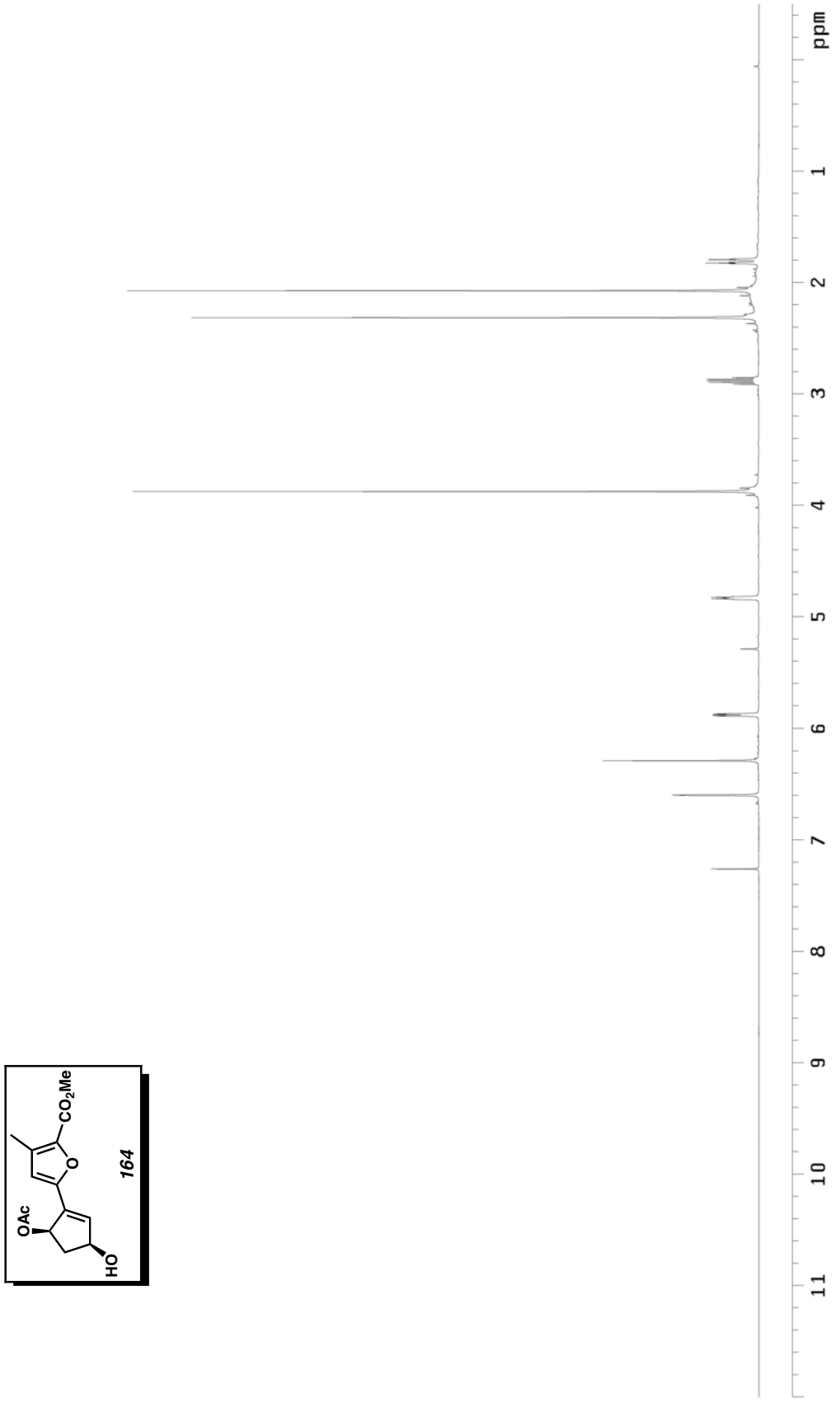


Figure A2.2.51 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **164**

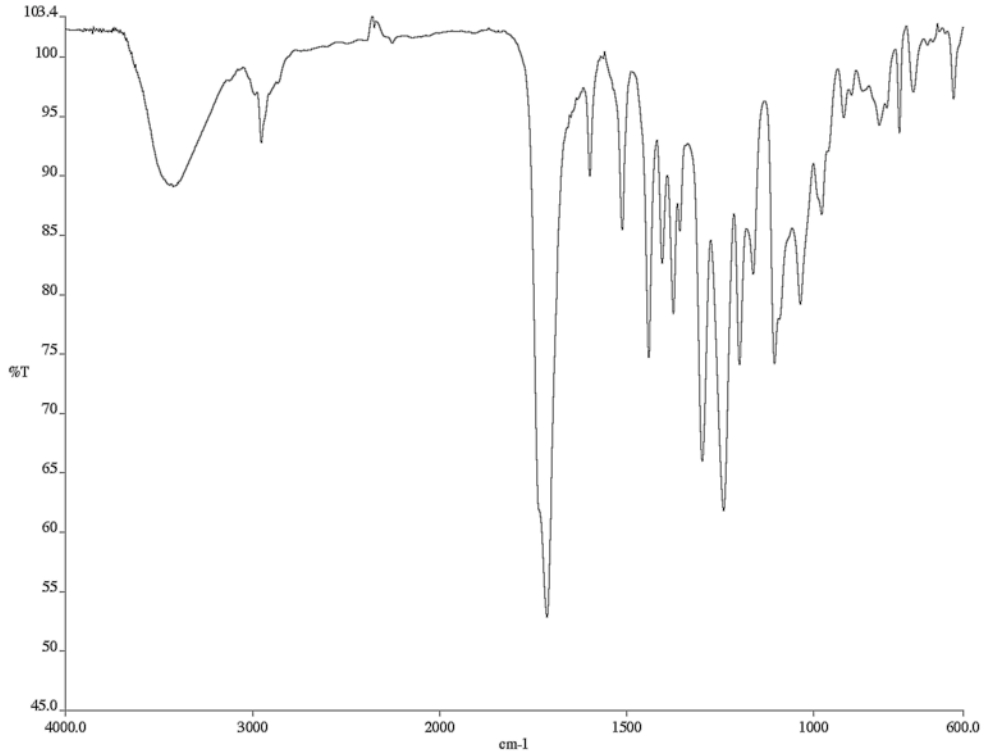


Figure A2.2.52 Infrared spectrum (film/NaCl) of compound **164**

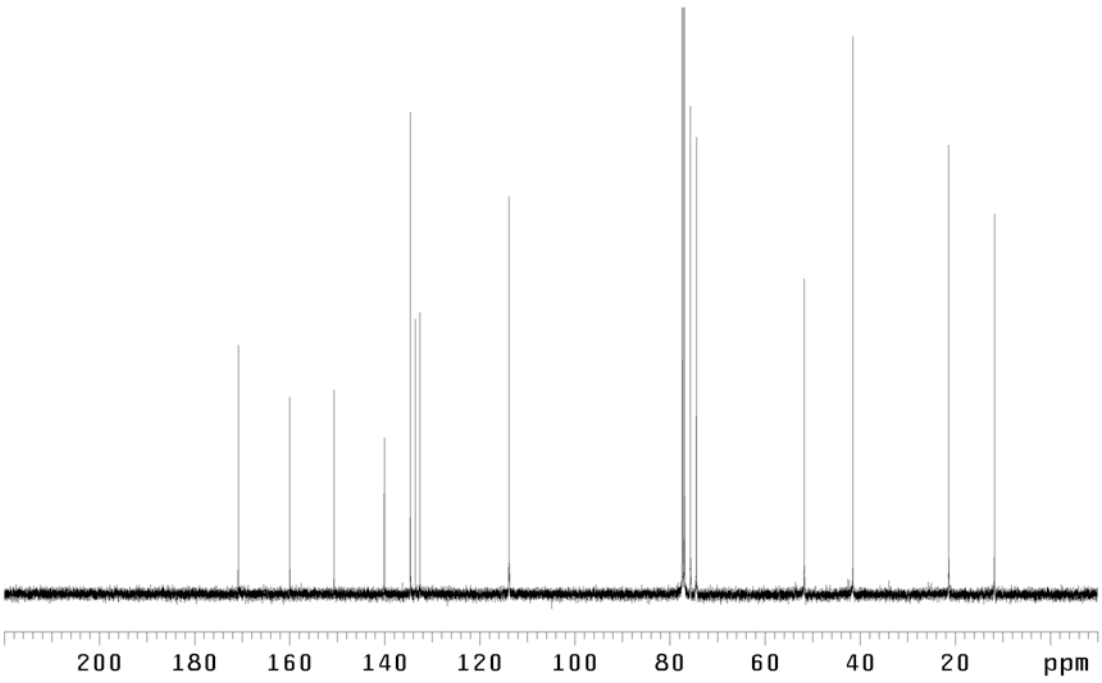


Figure A2.2.53 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **164**

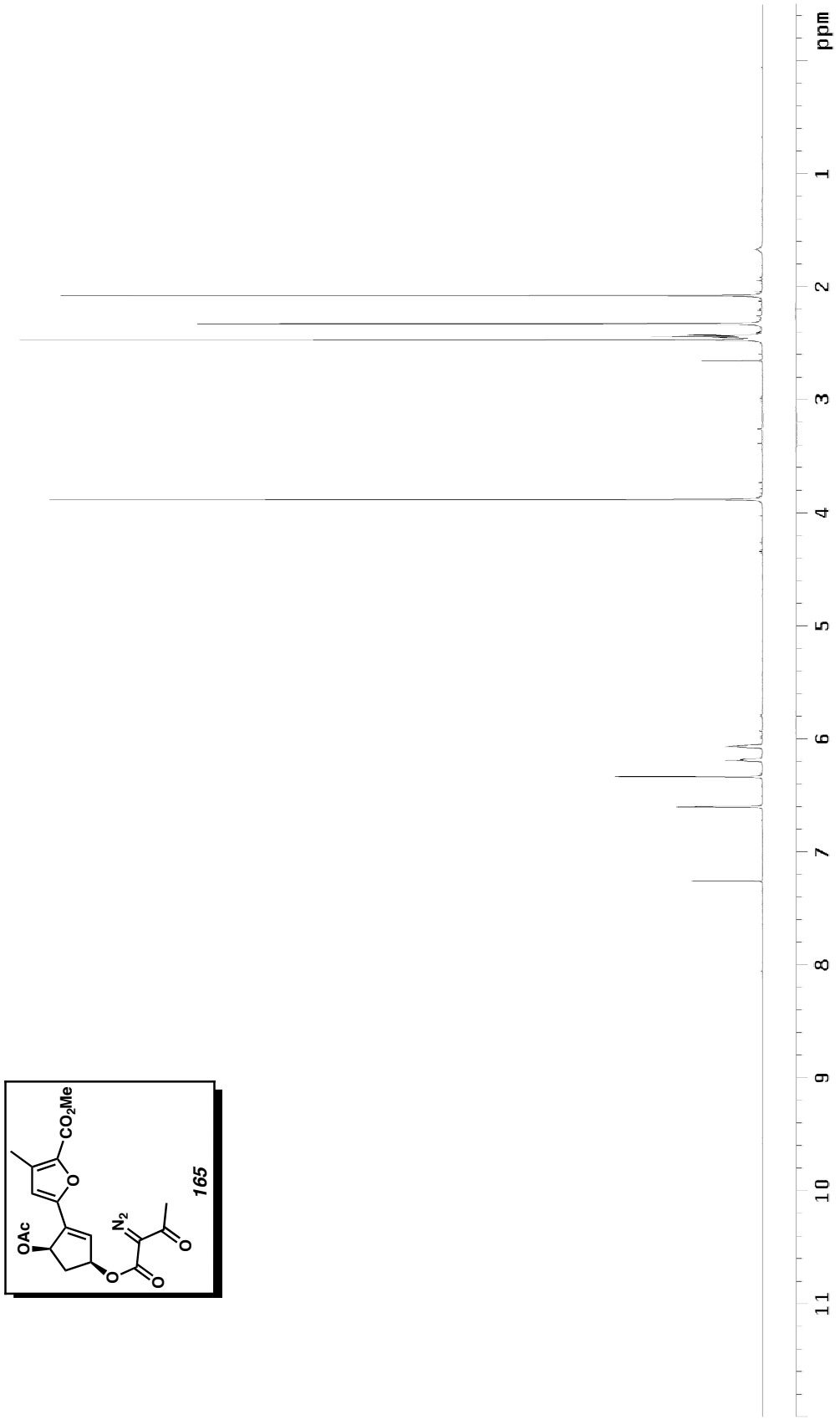


Figure A2.2.54 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **165**

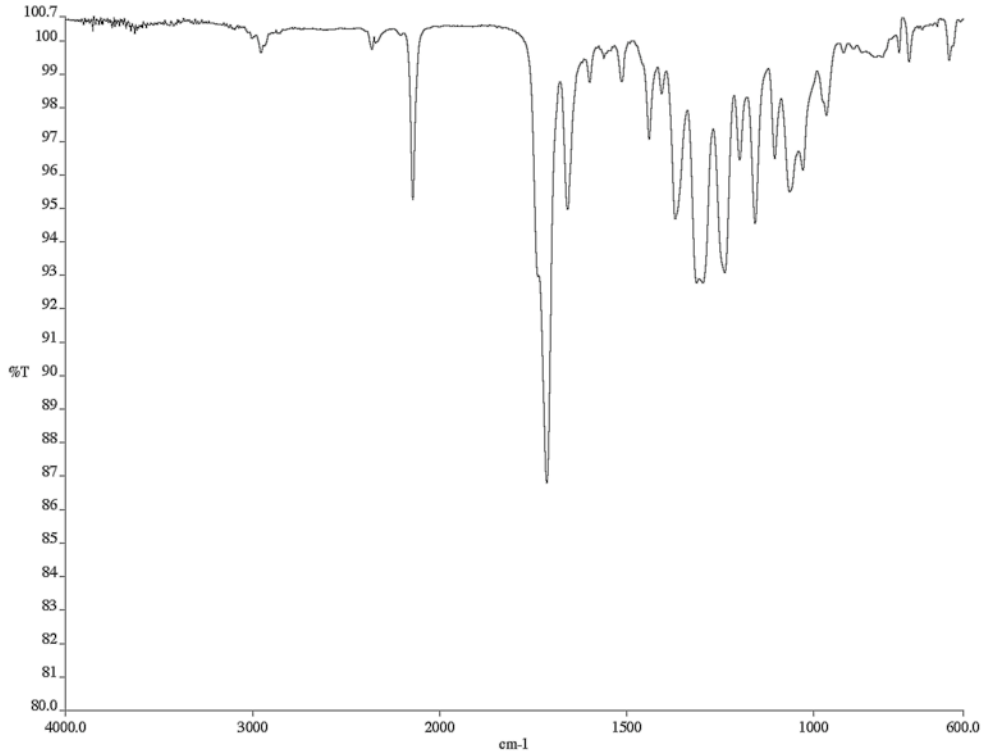


Figure A2.2.55 Infrared spectrum (film/NaCl) of compound **164**

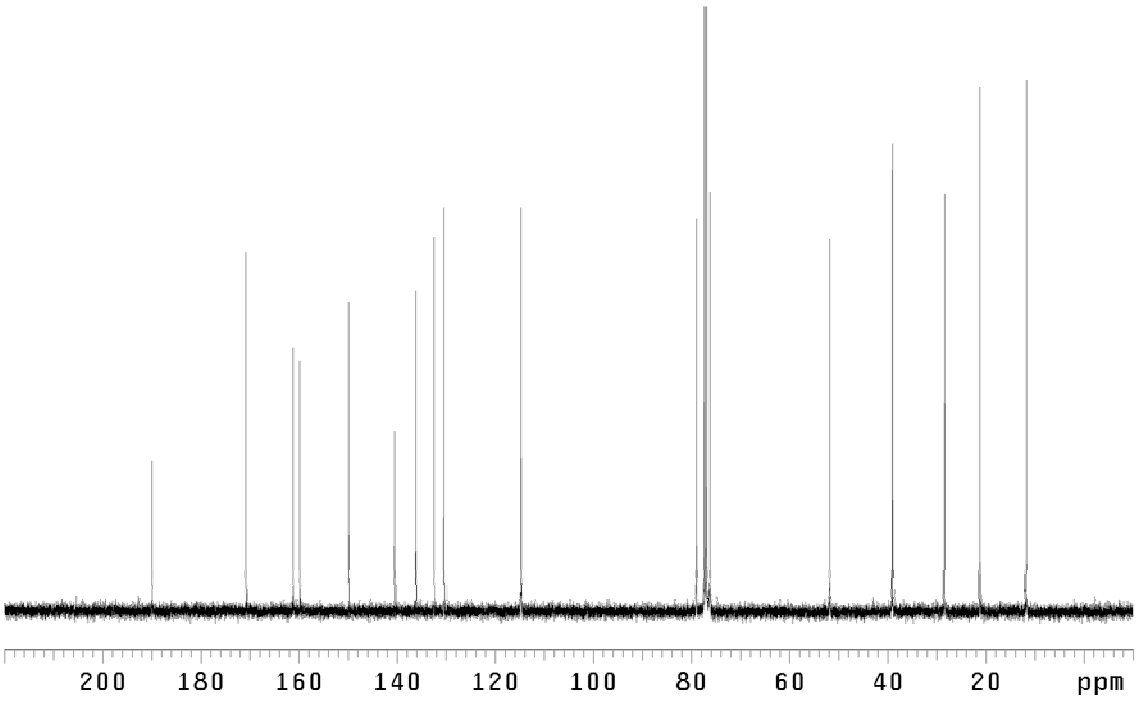


Figure A2.2.56 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **164**

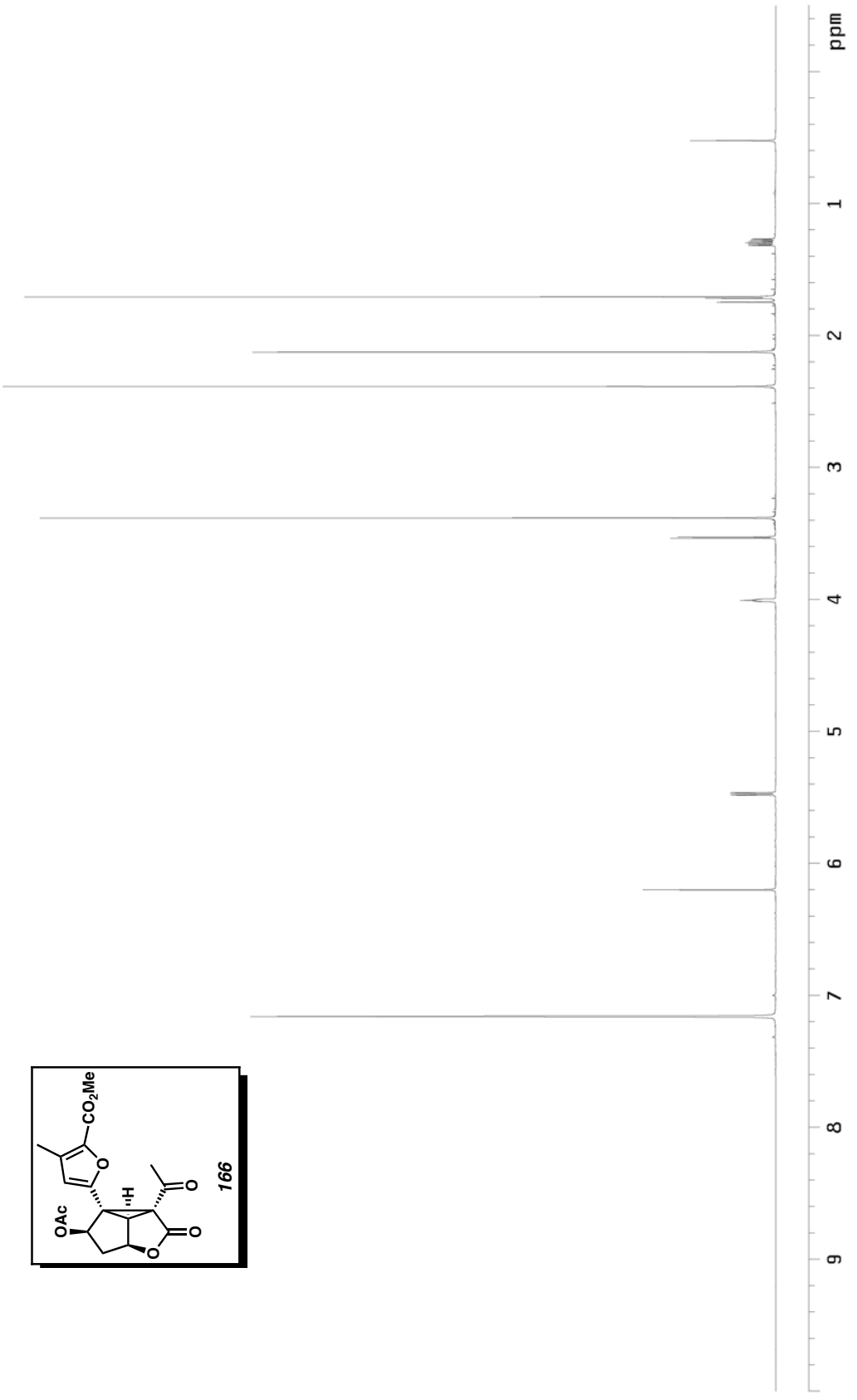


Figure A2.2.57 ^{1}H NMR (500 MHz, C_6D_6) of compound **166**

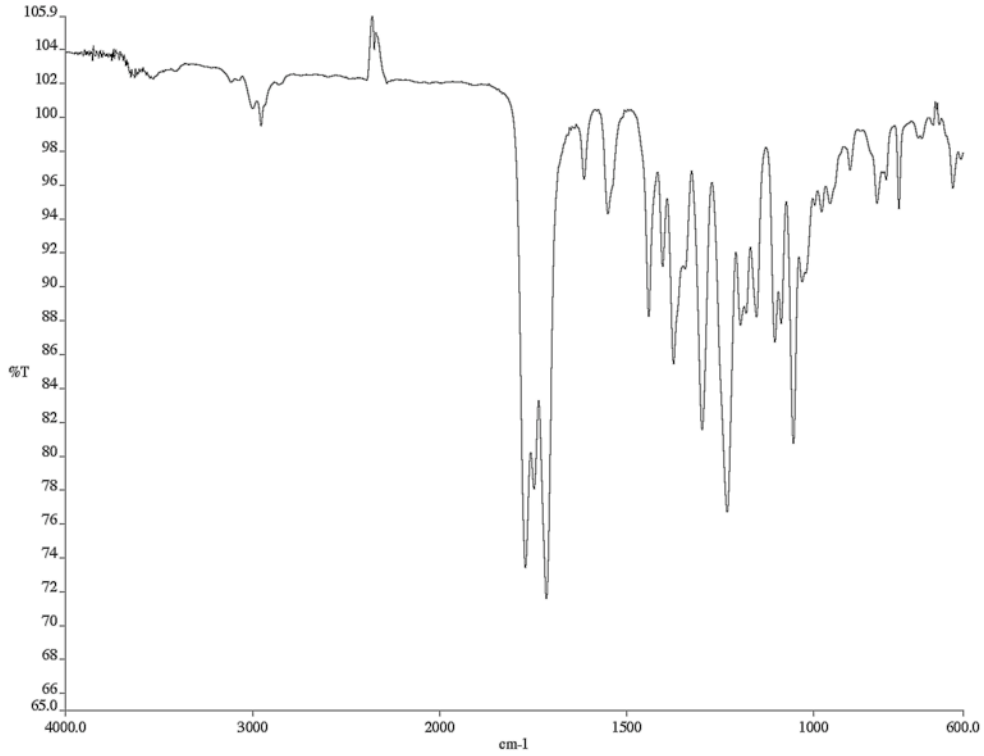


Figure A2.2.58 Infrared spectrum (film/NaCl) of compound **166**

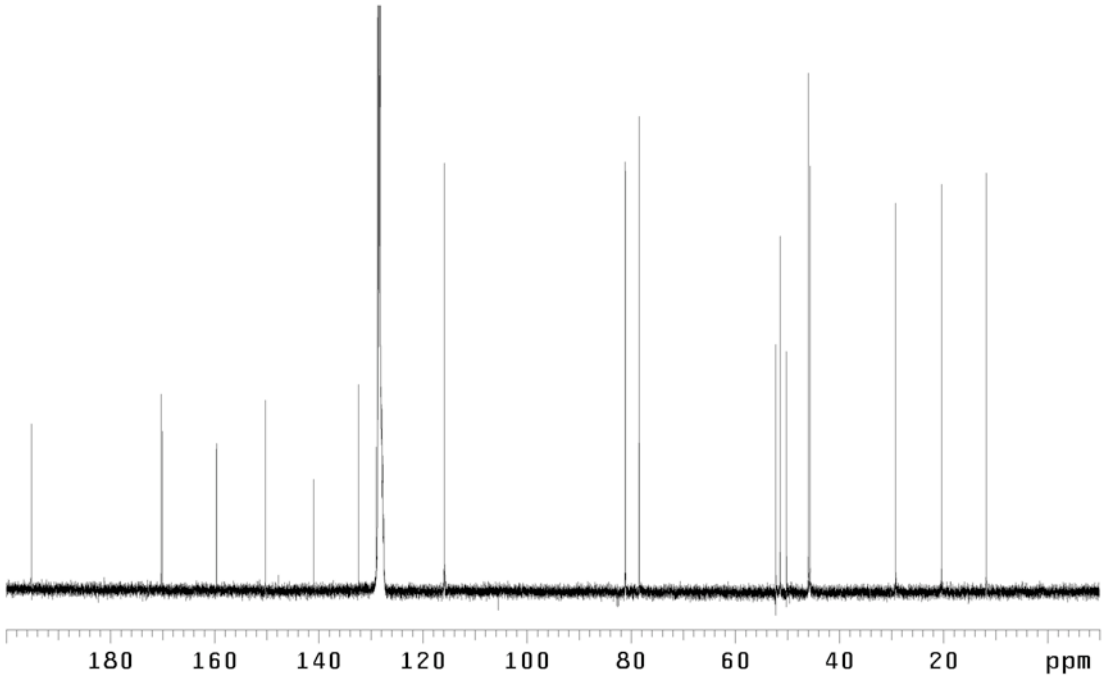


Figure A2.2.59 ^{13}C NMR (125 MHz, C_6D_6) of compound **166**

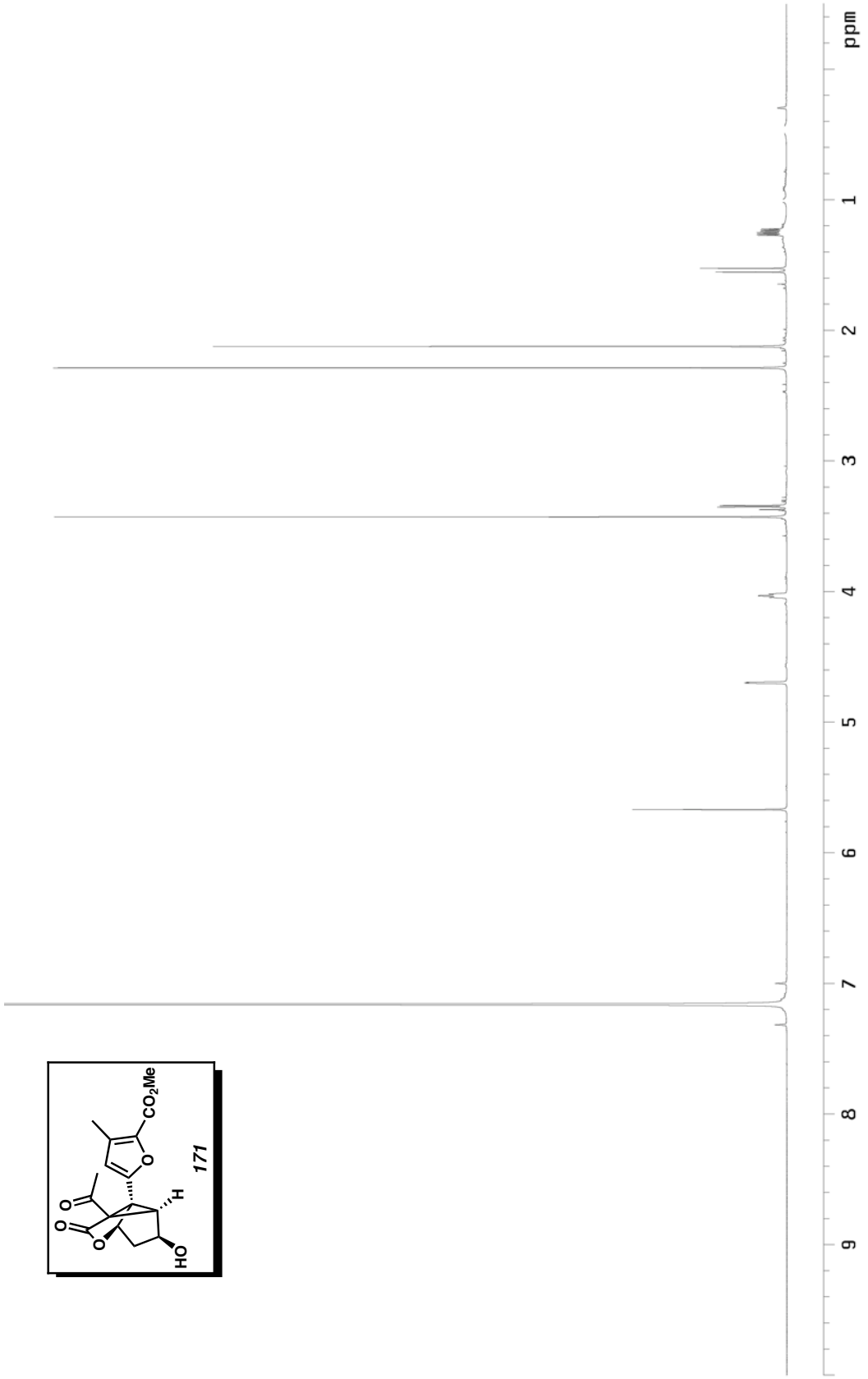


Figure A2.2.60 ^{1}H NMR (500 MHz, C_6D_6) of compound **171**

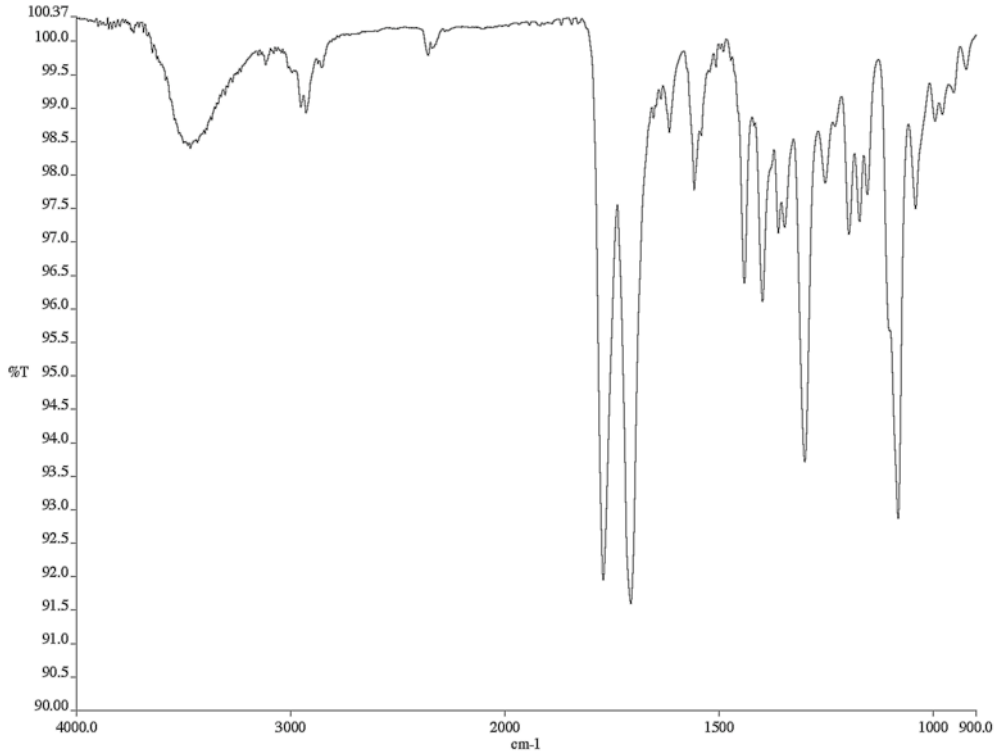


Figure A2.2.61 Infrared spectrum (film/NaCl) of compound **171**

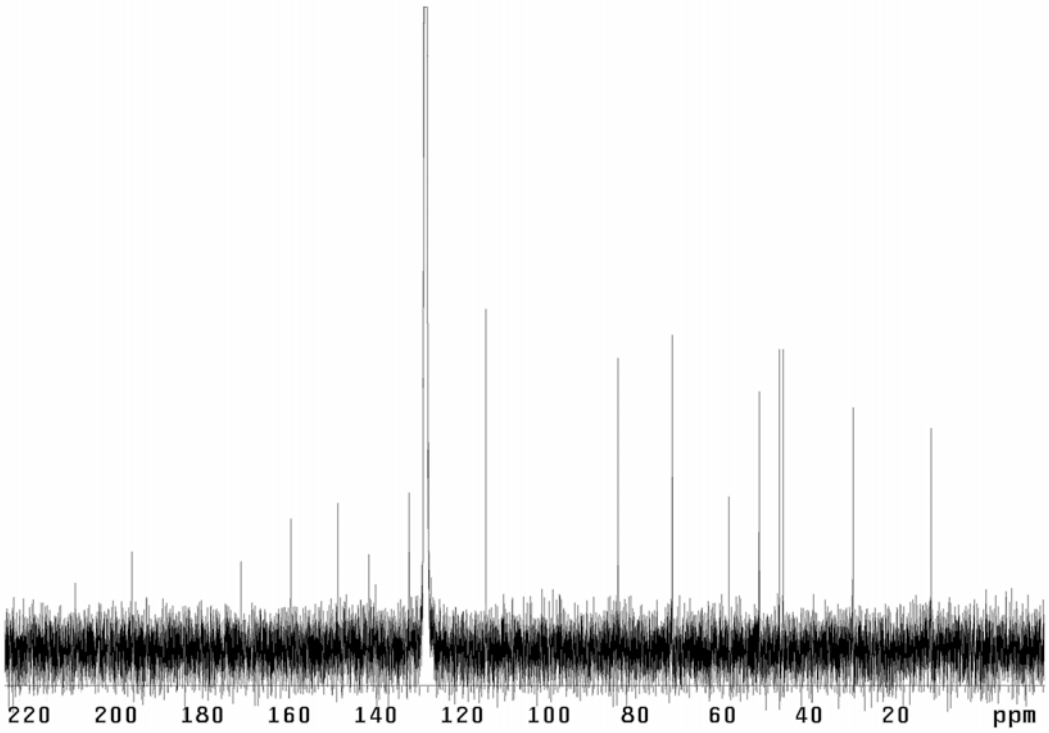


Figure A2.2.62 ^{13}C NMR (125 MHz, C_6D_6) of compound **171**

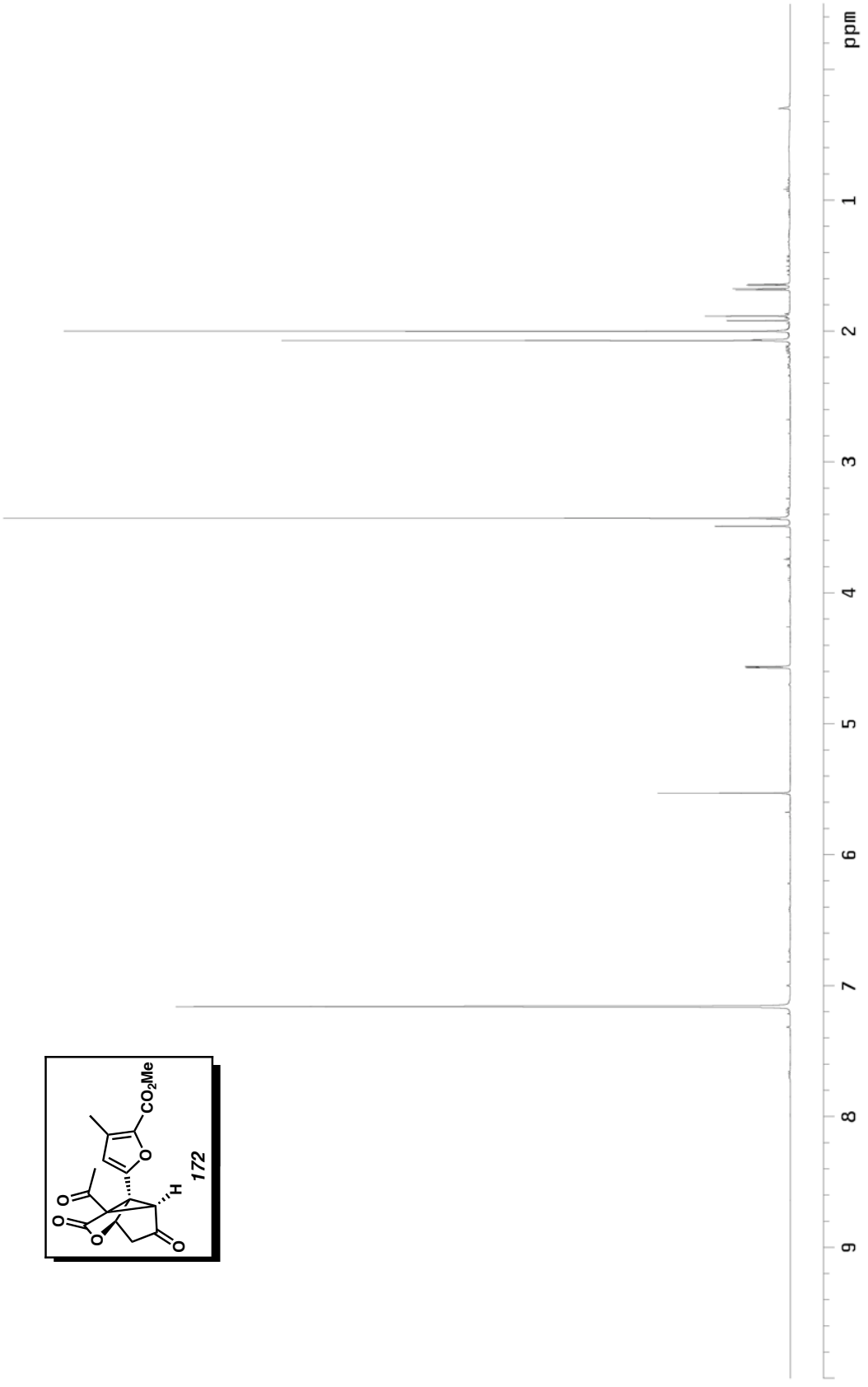


Figure A2.2.63 ^{1}H NMR (500 MHz, C_6D_6) of compound **172**

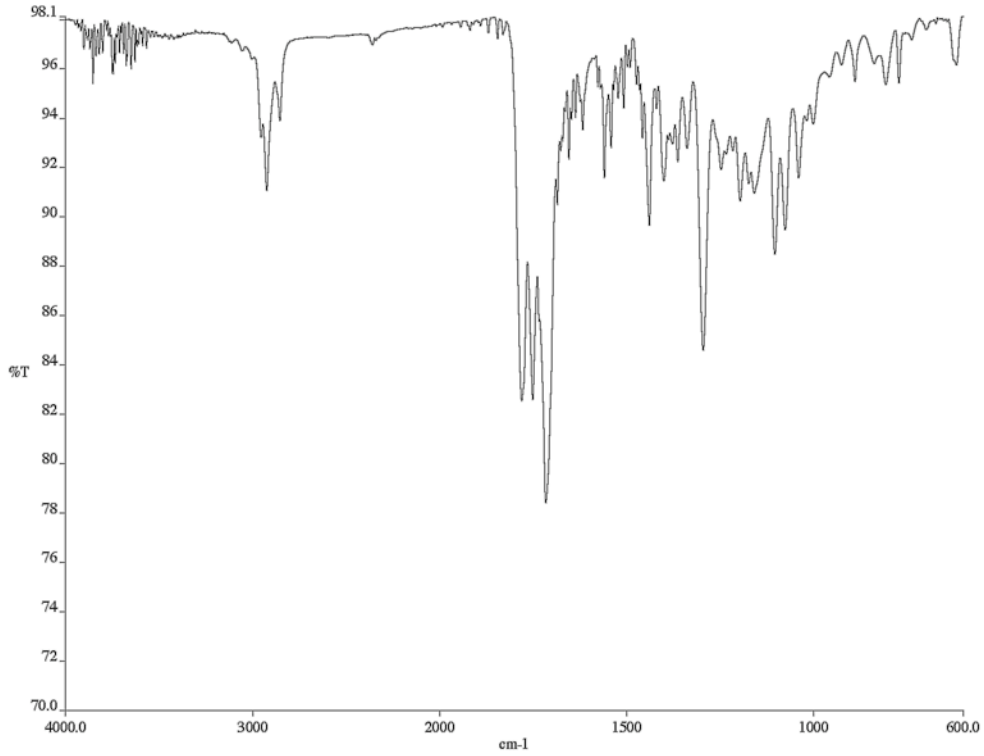


Figure A2.2.64 Infrared spectrum (film/NaCl) of compound **172**

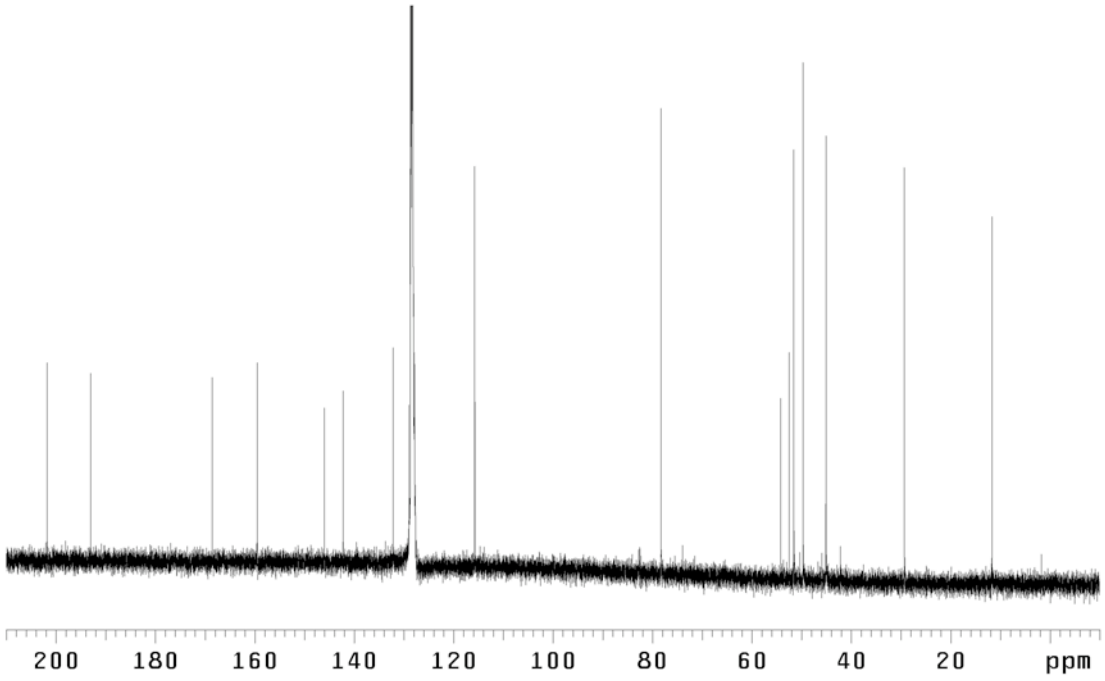


Figure A2.2.65 ^{13}C NMR (125 MHz, C_6D_6) of compound **172**

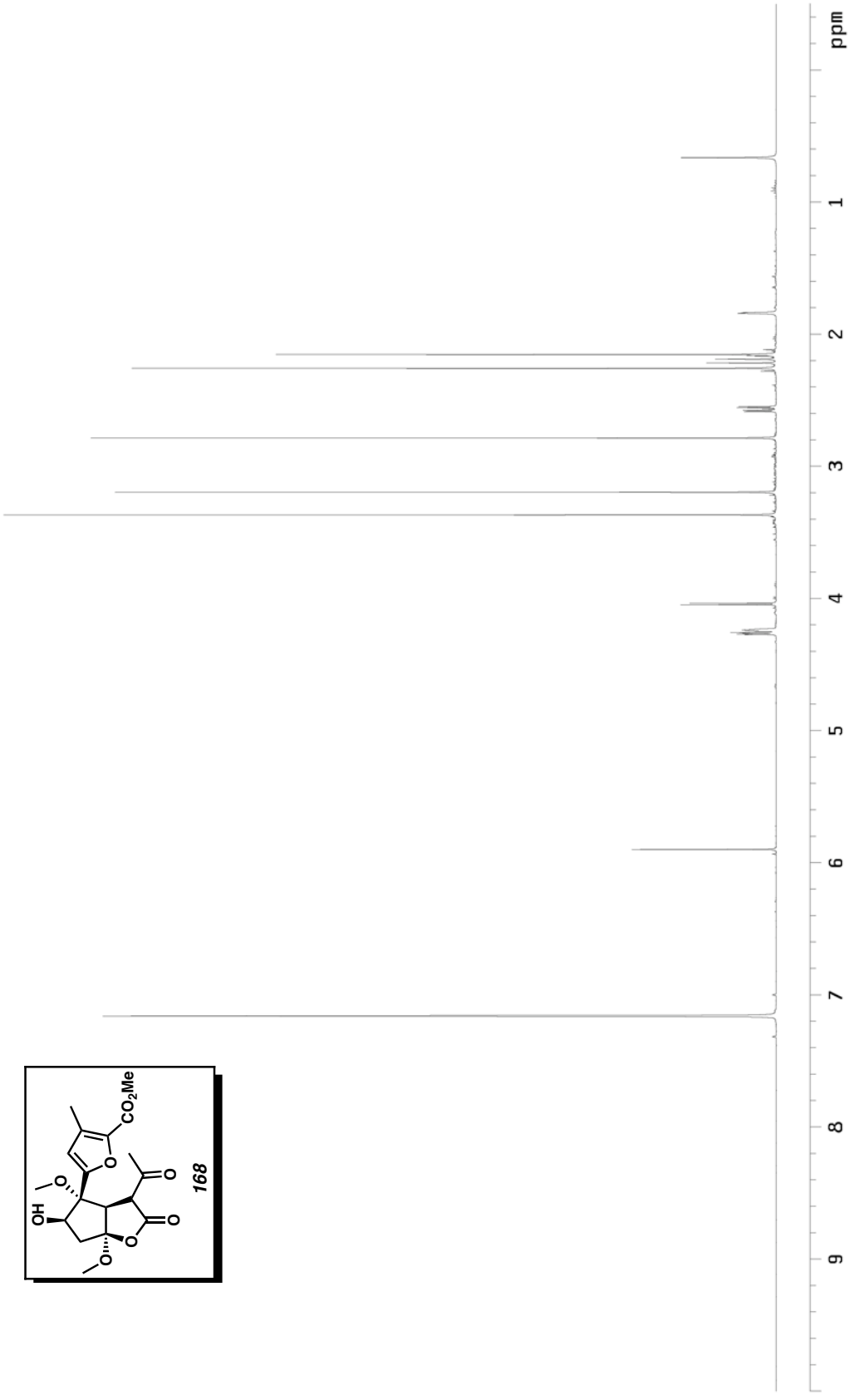


Figure A2.2.66 ^{1}H NMR (500 MHz, C_6D_6) of compound **168**

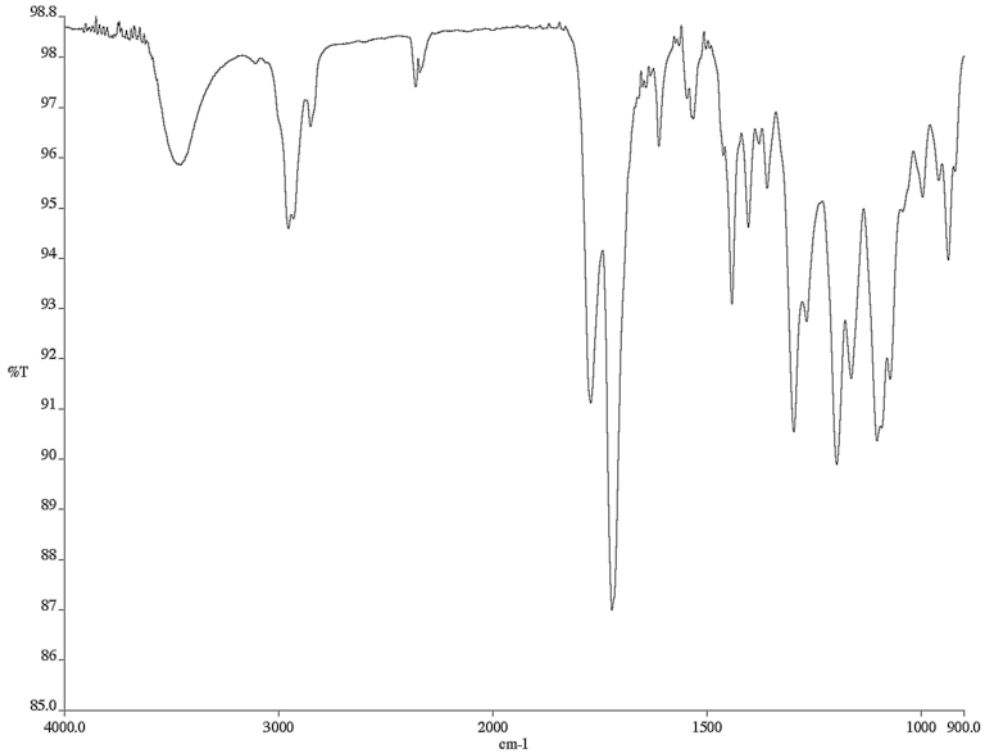


Figure A2.2.67 Infrared spectrum (film/NaCl) of compound **168**

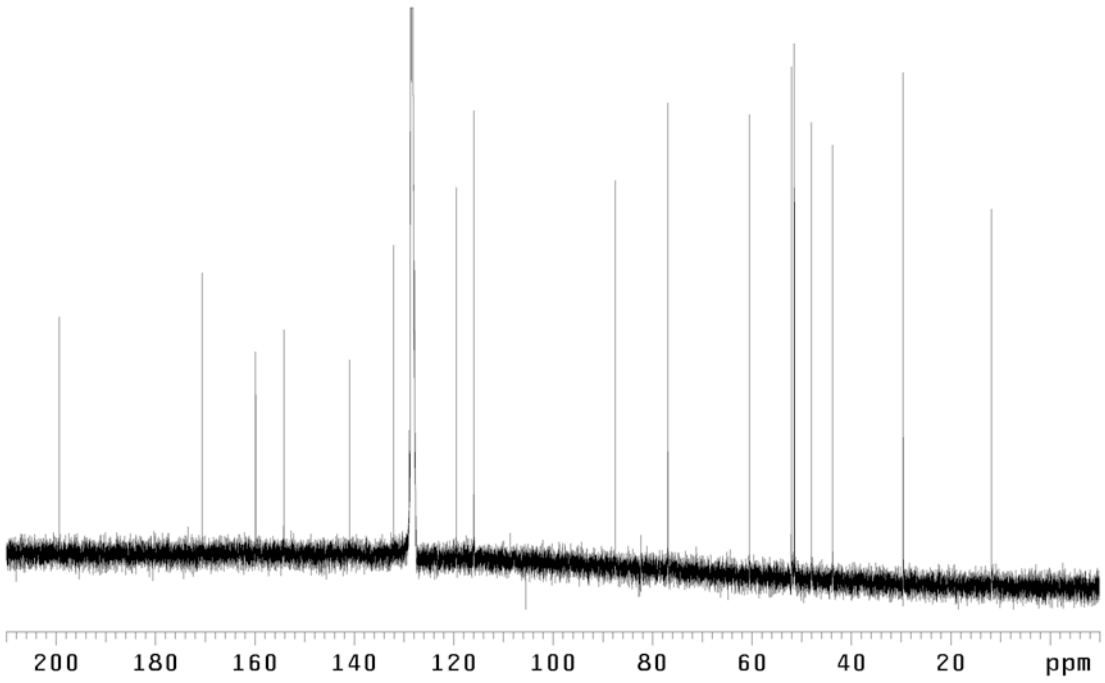


Figure A2.2.68 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **168**

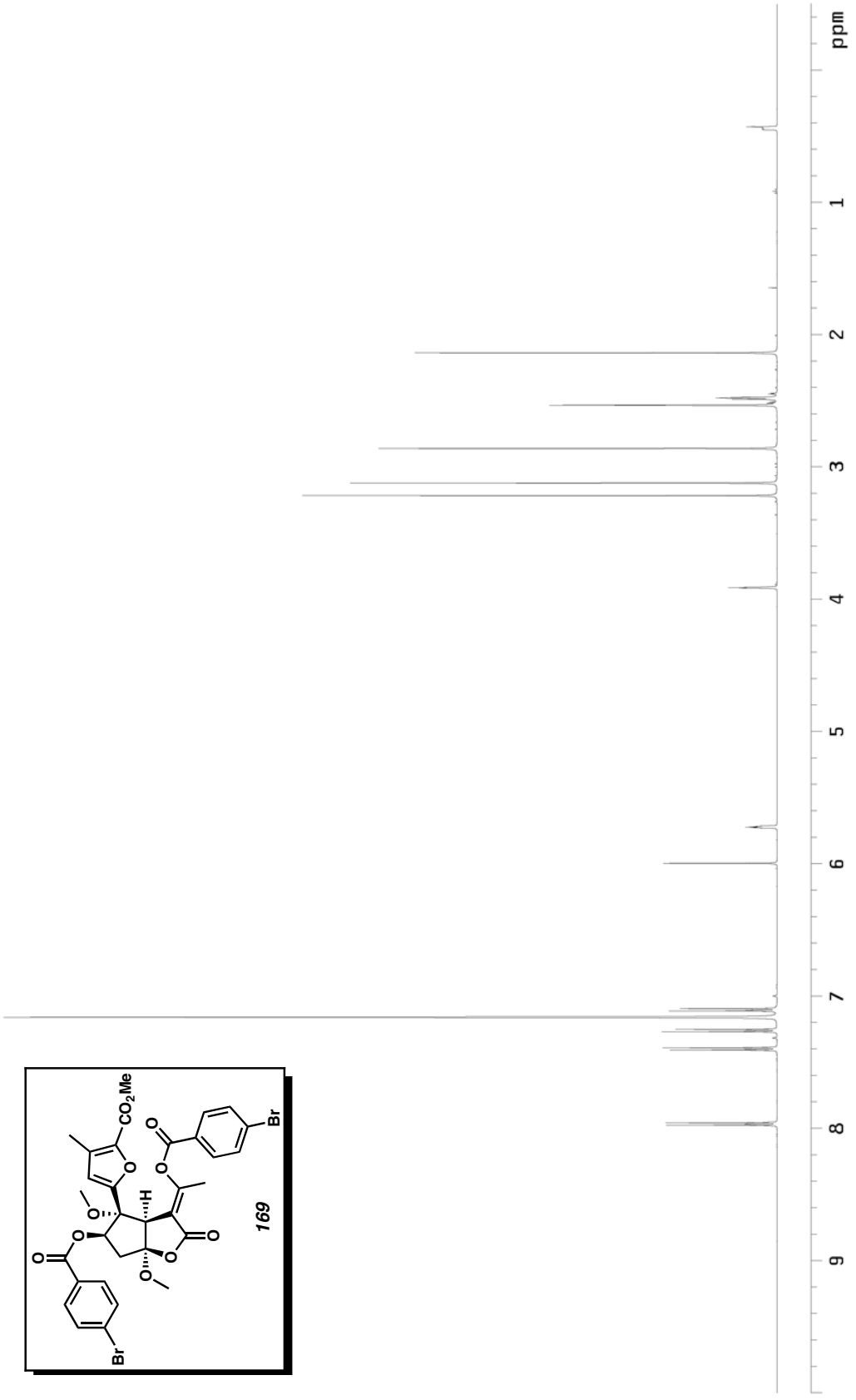


Figure A2.2.69 ^{1}H NMR (500 MHz, C_6D_6) of compound **169**

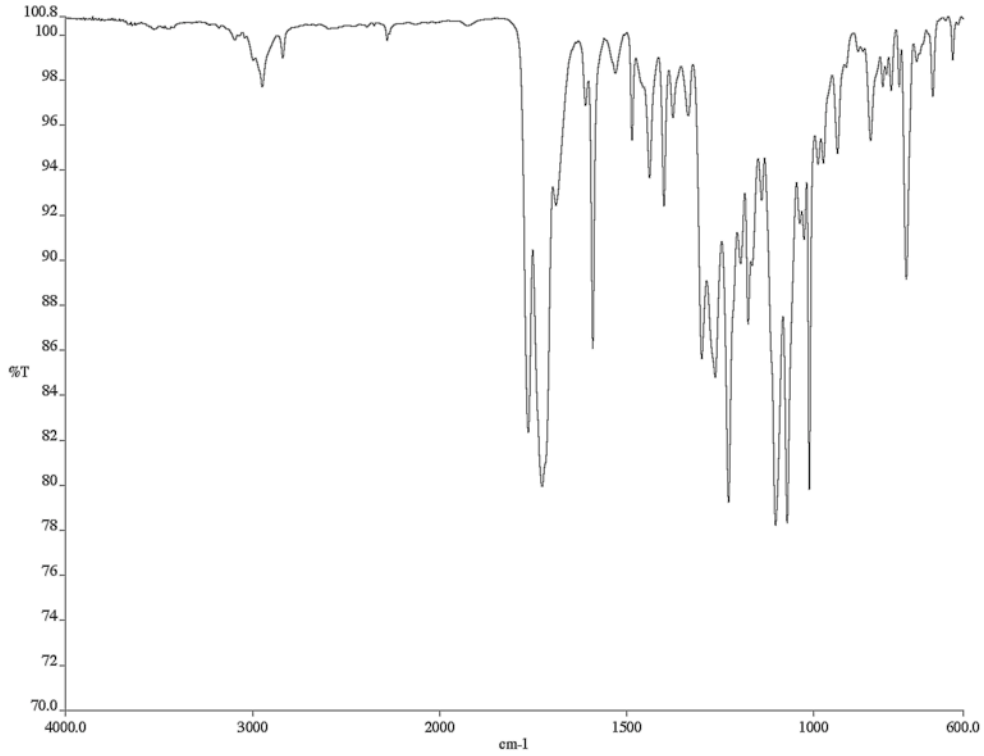


Figure A2.2.70 Infrared spectrum (film/NaCl) of compound **169**

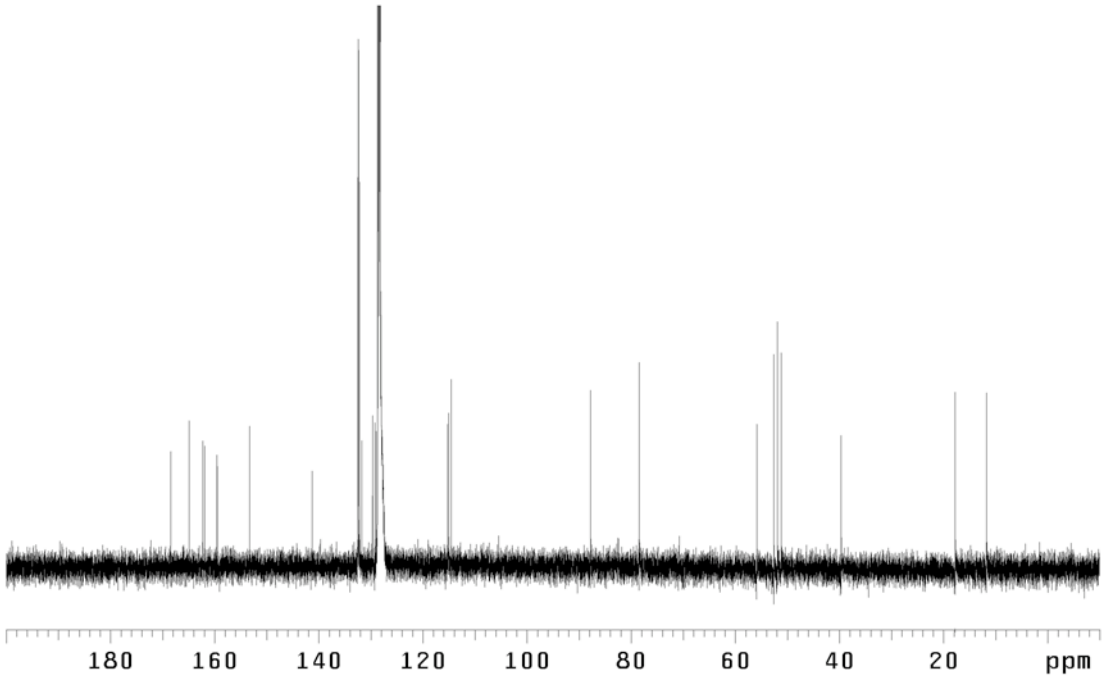


Figure A2.2.71 ^{13}C NMR (125 MHz, C_6D_6) of compound **169**

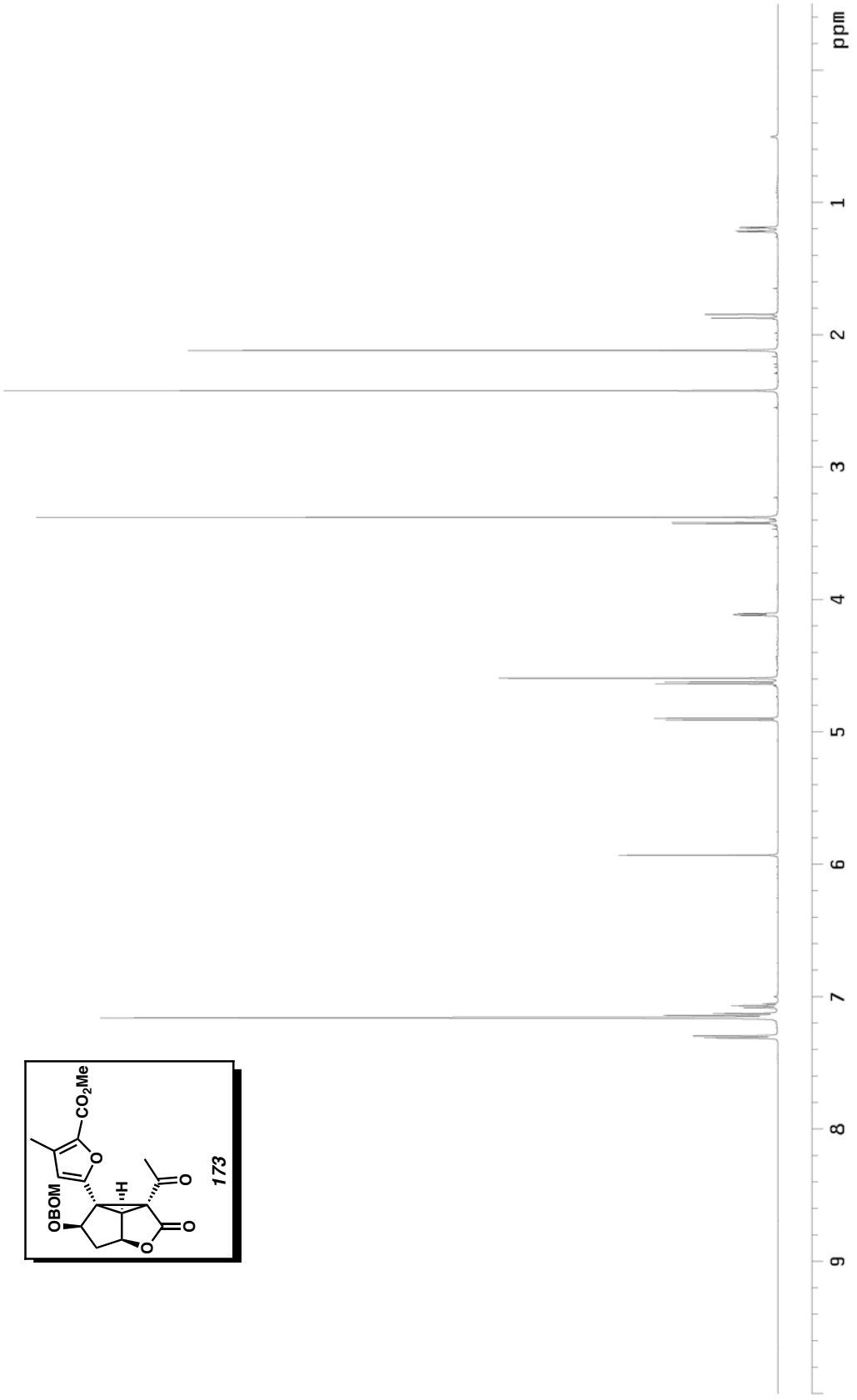


Figure A2.2.72 ^{1}H NMR (500 MHz, C_6D_6) of compound **173**

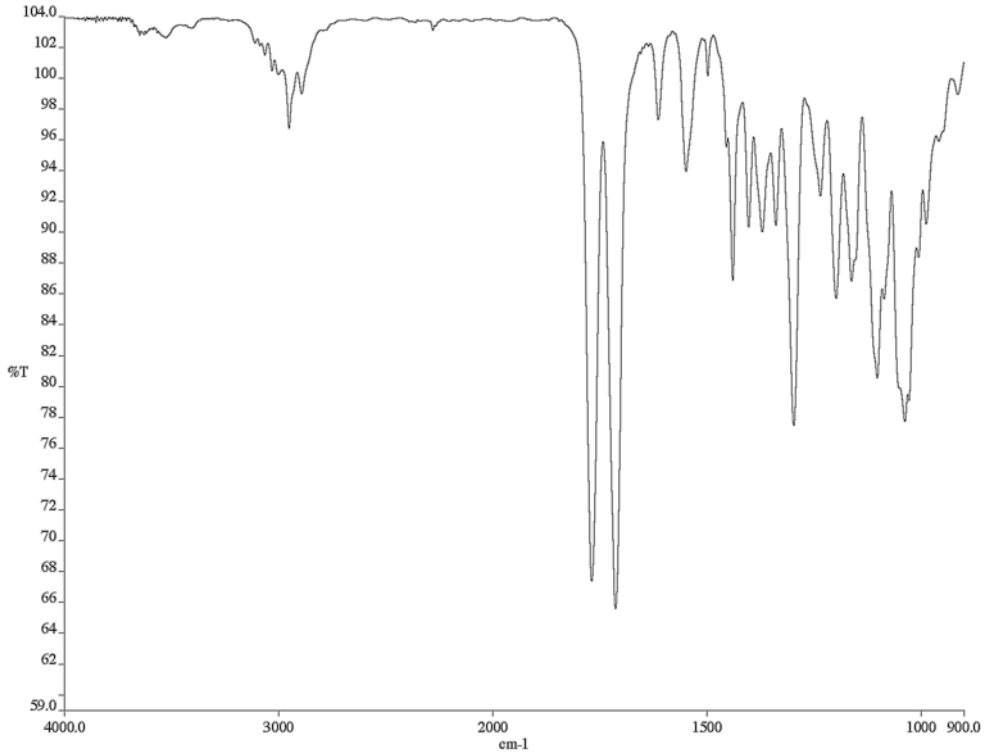


