TRANSITION METAL CATALYZED APPROACHES TO THE ASYMMETRIC CONSTRUCTION OF ALL-CARBON QUATERNARY CENTERS

Thesis by

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In Partial Fulfillment of the Requirements for

the Degree of

Doctor of Philosophy

CALIFORNIA INSTITUTE OF TECHNOLOGY
Pasadena, California

2026

(Defended June 11th, 2025)

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To my dear mother

ACKNOWLEDGEMENTS

As my time at Caltech comes to an end, I have so many people to thank for enabling my completion of the PhD. First, I would like to express my utmost appreciation to my advisor, Professor Brian Stoltz, who has made me feel welcome at Caltech ever since my visit as a prospective graduate student. I am grateful that you took a chance on me as a member of your lab and appreciate the guidance you have given me over the years. I have learned so much from you and have appreciated our interactions in both professional and casual settings. Indeed, you and your family made me feel like a part of something during my time at Caltech. I look forward to continuing to work with you as you consult with Cytokinetics, and hopefully I will have the privilege of hosting you and the Stoltz's as you visit the better half of California.

In a similar vein, I am extremely indebted to former graduate students and postdocs in the group for making the lab a great place to work for a young researcher with imposter syndrome. While COVID could have completely killed the lab social scene, we found a way to hang out both during and after the strict campus policies, and my first two years at Caltech will be a highlight of my life which I will always look upon fondly. I also had the privilege of being one of a seven student cohort to join the Stoltz group in 2020. It has been an honor growing as a person and as a chemist alongside the rest of you, and we will forever be bonded by our shared experiences during unusual times to do graduate research. I wish you the best in your careers, be they academic or industrial in nature, and I am sure that our paths will overlap in the small world of organic chemistry and Pharma.

I would further like to express my appreciation for the many other faculty and staff at Caltech that made it possible for me to reach this point. Of course, Dr. Scott Virgil has been

indispensable to research in the Stoltz group, maintaining the Catalysis Center and liberally providing his know-how as both a chemist and engineer to the students, even when he is swamped with work. I am so pleased to have met you and Silva and to have been welcomed into your lovely home for your annual holiday celebrations. I am thankful for Leslie for being a positive presence on the floor and working so hard to keep the workplace a clean and safe environment. As a first and second year, I was fortunate enough to take courses with Caltech professors such as Prof. Greg Fu and Prof. Theo Agapie, and I am sure that I will reflect on what I learned in those courses throughout my career.

The journey to reach Caltech was certainly not a linear one, and I have a lot of people to acknowledge for their roles in setting me on this path. My profound gratitude goes out to the teachers who I interacted with throughout my early academic career, as they taught me so much about life and their respective disciplines that I continue to use today. Indeed, it was at an early stage where my passion for science arose, and I would like to thank Ms. Cahatol and Mrs. Nakamatsu for their chemistry courses in high school that refined by interests and gave me the tools I would need to succeed at the next level. I am thankful for Prof. Chueh at Stanford, who generously allowed me to conduct research in his laboratory as a high schooler and for my managers at Applied Materials for giving me insight into the semiconductor industry over the course of three summer internships.

While it was not my dream school coming out of high school, UCSB did turn out to be the school of my dreams. The decision to attend UCSB turned out to be one of the best decisions of my life, followed closely by the leap of faith away from materials science and into organic chemistry. To that end, I am forever grateful to Profs. Aue and Lipshutz for turning a subject I thought I would dread into a calling through their engaging organic

chemistry lectures. I am so fortunate that Prof. Lipshutz took me into his lab and paired me with Nick Lee, who was an excellent mentor for a young chemist and taught me many of the techniques I still use to this day. Prof. Lipshutz has been supportive of my efforts both in and out of the lab, and his tutelage is undoubtedly the main factor leading me to my current position. I am grateful that he has continued to be a reliable point of contact and support system even after my time at UCSB, and I look forward to our paths continuing to cross in the future.

Last, but certainly not least, I have to thank my family for being my support system and for nurturing me throughout my life. During my post-secondary education, our family lost two beloved members in my grandmother, Irandokht, and aunt, Shabnam (or "Shaby Joon"). Though they are not with us to celebrate the completion of my studies, I know they would be so proud and effusive with praise. Their life lessons and love are reflected in everything I accomplish, and I am lucky to have been raised by a group of such incredible women. It is a true shame that only in loss can one fully appreciate a person. I miss you both and hope that we will be reunited one day as a whole, happy family. Shahab, you have been the most caring brother ever since I was born, and I have been so fortunate to have an intelligent and gentle-spirited older brother as a role model. Dad, all the hard work you have done to provide for our family do not go unnoticed. Your work ethic and commitment to the people you love has inspired me and will continue to serve as a model for my future.

Mom…I was questioning whether or not to even write anything here, as no words would do justice to the amount that I love and appreciate you or to what you have meant to my growth. You are the single purest and most loving person I have ever met, and you have loved me as much as anyone can hoped to be loved as a son. You are part of my conscience,

and our hearts are inextricably intertwined. I am so happy that I will be coming home soon and that I will be able to see you on a regular basis again. It has been a long time, but we finally made it.

ABSTRACT

In the Stoltz group, chemical research leverages the interplay between methods development and total synthesis, wherein new synthetic technologies enable the pursuit of novel target compounds and challenges encountered during synthetic campaigns inspire the invention of methodologies. Given the stereochemical complexity of natural products and emerging pharmaceuticals, methods development in our group has focused in particular on the asymmetric construction of all-carbon quaternary centers. Herein is described the development of transition metal catalyzed approaches to the formation of such centers with high levels of stereocontrol. Chapter 1 describes the discovery of an Ir-catalyzed asymmetric allylic alkylation reaction efficiently merging linear, trisubstituted allylic electrophiles with prototypical malonate nucleophiles to generate enantioenriched β-quaternary carbonyl products. The reaction proceeds with low catalyst loadings of iridium and at ambient temperature, marking the first reaction of its kind to be performed under such mild conditions. Appendix 2 highlights recent efforts to develop an Ir-catalyzed process for the doubly stereoselective formation of vicinal quaternary stereocenters. Chapter 2 discloses a more sustainable, Mo-catalyzed alternative to the Ir-catalyzed process in Chapter 1, unveiling thus far unknown reactivity with molybdenum and generating the desired products with outstanding enantioselectivity. This advance was enabled by exhaustive investigation of suitable ligand scaffolds, ultimately leading to the creation of the novel, C1-symmetric ShabyDACH ligand. Chapter 3 discusses the elaboration of a Pd-catalyzed a-vinylation of lactam nucleophiles to forge a-quaternary carbonyls. These products could further be diversified to a range of elusive scaffolds, highlighting their synthetic utility.

PUBLISHED CONTENT AND CONTRIBUTIONS

1. **Moghadam, F. A**.‡; Hicks, E. F.‡; Sercel, Z. P.; Cusumano, A. Q.; Bartberger, M. D.; Stoltz, B. M. Ir-Catalyzed Asymmetric Allylic Alkylation of Dialkyl Malonates Enabling the Construction of Enantioenriched All-Carbon Quaternary Centers. *J. Am. Chem. Soc.* **2022**, *144*, 7983–7987. DOI:10.1021/jacs.2c02960.
    - F. A. M participated in reaction optimization, experimental work, data analysis, and manuscript preparation.
2. Reimann, C. E.; Kim, K. E.; Rand, A. W.; **Moghadam, F. A**.; Stoltz, B. M. *Tetrahedron* **2023**, *130*, 133176. DOI: 10.1016/j.tet.2022.133176.
    - F. A. M participated in collecting references and manuscript preparation.
3. **Moghadam, F. A**.‡; Barbor, J. P.‡; Chan, M.‡; Jette, C.; Sakurai, S.; Stoltz, B. M. Formation of All-Carbon Quaternary Centers via Enantioselective Pd-catalyzed α-Vinylation of γ-Lactams. *Org. Lett.* **2024**, *26*, 7551–7554. DOI: 10.1021.acs.orglett.4c02551.
    - F. A. M participated in reaction optimization, experimental work, data analysis, and manuscript preparation.
4. **Moghadam, F. A**.‡; Cerione, C. S.‡; Stoltz, B. M. Mo-Catalyzed Asymmetric Allylic Alkylation Enabling the Construction of Highly Enantioenriched 1,4-Dicarbonyl Scaffolds. *ChemRxiv* **2025**. DOI: 10.26434/chemrxiv-2025-41644.
    - F. A. M participated in reaction optimization, experimental work, data analysis, and manuscript preparation.

5. Xuyu, Y.; Lee, J.; **Moghadam, F. A**.; Steiner, J.; Soo-Kyung, S.; de Almenara, A. J.; Stoltz, B. M. Predicted new molecules followed by experimental validation for protecting human neurons from oxidative stress induced cytotoxicity. *PNAS* **2025**, submitted.
    - F. A. M participated in reaction optimization, experimental work, data analysis, and manuscript preparation.

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LIST OF ABBREVIATIONS

$[\alpha]_D$	specific rotation at wavelength of sodium D line
ºC	degrees Celsius
Å	Angstrom
λ	wavelength
μ	micro
Aq	aqueous
Ar	aryl
atm	atmosphere
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
bp	boiling point
br	broad
Bz	benzoyl
c	concentration for specific rotation measurements
calc'd	calculated
cm^{-1}	wavenumer(s)
d	doublet
D	deuterium
dba	dibenzylideneacetone
DIBAL	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine

DMF	*N,N*-dimethylformamide
dr	diastereomeric ratio
e.g.	for example (Latin exempli gratia)
ee	enantiomeric excess
EI+	electron impact
equiv	equivalent(s)
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
G	grams
GC	gas chromatography
h	hours
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
Hz	hertz
i.e.	that is (Latin id est)
IPA	isopropanol
i-Pr	*iso*-propyl
IR	infrared (spectroscopy)
J	coupling constant (NMR), exchange coupling constant (diradicals)
K	Kelvin (absolute temperature)

kcal	kilocalorie
KHMDS	potassium hexamethyldisilazide
L	liter; ligand
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
M	multiplet, milli
m/z	mass to charge ratio
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mg	milligram(s)
MHz	megahertz
min	minutes
mol	mole(s)
n-Bu	*n*-butyl
NMR	nuclear magnetic resonance
Pd/C	palladium on carbon
Ph	phenyl
PHOX	phosphinooxazoline (ligand)
PHOX=O	phosphinooxazoline oxide (ligand)
ppm	parts per million
PTSA	*para*-toluenesulfonic acid

q	quartet
R	generic for any atom or functional groups
S	singlet
SCF	self-consistent field
SFC	supercritical fluid chromatography
t	triplet
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
t_R	retention time
UV	ultraviolet
X	anionic ligand or electronegative element

CHAPTER 1

Ir-Catalyzed Asymmetric Allylic Alkylation of Dialkyl Malonates Enabling the Construction of Enantioenriched All-Carbon Quaternary Centers[†]

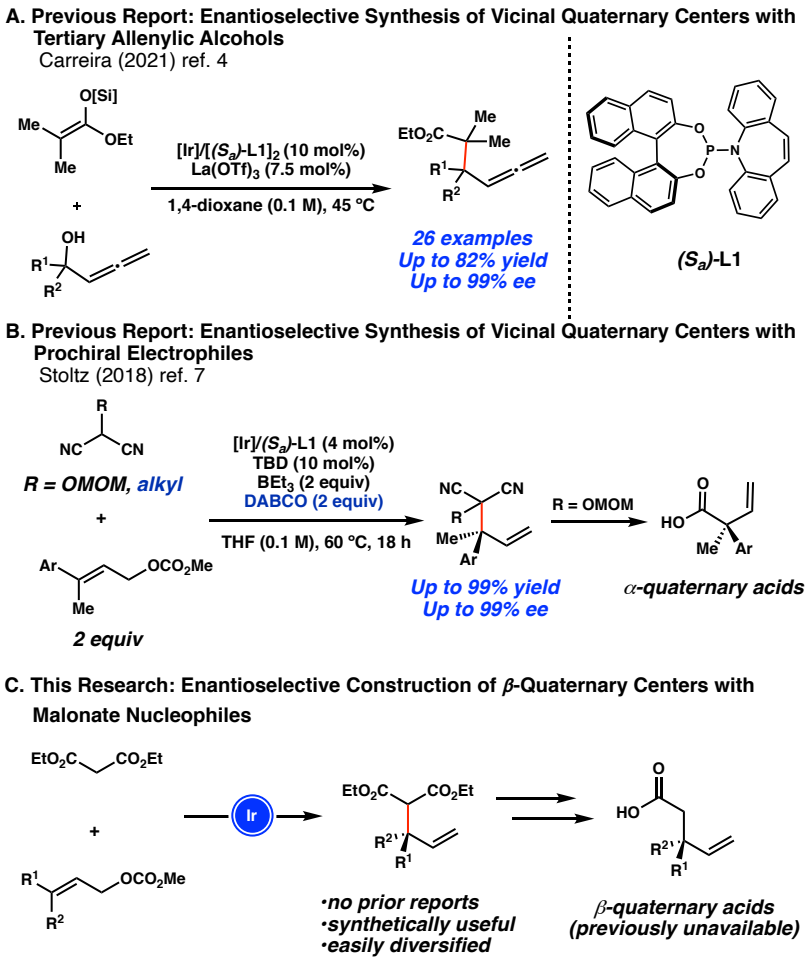
1.1 INTRODUCTION

The enantioselective construction of acyclic all-carbon quaternary centers is a challenging problem in synthetic organic chemistry.[1] Ir-catalyzed asymmetric allylic alkylation has emerged as a powerful methodology for the formation of acyclic stereogenic centers, owing to its exquisite branched regioselectivity.[2] While the enantioselective construction of tertiary stereocenters by virtue of this methodology is well-precedented,[3] the generation of enantioenriched all-carbon quaternary centers by Ir-catalysis remains underexplored.

Expanding on prior reports,[4] Carreira and coworkers disclosed an Ir-catalyzed process that forges enantioenriched quaternary products from silyl ketene acetal nucleophiles and tertiary allenylic alcohol electrophiles (Figure 1.1A).[5] In contrast, our group has most recently utilized linear trisubstituted electrophiles in concert with masked acyl cyanide[6] (Figure 1.1B, R = OMOM) and substituted malononitrile[7] nucleophiles (Figure 1B, R = alkyl) for the formation of all-carbon quaternary centers.

[†]Portions of this chapter have been reproduced with permission from Moghadam, F. A.[†]; Hicks, E. F.[†]; Sercel, Z. P.; Cusumano, A. Q.; Bartberger, M. D.; Stoltz, B. M. *J. Am. Chem. Soc.* **2022**, *144*, 7983–7987. © 2022 American Chemical Society. [†] denotes equal contribution.

Figure 1.1. *Construction of All-Carbon Quaternary Centers via Ir-Catalyzed Allylic Alkylation*



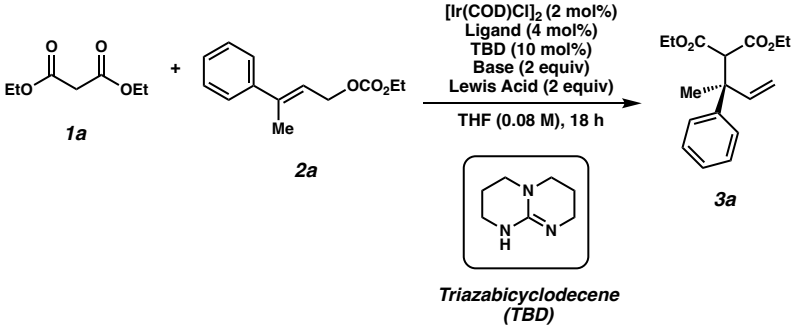
Inspired by these efforts, we aimed to expand the scope of this reaction to include malonate nucleophiles, allowing the formation of β-quaternary 1,3-dicarbonyl compounds (Figure 1.1C). These products could be converted to β-quaternary carboxylic acids, providing a functional handle for further diversification. While malonates have historically served as archetypal nucleophiles in allylic substitution

reactions,[8] their application to the enantioselective construction of β-quaternary centers remains unaddressed.[9] Herein, we report the reaction of malonates with 1,1',2-trisubstituted allylic electrophiles to form acyclic quaternary centers in high levels of enantioselectivity.

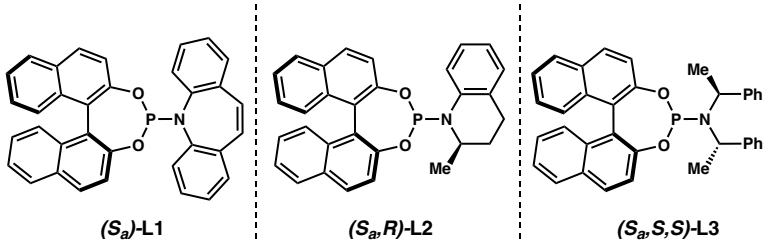
1.2 OPTIMIZATION EFFORTS

Applying our previously successful conditions for malononitrile nucleophiles to this reaction was unsuccessful (Table 1.1, entry 1). Instead, using LiO*t*-Bu as base provided a 23% yield of **3a** when ***(S$_a$)*-L1** was utilized (entry 2), whereas ***(S$_a$, R)*-L2**[10] and ***(S$_a$, S, S)*-L3**[11] performed poorly (entries 3 and 4). While NaOMe failed to improve conversion, employing LiHMDS as the base increased the yield to 46% (entries 5 and 6). Replacement of BEt_3 with commonly employed lithium salts[12] such as LiBr did not lead to appreciable product formation (entry 7). Likewise, employment of $Yb(OTf)_3$ led to minimal yield (entry 8). However, we were pleased that ZnI_2, in concert with LiO*t*-Bu, resulted in an elevated 50% yield (entry 9). Zinc salt additives have indeed proven beneficial to reactivity and selectivity in many related Ir-catalyzed allylic alkylations.[13] Combination of ZnI_2 with HMDS-derived bases resulted in up to 83% yield and 86% ee (entries 10–12). Finally, decreasing the reaction temperature to ambient 21 °C increased the enantiomeric excess to 97%, delivering the desired product in 83% isolated yield, with no detectable linear alkylation product (entry 14). Interestingly, alternative Zn^{2+} sources performed poorly (entries 15–17). VCD was utilized to determine the absolute stereochemistry of this model product (see Experimental Section).

Table 1.1. *Optimization Studies*[a, b, c]



Entry	Ligand	Base	Lewis Acid	Temp.	Yield (%)[a]	ee (%)[b]
1	(S_a)-L1	DABCO	BEt_3	60 °C	0	–
2	(S_a)-L1	LiO*t*-Bu	BEt_3	60 °C	23	–
3	(S_a,*R*)-L2	LiO*t*-Bu	BEt_3	60 °C	0	–
4	(S_a,*S*,*S*)-L3	LiO*t*-Bu	BEt_3	60 °C	<5	–
5	(S_a)-L1	NaOMe	BEt_3	60 °C	10	–
6	(S_a)-L1	LiHMDS	BEt_3	60 °C	46	–
7	(S_a)-L1	LiO*t*-Bu	LiBr	60 °C	<5	–
8	(S_a)-L1	LiO*t*-Bu	$Yb(OTf)_3$	60 °C	14	–
9	(S_a)-L1	LiO*t*-Bu	ZnI_2	60 °C	50	–
10	(S_a)-L1	KHMDS	ZnI_2	60 °C	28	–
11	(S_a)-L1	LiHMDS	ZnI_2	60 °C	80	75
12	(S_a)-L1	NaHMDS	ZnI_2	60 °C	88[c]	86
13	(S_a)-L1	NaHMDS	ZnI_2	40 °C	86	93
14	(S_a)-L1	NaHMDS	ZnI_2	21 °C	83	97
15	(S_a)-L1	NaHMDS	$ZnBr_2$	21 °C	14	–
16	(S_a)-L1	NaHMDS	$Zn(OTf)_2$	21 °C	0	–
17	(S_a)-L1	NaHMDS	$Zn(OAc)_2$	21 °C	83	79



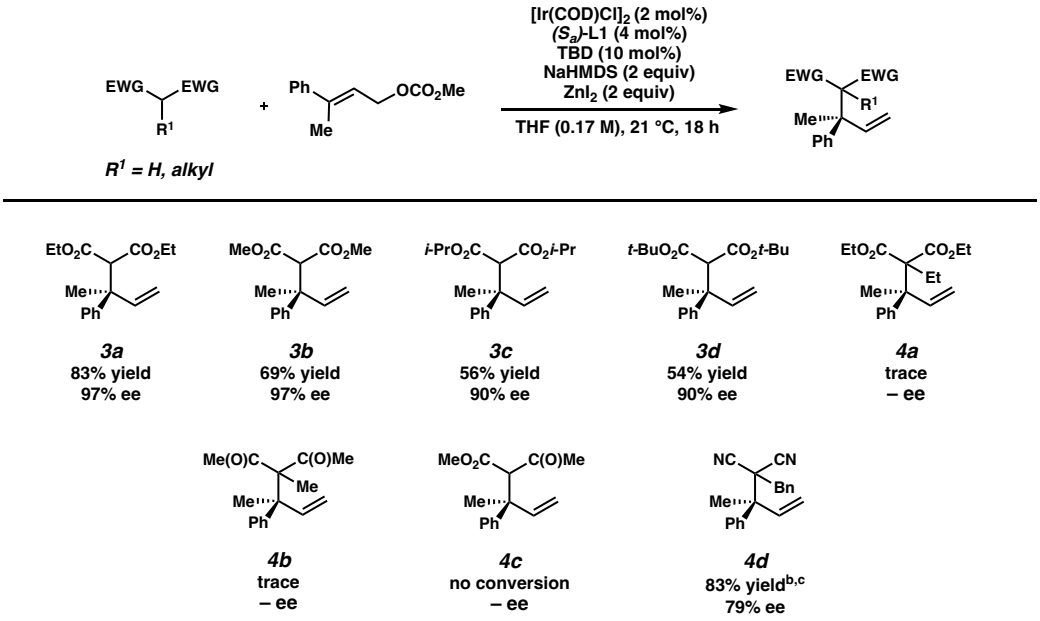
(S_a)-L1 (S_a,*R*)-L2 (S_a,*S*,*S*)-L3

[a]Yields determined by ^1H NMR relative to a CH_2Br_2 internal standard. Reactions conducted at 0.05 mmol scale, utilizing a 1:1 stoichiometry of **1a**:**2a**. [b]Determined by chiral SFC. [c]Average from two experiments.

1.3 SUBSTRATE SCOPE

With optimized reaction conditions in hand, the efficacy of other malonates was explored (Scheme 1.1A). The reaction utilizing dimethyl malonate afforded product **3b** in an identical 97% ee but decreased 69% yield. Use of *i*-Pr (**3c**) or *t*-Bu (**3d**) malonates resulted in diminished 54–56% yields and 90% ee. Unfortunately, substituted malonate **4a**, as well as other stabilized carbon nucleophiles (**4b, 4c**) were unsuccessful under these conditions. Intriguingly, allylic alkylation product **4d** from our prior report[7] could be synthesized in 83% yield but a diminished 79% ee. With diethyl malonate as the optimal nucleophile, we looked to elaborate the electrophile scope.

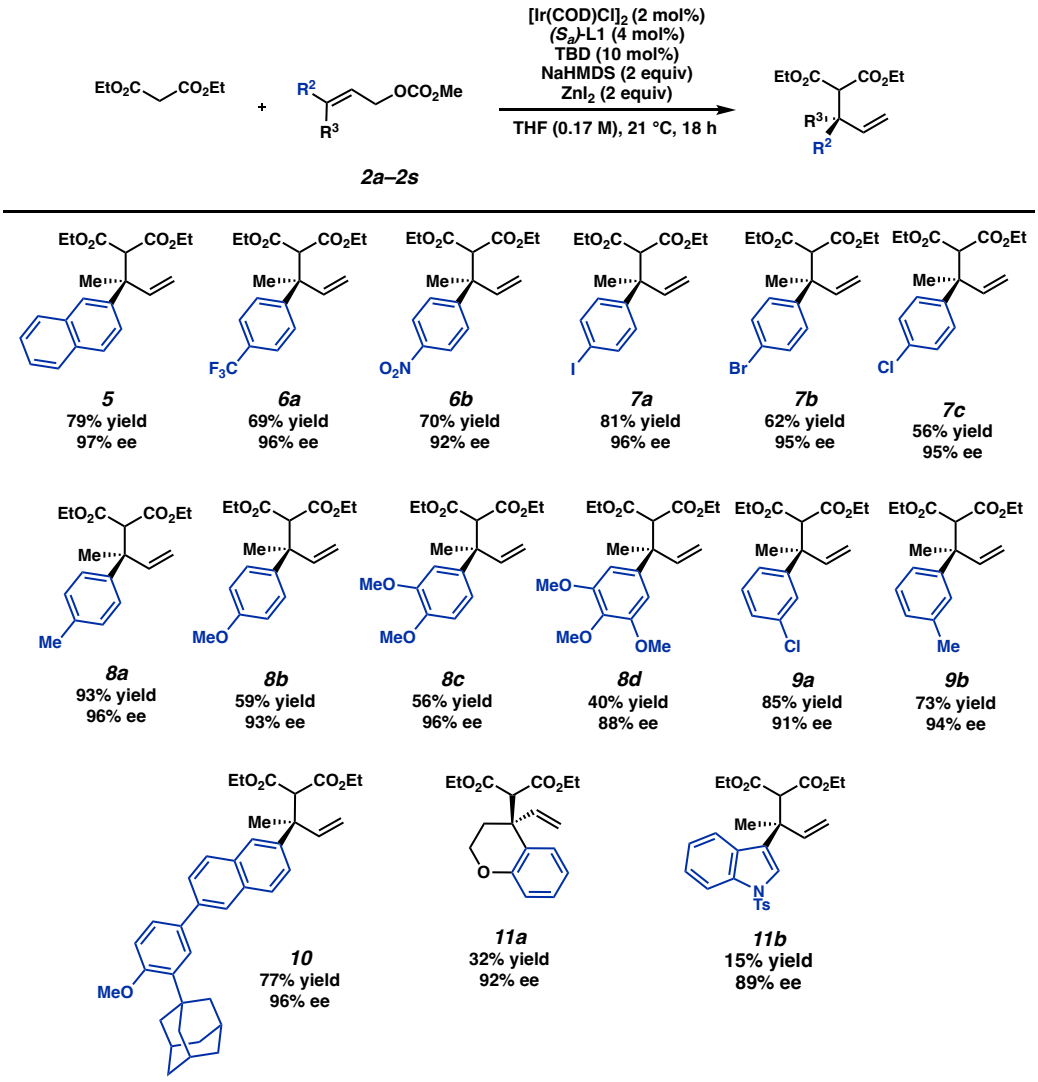
Scheme 1.1. *Nucleophile Investigation*[a,b,c]



[a]Reactions conducted at 0.1 mmol scale, with 1 equiv of both nucleophile and electrophile. [b]Yield determined by ^{1}H NMR relative to a CH_2Br_2 internal standard. [c]Reaction performed at 65 °C.

The alkylation protocol accommodated a range of aryl electrophiles (Scheme 1.2). The 2-naphthyl substituted electrophile underwent the alkylation process in 97% ee (**5**). Electron-withdrawing -CF_3 and -NO_2 substituents at the *para*-position led to the desired products in high yield and ee (**6a, 6b**). Electron-donating *para*-substituents also resulted in

Scheme 1.2. *Electrophile Scope*[a]

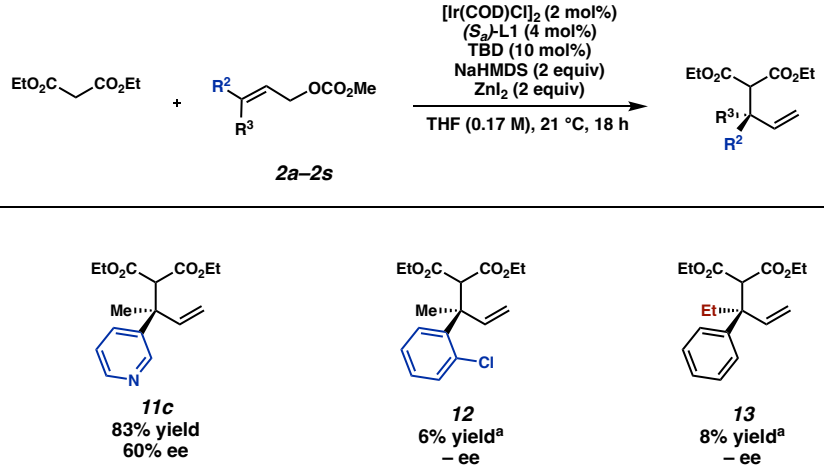


[a]Reactions conducted at 0.1 mmol scale, with 1 equiv of both nucleophile and electrophile.

moderate to high yields and excellent enantioselectivity (**8a, 8d**). *Meta*-substitution was well-tolerated (**9a, 9b**). Heterocyclic scaffolds bearing chromanone and indole-derived fragments proved compatible, (**11a, 11b**), though the 3-pyridyl suffered from poor enantioselectivity (**11c**). Exploring more structurally complex targets, we found that adapalene[14] could be converted to the corresponding allylic methyl carbonate, which underwent the allylic alkylation to yield **10** in 77% yield and 96% ee.

Similar to the limitations of our previous research,[6,7] *ortho*-substitution was not tolerated, possibly indicative of challenges related to oxidative addition (Scheme 1.3, **12**). Furthermore, replacement of the methyl substituent of the electrophile with an ethyl group dramatically decreased the yield to 8%. (**13**). Yield was somewhat recovered when this substituent was constrained in cyclic form, resulting in the

Scheme 1.3. *Electrophile Limitations*[a]

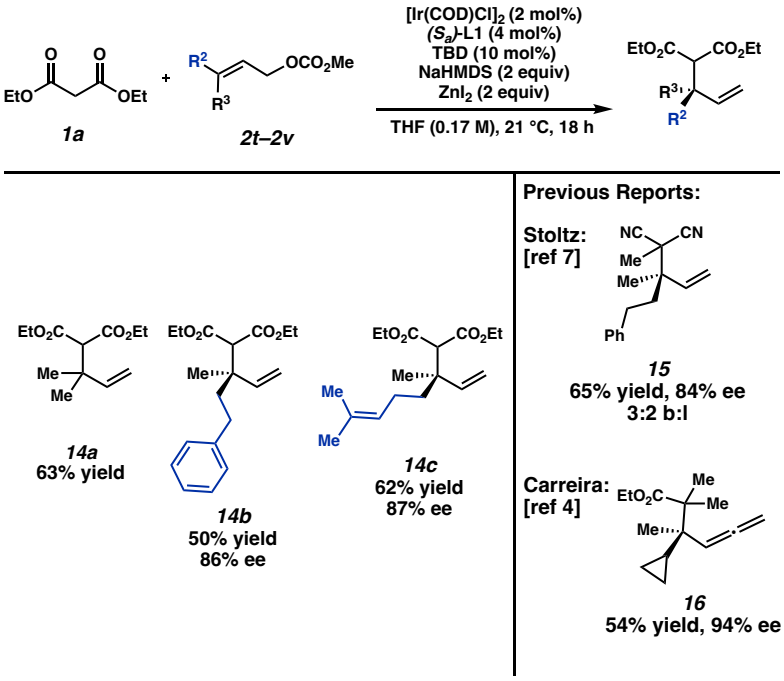


[a]Yields determined by CH_2Br_2 ^1H NMR standard. Reactions performed at 0.1 mmol scale.

formation of product **11a** in 32% yield and 92% ee. Additionally, other electrophile isomers led to poor conversion or poor enantioselectivity (see Experimental Section).

We then turned our attention to the historically challenging alkyl substituted electrophiles (**2t–2v**). Gratifyingly, the corresponding products could be formed in up to 63% yield (Scheme 1.4). Phenethyl-substituted compound **14b** and geranyl methyl carbonate-derived product **14c** were synthesized in 86% and 87% ee, respectively. To the best of our knowledge, the enantiomeric excess and branched-selectivity obtained in this study are among the highest reported for alkyl-substituted electrophiles. In our group's previous investigation, 2-methyl malononitrile reacted with the phenethyl

Scheme 1.4. *Fully-Alkyl Electrophiles: Novel Selectivity and Reactivity*[a]



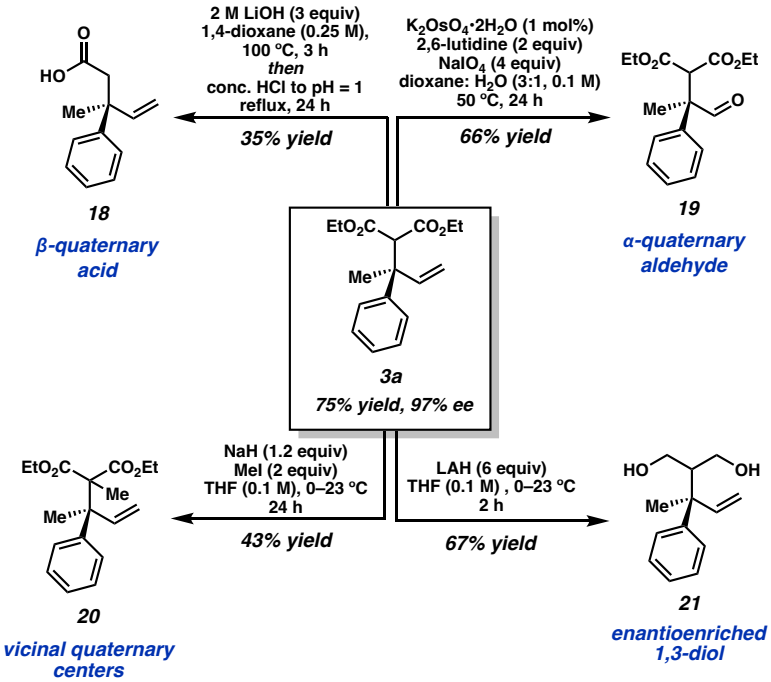
[a]Yields determined by CH_2Br_2 ^{1}H NMR standard. Reactions performed at 0.1 mmol scale.

methyl carbonate to form vicinal quaternary product **15** in a 65% yield and 84% ee, albeit as an inseparable mixture of constitutional isomers.[7] The Carreira group reported the substitution of a silyl ketene acetal with a cyclopropyl-substituted allenylic electrophile to form allene **16** in 94% ee,[4] but it is worth noting that the cyclopropyl substituent exhibits substantial sp^2 character and that the allenylic systems do not entail the same rationale for branched/linear selectivity.

1.4 DERIVATIZATIONS AND CONCLUSION

To explore the synthetic utility of this technology, **3a** and **8b** were prepared on a 1 mmol scale, the former in 75% yield and 97% ee and the latter in 59% yield and 96%

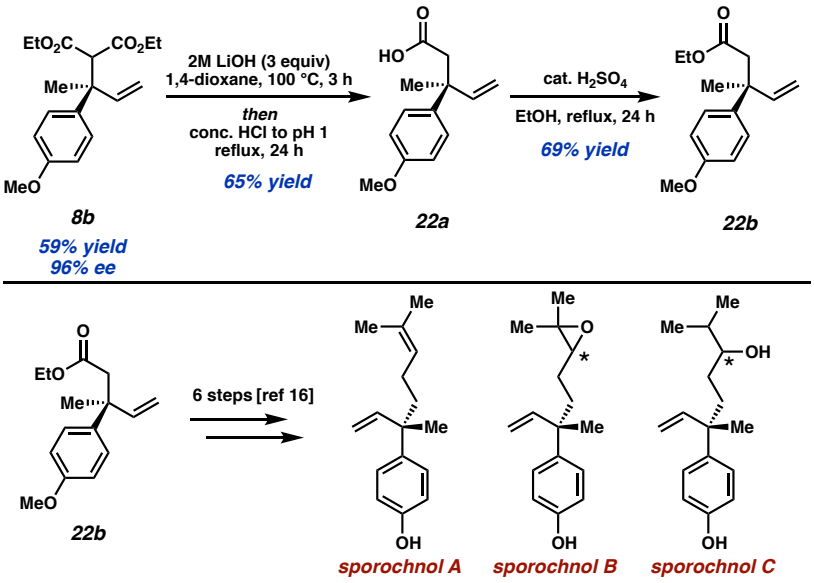
Scheme 1.5. *Product Diversification*



ee. A saponification-decarboxylation sequence furnished β-quaternary acid **18** in moderate yield (Scheme 1.5). Lemieux–Johnson oxidation[15] provided α-quaternary aldehyde **19** in 66% yield. Methylation of **3a** generated vicinal quaternary species **20** in 43% yield. Exhaustive reduction of the diester with lithium aluminum hydride afforded 1,3-diol **21** in 67% yield.

Utilizing the established saponification-decarboxylation, **8b** was converted to β-quaternary acid **22a** in 65% yield (Scheme 1.6). Subsequent Fischer esterification generated the desired ethyl ester **22b** in 69% yield. **22b** was previously prepared in racemic form by Prasad and coworkers in their formal synthesis of sporochnols A–C,[16,17] By accessing **22b** in enantioenriched form, we achieved an asymmetric formal synthesis of these sporochnol natural products.

Scheme 1.6. *Formal Asymmetric Synthesis of Sporochnols A–C*



In summary, we have developed a novel method for the synthesis of highly enantioenriched, acyclic β-quaternary carbonyl compounds via an Ir-catalyzed allylic alkylation. This transformation proceeds under mild conditions, and a broad range of allylic electrophiles, including fully alkyl-substituted substrates, are well-tolerated. Further exploration of the reaction mechanism is currently underway.

1.5 EXPERIMENTAL SECTION

1.5.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[18] Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 μm) was used for flash chromatography. ^{1}H NMR spectra were recorded on Varian Inova 500 MHz and Bruker 400 MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm). ^{13}C NMR spectra were recorded on a Varian Inova 500 MHz spectrometer (125 MHz) and Bruker 400 MHz spectrometers (100 MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet. Data for ^{13}C NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium

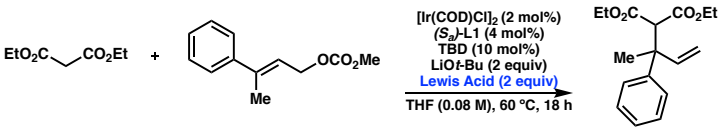
D-line (589 nm), using a 100 mm path-length cell. Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system utilizing Chiralpak (AD-H, AS-H or IC) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing Chiralpak (IH) or Chiralcel (OD-H) columns (4.6 mm x 25 cm) both obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in field ionization (FI+) or field desorption (FD+) mode, or an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI), or mixed ionization mode (MM: ESI-APCI+). Absolute configuration of **3a** was determined by vibrational circular dichroism, and all other products are assigned by analogy. Reagents were purchased from commercial sources and used as received unless otherwise stated. Ligand ***(S$_a$)-L1*** was prepared according to a literature procedure.[11]

List of Abbreviations:

ee – enantiomeric excess, SFC – supercritical fluid chromatography, HPLC – high-performance liquid chromatography, TLC – thin-layer chromatography, TBD – 1,5,7-triazabicyclo[4.4.0]dec-5-ene, COD – *cis,cis*-1,5-cyclooctadiene, COE – *cis*-cyclooctene, DIBAL – diisobutylaluminum hydride, LAH – lithium aluminum hydride, NaHMDS – sodium bis(trimethylsilyl)amide, IPA – isopropanol, EtOAc – ethyl acetate, Dr – dram

1.5.2 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

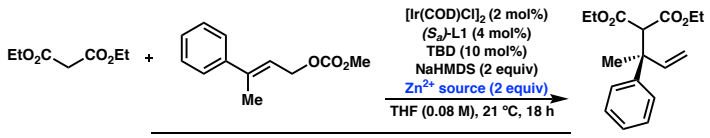
Table 1.2. *Evaluation of Additional Lewis Acids*



Entry	Lewis Acid	Yield[a]
1	BEt_3	23%
2	BPh_3	23%
3	CPh_3BF_4	0
4	$Yb(OTf)_3$	14%
5	$ZrCl_4$	trace
6	$Sc(OTf)_3$	0
7	$La(O\textit{i}\text{-}Pr)_3$	0
8	ZnI_2	50%

[a]determined by ^{1}H NMR with CH_2Br_2 as internal standard.

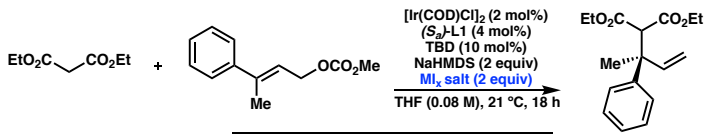
Table 1.3. *Evaluation of Other Zn(II) Sources*



Entry	Zn^{2+} source	Yield[a]	ee[b]
1	ZnI_2	83%	97%
2	$Zn(OTf)_2$	0	n.d.
3	$ZnBr_2$	14%	n.d.
4	$ZnCl_2$	17%	n.d.
5	ZnF_2	0	n.d.
6	$Zn(OAc)_2$	83%	79%

[a]determined by ^{1}H NMR with CH_2Br_2 as internal standard. [b]determined by chiral SFC.

Table 1.4. *Evaluation of other I⁻ Sources*



Entry	I⁻ salt	Zn additive	Yield[a]
1	TBAI	$ZnCl_2$	9%
2	NaI	$ZnCl_2$	17%
3	CuI	none	19%

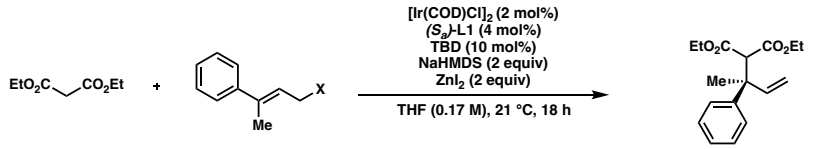
[a]determined by ^{1}H NMR with CH_2Br_2 as internal standard.

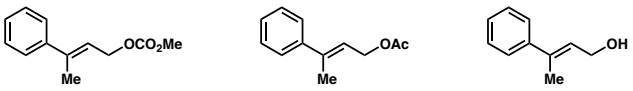
Table 1.5. *Evaluation of Solvents*

Entry	Solvent	Yield[a]	ee[b]
1	THF	83%	97%
2	Et_2O	0	n.d.
3	MTBE	trace	n.d.
4	1,4-dioxane	trace	n.d.
5	PhMe	trace	n.d.
6	2-Me-THF	68%	90%

[a]isolated yields. [b]determined by chiral SFC.

Scheme 1.7. *Evaluation of Other Leaving Groups*

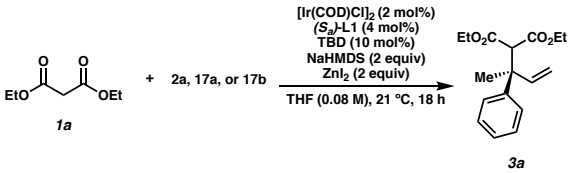




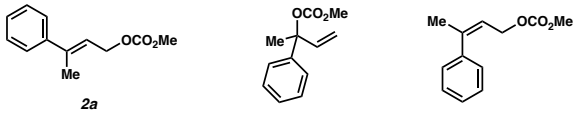
2a	*2aa*	*2ab*
83% yield, 97% ee	no conversion	18% yield[a]

[a]yield determined by ^{1}H NMR internal standard

Scheme 1.8. *Isomers of Model Electrophile*

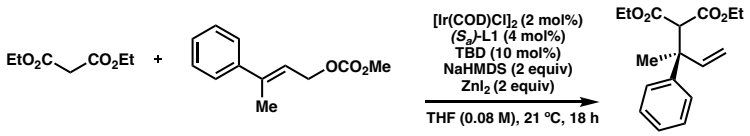


Isomers of Electrophile



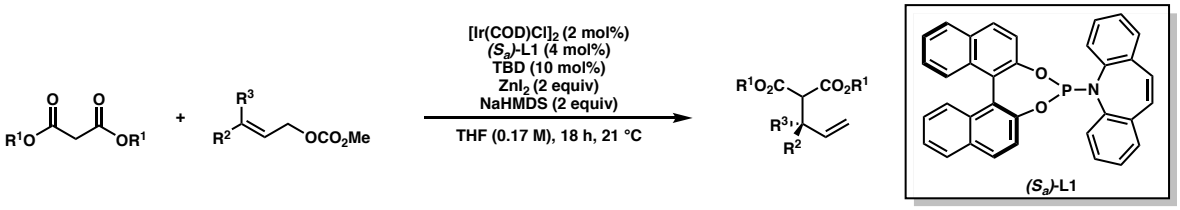
2a	*17a*	*17b*
83% yield 97% ee	87% yield 0% ee	14% yield[a] – ee

Table 1.6. *Control Studies*

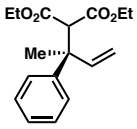


Entry	Deviation from Standard	Result[ab]
1	No TBD	trace
2	No Catalyst	no conversion
3	No NaHMDS	no conversion
4	No ZnI_2	no conversion
5	1 equiv NaHMDS	13% yield
6	1 equiv ZnI_2	86% yield, 90% ee
7	8 mol% (S_a)-L1	trace
8	$[Ir(COE)Cl]_2$	trace

Iridium-Catalyzed Allylic Alkylation Reactions: General Procedure A

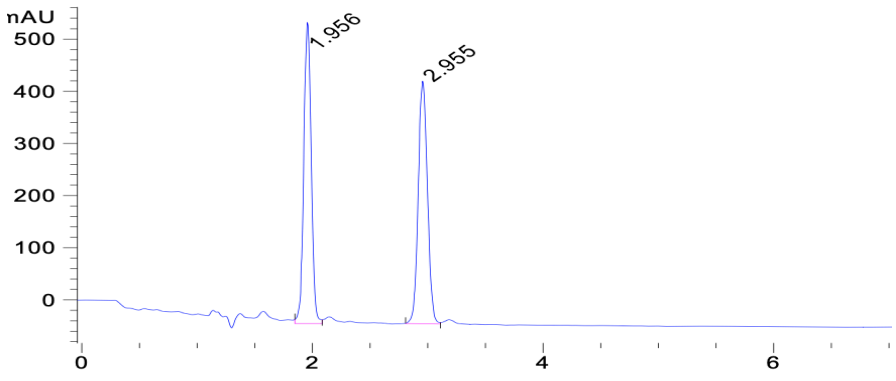


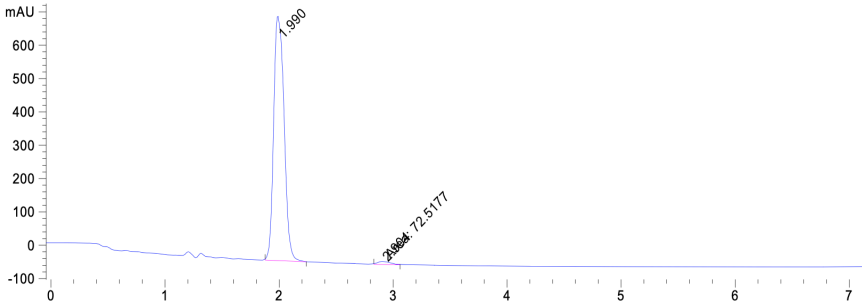
In a nitrogen-filled glovebox, a catalyst solution of $[Ir(COD)Cl]_2$ (6.5 mg/mL), ***(S_a)-L1*** (10 mg/mL), and TBD (7 mg/mL) in THF was stirred for 20 min at 25 °C. In separate vials, solutions of *(E)*-allylic carbonate (0.5 mmol/mL) and of malonate nucleophile (0.5 mmol/mL) were prepared in THF. During that time, the reaction vial was charged with ZnI_2 (63.8 mg, 0.2 mmol, 2.0 equiv) and NaHMDS (36.7 mg, 0.2 mmol, 2.0 equiv). 0.2 mL of the nucleophile solution (0.1 mmol, 1.0 equiv) was added to the reaction vial and stirred for 5 min, followed by 0.2 mL of catalyst solution, and finally 0.2 mL of allylic carbonate solution (0.1 mmol, 1.0 equiv). The vial was sealed with a Teflon-lined cap, removed from the glovebox, and stirred at 21 °C for 18 h unless noted otherwise. After 18 h, 3 mL 0.5 M HCl was added to the crude reaction mixture, which was then extracted three times with ethyl acetate, dried over $MgSO_4$, concentrated, and purified by silica gel flash chromatography or preparatory TLC to provide the desired alkylation product.



Diethyl (*R*)-2-(2-phenylbut-3-en-2-yl)malonate (3a)

Prepared according to general procedure A using carbonate **2a** (20.6 mg, 0.1 mmol) and diethyl malonate (16.0 mg, 0.1 mmol). Purification by preparative TLC (10% EtOAc in hexanes) to provide a colorless oil (24.1 mg, 83% yield, 97% ee). The general procedure using carbonate **2a** (206.1mg, 1.0 mmol) and diethyl malonate (160.2 mg, 1.0 mmol). Purification by column chromatography (10% EtOAc in hexanes) provided a light orange oil (217 mg, 75% yield, 97% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 4H), 7.21 – 7.17 (m, 1H), 6.59 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.25 (dd, *J* = 10.8, 1.0 Hz, 1H), 5.12 (dd, *J* = 17.5, 1.0 Hz, 1H), 4.10 – 4.00 (m, 5H), 1.68 (s, 3H), 1.13 (td, *J* = 7.1, 5.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 145.6, 128.2, 126.3, 114.4, 61.1, 61.0, 60.9, 46.3, 23.6, 14.0, 13.9; IR (Neat Film, NaCl) 3055, 2981, 1755, 1731, 1599, 1493, 1444, 1413, 1368, 1320, 1268, 1230, 1133, 1096, 1037, 919, 761, 700 cm^{-1}; HRMS (FI+) *m/z* calc'd for $C_{17}H_{22}O_4$: 290.1513, found 290.1527; $[\alpha]_D^{25}$ –7.4 (*c* 1.0, $CHCl_3$); SFC Conditions: 5% MeOH, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R (min): major = 1.99, minor = 2.90.





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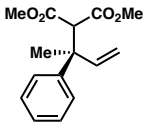
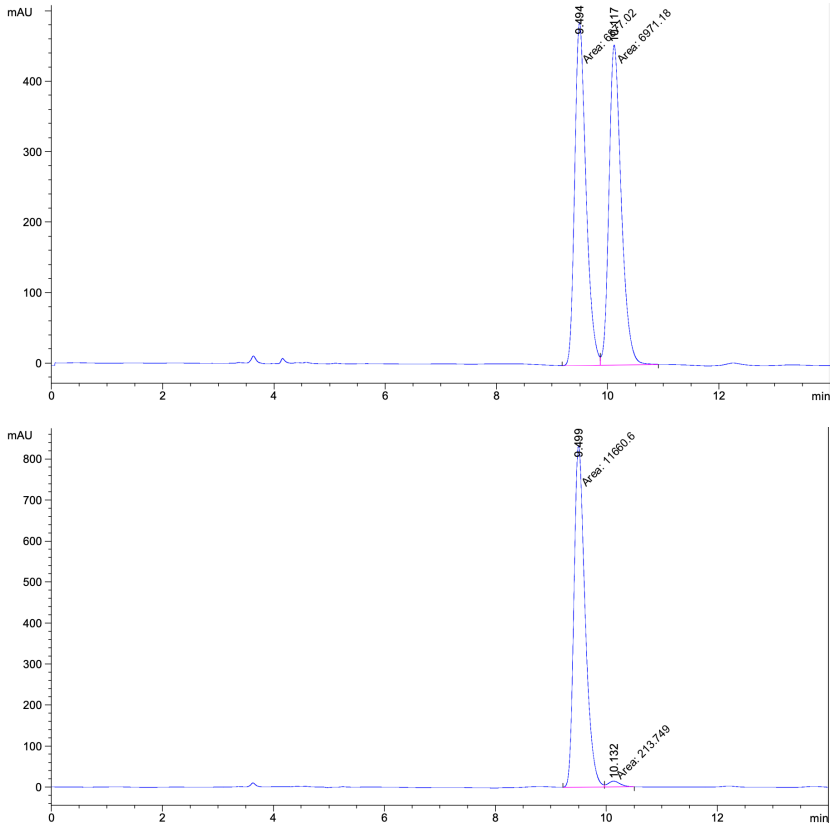


Dimethyl (*R*)-2-(2-phenylbut-3-en-2-yl)malonate (3b)

Prepared according to general procedure A using carbonate **2a** (20.6 mg, 0.1 mmol) and dimethyl malonate (13.2 mg, 0.1 mmol). Purification by preparative TLC (10% EtOAc in hexanes) provided a colorless oil (18.0 mg, 69% yield, 97% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 4H), 7.20 (ddt, *J* = 7.1, 6.1, 1.9 Hz, 1H), 6.58 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.26 (dd, *J* = 10.8, 1.0 Hz, 1H), 5.12 (dd, *J* = 17.5, 1.0 Hz, 1H), 4.08 (s, 1H), 3.59 (d, *J* = 1.1 Hz, 6H), 1.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 168.2, 145.5, 142.7, 128.4, 126.6, 126.3, 114.6, 60.9, 52.3, 52.2, 46.4, 23.7; IR (Neat Film, NaCl) 2951, 1758, 1735, 1433, 1321, 1231, 1133, 1029, 925 cm^{-1}; HRMS (FI+) *m/z* calc'd for $C_{15}H_{18}O_4$: 262.1110 found 262.1214; $[\alpha]_D^{25}$ +15.8 (*c* 1.0, $CHCl_3$); HPLC Conditions: 2% IPA, 1.0 mL/min, Chiralcel OD-H column, λ = 210 nm, t_R (min): major = 9.50, minor = 10.13.



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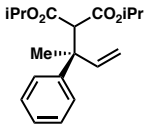
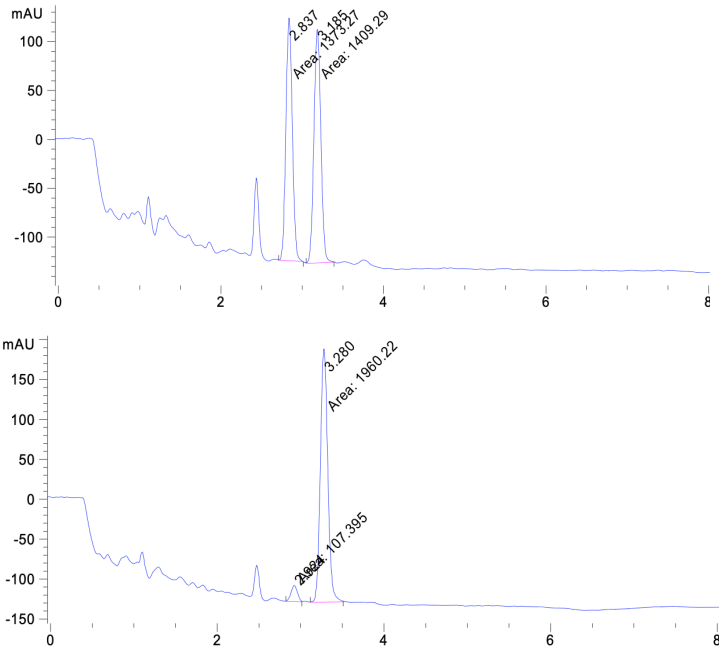
2	10.132	FM	0.2497	213.74857	14.26826	1.8001



Diisopropyl (*R*)-2-(2-phenylbut-3-en-2-yl)malonate (3c)

Prepared according to general procedure A using carbonate **2a** (20.6 mg, 0.1 mmol) and diisopropyl malonate (18.8 mg, 0.1 mmol). Purification by preparative TLC (10% EtOAc in hexanes) provided a colorless oil (17.9 mg, 56% yield, 90% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 4H), 7.18 (ddt, J = 7.7, 6.6, 1.4 Hz, 1H), 6.59 (dd, J = 17.5, 10.8 Hz, 1H), 5.25 (dd, J = 10.8, 1.1 Hz, 1H), 5.11 (dd, J = 17.5, 1.1 Hz, 1H), 4.91 (dp, J = 10.6,

6.2 Hz, 2H), 3.99 (s, 1H), 1.67 (s, 3H), 1.18 – 1.06 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 146.0, 142.9, 128.3, 126.4, 126.4, 114.5, 68.8, 68.6, 61.3, 46.3, 24.0, 21.7, 21.7, 21.5. IR (Neat Film, NaCl) 2980, 2938, 1754, 1728, 1446, 1374, 1315, 1276, 1232, 1140, 1102, 1028, 913 cm^{-1}; HRMS (FI+) *m/z* calc'd for $C_{19}H_{26}O_4$: 318.1826, found 318.1843; $[\alpha]_D^{25}$ +12.0 (*c* 1.0, $CHCl_3$); SFC Conditions: 5% IPA, 2.5 mL/min, Chiralpak IC column, λ = 210 nm, t_R (min): minor = 2.92, major = 3.28.



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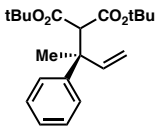
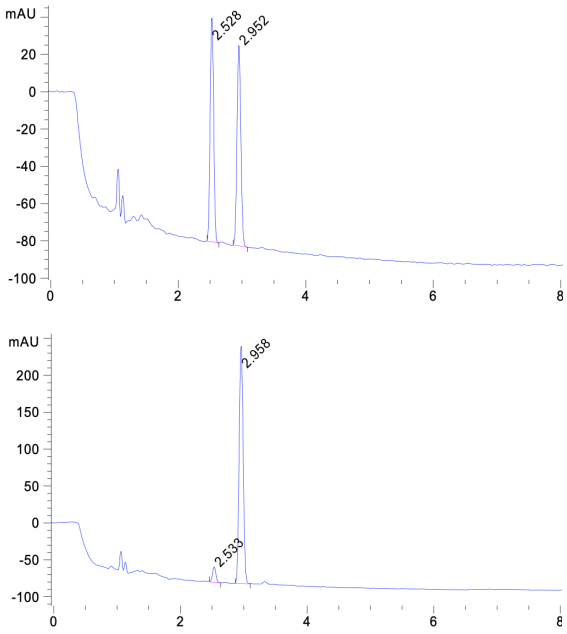


Di-*tert*-butyl (*R*)-2-(2-phenylbut-3-en-2-yl)malonate (3d)

Prepared according to general procedure A using carbonate **2a** (20.6 mg, 0.1 mmol) and di-*tert*-butyl malonate (21.6 mg, 0.1 mmol). Purification by preparative TLC (5% EtOAc in hexanes) provided a colorless oil (18.6 mg, 54% yield, 90% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 4H), 7.22 – 7.14 (m, 1H), 6.58 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.25 (dd, *J* = 10.7, 1.2 Hz, 1H), 5.11 (dd, *J* = 17.6, 1.2 Hz, 1H), 3.87 (s, 1H), 1.65 (s, 3H), 1.34 (s, 9H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 167.3, 146.4, 143.1, 128.2, 126.4, 126.3, 114.3, 81.7, 81.5, 62.7, 46.3, 27.9, 27.8, 24.1; IR (Neat Film, NaCl) 2976, 1727, 1455, 1392, 1367, 1317, 1246, 1123, 972, 914, 845, 746, 699, 668 cm^{-1}; HRMS (FI+) *m/z* calc'd for $C_{21}H_{30}O_4$: 346.2139 found 346.2151; $[\alpha]_D^{25}$ –6.5 (*c* 1.0, $CHCl_3$); SFC Conditions: 5% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): minor = 2.53, major = 2.95.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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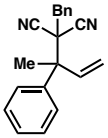
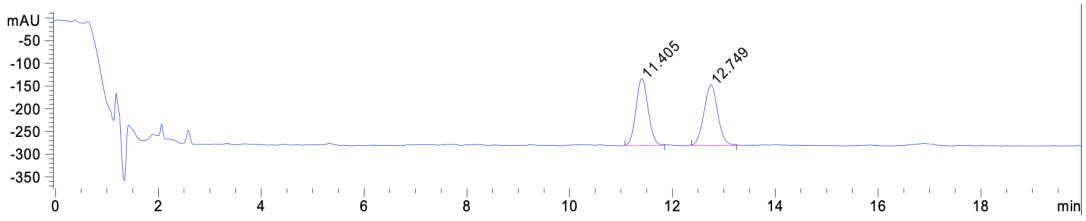
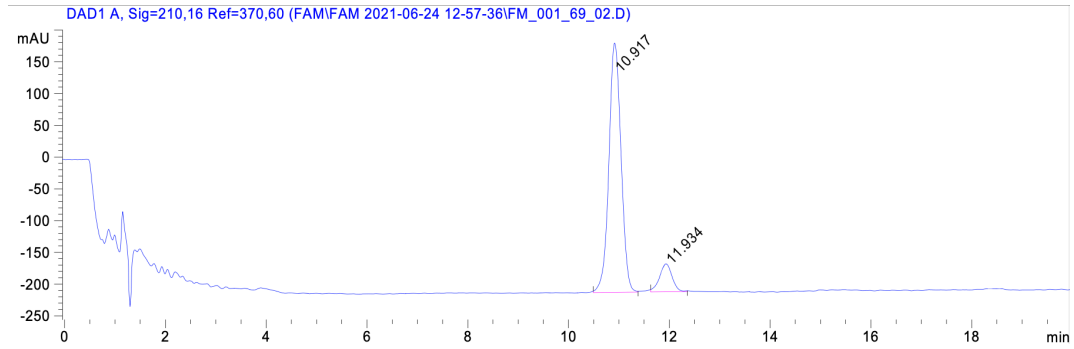
2	2.958	BB	0.0684	1396.19421	322.89331	94.7399



2-Benzyl-2-(2-phenylbut-3-en-2-yl)malononitrile[19] (4d)

Prepared according to general procedure A using carbonate **2a** (20.6 mg, 0.1 mmol) and benzyl malononitrile (15.6 mg, 0.1 mmol). Purification by preparative TLC (10% EtOAc in hexanes) afforded a colorless oil (83% yield, 79% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.60 (m, 2H), 7.48 – 7.29 (m, 8H), 6.64 (dd, *J* = 17.3, 10.9 Hz, 1H), 5.60 (d, *J* = 11.0 Hz, 1H), 5.46 (d, *J* = 17.3 Hz, 1H), 3.01 (d, *J* = 13.5 Hz, 1H), 2.94 (d, *J* = 13.4 Hz, 1H), 1.93 (s, 3H). All characterization data matched those reported in the literature.





Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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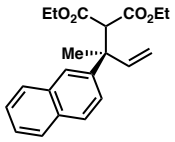
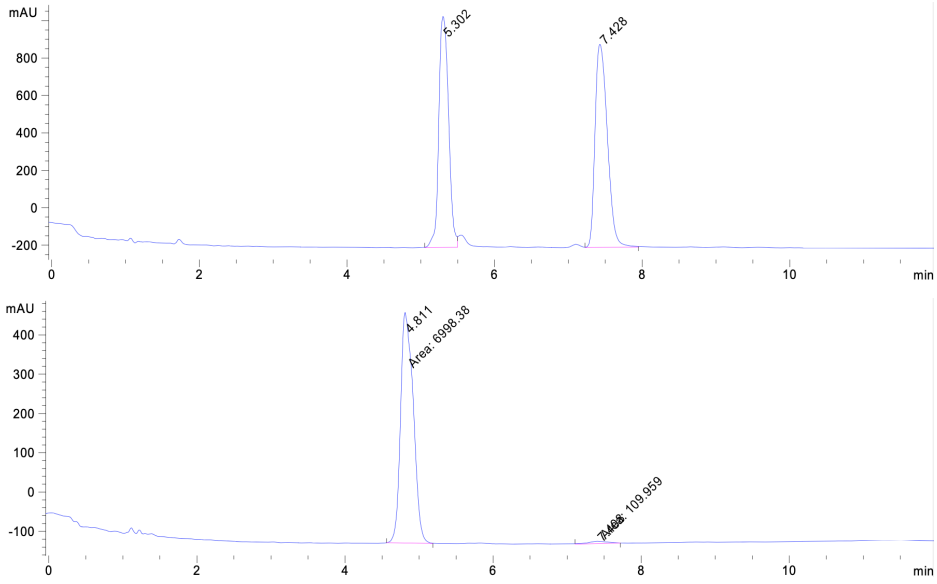
2	11.934	BB	0.2621	763.25513	44.05166	10.4225

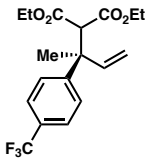


Diethyl (*R*)-2-(2-(naphthalen-2-yl)but-3-en-2-yl)malonate (5)

Prepared according to general procedure A using carbonate **2b** (25.6 mg, 0.1 mmol) and diethyl malonate (16.0 mg, 0.1 mmol). Purification by preparative TLC (10% EtOAc in hexanes) provided a colorless oil (26.8 mg, 79% yield, 97% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.68 (m, 4H), 7.46 (dtd, *J* = 14.5, 7.9, 3.6 Hz, 3H), 6.69 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.32 (dd, *J* = 10.9, 1.0 Hz, 1H), 5.17 (dd, *J* = 17.6, 1.0 Hz, 1H), 4.18 (s, 1H), 4.04 (qd, *J* = 7.1, 2.1 Hz, 4H), 1.78 (s, 3H), 1.08 (td, *J* = 7.1, 4.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 167.8, 143.0, 142.8, 133.4, 132.1, 128.2, 127.9, 127.5, 126.1, 125.9, 125.2, 124.8, 114.8, 61.3, 61.2, 60.8, 46.6, 23.8, 14.0, 14.0; IR (Neat Film, NaCl) 2977, 1754, 1728, 1367, 1314, 1229, 1131, 1034, 921, 749, cm^{-1}; HRMS (FI+) *m/z* calc'd for $C_{21}H_{24}O_4$: 340.1669 found 340.1695; $[\alpha]_D^{25}$ +18.5 (*c* 1.0, $CHCl_3$); SFC Conditions: 5% MeOH, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R (min): minor = 5.21, major = 5.92.

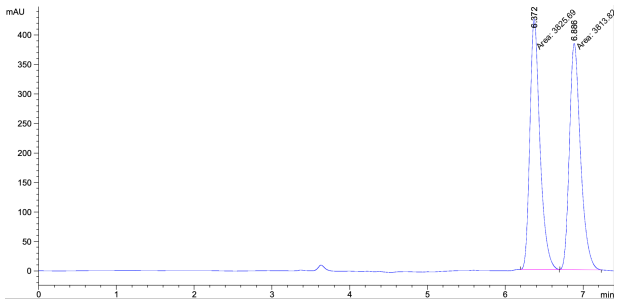


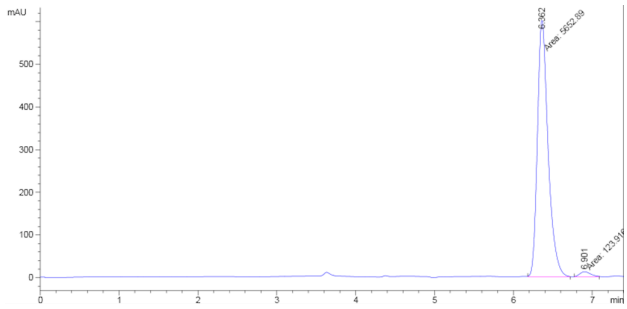
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.811	MM	0.1988	6998.37939	586.80725	98.4531
2	7.408	MM	0.3068	109.95891	5.97275	1.5469



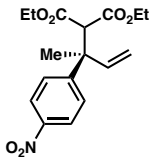
Diethyl (*R*)-2-(2-(4-(trifluoromethyl)phenyl)but-3-en-2-yl)malonate (6a)

Prepared according to general procedure A using carbonate **2c** (27.4 mg, 0.1 mmol) and diethyl malonate (16.0 mg, 0.1 mmol). Purification by preparative TLC (10% EtOAc in hexanes) provided a pale yellow oil (24.6 mg, 69% yield, 96% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 – 7.52 (m, 2H), 7.48 – 7.42 (m, 2H), 6.57 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.30 (dd, *J* = 10.9, 0.8 Hz, 1H), 5.14 (dd, *J* = 17.5, 0.8 Hz, 1H), 4.10 – 4.04 (m, 4H), 4.04 (s, 1H), 1.68 (s, 3H), 1.14 (td, *J* = 7.1, 5.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 167.4, 149.8, 149.8, 141.9, 129.2, 128.9, 128.5, 128.2, 126.7, 125.2, 125.2, 125.1, 125.1, 115.3, 61.3, 61.2, 60.6, 46.3, 23.8, 13.9, 13.9, the splitting pattern between 128–129 ppm is caused by ^{19}F and also present in the parent carbonate; ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.5; IR (Neat Film, NaCl) 2983, 1756, 1731, 1617, 1447, 1414, 1369, 1328, 1232, 1169, 1125, 1080, 1056, 1037, 1014, 925, 843, 675 cm^{-1}; HRMS (FI+) *m/z* calc'd for $C_{18}H_{21}O_4F_3$: 358.1387, found 358.1403; $[\alpha]_D^{25}$ –5.6 (*c* 0.5, $CHCl_3$); HPLC Conditions: 2% IPA, 1.0 mL/min, Chiralcel OD-H column, λ = 210 nm, t_R (min): major = 6.36, minor = 6.90.



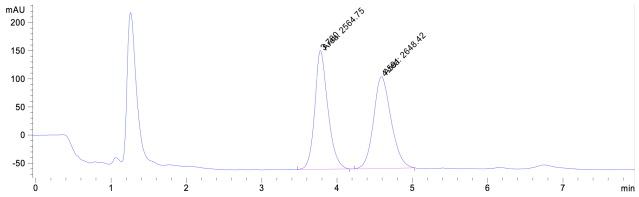


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.362	MM	0.1566	5652.89453	601.51556	97.8549
2	6.901	MM	0.1663	123.91565	12.41713	2.1451



Diethyl (*R*)-2-(2-(4-nitrophenyl)but-3-en-2-yl)malonate (6b)

Prepared according to general procedure A using carbonate **2d** (25.1 mg, 0.1 mmol) and diethyl malonate (16.0 mg, 0.1 mmol). Purification by preparative TLC (10% EtOAc in hexanes) provided a pale yellow oil (23.6 mg, 70% yield, 92% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 9.0 Hz, 2H), 7.50 (d, *J* = 8.9 Hz, 2H), 6.56 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.34 (dd, *J* = 10.8, 0.7 Hz, 1H), 5.16 (dd, *J* = 17.5, 0.7 Hz, 1H), 4.14 – 4.01 (m, 5H), 1.68 (s, 3H), 1.16 (dt, *J* = 8.3, 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 167.3, 153.6, 146.5, 141.4, 127.4, 123.6, 116.0, 61.6, 61.5, 60.7, 46.6, 24.1, 14.1, 14.1; IR (Neat Film, NaCl) 2981, 1731, 1595, 1520, 1347, 1367, 1347, 1231, 1135, 1038, 931, 851, 698 cm^{-1}; HRMS (FI+) *m/z* calc'd for $C_{17}H_{21}NO_6$: 335.1363, found 335.1375; $[\alpha]_D^{25}$ +9.5 (*c* 0.5, $CHCl_3$); SFC Conditions: 5% IPA, 2.5 mL/min, Chiralcel OB-H column, λ = 210 nm, t_R (min): major = 3.70, minor = 4.50.



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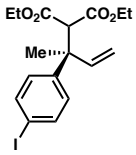
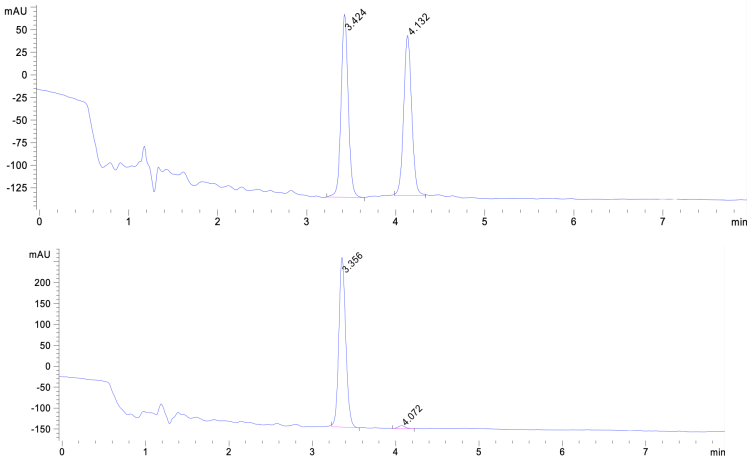
1	3.698	MM	0.1892	4249.46777	374.28323	96.6506
2	4.498	MM	0.2219	147.26280	11.06176	3.3494



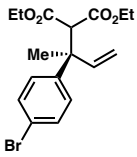
Diethyl (*R*)-2-(2-(4-iodophenyl)but-3-en-2-yl)malonate (7a)

Prepared according to general procedure A using carbonate **2e** (33.2 mg, 0.1 mmol) and diethyl malonate (16.0 mg, 0.1 mmol). Purification by preparative TLC (10% EtOAc in hexanes) provided a light yellow oil (33.7 mg, 81% yield, 96% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.6 Hz, 2H), 7.07 (d, *J* = 8.7 Hz, 2H), 6.52 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.25 (dd, *J* = 10.8, 0.9 Hz, 1H), 5.10 (dd, *J* = 17.6, 0.9 Hz, 1H), 4.06 (q, *J* = 7.1 Hz, 4H), 3.97 (s, 1H), 1.63 (s, 3H), 1.14 (td, *J* = 7.1, 1.3 Hz, 6H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 167.2, 145.3, 141.9, 137.0, 128.3, 114.7, 91.8, 61.1, 61.0, 60.4, 45.8, 23.4, 13.8, 13.7; IR (Neat Film, NaCl) 2980, 1755, 1730, 1486, 1465, 1412, 1392, 1367, 1322, 1264, 1231, 1133, 1095, 1078, 1037, 1003, 923, 860, 822 cm^{-1}; HRMS (FI+) *m/z* calc'd for $C_{29}H_{30}O_4I$: 416.0479, found 416.0472; $[\alpha]_D^{25}$ +12.9 (*c* 1.0,

$CHCl_3$); SFC Conditions: 5% IPA, 2.5 mL/min, Chiralpak OJ-H column, λ = 210 nm, t_R (min): major = 3.36, major = 4.07.



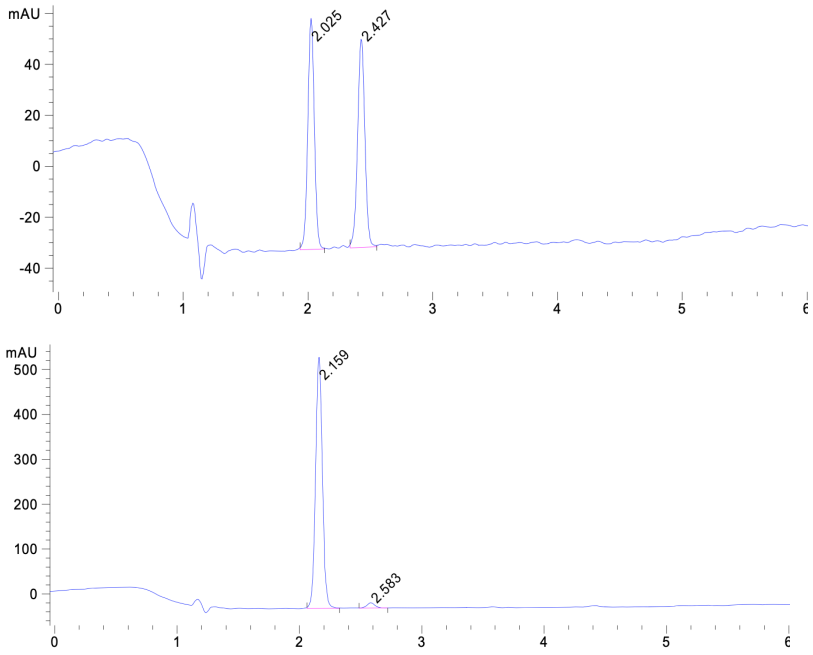
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.356	BB	0.0893	2337.94263	405.50409	98.3082
2	4.072	BB	0.0901	40.23287	6.89535	1.6918



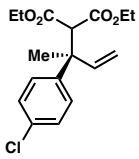
Diethyl (*R*)-2-(2-(4-bromophenyl)but-3-en-2-yl)malonate (7b)

Prepared according to general procedure A using carbonate **2f** (28.5 mg, 0.1 mmol) and diethyl malonate (16.0 mg, 0.1 mmol). Purification by preparative TLC (10% EtOAc in hexanes) provided a pale yellow oil (22.7 mg, 62% yield, 95% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.7 Hz, 2H), 7.20 (d, *J* = 8.7 Hz, 2H), 6.53 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.26 (dd, *J* = 10.8, 0.9 Hz, 1H), 5.10 (dd, *J* = 17.5, 0.9 Hz, 1H), 4.06 (q, *J* = 7.1 Hz, 4H), 3.97 (s, 1H), 1.64 (s, 3H), 1.14 (td, *J* = 7.1, 1.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 167.6, 144.9, 142.3, 131.4, 128.3, 120.6, 115.0, 61.4, 61.3, 60.8, 46.1, 23.8, 14.1, 14.1; IR (Neat Film, NaCl) 2981, 1755, 1731, 1488, 1394, 1367, 1321, 1268, 1229, 1133,

1095, 1081, 1038, 1008, 925, 812 cm^{-1}; HRMS (FI+) *m/z* calc'd for $C_{17}H_{21}O_4Br$: 368.0617, found 368.0638; $[\alpha]_D^{25}$ +4.5 (*c* 1.0, $CHCl_3$); SFC Conditions: 10% MeOH, 2.5 mL/min, Chiralpak OJ-H column, λ = 210 nm, t_R (min): major = 2.16, minor = 2.58.



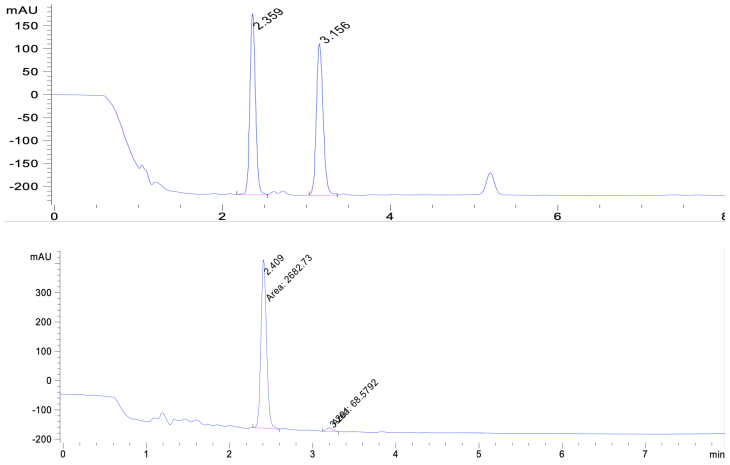
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.159	BB	0.0613	2173.74390	560.06818	97.5552
2	2.583	BB	0.0693	54.47504	11.93149	2.4448



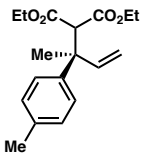
Diethyl (*R*)-2-(2-(4-chlorophenyl)but-3-en-2-yl)malonate (7c)

Prepared according to general procedure A using carbonate **2g** (12.0 mg, 0.05 mmol) and diethyl malonate (8.0 mg, 0.05 mmol). Purification by preparative TLC (10% EtOAc in hexanes) provided a light yellow oil (9.0 mg, 56% yield, 95% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (m, 4H), 6.54 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.26 (dd, *J* = 10.8, 0.9 Hz, 1H),

5.11 (dd, J = 17.5, 0.9 Hz, 1H), 4.07 (q, J = 7.1 Hz, 4H), 3.98 (s, 1H), 1.65 (s, 3H), 1.15 (td, J = 7.1, 1.7 Hz, 6H). The aromatic protons are tightly spaced underneath the residual chloroform signal, but are clearly present (see HSQC spectrum); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 167.6, 144.3, 142.4, 132.4, 128.4, 127.9, 115.0, 61.4, 61.3, 60.9, 46.0, 23.9, 14.1, 14.1; IR (Neat Film, NaCl) 2980, 1755, 1730, 1486, 1392, 1367, 1322, 1231, 1132, 1037, 1003, 923, 822 cm^{-1}; HRMS (FI+) *m/z* calc'd for $C_{17}H_{21}O_4Cl$: 324.1123, found 324.1142; $[\alpha]_D^{25}$ +4.2 (*c* 0.5, $CHCl_3$); SFC Conditions: 10% IPA, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R (min): major = 2.41, minor = 3.20.



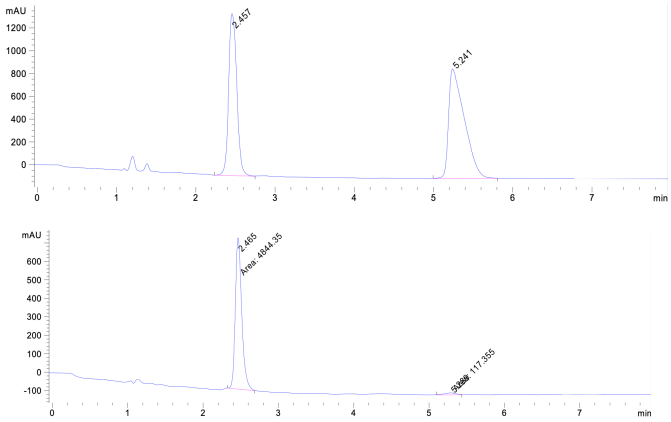
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.409	MM	0.0776	2682.73145	576.25537	97.5074
2	3.201	MM	0.0892	68.57921	12.81879	2.4926



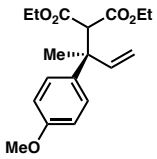
Diethyl (*R*)-2-(2-(*p*-tolyl)but-3-en-2-yl)malonate (8a)

Prepared according to general procedure A using carbonate **2h** (22.0 mg, 0.1 mmol) and diethyl malonate (16.0 mg, 0.1 mmol). Purification by preparative TLC (10% EtOAc in

hexanes) provided a colorless oil (28.3 mg, 93% yield, 96% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.3 Hz, 2H), 7.12 – 7.07 (m, 2H), 6.57 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.23 (dd, *J* = 10.9, 1.0 Hz, 1H), 5.10 (dd, *J* = 17.6, 1.1 Hz, 1H), 4.06 (qd, *J* = 7.1, 1.4 Hz, 4H), 4.02 (s, 1H), 2.30 (s, 3H), 1.65 (s, 3H), 1.13 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 167.8, 143.0, 142.7, 136.0, 129.0, 126.2, 114.2, 61.2, 61.1, 61.0, 46.0, 23.7, 21.0, 14.1, 14.0; IR (Neat Film, NaCl) 2980, 1757, 1729, 1691, 1444, 1367, 1316, 1228, 1132, 1038, 922, 817 cm^{-1}; HRMS (FI+) *m/z* calc'd for $C_{18}H_{24}O_4$: 304.1667 found 304.1686; $[\alpha]_D^{25}$ –1.1 (*c* 1.0, $CHCl_3$); SFC Conditions: 2% MeOH, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R (min): major = 2.47, minor = 5.29.



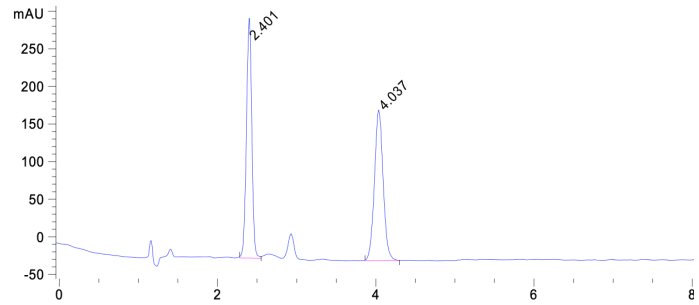
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.465	MM	0.0983	4844.34570	821.30530	97.6348
2	5.289	MM	0.1854	117.35537	10.55191	2.3652

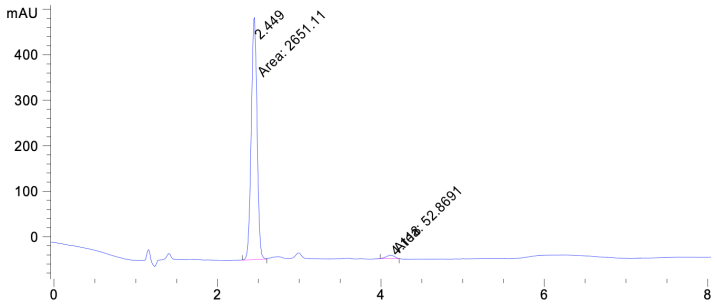


Diethyl (*R*)-2-(2-(4-methoxyphenyl)but-3-en-2-yl)malonate (8b)

Prepared according to general procedure A using carbonate **2i** (23.6 mg, 0.1 mmol) and diethyl malonate (16.0 mg, 0.1 mmol). Purification by preparative TLC (10% EtOAc in

hexanes) provided a colorless oil (17.9 mg, 56% yield, 96% ee). Prepared by the general procedure using carbonate **2i** (236.3 mg, 1.0 mmol) and diethyl malonate (160.2 mg, 1.0 mmol). Purification by column chromatography (10% EtOAc in hexanes) provided a light orange oil (166.4 mg, 52% yield, 96% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 9.0 Hz, 3H), 6.82 (d, J = 9.0 Hz, 2H), 6.55 (dd, J = 17.5, 10.8 Hz, 1H), 5.22 (dd, J = 10.8, 1.0 Hz, 1H), 5.08 (dd, J = 17.5, 1.0 Hz, 1H), 4.05 (qd, J = 7.1, 5.3 Hz, 4H), 3.98 (s, 1H), 3.78 (s, 3H), 1.65 (s, 3H), 1.13 (td, J = 7.1, 3.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 167.7, 158.0, 143.0, 137.5, 127.4, 114.0, 113.5, 61.1, 61.0, 61.0, 55.2, 45.7, 23.6, 14.0, 14.0; IR (Neat Film, NaCl) 2981, 1709, 1621, 1368, 1280, 1231, 1168, 1042, 854, 816, 750 cm^{-1}; HRMS (FI+) *m/z* calc'd for $C_{18}H_{24}O_5$: 320.1618, found 320.1635; $[\alpha]_D^{25}$ +1.6 (*c* 0.5, $CHCl_3$); SFC Conditions: 10% IPA, 2.5 mL/min, Chiralpak OJ-H column, λ = 210 nm, t_R (min): major = 2.45, minor = 4.12.





Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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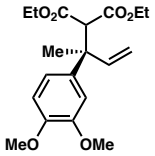
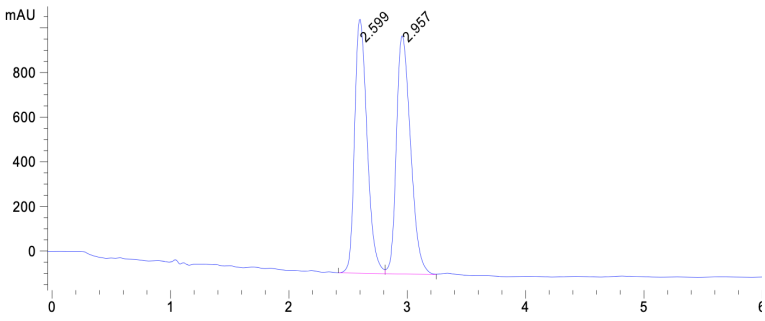
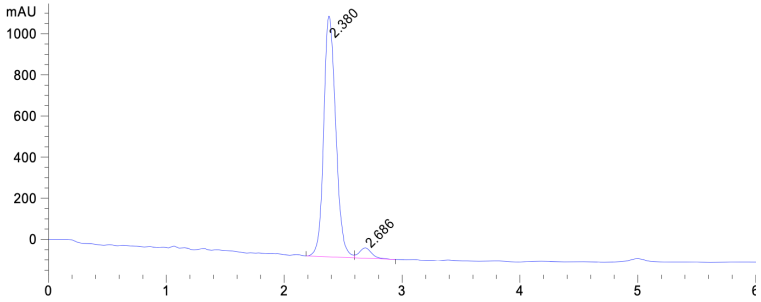
2	4.118	MM	0.1196	52.86905	7.36877	1.9552



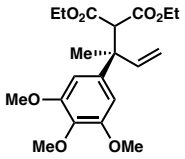
Diethyl (*R*)-2-(2-(3,4-dimethoxyphenyl)but-3-en-2-yl)malonate (8c)

Prepared according to general procedure A using carbonate **2j** (26.6 mg, 0.1 mmol) and diethyl malonate (16.0 mg, 0.1 mmol). Purification by preparative TLC (10% EtOAc in hexanes) provided a colorless oil (20.5 mg, 59% yield, 93% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 – 6.83 (m, 2H), 6.80 – 6.76 (m, 1H), 6.56 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.23 (dd, *J* = 10.8, 1.0 Hz, 1H), 5.10 (dd, *J* = 17.5, 1.1 Hz, 1H), 4.05 (qd, *J* = 7.1, 1.5 Hz, 4H), 3.99 (s, 1H), 3.85 (d, *J* = 5.1 Hz, 6H), 1.65 (s, 3H), 1.13 (td, *J* = 7.1, 0.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 167.8, 148.6, 147.6, 143.0, 138.2, 118.6, 114.3, 110.8, 110.2, 61.2, 61.1, 61.1, 56.0, 55.9, 46.1, 24.0, 14.1, 14.1; IR (Neat Film, NaCl) 2980, 1756, 1730, 1588, 1518, 1460, 1412, 1366, 1322, 1258, 1149, 1029, 922, 866 cm^{-1}; HRMS (FI+) *m/z* calc'd for $C_{19}H_{26}O_6$: 350.1724 found 350.1730; $[\alpha]_D^{25}$ +2.6 (*c* 1.0, $CHCl_3$); SFC Conditions: 2% MeOH, 2.5 mL/min, Chiralpak OJ-H column, λ = 210 nm, t_R (min): major = 2.38, major = 2.69.



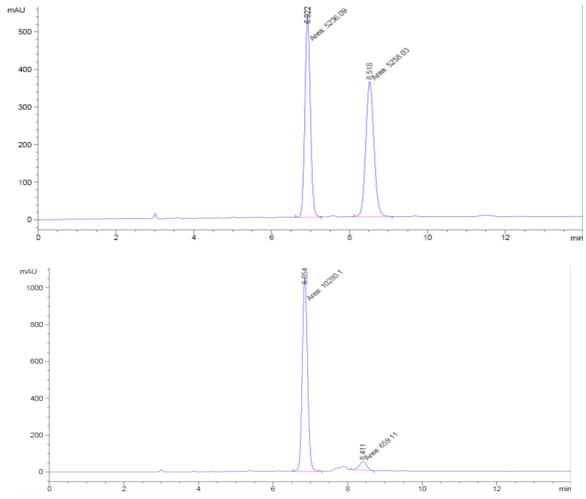


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.380	VV	0.1127	8309.95898	1172.47168	95.8458
2	2.686	VB	0.1071	360.17776	50.56734	4.1542

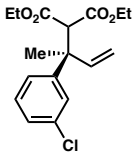


Diethyl (*R*)-2-(2-(3,4,5-trimethoxyphenyl)but-3-en-2-yl)malonate (8d)

Prepared according to general procedure A using carbonate **2k** (29.6 mg, 0.1 mmol) and diethyl malonate (16.0 mg, 0.1 mmol). Purification by preparative TLC (20% EtOAc in hexanes) provided a light orange oil (15.0 mg, 40% yield, 88% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 (dd, *J* = 17.5, 10.8 Hz, 1H), 6.53 (s, 2H), 5.27 (dd, *J* = 10.9, 1.0 Hz, 1H), 5.14 (dd, *J* = 17.6, 1.1 Hz, 1H), 4.13 – 4.03 (m, 4H), 4.01 (s, 1H), 3.84 (s, 6H), 3.81 (s, 3H), 1.66 (s, 3H), 1.15 (dt, *J* = 11.3, 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 167.7, 152.9, 142.5, 141.5, 136.7, 114.7, 103.9, 61.4, 61.2, 61.1, 60.9, 56.2, 46.7, 24.2, 14.1, 14.1; IR (Neat Film, NaCl) 2979, 1730, 1586, 1512, 1456, 1413, 1367, 1321, 1231, 1125, 1036 cm^{-1}; HRMS (FI+) *m/z* calc'd for $C_{20}H_{28}O_7$: 380.1829 found 380.1855; $[\alpha]_D^{25}$ +1.7 (*c* 0.5, $CHCl_3$); HPLC Conditions: 5% IPA, 1.0 mL/min, Chiralcel OD-H column, λ = 210 nm, t_R (min): major = 6.85, minor = 8.41.



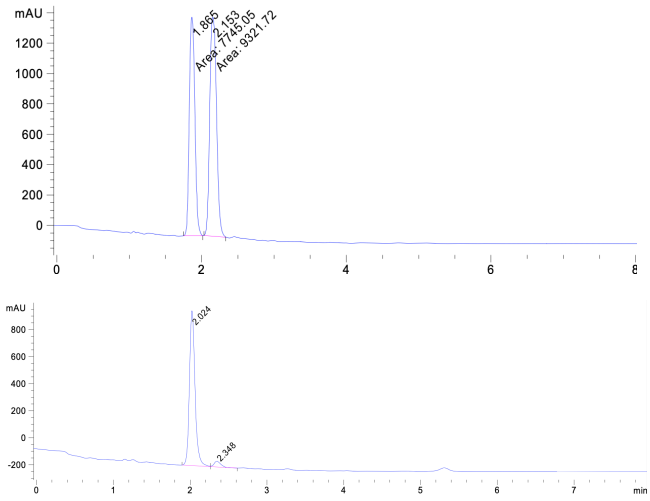
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.854	MM	0.1629	1.02801e4	1052.01624	93.9748
2	8.411	MM	0.2360	659.11011	46.55566	6.0252



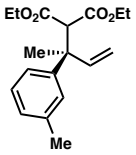
Diethyl (*R*)-2-(2-(3-chlorophenyl)but-3-en-2-yl)malonate (9a)

Prepared according to general procedure A using carbonate **2l** (24.0 mg, 0.1 mmol) and diethyl malonate (16.0 mg, 0.1 mmol). Purification by preparative TLC (10% EtOAc in hexanes) provided a colorless oil (27.6 mg, 85% yield, 91% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.23 (m, 1H), 7.17 – 7.08 (m, 3H), 6.46 (dd, *J* = 17.5, 10.9 Hz, 1H), 5.21 (dd, *J* = 10.9, 0.9 Hz, 1H), 5.05 (dd, *J* = 17.5, 0.9 Hz, 1H), 4.07 – 3.95 (m, 4H), 3.92 (s, 1H), 1.58 (s, 3H), 1.07 (td, *J* = 7.1, 3.5 Hz, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 167.5, 148.0, 142.1, 134.3, 129.6, 126.9, 126.7, 124.6, 115.2, 61.4, 61.3, 60.8, 46.3, 23.8, 14.1, 14.0; IR (Neat Film, NaCl) 2981, 2937, 1755, 1730, 1593, 1571, 1465, 1445, 1415, 1367, 1322, 1267, 1232, 1134, 1097, 1037, 924, 861, 785, 740 cm^{-1}; HRMS (FI+) *m/z* calc'd for $C_{17}H_{21}O_4Cl$: 324.1123 found 324.1136; $[\alpha]_D^{25}$ –1.0 (*c* 1.0, $CHCl_3$); SFC

Conditions: 2% MeOH, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R (min): major = 2.02, minor = 2.35.



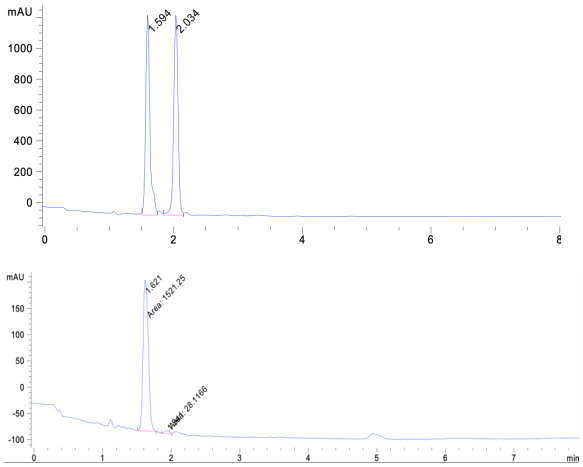
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.024	BV	0.0788	5787.72168	1147.99402	95.7894
2	2.348	VV	0.0868	254.41066	43.14692	4.2106



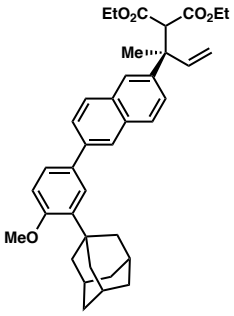
Diethyl (*R*)-2-(2-(*m*-tolyl)but-3-en-2-yl)malonate (9b)

Prepared according to general procedure A using carbonate **2m** (22.0 mg, 0.1 mmol) and diethyl malonate (16.0 mg, 0.1 mmol). Purification by preparative TLC (10% EtOAc in hexanes) provided a colorless oil (22.3 mg, 73% yield, 94% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 – 7.02 (m, 3H), 6.94 – 6.91 (m, 1H), 6.51 (dd, *J* = 17.5, 10.9 Hz, 1H), 5.17 (dd, *J* = 10.9, 1.1 Hz, 1H), 5.04 (dd, *J* = 17.6, 1.1 Hz, 1H), 4.06 – 3.91 (m, 5H), 2.25 (s, 3H), 1.58 (s, 3H), 1.05 (td, *J* = 7.1, 5.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 145.6, 142.8, 137.6, 128.1, 127.1, 127.0, 123.2, 114.3, 61.1, 61.0, 60.9, 46.2, 23.7, 21.7, 14.0, 13.9; IR (Neat Film, NaCl) 2981, 1757, 1730, 1605, 1447, 1367, 1321, 1224, 1132,

1097, 1038, 924, 705 cm^{-1}; HRMS (FI+) *m/z* calc'd for $C_{18}H_{24}O_4$: 304.1669 found 304.1669; $[\alpha]_D^{25}$ –4.9 (*c* 1.0, $CHCl_3$); SFC Conditions: 5% MeOH, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R (min): major = 1.62, minor = 1.94.



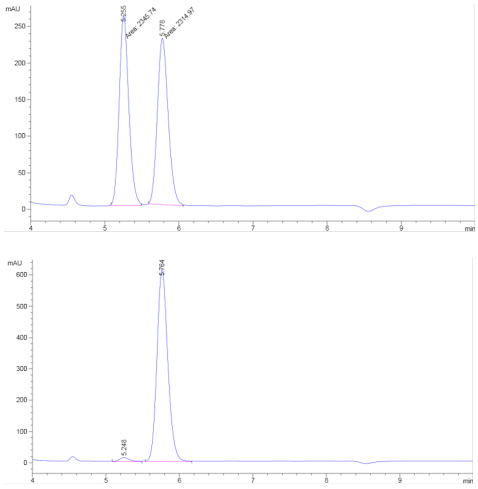
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.621	MM	0.0879	1521.25269	288.32150	98.1853
2	1.941	MM	0.0876	28.11655	5.35145	1.8147



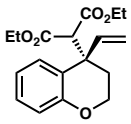
Diethyl 2-((2*R*)-2-(6-(3-((1*S*,3*S*)-adamantan-1-yl)-4-methoxyphenyl)naphthalen-2-yl)but-3-en-2-yl)malonate (10)

Prepared according to general procedure A using carbonate **2n** (49.6 mg, 0.1 mmol) and diethyl malonate (16.0 mg, 0.1 mmol). Purification by preparative TLC (10% EtOAc in hexanes) provided a colorless oil which slowly solidified on standing to a white amorphous

solid (44.7 mg, 77% yield, 92% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 1.8 Hz, 1H), 7.84 (dd, *J* = 8.7, 3.3 Hz, 2H), 7.79 (d, *J* = 2.0 Hz, 1H), 7.73 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.60 (d, *J* = 2.3 Hz, 1H), 7.56 – 7.49 (m, 2H), 6.99 (d, *J* = 8.5 Hz, 1H), 6.72 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.34 (dd, *J* = 10.9, 1.0 Hz, 1H), 5.19 (dd, *J* = 17.6, 1.1 Hz, 1H), 4.20 (s, 1H), 4.06 (qd, *J* = 7.1, 3.3 Hz, 4H), 3.90 (s, 3H), 2.23 – 2.19 (m, 6H), 2.18 (s, 1H), 2.15 – 2.09 (m, 4H), 1.85 – 1.79 (m, 8H), 1.11 (td, *J* = 7.1, 5.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 167.8, 158.6, 142.8, 142.6, 138.9, 138.9, 133.2, 132.5, 132.1, 128.5, 128.0, 125.9, 125.6, 125.1, 124.9, 124.5, 114.8, 112.2, 61.2, 61.1, 60.8, 55.2, 46.6, 40.7, 37.3, 37.2, 31.0, 29.2, 23.7, 14.0, 14.0; IR (Neat Film, NaCl) 2904, 1755, 1731, 1603, 1462, 1368, 1235, 1133, 1031, 883, 810 cm^{-1}; HRMS (FI+) *m/z* calc'd for $C_{38}H_{34}O_5$: 580.3183 found 580.3188;); $[\alpha]_D^{25}$ +23.2 (*c* 1.0, $CHCl_3$); HPLC Conditions: 10% IPA, 1.0 mL/min, Chiralcel OB-H column, λ = 210 nm, t_R (min): minor = 5.25, major = 5.76.

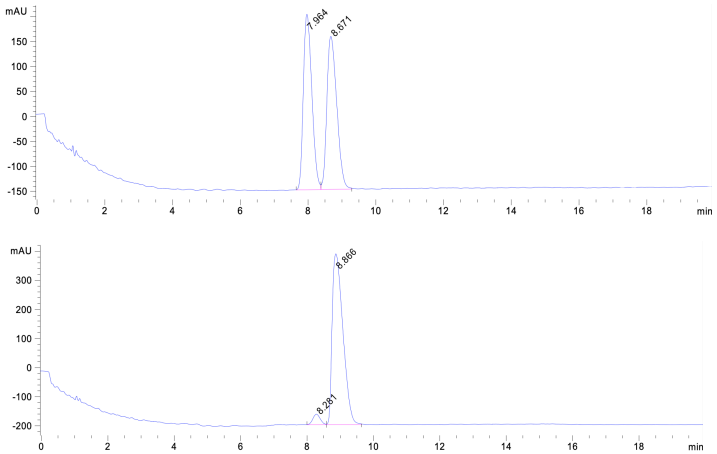


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	5.248	BB	0.1489	129.75508	12.95858	2.0203
2	5.764	BB	0.1576	6292.72559	613.15375	97.9797

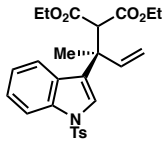


Diethyl (*R*)-2-(2-(naphthalen-2-yl)but-3-en-2-yl)malonate (11a)

Prepared according to general procedure A using carbonate **2o** (23.4 mg, 0.1 mmol) and diethyl malonate (16.0 mg, 0.1 mmol). Purification by preparative TLC (10% EtOAc in hexanes) provided a colorless oil (10.1 mg, 32% yield, 92% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 – 7.07 (m, 2H), 6.88 – 6.78 (m, 2H), 6.22 (ddd, *J* = 17.1, 10.5, 1.7 Hz, 1H), 5.24 (ddd, *J* = 10.5, 2.1, 1.0 Hz, 1H), 4.76 (ddd, *J* = 17.1, 2.0, 0.9 Hz, 1H), 4.23 (tdd, *J* = 7.1, 5.2, 1.8 Hz, 3H), 4.08 (d, *J* = 1.7 Hz, 1H), 4.01 – 3.87 (m, 3H), 2.91 (dddd, *J* = 14.2, 12.4, 4.0, 1.7 Hz, 1H), 2.03 (ddt, *J* = 14.1, 3.1, 1.9 Hz, 1H), 1.28 (td, *J* = 7.1, 1.7 Hz, 3H), 0.97 (td, *J* = 7.1, 1.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 167.3, 155.6, 143.3, 128.6, 128.2, 123.6, 120.1, 117.6, 117.4, 62.6, 61.6, 61.2, 59.2, 43.3, 29.0, 14.2, 13.8; IR (Neat Film, NaCl) 2981, 1749, 1732, 1489, 1449, 1366, 1304, 1226, 1169, 1031, 931 cm^{-1}; HRMS (FD+) *m/z* calc'd for $C_{18}H_{22}O_5$ $[M]^+$: 318.1462 found 318.1469; $[\alpha]_D^{25}$ +2.5 (*c* 0.5, $CHCl_3$); SFC Conditions: 2% MeOH, 2.5 mL/min, Chiralpak IC column, λ = 210 nm, t_R (min): minor = 8.28, major = 8.87.

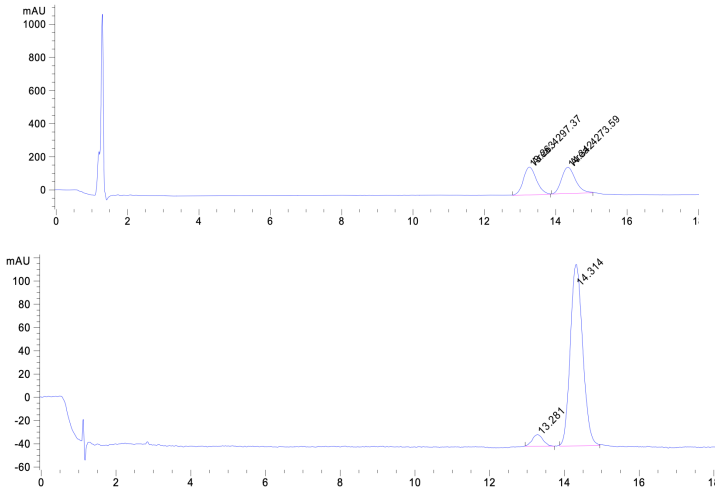


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.281	BV	0.2319	558.66656	36.22104	4.0546
2	8.866	VB	0.3546	1.32198e4	587.27740	95.9454

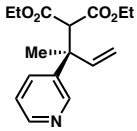


Diethyl (*R*)-2-(2-(1-tosyl-1H-indol-3-yl)but-3-en-2-yl)malonate (11b)

Prepared according to general procedure A using carbonate **2p** (39.9 mg, 0.1 mmol) and diethyl malonate (16.0 mg, 0.1 mmol). Purification by preparative TLC (100% CH_2Cl_2) provided a light yellow oil (7.1 mg, 15% yield, 89% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.76 – 7.70 (m, 2H), 7.59 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.43 (s, 1H), 7.28 – 7.17 (m, 4H), 6.54 (dd, *J* = 17.4, 10.7 Hz, 1H), 5.20 (dd, *J* = 10.7, 0.9 Hz, 1H), 5.03 (dd, *J* = 17.4, 0.9 Hz, 1H), 4.20 (s, 1H), 4.07 – 3.96 (m, 2H), 3.89 – 3.74 (m, 2H), 2.34 (s, 3H), 1.80 (s, 3H), 1.05 (t, *J* = 7.1 Hz, 3H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 167.3, 144.9, 141.2, 135.8, 135.3, 129.9, 128.9, 127.0, 126.6, 124.4, 124.4, 122.9, 122.1, 115.2, 114.0, 61.2, 61.0, 58.6, 43.3, 22.4, 21.7, 14.0, 13.7; IR (Neat Film, NaCl) 2982, 1731, 1446, 1369, 1298, 1225, 1174, 1136, 1091, 1037, 959, 809, 753, 687 cm^{-1}; HRMS (ESI +) *m/z* calc'd for $C_{26}H_{29}NO_6S$ $[M+NH_4]^+$: 501.2054 found 501.2077; $[\alpha]_D^{25}$ +10.4 (*c* 0.3, $CHCl_3$); SFC Conditions: 10% IPA, 2.5 mL/min, Chiralpak IC column, λ = 210 nm, t_R (min): minor = 13.28, major = 14.31.

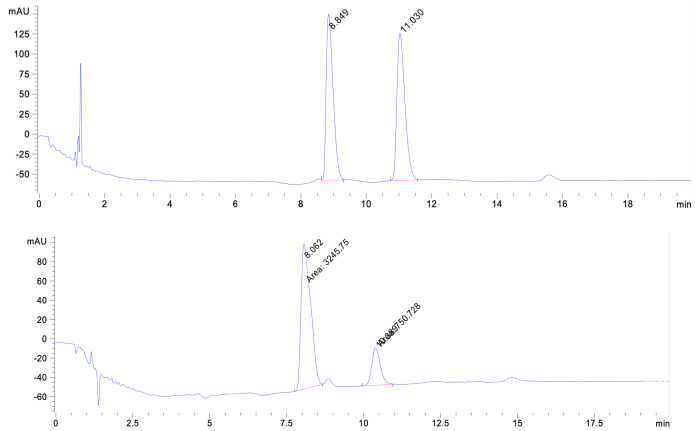


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.281	BB	0.2555	203.75606	10.09447	5.3448
2	14.314	BB	0.3637	3608.45264	156.11813	94.6552



Diethyl (*R*)-2-(2-(pyridin-3-yl)but-3-en-2-yl)malonate (11c)

Prepared according to general procedure A using carbonate **2q** (20.7 mg, 0.1 mmol) and diethyl malonate (16.0 mg, 0.1 mmol). Purification by preparative TLC (10% EtOAc in hexanes) provided a colorless oil (24.3 mg, 83% yield, 63% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.68 (m, 4H), 7.46 (dtd, *J* = 14.5, 7.9, 3.6 Hz, 3H), 6.69 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.32 (dd, *J* = 10.9, 1.0 Hz, 1H), 5.17 (dd, *J* = 17.6, 1.0 Hz, 1H), 4.18 (s, 1H), 4.04 (qd, *J* = 7.1, 2.1 Hz, 4H), 1.78 (s, 3H), 1.08 (td, *J* = 7.1, 4.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 167.3, 148.2, 147.5, 141.6, 141.5, 135.3, 123.4, 115.7, 61.5, 61.5, 60.5, 45.1, 23.7, 14.1, 14.0; $[\alpha]_D^{25}$ –0.6 (*c* 1.0, $CHCl_3$) SFC Conditions: 5% MeOH, 2.5 mL/min, Chiralpak IC column, λ = 210 nm, t_R (min): major = 8.06, minor = 10.39.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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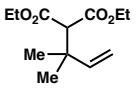
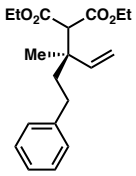


Diethyl 2-(2-methylbut-3-en-2-yl)malonate[20] (14a)

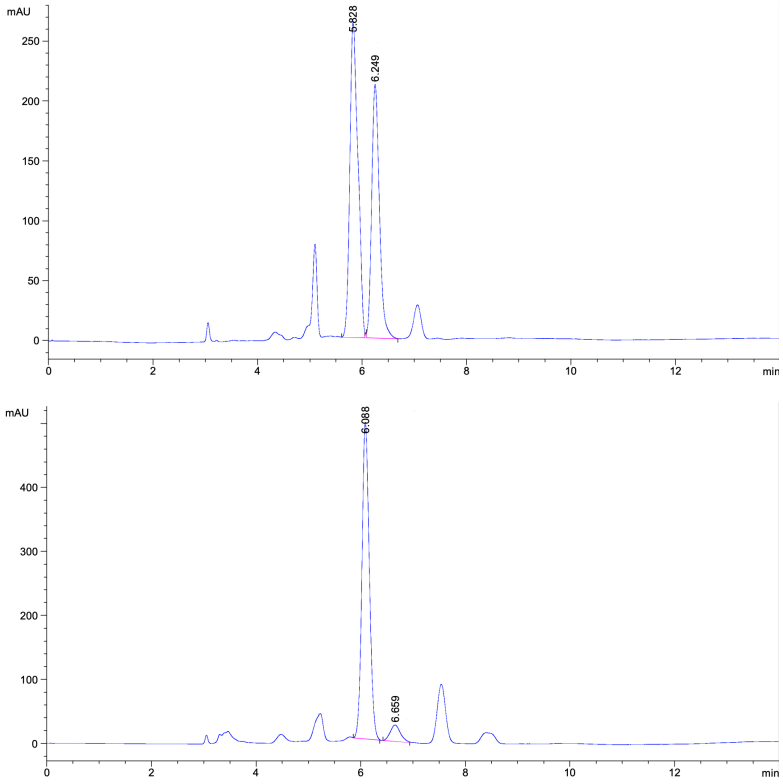
Prepared according to general procedure A using carbonate **2t** (14.4 mg, 0.1 mmol) and diethyl malonate (16.0 mg, 0.1 mmol). Purification by preparative TLC (10% EtOAc in hexanes) provided a colorless oil (14.3 mg, 63% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.11 – 4.94 (m, 2H), 4.16 (q, *J* = 7.1 Hz, 4H), 3.32 (s, 1H), 1.32 – 1.19 (m, 12H).



Diethyl (*R*)-2-(3-methyl-5-phenylpent-1-en-3-yl)malonate (14b)

Prepared according to general procedure A using carbonate **2u** (23.4 mg, 0.1 mmol) and diethyl malonate (16.0 mg, 0.1 mmol). Purification by preparative TLC (5% EtOAc in hexanes, eluted twice) provided 16.0 mg of a colorless oil. Small amounts of unidentified impurity persisted despite extensive attempts to further purify the title compound. This impurity did not affect product assignment or assignment of enantiomers, but as a result, the yield is reported by NMR relative to an internal (CH_2Br_2) standard (50% yield by ^{1}H NMR, 86% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.16 (m, 5H), 6.12 – 6.01 (m, 1H), 5.17 (dt, *J* = 10.8, 0.9 Hz, 1H), 5.08 (dt, *J* = 17.5, 0.9 Hz, 1H), 4.25 – 4.09 (m, 4H), 3.47 (s, 1H), 2.60 – 2.50 (m, 2H), 1.96 – 1.76 (m, 2H), 1.35 (s, 3H), 1.25 (tdd, *J* = 7.1, 3.5, 0.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 167.9, 143.1, 142.6, 128.5, 128.5, 128.4,

128.4, 125.9, 125.9, 114.2, 61.2, 61.1, 60.1, 42.3, 41.4, 30.6, 20.1, 14.3, 14.2; IR (Neat Film, NaCl) 2970, 1729, 1470, 1167, 1040, 851 cm^{-1}; HRMS (FI+) *m/z* calc'd for $C_{19}H_{26}O_4$: 318.1826 found 318.1846; $[\alpha]_D^{25}$ +1.3 (*c* 0.5, $CHCl_3$); HPLC Conditions: 0.07% IPA, 1.0 mL/min, Chiralpak IH column, λ = 210 nm, t_R (min): major = 6.09, minor = 6.66.



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
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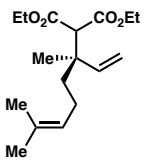
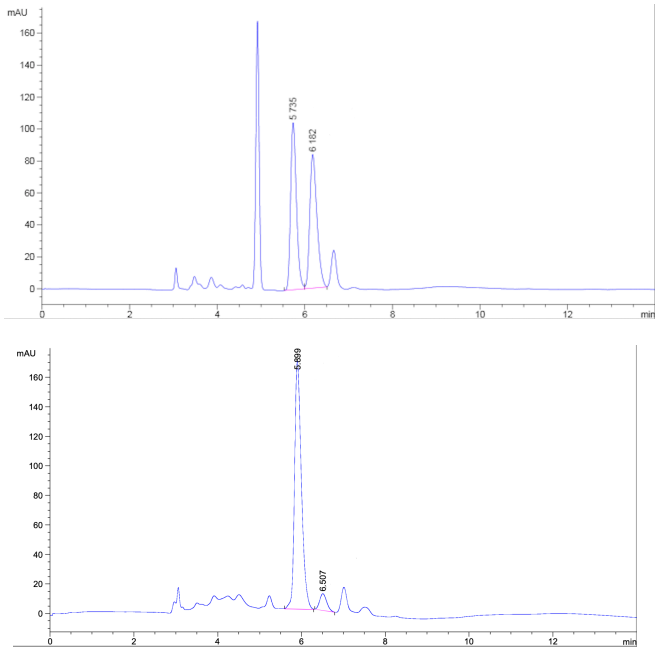
2	6.659	MM	0.2294	355.56625	25.83048	6.8191



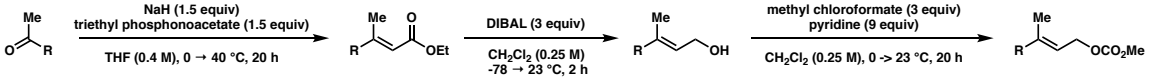
Diethyl (*R*)-2-(3,7-dimethylocta-1,6-dien-3-yl)malonate (14c)

Prepared according to general procedure A using carbonate **2v** (21.2 mg, 0.1 mmol) and diethyl malonate (16.0 mg, 0.1 mmol). Purification by preparative TLC (5% EtOAc in hexanes, eluted twice) provided 18.3 mg of a colorless oil. Small amounts of unidentified impurity persisted despite extensive attempts to further purify the title compound. This impurity did not affect product assignment or assignment of enantiomers, but as a result, the yield is reported by NMR relative to an internal (CH_2Br_2) standard (63% yield by ^{1}H NMR, 87% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99 (dd, *J* = 17.5, 10.9 Hz, 1H), 5.14 – 4.95 (m, 3H), 4.16 (dq, *J* = 8.5, 7.1 Hz, 4H), 3.41 (s, 1H), 1.94 – 1.85 (m, 2H), 1.66 (d, *J* = 1.4 Hz, 3H), 1.57 (d, *J* = 1.2 Hz, 4H), 1.32 – 1.18 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 168.0, 143.3, 131.7, 124.3, 113.8, 61.1, 61.1, 60.2, 42.2, 39.3, 25.8, 22.8, 20.0, 17.7, 14.3, 14.2; IR (Neat Film, NaCl) 2985, 1982, 1755, 1736, 1444, 1166, 1035, 912, 681 cm^{-1}; HRMS (FI+) *m/z* calc'd for $C_{17}H_{28}O_4$: 296.1982 found 296.2001; $[\alpha]_D^{25}$ +1.1 (*c* 1.0, $CHCl_3$); HPLC Conditions: 0.06% IPA, 1.0 mL/min, Chiralpak IH column, λ = 210 nm, t_R (min): major = 5.90, minor = 6.50.



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	5.899	MM	0.1884	1901.37109	168.21719	93.4025
2	6.507	MM	0.1957	134.30399	11.43600	6.5975

Synthesis of Allylic Carbonate Electrophiles: General Procedure B



To a flame-dried round bottom flask was added NaH (60% dispersion in mineral oil, 1.5 equiv). The flask was purged and backfilled three times with nitrogen. Then THF (0.4 M) was added, and the resulting gray suspension was cooled to 0 °C and stirred. To the cooled suspension was added neat triethyl phosphonoacetate (1.5 equiv) dropwise, causing rapid gas evolution, and stirred for 30 minutes, during which time the solution became clear. The solution was allowed to warm to 21 °C then heated to 40 °C using a metal heating block or oil bath. A solution of ketone (1.0 equiv, 1.0 M in THF) was added slowly to the reaction mixture and allowed to stir overnight. After stirring for ~20h, the mixture was cooled to 0 °C, diluted with Et_2O and quenched with water. The layers were separated and extracted three times with EtOAc (75 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue showed the desired (*E*)-alkene product in ratios ranging from 2:1 to 10:1 depending on the substrate. These geometric isomers were separated by silica gel flash column chromatography to afford the desired (*E*)-products.

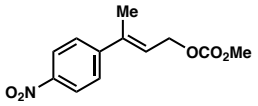
To a flame-dried round bottom flask was added the (*E*)-alkene (1.0 equiv) and CH_2Cl_2 (0.25 M), and the solution was cooled to –78 °C. DIBAL (3 equiv) was added neat dropwise. The solution was stirred at –78 °C for 1h, before warming to room temperature and stirring for an additional hour. Upon completion as determined by TLC analysis, the reaction was quenched with EtOAc and diluted twofold with Et_2O. A large excess of a saturated

Rochelle's salt solution was added and allowed to stir until two clear layers had formed. The layers were separated and extracted three times with Et_2O (75 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude allylic alcohol products were used directly in the subsequent step without further purification.

To a flame-dried round bottom flask was added crude allylic alcohol (1.0 equiv) followed by dichloromethane (0.25 M) and pyridine (9.0 equiv), and the resulting mixture stirred at 0 °C for 5 min. Methyl chloroformate (3 equiv) was added dropwise (neat). The reaction mixture was then allowed to stir and gradually reach 23 °C overnight. After stirring for 20h the crude reaction mixture was diluted with and equal volume of Et_2O and quenched with 1N HCl (8 equiv). The layers were separated, and the aqueous layer was extracted three times with EtOAc (70 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography to afford the desired allylic carbonate. Yields reported refer to the formation of the allylic carbonate from the corresponding ester unless otherwise stated.

Spectroscopic Data for the Synthesis of New Allylic Carbonate Electrophiles

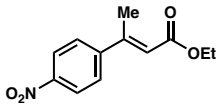
Note: ^{1}H NMR spectral data for the corresponding *(E)*-ester intermediate for each carbonate is also included.



(*E*)-methyl (3-(4-nitrophenyl)but-2-en-1-yl) carbonate (2d)

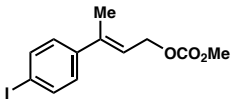
Prepared from ethyl (*E*)-3-(4-nitrophenyl)but-2-enoate according to general procedure B. Purified by column chromatography (5% EtOAc in hexanes) to provide the title compound

product as a light orange amorphous solid (195.3 mg, 39% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.7 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H), 6.05 (dd, *J* = 7.5, 5.9 Hz, 1H), 4.88 (d, *J* = 6.7 Hz, 2H), 3.82 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 148.9, 147.3, 138.9, 126.8, 124.6, 123.8, 64.7, 55.1, 16.4; IR (Neat Film, NaCl) 2961, 1742, 1592, 1515, 1438, 1345, 1271, 968, 860, 792, 744 cm^{-1}; HRMS (FI+) *m/z* calc'd for $C_{12}H_{13}NO_5$: 251.0788, found 251.0796.



Ethyl (*E*)-3-(4-nitrophenyl)but-2-enoate[21] (2da)

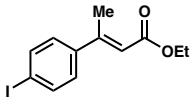
Prepared according to general procedure B; reaction did not achieve full conversion. *E:Z* (3:1) by crude ^{1}H NMR. Purified by silica gel chromatography (10% EtOAc in hexanes) to afford a white solid (505 mg, 27% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 2H), 6.18 (q, *J* = 1.4 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 3H), 2.59 (d, *J* = 1.4 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H). All characterization data matched those reported in the literature.



(*E*)-3-(4-iodophenyl)but-2-en-1-yl methyl carbonate (2e)

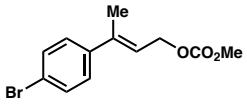
Prepared from ethyl (*E*)-3-(4-iodophenyl)but-2-enoate according to general procedure B. Purified by column chromatography (10% EtOAc in hexanes) to provide the title compound as a yellow solid (165 mg, 57% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.5 Hz, 2H), 7.14 (d, *J* = 8.5 Hz, 2H), 5.91 (tq, *J* = 6.9, 1.4 Hz, 1H), 4.83 (dd, *J* = 6.9, 0.9 Hz, 2H), 3.80 (s, 3H), 2.09 (dt, *J* = 1.5, 0.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 142.0, 140.1, 137.5, 127.9, 121.4, 93.3, 64.9, 55.0, 16.2; IR (Neat Film, NaCl) 2955,

1744, 1687, 1582, 1483, 1442, 1392, 1262, 1125, 1073, 1004, 945, 849, 818, 793, 742 cm^{-1}; HRMS (FI+) *m/z* calc'd for $C_{12}H_{13}O_3I$: 331.9904, found 331.9922.



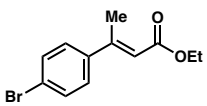
Ethyl (*E*)-3-(4-iodophenyl)but-2-enoate[22] (2ea)

Prepared according to general procedure B; the reaction did not achieve full conversion. *E*:*Z* (>10:1) by crude ^1H NMR. Purified by silica gel chromatography (5% EtOAc in hexanes) to afford a light yellow oil (521 mg, 25% yield); ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 8.2 Hz, 2H), 6.11 (s, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 2.54 (d, *J* = 1.4 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). All characterization data matched those reported in the literature.



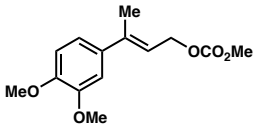
(*E*)-3-(4-bromophenyl)but-2-en-1-yl methyl carbonate (2f)

Prepared from ethyl (*E*)-3-(4-bromophenyl)but-2-enoate according to general procedure B. Purified with a short silica plug eluting with 5% EtOAc in hexanes to provide the title compound as a white amorphous solid (1.04 g, 50% yield); ^1H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.42 (m, 2H), 7.30 – 7.24 (m, 2H), 5.91 (td, *J* = 6.7, 3.3 Hz, 1H), 4.84 (d, *J* = 6.9 Hz, 2H), 3.81 (d, *J* = 1.3 Hz, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 141.4, 140.0, 131.5, 127.7, 121.8, 121.4, 64.9, 55.0, 16.3; IR (Neat Film, NaCl) 2954, 1744, 1442, 1262, 940, 791 cm^{-1}; HRMS (FI+) *m/z* calc'd for $C_{12}H_{13}O_3$: 284.0042, found 284.0056.



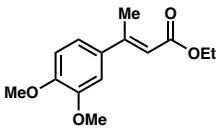
Ethyl (*E*)-3-(4-bromophenyl)but-2-enoate[23] (2fa)

Prepared according to general procedure B, *E:Z* (9:1) by crude ^{1}H NMR. Purified by silica gel chromatography (10% EtOAc in hexanes) to afford the product as a white solid (1.38 g, 60% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 6.11 (s, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 2.55 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). All characterization data matched those reported in the literature.



(*E*)-3-(3,4-dimethoxyphenyl)but-2-en-1-yl methyl carbonate (2j)

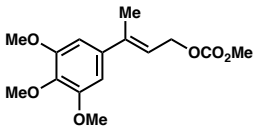
Prepared from ethyl (*E*)-3-(3,4-dimethoxyphenyl)but-2-enoate according to general procedure B. Purification by silica gel chromatography (10% EtOAc in hexanes) afforded the title compound as a colorless oil (224 mg, 84% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 – 6.92 (m, 2H), 6.83 (d, *J* = 8.3 Hz, 2H), 5.88 (ddt, *J* = 7.1, 5.7, 1.3 Hz, 1H), 4.85 (dq, *J* = 7.1, 0.7 Hz, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 3.80 (s, 3H), 2.14 – 2.10 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 149.0, 148.8, 140.9, 135.4, 119.4, 118.5, 110.9, 109.3, 65.2, 56.1, 56.1, 55.0, 16.5; (Neat Film, NaCl) 2954, 2856, 1746, 1601, 1583, 1517, 1444, 1416, 1376, 1340, 1255, 1174, 1149, 1026, 944, 905, 860, 792, 767 cm^{-1}; HRMS (FI+) *m/z* calc'd for $C_{14}H_{18}O_5$: 266.1149, found 266.1173.



Ethyl (*E*)-3-(3,4-dimethoxyphenyl)but-2-enoate[24] (2ja)

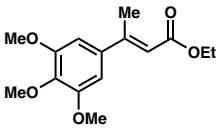
Prepared according to general procedure B; the reaction did not achieve full conversion. *E:*Z (6.3:1) by crude ^{1}H NMR. Purified by silica gel chromatography (5% EtOAc in hexanes) to afford a colorless oil (236 mg, 35% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.01 (d, *J* = 2.2 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.11 (q, *J* =

1.3 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.91 (d, *J* = 4.6 Hz, 6H), 2.57 (d, *J* = 1.3 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). All characterization data matched those reported in the literature.



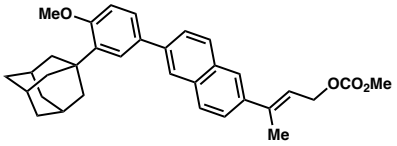
(*E*)-methyl (3-(3,4,5-trimethoxyphenyl)but-2-en-1-yl) carbonate (2k)

Prepared from ethyl (*E*)-3-(3,4,5-trimethoxyphenyl)but-2-enoate according to general procedure B. Purification by silica gel chromatography (10 → 20% EtOAc in hexanes) afforded the title compound as a colorless oil (692 mg, 39% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (s, 2H), 5.87 (tq, *J* = 7.0, 1.4 Hz, 1H), 4.84 (dd, *J* = 7.0, 0.9 Hz, 2H), 3.87 (s, 6H), 3.85 (s, 3H), 3.80 (s, 3H), 2.11 (dd, *J* = 1.4, 0.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 153.0, 141.1, 138.4, 137.8, 120.5, 103.3, 64.9, 60.9, 56.2, 54.9, 16.6. IR (Neat Film, NaCl) 3478, 2968, 1500, 2160, 2020, 1954, 1754, 1584, 1412, 1253, 1122, 943, 794 cm^{-1}; HRMS (FI+) *m/z* calc'd for $C_{15}H_{20}O_6$: 296.1254, found 296.1277.



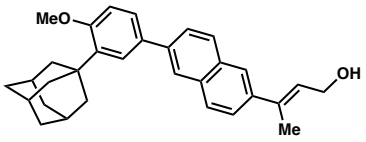
Ethyl (*E*)-3-(3,4,5-trimethoxyphenyl)but-2-enoate[25] (2ka)

Prepared according to general procedure B. *E:*Z (14:1) by crude ^{1}H NMR. Purified by silica gel chromatography (5% EtOAc in hexanes) to afford a colorless oil (845 mg, 30% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (s, 2H), 6.10 (d, *J* = 1.3 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 6H), 3.87 (s, 3H), 2.56 (d, *J* = 1.3 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H). All characterization data matched those reported in the literature.



(*E*)-3-(6-(3-((1*s*,3*s*)-adamantan-1-yl)-4-methoxyphenyl)naphthalen-2-yl)but-2-en-1-yl methyl carbonate (2n)

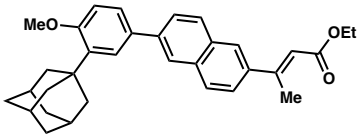
Compound **10d** was treated with methyl chloroformate according to general procedure B. Purification by silica gel chromatography (15% EtOAc in hexanes) afforded the title compound as an amorphous white solid (557 mg, 90% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 1.8 Hz, 1H), 7.90 – 7.80 (m, 3H), 7.73 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.59 (td, *J* = 4.1, 1.8 Hz, 2H), 7.53 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 6.11 (tt, *J* = 5.6, 1.3 Hz, 1H), 4.93 (dd, *J* = 7.0, 0.9 Hz, 2H), 3.90 (s, 3H), 3.83 (s, 3H), 2.25 (d, *J* = 1.3 Hz, 3H), 2.19 (d, *J* = 3.0 Hz, 6H), 2.10 (t, *J* = 3.3 Hz, 3H), 1.81 (d, *J* = 2.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 155.9, 140.8, 139.1, 139.1, 138.9, 133.2, 133.1, 132.1, 128.6, 128.0, 126.1, 125.9, 125.6, 124.6, 124.5, 124.4, 121.0, 112.1, 65.1, 55.2, 54.9, 40.6, 37.2, 37.2, 29.1, 16.3; IR (neat film, NaCl) 2903, 1746, 1443, 1266, 948, 813; HMRS (FD+) *m/z* calc'd for $C_{33}H_{36}O_4$: 496.2608, found 496.2634.



(*E*)-3-(6-(3-((1*s*,3*s*)-adamantan-1-yl)-4-methoxyphenyl)naphthalen-2-yl)but-2-en-1-ol (10d)

Compound **10c** was reduced as outlined in general procedure B, extracting with dichloromethane instead of Et_2O, affording the title compound as a white powder (560 mg, quantitative) which was used without further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 1.8 Hz, 1H), 7.90 – 7.80 (m, 3H), 7.73 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.65 – 7.57

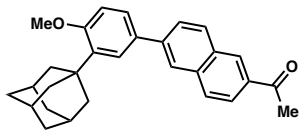
(m, 2H), 7.53 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.17 (tq, *J* = 6.7, 1.3 Hz, 1H), 4.48 – 4.41 (m, 2H), 3.90 (s, 3H), 2.24 – 2.15 (m, 9H), 2.14 – 2.08 (m, 3H), 1.81 (d, *J* = 3.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 139.7, 139.1, 139.0, 137.8, 133.2, 133.2, 132.3, 128.6, 128.5, 128.1, 126.9, 126.1, 126.0, 125.7, 124.8, 124.6, 124.4, 112.2, 60.3, 55.3, 40.8, 37.3, 37.3, 29.3, 16.2; IR (neat film, NaCl) 2901, 2846, 1601, 1452, 1235, 1180, 1138, 1025, 881, 807, 738; HMRS (FD+) *m/z* calc'd for $C_{31}H_{34}O_2$: 438.2553, found 438.2574.



Ethyl (*E*)-3-(6-(3-((1*s*,3*s*)-adamantan-1-yl)-4-methoxyphenyl)naphthalen-2-yl)but-2-enoate (10c)

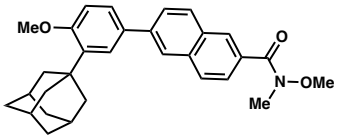
1-(6-(3-((1*s*,3*s*)-adamantan-1-yl)-4-methoxyphenyl)naphthalen-2-yl)ethan-1-one was subjected to Horner-Wadsworth-Emmons conditions as detailed in general procedure B. *E:Z* (2.5:1) by crude ^{1}H NMR. Purification of the crude material by silica gel chromatography (0 → 5% EtOAc in hexanes followed by 5 → 20% followed by 100% EtOAc in hexanes) afforded the title compound as a white powder (619 mg, 38%, mixed fractions containing both geometric olefin isomers were not collected). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.94 (m, 2H), 7.89 (dd, *J* = 11.7, 8.6 Hz, 2H), 7.76 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.66 – 7.57 (m, 2H), 7.54 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 6.32 (q, *J* = 1.3 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.91 (s, 3H), 2.71 (d, *J* = 1.3 Hz, 3H), 2.19 (d, *J* = 3.1 Hz, 6H), 2.11 (br t, *J* = 3.2 Hz, 3H), 1.81 (d, *J* = 3.2 Hz, 6H), 1.35 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 158.9, 155.4, 140.0, 139.1, 139.0, 134.0, 133.0, 132.0, 129.0, 128.4, 126.4, 126.0, 125.9, 125.7, 124.8, 124.4, 117.4, 112.2, 60.0, 55.3, 40.8, 37.3, 37.3, 29.3, 18.0, 14.5; IR (neat film, NaCl) 2904, 2848, 1710, 1620, 1475, 1367, 1341,

1265, 1238, 1156, 1041, 873, 812, 737, 660; HMRS (FD+) *m/z* calc'd for $C_{33}H_{36}O_3$: 480.2659, found 480.2668.



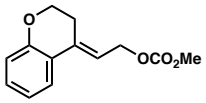
1-(6-(3-((1*s*,3*s*)-adamantan-1-yl)-4-methoxyphenyl)naphthalen-2-yl)ethan-1-one (10b)

To a flame-dried flask was added compound **10a** (1.83 g, 4.02 mmol, 1.0 equiv). The reaction vessel was purged and backfilled. THF (20 mL) was added and the solution was stirred and cooled to 0 °C. MeMgBr (3.0 M in Et_2O, 2.0 mL, 6.03 mmol, 1.5 equiv) was added dropwise to the stirred solution. The solution was stirred at 0 °C for 40 min. Then saturated aqueous NH_4Cl was added. CH_2Cl_2 was added, the layers were partitioned, and the aqueous layer was extracted four times with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and concentrated. The title compound was afforded relatively cleanly by NMR and was used without further purification (1.40 g, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 1.7 Hz, 1H), 8.08 – 7.97 (m, 3H), 7.93 (d, *J* = 8.7 Hz, 1H), 7.81 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.61 (d, *J* = 2.4 Hz, 1H), 7.55 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 3.91 (s, 3H), 2.74 (s, 3H), 2.19 (d, *J* = 3.1 Hz, 6H), 2.15 – 2.08 (m, 3H), 1.81 (t, *J* = 3.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 159.1, 141.8, 139.2, 136.2, 134.2, 132.6, 131.4, 130.1, 130.1, 128.6, 126.7, 126.1, 125.9, 124.9, 124.4, 112.2, 55.3, 40.7, 37.3, 37.3, 29.2, 26.8; IR (neat film, NaCl) 2901, 2845, 1676, 1624, 1472, 1285, 1237, 1138, 1029, 878, 819; HMRS (FD+) *m/z* calc'd for $C_{29}H_{30}O_2$: 410.2240, found 410.2259.



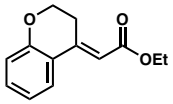
6-(3-((1*s*,3*s*)-adamantan-1-yl)-4-methoxyphenyl)-*N*-methoxy-*N*-methyl-2-naphthamide (10a)[26]

Prepared by the literature procedure of Lu and coworkers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 – 8.21 (m, 1H), 8.00 (d, *J* = 1.8 Hz, 1H), 7.92 (dd, *J* = 17.4, 8.6 Hz, 2H), 7.77 (ddd, *J* = 8.5, 3.0, 1.8 Hz, 2H), 7.59 (d, *J* = 2.4 Hz, 1H), 7.54 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 3.91 (s, 3H), 3.59 (s, 3H), 3.43 (s, 3H), 2.19 (d, *J* = 3.0 Hz, 6H), 2.10 (s, 3H), 1.81 (d, *J* = 3.1 Hz, 6H).



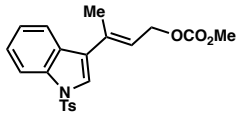
(*E*)-2-(chroman-4-ylidene)ethyl methyl carbonate (2o)

Prepared from ethyl (*E*)-2-(chroman-4-ylidene)acetate according to general procedure B. Purified by column chromatography (10% EtOAc in hexanes) to provide the title compound as a colorless oil (514 mg, 80% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.21 (ddd, *J* = 8.5, 7.2, 1.6 Hz, 1H), 6.93 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 6.88 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.20 (tt, *J* = 7.3, 1.7 Hz, 1H), 4.87 (d, *J* = 7.3 Hz, 2H), 4.29 – 4.24 (m, 2H), 3.83 (s, 3H), 2.83 – 2.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 155.1, 134.7, 129.9, 124.4, 121.5, 121.0, 117.8, 114.3, 66.0, 64.0, 55.0, 26.0; IR (Neat Film, NaCl) 2957, 1744, 1650, 1605, 1575, 1484, 1454, 1375, 1351, 1264, 1119, 1051, 939 cm^{-1}; HRMS (FD+) *m/z* calc'd for $C_{13}H_{14}O_4$: 234.0887, found 234.0888.



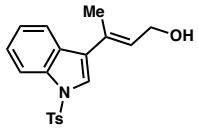
Ethyl (*E*)-2-(chroman-4-ylidene)acetate[27] (2oa)

Prepared according to general procedure B. Purified by silica gel chromatography to afford a white solid (1.30 g, 70% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.30 – 7.25 (m, 1H), 7.00 – 6.81 (m, 2H), 6.35 (t, *J* = 1.7 Hz, 1H), 4.32 – 4.13 (m, 4H), 3.40 (ddd, *J* = 7.2, 5.5, 1.8 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H). All characterization data matched those reported in the literature.



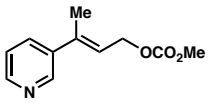
(*E*)-methyl (3-(1-tosyl-1*H*-indol-3-yl)but-2-en-1-yl) carbonate (2p)

Prepared from (*E*)-3-(1-tosyl-1*H*-indol-3-yl)but-2-en-1-ol according to general procedure B. Purified by silica gel chromatography (35% EtOAc in hexanes) afforded the title compound as a colorless oil (278 mg, 69% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.80 – 7.70 (m, 3H), 7.32 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.32 – 7.17 (m, 3H), 6.13 (ddt, *J* = 8.4, 7.1, 1.4 Hz, 1H), 4.89 (dd, *J* = 7.0, 0.8 Hz, 2H), 3.80 (s, 3H), 2.33 (s, 3H), 2.19 – 2.11 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 145.2, 135.6, 135.2, 133.8, 130.1, 128.7, 126.9, 125.0, 124.8, 123.8, 123.6, 121.6, 121.3, 113.9, 64.6, 55.0, 21.7, 17.1. IR (neat film, NaCl) 3136, 2956, 1748, 1648, 1596, 1446, 1372, 1268, 1176, 1140, 1092, 1055, 940, 812, 792, 747, 703, 669, 622, 603 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{21}H_{21}NO_5S$ $[M+H]^+$: 400.1140, found 400.1204.



(*E*)-3-(1-tosyl-1*H*-indol-3-yl)but-2-en-1-ol (2pb)

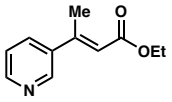
To a flame dried 40 mL vial was added lithium aluminum hydride. The vial was cooled to 0 °C and THF (3.0 mL) was added. Ethyl (*E*)-3-(1-tosyl-1*H*-indol-3-yl)but-2-enoate[28] (520 mg, 1.36 mmol, 1.0 equiv) was dissolved in THF (2.0 mL), and this solution was slowly added to the stirring lithium aluminum hydride suspension using additional THF (0.4 mL) to complete the transfer. After 20 minutes, saturated aqueous NH_4Cl (10 mL) was slowly added at 0 °C. Then saturated aqueous sodium potassium tartrate (100 mL) was added and stirred at 23 °C. The layers were separated and extracted three times with EtOAc (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by automated silica gel flash chromatography (Teledyne ISCO, 0 → 100% EtOAc in hexanes) to afford the title compound as a colorless oil (341 mg, 73% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.82 – 7.69 (m, 3H), 7.54 (s, 1H), 7.32 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.28 – 7.16 (m, 3H), 6.17 (ddt, *J* = 6.7, 5.3, 1.4 Hz, 1H), 4.41 (d, *J* = 6.7 Hz, 2H), 2.33 (d, *J* = 1.0 Hz, 3H), 2.10 (dd, *J* = 1.4, 0.8 Hz, 3H), 1.55 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 135.6, 135.2, 130.6, 130.0, 128.9, 127.6, 127.0, 125.3, 124.9, 123.6, 123.5, 121.3, 113.9, 59.7, 21.7, 16.9. IR (neat film, NaCl) 3353, 2924, 1597, 1446, 1370, 1276, 1174, 1139, 1092, 985, 812, 746, 670; HRMS (ESI+) *m/z* calc'd for $C_{19}H_{19}NO_3S$ $[M+H]^+$: 342.1158, found 342.1159.



(*E*)-methyl (3-(pyridin-3-yl)but-2-en-1-yl) carbonate (2q)

Prepared from compound **2qa** according to general procedure B. Purification by silica gel chromatography (0 → 100% EtOAc in hexanes) afforded the title compound as a colorless oil (564 mg, 30% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 – 8.60 (m, 1H), 8.48 (dd, *J* =

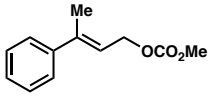
4.8, 1.6 Hz, 1H), 7.65 (ddd, *J* = 8.0, 2.3, 1.6 Hz, 1H), 7.22 (ddd, *J* = 8.0, 4.8, 0.9 Hz, 1H), 5.92 (tq, *J* = 6.9, 1.5 Hz, 1H), 4.83 (dd, *J* = 6.8, 0.9 Hz, 2H), 3.77 (s, 3H), 2.11 (dt, *J* = 1.5, 0.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 148.9, 147.4, 138.0, 137.8, 133.2, 123.2, 122.5, 64.6, 54.9, 16.1. IR (neat film, NaCl) 2957, 1748, 1568, 1444, 1415, 1378, 1327, 1263, 1129, 1022, 944, 792, 711, 624; HRMS (ESI+) *m/z* calc'd for $C_{11}H_{13}NO_3$ $[M+H]^+$: 208.0968, found 208.0972.



Ethyl (*E*)-3-(pyridin-3-yl)but-2-enoate[29] (2qa)

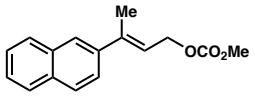
Prepared according to general procedure B. *E:*Z (3.3:1) by crude ^{1}H NMR. Purified by silica gel chromatography to afford a light yellow oil (2.24 g, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (dd, *J* = 2.5, 0.9 Hz, 1H), 8.59 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.75 (ddd, *J* = 8.0, 2.4, 1.6 Hz, 1H), 7.31 (ddd, *J* = 8.0, 4.8, 0.9 Hz, 1H), 6.14 (q, *J* = 1.4 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 2.58 (d, *J* = 1.4 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). All characterization data matched those reported in the literature.

^{1}H NMR Data of Previously Synthesized Allylic Carbonate Electrophiles



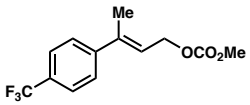
(*E*)-methyl (3-phenylbut-2-en-1-yl) carbonate (2a)[30]

Prepared according to general procedure B. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 7.7, 1.7 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 7.2 Hz, 1H), 5.93 (td, *J* = 7.0, 1.5 Hz, 1H), 4.86 (d, *J* = 7.0 Hz, 2H), 3.81 (s, 3H), 2.14 (s, 3H). All characterization data matched those reported in the literature.



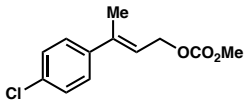
(*E*)-methyl (3-(naphthalen-2-yl)but-2-en-1-yl) carbonate (2b)[31]

Prepared according to general procedure B. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.76 (m, 4H), 7.58 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.51 – 7.43 (m, 2H), 6.08 (tq, *J* = 7.0, 1.3 Hz, 1H), 4.92 (dt, *J* = 7.0, 0.7 Hz, 2H), 3.82 (s, 3H), 2.24 (dt, *J* = 1.4, 0.7 Hz, 3H). All characterization data matched those reported in the literature.



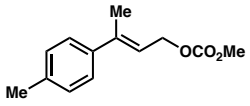
(*E*)-methyl (3-(4-(trifluoromethyl)phenyl)but-2-en-1-yl) carbonate (2c)[32]

Prepared according to general procedure B. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.54 (m, 2H), 7.53 – 7.45 (m, 2H), 6.02 – 5.93 (m, 1H), 4.86 (dd, *J* = 6.8, 0.9 Hz, 2H), 3.81 (s, 3H), 2.14 (dt, *J* = 1.5, 0.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 145.9, 145.9, 139.7, 130.1, 129.8, 129.4, 129.1, 126.2, 125.3, 125.3, 122.8, 64.7, 54.9, 16.2. All characterization data matched those reported in the literature.



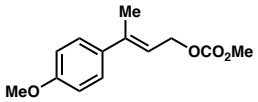
(*E*)-3-(4-chlorophenyl)but-2-en-1-yl methyl carbonate (2g)[32]

Prepared according to general procedure B. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 4H), 5.91 (dd, *J* = 7.8, 6.1 Hz, 1H), 4.84 (d, *J* = 7.0 Hz, 2H), 3.81 (s, 3H), 2.11 (s, 3H). All characterization data matched those reported in the literature.



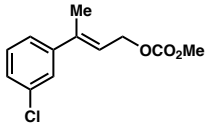
(*E*)-methyl (3-(*p*-tolyl)but-2-en-1-yl) carbonate (2h)[32]

Prepared according to general procedure B. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 2H), 7.18 – 7.09 (m, 2H), 5.90 (tq, *J* = 7.1, 1.3 Hz, 1H), 4.84 (dd, *J* = 7.1, 0.8 Hz, 2H), 3.80 (s, 3H), 2.34 (s, 3H), 2.11 (dd, *J* = 1.4, 0.8 Hz, 3H). All characterization data matched those reported in the literature.



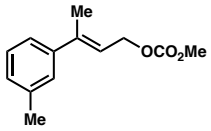
(*E*)-3-(4-methoxyphenyl)but-2-en-1-yl methyl carbonate (2i)[19]

Prepared according to general procedure B. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 2H), 6.89 – 6.83 (m, 2H), 5.87 (t, *J* = 7.1 Hz, 1H), 4.84 (d, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 2.11 (s, 3H). All characterization data matched those reported in the literature.



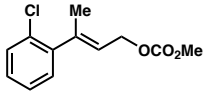
(*E*)-3-(3-chlorophenyl)but-2-en-1-yl methyl carbonate (2l)[19]

Prepared according to general procedure B. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (q, *J* = 1.5 Hz, 1H), 7.29 – 7.23 (m, 3H), 5.92 (tq, *J* = 7.0, 1.4 Hz, 1H), 4.84 (dq, *J* = 6.9, 0.9 Hz, 2H), 3.81 (s, 3H), 2.10 (dt, *J* = 1.4, 0.8 Hz, 3H). All characterization data matched those reported in the literature.



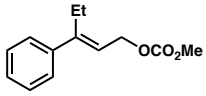
(*E*)-methyl (3-(*m*-tolyl)but-2-en-1-yl) carbonate (2m)[32]

Prepared according to general procedure B. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.18 (m, 3H), 7.11 – 7.08 (m, 1H), 5.95 – 5.86 (m, 1H), 4.85 (dq, *J* = 7.0, 0.7 Hz, 2H), 3.80 (s, 3H), 2.36 (d, *J* = 0.8 Hz, 3H), 2.12 (dt, *J* = 1.3, 0.7 Hz, 3H). All characterization data matched those reported in the literature.



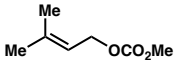
(*E*)-3-(2-chlorophenyl)but-2-en-1-yl methyl carbonate (2r)[32]

Prepared according to general procedure B. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 5.78 (t, *J* = 7.0 Hz, 1H), 4.85 (d, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 2.64 – 2.53 (m, 2H), 1.55 (s, 1H), 1.00 (t, *J* = 7.5 Hz, 3H). All characterization data matched those reported in the literature.



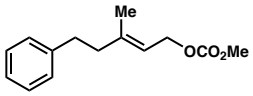
(*E*)-methyl (3-phenylpent-2-en-1-yl) carbonate (2s)[32]

Prepared according to general procedure B. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 1H), 7.24 – 7.15 (m, 3H), 5.59 (ddt, *J* = 6.9, 5.4, 1.5 Hz, 1H), 4.83 (dq, *J* = 6.9, 0.8 Hz, 2H), 3.81 (s, 3H), 2.07 (dt, *J* = 1.5, 0.8 Hz, 3H). All characterization data matched those reported in the literature.



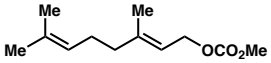
Methyl (3-methylbut-2-en-1-yl) carbonate (2t)[33]

Prepared according to general procedure B from 3-methyl-2-buten-1-ol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38 (ddq, *J* = 8.7, 5.9, 1.4 Hz, 1H), 4.63 (dp, *J* = 7.3, 0.8 Hz, 2H), 3.77 (s, 3H), 1.76 (dd, *J* = 1.4, 0.8 Hz, 3H), 1.74 – 1.71 (m, 3H). All characterization data matched those reported in the literature.



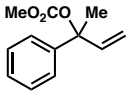
(*E*)-methyl (3-methyl-5-phenylpent-2-en-1-yl) carbonate (2u)[32]

Prepared according to general procedure B. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 7.22 – 7.15 (m, 3H), 5.40 (tq, *J* = 7.1, 1.3 Hz, 1H), 4.69 – 4.62 (m, 2H), 3.78 (s, 3H), 2.78 – 2.69 (m, 2H), 2.39 – 2.30 (m, 2H), 1.78 – 1.76 (m, 3H). All characterization data matched those reported in the literature.



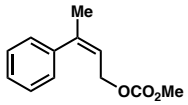
(*E*)-3,7-dimethylocta-2,6-dien-1-yl methyl carbonate (2v)[33]

Prepared according to general procedure B from geraniol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37 (ddq, *J* = 7.2, 5.7, 1.3 Hz, 1H), 5.07 (dddd, *J* = 6.8, 5.4, 2.9, 1.4 Hz, 1H), 4.65 (dq, *J* = 7.2, 0.7 Hz, 2H), 3.77 (s, 3H), 2.15 – 1.99 (m, 4H), 1.73 – 1.71 (m, 3H), 1.68 (q, *J* = 1.3 Hz, 3H), 1.60 (d, *J* = 1.3 Hz, 3H). All characterization data matched those reported in the literature.



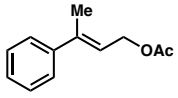
Methyl (2-phenylbut-3-en-2-yl) carbonate (17a)[34]

Prepared according to a literature procedure from 2-phenylbut-3-en-2-ol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.27 (m, 5H), 6.29 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.37 – 5.25 (m, 2H), 3.70 (s, 3H), 1.92 (s, 3H). All characterization data matched those reported in the literature.



(*Z*)-methyl (3-phenylbut-2-en-1-yl) carbonate (17b)[31]

Prepared according to general procedure B from ethyl (*Z*)-3-phenylbut-2-enoate. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.33 (m, 2H), 7.31 – 7.27 (m, 1H), 7.20 – 7.16 (m, 2H), 5.70 (td, *J* = 7.3, 1.6 Hz, 1H), 4.56 (dt, *J* = 7.2, 1.1 Hz, 2H), 3.77 (d, *J* = 0.8 Hz, 3H), 2.11 (t, *J* = 1.3 Hz, 3H). All characterization data matched those reported in the literature.

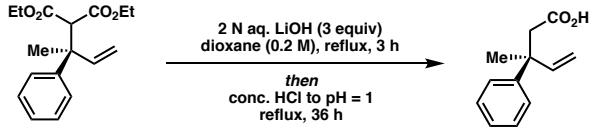


(*E*)-3-phenylbut-2-en-1-yl acetate (2aa)[35]

Prepared according to a literature procedure from the corresponding allylic alcohol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.39 (m, 2H), 7.36 – 7.26 (m, 3H), 5.90 (tq, *J* = 6.9, 1.4 Hz, 1H), 4.79 (dq, *J* = 7.1, 0.8 Hz, 2H), 2.12 (dt, *J* = 1.5, 0.8 Hz, 3H), 2.09 (s, 3H). All characterization data matched those reported in the literature.

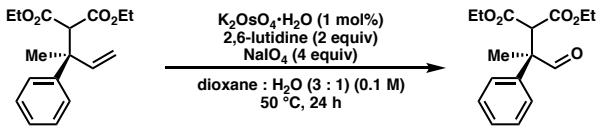
Derivatization of Alkylation Products

Note: Derivatization procedures are unoptimized.



(*S*)-3-methyl-3-phenylpent-4-enoic acid (18)

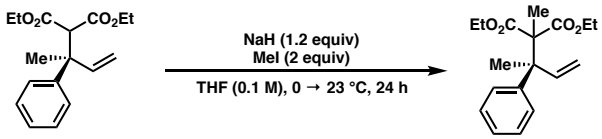
To a round bottom flask with stir bar and reflux condenser was added diester **3a** (145 mg, 0.5 mmol, 1.0 equiv) in dioxane (2.5 mL). 2 N aq. LiOH (0.75 mL) was added, and the mixture was heated to reflux. After 3h, TLC analysis indicated full consumption of the starting material. The solution was allowed to cool to room temperature, then concentrated HCl was added until the solution reached a pH of 1. The reaction mixture was then heated to reflux and periodically monitored by LC/MS. After 36h, although full conversion of the diacid to the decarboxylated product was not entirely complete, ethyl acetate was added, and the layers were partitioned and extracted three times with ethyl acetate (5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude reaction mixture was purified by silica gel chromatography (20% EtOAc, 1% AcOH in hexanes) to afford a yellow oil (33.0 mg, 35% yield); $[\alpha]_D^{25}$ –4.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 4H), 7.21 (ddt, *J* = 6.1, 5.4, 2.6 Hz, 1H), 6.15 (dd, *J* = 17.4, 10.7 Hz, 1H), 5.16 (dd, *J* = 10.6, 0.9 Hz, 1H), 5.09 (dd, *J* = 17.4, 0.9 Hz, 1H), [2.83, 2.82] (ABq, 2H, J_{AB} = 14.5 Hz), 1.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 145.9, 145.2, 128.4, 126.5, 126.4, 112.9, 45.4, 43.4, 25.6. HRMS (FI+) *m/z* calc'd for $C_{12}H_{14}O_2$: 190.0984, found 190.0988.



Diethyl (*R*)-2-(1-oxo-2-phenylpropan-2-yl)malonate (19)

To a flame-dried 1 Dr vial with stir bar was added the malonate product **3a** (29.0 mg, 0.1 mmol, 1.0 equiv) and K_2OsO_4•$2H_2O$ (0.4 mg, 0.001 mmol, 1 mol %). 2,6 lutidine (21.4 mg, 0.2 mmol, 2.0 equiv) was added as a solution in dioxane:H_2O (1.0 mL). To the stirring

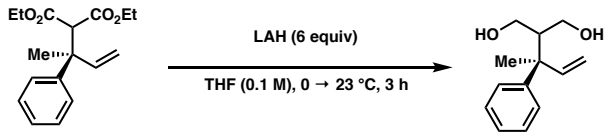
mixture was then added $NaIO_4$ (86 mg, 0.4 mmol, 4.0 equiv). The reaction vial was then heated to 50 °C for 24 h. After 24 h, the starting material had been consumed by TLC. The reaction mixture was cooled to room temperature and filtered through a pad of celite, eluting with dichloromethane (10 mL) and EtOAc (5 mL). Water was then added, and the layers were separated and extracted three times with dichloromethane. The combined organic layers were washed with brine, then dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by silica gel flash chromatography (10% EtOAc in hexanes) to afford the product as a colorless oil (19.0 mg, 67% yield); $[\alpha]_D^{25}$ +0.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.38 – 7.27 (m, 5H), 4.35 (s, 1H), 4.19 (qd, *J* = 7.2, 2.7 Hz, 2H), 3.96 (q, *J* = 7.1 Hz, 2H), 1.88 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.99 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 167.6, 167.5, 136.7, 129.0, 128.1, 127.6, 61.8, 61.4, 57.3, 54.6, 16.0, 14.1, 13.9; IR (Neat Film, NaCl) 2982, 1728, 1446, 1368, 1310, 1232, 1164, 1078, 1029 cm^{-1}; HRMS (FI+) ionization resulted in decomposition of product; *m/z* calc'd for $C_{16}H_{20}O_5$ $[M+Na]^+$: 315.1209, found 315.1203.



Diethyl (*S*)-2-methyl-2-(2-phenylbut-3-en-2-yl)malonate (20)

Sodium hydride (60 % dispersion in mineral oil, 0.12 mmol) was added to a 1 Dr vial. The vessel was purged and backfilled three times with nitrogen. THF (0.25 mL) was added and the suspension was cooled to 0°C. Diester **3a** (29.0 mg, 0.1 mmol, 1.0 equiv) was added as a solution in THF (0.25 mL). The solution was allowed to warm to 23°C over the course of one hour. Methyl iodide (0.2 mmol) in THF (0.5 mL) was then added dropwise to the stirred solution. After 24 hours the crude reaction mixture was diluted with ethyl acetate, then water was added and the mixture was stirred for 10 minutes. The layers were separated and extracted three times with EtOAc (20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue

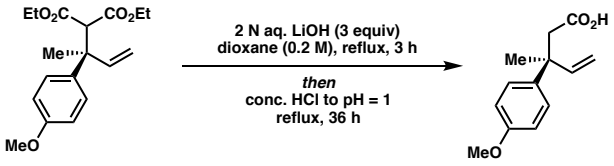
was purified by silica gel flash chromatography (2% to 10% EtOAc in hexanes; 2% increments, 50 mL each) to afford a colorless oil (13.0 mg, 43% yield); $[\alpha]_D^{25}$ +15.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 2H), 7.25 – 7.16 (m, 2H), 6.90 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.21 (dd, *J* = 11.0, 1.1 Hz, 1H), 5.02 (dd, *J* = 17.5, 1.2 Hz, 1H), 4.12 – 4.02 (m, 4H), 1.72 (s, 3H), 1.49 (s, 3H), 1.17 (dt, *J* = 14.5, 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 171.4, 144.6, 144.2, 128.9, 127.4, 126.5, 114.4, 61.3, 61.2, 61.1, 49.1, 23.2, 19.8, 14.0, 14.0; IR (Neat Film, NaCl) 2981, 1729, 1445, 1381, 1254, 1026, 917, 753, 702 cm^{-1}; HRMS (FI+) *m/z* calc'd for $C_{18}H_{24}O_4$: 304.1669, found 304.1683.



(*R*)-2-(2-phenylbut-3-en-2-yl)propane-1,3-diol (21)

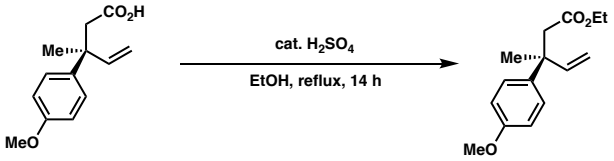
LAH (0.6 mmol, 6.0 equiv) was added to a flame dried 1 Dr vial fitted with septum. The vial was cooled to 0 °C and 0.5 mL THF was added. The diester **3a** (29.0 mg, 0.1 mmol, 1.0 equiv) was dissolved in 0.5 mL THF and added to the stirred LAH suspension. After stirring for 3 h, the reaction was cooled to 0 °C. 0.5 mL EtOAc was added to quench the reaction, which was then diluted with Et_2O followed by addition of a twofold excess of saturated potassium sodium tartrate. The layers were partitioned, the aqueous layer was extracted three times with ethyl acetate (10 mL), washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude mixture was purified by preparative TLC (50 % EtOAc in hexanes) affording a colorless oil (13.8 mg, 67%); $[\alpha]_D^{25}$ +4.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 4H), 7.20 (ddt, *J* = 6.6, 5.6, 2.3 Hz, 1H), 6.13 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.19 (dd, *J* = 10.8, 1.0 Hz, 1H), 5.11 (dd, *J* = 17.5, 1.0 Hz, 1H), 3.85 (ddd, *J* = 10.7, 3.3, 1.4 Hz, 1H), 3.77 – 3.64 (m, 3H), 2.61 (br s, 1H), 2.51 (br s, 1H), 2.40 (tdd, *J* = 8.6, 4.1, 3.2 Hz, 1H), 1.37 (s, 3H; ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 144.3, 128.6, 126.4, 126.3, 113.6, 64.9, 64.9, 50.1, 45.4, 21.7; IR (Neat Film, NaCl)

3304 (br), 2935, 1599, 1444, 1066, 1009, 919, 763, 730, 702 cm^{-1}; HRMS (FI+) *m/z* calc'd for $C_{13}H_{18}O_2$: 206.1301, found 206.1315.



(*S*)-3-(4-methoxyphenyl)-3-methylpent-4-enoic acid (22a)

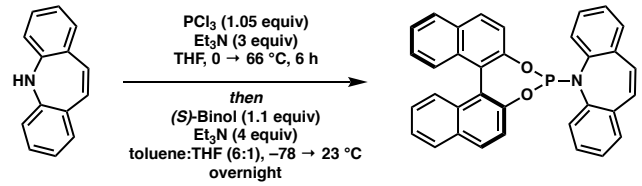
To a round bottom flask with stir bar and reflux condenser was added diester **7b** (246 mg, 0.77 mmol) in dioxane (3 mL). 2 N aq. LiOH (1.15 mL) was added, and the mixture was heated to reflux. After 3h, TLC analysis indicated full consumption of the starting material. The solution was allowed to cool to room temperature, then concentrated HCl was added until the solution reached a pH of 1. The reaction mixture was then heated to reflux and periodically monitored by LC/MS until consumption of the diacid was observed. After 36h, ethyl acetate was added, the layers were partitioned and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was re-dissolved in a minimal amount of ethyl acetate (0.1 mL), 2 M K_2CO_3 (5 mL) was added and the solution was stirred vigorously for 2h. The layers were separated and concentrated HCl was added until the solution reached a pH of 1. The aqueous layer was extracted four times with ethyl acetate (5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to afford an oil that solidified to an off-white amorphous solid (110 mg, 65% yield); $[\alpha]_D^{25}$ –5.5 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.22 (m, 2H), 6.89 – 6.79 (m, 2H), 6.12 (dd, J = 17.4, 10.7 Hz, 1H), 5.22 – 5.01 (m, 2H), 3.79 (s, 3H), [2.81, 2.78] (ABq, 2H, J_{AB} = 14.3 Hz), 1.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 158.1, 145.6, 137.9, 127.5, 113.7, 112.5, 55.3, 45.5, 42.8, 25.7; IR (Neat Film, NaCl) 2929, 1706, 1609, 1581, 1512, 1462, 1413, 1294, 1248, 1182, 1163, 1034, 921, 827 cm^{-1}; HRMS (FI+) *m/z* calc'd for $C_{13}H_{16}O_3$: 220.1094, found 220.1108.



Ethyl (*S*)-3-(4-methoxyphenyl)-3-methylpent-4-enoate (22b)

To a flame-dried round bottom 5 mL flask with stir bar and reflux condenser was added the β-quaternary acid **22a** (20 mg, 0.09 mmol) in ethanol (1 mL). Catalytic H_2SO_4 (0.05 mL) was added, and the mixture was heated to reflux. After 14h, TLC and LC/MS analysis indicated full consumption of the starting material. The solution was allowed to cool to room temperature, then neutralized with $NaHCO_3$, extracted 3x with ethyl acetate, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The product was purified by preparative TLC (20% ethyl acetate in hexanes) affording a colorless oil (15.3 mg, 69% yield); $[\alpha]_D^{25}$ –6.9 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.22 (m, 2H), 6.87 – 6.81 (m, 2H), 6.13 (dd, *J* = 17.4, 10.7 Hz, 1H), 5.15 – 5.02 (m, 2H), 4.00 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), [2.77, 2.72] (ABq, 2H, J_{AB} = 13.9 Hz), 1.55 (s, 3H), 1.12 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 158.0, 146.0, 138.2, 127.6, 113.6, 112.1, 60.2, 55.4, 46.0, 43.0, 25.7, 14.3; IR (Neat Film, NaCl) 2976, 2834, 1733, 1609, 1512, 1462, 1366, 1296, 1251, 1183, 1034, 911, 861, 831 cm^{-1}; HRMS (FI+) *m/z* calc'd for $C_{15}H_{20}O_3$: 248.1407, found 248.1424.

Ligand Synthesis



5-((11b*S*)-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yl)-5*H*-dibenzo[*b*,*f*]azepine ((S_a)-L1)[36]

The ligand was prepared according to a modified procedure disclosed by You and coworkers;[11] A flame-dried 250 mL 3-necked round bottomed flask equipped with a reflux condenser and addition funnel was charged with PCl_3 (504 mg (0.32 mL), 3.68 mmol, 1.05 equiv) and THF (5 mL). The solution was cooled to 0 ºC. Iminostilbene (676 mg, 3.0 mmol, 1 equiv) and Et_3N (1.06 g (1.46 mL), 10.5 mmol, 3 equiv) in THF (12 mL) were added dropwise. After the addition was complete, the solution was warmed to 23 °C then heated to reflux for 6 h. After TLC indicated consumption of the amine, the solution was cooled to –78 °C. A solution of *(S)*-Binol (1.10 g, 3.85 mmol, 1.1 equiv) and Et_3N (1.42 g (1.95 mL), 14 mmol, 4 equiv) in THF (10 mL) in toluene (60 mL) was added dropwise. After addition the solution was allowed to warm to 23 °C and stir overnight. The solution was then filtered over celite and silica eluting with ethyl acetate. The crude reaction mixture was concentrated and purified by silica gel chromatography (25% → 50% toluene in hexanes) to afford the desired ligand as a white solid (600 mg, 34% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.8 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.78 – 7.73 (m, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.45 – 7.32 (m, 3H), 7.30 – 7.07 (m, 9H), 7.02 – 6.89 (m, 3H), 6.84 (d, *J* = 8.8 Hz, 1H), 6.53 (td, *J* = 7.6, 1.6 Hz, 1H). All characterization data matched those reported in the literature.

1.5.3 DETERMINATION OF ABSOLUTE CONFIGURATION OF 3a VIA VIBRATIONAL CIRCULAR DICHROISM (VCD)

Experimental Protocol. A solution of **3a** (50 mg/mL) in $CDCl_3$ was loaded into a front-loading SL-4 cell (International Crystal Laboratories) possessing BaF_2 windows and a 100 mm path length. Infrared (IR) and VCD spectra were acquired on a BioTools ChiralIR-2X VCD spectrometer as a set of 24 one-hour blocks (24 blocks, 3120 scans per block) in dual PEM mode. A 15-minute acquisition of neat (+)-α-pinene control yielded a VCD spectrum in agreement with literature spectra. IR and VCD spectra were background corrected using

a 30-minute block IR acquisition of the empty instrument chamber under gentle N_2 purge, and were solvent corrected using a 16-hour (16 blocks, 3120 scans per block) IR/VCD acquisition of $CDCl_3$ in the same 100 μm BaF2 cell. The reported spectra represent the result of block averaging.

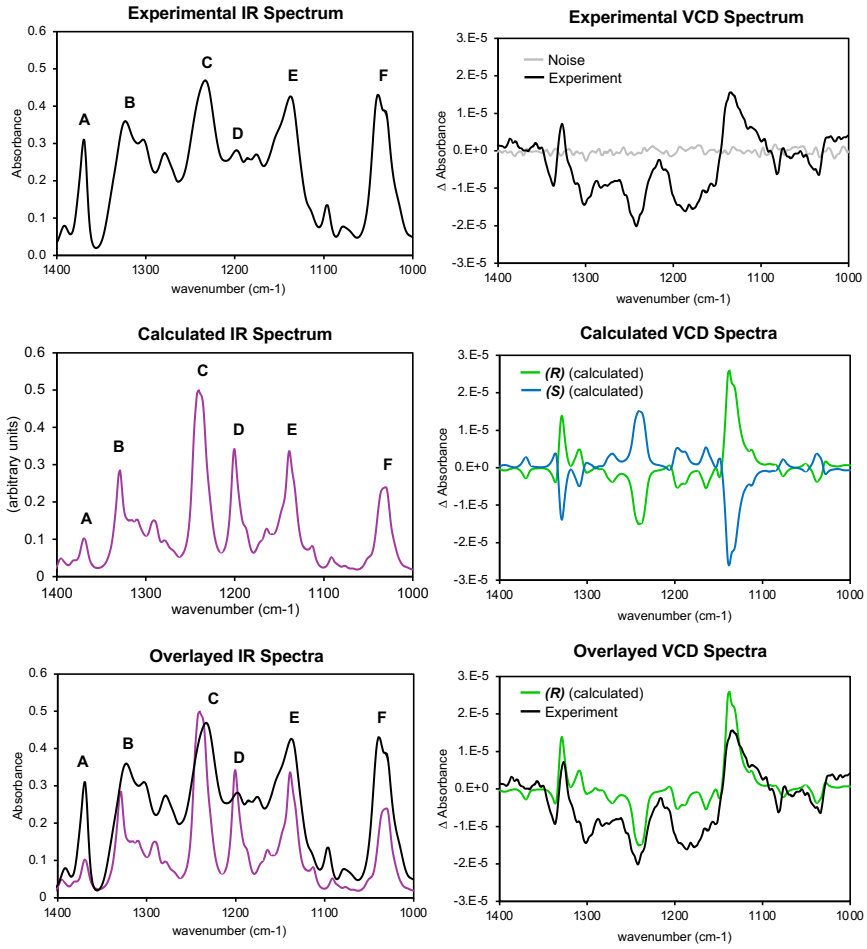
Computational Protocol. The arbitrarily chosen *(S)* enantiomer of compound **3a** was subjected to an exhaustive initial molecular mechanics-based conformational search (OPLS_2005 force field, $CHCl_3$ solvent, 10.0 kcal/mol cutoff, "Enhanced" torsional sampling) as implemented in MacroModel program.[37] The resulting ensemble containing 202 conformers was iteratively refined using the CENSO program of the Grimme group, interfaced to the Orca program of Neese, et. al. The refinement procedure includes the following steps:

1. Single point calculations with the B97-3c method. To these electronic energies are added thermochemical contributions calculated at the GFN2-xTB semi-empirical level of theory. 174 conformers remain within an energy window of 4.0 kcal/mol.
2. The conformer geometries are then optimized at the B97-3c level of theory employing a batchwise optimization procedure searching for parallel potential energy surfaces (default parameters in CENSO). 99 unique conformers remain.
3. Free energies are derived from adding thermochemical contributions calculated at the GFN2-xTB level of theory to the final electronic energies (B97-3c) from the optimizations. The 76 lowest energy conformers account for 99% of the Boltzmann population of conformers at 298.15 K (see table below).

ΔG (kcal/mol)	# conformers	Sum(Boltzmann_Pop)
0.0 – 0.5	17	64%
0.0 – 1.0	26	78%
0.0 – 1.5	46	93%

0.0 – 2.0	56	96%
0.0 – 2.5	**76**	**99%**
0.0 – 3.0	92	>99%
0.0 – 3.5	95	>99%
0.0 – 4.0	96	>99%
0.0 – 4.5	99	100%

The 76 lowest energy conformers are subsequently optimized using the B3PW91 functional, cc-pVTZ(-f) basis, and implicit PBF solvation model for chloroform using the Jaguar program. [38] Harmonic frequencies computed at the B3PW91/cc-pVTZ(-f)/PBF(chloroform) level were scaled by 0.98. The resultant 55 structurally unique conformers possessing all positive Hessian eigenvalues were Boltzmann weighted by relative free energy at 298.15 K. The predicted IR and VCD frequencies and intensities of the retained conformers were convolved using Lorentzian line shapes (γ = 4 cm^{-1}) and summed using the respective Boltzmann weights to yield the final predicted IR and VCD spectra of the *(S)* enantiomer of **3a**. The predicted VCD of the corresponding *(R)* enantiomer was generated by inversion of sign. From the reasonable agreement between the predicted and measured IR and VCD spectra in the useful range (1000–1400 cm^{-1}, see below), the absolute configuration of **3a** was assigned as *(R)*.



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APPENDIX 1

Spectra Relevant to Chapter 1:

Ir-Catalyzed Asymmetric Allylic Alkylation of Dialkyl Malonates Enabling the Construction of Enantioenriched All-Carbon Quaternary Centers

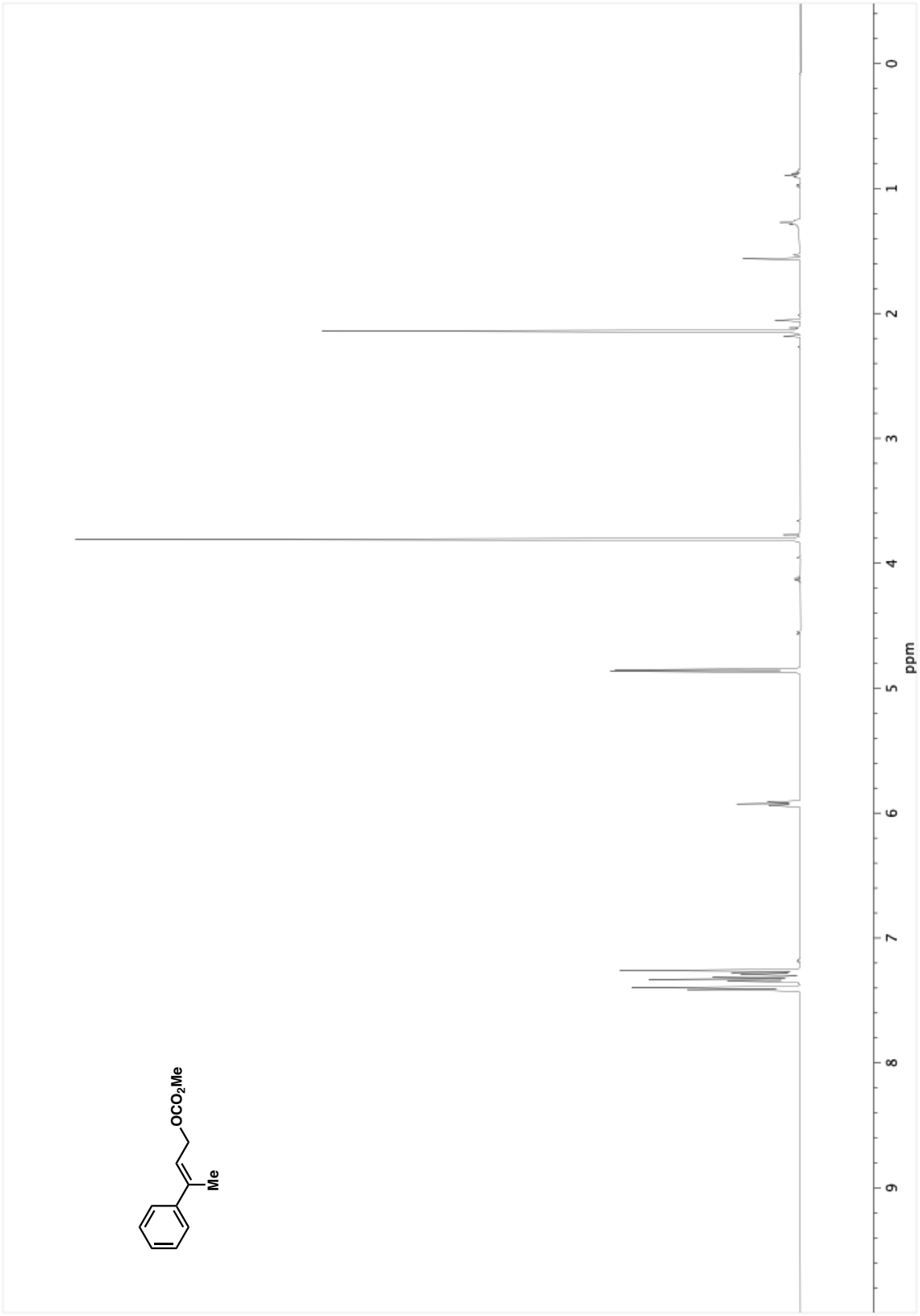


Figure A1.1. *^1H NMR (500 MHz, $CDCl_3$) of compound* ***2a***.

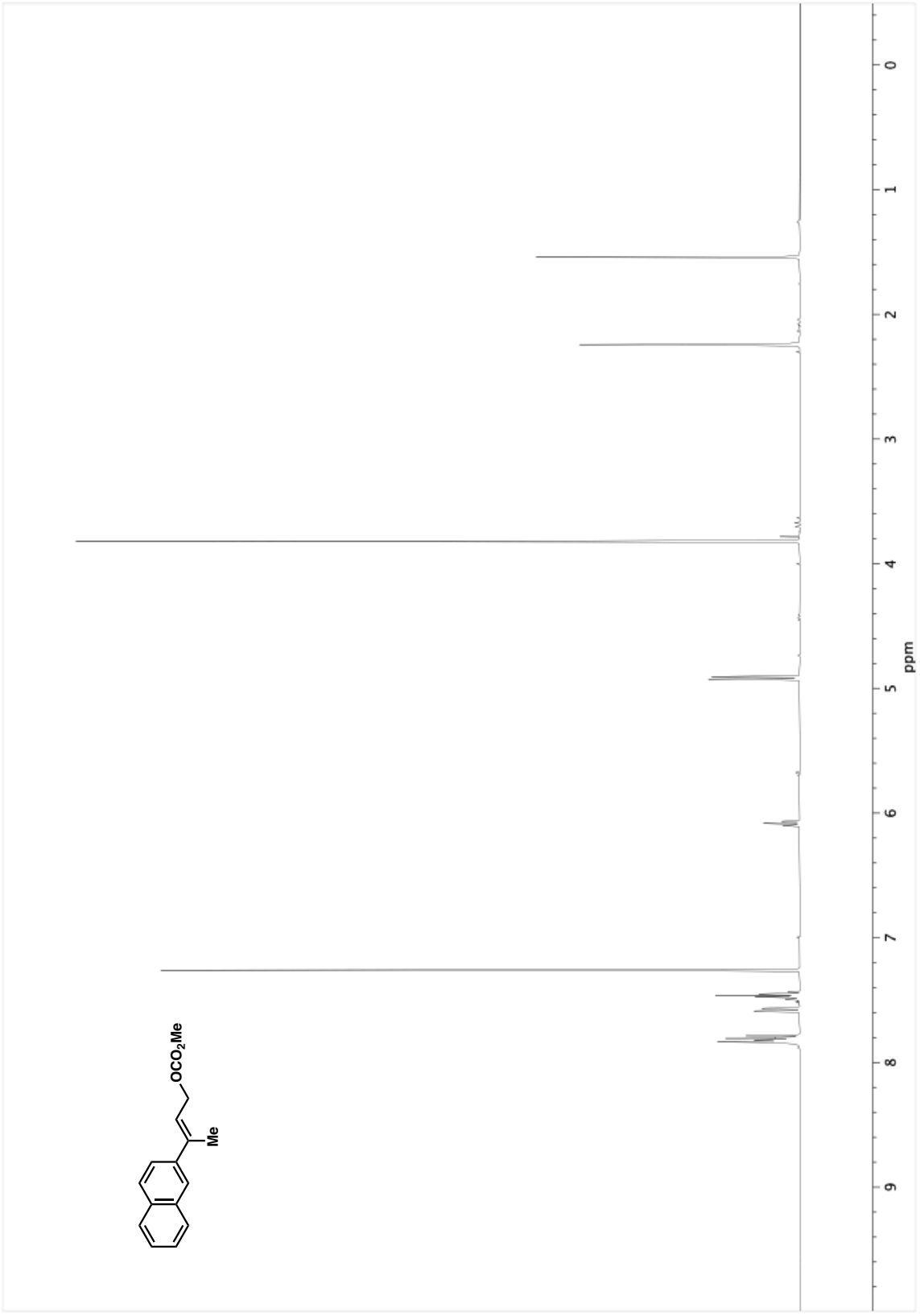


Figure A1.2. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***2b***.

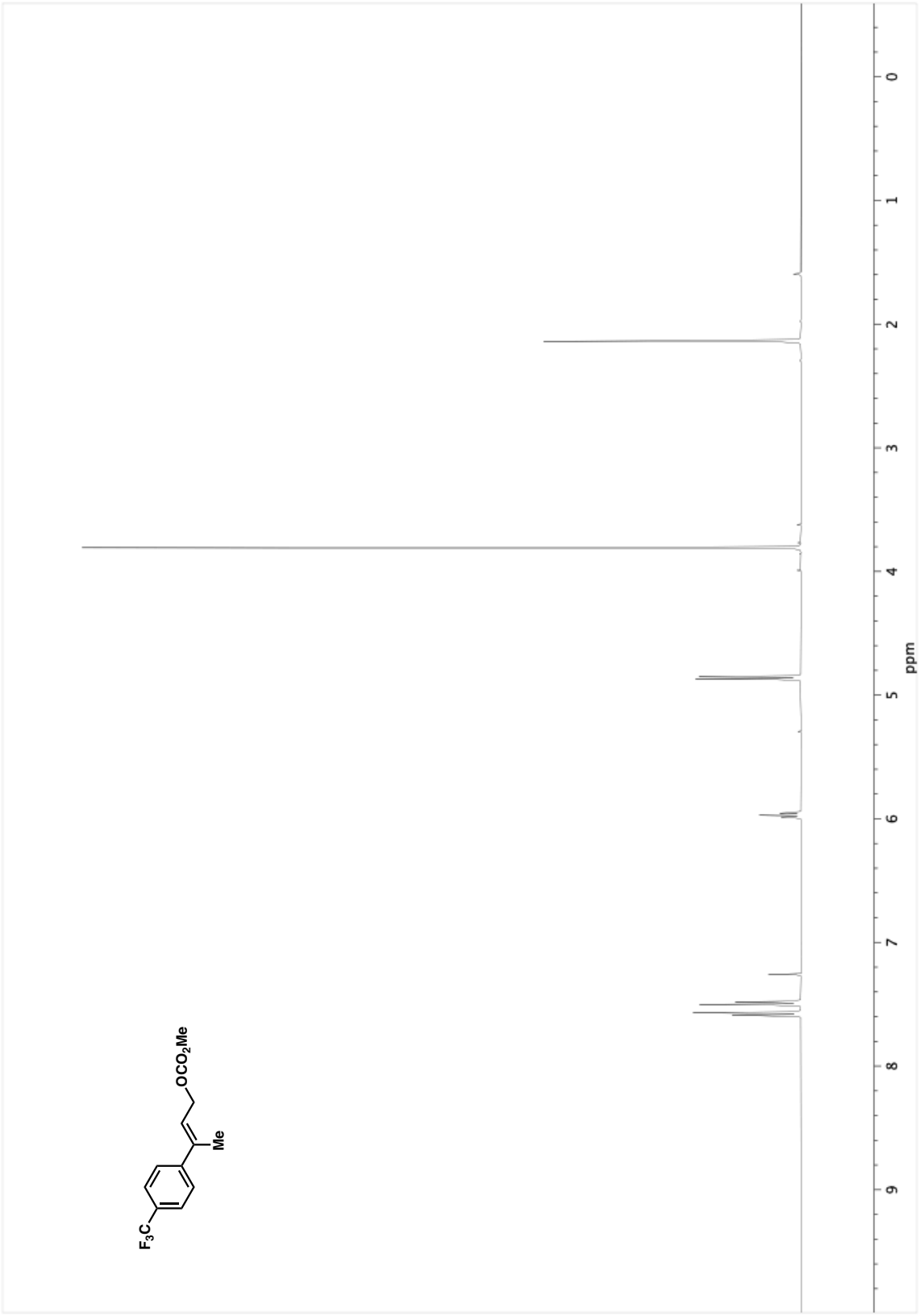


Figure A1.3. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***2c****.*

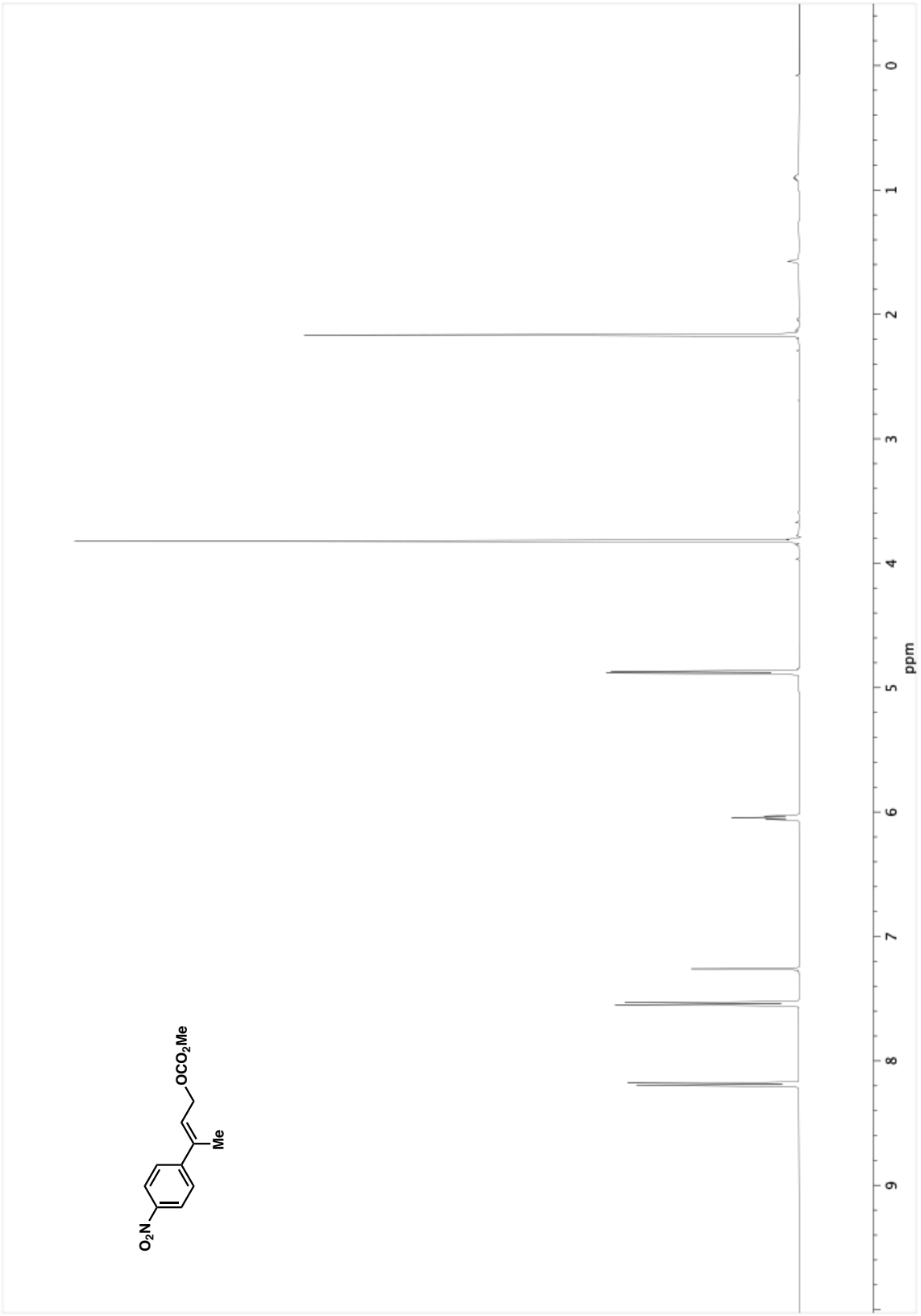


Figure A1.4. *^1H NMR (500 MHz, $CDCl_3$) of compound* ***2d****.*

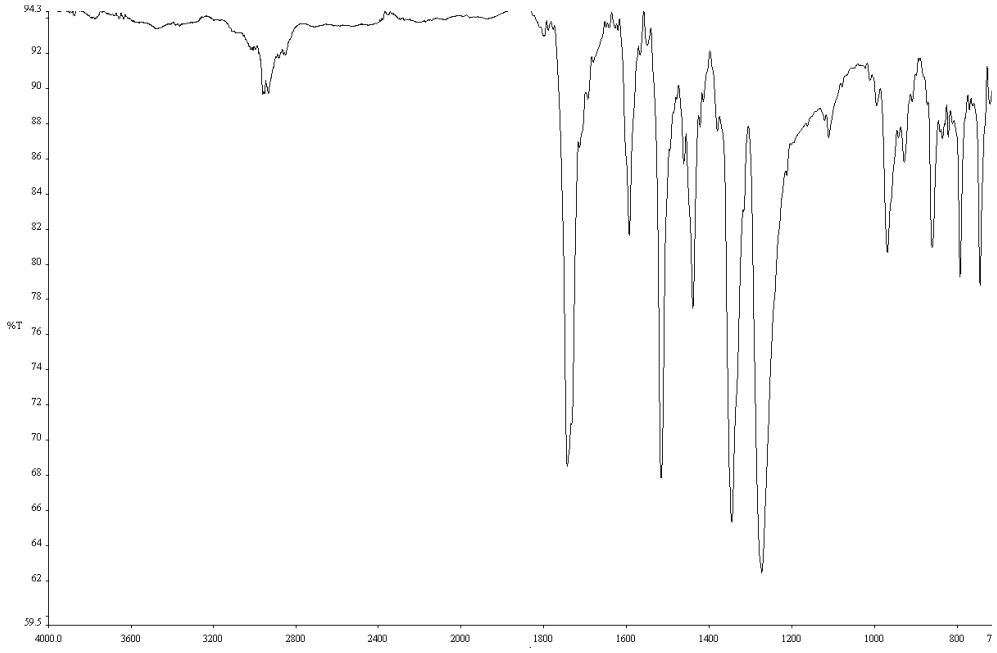


Figure A1.5. *Infrared spectrum (Thin Film, NaCl) of compound* ***2d.***

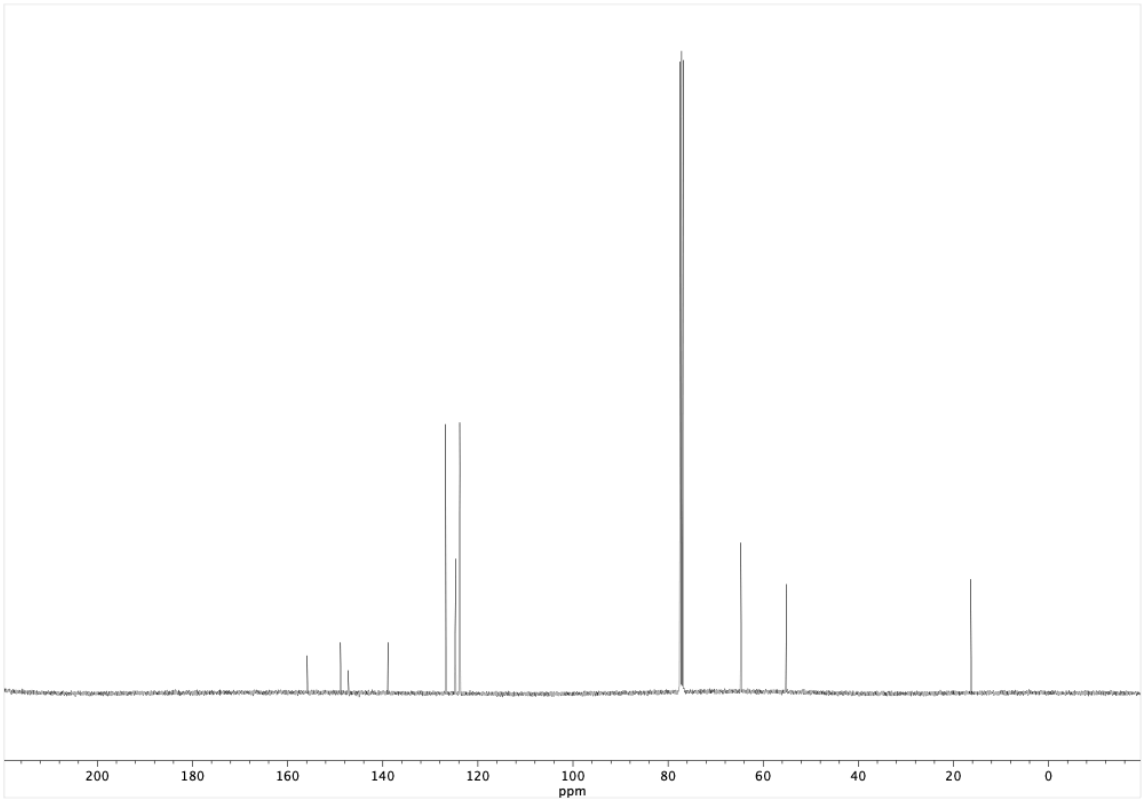


Figure A1.6. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***2d.***

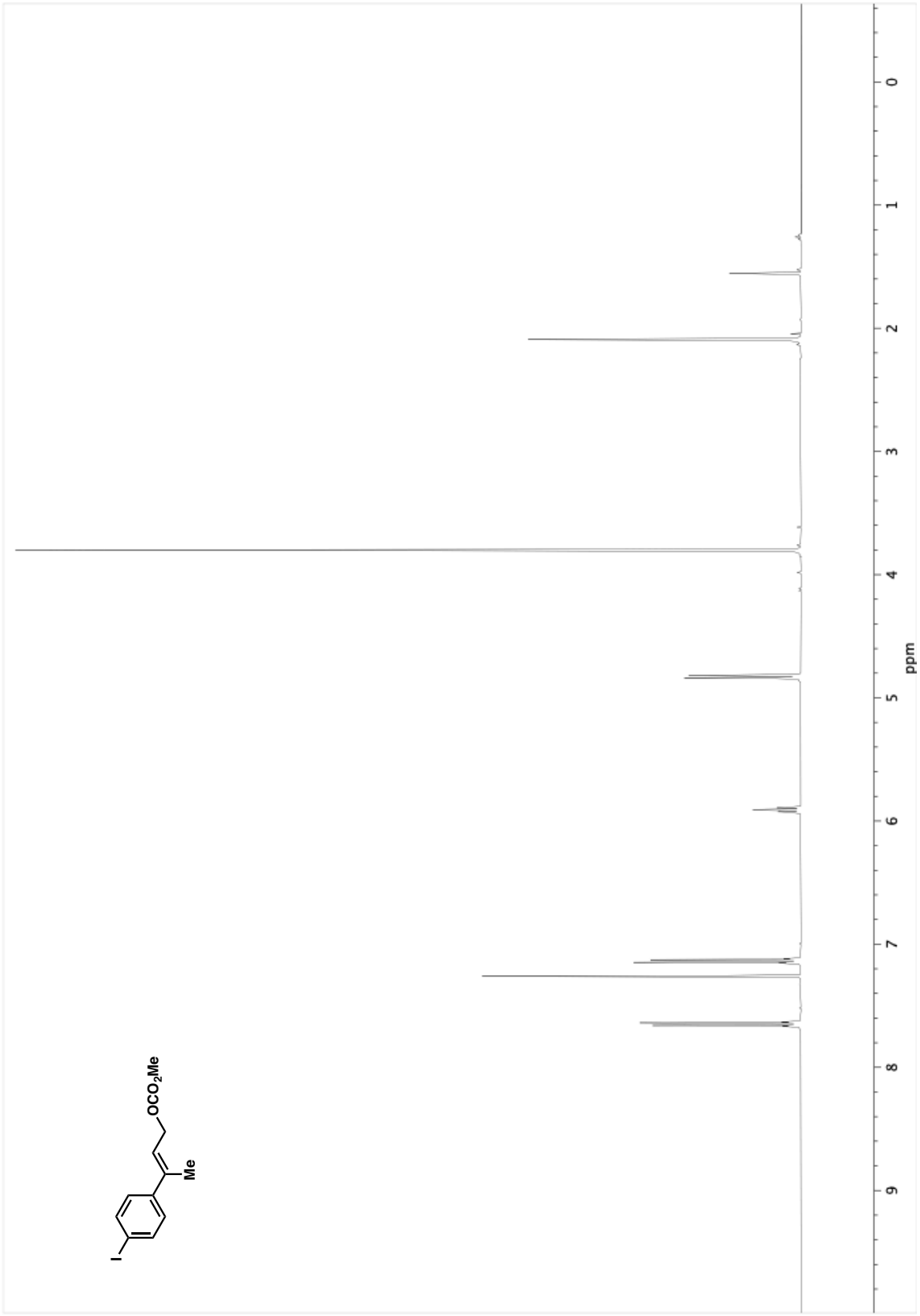


Figure A1.7. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* **2e**.

