PALLADIUM-CATALYZED ASYMMETRIC ALLYLIC ALKYLATION: INSIGHTS, APPLICATION TOWARD CYCLOPENTANOID AND CYCLOHEPTANOID MOLECULES, AND THE TOTAL SYNTHESIS OF SEVERAL DAUCANE SESQUITERPENES

Thesis by

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To my wife,
Chanel, and
my son, Eli

ACKNOWLEDGEMENTS

Brian frequently refers to the graduate school experience as “a marathon and not a sprint.” While this sentiment expresses the exhaustive nature of the effort that necessitates pacing oneself, the metaphor also suggests a reward is achieved upon completion of the task. Ultimately, my graduate experience has been immensely rewarding, and one of the greatest aspects of that is finally seeing my last five years of work condensed into this volume. Gratefully, the “race” that encompasses this pursuit was not run alone and I have many to thank for inspiring, encouraging, and helping me to attain my doctorate.

First, I would like to thank Brian Stoltz for being my advisor. When I was accepted to Caltech, Brian allowed me to begin my research early, before classes started in the fall. This arrangement was made with the understanding that I may ultimately join another lab. I have always been very grateful to him for supporting me as I adjusted to graduate life over that summer, since I know this time was more beneficial for me than for him. Close to the end of my graduate experience, Brian also arranged postgraduate funding for me before my postdoc was set to begin. I really appreciate how he has helped me provide for my family.

In the lab, Brian has granted a fair amount of flexibility on my projects, encouraging me to focus on the problems I found exciting and to even explore reactions outside of my main pursuits. This freedom has allowed me to try a variety of transformations and learn multiple techniques. In these efforts, Brian has provided numerous ideas on how to overcome difficult obstacles, and I quickly learned that the reactions he suggests almost always work and usually helped me get past the problem I

was facing. I also enjoyed the time I spent in his office crafting my research into the outline of a paper, working side by side as everything came together.

Brian is also an excellent instructor. I have had the privilege to not only take a class from him, but have also served as his teaching assistant while he lectured the undergraduate organic series. He teaches his courses with great depth and clarity, and I know his students appreciate him.

My committee members have also been very helpful during my time at Caltech. Professor Sarah Reisman began teaching at Caltech at the start of my program, and we incidentally had our sons around the same time. From a number of experiences, I have come to think of Sarah as a friend. She has been especially supportive over the last few months and has served as somewhat of a surrogate advisor while Brian has been away. Sarah has offered a lot of advice on my most recent research, and I am particularly appreciative of her insight into samarium diiodide reductions. Most importantly, I am very grateful for her willingness to have acted as my committee chairman.

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wonderful time at their home one evening and enjoy seeing her at department and holiday parties. They are warm and generous people that I am so happy to have come to know.

I ambushed Professor Greg Fu to ask him to be the final member of my committee while he was visiting from MIT for a recruiting weekend prior to his move to Caltech. He had never met me before, but did not hesitate to accept. I am grateful for the time he has taken to offer advice on my research, proposals, and a publication we were preparing for submission.

While at Caltech, I have been blessed to work with numerous graduate students and postdocs. When I began my graduate studies, we were located in the Crellin building and my first baymate was Jenn Stockdill. As I was a young and inexperienced graduate student, Jenn taught me a lot of laboratory techniques and helped me set up my first LDA reaction; I have since run many. I credit Jenn for introducing me to "Wait, Wait Don't Tell Me" and Billy Joel, both of which I now listen to frequently. Jenn is currently a professor at Wayne State University and I wish her the best.

With our move to the Schlinger laboratory, I shared a hood with Allen Hong. Allen is a persistent and detail-oriented scientist. He is always positive, even when things are not going as expected. We have worked on several projects together that have resulted in a number of publications; our joint efforts encompass Chapter 2 of my thesis. Allen is now a postdoc at UC Irvine with Prof. Chris Vanderwal. When Brian heard that we would both be moving to Irvine for our postdocs, he jokingly suggested that we find some way to continue our collaborative efforts. I am really grateful for Allen's friendship and for all of the projects we have worked on together.

I have had a number of other baymates over the last five years. Dr. Chris Henry taught me a lot about laboratory technique and NMR analysis. He likely looked at every spectra during my first year and helped me figure out coupling constants on several occasions. I am grateful for his friendship in the lab and on the basketball court. Nat Sherden taught me so much about the mechanistic aspects of the Tsuji allylation and Futurama. Max Loewinger is a good friend with an infectious excitement for chemistry. Seojung Han is one of the most diligent chemists I have met. Dr. Wen-Bo (Boger) Liu was a great collaborator on the allylic alkylation research; our joint work is discussed in Chapter 1 of my thesis. I also appreciate all of the things he has proofread for me.

Chris Gilmore and Pam Tadross became great friends to my wife and I. Chris and his hoodmate, Dr. Florian Vogt, kept things lively in our bay. Flo instituted weekly Queen and ABBA nights, and I credit him for my interest in classic music. Between the two, there was always an interesting conversation or podcast coming from their hood. Although not my baymate, Pam was particularly helpful in sculpting my development as a chemist. She read almost everything I wrote before she graduated, and I always appreciated her straightforward comments and insights. She will make an excellent professor one day because she cares about others and works tirelessly to see them succeed. I appreciate how Pam and Chris always talked with my wife at group parties and kept her involved, and how they were so excited for the birth of our son. We are so happy they found each other and got married. It was also great to meet Chris' parents upon their move to Pasadena. They are awesome people, and we've enjoyed visiting with them at their home and various group parties.

Thomas Jensen is one of the best examples of an organic chemist I have seen. He set up so many reactions on a daily basis and was extremely diligent at getting things done. I remember one day when his hoodmate thought he had run more reactions than Thomas only to discover Thomas had actually set up a robotic screen that crushed the hoodmate's number. My goal everyday was to strive to be a little more like Thomas.

The research presented in Chapter 1 was performed in conjunction with Doug Duquette. While I wrote the paper, Doug finished collecting the laboratory data we needed. I was really impressed with how quickly he took care of everything and how fast we got that paper out. Doug is a great scientist and I am happy to have worked with him. I am also grateful to Drs. Jimin Kim, Wen-Bo (Boger) Liu, Alex Marziale, and Doug Behenna for contributing to these efforts.

Although not discussed in my thesis, I recently began working with Kelvin Bates on a collaborative project with Professors Paul Wennberg and John Seinfeld where we are making compounds that are hypothesized to exist in the atmosphere. Kelvin had no prior synthesis experience, but he has learned quickly and I know he will do well.

There have been many people in our lab during my time here. In my year, Alex Goldberg, Jonny Gordon, and Boram Hong have been great. Early on, Alex, Jonny, and I played basketball weekly. A number of students who preceded me had good advice and helped in my development including Mike Krout, Kevin Allan, and John Enquist. I know that I have inevitably neglected many that I have interacted with, and I greatly apologize for this. So many have contributed to my graduate experience, and it has been a great pleasure to work with my fellow Stoltz group members.

I must also thank several others for editing my proposals and thesis. Doug Duquette, Christopher Haley, Dr. Alex Marziale, Nick O'Connor, Gloria Sheng, and Ximena De Silva Tavares Bongoll each read one of my proposals. They provided invaluable perspective on the chemistry I proposed and caught all of the mistakes I made. I am also extremely grateful to Jeff Holder, Kelly Kim, Katerina Korch, Dr. Wen-Bo (Boger) Liu, Yiyang Liu, Nick O'Connor, and Beau Pritchett for reading and editing portions of my thesis.

In addition to the awesome students and postdocs at Caltech, we have the highest quality of staff. Agnes Tong is very understanding and really takes the time to listen. She was always willing to work out teaching assignments and other things to accommodate my schedule. Agnes does so much for the department and still finds time to care about each of the students individually. This is extremely challenging, but she juggles it all beautifully.

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Assistant Dean Natalie Gilmore has also been amazing and has helped my family immensely. She listened to our needs, especially as we were preparing for the birth of

our son, and has helped us in so many ways. We are indebted to her for her many kindnesses, especially for my appointment as an ARCS foundation scholar.

The ARCS foundation is a wonderful organization that recognizes and supports both undergraduate and graduate students who are pursuing degrees in science. My wife and I are so grateful for the fellowship they provided us. I have always enjoyed meeting with the different members during our yearly luncheon. They are kind people who care about our country's future and are striving to promote American innovation by funding scientific research.

I would not have arrived at Caltech without the guidance and direction of several professors from my undergraduate experience. The most influential of these was Prof. Steven Fleming. I worked for "Doc" during my junior and senior years performing research on a photochemical rearrangement. Doc believes in his students and pushes them to be their best. He met with us late in the evening every week where we went through countless organic chemistry problems. I learned so much from these sessions and from his physical organic chemistry course. Ultimately, Doc taught me to think like an organic chemist. Our weekly group meetings and the parties at his home are some of the best memories from my time at BYU.

While at BYU, I also performed research jointly under Professors Noel Owen and Steven Wood. Dr. Owen took a chance accepting me into his lab since my only previous interaction with him had been as a student in a religion class he taught. My time spent isolating bioactive metabolites from plant endophytes contributed greatly to my interest in the total synthesis of natural products. One of the experiences I enjoyed with Professor

Wood was the trip that several students and I took with him to an ACS regional meeting in Nevada where we presented a poster on our research.

Although I never performed research in his lab, I am also deeply indebted to Professor Steven Castle. Professor Castle taught my advanced organic chemistry laboratory course, which helped cement my desire to pursue graduate studies in organic synthesis. I learned to solve and love NMR problems in this class, and to this day, 2D NMR spectra are one of my favorite aspects of research. I also served as a teaching assistant to Dr. Castle for the same course and learned a lot under his guidance. I am especially grateful for the many times he has written letters of recommendation on my behalf.

Finally and most importantly, I would like to thank my family. My parents have been so supportive of my education. When I was little, my mother and father set a wonderful example on the importance of learning and pushed me to perform. I loved school and wanted to do well because of them. I remember my mother staying up with me in fifth grade to help finish my state report the night before it was due. In high school, she taught me how to write and edited all of my papers. While growing up, my father helped me figure out math and science. I appreciated how he would discuss with me what college classes I should take. His guidance on my career has been so helpful. I am so grateful for their interest in my undergraduate education and that they encouraged me to pursue my doctorate. Chanel's family has been equally supportive and accepted me as one of their own from the start. They have kept me well fed and provided numerous sweets. I love being in their home and have so many memories from time spent there.

I first met my wife, Chanel, at the beginning of my graduate studies and we were married shortly thereafter. It was good we met when we did, as I do not know how I would have gotten through everything without her. The timing of our meeting and courtship likely helped her deal with my long hours in the lab since this is the only life we have known together. She is a fabulous wife and mother. Our son, Eli, is so much fun. I love how he would wave and say, "bye-bye" from the front door as I headed off to the lab every morning, and I was always so happy to see his smiling face when I returned. I love them both so much and am so grateful for their love and support.

ABSTRACT

The asymmetric construction of quaternary stereocenters is a topic of great interest in the organic chemistry community given their prevalence in natural products and biologically active molecules. Over the last decade, the Stoltz group has pursued the synthesis of this challenging motif via a palladium-catalyzed allylic alkylation using chiral phosphinooxazoline (PHOX) ligands. Recent results indicate that the alkylation of lactams and imides consistently proceeds with enantioselectivities substantially higher than any other substrate class previously examined in this system. This observation prompted exploration of the characteristics that distinguish these molecules as superior alkylation substrates, resulting in newfound insights and marked improvements in the allylic alkylation of carbocyclic compounds.

General routes to cyclopentanoid and cycloheptanoid core structures have been developed that incorporate the palladium-catalyzed allylic alkylation as a key transformation. The unique reactivity of α-quaternary vinylogous esters upon addition of hydride or organometallic reagents enables divergent access to γ-quaternary acylcyclopentenes or cycloheptenones through respective ring contraction or carbonyl transposition pathways. Derivatization of the resulting molecules provides a series of mono-, bi-, and tricyclic systems that can serve as valuable intermediates for the total synthesis of complex natural products.

The allylic alkylation and ring contraction methodology has been employed to prepare variably functionalized bicyclo[5.3.0]decane molecules and enables the enantioselective total syntheses of daucene, daucenal, epoxydaucenal B, and 14-*p*-anisoyloxydauc-4,8-diene. This route overcomes the challenge of accessing β-substituted acylcyclopentenes by employing a siloxyenone to effect the Grignard addition and ring opening in a single step. Subsequent ring-closing metathesis and aldol reactions form the hydroazulene core of these targets. Derivatization of a key enone intermediate allows access to either the daucane sesquiterpene or sphenobolane diterpene carbon skeletons, as well as other oxygenated scaffolds.

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LIST OF ABBREVIATIONS

$[\alpha]_D$	angle of optical rotation of plane-polarized light
Å	angstrom(s)
p-ABSA	*para*-acetamidobenzenesulfonyl azide
Ac	acetyl
AIBN	azobisisobutyronitrile
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
Ar	aryl group
At	benztriazolyl
atm	atmosphere(s)
BHT	2,6-di-*tert*-butyl-4-methylphenol ("butylated hydroxytoluene")
BINAP	(1,1'-binaphthalene-2,2'-diyl)bis(diphenylphosphine)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
br	broad
Bu	butyl
i-Bu	*iso*-butyl
n-Bu	butyl or *norm*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl

c	concentration of sample for measurement of optical rotation
^{13}C	carbon-13 isotope
^{14}C	carbon-14 isotope
/C	supported on activated carbon charcoal
°C	degrees Celcius
calc'd	calculated
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
CCDC	Cambridge Crystallographic Data Centre
CDI	1,1'-carbonyldiimidazole
cf.	consult or compare to (Latin: *confer*)
cm^{-1}	wavenumber(s)
cod	1,5-cyclooctadiene
comp	complex
conc.	concentrated
Cy	cyclohexyl
CSA	camphor sulfonic acid
d	doublet
d	dextrorotatory
D	deuterium
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBDMH	*N,N*'-dibromo-5,5-dimethylhydantoin

DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexyl carbodiimide
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
de	diastereomeric excess
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutyl aluminum hydride
DMA	dimethylacetamide
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin periodinane (1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one)
DMSO	dimethylsulfoxide
DMTS	dimethylthexylsilyl
DPPA	diphenylphosphorylazide
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
DTT	dithiothreitol
ee	enantiomeric excess
E	methyl carboxylate (CO_2CH_3)
E^+	electrophile

E	trans (entgegen) olefin geometry
EDCI	*N*-(3-Dimethylaminopropyl)-*N*-2-ethylcarbodiimide hydrochloride
e.g.	for example (Latin: *exempli gratia*)
EI	electron impact
eq	equation
equiv	equivalent(s)
ESI	electrospray ionization
Et	ethyl
et al.	and others (Latin: *et alii*)
FAB	fast atom bombardment
Fmoc	fluorenylmethyloxycarbonyl
g	gram(s)
h	hour(s)
^{1}H	proton
^{2}H	deuterium
^{3}H	tritium
[H]	reduction
HATU	2-(7-aza-1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMDS	hexamethyldisilamide or hexamethyldisilazide
HMPT	hexamethylphosphoramide
$h\nu$	light
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry

Hz	hertz
IBX	2-iodoxybenzoic acid
IC_{50}	half maximal inhibitory concentration (50%)
i.e.	that is (Latin: *id est*)
IR	infrared spectroscopy
J	coupling constant
k	rate constant
kcal	kilocalorie(s)
kg	kilogram(s)
KHMDS	potassium bis(trimethylsilyl)amide
L	liter or neutral ligand
l	levorotatory
LA	Lewis acid
LD_{50}	median lethal dose (50%)
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
LICA	lithium isopropylcyclohexylamide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
m	multiplet or meter(s)
M	molar or molecular ion
m	meta
µ	micro
m-CPBA	*meta*-chloroperbenzoic acid

Me	methyl
mg	milligram(s)
MHz	megahertz
MIC	minimum inhibitory concentration
min	minute(s)
mL	milliliter(s)
MM	mixed method
mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular seives
m/*z*	mass-to-charge ratio
N	normal or molar
NBS	*N*-bromosuccinimide
nm	nanometer(s)
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
Nu^-	nucleophile
o	ortho
[O]	oxidation
t-Oct	*tert*-octyl (1,1,3,3-tetramethylbutyl)

p	para
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
Piv	pivalate
pK_a	acid dissociation constant
PKS	polyketide synthase
PMB	*para*-methoxybenzyl
pmdba	bis(4-methoxybenzylidene)acetone
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
i-Pr	isopropyl
n-Pr	propyl or *norm*-propyl
psi	pounds per square inch
py	pyridine
q	quartet
R	alkyl group
R	rectus
RCM	ring-closing metathesis
REDAL	sodium bis(2-methoxyethoxy)aluminum hydride
ref.	reference

R_f	retention factor
s	singlet or seconds
S	sinister
sat.	saturated
SEM	2-(trimethylsilyl)ethoxymethyl
SOD	superoxide dismutase
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBAT	tetra-*n*-butylammonium difluorotriphenylsilicate
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TCA	trichloroacetic acid
temp	temperature
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
THIQ	tetrahydroisoquinoline
TIPS	triisopropylsilyl
TLC	thin layer chromatography

TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
TOF	time-of-flight
tol	tolyl
Tr	triphenylmethane (trityl)
Troc	2,2,2-trichloroethoxycarbonyl
Ts	*para*-toluenesulfonyl (tosyl)
UV	ultraviolet
w/v	weight per volume
v/v	volume per volume
X	anionic ligand or halide
Z	cis (zusammen) olefin geometry

CHAPTER 1

Expanding Insight into the Asymmetric Palladium-Catalyzed Allylic Alkylation of N-Heterocyclic Molecules and Cyclic Ketones[†]

1.1 INTRODUCTION AND BACKGROUND

The asymmetric construction of quaternary stereocenters is a topic of great interest in the organic chemistry community. Among the available methods that afford this motif,[1] palladium-catalyzed decarboxylative allylic alkylation[2,3] has proven particularly effective and, over the last decade, our group has pursued this strategy employing chiral phosphinooxazoline (PHOX) ligands.[4,5] Our initial efforts in this area led to the preparation of enantioenriched α-quaternary ketones (e.g., **2a**) in good yields and enantioselectivities using (*S*)-*t*-BuPHOX (**3**)[5a–b] as a chiral ligand (Scheme 1.1A).[6] Since these early results, we have considerably expanded the scope,[7] demonstrated multiple applications,[8] and performed mechanistic investigations[9] of this powerful