Figure A2.2.73 Infrared spectrum (film/NaCl) of compound **173**

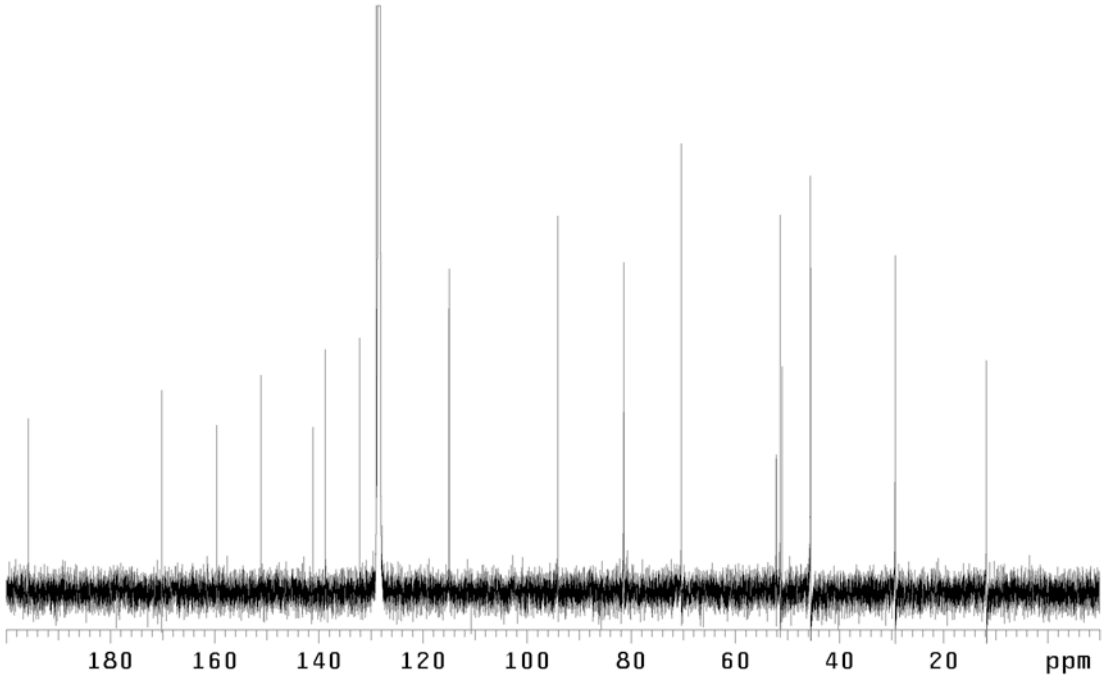


Figure A2.2.74 ^{13}C NMR (125 MHz, C_6D_6) of compound **173**

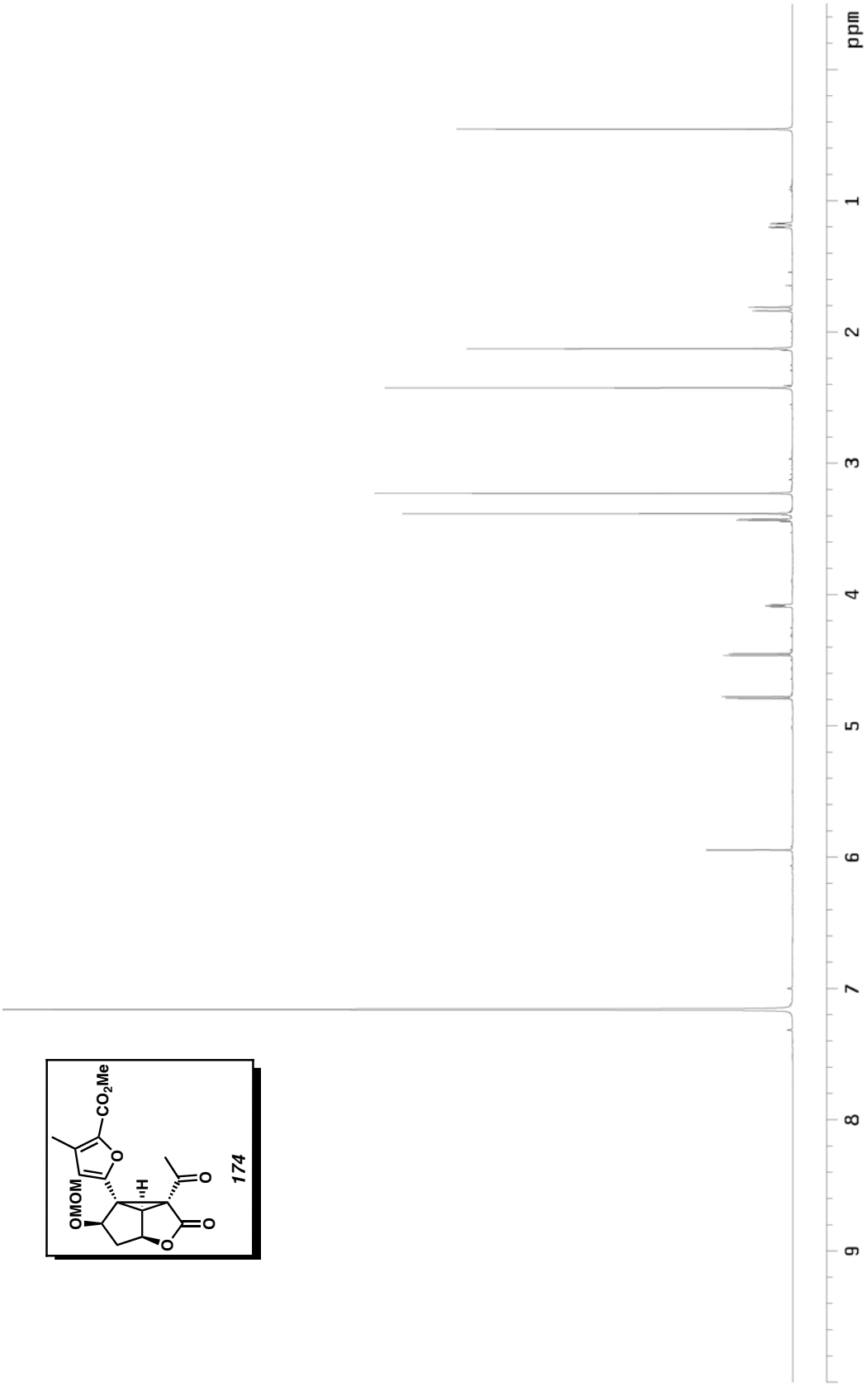


Figure A2.2.75 ^{1}H NMR (500 MHz, C_6D_6) of compound **174**

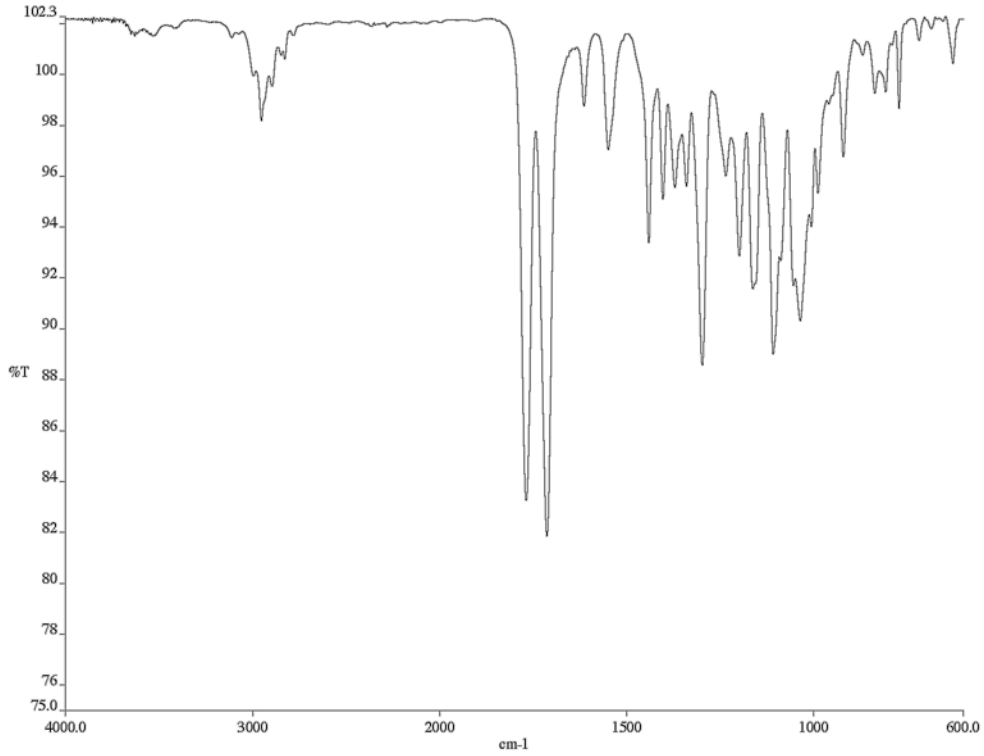


Figure A2.2.76 Infrared spectrum (film/NaCl) of compound **174**

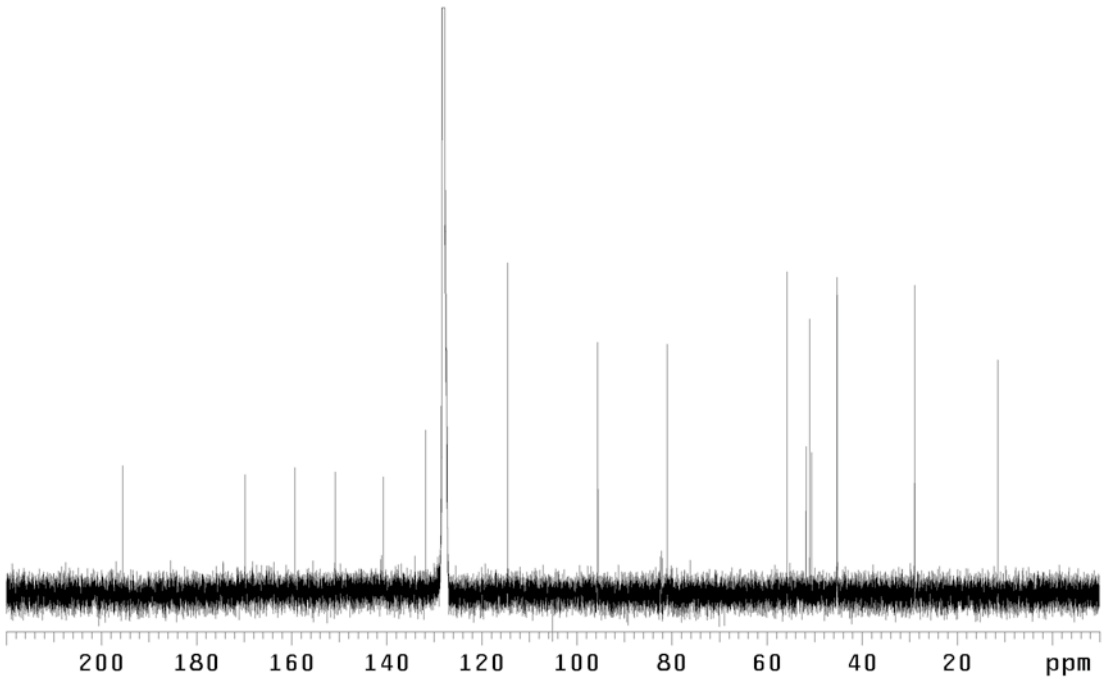


Figure A2.2.77 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **174**

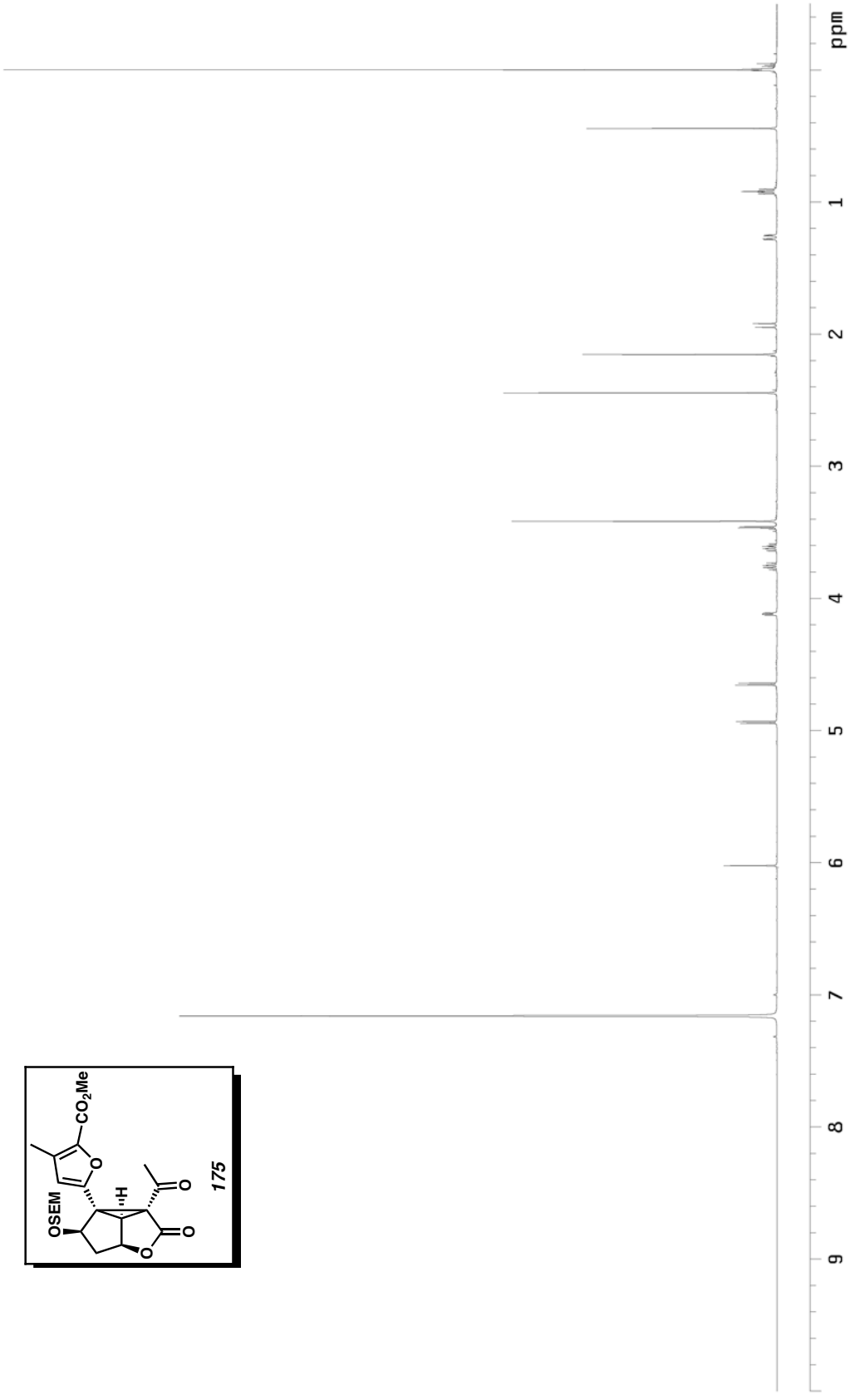


Figure A2.2.78 ^{1}H NMR (500 MHz, C_6D_6) of compound **175**

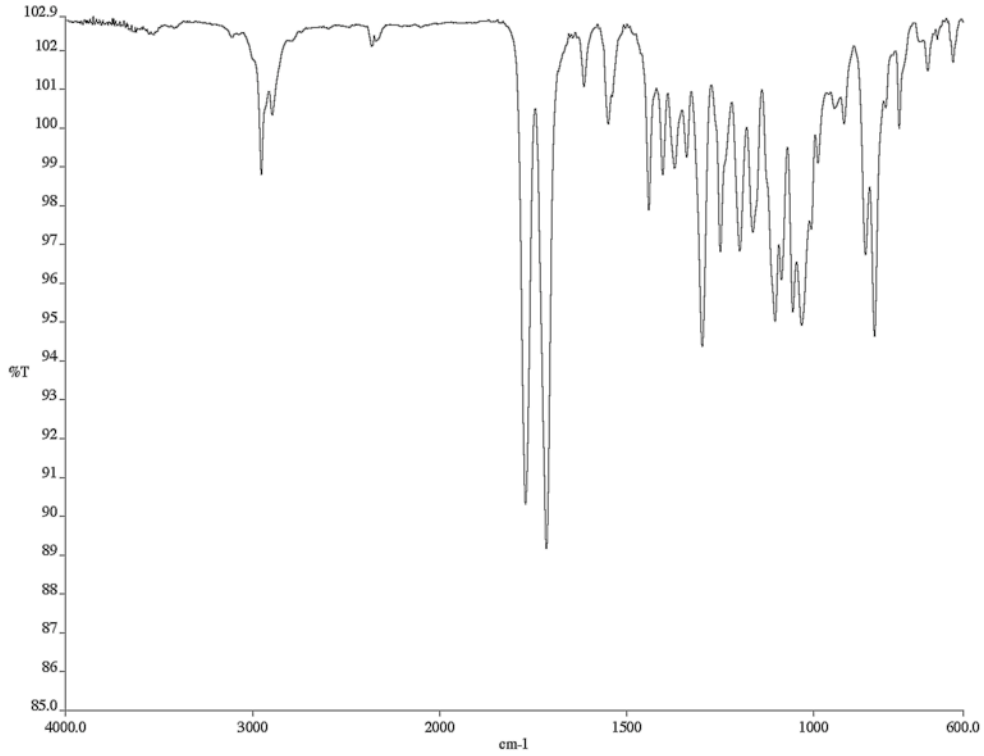


Figure A2.2.79 Infrared spectrum (film/NaCl) of compound **175**

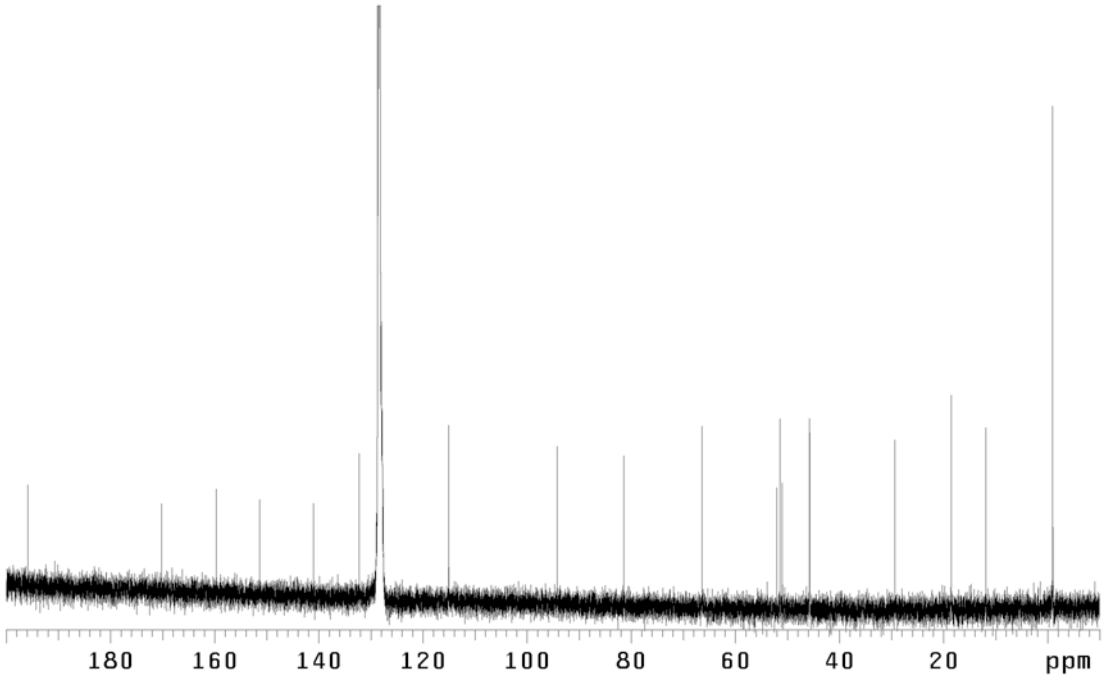


Figure A2.2.80 ^{13}C NMR (125 MHz, C_6D_6) of compound **175**

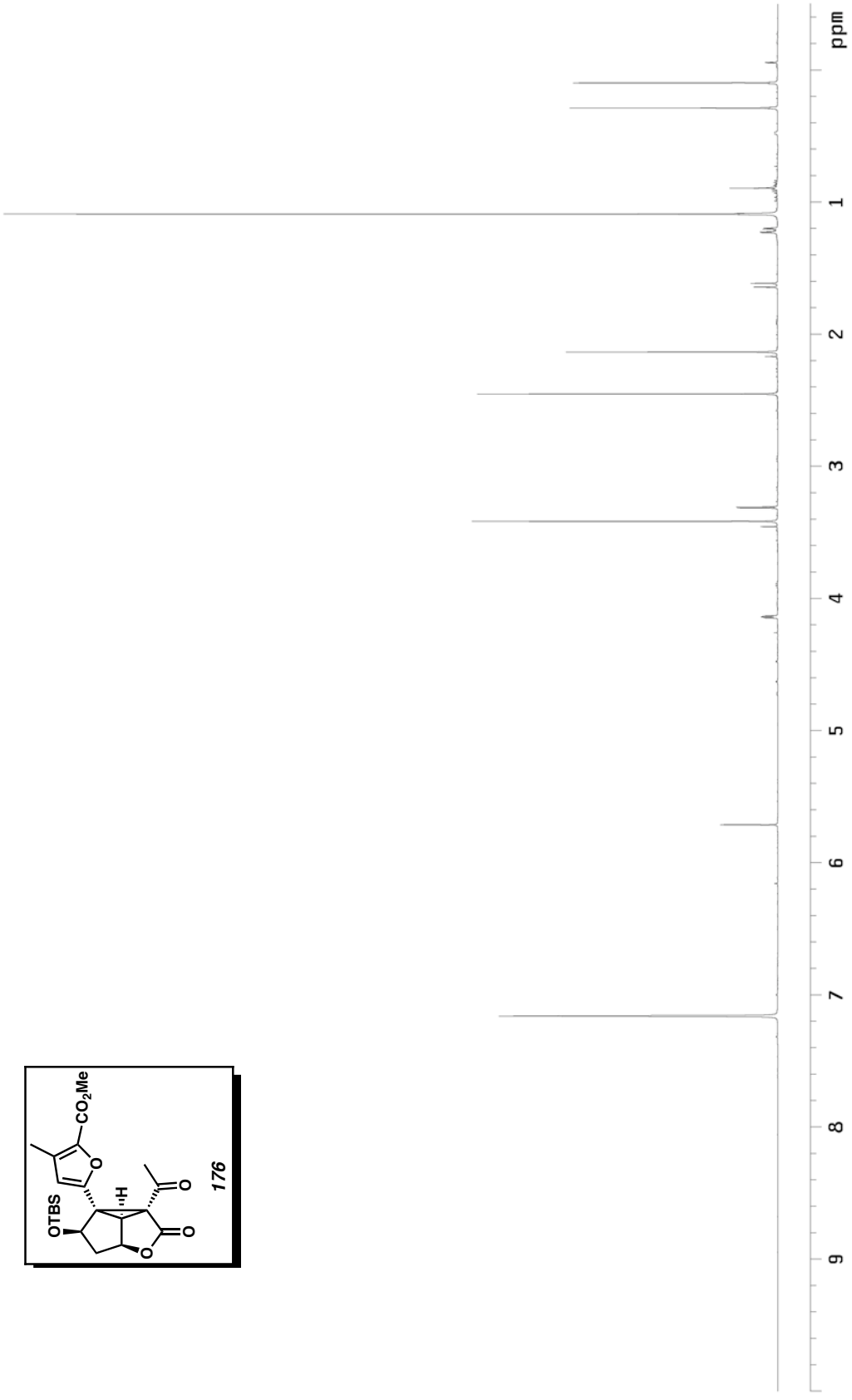


Figure A2.2.81 ^{1}H NMR (500 MHz, C_6D_6) of compound **176**

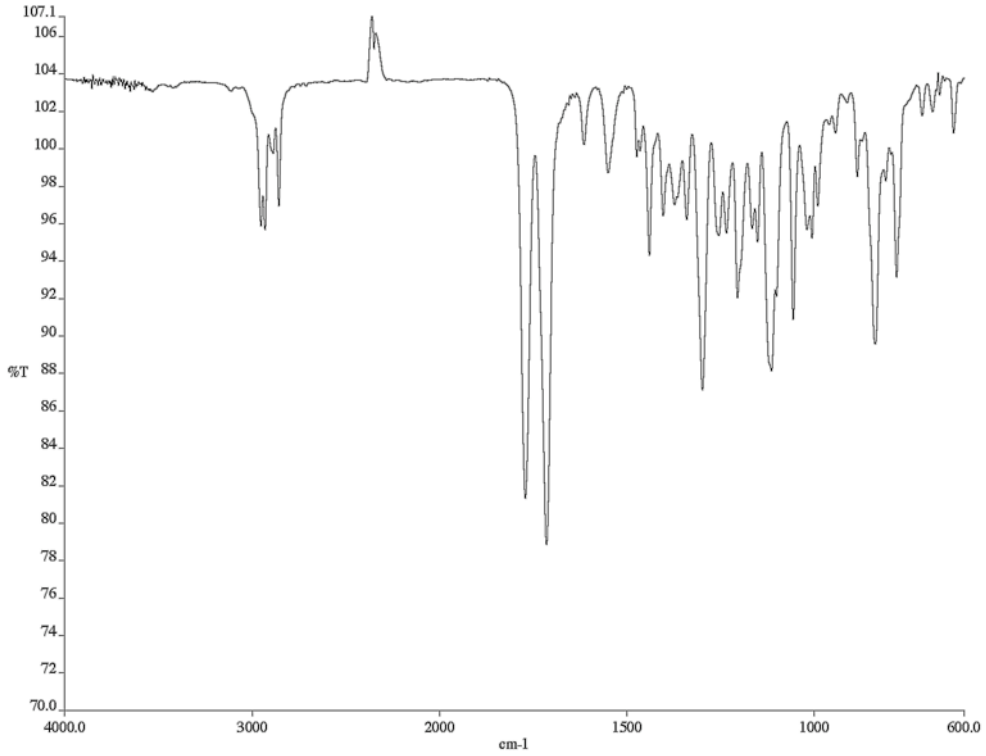


Figure A2.2.82 Infrared spectrum (film/NaCl) of compound **176**

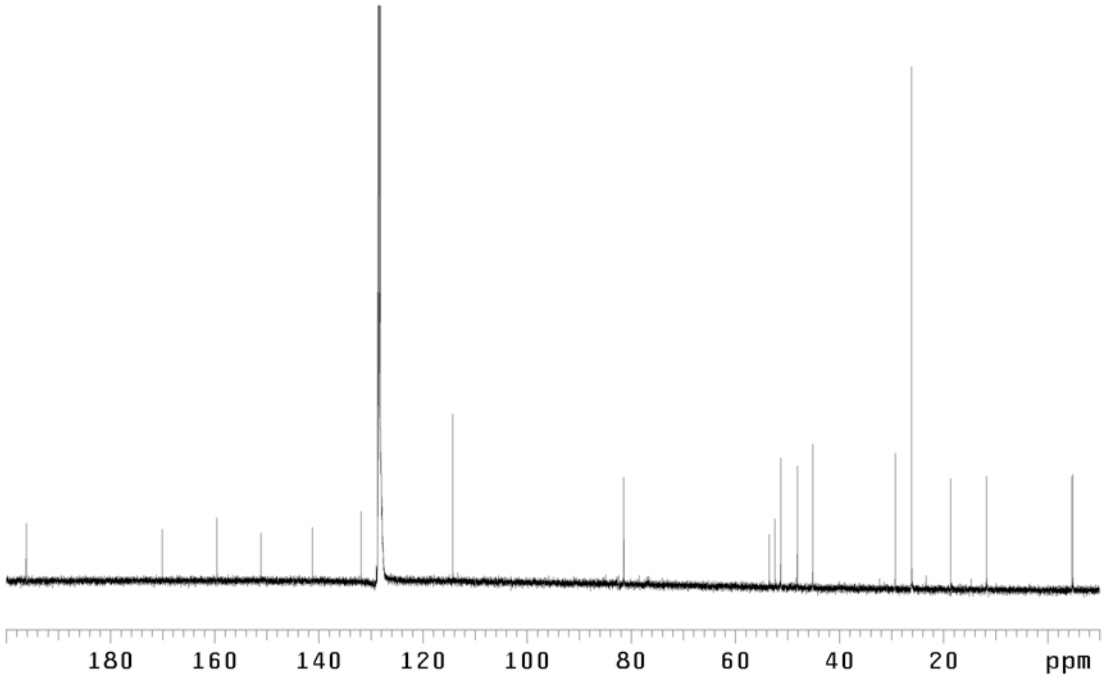


Figure A2.2.83 ^{13}C NMR (125 MHz, C_6D_6) of compound **176**

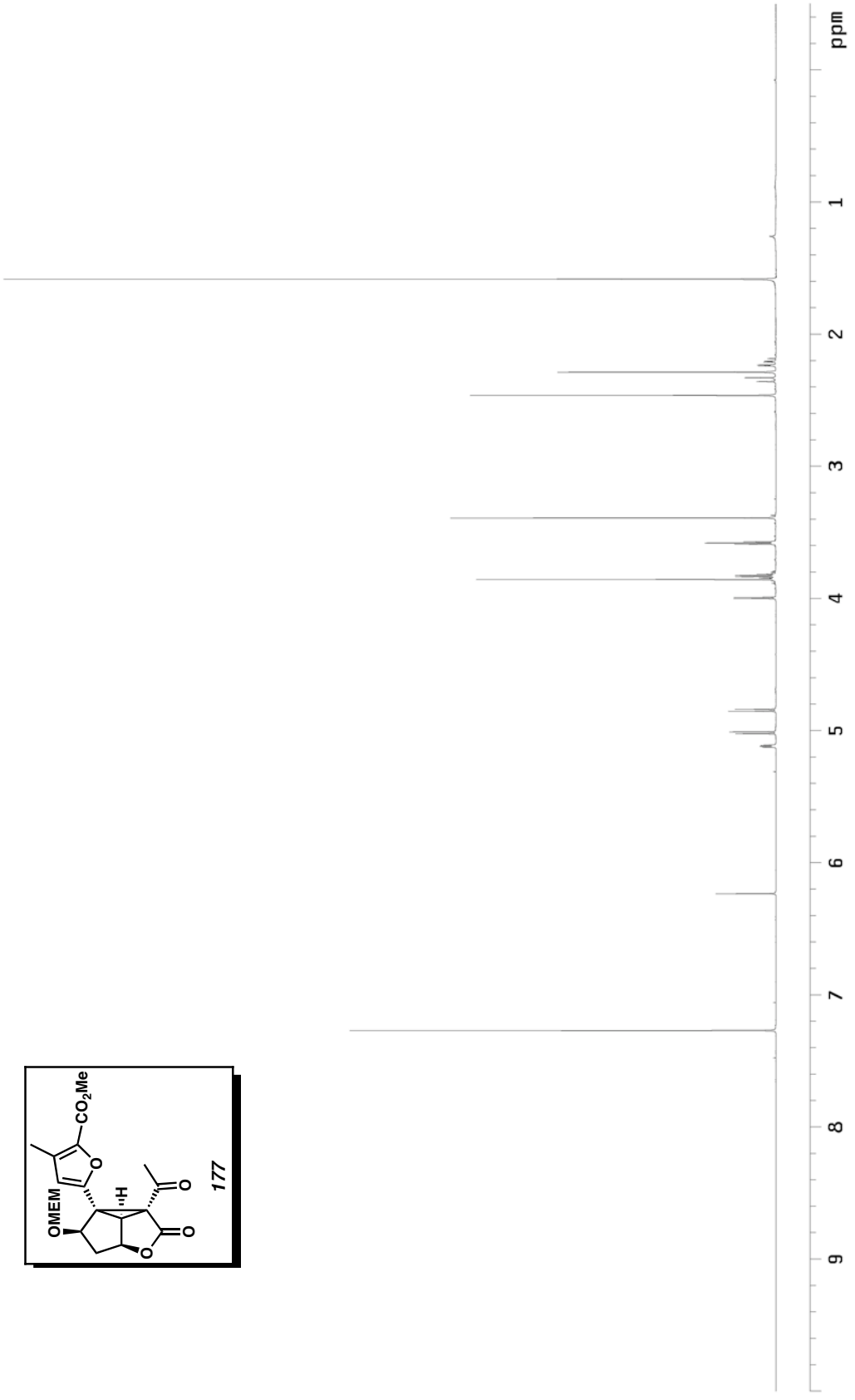


Figure A2.2.84 ^{1}H NMR (500 MHz, C_6D_6) of compound **177**

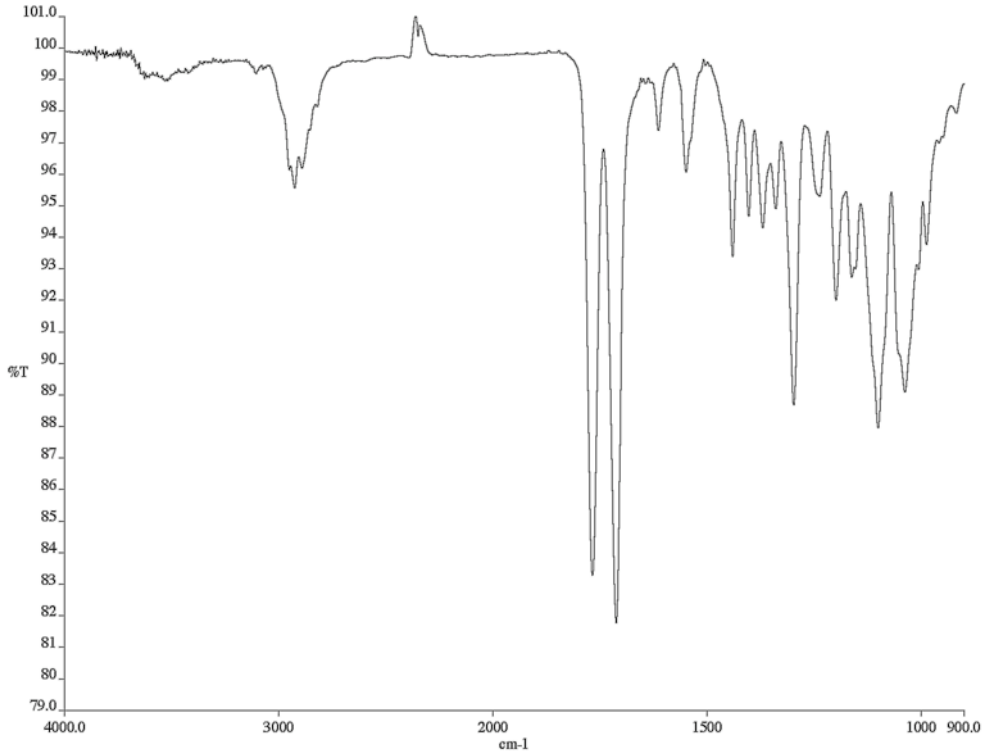


Figure A2.2.85 Infrared spectrum (film/NaCl) of compound **177**

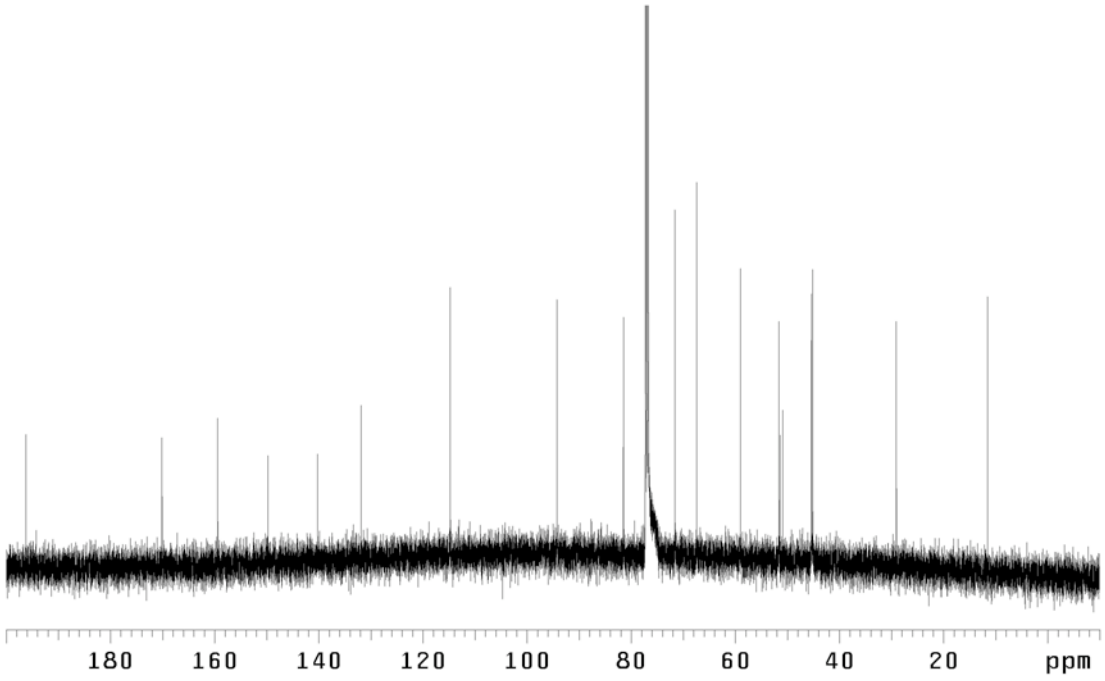


Figure A2.2.86 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **177**

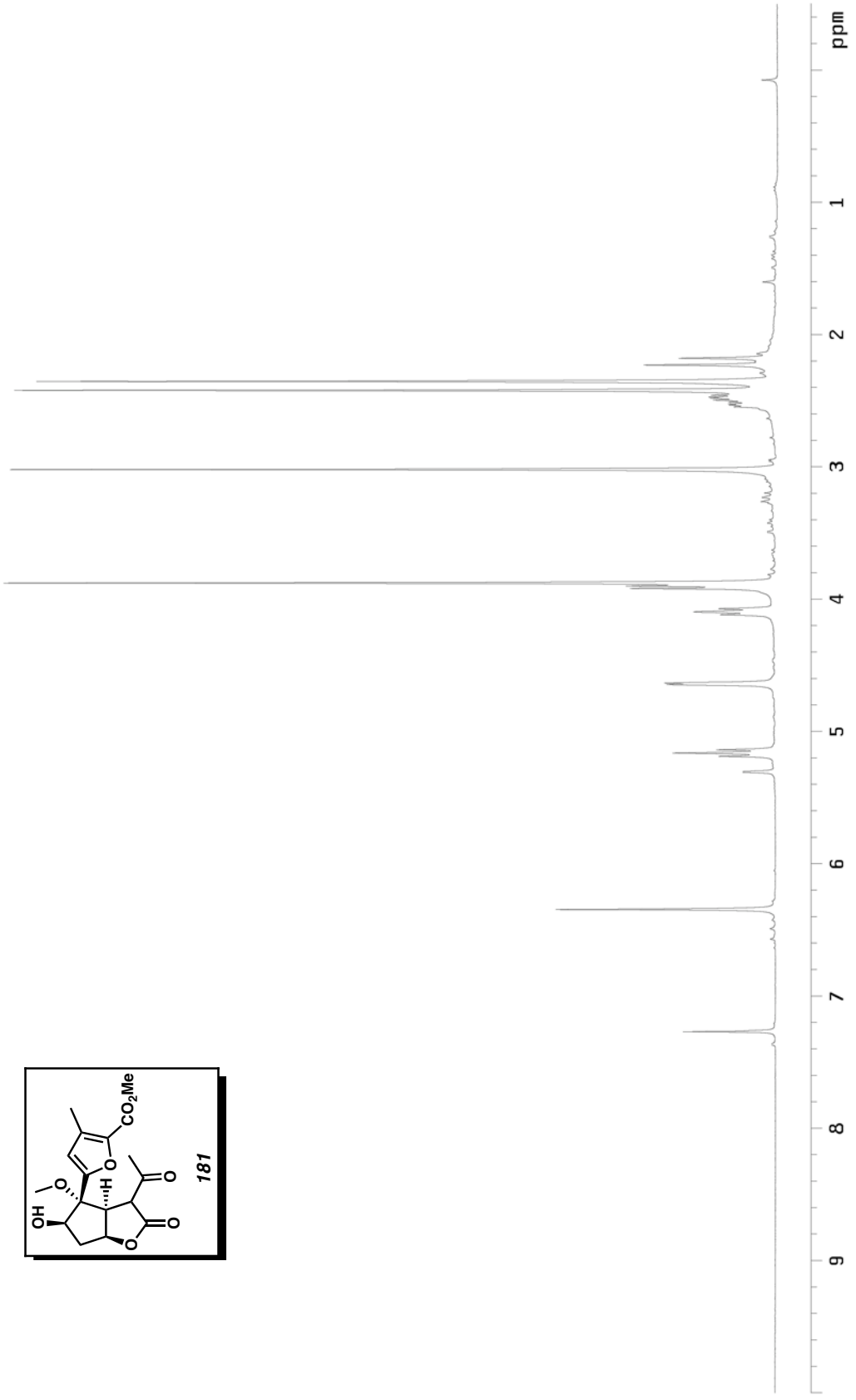


Figure A2.2.87 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **181**

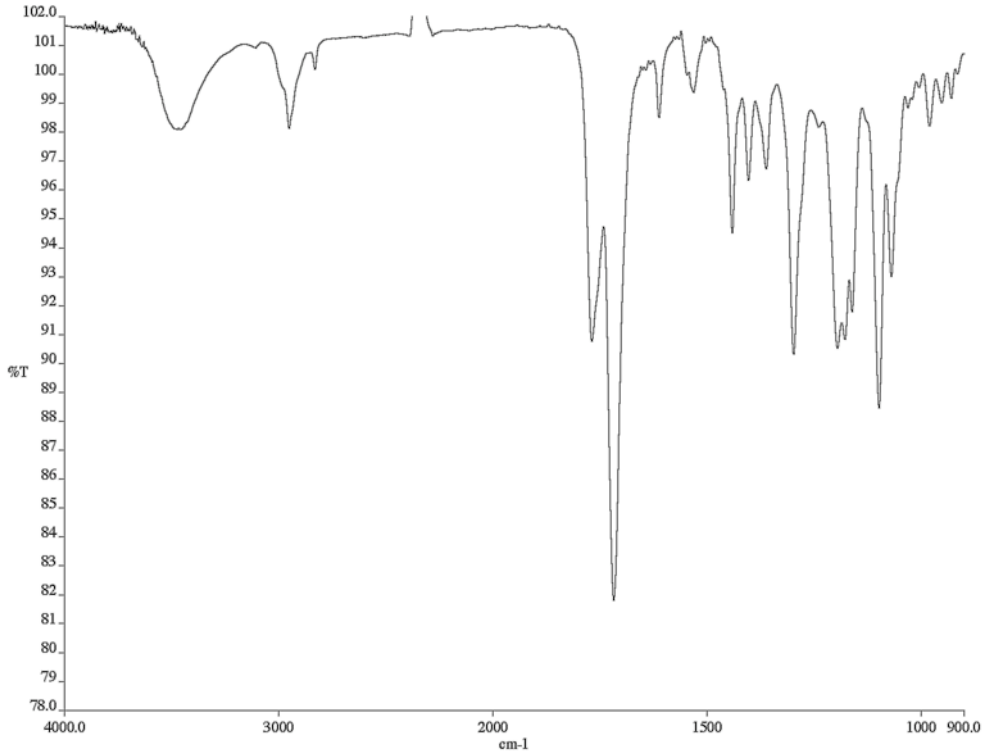


Figure A2.2.88 Infrared spectrum (film/NaCl) of compound **181**

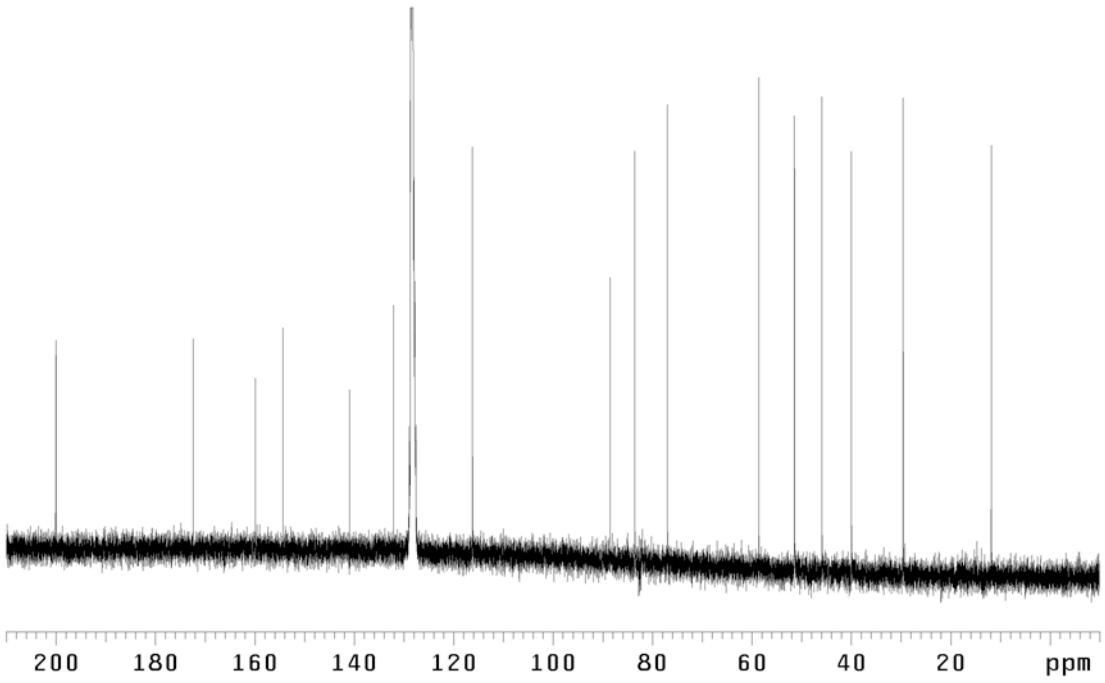


Figure A2.2.89 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **181**

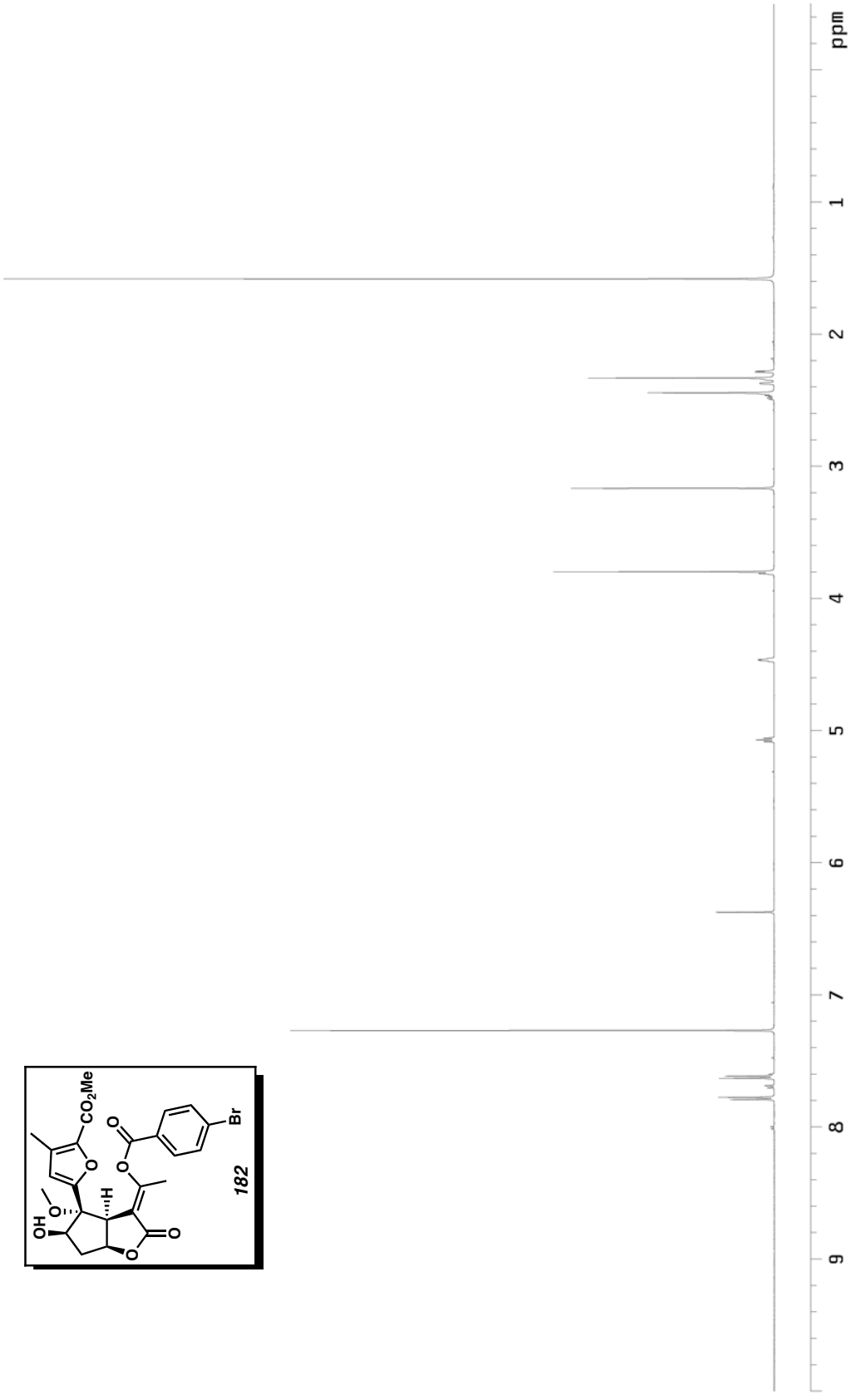


Figure A2.2.90 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **182**

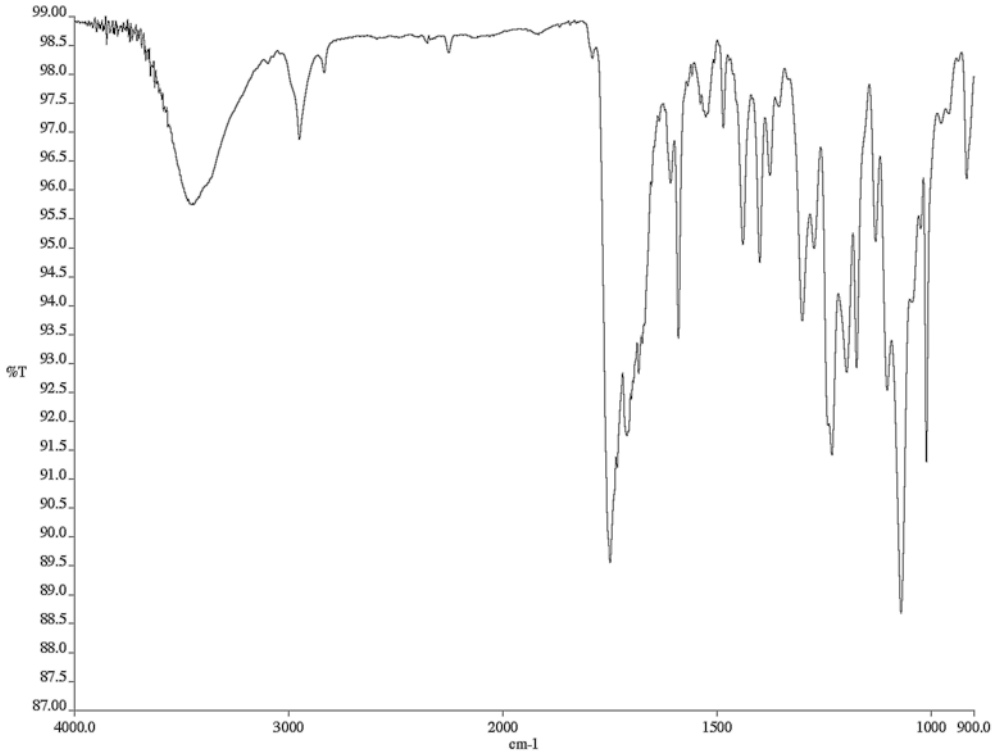


Figure A2.2.91 Infrared spectrum (film/NaCl) of compound **182**

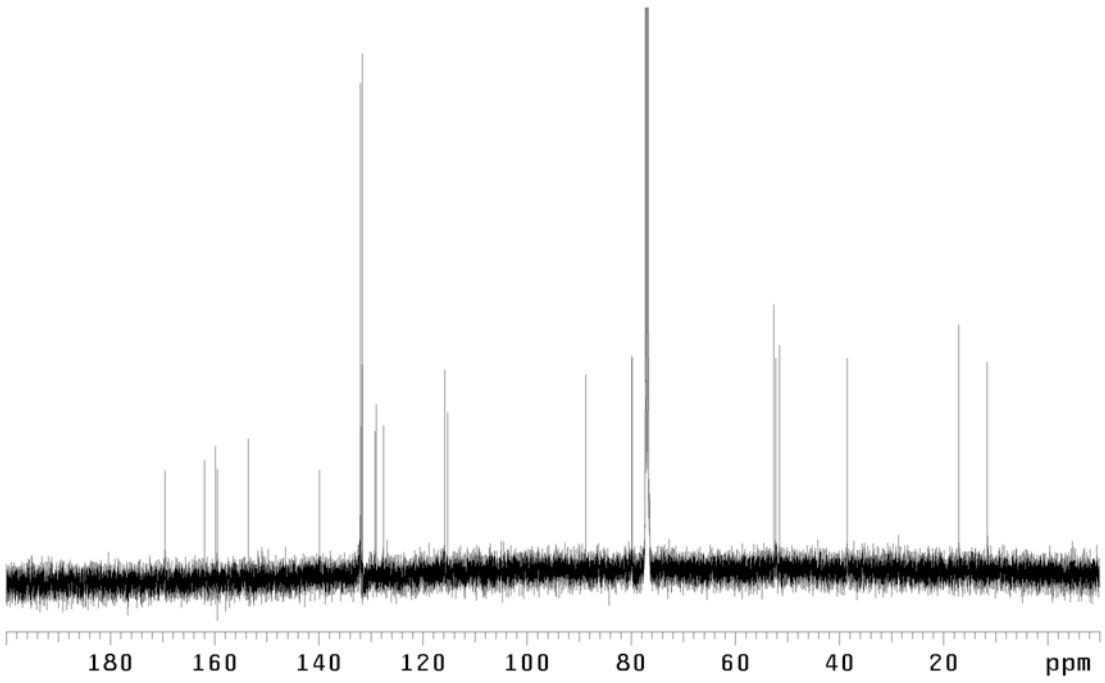


Figure A2.2.92 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **182**

Appendix 2.3

X-Ray Crystallographic Data Relevant to Chapter Two

CALIFORNIA INSTITUTE OF TECHNOLOGY

BECKMAN INSTITUTE

X-RAY CRYSTALLOGRAPHY LABORATORY

Crystal Structure Analysis of:

Alcohol 182

(CCDC 606989)

Contents

Figure A2.3.1 Representation of alcohol **182**.