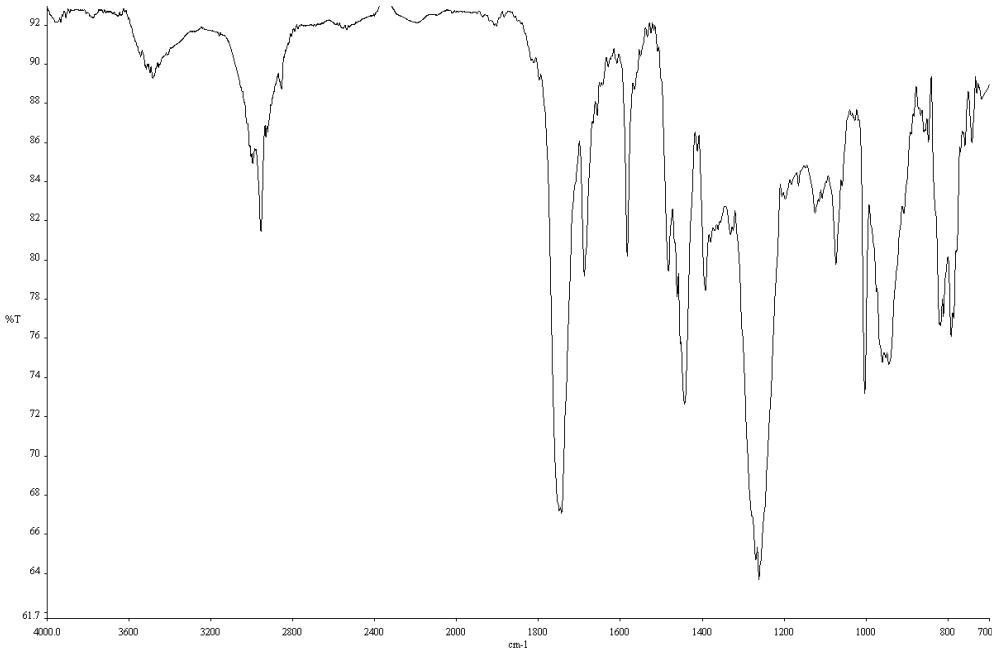


Figure A1.8. *Infrared spectrum (Thin Film, NaCl) of compound* ***2e****.*

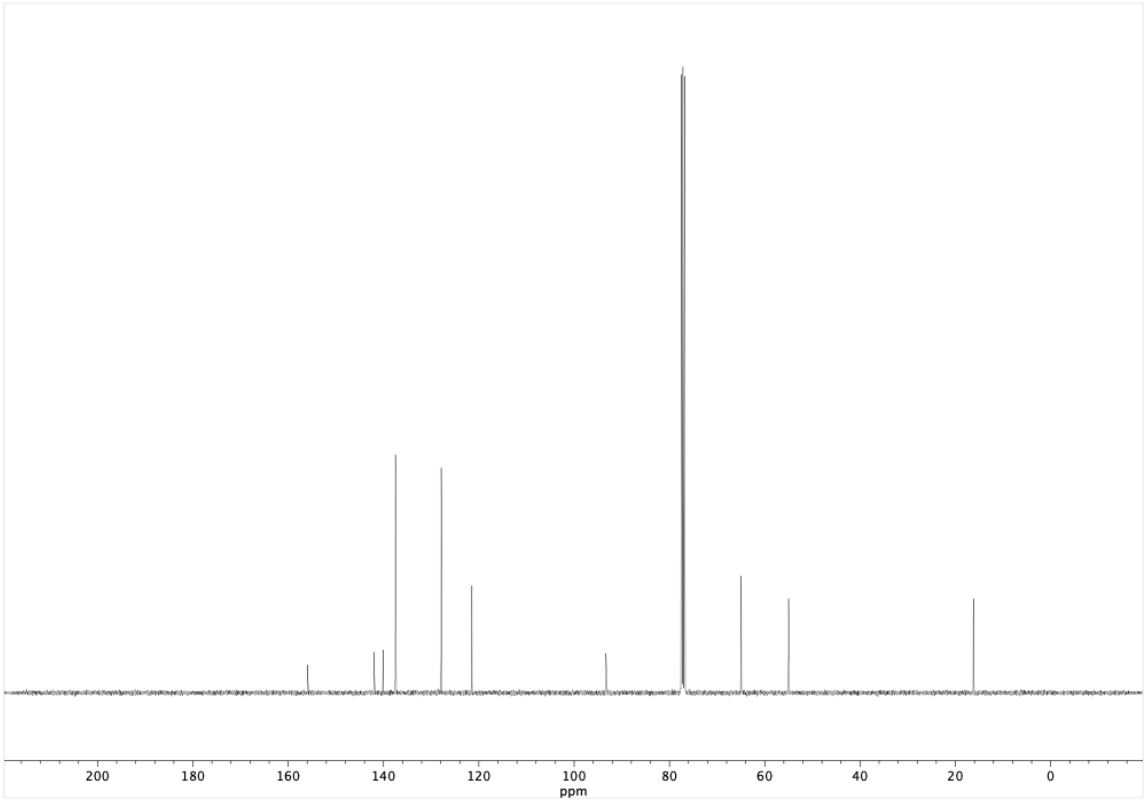


Figure A1.9. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***2e.***

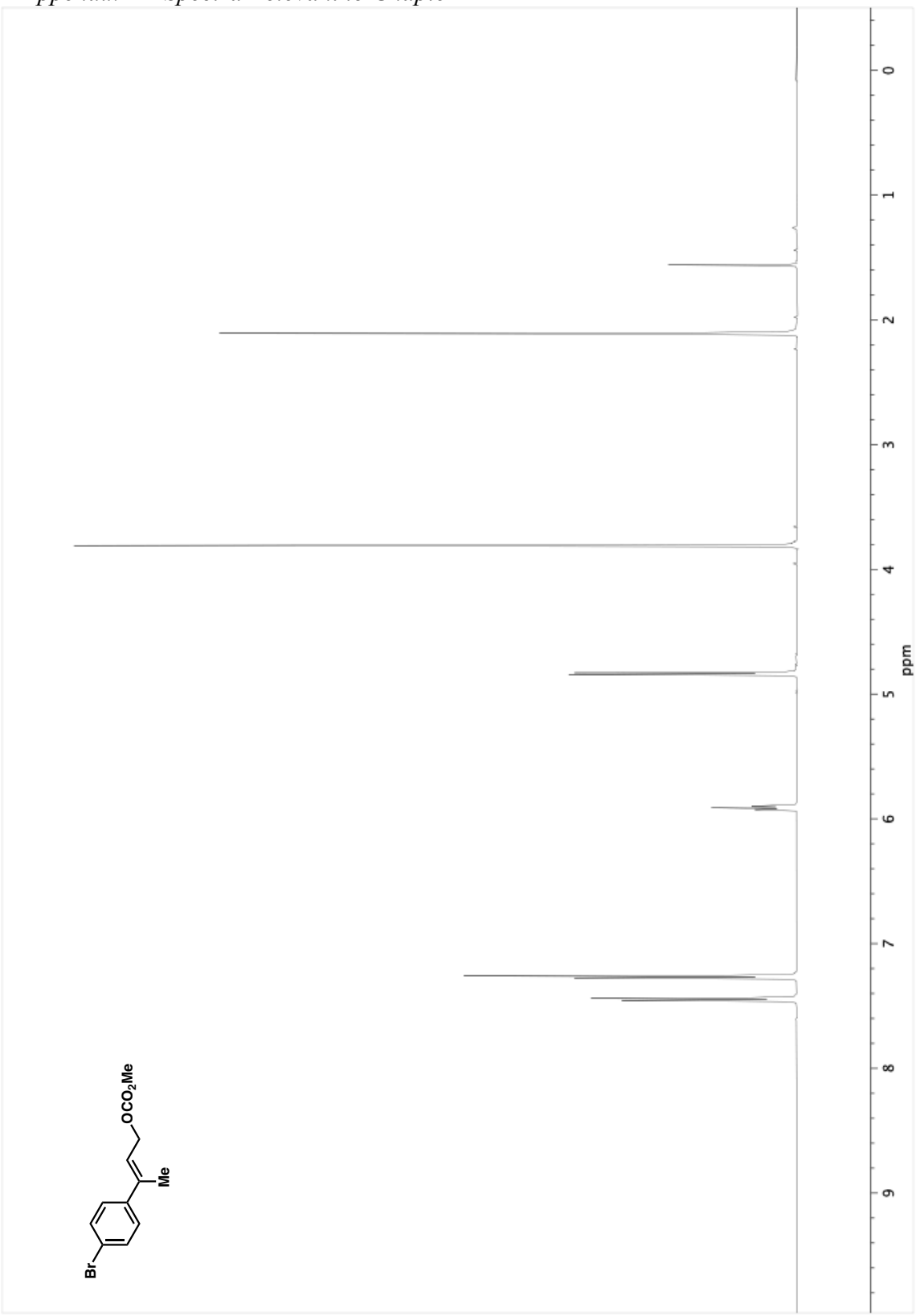


Figure A1.10. *^{1}H NMR (500 MHz, $CDCl_3$) of compound* ***2f.***

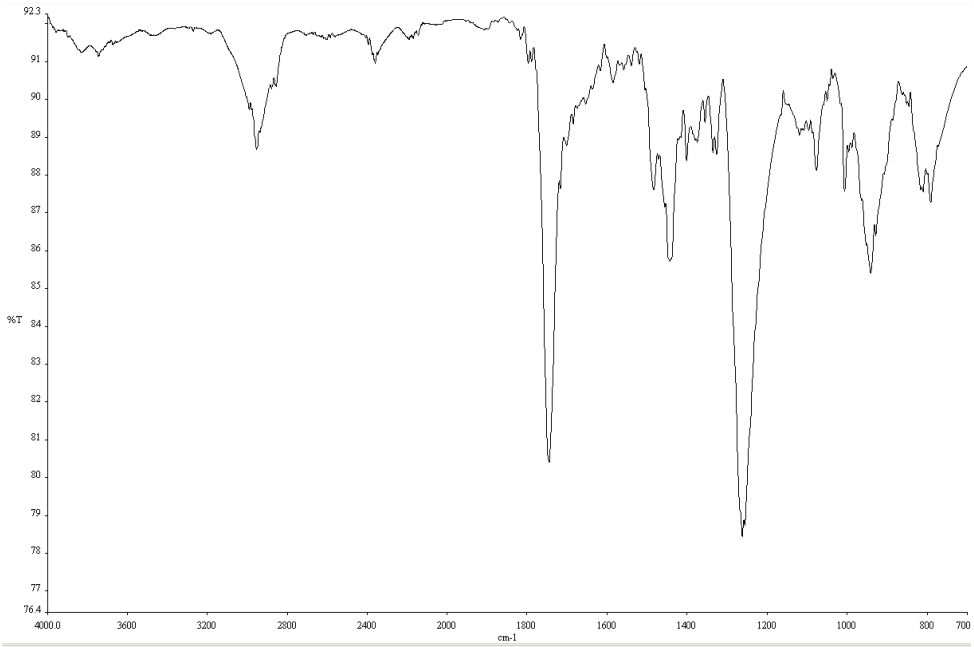


Figure A1.11. *Infrared spectrum (Thin Film, NaCl) of compound* ***2f****.*

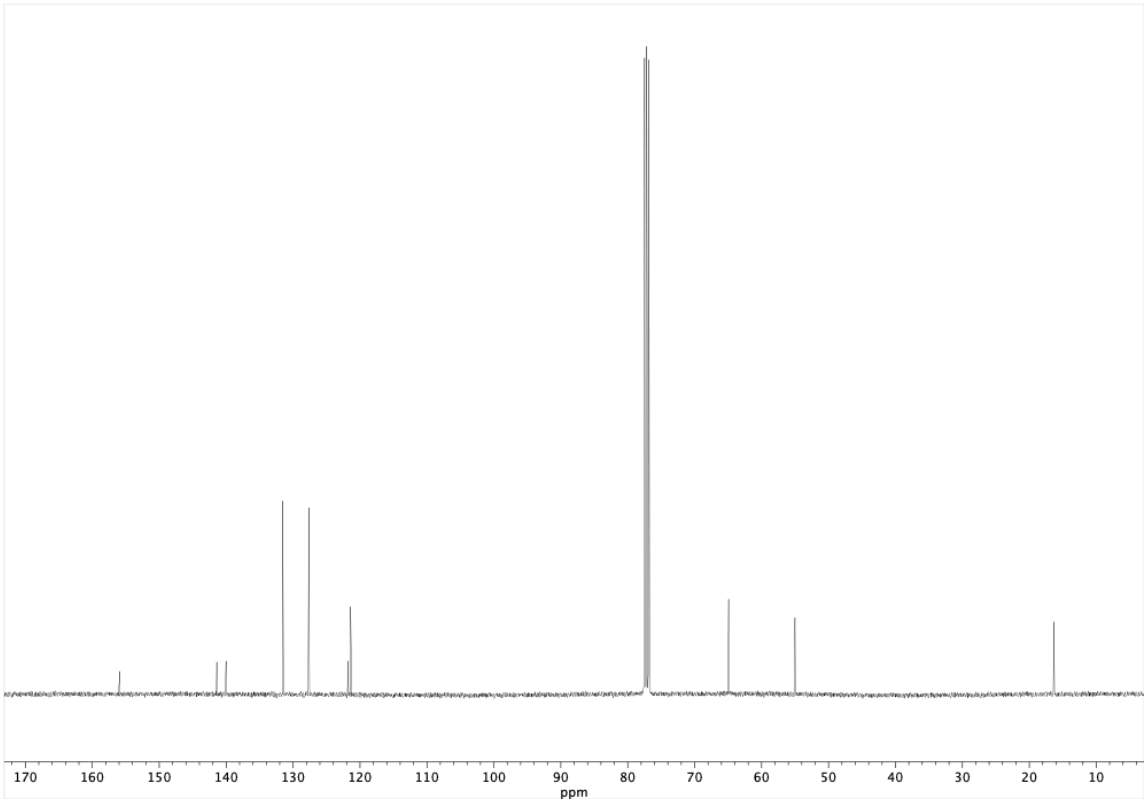


Figure A1.12. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***2f****.*

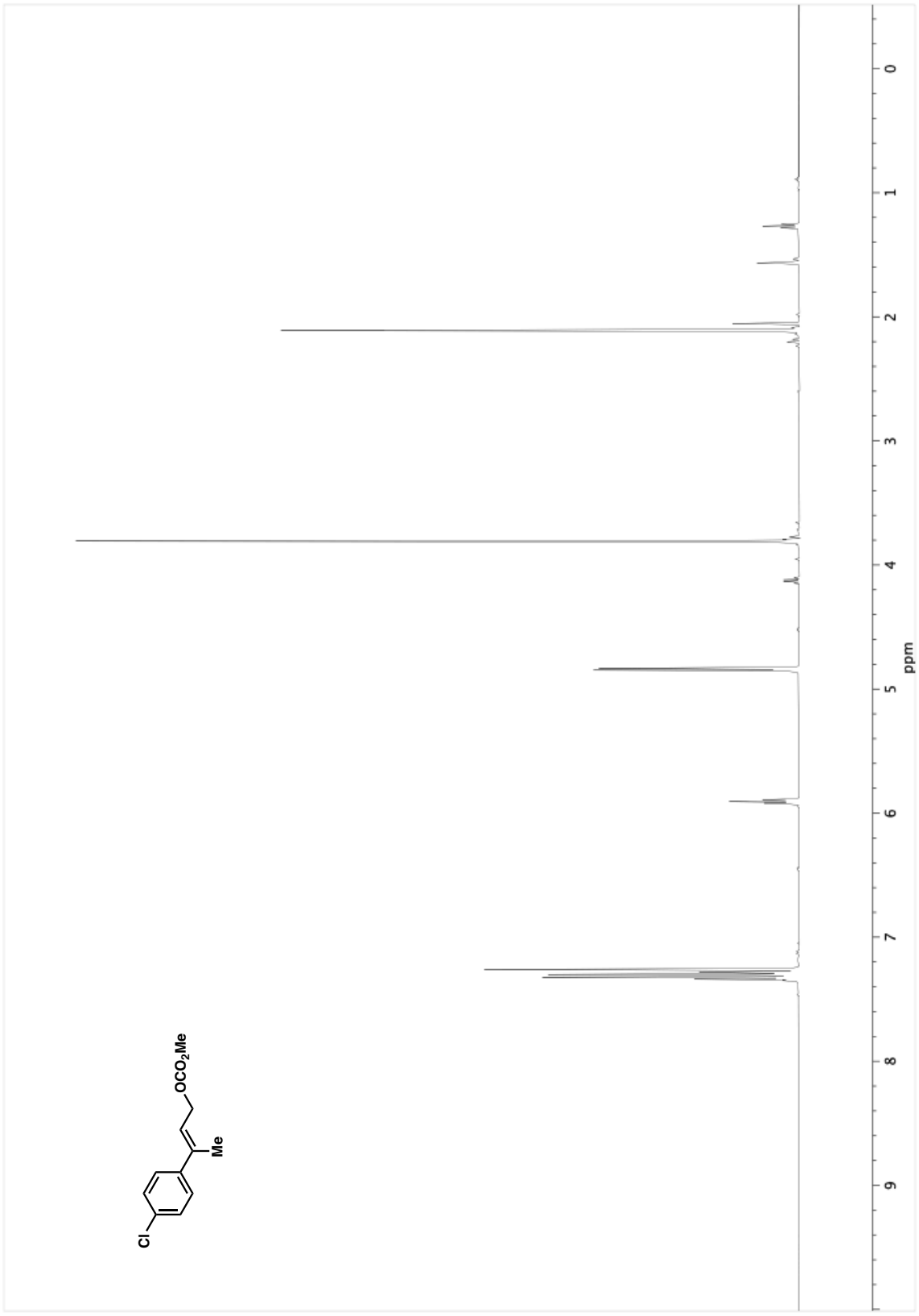


Figure A1.13. *^{1}H NMR (500 MHz, $CDCl_3$) of compound* ***2g.***

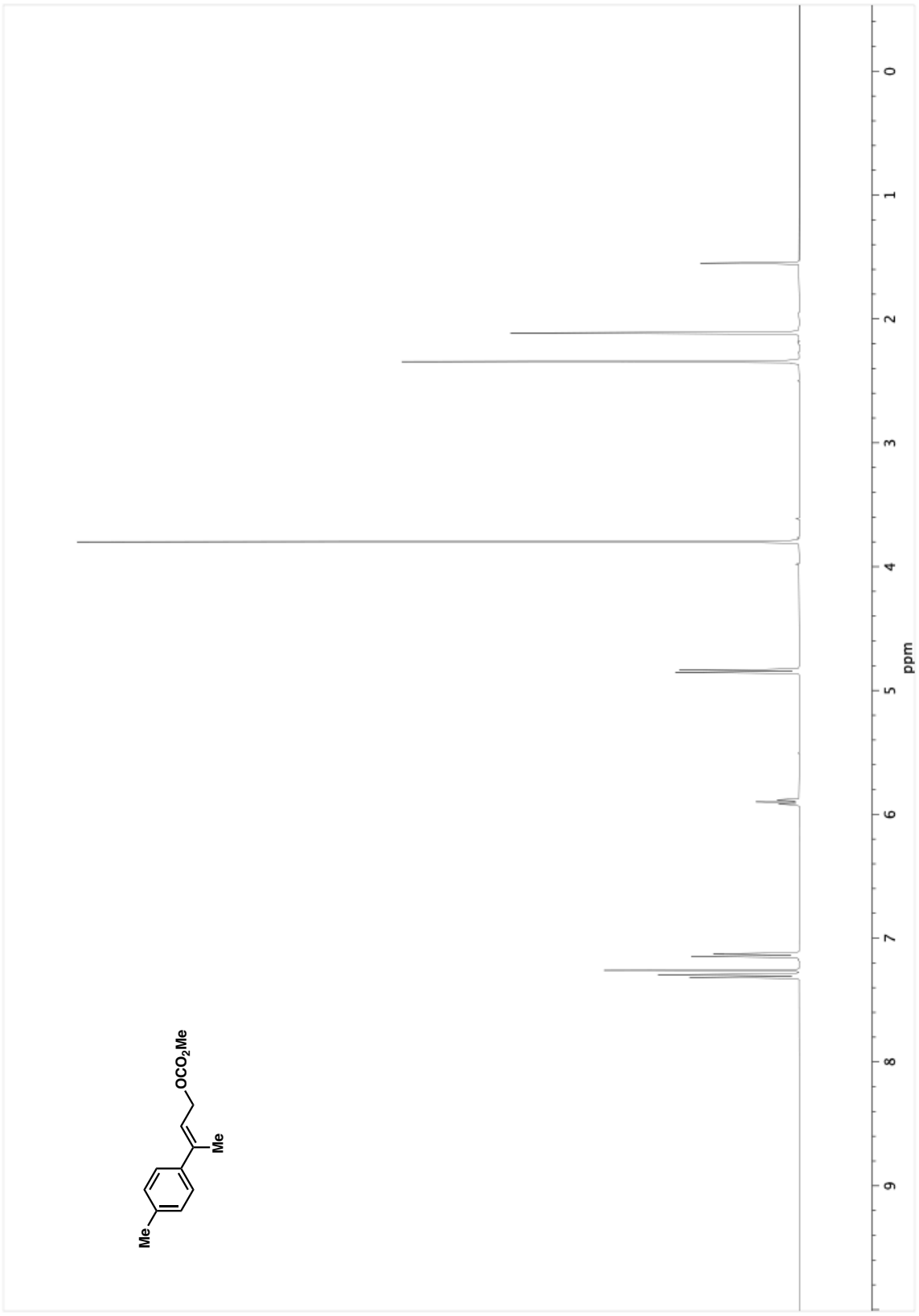


Figure A1.14. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***2h****.*

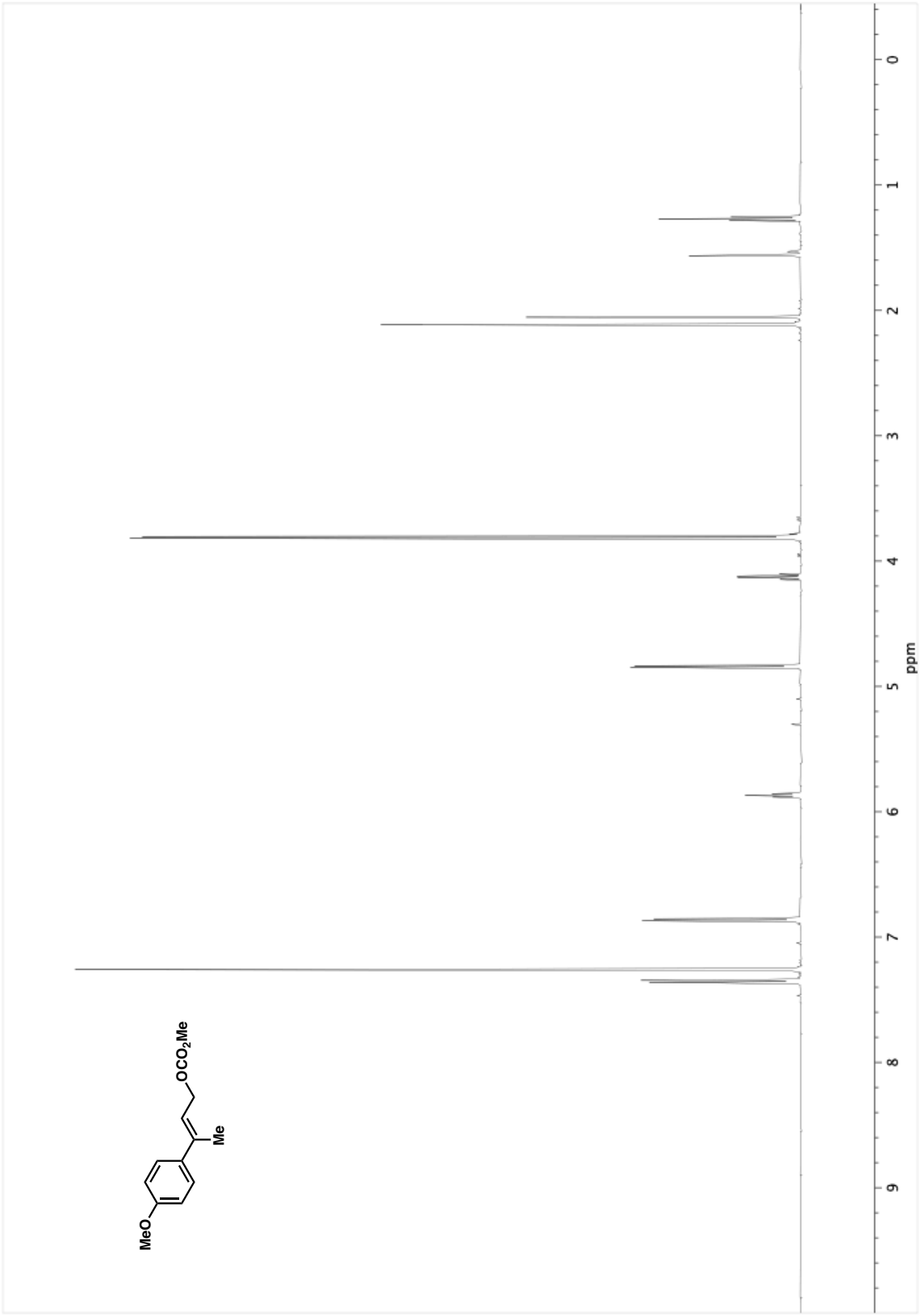


Figure A1.15. *^{1}H NMR (500 MHz, $CDCl_3$) of compound* ***2i.***

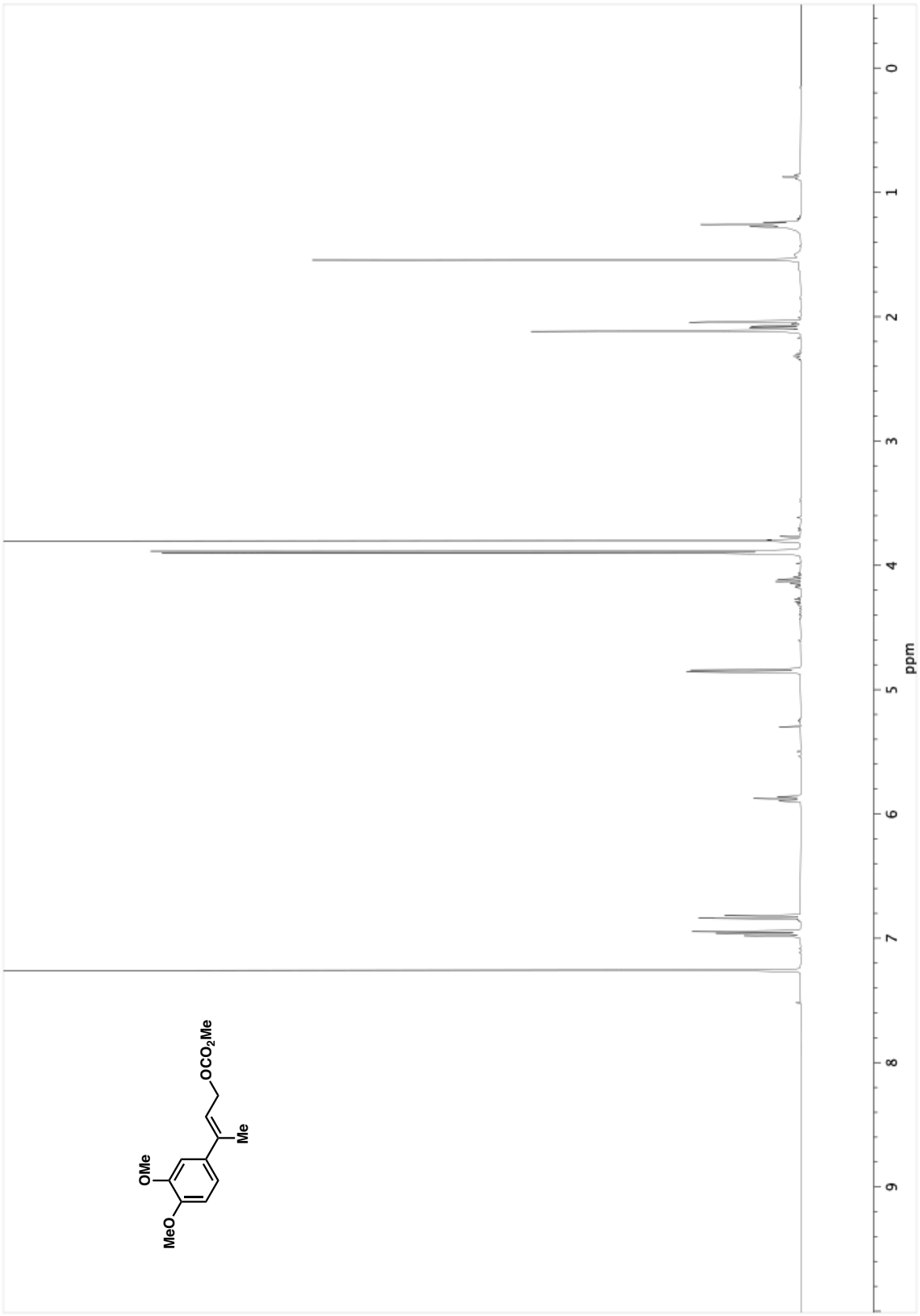


Figure A1.16. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***2j****.*

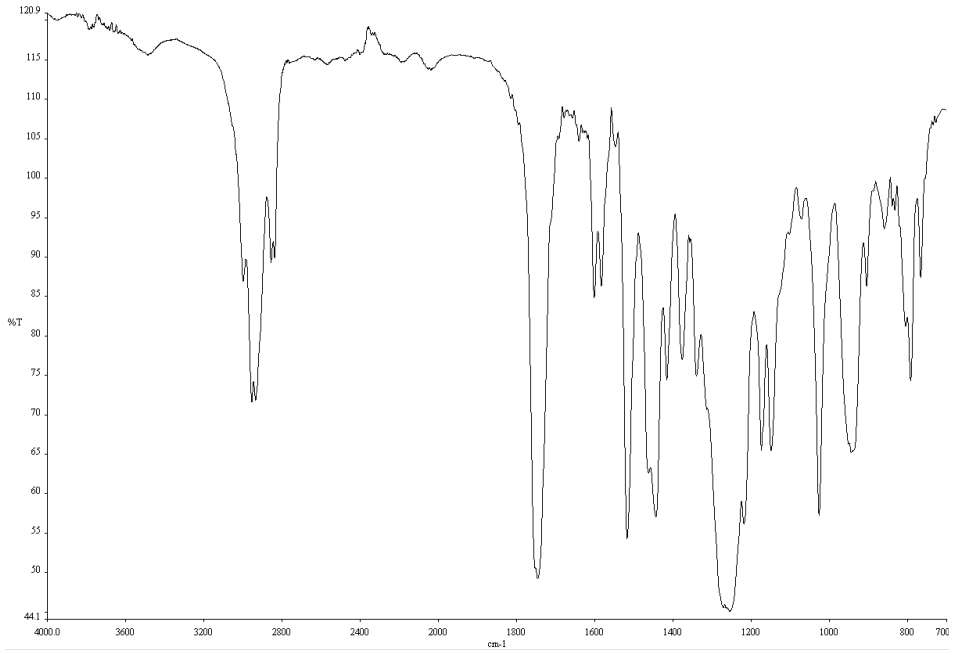


Figure A1.17. *Infrared spectrum (Thin Film, NaCl) of compound* ***2j.***

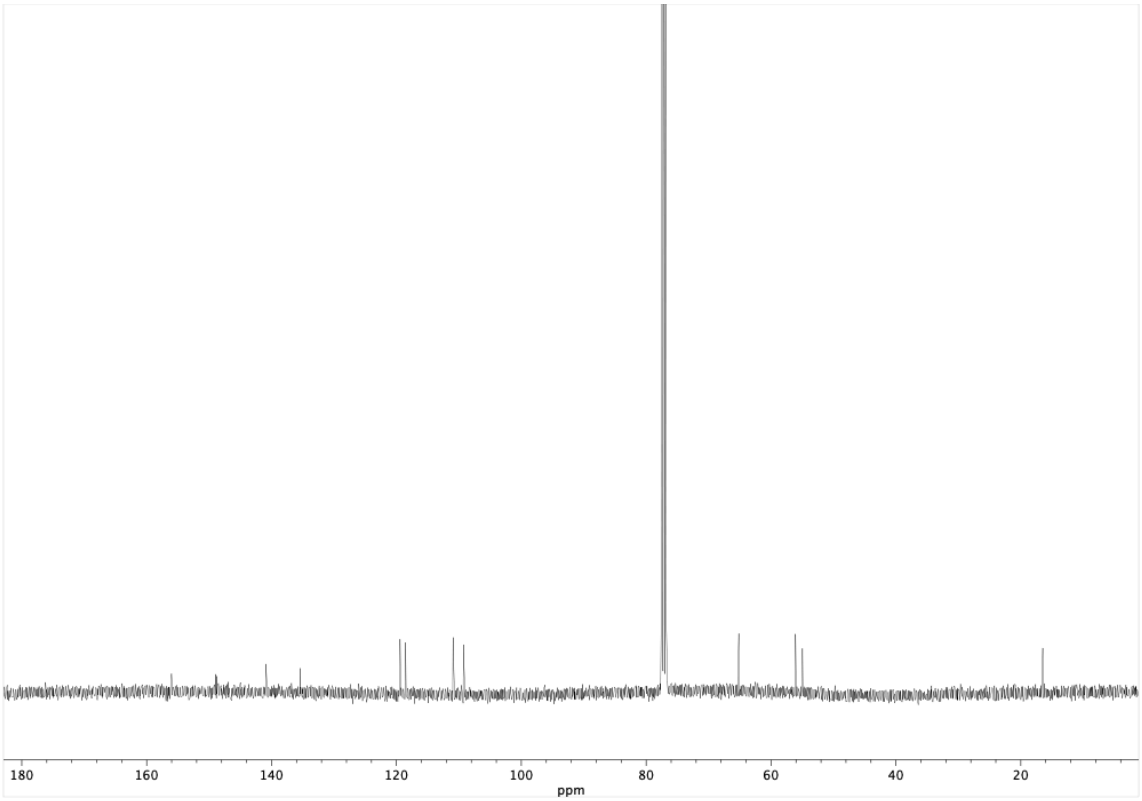


Figure A1.18. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***2j****.*

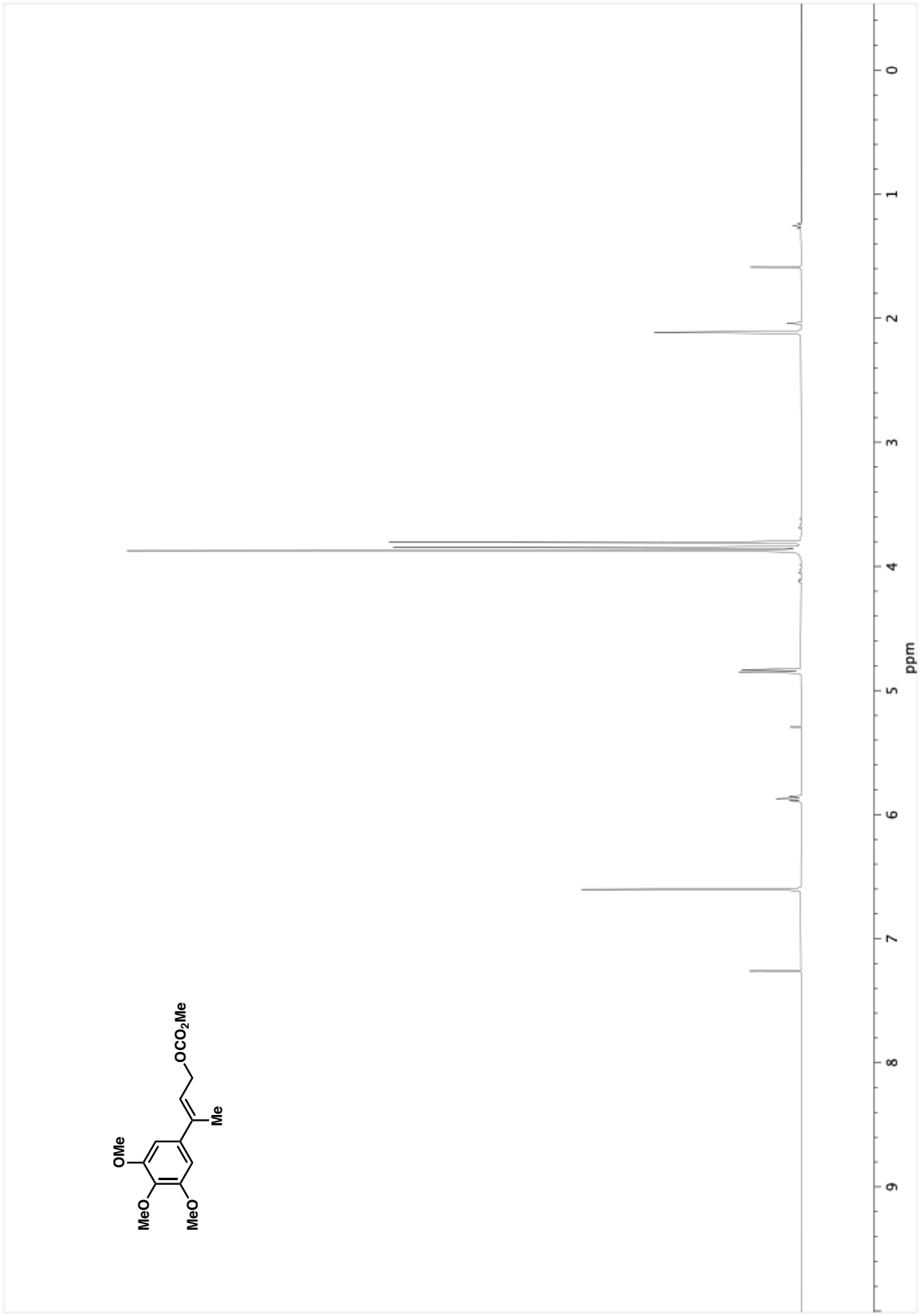


Figure A1.19. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***2k.***

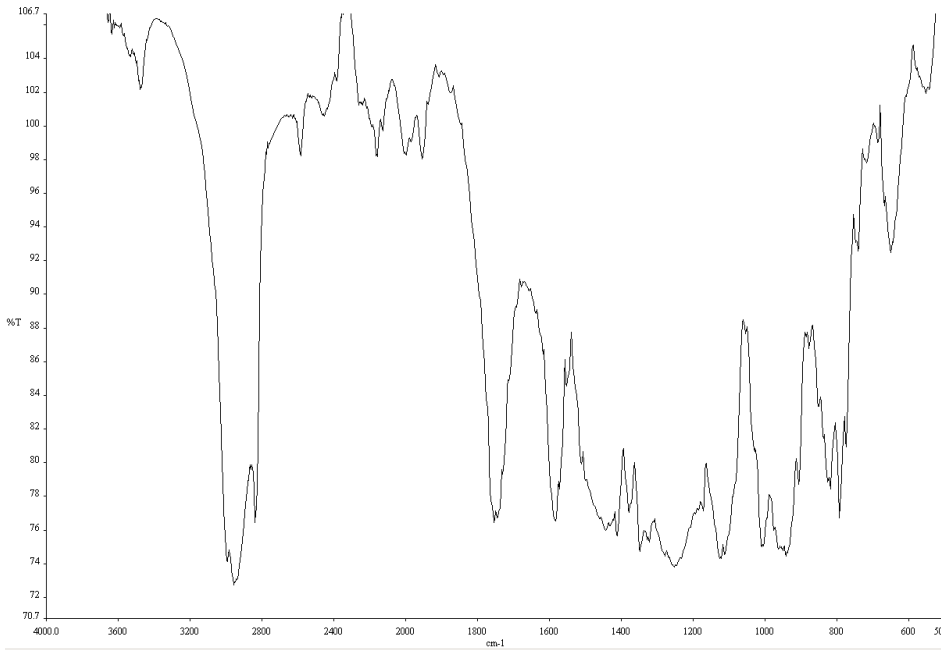


Figure A1.20. *Infrared spectrum (Thin Film, NaCl) of compound* ***2k****.*

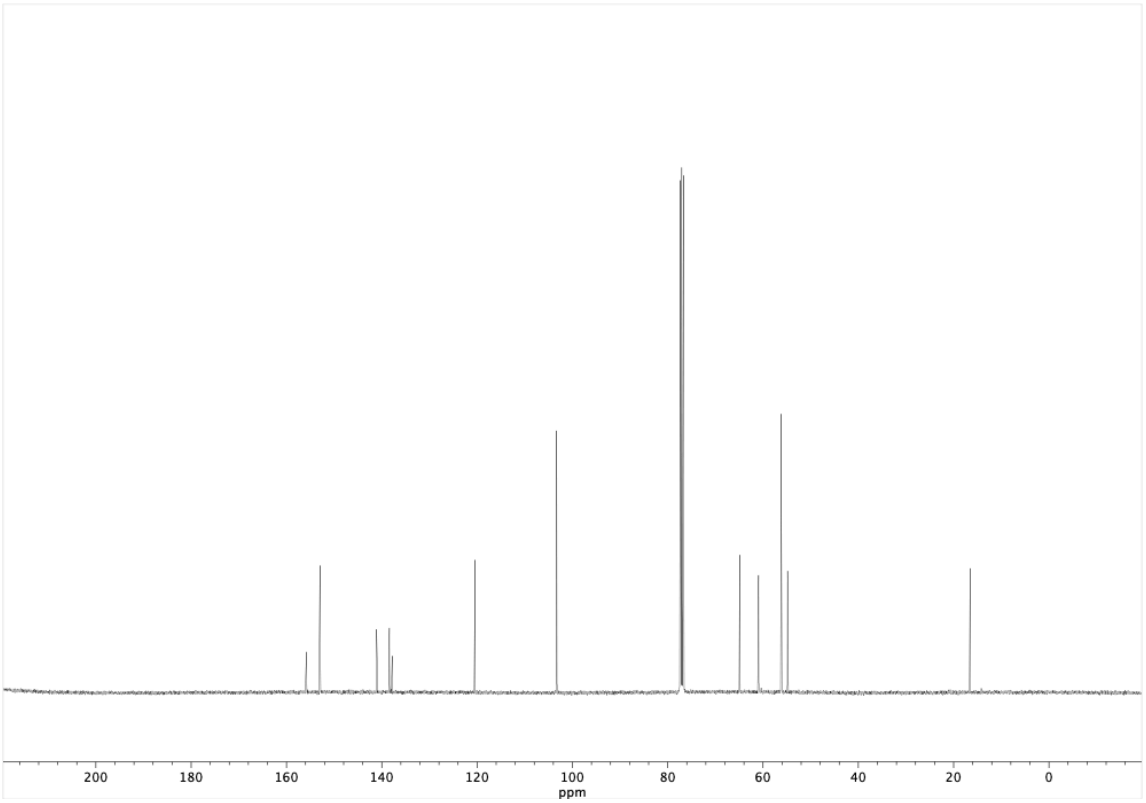


Figure A1.21. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***2k****.*

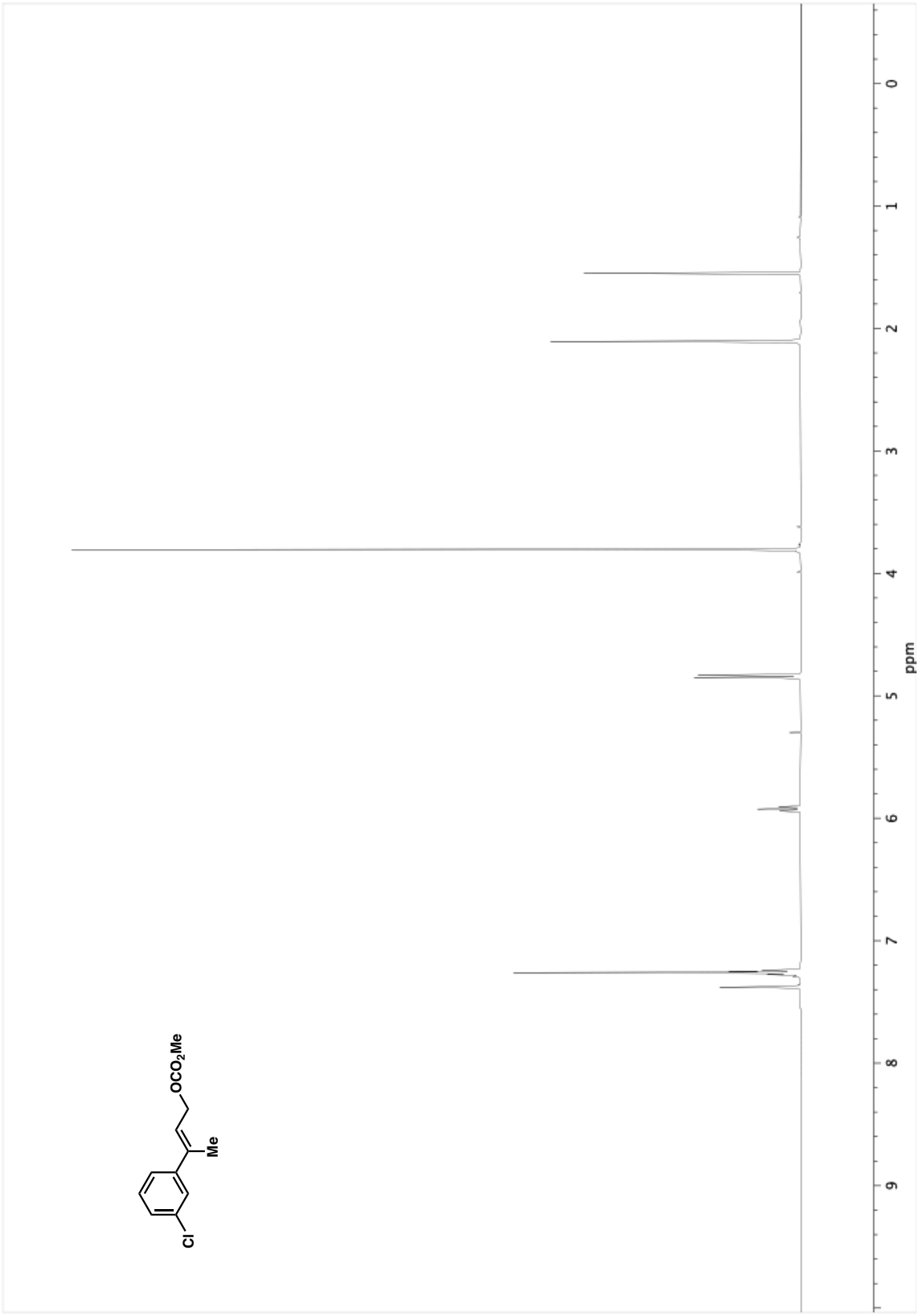


Figure A1.22. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***2l.***

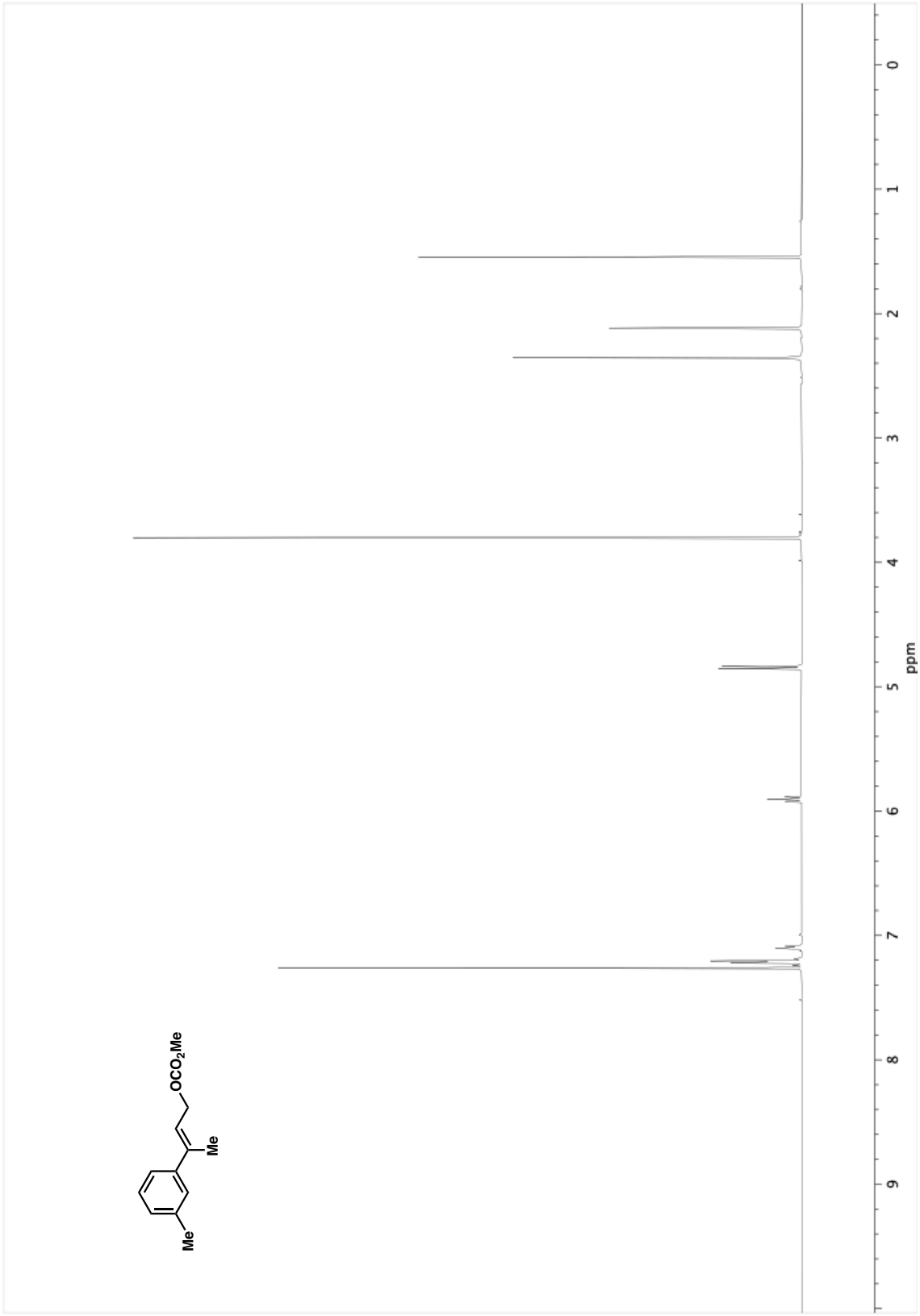


Figure A1.23. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***2m.***

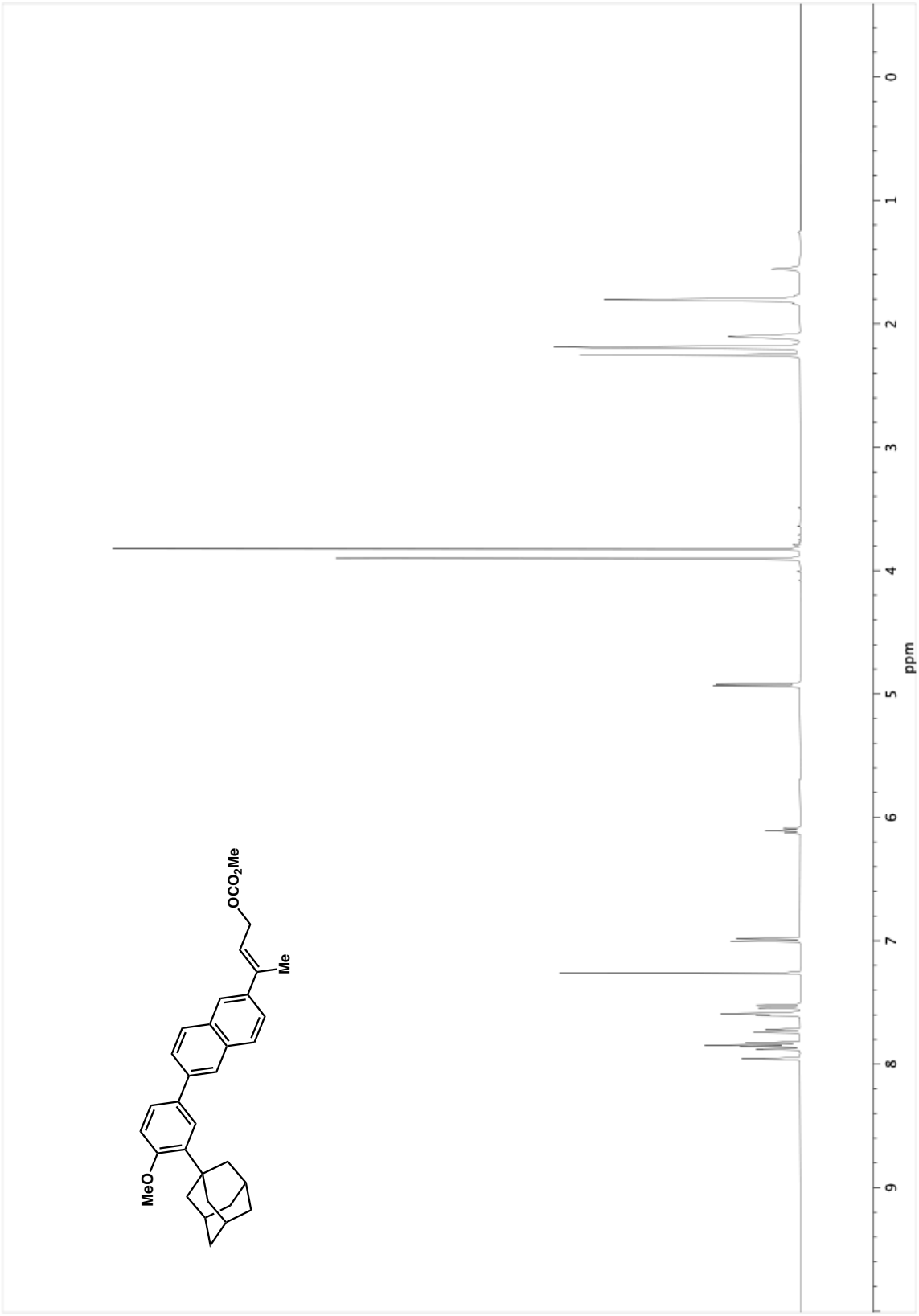


Figure A1.24. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***2n.***

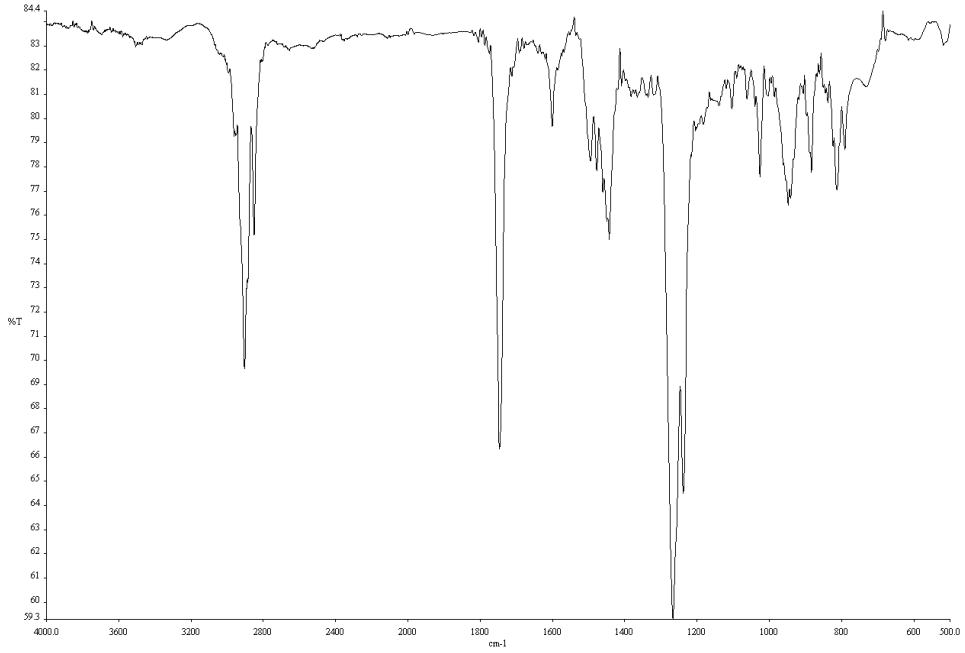


Figure A1.25. *Infrared spectrum (Thin Film, NaCl) of compound* ***2n****.*

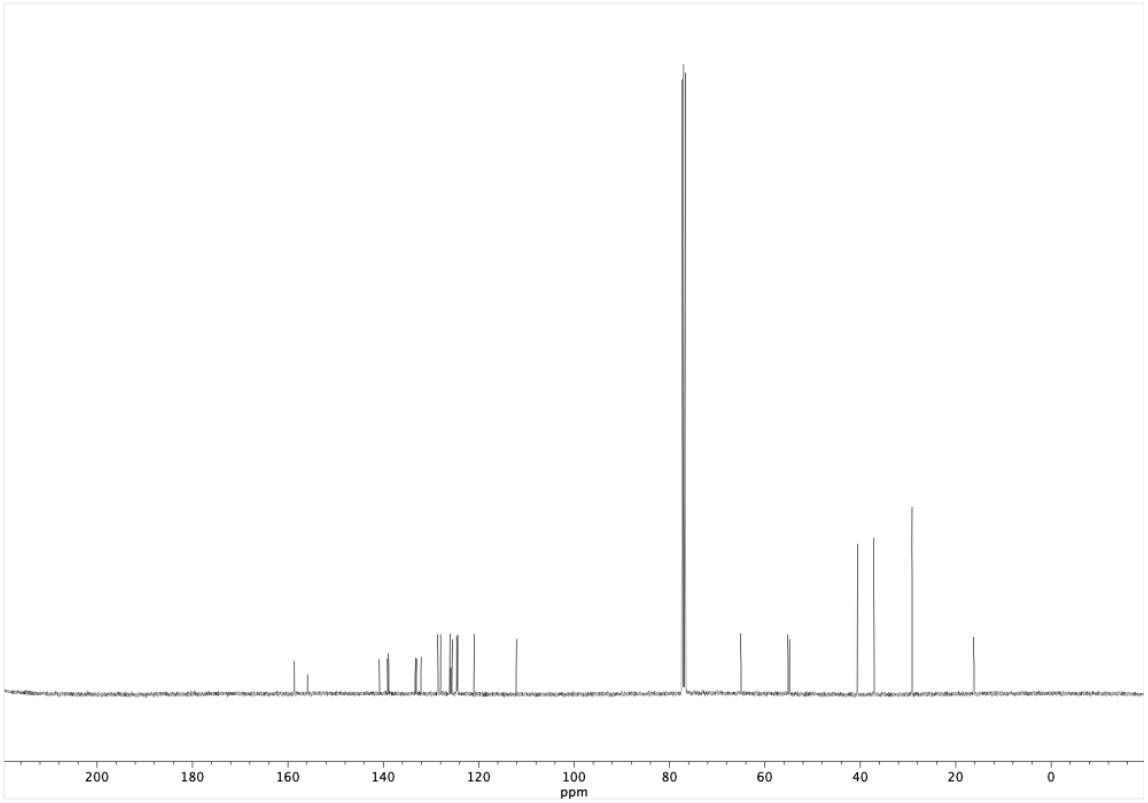


Figure A1.26. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***2n.***

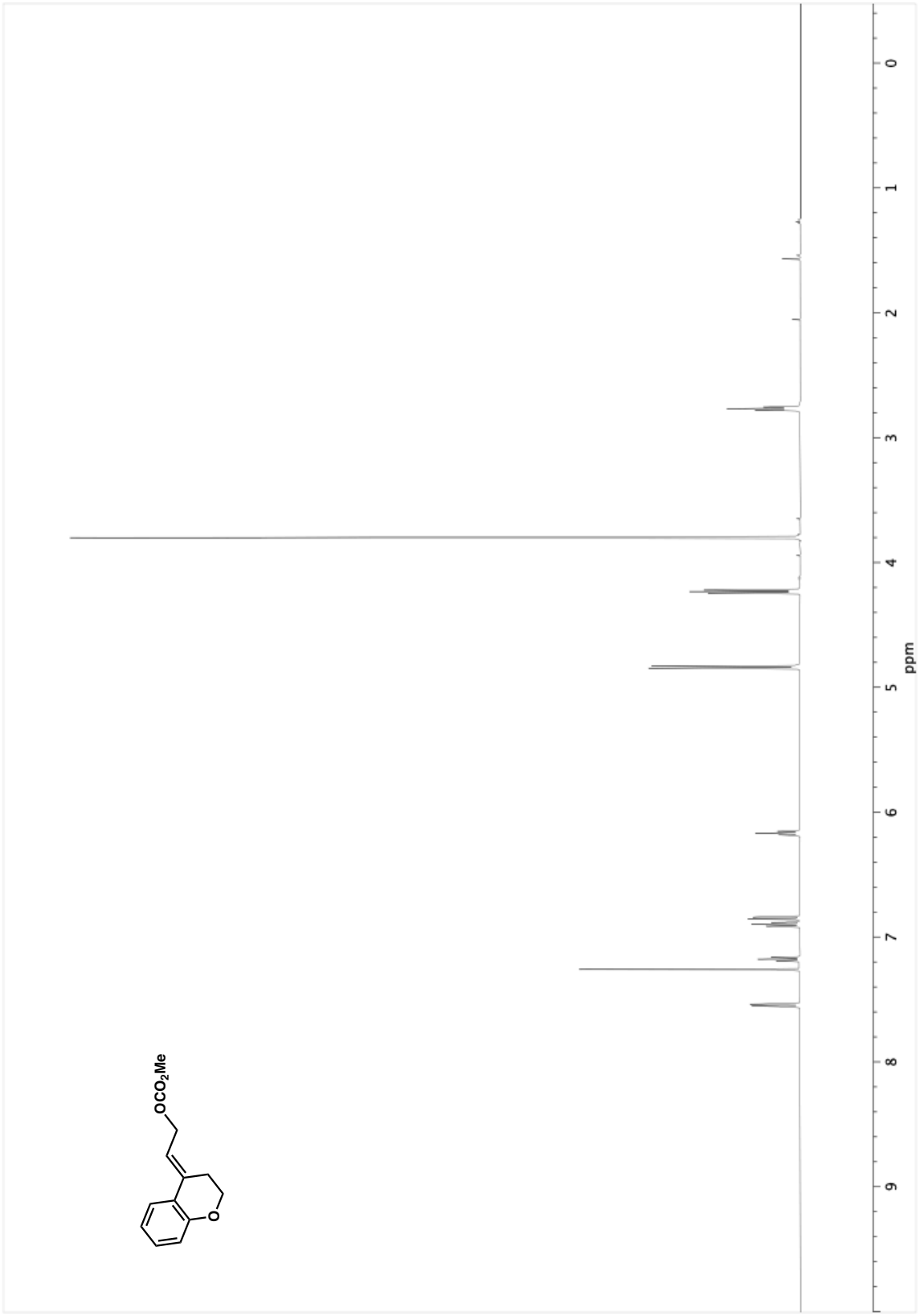


Figure A1.27. *^1H NMR (500 MHz, $CDCl_3$) of compound* ***2o.***

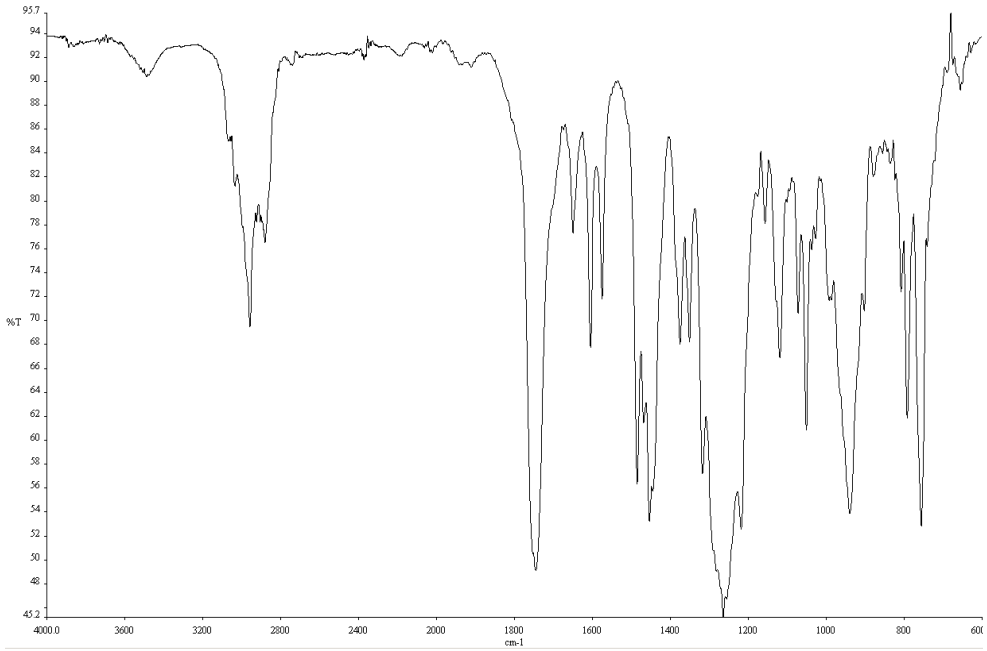


Figure A1.28. *Infrared spectrum (Thin Film, NaCl) of compound* ***2o****.*

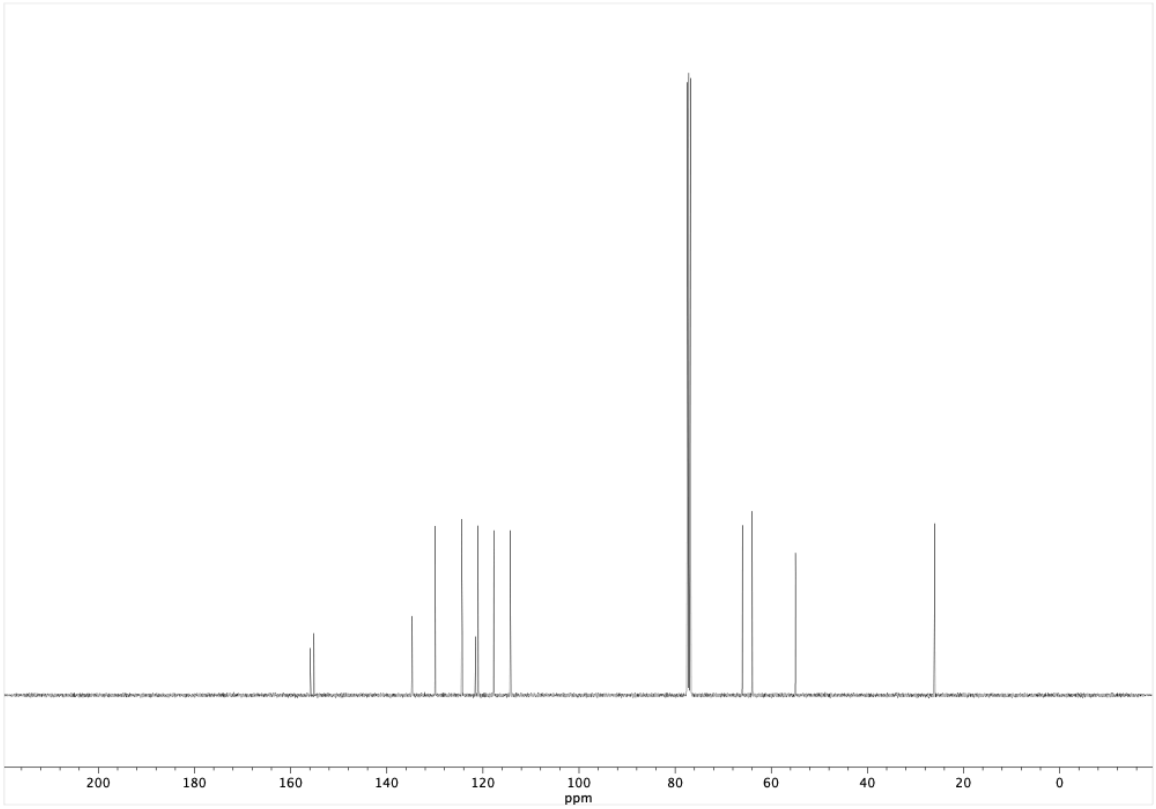


Figure A1.29. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***2o.***

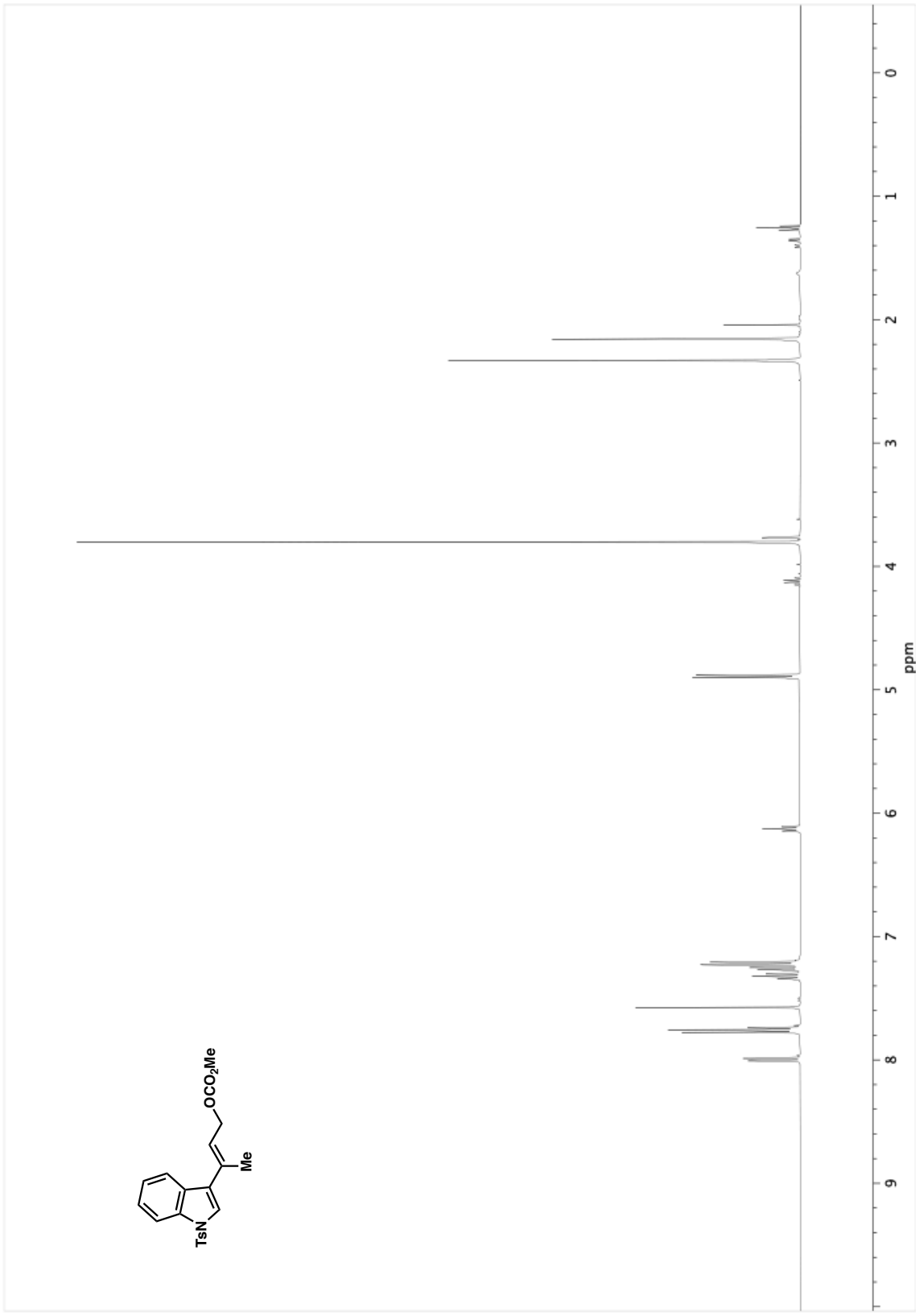


Figure A1.30. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***2p.***

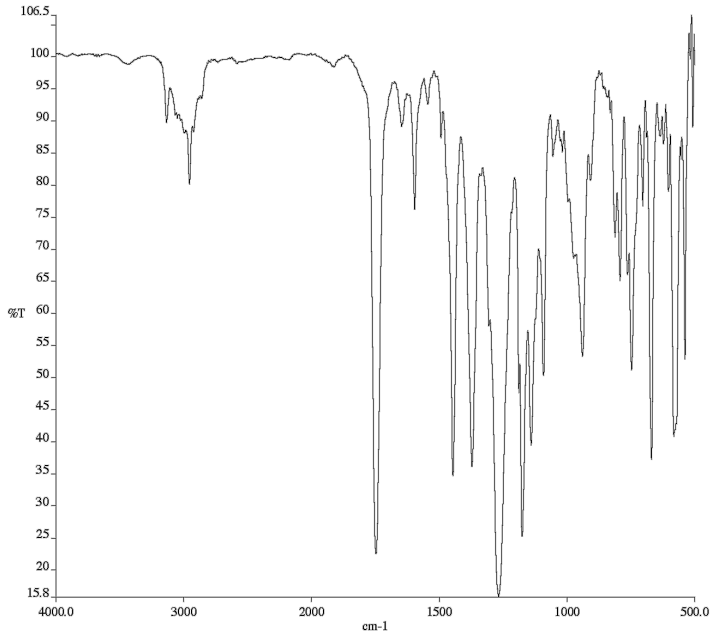


Figure A1.31. *Infrared spectrum (Thin Film, NaCl) of compound* ***2p****.*

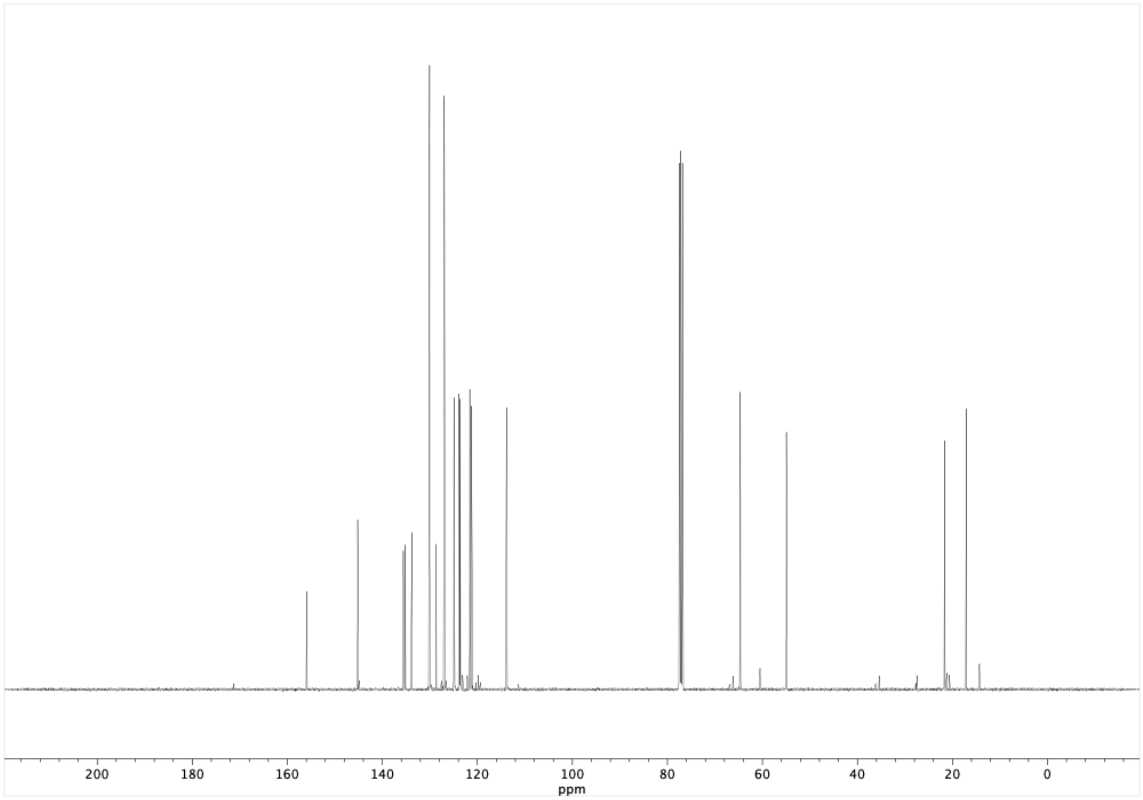


Figure A1.32. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***2p.***

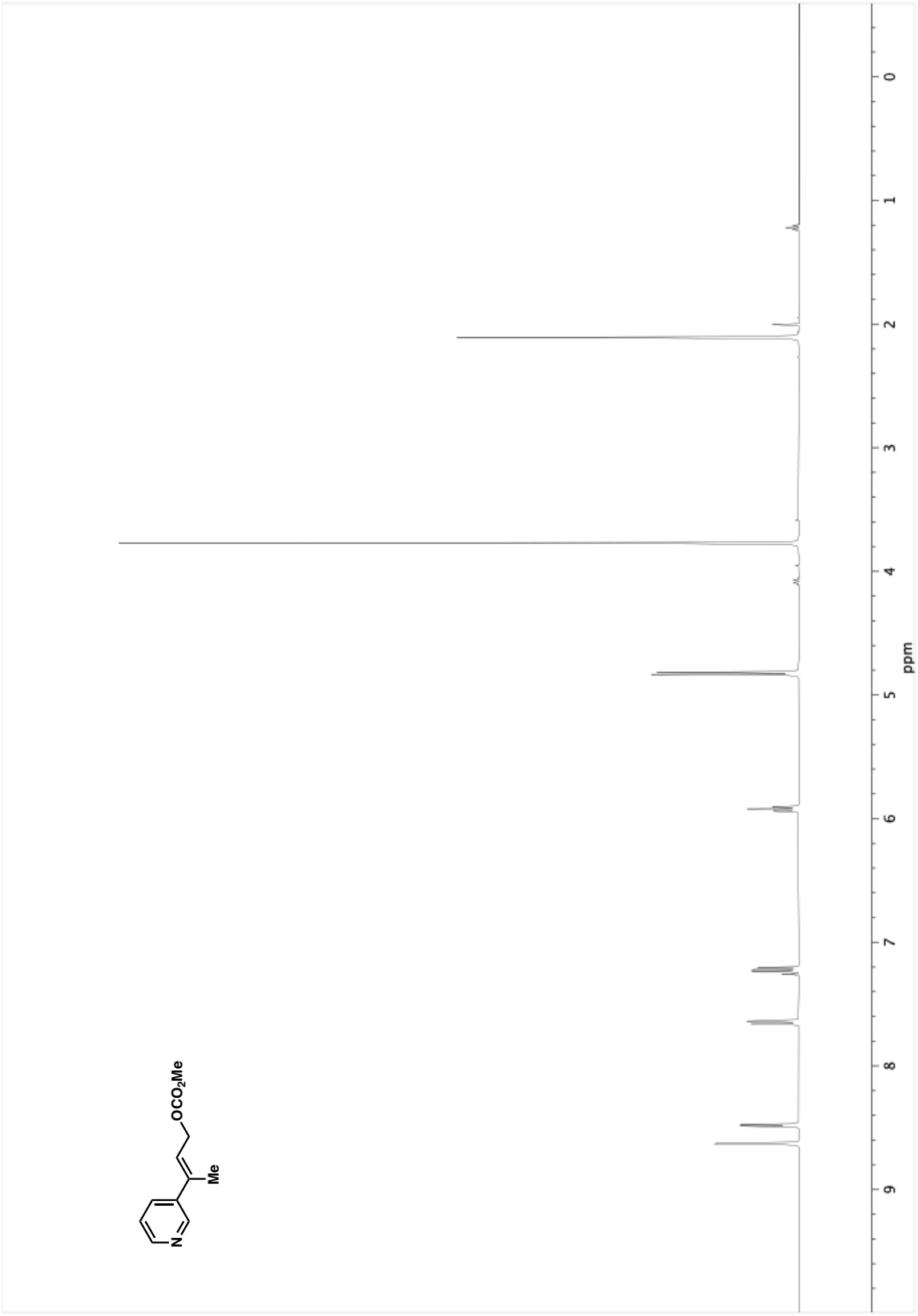


Figure A1.33. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***2q.***

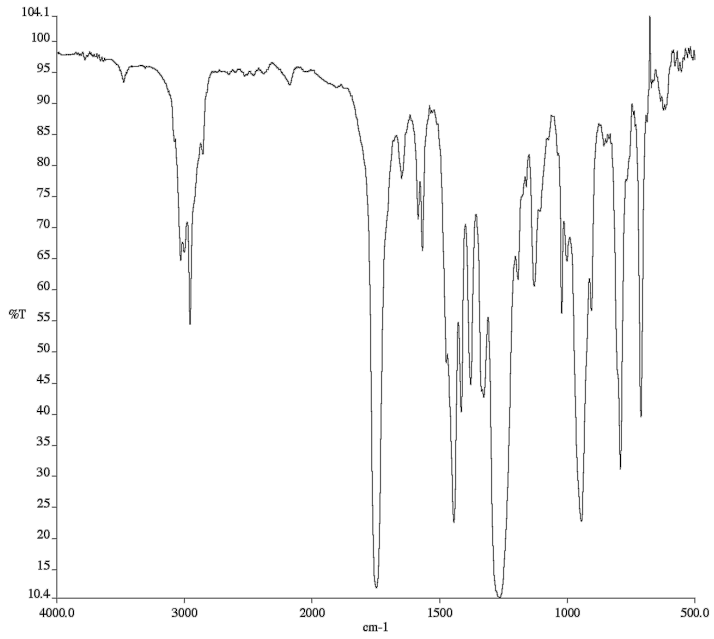


Figure A1.34. *Infrared spectrum (Thin Film, NaCl) of compound* ***2q****.*

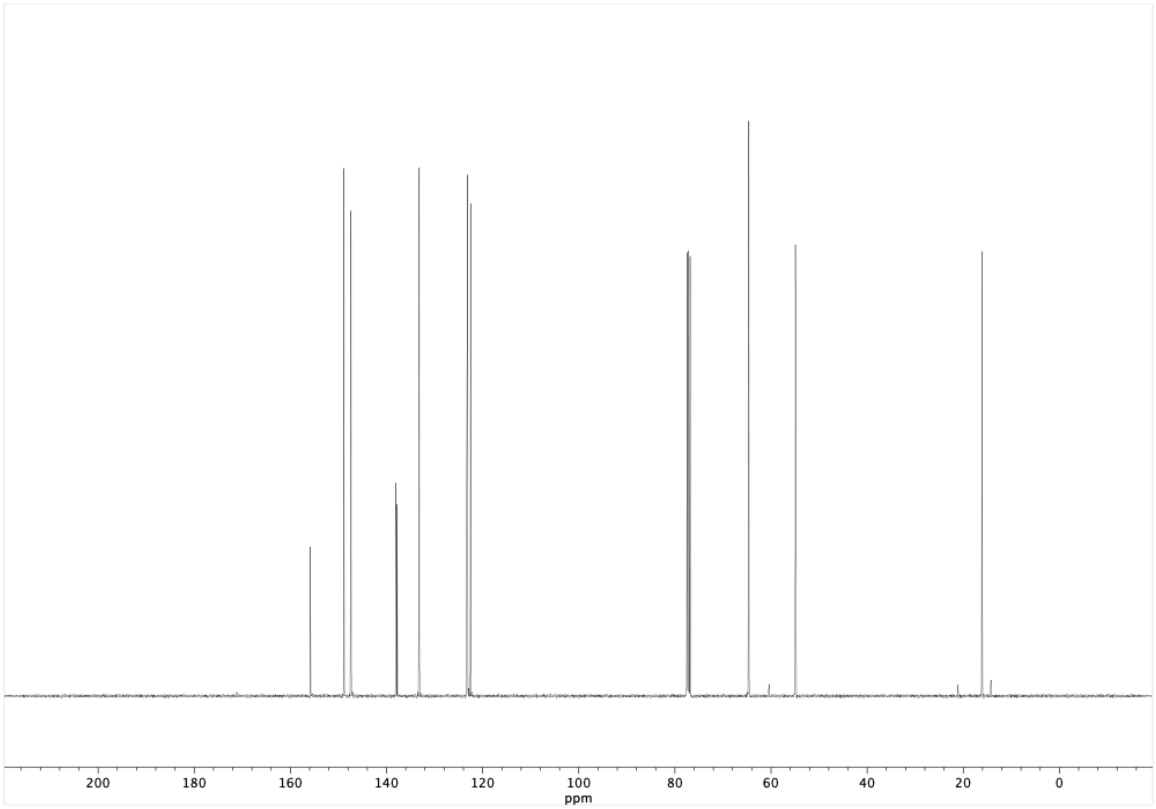


Figure A1.35. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***2q****.*

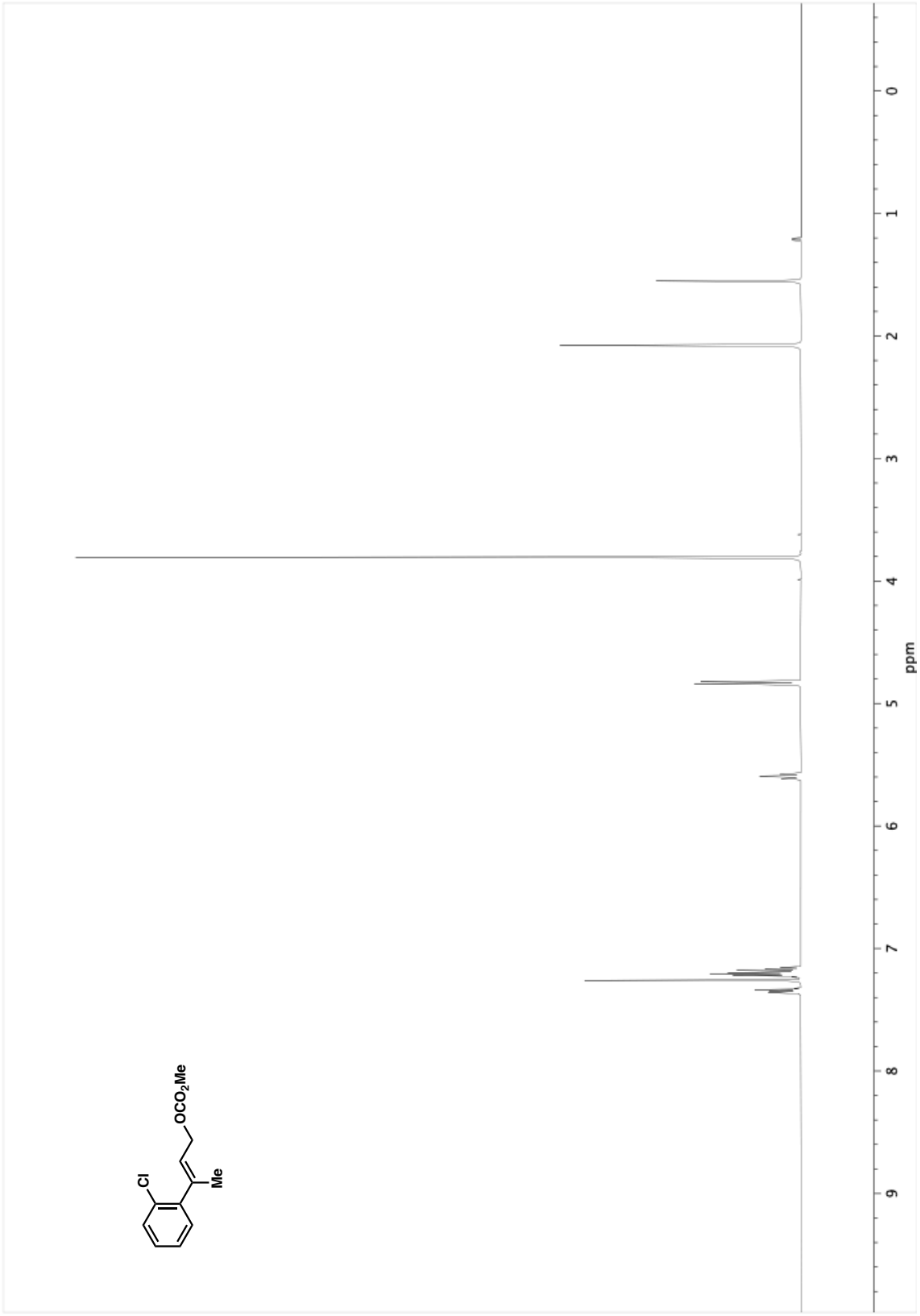


Figure A1.36. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***2r.***

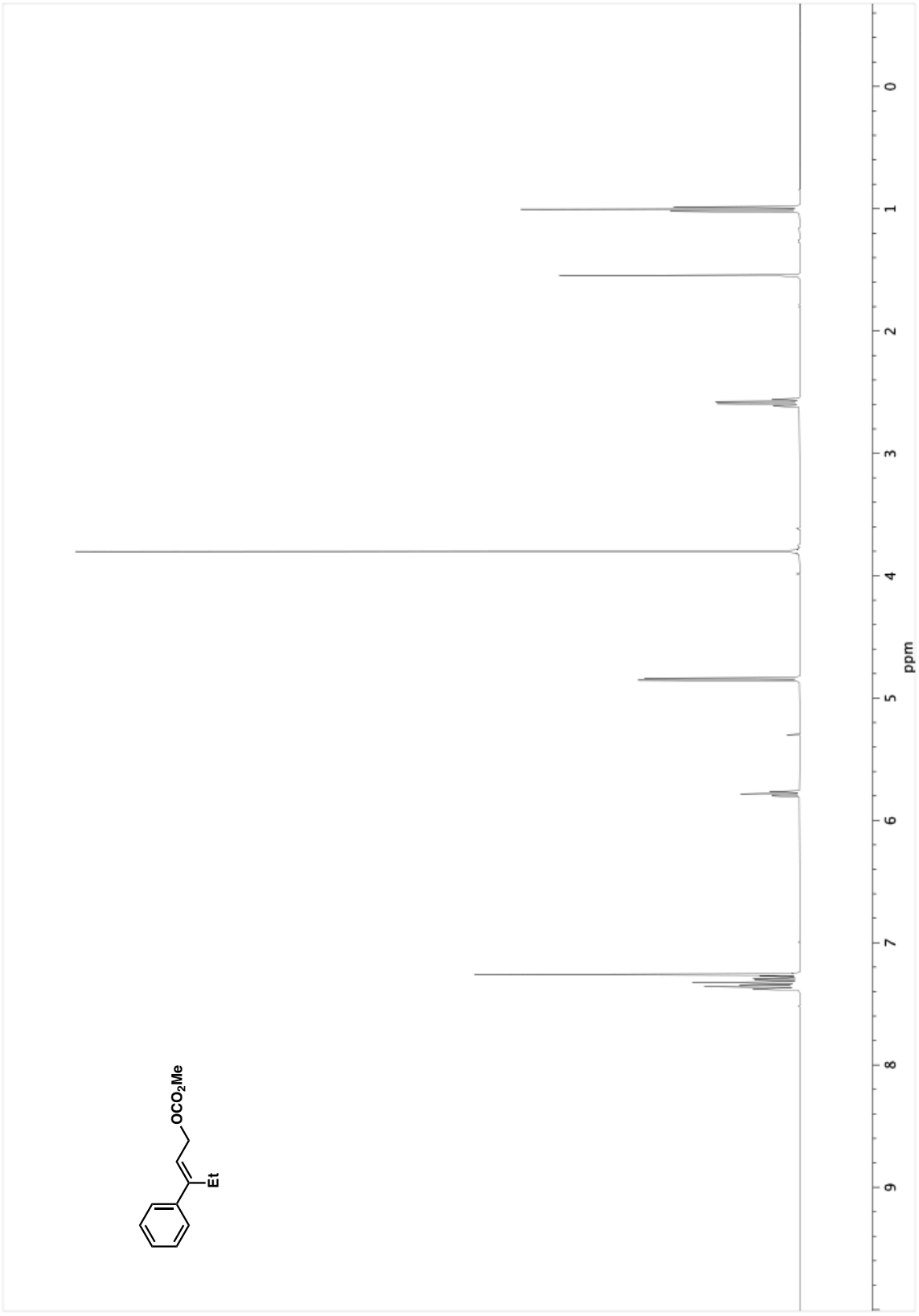


Figure A1.37. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***2s.***

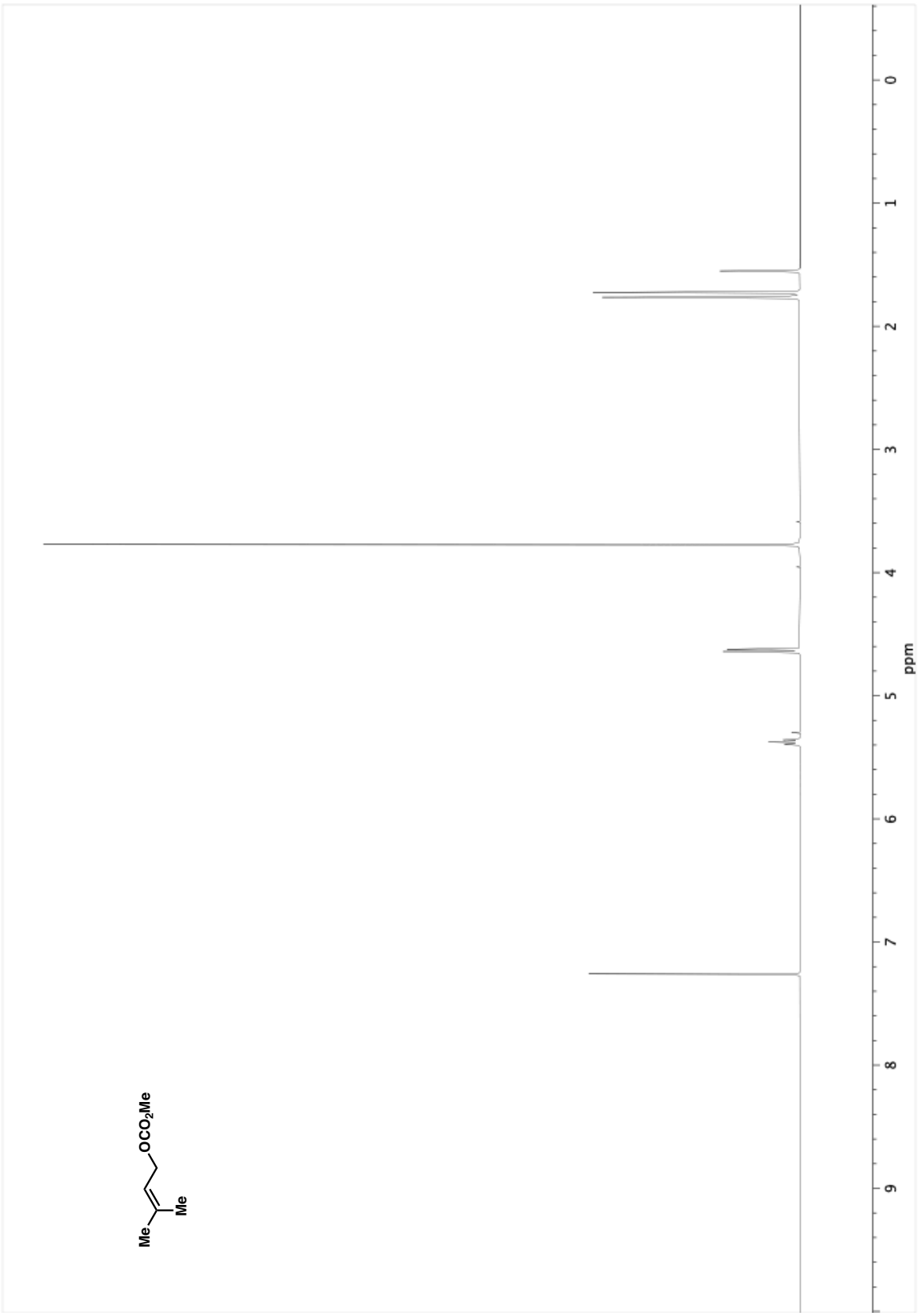


Figure A1.38. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***2t.***

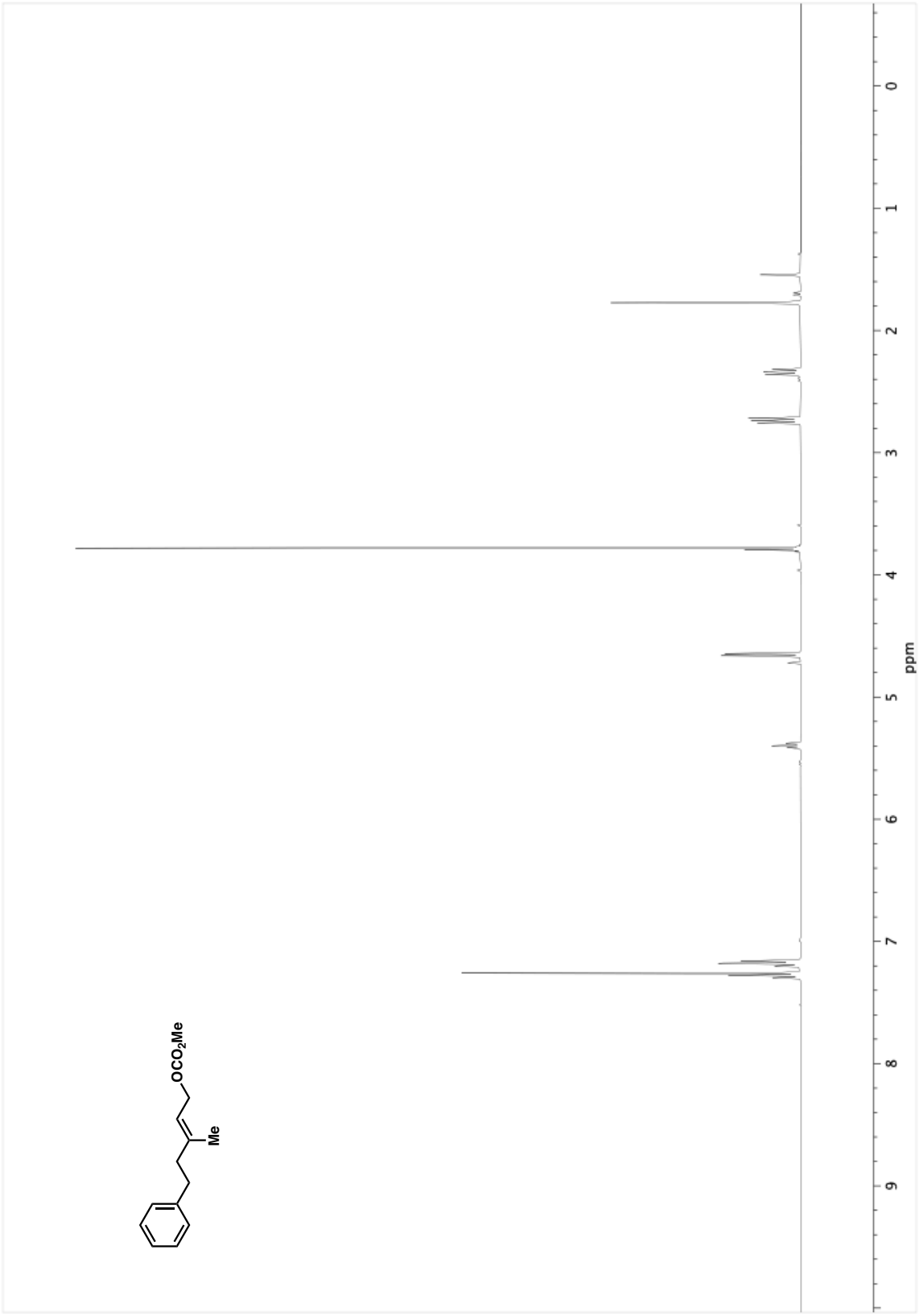


Figure A1.39. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***2u.***

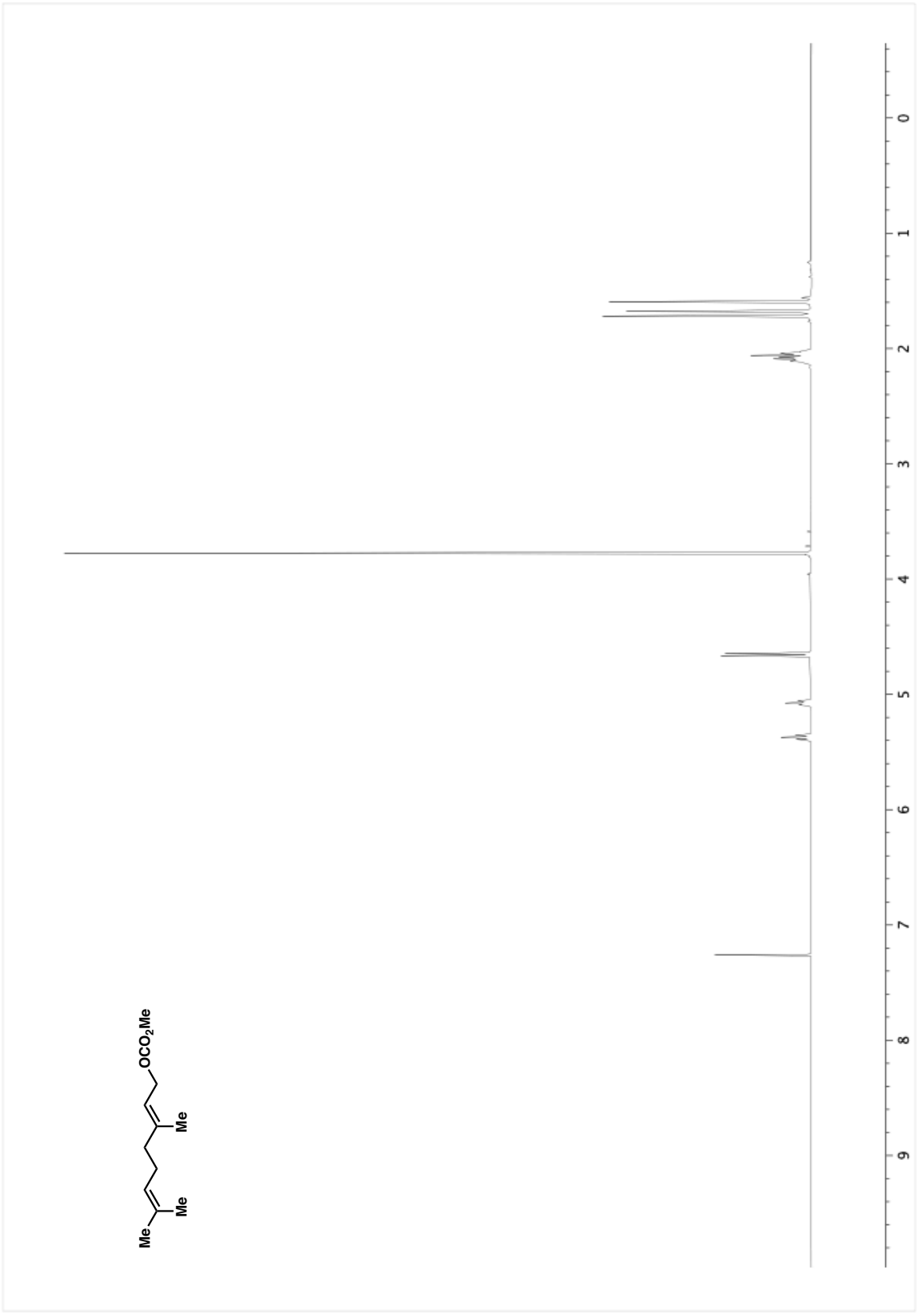


Figure A1.40. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***2v.***

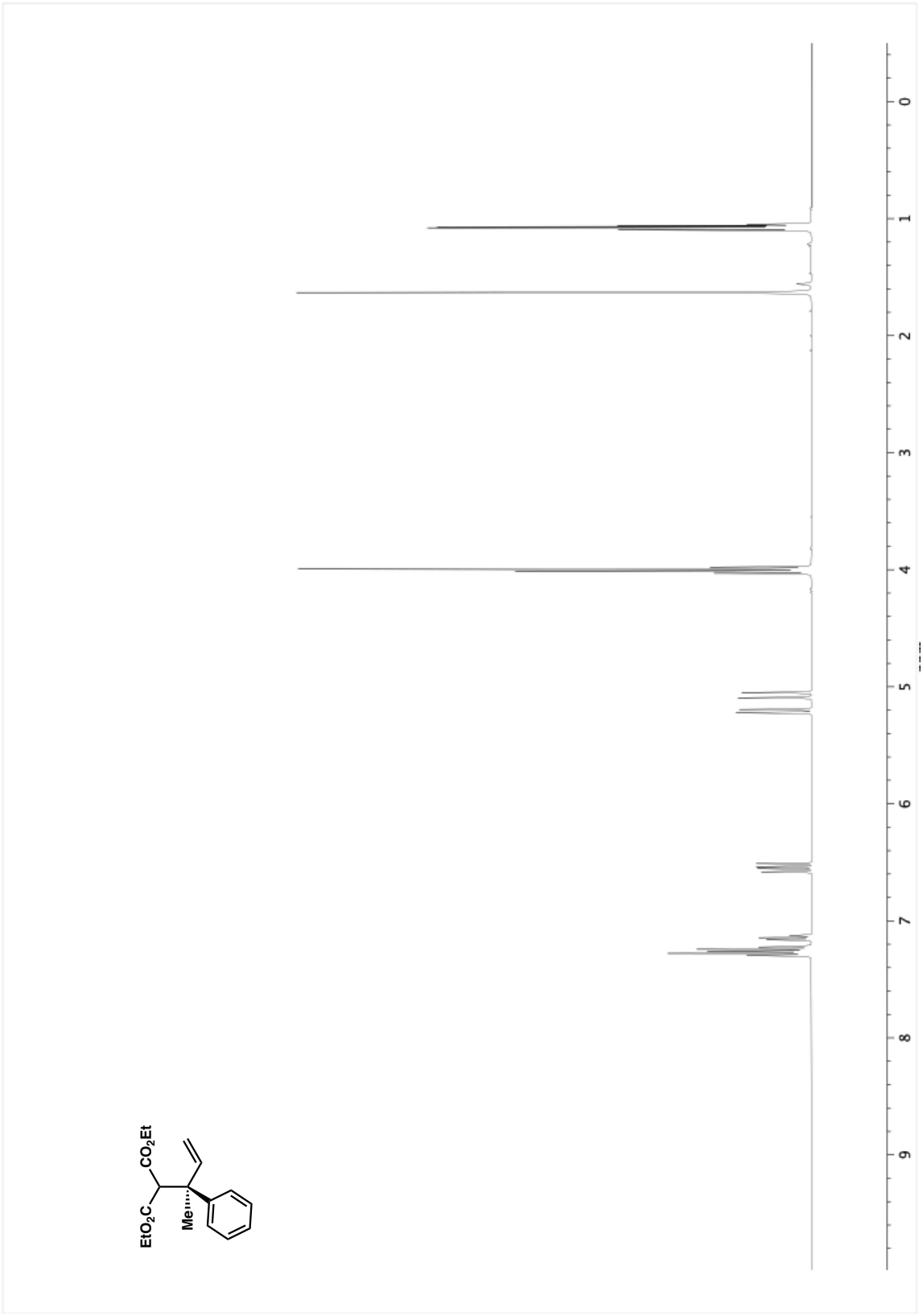


Figure A1.41. *^1H NMR (500 MHz, $CDCl_3$) of compound* ***3a.***

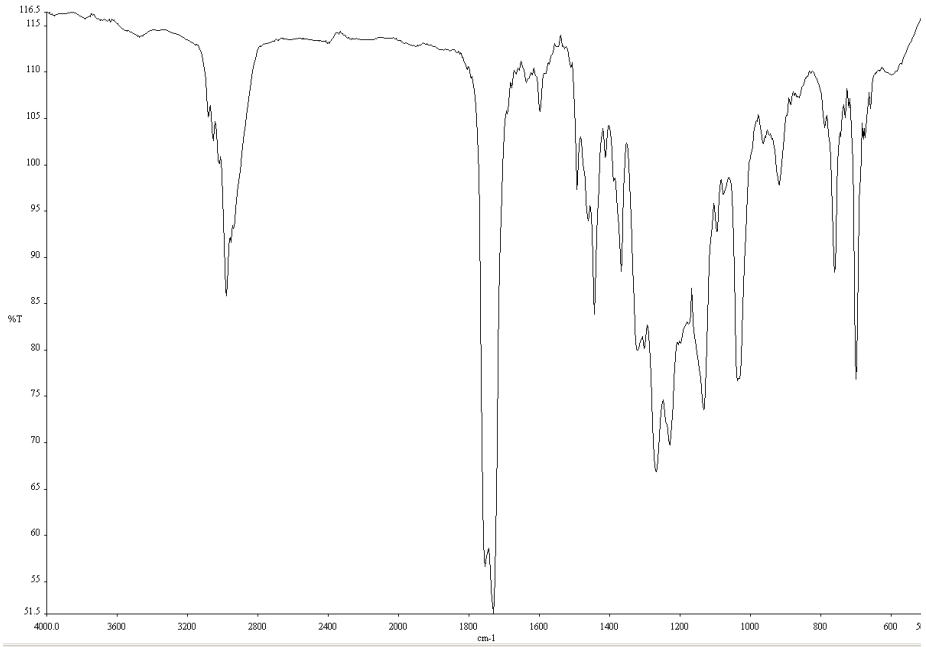


Figure A1.42. *Infrared spectrum (Thin Film, NaCl) of compound* ***3a****.*

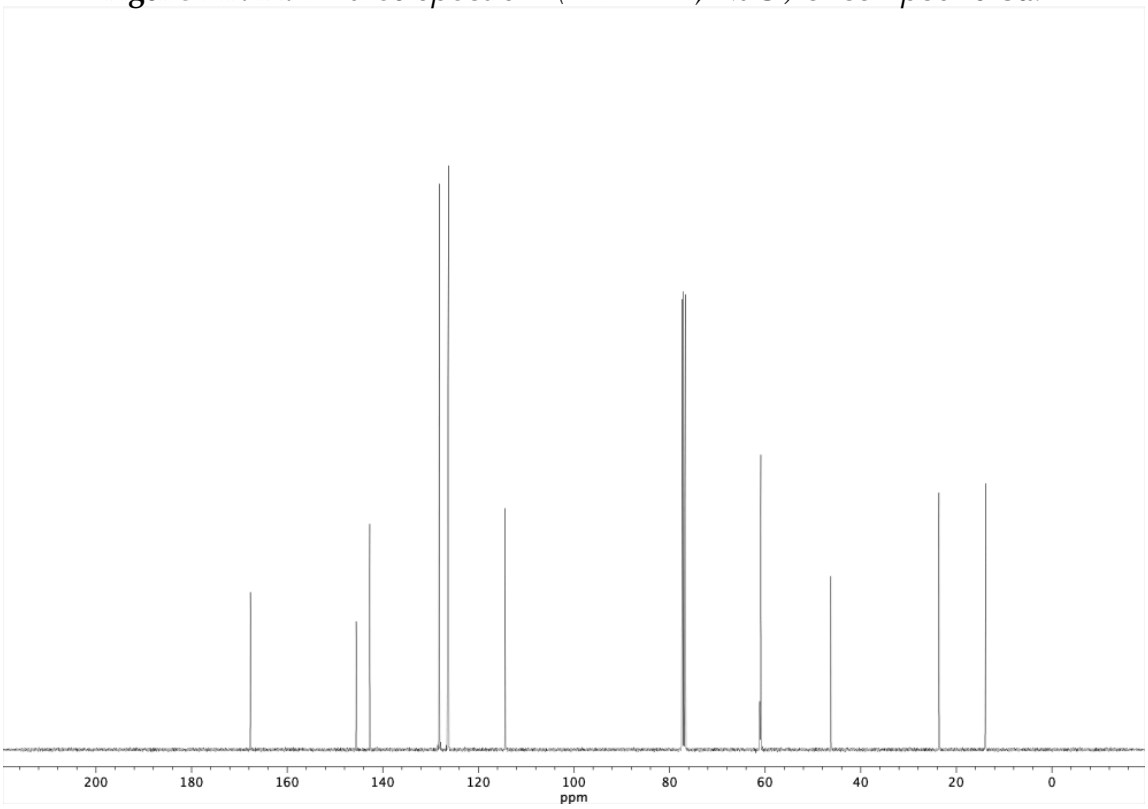


Figure A1.43. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***3a.***

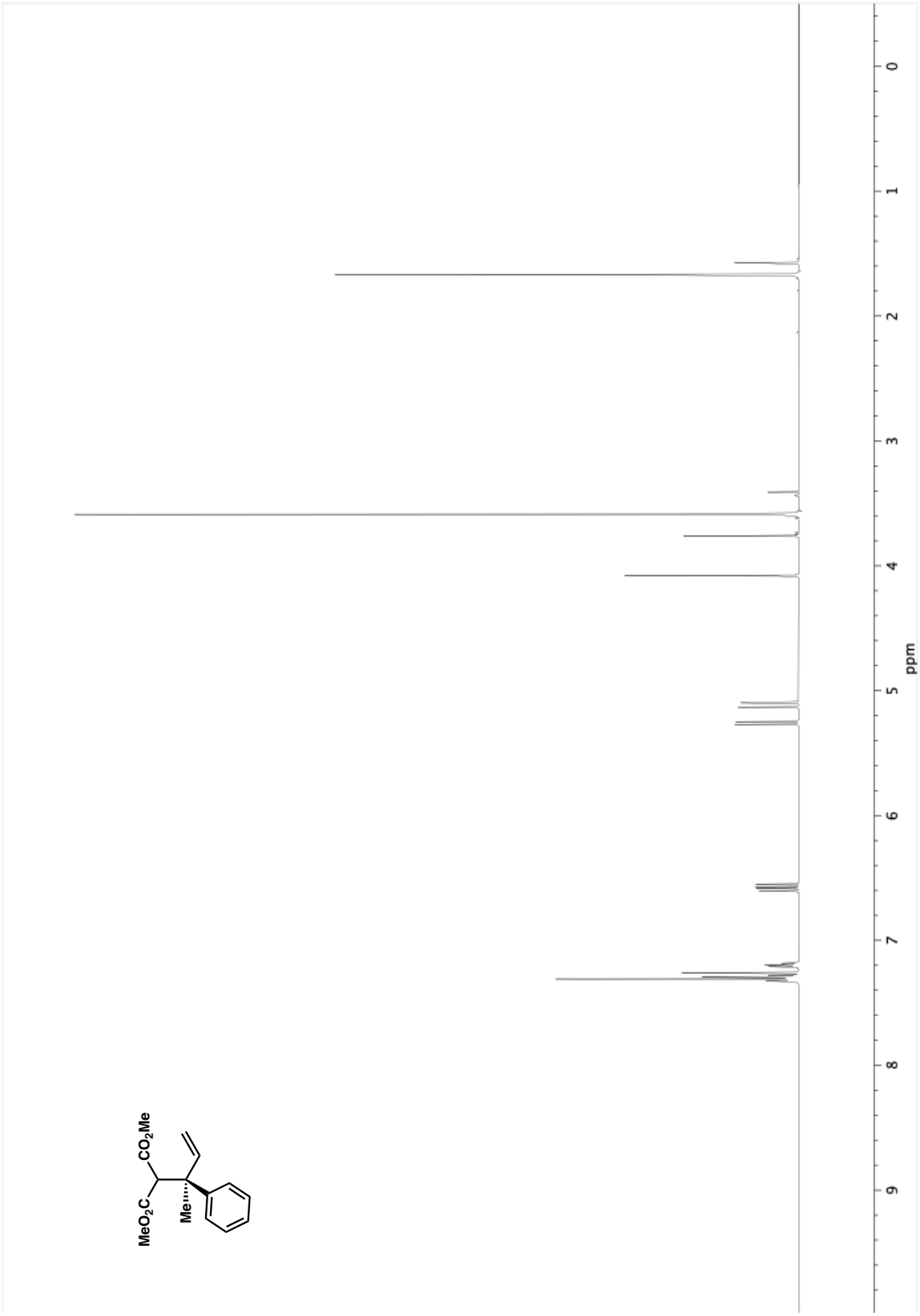


Figure A1.44. *^1H NMR (500 MHz, $CDCl_3$) of compound* ***3b.***

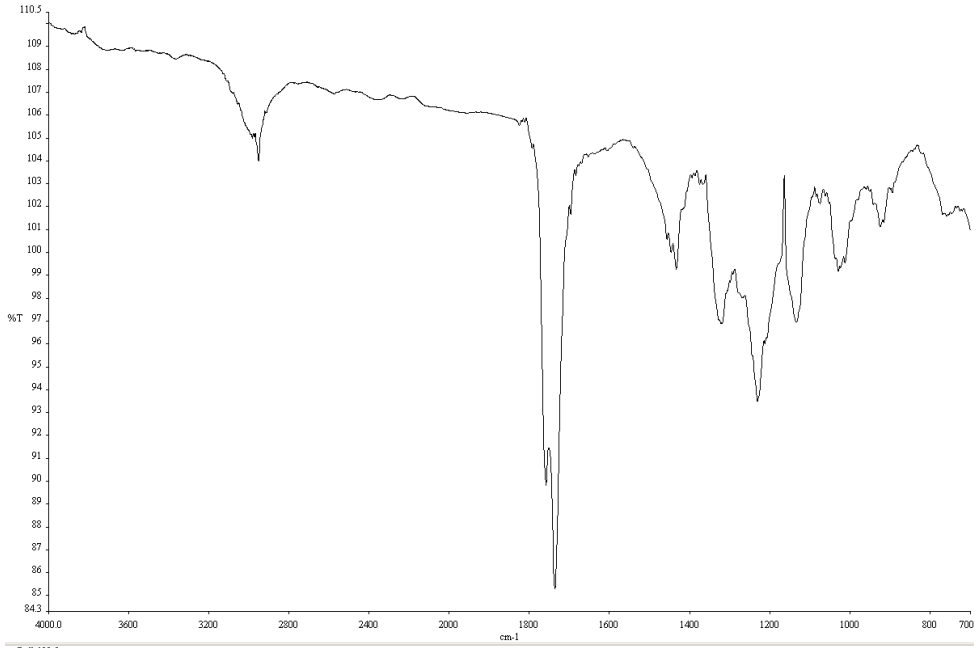


Figure A1.45. *Infrared spectrum (Thin Film, NaCl) of compound* ***3b.***

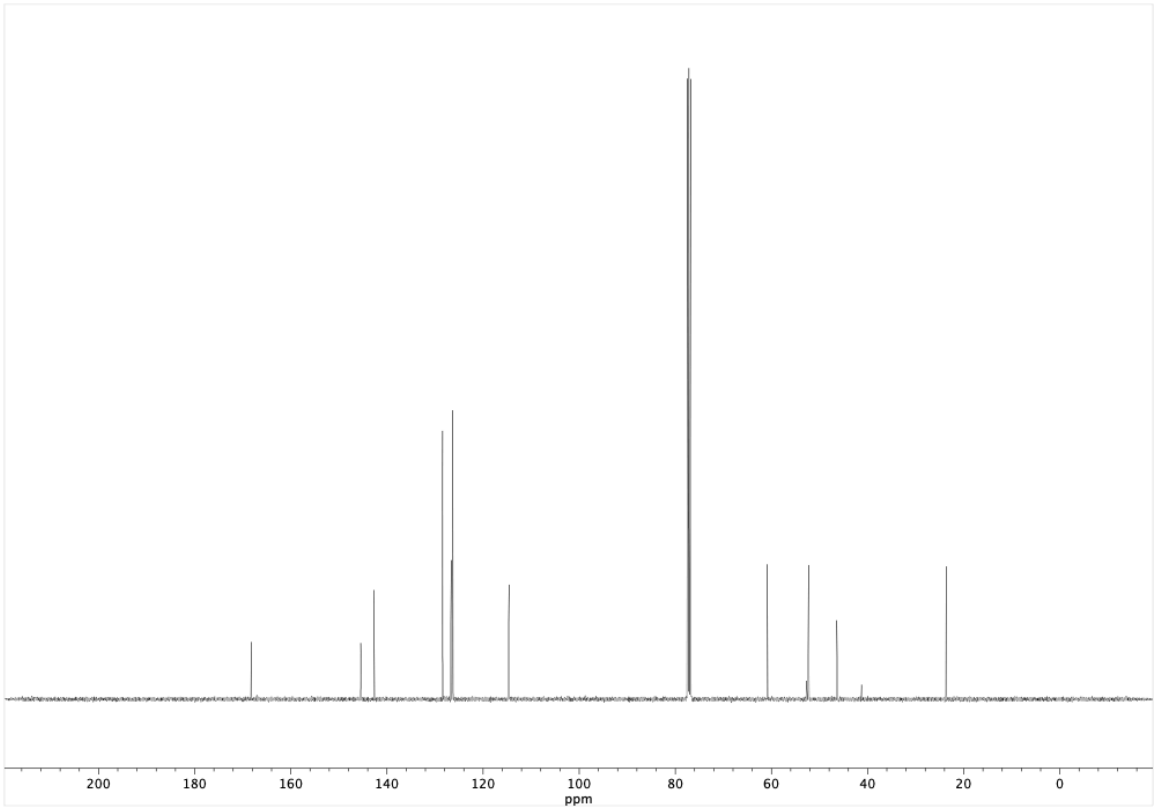


Figure A1.46. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***3b.***

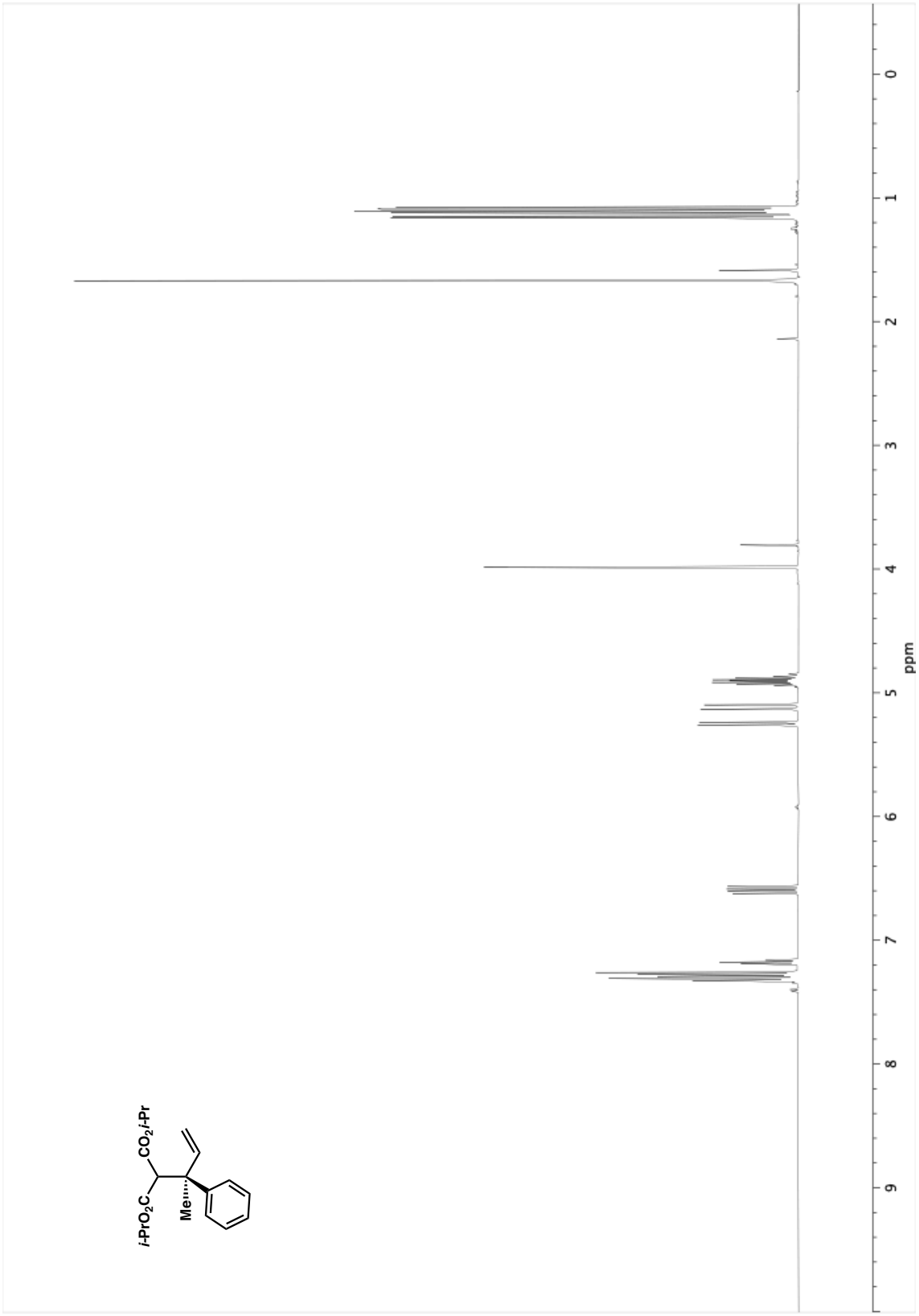


Figure A1.47. *^1H NMR (500 MHz, $CDCl_3$) of compound* ***3c.***

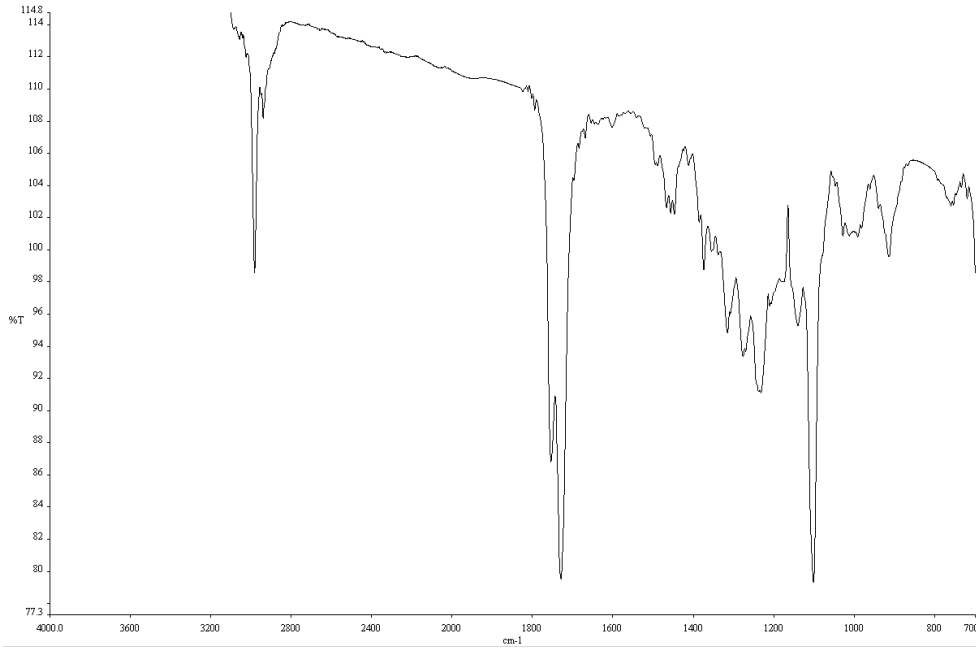


Figure A1.48. *Infrared spectrum (Thin Film, NaCl) of compound* ***3c.***

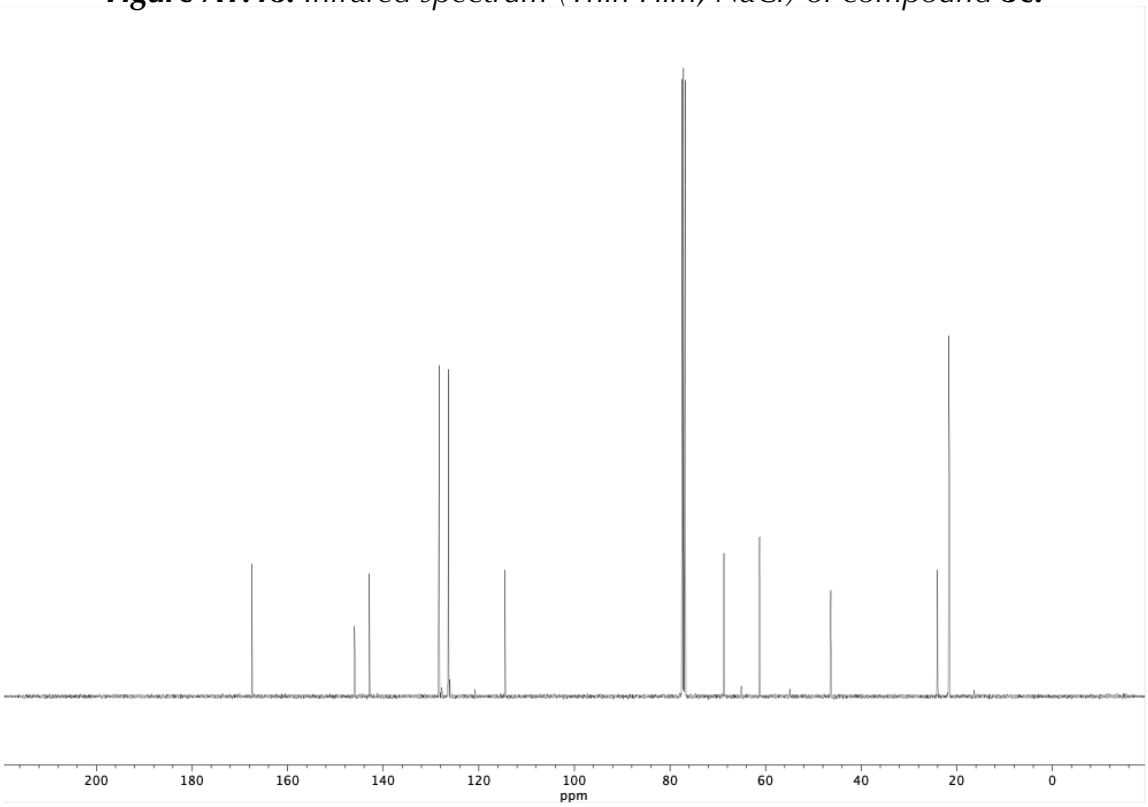


Figure A1.49. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***3c.***

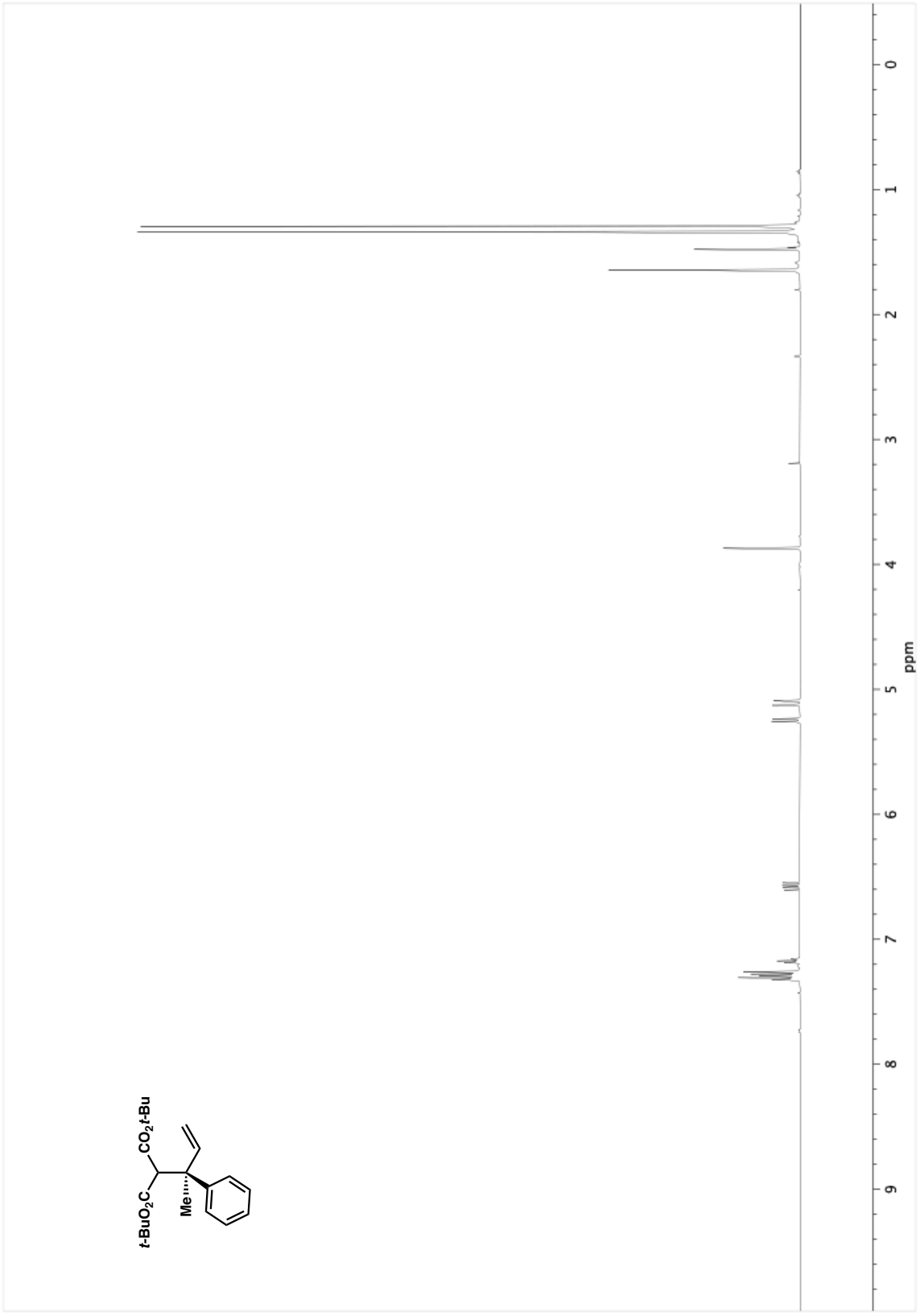


Figure A1.50. *^1H NMR (500 MHz, $CDCl_3$) of compound* ***3d.***

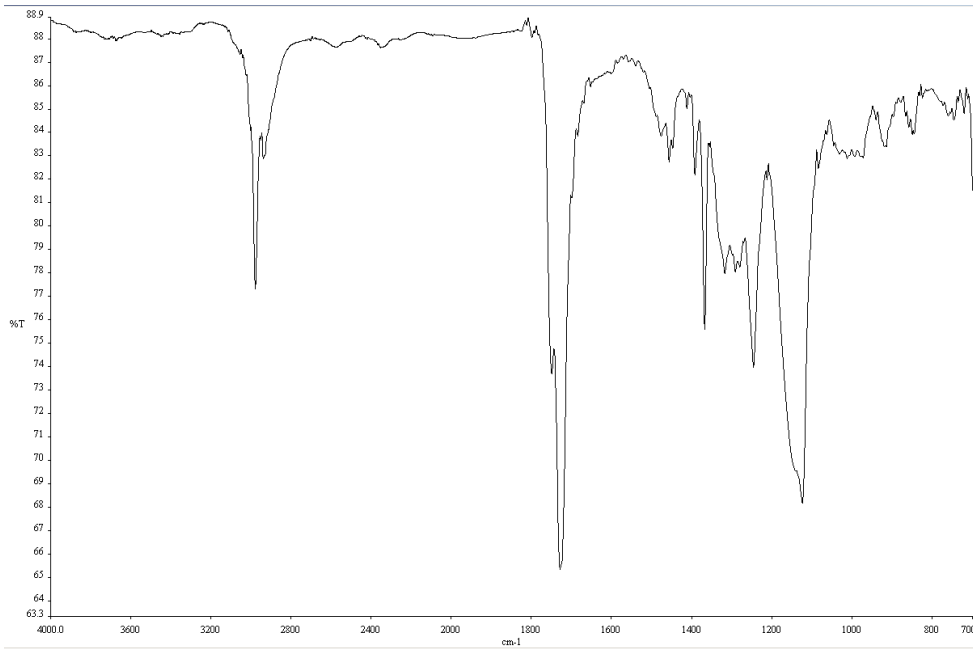


Figure A1.51. *Infrared spectrum (Thin Film, NaCl) of compound* ***3d.***

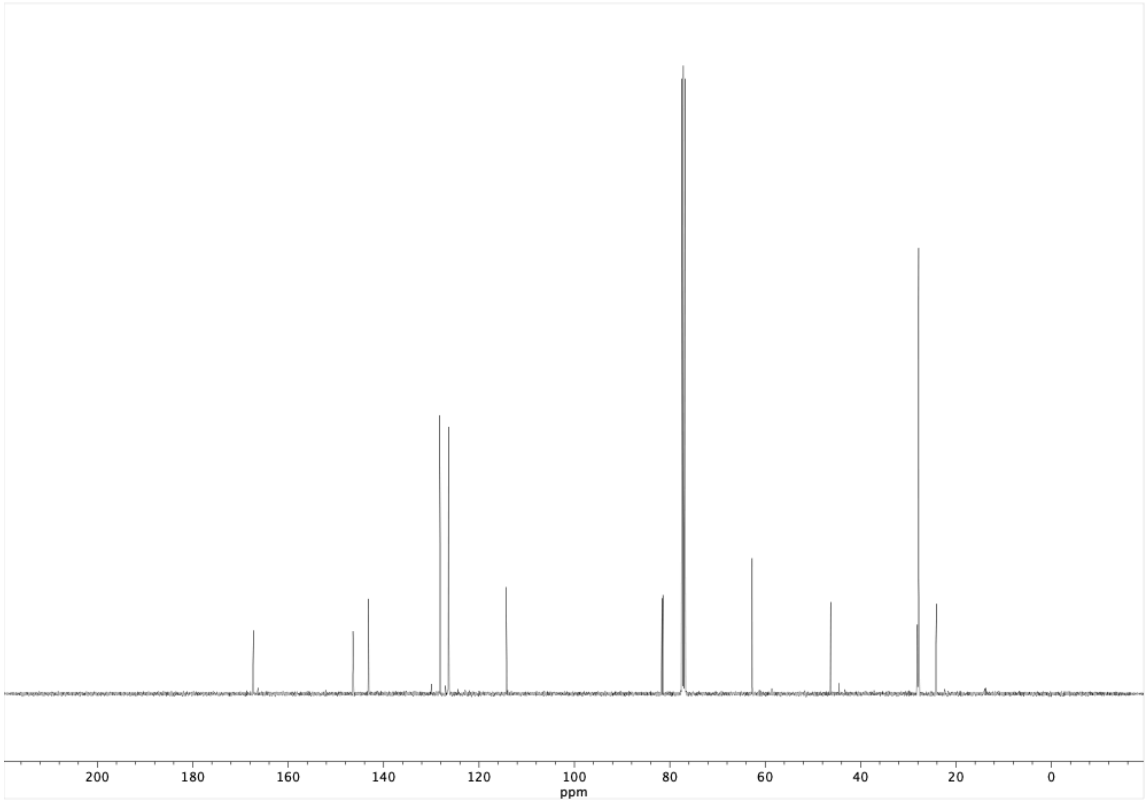


Figure A1.52. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***3d.***

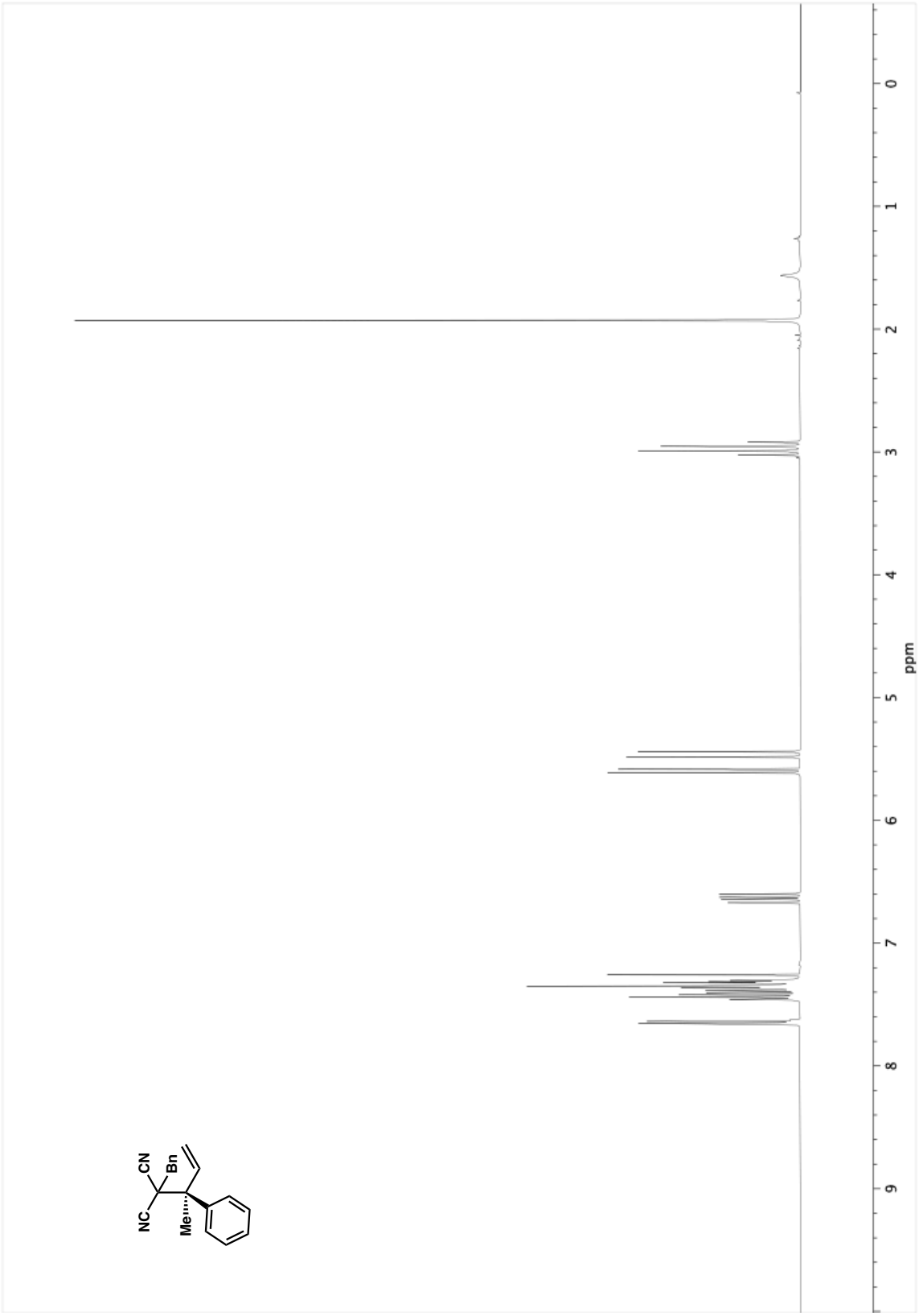


Figure A1.53. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***4d.***

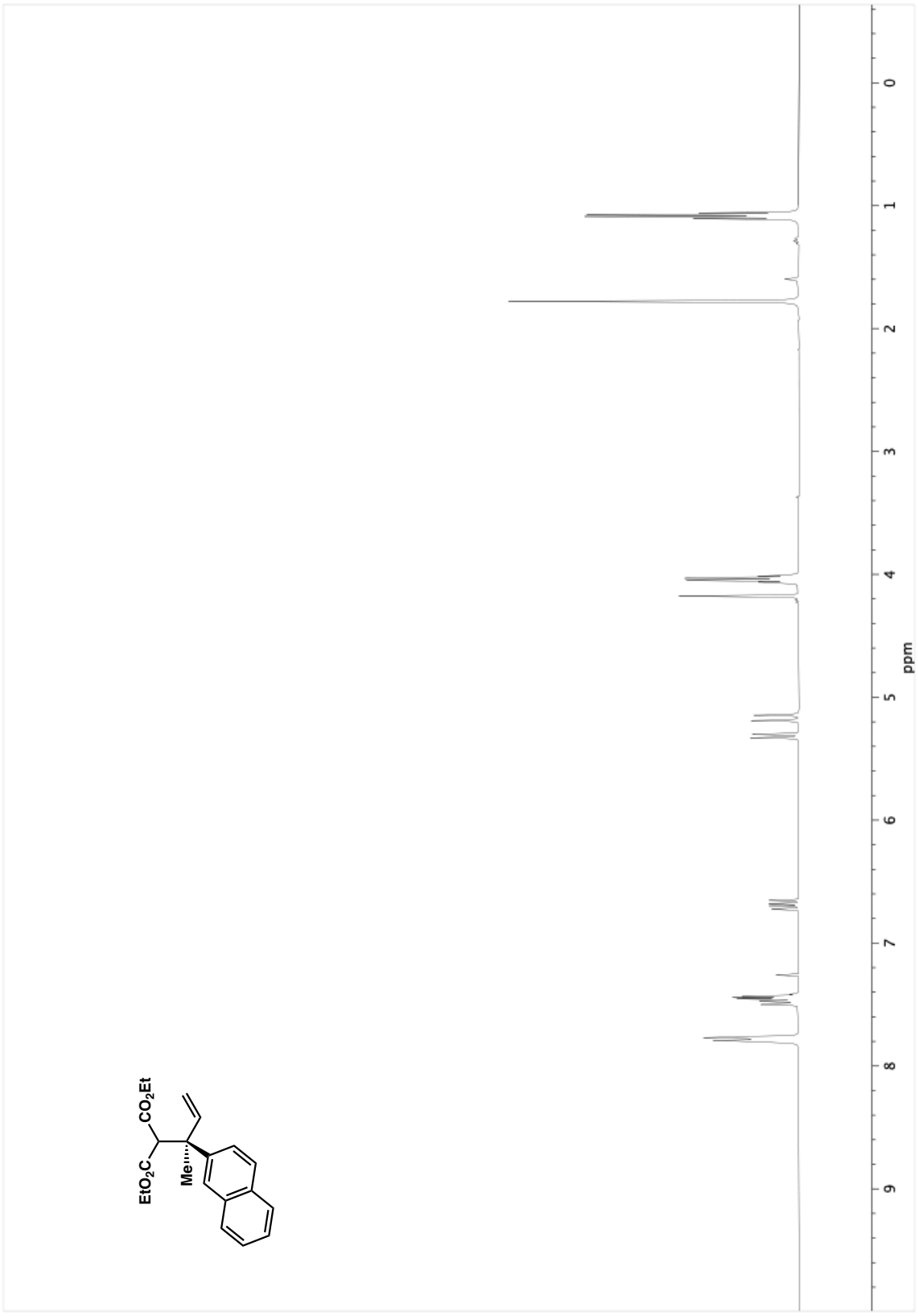


Figure A1.54. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***5.***

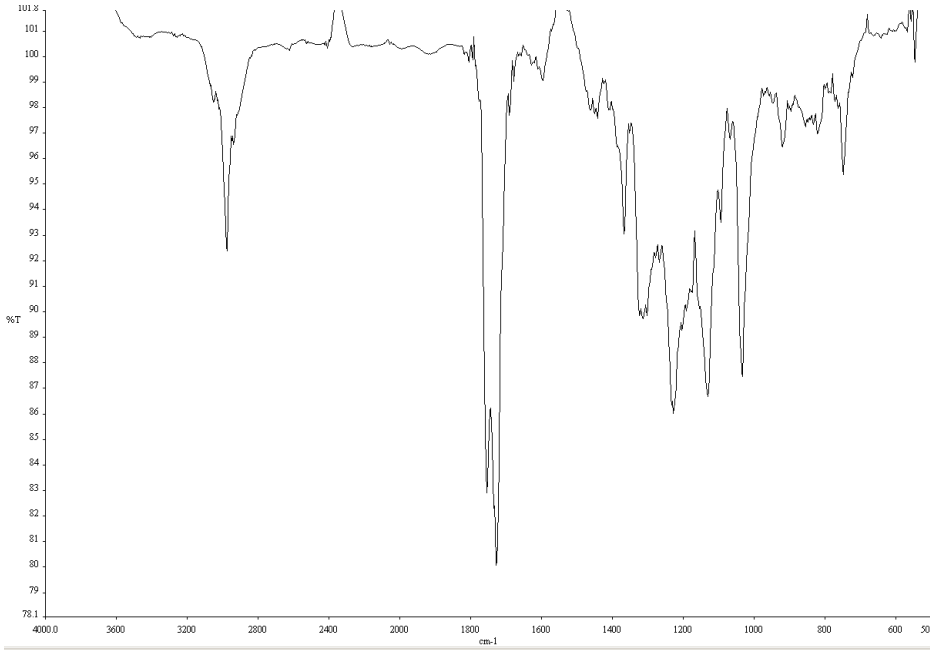


Figure A1.55. *Infrared spectrum (Thin Film, NaCl) of compound* ***5.***

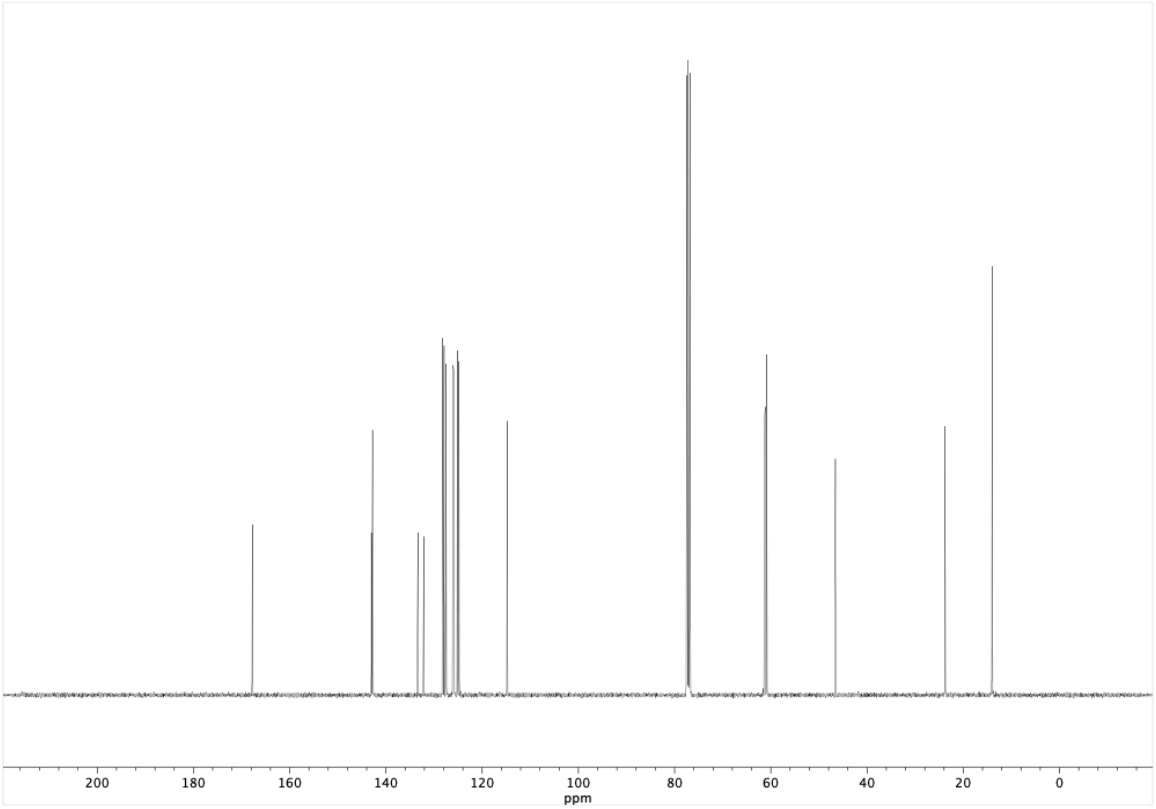


Figure A1.56. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***5.***

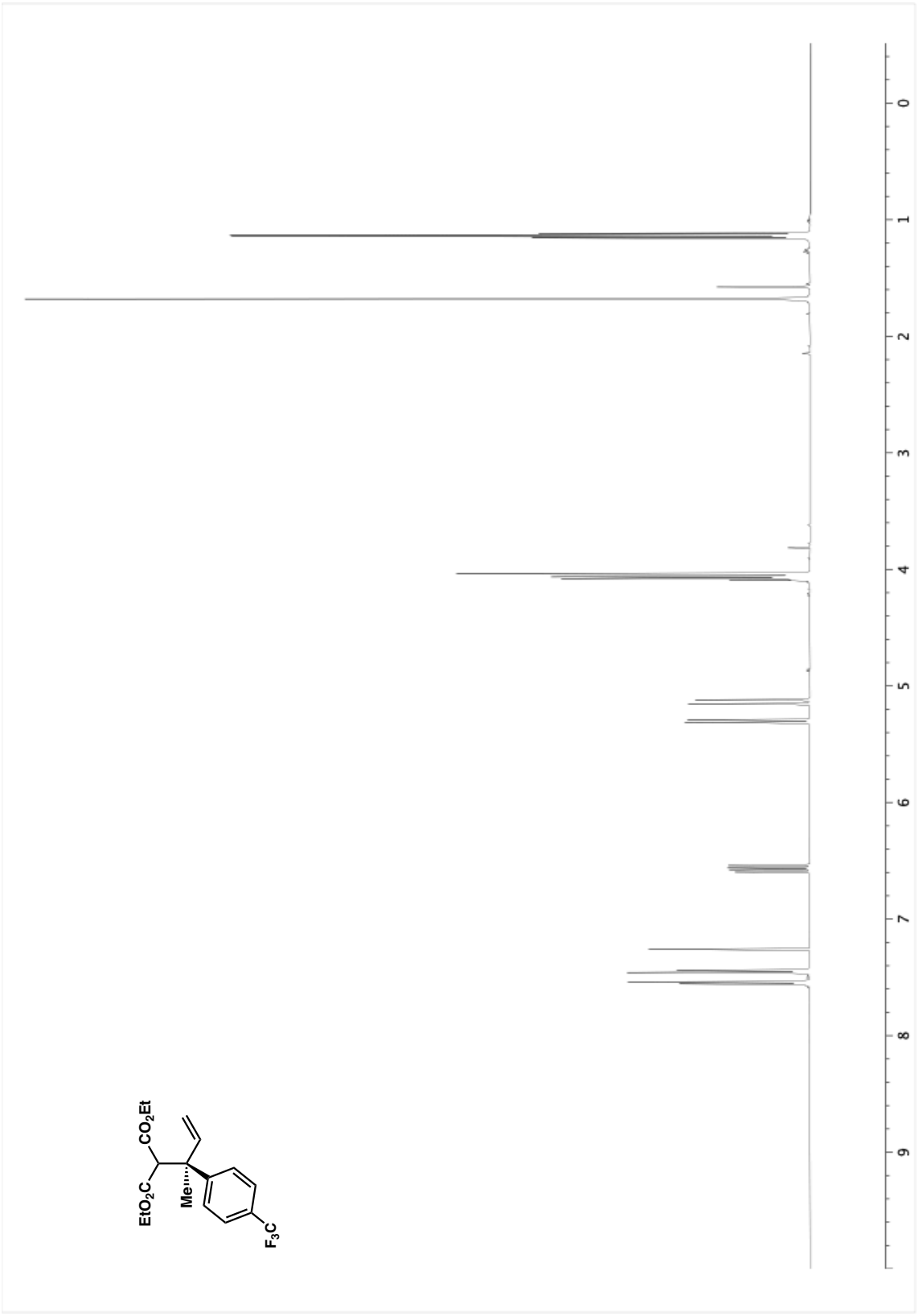


Figure A1.57. *^{1}H NMR (500 MHz, $CDCl_3$) of compound* ***6a.***

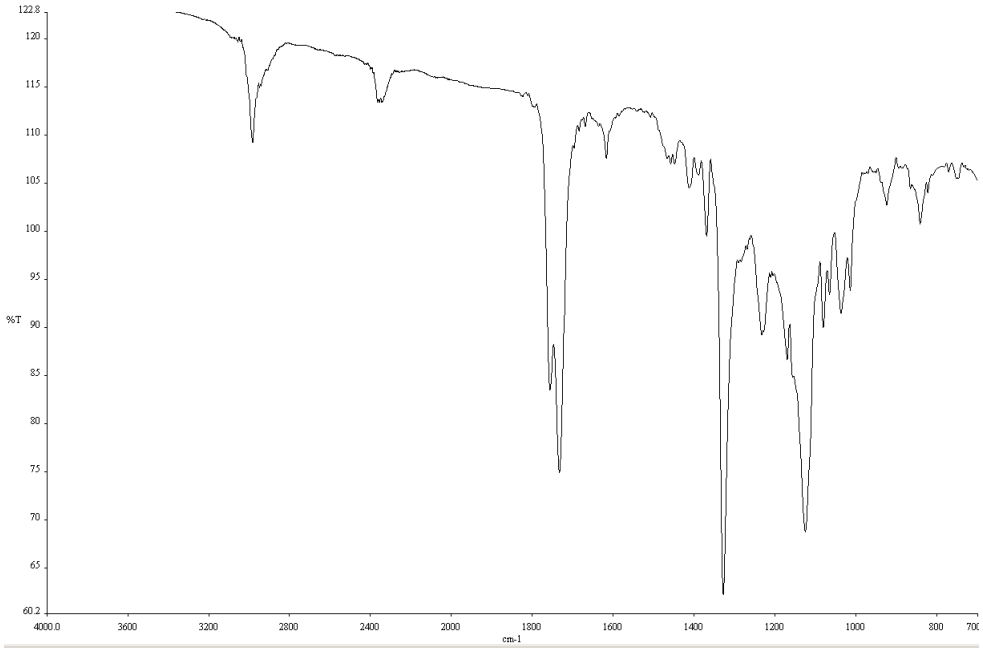


Figure A1.58. *Infrared spectrum (Thin Film, NaCl) of compound* ***6a.***

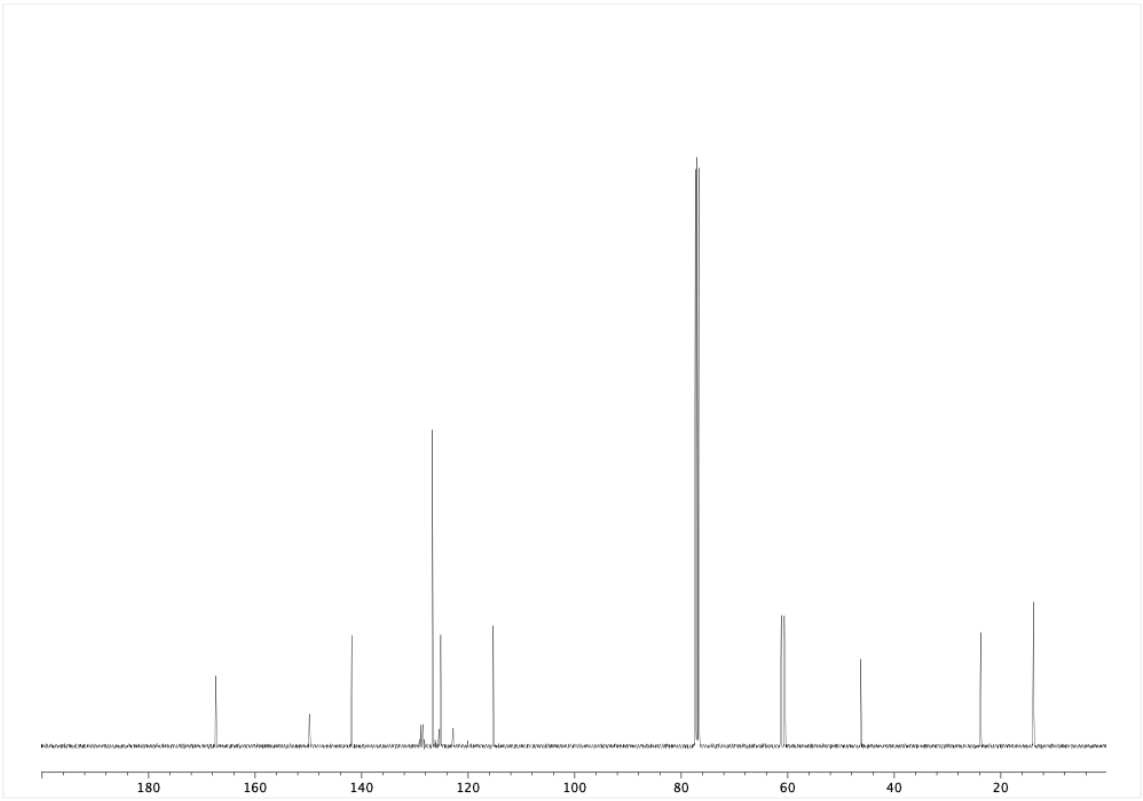


Figure A1.59. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***6a.***

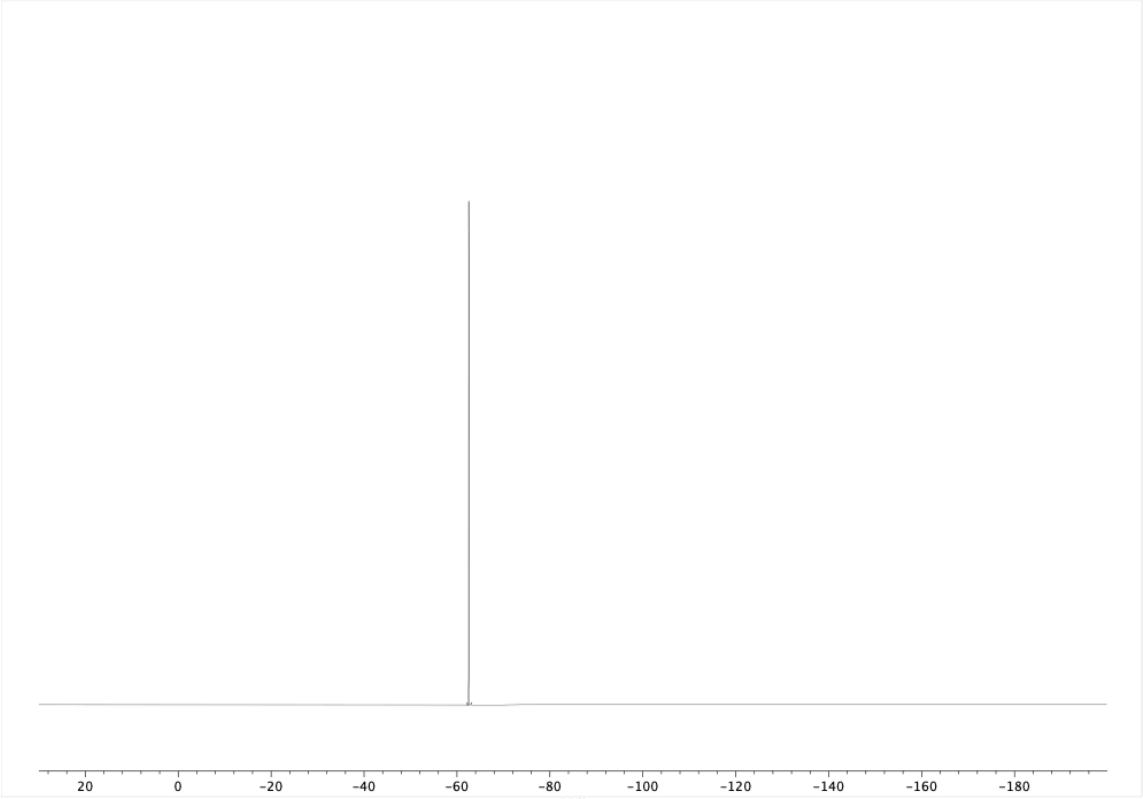


Figure A1.60. *^{19}F NMR (377 MHz, $CDCl_3$) of compound* ***6a***

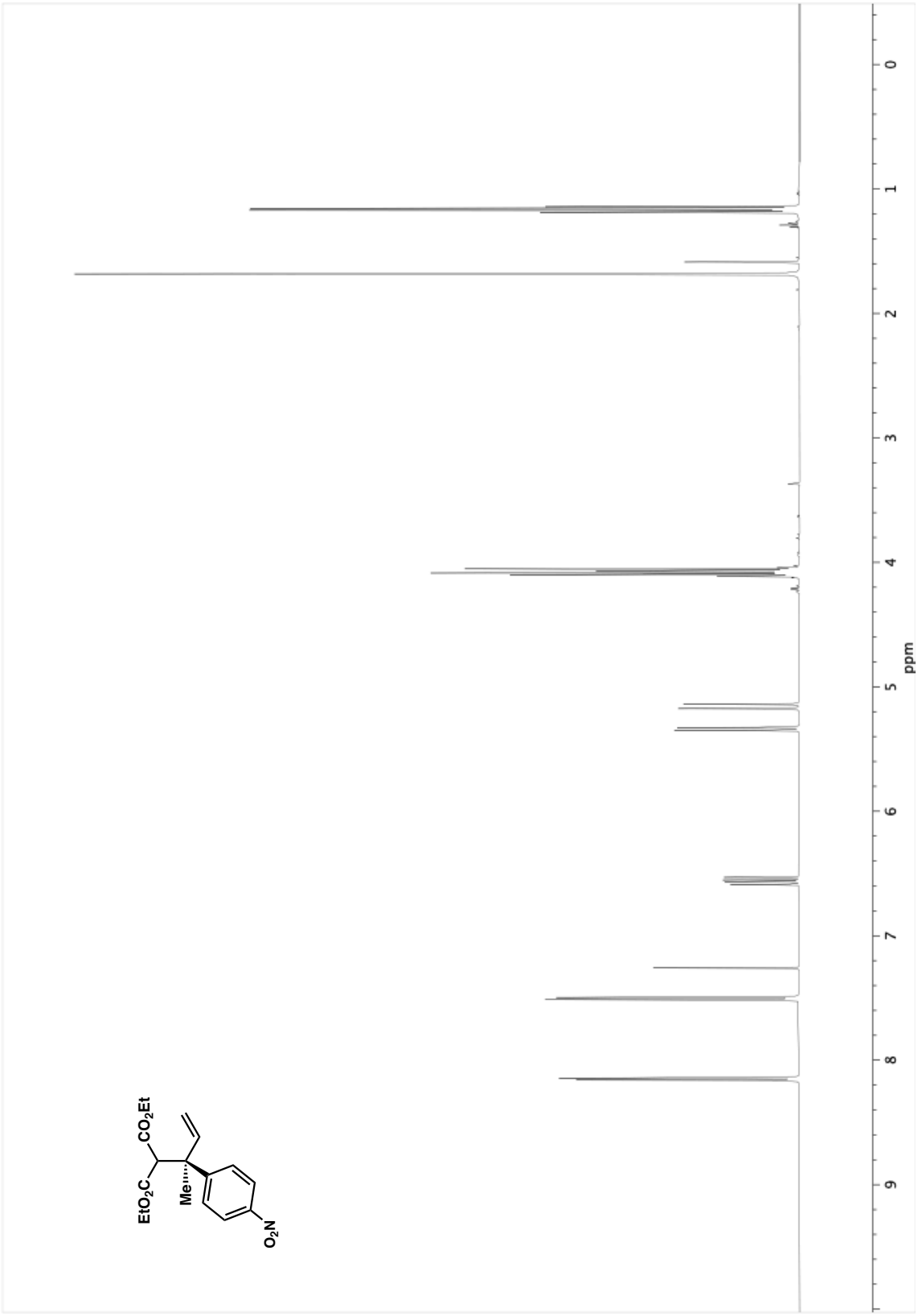


Figure A1.61. *^{1}H NMR (500 MHz, $CDCl_3$) of compound* ***6b.***

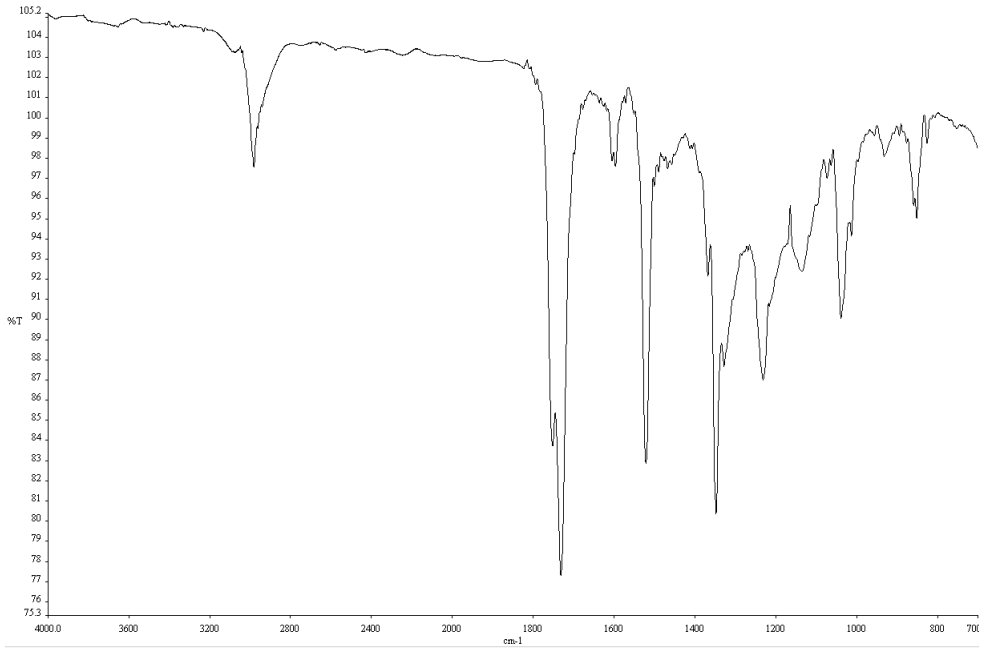


Figure A1.62. *Infrared spectrum (Thin Film, NaCl) of compound* ***6b.***

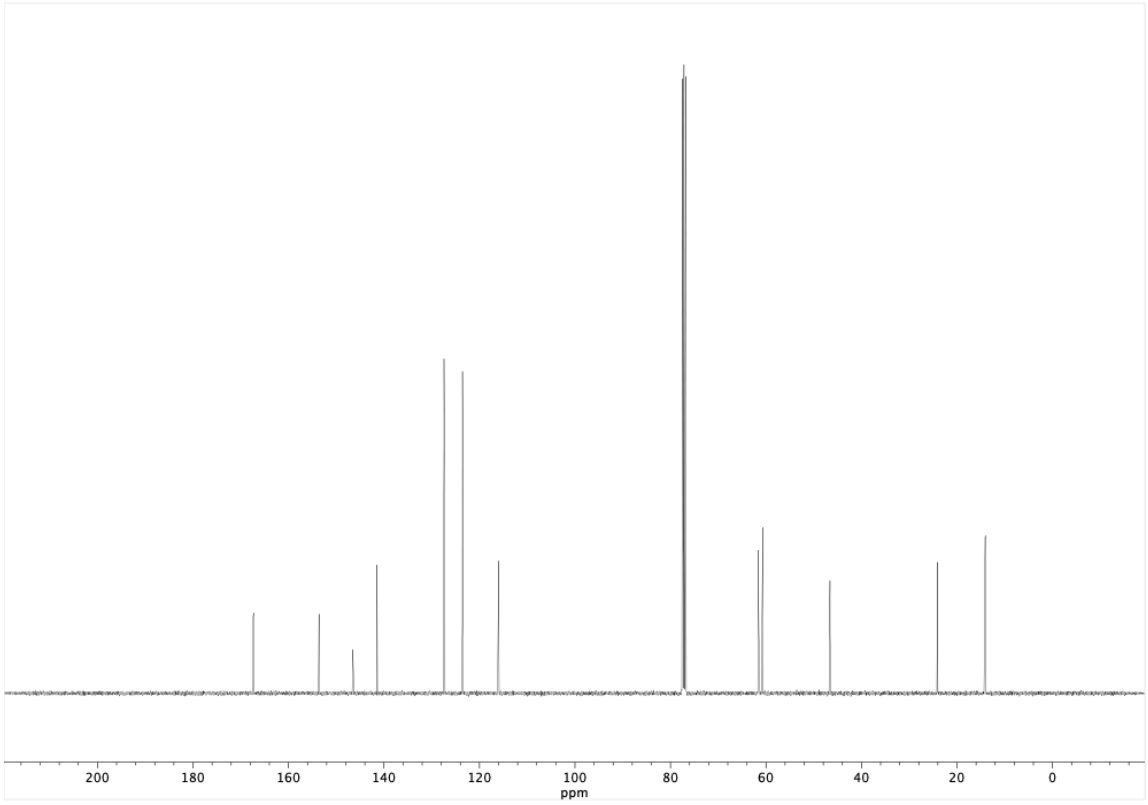


Figure A1.63. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***6b.***

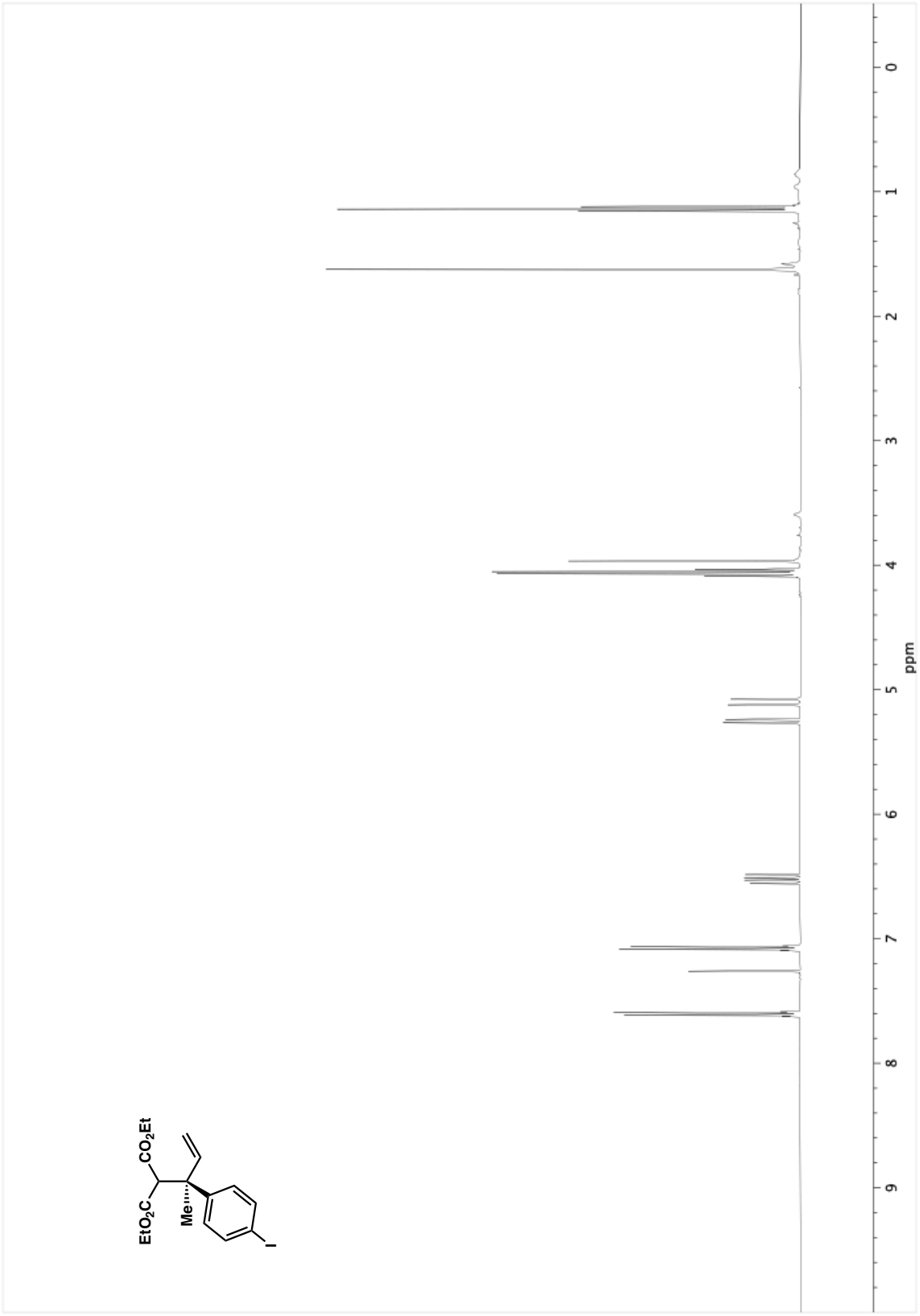


Figure A1.64. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***7a.***

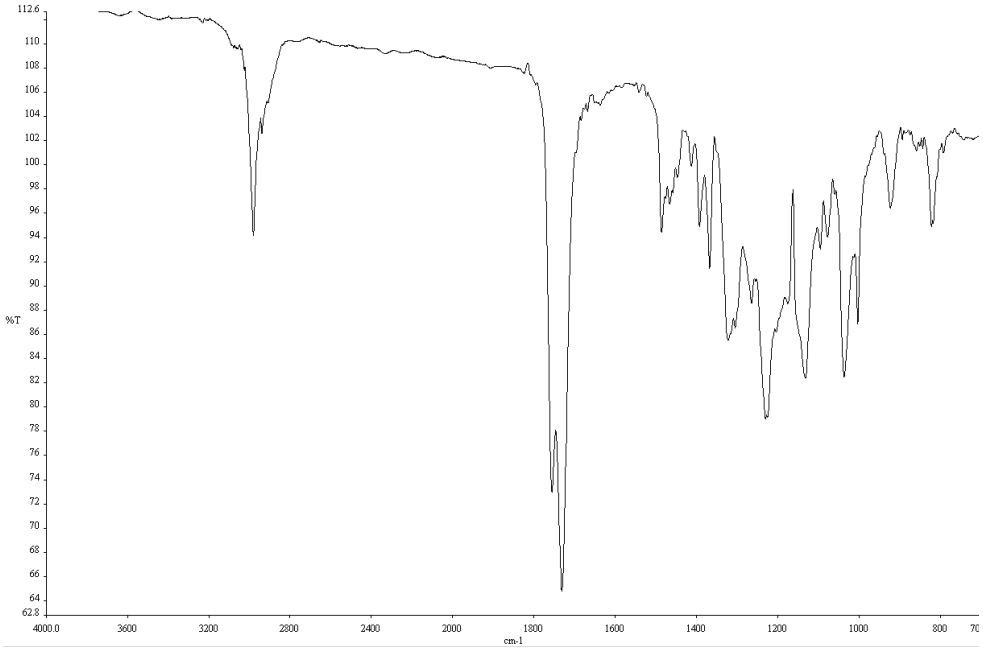


Figure A1.65. *Infrared spectrum (Thin Film, NaCl) of compound* ***7a.***

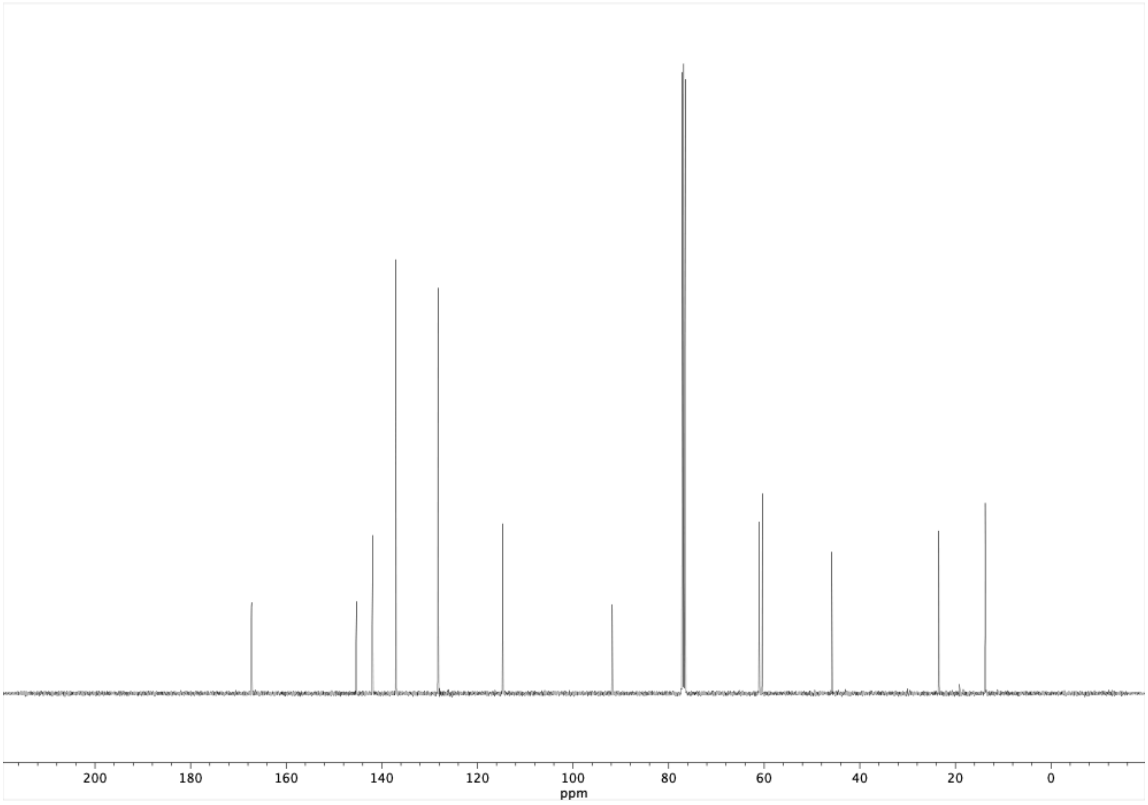


Figure A1.66. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***7a.***

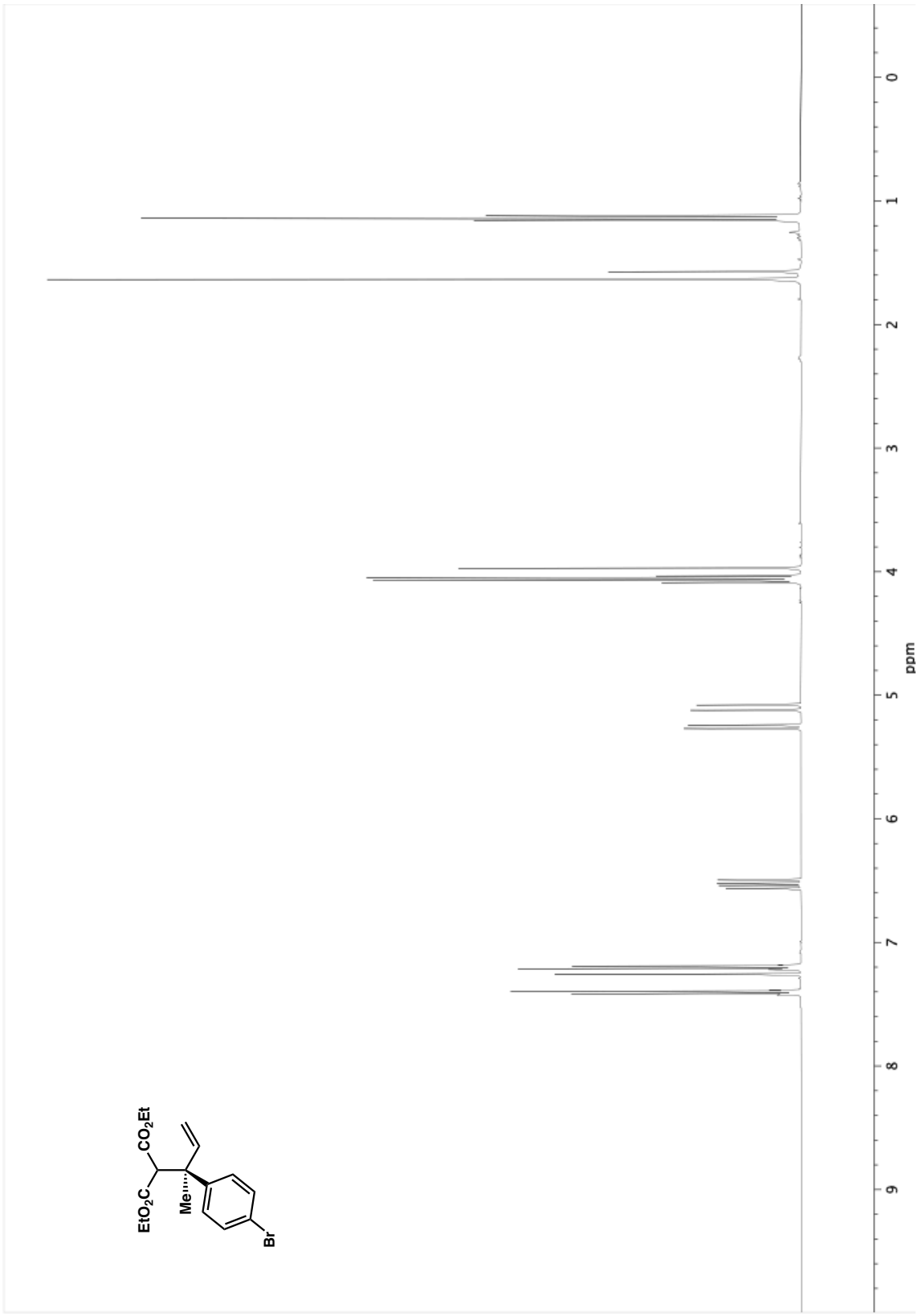


Figure A1.67. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***7b.***

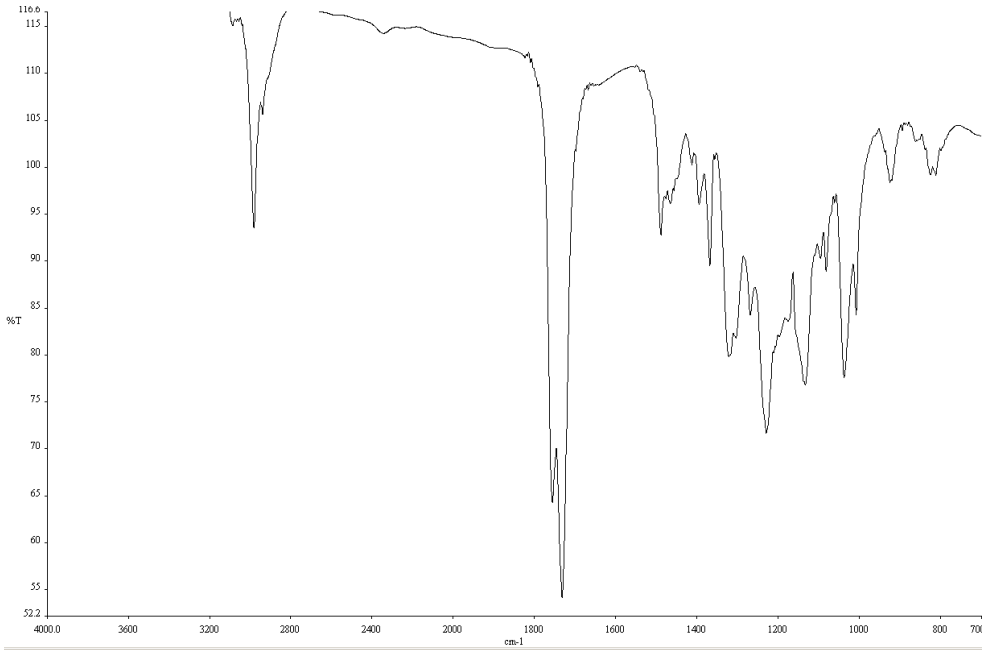


Figure A1.68. *Infrared spectrum (Thin Film, NaCl) of compound* ***7b.***

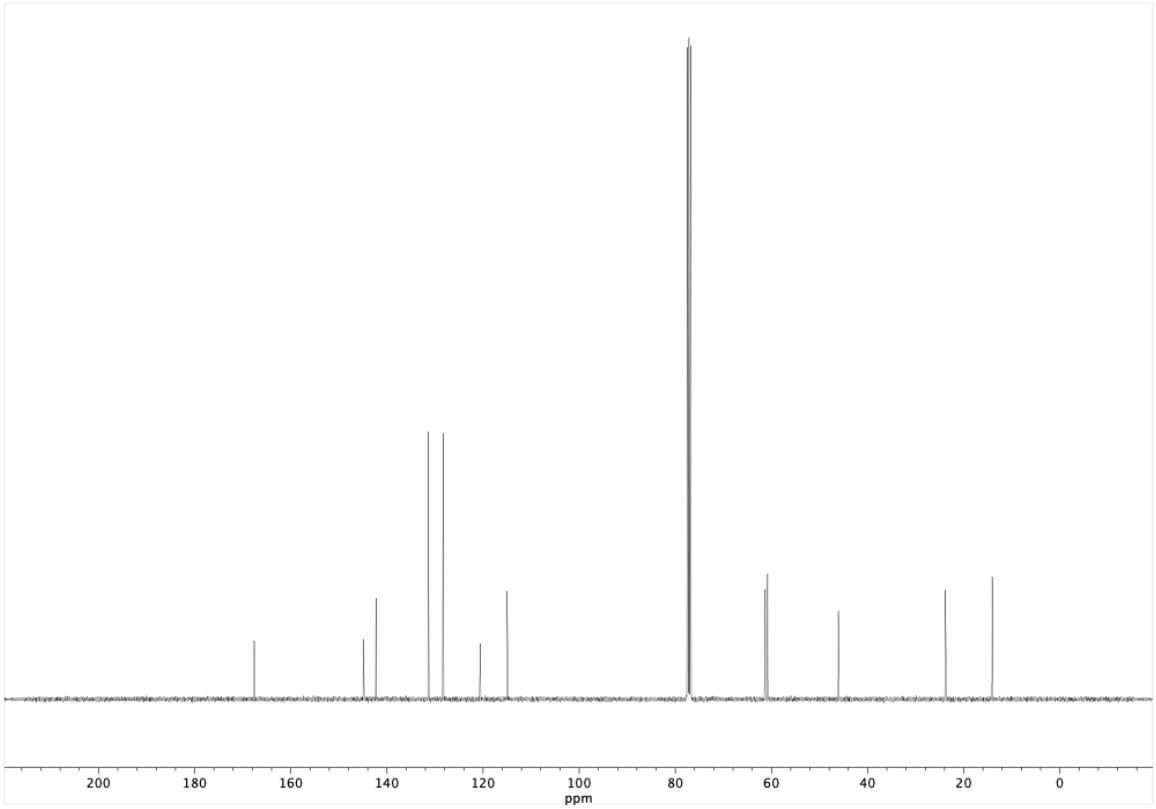


Figure A1.69. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***7b.***

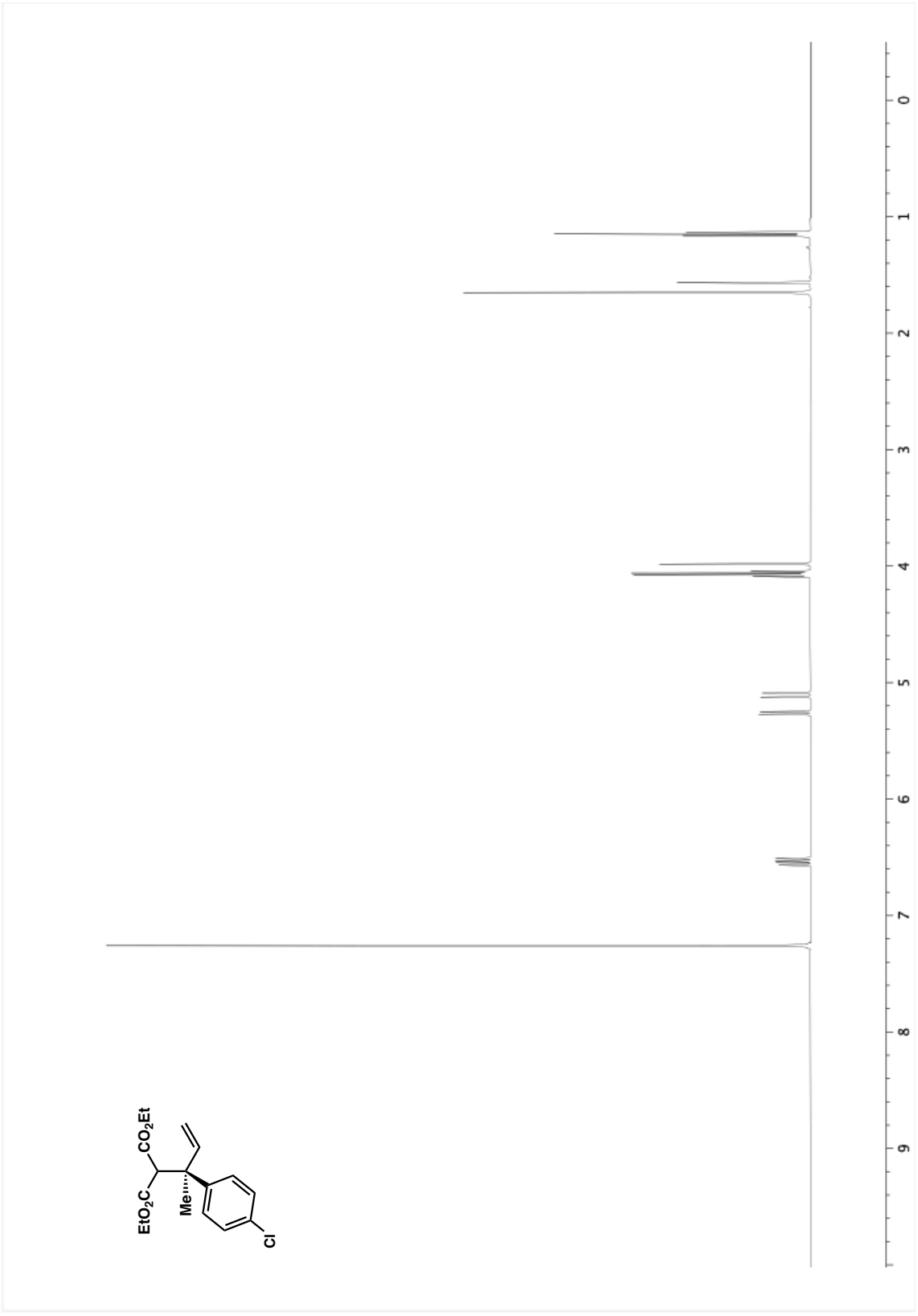


Figure A1.70. *^1H NMR (500 MHz, $CDCl_3$) of compound* ***7c.***

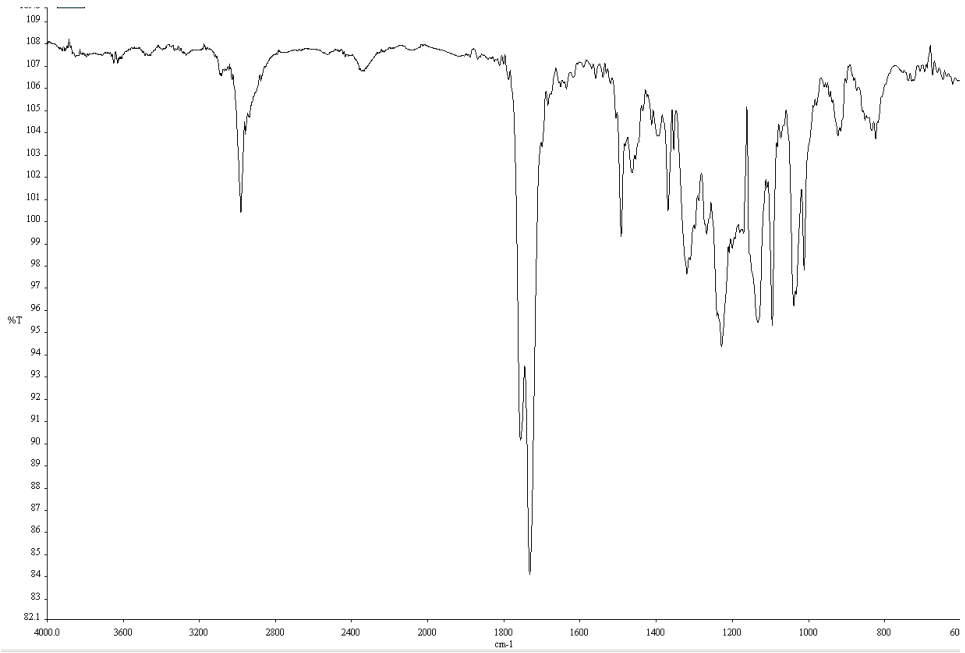


Figure A1.71. *Infrared spectrum (Thin Film, NaCl) of compound* ***7c.***

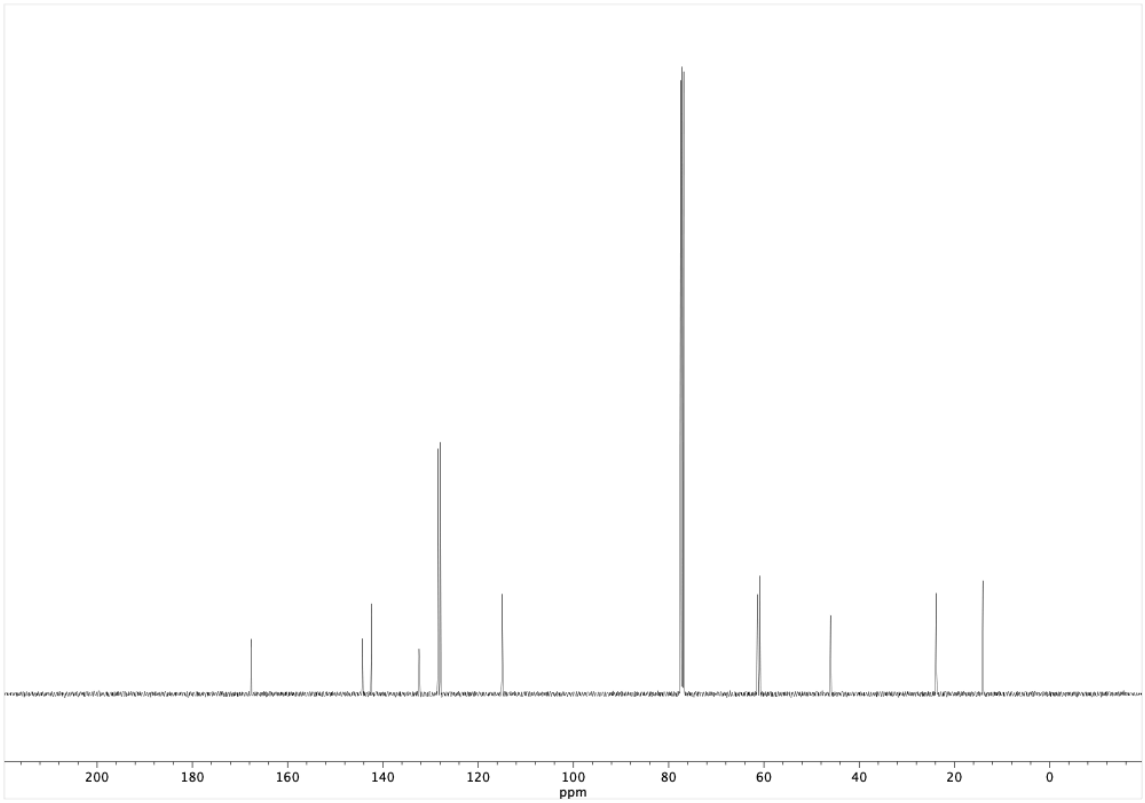


Figure A1.72. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***7c.***

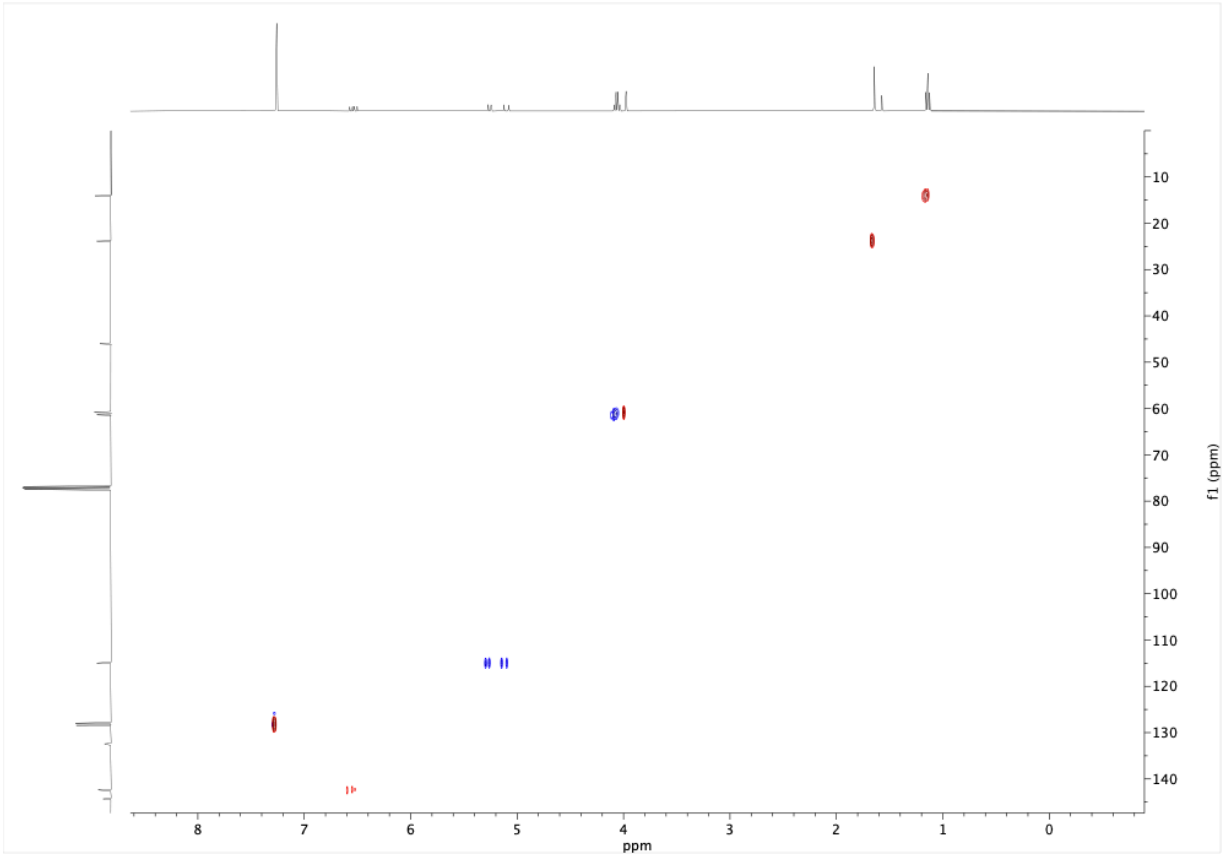


Figure A1.73. *^{1}H-^{13}C HSQC ($CDCl_3$) of compound* ***7c.***

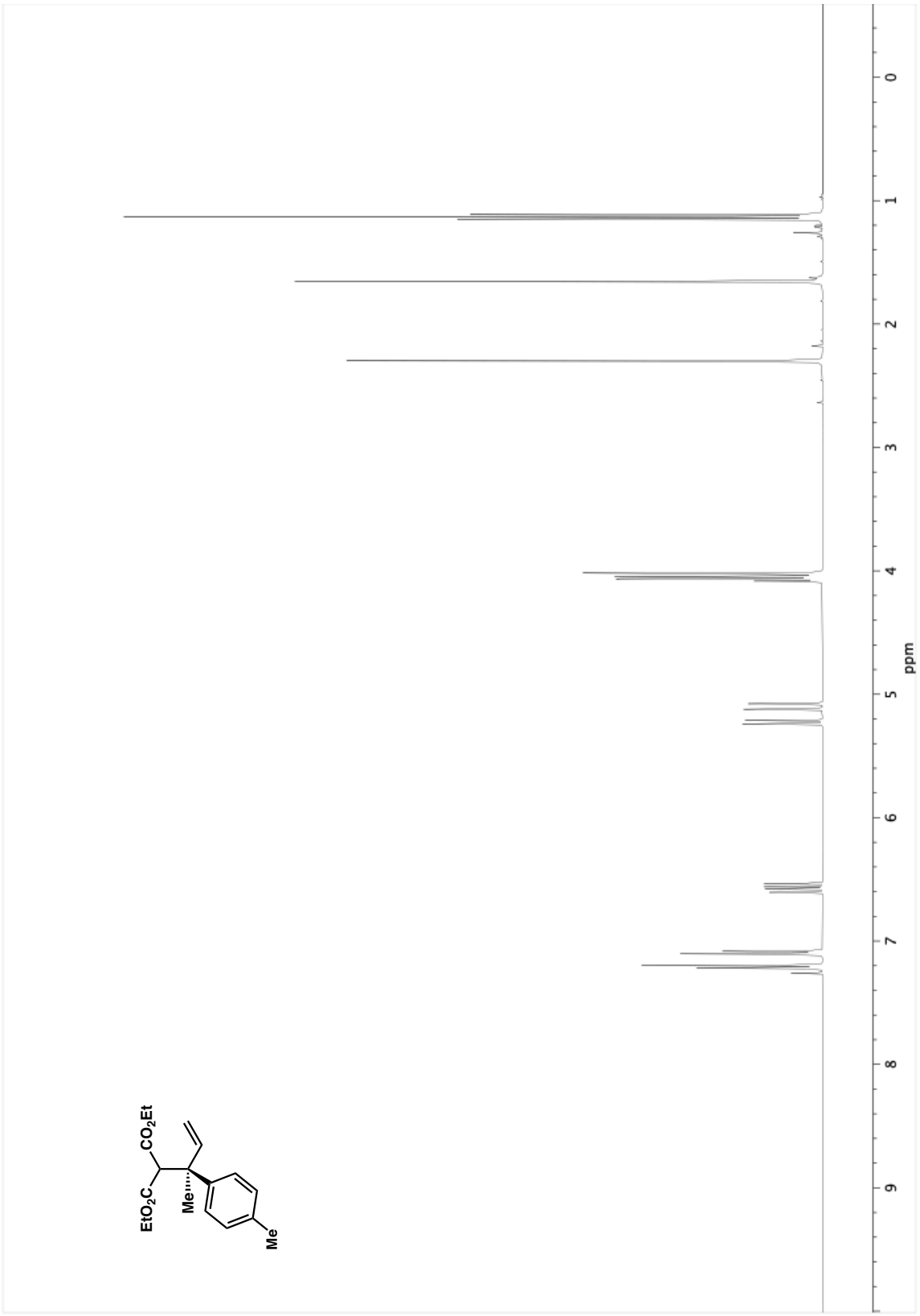


Figure A1.74. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***8a.***

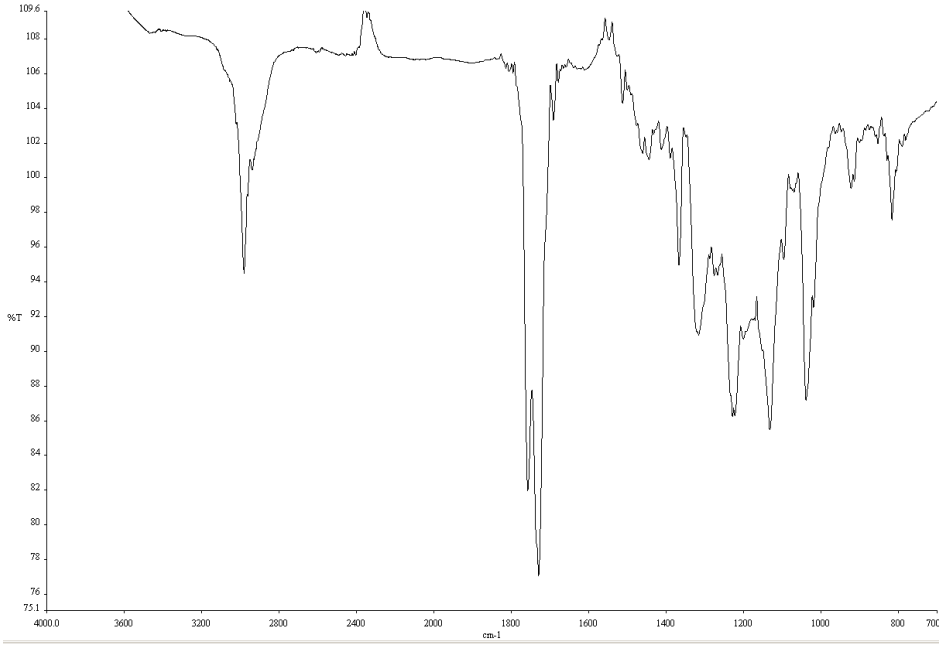


Figure A1.75. *Infrared spectrum (Thin Film, NaCl) of compound* ***8a.***

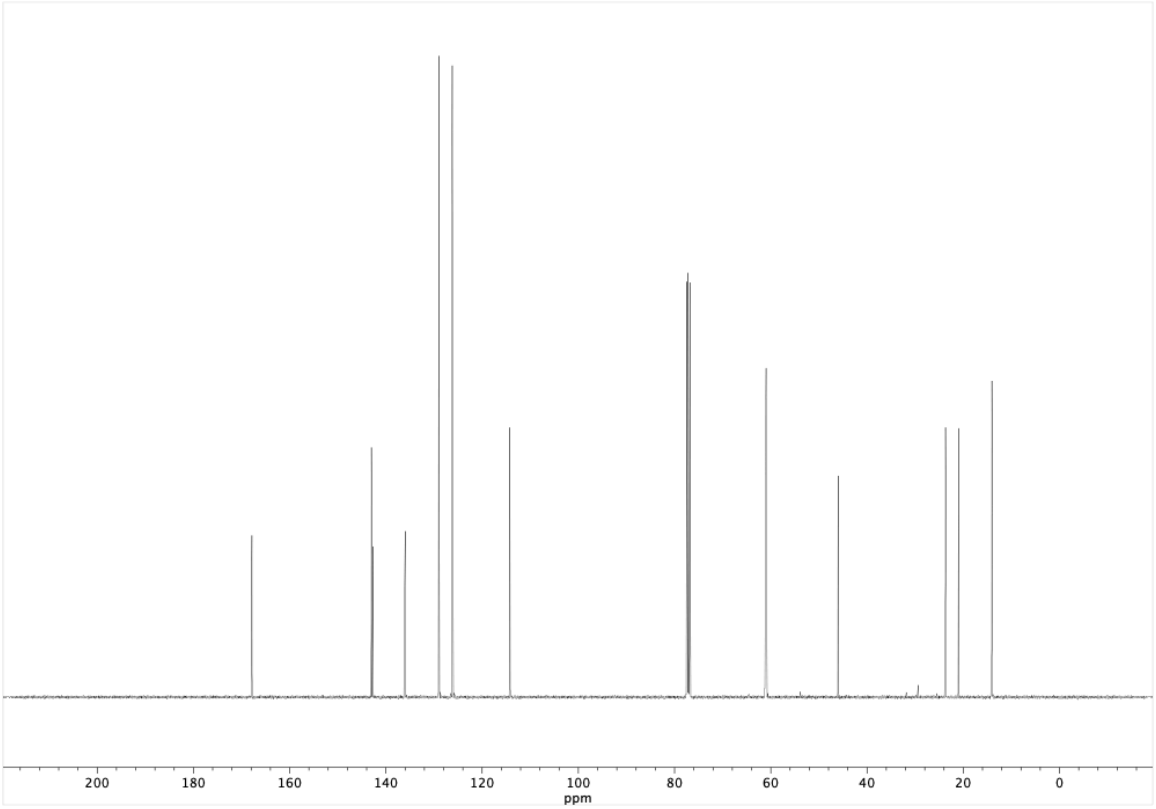


Figure A1.76. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***8a.***

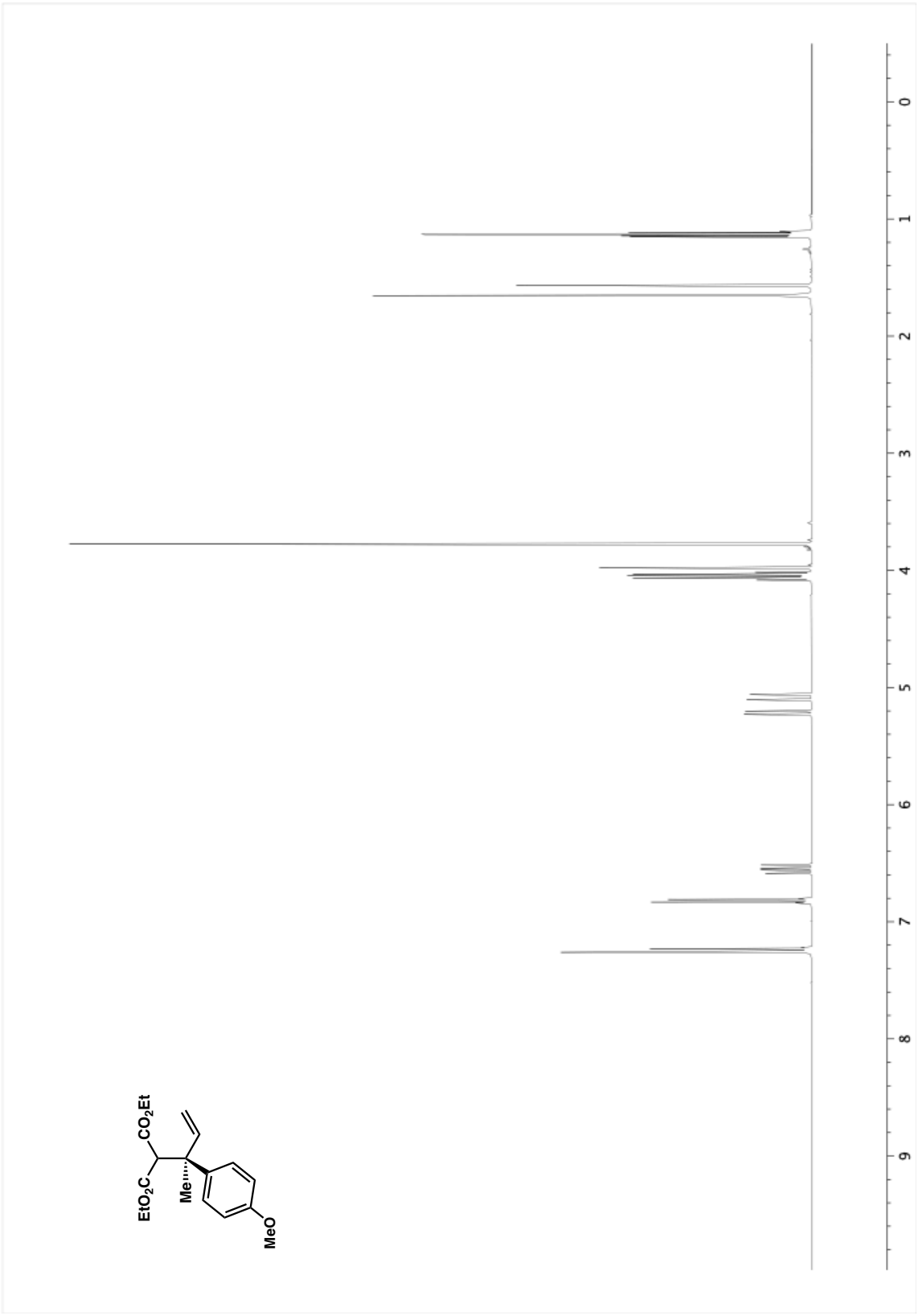


Figure A1.77. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***8b.***

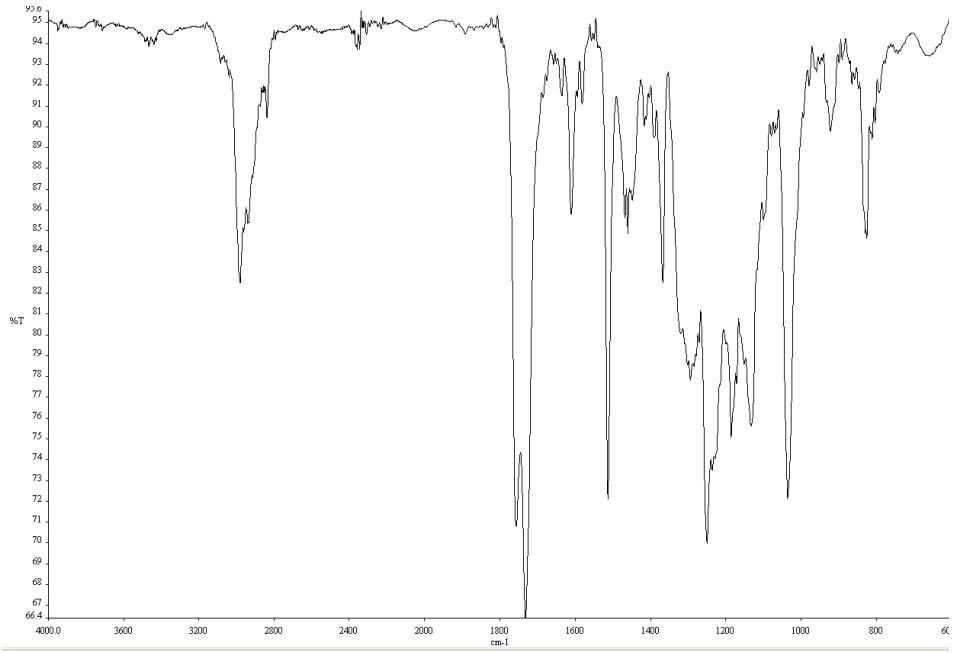


Figure A1.78. *Infrared spectrum (Thin Film, NaCl) of compound* ***8b.***

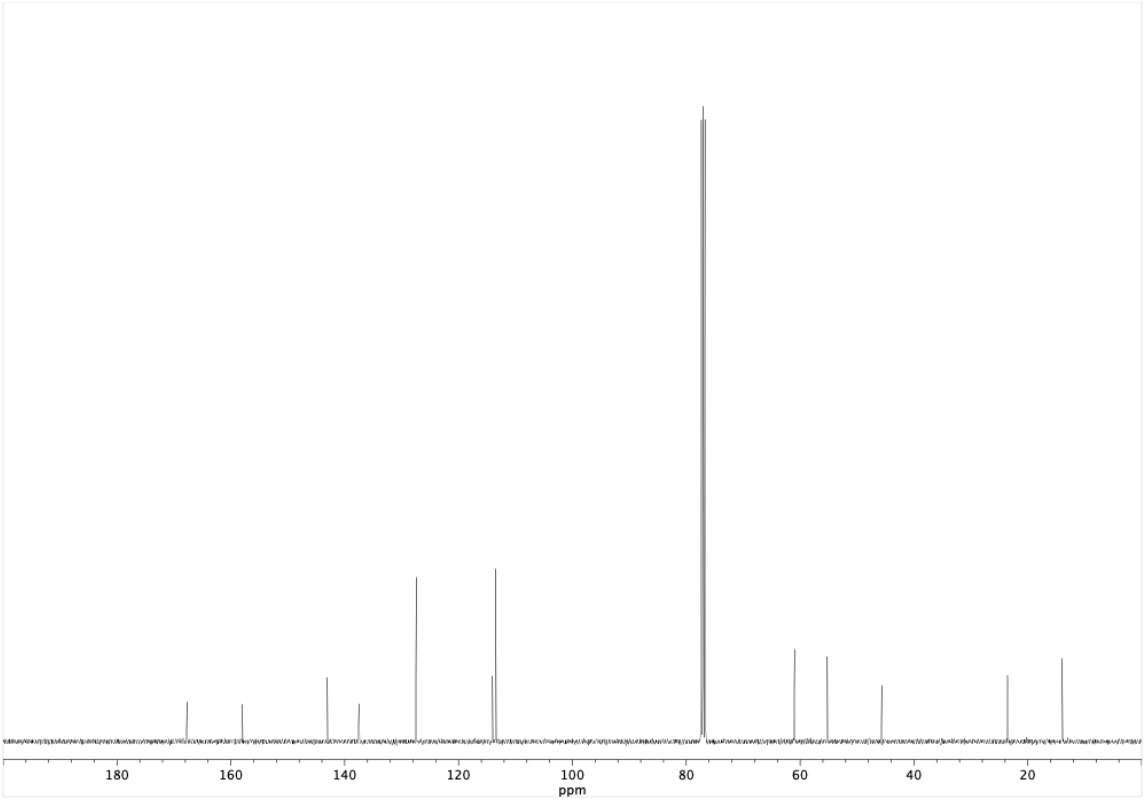


Figure A1.79. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***8b.***

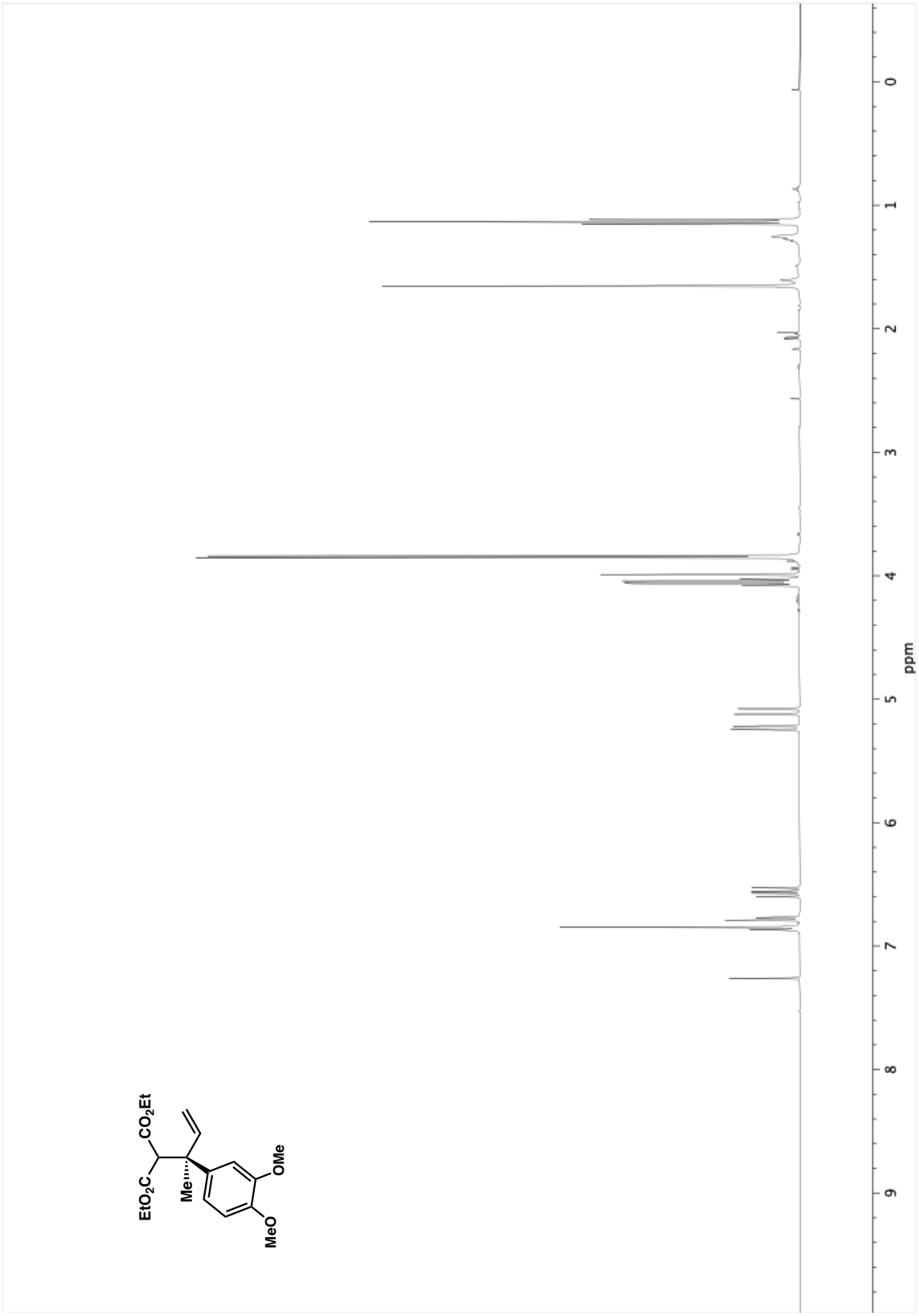


Figure A1.80. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***8c.***

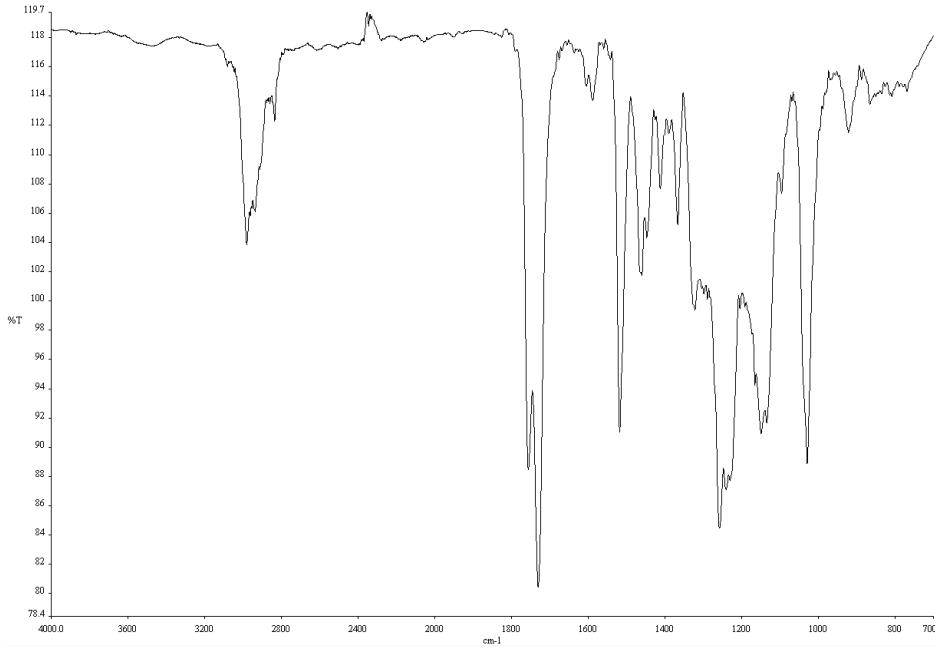


Figure A1.81. *Infrared spectrum (Thin Film, NaCl) of compound* ***8c.***

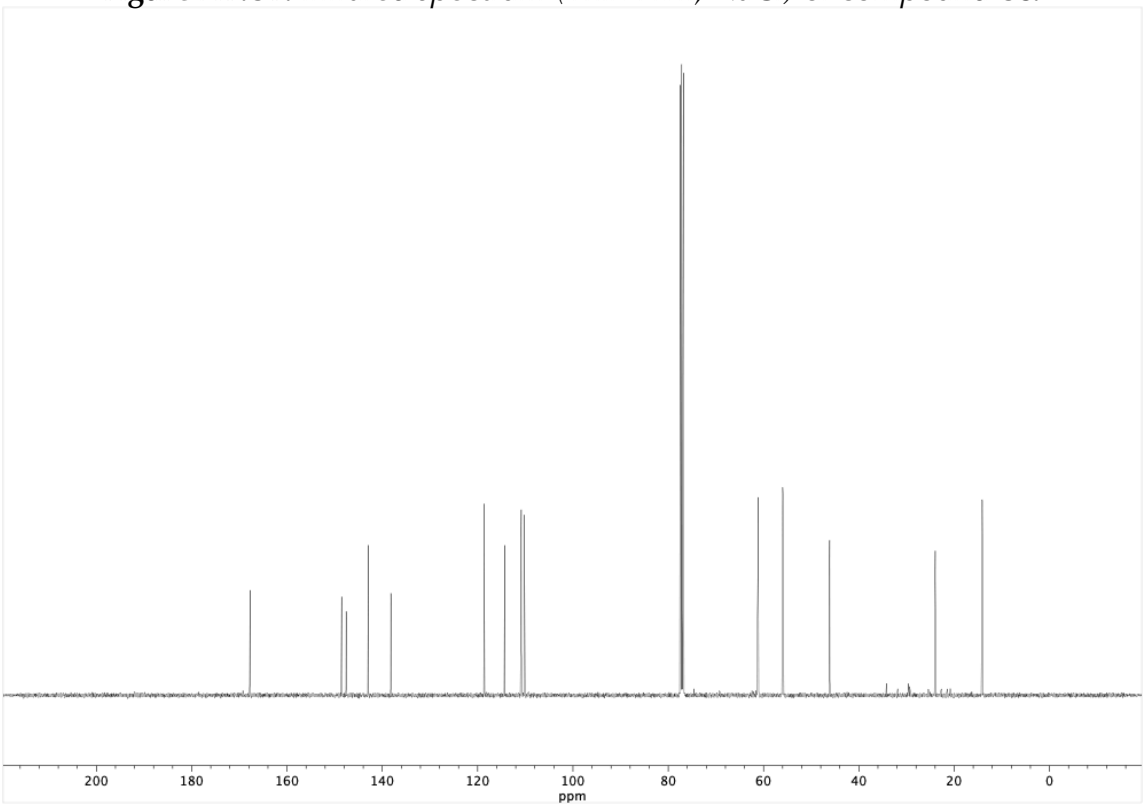


Figure A1.82. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***8c.***

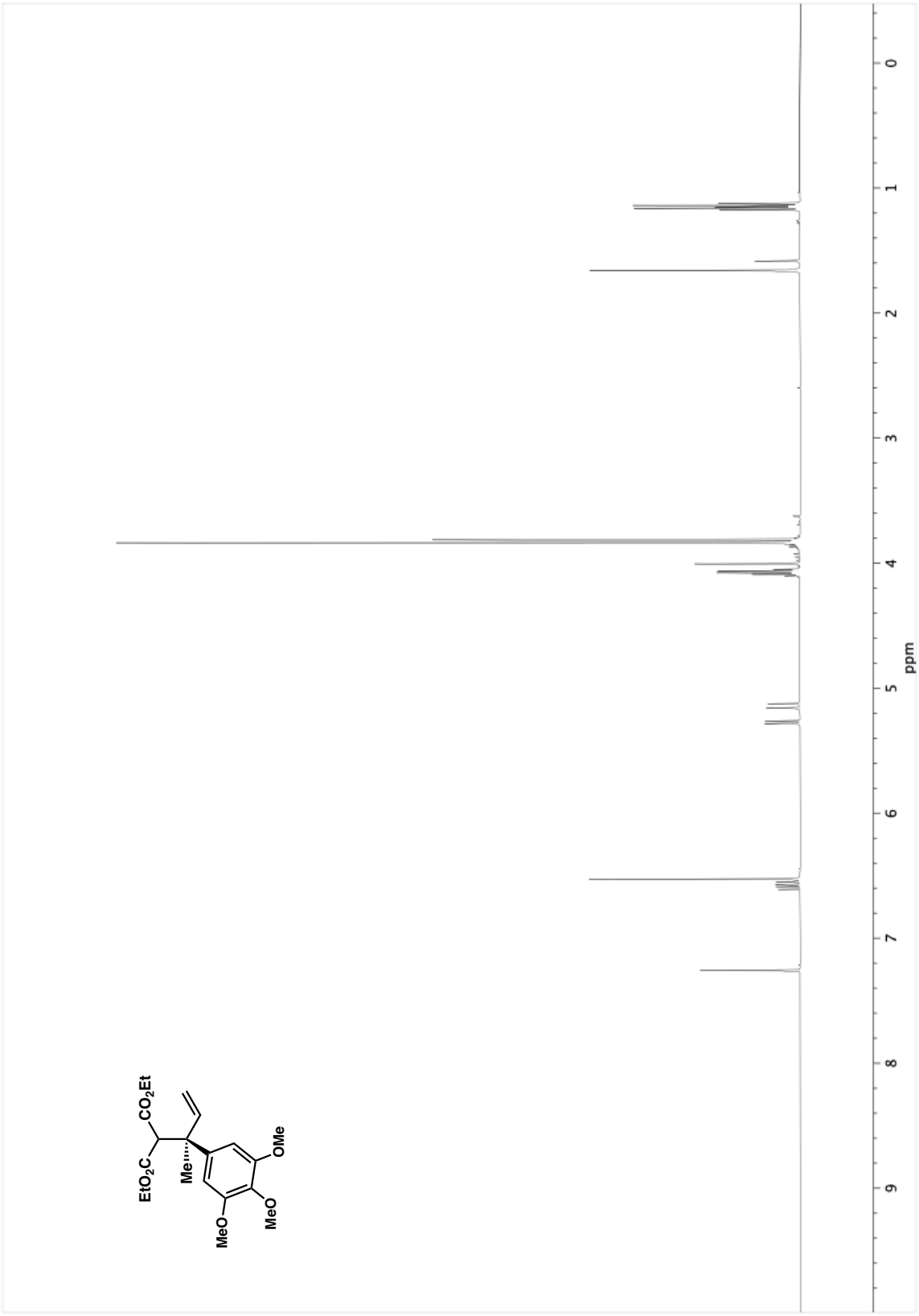


Figure A1.83. *^{1}H NMR (500 MHz, $CDCl_3$) of compound* ***8d.***

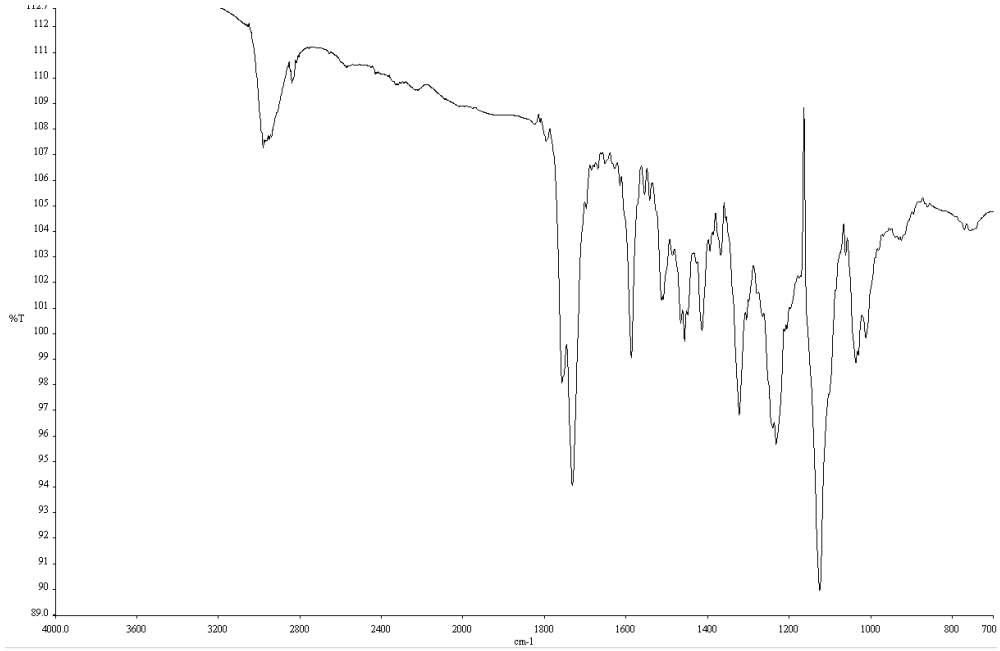


Figure A1.84. *Infrared spectrum (Thin Film, NaCl) of compound* ***8d.***

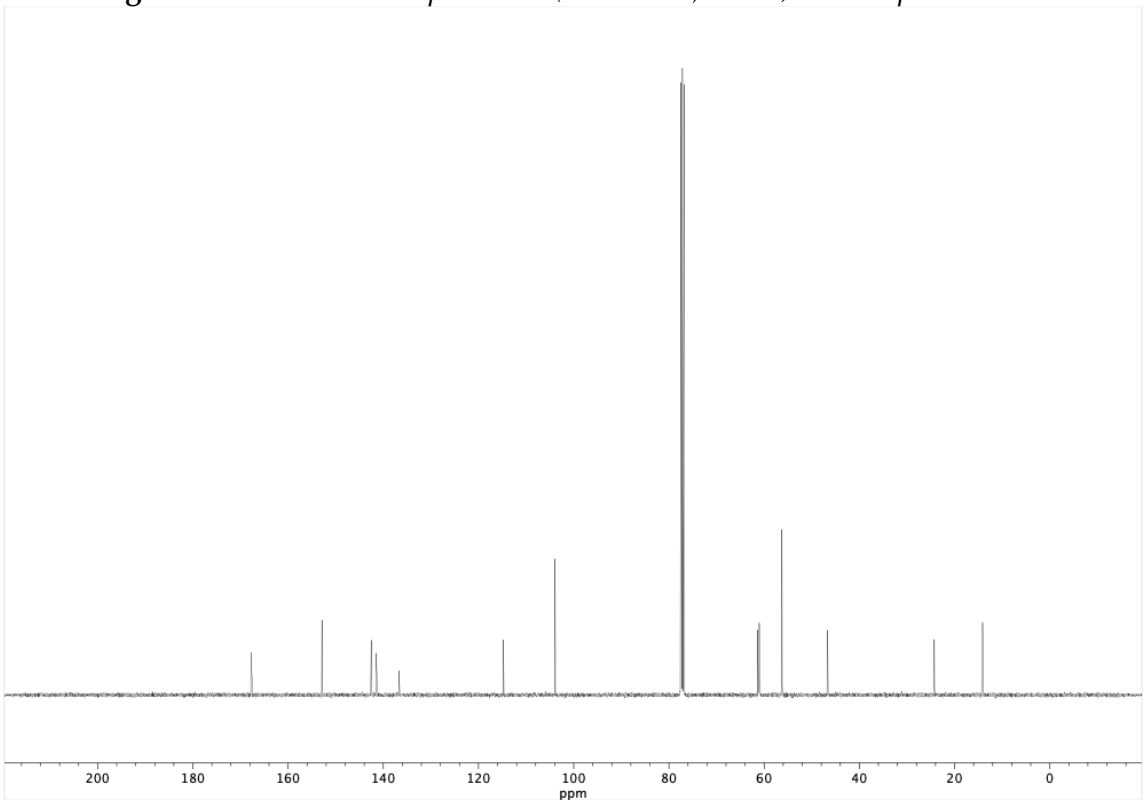


Figure A1.85. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***8d.***

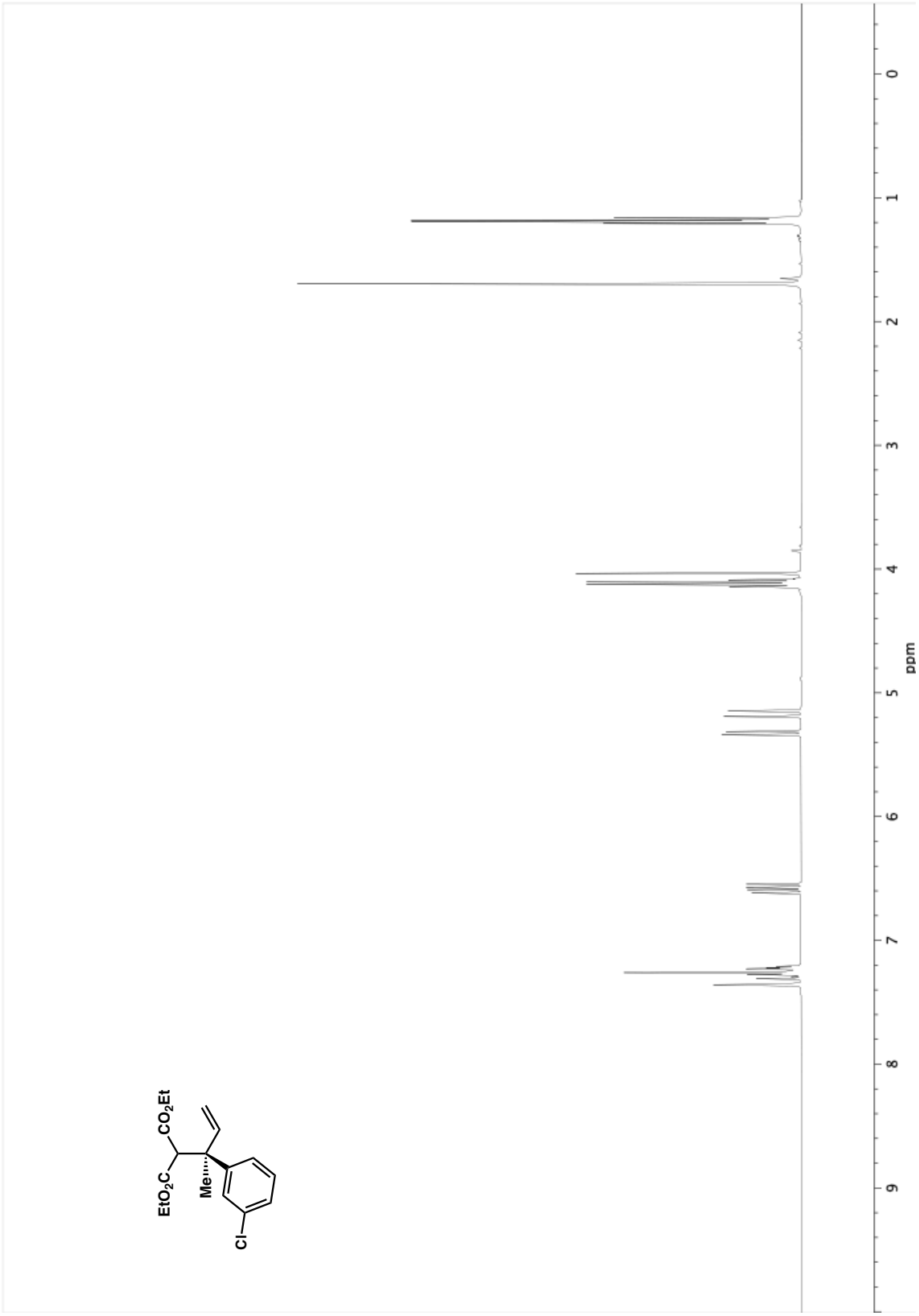


Figure A1.86. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***9a.***

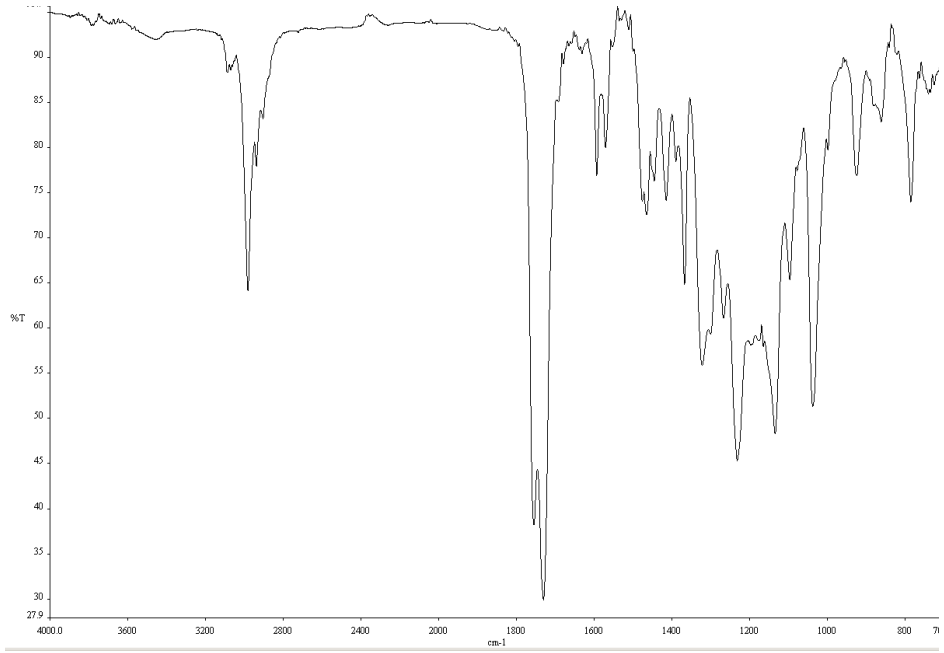


Figure A1.87. *Infrared spectrum (Thin Film, NaCl) of compound* ***9a.***

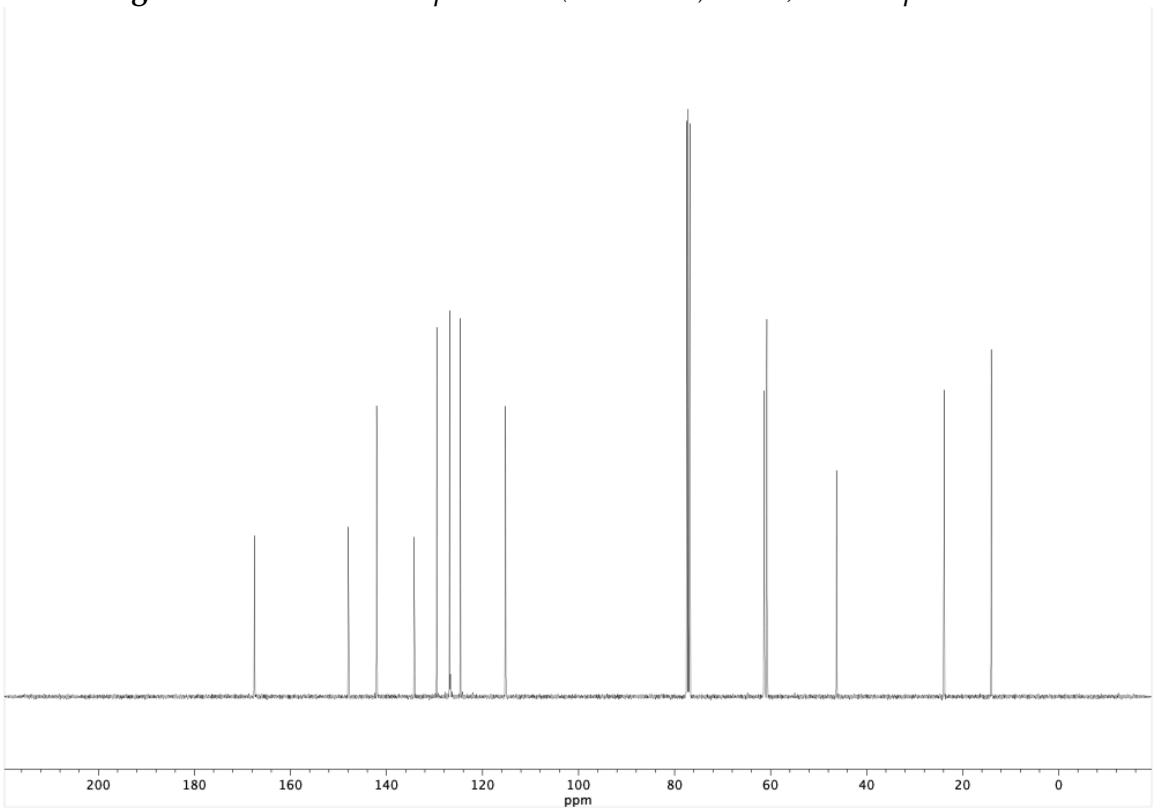


Figure A1.88. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***9a.***

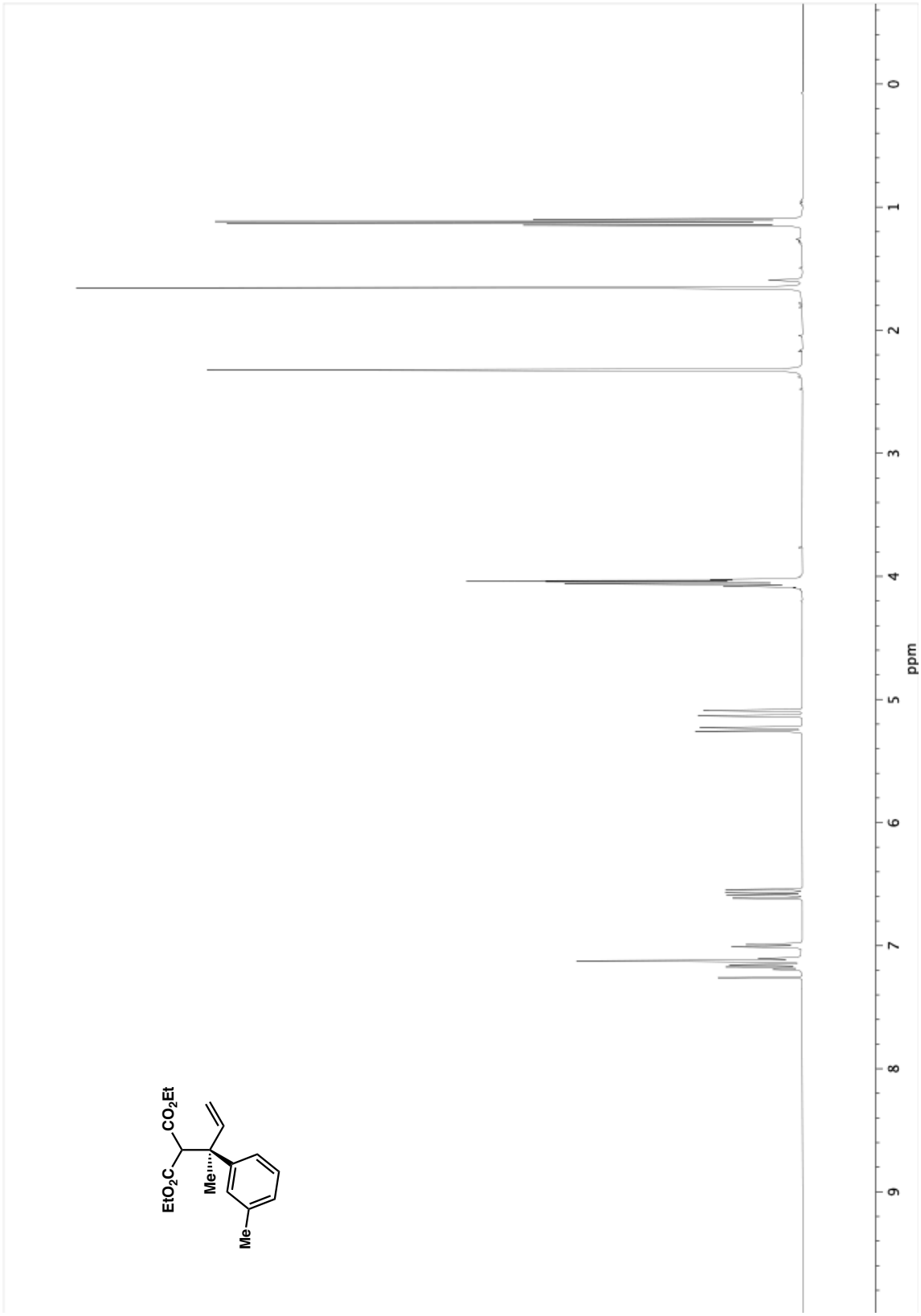


Figure A1.89. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***9b.***

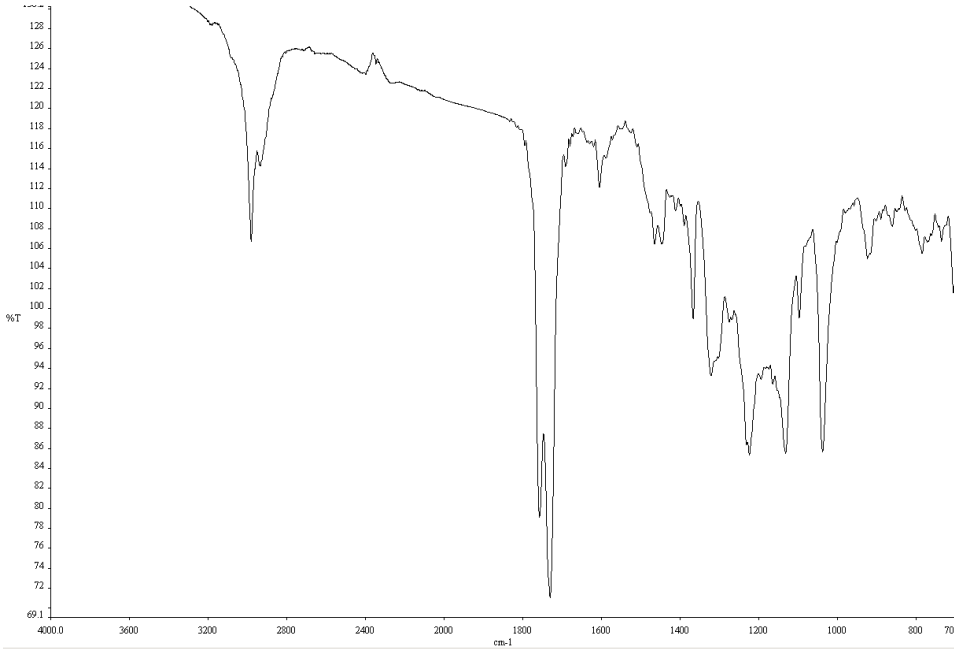


Figure A1.90. *Infrared spectrum (Thin Film, NaCl) of compound* ***9b.***

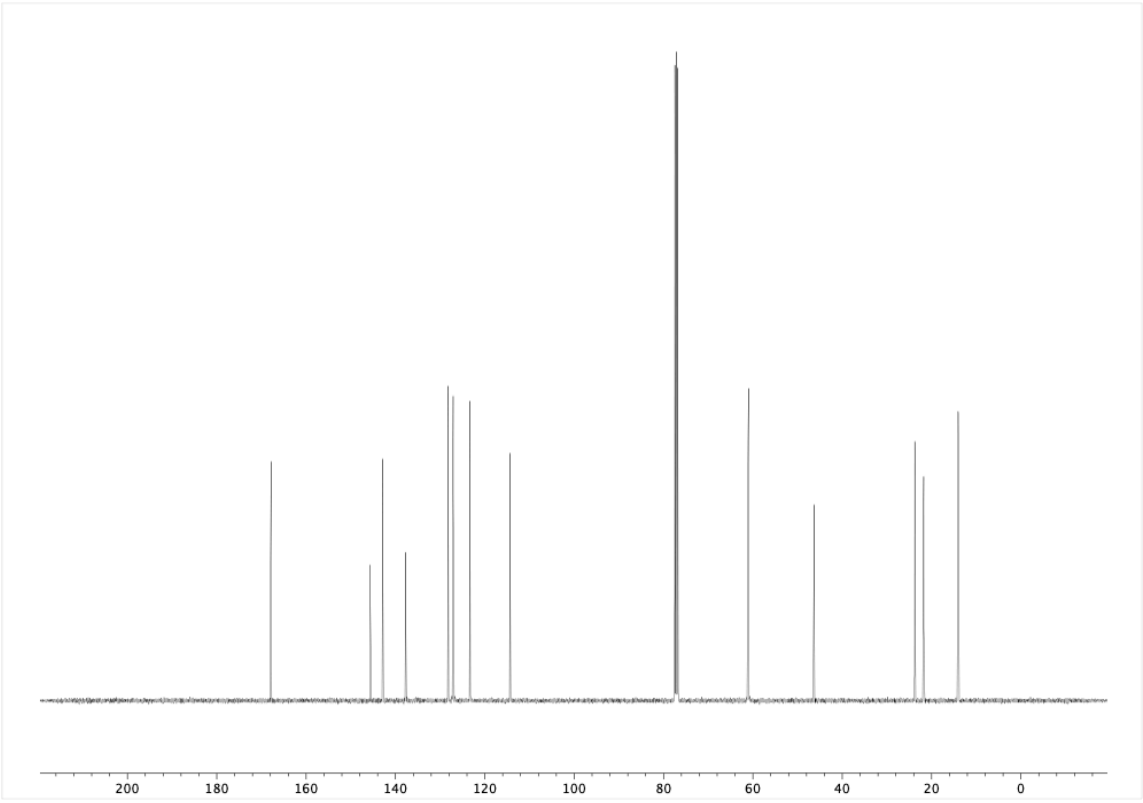


Figure A1.91. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***9b.***

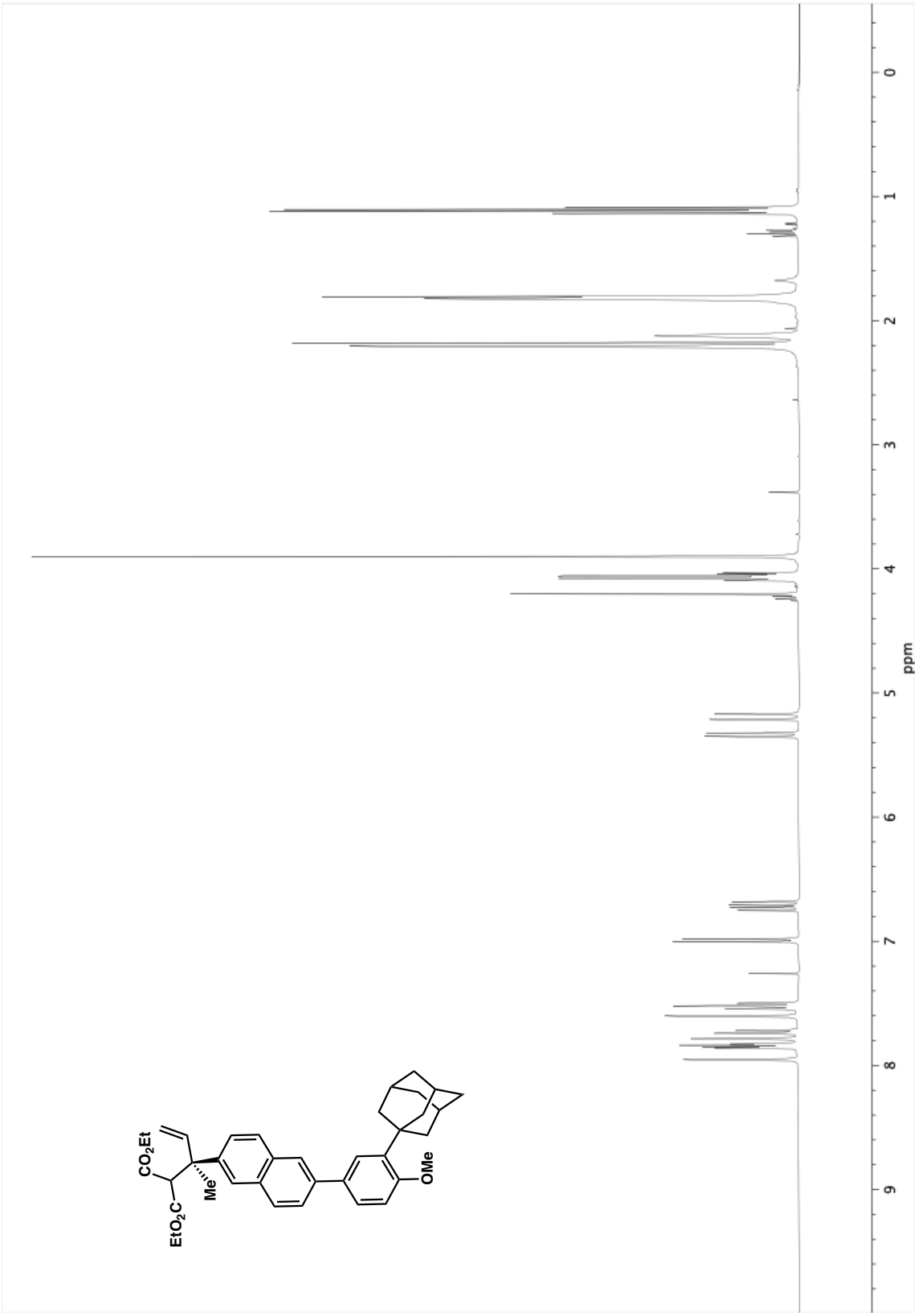


Figure A1.92. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***10.***

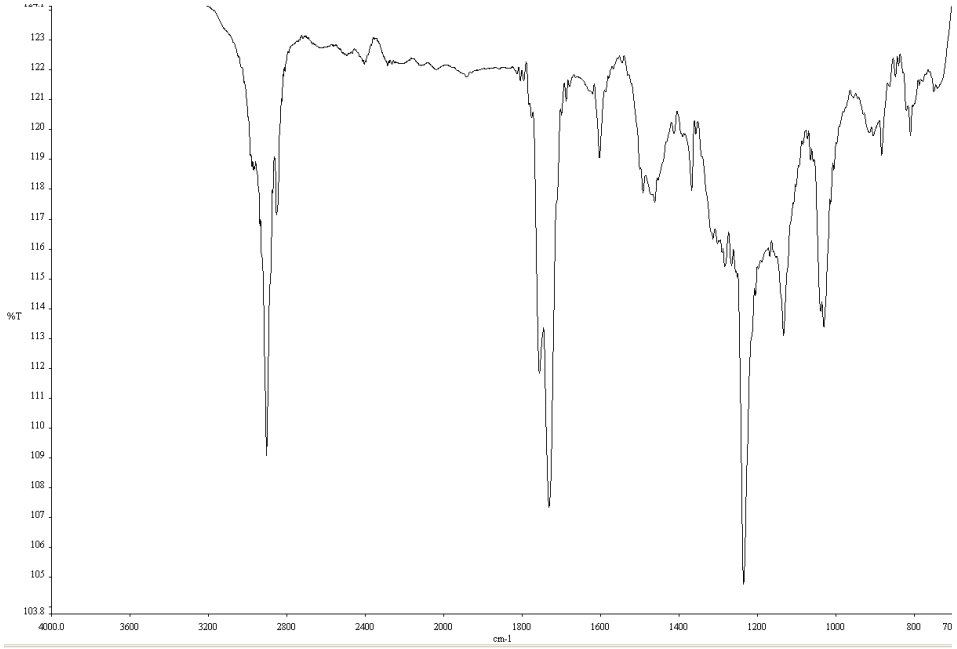


Figure A1.93. *Infrared spectrum (Thin Film, NaCl) of compound* ***10.***

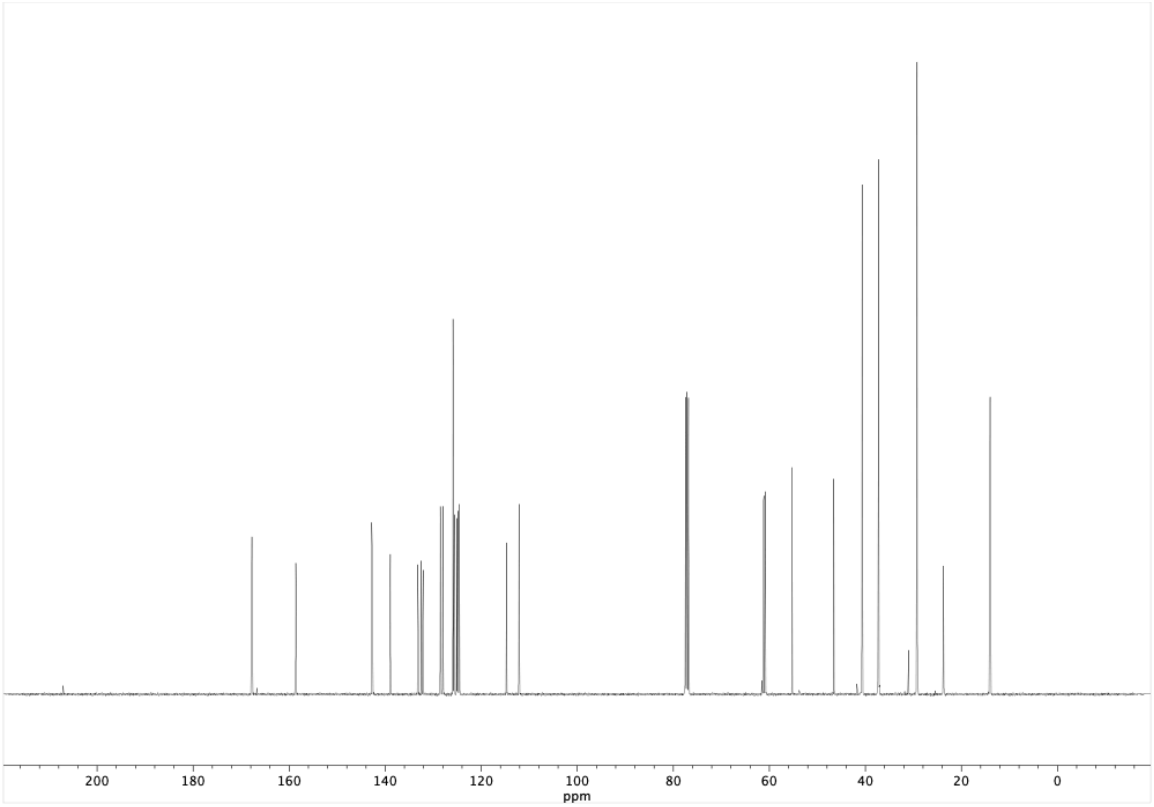


Figure A1.94. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***10.***

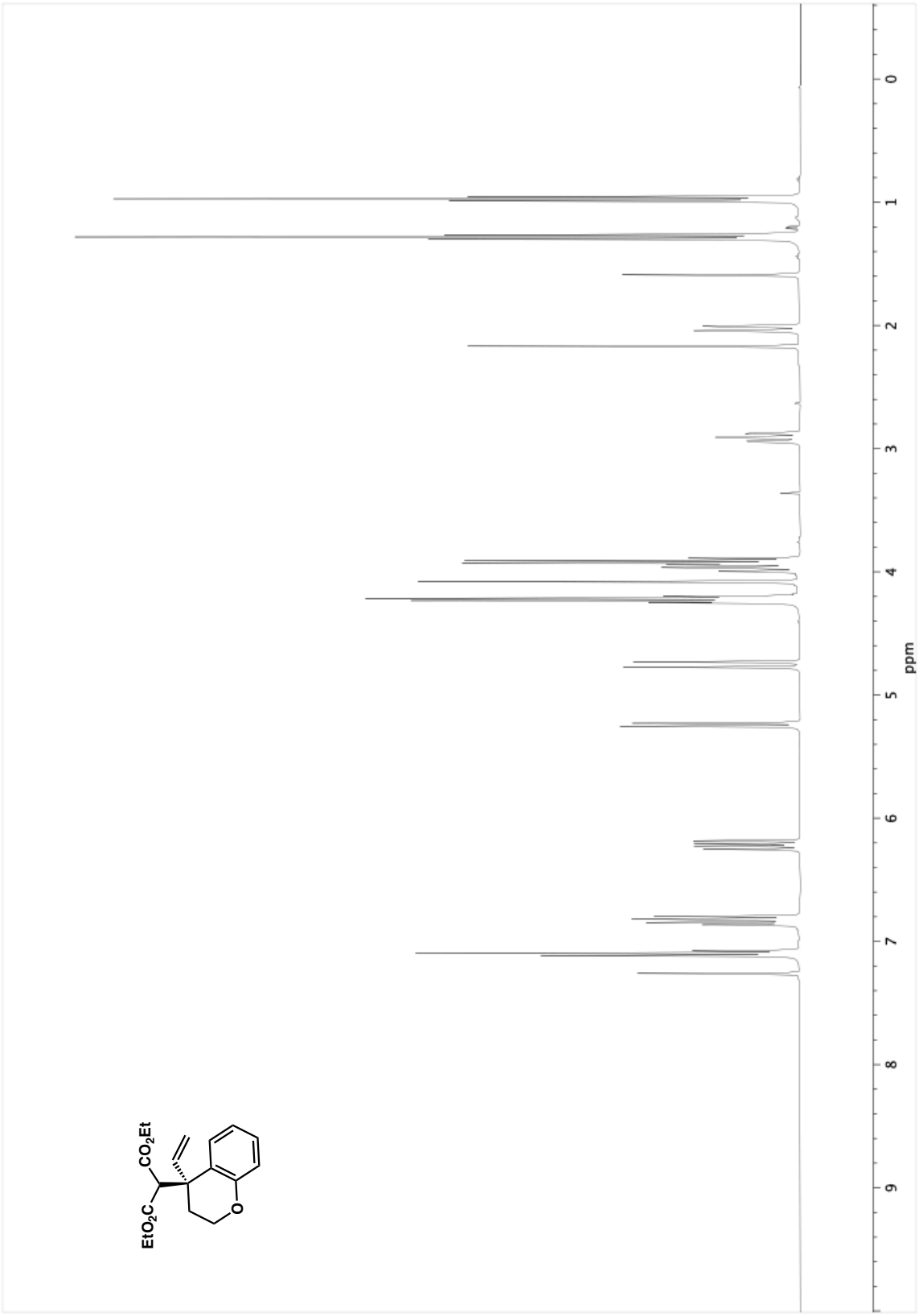


Figure A1.95. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***11a.***

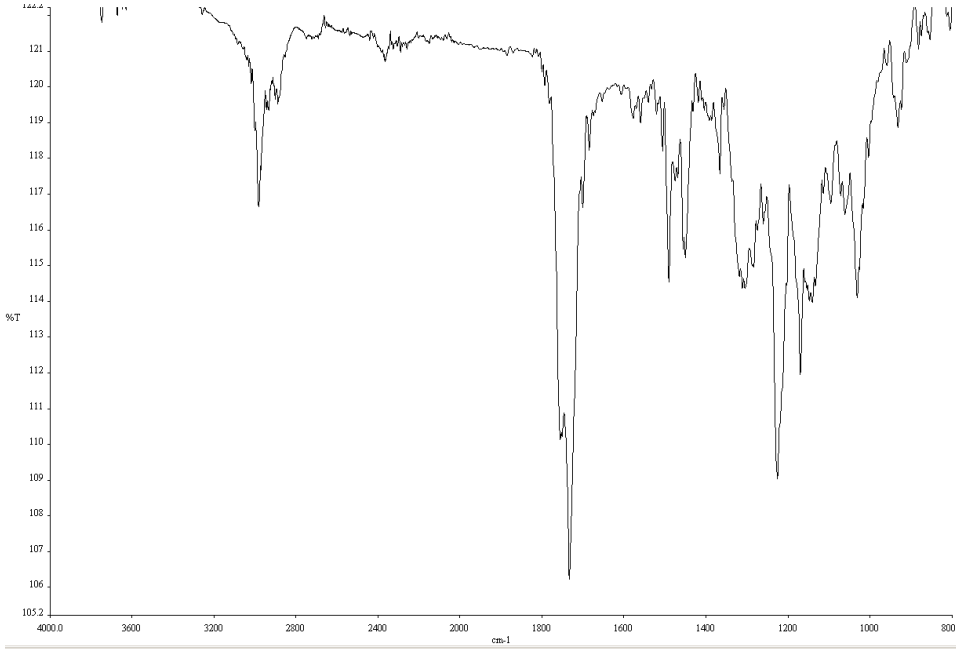


Figure A1.96. *Infrared spectrum (Thin Film, NaCl) of compound* ***11a.***

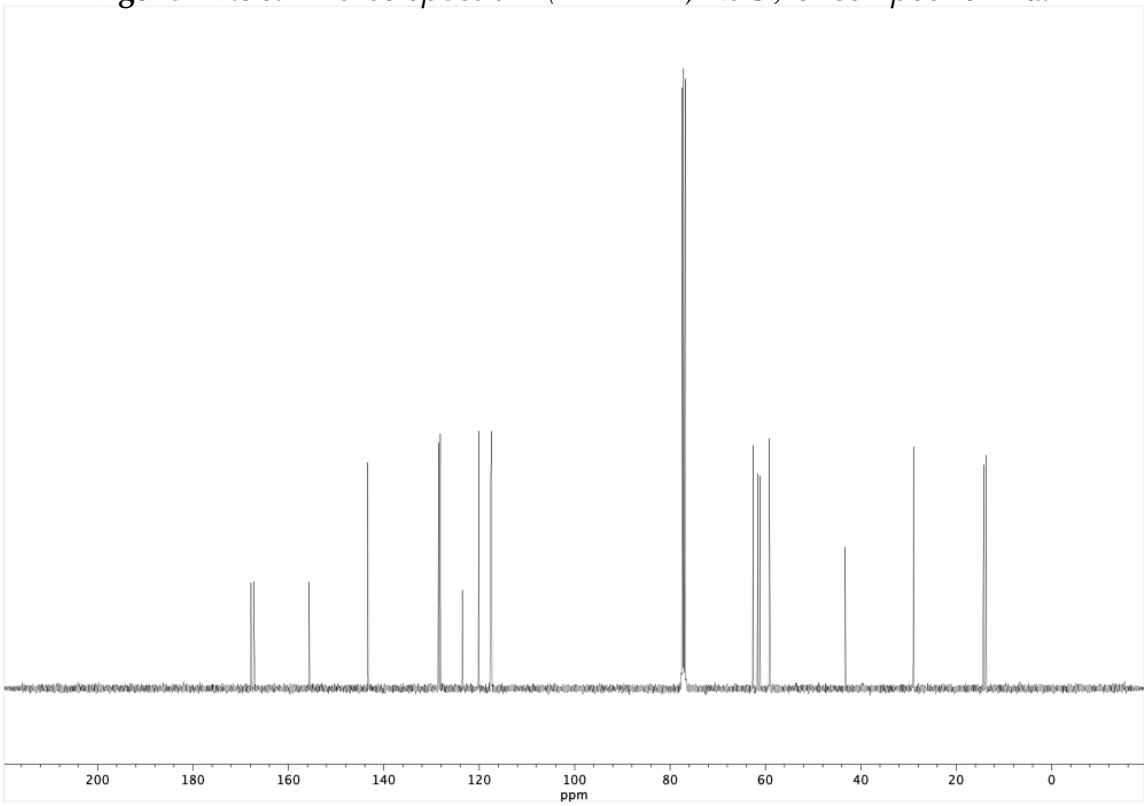


Figure A1.97. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***11a.***

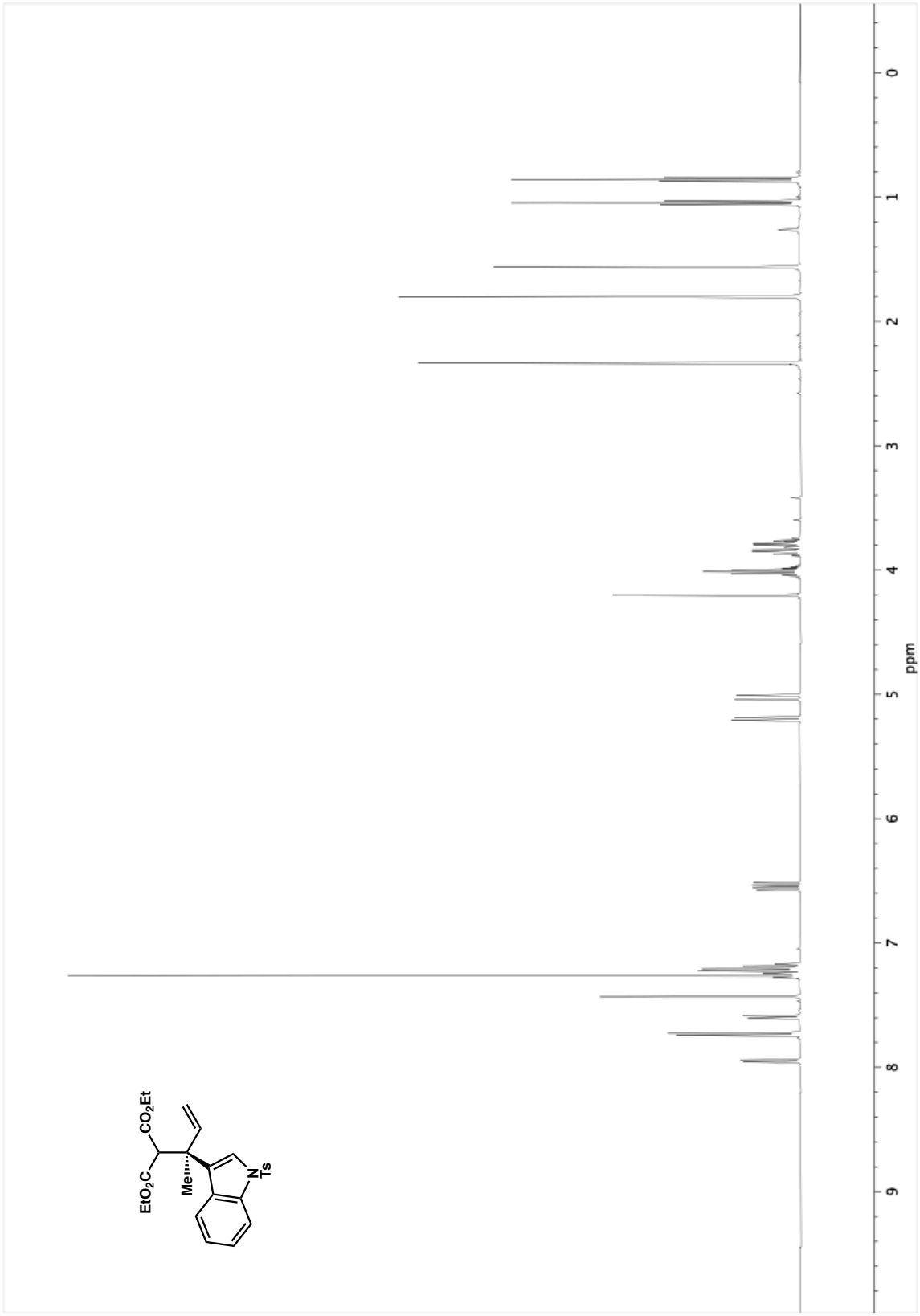


Figure A1.98. *^{1}H NMR (500 MHz, $CDCl_3$) of compound* ***11b.***

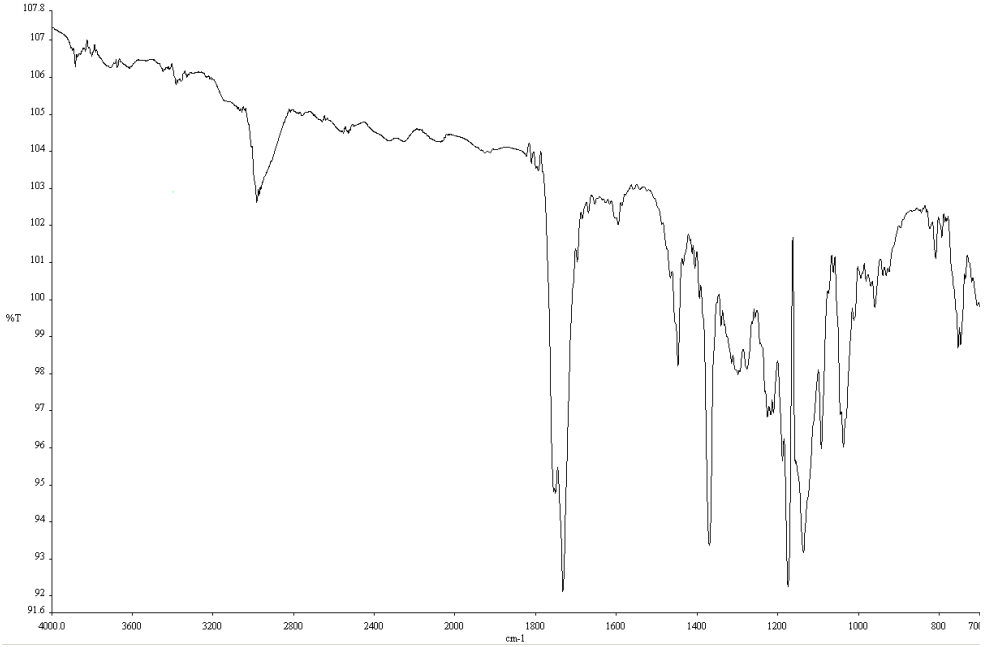


Figure A1.99. *Infrared spectrum (Thin Film, NaCl) of compound* ***11b.***

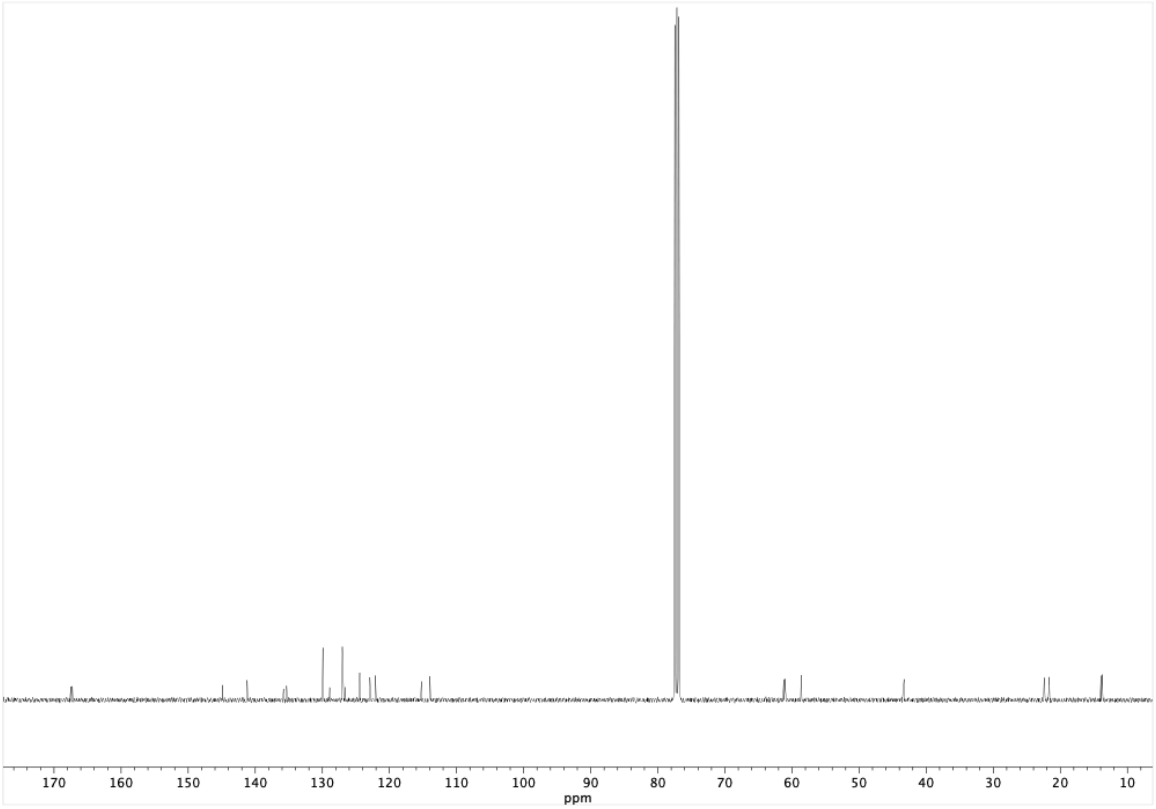


Figure A1.100. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***11b.***

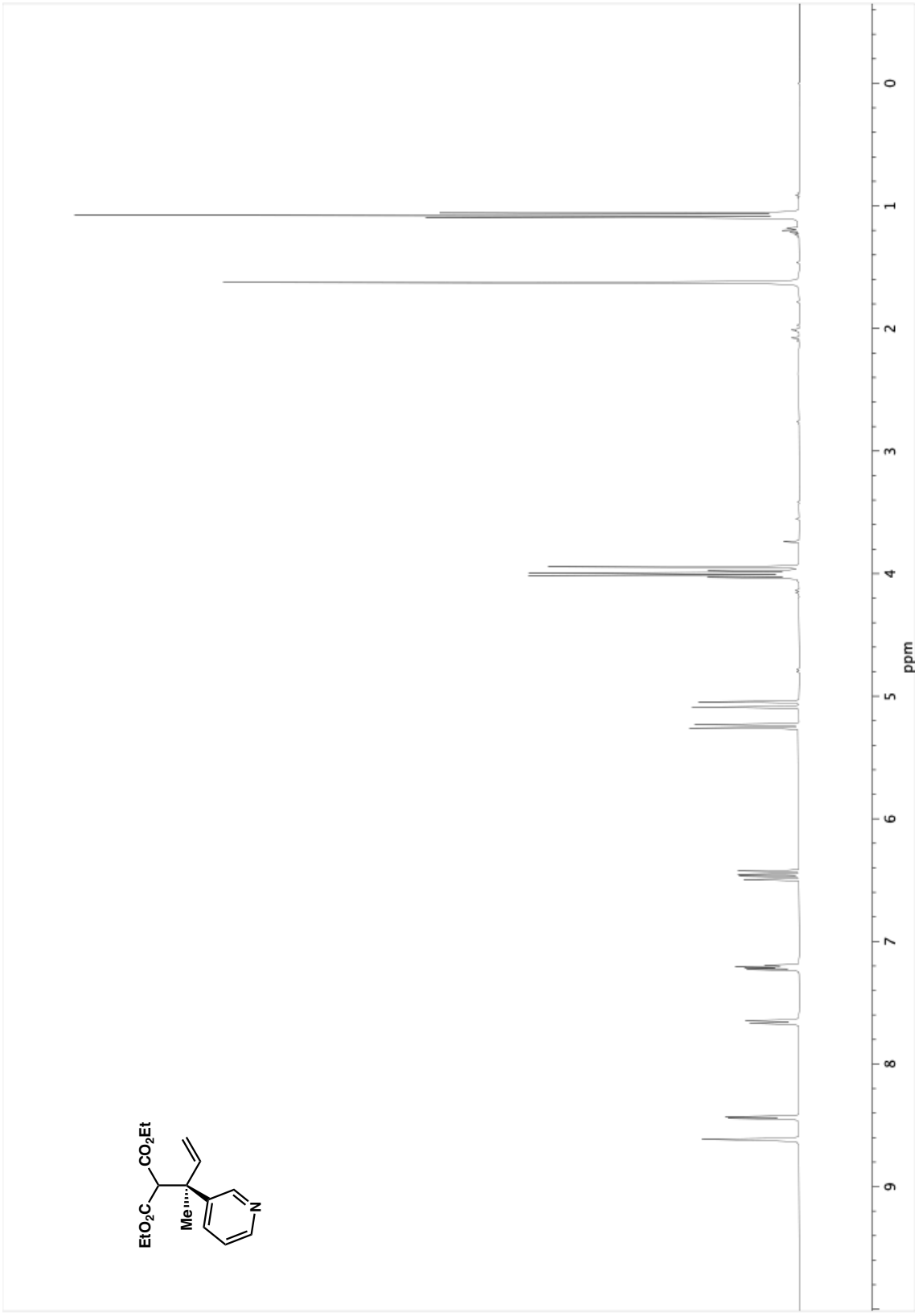


Figure A1.101. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***11c.***

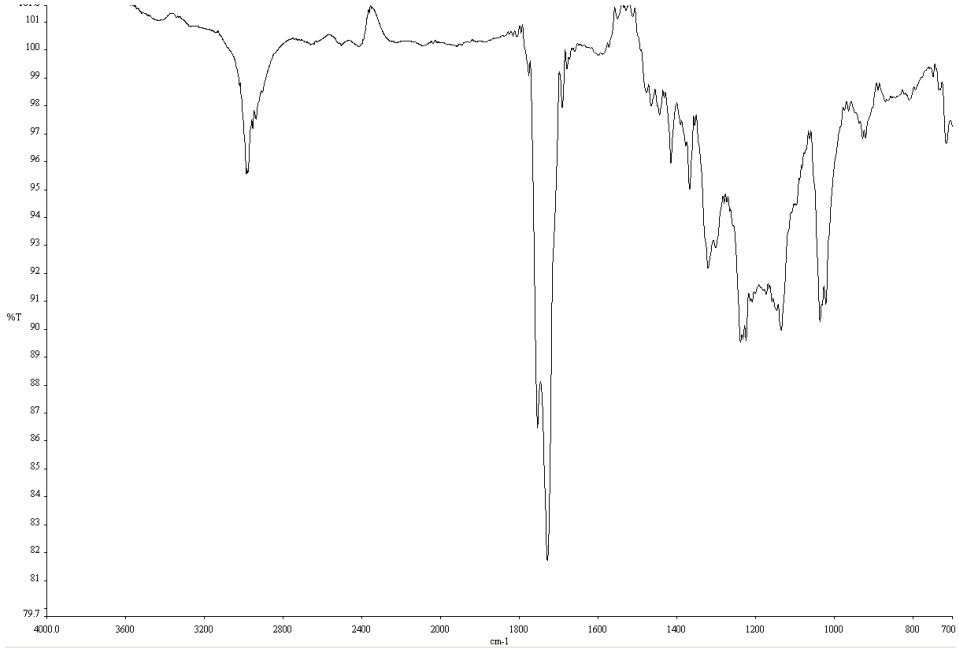


Figure A1.102. *Infrared spectrum (Thin Film, NaCl) of compound* ***11c.***

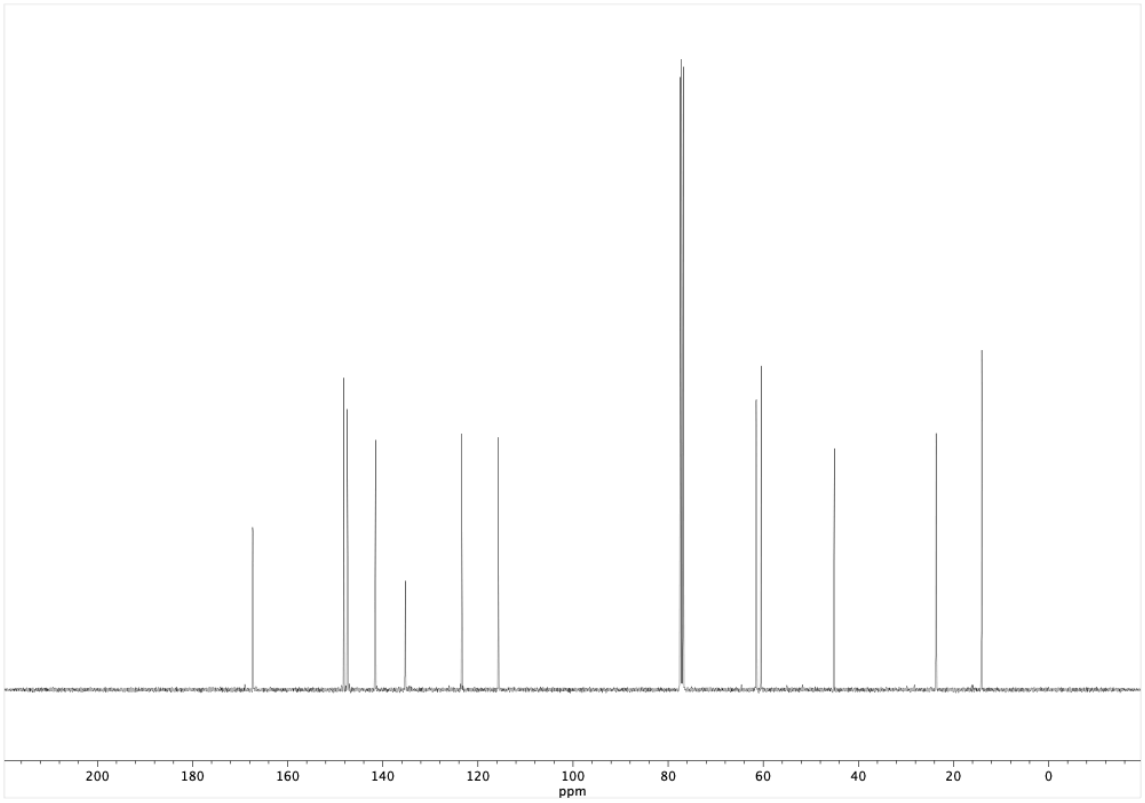


Figure A1.103. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***11c.***

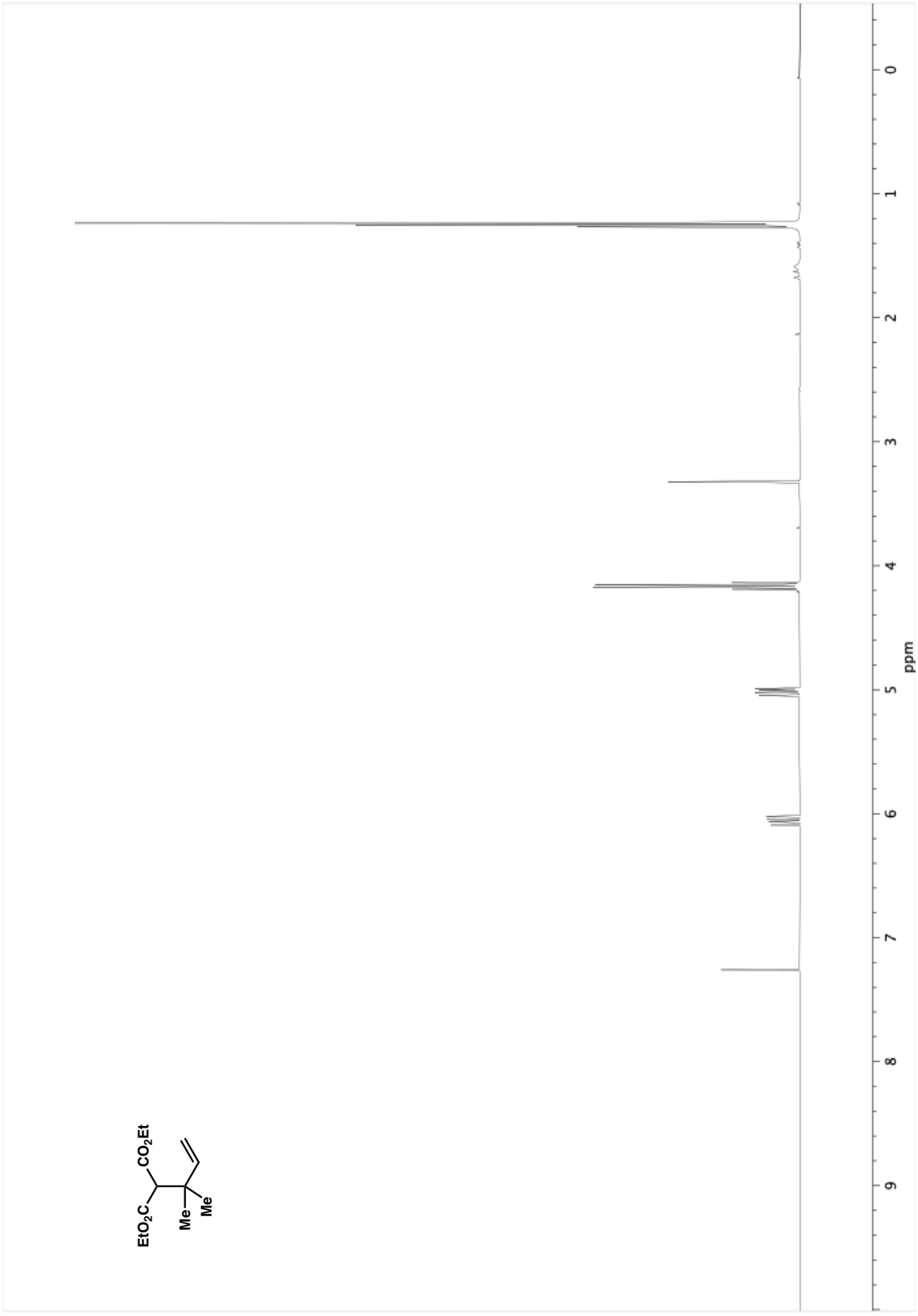


Figure A1.104. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***14a.***

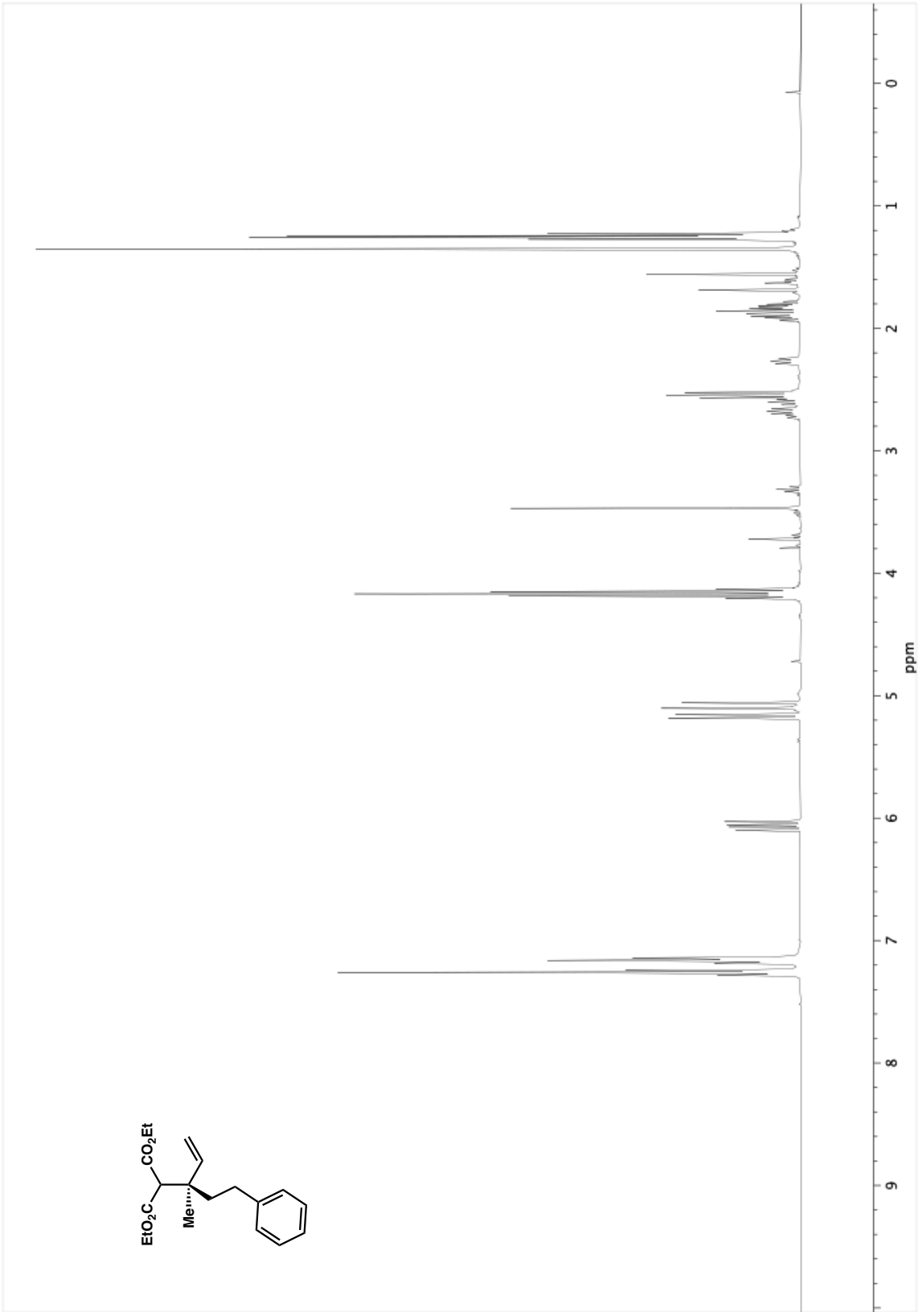


Figure A1.105. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***14b.***

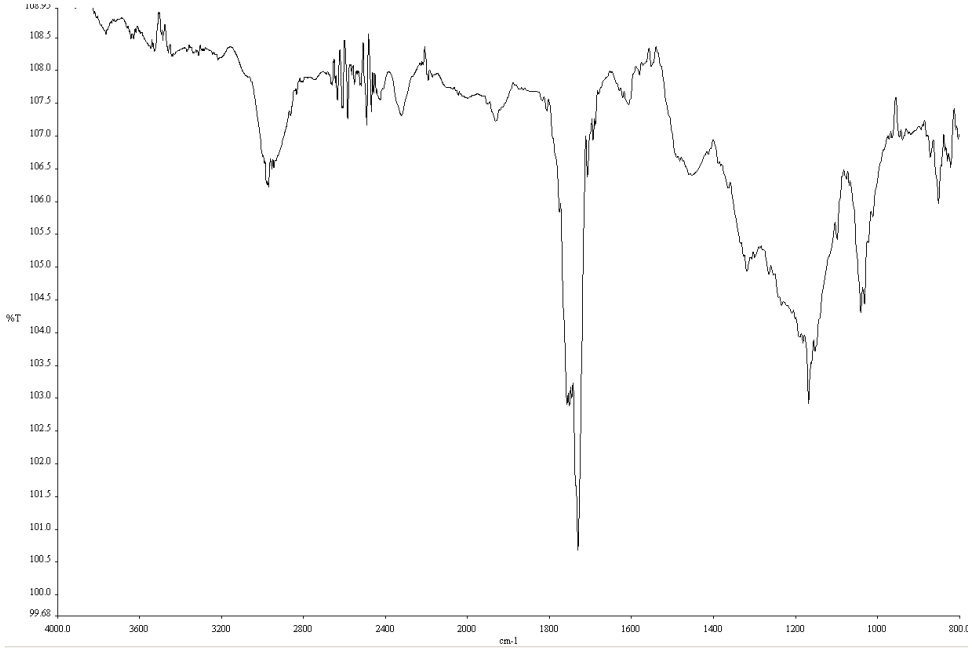


Figure A1.106. *Infrared spectrum (Thin Film, NaCl) of compound* ***14b.***

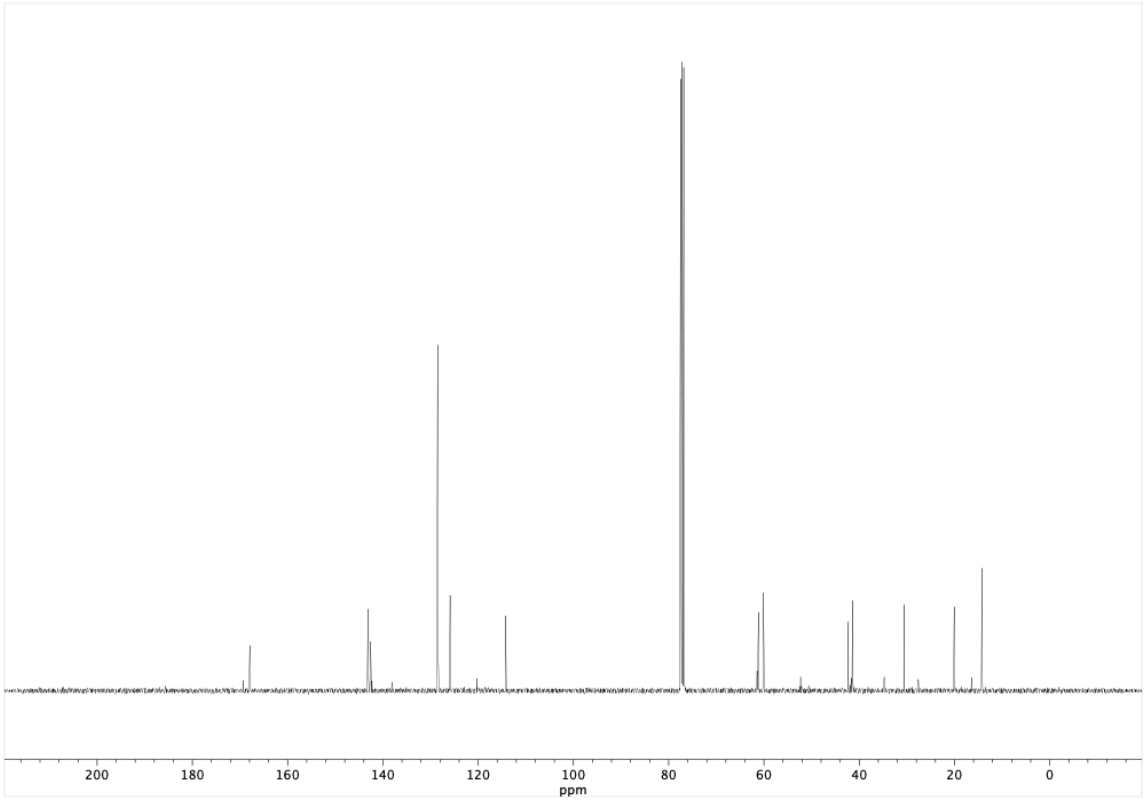


Figure A1.107. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***14b.***

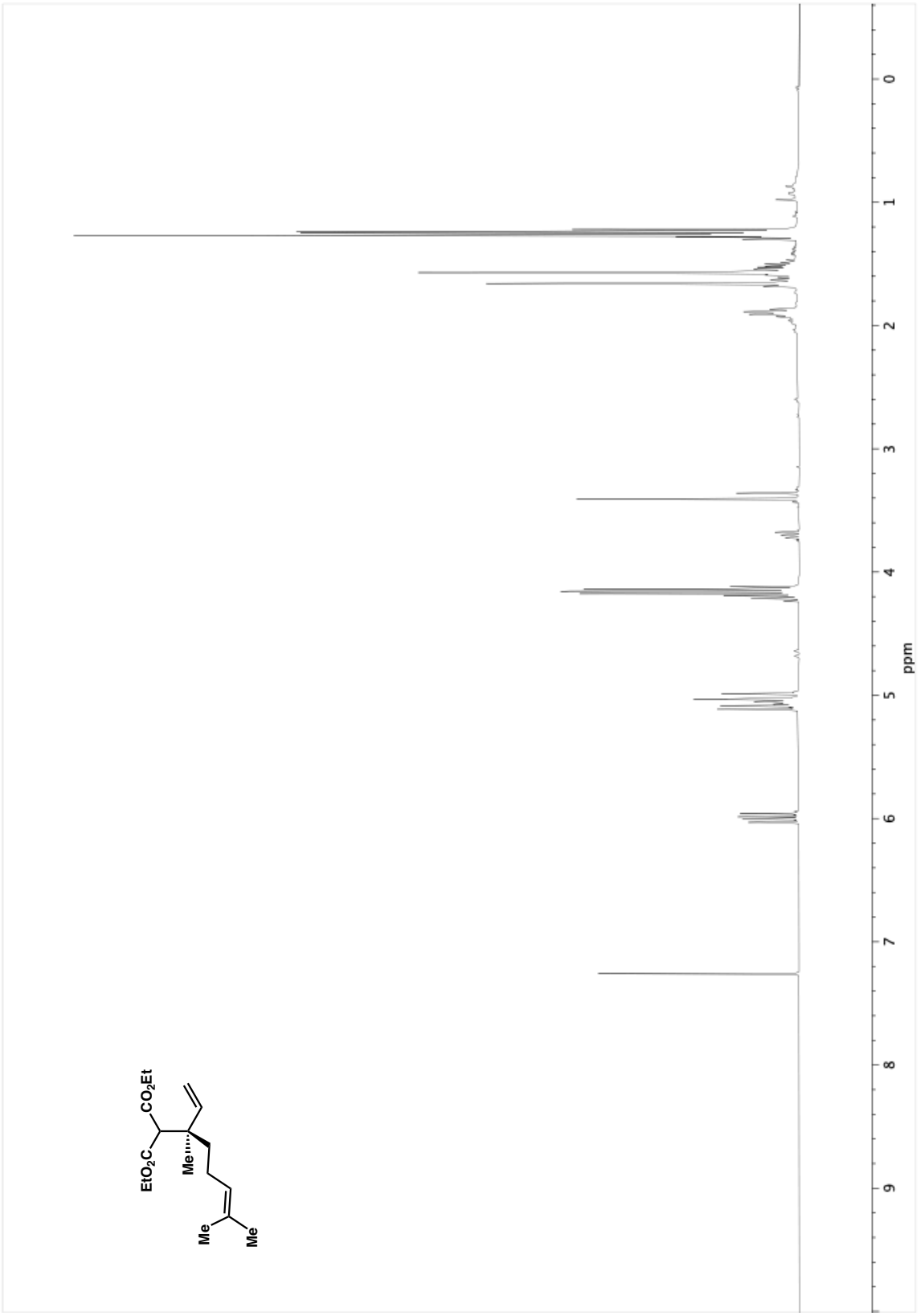


Figure A1.108. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***14c.***

Figure A1.109. *Infrared spectrum (Thin Film, NaCl) of compound* ***14c.***

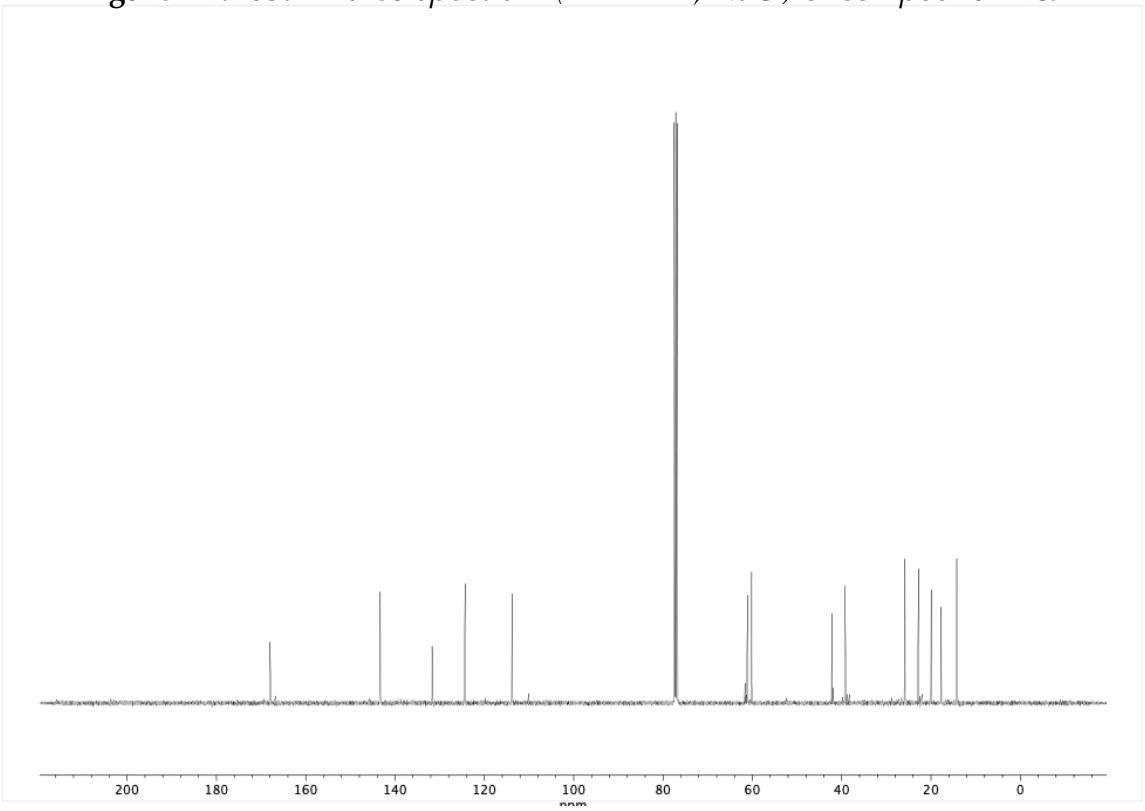


Figure A1.110. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***14c.***

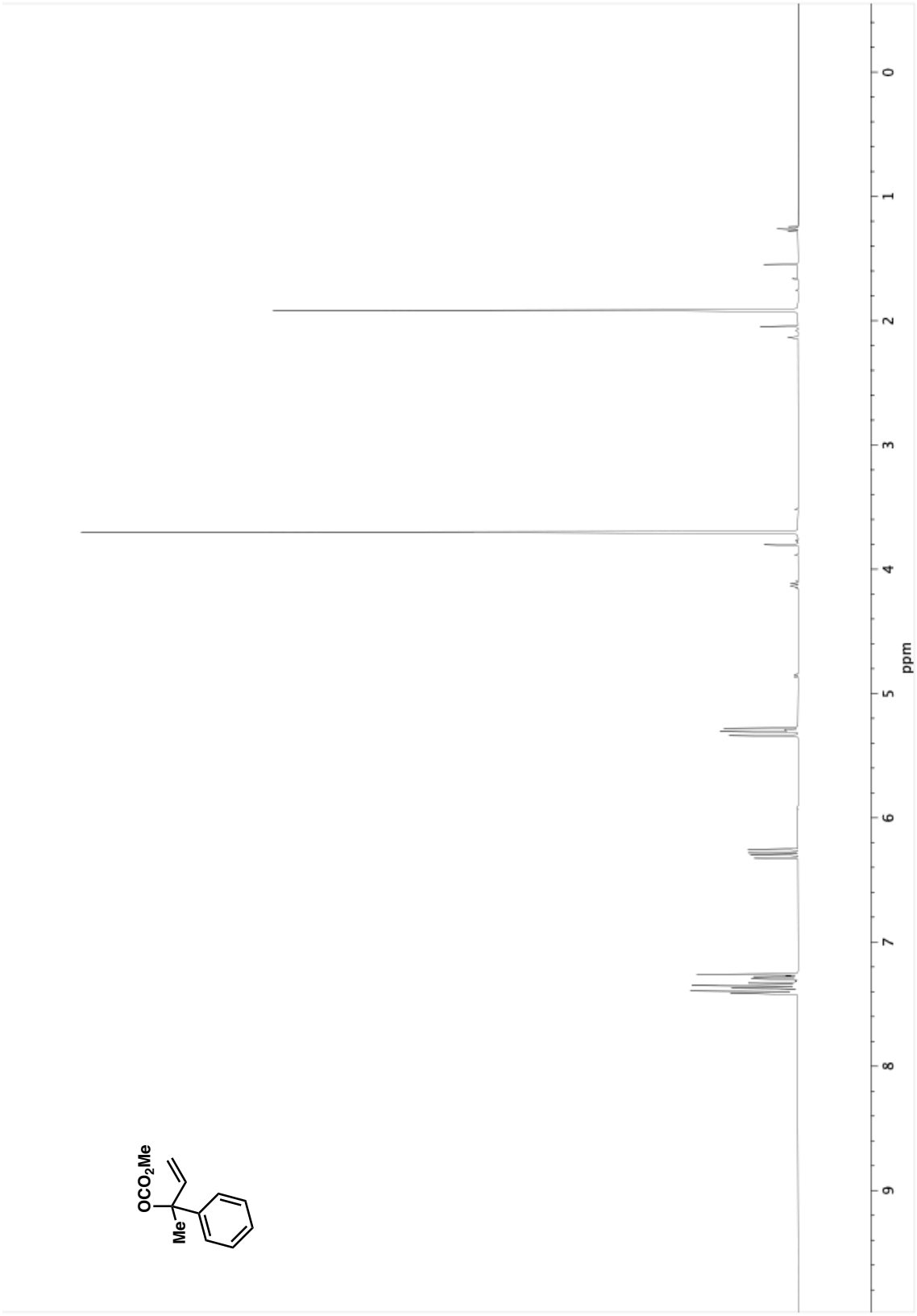


Figure A1.111. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***17a.***

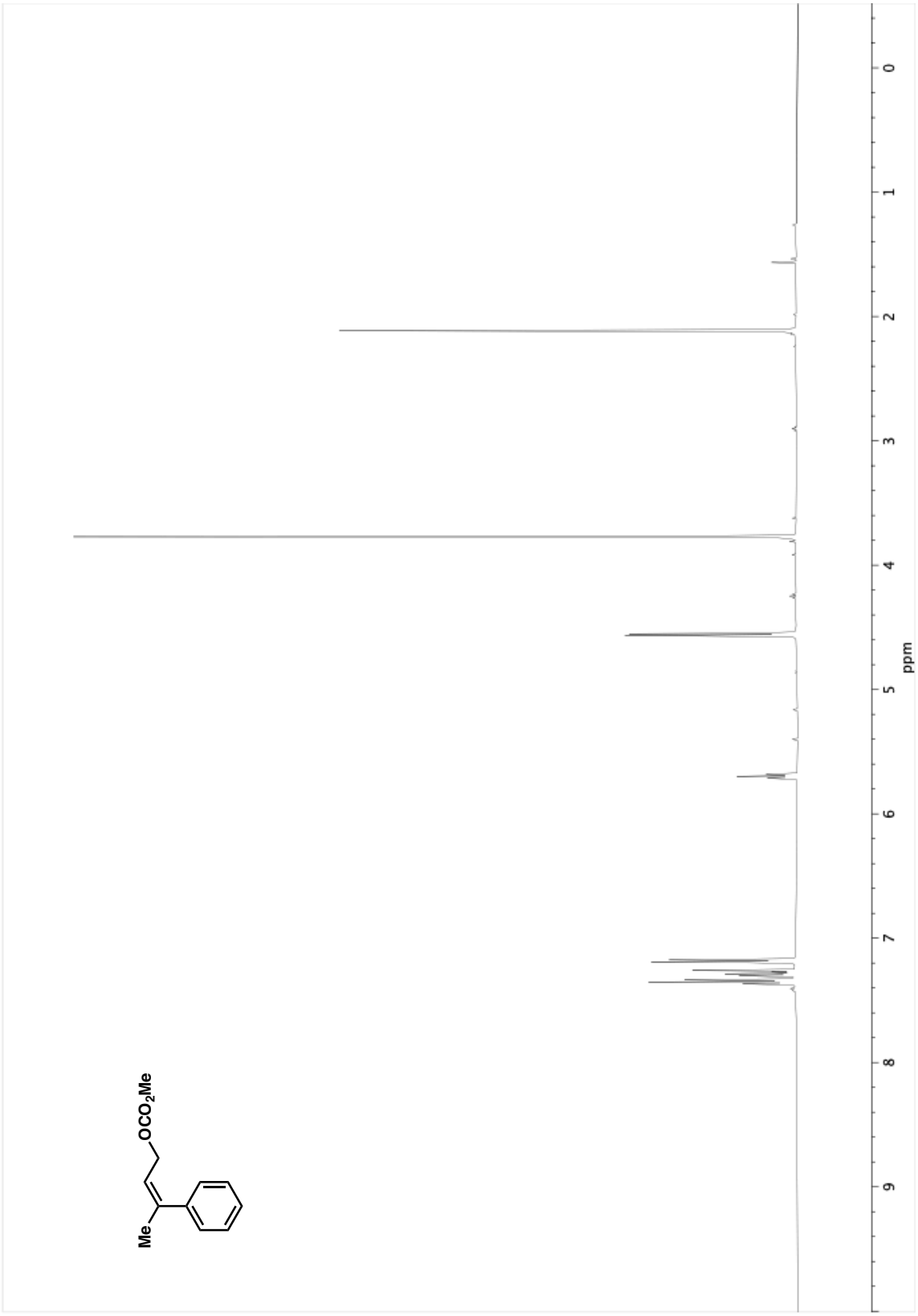


Figure A1.112. *^1H NMR (500 MHz, $CDCl_3$) of compound* ***17b.***

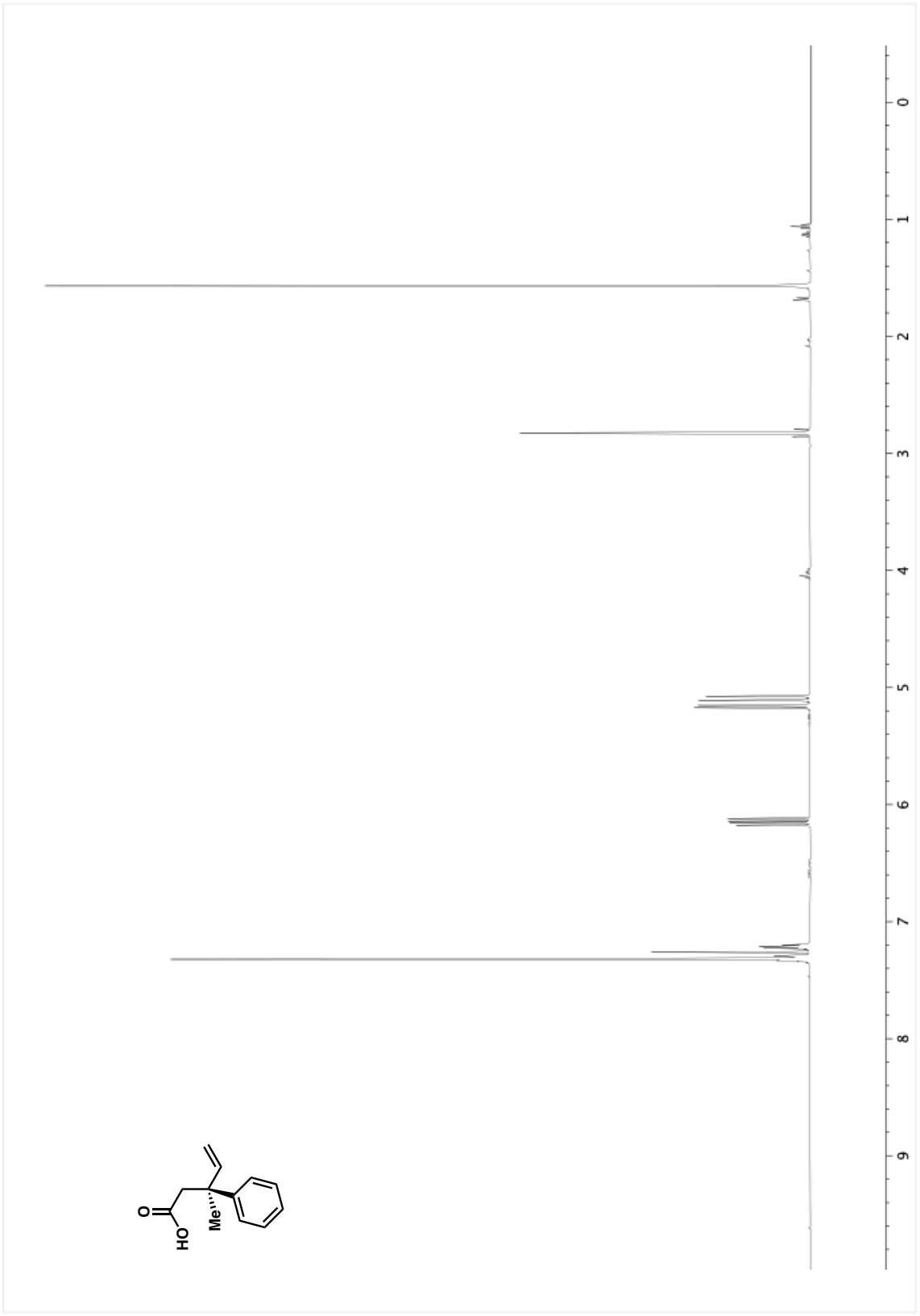


Figure A1.113. *^1H NMR (500 MHz, $CDCl_3$) of compound* ***18.***

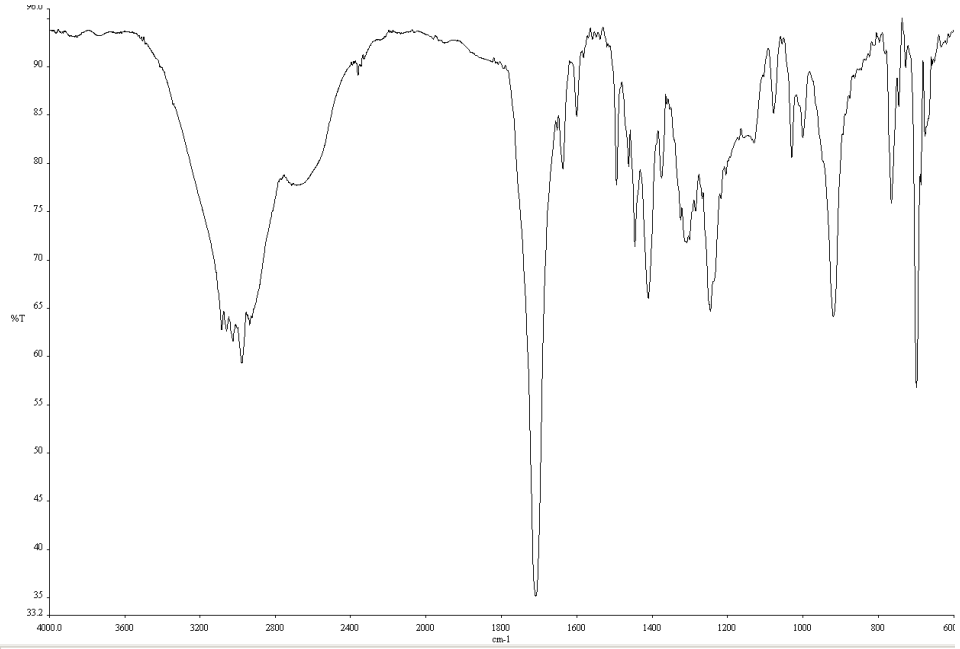


Figure A1.114. *Infrared spectrum (Thin Film, NaCl) of compound* ***18.***

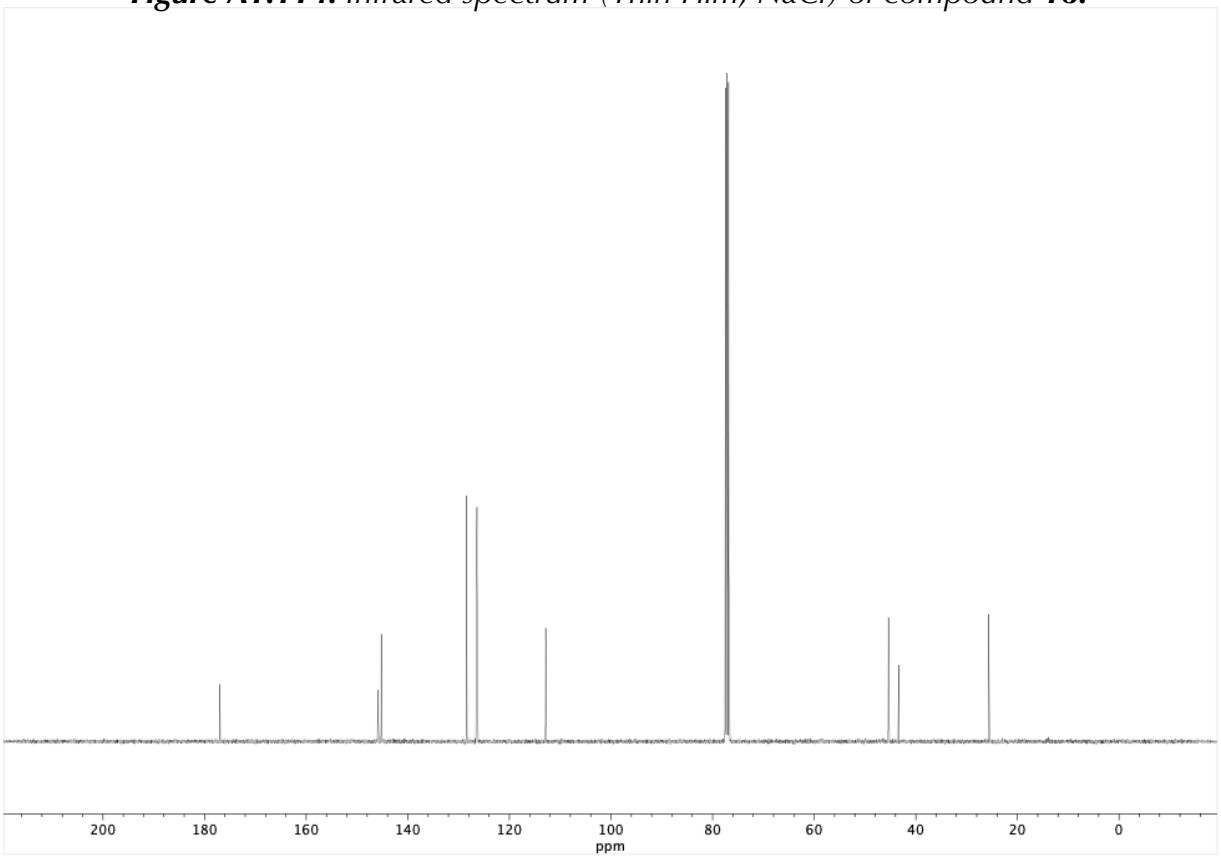


Figure A1.115. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***18.***

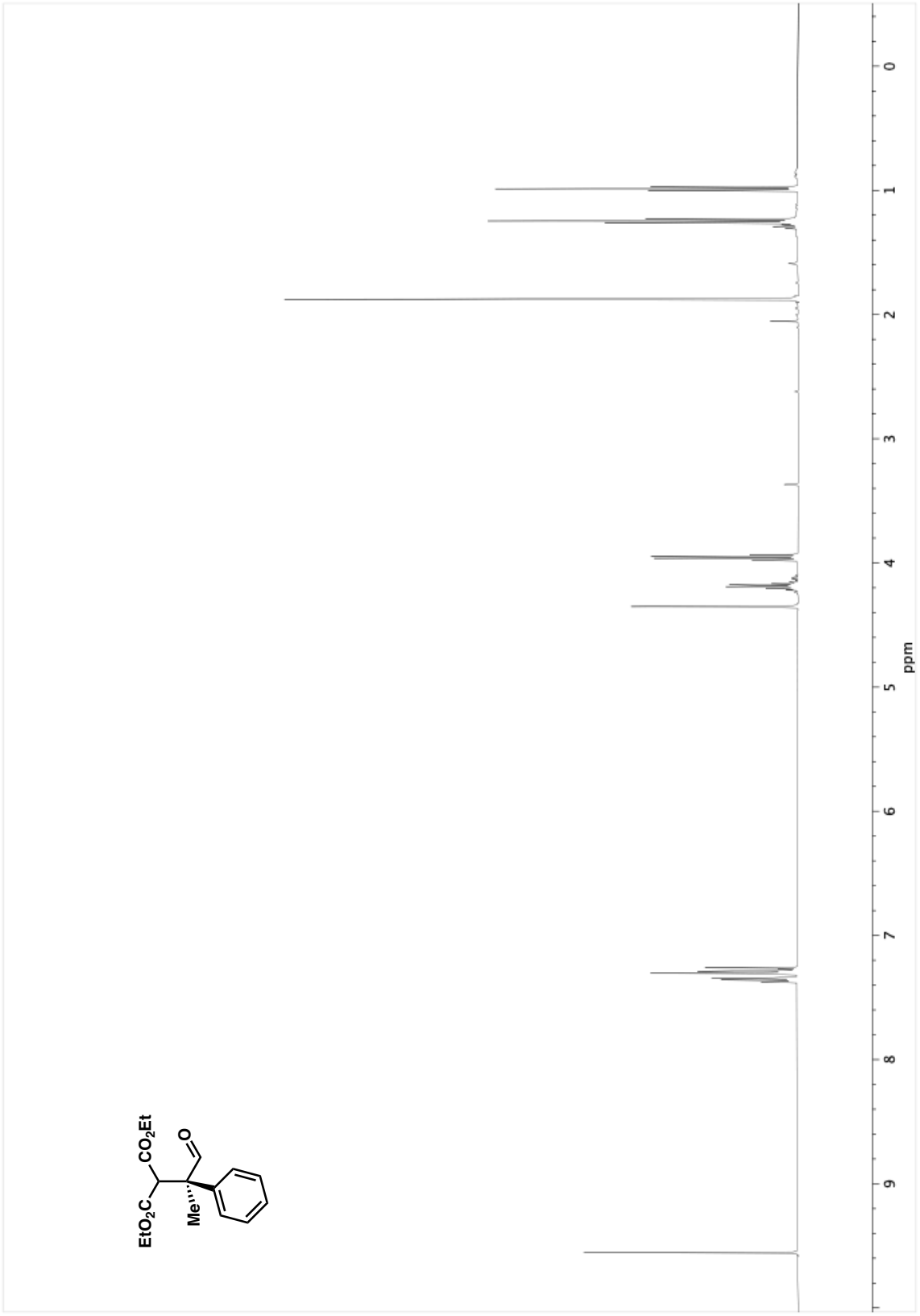


Figure A1.116. *^{1}H NMR (500 MHz, $CDCl_3$) of compound* ***19.***

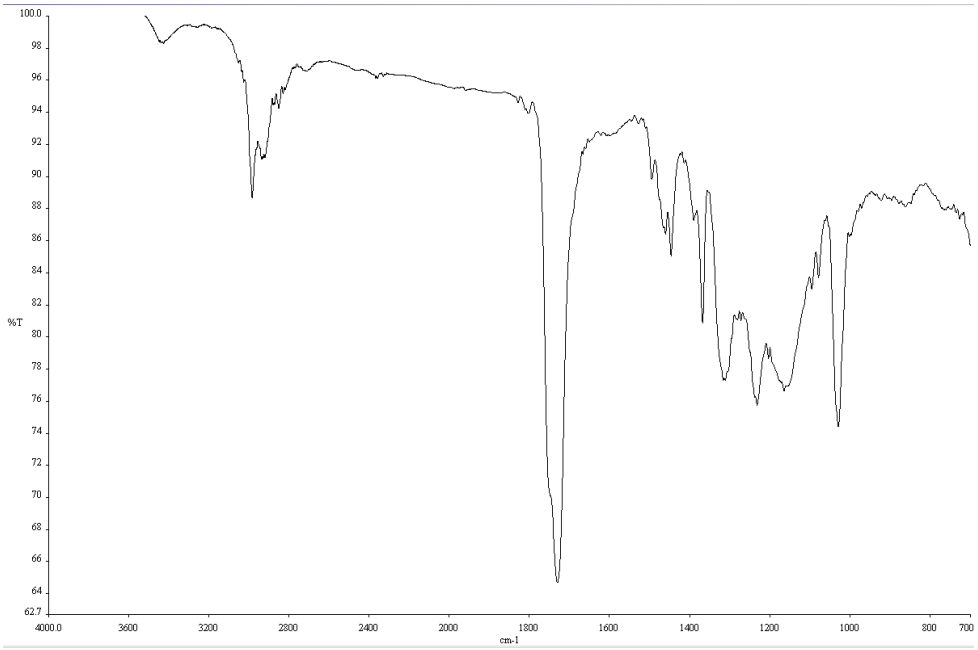


Figure A1.117. *Infrared spectrum (Thin Film, NaCl) of compound* ***19.***

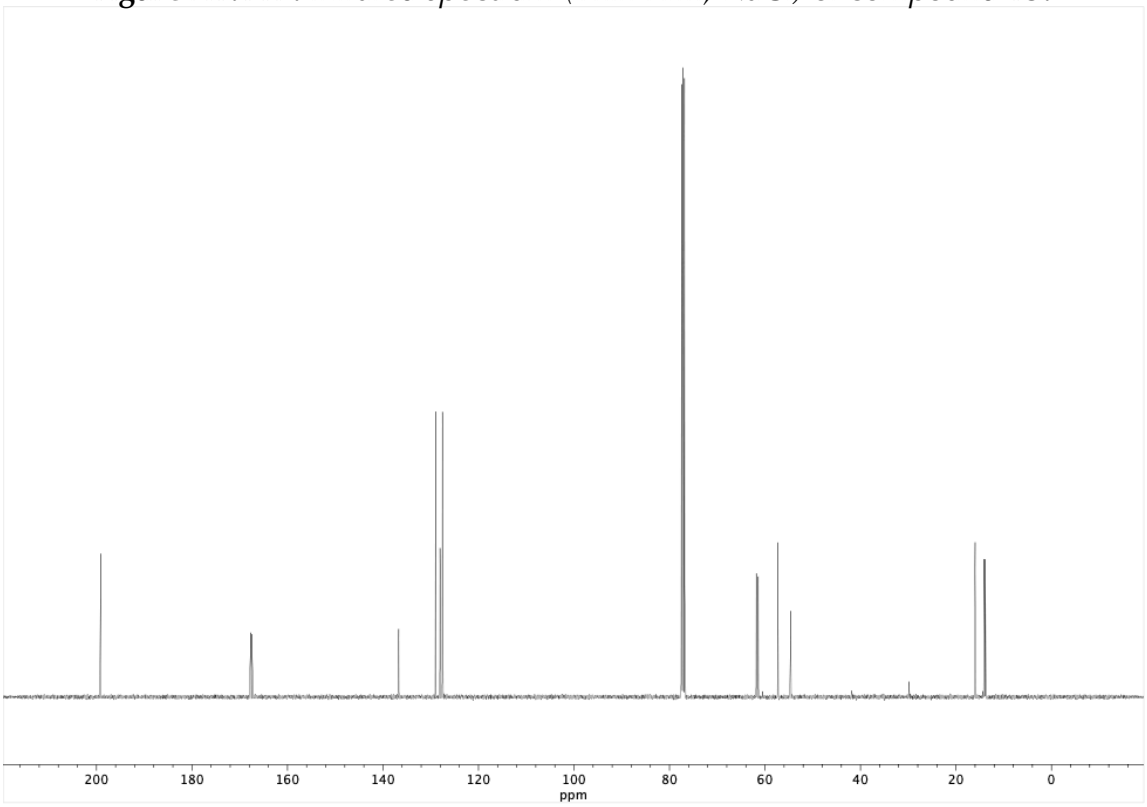


Figure A1.118. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***19.***

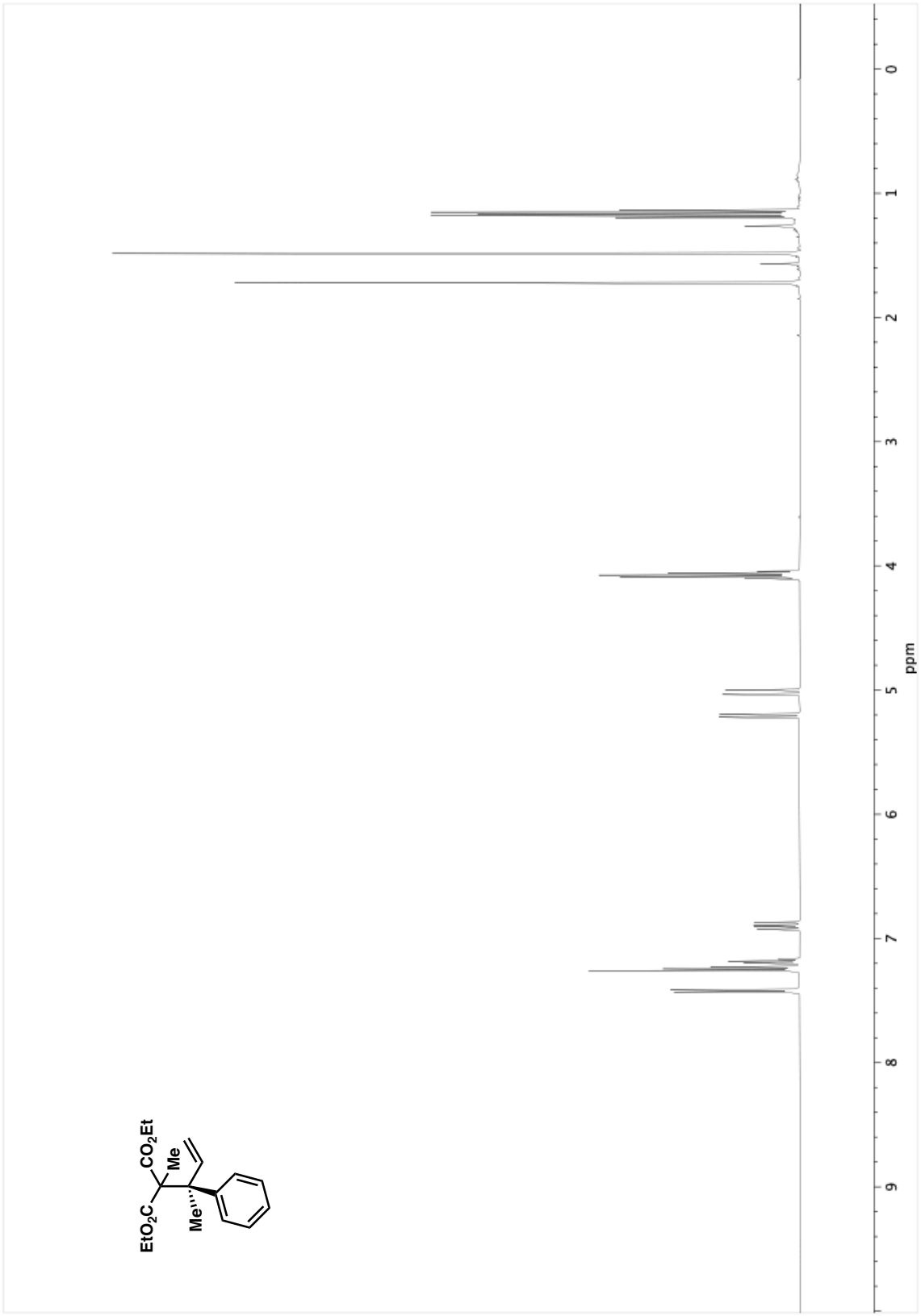


Figure A1.119. *^{1}H NMR (500 MHz, $CDCl_3$) of compound* ***20.***

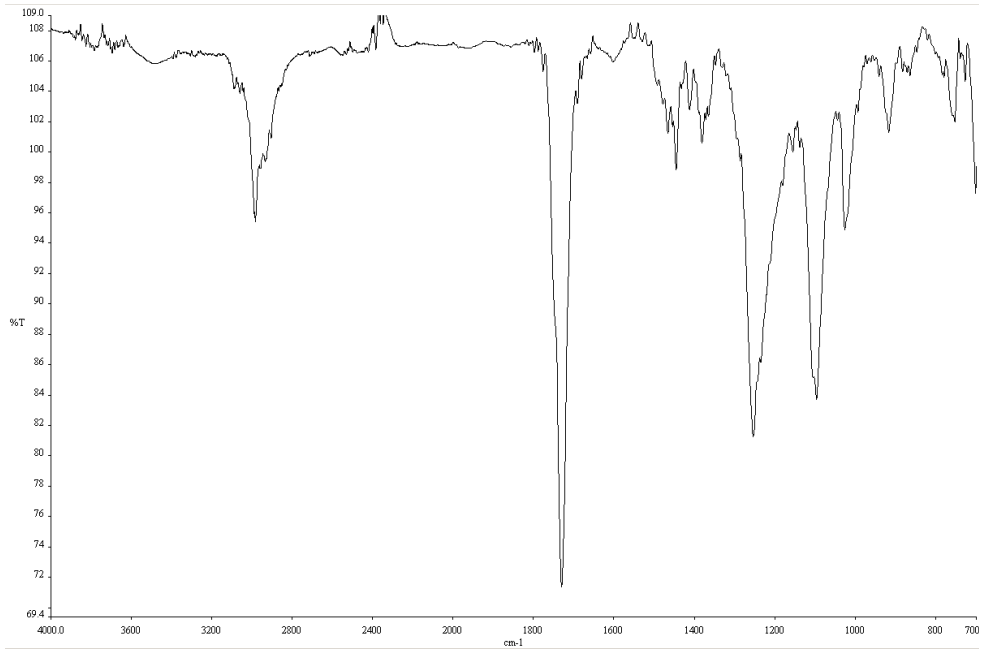


Figure A1.120. *Infrared spectrum (Thin Film, NaCl) of compound* ***20.***

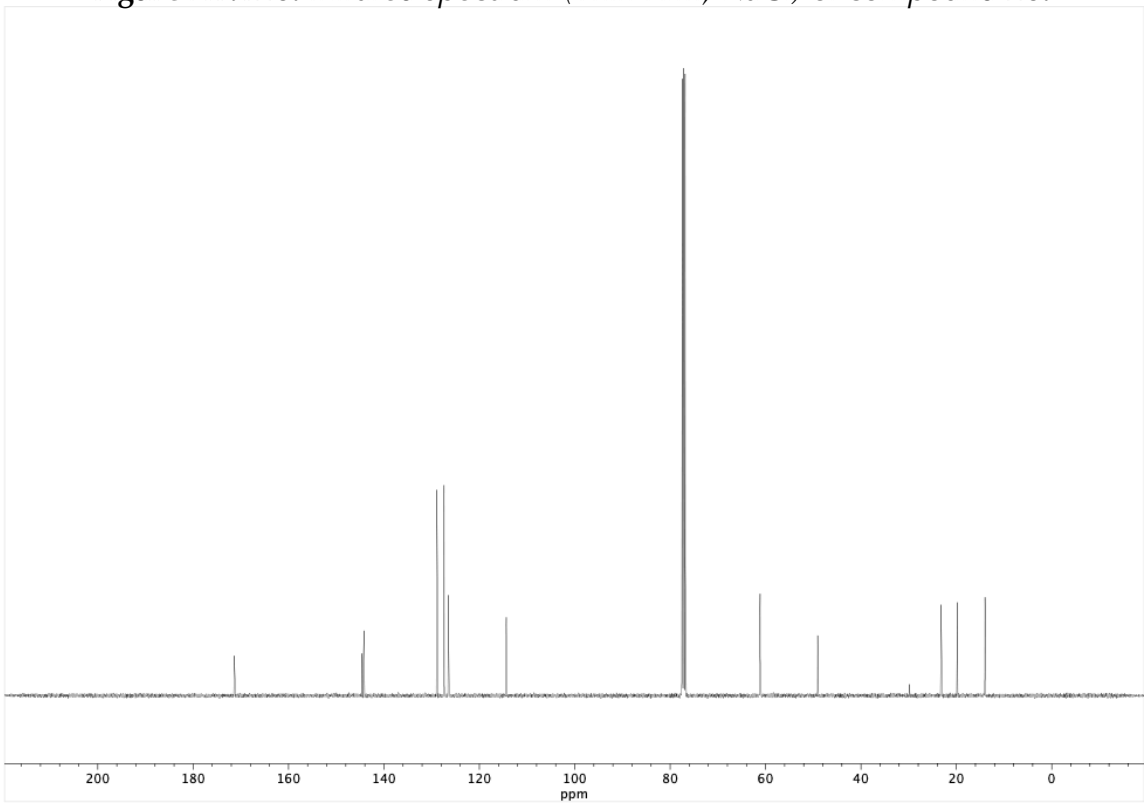


Figure A1.121. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***20.***

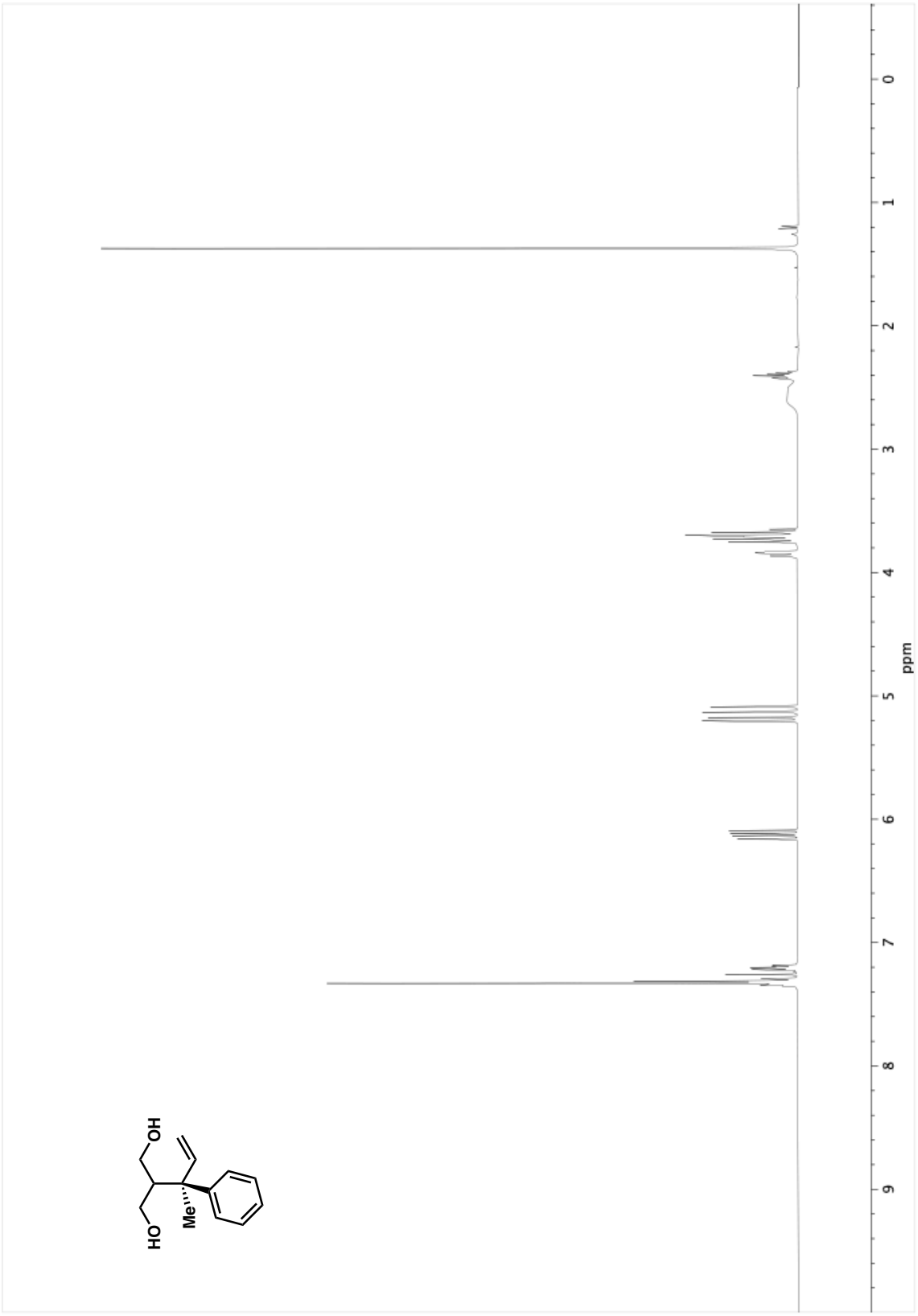


Figure A1.122. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***21.***

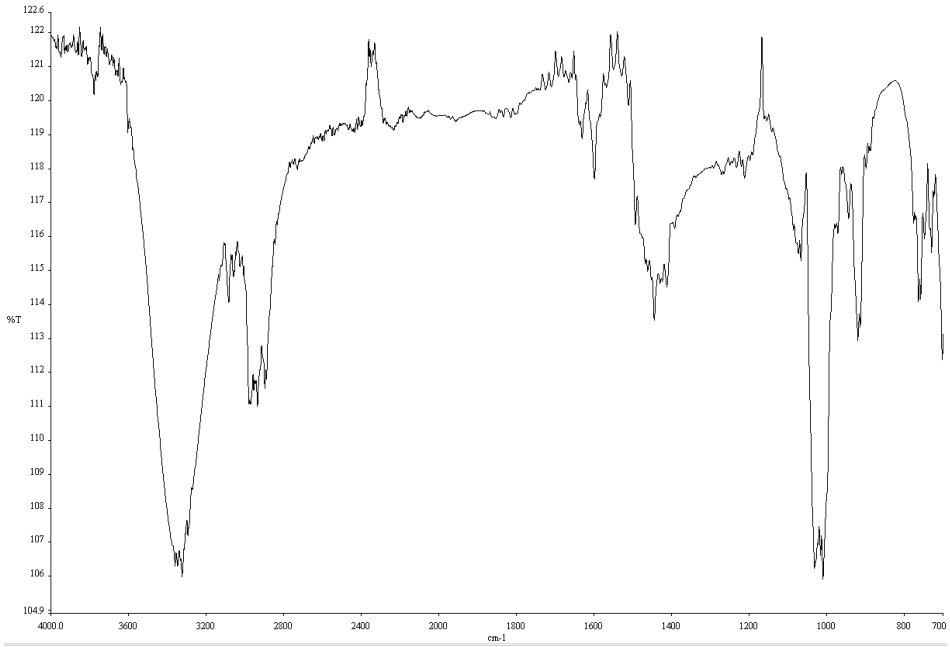


Figure A1.123. *Infrared spectrum (Thin Film, NaCl) of compound* ***21.***

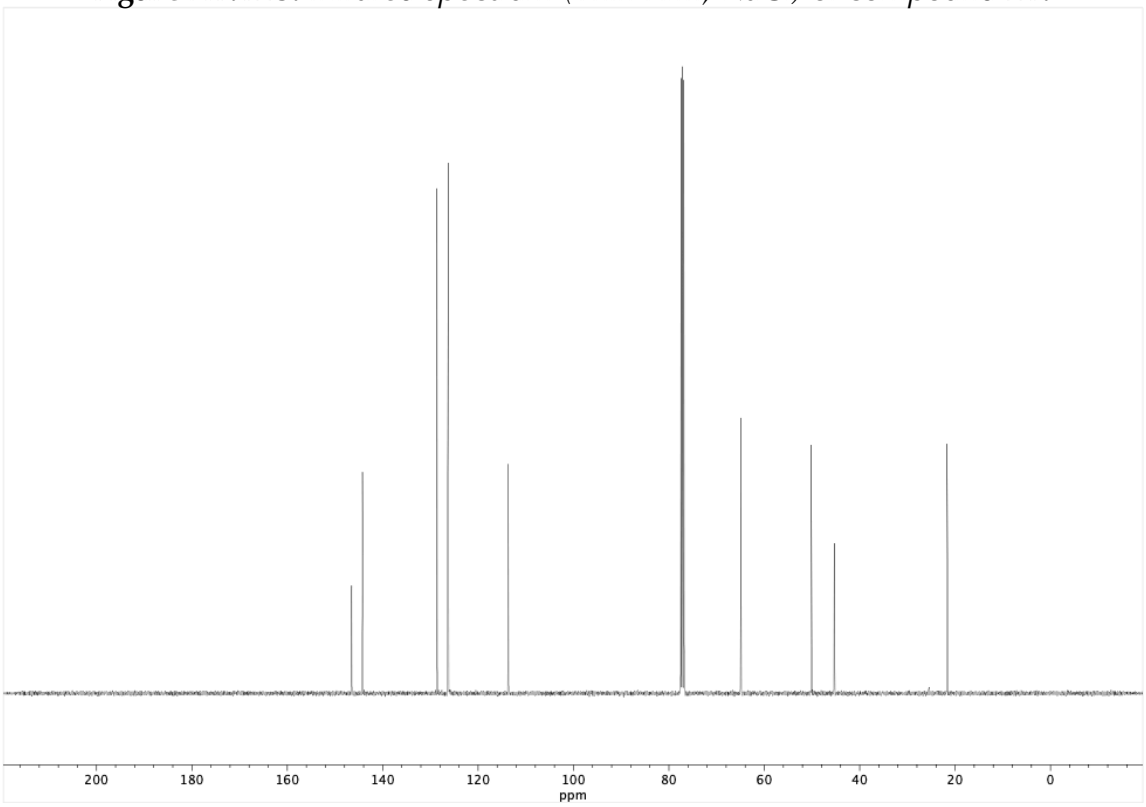


Figure A1.124. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***21.***

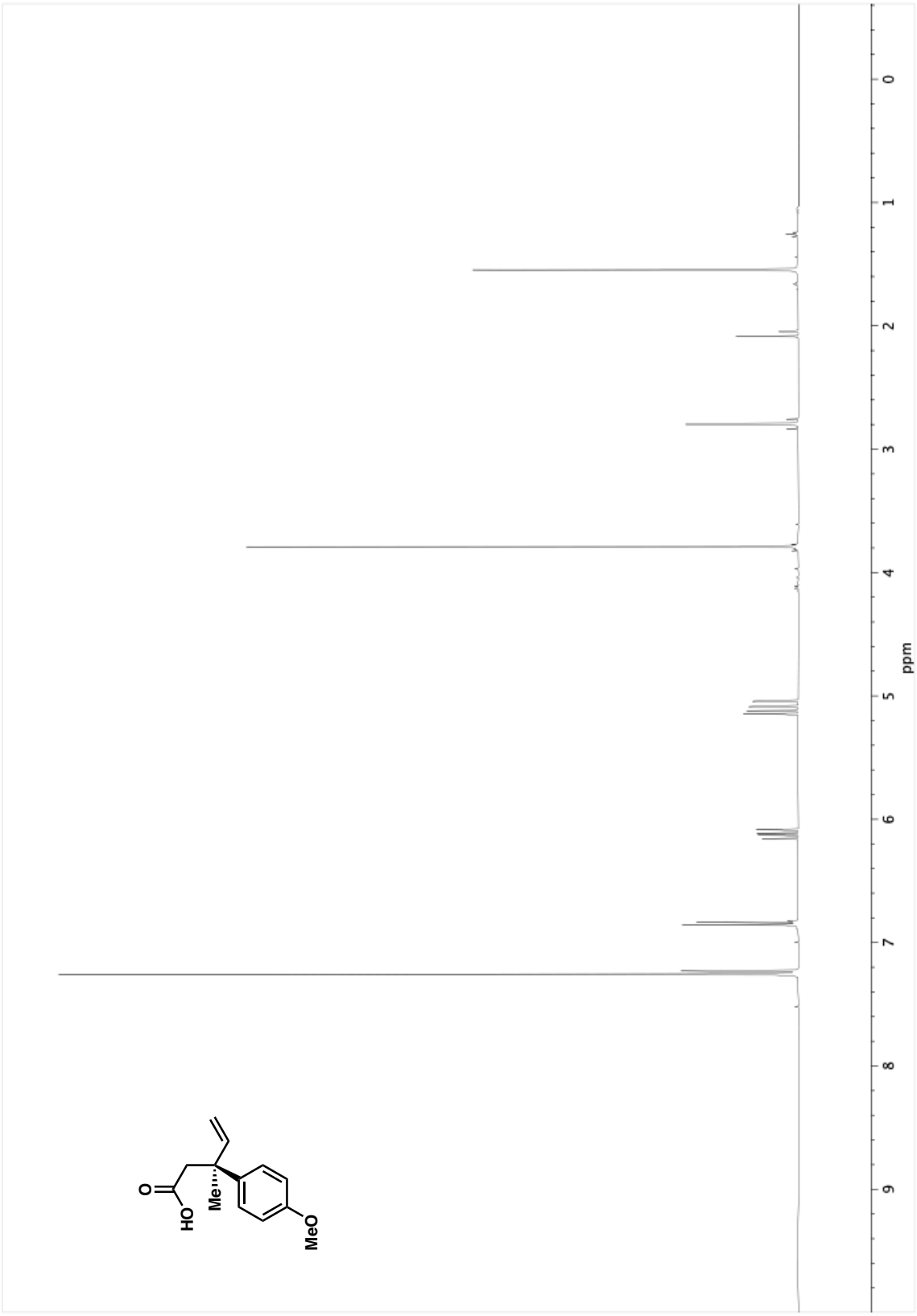


Figure A1.125. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***22a.***

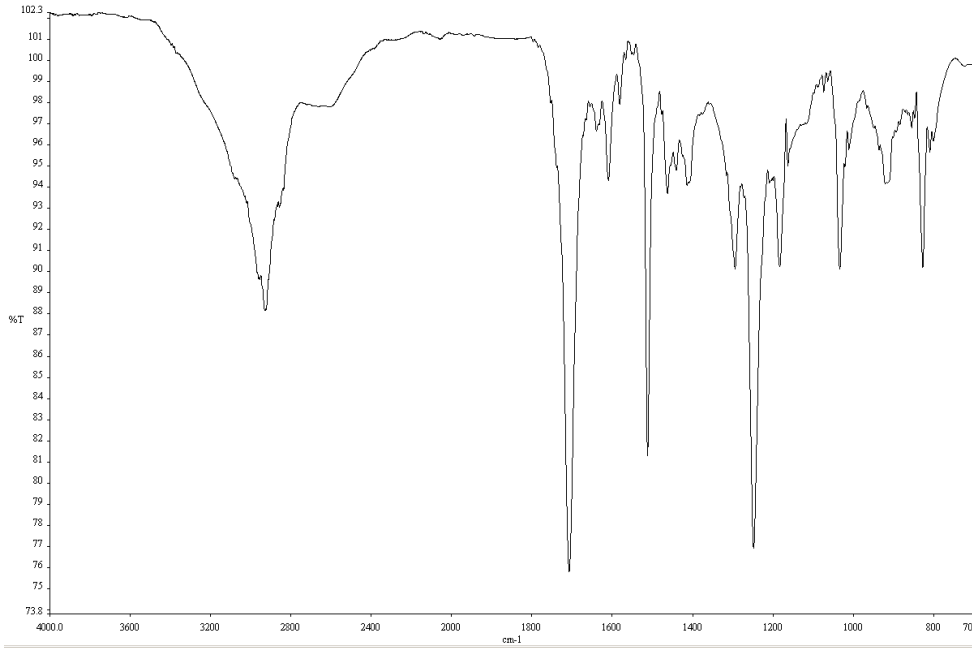


Figure A1.126. *Infrared spectrum (Thin Film, NaCl) of compound* ***22a.***

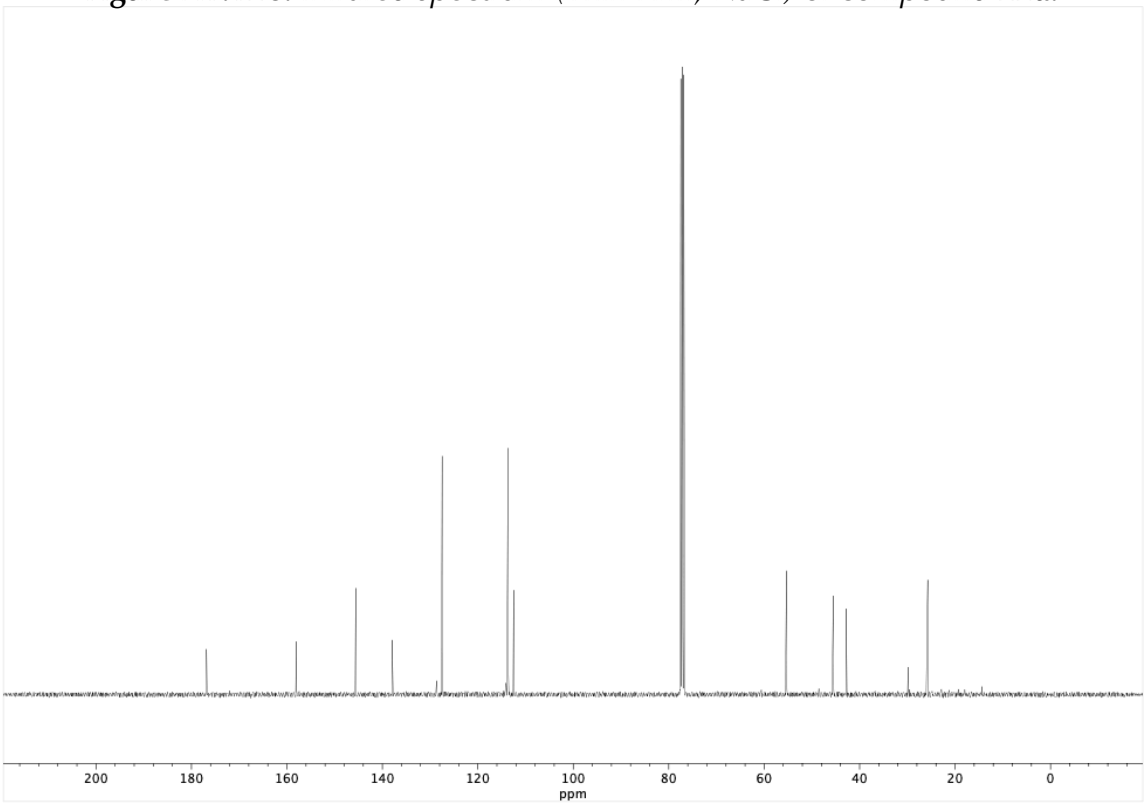


Figure A1.127. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***22a.***

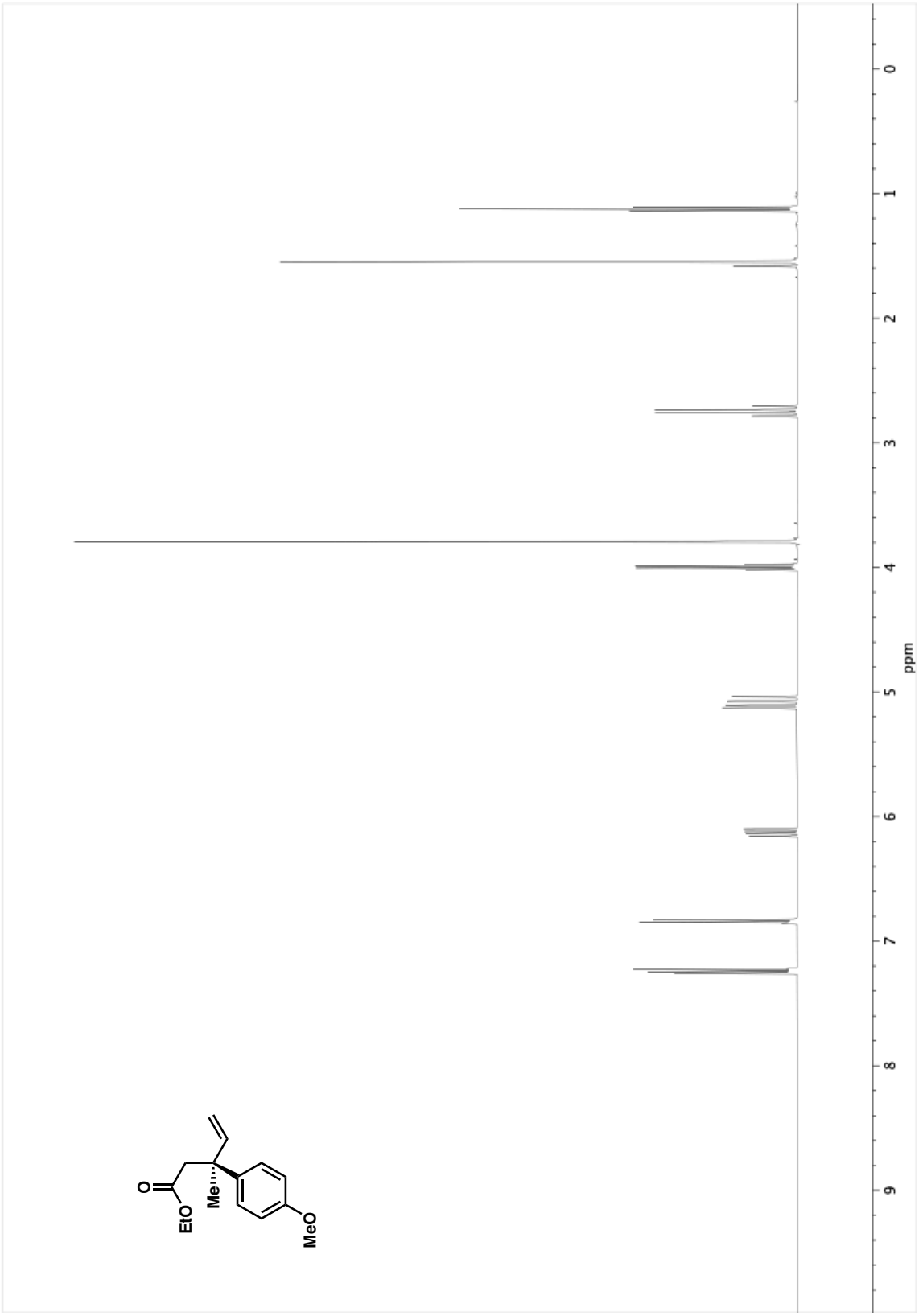


Figure A1.128. *^1H NMR (500 MHz, $CDCl_3$) of compound* ***22b.***

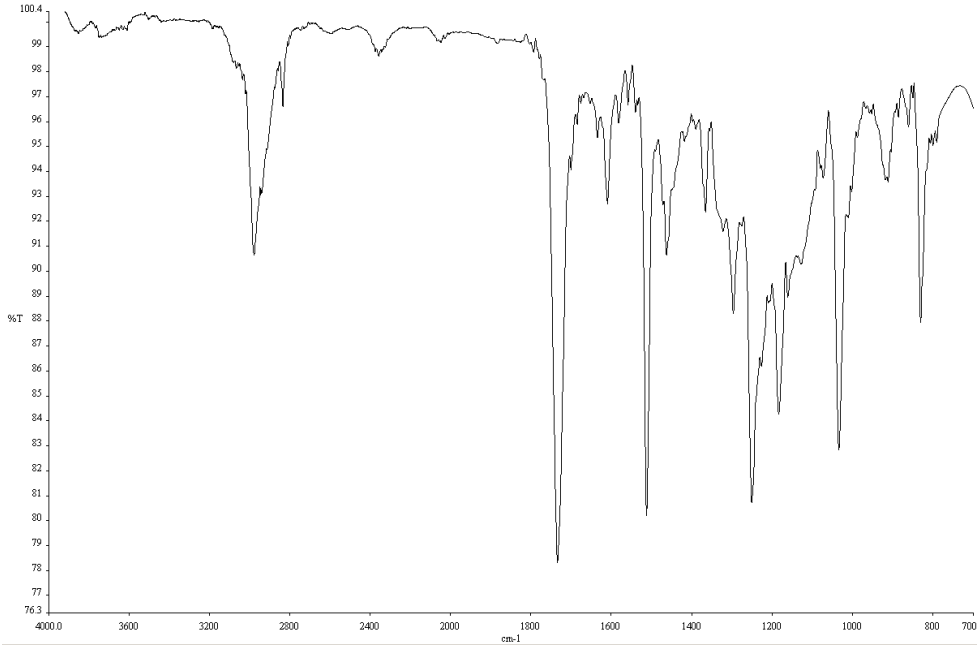


Figure A1.129. *Infrared spectrum (Thin Film, NaCl) of compound* ***22b.***

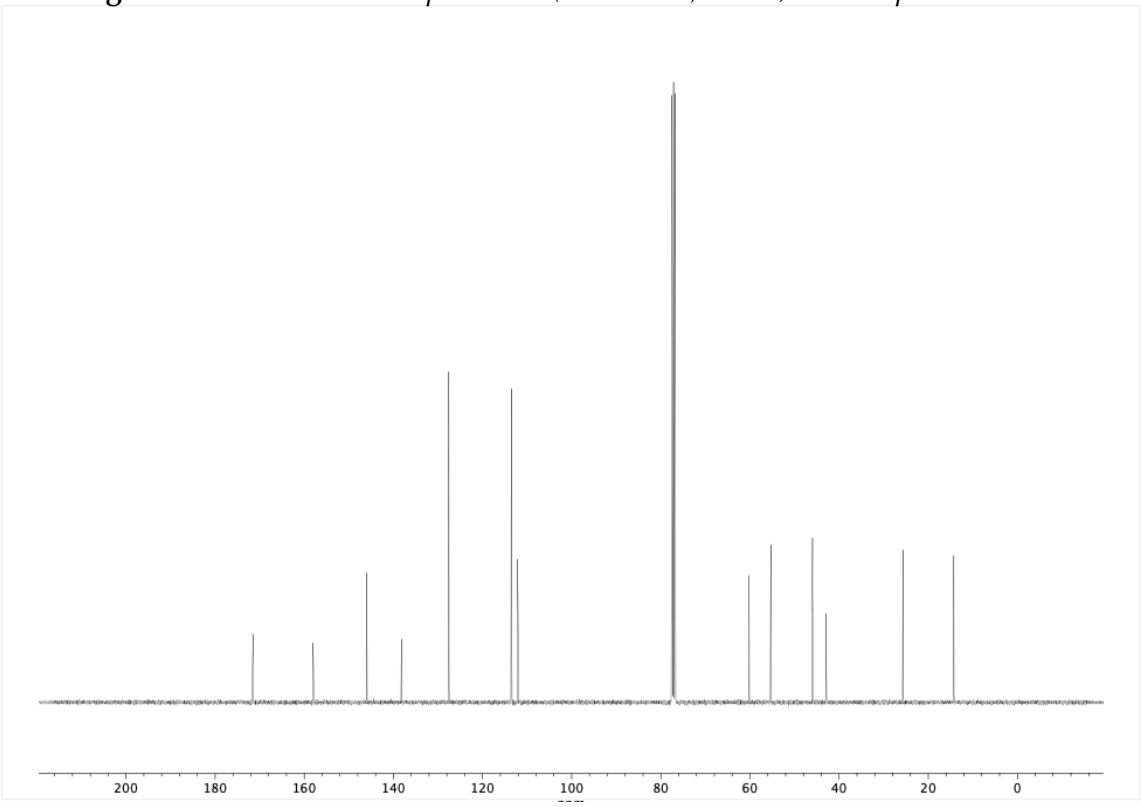


Figure A1.130. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***22b.***

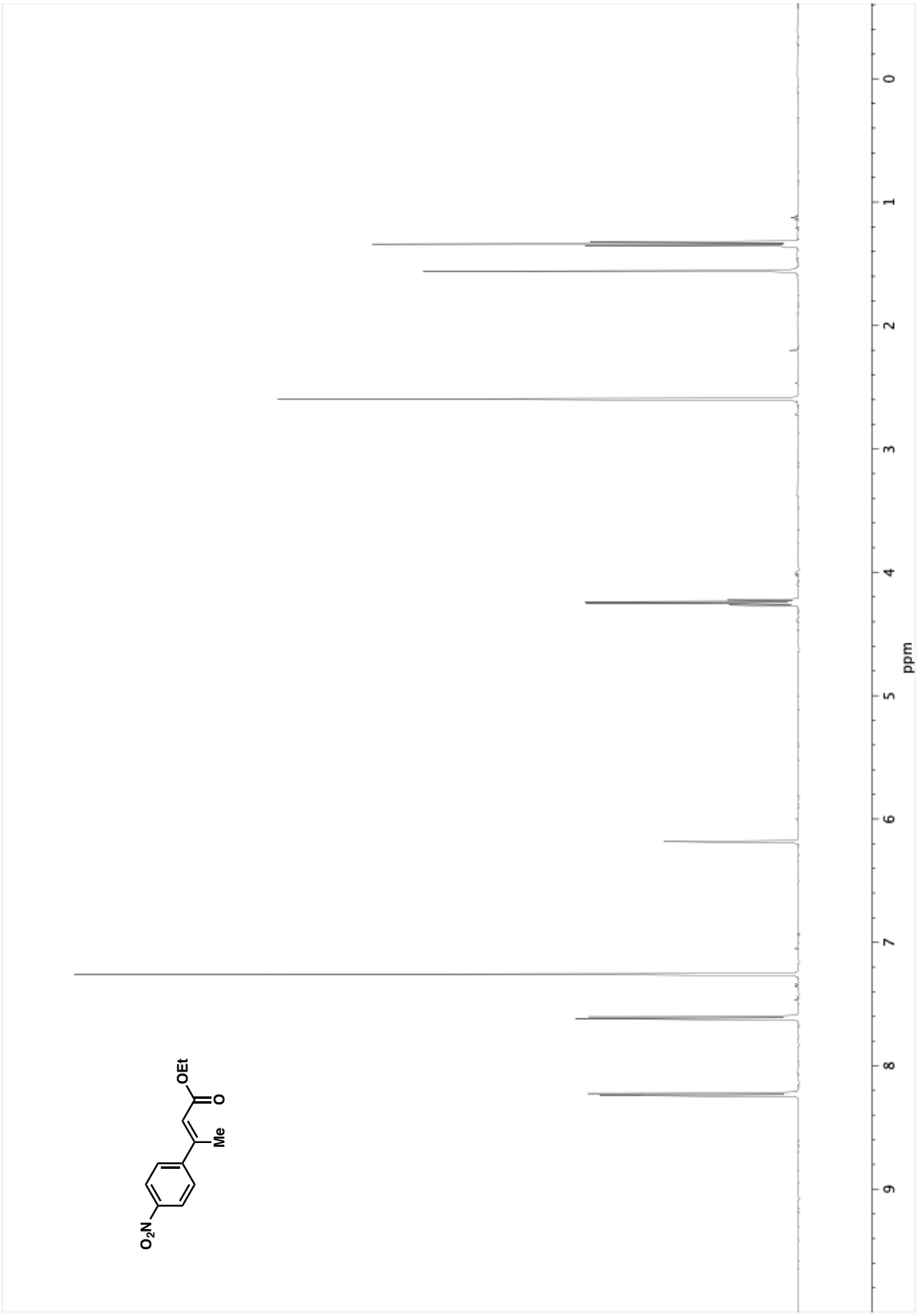


Figure A1.131. *^1H NMR (500 MHz, $CDCl_3$) of compound* ***2da.***

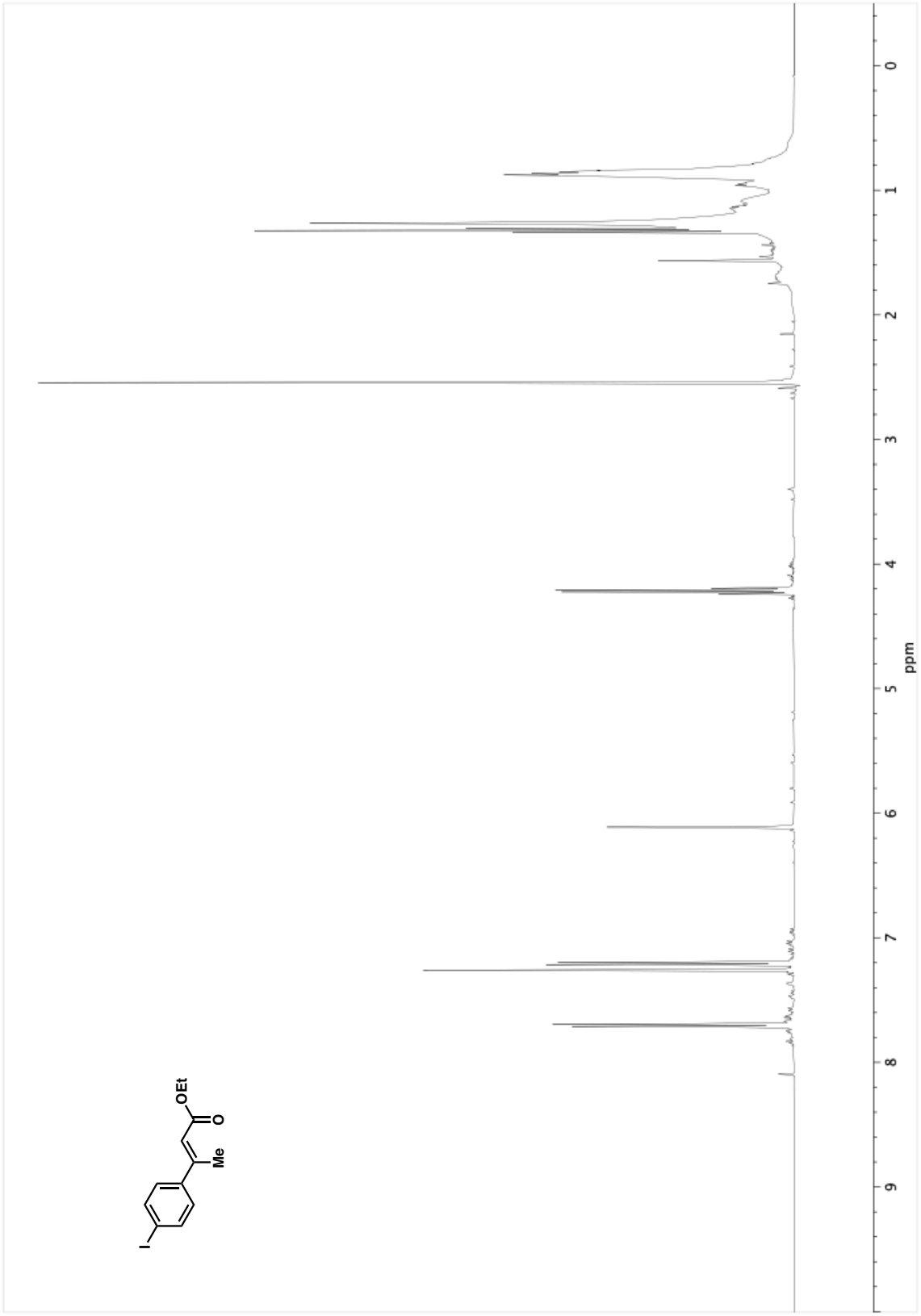


Figure A1.132. *^1H NMR (500 MHz, $CDCl_3$) of compound* **2ea.**

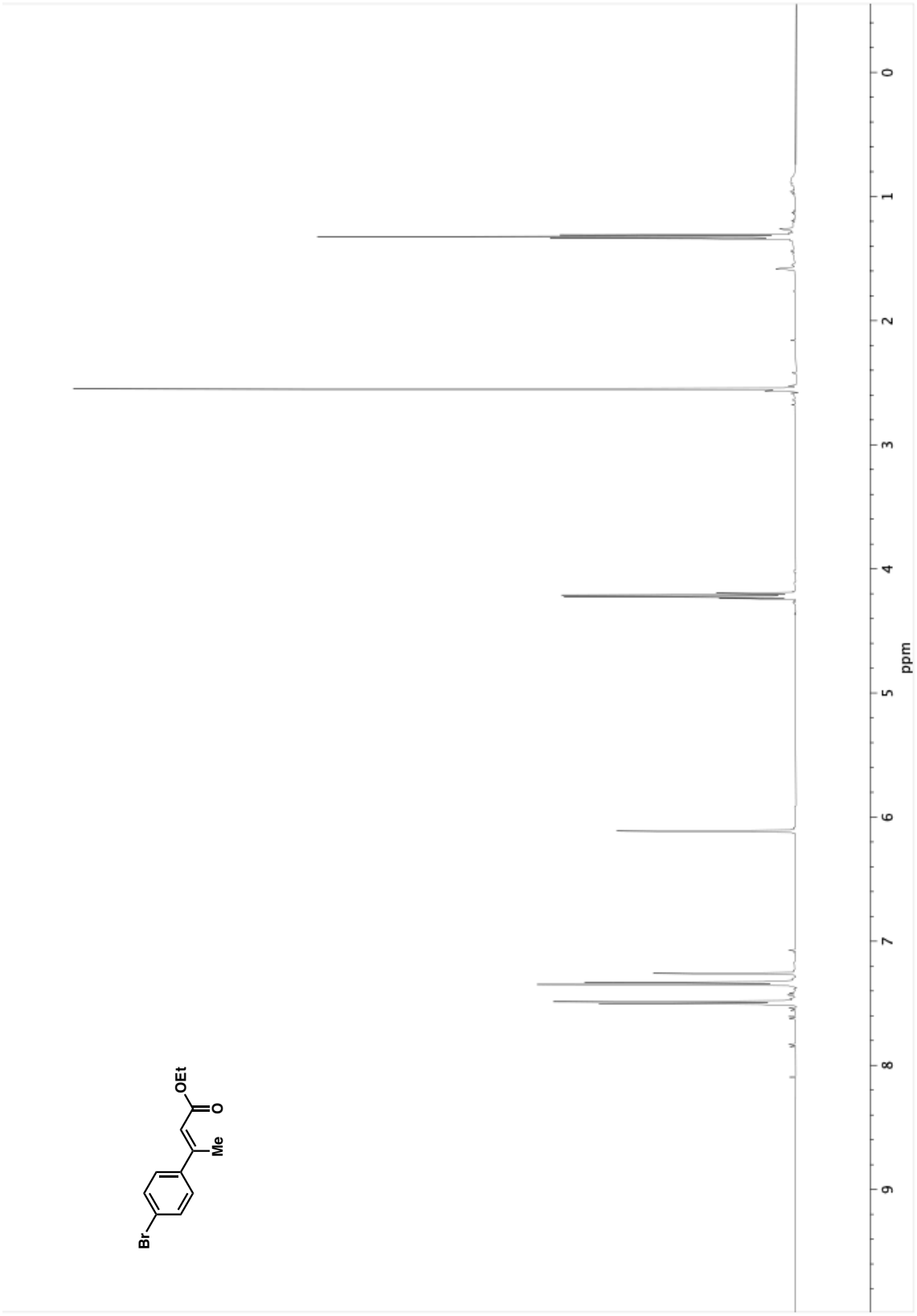


Figure A1.133. *^{1}H NMR (500 MHz, $CDCl_3$) of compound* ***2fa.***

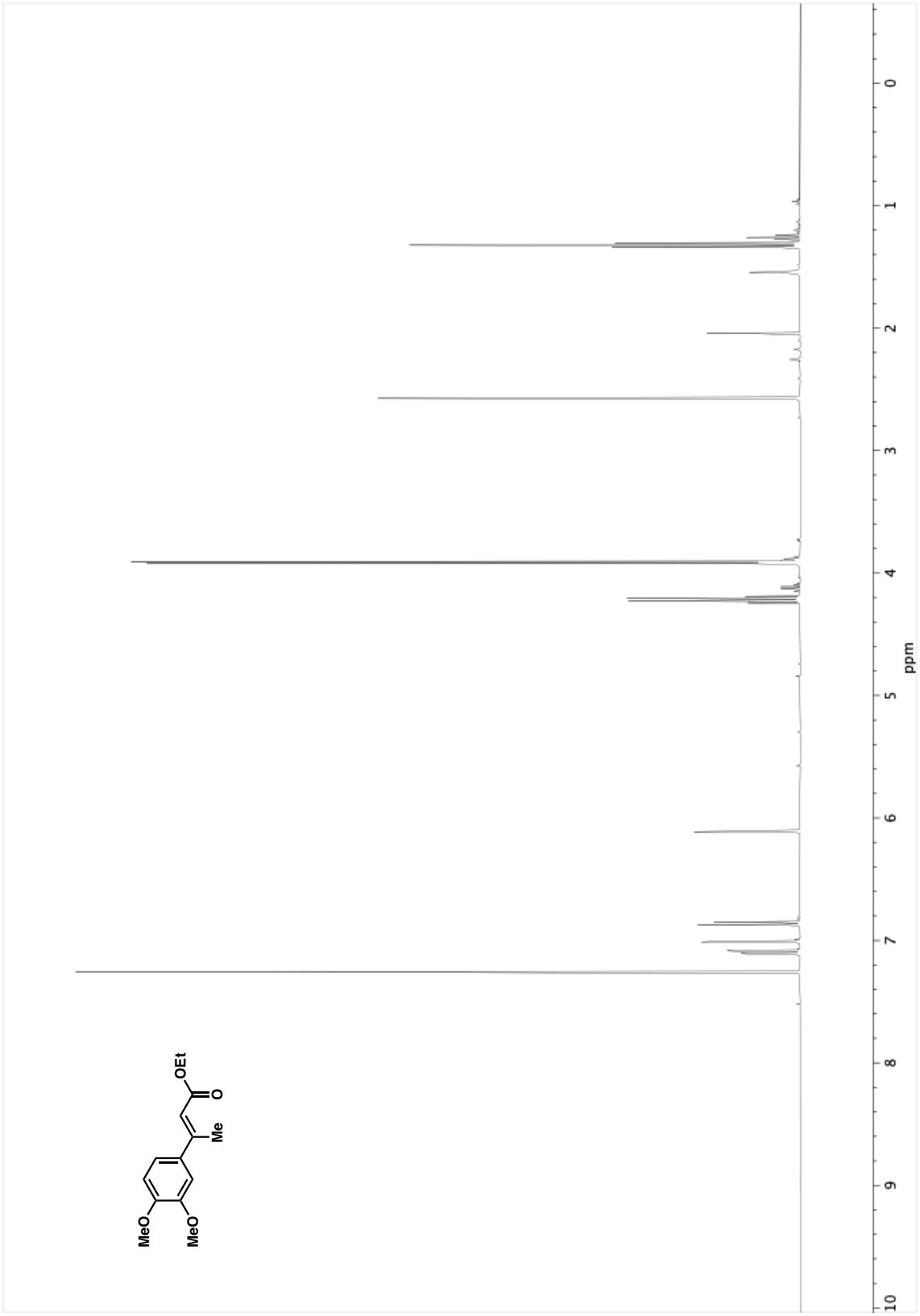


Figure A1.134. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***2ja.***

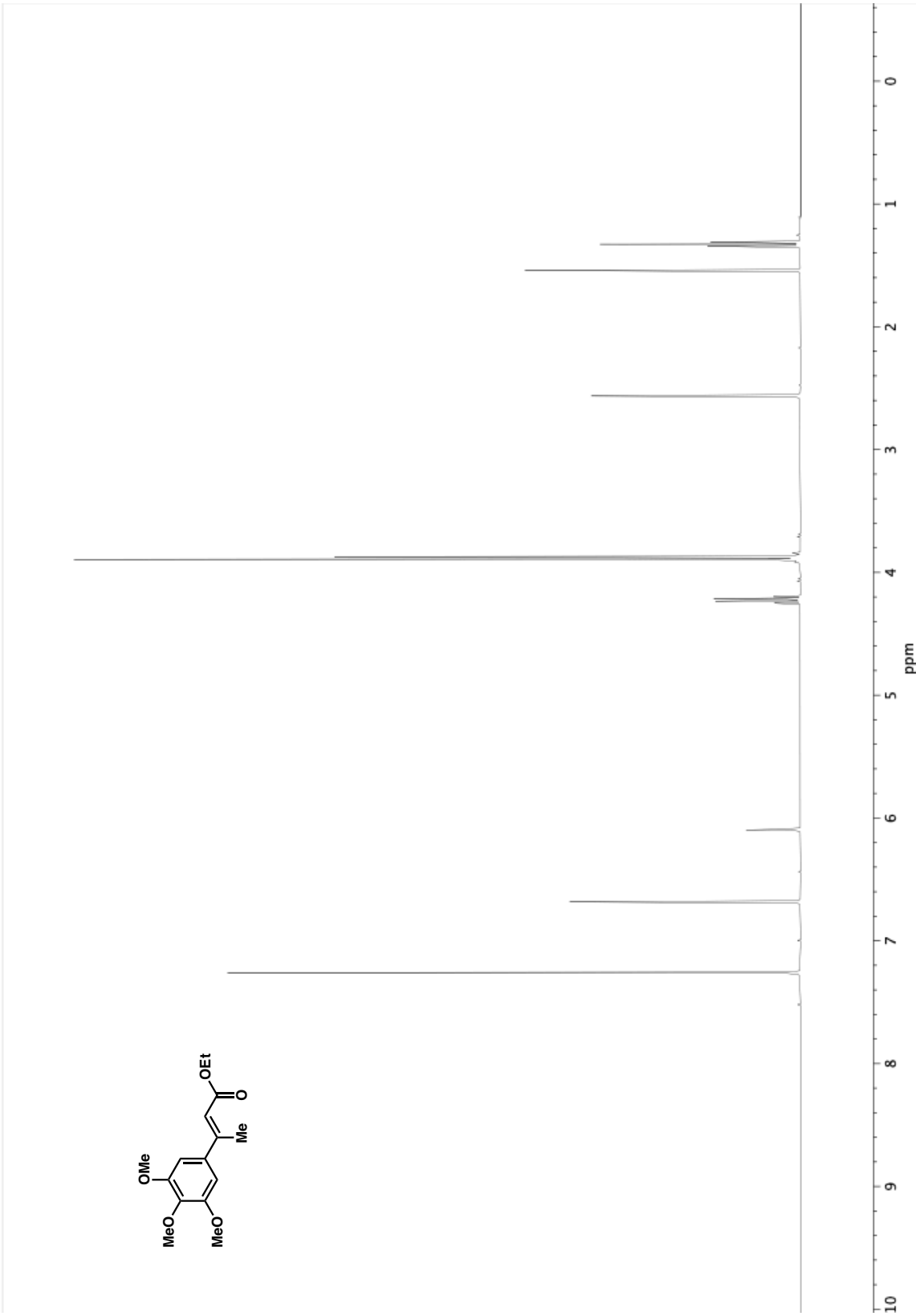


Figure A1.135. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***2ka.***

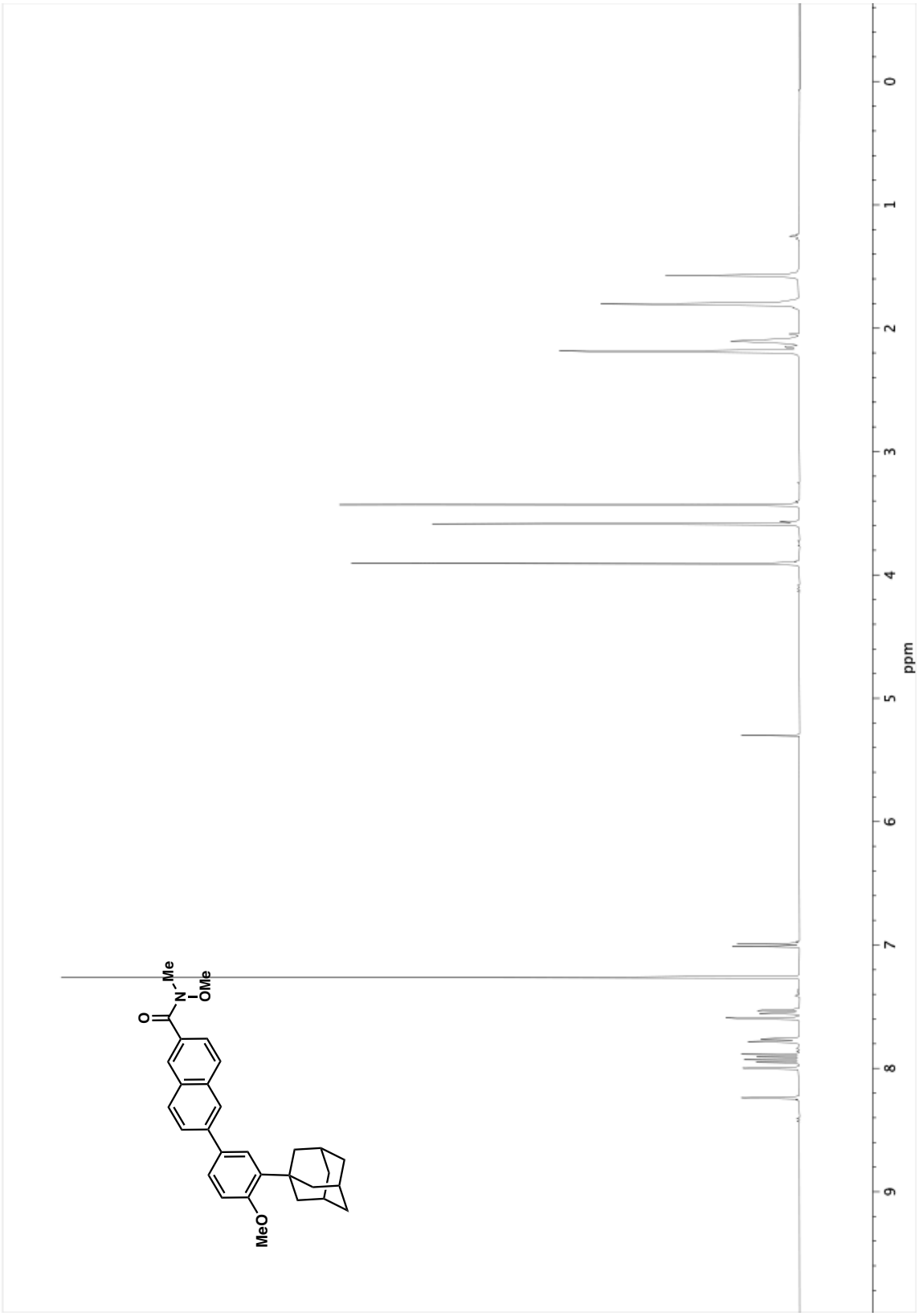


Figure A1.136. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***10a.***

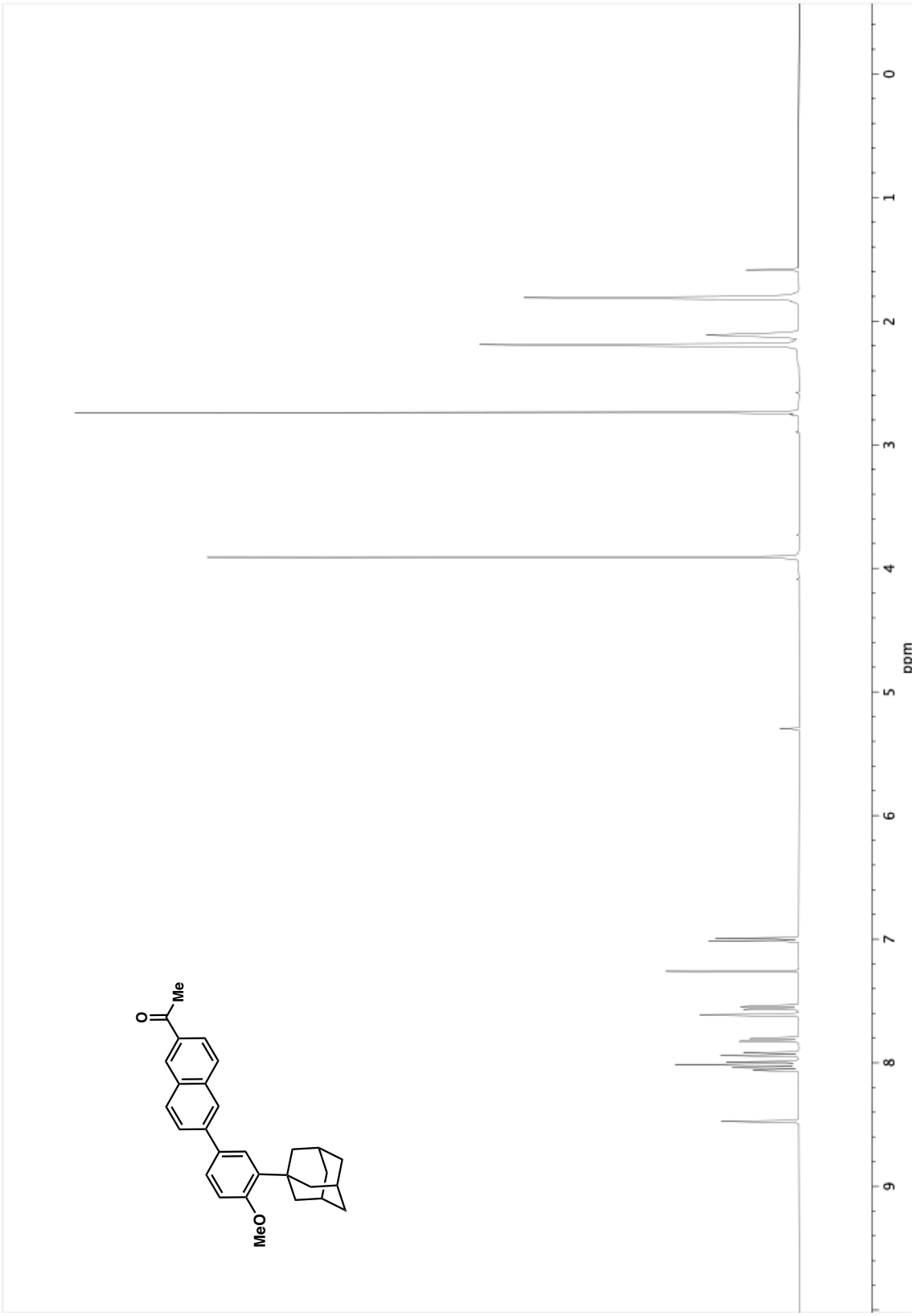


Figure A1.137. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***10b.***

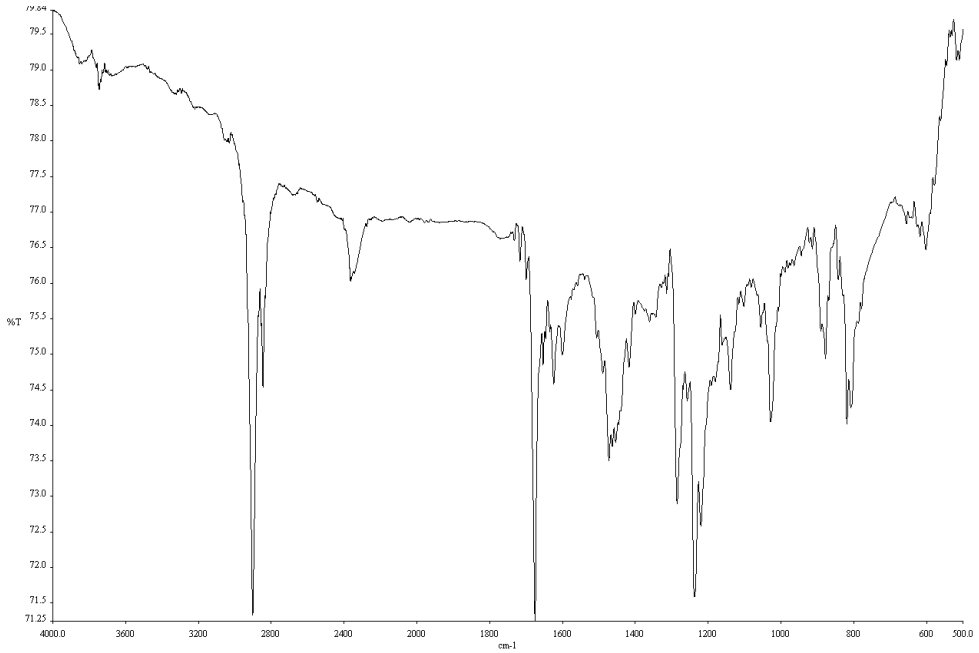


Figure A1.138. *Infrared spectrum (Thin Film, NaCl) of compound* ***10b.***

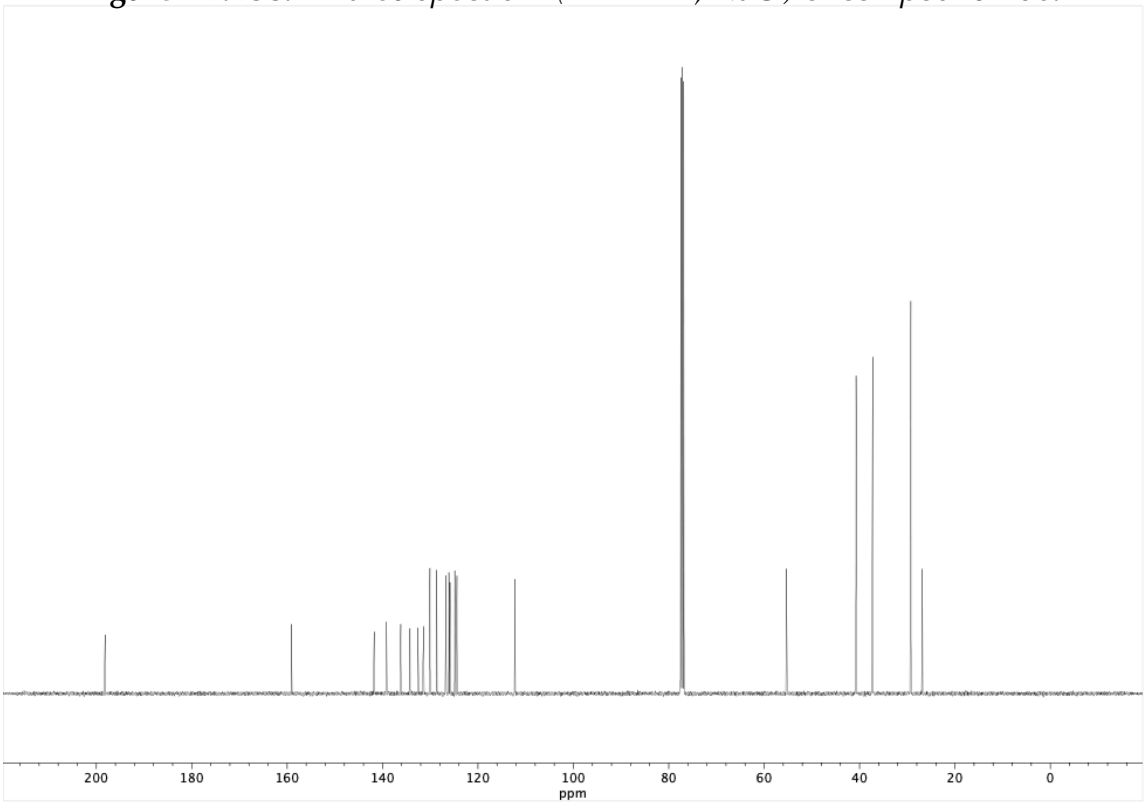


Figure A1.139. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***10b.***

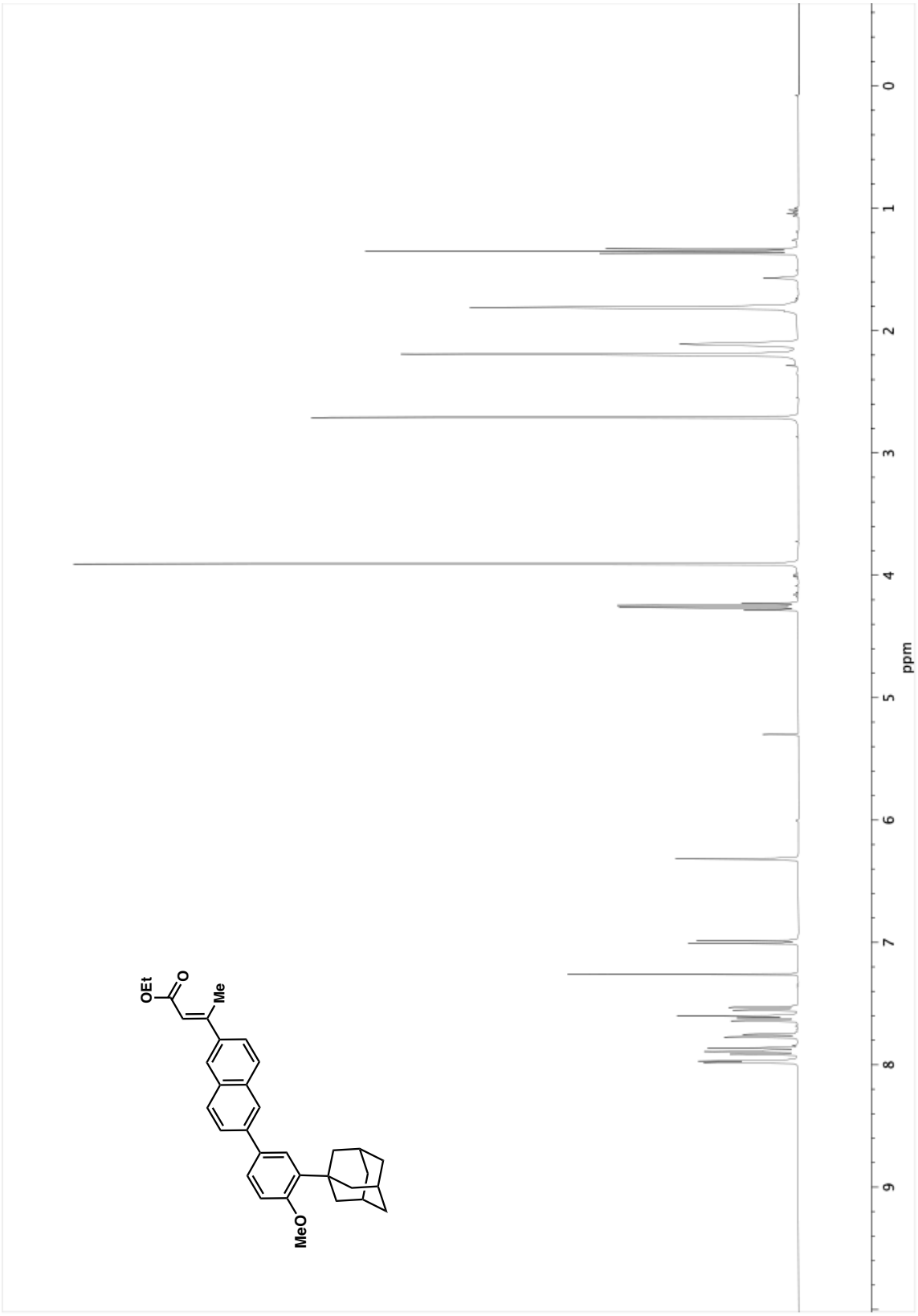


Figure A1.140. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***10c.***

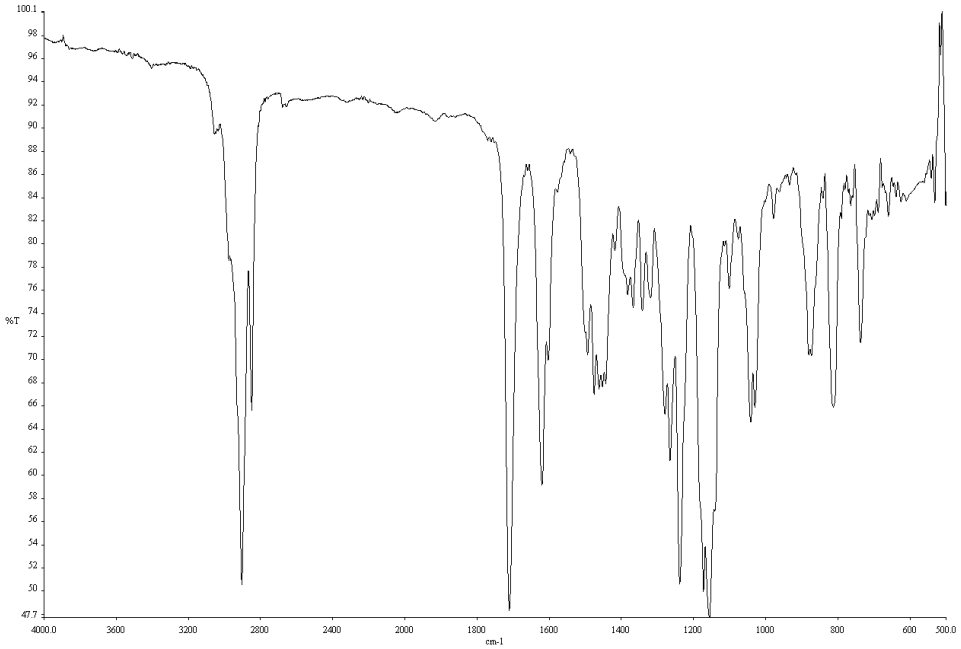


Figure A1.141. *Infrared spectrum (Thin Film, NaCl) of compound* ***10c.***

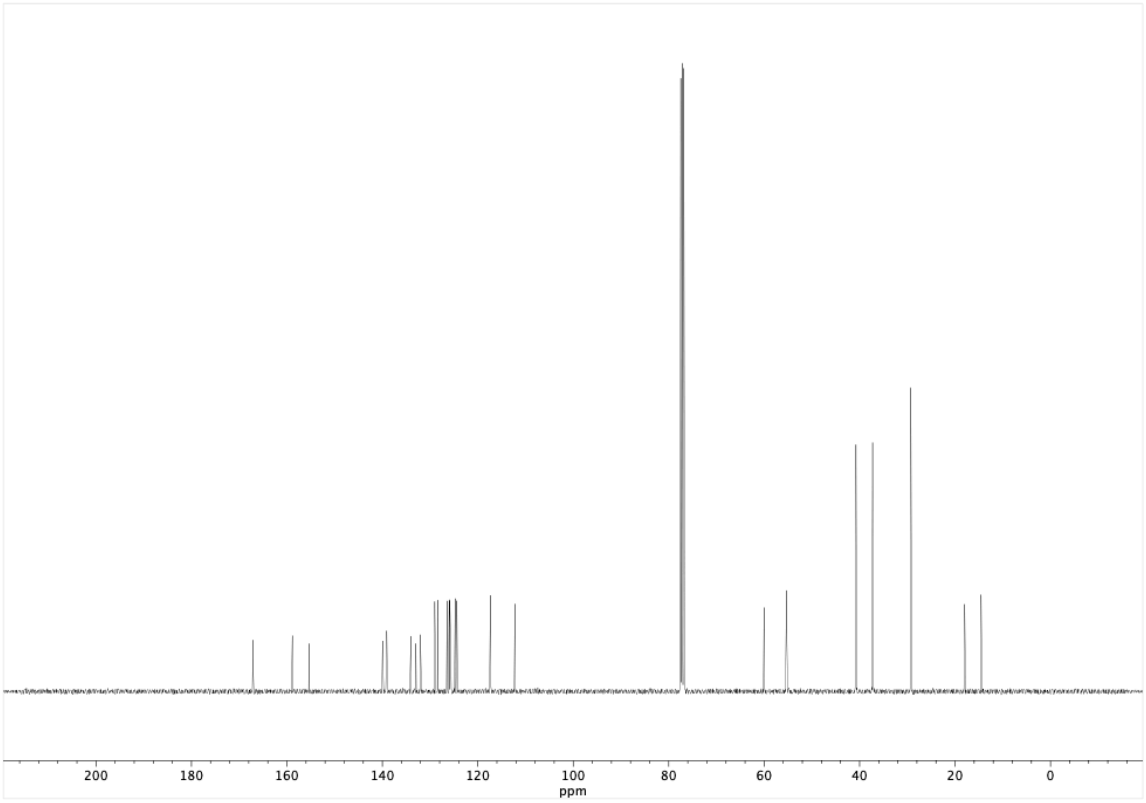


Figure A1.142. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***10c.***

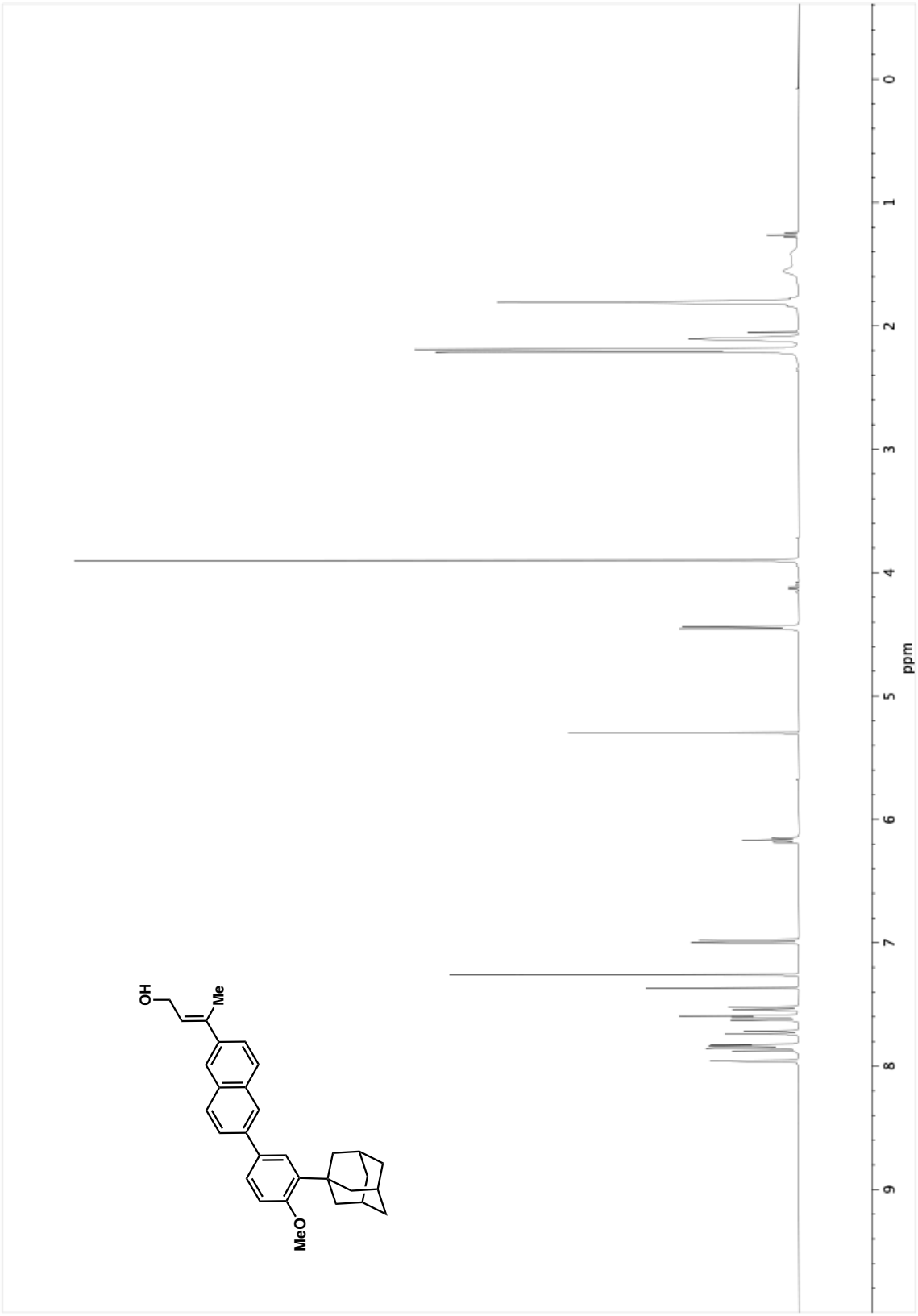


Figure A1.143. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***10d.***

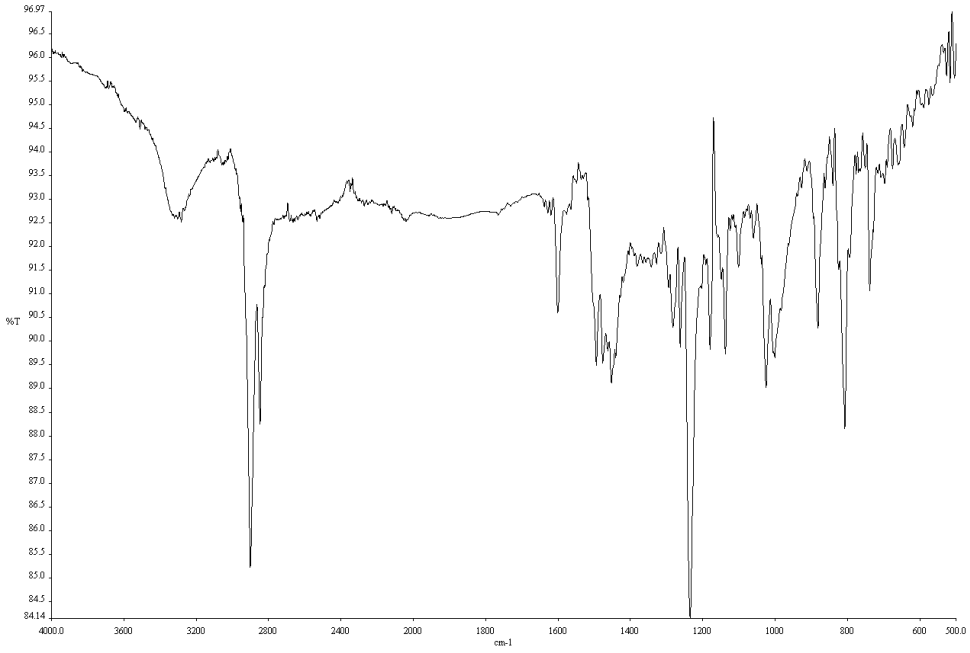


Figure A1.144. *Infrared spectrum (Thin Film, NaCl) of compound* ***10d.***

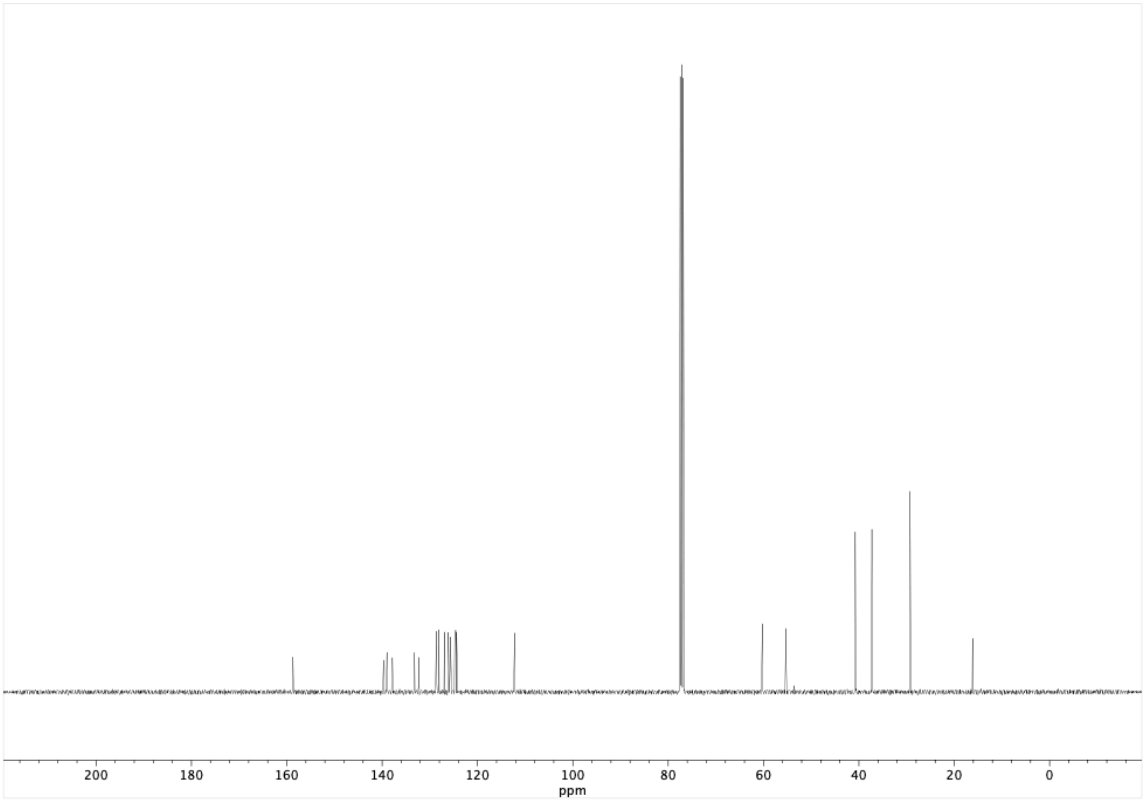


Figure A1.145. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***10d.***

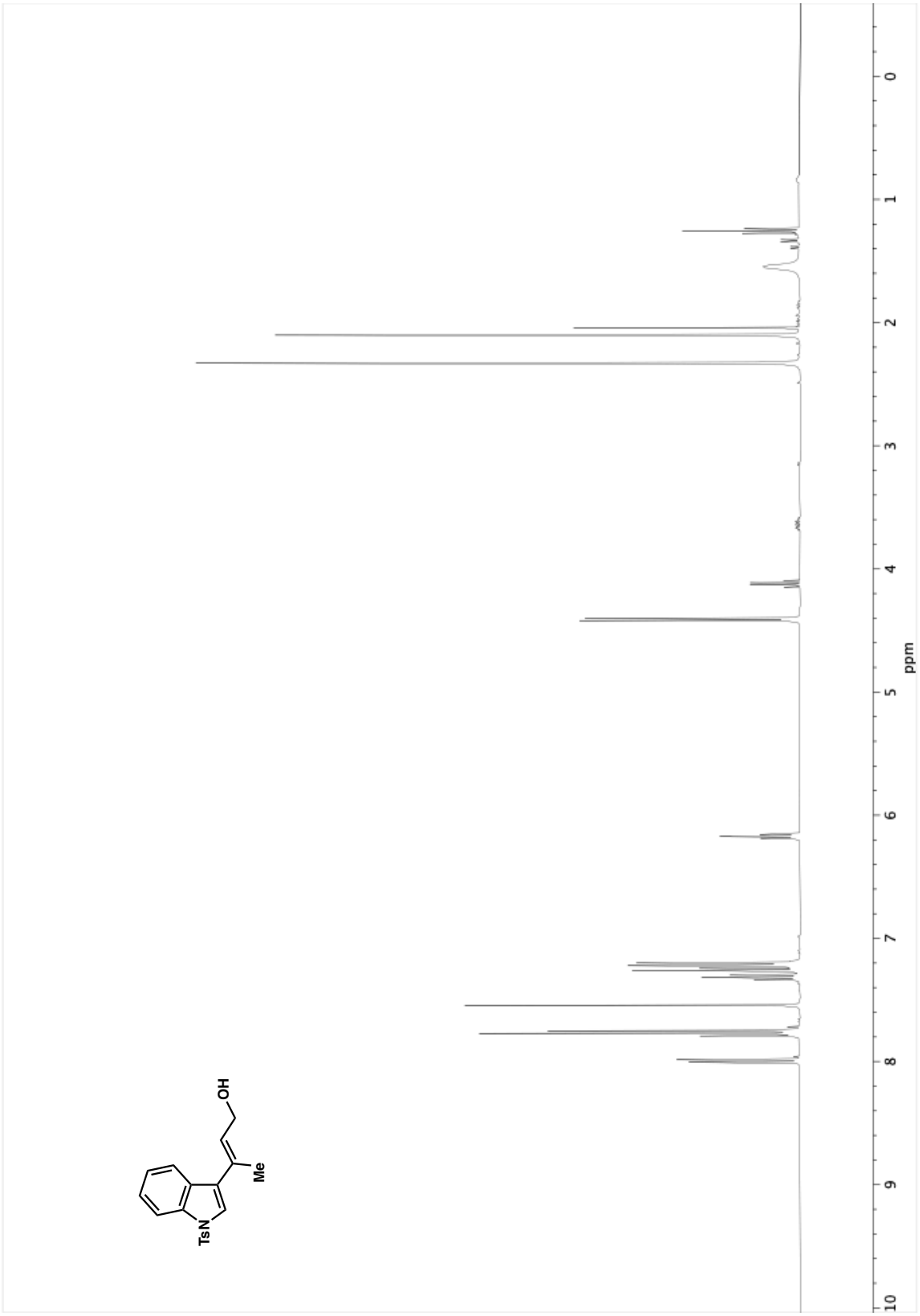


Figure A1.146. *^1H NMR (500 MHz, $CDCl_3$) of compound* ***2pb.***

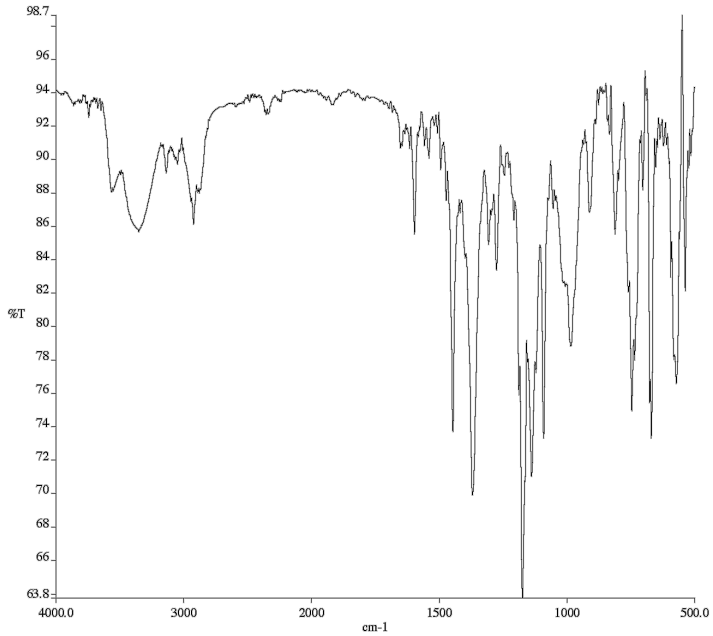


Figure A1.147. *Infrared spectrum (Thin Film, NaCl) of compound* ***2pb.***

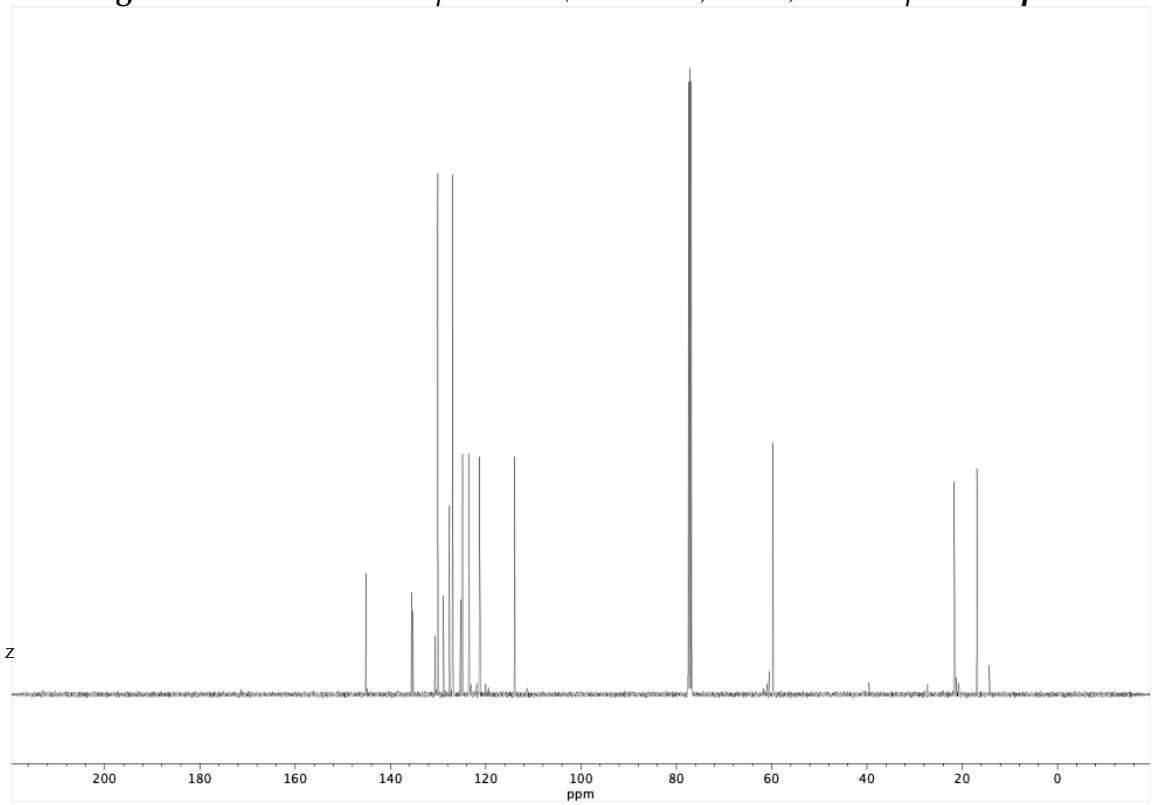


Figure A1.148. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***2pb.***

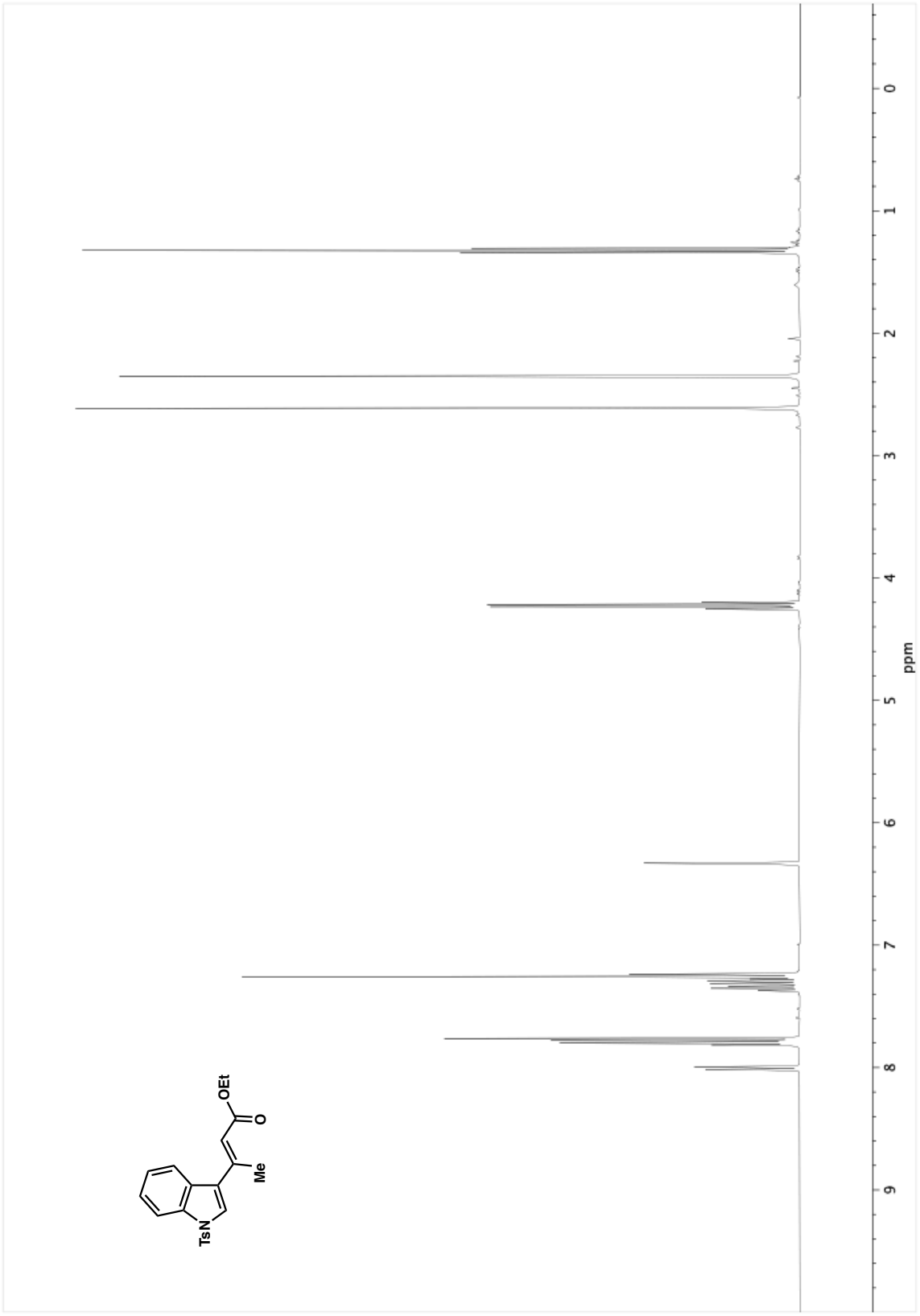


Figure A1.149. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***2pa.***

Z

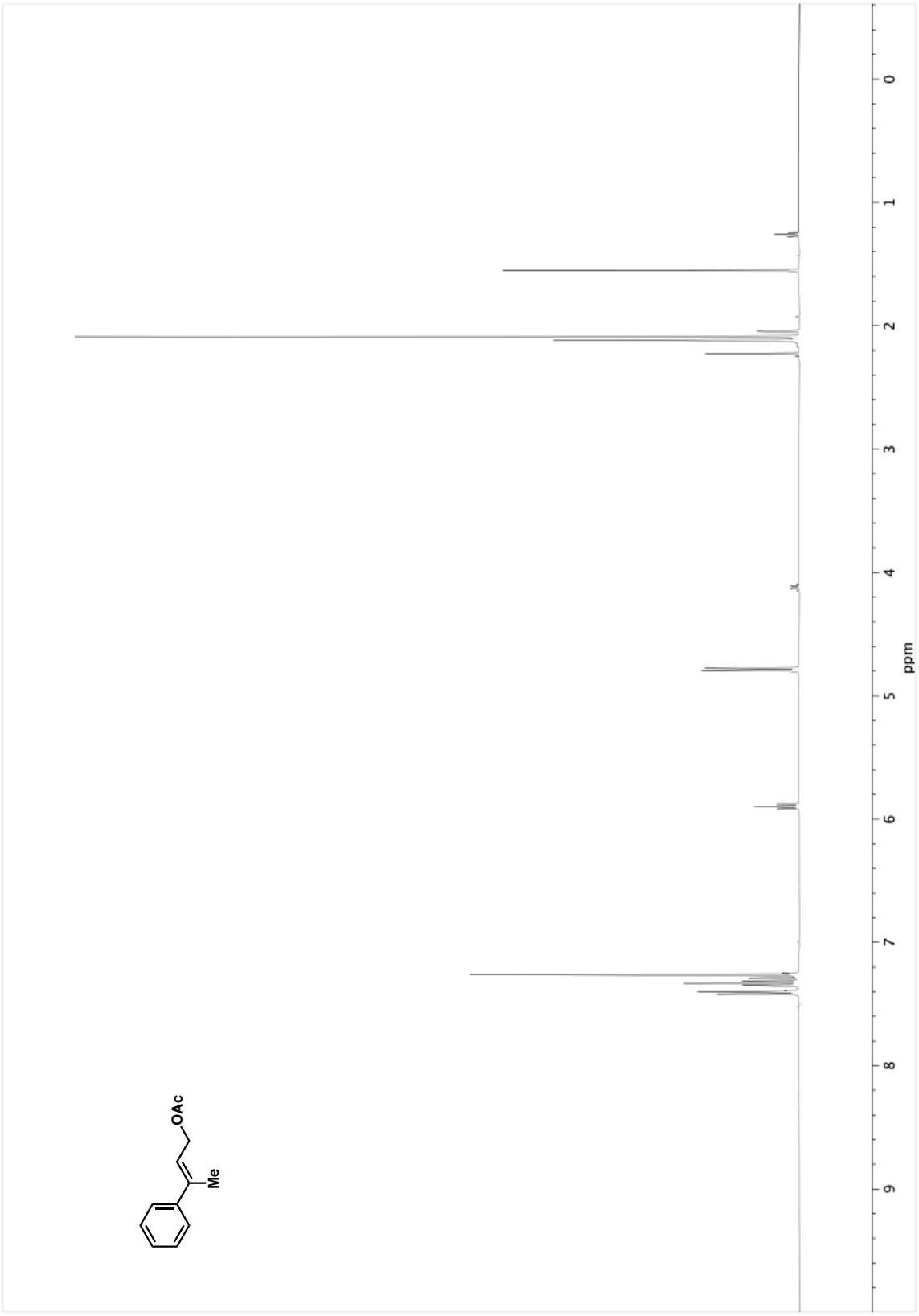


Figure A1.150. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***2aa.***

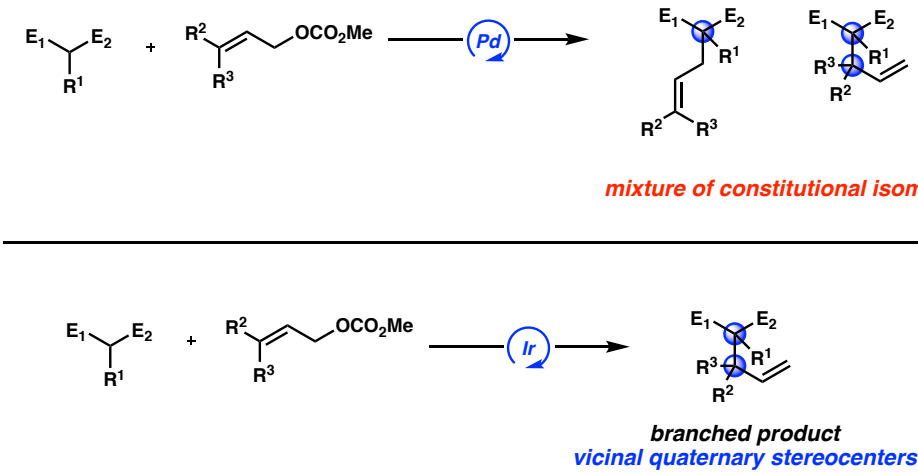
APPENDIX 2

Doubly Stereoselective Construction of Vicinal Quaternary Stereocenters via Ir-Catalyzed Asymmetric Allylic Alkylation

A2.1 INTRODUCTION

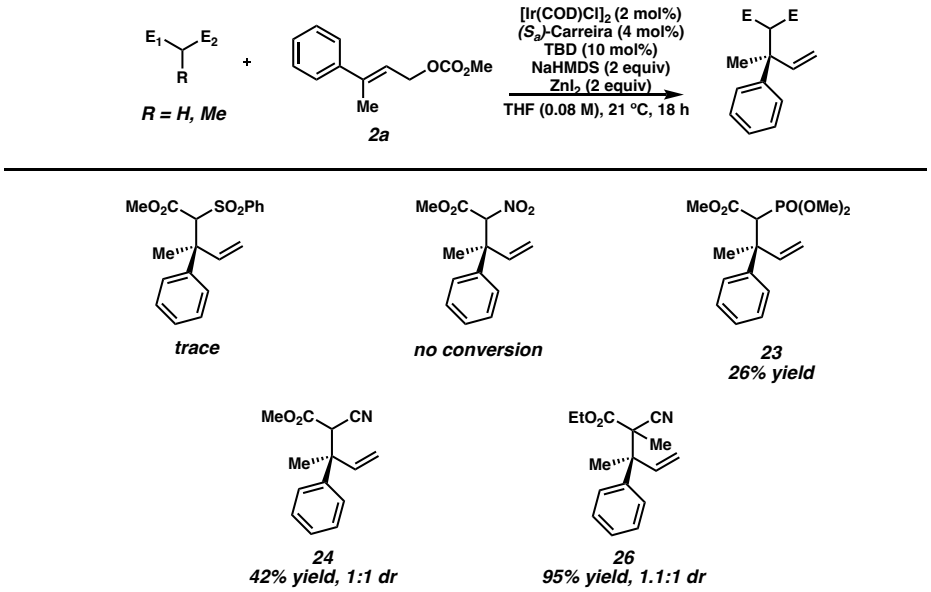
Gratified by the success of our efforts with the malonate nucleophile class, we looked to pursue the more challenging enantio- and diastereoselective formation of vicinal quaternary centers by virtue of this methodology. In the more typical Pd-catalyzed regime, reaction of a prochiral nucleophile with the same class of linear, trisubstituted electrophile utilized in our previous studies would likely exhibit poor regioselectivity, affording a mixture of constitutional isomers with little synthetic utility.[1] Otherwise, specialized ligand systems are necessary to override the intrinsic selectivity of this catalyst for the linear product.[2] Leveraging the exquisite selectivity of iridium for the branched alkylation product, one can imagine that these coupling partners would, in the case of this catalyst, result in the formation of vicinal quaternary stereogenic centers, a property that has thus far not been leveraged successfully (Scheme A2.1). Indeed, only a limited number of catalytic methods involving the construction of vicinal quaternary centers have been developed, with cyclopropanation, cycloaddition, and allylic alkylation prominent among these reports.[3,4] Many of the reactions, however, are either intramolecular in nature, involve highly tailored coupling partners, or proceed with poor diastereoselectivity, limiting their synthetic utility.

Scheme A2.1. *Prochiral Nucleophiles in Asymmetric Allylic Alkylation*



In previous reports detailing the generation of vicinal quaternary centers in Ir-catalyzed allylic alkylation, the issue of diastereoselectivity has been avoided through the use of nucleophiles containing symmetrical substitution patterns. During our investigations with the diethyl malonate system, we were pleased to find that while most stabilized carbon nucleophiles were not compatible with our chemistry (Scheme A2.2), the unsubstituted α-cyano ester afforded the desired product in 42% yield and 1:1 dr (**24**). More excitingly, a substituted derivative of this substrate class led to the formation of the vicinal quaternary product in a 95% NMR yield, albeit as a 1.1:1 mixture of diastereomers (**26**). Additional nucleophiles probed under similar conditions are included in the Experimental Section. Considering the remarkable reactivity of the cyanoester nucleophile under our reaction conditions, we imagined that this nucleophile would serve as a suitable template for the development of an allylic alkylation reaction with stereocontrol at two generated quaternary stereocenters.

Scheme A2.2. *Miscellaneous Stabilized Carbon Nucleophiles*[a]

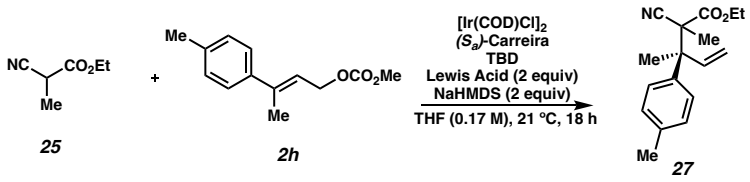


[a] Yield determined by ^{1}H NMR relative to a CH_2Br_2 internal standard.

A2.2 RESULTS

Using the *p*-Me substituted allylic methyl carbonate **2h** as the model electrophile, an isolated yield of 85% and 1.1:1 dr of **27** was obtained with nucleophile **25** under the previously optimized conditions (Scheme A2.3). We were pleased to find that reduction of the catalyst loading to 1 mol% $[Ir(COD)Cl]_2$ did not lead to any deterioration in the yield, so this new stoichiometry would be employed therein. Later optimization would reveal that decreasing the catalyst loading by another factor of 2 — to just 0.5 mol% of the dimer — facilitated quantitative conversion to product as observed by NMR analysis of the crude mixture. Further, the ZnI_2 stoichiometry could be reduced to 1.2 equivalents without any detriment to the reaction.

Scheme A2.3. *Initial Optimization of Substituted α-Cyanoester Coupling*[a]



Entry	$[Ir(COD)Cl]_2$	(S_a)-Carreira	TBD	Lewis Acid	Yield	dr[a]
1	2 mol%	4 mol%	10 mol%	ZnI_2	85%	1.1:1
2	2 mol%	4 mol%	10 mol%	CuI	51%	1.1:1
3	1 mol%	2 mol%	5 mol%	ZnI_2	87%	1.1:1

[a]Yield determined by ^{1}H NMR relative to a CH_2Br_2 internal standard.

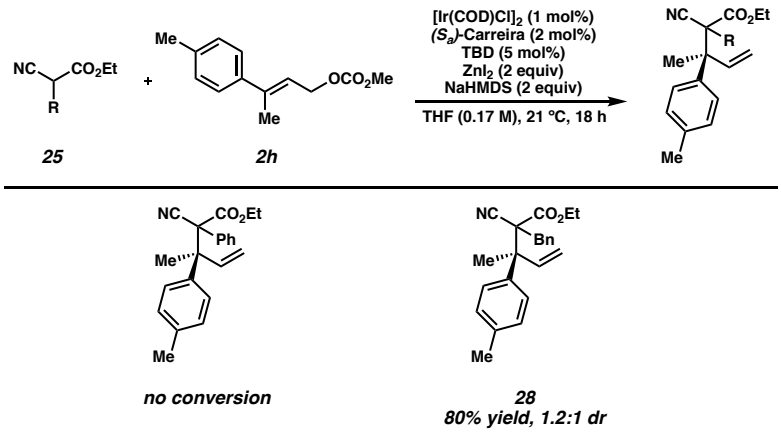
In an effort to improve the stereoselectivity, we predicted that perhaps a more π-philic metal could bind to both functional groups of the nucleophile. CuI was thus probed as a replacement for ZnI_2. However, much like in the case of the malonate nucleophiles, this caused a significant decrease in yield to 51%, albeit with no change in the dr. While the ee of each diastereomer of **27** could not be determined explicitly, SFC analysis indicated an average ee of 93% through combined integration of the two major peaks and two minor peaks.

A2.2.1 INITIAL SUBSTRATE SCOPE

An elementary substrate investigation was conducted to gauge the breadth of this transformation with respect to nucleophile substitution patterns (Scheme A2.4). While the phenyl-substituted cyanoester did not prove suitable in the reaction, we were delighted that a benzyl substituent was accommodated, leading to the formation of vicinal quaternary scaffold **28** in 80% yield and 1.2:1 dr. Like the model product, **28**

was produced in enantioenriched form, with an estimated 93% average ee for the two diastereomers.

Scheme A2.4. *Initial Survey of Nucleophile Substitution*

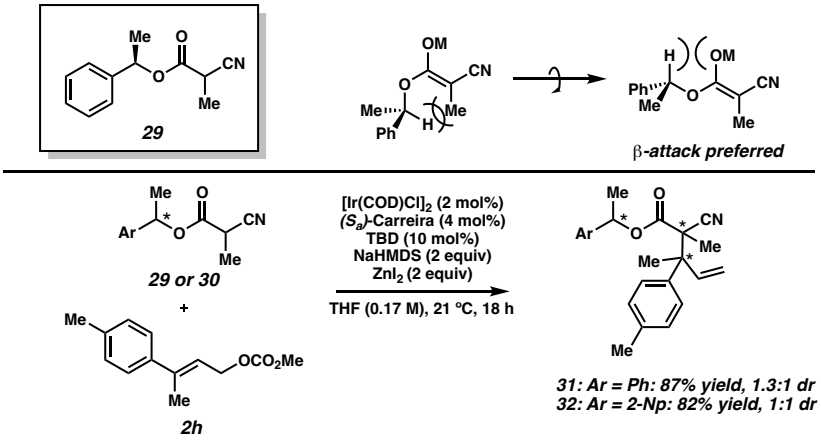


A2.2.2 CHIRAL ESTER APPROACH

Understanding that perhaps the lack of diastereoselectivity in this reaction could be attributed to poor facial selectivity for attack of the electrophile from a given isomer of the enolate, we imagined that a chiral auxiliary could be appended to the ester, resulting in an $A_{1,3}$ minimized enolate conformation (Scheme A2.5) preferring alkylation over the less sterically encumbered face.

With *(R)*-1-phenylethanol as the model auxiliary, we found that the corresponding nucleophile (**29**) could undergo the desired reaction to form **31** in 87% NMR yield but only a moderately improved 1.3:1 dr. Surprisingly, replacement of the phenyl group with a more sterically demanding 2-napthyl substituent in nucleophile **30** resulted in a decrease of the dr to 1:1 (**32**), implying that either the hypothesized enolate projection

Scheme A2.5. *Chiral Ester Approach to Facial Selectivity of Enolate Addition*[a]



[a]Yield determined by ^{1}H NMR relative to a CH_2Br_2 internal standard.

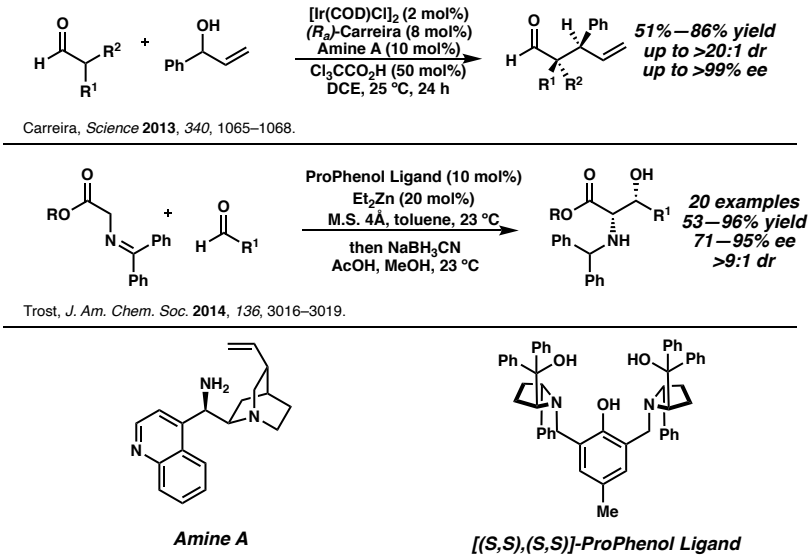
was incorrect or that poor control over the enolate geometry is at least partially responsible for the low dr.

A2.2.3 CHIRAL LEWIS ACID

We were then inspired by other strategies employed in diastereoselective couplings of enolate nucleophiles, such as those employed by Carreira and Trost (Scheme A2.6).[5] In the former case, the Carreira group was able to subject an aldehyde nucleophile to typical allylic alkylation conditions in the presence of a cinchona alkaloid-derived amine to form the corresponding coupling product in high levels of diastereoselectivity. Trost, on the other hand, found that stabilized carbon nucleophiles could be treated with a chiral zinc complex bearing a ProPhenol ligand to facilitate a stereoselective carbonyl addition process.

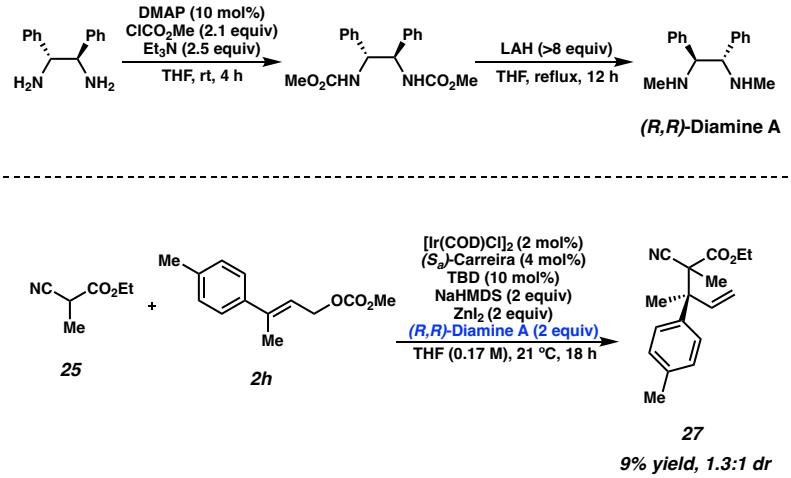
Combining these concepts, we looked to investigate the effect of a chiral Zn lewis

Scheme A2.6. *Strategies for Diastereoselective Enolate Alkylation*



acid on the Ir-catalyzed allylic alkylation we have developed. Starting from commercially available *(1R,2R)*-diphenylethylenediamine, a simple acylation-reduction sequence resulted in the demethylated analog (Scheme A2.7). Reasoning that a C_2-symmetric zinc complex could impart facial selectivity upon the enolate, we added the potential diamine ligand to the reaction mixture. Unfortunately, inclusion of 2 equivalents of this compound resulted in a precipitous decrease in the yield to 9% by NMR, as well as a relatively similar 1.3:1 dr. Together with the failure of the chiral esters to effect diastereoselectivity, this suggested that either our understanding of the mechanism as involving outer sphere nucleophilic substitution is erroneous or that the enolate geometry is the factor that must be controlled.

Scheme A2.7. *C_2-Symmetric Zn System in Ir-catalyzed Allylic Alkylation*[a]



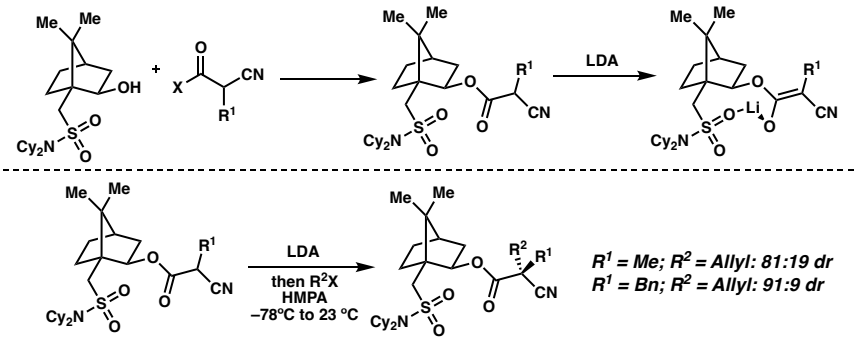
[a]Yield determined by ^{1}H NMR relative to a CH_2Br_2 internal standard.

A2.2.4 ISOBORNEOL-DERIVED CYANOESTER

We were also intrigued by a report from Cativiela and coworkers[6] where an isoborneol-derived chiral auxiliary was utilized for similar alkyl-substituted cyanoester systems, forming a Li-chelate upon treatment with LDA. This species could then be trapped by an electrophile to form the corresponding alkylated product in high levels of diastereoselectivity (Scheme A2.8). This is of particular note, as some of the substrates employed in the study greatly resemble those that have already proven competent under our Ir-catalyzed conditions, including methyl and benzyl substitution patterns.

Following the known synthesis for the *N*-dicyclohexylsulfamoyl auxiliary, the α-methyl cyanoester bearing this unique group (**33**) was obtained via coupling with the parent carboxylic acid. We were delighted to find that when subjected to our reaction,

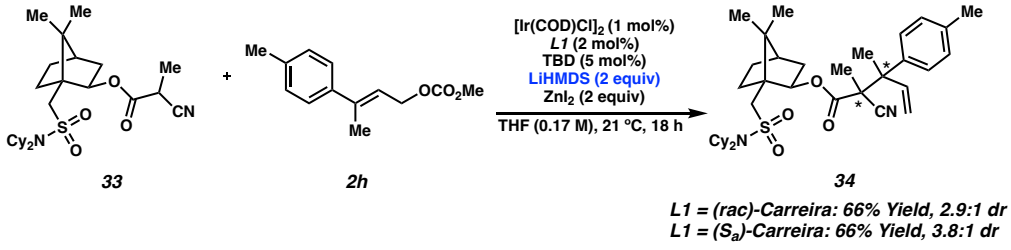
Scheme A2.8. *Isoborneol-derived Chiral Auxiliary in Asymmetric Alkylation*



with LiHMDS used instead of NaHMDS to ensure the formation of a Li chelate, the reaction proceeded in a 66% yield and improved 2.9:1 dr with **(*rac*)-L1**. When **(S_a)-L1** was employed instead, the dr increased to 3.8:1, suggestive of a match between substrate and catalyst stereochemistry (Scheme A2.9).

While not exquisitely stereoselective, this result provided encouraging evidence that a fully stereocontrolled process is attainable. Nevertheless, due to the laborious

Scheme A2.9. *Application of Nucleophile **33** to Ir-catalyzed Asymmetric Allylic Alkylation*[a]



[a]Yield determined by ^{1}H NMR relative to a CH_2Br_2 internal standard.

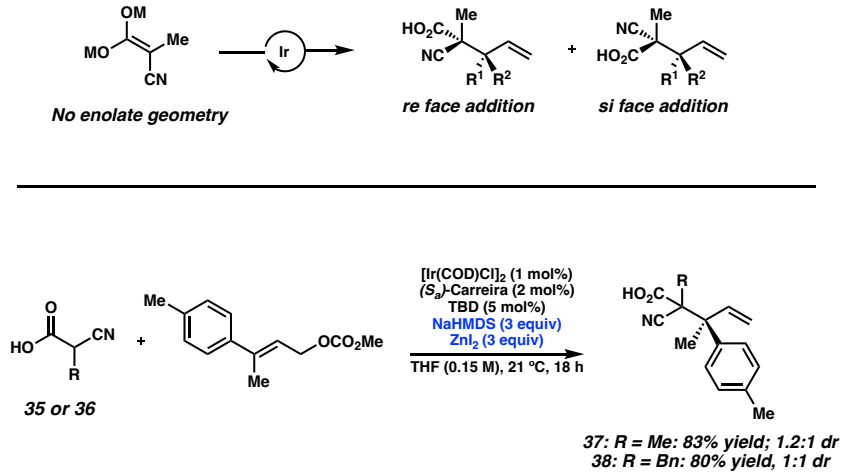
synthesis of the chiral auxiliary and the moderate levels of diastereoselectivity from our initial results, this approach was abandoned in favor of changes to the substrate design that would control factors pertinent to the stereochemical outcome.

A2.2.5 CYANOACID NUCLEOPHILES

Controlling for the assumption that enolate geometry may be entirely responsible for the observed diastereomeric mixture of products, we envisioned that use of a α-cyanoacid nucleophile rather than the α-cyanoester scaffold may be effective. Following two deprotonation events of the cyanoacid, the resulting enolate would not exhibit geometric isomerism, delivering diastereomeric products entirely on the basis of facial bias. Under modified reaction conditions, with larger stoichiometries of Lewis acid and base, we were delighted to observe the competency of these nucleophiles, as we obtained the corresponding allylic alkylation products in good yields (Scheme A2.10). Unfortunately, this was not accompanied by an improvement to the diastereoselectivity, providing further evidence that both facial selectivity and enolate geometry must be controlled in order to induce a stereochemical preference at the nucleophile-derived quaternary stereocenter.

Intrigued by the prospect of substrate design to eliminate enolate isomerism, we posited that a nucleophile with a larger steric profile retaining this feature would provide sufficient differentiation of the diastereomeric transition states of nucleophilic attack. The most obvious way that we imagined this could be done was to constrain the

Scheme A2.10. *Cyanoacid Nucleophile*[a]



[a]Yield determined by ^{1}H NMR relative to a CH_2Br_2 internal standard.

enolate in the form of a cyclic scaffold. As such, we targeted α-cyano γ-lactones as our next nucleophile of choice.

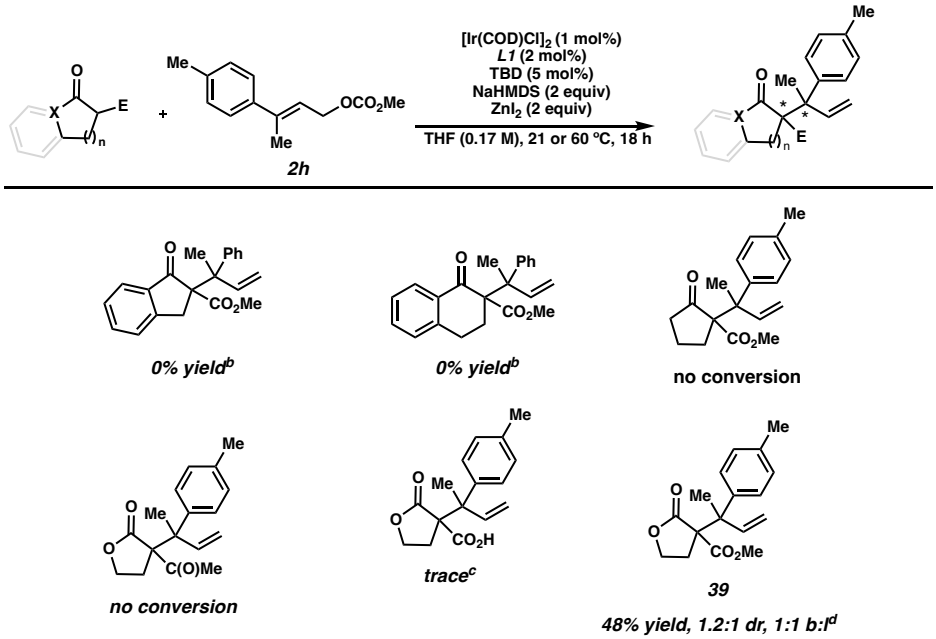
A2.2.6 CYCLIC MANIFOLDS

Indeed, our group has found in the past that cyclic and acyclic manifolds often behave much differently under Ir-catalyzed regimes,[14] with the former in some cases offering superior stereocontrol. Considering the notable differences in reactivity between the two classes of nucleophiles, we first decided to investigate a library of cyclic stabilized carbon nucleophiles resembling the acyclic nucleophiles that we had probed in our earlier investigations, with the hope that they may offer sufficient reactivity and an opportunity for improved diastereoselectivity.

Empirically, we found that motifs posing challenges in the acyclic systems were also not suitable in a cyclic manifold, even at elevated temperatures (Scheme A2.11).

Though the yield was below synthetically useful levels, we were intrigued by the reactivity of the α-carboxy lactone system to form **39**, comparing favorably to the results observed for its acyclic relatives. Nevertheless, the product was formed as a mixture both of diastereomers and constitutional isomers, limiting its utility.

Scheme A2.11. *Cyclic Nucleophiles Under Typical Reaction Conditions*[a,b,c,d]



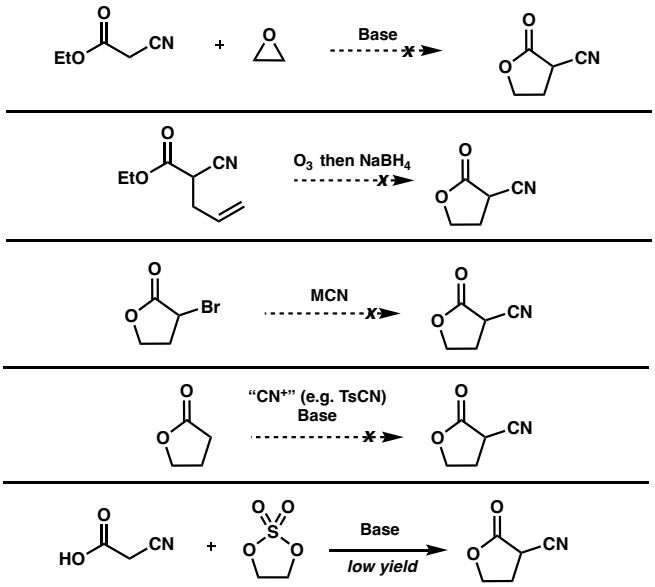