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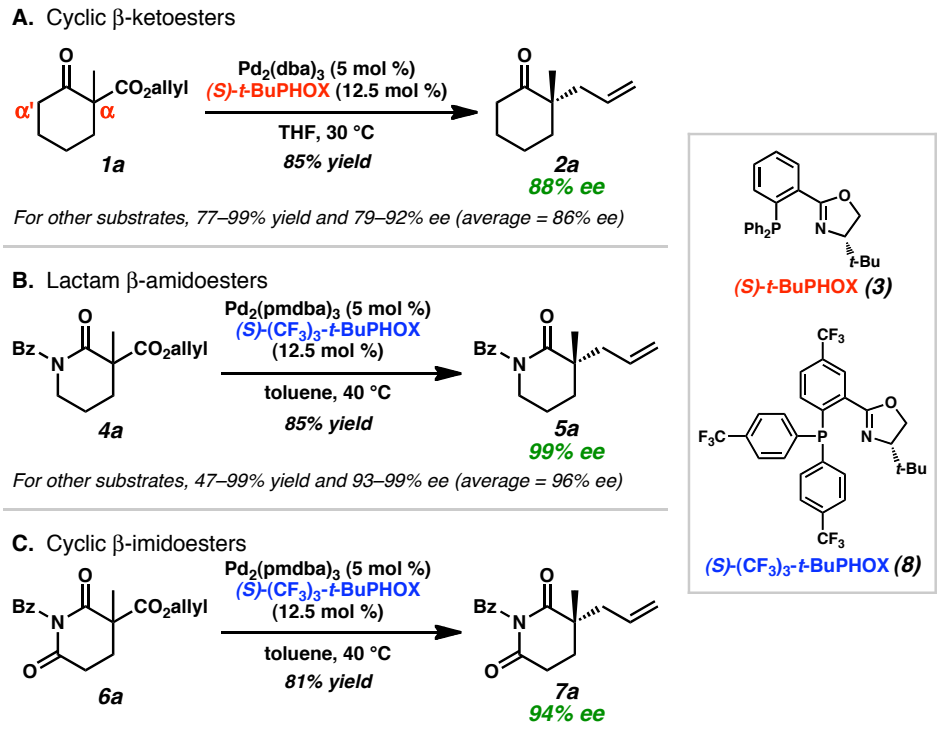
[†] This research was performed in collaboration with Douglas C. Duquette and Drs. Jimin Kim, Wen-Bo Liu, Alexander N. Marziale, Douglas C. Behenna, Scott C. Virgil and has been published. See: Bennett, N. B.[‡]; Duquette, D. C.[‡]; Kim, J.; Liu, W.-B.; Marziale, A. N.; Behenna, D. C.; Virgil, S. C.; Stoltz, B. M. *Chem.—Eur. J.* **2013**, *19*, 4414–4418. [‡]N.B.B. and D.C.D contributed equally to this article.

transformation. Recently, we discovered that the allylic alkylation of lactams (**4a** to **5a**) and imides (**6a** to **7a**) with (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**)[5c] consistently proceeds with enantioselectivities substantially higher than any other substrate class previously examined in this system (Scheme 1.1B and C).[10] This observation prompted us to investigate which characteristics distinguish these molecules as superior alkylation substrates. The basic distinctions between these ketone and *N*-heterocyclic molecules are the deviation in electronic nature of the enolate and the identity of the α'-functionality (i.e., the group flanking the carbonyl at the site opposite of alkylation). Thus, we have designed several new alkylation substrates to examine the relative contribution of each effect. We have found that the exceptional enantioselectivities observed in the lactam/imide series are likely not a result of a purely electronic effect, but a combination of stereoelectronic and steric factors associated with the α'-substituent. To provide a more complete perspective on allylic alkylation selectivity, this chapter also discusses related research efforts performed by other groups.

Scheme 1.1. Comparison of allylic alkylation of ketones, lactams, and imides.

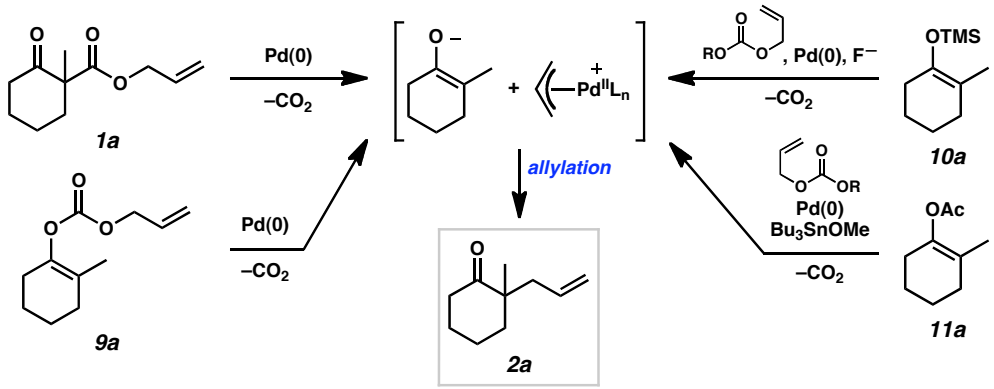


1.1.1 Pd-Catalyzed Asymmetric Allylic Alkylation Background

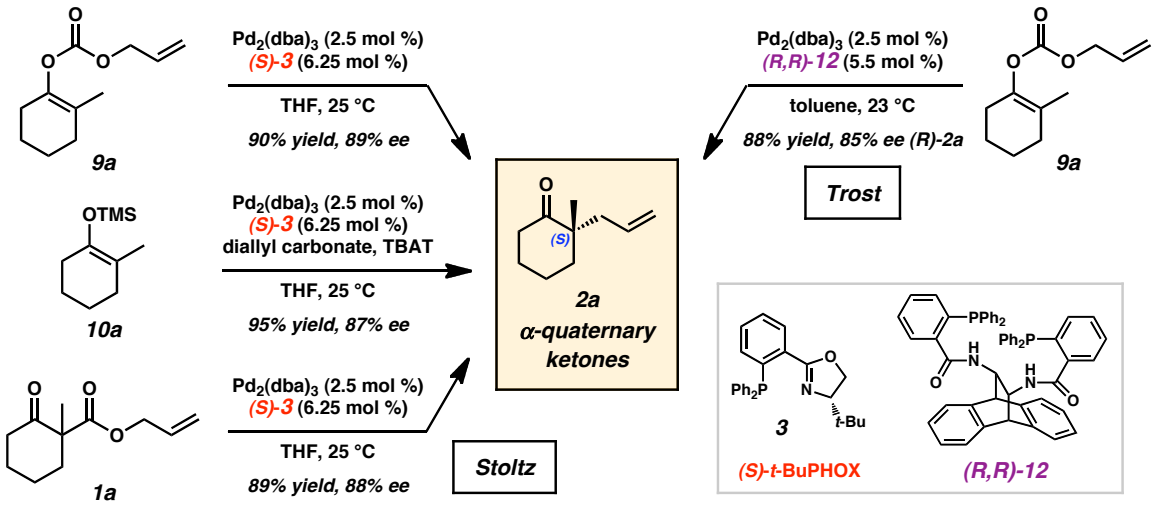
Our entry into asymmetric allylic alkylation methodology began in 2004, when we reported the preparation of α-quaternary cyclic ketones from allyl enol carbonates (**9**) and silyl enol ethers (**10**).[6a] Twenty years prior, Tsuji performed the regioselective allylation of these and other unstabilized enolate precursors under essentially neutral conditions with Pd(0) catalysts (Scheme 1.2).[11] Inspired by Tsuji's approach, we screened a series of chiral *P*,*P*-, *P*,*O*-, and *P*,*N*-ligands in the allylic alkylation of allyl enol carbonate **9a** with $Pd_2(dba)_3$ as a Pd(0) source. Gratifyingly, *P*,*N*-ligands generate the desired enantioenriched ketone product in good yield and ee, with (*S*)-*t*-BuPHOX (**3**) providing the greatest enhancement in selectivity (Scheme 1.3). Silyl enol ethers (**10**)

necessitate the addition of a fluoride source and allyl carbonate, but provide similar results.[6a] We later found that racemic β-ketoesters (**1**) are also excellent substrates under the standard enol carbonate conditions. Notably, β-ketoesters are easy to prepare, are often more stable than the corresponding allyl enol carbonates, and avoid regioselectivity issues in enolate formation with α,β-unsaturated substrates. Following our initial publication, Trost disclosed allylic alkylation conditions for allyl enol carbonates with their C_2-symmetric *P*,*P*-ligands (e.g., (*R*,*R*)-**12**, Scheme 1.3).[2a,12] These initial publications by Stoltz and Trost represent the first examples of the regioselective and enantioselective alkylation of ketones with multiple acidic sites. Although not discussed in this chapter, Hayashi,[13] Ito,[14] Trost,[2a,15] and Hou and Dai[16] have also performed asymmetric alkylation of ketones, however, their approaches require the substrate to possess an occluded α'-position (i.e., one deprotonation site) or a stabilizing α-group (i.e., favored deprotonation site).

Scheme 1.2. Various enolate precursors investigated in the Tsuji reaction.

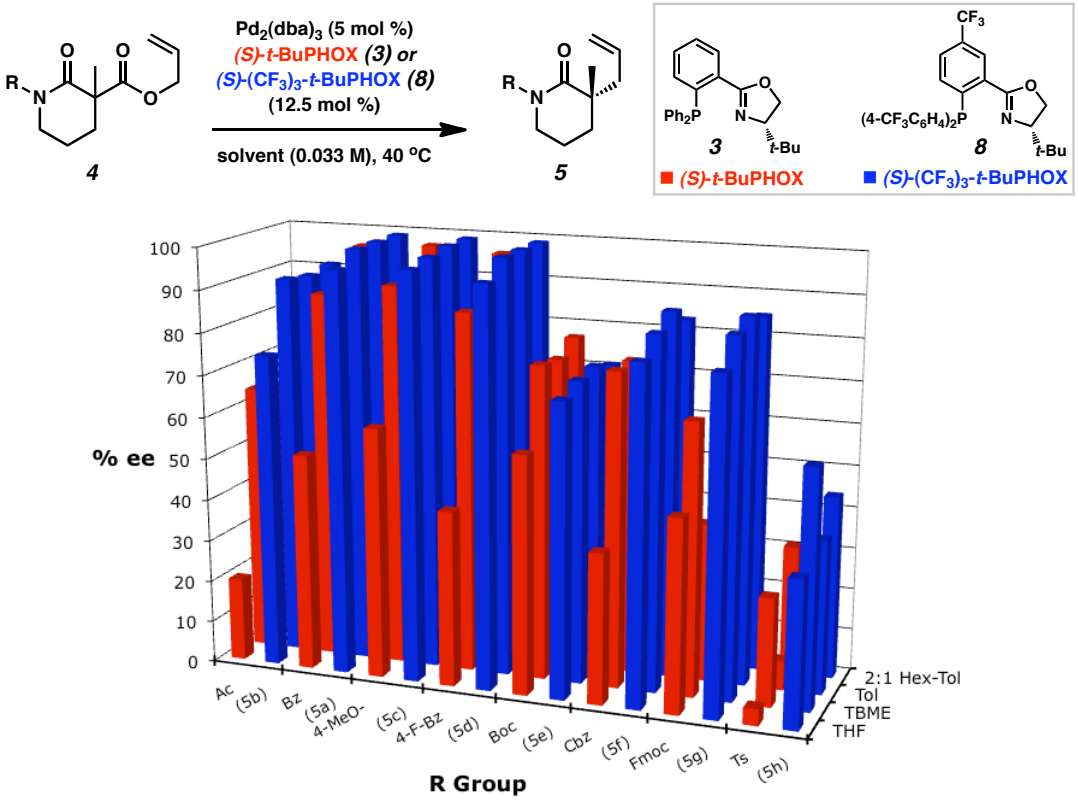


Scheme 1.3. Pd-catalyzed asymmetric allylic alkylations performed by Stoltz and Trost.



As part of our efforts to expand the reaction scope, we explored nitrogen-containing substrates including lactams.[10] Early efforts indicated the *N*-substituent plays a significant role in conversion and enantioselectivity. Notably, electron-rich lactams (*N*-group = Me or Bn) exhibit little to no conversion to the desired products and, as such, are poor alkylation substrates. We consequently prepared a variety of lactams with electron-withdrawing functionality (**4a**–**h**) and screened these molecules against two electronically differentiated chiral ligands, (*S*)-**3** and (*S*)-**8**, and four solvents of varying polarity: tetrahydrofuran (THF), *tert*-butyl methyl ether (TBME), toluene, and 2:1 hexane–toluene (Table 1.1). In general, higher enantioselectivities are observed in less polar solvents with (*S*)-**8** as a ligand. Among the *N*-substituent, benzoyl is optimal and provides nearly perfect selectivity. The transformation is also tolerant of various α-groups and ring sizes and additionally provides high ee for cyclic imides. By comparison, α-quaternary ketones are formed with approximately 10% lower ee, prompting us to question what characteristics distinguish lactams and imides as better substrates.

Table 1.1. Lactam allylic alkylation screen.[a]



					Enantiomeric Excess (% ee)[b]			
entry	substrate *4*	R	product *5*	ligand	THF	TBME	Toluene	2:1 Hex–Tol
1 2	*4b*	Ac	*5b*	*3* *8*	20 75	64 91[d]	62 90[d]	83 91[d]
3 4	*4a*	Bz	*5a*	*3* *8*	52 96	88 99	86 99	96 99
5 6	*4c*	4-MeO-Bz	*5c*	*3* *8*	60 97	91 98	87 99	97 99
7 8	*4d*	4-F-Bz	*5d*	*3* *8*	42 95	86 99	83 99	96 99
9 10	*4e*	Boc[c]	*5e*	*3* *8*	57 70	75 72	74 73	77 71
11 12	*4f*	Cbz	*5f*	*3* *8*	36 80	75 84	75 87	72 83
13 14	*4g*	Fmoc	*5g*	*3* *8*	46 79	65 85	38 87	45 85
15 16	*4h*	Ts[c]	*5h*	*3* *8*	4 35	26 57	7 37	31 44

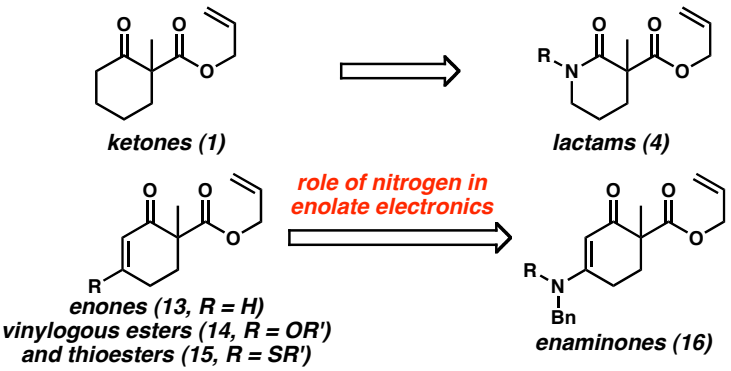
[a] *Conditions*: lactam **4** (1.0 equiv), $Pd_2(dba)_3$ (5 mol %), and *(S)*-*t*-BuPHOX (**3**) or *(S)*-$(CF_3)_3$-*t*-BuPHOX (**8**) (12.5 mol %) in solvent (0.033 M) at 40 °C. [b] Determined by GC, HPLC, or SFC analysis. Red = with *(S)*-(**3**) as ligand and blue = with *(S)*-(**8**) as ligand. [c] Reaction performed with $Pd_2(pmdba)_3$ at 50 °C. [d] Reaction performed at 60 °C.

1.2 RESULTS AND DISCUSSION

1.2.1 Electronically Variable Substrates

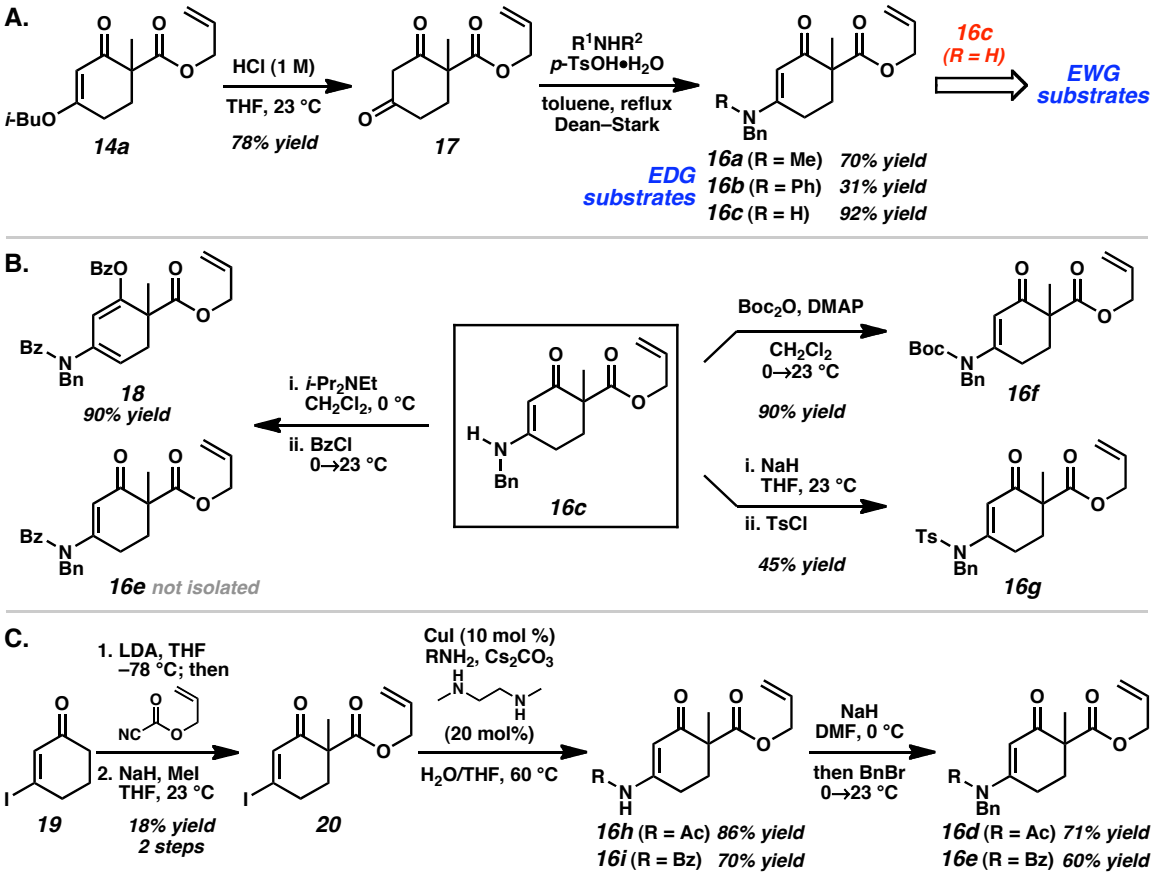
Initially, we hypothesized that the divergence in enolate electronics between the substrate classes depicted in Scheme 1.1 could be the major determining factor of the observed enantioselectivities. Insight from our previous work[9,10] suggested that selectivity in the alkylation of electron-poor and -rich molecules could be considerably different. To investigate the electronic effect of the nitrogen atom on alkylation selectivity without the influence of α'-functionality, we examined variably functionalized enaminones (**16**, i.e., vinylogous amides)[17] as electronic analogues of lactams (**4**, Figure 1.1). We were particularly drawn to this new class of compounds as our past experience with vinylogous esters (**14**)[18] and thioesters (**15**)[18b,19] would provide a foundation and comparison point.[20]

Figure 1.1. Ketone and lactam enantioselectivity divergence as inspiration for investigation of enolate electronics using vinylogous systems.