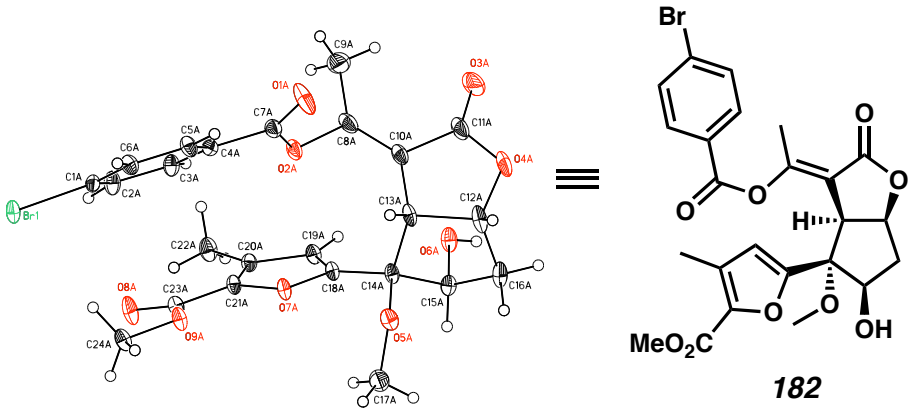


Table 1. Crystal data and structure refinement for alcohol 182 (CCDC 606989).

Empirical formula	$C_{24}H2_3O_9Br$
Formula weight	535.33
Crystallization Solvent	Ethyl acetate/hexanes
Crystal Habit	Fragment
Crystal size	0.34 x 0.26 x 0.18 mm^3
Crystal color	Colorless

Data Collection

Type of diffractometer	Bruker SMART 1000	
Wavelength	0.71073 Å MoKα	
Data Collection Temperature	100(2) K	
θ range for 20114 reflections used in lattice determination	2.43 to 41.82°	
Unit cell dimensions	a = 11.1074(2) Å b = 13.5443(3) Å c = 16.7177(4) Å	α= 106.8590(10)° β= 104.9520(10)° γ = 98.6060(10)°
Volume	2255.89(8) $Å^3$	
Z	4	
Crystal system	Triclinic	
Space group	P-1	
Density (calculated)	1.576 Mg/m^3	
F(000)	1096	
Data collection program	Bruker SMART v5.630	
θ range for data collection	1.71 to 42.84°	
Completeness to θ = 42.84°	87.4 %	
Index ranges	$-21 \le h \le 21, -24 \le k \le 25, -31 \le l \le 31$	
Data collection scan type	ω scans at 8 ϕ settings	
Data reduction program	Bruker SAINT v6.45A	
Reflections collected	68261	
Independent reflections	28932 [R_{int}= 0.0502]	
Absorption coefficient	1.876 mm^{-1}	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.000000 and 0.820201	

Table 1 (cont.)

Structure solution and Refinement

Structure solution program	Bruker XS v6.12
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Difference Fourier map
Structure refinement program	Bruker XL v6.12
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	28932 / 0 / 797
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F^2	1.189
Final R indices [I>2σ(I), 18290 reflections]	R1 = 0.0407, *w*R2 = 0.0734
R indices (all data)	R1 = 0.0831, *w*R2 = 0.0812
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.007
Average shift/error	0.000
Largest diff. peak and hole	0.844 and -0.543 e.Å^{-3}

Special Refinement Details

Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for alcohol 182 (CCDC 606989). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
Br(1)	11019(1)	1482(1)	10581(1)	19(1)
O(1A)	4709(1)	873(1)	8210(1)	34(1)
O(2A)	5774(1)	1287(1)	7327(1)	20(1)
O(3A)	2091(1)	777(1)	5288(1)	36(1)
O(4A)	2261(1)	2445(1)	6087(1)	25(1)
O(5A)	5897(1)	4595(1)	7735(1)	19(1)
O(6A)	4432(1)	3010(1)	5395(1)	20(1)
O(7A)	7570(1)	3438(1)	7662(1)	16(1)
O(8A)	10665(1)	2911(1)	8096(1)	26(1)
O(9A)	9571(1)	3647(1)	8987(1)	18(1)
C(1A)	9361(1)	1314(1)	9804(1)	16(1)
C(2A)	9229(1)	1148(1)	8922(1)	20(1)
C(3A)	8037(1)	1072(1)	8348(1)	18(1)
C(4A)	6990(1)	1154(1)	8661(1)	15(1)
C(5A)	7140(1)	1289(1)	9543(1)	18(1)
C(6A)	8330(1)	1375(1)	10125(1)	18(1)
C(7A)	5707(1)	1080(1)	8070(1)	18(1)
C(8A)	4599(1)	1014(1)	6651(1)	22(1)
C(9A)	4200(2)	-138(1)	6108(1)	34(1)
C(10A)	4018(1)	1783(1)	6549(1)	19(1)
C(11A)	2731(1)	1566(1)	5895(1)	24(1)
C(12A)	3206(1)	3353(1)	6785(1)	22(1)
C(13A)	4414(1)	2941(1)	7101(1)	17(1)
C(14A)	5506(1)	3668(1)	6955(1)	15(1)
C(15A)	4787(1)	3946(1)	6159(1)	17(1)
C(16A)	3600(1)	4196(1)	6402(1)	21(1)
C(17A)	6832(1)	5468(1)	7761(1)	25(1)
C(18A)	6643(1)	3217(1)	6874(1)	14(1)
C(19A)	6986(1)	2623(1)	6200(1)	16(1)
C(20A)	8221(1)	2463(1)	6582(1)	16(1)
C(21A)	8535(1)	2986(1)	7470(1)	16(1)
C(22A)	8979(1)	1840(1)	6099(1)	22(1)
C(23A)	9698(1)	3171(1)	8201(1)	17(1)
C(24A)	10696(1)	3849(1)	9740(1)	20(1)
Br(2)	3493(1)	3385(1)	-883(1)	18(1)
O(1B)	9806(1)	4309(1)	1640(1)	28(1)
O(2B)	8714(1)	3943(1)	2530(1)	19(1)
O(3B)	12418(1)	4788(1)	4624(1)	30(1)
O(4B)	12534(1)	3196(1)	3826(1)	23(1)
O(5B)	9146(1)	747(1)	2103(1)	20(1)
O(6B)	10420(1)	2346(1)	4444(1)	19(1)
O(7B)	7219(1)	1646(1)	2160(1)	16(1)
O(8B)	4007(1)	1961(1)	1733(1)	21(1)
O(9B)	5099(1)	1226(1)	841(1)	18(1)
C(1B)	5143(1)	3643(1)	-75(1)	15(1)
C(2B)	5228(1)	3750(1)	794(1)	17(1)

C(3B)	6417(1)	3885(1)	1395(1)	17(1)
C(4B)	7512(1)	3913(1)	1131(1)	14(1)
C(5B)	7415(1)	3819(1)	261(1)	17(1)
C(6B)	6229(1)	3685(1)	-347(1)	17(1)
C(7B)	8798(1)	4077(1)	1764(1)	17(1)
C(8B)	9866(1)	4308(1)	3237(1)	19(1)
C(9B)	10039(1)	5424(1)	3807(1)	28(1)
C(10B)	10611(1)	3636(1)	3334(1)	18(1)
C(11B)	11900(1)	3974(1)	4011(1)	21(1)
C(12B)	11713(1)	2235(1)	3104(1)	22(1)
C(13B)	10398(1)	2503(1)	2764(1)	17(1)
C(14B)	9408(1)	1648(1)	2882(1)	16(1)
C(15B)	10213(1)	1430(1)	3687(1)	18(1)
C(16B)	11459(1)	1343(1)	3466(1)	22(1)
C(17B)	8407(1)	-225(1)	2091(1)	25(1)
C(18B)	8174(1)	1940(1)	2947(1)	14(1)
C(19B)	7771(1)	2456(1)	3621(1)	15(1)
C(20B)	6467(1)	2480(1)	3241(1)	14(1)
C(21B)	6179(1)	1972(1)	2353(1)	15(1)
C(22B)	5613(1)	2941(1)	3728(1)	20(1)
C(23B)	4983(1)	1725(1)	1626(1)	15(1)
C(24B)	3965(1)	998(1)	90(1)	20(1)

Table 3. Bond lengths [Å] and angles [°] for alcohol 182 (CCDC 606989).

Br(1)-C(1A)	1.8967(11)	C(20A)-C(21A)	1.3699(16)
O(1A)-C(7A)	1.2006(15)	C(20A)-C(22A)	1.4966(15)
O(2A)-C(7A)	1.3673(15)	C(21A)-C(23A)	1.4612(15)
O(2A)-C(8A)	1.4031(14)	C(22A)-H(22A)	0.86(2)
O(3A)-C(11A)	1.2030(18)	C(22A)-H(22B)	0.89(2)
O(4A)-C(11A)	1.3573(18)	C(22A)-H(22C)	0.91(2)
O(4A)-C(12A)	1.4575(16)	C(24A)-H(24A)	0.945(19)
O(5A)-C(17A)	1.4344(17)	C(24A)-H(24B)	0.950(18)
O(5A)-C(14A)	1.4363(14)	C(24A)-H(24C)	0.921(17)
O(6A)-C(15A)	1.4308(15)	Br(2)-C(1B)	1.8886(10)
O(6A)-H(6A)	0.76(2)	O(1B)-C(7B)	1.2031(14)
O(7A)-C(18A)	1.3641(13)	O(2B)-C(7B)	1.3679(14)
O(7A)-C(21A)	1.3745(12)	O(2B)-C(8B)	1.4040(13)
O(8A)-C(23A)	1.2169(13)	O(3B)-C(11B)	1.2033(17)
O(9A)-C(23A)	1.3406(14)	O(4B)-C(11B)	1.3588(17)
O(9A)-C(24A)	1.4513(14)	O(4B)-C(12B)	1.4660(16)
C(1A)-C(6A)	1.3878(15)	O(5B)-C(17B)	1.4358(18)
C(1A)-C(2A)	1.3900(17)	O(5B)-C(14B)	1.4305(13)
C(2A)-C(3A)	1.3897(16)	O(6B)-C(15B)	1.4301(15)
C(2A)-H(2A)	0.969(18)	O(6B)-H(6B)	0.79(2)
C(3A)-C(4A)	1.3984(15)	O(7B)-C(18B)	1.3659(13)
C(3A)-H(3A)	0.929(18)	O(7B)-C(21B)	1.3763(12)
C(4A)-C(5A)	1.3950(16)	O(8B)-C(23B)	1.2158(13)
C(4A)-C(7A)	1.4795(15)	O(9B)-C(23B)	1.3397(14)
C(5A)-C(6A)	1.3897(16)	O(9B)-C(24B)	1.4497(14)
C(5A)-H(5A)	0.891(17)	C(1B)-C(6B)	1.3940(14)
C(6A)-H(6A1)	0.951(16)	C(1B)-C(2B)	1.3935(16)
C(8A)-C(10A)	1.3341(19)	C(2B)-C(3B)	1.3865(16)
C(8A)-C(9A)	1.489(2)	C(2B)-H(2B)	0.901(16)
C(9A)-H(9A1)	0.88(2)	C(3B)-C(4B)	1.3958(15)
C(9A)-H(9A2)	0.97(2)	C(3B)-H(3B)	0.927(18)
C(9A)-H(9A3)	0.96(2)	C(4B)-C(5B)	1.3976(16)
C(10A)-C(11A)	1.4857(15)	C(4B)-C(7B)	1.4823(15)
C(10A)-C(13A)	1.5001(18)	C(5B)-C(6B)	1.3904(15)
C(12A)-C(16A)	1.525(2)	C(5B)-H(5B)	0.910(18)
C(12A)-C(13A)	1.5563(15)	C(6B)-H(6B1)	0.944(15)
C(12A)-H(12A)	0.902(19)	C(8B)-C(10B)	1.3346(18)
C(13A)-C(14A)	1.5609(16)	C(8B)-C(9B)	1.4872(19)
C(13A)-H(13A)	0.941(16)	C(9B)-H(9B1)	0.91(2)
C(14A)-C(18A)	1.5024(14)	C(9B)-H(9B2)	0.99(2)
C(14A)-C(15A)	1.5430(16)	C(9B)-H(9B3)	0.93(2)
C(15A)-C(16A)	1.5315(15)	C(10B)-C(11B)	1.4851(15)
C(15A)-H(15A)	0.966(16)	C(10B)-C(13B)	1.4994(18)
C(16A)-H(16A)	0.928(17)	C(12B)-C(16B)	1.522(2)
C(16A)-H(16B)	0.958(17)	C(12B)-C(13B)	1.5604(15)
C(17A)-H(17A)	0.95(2)	C(12B)-H(12B)	0.921(16)
C(17A)-H(17B)	0.95(2)	C(13B)-C(14B)	1.5654(17)
C(17A)-H(17C)	0.88(2)	C(13B)-H(13B)	0.937(16)
C(18A)-C(19A)	1.3602(15)	C(14B)-C(18B)	1.5037(14)
C(19A)-C(20A)	1.4326(15)	C(14B)-C(15B)	1.5461(16)
C(19A)-H(19A)	0.968(16)	C(15B)-C(16B)	1.5338(15)

C(15B)-H(15B)	0.959(16)
C(16B)-H(16C)	0.941(18)
C(16B)-H(16D)	0.940(19)
C(17B)-H(17D)	0.965(17)
C(17B)-H(17E)	0.967(18)
C(17B)-H(17F)	0.940(19)
C(18B)-C(19B)	1.3621(15)
C(19B)-C(20B)	1.4325(14)
C(19B)-H(19B)	1.020(17)
C(20B)-C(21B)	1.3693(15)
C(20B)-C(22B)	1.4940(14)
C(21B)-C(23B)	1.4673(15)
C(22B)-H(22D)	0.88(2)
C(22B)-H(22E)	0.92(2)
C(22B)-H(22F)	0.95(2)
C(24B)-H(24D)	0.925(17)
C(24B)-H(24E)	0.949(19)
C(24B)-H(24F)	0.96(2)

C(7A)-O(2A)-C(8A)	115.48(9)
C(11A)-O(4A)-C(12A)	112.39(9)
C(17A)-O(5A)-C(14A)	115.97(9)
C(15A)-O(6A)-H(6A)	108.2(15)
C(18A)-O(7A)-C(21A)	106.33(8)
C(23A)-O(9A)-C(24A)	114.99(9)
C(6A)-C(1A)-C(2A)	121.98(10)
C(6A)-C(1A)-Br(1)	120.04(9)
C(2A)-C(1A)-Br(1)	117.97(8)
C(3A)-C(2A)-C(1A)	119.10(10)
C(3A)-C(2A)-H(2A)	117.5(11)
C(1A)-C(2A)-H(2A)	123.2(11)
C(2A)-C(3A)-C(4A)	119.89(11)
C(2A)-C(3A)-H(3A)	120.5(11)
C(4A)-C(3A)-H(3A)	119.6(11)
C(3A)-C(4A)-C(5A)	119.86(10)
C(3A)-C(4A)-C(7A)	121.46(10)
C(5A)-C(4A)-C(7A)	118.68(10)
C(6A)-C(5A)-C(4A)	120.73(10)
C(6A)-C(5A)-H(5A)	121.7(11)
C(4A)-C(5A)-H(5A)	117.5(11)
C(1A)-C(6A)-C(5A)	118.40(11)
C(1A)-C(6A)-H(6A1)	122.4(10)
C(5A)-C(6A)-H(6A1)	119.2(10)
O(1A)-C(7A)-O(2A)	122.51(11)
O(1A)-C(7A)-C(4A)	125.43(12)
O(2A)-C(7A)-C(4A)	112.05(10)
C(10A)-C(8A)-O(2A)	118.54(12)
C(10A)-C(8A)-C(9A)	128.62(12)
O(2A)-C(8A)-C(9A)	112.79(12)
C(8A)-C(9A)-H(9A1)	110.0(14)
C(8A)-C(9A)-H(9A2)	108.7(12)
H(9A1)-C(9A)-H(9A2)	112.6(18)
C(8A)-C(9A)-H(9A3)	107.5(13)
H(9A1)-C(9A)-H(9A3)	111.6(18)
H(9A2)-C(9A)-H(9A3)	106.3(17)
C(8A)-C(10A)-C(11A)	122.62(12)
C(8A)-C(10A)-C(13A)	128.54(10)
C(11A)-C(10A)-C(13A)	108.45(11)
O(3A)-C(11A)-O(4A)	119.81(12)
O(3A)-C(11A)-C(10A)	131.28(14)
O(4A)-C(11A)-C(10A)	108.86(11)
O(4A)-C(12A)-C(16A)	109.45(10)
O(4A)-C(12A)-C(13A)	106.21(11)
C(16A)-C(12A)-C(13A)	107.12(9)
O(4A)-C(12A)-H(12A)	105.6(12)
C(16A)-C(12A)-H(12A)	114.7(12)
C(13A)-C(12A)-H(12A)	113.4(12)
C(10A)-C(13A)-C(12A)	103.48(9)
C(10A)-C(13A)-C(14A)	117.70(9)
C(12A)-C(13A)-C(14A)	103.81(10)
C(10A)-C(13A)-H(13A)	109.9(10)
C(12A)-C(13A)-H(13A)	113.2(10)
C(14A)-C(13A)-H(13A)	108.6(10)
O(5A)-C(14A)-C(18A)	109.54(9)
O(5A)-C(14A)-C(15A)	109.05(10)
C(18A)-C(14A)-C(15A)	116.10(9)
O(5A)-C(14A)-C(13A)	102.55(8)
C(18A)-C(14A)-C(13A)	115.37(10)
C(15A)-C(14A)-C(13A)	103.20(9)
O(6A)-C(15A)-C(16A)	110.76(10)
O(6A)-C(15A)-C(14A)	107.37(10)
C(16A)-C(15A)-C(14A)	101.58(9)
O(6A)-C(15A)-H(15A)	111.0(9)
C(16A)-C(15A)-H(15A)	115.1(9)
C(14A)-C(15A)-H(15A)	110.4(9)
C(12A)-C(16A)-C(15A)	104.43(10)
C(12A)-C(16A)-H(16A)	110.8(11)
C(15A)-C(16A)-H(16A)	108.7(11)
C(12A)-C(16A)-H(16B)	110.1(10)
C(15A)-C(16A)-H(16B)	113.1(10)
H(16A)-C(16A)-H(16B)	109.6(14)
O(5A)-C(17A)-H(17A)	112.3(12)
O(5A)-C(17A)-H(17B)	106.5(12)
H(17A)-C(17A)-H(17B)	109.6(16)
O(5A)-C(17A)-H(17C)	109.7(15)
H(17A)-C(17A)-H(17C)	110.7(18)
H(17B)-C(17A)-H(17C)	108.0(18)
C(19A)-C(18A)-O(7A)	110.52(9)
C(19A)-C(18A)-C(14A)	135.62(10)
O(7A)-C(18A)-C(14A)	113.85(9)
C(18A)-C(19A)-C(20A)	107.01(10)
C(18A)-C(19A)-H(19A)	126.8(10)
C(20A)-C(19A)-H(19A)	126.2(10)
C(21A)-C(20A)-C(19A)	105.30(9)
C(21A)-C(20A)-C(22A)	128.17(10)
C(19A)-C(20A)-C(22A)	126.52(10)
C(20A)-C(21A)-O(7A)	110.82(9)
C(20A)-C(21A)-C(23A)	131.59(10)

O(7A)-C(21A)-C(23A)	117.52(9)	C(11B)-C(10B)-C(13B)	108.95(10)
C(20A)-C(22A)-H(22A)	109.5(13)	O(3B)-C(11B)-O(4B)	120.34(11)
C(20A)-C(22A)-H(22B)	109.0(13)	O(3B)-C(11B)-C(10B)	130.84(13)
H(22A)-C(22A)-H(22B)	113.7(18)	O(4B)-C(11B)-C(10B)	108.76(11)
C(20A)-C(22A)-H(22C)	113.4(14)	O(4B)-C(12B)-C(16B)	109.34(10)
H(22A)-C(22A)-H(22C)	107.2(18)	O(4B)-C(12B)-C(13B)	106.11(10)
H(22B)-C(22A)-H(22C)	104.0(18)	C(16B)-C(12B)-C(13B)	107.02(9)
O(8A)-C(23A)-O(9A)	124.47(11)	O(4B)-C(12B)-H(12B)	103.6(10)
O(8A)-C(23A)-C(21A)	123.07(11)	C(16B)-C(12B)-H(12B)	115.6(10)
O(9A)-C(23A)-C(21A)	112.46(9)	C(13B)-C(12B)-H(12B)	114.6(10)
O(9A)-C(24A)-H(24A)	109.4(11)	C(10B)-C(13B)-C(12B)	103.30(9)
O(9A)-C(24A)-H(24B)	104.7(11)	C(10B)-C(13B)-C(14B)	117.00(9)
H(24A)-C(24A)-H(24B)	114.6(15)	C(12B)-C(13B)-C(14B)	103.80(10)
O(9A)-C(24A)-H(24C)	110.5(10)	C(10B)-C(13B)-H(13B)	112.2(10)
H(24A)-C(24A)-H(24C)	110.9(15)	C(12B)-C(13B)-H(13B)	111.4(10)
H(24B)-C(24A)-H(24C)	106.6(14)	C(14B)-C(13B)-H(13B)	108.7(10)
C(7B)-O(2B)-C(8B)	115.66(9)	O(5B)-C(14B)-C(18B)	109.68(8)
C(11B)-O(4B)-C(12B)	112.32(9)	O(5B)-C(14B)-C(15B)	109.46(10)
C(17B)-O(5B)-C(14B)	115.45(10)	C(18B)-C(14B)-C(15B)	115.52(9)
C(15B)-O(6B)-H(6B)	106.6(16)	O(5B)-C(14B)-C(13B)	102.99(9)
C(18B)-O(7B)-C(21B)	106.33(8)	C(18B)-C(14B)-C(13B)	115.51(10)
C(23B)-O(9B)-C(24B)	115.07(8)	C(15B)-C(14B)-C(13B)	102.78(9)
C(6B)-C(1B)-C(2B)	121.43(10)	O(6B)-C(15B)-C(16B)	111.39(10)
C(6B)-C(1B)-Br(2)	120.97(8)	O(6B)-C(15B)-C(14B)	106.82(10)
C(2B)-C(1B)-Br(2)	117.56(8)	C(16B)-C(15B)-C(14B)	101.42(9)
C(3B)-C(2B)-C(1B)	119.09(10)	O(6B)-C(15B)-H(15B)	111.5(9)
C(3B)-C(2B)-H(2B)	118.7(10)	C(16B)-C(15B)-H(15B)	114.3(9)
C(1B)-C(2B)-H(2B)	122.2(10)	C(14B)-C(15B)-H(15B)	110.7(9)
C(2B)-C(3B)-C(4B)	120.33(10)	C(12B)-C(16B)-C(15B)	104.35(10)
C(2B)-C(3B)-H(3B)	118.2(11)	C(12B)-C(16B)-H(16C)	112.9(11)
C(4B)-C(3B)-H(3B)	121.5(11)	C(15B)-C(16B)-H(16C)	111.9(11)
C(3B)-C(4B)-C(5B)	119.95(10)	C(12B)-C(16B)-H(16D)	111.3(12)
C(3B)-C(4B)-C(7B)	121.41(10)	C(15B)-C(16B)-H(16D)	108.7(12)
C(5B)-C(4B)-C(7B)	118.61(9)	H(16C)-C(16B)-H(16D)	107.6(15)
C(6B)-C(5B)-C(4B)	120.25(10)	O(5B)-C(17B)-H(17D)	111.8(10)
C(6B)-C(5B)-H(5B)	119.5(11)	O(5B)-C(17B)-H(17E)	105.7(11)
C(4B)-C(5B)-H(5B)	120.2(11)	H(17D)-C(17B)-H(17E)	107.5(14)
C(1B)-C(6B)-C(5B)	118.94(10)	O(5B)-C(17B)-H(17F)	111.6(11)
C(1B)-C(6B)-H(6B1)	119.9(9)	H(17D)-C(17B)-H(17F)	109.7(15)
C(5B)-C(6B)-H(6B1)	121.2(9)	H(17E)-C(17B)-H(17F)	110.4(15)
O(1B)-C(7B)-O(2B)	122.88(10)	C(19B)-C(18B)-O(7B)	110.36(9)
O(1B)-C(7B)-C(4B)	125.44(11)	C(19B)-C(18B)-C(14B)	134.82(10)
O(2B)-C(7B)-C(4B)	111.68(9)	O(7B)-C(18B)-C(14B)	114.81(9)
C(10B)-C(8B)-O(2B)	118.62(11)	C(18B)-C(19B)-C(20B)	107.13(9)
C(10B)-C(8B)-C(9B)	129.16(11)	C(18B)-C(19B)-H(19B)	129.1(10)
O(2B)-C(8B)-C(9B)	112.17(11)	C(20B)-C(19B)-H(19B)	123.7(10)
C(8B)-C(9B)-H(9B1)	108.9(13)	C(21B)-C(20B)-C(19B)	105.29(9)
C(8B)-C(9B)-H(9B2)	108.8(11)	C(21B)-C(20B)-C(22B)	128.21(10)
H(9B1)-C(9B)-H(9B2)	111.2(17)	C(19B)-C(20B)-C(22B)	126.48(10)
C(8B)-C(9B)-H(9B3)	110.2(13)	C(20B)-C(21B)-O(7B)	110.88(9)
H(9B1)-C(9B)-H(9B3)	109.1(17)	C(20B)-C(21B)-C(23B)	130.75(9)
H(9B2)-C(9B)-H(9B3)	108.6(16)	O(7B)-C(21B)-C(23B)	118.37(9)
C(8B)-C(10B)-C(11B)	122.54(12)	C(20B)-C(22B)-H(22D)	112.6(13)
C(8B)-C(10B)-C(13B)	128.24(10)	C(20B)-C(22B)-H(22E)	111.6(13)

H(22D)-C(22B)-H(22E)	110.7(18)
C(20B)-C(22B)-H(22F)	107.9(13)
H(22D)-C(22B)-H(22F)	108.0(18)
H(22E)-C(22B)-H(22F)	105.6(18)
O(8B)-C(23B)-O(9B)	124.50(10)
O(8B)-C(23B)-C(21B)	123.17(10)
O(9B)-C(23B)-C(21B)	112.32(9)
O(9B)-C(24B)-H(24D)	111.4(10)
O(9B)-C(24B)-H(24E)	107.6(11)
H(24D)-C(24B)-H(24E)	107.5(14)
O(9B)-C(24B)-H(24F)	109.6(11)
H(24D)-C(24B)-H(24F)	109.1(15)
H(24E)-C(24B)-H(24F)	111.6(15)

Table 4. Anisotropic displacement parameters ($Å^2 x 10^4$) for alcohol 182 (CCDC 606989). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	146(1)	261(1)	176(1)	80(1)	24(1)	90(1)
O(1A)	132(4)	651(8)	255(5)	227(5)	30(3)	27(4)
O(2A)	141(3)	272(5)	191(4)	141(3)	1(3)	29(3)
O(3A)	266(5)	363(6)	294(6)	129(5)	-109(4)	-32(4)
O(4A)	120(3)	405(6)	231(4)	158(4)	-4(3)	56(3)
O(5A)	164(3)	229(4)	146(4)	15(3)	41(3)	60(3)
O(6A)	186(3)	296(5)	108(4)	66(3)	31(3)	101(3)
O(7A)	113(3)	235(4)	120(3)	52(3)	32(3)	71(3)
O(8A)	138(3)	413(6)	195(4)	45(4)	41(3)	119(4)
O(9A)	129(3)	280(4)	136(4)	62(3)	27(3)	68(3)
C(1A)	139(4)	167(5)	153(5)	58(4)	20(3)	59(4)
C(2A)	169(4)	287(6)	186(5)	88(5)	69(4)	112(4)
C(3A)	170(4)	245(6)	148(5)	81(4)	47(4)	82(4)
C(4A)	140(4)	165(5)	161(5)	75(4)	32(3)	32(4)
C(5A)	129(4)	256(6)	171(5)	88(4)	50(4)	40(4)
C(6A)	152(4)	226(6)	152(5)	73(4)	36(4)	42(4)
C(7A)	151(4)	212(5)	186(5)	97(4)	26(4)	31(4)
C(8A)	157(4)	274(6)	187(5)	120(5)	-6(4)	-10(4)
C(9A)	345(7)	232(7)	320(8)	102(6)	-71(6)	0(6)
C(10A)	132(4)	275(6)	146(5)	108(4)	7(3)	21(4)
C(11A)	154(4)	342(7)	211(6)	158(5)	-20(4)	11(4)
C(12A)	135(4)	384(7)	144(5)	92(5)	46(4)	110(4)
C(13A)	115(4)	285(6)	117(4)	83(4)	30(3)	65(4)
C(14A)	124(4)	208(5)	123(4)	46(4)	37(3)	64(4)
C(15A)	169(4)	226(5)	144(5)	77(4)	52(4)	87(4)
C(16A)	190(5)	311(7)	157(5)	77(5)	47(4)	143(4)
C(17A)	214(5)	221(6)	275(7)	41(5)	46(5)	56(5)
C(18A)	112(4)	194(5)	124(4)	61(4)	31(3)	50(3)
C(19A)	132(4)	214(5)	130(5)	53(4)	38(3)	54(4)
C(20A)	132(4)	188(5)	163(5)	67(4)	59(3)	57(4)
C(21A)	113(4)	210(5)	161(5)	74(4)	49(3)	61(3)
C(22A)	174(5)	281(6)	196(6)	42(5)	74(4)	101(4)
C(23A)	131(4)	214(5)	163(5)	66(4)	37(4)	49(4)
C(24A)	139(4)	276(6)	168(5)	68(4)	18(4)	43(4)
Br(2)	116(1)	277(1)	151(1)	84(1)	26(1)	65(1)
O(1B)	129(3)	509(6)	203(4)	165(4)	39(3)	30(4)
O(2B)	126(3)	287(5)	155(4)	117(3)	11(3)	22(3)
O(3B)	251(4)	294(5)	232(5)	88(4)	-79(4)	-27(4)
O(4B)	104(3)	370(5)	184(4)	100(4)	-9(3)	25(3)
O(5B)	137(3)	262(4)	155(4)	1(3)	29(3)	61(3)
O(6B)	161(3)	297(5)	114(4)	66(3)	14(3)	82(3)
O(7B)	97(3)	248(4)	115(3)	45(3)	21(2)	59(3)
O(8B)	131(3)	308(5)	183(4)	55(3)	41(3)	89(3)
O(9B)	120(3)	273(4)	128(4)	50(3)	18(3)	60(3)

C(1B)	116(4)	195(5)	132(4)	60(4)	22(3)	39(3)
C(2B)	138(4)	241(6)	150(5)	71(4)	58(4)	58(4)
C(3B)	149(4)	226(6)	130(5)	71(4)	42(3)	49(4)
C(4B)	120(4)	170(5)	140(4)	62(4)	30(3)	30(3)
C(5B)	128(4)	237(6)	164(5)	81(4)	48(4)	39(4)
C(6B)	139(4)	250(6)	130(5)	79(4)	42(3)	46(4)
C(7B)	137(4)	217(5)	141(5)	78(4)	31(3)	37(4)
C(8B)	143(4)	259(6)	144(5)	88(4)	11(4)	2(4)
C(9B)	261(6)	229(6)	276(7)	70(5)	-1(5)	26(5)
C(10B)	121(4)	283(6)	110(4)	75(4)	8(3)	2(4)
C(11B)	146(4)	313(7)	150(5)	110(5)	-6(4)	-2(4)
C(12B)	107(4)	382(7)	132(5)	51(5)	20(3)	67(4)
C(13B)	100(4)	294(6)	110(4)	62(4)	14(3)	50(4)
C(14B)	107(4)	233(5)	109(4)	31(4)	15(3)	56(4)
C(15B)	134(4)	240(6)	153(5)	64(4)	19(3)	69(4)
C(16B)	136(4)	309(7)	189(5)	51(5)	19(4)	103(4)
C(17B)	158(5)	254(6)	273(7)	15(5)	36(4)	52(4)
C(18B)	99(4)	213(5)	109(4)	50(4)	18(3)	42(3)
C(19B)	127(4)	204(5)	117(4)	61(4)	33(3)	50(3)
C(20B)	127(4)	174(5)	141(4)	66(4)	53(3)	51(3)
C(21B)	105(4)	209(5)	135(4)	65(4)	41(3)	51(3)
C(22B)	167(4)	261(6)	174(5)	54(4)	78(4)	90(4)
C(23B)	118(4)	194(5)	148(5)	70(4)	37(3)	44(3)
C(24B)	137(4)	256(6)	154(5)	51(4)	7(4)	40(4)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for alcohol 182 (CCDC 606989).

	x	y	z	U_{iso}
H(6A)	4022(19)	3125(16)	5005(13)	34(5)
H(2A)	9944(17)	1133(14)	8691(12)	29(5)
H(3A)	7926(17)	956(14)	7756(12)	29(5)
H(5A)	6455(17)	1346(14)	9721(11)	25(4)
H(6A1)	8415(15)	1494(12)	10728(10)	16(4)
H(9A1)	3480(20)	-272(16)	5676(14)	44(6)
H(9A2)	4130(20)	-548(16)	6491(14)	43(6)
H(9A3)	4890(20)	-310(17)	5886(14)	45(6)
H(12A)	2831(18)	3565(15)	7202(12)	33(5)
H(13A)	4643(15)	3019(12)	7703(10)	16(4)
H(15A)	5328(15)	4527(12)	6094(10)	15(4)
H(16A)	3834(16)	4872(13)	6823(11)	22(4)
H(16B)	2907(16)	4157(13)	5905(11)	20(4)
H(17A)	7453(19)	5236(15)	7498(13)	36(5)
H(17B)	7248(19)	5884(16)	8368(14)	39(5)
H(17C)	6440(20)	5868(18)	7502(15)	53(7)
H(19A)	6485(16)	2343(13)	5581(11)	20(4)
H(22A)	9760(20)	1990(16)	6439(13)	39(5)
H(22B)	8910(20)	1969(17)	5596(14)	42(6)
H(22C)	8670(20)	1125(18)	5922(14)	50(6)
H(24A)	10882(17)	3196(15)	9758(12)	29(5)
H(24B)	10482(17)	4239(14)	10234(12)	28(5)
H(24C)	11386(16)	4291(13)	9709(10)	19(4)
H(6B)	10850(20)	2237(17)	4856(14)	45(6)
H(2B)	4532(16)	3722(13)	977(11)	20(4)
H(3B)	6458(17)	3951(14)	1970(12)	27(4)
H(5B)	8127(17)	3839(14)	87(11)	26(4)
H(6B1)	6152(15)	3634(12)	-935(10)	15(4)
H(9B1)	9470(20)	5439(16)	4110(14)	43(6)
H(9B2)	9907(19)	5870(16)	3429(13)	38(5)
H(9B3)	10870(20)	5685(16)	4206(13)	42(6)
H(12B)	12161(15)	2122(12)	2706(10)	17(4)
H(13B)	10187(16)	2419(13)	2165(11)	21(4)
H(15B)	9775(15)	799(13)	3743(10)	18(4)
H(16C)	12138(17)	1399(14)	3962(12)	27(4)
H(16D)	11321(18)	673(15)	3039(12)	33(5)
H(17D)	8936(16)	-580(13)	2410(11)	19(4)
H(17E)	8073(17)	-680(14)	1479(12)	29(5)
H(17F)	7731(18)	-109(14)	2320(12)	30(5)
H(19B)	8272(17)	2803(14)	4277(12)	28(5)
H(22D)	4980(20)	3105(15)	3392(13)	37(5)
H(22E)	6070(20)	3520(17)	4226(14)	45(6)
H(22F)	5250(20)	2420(18)	3935(14)	50(6)
H(24D)	3248(16)	632(13)	160(11)	20(4)
H(24E)	4109(18)	552(15)	-413(12)	31(5)
H(24F)	3812(18)	1649(15)	20(12)	32(5)

Table 6. Hydrogen bonds for alcohol 182 (CCDC 606989) [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(6A)-H(6A)...O(4B)#1	0.76(2)	2.26(2)	3.0125(12)	169(2)
O(6B)-H(6B)...O(4A)#2	0.79(2)	2.16(2)	2.9238(12)	163(2)

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

CALIFORNIA INSTITUTE OF TECHNOLOGY

BECKMAN INSTITUTE

X-RAY CRYSTALLOGRAPHY LABORATORY

Crystal Structure Analysis of:

Furan 169

(CCDC 602164)

Contents

Figure A2.3.2 Representation of Furan **169**.

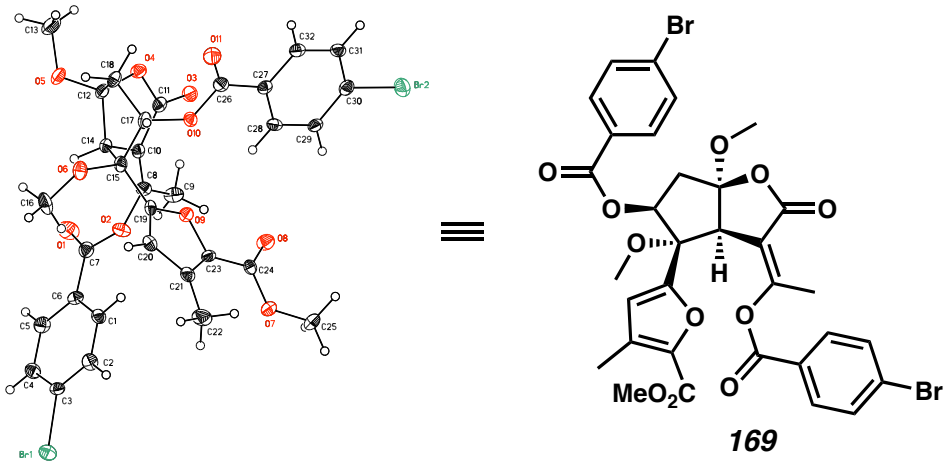


Table 1. Crystal data and structure refinement for furan 169 (CCDC 602164).

Empirical formula	$C_{32}H_{28}O_{11}Br_2$
Formula weight	748.36
Crystallization Solvent	Ethylacetate/n-heptane
Crystal Habit	Blade
Crystal size	0.31 x 0.24 x 0.11 mm^3
Crystal color	Colorless

Data Collection

Type of diffractometer	Bruker SMART 1000
Wavelength	0.71073 Å MoKα
Data Collection Temperature	100(2) K
θ range for 10496 reflections used in lattice determination	2.30 to 28.23°
Unit cell dimensions	a = 17.2333(11) Å b = 10.2395(7) Å β= 104.5150(10)° c = 18.3237(12) Å
Volume	3130.2(4) $Å^3$
Z	4
Crystal system	Monoclinic
Space group	$P2_1/c$
Density (calculated)	1.588 Mg/m^3
F(000)	1512
Data collection program	Bruker SMART v5.630
θ range for data collection	1.22 to 28.58°
Completeness to θ = 28.58°	93.7 %
Index ranges	$-22 \le h \le 22$, $-13 \le k \le 13$, $-23 \le l \le 23$
Data collection scan type	ω scans at 5 ϕ settings
Data reduction program	Bruker SAINT v6.45A
Reflections collected	49507
Independent reflections	49509 [R_{int}= 0.0820]
Absorption coefficient	2.651 mm^{-1}
Absorption correction	TWINABS
Max. and min. transmission	1.0000 and 0.6884

Table 1 (cont.)

Structure solution and Refinement

Structure solution program	Bruker XS v6.12
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Geometric positions
Structure refinement program	Bruker XL v6.12
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	49509 / 0 / 412
Treatment of hydrogen atoms	Riding
Goodness-of-fit on F^2	1.273
Final R indices [I>2σ(I), 35818 reflections]	R1 = 0.0465, *w*R2 = 0.0991
R indices (all data)	R1 = 0.0708, *w*R2 = 0.1032
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.002
Average shift/error	0.000
Largest diff. peak and hole	1.202 and -0.725 e.Å^{-3}

Special Refinement Details

The crystal is twinned. CELL_NOW was used to define the two domains and produce a matrix for the twin law as follows;

751 reflections within 0.100 of an integer index assigned to domain 1,
751 of them exclusively; 248 reflections not yet assigned to a domain

Rotated from first domain by 179.7 degrees about
reciprocal axis 1.000 0.002 0.000 and real axis 1.000 -0.003 0.237

474 reflections within 0.100 of an integer index assigned to domain 2,
233 of them exclusively; 14 reflections not yet assigned to a domain

Twin Law:
Transforms h1 -> h2
1.00010 -0.00089 0.47107
0.00022 -0.99985 0.00031
-0.00044 -0.00057 -1.00002

The data was integrated with SAINT then TWINABS was used to write the file used for refinement. From TWINABS;

13830 data (3969 unique) involve component 1 only, mean I/sigma 7.8
13557 data (3916 unique) involve component 2 only, mean I/sigma 5.4
23827 data (6687 unique) involve 2 components, mean I/sigma 7.3
36 data (36 unique) involve 3 components, mean I/sigma 4.0

Refinement using an HKLF 5 type file produced a final set of atomic parameters and a scale factor between the two domains, BASF=0.33261

Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of F^2 >

$2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for furan 169 (CCDC 602164). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
Br(1)	1046(1)	2805(1)	-1563(1)	22(1)
Br(2)	6652(1)	13142(1)	1456(1)	27(1)
O(1)	1187(1)	9543(1)	-1711(1)	35(1)
O(2)	2058(1)	9038(1)	-609(1)	20(1)
O(3)	3071(1)	12918(1)	41(1)	21(1)
O(4)	2149(1)	12868(1)	709(1)	19(1)
O(5)	786(1)	12476(1)	499(1)	23(1)
O(6)	1221(1)	9189(1)	1375(1)	22(1)
O(7)	4613(1)	6506(1)	716(1)	22(1)
O(8)	4502(1)	8654(1)	420(1)	23(1)
O(9)	3103(1)	8783(1)	845(1)	16(1)
O(10)	3048(1)	10949(1)	1772(1)	17(1)
O(11)	3322(1)	12169(1)	2836(1)	25(1)
C(1)	1757(1)	6474(2)	-736(1)	18(1)
C(2)	1655(1)	5142(2)	-808(1)	21(1)
C(3)	1145(1)	4653(2)	-1455(1)	16(1)
C(4)	728(1)	5454(2)	-2020(1)	20(1)
C(5)	839(1)	6796(2)	-1941(1)	21(1)
C(6)	1362(1)	7304(2)	-1303(1)	17(1)
C(7)	1500(1)	8738(2)	-1257(1)	20(1)
C(8)	2396(1)	10292(2)	-517(1)	17(1)
C(9)	2936(1)	10604(2)	-1014(1)	25(1)
C(10)	2250(1)	10981(2)	45(1)	14(1)
C(11)	2562(1)	12316(2)	235(1)	17(1)
C(12)	1542(1)	11995(2)	853(1)	18(1)
C(13)	607(1)	13733(2)	765(1)	32(1)
C(14)	1668(1)	10657(2)	502(1)	14(1)
C(15)	1918(1)	9702(2)	1191(1)	17(1)
C(16)	684(1)	8458(2)	792(1)	30(1)
C(17)	2263(1)	10637(2)	1858(1)	17(1)
C(18)	1709(1)	11803(2)	1706(1)	19(1)
C(19)	2474(1)	8589(2)	1155(1)	15(1)
C(20)	2489(1)	7352(2)	1426(1)	19(1)
C(21)	3171(1)	6719(2)	1281(1)	18(1)
C(22)	3450(1)	5356(2)	1519(1)	28(1)
C(23)	3523(1)	7618(2)	921(1)	15(1)
C(24)	4257(1)	7678(2)	656(1)	17(1)
C(25)	5373(1)	6476(2)	504(1)	26(1)
C(26)	3520(1)	11758(2)	2291(1)	19(1)
C(27)	4283(1)	12027(2)	2093(1)	16(1)
C(28)	4504(1)	11392(2)	1500(1)	17(1)
C(29)	5210(1)	11697(2)	1320(1)	17(1)
C(30)	5693(1)	12672(2)	1724(1)	19(1)
C(31)	5490(1)	13312(2)	2315(1)	19(1)
C(32)	4787(1)	12986(2)	2499(1)	18(1)

Table 3. Bond lengths [Å] and angles [°] for furan 169 (CCDC 602164).

Br(1)-C(3)	1.9056(18)	C(11)-O(4)-C(12)	111.90(14)
Br(2)-C(30)	1.900(2)	C(12)-O(5)-C(13)	114.44(15)
O(1)-C(7)	1.198(2)	C(15)-O(6)-C(16)	116.16(14)
O(2)-C(7)	1.363(2)	C(24)-O(7)-C(25)	114.82(15)
O(2)-C(8)	1.402(2)	C(19)-O(9)-C(23)	106.47(14)
O(3)-C(11)	1.196(2)	C(26)-O(10)-C(17)	118.12(15)
O(4)-C(11)	1.376(2)	C(2)-C(1)-C(6)	120.62(18)
O(4)-C(12)	1.450(2)	C(1)-C(2)-C(3)	118.70(18)
O(5)-C(12)	1.392(2)	C(4)-C(3)-C(2)	122.03(18)
O(5)-C(13)	1.438(2)	C(4)-C(3)-Br(1)	119.91(15)
O(6)-C(15)	1.425(2)	C(2)-C(3)-Br(1)	118.05(14)
O(6)-C(16)	1.437(2)	C(3)-C(4)-C(5)	118.68(18)
O(7)-C(24)	1.340(2)	C(6)-C(5)-C(4)	120.12(18)
O(7)-C(25)	1.458(2)	C(1)-C(6)-C(5)	119.81(18)
O(8)-C(24)	1.206(2)	C(1)-C(6)-C(7)	121.52(18)
O(9)-C(19)	1.357(2)	C(5)-C(6)-C(7)	118.65(17)
O(9)-C(23)	1.385(2)	O(1)-C(7)-O(2)	123.04(19)
O(10)-C(26)	1.366(2)	O(1)-C(7)-C(6)	127.05(19)
O(10)-C(17)	1.436(2)	O(2)-C(7)-C(6)	109.91(17)
O(11)-C(26)	1.209(2)	C(10)-C(8)-O(2)	115.29(18)
C(1)-C(2)	1.377(2)	C(10)-C(8)-C(9)	129.09(19)
C(1)-C(6)	1.383(2)	O(2)-C(8)-C(9)	115.29(16)
C(2)-C(3)	1.381(2)	C(8)-C(10)-C(11)	123.14(18)
C(3)-C(4)	1.374(2)	C(8)-C(10)-C(14)	127.04(18)
C(4)-C(5)	1.390(2)	C(11)-C(10)-C(14)	109.23(16)
C(5)-C(6)	1.386(2)	O(3)-C(11)-O(4)	120.67(18)
C(6)-C(7)	1.486(3)	O(3)-C(11)-C(10)	131.11(19)
C(8)-C(10)	1.324(2)	O(4)-C(11)-C(10)	108.22(17)
C(8)-C(9)	1.489(2)	O(5)-C(12)-O(4)	109.29(15)
C(10)-C(11)	1.478(2)	O(5)-C(12)-C(18)	115.84(17)
C(10)-C(14)	1.495(2)	O(4)-C(12)-C(18)	107.84(16)
C(12)-C(18)	1.529(2)	O(5)-C(12)-C(14)	109.33(16)
C(12)-C(14)	1.552(2)	O(4)-C(12)-C(14)	106.62(15)
C(14)-C(15)	1.570(2)	C(18)-C(12)-C(14)	107.52(15)
C(15)-C(19)	1.502(3)	C(10)-C(14)-C(12)	102.71(15)
C(15)-C(17)	1.548(2)	C(10)-C(14)-C(15)	120.16(16)
C(17)-C(18)	1.511(2)	C(12)-C(14)-C(15)	104.72(14)
C(19)-C(20)	1.359(2)	O(6)-C(15)-C(19)	108.41(15)
C(20)-C(21)	1.423(3)	O(6)-C(15)-C(17)	102.80(15)
C(21)-C(23)	1.361(2)	C(19)-C(15)-C(17)	112.34(16)
C(21)-C(22)	1.504(2)	O(6)-C(15)-C(14)	110.07(16)
C(23)-C(24)	1.467(3)	C(19)-C(15)-C(14)	119.06(16)
C(26)-C(27)	1.475(3)	C(17)-C(15)-C(14)	102.90(15)
C(27)-C(32)	1.397(3)	O(10)-C(17)-C(18)	111.90(16)
C(27)-C(28)	1.398(2)	O(10)-C(17)-C(15)	103.75(15)
C(28)-C(29)	1.374(3)	C(18)-C(17)-C(15)	104.04(15)
C(29)-C(30)	1.388(2)	C(17)-C(18)-C(12)	103.76(15)
C(30)-C(31)	1.384(2)	O(9)-C(19)-C(20)	110.22(17)
C(31)-C(32)	1.377(3)	O(9)-C(19)-C(15)	119.53(17)
		C(20)-C(19)-C(15)	130.16(19)
C(7)-O(2)-C(8)	119.53(15)	C(19)-C(20)-C(21)	107.29(18)

C(23)-C(21)-C(20)	105.73(17)
C(23)-C(21)-C(22)	128.2(2)
C(20)-C(21)-C(22)	125.96(18)
C(21)-C(23)-O(9)	110.29(17)
C(21)-C(23)-C(24)	135.72(19)
O(9)-C(23)-C(24)	113.77(16)
O(8)-C(24)-O(7)	125.31(19)
O(8)-C(24)-C(23)	124.23(19)
O(7)-C(24)-C(23)	110.46(17)
O(11)-C(26)-O(10)	123.0(2)
O(11)-C(26)-C(27)	126.35(19)
O(10)-C(26)-C(27)	110.68(17)
C(32)-C(27)-C(28)	119.08(19)
C(32)-C(27)-C(26)	118.29(17)
C(28)-C(27)-C(26)	122.59(19)
C(29)-C(28)-C(27)	120.74(19)
C(28)-C(29)-C(30)	118.97(18)
C(31)-C(30)-C(29)	121.5(2)
C(31)-C(30)-Br(2)	119.30(16)
C(29)-C(30)-Br(2)	119.23(15)
C(32)-C(31)-C(30)	119.16(19)
C(31)-C(32)-C(27)	120.55(18)

Table 4. Anisotropic displacement parameters ($Å^2 x 10^4$) for furan 169 (CCDC 602164). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	259(1)	175(1)	232(1)	-2(1)	60(1)	-29(1)
Br(2)	217(1)	295(1)	321(1)	-33(1)	84(1)	-52(1)
O(1)	409(12)	190(8)	336(9)	75(7)	-96(8)	28(8)
O(2)	278(10)	146(8)	156(8)	-5(6)	22(7)	-13(7)
O(3)	187(9)	183(8)	266(8)	10(7)	98(7)	-23(7)
O(4)	202(9)	162(8)	232(8)	-2(6)	101(7)	6(7)
O(5)	163(9)	238(9)	276(8)	6(6)	50(7)	74(7)
O(6)	161(9)	270(9)	240(8)	29(6)	98(7)	-26(7)
O(7)	190(9)	174(8)	288(8)	-13(6)	64(7)	32(7)
O(8)	256(10)	190(8)	273(8)	27(7)	119(7)	14(7)
O(9)	163(9)	151(7)	180(7)	25(6)	57(7)	5(6)
O(10)	149(9)	199(8)	161(7)	-36(6)	39(7)	-12(7)
O(11)	250(9)	324(9)	186(8)	-78(7)	87(7)	4(8)
C(1)	176(13)	181(12)	158(11)	-17(9)	2(10)	-4(10)
C(2)	213(14)	201(12)	191(12)	42(9)	30(11)	-11(10)
C(3)	184(13)	135(11)	176(11)	-18(9)	72(10)	6(10)
C(4)	208(13)	229(12)	150(11)	-37(9)	22(10)	-9(10)
C(5)	231(14)	200(12)	178(11)	35(9)	14(10)	33(10)
C(6)	201(13)	150(11)	168(11)	1(9)	72(9)	21(10)
C(7)	183(14)	225(12)	189(12)	-11(10)	50(10)	12(11)
C(8)	207(14)	113(11)	174(11)	51(9)	5(10)	19(10)
C(9)	322(15)	188(12)	250(12)	-10(10)	115(11)	16(11)
C(10)	132(12)	131(11)	153(11)	47(9)	15(10)	18(9)
C(11)	165(13)	184(12)	134(11)	34(9)	7(10)	42(10)
C(12)	144(13)	179(12)	208(11)	3(9)	56(10)	35(10)
C(13)	287(15)	274(13)	411(15)	14(11)	101(12)	117(12)
C(14)	125(12)	159(11)	144(11)	9(9)	21(9)	12(9)
C(15)	135(13)	194(12)	188(12)	26(9)	72(10)	-18(10)
C(16)	183(14)	335(14)	345(14)	41(11)	18(11)	-110(11)
C(17)	138(13)	236(12)	145(11)	18(9)	59(10)	11(10)
C(18)	153(13)	230(12)	198(11)	4(9)	87(10)	35(10)
C(19)	110(12)	199(12)	125(11)	2(9)	17(9)	-8(10)
C(20)	174(13)	191(12)	190(11)	-3(10)	44(10)	-45(10)
C(21)	182(14)	187(11)	147(11)	-20(9)	-24(10)	-6(10)
C(22)	338(16)	166(12)	330(14)	39(10)	67(12)	-22(11)
C(23)	172(13)	119(11)	142(11)	-10(9)	9(9)	36(9)
C(24)	147(13)	197(12)	136(11)	-28(9)	-20(9)	-4(10)
C(25)	201(14)	243(13)	332(13)	-28(10)	62(11)	77(11)
C(26)	203(14)	134(11)	193(11)	43(9)	-5(10)	24(10)
C(27)	180(13)	143(11)	128(10)	24(9)	14(9)	44(10)
C(28)	213(14)	120(11)	152(11)	-15(9)	11(10)	7(10)
C(29)	181(13)	163(11)	171(11)	-23(9)	48(10)	41(10)
C(30)	184(13)	177(11)	214(11)	34(10)	44(10)	39(10)
C(31)	208(14)	135(11)	199(12)	-13(9)	-12(10)	24(10)
C(32)	218(14)	159(12)	137(11)	-11(9)	-3(10)	48(10)

.