[a]Yield determined by ^{1}H NMR relative to a CH_2Br_2 internal standard. [b]Reaction performed using 2a instead of 2h. Conducted at 60 °C with 1.2 equiv ZnI_2. [c]Conducted with 3 equiv each of NaHMDS and ZnI_2. [d] 2 mol% $[Ir(COD)Cl]_2$ employed and reaction conducted at 60 °C.

A2.2.7 CYANOLACTONE SYNTHESIS AND APPLICATION

Convinced by the specter that control of enolate geometry could still govern the dr of the reaction with cyanoester nucleophiles, we embarked in earnest on a campaign to synthesize the cyanolactone scaffold. Despite our best efforts, several methods to

access the unsubstituted model substrate (α-cyano γ-butyrolactone) proved unsuccessful (Figure A2.1). Base-promoted opening of ethylene oxide with ethyl cyanoacetate and subsequent ring-closing did not lead to detectable amounts of the desired product. Similarly, reductive ozonolysis of the allylated cyanoester did not afford the cyanolactone. Both nucleophilic and electrophilic cyanation were investigated to no avail, and only a trace amount of the cyclic compound was observed upon treatment of cyanoacetic acid with ethylene sulfate in the presence of base.

Figure A2.1. *Failed Routes to Access α-Cyano γ-Lactones*

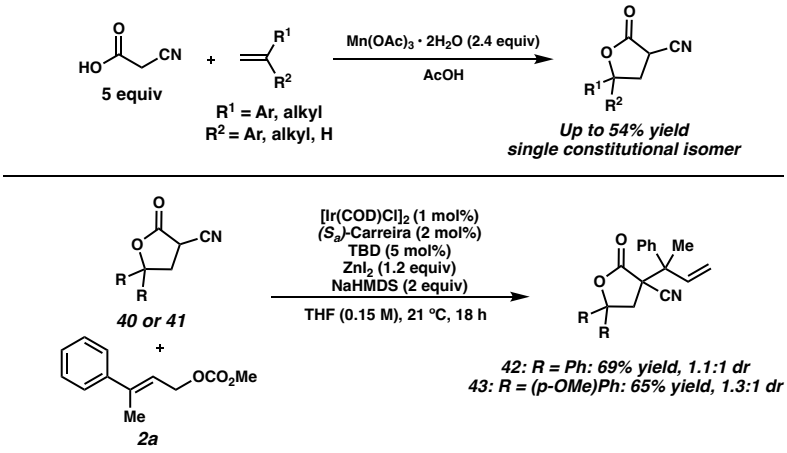


After exhaustive literature investigation, we uncovered a Mn(III)-mediated oxidative cyclization uniting cyanoacetic acid and olefins regioselectively. First discovered by Heiba and Finkbauer in 1968[7] and expanded by Fristad and Corey in 1985,[8] this reaction is predicated on the formation of an enolate radical intermediate, which undergoes regioselective addition into an olefin to form the more stable alkyl

radical.[9] This radical is then oxidized and trapped by the acid moiety to furnish substituted lactone products. Applying this technology, we were able to access a range of substituted cyanolactone substrates, including γ-disubstituted variants we were hopeful would be compatible to our reaction (Scheme A2.12).

However, as had been the case with many of our explored nucleophile classes, we found that the cyanolactones could indeed undergo the allylic alkylation in moderate yield, but no improvement in the diastereoselectivity was evident. This confirmed that, in addition to control of enolate geometry, an explicit facial bias would need to be installed into the nucleophile for stereocontrol at the nucleophile-derived center.

Scheme A2.12. *Synthesis and Application of Cyanolactone Substrates*



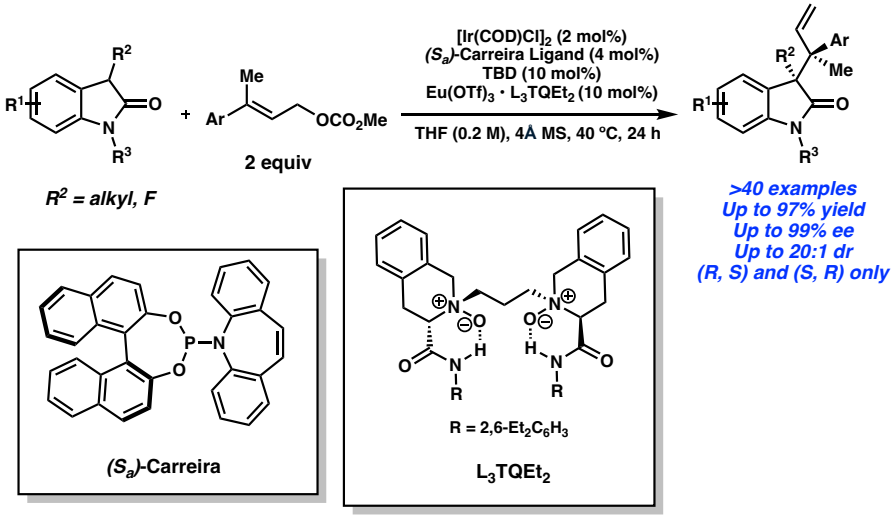
[a]Yield determined by ^{1}H NMR relative to a CH_2Br_2 internal standard.

A2.2.8 FENG REPORT CONSTRUCTING VICINAL QUATERNARY CENTERS

During our studies, Feng and coworkers reported the first and only example of an enantio- and diastereoselective Ir-catalyzed allylic alkylation forging the vicinal

quaternary motif, employing the linear electrophiles and catalytic system pursued by our research group in the construction of electrophile-derived quaternary stereocenters (Scheme A2.13).[10] In their transformation, a europium co-catalyst bound to a chiral bis(*N*-oxide) ligand serves to generate the operative enolate. While the enantioenriched ligand does indeed provide high levels of both enantio- and diastereoselectivity, only 2 of 4 possible stereoisomers could be accessed through the protocol.

Scheme A2.13. *First Reported Example of Doubly Stereoselective Construction of Vicinal Quaternary Centers via Ir-catalyzed Allylic Alkylation by Feng*



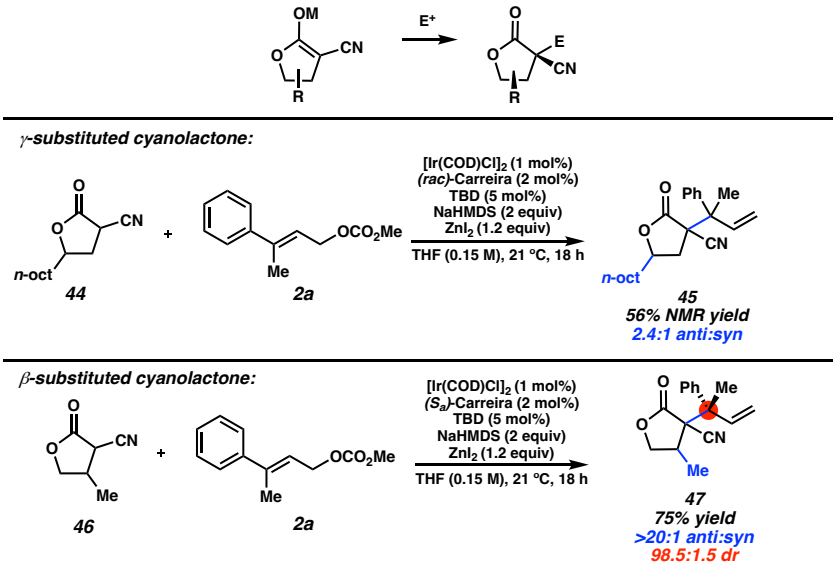
Despite this report, we remained interested in taking advantage of the incredible reactivity of cyanoesters under our developed reaction conditions, and we believed the cyanolactone scaffold remained a good candidate for substrate design enforcing the necessary facial bias to confer diastereoselectivity. We hypothesized that a cyanolactone nucleophile containing a substituent at either the γ- or β-position could

promote nucleophilic attack over the less sterically encumbered face of the lactone, finally effecting stereocontrol at the nucleophile-derived center.

A2.2.9 MONO-SUBSTITUTED CYANOLACTONES

Gratifyingly, we found that a γ-monosubstituted cyanolactone, synthesized by the Mn(III)-promoted oxidative coupling reaction, generated a 2.4:1 mixture of products corresponding to *anti*- or *syn*-addition relative to the γ-substituent (Scheme A2.14). Naturally, we wondered if shifting this group one methylene closer to the site of nucleophilic attack would further improve the stereoselectivity. To our delight, β-methyl cyanolactone **46** could be subjected successfully to our optimized reaction conditions, resulting in exquisite selectivity for *anti*-addition. The configuration at the electrophile-borne center was governed by the chiral catalyst, and **47** was obtained with

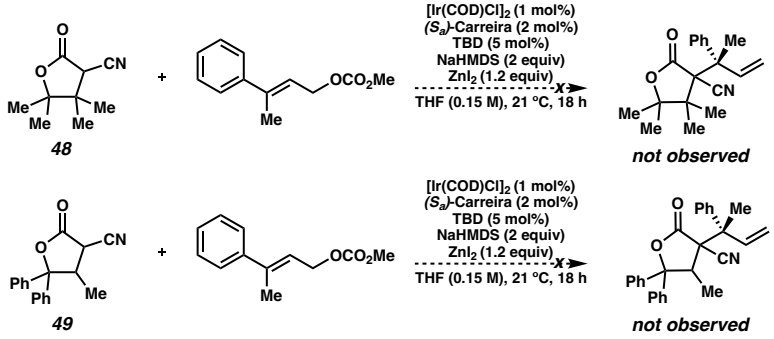
Scheme A2.14. *Application of Mono-substituted Cyanolactone Nucleophiles*



excellent levels of stereocontrol at both quaternary centers.

Attempts to utilize higher order substitution patterns on the lactone, including incorporation of a quaternary center at the γ-position along with tertiary or quaternary substitution at the β-position, did not result in product formation (Scheme A2.15).

Scheme A2.15. *Highly-substituted Cyanolactones*

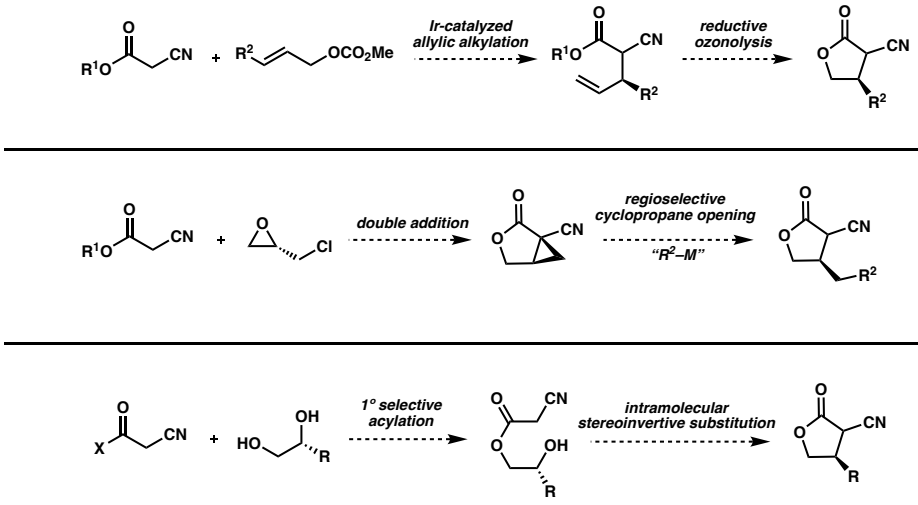


A2.2.10 SYNTHESIS AND APPLICATION OF STEREOENRICHED SUBSTRATE

Given that a third stereocenter was introduced to the substrate, we were aware that to obtain only one stereoisomer of product as the major reaction outcome, a nucleophile stereoenriched at the β-position would need to be employed. The pursuit of such lactones served as another synthetic challenge (Figure A2.2). An initial approach involved a precedented Ir-catalyzed allylic alkylation of a cyanoester nucleophile with disubstituted allylic electrophiles,[11] after which a reductive ozonolysis of the terminal olefin would furnish the stereoenriched material. Unfortunately, this plan was plagued with irreproducible enantioselectivity of the allylic alkylation and competitive reduction of the cyanoester observed upon attempted reduction of the aldehyde.

Another attempt, inspired by a literature protocol,[12] involved the reaction of cyanoesters with abundant chiral epichlorohydrin, resulting in the formation of a fused cyclopropane. This intermediate could then undergo regioselective opening at the secondary carbon of the cyclopropane with an organometallic reagent, delivering stereoenriched β-susbstituted α-cyano lactones. While the cyclopropane was possibly constructed in trace amounts, the subsequent ring-opening reaction did not prove fruitful under a range of conditions.

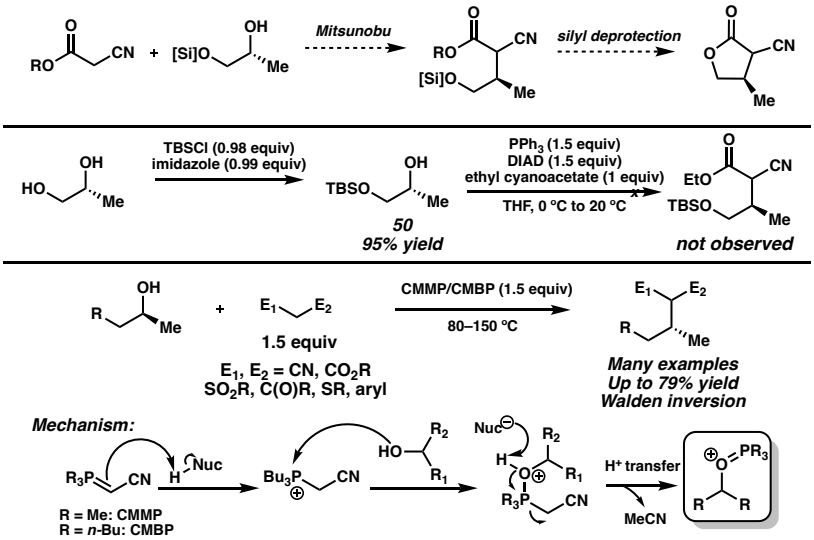
Figure A2.2. *Early Approaches to the Construction of Stereoenriched Cyanolactones.*



Without much literature precedent for asymmetric conjugate addition into α-cyanobutenolides or of their asymmetric hydrogenation, we resigned ourselves to a stepwise approach, with an envisioned acylation of the primary alcohol of a commercial, enantiopure 1,2-diol with cyanoacetic acid or a derivative thereof, followed by stereoinvertive, intramolecular substitution.

Despite a range of explored conditions, the acylation of these alcohols at exclusively the primary alcohol could not be achieved. As such, a "substitution first" strategy was employed, wherein the diol could be TBS-protected at the primary alcohol with well-precedented regiocontrol, and the secondary alcohol would be functionalized either in-situ or prior to introduction of the cyanoester nucleophile. The former, which would reduce the complexity of substrate synthesis, was examined first.

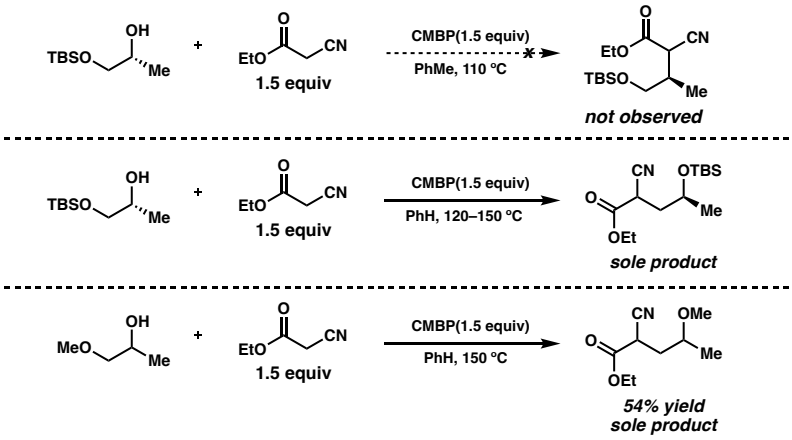
Scheme A2.16. *Attempted Intermolecular Mitsunobu Reaction*



Appel conditions did not furnish any of the desired product, but we were hopeful that treatment with a Mitsunobu reagent would allow for the desired reaction (Scheme A2.16). When DIAD did not prove compatible with the desired substitution, we turned to a series of reagents developed by Tsunoda and coworkers.[13] Unlike the traditional Mitsunobu conditions, these functionalized ylides have been utilized for the coupling of secondary alcohols with numerous stabilized carbon nucleophiles, enabled by the

temperature stability of CMMP/CMBP and the basicity of the coupling reagent. Nevertheless, in our hands, use of these conditions with ethyl cyanoacetate as the nucleophile did not lead to any observed product (Scheme A2.17). When the temperature was increased, the sole compound observed corresponded to TBS migration to the secondary alcohol and substitution at the primary position. The same phenomenon was observed even when a methyl group was used to protect the primary alcohol, dissuading us from further investigation of the Mitsunobu reaction.

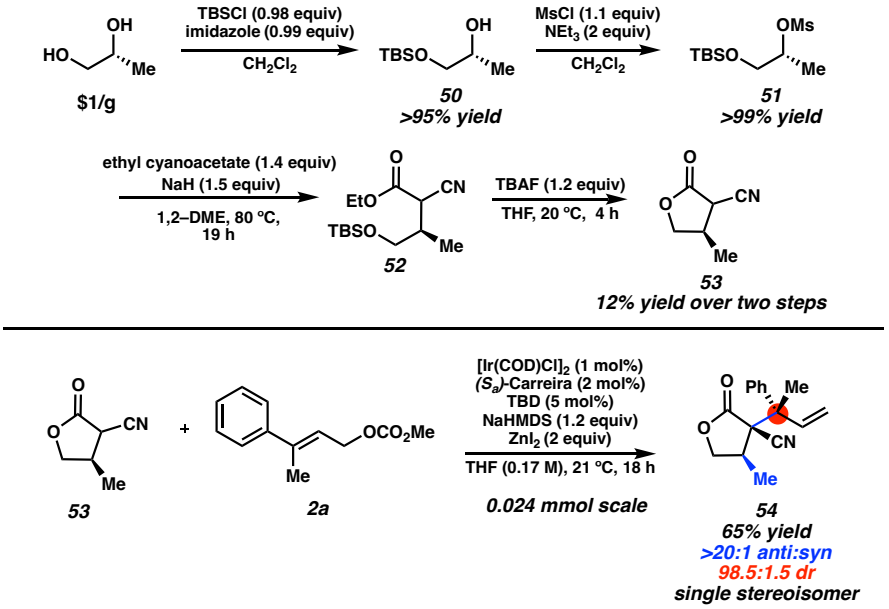
Scheme A2.17. *Tsunoda Reagents as Applied to Desired System*



With all other options exhausted, we settled upon the most elementary strategy we could imagine – activation of the secondary alcohol as a pseudo-halide and nucleophilic substitution in a separate step under forcing conditions. We ultimately arrived at the conditions presented in Scheme A2.18, allowing for the isolation of stereoenriched cyanolactone **54**. A slightly improved set of conditions for the substitution reaction is described in the Experimental Section. As anticipated, **54** could undergo the reaction

under optimal conditions to form the corresponding product containing three contiguous stereocenters as one major stereoisomer.

Scheme A2.18. *Synthesis and Coupling of Stereoenriched Cyanolactone Substrate*

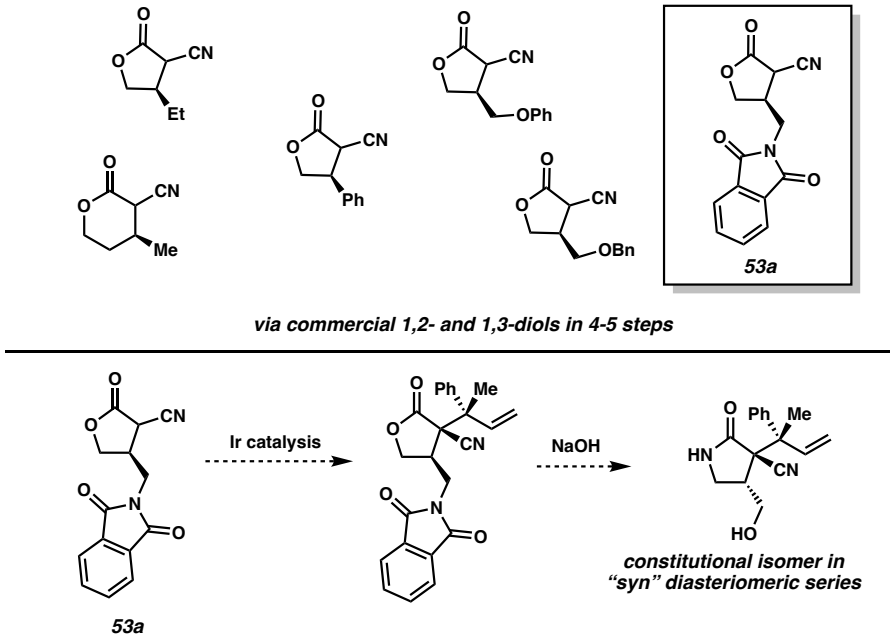


A2.3 CONCLUSION

Utilizing this synthetic sequence and a related protocol involving an intramolecular substitution, we were able to access several nucleophiles we imagine could be suitable to the desired reaction, with varying substitution at the β-position and varying ring sizes represented in the library of substrates (Scheme A2.3). Efforts are ongoing to determine the applicability of the reaction to these nucleophiles and electrophiles with differential substitution on the arene. We are particularly excited by products containing peripheral functionality, such as **53a**, which we imagine could undergo the allylic alkylation, followed by deprotection to the primary amine and lactamization to deliver a lactam

with the opposite relative stereochemistry between the α- and β-positions, thereby giving some access to the "*syn*" diastereomeric series of materials.

Figure A2.3. *Prospective Nucleophile Scope and Inversion of Relative Stereochemistry.*



In conclusion, we are enthusiastic about the pursuit of an efficient cross-coupling of two highly substituted reaction partners to form vicinal quaternary stereocenters in a doubly stereoselective fashion. Though the diastereoselectivity of the reaction we have developed has thus far only been substantially improved by the introduction of a stereocenter on the nucleophile, we are hopeful that these promising results, invoking atypically low catalyst loadings and mild reaction conditions, lay the groundwork for future research in our group's Ir-catalysis program.

A2.4 EXPERIMENTAL SECTION

A2.4.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[14] Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 μm) was used for flash chromatography. ^{1}H NMR spectra were recorded on Varian Inova 500 MHz and Bruker 400 MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm). ^{13}C NMR spectra were recorded on a Varian Inova 500 MHz spectrometer (125 MHz) and Bruker 400 MHz spectrometers (100 MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet. Data for ^{13}C NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell. Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system utilizing Chiralpak (AD-H, AS-H or IC) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing Chiralpak (IH) or Chiralcel (OD-H) columns (4.6 mm x 25 cm) both obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H

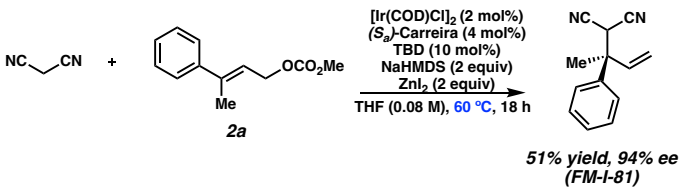
High Resolution Mass Spectrometer in field ionization (FI+) or field desorption (FD+) mode, or an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI), or mixed ionization mode (MM: ESI-APCI+). Absolute configuration of **3a** was determined by vibrational circular dichroism, and all other products are assigned by analogy. Reagents were purchased from commercial sources and used as received unless otherwise stated.

List of Abbreviations:

ee – enantiomeric excess, SFC – supercritical fluid chromatography, HPLC – high-performance liquid chromatography, TLC – thin-layer chromatography, TBD – 1,5,7-triazabicyclo[4.4.0]dec-5-ene, COD – *cis,cis*-1,5-cyclooctadiene, COE – *cis*-cyclooctene, DIBAL – diisobutylaluminum hydride, LAH – lithium aluminum hydride, NaHMDS – sodium bis(trimethylsilyl)amide, IPA – isopropanol, EtOAc – ethyl acetate, Dr – dram

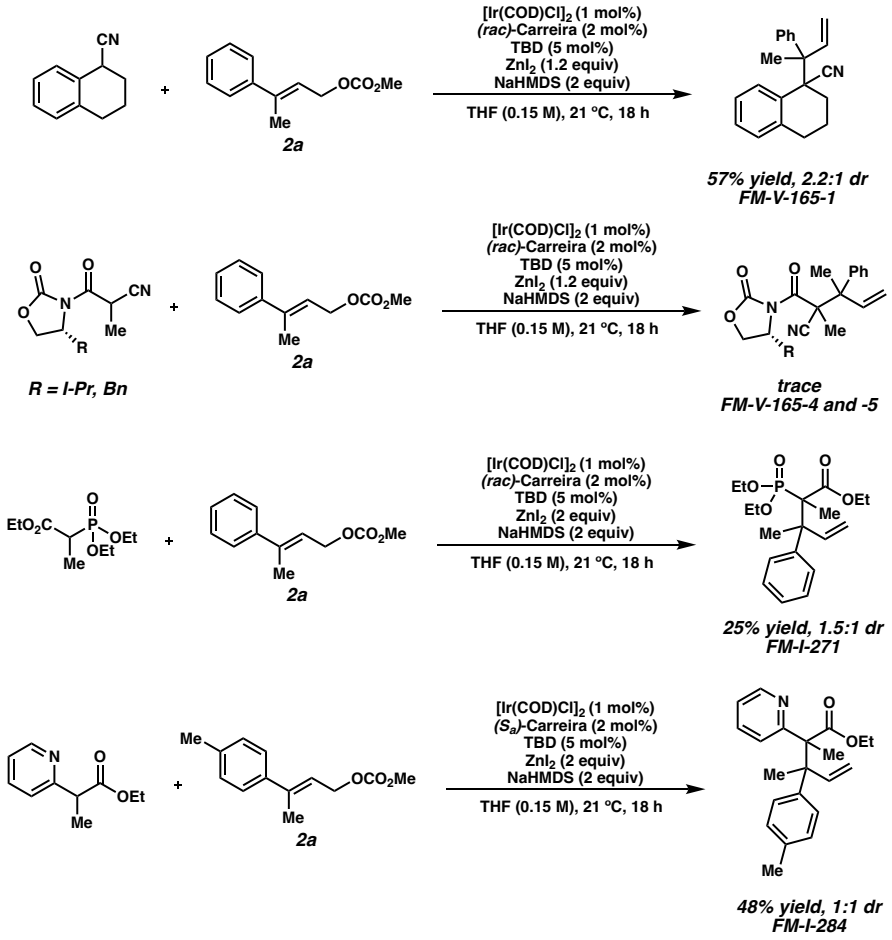
A2.4.2 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

Scheme A2.19. *Performance of Malononitrile*[a]



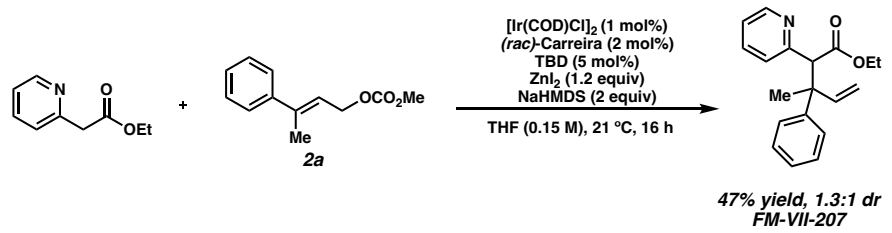
[a]Yield determined by ^{1}H NMR relative to a CH_2Br_2 internal standard.

Scheme A2.20. *Performance of Other Trisubstituted Nucleophiles*[a]



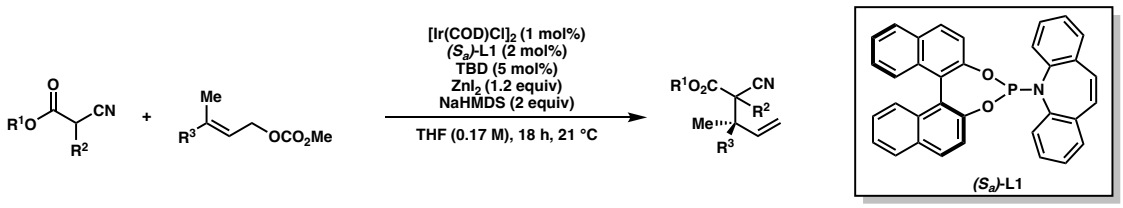
[a]Yield determined by ^{1}H NMR relative to a CH_2Br_2 internal standard.

Scheme A2.21. *Performance of Ethyl 2-Pyridyl Acetate*

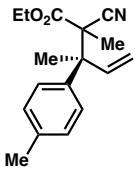


crude NMR: possible 2.5:1 mixture of branched and linear product isomers

Iridium-Catalyzed Allylic Alkylation Reactions: General Procedure A (0.1mmol scale)



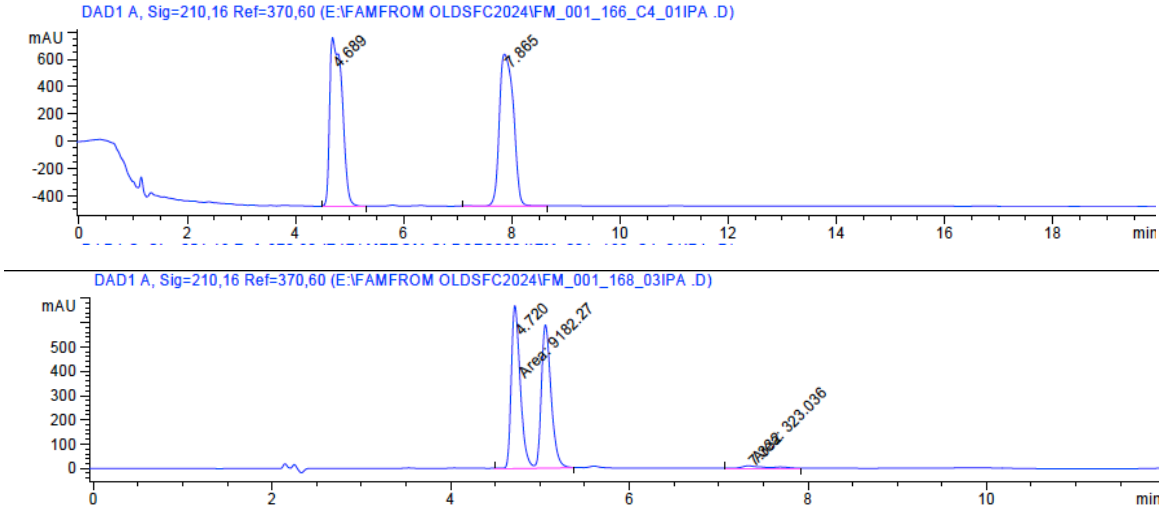
In a nitrogen-filled glovebox, a catalyst (2 mol% [Ir]) solution of $[Ir(COD)Cl]_2$ (3.3 mg/mL), ***(S$_a$)-L1*** (5 mg/mL), and TBD (3.5 mg/mL) in THF was stirred for 20 min at 25 °C. In separate vials, solutions of *(E)*-allylic carbonate (0.5 mmol/mL) and of nucleophile (0.5 mmol/mL) were prepared in THF. During that time, the reaction vial was charged with ZnI_2 (64 mg, 0.12 mmol, 1.2 equiv) and NaHMDS (36.7 mg, 0.2 mmol, 2.0 equiv). 0.23 mL of the nucleophile solution (0.1 mmol, 1.0 equiv) was added to the reaction vial and stirred for 5 min, followed by 0.20 mL of catalyst solution, and finally 0.22 mL of allylic carbonate solution (0.1 mmol, 1.0 equiv). The vial was sealed with a Teflon-lined cap, removed from the glovebox, and stirred at 21 °C for 18 h unless noted otherwise. After 18 h, 3 mL 0.5 M HCl was added to the crude reaction mixture, which was then extracted three times with ethyl acetate, dried over Na_2SO_4, concentrated, and purified by preparatory TLC to provide the desired alkylation product.



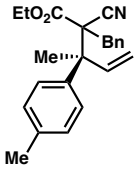
ethyl (3*S*)-2-cyano-2,3-dimethyl-3-(*p*-tolyl)pent-4-enoate (27)

Purified by preparatory TLC (10% EtOAc/Hexanes) to deliver **27** as a clear oil (23.5 mg, 0.087 mmol, 87% yield, 93% avg. ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.32 (m, 2H), 7.17 – 7.09 (m, 2H), 6.84 – 6.61 (m, 1H), 5.40 – 5.32 (m, 1H), 5.26 – 5.16 (m, 1H), 4.11 – 3.93 (m, 2H), 2.36 – 2.30 (m, 3H), 1.75 – 1.64 (m, 3H), 1.55 – 1.49 (m, 3H), 1.13 – 1.03

(m, 3H). SFC Conditions: 7% IPA, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R (min): minor = 7.87, major = 4.72.

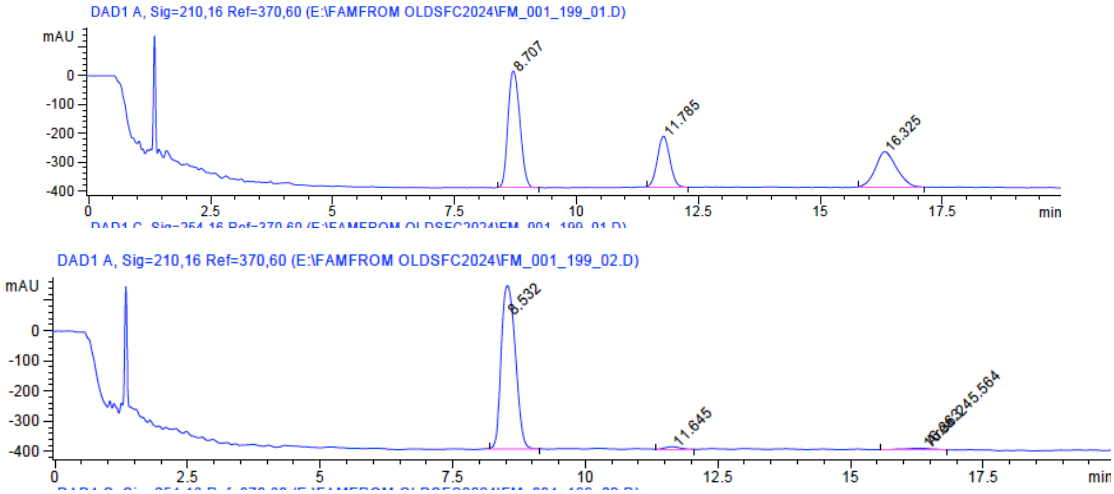


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.720	MM	0.2272	9182.27051	673.68793	96.6015
2	7.332	MM	0.4251	323.03613	12.66609	3.3985

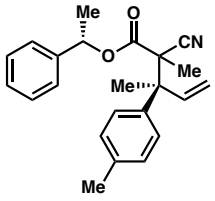


ethyl (3*S*)-2-benzyl-2-cyano-3-methyl-3-(*p*-tolyl)pent-4-enoate (28)

Purified by preparatory TLC (10% EtOAc/Hexanes) to deliver **28** as a clear oil (27.9 mg, 0.080 mmol, 80% yield, 93% avg. ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.38 (m, 2H), 7.32 – 7.20 (m, 5H), 7.19 – 7.10 (m, 2H), 7.06 – 6.86 (m, 1H), 5.50 – 5.40 (m, 1H), 5.36 – 5.26 (m, 1H) 3.95 – 3.73 (m, 2H), 3.56 – 2.78 (m, 2H), 2.36 – 2.31 (m, 3H), 1.88 – 1.81 (m, 3H), 0.86 (q, J = 7.3 Hz, 3H). SFC Conditions: 1% IPA, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R (min): minor = 11.79 and 16.33, major = 8.53.

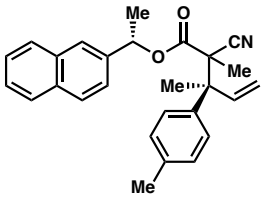


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.532	BB	0.3008	1.00230e4	539.46515	96.3114
2	11.645	BB	0.2457	138.30000	7.84340	1.3289
3	16.363	MM	0.7200	245.56386	5.68445	2.3596



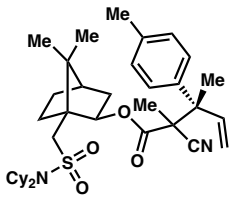
(*S*)-1-phenylethyl (3*S*)-2-cyano-2,3-dimethyl-3-(*p*-tolyl)pent-4-enoate (31)

Crude yield determined by ^{1}H NMR relative to CH_2Br_2 internal standard (30.0 mg) assuming peaks at 6.59 ppm and 6.81 ppm belong to diastereomers of product and integrate to 1H (87% yield, 1.3:1 dr).



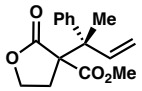
(*S*)-1-(naphthalen-2-yl)ethyl (3*S*)-2-cyano-2,3-dimethyl-3-(*p*-tolyl)pent-4-enoate (32)

Crude yield determined by ^{1}H NMR relative to CH_2Br_2 internal standard (26.2 mg) assuming peaks at 6.68 ppm and 6.76 ppm belong to diastereomers of product and integrate to 1H (82% yield, 1:1 dr).



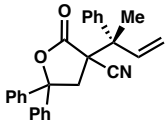
(1*R*,2*R*,4*R*)-1-((*N*,*N*-dicyclohexylsulfamoyl)methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-yl (3*S*)-2-cyano-2,3-dimethyl-3-(*p*-tolyl)pent-4-enoate (34)

Crude yield determined by ^{1}H NMR relative to CH_2Br_2 internal standard (25.1 mg) assuming peaks at 6.67 ppm and 7.00 ppm belong to diastereomers of product and integrate to 1H (66% yield, 3.8:1 dr).



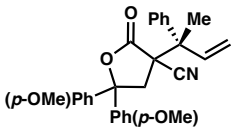
methyl 2-oxo-3-((*S*)-2-phenylbut-3-en-2-yl)tetrahydrofuran-3-carboxylate (39)

Crude yield determined by ^{1}H NMR relative to CH_2Br_2 internal standard assuming peaks at 5.17 ppm and 5.08 ppm belong to diastereomers of product and integrate to 1H (48% yield, 1.2:1 dr).



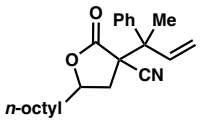
2-oxo-5,5-diphenyl-3-((*S*)-2-phenylbut-3-en-2-yl)tetrahydrofuran-3-carbonitrile (42)

Crude yield determined by ^{1}H NMR relative to CH_2Br_2 internal standard (25.4 mg) assuming combined peaks at 5.27 ppm and 5.45 ppm belong to diastereomers of product and integrate to 2H (69% yield, 1.1:1 dr).



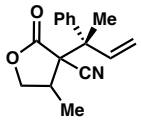
5,5-bis(4-methoxyphenyl)-2-oxo-3-((*S*)-2-phenylbut-3-en-2-yl)tetrahydrofuran-3-carbonitrile (43)

Crude yield determined by ^{1}H NMR relative to CH_2Br_2 internal standard (24.5 mg) assuming peaks at 6.20 ppm and 6.28 ppm belong to diastereomers of product and integrate to 1H (65% yield, 1.3:1 dr).



5-octyl-2-oxo-3-(2-phenylbut-3-en-2-yl)tetrahydrofuran-3-carbonitrile (45)

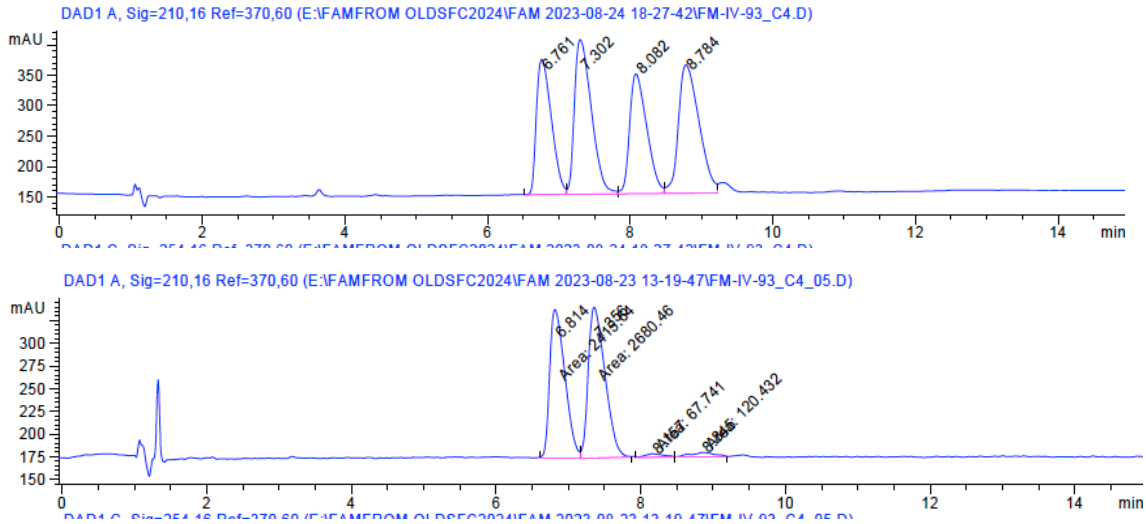
Reaction performed with racemic ligand using 1.2 equiv of **44**. Crude yield determined by by ^{1}H NMR relative to CH_2Br_2 internal standard (30.7 mg) assuming peaks at 6.35 ppm, 6.50 ppm, 6.59 ppm, and 6.69 ppm belong to diastereomers of product and integrate to 1H (56% yield, 2.4:1 dr).



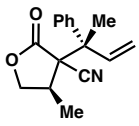
4-methyl-2-oxo-3-((*S*)-2-phenylbut-3-en-2-yl)tetrahydrofuran-3-carbonitrile (47)

Reaction performed using 1.5 equiv of **48**. Purified by silica gel chromatography (20–60% EtOAc/Hexanes) to afford **47** as a waxy solid (19.4 mg, 0.076mmol, 76% yield). ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.54 – 7.43 (m, 2H), 7.42 – 7.30 (m, 3H), 6.71 – 6.52 (m, 1H), 5.55 – 5.37 (m, 1H), 5.31 – 5.19 (m, 1H), 3.71 – 3.59 (m, 1H), 3.53 – 3.36 (m, 1H), 2.77 – 2.57 (m, 1H), 1.93 – 1.76 (m, 3H), 1.12 – 0.92 (m, 3H). SFC Conditions: 5% IPA, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R (min): minor = 8.08 and 8.78, major = 6.81 and 7.36.



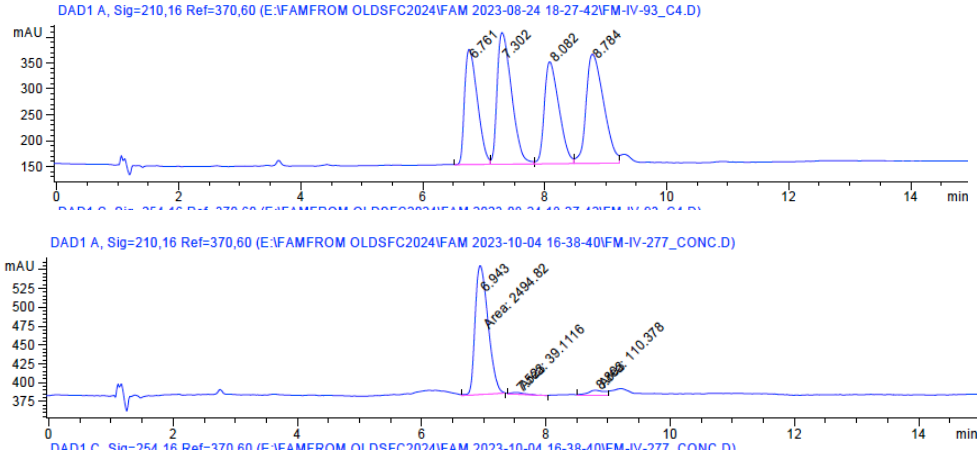
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.814	MM	0.2449	2415.64038	164.38982	159.9982
2	7.356	MM	0.2686	2680.45825	166.32680	177.5383
3	8.157	MM	0.2775	67.74096	4.06903	4.4868
4	8.845	MM	0.3913	120.43221	5.12974	7.9767
Totals :				5284.27180	339.91538	



(4*R*)-4-methyl-2-oxo-3-((*S*)-2-phenylbut-3-en-2-yl)tetrahydrofuran-3-carbonitrile (54)

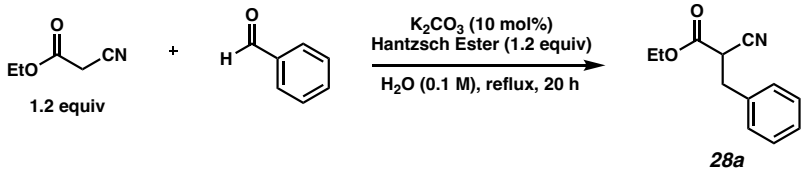
Reaction performed at 0.024 mmol scale. Purified by silica gel chromatography to afford **54** as an oil (3.5 mg, 0.016 mmol, 65% yield, >20:1 dr, 98.5:1.5 dr). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.44 (m, 2H), 7.43 – 7.28 (m, 3H), 6.58 (dd, J = 17.5, 11.1 Hz, 1H), 5.49 (d, J = 11.1 Hz, 1H), 5.26 (d, J = 17.5 Hz, 1H), 3.63 (dd, J = 9.1, 5.5 Hz, 1H), 3.41 (dd, J

= 9.2, 7.5 Hz, 1H), 2.71 (pd, J = 7.2, 5.5 Hz, 3H), 1.82 (s, 1H), 1.01 (d, J = 7.1 Hz, 3H). SFC Conditions: 5% IPA, 2.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R (min): minor = 7.52 and 8.80, major = 6.94.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.943	MM	0.2427	2494.81714	171.31042	330.2136
2	7.523	MM	0.2654	39.11162	2.45623	5.1768
3	8.803	MM	0.2976	110.37820	6.18095	14.6096
Totals :				2644.30695	179.94760	

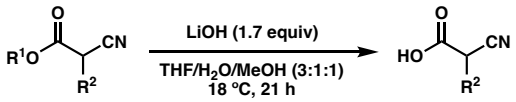
Synthesis of Benzyl-Substituted Cyanoester 28a[15]



Ethyl cyanoacetate (542.9 mg, 4.8 mmol, 1.2 equiv), benzaldehyde (424.5 mg, 4 mmol), K_2CO_3 (55.3 mg, 0.4 mmol, 0.1 equiv), and Hantzsch ester (1.216 g, 4.8 mmol, 1.2 equiv) were combined in a roundbottom flask equipped with a stir bar and dissolved in H2O (40 mL, 0.1 M). The reaction was then heated to reflux and stirred for 20 h, at which point the temperature was lowered to ambient conditions. The solution was extracted three times with ethyl acetate, and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (10%

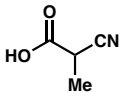
EtOAc/Hexanes), resulting in a mixture of the product and the pyridine biproduct. This was dissolved in EtOAc and washed three times with 5 M aq. H_2SO_4, and the organic layer was dried, filtered, and concentrated to deliver ethyl 2-cyano-3-phenylpropanoate (**28a**) as a clear oil (142 mg, 0.7 mmol, 18% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 5H), 4.30 – 4.18 (m, 2H), 3.72 (dd, J = 8.4, 5.8 Hz, 1H), 3.33 – 3.14 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H). Characterization data was in agreement with the literature.

Saponification of Cyanoester Substrates[16]



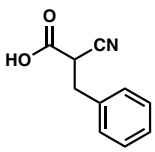
35 or 36

The appropriate cyanoester (10 mmol) was dissolved in a mixture of THF, H_2O and MeOH (THF:H_2O:MeOH = 30 mL: 10 mL: 10 mL), and LiOH (0.713 g, 17 mmol, 1.7 equiv) was added. The reaction was stirred at 18 ºC for 21 h, at which point it was quenched with 20 mL 1.0 M aq. HCl. The mixture was extracted with ethyl acetate, dried with Na_2SO_4, filtered, and concentrated to deliver the cyanoacid without the need for further purification.



2-cyanopropanoic acid (35)

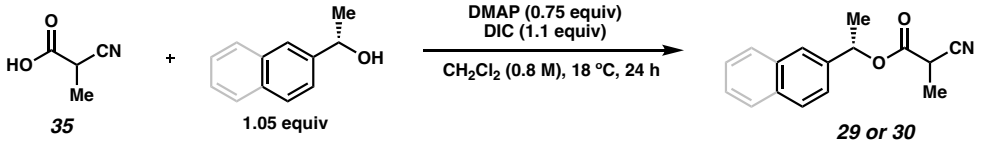
Product was obtained as a yellow oil (980 mg, 9.9 mmol, 99% yield) from ethyl 2-cyanopropanoate. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.65 (q, J = 7.4 Hz, 1H), 1.67 (d, J = 7.4 Hz, 3H). Characterization data was in agreement with the literature.[17]



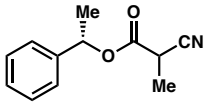
2-cyano-3-phenylpropanoic acid (36)

Reaction performed at 7.2 mmol scale using **28a**. Additional purification involved extraction from CH_2Cl_2 with 1 M NaOH, followed by acidification of the aqueous layer with 2 M HCl and extraction from the aqueous phase with ethyl acetate. Product was obtained as a clear oil (145 mg, 0.83 mmol, 12% yield). ^{1}H NMR (400 MHz, MeOD) δ 7.50 – 7.14 (m, 5H), 3.63 (dd, J = 9.2, 5.5 Hz, 1H), 3.28 – 3.04 (m, 2H).

Esterification of Cyanoacids[18]

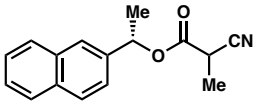


A mixture of cyanoacid **35** (396.4 mg, 4 mmol), chiral alcohol (4.2 mmol, 1.05 equiv), and DMAP (366.5 mg, 3 mmol, 0.75 equiv) was prepared under inert atmosphere and dissolved in CH_2Cl_2 (5 mL, 0.8 M). Diisopropylcarbodiimide (555.3 mg, 0.69 mL, 1.1 equiv) was then added via syringe, and the solution was stirred at 18 ºC for 24 h. The reaction mixture was then filtered and washed thoroughly with ethyl acetate. The filtrant was concentrated and purified by silica gel chromatography (20% EtOAc/Hexanes) to furnish the corresponding chiral ester.



(*S*)-1-phenylethyl 2-cyanopropanoate (29)

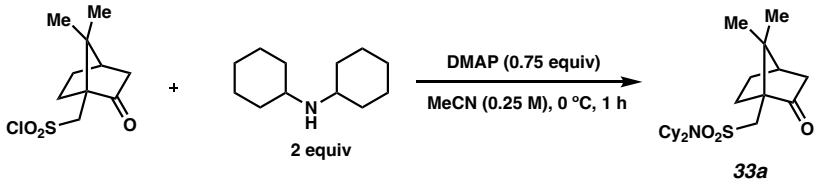
Isolated as a white solid (652 mg, 3.2 mmol, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 5H), 5.94 (q, J = 6.6 Hz, 1H), 3.55 (dq, J = 14.8, 7.4 Hz, 1H), 1.65 – 1.54 (m, 6H).



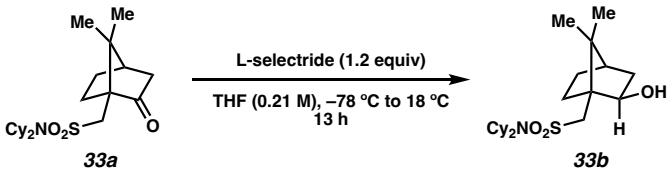
(*S*)-1-(naphthalen-2-yl)ethyl 2-cyanopropanoate (30)

Isolated as a white solid (680 mg, 2.68 mmol, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.80 (m, 4H), 7.55 – 7.45 (m, 3H), 6.11 (q, J = 6.6 Hz, 1H), 3.65 – 3.50 (m, 1H), 1.70 (dd, J = 6.7, 4.5 Hz, 3H), 1.58 (dd, J = 7.4, 3.5 Hz, 3H).

Synthesis of Isoborneol-Derived Chiral Cyanoester 33

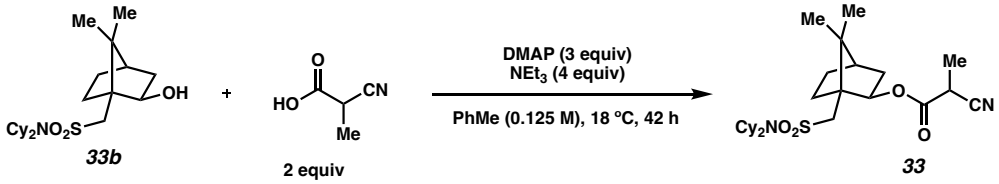


Amidation[19]**:** Inspired by a literature protocol, (+)-camphor-10-sulfonyl chloride (1.25 g, 5 mmol) was dissolved in acetonitrile (20 mL, 0.25 M) under N_2. To this solution at 0 ºC were added dicyclohexylamine (1.82 mL, 10 mmol, 2 equiv) and DMAP (160 mg, 1.32 mmol, 0.26 equiv). The reaction proceeded for 1 h at this temperature, at which point it was quenched with H_2O (13 mL), 1 M aq. HCl (4 mL), and 2 M aq. HCl (2 mL). The mixture was extracted three times with ethyl acetate, and the organic layers were combined, dried with Na_2SO_4, filtered, and concentrated. Crude sulfonamide **33a** was advanced to the next step without additional purification.



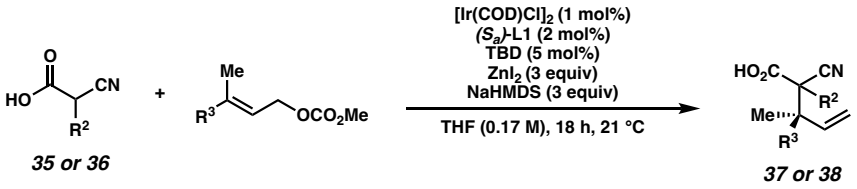
Reduction[20]**:** Sulfonamide **33a** was then dissolved in THF (9 mL, 0.21 M) under inert atmosphere and cooled to –78 ºC. A solution of L-selectride (2.27 mL, 1.0 M in THF, 1.19

equiv) was added, and the resulting mixture was allowed to warm slowly to ambient temperature overnight. After 13 h, the reaction was deemed complete by TLC and quenched by the addition of 8 mL H_2O and 2 mL sat. aq. Na_2CO_3. Three extractions were performed with ethyl acetate, and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel chromatography (0–20% EtOAc/Hexanes) to deliver N,N-dicyclohexyl-1-(*(1R,2R,4R)*-2-hydroxy-7,7-dimethylbicyclo[2.2.1]heptan-1-yl)methanesulfonamide [**33b**] (894.3 mg, 2.25 mmol, 45% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09 (dt, J = 7.9, 4.0 Hz, 1H), 3.50 (d, J = 3.7 Hz, 1H), 3.34 – 3.19 (m, 3H), 2.66 (d, J = 13.3 Hz, 1H), 1.90 – 1.56 (m, 20H), 1.39 – 1.08 (m, 6H), 1.06 (s, 3H), 0.81 (s, 3H). Characterization data was in agreement with the literature.

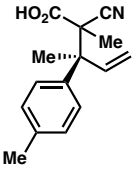


Esterification[21]: To a solution of DMAP (367 mg, 3 mmol, 3 equiv), NEt_3, (404.8mg, 0.558 mL, 4 mmol, 4 equiv), cyanoacid **35** (200 mg, 2 mmol, 2 equiv) and isoborneol **33** (397.6 mg, 1 mmol) in PhMe (8 mL, 0.125 M) and under N_2 was added 2,4,6-trichlorobenzoylchloride (731.7 mg, 0.469 mL, 3 mmol, 3 equiv). The reaction was stirred for 42 h at this temperature and quenched by the addition of 3 mL sat. aq. NH_4Cl. The mixture was extracted three times with ethyl acetate. The organic extracts were dried with Na_2SO_4, filtered, concentrated, and purified by silica gel chromatography (20% EtOAc/Hexanes) to deliver *(1R,2R,4R)*-1-((N,N-dicyclohexylsulfamoyl)methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-yl 2-cyanopropanoate [**33**] (148.5 mg, 0.62 mmol, 62% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.05 (ddd, J = 7.6, 4.8, 2.8 Hz, 1H), 3.53 (dq, J = 15.1, 7.5 Hz, 1H), 3.37 (dd, J = 20.9, 13.3 Hz, 1H), 3.33 – 3.22 (m, 2H), 2.66 (dd, J = 14.9, 13.3 Hz, 1H), 2.06 – 1.58 (m, 23H), 1.48 – 1.09 (m, 7H), 1.08 (s, 3H), 0.90 (s, 3H). Characterization data was in agreement with the literature.

Iridium-Catalyzed Allylic Alkylation of Cyanoacid Nucleophiles

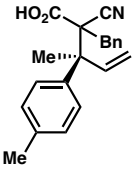


The allylic alkylation of cyanoacid nucleophiles was conducted via General Procedure A, with the exception of the stoichiometries of ZnI_2 and NaHMDS. Both were used in greater excess (3 equiv), equating to 95.8 mg ZnI_2 and 55.0 mg NaHMDS.



(3*S*)-2-cyano-2,3-dimethyl-3-(*p*-tolyl)pent-4-enoic acid (37)

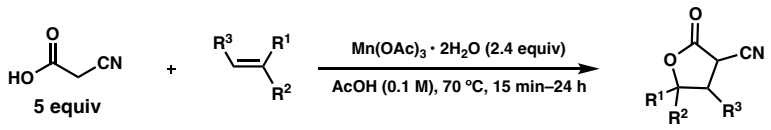
Crude yield determined by ^{1}H NMR relative to CH_2Br_2 internal standard (21.6 mg) assuming peaks at 6.62 ppm and 6.76 ppm belong to diastereomers of product and integrate to 1H (83% yield, 1.2:1 dr).



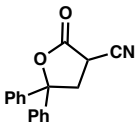
(3*S*)-2-benzyl-2-cyano-3-methyl-3-(*p*-tolyl)pent-4-enoic acid (38)

Crude yield determined by ^{1}H NMR relative to CH_2Br_2 internal standard (27.9 mg) assuming peaks at 6.83 ppm and 6.95 ppm belong to diastereomers of product and integrate to 1H (80% yield, 1:1 dr).

Mn-mediated Oxidative Cyclization

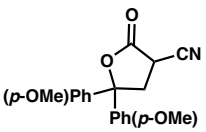


Cyanoacetic acid (1.7 g, 20 mmol, 8 equiv), $Mn(OAc)_2$•H2O (1.6 g, 6 mmol, 2.4 equiv), and the olefin (2.5 mmol) were dissolved in AcOH (25 mL, 0.1 M). The mixture was heated to 70 ºC, and the reaction proceeded at this temperature until a color change from deep red to clear was observed or after 21 h. At this point, the reaction was cooled to ambient temperature and carefully neutralized with sat. aq. $NaHCO_3$. Three extractions were performed with either Et_2O, EtOAc, or CH_2Cl_2, then the organics were dried with Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatography (10% EtOAc/Hexanes) to deliver the corresponding cyanolactone.



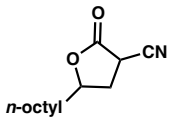
2-oxo-5,5-diphenyltetrahydrofuran-3-carbonitrile (40)

Isolated as a waxy solid (303.6 mg, 1.15 mmol, 46% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.28 (m, 10H), 3.68 (dd, J = 12.2, 8.0 Hz, 1H), 3.47 (dd, J = 12.7, 8.0 Hz,1H), 3.14 (dd, J = 12.8, 12.2 Hz, 1H). Characterization data was in agreement with the literature.[22]



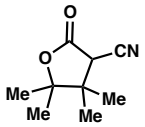
5,5-bis(4-methoxyphenyl)-2-oxotetrahydrofuran-3-carbonitrile (41)

Isolated as a waxy solid (135 mg, 0.42 mmol, 14% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 – 7.12 (m, 2H), 7.12 – 7.06 (m, 2H), 6.96 – 6.92 (m, 2H), 6.86 – 6.79 (m, 2H), 5.89 (t, J = 7.4 Hz, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 3.15 (d, J = 7.4 Hz, 2H).