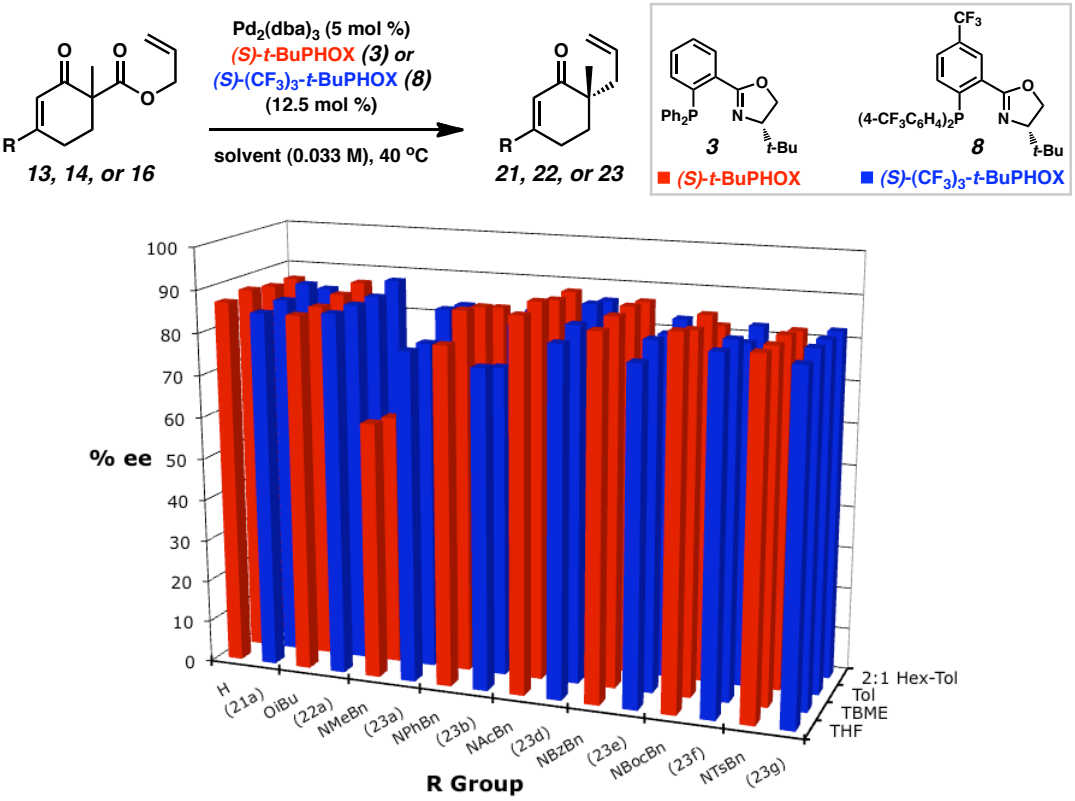
To this end, we prepared a number of racemic enaminone alkylation precursors from vinylogous ester **14a** (Scheme 1.4A). Treatment of vinylogous ester **14a** with hydrochloric acid in THF selectively removes the vinylogous group without hydrolyzing the carboxylic ester, as reported by Desmaële.[21] The resulting dione (**17**) can be condensed with an amine under dehydrative conditions to generate enaminones **16a–c**, which bear electron-donating groups.[22,23,24] To prepare substrates with electron-withdrawing functionality, we explored derivatization of enaminone **16c** to acetyl (**16d**), benzoyl (**16e**), tosyl (**16g**), and Boc (**16f**) accessorized products (Scheme 1.4B). The acylation of secondary enaminones using an amine base has previously been reported;[23a,25] however, exposure of intermediate **16c** to diisopropylethylamine (*i*-Pr_2NEt) and benzoyl chloride surprisingly produces diene **18** in 90% yield. We also examined other amine bases (e.g., pyridine and Et_3N), reagent equivalents, and the order of reagent addition, but in each case isolated a mixture of over acylated product and desired enaminone **16e**.[26] Similar results were obtained with acetyl chloride. The use of sodium hydride[27] eliminates over acylation, but provides enaminone **16e** with insufficient purity. Nevertheless, these conditions are amenable to the synthesis of tosyl enaminone **16g**, albeit in low yield.[28] The acylated and benzoylated enaminones (**16d** and **e**) can ultimately be obtained from iodoenone **19**[29] through a Buchwald coupling[30] and alkylation sequence (Scheme 1.4C). Boc functionalized enaminone **16f** is prepared without complication following the precedent of Hiemstra (Scheme 1.4B).[31]

Scheme 1.4. Preparation of enaminone alkylation precursors.



With a number of enaminones in hand, we screened a series of palladium-catalyzed decarboxylative allylic alkylation conditions (Table 1.2). Enaminone substrates that possess a hydrogen on the nitrogen (e.g., **16c** and **i**) generate a number of alkylation products with a Pd(PHOX) system and were consequently excluded from this study. The enaminone screen was performed in a manner similar to the previous investigation of lactams,[10,32] employing the ligands (*S*)-**3** and (*S*)-**8** and the same four solvents: tetrahydrofuran (THF), *tert*-butyl methyl ether (TBME), toluene, and 2:1 hexane–toluene.

Table 1.2. Enaminone allylic alkylation screen.[a]



					Enantiomeric Excess (% ee)[b]			
entry	substrate	R	product	ligand	THF	TBME	Toluene	2:1 Hex–Tol
1 2	*13a*	H	*21a*	*3* *8*	87 85	88 86	87 88	87 85
3 4	*14a*	O*i*-Bu	*22a*	*3* *8*	85 86	85 86	86 86	87 88
5 6	*16a*	NMe(Bn)	*23a*	*3* *8*	61 79	60 78	55 84	52 83
7 8	*16b*	NPh(Bn)	*23b*	*3* *8*	81 76	87 74	85 82	83 83
9 10	*16d*	NAc(Bn)	*23d*	*3* *8*	89 83	90 85	88 88	88 86
11 12	*16e*	NBz(Bn)	*23e*	*3* *8*	86 80	87 83	88 82	87 83
13 14	*16f*	NBoc(Bn)	*23f*	*3* *8*	87 84	86 84	87 81	82 83
15 16	*16g*	NTs(Bn)	*23g*	*3* *8*	84 82	83 83	83 83	82 83

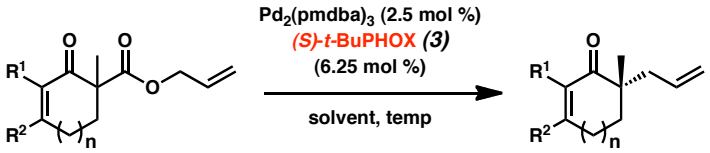
[a] *Conditions*: enone **13a**, vinylogous ester **14a**, or enaminone **16a, b, d–g** (1.0 equiv), $Pd_2(dba)_3$ (5 mol %), and *(S)*-*t*-BuPHOX (**3**) or *(S)*-$(CF_3)_3$-*t*-BuPHOX (**8**) (12.5 mol %) in solvent (0.033 M) at 40 °C. [b] Determined by GC, HPLC, or SFC analysis. Red = with *(S)*-(**3**) as ligand and blue = with *(S)*-(**8**) as ligand.

We made several observations upon analysis of the ligand, solvent, and substrate trends that distinguished this substrate class considerably from the previously examined lactams. First, enaminones are obtained in modestly better selectivity with (*S*)-**3** as a ligand in most solvents (entries 7–16), with the exception of methyl enaminone **23a**, which significantly favors (*S*)-**8** (entries 5–6). Second, no significant solvent trend is observed for enaminones overall. Third, electron-rich enaminones (i.e., **16a** and **b**) display decreased enantioselectivities and also require extended reaction times for completion,[33] while enaminones bearing electron-withdrawing substituents (**23d–g**) are all generated in 80–90% ee. By comparison, lactam substrates perform with much higher enantioselectivity with ligand (*S*)-**8** in non-polar solvents.[10,34] Furthermore, the modest distinction in enantioselectivity for the electron-withdrawing enaminones sharply contrasts with the corresponding lactam series, where the *N*-substituent plays a considerable role, producing significant variation in selectivity.[10,35] These differences suggest that the *N*-functional group does not contribute to enantioselectivity solely through a perturbation of enolate electronics.

Beyond these considerations, the most striking feature of the screen is that enantioselectivities observed for enaminones **23d–g** are approximately equivalent to results obtained for enone **21a**,[36] vinylogous ester **22a**, previously investigated vinylogous molecules (Table 1.3),[18b,19] and even more general ketone substrates. Of all the enaminones screened, acetyl variant **23d** provides the highest selectivity at 90% ee in TBME, which is only marginally better than the optimal values for the related vinylogous systems. The modest differences between these vinylogous molecules (i.e., **21–23**)

further suggest that the electronic nature of the enolate is not likely the predominant factor in providing high enantioselectivity for lactams and imides.

Table 1.3. Alkylation of other vinylogous esters and thioesters.[a]



14/24 and 15/25 ***22/27 and 26/28***

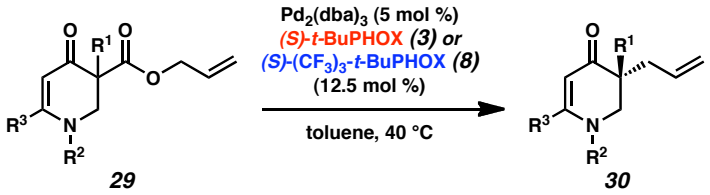
entry	substrate	n	R^1	R^2	product	solvent	temp (°C)	yield (%)	ee (%)[b]	ref.
1	***14b***	1	Me	O*i*-Bu	***22b***	toluene	80	86	75	19a
2	***15a***	1	Me	SPh	***26a***	toluene	50	85	92	19a
3	***15a***	1	Me	SPh	***26a***	benzene	50	61[c]	92	19a
4	***15a***	1	Me	SPh	***26a***	THF	50	88	92	19a
5	***15a***	1	Me	SPh	***26a***	1,4-dioxane	50	88	92	19a
6	***24a***	2	H	O*i*-Bu	***27a***	Et_2O	30	93	86	18b
7	***25a***	2	H	SPh	***28a***	Et_2O	30	86	89	18b

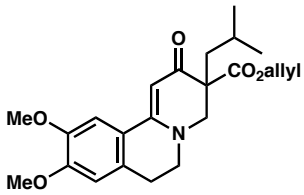
[a] *Conditions*: vinylogous ester **14**/**24** or vinylogous thioester **15**/**25**, $Pd_2(pmdba)_3$ (2.5 mol %), and *(S)-t*-BuPHOX (**3**) (6.25 mol %) in solvent at temp. [b] Determined by HPLC or SFC analysis. [c] β-Ketoester **15a** recovered in 26% yield.

While pursuing enaminones, we also briefly examined the related 2,3-dihydropyridin-4-ones, which possess the nitrogen within the ring (Table 1.4). Acylation and alkylation (or vice versa) of known dihydropyridinones[37,38,39] allows preparation of the reaction precursors **29a–d**. Under our standard palladium-catalyzed conditions, *N*-carboxybenzyl substituted product **30a** is formed with enantioselectivities similar to electronically related enaminones. Electron-rich 2,3-dihydropyridin-4-ones **30b** and **c** are curiously also generated in the same range. Even 2,3-dihydropyridin-4-one **30d** is produced in excellent enantioselectivity, despite the highly electron-rich nature of the

enolate. These results again allude to other factors beyond enolate electronics that direct alkylation selectivity.

Table 1.4. Allylic alkylation of 2,3-dihydropyridin-4-ones.[a]



entry	substrate *29*	R^1	R^2	R^3	product *30*	ligand	yield (%)	ee (%)[b]
1	*29a*	Me	Cbz	H	*30a*	*3*	80	86
2						*8*	98	84
3	*29b*	Me	Bn	H	*30b*	*3*	82	88
4						*8*	94	86
5	*29c*	*i*-Bu	Bn	H	*30c*	*3*	85	84
6						*8*	81	88
7	*29d*				*30d*	*8*	81	91

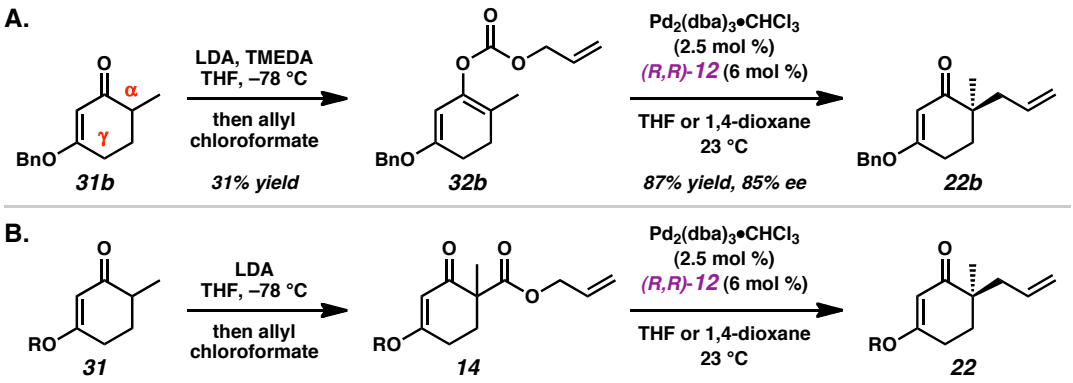
[a] *Conditions*: 2,3-dihydropyridin-4-ones **29**, $Pd_2(dba)_3$ (5 mol %), and *(S)*-*t*-BuPHOX (**3**) or *(S)*-$(CF_3)_3$-*t*-BuPHOX (**8**) (12.5 mol %) in toluene (0.033 M) at 40 °C. [b] Determined by HPLC or SFC analysis. Red = with *(S)*-**3** as ligand and blue = with *(S)*-**8** as ligand.

1.2.1.1 Other Reports of Allylic Alkylation on Vinylogous Molecules

Trost has also reported the palladium-catalyzed allylic alkylation of vinylogous esters and thioesters employing their C_2-symmetric *P*,*P*-ligands. In particular, their 2006 study prepares a range of related α-quaternary vinylogous products using (*R*,*R*)-**12**.[20a] This effort first focused on the transformation of vinylogous esters into allyl enol carbonate alkylation precursors. However, enolate regioselectivity (α vs. γ deprotonation) is poor for a number of vinylogous alkoxy groups except benzyl (**32b**),

although this carbonate product is formed in low yield (Scheme 1.5A). Several β-ketoesters were alternatively examined, but lower conversions were observed with these substrates than with enol carbonate **32b** (Scheme 1.5B). The best results were obtained with phenyl and Boc substituted β-ketoesters (**14e** and **f**), which have decreased electron-donating contribution from the vinylogous oxygen. Trost consequently investigated the analogous thioesters, reasoning that sulfur would have less orbital overlap. Vinylogous thioester **14b** performs with good yield and perfect enantioselectivity (Scheme 1.6), and a variety of other thioesters are also produced with good to excellent ee. Trost has also examined exocyclic vinylogous esters and carried the enantioenriched products onto the natural products hamigeran B[20b,c] and allocyathin B_2.[20d]

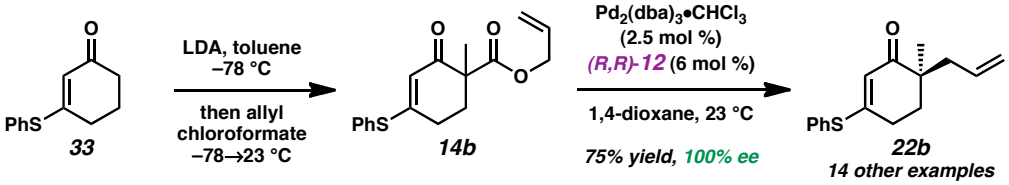
Scheme 1.5. Asymmetric allylic alkylation of vinylogous esters performed by Trost.



entry	substrate *31*	R^1	product *14*	yield (%)[b]	product *22*	yield (%)[b]	ee (%)[c]
1	*31b*	Bn	*14b*	87	*22b* [e]	51	91
2	*31c*	Et	*14c*	85	*22c* [d]	26	94
3	*31d*	*t*-Bu	*14d*	85	*22d* [d]	29	97
4	*31e*	Ph	*14e*	91	*22e* [d]	70	96
5	*31f*	Boc	*14f*	32	*22f* [e]	66	94

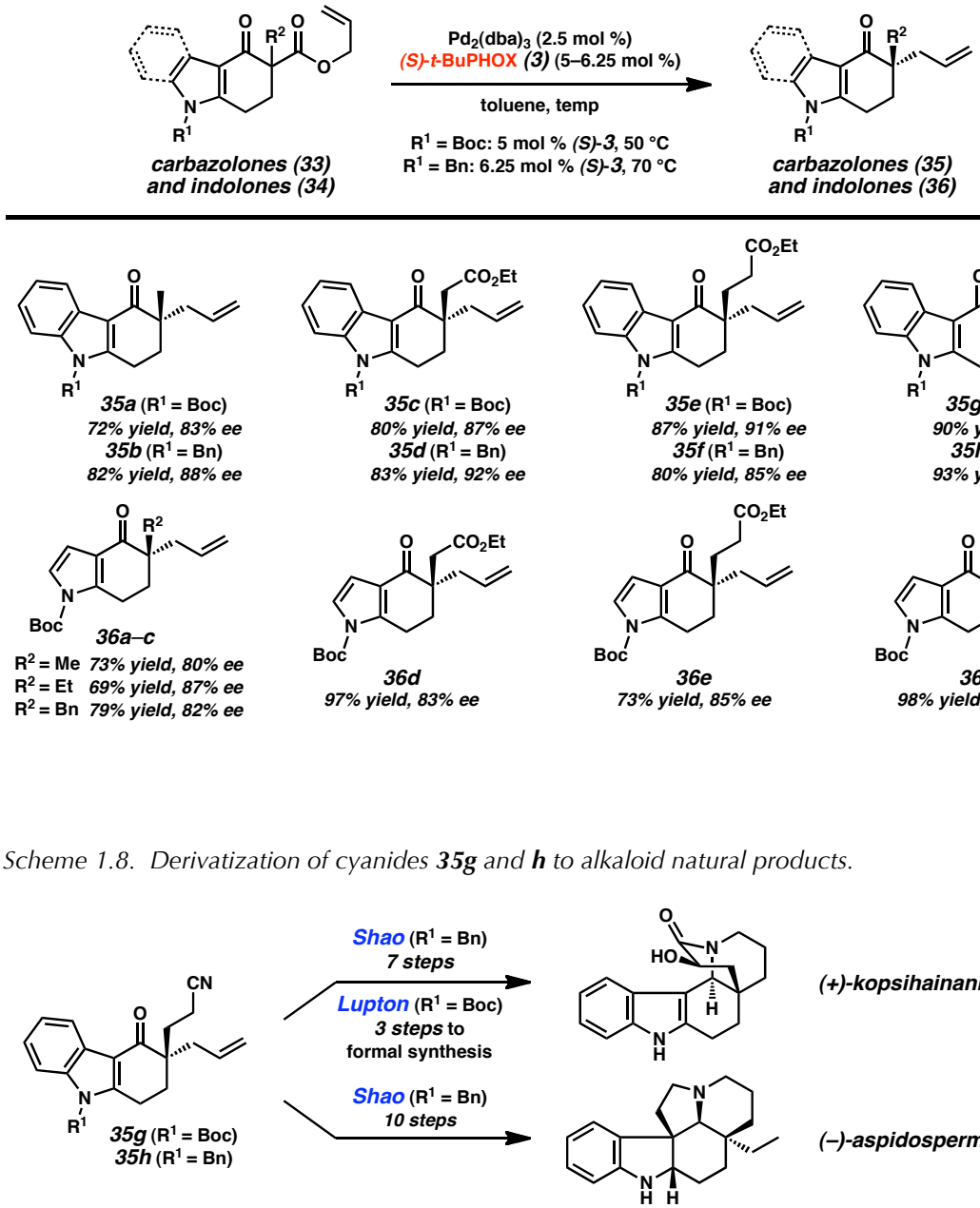
[a] *Conditions*: vinylogous ester **16**, $Pd_2(dba)_3$ (5 mol %), and *(R,R)*-**12** (6 mol %) in solvent (0.1 M) at 23 °C. [b] Isolated yield. [c] Determined by HPLC analysis. [d] 1,4-dioxane as solvent. [e] THF as solvent.