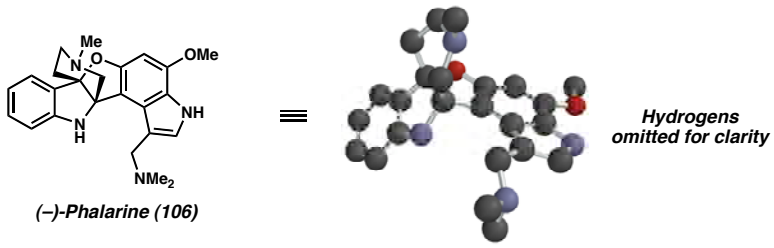
CHAPTER 3

Synthetic Efforts Toward (–)-Phalarine Using Palladium(II)-catalyzed Oxidative Heterocyclizations

3.1 Introduction and Biosynthesis

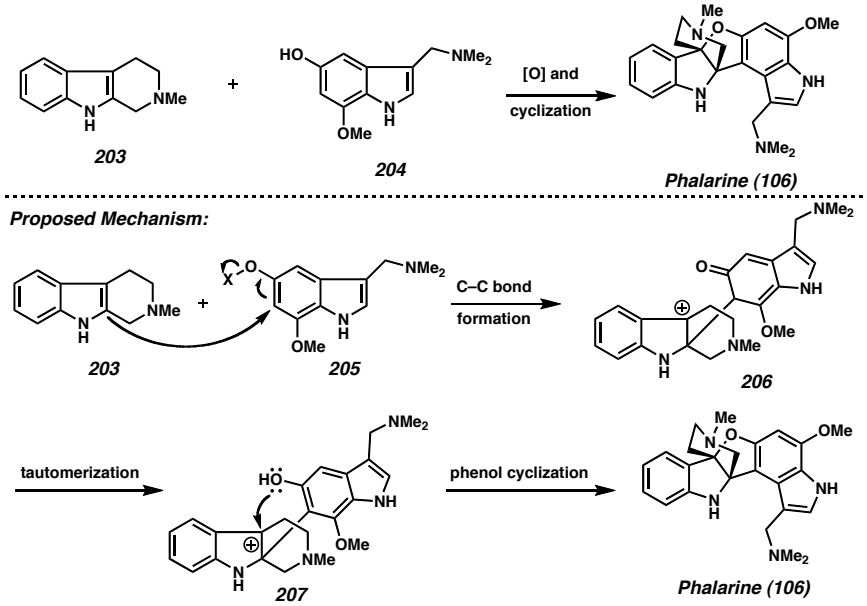
In 1999, (–)-phalarine (**106**) was isolated from *Phalaris coerulescens* and displayed a [4.3.3.0] fused tricyclic core structure including a novel furano*bis*indole ring system (Figure 3.1.1).[1,2] In addition, the natural product contains vicinal stereocenters that are contained within the propellar-like core. Although (–)-phalarine (**106**) is not reported to be biologically active, the properties of this molecule still warrants medicinal evaluation since many alkaloids isolated from the genus *Phalaris* have proven to be poisonous to livestock when the native plant was ingested (e.g., canary grass, *P. arundinacea*).

*Figure 3.1.1 (–)-Phalarine (**106**) in Two and Three Dimensions.*



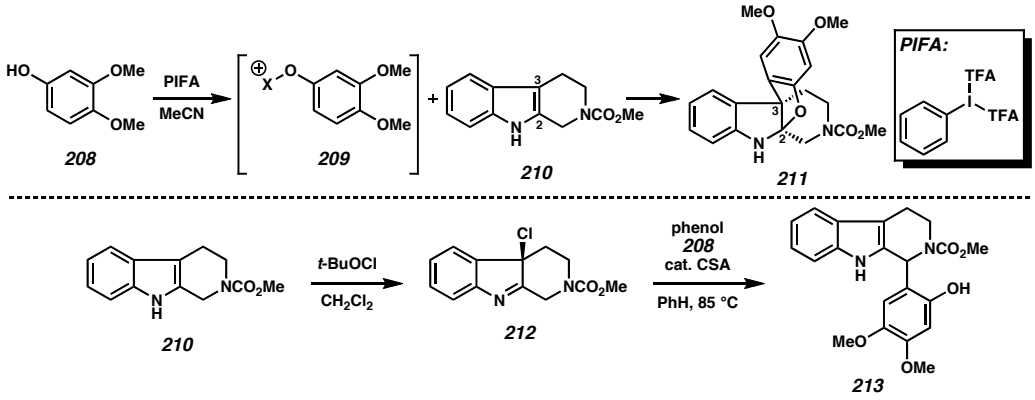
Although the biosynthesis of (–)-phalarine (**106**) has not been fully elucidated, it is proposed by the isolation chemists that (–)-phalarine (**106**) is obtained via an oxidative coupling of known tetrahydro-β-carboline **203** with a functionalized indole akin to phenol **204** (Scheme 3.1.1).[3] It is hypothesized that indole **204** is oxidized to an intermediate similar to arene **205**. This activated intermediate undergoes addition by tetrahydro-β-carboline **203** to provide cationic species **206**, which will undergo rapid tautomerization to provide enol **207**. Formation of the natural product (**106**) is accomplished by the addition of the phenol in intermediate **207** onto the benzylic cation.

Scheme 3.1.1



Initial synthetic efforts by the Danishefsky laboratory to access the skeletal framework of the natural product using a biosynthetic approach proved unsuccessful. Their first attempt began with oxidation of phenol **208** to generate intermediate **209** (Scheme 3.1.2). Treatment of this intermediate with tetrahydro-β-carboline **210** provided polycycle **211** exclusively; however, the reaction occurred with undesired regioselectivity in the formation of the bridging dihydobenzofuran functionality.[4] A second generation approach employed oxidation of tetrahydro-β-carboline **210** with *t*-butyl hypochlorite to yield α-chloroimine **212**. Unfortunately, exposing imine **212** to phenol **208** in the presence of a catalytic amount of camphorsulfonic acid (CSA) in refluxing benzene afforded indole **213** as the sole product.[5]

Scheme 3.1.2



In the end, Danishefsky's efforts to synthesize the core of (–)-phalarine using a biomimetic strategy failed due to the lack of regio-control in the oxidative coupling step. These results infer that the proposed biosynthesis of (–)-phalarine (**106**) are likely catalyzed in a chiral environment that effects the key oxidative coupling reaction to provide the correct regiochemistry. Despite these synthetic challenges, Danishefsky's laboratory persisted, and in 2007 accomplished a total synthesis of racemic phalarine.

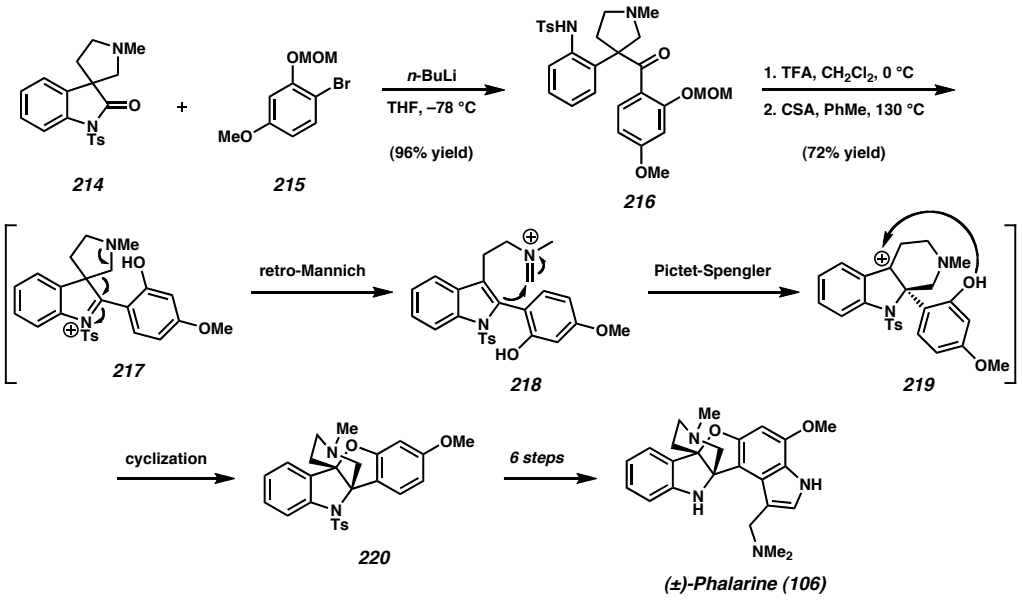
More recently, Danishefsky's laboratory completed an asymmetric synthesis of (–)-phalarine using a C(2)-functionalized tryptophan. The results of their work will be discussed in the next section.

3.2 Previous Efforts Toward the Total Synthesis of Phalarine

The only total syntheses of phalarine were reported by the Danishefsky laboratory in 2007 and 2010.[6] The synthesis of racemic phalarine was accomplished using a key retro-Mannich reaction followed by a Pictet-Spengler cyclization to provide the core of the natural product (Scheme 3.2.1).

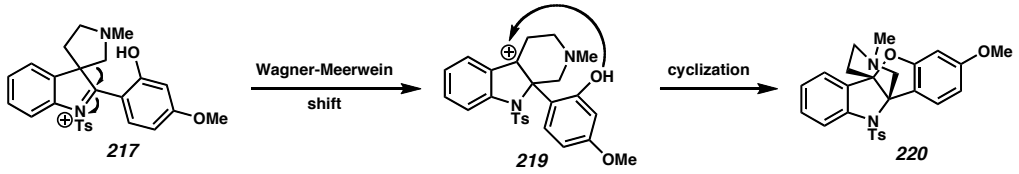
The key steps of the synthesis began with addition of lithiated arene **215** into oxindole **214** to provide ketone **216** in excellent yield. Exposing ketone **216** to two sequential organic acids first cleaved the MOM group, and then facilitated the condensation of the aniline onto the pendant ketone to provide iminium **217**. This activated species underwent a retro-Mannich reaction to generate intermediate **218**, which cyclized in a Pictet-Spengler fashion to form cationic intermediate **219**. Finally, cyclization of the phenol moiety furnished the core of phalarine (**220**) in 72% yield from ketone **216**.

Scheme 3.2.1



Although an alternate mechanism invoking a Wagner-Meerwein ring-expansion is plausible (Scheme 3.2.2), Danishefsky found that treatment of enantioenriched ketone **217** under the same conditions provided product **220** as a racemic mixture.[7] This result indicates the formation of an achiral intermediate, such as iminium **218**, prior to product formation.

Scheme 3.2.2



With a rapid synthesis of pentacycle **220** complete, Danishefsky sought to complete the molecule by synthesizing the indole unit and appending the gramine side chain (Scheme 3.2.3).[8] Although the synthesis of pentacycle **220** is rapid, the completion of phalarine required an additional six steps to synthesize the gramine moiety of the natural product.

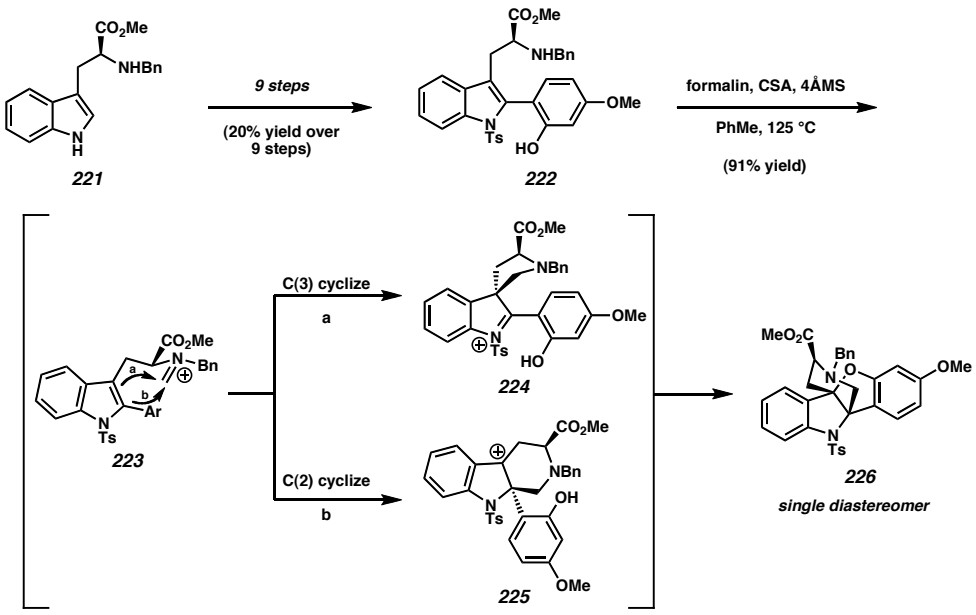
Scheme 3.2.3

220 ***(±)-Phalarine (106)***

Danishefsky's synthesis of racemic phalarine (**106**) required nine synthetic steps starting from oxindole **214**[9] and provided the core of the natural product via a retro-Mannich reaction/Pictet-Spengler addition cascade sequence. Unfortunately, this reaction sequence occurred through an achiral intermediate, thus initially negating an asymmetric synthesis.

However, Danishefsky recently published an asymmetric synthesis of (–)-phalarine utilizing a chiral variant of iminium **218** (cf. Scheme 3.2.1). In an ingenuous attempt, Danishefsky began with L-tryptophan methyl ester (**221**) to synthesize indole **222** in nine steps (Scheme 3.2.4). Exposing indole **222** to formalin under acidic conditions provided iminium **223**. This species underwent a Pictet-Spengler cyclization with either C(2) or C(3) of the indole moiety to provide intermediates **224** and **225**, respectively. Although it is unclear which mechanism is operative,[10] the desired pentacycle (**226**) is obtained as a single diastereomer in 91% yield beginning from indole **222**. At this stage, an additional ten synthetic operations provided the desired natural product.

Scheme 3.2.4

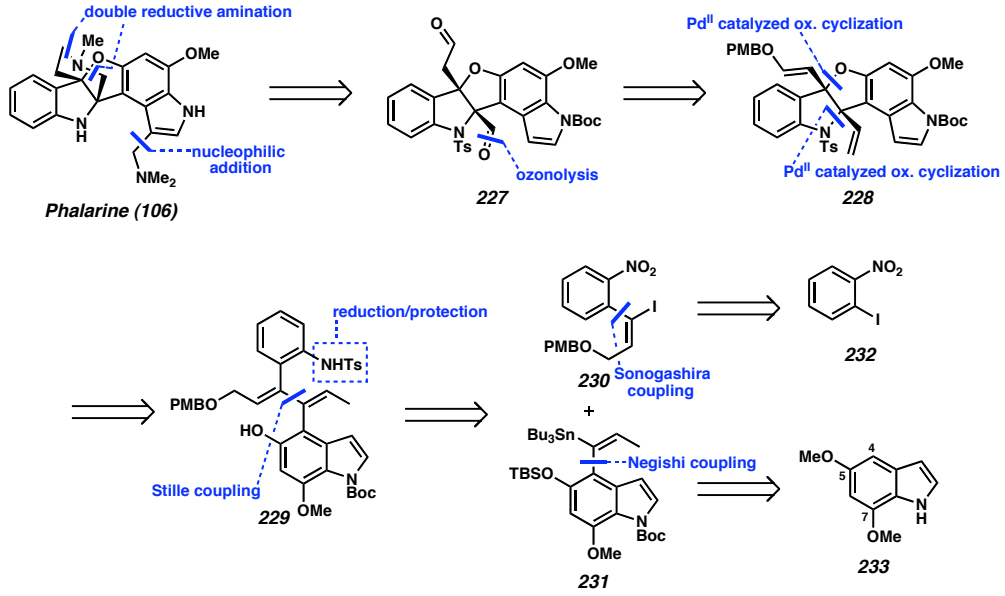


3.3 Retrosynthetic Analysis of Phalarine

Our retrosynthetic analysis of phalarine (**106**) began with late-stage formation of the bridging piperidine ring via a double reductive amination of bis-aldehyde **227** and methylamine (Scheme 3.3.1). We envisioned unveiling the two aldehyde units by an ozonolysis of a terminal olefin and hydrolysis of a PMB vinyl ether, which led us to intermediate **228**. We anticipated the formation of pentacycle **228** via a double palladium(II)-catalyzed oxidative heterocyclization beginning from diene **229**. At this stage, we planned to synthesize diene **229** from a Stille coupling between vinyl iodide **230** and vinyl stannane **231**. The synthesis of vinyl iodide **230** was seen to arise from known compound **232** by a Sonogashira coupling. However, we anticipated that the synthesis of vinyl stannane **231** would be difficult since fully differentiated 4,5,7-substituted indoles lack an efficient synthetic route that is compatible with many common

functional groups. Instead of addressing this problem prior to indole formation, we sought out indole **233** as a suitable starting point to effect differentiation between C(5) and C(7), and allow for selective C(4) functionalization.

Scheme 3.3.1

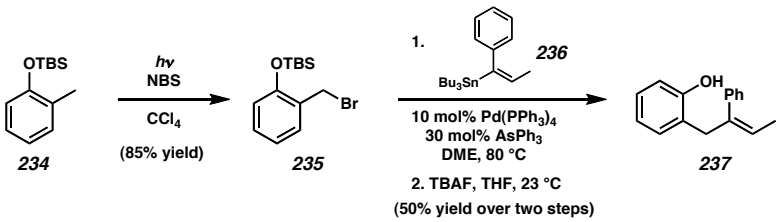


3.4 Model System Studies

There are very few examples of palladium(II)-catalyzed oxidative heterocyclizations onto styrenyl or conjugated olefins.[11] Thus, we decided to investigate the palladium(II)-catalyzed oxidative phenol cyclization using a model system.

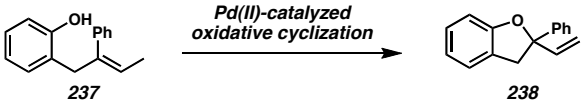
We envisioned phenol **237** (Scheme 3.4.1) as a suitable substrate to test the palladium(II)-catalyzed oxidative cyclization since it possessed a trisubstituted styrenyl olefin that is similar to diene **229** (cf. Scheme 3.3.1). The synthesis of phenol **237** began with a radical bromination of arene **234** to provide benzyl bromide **235** in excellent yield.[12] From here, Stille coupling using known vinyl stannane **236** provided the desired product, which then underwent silyl cleavage to arrive at phenol **237** in 50% yield.[13]

Scheme 3.4.1



With the model substrate in hand, phenol **237** was subjected to the DMSO/O_2 conditions as well as conditions for the palladium(II)-catalyzed oxidative cyclization previously developed in our group.[14,15] As shown in Table 3.4.1, using the DMSO/O_2 conditions without NaOAc allowed for an 80% yield of dihydrobenzofuran **238** in only 4 hours.[16] Under our optimized conditions (Entry 3), the formation of dihydrobenzofuran **238** was significantly slower than the DMSO/O_2 conditions. Nevertheless, all entries in Table 3.4.1 provided dihydrobenzofuran **238** as the only observable product, with the remaining mass recovered as unreacted starting material.

*Table 3.4.1 Attempts at the Pd(II)-catalyzed Oxidative Cyclization of Phenol **237**.*



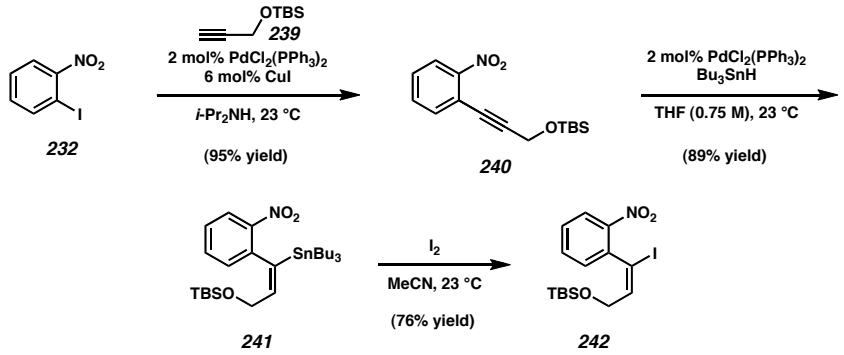
Entry	Conditions	Time (h)	Yield (%)[a]
1.	5 mol% $Pd(TFA)_2$ 20 mol% pyridine	3	30
2.	3ÅMS, Na_2CO_3, O_2 PhMe, 80 °C	18	60
3.	10 mol% $Pd(OAc)_2$ 40 mol% pyridine 3ÅMS, O_2 PhMe, 80 °C	2	25
4.	10 mol% $Pd(OAc)_2$, O_2 DMSO, 60 °C	4	80
5.	5 mol% $Pd(OAc)_2$, NaOAc (2 equiv), O_2 DMSO, 60 °C	3	20

[a] Isolated yield.

3.5 Initial Synthetic Efforts

Our initial synthetic efforts focused on the synthesis of diene **229**, which could be used to test both the phenol and aniline palladium(II)-catalyzed oxidative heterocyclizations. Thus, beginning with 2-nitro iodobenzene (**232**), Sonogashira coupling of alkyne **239** provided arene **240** in high yield (Scheme 3.5.1). Regioselective hydrostannylation of alkyne **240** using conditions developed by Alami, provided vinyl stannane **241** in 65% yield.[17] Subsequent exposure of this intermediate to I_2 in acetonitrile provided vinyl iodide **242** in 76% yield.[18]

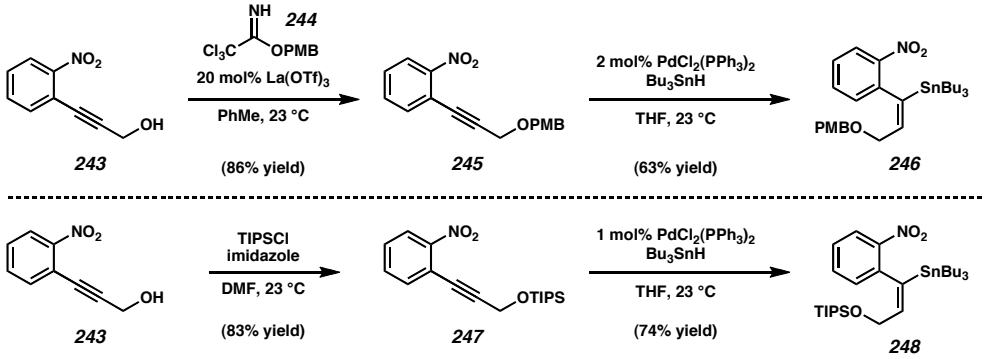
Scheme 3.5.1



Although we were confident that the TBS moiety in vinyl iodide **242** would be stable in upcoming transformations, we decided to synthesize vinyl stannanes **246** and **248**. We hypothesized that the TIPS group would provide greater bulk and stability, while the PMB moiety was an orthogonal functional group that would allow for a silyl protecting group on indole fragment **231** (Scheme 3.5.2). Accordingly, exposure of alcohol **243**[19] to 20 mol% $La(OTf)_3$ and trichloroacetimidate **244**[20] provided alkyne **245** in 86% yield. Hydrostannylation of this product provided vinyl stannane **246** in 63% yield. The analogous TIPS protected intermediate was obtained via the aforementioned strategy. Silylation of alcohol **243** with TIPSCl proceeded in 83% yield, affording nitro-

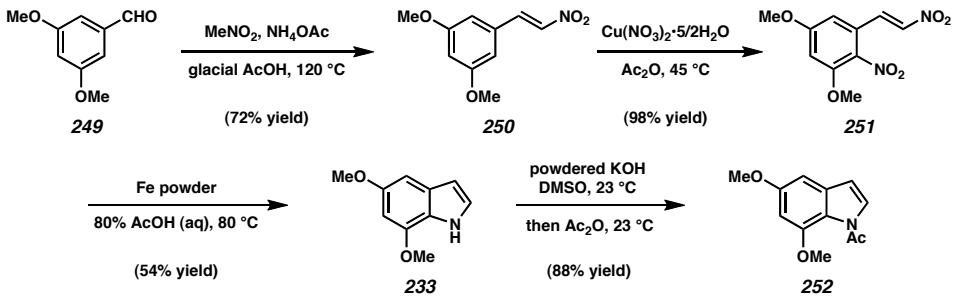
arene **247**. As expected, hydrostannylation of alkyne **247** proceeded regioselectively to furnish vinyl stannane **248** in 74% yield.

Scheme 3.5.2



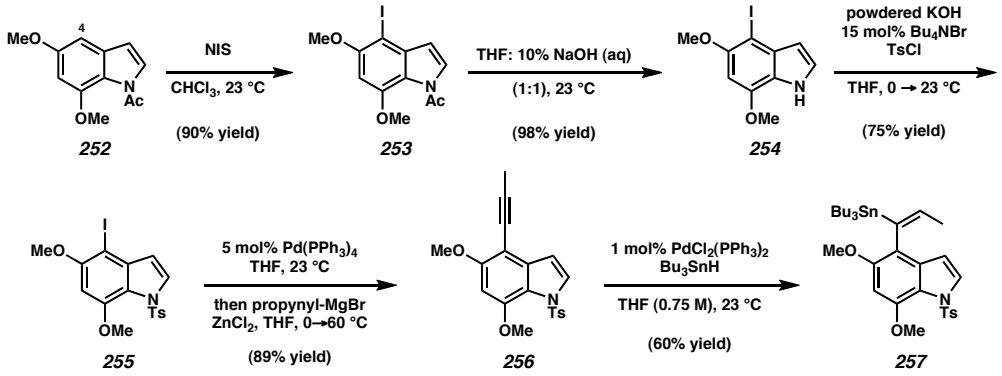
The second coupling partner needed for the Stille coupling, substituted indole **231**, was obtained from 5,7-dimethoxy indole (**233**).[21,22] The synthesis of this indole is shown below in Scheme 3.5.3. Initial exposure of commercially available 3,5-dimethoxy benzaldehyde (**249**) to nitromethane under acidic conditions effected a Henry reaction to provide arene **250** in 72% yield.[23] Subsequent nitration using copper(II)nitrate in acetic anhydride provided nitro-arene **251** in 98% yield. At this stage, reductive cyclization afforded indole **233**, which underwent protection of the indole nitrogen as an amide, providing *N*-acyl indole **252** in 88% yield.

Scheme 3.5.3



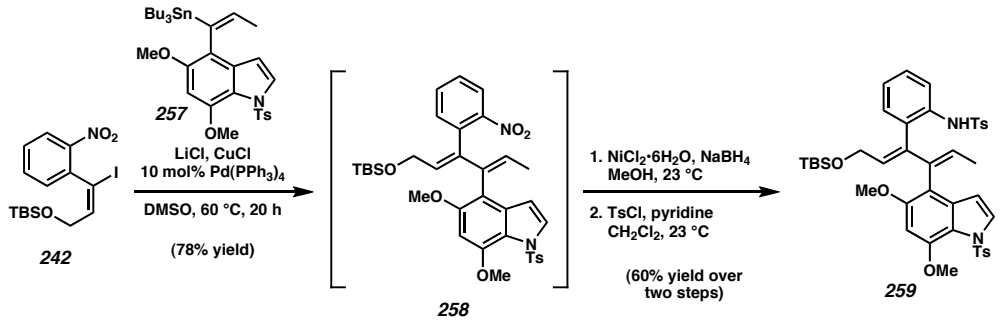
With the synthesis of indole **252** complete, we attempted to demethylate the two methoxy substituents on the indole core. Dimethoxy indole **252** proved surprisingly difficult to demethylate and all attempts were unsuccessful.[24] Hence, we elected to use this dimethylated system to probe the feasibility of the palladium(II)-catalyzed oxidative aniline cyclization. To this end, we needed to first functionalize, and then transform, C(4) of indole **252** to the appropriate vinyl stannane for the Stille coupling. Black has shown that formylation of 5,7-dimethoxyindoles occurs exclusively at C(4), rather than at C(3), when an acyl group (e.g., Ac, Piv, or Boc) is protecting the indole nitrogen.[25] Hence, selective C(4) functionalization commenced with iodination of indole **252** using NIS to provide intermediate **253** in excellent yield (Scheme 3.5.4). At this stage, it was found that the acetyl moiety was not stable toward further functionalization at C(4) via a Negishi coupling. To address this chemoselectivity issue, we sought a more robust protecting group. Thus, cleavage of the acyl amide provided indole **254** in nearly quantitative yield. Reprotection of the indole nitrogen in arene **254** as a sulfonamide afforded indole **255** in 75% yield. Further elaboration at C(4) occurred smoothly via a Negishi coupling providing alkyne **256** in excellent yield. Completion of the Stille coupling partner (**257**) was accomplished in 65% yield using a regioselective palladium-catalyzed hydrostannylation reaction.[10]

Scheme 3.5.4



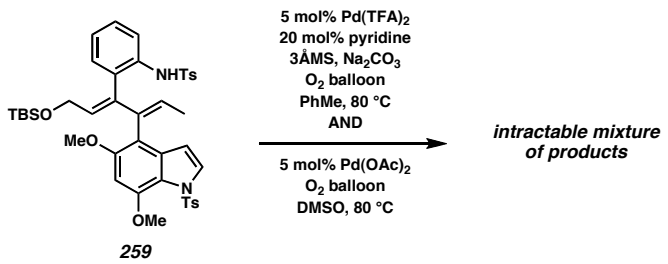
With both Stille coupling fragments in hand, we attempted the carbon-carbon bond-forming reaction. In the event, coupling of arene **242** with indole **257** provided intermediate **258** in good yield using conditions developed by Han, Stoltz, and Corey (Scheme 3.5.5).[26] At this stage, reduction of the nitro functionality was accomplished under pH-neutral conditions, followed by formation of a sulfonamide to afford diene **259** in 55% yield over the two steps.[27]

Scheme 3.5.5



We then subjected tosyl aniline **259** to our conditions developed for the palladium(II)-catalyzed oxidative cyclization conditions (Scheme 3.5.6). Unfortunately, these conditions afforded an intractable mixture of products. We also tried DMSO/O_2, although the same mixture of products was formed.[28]

Scheme 3.5.6



259

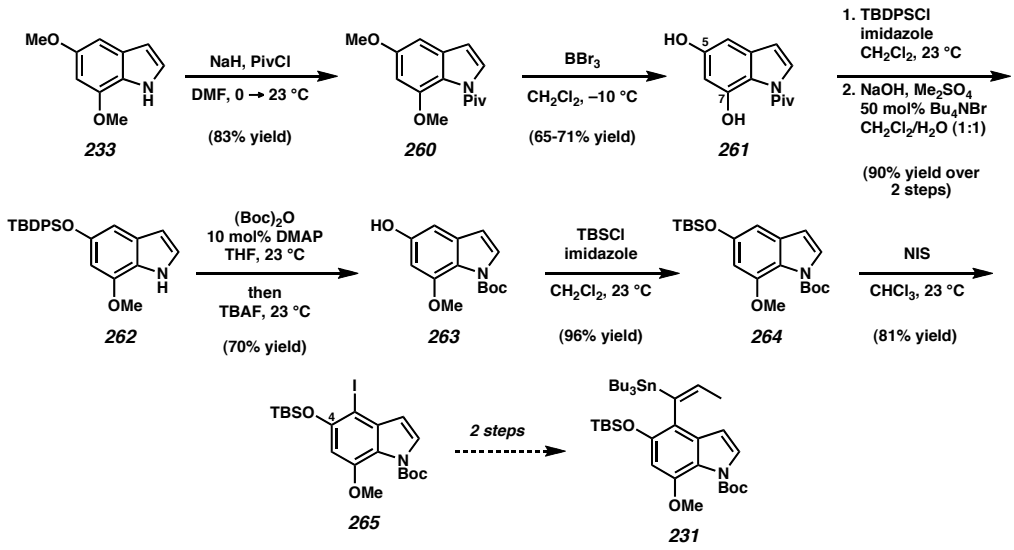
Since our phenolic model system was successful, we reconcentrated our efforts toward accessing the C(5) phenol contained on the indole fragment.

3.6 Further Studies Toward the Pd(II)-catalyzed Oxidative Phenol Cyclization

As previously stated, attempts to demethylate *N*-acetyl 5,7-dimethoxyindole (**252**, cf. Scheme 3.5.3) were unsuccessful. We speculated that the acetyl unit was cleaved when demethylation was attempted using BBr_3. Thus, we replaced the acetyl moiety with a pivaloyl group to provide greater stability and steric bulk, as well as to preserve exclusive functionalization at C(4) (Scheme 3.6.1). Beginning with 5,7-dimethoxyindole (**233**), protection of the indole nitrogen using pivaloyl chloride provided arene **260** in 83% yield. To our delight, demethylation of indole **260** occurred smoothly at –10 °C using BBr_3 to provide bis-phenol **261** in good yield.[29] At this stage, selective silylation of the C(5) phenol using TBDPSCl under standard conditions, followed by methylation at C(7) and pivaloate removal led to indole **262** in 90% overall yield. Further functionalization of indole **262** was accomplished by a two-step sequence beginning with Boc protection of the indole nitrogen, followed by silyl cleavage to arrive at phenol **263** in 70% overall yield. It was found that the TBDPS group prevented iodination at C(4) of

the indole, likely because of steric hindrance, and thus, was replaced with a TBS group. With phenol **263** in hand, protection as a TBS silyl ether occurred readily to yield arene **264**. Subsequent iodination using NIS provided indole **265** in 80% yield. By accessing indole **265**, we have accomplished our goal of synthesizing a differentially substituted 4,5,7-substituted indole from indole **233**. Furthermore, indole **265** should provide vinyl stannane **231** in two additional synthetic transformations.

Scheme 3.6.1



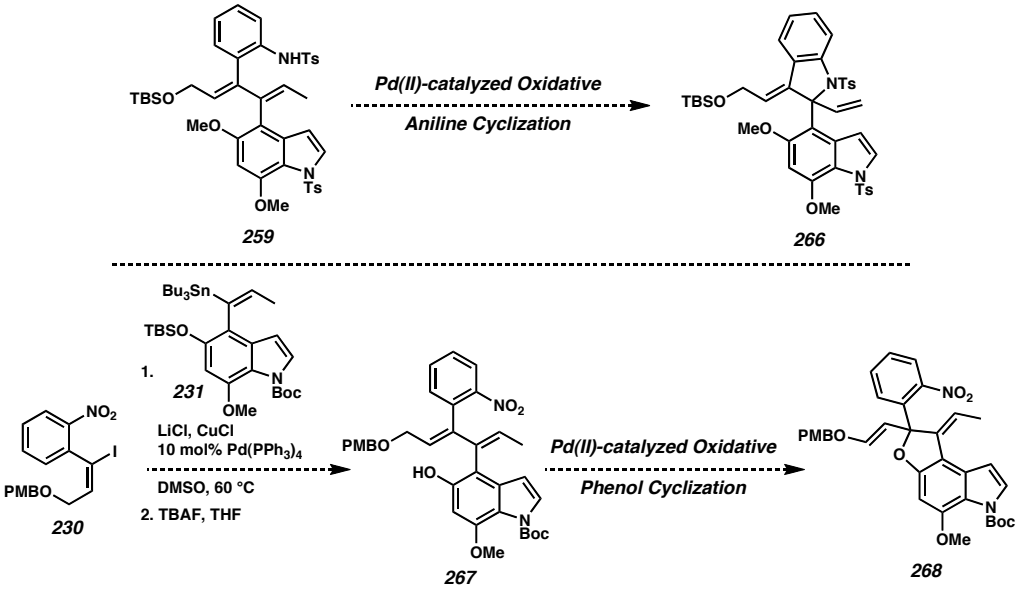
Although we are now able to access the C(5) phenol, further functionalization at C(4) is required to reach vinyl stannane **231**, which is needed for a Stille coupling and subsequent palladium(II)-catalyzed oxidative phenol cyclization. Thus, optimization of our protecting group strategy, as well as the synthesis of vinyl stannane **231** must occur to continue the synthesis.

3.7 Conclusions and Future Directions

The efforts described in this chapter have established an efficient synthesis to advanced intermediates that can be further functionalized and modified en route to phalarine. In general, the synthesis of 4,5,7 differentially substituted indoles can be difficult; nevertheless, we have developed an efficient route that allows for selective functionalization at each position, and thus allows for the possibility of accessing novel indoles that may be bioactive or found in nature.

The key aspects of the proposed synthesis of phalarine involved two palladium(II)-catalyzed oxidative heterocyclizations. Due to the efforts in this chapter, the aniline cyclization can be tested immediately. Furthermore, the synthesis of phenol **267**, needed for testing the other palladium(II)-catalyzed oxidative cyclization, is only several synthetic operations away from being synthesized (Scheme 3.7.1).

Scheme 3.7.1



Once results from the two palladium(II)-catalyzed oxidative heterocyclizations, shown in Scheme 3.7.1, have been obtained, it should become evident as to how to complete the synthesis of phalarine.

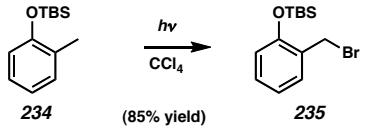
3.8 Experimental Procedures

3.8.1 *Materials and Methods*

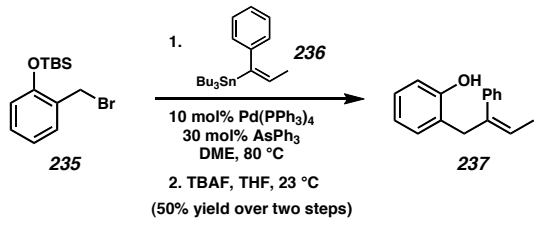
Unless otherwise stated, reactions were performed at ambient temperature (typically 20–22 ºC) in flame-dried glassware under an argon or nitrogen atmosphere using dry solvents. Solvents were dried by passage through an activated alumina column under argon. Et_3N, iPr_2NH, iPr_2NEt, and pyridine were freshly distilled from CaH_2. Trifluoroacetic acid (99%) was purchased from Aldrich. Tf_2O was freshly distilled from P_2O_5. All other commercially obtained reagents were used as received. 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, $KMnO_4$, or CAM staining. ICN silica gel (particle size 0.032–0.063 mm) was used for flash chromatography. Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz respectively), or a Varian Inova 500 (at 500 MHz and 125 MHz respectively) and are reported relative to solvent for ^1H NMR ($CHCl_3$ = 7.27 ppm, C_6H_6 = 7.16 ppm, CH_2Cl_2 = 5.30 ppm, DMSO = 2.51 ppm) and ^{13}C NMR ($CDCl_3$ = 77.0 ppm, C_6D_6 = 128.4 ppm). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicitiy, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, hex = hextet, dq = doublet of quartets, dt = doublet of triplets, td = triplet of doublets, dd = doublet of doublets, m = multiplet, comp. m = complex multiplet, app. = apparent, bs = broad singlet. IR spectra were recorded on a Perkin Elmer BX-11 FT-IR spectrometer and are reported in

frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility. For reactions involving UV light, a Mercury UV-lamp was used.

3.8.2 *Preparation of Compounds*



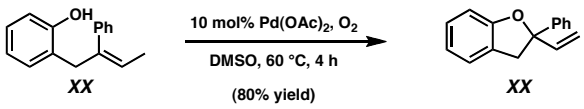
Benzyl Bromide 235. To a solution of arene **234**[12] (1.00 g, 4.50 mmol, 1.00 equiv) in CCl_4 (40 mL) at ambient temperature was added NBS (881 mg, 4.95 mmol, 1.10 equiv). A reflux condenser was fitted onto the reaction (no water) as a precaution. The reaction mixture was then stirred for 2 hours with continuous irradiation using UV light. At this time, TLC (100% Hexanes) showed the reaction was complete. The reaction mixture was filtered with filter paper, washed with minimal CH_2Cl_2, and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography using 100% Hexanes to provide a clear oil (1.15 g, 85%). All spectroscopic data of benzyl bromide **235** matched those reported by Hartwig.[12]



Phenol 237. A round-bottom flask was charged with benzyl bromide **235** (510 mg, 1.69 mmol, 1.00 equiv) and vinyl stannane **236**[13] (825 mg, 2.03 mmol, 1.20 equiv), followed

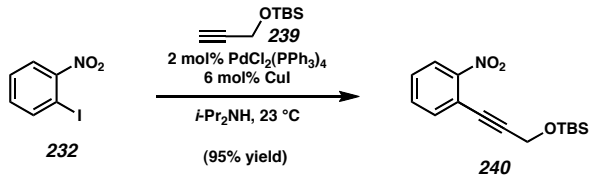
by DME (17 mL). This solution was sparged for 10 minutes with argon, followed by the sequential addition of $AsPh_3$ (155 mg, 0.507 mmol, 0.300 equiv) and $Pd(PPh_3)_4$ (195 mg, 0.169 mmol, 0.100 equiv) at ambient temperature, and fitted with a reflux condenser (no water). The reaction mixture was heated to 80 °C, and monitored by TLC (100% Hexanes). After 6–8 hours, the reaction was complete and diluted with Et_2O to provide a white precipitate. This suspension was filtered through a small pad of celite, and the Et_2O layer was washed with water and brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to provide a crude oil.

To this oil was added THF (17 mL) at ambient temperature, followed by TBAF (2.03 mL of 1.0 M solution in THF, 2.03 mmol, 1.20 equiv). After 1 hour , TLC (10:90 EtOAc:Hexanes) showed the reaction was complete. The reaction was diluted with Et_2O and water, and the layers were separated. The aqueous layer was extracted 2x with Et_2O, and the Et_2O layers were combined and washed with water and brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to provide an oil. This crude oil was purified by flash chromatography using 7:93 EtOAc:Hexanes to provide phenol **237** as a clear oil (189 mg, 50% yield over two steps). R_F = 0.40 (15:85 EtOAc:Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (t, *J* = 7.3 Hz, 2H), 7.24 (t, *J* = 7.3 Hz, 1H), 7.14 (m, 3H), 7.02 (d, *J* = 6.8 Hz, 1H), 6.82 (t, *J* = 8.3 Hz, 2H), 5.64 (q, *J* = 6.8 Hz, 1H), 5.04 (s, 1H), 3.68 (s, 2H), 1.62 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 140.2, 139.8, 131.1, 128.3, 128.2, 127.9, 126.8, 124.9, 123.4, 120.8, 115.9, 40.5, 14.7; IR (film) 3468, 3030, 2914, 1592, 1489, 1455, 1215 cm^{-1}; HRMS (FAB$^+$) calc'd for $[C_{16}H_{16}O]^+$: *m/z* 224.1201, found 224.1206.

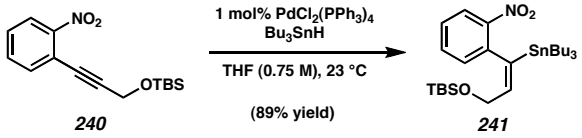


XX *XX*

Dihydrobenzofuran 238. To a 14/20 fitted glass tube (6.00 mL capacity) containing phenol **237** (10.0 mg, 44.6 μmol, 1.00 equiv) was added $Pd(OAc)_2$ (1.00 mg, 4.46 μmol, 0.100 equiv) followed immediately by DMSO (890 μL) at ambient temperature. A 14/20 fitted glass three-way adapter containing an O_2 balloon was attached accordingly. The reaction mixture was purged under vacuum and backfilled with O_2, and repeated 4x. The reaction mixture was then heated to 60 °C and monitored by TLC (20:80 EtOAc:Hexanes). After 4 hours the reaction was complete. The reaction mixture was allowed to cool to ambient temperature, and the dark solution was transferred to a biphasic system of Et_2O:brine (2:1). The layers were separated, and the aqueous layer was extracted 3x with Et_2O. The Et_2O layers were combined and washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to provide an oil that was purified by flash chromatography using 20:80 EtOAc:Hexanes to provide dihydrobenzofuran **238** as a colorless oil (8.00 mg, 80%). R_F = 0.35 (30:70 EtOAc:Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.3 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.28 (app. d, *J* = 7.3 Hz, 1H), 7.16 (m, 2H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.86 (t, *J* = 7.6 Hz, 1H), 6.23 (dd, *J* = 10.5, 17.1 Hz, 1H), 5.30 (dd, *J* = 0.9, 17.1 Hz, 1H), 5.18 (dd, *J* = 0.9, 10.5 Hz, 1H), 3.60 (d, *J* = 15.4 Hz, 1H), 3.56 (d, *J* = 15.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 144.0, 141.0, 128.3, 128.2, 127.3, 125.9, 125.4, 124.9, 120.7, 114.0, 109.5, 90.7, 42.8; IR (film) 3056, 3031, 1598, 1480, 1462, 1241; HRMS (FAB^+) calc'd for $[C_{16}H_{14}O]^+$: *m*/*z* 222.1045, found 222.1035.

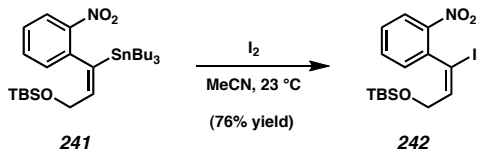


Alkyne 240. To a solution of arene **232** (2.50 g, 10.0 mmol, 1.00 equiv) and alkyne **239** (5.11 g, 30.0 mmol, 3.00 equiv) in *N,N*-diisopropylamine (33 mL) at ambient temperature, $PdCl_2(PPh_3)_2$ (140 mg, 0.200 mmol, 0.0200 equiv) and CuI (115 mg, 0.600 mmol, 0.0600 equiv) were added sequentially to the reaction. A slurry formed after several minutes, and the reaction mixture was monitored by TLC (20:80 EtOAc:Hexanes). After 30–60 minutes, the reaction was complete, and diluted with saturated $NaHCO_3$ (aq.). The aqueous layer was extracted 3x with Et_2O, and the Et_2O layer was then washed 2x with water, once with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to provide an oil that was purified by flash chromatography using 5:95 EtOAc:Hexanes to provide alkyne **240** as an oil (2.77 g, 95% yield). All spectroscopic data were identical to those reported by Sakamoto.[30]



Vinyl Stannane 241. To a solution of alkyne **240** (1.00 g, 3.43 mmol, 1.00 equiv) and $PdCl_2(PPh_3)_2$ (24.0 mg, 0.0343 mmol, 0.0100 equiv) in THF (4.60 mL) at ambient temperature was added Bu_3SnH (1.10 mL, 4.12 mmol, 1.20 equiv) over 30 seconds, and the reaction was monitored by TLC (5:95 EtOAc:Hexanes). After 3 hours, the reaction was complete and was concentrated in vacuo to provide a dark oil that was purified by flash chromatography using 1:99 EtOAc:Hexanes to provide vinyl stannane **241** as a

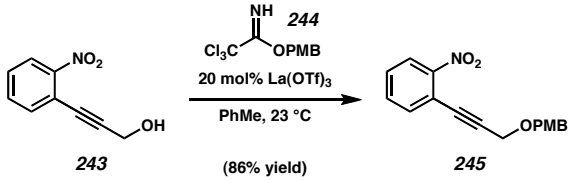
yellow oil (1.78 g, 89% yield). R_F = 0.35 (5:95 EtOAc:Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.3 Hz, 1H), 7.54 (dt, *J* = 0.7, 7.5 Hz, 1H), 7.33 (dt, *J* = 1.0, 7.3 Hz, 1H), 7.10 (d, *J* = 7.8 Hz, 1H), 5.94 (t, *J* = 5.6 Hz, 1H), 4.02 (t, *J* = 5.8 Hz, 2H), 1.44 (m, 6H), 1.30 (hex, *J* = 7.3 Hz, 6H), 0.97–0.84 (m, 24H), 0.020 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.0, 143.7, 141.0, 139.9, 133.0, 129.2, 126.0, 124.5, 61.7, 28.8, 27.3, 25.8, 18.2, 13.6, 10.6, –5.2, –5.3; IR (film) 2957, 2929, 2856, 1523, 1464, 1343, 1254, 1102 cm^{-1}; HRMS (FAB$^+$) calc'd for $[C_{27}H_{48}SiSnO_3N]^+$: *m/z* 582.2426, found 582.2451.



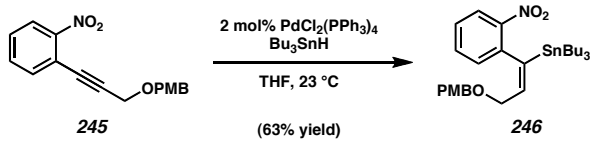
241 ***242***

Vinyl Iodide 242. To a solution vinyl stannane **241** (1.10 g, 1.89 mmol, 1.00 equiv) in MeCN (19.0 mL) at ambient temperature was added I_2 (528 mg, 2.08 mmol, 1.10 equiv) in several portions, and the reaction was monitored by TLC (5:95 EtOAc:Hexanes). After 1 hour, the reaction was complete, and was quenched with 5% $Na_2S_2O_3$ (aq.). The reaction mixture was diluted with water and Et_2O, and the layers were then separated. The Et_2O layer was washed with water and brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to provide an oil that was purified by flash chromatography using 2:98→5:95 EtOAc:Hexanes to provide vinyl iodide **242** as a pale-yellow oil (600 mg, 76% yield) R_F = 0.40 (10:90 EtOAc:Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 1.1, 8.2 Hz, 1H), 7.62 (dt, *J* = 1.2, 7.5 Hz, 1H), 7.48 (dt, *J* = 1.5, 8.2 Hz, 1H), 7.38 (dd, *J* = 1.2, 7.6 Hz, 1H), 6.63 (t, *J* = 6.5 Hz, 1H), 3.88 (dq, *J* = 6.5, 13.2 Hz, 2H), 0.82 (s, 9H), –0.060 (s, 3H), –0.072 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.0, 143.2, 136.3,

133.3, 130.7, 129.4, 124.7, 88.5, 61.9, 25.8, 18.2, –5.4, –5.5; IR (film) 2954, 2929, 2857, 1529, 1472, 1348, 1257, 1103 cm^{-1}; HRMS (FAB^+) calc'd for $[C_{15}H_{23}O_3NISi]^+$: *m/z* 470.0492, found 420.0480.

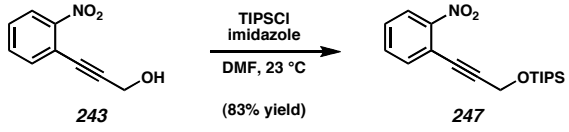


Alkyne 245. To a solution of alcohol **243** (448 mg, 2.53 mmol, 1.00 equiv) and reagent **244**[20a] (1.00 g, 3.54 mmol, 1.40 equiv) in PhMe (12.7 mL) at ambient temperature was added $La(OTf)_3$ (296 mg, 0.506 mmol, 0.200 equiv), and the reaction was monitored by TLC (20:80 EtOAc:Hexanes). After 24 hours the reaction was complete by TLC, and quenched with water. The reaction mixture was diluted with Et_2O, and the layers are separated. The organic extract was washed with water and brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to provide a crude oil that was purified by flash chromatography using 15:85 EtOAc:Hexanes to obtain alkyne **245** as a red-orange semi-solid (650 mg, 86% yield). R_F = 0.40 (30:70 EtOAc:Hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.8 Hz, 1H), 7.65 (dd, *J* = 1.0, 7.8 Hz, 1H), 7.59 (dt, *J* = 1.0, 7.8 Hz, 1H), 7.48 (dt, *J* = 1.5, 7.8 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 4.67 (s, 2H), 4.44 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 149.8, 134.9, 132.8, 130.0, 129.3, 128.8, 124.6, 118.1, 113.9, 93.6, 81.6, 71.3, 57.3, 55.3; IR (film) 2838, 1610, 1525, 1514, 1343, 1248, 1073, 1034 cm^{-1}; HRMS (FAB^+) calc'd for $[C_{17}H_{15}O_4N]^+$: *m/z* 297.1001, found 297.1007.



245 *246*

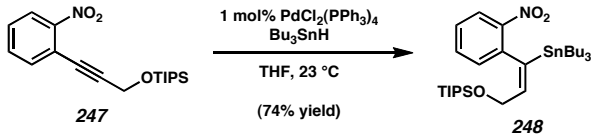
Vinyl Stannane 246. To a solution of alkyne **245** (605 mg, 2.03 mmol, 1.00 equiv) and $PdCl_2(PPh_3)_2$ (28.5 mg, 0.0406 mmol, 0.0200 equiv) in THF (2.70 mL) at ambient temperature was added Bu_3SnH (655 μL, 2.44 mmol, 1.20 equiv) over 60 seconds. The reaction was monitored by TLC (20:80 EtOAc:Hexanes), and was complete after 30 minutes. The reaction mixture was concentrated in vacuo, and the residue was purified by flash chromatography using 6:94 EtOAc:Hexanes to provide vinyl stannane **246** as a neon oil (755 mg, 63% yield). R_F = 0.35 (20:80 EtOAc:Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.3 Hz, 1H), 7.48 (dt, *J* = 1.0, 7.8 Hz, 1H), 7.28 (dt, *J* = 1.5, 8.3 Hz, 1H), 7.18 (d, *J* = 8.3 Hz, 2H), 7.04 (dd, *J* = 1.0, 7.8 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 2H), 5.96 (t, *J* = 5.9 Hz, 1H), 4.32 (d, *J* = 11.2 Hz, 1H), 4.30 (d, *J* = 11.2 Hz, 1H), 3.80 (comp. m, 5H), 1.44 (hex, *J* = 7.3 Hz, 6H), 1.26 (hex., *J* = 7.3 Hz, 6H), 0.88 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1,147.2, 145.9, 140.9, 136.7, 133.0, 130.3, 129.3, 129.1, 126.1, 124.5, 113.7, 71.8, 67.9, 55.2, 28.8, 27.3, 13.6, 10.7; IR (film) 2956, 2927, 2853, 1613, 1517, 1464, 1342, 1285, 1080, 1038 cm^{-1}; HRMS (FAB$^+$) calc'd for $[C_{25}H_{34}SnO_4N]^+$ (–Bu group): *m*/*z* 532.1510, found 532.1524.



243 *247*

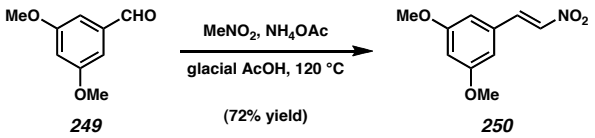
Alkyne 247. To a solution of alcohol **243** (2.49 g, 14.1 mmol, 1.00 equiv) and imidazole (2.01g, 29.6 mmol, 2.10 equiv) in DMF (56.0 mL) at 0 °C was added TIPSCl (3.04 mL, 14.8 mmol, 1.05 equiv). The reaction mixture was allowed to warm to ambient

temperature and stir overnight. TLC analysis (30:70 EtOAc:Hexanes) revealed the reaction was complete. The reaction mixture was diluted with water and Et_2O, and the layers were separated. The aqueous layer was extracted 3x with Et_2O, the Et_2O layers were combined, washed 3x with water, once with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to provide an oil that was purified by flash chromatography using 5:95 EtOAc:Hexanes to provide alkyne **247** as a light-yellow oil (3.92 g, 83% yield). R_F = 0.30 (10:90 EtOAc:Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 1.2, 8.3 Hz, 1H), 7.63 (dd, *J* = 1.5, 7.8 Hz, 1H), 7.54 (dt, *J* = 1.2, 7.8 Hz, 1H), 4.69 (s, 2H), 1.20 (comp. m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.4, 134.9, 132.7, 128.6, 124.5, 118.4, 96.2, 79.6, 52.6, 17.9, 12.0; IR (film) 2944, 2866, 1609, 1569, 1530, 1463, 1344, 1261, 1098 cm^{-1}; HRMS (FAB$^+$) calc'd for $[C_{18}H_{28}NSiO_3]^+$: *m/z* 334.1838, found 334.1843.

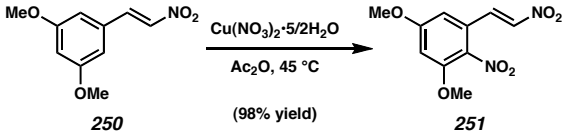


Vinyl Stannane 248. To a solution of alkyne **247** (3.90 g, 11.7 mmol, 1.00 equiv) and $PdCl_2(PPh_3)_2$ (82.1 mg, 0.117 mmol, 0.0100 equiv) in THF (16.0 mL) at ambient temperature was added Bu_3SnH (3.47 mL, 12.9 mmol, 1.10 equiv) over 30–45 seconds. The reaction darkens, and was monitored by TLC (5:95 EtOAc:Hexanes). After stirring overnight, the reaction mixture was concentrated in vacuo to provide a crude oil that was purified by flash chromatography using 2:98 EtOAc:Hexanes to provide vinyl stannane **248** as a neon-yellow liquid (5.44 g, 74% yield). R_F = 0.40 (5:95 EtOAc:Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.0 (dd, *J* = 1.2, 8.2 Hz, 1H), 7.50 (dt, *J* = 1.2, 7.6 Hz, 1H), 7.28 (dt, *J* = 1.5, 8.3 Hz, 1H), 7.08 (dd, *J* = 1.5, 7.8 Hz, 1H), 5.93 (t, *J* = 5.5 Hz, 1H), 4.02

(m, 2H), 1.44 (hex, J = 7.1 Hz, 6H), 1.25 (hex, J = 7.3 Hz, 6H), 1.00 (s, 18H), 0.86 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.1, 143.2, 141.0, 140.3, 133.0, 129.2, 126.0, 124.5, 61.9, 28.8, 27.3, 17.9, 13.6, 12.0, 10.7; IR (film) 2957, 2867, 1524, 1464, 1342, 1105, 1064 cm^{-1}; HRMS (FAB$^+$) calc'd for $[C_{26}H_{46}O_3NSnSi]^+$: m/z 568.2269, found 568.2268.