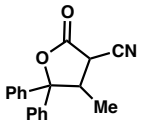
5-octyl-2-oxotetrahydrofuran-3-carbonitrile (44)

Isolated as a crusty solid (285 mg, 1.28 mmol, 51% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.49 (ddt, J = 10.5, 7.6, 5.5 Hz, 1H), 3.71 (dd, J = 11.9, 8.9 Hz, 1H), 2.79 (ddd, J = 12.8, 9.0, 5.5 Hz, 1H), 2.29 – 2.19 (m, 1H), 1.98 – 0.75 (m, 17H). Characterization data was in agreement with the literature.[8]



4,4,5,5-tetramethyl-2-oxotetrahydrofuran-3-carbonitrile (48)

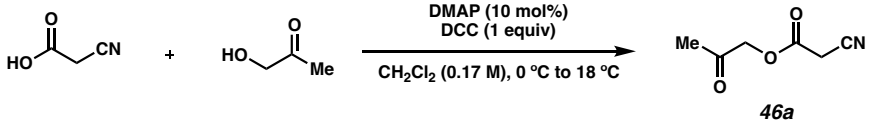
Reaction performed at 5 mmol scale. Isolated as a clear oil (84 mg, 0.50 mmol, 10% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 1H), 1.42 (s, 3H), 1.37 (s, 3H), 1.28 (s, 3H), 1.23 (s, 3H). Characterization data was in agreement with the literature.[8]



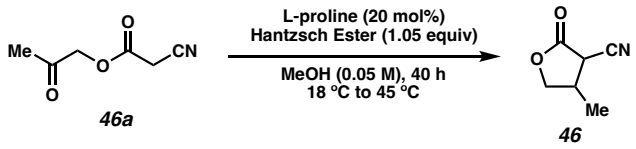
4-methyl-2-oxo-5,5-diphenyltetrahydrofuran-3-carbonitrile (49)

Reaction performed at 2 mmol scale (362 mg, 1.31 mmol, 65% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.48 (m, 1H), 7.44 – 7.27 (m, 8H), 7.08 – 7.02 (m, 1H), 3.91 – 3.41 (m, 2H), 1.32 – 1.01 (m, 3H).

Synthesis of Racemic β-substituted Cyanolactone 46



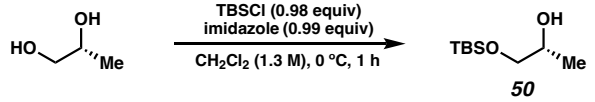
Steglich Esterification: Cyanoacetic acid (850.6 mg, 10 mmol), acetol (740 mg, 0.7 mL, 10 mmol, 1 equiv), and DMAP (122 mg, 1 mmol, 0.1 equiv) were combined in a flask under N_2 and CH_2Cl_2 (40 mL, 0.25 M) was added. The mixture was cooled to 0 ºC. To another flask under N2 were added DCC (2.063 g, 10 mmol, 1 equiv) and CH_2Cl_2 (20 mL, 0.5 M). The DCC solution was added to the first mixture at 0 ºC, and the reaction was allowed to warm slowly to ambient temperature. After 4 h, the reaction mixture was filtered and washed with CH_2Cl_2. The filtrant was concentrated and purified by silica gel chromatography (50% EtOAc/Hexanes) to afford 2-oxopropyl 2-cyanoacetate [**46a**] (0.919 g, 6.52 mmol, 65% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.80 (s, 2H), 3.61 (s, 2H), 2.20 (s, 3H). Characterization data was in agreement with the literature.[23]



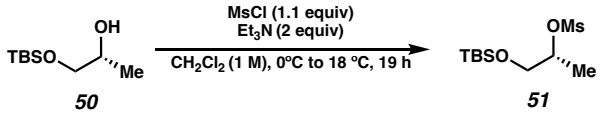
Reductive Knoevenagel[24]: The ketoester **46a** (0.919 g, 6.52 mmol), L-proline (150 mg, 1.30 mmol, 0.2 equiv), and Hantzsch ester (1.672 g, 6.6 mmol, 1.05 equiv) were combined in MeOH (130 mL, 0.05 M). The reaction was stirred at 18 ºC for 20 h, and then the temperature was raised to 45 ºC. After another 20 h, the reaction was cooled back to ambient temperature and concentrated by rotatory evaporation to remove methanol. To the residue were added ethyl acetate and water, and three extractions were performed with ethyl acetate before the organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (50% EtOAc/Hexanes) to deliver a mixture of the desired product and the unsaturated cyanobutenolide. This mixture of white solids and a viscous oil was forced through a small plug of cotton to remove the

solids. The remaining oil was found to contain solely 4-methyl-2-oxotetrahydrofuran-3-carbonitrile (**46**), which was then used in the allylic alkylation without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.59 – 4.42 (m, 1H), 4.17 – 3.23 (m, 2H), 3.06 – 2.90 (m, 1H), 1.41 – 1.31 (m, 3H).

Synthesis of Stereoenriched β-substituted Cyanolactone 53

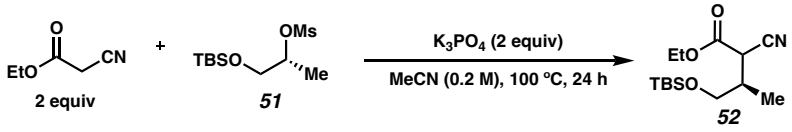


Regioselective TBS-protection[25]: To a solution of (*R*)-propane 1,2-diol (761 mg, 0.732 mL, 15 mmol) and imidazole (1.011 g, 14.85 mmol, 0.99 equiv) in CH_2Cl_2 (11.4 mL, 1.3 M) at 0 ºC was added TBSCl (2.204 g, 14.63 mmol, 0.975 equiv).The mixture was stirred at this temperature for 1 h, at which point it was filtered and rinsed with CH_2Cl2. Concentration afforded crude *(R)*-1-((tert-butyldimethylsilyl)oxy)propan-2-ol **50** as a clear oil (2.96 g, 15 mmol, quant.), which was pure enough to advance without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.82 (td, J = 9.3, 4.7 Hz, 1H), 3.60 (dd, J = 9.9, 3.4 Hz, 1H), 3.35 (dd, J = 9.9, 7.8 Hz, 1H), 1.13 (d, J = 6.3 Hz, 3H), 0.92 (s, 9H), 0.09 (s, 6H). Characterization data was in agreement with the literature.

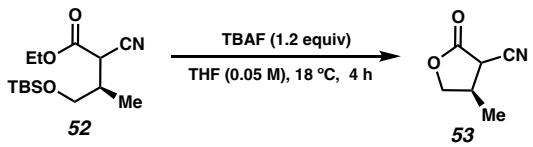


Mesylation[26]: To a roundbottom flask equipped with a stir bar and under N_2 were added **50** (190.4 mg, 1 mmol), Et_3N (202.4 mg, 0.279 mL, 2 mmol, 3 equiv), and CH_2Cl_2 (1 mL, 1 M). The solution was cooled to 0 ºC and MsCl (126.1 mg, 85.2 uL, 1.1 mmol, 1.1 equiv) was added slowly in a single portion. The reaction was allowed to warm to ambient temperature and reacted for 19 h until it was quenched by the addition of 1 mL sat. aq. NH_4Cl. Following three extractions with CH_2Cl_2, the organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel

chromatography (10% Et_2O/Pentanes) to afford *(R)*-1-((tert-butyldimethylsilyl)oxy)propan-2-yl methanesulfonate (**51**) as a clear oil (275 mg, 1 mmol, quant.). Use of crude material without silica gel chromatography was also successful. 1H NMR (400 MHz, $CDCl_3$) δ 4.75 (pd, J = 6.5, 3.9 Hz, 1H), 3.76 – 3.61 (m, 2H), 3.03 (s, 3H), 1.38 (d, J = 6.4 Hz, 3H), 0.90 (s, 9H), 0.08 (d, J = 2.4 Hz, 6H). Characterization data was in agreement with the literature.



Intermolecular Substitution: To a mixture of ethylcyanoacetate (43 uL, 0.4 mmol, 2 equiv) and K_3PO_4 (85 mg, 0.4 mmol, 2 equiv) and MeCN (1 mL, 0.2 M) in a microwave vial under N_2 was added mesylate **51** (54 mg, 0.2 mmol). The reaction was heated to 100 ºC and stirred at this temperature for 24 h. The vessel was cooled to ambient temperature, and 50 mL sat. aq. NH4Cl was added. Three extractions were performed with ethyl acetate, and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel chromatography (10% EtOAc/Hexanes) to deliver ethyl (3*R*)-4-((*tert*-butyldimethylsilyl)oxy)-2-cyano-3-methylbutanoate [**52**] (16.2 mg, 0.057 mmol, 28% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.32 – 4.20 (m, 2H), 4.05 – 3.39 (m, 3H), 2.52 – 2.42 (m, 1H), 1.43 – 1.22 (m, 3H), 1.14 – 0.97 (m, 3H), 0.94 – 0.88 (m, 9H), 0.15 – 0.02 (m, 6H).



TBAF Deprotection/Lactonization: To a solution of **52** (10.8 mg, 0.04 mmol) in THF (0.8 mL, 0.05 M) was added a solution of TBAF (0.06 mL, 1.0 M in THF, 0.06 mmol). The reaction was stirred for 4 h at 18 ºC and quenched with 1 mL sat. aq. NH_4Cl. Three

extractions were performed with ethyl acetate, and the combined organic extracts were dried with Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography (50% EtOAc/Hexanes) to afford the stereoenriched cyanolactone **53** as a light yellow, maple-scented oil (3 mg, 0.026 mmol, 64% yield). ^{1}H NMR data consistent with **46**.

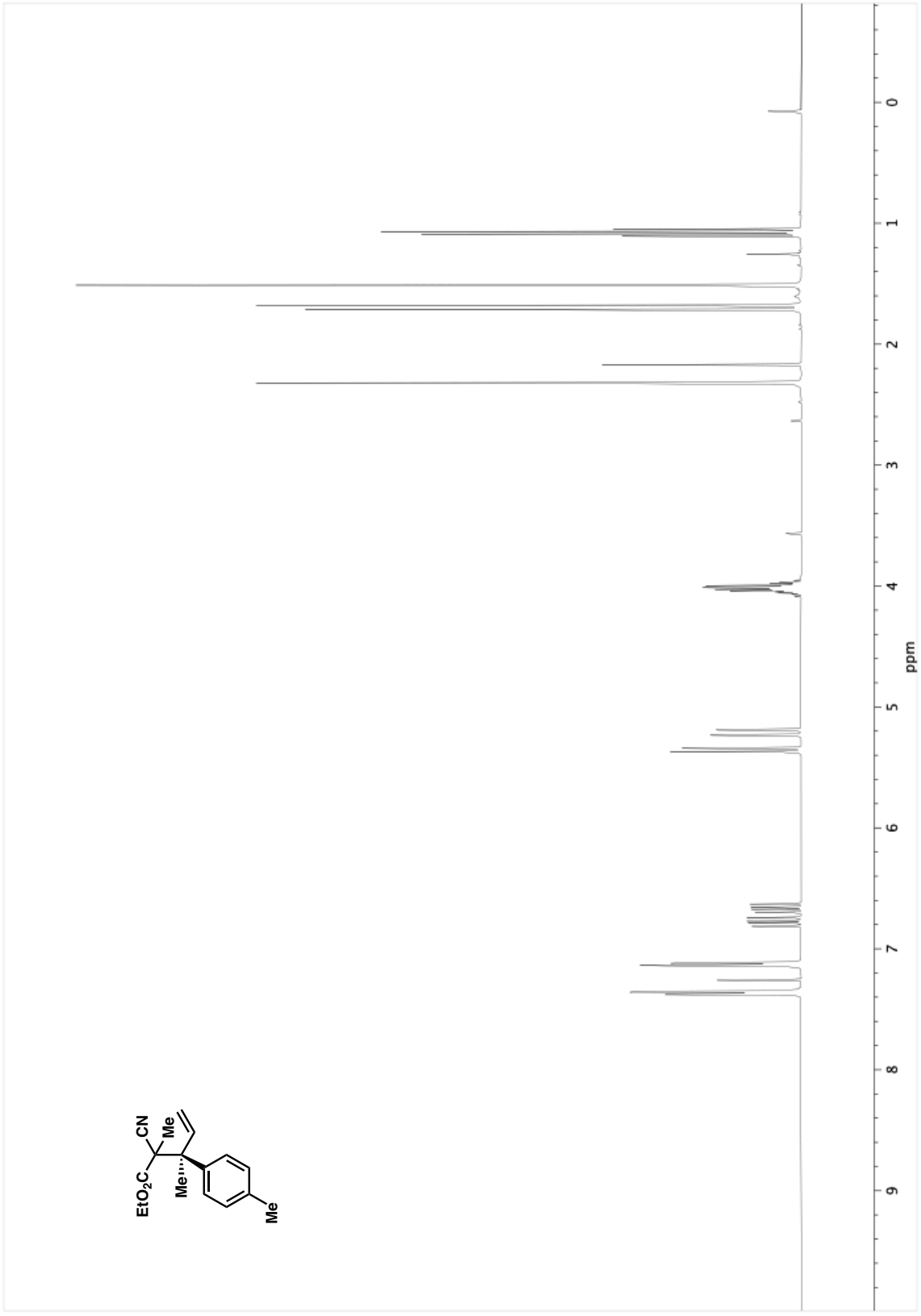


Figure A2.4. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***27****.*

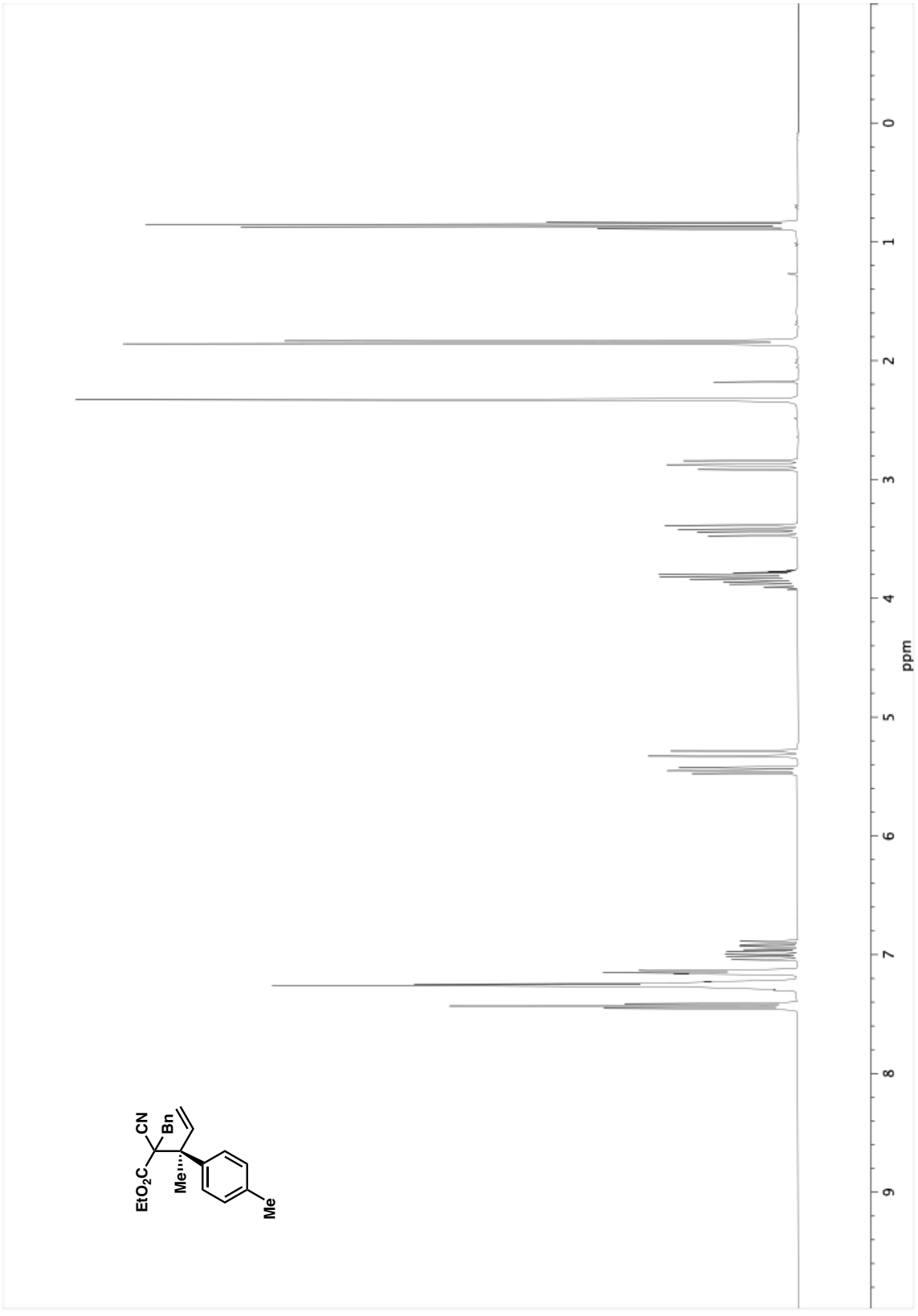


Figure A2.5. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***28****.*

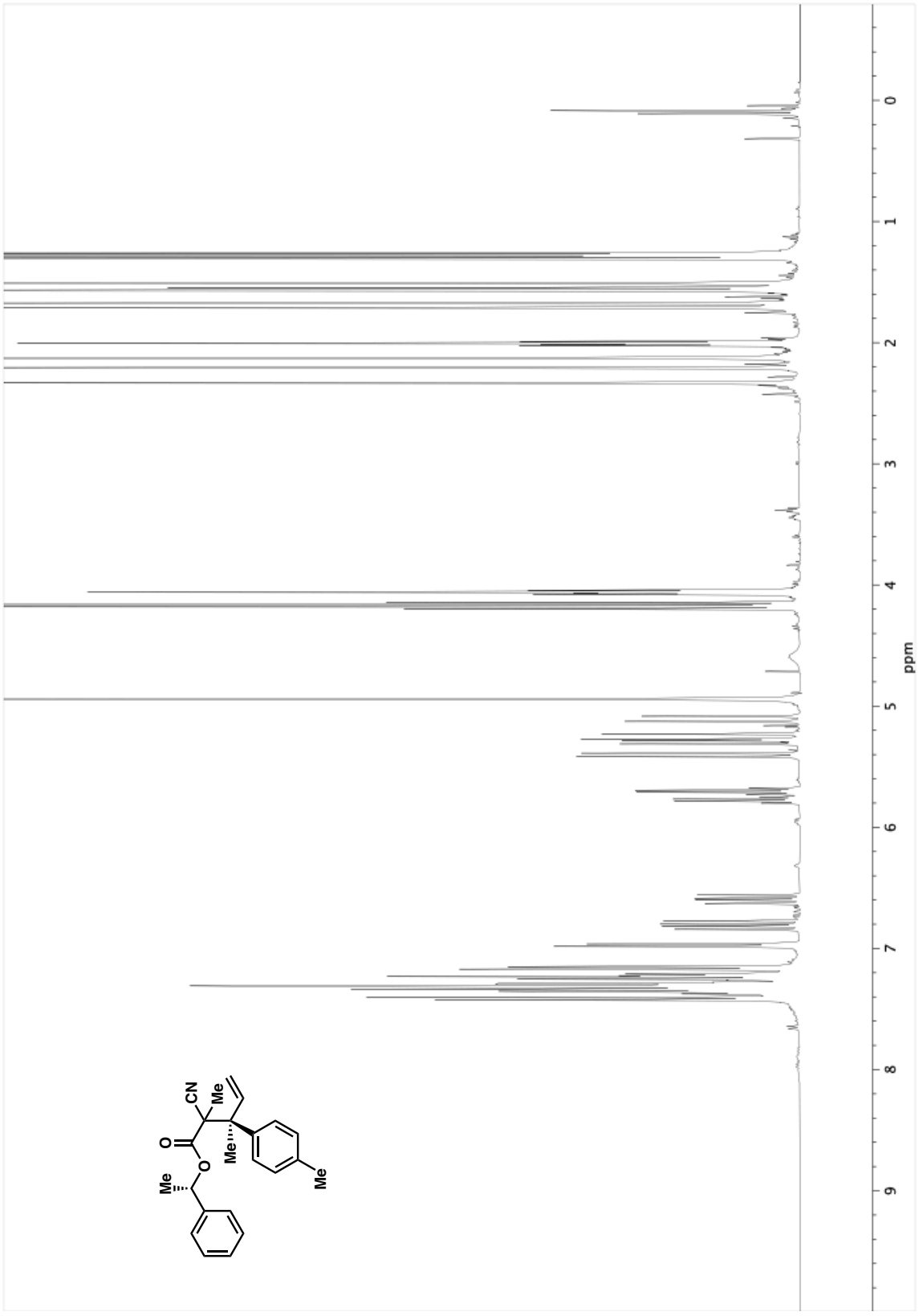


Figure A2.6. *Crude ^{1}H NMR (400 MHz, $CDCl_3$) of compound **31**.*

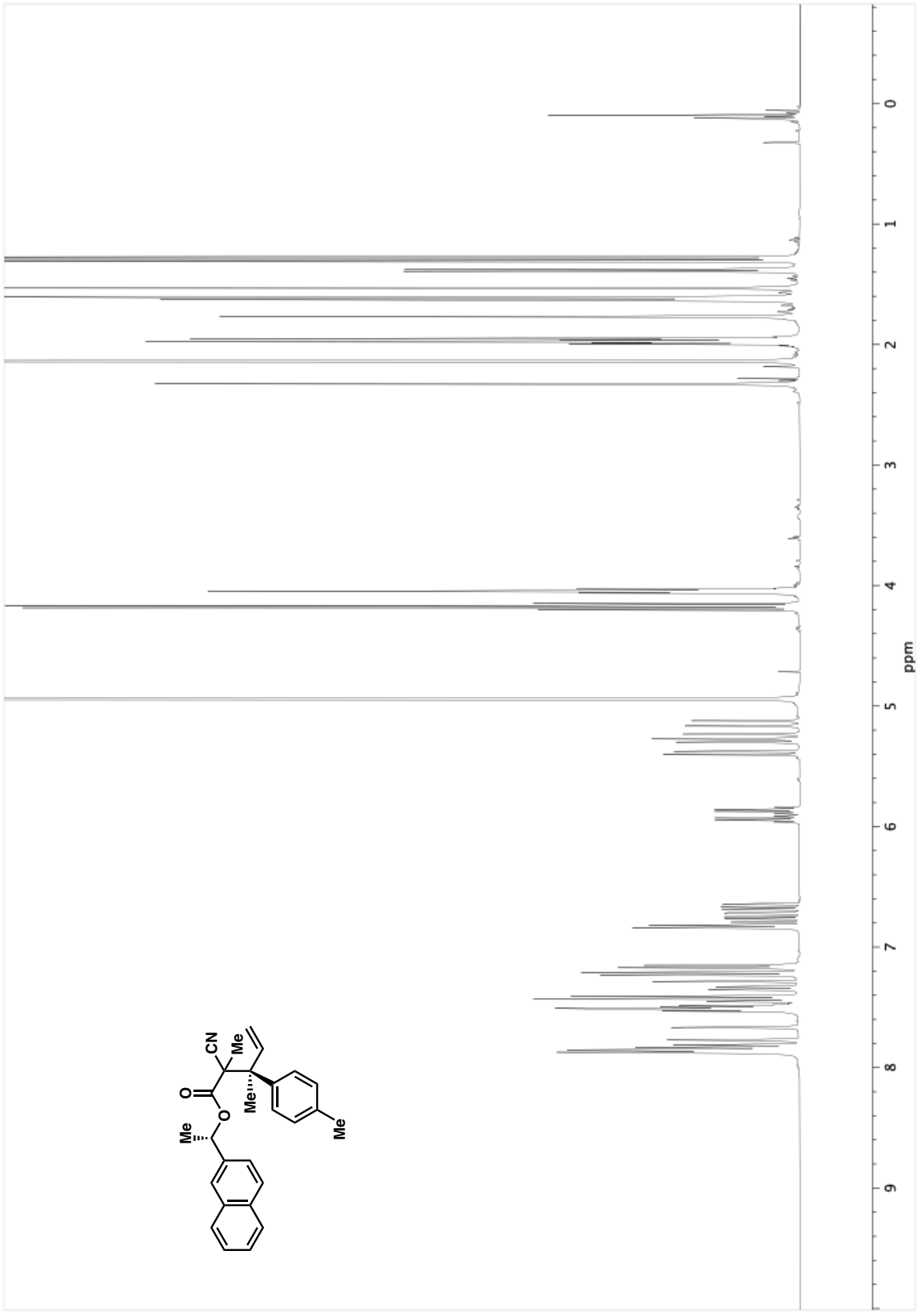


Figure A2.7. *Crude ^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***32***.

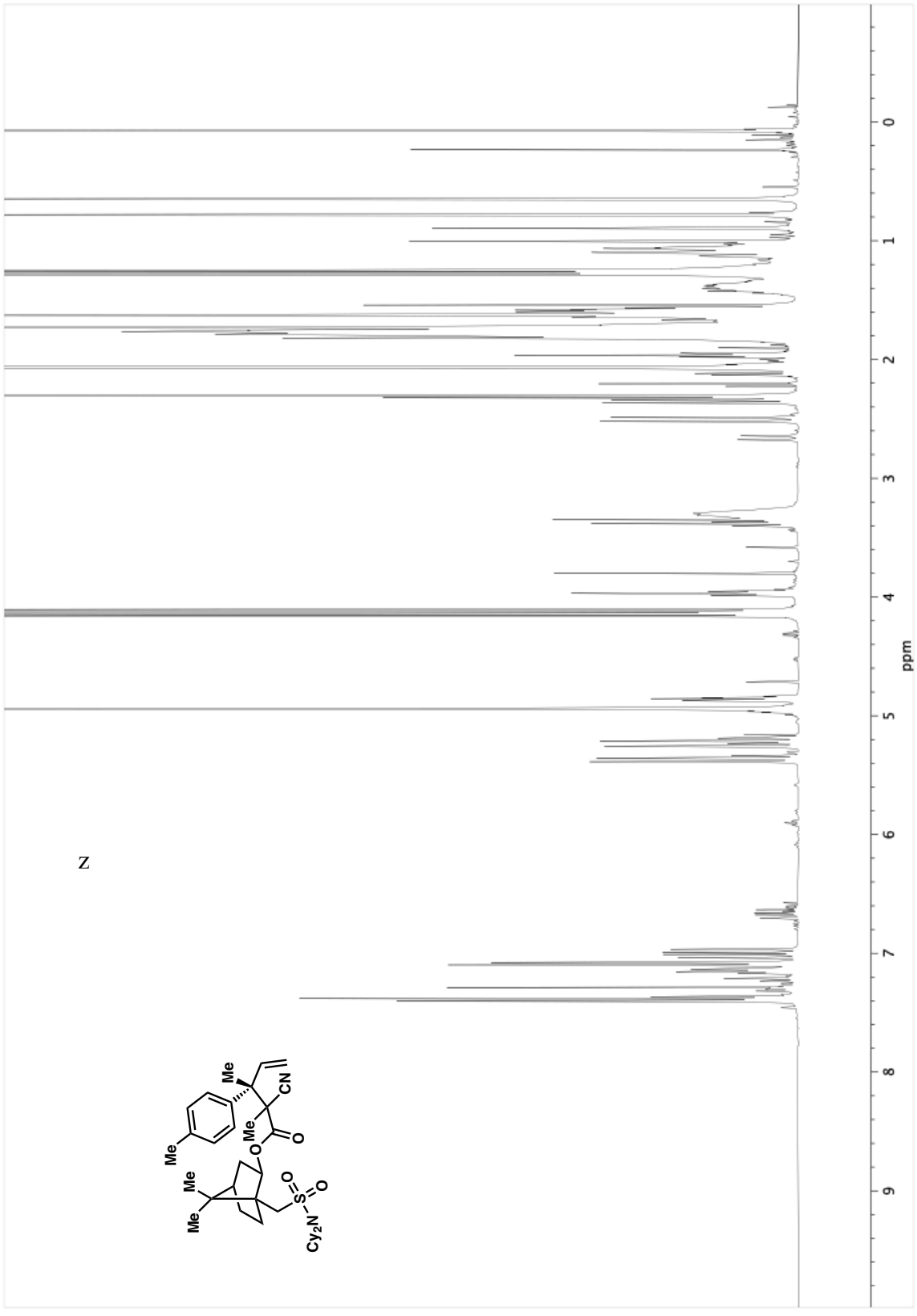


Figure A2.8. *Crude ^1H NMR (400 MHz, $CDCl_3$) of compound **34**.*

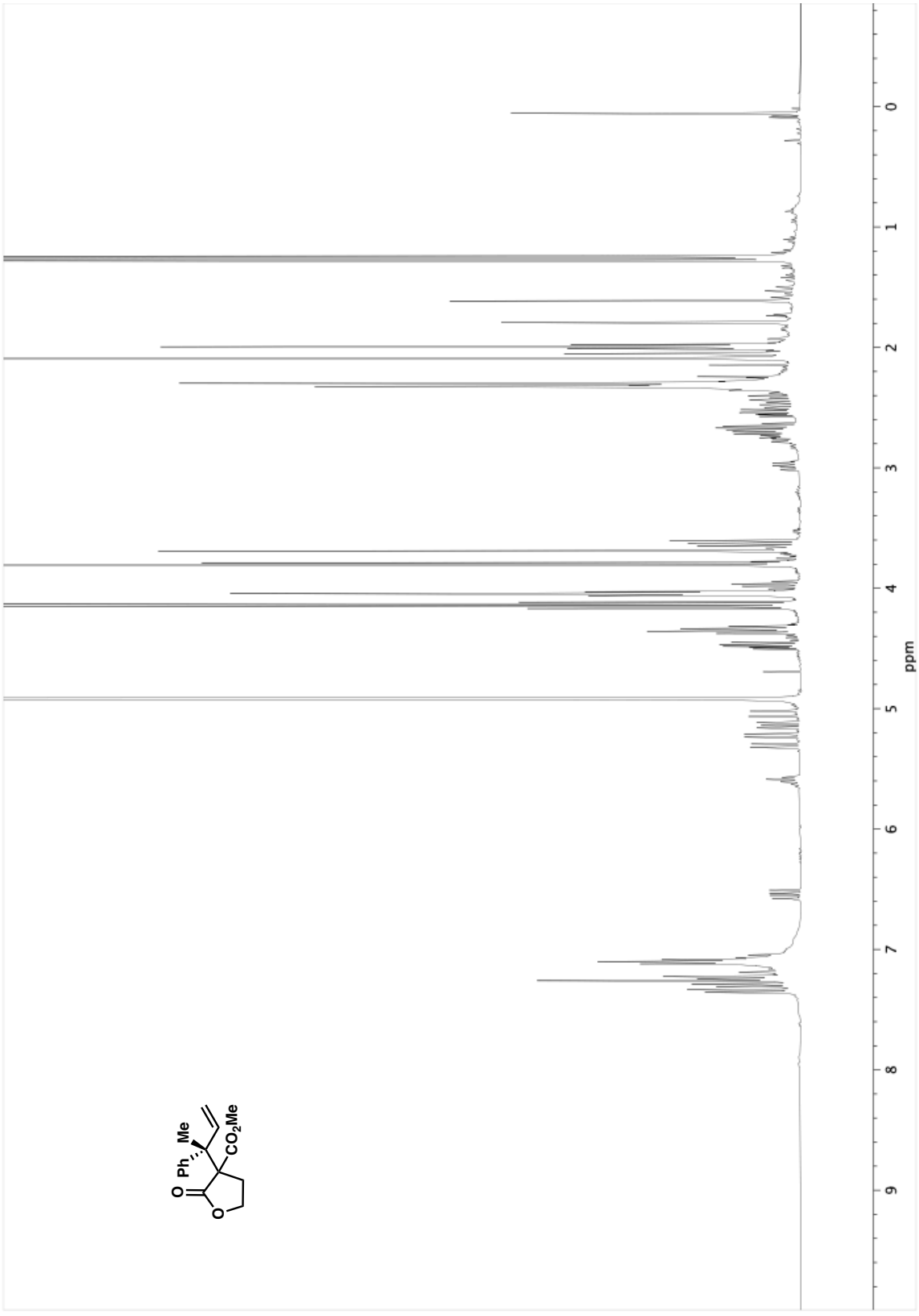


Figure A2.9. *Crude ^{1}H NMR (400 MHz, $CDCl_3$) of compound **39**.*

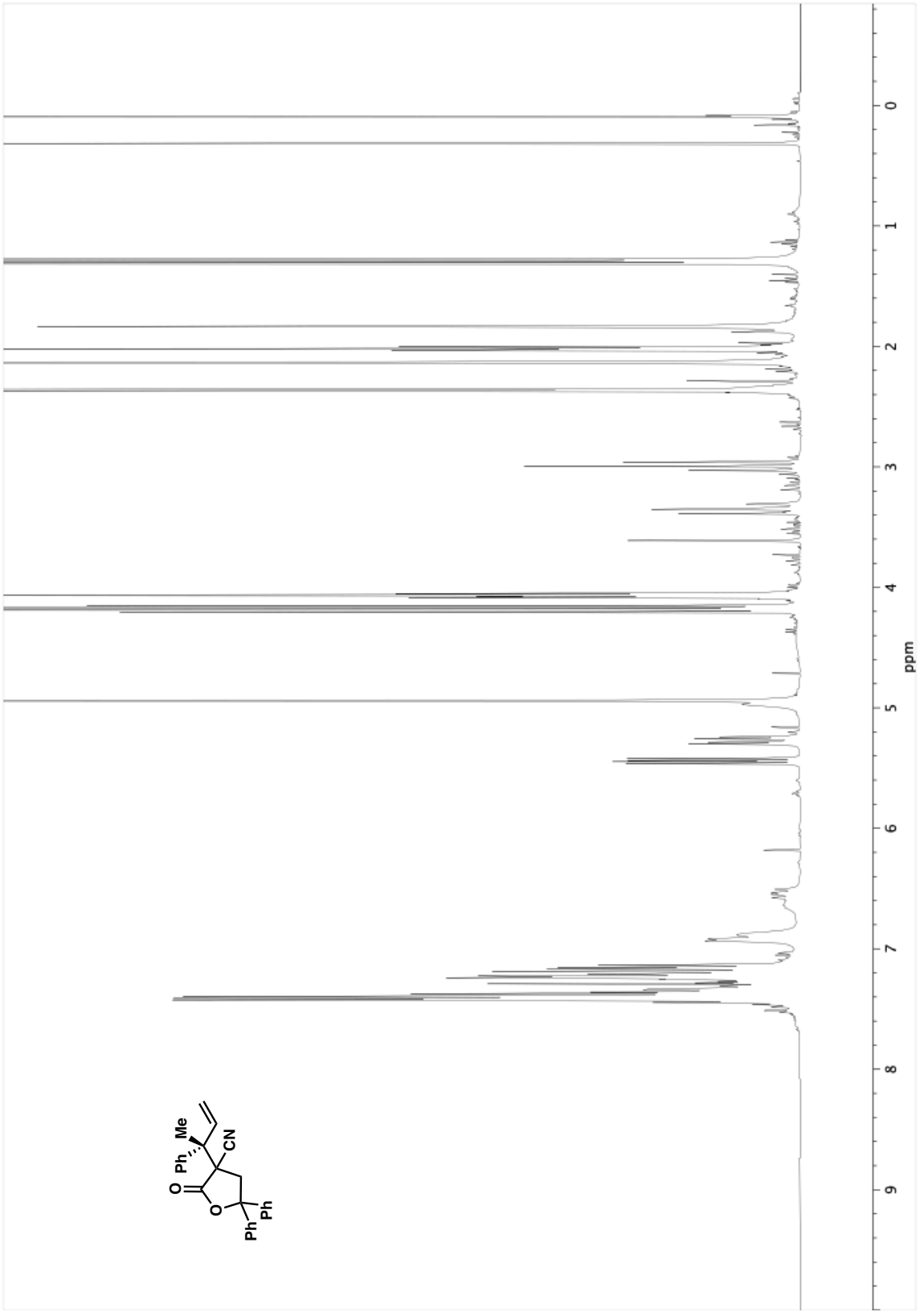


Figure A2.10. *Crude ^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***42****.*

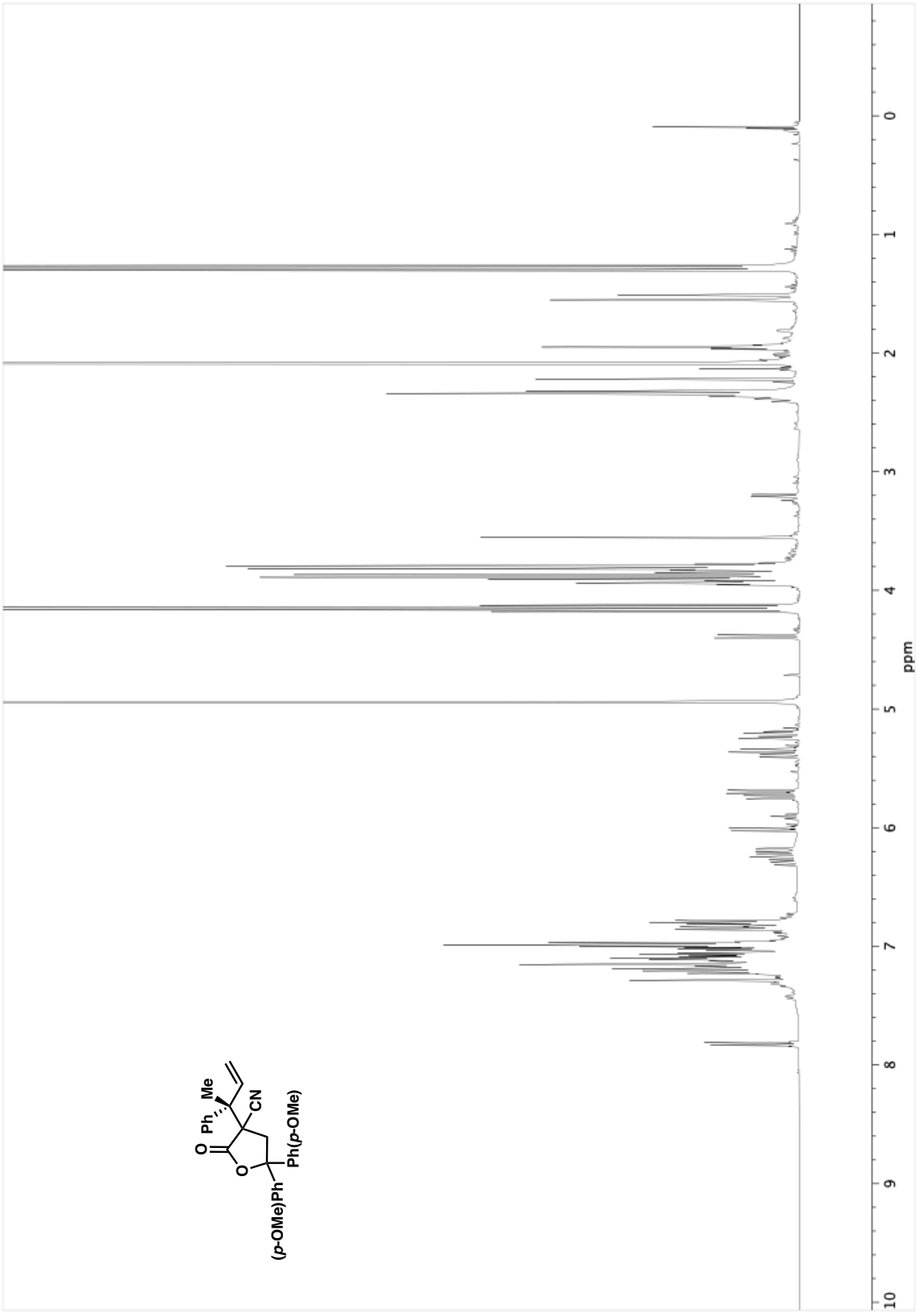


Figure A2.11. *Crude ^1H NMR (400 MHz, $CDCl_3$) of compound* ***43***.

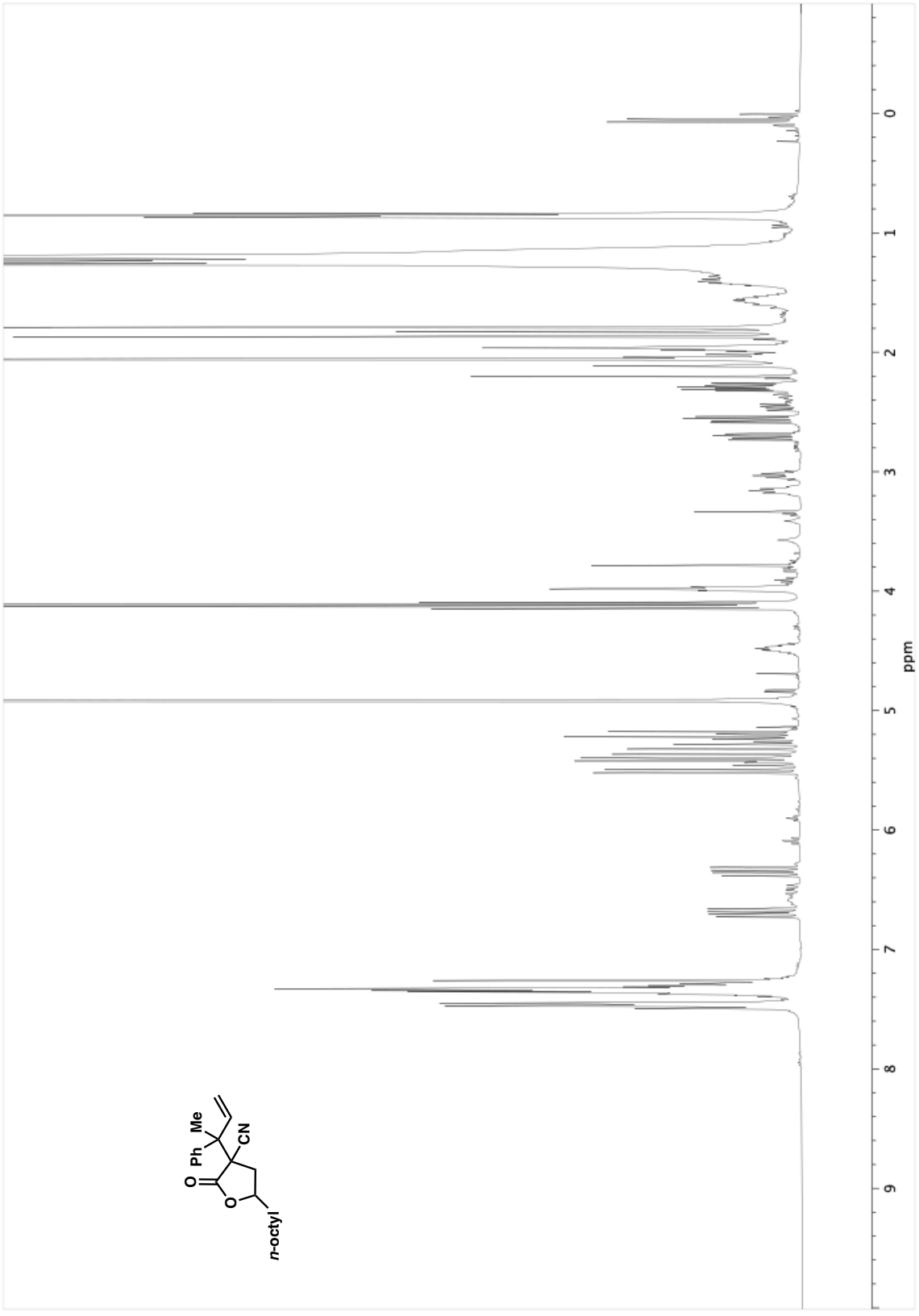


Figure A2.12. *Crude ^{1}H NMR (400 MHz, $CDCl_3$) of compound **45**.*

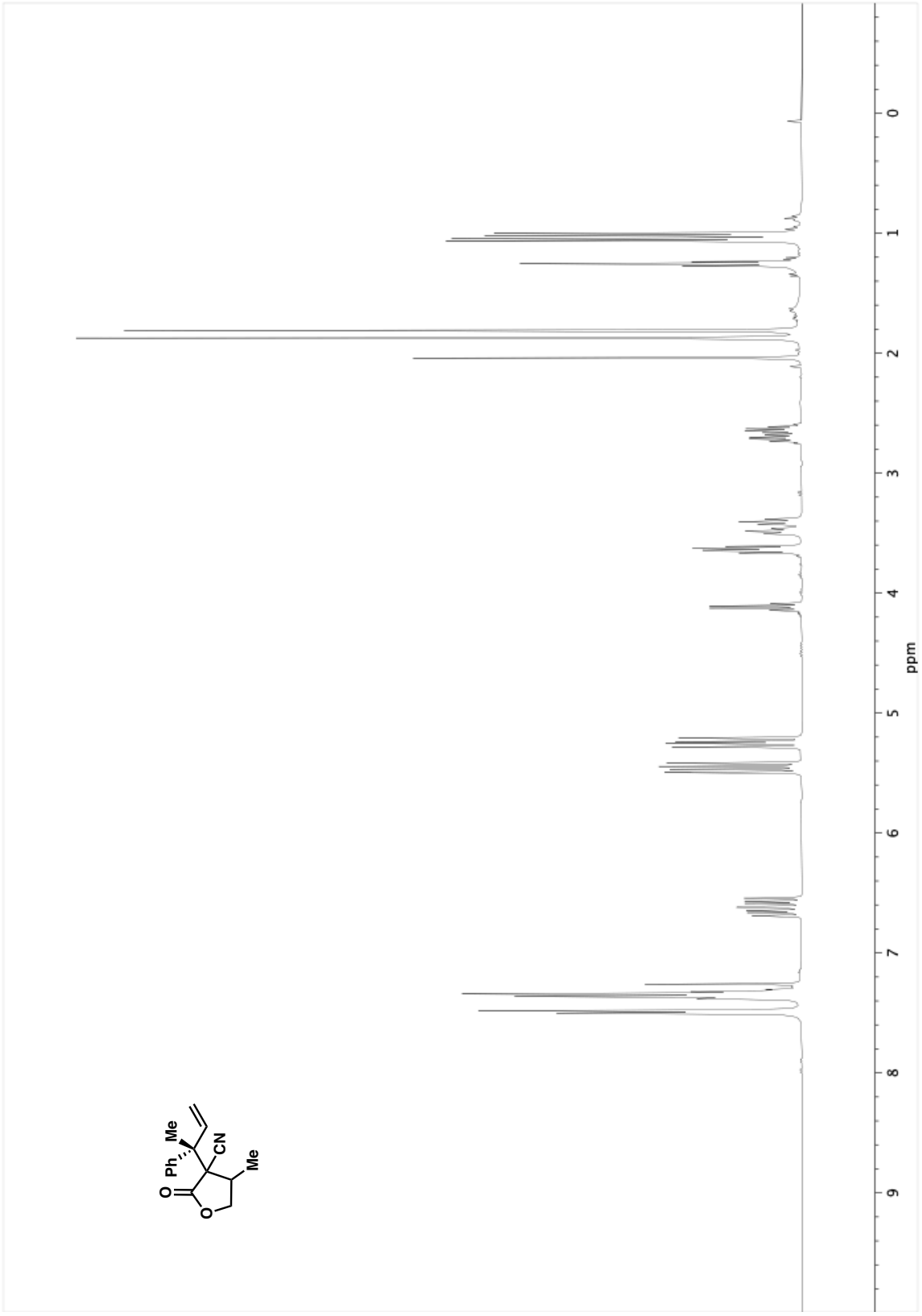


Figure A2.13. *^{1}H NMR (400 MHz, $CDCl_3$) of compound **47**.*

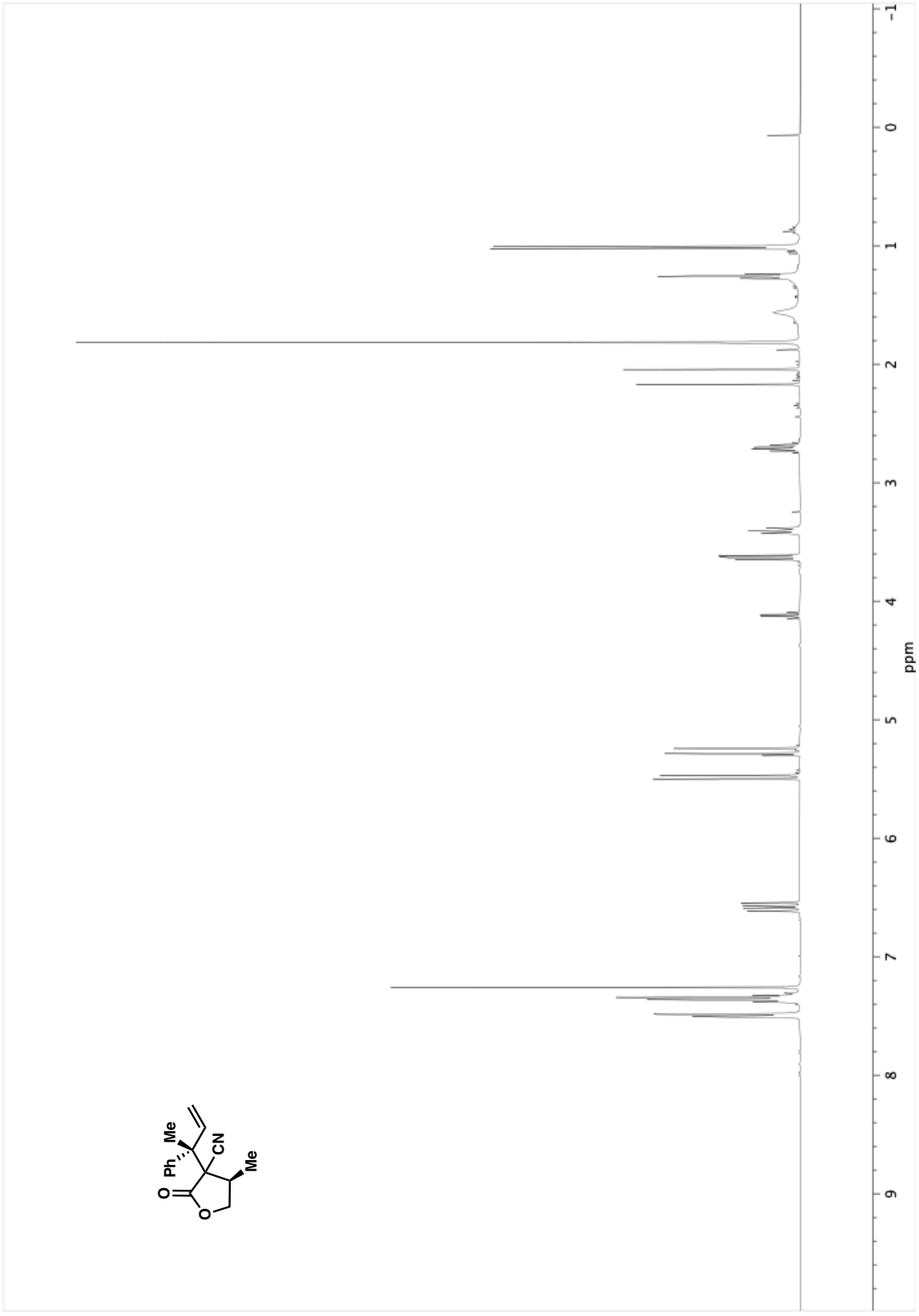


Figure A2.14. *^1H NMR (400 MHz, $CDCl_3$) of compound **54**.*

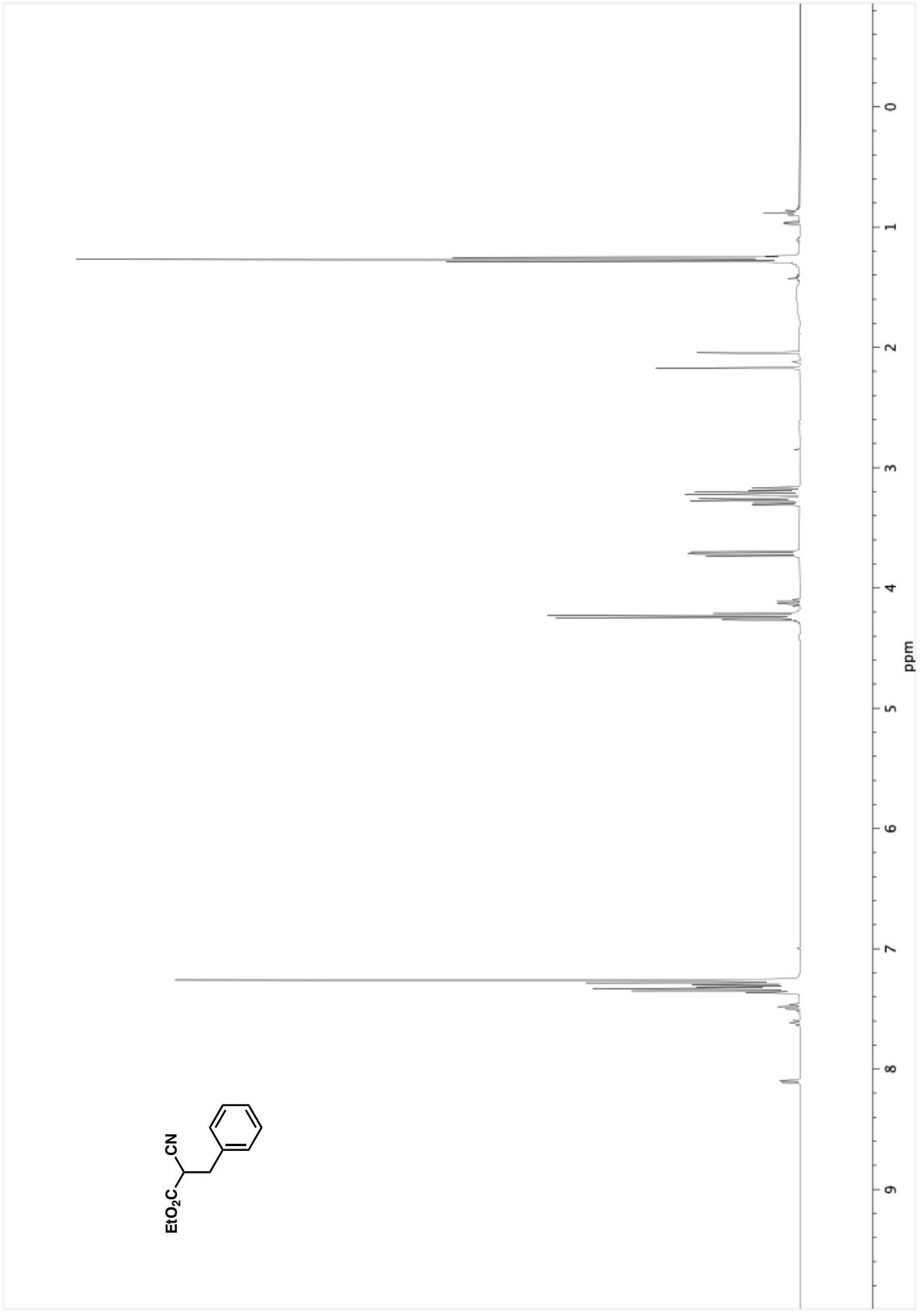


Figure A2.15. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***28a****.*

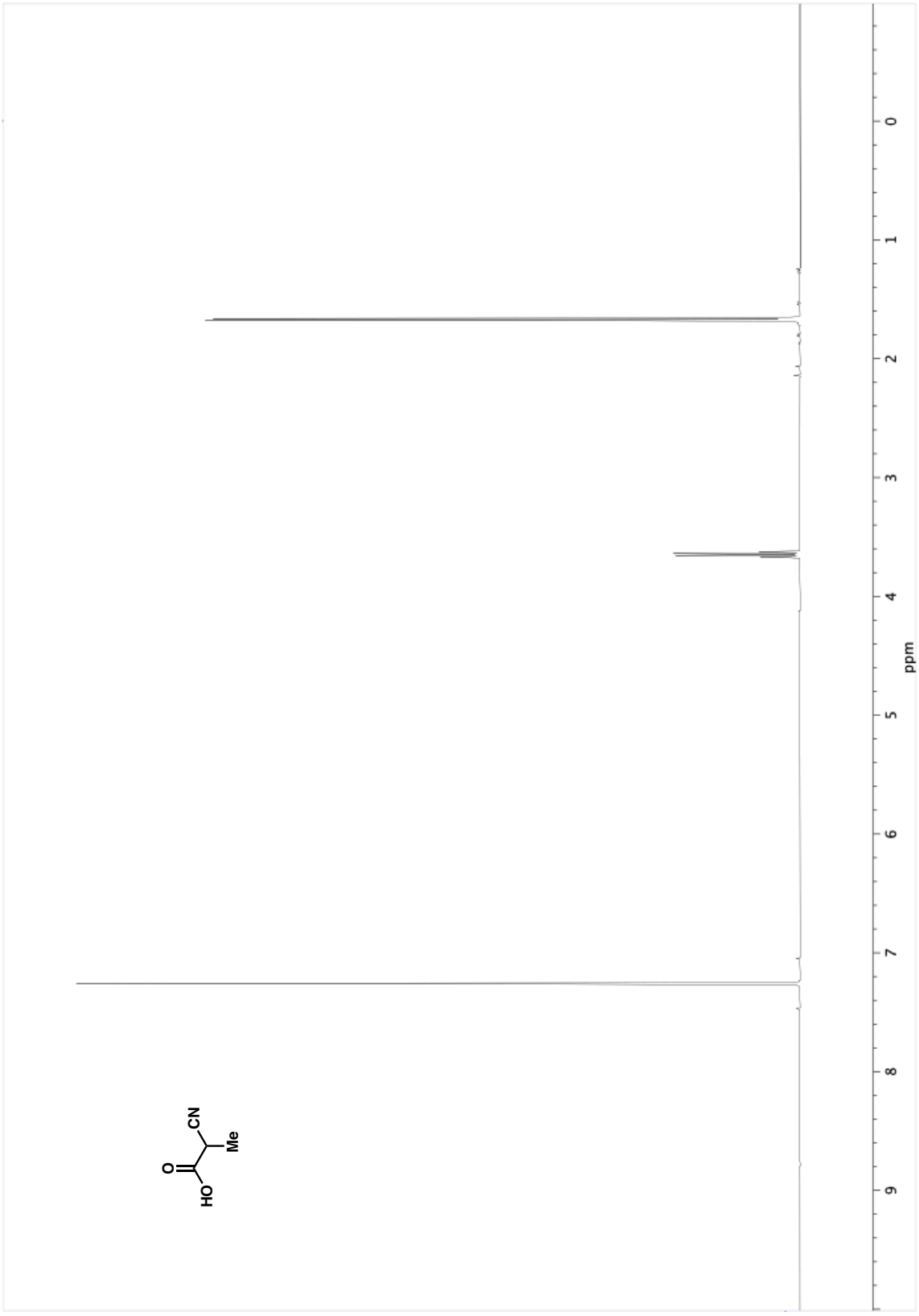


Figure A2.16. *^1H NMR (500 MHz, $CDCl_3$) of compound* ***35****.*

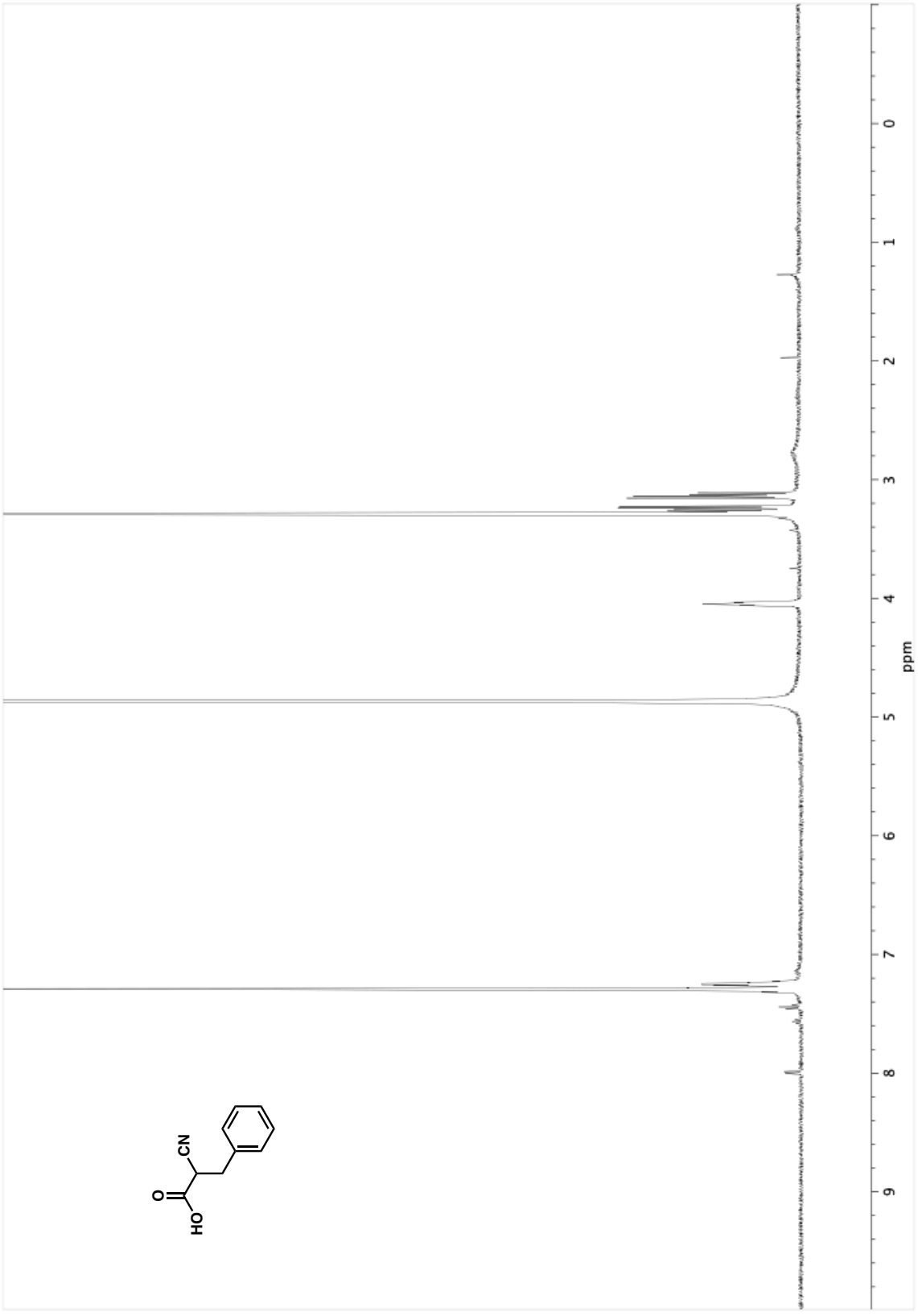


Figure A2.17. *^1H NMR (400 MHz, $CDCl_3$) of compound **36**.*

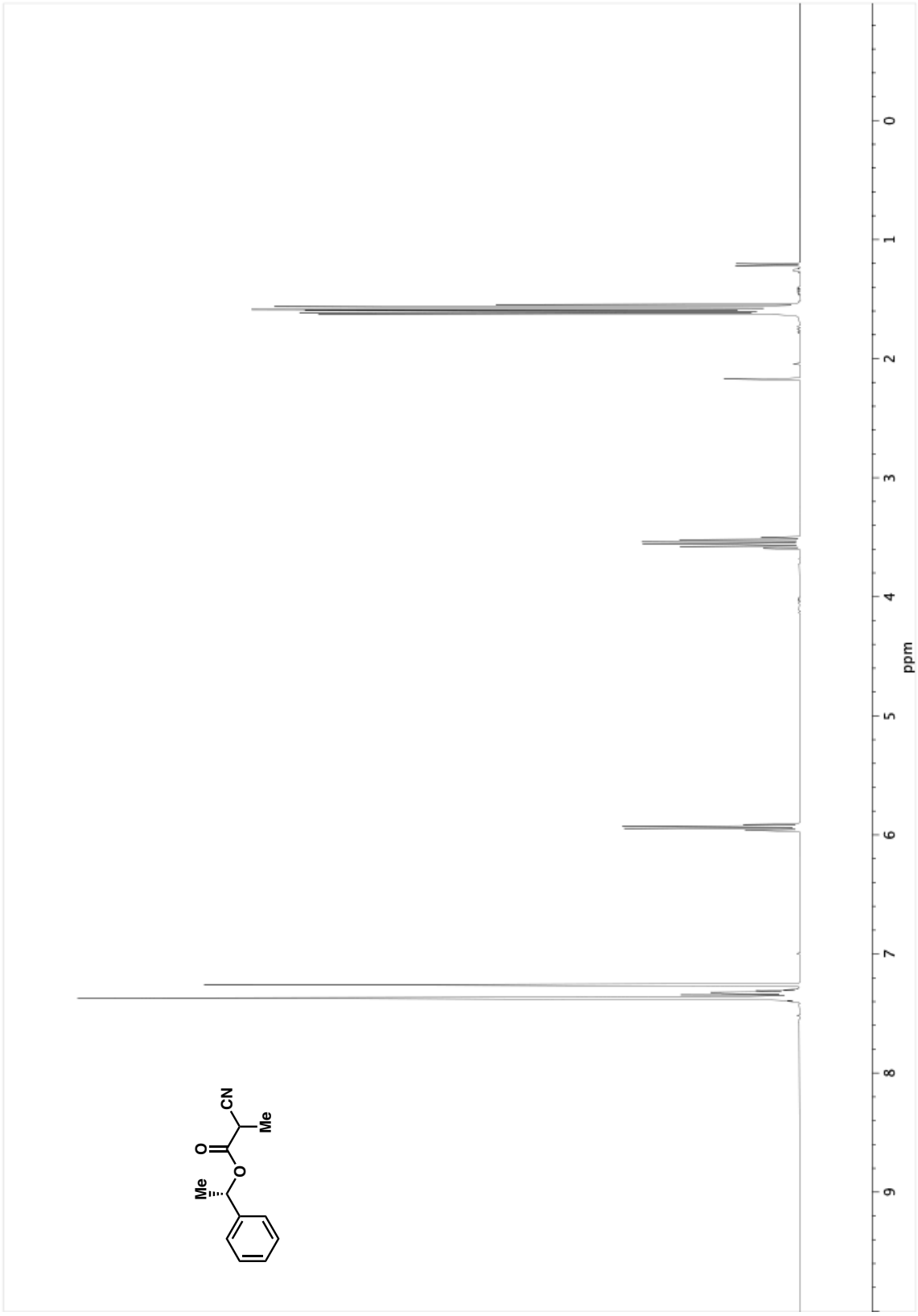


Figure A2.18. *^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***29****.*

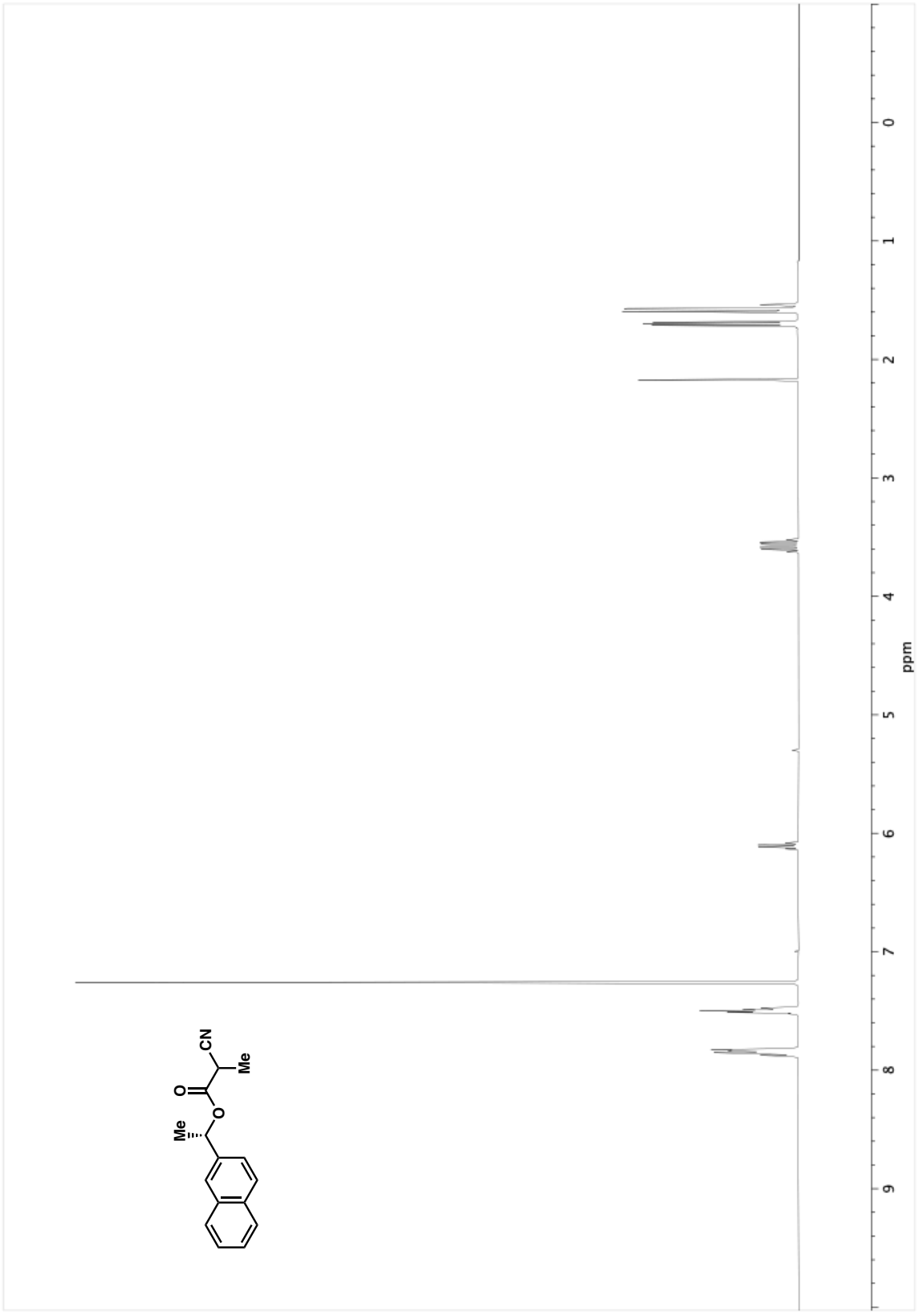


Figure A2.19. *^1H NMR (400 MHz, $CDCl_3$) of compound **30**.*

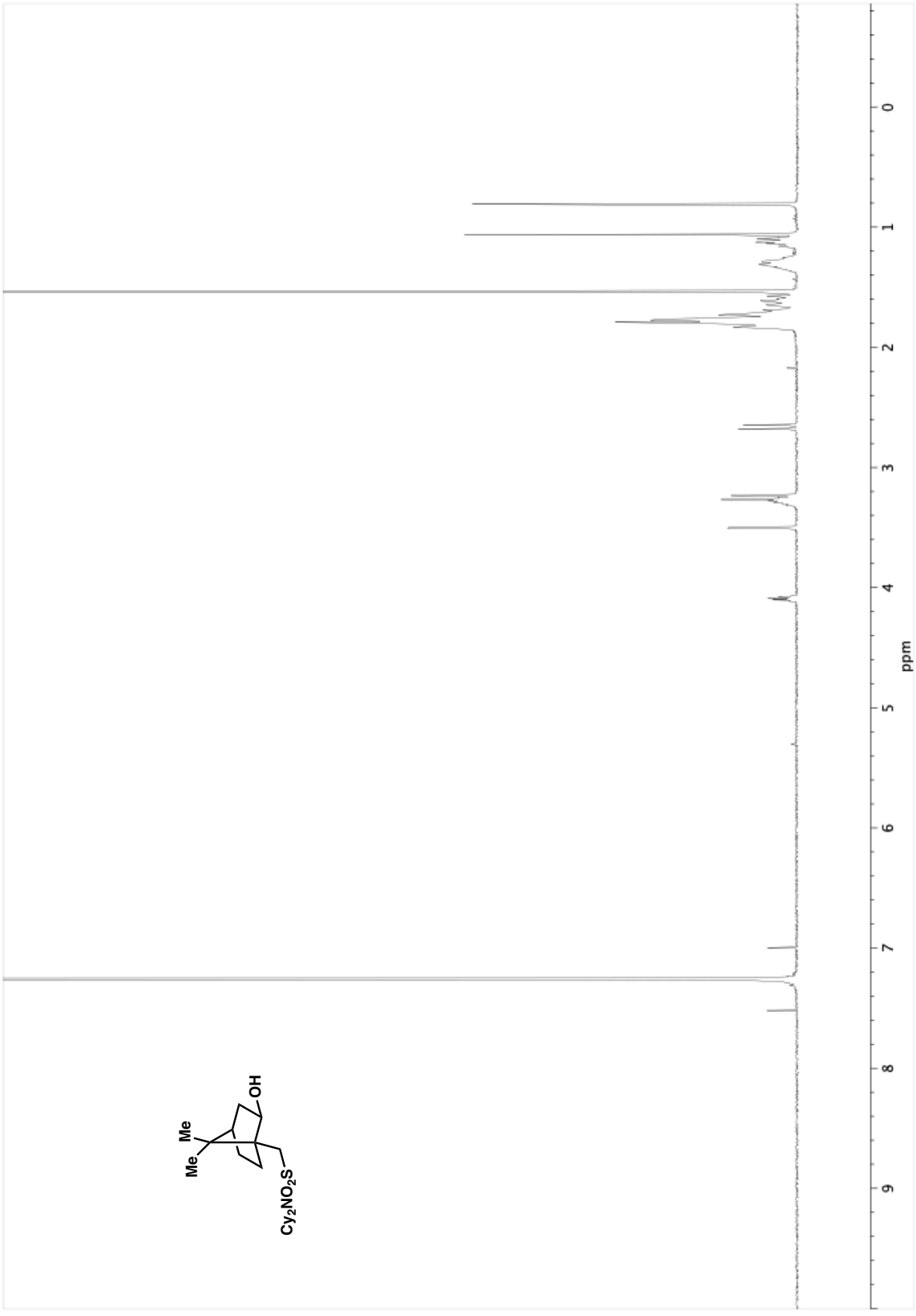


Figure A2.20. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***33b****.*

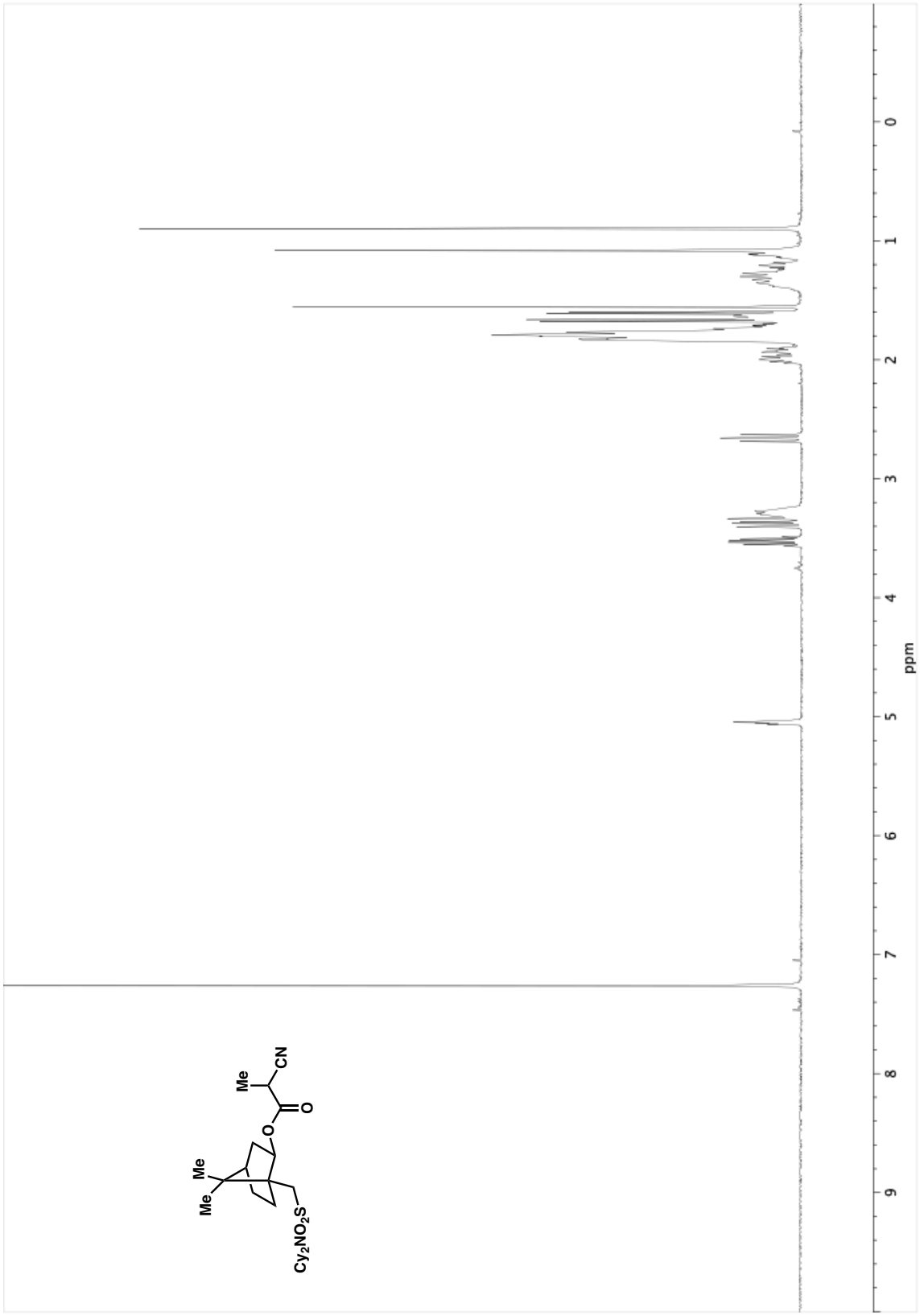


Figure A2.21. *^1H NMR (500 MHz, $CDCl_3$) of compound* ***33****.*

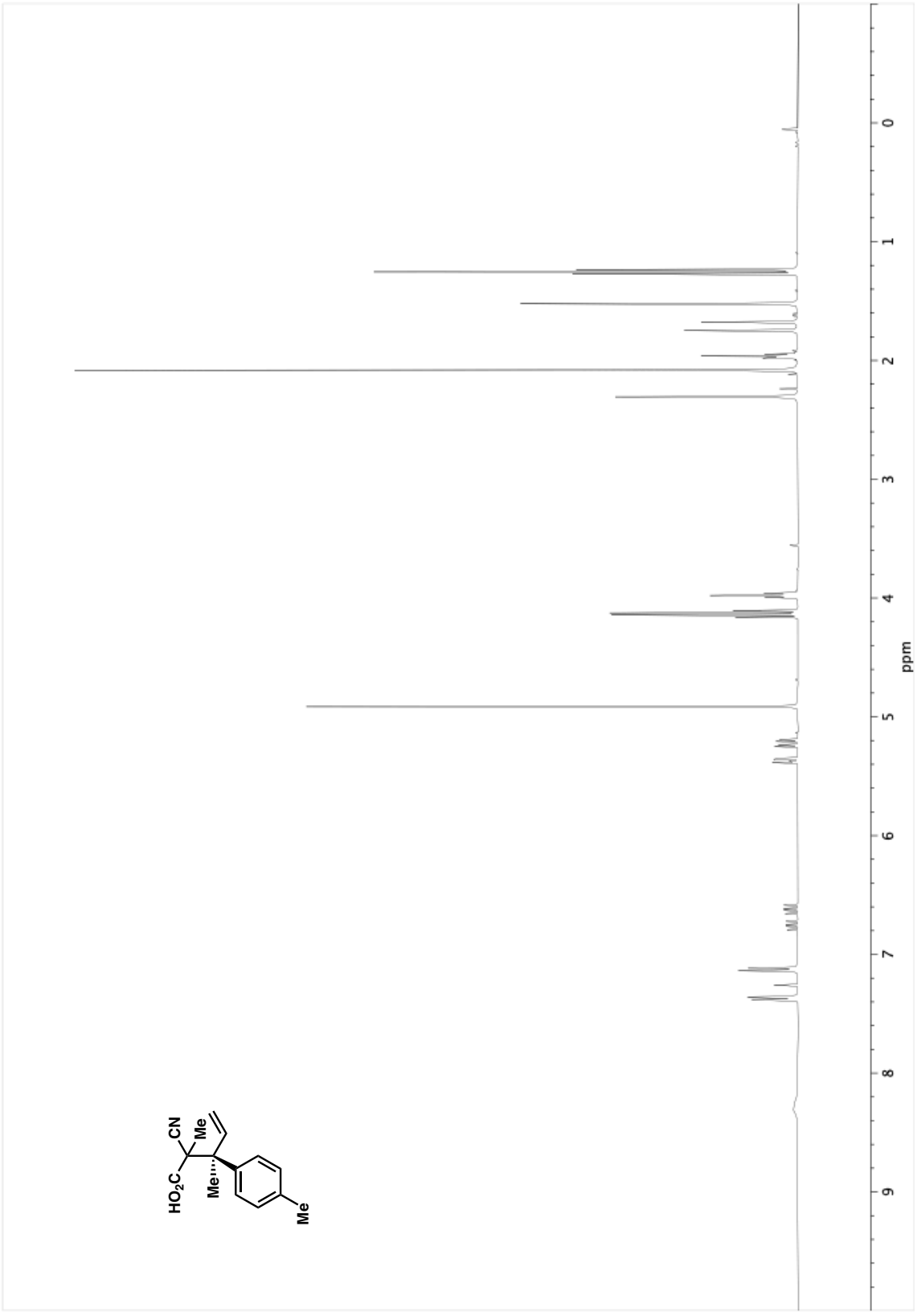


Figure A2.22. *Crude ^{1}H NMR (400 MHz, $CDCl_3$) of compound* ***37****.*

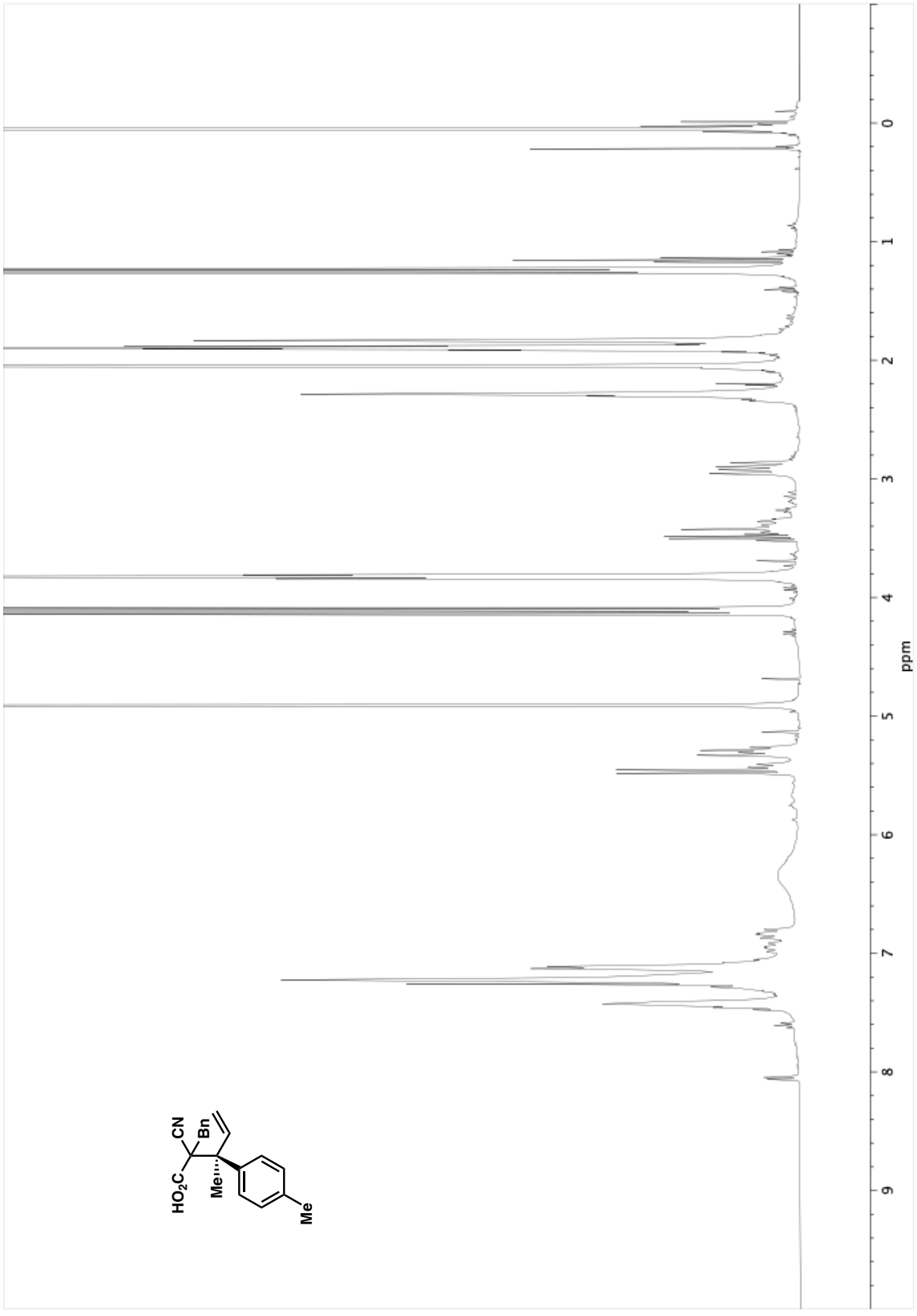


Figure A2.23. *Crude ^1H NMR (400 MHz, $CDCl_3$) of compound **38**.*

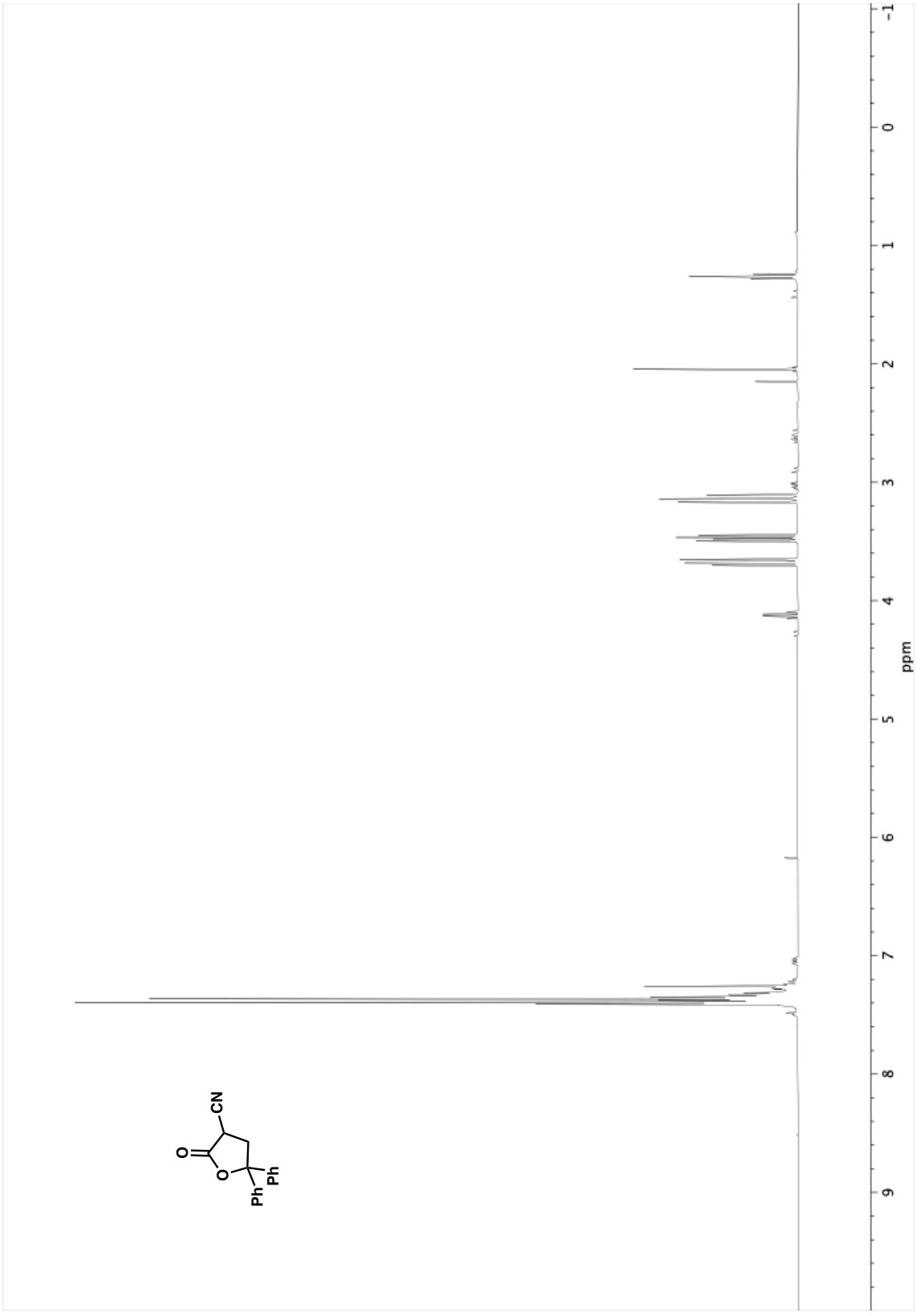


Figure A2.24. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***40****.*

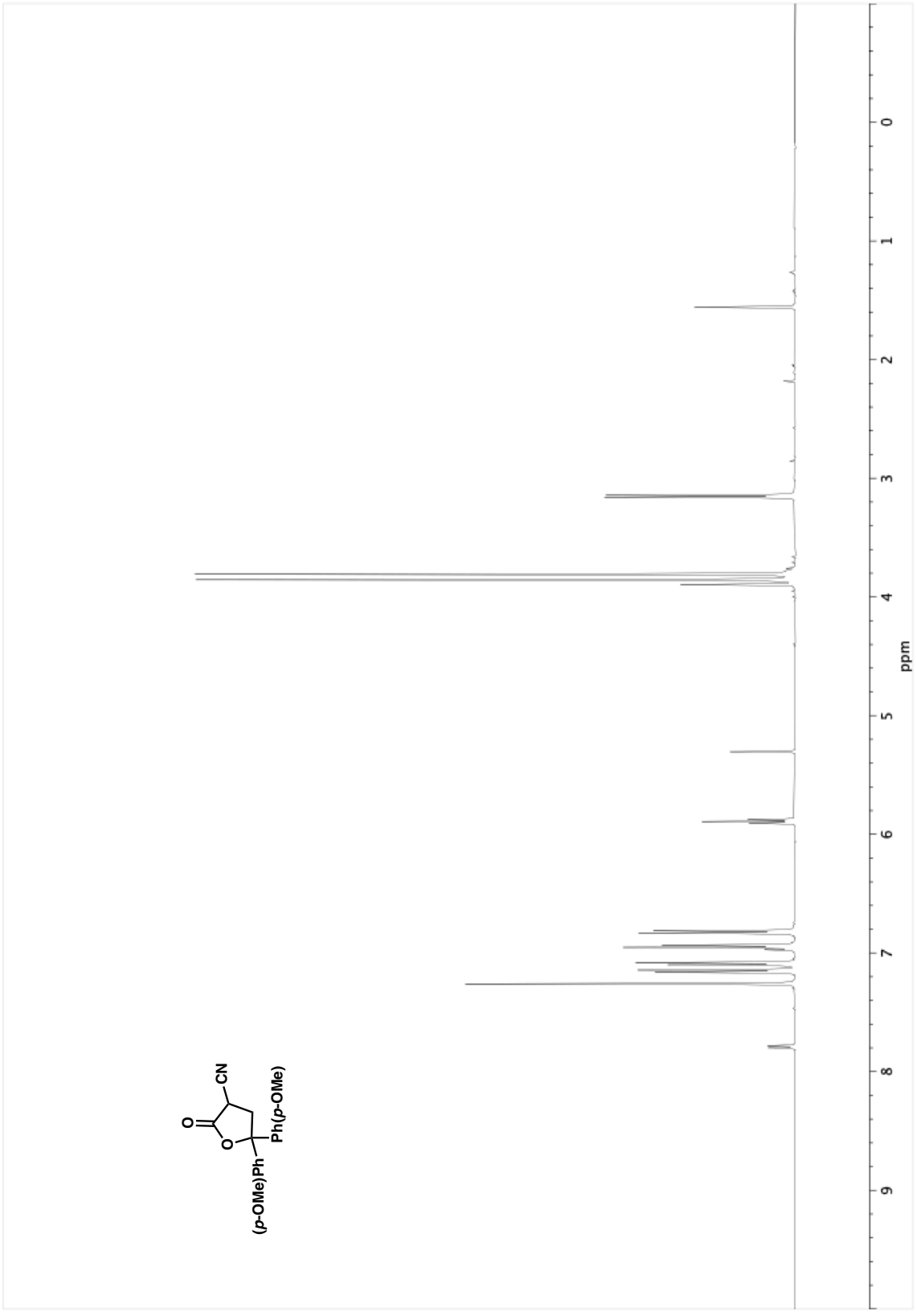


Figure A2.25. *^1H NMR (500 MHz, $CDCl_3$) of compound* ***41****.*

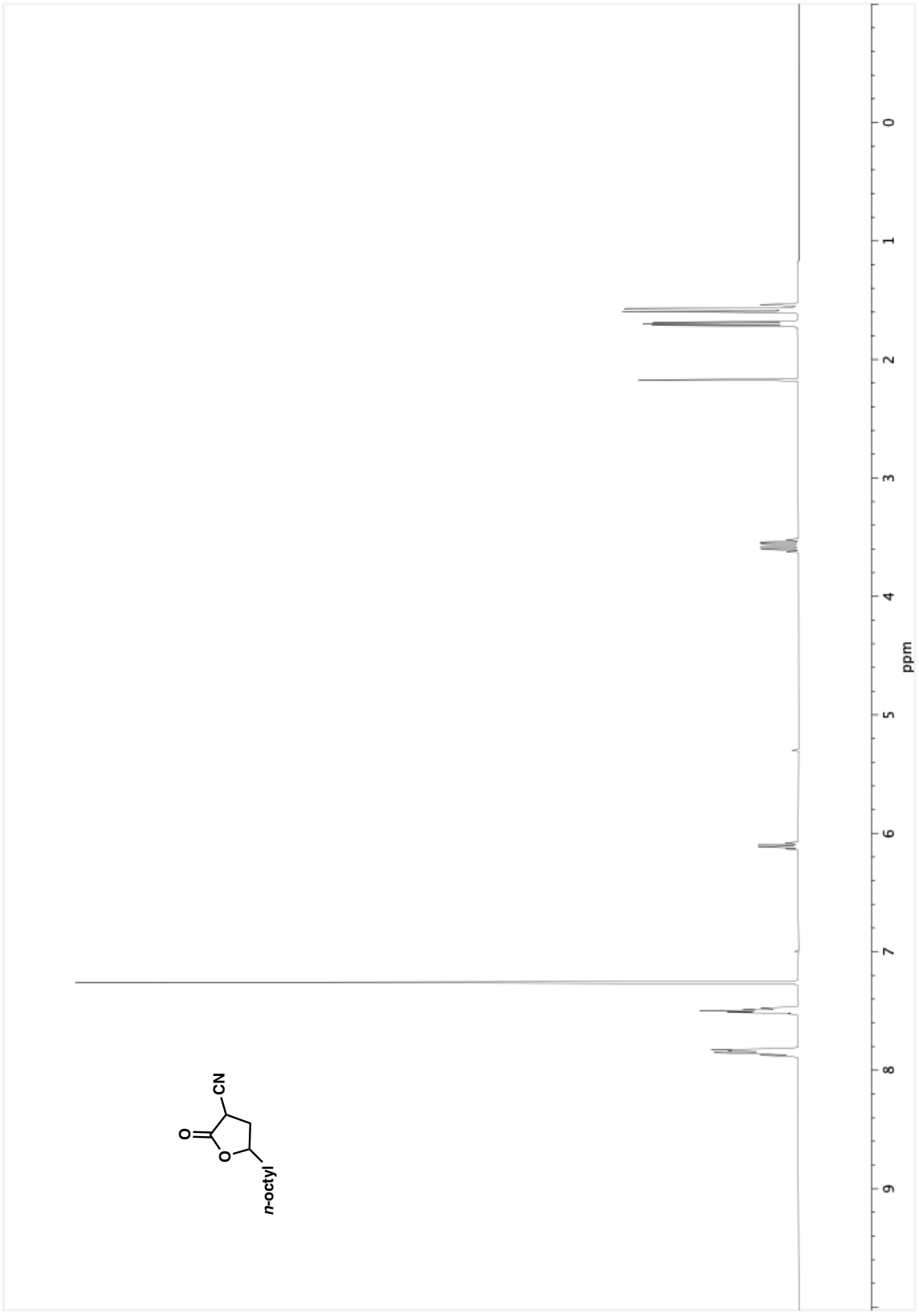


Figure A2.26. *^1H NMR (500 MHz, $CDCl_3$) of compound* ***44****.*

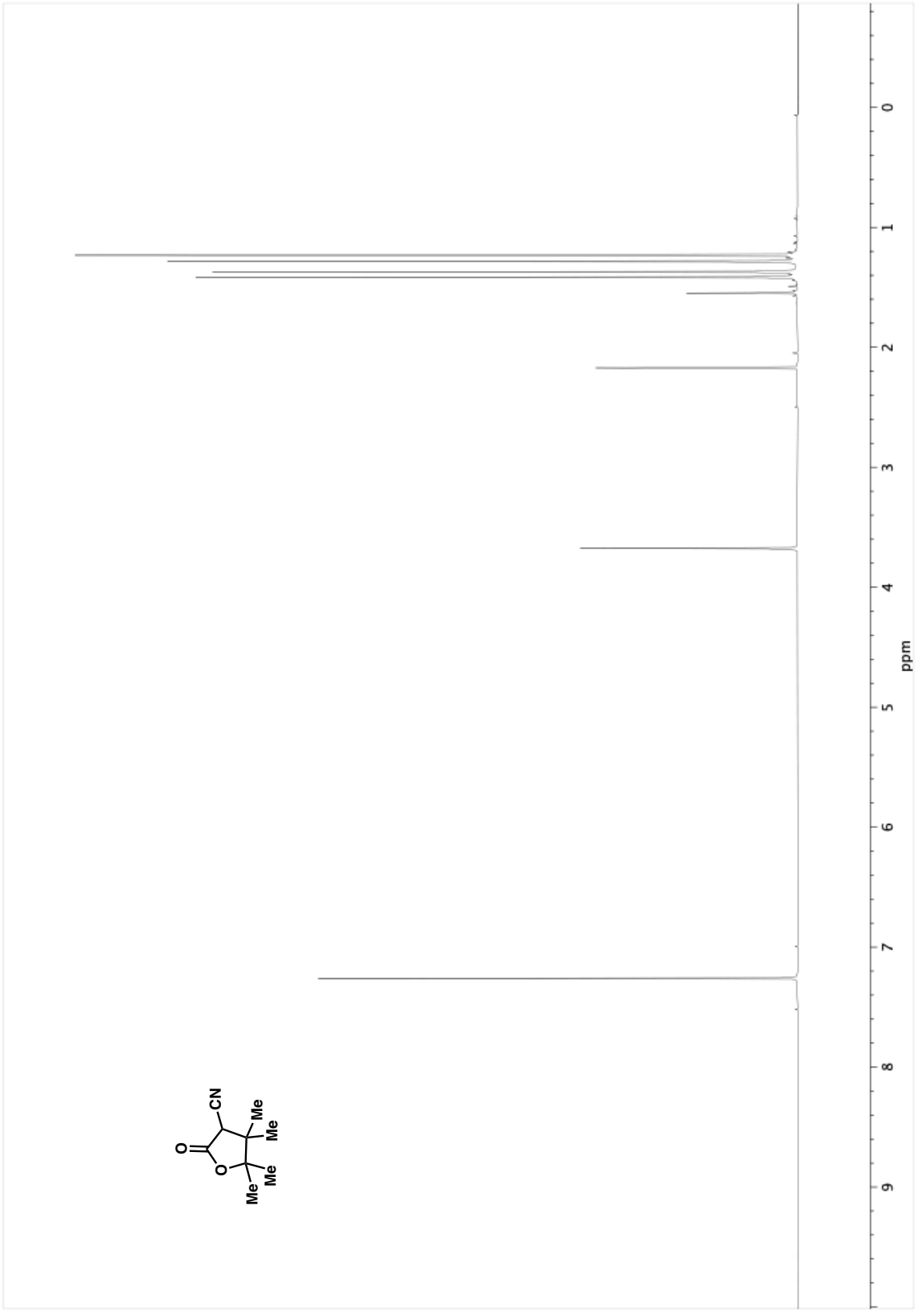


Figure A2.27. *^1H NMR (400 MHz, $CDCl_3$) of compound* ***48****.*

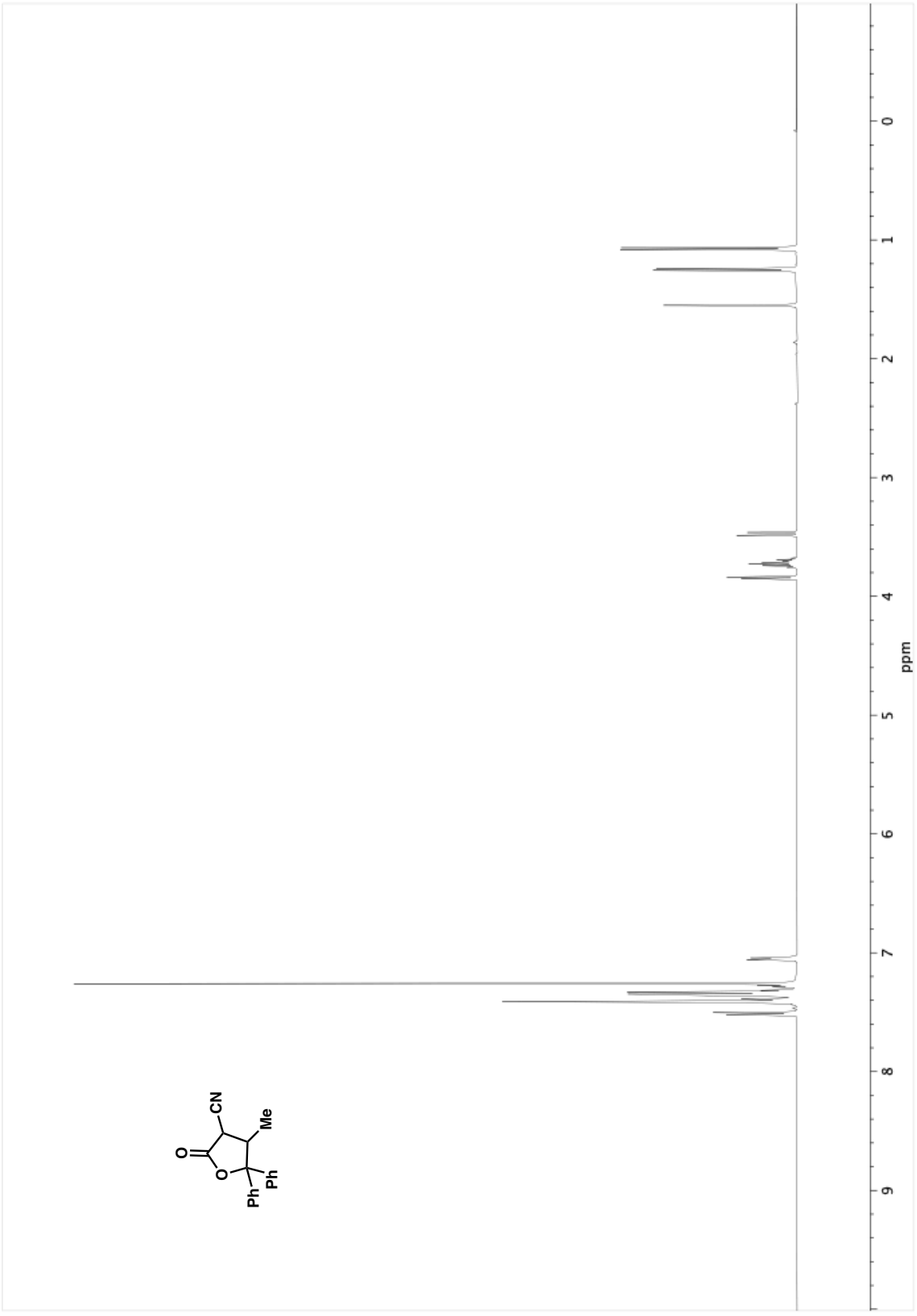


Figure A2.28. *^1H NMR (500 MHz, $CDCl_3$) of compound* ***49***.

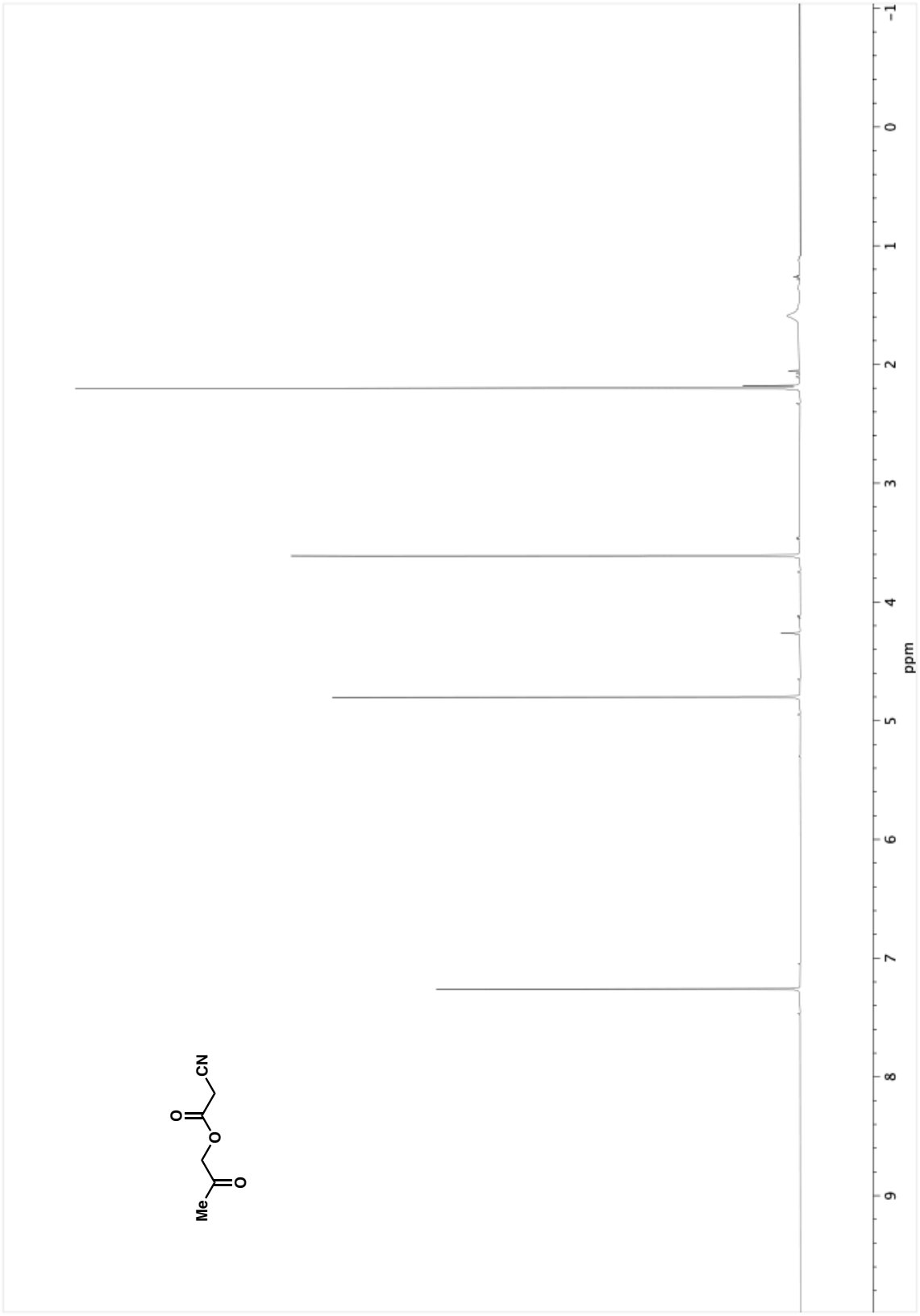


Figure A2.29. *^{1}H NMR (500 MHz, $CDCl_3$) of compound* ***46a****.*

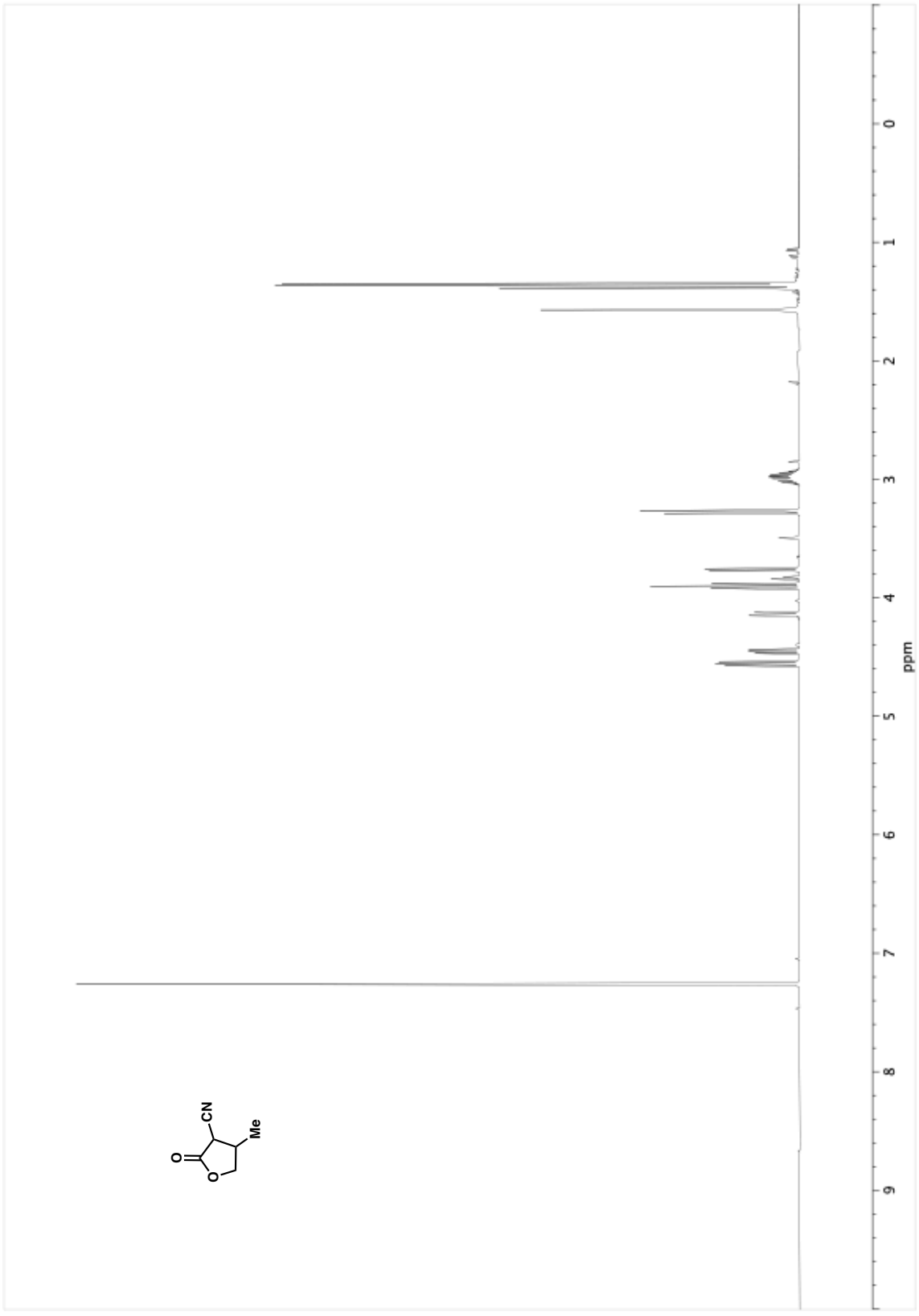


Figure A2.30. *^1H NMR (500 MHz, $CDCl_3$) of compound* ***46****.*

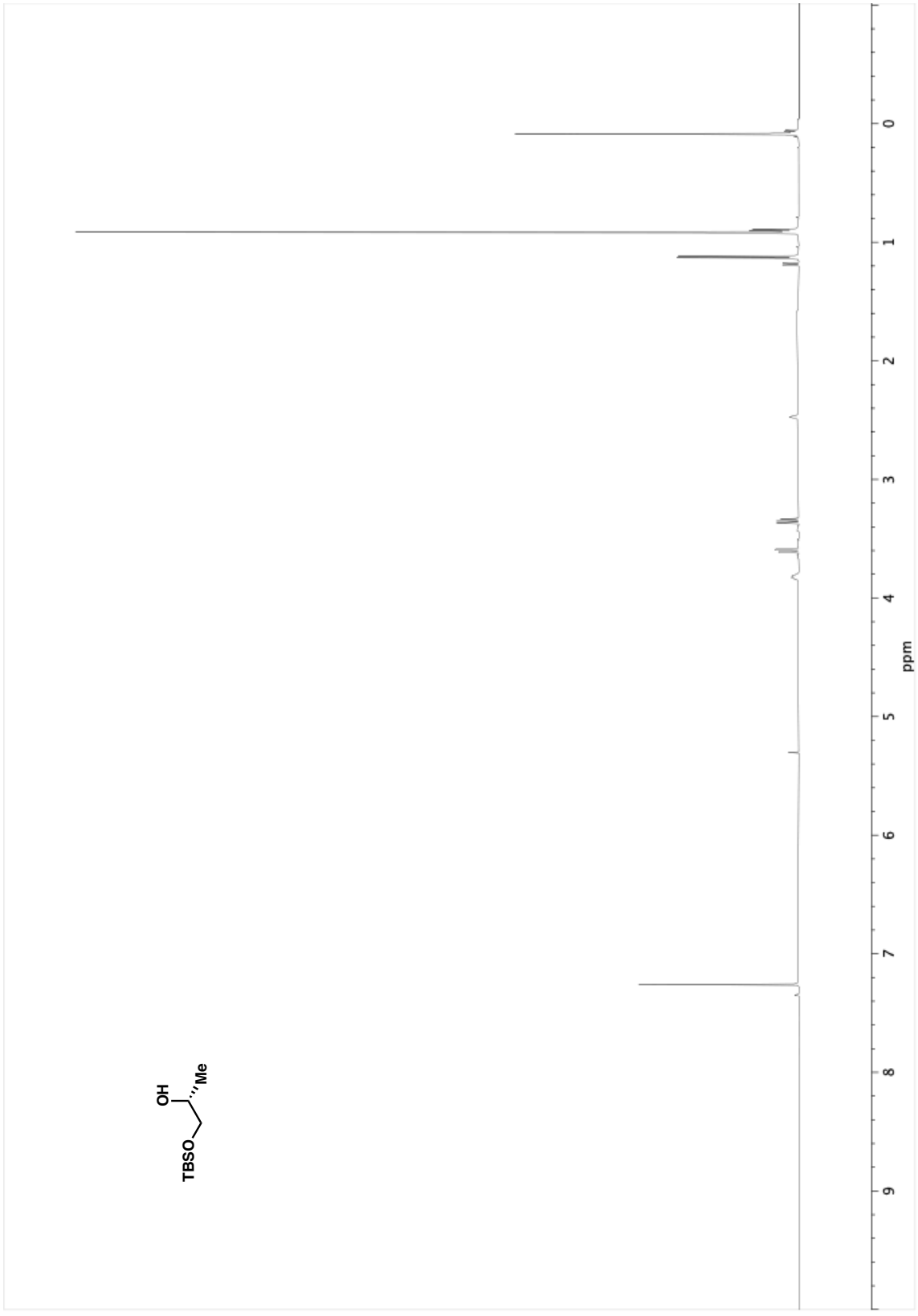


Figure A2.31. *^1H NMR (500 MHz, $CDCl_3$) of compound **50**.*

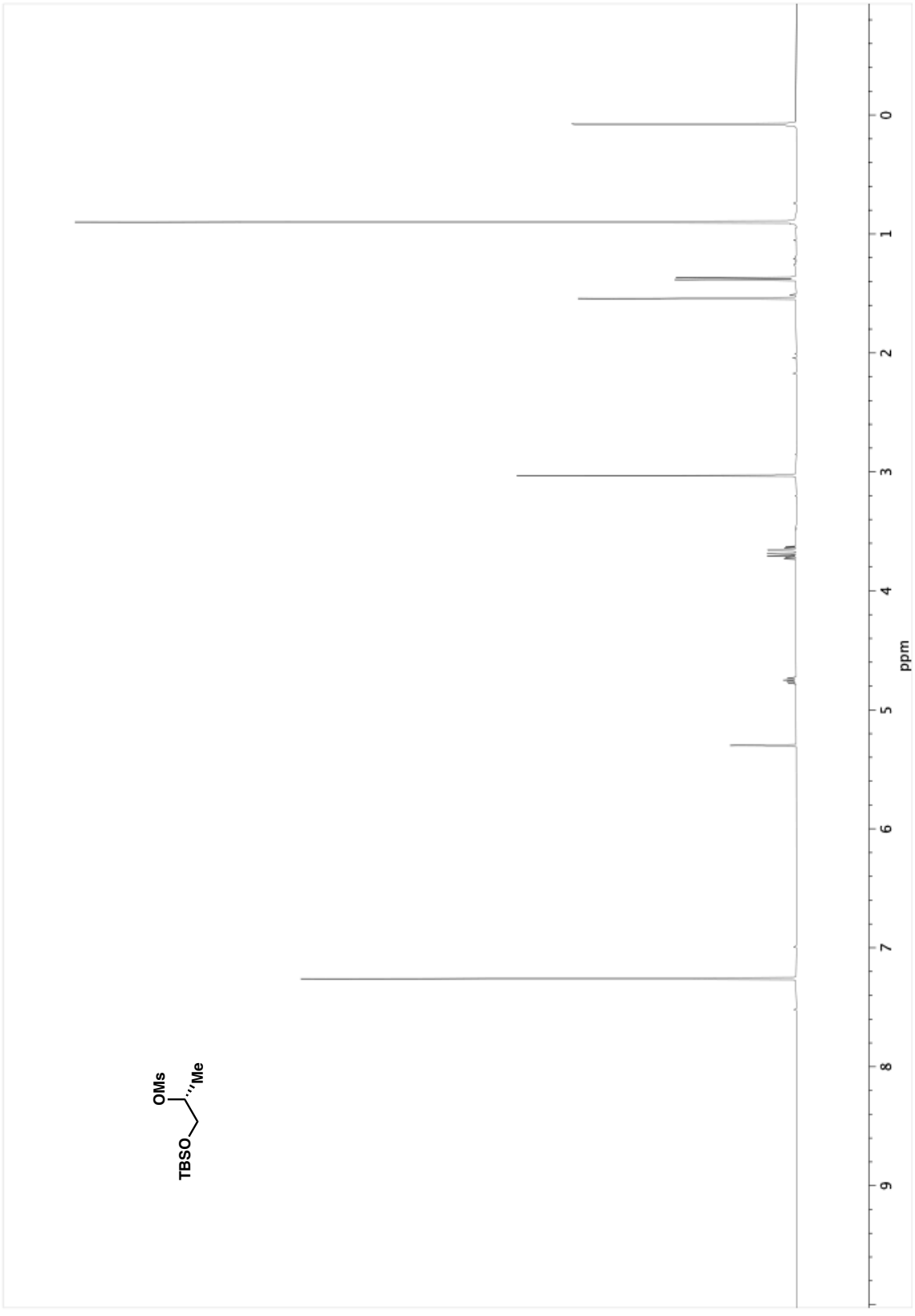


Figure A2.32. *^{1}H NMR (400 MHz, $CDCl_3$) of compound **51**.*

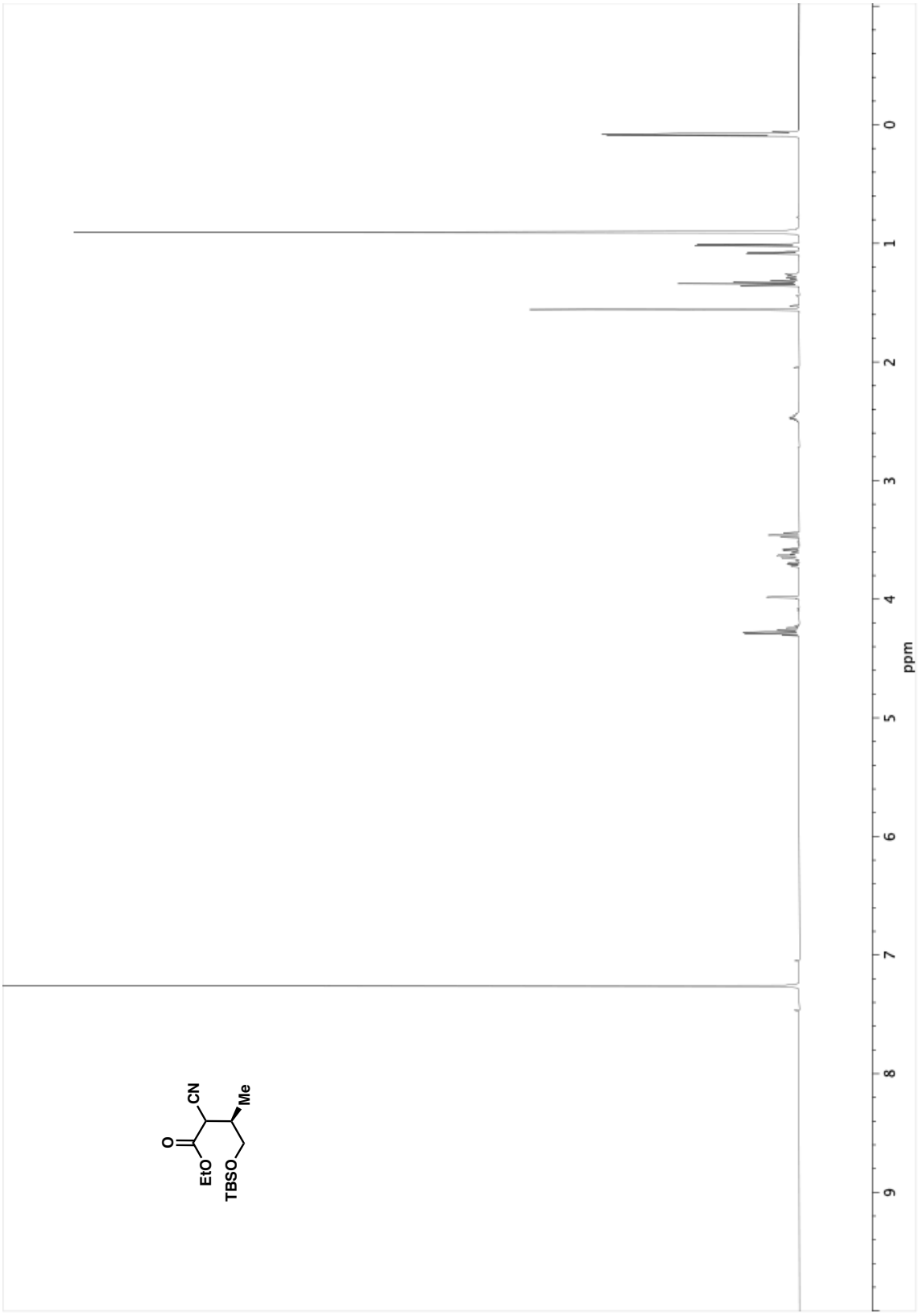


Figure A2.33. *^1H NMR (500 MHz, $CDCl_3$) of compound* ***52****.*

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CHAPTER 2

Mo-Catalyzed Asymmetric Allylic Alkylation Enabling the Construction of Highly Enantioenriched 1,4-Dicarbonyl Scaffolds[†]

2.1 INTRODUCTION

The construction of all-carbon quaternary stereocenters in enantioenriched form has been an ongoing challenge for organic chemists,[1] motivated in part by increasing evidence correlating molecular complexity with therapeutic value.[2] Transition-metal catalyzed allylic alkylation has emerged as an effective means for accessing these motifs.[3] In general, our group's approaches have centered on Pd-catalyzed decarboxylative allylic alkylation,[4] as well as Ir-catalyzed reactions favoring the branched isomer of product.[5] Within the latter class of reactions, our group has pioneered the use of tri-substituted allylic electrophiles to construct scaffolds containing quaternary stereocenters that originate from the electrophile. We found that masked acyl cyanides,[6] substituted malononitriles,[7] and dialkyl malonates[8] could be employed in conjunction with these electrophiles to access enantioenriched structures of high synthetic value (Scheme 2.1A).

Aiming to explore more abundant metals in branched-selective allylic alkylation, we were encouraged that molybdenum, a non-precious second-row transition metal, has

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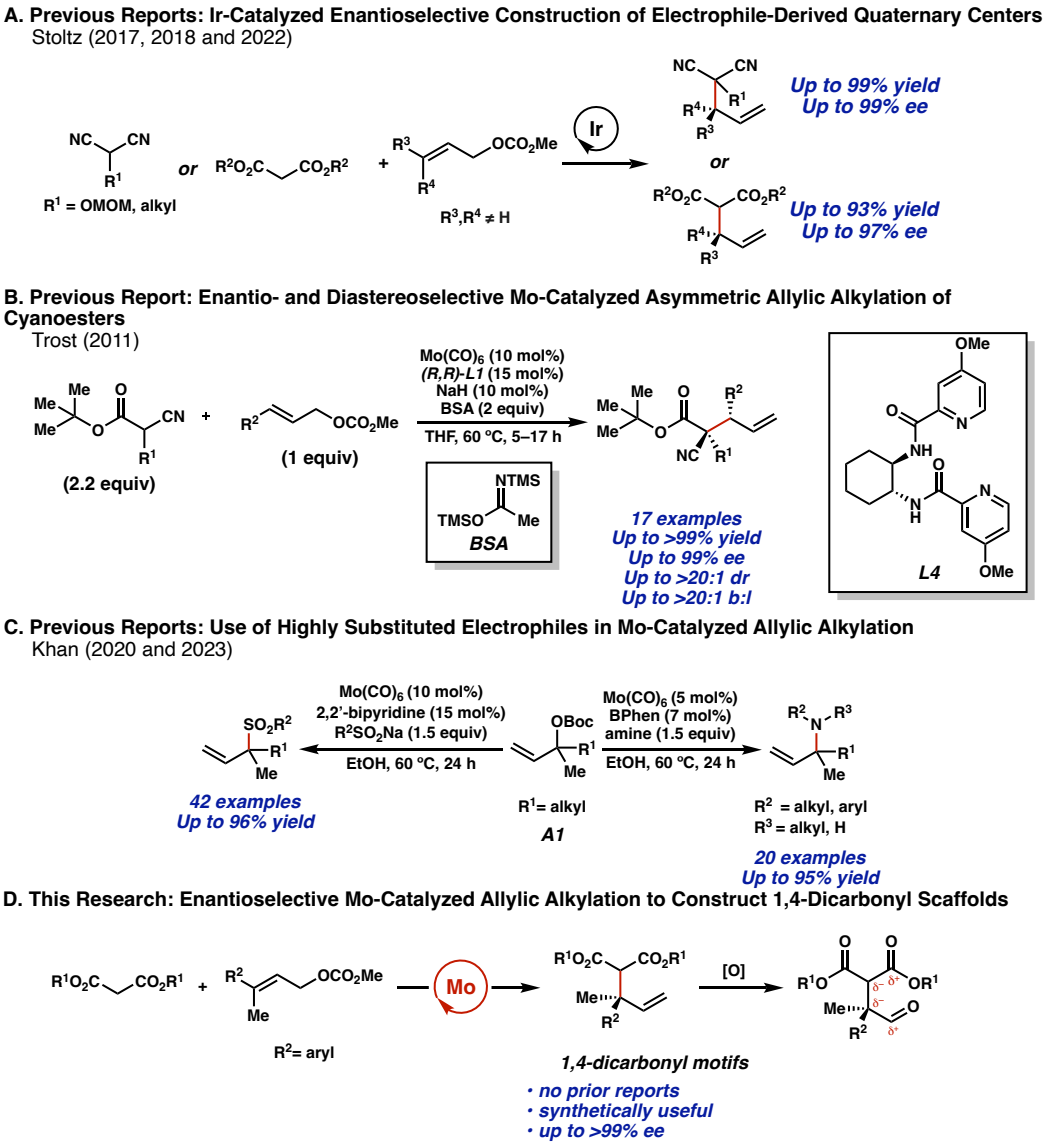
demonstrated exquisite preference for the branched product in prior reports.[9] Of particular significance, Trost and coworkers demonstrated a doubly stereoselective molybdenum-catalyzed allylic alkylation of substituted cyanoesters with disubstituted allylic electrophiles, constructing products bearing vicinal quaternary and tertiary stereocenters with excellent yields and stereocontrol (Scheme 2.1B).[10] This transformation features an electron-rich *para*-methoxy bispyridylamide ligand (**L4**), which helps to promote oxidative addition of the allylic electrophile and improves regioselectivity.

Despite molybdenum ($29.137/ lb)[11a] being significantly cheaper than palladium ($992.00/lb)[11b] and iridium ($4150.00/oz)[11c], Mo-catalyzed allylic alkylation remains relatively less-developed for transformations involving challenging, tri-substituted linear allylic electrophiles. To our knowledge, there have only been two publications utilizing highly substituted electrophiles in Mo-catalyzed allylic substitution reactions to construct tetrasubstituted centers, limited to ofully alkyl allylic electrophiles (Scheme 2.1C).[12] However, there have been no studies detailing the construction of electrophile-derived all-carbon quaternary stereocenters via compound **A1** or its linear congener. Herein, we report a highly enantioselective Mo-catalyzed allylic alkylation, representing the first example of the formation of electrophile-derived all-carbon quaternary centers by Mo catalysis. We found that rapid ozonolysis following the allylic alkylation affords 1,4-dicarbonyl compounds, which are synthetically challenging to access due to the intrinsic mismatch of the carbonyl polarity (Scheme 2.1D).[13]

Scheme 2.1. *Asymmetric Allylic Alkylation: State of the Art*



2.2 OPTIMIZATION EFFORTS

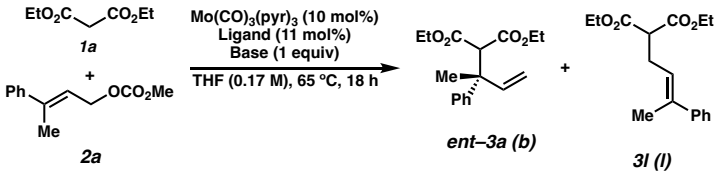
Given the stability of $Mo(CO)_6$, which necessitates high reaction times and temperatures to perform ligand exchange,[14] we first selected a more reactive Mo(0) source. While $Mo(CO)_3(EtCN)_3$[15] and $Mo(CO)_3(C_7H_8)$[16] have been leveraged in allylic alkylation

processes, these precatalysts suffer from poor bench stability and require synthesis in the absence of air and water. We instead employed bench stable $Mo(CO)_3(pyr)_3$ [17] as a precatalyst in combination with the DACH-pyridyl ligand **L5** and NaH as a base. This reaction provided a 20% yield of the desired branched product (b) in a 2:1 ratio with the linear isomer (l) [Table 2.1, entry 1], constituting the first application of $Mo(CO)_3(pyr)_3$ in allylic substitution. Surprisingly, a non-symmmetrical picolinamide/benzamide ligand **L6**, which has been previously demonstrated to improve regioselectivity,[18] resulted in no conversion of starting material (entry 2). Other changes to the scaffold, such as replacement of the amides with esters, replacement of the carbonyls with thiocarbonyls, modification of the diamide backbone, and employment of a traditional Trost DACH ligand all led to a complete loss of reactivity (Experimental Section, Table 2.8). Moreover, a chiral Schiff base ligand **L7** resulted in trace conversion (entry 3).[19] In terms of the base additive, LiH performed similarly to NaH but exhibited poor mass balance (entry 4). Intriguingly, the counterion effect with the HMDS bases was quite pronounced, with LiHMDS delivering an improved 30% yield, while KHMDS resulted in trace product (entries 5-7). It is possible that either the lithiated diethyl malonate is more reactive, or that the lithium additive serves as both a base and Lewis acid to ionize the allylic electrophile.

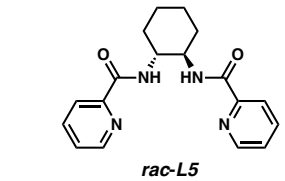
To improve reaction conversion, pyridyl substitution patterns on the C_2-symmetric ligand were explored. Electron-rich *para*-morpholine substitution on the pyridine ring led to enhanced reactivity and selectivity, delivering the product in an improved 32% yield and

3.4:1 b:l ratio with NaH as the base (entry 8). This could be improved further to 38% yield with LiHMDS as the base (entry 9). Intriguingly, an electron-deficient *para*-CF_3

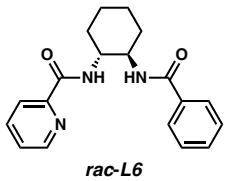
Table 2.1. *Optimization Studies*[a,b,c]



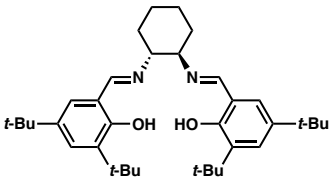
Entry	Ligand	Base	Yield (%)[a]	b/l[b]
1	*rac*-L5	NaH	20	2:1
2	*rac*-L6	NaH	0	-
3	*rac*-L7	NaH	0	-
4	*rac*-L5	LiH	23	1:1
5	*rac*-L5	LiHMDS	30	1.6:1
6	*rac*-L5	NaHMDS	19	1.8:1
7	*rac*-L5	KHMDS	<5	-
8	*rac*-L8	NaH	32	3.4:1
9	*rac*-L8	LiHMDS	38	2.4:1
10	*rac*-L9	NaH	31	1.6:1
11	*rac*-L10	LiHMDS	52	2.6:1
12[c]	*rac*-L10	LiHMDS	61	2.6:1



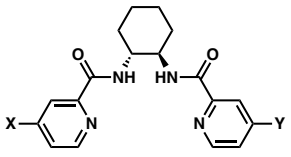
rac-L5



rac-L6



rac-L7



rac-L8: X = Y = N-morpholine

rac-L9: X = Y = CF_3

rac-L10: X = N-morpholine, Y = CF_3

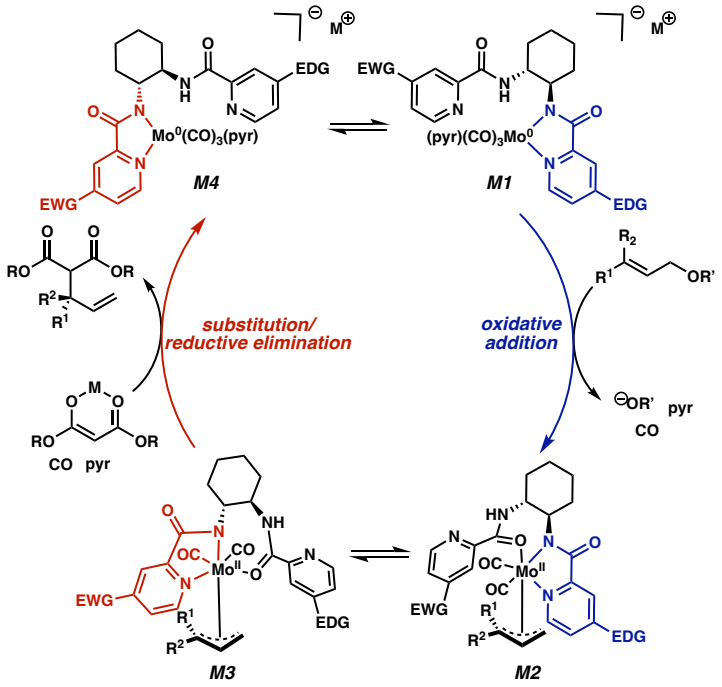
[a]Yields determined by ^{1}H NMR relative to a CH_2Br_2 internal standard. Reactions conducted on a 0.1 mmol scale. [b]b/l = branched to linear isomeric ratio. [c]Reaction performed with 15 mol% $Mo(CO)_3pyr_3$, 17 mol% ligand and a 48 h reaction time.

substituted ligand led to a similar yield with NaH, albeit with poor regioselectivity (entry 10). Given these results, we envisioned that employment of a C_1-symmetric ligand containing both electron-rich and electron-deficient pyridyl moieties could be beneficial. Inspired by the elementary steps proposed by Moberg with disubstituted allylic electrophiles,[20] we imagined that at first, an electron-rich pyridine could be bound to the Mo catalyst (**M1**) (Figure 2.1), facilitating oxidative addition to **M2**. At this point, a dynamic equilibration process could result in the electron-poor pyridine becoming bound to the metal (**M3**), accelerating the reductive elimination step to form product and **M4**.

Given our mechanistic hypothesis, various non-symmetrical ligands were explored in the transformation (Experimental Section, Table 2.6). We were delighted to find that C_1-symmetric *ShabyDACH* (**L10**), which contains both electron-rich *para*-morpholine and electron-deficient *para*-CF_3 fragments, promoted the desired transformation in 52% yield (Table 2.1, entry 11). This could be further improved to 61% yield when both an increased 48 h reaction time and 15 mol% Mo catalyst were employed (entry 12). Unfortunately, an extensive evaluation of additives demonstrated to be beneficial in other branched-selective allylic alkylation systems proved ineffective at improving the regioselectivity.[21]

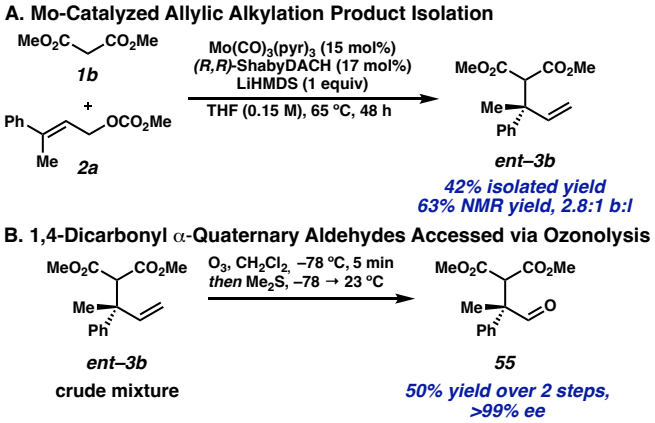
Separation of the branched and linear isomers by silica gel chromatography proved challenging. Sequential elutions by preparatory TLC allowed for isolation of branched product ***ent*-3b** in a diminished 42% yield (Scheme 2.2A). Given the inconsistencies in yield upon direct isolation of ***ent*-3b**, we considered an alternative approach to separate the

Figure 2.1. *Proposed Catalytic Cycle*



product isomers while also enhancing the synthetic value of the product. Ozonoloysis of the crude reaction mixture containing ***ent*-3b** could be performed to access the corresponding α-quaternary aldehyde **55** as a single constitutional isomer in 50% yield over two steps and excellent enantiopurity (>99% ee) (Scheme 2.2B). It is spectulated that the high enantioselectivity originates from rapid π-σ-π equilibration prior to nucleophilic attack. In support of this hypothesis, a racemic branched tri-substituted allylic electrophile **17a** preformed similarly to the achiral linear allylic electrophile, providing 96% ee (Experimental Section, Scheme 2.10).

Scheme 2.2. *Isolation of β-Quaternary Carbonyl Products*

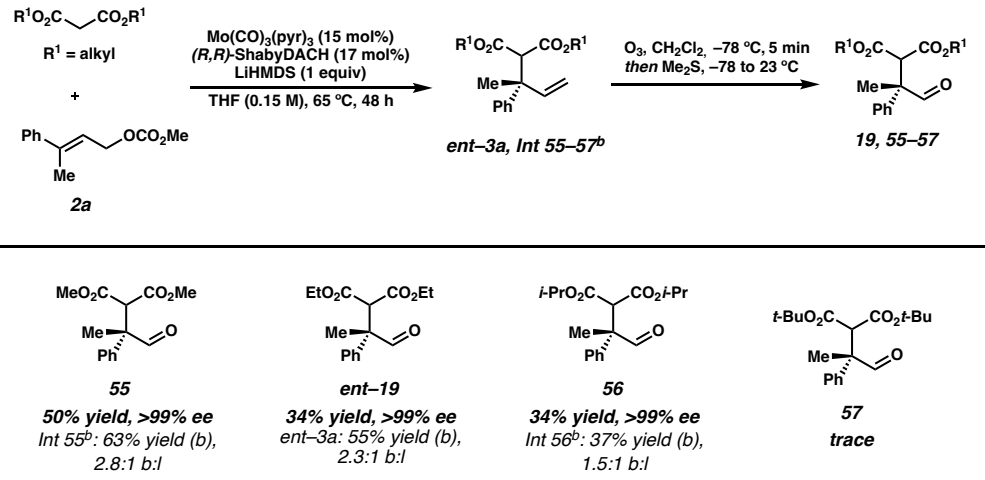


2.3 SUBSTRATE SCOPE

We next evaluated other dialkyl malonates under the optimized reaction conditions (Scheme 2.3). A substantial and predictable trend was observed favoring the linear product as the size of the malonate alkyl chain increased (***ent*–19, 55–57**).[22] Di-*tert*-butyl malonate proved too sterically hindered to participate in the reaction. Nevertheless, ee's of >99% were operative for each substrate. Unfortunately, other stabilized nucleophiles performed poorly in comparison to malonate nucleophiles (Experimental Section, Scheme 2.11).

We were pleased to find that our methodology could be applied to allylic electrophiles with a range of substitution patterns on the arene fragment (Scheme 2.4). The *para*-methyl substituted electrophile underwent the alkylation-ozonolysis sequence in 53% overall yield and >99% ee (**58**). Similarly, electron-rich *para*-methoxy substitution performed well in the alkylation-ozonolysis sequence (**59**), but an electron-deficient *para*-CF_3 substrate underwent the allylic alkylation with lower regioselectivity and yield (**60**). The *para*-nitro

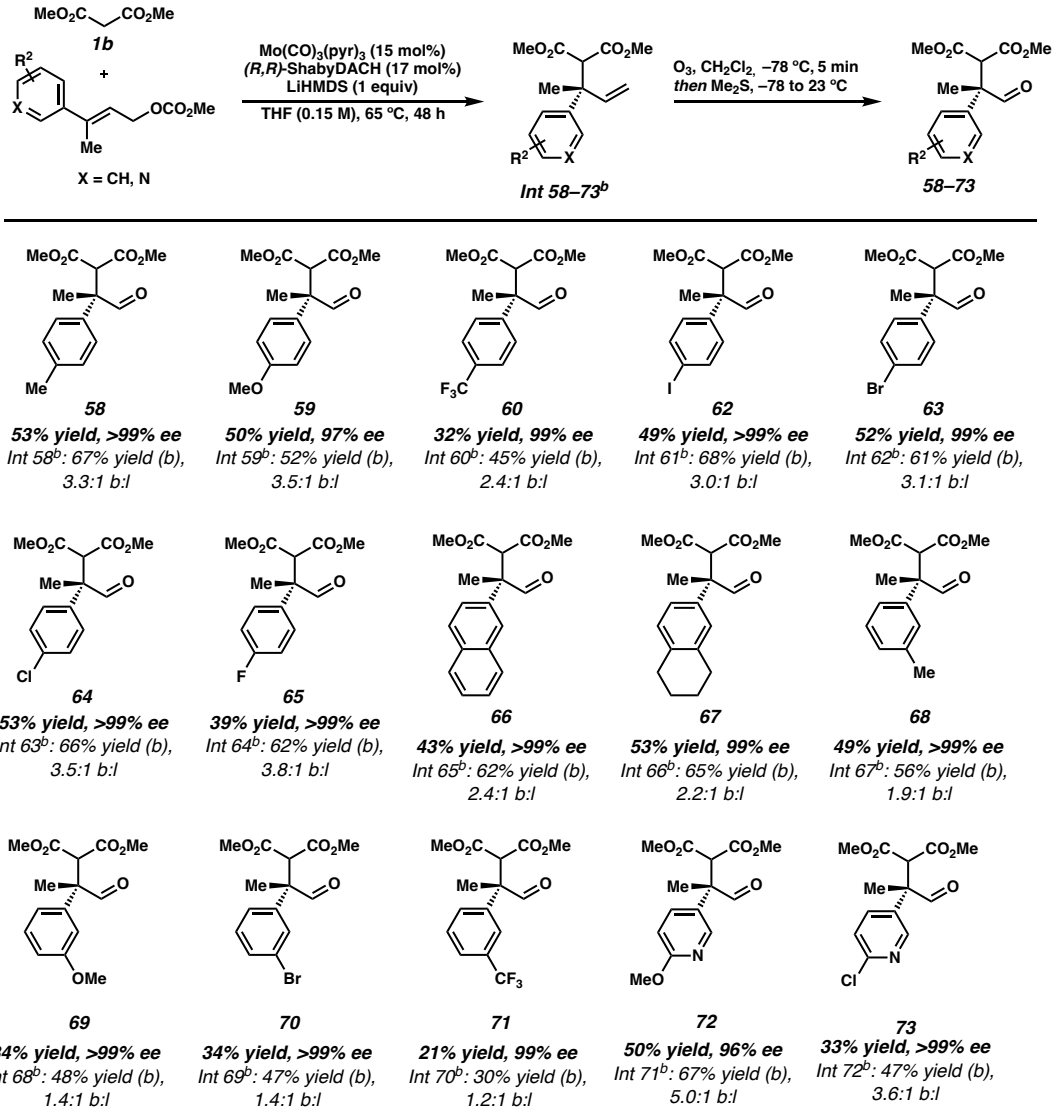
Scheme 2.3. *Performance of Malonate Nucleophiles*[a,b]



[a]Reactions conducted at 0.1 mmol scale, with 1 equiv of both nucleophile and electrophile. [b]Yield of branched product and b:l for intermediates determined by ^{1}H NMR relative to a CH_2Br_2 internal standard and as an average of two experiments. Crude mixture with linear isomer was advanced to ozonolysis.

product was not accessible under the reaction conditions *(***61**). To our delight, *para*-substitution with halides gave uniformly good yields in the allylic alkylation, as well as high enantioselectivities (**62**–**65**), offering a useful synthetic handle for future elaboration of the stereoenriched compounds and providing a stark contrast with Pd catalysts prone to oxidative addition into these bonds. More sterically demanding naphthyl and tetrahydronaphthyl substrates were also tolerated, though they led to diminished b:l regioselectivity (**66** and **67**). *Meta*-substitution was also accommodated with our protocol, though diminished regioselectivity was observed in all cases (**68** – **71**). Substrates bearing 2,5-disubstituted pyridine fragments resulted in moderate to high yields, enhanced

Scheme 2.4. *Electrophile Investigation*[a,b]



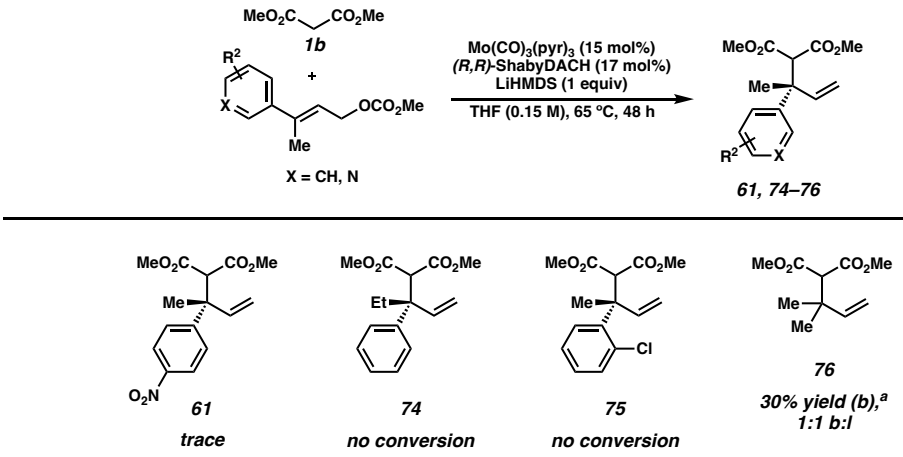
[a]Reactions conducted at 0.1 mmol scale, with 1 equiv of both nucleophile and electrophile. [b]Yield of branched product and b:l for intermediates determined by ^{1}H NMR relative to a CH_2Br_2 internal standard and as an average of two experiments. Crude mixture with linear isomer was advanced to ozonolysis.

regioselectivity and excellent enantioselectivity, offering further potential for product

elaboration through pyridinone reactivity or cross-coupling (**72** and **73**).

Generally, this methodology is limited to a methyl substituent *ipso* to the arene on the electrophile (**74**) and fails with *ortho*-substituted arenes (**75**), similar to the Ir-catalyzed approach (Scheme 2.5). Furthermore, the employment of a fully-alkyl allylic electrophile resulted in the reverse-prenylated product (**76**) in a decreased 30% NMR yield and an observed 1:1 b:l mixture, possibly due to a slower rate of oxidative addition into the molybdenum center. Related substrates were ineffective in the transformation (Scheme 2.9)

Scheme 2.5. *Limitations*[a]



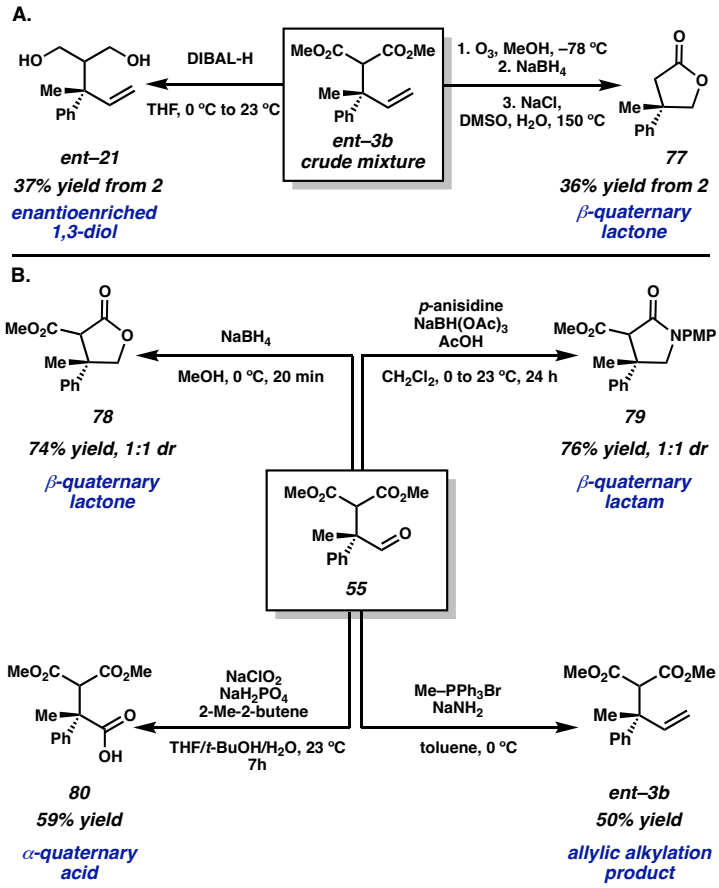
[a]Yield of branched product and b:l for intermediates determined by ^{1}H NMR relative to a CH_2Br_2 internal standard and as an average of two experiments.

2.4 DERIVATIZATIONS AND CONCLUSION

We were next interested in derivatizations of the allylic alkylation and ozonolysis products to demonstrate their synthetic utility (Scheme 2.6). Subjecting the crude product mixture containing ***ent*–3b** to DIBAL-H following allylic alkylation effected an exhaustive reduction of the malonate to the corresponding 1,3-diol ***ent*–21** (Scheme 2.6A). The

constitutional isomers arising in this case were readily separable by preparatory TLC, and ***ent*–21** was isolated in a 37% yield over two steps. Moreover, we found that quenching the ozonolysis reaction with $NaBH_4$ (rather than Me_2S) then performing a Krapcho decarboxylation provided the enantioenriched β-quaternary lactone **77** in 36% overall yield from **2a**. Starting instead from α-quaternary aldehyde **55**, which could be prepared on a

Scheme 2.6. *Product Diversification*



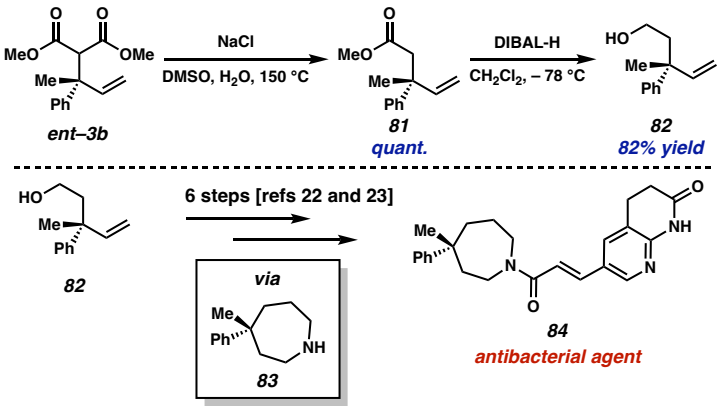
2 mmol scale in 47% overall yield and >99% ee, reduction with $NaBH_4$ afforded lactone **78** as a mixture of diastereomers in 74% yield (Scheme 2.6B). Reductive

amination/lactamization of aldehyde **55** with *p*-anisidine delivered the protected lactam **79** in 76% yield. Pinnick oxidation was also successful, delivering a 59% yield of the crystalline α-quaternary acid product **80** and enabling determination of absolute stereochemistry by X-ray crystallography (see Experimental Section). Lastly, a salt-free Wittig olefination of **55** gave rise to the Mo-catalyzed allylic alkylation product ***ent*–3b** in 50% yield.

Lastly, we hoped to apply our methodology toward an asymmetric formal synthesis of an antibacterial agent (Scheme 2.7). To that end, ***ent*–3b** was demonstrated to undergo a Krapcho decarboxylation to afford ester **81**. This intermediate was then reduced exhaustively with DIBAL-H to deliver alcohol **82**. Alcohol **82** is a known intermediate in the synthesis of enantioenriched azepane **83**.[23] This intermediate could be further elaborated to access antibacterial agent **84** in nearly perfect levels of enantiopurity for the first time.[24]

In summary, we have developed the first example of a Mo-catalyzed asymmetric allylic alkylation that forges a quaternary stereocenter derived from the electrophile. This reaction proceeds with nearly perfect enantioselectivity, broadly improving upon the enantiomeric excesses observed in our Ir-catalyzed protocol. The transformation exhibits modest regioselectivity and electronic limitations not observed with Ir. Overall, the two-step alkylation-ozonolysis procedure provides access to electronically dissonant 1,4-dicarbonyl scaffolds, which are often synthetically difficult to access.[13] As the importance of sustainable, inexpensive, and non-toxic base metal catalysts grows, we envision that this

Scheme 2.7. *Formal Synthesis of Enantioenriched Antibacterial Azepane*



Mo-mediated technique will motivate further development of alternatives to precious metal catalysis in asymmetric allylic alkylation in our laboratory and other research groups around the globe.

2.5 EXPERIMENTAL SECTION

2.5.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[25] Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 μm) and Teledyne Isco CombiFlash Rf+ UV with Luknova standard silica (avg particle size 50μm) flash columns were used for flash chromatography. ^1H NMR spectra were recorded on Varian Inova 500 MHz, Varian 600 MHz, and Bruker 400 MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm) or CH_2Cl_2 (δ 5.30 ppm). ^{13}C NMR spectra were recorded on a Varian Inova 500

MHz spectrometer (125 MHz) and Bruker 400 MHz spectrometers (100 MHz) and are reported relative to $CDCl_3$ (δ 77.16 ppm). ^{19}F NMR spectra were recorded on a Bruker 400 MHz spectrometer (376 MHz) and referenced to an external standard: hexafluorobenzene; ^{19}F NMR (376 MHz, $CDCl_3$) δ -161.64. Data for ^1H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet. Data for ^{13}C NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell. Analytical SFC was performed with an Agilent 1260 Infinity II supercritical CO_2 analytical chromatography system utilizing Chiralpak (IC-3, AD-3, ID-3, IF-3, IG-3, IH-3) or Chiralcel (OD-3, OJ-3) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in field ionization (FI+) or field desorption (FD+) mode, or an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI), or mixed ionization mode (MM: ESI-APCI+). Reagents were purchased from commercial sources and used as received unless otherwise stated.

Low-temperature diffraction data (ϕ-and ω-scans) were collected on a Bruker AXS D8 VENTURE KAPPA diffractometer coupled to a PHOTON II CPAD detector with Mo K_α radiation (λ = 0.71073 Å) or Cu K_α radiation (λ = 1.54178 Å) from an IμS micro-source for the structure of compound V24319. The structure was solved by direct methods using SHELXS[26] and refined against F^2 on all data by full-matrix least squares with SHELXL-2019[27] using established refinement techniques.[28] All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included into the model at geometrically

calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the *U* value of the atoms they are linked to (1.5 times for methyl groups).

Compound V24319 crystallizes in the triclinic space group *P*1 with four molecules in the asymmetric unit. The coordinates for the hydrogen atoms bound to O2, O22, O42 and O62 were located in the difference Fourier synthesis and refined semi-freely with the help of a restraint on the O-H distance (0.84(4) Å).

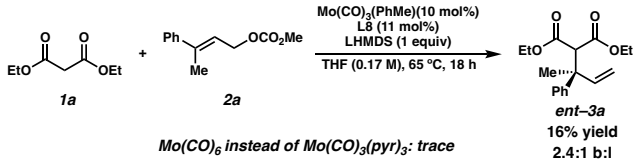
The crystal was non-merohedrally twinned. Two independent orientation matrices for the unit cell were determined using the program CELL_NOW[29], and data reduction taking into account the twinning was performed with SAINT[30]. The program TWINABS[31] was used to perform absorption correction and scaling, as well as detwin the data using a single domain. This procedure resulted in the merging of equivalent reflections.

List of Abbreviations:

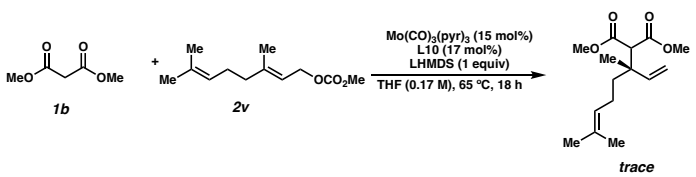
ee – enantiomeric excess, SFC – supercritical fluid chromatography, HPLC – high-performance liquid chromatography, TLC – thin-layer chromatography, Dr – dram, DACH – diaminocyclohexane

2.5.2 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

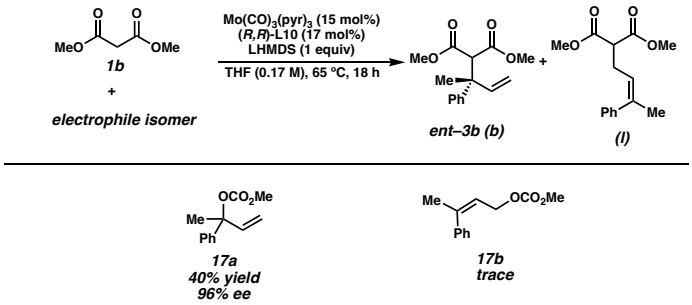
Scheme 2.8. *Alternative Mo Precatalyst*



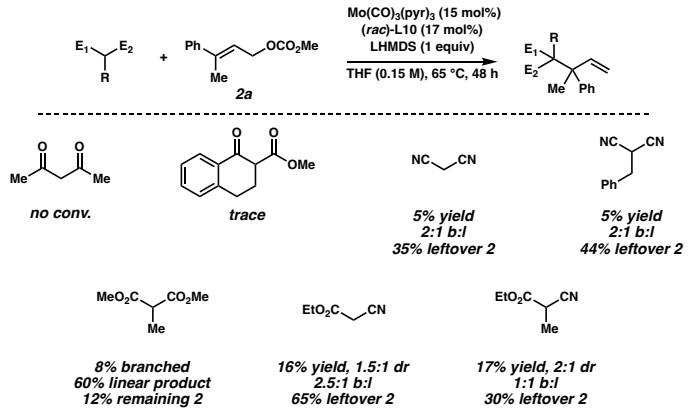
Scheme 2.9. *All-Alkyl Electrophile*



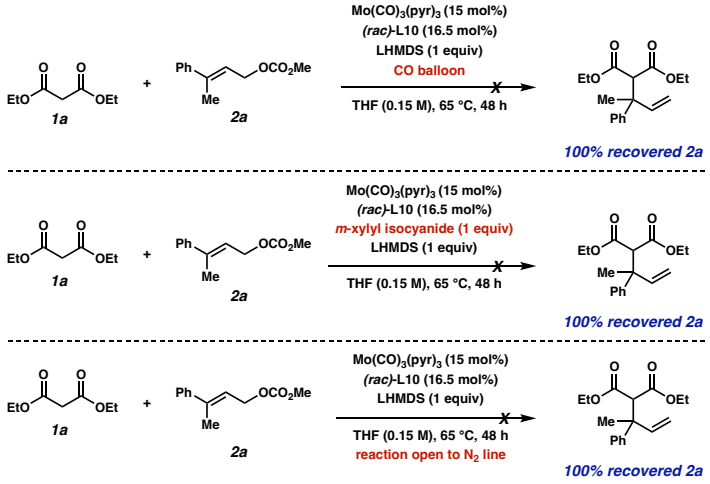
Scheme 2.10. *Reactivity of Electrophile Isomers*



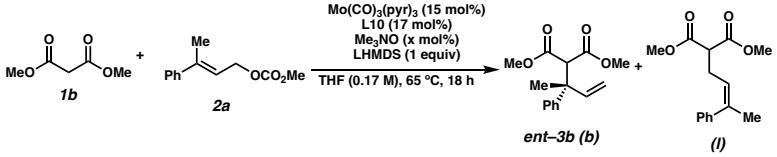
Scheme 2.11. *Compatibility of Other Stabilized Carbon Nucleophiles*



Scheme 2.12. *Probing the Role of CO*

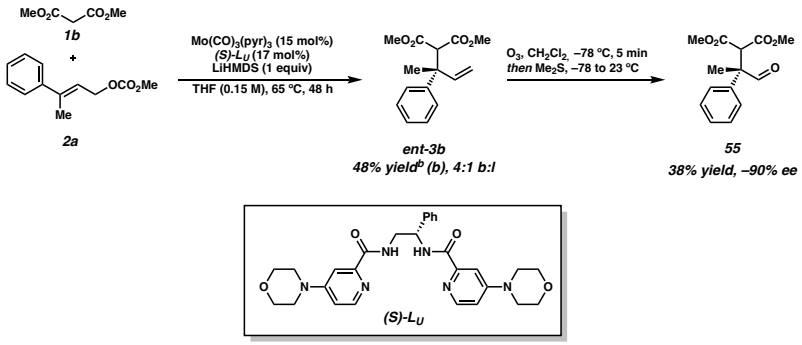


Scheme 2.13. *Trimethylamine Oxide as CO Scavenger*



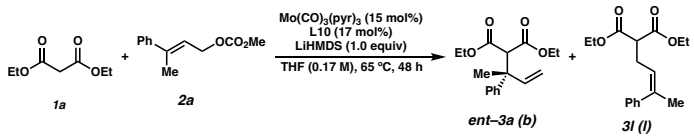
Me_3NO	Result
15 mol%	55% yield, 3:0:1 b:l
30 mol%	12% yield, 1.9:1 b:l
45 mol%	trace

Scheme 2.14. *Performance of Ligand with Unsymmetrical Backbone*



[a]Reaction conducted at 0.1 mmol scale, with 1 equiv of both nucleophile and electrophile. [b]Yield of branched product and b:l for intermediates determined by ^1H NMR relative to a CH_2Br_2 internal standard and as an average of two experiments. Crude mixture with linear isomer was advanced to ozonolysis.

Table 2.2. *Control Reactions*



Entry	Deviation from Standard	Leftover SM (%)	Yield 3 (%)[a]	b/l[b]
1	None	<5	61	2.6:1
2	No Precatalyst	100	0	-
3	No Ligand	64	<5	-
4	No LHMDS	100	0	-
5	34 mol% L10	6	35	2.3:1
6	2.0 equiv LiHMDS	50	4	1:3
7	0.5 equiv LiHMDS	31	32	2.3:1
8	2.0 equiv 2a	9	49	2.5:1
9	2.0 equiv 1a and LiHMDS	<5	48	1.6:1

[a]Yields determined by ^1H NMR relative to a CH_2Br_2 internal standard. Reactions conducted on a 0.1 mmol scale. [b]b/l = branched to linear isomeric ratio.

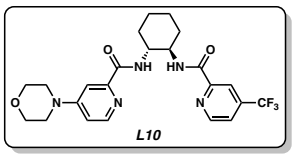
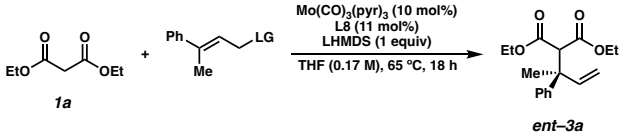


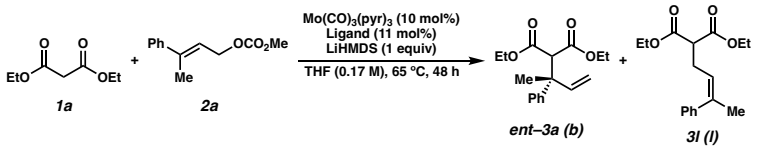
Table 2.3. *Leaving Group Survey*



Entry	LG =	Yield (%)[a]	b/l[b]
1	OCO_2Me	38	2.4:1
2	Cl	5	1:7
3	$OPO(OEt)_2$	42	2.2:1
4	$OC(O)CF_3$	22	1:1.25
5	OBz	5	3.3:1
6	$(4\text{-}CF_3)OBz$	15	2.3:1
7	(2,4,6-Me)OBz	<5	-

[a]Yields determined by ^1H NMR relative to a CH_2Br_2 internal standard. Reactions conducted on a 0.1 mmol scale. [b]b/l = branched to linear isomeric ratio.

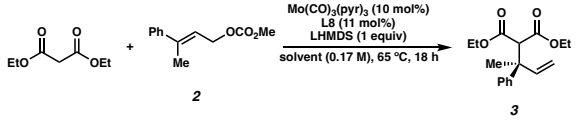
Table 2.4. *Enantiomeric Excess with Other Ligands*



Entry	Ligand	Yield 3 (%)[a]	b:l[a]	ee[b]
1	(*R,R*)-L5	37	1.7:1	>99%
2	(*R,R*)-L8	40	2.4:1	>99%
3	(*R,R*)-L10	52	2.6:1	>99%

[a]Yields determined by ^1H NMR relative to a CH_2Br_2 internal standard. Reactions conducted on a 0.1 mmol scale. [b]Ee determined by chiral SFC following DIBAL-H reduction.

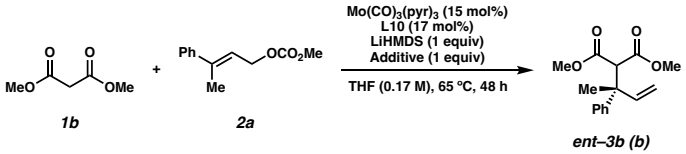
Table 2.5. *Solvent Investigation*



Entry	solvent	Yield (%)[a]	b/l[b]
1	2-MeTHF	46	2.2:1
2	DME	39	2.2:1
3	MTBE	16	1.2:1
4	Dioxane	31	2.3:1
5	Toluene	16	1:1
6	DMF	0	-
7	DCE	29	2:1

[a]Yields determined by ^1H NMR relative to a CH_2Br_2 internal standard. Reactions conducted on a 0.1 mmol scale. [b]b/l = branched to linear isomeric ratio.

Table 2.6. *Additive Study*



Entry	Additive	Leftover SM (%)	Yield 5 (%)[a]	b/l[b]
1	none	<5	61	2.6:1
2	BEt_3	<5	33	1:1.2
3	BPh_3	<5	46	1.8:1
4	LiBr	10	30	2:1
5	LiCl	19	34	2:1
6	ZnI_2	<5	<5	1:10
7	$MgBr_2$	22	0	28% linear
8	$ZrCl_4$	100	0	-
9	pyridine	<5	48	2.4:1
10	BSA	<5	52	2.4:1
11	HMDS (2 equiv)	<5	62	2.7:1
12	HMDS (4 equiv)	<5	58	2.6:1

[a]Yields determined by ^1H NMR relative to a CH_2Br_2 internal standard. Reactions conducted on a 0.1 mmol scale. [b]b/l = branched to linear isomeric ratio.

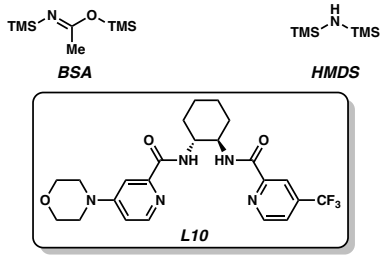
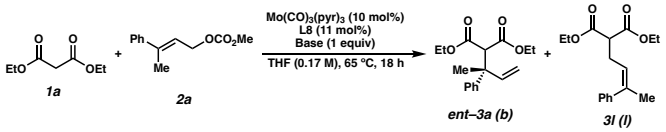


Table 2.7. *Base Investigation with* ***L8***



Entry	Base	Yield 3 (%)[a]	b/l[b]
1	LiO*t*-Bu	41	2.5:1
2	NaO*t*-Bu	<5	-
3	LiOMe	31	2.5:1
4	NaOMe	<5	-

[a]Yields determined by ^1H NMR relative to a CH_2Br_2 internal standard. Reactions conducted on a 0.1 mmol scale. [b]b/l = branched to linear isomeric ratio.

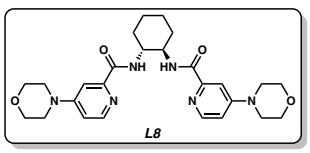
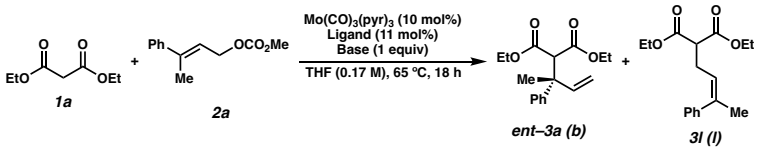
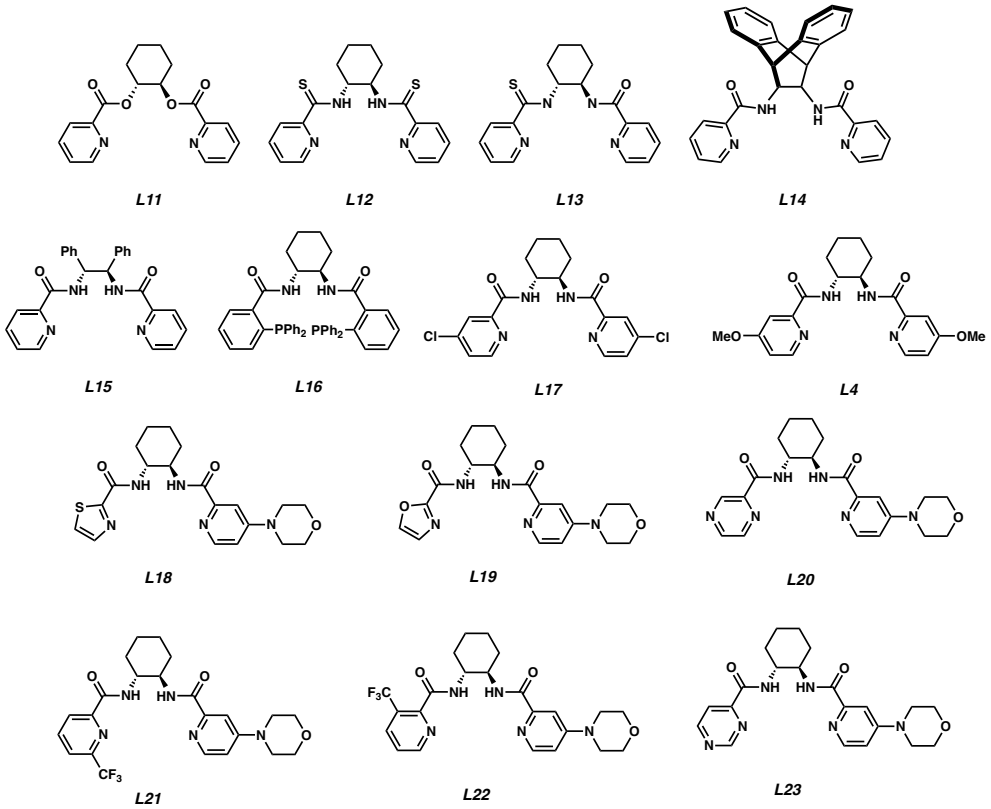


Table 2.8. *Ligand Evaluation*

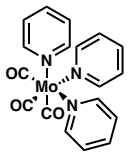


Entry	Ligand	Base	Yield 3 (%)[a]	b/l[b]
1	*L11*	NaH	0	-
2	*L12*	NaH	0	-
3	*L13*	NaH	<5	-
4	*L14*	NaH	<5	-
5	*L15*	NaH	<5	-
6	*L16*	NaH	<5	-
7	*L17*	NaH	23	2.4:1
8	*L4*	NaH	15	1.6:1
9	*L18*	LiHMDS	33	2.2:1
10	*L19*	LiHMDS	22	1.7:1
11	*L20*	LiHMDS	31	1.9:1
12	*L21*	LiHMDS	0	-
13	*L22*	LiHMDS	<5	-
14	*L23*	LiHMDS	36	2:1

[a]Yields determined by ^{1}H NMR relative to a CH_2Br_2 internal standard. Reactions conducted on a 0.1 mmol scale. [b]b/l = branched to linear isomeric ratio.

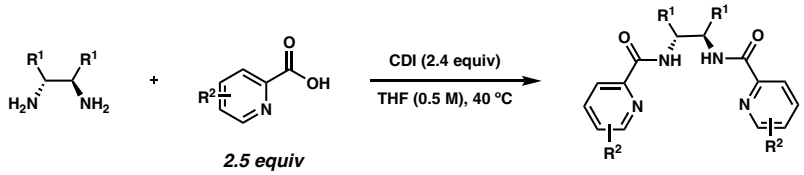


Synthesis of $Mo(CO)_3(pyr)_3$



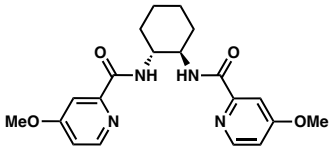
Following a modified literature procedure,[17] $Mo(CO)_6$ (1.06 g, 4.0 mmol) was dissolved in pyridine (2.689 g, 34 mmol, 2.7 mL) and the mixture was heated to 80 ºC for 2 h. At this point, the temperature was increased to 130 ºC and the reaction proceeded for 17 h at this temperature. Upon completion of the reaction, the solution was slowly cooled to ambient temperature without stirring. The resultant slurry was further cooled to 0 ºC then diluted with cold pyridine. The product was obtained as a crystalline yellow solid following filtration and repeated rinsing with cold pyridine (1.536 g, 3.7 mmol, 92% yield). ^{1}H NMR (500 MHz, DMSO) δ 8.61 – 8.54 (m, 6H), 7.78 (tt, *J* = 7.6, 1.8 Hz, 3H), 7.38 (ddd, *J* = 7.6, 4.2, 1.5 Hz, 6H).

Synthesis of C_2-Symmetric Ligands: General Procedure A



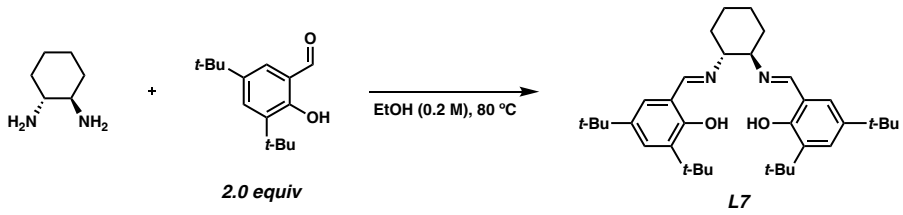
A flame-dried flask equipped with a stir bar was charged with carbonyldiimidazole (2.4 equiv) and then subjected to three purge-backfill cycles with N_2. THF (0.5 M) was added, followed by the picolinic acid derivative (2.5 equiv). The mixture was stirred at 40 ºC for 1 h. The diamine (1 equiv) was then added slowly via syringe. The reaction was monitored by TLC and LCMS. Upon completion (typically 16–24 h), the vessel was cooled to 23 °C and quenched by the addition of H_2O. Three extractions were performed with ethyl acetate, and the combined organic layers were dried with Na_2SO_4, filtered, and

concentrated. The crude product was purified by silica gel chromatography to afford the desired product.



_N_,_N_'-(cyclohexane-1,2-diyl)bis(4-methoxypicolinamide) (L4)

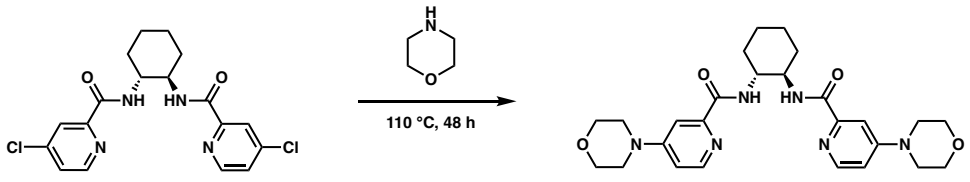
Prepared according to General Procedure A and purified by silica gel chromatography to afford **L4** as a white solid (350 mg, 0.91 mmol, 57% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 5.7, 0.6 Hz, 2H), 8.23 (d, *J* = 6.8 Hz, 2H), 7.61 (dd, *J* = 2.7, 0.5 Hz, 2H), 6.84 (dd, *J* = 5.6, 2.6 Hz, 2H), 4.09 – 3.98 (m, 2H), 3.85 (s, 6H), 2.25 – 2.14 (m, 2H), 1.87 – 1.78 (m, 2H), 1.51 – 1.39 (m, 4H). Characterization data was in agreement with the literature.[32]



6,6'-((1E,1'E)-(((1*R*,2*R*)-cyclohexane-1,2-diyl)bis(azaneylylidene))bis(methaneylylidene))bis(2,4-di-tert-butylphenol) (L7)

Preparation: In accordance with a literature protocol,[3] 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (0.469 g, 2 mmol, 2 equiv) was added to a solution of *trans*-1,2-diaminocyclohexane (0.12 mL, 1 mmol, 1 equiv) in absolute ethanol (5 mL, 0.2 M). The mixture was heated to reflux for 1 h and then cooled to 23 °C. The resulting solid was collected by filtration and washed with a small portion of ethanol (2 mL) to afford **L7** as a fluffy yellow solid (0.546 g, quant.). ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.69 (s, 2H), 8.29 (s, 2H), 7.29 (d, *J* = 2.4 Hz, 2H), 6.97 (d, *J* = 2.4 Hz, 2H), 3.33 – 3.28 (m, 2H), 1.90 (dd, *J* =

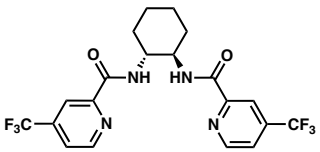
41.5, 11.3 Hz, 4H), 1.73 (m, 2H), 1.49 – 1.42 (m, 2H), 1.40 (s, 18H), 1.22 (s, 18H). Characterization data was in agreement with the literature.[33]



L17 *L5*

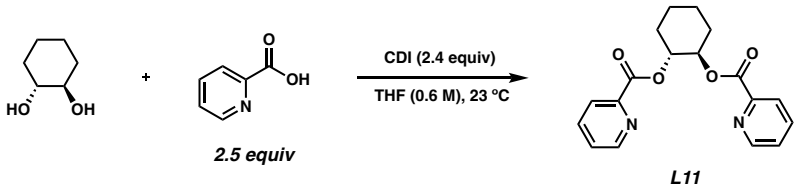
_N,N'_-((1_R_,2_R_)-cyclohexane-1,2-diyl)bis(4-morpholinopicolinamide) (L8)

Preparation: (*R,R*)-**L17** (500mg, 1.28 mmol, 1 equiv) was added to a flame-dried flask equipped with a reflux condenser and stir bar then subjected to three purge-backfill cycles with N_2. Morpholine (15 mL, 174 mmol, 136 equiv) was then added and the mixture was heated to 110 ºC. The reaction was monitored by LCMS and after 48 h all starting material was consumed. The reaction was then cooled to 23 °C and then concentrated by rotary evaporation. The residue was purified by silica gel chromatography (100% EtOAc then 0–10% MeOH/CH_2Cl_2) to afford **L8** as a yellow-orange solid (470 mg, 0.95 mmol, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 7.1 Hz, 2H), 8.19 (d, *J* = 5.8 Hz, 2H), 7.51 (d, *J* = 2.7 Hz, 2H), 6.65 (dd, *J* = 5.9, 2.7 Hz, 2H), 4.02 (t, *J* = 5.0 Hz, 2H), 3.79 (dd, *J* = 6.0, 3.9 Hz, 8H), 3.31 (dd, *J* = 6.0, 3.9 Hz, 8H), 2.23 – 2.12 (m, 2H), 1.81 (s, 4H), 1.52 – 1.34 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 156.1, 150.8, 149.0, 109.6, 106.8, 66.5, 53.2, 46.3, 32.8, 24.9. IR (thin film, NaCl) 3355, 2930, 2856, 1659, 1598, 1518, 1447, 1373, 1256, 1120, 993, 918, 731 cm^{-1}. HRMS (MM:FD+) m/z calc'd for $C_{26}H_{34}N_6O_4$ $[M]^{+\bullet}$: 494.2636, found 494.2617. $[\alpha]_D^{23}$ +57.35 (*c* 1.0, $CHCl_3$).



_N,N'_-(cyclohexane-1,2-diyl)bis(4-(trifluoromethyl)picolinamide) (L9)

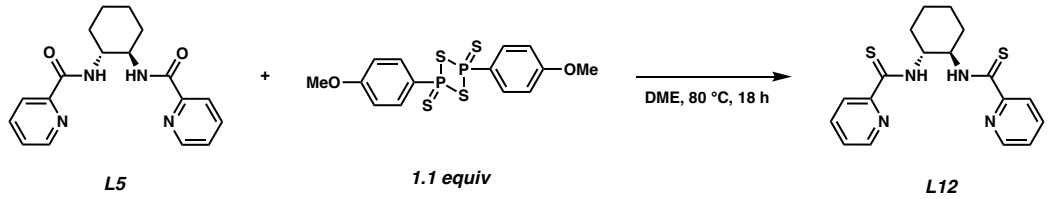
Prepared according to General Procedure A and purified by silica gel chromatography (20% EtOAc/Hexanes) to afford **L9** as a white solid (446 mg, 0.97 mmol, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 5.0 Hz, 2H), 8.35 – 8.24 (m, 2H), 8.24 – 8.11 (m, 2H), 7.58 (dd, *J* = 5.2, 1.7 Hz, 2H), 4.20 – 3.93 (m, 2H), 2.28 – 2.14 (m, 2H), 1.93 – 1.79 (m, 2H), 1.58 – 1.39 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 151.3, 149.4, 139.8 (q, *J* = 34.5 Hz), 121.8 (q, *J* = 3.6 Hz), 121.3, 118.3 (q, *J* = 3.6 Hz), 53.7, 32.7, 24.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.7. IR (thin film, NaCl) 3308, 2936, 2857, 1666, 1609, 1531, 1409, 1335, 1320, 1268, 1230, 1136, 1079, 914, 781, 732, 666 cm^{-1}. HRMS (MM:FD+) m/z calc'd for $C_{20}H_{18}N_4O_2F_6$ $[M]^{+\bullet}$: 460.1329, found 460.1318.



Cyclohexane-1,2-diyl dipicolinate (L11)

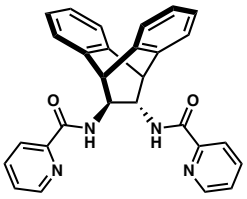
Preparation: Adopted from a literature protocol,[4] a flame-dried flask equipped with a stir bar was charged with carbonyldiimidazole (2.175 g, 13.4 mmol, 2.4 equiv) and then subjected to three purge-backfill cycles with N_2. THF (10 mL, 0.6 M) was added, followed by picolinic acid (1.725 g, 14 mmol, 2.5 equiv). The mixture was stirred at 23 ºC for 1 h. *Trans*-1,2-cyclohexanediol (650 mg, 5.6 mmol, 1 equiv) was then added slowly via syringe. The reaction was stirred at 23 °C for 18 h and monitored by LCMS. Upon completion, the reaction was quenched by the addition of water. Three extractions were performed with CH_2Cl_2 and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatography (5% MeOH/EtOAc). To remove remaining impurities, trituration was performed with hot hexanes, delivering **L11** as a white solid (1.10 g, 3.37 mmol, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (ddd, J = 4.7, 1.8, 0.9 Hz, 2H), 8.01 (dt, J = 7.9, 1.1 Hz, 2H), 7.75 (td, J = 7.7, 1.7 Hz, 2H), 7.39 (ddd, J = 7.7, 4.7, 1.2 Hz, 2H), 5.46 – 5.30 (m, 2H), 2.41 – 2.22 (m, 2H), 1.91 – 1.80 (m, 2H),

1.77 – 1.61 (m, 2H), 1.54 – 1.44 (m, 2H). Characterization data was in agreement with the literature.[34]



_N_,_N_'-(cyclohexane-1,2-diyl)bis(pyridine-2-carbothioamide) (L12)

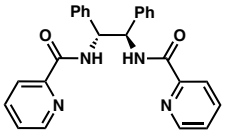
Preparation: In accordance with a literature protocol,[35] Lawesson's reagent (134 mg, 0.33 mmol, 1.1 equiv) was added to a stirring solution of *rac*-**L5** (100 mg, 0.3 mmol, 1 equiv) in DME (1 mL, 0.3 M), and the reaction was heated to 80 ºC for 18 h. The crude reaction was passed through a plug of Al_2O_3 and rinsed several times with CH_2Cl_2. The residue was purified by silica gel chromatography (0 – 50% EtOAc/Hexanes) to afford **L12** as a yellow solid (83.2 mg, 0.23 mmol, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.44 (s, 2H), 8.54 (dt, J = 8.0, 1.1 Hz, 2H), 8.46 (ddd, J = 4.7, 1.8, 0.9 Hz, 2H), 7.72 (td, J = 7.7, 1.7 Hz, 2H), 7.34 (ddd, J = 7.6, 4.7, 1.2 Hz, 2H), 5.06 – 4.88 (m, 2H), 2.47 – 2.38 (m, 2H), 1.97 – 1.85 (m, 2H), 1.55 (m, 4H). ^{13}C NMR (100 MHz, CDCl3) δ 191.1, 150.9, 147.0, 137.0, 125.9, 124.9, 58.5, 31.0, 24.6. IR (thin film, NaCl) 3247, 2931, 1509, 1433, 1344, 989, 734 cm^{-1}. HRMS (MM:FD+) m/z calc'd for $C_{18}H_{20}N_4S_2[M]^{+\bullet}$: 356.1124, found 356.1119.



_N_,_N_'-(9,10-dihydro-9,10-ethanoanthracene-11,12-diyl)dipicolinamide (L14)

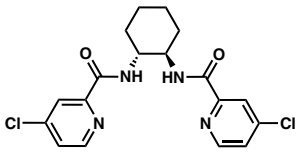
Prepared according to General Procedure A and purified by silica gel chromatography (0–100% EtOAc/Hexanes) to afford **L14** as a white solid (1.24 g, 2.78 mmol, 92% yield). ^{1}H

NMR (400 MHz, $CDCl_3$) δ 8.43 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 2H), 8.14 (dt, *J* = 7.8, 1.1 Hz, 2H), 7.90 (d, *J* = 8.2 Hz, 2H), 7.79 (td, *J* = 7.7, 1.7 Hz, 2H), 7.46 (dd, *J* = 7.1, 1.4 Hz, 2H), 7.40 – 7.31 (m, 4H), 7.25 – 7.16 (m, 4H), 4.54 (d, *J* = 2.5 Hz, 2H), 4.41 – 4.29 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 149.5, 148.2, 141.3, 139.0, 137.3, 127.0, 126.9, 126.3, 126.0, 124.9, 122.23, 57.1, 49.6. IR (thin film, NaCl) 3374, 3353, 2950, 1672, 1590, 1514, 1462, 1434, 1226, 996, 912, 746, 631 cm^{-1}. HRMS (MM:FD+) m/z calc'd for $C_{28}H_{23}N_4O_2[M+H]^+$: 447.1816, found 447.1786.



***N,N'*-(1,2-diphenylethane-1,2-diyl)dipicolinamide (L15)**

Prepared according to General Procedure A and purified by silica gel chromatography (0–100% EtOAc then 5% MeOH/EtOAc) to afford **L15** as a white solid (422 mg, 1.00 mmol, 20% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 9.02 – 8.90 (m, 2H), 8.58 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 2H), 8.15 (dt, *J* = 7.8, 1.1 Hz, 2H), 7.80 (td, *J* = 7.7, 1.7 Hz, 2H), 7.41 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 2H), 7.32 – 7.22 (m, 10H), 5.67 (dd, *J* = 6.1, 2.6 Hz, 2H). Characterization data was in agreement with the literature.[36]

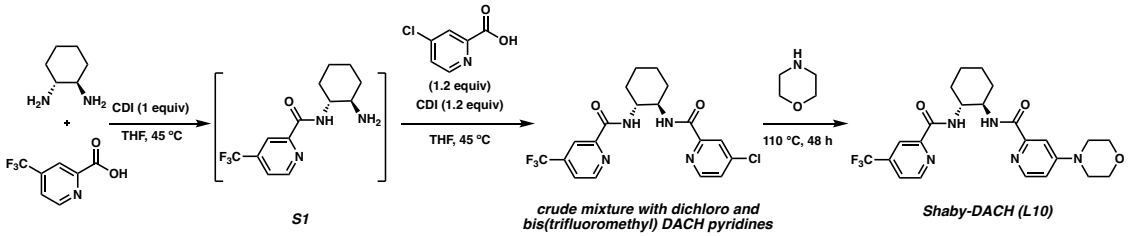


***N,N'*-(cyclohexane-1,2-diyl)bis(4-chloropicolinamide) (L17)**

Prepared according to General Procedure A and purified by silica gel chromatography (0–100% EtOAc/Hexanes) to afford **L17** as a yellow solid (1.74 g, 4.42 mmol, 88% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 8.43 (d, *J* = 5.2 Hz, 2H), 8.19 – 8.11 (m, 2H), 8.06 (d, *J* = 2.1 Hz, 2H), 7.36 (dd, *J* = 5.2, 2.1 Hz, 2H), 4.10 – 3.95 (m, 2H), 2.27 – 2.10 (m, 2H), 1.94 –

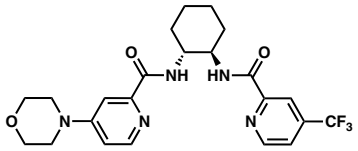
1.78 (m, 2H), 1.52 – 1.40 (m, 4H). Characterization data was in agreement with the literature.[32]

Synthesis of Shaby-DACH (L10) (Two-step, one-pot)



A flame-dried flask equipped with a stir bar was subjected to three purge-backfill cycles with N_2. (*R,R*)-1,2-diaminocyclohexane (114 mg, 1 mmol, 1 equiv) was added via syringe, followed by THF (2 mL, 0.5 M). In another flame-dried flask equipped with a stir bar, carbonyldiimidazole (162 mg, 1 mmol, 1 equiv) was added and the vessel was placed under N_2 atmosphere then charged with THF (1 mL). 4-CF_3 picolinic acid (191 mg, 1 mmol, 1 equiv) was added to the carbonyldiimidazole slurry, and the mixture was stirred at 45 ºC for 1 h. This solution was then transferred dropwise to the diamine solution via cannula at 45 ºC. The resulting mixture was stirred for 4 h. In a separate flame-dried flask equipped with a stir bar, carbonyldiimidazole (195 mg, 1.2 mmol, 1.2 equiv) was added and the vessel was placed under N_2 atmosphere then charged with THF (1 mL). 4-Cl picolinic acid (189 mg, 1.2 mmol, 1.2 equiv) was added to the carbonyldiimidazole slurry, and the mixture was stirred at 45 ºC for 1 h. This solution was added to the picolinamide mixture containing **S1** via cannula at 45 °C, which was then stirred for another 8 h and monitored by TLC and LCMS. Upon completion, the reaction was cooled to 23 °C and quenched by the addition of H_2O. Three extractions were performed with ethyl acetate, and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatography (20–50 % EtOAc/Hexanes) to isolate an inseparable statistical mixture of DACH pyridines from other impurities.

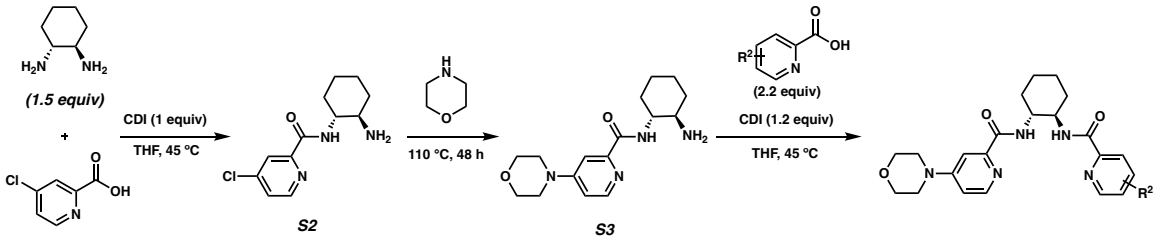
The mixture of DACH pyridines was then added to a flame-dried flask equipped with a reflux condenser and stir bar and then subjected to three purge-backfill cycles with N_2. Morpholine (10 mL, 116 mmol) was then added and the mixture was heated to 110 ºC. The reaction was monitored by LCMS and after 48 h all starting material was consumed. The reaction was then cooled to 23 °C and then concentrated by rotary evaporation. The residue was purified by silica gel chromatography (20–100% EtOAc/Hexanes then 10% MeOH/CH_2Cl_2) to isolate **L10** as an off-white solid (146 mg, 0.31 mmol, 31% yield over three steps).



4-morpholino-N-((1*R*,2*R*)-2-(4-(trifluoromethyl)picolinamido)cyclohexyl)picolinamide (L10)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, *J* = 5.0 Hz, 1H), 8.29 (dt, *J* = 1.6, 0.8 Hz, 1H), 8.23 (dd, *J* = 16.3, 8.1 Hz, 2H), 8.17 (d, *J* = 5.8 Hz, 1H), 7.57 – 7.52 (m, 1H), 7.46 (d, *J* = 2.7 Hz, 1H), 6.64 (dd, *J* = 5.9, 2.8 Hz, 1H), 4.13 – 3.94 (m, 2H), 3.82 – 3.71 (m, 4H), 3.32 – 3.23 (m, 4H), 2.26 – 2.08 (m, 2H), 1.89 –1.74 (m, 2H), 1.56 – 1.35 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 163.2, 156.1, 151.6, 150.5, 149.3, 149.0, 139.7 (q, *J* = 34.6 Hz), 124.0, 121.5 (q, *J* = 3.2 Hz), 118.3 (q, *J* = 3.5 Hz), 109.7, 106.6, 66.4, 54.2, 52.8, 46.2, 32.7, 32.6, 25.0, 24.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.7. IR (thin film, NaCl) 3329, 2931, 2858, 1661, 1600, 1519, 1335, 1168, 1145, 993, 735 cm^{-1}. HRMS (MM:FD+) m/z calc'd for $C_{23}H_{26}F_3N_6O_3$ $[M]^{+\bullet}$: 477.1982, found 477.1980. $[\alpha]_D^{23}$ –60.86 (*c* 1.0, $CHCl_3$).

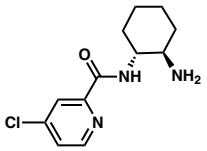
Synthesis of C_1-Symmetric Ligands (Stepwise): General Procedure B



A flame-dried flask equipped with a stir bar was subjected to three purge-backfill cycles with N_2. *Trans*-1,2-diaminocyclohexane (3.60 mL, 30 mmol, 1.5 equiv) was added via syringe, followed by THF (15 mL, 1.3 M). In another flame-dried flask equipped with a stir bar, carbonyldiimidazole (3.243 g, 20 mmol, 1 equiv) was added and the vessel was placed under N_2 atmosphere then charged with THF (40 mL, 0.5 M). 4-Cl picolinic acid (3.151 g, 20 mmol, 1 equiv) was added to the carbonyldiimidazole slurry, and the mixture was stirred at 45 ºC for 1 h. The diamine solution was then added dropwise to the carbonyldiimidazole/carboxylic acid solution via cannula at 45 ºC. The reaction was stirred at 45 °C and monitoried via TLC and LCMS. Upon completion (typically 8 h), the reaction was cooled to 23 °C and quenched by the addition of H_2O. Three extractions were performed with ethyl acetate, and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The residue was purified via silica gel chromatography (2/10/88 Et_3N/MeOH/CH_2Cl_2) to isolate the product as a mixture with imidazole. A trituration was performed with hot H_2O to remove most of the imidazole, affording mono-picolinamide **S2** as a white solid (3.031 g, 11.95 mmol, 50% yield).

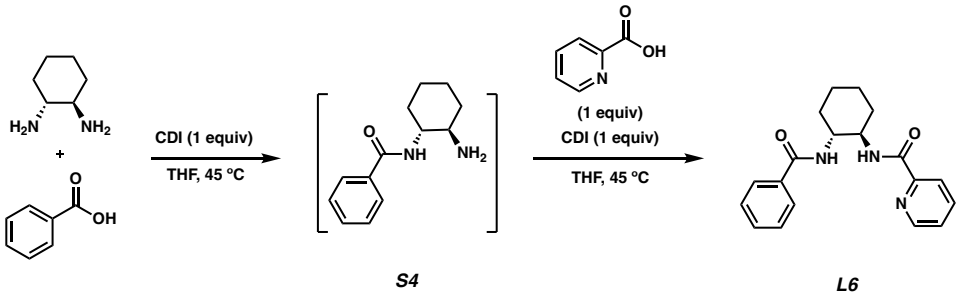
S2 (300 mg, 1.18 mmol, 1 equiv) was then added to a flame-dried flask equipped with a reflux condenser and stir bar, then subjected to three purge-backfill cycles with N_2. Morpholine (4.5 mL, 52 mmol, 44 equiv) was then added and the mixture was heated to 110 ºC. The reaction was monitored by LCMS and after 48 h all starting material was consumed. The reaction was then cooled to 23 °C and then concentrated by rotary evaporation. The crude product **S3** was advanced to the next step without additional purification.

S3 was then added to a flame-dried flask equipped with a stir bar under N_2 atmosphere and was then charged with THF (0.2 M). In another flame-dried flask equipped with a stir bar, the corresponding carboxylic acid (2.2 equiv) and THF (0.25 M) were added under N_2 atmosphere. Carbonyldiimidazole (2.2 equiv) was then added to the carboxylic acid solution and the mixture was stirred at 45 ºC for 1 h. This solution was then added to the picolinamide mixture containing **S3** via syringe or cannula. The mixture was stirred at 45 ºC and monitored by LCMS. Upon completion (typically 8 h), the reaction was cooled to 23 °C and quenched by the addition of H_2O. Three extractions were performed with ethyl acetate, and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatography to afford the desired product.



N-(2-aminocyclohexyl)-4-chloropicolinamide (S2)

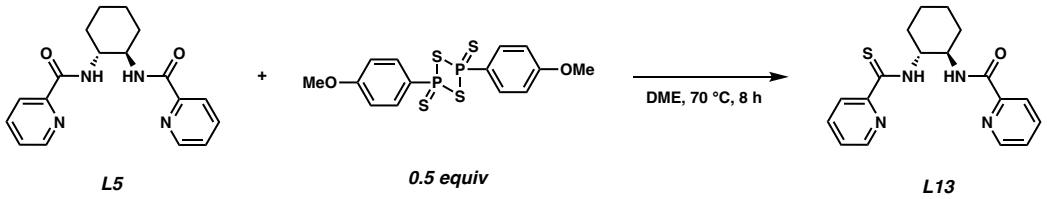
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (dd, *J* = 5.2, 0.6 Hz, 1H), 8.22 (dd, *J* = 2.1, 0.6 Hz, 1H), 7.90 (d, *J* = 9.2 Hz, 1H), 7.43 (dd, *J* = 5.2, 2.1 Hz, 1H), 3.77 – 3.64 (m, 1H), 2.55 (td, *J* = 10.2, 4.0 Hz, 1H), 2.10 – 1.97 (m, 2H), 1.81 – 1.74 (m, 2H), 1.47 – 1.18 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 157.3, 122.4, 53.3, 45.7, 32.4, 24.6, 8.5. IR (thin film, NaCl) 3378, 3044, 2937, 2858, 2597, 2472, 2359, 2232, 1693, 1680, 1555, 1536, 1451, 1414, 1281, 1185, 1104, 996, 909, 837, 806, 730, 682, 645 cm^{-1}. HRMS (MM:ESI+) m/z calc'd for $C_{12}H_{17}N_3OCl$ $[M+H]^+$: 254.1055, found 254.1052.



N-(2-benzamidocyclohexyl)picolinamide) (L6)

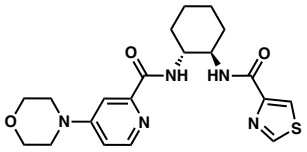
Preparation: In accordance with a literature protocol,[18] a flame-dried flask equipped with a stir bar was subjected to three purge-backfill cycles with N_2. *Trans*-1,2-diaminocyclohexane (1.884 g, 16.5 mmol, 1 equiv) was added via syringe, followed by THF (7.5 mL, 2.2 M). In another flame-dried flask equipped with a stir bar, benzoic acid (2.015 g, 16.5 mmol, 1 equiv) and THF (12 mL, 1.4 M) were added under N_2 atmosphere. Carbonyldiimidazole (2.675 g, 16.5 mmol, 1 equiv) was then added to the carboxylic acid solution and the mixture was stirred at 23 ºC for 1 h. This solution was then transferred dropwise to the diamine solution via syringe pump over 30 minutes. The resulting mixture was stirred at 23 °C for 18 h. In a separate flame-dried flask equipped with a stir bar, 2-picolinic acid (2.031 g, 16.5 mmol, 1 equiv) and THF (12 mL, 1.4 M) were added under N_2 atmosphere. Carbonyldiimidazole (2.675 g, 16.5 mmol, 1 equiv) was then added to the carboxylic acid solution and the mixture was stirred at 23 ºC for 1 h. This solution was then added to the benzamide solution containing **S4** via syringe pump over 1 hour. An additional 8 mL of THF was added to decrease the viscosity of the slurry. The mixture was stirred at 23 °C for 4 hours. Upon completion, dichloromethane (25 mL) and water (38 mL) were added and the two layers were partitioned. The organic layer was concentrated to a solid and then redissolved in CH_2Cl_2 (20 mL). This solution was extracted five times with 3 M aq. HCl (20 mL). The aqueous layer was made alkaline by adding 50% aq. NaOH (20 mL), then was extracted two times with CH_2Cl_2 (38 mL) and concentrated. The resulting solid was purified by silica gel chromatography (20% EtOAc/Hexanes) to afford **L6** as a white solid (746 mg, 2.31 mmol, 14% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (ddd, J = 4.8,

1.8, 1.0 Hz, 1H), 8.16 (d, *J* = 8.6 Hz, 1H), 8.13 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.82 – 7.74 (m, 3H), 7.43 – 7.34 (m, 4H), 7.24 (d, *J* = 7.0 Hz, 1H), 4.06 (tdd, *J* = 12.1, 8.8, 4.0 Hz, 1H), 3.91 (tdd, *J* = 11.1, 7.2, 4.0 Hz, 1H), 2.45 – 2.33 (m, 1H), 2.17 – 2.08 (m, 1H), 1.92 – 1.72 (m, 2H), 1.58 (qd, *J* = 12.5, 3.8 Hz, 1H), 1.48 – 1.41 (m, 2H),1.32 (tdd, *J* = 12.8, 11.3, 3.6 Hz, 1H). Characterization data was in agreement with the literature.[7]



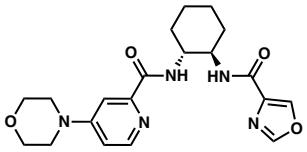
N-(2-(pyridine-2-carbothioamido)cyclohexyl)picolinamide (L13)

Preparation: In a modified procedure,[5] Lawesson's reagent (61 mg, 0.15 mmol, 0.5 equiv) was added to a stirring solution of *rac*-**L5** (100 mg, 0.3 mmol) in DME (2 mL, 0.15 M), and the temperature was elevated to 70 ºC. After 8 h, the reaction was allowed to cool slowly to 23 °C, at which point the crude mixture was plugged through Al_2O_3 with CH_2Cl_2 and EtOAc. The residue was purified by silica gel chromatography (0-100% EtOAc/Hexanes) to deliver the **L13** as a yellow solid (40.2 mg, 0.12 mmol, 39% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (d, *J* = 8.7 Hz, 1H), 8.56 (dt, *J* = 8.0, 1.1 Hz, 1H), 8.48 (dddd, *J* = 6.6, 4.7, 1. 8, 0.9 Hz, 2H), 8.29 – 8.22 (m, 1H), 8.05 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.72 (tdd, *J* = 7.8, 4.4, 1.7 Hz, 2H), 7.33 (ddt, *J* = 7.7, 4.8, 0.9 Hz, 2H), 4.79 – 4.66 (m, 1H), 4.36 – 4.23 (m, 1H), 2.49 – 2.38 (m, 1H), 2.27 – 2.15 (m, 1H), 1.92 – 1.81 (m, 2H), 1.63 – 1.39 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 164.6, 151.1, 149.6, 148.2, 147.0, 137.1, 136.9, 126.1, 125.8, 124.9, 122.1, 59.1, 52.7, 32.6, 30.8, 24.9, 24.5. IR (thin film, NaCl) 3254, 3054, 2929, 2858, 1668, 1516, 1447, 1433, 1348, 1151, 1045, 996, 981, 913, 734, 684 cm^{-1}. HRMS (MM:FD+) m/z calc'd for $C_{18}H_{20}N_4OS[M]^{+\bullet}$: 340.1352, found 340.1346.



_N_-(2-(4-morpholinopicolinamido)cyclohexyl)thiazole-4-carboxamide (L18)

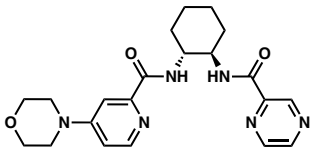
Prepared according to General Procedure B and purified by silica gel chromatography (100% CH_2Cl_2 to 1/10/89 Et_3N/MeOH/CH_2Cl_2) to afford **L18** as a yellow solid (103 mg, 0.25 mmol, 83% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J = 2.2 Hz, 1H), 8.31 – 8.12 (m, 2H), 8.05 (d, J = 2.1 Hz, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.52 (d, J = 2.7 Hz, 1H), 6.66 (dd, J = 5.9, 2.8 Hz, 1H), 4.01 (tdd, J = 11.5, 8.4, 3.5 Hz, 2H), 3.84 – 3.77 (m, 4H), 3.35 – 3.28 (m, 4H), 2.38 – 2.02 (m, 2H), 1.81 (d, J = 7.5 Hz, 2H), 1.55 – 1.32 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 161.1, 156.2, 152.6, 151.4, 150.6, 149.0, 123.0, 109.7, 106.8, 66.5, 54.1, 52.8, 46.3, 32.7, 32.7, 25.0, 24.8. IR (thin film, NaCl) 3353, 2929, 2856, 1654, 1598, 1533, 1485, 1446, 1261, 1121, 992, 912, 885, 731 cm^{-1}. HRMS (MM:FD+) m/z calc'd for $C_{20}H_{25}N_5O_3S$ $[M]^{+\bullet}$: 415.1673, found 415.1657.



_N_-(2-(4-morpholinopicolinamido)cyclohexyl)oxazole-4-carboxamide (L19)

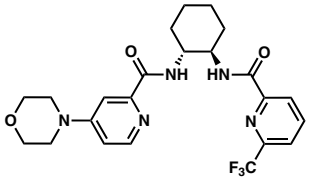
Prepared according to General Procedure B and purified by silica gel chromatography (100% CH_2Cl_2 to 1/10/89 Et_3N/MeOH/CH_2Cl_2) to afford **L19** as a yellow solid (89 mg, 0.23 mmol, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 5.9 Hz, 2H), 8.11 (d, J = 1.0 Hz, 1H), 7.80 (d, J = 1.0 Hz, 1H), 7.55 (d, J = 2.7 Hz, 1H), 7.43 (d, J = 7.9 Hz, 1H), 6.67 (dd, J = 5.9, 2.8 Hz, 1H), 4.08 – 3.87 (m, 2H), 3.86 – 3.74 (m, 4H), 3.33 (dd, J = 5.9, 4.1 Hz, 4H), 2.29 – 2.04 (m, 2H), 1.99 – 1.66 (m, 2H), 1.59 – 1.27 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 160.5, 156.2, 150.6, 150.5, 149.0, 141.2, 136.2, 109.7, 106.8, 66.5, 54.3, 52.6, 46.3, 32.60, 32.57, 25.0, 24.7. IR (thin film, NaCl) 3340, 3131, 2930, 2856, 2239,

1658, 1598, 1517, 1448, 1383, 1319, 1257, 1121, 1100, 1061, 993, 971, 953, 913, 891, 822, 730, 644 cm^{-1}. HRMS (MM:FD+) m/z calc'd for $C_{20}H_{25}N_5O_4$ $[M]^{+\bullet}$: 399.1901, found 399.1886.



***N*-(2-(4-morpholinopicolinamido)cyclohexyl)pyrazine-2-carboxamide (L20)**

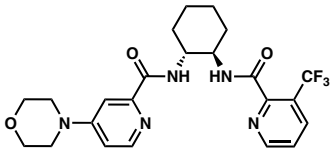
Prepared according to General Procedure B and purified by silica gel chromatography (100% CH_2Cl_2 to 1/10/89 Et_3N/MeOH/CH_2Cl_2) to afford **L20** as a yellow solid (52 mg, 0.13 mmol, 41% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (d, *J* = 1.5 Hz, 1H), 8.63 (d, *J* = 2.5 Hz, 1H), 8.48 (dd, *J* = 2.5, 1.5 Hz, 1H), 8.27 – 8.00 (m, 3H), 7.45 (d, *J* = 2.7 Hz, 1H), 6.63 (dd, *J* = 5.9, 2.8 Hz, 1H), 4.14 – 3.88 (m, 2H), 3.86 – 3.73 (m, 4H), 3.32 – 3.20 (m, 4H), 2.37 – 2.09 (m, 2H), 1.80 (s, 2H), 1.59 – 1.33 (m, 4H).^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 163.1, 156.0, 150.3, 148.9, 146.9, 144.6, 144.3, 142.7, 109.6, 106.5, 66.3, 54.1, 52.6, 46.1, 32.54, 28.7, 24.9, 24.7. IR (thin film, NaCl) 3333, 3053, 2931, 2855, 2352, 1666, 1599, 1519, 1448, 1400, 1383, 1321, 1265, 1256, 1155, 1122, 1068, 1048, 1019, 993, 971, 928, 891, 869, 783, 753, 732 cm^{-1}. HRMS (MM:ESI+) m/z calc'd for $C_{21}H_{27}N_6O_3$ $[M+H]^+$: 411.2139, found 411.2138.



4-morpholino-*N*-(2-(6-(trifluoromethyl)picolinamido)cyclohexyl)picolinamide (L21)

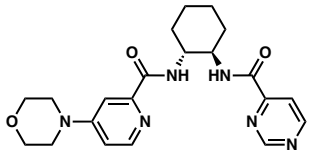
Prepared according to General Procedure B and purified by silica gel chromatography (100% EtOAc) to afford **L21** as a yellow solid (61 mg, 0.13 mmol, 64% yield). ^{1}H NMR (400

MHz, $CDCl_3$) δ 8.40 (d, *J* = 7.8 Hz, 1H), 8.28 (d, *J* = 7.8 Hz, 1H), 8.16 (dd, *J* = 10.1, 7.2 Hz, 2H), 7.95 (t, *J* = 7.8 Hz, 1H), 7.73 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.57 (d, *J* = 2.7 Hz, 1H), 6.64 (dd, *J* = 5.9, 2.8 Hz, 1H), 4.19 – 4.04 (m, 1H), 4.05 – 3.84 (m, 1H), 3.87 – 3.73 (m, 4H), 3.40 – 3.23 (m, 4H), 2.37 – 2.09 (m, 2H) , 1.92 – 1.73 (m, 2H), 1.59 – 1.36 (m, 4H).^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 163.3, 156.1, 150.6, 150.5, 148.9, 146.9 (q, *J* = 35.4 Hz), 138.9, 125.0, 122.6, 122.5, 109.6, 106.9, 66.5, 55.0, 52.6, 46.2, 32.6, 32.4, 25.1, 24.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -67.5. IR (thin film, NaCl) 3332, 2933, 2856, 1673, 1599, 1523, 1449, 1343, 1257, 1191, 1141, 1112, 1079, 993, 909, 730 cm^{-1}. HRMS (MM:FD+) m/z calc'd for $C_{23}H_{26}F_3N_5O_3$ $[M]^{+\bullet}$: 477.1982, found 477.1957.



4-morpholino-*N*-(2-(3-(trifluoromethyl)picolinamido)cyclohexyl)picolinamide (L22)

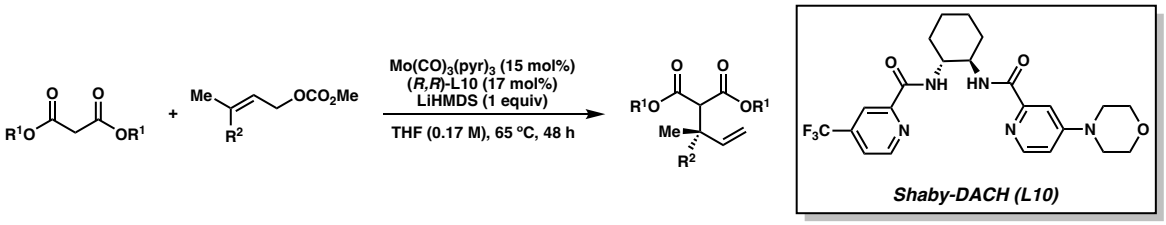
Prepared according to General Procedure B and purified by silica gel chromatography (100% EtOAc) to afford **L22** as a yellow solid (132 mg, 0.28 mmol, 55% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.26 (d, *J* = 7.9 Hz, 1H), 8.20 (d, *J* = 5.8 Hz, 1H), 8.04 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.92 (d, *J* = 7.1 Hz, 1H), 7.46 (dd, *J* = 8.2, 4.0 Hz, 2H), 6.67 (dd, *J* = 5.9, 2.7 Hz, 1H), 4.09 – 3.91 (m, 2H), 3.87 – 3.73 (m, 4H), 3.36 – 3.25 (m, 4H), 2.36 – 2.08 (m, 2H), 1.91 – 1.72 (m, 2H), 1.55 – 1.35 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 163.7, 156.2, 150.6 (q, *J* = 30.0 Hz), 149.8, 149.0, 136.0, 135.9, 125.8 (q, *J* = 34.3 Hz), 125.0, 121.6, 109.8, 106.6, 66.5, 54.5, 52.8, 46.3, 32.8, 32.4, 25.0, 24.8 ^{19}F NMR (376 MHz, $CDCl_3$) δ -59.4. IR (thin film, NaCl) 3302, 2933, 2857, 2245, 1663, 1599, 1517, 1444, 1373, 1314, 1258, 1156, 1120, 1032, 992, 912, 894, 819, 730, 637 cm^{-1}. HRMS (MM:FD+) m/z calc'd for $C_{23}H_{26}F_3N_5O_3$ $[M]^{+\bullet}$: 477.1982, found 477.1960.



***N*-(2-(4-morpholinopicolinamido)cyclohexyl)pyrimidine-4-carboxamide (L23)**

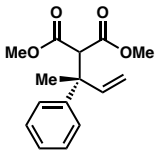
Prepared according to General Procedure B and purified by silica gel chromatography (100% CH_2Cl_2 to 1/10/89 Et_3N/MeOH/CH_2Cl_2) to afford **L23** as a yellow solid (142 mg, 0.35 mmol, 60% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (t, *J* = 1.4 Hz, 1H), 8.87 (dd, *J* = 5.0, 1.4 Hz, 1H), 8.34 (d, *J* = 8.3 Hz, 1H), 8.21 – 8.12 (m, 2H), 8.00 (dt, *J* = 5.1, 1.4 Hz, 1H), 7.50 (dd, *J* = 2.8, 1.3 Hz, 1H), 6.66 (ddd, *J* = 5.9, 2.8, 1.2 Hz, 1H), 4.15 – 3.90 (m, 2H), 3.86 – 3.76 (m, 4H), 3.35 – 3.25 (m, 4H), 2.34 – 2.07 (m, 2H), 1.84 (s, 2H), 1.56 – 1.34 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 162.8, 158.9, 157.8, 156.4, 156.0, 150.3, 148.8, 118.5, 109.6, 106.6, 66.3, 54.5, 52.4, 46.1, 32.5, 32.3, 24.9, 24.6. IR (thin film, NaCl) 3348, 2934, 2856, 2245, 1667, 1599, 1523, 1449, 1385, 1267, 1256, 1146, 1122, 1068, 993, 912, 734 cm^{-1}. HRMS (MM:FD+) m/z calc'd for $C_{21}H_{26}N_6O_3$ $[M]^{+\bullet}$: 410.2061, found 410.2041.

Mo-catalyzed Allylic Alkylation: General Procedure C (0.1 mmol scale)



In a nitrogen-filled glovebox, a catalyst solution of $Mo(CO)_3(pyr)_3$ (6.3 mg, 0.015 mmol, 0.15 equiv) and *(R,R)*-ShabyDACH (8.0 mg , 0.017 mmol, 0.17 equiv) in THF (0.2 mL) was stirred for 20 min at 40 °C. In a separate vial, a stock solution of malonate nucleophile (0.5 mmol/mL) in THF was prepared and subsequently LiHMDS (0.5 mmol/mL) was added. In a separate vial, a stock solution of the (*E*)-allylic carbonate (0.5 mmol/mL) in THF was prepared. After the catalyst pre-stir was complete, the malonate stock solution

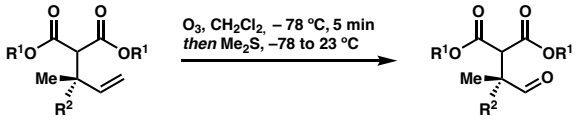
(0.23 mL, 0.1 mmol, 1 equiv) was added to the catalyst solution, followed by the allylic carbonate stock solution (0.22 mL, 0.1 mmol, 1 equiv). The reaction vessel was sealed with a Teflon-lined cap, removed from the glovebox, and stirred at 65 °C in a metal heating block for 48 h, unless noted otherwise. After 48 h, 0.5 M aq. HCl (1 mL) was added to the crude reaction mixture, which was then extracted three times with ethyl acetate, dried over Na_2SO_4, filtered, and concentrated. The residue was then run through a plug of silica gel (50% EtOAc/Hexanes) to remove polar impurities.



Dimethyl (*S*)-2-(2-phenylbut-3-en-2-yl)malonate (ent–3b)

Prepared according to General Procedure C and purified by three preparative TLC elutions (10% EtOAc/Hexanes) affording a colorless oil (11.0 mg, 0.042 mmol, 42% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 4H), 7.20 (ddt, J = 7.1, 5.8, 2.1 Hz, 1H), 6.58 (dd, J = 17.5, 10.9 Hz, 1H), 5.26 (dd, J = 10.9, 1.0 Hz, 1H), 5.11 (dd, J = 17.5, 1.0 Hz, 1H), 4.07 (s, 1H), 3.58 (d, J = 1.4 Hz, 6H), 1.66 (s, 3H). $[\alpha]_D^{23}$ +5.58 (*c* 0.5, $CHCl_3$). Characterization data was in agreement with the literature.[8]

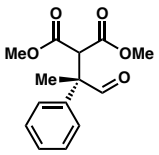
Ozonolysis: General Procedure D (0.1 mmol scale)



crude mixture

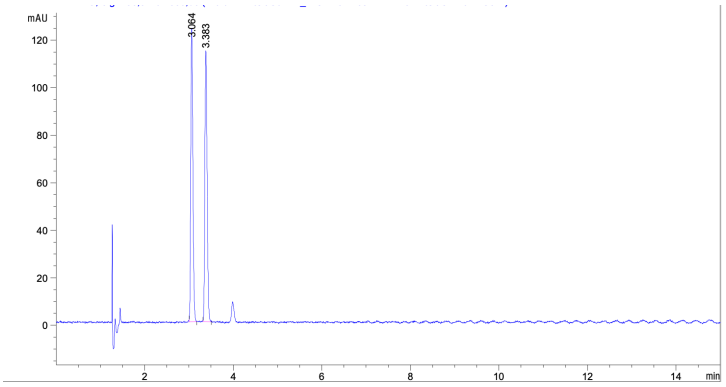
The crude mixture isolated following General Procedure C was dissolved in CH_2Cl_2 (20 mL, 0.05 M), and a pipette tip of Sudan III was added. The flask was cooled to –78 ºC and O_2 gas was bubbled through the solution using a gas diffuser. After 5 min of vigorous O_2 flow, a VMUS-4 Ozone Generator was turned to the lowest ozone output setting. After 3–

4 minutes, the color of the solution was observed to change from a vibrant red to a pale orange/brown color, and the ozonator was turned off. O_2 was bubbled through the solution for an additional 5 minutes, then the diffuser was removed. A stir bar was added to the flask, and a septum with an Ar balloon was affixed to the flask. The reaction was quenched with Me_2S (80 equiv, 0.4 mL), and the mixture was allowed to stir at –78 ºC for 1 h, then stirred at 23 °C for an additional 2 h. The solvent and Me_2S were then removed by rotatory evaporation. The residue was purified by preparatory TLC (20% EtOAc/Hexanes) to afford the desired α-quaternary aldehyde.

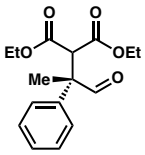


Dimethyl (*S*)-2-(1-oxo-2-phenylpropan-2-yl)malonate (55)

Prepared according to General Procedures C and D and isolated as a yellow oil (13.0 mg, 0.050 mmol, 50% yield over 2 steps, >99% ee). At 2 mmol scale, General Procedures C and D were scaled accordingly, and silica gel chromatography (20% EtOAc/Hexanes) delivered **6** (241 mg, 0.94 mmol, 47% overall yield, >99% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 7.40 – 7.27 (m, 5H), 4.37 (s, 1H), 3.72 (s, 3H), 3.48 (s, 3H), 1.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 168.02, 167.96, 136.4, 129.1, 128.2, 127.5, 56.9, 54.7, 52.8, 52.4, 15.9. IR (thin film, NaCl) 3451, 3059, 3002, 2953, 2847, 2712, 2361, 1738, 1731, 1599, 1495, 1434, 1376, 1326, 1236, 1202, 1155, 1078, 1025, 913, 850, 763, 736, 700, 678, 642 cm^{-1}. HRMS (MM:FD+) m/z calc'd for $C_{14}H_{17}O_5$ $[M+H]^+$: 265.1071, found 294.1062. $[\alpha]_D^{23}$ +154.06 (*c* 1.0, $CHCl_3$). SFC Conditions: 5% IPA, 2.5 mL/min, Chiralcel OD-3 column, λ = 230.8 nm, t_R (min): major = 3.01, minor = 3.38.



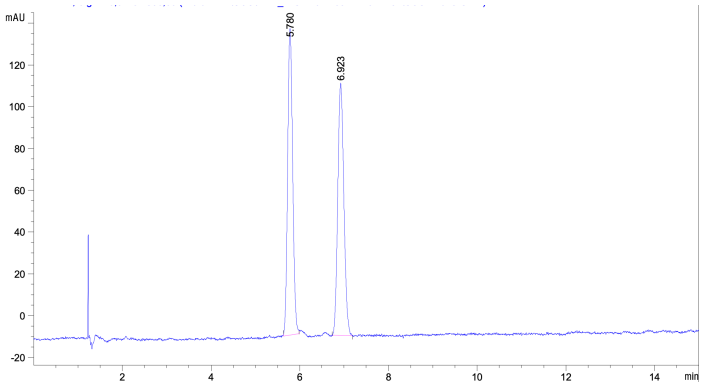
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.005	BB	0.0520	765.79242	229.09042	100.0000



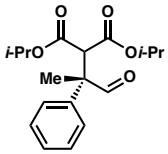
Diethyl (*S*)-2-(1-oxo-2-phenylpropan-2-yl)malonate (ent–19)

Prepared according to General Procedures C and D and isolated as a clear oil (9.9 mg, 0.034 mmol, 34% yield over 2 steps, >99% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (s, 1H), 7.39 – 7.27 (m, 5H), 4.35 (s, 1H), 4.18 (qd, J = 7.1, 1.7 Hz, 2H), 3.95 (q, J = 7.1 Hz, 2H), 1.87 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H), 0.98 (t, J = 7.1 Hz, 3H). $[\alpha]_D^{23}$ +115.94 (*c* 1.0, $CHCl_3$). SFC Conditions: 5% IPA, 2.5 mL/min, Chiralcel IC-3 column, λ = 210.8 nm, t_R

(min): major = 5.71, minor = 6.92. Characterization data was in agreement with the literature.[8]



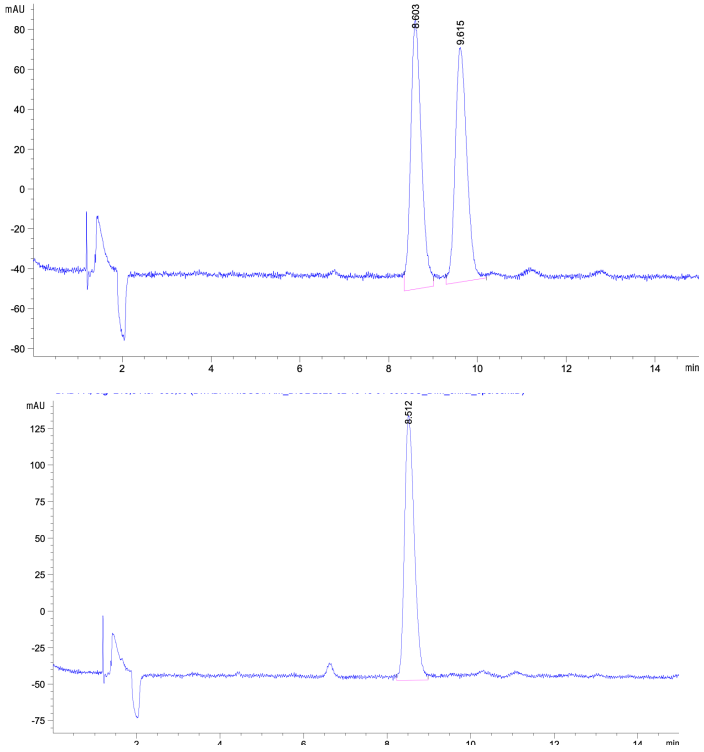
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.713	BB	0.1257	1359.34192	173.02917	100.0000



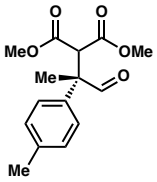
Diisopropyl (*S*)-2-(1-oxo-2-phenylpropan-2-yl)malonate (56)

Prepared according to General Procedures C and D and isolated as a clear oil (11.0 mg, 0.034 mmol, 34% yield over 2 steps, >99% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.38 – 7.27 (m, 5H), 5.03 (sept, J = 6.3 Hz, 1H), 4.82 (sept, J = 6.3 Hz, 1H), 4.31 (s, 1H),

1.85 (s, 3H), 1.22 (dd, J = 12.3, 6.3 Hz, 6H), 1.01 (dd, J = 55.8, 6.3 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 167.5, 167.3, 137.2, 129.3, 128.3, 127.9, 69.9, 69.3, 58.0, 54.8, 22.02, 21.97, 21.8, 21.7, 16.5. IR (thin film, NaCl) 2981, 2935, 1726, 1493, 1466, 1374, 1354, 1313, 1279, 1236, 1181, 1101, 1011, 903, 762, 698, 676 cm^{-1}. HRMS (MM:FD+) m/z calc'd for $C_{18}H_{25}O_5$ $[M+H]^+$: 321.1697, found 321.1698. $[\alpha]_D^{23}$ +42.44 (*c* 1.0, $CHCl_3$). SFC Conditions: 3% IPA, 2.5 mL/min, Chiralcel IC-3 column, λ = 210.8 nm, t_R (min): major = 8.51, minor = 9.62.

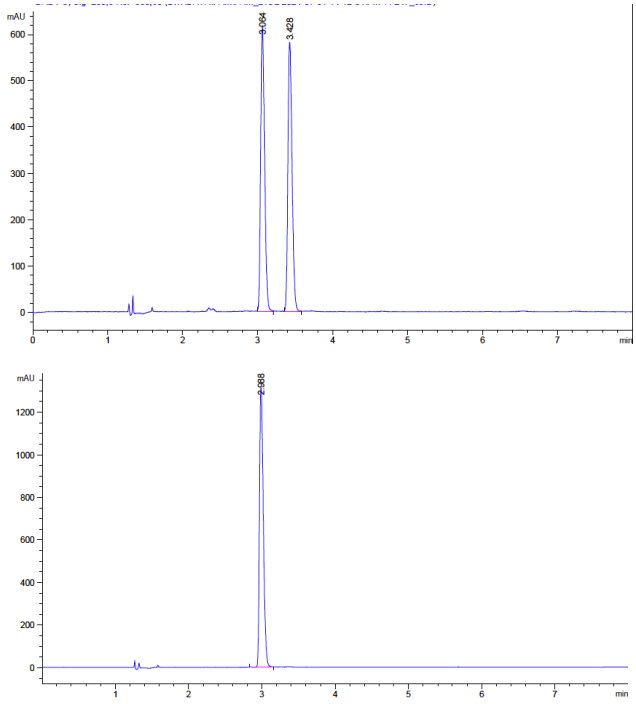


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.512	VB	0.1992	2949.94751	180.90695	100.0000

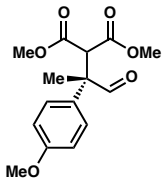


Dimethyl (*S*)-2-(1-oxo-2-(*p*-tolyl)propan-2-yl)malonate (58)

Prepared according to General Procedures C and D and isolated as a yellow oil (13.6 mg, 0.049 mmol, 49% yield over 2 steps, >99% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (s, 1H), 7.16 (s, 4H), 4.35 (s, 1H), 3.72 (s, 3H), 3.50 (s, 3H), 2.32 (s, 3H), 1.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 168.1, 168.0, 138.0, 133.3, 129.8, 127.4, 56.8, 54.4, 52.7, 52.4, 21.1, 15.9. IR (thin film, NaCl) 2924, 1738, 1434, 1320, 1239, 1038, 813 cm^{-1}. HRMS (MM:FI+) m/z calc'd for $C_{15}H_{18}O_5$ $[M]^{+\bullet}$: 278.1149, found 278.1141. $[\alpha]_D^{23}$ +149.00 (*c* 1.0, $CHCl_3$). SFC Conditions: 5% IPA, 2.5 mL/min, Chiralcel OD-3 column, λ = 230.8 nm, t_R (min): major = 2.99, minor = 3.43.

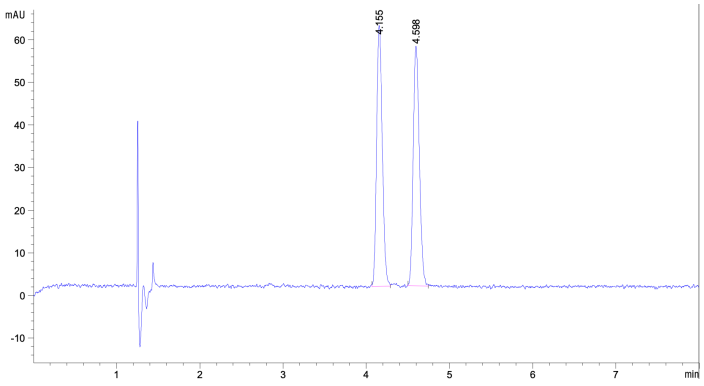


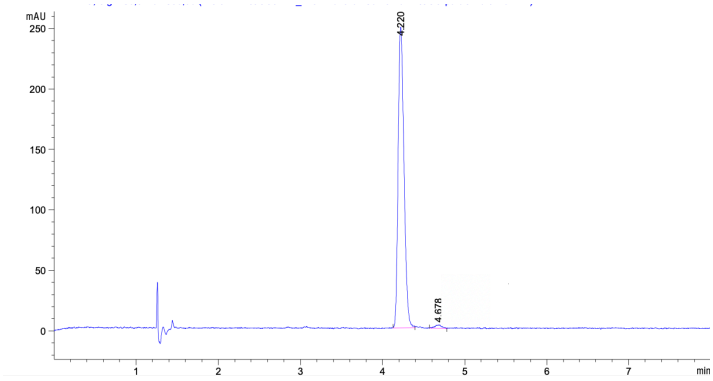
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.988	BB	0.0576	4802.27246	1313.69421	100.0000



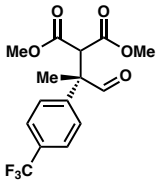
Dimethyl (*S*)-2-(2-(4-methoxyphenyl)-1-oxopropan-2-yl)malonate (59)

Prepared according to General Procedures C and D and isolated as a yellow oil (14.5 mg, 50% yield over 2 steps, 97% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1H), 7.22 – 7.17 (m, 2H), 6.91 – 6.86 (m, 2H), 4.34 (s, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 3.49 (s, 3H), 1.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 168.10, 168.07, 159.4, 128.8, 127.9, 114.5, 56.8, 55.4, 54.0, 52.8, 52.5, 15.8. IR (thin film, NaCl) 3441, 2955, 2844, 2722, 1735, 1606, 1450, 1255, 1078, 1033, 908, 833, 681 cm^{-1}. HRMS (MM:FD+) m/z calc'd for $C_{15}H_{18}O_6$ $[M]^{+\bullet}$: 294.1098, found 294.1092. $[\alpha]_D^{23}$ +150.80 (*c* 1.0, $CHCl_3$). SFC Conditions: 5% IPA, 2.5 mL/min, Chiralcel OD-3 column, λ = 230.8 nm, t_R (min): major = 4.22, minor = 4.68.



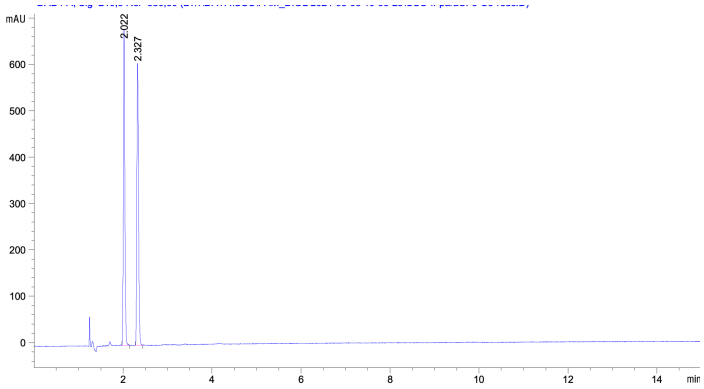


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.220	BB	0.0786	1226.80847	248.66557	98.6100
2	4.678	MM	0.0990	17.29294	2.91058	1.3900

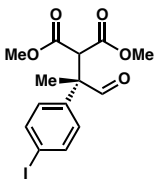


Dimethyl (*S*)-2-(1-oxo-2-(4-(trifluoromethyl)phenyl)propan-2-yl)malonate (60)

Prepared according to General Procedures C and D and isolated as a yellow oil (10.5 mg, 0.032 mmol, 32% yield over 2 steps, 99% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.67 – 7.60 (m, 2H), 7.46 – 7.40 (m, 2H), 4.37 (s, 1H), 3.73 (s, 3H), 3.52 (s, 3H), 1.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 167.4, 167.3, 140.6, 130.3, 129.9, 127.7, 125.6 (q, J = 3.7 Hz), 56.7, 54.3, 52.7, 52.3, 16.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.7. IR (thin film, NaCl) 2955, 2848, 1734, 1617, 1436, 1412, 1327, 1240, 1169, 1125, 1082, 1066, 1015, 913, 836, 709 cm^{-1}. HRMS (MM:FD+) m/z calc'd for $C_{15}H_{16}O_5F_3$ $[M+H]^+$: 333.0944, found 333.0934. $[\alpha]_D^{23}$ +74.03 (*c* 1.0, $CHCl_3$). SFC Conditions: 5% IPA, 2.5 mL/min, Chiralcel OD-3 column, λ = 210.8 nm, t_R (min): major = 2.05, minor = 2.34.



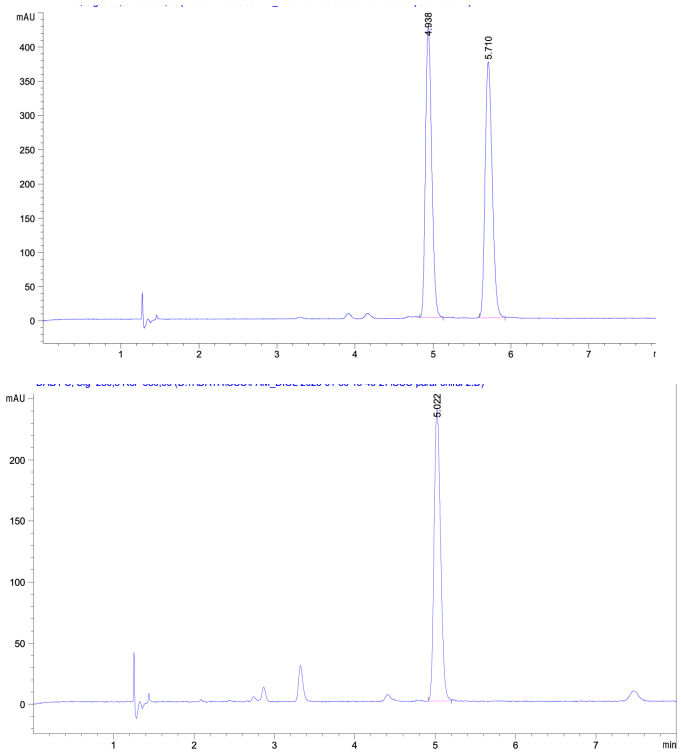
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.049	BB	0.0392	4283.13086	1713.86987	99.4647
2	2.336	BB	0.0593	23.05232	5.14272	0.5353



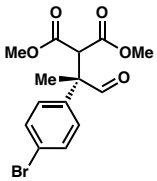
Dimethyl (*S*)-2-(2-(4-iodophenyl)-1-oxopropan-2-yl)malonate (62)

Prepared according to General Procedures C and D and isolated as a yellow oil (15.5 mg, 0.040 mmol, 40% yield over 2 steps, >99% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.72 – 7.66 (m, 2H), 7.06 – 7.00 (m, 2H), 4.32 (s, 1H), 3.72 (s, 3H), 3.53 (s, 3H), 1.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 167.8, 167.7, 138.2, 136.4, 129.4, 94.3, 56.8, 54.4, 52.9, 52.6, 16.1. IR (thin film, NaCl) 3453, 2952, 2845, 1738, 1731, 1582, 1488, 1434,

1395, 1328, 1237, 1203, 1155, 1079, 1027, 1004, 914, 850, 816, 765, 700, 679 cm^{-1}. HRMS (MM:FI+) m/z calc'd for $C_{14}H_{15}O_5I$ $[M]^{+\bullet}$: 389.9959, found 389.9972. $[\alpha]_D^{23}$ +81.59 (*c* 1.0, $CHCl_3$). SFC Conditions: 5% IPA, 2.5 mL/min, Chiralcel OD-3 column, λ = 230.8 nm, t_R (min): major = 5.02, minor = 5.71.