Scheme 1.6. Asymmetric allylic alkylation of vinylogous thioesters performed by Trost.



Concurrent with our efforts on enaminones, Lupton[40] and Shao[41] independently published sequential reports on the Pd-catalyzed allylic alkylation of two other vinylogous amide classes, carbazolones (**33**) and indolones (**34**) (Scheme 1.7). The reaction parameters between the two papers are almost identical (Lupton: 5 mol% ligand, 50 °C; Shao: 6.25 mol % ligand, 70 °C)[42] and many of the substrates are also related. In these efforts, Lupton selects a Boc *N*-protecting group, while Shao employs a benzyl substituent. The enantioselectivities of the methyl/allyl α-quaternary carbazolones (**35a** and **b**) and indolones (**36a**) are comparable to our results with enaminones that possess electron-withdrawing functionality. Even the *N*-benzyl carbazolones are produced in good to excellent ee, unlike the enaminones that bear electron-rich groups (**23a** and **b**). In addition to screening several alkylation precursors, both laboratories advance their enriched cyanide alkylation products (**35g** and **h**) onto (+)-kopsihainanine A (**37**) through total and formal synthetic routes, and Shao also completes the alkaloid (–)-aspidospermidine (**38**, Scheme 1.8).

Scheme 1.7. Alkylation of carbazolone (Lupton, R^1 = Boc; Shao, R^1 = Bn) and indolone (Lupton) substrates reported in 2013.

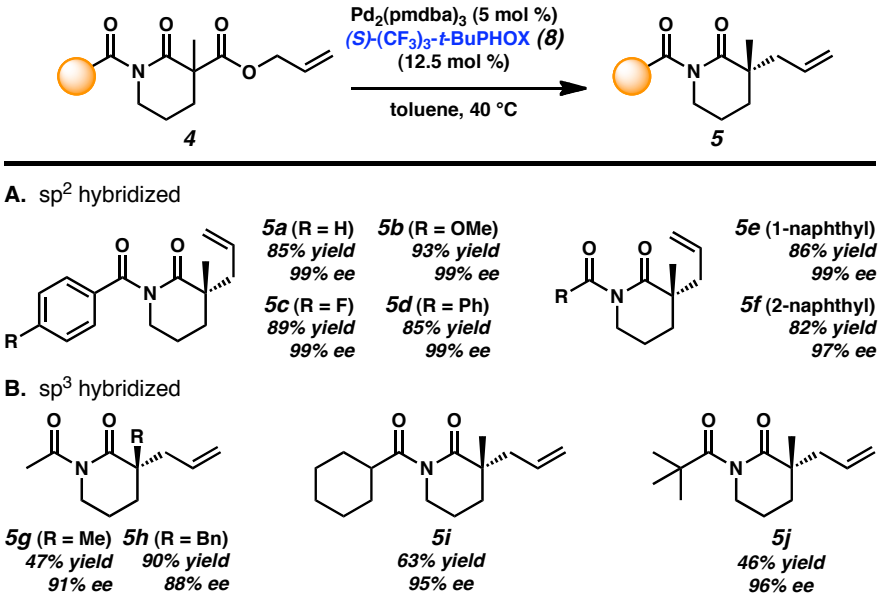


*Scheme 1.8. Derivatization of cyanides **35g** and **h** to alkaloid natural products.*

1.2.2 α'-Functionalized Substrates

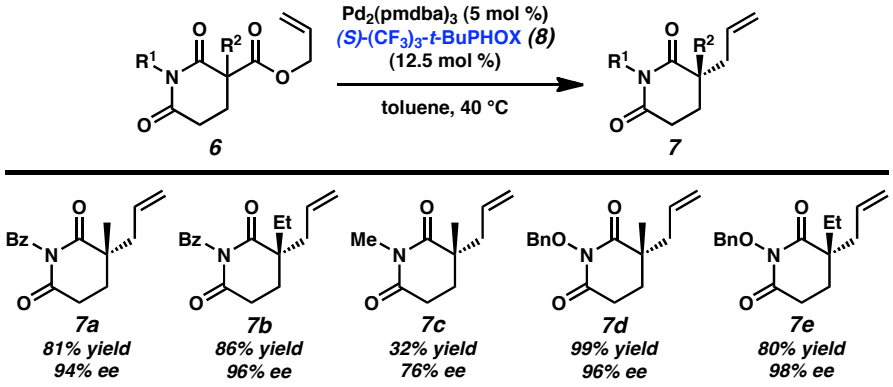
Having investigated the impact of enolate electronics, we diverted our efforts to study the influence of α'-functionality on alkylation selectivity (Scheme 1.9). Our previous lactam screen identified the benzoyl moiety as the optimal protecting group,[10] providing high to nearly perfect enantioselectivities for a variety of lactams (e.g., **5a**). Interestingly, both electron-rich and electron-poor benzoyl lactams (**5b–d**) as well as naphthoyl lactams (**5e** and **f**) display excellent ee, whereas acetyl lactams (e.g., **5g** and **h**) provide lower selectivity. This prompted us to question whether these results are due to a hybridization or steric effect. Consequently, we synthesized the bulky sp^3 hybridized cyclohexoyl lactam **4i** and pivaloyl lactam **4j**, which proceed in improved enantioselectivities compared to analogous acetyl lactam **4g**, supporting a steric effect.[43]

Scheme 1.9. Impact of various sp^3 and sp^2 acyl groups on allylic alkylation enantioselectivity for lactams.



In conjunction with our investigation of the asymmetric allylic alkylation of lactams, we found that *N*-benzoyl cyclic imides **7a** and **b** are furnished in excellent ee (Scheme 1.10). However, we observed that formation of *N*-methyl imide **7c** proceeds with moderate enantioselectivity and is hampered by low reactivity.[43] As this substrate also generates an intermediate imido enolate (as do lactams **5a**–**j**, Scheme 1.9), this result further supports our conclusion that enolate electronics do not play a major role in the enhanced enantioselectivities observed for *N*-benzoyl lactams. As such, we examined the influence of alternate *N*-substituents in the context of the allylic alkylation with imides.

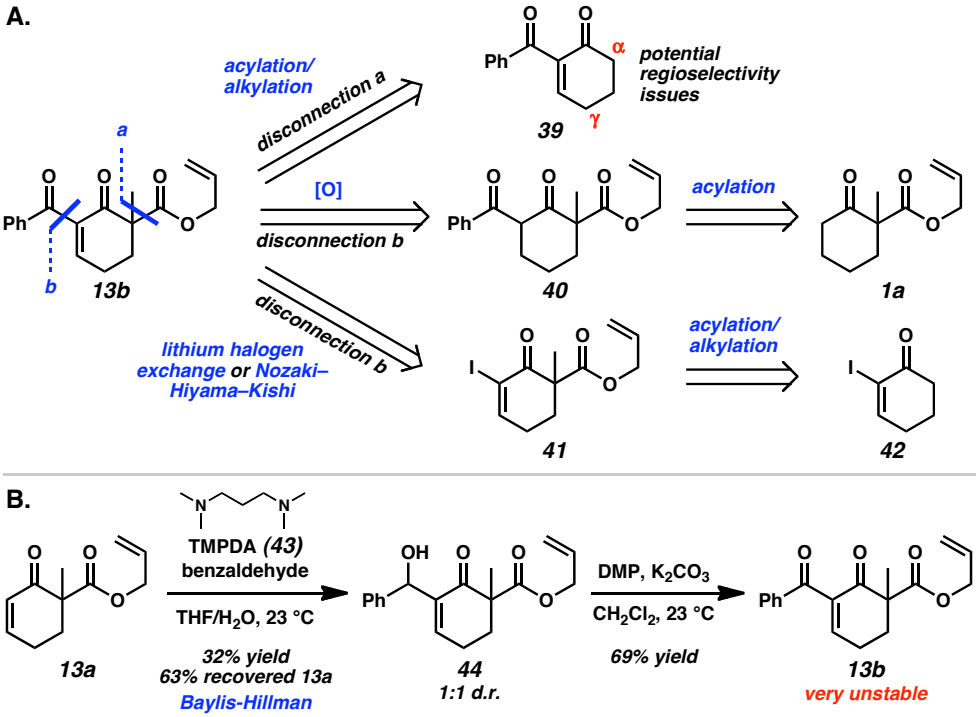
Scheme 1.10. Allylic alkylation of cyclic imides.



Gratifyingly, we identified *N*-benzyloxy imides as excellent substrates for this methodology, generating imides **7d** and **e** in yields and enantioselectivities comparable to their *N*-benzoyl counterparts. In conjunction with the results obtained for substituted *N*-acyl lactams **5g**–**j**, we reason that the nature of the α'-substituent leads to the observed enhancements in enantioselectivity, though enolate electronics have been shown to dramatically affect the reaction rate.

We sought to further probe the α'-group contribution without the influence of nitrogen and consequently focused on a series of α'-functionalized enones, including benzoyl enone **13b** (Scheme 1.11). Previous research suggested enolization regioselectivity issues may arise in acylating/alkylating enone **39** (α vs. γ, path A),[6b] prompting us to pursue approaches to enone **13b** through retrosynthetic disconnection of the benzoyl substituent (path B). Unfortunately, attempts to acylate and oxidize β-ketoester **1a** proved unsuccessful. Both lithium halogen exchange and Nozaki–Hiyama–Kishi coupling on iodoenone **41** also failed to install the benzoyl group. The synthesis of enone **13b** is ultimately possible via a Baylis–Hillman[44] reaction and oxidation sequence (Scheme 1.11B). A number of oxidants were examined in the latter transformation, but only Dess–Martin periodinane (DMP) proved successful. Benzoyl enone **13b** is very sensitive to alkene isomerization, and thus the addition of potassium carbonate as a buffer and the use of triethylamine deactivated silica gel for purification are necessary. Although we were able to prepare enone **13b**, stability issues make this molecule a poor alkylation substrate and prohibit the isolation of the desired methyl/allyl α-quaternary enone under our standard palladium-catalyzed conditions.

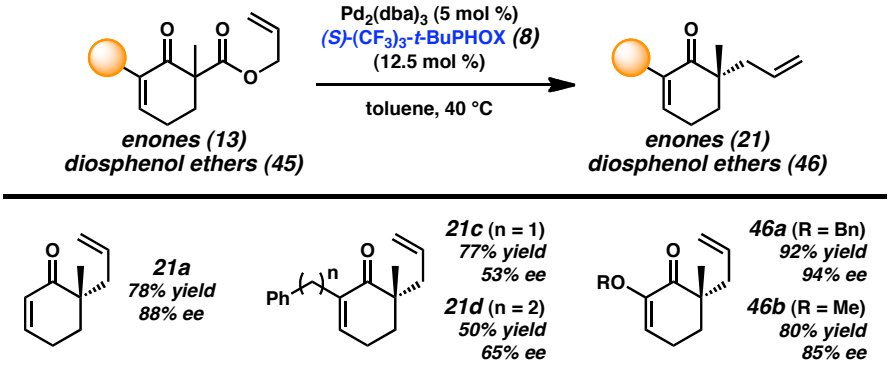
Scheme 1.11. Retrosynthetic approaches and successful route to benzoyl enone ***13b****.*



Despite the complications with benzoyl enone **13b**, we were able to synthesize enones **13c** and **d** and diosphenol ethers **45a** and **b** under standard acylation/alkylation conditions. To examine the relative merit of the steric and stereoelectronic effects associated with the α'-substituent, we subjected these substrates to the palladium-catalyzed alkylation parameters employed with lactams and imides (Scheme 1.12). In this transformation, enones **21c** and **d** are formed in low enantioselectivity. By contrast, benzyl diosphenol ether **46a**, which differs from **21d** only in the substitution of oxygen for a methylene group, is generated in 92% yield and 94% ee. This suggests that purely steric or π-stacking interactions are not the sole contributing factors to enantioselectivity. Rather, electronic effects of the α'-substituent exert an important influence on the stereoselectivity of the reaction. However, a certain amount of steric bulk appears critical

in obtaining high enantioselectivity as methyl diosphenol ether **46b** is produced in 85% ee. In comparison, analogous enone **21a**, which bears no α'-functionality, proceeds under the same conditions to afford enone **21a** in 88% ee,[36] with vinylogous amides and esters also in the ~80–90% ee range (*vide supra*). Overall, our studies on the role of the α'-substituent have culminated in the discovery of substrate **45a**, which proceeds with the greatest enantioselectivity observed in a Pd(PHOX) catalyst system for a carbocyclic substrate bearing an α-methyl and unsubstituted allyl moiety.

Scheme1.12. Allylic alkylation of α'-functionalized enones and diosphenol ethers.



1.3 CONCLUDING REMARKS

In summary, we have designed and evaluated a number of novel substrates to probe the influence of enolate electronics and the role of α'-functionality on selectivity in the palladium-catalyzed decarboxylative allylic alkylation. Based on these results, we reason that the high enantioselectivities observed with lactams and imides are a consequence of both electronic and steric effects associated with α'-substituents, and that enolate electronics alone contribute relatively little to the stereochemical outcome of the

reaction. Both experimental and theoretical investigations are currently underway in our group to determine the nature and origin of the effect of α'-substitution on this transformation and to use this insight to improve and expand our methods.

1.4 EXPERIMENTAL SECTION

1.1.1 MATERIALS AND METHODS

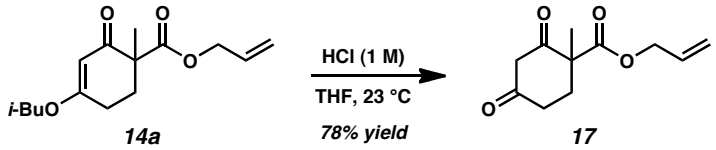
Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[45] Acetone was used directly from a Sigma-Aldrich ACS reagent grade bottle. Brine solutions are saturated aqueous solutions of sodium chloride. Reagents were purchased from Sigma-Aldrich, Acros Organics, Strem, or Alfa Aesar and used as received unless otherwise stated. (*S*)-*t*-BuPHOX (**3**),[5ab] (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**),[5c] and allyl cyanoformate[46] were prepared by known methods. Reaction temperatures were controlled by an IKAmag temperature modulator. Reaction progress was monitored by thin-layer chromatography (TLC). 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. ICN silica gel (particle size 0.032-0.0653 mm) was used for flash column chromatography. Preparative HPLC purification was performed on an Agilent 1200 Series HPLC using an Agilent Prep-SIL column (5 μm, 30 x 250 mm) at ambient temperature with a flow rate of 50 mL/min. Separation was monitored by UV (λ = 254 nm) and fractions were collected at the valleys between peaks. ^{1}H NMR spectra were recorded on a Varian Mercury 300 MHz or Varian Inova 500 MHz spectrometer and are reported relative to residual $CHCl_3$ (δ 7.26 ppm) or benzene-d_6 (δ 7.16 ppm). ^{13}C NMR spectra are recorded on a Varian Mercury 300 MHz or Varian Inova 500 MHz spectrometer (75 or 125 MHz respectively) and are reported relative to $CDCl_3$ (δ 77.16 ppm) or benzene-d_6 (δ 128.06

ppm). Variable temperature NMR experiments were performed on a Varian Inova 500 MHz spectrometer and are reported relative to residual DMSO (δ 2.50 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, dm = doublet of multiplets, br s = broad singlet, br d = broad doublet, app = apparent. Data for ^{13}C are reported in terms of chemical shifts (δppm). 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 and are reported as: $[\alpha]_D^T$ (concentration in g/100 mL, solvent, *ee*). Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralpak (AD, AD-H, or AS) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. Analytical chiral SFC was performed with a JASCO 2000 series instrument or a Thar SFC utilizing Chiralpak (AD-H or AS-H) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm), or a Chiralpak IC column (4.6 mm x 10 cm) obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility (GC-EI+, EI+, or FAB+) or 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+).

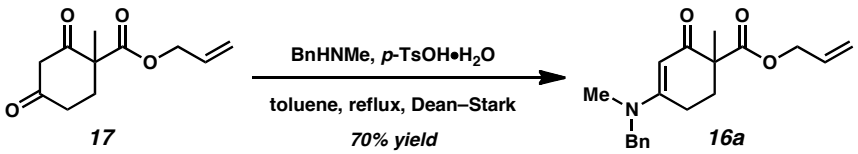
1.4.2 PREPARTIVE PROCEDURES

1.4.2.2 Preparation of Compounds Related to Enaminone Screen

1.4.2.2.1 *Enaminone Allylic Alkylation Precursors*

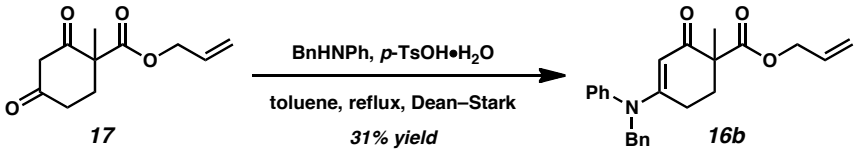


Dione 17. Procedure adapted from report by Desmaële.[21] A 100 mL round-bottom flask equipped with a magnetic stir bar was charged with vinylogous ester **14a**[18c] (3.08 g, 11.58 mmol, 1.00 equiv), THF (30 mL, 0.39 M), and aq HCl (1 M in H_2O, 14.00 mL, 14.00 mmol, 1.21 equiv). The reaction mixture was initially a suspension that developed into a solution over time. After 7 h of vigorous stirring at ambient temperature, the reaction was diluted with EtOAc (30 mL) and transferred to a separatory funnel where the aqueous layer was extracted seven times with EtOAc. The combined organics (400 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 31 x 5 cm, 100% hexanes→20%→50% EtOAc in hexanes) to afford dione **17** (1.89 g, 11.58 mmol, 78% yield) as a pale yellow oil; R_f = 0.17 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) mixture of keto-enol tautomers, see spectra section; IR (Neat Film NaCl) 3500–2500 (broad stretch), 3088, 2983, 2939, 2657, 2591, 1734, 1595, 1457, 1413, 1383, 1358, 1343, 1309, 1272, 1249, 1190, 1114, 986, 932, 853 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{11}H_{15}O_4$ $[M+H]^+$: 211.0965, found 211.0966.