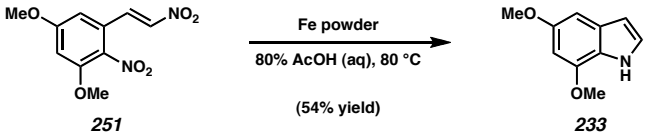


Arene 250. 3,5-dimethoxybenzaldehyde (**249**) (50.0g, 0.301 mol, 1.00 equiv), nitromethane (50.1 mL, 0.923 mol, 3.07 equiv), and ammonium acetate (76.0 g, 0.998 mol, 1.07 equiv) were dissolved in glacial acetic acid (615 mL) and refluxed for 2 h. The reaction mixture was allowed to cool to ambient temperature, at which time yellow crystals form. The suspension was placed in an ice bath for 30 minutes, and the product was then filtered and washed with cold 95% ethanol to provide compound **250** as yellow needles (45.3 g, 72% yield). All spectroscopic data of arene **250** matched those reported by Black.[12]



Arene 251. To a flask containing acetic anhydride (380 mL) warmed to 65 °C was added compound **250** (40.0 g, 0.191 mol, 1.00 equiv). This suspension was stirred at 65 °C until all of compound **250** had dissolved. Once homogeneous, the solution was allowed to cool to 45 °C, and $Cu(NO_3)_2$•5/2 H_2O (30.9 g, 0.105 mol, 0.550 equiv) was added in

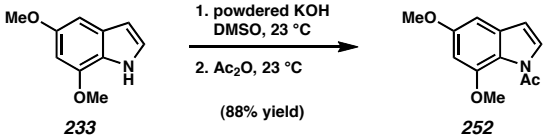
4–5 portions over 1–2 minutes. A slight exotherm occurs, and once brown fumes appeared (ca. 5 min), the reaction was complete and allowed to cool to ambient temperature. The reaction mixture was poured over ice and allowed to stir and warm to ambient temperature overnight. The resulting yellow solid was filtered and washed with water 3x to provide arene **251** (47.6 g, 98% yield). All spectroscopic data of arene **251** matched those reported by Black.[12]



251 *233*

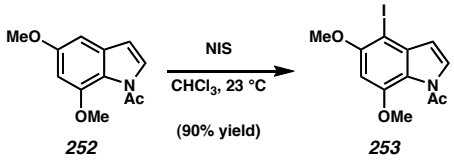
Indole 233. Iron powder (32.0 g, 576 mmol, 38.5 equiv) was added to a solution of arene **251** (4.00 g, 15.7 mmol, 1 equiv) in 80% acetic acid (130 mL) and the suspension was stirred mechanically. After an exotherm that lasts approximately 30 minutes, 40 mL of water was added and the suspension was heated to 80 °C for 1 hour. The reaction mixture was then allowed to cool to ambient temperature. Upon cooling, the reaction mixture hardens to become a single solid. This solid was partially dissolved by adding CH_2Cl_2 and 10% HCl (aq.), followed by manual irritation using a sturdy spatula until stirring with a mechanical stirrer became possible. This suspension stirred for an additional hour, and was then filtered over a large pad of celite. The solids were washed 6x with CH_2Cl_2, and the resulting biphasic solution was separated respectively. The CH_2Cl_2 layer was washed 3x with water, followed by slow addition of saturated cold Na_2CO_3 (aq.) until the organic layer was only slightly acidic (pH = 5–6). The organic layer was then washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to provide a black solid. This residue was dissolved in minimal CH_2Cl_2, and purified by

flash chromatography using 10:90 EtOAc:Hexanes to provide indole **233** as a white crystalline solid (1.50 g, 54% yield).[31] All spectroscopic data of arene **233** matched those reported by Black.[12]



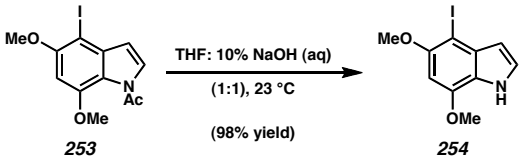
233 *252*

Indole 252. To powdered KOH (0.95 g, 16.9 mmol, 3.70 equiv) was added DMSO (20.0 mL) and the suspension was stirred at ambient temperature for 10 min. Indole **233** (0.800 g, 4.52 mmol, 1.00 equiv) was then added in one portion, and the suspension was allowed to stir for 1 hour. At this stage, the resulting solution was rapidly decanted from the excess KOH and transferred to a separate round-bottom flask containing chilled Ac_2O (4.00 mL, excess) (ice-bath). The excess KOH was washed rapidly with DMSO (5.00 mL) and quickly transferred to the solution of Ac_2O. This solution was allowed to warm to ambient temperature, and stirred under N_2 overnight. The reaction mixture was diluted with water and extracted 3x with Et_2O. The organic layer was washed with water and brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to provide an oil that was purified by flash chromatography using 10:90 EtOAc:Hexanes to provide indole **252** as a beige solid (867 g, 88% yield). All spectroscopic data of arene **252** matched those reported by Black.[12]



252 *253*

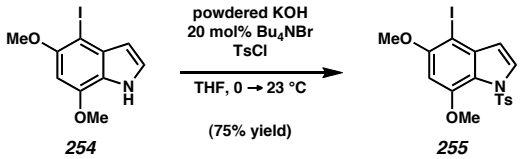
Arene 253. To a solution of indole **252** (4.62 g, 21.1 mmol, 1.00 equiv) in $CHCl_3$ (85.0 mL) at 0 °C, was added *N*-iodosuccinimide (5.22 g, 23.2 mmol, 1.10 equiv) in one portion, and the reaction was monitored by TLC (50:50 CH_2Cl_2:Hexanes). After 1 hour, the reaction was complete. The reaction mixture was diluted with water and Et_2O, and the layers were separated. The aqueous layer was extracted once with Et_2O, and the organic extracts were combined and washed successively with 20% $Na_2S_2O_3$ (aq.), water, and brine. The Et_2O layer was dried with $MgSO_4$, filtered, and concentrated in vacuo to provide a solid. This solid was dissolved in minimial CH_2Cl_2, and was purified by flash chromatography using 50:50 CH_2Cl_2:Hexanes to obtain arene **253** as a tan solid (6.37 g, 90% yield). R_F = 0.20 (15:85 EtOAc:Hexanes); ^{1}H NMR (500 Mhz, $CDCl_3$) δ 7.63 (d, *J* = 3.7 Hz, 1H), 6.58 (d, *J* = 3.7 Hz, 1H), 6.52 (s, 1H), 3.99 (s, 3H), 3.96 (s, 3H), 2.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 155.8, 148.9, 138.3, 128.7, 119.4, 111.4, 94.2, 67.4, 57.5, 56.1, 25.6; IR (film) 2939, 2842, 1733, 1682, 1577, 1371, 1206, 1116, 1100 cm^{-1}; HRMS (FAB)$^+$ calc'd for $[C_{12}H_{12}NO_3I]^+$: *m/z* 344.9862, found 344.9849.



253 *254*

Indole 254. Indole **253** (5.97 g, 17.3 mmol, 1.00 equiv) was dissolved in THF (80.0 mL) at ambient temperature and stirred vigorously. At this stage, 10% NaOH (aq.) (80.0 mL) was added and the reaction stirred until complete consumption of indole **253** (ca. 1 hour).

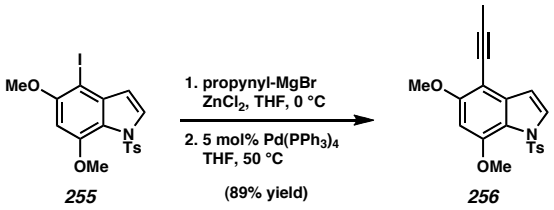
The reaction mixture was diluted with water and EtOAc, and the layers were separated. The aqueous layer was washed once with EtOAc, and the organic extracts were combined and washed with water and brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to provide indole **254** as a light-yellow solid (5.20 g, 98% yield).[32] R_F = 0.25 (20:80 EtOAc:Hexanes); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.4 (br, 1H), 7.28 (t, J = 2.7 Hz, 1H), 6.60 (s, 1H), 6.18 (dt, J = 0.7, 2.2 Hz, 1H), 3.97 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (125, MHz, DMSO-d_6) δ 152.4, 146.9, 132.6, 125.9, 121.1, 104.4, 91.9, 65.7, 57.9, 55.7; IR (film) cm^{-1}; HRMS (FAB$^+$) calc'd for $[C_{10}H_{10}O_2NI]^+$: m/z 302.9756, found 302.9754.



254 *255*

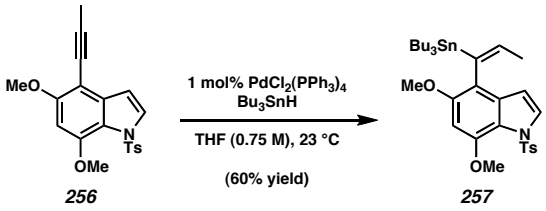
Arene 255. To a suspension of powdered KOH (4.95 g, 16.3 mmol, 1.15 equiv) and Bu_4NBr (788 mg, 2.45 mmol, 0.15 equiv) was added THF (125 mL), and the suspension was cooled to 0 °C. Indole **254** (4.95 g, 16.3 mmol, 1.00 equiv) was then added in one portion to the reaction mixture, and the solution was allowed to stir for 45 minutes at 0 °C. At this stage, TsCl (3.57 g, 18.8 mmol, 1.15 equiv) was added to the reaction mixture in a single portion, and the mixture was allowed to stir for an additional 10 minutes at 0 °C. The reaction mixture was then allowed to warm to ambient temperature and stir overnight. TLC analysis (35:65 CH_2Cl_2:Hexanes) showed that minimal amounts of indole **254** remained, and thus, the reaction mixture was diluted with water and Et_2O. The layers were separated, and the aqueous layer was extracted 2x with Et_2O. The organic layers were combined and washed once with water and brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to yield a tan solid. This solid was dissolved in

minimal $CHCl_3$, and purified by flash chromatography using 35:65→75:25 CH_2Cl_2:Hexanes to afford indole **255** as a white solid (5.51 g, 75% yield).[33] R_F = 0.30 (40:60 CH_2Cl_2:Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 3.9 Hz, 1H), 7.70 (d, *J* = 8.3 Hz, 1H), 7.27 (d, *J* = 8.1 Hz, 1H), 6.64 (d, *J* = 3.7 Hz), 6.36 (s, 1H), 3.89 (s, 3H), 3.74 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 148.2, 144.3, 137.7, 137.0, 129.8, 129.4, 127.3, 119.3, 110.5, 94.2, 67.1, 57.5, 55.8, 21.6; IR (film) 3148, 2939, 2845, 1578, 1463, 1352, 1255, 1213, 1171, 1134, 994 cm^{-1}; HRMS (FAB$^+$) calc'd for $[C_{17}H_{16}O_4INS]^+$: *m/z* 456.9845, found 456.9833.



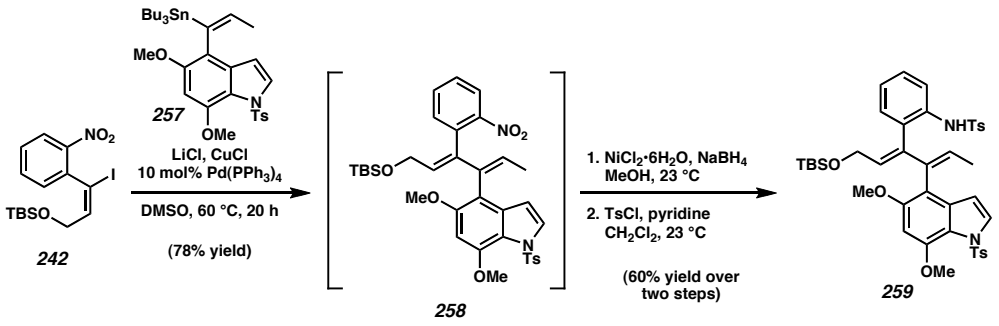
Alkyne 256. $ZnCl_2$ (2.84 mL of 0.5 M solution in THF, 1.42 mmol, 1.30 equiv) was added to THF (5.00 mL) at ambient temperature. The reaction mixture was then cooled to 0 °C, and $CH_3CCMgBr$ (2.84 mL of 0.5 M solution in THF, 1.42 mmol, 1.30 equiv) was added and a white precipitate formed. The suspension was stirred for an additional 30 minutes at 0 °C. Indole **255** (500 mg, 1.09 mmol, 1.00 equiv) was charged into a separate round-bottom flask, followed by $Pd(PPh_3)_4$ (63.1 mg, 0.0545 mmol, 0.050 equiv) and THF (1.30 mL). This solution was then transferred via cannula to the white suspension at 0 °C, and the resultant suspension was allowed to warm to ambient temperature over 10 minutes. The reaction mixture was then heated to 60 °C and monitored by TLC (30:70 EtOAc:Hexanes). After 40 minutes, the reaction was complete and allowed to cool to ambient temperature. The reaction mixture was diluted with water

and Et_2O, and the layers were then separated. The aqueous layer was washed 2x with Et_2O, and the Et_2O layers were combined and washed 2x with water, brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to provide a solid residue. This residue was recrystalized from EtOH to provide alkyne **256** as white flakes (357 mg, 89% yield). R_F = 0.40 (30:70 EtOAc:Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 3.7 Hz, 1H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 6.76 (d, *J* = 3.7 Hz, 1H), 6.30 (s, 1H), 3.90 (s, 3H), 3.81 (s, 3H), 2.40 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6, 147.2, 144.2, 137.0, 136.1, 129.7, 129.3, 127.2, 119.0, 106.7, 96.9, 93.6, 91.6, 73.2, 56.9, 55.6, 21.5, 4.9; IR (film) 3153, 2940, 2847, 1595, 1490, 1360, 1262, 1209, 1172, 1130, 1107 cm^{-1}; HRMS (FAB$^+$) calc'd for $[C_{20}H_{19}O_4NS]^+$: *m/z* 369.1035, found 369.1033.



Vinyl Stannane 257. To a solution of alkyne **256** (650 mg, 1.76 mmol, 1.00 equiv) in THF (2.50 mL), $PdCl_2(PPh_3)_2$ (12.4 mg, 0.0176 mmol, 0.0100 equiv) was added and allowed to stir for 5 minutes at ambient temperature. At this stage, Bu_3SnH (595 μL, 2.20 mmol, 1.25 equiv) was added dropwise, and the reaction was monitored by TLC (5:95 EtOAc:Hexanes). After 6 hours, the reaction mixture was concentrated, and the crude oil underwent flash chromatography using 5:95 EtOAc:Hexanes to afford vinyl stannane **257** as a pale-yellow oil (700 mg, 60% yield). R_F = 0.45 (10:90 EtOAc:Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (m, 3H), 7.25 (dd, *J* = 0.5, 8.5 Hz,

2H), 6.36 (m, 2H), 6.00 (q, J = 6.4 Hz, 1H), 3.74 (s, 3H), 3.70 (s, 3H), 2.40 (s, 3H), 1.56 (d, J = 6.6 Hz, 3H), 1.36 (m, 6H), 1.20 (hex, J = 7.3 Hz, 6H), 0.80 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5, 145.3, 143.8, 139.8, 137.5, 137.3, 131.3, 129.2, 128.8, 127.2, 119.4, 117.7, 107.3, 94.4, 56.5, 56.0, 28.9, 27.3, 21.6, 17.0, 13.6, 10.2; IR (film) 2955, 2927, 2848, 1592, 1481, 1464, 1360, 1173, 1126 cm^{-1}; HRMS (FAB$^+$) calc'd for $[C_{32}H_{46}O_4NSSn]^+$: *m/z* 660.2170, found 660.2198.



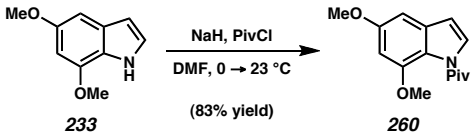
Diene 259. A Schlenck tube (20 mL) was charged with LiCl (118 mg, 2.78 mmol, 6.00 equiv) and flame-dried under vacuum. Upon cooling to ambient temperature, $Pd(PPh)_4$ (53.7 mg, 0.0464 mmol, 0.100 equiv) and CuCl (230 mg, 2.32 mmol, 5.00 equiv) were added, and the mixture was degassed 4x under vacuum with an Ar purge. DMSO (2.50 mL) was introduced with concomitant stirring, followed by a solution of arene **242** (195 mg, 0.464 mmol, 1.00 equiv) and vinyl stannane **257** (368 mg, 0.557 mmol, 1.20 equiv) in DMSO (800 μL, 400 μL rinse). The resulting mixture was rigorously degassed with Ar 4x by the freeze-pump-thaw process (–78 → 23 °C, Ar). The reaction mixture was stirred for an additional 30 minutes at ambient temperature, then heated to 60 °C and followed by TLC (30:70 EtOAc:Hexanes). After 20 hours, the reaction was complete and allowed to cool to ambient temperature. The reaction mixture was diluted with Et_2O and washed with a 6:1 mixture of brine:5% NH_4OH (aq.). A precipitate forms in the

aqueous layer, and the two layers are separated. The aqueous layer was extracted 2x with Et_2O, and the Et_2O extracts are combined and filtered over a small pad of celite. The filtrate was then washed 2x with water and brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to provide an oil that was purified by flash chromatography using 25:75 EtOAc:Hexanes to provide diene **258** as a glue (240 mg, 78% yield). This material was used directly in the next reaction.

To a solution of diene **258** (220 mg, 0.332 mmol, 1.00 equiv) in MeOH (6.60 mL) at 0 °C was added $NiCl_2•6H_2O$ (13.0 mg, 0.664 mmol, 2.00 equiv), and the reaction mixture was allowed to stir until the majority of the $NiCl_2•6H_2O$ was dissolved. At this stage, $NaBH_4$ (50.2 mg, 1.33 mmol, 4.00 equiv) was added in several portions over 30 seconds, the reaction mixture was then allowed to warm to ambient temperature, and was monitored by TLC (30:70 EtOAc:Hexanes). After 90 minutes the reaction was complete and was quenched with water. The reaction mixture was diluted with Et_2O and the layers are separated. The aqueous layer was extracted 3x with Et_2O, and the organic extracts are combined, washed with water and brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to provide an oil that was purified by flash chromatography using 20:80 EtOAc:Hexanes to provide an aniline as a white glue (200 mg, 95% yield). This material was used directly in the next reaction.

To a solution of the aniline (96.0 mg, 0.152 mmol, 1.00 equiv) in CH_2Cl_2 (3.00 mL) at ambient temperature was added pyridine (132 μL, 1.22 mmol, 8.00 equiv), and the reaction mixture was stirred for 10 minutes. TsCl (31.8 mg, 0.167 mmol, 1.10 equiv) was then added in one portion, and the reaction was followed by TLC (30:70 EtOAc:Hexanes). After 8 hours, the reaction color was orange-red and was complete.

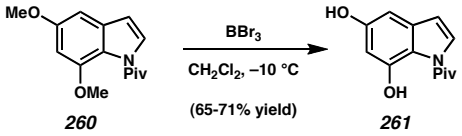
The reaction mixture was concentrated in vacuo to provide a crude residue. To this residue was added heptane, and the volatiles were removed in vacuo (2x). The resulting residue was purified by flash chromatography using 20:80 EtOAc:Hexanes to provide aniline **259** as a white foam (76 mg, 63% yield). R_F = 0.30 (30:70 EtOAc:Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (m, 4H), 7.68 (m, 3H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.27 (dt, *J* = 1.7, 7.8 Hz, 1H), 7.16 (d, *J* = 8.1 Hz, 2H), 7.04 (dt, *J* = 1.0, 7.3 Hz, 1H), 7.00 (dd, *J* = 1.6, 7.4 Hz, 1H), 6.57 (s, 1H), 6.32 (d, *J* =3.7 Hz, 1H), 5.22 (t, *J* = 6.4 Hz, 1H), 5.12 (q, *J* = 6.8 Hz, 1H), 4.02 (s, 3H), 3.8 (s, 3H), 3.64 (dd, *J* = 6.4, 13.7 Hz, 1H), 3.50 (dd, *J* = 6.4, 13.7 Hz, 1H), 2.44 (s, 3H), 2.33 (s, 3H), 1.22 (d, *J* = 6.8 Hz, 3H), 0.77 (s, 9H), –0.18 (s, 3H), –0.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 147.0, 144.1, 143.4, 137.7, 137.3, 136.5, 136.3, 135.1, 133.8, 131.3, 130.5, 129.6, 129.4, 129.0, 128.6, 127.7, 127.5, 127.4, 127.38, 123.1, 119.2, 117.6, 110.5, 106.4, 94.1, 60.8, 56.9, 55.8, 25.8, 21.6, 21.5, 18.1, 15.4, –5.2, –5.3; IR (film) 3283, 2918, 2850,1598, 1493, 1349, 1254, 1168, 1092 cm^{-1}; HRMS (FAB$^+$) calc'd for $[C_{42}H_{50}O_7SiS_2N_2]^+$: *m/z* 786.2829, found 786.2862.



233 ***260***

Indole 260. DMF (82 mL) was added to a round-bottom flask charged with NaH (1.33 g, 55.5 mmol, 3.00 equiv) at ambient temperature. The suspension was cooled to 0 °C and allowed to stir for 10 minutes. Subsequent dropwise addition of a solution of indole **233** (3.28 g, 18.5 mmol, 1.00 equiv) in DMF (8.00 mL, 4.00 mL rinse) to the NaH suspension resulted in bubbling. The reaction mixture was stirred for 20 minutes at 0 °C, PivCl (9.10 mL, 74.0 mmol, 4.00 equiv) was added, and the reaction mixture was allowed to slowly

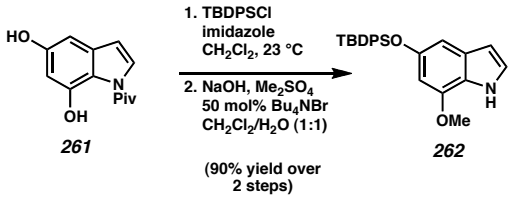
warm to ambient temperature over 3 hours. After 3 additional hours of stirring, the reaction was complete by TLC (10:90 EtOAc:Hexanes). The reaction mixture was diluted with water and Et_2O, and the layers were separated. The aqueous layer was extracted 3x with Et_2O, and the organic extracts were combined and washed 3x with water, once with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to provide an oil that was purified by flash chromatography using 5:95 EtOAc:Hexanes to afford indole **260** as a clear oil (4.03 g, 83% yield). R_F = 0.40 (20:80 EtOAc:Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 3.4 Hz, 1H), 6.66 (d, *J* = 2.1 Hz, 1H), 6.49 (d, *J* = 3.4 Hz, 1H), 6.47 (d, *J* = 2.1 Hz, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.4, 157.0, 148.4, 131.7, 126,4, 121.7, 106.2, 96.6, 94.3, 55.8, 55.6, 42.5, 28.6; IR (film) 2968, 1719, 1612, 1592, 1478, 1287, 1204, 1174 cm^{-1}; HRMS (FAB$^+$) calc'd for $[C_{15}H_{19}NO_3]^+$: *m/z* 261.1365, found 261.1356.



260 ***261***

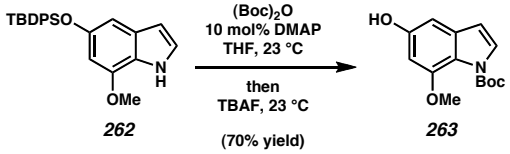
Bis Phenol 261. A solution of indole **260** (500 mg, 1.91 mmol, 1.00 equiv) in CH_2Cl_2 (38.0 mL) was cooled to –10 °C (super-saturated brine/ice bath), and stirred for 5 minutes. At this stage, BBr_3 (3.83 mL of a 1.0 M solution in CH_2Cl_2, 3.83 mmol, 2.00 equiv) was added dropwise over 2 minutes. The reaction was monitored by TLC (20:80 EtOAc:Hexanes), and was complete after ca. 25 minutes. The reaction mixture was quenched and diluted with water, and the solution was allowed to warm to ambient temperature. The layers were separated, and the aqueous layer was extracted 3x with EtOAc, The organic extracts were combined, washed with brine, dried with $MgSO_4$,

filtered, and concentrated in vacuo to provide a crude oil that was purified by flash chromatography using 10:90 EtOAc:Hexanes to provide indole **261** as a white solid (315 mg, 71% yield). R_F = 0.45 (30:70 EtOAc:Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.17 (s, 1H), 7.64 (d, *J* = 3.9 Hz, 1H), 6.52 (d, *J* = 3.9 Hz, 1H), 6.46 (d, *J* = 2.2 Hz, 1H), 6.42 (d, *J* = 2.2 Hz), 4.81 (br, 1H), 1.56 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 154.6, 146.5, 133.4, 126.7, 119.7, 110.9, 102.2, 97.5, 41.2, 29.1; IR (film) 3370, 2982, 2936, 1646, 1603, 1462, 1412, 1340, 1300, 1190 cm^{-1}; HRMS (FAB$^+$) calc'd for $[C_{13}H_{15}O_3N]^+$: *m/z* 233.1052, found 233.1049.



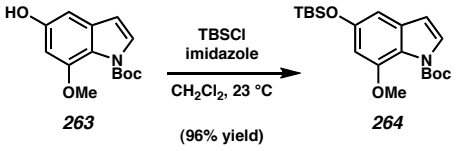
Arene 262. Indole **261** (1.43 g, 6.13 mmol, 1.00 equiv) and imidazole (920 mg, 13.5 mmol, 2.20 equiv) were dissolved in CH_2Cl_2 (61 mL) at ambient temperature. To this solution was added TBDPSCl (1.75 mL, 6.74 mmol, 1.10 equiv), and after 1–2 minutes a white precipitate formed. The reaction mixture was allowed to stir at ambient temperature for 6–12 hours, and monitored by TLC (20:80 EtOAc:Hexanes). Upon completion, the reaction mixture was quenched with water and then diluted with Et_2O. The layers were separated, the aqueous layer was washed 2x with Et_2O, and the organic extracts were combined and washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to provide an oil that was used directly in the next reaction (2.83 g, 98% yield).

To a solution of the previous product (5.85 g, 12.4 mmol, 1.00 equiv) and Bu_4NBr (2.00 g, 6.20 mmol, 0.500 equiv) in CH_2Cl_2 (225 mL) at ambient temperature was added dimethyl sulfate (2.36 mL, 24.8 mmol, 2.00 equiv), and the reaction mixture was allowed to stir for several minutes. At this stage, a solution of NaOH (1.50 mg, 37.2 mmol, 3.00 equiv) in water (225 mL) was added, and the reaction mixture was stirred vigorously and monitored by TLC (20:80 EtOAc:Hexanes). After 3 hours, the reaction was complete, and the layers were separated. The aqueous layer was extracted once with CH_2Cl_2. The organic extracts were combined and washed with water, brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to provide an oil that was purified by flash chromatography using 7:93 EtOAc:Hexanes to provide indole **262** as a white foam (4.60 g, 92% yield, 90% yield over 2 steps). R_F = 0.40 (20:80 EtOAc:Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (br, 1H), 7.78 (app. d, *J* = 6.8 Hz, 4H), 7.40 (m, 6H), 7.08 (s, 1H), 6.60 (s, 1H), 6.28 (s, 1H), 6.20 (s, 1H), 3.75 (s, 3H), 1.18 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 145.7, 135.7, 133.7, 129.6, 128.4, 127.6, 123.8, 121.8, 102.6, 101.9, 97.5, 55.1, 26.7, 19.5; IR (film) 3436, 2958, 2932, 2858, 1586, 1478, 1428, 1313, 1151, 1114 cm^{-1}; HRMS (FAB$^+$) calc'd for $[C_{25}H_{27}O_2SiN]^+$: *m/z* 401.1811, found 401.1831.



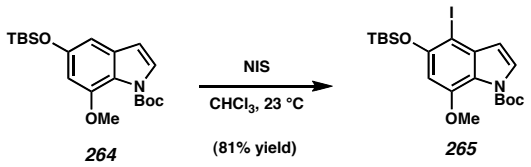
Phenol 263. To a solution of indole **262** (4.41 g, 11.0 mmol, 1.00 equiv) and DMAP (134 mg, 1.10 mmol, 0.100 equiv) in THF (110 mL) at ambient temperature was added $(Boc)_2O$ (2.92 mL, 12.7 mmol, 1.15 equiv), and the reaction was monitored by TLC (20:80 EtOAc:Hexanes). Once complete (ca. 1 h), TBAF (12.1 mL from 1.0 M solution

in THF, 12.1 mmol, 1.10 equiv) was added to the reaction and monitored by TLC (20:80 EtOAc:Hexanes). The reaction was complete after 2–3 hours, and all the volatiles were removed in vacuo to provide an oil that was purified by flash chromatography using 20:80 EtOAc:Hexanes to provide phenol **263** as a light-red oil (2.00 g, 70% yield over 2 steps). R_F = 0.35 (30:70 EtOAc:Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 3.4 Hz, 1H), 6.56 (d, *J* = 2.4 Hz, 1H), 6.41 (d, *J* = 2.4 Hz, 1H), 6.39 (d, *J* = 3.4 Hz, 1H), 5.02 (br, 1H), 3.90 (s, 3H), 1.61 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.6, 149.5, 148.9, 133.9, 129.2, 119.5, 106.7, 98.0, 97.0, 83.1, 55.8, 28.0; IR (film) 3428, 2980, 2935, 1727, 1596, 1369, 1345, 1303, 1258, 1145 cm^{-1}; HRMS (FAB$^+$) calc'd for $[C_{14}H_{17}O_4N]^+$: *m/z* 263.1158, found 263.1167.



Indole 264. To a solution of phenol **263** (575 mg, 2.18 mmol, 1.00 equiv) and imidazole (327 mg, 4.80 mmol, 2.20 equiv) in CH_2Cl_2 (21.8 mL) at ambient temperature was added TBSCl (362 mg, 2.40 mmol, 1.10 equiv), and a white precipitate formed after 1 minute. The reaction mixture was allowed to stir and monitored by TLC (5:95 EtOAc:Hexanes). After 6 hours the reaction was complete. The reaction mixture was filtered through filter paper, washed with CH_2Cl_2, and concentrated in vacuo to provide an oil that was purified by flash chromatography using 3:97 EtOAc:Hexanes to provide indole **264** as a clear oil (1.05 g, 96% yield). R_F = 0.40 (10:90 EtOAc:Hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 3.6 Hz, 1H), 6.60 (d, *J* = 2.0 Hz, 1H), 6.42 (d, *J* = 3.6 Hz, 1H), 6.38 (d, *J* = 2.0 Hz, 1H), 3.91 (s, 3H), 1.63 (s, 9H), 1.01 (s, 3H), 0.23 (s, 6H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 152.3, 149.5, 148.5, 133.7, 128.9, 120.0, 106.9, 103.1, 101.5, 82.9, 55.8, 28.0, 25.8, 18.2, -4.4; IR (film) 2956, 2931, 2858, 1728, 1586, 1473, 1368, 1294, 1150 cm^{-1}; HRMS (FAB^+) calc'd for $[C_{20}H_{31}SiNO_4]^+$: *m/z* 377.2022, found 377.2005.



Arene 265. To a solution of indole **264** (765 mg, 2.03 mmol, 1.00 equiv) in $CHCl_3$ (15.0 mL) at ambient temperature was added *N*-iodosuccinimide (477 mg, 2.13 mmol, 1.05 equiv) in one portion, and the reaction was monitored by TLC (5:95 EtOAc:Hexanes). The reaction mixture color changes upon the addition of NIS from colorless to wine-red over 30–60 minutes. The reaction was complete after 3 hours, and was quenched with H_2O (3.00 mL). To this mixture was added 5 drops of saturated $Na_2S_2O_3$ (aq.), and the mixture was allowed to stir for 20 minutes. At this stage, the layers were separated, the organic layer was diluted with Et_2O, washed once with brine, dried with $MgSO_4$, filtered, concentrated in vacuo to provide a dark oil that was purified by flash chromatography using 5:95 EtOAc:Hexanes to provide arene **265** as a clear oil (830 mg, 81% yield). R_F = 0.40 (30:70 EtOAc:Hexanes); R_F = 0.40 (10:90 EtOAc:Hexanes); ^1H NMR (500 MHz, C_6D_6) δ 7.48 (d, *J* = 3.7 Hz, 1H), 6.58 (d, *J* = 3.7 Hz, 1H), 6.38 (s, 1H), 3.38 (s, 3H), 1.38 (s, 9H), 1.16 (s, 9H), 0.24 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8, 149.8, 138.5, 129.8, 128.7, 120.6, 111.6, 101.0, 83.1, 71.9, 55.8, 28.1, 26.6, 19.0, -3.3; IR (film) 2957, 2931, 2858, 1732, 1574, 1469, 1360, 1292, 1271, 1209, 1158 cm^{-1}; HRMS (FAB^+) calc'd for $[C_{20}H_3O_4NSiI]^+$: *m/z* 503.0989, found 503.1011.

3.9 Notes and References

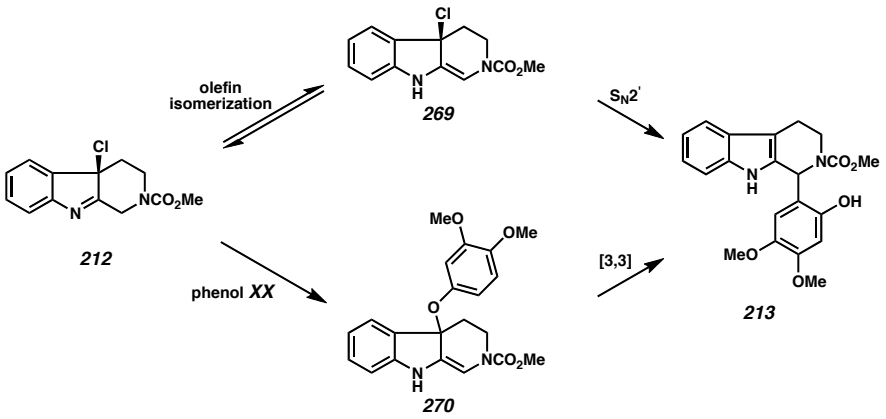
[1] Anderton, N.; Cockrum, P. A.; Colegate, S. M.; Edgar, J. A.; Flower, K.; Gardner, D.; Willing, R. I. *Phytochemistry* **1999**, *51*, 153–157.

[2] Energy minimization calculations for Spartan were accomplished using AM1, equilibration geometry.

[3] Chan, C.; Li, C.; Zhang, F.; Danishefsky, S. J. *Tetrahedron Lett.* **2006**, *47*, 4839–4841.

[4] The phenolic oxygen is bound to C(3) of the indole in the natural product, not C(2).

[5] The mechanism for formation of phenol **213** has not been fully elucidated; however, Danishefsky proposes two possible mechanisms (ref. 3):



[6] For the synthesis of racemic phalarine, see: Li, C.; Chan, C.; Heimann, A. C.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 1448–1550. For the asymmetric synthesis, see: Trzupek, J. D.; Lee, D.; Crowley, B. M.; Marathias, V. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2010**, *132*, 8506–8512.

[7] Li, C.; Chan, C.; Heimann, A. C.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 1444–1447.

[8] Gramine is 2-(*N*,*N*-dimethylaminomethylene)indole.

[9] The synthesis of oxindole **214** required three additional steps starting from tetrahydro-β-carboline **203**. See: ref. 8 for synthetic details.

[10] The mechanisms for the conversion of intermediates **224** and **225** to pentacycle **226** were shown in Schemes 3.2.1 and 3.2.2.

[11] For several examples of palladium(II)-catalyzed oxidative heterocyclizations onto styrenyl olefins, see: a) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, *61*, 3584–3585. b) Larock, R. C.; Wei, L.; Hightower, T. R. *Synlett* **1998**, 522–524. c) Trend, R.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778–17788.

[12] For the synthesis of arene **234**, see: Kataoko, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553–5566.

[13] For the synthesis of vinyl stannane **236**, see: Miyake, H.; Yamamura, K. *Chem. Lett.* **1989**, *18*, 981–984.

[14] For examples of phenol cyclizations, see: a) Larock, R. C.; Wei, L.; Hightower, T. *Synlett* **1998**, 522–524. b) For examples of alcohol cyclizations, see, Rönn, M.; Bäckvall, J.-E.; Andersson, P. G. *Tetrahedron Lett.* **1995**, *36*, 7749–7752. c) For examples of acid cyclizations, see: Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298–5300. d) For examples of tosylamide cyclizations, see: Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, *61*, 3584–3585, and references therein.

[15] a) Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2003**, *42*, 2892–2895. b) Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778–17788.

[16] Most cyclizations of this type using either Stoltz's conditions or DMSO/O_2 require >12 hours for acceptable conversion (>50%).

[17] Liron, F.; Garrec, P. L.; Alami, M. *Synlett* **1999**, 246–248.

[18] Liron, F.; Gervais, M.; Peyrat, J.-F.; Alami, M.; Brion, J.-D. *Tetrahedron Lett.* **2003**, *44*, 2789–2794.

[19] Yin, Y.; Ma, W.; Chai, Z.; Zhao, G. *J. Org. Chem.* **2007**, *72*, 5731–5736.

[20] a) Audia, J. E.; Boisvert, L.; Patten, A. D.; Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 3738–3740. b) Rai, A. N.; Basu, A. *Tetrahedron Lett.* **2003**, *44*, 2267-2269.

[21] Condie, G. C.; Channon, M. F.; Ivory, A. J.; Kumar, N.; Black, D. S. *Tetrahedron* **2005**, *61*, 4989–5004.

[22] Slight modifications to the first two reaction conditions provided higher yields. See S.I. for reaction details.

[23] Henry, L. *Compt. Rend.* **1895**, *120*, 1265. For more recent examples, see: a) Palomo, C.; Oiarbide, M.; Laso, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 3881–3884. b) Chung, W. K.; Chiu, P. *Synlett* **2005**, 55–58. c) Bernardi, L.; Bomini, B. F.; Capito, E.; Dessole, G.; Comes-Franchini, M.; Fochi, M.; Ricci, A. *J. Org. Chem.* **2004**, *69*, 8168–8171.

[24] Conditions screened include: BBr_3, BCl_3, $TiCl_4$, TMSI, and NaSEt with Δ.

[25] All other electron donating protecting groups, as well as a tosyl protecting group, led to C(2) or C(3) functionalization of indole **252**.

[26] Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600–7605.

[27] The formation of the sulfonamide was a surprisingly difficult reaction. The starting aniline and the product seemed to be sensitive to both acid and base, resulting in an unidentified impurity that made purification difficult.

[28] Although we were able to test the palladium(II)-catalyzed oxidative aniline cyclization, it appears that the aniline cyclized onto the wrong olefin Even though it is not conclusive, there is no N-H stretch in the IR, and a HRMS of the products shows a mass corresponding to loss of H_2. Moreover, the ^{1}H NMR clearly shows which vinyl proton remains in the product.

[29] It should be noted that demethylation with one equivalent of BBr_3 cleanly afforded the C(7) mono-demethylated product. Although undesired for our studies, this selective transformation could prove valuable for the synthesis of other natural products or biologically active molecules.

[30] Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004**, *69*, 1126–1136.

[31] a) When the reaction is run with 25 g of arene **251**, the yield for indole **233** is between 40–45%. b) The synthesis of indole **233** is also reported by Borchardt; however, several attempts using this procedure resulted in 30–40% yields of indole **233**, see: Sinhababu, A. K.; Borchardt, R. T. *J. Org. Chem.* **1983**, *48*, 3347–3349.

[32] Indole **254** should be kept in a –20 °C freezer under Ar, away from light.

[33] Indole **255** can also be recrystallized from hot EtOH. However, prolonged heating to dissolve the final 5% of solid should be avoided, as decomposition and darkening of the solution occurs. Instead, once 95% of indole **255** has dissolved, perform a hot filtration and rinse, followed by cooling to effect crystallization and avoid decomposition.