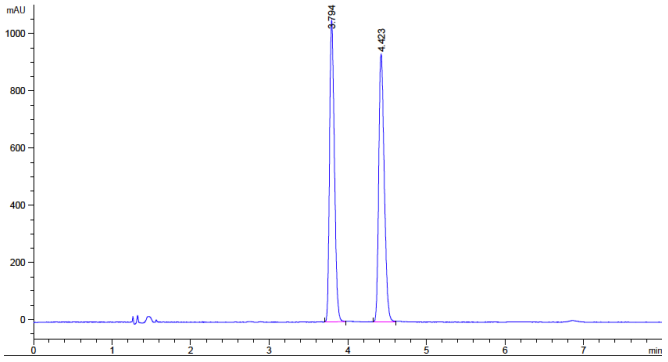


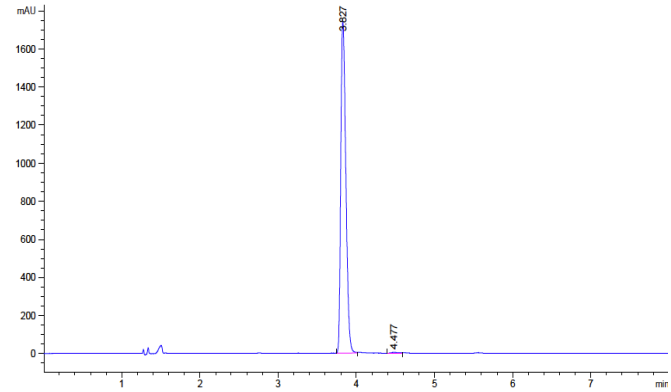
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.022	BB	0.0887	1346.37964	239.04323	100.0000



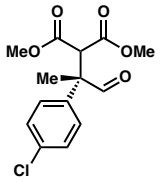
Dimethyl (*S*)-2-(2-(4-bromophenyl)-1-oxopropan-2-yl)malonate (63)

Prepared according to General Procedures C and D and isolated as a colorless oil (17.4 mg, 0.051 mmol, 51% yield over 2 steps, 99% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.52 – 7.46 (m, 2H), 7.20 – 7.13 (m, 2H), 4.32 (s, 1H), 3.72 (s, 3H), 3.52 (s, 3H), 1.84 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 167.81, 167.75 135.7, 132.2, 129.3, 122.6, 56.8, 54.3, 52.9, 52.6, 16.2. IR (thin film, NaCl) 2956, 2925, 2360, 1731, 1491, 1435, 1329, 1243, 1157, 1082, 1024, 1008, 910, 820 cm^{-1}. HRMS (MM:FD+) m/z calc'd for $C_{14}H_{16}O_5Br$ $[M+H]^+$: 343.0176, found 343.0167. $[\alpha]_D^{23}$ +115.94 (*c* 1.0, $CHCl_3$). SFC Conditions: 5% IPA, 2.5 mL/min, Chiralcel OD-3 column, λ = 230.8 nm, t_R (min): major = 3.83, minor = 4.48.



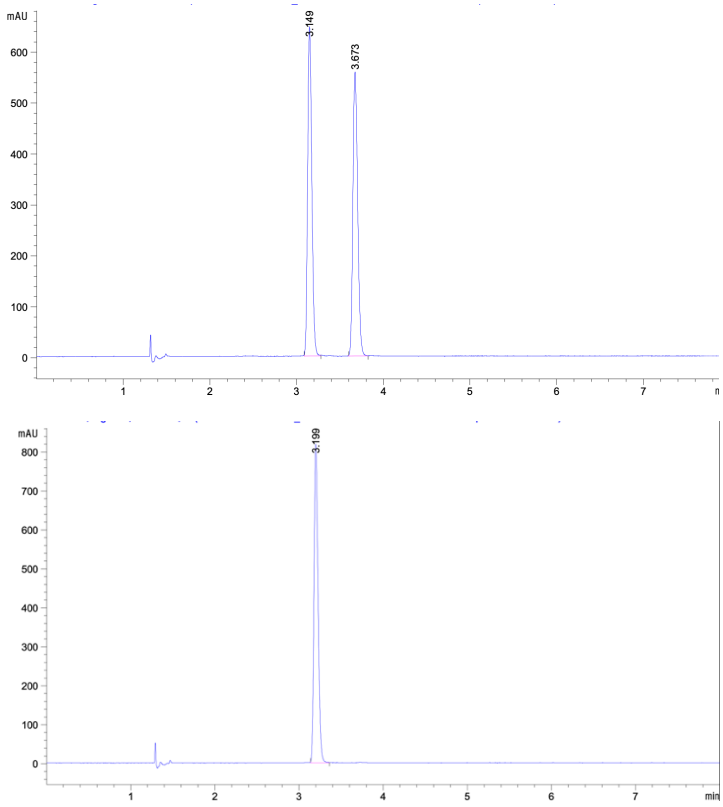


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.827	BB	0.0704	7811.93848	1738.01929	99.6089
2	4.477	BB	0.0794	30.67265	4.81220	0.3911

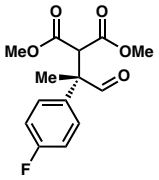


Dimethyl (*S*)-2-(2-(4-chlorophenyl)-1-oxopropan-2-yl)malonate (64)

Prepared according to General Procedures C and D and isolated as a yellow oil (16.0 mg, 0.053 mmol, 53% overall yield, >99% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.37 – 7.31 (m, 2H), 7.25 – 7.20 (m, 2H), 4.33 (s, 1H), 3.72 (s, 3H), 3.52 (s, 3H), 1.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7, 167.83, 167.78, 135.1, 134.4, 129.2, 129.0, 56.9, 54.2, 52.9, 52.6, 16.2. IR (thin film, NaCl) 2952, 2850, 1731, 1493, 1434, 1403, 1310, 1239, 1154, 1097, 1012, 912, 825, 711 cm^{-1}. HRMS (MM:FI+) m/z calc'd for $C_{14}H_{15}O_5Cl$ $[M]^{+\bullet}$: 298.0603, found 298.0606. $[\alpha]_D^{23}$ +137.23 (*c* 1.0, $CHCl_3$). SFC Conditions: 5% IPA, 2.5 mL/min, Chiralcel OD-3 column, λ = 230.8 nm, t_R (min): major = 3.20, minor = 3.67.

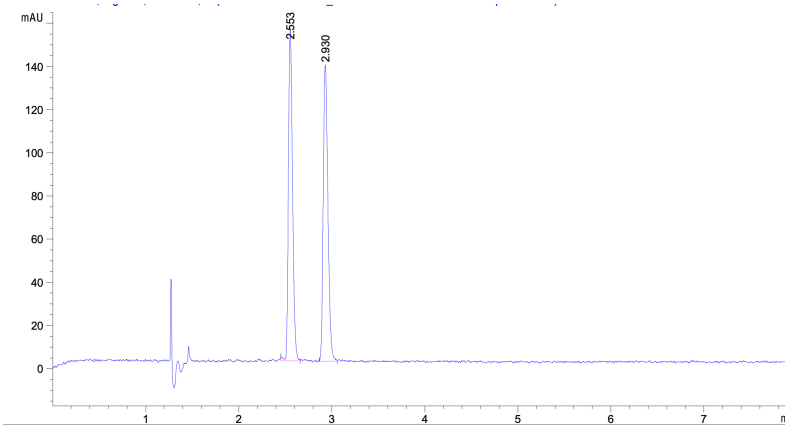


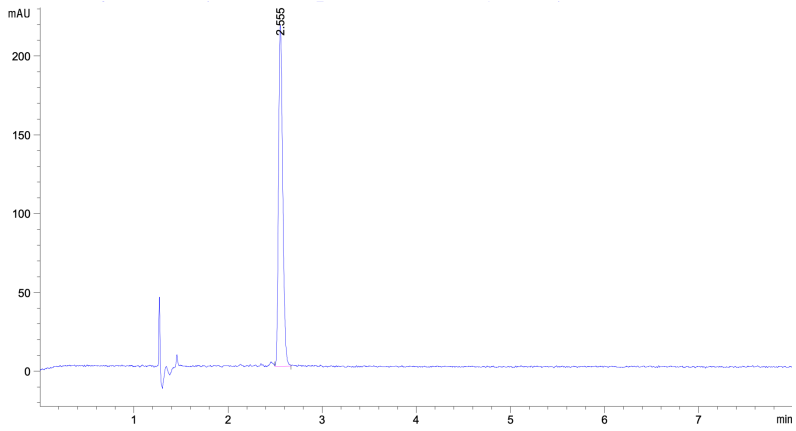
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.199	BB	0.0535	2765.67383	816.97144	100.0000



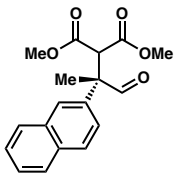
Dimethyl (*S*)-2-(2-(4-fluorophenyl)-1-oxopropan-2-yl)malonate (65)

Prepared according to General Procedures C and D and isolated as a yellow oil (11.0 mg, 0.039 mmol, 39% yield over 2 steps, >99% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.30 – 7.24 (m, 2H), 7.09 – 7.02 (m, 2H), 4.33 (s, 1H), 3.72 (s, 3H), 3.50 (s, 3H), 1.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 168.2, 164.0, 161.6, 132.5 (d, J = 3.5 Hz), 129.7 (d, J = 8.2 Hz), 116.4 (d, J = 21.6 Hz), 57.3, 54.4, 53.2, 52.8, 16.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.7 (tt, J = 8.2, 5.1 Hz). IR (thin film, NaCl) 3450, 2955, 2848, 1738, 1731, 1602, 1512, 1434, 1372, 1331, 1282, 1240, 1198, 1169, 1075, 1029, 909, 835 cm^{-1}. HRMS (MM:FI+) m/z calc'd for $C_{14}H_{16}O_5F$ $[M+H]^+$: 283.0976, found 283.0982. $[\alpha]_D^{23}$ +97.74 (*c* 1.0, $CHCl_3$). SFC Conditions: 5% IPA, 2.5 mL/min, Chiralcel OD-3 column, λ = 230.8 nm, t_R (min): major = 2.56, minor = 2.93.



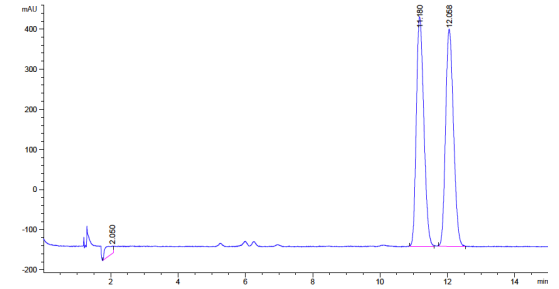


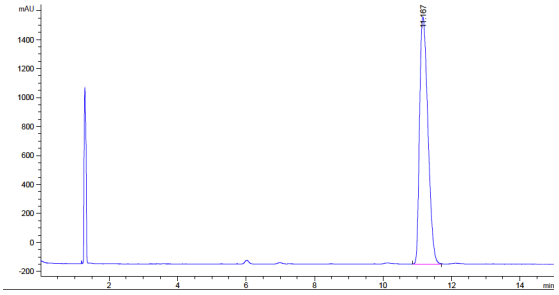
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.555	VB	0.0482	670.94562	216.15450	100.0000



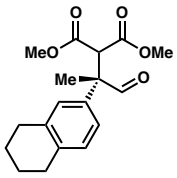
Dimethyl (*S*)-2-(2-(naphthalen-2-yl)but-3-en-2-yl)malonate (66)

Prepared according to General Procedures C and D and isolated as a clear oil (13.4 mg, 0.043 mmol, 43% yield over 2 steps, >99% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.88 – 7.77 (m, 3H), 7.75 (d, *J* = 2.1 Hz, 1H), 7.50 (dt, *J* = 6.3, 3.5 Hz, 2H), 7.40 (dd, *J* = 8.7, 2.1 Hz, 1H), 4.51 (s, 1H), 3.74 (s, 3H), 3.43 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 168.1, 168.0, 133.8, 133.4, 132.7, 128.8, 128.4, 127.6, 127.2, 126.9, 126.6, 124.6, 56.8, 54.8, 52.8, 52.5, 16.1. IR (thin film, NaCl) 2955, 2848, 1731, 1434, 1322, 1234, 1018, 911, 818, 751 cm^{-1}. HRMS (MM:FI+) m/z calc'd for $C_{18}H_{18}O_5$ $[M]^{+\bullet}$: 314.1149, found 314.1164. $[\alpha]_D^{23}$ +172.90 (*c* 1.0, $CHCl_3$). SFC Conditions: 5% IPA, 2.5 mL/min, Chiralcel IC-3 column, λ = 230.8 nm, t_R (min): major = 11.17, minor = 12.06.



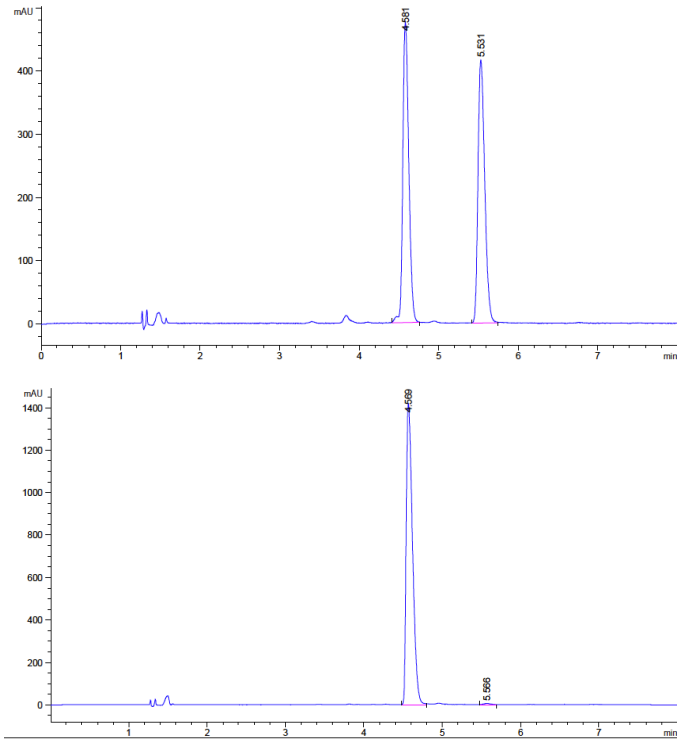


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.167	BB	0.2640	2.87614e4	1703.43530	100.0000

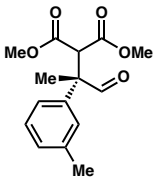


Dimethyl (*S*)-2-(2-(5,6,7,8-tetrahydronaphthalen-2-yl)but-3-en-2-yl)malonate (67)

Prepared according to General Procedures C and D and isolated as a clear oil (16.8 mg, 0.053 mmol, 53% yield over 2 steps, 99% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (s, 1H), 7.04 (d, *J* = 8.1 Hz, 1H), 6.97 (dd, *J* = 8.1, 2.2 Hz, 1H), 6.93 (d, *J* = 2.2 Hz, 1H), 4.34 (s, 1H), 3.73 (s, 3H), 3.53 (s, 3H), 2.77 – 2.68 (m, 4H), 1.82 (s, 3H), 1.77 (dq, *J* = 6.6, 3.2 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 168.2, 168.0, 137.9, 137.3, 133.2, 129.8, 128.1, 124.3, 56.7, 54.5, 52.7, 52.4, 29.6, 29.0, 23.2, 23.1, 15.9. IR (thin film, NaCl) 2924, 1737, 1433, 1322, 1238, 1026 cm^{-1}. HRMS (MM:FI+) m/z calc'd for $C_{18}H_{22}O_5$ $[M]^{+\bullet}$: 318.1462, found 318.1453. $[\alpha]_D^{23}$ +118.45 (*c* 1.0, $CHCl_3$). SFC Conditions: 5% IPA, 2.5 mL/min, Chiralcel OD-3 column, λ = 230.8 nm, t_R (min): major = 4.57, minor = 5.57.



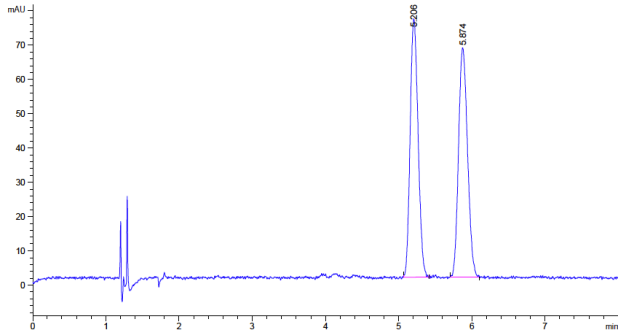
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.569	BB	0.0872	7916.20752	1415.96130	99.5956
2	5.566	BB	0.0747	32.14148	5.62010	0.4044



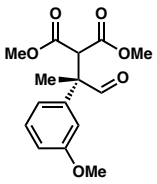
Dimethyl (*S*)-2-(2-(*m*-tolyl)but-3-en-2-yl)malonate (68)

Prepared according to General Procedures C and D and isolated as a yellow oil (13.7 mg, 0.050 mmol, 50% yield over 2 steps, >99% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.30–7.21 (m, 1H), 7.14 – 7.03 (m, 3H), 4.36 (s, 1H), 3.73 (s, 3H), 3.50 (s, 3H), 2.34 (s, 3H), 1.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 168.1, 168.0, 138.8, 136.4, 128.9,

128.1, 124.4, 56.8, 54.6, 52.8, 52.4, 21.7, 15.9. IR (thin film, NaCl) 2925, 2332, 1737, 1443, 1316, 1226, 1152, 1026 cm^{-1}. HRMS (MM:FI+) m/z calc'd for $C_{15}H_{18}O_5$ $[M]^{+\bullet}$: 278.1149, found 278.1138. $[\alpha]_D^{23}$ +133.04 (*c* 1.0, $CHCl_3$). SFC Conditions: 5% IPA, 2.5 mL/min, Chiralcel IC-3 column, λ = 230.8 nm, t_R (min): major = 4.80, minor = 5.88.

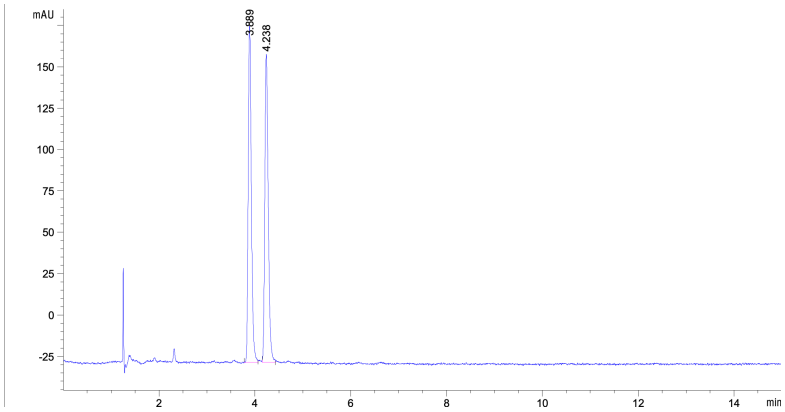


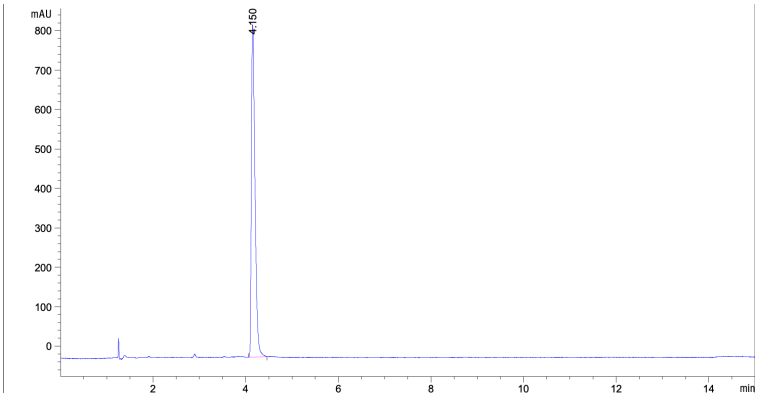
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.799	BB	0.1081	2507.02368	360.73822	100.0000



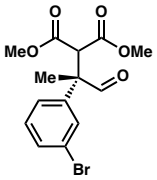
Dimethyl (*S*)-2-(2-(3-methoxyphenyl)-1-oxopropan-2-yl)malonate (69)

Prepared according to General Procedures C and D and isolated as a yellow oil (10.0 mg, 0.034 mmol, 34% yield over 2 steps, >99% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.31 – 7.27 (m, 1H), 6.88 – 6.79 (m, 3H), 4.36 (s, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 3.51 (s, 3H), 1.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 167.9, 167.8, 160.0, 138.0, 129.9, 119.6, 113.6, 113.1, 56.7, 55.3, 54.5, 52.7, 52.4, 15.9. IR (thin film, NaCl) 2951, 2916, 2847, 1734, 1599, 1582, 1490, 1432, 1292, 1230, 1030, 891, 785, 698 cm^{-1}. HRMS (MM:FD+) m/z calc'd for $C_{15}H_{18}O_6$ $[M]^{+\bullet}$: 294.1098, found 294.1091. $[\alpha]_D^{23}$ +120.12 (*c* 1.0, $CHCl_3$). SFC Conditions: 5% IPA, 2.5 mL/min, Chiralcel ID-3 column, λ = 210.8 nm, t_R (min): major = 4.15, minor = 3.89.



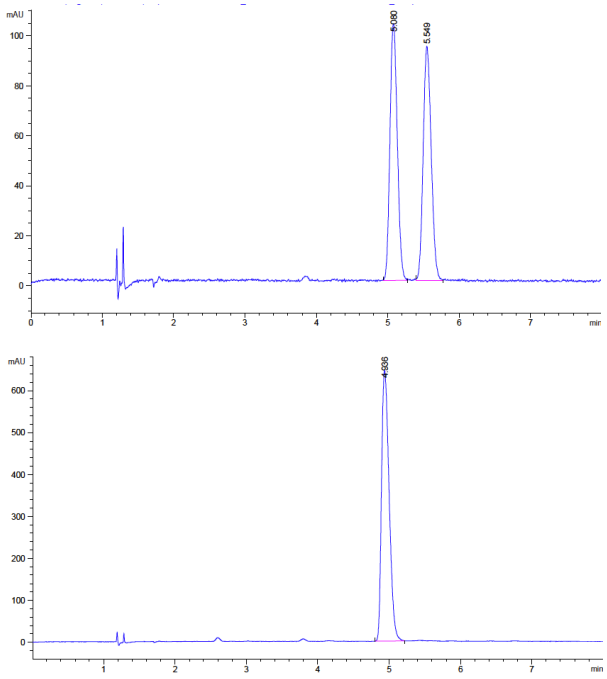


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.150	BB	0.0828	4530.87939	842.01764	100.0000

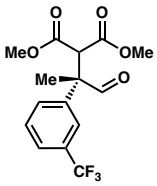


Dimethyl (*S*)-2-(2-(3-bromophenyl)but-3-en-2-yl)malonate (70)

Prepared according to General Procedures C and D and isolated as a yellow oil (12.9 mg, 0.038 mmol, 38% yield over 2 steps, >99% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 7.44 (dd, *J* = 6.1, 1.7 Hz, 2H), 7.29 – 7.18 (m, 2H), 4.32 (s, 1H), 3.72 (s, 3H), 3.53 (s, 3H), 1.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 167.8, 167.7, 139.1, 131.4, 130.7, 130.5, 126.2, 123.3, 56.9, 54.4, 52.9, 52.6, 16.2. IR (thin film, NaCl) 3444, 2955, 2926, 2916, 2848, 1731, 1568, 1436, 1236, 1026, 908, 789 cm^{-1}. HRMS (MM:FD+) m/z calc'd for $C_{14}H_{16}O_5Br$ $[M+H]^+$: 343.0176, found 343.0191. $[\alpha]_D^{23}$ +106.01 (*c* 1.0, $CHCl_3$). SFC Conditions: 5% IPA, 2.5 mL/min, Chiralcel IC-3 column, λ = 230.8 nm, t_R (min): major = 4.94, minor = 5.55.

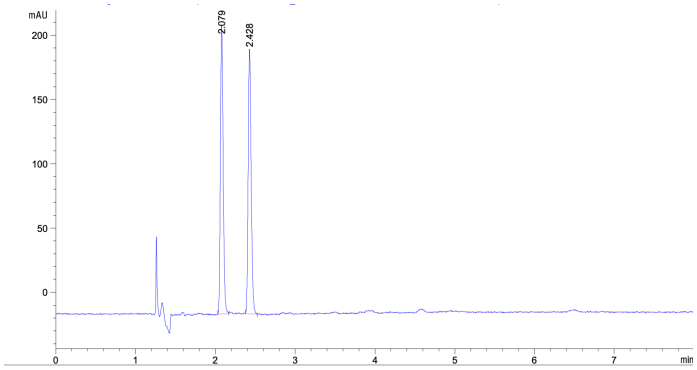


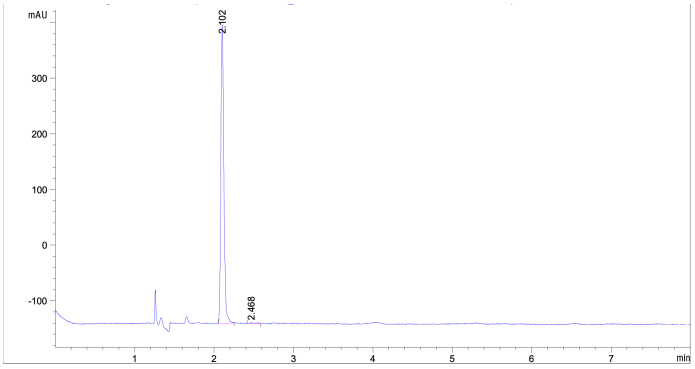
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.936	BB	0.1172	4770.54395	645.57373	100.0000



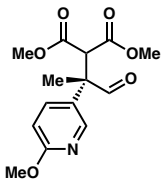
Dimethyl (*S*)-2-(1-oxo-2-(3-(trifluoromethyl)phenyl)propan-2-yl)malonate (71)

Prepared according to General Procedures C and D and isolated as a yellow oil (7.0 mg, 0.021 mmol, 21% yield over 2 steps, 99% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.62 – 7.54 (m, 2H), 7.52 – 7.48 (m, 2H), 4.35 (s, 1H), 3.73 (s, 3H), 3.51 (s, 3H), 1.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 167.4, 167.3, 137.7, 131.0 (q, J = 32.5 Hz), 130.8, 129.2, 124.7 (q, J = 4.2 Hz), 123.9 (q, J = 3.6 Hz), 56.8, 54.2, 52.6, 52.3, 29.5, 16.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.5. IR (thin film, NaCl) 2915, 1733, 1434, 1327, 1123 cm^{-1}. HRMS (MM:FI+) m/z calc'd for $C_{15}H_{16}O_5F_3$ $[M+H]^+$: 333.0944, found 333.0958. $[\alpha]_D^{23}$ +67.22 (*c* 1.0, $CHCl_3$). SFC Conditions: 5% IPA, 2.5 mL/min, Chiralcel OD-3 column, λ = 210.8 nm, t_R (min): major = 2.10, minor = 2.47.



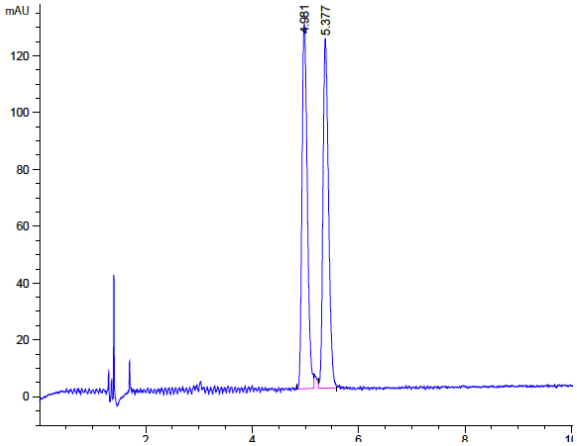


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.102	BB	0.0407	1406.77490	535.29431	99.6462
2	2.468	BB	0.0447	4.99526	1.39721	0.3538

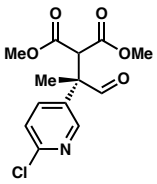


Dimethyl (*S*)-2-(2-(6-methoxypyridin-3-yl)but-3-en-2-yl)malonate (72)

Prepared according to General Procedures C and D and isolated as an orange oil (14.5 mg, 0.049 mmol, 49% yield over 2 steps, 96% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 8.10 (d, *J* = 2.7 Hz, 1H), 7.50 (dd, *J* = 9.0, 2.6 Hz, 1H), 6.74 (d, *J* = 8.8 Hz, 1H), 4.31 (s, 1H), 3.92 (s, 3H), 3.73 (s, 3H), 3.55 (s, 3H), 1.85 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 167.82, 167.77, 163.9, 146.3, 138.0, 124.8, 111.2, 56.7, 53.7, 52.9, 52.6, 16.1. IR (thin film, NaCl) 2951, 1732, 1603, 1496, 1383, 1295, 1026 cm^{-1}. $[\alpha]_D^{23}$ +197.7 (*c* 1.0, $CHCl_3$). HRMS (MM:FD+) m/z calc'd for $C_{14}H_{17}NO_6$ $[M]^{+\bullet}$: 295.1050, found 295.1036. SFC Conditions: 3% IPA, 2.5 mL/min, Chiralcel OD-3 column, λ = 230.8 nm, t_R (min): major = 4.87, minor = 5.31.



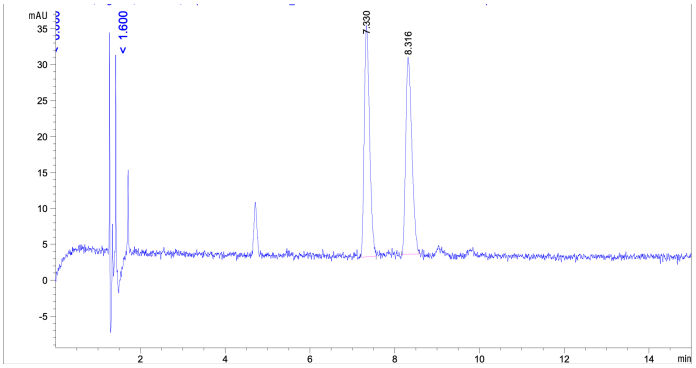
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.867	BB	0.1062	6744.15430	969.23120	98.1909
2	5.314	BB	0.1033	124.25487	18.29177	1.8091



Dimethyl (*S*)-2-(2-(6-chloropyridin-3-yl)but-3-en-2-yl)malonate (73)

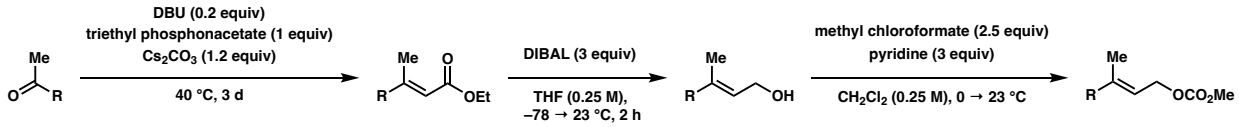
Prepared according to General Procedures C and D and isolated as a clear oil (16 mg, 0.053 mmol, 53% yield over 2 steps, >99% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1H), 8.39

– 8.21 (m, 1H), 7.62 (dd, J = 8.5, 2.8 Hz, 1H), 7.33 (dd, J = 8.5, 0.7 Hz, 1H), 4.30 (s, 1H), 3.73 (s, 3H), 3.58 (s, 3H), 1.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 167.4, 167.3, 151.4, 148.9, 138.2, 131.7, 124.3, 56.9, 53.0, 52.7, 52.6, 16.7. IR (thin film, NaCl) 2952, 1731, 1465, 1163, 1017 cm^{-1}. HRMS (MM:FD+) m/z calc'd for $C_{13}H_{15}O_5NCl$ $[M+H]^+$: 300.0633, found 333.0619. $[\alpha]_D^{23}$ +38.92 (*c* 0.5, $CHCl_3$). SFC Conditions: 3% IPA, 2.5 mL/min, Chiralcel OD-3 column, λ = 230.8 nm, t_R (min): major = 7.21, minor = 8.32.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.208	BB	0.1337	312.72949	35.52005	100.0000

Synthesis of Allylic Electrophiles: General Procedure E

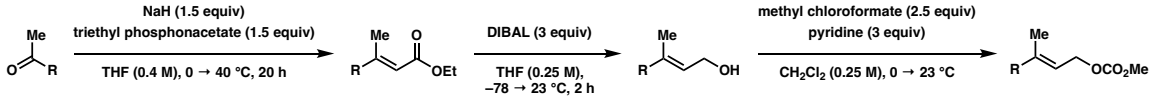


Method A: In accordance with a literature protocol,[37] a highly (*E*)-selective Horner-Wadsworth-Emmons reaction was utilized in the synthesis of the linear electrophiles. To a flame dried flask equipped with a large stir bar was added Cs_2CO_3 (1.2 equiv) and the acetophenone derivative (if solid, 1.1 equiv). The flask was purged and backfilled with N_2, at which point triethyl phosphonoacetate (1 equiv) was added via syringe, followed by DBU (20 mol%) and the acetophenone derivative (if liquid, 1.1 equiv). The mixture was heated to 40 ºC and stirred for 3 days. Minimal THF was used to rinse the sides of the flask and ensure even stirring over the course of the reaction, if necessary. After 3 days, the reaction mixture was diluted with water and ethyl acetate. Three extractions were performed with ethyl acetate, then the combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude extract was purified by silica gel chromatography to afford the desired (*E*)-esters.

The purified ester was dissolved in THF (0.25 M) and transferred to a flame-dried flask, equipped with a stir bar under N_2 atmosphere. The flask was cooled to –78 ºC, then DIBAL-H (3 equiv) was added dropwise via syringe. The reaction was allowed to stir at 23 °C and monitored by TLC. Upon completion (typically 2 h), the reaction was quenched and concentrated following the Fieser protocol.[38] No further purification was needed.

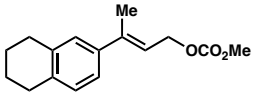
The crude alcohol was dissolved in CH_2Cl_2 (0.25 M) and transferred to a flame-dried flask containing a stir bar under N_2 atmosphere. Freshly distilled pyridine (3 equiv) was added via syringe. The mixture was cooled to 0 ºC, and then methyl chloroformate (2.5 equiv) was added dropwise via syringe. The solution was observed to become radiantly yellow or orange during the addition of this reagent. The reaction was stirred at 23 °C and monitored by TLC. Upon completion (typically 2 h), the reaction was quenched with 1 M aq. HCl, and three extractions were performed with CH_2Cl_2. The combined organic layers

were washed with saturated aq. $NaHCO_3$ solution, then dried with Na_2SO_4, filtered, and concentrated. The residue was purified via silica gel chromatography to deliver the desired allylic methyl carbonate.



Method B[8]: To a flame-dried round bottom flask was added NaH (60% dispersion in mineral oil, 1.5 equiv). The flask was purged and backfilled three times with N_2. Then THF (0.4 M) was added, and the resulting gray suspension was cooled to 0 °C and stirred. To the cooled suspension was added neat triethyl phosphonoacetate (1.5 equiv) dropwise, causing rapid gas evolution, and stirred for 30 minutes, during which time the solution became clear. The solution was allowed to warm to 23 °C, then heated to 40 °C using a metal heating block or oil bath. A solution of the acetophenone derivative (1.0 equiv, 1.0 M in THF) was added slowly to the reaction mixture. After stirring for 20 h, the mixture was cooled to 0 °C, diluted with Et_2O and quenched with water. The layers were separated and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude residue contained the desired (*E*)-alkene product in ratios ranging from 2:1 to 10:1 depending on the substrate. These geometric isomers were separated by silica gel flash column chromatography to afford the desired (*E*)-ester products.

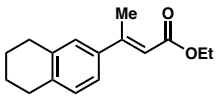
Subsequent synthetic steps performed in analogy to Method A.



(*E*)-methyl (3-(5,6,7,8-tetrahydronaphthalen-2-yl)but-2-en-1-yl) carbonate (67a)

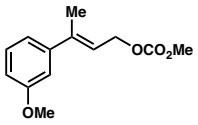
Prepared from **67b** according to General Procedure E and purified by silica gel chromatography (0–15% EtOAc/Hexanes) to afford **67a** as a clear oil (536 mg, 2.06 mmol, 41% yield over 3 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (dd, J = 7.9, 2.0 Hz, 1H), 7.11 (d, J = 2.0 Hz, 1H), 7.03 (d, J = 7.9 Hz, 1H), 5.88 (td, J = 7.0, 1.5 Hz, 1H), 4.84 (d, J = 7.0

Hz, 2H), 3.80 (s, 3H), 2.77 (d, *J* = 5.3 Hz, 4H), 2.11 (d, *J* = 1.3 Hz, 3H), 1.80 (p, *J* = 3.3 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 141.3, 139.8, 137.1, 137.0, 129.2, 126.7, 123.2, 119.8, 65.2, 54.9, 29.6, 29.3, 23.4, 23.3, 16.4. IR (thin film, NaCl) 2925, 2355, 1747, 1442, 1267, 938, 826 cm^{-1}. HRMS (MM:FD+) m/z calc'd for $C_{16}H_{20}O_3$ $[M]^{+\bullet}$: 260.1407, found 260.1404.



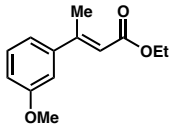
Ethyl (*E*)-3-(5,6,7,8-tetrahydronaphthalen-2-yl)but-2-enoate (67b)

Prepared via Method A of General Procedure E. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 7.9, 2.1 Hz, 1H), 7.19 (d, *J* = 2.0 Hz, 1H), 7.07 (d, *J* = 7.9 Hz, 1H), 6.12 (d, *J* = 1.4 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.81 – 2.75 (m, 4H), 2.56 (s, 3H), 1.81 (p, *J* = 3.3 Hz, 4H), 1.32 (t, *J* = 7.1 Hz, 3H). Characterization data was in agreement with the literature.[39]



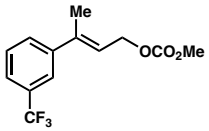
(*E*)-3-(3-methoxyphenyl)but-2-en-1-yl methyl carbonate (69a)

Prepared from **69b** according to General Procedure E and purified by silica gel chromatography (10% EtOAc/Hexanes) to afford **69a** as a clear oil (733 mg, 3.10 mmol, 62% yield over 3 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.22 (m, 1H), 7.00 (ddd, *J* = 7.7, 1.7, 0.9 Hz, 1H), 6.93 (t, *J* = 2.1 Hz, 1H), 6.83 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 5.93 (td, *J* = 7.0, 1.5 Hz, 1H), 4.85 (d, *J* = 7.0 Hz, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 156.0, 144.1, 141.0, 129.4, 121.0, 118.6, 113.1, 111.9, 65.1, 55.4, 55.0, 16.5. IR (thin film, NaCl) 2954, 2348, 1747, 1578, 1440, 1256, 1045, 948 cm^{-1}. HRMS (MM:FI+) m/z calc'd for $C_{13}H_{16}O_4$ $[M]^{+\bullet}$: 236.1043, found 236.1044.



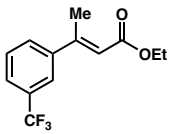
Ethyl (*E*)-3-(3-methoxyphenyl)but-2-enoate (69b)

Prepared via Method A of General Procedure E. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, *J* = 8.0 Hz, 1H), 7.06 (ddd, *J* = 7.7, 1.7, 0.9 Hz, 1H), 6.99 (dd, *J* = 2.5, 1.7 Hz, 1H), 6.90 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 6.13 (q, *J* = 1.3 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 2.57 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H). Characterization data was in agreement with the literature.[40]



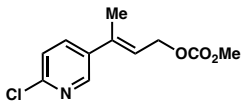
(*E*)-methyl (3-(3-(trifluoromethyl)phenyl)but-2-en-1-yl) carbonate (71a)

Prepared from **71b** according to General Procedure E and purified by silica gel chromatography (10% EtOAc/Hexanes) to afford **71a** as a clear oil (0.777 g, 2.83 mmol, 57% yield over 3 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.33 (m, 4H), 5.98 (tt, *J* = 6.9, 1.3 Hz, 1H), 4.88 (d, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 143.2, 139.6, 130.6 (q, *J* = 32.1 Hz), 129.2 (d, *J* = 1.5 Hz), 128.8, 124.3 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 272.4 Hz), 122.7 (q, *J* = 3.9 Hz), 122.4, 64.7, 54.9, 16.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.5. IR (thin film, NaCl) 2959, 2357, 1746, 1444, 1380, 1328, 1265, 1119, 944, 797 cm^{-1}. HRMS (MM:FI+) m/z calc'd for $C_{13}H_{13}O_3F_3$ $[M]^{+\bullet}$: 274.0811, found 274.0816.



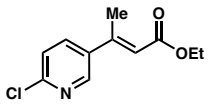
Ethyl (*E*)-3-(3-(trifluoromethyl)phenyl)but-2-enoate (71b)

Prepared via Method A of General Procedure E. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 1.8 Hz, 1H), 7.65 (d, *J* = 7.7 Hz, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 6.15 (q, *J* = 1.3 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 2.60 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 153.8, 143.2, 131.0 (q, *J* = 32.5 Hz), 129.72, 129.70, 129.2, 125.7 (q, *J* = 3.7 Hz) , 123.3 (q, *J* = 3.9 Hz), 118.8, 60.2, 18.1, 14.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.6. IR (thin film, NaCl) 3411, 2983, 1905, 1713, 1632, 1434, 1368, 1330, 1259, 1165, 1133,1073, 1043, 904, 874, 827,803, 728, 698, 658 cm^{-1}. HRMS (MM:FI+) m/z calc'd for $C_{13}H_{13}O_2F_3$ $[M]^{+\bullet}$: 258.0862, found 258.0873.



(*E*)-3-(6-chloropyridin-3-yl)but-2-en-1-yl methyl carbonate (73a)

Prepared from **72b** according to General Procedure E and purified by silica gel chromatography (10–20% EtOAc/Hexanes) to afford **72a** as a clear solid (86 mg, 0.36 mmol, 18% yield over 3 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 1.9 Hz, 1H), 7.65 (dd, *J* = 8.4, 2.6 Hz, 1H), 7.29 (dd, *J* = 8.4, 0.7 Hz, 1H), 5.95 (tq, *J* = 6.9, 1.4 Hz, 1H), 4.85 (d, *J* = 6.8 Hz, 2H), 3.81 (s, 3H), 2.12 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 150.5, 147.1, 136.7, 136.0, 123.8, 123.1, 64.4, 55.0, 16.1. IR (thin film, NaCl) 1747, 1458, 1262, 1169, 942 cm^{-1}. HRMS (MM:FD+) m/z calc'd for $C_{11}H_{12}NO_3Cl$ $[M]^{+\bullet}$: 241.0500, found 241.0491.

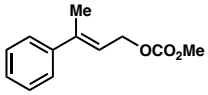


Ethyl (*E*)-3-(6-chloropyridin-3-yl)but-2-enoate (73b)

Prepared via Method A of General Procedure E. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (dd, *J* = 2.7, 0.7 Hz, 1H), 7.72 (dd, *J* = 8.4, 2.6 Hz, 1H), 7.34 (dd, *J* = 8.4, 0.7 Hz, 1H), 6.13 (q, *J* = 1.4 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 2.56 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 151.9, 150.6, 147.5, 136.7, 136.5, 124.2, 119.2, 60.4, 17.8,

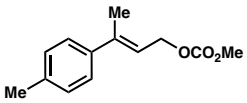
14.4. IR (thin film, NaCl) 2980, 1713, 1630, 1458, 1276, 1168, 1109, 1041, 822 cm^{-1}. HRMS (MM:FD+) m/z calc'd for $C_{11}H_{12}NO_2Cl$ $[M]^{+\bullet}$: 225.0551, found 225.0541.

^{1}H NMR Data of Previously Synthesized Allylic Carbonate Electrophiles



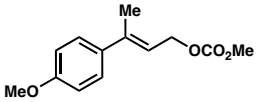
(*E*)-methyl (3-phenylbut-2-en-1-yl) carbonate (2a)

Prepared via Method A of General Procedure E (5.389 g, 26.1 mmol, 66% yield over 3 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.37 (m, 2H), 7.35 – 7.31 (m, 2H), 7.30 – 7.27 (m, 1H), 5.93 (tq, *J* = 7.0, 1.3 Hz, 1H), 4.86 (dd, *J* = 6.9, 0.9 Hz, 2H), 3.81 (s, 3H), 2.14 (s, 3H). Characterization data was in agreement with the literature.[8]



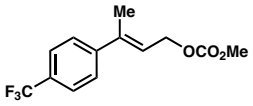
(*E*)-methyl (3-(p-tolyl)but-2-en-1-yl) carbonate (2h)

Prepared via Method B of General Procedure E. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.2 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 5.90 (tq, *J* = 7.1, 1.4 Hz, 1H), 4.85 (d, *J* = 7.0 Hz, 2H), 3.81 (s, 3H), 2.35 (s, 3H), 2.12 (s, 3H). Characterization data was in agreement with the literature.[8]



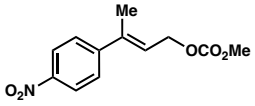
(*E*)-3-(4-methoxyphenyl)but-2-en-1-yl methyl carbonate (2i)

Prepared via Method B of General Procedure E. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.87 (td, *J* = 7.1, 1.4 Hz, 1H), 4.84 (d, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 2.11 (s, 3H). Characterization data was in agreement with the literature.[8]



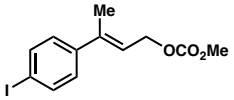
(*E*)-methyl (3-(4-(trifluoromethyl)phenyl)but-2-en-1-yl) carbonate (2c)

Prepared via Method A of General Procedure E (0.418 g, 1.52 mmol, 28% yield over 3 steps). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 52.4, 8.2 Hz, 4H), 5.97 (ddt, *J* = 6.9, 5.5, 1.4 Hz, 1H), 4.86 (d, *J* = 6.8 Hz, 2H), 3.81 (s, 3H), 2.14 (s, 3H). Characterization data was in agreement with the literature.[8]



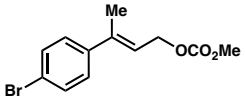
(*E*)-methyl (3-(4-nitrophenyl)but-2-en-1-yl) carbonate (2d)

Prepared via Method A of General Procedure E (0.601 g, 2.39 mmol, 48% yield over 3 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.9 Hz, 2H), 6.05 (tq, *J* = 6.8, 1.4 Hz, 1H), 4.88 (dd, *J* = 6.8, 1.0 Hz, 2H), 3.82 (s, 3H), 2.17 (s, 3H). Characterization data was in agreement with the literature.[8]



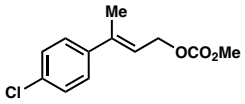
(*E*)-3-(4-iodophenyl)but-2-en-1-yl methyl carbonate (2e)

Prepared via Method A of General Procedure E (0.520 g, 1.57 mmol, 28% yield over 3 steps). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 – 7.50 (m, 2H), 7.18 – 7.02 (m, 2H), 5.91 (tq, *J* = 6.9, 1.3 Hz, 1H), 4.83 (d, *J* = 6.9 Hz, 2H), 3.80 (s, 3H), 2.09 (s, 3H). Characterization data was in agreement with the literature.[8]



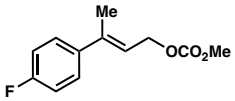
(*E*)-3-(4-bromophenyl)but-2-en-1-yl methyl carbonate (2f)

Prepared via Method B of General Procedure E. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 7.8 Hz, 2H), 5.94 – 5.88 (m, 1H), 4.84 (d, *J* = 6.9 Hz, 2H), 3.81 (s, 3H), 2.11 (s, 3H). Characterization data was in agreement with the literature.[8]



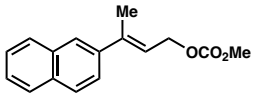
(*E*)-3-(4-chlorophenyl)but-2-en-1-yl methyl carbonate (2g)

Prepared via Method A of General Procedure E (0.385 g, 1.60 mmol, 29% yield over 3 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 4H), 5.90 (tq, *J* = 7.0, 1.4 Hz, 1H), 4.84 (d, *J* = 7.0 Hz, 2H), 3.80 (s, 3H), 2.10 (s, 3H). Characterization data was in agreement with the literature.[8]



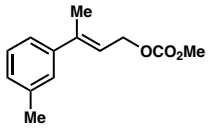
(*E*)-3-(4-fluorophenyl)but-2-en-1-yl methyl carbonate (65a)

Prepared via Method A of General Procedure E (0.435 g, 1.94 mmol, 39% yield over 3 steps). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.32 (m, 2H), 7.04 – 6.96 (m, 2H), 5.87 (td, *J* = 7.0, 1.5 Hz, 1H), 4.84 (d, *J* = 7.0 Hz, 2H), 3.80 (s, 3H), 2.11 (s, 3H). Characterization data was in agreement with the literature.[41]



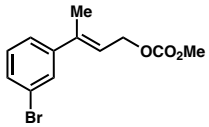
(*E*)-methyl (3-(naphthalen-2-yl)but-2-en-1-yl) carbonate (2b)

Prepared via Method B of General Procedure E. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 – 7.79 (m, 4H), 7.58 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.49 (tt, *J* = 6.9, 5.2 Hz, 2H), 6.08 (td, *J* = 7.0, 1.5 Hz, 1H), 4.92 (d, *J* = 7.0 Hz, 2H), 3.83 (s, 3H), 2.25 (s, 3H). Characterization data was in agreement with the literature.[8]



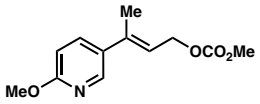
(*E*)-methyl (3-(m-tolyl)but-2-en-1-yl) carbonate (2m)

Prepared via Method A of General Procedure E (626 mg, 2.84 mmol, 57% yield over 3 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.17 (m, 2H), 7.13 – 7.07 (m, 2H), 5.91 (tt, *J* = 6.9, 1.4 Hz, 1H), 4.85 (d, *J* = 7.0 Hz, 2H), 3.81 (s, 3H), 2.36 (s, 3H), 2.13 (s, 3H). Characterization data was in agreement with the literature.[8]



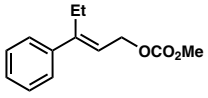
(*E*)-3-(3-bromophenyl)but-2-en-1-yl methyl carbonate (70a)

Prepared via Method A of General Procedure E (1.16 g, 4.07 mmol, 81% yield over 3 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (t, *J* = 1.9 Hz, 1H), 7.40 (ddd, *J* = 7.9, 2.0, 1.0 Hz, 1H), 7.32 (ddd, *J* = 7.8, 1.8, 1.0 Hz, 1H), 7.20 (t, *J* = 7.9 Hz, 1H), 5.91 (tt, *J* = 6.9, 1.3 Hz, 1H), 4.84 (d, *J* = 6.9 Hz, 2H), 3.81 (s, 3H), 2.11 (s, 3H). Characterization data was in agreement with the literature.[41]



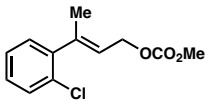
(*E*)-3-(6-methoxypyridin-3-yl)but-2-en-1-yl methyl carbonate (72a)

Prepared via Method A of General Procedure E (484 mg, 2.04 mmol, 41% yield over 3 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 – 8.10 (m, 1H), 7.62 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.70 (d, *J* = 8.6 Hz, 1H), 5.86 (tq, *J* = 7.0, 1.3 Hz, 1H), 4.83 (d, *J* = 7.0 Hz, 2H), 3.93 (s, 3H), 3.80 (s, 3H), 2.11 (s, 3H). Characterization data was in agreement with the literature.[42]



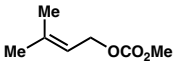
(*E*)-methyl (3-phenylpent-2-en-1-yl) carbonate (2s)

Prepared via Method B of General Procedure E. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.35 (m, 2H), 7.35 – 7.30 (m, 2H), 7.30 – 7.26 (m, 1H), 5.79 (t, *J* = 7.0 Hz, 1H), 4.85 (d, *J* = 7.0 Hz, 2H), 3.81 (s, 3H), 2.59 (q, *J* = 7.6 Hz, 2H), 1.01 (t, *J* = 7.5 Hz, 3H). Characterization data was in agreement with the literature.[8]



(*E*)-3-(2-chlorophenyl)but-2-en-1-yl methyl carbonate (2r)

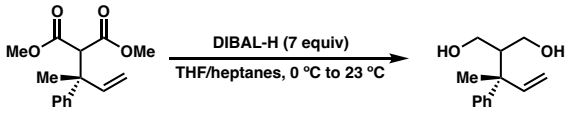
Prepared via Method B of General Procedure E. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 1H), 7.25 – 7.14 (m, 3H), 5.60 (tt, *J* = 5.5, 1.5 Hz, 1H), 4.83 (d, *J* = 6.8 Hz, 2H), 3.81 (s, 3H), 2.08 (s, 3H). Characterization data was in agreement with the literature.[8]



Methyl (3-methylbut-2-en-1-yl) carbonate (2t)

Synthesized from prenol according to the final step in General Procedure E Method A (1.44 g, 10 mmol, quant.). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38 (tp, *J* = 7.2, 1.4 Hz, 1H), 4.63 (d, *J* = 7.3 Hz, 2H), 3.78 (s, 3H), 1.77 (s, 3H), 1.73 (s, 3H). Characterization data was in agreement with the literature.[8]

Derivatization of Allylic Alkylation Products



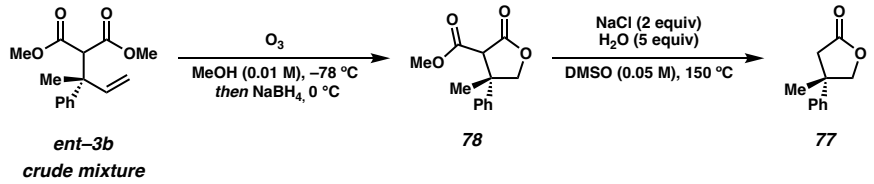
ent–3b
crude mixture

ent–21

2-(2-phenylbut-3-en-2-yl)propane-1,3-diol (29)

Following General Procedure C, the crude mixture containing **ent–3b** was dissolved in THF (1 mL, 0.1 M) under N_2, and the vial was cooled to 0 ºC. DIBAL-H in heptanes (0.7 mL 1.0 M solution, 7 equiv) was added, and the reaction was allowed to warm to 23 °C. After stirring for 18 h, the reaction was quenched via the Fieser method.[10] The mixture was filtered, and concentrated. The crude residue was purified by preparatory TLC (100% EtOAc) to deliver **ent–21** as a clear oil (7.6 mg, 0.037 mmol, 37% over 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.22 (m, 4H), 7.17 – 7.10 (m, 1H), 6.06 (dd, J = 17.4, 10.8 Hz, 1H), 5.18 – 4.96 (m, 2H), 3.79 (ddd, J = 10.7, 3.3, 1.5 Hz, 1H), 3.73 – 3.58 (m, 3H), 2.62 – 2.18 (m, 3H), 1.31 (s, 3H). $[\alpha]_D^{23}$ 48.23 (*c* 0.3, $CHCl_3$).

Characterization data was in agreement with the literature.[8]



ent–3b crude mixture — *78* — *77*

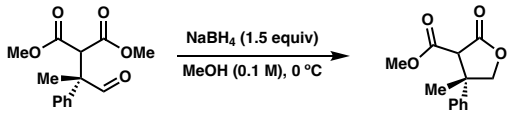
4-methyl-4-phenyldihydrofuran-2(3H)-one (77)

Following General Procedure C, the crude mixture containing **ent–3b** (0.2 mmol scale) was dissolved in MeOH (20 mL, 0.01 M) and a pipette tip of Sudan III was added. The flask was cooled to –78 ºC and O_2 gas was bubbled through the solution using a gas diffuser. After 5 min of vigorous O_2 flow, a VMUS-4 Ozone Generator was turned to the lowest ozone output setting. After 3 minutes, the color of the solution was observed to change from a vibrant red to a pale orange/brown color, and the ozonator was turned off. O_2 was bubbled through the solution for an additional 5 minutes, then the diffuser was removed. A stir bar was added to the flask, and a septum with an Ar balloon was affixed to the flask. The reaction was moved to a 0 °C bath and $NaBH_4$ (22.7 mg, 0.6 mmol, 3 equiv) was added slowly. The mixture was stirred at 0 ºC for 20 min. The reaction was quenched with NH_4Cl (6 mL) at 0 °C and then warmed to 23 ºC. Three extractions with CH_2Cl_2 were performed, and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated.

Purification by silica gel chromatography (20% EtOAc/Hexanes) afforded **31** as a clear oil (23 mg, 0.098 mmol 49% yield over 2 steps). ^{1}H NMR was consistent with that obtained for **78**.

To a flame-dried microwave vial equipped with a stir bar, was added lactone **78** (23 mg, 0.098 mmol, 1 equiv) and sodium chloride (11.4 mg, 0.196 mmol, 2 equiv), followed by water (8 μL, 0.49 mmol, 5 equiv) and DMSO (1.82 mL). The microwave vial was sealed then heated to 150 °C for 18 hours. The reaction was then cooled to 23 °C and diluted with water (3 mL) and brine (3 mL). The mixture was extracted three times with ethyl acetate, and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated. Purification by silica gel column chromatography (20% EtOAc/Hexanes) afforded **77** as a clear oil (13 mg, 0.074 mmol, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.33 (m, 2H), 7.33 – 7.27 (m, 1H), 7.23 – 7.15 (m, 2H), 4.47 – 4.37 (m, 2H), 2.92 (d, J = 16.8 Hz, 1H), 2.68 (d, J = 17.5 Hz, 1H), 1.53 (s, 3H). $[\alpha]_D^{23}$ –16.30 (*c* 1.0, $CHCl_3$).

Characterization data was in agreement with the literature.[43]

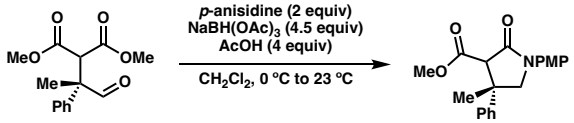


55 ***78***

Methyl (4*S*)-4-methyl-2-oxo-4-phenyltetrahydrofuran-3-carboxylate (78)

To a flame-dried one-dram vial equipped with a stir bar and septum was added aldehyde **55** (26.5 mg, 0.1 mmol, 1 equiv) and MeOH (1 mL, 0.1 M) under N_2 atmosphere. The solution was cooled to 0 ºC. $NaBH_4$ (6 mg, 0.15 mmol, 1.5 equiv) was then added in a single portion, and the reaction was stirred at 0 °C for 20 minutes and monitored by TLC. Upon completion, the reaction was quenched with 1 mL sat. aq. NH_4Cl solution, and the mixture warmed to 23 °C. Three extractions with EtOAc were performed, and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The material was purified via preparatory TLC (20% EtOAc/Hexanes) to afford **78** as a clear oil (17.4

mg, 0.074 mmol, 74% yield, 1.2:1 dr). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.27 (m, 4H), 7.15 – 7.09 (m, 1H), 5.08 (d, *J* = 8.3 Hz, 0.6H), 4.53 – 4.39 (m, 1.6H), 3.89 (s, 0.5H), 3.84 (s, 1.5H), 3.66 (s, 0.5H), 3.43 (s, 1.6H), 1.57 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 171.92, 171.87 167.4, 166.8, 143.2, 141.1, 129.3, 129.0, 127.8, 127.6, 125.5, 125.3, 77.8, 76.8, 59.1, 57.0, 52.9, 52.6, 48.5, 48.1, 29.9, 23.3. IR (thin film, NaCl) 2961, 2354, 1778, 1445, 1139, 1021, 763, 697 cm^{-1}. HRMS (MM:FD+) m/z calc'd for $C_{13}H_{14}O_4$ $[M]^{+\bullet}$: 234.0887, found 234.0886. $[\alpha]_D^{23}$ –21.48 (*c* 1.0, $CHCl_3$).

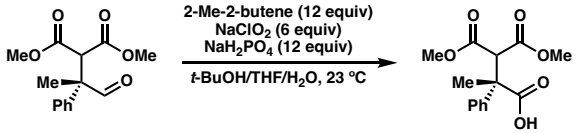


55 ***79***

Methyl (4*S*)-1-(4-methoxyphenyl)-4-methyl-2-oxo-4-phenylpyrrolidine-3-carboxylate (79)

To a flame-dried one-dram vial equipped with a stir bar and septum was added aldehyde **55** (26.5 mg, 0.1 mmol, 1 equiv) and CH_2Cl_2 (0.5 mL, 0.2 M) under N_2 atmosphere. The solution was cooled to 0 ºC. AcOH (12 μL, 0.2 mmol, 2 equiv), *p*-anisidine (24.6 mg, 0.2 mmol, 2 equiv), and $NaBH(OAc)_3$ (53 mg, 0.25 mmol, 2.5 equiv) were then added successively to the reaction. The reaction was then slowly warmed to 23 °C and was monitored by LCMS. After 3.5 h, additional $NaBH(OAc)_3$ (42 mg, 0.2 mmol, 2 equiv) and AcOH (10 μL, 0.17 mmol, 1.7 equiv) were added. The reaction was stirred at 23 °C for an additional 18.5 h and monitored by LCMS. Upon completion, the reaction was quenched with H_2O. Three extractions with EtOAc were performed, and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The material was purified via preparatory TLC (40% EtOAc/Hexanes) to afford **79** as a pale yellow oil (25.8 mg, 0.076 mmol, 76% yield, 1.7:1 dr). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.39 (m, 2H), 7.36 – 7.10 (m, 5H), 6.91 – 6.80 (m, 2H), 4.68 (d, *J* = 8.8 Hz, 0.6H), 4.09 – 3.89 (m, 0.7H), 3.87 (s, 0.4H), 3.74 (s, 3H), 3.73 – 3.70 (m, 1.7H), 3.66 (s, 0.6H), 3.33 (d, *J* = 0.7 Hz, 1.9H),

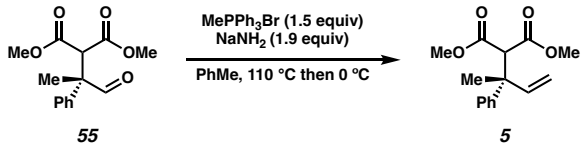
1.51 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 168.8, 168.48, 168.45, 157.3, 157.2, 145.5, 143.1, 132.2, 131.9, 129.1, 128.8, 127.3, 127.1, 125.5, 125.4, 122.7, 122.2, 114.33, 114.29, 62.6, 60.8, 60.6, 58.9, 55.63, 55.61, 52.5, 52.2, 44.4, 43.7, 31.5, 24.4. IR (thin film, NaCl) 2953, 2340, 1738, 1695, 1514, 1322, 1297, 1248, 1032, 831 cm^{-1}. HRMS (MM:FD+) m/z calc'd for $C_{20}H_{21}NO_4$ $[M]^{+\bullet}$: 339.1465, found 339.1477. $[\alpha]_D^{23}$ –87.15 (*c* 1.0, $CHCl_3$).



55 ***80***

(*S*)-4-methoxy-3-(methoxycarbonyl)-2-methyl-4-oxo-2-phenylbutanoic acid (80)

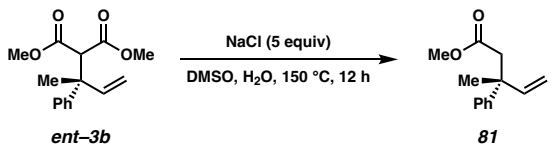
To a flame-dried one-dram vial equipped with a stir bar and septum was added aldehyde **55** (26.5 mg, 0.1 mmol, 1 equiv) and 2-Me-2-butene (127 μL, 1.2 mmol, 12 equiv) in *t*-BuOH (0.5 mL, 0.2 M) and THF (1 mL, 0.1 M) under N_2 atmosphere. To this mixture was added a solution of $NaClO_2$ (54 mg, 0.6 mmol, 6 equiv) and NaH_2PO_4 (144 mg, 1.2 mmol, 12 equiv) in H_2O (0.5 mL, 0.4 M) dropwise. The reaction was stirred at 23 °C for 6.5 h and monitored by LCMS. Upon completion, the reaction was quenched with 1 mL 1 M aq. HCl. The mixture was extracted with EtOAc three times, and the combined organic layers were washed with a sat. aq. Na_2SO_3 then dried with Na_2SO_4, filtered, and concentrated. The material was purified by preparatory TLC (0.5% AcOH/5% MeOH/94.5% CH_2Cl_2) to afford **80** as a white solid (16.4 mg, 0.059 mmol, 59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.33 (m, 2H), 7.30 – 7.16 (m, 3H), 4.46 (s, 1H), 3.66 (s, 3H), 3.36 (s, 3H), 1.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.5, 168.4, 167.9, 139.0, 128.7, 128.0, 126.5, 58.5, 52.8, 52.4, 51.0, 17.7. IR (thin film, NaCl) 2953, 1737, 1436, 1236, 1026 cm^{-1}. HRMS (MM:FD+) m/z calc'd for $C_{14}H_{17}O_6$ $[M+H]^+$: 281.1020, found 281.1007. $[\alpha]_D^{23}$ +134.17 (*c* 1.0, $CHCl_3$).



Dimethyl (*S*)-2-(2-phenylbut-3-en-2-yl)malonate (ent–3b)

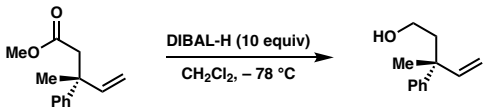
In accordance with a literature protocol,[44] an oven dried two-neck conical flask equipped with a stir bar and reflux condenser was charged with $MePPh_3Br$ (536 mg, 15 equiv, 1.5 mmol) and $NaNH_2$ (146 mg, 18.8 equiv, 1.88 mmol) in toluene (5 mL) under N_2 atmosphere. After 2 h, the resulting yellow suspension was cooled to 23 °C, and the solids were allowed to settle to the bottom of the flask over 16 h. To a separate flame-dried 25 mL flask equipped with a stir bar, was added aldehyde **55** (26.5 mg, 0.1 mmol, 1 equiv) in PhMe (2 mL, 0.05 M) under N_2 atmosphere. The solution was then cooled to 0 ºC. To this mixture was added the methylene ylide solution (0.2 mL, 0.6 mmol, 6 equiv) (no solids) dropwise. The reaction was stirred at 0 ºC for 5 h and monitored by TLC. Upon completion, the reaction was diluted with Et_2O (10 mL) and quenched with sat. aq. NaCl (10 mL). The aqueous phase was extracted three times with Et_2O, and the combined organics were dried with Na_2SO_4, filtered, and concentrated. The material was purified by silica gel chromatography (0–10% EtOAc/Hexanes) to afford **ent–3b** as a clear oil (13 mg, 0.05 mmol, 50% yield). Characterization was in agreement with the literature.[8]

Synthetic Sequence toward Pharmaceutically Relevant Enantioenriched Azepane Motif (81)



Methyl (*R*)-3-methyl-3-phenylpent-4-enoate (81)

To a flame-dried microwave vial equipped with a stir bar was added NaCl (13 mg, 0.22 mmol, 5 equiv). A solution of **ent–3b** (11 mg, 0.042 mmol, 1 equiv) in DMSO (0.8 mL, 0.05 M) was introduced, followed by H_2O (8 μL, 0.44 mmol, 10 equiv). The reaction was sealed and heated to 150 ºC for 12 h. The reaction was then cooled to 23 °C and diluted with water (2 mL) and brine (2 mL). Three extractions were performed with Et_2O, then the organic phase was washed two times with brine in an effort to remove residual DMSO. The residue was purified by preparatory TLC (20% EtOAc/Hexanes) to afford ester **81** as a clear, volatile liquid (8.6 mg, 0.042 mmol, quant.). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.23 (m, 4H), 7.16 (ddd, *J* = 8.5, 5.9, 2.4 Hz, 1H), 6.10 (dd, *J* = 17.4, 10.7 Hz, 1H), 5.19 – 5.04 (m, 2H), 3.48 (s, 3H), 2.78 – 2.71 (m, 2H), 1.51 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 146.2, 145.5, 128.4, 128.3, 126.5, 126.4, 126.4, 112.6, 51.4, 45.6, 43.5, 25.6. IR (thin film, NaCl) 2361, 1732, 822 cm^{-1}. HRMS (MM:FI+) m/z calc'd for $C_{13}H_{16}O_2$ $[M]^{+\bullet}$: 204.1145, found 204.1136. $[\alpha]_D^{23}$ -56.14 (*c* 1.0, $CHCl_3$).



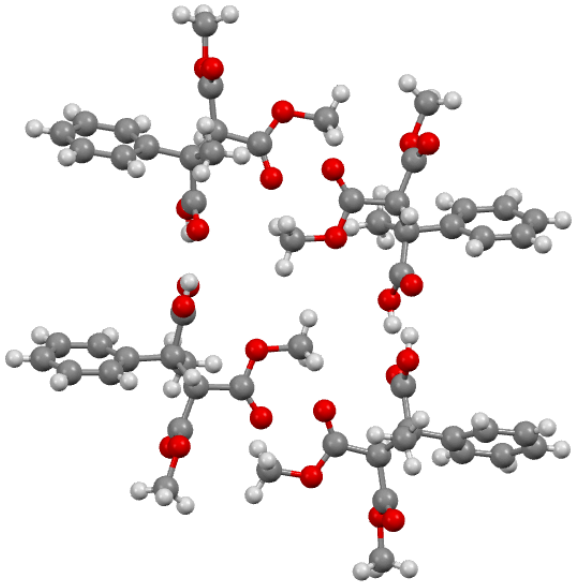
81 ***82***

(*R*)-3-methyl-3-phenylpent-4-en-1-ol (82)

To a flame-dried 10 mL round bottom flask and stir bar was added ester **81** (4.3 mg, 0.02 mmol) in CH_2Cl_2 (1 mL, 0.02 M) under N_2 atmosphere. The flask was cooled to –78 ºC and then DIBAL-H (0.04 mL, 0.2 mmol, 10 equiv) was added dropwise via syringe. The mixture was then slowly warmed to 23 ºC. The reaction was stirred at 23 °C for 2 h and monitored by TLC. Upon completion, the reaction was quenched following the Fieser protocol,[10] and the resultant solution was filtered, and concentrated. The residue was purified by preparatory TLC (50% EtOAc/Hexanes) to deliver alcohol **82** as a clear oil (2.9 mg, 0.016 mmol, 82% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 4H), 7.24 – 7.17 (m, 1H), 6.06 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.17 – 5.07 (m, 2H), 3.74 – 3.53 (m, 2H),

2.11 (dddd, J = 38.5, 13.8, 8.6, 6.1 Hz, 2H), 1.43 (s, 3H). $[\alpha]_D^{23}$ -10.00. (*c* 0.1, $CHCl_3$). Characterization data was in agreement with the literature.[23]

2.5.3 CRYSTAL STRUCTURE ANALYSIS OF (*S*)-4-METHOXY-3-(METHOXYCARBONYL)-2-METHYL-4-OXO-2-PHENYLBUTANOIC ACID (CSD2414384)



Compound **80** was crystallized by rotary evaporation of the sample in $CDCl_3$, followed by further drying under vacuum to provide crystals suitable for X-ray analsysis. Compound V24319_t4 (CSD2414384) crystallizes in the triclinic space group P1 with four molecules in the asymmetric unit.

Table 2.9. *Crystal data and structure refinement for V24319_t4.*

Identification code	V24319_t4
Empirical formula	C14 H16 O6
Formula weight	280.27
Temperature	100(2) K
Wavelength	1.54178 Å

Crystal system	Triclinic
Space group	P1
Unit cell dimensions	a = 6.0838(4) Å a= 96.716(4)°.
	b = 14.8985(11) Å b= 90.717(8)°.
	c = 15.1604(7) Å g = 95.622(6)°.
Volume	1357.74(15) Å3
Z	4
Density (calculated)	1.371 Mg/m3
Absorption coefficient	0.911 mm-1
F(000)	592
Crystal size	0.200 x 0.200 x 0.150 mm3
Theta range for data collection	2.936 to 74.534°.
Index ranges	?<=h<=?, ?<=k<=?, ?<=l<=?
Reflections collected	10269
Independent reflections	10269 [R(int) = ?]
Completeness to theta = 67.679°	99.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.753817 and 0.646780
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	10269 / 7 / 745
Goodness-of-fit on F2	1.043
Final R indices [I>2sigma(I)]	R1 = 0.0299, wR2 = 0.0765
R indices (all data)	R1 = 0.0318, wR2 = 0.0775
Absolute structure parameter	0.01(6)
Extinction coefficient	n/a
Largest diff. peak and hole	0.169 and -0.202 e.Å-3

Table 2.10. *Atomic coordinates (x 104) and equivalent isotropic displacement parameters (Å2x 103)for V24319_t4. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.*

	x	y	z	U(eq)
C(1)	8567(4)	2133(1)	2127(2)	16(1)
C(2)	10400(4)		2172(2)	1587(2) 22(1)
C(3)	10249(5)		1787(2)	705(2) 28(1)
C(4)	8267(5)	1348(2)	346(2)	28(1)
C(5)	6445(5)	1302(2)	878(2)	31(1)
C(6)	6576(4)	1699(2)	1757(2)	23(1)
C(7)	8735(3)	2621(1)	3086(2)	14(1)
C(9)	11025(3)		2611(2)	3517(2) 18(1)
C(10)	8349(4)	3608(2)	2964(2)	14(1)
O(1)	9872(2)	4209(1)	2979(1)	17(1)
O(2)	6279(2)	3720(1)	2783(1)	18(1)
C(8)	6882(3)	2218(1)	3665(1)	13(1)
C(11)	6812(4)	1186(1)	3640(1)	14(1)
O(3)	8385(3)	764(1)	3669(1)	20(1)
O(4)	4705(2)	821(1)	3592(1)	17(1)
C(12)	4373(4)	-158(2)	3596(2)	22(1)
C(13)	7059(3)	2629(2)	4636(2)	16(1)
O(5)	6987(3)	2197(1)	5259(1)	20(1)
O(6)	7232(3)	3535(1)	4694(1)	21(1)
C(14)	7369(5)	4010(2)	5593(2)	29(1)
C(21)	7416(3)	6612(1)	944(1)	13(1)
C(22)	5656(4)	6175(2)	414(2)	21(1)
C(23)	5901(4)	5924(2)	-489(2)	26(1)
C(24)	7921(4)	6105(2)	-878(2)	22(1)
C(25)	9695(4)	6531(2)	-357(2)	22(1)
C(26)	9451(4)	6780(2)	547(2)	18(1)
C(27)	7123(3)	6834(1)	1955(1)	12(1)

C(29)	4786(3)	7096(2)	2172(2)	15(1)
O(21)	5920(2)	5409(1)	2506(1)	16(1)
O(22)	9550(2)	5780(1)	2384(1)	14(1)
C(30)	7468(3)	5944(1)	2331(1)	12(1)
C(28)	8916(3)	7582(1)	2363(1)	13(1)
C(31)	8951(4)	8468(2)	1949(1)	14(1)
O(23)	7366(3)	8826(1)	1749(1)	20(1)
O(24)	11055(3)		8804(1)	1852(1) 21(1)
C(32)	11309(5)		9695(2)	1544(2) 30(1)
C(33)	8684(3)	7755(1)	3369(2)	13(1)
O(25)	8216(3)	7167(1)	3833(1)	18(1)
O(26)	9119(3)	8634(1)	3656(1)	16(1)
C(34)	8950(4)	8884(2)	4604(2)	18(1)
C(41)	1603(4)	3539(1)	9069(2)	15(1)
C(42)	77(4)	4003(2)	9579(2)	20(1)
C(43)	520(4)	4305(2)	10476(2)	25(1)
C(44)	2469(4)	4143(2)	10877(2)	25(1)
C(45)	4000(4)	3682(2)	10382(2)	23(1)
C(46)	3571(4)	3385(2)	9483(2)	18(1)
C(47)	1145(3)	3281(1)	8062(1)	13(1)
C(49)	-1335(3)	3043(2)	7837(2)	16(1)
O(41)	4106(3)	4310(1)	7610(1)	18(1)
O(42)	650(3)	4686(1)	7488(1)	19(1)
C(50)	2055(4)	4144(1)	7671(1)	13(1)
C(48)	2501(3)	2510(1)	7680(1)	13(1)
C(51)	2075(4)	1643(1)	8120(1)	15(1)
O(43)	304(3)	1302(1)	8315(1)	24(1)
O(44)	3992(3)	1293(1)	8249(1)	21(1)
C(52)	3754(5)	419(2)	8585(2)	30(1)
C(53)	2141(3)	2313(1)	6674(2)	13(1)
O(45)	1952(3)	2892(1)	6195(1)	20(1)
O(46)	2118(3)	1432(1)	6404(1)	16(1)
C(54)	1860(4)	1172(2)	5454(2)	19(1)
C(61)	5859(4)	7874(1)	7801(2)	15(1)

C(62)	7906(4)	8327(2)	8083(2)	23(1)
C(63)	8221(4)	8770(2)	8945(2)	29(1)
C(64)	6521(5)	8762(2)	9541(2)	25(1)
C(65)	4457(5)	8333(2)	9262(2)	25(1)
C(66)	4133(4)	7900(2)	8401(2)	20(1)
C(67)	5487(3)	7353(1)	6860(1)	14(1)
C(69)	7644(3)	7275(2)	6357(2)	17(1)
O(61)	2430(3)	6269(1)	7148(1)	19(1)
O(62)	5792(3)	5787(1)	7014(1)	18(1)
C(70)	4455(3)	6399(2)	7005(1)	13(1)
C(68)	3751(3)	7805(1)	6336(2)	13(1)
C(71)	4067(4)	8842(2)	6409(1)	15(1)
O(63)	2544(3)	9297(1)	6485(1)	23(1)
O(64)	6178(3)	9164(1)	6369(1)	17(1)
C(72)	6668(4)	10145(2)	6446(2)	23(1)
C(73)	3548(3)	7428(2)	5356(2)	14(1)
O(65)	3637(3)	7885(1)	4750(1)	19(1)
O(66)	3200(3)	6524(1)	5266(1)	19(1)
C(74)	2981(5)	6078(2)	4360(2)	25(1)

***Table 2.11**. Bond lengths [Å] and angles [°] for V24319_t4.*

C(1)-C(2)	1.393(3)
C(1)-C(6)	1.394(3)
C(1)-C(7)	1.545(3)
C(2)-C(3)	1.390(4)
C(2)-H(2)	0.9500
C(3)-C(4)	1.387(4)
C(3)-H(3)	0.9500
C(4)-C(5)	1.380(4)
C(4)-H(4)	0.9500
C(5)-C(6)	1.391(4)
C(5)-H(5)	0.9500
C(6)-H(6)	0.9500
C(7)-C(9)	1.534(3)
C(7)-C(10)	1.542(3)
C(7)-C(8)	1.556(3)
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800
C(10)-O(1)	1.222(3)
C(10)-O(2)	1.316(3)
O(2)-H(2O)	0.83(2)
C(8)-C(13)	1.525(3)
C(8)-C(11)	1.529(3)
C(8)-H(8)	1.0000
C(11)-O(3)	1.199(3)
C(11)-O(4)	1.340(3)
O(4)-C(12)	1.452(3)
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800
C(13)-O(5)	1.202(3)

C(13)-O(6)	1.335(3)
O(6)-C(14)	1.458(3)
C(14)-H(14A)	0.9800
C(14)-H(14B)	0.9800
C(14)-H(14C)	0.9800
C(21)-C(22)	1.391(3)
C(21)-C(26)	1.397(3)
C(21)-C(27)	1.545(3)
C(22)-C(23)	1.390(3)
C(22)-H(22)	0.9500
C(23)-C(24)	1.386(4)
C(23)-H(23)	0.9500
C(24)-C(25)	1.385(4)
C(24)-H(24)	0.9500
C(25)-C(26)	1.391(3)
C(25)-H(25)	0.9500
C(26)-H(26)	0.9500
C(27)-C(30)	1.535(3)
C(27)-C(29)	1.540(3)
C(27)-C(28)	1.549(3)
C(29)-H(29A)	0.9800
C(29)-H(29B)	0.9800
C(29)-H(29C)	0.9800
O(21)-C(30)	1.225(3)
O(22)-C(30)	1.317(3)
O(22)-H(22O)	0.86(2)
C(28)-C(31)	1.525(3)
C(28)-C(33)	1.527(3)
C(28)-H(28)	1.0000
C(31)-O(23)	1.199(3)
C(31)-O(24)	1.344(3)
O(24)-C(32)	1.452(3)
C(32)-H(32A)	0.9800
C(32)-H(32B)	0.9800

C(32)-H(32C)	0.9800
C(33)-O(25)	1.202(3)
C(33)-O(26)	1.331(3)
O(26)-C(34)	1.450(3)
C(34)-H(34A)	0.9800
C(34)-H(34B)	0.9800
C(34)-H(34C)	0.9800
C(41)-C(46)	1.396(3)
C(41)-C(42)	1.399(3)
C(41)-C(47)	1.545(3)
C(42)-C(43)	1.395(3)
C(42)-H(42)	0.9500
C(43)-C(44)	1.381(4)
C(43)-H(43)	0.9500
C(44)-C(45)	1.388(4)
C(44)-H(44)	0.9500
C(45)-C(46)	1.396(3)
C(45)-H(45)	0.9500
C(46)-H(46)	0.9500
C(47)-C(50)	1.535(3)
C(47)-C(49)	1.540(3)
C(47)-C(48)	1.541(3)
C(49)-H(49A)	0.9800
C(49)-H(49B)	0.9800
C(49)-H(49C)	0.9800
O(41)-C(50)	1.255(3)
O(42)-C(50)	1.282(3)
O(42)-H(42O)	0.85(2)
C(48)-C(51)	1.524(3)
C(48)-C(53)	1.528(3)
C(48)-H(48)	1.0000
C(51)-O(43)	1.201(3)
C(51)-O(44)	1.345(3)
O(44)-C(52)	1.448(3)

C(52)-H(52A)	0.9800
C(52)-H(52B)	0.9800
C(52)-H(52C)	0.9800
C(53)-O(45)	1.203(3)
C(53)-O(46)	1.327(3)
O(46)-C(54)	1.450(3)
C(54)-H(54A)	0.9800
C(54)-H(54B)	0.9800
C(54)-H(54C)	0.9800
C(61)-C(62)	1.394(3)
C(61)-C(66)	1.398(3)
C(61)-C(67)	1.546(3)
C(62)-C(63)	1.396(4)
C(62)-H(62)	0.9500
C(63)-C(64)	1.381(4)
C(63)-H(63)	0.9500
C(64)-C(65)	1.389(4)
C(64)-H(64)	0.9500
C(65)-C(66)	1.390(3)
C(65)-H(65)	0.9500
C(66)-H(66)	0.9500
C(67)-C(69)	1.534(3)
C(67)-C(70)	1.537(3)
C(67)-C(68)	1.563(3)
C(69)-H(69A)	0.9800
C(69)-H(69B)	0.9800
C(69)-H(69C)	0.9800
O(61)-C(70)	1.254(3)
O(62)-C(70)	1.282(3)
O(62)-H(62O)	0.87(2)
C(68)-C(73)	1.525(3)
C(68)-C(71)	1.528(3)
C(68)-H(68)	1.0000
C(71)-O(63)	1.200(3)

C(71)-O(64)	1.331(3)
O(64)-C(72)	1.453(3)
C(72)-H(72A)	0.9800
C(72)-H(72B)	0.9800
C(72)-H(72C)	0.9800
C(73)-O(65)	1.205(3)
C(73)-O(66)	1.333(3)
O(66)-C(74)	1.453(3)
C(74)-H(74A)	0.9800
C(74)-H(74B)	0.9800
C(74)-H(74C)	0.9800

C(2)-C(1)-C(6)	118.1(2)
C(2)-C(1)-C(7)	120.0(2)
C(6)-C(1)-C(7)	121.85(19)
C(3)-C(2)-C(1)	120.9(2)
C(3)-C(2)-H(2)	119.5
C(1)-C(2)-H(2)	119.5
C(4)-C(3)-C(2)	120.5(2)
C(4)-C(3)-H(3)	119.7
C(2)-C(3)-H(3)	119.7
C(5)-C(4)-C(3)	118.9(2)
C(5)-C(4)-H(4)	120.5
C(3)-C(4)-H(4)	120.5
C(4)-C(5)-C(6)	120.8(3)
C(4)-C(5)-H(5)	119.6
C(6)-C(5)-H(5)	119.6
C(5)-C(6)-C(1)	120.7(2)
C(5)-C(6)-H(6)	119.6
C(1)-C(6)-H(6)	119.6
C(9)-C(7)-C(10)	109.25(18)
C(9)-C(7)-C(1)	112.38(17)
C(10)-C(7)-C(1)	103.34(17)
C(9)-C(7)-C(8)	111.27(17)

C(10)-C(7)-C(8) 109.38(16)
C(1)-C(7)-C(8) 110.90(17)
C(7)-C(9)-H(9A) 109.5
C(7)-C(9)-H(9B) 109.5
H(9A)-C(9)-H(9B) 109.5
C(7)-C(9)-H(9C) 109.5
H(9A)-C(9)-H(9C) 109.5
H(9B)-C(9)-H(9C) 109.5
O(1)-C(10)-O(2) 123.9(2)
O(1)-C(10)-C(7) 121.99(19)
O(2)-C(10)-C(7) 113.97(18)
C(10)-O(2)-H(2O) 110(2)
C(13)-C(8)-C(11)107.93(17)
C(13)-C(8)-C(7) 113.25(17)
C(11)-C(8)-C(7) 112.77(17)
C(13)-C(8)-H(8) 107.5
C(11)-C(8)-H(8) 107.5
C(7)-C(8)-H(8) 107.5
O(3)-C(11)-O(4) 124.8(2)
O(3)-C(11)-C(8) 125.8(2)
O(4)-C(11)-C(8) 109.47(17)
C(11)-O(4)-C(12) 115.77(17)
O(4)-C(12)-H(12A) 109.5
O(4)-C(12)-H(12B) 109.5
H(12A)-C(12)-H(12B) 109.5
O(4)-C(12)-H(12C) 109.5
H(12A)-C(12)-H(12C) 109.5
H(12B)-C(12)-H(12C) 109.5
O(5)-C(13)-O(6) 125.1(2)
O(5)-C(13)-C(8) 124.6(2)
O(6)-C(13)-C(8) 110.27(18)
C(13)-O(6)-C(14) 115.53(19)
O(6)-C(14)-H(14A) 109.5
O(6)-C(14)-H(14B) 109.5

H(14A)-C(14)-H(14B)	109.5
O(6)-C(14)-H(14C)	109.5
H(14A)-C(14)-H(14C)	109.5
H(14B)-C(14)-H(14C)	109.5
C(22)-C(21)-C(26)	118.2(2)
C(22)-C(21)-C(27)	119.74(19)
C(26)-C(21)-C(27)	121.93(19)
C(23)-C(22)-C(21)	121.1(2)
C(23)-C(22)-H(22)	119.5
C(21)-C(22)-H(22)	119.5
C(24)-C(23)-C(22)	120.2(2)
C(24)-C(23)-H(23)	119.9
C(22)-C(23)-H(23)	119.9
C(25)-C(24)-C(23)	119.4(2)
C(25)-C(24)-H(24)	120.3
C(23)-C(24)-H(24)	120.3
C(24)-C(25)-C(26)	120.4(2)
C(24)-C(25)-H(25)	119.8
C(26)-C(25)-H(25)	119.8
C(25)-C(26)-C(21)	120.7(2)
C(25)-C(26)-H(26)	119.6
C(21)-C(26)-H(26)	119.6
C(30)-C(27)-C(29)	109.43(17)
C(30)-C(27)-C(21)	104.16(16)
C(29)-C(27)-C(21)	111.82(17)
C(30)-C(27)-C(28)	108.77(17)
C(29)-C(27)-C(28)	111.18(16)
C(21)-C(27)-C(28)	111.20(16)
C(27)-C(29)-H(29A)	109.5
C(27)-C(29)-H(29B)	109.5
H(29A)-C(29)-H(29B)	109.5
C(27)-C(29)-H(29C)	109.5
H(29A)-C(29)-H(29C)	109.5
H(29B)-C(29)-H(29C)	109.5

C(30)-O(22)-H(22O)	111(2)
O(21)-C(30)-O(22)	123.39(19)
O(21)-C(30)-C(27)	122.31(18)
O(22)-C(30)-C(27)	114.11(18)
C(31)-C(28)-C(33)	110.65(17)
C(31)-C(28)-C(27)	113.89(17)
C(33)-C(28)-C(27)	110.52(17)
C(31)-C(28)-H(28)	107.1
C(33)-C(28)-H(28)	107.1
C(27)-C(28)-H(28)	107.1
O(23)-C(31)-O(24)	124.4(2)
O(23)-C(31)-C(28)	126.0(2)
O(24)-C(31)-C(28)	109.51(18)
C(31)-O(24)-C(32)	114.69(19)
O(24)-C(32)-H(32A)	109.5
O(24)-C(32)-H(32B)	109.5
H(32A)-C(32)-H(32B)	109.5
O(24)-C(32)-H(32C)	109.5
H(32A)-C(32)-H(32C)	109.5
H(32B)-C(32)-H(32C)	109.5
O(25)-C(33)-O(26)	125.2(2)
O(25)-C(33)-C(28)	123.88(19)
O(26)-C(33)-C(28)	110.87(17)
C(33)-O(26)-C(34)	115.96(17)
O(26)-C(34)-H(34A)	109.5
O(26)-C(34)-H(34B)	109.5
H(34A)-C(34)-H(34B)	109.5
O(26)-C(34)-H(34C)	109.5
H(34A)-C(34)-H(34C)	109.5
H(34B)-C(34)-H(34C)	109.5
C(46)-C(41)-C(42)	118.1(2)
C(46)-C(41)-C(47)	122.27(18)
C(42)-C(41)-C(47)	119.4(2)
C(43)-C(42)-C(41)	120.7(2)

C(43)-C(42)-H(42)	119.6
C(41)-C(42)-H(42)	119.6
C(44)-C(43)-C(42)	120.5(2)
C(44)-C(43)-H(43)	119.8
C(42)-C(43)-H(43)	119.8
C(43)-C(44)-C(45)	119.6(2)
C(43)-C(44)-H(44)	120.2
C(45)-C(44)-H(44)	120.2
C(44)-C(45)-C(46)	120.1(2)
C(44)-C(45)-H(45)	119.9
C(46)-C(45)-H(45)	119.9
C(45)-C(46)-C(41)	120.9(2)
C(45)-C(46)-H(46)	119.5
C(41)-C(46)-H(46)	119.5
C(50)-C(47)-C(49)	111.39(18)
C(50)-C(47)-C(48)	107.21(16)
C(49)-C(47)-C(48)	111.19(17)
C(50)-C(47)-C(41)	102.71(16)
C(49)-C(47)-C(41)	112.27(17)
C(48)-C(47)-C(41)	111.68(17)
C(47)-C(49)-H(49A)	109.5
C(47)-C(49)-H(49B)	109.5
H(49A)-C(49)-H(49B)	109.5
C(47)-C(49)-H(49C)	109.5
H(49A)-C(49)-H(49C)	109.5
H(49B)-C(49)-H(49C)	109.5
C(50)-O(42)-H(42O)	114(2)
O(41)-C(50)-O(42)	123.9(2)
O(41)-C(50)-C(47)	119.05(19)
O(42)-C(50)-C(47)	116.81(19)
C(51)-C(48)-C(53)	110.79(17)
C(51)-C(48)-C(47)	113.91(17)
C(53)-C(48)-C(47)	110.62(17)
C(51)-C(48)-H(48)	107.1

C(53)-C(48)-H(48)	107.1
C(47)-C(48)-H(48)	107.1
O(43)-C(51)-O(44)	124.0(2)
O(43)-C(51)-C(48)	126.1(2)
O(44)-C(51)-C(48)	109.91(18)
C(51)-O(44)-C(52)	114.4(2)
O(44)-C(52)-H(52A)	109.5
O(44)-C(52)-H(52B)	109.5
H(52A)-C(52)-H(52B)	109.5
O(44)-C(52)-H(52C)	109.5
H(52A)-C(52)-H(52C)	109.5
H(52B)-C(52)-H(52C)	109.5
O(45)-C(53)-O(46)	125.1(2)
O(45)-C(53)-C(48)	123.67(19)
O(46)-C(53)-C(48)	111.20(18)
C(53)-O(46)-C(54)	115.81(17)
O(46)-C(54)-H(54A)	109.5
O(46)-C(54)-H(54B)	109.5
H(54A)-C(54)-H(54B)	109.5
O(46)-C(54)-H(54C)	109.5
H(54A)-C(54)-H(54C)	109.5
H(54B)-C(54)-H(54C)	109.5
C(62)-C(61)-C(66)	117.9(2)
C(62)-C(61)-C(67)	121.66(19)
C(66)-C(61)-C(67)	120.5(2)
C(61)-C(62)-C(63)	120.6(2)
C(61)-C(62)-H(62)	119.7
C(63)-C(62)-H(62)	119.7
C(64)-C(63)-C(62)	120.8(2)
C(64)-C(63)-H(63)	119.6
C(62)-C(63)-H(63)	119.6
C(63)-C(64)-C(65)	119.1(2)
C(63)-C(64)-H(64)	120.4
C(65)-C(64)-H(64)	120.4

C(64)-C(65)-C(66)	120.1(2)
C(64)-C(65)-H(65)	119.9
C(66)-C(65)-H(65)	119.9
C(65)-C(66)-C(61)	121.3(2)
C(65)-C(66)-H(66)	119.3
C(61)-C(66)-H(66)	119.3
C(69)-C(67)-C(70)	109.39(17)
C(69)-C(67)-C(61)	112.62(18)
C(70)-C(67)-C(61)	105.25(17)
C(69)-C(67)-C(68)	112.17(18)
C(70)-C(67)-C(68)	107.62(17)
C(61)-C(67)-C(68)	109.45(17)
C(67)-C(69)-H(69A)	109.5
C(67)-C(69)-H(69B)	109.5
H(69A)-C(69)-H(69B)	109.5
C(67)-C(69)-H(69C)	109.5
H(69A)-C(69)-H(69C)	109.5
H(69B)-C(69)-H(69C)	109.5
C(70)-O(62)-H(62O)	112(2)
O(61)-C(70)-O(62)	123.8(2)
O(61)-C(70)-C(67)	119.88(19)
O(62)-C(70)-C(67)	116.21(18)
C(73)-C(68)-C(71)	108.71(17)
C(73)-C(68)-C(67)	112.87(17)
C(71)-C(68)-C(67)	115.66(17)
C(73)-C(68)-H(68)	106.3
C(71)-C(68)-H(68)	106.3
C(67)-C(68)-H(68)	106.3
O(63)-C(71)-O(64)	125.1(2)
O(63)-C(71)-C(68)	122.34(19)
O(64)-C(71)-C(68)	112.61(18)
C(71)-O(64)-C(72)	117.15(18)
O(64)-C(72)-H(72A)	109.5
O(64)-C(72)-H(72B)	109.5

H(72A)-C(72)-H(72B)	109.5
O(64)-C(72)-H(72C)	109.5
H(72A)-C(72)-H(72C)	109.5
H(72B)-C(72)-H(72C)	109.5
O(65)-C(73)-O(66)	124.9(2)
O(65)-C(73)-C(68)	124.6(2)
O(66)-C(73)-C(68)	110.42(18)
C(73)-O(66)-C(74)	115.95(18)
O(66)-C(74)-H(74A)	109.5
O(66)-C(74)-H(74B)	109.5
H(74A)-C(74)-H(74B)	109.5
O(66)-C(74)-H(74C)	109.5
H(74A)-C(74)-H(74C)	109.5
H(74B)-C(74)-H(74C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 2.12. *Anisotropic displacement parameters (Å2x 103) for V24319_t4. The anisotropic displacement factor exponent takes the form: -2p2[h2 a*2U11 + ... + 2 h k a* b* U12]*

	U11	U22	U33	U23	U13	U12
C(1)	18(1)	13(1)	17(1)	7(1)	2(1)	4(1)
C(2)	22(1)	17(1)	27(1)	4(1)	8(1)	-1(1)
C(3)	35(1)	23(1)	26(1)	3(1)	15(1)	0(1)
C(4)	42(2)	24(1)	18(1)	2(1)	6(1)	-1(1)
C(5)	35(1)	35(1)	20(1)	3(1)	-2(1)	-7(1)
C(6)	20(1)	30(1)	19(1)	4(1)	3(1)	-2(1)
C(7)	12(1)	13(1)	19(1)	6(1)	1(1)	2(1)
C(9)	11(1)	17(1)	26(1)	8(1)	0(1)	2(1)
C(10)	14(1)	15(1)	14(1)	4(1)	1(1)	2(1)
O(1)	14(1)	15(1)	23(1)	6(1)	-2(1)	1(1)
O(2)	13(1)	13(1)	28(1)	8(1)	-2(1)	2(1)
C(8)	11(1)	13(1)	16(1)	4(1)	1(1)	2(1)
C(11)	16(1)	14(1)	13(1)	4(1)	1(1)	0(1)
O(3)	16(1)	16(1)	30(1)	7(1)	1(1)	4(1)
O(4)	14(1)	14(1)	22(1)	2(1)	0(1)	-1(1)
C(12)	22(1)	14(1)	29(1)	2(1)	1(1)	-4(1)
C(13)	11(1)	16(1)	21(1)	3(1)	2(1)	2(1)
O(5)	24(1)	20(1)	18(1)	6(1)	1(1)	1(1)
O(6)	30(1)	14(1)	18(1)	0(1)	2(1)	4(1)
C(14)	44(2)	21(1)	21(1)	-4(1)	2(1)	5(1)
C(21)	17(1)	10(1)	14(1)	3(1)	-1(1)	3(1)
C(22)	18(1)	21(1)	22(1)	-1(1)	-2(1)	1(1)
C(23)	26(1)	27(1)	22(1)	-5(1)	-8(1)	3(1)
C(24)	32(1)	22(1)	14(1)	0(1)	-2(1)	9(1)
C(25)	25(1)	24(1)	18(1)	4(1)	5(1)	3(1)
C(26)	18(1)	19(1)	17(1)	1(1)	-1(1)	1(1)
C(27)	11(1)	11(1)	13(1)	2(1)	-1(1)	1(1)

C(29)	13(1)	15(1)	19(1)	2(1)	0(1)	3(1)
O(21)	13(1)	13(1)	22(1)	5(1)	0(1)	0(1)
O(22)	12(1)	12(1)	19(1)	6(1)	0(1)	2(1)
C(30)	14(1)	12(1)	10(1)	-1(1)	0(1)	2(1)
C(28)	12(1)	12(1)	14(1)	2(1)	-1(1)	0(1)
C(31)	19(1)	12(1)	11(1)	0(1)	1(1)	-1(1)
O(23)	23(1)	16(1)	21(1)	6(1)	-3(1)	2(1)
O(24)	20(1)	16(1)	26(1)	7(1)	2(1)	-4(1)
C(32)	36(1)	21(1)	34(1)	14(1)	-1(1)	-9(1)
C(33)	10(1)	12(1)	16(1)	2(1)	-1(1)	2(1)
O(25)	24(1)	15(1)	15(1)	4(1)	1(1)	0(1)
O(26)	21(1)	11(1)	13(1)	0(1)	0(1)	-1(1)
C(34)	24(1)	16(1)	12(1)	-1(1)	-2(1)	1(1)
C(41)	19(1)	11(1)	14(1)	3(1)	3(1)	-1(1)
C(42)	23(1)	18(1)	19(1)	1(1)	2(1)	6(1)
C(43)	30(1)	21(1)	22(1)	-3(1)	7(1)	3(1)
C(44)	34(1)	22(1)	15(1)	-2(1)	2(1)	-7(1)
C(45)	20(1)	28(1)	20(1)	3(1)	-2(1)	-4(1)
C(46)	16(1)	19(1)	16(1)	1(1)	2(1)	-1(1)
C(47)	14(1)	11(1)	14(1)	1(1)	1(1)	1(1)
C(49)	13(1)	16(1)	19(1)	2(1)	2(1)	1(1)
O(41)	16(1)	16(1)	22(1)	3(1)	2(1)	-2(1)
O(42)	21(1)	13(1)	24(1)	6(1)	-1(1)	3(1)
C(50)	15(1)	12(1)	11(1)	-2(1)	-1(1)	2(1)
C(48)	13(1)	13(1)	13(1)	1(1)	0(1)	1(1)
C(51)	22(1)	12(1)	12(1)	0(1)	1(1)	4(1)
O(43)	28(1)	19(1)	27(1)	6(1)	10(1)	2(1)
O(44)	26(1)	16(1)	24(1)	6(1)	-5(1)	6(1)
C(52)	50(2)	17(1)	26(1)	7(1)	-8(1)	10(1)
C(53)	11(1)	12(1)	16(1)	1(1)	2(1)	0(1)
O(45)	27(1)	15(1)	17(1)	4(1)	1(1)	2(1)
O(46)	22(1)	12(1)	14(1)	0(1)	1(1)	2(1)
C(54)	24(1)	17(1)	14(1)	-2(1)	0(1)	0(1)
C(61)	18(1)	12(1)	16(1)	6(1)	-2(1)	2(1)

C(62)	19(1)	28(1)	22(1)	1(1)	-2(1)	1(1)
C(63)	24(1)	31(1)	29(1)	-2(1)	-11(1)	1(1)
C(64)	38(1)	21(1)	16(1)	2(1)	-8(1)	6(1)
C(65)	34(1)	22(1)	18(1)	3(1)	4(1)	0(1)
C(66)	22(1)	18(1)	21(1)	2(1)	2(1)	-2(1)
C(67)	13(1)	14(1)	15(1)	4(1)	-1(1)	2(1)
C(69)	13(1)	18(1)	20(1)	6(1)	1(1)	2(1)
O(61)	15(1)	16(1)	25(1)	5(1)	2(1)	-1(1)
O(62)	20(1)	14(1)	21(1)	5(1)	2(1)	3(1)
C(70)	14(1)	15(1)	11(1)	2(1)	-1(1)	2(1)
C(68)	11(1)	13(1)	16(1)	3(1)	0(1)	1(1)
C(71)	18(1)	15(1)	11(1)	2(1)	0(1)	1(1)
O(63)	20(1)	17(1)	33(1)	2(1)	1(1)	7(1)
O(64)	17(1)	12(1)	22(1)	4(1)	2(1)	-1(1)
C(72)	28(1)	13(1)	26(1)	1(1)	5(1)	-3(1)
C(73)	12(1)	14(1)	17(1)	2(1)	-1(1)	1(1)
O(65)	22(1)	19(1)	17(1)	5(1)	0(1)	1(1)
O(66)	25(1)	14(1)	18(1)	1(1)	-3(1)	0(1)
C(74)	34(1)	20(1)	19(1)	-4(1)	-5(1)	3(1)

Table 2.13. *Hydrogen coordinates (x 104) and isotropic displacement parameters (Å2x 10 3)for V24319_t4.*

	x	y	z	U(eq)		
H(2)	11773	2466	1824	27		
H(3)	11513	1826	344	33		
H(4)	8165	1083	-256	34		
H(5)	5085	996	641	37		
H(6)	5295	1675	2109	28		
H(9A)	12125	2971	3202	27		
H(9B)	11404	1983	3483	27		
H(9C)	11009	2871	4141	27		
H(2O)	6160(50)		4262(16)		2720(20)	26
H(8)	5436	2355	3419	16		
H(12A)	5192	-454	3110	33		
H(12B)	2796	-363	3514	33		
H(12C)	4908	-317	4164	33		
H(14A)	6049	3822	5915	43		
H(14B)	7467	4666	5566	43		
H(14C)	8686	3860	5901	43		
H(22)	4264	6046	673	25		
H(23)	4680	5627	-841	31		
H(24)	8087	5939	-1496	27		
H(25)	11087	6653	-619	27		
H(26)	10682	7069	898	22		
H(29A)	3709	6564	2025	23		
H(29B)	4440	7580	1822	23		
H(29C)	4723	7311	2806	23		
H(22O)	9670(50)		5290(17)		2620(20)	21
H(28)	10381	7345	2252	15		
H(32A)	10687	9654	940	45		

H(32B)	12881	9915	1546	45			
H(32C)	10530	10119	1940	45			
H(34A)	7576	8585	4811	26			
H(34B)	8947	9544	4729	26			
H(34C)	10213	8690	4915	26			
H(42)	-1276	4114	9313	24			
H(43)	-527	4624	10812	30			
H(44)	2760	4347	11489	30			
H(45)	5343	3568	10655	28			
H(46)	4633	3073	9148	21			
H(49A)	-2121	3580	7994	24			
H(49B)	-1922	2554	8175	24			
H(49C)	-1539	2843	7200	24			
H(42O)	1230(50)		5203(17)		7390(20)	29	
H(48)	4095	2735	7791	16			
H(52A)	3122	485	9178	45			
H(52B)	5206	191	8621	45			
H(52C)	2773	-10	8184	45			
H(54A)	418	1320	5251	28			
H(54B)	1956	517	5322	28			
H(54C)	3033	1503	5149	28			
H(62)	9098	8335	7684	28			
H(63)	9623	9080	9125	35			
H(64)	6761	9046	10133	30			
H(65)	3265	8337	9661	30			
H(66)	2710	7615	8216	24			
H(69A)	8677	6984	6705	25			
H(69B)	8300	7882	6262	25			
H(69C)	7332	6907	5781	25			
H(62O)	5190(50)		5306(18)		7220(20)	27	
H(68)	2286	7643	6598	16			
H(72A)	6356	10359	5875	34			
H(72B)	8231	10307	6611	34			
H(72C)	5749	10429	6903	34			

H(74A)	1775	6312	4050	37
H(74B)	2656	5422	4368	37
H(74C)	4364	6200	4051	37

Table 2.14. *Torsion angles [°] for V24319_t4.*

C(6)-C(1)-C(2)-C(3)	-0.2(3)
C(7)-C(1)-C(2)-C(3)	-175.9(2)
C(1)-C(2)-C(3)-C(4)	-0.6(4)
C(2)-C(3)-C(4)-C(5)	0.3(4)
C(3)-C(4)-C(5)-C(6)	0.8(4)
C(4)-C(5)-C(6)-C(1)	-1.7(4)
C(2)-C(1)-C(6)-C(5)	1.3(4)
C(7)-C(1)-C(6)-C(5)	176.9(2)
C(2)-C(1)-C(7)-C(9)	-34.2(3)
C(6)-C(1)-C(7)-C(9)	150.4(2)
C(2)-C(1)-C(7)-C(10)	83.5(2)
C(6)-C(1)-C(7)-C(10)	-92.0(2)
C(2)-C(1)-C(7)-C(8)	-159.40(19)
C(6)-C(1)-C(7)-C(8)	25.1(3)
C(9)-C(7)-C(10)-O(1)	18.6(3)
C(1)-C(7)-C(10)-O(1)	-101.2(2)
C(8)-C(7)-C(10)-O(1)	140.6(2)
C(9)-C(7)-C(10)-O(2)	-165.94(18)
C(1)-C(7)-C(10)-O(2)	74.2(2)
C(8)-C(7)-C(10)-O(2)	-43.9(2)
C(9)-C(7)-C(8)-C(13)	50.2(2)
C(10)-C(7)-C(8)-C(13)	-70.6(2)
C(1)-C(7)-C(8)-C(13)	176.03(17)
C(9)-C(7)-C(8)-C(11)	-72.8(2)
C(10)-C(7)-C(8)-C(11)	166.43(18)
C(1)-C(7)-C(8)-C(11)	53.1(2)
C(13)-C(8)-C(11)-O(3)	-84.0(3)
C(7)-C(8)-C(11)-O(3)	41.9(3)
C(13)-C(8)-C(11)-O(4)	95.1(2)
C(7)-C(8)-C(11)-O(4)	-139.06(18)
O(3)-C(11)-O(4)-C(12)	1.2(3)

C(8)-C(11)-O(4)-C(12)	-177.85(19)
C(11)-C(8)-C(13)-O(5)	-5.0(3)
C(7)-C(8)-C(13)-O(5)	-130.6(2)
C(11)-C(8)-C(13)-O(6)	177.08(17)
C(7)-C(8)-C(13)-O(6)	51.5(2)
O(5)-C(13)-O(6)-C(14)	0.9(3)
C(8)-C(13)-O(6)-C(14)	178.84(19)
C(26)-C(21)-C(22)-C(23)	-0.9(3)
C(27)-C(21)-C(22)-C(23)	-176.6(2)
C(21)-C(22)-C(23)-C(24)	0.1(4)
C(22)-C(23)-C(24)-C(25)	0.6(4)
C(23)-C(24)-C(25)-C(26)	-0.4(4)
C(24)-C(25)-C(26)-C(21)	-0.4(4)
C(22)-C(21)-C(26)-C(25)	1.1(3)
C(27)-C(21)-C(26)-C(25)	176.7(2)
C(22)-C(21)-C(27)-C(30)	82.3(2)
C(26)-C(21)-C(27)-C(30)	-93.3(2)
C(22)-C(21)-C(27)-C(29)	-35.8(3)
C(26)-C(21)-C(27)-C(29)	148.6(2)
C(22)-C(21)-C(27)-C(28)	-160.76(19)
C(26)-C(21)-C(27)-C(28)	23.7(3)
C(29)-C(27)-C(30)-O(21)	21.2(3)
C(21)-C(27)-C(30)-O(21)	-98.5(2)
C(28)-C(27)-C(30)-O(21)	142.8(2)
C(29)-C(27)-C(30)-O(22)	-163.64(18)
C(21)-C(27)-C(30)-O(22)	76.7(2)
C(28)-C(27)-C(30)-O(22)	-42.0(2)
C(30)-C(27)-C(28)-C(31)	172.09(17)
C(29)-C(27)-C(28)-C(31)	-67.4(2)
C(21)-C(27)-C(28)-C(31)	58.0(2)
C(30)-C(27)-C(28)-C(33)	-62.6(2)
C(29)-C(27)-C(28)-C(33)	57.9(2)
C(21)-C(27)-C(28)-C(33)	-176.76(16)
C(33)-C(28)-C(31)-O(23)	-83.6(3)

C(27)-C(28)-C(31)-O(23) 41.6(3)
C(33)-C(28)-C(31)-O(24) 95.4(2)
C(27)-C(28)-C(31)-O(24) -139.40(18)
O(23)-C(31)-O(24)-C(32) 4.8(3)
C(28)-C(31)-O(24)-C(32) -174.1(2)
C(31)-C(28)-C(33)-O(25) 166.0(2)
C(27)-C(28)-C(33)-O(25) 38.9(3)
C(31)-C(28)-C(33)-O(26) -15.5(2)
C(27)-C(28)-C(33)-O(26) -142.58(17)
O(25)-C(33)-O(26)-C(34) -1.6(3)
C(28)-C(33)-O(26)-C(34) 179.94(17)
C(46)-C(41)-C(42)-C(43) 0.3(3)
C(47)-C(41)-C(42)-C(43) -175.2(2)
C(41)-C(42)-C(43)-C(44) -0.6(4)
C(42)-C(43)-C(44)-C(45) 0.4(4)
C(43)-C(44)-C(45)-C(46) 0.1(4)
C(44)-C(45)-C(46)-C(41) -0.4(4)
C(42)-C(41)-C(46)-C(45) 0.2(3)
C(47)-C(41)-C(46)-C(45) 175.6(2)
C(46)-C(41)-C(47)-C(50) -89.9(2)
C(42)-C(41)-C(47)-C(50) 85.4(2)
C(46)-C(41)-C(47)-C(49) 150.3(2)
C(42)-C(41)-C(47)-C(49) -34.4(3)
C(46)-C(41)-C(47)-C(48) 24.7(3)
C(42)-C(41)-C(47)-C(48) -160.06(19)
C(49)-C(47)-C(50)-O(41) -163.29(19)
C(48)-C(47)-C(50)-O(41) -41.4(3)
C(41)-C(47)-C(50)-O(41) 76.3(2)
C(49)-C(47)-C(50)-O(42) 21.7(3)
C(48)-C(47)-C(50)-O(42) 143.59(19)
C(41)-C(47)-C(50)-O(42) -98.6(2)
C(50)-C(47)-C(48)-C(51) 170.13(18)
C(49)-C(47)-C(48)-C(51) -67.9(2)
C(41)-C(47)-C(48)-C(51) 58.4(2)

C(50)-C(47)-C(48)-C(53) -64.3(2)
C(49)-C(47)-C(48)-C(53) 57.7(2)
C(41)-C(47)-C(48)-C(53) -176.06(17)
C(53)-C(48)-C(51)-O(43) -82.8(3)
C(47)-C(48)-C(51)-O(43) 42.7(3)
C(53)-C(48)-C(51)-O(44) 96.2(2)
C(47)-C(48)-C(51)-O(44) -138.35(19)
O(43)-C(51)-O(44)-C(52) 4.7(3)
C(48)-C(51)-O(44)-C(52) -174.30(19)
C(51)-C(48)-C(53)-O(45) 165.2(2)
C(47)-C(48)-C(53)-O(45) 37.8(3)
C(51)-C(48)-C(53)-O(46) -16.3(2)
C(47)-C(48)-C(53)-O(46) -143.57(17)
O(45)-C(53)-O(46)-C(54) 0.5(3)
C(48)-C(53)-O(46)-C(54) -178.02(17)
C(66)-C(61)-C(62)-C(63) 1.7(4)
C(67)-C(61)-C(62)-C(63) -178.0(2)
C(61)-C(62)-C(63)-C(64) 0.6(4)
C(62)-C(63)-C(64)-C(65) -2.3(4)
C(63)-C(64)-C(65)-C(66) 1.6(4)
C(64)-C(65)-C(66)-C(61) 0.7(4)
C(62)-C(61)-C(66)-C(65) -2.3(3)
C(67)-C(61)-C(66)-C(65) 177.4(2)
C(62)-C(61)-C(67)-C(69) 8.9(3)
C(66)-C(61)-C(67)-C(69) -170.8(2)
C(62)-C(61)-C(67)-C(70) 128.0(2)
C(66)-C(61)-C(67)-C(70) -51.7(2)
C(62)-C(61)-C(67)-C(68) -116.6(2)
C(66)-C(61)-C(67)-C(68) 63.7(2)
C(69)-C(67)-C(70)-O(61) -158.2(2)
C(61)-C(67)-C(70)-O(61) 80.6(2)
C(68)-C(67)-C(70)-O(61) -36.1(3)
C(69)-C(67)-C(70)-O(62) 25.2(3)
C(61)-C(67)-C(70)-O(62) -96.0(2)

C(68)-C(67)-C(70)-O(62) 147.31(19)
C(69)-C(67)-C(68)-C(73) 45.3(2)
C(70)-C(67)-C(68)-C(73) -75.1(2)
C(61)-C(67)-C(68)-C(73) 171.05(16)
C(69)-C(67)-C(68)-C(71) -80.8(2)
C(70)-C(67)-C(68)-C(71) 158.84(17)
C(61)-C(67)-C(68)-C(71) 45.0(2)
C(73)-C(68)-C(71)-O(63) 92.3(2)
C(67)-C(68)-C(71)-O(63) -139.5(2)
C(73)-C(68)-C(71)-O(64) -87.1(2)
C(67)-C(68)-C(71)-O(64) 41.1(3)
O(63)-C(71)-O(64)-C(72) 1.5(3)
C(68)-C(71)-O(64)-C(72) -179.10(19)
C(71)-C(68)-C(73)-O(65) 0.3(3)
C(67)-C(68)-C(73)-O(65) -129.4(2)
C(71)-C(68)-C(73)-O(66) -178.04(17)
C(67)-C(68)-C(73)-O(66) 52.2(2)
O(65)-C(73)-O(66)-C(74) 1.8(3)
C(68)-C(73)-O(66)-C(74) -179.86(18)

Symmetry transformations used to generate equivalent atoms:

***Table 2.15**. Hydrogen bonds for V24319_t4 [Å and °].*

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(12)-H(12A)...O(23)#1	0.98	2.64	3.622(3)	176.7
C(12)-H(12B)...O(26)#2	0.98	2.59	3.519(3)	158.0
C(14)-H(14C)...O(45)#3	0.98	2.63	3.547(3)	155.9
O(22)-H(22O)...O(1)	0.86(2)	1.78(2)	2.628(2)	173(3)
C(34)-H(34A)...O(64)	0.98	2.60	3.188(3)	118.6
C(34)-H(34A)...O(65)	0.98	2.51	3.444(3)	158.3
C(34)-H(34B)...O(3)#4	0.98	2.61	3.329(3)	130.6
C(34)-H(34C)...O(65)#3	0.98	2.50	3.359(3)	145.6
O(42)-H(42O)...O(61)	0.85(2)	1.76(2)	2.606(2)	178(3)
C(52)-H(52C)...O(63)#1	0.98	2.66	3.454(3)	138.6
C(54)-H(54A)...O(5)#5	0.98	2.57	3.491(3)	156.7
C(54)-H(54C)...O(5)	0.98	2.52	3.368(3)	144.9
O(62)-H(62O)...O(41)	0.87(2)	1.73(2)	2.599(2)	177(3)
C(72)-H(72C)...O(44)#4	0.98	2.58	3.552(3)	169.7
C(74)-H(74A)...O(25)#5	0.98	2.65	3.583(3)	158.5

Symmetry transformations used to generate equivalent atoms:
#1 x,y-1,z #2 x-1,y-1,z #3 x+1,y,z #4 x,y+1,z
#5 x-1,y,z

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APPENDIX 3

Spectra Relevant to Chapter 2:

Mo-Catalyzed Asymmetric Allylic Alkylation Enabling the Construction of Highly Enantioenriched 1,4-Dicarbonyl Scaffolds

Figure A3.1. *^{1}H NMR (500 MHz, DMSO-d6) of* ***$Mo(CO)_3(pyr)_3$.***

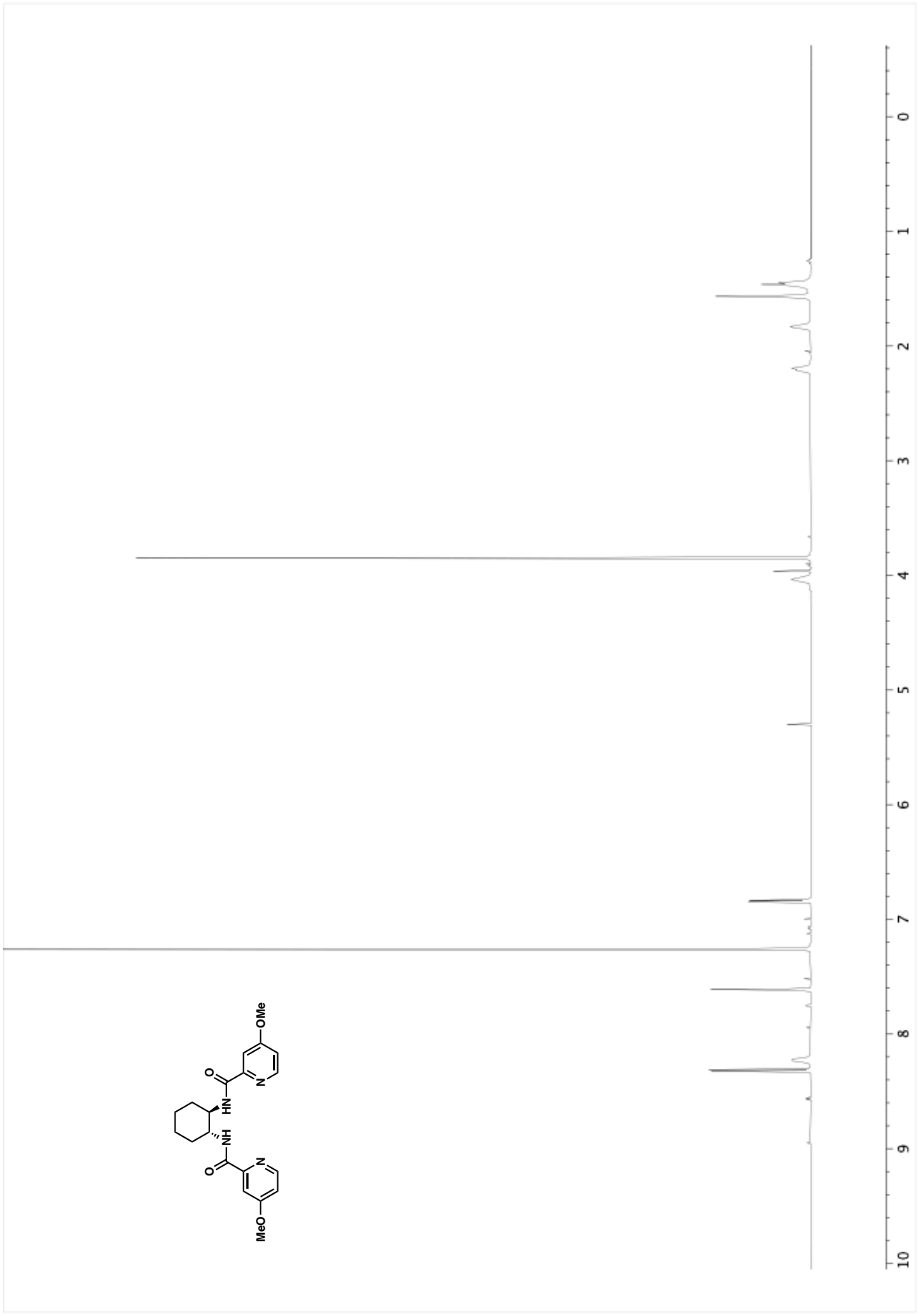

Figure A3.2. *^{1}H NMR (400 MHz, $CDCl_3$) of* ***L4.***

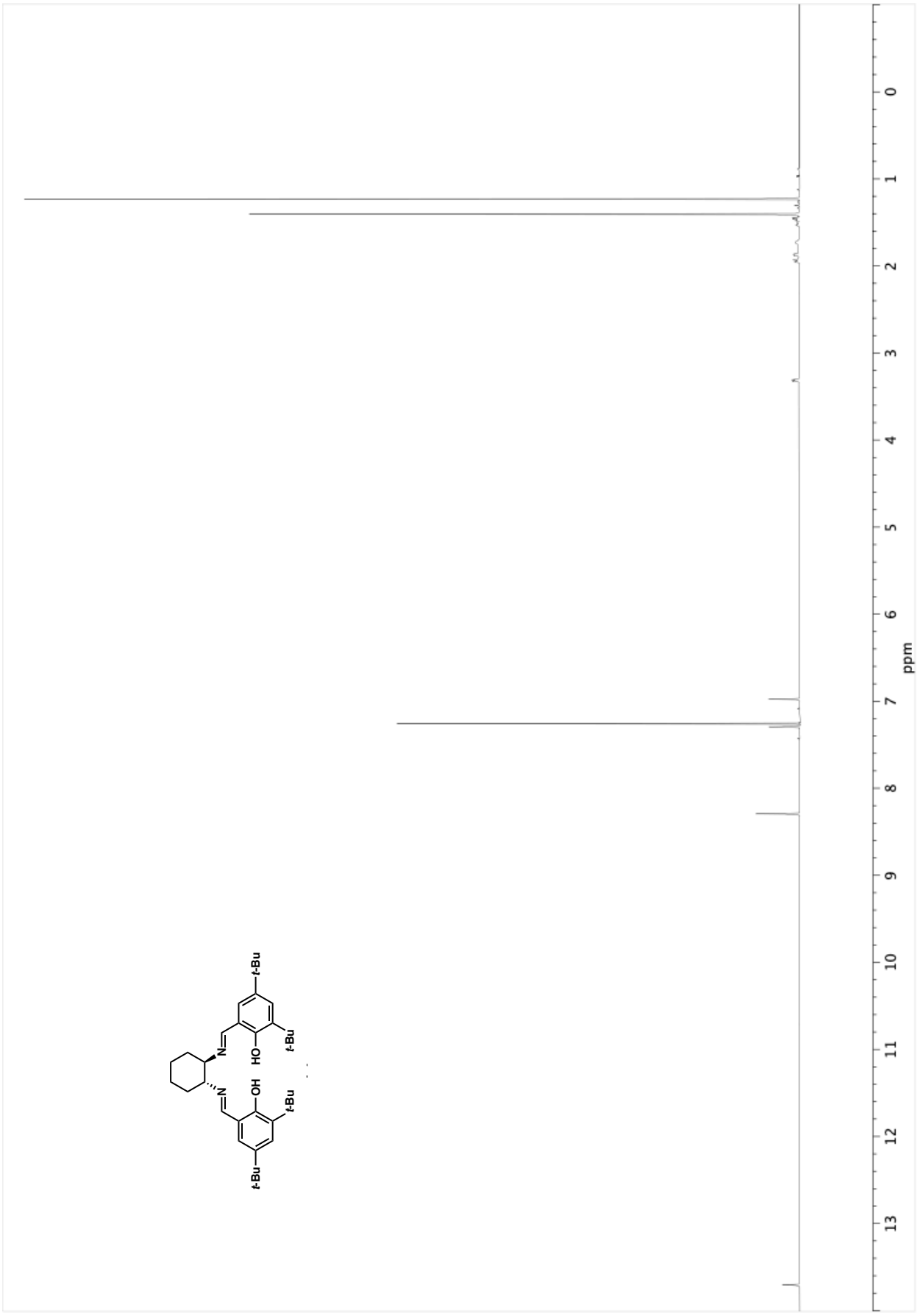

Figure A3.3. *^{1}H NMR (600 MHz, $CDCl_3$) of **L7**.*

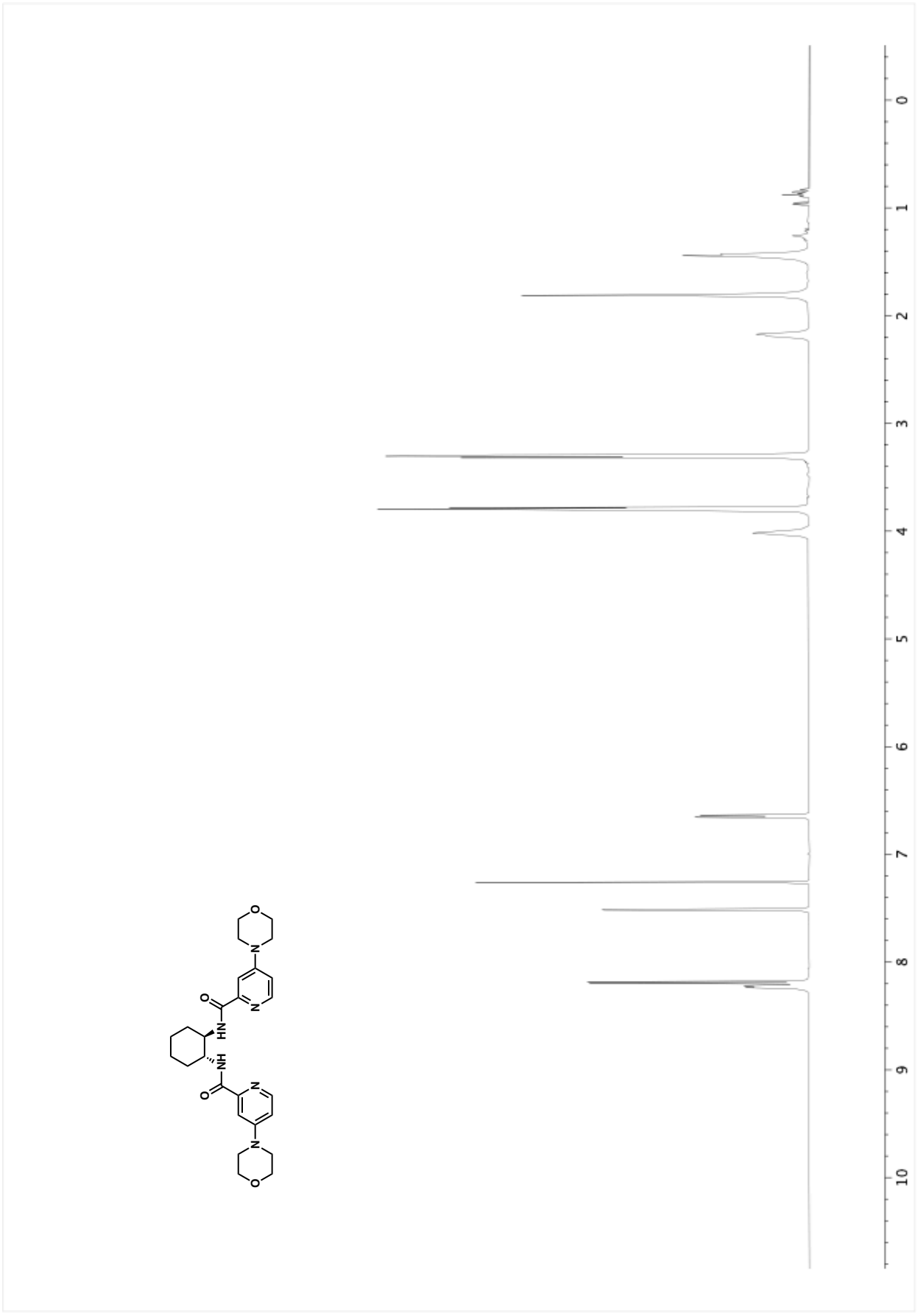

Figure A3.4. *^{1}H NMR (400 MHz, $CDCl_3$) of* ***L8.***

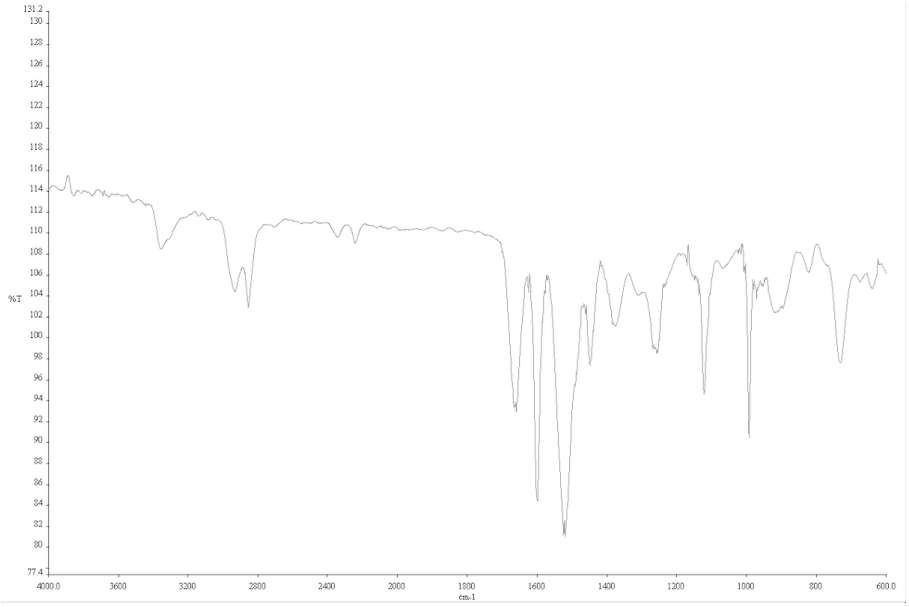

Figure A3.5. *Infrared spectrum (Thin Film, NaCl) of* ***L8****.*

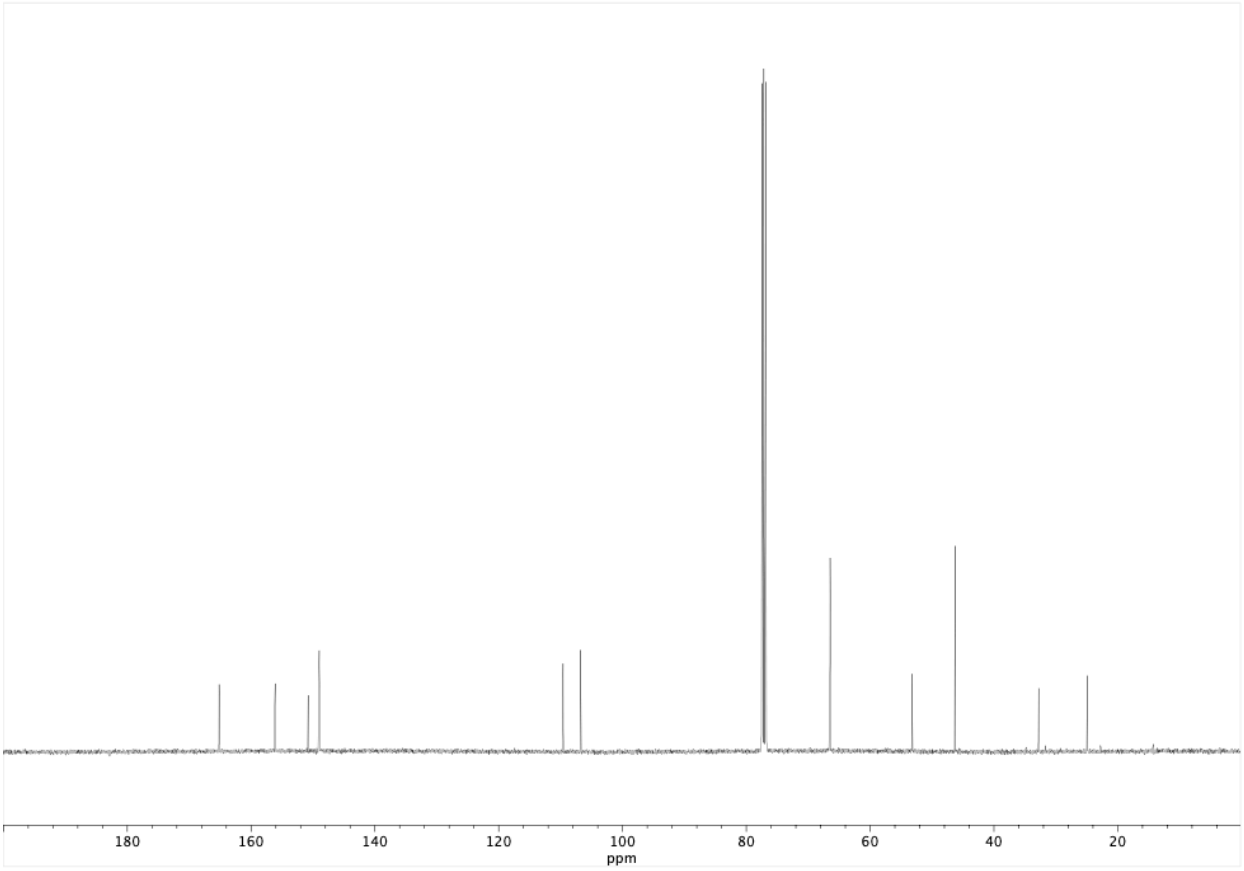

Figure A3.6. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***L8.***

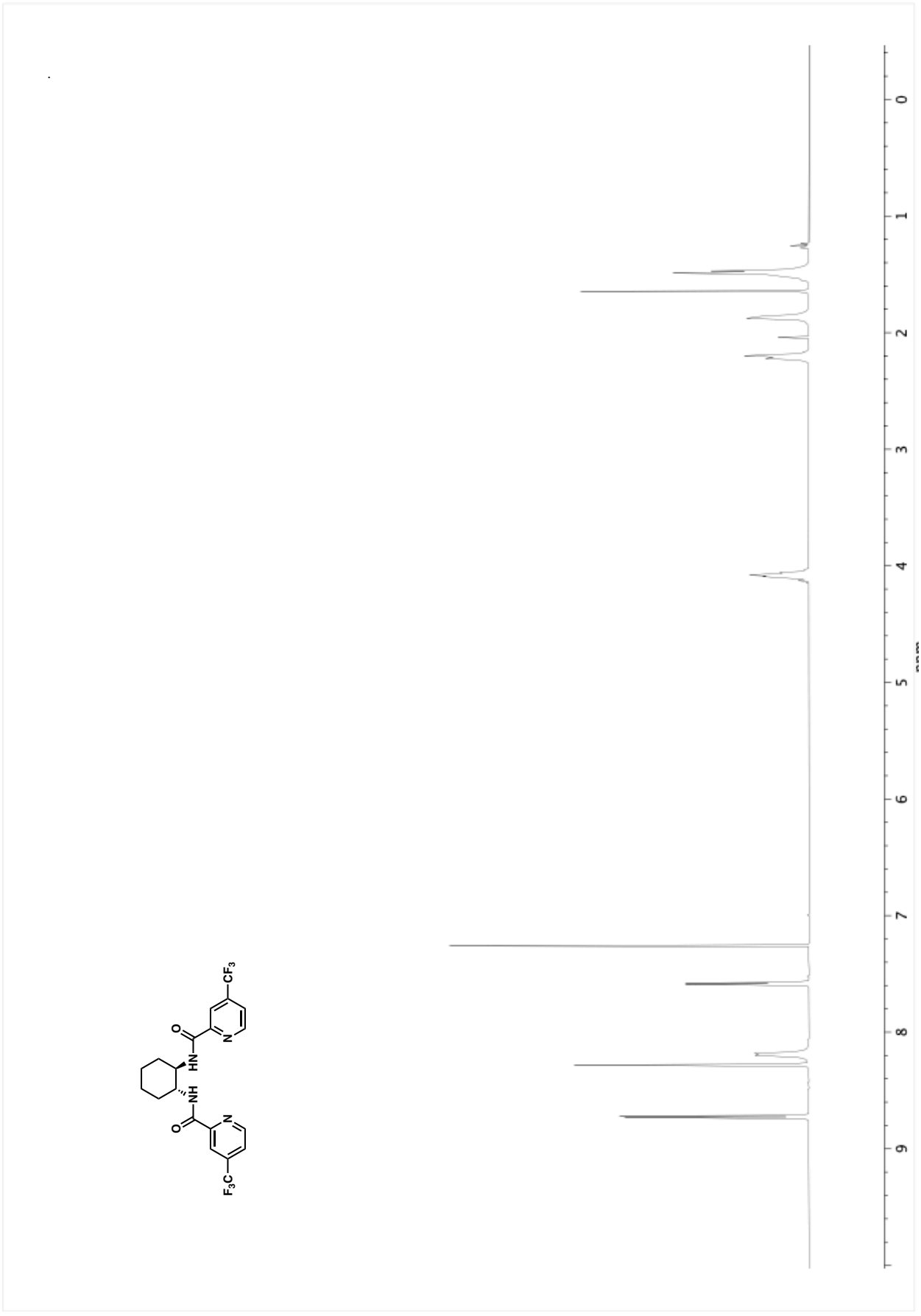

Figure A3.7. *^{1}H NMR (400 MHz, $CDCl_3$) of* ***L9.***

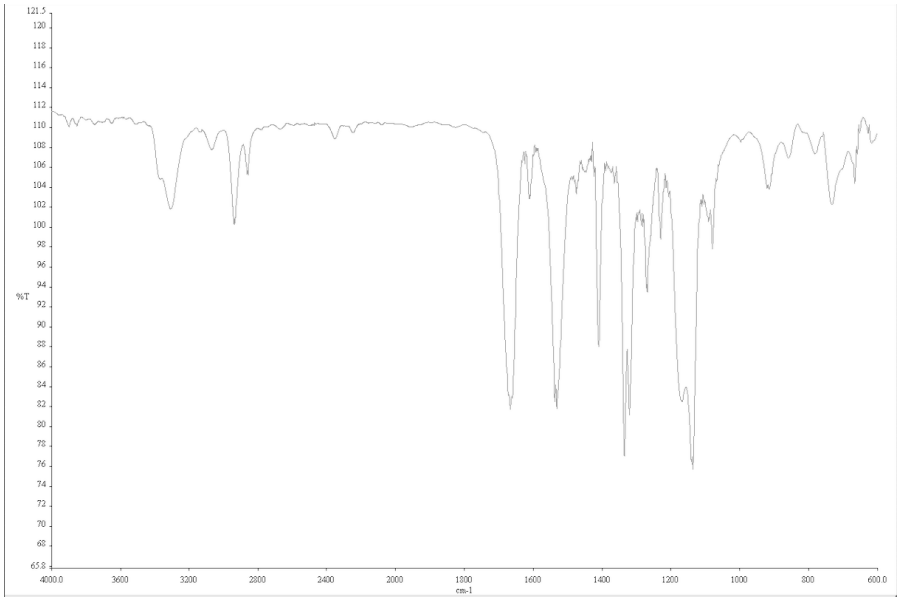

Figure A3.8. *Infrared spectrum (Thin Film, NaCl) of* ***L9.***

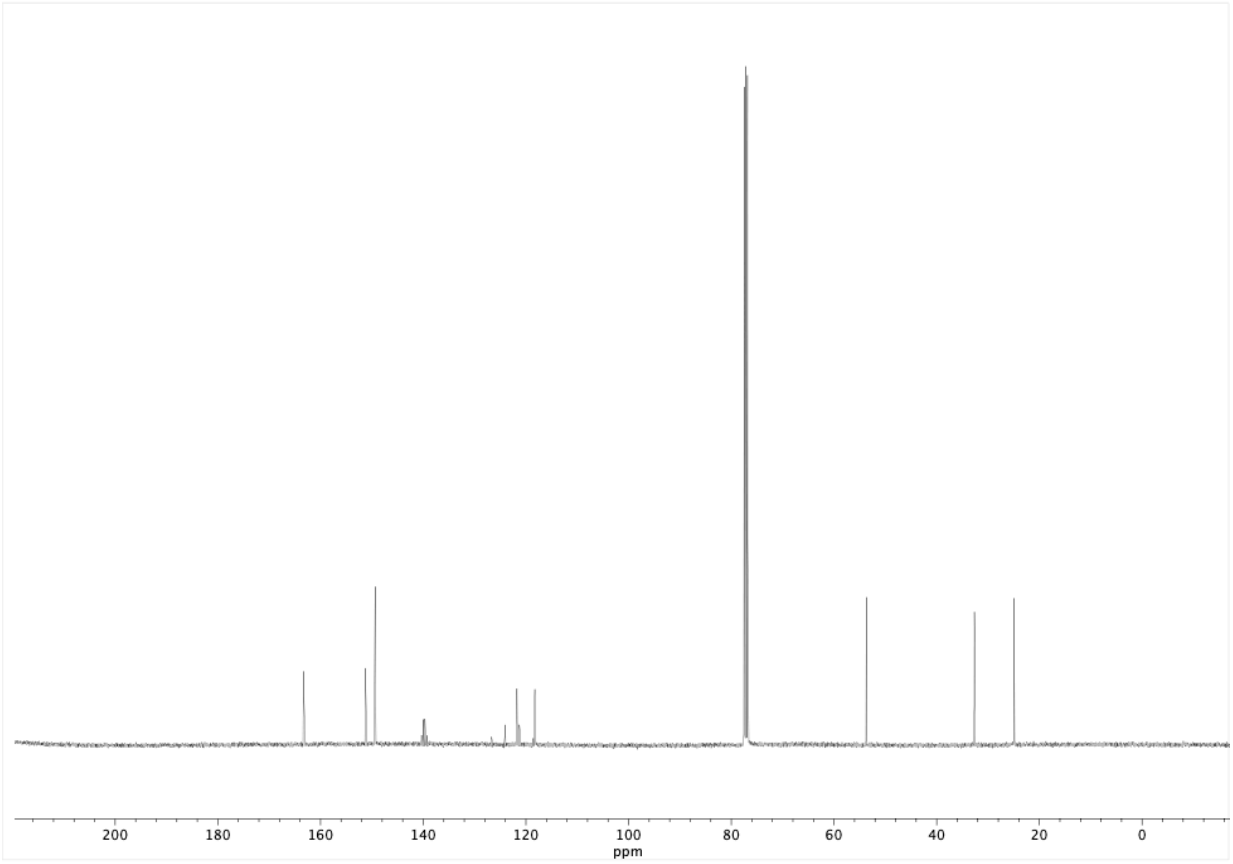

Figure A3.9. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***L9.***

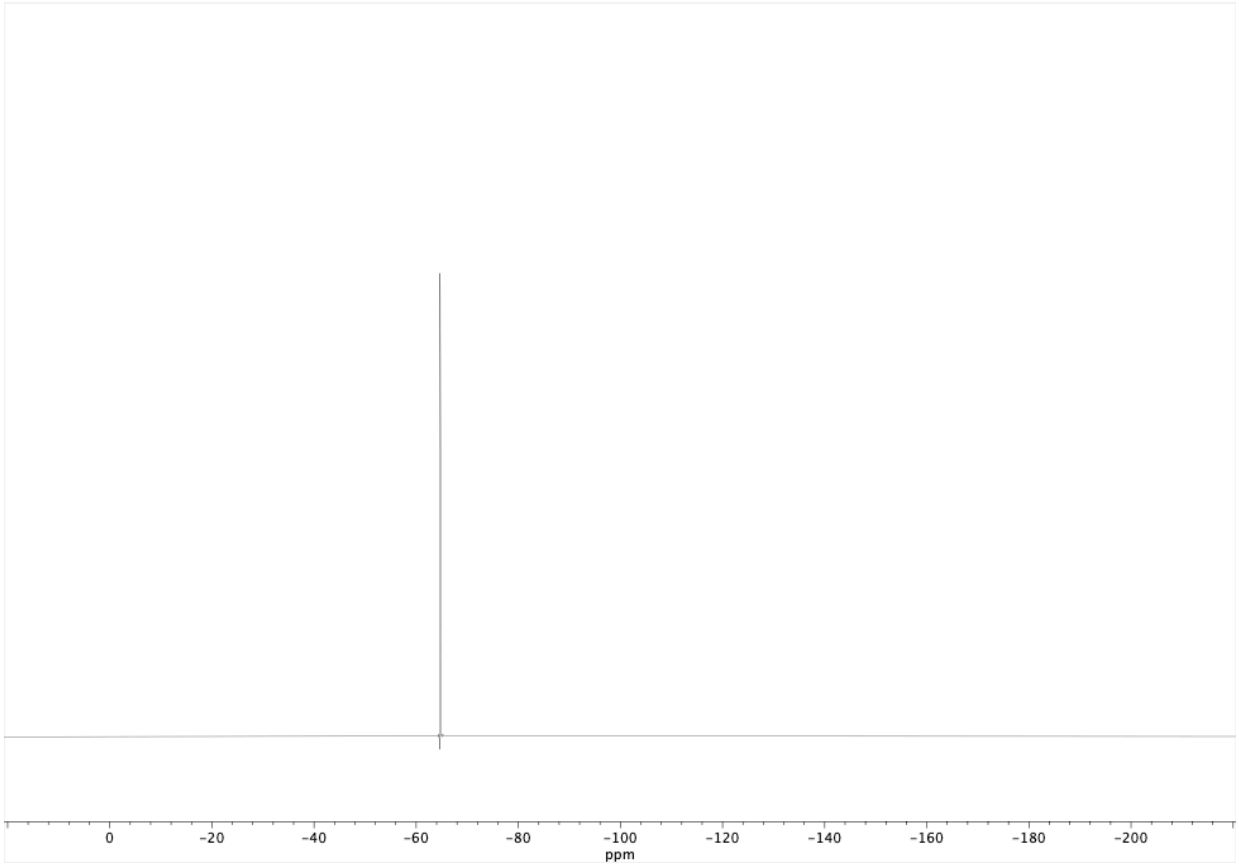

Figure A3.10. *^{19}F NMR (376 MHz, $CDCl_3$) of* ***L9.***

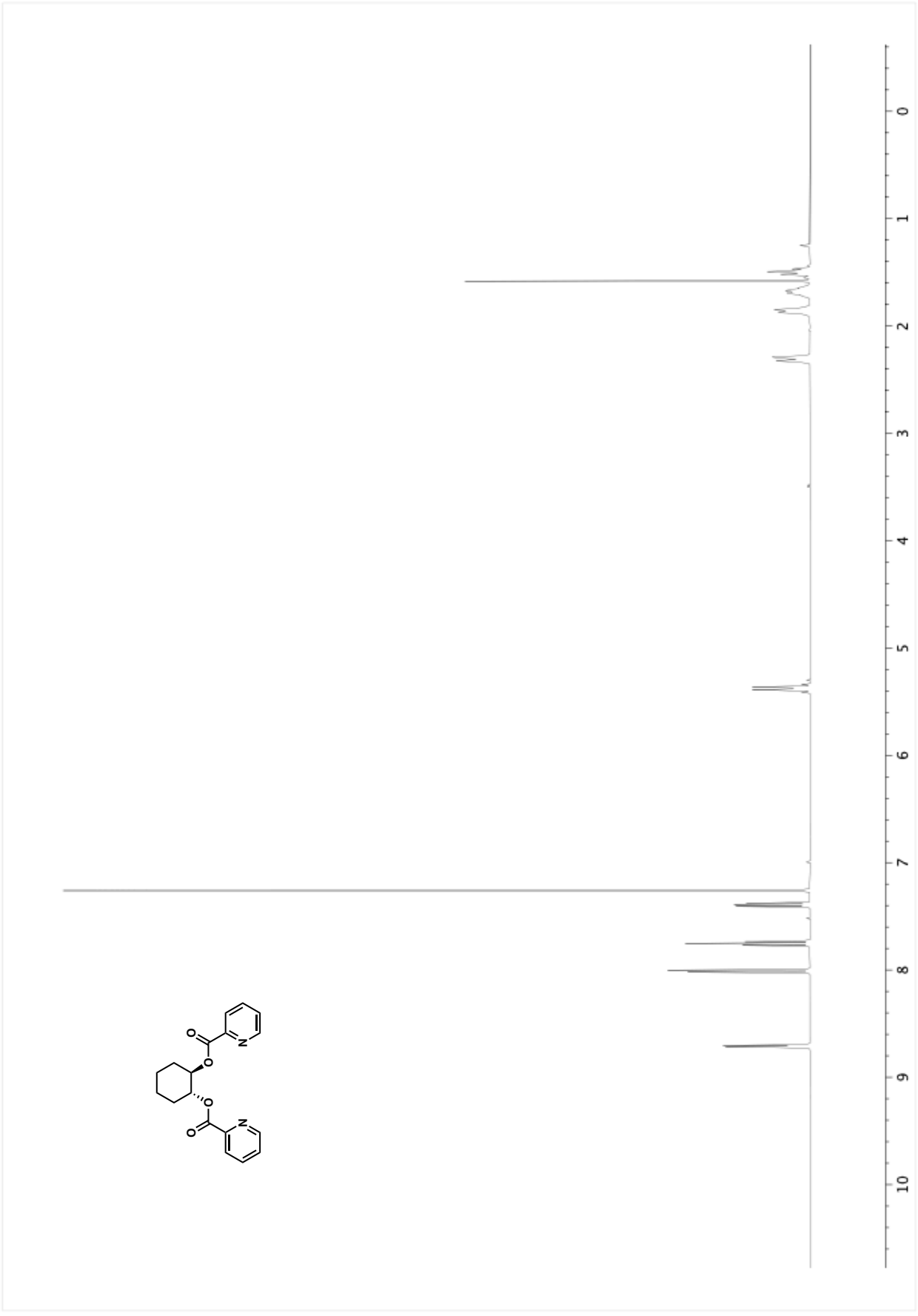

Figure A3.11. *^1H NMR (400 MHz, $CDCl_3$) of* ***L11.***

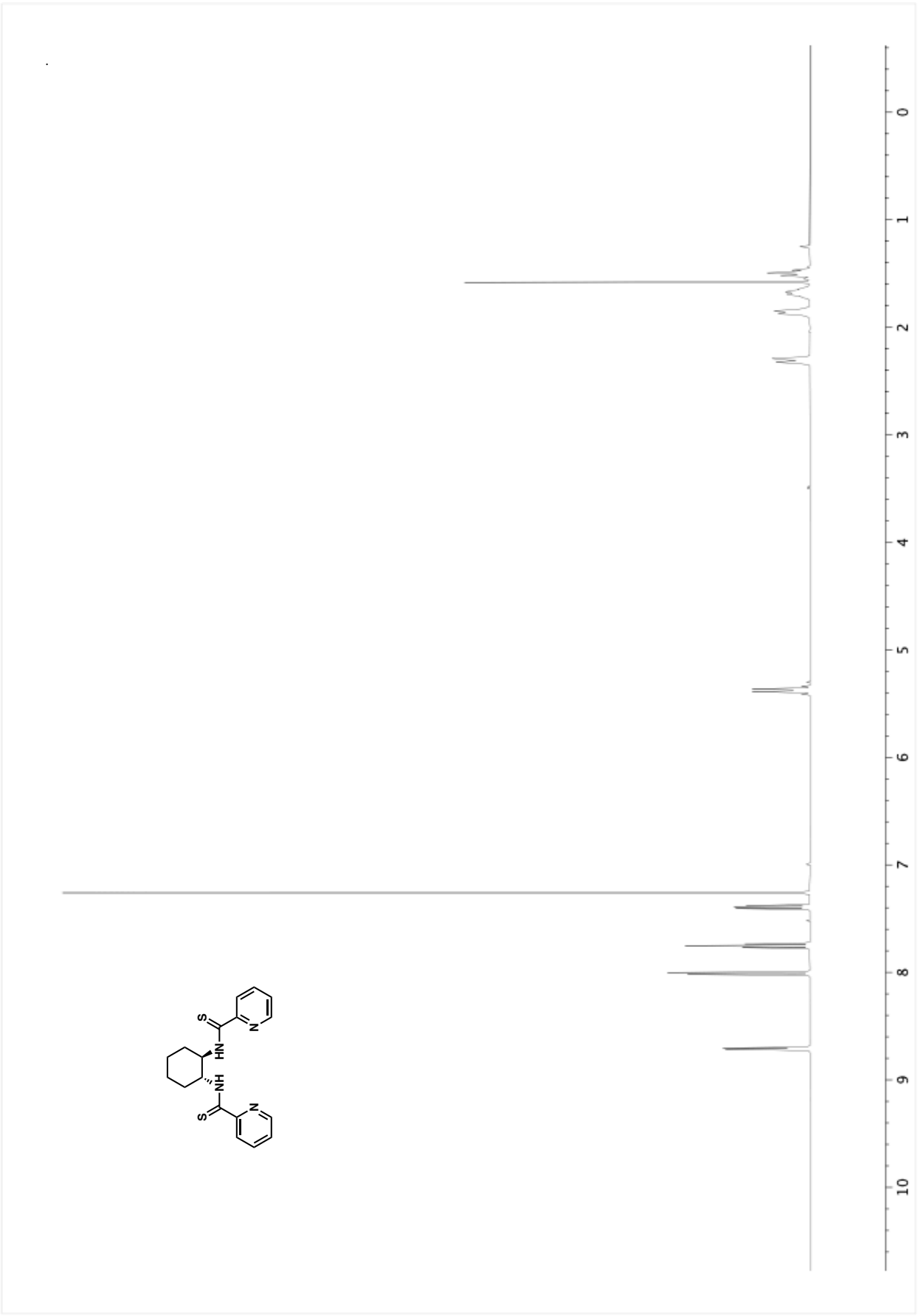

Figure A3.12. *^1H NMR (400 MHz, $CDCl_3$) of* ***L12****.*

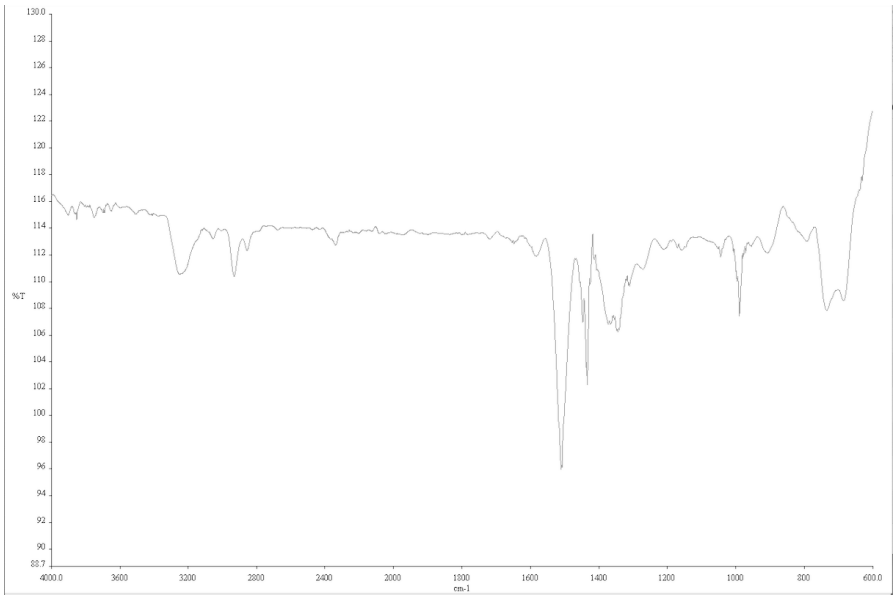

Figure A3.13. *Infrared spectrum (Thin Film, NaCl) of* ***L12.***

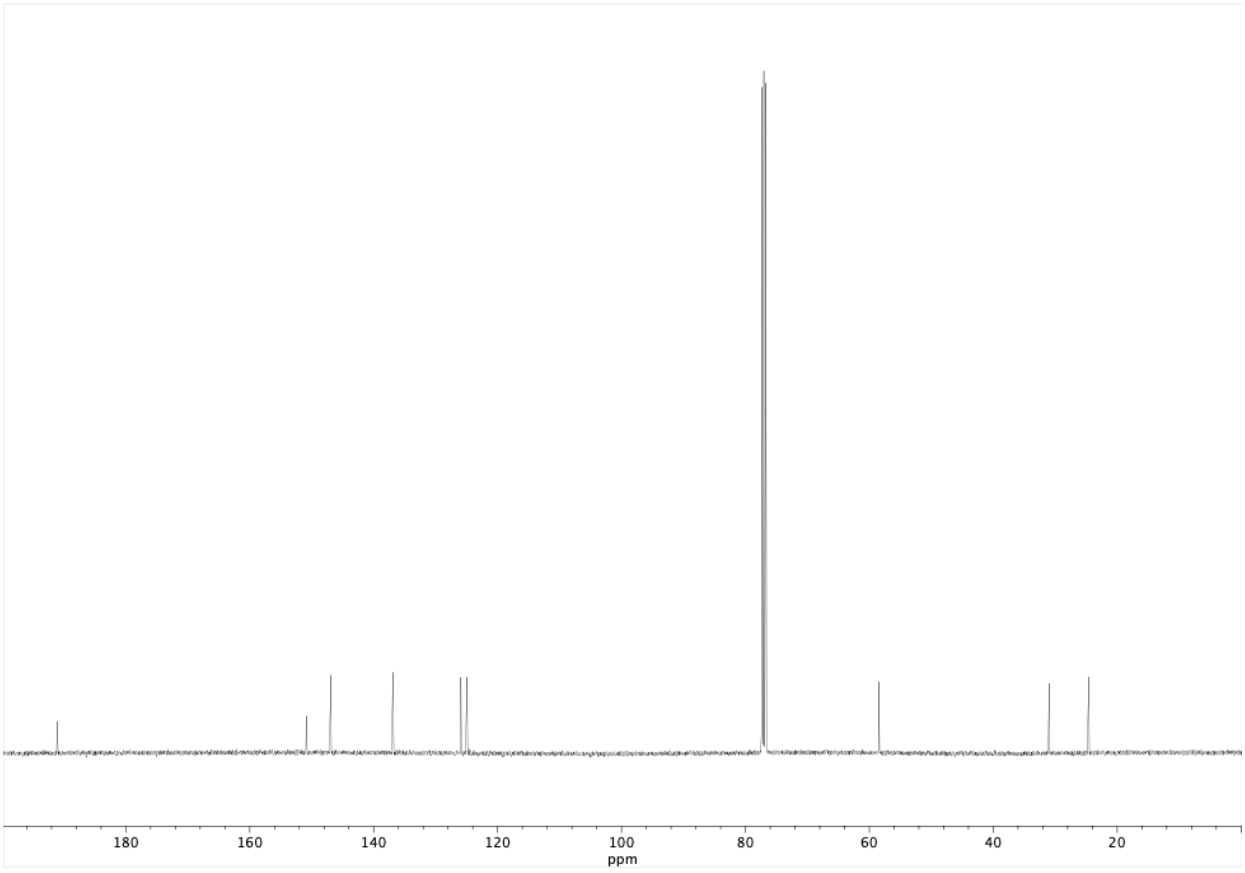

Figure A3.14. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***L12.***

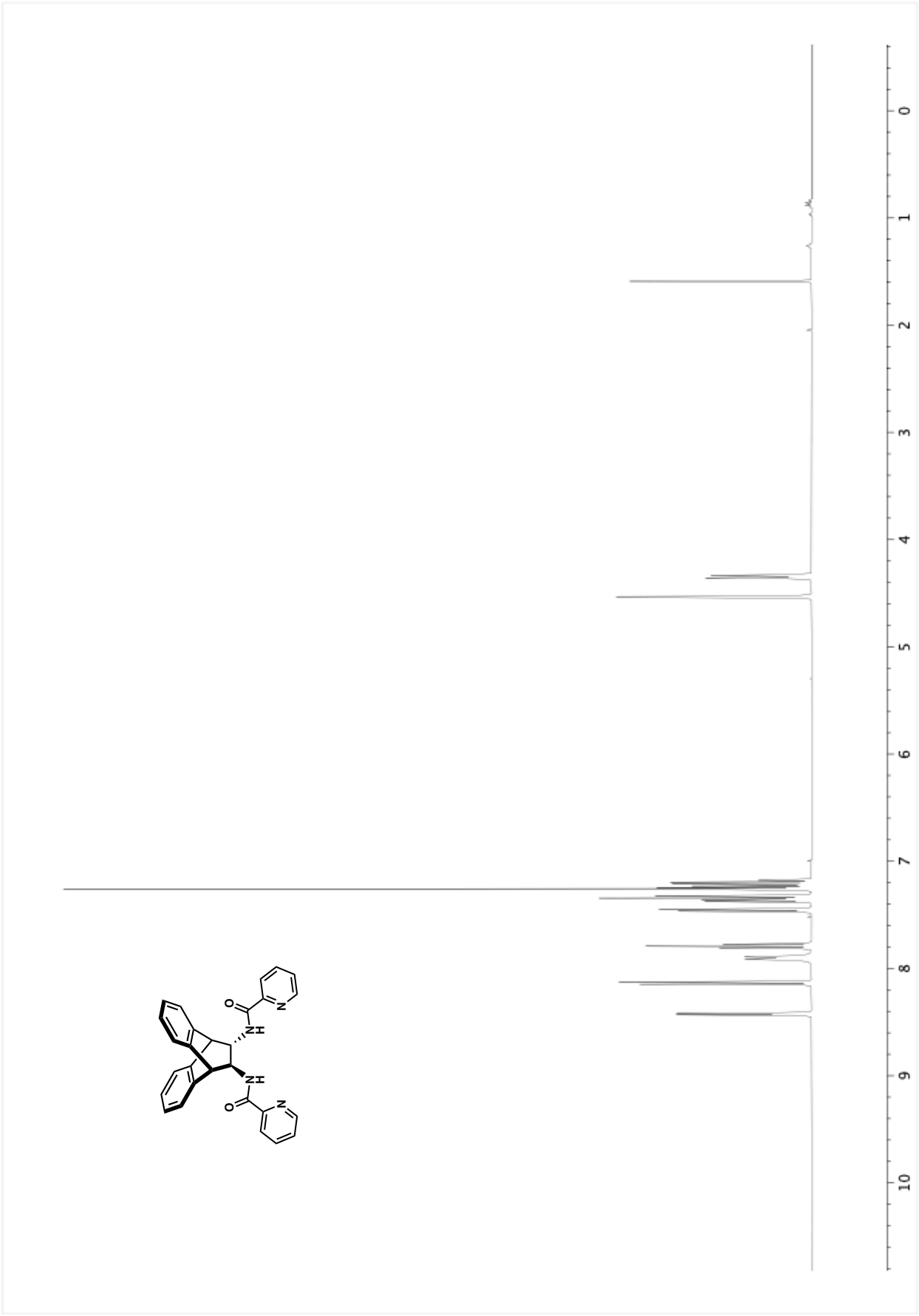

Figure A3.15. *^1H NMR (400 MHz, $CDCl_3$) of* ***L14****.*

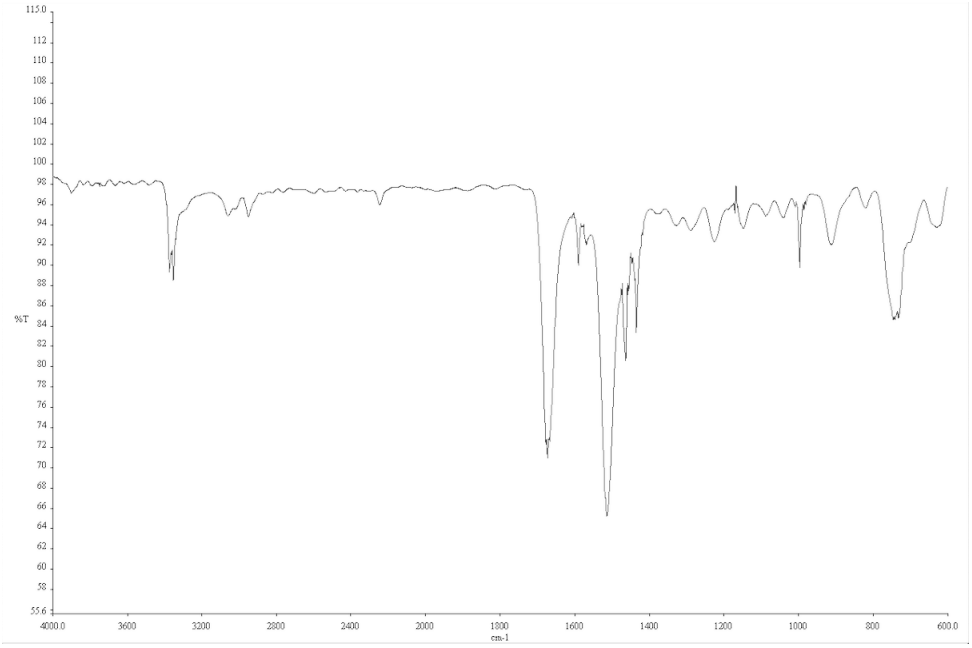

Figure A3.16. *Infrared spectrum (Thin Film, NaCl) of* ***L14****.*

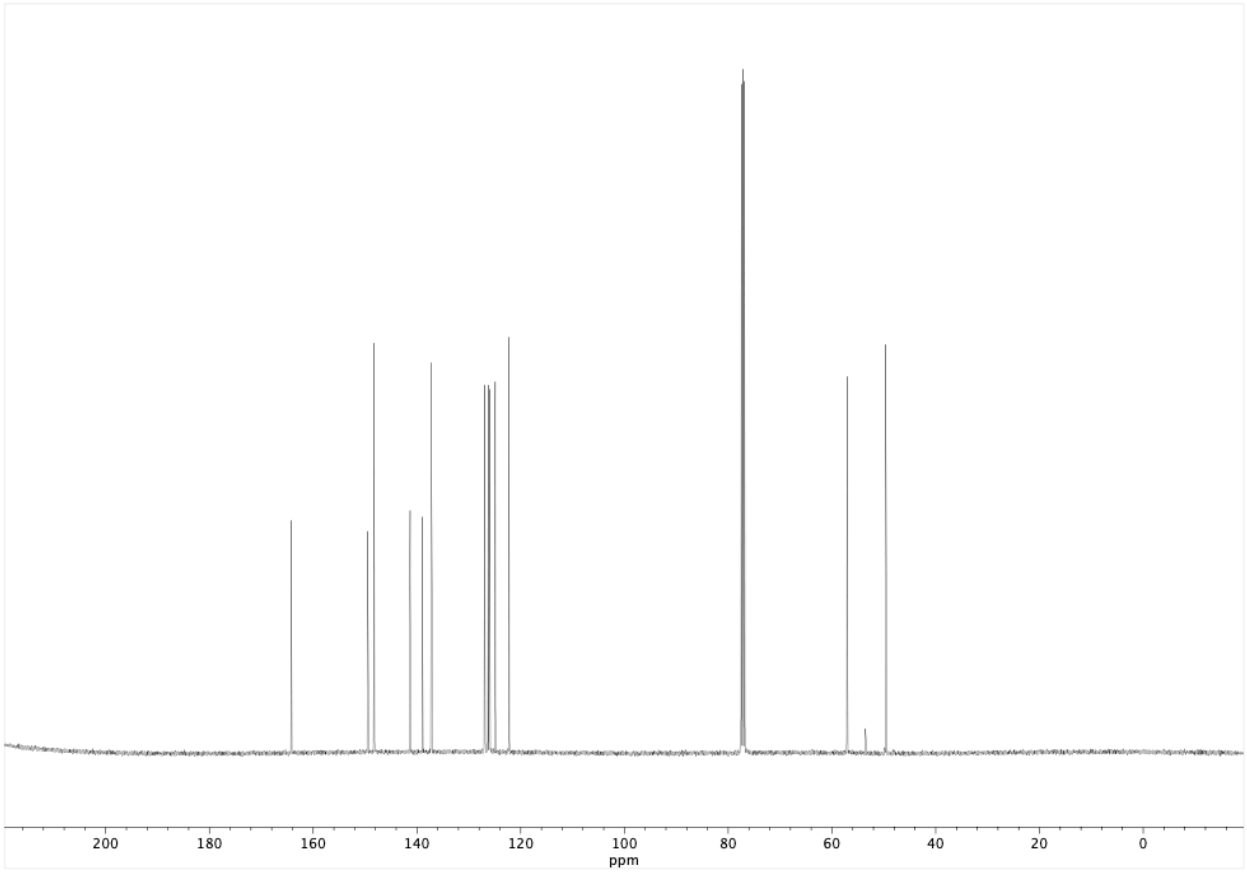

Figure A3.17. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***L14.***

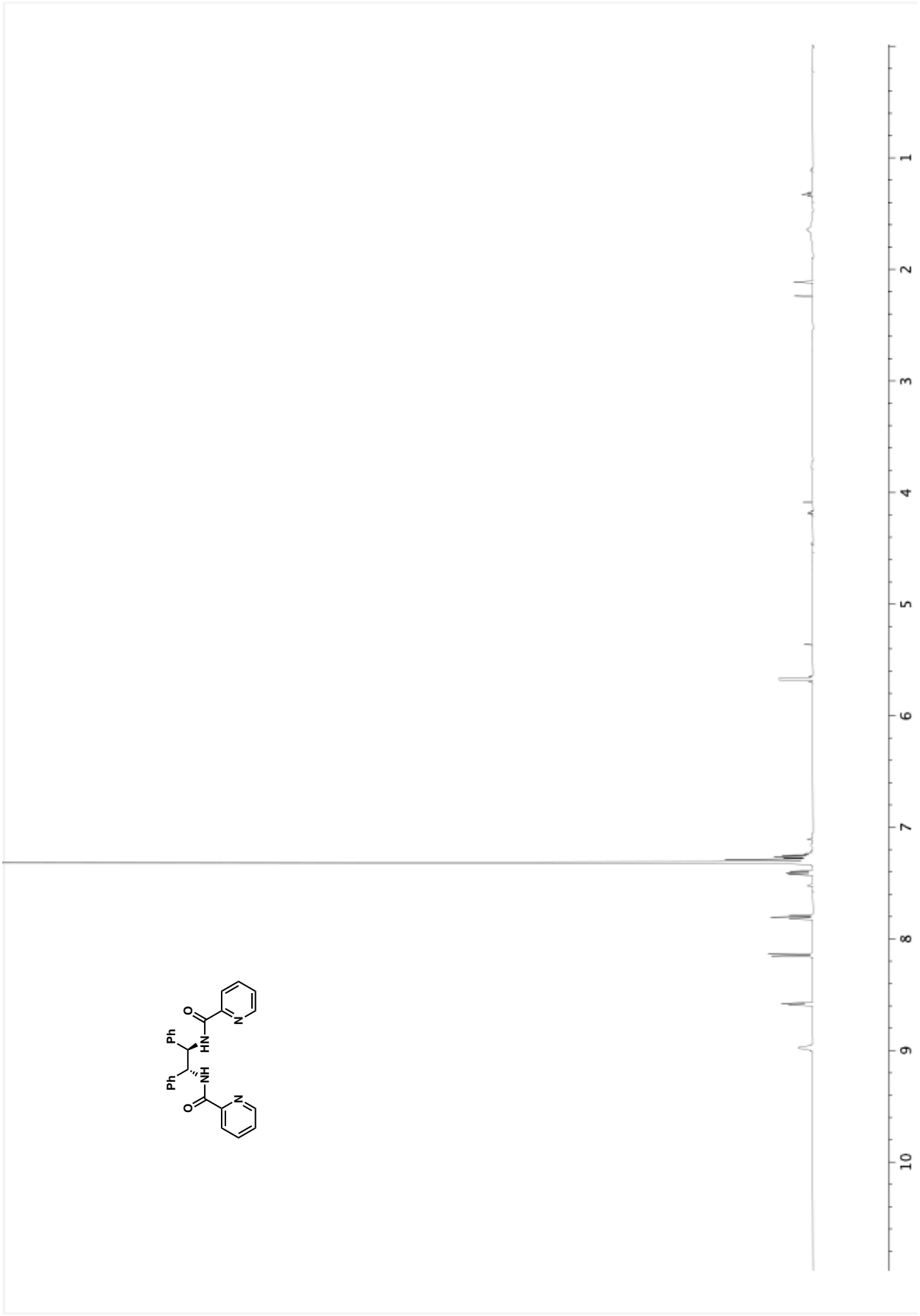

Figure A3.18. *^{1}H NMR (500 MHz, $CDCl_3$) of* ***L15****.*

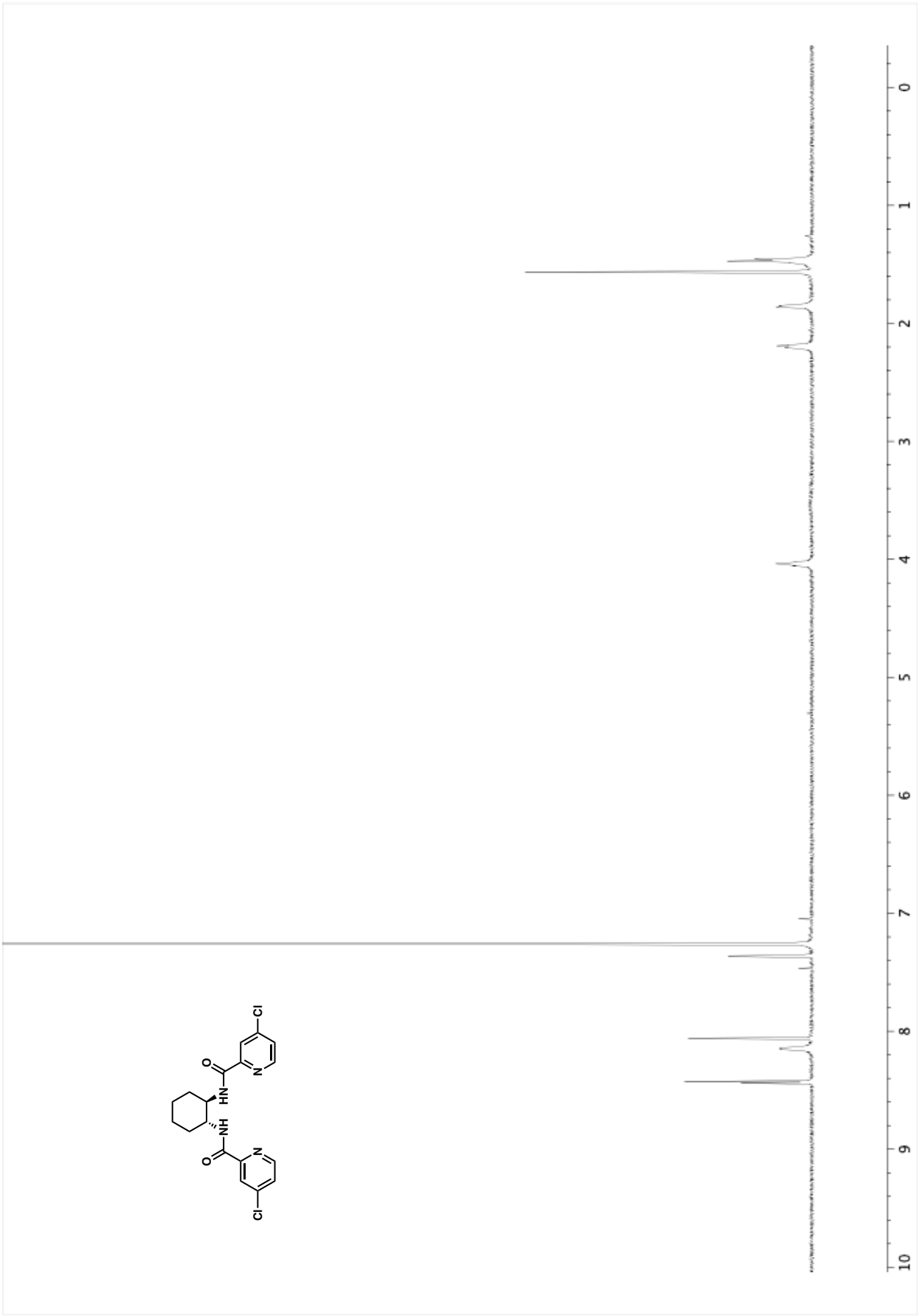

Figure A3.19. *^{1}H NMR (500 MHz, $CDCl_3$) of* ***L17.***

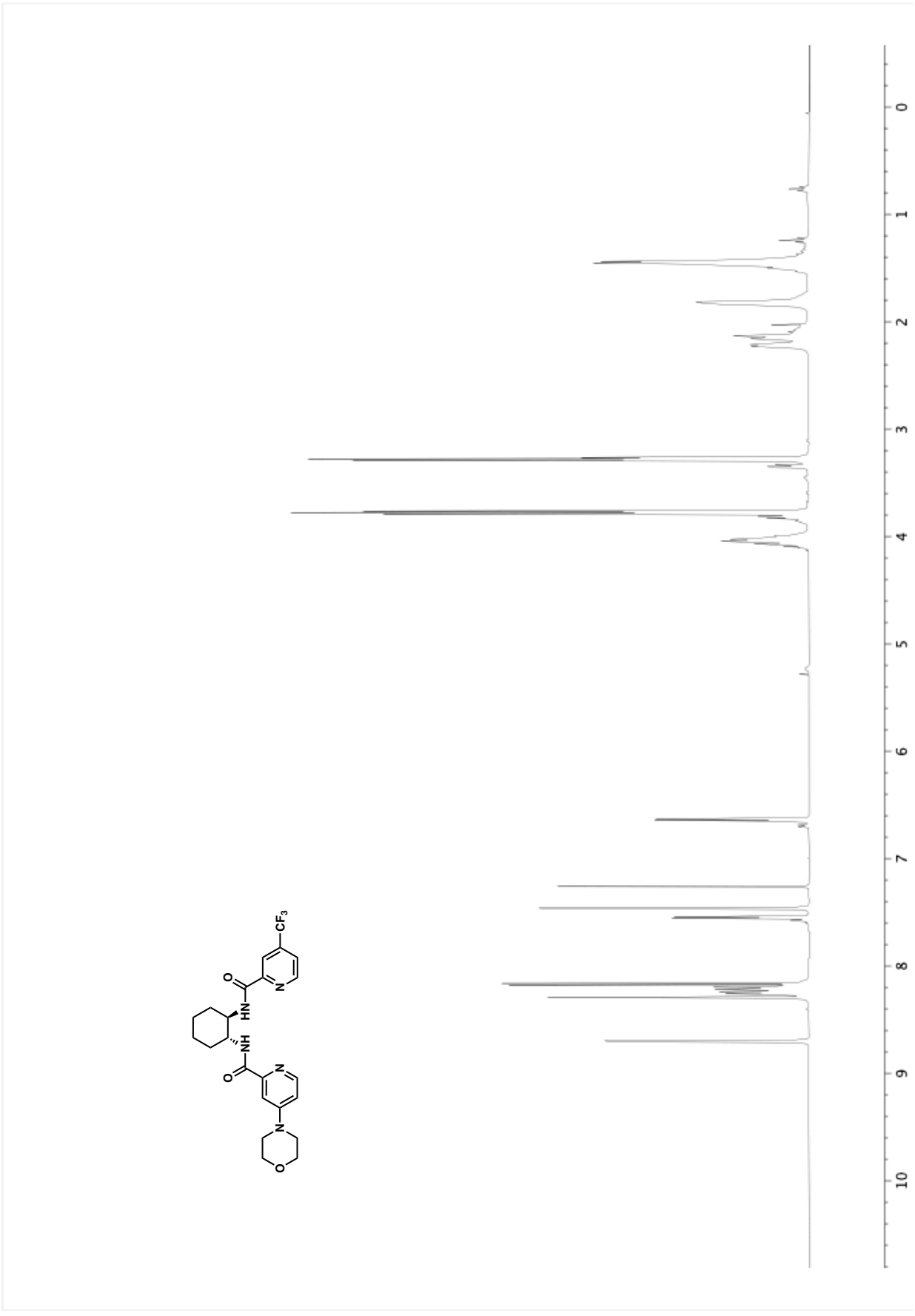

Figure A3.20. *^{1}H NMR (400 MHz, $CDCl_3$) of* ***L10****.*

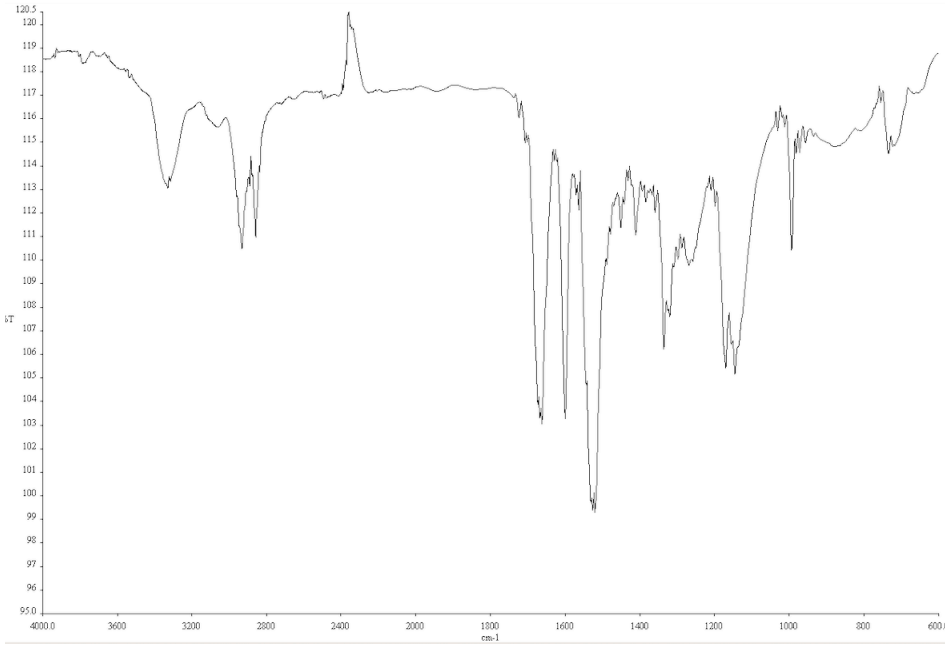

Figure A3.21. *Infrared spectrum (Thin Film, NaCl) of* ***L10.***

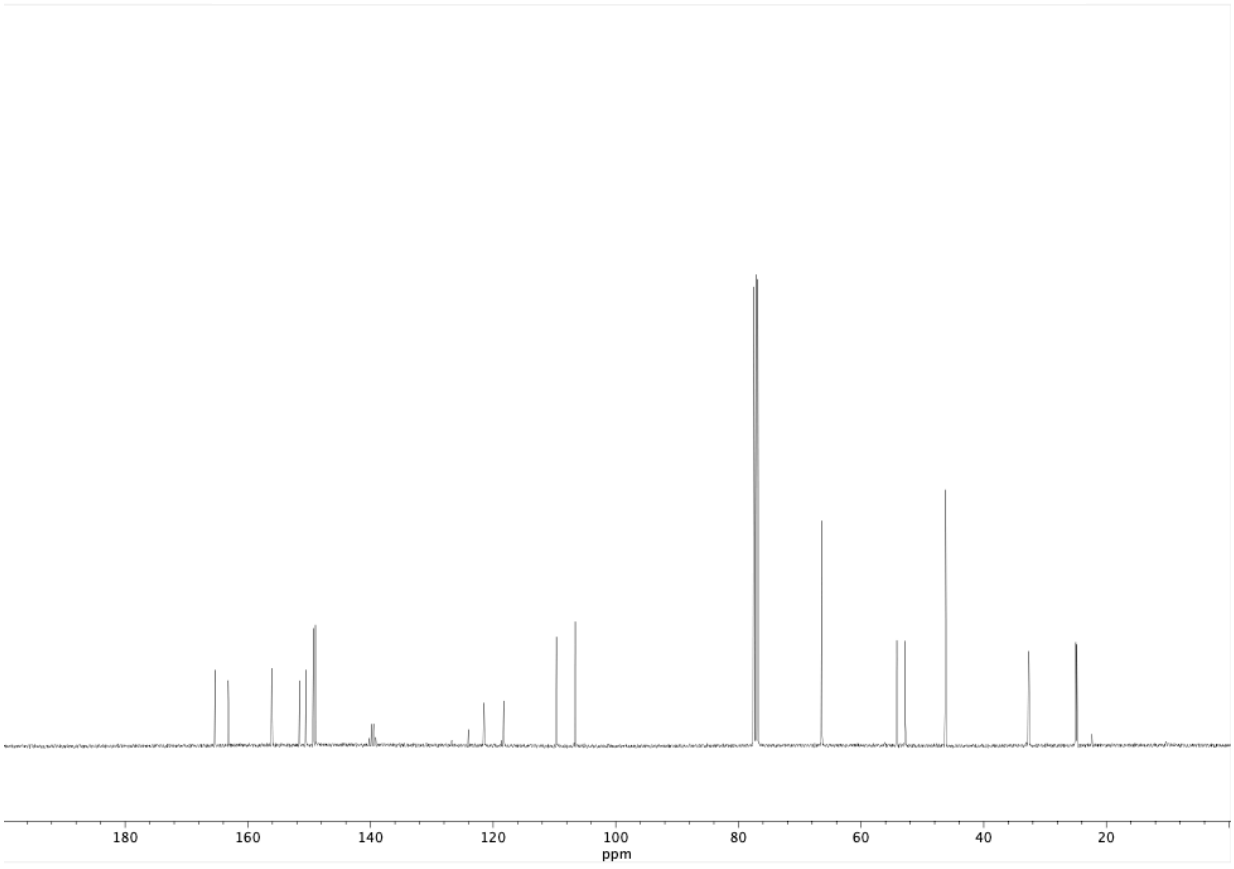

Figure A3.22. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***L10.***

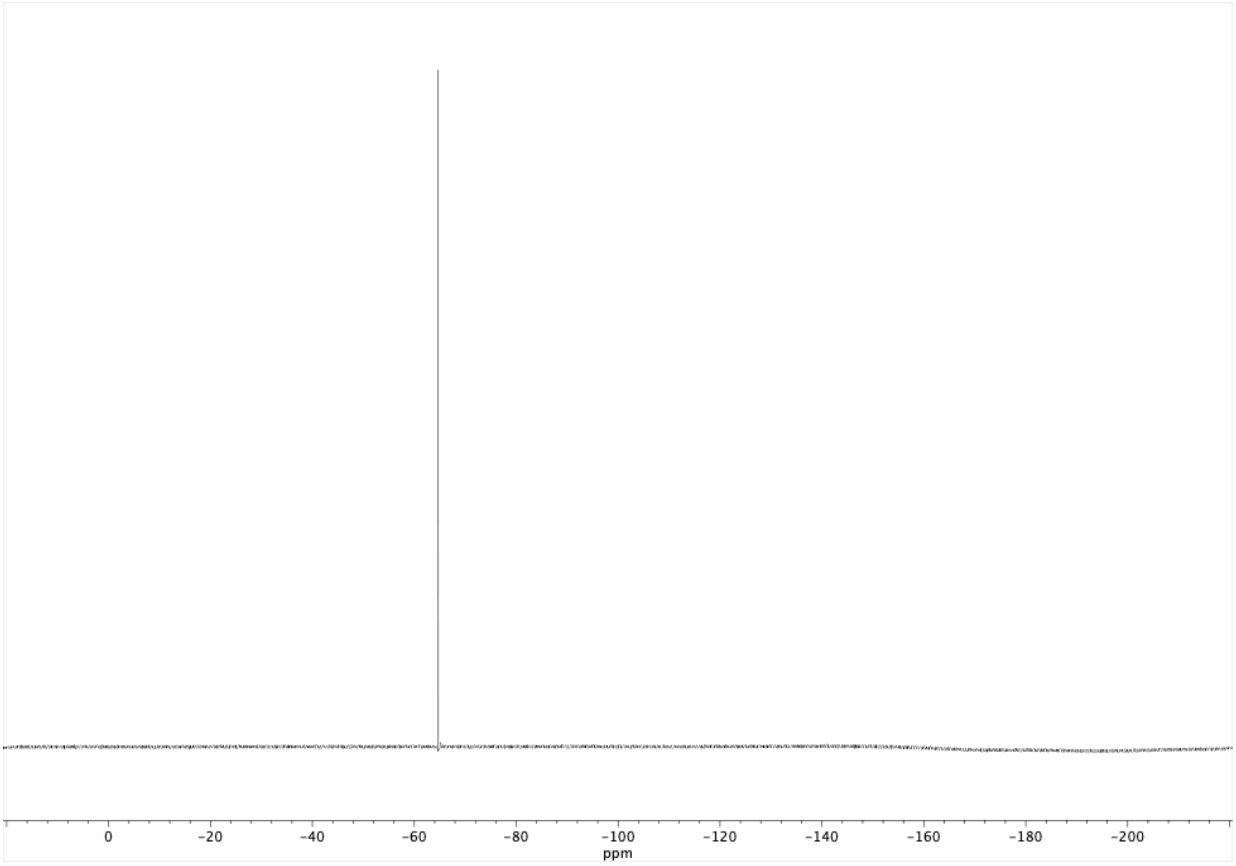

Figure A3.23. *^{19}F NMR (376 MHz, $CDCl_3$) of* ***L10.***

Figure A3.24. *^{1}H NMR (400 MHz, $CDCl_3$) of* ***S2.***

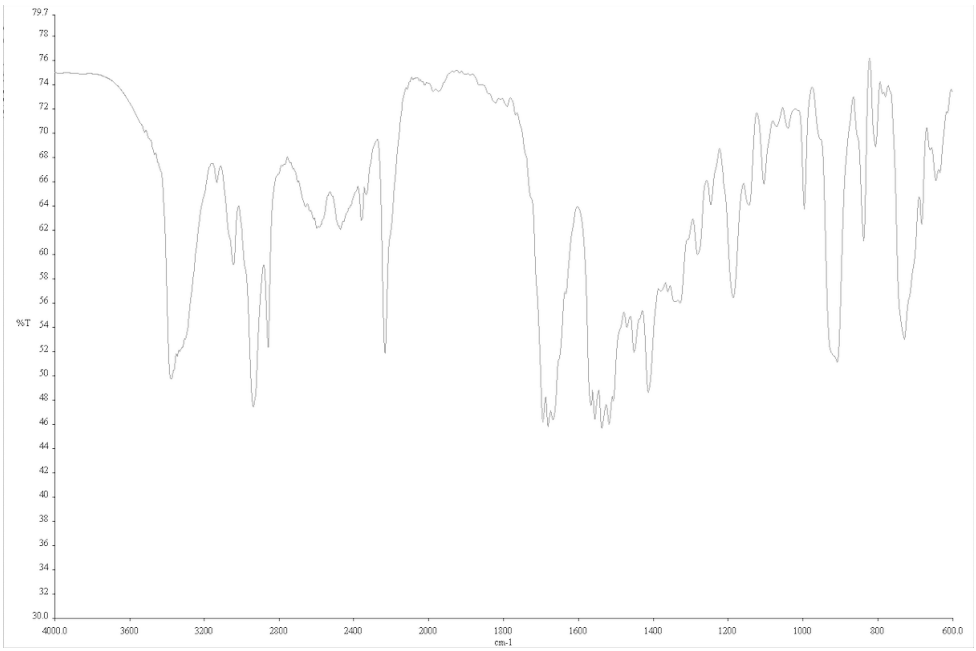

Figure A3.25. *Infrared spectrum (Thin Film, NaCl) of* ***S2.***

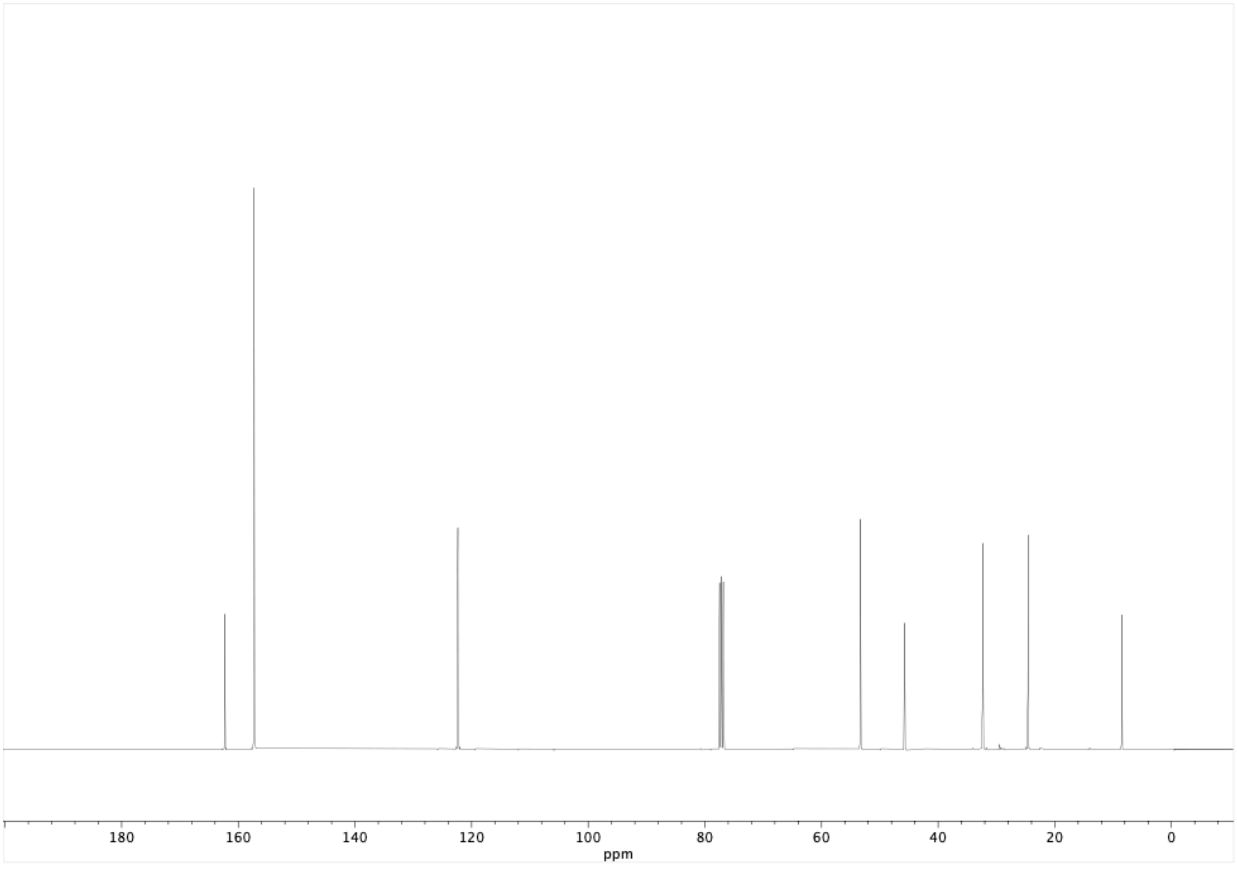

Figure A3.26. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***S2.***

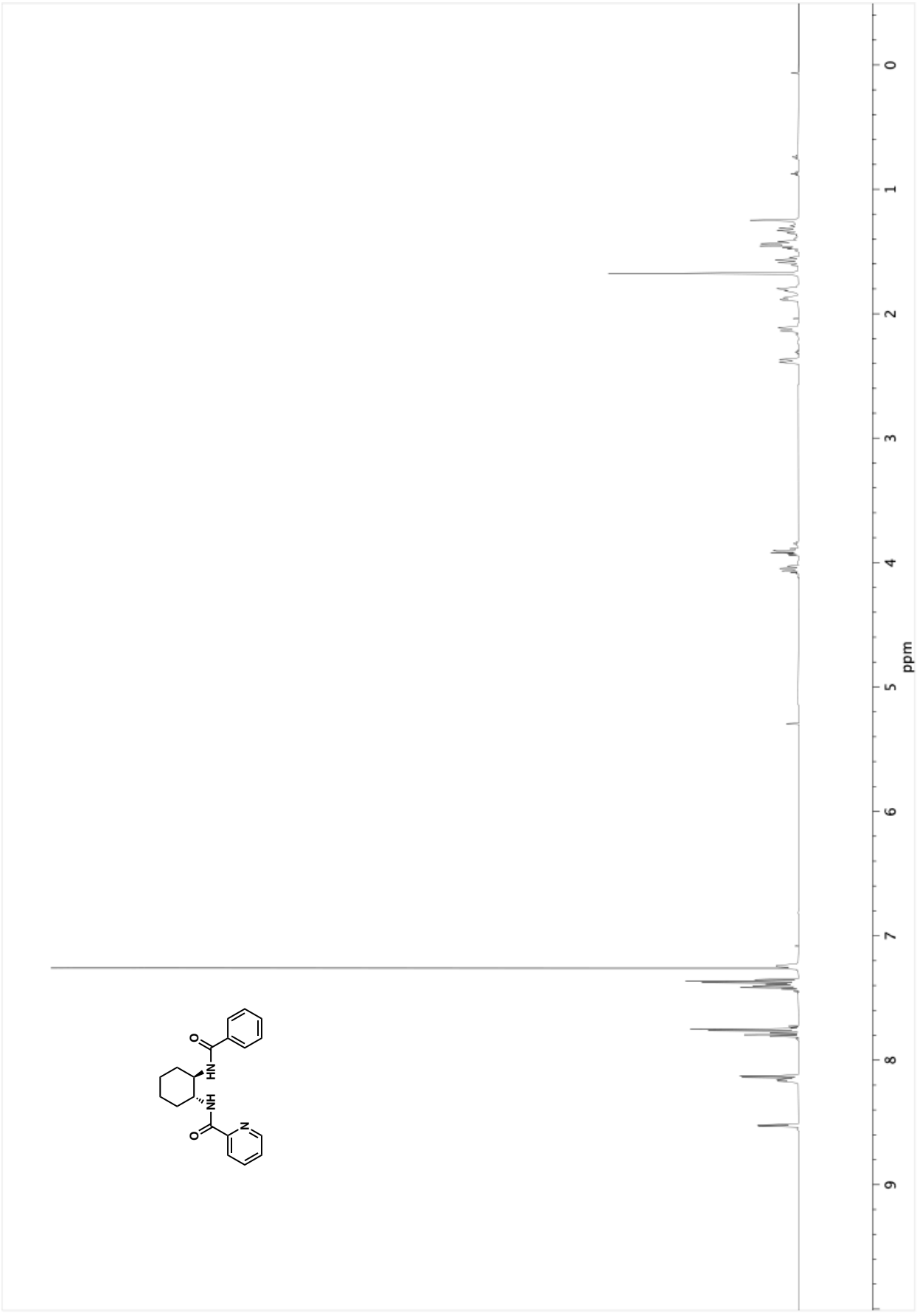

Figure A3.27. *^{1}H NMR (600 MHz, $CDCl_3$) of* ***L6***.

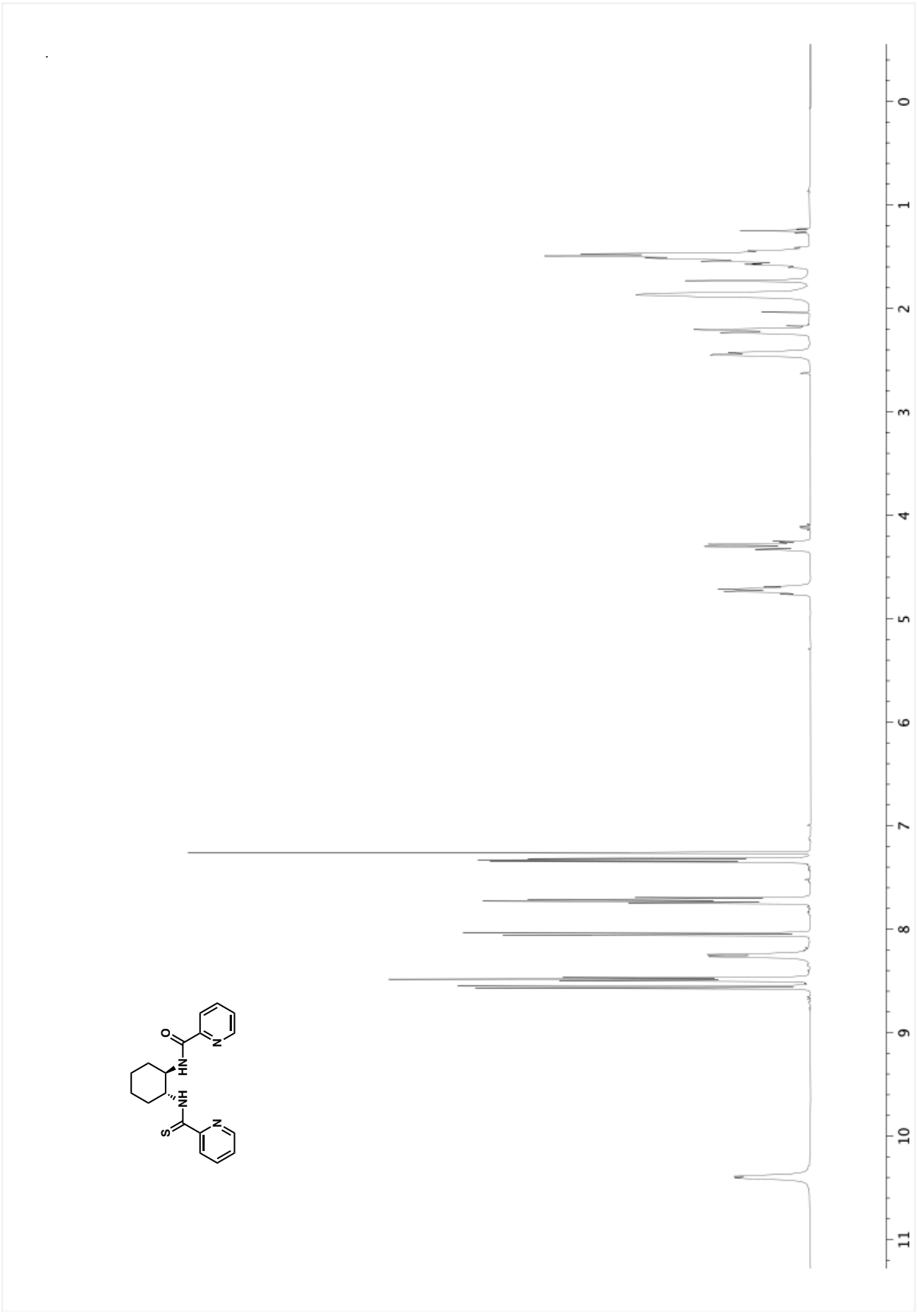

Figure A3.28. *^{1}H NMR (400 MHz, $CDCl_3$) of* ***L13****.*

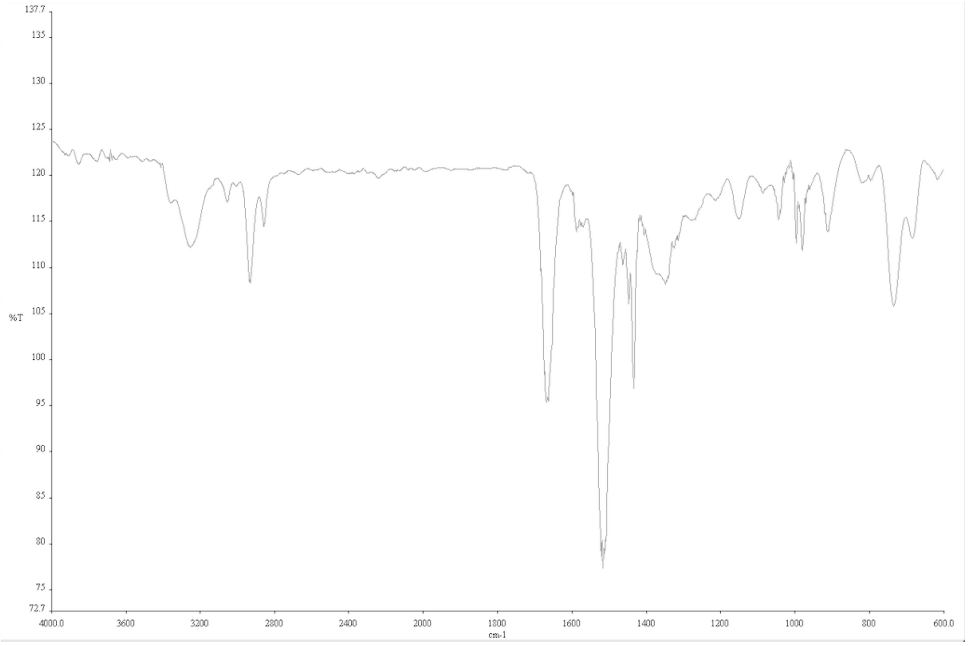

Figure A3.29. *Infrared spectrum (Thin Film, NaCl) of* ***L13.***

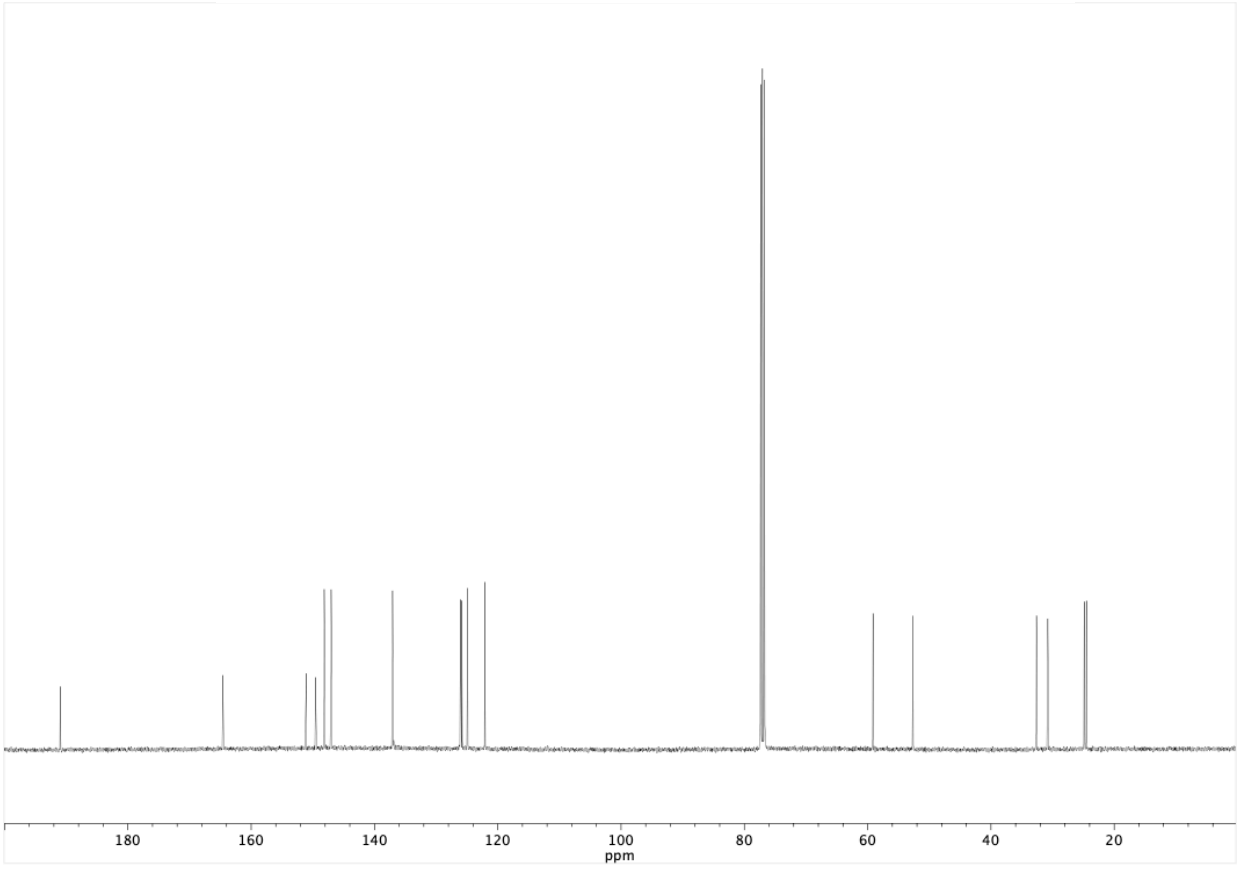

Figure A3.30. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***L13.***

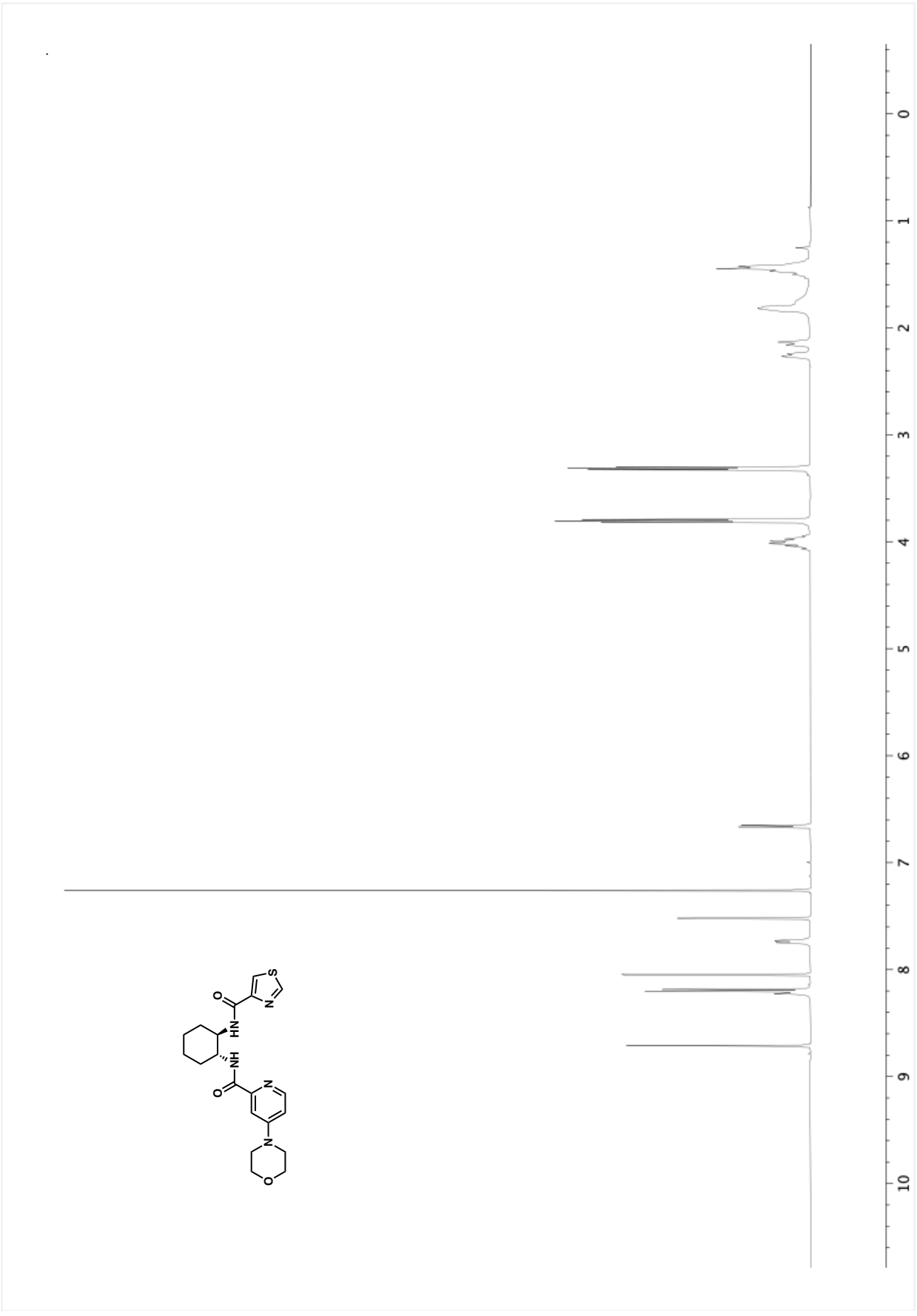

Figure A3.31. *^{1}H NMR (400 MHz, $CDCl_3$) of* ***L18****.*

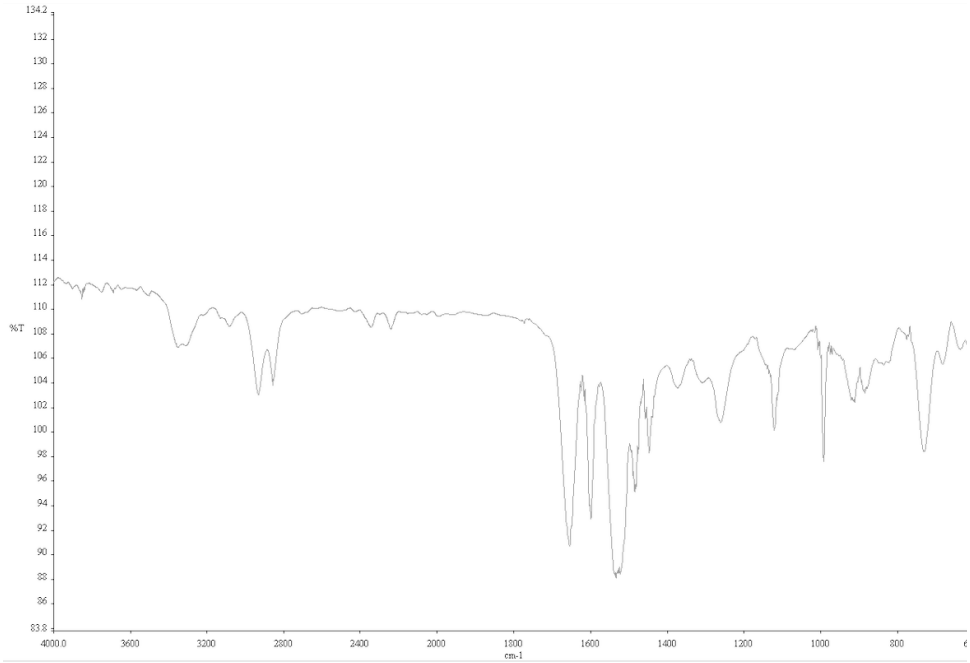

Figure A3.32. *Infrared spectrum (Thin Film, NaCl) of* ***L18.***

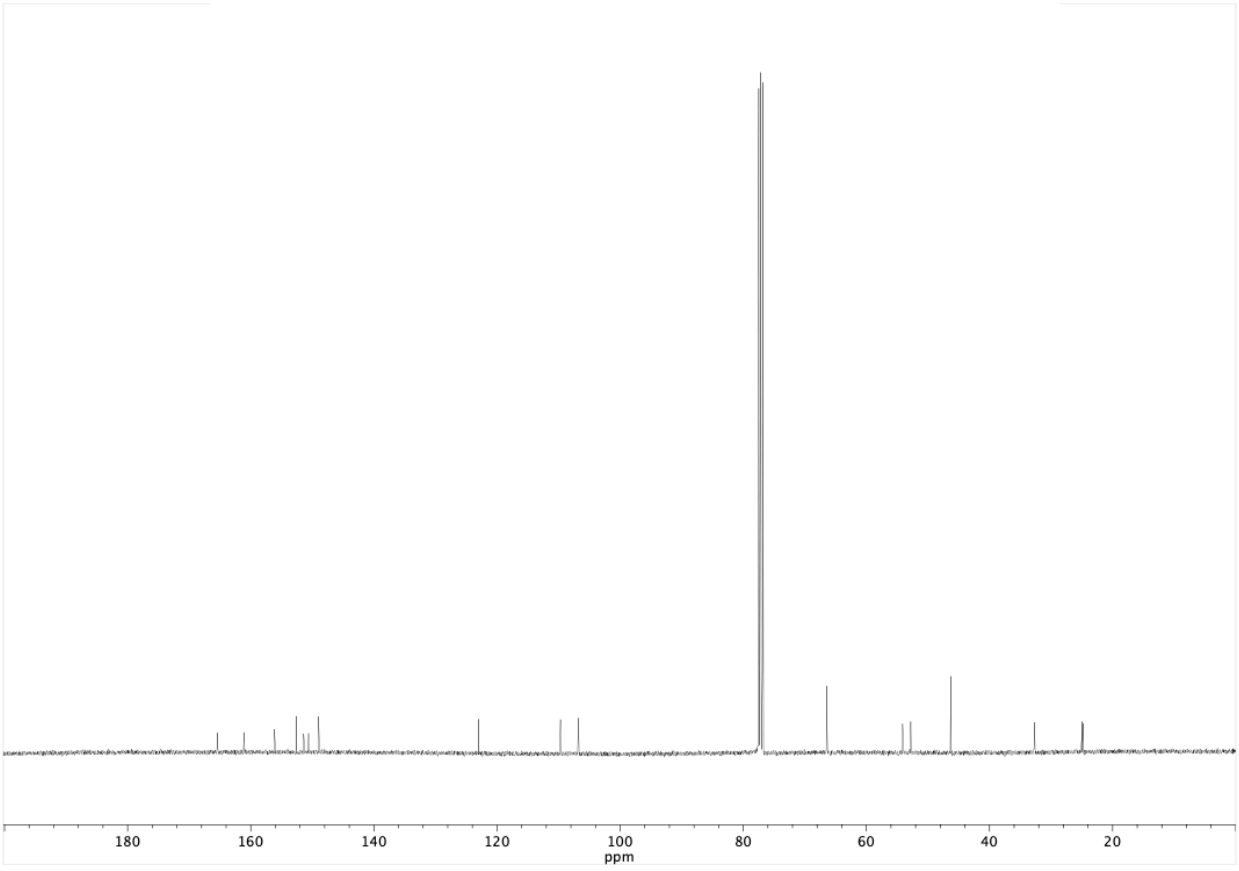

Figure A3.33. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***L18.***

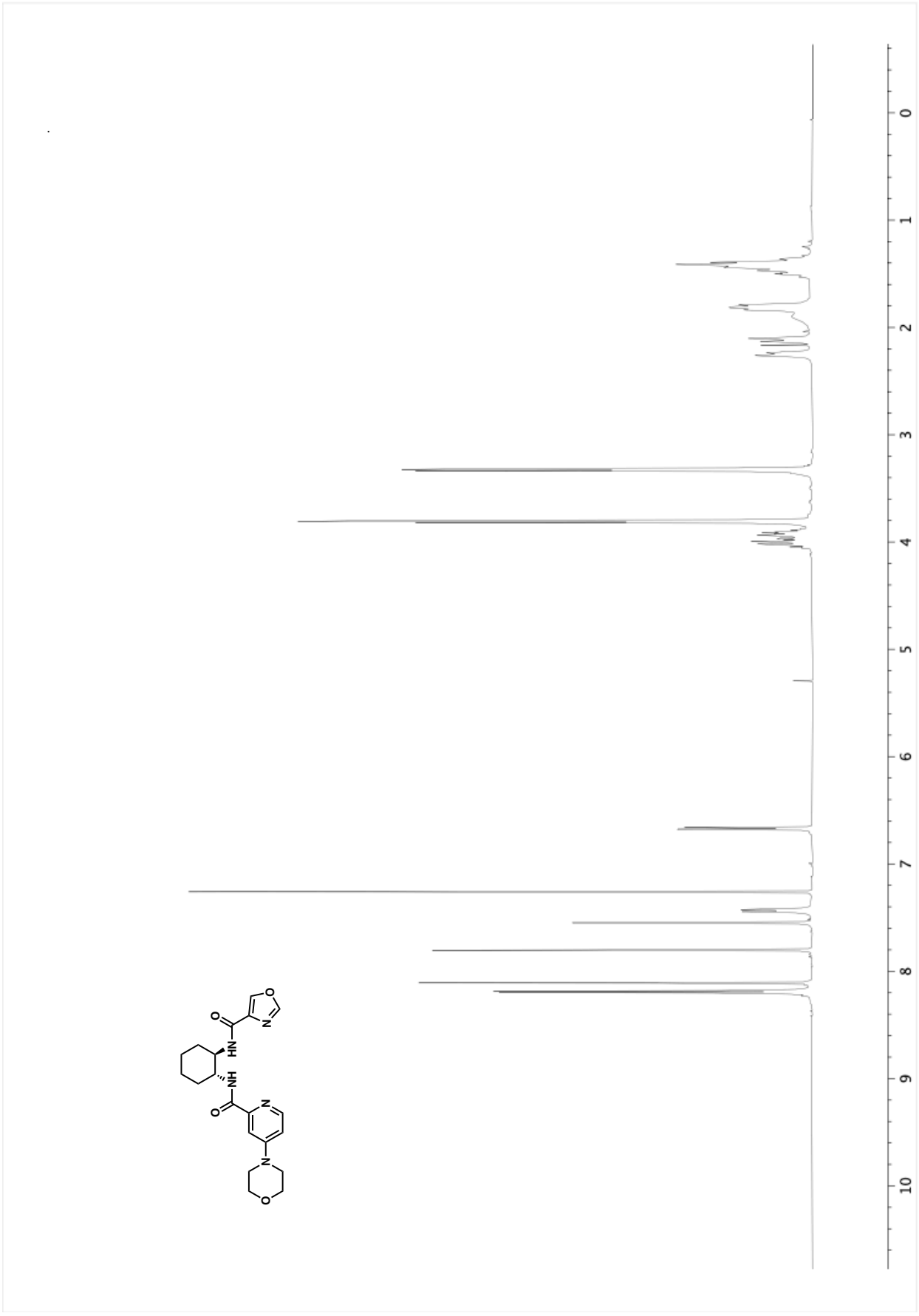

Figure A3.34. *^{1}H NMR (400 MHz, $CDCl_3$) of* ***L19***.