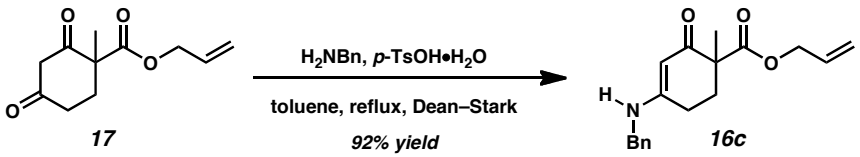
Enaminone 16a. A 50 mL round-bottom flask containing a magnetic stir bar was charged with dione **17** (465.4 mg, 2.21 mmol, 1.00 equiv), toluene (24 mL, 0.09 M), benzylmethylamine (320 µL, 2.48 mmol, 1.12 equiv), and *p*-toluenesulfonic acid monohydrate (42.3 mg, 0.22 mmol, 10 mol %). The flask was equipped with a Dean–Stark trap and water condenser and was lowered into a preheated oil bath (135 °C). After 2 h of refluxing, the solution was removed from the oil bath and allowed to cool to room temperature. The solution was quenched with a sat. Na_2CO_3 solution (20 mL) and transferred to a separatory funnel where the aqueous layer was extracted four times with CH_2Cl_2. The combined organics (200 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 27 x 3 cm, 100% hexanes→20%→50%→60%→70% EtOAc in hexanes) to afford enaminone **16a** (484.8 mg, 1.55 mmol, 70% yield) as a yellow/orange oil; R_f = 0.24 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.33 (m, 2H), 7.32–7.27 (m, 1H), 7.09 (d, J = 7.4 Hz, 2H), 5.93–5.83 (m, 1H), 5.29 (dq, J = 17.3, 1.5 Hz, 1H), 5.26 (s, 1H), 5.18 (dq, J = 10.5, 1.4 Hz, 1H), 4.66–4.56 (m, 2H), 4.51 (s, 2H), 2.96 (s, 3H), 2.74–2.63 (m, 1H), 2.56–2.45 (m, 2H), 1.95–1.84 (m, 1H), 1.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ193.9, 173.7, 164.3, 132.2, 129.1, 127.8, 126.7, 118.0, 98.1, 65.6, 55.2, 51.1, 38.5, 32.6, 24.4, 21.0; IR (Neat Film NaCl) 3063, 3028, 2933, 2873, 1733, 1615, 1585, 1563, 1557, 1495, 1455, 1415, 1377, 1352, 1332, 1295, 1258, 1222,

1203, 1174, 1113, 1028, 989, 929, 821, 735 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{19}H_{24}NO_3$ $[M+H]^+$: 314.1751, found 314.1754.



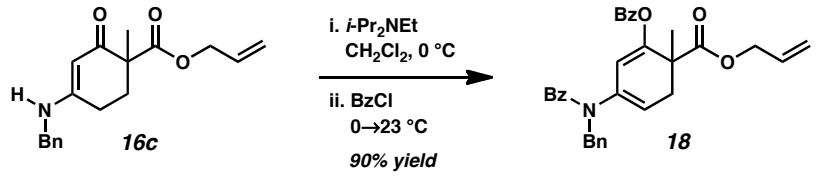
Enaminone 16b. A 50 mL round-bottom flask containing a magnetic stir bar was charged with dione **17** (500.3 mg, 2.38 mmol, 1.00 equiv), toluene (24 mL, 0.10 M), benzylphenylamine (480.0 mg, 2.62 mmol, 1.10 equiv), and *p*-toluenesulfonic acid monohydrate (45.6 mg, 0.24 mmol, 10 mol %). The flask was equipped with a Dean–Stark trap and water condenser and was lowered into a preheated oil bath (135 °C). After 8 h of refluxing, the solution was removed from the oil bath and allowed to cool to room temperature. The solution was quenched with a sat. Na_2CO_3 solution (20 mL) and transferred to a separatory funnel where the aqueous layer was extracted four times with CH_2Cl_2. The combined organics (200 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified twice by flash column chromatography (SiO_2, 26 x 3 cm, 100% hexanes→10%→15%→20%→30%→40% EtOAc in hexanes ***then*** SiO_2, 26.5 x 3 cm, 100% hexanes→ 5%→10%→15% →20%→30%→ 50% EtOAc in hexanes) to afford enaminone **16b** (276.6 mg, 0.74 mmol, 31% yield) as a yellow oil; R_f = 0.50 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.33 (m, 2H), 7.33–7.24 (m, 4H), 7.21–7.18 (m, 2H), 7.13–7.10 (m, 2H), 5.90 (dddd, J = 17.2, 10.7, 5.4, 5.4 Hz, 1H), 5.39 (s, 1H), 5.31 (dq, J = 17.2, 1.6 Hz, 1H), 5.21 (dq, J = 10.5, 1.4 Hz, 1H), 4.83 (s, 2H), 4.68–4.63 (m, 1H), 4.62–4.57 (m, 1H),

2.55–2.47 (m, 1H), 2.42 (ddd, J = 13.3, 6.1, 4.9 Hz, 1H), 2.33–2.27 (m, 1H), 1.84 (ddd, J = 13.5, 8.7, 4.9 Hz, 1H), 1.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.6, 173.3, 163.9, 144.3, 136.4, 132.2, 129.9, 128.9, 128.0, 127.9, 127.7, 127.1, 118.0, 100.4, 65.6, 56.8, 51.6, 32.9, 25.9, 21.0; IR (Neat Film NaCl) 3061, 3031, 2975, 2933, 2872, 1734, 1623, 1560, 1494, 1453, 1426, 1408, 1377, 1346, 1327, 1293, 1255, 1210, 1174, 1112, 1080, 1061, 1022, 989, 929, 885, 825, 779, 733, 702 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{24}H_{26}NO_3$ $[M+H]^+$: 376.1907, found 376.1903.



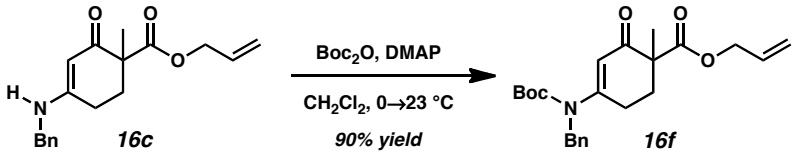
Enaminone 16c. A 250 mL round-bottom flask containing a magnetic stir bar was charged with dione **17** (1.89 g, 8.98 mmol, 1.00 equiv), toluene (90 mL, 0.10 M), benzylamine (1.1 mL, 10.04 mmol, 1.12 equiv), and *p*-toluenesulfonic acid monohydrate (169.0 mg, 0.89 mmol, 10 mol %). The flask was equipped with a Dean–Stark trap and water condenser and was lowered into a preheated oil bath (135 °C). After 5.5 h of refluxing, the solution was removed from the oil bath and allowed to cool to room temperature. The solution was quenched with a sat. Na_2CO_3 solution (50 mL) and transferred to a separatory funnel where the aqueous layer was extracted once with Et_2O and three times with dichloromethane. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 31 x 5 cm, 100% hexanes→20%→50% EtOAc in hexanes) to afford enaminone **16c** (2.48 g, 8.28 mmol, 92% yield) as a yellow solid; R_f =

0.27 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.30 (m, 3H), 7.29 (s, 2H), 5.95–5.82 (m, 1H), 5.30 (dq, J = 17.2, 1.6 Hz, 1H), 5.22 (s, 1H), 5.20 (dq, J = 10.5, 1.4 Hz, 1H), 4.62 (tt, J = 5.6, 1.5 Hz, 2H), 4.56 (br s, 1H), 4.24 (d, J = 5.0 Hz, 2H), 2.59 (ddd, J = 16.5, 8.8, 4.9 Hz, 1H), 2.50 (ddd, J = 13.3, 6.2, 4.9 Hz, 1H), 2.33 (dt, J = 16.6, 5.3 Hz, 1H), 1.91 (ddd, J = 13.6, 8.8, 5.0 Hz, 1H), 1.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.4, 173.4, 162.6, 136.7, 132.2, 129.1, 128.2, 128.0, 118.0, 96.7, 65.6, 52.1, 47.5, 32.4, 26.7, 21.1; IR (Neat Film NaCl) 3260, 3064, 2978, 2933, 2868, 1730, 1576, 1545, 1452, 1427, 1375, 1359, 1297, 1253, 1218, 1199, 1172, 1107, 1028, 987, 929, 822, 735 cm^{-1}; HRMS (GC-EI+) *m/z* calc'd for $C_{18}H_{21}NO_3$ $[M+\bullet]^+$: 299.1521, found 299.1522.



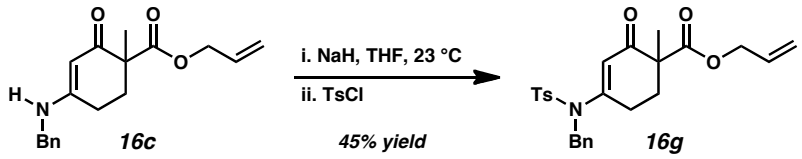
Diene 18. A 1 dram (4 mL) vial equipped with a stir bar and Teflon septa was charged with enaminone **16c** (49.9 mg, 0.167 mmol, 1.00 equiv) and lowered into a 0 °C bath (ice/water). Dichloromethane (1.7 mL, 0.10 M), *i*-Pr_2NEt (150 μL, 0.861 mmol, 5.17 equiv), and benzoyl chloride (40 μL, 0.345 mmol, 2.07 equiv) were added and the reaction was allowed to warm to room temperature over time. After 13 h, TLC analysis indicated consumption of starting material. The reaction was subsequently quenched with water (5 mL) and the aqueous layer was extracted four times with dichloromethane. The combined organics (50 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography (SiO_2, 26 x 1 cm, 5%→10%→15% EtOAc in hexanes) to afford diene **18** (75.8 mg, 0.149 mmol,

90% yield) as a yellow oil; R_f = 0.77 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07–8.02 (m, 2H), 7.65–7.59 (m, 1H), 7.56–7.51 (m, 2H), 7.50–7.45 (m, 2H), 7.39 (s, 2H), 7.37–7.32 (m, 3H), 7.32–7.30 (m, 2H), 7.28–7.24 (m, 1H), 6.20 (s, 1H), 5.81–5.72 (m, 1H), 5.22 (dt, J = 17.2, 1.4 Hz, 1H), 5.13 (dt, J = 10.3, 1.3 Hz, 1H), 4.97–4.79 (m, 3H), 4.56–4.43 (m, 2H), 2.75 (dd, J = 17.4, 4.6 Hz, 1H), 2.03 (dd, J = 17.4, 4.7 Hz, 1H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 170.7, 164.0, 150.5, 137.2, 136.2, 136.1, 133.9, 131.7, 130.2, 130.0, 129.4, 129.0, 128.8, 128.5, 128.3, 128.1, 127.5, 120.2, 118.6, 113.4, 66.1, 50.6, 46.4, 35.1, 20.4; IR (Neat Film NaCl) 3062, 3030, 2981, 2934, 1740, 1646, 1600, 1577, 1495, 1451, 1400, 1349, 1326, 1244, 1176, 1145, 1112, 1077, 1050, 1023, 1001, 980, 935, 824, 797, 755 cm^{-1}; HRMS (MM: ESI-APCI+) calc'd for $C_{32}H_{30}O_5N$ $[M+H]^+$: 508.2118, found 508.2122.



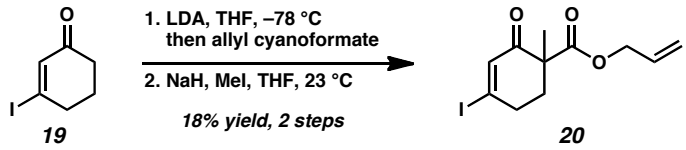
Enaminone 16f. A flame-dried 25 mL round-bottom flask containing a magnetic stir bar was loaded with enaminone **16c** (300.1 mg, 1.00 mmol, 1.00 equiv) and 4-dimethylaminopyridine (9.5 mg, 0.078 mmol, 7.8 mol %). The flask was charged with dichloromethane (10 mL, 0.10 M) and lowered into a 0 °C bath (ice/water). Di-*tert*-butyl dicarbonate (252.7 mg, 1.16 mmol, 1.15 equiv) was added, and the solution transitioned from yellow to clear. The ice bath was allowed to expire as the reaction was stirred overnight. After 22 h, the stir bar was removed from the flask, the reaction contents were concentrated under reduced pressure, and the resulting crude oil was purified by flash

column chromatography (SiO_2, 26.5 x 3 cm, 100% hexanes→5%→10%→15%→20% EtOAc in hexanes) to afford enaminone **16f** (360.0 mg, 0.90 mmol, 90% yield) as a pale yellow oil; R_f = 0.79 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.28 (m, 2H), 7.26–7.21 (m, 1H), 7.16–7.12 (m, 2H), 5.85 (dddd, J = 17.2, 10.5, 5.5, 5.5 Hz, 1H), 5.73 (t, J = 0.9 Hz, 1H), 5.27 (dq, J = 17.2, 1.6 Hz, 1H), 5.20 (dq, J = 10.5, 1.3 Hz, 1H), 4.80 (s, 2H), 4.58 (dddd, J = 5.6, 2.8, 1.5, 1.5 Hz, 2H), 2.92–2.77 (m, 2H), 2.45 (dt, J = 13.5, 5.3 Hz, 1H), 1.86 (ddd, J = 13.5, 7.7, 5.7 Hz, 1H), 1.42 (s, 9H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.8, 172.6, 162.2, 152.9, 137.2, 131.9, 128.8, 127.5, 126.3, 118.3, 114.8, 83.0, 65.8, 53.0, 52.5, 33.6, 28.1, 27.5, 20.4; IR (Neat Film NaCl) 3090, 3064, 3034, 2978, 2935, 2873, 1718, 1662, 1654, 1595, 1497, 1453, 1425, 1369, 1344, 1317, 1300, 1248, 1210, 1150, 1113, 1029, 989, 937, 856, 815, 769, 737 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{23}H_{30}NO_5$ $[M+H]^+$: 400.2118, found 400.2127.



Enaminone 16g. A flame-dried 25 mL round-bottom flask containing a magnetic stir bar was cycled into a glove box and loaded with sodium hydride (95% by weight, 32.6 mg, 1.29 mmol, 1.29 equiv). The flask was removed from the glove box, reconnected to an Ar-filled manifold, and charged with THF (6 mL). Enaminone **16c** (300.3 mg, 1.00 mmol, 1.00 equiv) was added in one portion and the grey suspension bubbled and became a yellow solution over time. The flask was rinsed with additional THF (4 mL, 10 mL total, 0.10 M). The reaction was stirred vigorously for 70 min before *p*-toluenesulfonyl

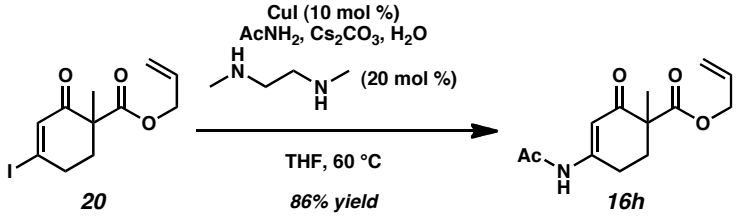
chloride (287.6 mg, 1.51 mmol, 1.50 equiv) was added in one portion. After 6 h, the flask was lowered into a 0 °C bath (ice/water) and quenched with water (reaction mixture bubbled). The mixture was transferred to a separatory funnel where the aqueous layer was extracted four times with CH_2Cl_2. The combined organics (100 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 27 x 3 cm, 100% hexanes→5%→10%→15%→ 50% EtOAc in hexanes) to afford enaminone **16g** (203.8 mg, 0.45 mmol, 45% yield) as a yellow oil; R_f = 0.68 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.33–7.25 (m, 3H), 7.23 (d, J = 6.6 Hz, 2H), 5.75 (dddd, J = 17.3, 10.8, 5.6, 5.6 Hz, 1H), 5.68 (t, J = 1.1 Hz, 1H), 5.24–5.15 (m, 2H), 4.81–4.69 (m, 2H), 4.48 (dddd, J = 13.5, 5.6, 1.4, 1.4 Hz, 1H), 4.40 (dddd, J = 13.2, 5.6, 1.4, 1.4 Hz, 1H), 2.67–2.55 (m, 2H), 2.46 (s, 3H), 2.32 (dt, J = 13.9, 5.2 Hz, 1H), 1.69 (ddd, J = 13.8, 8.0, 5.9 Hz, 1H), 1.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.0, 171.9, 158.4, 144.8, 135.6, 135.3, 131.7, 130.2, 128.9, 128.1, 127.6, 127.5, 119.5, 118.5, 65.9, 53.0, 52.2, 32.4, 27.9, 21.8, 20.0; IR (Neat Film NaCl) 3064, 3032, 2981, 2935, 2873, 1735, 1669, 1596, 1496, 1454, 1424, 1359, 1321, 1292, 1255, 1164, 1115, 1089, 1058, 1028, 984, 910, 883, 816, 773, 743 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{25}H_{28}NSO_5$ $[M+H]^+$: 454.1683, found 454.1691.



β-Iodoenone 20. A 200 mL round-bottom flask equipped with a magnetic stir bar was charged with diisopropyl amine (1.52 mL, 10.85 mmol, 1.19 equiv) and THF (36 mL). The flask was lowered into a 0 °C bath (ice/water) and *n*-BuLi (4.5 mL, 2.3 M in hexanes, 10.35 mmol, 1.14 equiv) was added dropwise over several minutes. The reaction was stirred for 15 min before the ice bath was removed and replaced with a –78 °C bath (dry ice/acetone). β-Iodoenone **19**[29] (2.00 g, 9.09 mmol, 1.00 equiv) was transferred via cannula to the flask using several THF rinses (1 x 14 mL and 2 x 5 mL rinses, total added = 60 mL, 0.15 M), producing a yellow solution that transitioned to red over time. The reaction was stirred for 1 h before allyl cyanoformate (1.12 mL, 10.38 mmol, 1.14 equiv) was added dropwise. After 2.25 h, the reaction was quenched with sat. NH_4Cl solution and allowed to warm to room temperature. The reaction contents were transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was filtered through a short silica gel plug to afford an orange oil.