Appendix 3.1

Spectra of Compounds Relevant to Chapter Three

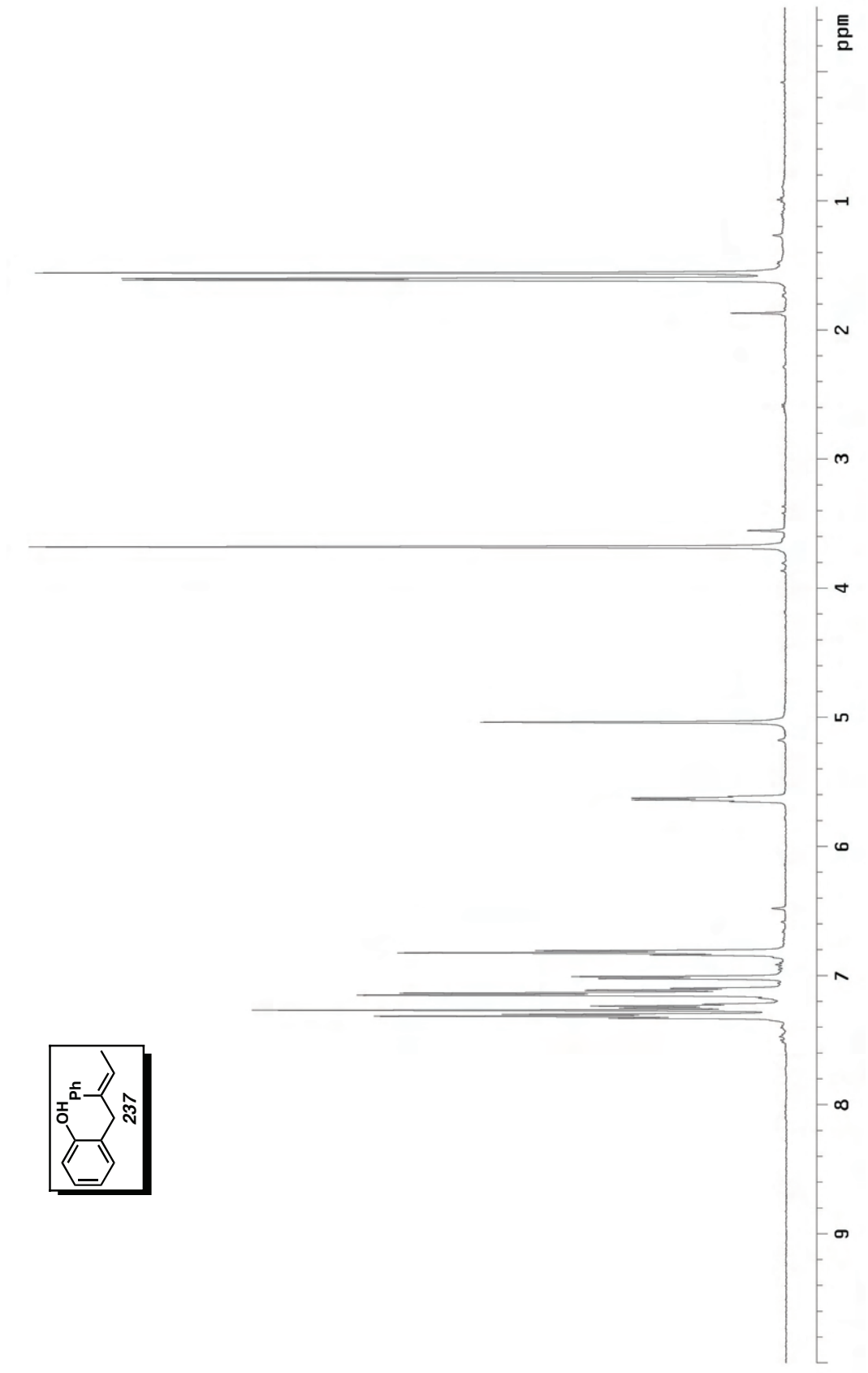


Figure A3.1.1 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **237**

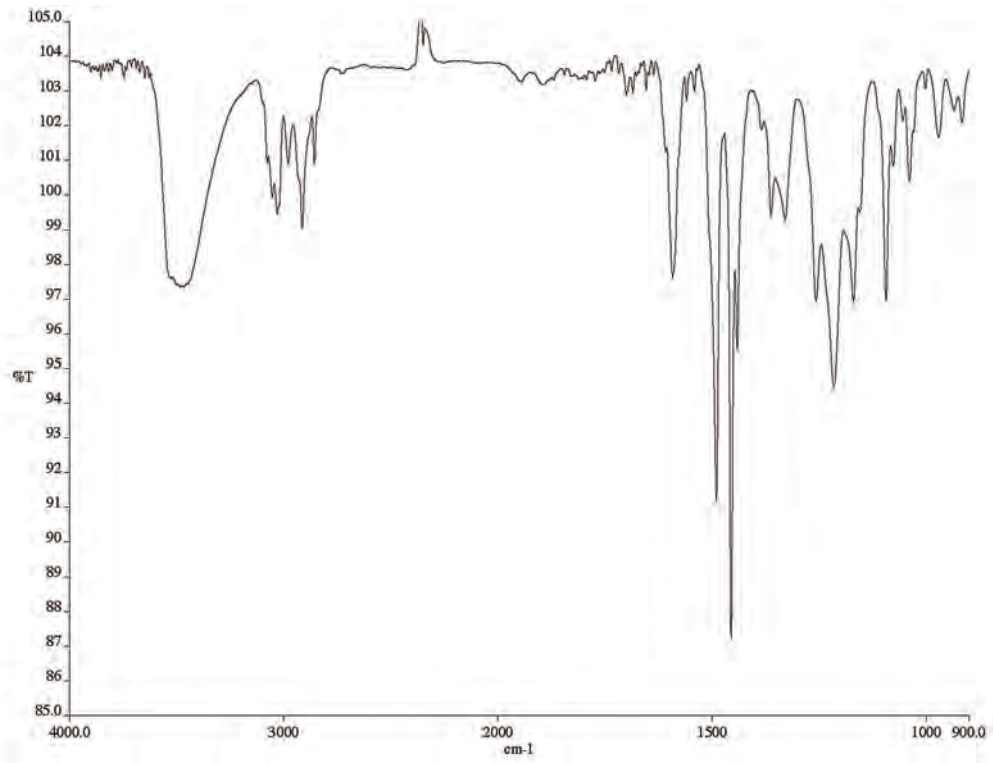


Figure A3.1.2 Infrared spectrum (film/NaCl) of compound **237**

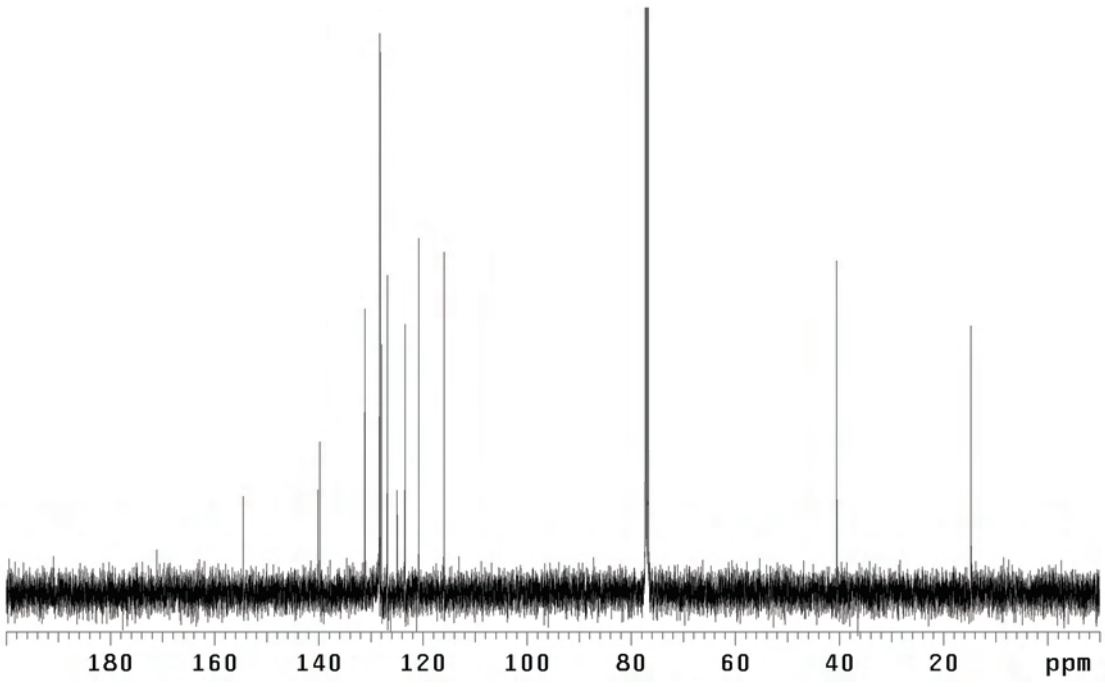


Figure A3.1.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **237**

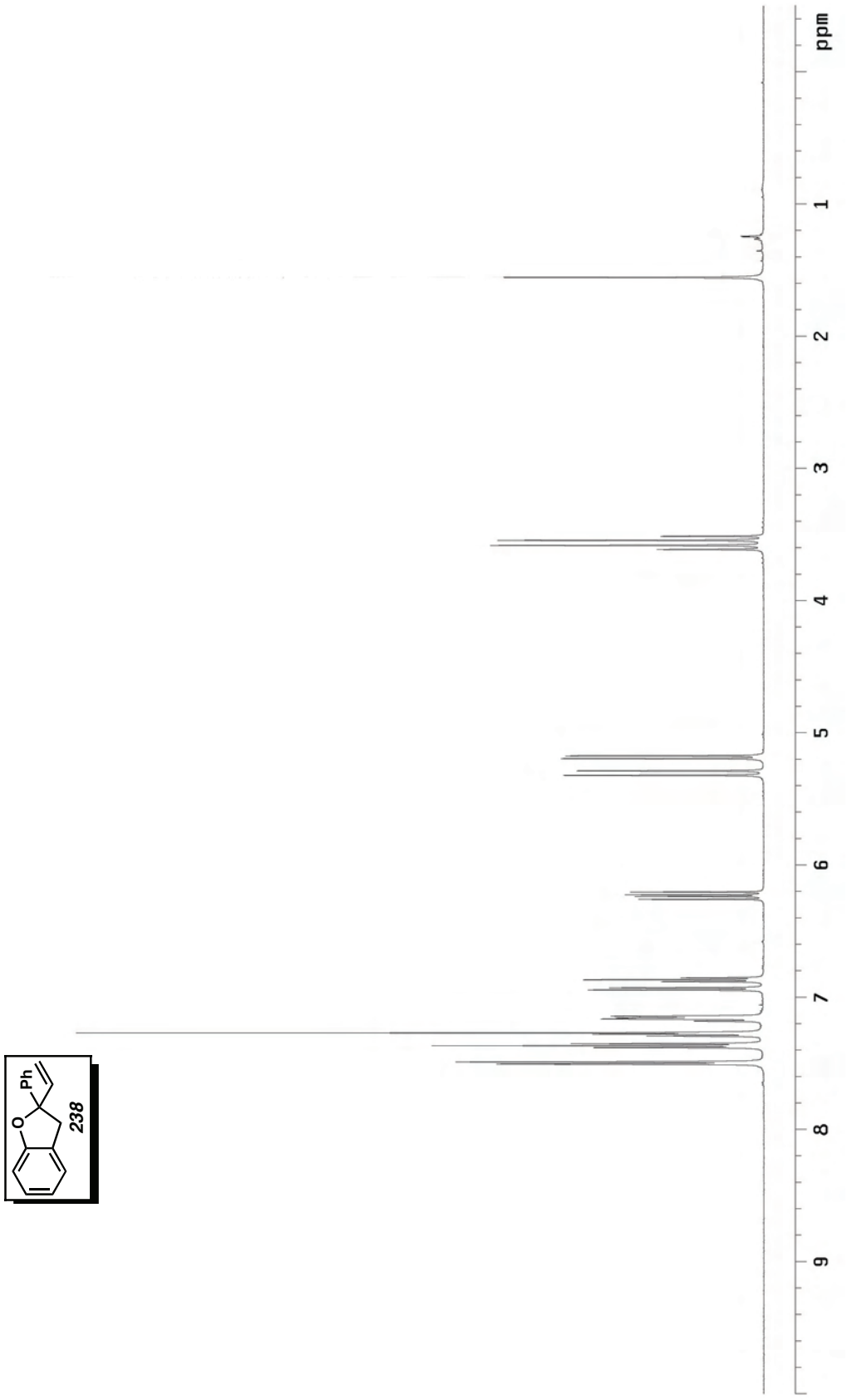


Figure A3.1.4 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **238**

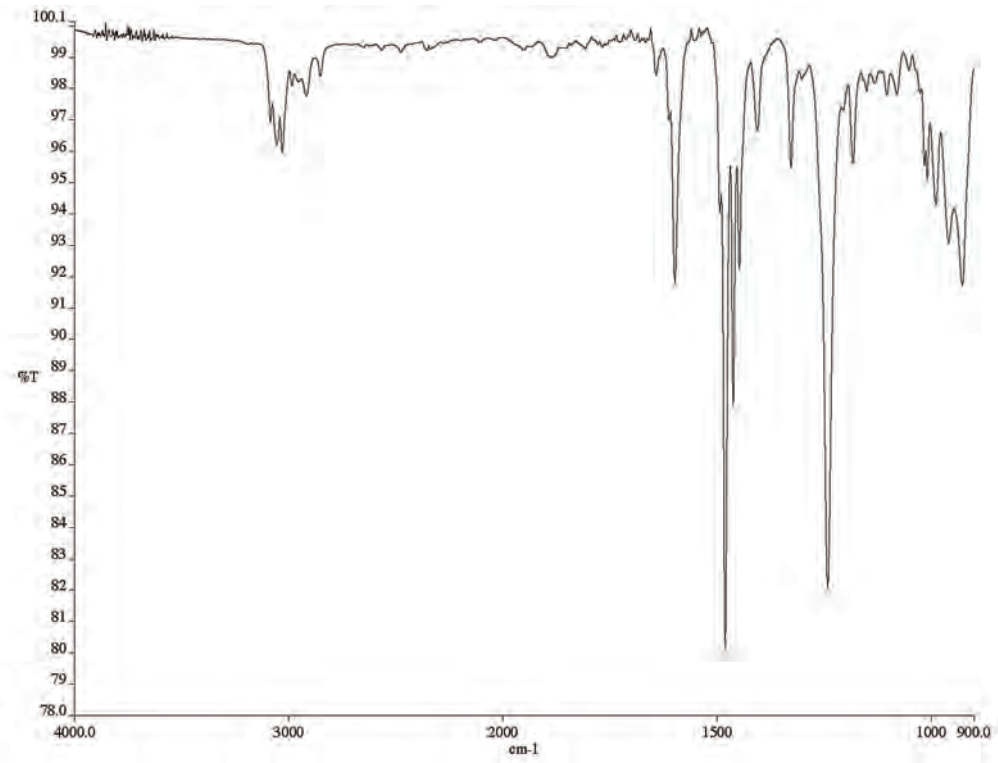


Figure A3.1.5 Infrared spectrum (film/NaCl) of compound **238**

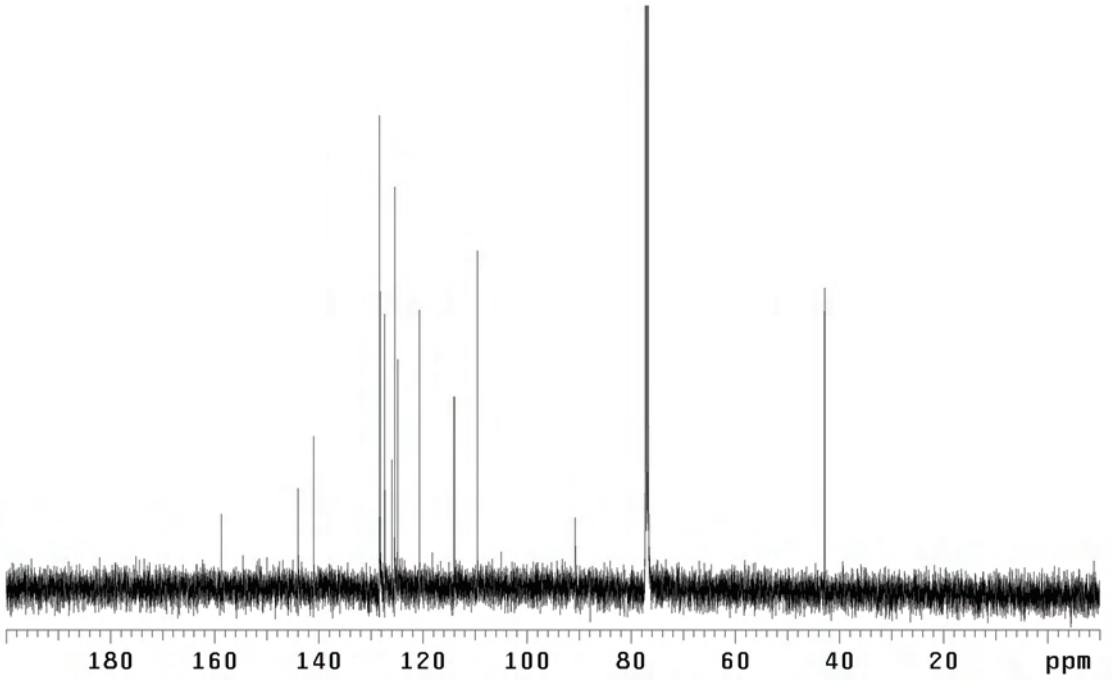


Figure A3.1.6 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **238**

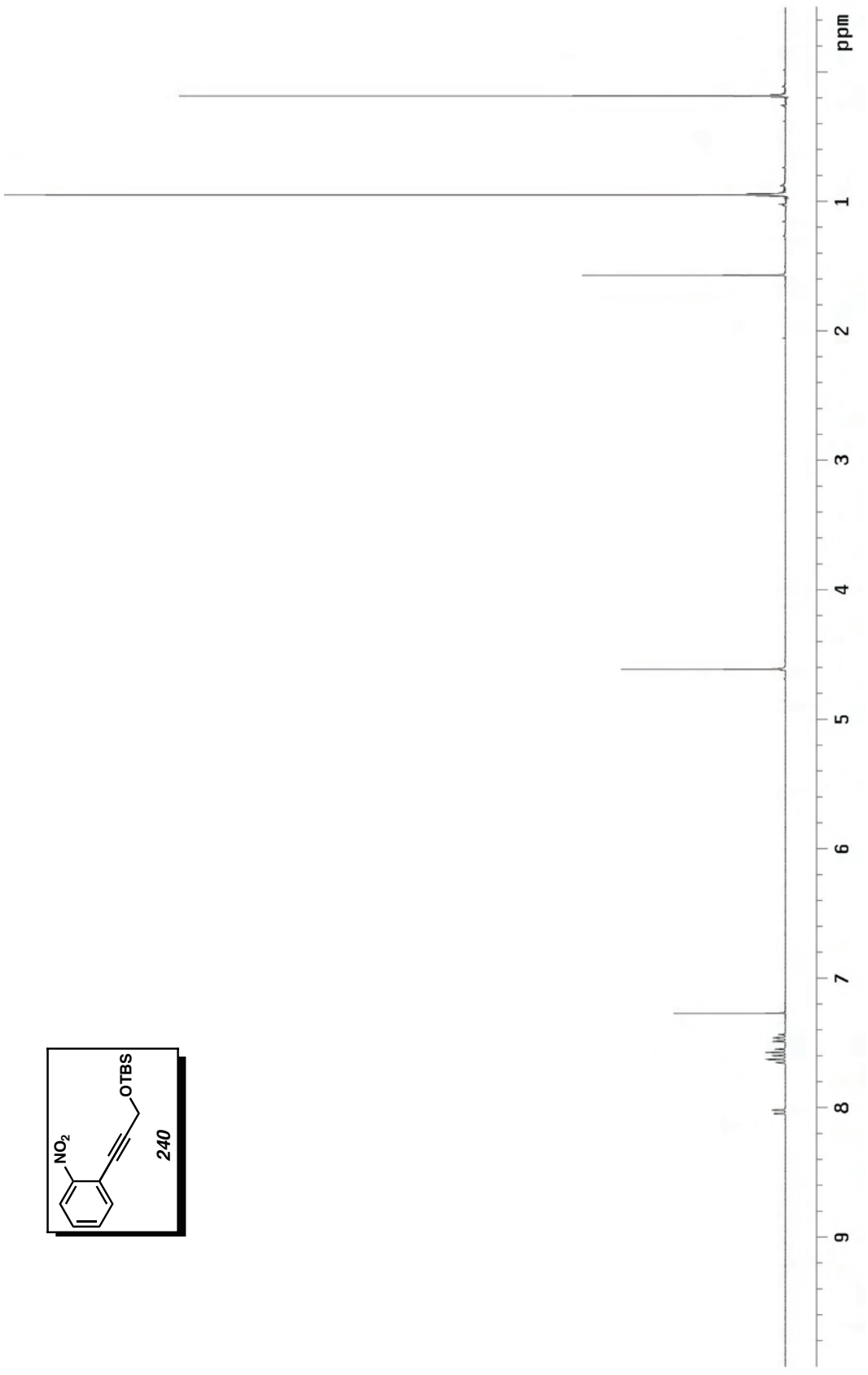


Figure A3.1.7 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **240**

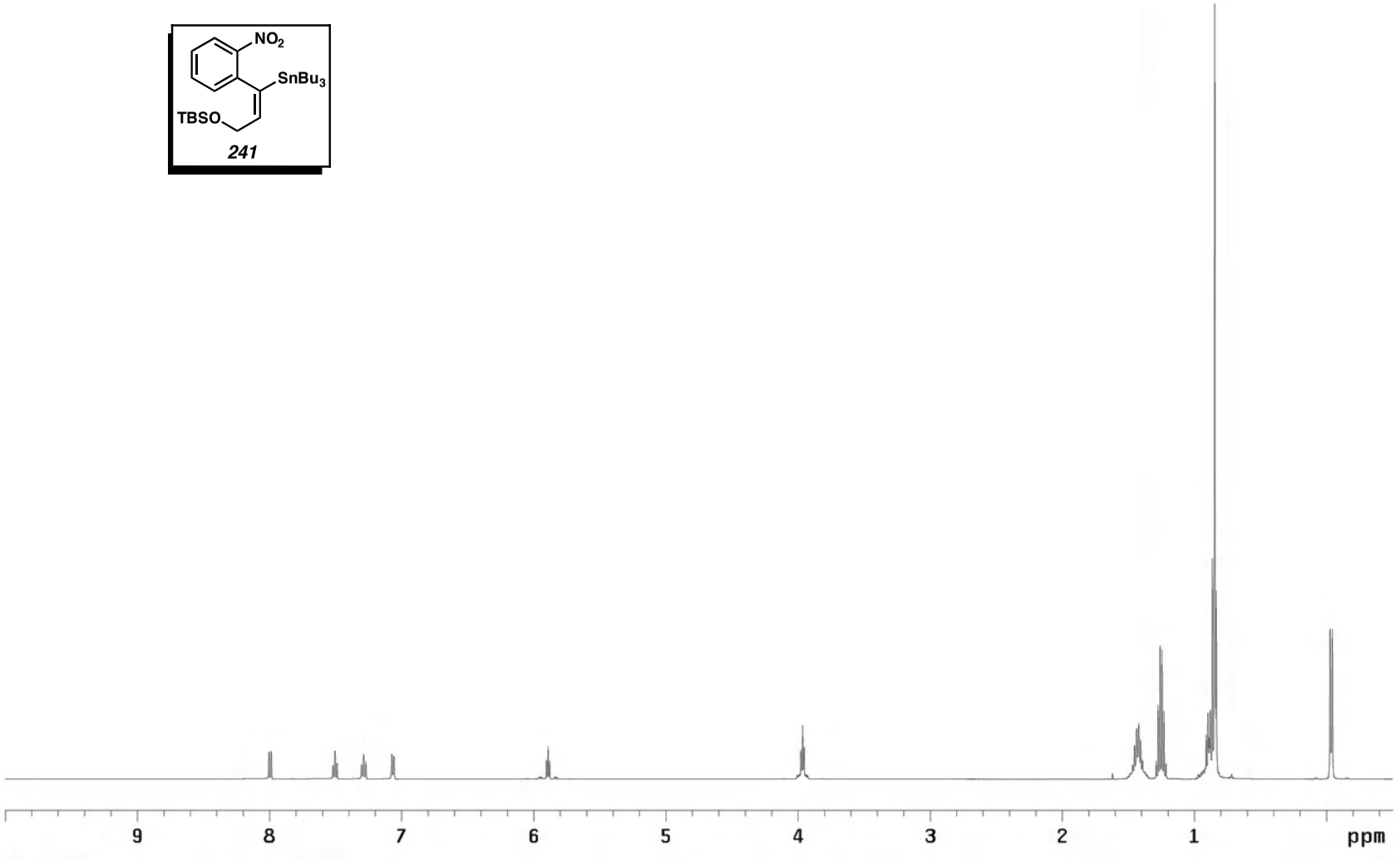


Figure A3.1.8 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **241**

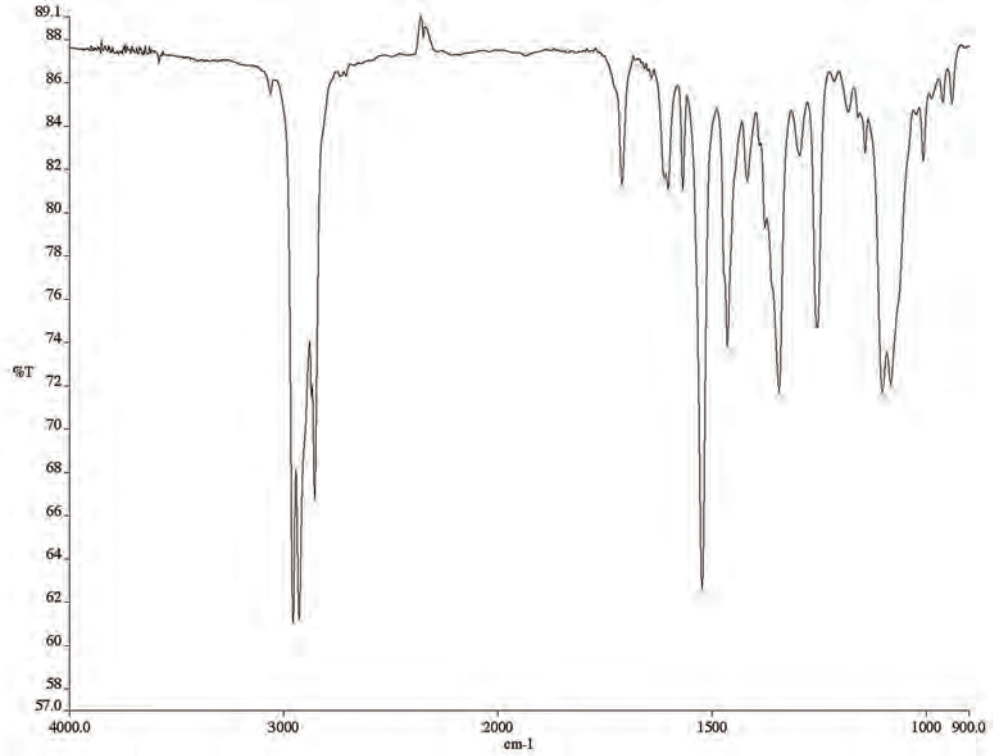


Figure A3.1.9 Infrared spectrum (film/NaCl) of compound **241**

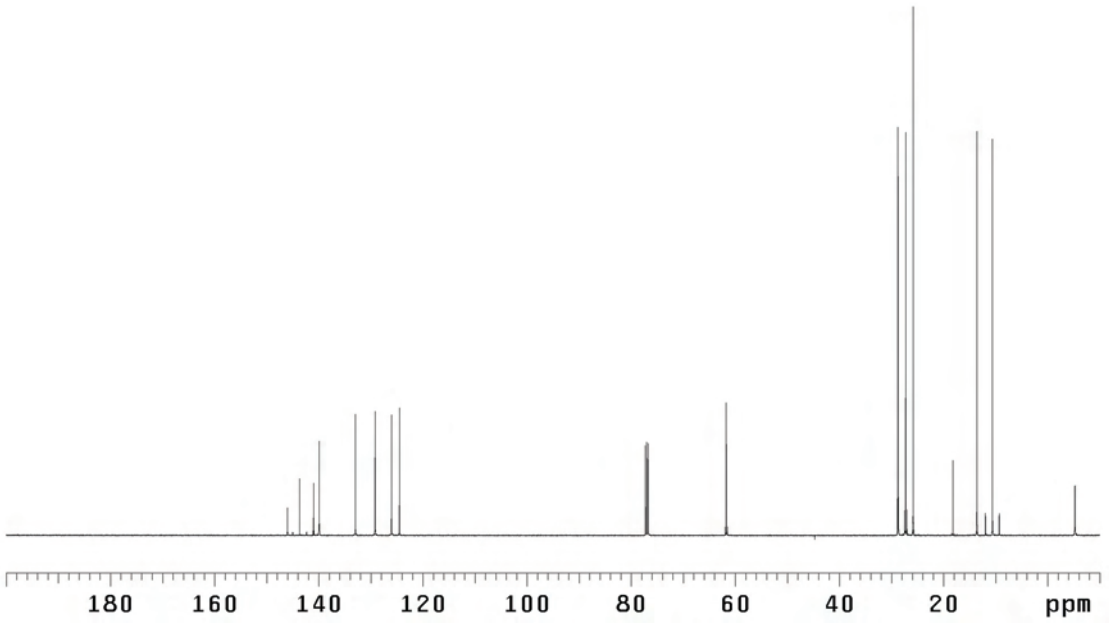


Figure A3.1.10 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **241**

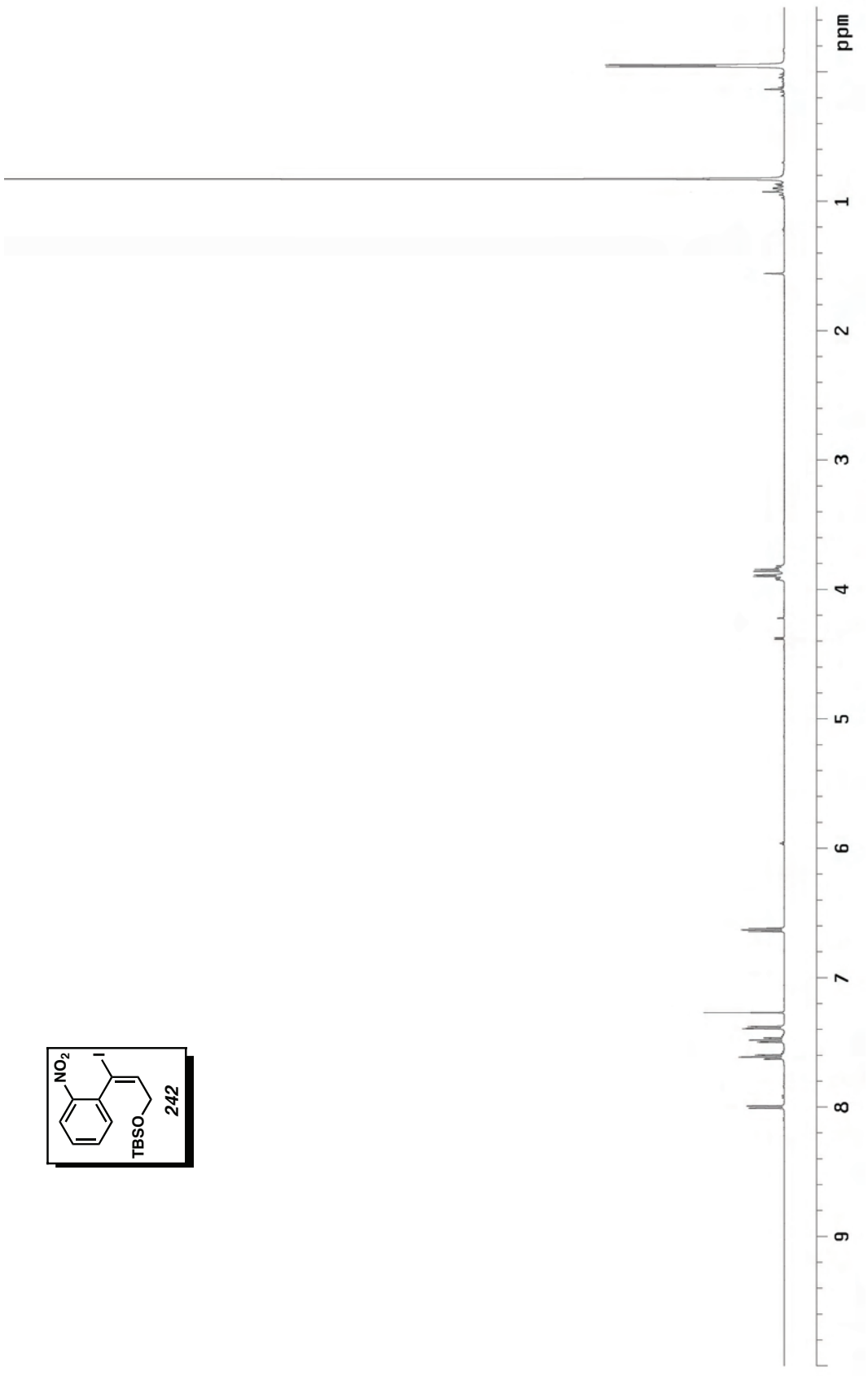


Figure A3.1.11 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **242**

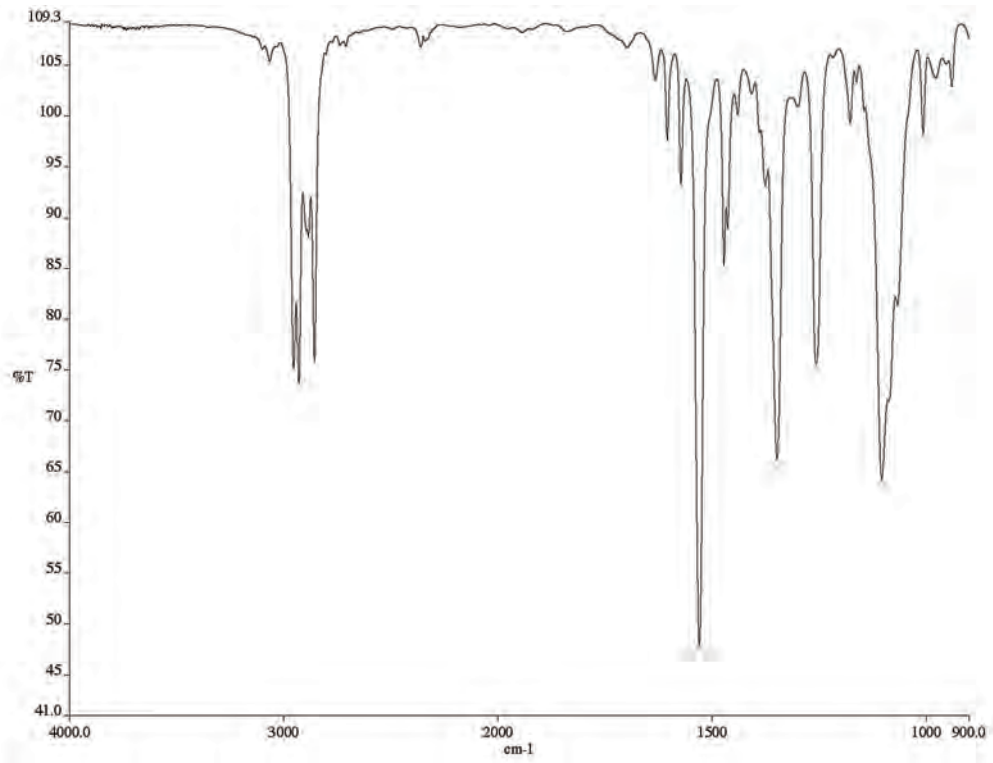


Figure A3.1.12 Infrared spectrum (film/NaCl) of compound **242**

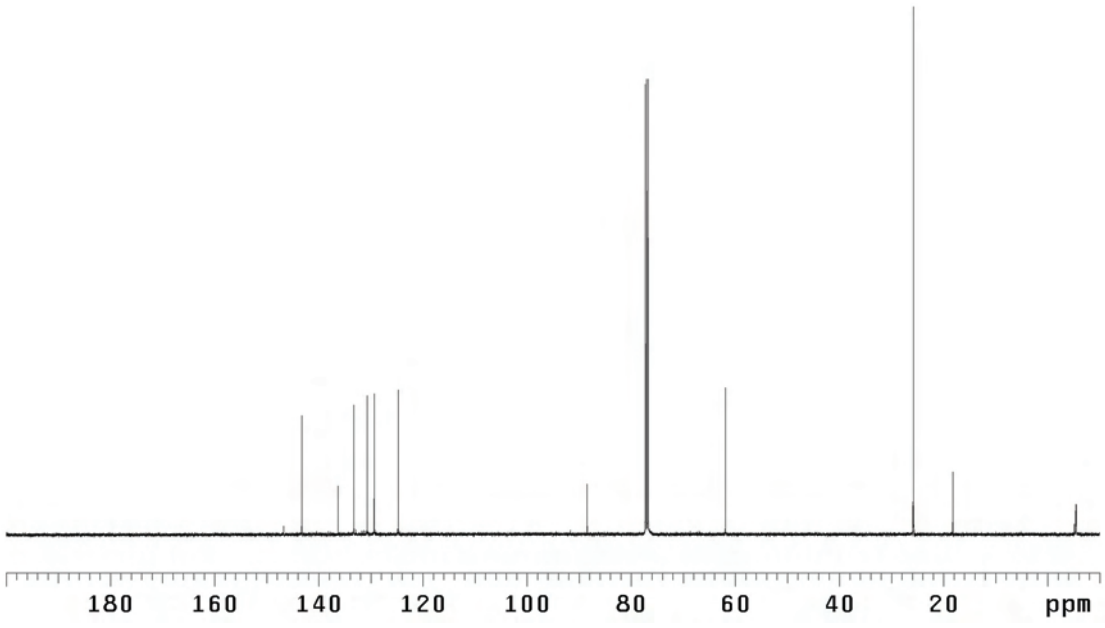


Figure A3.1.13 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **242**

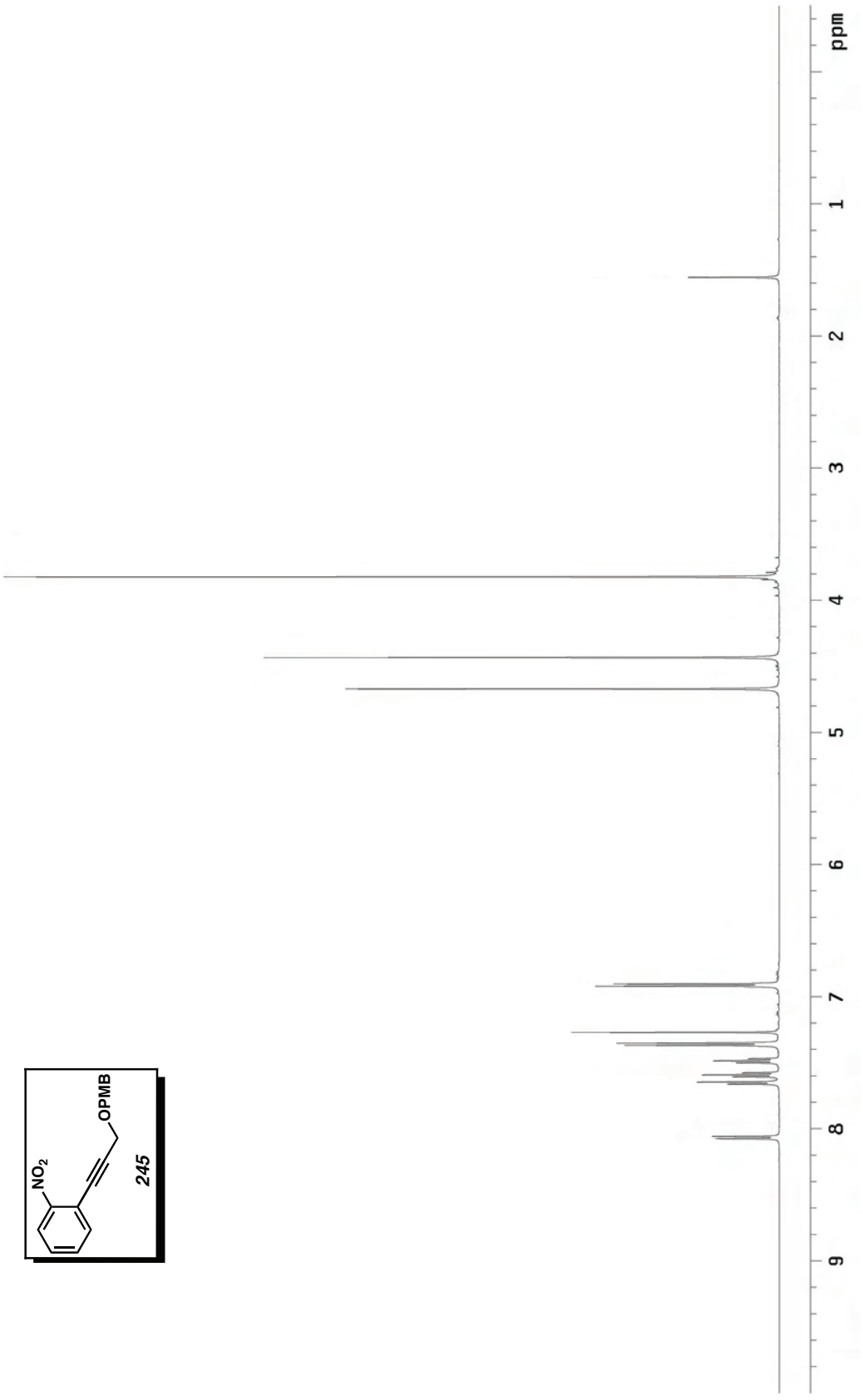


Figure A3.1.14 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **245**

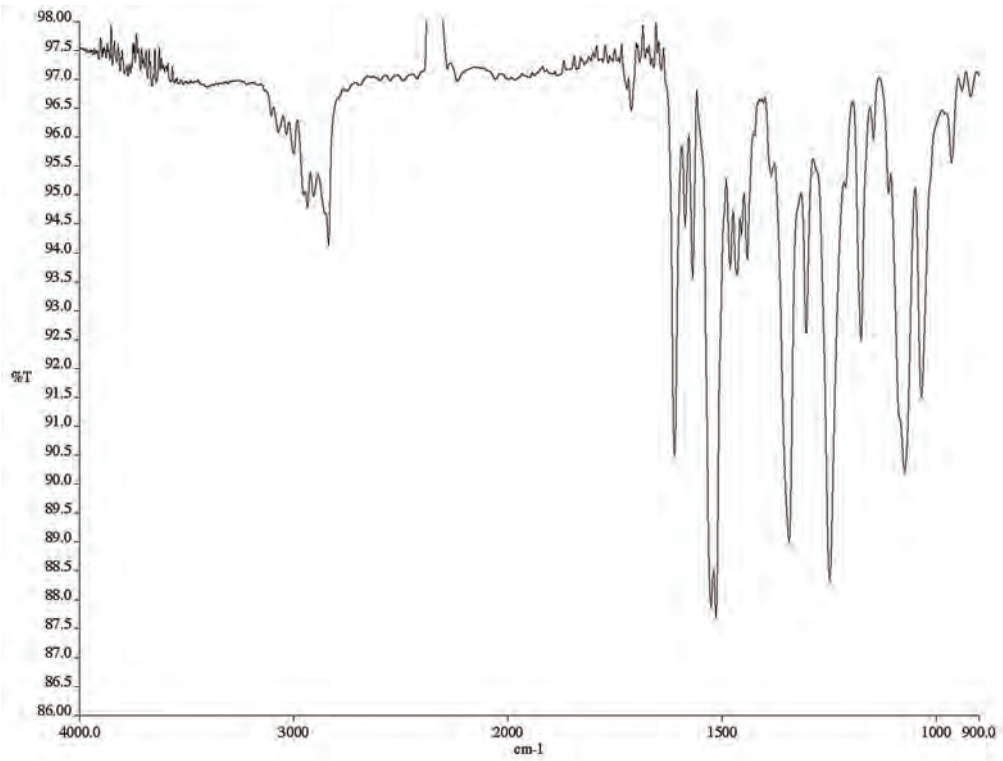


Figure A3.1.15 Infrared spectrum (film/NaCl) of compound **245**

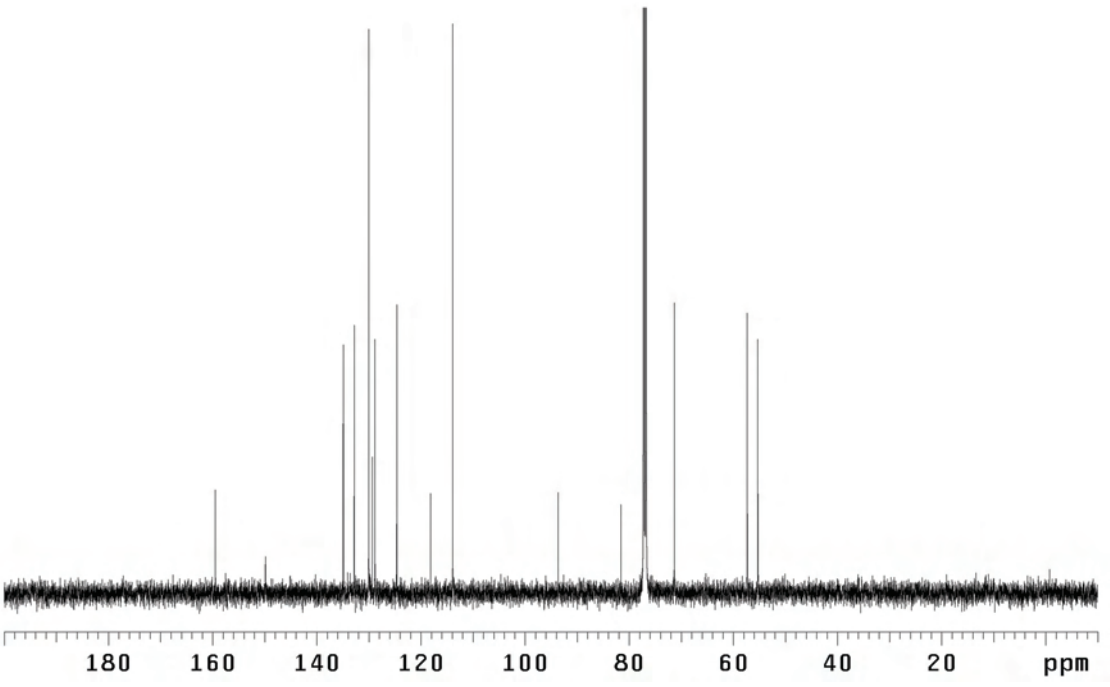


Figure A3.1.16 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **245**

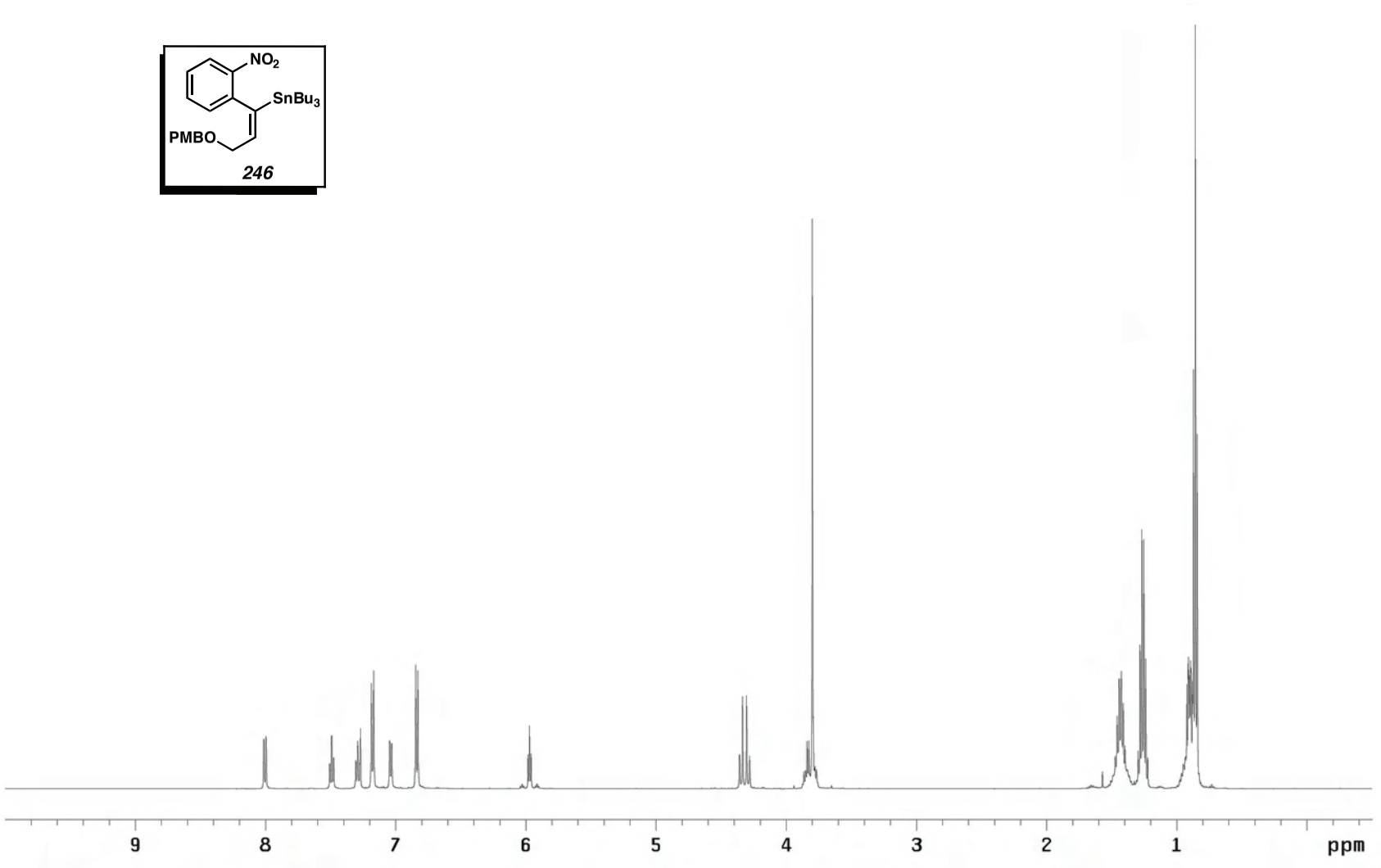


Figure A3.1.17 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **246**

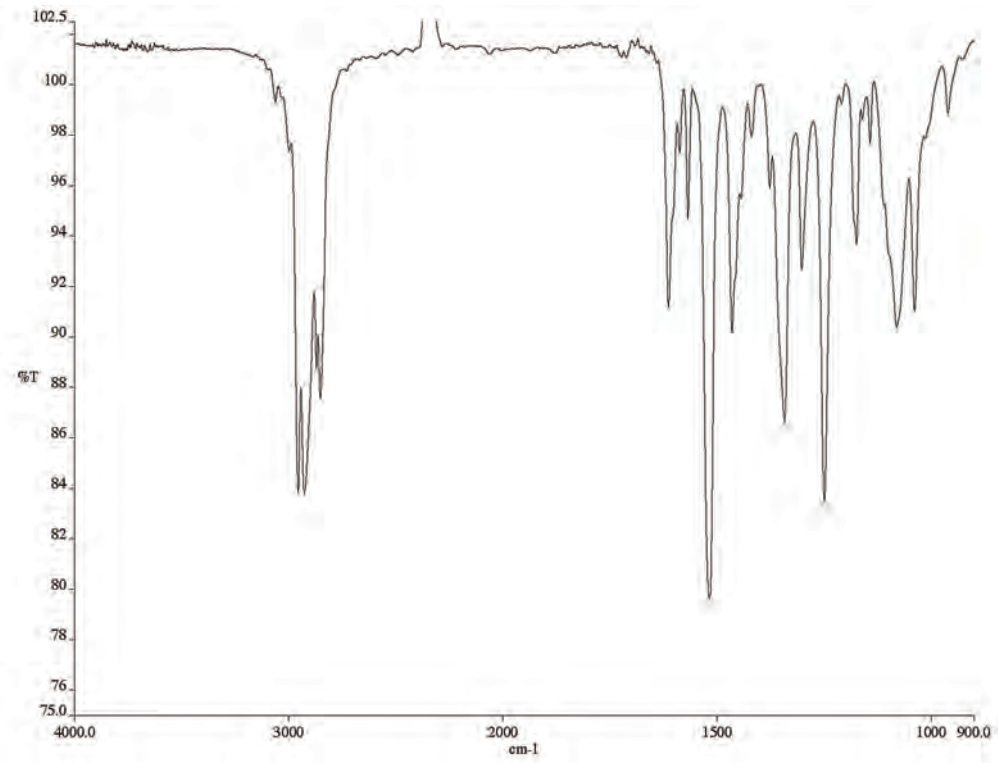


Figure A3.1.18 Infrared spectrum (film/NaCl) of compound **246**

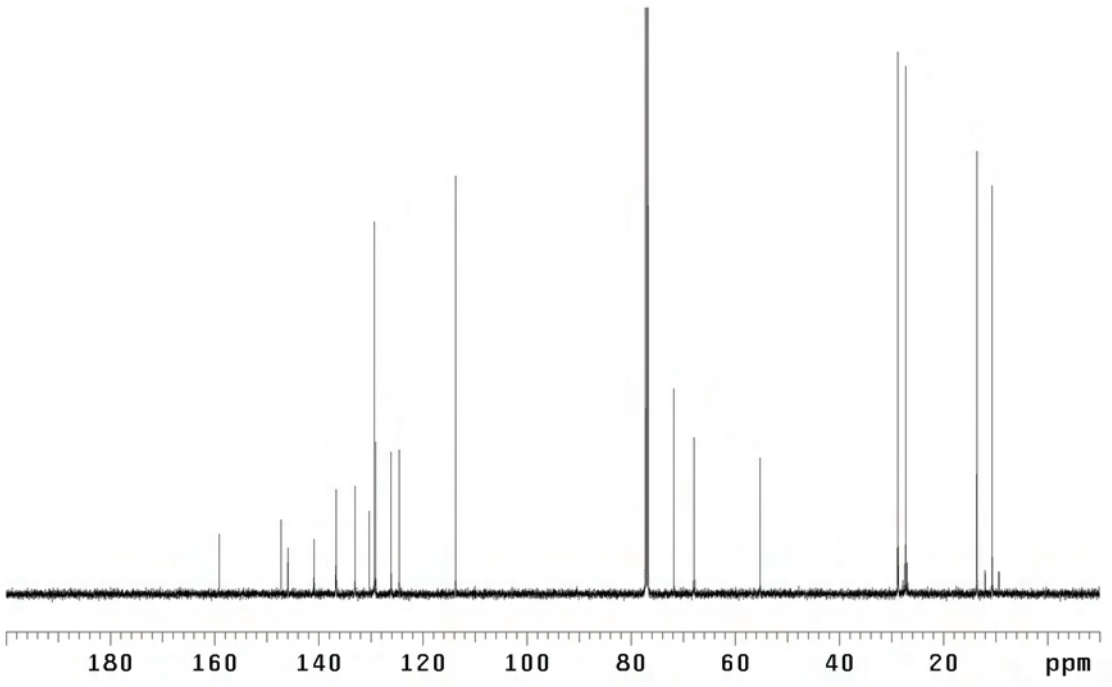


Figure A3.1.19 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **246**

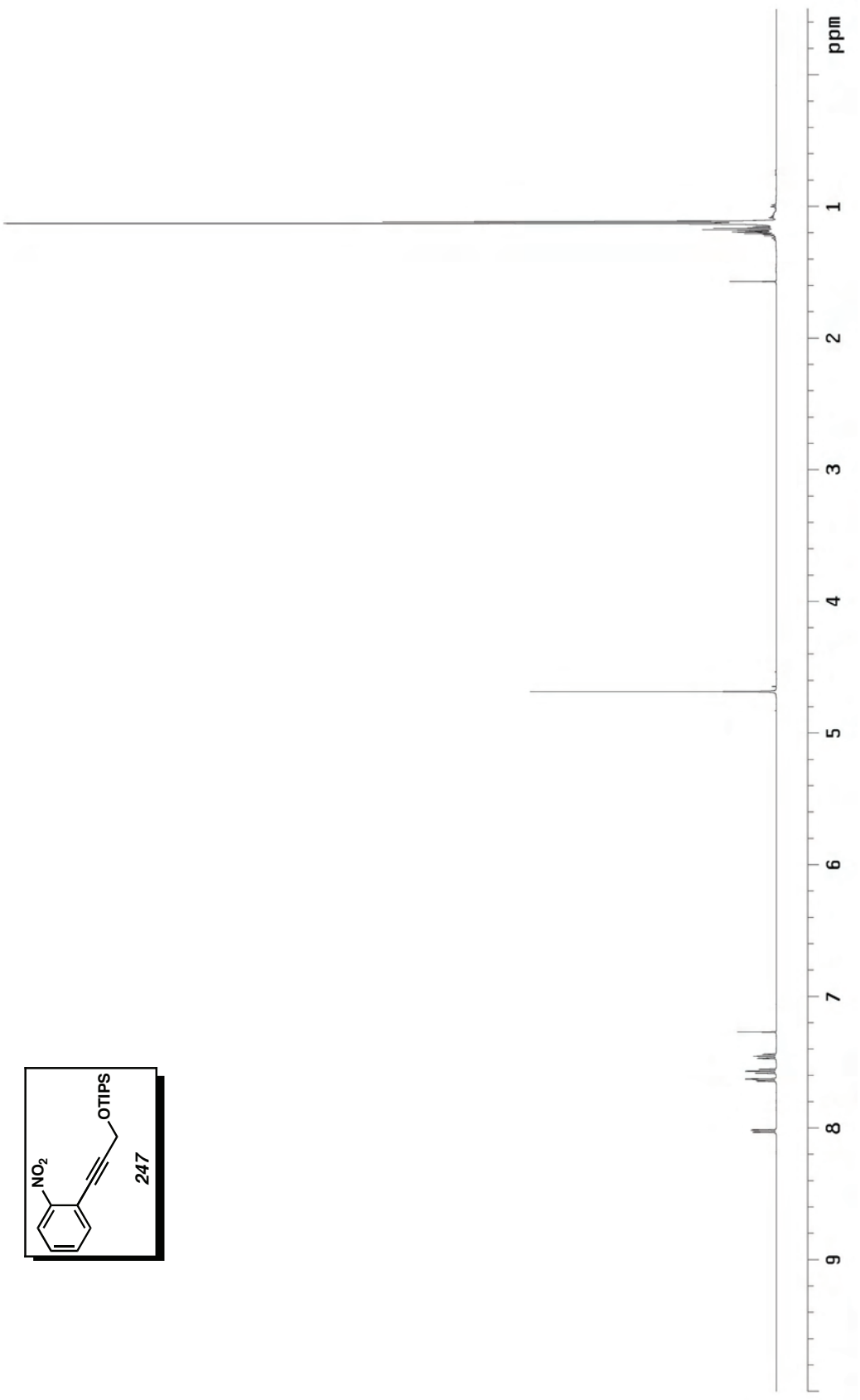


Figure A3.1.20 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **247**

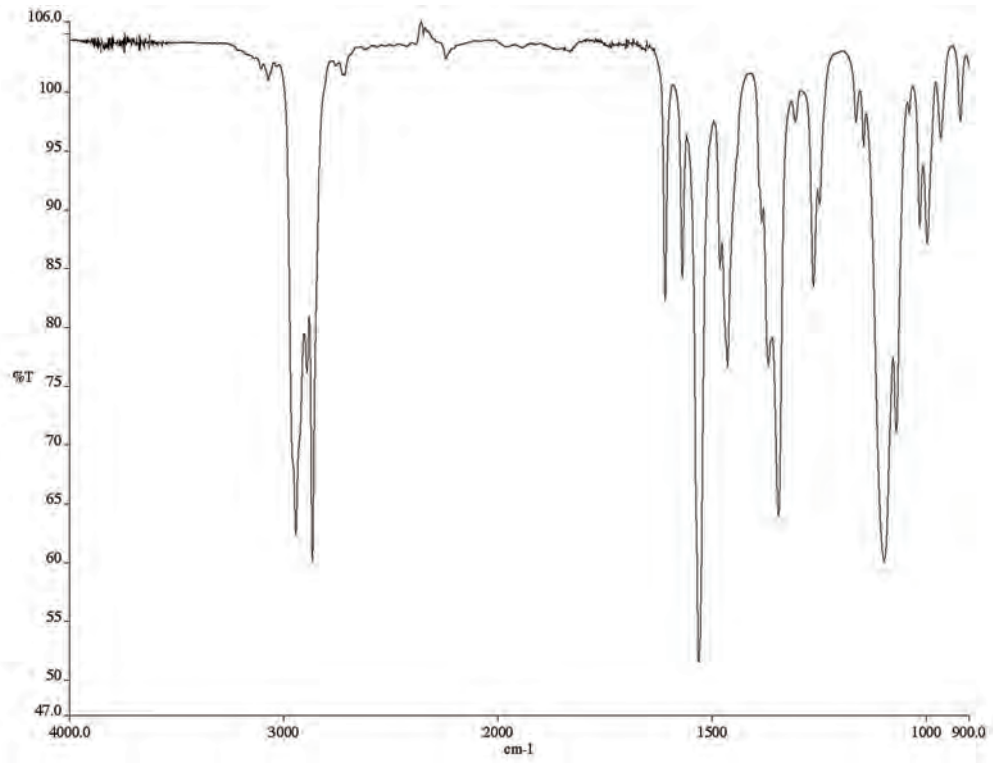


Figure A3.1.21 Infrared spectrum (film/NaCl) of compound **247**

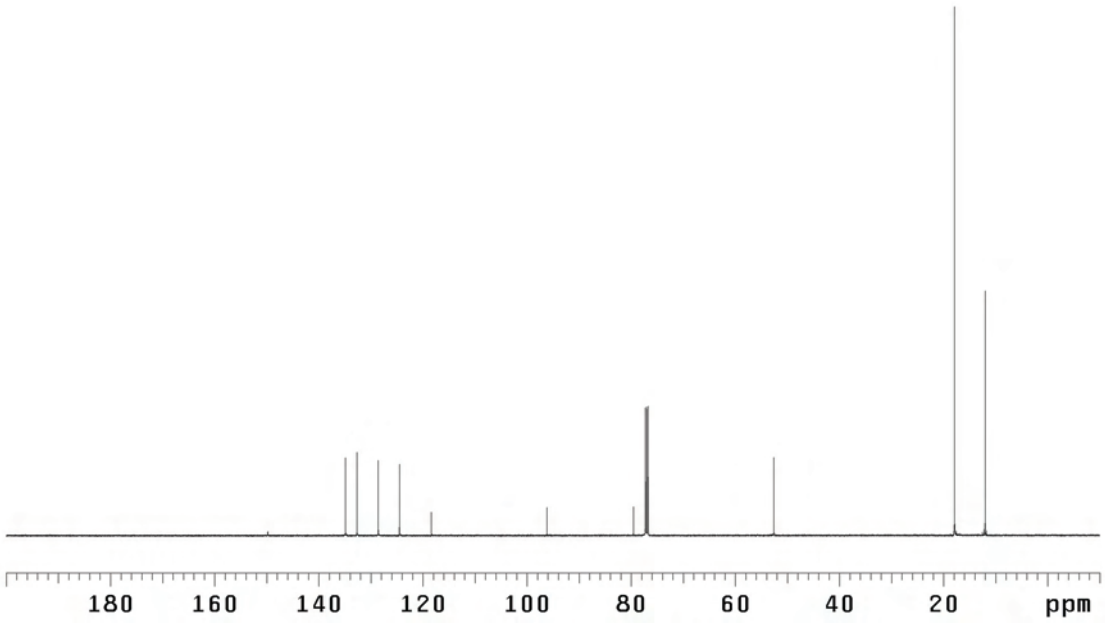


Figure A3.1.22 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **247**

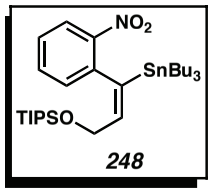


Figure A3.1.23 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **248**

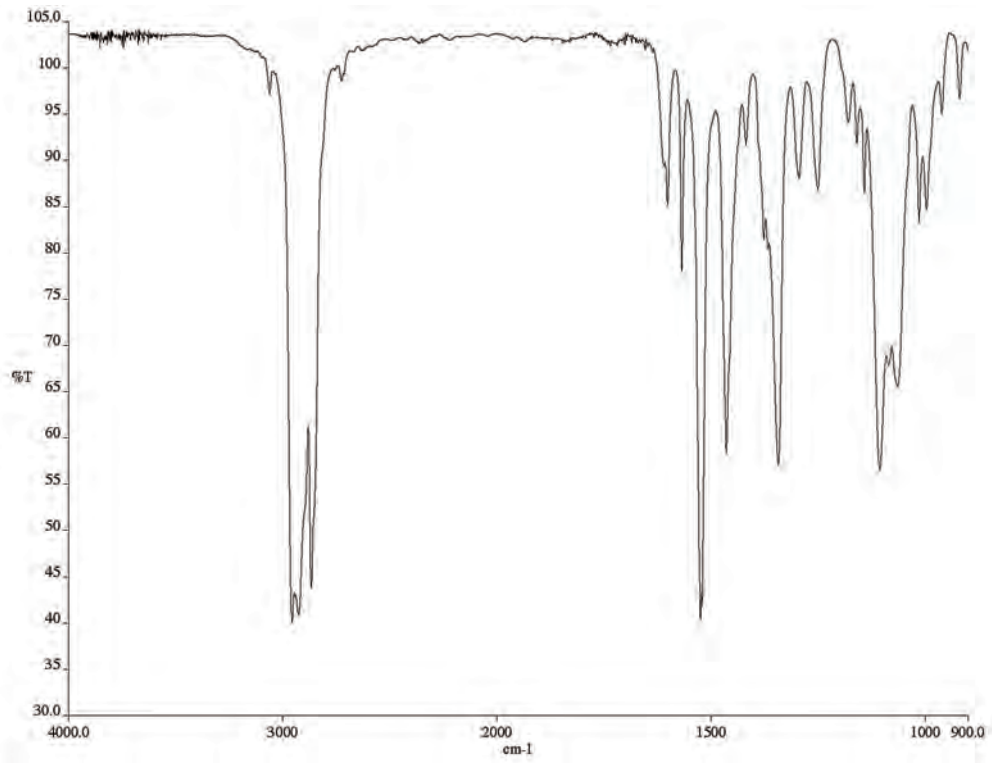


Figure A3.1.24 Infrared spectrum (film/NaCl) of compound **248**

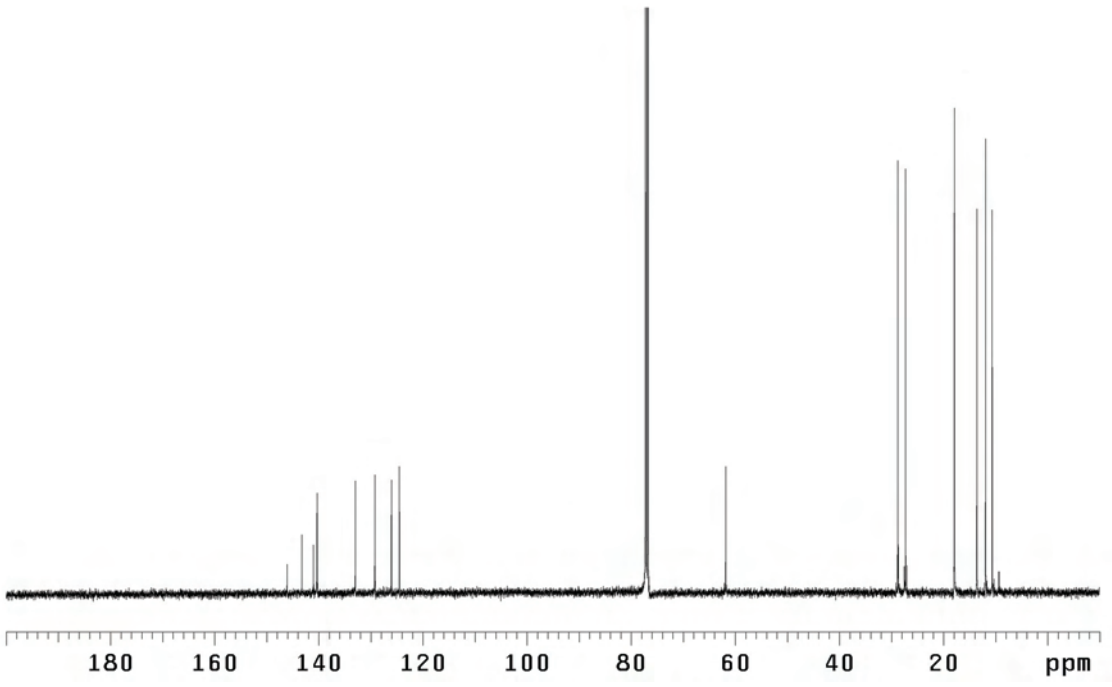


Figure A3.1.25 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **248**

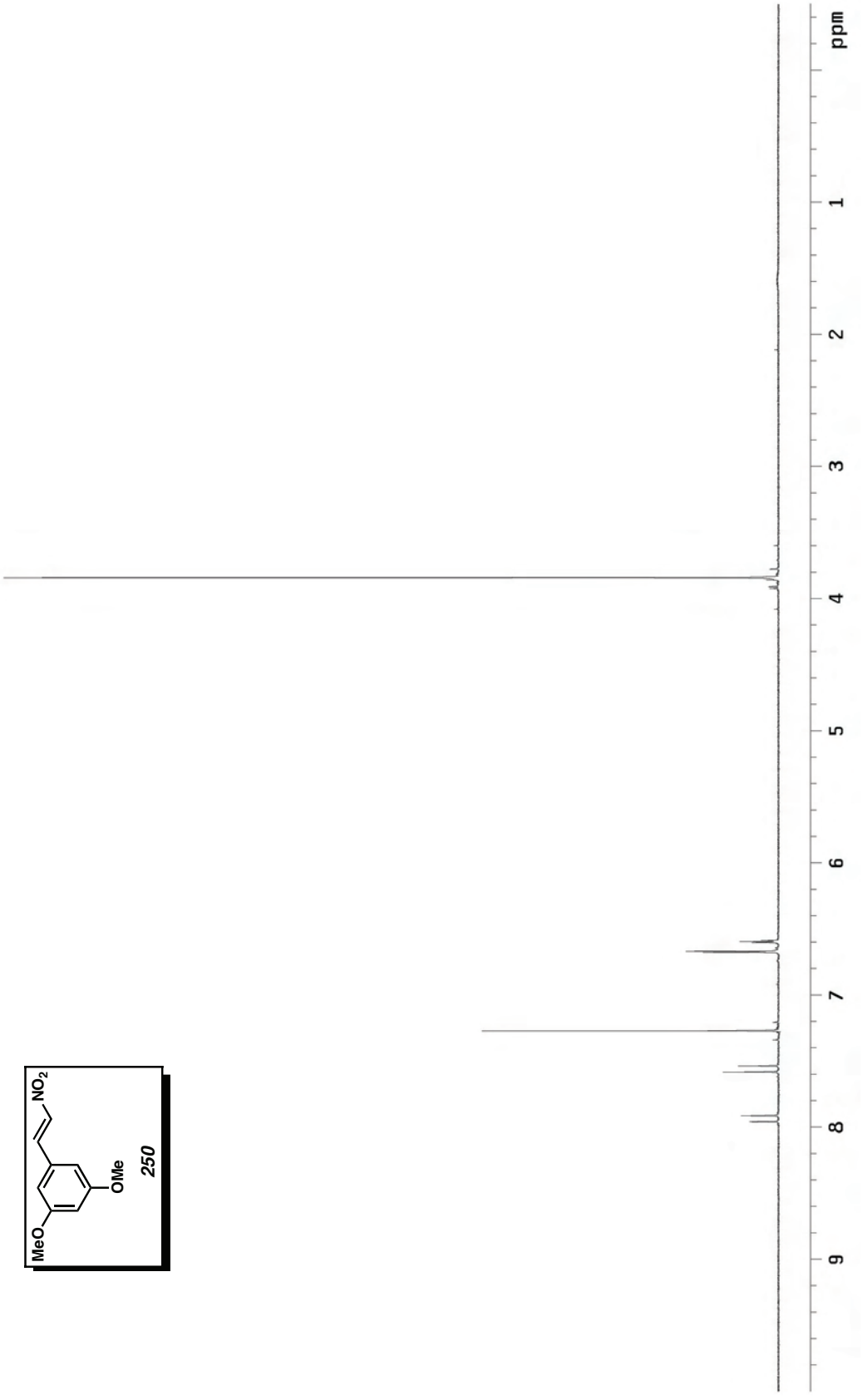


Figure A3.1.26 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **250**

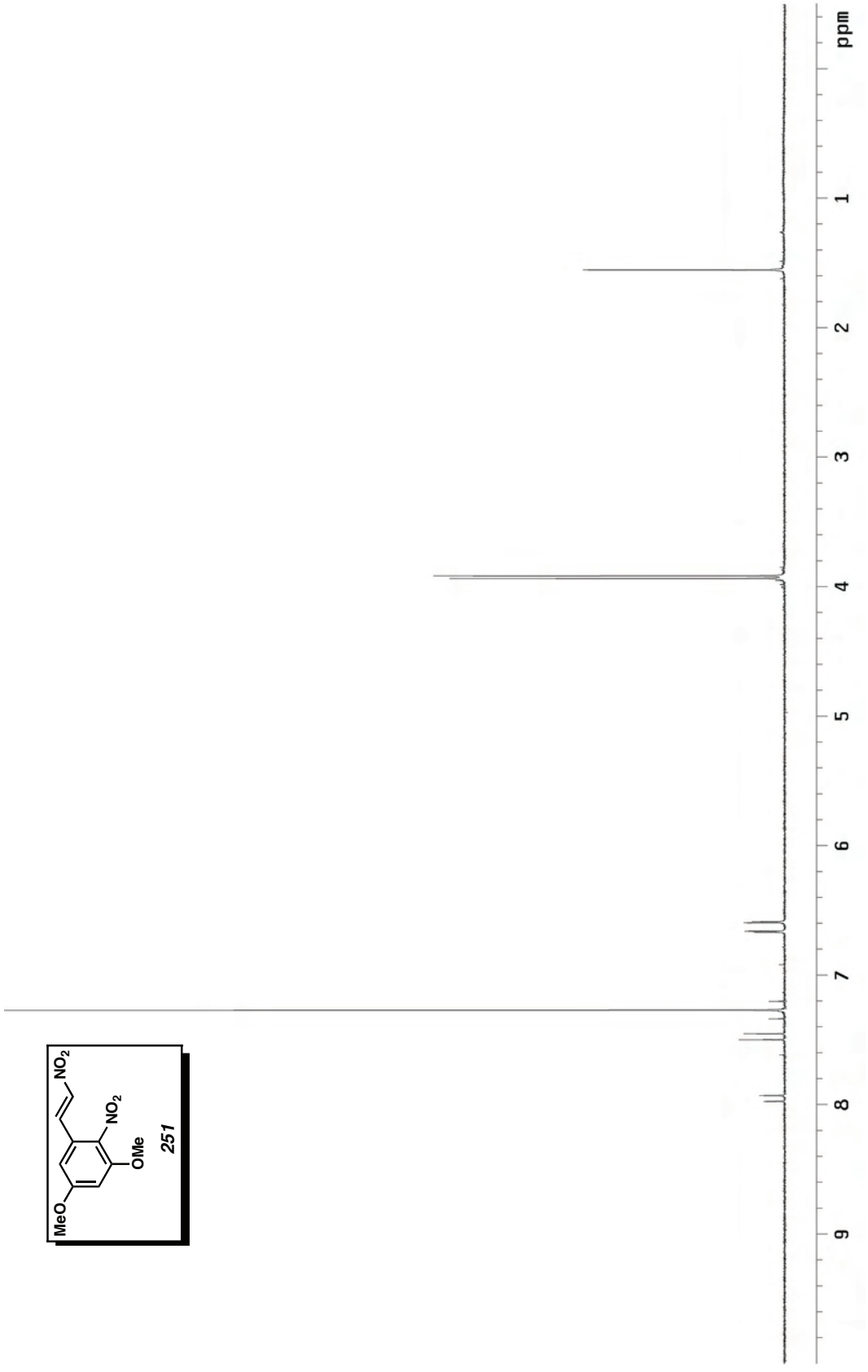


Figure A3.1.27 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **251**

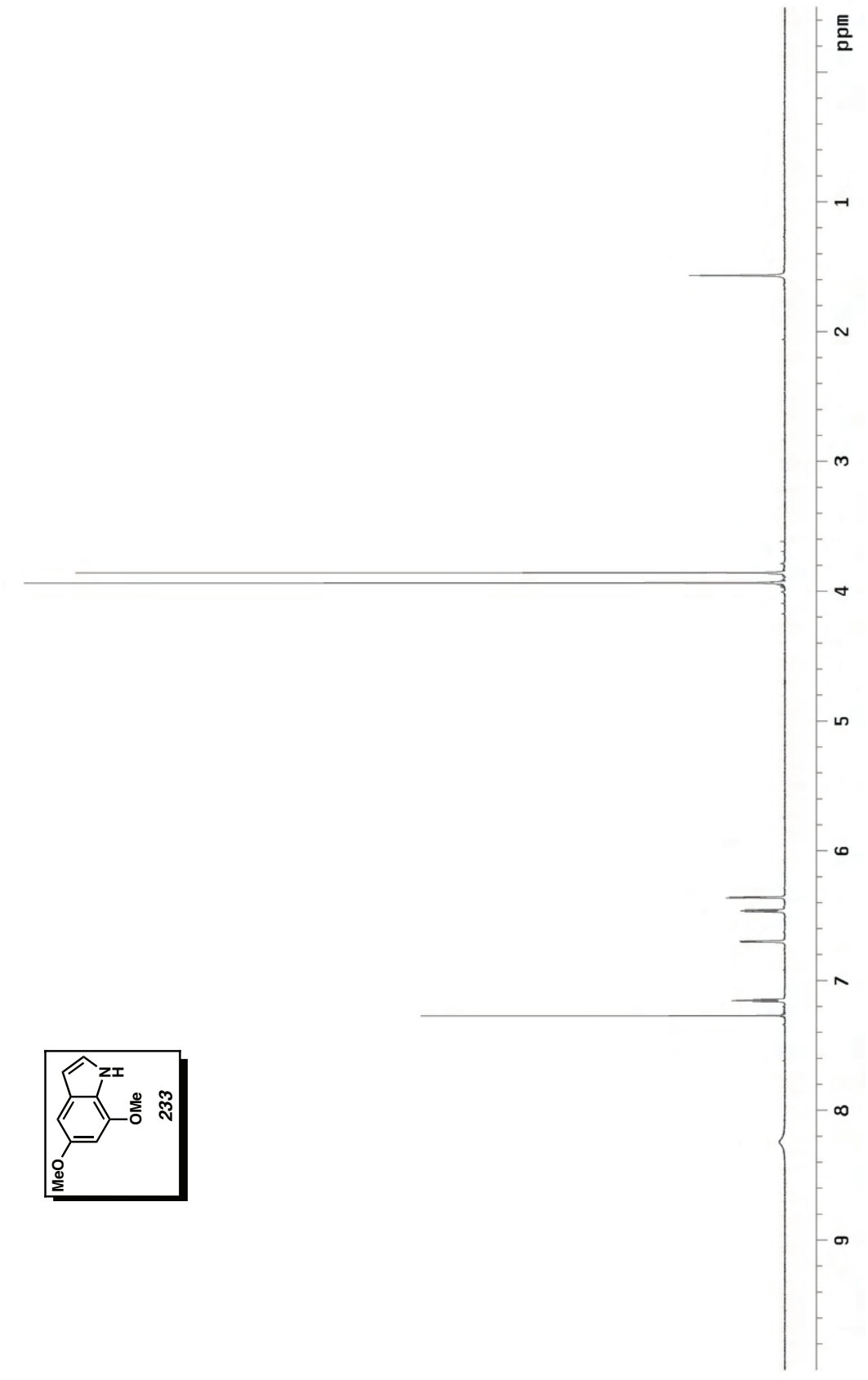


Figure A3.1.28 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **233**

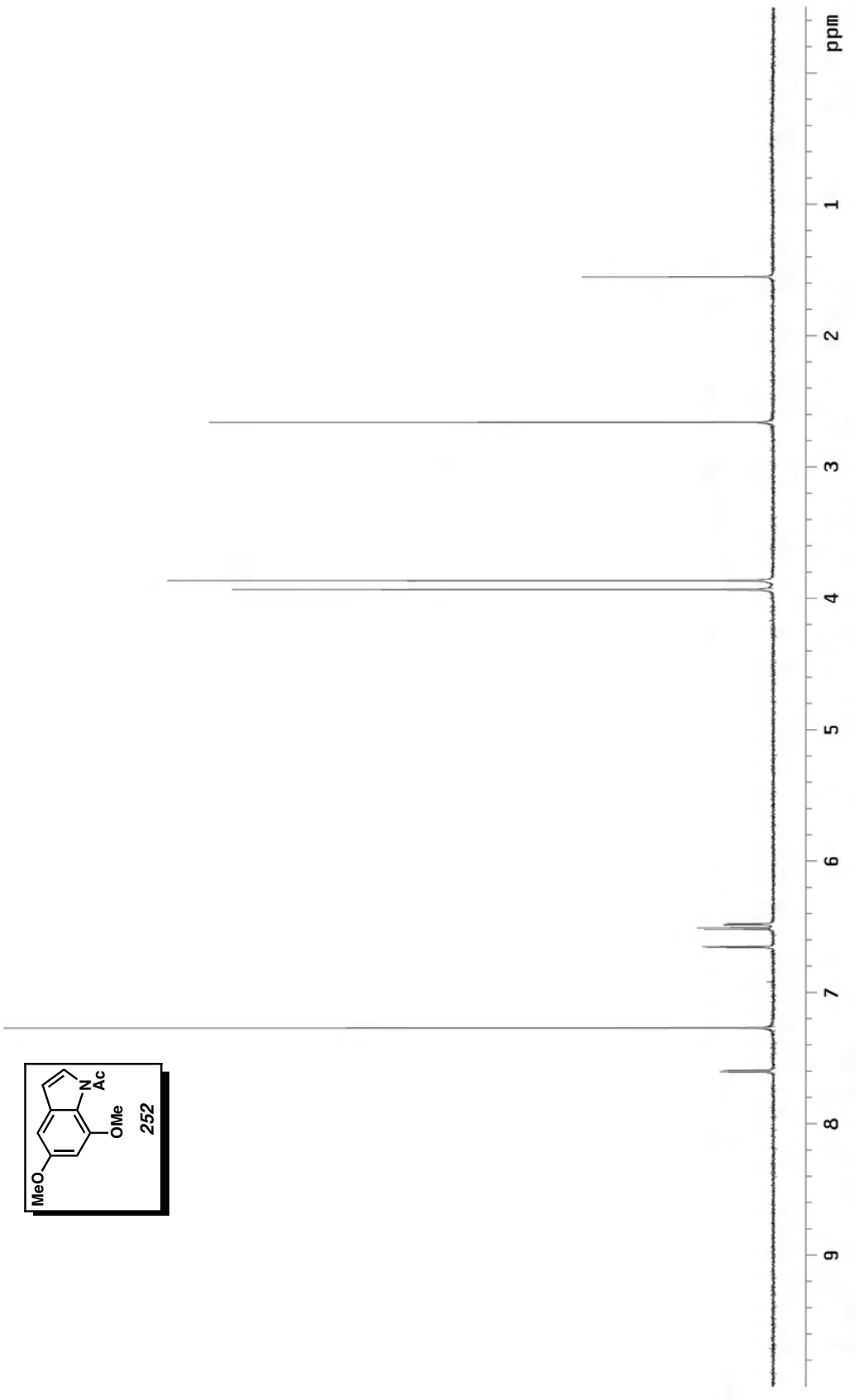


Figure A3.1.29 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **252**

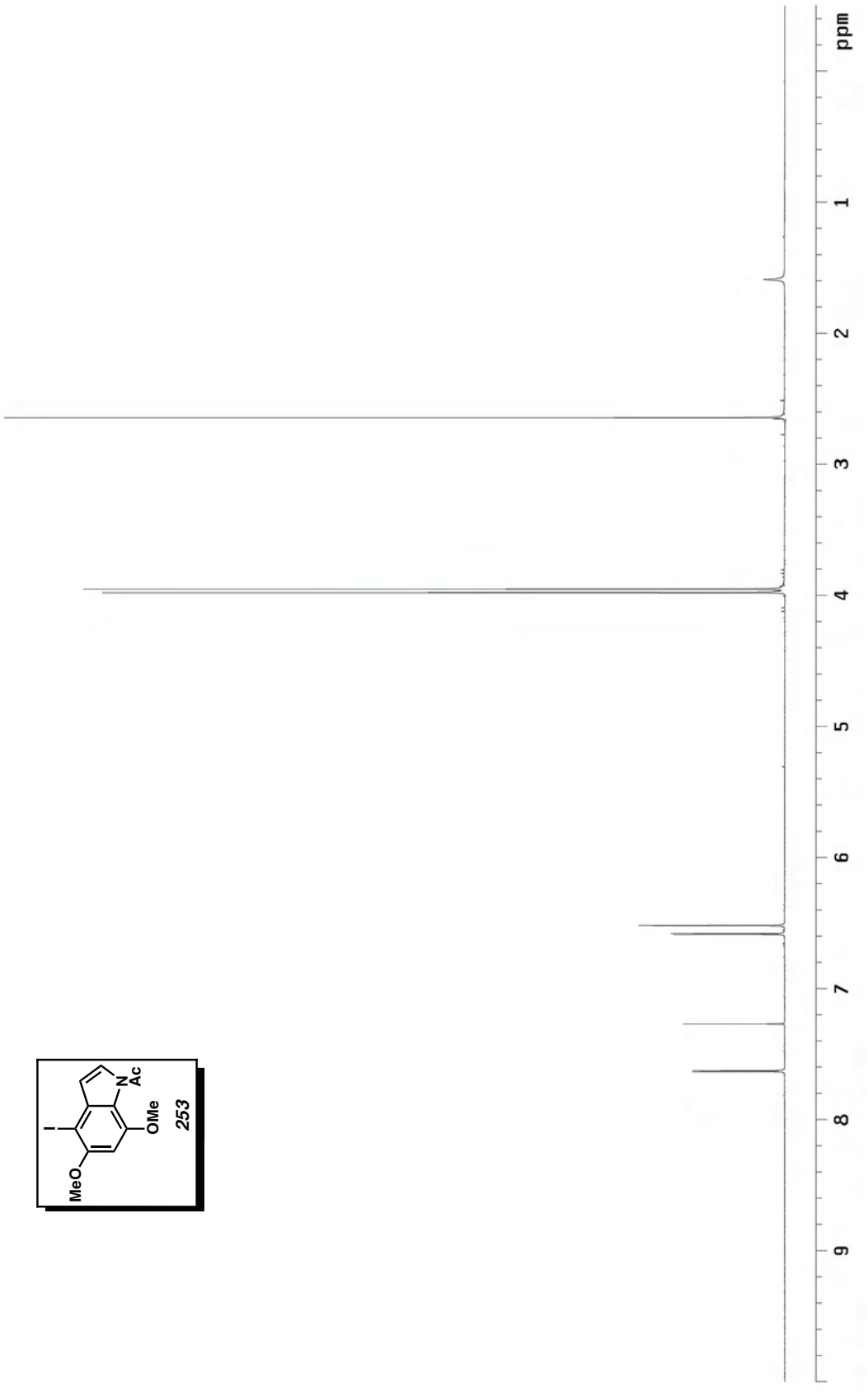


Figure A3.1.30 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **253**

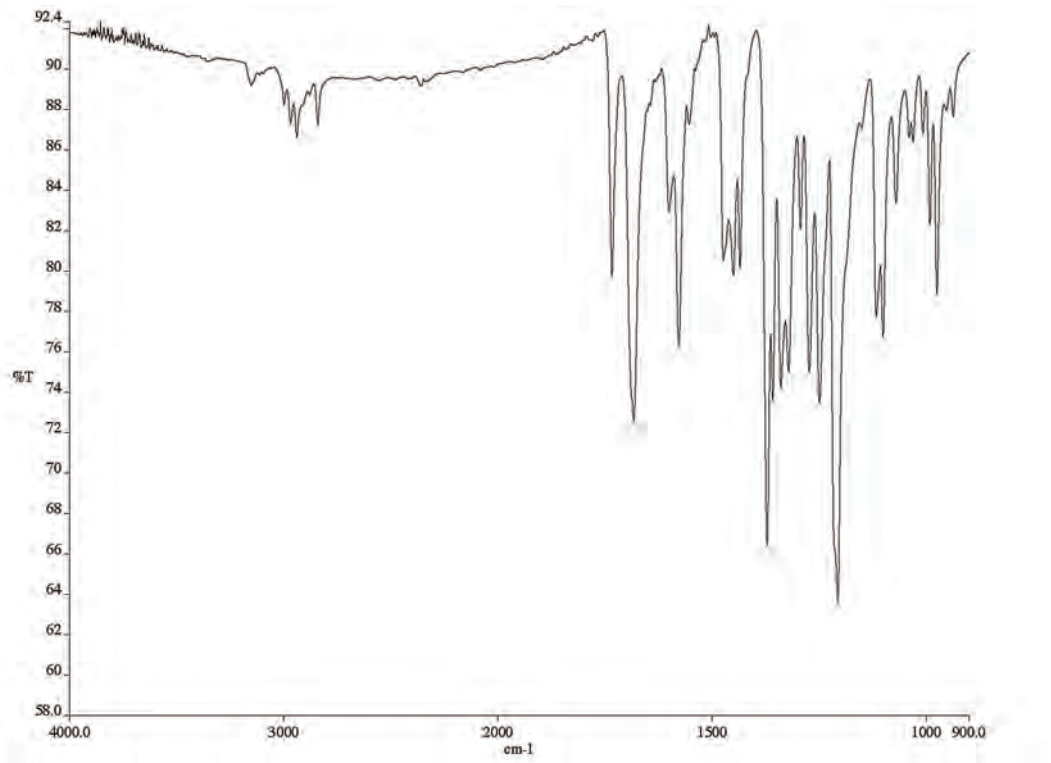


Figure A3.1.31 Infrared spectrum (film/NaCl) of compound **253**

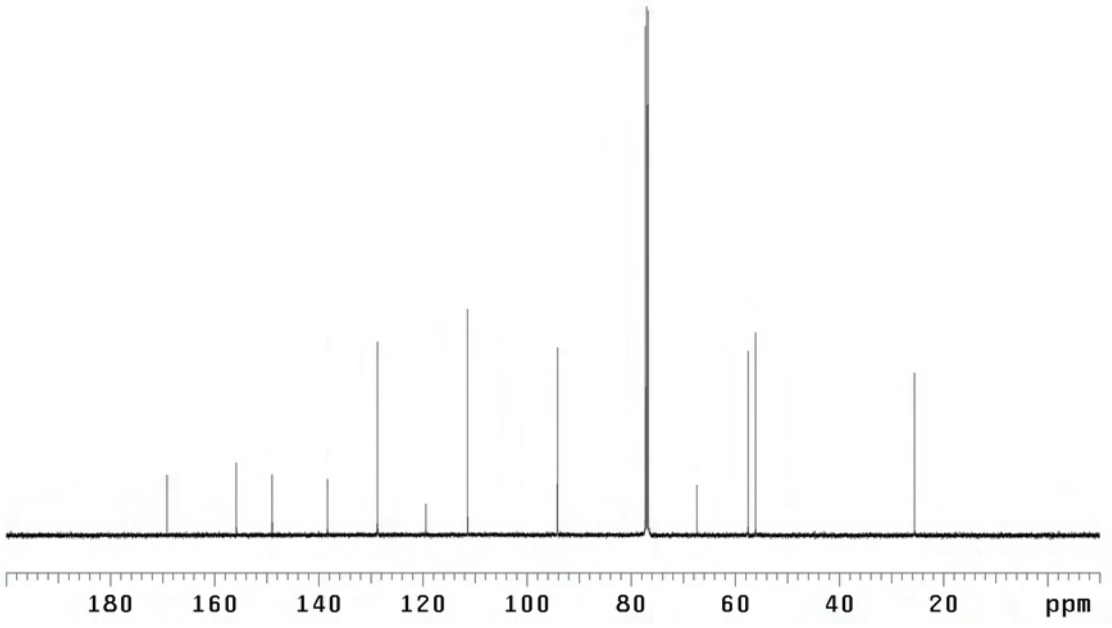


Figure A3.1.32 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **253**

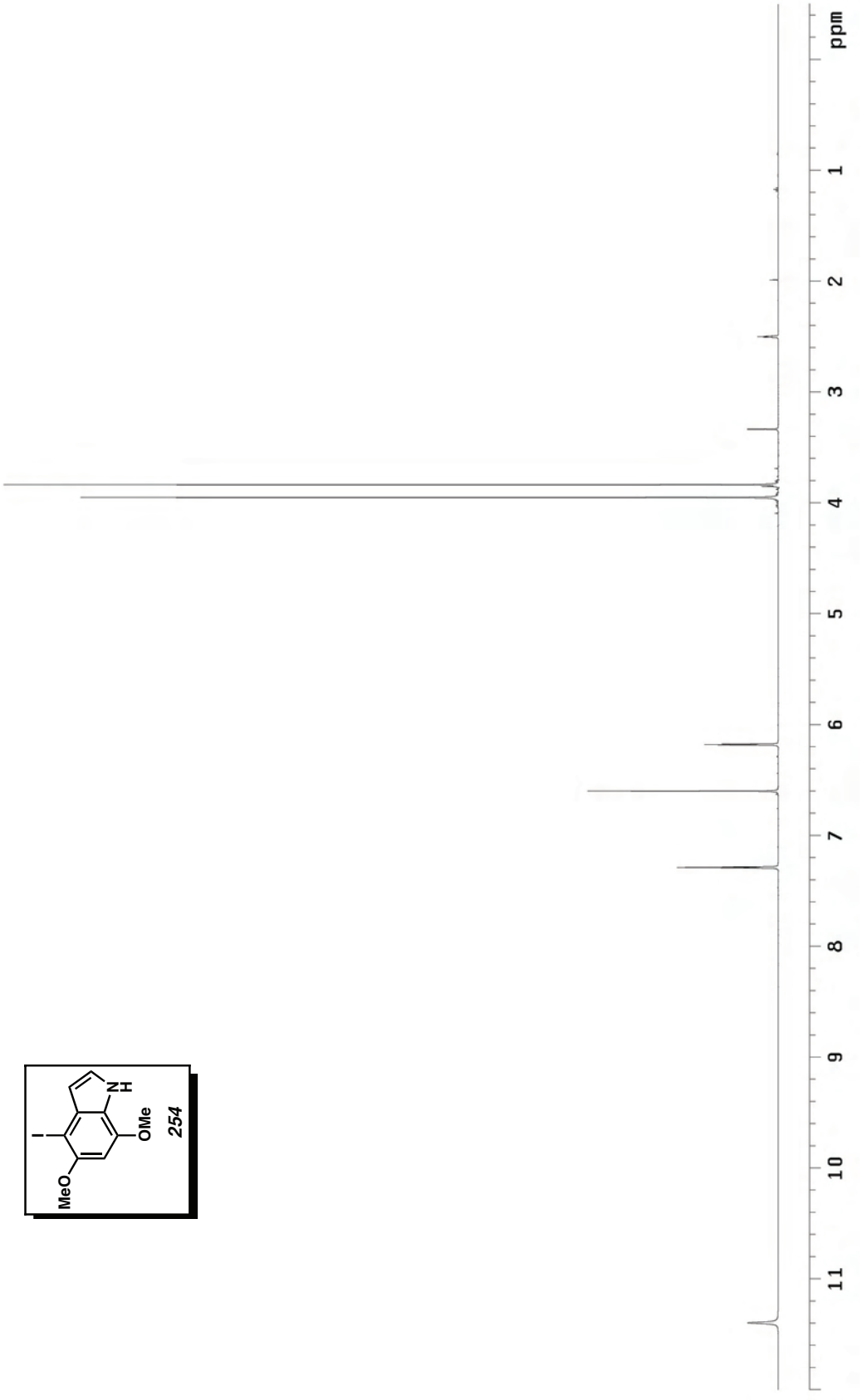


Figure A3.1.33 ^{1}H NMR (500 MHz,d_6-DMSO) of compound **254**

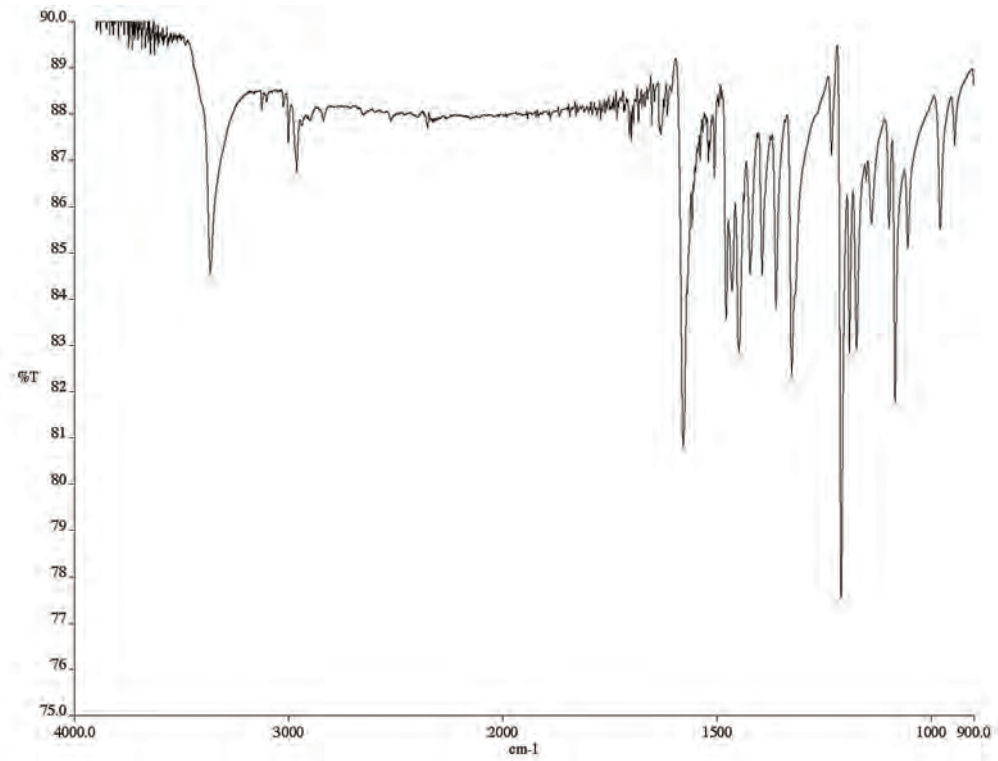


Figure A3.1.34 Infrared spectrum (film/NaCl) of compound **254**

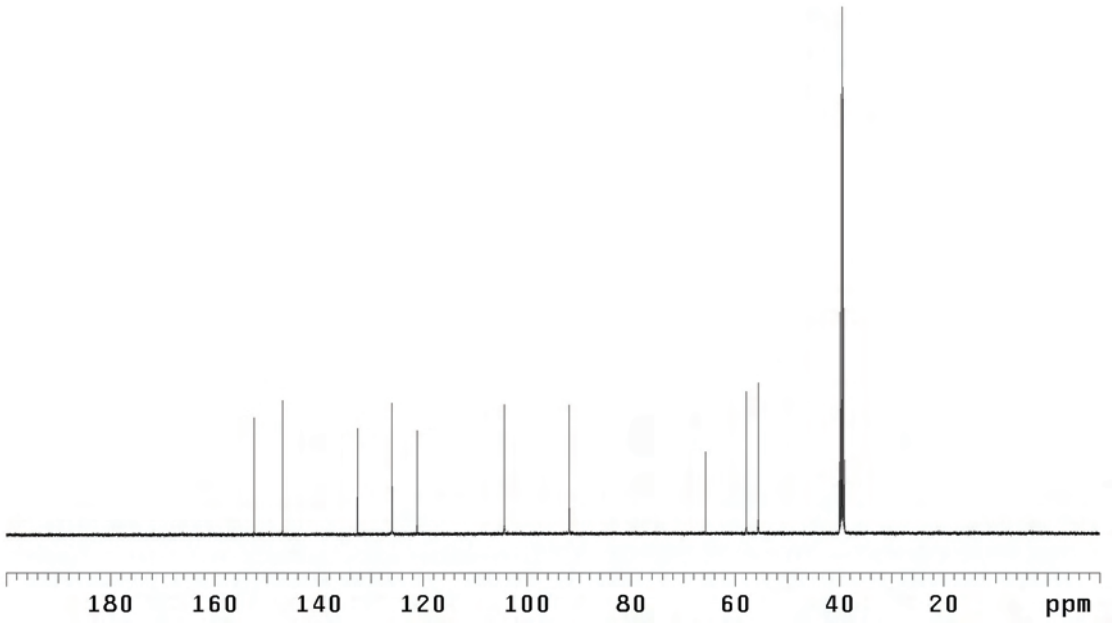


Figure A3.1.35 ^{13}C NMR (125 MHz, d_6-DMSO) of compound **254**

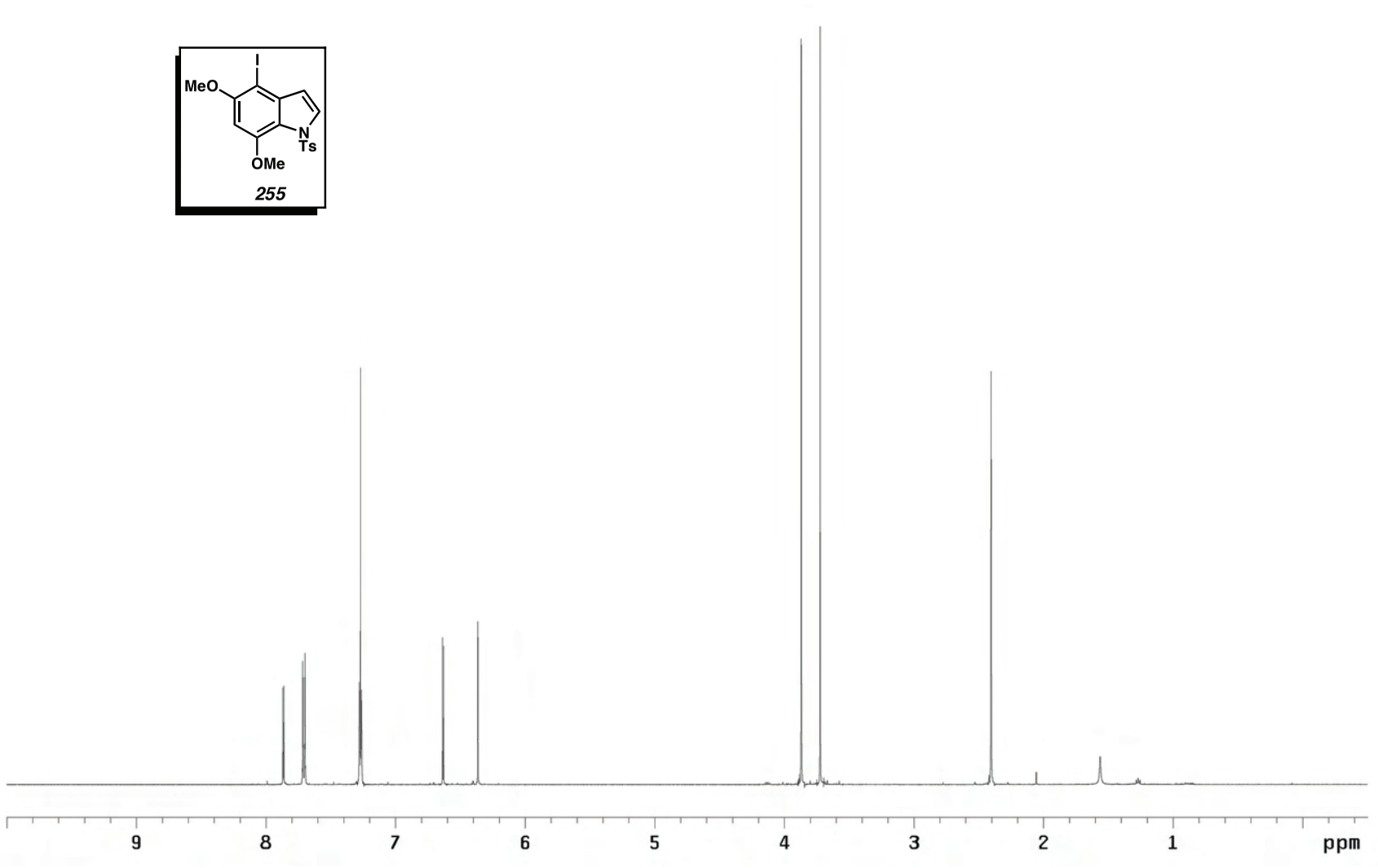


Figure A3.1.36 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **255**

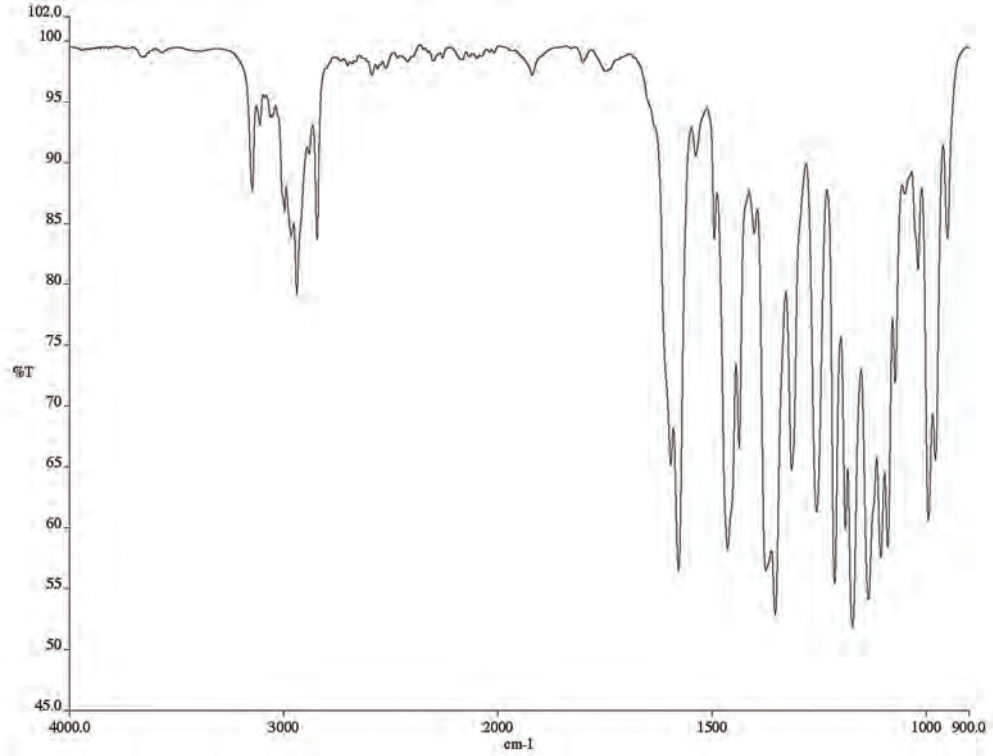