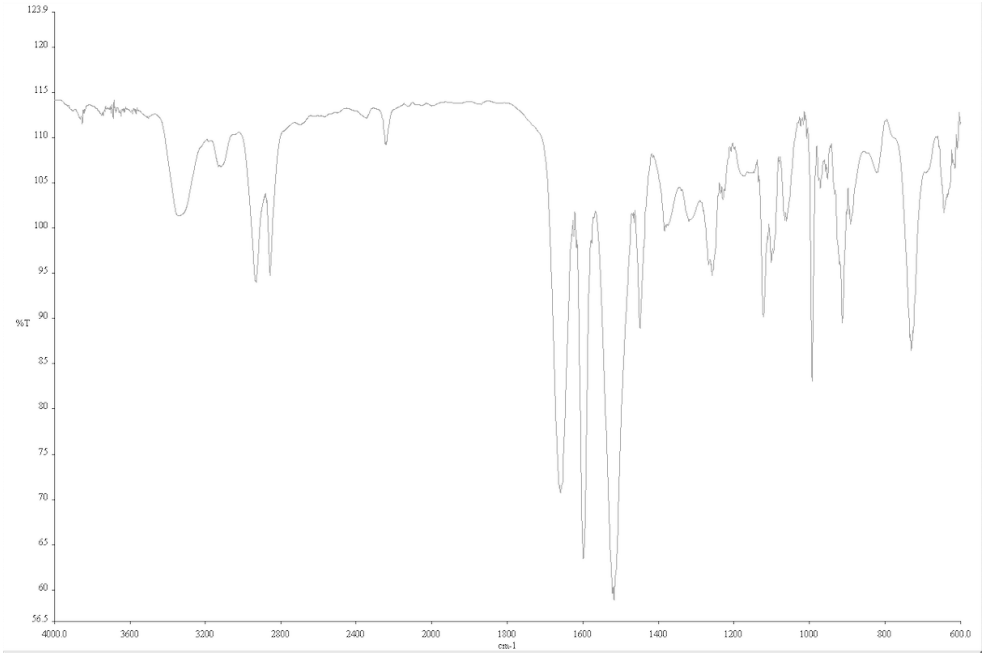

Figure A3.35. *Infrared spectrum (Thin Film, NaCl) of* ***L19.***

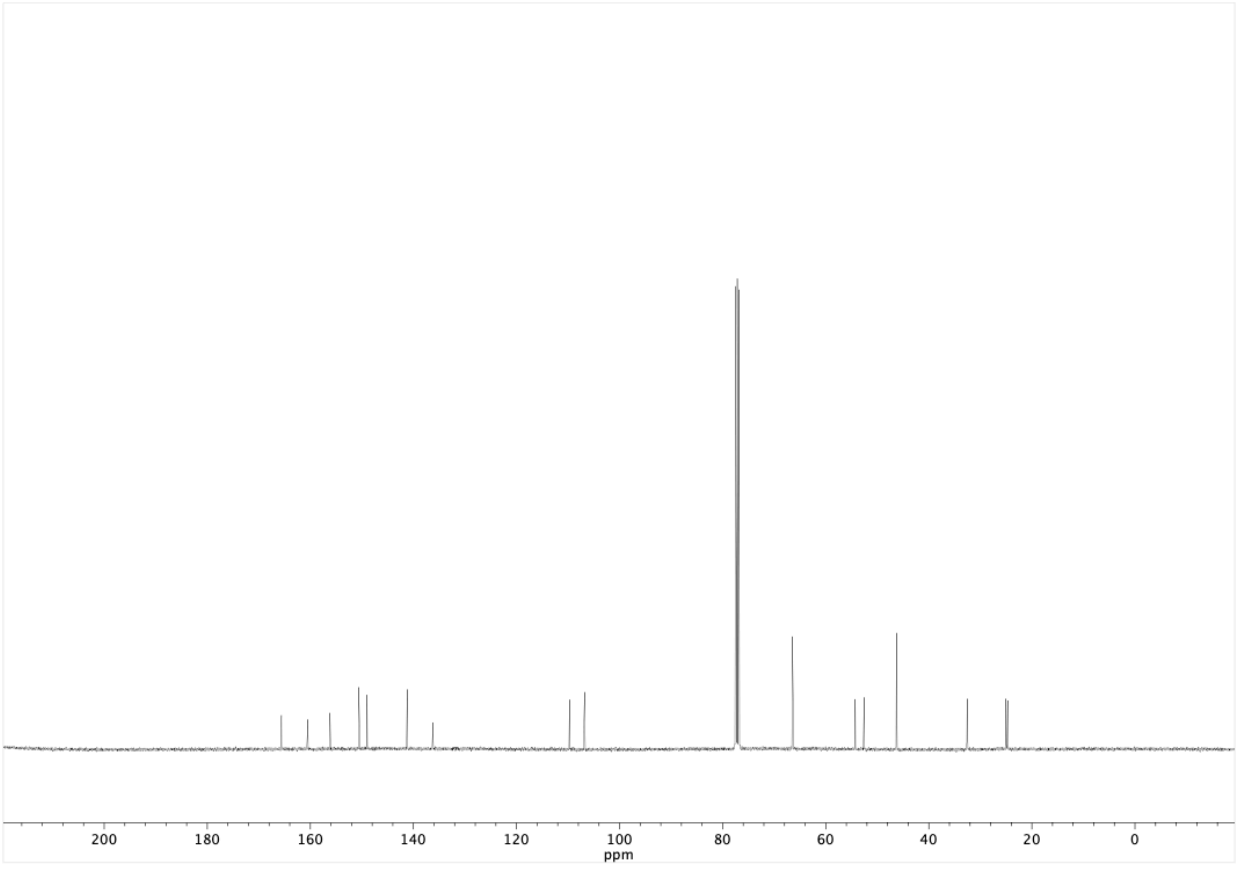

Figure A3.36. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***L19.***

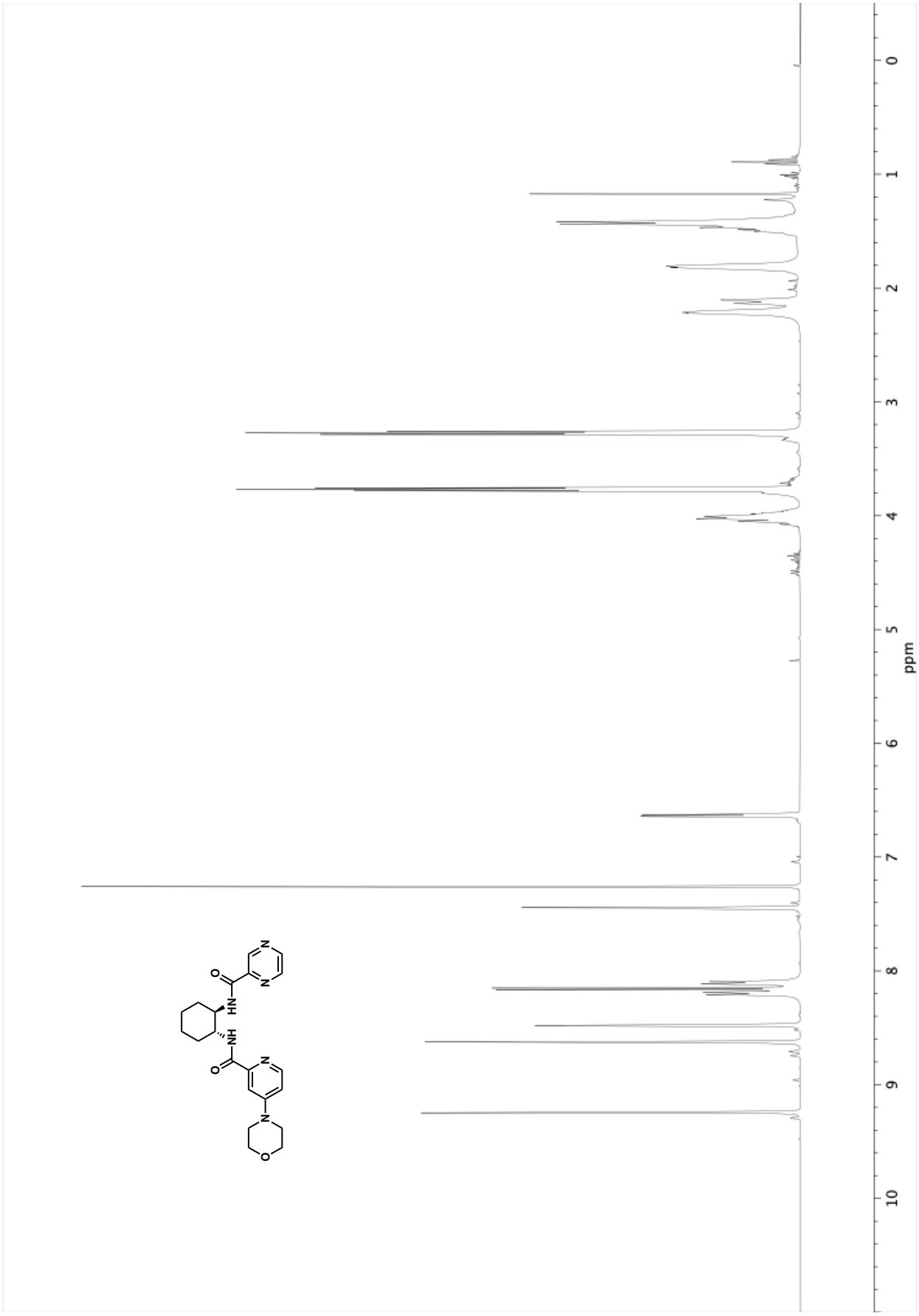

Figure A3.37. *^1H NMR (400 MHz, $CDCl_3$) of* ***L20****.*

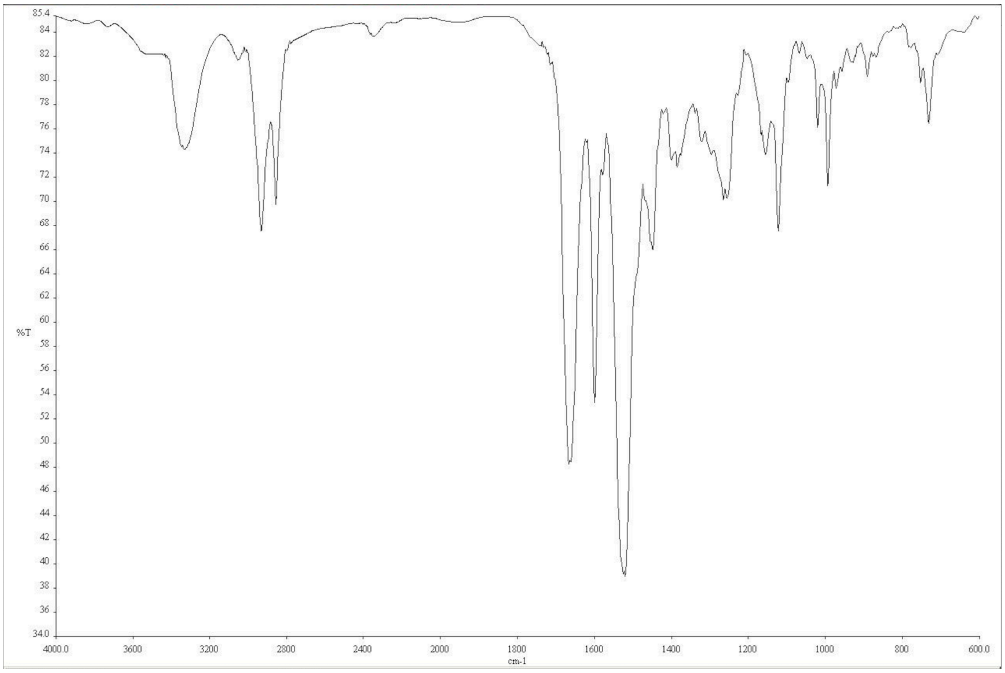

Figure A3.38. *Infrared spectrum (Thin Film, NaCl) of* ***L20****.*

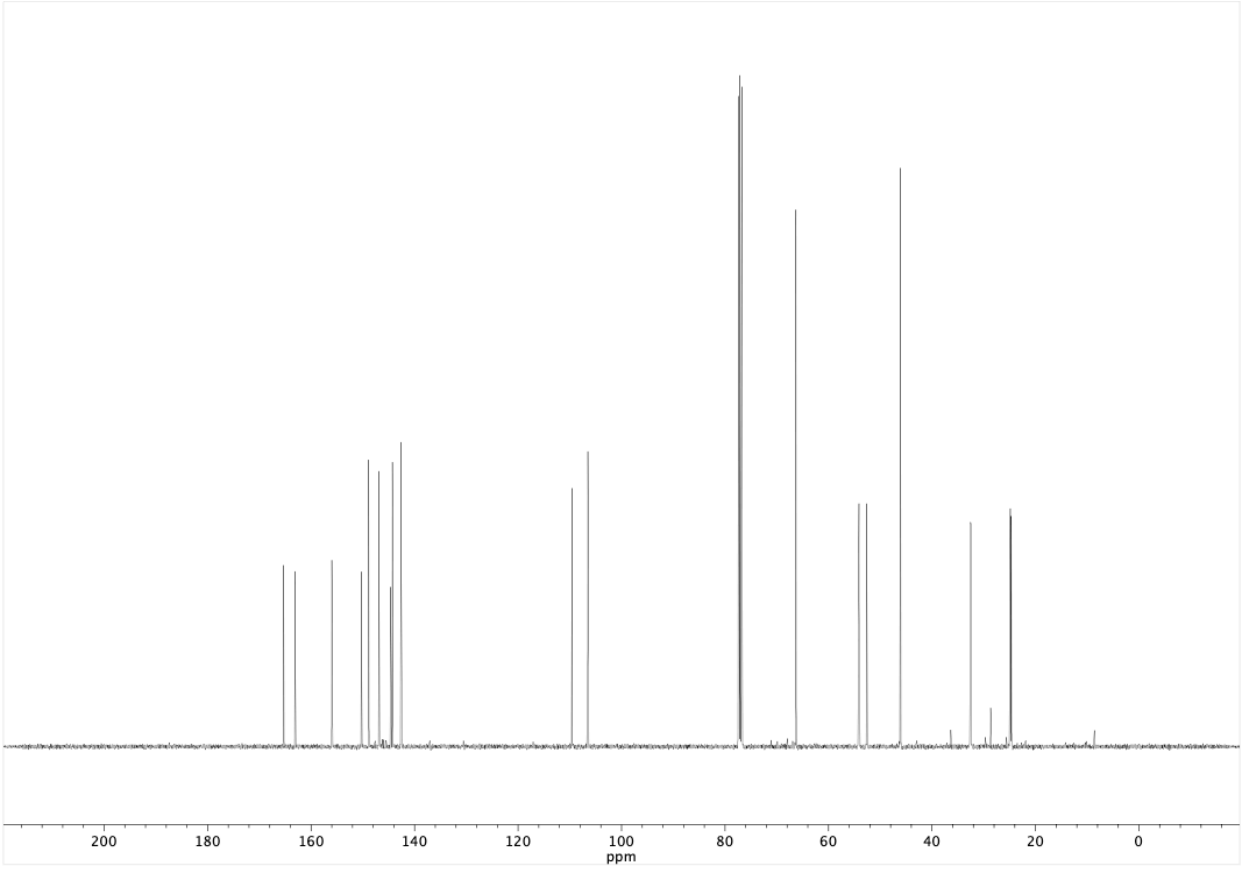

Figure A3.39. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***L20.***

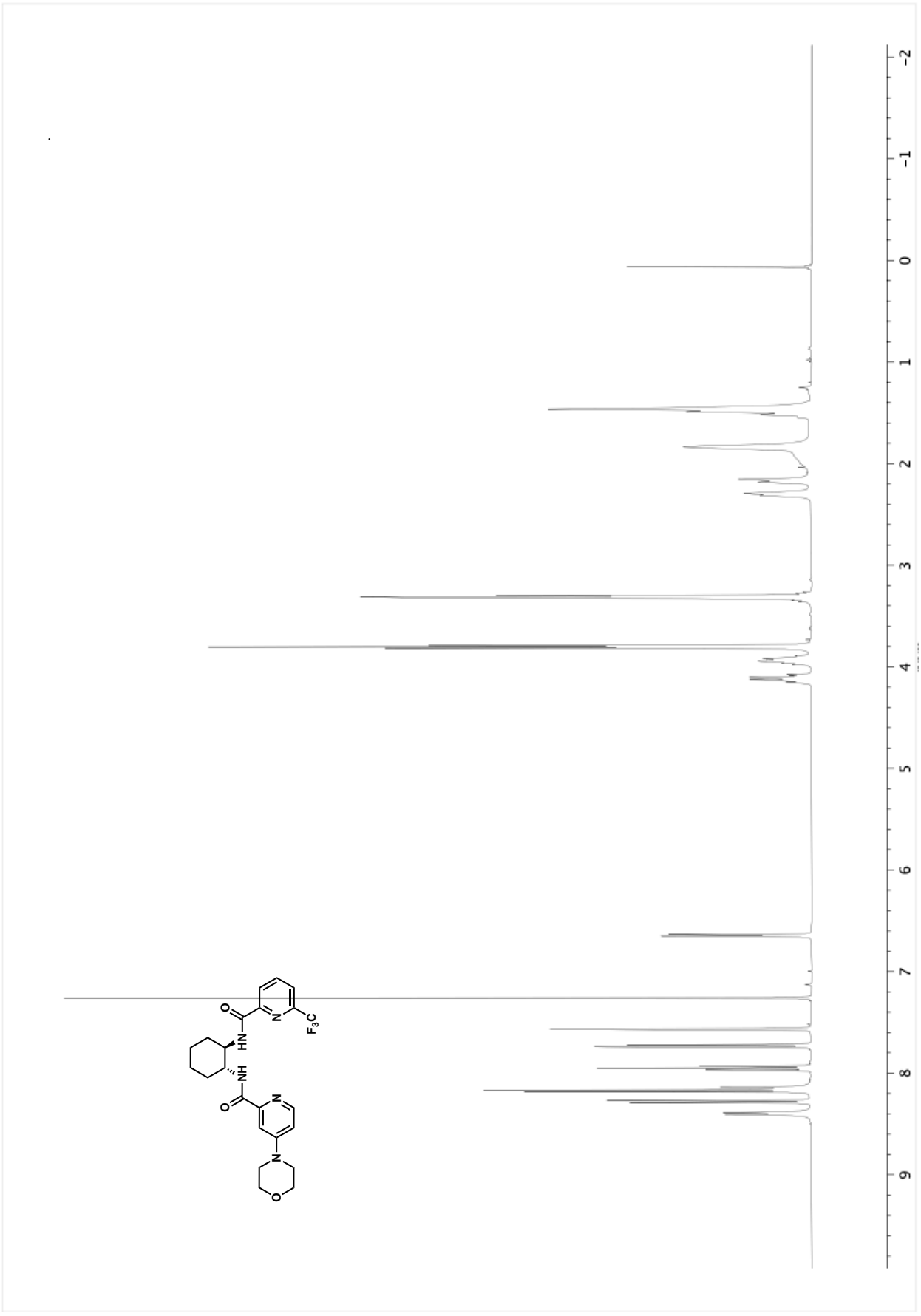

Figure A3.40. *^{1}H NMR (400 MHz, $CDCl_3$) of* ***L21****.*

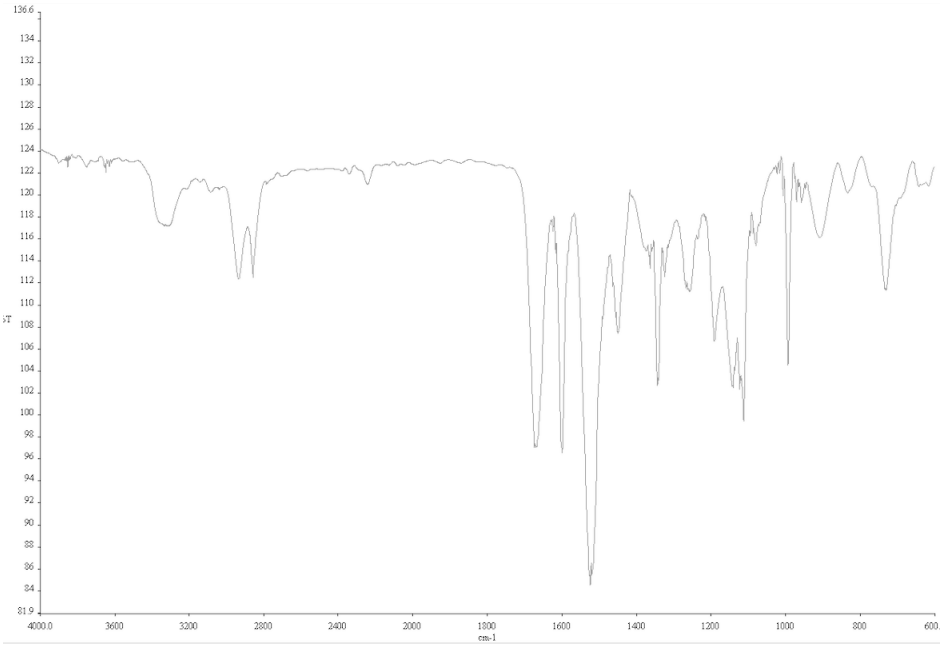

Figure A3.41. *Infrared spectrum (Thin Film, NaCl) of* ***L21.***

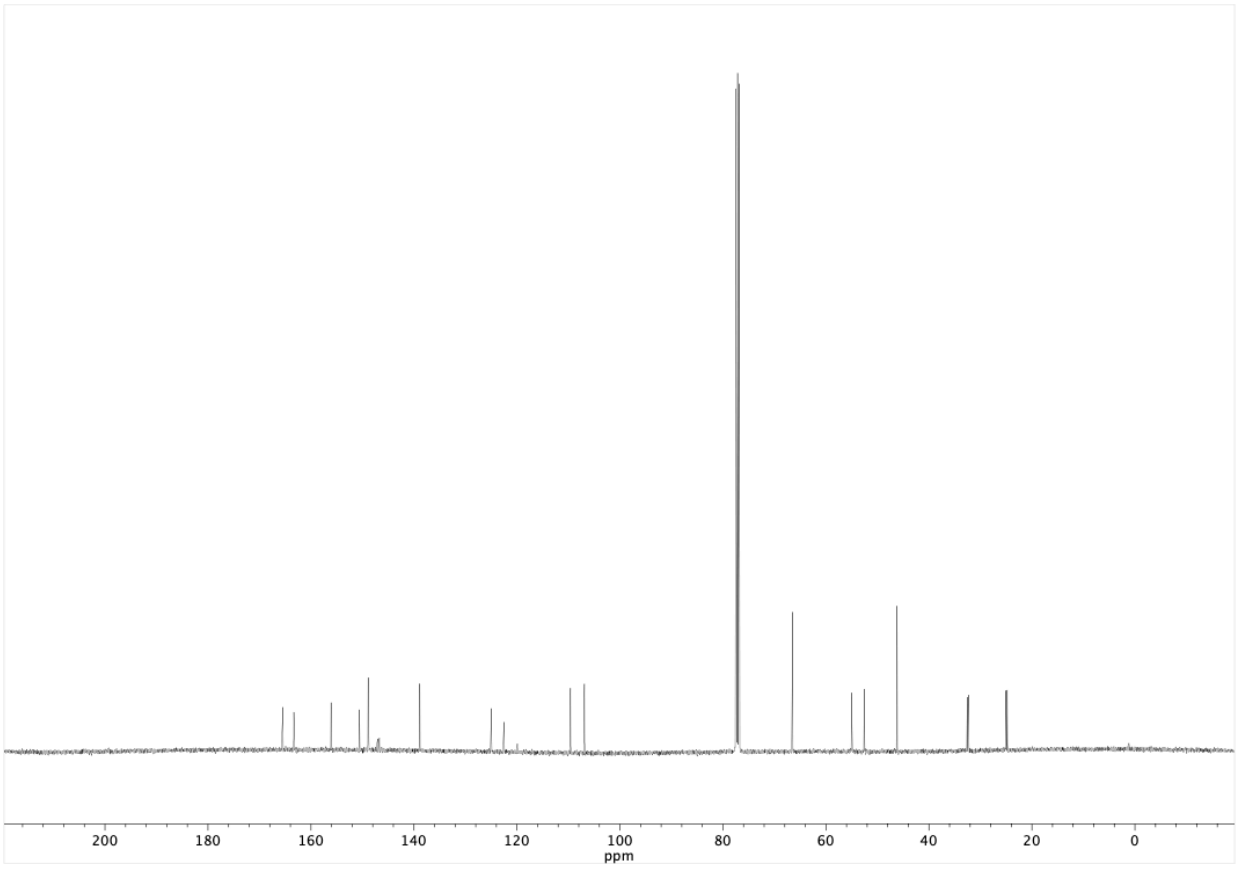

Figure A3.42. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***L21.***

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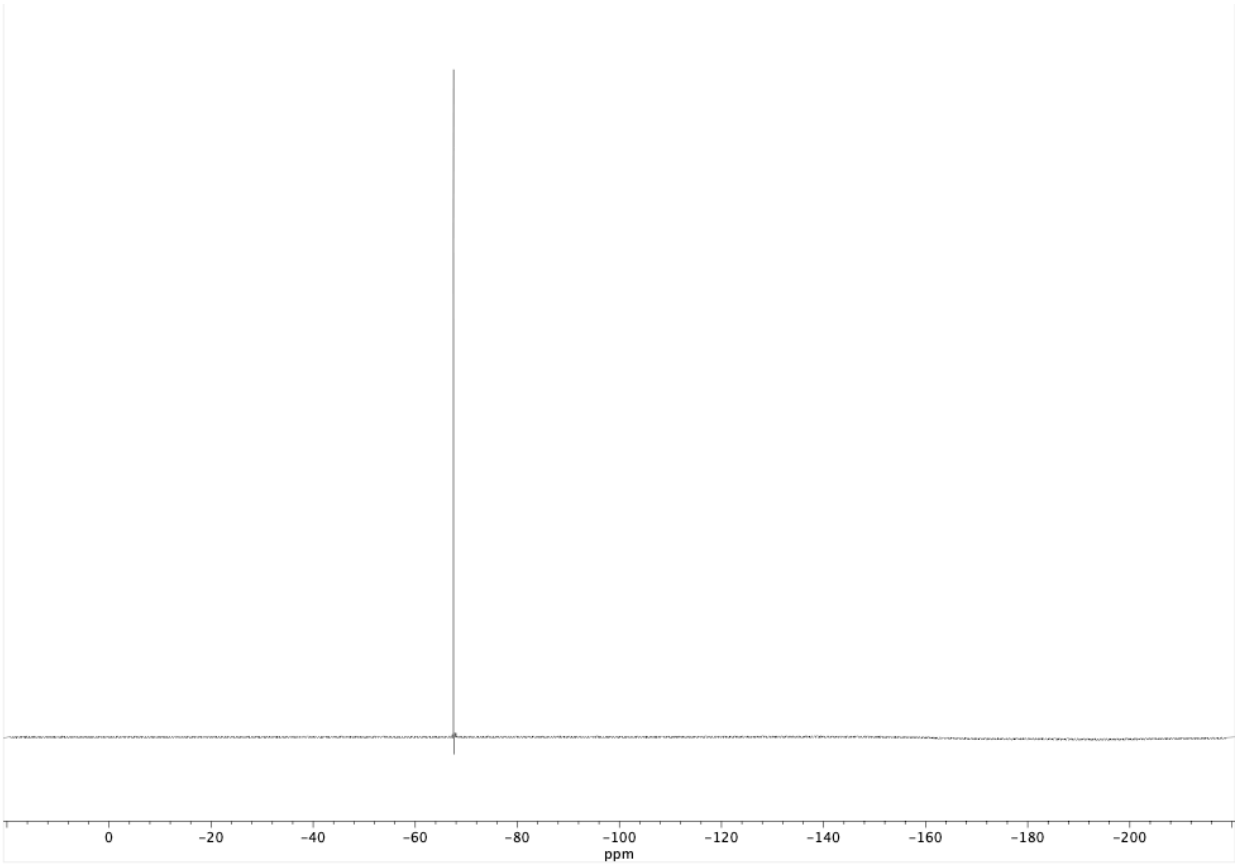

Figure A3.43. *^{19}F NMR (376 MHz, $CDCl_3$) of* ***L21.***

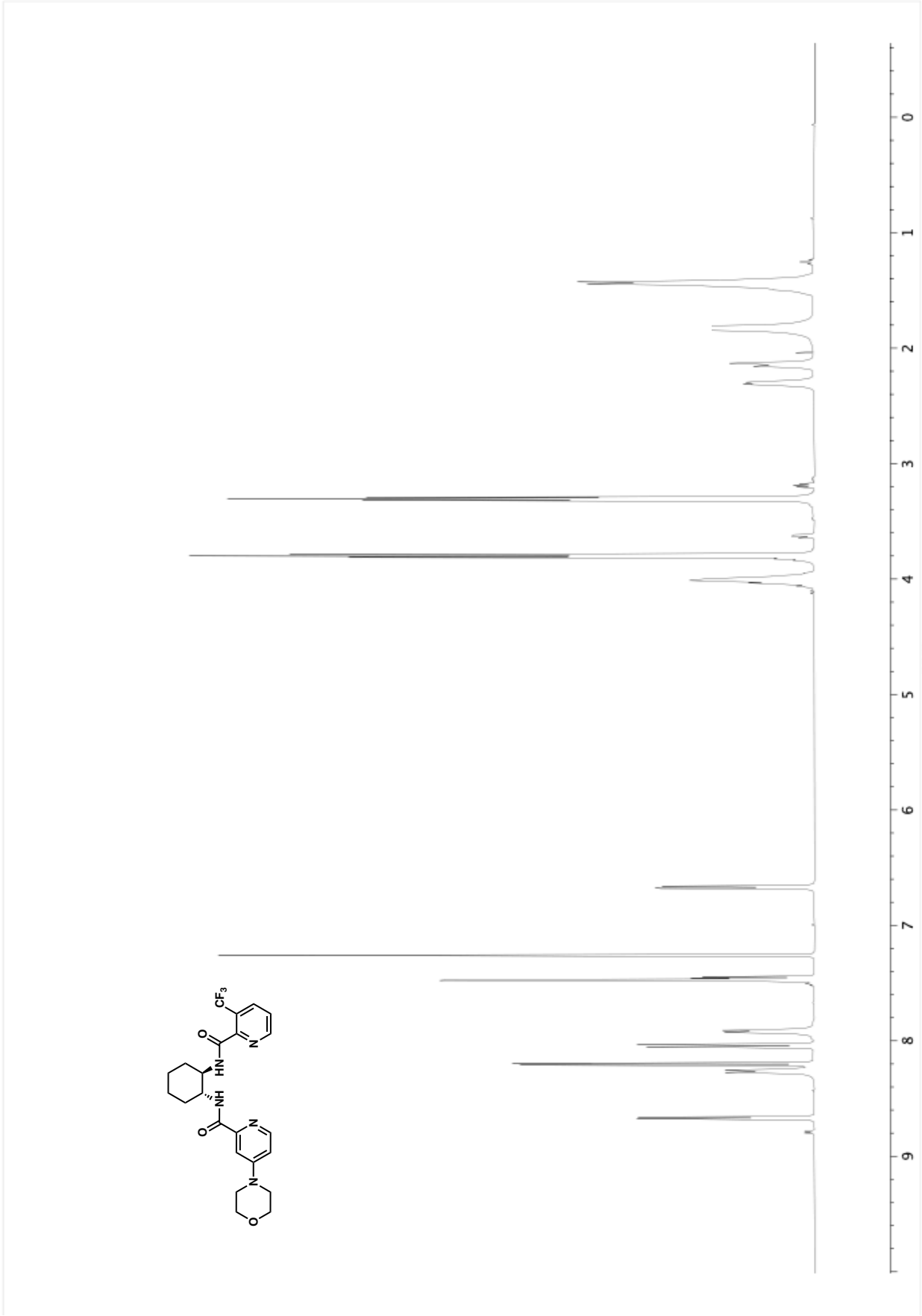

Figure A3.44. *^1H NMR (400 MHz, $CDCl_3$) of* ***L22****.*

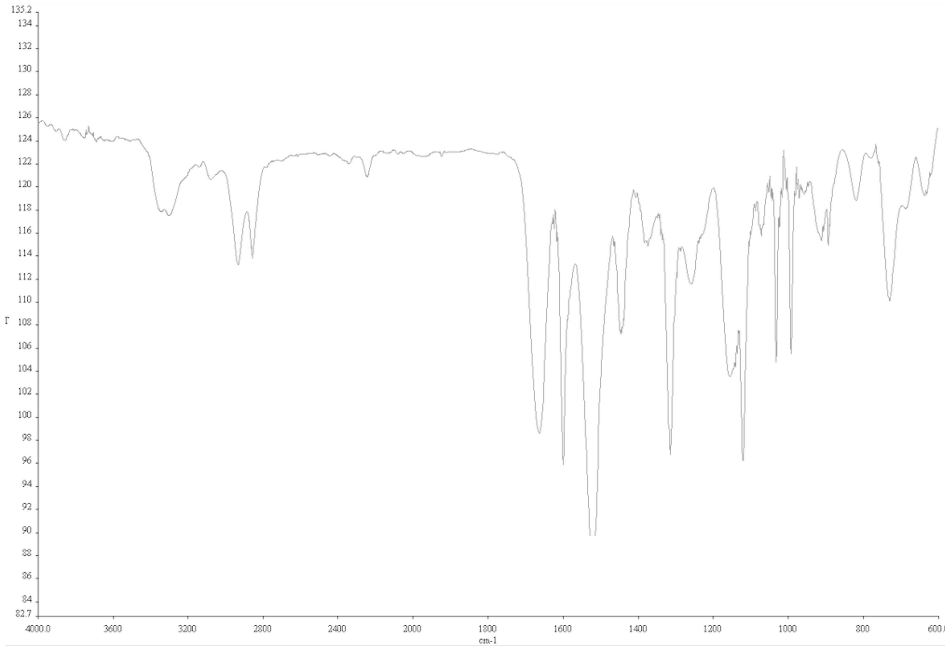

Figure A3.45. *Infrared spectrum (Thin Film, NaCl) of* ***L22.***

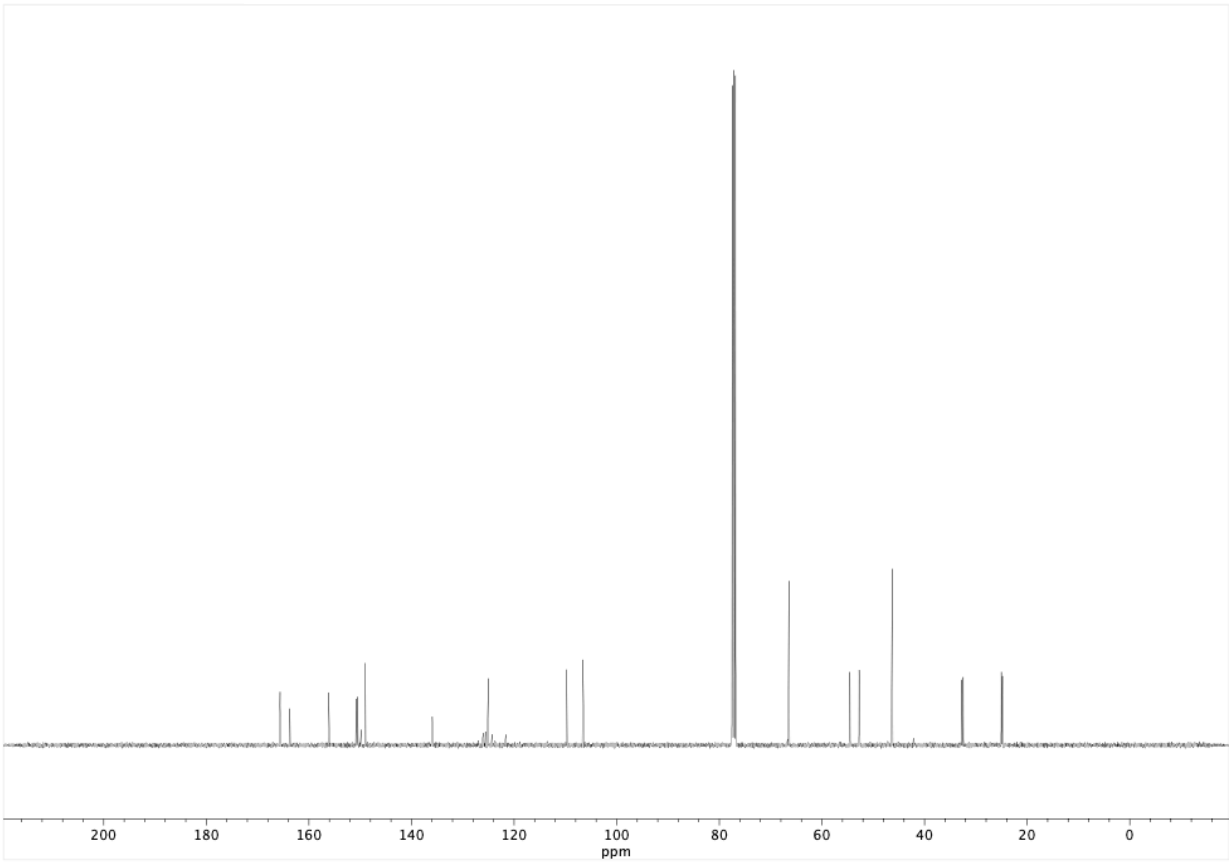

Figure A3.46. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***L22.***

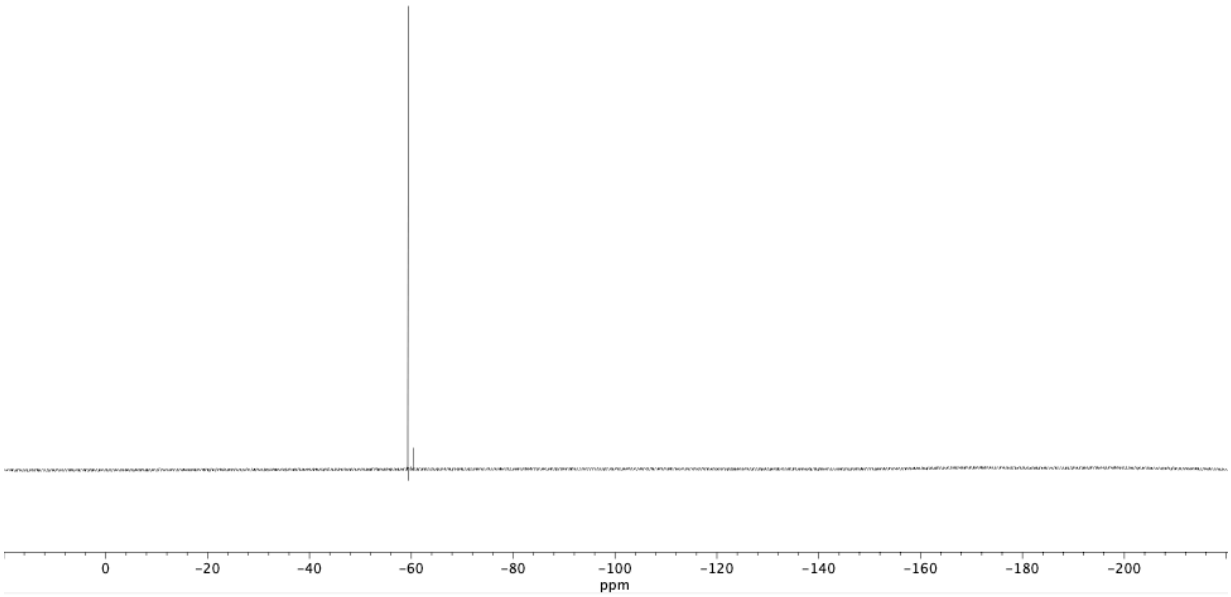

Figure A3.47. *^{19}F NMR (376 MHz, $CDCl_3$) of* ***L22.***

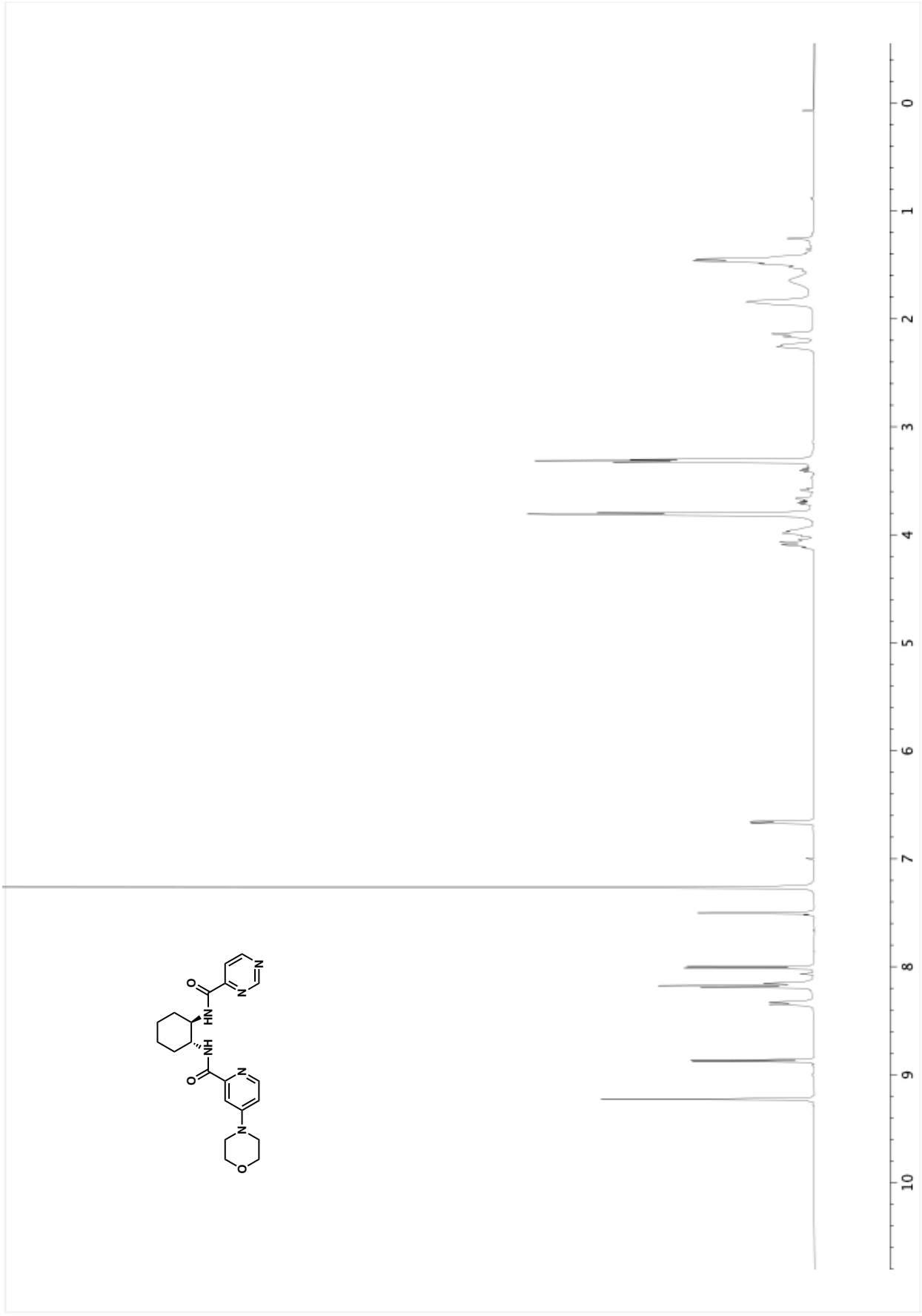

Figure A3.48. *^{1}H NMR (400 MHz, $CDCl_3$) of* ***L23.***

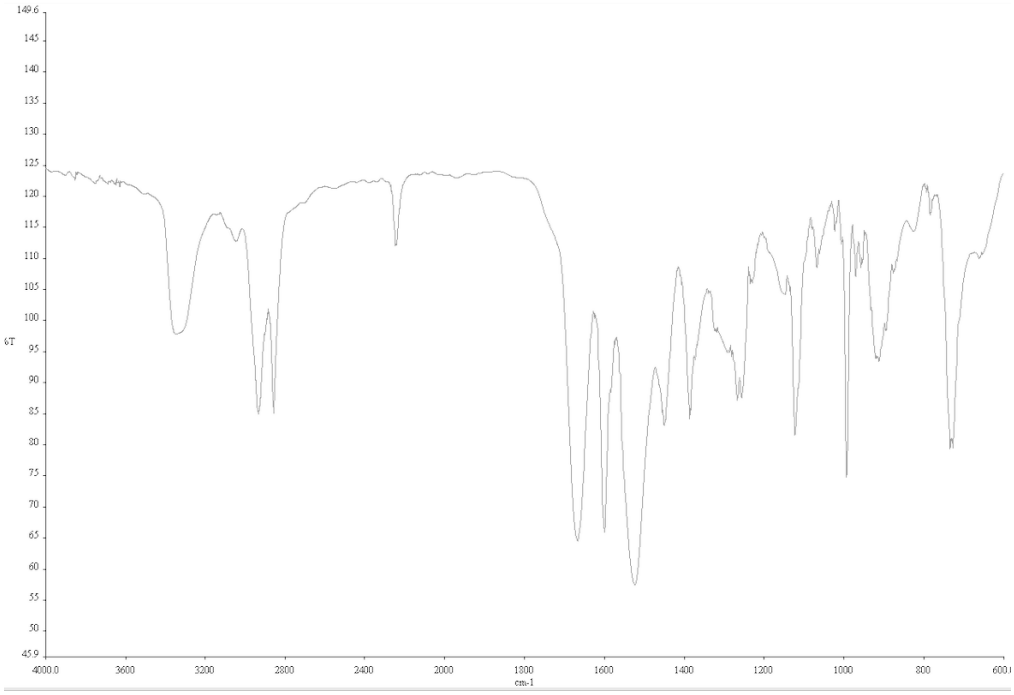

Figure A3.49. *Infrared spectrum (Thin Film, NaCl) of* ***L23.***

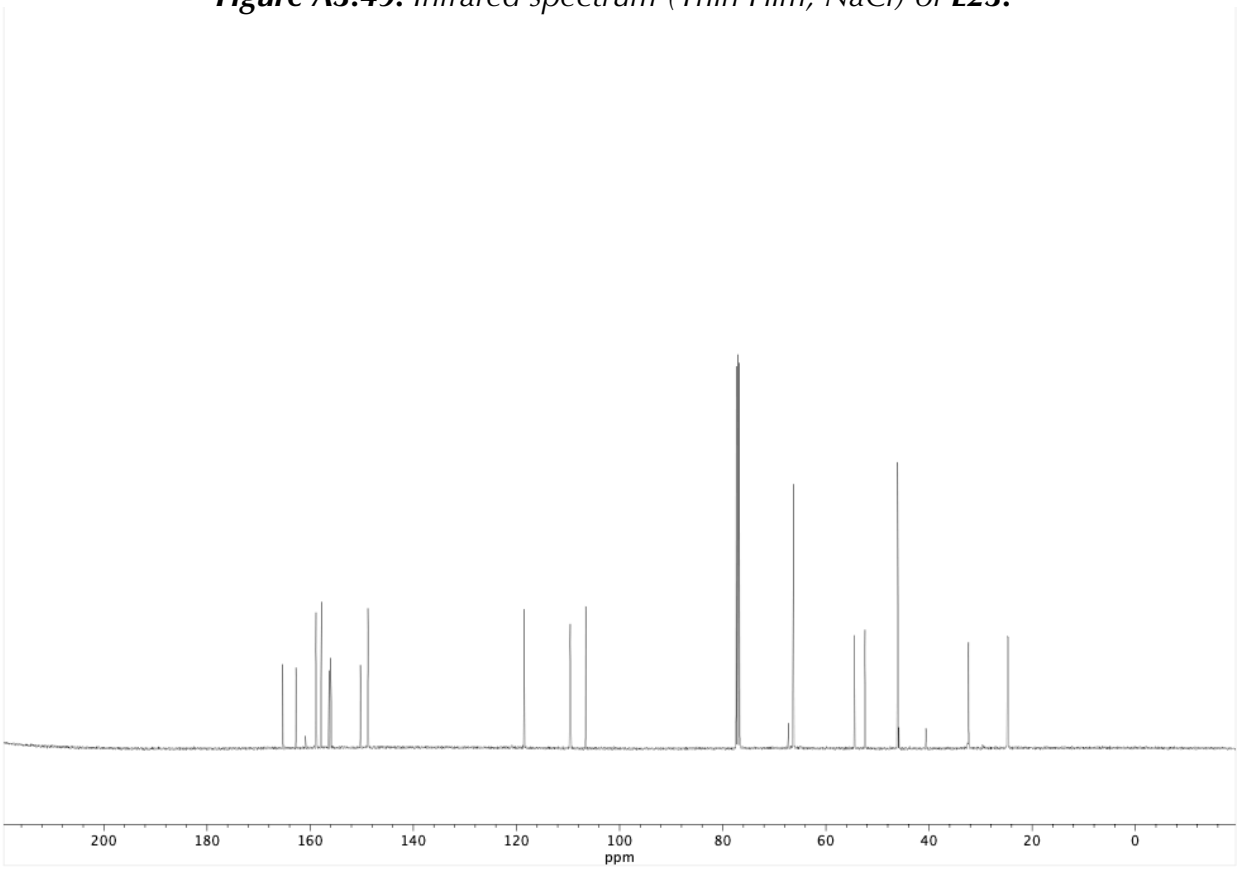

Figure A3.50. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***L23.***

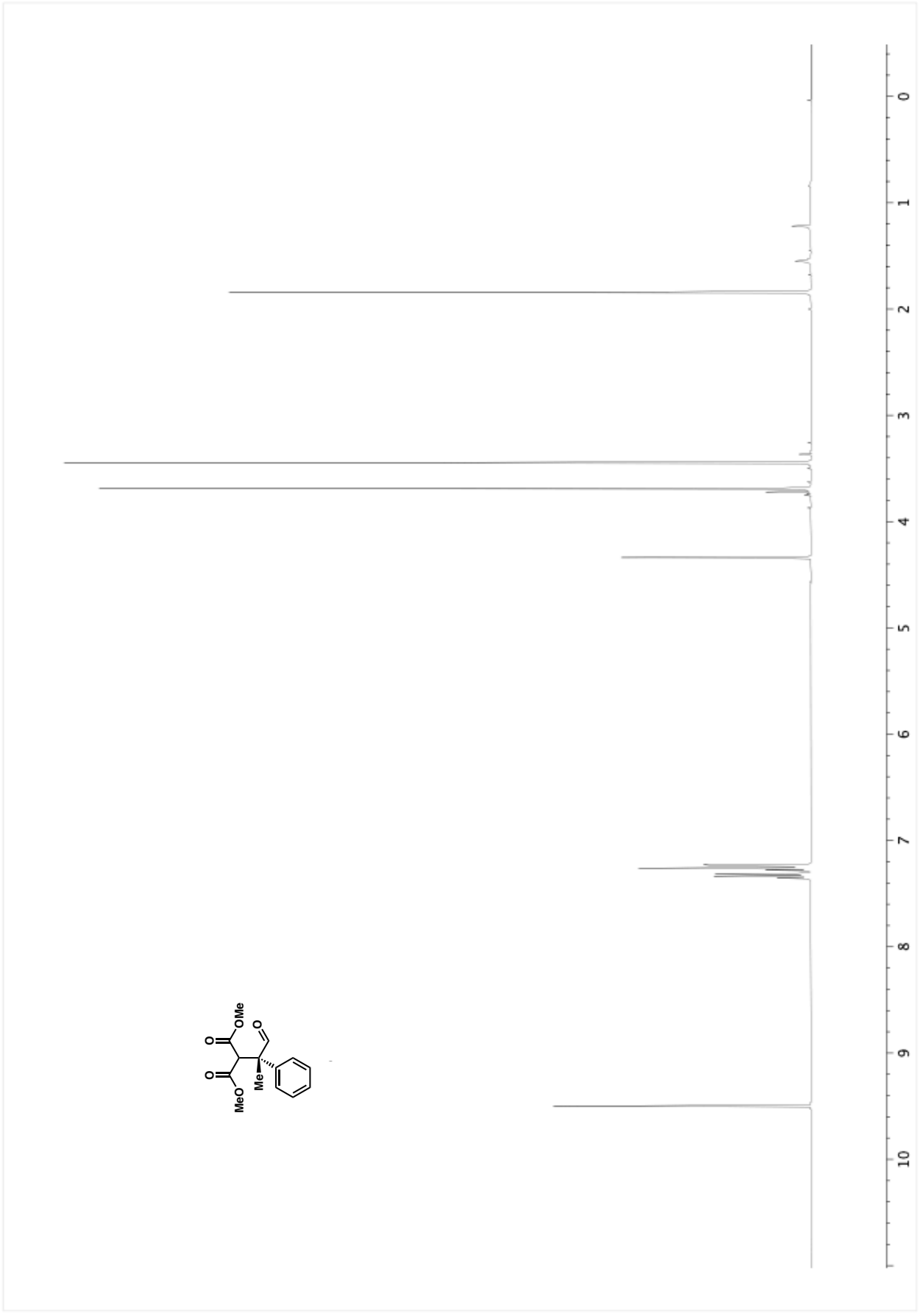

Figure A3.51. *^{1}H NMR (400 MHz, $CDCl_3$) of* ***55****.*

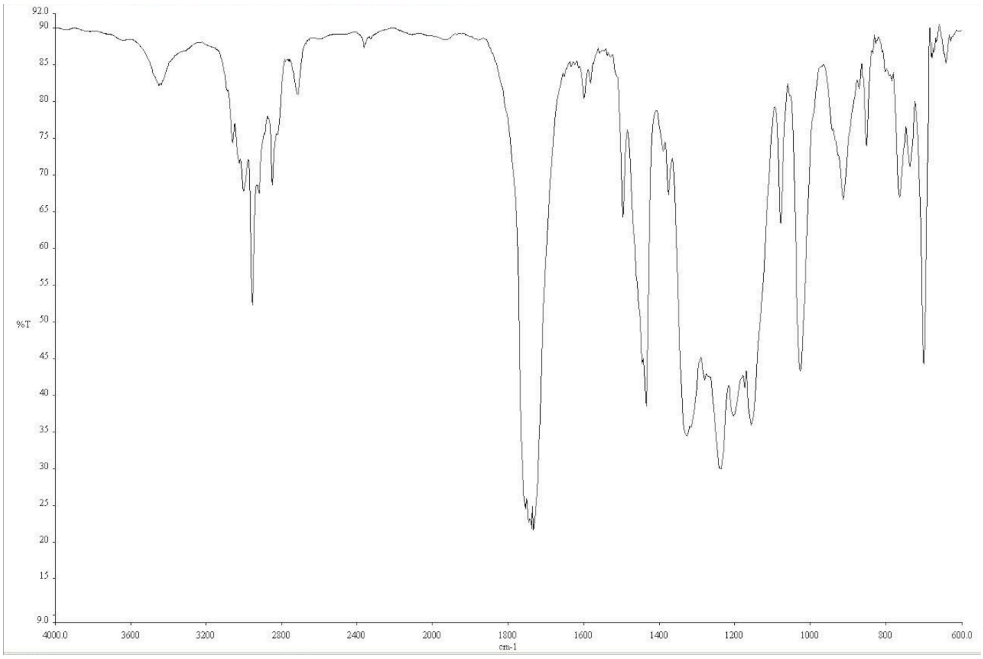

Figure A3.52. *Infrared spectrum (Thin Film, NaCl) of* ***55.***

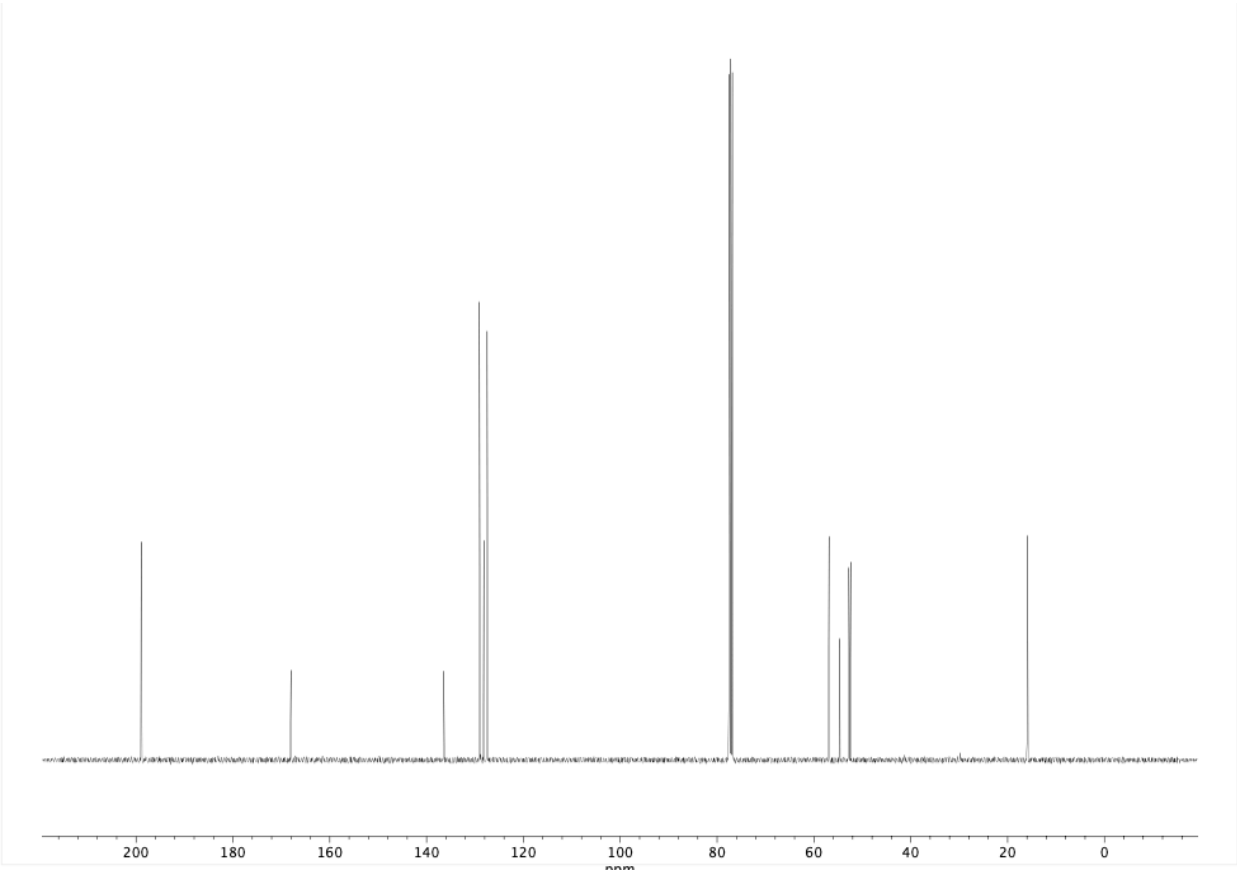

Figure A3.53. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***55.***

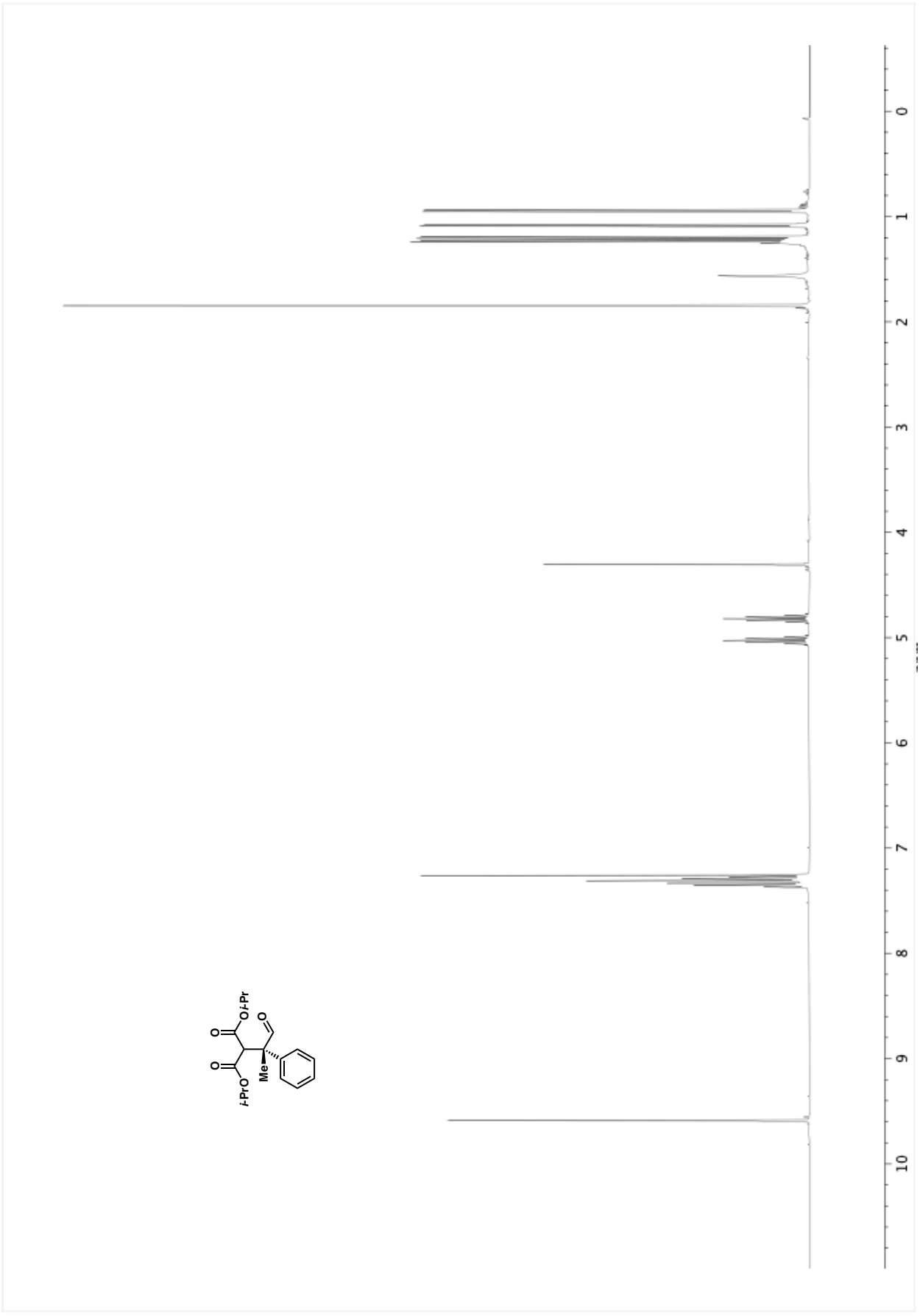

Figure A3.54. *^{1}H NMR (400 MHz, $CDCl_3$) of* ***56****.*

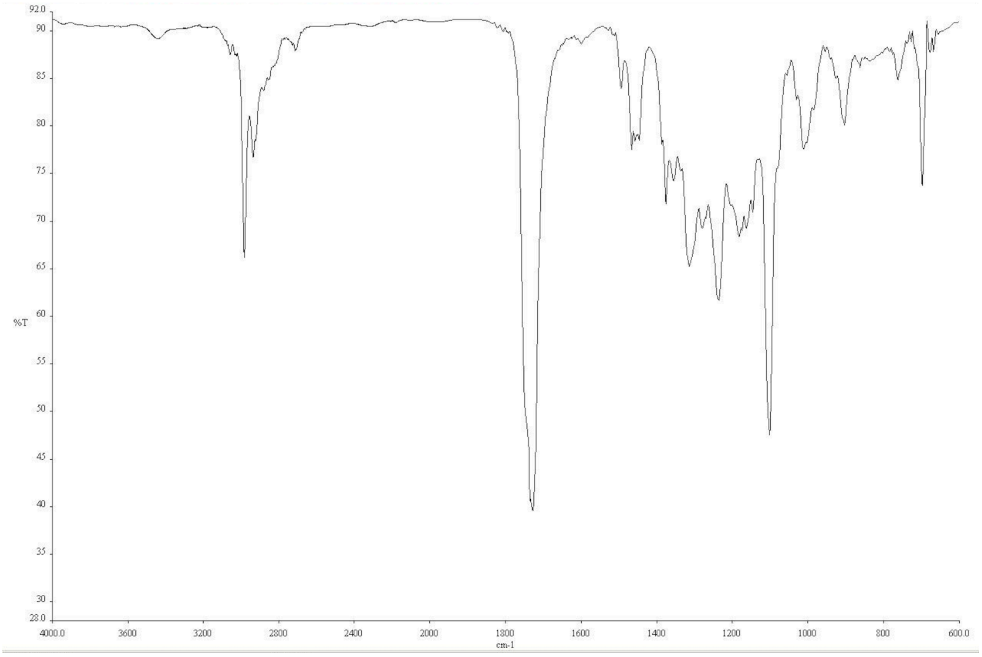

Figure A3.55. *Infrared spectrum (Thin Film, NaCl) of* ***56****.*

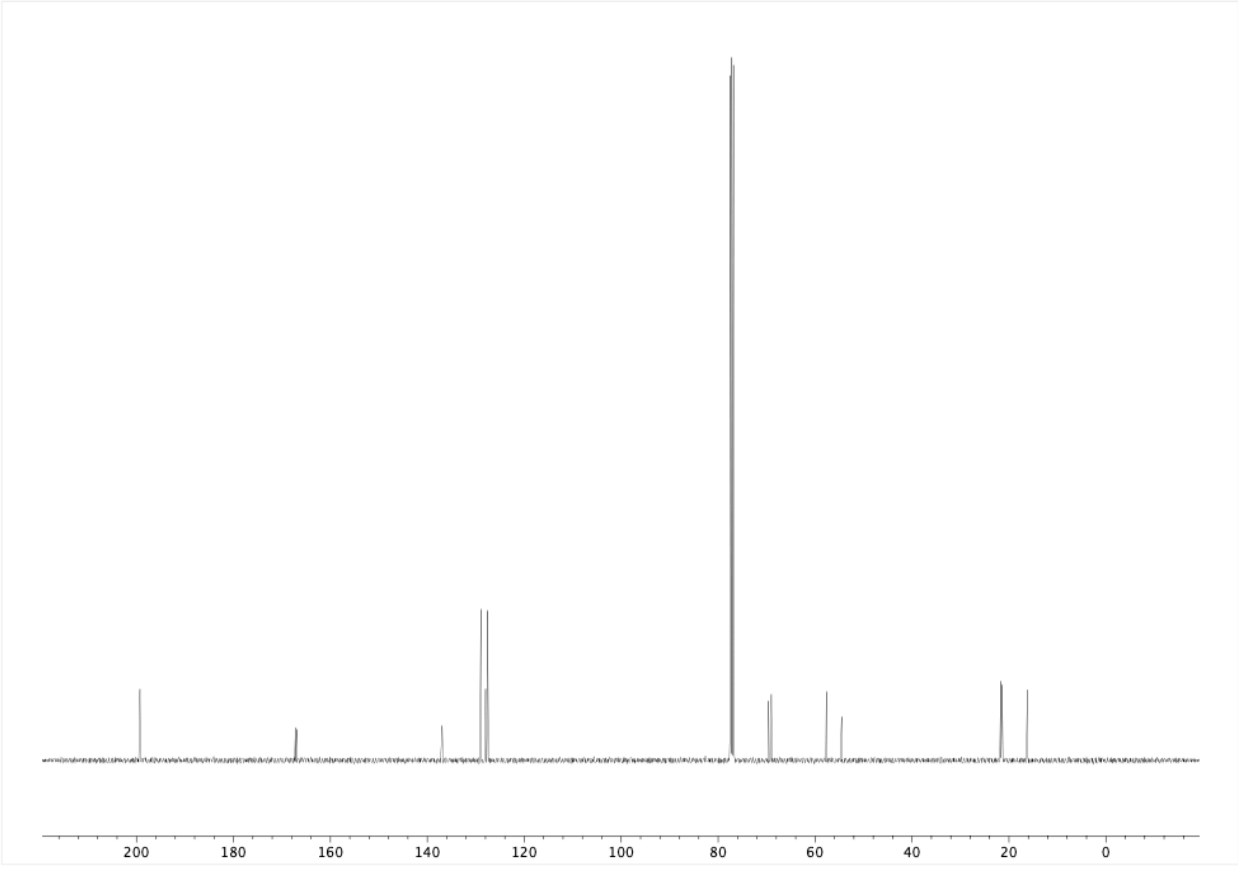

Figure A3.56. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***56.***

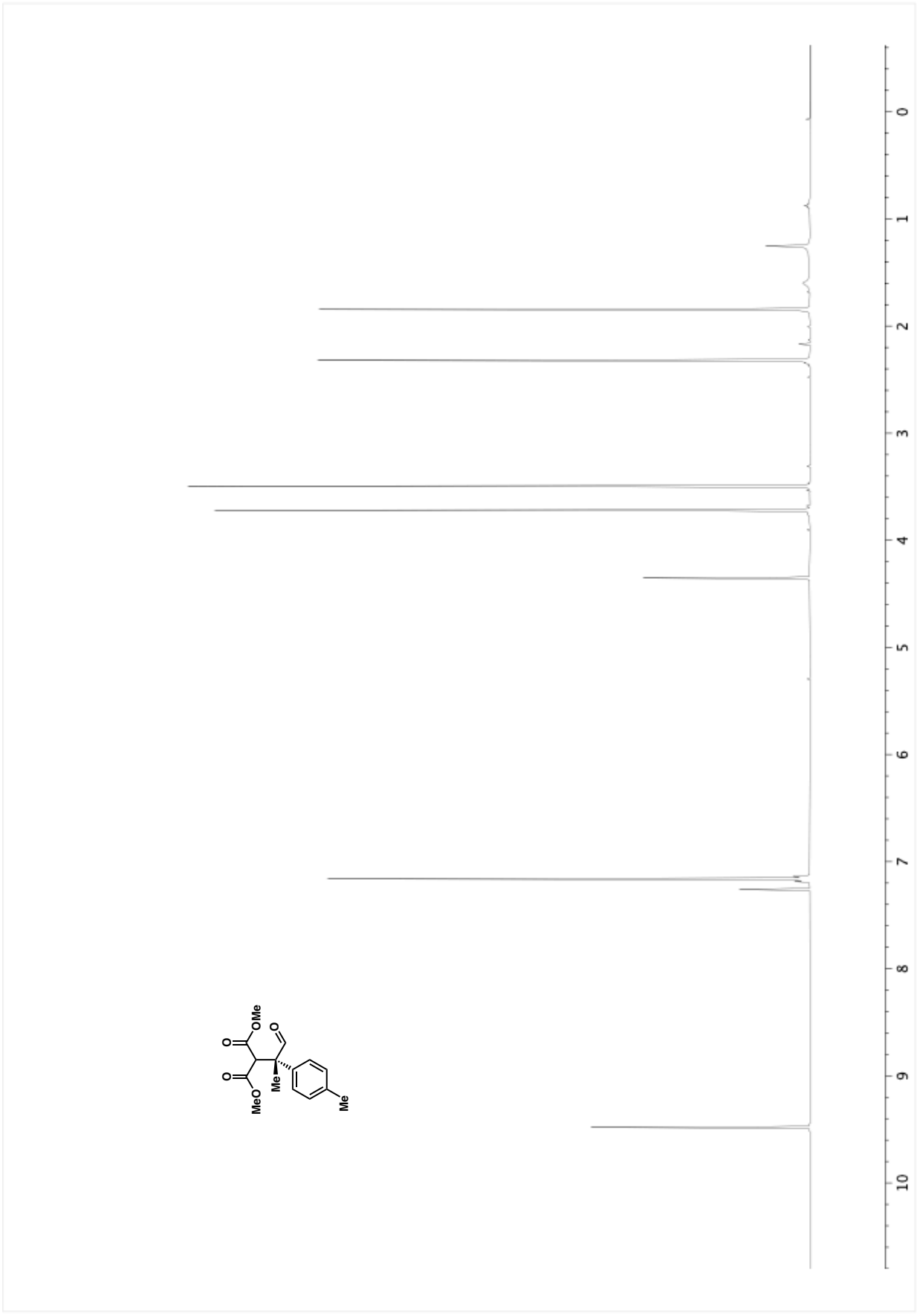

Figure A3.57. *^1H NMR (400 MHz, $CDCl_3$) of* ***58****.*

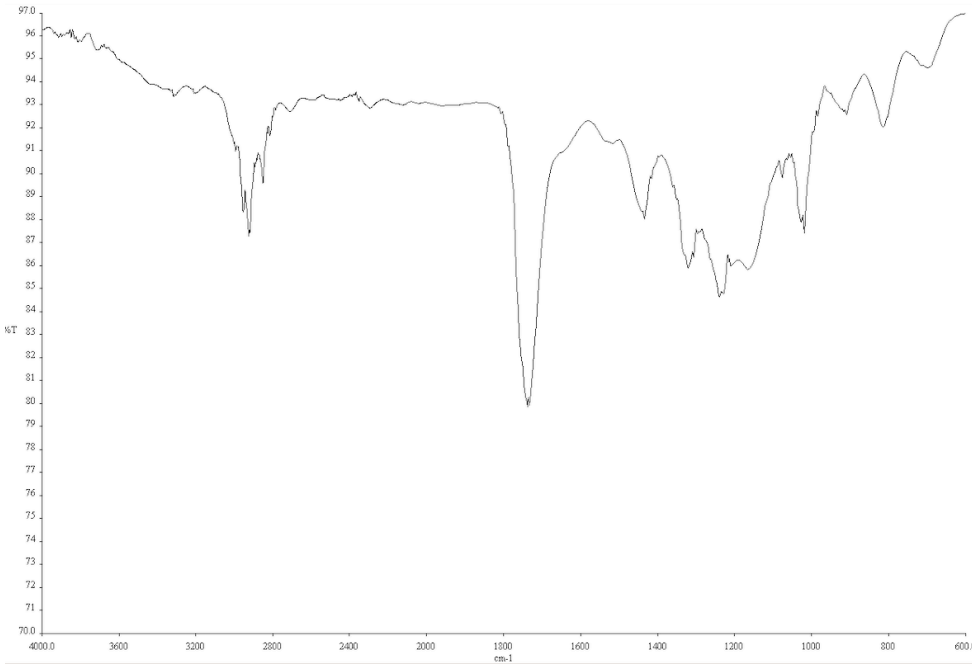

Figure A3.58. *Infrared spectrum (Thin Film, NaCl) of* ***58.***

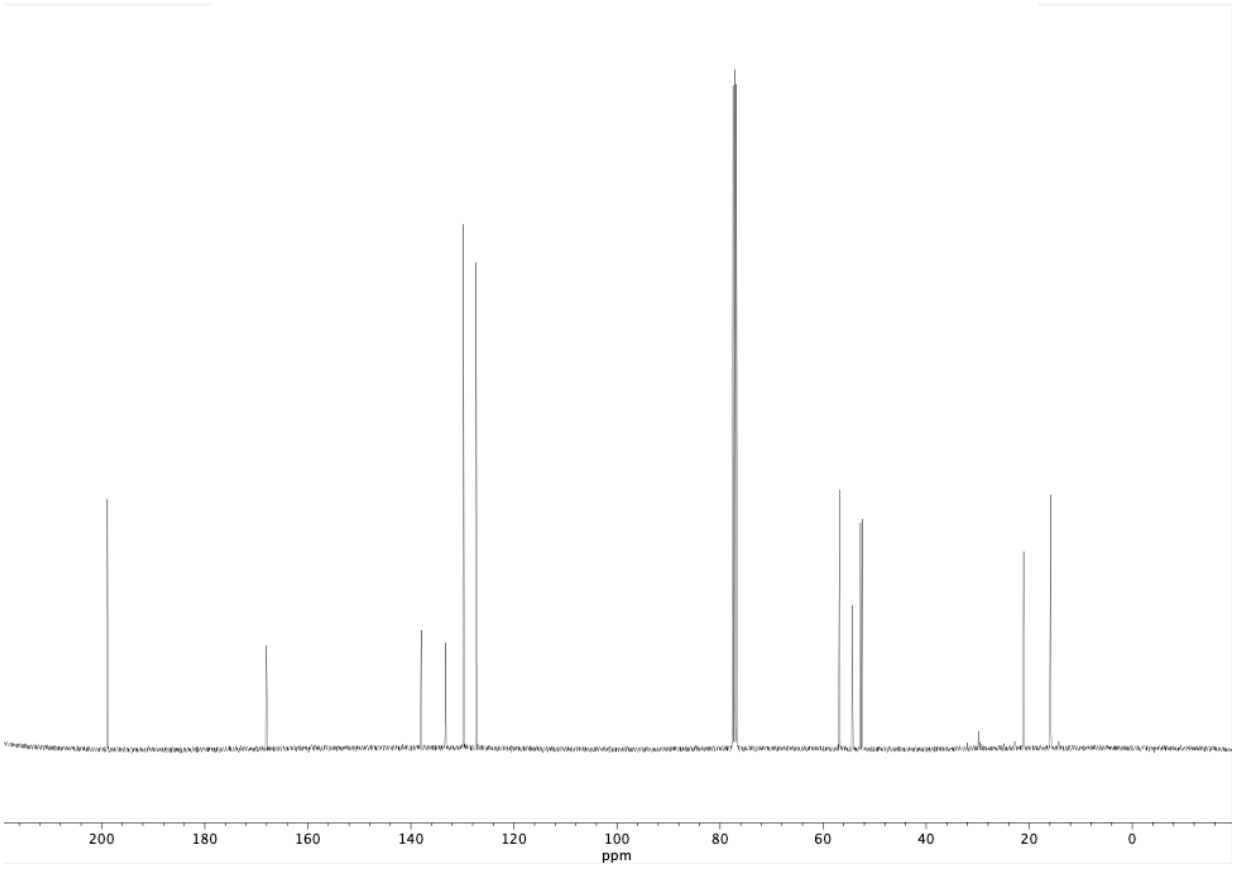

Figure A3.59. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***58.***

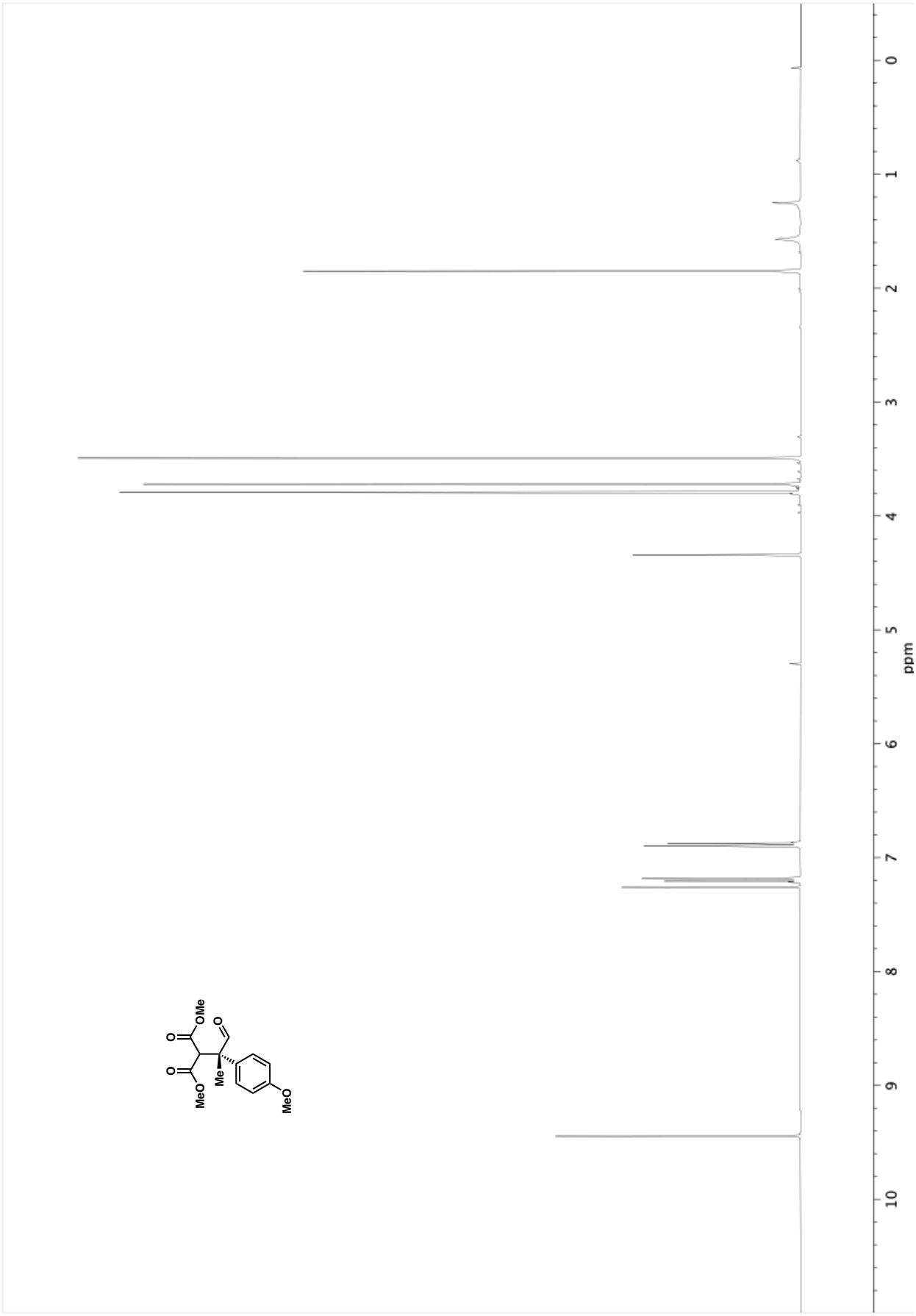

Figure A3.60. *^1H NMR (400 MHz, $CDCl_3$) of* ***59***.

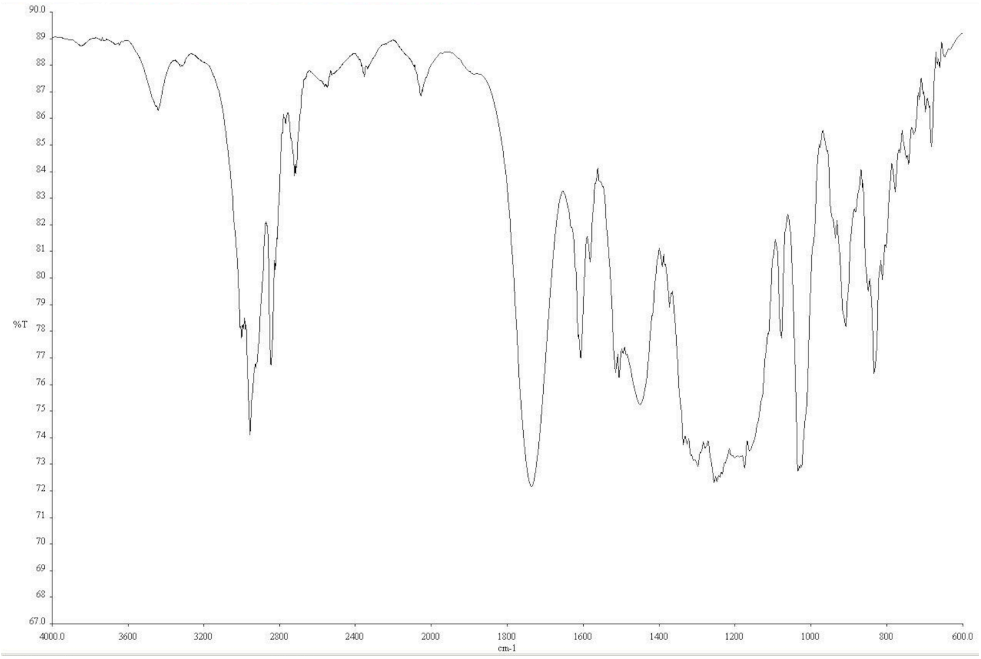

Figure A3.61. *Infrared spectrum (Thin Film, NaCl) of* ***59****.*

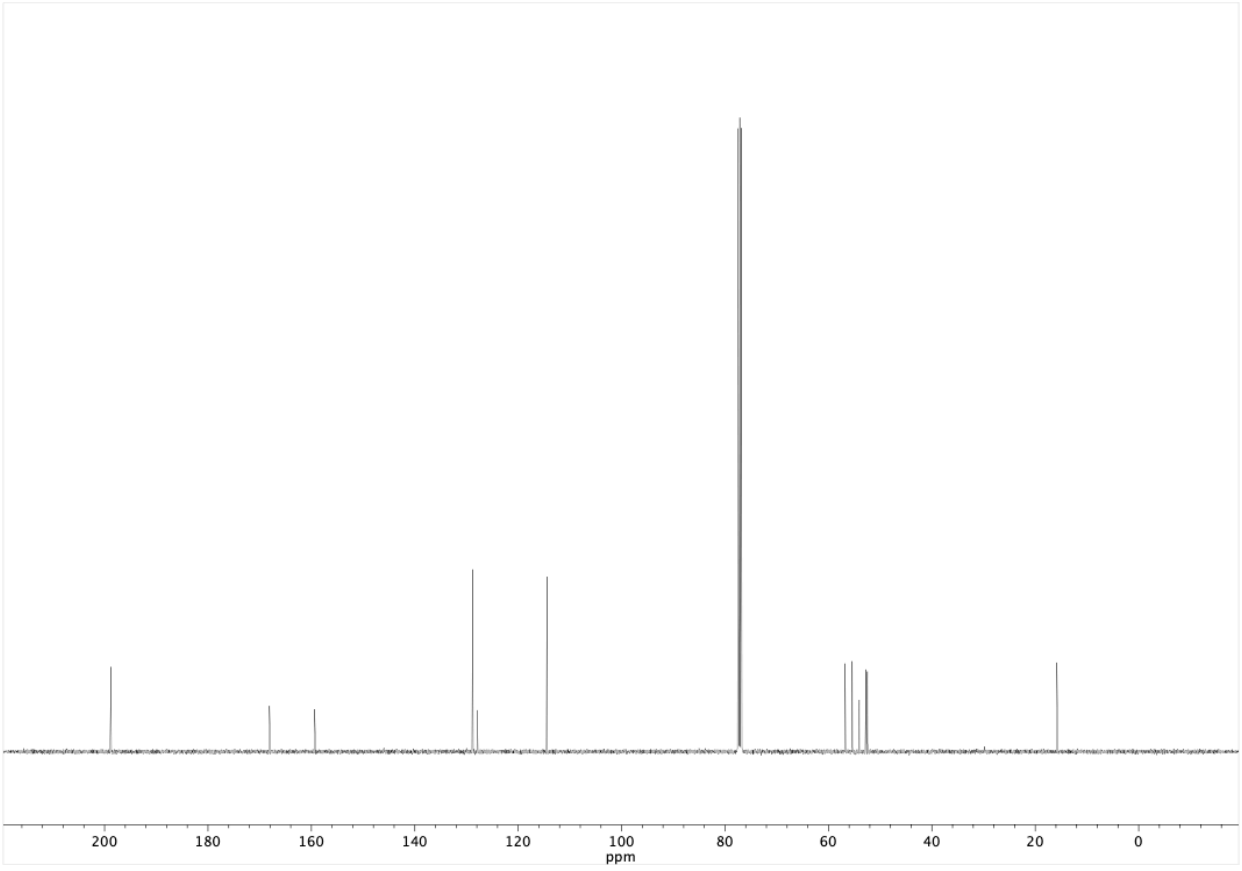

Figure A3.62. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***59.***

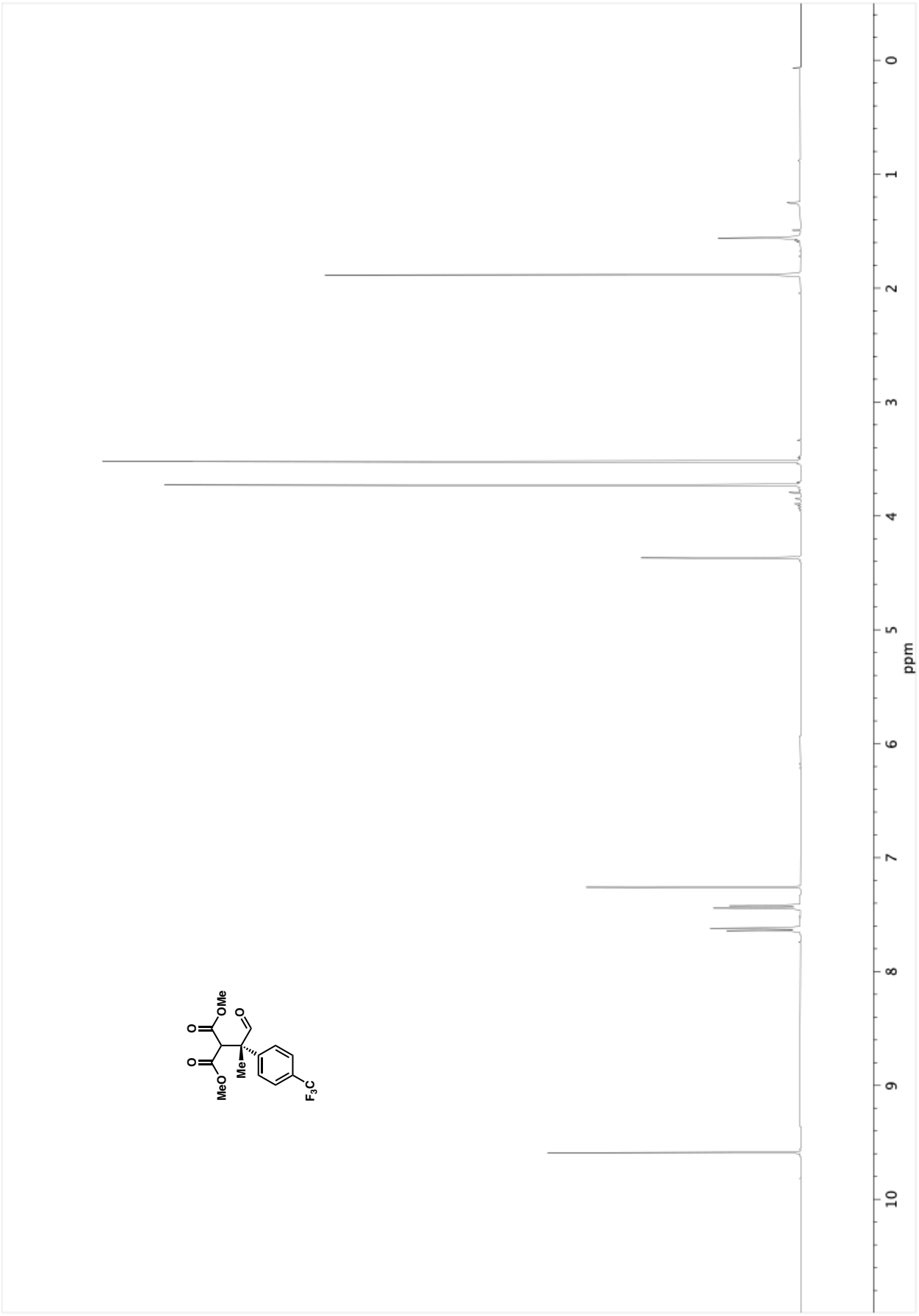

Figure A3.63. *^1H NMR (400 MHz, $CDCl_3$) of* ***60****.*

z

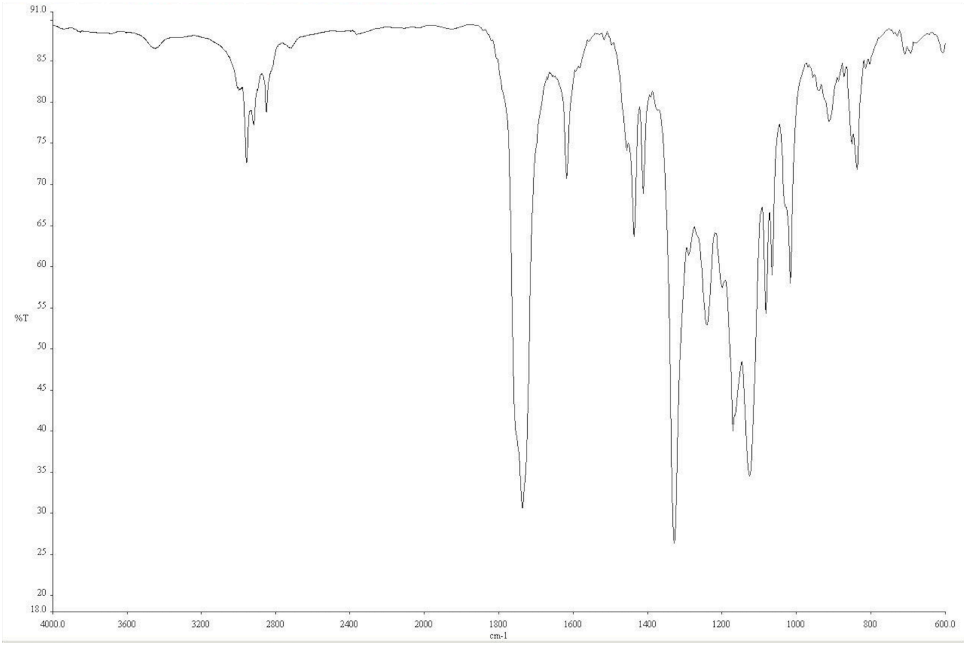

Figure A3.64. *Infrared spectrum (Thin Film, NaCl) of* ***60****.*

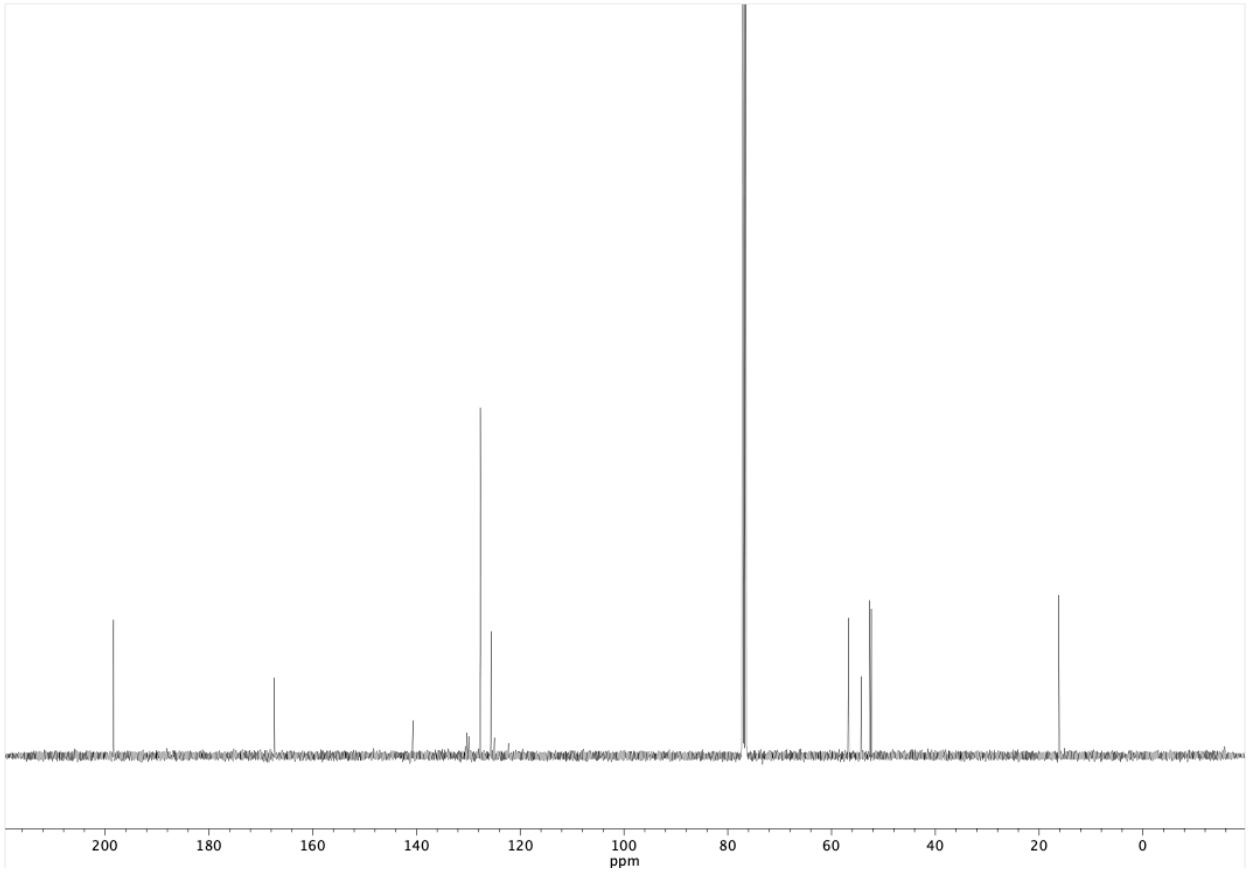

Figure A3.65. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***60.***

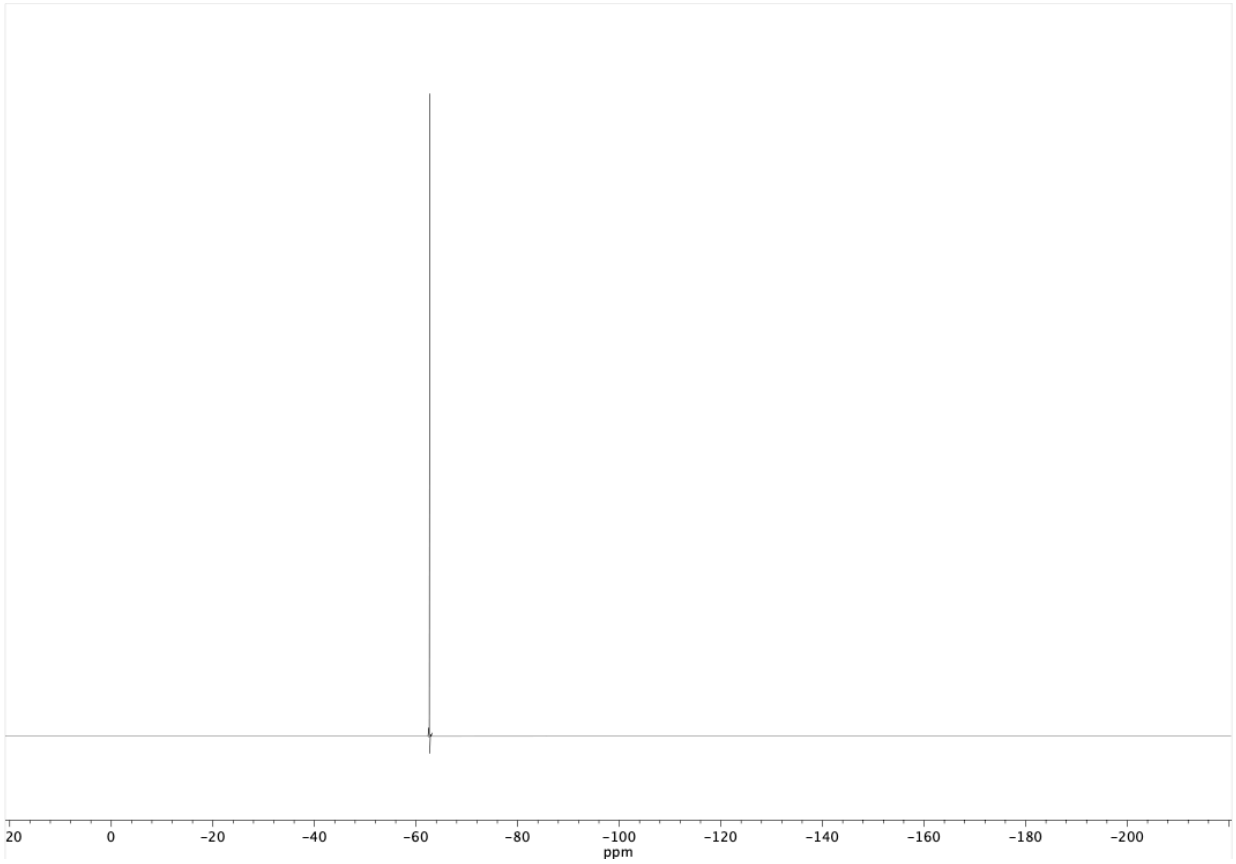

Figure A3.66. *^{19}F NMR (376 MHz, $CDCl_3$) of* ***60.***

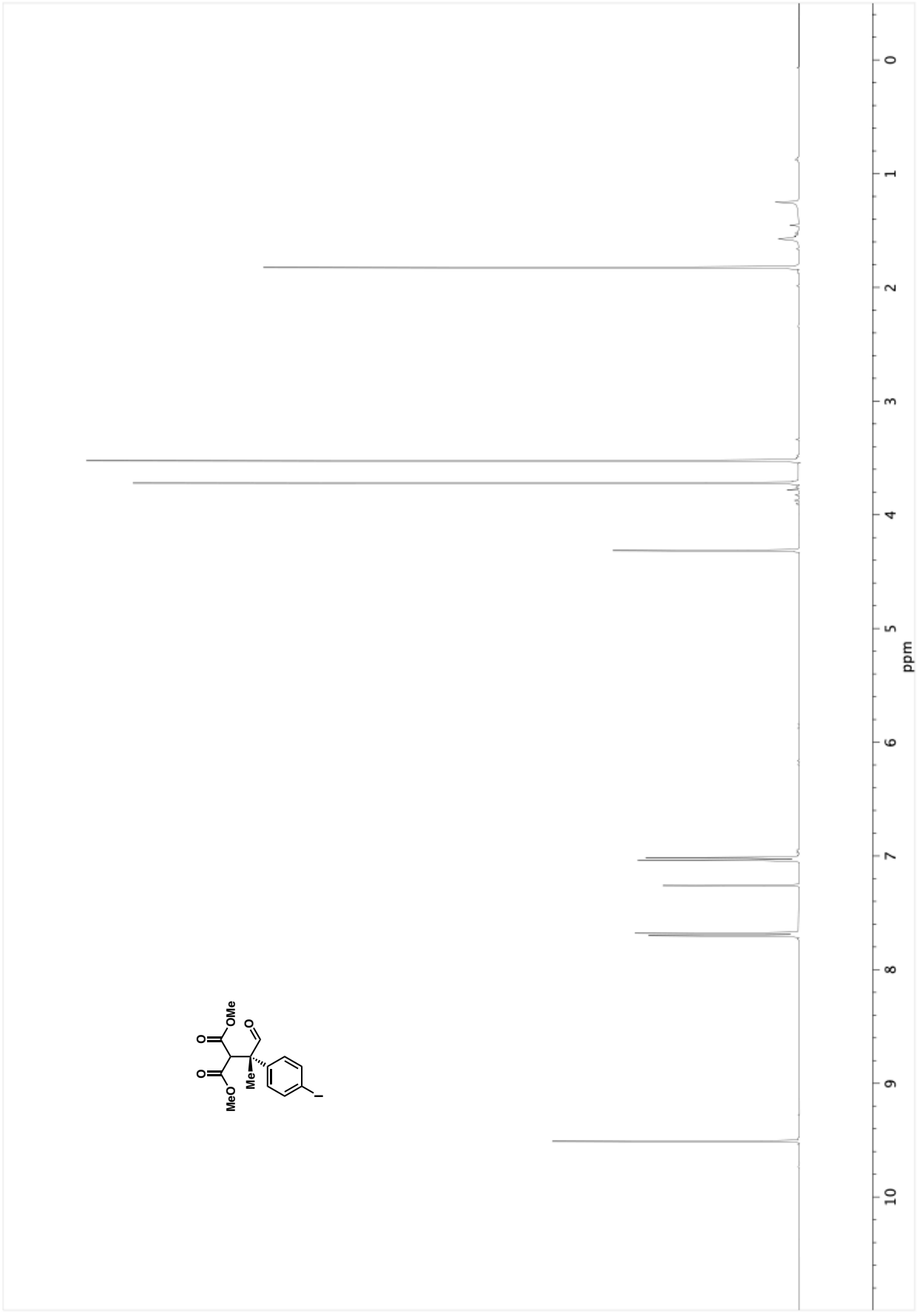

Figure A3.67. *^1H NMR (400 MHz, $CDCl_3$) of* ***62****.*

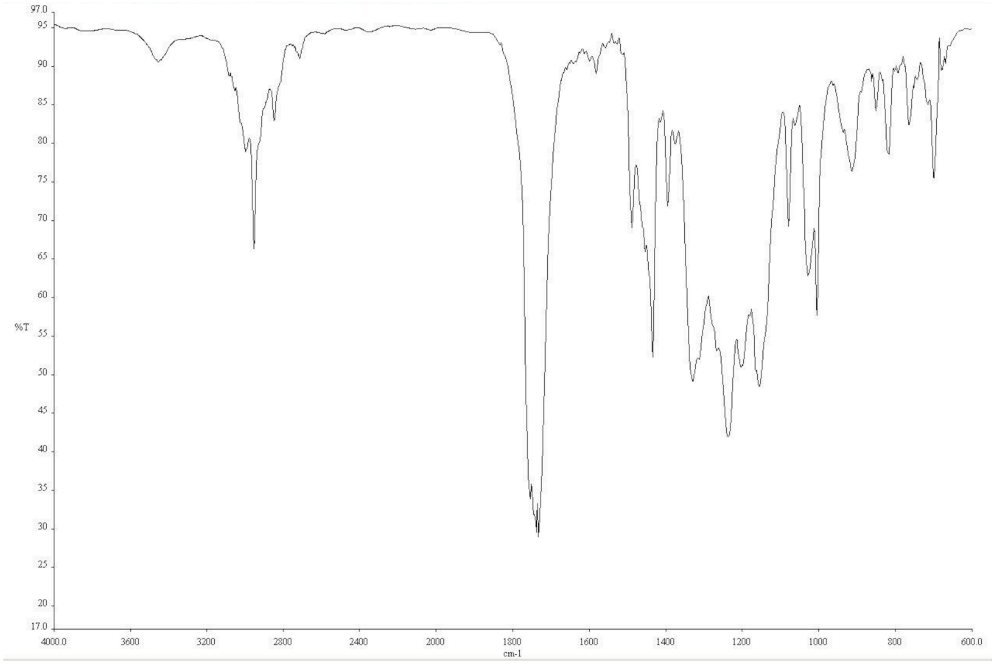

Figure A3.68. *Infrared spectrum (Thin Film, NaCl) of* ***62****.*

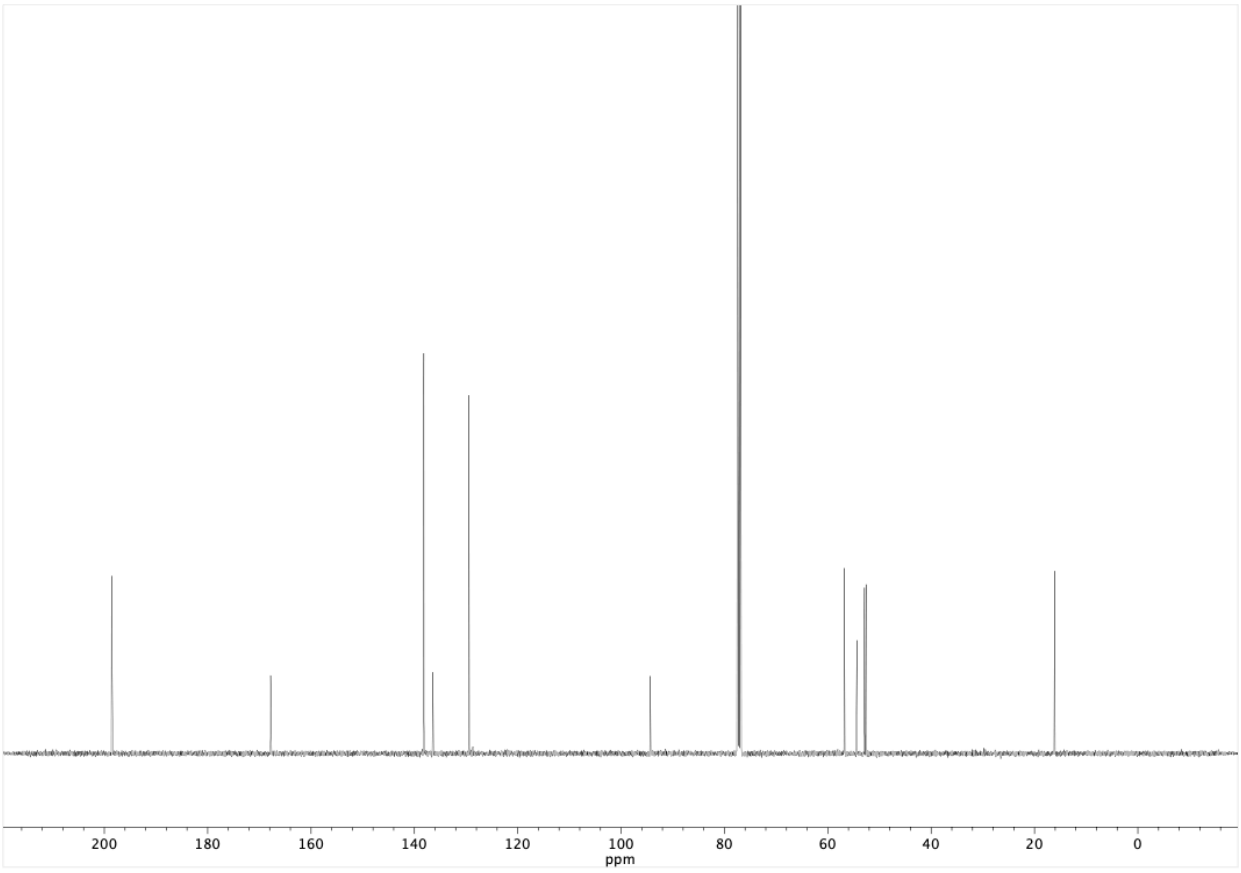

Figure A3.69. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***62.***

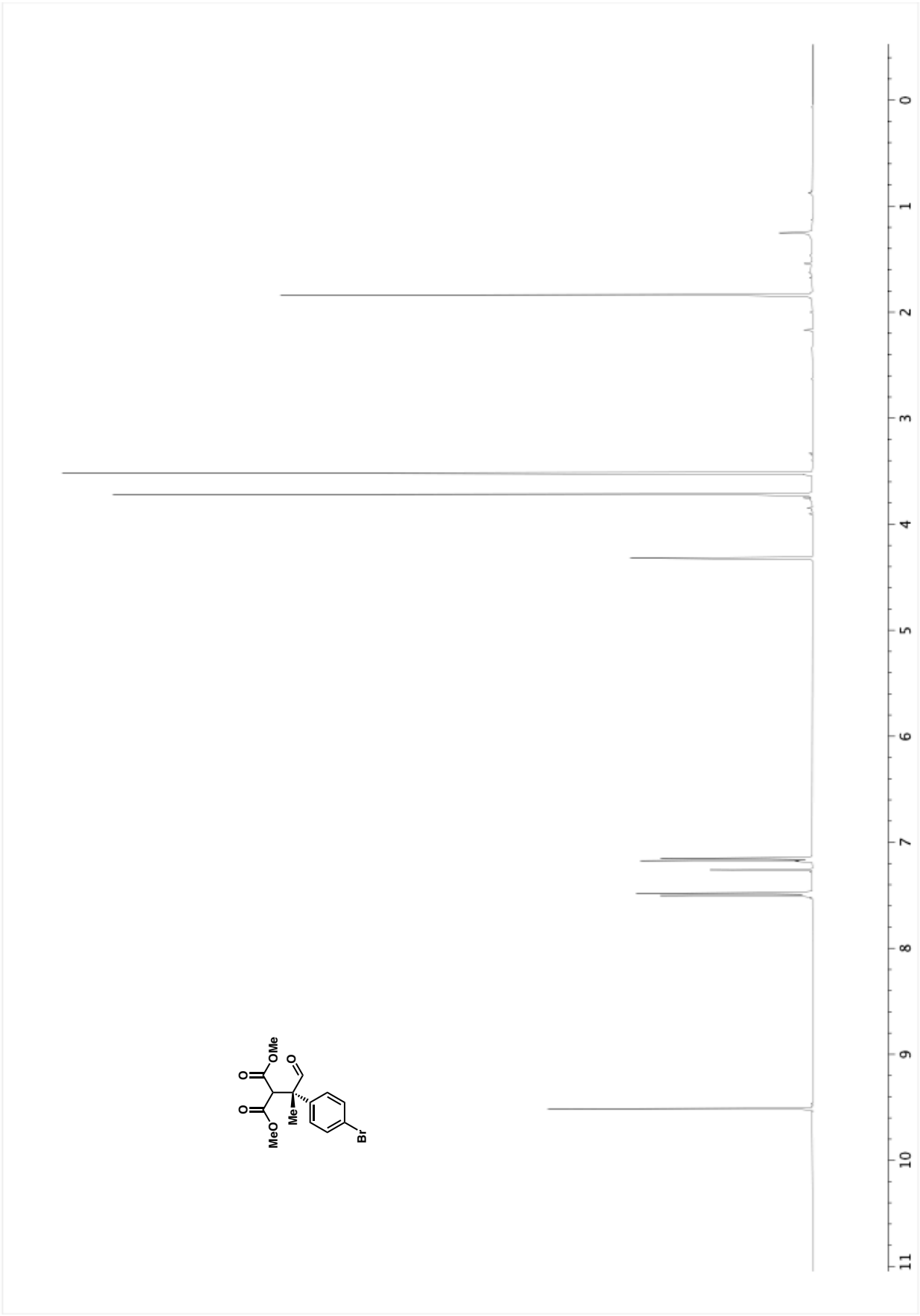

Figure A3.70. *^1H NMR (400 MHz, $CDCl_3$) of* ***63****.*

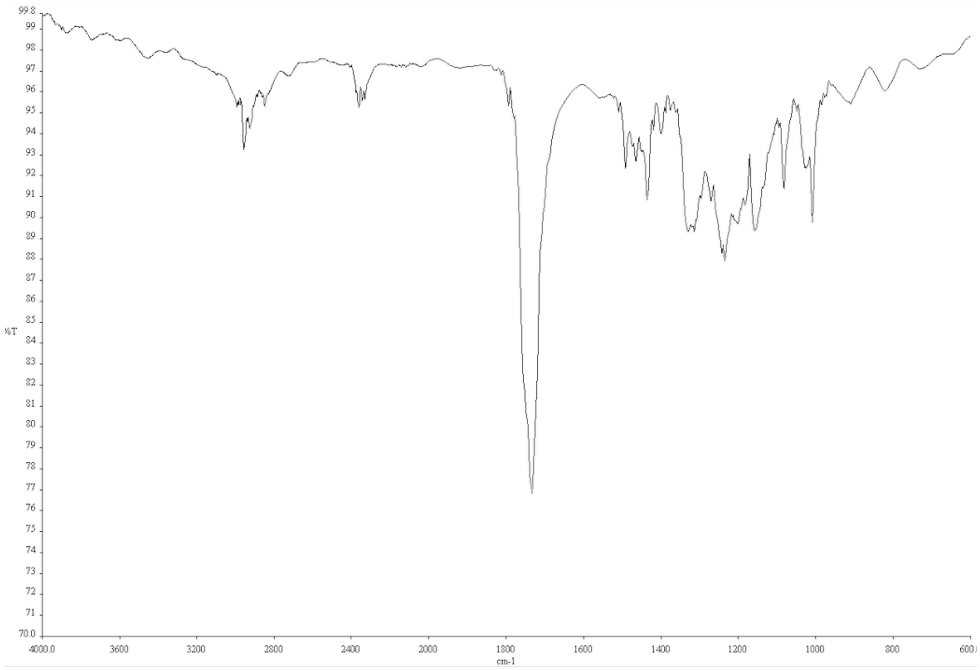

Figure A3.71. *Infrared spectrum (Thin Film, NaCl) of* ***63.***

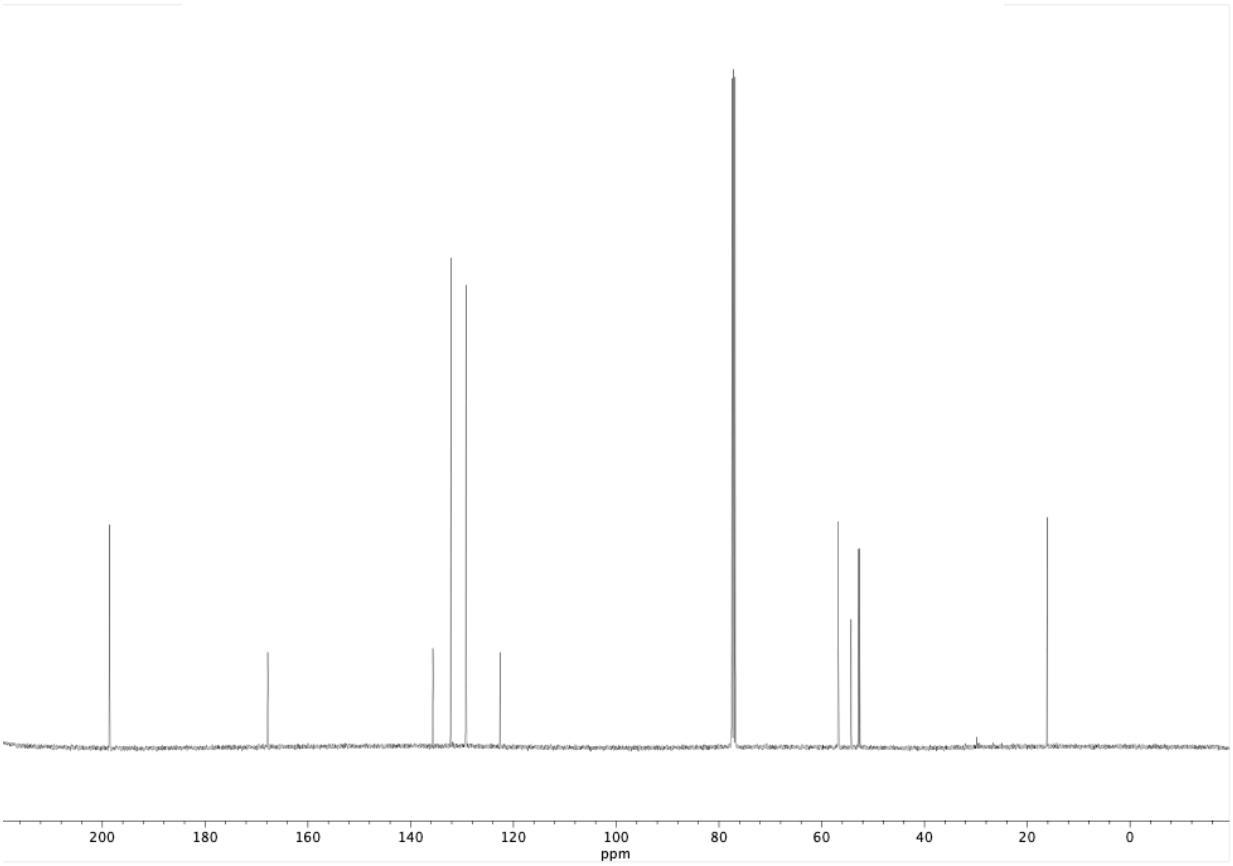

Figure A3.72. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***63.***

Figure A3.73. *^{1}H NMR (400 MHz, $CDCl_3$) of* ***64.***

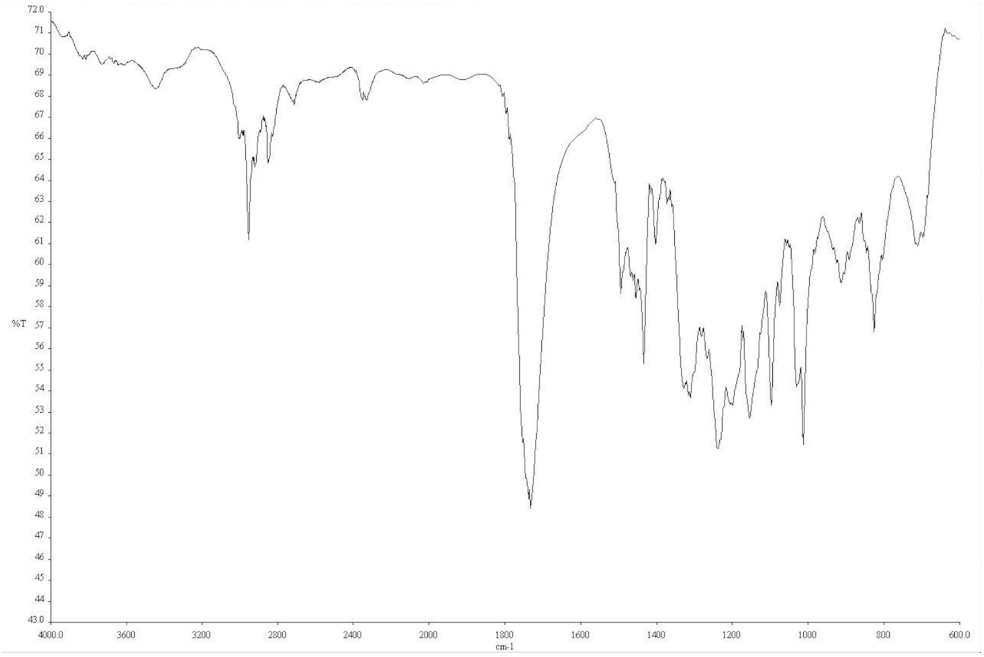

Figure A3.74. *Infrared spectrum (Thin Film, NaCl) of* ***64****.*

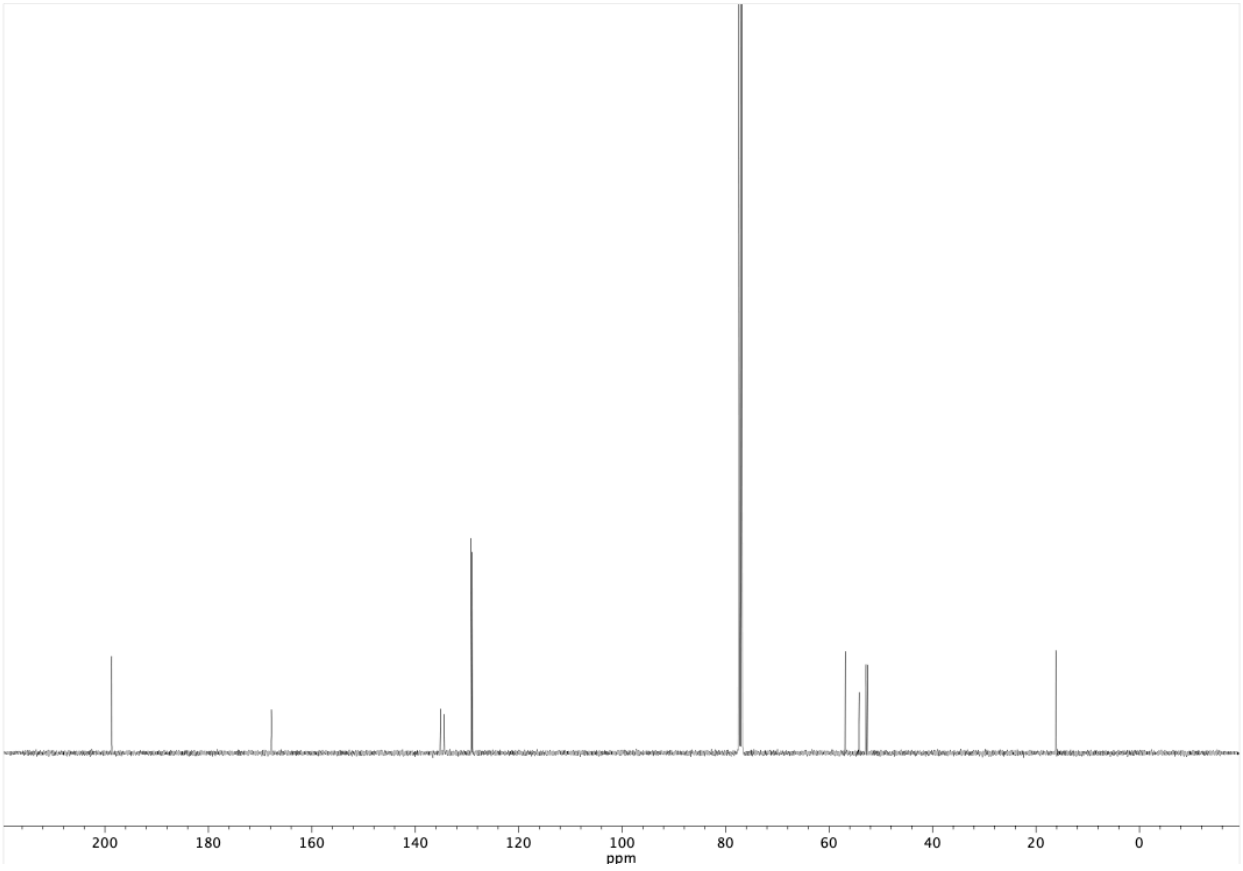

Figure A3.75. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***64.***

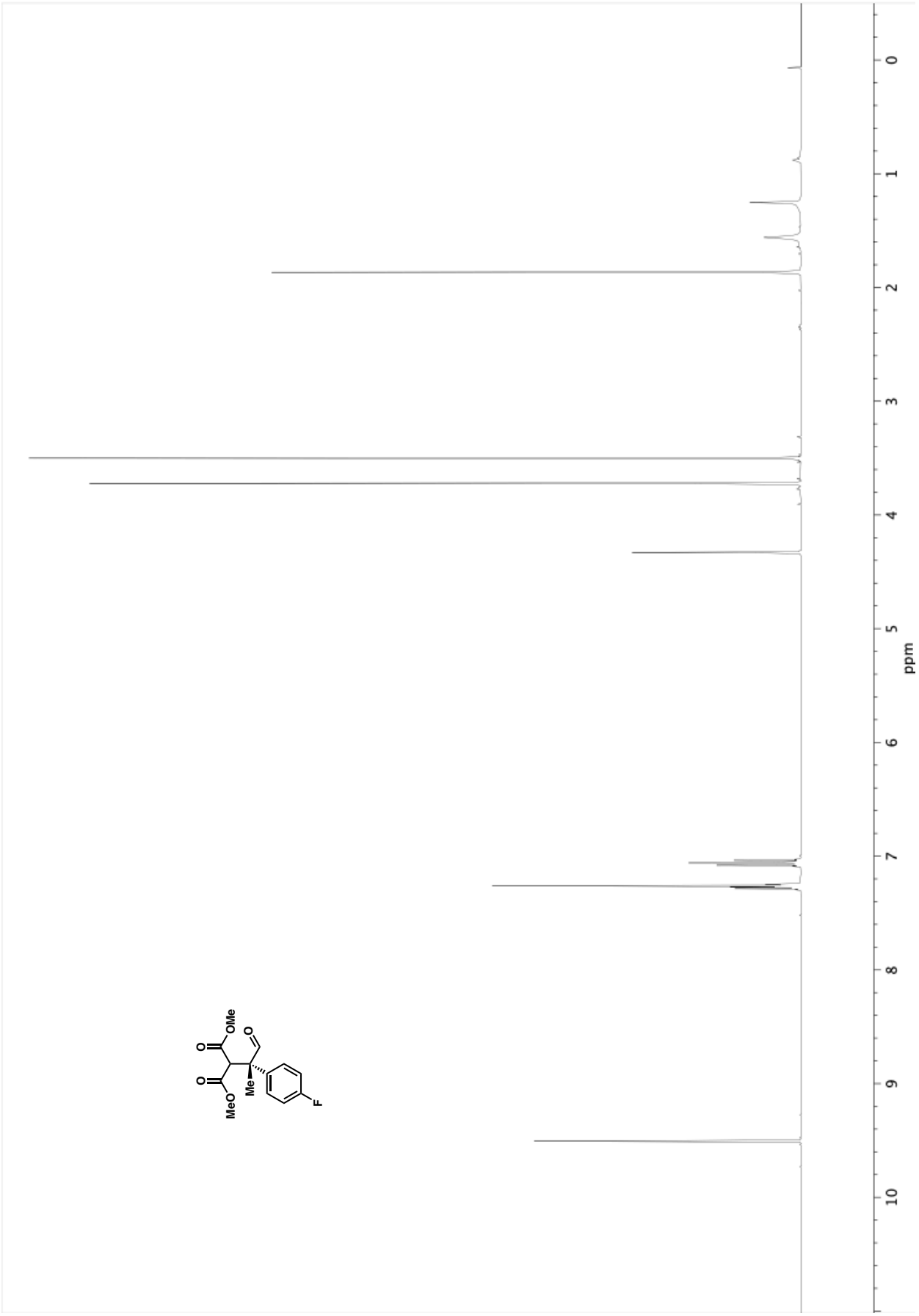

Figure A3.76. *^1H NMR (400 MHz, $CDCl_3$) of* ***65****.*

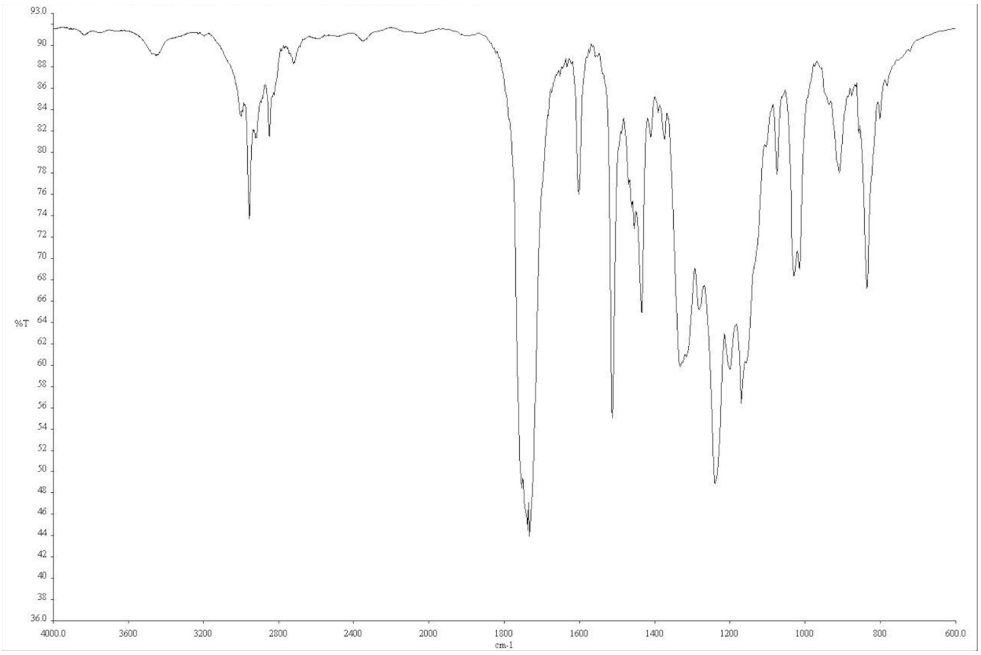

Figure A3.77. *Infrared spectrum (Thin Film, NaCl) of* ***65****.*

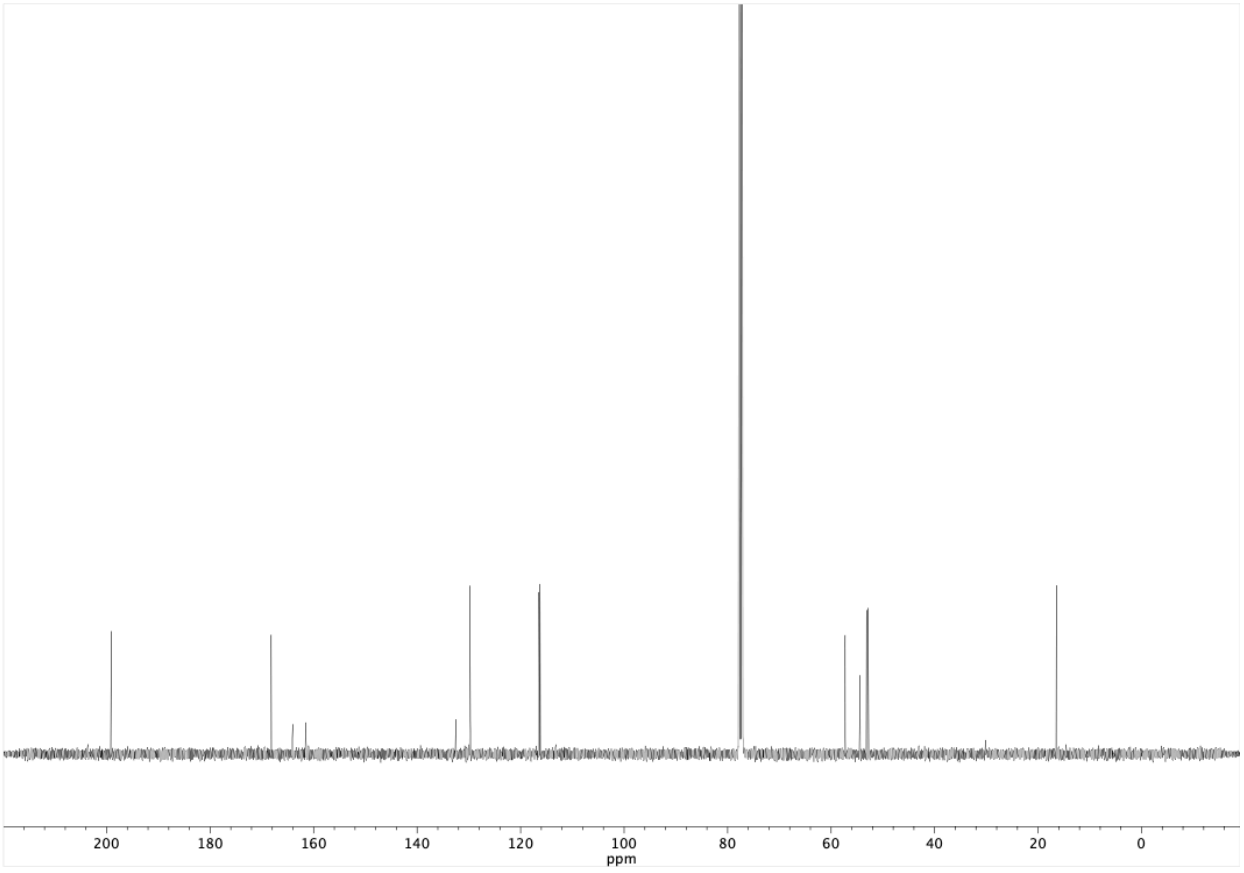

Figure A3.78. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***65.***

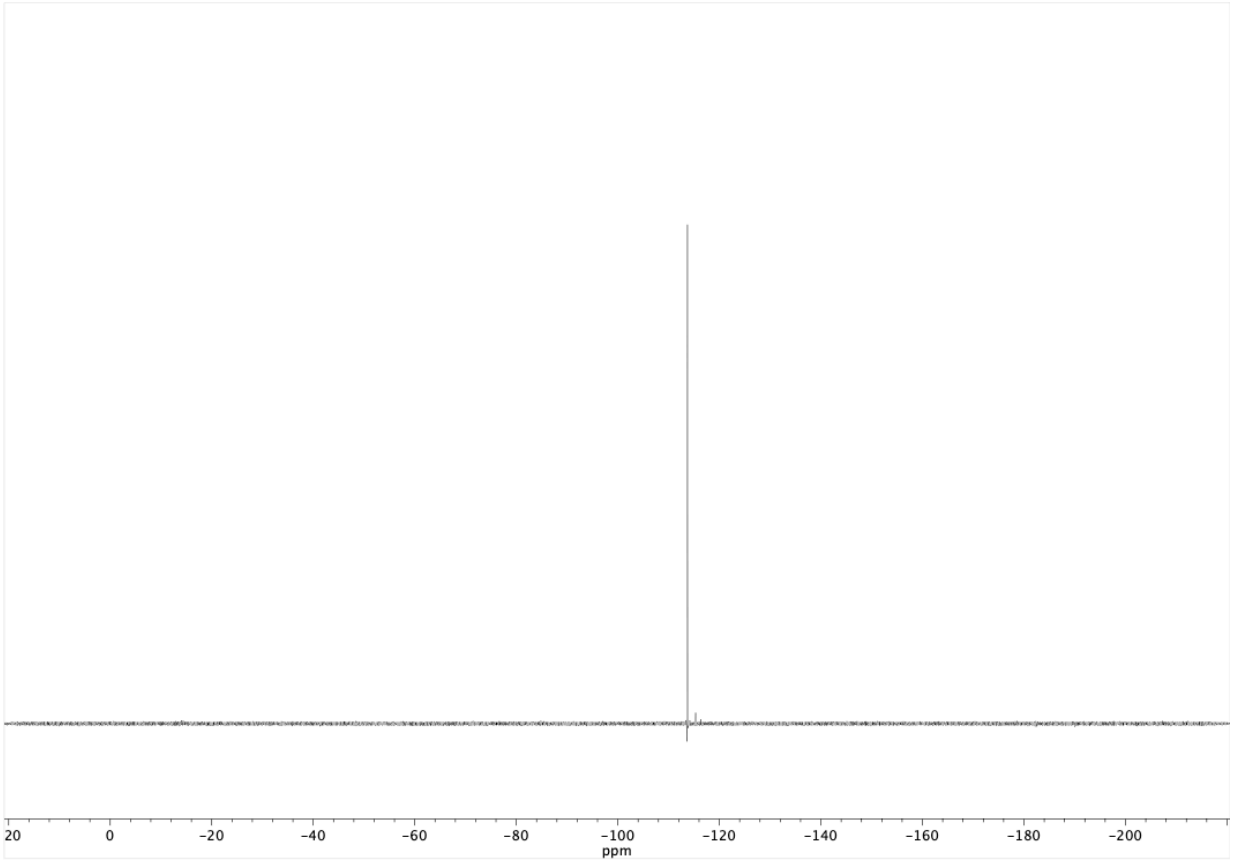

Figure A3.79. *^{19}F NMR (376 MHz, $CDCl_3$) of* ***65.***

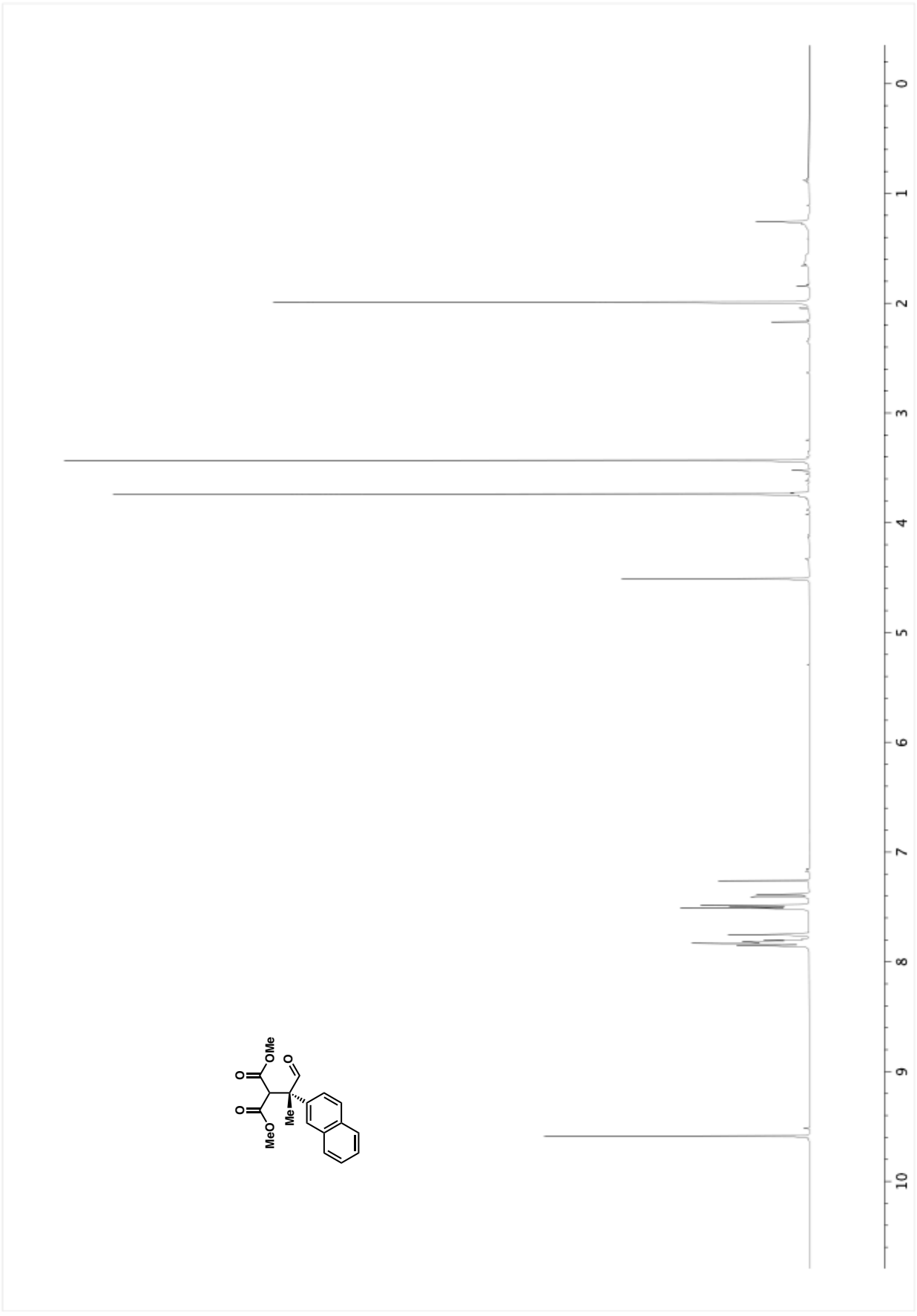

Figure A3.80. *^{1}H NMR (400 MHz, $CDCl_3$) of* ***66****.*

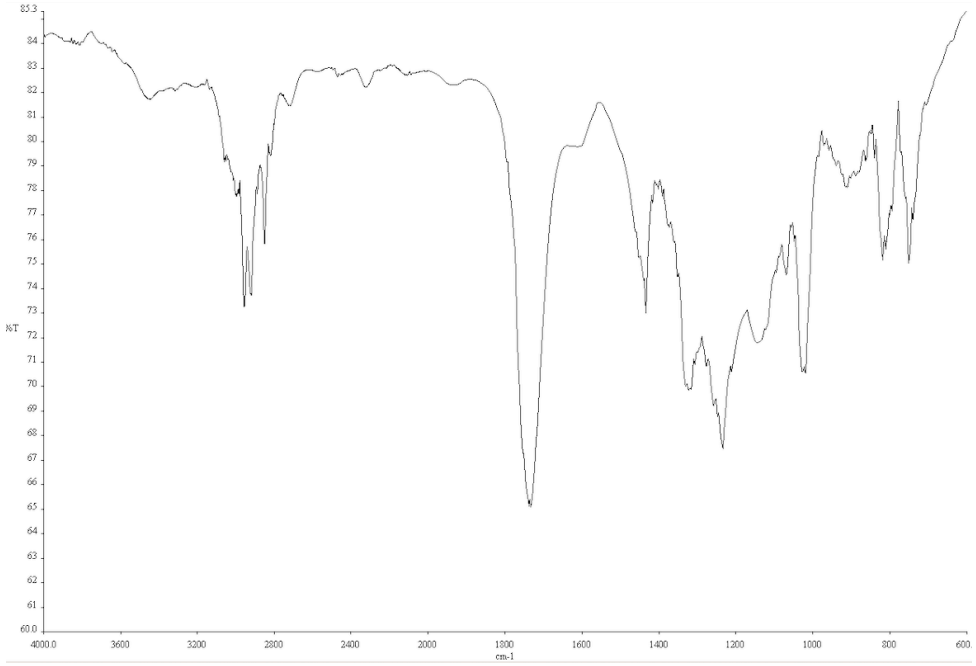

Figure A3.81. *Infrared spectrum (Thin Film, NaCl) of* ***66.***

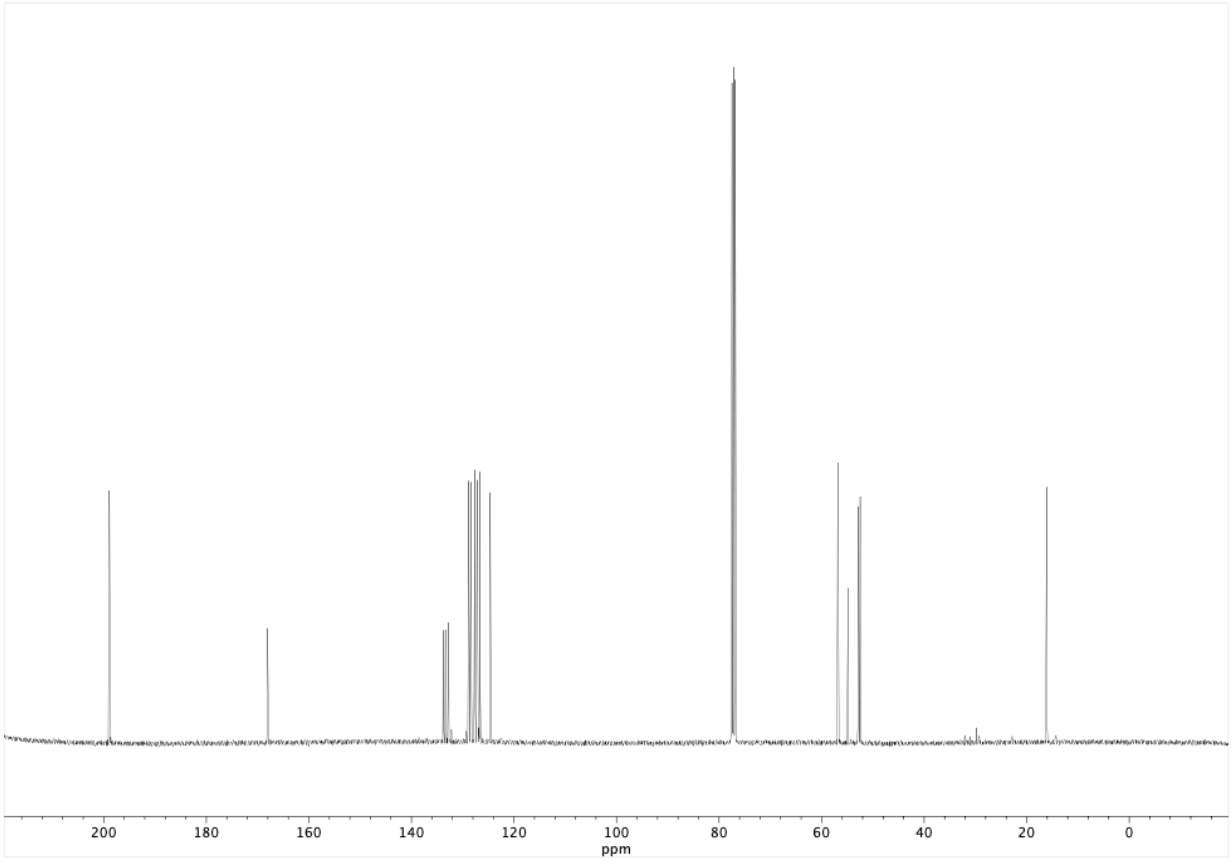

Figure A3.82. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***66.***

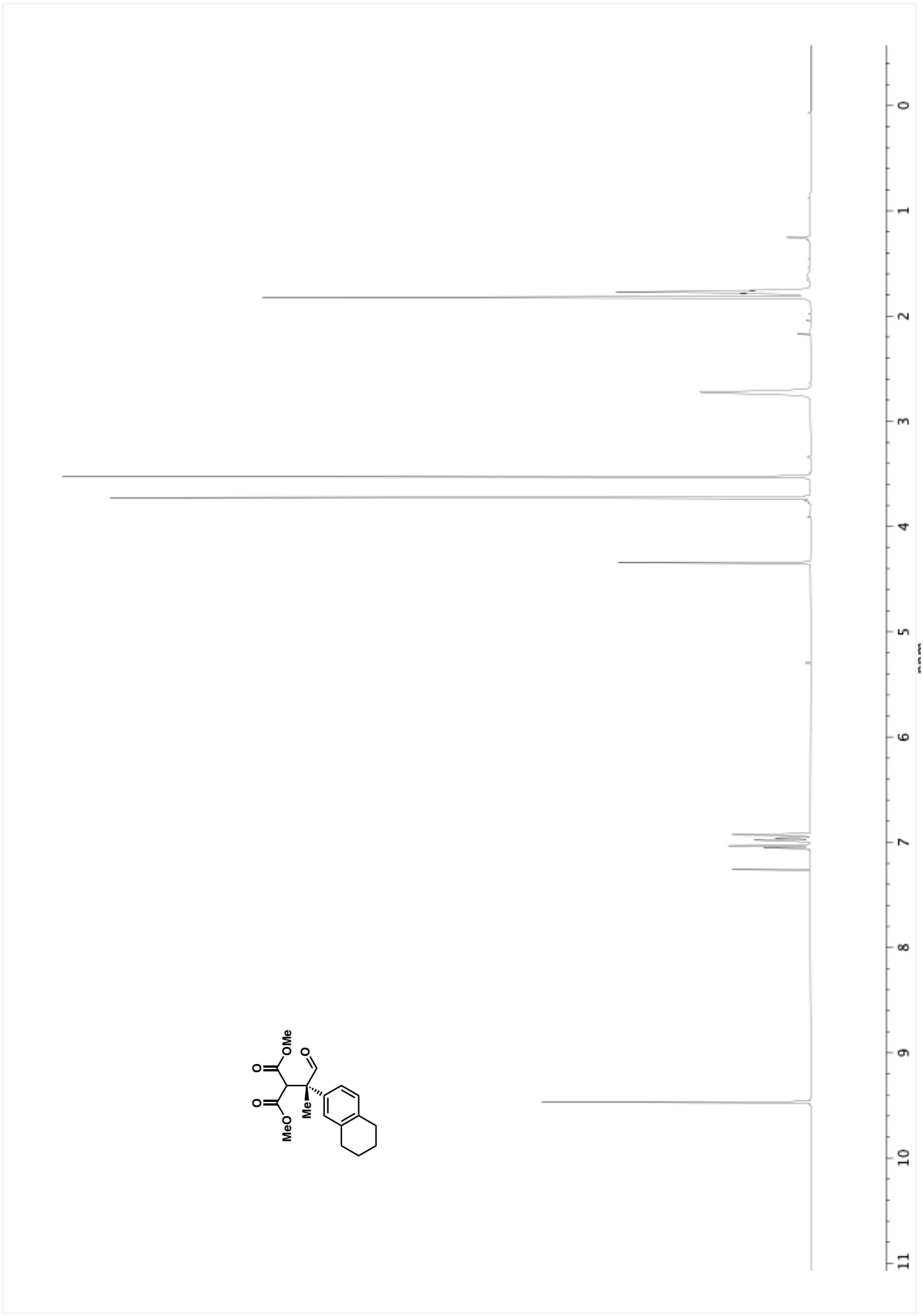

Figure A3.83. *^{1}H NMR (400 MHz, $CDCl_3$) of* ***67****.*

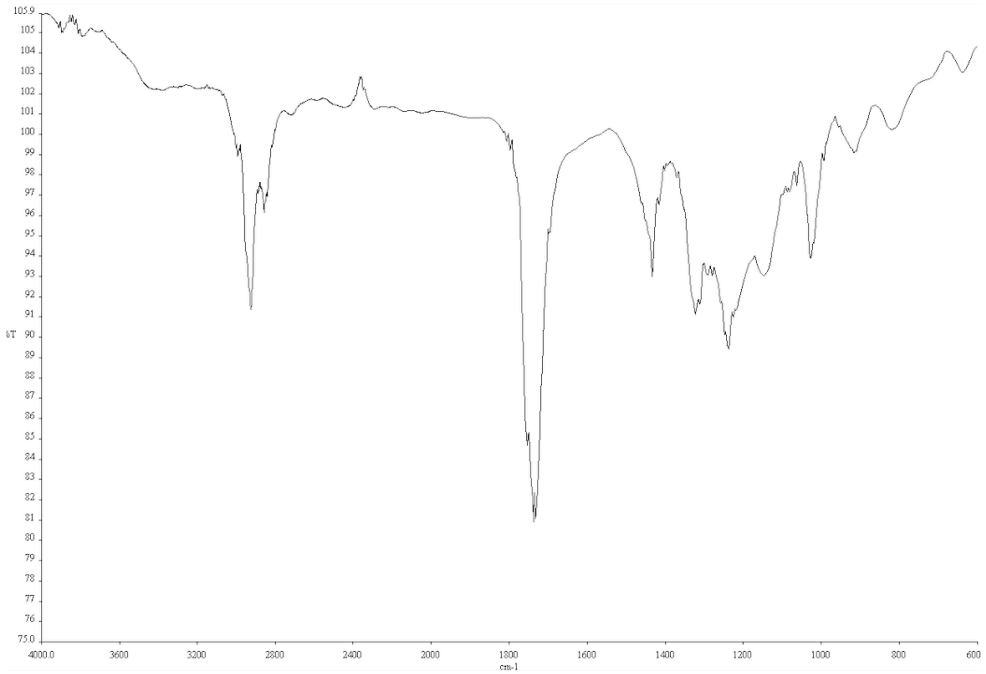

Figure A3.84. *Infrared spectrum (Thin Film, NaCl) of* ***67.***

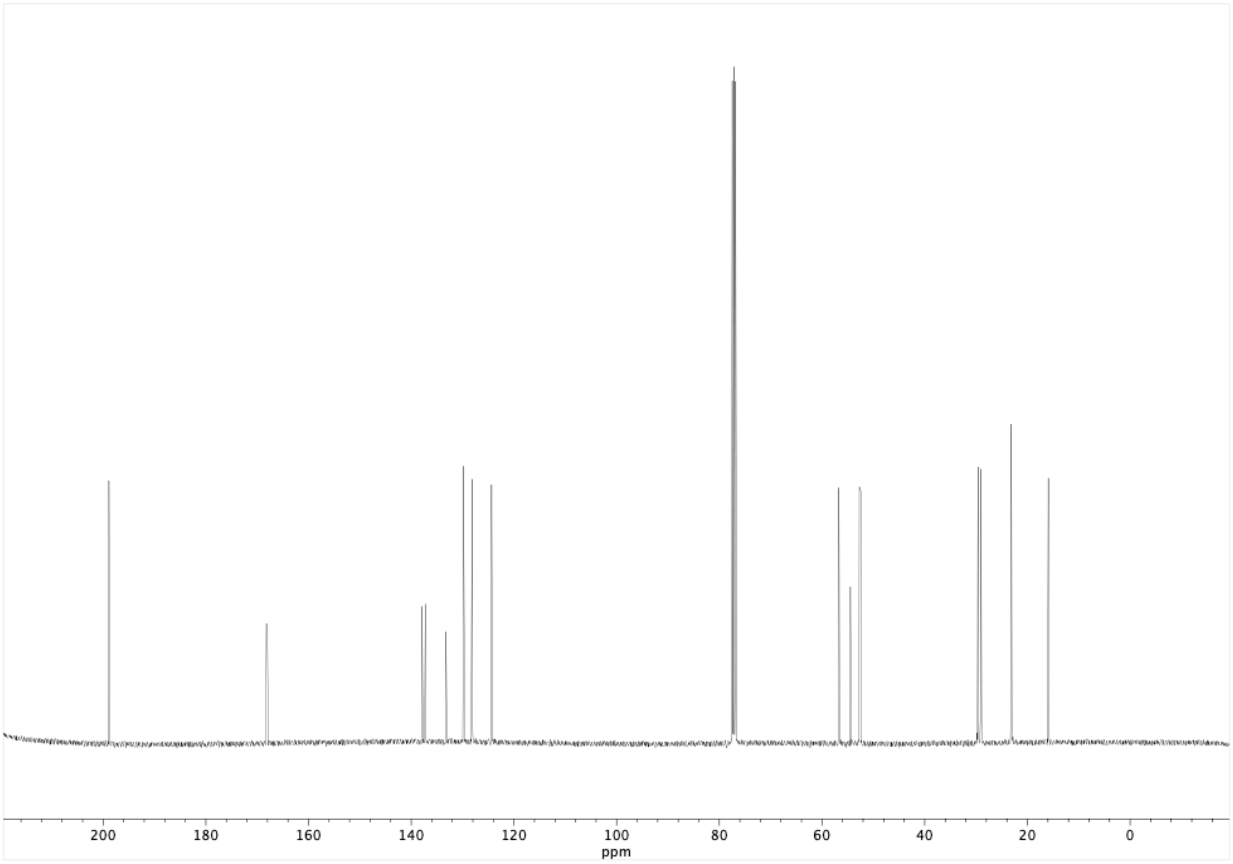

Figure A3.85. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***67.***

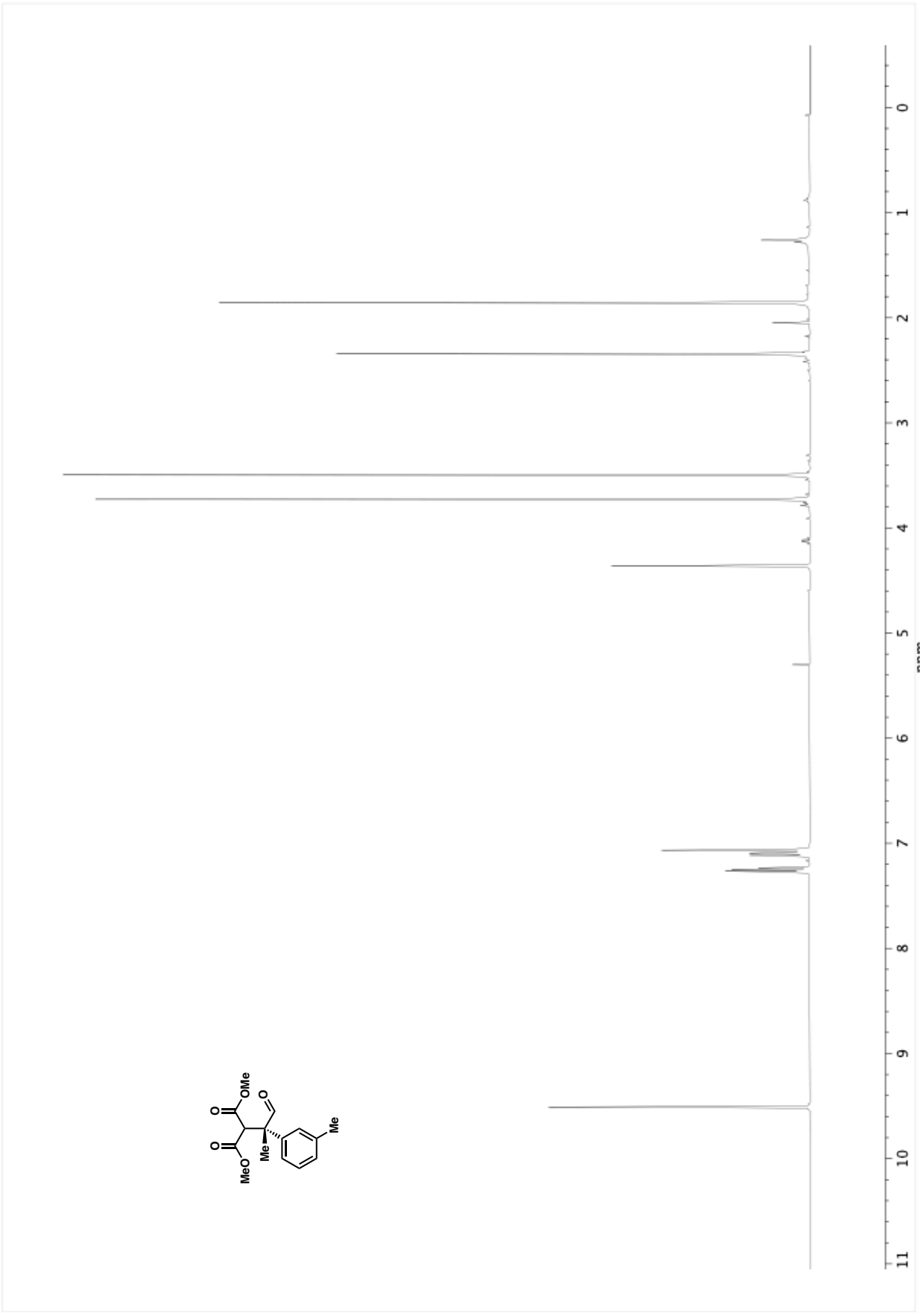

Figure A3.86. *^{1}H NMR (400 MHz, $CDCl_3$) of* ***68****.*

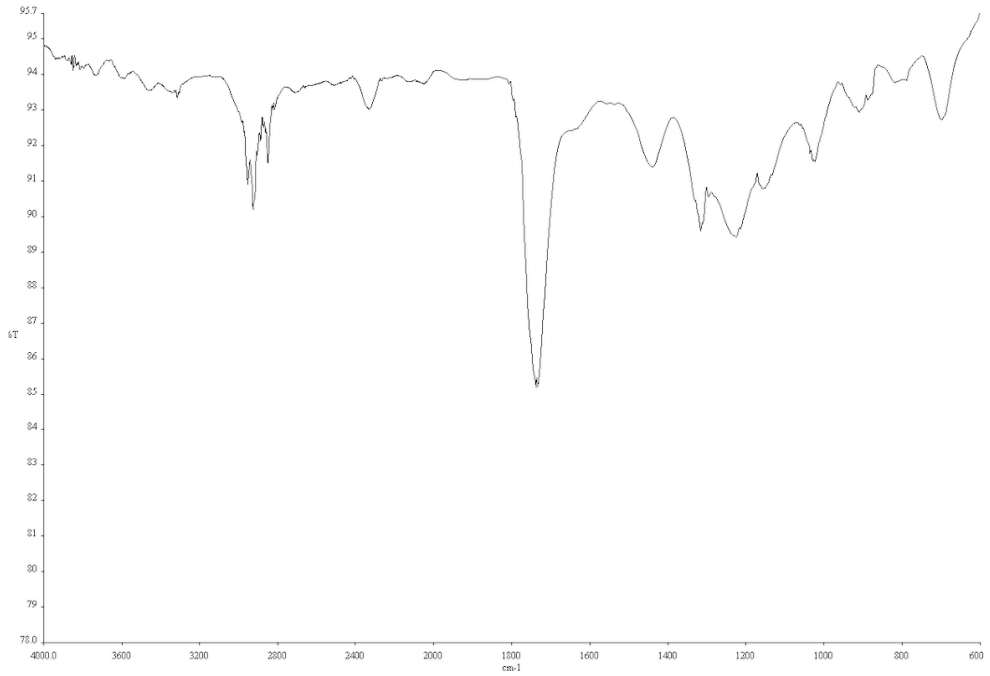

Figure A3.87. *Infrared spectrum (Thin Film, NaCl) of* ***68.***

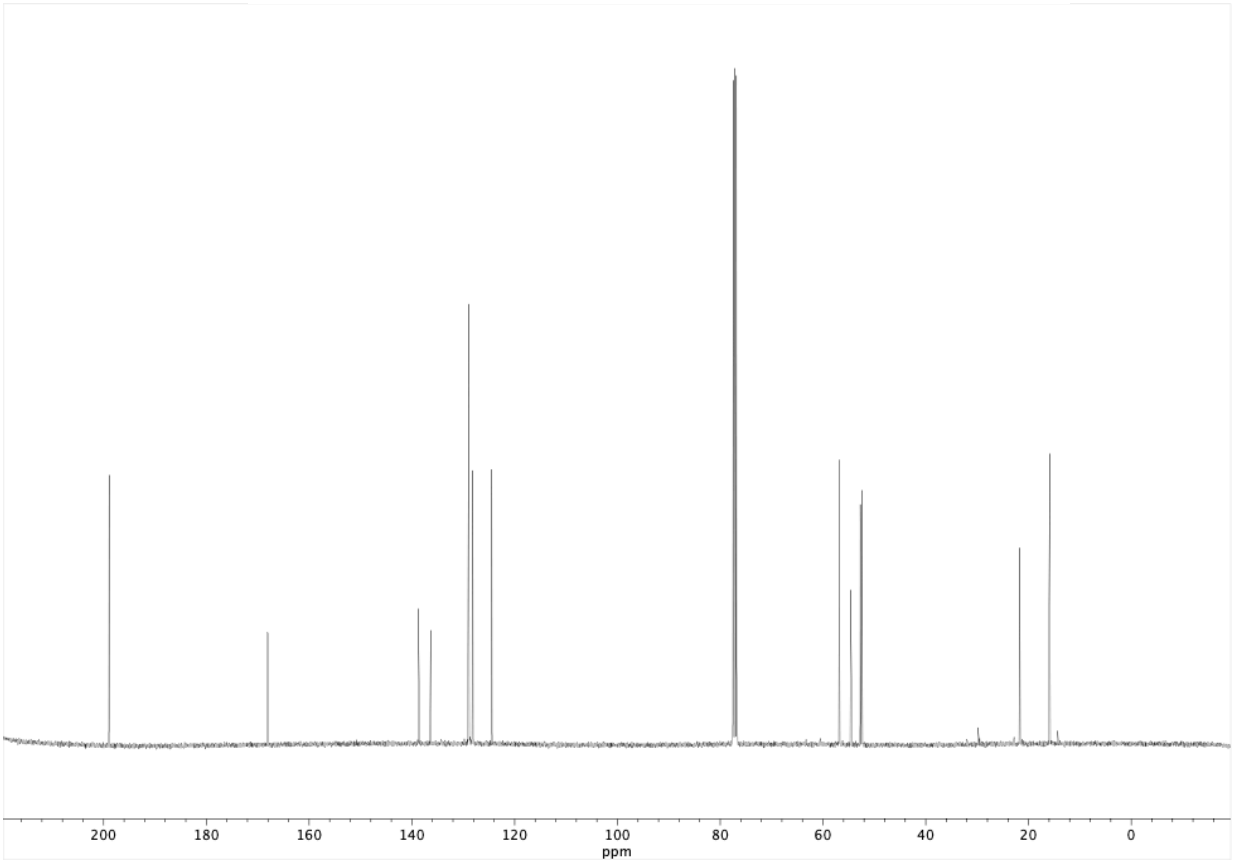

Figure A3.88. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***68.***

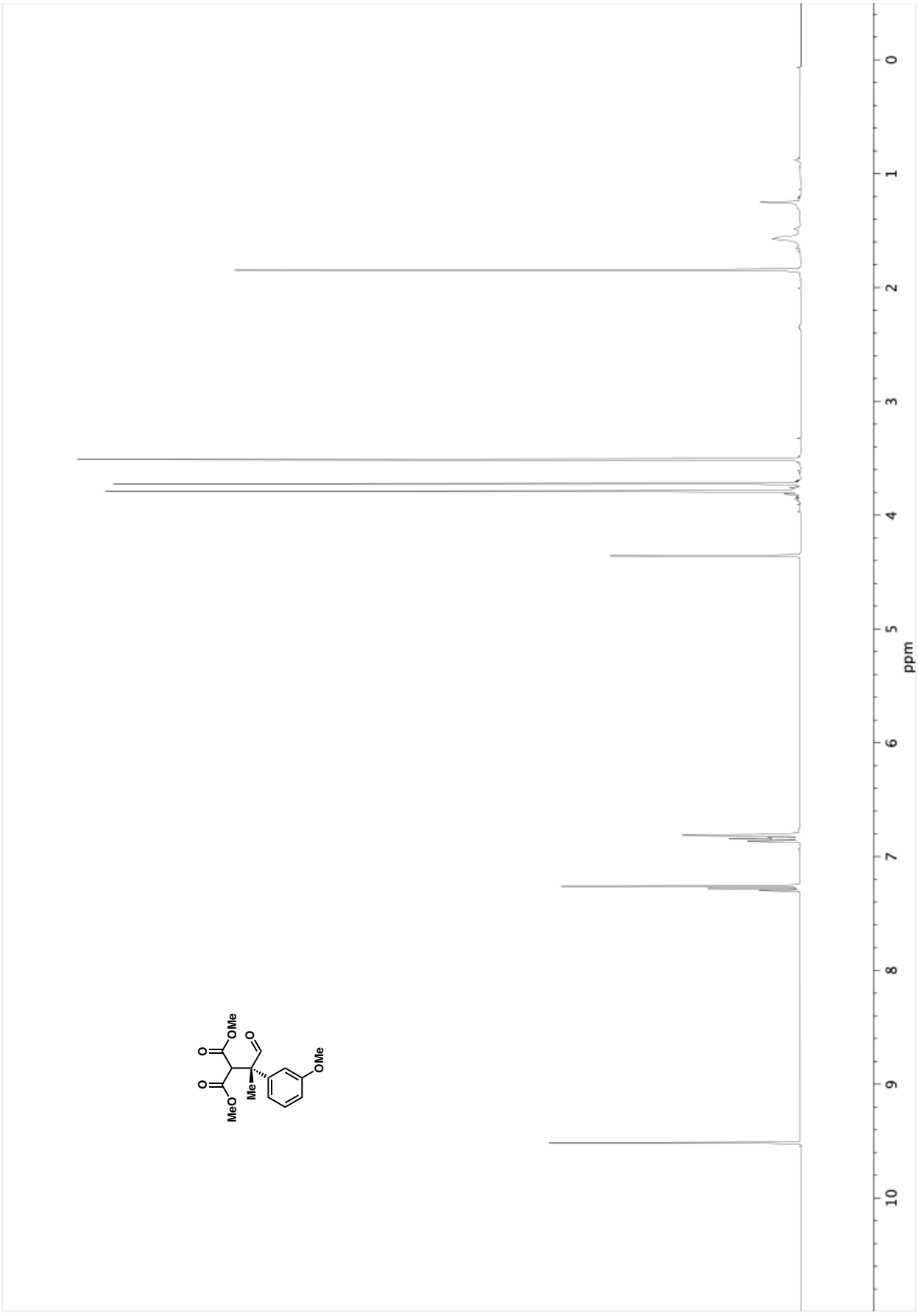

Figure A3.89. *^{1}H NMR (400 MHz, $CDCl_3$) of* ***69****.*

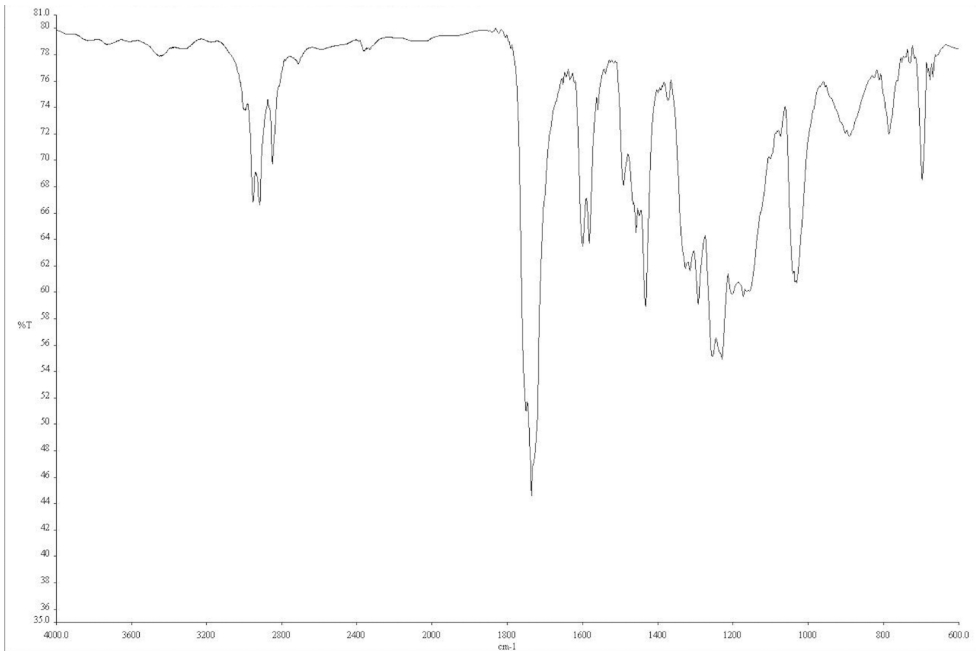

Figure A3.90. *Infrared spectrum (Thin Film, NaCl) of* ***69****.*

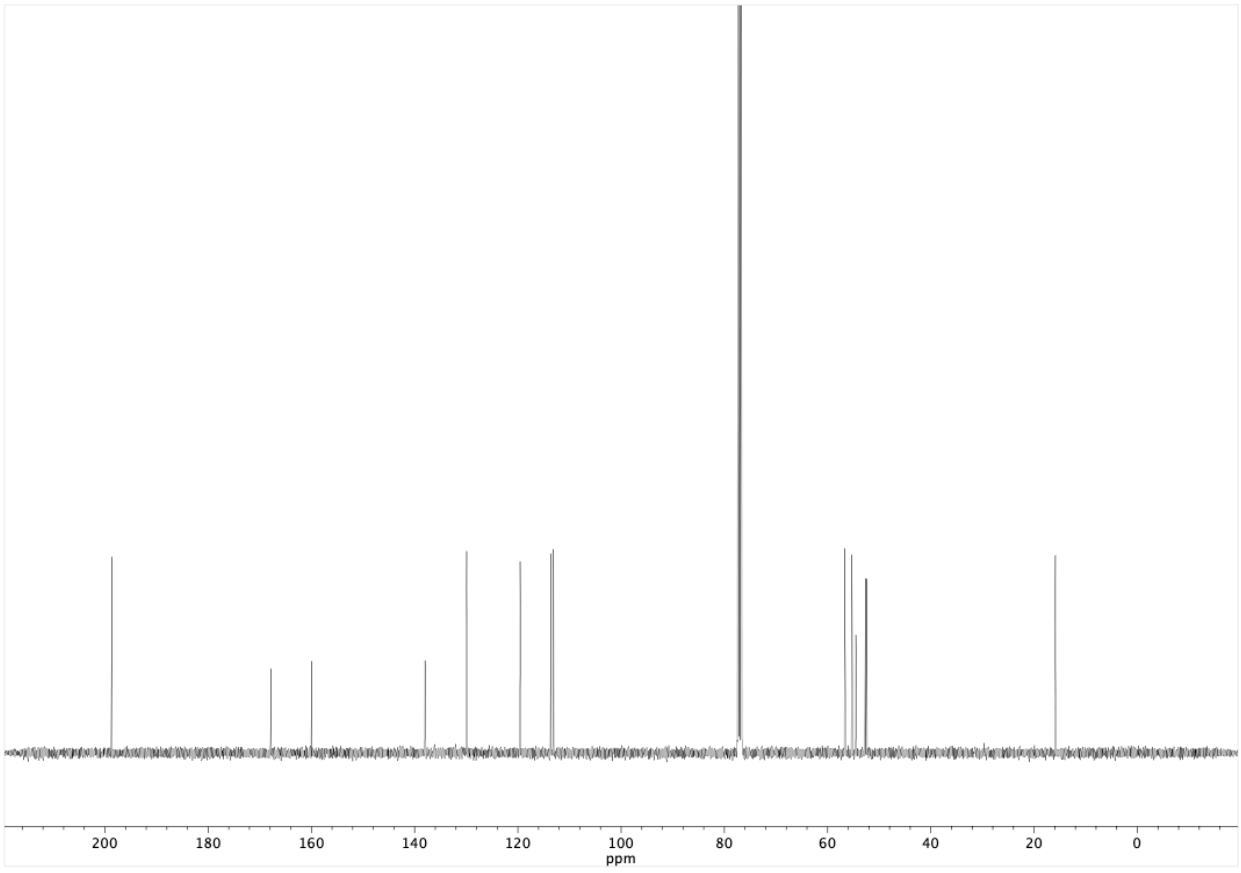

Figure A3.91. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***69.***

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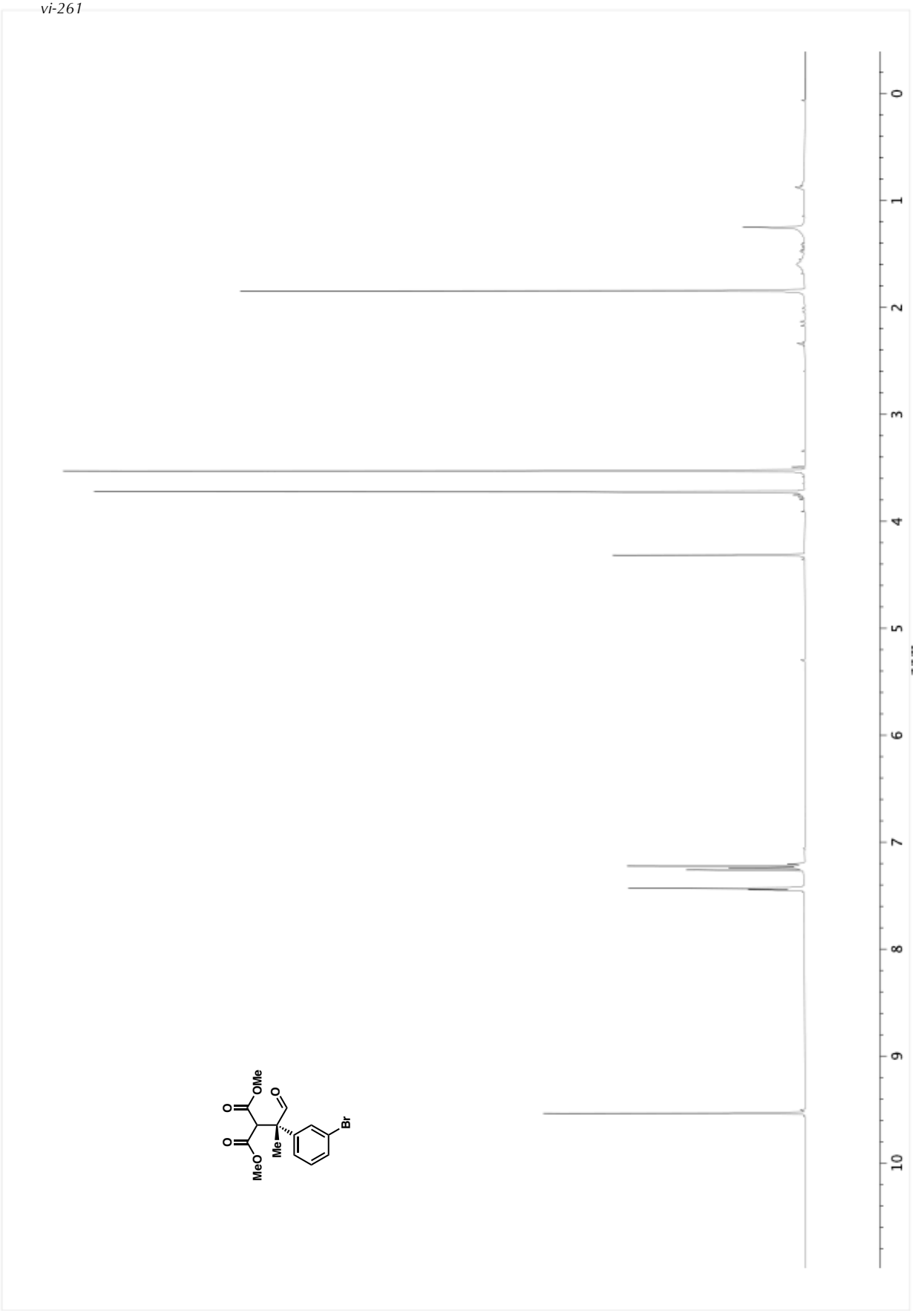

Figure A3.92. *^{1}H NMR (400 MHz, $CDCl_3$) of* ***70****.*

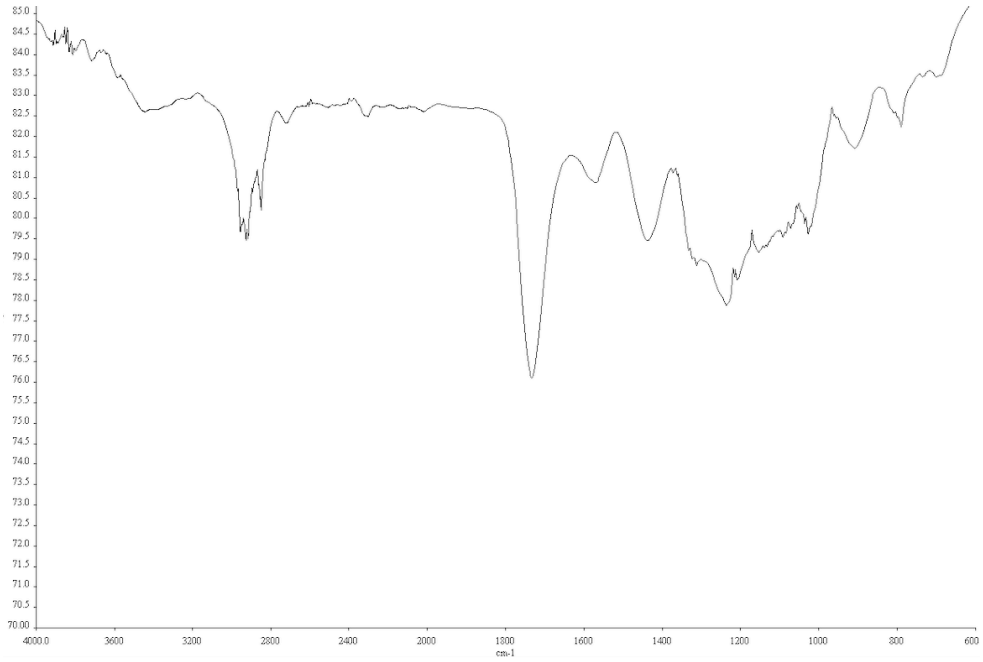

Figure A3.93. *Infrared spectrum (Thin Film, NaCl) of* ***70.***

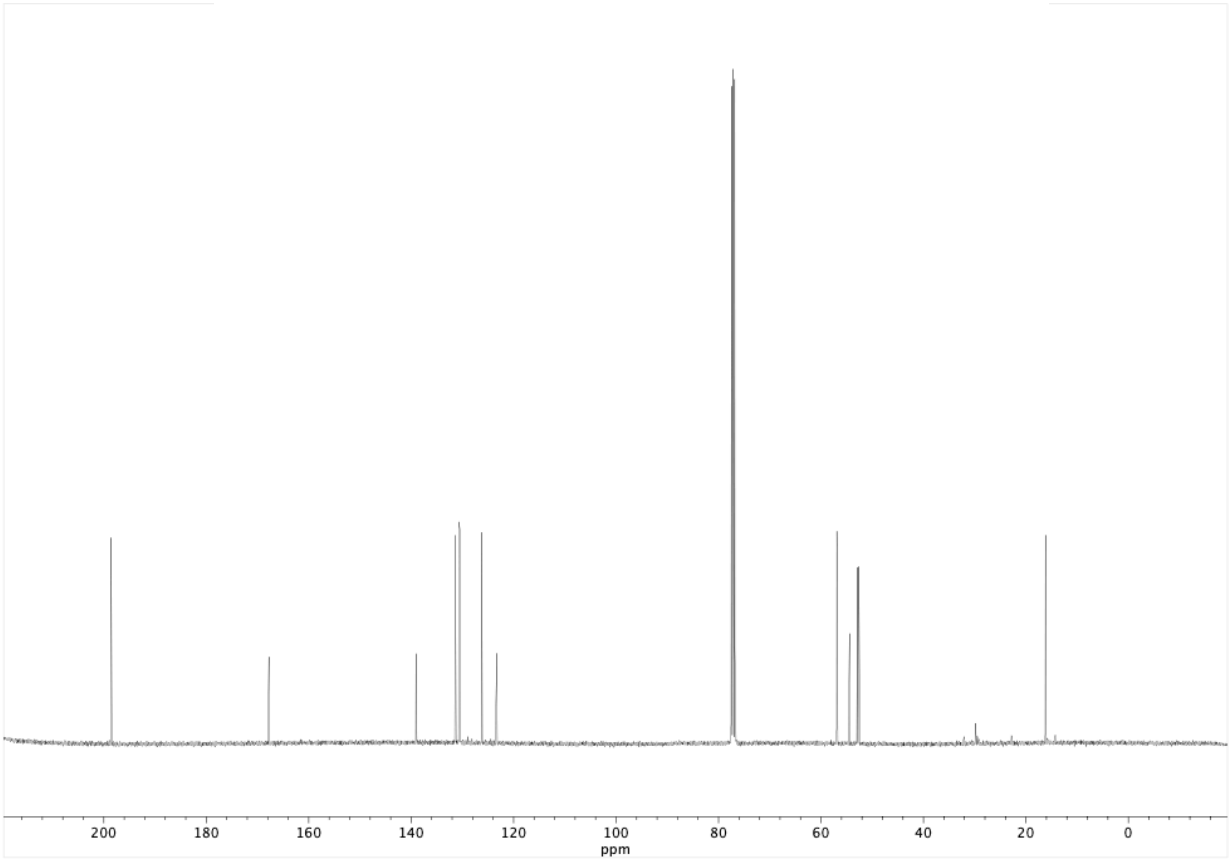

Figure A3.94. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***70.***

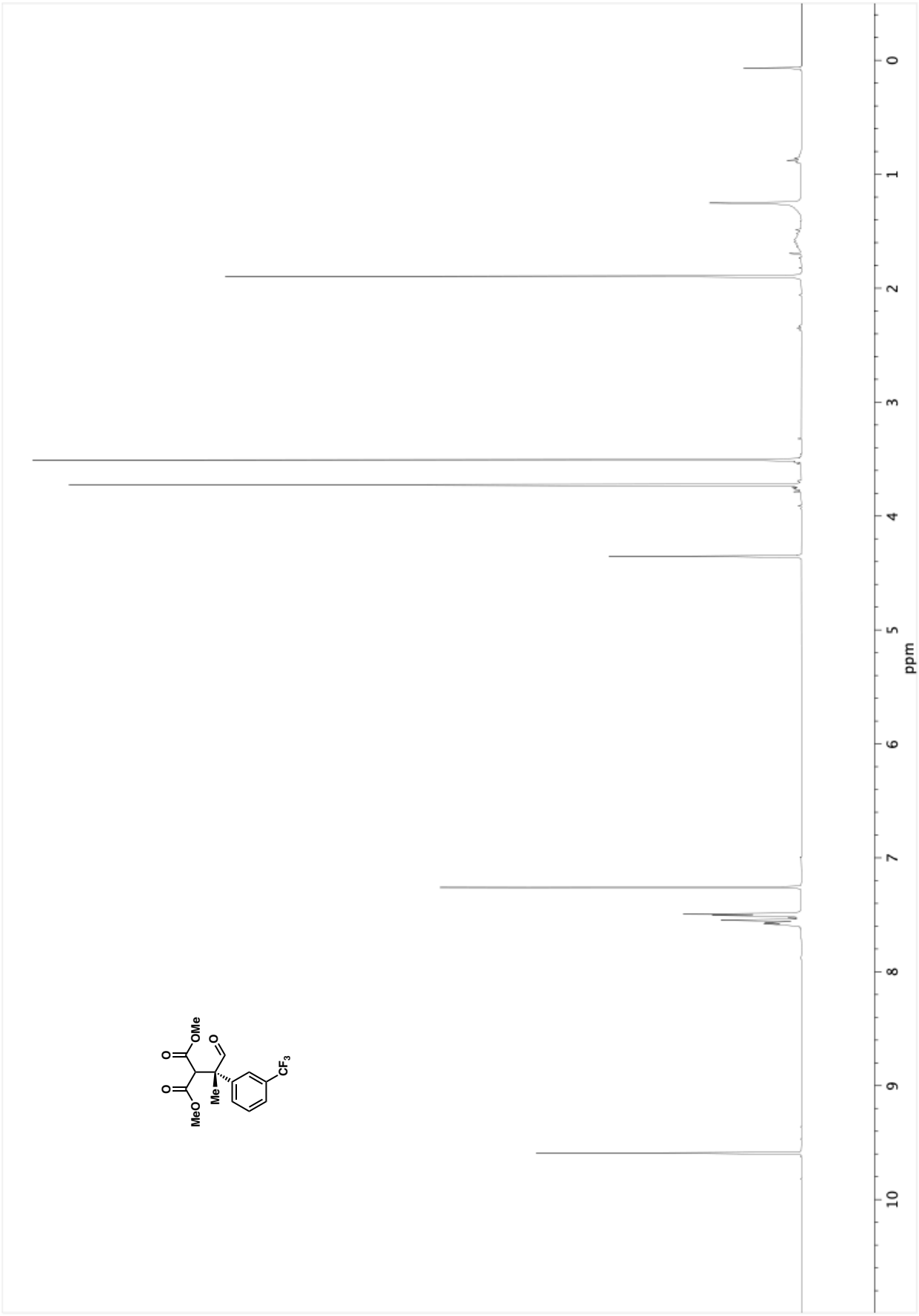

Figure A3.95. *^1H NMR (400 MHz, $CDCl_3$) of* ***71****.*

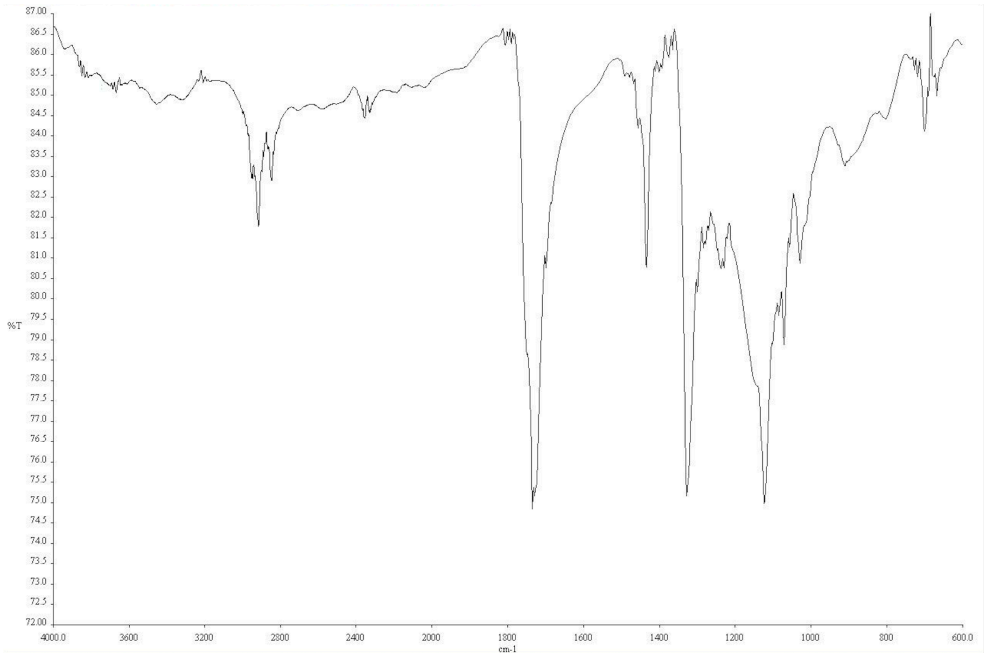

Figure A3.96. *Infrared spectrum (Thin Film, NaCl) of* ***71****.*

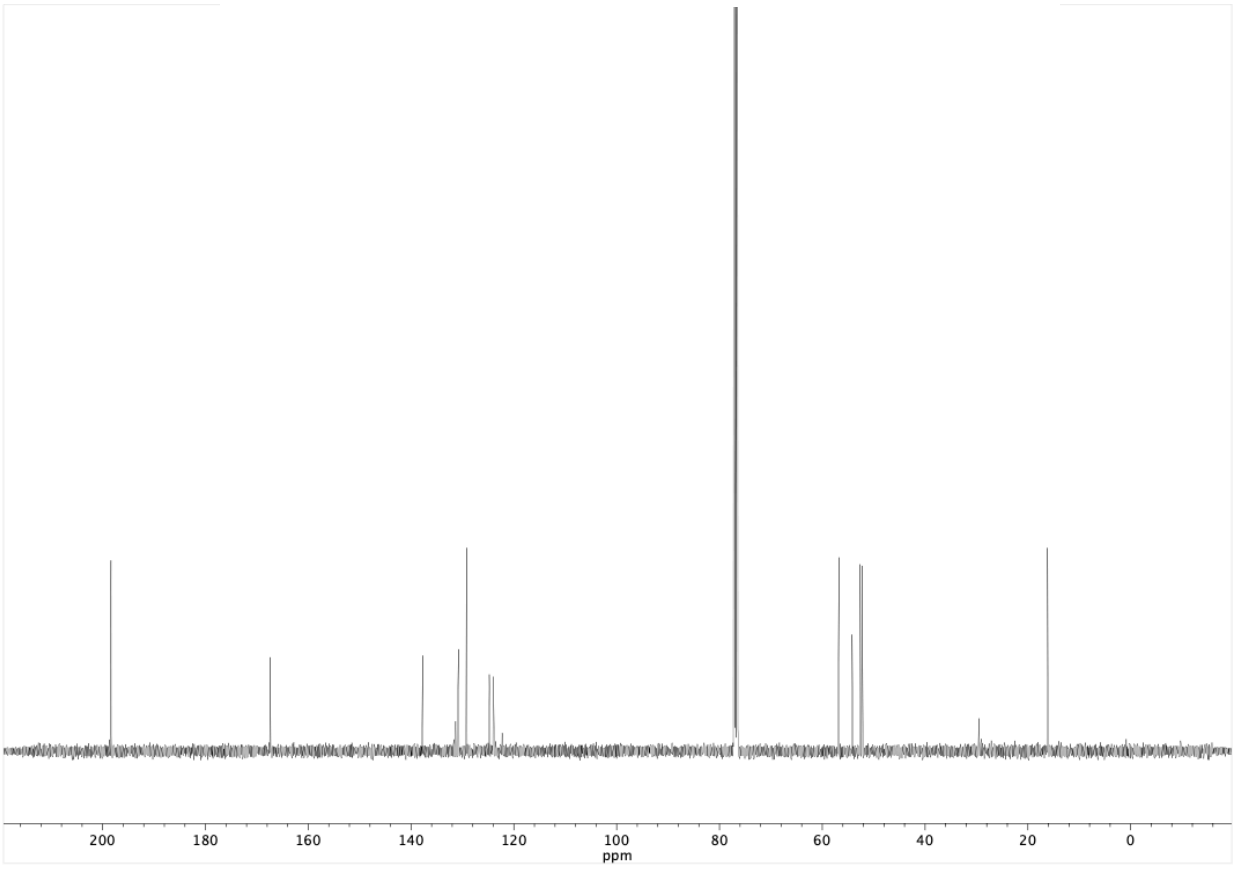

Figure A3.97. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***71.***

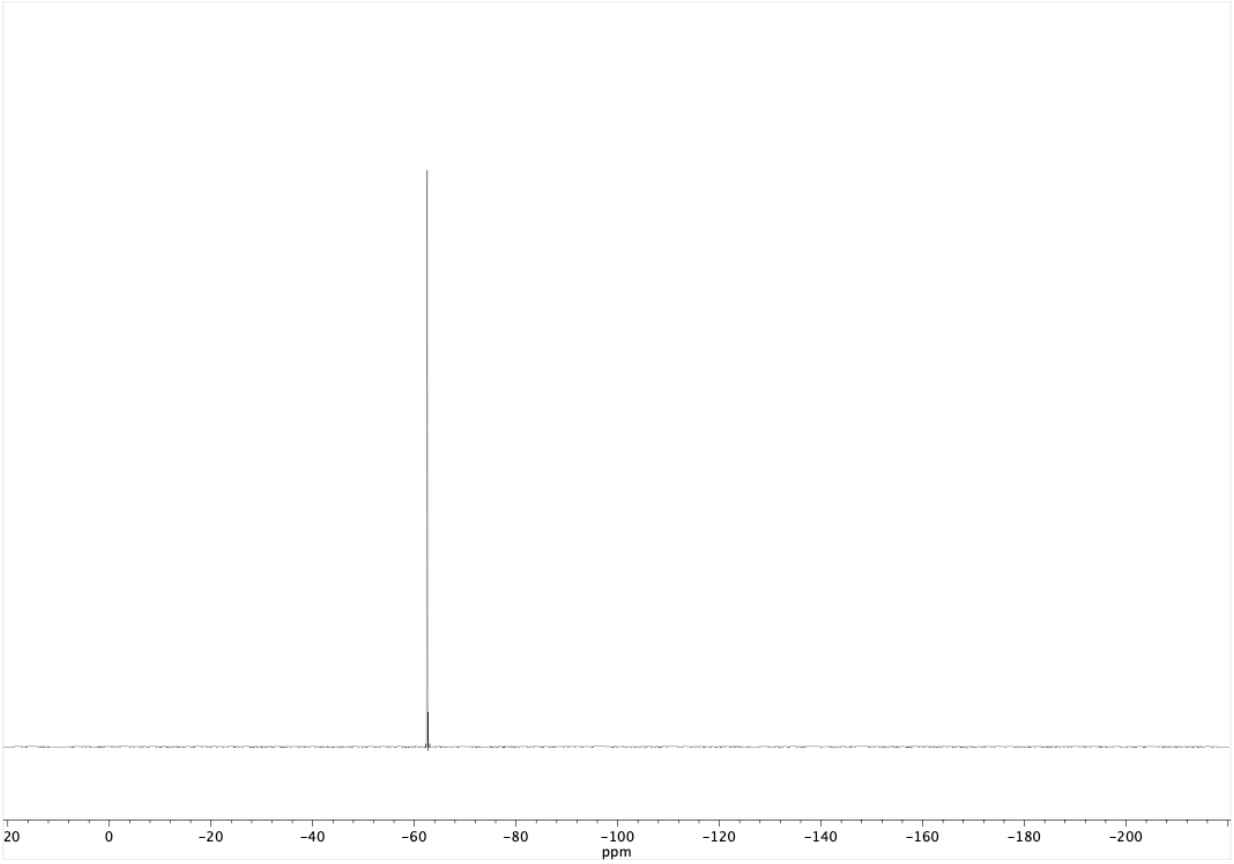

Figure A3.98. *^{19}F NMR (376 MHz, $CDCl_3$) of* ***71.***

Figure A3.99. *^1H NMR (400 MHz, $CDCl_3$) of* ***72****.*

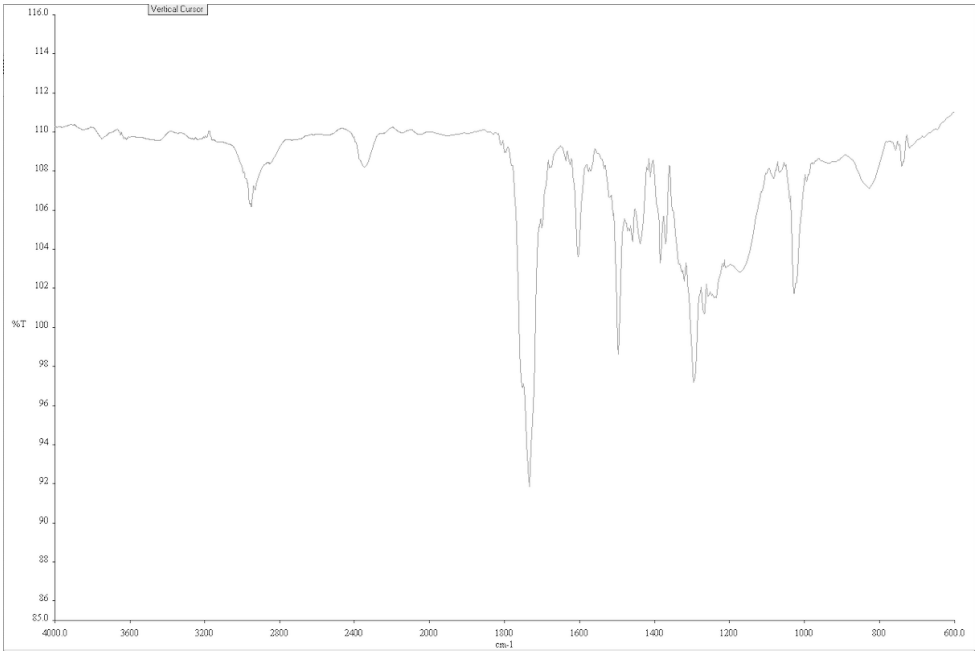

Figure A3.100. *Infrared spectrum (Thin Film, NaCl) of* ***72***

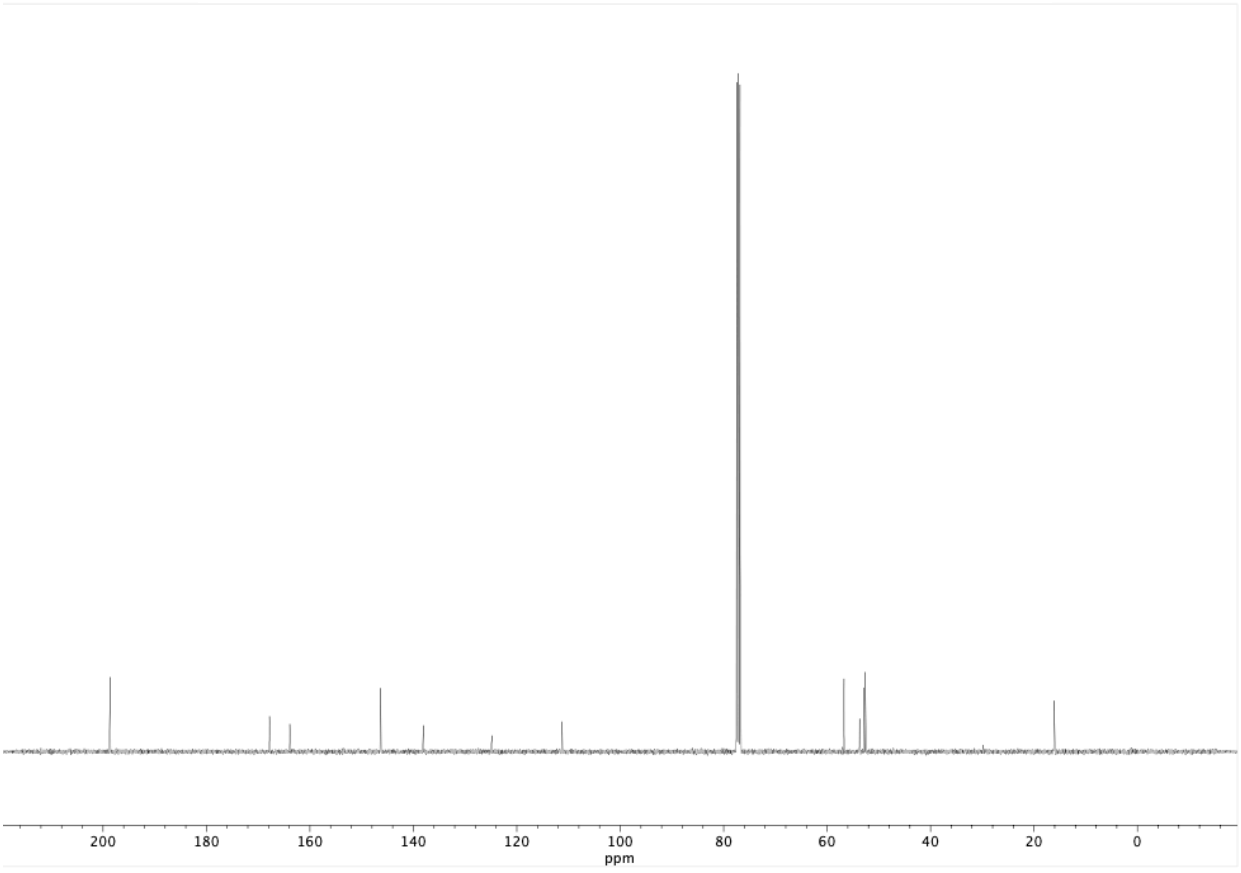

Figure A3.101. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***72***

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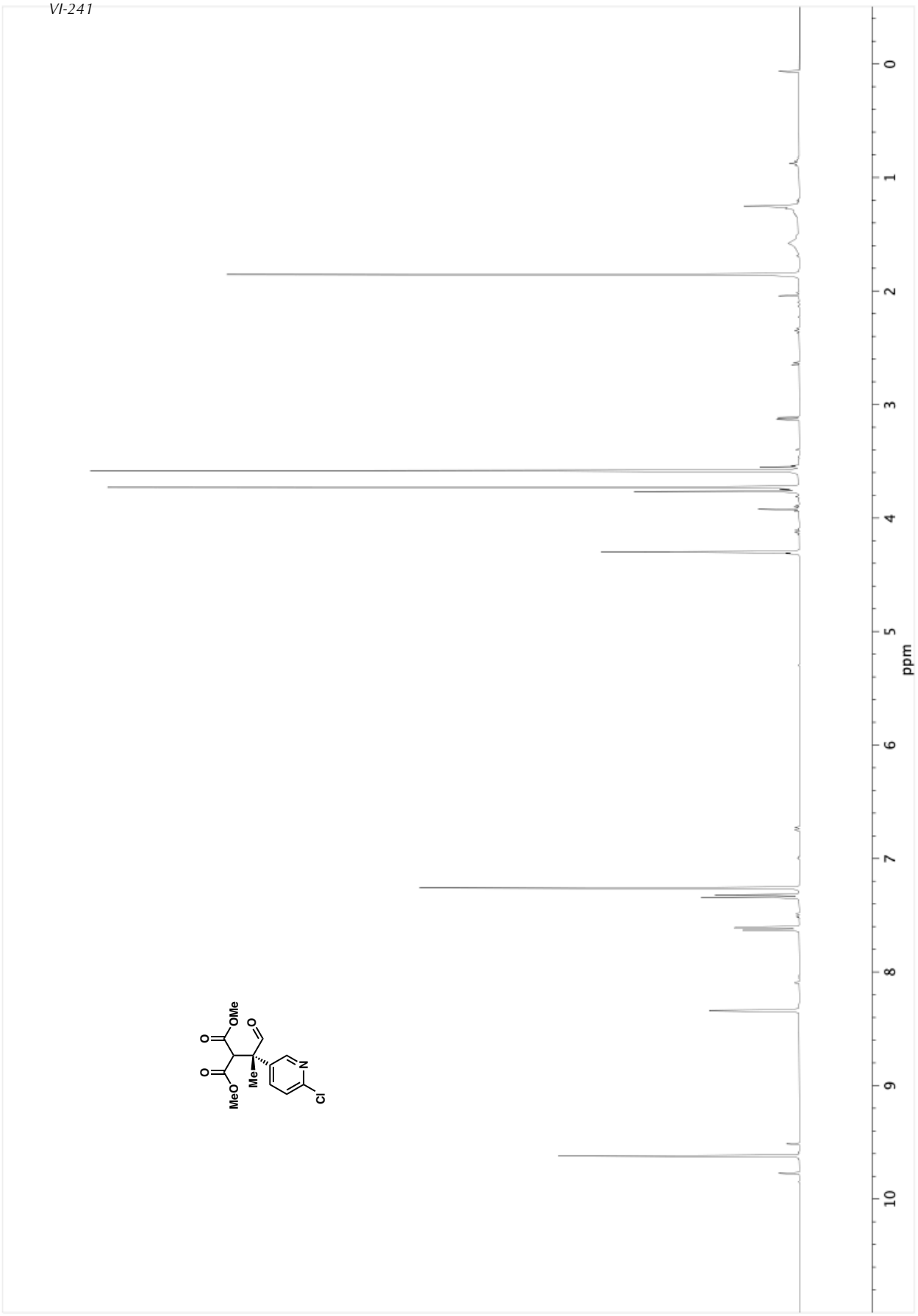


Figure A3.102. *^{1}HNMR (400 MHz, $CDCl_3$) of* ***73****.*

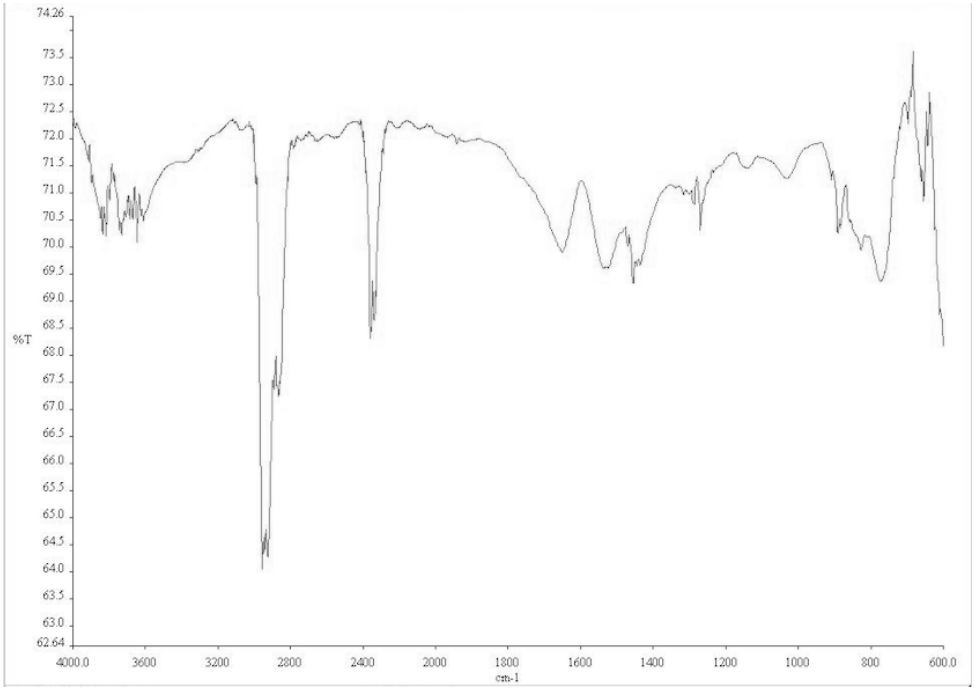


Figure A3.103. *Infrared spectrum (Thin Film, NaCl) of* ***73****.*

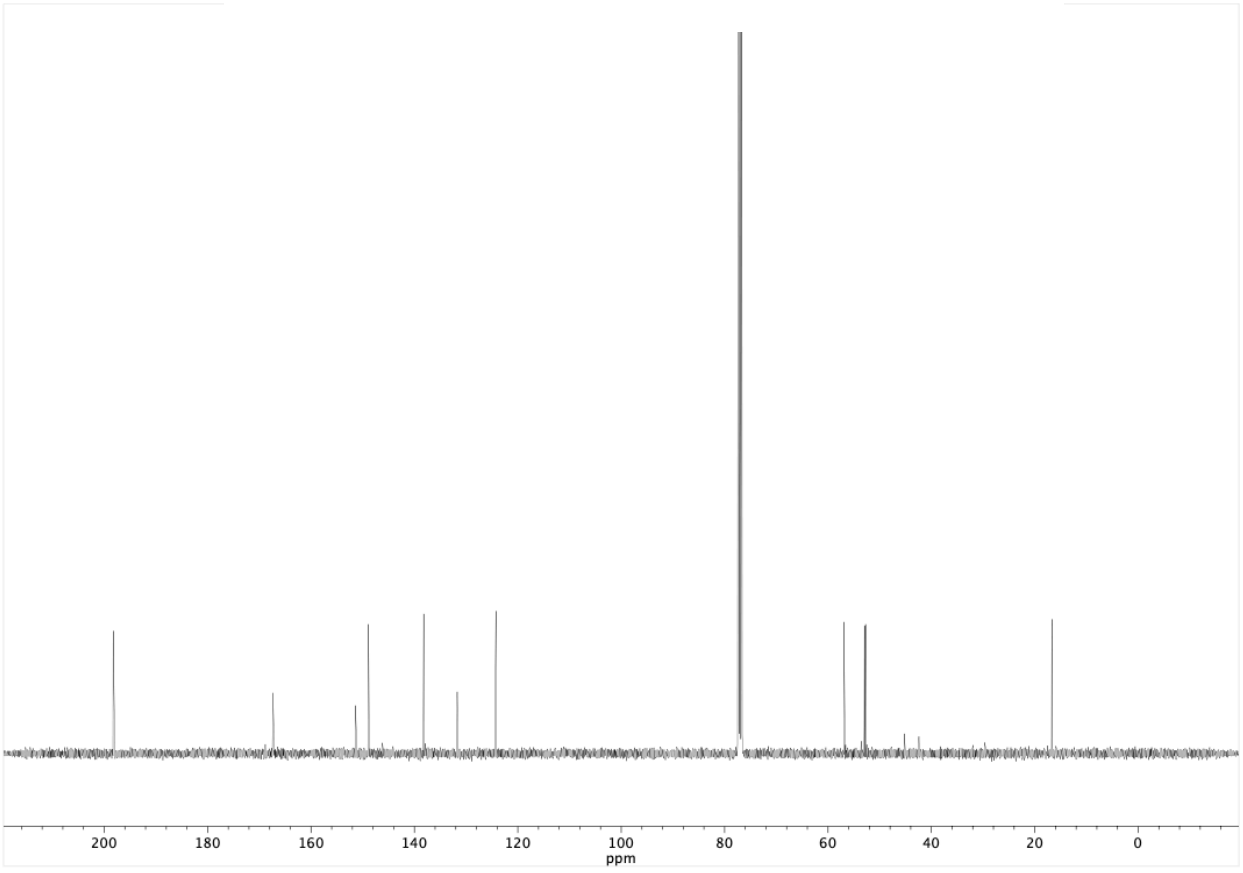


Figure A3.104. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***73.***

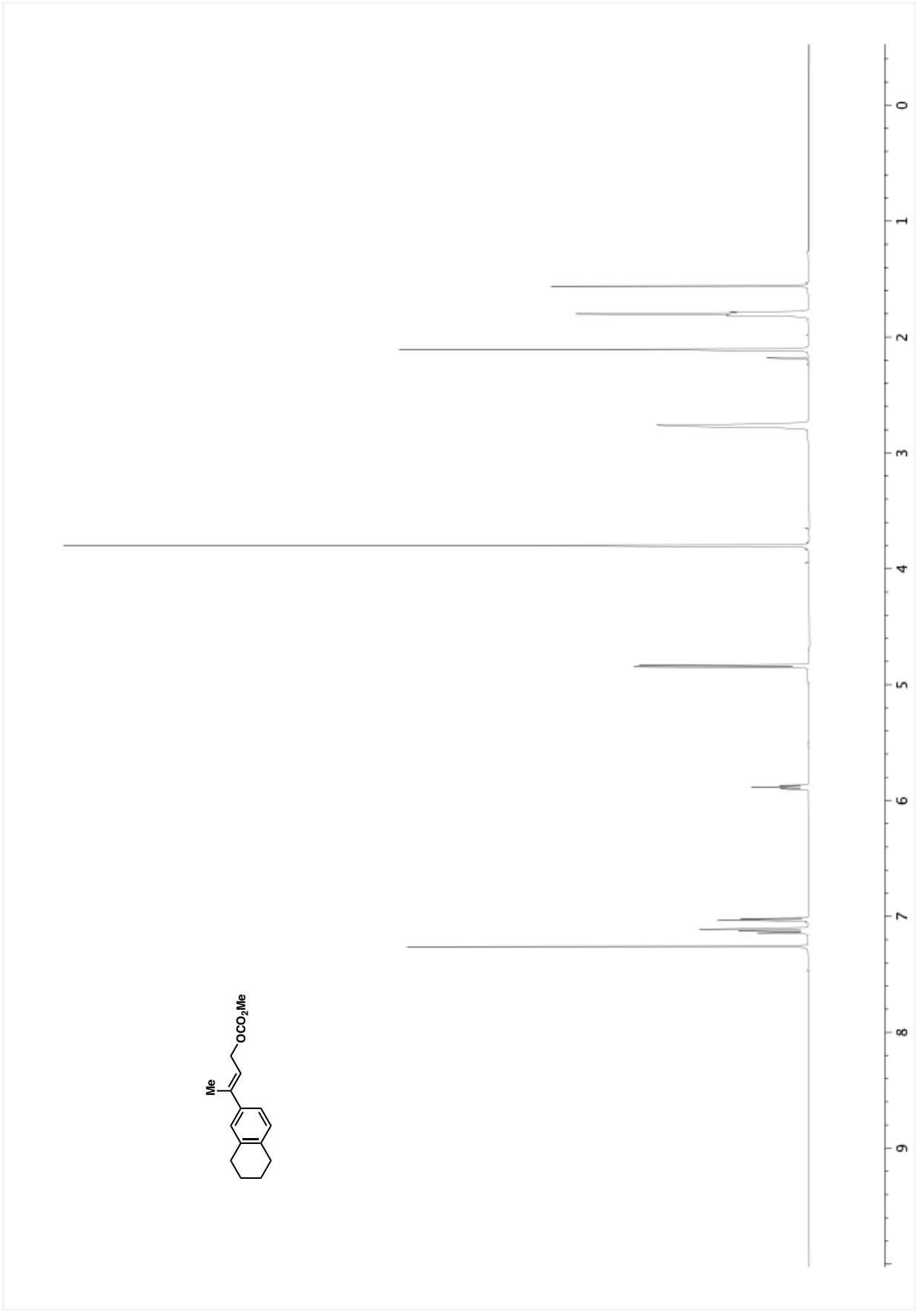


Figure A3.105. *^1H NMR (500 MHz, $CDCl_3$) of* ***67a****.*

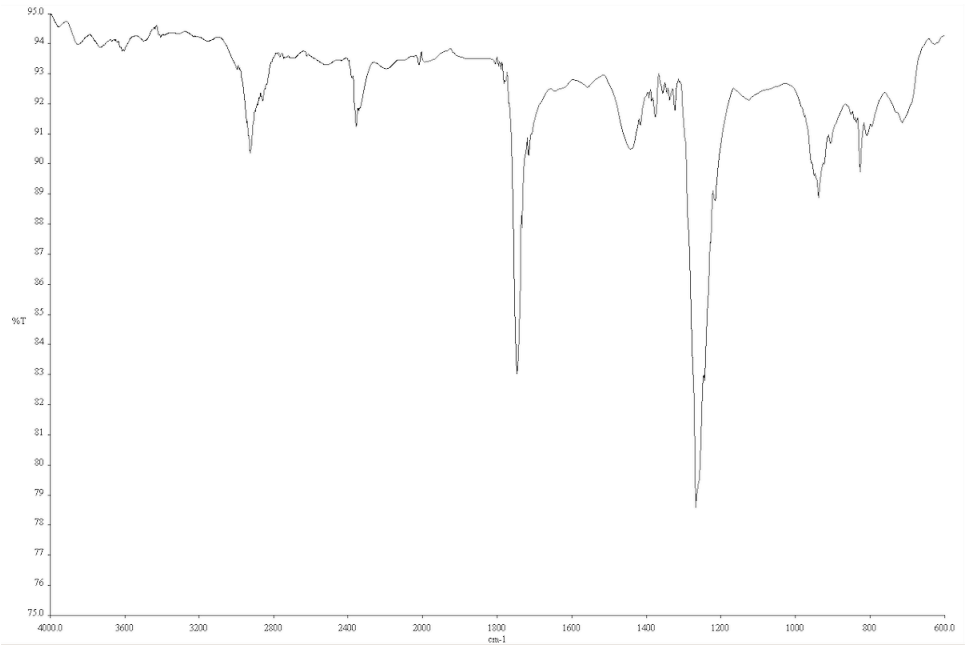


Figure A3.106. *Infrared spectrum (Thin Film, NaCl) of* ***67a****.*

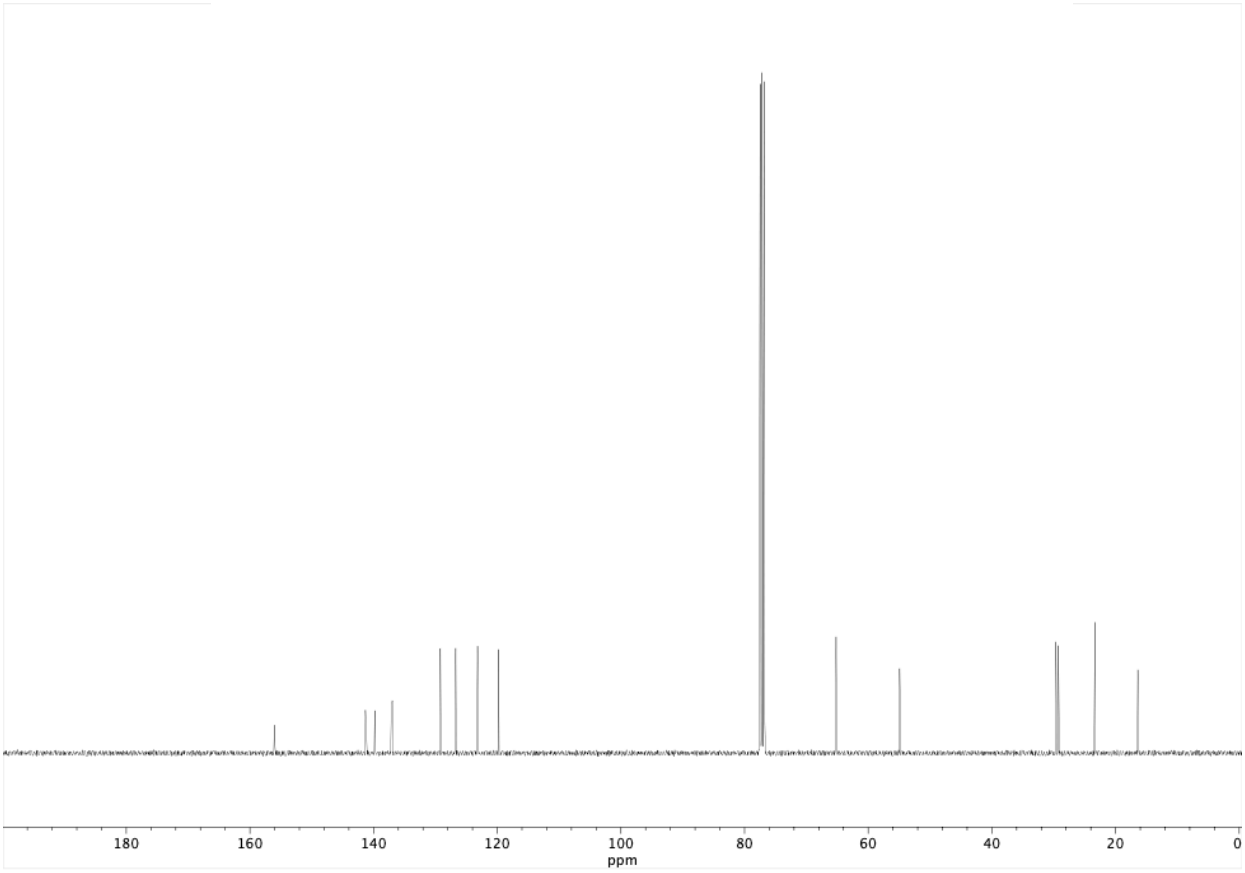


Figure A3.107. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***67a.***

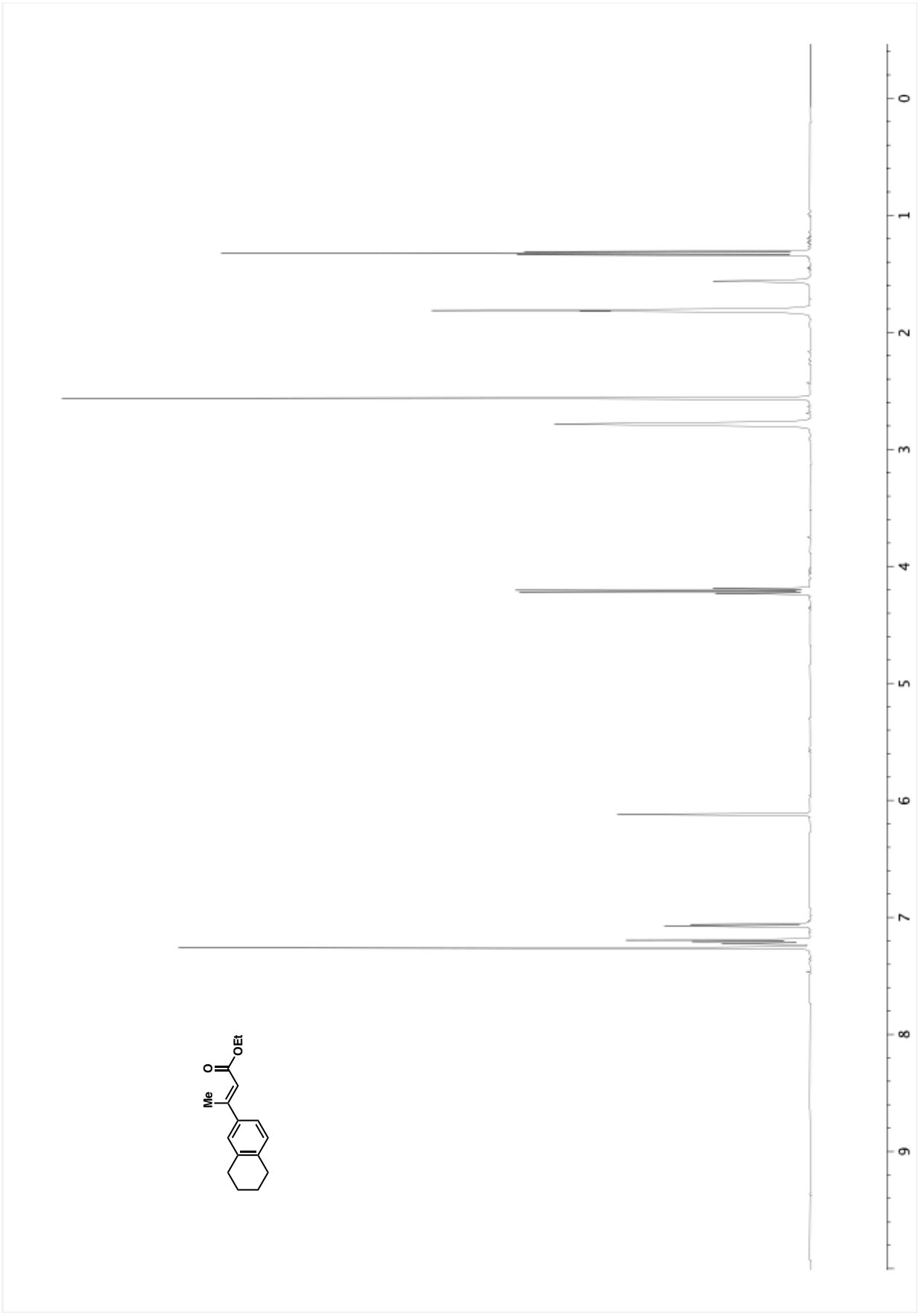


Figure A3.108. *^1H NMR (500 MHz, $CDCl_3$) of* ***67b****.*

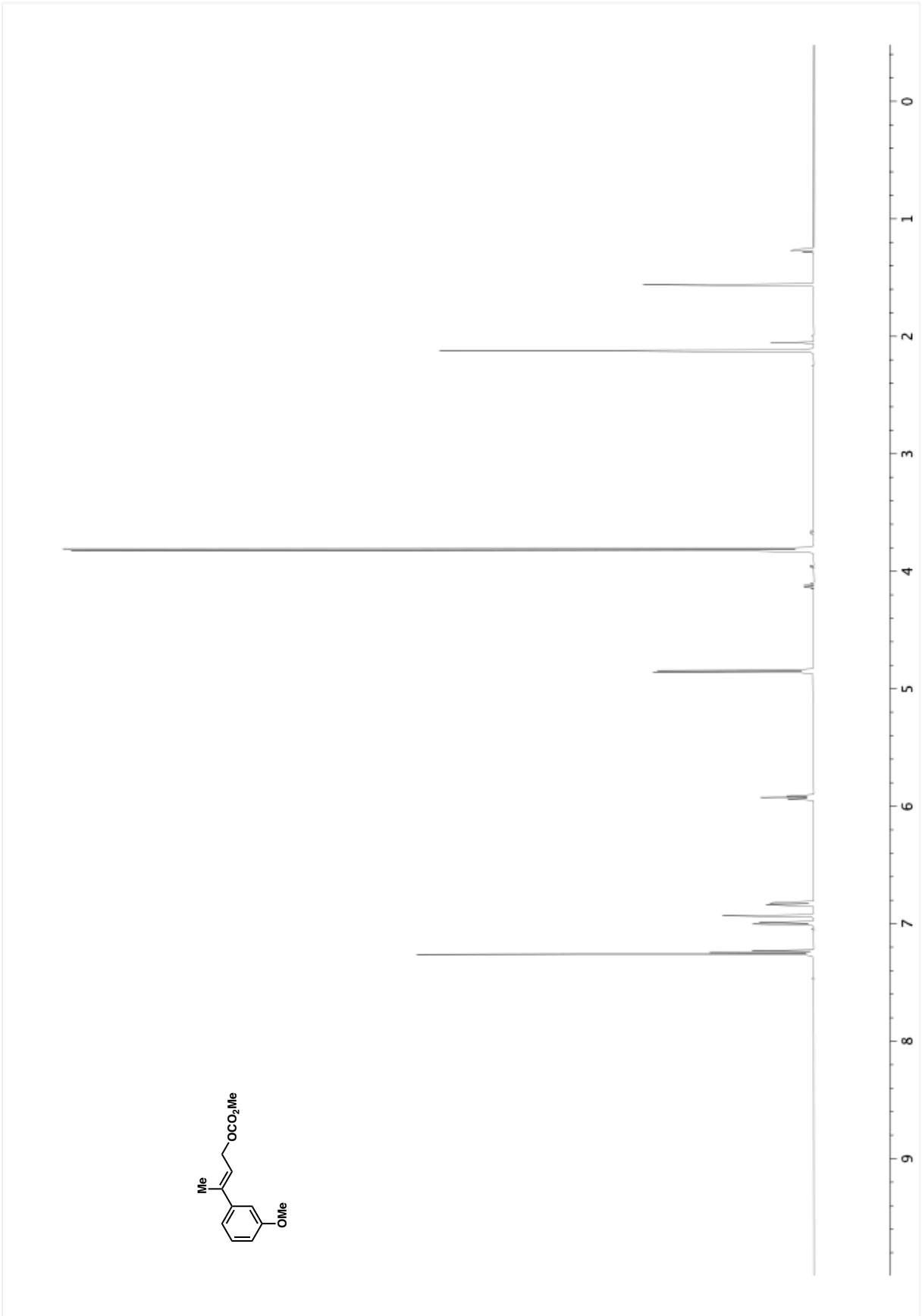


Figure A3.109. *^1H NMR (500 MHz, $CDCl_3$) of* ***69a.***

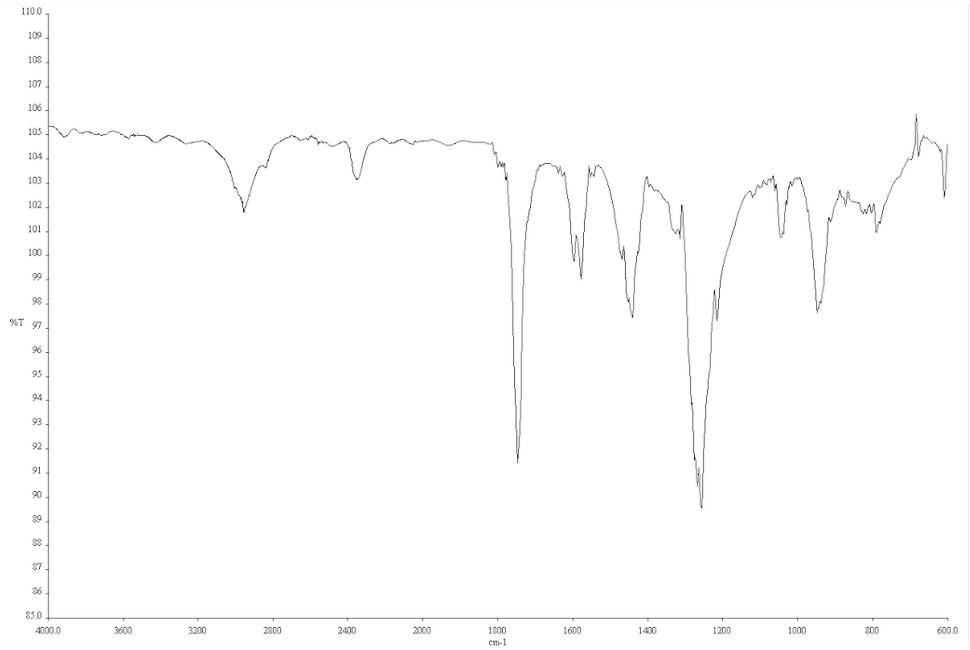


Figure A3.110. *Infrared spectrum (Thin Film, NaCl) of* ***69a.***

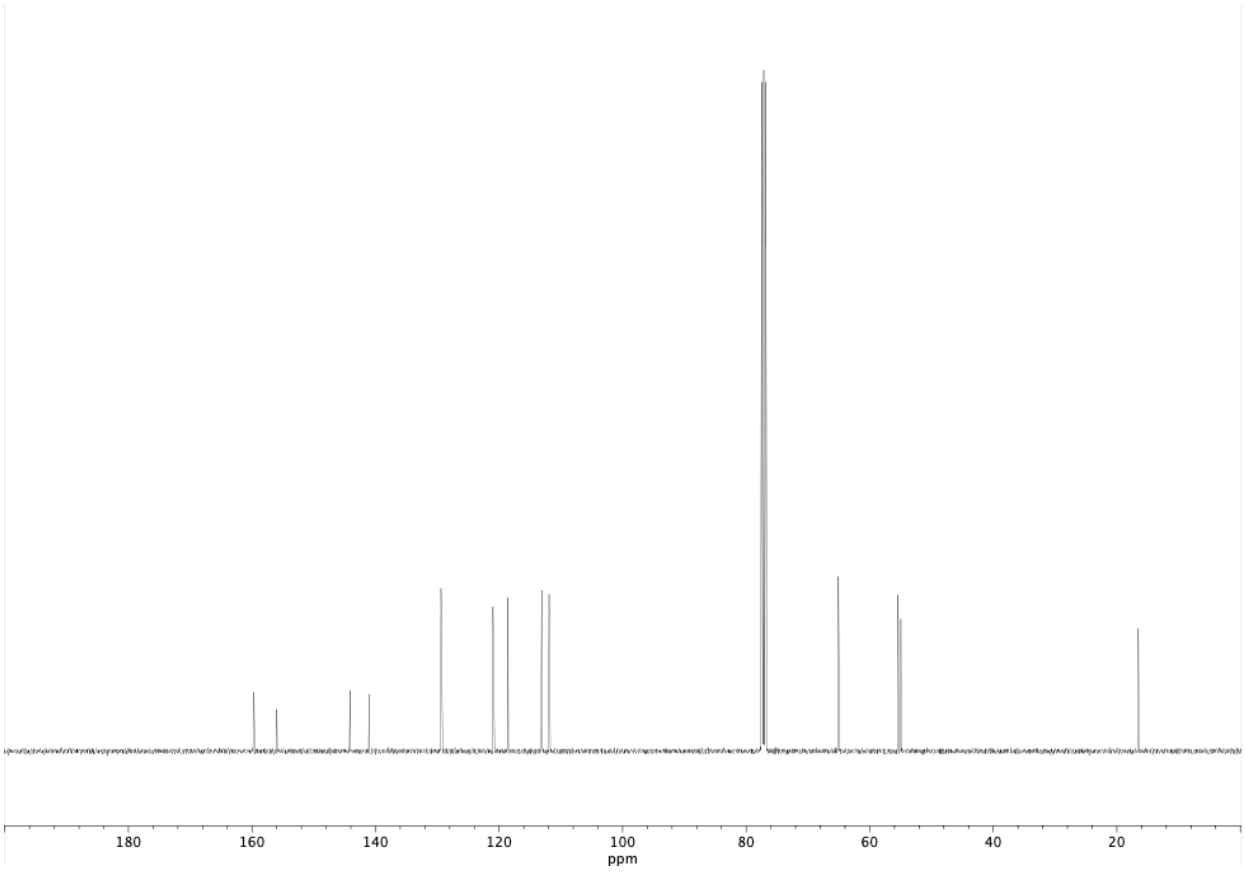


Figure A3.111. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***69a.***

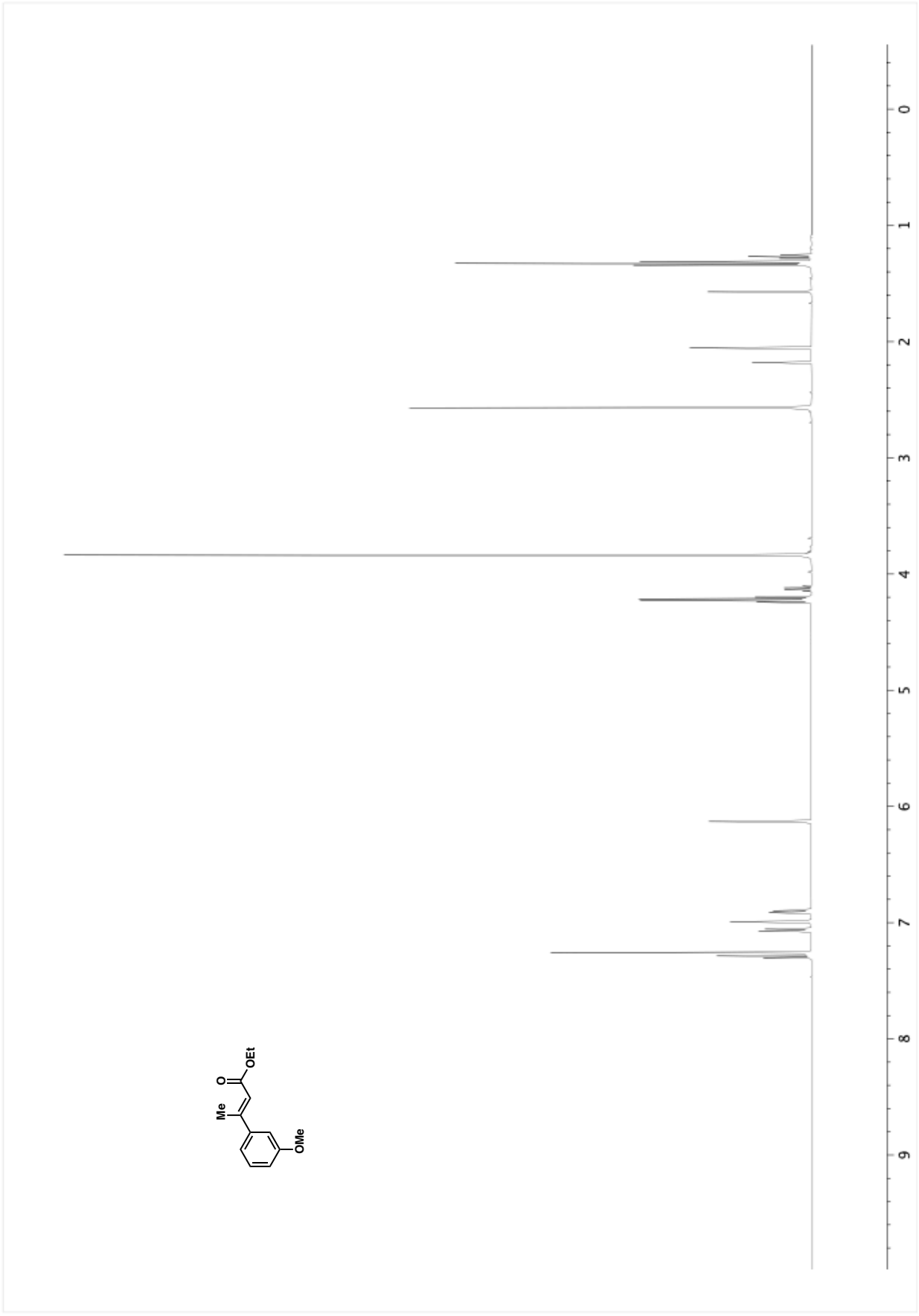


Figure A3.112. *^{1}H NMR (500 MHz, $CDCl_3$) of* ***69b****.*

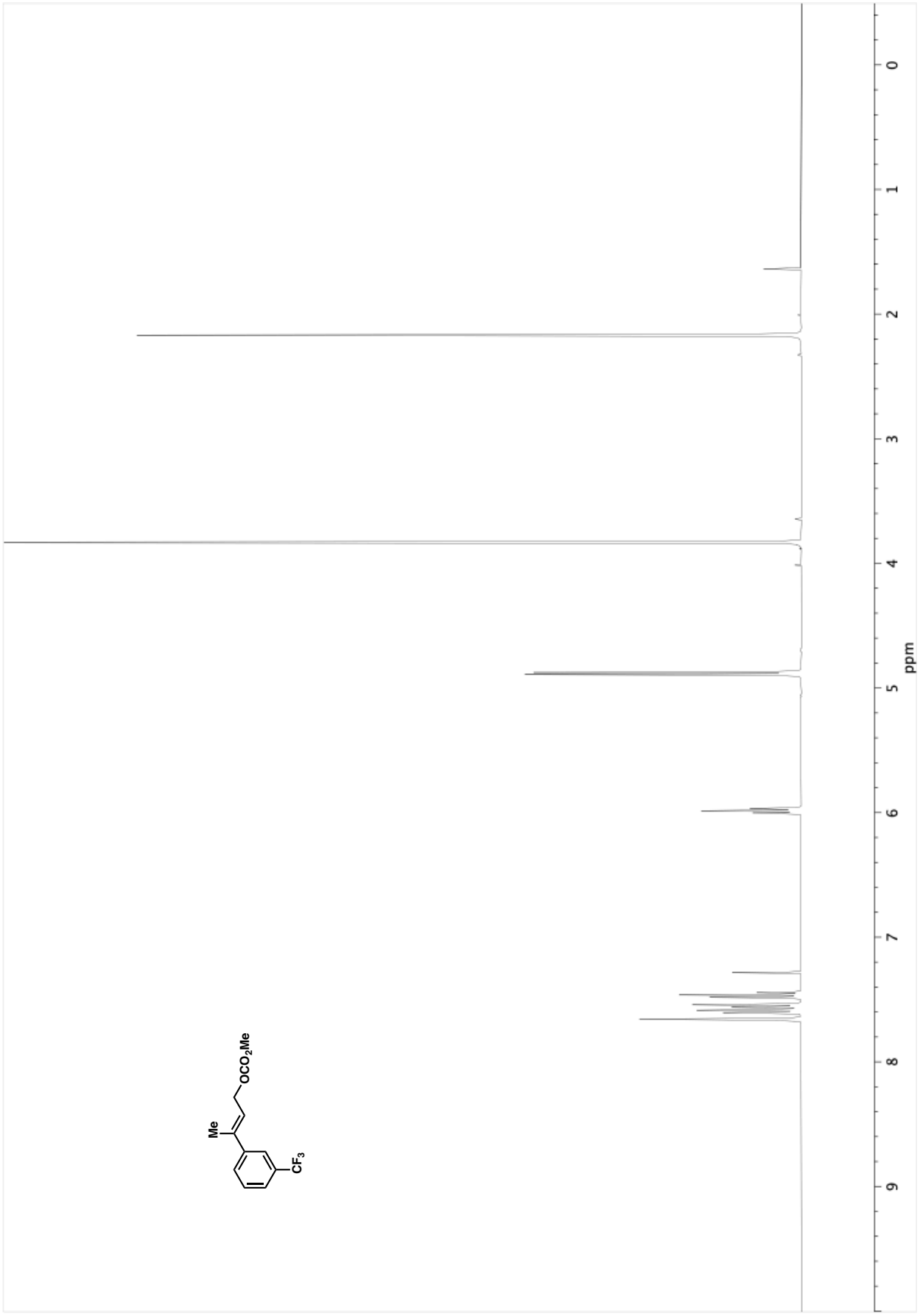


Figure A3.113. *^1H NMR (400 MHz, $CDCl_3$) of* ***71a****.*

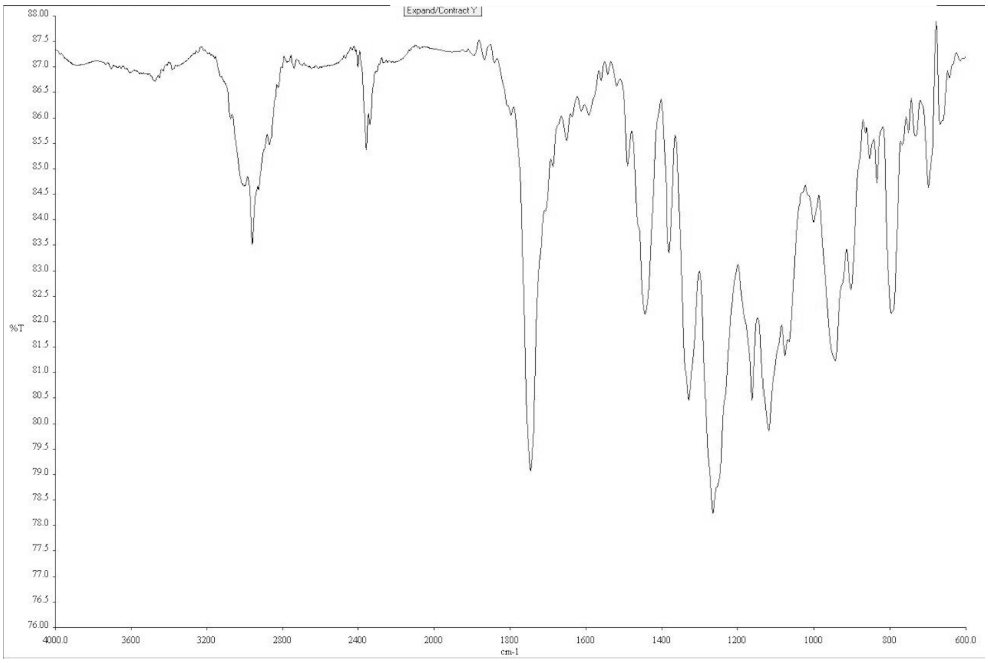


Figure A3.114. *Infrared spectrum (Thin Film, NaCl) of* ***71a****.*

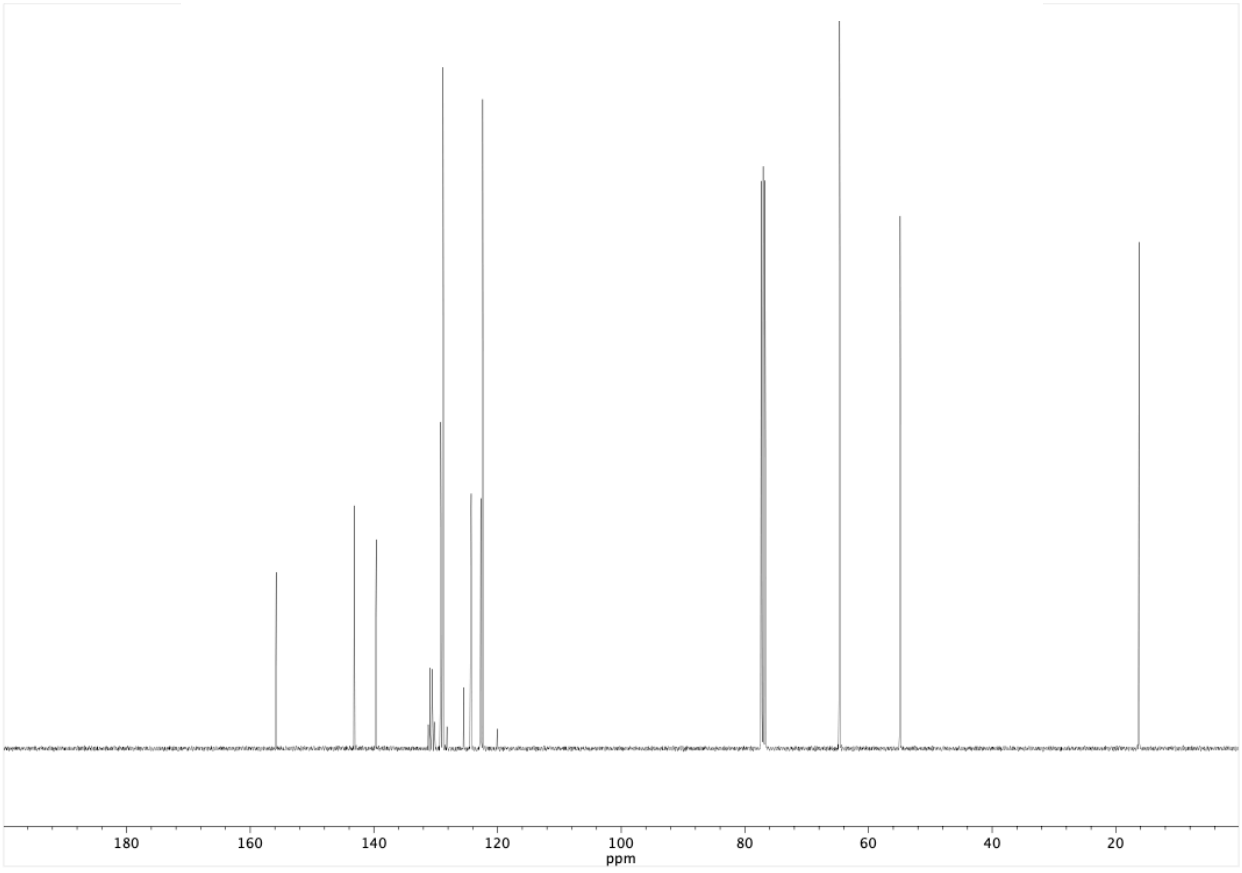


Figure A3.115. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***71a.***

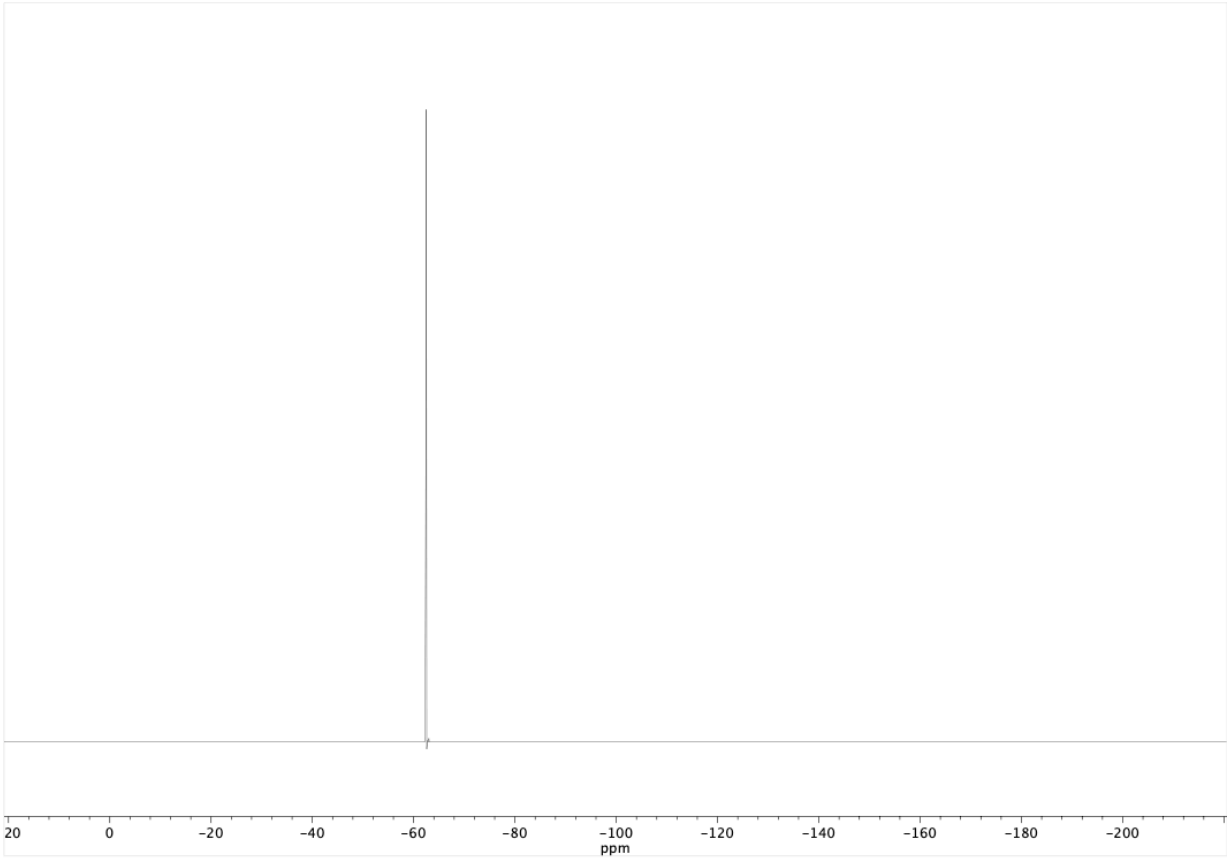


Figure A3.116. *^{19}F NMR (376 MHz, $CDCl_3$) of* ***71a.***

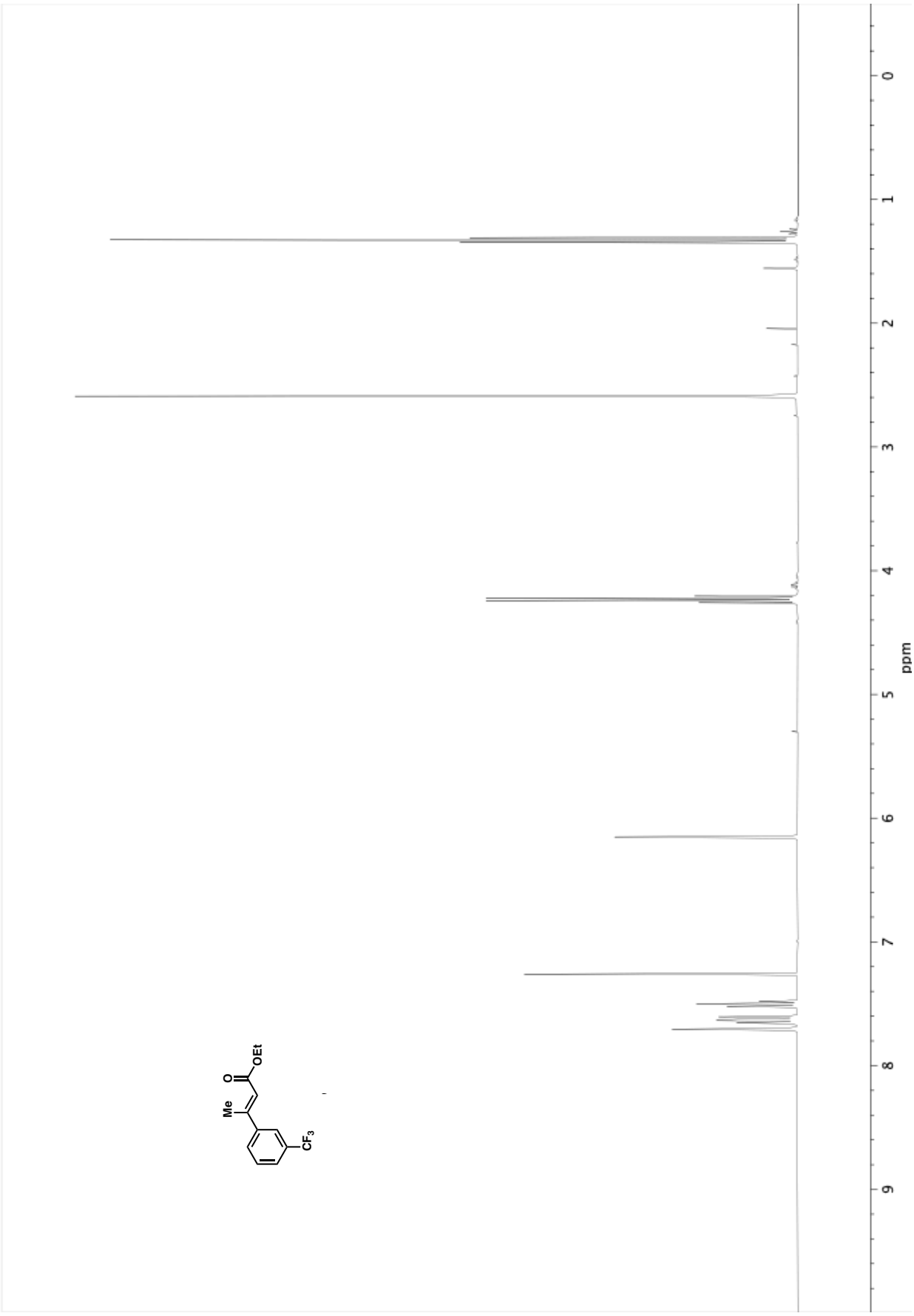


Figure A3.117. *^1H NMR (500 MHz, $CDCl_3$) of* ***71b***.