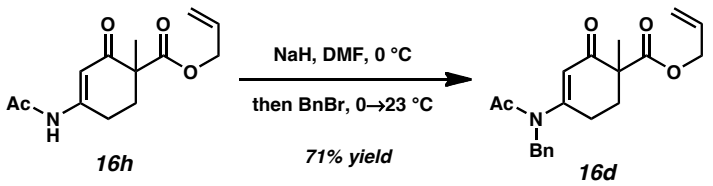
A 50 mL round-bottom flask equipped with a magnetic stir bar was cycled into a glove box and loaded with sodium hydride (161.0 mg, 95% by weight, 6.37 mmol, 1.21 equiv). The flask was removed from the glove box, reconnected to an Ar-filled manifold, and charged with THF (6 mL). The crude orange oil from the previous step (1.61 g, 5.27 mmol, 1.00 equiv) was transferred via cannula to the flask using several THF rinses (1 x

5 mL + 3 x 2 mL, total added = 21.0 mL, 0.25 M). The grey suspension bubbled and became a yellow solution that transitioned to red over time. The reaction was stirred for 30 min before methyl iodide (400 μL, 6.43 mmol, 1.22 equiv) was added dropwise. After 3.5 h, the reaction was quenched with water and extracted four times with dichloromethane. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 28.5 x 4 cm, 100% hexanes→5% EtOAc in hexanes) to afford β-Iodoenone **20** (536.3 mg, 1.68 mmol, 18% yield over two steps) as a yellow oil; R_f = 0.72 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (dd, J = 2.2, 1.2 Hz, 1H), 5.94–5.79 (m, 1H), 5.32–5.26 (m, 1H), 5.24 (dt, J = 10.5, 1.1 Hz, 1H), 4.67–4.56 (m, 2H), 3.05–2.96 (m, 1H), 2.93–2.85 (m, 1H), 2.43 (dt, J = 13.8, 4.9 Hz, 1H), 1.95 (ddd, J = 14.0, 9.0, 5.3 Hz, 1H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.6, 171.7, 139.6, 131.6, 125.5, 118.8, 66.1, 52.7, 38.6, 35.0, 20.3; IR (Neat Film NaCl) 3084, 2982, 2936, 2868, 1732, 1682, 1597, 1455, 1424, 1378, 1333, 1295, 1246, 1169, 1098, 1033, 986, 926, 852, 770, 737 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{11}H_{14}O_3I$ $[M+H]^+$: 320.9982, found 320.9981.



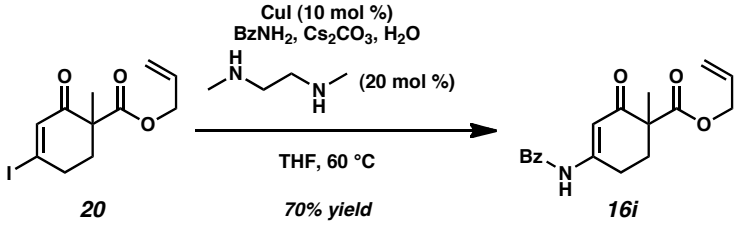
Enaminone 16h. Adapted from procedure by Buchwald.[30] CuI (24 mg, 0.13 mmol, 0.10 equiv), Cs_2CO_3 (624 mg, 1.92 mmol, 1.50 equiv) and acetamide (91 mg, 1.5 mmol, 1.2

equiv) were added to a 25 mL Schlenck bomb equipped with a stir bar under argon atmosphere. The Schlenck bomb was evacuated and backfilled with argon three times. A solution of vinyl iodide **20** (409 mg, 1.28 mmol, 1.00 equiv), *N,N'*-dimethylethylenediamine (23 mg, 0.26 mmol, 0.20 equiv) and nanopure water (23 mg, 1.3 mmol, 1.0 equiv) in THF (2.6 mL, 0.5 M) was added via syringe. The reaction flask was lowered into a 60 °C oil bath. After 12 h of stirring, TLC analysis indicated complete conversion of starting material. The reaction was subsequently diluted with 15 mL CH_2Cl_2, transferred to a separatory funnel and washed twice with 5% aqueous NH_4OH (10 mL). The combined aqueous layers were extracted twice with CH_2Cl_2 (15 mL). The combined organics were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography (SiO_2, 12 x 3 cm, 20→33→50→67% EtOAc in hexanes) to afford enaminone **16h** (276 mg, 1.10 mmol, 86% yield) as a pale yellow oil; R_f = 0.10 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 1H), 6.60 (s, 1H), 5.90–5.77 (m, 1H), 5.27 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.19 (dq, *J* = 10.5, 1.2 Hz, 1H), 4.58 (dq, *J* = 5.6, 1.3 Hz, 2H), 2.78 – 2.64 (m, 1H), 2.62–2.43 (m, 1H), 2.54–2.45 (m, 1H), 2.11 (s, 3H), 2.02–1.83 (m, 1H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.8, 172.5, 169.9, 155.9, 131.7, 118.5, 110.1, 65.9, 52.3, 31.9, 25.7, 25.0, 20.6; IR (Neat Film NaCl) 3299, 3135, 2937, 1728, 1626, 1520, 1456, 1426, 1370, 1259, 1220, 1184, 1114, 999, 939, 877 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{13}H_{18}NO_4$ $[M+H]^+$: 252.1230, found 252.1219.

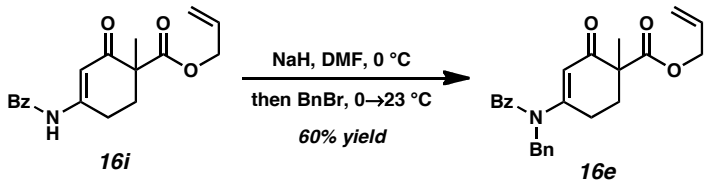


Enaminone 16d. In a 5 mL round bottom flask equipped with a stir bar under nitrogen atmosphere, enaminone **16h** (63 mg, 0.25 mmol, 1.0 equiv) was taken up in dry DMF (2.8 mL, 0.089 M) and cooled to 0 °C with an ice/water bath. Sodium hydride (60% suspension in mineral oil, 12 mg, 0.30 mmol, 1.2 equiv) was added to the mixture, accompanied by the formation of bubbles. The reaction was stirred for 1 h before the dropwise addition of benzyl bromide (36 μL, 0.30 mmol, 1.2 equiv) by syringe. The reaction temperature was maintained at 0 °C for 5 h before allowing the ice bath to gradually expire. After an additional 6 h at 23 °C, TLC analysis indicated complete conversion of starting material. The reaction was subsequently diluted with EtOAc (10 mL) and sat. NH_4Cl sol. (10 mL) and transferred to a separatory funnel. The organic layer was separated from the aqueous layer, and the aqueous layer was extracted twice with EtOAc (2 x 10 mL). The combined organics were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography (SiO_2, 15 x 3 cm, 20% acetone in hexanes) to afford enaminone **16d** (61 mg, 0.18 mmol, 71% yield) as a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.29 (m, 2H), 7.29–7.24 (m, 1H), 7.19–7.16 (m, 2H), 5.87–5.79 (m, 1H), 5.78 (s, 1H), 5.27 (dt, J = 17.2, 1.4 Hz, 1H), 5.21 (dt, J = 10.5, 1.3 Hz, 1H), 4.89–4.84 (m, 1H), 4.78–4.72 (m, 1H), 4.56 (dt, J = 5.7, 1.3 Hz, 2H), 2.58 (ddd, J = 9.3, 4.9, 1.6 Hz, 1H), 2.56–2.48 (m, 1H), 2.44 (dtd, J = 13.8, 4.8, 1.2 Hz, 1H), 2.16 (s, 3H), 1.87–1.78 (m, 1H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.2, 172.0, 170.0,

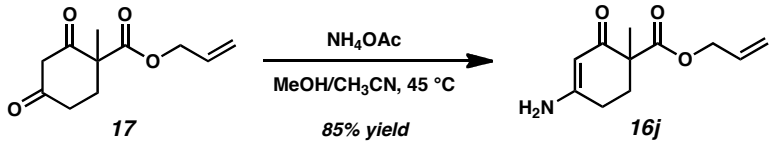
160.8, 136.5, 131.6, 129.0, 127.9, 127.5, 123.8, 1190, 66.1, 52.6, 50.8, 32.8, 27.3, 23.2, 20.2; IR (Neat Film NaCl) 3063, 3030, 2981, 2937, 2873, 1731, 1667, 1624, 1496, 1454, 1424, 1387, 1375, 1344, 1312, 1250, 1190, 1113, 1029, 986, 948, 882, 738 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{20}H_{24}O_4N$ $[M+H]^+$: 342.1700, found 342.1705.



Enaminone 16i. Adapted from procedure by Buchwald.[30] Prepared from **20** in an analogous manner to **16h**. Purified by flash chromatography (SiO_2, 12 x 3 cm, 20→33→50% EtOAc in hexanes) to afford enaminone **16i** (220 mg, 0.702 mmol, 70% yield) as a pale yellow oil that solidified to a pale yellow amorphous solid upon standing at –20 °C; R_f = 0.10 (50% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.83 – 7.74 (m, 2H), 7.56–7.47 (m, 1H), 7.47–7.40 (m, 2H), 6.70 (s, 1H), 5.88–5.75 (m, 1H), 5.25 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.17 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.55 (dq, *J* = 5.5, 1.5 Hz, 2H), 2.92–2.82 (m, 1H), 2.79–2.69 (m, 1H), 2.53 (dt, *J* = 13.7, 5.4 Hz, 1H), 1.99–1.87 (m, 1H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.2, 172.5, 166.5, 155.6, 133.8, 132.7, 131.7, 128.9, 127.5, 118.4, 111.1, 65.8, 52.3, 32.0, 25.9, 20.5; IR (Neat Film NaCl) 3334, 2936, 1732, 1694, 1621, 1514, 1492, 1376, 1258, 1185, 1115, 1071, 1023, 931, 710 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{18}H_{20}NO_4$ $[M+H]^+$: 314.1387, found 314.1381.



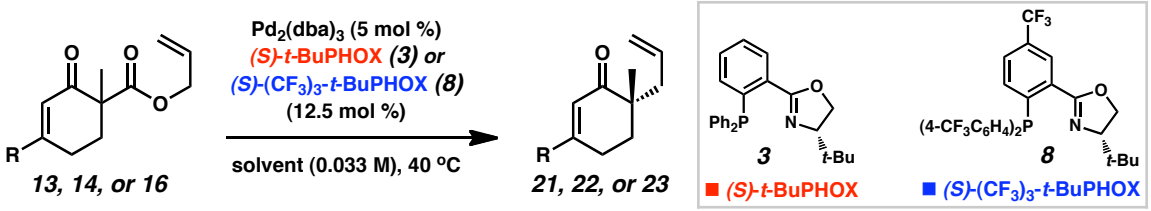
Enaminone 16e. Prepared from **16i** in an analogous manner to **16d**. Purified by flash chromatography (SiO_2, 15 x 3 cm, 20% acetone in hexanes) to afford enaminone **16e** (134 mg, 0.332 mmol, 60% yield) as a yellow oil; R_f = 0.63 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65–7.55 (m, 2H), 7.52–7.43 (m, 1H), 7.43–7.37 (m, 2H), 7.36–7.26 (m, 5H), 5.84 (s, 1H), 5.83–5.71 (m, 1H), 5.28–5.15 (m, 2H), 5.10–4.98 (m, 2H), 4.58–4.38 (m, 2H), 2.38–2.26 (m, 1H), 2.26–2.13 (m, 2H), 1.56 (s, 6H), 1.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.9, 171.8, 161.8, 136.8, 136.0, 131.8, 131.6, 128.9, 128.8, 128.2, 127.9, 127.7, 127.7, 121.4, 118.5, 65.9, 52.8, 52.4, 32.6, 28.8, 20.2; IR (Neat Film NaCl) 2936, 1733, 1661, 1601, 1496, 1447, 1377, 1344, 1300, 1253, 1174, 1111, 974, 794, 724 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{25}H_{26}NO_4$ $[M+H]^+$: 404.1856, found 404.1850.



Enaminone 16j. A flame-dried 50 mL round-bottom flask containing a stir bar was cycled into a glove box and loaded with ammonium acetate (185.3 mg, 2.40 mmol, 1.16 equiv). The flask was removed from the glove box, reconnected to an Ar-filled manifold, and charged with MeOH (1.5 mL). Dione **17** (437.5 mg, 2.08 mmol, 1.00 equiv) was transferred to the flask via cannula using MeOH (5 mL, total added = 6.5 mL, 0.32 M) and CH_3CN (6.5 mL, 0.32 M) rinses. The flask was lowered into a preheated oil bath (45

°C) and the reaction was heated for five days before TLC analysis indicated consumption of starting material. The reaction was cooled to room temperature and the contents were concentrated under reduced pressure. The resulting crude material was recrystallized twice with toluene to produce enaminone **16j** (369.0 mg, 1.76 mmol, 85% yield) as a white crystal; R_f = 0.18 (EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (dddd, J = 17.2, 10.4, 5.5, 5.5 Hz, 1H), 5.29 (dq, J = 17.2, 1.6 Hz, 1H), 5.25 (d, J = 0.8 Hz, 1H), 5.20 (dq, J = 10.5, 1.4 Hz, 1H), 4.61 (dddd, J = 5.4, 3.9, 1.5, 1.5 Hz, 2H), 4.53 (broad s, 2H), 2.60–2.52 (m, 1H), 2.49 (ddd, J = 13.3, 5.8, 5.0 Hz, 1H), 2.35–2.28 (m, 1H), 1.93–1.86 (m, 1H), 1.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.7, 173.3, 163.7, 132.1, 118.1, 99.9, 65.7, 51.6, 32.3, 26.0, 21.0; IR (Neat Film NaCl) 3338, 3189, 3064, 2983, 2934, 2873, 1735, 1654, 1551, 1437, 1383, 1358, 1291, 1253, 1216, 1194, 1175, 1103, 989, 930, 841, 824 cm^{-1}; HRMS (MM: ESI-APCI+) calc'd for $C_{11}H_{16}O_3N$ $[M+H]^+$: 210.1125, found 210.1119.

1.4.2.2.2 *General Procedure for Screening Reactions*



					Enantiomeric Excess (% ee)[b]			
entry	substrate	R	product	ligand	THF	TBME	Toluene	2:1 Hex–Tol
1 2	*13a*	H	*21a*	*3* *8*	87 85	88 86	87 88	87 85
3 4	*14a*	O*i*-Bu	*22a*	*3* *8*	85 86	85 86	86 86	87 88
5 6	*16a*	NMe(Bn)	*23a*	*3* *8*	61 79	60 78	55 84	52 83
7 8	*16b*	NPh(Bn)	*23b*	*3* *8*	81 76	87 74	85 82	83 83
9 10	*16d*	NAc(Bn)	*23d*	*3* *8*	89 83	90 85	88 88	88 86
11 12	*16e*	NBz(Bn)	*23e*	*3* *8*	86 80	87 83	88 82	87 83
13 14	*16f*	NBoc(Bn)	*23f*	*3* *8*	87 84	86 84	87 81	82 83
15 16	*16g*	NTs(Bn)	*23g*	*3* *8*	84 82	83 83	83 83	82 83

[a] *Conditions*: enone **13a**, vinylogous ester **14a**, or enaminone **16a, b, d–g** (1.0 equiv), $Pd_2(dba)_3$ (5 mol %), and *(S)*-*t*-BuPHOX (**3**) or *(S)*-$(CF_3)_3$-*t*-BuPHOX (**8**) (12.5 mol %) in solvent (0.033 M) at 40 °C. [b] Determined by GC, HPLC, or SFC analysis. Red = with *(S)*-(**3**) as ligand and blue = with *(S)*-(**8**) as ligand.

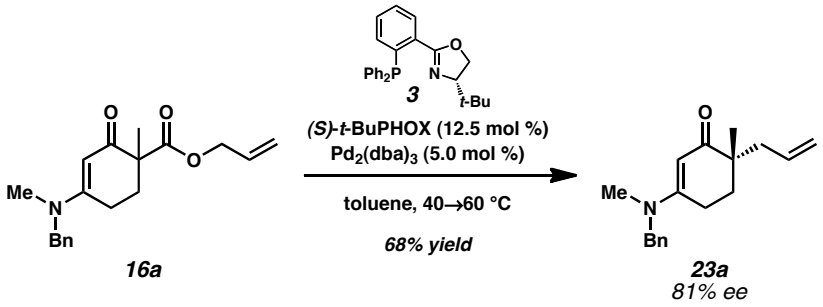
Enone 13a Screen Procedure. $Pd_2(dba)_3$ (2.4 mg, 0.00262 mmol, 0.05 equiv) and the appropriate PHOX ligand ((*S*)-*t*-BuPHOX (**3**): 2.5 mg, 0.00645 mmol, 0.125 equiv ***or*** (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**): 3.8 mg, 0.00643 mmol, 0.125 equiv) were added to an oven-dried 1 dram vial equipped with a magnetic stir bar. A separate oven-dried 1 dram vial was charged with enone **13a**[6] (10.0 mg, 0.0515 mmol, 1.00 equiv) and both vials were cycled into a nitrogen-filled glove box. The palladium/ligand vial was charged with

solvent (THF, TBME, toluene: 360 μL or 2:1 hexanes/toluene: 120 μL toluene and 340 μL hexanes) and stirred at ambient glove box temperature. After 30 min, enone **9a** was transferred to the reaction vial with several solvent rinses (THF, TBME, toluene: 3 x 400 μL, 1.56 mL total, 0.033 M or 2:1 hexanes/toluene: 400 μL toluene and 400 μL + 300 μL hexanes, 1.56 mL solvent total, 0.033 M). The vials were tightly sealed with a teflon lined cap and electrical tape, removed from the glove box, and lowered into a heating block set to 40 °C. After 2 days, the reaction were either loaded directly onto a column (toluene and 2:1 hexanes/toluene) or filtered through a celite plug and concentrated prior to chromatography (THF and TBME). All reactions were purified by flash column chromatography (SiO_2, ~22 x 1 cm, 2%→3% Et_2O in pentane), resuspended in Et_2O for analysis, and analyzed for enantiomeric excess with chiral GC. Characterization data for enone **21a** matches that previously reported.[6] As part of the screen, the yield was determined for enone **21a** with (*S*)-**8** in toluene (6.0 mg, 0.040 mmol, 78% yield).

Vinylogous Ester 14a and Enaminone Symyx Core Module Screen Procedure. All reagents were dispensed as solutions using a Symyx Core Module within a nitrogen-filled glovebox. Oven-dried half-dram vials were charged with a solution of the palladium source ($Pd_2(dba)_3$, 1.65 μmol, 0.05 equiv) in THF (400 μL). The palladium solutions were evaporated to dryness under reduced pressure using a Genevac centrifugal evaporator within the glovebox, and stirbars were added to the vials. The reaction vials were then charged with a solution of the PHOX ligand (4.13 μmol, 0.125 equiv) in the reaction solvent (300 μL) and stirred at 20 °C. After 30 min, a solution of vinylogous

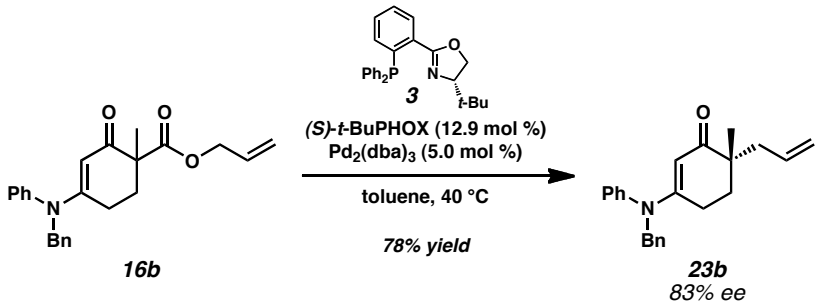
ester **14a** or the enaminone substrate (**16**, 33.0 μmol, 1.0 equiv) in the reaction solvent (700 μL) were added. The reaction vials were tightly capped and heated to the desired temperature (40 °C). The consumption of the starting material was observed by colorimetric change (from light yellow/green to red/orange) and after 5 days, the reactions were removed from the glovebox, filtered through a short silica gel plug (rinsing with EtOAc), concentrated under reduced pressure, resuspended in an appropriate solvent for analysis (HPLC: hexanes ***or*** SFC: MeOH), and analyzed for enantiomeric excess (see Methods for the Determination of Enantiomeric Excess). Characterization data for vinylogous ester **22a** matches that previously reported.[18c] Experimental procedures and characterization data for enaminones **23a**, **b**, **d**–**g** follows.