Figure A3.1.37 Infrared spectrum (film/NaCl) of compound **255**

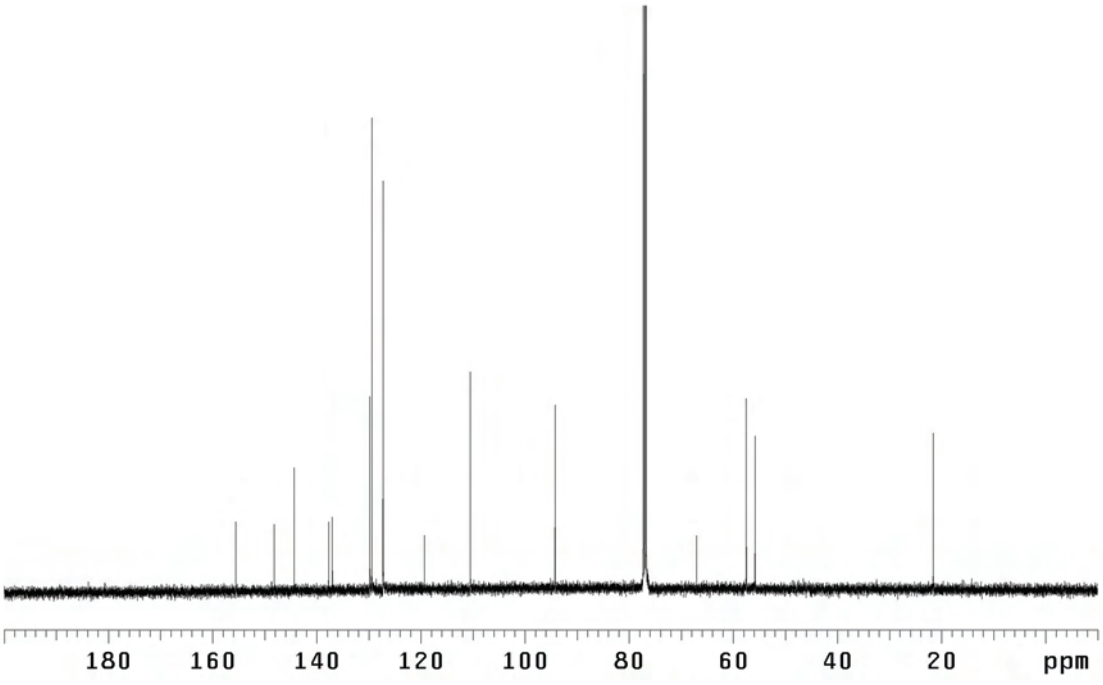


Figure A3.1.38 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **255**

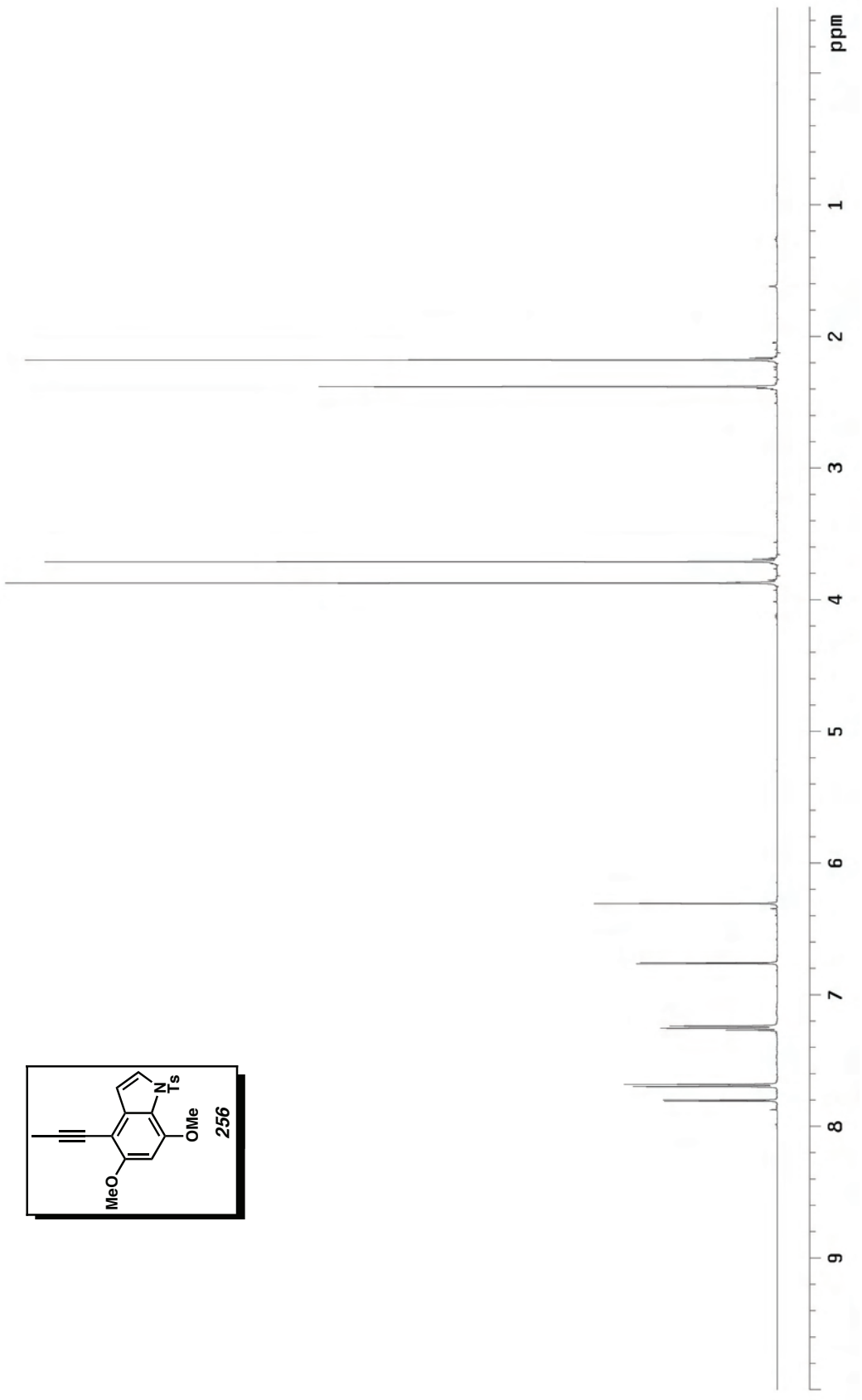


Figure A3.1.39 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **256**

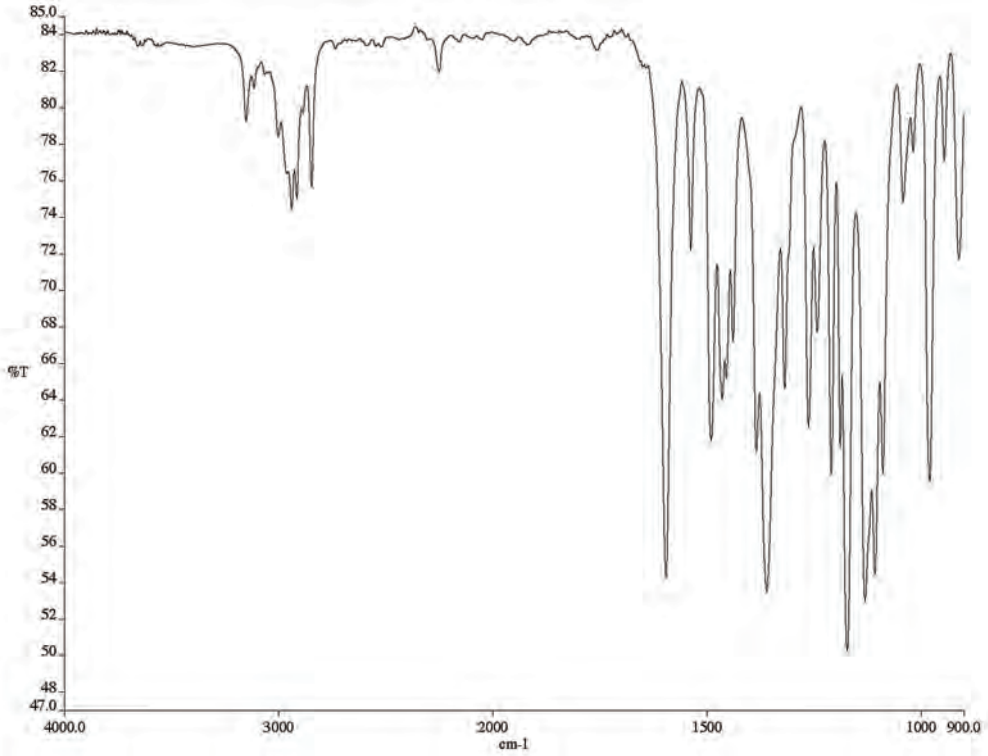


Figure A3.1.40 Infrared spectrum (film/NaCl) of compound **256**

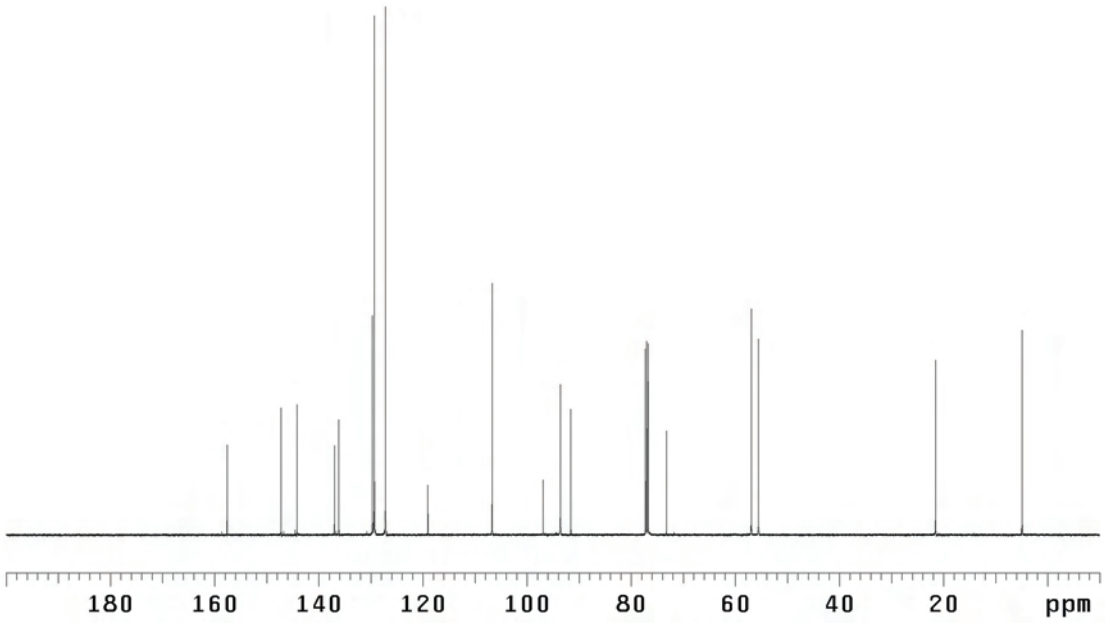


Figure A3.1.41 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **256**

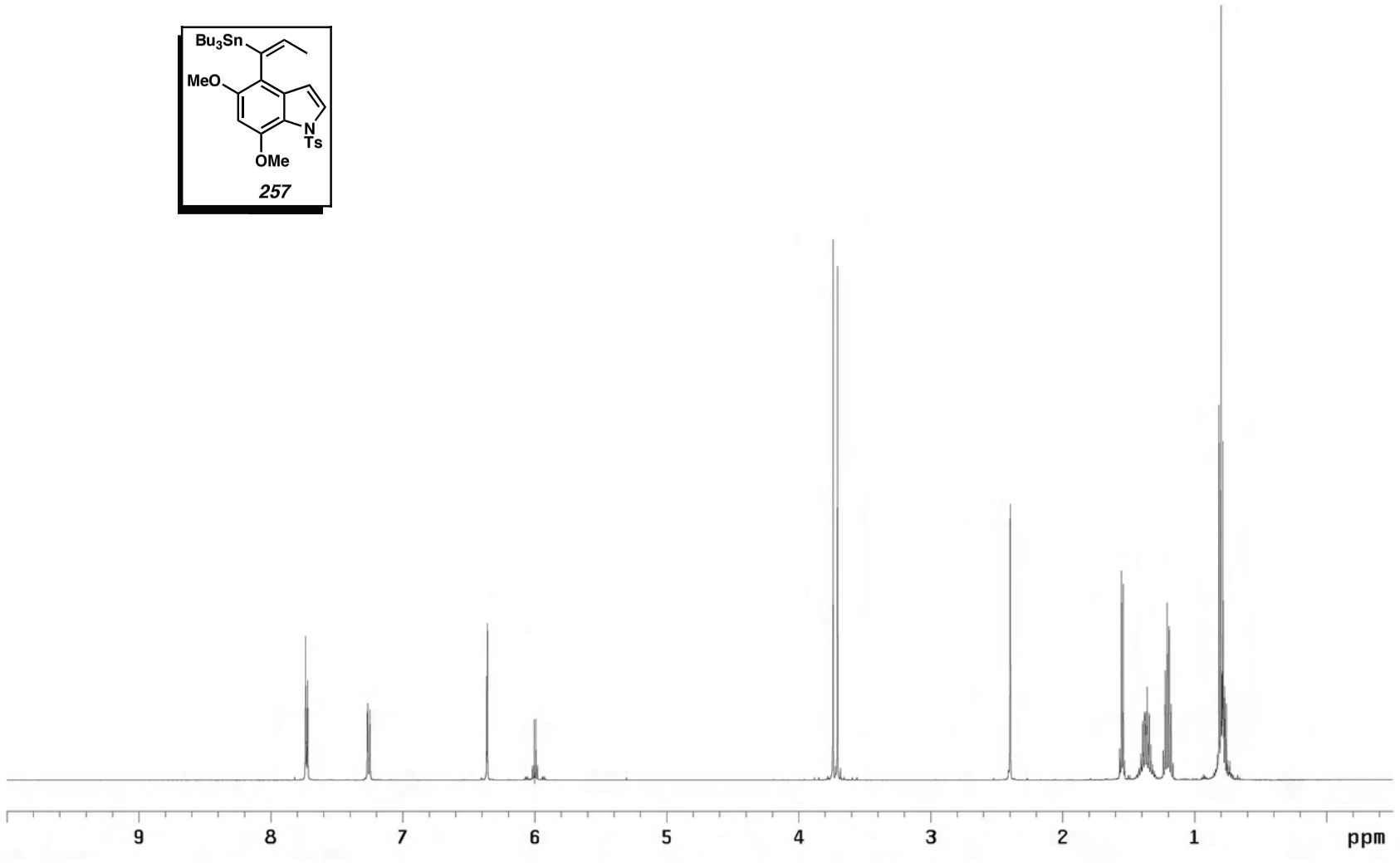


Figure A3.1.42 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **257**

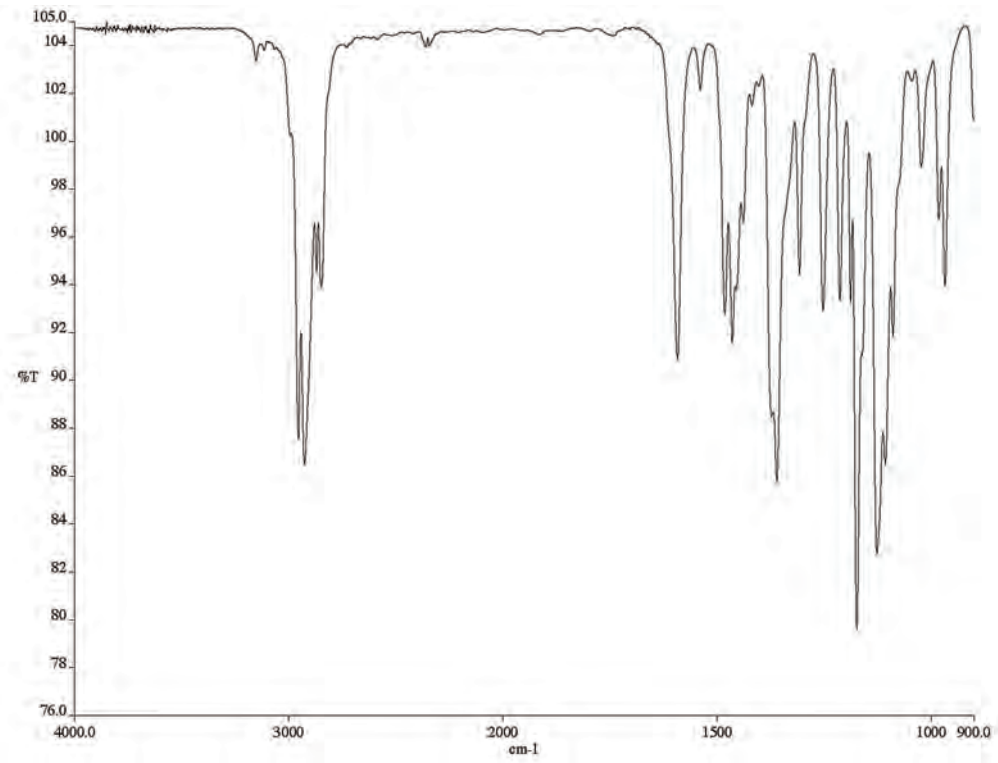


Figure A3.1.43 Infrared spectrum (film/NaCl) of compound **257**

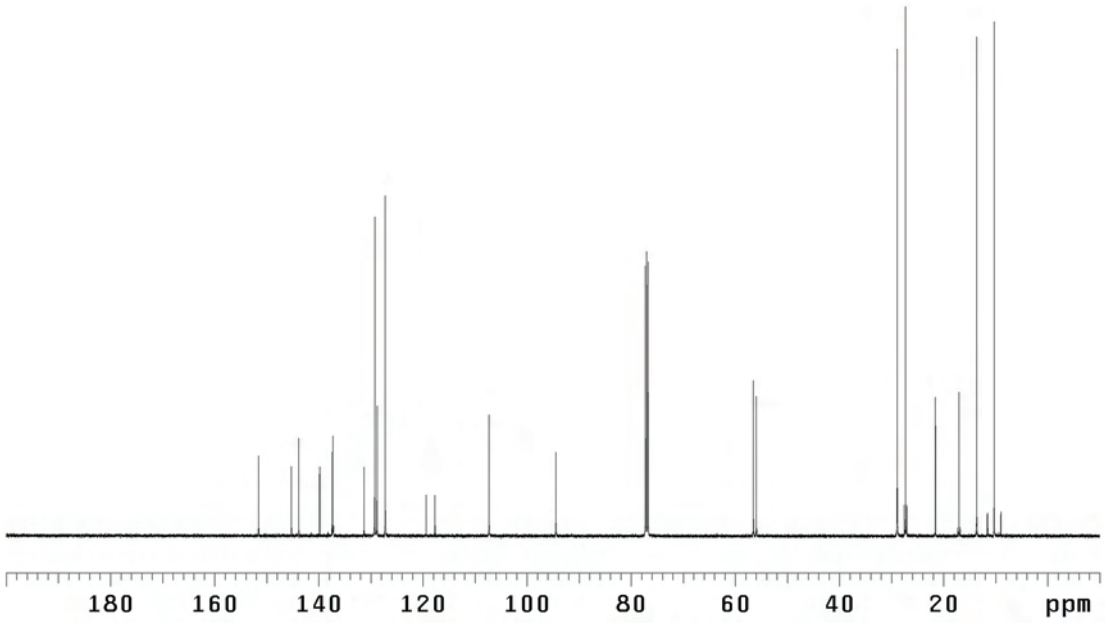


Figure A3.1.44 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **257**

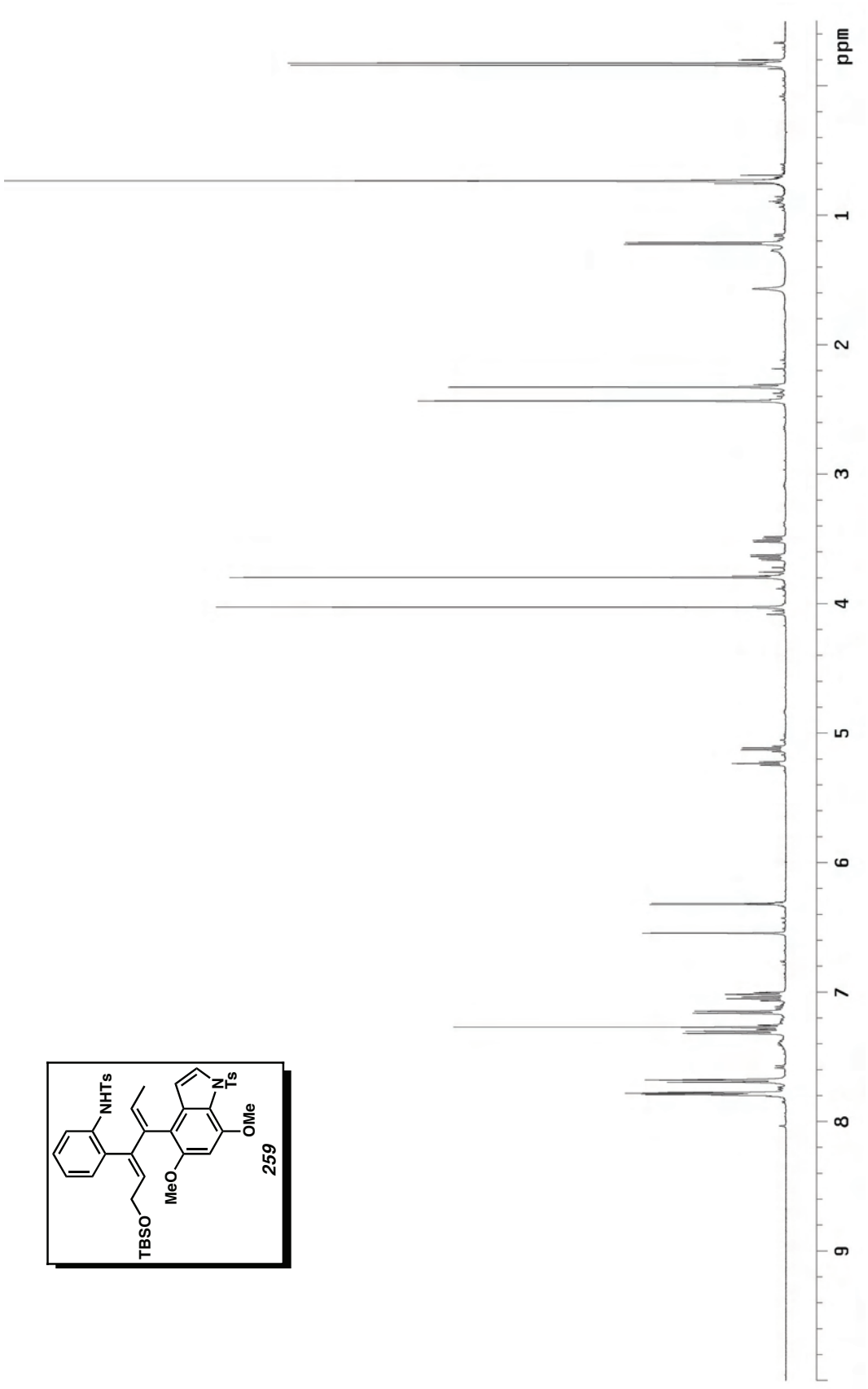


Figure A3.1.45 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **259**

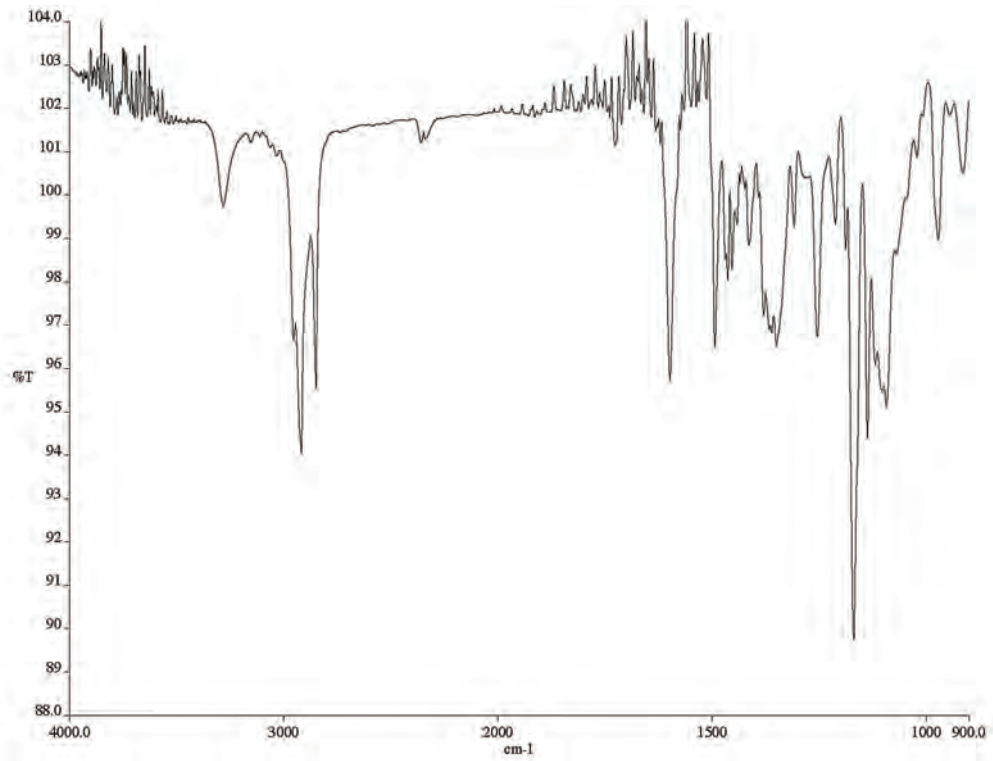


Figure A3.1.46 Infrared spectrum (film/NaCl) of compound **259**

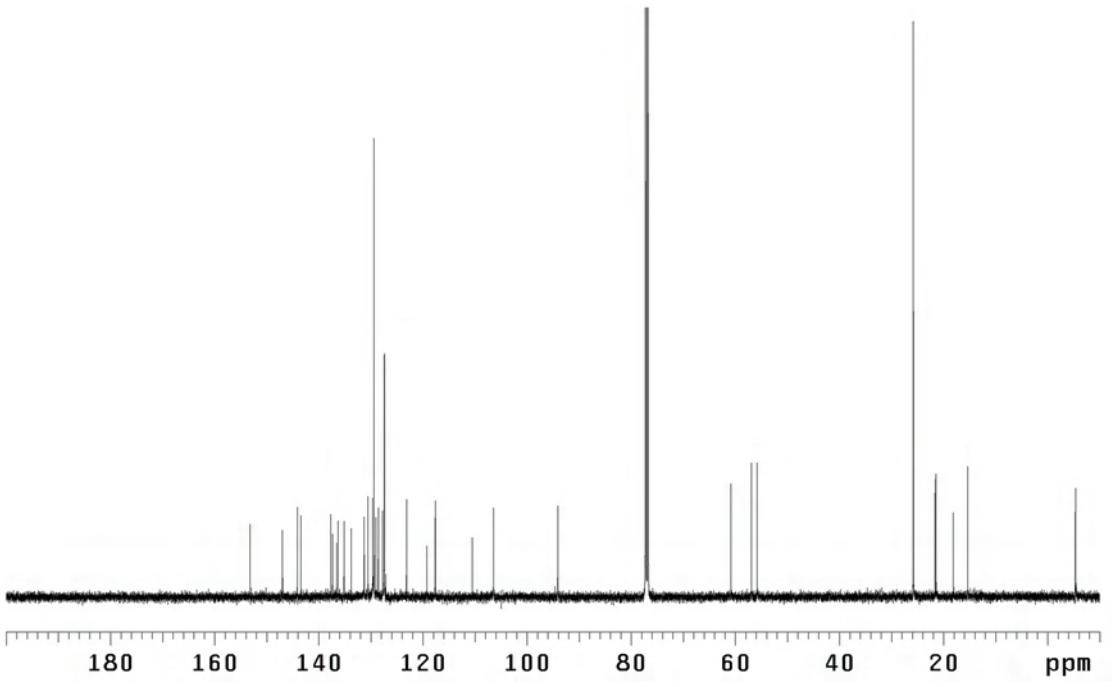


Figure A3.1.47 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **259**

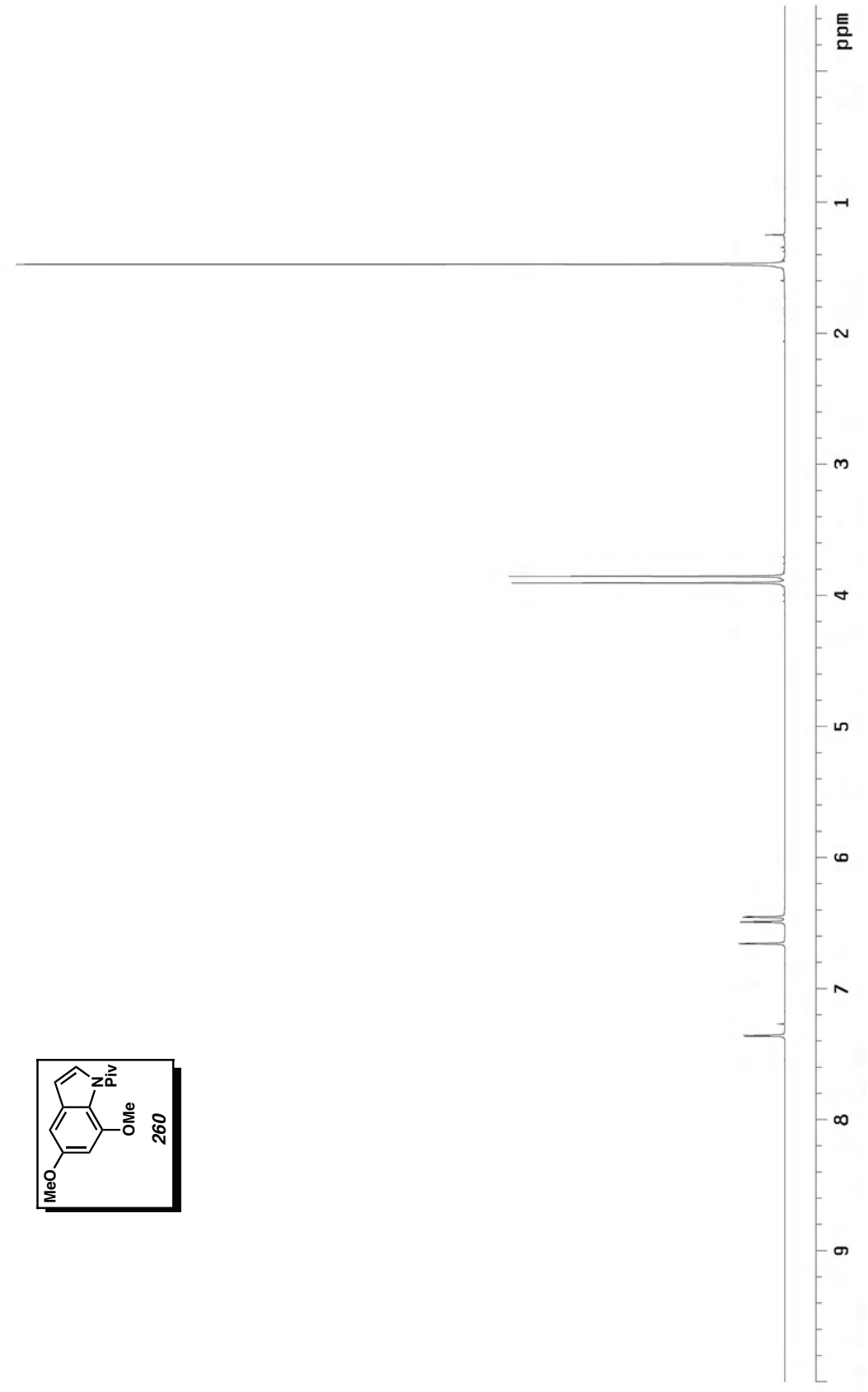


Figure A3.1.48 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **260**

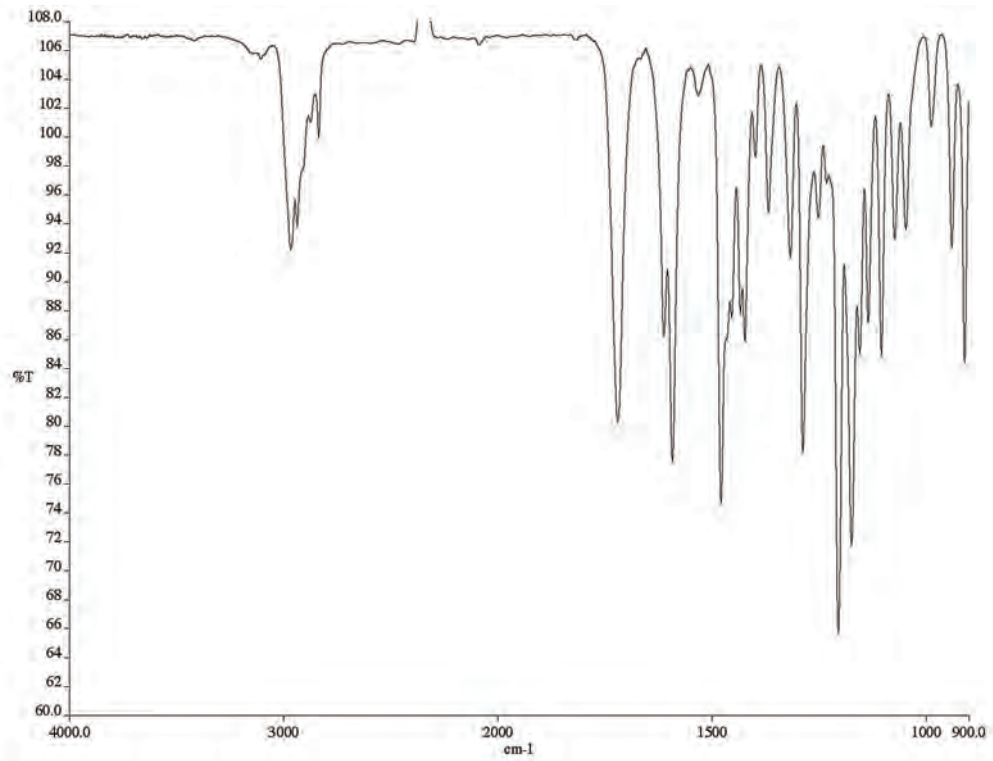


Figure A3.1.49 Infrared spectrum (film/NaCl) of compound **260**

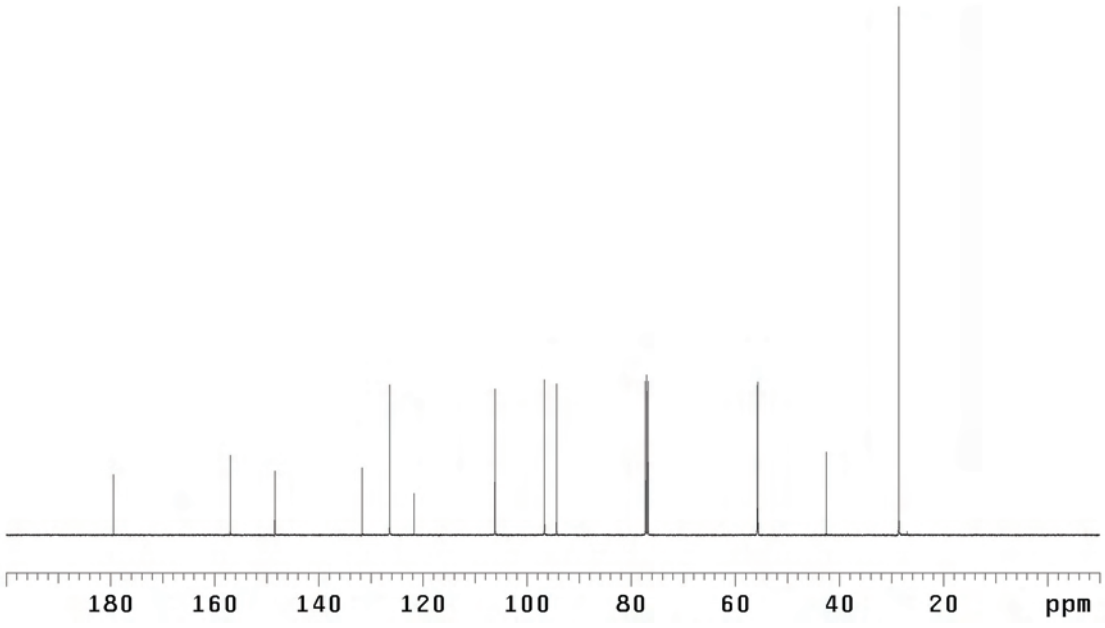


Figure A3.1.50 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **260**

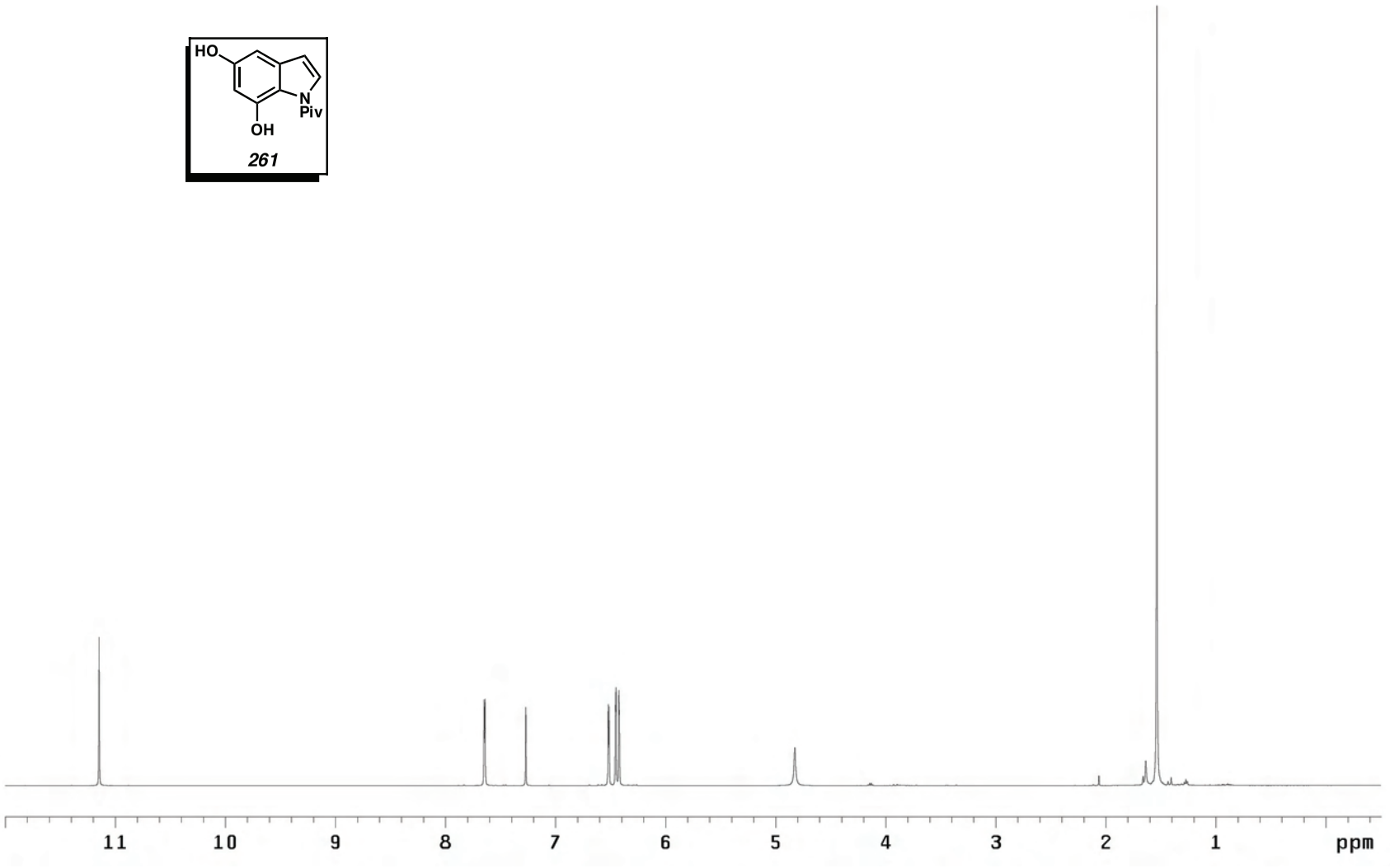


Figure A3.1.51 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **261**

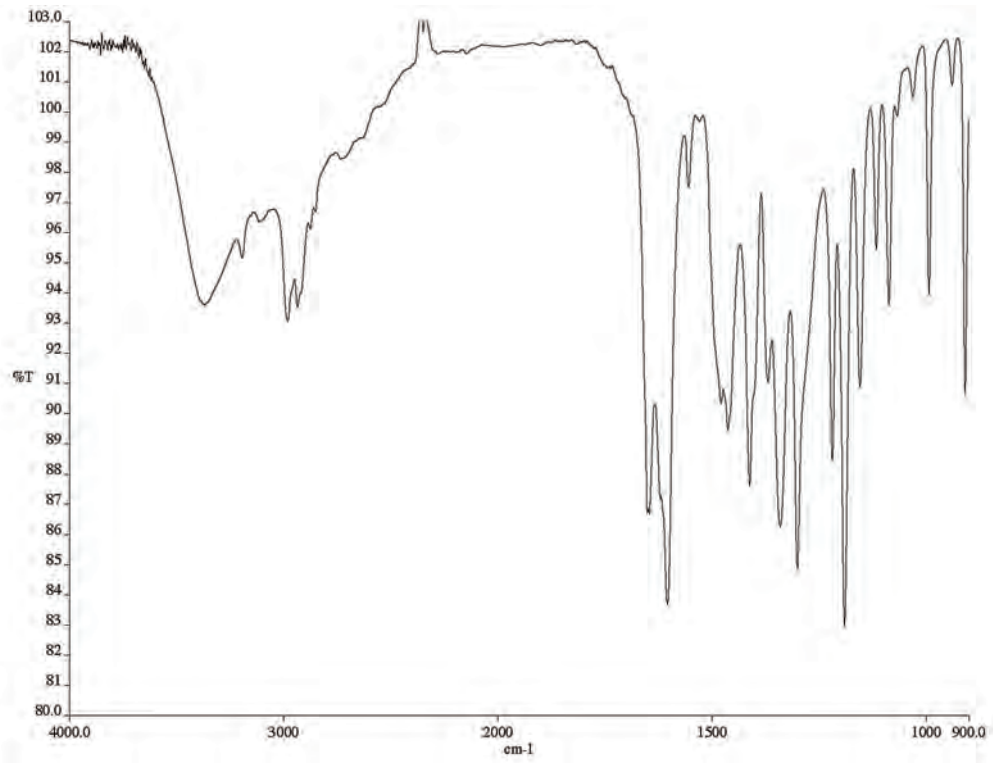


Figure A3.1.52 Infrared spectrum (film/NaCl) of compound **261**

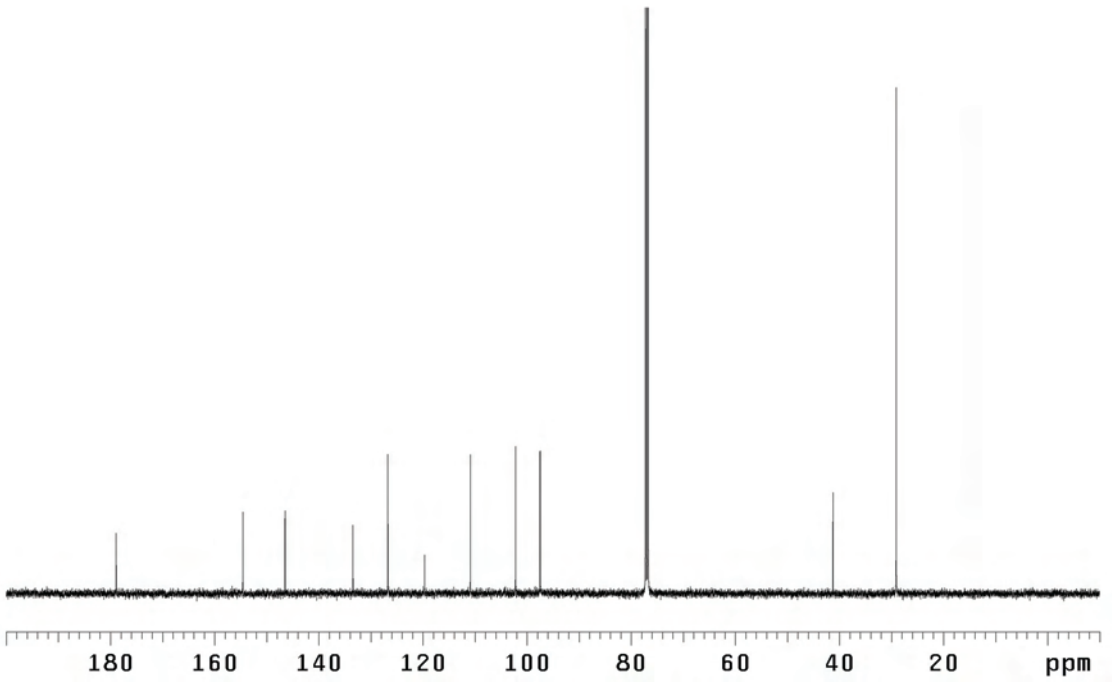


Figure A3.1.53 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **261**

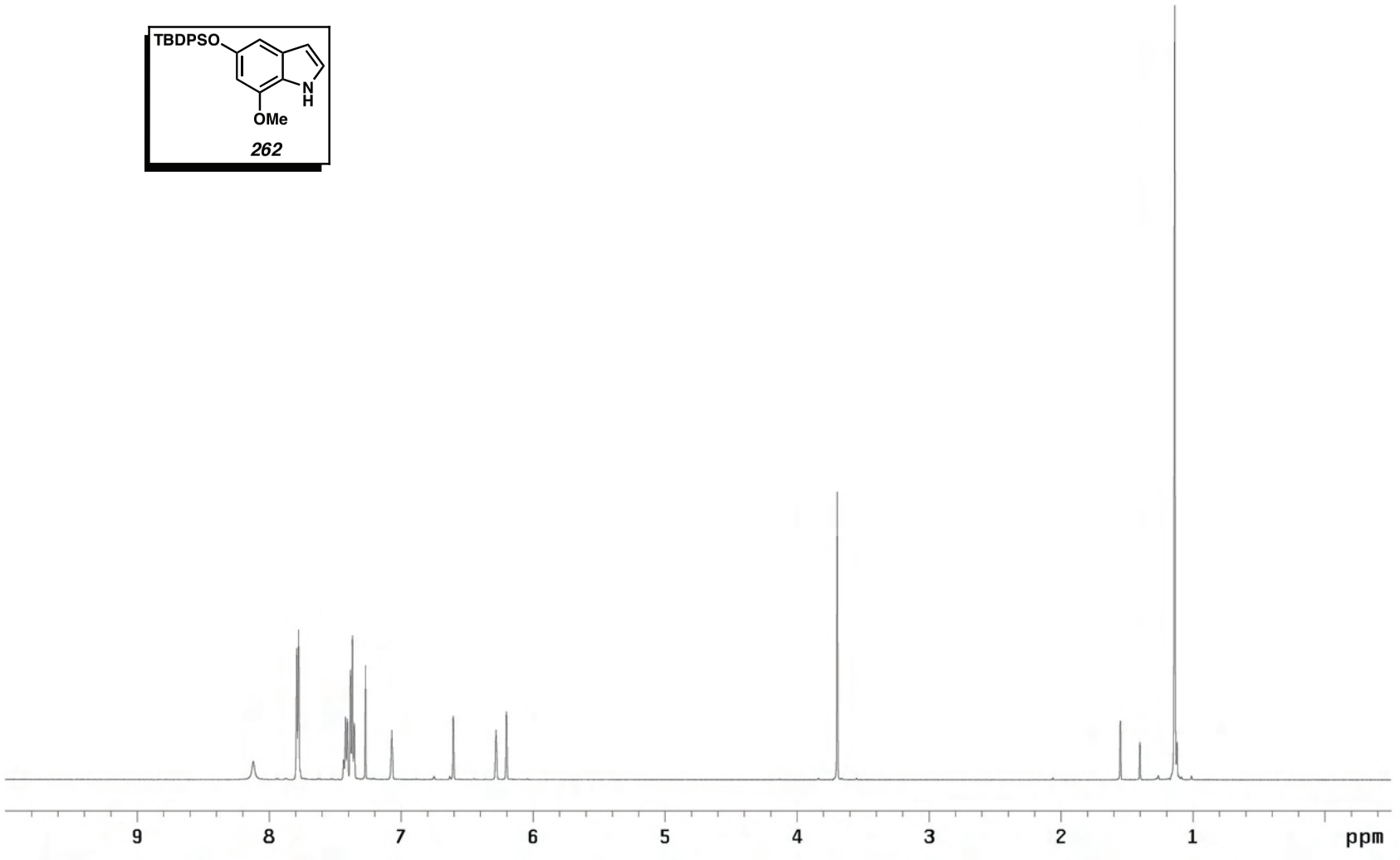


Figure A3.1.54 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **262**

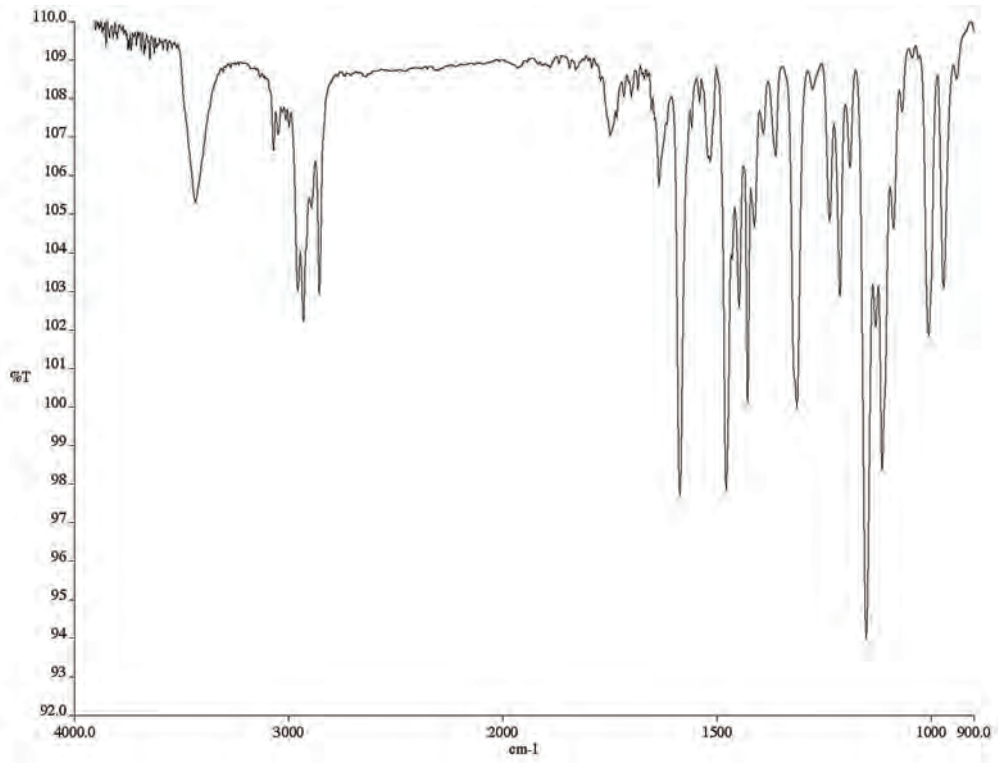


Figure A3.1.55 Infrared spectrum (film/NaCl) of compound **262**

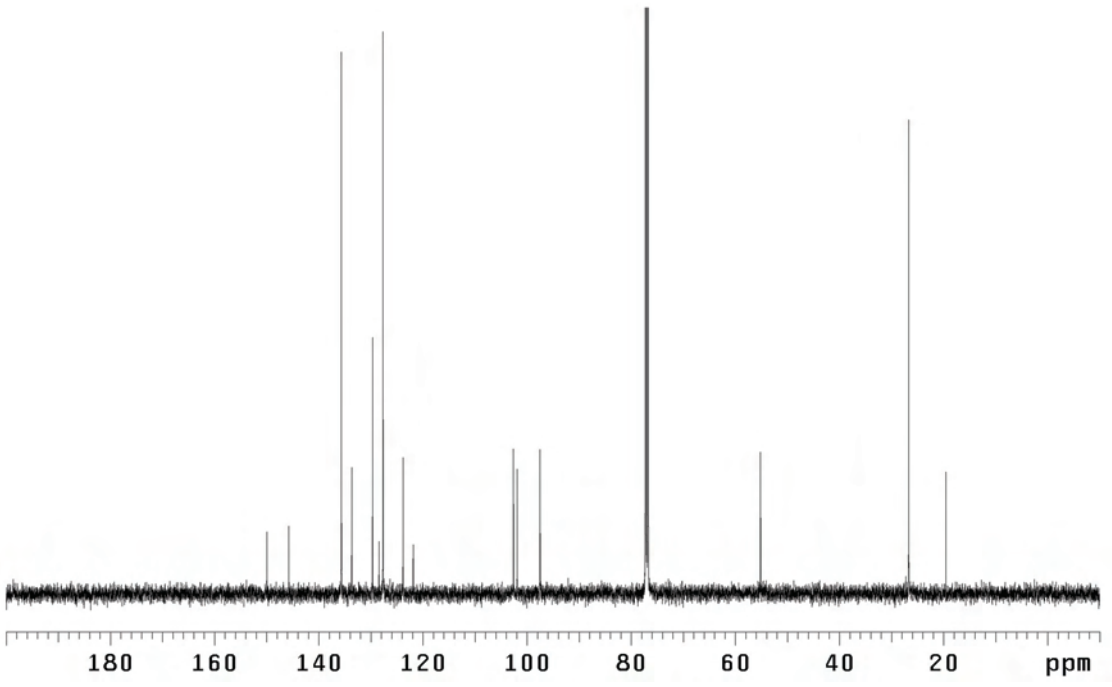


Figure A3.1.56 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **262**

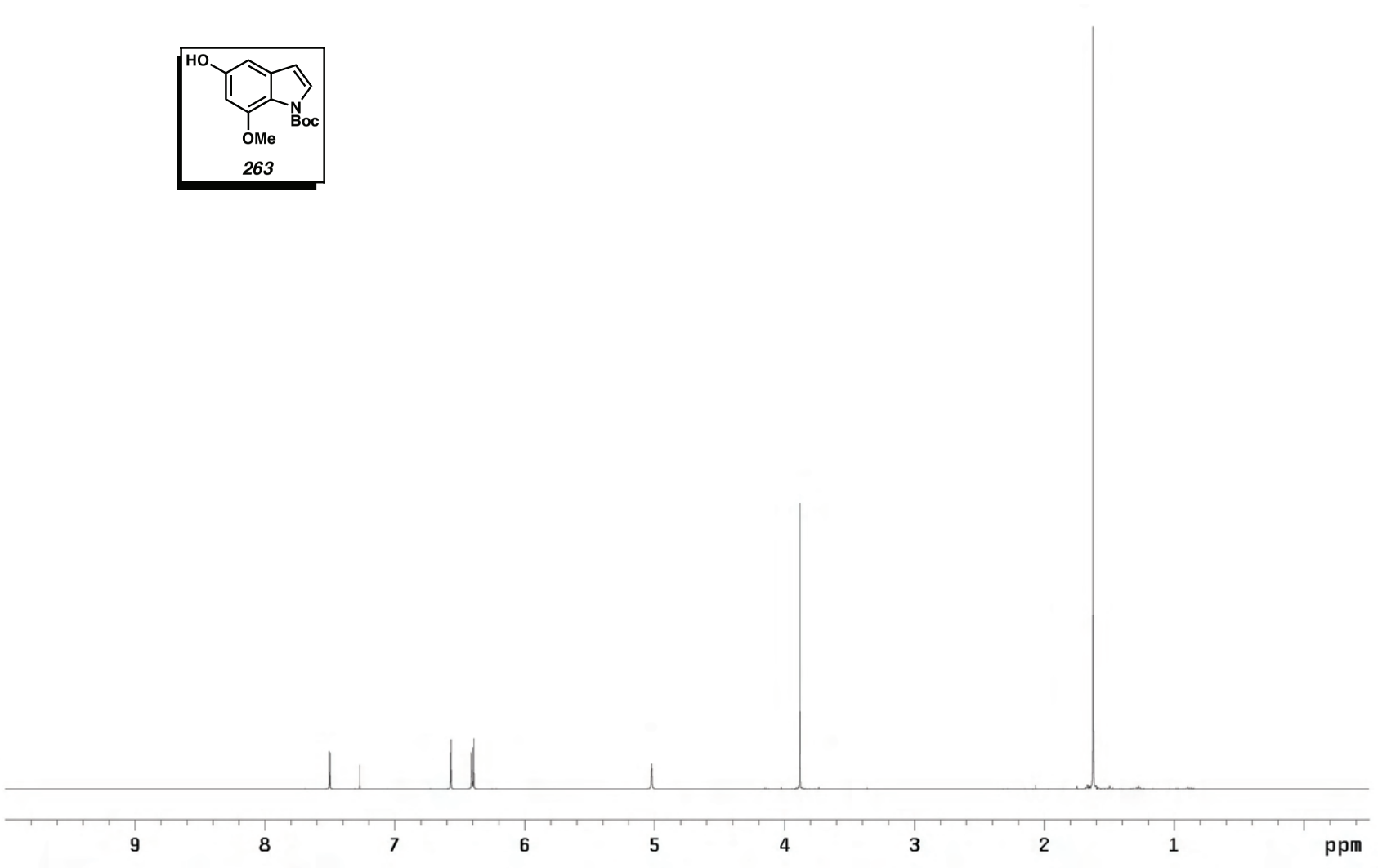


Figure A3.157 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **263**

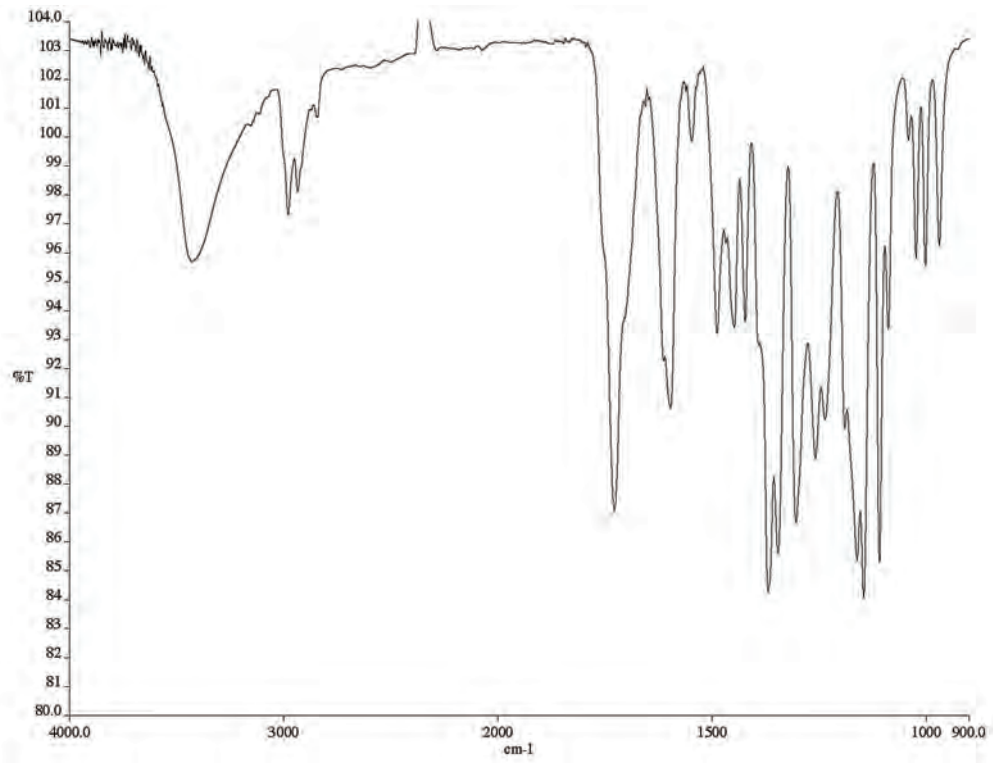


Figure A3.1.58 Infrared spectrum (film/NaCl) of compound **263**

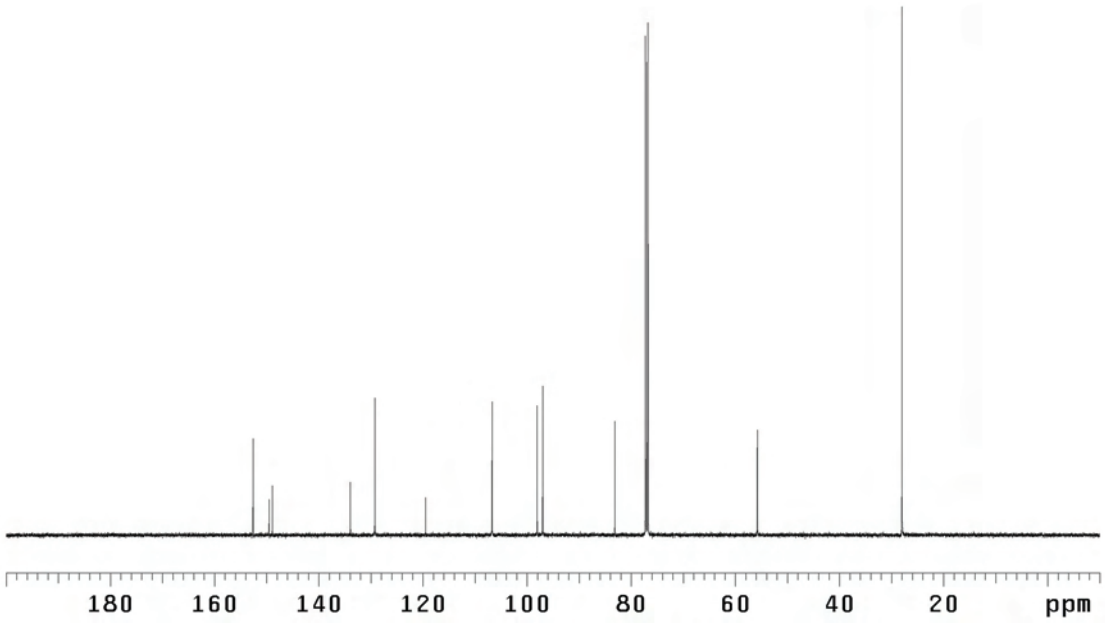


Figure A3.1.59 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **263**

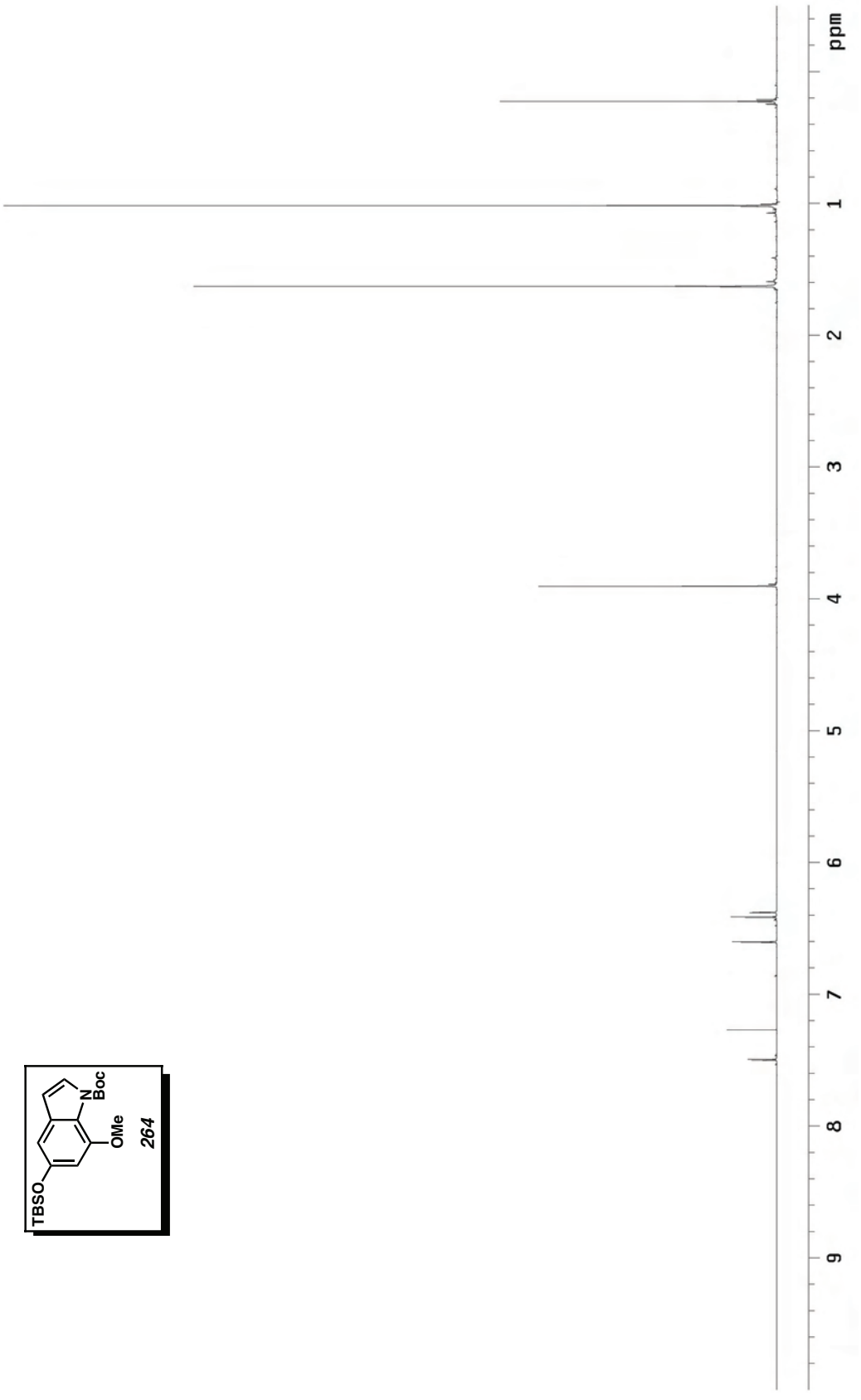


Figure A3.1.60 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **264**

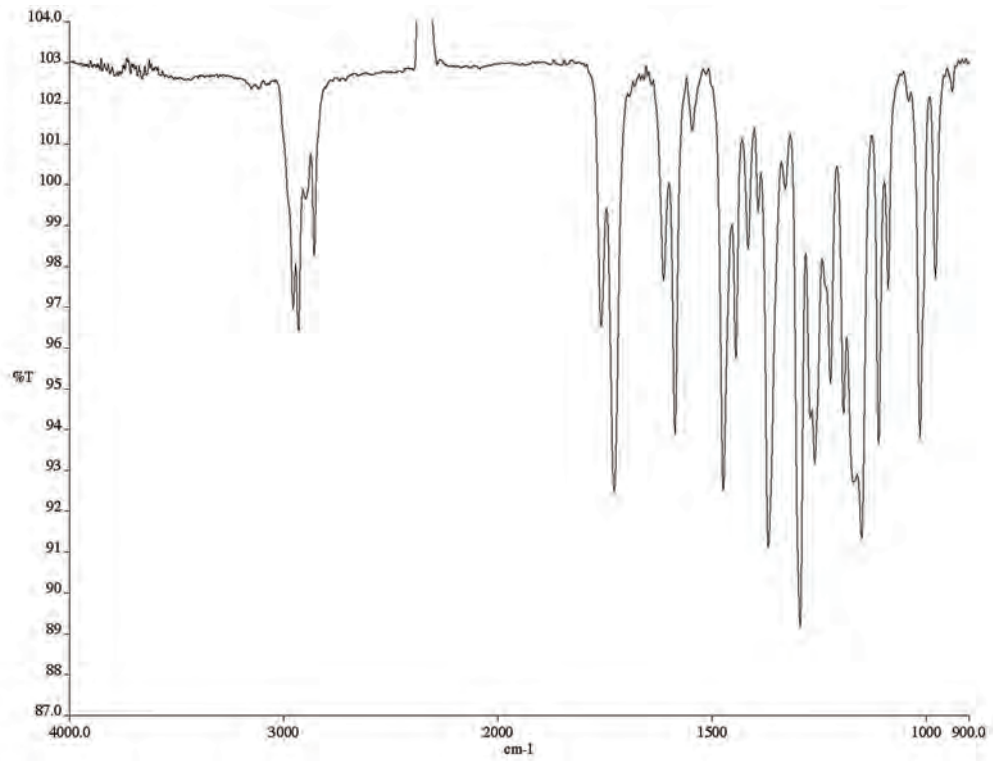


Figure A3.1.61 Infrared spectrum (film/NaCl) of compound **264**

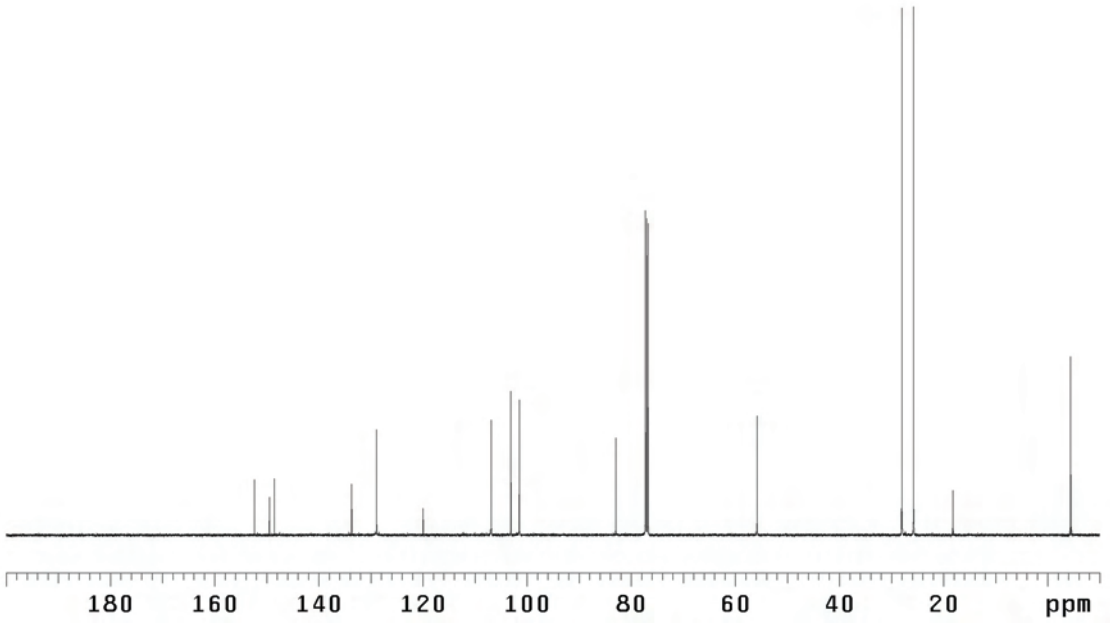


Figure A3.1.62 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **264**

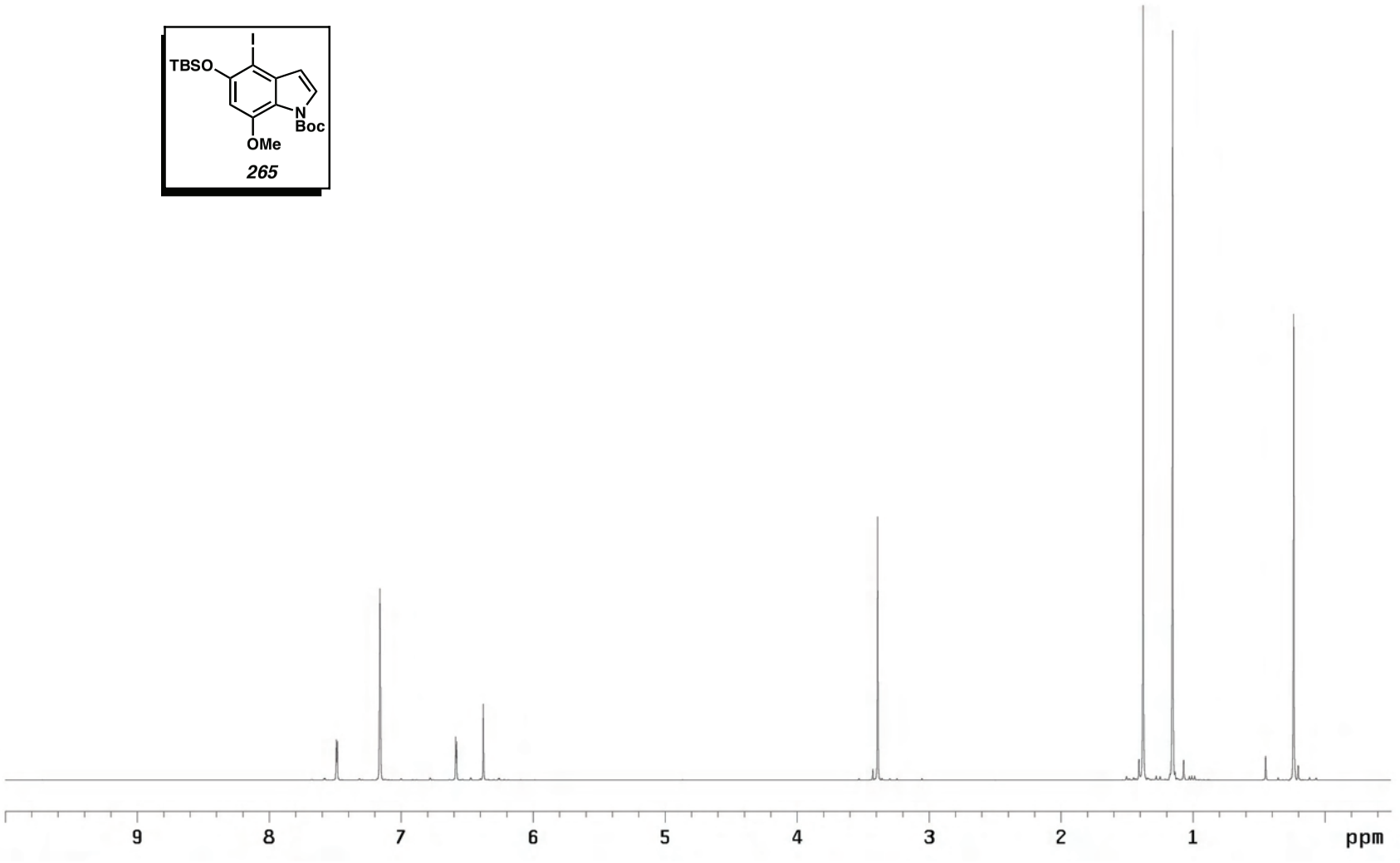


Figure A3.1.63 ^{1}H NMR (500 MHz, $CDCl_3$) of compound **265**

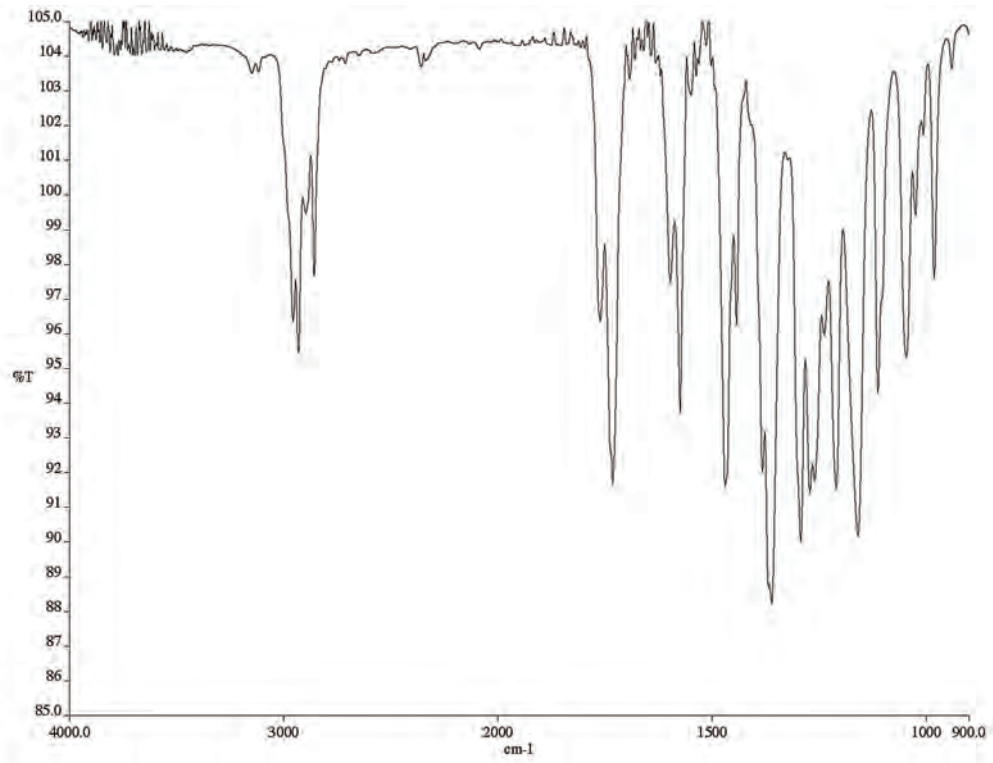


Figure A3.1.64 Infrared spectrum (film/NaCl) of compound **265**

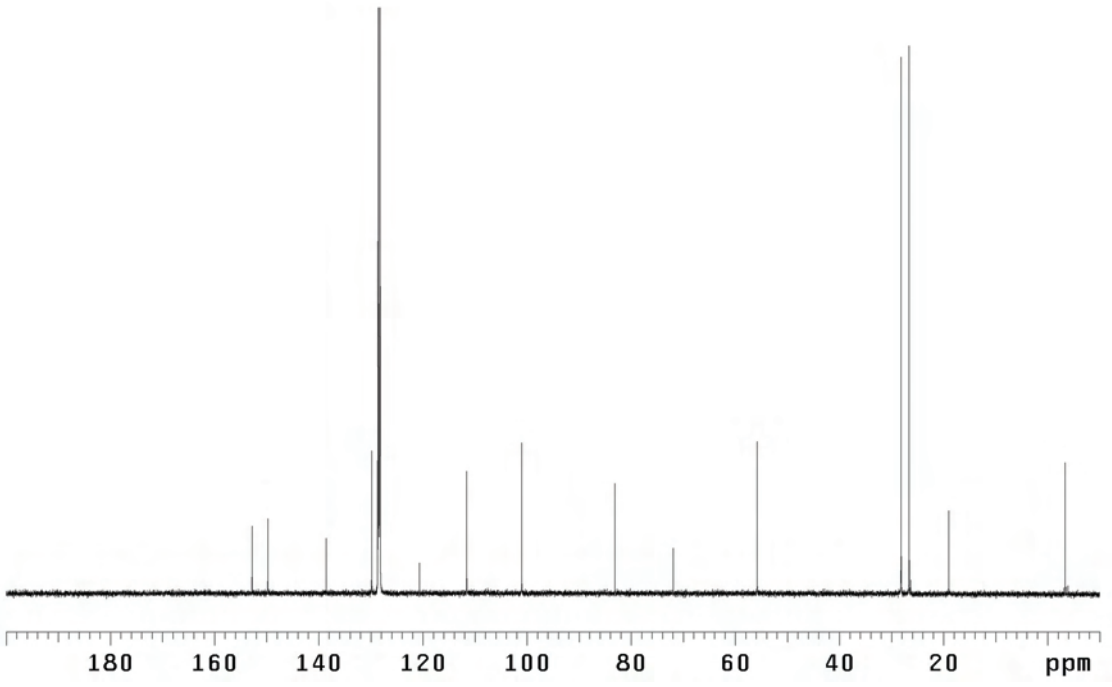


Figure A3.1.65 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **265**

Index

Notebook Cross-Reference

The following notebook cross-reference has been included to facilitate access to the original spectroscopic data obtained for the compounds presented in this thesis. All of the spectroscopic data for every compound listed below can also be found in a hardcopy characterization binder labeled "MEM-CHARACTER", which can be found in the Stoltz archives.

Table NCR-1 Compounds Appearing in Chapter 2.

Compound	^{1}H NMR	^{13}C NMR	IR
Enone **136**	JHP-1-29	JHP-1-29	JHP-1-29
Alcohol **128**	MEM-16-299	MEM-16-299	MEM-16-299
Acid **139**	MEM-6-153	N/A	MEM-6-149
Enone **127**	MEM-17-63	MEM-17-63	MEM-17-63
Substrate **141**	MEM-6-151	N/A	MEM-6-151
Substrate **143**	MEM-6-165	MEM-6-165	MEM-6-165
Substrate **145**	MEM-6-187	MEM-6-187	MEM-6-187

Substrate **147**	MEM-6-199	N/A	MEM-6-199
Substrate **149**	MEM-6-195	MEM-6-195	MEM-6-195
Substrate **151**	MEM-6-207	N/A	MEM-6-207
Substrate **153**	MEM-6-159	MEM-6-159	MEM-6-159
Substrate **155**	MEM-6-165	MEM-6-165	MEM-6-165