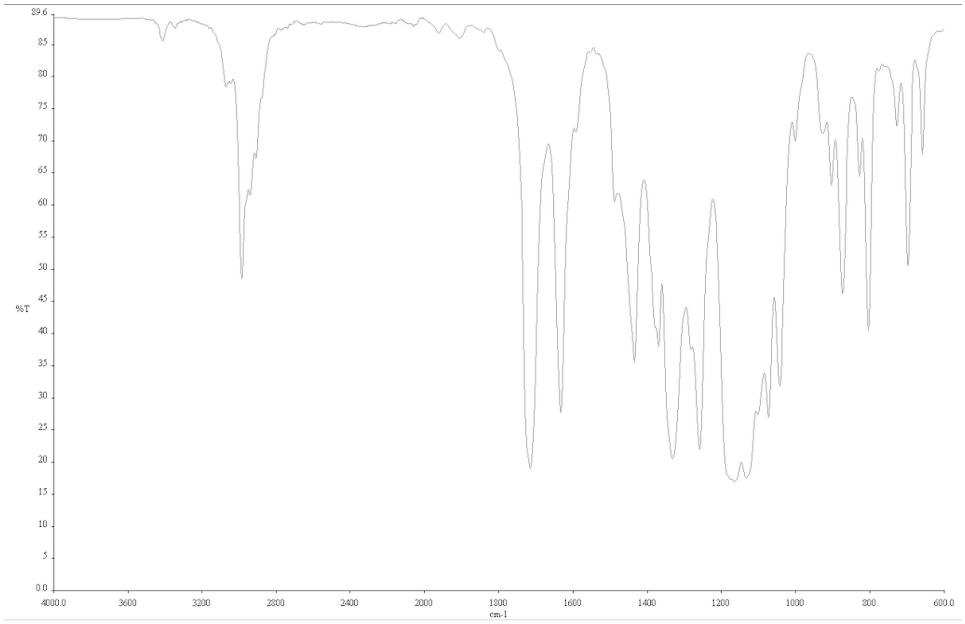


Figure A3.118. *Infrared spectrum (Thin Film, NaCl) of* ***71b****.*

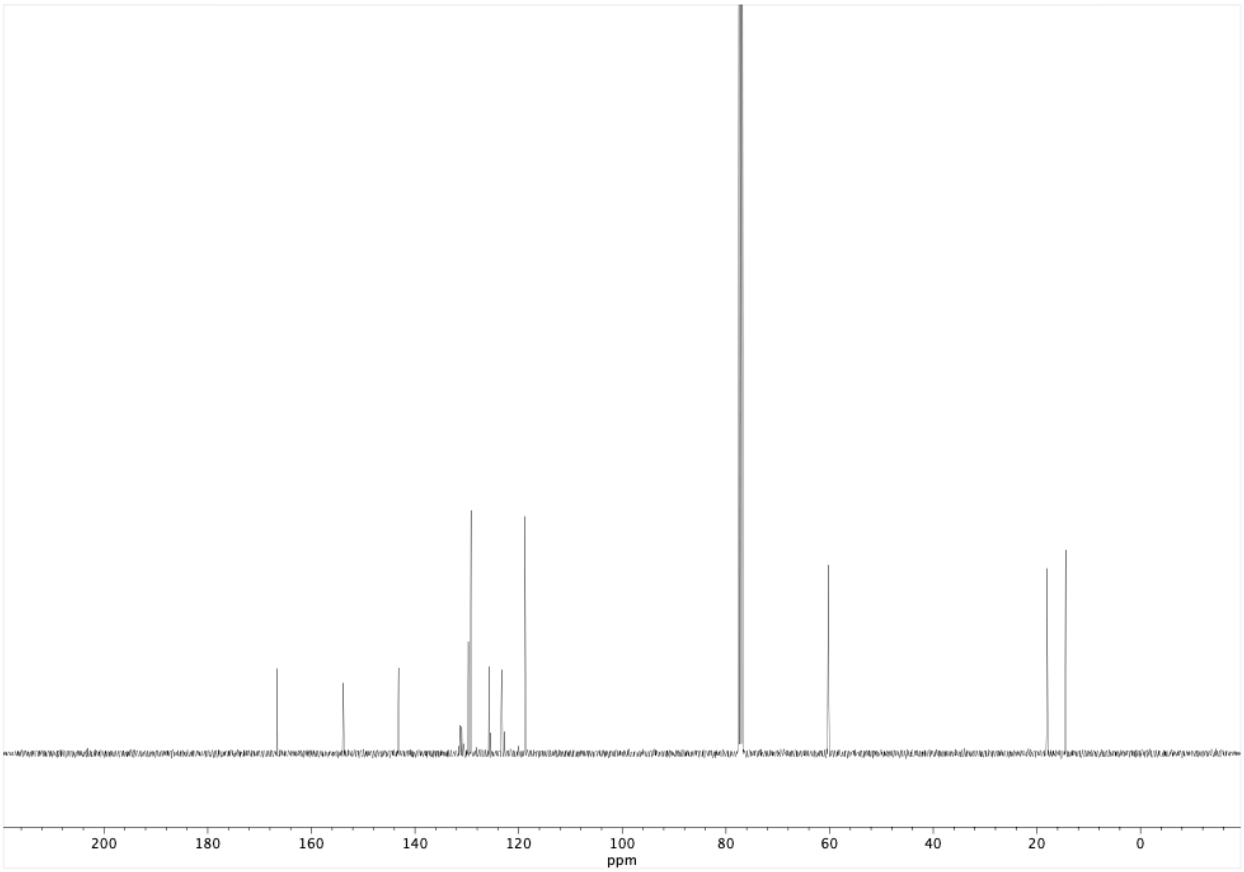


Figure A3.119. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***71b.***

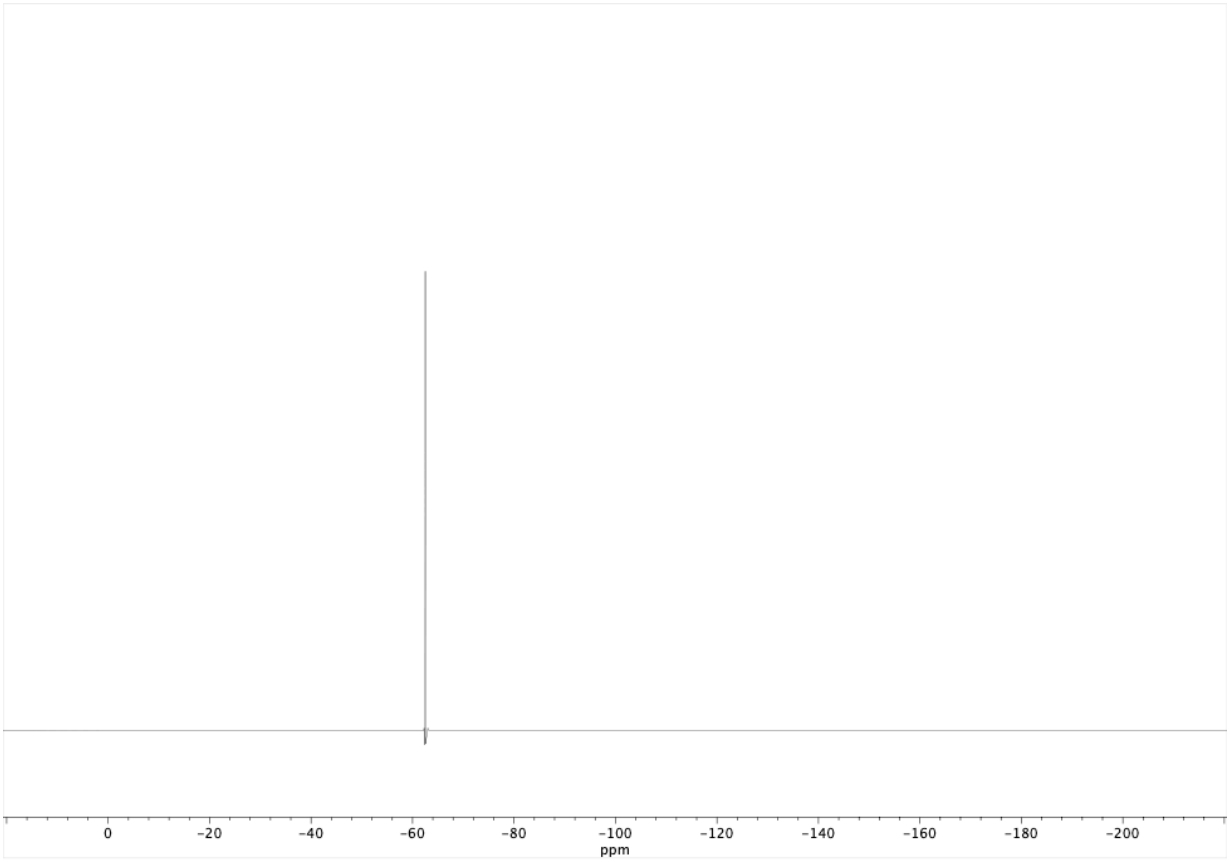


Figure A3.120. *^{19}F NMR (376 MHz, $CDCl_3$) of* ***71b.***

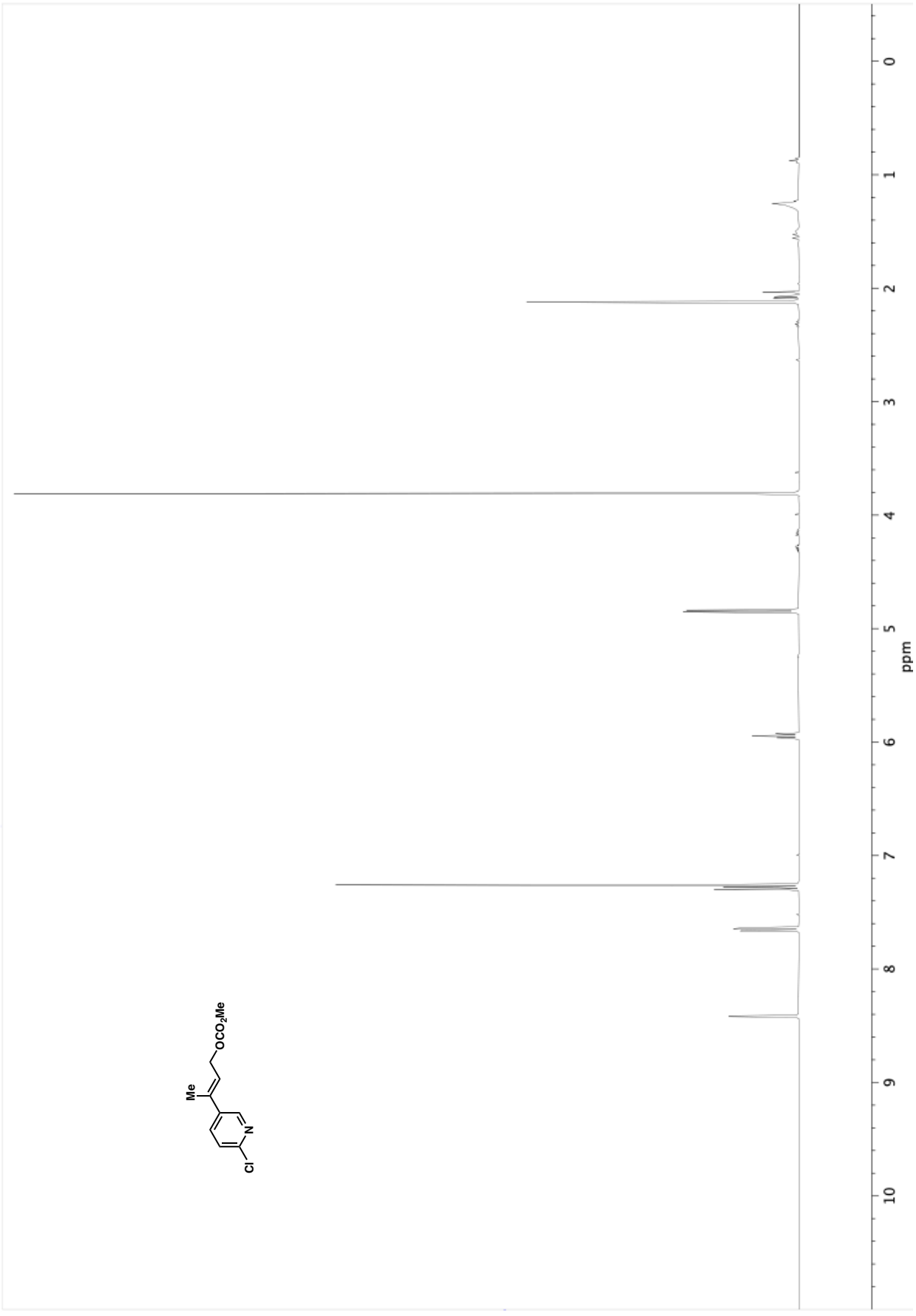


Figure A3.121. *^1H NMR (400 MHz, $CDCl_3$) of* ***73a.***

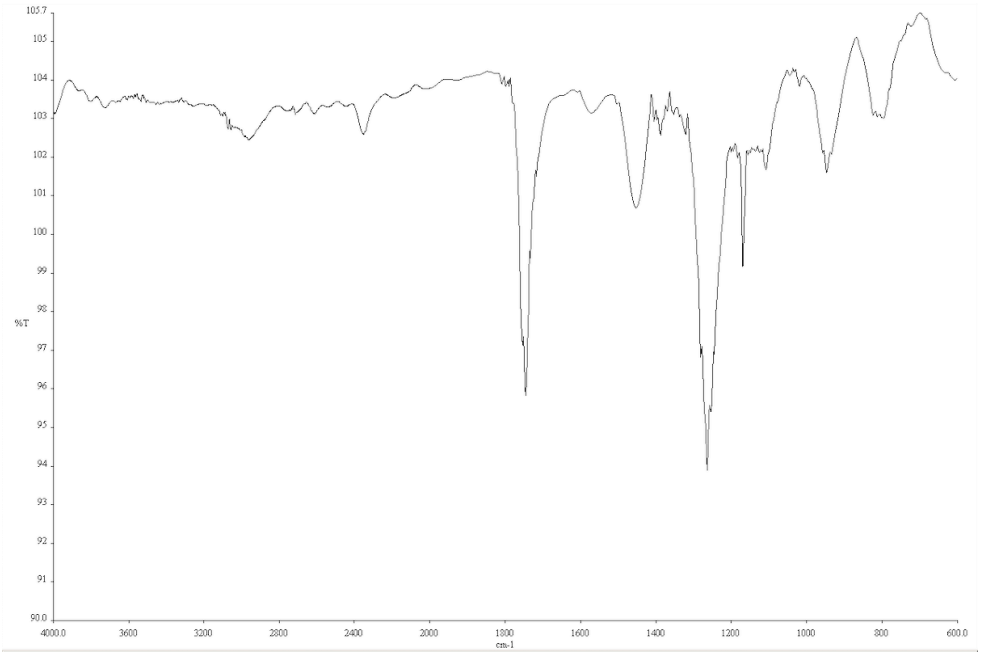


Figure A3.122. *Infrared spectrum (Thin Film, NaCl) of* ***73a***

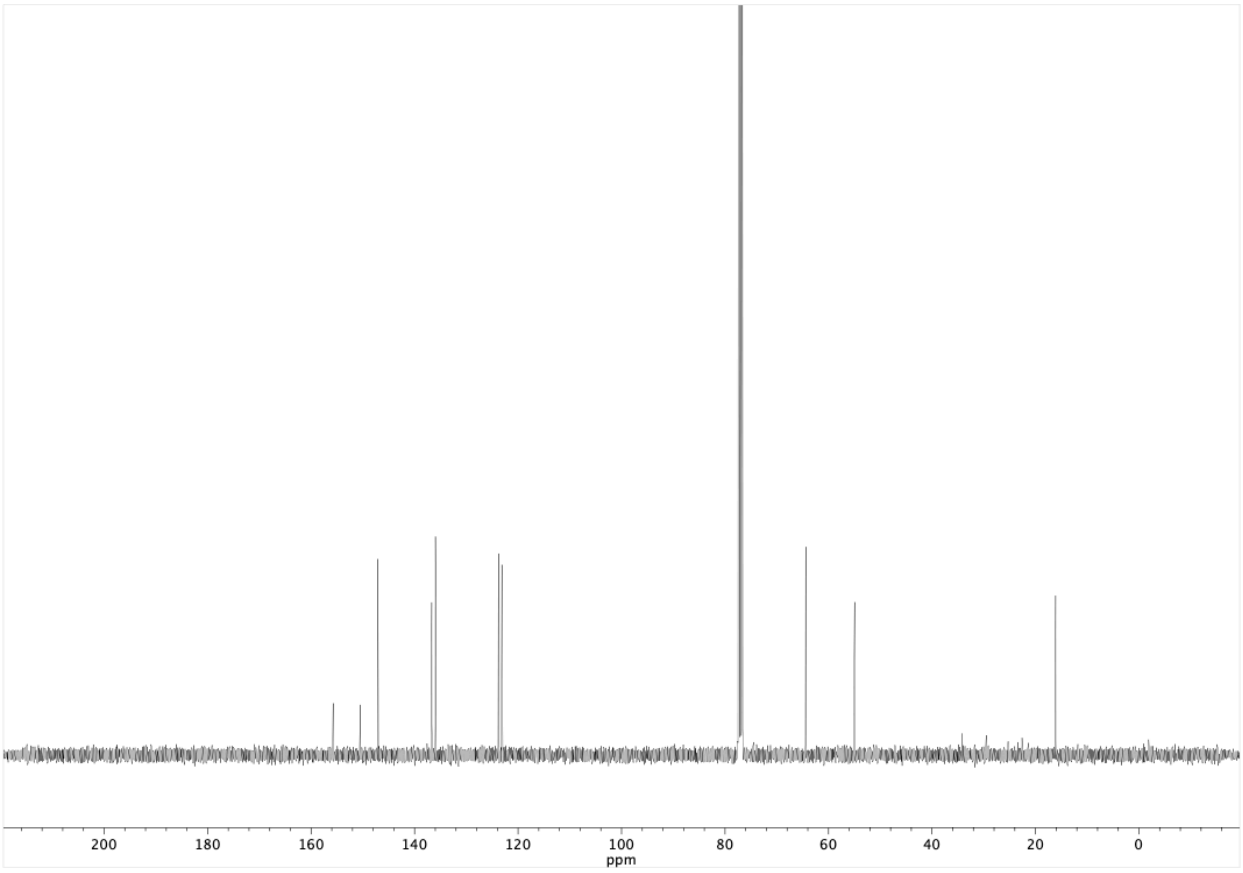


Figure A3.123. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***73a***

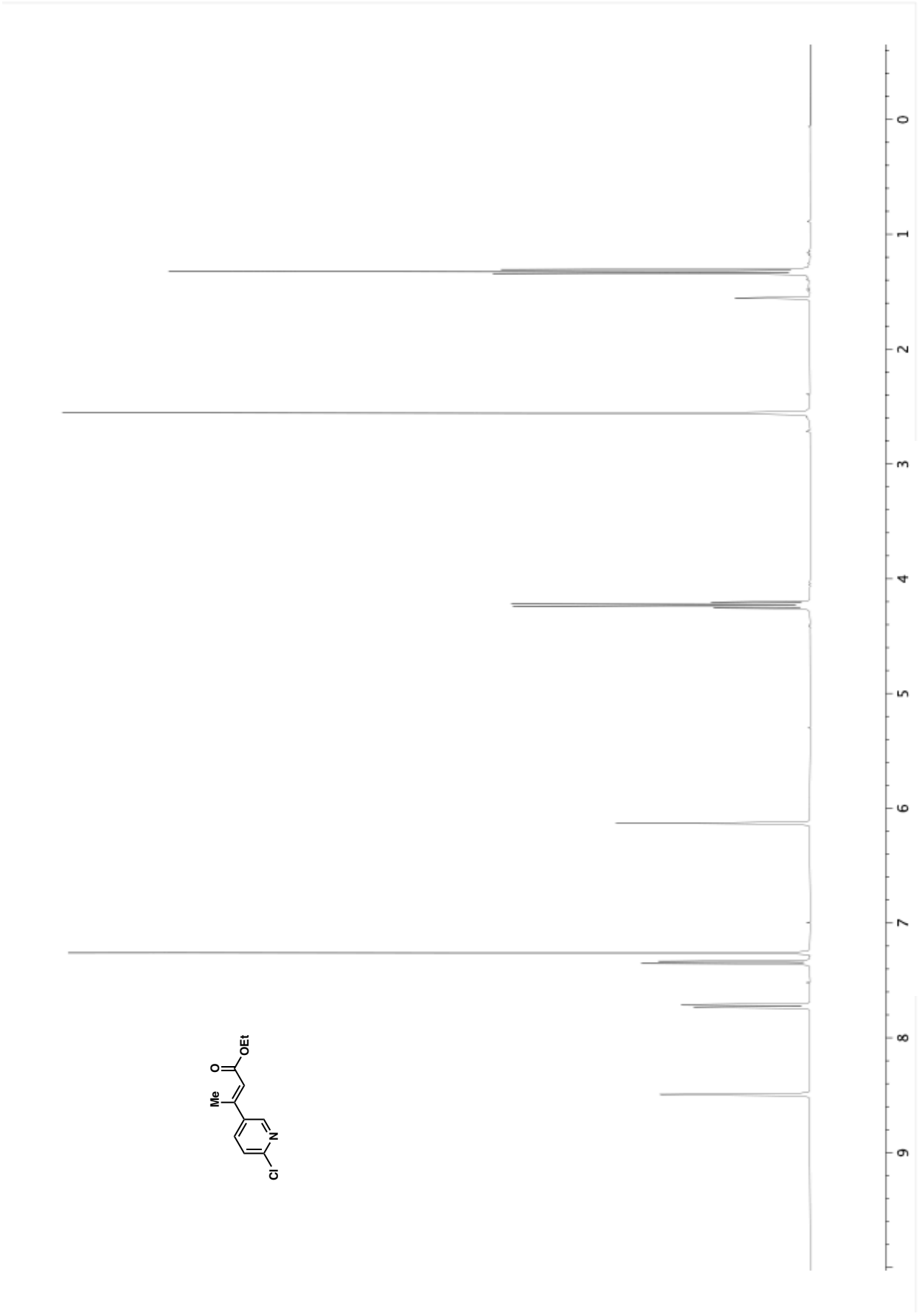


Figure A3.124. *^{1}H NMR (400 MHz, $CDCl_3$) of* ***73b****.*

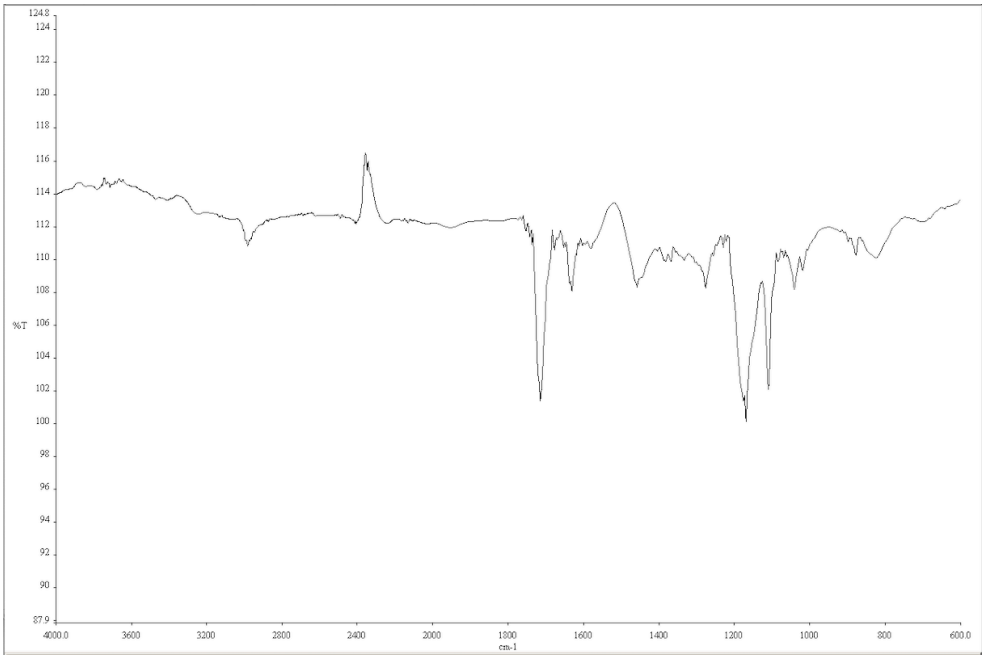


Figure A3.125. *Infrared spectrum (Thin Film, NaCl) of* ***73b.***

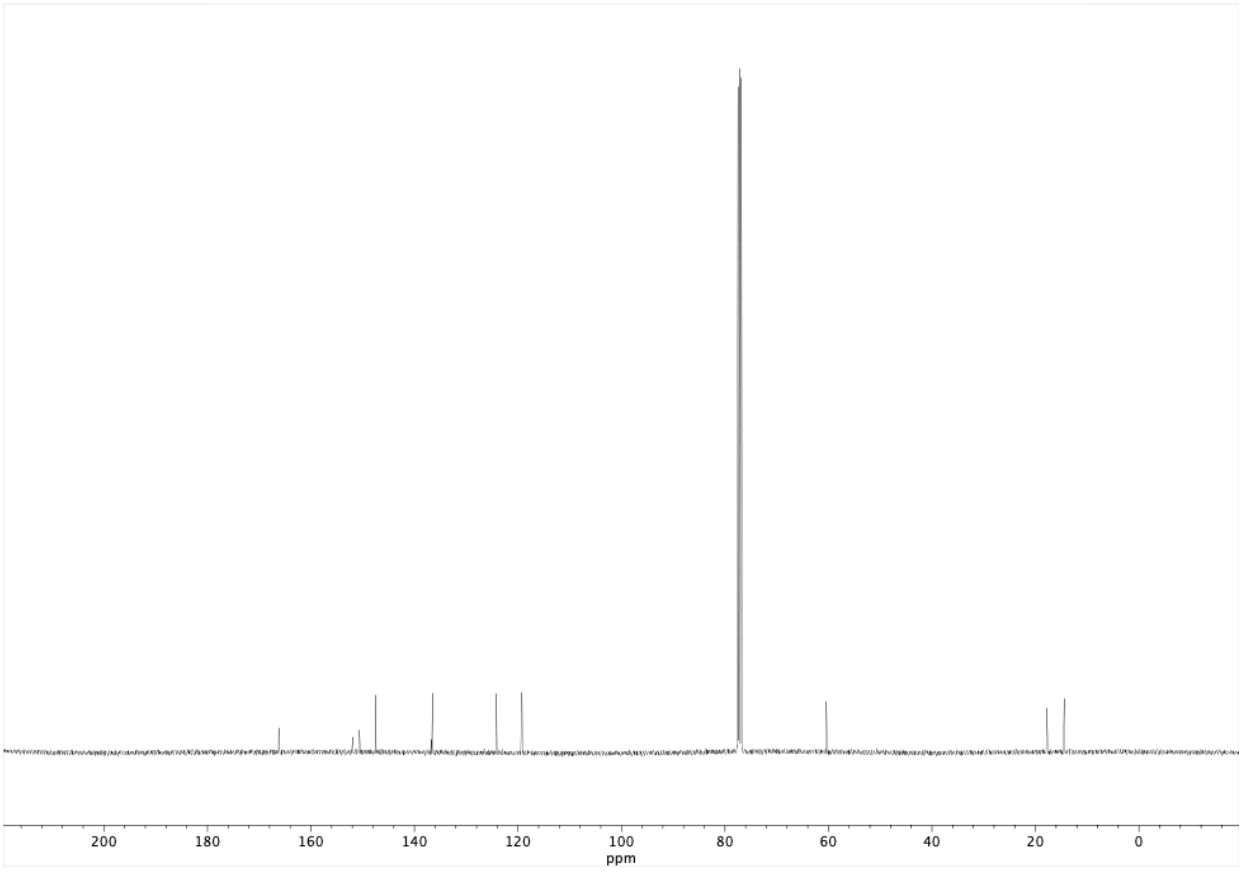


Figure A3.126. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***73b.***

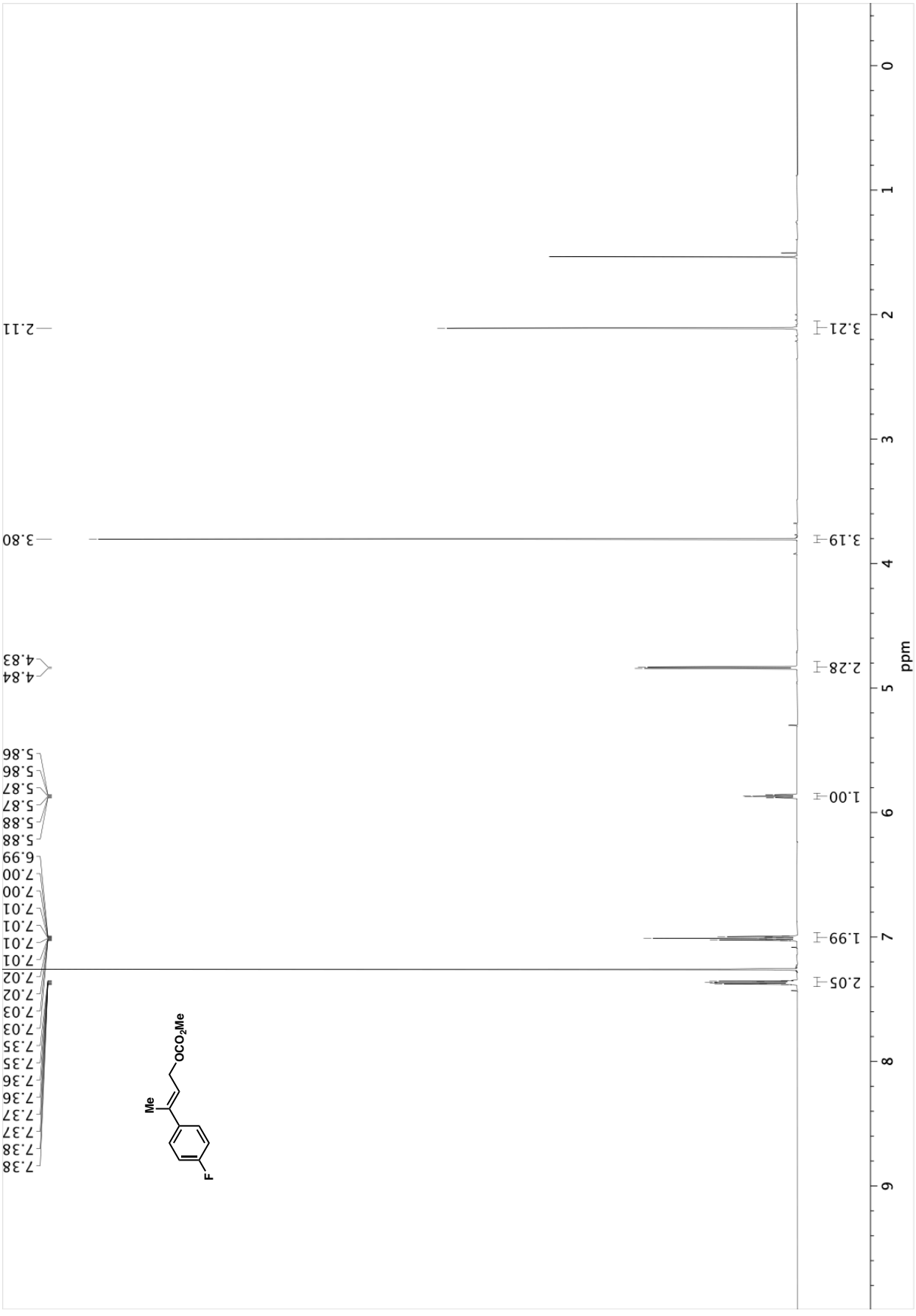


Figure A3.127. *^1H NMR (600 MHz, $CDCl_3$) of* ***65a****.*

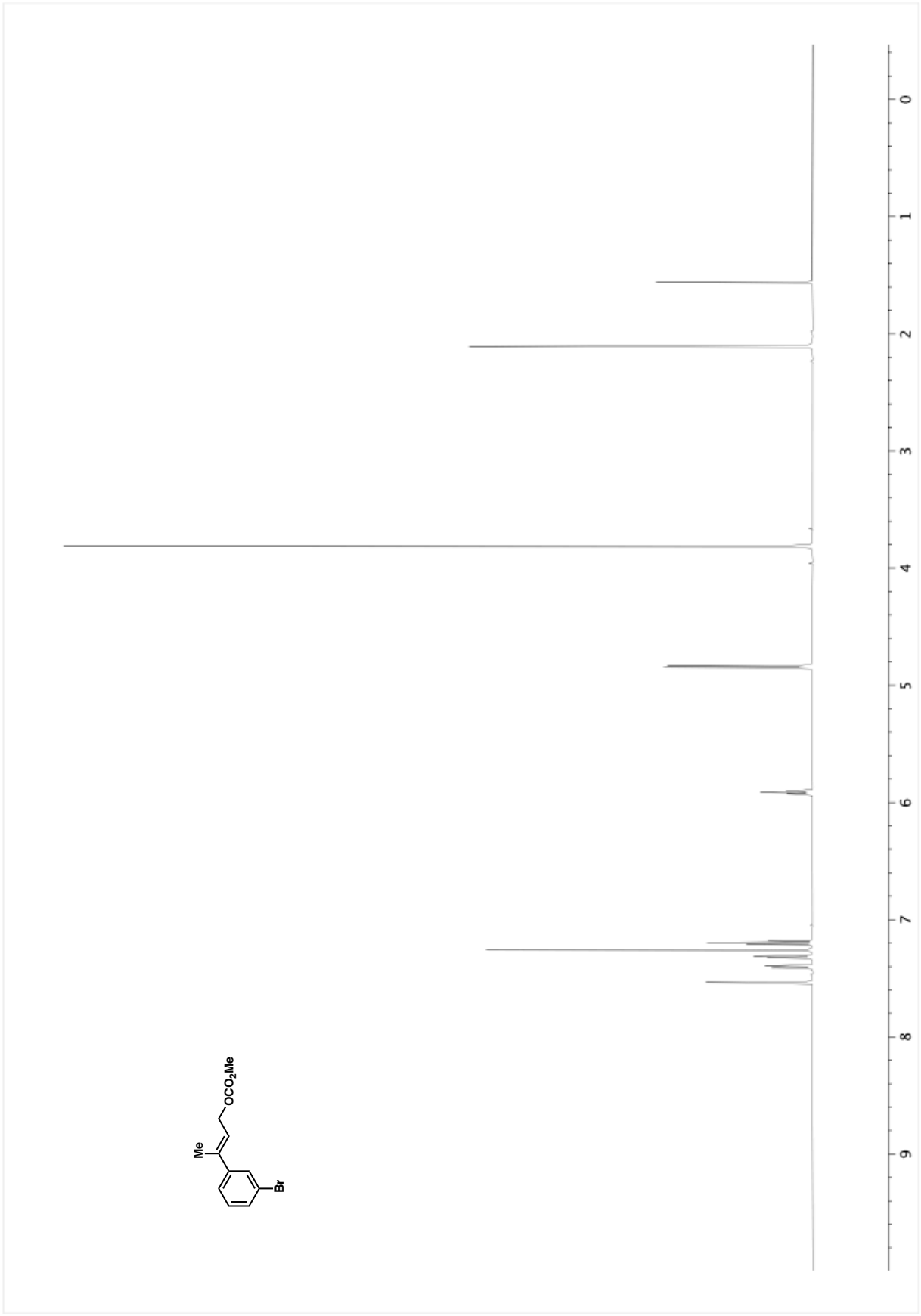


Figure A3.128. *^{1}H NMR (500 MHz, $CDCl_3$) of* ***70a.***

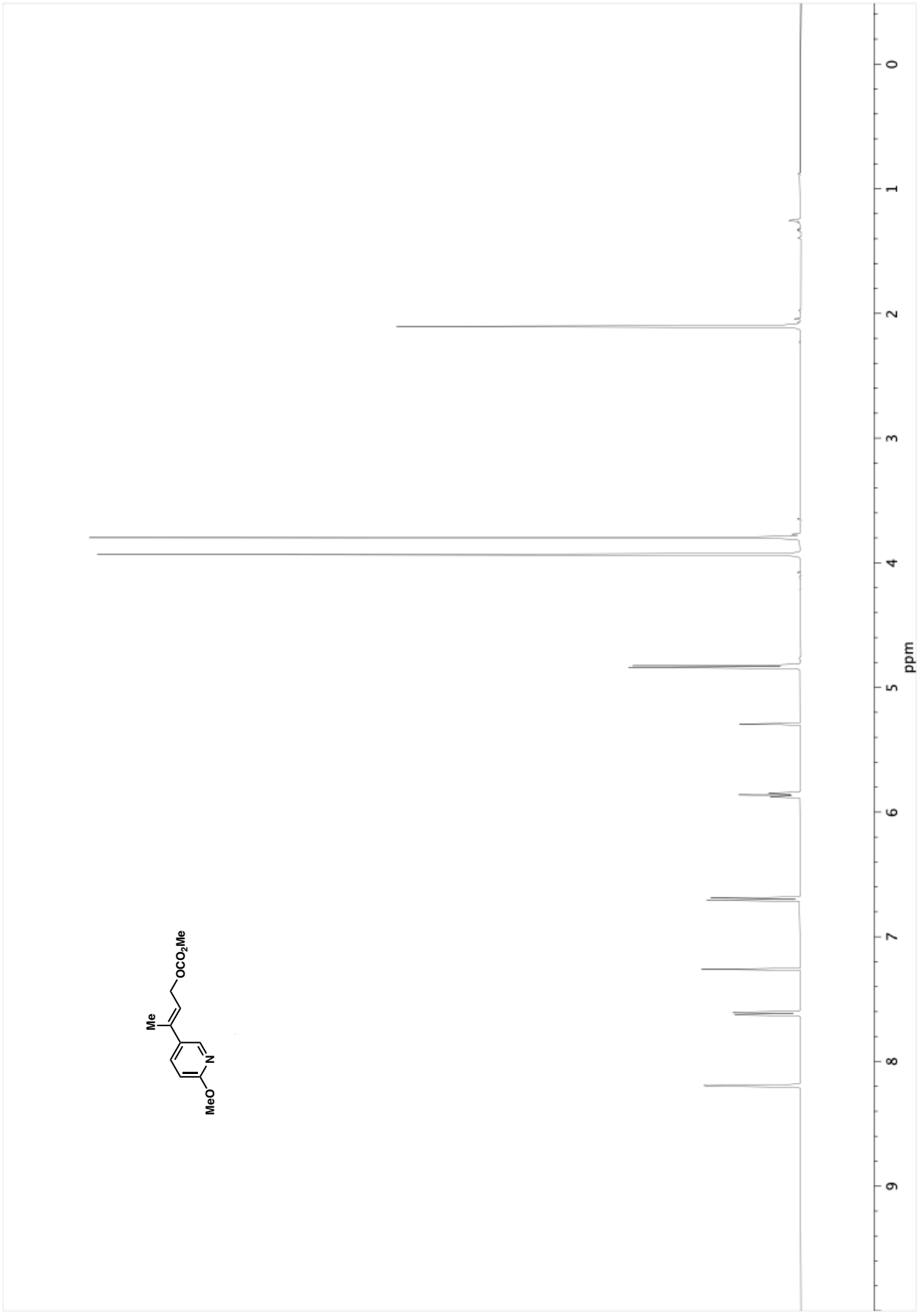


Figure A3.129. *^1H NMR (500 MHz, $CDCl_3$) of* ***72a****.*

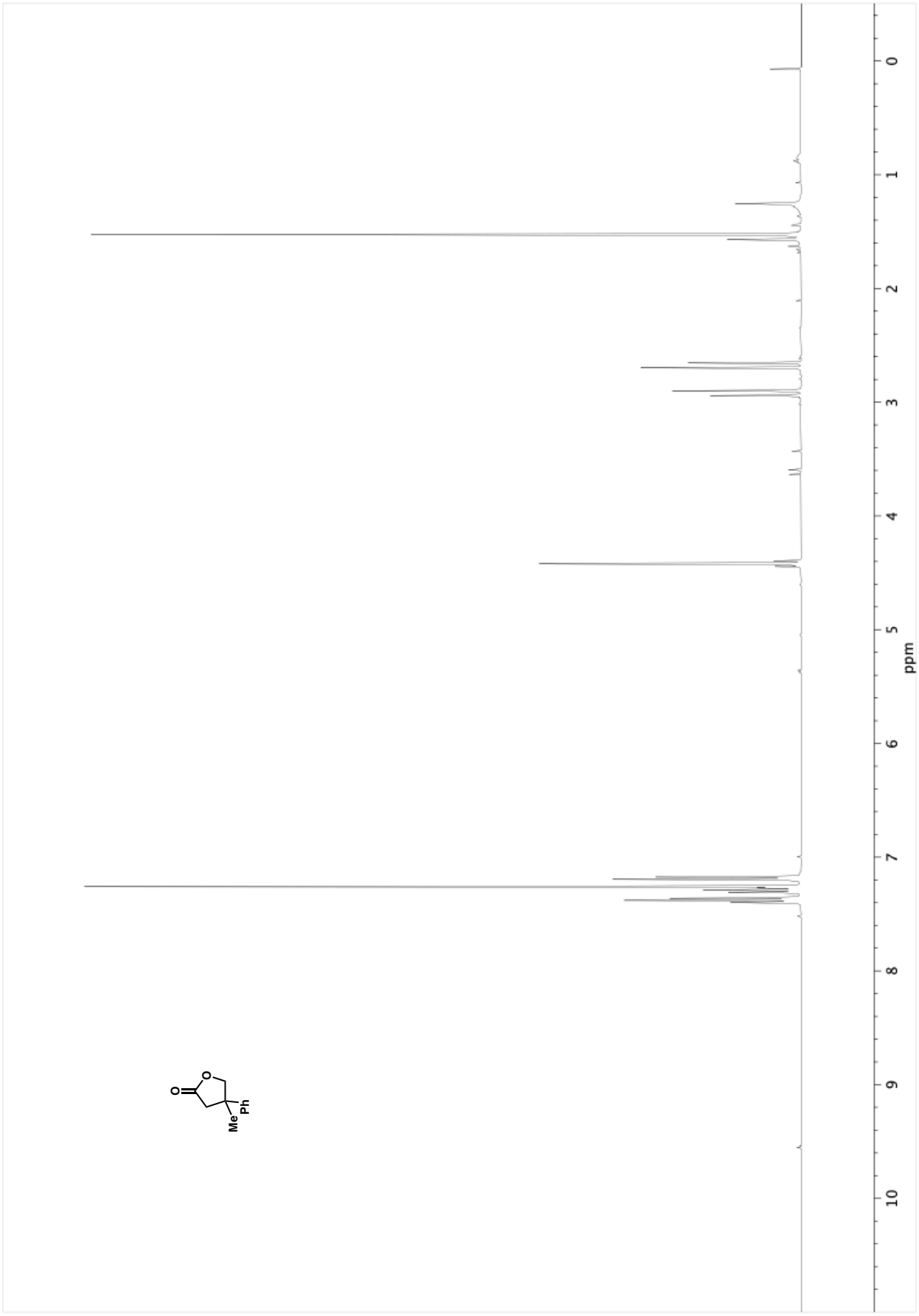


Figure A3.130. *^{1}H NMR (400 MHz, $CDCl_3$) of* ***77****.*

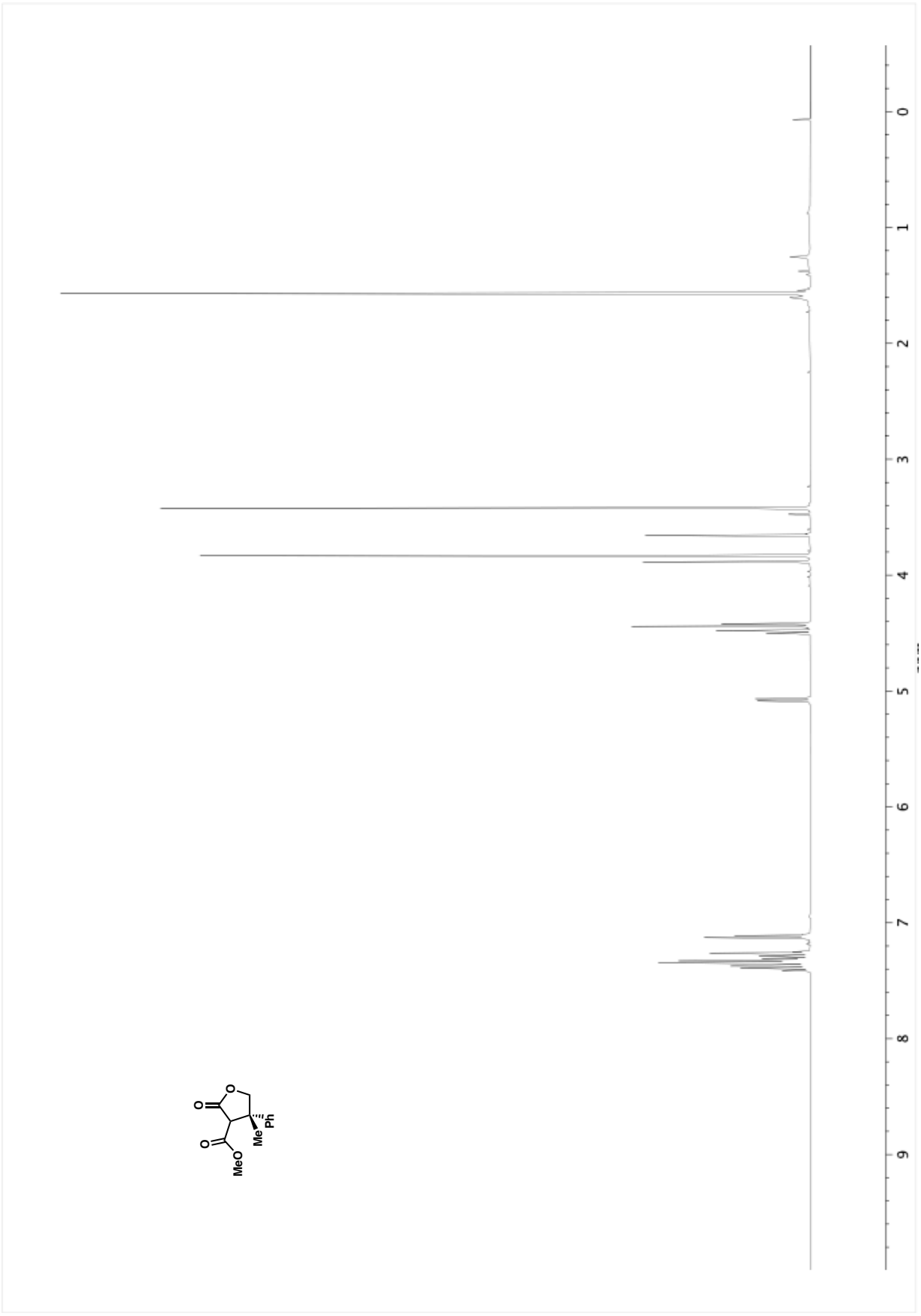


Figure A3.131. *^1H NMR (400 MHz, $CDCl_3$) of* ***78****.*

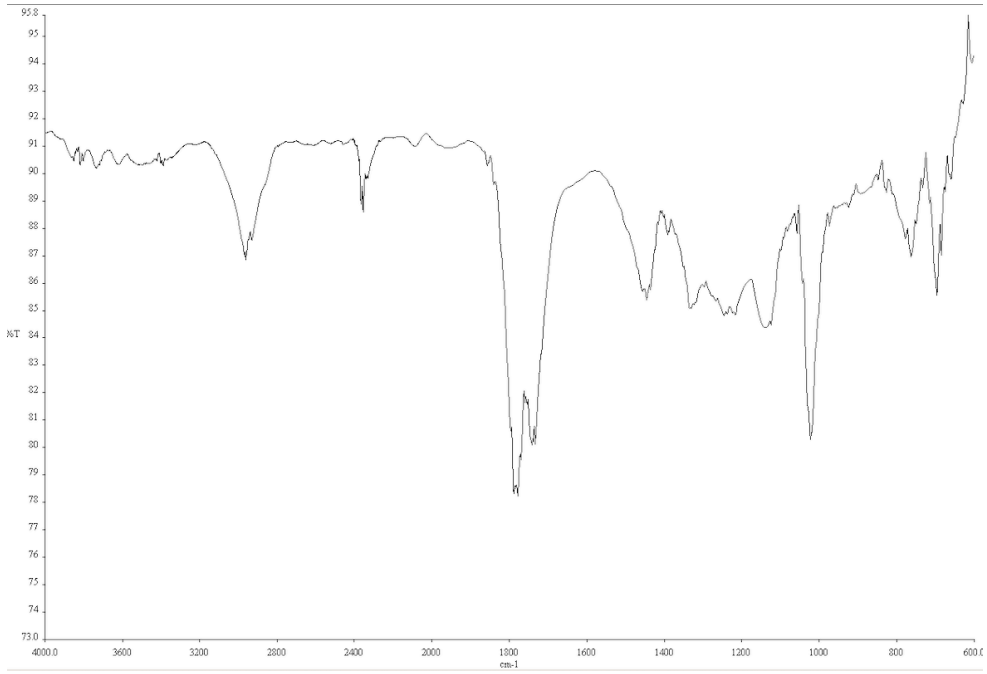


Figure A3.132. *Infrared spectrum (Thin Film, NaCl) of* ***78.***

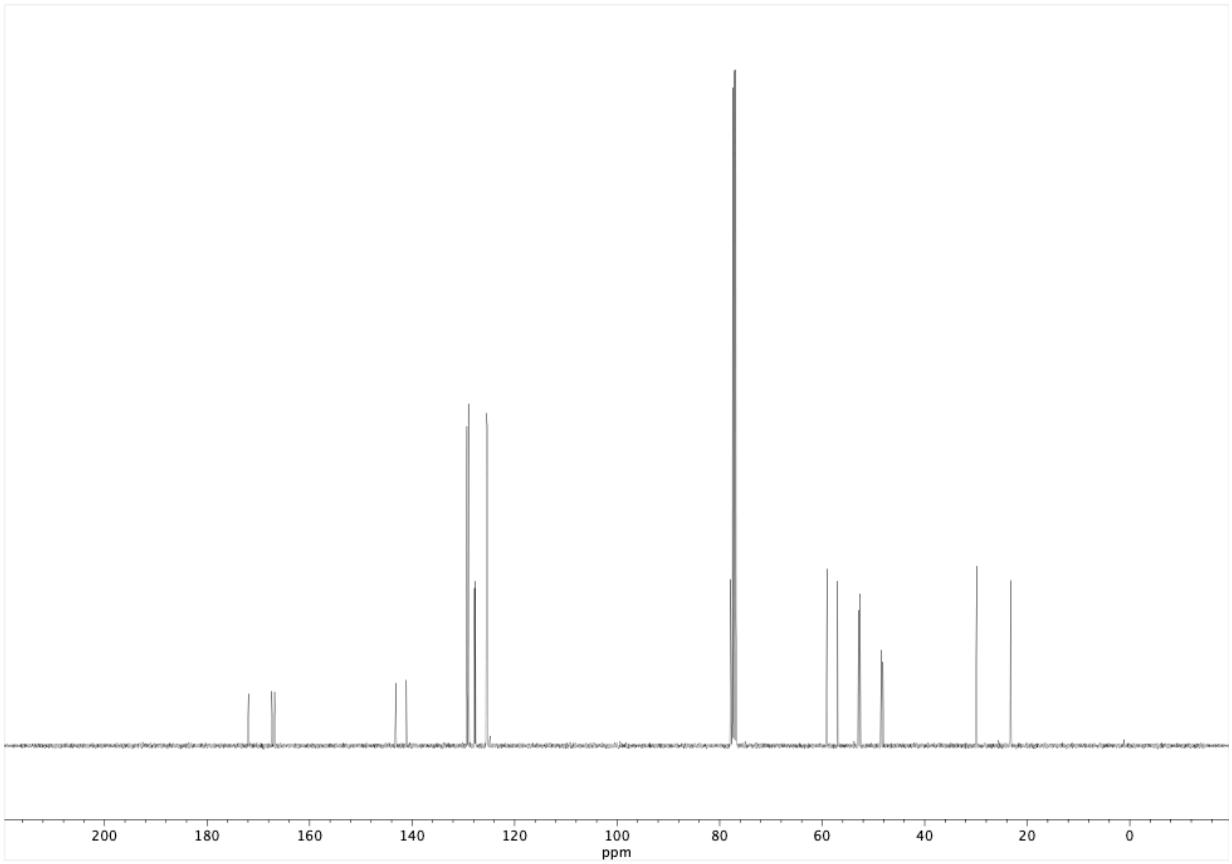


Figure A3.133. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***78.***

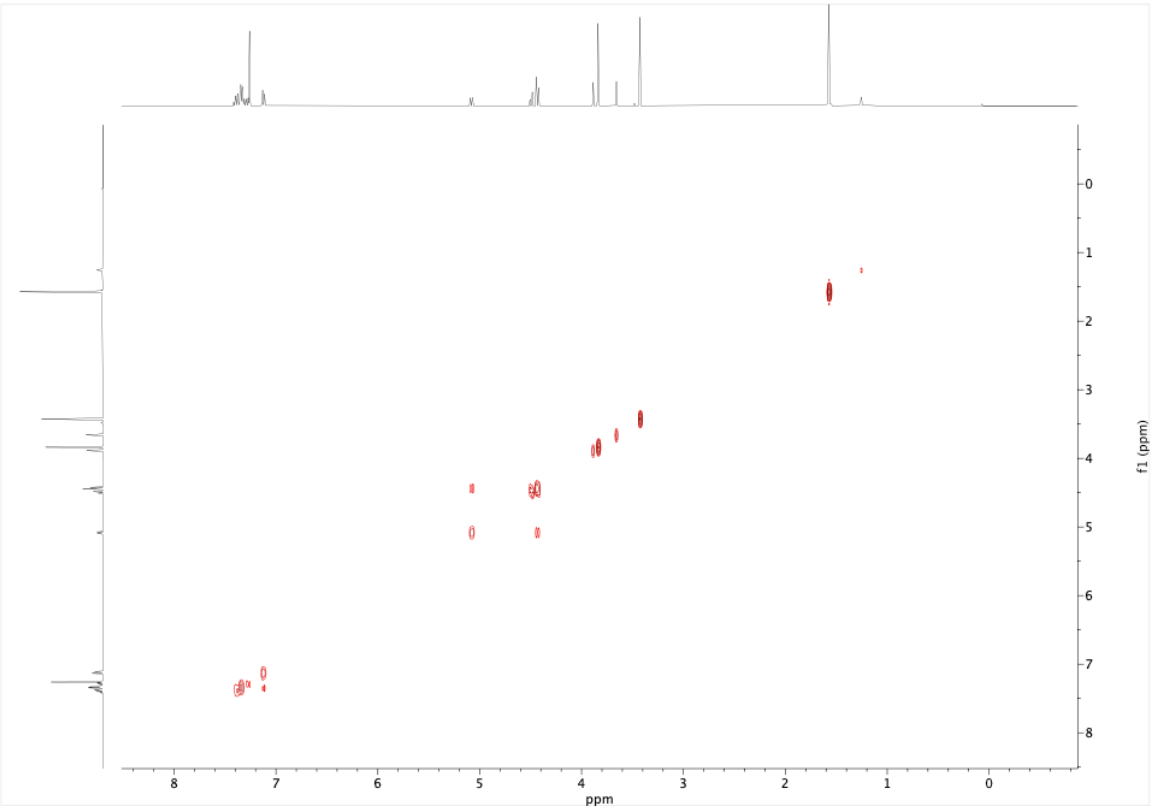


Figure A3.134. *^{1}H-^{13}C HSQC ($CDCl_3$) of compound* ***78.***

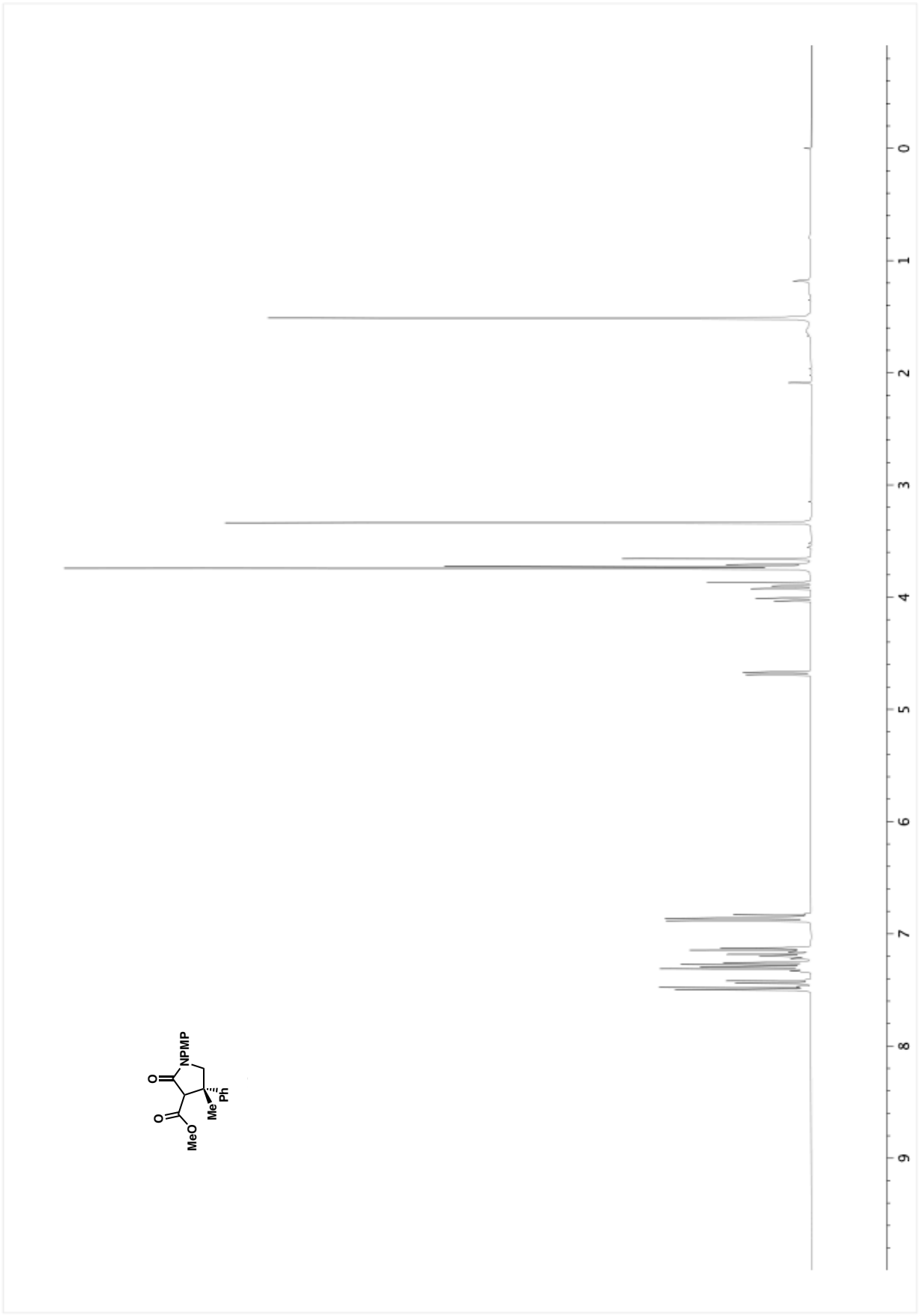


Figure A3.135. *^1H NMR (400 MHz, $CDCl_3$) of* ***79****.*

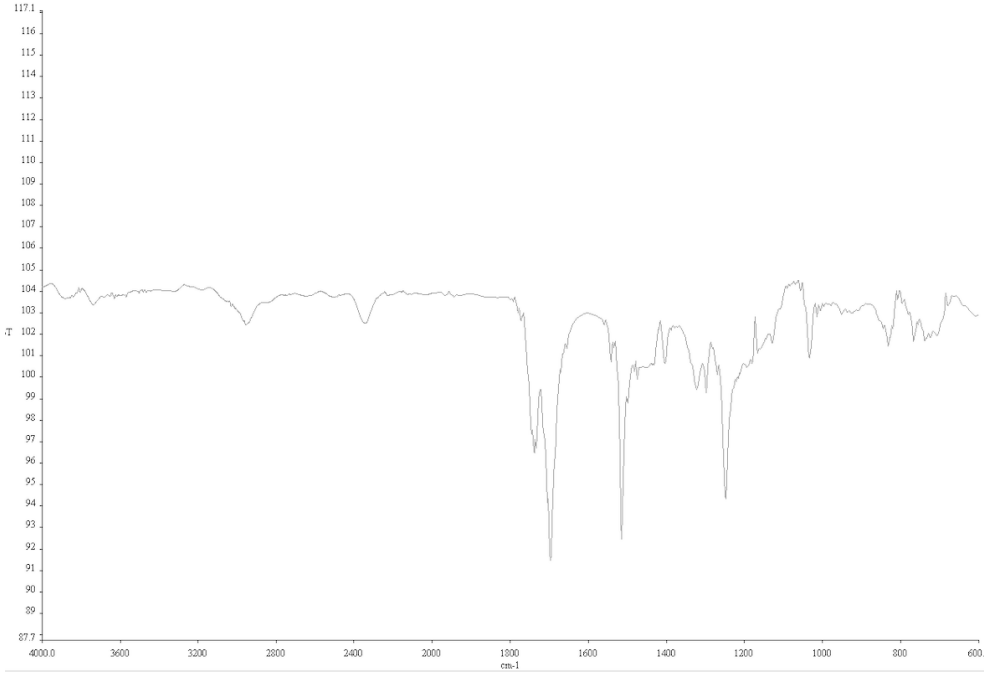


Figure A3.136. *Infrared spectrum (Thin Film, NaCl) of* ***79.***

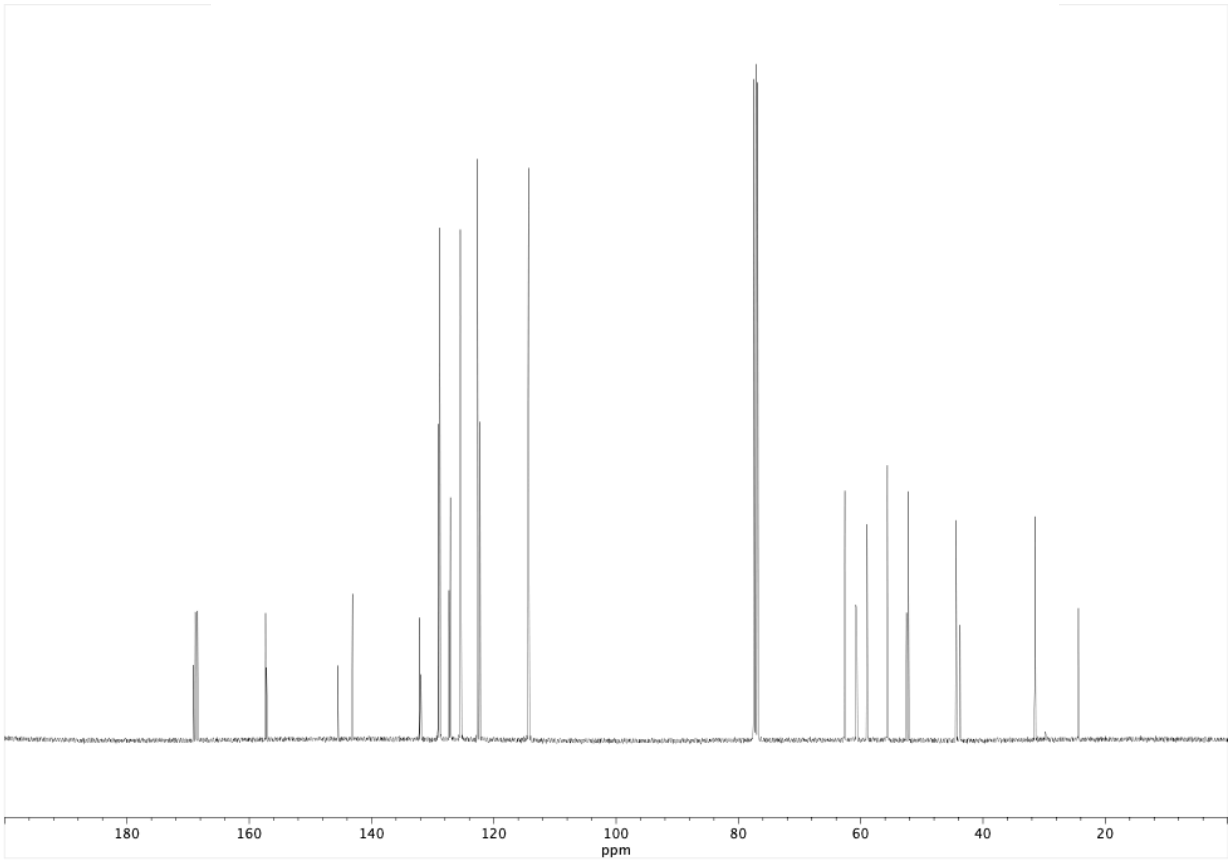


Figure A3.137. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***79.***

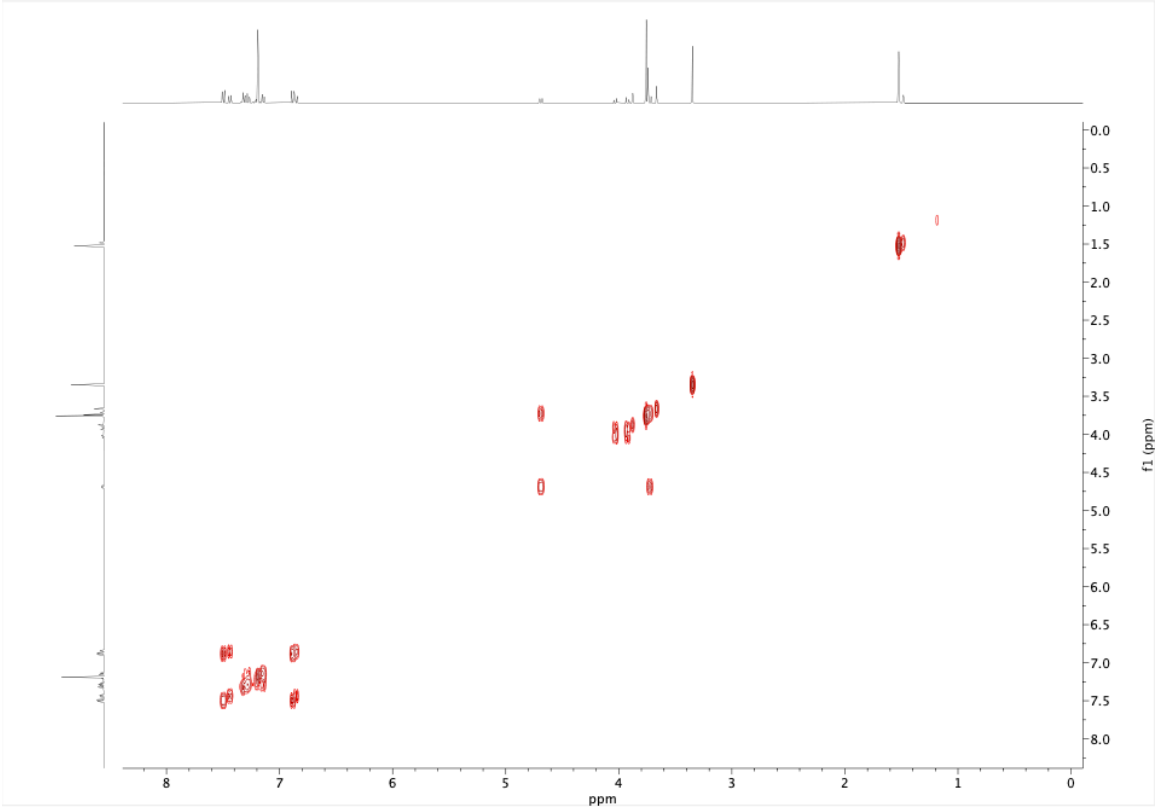


Figure A3.138. *^{1}H-^{13}C HSQC ($CDCl_3$) of compound* ***79.***

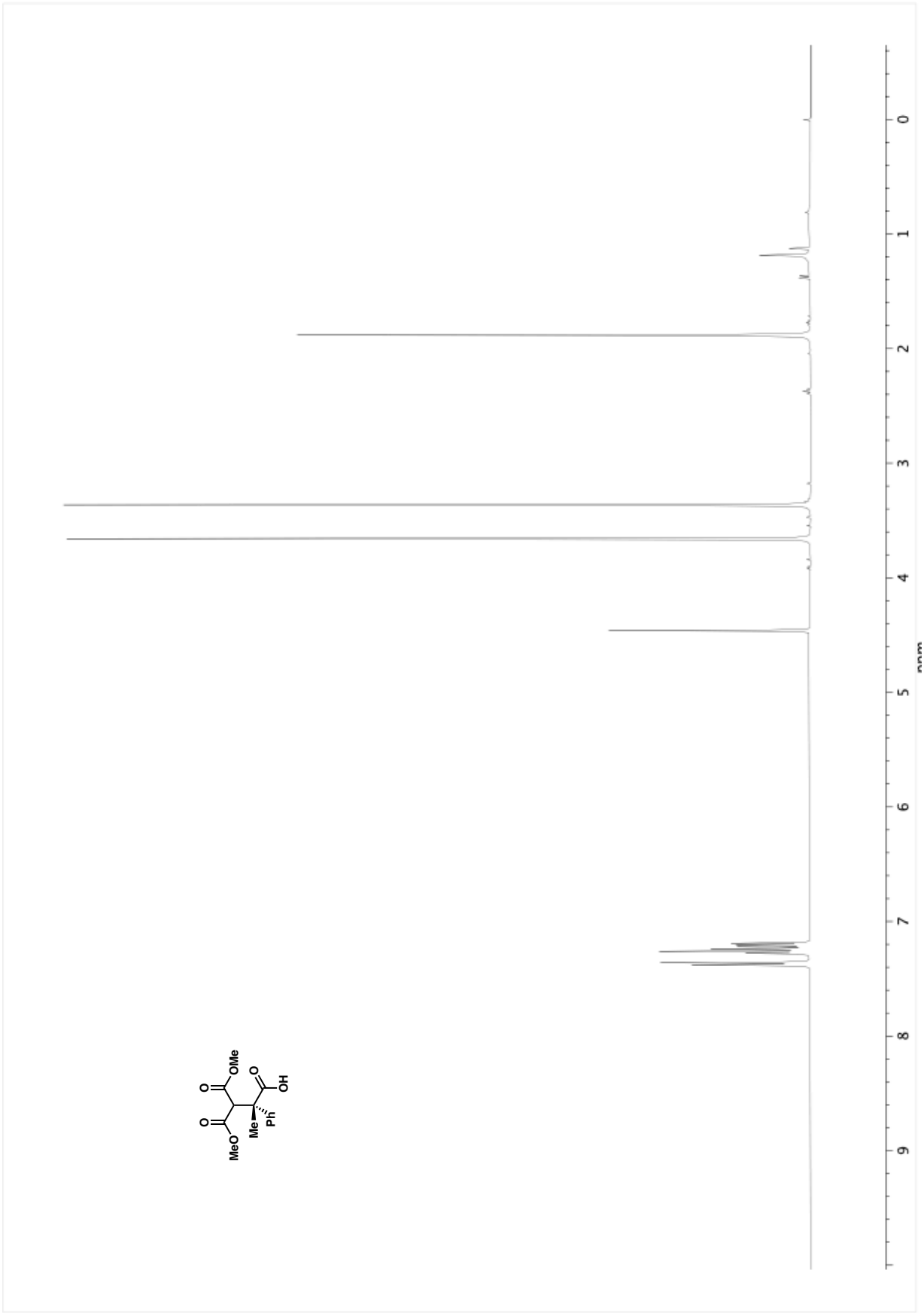


Figure A3.139. *^1H NMR (400 MHz, $CDCl_3$) of* ***80****.*

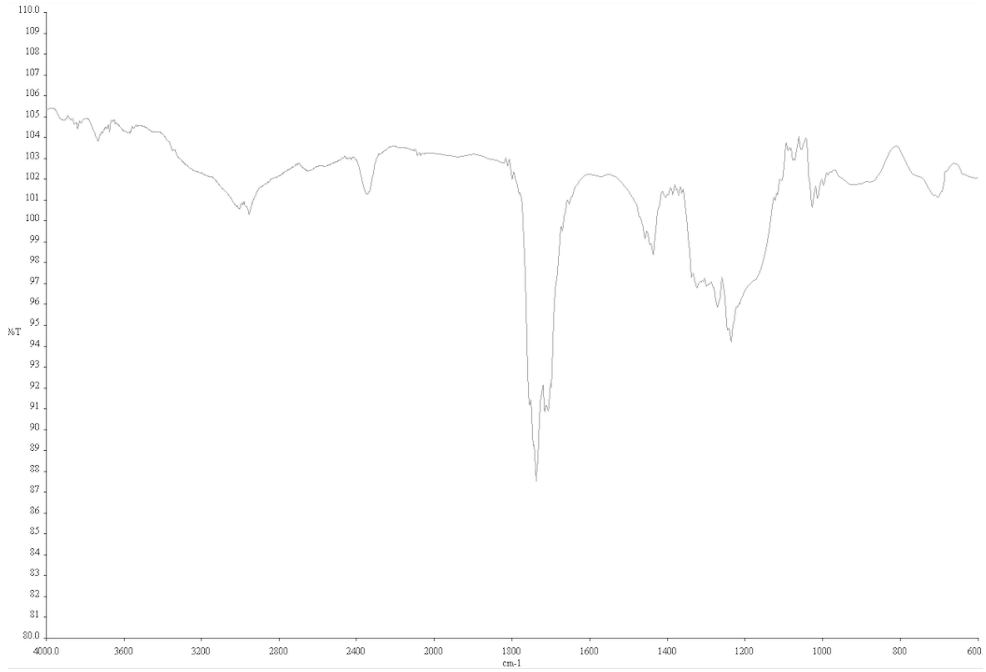


Figure A3.140. *Infrared spectrum (Thin Film, NaCl) of* ***80.***

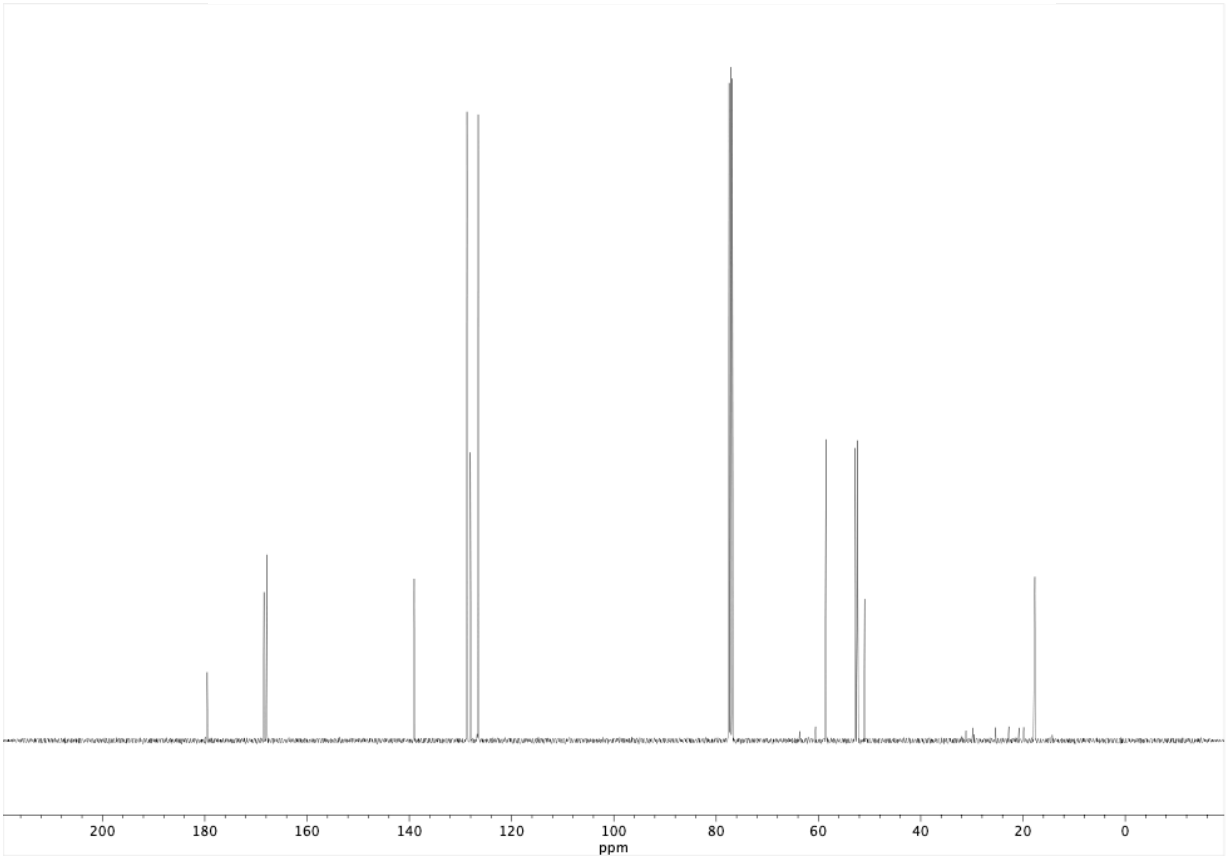


Figure A3.141. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***80.***

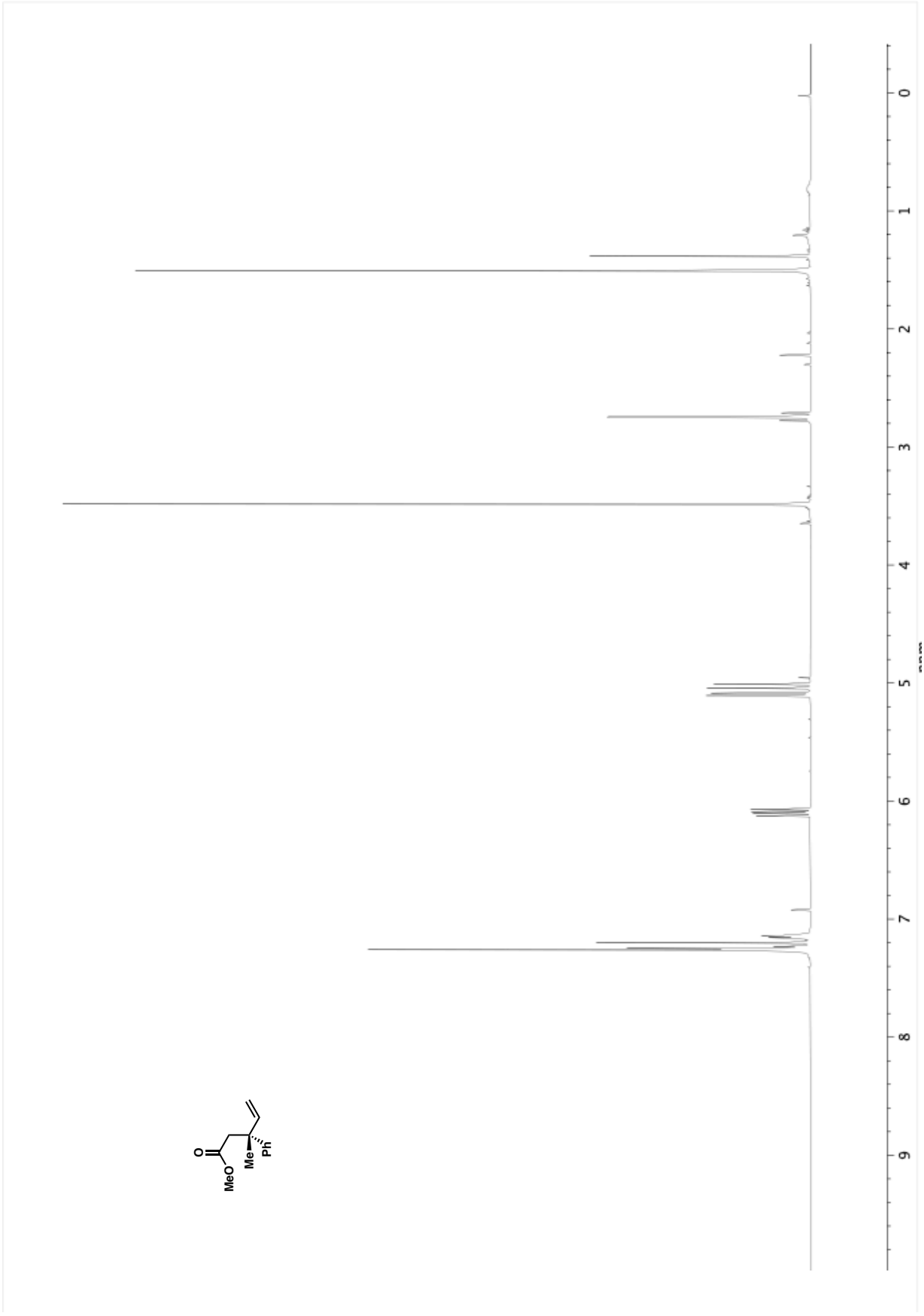


Figure A3.142. *^1H NMR (500 MHz, $CDCl_3$) of* ***81****.*

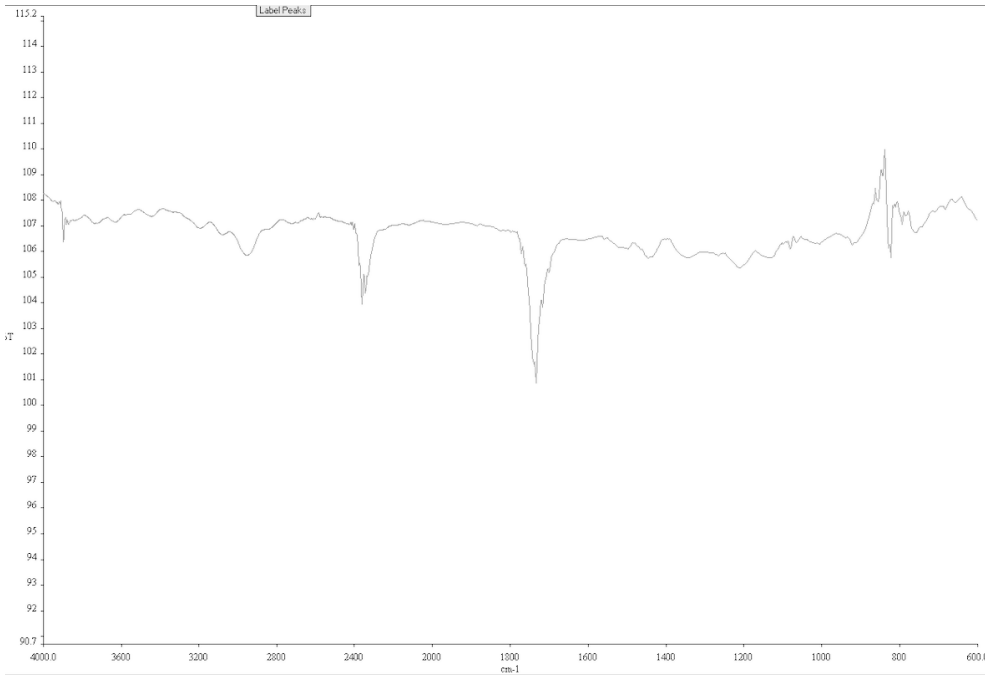


Figure A3.143. *Infrared spectrum (Thin Film, NaCl) of* ***81.***

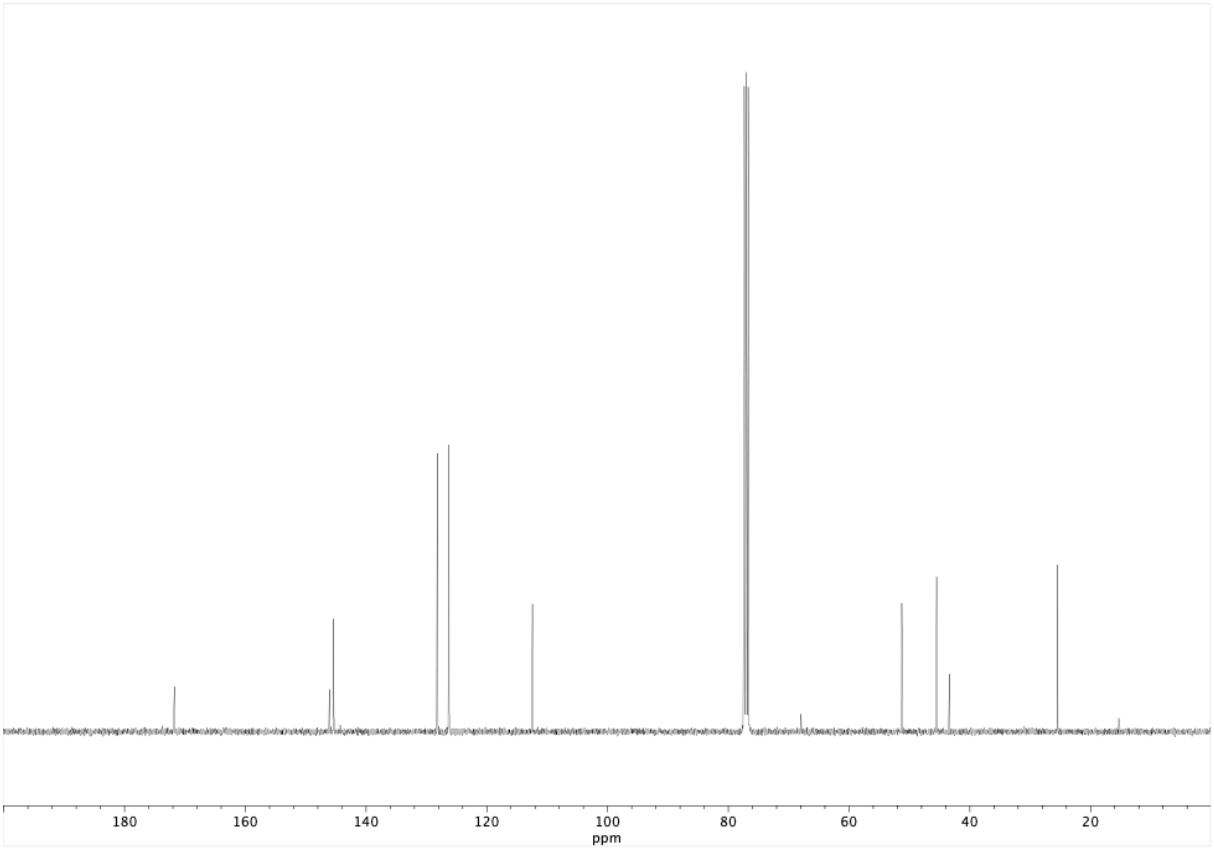


Figure A3.144. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***81.***

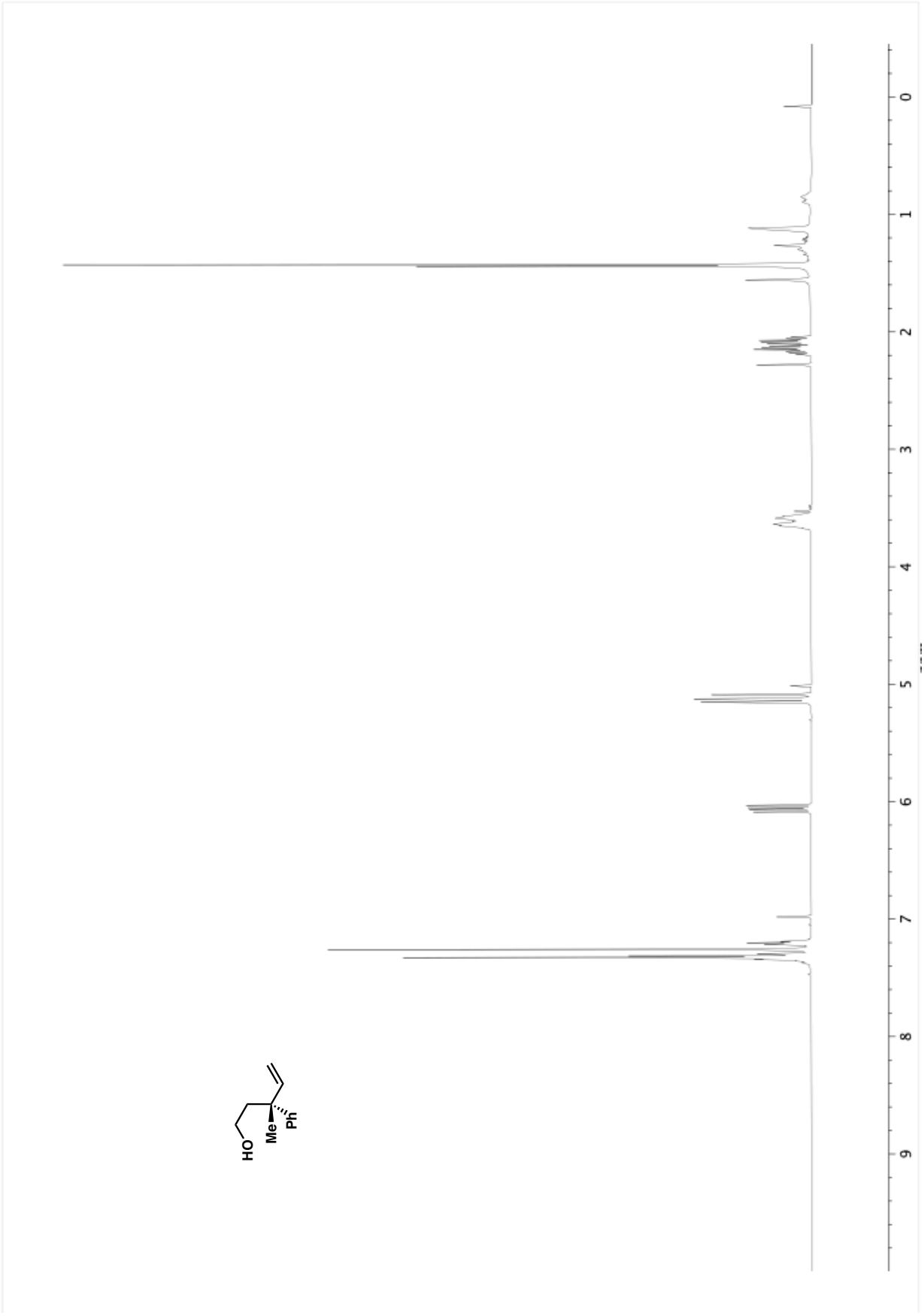


Figure A3.145. *^{1}H NMR (500 MHz, $CDCl_3$) of* ***82****.*

CHAPTER 3

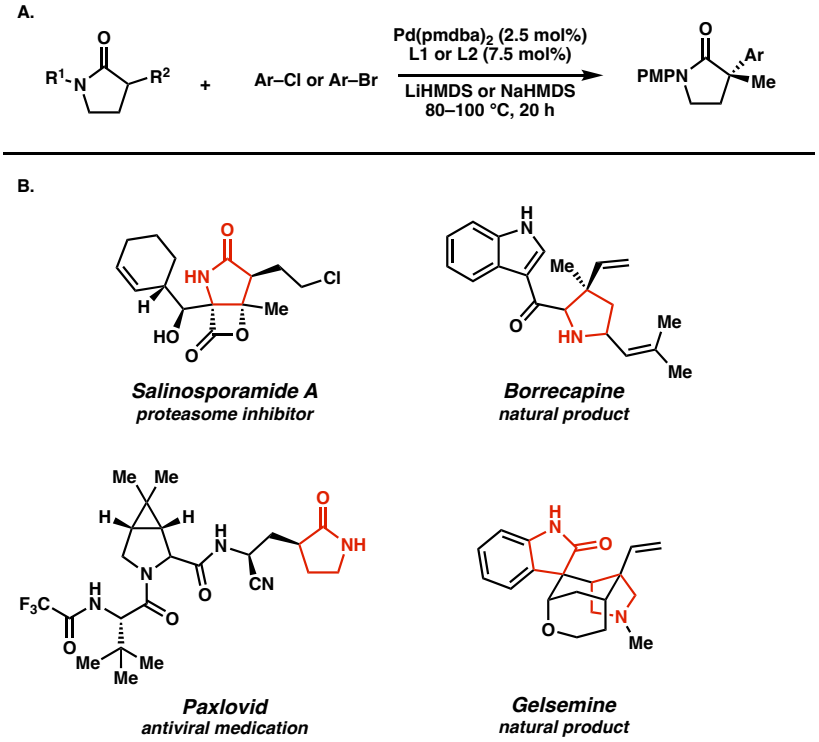
Formation of All-Carbon Quaternary Centers via Enantioselective Pd-Catalyzed α-Vinylation of γ-Lactams[†]

3.1 INTRODUCTION

γ-lactams are ubiquitous heterocyclic motifs found in pharmaceuticals and natural products alike (Figure 3.1).[1] Despite this, the direct vinylation of these and other[2] scaffolds largely remains an unsolved problem in organic synthesis, limiting the feasibility of convenient disconnections in the synthesis of complex scaffolds with potential biological and synthetic applications. Our group previously disclosed a novel, Pd-catalyzed strategy toward the α-arylation of PMP (para-methoxy phenyl)-protected γ-lactams containing substitution at the α-position.[3] As such, we successfully achieved the first asymmetric α-arylation of γ-lactams forming enantioenriched all-carbon quaternary centers. We were next interested in translating this reaction to the unprecedented vinylation of these nucleophiles.

[†]Portions of this chapter have been reproduced with permission from Moghadam M.[†]; , F. A.[†]; Barbor, J. B.[†]; Chan, Jette, C.; Sakurai, S.; Stoltz, B. M. *Org. Lett.* **2024**, *26*, 7551–7554. © 2024 American Chemical Society. [†] denotes equal contribution.

Figure 3.1. *A) Pd-Catalyzed α-Arylation of γ-Lactams B) Selected Examples of γ-Lactams in Pharmaceuticals and Natural Products*

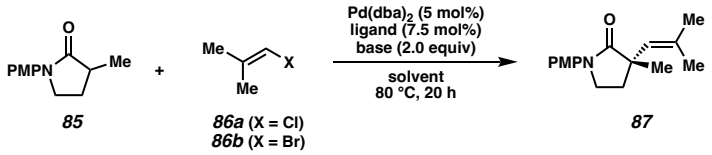


3.2 OPTIMIZATION EFFORTS

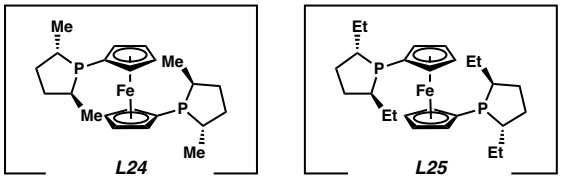
Our investigation commenced by utilizing the same catalytic conditions disclosed in our prior report. Initial efforts illustrated the superiority of vinyl chloride electrophiles and lithium bases (Table 3.1). We observed a dramatic counterion effect, as use of NaHMDS or KHMDS afforded no desired product, whereas LiHMDS afforded a 46% yield of the desired **87** with an excellent 90% ee. Exploration of similar lithium bases, like LiTMP, garnered diminished yields. Similarly, vinyl chlorides were found to be essential for both yield and enantioselectivity, as use of the corresponding vinyl bromide **86b** afforded **87** in a low 27% yield and 77% ee. Use of the more sterically encumbered ligand **L25** did not

improve the reaction further. Although we initially found that CPME (cyclopentyl methyl ether) resulted in a slight improvement of the ee to 92%, we found that 1,4–dioxane was ultimately the optimal solvent for this transformation. Additionally, dilution of the reaction to 0.05 M allowed for an improved 58% yield and 94% ee (entry 10).

Table 3.1. *Reaction Optimization*[a,b,c]



Entry	Ligand	X	Base	Solvent	Yield (%)	ee (%)
1	L24	Cl	NaHMDS	dioxane	0	–
2	L24	Cl	KHMDS	dioxane	0	–
3	L24	Cl	LiHMDS	dioxane	46	90
4	L24	Cl	LiTMP	dioxane	29	ND
5	L24	Br	LiHMDS	dioxane	27	77
6	L25	Cl	LiHMDS	dioxane	43	88
7[b]	L24	Cl	LiHMDS	THF	19	ND
8[b]	L24	Cl	LiHMDS	CPME	43	92
9[c]	L24	Cl	LiHMDS	CPME	38	ND
10[c]	L24	Cl	LiHMDS	dioxane	58	93



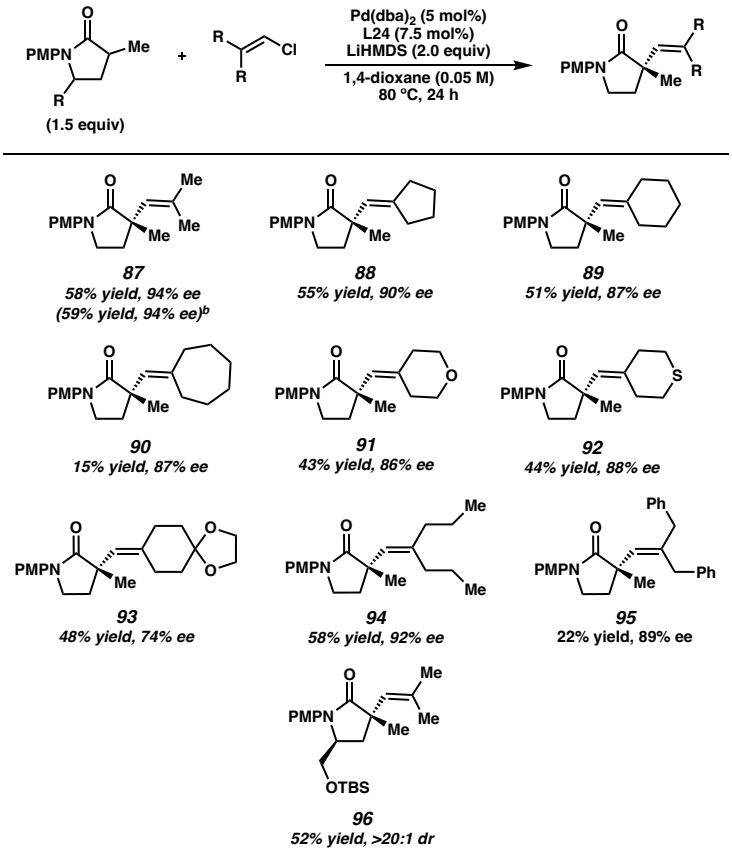
[a]Reactions performed at 0.1 mmol scale and 0.1 M. Yields determined by ^{1}H NMR with CH_2Br_2 internal standard. [b]Reaction performed at 70 °C for 48 h. [c]Reaction performed at 0.05 M concentration.

3.3 SUBSTRATE SCOPE

With optimized conditions in hand, we sought to investigate the range of compatible substitution patterns on the vinyl halide coupling partner (Scheme 3.1). Vinyl electrophiles featuring cyclopentyl, cyclohexyl and cycloheptyl substitution at the 2,2-position of the vinyl chloride afforded products **88**–**90** with high enantioselectivity, although formation of

product **90** was observed in diminished yields likely due to increased steric hindrance. Additionally, saturated heterocyclic moieties, such as a pyran and thiopyran, were well-tolerated (**91** and **92**). Although acyclic product **94** could also be obtained in comparable yield and ee, **95** was isolated in decreased yield. Substitution at the α-position was limited to methyl, but we were pleased to find that pre-existing substitution at the γ-position of the

Scheme 3.1. *Substrate Scope*[a,b,c]



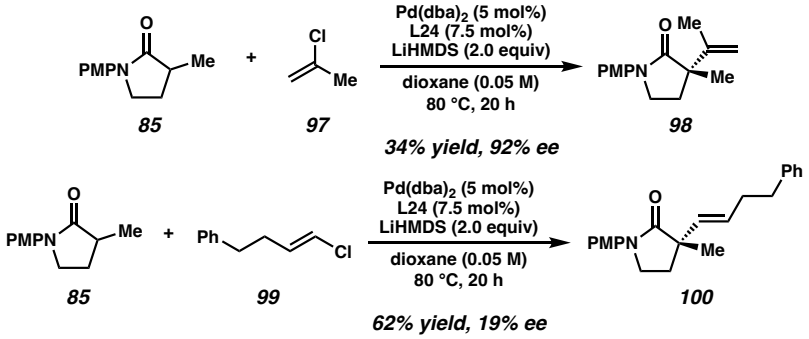
[a]Reactions performed on 0.1 mmol scale. [b]Reaction performed on 3 mmol scale. [c]Yields determined by ^{1}H NMR with CH_2Br_2 internal standard.

lactam resulted in a predictable match/mismatch situation. Enhancement of dr and higher reaction efficiency was observed for product **96**, whereas lower yield and

diastereoselectivity was observed for its epimer ***epi*-96**.[4] We were also able to implement our method at a 3 mmol scale, obtaining over 450 mg of **87** in similar yield and enantioselectivity (59% yield, 94% ee).

While exploring the scope of this transformation, we found that use of 1,1-disubstituted or *trans*-1,2-disubstituted electrophiles resulted in either diminished yield or enantioselectivity, respectively (Figure 3.2). Hypothesizing that reductive elimination is both inner-sphere and enantiodetermining,[5,6] we posit that the diminished yield of the 1,1-disubstituted electrophiles originates from steric congestion at the metal center, which may deter transmetallation of the lithium enolate to palladium. Conversely, we propose that the greatly minimized interactions between the ligand and *trans*-1,2-disubstituted electrophiles result in high conversion but with poor enantiocontrol.

Scheme 3.2. *Reaction with 1,1 and 1,2-Disubstituted Electrophiles*

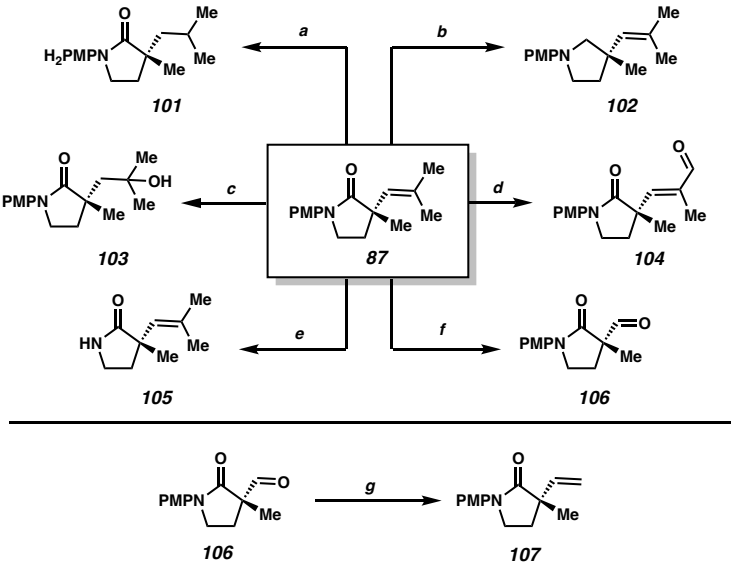


3.4 DERIVATIZATIONS AND CONCLUSION

These enantioenriched heterocycles, characterized by highly substituted quaternary centers, exhibit significant potential for pharmaceutical and total synthetic applications.[7] As a result, we embarked on a series of derivatizations of product **87** to generate

differentially substituted pyrrolidinone derivatives (Scheme 3.3). Our initial strategy involved the hydrogenation of product **87** to yield α-quaternary lactam **101**. Given the inherent challenges associated with enantioselective α-alkylation of lactams using conventional methods, we believe that this approach offers great synthetic value.

Scheme 3.3. *Product Derivitization*



Conditions: a) H_2, Pd/C (10 mol%), MeOH, 12 h, 74% yield. b) LAH (5 equiv), Et_2O, 0–18 °C, 21 h, 84% yield. c) PTSA, AcOH, 70 °C, 12 h, 59% yield. d) SeO_2, 1,4-dioxane, reflux, 15 min, 49% yield. e) CAN, H_2O, 60 ºC, 32 h, 40% yield. f) O_3, PPh_3, CH_2Cl_2, 15 min, 89% yield. g) KO*t*-Bu, methyltriphenylphosphonium bromide, THF, 0 ºC to reflux, 12 h, 84% yield.

Reduction of the lactam with lithium aluminum hydride yields β-quaternary pyrrolidine **102**. This derivative contains a heterocycle of significant pharmaceutical importance,[8] as pyrrolidines are ubiquitous in various existing drug molecules and natural products.[9] Hydration of the newly introduced vinyl group with *p*-TsOH produces tertiary alcohol

103.[10] Allylic oxidation with SeO_2 results in the formation of aldehyde **104**. Additionally, deprotection of the PMP group with ceric ammonium nitrate (CAN) reveals unprotected lactam **105**. Finally, **87** can undergo oxidative cleavage to yield the corresponding aldehyde **106** through ozonolysis. From **106**, a Wittig reaction can be conducted to generate vinylated lactam **107** with no substitution at the terminal position.[11]

In conclusion, our study showcases an enantioselective vinylation method for γ-lactams, yielding α-quaternary centers with up to 58% yield and 94% ee. Notably, the reaction exhibits distinct preferences among different classes of electrophiles. Particularly, we observed that tri-substituted vinyl chlorides outperformed other vinyl halides under these conditions in terms of both yield and ee. Moreover, these highly substituted γ-lactams hold significant synthetic potential, offering diverse functional handles for the synthesis of complex drug molecules or natural products.

3.5 EXPERIMENTAL SECTION

3.5.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. [12] Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 μm) and Teledyne Isco CombiFlash Rf+ UV with Luknova standard silica (avg particle size 50μm) flash columns were used for flash chromatography. ^{1}H NMR spectra were recorded on Varian Inova 500 MHz and Bruker

400 MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm). ^{13}C NMR spectra were recorded on a Varian Inova 500 MHz spectrometer (125 MHz) and Bruker 400 MHz spectrometers (100 MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm). Data for ^1H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet. Data for ^{13}C NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell. Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system utilizing Chiralpak (AD-3, AS-H or IC) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing Chiralpak (IH) or Chiralcel (OD-H) columns (4.6 mm x 25 cm) both obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in field ionization (FI+) or field desorption (FD+) mode, or an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI), or mixed ionization mode (MM: ESI-APCI+). Reagents were purchased from commercial sources and used as received unless otherwise stated.

Low-temperature diffraction data (ϕ-and ω-scans) were collected on a Bruker AXS D8 VENTURE KAPPA diffractometer coupled to a PHOTON II CPAD detector with K_α radiation (λ = 1.54178 Å) from an IμS micro-source for the structure of compound V24190. The structure was solved by direct methods using SHELXS[13] and refined against F^2 on all data by full-matrix least squares with SHELXL-2019[14] using established refinement techniques.[15] All non-hydrogen atoms were refined anisotropically. All hydrogen atoms

were included into the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the *U* value of the atoms they are linked to (1.5 times for methyl groups).

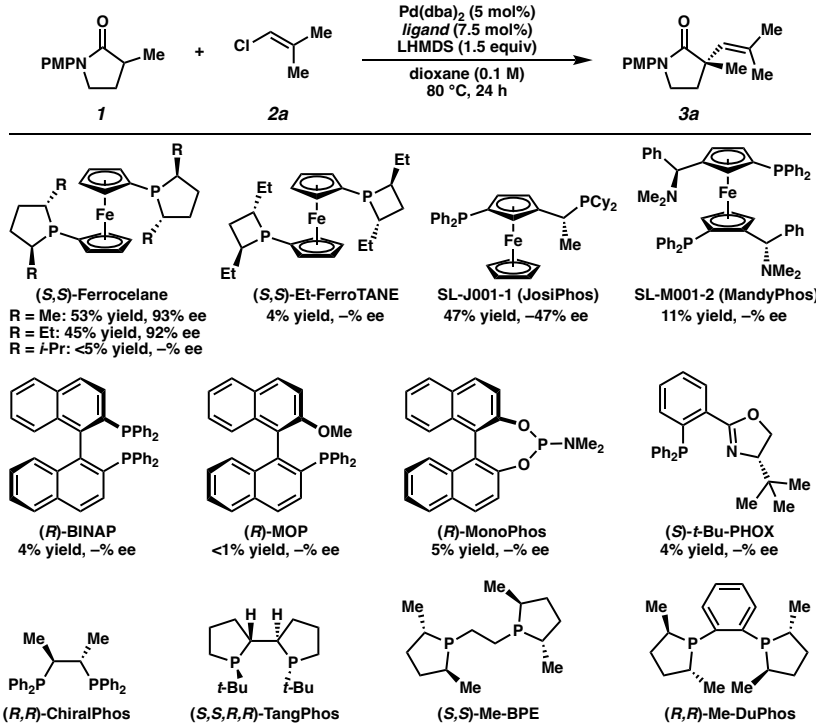
Compound V24190 crystallizes in the orthorhombic space group $P2_12_12_1$ with one molecule in the asymmetric unit.

List of Abbreviations:

ee – enantiomeric excess, SFC – supercritical fluid chromatography, HPLC – high-performance liquid chromatography, TLC – thin-layer chromatography, Dr – dram

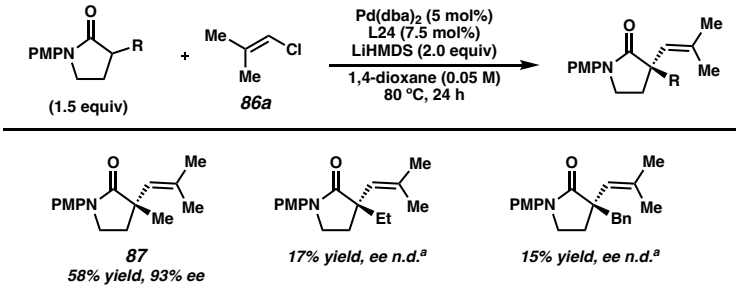
3.5.2 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

Table 3.2. *Ligand Evaluation*[a]



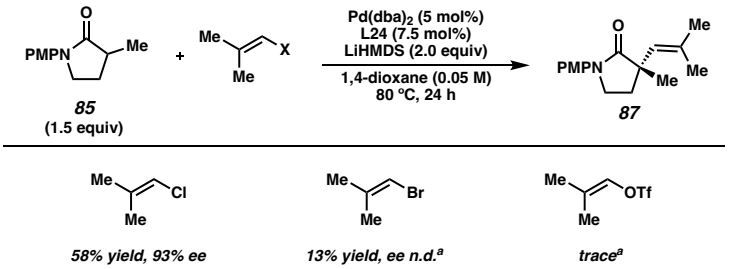
[a]Yields determined by ^{1}H NMR analysis of crude reaction mixture using 1,3,5-trimethoxybenzene as a standard. Enantiomeric excess (ee) was determined by chiral SFC analysis of the isolated product.

Scheme 3.4. *Nucleophile Substitution Patterns*[a]



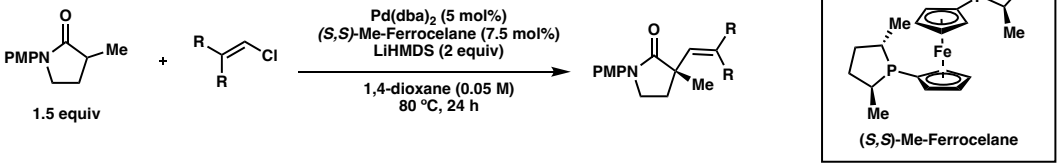
[a]Yields determined by 1H NMR with CH_2Br_2 internal standard.

Scheme 3.5. *Survey of Vinyl Halides and Pseudo-halides*[a]



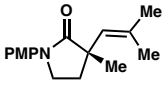
[a]Yields determined by ^{1}H NMR with CH_2Br_2 internal standard. Reaction performed with 1.5 eq of vinyl halide/pseudohalide, 1 equiv lactam, 1 equiv LiHMDS

Pd-catalyzed Vinylation Reactions: General Procedure A



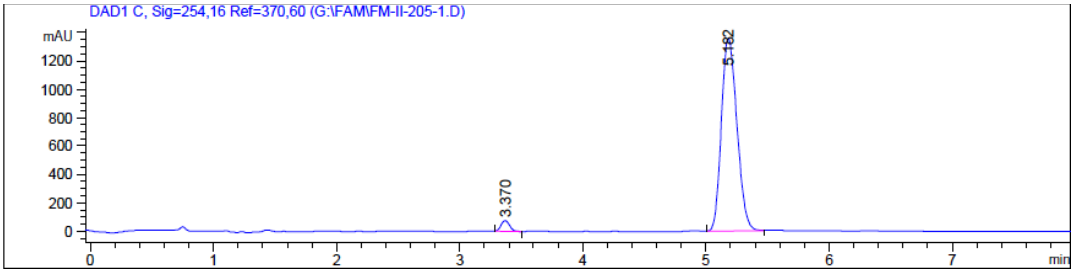
In a nitrogen-filled glovebox, a catalyst solution of $Pd(dba)_2$ (9.6 mg/mL) and *(S,S)-Me-Ferrocelane* (10.4 mg/mL) in 1,4-dioxane was stirred for 20 min at 40 °C. In a vial, the lactam was dissolved in 1,4-dioxane (1.5 equiv, 0.09 M), and subsequently LHMDS (2 equiv) was added. A 2 Dr vial was charged with neat vinyl chloride (0.1 mmol, 1 equiv) and a magnetic stir bar. After the catalyst pre-stir was complete, 0.4 mL of the catalyst solution was added to the vinyl chloride, followed by 1.6 mL of the nucleophile/base

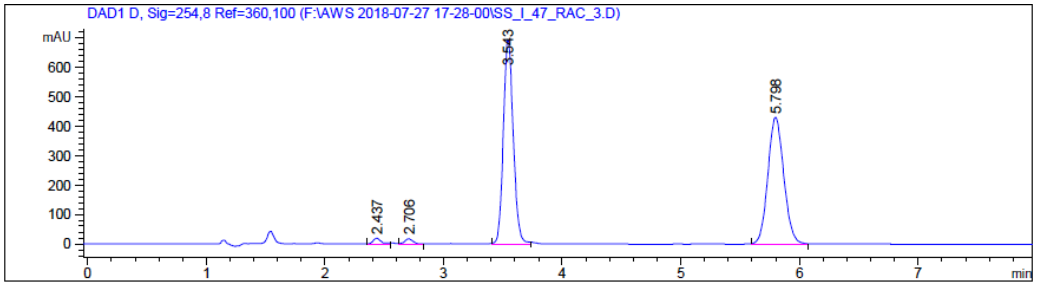
mixture. The vial was sealed with a Teflon-lined cap, removed from the glovebox, and stirred at 80 °C in a metal heating block for 24 h unless noted otherwise. After 24 h, 3 mL 0.5 M HCl or sat. NH_4Cl was added to the crude reaction mixture, which was then extracted three times with ethyl acetate, dried over Na_2SO_4, concentrated, and purified by silica gel flash chromatography to provide the desired vinylation product.



(*S*)-1-(4-methoxyphenyl)-3-methyl-3-(2-methylprop-1-en-1-yl)pyrrolidin-2-one (87)

Prepared according to general procedure A using vinyl chloride **86a** (0.1 mmol) and lactam **85**. Purification by silica gel chromatography (0-30% EtOAc/Hexanes) provided 15 mg (58%, 94% ee) of a yellow oil. The reaction was also performed using 3 mmol vinyl chloride to obtain 456 mg (59%) of a tan solid; $[\alpha]_D^{25}$ –79.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 9.2 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 5.46 (t, *J* = 1.4 Hz, 1H), 3.79 (s, 3H), 3.78 – 3.63 (m, 2H), 2.32 – 2.12 (m, 2H), 1.74 (d, *J* = 1.5 Hz, 3H), 1.69 (d, *J* = 1.4 Hz, 3H), 1.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.8, 156.5, 134.6, 133.3, 128.5, 121.6, 114.1, 55.6, 46.3, 45.7, 34.3, 27.1, 24.4, 19.2; IR (Neat Film, NaCl) 2965, 1694, 1513, 1400, 1297, 1250, 1170, 1089, 1063, 1033, 828 cm^{-1}; HRMS (MM:ESI-APCI+) m/z calc'd $C_{16}H_{22}NO_2$ $[M+H]^+$: 260.1645, found 260.1649. SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 3.37, major = 5.18.





Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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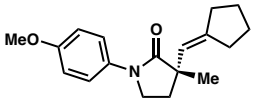
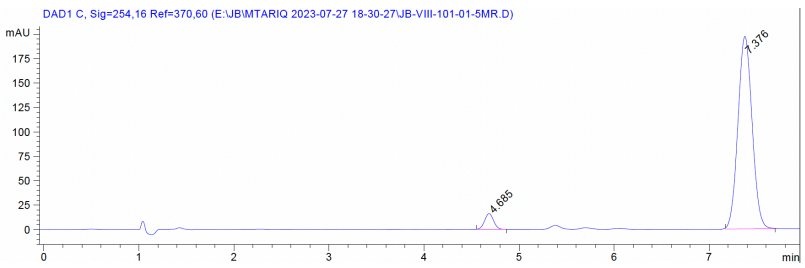
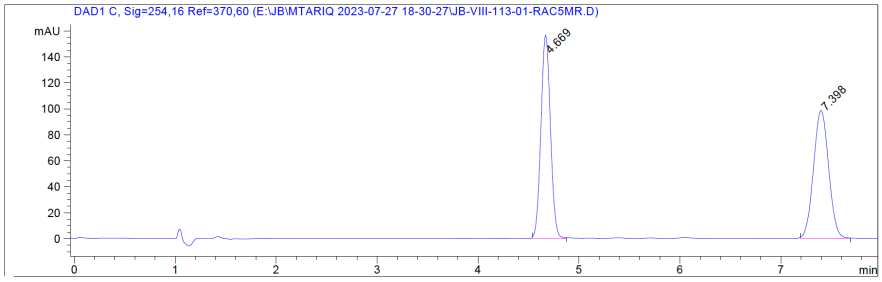
2	5.182	BB	0.1360	1.18716e4	1357.70581	97.0541



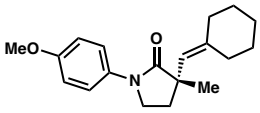
***(S)-3-(cyclopentylidenemethyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one* (88)**

Prepared according to general procedure A using **108**. Purification by column chromatography (0–25 % EtOAc/Hexanes) yielded **88** as a white solid (15.6 mg, 55% yield); 90% *ee*; $[\alpha]_D^{25}$ –56.8 (c 0.75, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 9.1 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 5.53 (p, *J* = 2.3 Hz, 1H), 3.79 (s, 3H), 3.75 – 3.51 (m, 2H), 2.26 (m, 5H), 2.15 – 1.87 (m, 1H), 1.88 – 1.60 (m, 2H), 1.60 – 1.42 (m, 2H), 1.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4, 156.5, 145.1, 133.3, 123.7, 121.5, 114.1, 55.6, 47.1, 45.8, 35.5, 34.0, 28.9, 27.3, 25.8, 23.9; IR (neat film, NaCl) 3835, 3732, 2951, 2866, 2360, 1693, 1511, 1455, 1395, 1298, 1248, 1181, 1084, 1035, 833, 662 cm^{-1}; HRMS (MM:ESI-APCI+) m/z calc'd for $C_{18}H_{24}NO_2$ $[M+H]^+$: 286.1802, found 286.1815; SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 4.69, major = 7.78.



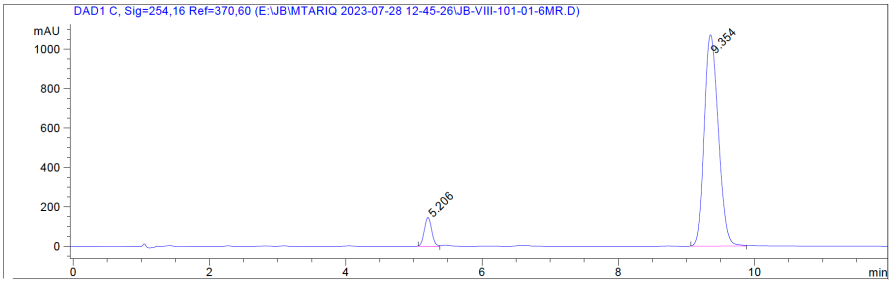


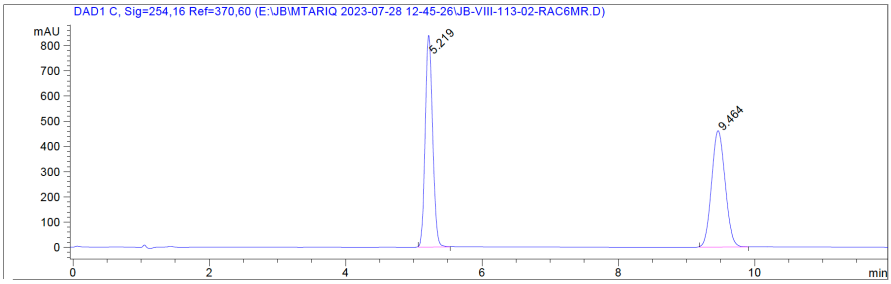
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.684	BB	0.1025	105.83888	16.14992	4.9139
2	7.376	BB	0.1631	2048.01367	197.34492	95.0861



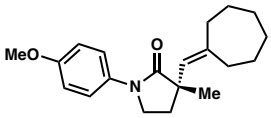
***(S)-3-(cyclohexylidenemethyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one* (89)**

Prepared according to general procedure A using **109**. Purification by column chromatography (0–25 % EtOAc/Hexanes) yielded **89** as a white solid (15.3 mg, 51% yield); 84% *ee*; $[\alpha]_D^{25}$ –64.5 (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 9.1 Hz, 2H), 6.80 (d, J = 9.1 Hz, 2H), 5.36 – 5.31 (m, 1H), 3.69 (s, 3H), 3.67 – 3.34 (m, 2H), 2.12 (m, 2H), 2.08 – 1.94 (m, 4H), 1.55 – 1.32 (m, 6H), 1.25 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.9, 156.4, 142.7, 133.2, 125.4, 121.5, 114.0, 55.5, 45.9, 45.6, 37.7, 34.6, 30.2, 28.7, 27.6, 26.5, 24.7; IR (neat film, NaCl) 3835, 3745, 2925, 2851, 2359, 1693, 1513, 1443, 1396, 1298, 1248, 1179, 1088, 1035, 828 cm^{-1}; HRMS (MM:ESI-APCI+) m/z calc'd for $C_{19}H_{26}NO_2$ $[M+H]^+$: 300.1958, found 300.1972; SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 5.21, major = 9.35.



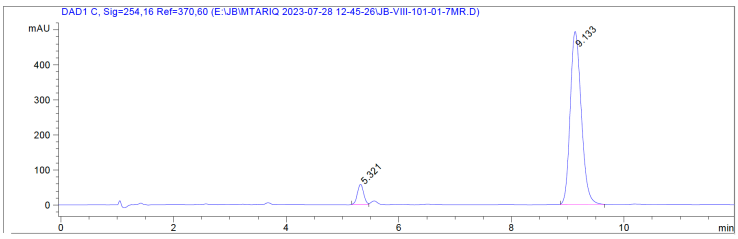


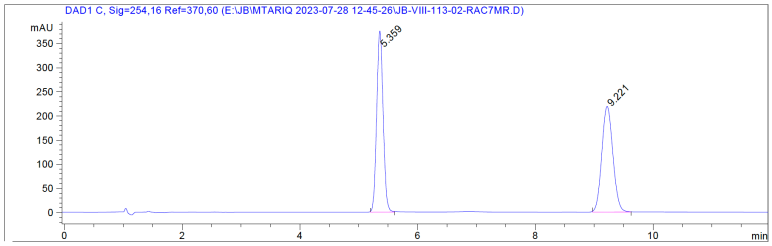
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.206	BB	0.1167	1079.90918	145.38251	6.5927
2	9.354	BB	0.2248	1.53006e4	1070.28064	93.4073



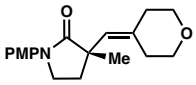
***(S)-3-(cycloheptylidenemethyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one* (90)**

Prepared according to general procedure A using **110**. Purification by column chromatography (0–25 % EtOAc/Hexanes) yielded **90** as a white solid (4.7 mg, 15% yield); 86% *ee*; $[\alpha]_D^{25}$ – 39.4 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 9.2 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 5.52 (p, *J* = 1.4 Hz, 1H), 3.80 (s, 3H), 3.77 – 3.32 (m, 2H), 2.86 – 1.98 (m, 6H), 1.84 – 1.40 (m, 8H), 1.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.9, 156.5, 144.2, 133.3, 128.8, 121.6, 121.6, 114.2, 55.6, 46.3, 45.8, 38.5, 34.1, 31.0, 29.9, 29.7, 29.3, 27.0, 24.4; IR (neat film, NaCl) 3834, 3732, 2923, 2849, 2341, 1693, 1511, 1395, 1298, 1247, 1087, 1035, 827 cm^{-1}; HRMS (MM:ESI-APCI+) m/z calc'd for $C_{20}H_{28}NO_2$ $[M+H]^+$: 314.2115, found 314.2029; SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 5.32, major = 9.13.



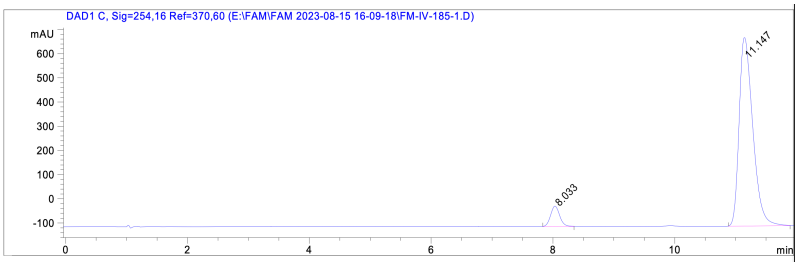


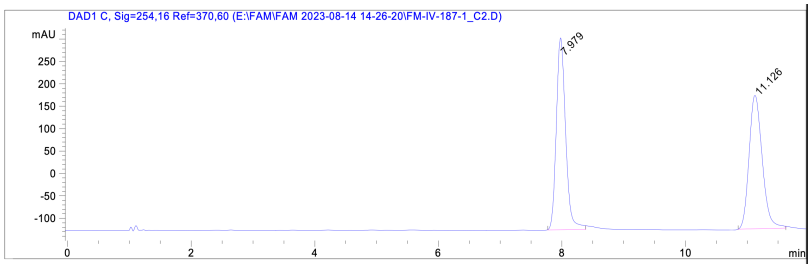
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.321	BV	0.1211	454.95865	58.26056	6.3215
2	9.133	BB	0.2113	6742.08643	493.82556	93.6785



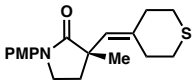
***(S)-3-(tetrahydropyranlidenemethyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one* (91)**

Prepared according to general procedure A using **111**. Purification by column chromatography (0–30% EtOAc/Hexanes) yielded **91** as a colorless oil (13.2 mg, 43%); 86% *ee*; $[\alpha]_D^{25}$ – 41.4 (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 5.54 (d, *J* = 1.3 Hz, 1H), 3.79 (s, 3H), 3.78 – 3.57 (m, 6H), 2.34 (tt, *J* = 5.8, 1.2 Hz, 2H), 2.29 – 2.17 (m, 4H), 1.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4, 156.6, 137.5, 133.1, 127.5, 121.6, 114.2, 69.8, 68.4, 55.6, 46.0, 45.7, 37.5, 34.9, 31.3, 24.8. IR (neat film, NaCl) 2958, 2839, 1691, 1511, 1462, 1396, 1286, 1269, 1246, 1087, 1032, 831 cm^{-1}; HRMS (MM:ESI-APCI+) m/z calc'd for $C_{18}H_{24}NO_3$ $[M+H]^+$: 302.1751, found 302.1750 ; SFC conditions: 20% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 8.03, major = 11.15.



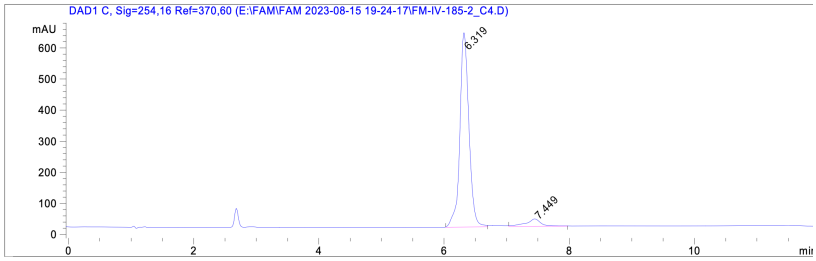


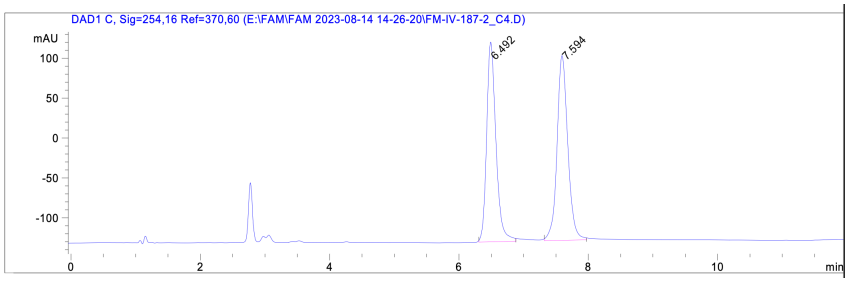
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.033	BB	0.1634	895.48993	84.67880	24.0017
2	11.147	BB	0.2379	1.21628e4	780.28503	325.9983



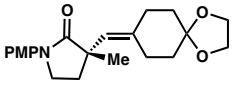
***(S)-3-(tetrahydro-thiopyranlidenemethyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one* (92)**

Prepared according to general procedure A using **112**. Purification by column chromatography (0–25 % EtOAc/Hexanes) yielded **92** as a colorless oil (13.5 mg, 44%); 88% *ee*; $[\alpha]_D^{25}$ –58.3 (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 9.1 Hz, 1H), 6.90 (d, *J* = 9.1 Hz, 1H), 5.55 (t, *J* = 1.0 Hz, 1H), 3.80 (s, 2H), 3.78 – 3.68 (m, 1H), 2.76 – 2.48 (m, 4H), 2.44 (td, *J* = 5.4, 2.5 Hz, 1H), 2.24 – 2.17 (m, 1H), 1.36 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4, 156.6, 139.6, 133.05, 129.0, 121.6, 114.2, 55.6, 45.9, 45.7, 39.4, 34.8, 32.2, 31.2, 29.9, 24.8. IR (neat film, NaCl) 2953, 1689, 1511, 1428, 1398, 1297, 1247, 1180, 1087, 1034, 821 cm^{-1}; HRMS (MM:ESI-APCI+) m/z calc'd for $C_{18}H_{24}NO_2S$ $[M+H]^+$: 318.1522, found 318.1520; SFC conditions: 20% IPA, 2.5 mL/min, Chiralcel OJ-3 column, λ = 254 nm, tR (min): minor = 7.45, major = 6.32.



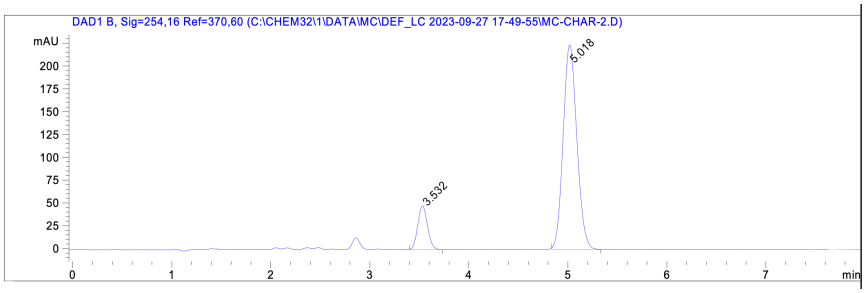


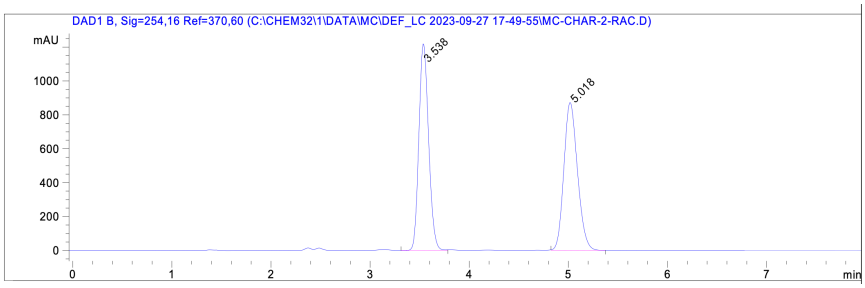
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.319	BB	0.1536	6285.17188	623.72955	328.2187
2	7.449	BB	0.2366	417.09830	24.25278	21.7813



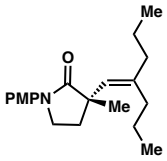
***(S)-3-((1,4-dioxaspiro[4.5]decan-8-ylidene)methyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one* (93)**

Prepared according to general procedure A using **113**. The crude product was purified by silica gel chromatography (30% EtOAc/Hexanes) to afford vinylated lactam **93** (48% yield, 74% ee) as a colorless oil; $[a]_D^{25}$ + 4.5 ° (*c* 0.52, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 9.1 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 5.54 (d, *J* = 1.7 Hz, 1H), 3.95 (s, 3H), 3.80 (s, 3H), 3.76 – 3.60 (m, 2H), 2.40 – 2.29 (m, 2H), 2.31 – 2.16 (m, 4H), 1.71 (td, *J* = 6.7, 3.9 Hz, 3H), 1.68 – 1.62 (m, 1H), 1.60 (s, 1H), 1.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.7, 156.6, 140.0, 133.2, 127.2, 121.6, 114.2, 114.1, 108.7, 77.5, 77.4, 77.2, 76.8, 64.5, 64.5, 55.6, 46.1, 45.7, 36.4, 35.3, 34.7, 34.5, 26.7, 24.7; IR (thin film, NaCl) 3465, 2950, 2886, 2320, 2009, 1902, 1693, 1681, 1513, 1433, 1401, 1298, 1276, 1248, 1226, 1181, 1171, 1120, 1082, 1032, 944, 906, 826, 738, 728 cm^{-1}; HRMS (ESI) m/z calc'd $C_{21}H_{27}NO_4Na$ $[M+Na]^+$: 380.1832, found: 380.1843; SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 3.53, major = 5.02.





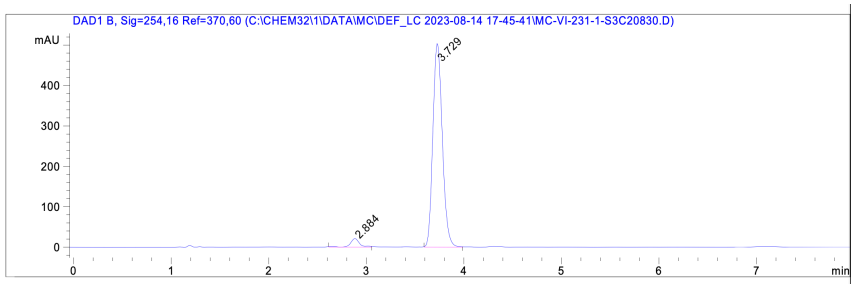
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.532	BB	0.1077	326.17273	47.72661	13.1365
2	5.018	BB	0.1523	2156.76880	223.97276	86.8635



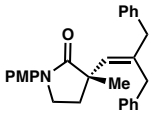
***(S)-1-(4-methoxyphenyl)-3-methyl-3-(2-propylpent-1-en-1-yl)pyrrolidin-2-one* (94)**

Prepared according to general procedure A using **114**. The crude product was purified by silica gel chromatography (30% EtOAc/Hexanes) to afford vinylated lactam **94** (58% yield, 92% ee) as a colorless oil; $[a]_D^{25}$ – 2.5 ° (*c* 0.35, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 9.1 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 5.50 (t, *J* = 1.0 Hz, 1H), 3.80 (d, *J* = 0.7 Hz, 3H), 3.78 – 3.67 (m, 2H), 2.34 – 2.25 (m, 1H), 2.25 – 2.17 (m, 1H), 2.12 – 2.03 (m, 1H), 2.03 – 1.94 (m, 3H), 1.48 – 1.38 (m, 4H), 1.36 (s, 3H), 0.93 – 0.84 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.9, 156.4, 142.4, 133.2, 128.5, 121.4, 114.0, 77.4, 77.2, 77.0, 76.7, 55.5, 46.2, 45.6, 38.8, 34.5, 33.0, 24.7, 21.3, 21.1, 14.6, 13.8. IR (thin film, NaCl) 2958, 2930, 2870, 1694, 1513, 1469, 1454, 1423, 1398, 1299, 1288, 1248, 1181, 1168, 1122, 1087, 1036, 836, 823, 805, 634 cm^{-1}; HRMS (MM:ESI-APCI+) m/z calc'd $C_{20}H_{29}NO_2Na$

$[M+Na]^+$: 338.2091, found: 338.2100; SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 2.88, major = 3.73.



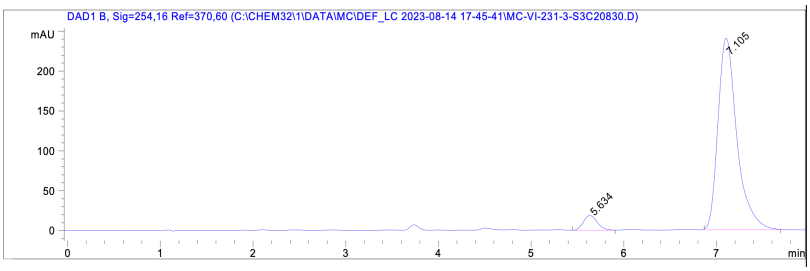
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.884	BB	0.0977	139.83130	21.00225	3.9512
2	3.729	BB	0.1069	3399.10669	502.66321	96.0488



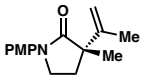
***(S)-3-(2-benzyl-3-phenylprop-1-en-1-yl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one* (95)**

Prepared according to general procedure A using **115**. The crude product was purified by silica gel chromatography (30% EtOAc/Hexanes) to afford vinylated lactam **95** (22% yield, 88% ee) as a colorless oil; $[a]_D^{25}$ – 12.4 ° (*c* 0.56, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 9.1 Hz, 2H), 7.38 – 7.32 (m, 2H), 7.30 – 7.23 (m, 3H), 7.23 – 7.17 (m, 2H), 7.17 – 7.10 (m, 2H), 6.95 (d, *J* = 9.1 Hz, 2H), 6.02 (t, *J* = 1.0 Hz, 1H), 3.86 (s, 3H), 3.84 – 3.74 (m, 2H), 3.54 – 3.38 (m, 2H), 3.27 (t, *J* = 1.6 Hz, 2H), 2.43 (dt, *J* = 12.5, 8.2 Hz, 1H), 2.30 (ddd, *J* = 12.5, 7.2, 3.6 Hz, 1H), 1.52 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4, 156.5, 139.8, 139.5, 139.0, 132.9, 132.8, 129.0, 128.9, 128.5, 128.3, 128.2, 126.1, 121.6,

114.1, 77.4, 77.2, 77.0, 76.7, 55.5, 46.4, 45.7, 43.3, 35.9, 34.1, 24.8. IR (thin film, NaCl) 3059, 3025, 2930, 2835,m 2340, 1682, 1600, 1520, 1493, 1453, 1398, 1298, 1240, 1181, 1120, 1088, 1031, 829, 734, 702 cm^{-1}; HRMS (MM:ESI-APCI+) m/z calc'd $C_{28}H_{29}NO_2Na$ $[M+Na]^+$: 434.2091, found: 434.2102; SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 5.63, major = 7.11.



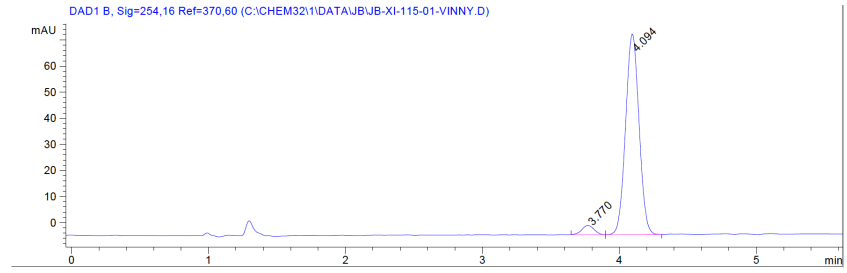
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.634	BB	0.1609	192.02281	18.53370	5.3335
2	7.105	BB	0.2136	3408.32178	240.14082	94.6665



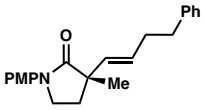
(S)-1-(4-methoxyphenyl)-3-methyl-3-(prop-1-en-2-yl)pyrrolidin-2-one (98)

Prepared according to general procedure A using **97**. The crude product was purified by silica gel chromatography (0–30% EtOAc/Hexanes) to afford vinylated lactam **98** (8.3 mg, 34% yield, 92% ee) as a white solid; $[a]_D^{25}$ – 125.8 ° (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 9.1 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 4.93 (s, 1H), 4.89 (s, 1H), 3.80 (s, 3H), 3.76 – 3.44 (m, 2H), 2.32 (ddd, *J* = 12.7, 7.0, 4.4 Hz, 1H), 1.94 (dt, *J* = 12.7, 7.8 Hz, 1H), 1.83 (d, *J* = 1.3 Hz, 3H), 1.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.3, 156.6, 145.4, 133.1, 121.7, 114.2, 114.1, 111.9, 55.6, 51.2, 45.9, 31.9, 22.5, 19.8; IR (thin film,

NaCl) 2933, 1738, 1693, 1643, 1512, 1455, 1396, 1297, 1248, 1181, 1088, 1034, 892, 828 cm^{-1}; HRMS (MM:ESI-APCI+) m/z calc'd $C_{15}H_{20}NO_2$ $[M+H]^+$: 246.1498, found 246.1495. SFC conditions: 30% IPA, 2.5 mL/min, Chiralcel AD-3 column, λ = 254 nm, tR (min): minor = 3.77, major = 4.09.



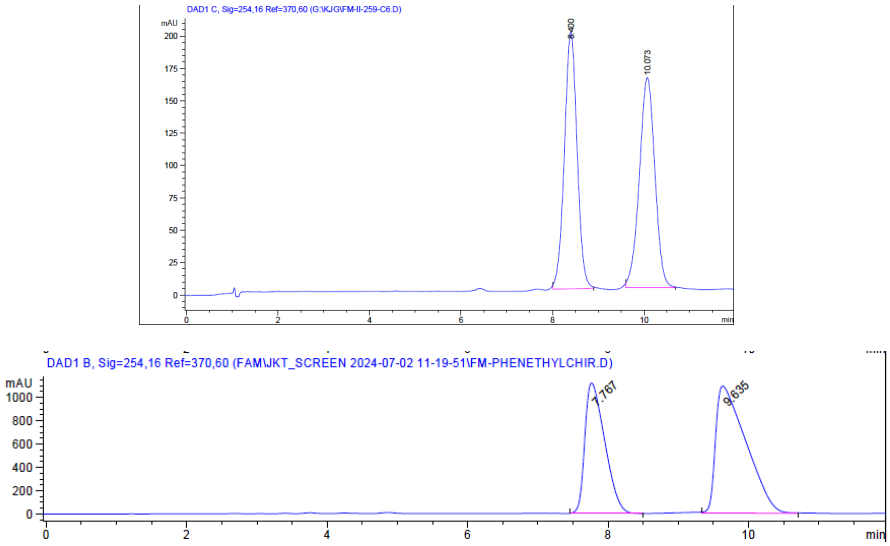
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.770	BV	0.1014	22.07811	3.50927	4.0399
2	4.094	VB	0.1078	524.42456	76.70352	95.9601
Totals :				546.50267	80.21279	



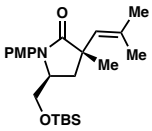
(S,E)-1-(4-methoxyphenyl)-3-methyl-3-(4-phenylbut-1-en-1-yl)pyrrolidin-2-one (100)

Prepared according to general procedure A using **99**. The crude product was purified by silica gel chromatography (0-30% EtOAc/Hexanes) to afford vinylated lactam **100** (20.6 mg, 62% yield, 19% ee) as a colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.38 (m, 2H), 7.22 – 7.12 (m, 2H), 7.12 – 6.99 (m, 3H), 6.89 – 6.73 (m, 2H), 5.57 – 5.38 (m, 2H), 3.72 (s, 3H), 3.63 – 3.49 (m, 2H), 2.66 – 2.53 (m, 2H), 2.35 – 2.19 (m, 2H), 2.07 (ddd, J = 12.4, 6.3, 5.0 Hz, 1H), 1.89 (dt, J = 12.5, 7.7 Hz, 1H), 1.23 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.4, 156.5, 141.9, 133.1, 133.1, 129.0, 128.7, 128.4, 125.9, 121.5, 114.1, 55.6,

47.8, 45.6, 35.9, 34.5, 32.7, 23.6; IR (thin film, NaCl) 2928, 1693, 1513, 1461, 1395, 1297, 1249, 1181, 1091, 1032, 974, 830, 798, 739, 700 cm^{-1}; HRMS (FD+) m/z calc'd $C_{22}H_{25}NO_2$ $[M]^{+\bullet}$, 335.1885, found 335.1890. SFC conditions: 20% IPA, 2.5 mL/min, Chiralcel OB-H column, λ = 254 nm, tR (min): minor = 7.77, major = 9.64.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.767	BB	0.3096	2.20195e4	1118.76477	40.2714
2	9.635	BB	0.4339	3.26582e4	1088.92627	59.7286
Totals :				5.46777e4	2207.69104	



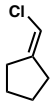
(3S,5S)-5-(((tert-butyldimethylsilyl)oxy)methyl)-1-(4-methoxyphenyl)-3-methyl-3-(2-methylprop-1-en-1-yl)pyrrolidin-2-one (96)

Prepared according to general procedure A using **86a** and lactam **118**. The crude product was purified by silica gel chromatography (0-30% EtOAc/Hexanes) to afford vinylated lactam **96** (21 mg, 52% yield) as a colorless oil; $[a]_D^{25}$ – 36.8 ° (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.21 (m, 2H), 6.92 – 6.86 (m, 2H), 5.41 (h, *J* = 1.4 Hz, 1H), 4.09 (dddd, *J* = 8.6, 5.8, 4.4, 2.8 Hz, 1H), 3.80 (s, 3H), 3.62 – 3.45 (m, 2H), 2.41 (dd, *J* = 12.9, 8.6 Hz, 1H), 2.13 (dd, *J* = 12.9, 5.7 Hz, 1H), 1.70 (dd, *J* = 3.6, 1.4 Hz, 6H), 1.47 (s, 3H),

0.84 (s, 9H), 0.07 (s, 3H), -0.09 (d, J = 13.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.9, 157.8, 134.1, 130.7, 129.8, 126.5, 114.3, 62.6, 58.5, 55.6, 45.3, 37.5, 27.1, 27.0, 26.0, 19.1, 18.4, 1.2, -5.5, -5.5. IR (thin film, NaCl) 2932, 2857, 1693, 1513, 1467, 1401, 1247, 1104, 1043, 826 cm^{-1}; HRMS (MM:ESI-APCI+) m/z calc'd $C_{23}H_{38}NO_3Si$ $[M+H]^+$: 404.2615, found 404.2626.

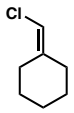
Preparation of Vinyl Chloride Substrates: General Procedure B

To a stirred suspension of (chloromethyl)triphenylphosphonium chloride (2.60 g, 7.50 mmol, 1.5 equiv) in diethyl ether (60 mL) was added sodium bis(hexamethylsilyl)amide (1.38 g, 7.50 mmol, 1.5 equiv) in diethyl ether (15 mL) at –78 °C or 0 ºC, and the resulting mixture was stirred at this temperature for 1 h. Then, ketone (5 mmol, 1.0 equiv) was added dropwise, and the reaction was allowed to slowly warm to room temperature and stirred overnight. After 18 h, the reaction was quenched with water (50 mL), transferred to a separatory funnel, and extracted with diethyl ether (20 mL) three times. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by silica gel chromatography to provide the desired vinyl chloride.



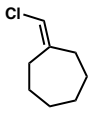
***(chloromethylene)cyclopentane* (108)**

Prepared according to general procedure B using cyclopentanone. Purification by column chromatography (100% Hexanes) yielded **108** as a clear oil (209 mg, 36% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (p, J = 2.4 Hz, 1H), 2.42 – 2.23 (m, 4H), 1.80 – 1.63 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.9, 108.0, 32.6, 30.7, 27.4, 25.8; IR (neat film, NaCl) 3817, 3645, 2955, 2359, 1650, 1455, 772, 653 cm^{-1}; HRMS (FI+) m/z calc'd for C_6H_9Cl $[M]^{+\bullet}$: 116.0400, found 116.0393.



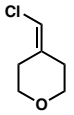
***(chloromethylene)cyclohexane* (109)**

Prepared according to general procedure B using cyclohexanone. Purification by silica gel chromatography (100% Hexanes) yielded **109** as a clear oil (419 mg, 64% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (p, J = 1.2 Hz, 1H), 2.32 (m, 2H), 2.13 (m, 2H), 1.55 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.3, 108.5, 34.2, 28.6, 28.0, 26.8, 26.5; IR (neat film, NaCl) 3817, 3732, 3064, 2937, 2356, 1636, 1541, 1455, 1336, 1293, 1231, 986, 786 cm^{-1}; HRMS (FI+) m/z calc'd for $C_7H_{11}Cl$ $[M]^{+\bullet}$: 130.0549, found 130.0558.



***(chloromethylene)cycloheptane* (110)**

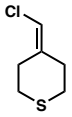
Prepared according to general procedure B using cycloheptanone. Purification by silica gel chromatography (100% Hexanes) yielded **110** as a colorless oil (557 mg, 77% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (p, *J* = 1.5 Hz, 1H), 2.45 – 2.36 (m, 2H), 2.30 – 2.22 (m, 2H), 1.70 – 1.55 (m, 4H), 1.53 – 1.43 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7, 111.7, 35.2, 30.9, 30.2, 29.4, 29.0, 26.2; IR (neat film, NaCl) 3380, 2921, 2859, 2360, 1674, 1506, 1069, 682 cm^{-1}; HRMS (FI+) m/z calc'd for $C_8H_{13}Cl$ $[M]^{+\bullet}$: 144.0712, found 144.0706.



***4-(chloromethylene)tetrahydro-2H-pyran* (111)**

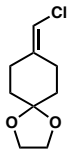
Prepared according to general procedure B using tetrahydro-4*H*-pyran-4-one. The crude product was purified by silica gel chromatography (0-20% EtOAc/Hexanes) to afford vinyl chloride **111** (136 mg, 45%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (t, *J* = 1.3 Hz, 1H), 3.69 (dt, *J* = 7.5, 5.5 Hz, 4H), 2.46 (ddd, *J* = 6.5, 5.3, 1.3 Hz, 2H), 2.27 (ddd,

J = 6.2, 5.0, 1.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.2, 110.6, 68.8, 68.0, 34.3, 29.5; IR (thin film, NaCl) 3069, 2961, 2907, 2848, 2747, 2704, 2360, 1954, 1645, 1466, 1432, 1380, 1356, 1323, 1296, 1228, 1165, 1099, 1021, 1000, 923, 859, 822, 792, 749, 663 cm^{-1}; HRMS (FI+) m/z calc'd for C_6H_9ClO $[M]^{+\bullet}$: 132.0342, found 132.0348.



***4-(chloromethylene)tetrahydro-2H-thiopyran* (112)**

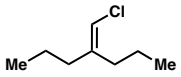
Prepared according to general procedure B using tetrahydro-4*H*-thiopyran-4-one. The crude product was purified by silica gel chromatography (0-20% EtOAc/Hexanes) to afford vinyl chloride **112** (189 mg, 81%) as a colorless, malodorous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (d, *J* = 1.1 Hz, 1H), 2.71 – 2.62 (m, 6H), 2.51 – 2.45 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.3, 111.7, 36.0, 30.5, 30.4, 29.4. IR (thin film, NaCl) 3065, 2949, 2907, 2829, 2360, 1649, 1626, 1425, 1337, 1323, 1291, 1270, 1223, 1171, 991, 975, 938, 822, 797 cm^{-1}; HRMS (FI+) m/z calc'd for C_6H_9ClS $[M]^{+\bullet}$: 148.0114, found 148.0123.



***8-(chloromethylene)-1,4-dioxaspiro[4.5]decane* (113)**

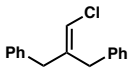
Prepared according to general procedure B using 1,4-dioxaspiro[4.5]decan-8-one. The crude product was purified by silica gel chromatography (100% Hexanes) to afford vinyl chloride **113** (79 yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (d, *J* = 1.4 Hz, 1H), 3.97 (s, 4H), 2.53 – 2.43 (m, 2H), 2.30 (td, *J* = 6.5, 1.3 Hz, 2H), 1.76 – 1.63 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.6, 110.0, 108.6, 77.5, 77.2, 76.8, 64.6, 35.6, 34.5, 30.9, 25.4; IR (thin film, NaCl) 3068, 2950, 2930, 2883, 2685, 2728, 2685, 1718, 1654, 1634, 1443, 1366, 1341, 1295, 1272, 1246, 1225, 1186, 1100, 1080, 1034, 962, 943, 908,

828, 797, 770., 748, 678 cm^{-1}; HRMS (FI+) m/z calc'd $C_9H_{13}ClO_2$ $[M]^{+\bullet}$: 188.0604, found: 188.0619.



***4-(chloromethylene)heptane* (114)**

Prepared according to general procedure B using 4-heptanone. The crude product was purified by silica gel chromatography (100% Hexanes) to afford vinyl chloride **114** (27% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 5.82 – 5.73 (m, 1H), 2.21 – 2.14 (m, 2H), 2.03 (td, J = 7.6, 1.3 Hz, 2H), 1.58 – 1.34 (m, 4H), 0.91 (dt, J = 16.5, 7.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.7, 112.1, 77.5, 77.2, 76.8, 37.0, 32.2, 21.0, 20.5, 14.1, 13.9; IR (thin film, NaCl) 3066, 2980, 2933, 2872, 1911, 1630, 1465, 1456, 1379, 1319, 1169, 1109, 836, 791, 766 cm^{-1}; HRMS (FI+) m/z calc'd $C_8H_{15}Cl$ $[M]^{+\bullet}$: 146.0862, found: 146.0872.

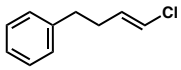


***(2-(chloromethylene)propane-1,3-diyl)dibenzene* (115)**

Prepared according to general procedure B using 1,3-diphenyl-2-propanone. The crude product was purified by silica gel chromatography (100% Hexanes) to afford vinyl chloride **115** (68% yield) as a colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 4H), 7.32 – 7.28 (m, 2H), 7.27 – 7.23 (m, 2H), 7.19 – 7.14 (m, 2H), 6.07 – 6.01 (m, 1H), 3.56 (s, 2H), 3.32 (d, J = 1.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.2, 138.3, 138.0, 129.1, 128.9, 128.6, 128.5, 126.6, 126.4, 114.9, 77.4, 77.0, 76.7, 40.4, 35.6; IR (thin film, NaCl) 3088, 3062, 3020, 2916, 2845, 2355, 1947, 1872, 1809, 1633, 1601, 1494, 1453, 1433, 1310, 1296, 1178, 1075, 1029, 960, 906, 870, 829,787, 740, 703, 634 cm^{-1}; HRMS (FI+) m/z calc'd $C_{16}H_{15}Cl$ $[M]^{+\bullet}$: 242.0862, found: 242.0889.

Synthesis of Vinyl Chloride 99

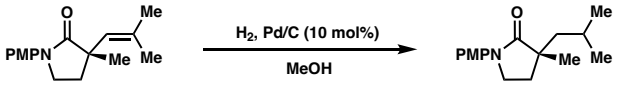
Inspired by a literature protocol, 4-phenyl-1-butyne (523 mg, 4.02 mmol) was dissolved in hexanes (1 M) in a two-neck flask. Under a N_2 atmosphere, neat DIBAL-H (0.788 mL, 1.1 equiv) was added slowly at ambient temperature. The reaction was heated to 50ºC for 2.5 h before being slowly chilled to 18 ºC, at which point Et_2O (2 M) was added. At –78ºC, solid NCS (1.08 g, 2 equiv) was quickly added through one neck of the flask. The reaction was allowed to warm to 18 ºC. After 16h, the reaction mixture was poured into a flask containing 30 mL pentane and 15 mL 6 M HCl with ice. The organic layer was extracted with Et_2O three times, after which it was washed with 10 mL 1 M NaOH then sat. $Na_2S_2O_3$ (10 mL). The organic layer was then dried with Na_2SO_4, filtered, and concentrated, at which point purification by silica gel chromatography (100% Hexanes) yielded the desired vinyl chloride **99** (205 mg, 25% yield).



***(E)-(4-chlorobut-3-en-1-yl)benzene* (99)**

Characterization data in agreement with the literature.[16] ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 (dd, J = 8.0, 6.8 Hz, 2H), 7.23 – 7.14 (m, 3H), 6.07 – 5.79 (m, 2H), 2.71 (dd, J = 8.7, 6.7 Hz, 2H), 2.45 – 2.26 (m, 2H).

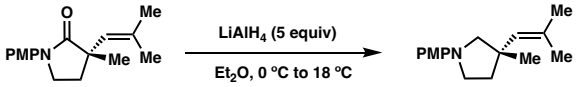
Derivatization of Vinylation Products



***(R)-3-isobutyl-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one* (101)**

A flame-dried one-dram vial was charged with a stir bar and starting material **87** (15 mg, 0.058mmol, 1 equiv) in MeOH (0.421 uL, 0.1M), followed by Pd/C (10%) (6.23mg, 0.058 mmol, 1 equiv). Reaction mixture was purged with N_2 for 5 minutes and then with H_2, and the mixture was stirred overnight with a H_2 balloon. Upon complete consumption of

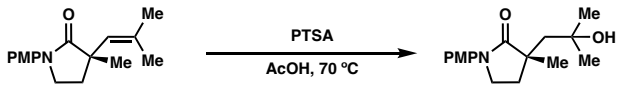
starting material as determined by TLC (30% EtOAc in Hexanes), the reaction was quenched by filtering through a pad of celite with DCM. The filtrate was concentrated in vacuo, and the crude product was purified by prep TLC (25% EtOAc/Hexanes) to afford lactam **101** (7.6 mg, 74% yield) as a pale yellow oil; $[\alpha]_D^{25}$ – 117.2 ° (*c* 0.20, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.44 (m, 2H), 7.04 – 6.81 (m, 2H), 3.80 (s, 3H), 3.77 – 3.65 (m, 2H), 2.17 (ddd, *J* = 12.7, 8.4, 7.0 Hz, 1H), 1.92 (ddd, *J* = 12.6, 7.8, 4.7 Hz, 1H), 1.79 (dqd, *J* = 8.3, 6.6, 4.6 Hz, 1H), 1.68 – 1.58 (m, 2H), 1.49 (dd, *J* = 14.1, 8.3 Hz, 1H), 1.21 (s, 3H), 0.94 (dd, *J* = 17.5, 6.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.6, 156.5, 133.3, 121.6, 114.1, 55.6, 46.2, 45.7, 45.2, 31.3, 25.2, 25.0, 23.8, 23.4; IR (thin film, NaCl) 3358, 2953, 2930, 2869, 2837, 2058, 1885, 1700, 1610, 1518, 1461, 1453, 1394, 1366, 1313, 1290, 1252, 1233, 1184, 1168, 1121, 1036, 1011, 830, 805, 743, 722; HRMS (MM:ESI-APCI+) m/z calc'd $C_{16}H_{23}NO_2Na$ $[M+Na]^+$: 284.1621, found: 284.1628.



***(S)-1-(4-methoxyphenyl)-3-methyl-3-(2-methylprop-1-en-1-yl)pyrrolidine* (102)**

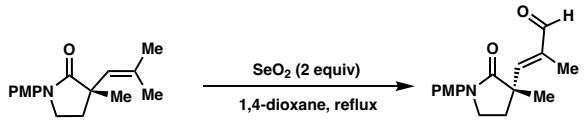
Following our previous report,[17] solid LAH was added to a solution of lactam **87** in Et_2O (0.1 M) at 0 ºC. The solution was stirred at this temperature for 5 min and then was allowed to warm to 18 ºC. After 21 h, the reaction was quenched with H_2O. Extractions were performed with EtOAc seven times, and the crude product was subjected to silica gel chromatography (0-40% EtOAc/Hexanes) to afford the desired product (**102**) as a white solid (22.5 mg, 84% yield). $[a]_D^{25}$ 5.5° (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, CDCl3) δ 6.85 (d, J = 8.5 Hz, 2H), 6.49 (d, J = 8.4 Hz, 2H), 5.34 (s, 1H), 3.76 (s, 3H), 3.35 – 3.13 (m, 4H), 2.10 – 2.00 (m, 1H), 1.92 (s, 1H), 1.73 (d, J = 1.3 Hz, 3H), 1.70 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (101 MHz, CDCl3) δ 132.7, 132.0, 115.2, 112.1, 61.5, 56.2, 47.1, 42.4, 39.7, 27.2,

25.8, 19.4; HRMS (MM:ESI-APCI+) m/z calc'd $C_{16}H_{24}NO$ $[M+H]^+$: 245.1780, found 245.1784.



***(S)-3-(2-hydroxy-2-methylpropyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one* (103)**

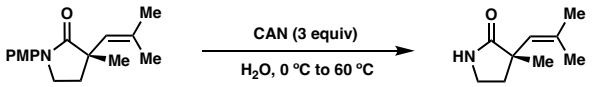
In a one-dram vial, starting material **87** (10.9 mg, 0.042 mmol, 1 equiv) was combined with PTSA (4mg, 0.021 mmol, 0.5 equiv) and acetic acid (700uL, 0.06M). The reaction mixture was heated to 70 ºC overnight, and reaction was tracked by LCMS. After completion, saturated aqueous $NaHCO_3$ was added to quench the reaction, and then extracted with DCM and washed with brine. The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified via prep TLC (50% EtOAc/Hexanes) to afford alcohol **104** (6.3 mg, 59% yield) as a colorless oil; $[\alpha]_D^{25}$ 4.1950 ° (*c* 0.60, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (d, *J* = 8.9 Hz, 2H), 6.58 (d, *J* = 8.9 Hz, 2H), 3.74 (s, 3H), 3.22 (ddd, *J* = 12.1, 8.7, 5.3 Hz, 1H), 3.12 (ddd, *J* = 12.1, 8.8, 6.7 Hz, 1H), 2.18 (d, *J* = 13.4 Hz, 1H), 2.07 – 1.78 (m, 3H), 1.47 (s, 3H), 1.39 (d, *J* = 5.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.6, 152.5, 142.3, 115.0, 114.4, 81.3, 77.5, 77.4, 77.2, 76.8, 55.9, 46.4, 44.1, 41.0, 38.7, 30.4, 30.2, 26.6; IR (thin film, NaCl) 3369, 2968, 2930, 2834, 2339, 1754, 1681, 1513, 1455, 1401, 1377, 1265, 1249, 182, 1171, 1115, 1098, 1035, 942, 824; HRMS (MM:ESI-APCI+) m/z calc'd $C_{16}H_{24}NO_3$ $[M+H]^+$: 278.1751, found: 278.1771.



***(S,E)-3-(1-(4-methoxyphenyl)-3-methyl-2-oxopyrrolidin-3-yl)-2-methylacrylaldehyde* (104)**

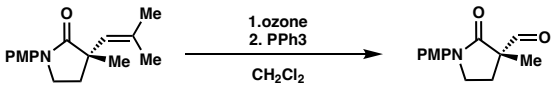
To a solution of **87** (26 mg, 0.1 mmol) in dioxane (0.2 M) was added SeO_2 (22 mg, 0.2 mmol), and the reaction was heated to reflux. After 15 minutes, starting material was

consumed by TLC. The crude reaction was concentrated and passed through a silica plug (ca. 1" silica), eluting with 35% EtOAc/Hexanes, to afford the desired aldehyde **104** as a tan solid (13.4 mg 49% yield); $[\alpha]_D^{25}$ –60.6º (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 7.53 (d, *J* = 9.2 Hz, 2H), 6.92 (d, *J* = 9.2 Hz, 2H), 6.89 (d, *J* = 1.4 Hz, 1H), 3.88 (m, 1H), 3.81 (s, 4H), 3.78 – 3.35 (m, 1H), 2.43 – 2.31 (m, 2H), 1.84 (d, *J* = 1.4 Hz, 3H), 1.48 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.8, 175.4, 157.0, 156.1, 139.7, 132.5, 121.8, 114.3, 55.6, 47.5, 45.8, 32.5, 22.9, 10.1; IR (neat film, NaCl) 3834, 3732, 2958, 2359, 1688, 1512, 1396, 1299, 1249, 1178, 1090, 1031, 833 cm^{-1}; HRMS (FI+) m/z calc'd for $C_{16}H_{19}NO_3$ $[M]^{+\bullet}$: 273.1365, found 273.1393.



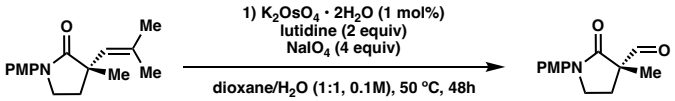
***(S)-3-methyl-3-(2-methylprop-1-en-1-yl)pyrrolidin-2-one* (105)**

A solution of CAN (82 mg, 0.15 mmol) in deionized H_2O (0.05 M) was added dropwise to a solution of **87** (26 mg, 0.1 mmol) at 0 °C, and the reaction was allowed to slowly warm to room temperature. After 12 hours, starting material remained by TLC. CAN (82 mg, 0.15 mmol) added, and the reaction was allowed to continue at 23 °C. After 2 h, the reaction was heated to 60 °C and continued for 18 hours, at which point starting material was consumed by TLC. The reaction was cooled, diluted with ethyl acetate and water, transferred to a separatory funnel, and the organic layer was separated. The aqueous layer was extracted twice with ethyl acetate, the combined organics were dried with Na_2SO_4, filtered, and concentrated. The material was purified with silica gel chromatography (5–10% MeOH/CH_2Cl_2) to afford the desired lactam **105** as a white solid (6.2 mg, 40% yield); $[\alpha]_D^{25}$ –15.7 (c 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.37 – 5.97 (bs, 1H), 5.38 (p, *J* = 1.4 Hz, 1H), 3.32 (ddd, *J* = 8.2, 5.5, 0.9 Hz, 2H), 2.39 – 1.87 (m, 2H), 1.72 (d, *J* = 1.5 Hz, 3H), 1.67 (d, *J* = 1.3 Hz, 3H), 1.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.8, 134.7, 128.1, 44.0, 39.0, 36.8, 27.0, 24.4, 19.1; IR (neat film, NaCl) 3835, 3732, 3229, 2964, 2927, 2358, 1697, 1454, 1281, 1062, 832 cm^{-1}; HRMS (MM:ESI-APCI+) m/z calc'd for $C_9H_{16}NO$ $[M+H]^+$: 154.1226, found 154.1230.



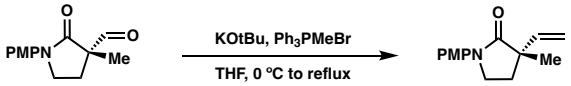
***(S)-1-(4-methoxyphenyl)-3-methyl-2-oxopyrrolidine-3-carbaldehyde* (106)**

Procedure A: A flamed-dried one-dram vial was charged with stir bar, and starting material **87** (50mg, 0.2 mmol, 1 equiv) was added with CH_2Cl_2 (482uL, 0.4M). The reaction mixture was cooled to – 78 ºC in a dry-ice bath, and ozone (1 atm) was bubbled through until all starting material was consumed as indicated by TLC. Then, O_2 gas was bubbled through to quench the residual ozone, and PPh_3 (101.2mg, 0.4 mmol, 2 equiv) was added and reaction was warmed to room temperature. The crude mixture was concentrated in vacuo and purified by silica gel chromatography (30% EtOAc/Hexanes) to afford aldehyde **106** (40 mg, 89% yield) as a white solid. $[a]_D^{25}$ – 26.8 ° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (d, *J* = 0.7 Hz, 1H), 7.56 – 7.43 (m, 2H), 6.96 – 6.83 (m, 2H), 3.93 – 3.67 (m, 5H), 2.75 (ddd, *J* = 12.9, 8.0, 4.8 Hz, 1H), 1.91 (dddd, *J* = 13.1, 8.6, 6.7, 0.7 Hz, 1H), 1.51 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.5, 171.3, 157.1, 132.2, 121.9, 114.3, 58.0, 55.6, 46.0, 25.9, 18.8. IR (thin film, NaCl) 2932, 2358, 1731, 1682, 1520, 1455, 1402, 1297, 1248, 1170, 1092, 1032, 825 cm^{-1}; HRMS (MM:ESI-APCI+) m/z calc'd $C_{13}H_{16}NO_3$ $[M+H]^+$: 234.1125, found 234.1121.



Procedure B[18]: A one dram vial was charged with a stir bar and compound **87**. To this vial, 2,6-lutidine (2 equiv) and K_2OsO_4 • 2 H_2O was added as a solution in dioxane/H_2O. To the stirring mixture, $NaIO_4$ was added and the temperature was increased to 50 ºC. After 24 h, the crude mixture was filtered through a pad of celite, eluting with CH_2Cl_2 and EtOAc. H_2O was added and CH_2Cl_2 was used to perform an extraction. The organic layer was

washed with brine and dried with Na_2SO_4. The crude compound was purified via silica gel chromatography to afford compound **106**.



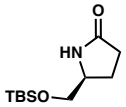
***(S)-1-(4-methoxyphenyl)-3-methyl-3-vinylpyrrolidin-2-one* (107)**

A one-dram vial was flame dried and charged with stir bar. The Ph_3PCH_3Br (51mg, 0.145mmol, 2.5 equiv) was added in THF (300uL, 0.1M) and cooled to 0 ºC. Reaction mixture was then charged with KOtBu (14mg, 0.128 mmol, 2.2 equiv) and stirred at 0 ºC for 20 minutes. Starting material **106** (13.2 mg, 0.057 mmol, 1 equiv) was added with the remaining THF (about 100 μL) and slowly warmed to room temperature and heated to reflux overnight. Second day all starting material was consumed by TLC (50% EtOAc/Hexanes) and reaction was quenched with NH_4Cl and extracted with EtOAc (3x) and washed with brine. The organic extracts were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resultant crude product was the purified by pipette column chromatography (15% EtOAc/Hexanes) to afford vinylated lactam **107** (11 mg, 84% yield) as a pale yellow oil; $[a]_D^{25}$ – 0.6 ° (*c* 0.35, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.48 (m, 2H), 6.95 – 6.80 (m, 2H), 5.97 (dd, *J* = 17.5, 10.6 Hz, 1H), 5.24 – 5.11 (m, 2H), 3.80 (s, 3H), 3.73 (ddt, *J* = 7.8, 5.0, 2.5 Hz, 2H), 2.26 (ddd, *J* = 12.3, 7.0, 5.0 Hz, 1H), 2.12 – 1.96 (m, 1H), 1.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0, 156.6, 140.6, 133.1, 121.6, 114.2, 114.0, 55.6, 48.6, 45.6, 32.0, 23.1; IR (Neat film, NaCl) 3360, 3077, 2962, 2927, 2060, 1693, 1512, 1504, 1455, 1394, 1315, 1299, 1246, 1182, 1170, 1124, 1111, 1090, 1034, 1005, 924, 913, 883, 825, 807, 731, 636 cm^{-1}; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{14}H_{17}NO_2Na$ $[M+Na]^+$: 254.1151, found 254.1155.

Synthesis of Substrates 118 and 118d

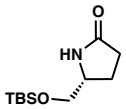
Following a literature protocol, enantiopure 5-(hydroxymethyl)pyrrolidin-2-one was dissolved in CH_2Cl_2 (0.86 M). Iteratively, TBSCl (1.2 equiv) and imidazole (1.5 equiv) were added. The reaction was stirred for 4h, after which it was quenched with H_2O and

separated into layers. The aqueous phase was extracted with CH_2Cl_2 two more times, and the combined organic extracts were dried with Na_2SO_4. The product was isolated as a colorless oil (quant.) and used in the next step without additional purification.



***(S)-5-(((tert-butyldimethylsilyl)oxy)methyl)pyrrolidin-2-one* (116)**

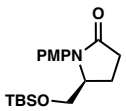
Prepared according to a literature procedure. Characterization data was in agreement with the literature.[19] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71 (s, 1H), 3.92 – 3.70 (m, 1H), 3.63 (dd, *J* = 10.1, 3.8 Hz, 1H), 3.44 (dd, *J* = 10.1, 7.9 Hz, 1H), 2.35 (ddd, *J* = 8.6, 7.2, 2.8 Hz, 2H), 2.25 – 2.09 (m, 1H), 1.73 (dddd, *J* = 13.2, 9.3, 7.7, 5.5 Hz, 1H), 0.90 (s, 9H), 0.07 (s, 6H).



***(R)-5-(((tert-butyldimethylsilyl)oxy)methyl)pyrrolidin-2-one* (116e)**

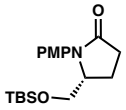
Refer to Compound 13 for ^{1}H NMR data.

In a flask equipped with a magnetic stir bar, CuI (0.5 mmol, 10 mol%) was combined with anhydrous K_2CO_3 (10 mmol, 2 equiv). The vial was purged and backfilled with N_2 three times. At this point, 5 mL of toluene was added, followed by N, N'-dimethylethylenediamine (1 mmol, 20 mol%), intermediate **116** or **116e** (6 mmol, 1.2 equiv), and p-Br anisole (5 mmol). The reaction mixture was allowed to react at 100 ºC for 24h. The crude reaction mixture was concentrated and purified by silica gel chromatography (0-100% EtOAc/Hexanes) to afford the product as a pale yellow oil (1.10 g, 66% yield).



***(S)-5-(((tert-butyldimethylsilyl)oxy)methyl)-1-(4-methoxyphenyl)pyrrolidin-2-one* (117)**

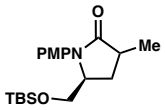
$[\alpha]_D^{25}$ –48.0º (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 4.12 (dtd, *J* = 8.6, 3.6, 2.5 Hz, 1H), 3.80 (3, 2H), 3.68 – 3.43 (m, 2H), 2.68 (ddd, *J* = 16.9, 10.1, 8.1 Hz, 1H), 2.49 (ddd, *J* = 16.9, 10.2, 4.6 Hz, 1H), 2.26 (ddt, *J* = 12.8, 10.1, 8.3 Hz, 1H), 2.09 (dddd, *J* = 12.7, 10.1, 4.6, 3.5 Hz, 1H), 0.86 (s, 9H), -0.04 (d, *J* = 11.3 Hz, 6H);^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 157.9, 130.5, 126.5, 114.5, 63.0, 62.0, 55.6, 31.6, 25.9, 21.5, 18.3, -5.47, -5.51. IR (thin film, NaCl) 2934, 1694, 1513, 1248, 1090, 834, 682 cm^{-1}; HRMS (MM:ESI-APCI+) m/z calc'd $C_{18}H_{30}NO_3Si$ $[M+H]^+$: 336.1989, found 336.1999.



***(R)-5-(((tert-butyldimethylsilyl)oxy)methyl)-1-(4-methoxyphenyl)pyrrolidin-2-one* (117e)**

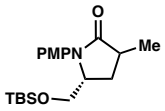
Refer to Compound **14** for ^1H NMR, 13C NMR, IR, and HRMS data. $[\alpha]_D^{25}$ 47.9º (c 1.0, $CHCl_3$).

A solution of LDA was prepared by the slow addition of n-BuLi (1.44 mL, 2.5 M in hexanes) to a solution of diisopropylamine (3.61 mmol) in THF (0.9 M) at -78ºC. After letting the mixture stir for 1h at this temperature, substrate **117** or **117e** was added slowly as a solution in THF (0.3 M). 30 min later, MeI (3.61 mmol) was added slowly to the reaction mixture, and it was allowed to warm up to 18 ºC. After 16h, the reaction was quenched with sat. NH_4Cl solution and extracted with CH_2Cl_2. The crude compound was concentrated and purified by silica gel chromatography (10-60% EtOAc/Hexanes) to afford the product as a dark solid (703 mg, 61% yield).



(5S)-5-(((tert-butyldimethylsilyl)oxy)methyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one **(118)**

$[\alpha]_D^{25}$ –30.0º (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 9.1 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 4.15 – 4.01 (m, 1H), 3.81 (s, 3H), 3.68 – 3.43 (m, 2H), 2.81 (td, *J* = 9.1, 7.1 Hz, 1H), 2.33 (ddd, *J* = 12.7, 9.0, 2.0 Hz, 1H), 1.90 (dt, *J* = 12.6, 9.1 Hz, 1H), 1.26 (d, *J* = 7.1 Hz, 3H), 0.86 (s, 9H), -0.03 (d, *J* = 11.9 Hz, 6H).^{13}C NMR (101 MHz, $CDCl_3$) δ 177.5, 157.5, 131.0, 125.7, 114.4, 63.0, 59.9, 55.6, 36.8, 30.9, 25.9, 18.3, 17.1, -5.45, -5.48; IR (thin film, NaCl) 2928, 1693, 1513, 1463, 1272, 1246, 1171, 1107, 1041, 832, 776, 681 cm^{-1}; HRMS (MM:ESI-APCI+) m/z calc'd $C_{19}H_{32}NO_3Si$ $[M+H]^+$: 350.2146, found 350.2143.



(5R)-5-(((tert-butyldimethylsilyl)oxy)methyl)-1-(4-methoxyphenyl)-3-methylpyrrolidin-2-one **(118d)**

Refer to Compound **15** for ^1H NMR, ^{13}C NMR, IR, and HRMS data. $[\alpha]_D^{25}$ 32.3º (c 1.0, $CHCl_3$).

3.5.3 CRYSTAL STRUCTURE ANALYSIS OF *(S)*-1-(4-METHOXYPHENYL)-3-METHYL-3-(2 METHYLPROP-1-EN-1-YL)PYRROLIDIN-2-ONE (SAMPLE NO.: V24190)

Compound **87** was crystallized from slow evaporation in hexanes at 23 °C to provide crystals suitable for X-ray analysis. Compound V24190 (CSD 2375577) crystallizes in the orthorhombic space group $P2_12_12_1$ with one molecule in the asymmetric unit.

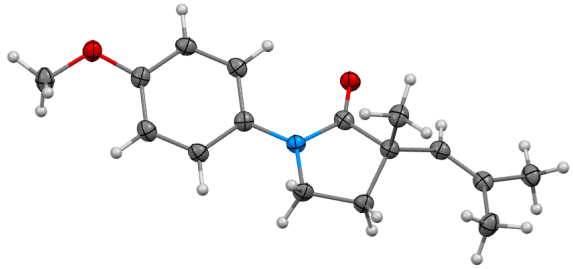


Table 3.3. *Crystal data and structure refinement for V24190.*

Identification code	V24190	
Empirical formula	C16 H21 N O2	
Formula weight	259.34	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.3874(10) Å	a= 90°.
	b = 9.1155(13) Å	b= 90°.
	c = 20.860(3) Å	g = 90°.
Volume	1404.7(3) Å3	
Z	4	
Density (calculated)	1.226 Mg/m3	
Absorption coefficient	0.636 mm-1	
F(000)	560	
Crystal size	0.150 x 0.100 x 0.005 mm3	
Theta range for data collection	4.239 to 74.536°.	
Index ranges	-9<=h<=9, -11<=k<=10, -26<=l<=26	
Reflections collected	21524	
Independent reflections	2879 [R(int) = 0.1102]	
Completeness to theta = 67.679°	99.9 %	

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7538 and 0.6287
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	2879 / 0 / 176
Goodness-of-fit on F2	1.062
Final R indices [I>2sigma(I)]	R1 = 0.0436, wR2 = 0.0947
R indices (all data)	R1 = 0.0574, wR2 = 0.1004
Absolute structure parameter	0.0(3)
Extinction coefficient	n/a
Largest diff. peak and hole	0.173 and -0.182 e.Å-3

Table 3.4. *Atomic coordinates (x 104) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for V24190. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.*

	x	y	z	U(eq)
C(1)	4790(4)	5751(3)	3452(1)	21(1)
O(1)	4177(3)	6906(2)	3656(1)	26(1)
C(2)	6222(4)	4815(3)	3796(1)	21(1)
C(5)	5146(4)	3885(3)	4282(1)	28(1)
C(6)	7569(4)	5786(3)	4137(1)	22(1)
C(7)	9203(4)	5434(3)	4356(1)	24(1)
C(8)	10344(4)	6545(3)	4705(1)	27(1)
C(9)	10082(4)	3964(3)	4275(2)	32(1)
C(3)	6944(4)	3841(3)	3251(1)	24(1)
C(4)	5384(4)	3742(3)	2771(1)	25(1)

N(1)	4290(3)	5050(2)	2897(1)	21(1)
C(10)	2709(4)	5361(3)	2530(1)	21(1)
C(11)	2486(4)	4690(3)	1933(1)	24(1)
C(12)	900(4)	4883(3)	1582(1)	25(1)
C(13)	-480(4)	5762(3)	1821(1)	23(1)
O(2)	-2108(3)	6022(2)	1528(1)	28(1)
C(16)	-2465(5)	5246(3)	947(1)	31(1)
C(14)	-238(4)	6463(3)	2410(1)	25(1)
C(15)	1327(4)	6257(3)	2761(1)	24(1)

Table 3.5. *Bond lengths [Å] and angles [°] for V24190.*

C(1)-O(1)	1.222(3)
C(1)-N(1)	1.373(3)
C(1)-C(2)	1.538(4)
C(2)-C(6)	1.509(4)
C(2)-C(3)	1.538(4)
C(2)-C(5)	1.542(4)
C(5)-H(5A)	0.9800
C(5)-H(5B)	0.9800
C(5)-H(5C)	0.9800
C(6)-C(7)	1.329(4)
C(6)-H(6)	0.9500
C(7)-C(9)	1.499(4)
C(7)-C(8)	1.506(4)
C(8)-H(8A)	0.9800

C(8)-H(8B)	0.9800
C(8)-H(8C)	0.9800
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800
C(3)-C(4)	1.529(4)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-N(1)	1.464(4)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
N(1)-C(10)	1.425(4)
C(10)-C(15)	1.394(4)
C(10)-C(11)	1.396(4)
C(11)-C(12)	1.393(4)
C(11)-H(11)	0.9500
C(12)-C(13)	1.389(4)
C(12)-H(12)	0.9500
C(13)-O(2)	1.370(4)
C(13)-C(14)	1.397(4)
O(2)-C(16)	1.427(3)
C(16)-H(16A)	0.9800
C(16)-H(16B)	0.9800
C(16)-H(16C)	0.9800
C(14)-C(15)	1.381(4)
C(14)-H(14)	0.9500
C(15)-H(15)	0.9500
O(1)-C(1)-N(1)	126.5(3)
O(1)-C(1)-C(2)	124.8(2)

N(1)-C(1)-C(2)	108.7(2)
C(6)-C(2)-C(1)	110.3(2)
C(6)-C(2)-C(3)	117.3(2)
C(1)-C(2)-C(3)	102.3(2)
C(6)-C(2)-C(5)	110.6(2)
C(1)-C(2)-C(5)	104.9(2)
C(3)-C(2)-C(5)	110.3(2)
C(2)-C(5)-H(5A)	109.5
C(2)-C(5)-H(5B)	109.5
H(5A)-C(5)-H(5B)	109.5
C(2)-C(5)-H(5C)	109.5
H(5A)-C(5)-H(5C)	109.5
H(5B)-C(5)-H(5C)	109.5
C(7)-C(6)-C(2)	128.2(2)
C(7)-C(6)-H(6)	115.9
C(2)-C(6)-H(6)	115.9
C(6)-C(7)-C(9)	124.8(3)
C(6)-C(7)-C(8)	120.8(3)
C(9)-C(7)-C(8)	114.4(3)
C(7)-C(8)-H(8A)	109.5
C(7)-C(8)-H(8B)	109.5
H(8A)-C(8)-H(8B)	109.5
C(7)-C(8)-H(8C)	109.5
H(8A)-C(8)-H(8C)	109.5
H(8B)-C(8)-H(8C)	109.5
C(7)-C(9)-H(9A)	109.5
C(7)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(7)-C(9)-H(9C)	109.5

H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
C(4)-C(3)-C(2)	104.8(2)
C(4)-C(3)-H(3A)	110.8
C(2)-C(3)-H(3A)	110.8
C(4)-C(3)-H(3B)	110.8
C(2)-C(3)-H(3B)	110.8
H(3A)-C(3)-H(3B)	108.9
N(1)-C(4)-C(3)	104.5(2)
N(1)-C(4)-H(4A)	110.8
C(3)-C(4)-H(4A)	110.8
N(1)-C(4)-H(4B)	110.8
C(3)-C(4)-H(4B)	110.8
H(4A)-C(4)-H(4B)	108.9
C(1)-N(1)-C(10)	125.6(2)
C(1)-N(1)-C(4)	112.4(2)
C(10)-N(1)-C(4)	121.2(2)
C(15)-C(10)-C(11)	118.6(3)
C(15)-C(10)-N(1)	122.1(2)
C(11)-C(10)-N(1)	119.3(2)
C(12)-C(11)-C(10)	120.9(3)
C(12)-C(11)-H(11)	119.6
C(10)-C(11)-H(11)	119.6
C(13)-C(12)-C(11)	120.1(3)
C(13)-C(12)-H(12)	120.0
C(11)-C(12)-H(12)	120.0
O(2)-C(13)-C(12)	125.7(2)
O(2)-C(13)-C(14)	115.2(2)
C(12)-C(13)-C(14)	119.1(3)

C(13)-O(2)-C(16)	117.1(2)
O(2)-C(16)-H(16A)	109.5
O(2)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
O(2)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5
C(15)-C(14)-C(13)	120.7(3)
C(15)-C(14)-H(14)	119.7
C(13)-C(14)-H(14)	119.7
C(14)-C(15)-C(10)	120.7(3)
C(14)-C(15)-H(15)	119.6
C(10)-C(15)-H(15)	119.6

Symmetry transformations used to generate equivalent atoms:

Table 3.6. *Anisotropic displacement parameters ($Å^2$ x 10^3) for V24190. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$*

	U11	U22	U33	U23	U13	U12
C(1)	25(1)	17(1)	22(1)	1(1)	2(1)	-4(1)
O(1)	30(1)	19(1)	27(1)	-4(1)	-3(1)	4(1)
C(2)	23(1)	18(1)	24(1)	1(1)	-1(1)	-1(1)
C(5)	27(2)	28(1)	28(1)	6(1)	-2(1)	-4(1)
C(6)	26(1)	16(1)	24(1)	-1(1)	2(1)	-2(1)

C(7)	27(2)	22(1)	23(1)	1(1)	2(1)	-5(1)
C(8)	29(1)	25(1)	28(1)	-2(1)	-2(1)	-5(1)
C(9)	30(2)	25(1)	40(2)	0(1)	-8(1)	3(1)
C(3)	25(1)	18(1)	28(1)	-2(1)	-2(1)	3(1)
C(4)	26(1)	18(1)	30(1)	-3(1)	-1(1)	4(1)
N(1)	24(1)	16(1)	23(1)	0(1)	-1(1)	2(1)
C(10)	25(1)	15(1)	23(1)	3(1)	0(1)	-1(1)
C(11)	29(1)	17(1)	25(1)	-1(1)	0(1)	2(1)
C(12)	33(2)	18(1)	24(1)	-1(1)	-2(1)	-1(1)
C(13)	24(1)	17(1)	27(1)	3(1)	-3(1)	-1(1)
O(2)	29(1)	26(1)	29(1)	-3(1)	-6(1)	2(1)
C(16)	37(2)	24(1)	31(1)	-2(1)	-10(1)	-2(1)
C(14)	28(2)	20(1)	26(1)	-1(1)	3(1)	1(1)
C(15)	29(2)	18(1)	24(1)	-1(1)	0(1)	-1(1)

Table 3.7. *Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for V24190.*

	x	y	z	U(eq)
H(5A)	5974	3226	4510	42
H(5B)	4233	3304	4055	42
H(5C)	4546	4534	4591	42
H(6)	7202	6773	4203	27

H(8A)	9672	7468	4744	41
H(8B)	11465	6717	4466	41
H(8C)	10637	6174	5134	41
H(9A)	9147	3206	4240	47
H(9B)	10851	3759	4648	47
H(9C)	10824	3966	3886	47
H(3A)	8025	4289	3050	28
H(3B)	7271	2855	3414	28
H(4A)	5844	3745	2326	29
H(4B)	4667	2839	2841	29
H(11)	3427	4093	1765	29
H(12)	761	4413	1179	30
H(16A)	-1567	5522	623	46
H(16B)	-3679	5496	793	46
H(16C)	-2394	4189	1027	46
H(14)	-1161	7088	2572	30
H(15)	1463	6731	3163	29

Table 3.8. *Torsion angles [°] for V24190.*

O(1)-C(1)-C(2)-C(6)	-36.0(4)
N(1)-C(1)-C(2)-C(6)	146.0(2)
O(1)-C(1)-C(2)-C(3)	-161.5(3)
N(1)-C(1)-C(2)-C(3)	20.4(3)
O(1)-C(1)-C(2)-C(5)	83.2(3)
N(1)-C(1)-C(2)-C(5)	-94.8(3)

C(1)-C(2)-C(6)-C(7)	-162.8(3)
C(3)-C(2)-C(6)-C(7)	-46.2(4)
C(5)-C(2)-C(6)-C(7)	81.6(4)
C(2)-C(6)-C(7)-C(9)	3.0(5)
C(2)-C(6)-C(7)-C(8)	-178.0(3)
C(6)-C(2)-C(3)-C(4)	-147.2(2)
C(1)-C(2)-C(3)-C(4)	-26.3(3)
C(5)-C(2)-C(3)-C(4)	84.9(3)
C(2)-C(3)-C(4)-N(1)	23.5(3)
O(1)-C(1)-N(1)-C(10)	-14.5(4)
C(2)-C(1)-N(1)-C(10)	163.5(2)
O(1)-C(1)-N(1)-C(4)	175.9(3)
C(2)-C(1)-N(1)-C(4)	-6.1(3)
C(3)-C(4)-N(1)-C(1)	-11.2(3)
C(3)-C(4)-N(1)-C(10)	178.7(2)
C(1)-N(1)-C(10)-C(15)	-11.4(4)
C(4)-N(1)-C(10)-C(15)	157.3(2)
C(1)-N(1)-C(10)-C(11)	172.0(2)
C(4)-N(1)-C(10)-C(11)	-19.3(4)
C(15)-C(10)-C(11)-C(12)	-1.4(4)
N(1)-C(10)-C(11)-C(12)	175.3(3)
C(10)-C(11)-C(12)-C(13)	0.5(4)
C(11)-C(12)-C(13)-O(2)	-179.0(3)
C(11)-C(12)-C(13)-C(14)	1.0(4)
C(12)-C(13)-O(2)-C(16)	4.4(4)
C(14)-C(13)-O(2)-C(16)	-175.7(2)
O(2)-C(13)-C(14)-C(15)	178.3(3)
C(12)-C(13)-C(14)-C(15)	-1.7(4)
C(13)-C(14)-C(15)-C(10)	0.9(4)

C(11)-C(10)-C(15)-C(14)	0.7(4)
N(1)-C(10)-C(15)-C(14)	-175.9(3)

3.6 REFERENCES

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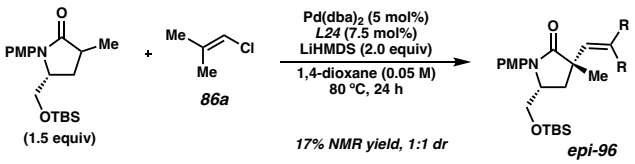
[4] In a matched/mis-matched case, we observed poor efficiency of the reaction to deliver compound ***epi-96***:



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[11] Synthesis of product **107** from vinyl chloride directly would be prohibitive, as this would require a toxic gas as the electrophile and would be unlikely to exhibit asymmetric induction in a Pd-catalyzed system.

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APPENDIX 4

Spectra Relevant to Chapter 3:

Formation of All-Carbon Quaternary Centers via Enantioselective Pd-catalyzed α-Vinylation of γ-Lactams

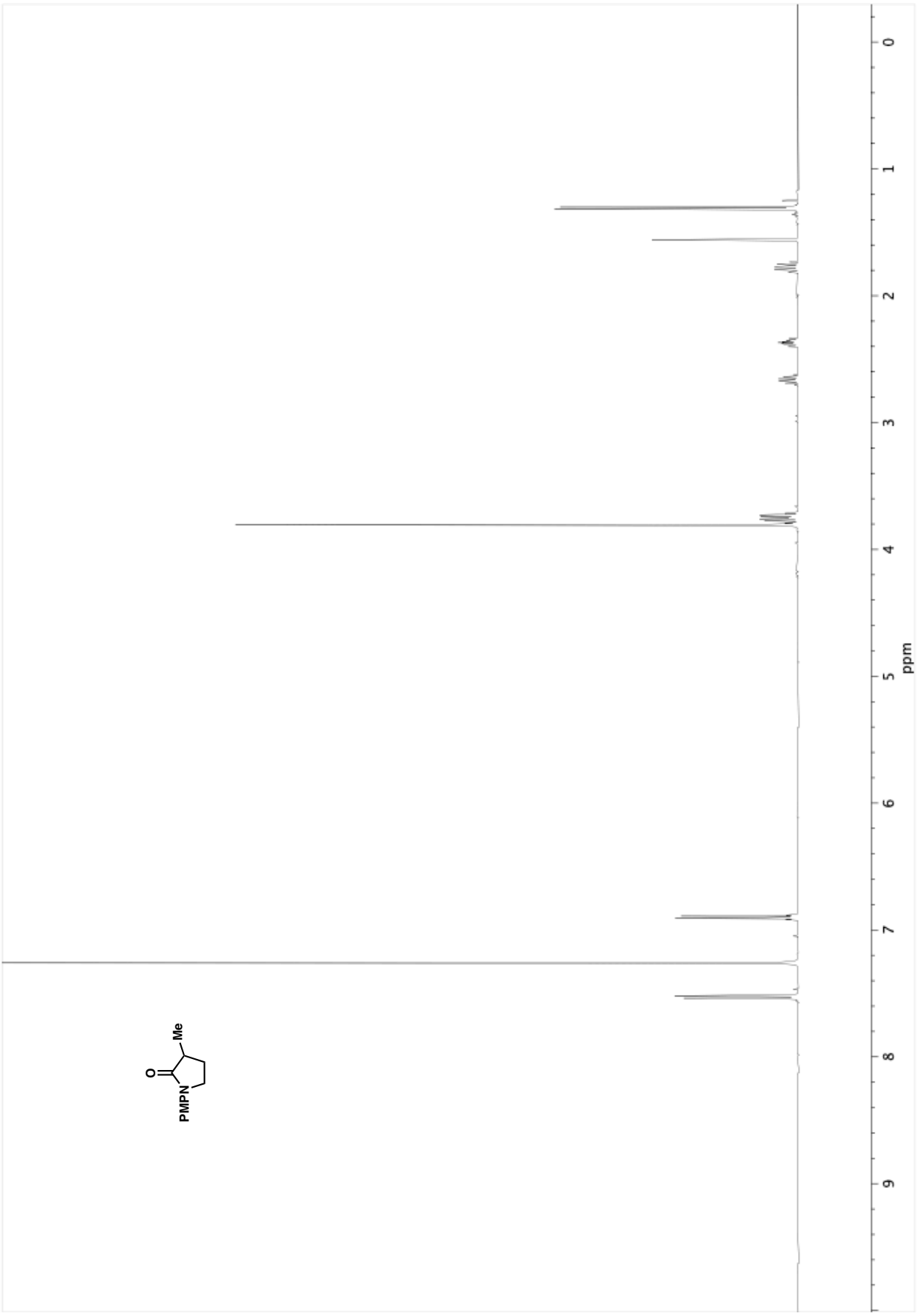

Figure A4.1. *^1H NMR (400 MHz, $CDCl_3$) of* ***85.***

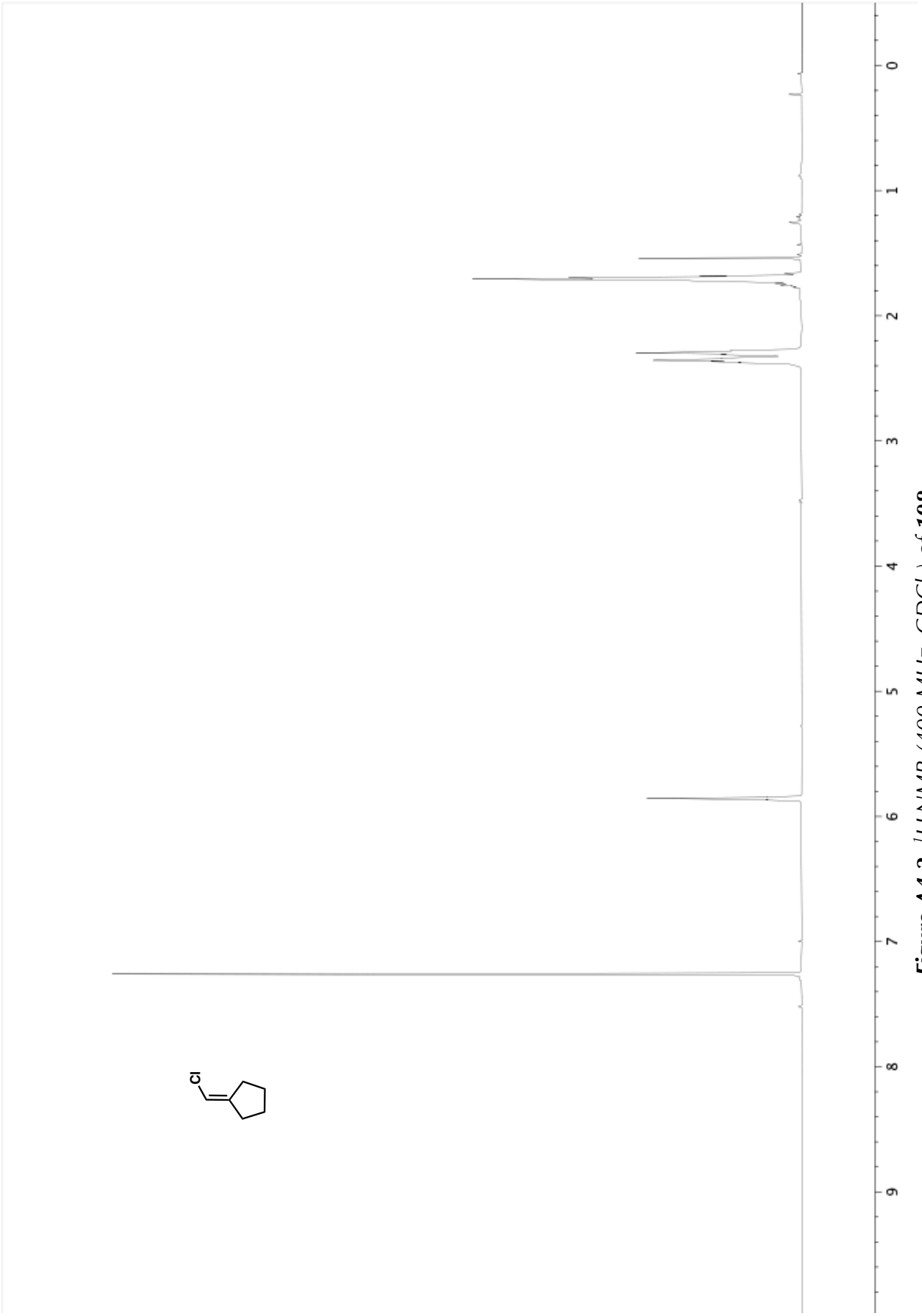

Figure A4.2. *^1H NMR (400 MHz, $CDCl_3$) of* ***108****.*

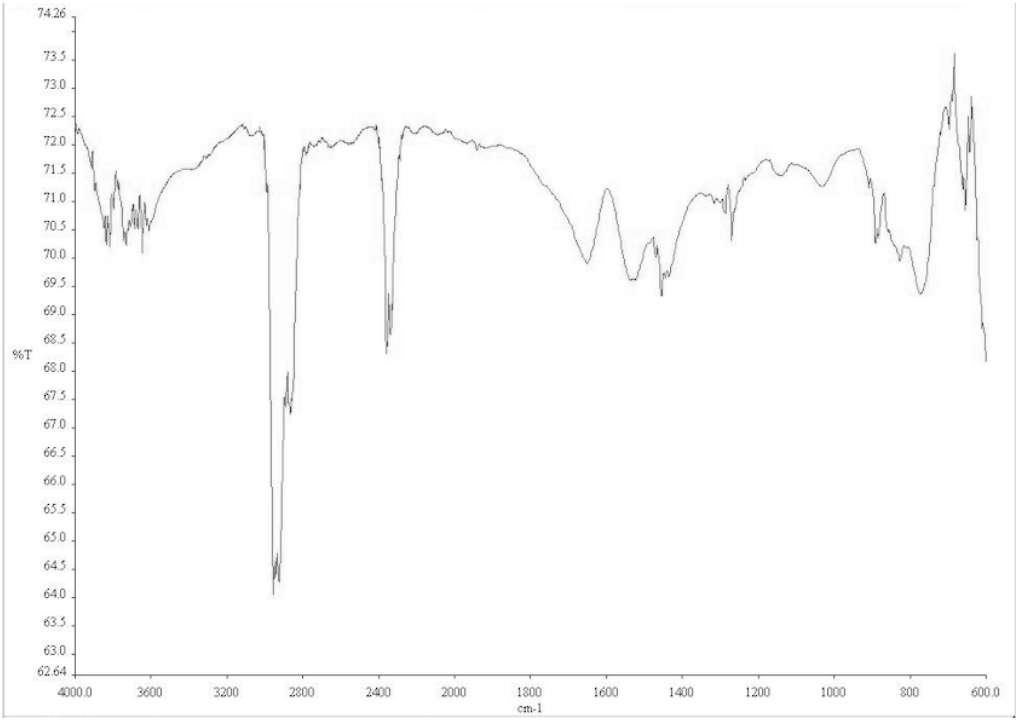

Figure A4.3. *Infrared spectrum (Thin Film, NaCl) of* ***108****.*

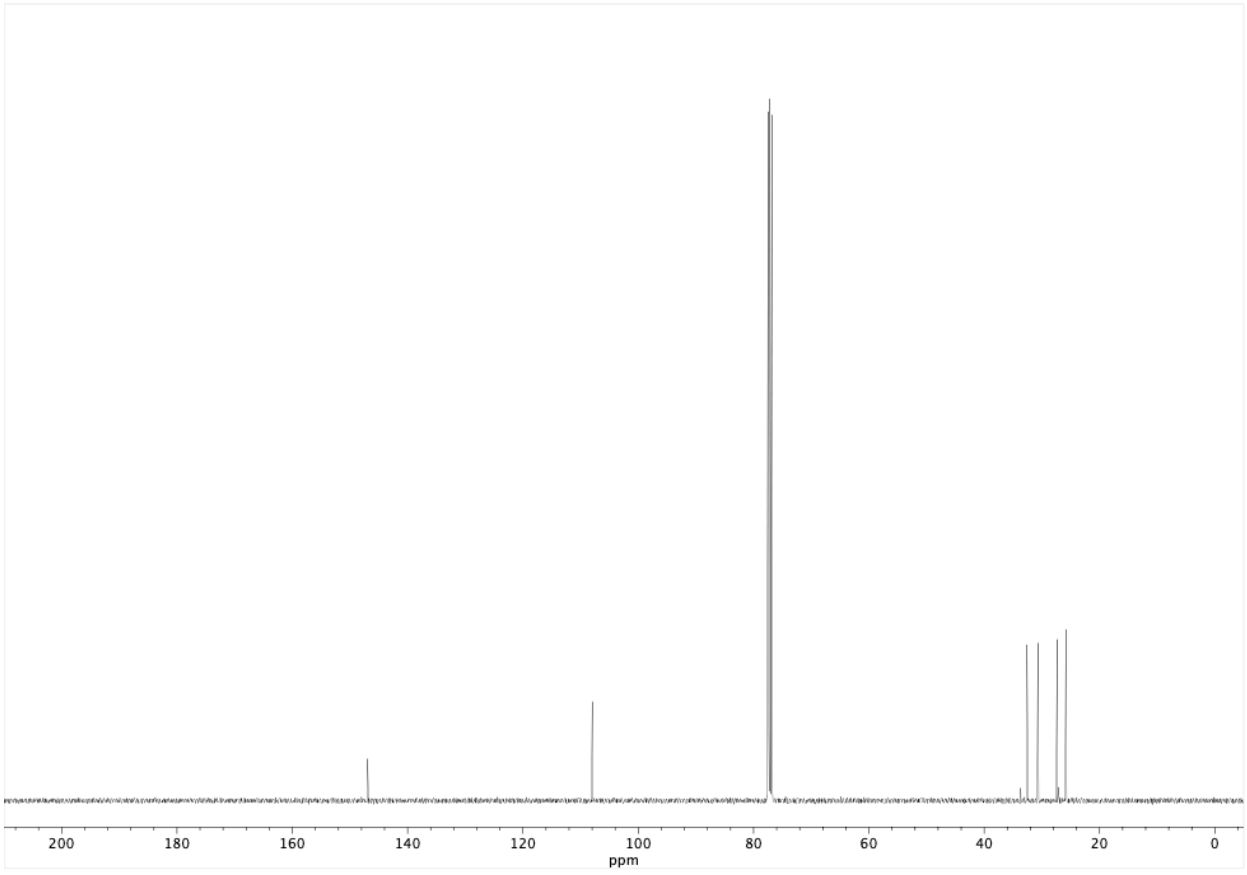

Figure A4.4. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***108.***

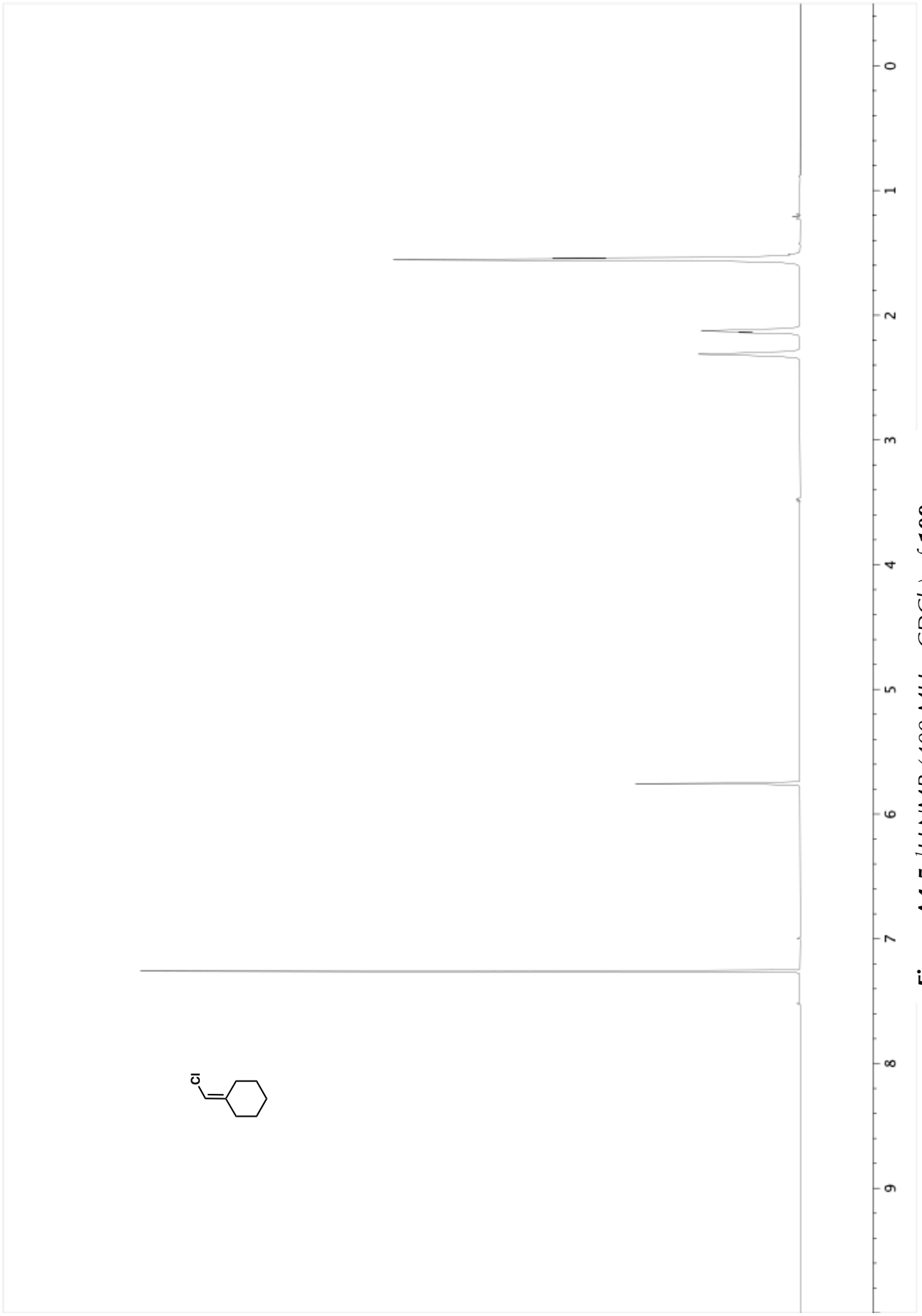

Figure A4.5. *^{1}H NMR (400 MHz, $CDCl_3$) of* ***109***.

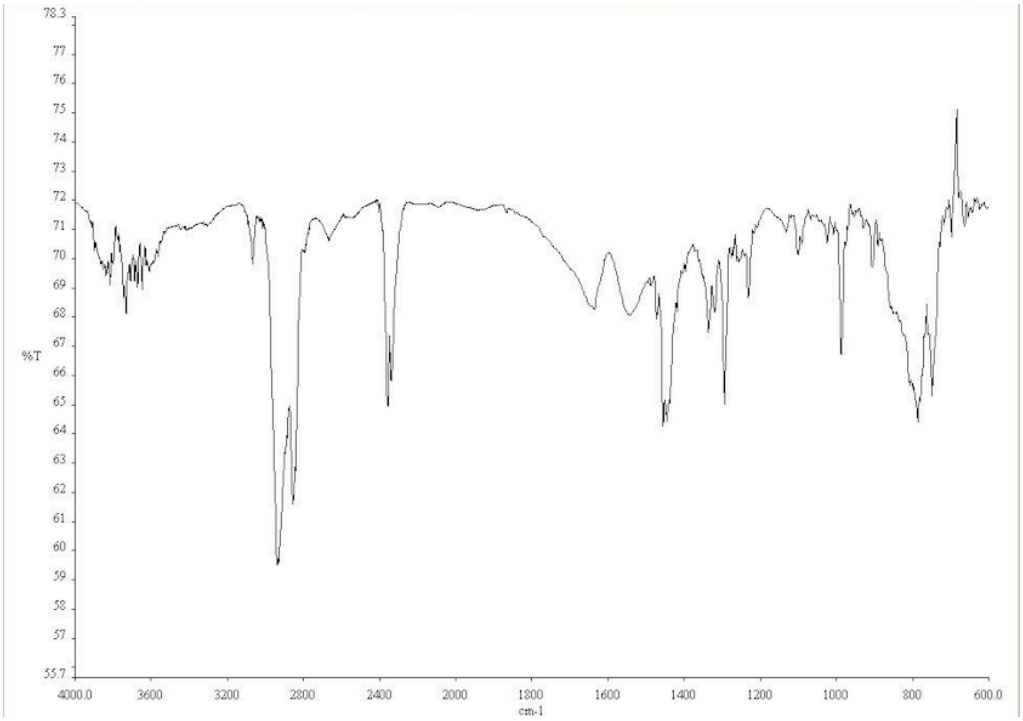

Figure A4.6. *Infrared spectrum (Thin Film, NaCl) of* ***109****.*

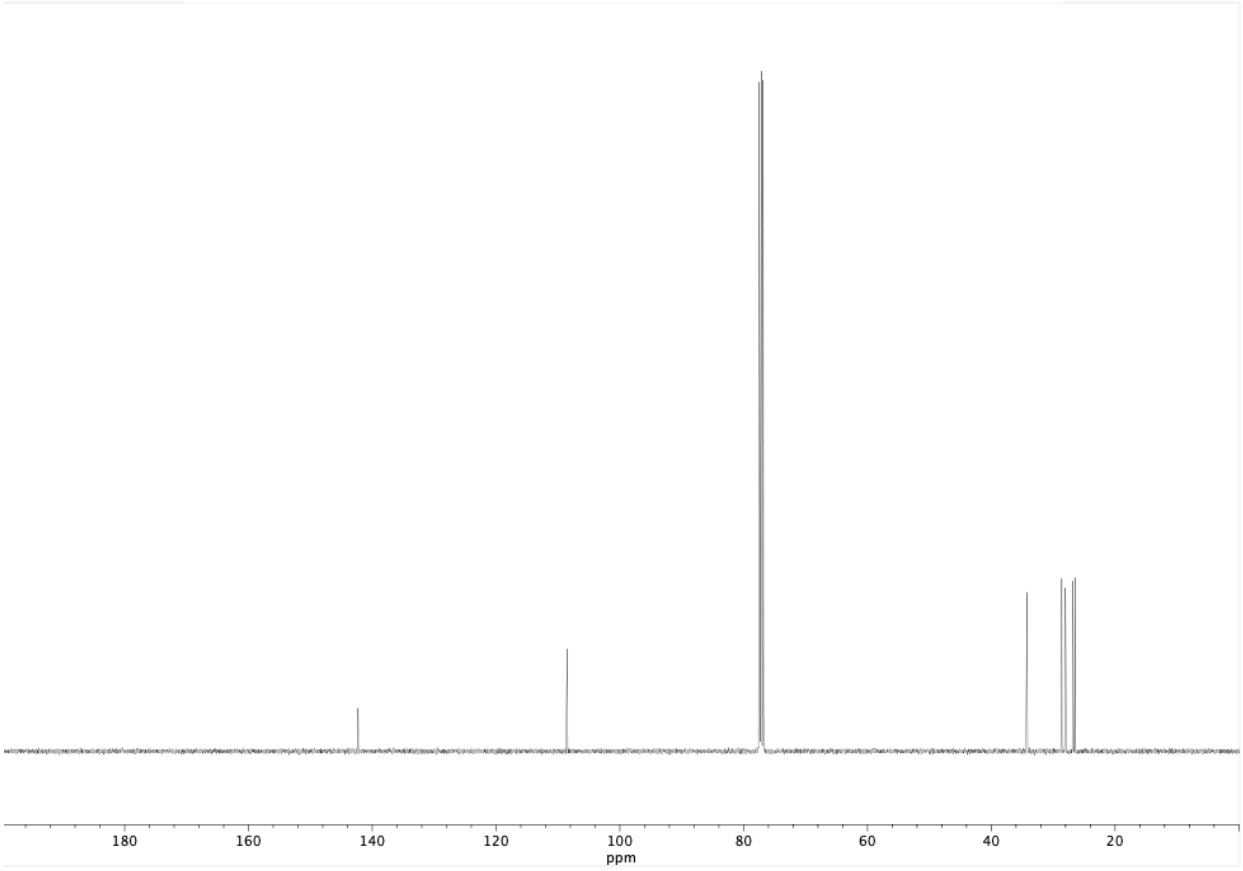

Figure A4.7. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***109.***

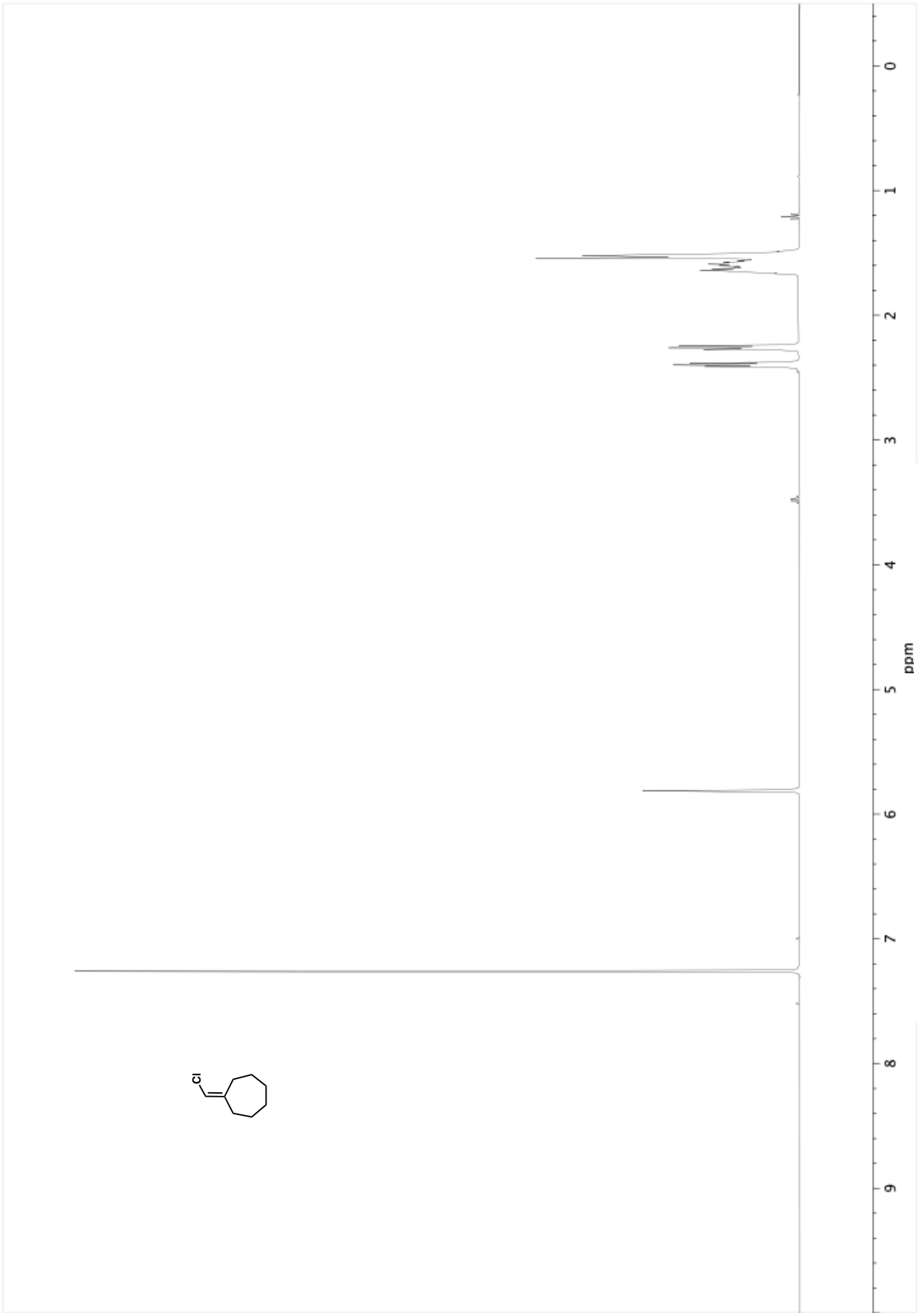

Figure A4.8. *^1H NMR (400 MHz, $CDCl_3$) of* ***110.***

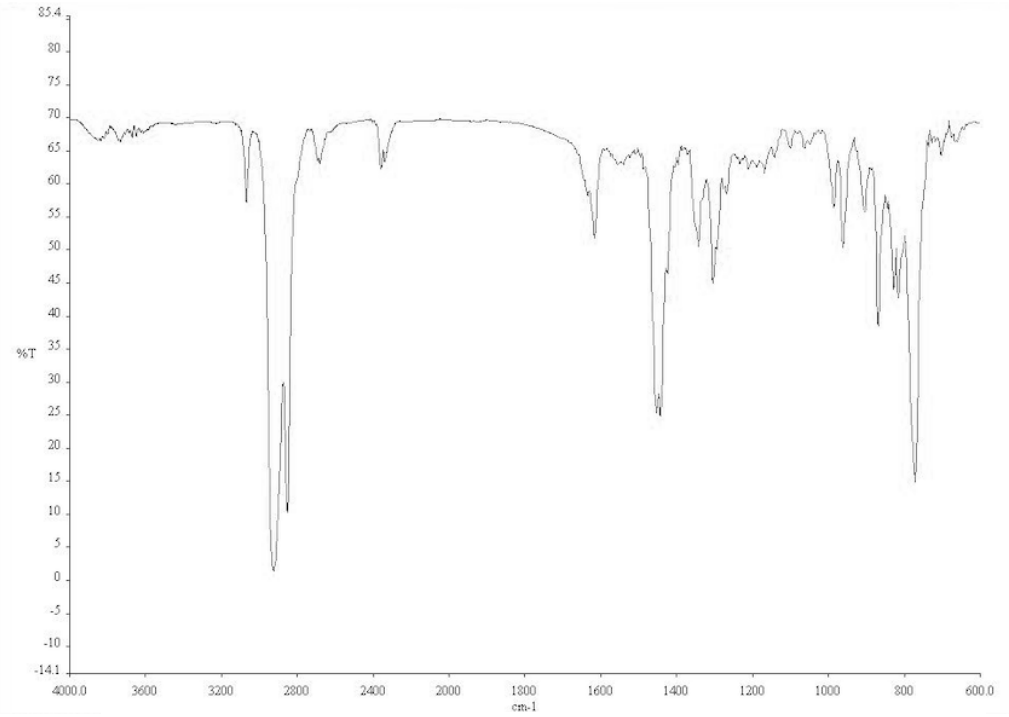

Figure A4.9. *Infrared spectrum (Thin Film, NaCl) of* ***110****.*

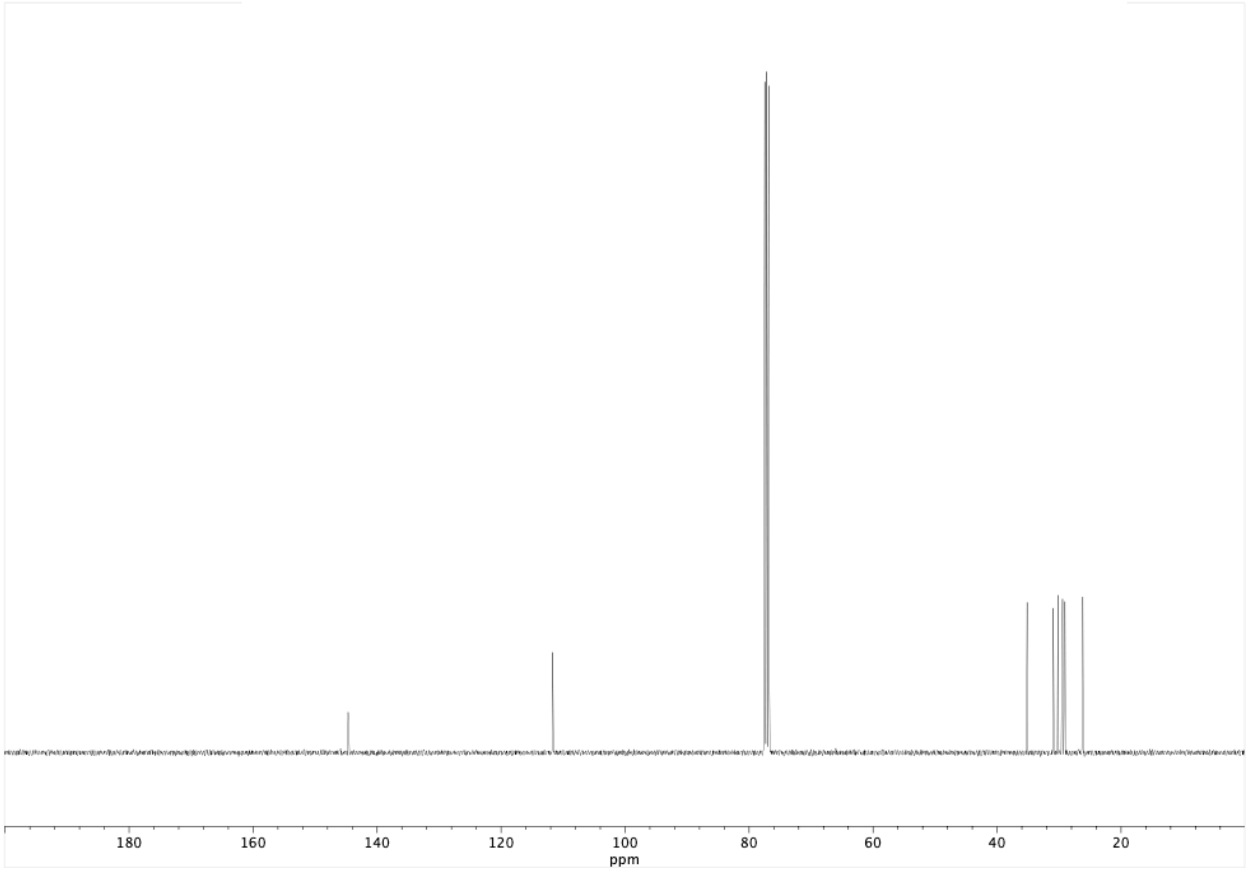

Figure A4.10. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***110****.*

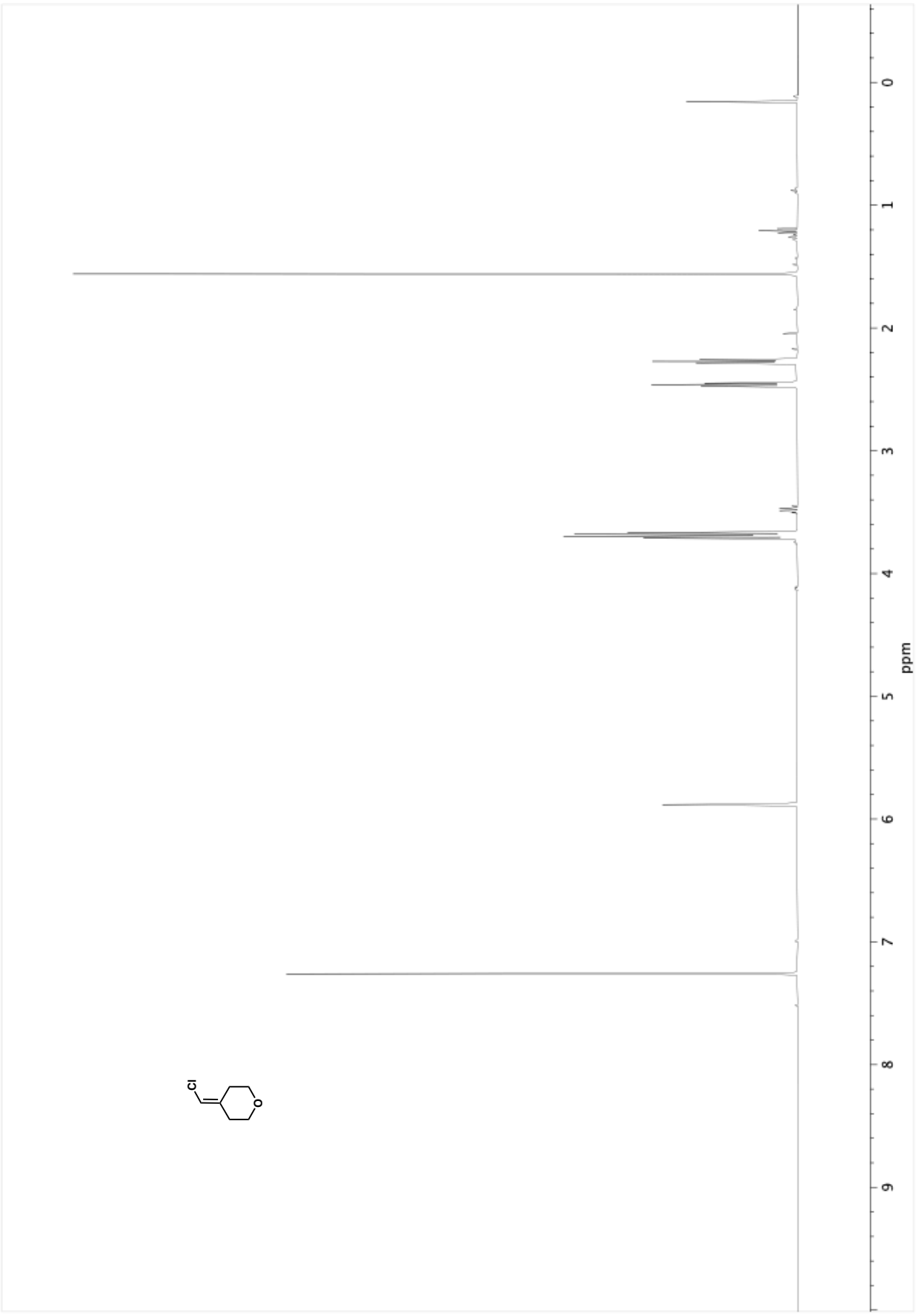

Figure A4.11. *^1H NMR (400 MHz, $CDCl_3$) of* ***111.***

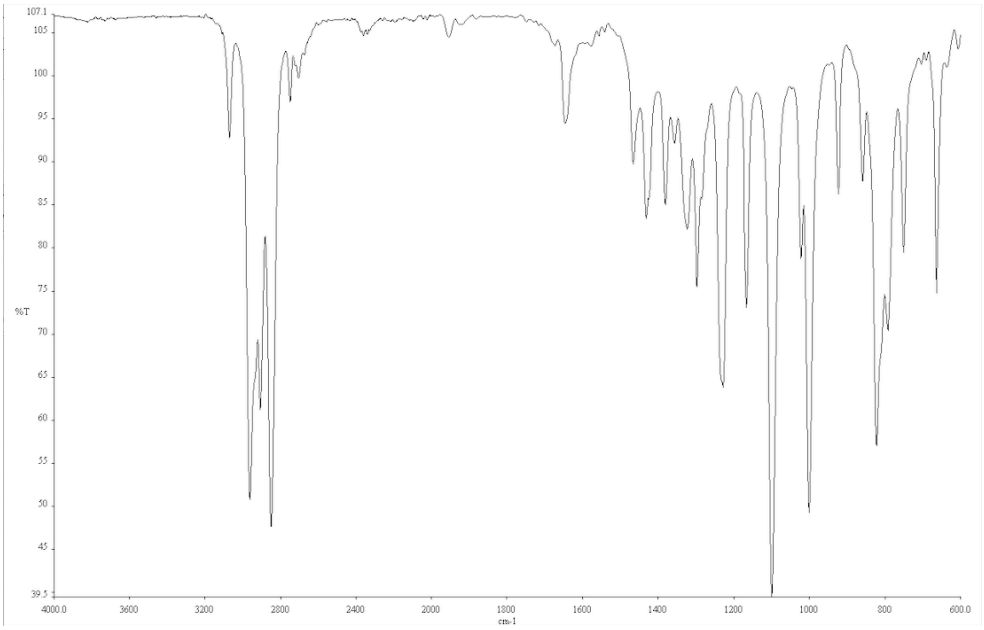

Figure A4.12. *Infrared spectrum (Thin Film, NaCl) of* ***111****.*

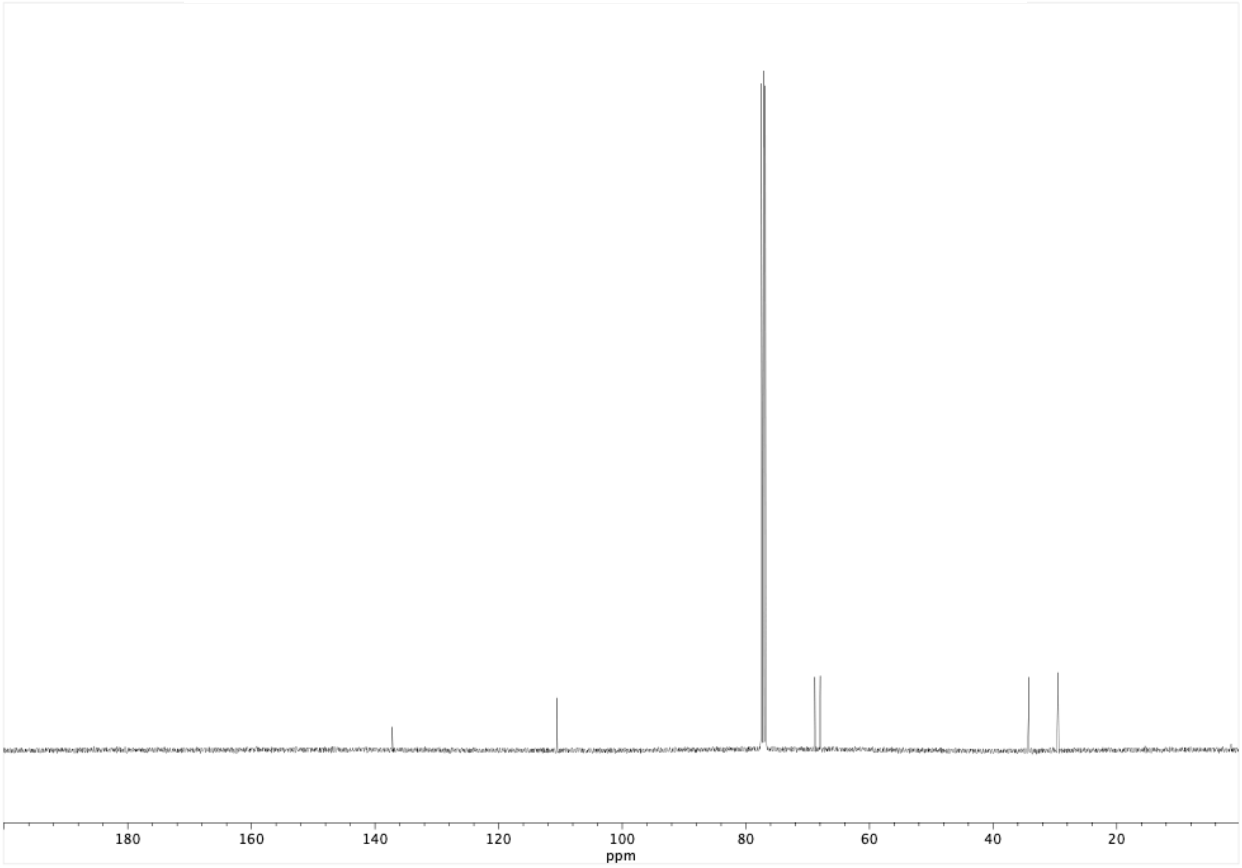

Figure A4.13. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***111****.*

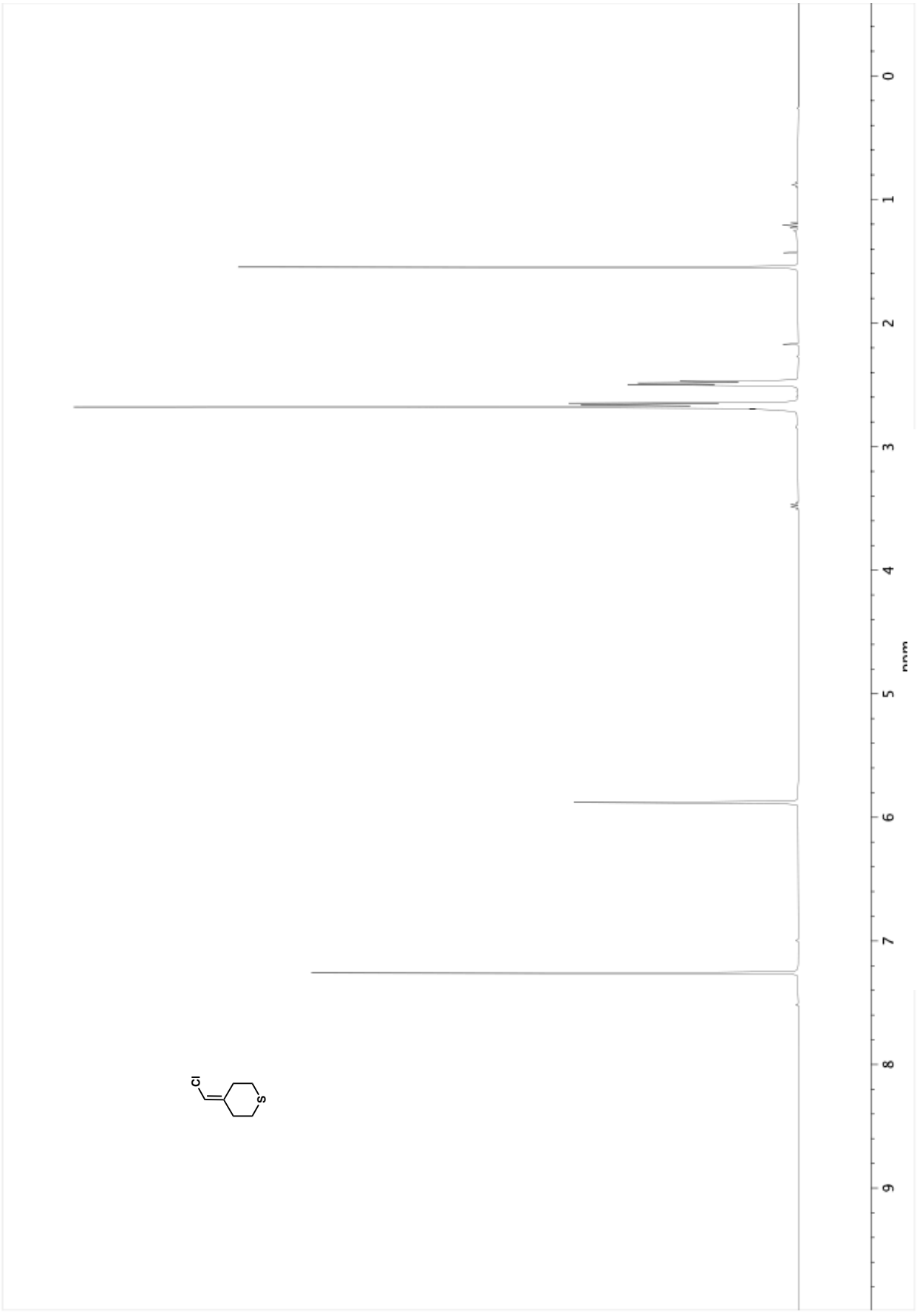

Figure A4.14. *^{1}HNMR (400 MHz, $CDCl_3$) of* ***112.***

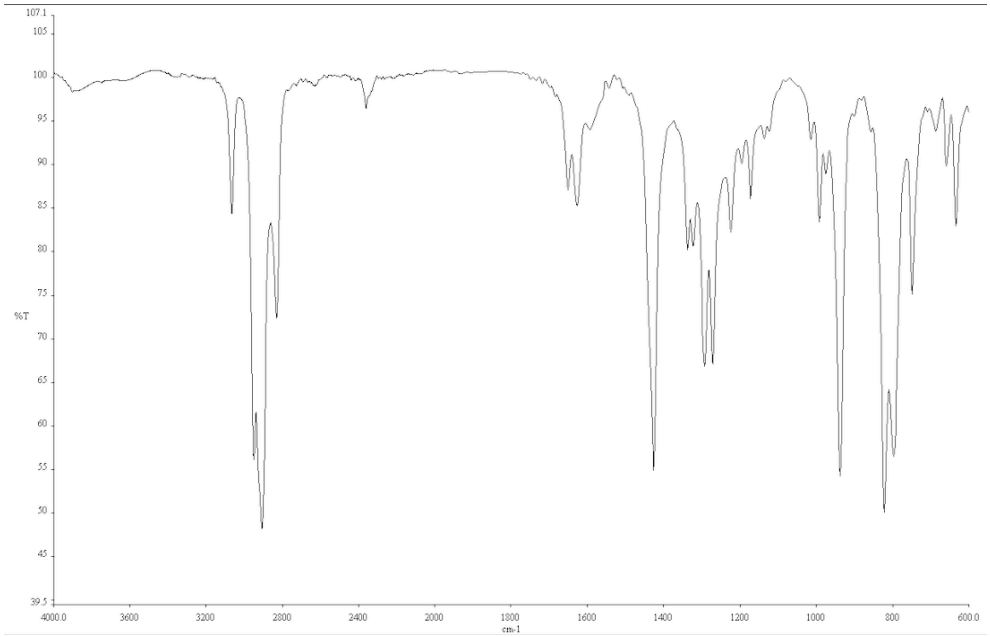

Figure A4.15. *Infrared spectrum (Thin Film, NaCl) of* ***112.***

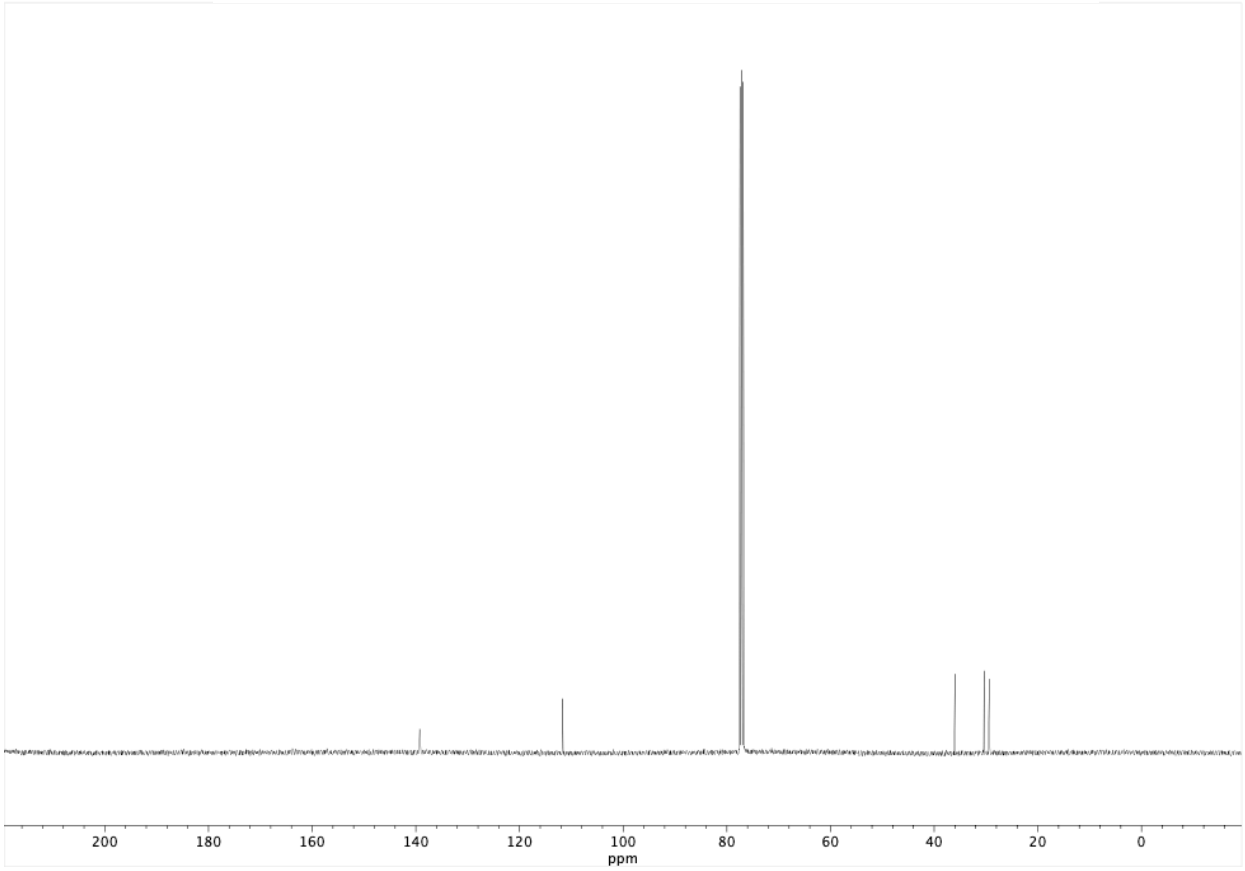

Figure A4.16. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***112.***

Figure A4.17. *^1H NMR (400 MHz, $CDCl_3$) of* ***113***.