1.4.2.2.3 *Enaminone Allylic Alkylation Products*



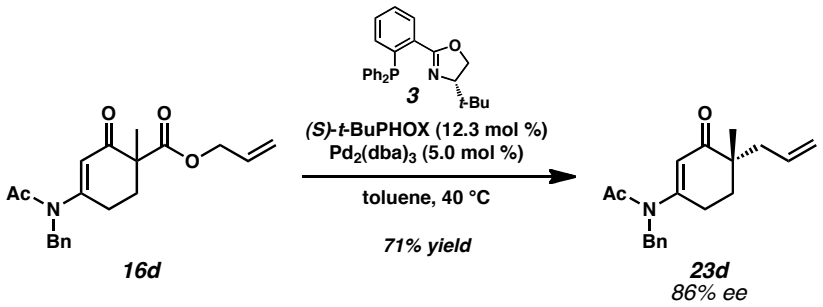
Enaminone 23a. $Pd_2(dba)_3$ (14.6 mg, 0.0159 mmol, 5.0 mol %) and (*S*)-*t*-BuPHOX (**3**, 15.5 mg, 0.0400 mmol, 12.5 mol %) were added to an oven-dried scintillation vial equipped with a magnetic stir bar and the vial was cycled into a glove box. The vial was charged with toluene (2 mL) and heated at 30 °C for 30 min, generating a red/orange solution. Enaminone **16a** (1 M in toluene, 320 μL, 0.320 mmol, 1.00 equiv) and additional toluene (7.35 mL, total added = 9.67 mL, 0.033 M) were added, producing a

green solution. The vial was sealed with a Teflon-lined cap, removed from the glove box, and lowered into a heating block (40 °C). After 5 days, the temperature was raised to 60 °C and heated for an additional day before the reaction mixture transitioned back to a red/orange solution. The reaction was filtered through a silica gel plug, rinsed with EtOAc, and concentrated under reduced pressure. The crude oil was purified twice by flash column chromatography (SiO_2, 27.5 x 2 cm, 100% hexanes→20%→30%→50% EtOAc in hexanes→ 100% EtOAc ***then*** SiO_2, 26.5 x 1.5 cm, 100% hexanes→20%→30%→40% EtOAc in hexanes) to afford enaminone **23a** (58.9 mg, 0.219 mmol, 68% yield) as a pale yellow oil; R_f = 0.12 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.33 (m, 2H), 7.31–7.26 (m, 1H), 7.10 (d, J = 7.2 Hz, 2H), 5.84–5.74 (m, 1H), 5.17 (s, 1H), 5.07–5.00 (m, 2H), 4.51 (s, 2H), 2.95 (s, 3H), 2.58–2.44 (m, 2H), 2.38 (dddd, J = 13.7, 7.1, 1.2, 1.2 Hz, 1H), 2.23–2.18 (m, 1H), 1.93 (ddd, J = 13.2, 7.5, 5.5 Hz, 1H), 1.71 (ddd, J = 13.7, 6.9, 5.4 Hz, 1H), 1.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.2, 163.7, 136.9, 135.2, 129.1, 127.7, 126.3, 117.5, 98.1, 55.0, 42.1, 41.8, 38.5, 32.8, 24.0, 22.6; IR (Neat Film NaCl) 3066, 3029, 2958, 2926, 2867, 1728, 1615, 1557, 1495, 1451, 1412, 1373, 1354, 1333, 1315, 1297, 1276, 1253, 1204, 1156, 1103, 1077, 1029, 1001, 924, 823, 792, 733 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{18}H_{23}ON$ $[M+\bullet]^+$: 269.1780, found 269.1782; $[\alpha]_D^{25.0}$ –24.18 (c 1.04, $CHCl_3$, 81% ee); JASCO SFC conditions: 5% MeOH in CO_2, 5 mL/min, Chiralcel OD-H column, λ = 210 nm, t_R (min): major = 10.45, minor = 9.60.



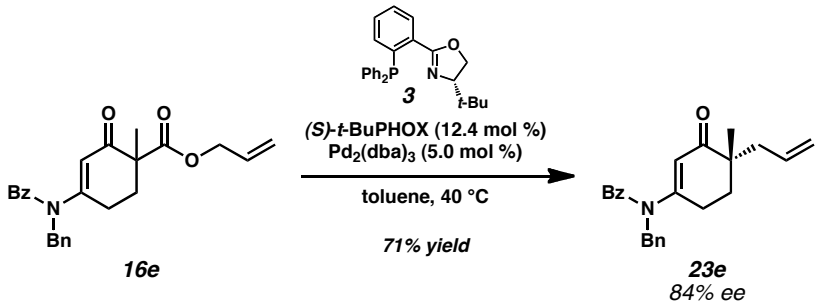
Enaminone 23b. $Pd_2(dba)_3$ (3.5 mg, 0.00382 mmol, 5.0 mol %) and (*S*)-*t*-BuPHOX (**3**, 3.8 mg, 0.00981 mmol, 12.9 mol %) were added to an oven-dried scintillation vial equipped with a magnetic stir bar and the vial was cycled into a glove box. The vial was charged with toluene (0.5 mL) and heated at 30 °C for 30 min, generating a red/orange solution. Enaminone **16b** (28.6 mg, 0.0762 mmol, 1.00 equiv) was transferred to the flask with several toluene rinses (1 x 0.81 mL + 2 x 0.5 mL, total added = 2.31 mL, 0.033 M), producing a green solution. The vial was sealed with a Teflon-lined cap, removed from the glove box, and lowered into a heating block (40 °C). After 4 days, the reaction mixture transitioned back to an orange solution. Subsequently, the reaction was filtered through a silica gel plug, rinsed with EtOAc, and concentrated under reduced pressure. The crude oil was purified twice by flash column chromatography (SiO_2, 19.5 x 1.5 cm, 100% hexanes→50% EtOAc in hexanes→100% EtOAc ***then*** SiO_2, 23.5 x 1 cm, 100% hexanes→10%→20%→30%→40% EtOAc in hexanes) to afford enaminone **23b** (19.7 mg, 0.0594 mmol, 78% yield) as a frosty colorless oil; R_f = 0.63 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.33 (m, 2H), 7.33–7.29 (m, 2H), 7.29–7.22 (m, 2H), 7.22–7.18 (m, 2H), 7.15–7.11 (m, 2H), 5.76 (dddd, J = 15.8, 11.3, 7.8, 7.0 Hz, 1H), 5.29 (s, 1H), 5.05–5.00 (m, 2H), 4.83 (s, 2H), 2.38 (dddd, J = 13.8, 7.1, 1.3, 1.3 Hz, 1H), 2.35–2.31 (m, 2H), 2.19 (dddd, J = 13.7, 7.8, 1.1, 1.1 Hz, 1H),

1.90–1.83 (m, 1H), 1.65 (ddd, J = 13.5, 6.5, 5.6 Hz, 1H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.8, 163.3, 144.6, 136.7, 135.0, 129.8, 128.8, 128.0, 127.6, 127.5, 127.0, 117.6, 100.5, 56.7, 42.2, 42.0, 33.0, 25.5, 22.6; IR (Neat Film NaCl) 3063, 3031, 2959, 2926, 2863, 1622, 1563, 1494, 1453, 1426, 1404, 1374, 1351, 1329, 1275, 1204, 1156, 1078, 1060, 1028, 1002, 911, 830, 730 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{23}H_{26}ON$ $[M+H]^+$: 332.2009, found 332.1999; $[\alpha]_D^{25.0}$ –29.79 (c 1.91, $CHCl_3$, 83% ee); JASCO SFC conditions: 5% MeOH in CO_2, 5 mL/min, Chiralpak AS-H column, λ = 254 nm, t_R (min): major = 8.60, minor = 6.48.



Enaminone 23d. $Pd_2(dba)_3$ (2.6 mg, 0.00284 mmol, 5.0 mol %) and (*S*)-*t*-BuPHOX (**3**, 2.7 mg, 0.00697 mmol, 12.3 mol %) were added to an oven-dried scintillation vial equipped with a magnetic stir bar and the vial was cycled into a glove box. The vial was charged with toluene (0.51 mL) and heated at 30 °C for 30 min, generating a red/orange solution. Enaminone **16d** (19.3 mg, 0.0565 mmol, 1.00 equiv) was transferred to the flask with several toluene rinses (4 x 0.3 mL, total added = 1.71 mL, 0.033 M), producing a yellow solution. The vial was sealed with a Teflon-lined cap, removed from the glove box, and lowered into a heating block (40 °C). After 2 days, the reaction mixture transitioned back to an orange solution. Subsequently, the reaction was filtered through a

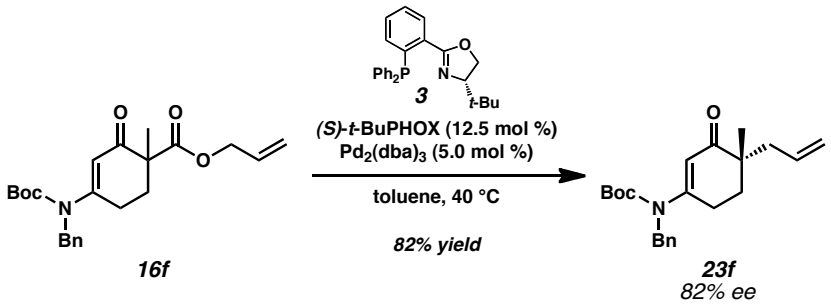
silica gel plug, rinsed with EtOAc, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 19.5 x 1.5 cm, 5%→10%→20%→30% EtOAc in hexanes) to afford enaminone **23d** (12.0 mg, 0.0404 mmol, 71% yield) as a yellow oil; R_f = 0.46 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (ddt, J = 8.1, 6.7, 1.2 Hz, 2H), 7.30–7.23 (m, 1H), 7.19 (ddt, J = 7.3, 1.4, 0.7 Hz, 2H), 5.68 (t, J = 1.3 Hz, 1H), 5.66 (ddt, J = 16.9, 10.1, 7.3 Hz, 1H), 5.05 (ddt, J = 10.1, 1.9, 0.9 Hz, 1H), 4.99 (ddt, J = 17.0, 2.1, 1.4 Hz, 1H), 4.81 (s, 2H), 2.50–2.39 (m, 2H), 2.21 (ddt, J = 13.8, 7.3, 1.2 Hz, 1H), 2.17 (s, 3H), 2.10 (ddt, J = 13.8, 7.5, 1.1 Hz, 1H), 1.87 (dt, J = 13.8, 5.9 Hz, 1H), 1.69 (ddd, J = 13.8, 6.6, 5.7 Hz, 1H), 1.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.1, 169.7, 160.1, 136.6, 133.6, 128.9, 127.9, 127.7, 123.8, 118.6, 50.9, 43.6, 40.8, 32.6, 27.1, 23.2, 21.5; IR (Neat Film NaCl) 3066, 2926, 2854, 1663, 1624, 1496, 1453, 1387, 1371, 1189, 991, 916 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{24}NO_2$ $[M+H]^+$: 298.1807, found 298.1794; $[\alpha]_D^{25.0}$ –14.12 (c 1.20, $CHCl_3$, 86% ee); Thar SFC conditions: 5% MeOH in CO_2, 3 mL/min, Chiralpak AD-H column, λ = 254 nm, t_R (min): major = 8.45, minor = 10.35.



Enaminone 23e. $Pd_2(dba)_3$ (4.6 mg, 0.00502 mmol, 5.0 mol %) and (*S*)-*t*-BuPHOX (**3**, 4.8 mg, 0.0124 mmol, 12.4 mol %) were added to an oven-dried scintillation vial

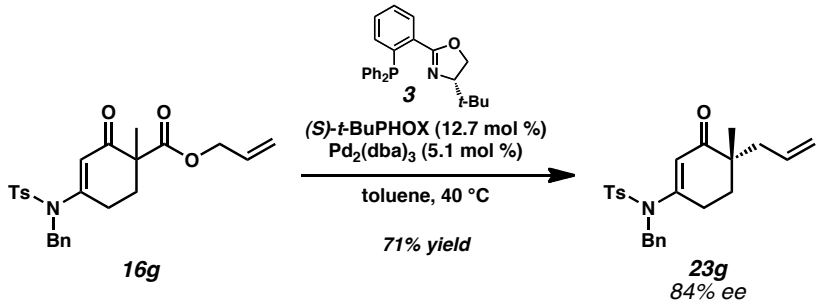
equipped with a magnetic stir bar and the vial was cycled into a glove box. The vial was charged with toluene (0.93 mL) and heated at 30 °C for 30 min, generating a red/orange solution. Enaminone **16e** (1 M in toluene, 100 μL, 0.100 mmol, 1.00 equiv) was transferred to the flask with more toluene (1 mL, total added including enaminone solution = 3.03 mL, 0.033 M), producing a yellow/orange solution. The vial was sealed with a Teflon-lined cap, removed from the glove box, and lowered into a heating block (40 °C). After 2 days, the reaction mixture transitioned back to an orange solution. Subsequently, the reaction was filtered through a silica gel plug, rinsed with EtOAc, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 19.5 x 1.5 cm, 5%→10%→15% EtOAc in hexanes) to afford enaminone **23e** (26.3 mg, 0.0713 mmol, 71% yield, 95% purity) as a yellow oil; $R_f = 0.57$ (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63–7.59 (m, 2H), 7.50–7.43 (m, 1H), 7.39 (ddt, J = 8.2, 6.6, 1.1 Hz, 2H), 7.35–7.29 (m, 4H), 7.29–7.25 (m, 1H), 5.74 (t, J = 1.1 Hz, 1H), 5.54 (ddt, J = 17.3, 10.1, 7.4 Hz, 1H), 5.09 (d, J = 15.3 Hz, 1H), 5.00 (d, J = 15.3 Hz, 1H), 4.98 (dm, J = 9.9 Hz, 1H), 4.86 (dm, J = 17.0 Hz, 1H), 2.11–2.08 (m, 2H), 2.03 (dd, J = 14.2, 7.9 Hz, 1H), 1.95 (ddt, J = 13.8, 7.3, 1.2 Hz, 1H), 1.59 (ddd, J = 13.7, 6.5, 5.4 Hz, 1H), 1.41 (ddd, J = 13.4, 6.8, 5.3 Hz, 1H), 0.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.7, 170.8, 160.9, 136.8, 136.2, 133.6, 131.6, 128.9, 128.7, 128.1, 128.0, 127.9, 122.3, 118.4, 52.5, 43.3, 40.6, 32.4, 28.4, 21.3; IR (Neat Film NaCl) 3063, 3030, 2961, 2928, 2855, 1655, 1610, 1496, 1447, 1384, 1374, 1347, 1324, 1273, 1189, 1140, 1076, 1028, 1001, 974, 919, 792 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{24}H_{26}NO_2$ $[M+H]^+$: 360.1964, found 360.1956; $[\alpha]_D^{25.0}$ –26.61 (c 1.87, $CHCl_3$, 84% ee); Thar SFC

conditions: 7% MeOH in CO_2, 2.5 mL/min, Chiralpak AD-H column, λ = 254 nm, t_R (min): major = 18.14, minor = 20.28.



Enaminone 16f. $Pd_2(dba)_3$ (11.5 mg, 0.0126 mmol, 5.0 mol %) and (*S*)-*t*-BuPHOX (**3**, 12.1 mg, 0.0312 mmol, 12.5 mol %) were added to an oven-dried scintillation vial equipped with a magnetic stir bar and the vial was cycled into a glove box. The vial was charged with toluene (2 mL) and heated at 30 °C for 30 min, generating a red/orange solution. Enaminone **16f** (1 M in toluene, 250 μL, 0.250 mmol, 1.00 equiv) and additional toluene (6.34 mL, total added = 7.59 mL, 0.033 M) were added, producing a green solution. The vial was sealed with a Teflon-lined cap, removed from the glove box, and lowered into a heating block (40 °C). After 2 days, the reaction mixture transitioned back to an orange solution. Subsequently, the reaction was filtered through a silica gel plug, rinsed with EtOAc, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 28 x 3 cm, 100% hexanes→5%→10% EtOAc in hexanes) to afford enaminone **23f** (72.6 mg, 0.204 mmol, 82% yield) as a pale yellow oil; R_f = 0.65 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.29 (m, 2H), 7.26–7.22 (m, 1H), 7.17–7.14 (m, 2H), 5.69 (dddd, J = 16.8, 10.2, 7.4, 7.4 Hz, 1H), 5.63 (t, J = 0.9 Hz, 1H), 5.07–4.99 (m, 2H), 4.78 (s, 2H), 2.75 (tm,

J = 6.1 Hz, 2H), 2.29 (dddd, J = 13.7, 7.3, 1.2, 1.2 Hz, 1H), 2.13 (dddd, J = 13.7, 7.5, 1.2, 1.2 Hz, 1H), 1.90–1.84 (m, 1H), 1.71–1.65 (m, 1H), 1.43 (s, 9H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.6, 161.6, 153.0, 137.4, 134.1, 128.8, 127.4, 126.4, 118.2, 115.4, 82.6, 52.9, 43.2, 41.2, 33.5, 28.2, 27.2, 21.9; IR (Neat Film NaCl) 3066, 3031, 3004, 2976, 2931, 2868, 1716, 1656, 1598, 1497, 1455, 1428, 1382, 1368, 1350, 1326, 1302, 1243, 1209, 1192, 1153, 1076, 1030, 998, 946, 916, 858, 779, 767, 734 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{22}H_{30}O_3N$ $[M+H]^+$: 356.2229, found 356.2220; $[\alpha]_D^{25.0}$ –23.61 (c 0.92, $CHCl_3$, 82% ee); JASCO SFC conditions: 7% MeOH in CO_2, 5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): major = 4.04, minor = 2.20.