Substrate **157**	MEM-6-227	MEM-6-227	MEM-6-227
Hydroxy Enone **158**	MEM-6-267	MEM-6-257	MEM-6-267
Substrate **159**	MEM-6-261	MEM-6-261	MEM-6-261
Substrate **161**	MEM-6-287	MEM-6-287	MEM-6-287
Substrate **163**	MEM-6-203	MEM-6-203	MEM-6-203
Alcohol **37**	MEM-17-71	MEM-17-71	MEM-17-71
Allylic Alcohol **164**	JHP-1-49	JHP-1-49	JHP-1-49
Ester **165**	JHP-1-149	JHP-1-149	JHP-1-149
Cyclopropane **166**	JHP-1-237	JHP-1-237	JHP-1-237
Alcohol **171**	JHP-1-243	JHP-1-243	JHP-1-243
Ketone **172**	JHP-2-131	JHP-2-131	JHP-2-131
Alcohol **168**	JHP-2-207	JHP-2-207	JHP-2-207
Furan **169**	JHP-3-43	JHP-3-43	JHP-3-43
Cyclopropane **173**	JHP-3-181	JHP-3-181	JHP-3-181
Cyclopropane **174**	JHP-3-179	JHP-3-179	JHP-3-179
Cyclopropane **175**	JHP-3-183	JHP-3-183	JHP-3-183
Cyclopropane **176**	JHP-3-303	JHP-3-303	JHP-3-303

Cyclopropane **177**	MEM-9-83	MEM-9-83	MEM-9-83
Furan **182**	MEM-8-231	MEM-8-231	MEM-8-231

Table NCR-2 Compounds Appearing in Chapter 3.

Compound	^{1}H NMR	^{13}C NMR	IR
Phenol **237**	MEM-17-109	MEM-17-109	MEM-17-109
Dihydrobenzofuran **238**	MEM-16-167	MEM-16-167	MEM-16-167
Alkyne **240**	MEM-12-143	N/A	MEM-12-143
Vinyl Stannane **241**	MEM-14-163	MEM-14-163	MEM-14-163
Vinyl Iodide **242**	MEM-14-167	MEM-14-167	MEM-14-167
Alkyne **245**	MEM-17-49	MEM-17-49	MEM-17-49
Vinyl Stannane **246**	MEM-17-51	MEM-17-51	MEM-17-51
Alkyne **247**	MEM-15-197	MEM-15-197	MEM-15-197
Vinyl Stannane **248**	MEM-15-199	MEM-15-199	MEM-15-199
Arene **250**	MEM-12-261	N/A	N/A
Arene **251**	MEM-12-265	N/A	N/A
Indole **233**	MEM-13-35	N/A	N/A
Indole **252**	MEM-13-253	N/A	N/A
Arene **253**	MEM-14-133	MEM-14-133	MEM-14-133
Indole **254**	MEM-15-177	MEM-15-177	MEM-15-177
Arene **255**	MEM-14-195	MEM-14-195	MEM-14-195
Alkyne **256**	MEM-14-209	MEM-14-209	MEM-14-209

Vinyl Stannane **257**	MEM-15-119	MEM-15-119	MEM-15-119
Diene **259**	MEM-15-107(103)	MEM-15-107(103)	MEM-15-107
Indole **260**	MEM-16-175	MEM-16-175	MEM-16-175
Bis Phenol **261**	MEM-16-177	MEM-16-177	MEM-16-177
Arene **262**	MEM-16-207(203)	MEM-16-207(203)	MEM-16-207
Phenol **263**	MEM-16-221	MEM-16-221	MEM-16-221
Indole **264**	MEM-17-127	MEM-17-127	MEM-17-127
Arene **265**	MEM-17-129	MEM-17-129	MEM-17-129

All notebook entries (e.g., MEM-16-207) refer not only to notebook page, but also the NMR file. If (#) follows the notebook entry, this means that the NMR file was incorrectly saved with the wrong page number (e.g., Arene **262**'s notebook reference is MEM-16-207, but its NMR file is MEM-16-203).

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About the Author

Michael was born in 1980 and was raised in San Mateo throughout his adolescent years. Apparently Michael was a handful as a baby, and his mother quickly declared "No more!" Thus, he is an only child. Instead of being a good jewish boy and going to Sunday school, he was learning and playing baseball every weekend of each year. Michael became a huge sports fan by growing up watching the SF Giants, 49ers, Oakland Warriors, and Cal Bears. In high school, during Mr. Tong's chemistry class, Michael discovered the direction in his life when he couldn't solve a chemistry problem, and ended up creating his own equation, now called Meyer's Law in Mr. Tong's class, that provided him with more than just the answer to the problem, it provided him a guide to his career.

In college, Michael had to let go of organized baseball, and become a full time student majoring in chemistry. Fortunately for him, as one hobby disappeared, he found a new hobby with organic chemistry. He excelled in his chemistry courses, cruised in his general courses, applied to graduate schools, and then left for London for one final quarter. In London, Michael had an amazing time traveling Europe and experiencing different cultures. Upon his return to the States, he found out he was accepted to Caltech.

After 9 months of reacclimation, Michael began his studies in the Stoltz laboratory researching natural product synthesis. Although it has been a long and difficult ride, his experiences at Caltech will no doubt prove invaluable as he moves forward and begins his adult life. Michael is looking forward to a life of chemistry, baseball, golf, more golf, dogs and cats, vacations, seeing friends, and eventually starting a family.