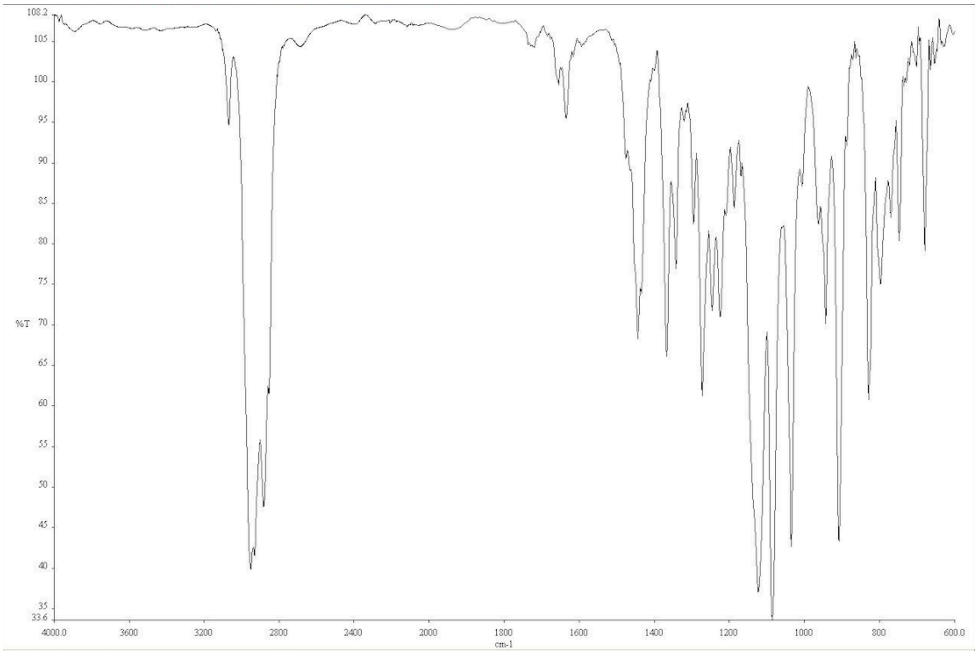

Figure A4.18. *Infrared spectrum (Thin Film, NaCl) of* ***113****.*

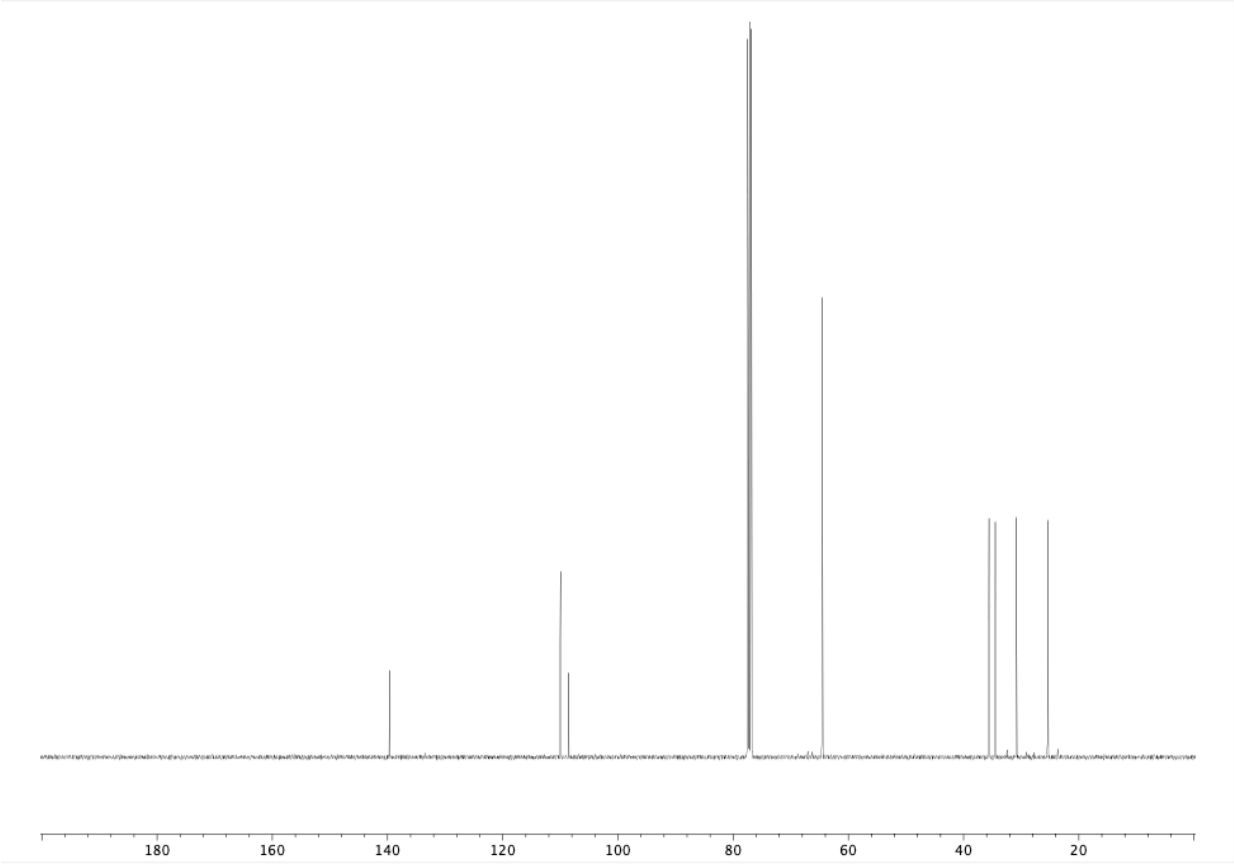

Figure A4.19. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***113****.*

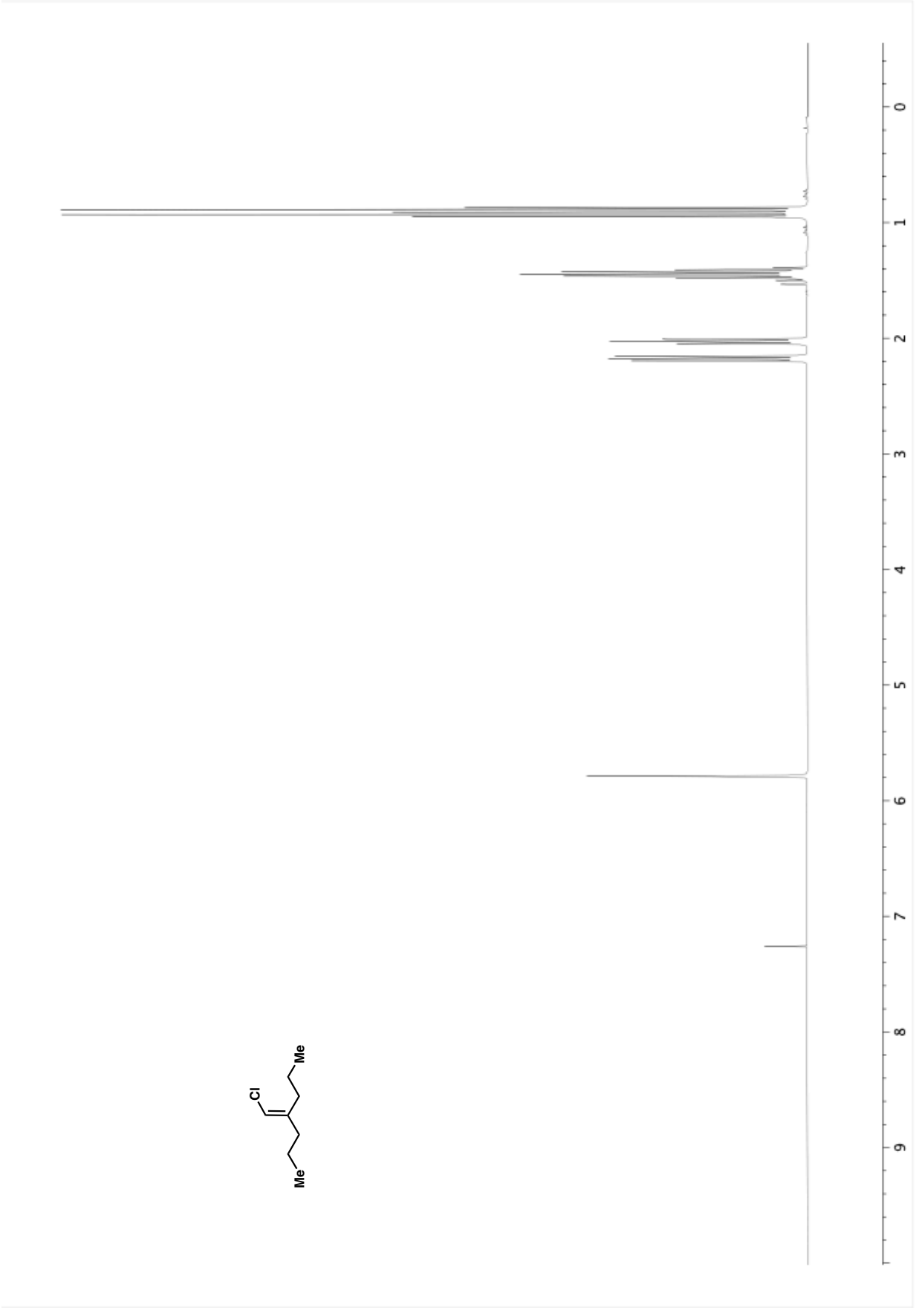

Figure A4.20. *^{1}H NMR (400 MHz, $CDCl_3$) of* ***114****.*

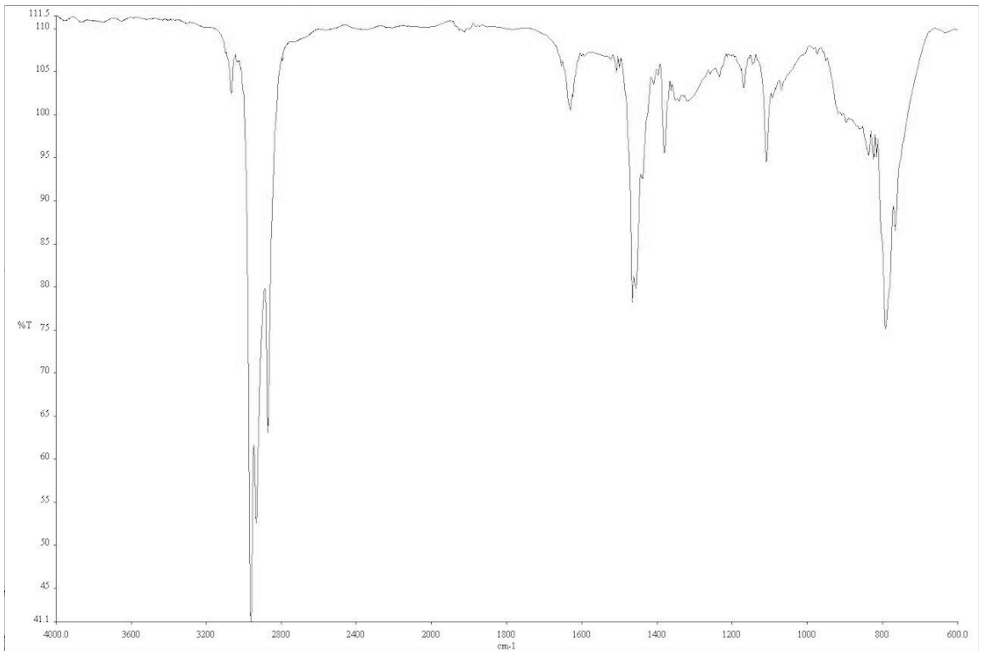

Figure A4.21. *Infrared spectrum (Thin Film, NaCl) of* ***114****.*

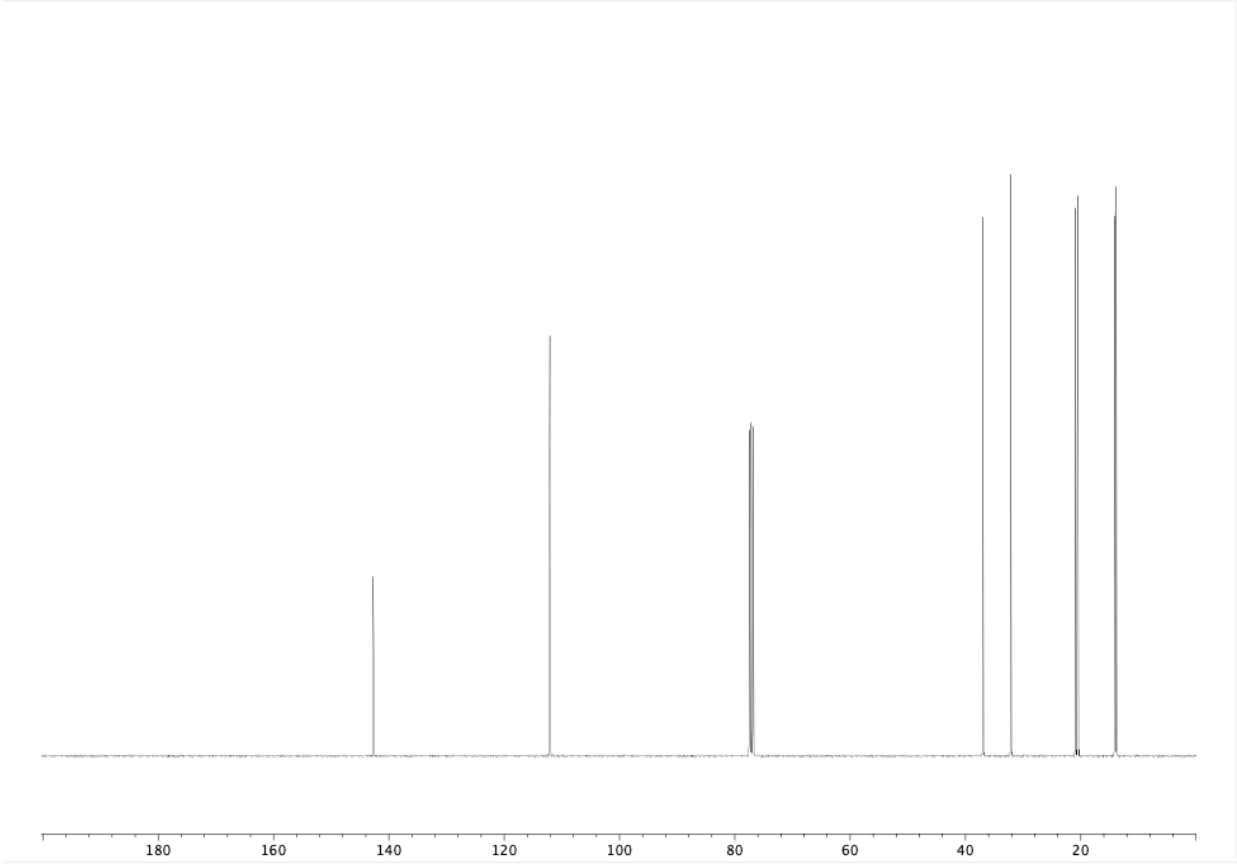

Figure A4.22. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***114****.*

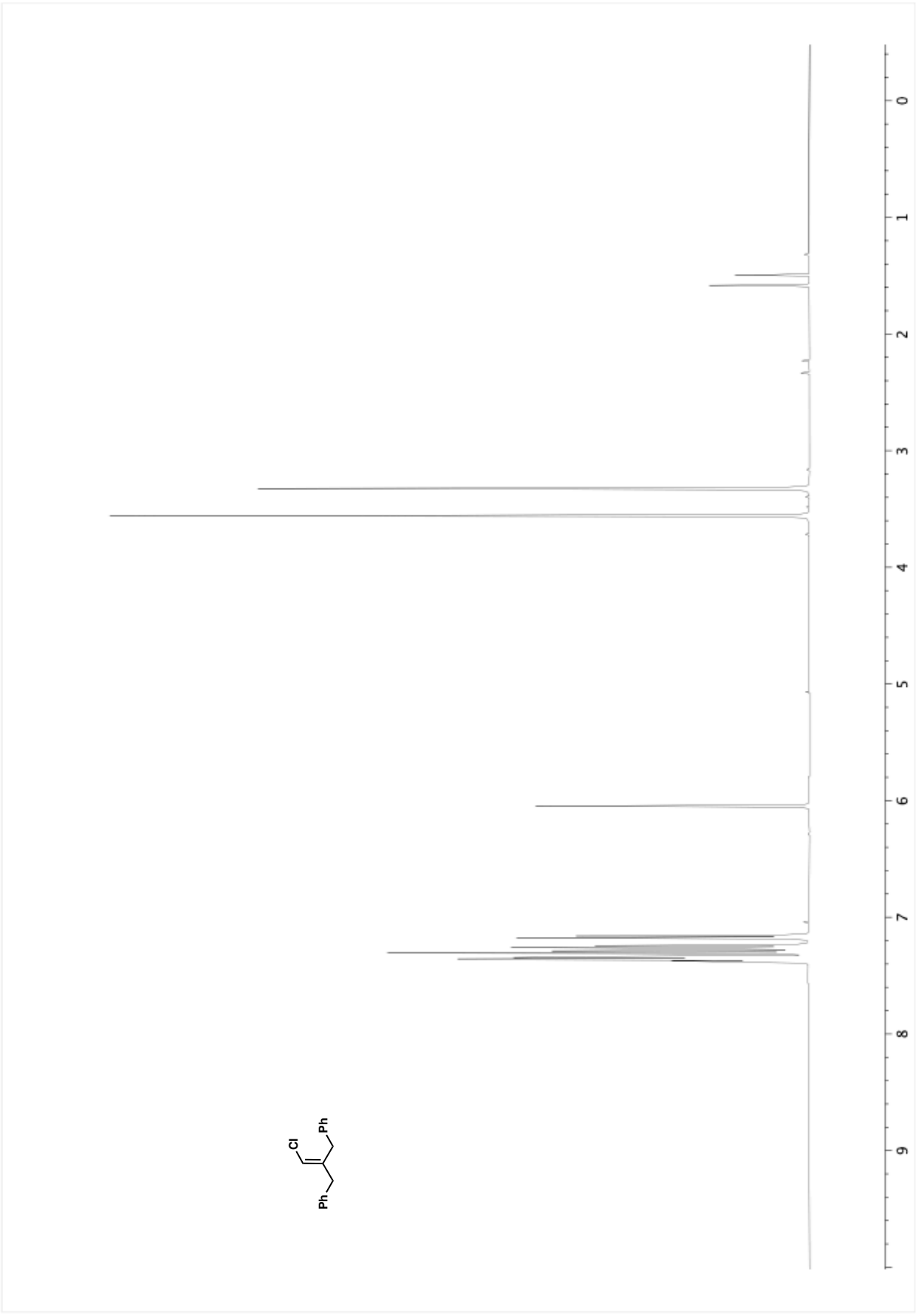

Figure A4.23. *^{1}H NMR (400 MHz, $CDCl_3$) of* ***115****.*

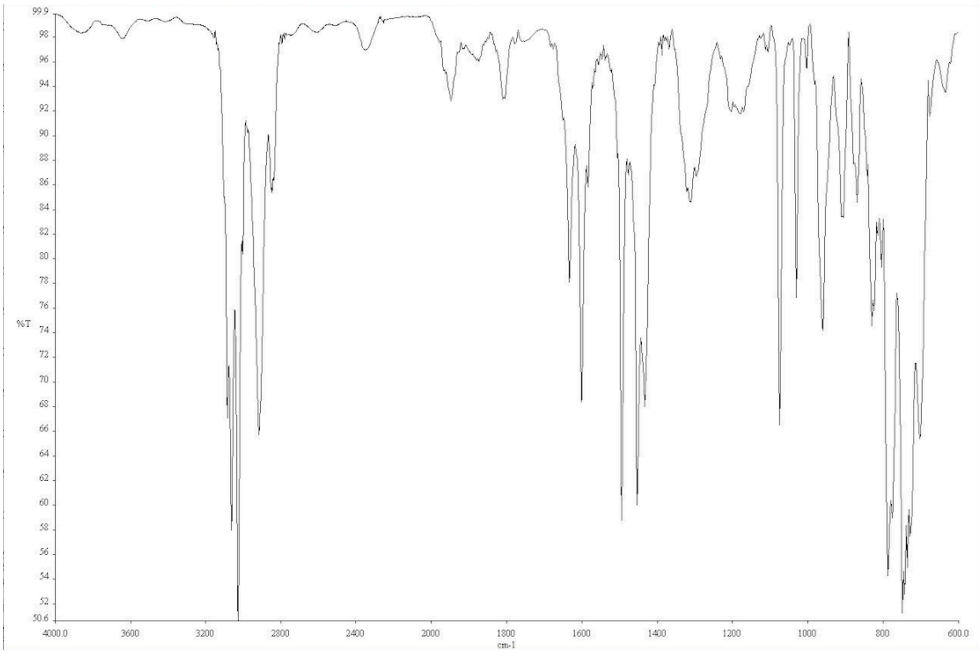

Figure A4.24. *Infrared spectrum (Thin Film, NaCl) of* ***115.***

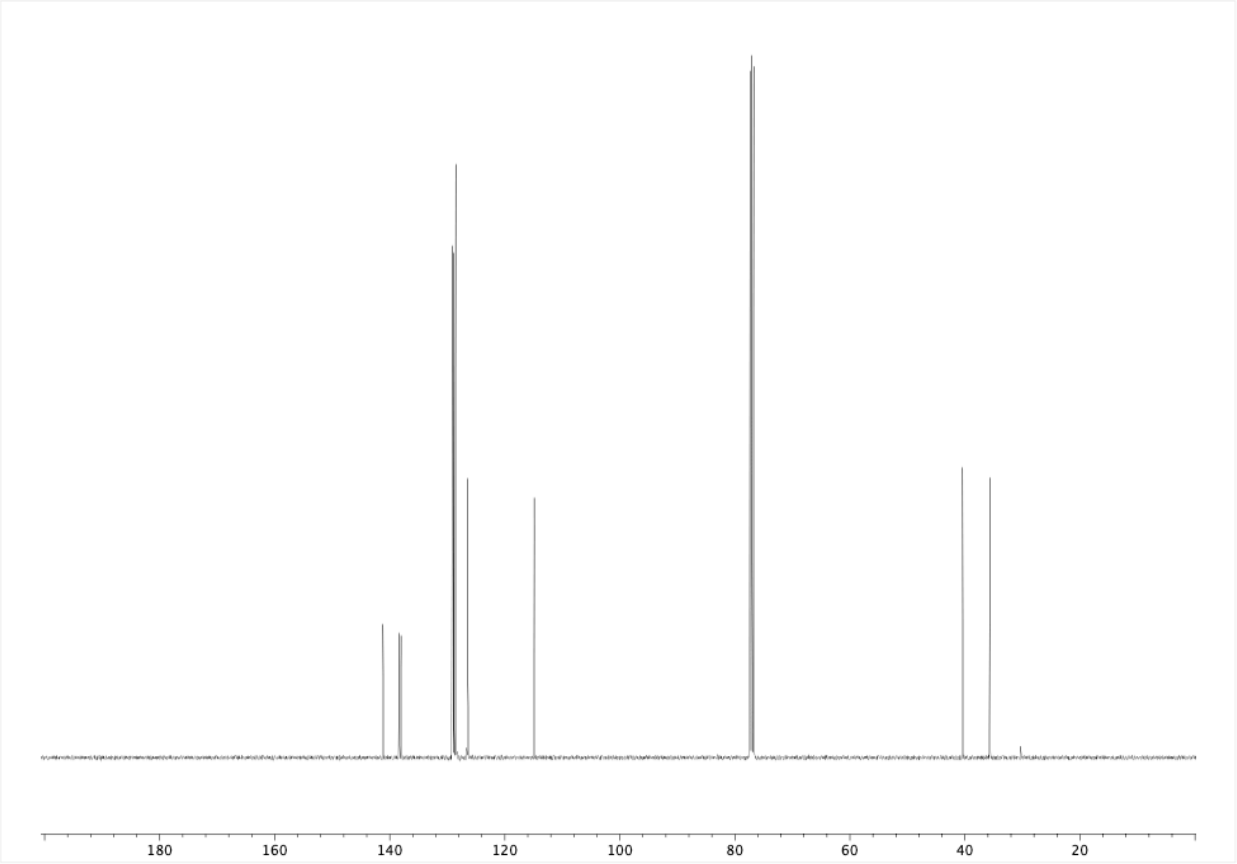

Figure A4.25. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***115****.*

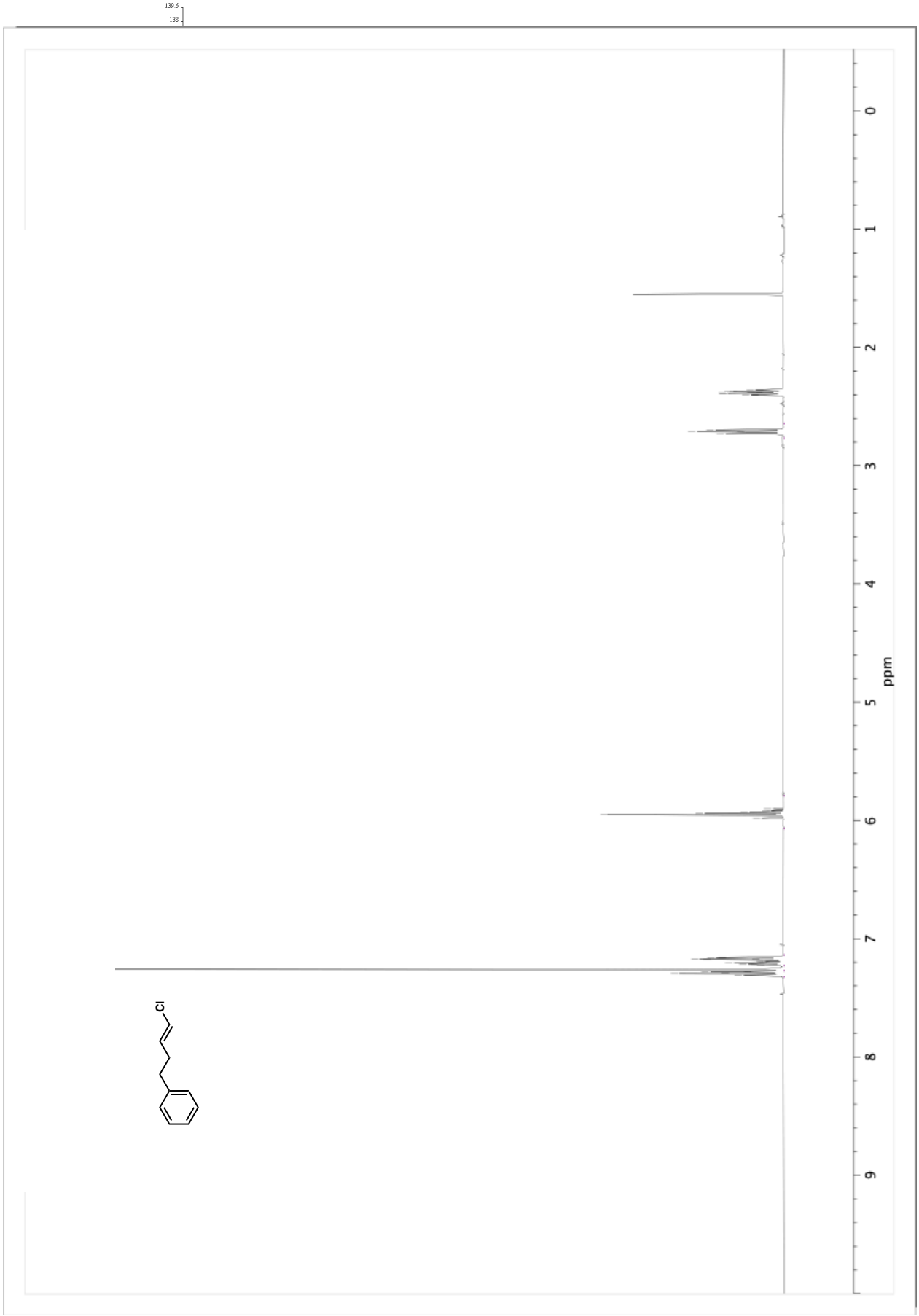

Figure A4.26. *^1H NMR (500 MHz, $CDCl_3$) of* ***99***.

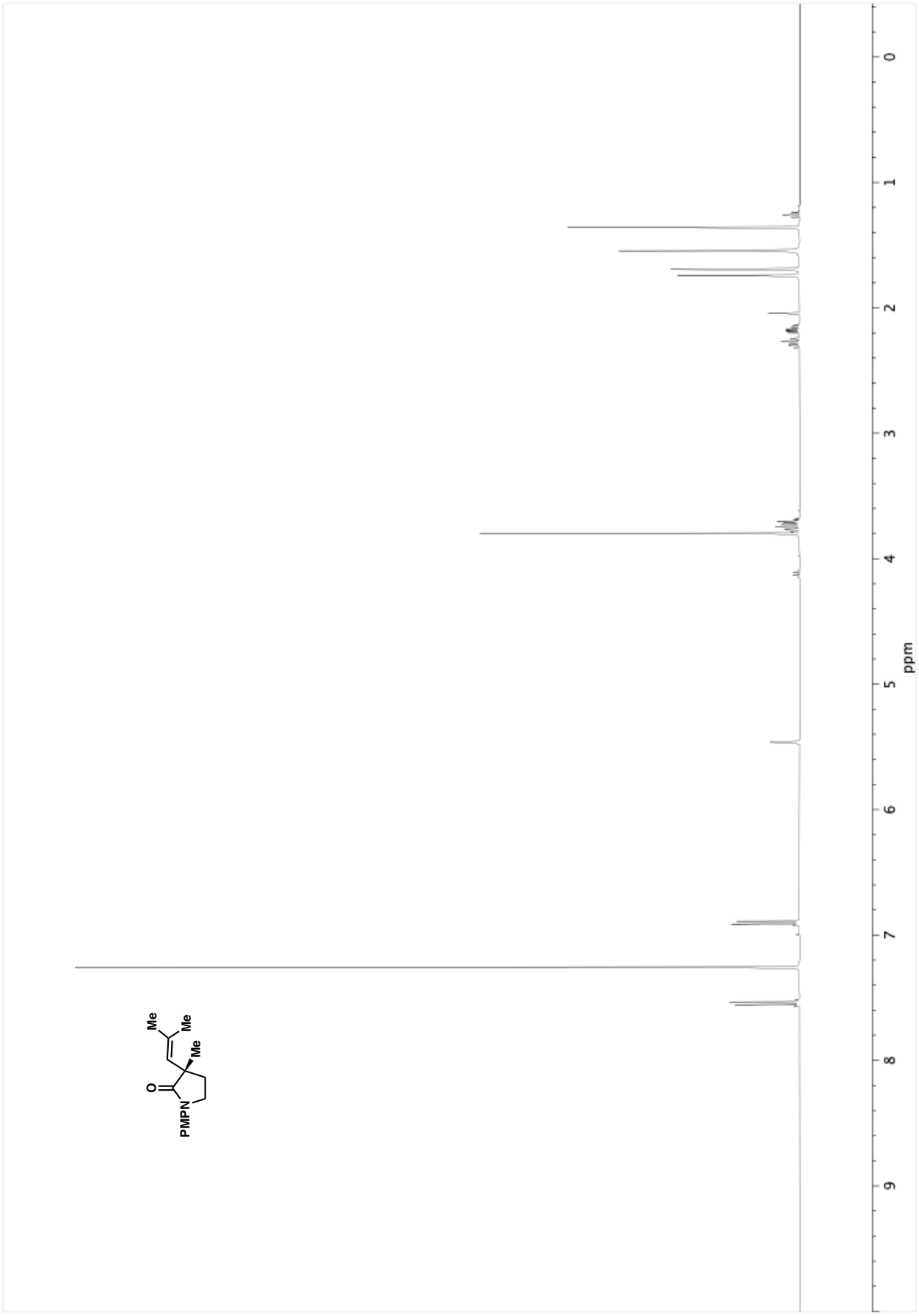

Figure A4.27. *^1H NMR (400 MHz, $CDCl_3$) of* ***87****.*

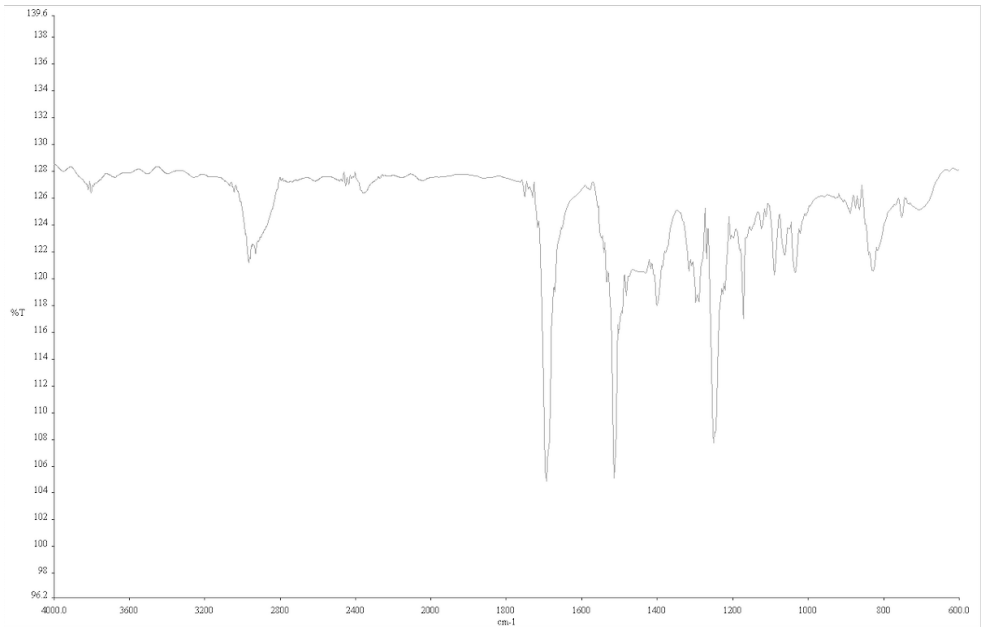

Figure A4.28. *Infrared spectrum (Thin Film, NaCl) of* ***87****.*

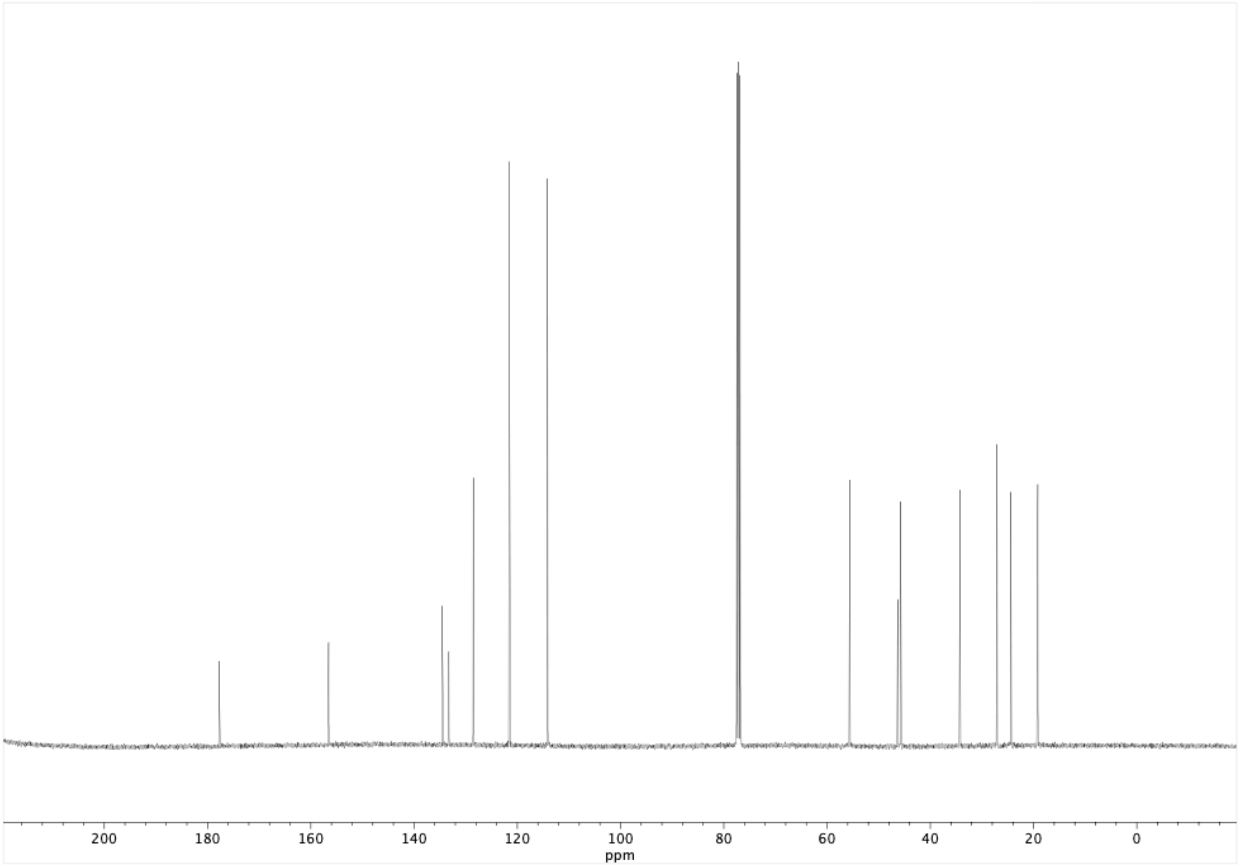

Figure A4.29. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***87****.*

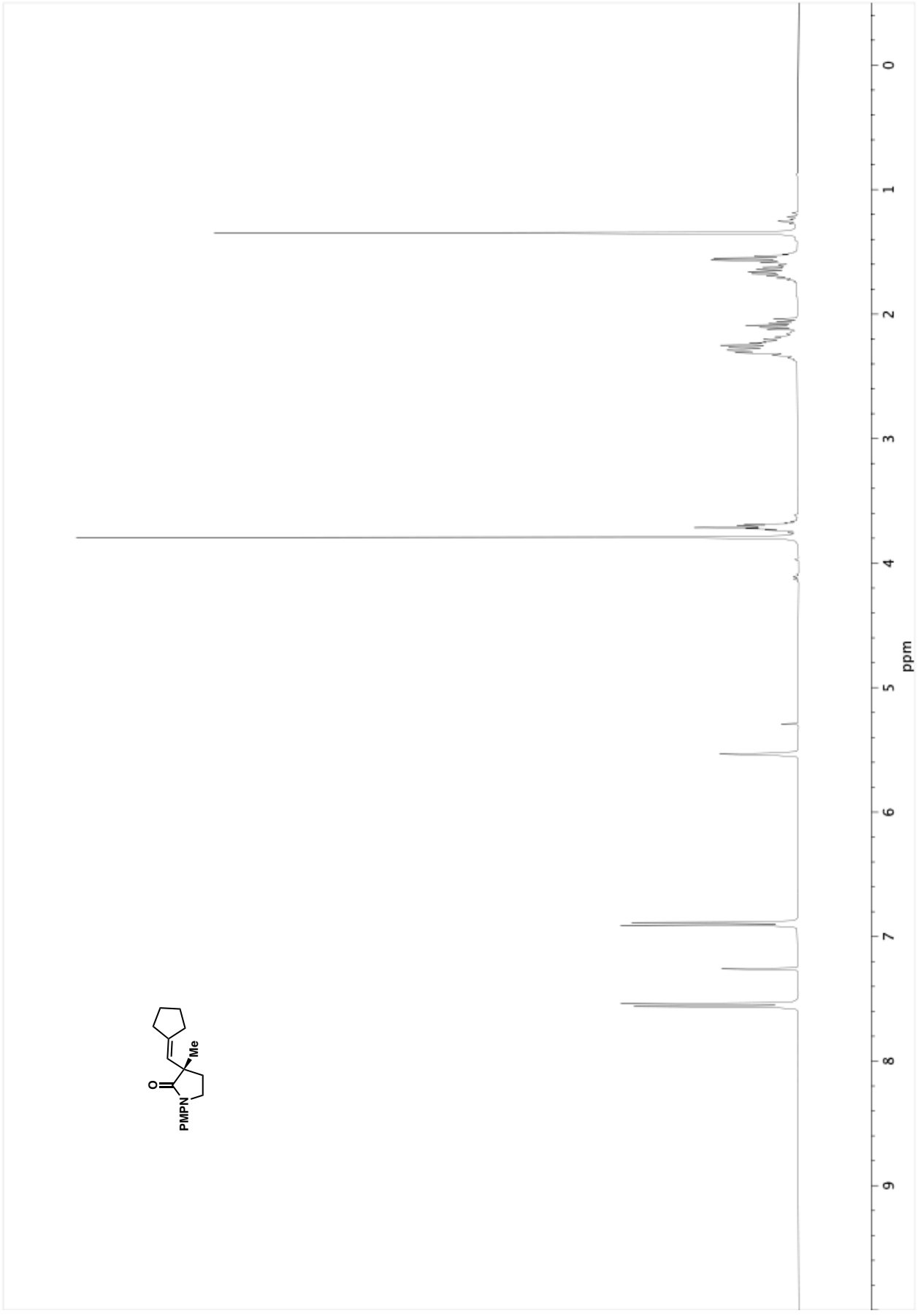

Figure A4.30. *^{1}H NMR (400 MHz, $CDCl_3$) of **88**.*

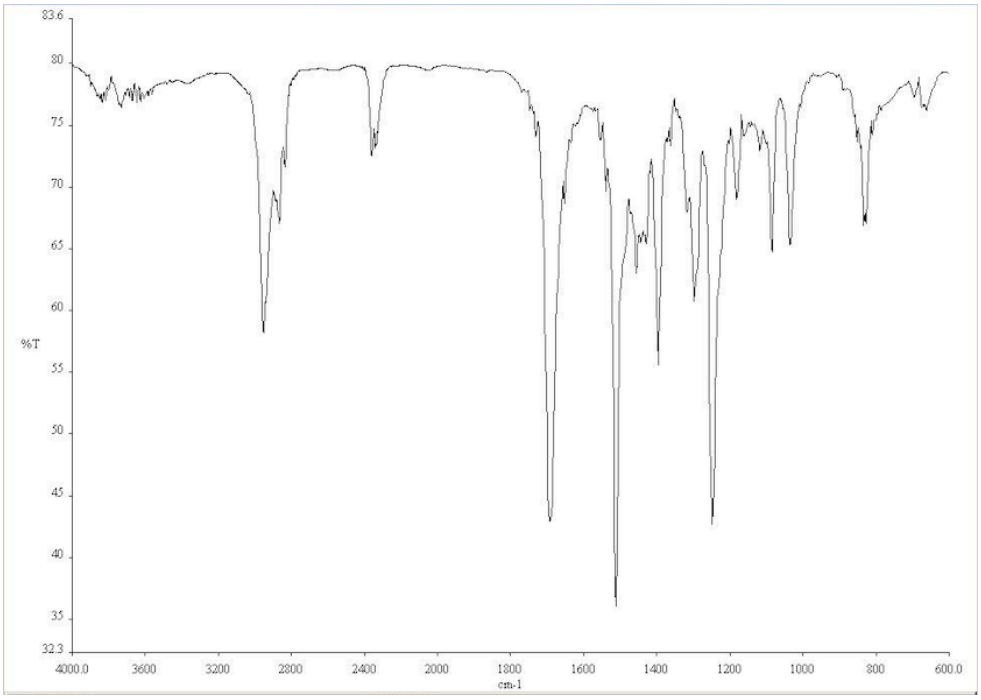

Figure A4.31. *Infrared spectrum (Thin Film, NaCl) of* ***88****.*

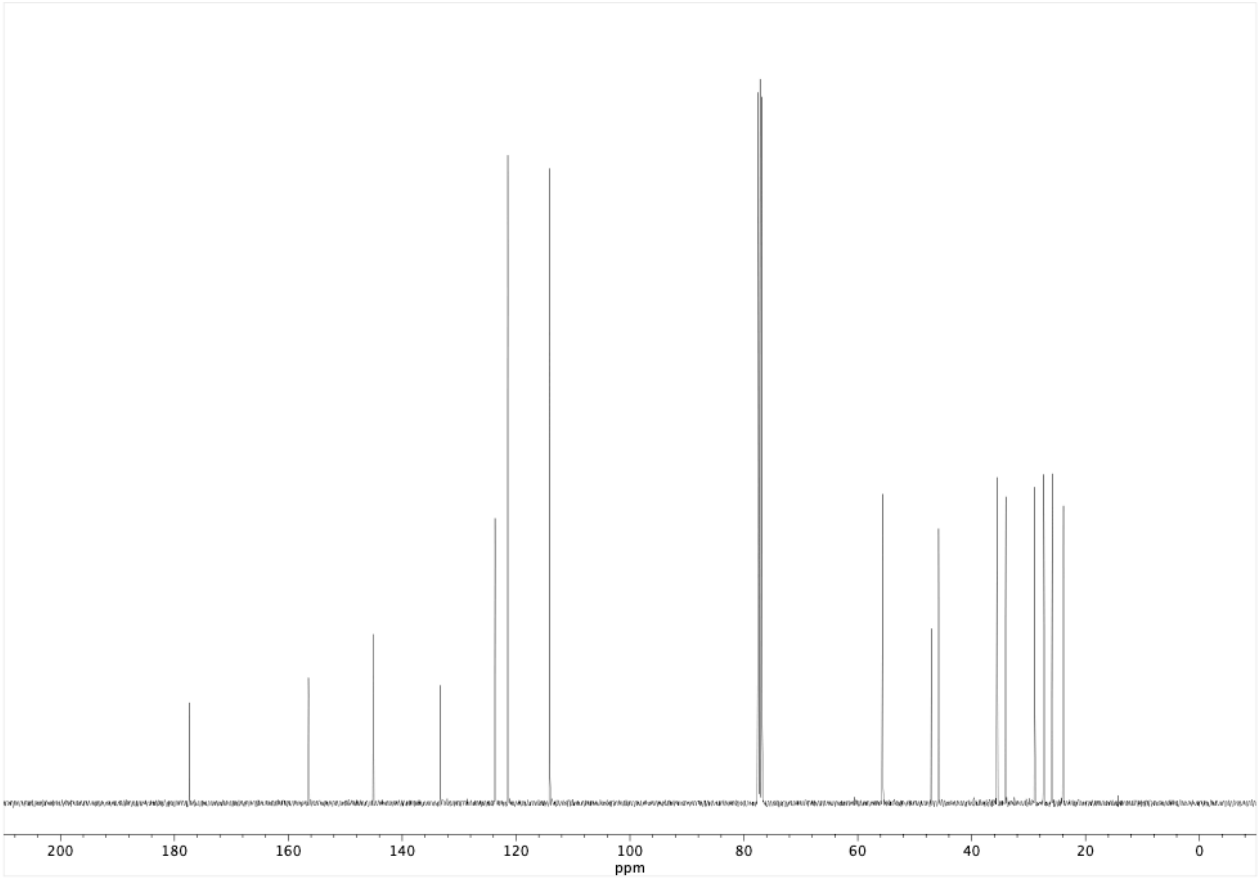

Figure A4.32. *^{13}C NMR (100 MHz, $CDCl_3$) of compound* ***88****.*

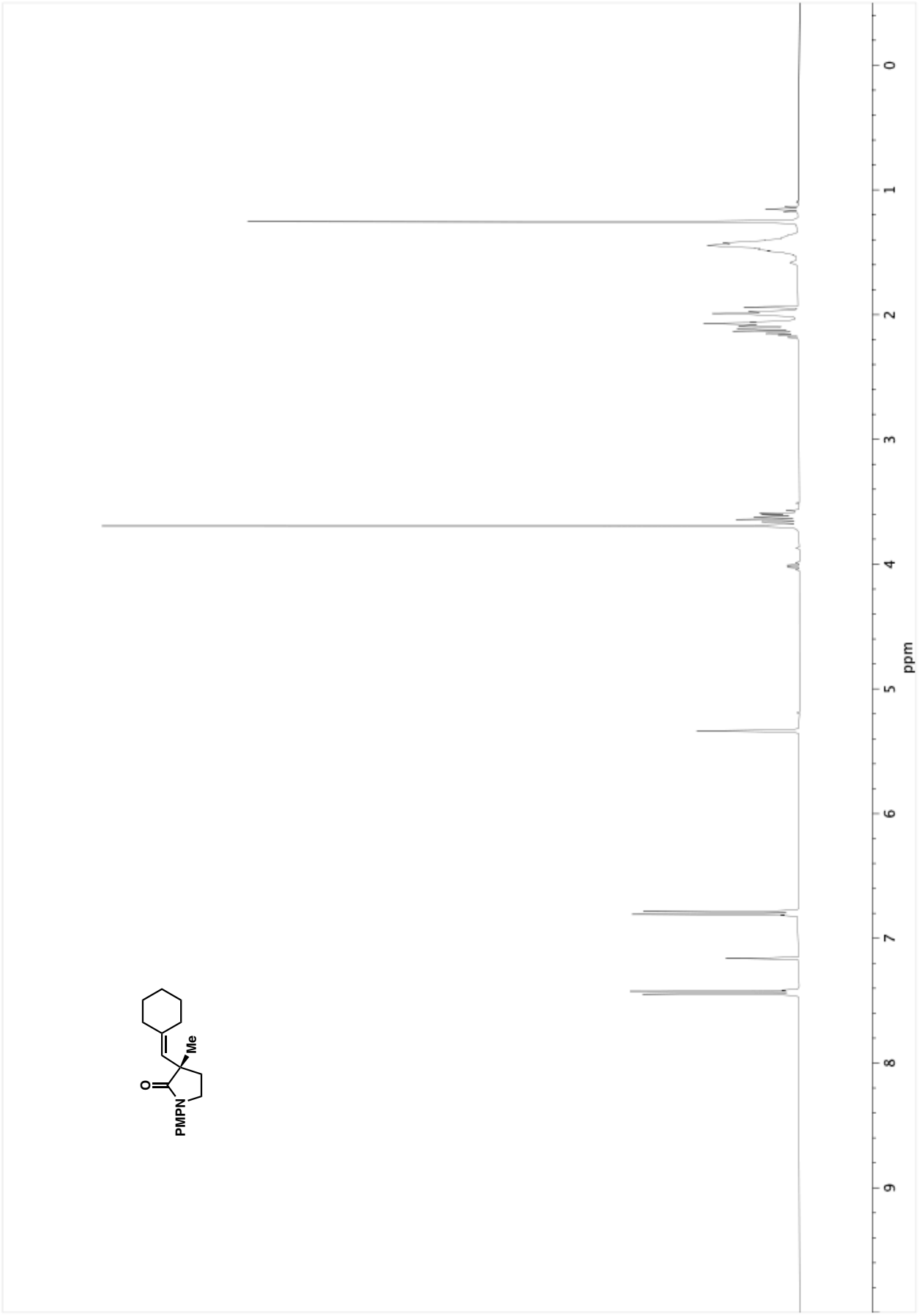

Figure A4.33. *^1H NMR (400 MHz, $CDCl_3$) of* ***89***.

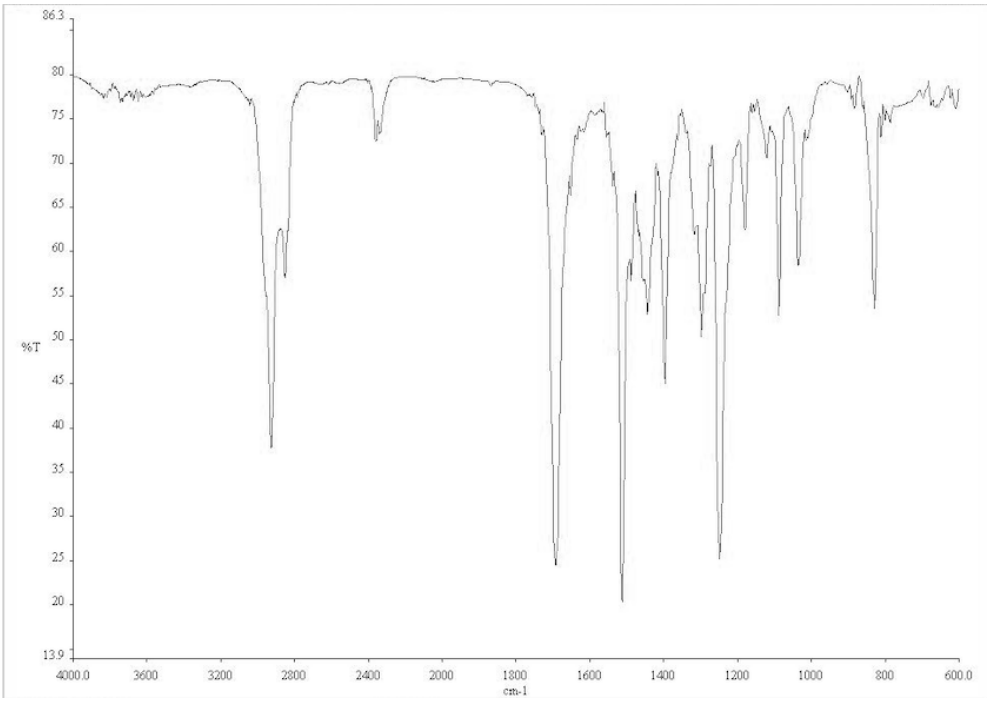

Figure A4.34. *Infrared spectrum (Thin Film, NaCl) of* ***89****.*

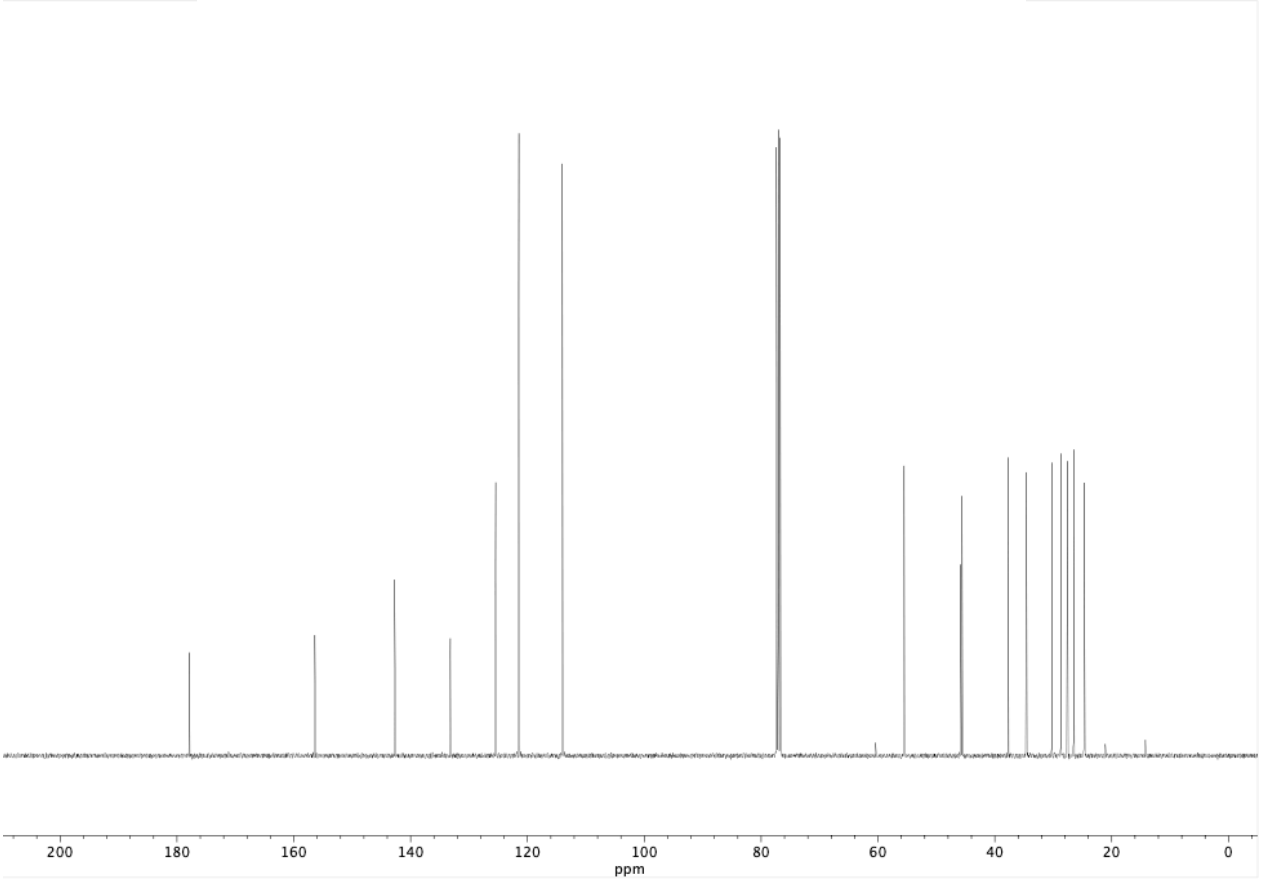

Figure A4.35. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***89.***

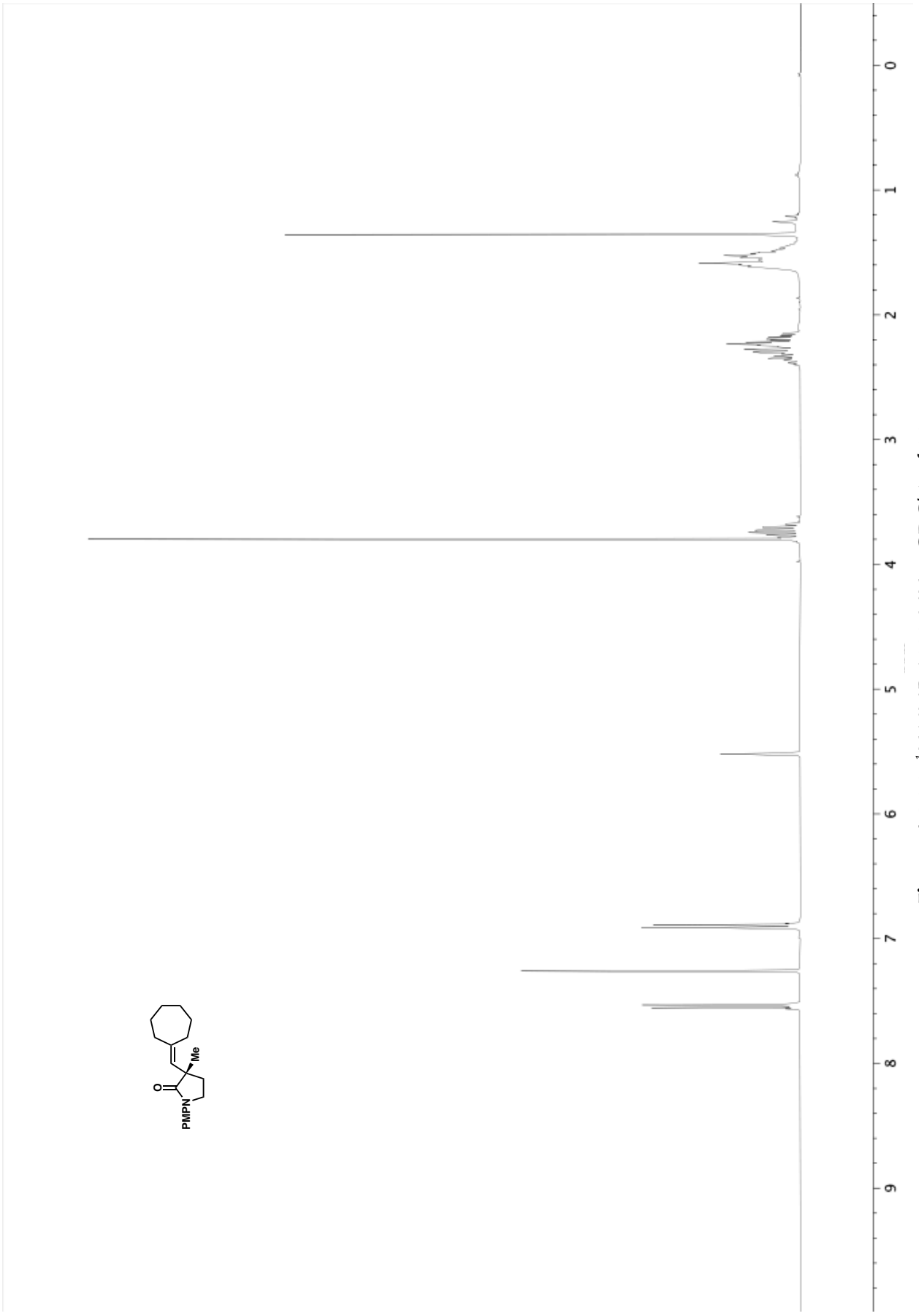

Figure A4.36. *^{1}H NMR (400 MHz, $CDCl_3$) of* ***90****.*

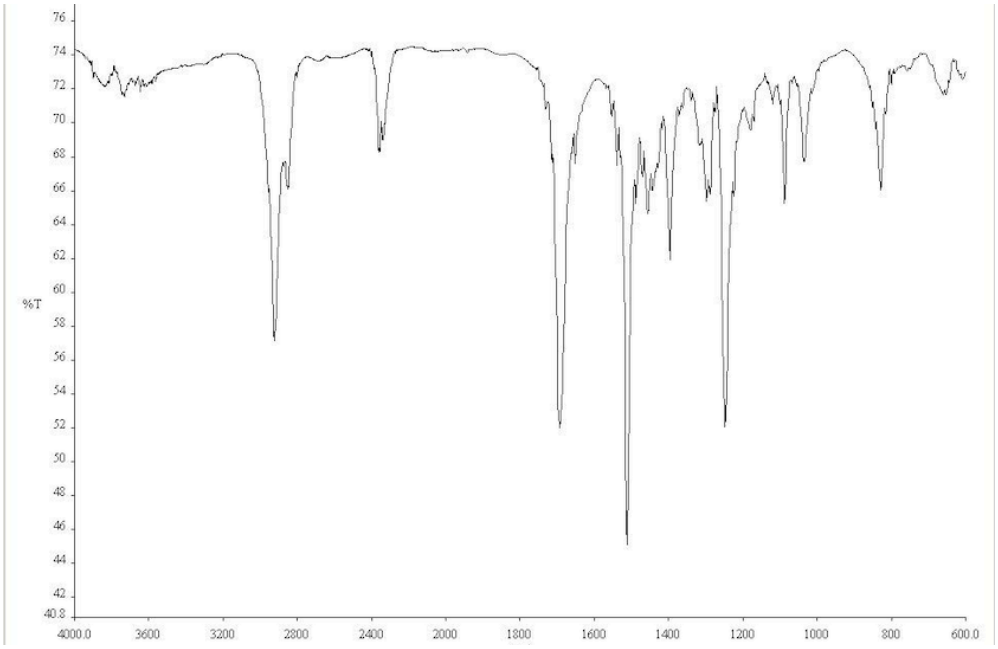

Figure A4.37. *Infrared spectrum (Thin Film, NaCl) of* ***90****.*

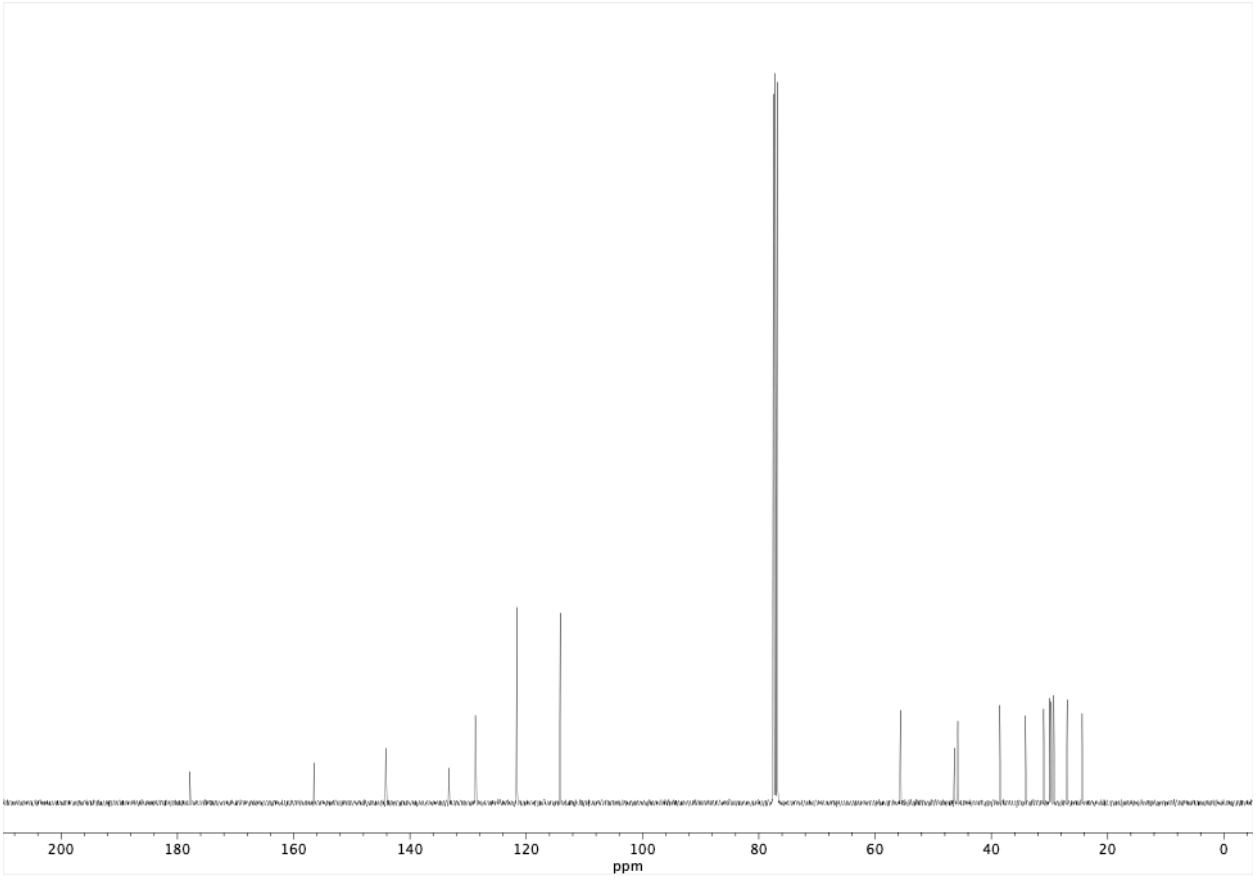

Figure A4.38. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***90****.*

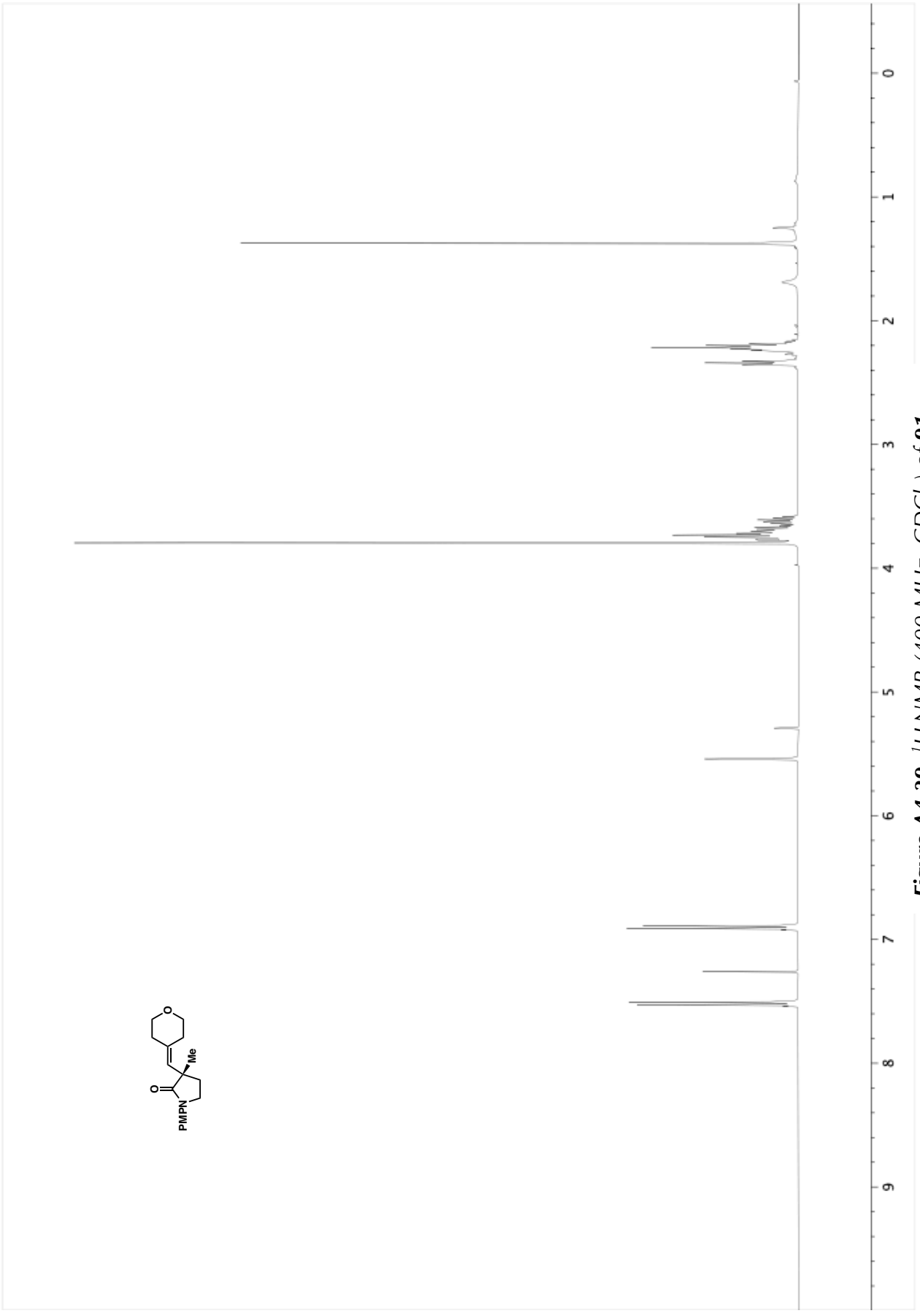

Figure A4.39. *^{1}H NMR (400 MHz, $CDCl_3$) of* ***91****.*

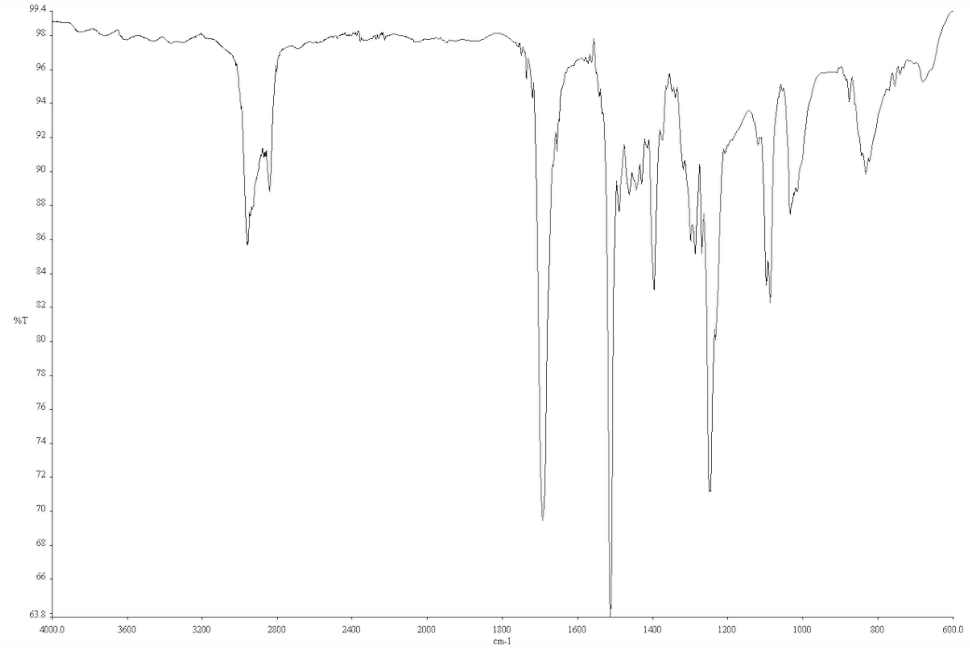

Figure A4.40. *Infrared spectrum (Thin Film, NaCl) of* ***91****.*

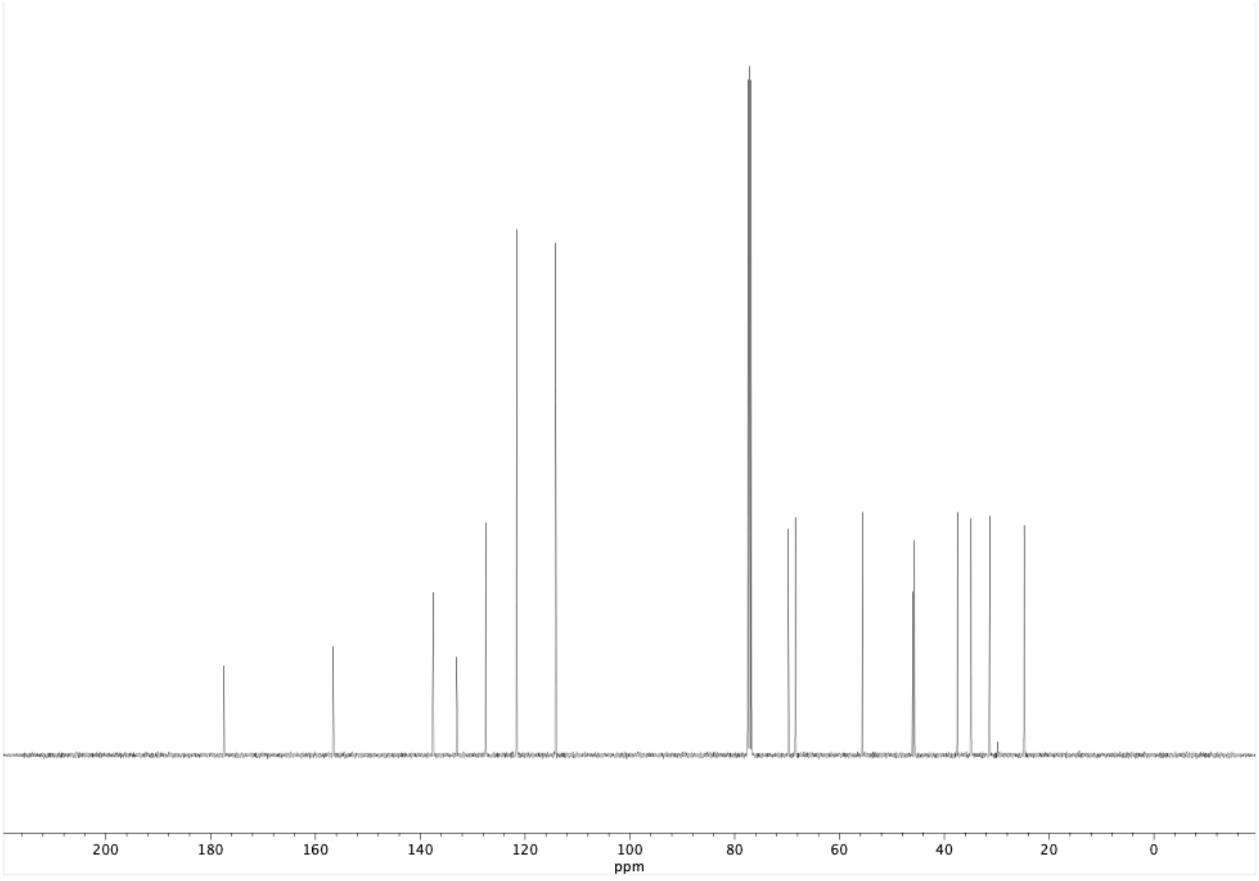

Figure A4.41. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***91****.*

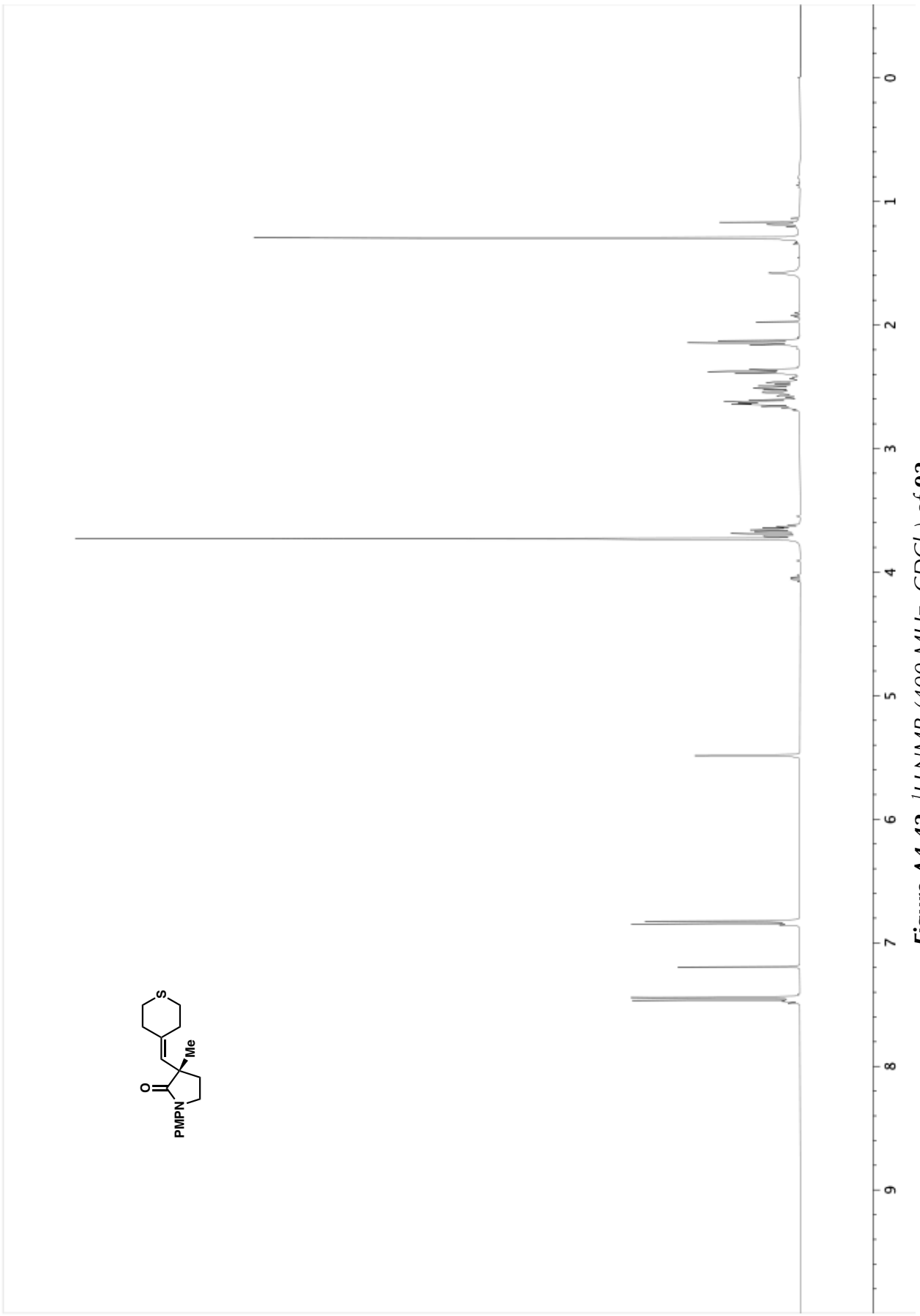

Figure A4.42. *^1H NMR (400 MHz, $CDCl_3$) of* ***92****.*

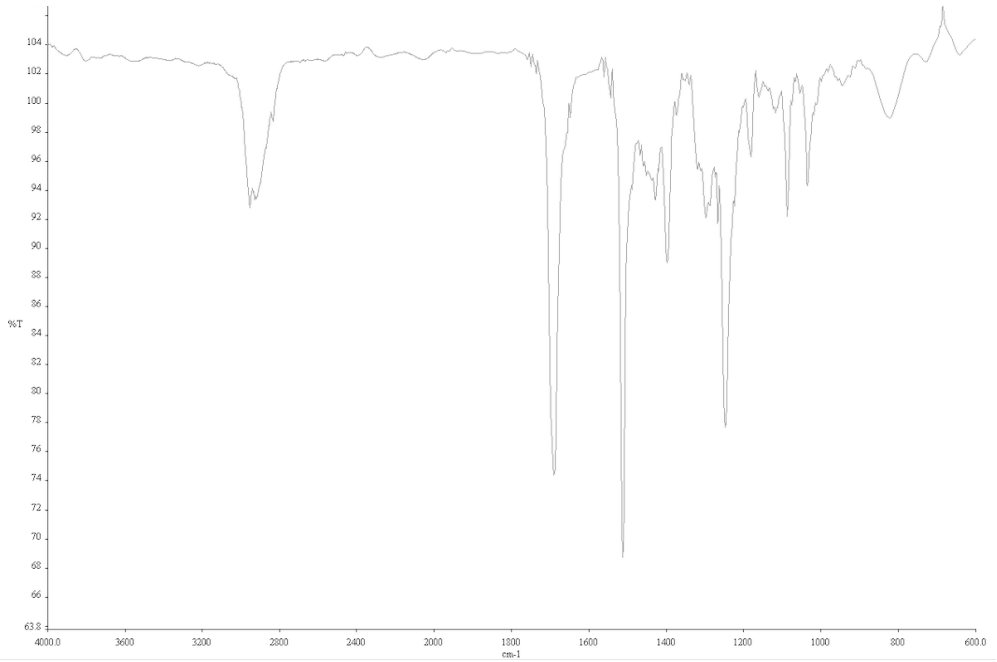

Figure A4.43. *Infrared spectrum (Thin Film, NaCl) of* ***92****.*

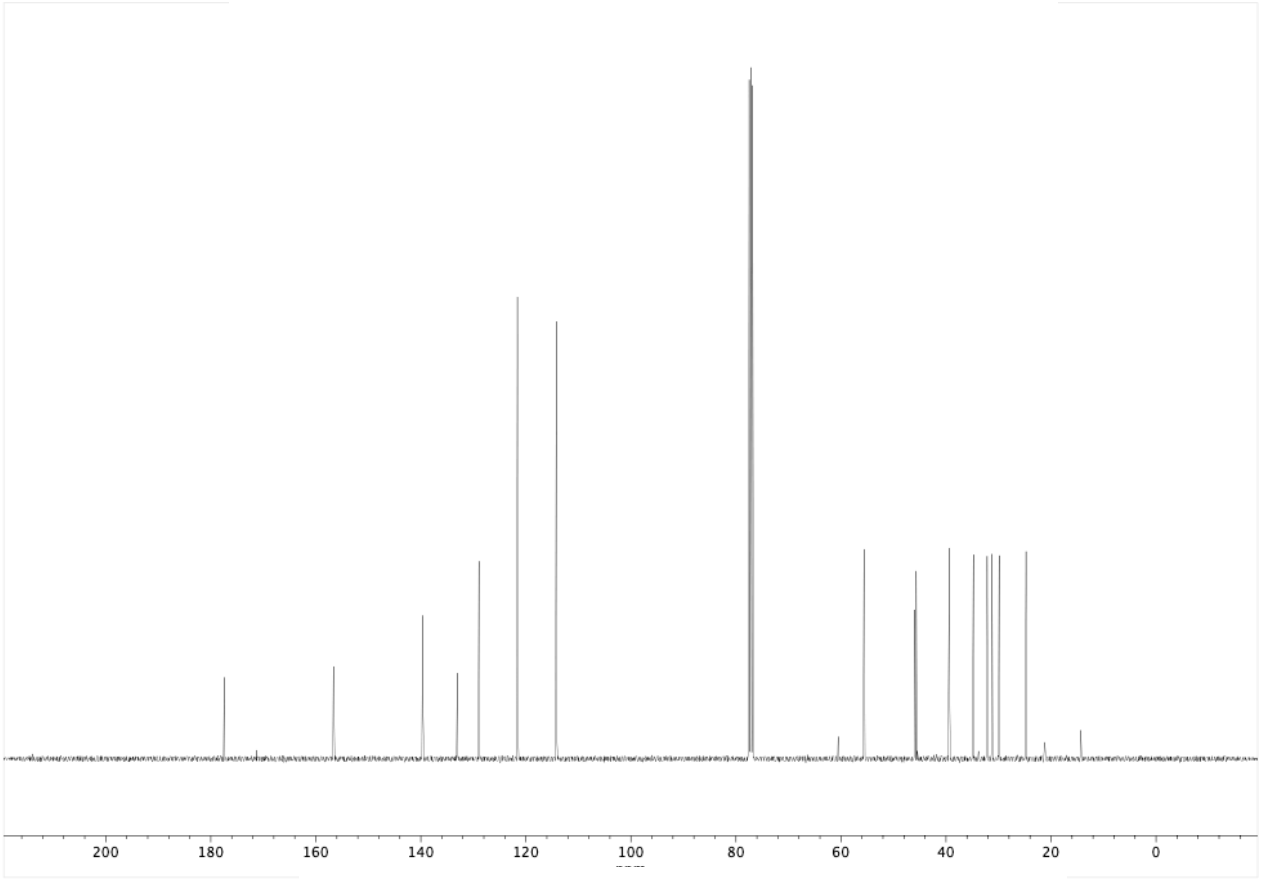

Figure A4.44. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***92****.*

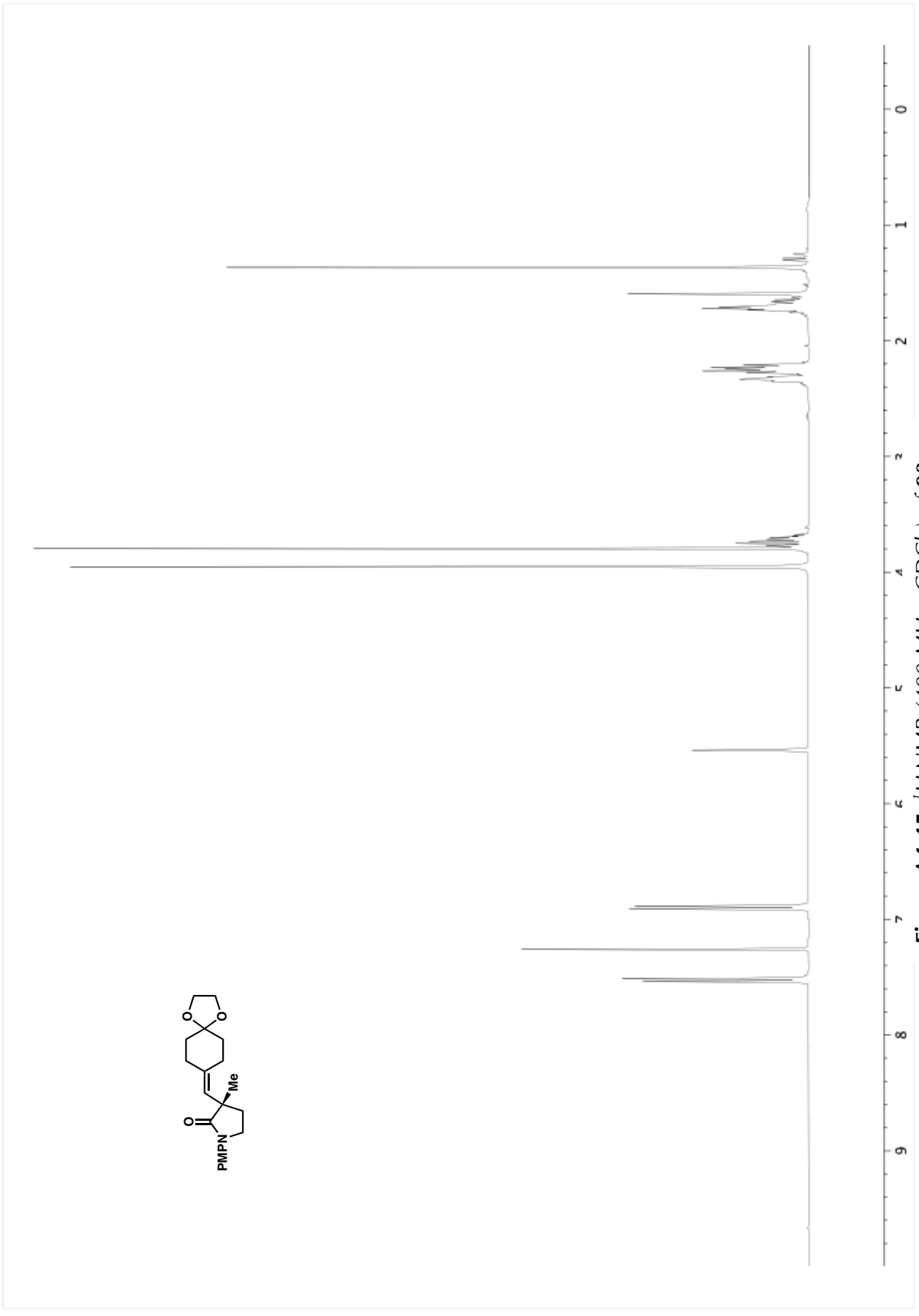

Figure A4.45. *^1H NMR (400 MHz, $CDCl_3$) of* ***93****.*

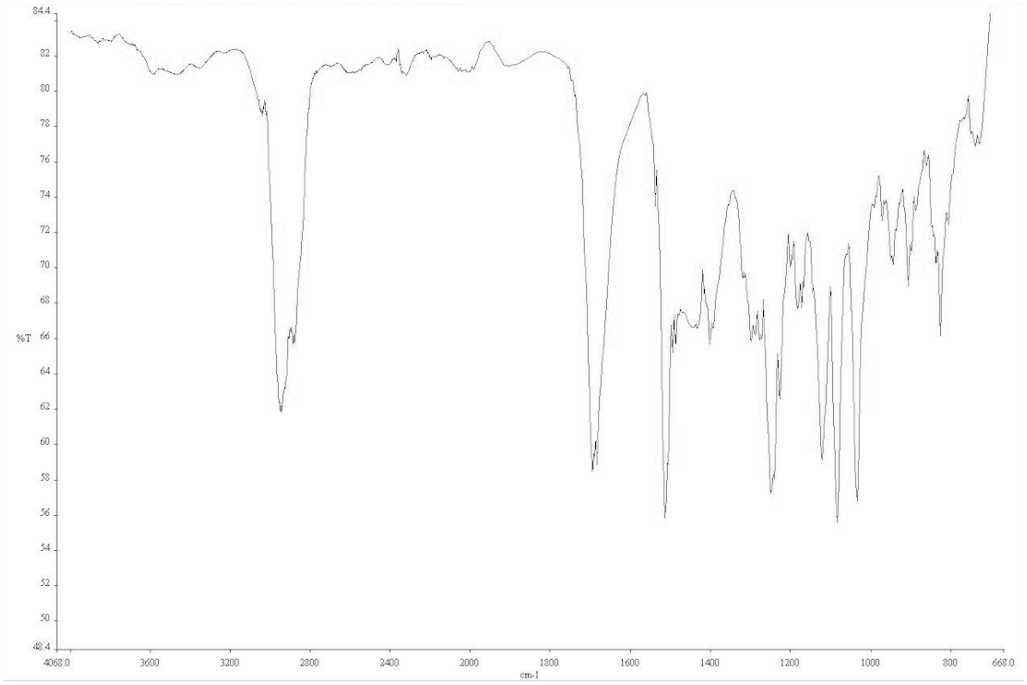

Figure A4.46. *Infrared spectrum (Thin Film, NaCl) of* ***93.***

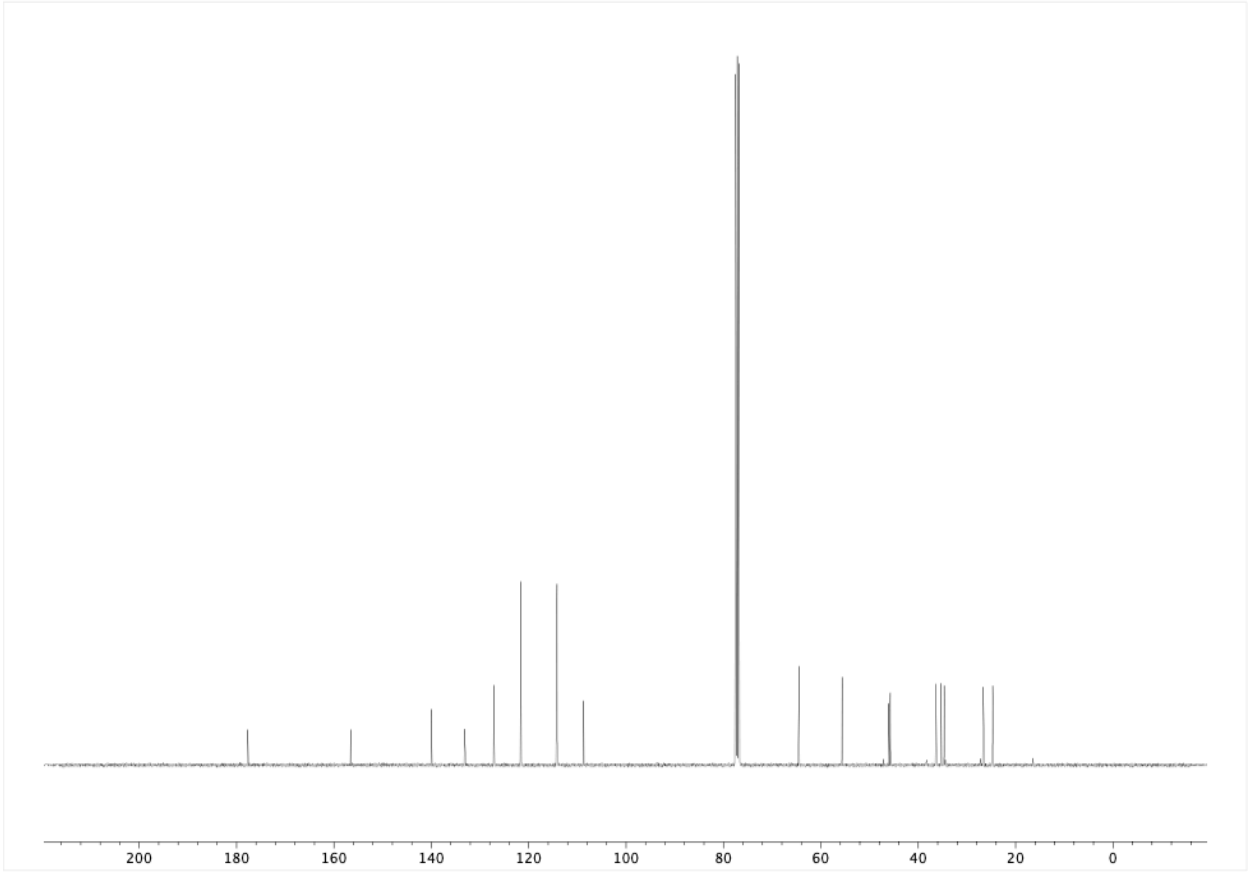

Figure A4.47. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***93****.*

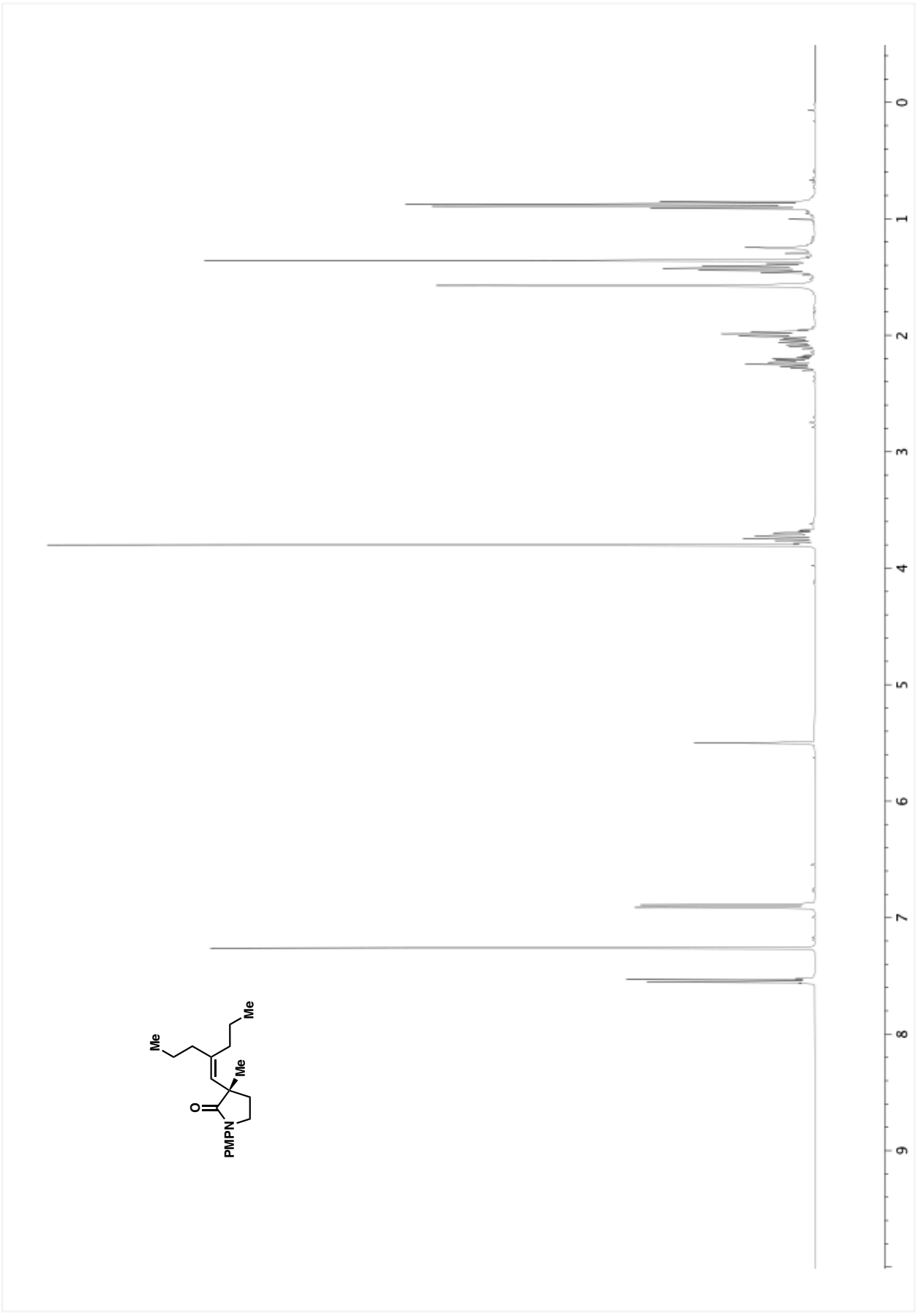

Figure A4.48. *^1H NMR (400 MHz, $CDCl_3$) of* ***94.***

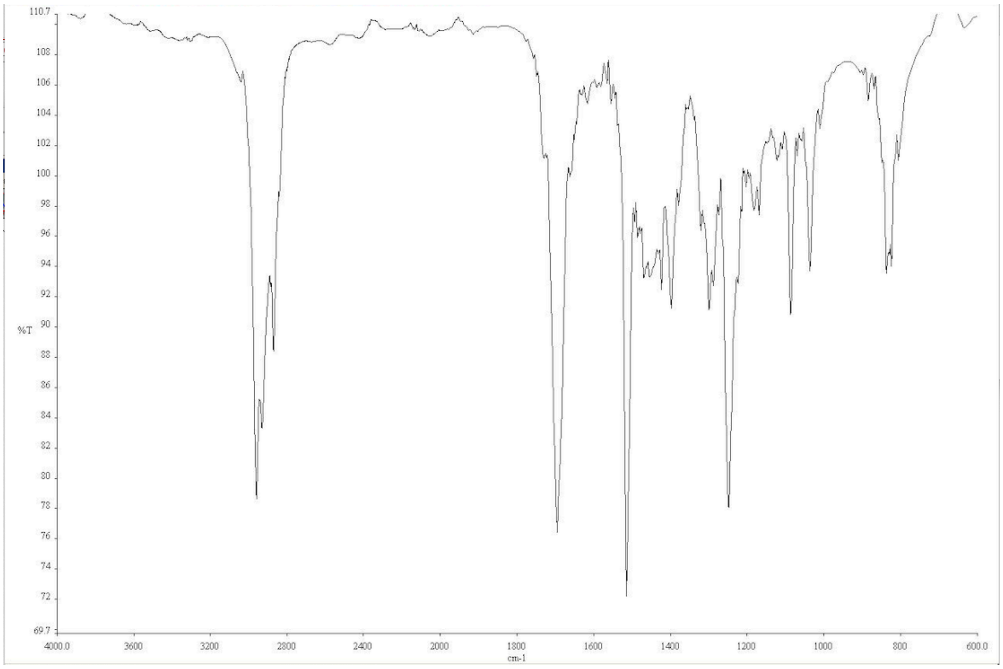

Figure A4.49. *Infrared spectrum (Thin Film, NaCl) of* ***94****.*

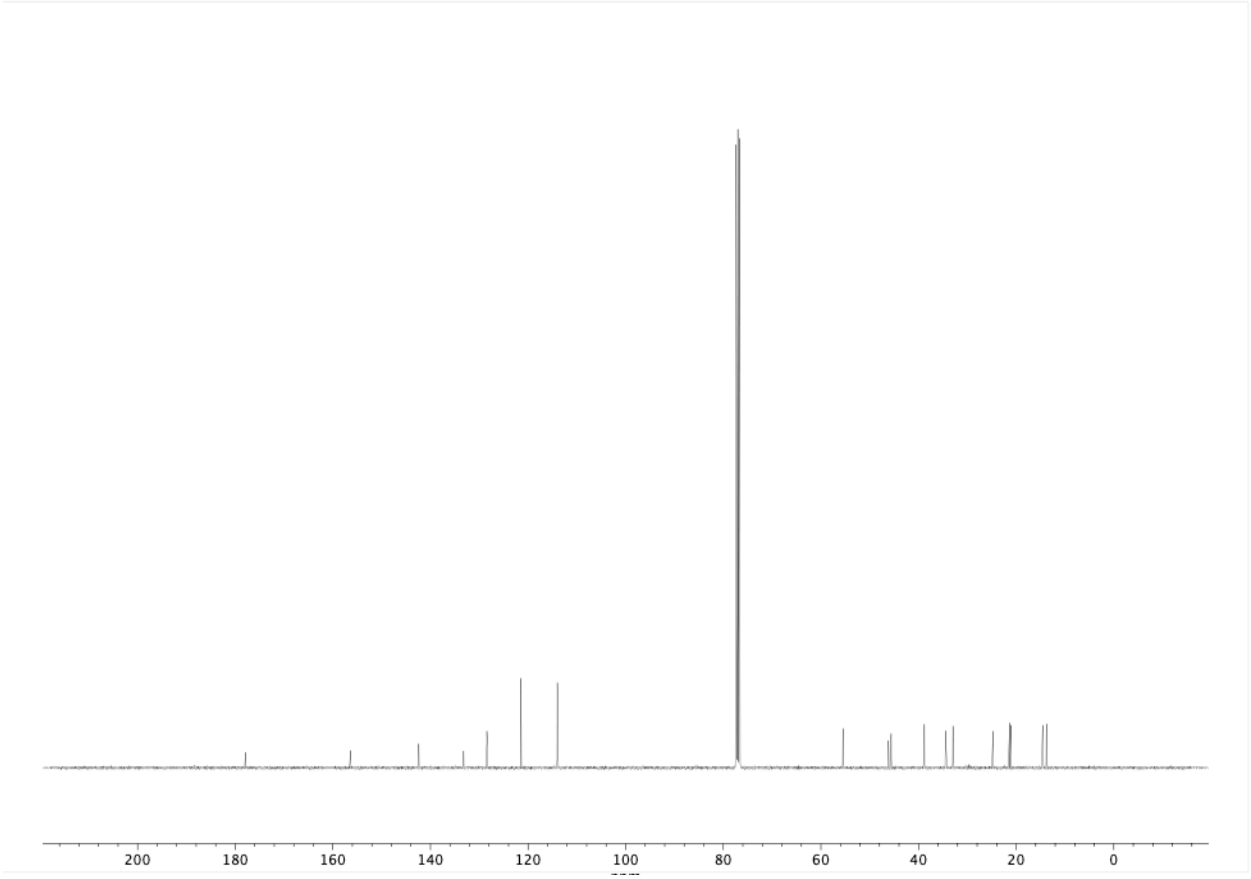

Figure A4.50. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***94****.*

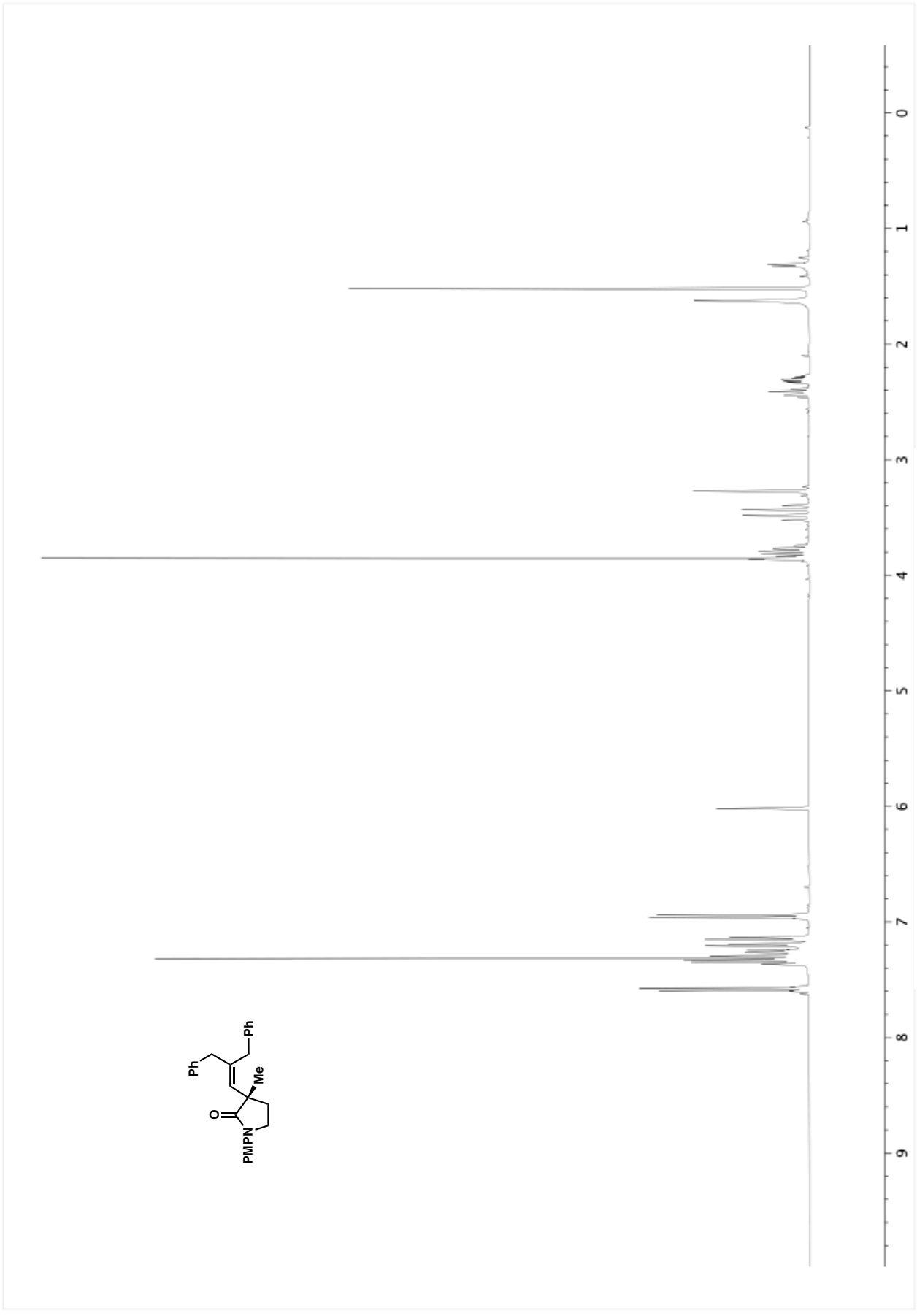

Figure A4.51. *^1H NMR (400 MHz, $CDCl_3$) of **95**.*

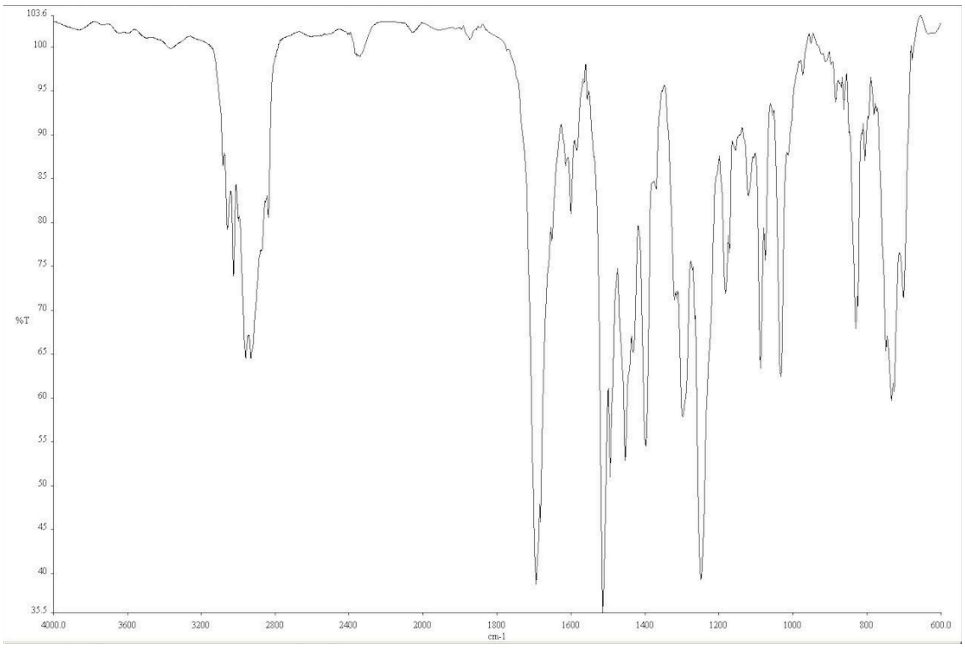

Figure A4.52. *Infrared spectrum (Thin Film, NaCl) of* ***95****.*

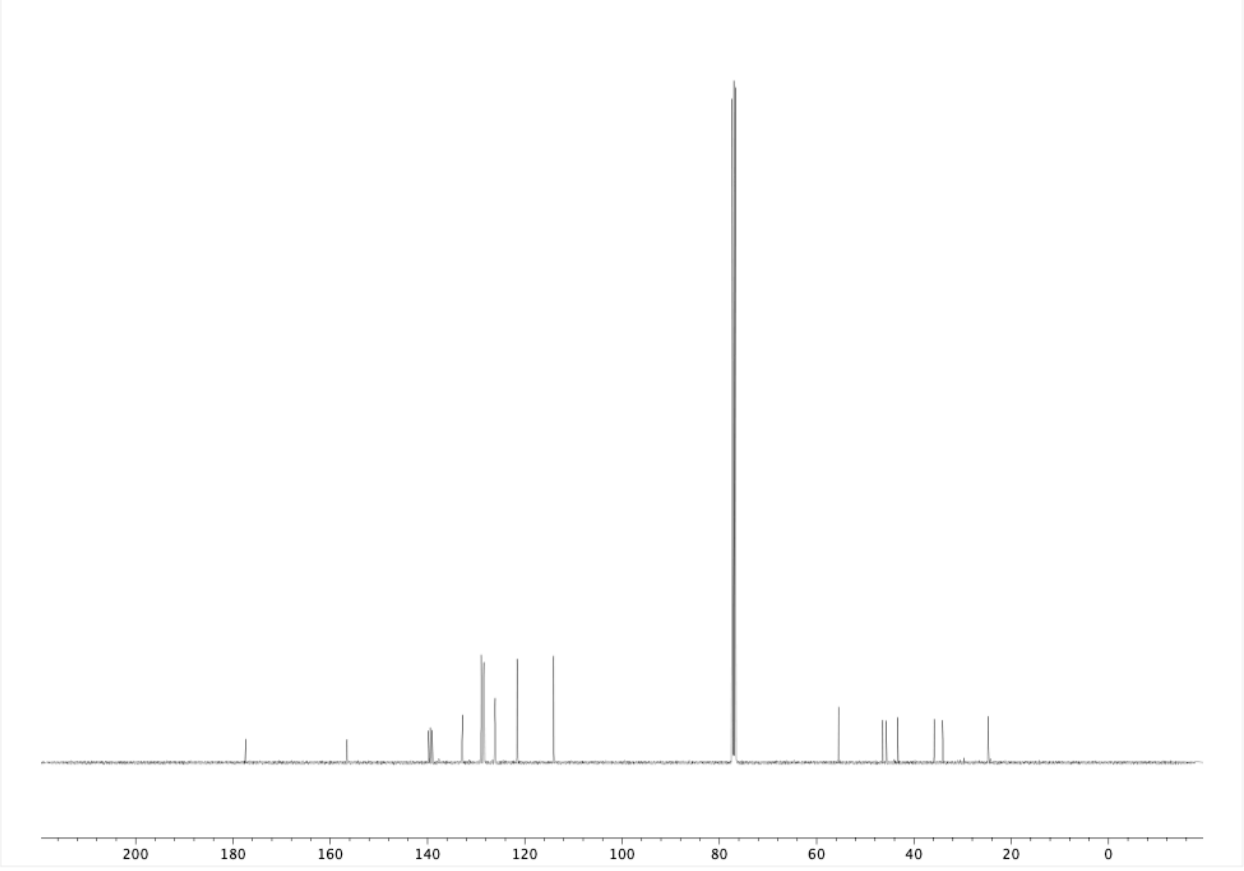

Figure A4.53. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***95****.*

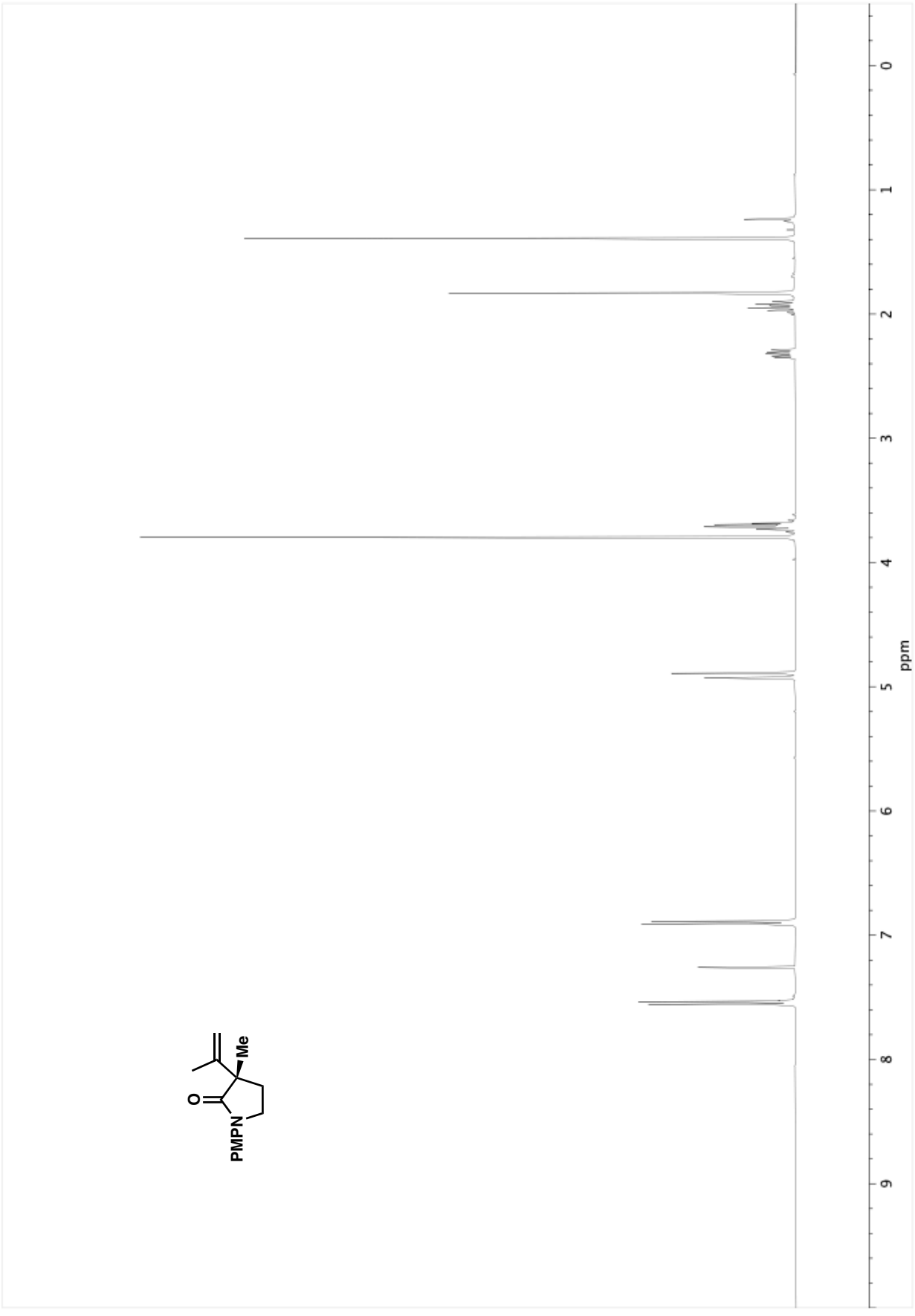

Figure A4.54. *^1H NMR (400 MHz, $CDCl_3$) of* ***98****.*

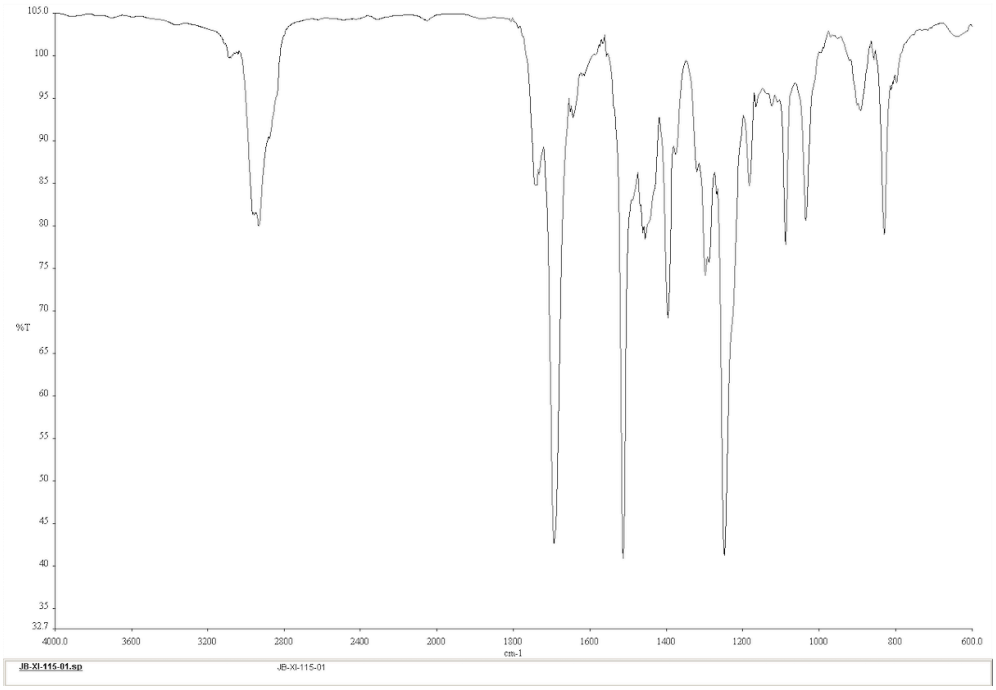

Figure A4.55. *Infrared spectrum (Thin Film, NaCl) of* ***98****.*

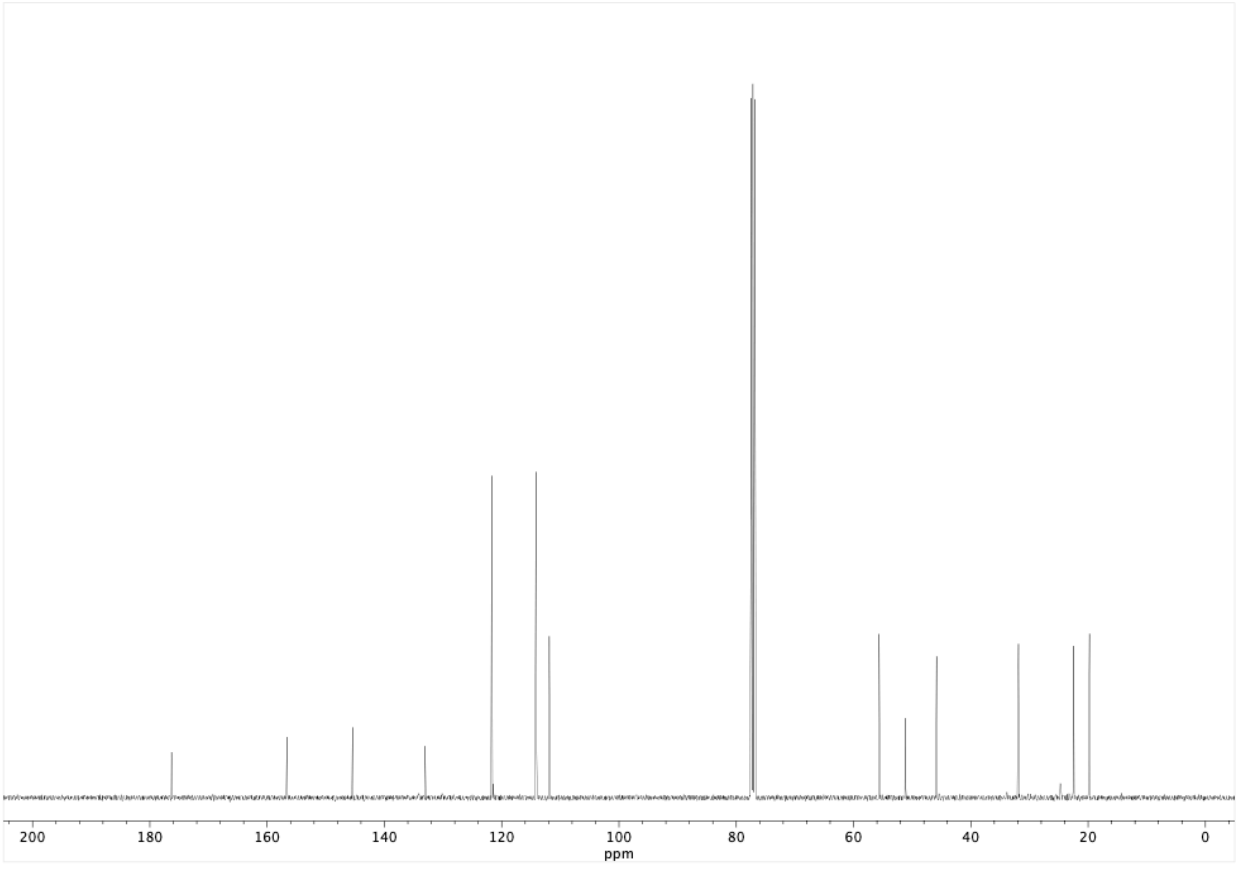

Figure A4.56. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***98****.*

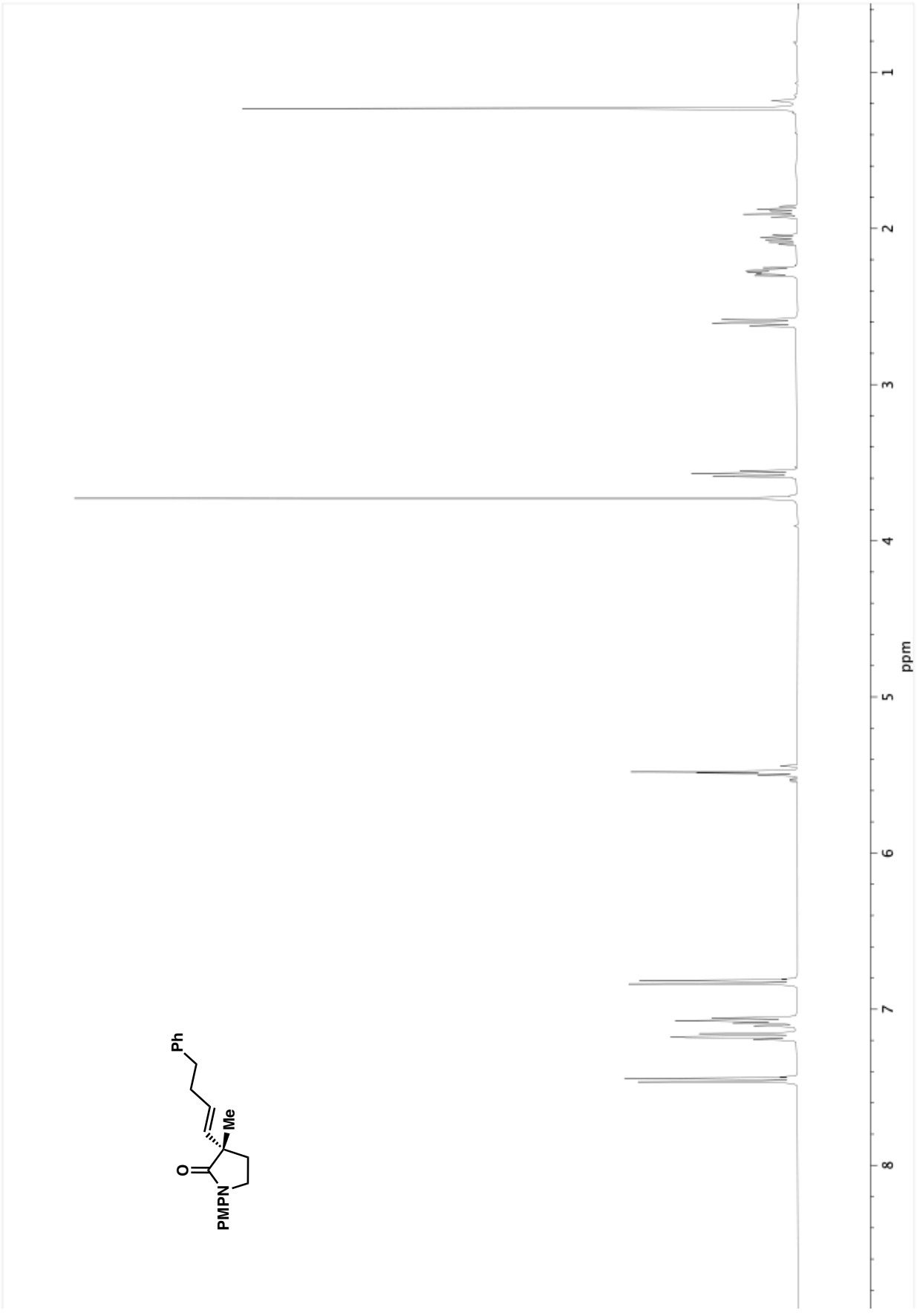

Figure A4.57. *^1H NMR (500 MHz, $CDCl_3$) of* ***100****.*

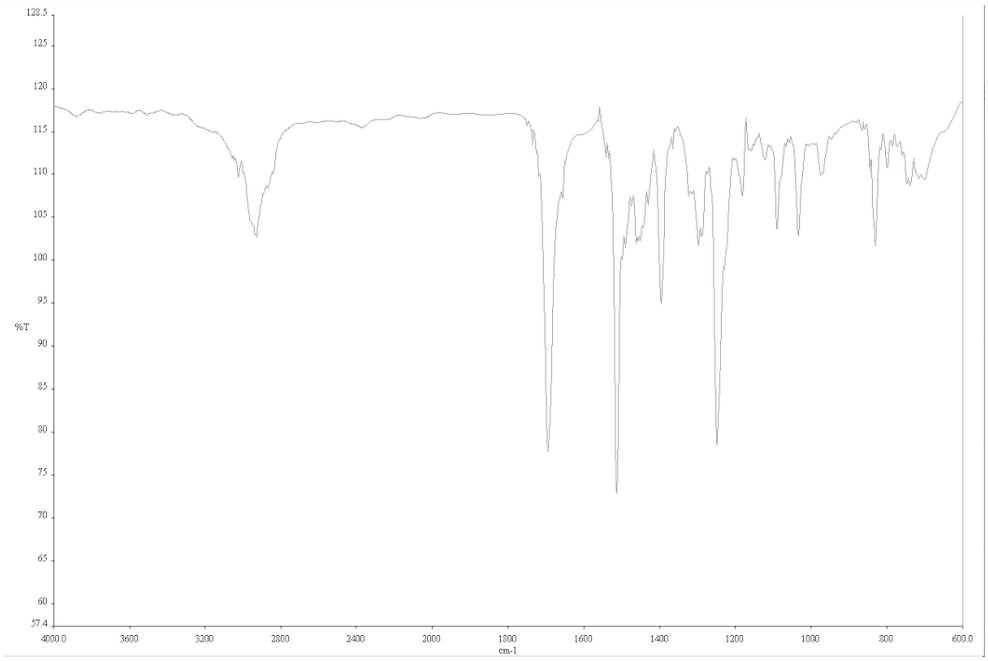

Figure A4.58. *Infrared spectrum (Thin Film, NaCl) of*

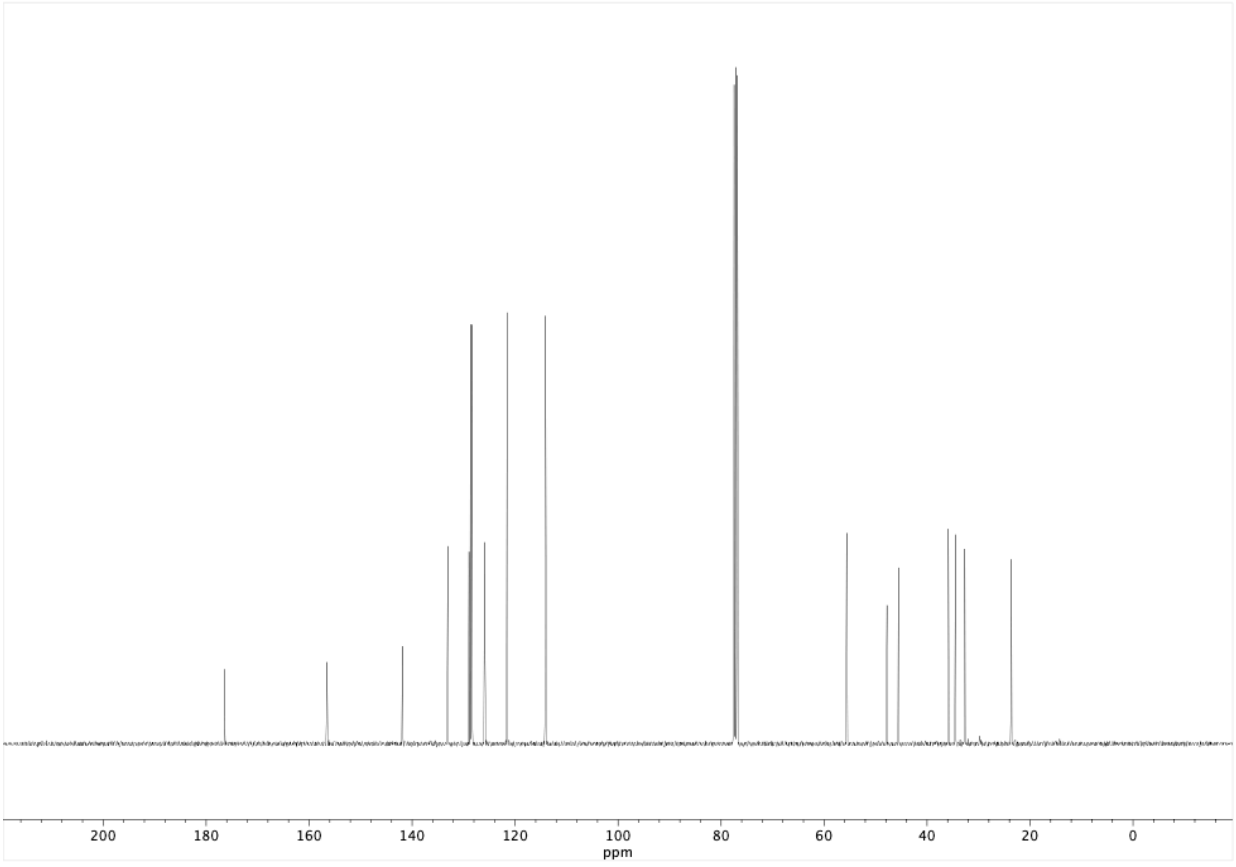

Figure A4.59. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***100****.*

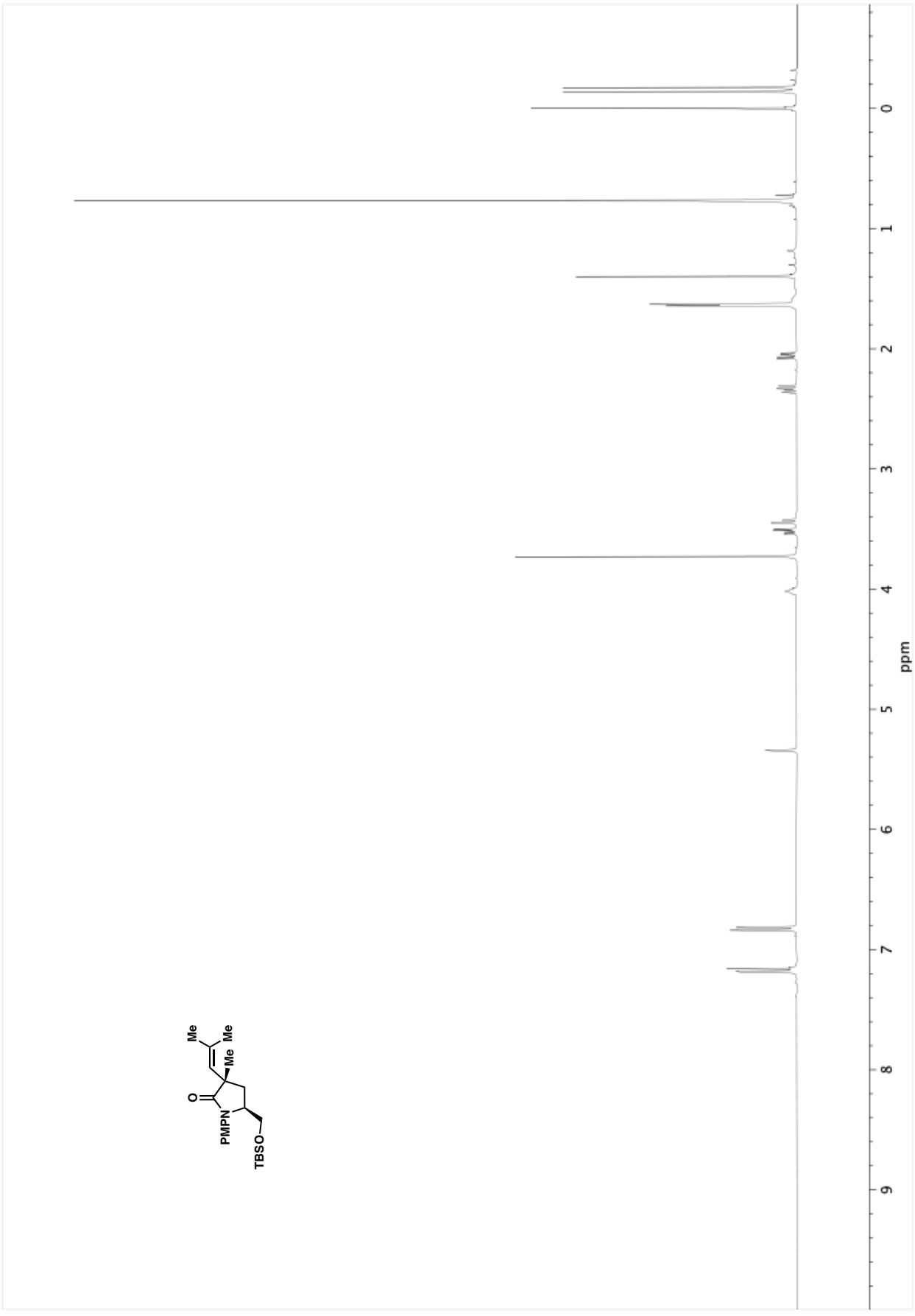

Figure A4.60. *^1H NMR (400 MHz, $CDCl_3$) of* ***96****.*

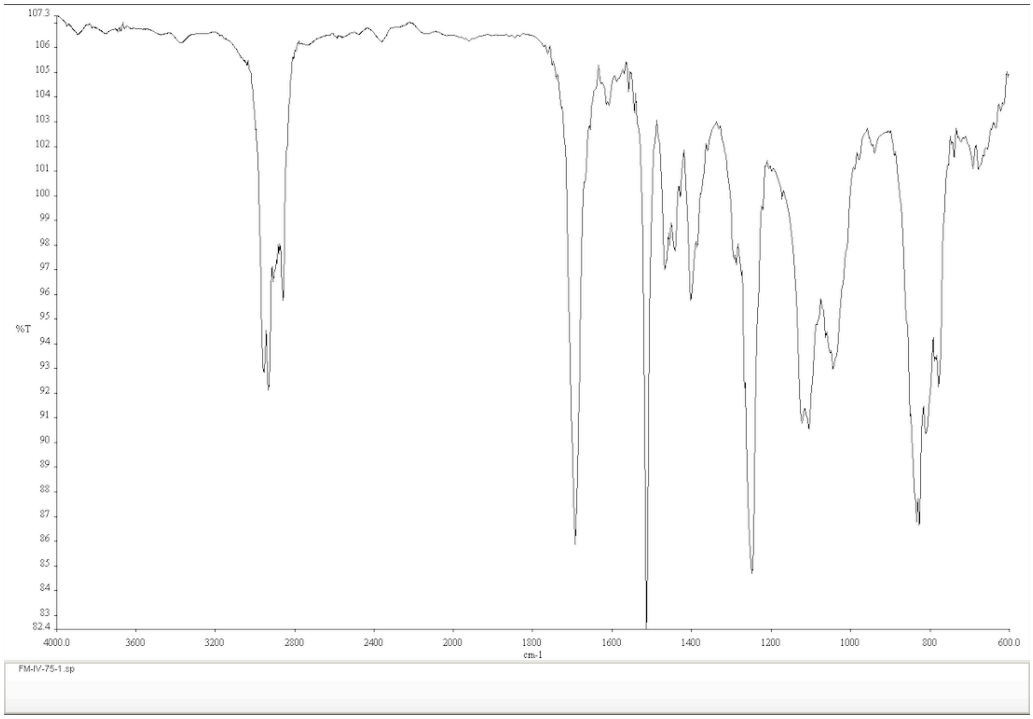

Figure A4.61. *Infrared spectrum (Thin Film, NaCl) of* ***96****.*

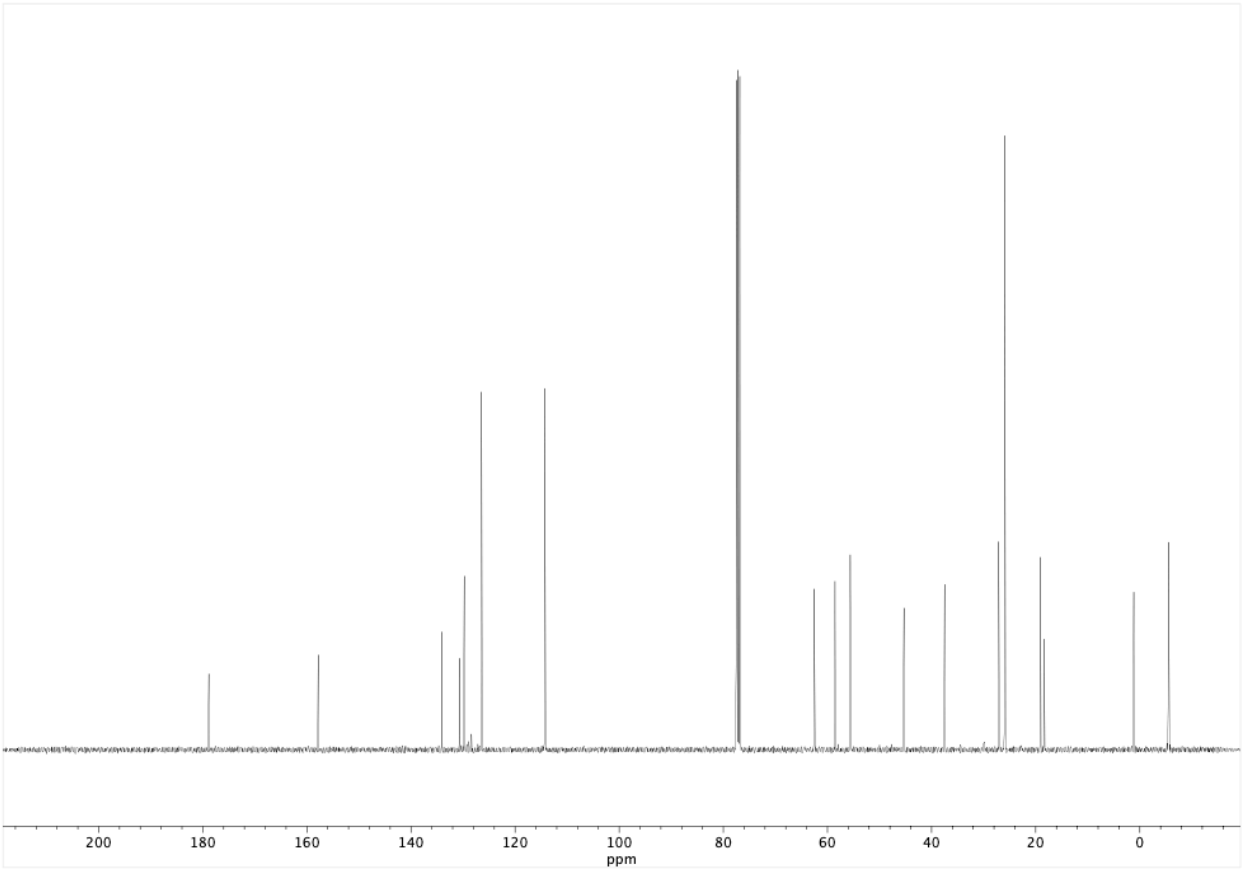

Figure A4.62. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***96****.*

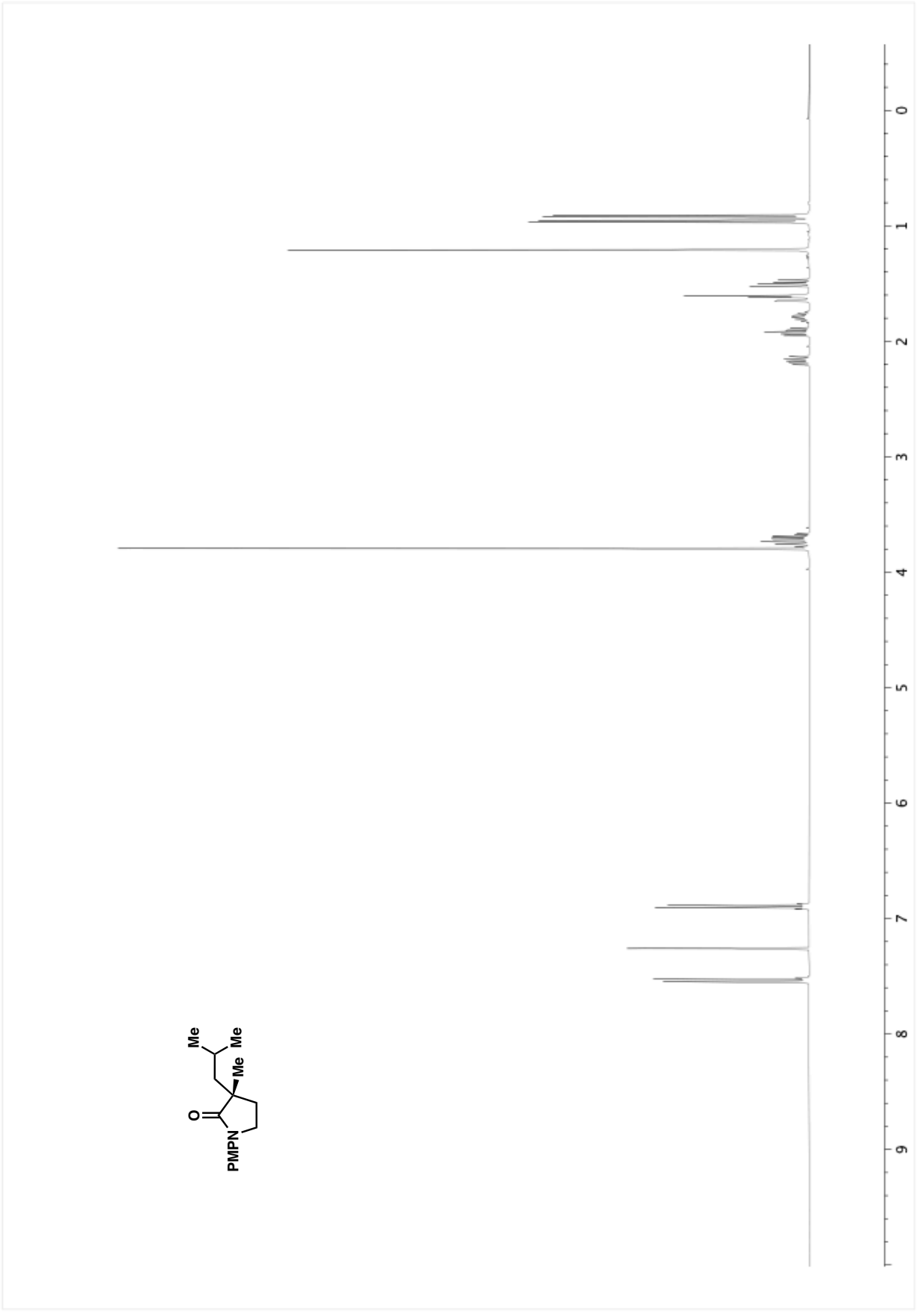

Figure A4.63. *^1H NMR (400 MHz, $CDCl_3$) of* ***101****.*

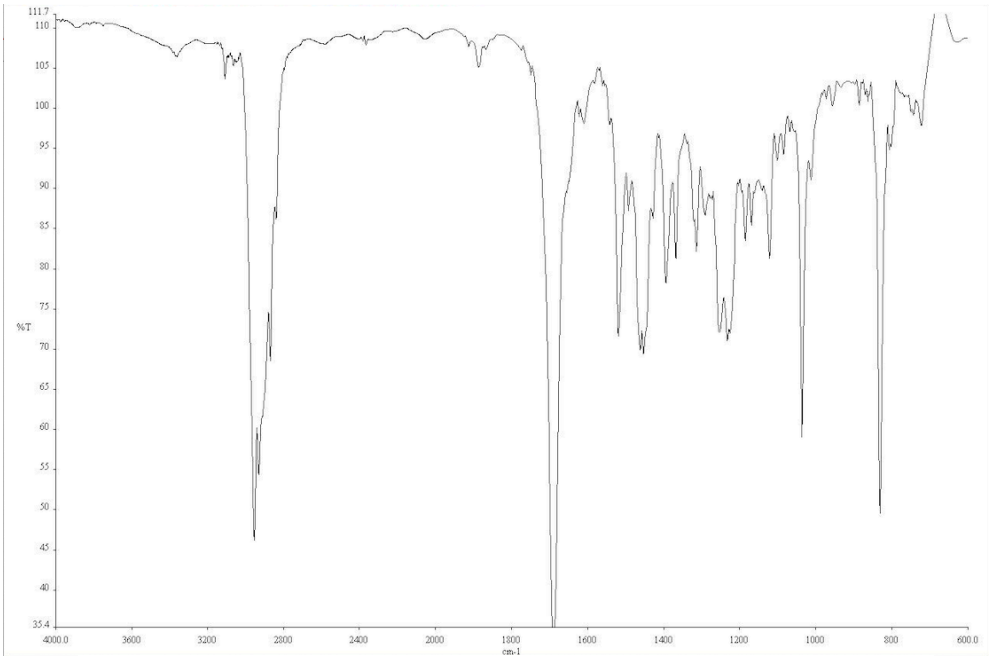

Figure A4.64. *Infrared spectrum (Thin Film, NaCl) of* ***101****.*

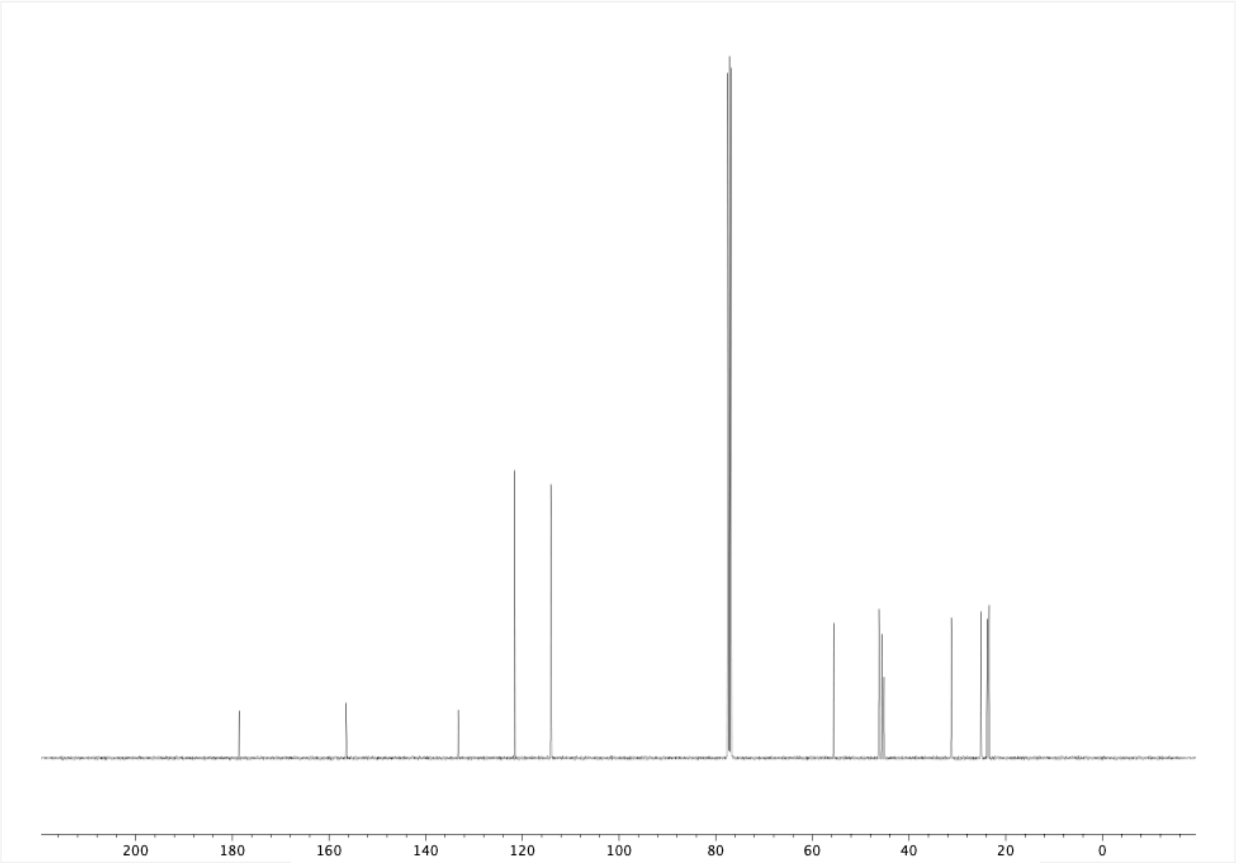

Figure A4.65. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***101****.*

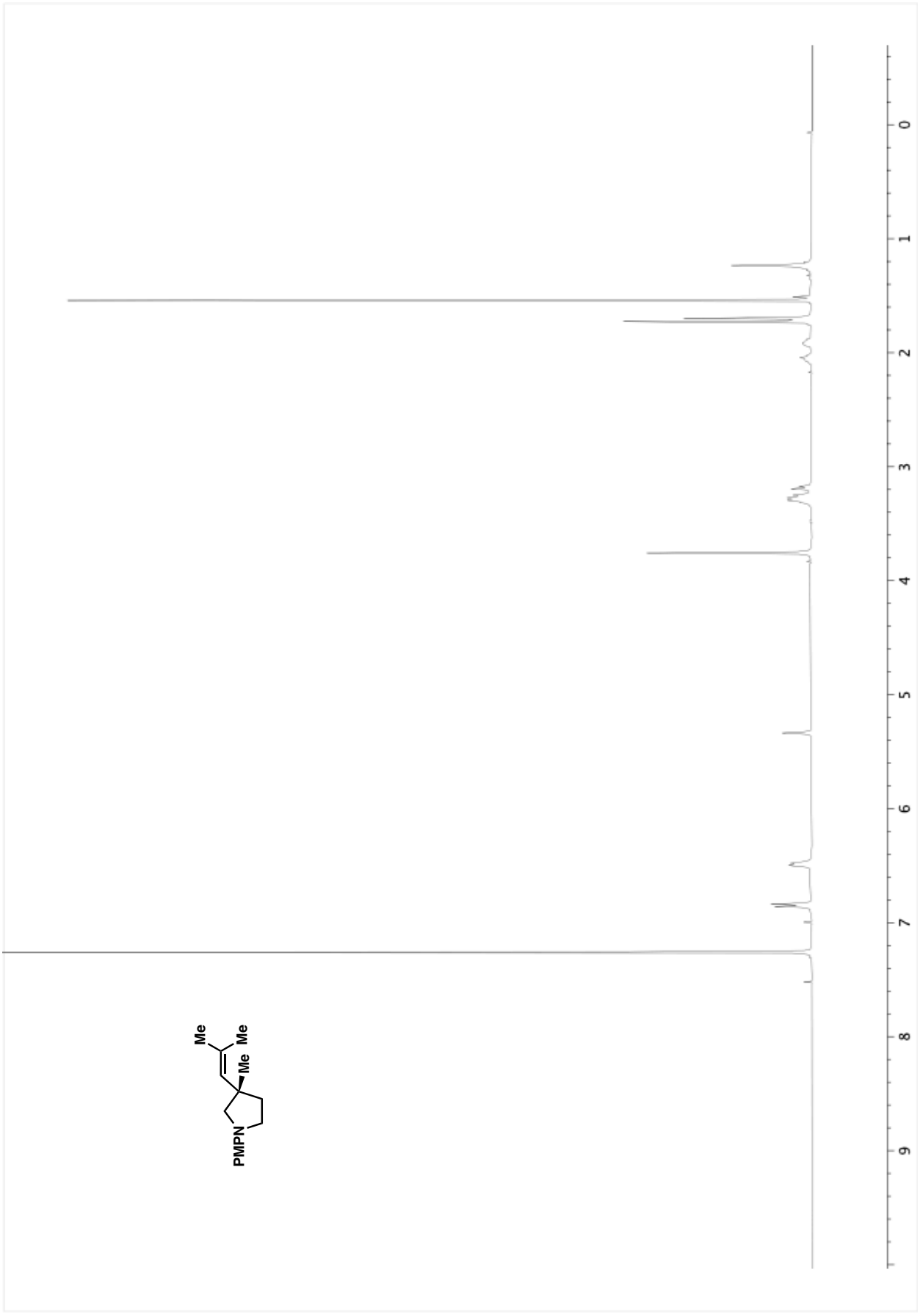

Figure A4.66. *^{1}H NMR (400 MHz, $CDCl_3$) of* ***102.***

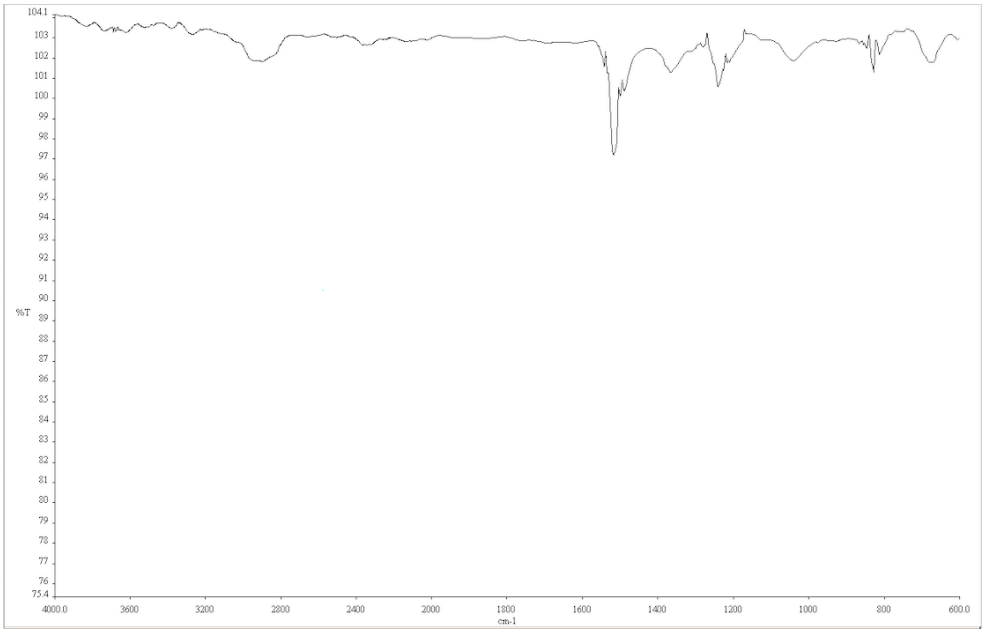

Figure A4.67. *Infrared spectrum (Thin Film, NaCl) of* ***102****.*

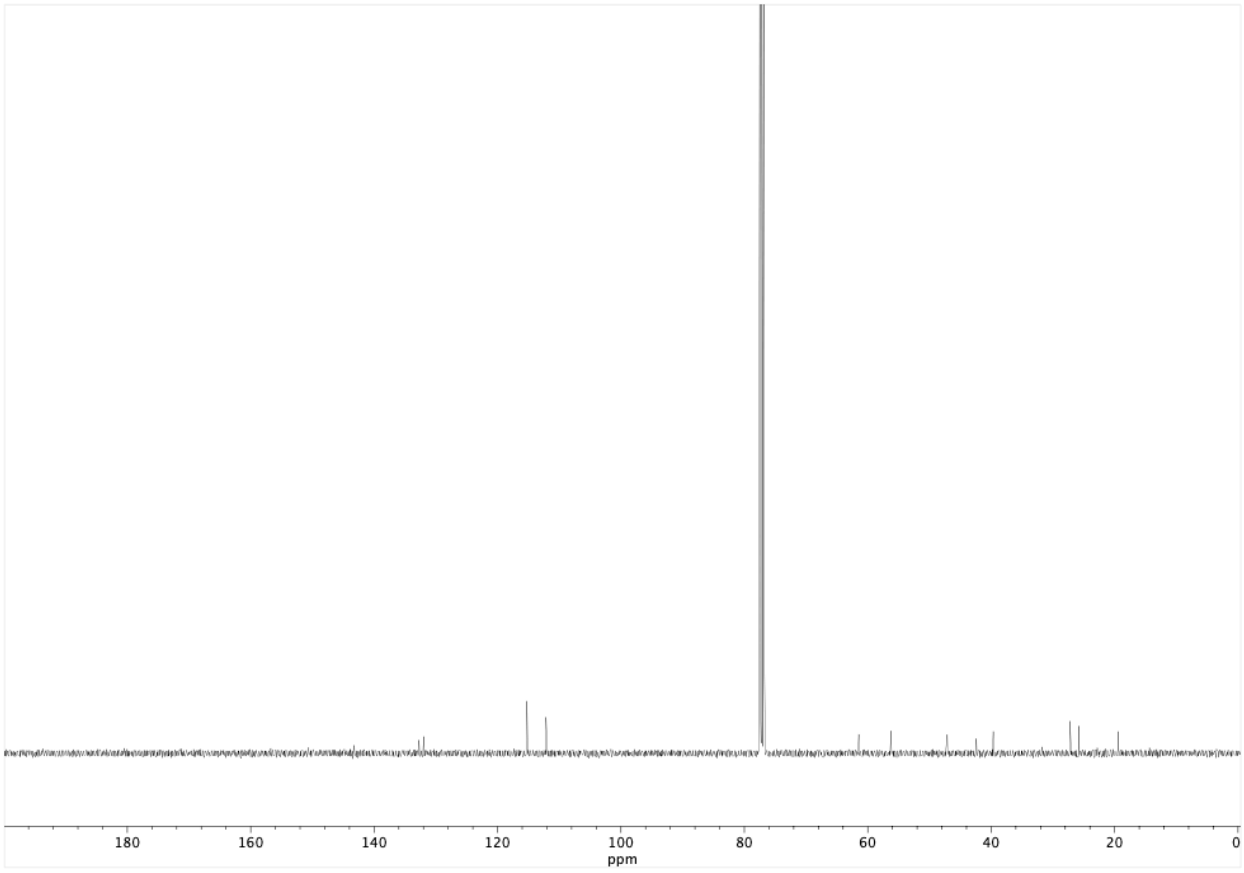

Figure A4.68. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***102****.*

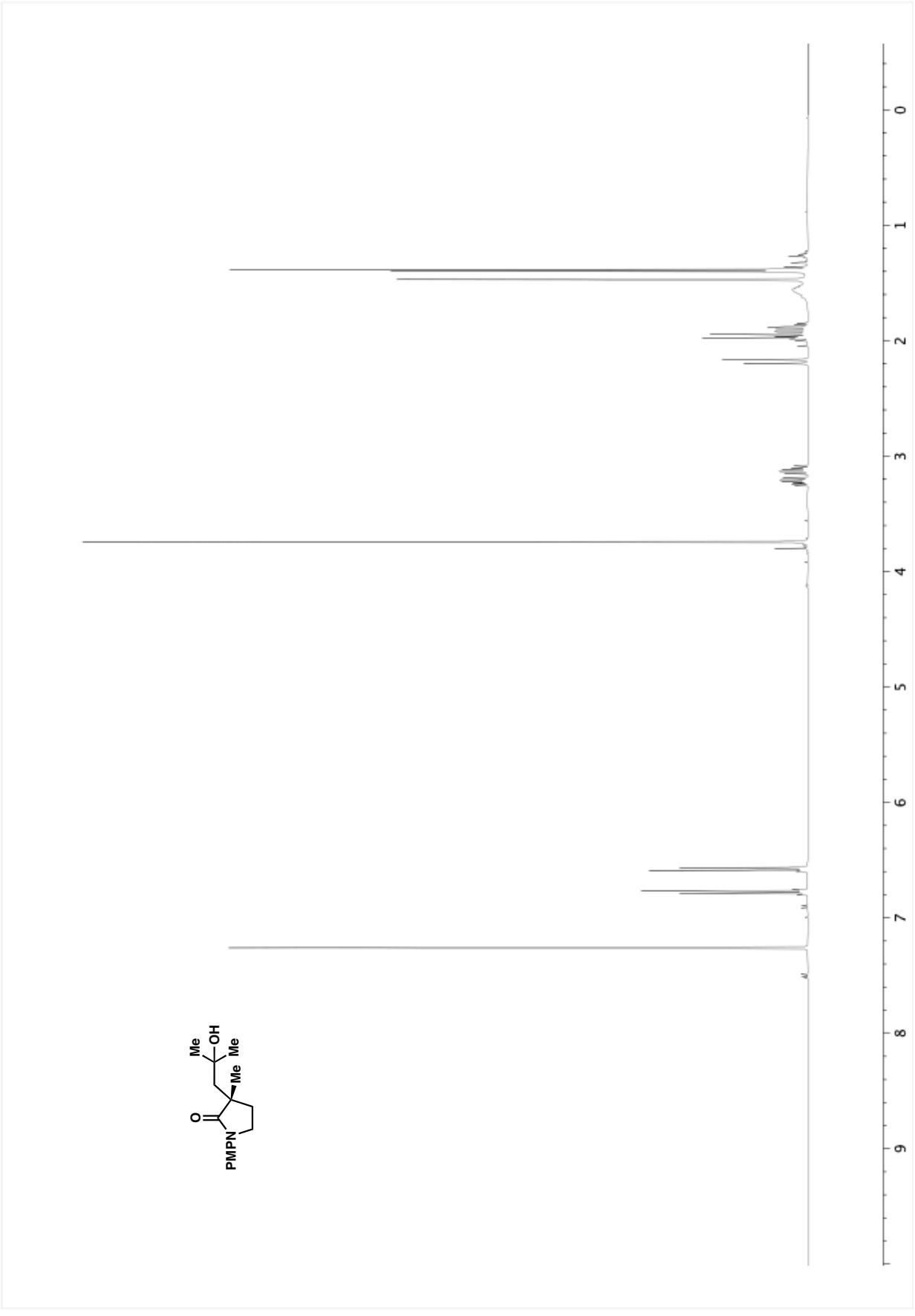

Figure A4.69. *^1H NMR (400 MHz, $CDCl_3$) of* ***103****.*

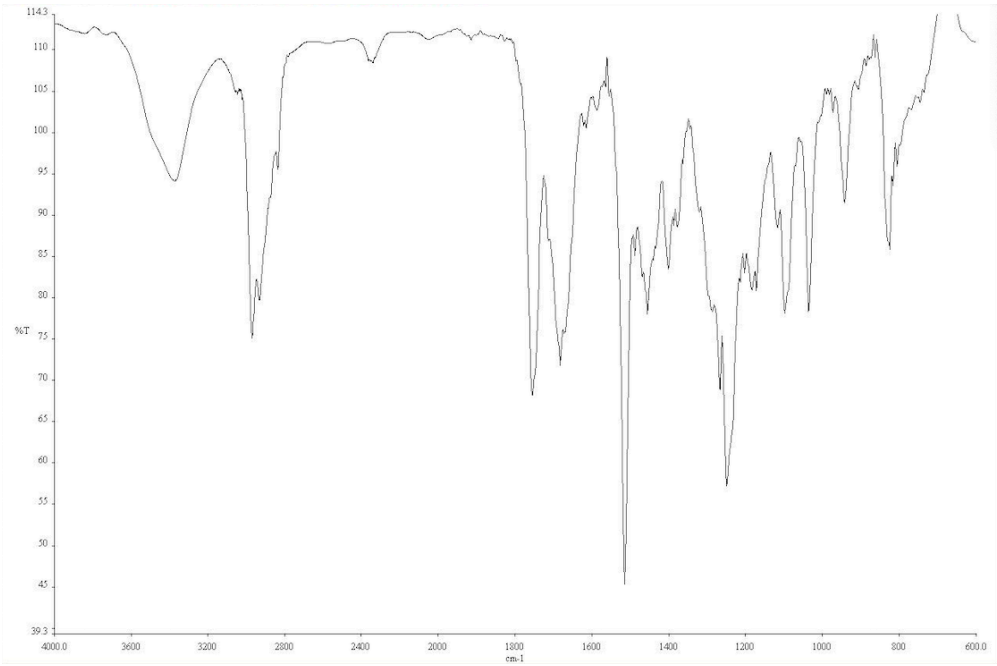

Figure A4.70. *Infrared spectrum (Thin Film, NaCl) of* ***103****.*

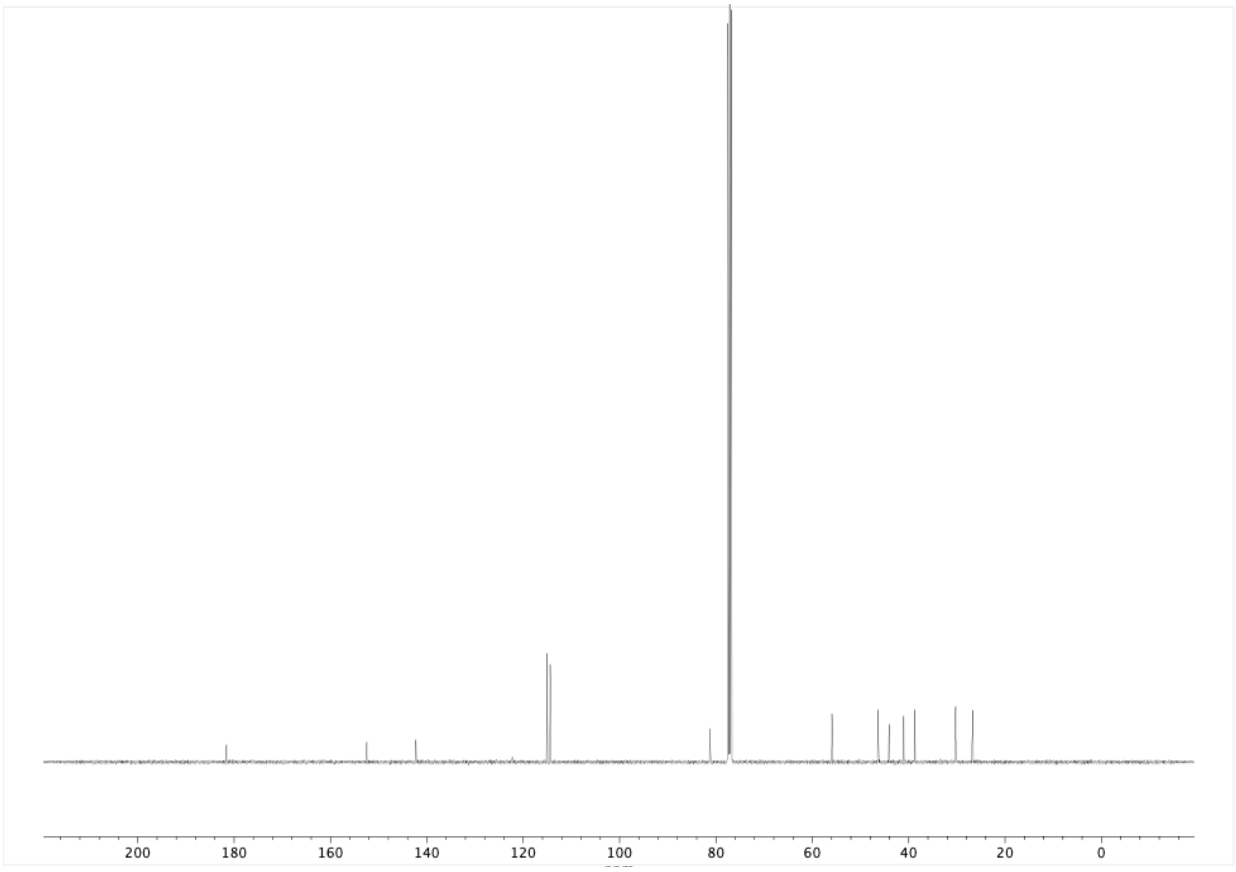

Figure A4.71. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***103****.*

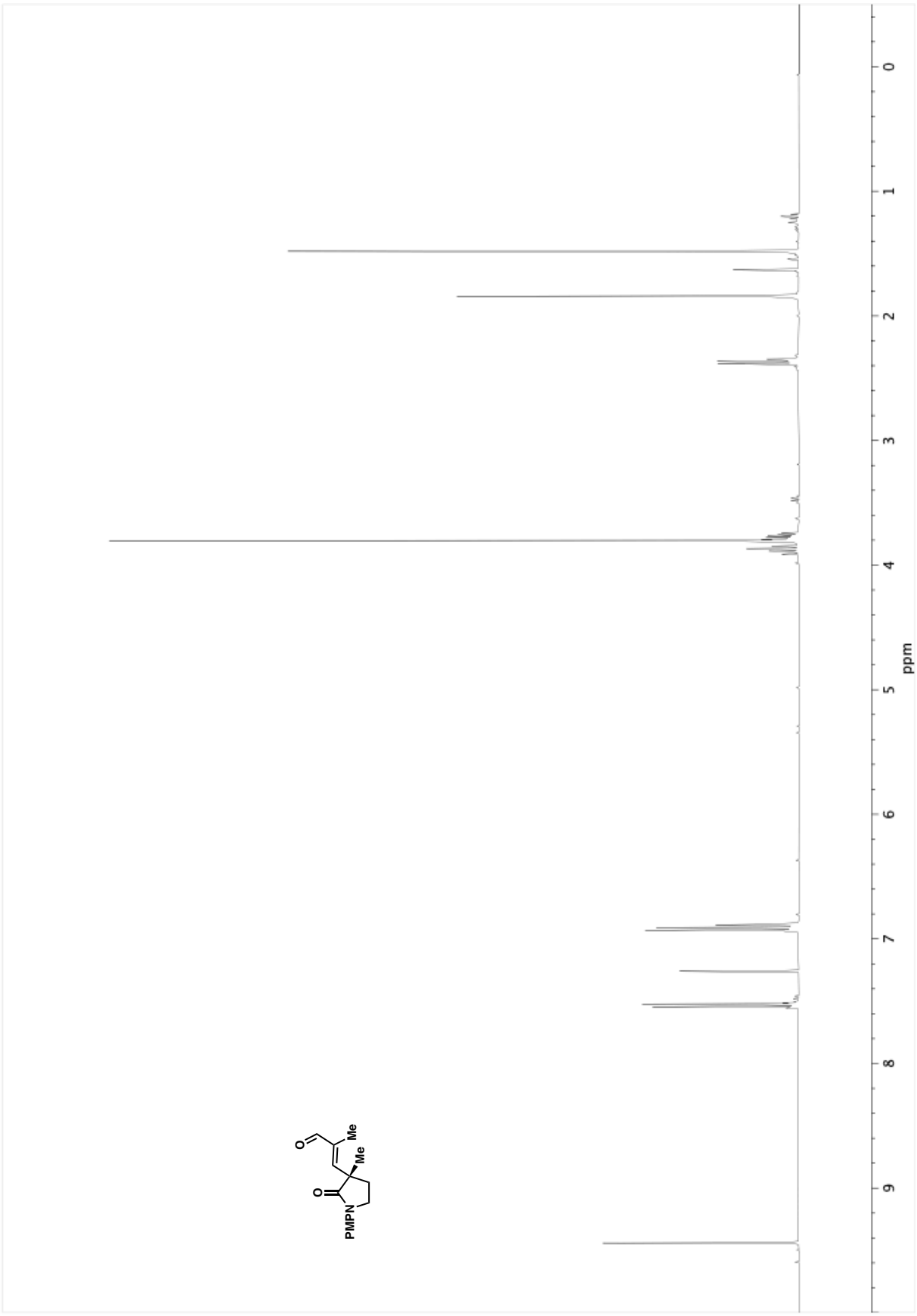

Figure A4.72. *^1H NMR (400 MHz, $CDCl_3$) of* ***104****.*

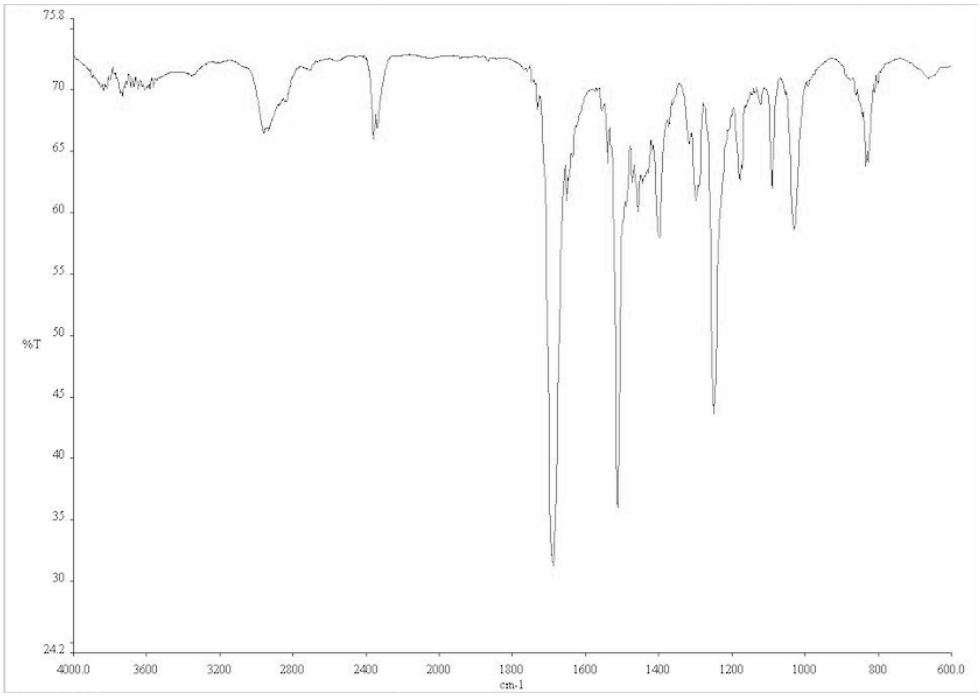

Figure A4.73. *Infrared spectrum (Thin Film, NaCl) of* ***104****.*

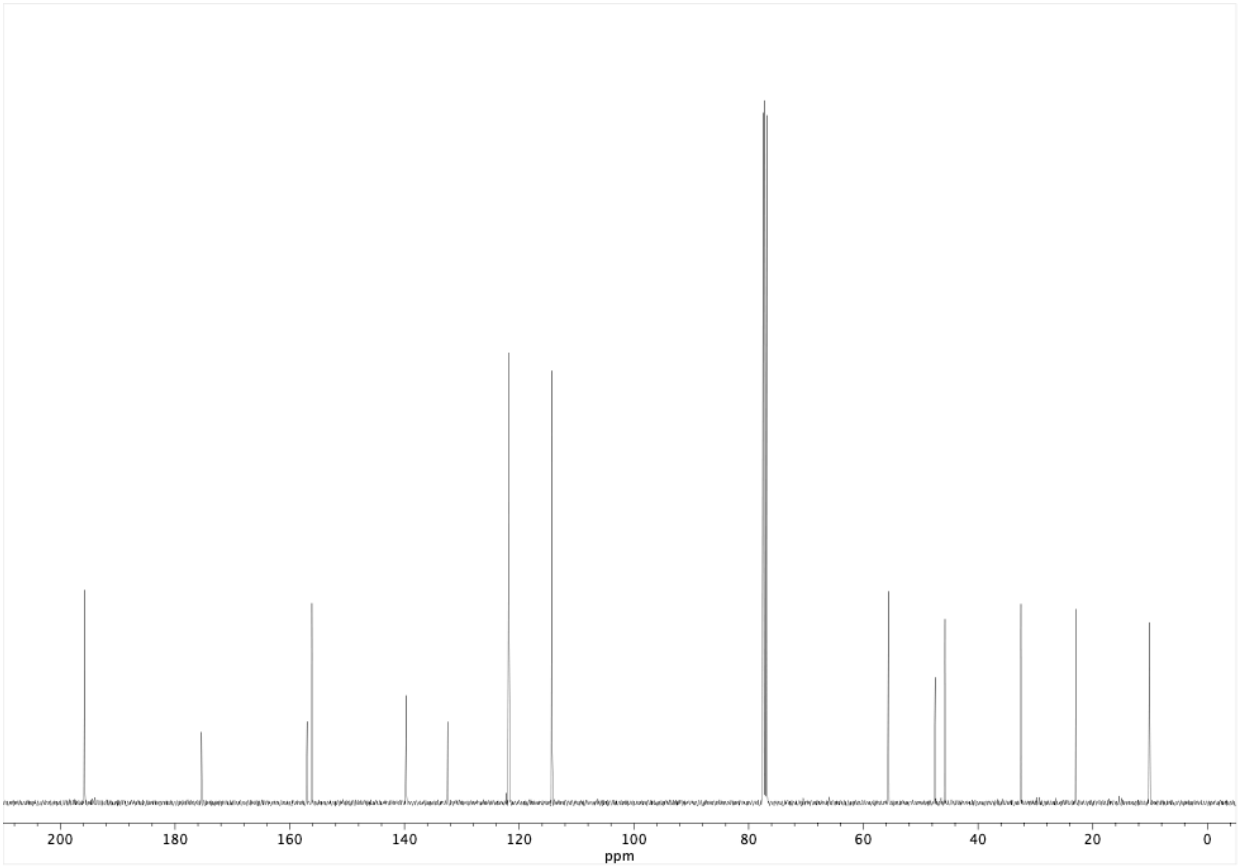

Figure A4.74. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***104****.*

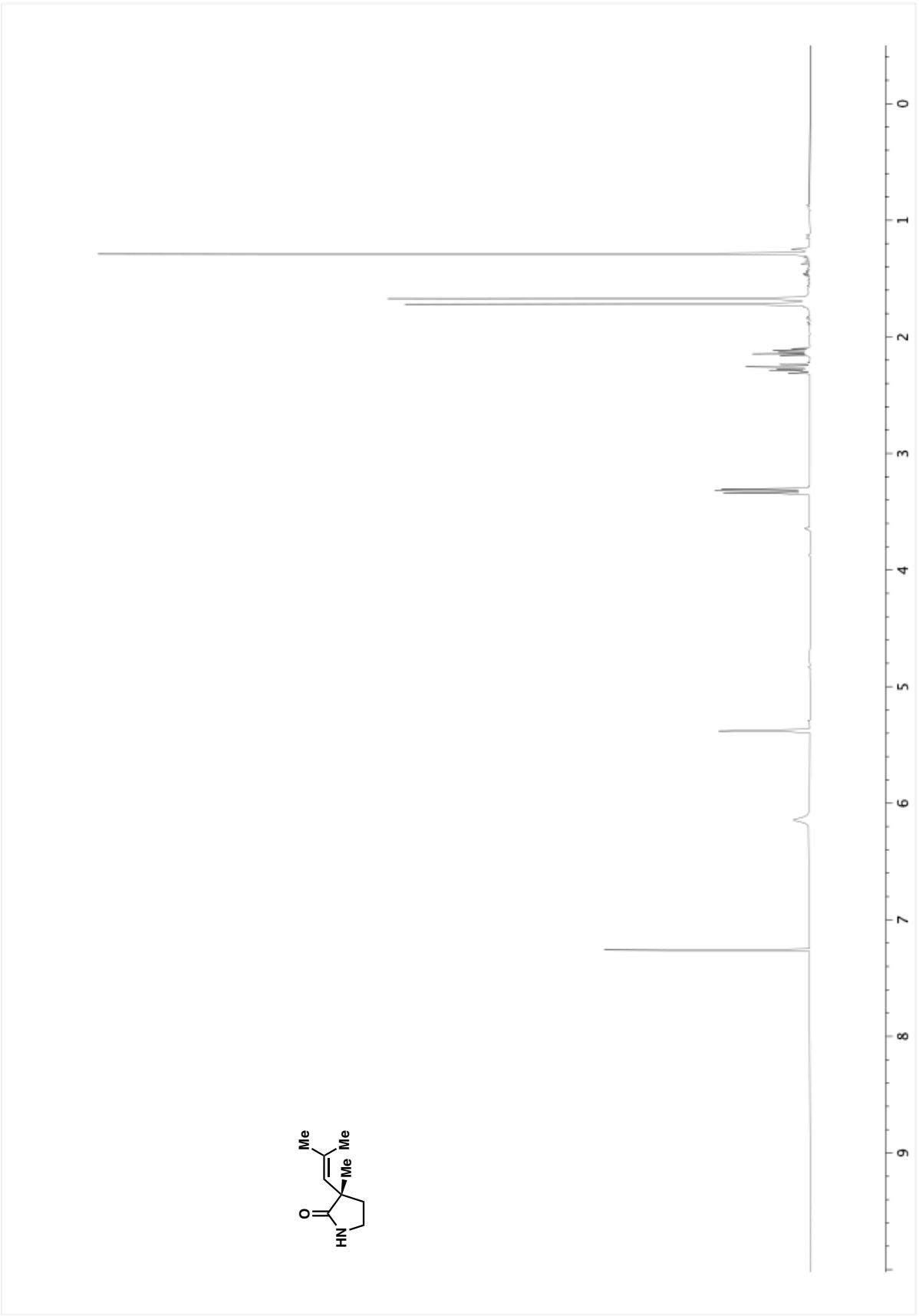

Figure A4.75. *^1H NMR (400 MHz, $CDCl_3$) of* ***105.***

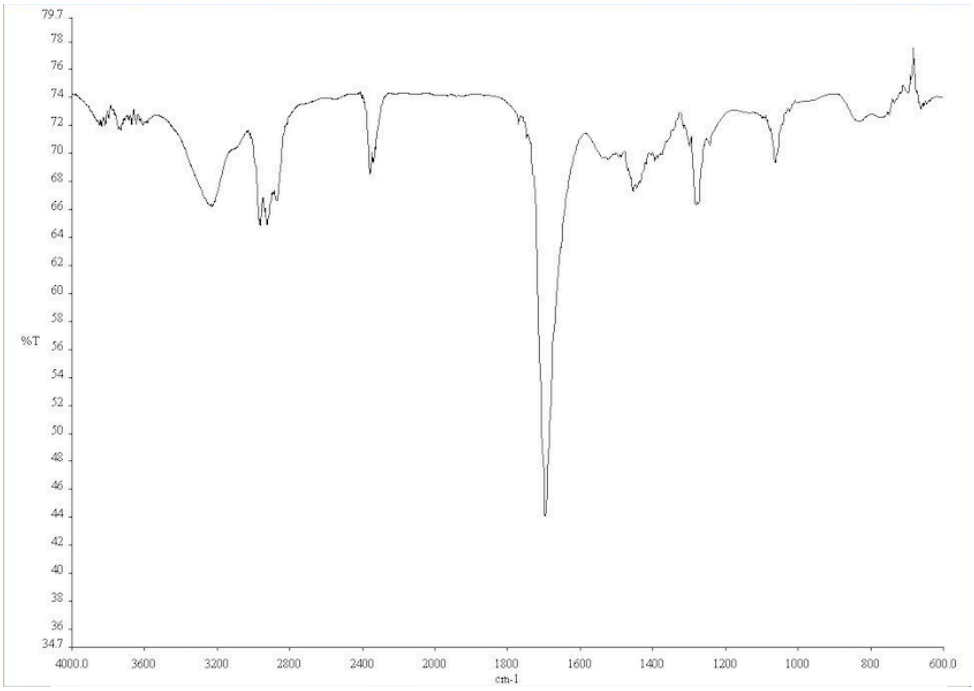

Figure A4.76. *Infrared spectrum (Thin Film, NaCl) of* ***105****.*

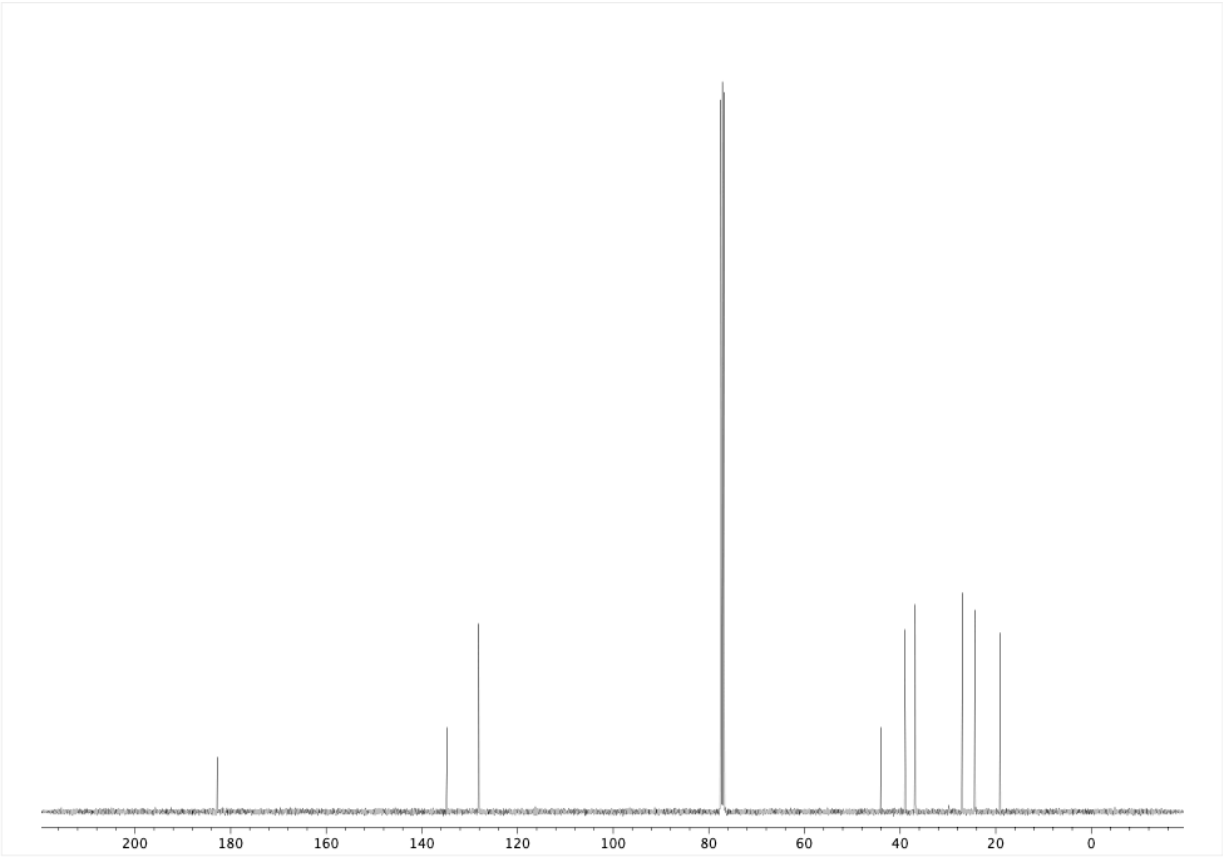

Figure A4.77. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***105****.*

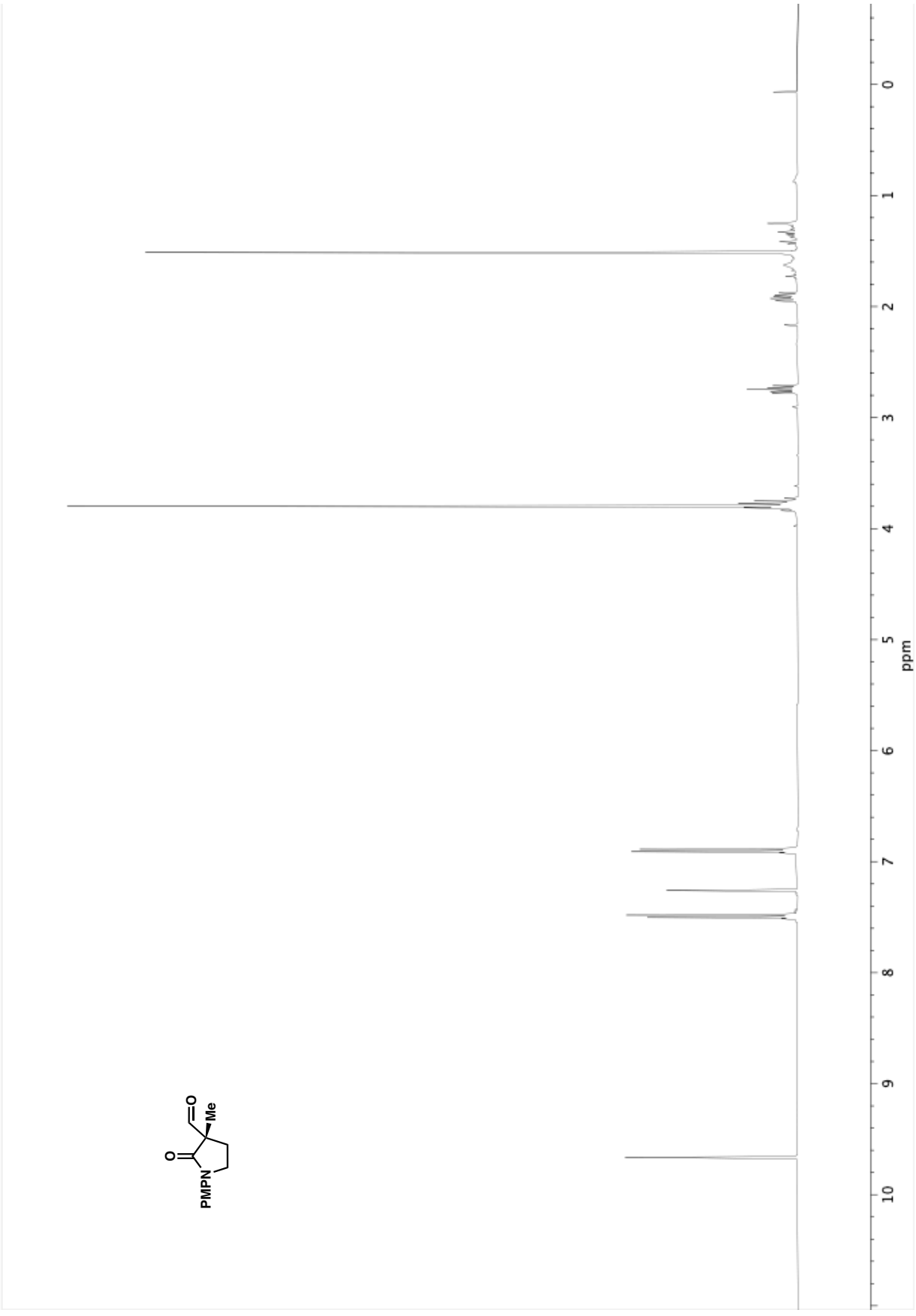

Figure A4.78. *^{1}H NMR (400 MHz, $CDCl_3$) of* ***106****.*

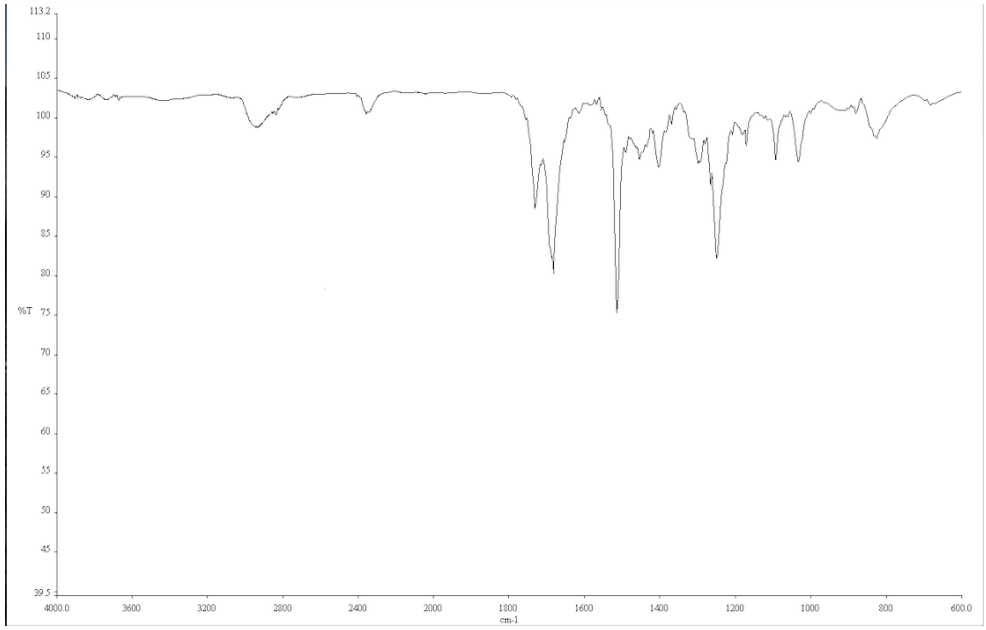

Figure A4.79. *Infrared spectrum (Thin Film, NaCl) of* ***106****.*

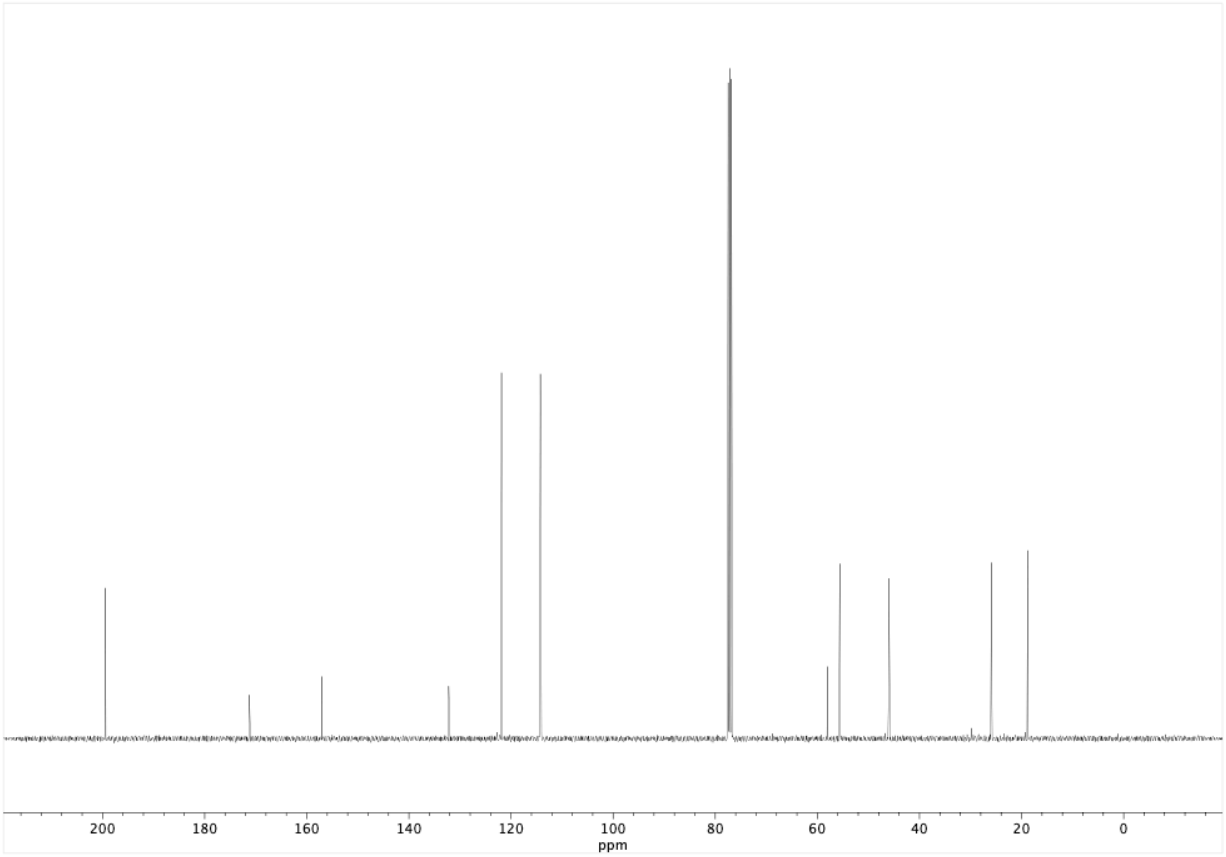

Figure A4.80. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***106****.*

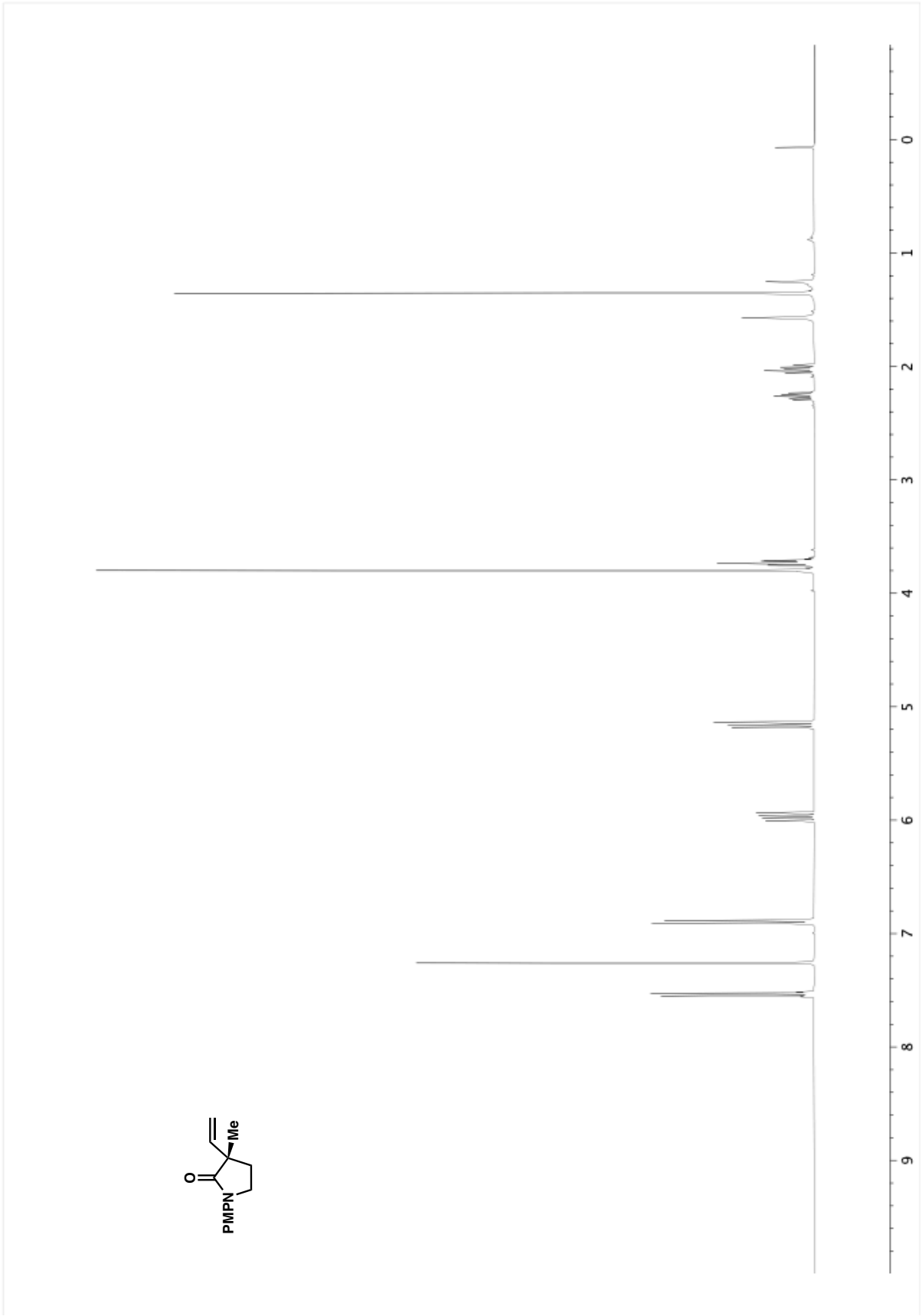

Figure A4.81. *^1H NMR (400 MHz, $CDCl_3$) of* ***107.***

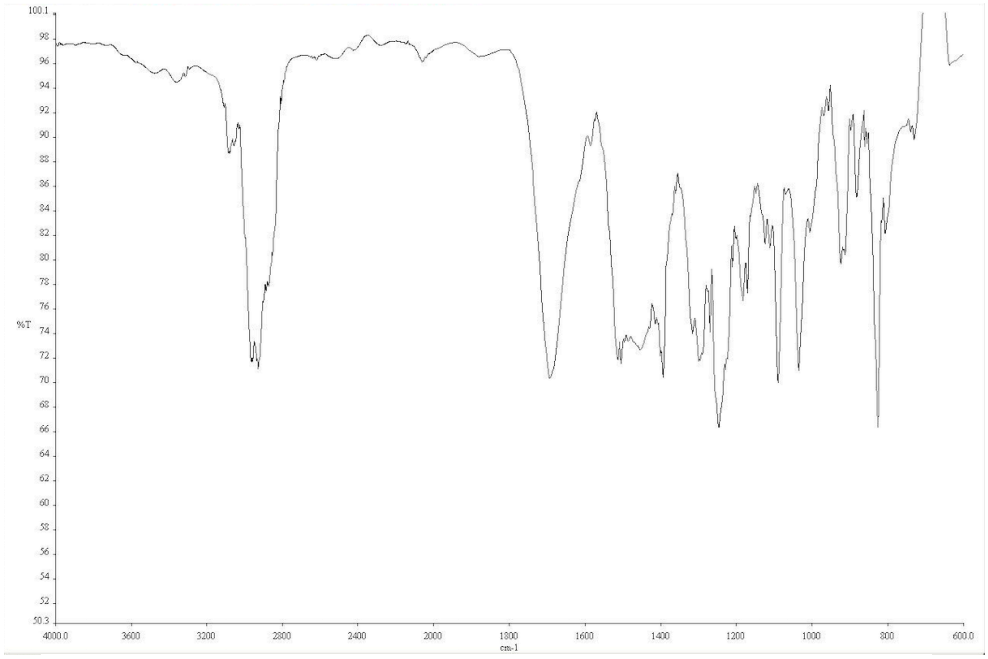

Figure A4.82. *Infrared spectrum (Thin Film, NaCl) of* ***107****.*

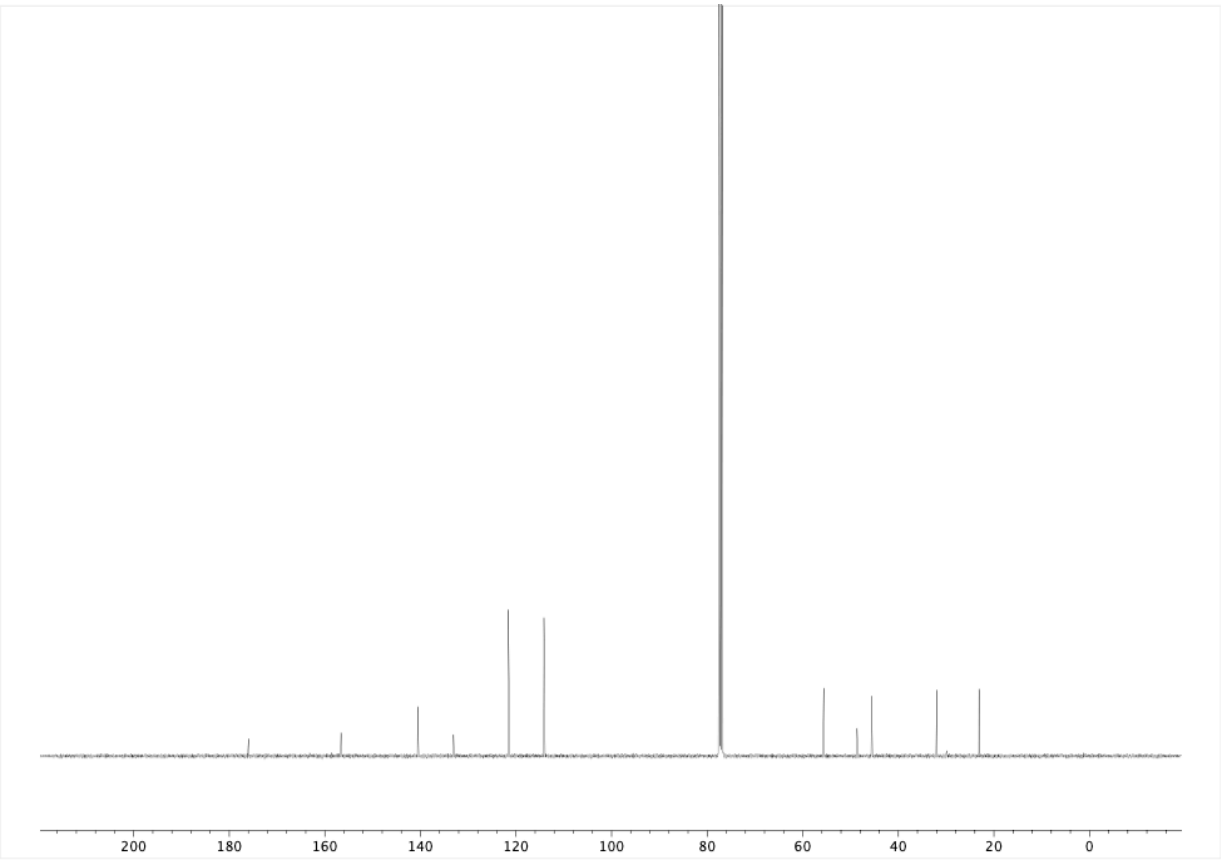

Figure A4.83. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***107****.*

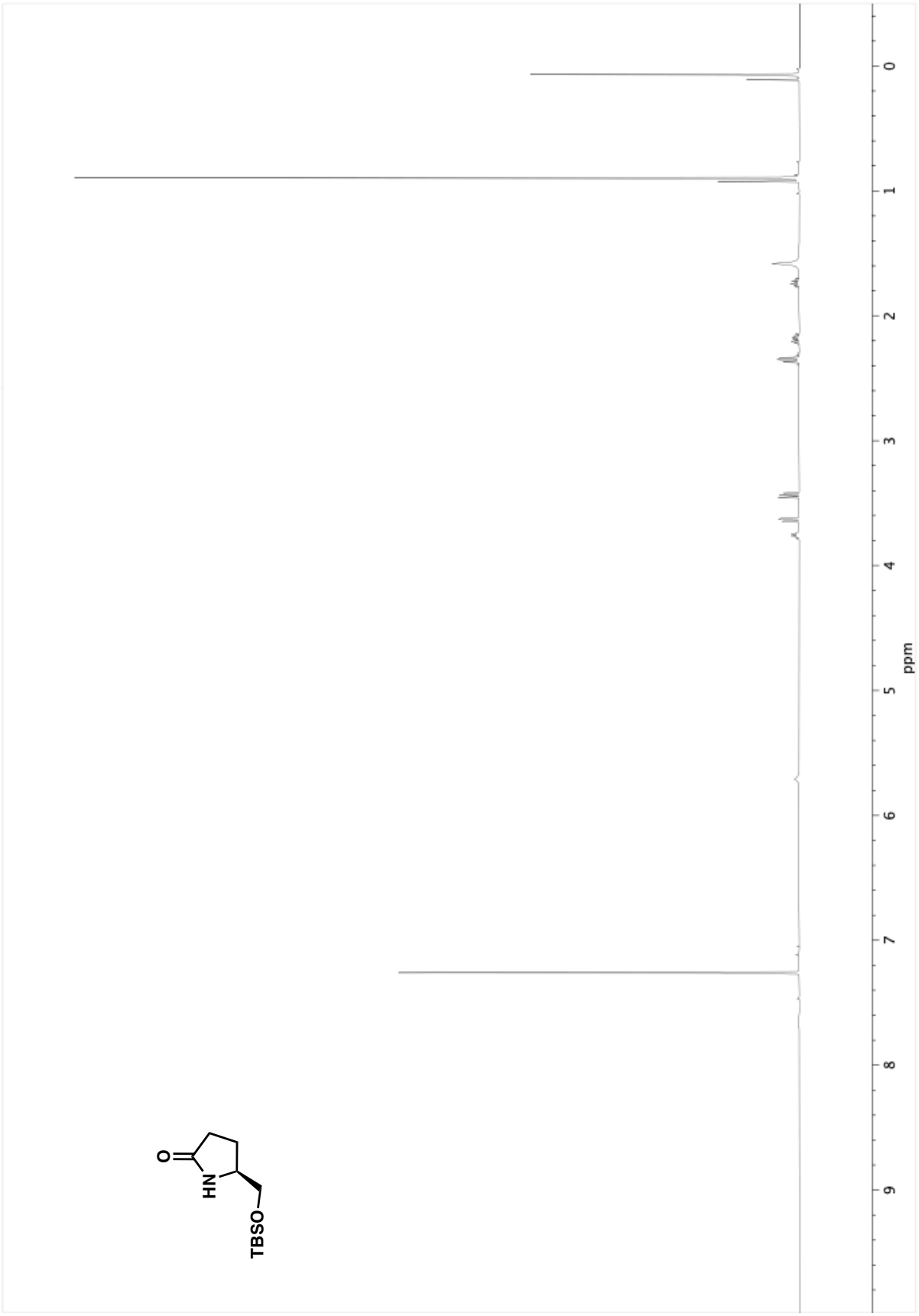

Figure A4.84. *^1H NMR (500 MHz, $CDCl_3$) of* ***116.***

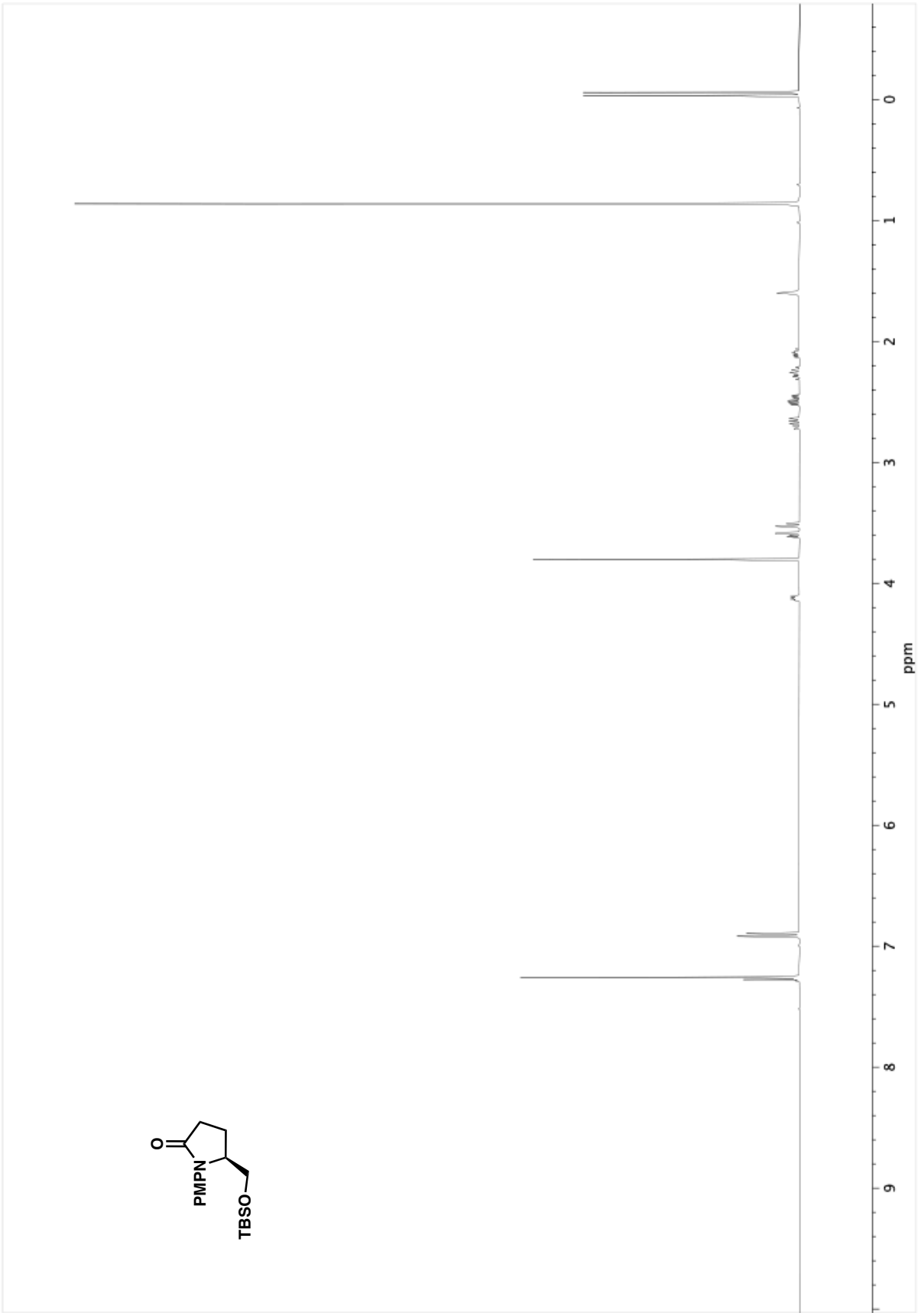

Figure A4.85. *^1H NMR (400 MHz, $CDCl_3$) of* ***117.***

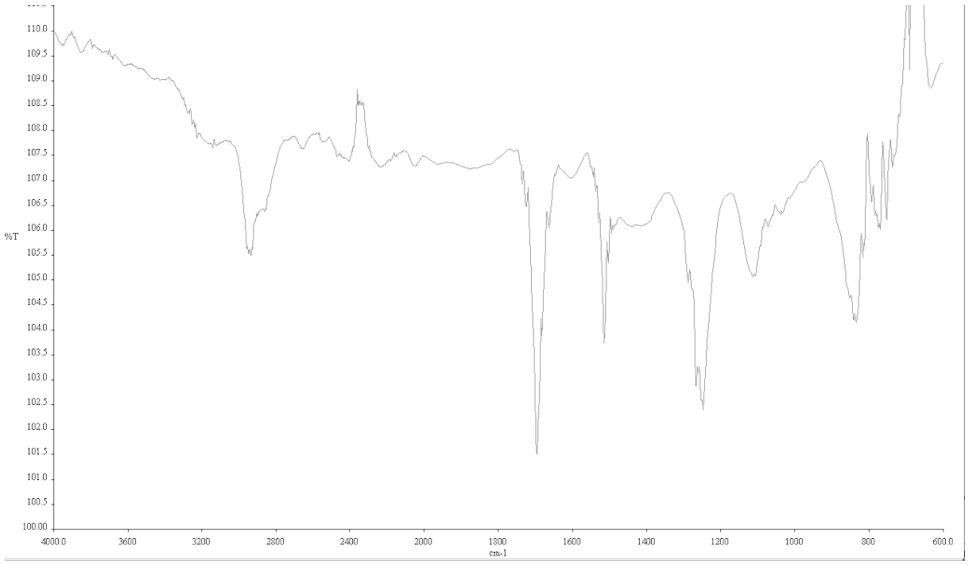

Figure A4.86. *Infrared spectrum (Thin Film, NaCl) of* ***117****.*

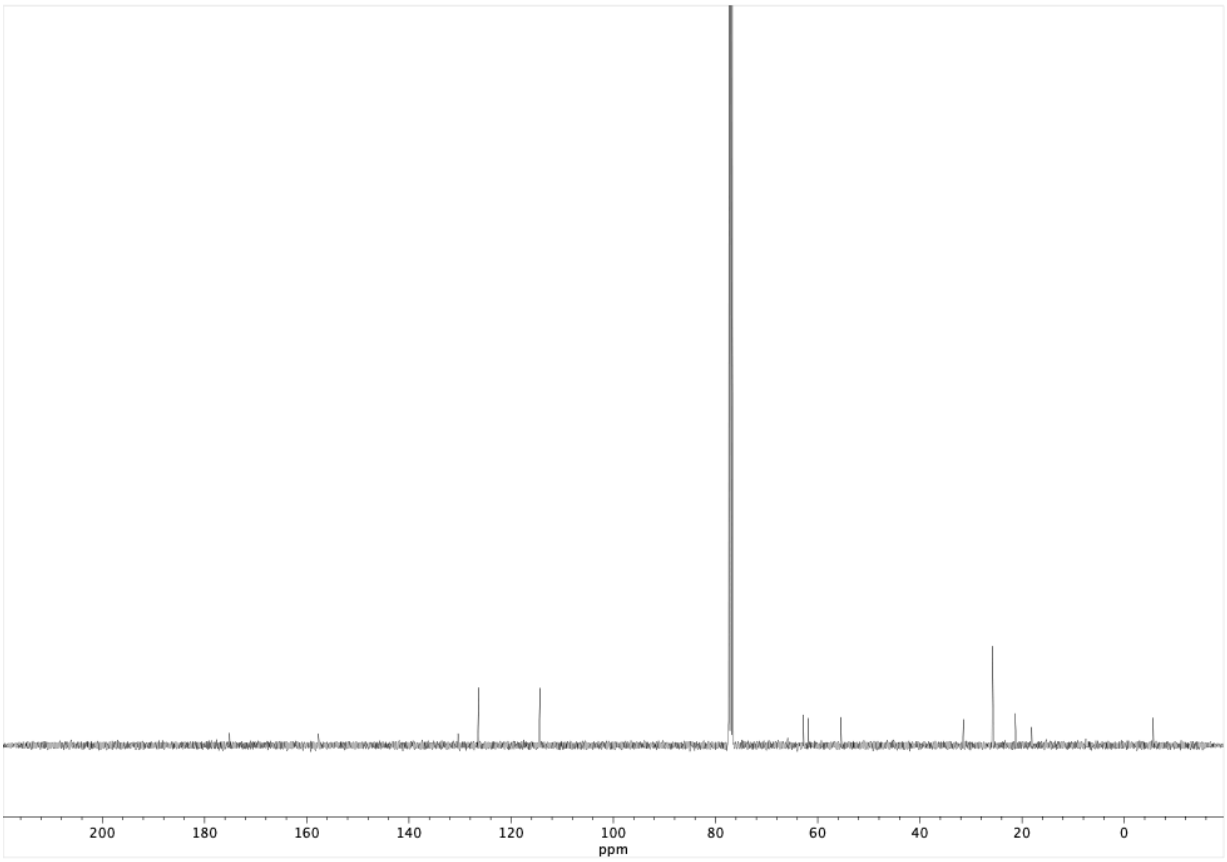

Figure A4.87. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***117****.*

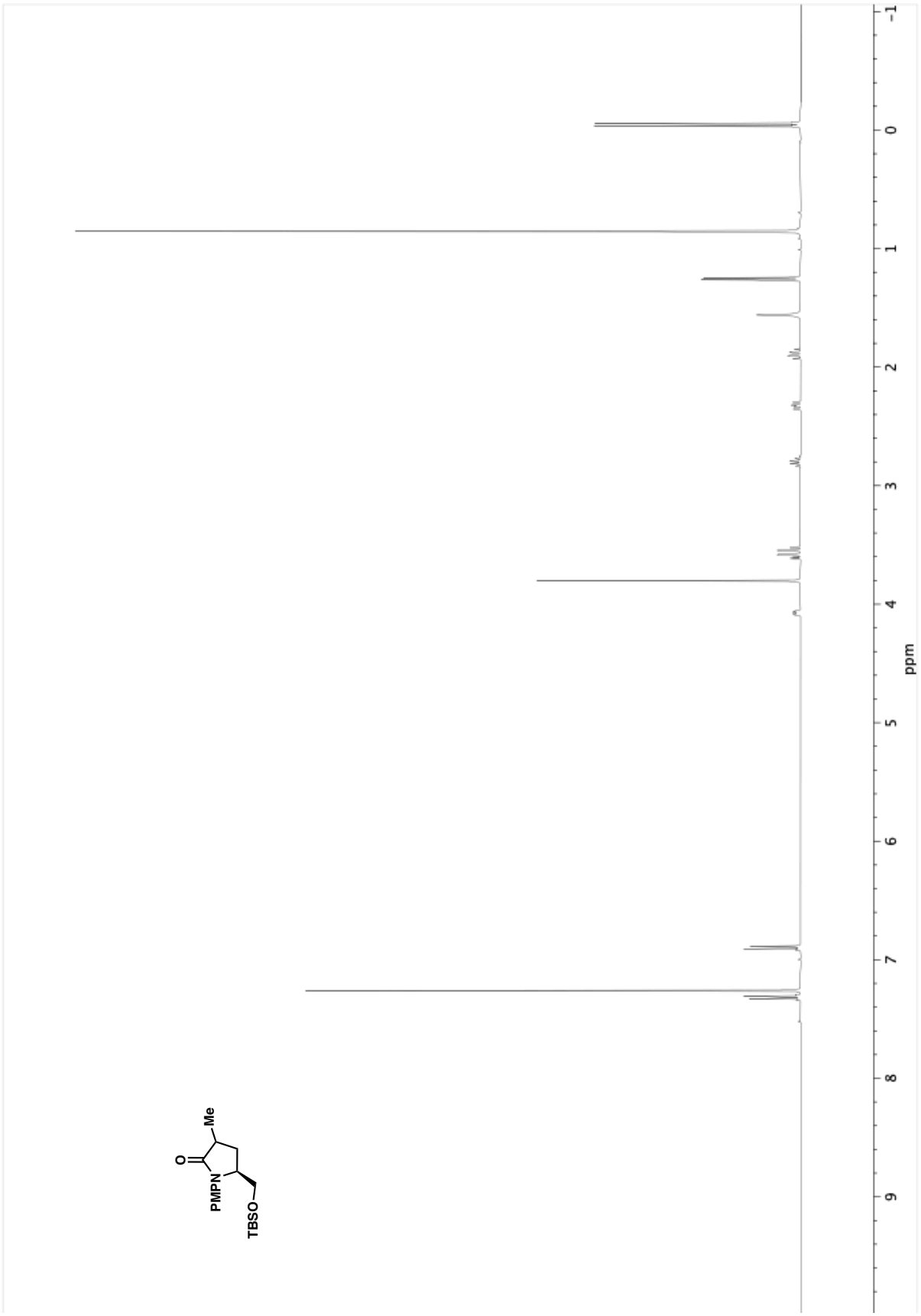

Figure A4.88. *^1H NMR (500 MHz, $CDCl_3$) of* ***118.***

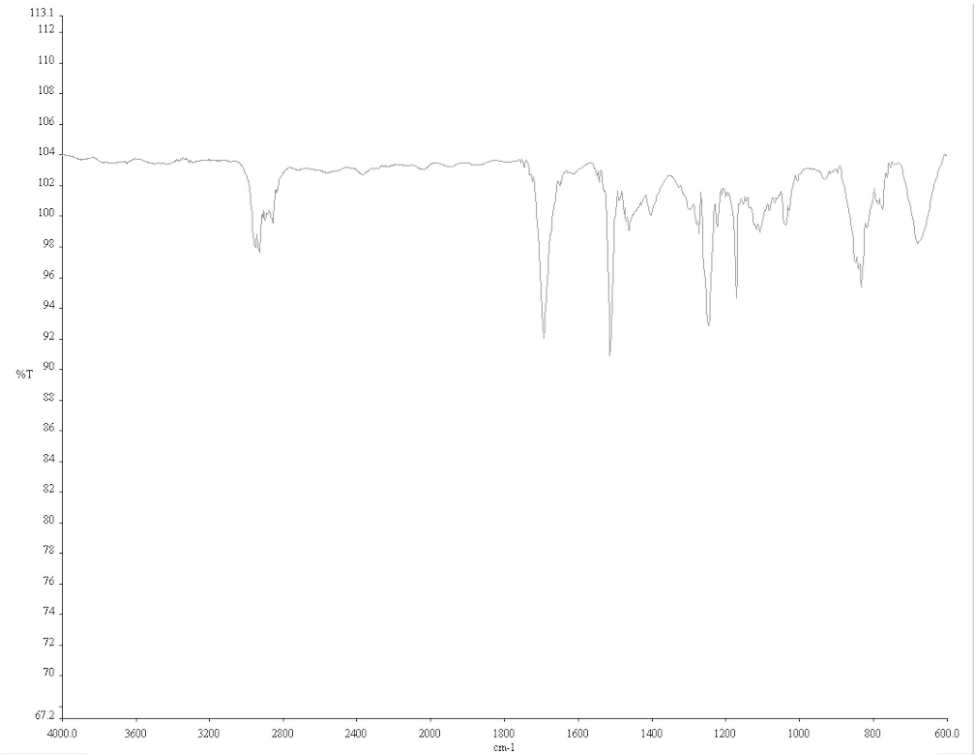

Figure A4.89. *Infrared spectrum (Thin Film, NaCl) of* ***118****.*

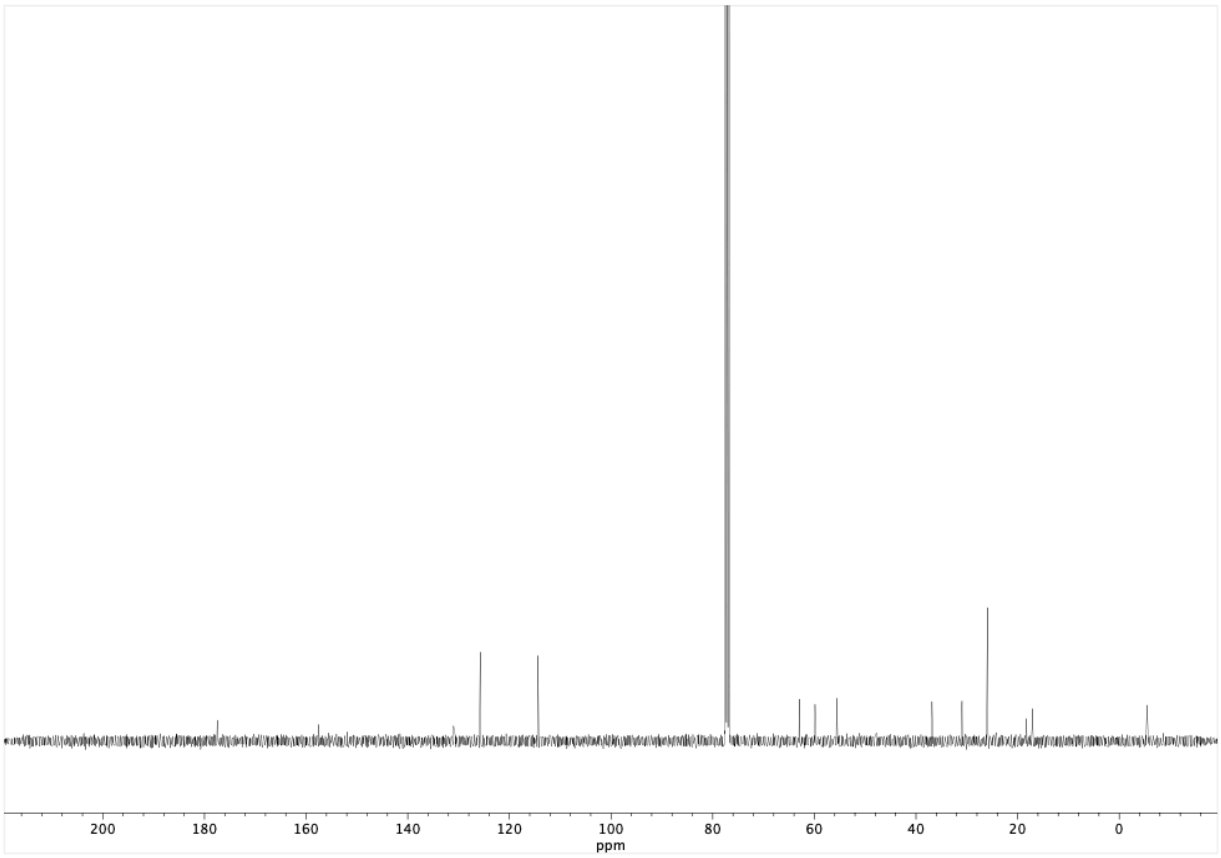

Figure A4.90. *^{13}C NMR (100 MHz, $CDCl_3$) of* ***118****.*

APPENDIX 5

Notebook Cross-Reference for New Compounds

Table A5.1. *Notebook Cross-Reference for Chapter 1*

CHAPTER 1	
COMPOUND NO.	**NOTEBOOK REF.**
2d	EFH-I-219
2e	EFH-I-261
2f	EFH-II-111
2j	FM-I-124-2
2k	FM-I-89-4
2n	ZPS-VII-29
2o	EFH-II-229
2pb	ZPS-VI-209
2p	ZPS-VI-225
2q	ZPS-VI-257
3a	FM-I-128
3b	EFH-II-133
3c	EFH-II-135
3d	EFH-II-137
5	FM-I-128-5
6a	EFH-II-123
6b	EFH-II-125
7a	EFH-II-119
7b	EFH-II-121
7c	EFH-II-117
8a	FM-I-130-3
8b	EFH-I-283
8c	FM-I-130-3
8d	EFH-II-127
9a	FM-I-128-2
9b	FM-I-128-3
10	FM-I-142
10b	ZPS-VI-297
10c	ZPS-VI-299
10d	ZPS-VI-301
11a	FM-I-151-3
11b	EFH-II-131
11c	FM-I-128-4
14b	FM-I-177-2
14c	FM-I-177-1
18	EFH-III-75
19	EFH-II-165
20	EFH-II-167
21	FM-I-138
22a	EFH-II-161
22b	EFH-II-179

Table A5.2. *Notebook Cross-Reference for Appendix 2*

APPENDIX 2	
COMPOUND NO.	**NOTEBOOK REF.**
27	FM-I-191-2
28	FM-I-199-2
31	FM-I-178-2
32	FM-I-210-2
34	FM-I-196-2
39	FM-I-245-1
42	FM-I-279
43	FM-I-293
45	FM-IV-77-2
47	FM-IV-93
54	FM-IV-277
36	FM-I-283
29	FM-I-176
30	FM-I-207
33	FM-I-226
33b	FM-I-220
37	FM-I-274-1
38	FM-I-285-1
41	FM-I-291
49	FM-IV-105
46	FM-IV-57
52	FM-IV-267
53	FM-IV-273

Table A5.3. *Notebook Cross-Reference for Chapter 2*

CHAPTER 2	
COMPOUND NO.	**NOTEBOOK REF.**
L_u	CSC-III-215
L8	FM-II-197
L9	FM-III-71
L12	FM-III-37
L14	FM-II-129
L10	FM-VI-205
S2	FM-III-197
L13	FM-III-47
L18	FM-III-175
L19	FM-III-173
L20	CSC-I-49
L21	FM-III-205
L22	FM-III-243
L23	FM-III-221
55	CSC-III-15
56	CSC-II-255
58	FM-VI-263
59	CSC-II-223
60	CSC-II-235
62	CSC-II-279
63	FM-VI-257
64	CSC-II-289
65	CSC-II-251
66	FM-VI-259
67	FM-VI-261
67a	FM-VI-151
68	FM-VI-265
69	CSC-II-239
69a	FM-VI-241
70	FM-VI-267
71	CSC-II-229
71a	CSC-II-173
71b	FM-VII-167
72	FM-VII-123
73	CSC-III-95
73a	CSC-III-89
73b	FM-VII-57
78	FM-VI-273
79	FM-VI-297
80	FM-VI-297
81	FM-VII-161

Table A5.4. *Notebook Cross-Reference for Chapter 3*

CHAPTER 3	
COMPOUND NO.	**NOTEBOOK REF.**
87	FM-IV-227
88	JB-VIII-101-1
89	JB-VIII-101-2
90	JB-VIII-101-3
91	FM-IV-185-1
92	FM-IV-185-2
93	MC-VI-221-2
94	MC-VI-221-1
95	MC-VI-231-1
96	FM-IV-75-1
98	JB-XI-115-1
100	FM-II-255
101	MC-VI-95
102	FM-IV-231
103	MC-VI-265
104	JB-VIII-237
105	JB-VIII-281
106	FM-IV-233
107	MC-VII-41
108	JB-VIII-67-1
109	JB-VIII-67-2
110	JB-VIII-67-3
111	FM-IV-181
112	FM-IV-183
113	MC-VI-297
114	MC-VI-203-1
115	MC-VI-203-3
117	FM-VI-125
118	FM-IV-65

ABOUT THE AUTHOR

Farbod Arya Moghadam was born in Santa Clara, CA on April 7, 1998. He is the younger of two brothers, who are separated by three years of age. Farbod grew up in quaint Saratoga, CA, where he attended Saratoga High School and began to explore his blossoming love for chemistry through Honors and AP Chemistry courses. He joined the Chueh lab at Stanford University for two summers investigating perovskites and their potential applications in energy storage technology. Farbod graduated from high school in 2016 and matriculated at UC Santa Barbara, where he initially intended on pursuing a BS/MS degree in materials science. Though he was initially skeptical of organic chemistry due to his distaste for prior biology classes, Farbod was surprised to develop an affinity for the subject while taking the honors organic chemistry sequence at UCSB. In the second term, the course was taught by Prof. Bruce Lipshutz, whose passion for the science ushered Farbod to inquire about research in his laboratory and ultimately join the group.

After more than two years in the Lipshutz lab researching the applicability of transition metal catalyzed transformations in aqueous micellar media, Farbod completed his degree in March 2020. Luckily enough, Farbod was able to visit Caltech in person, before such visits were prohibited due to COVID, and upon meeting the Stoltz group had his mind made up on the next step in his academic career. Farbod began as a PhD student at Caltech in September of 2020 and officially joined the Stoltz group in December of that year. During his time in the group, Farbod continued to pursue his fascination with transition metal catalysis, focusing primarily on the construction of stereoenriched quaternary centers via branched-selective allylic alkylation. Upon completion of his PhD in June 2025, Farbod

will join the medicinal chemistry team at Cytokinetics in South San Francisco, accomplishing a long-awaited return home to the Bay Area.