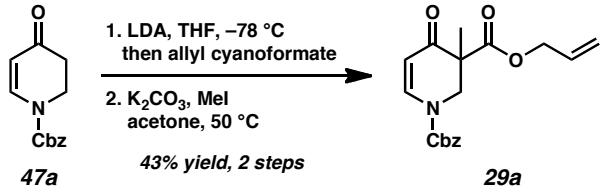


Enaminone 23g. $Pd_2(dba)_3$ (10.2 mg, 0.0111 mmol, 5.1 mol %) and (*S*)-*t*-BuPHOX (**3**, 10.8 mg, 0.0279 mmol, 12.7 mol %) were added to an oven-dried scintillation vial equipped with a magnetic stir bar and the vial was cycled into a glove box. The vial was charged with toluene (2 mL) and heated at 30 °C for 30 min, generating a red/orange solution. Enaminone **16g** (1 M in toluene, 220 μL, 0.220 mmol, 1.00 equiv) and additional toluene (5.46 mL, total added = 6.68 mL, 0.033 M) were added, producing a green solution. The vial was sealed with a Teflon-lined cap, removed from the glove box, and lowered into a heating block (40 °C). After 2 days, the reaction mixture

transitioned back to an orange solution. Subsequently, the reaction was filtered through a silica gel plug, rinsed with EtOAc, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 27 x 2 cm, 100% hexanes→5%→10%→15% EtOAc in hexanes) to afford enaminone **23g** (64.1 mg, 0.157 mmol, 71% yield) as a pale yellow oil; R_f = 0.55 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (dm, J = 8.3 Hz, 2H), 7.35 (dm, J = 8.6 Hz, 2H), 7.33–7.26 (m, 3H), 7.25–7.22 (m, 2H), 5.60–5.50 (m, 2H), 4.98 (dm, J = 10.2 Hz, 1H), 4.86 (dm, J = 17.0 Hz, 1H), 4.74 (d, J = 15.0 Hz, 1H), 4.66 (d, J = 15.0 Hz, 1H), 2.56–2.44 (m, 2H), 2.46 (s, 3H), 1.99–1.86 (m, 2H), 1.70 (ddd, J = 13.9, 6.6, 5.3 Hz, 1H), 1.55 (ddd, J = 13.9, 7.2, 5.5 Hz, 1H), 0.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.9, 157.74, 144.7, 135.4, 135.3, 133.7, 130.1, 128.9, 128.1, 127.9, 127.5, 120.7, 118.3, 53.1, 43.2, 40.6, 32.2, 27.9, 21.8, 21.3; IR (Neat Film NaCl) 3066, 3027, 2963, 2928, 2868, 1663, 1654, 1597, 1496, 1453, 1424, 1355, 1306, 1164, 1089, 1055, 1028, 1001, 912, 859, 814, 745 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{24}H_{28}O_3NS$ $[M+H]^+$: 410.1784, found 410.1792; $[\alpha]_D^{25.0}$ –33.05 (c 0.37, $CHCl_3$, 84% ee); JASCO SFC conditions: 10% MeOH, 5 mL/min, AD-H column, λ = 210 nm, t_R (min): major = 5.60, minor = 4.73.

1.4.2.3 Preparation of 2,3-Dihydropyridin-4-ones

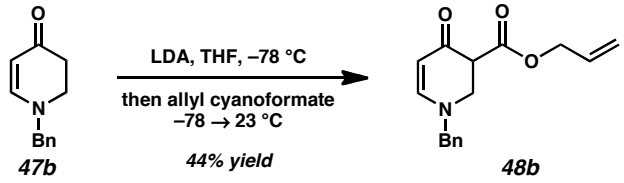
1.1.1.1.4 *2,3-Dihydropyridin-4-one Allylic Alkylation Precursors*



2,3-Dihydropyridin-4-one 29a. A 100 mL round-bottom flask equipped with a magnetic stir bar was charged with diisopropyl amine (442 µL, 3.01 mmol, 1.20 equiv) and THF (28 mL). The flask was cooled to –78 °C bath (dry ice/IPA) and *n*-BuLi (1.30 mL, 3.01 mmol, 2.32 M in hexanes, 1.20 equiv) was added. The reaction was allowed to warm to 0 °C over 1 h. The solution was cooled back to –78 °C and added dropwise to a solution of 2,3-dihydropyridin-4-one **47a**[37] (580 mg, 2.51 mmol, 1.0 equiv) in THF (40 mL) at –78 °C using positive pressure cannulation. The reaction was stirred for 1 h at this temperature before allyl cyanoformate (300 µL, 2.88 mmol, 1.15 equiv) was added dropwise. The flask was removed from the bath, allowed to warm to room temperature slowly, and stirred overnight. The reaction was quenched with water and sat. NH_4Cl solution. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduce pressure. The resulting yellow oil was purified by flash-chromatography (2:1 Et_2O/hexanes).

The yellow oil was transferred to an argon filled 25 mL Schlenk tube equipped with a magnetic stir bar using several acetone rinses (3 x 2 mL). K_2CO_3 (252 mg, 1.83 mmol, 2.0 equiv) and methyl iodide (115 µL, 1.84 mmol, 2.02 equiv) were added to the

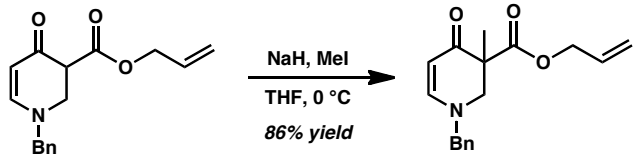
reaction. The resulting suspension was heated to 50 °C and vigorously stirred for 14 h. Upon completion, the reaction was allowed to cool to room temperature and filtered through a plug of celite. The resulting yellow solution was concentrated under reduced pressure and purified by flash-chromatography (1:1 Et_2O/hexanes) to afford 2,3-Dihydropyridin-4-one **29a** (210 mg, 0.64 mmol, 43% yield over two steps) as a yellow oil; R_f = 0.38 (1:1 Et_2O/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (br s, J = 22.5 Hz, 1H), 7.45–7.31 (m, 5H), 5.82 (ddt, J = 17.2, 10.4, 5.6 Hz, 1H), 5.37 (br s, 1H), 5.27 (s, 2H), 5.26 (dq, J = 17.1, 1.5 Hz, 1H), 5.20 (dq, J = 10.5, 1.3 Hz, 1H), 4.64 (dd, J = 13.5, 0.9 Hz, 1H), 4.59 (dt, J = 5.6, 1.5 Hz, 2H), 3.63 (d, J = 13.5 Hz, 1H), 1.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ190.9, 170.1, 152.5, 142.7, 134.8, 131.3, 128.8, 128.7, 128.4, 118.6, 106.2, 69.2, 66.1, 51.6, 50.5, 17.9; IR (Neat Film, NaCl) 3076, 3034, 2965, 2929, 2360, 2922, 1729, 1668, 1605, 1498, 1456, 1418, 1393, 1344, 1302, 1205, 1157, 1101, 1029, 966, 917, 814, 763 cm^{-1}; HRMS (MM: ESI/APCI+) *m/z* calc'd for $C_{18}H_{20}NO_5$ $[M+H]^+$: 330.1335, found 330.1335.



47b *48b*

2,3-Dihydropyridin-4-one 48b. To a flame-dried 50 mL Schlenk round-bottom flask equipped with a magnetic stir bar was added 2,3-dihydropyridin-4-one **47b**[38] (162.0 mg, 0.87 mmol) and THF (10 mL). The solution was cooled to –78 °C and LDA (0.1 M in THF, 9.10 mL, 0.91 mmol, 1.05 equiv) was added dropwise by syringe. After 1 h at –78 °C, allyl cyanoformate (105.2 mg, 0.96 mmol, 1.10 equiv) was added, and the reaction

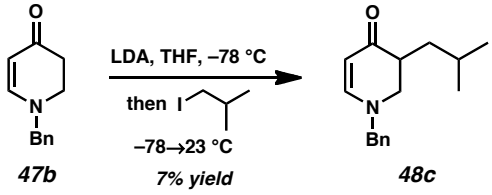
was stirred for another 3 h and then quenched with a sat. NH_4Cl sol. The reaction was transferred to a separatory funnel where the aqueous layer was extracted with CH_2Cl_2 (4 x 30 mL). The combined organics were washed with brine, dried over $MgSO_4$, fitered, and concentrated under reduced pressure. The resulting crude mixture was purified by flash chromatography (SiO_2, 10 x 2.5 cm, 30% EtOAc → 50% EtOAc in hexanes) to afford 2,3-dihydropyridin-4-one **48b** (104.8 mg, 0.38 mmol, 44% yield) as a yellow oil; R_f = 0.30 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.31 (m, 3H), 7.28–7.23 (m, 2H), 7.17 (d, *J* = 7.5 Hz, 1H), 5.87 (ddt, *J* = 17.2, 10.5, 5.7 Hz, 1H), 5.32 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.22 (dq, *J* = 10.4, 1.3 Hz, 1H), 5.06 (d, *J* = 7.5 Hz, 1H), 4.69–4.55 (m, 2H), 4.40 (d, *J* = 2.5 Hz, 2H), 3.76 (dd, *J* = 13.3, 8.7 Hz, 1H), 3.51 (dd, *J* = 13.3, 5.9 Hz, 1H), 3.40 (dd, *J* = 8.7, 5.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.2, 168.8, 153.6, 135.1, 131.6, 129.1, 128.5, 127.8, 118.6, 97.7, 66.0, 60.0, 50.5, 48.4; IR (Neat Film NaCl) 3029, 2935, 2853, 1732, 1641, 1588, 1494, 1455, 1393, 1361, 1321, 1204, 1154, 1078, 1028, 991, 967, 935, 78, 731 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{18}NO_3$ $[M+H]^+$: 272.1287, found 272.1314.



48b *29b*

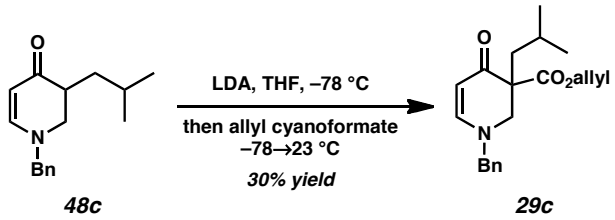
2,3-Dihydropyridin-4-one 29b. To a flame-dried 25 mL round-bottom flask equipped with a magnetic stir bar was cycled into a glove box and loaded with sodium hydride (9.3 mg, 0.39 mmol, 1.00 equiv). The flask was removed from the glove box, reconnected to an Ar-filled manifold, charged with THF (3 mL), and cooled to 0 °C. A solution of 2,3-

dihydropyridin-4-one **48b** (104.2 mg, 0.39 mmol, 1.00 equiv) was added by syringe and the mixture was stirred at 0 °C for 30 min. The reaction was quenched with water, transferred to a separatory funnel, and extracted four times with CH_2Cl_2. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 10 x 2.5 cm, 30% EtOAc in hexanes) to afford 2,3-dihydropyridin-4-one **29b** (95.9 mg, 0.34 mmol, 86% yield) as a colorless oil; R_f = 0.40 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.30 (m, 3H), 7.25–7.20 (m, 2H), 7.13 (d, *J* = 7.4 Hz, 1H), 5.83 (ddt, *J* = 17.1, 10.8, 5.5 Hz, 1H), 5.27 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.19 (dq, *J* = 10.5, 1.3 Hz, 1H), 5.01 (d, *J* = 7.4 Hz, 1H), 4.56 (qdt, *J* = 13.4, 5.5, 1.5 Hz, 2H), 4.46–4.30 (m, 2H), 3.78 (d, *J* = 13.2 Hz, 1H), 3.15 (d, *J* = 13.3 Hz, 1H), 1.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.1, 171.7, 152.8, 135.2, 131.8, 129.1, 128.5, 128.1, 118.2, 97.1, 65.9, 60.1, 55.1, 51.4, 18.6; IR (Neat Film NaCl) 3029, 2979, 2934, 2871, 1732, 1642, 1592, 1494, 1455, 1393, 1372, 1359, 1343, 1295, 1223, 1166, 1115, 1028, 975, 937, 792, 732 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{20}NO_3$ $[M+H]^+$: 286.1443, found 286.1480.



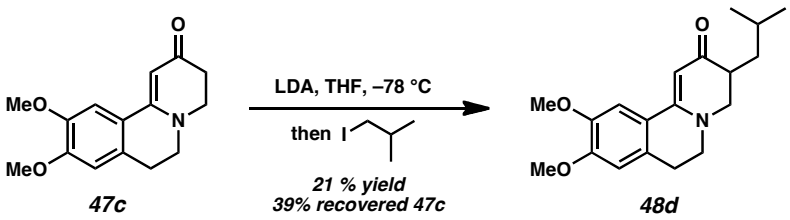
2,3-Dihydropyridin-4-one 48c. To a flame-dried 100 mL Schlenk round-bottom flask equipped with a magnetic stir bar was added 2,3-dihydropyridin-4-one **47b**[38] (0.68 g, 3.63 mmol) and THF (30 mL). The solution was cooled to –78 °C and LDA (19.0 mL, 3.80

mmol, 1.05 equiv, 0.2 M in THF) was added dropwise by syringe. After 1 h at –78 °C, 1-iodo-2-methylpropane (0.87 g, 4.73 mmol, 1.30 equiv) was added, and the reaction was stirred for another 1 h at –78 °C, brought to room temperature, and stirred overnight. The reaction was quenched with a sat. NH_4Cl sol., transferred to a separatory funnel, and extracted with CH_2Cl_2 (50 mL x 3). The combined organics were washed with brine, dried over $MgSO_4$, fitered, and concentrated. The crude mixture was purified by flash chromatography (SiO_2, 10 x 3 cm, 30% EtOAc in hexanes) to afford 2,3-dihydropyridin-4-one **48c** (58.2 mg, 0.24 mmol, 7% yield) as a yellow oil; R_f = 0.50 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.32 (m, 3H), 7.29–7.25 (m, 2H), 7.12 (d, J = 7.4 Hz, 1H), 4.96 (d, J = 7.4 Hz, 1H), 4.43–4.28 (m, 2H), 3.38 (dd, J = 13.0, 5.4 Hz, 1H), 3.08 (dd, J = 13.0, 7.7 Hz, 1H), 2.29 (ddt, J = 10.1, 7.6, 5.2 Hz, 1H), 1.56 (ddd, J = 14.0, 9.3, 5.0 Hz, 1H), 1.37 (dpd, J = 9.3, 6.6, 5.2, 1H), 1.18 (ddd, J = 13.7, 9.6, 5.3 Hz, 1H), 0.82 (d, J = 6.5 Hz, 3H), 0.78 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.0, 152.8, 135.8, 128.9, 128.3, 127.8, 97.7, 60.0, 50.4, 42.0, 37.5, 25.0, 23.3, 21.4; IR (Neat Film NaCl) 3029, 2954, 2868, 1633, 1593, 1494, 1463, 1455, 1385, 1361, 1302, 1210, 1161, 1077, 778, 730 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{22}NO$ $[M+H]^+$: 244.1701, found 244.1707.

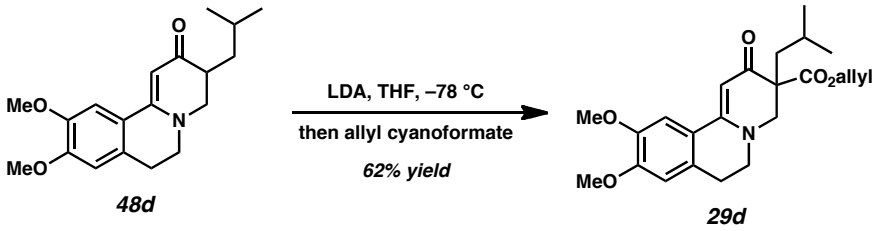


48c ***29c***

2,3-Dihydropyridin-4-one 29c. To a flame-dried 25 mL Schlenk tube equipped with a magnetic stir bar was added 2,3-dihydropyridin-4-one **48c** (50.5 mg, 0.21 mmol) and THF (5 mL). After the solution was cooled to -78 °C, LDA (2.2 mL, 0.22 mmol, 1.06 equiv, 0.1 M in THF) was added dropwise by syringe. The mixture was stirred for 1 h at -78 °C and allyl cyanoformate (26.4 mg, 0.24 mmol, 1.20 equiv) was added. The reaction was stirred for another 3 h and quenched with saturated NH_4Cl aqueous. The aqueous layer was extracted with CH_2Cl_2 (30 mL x 4) and the combined organics were washed with brine, dried over $MgSO_4$, and concentrated. The crude mixture was purified by flash chromatography (SiO_2, 10 x 1 cm, 30% EtOAc in hexanes) to afford **29c** (19.8 mg, 0.06 mmol, 30% yield) as a yellow oil; R_f = 0.30 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.31 (m, 3H), 7.29–7.19 (m, 2H), 7.07 (d, *J* = 7.4 Hz, 1H), 5.86 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.32 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.20 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.96 (d, *J* = 7.3 Hz, 1H), 4.67–4.51 (m, 2H), 4.43 (s, 2H), 3.82 (d, *J* = 13.4 Hz, 1H), 3.27 (d, *J* = 13.4 Hz, 1H), 2.03 (dd, *J* = 14.2, 7.1 Hz, 1H), 1.64–1.45 (m, 2H), 0.85 (d, *J* = 6.5 Hz, 3H), 0.80 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ187.7, 170.9, 152.2, 135.1, 131.7, 129.0, 128.1, 118.4, 96.7, 65.8, 60.1, 54.4, 52.6, 40.4, 24.6, 24.3, 23.2; IR (Neat Film NaCl) 3029, 2957, 2870, 1729, 1644, 1593, 1455, 1360, 1267, 1215, 1159, 1132, 1077, 1029, 971, 778, 735 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{20}H_{26}NO_3$ $[M+H]^+$: 328.1913, found 328.1947.



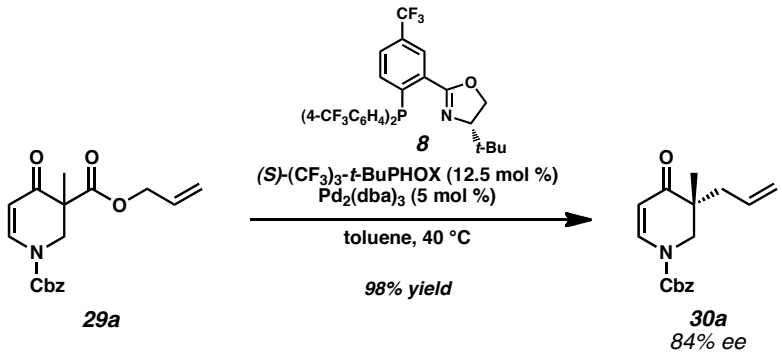
2,3-Dihydropyridin-4-one 48d. To a cooled (–78 °C) solution of **47c**[39] (0.67 g, 2.6 mmol, 1 equiv) in THF (25 mL) was added LDA (30 mL, 0.1 M, in THF, 30 mmol, 1.15 equiv) dropwise over 10 min. The reaction was stirred for 1 h before 1-iodo-2-methylpropane (0.57 g, 3.1 mmol, 1.20 equiv) was added dropwise. After 2 h, the reaction was brought to room temperature and stirred overnight. The reaction was quenched with sat. NH_4Cl sol. and transferred to a separatory funnel where the aqueous phase was extracted four times with CH_2Cl_2. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude mixture purified by flash column chromatography (SiO_2, 15 x 3 cm, 50% EtOAc in hexanes→100% EtOAc) to afford recovered **47c** (0.26 g, 1.01 mmol, 39% recovered) and also **48d** (0.17 g, 0.54 mmol, 21% yield) as a yellow solid; R_f = 0.20 (50% EtOAc in hexanes). Spectral data matches that reported previously.[47] NMR data is included to assist the reader. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (s, 1H), 6.65 (s, 1H), 5.62 (s, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.64 (dd, J = 12.5, 5.3 Hz, 1H), 3.45–3.24 (m, 3H), 2.94 (td, J = 6.3, 3.5 Hz, 2H), 2.51–2.35 (m, 1H), 1.80–1.59 (m, 2H), 1.36–1.19 (m, 1H), 0.96 (d, J = 6.2 Hz, 3H), 0.91 (d, J = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.5, 156.6, 151.5, 148.1, 129.0, 120.9, 110.5, 108.4, 94.4, 56.1, 55.9, 49.2, 42.1, 37.6, 28.6, 25.6, 23.6, 21.9.



2,3-Dihydropyridin-4-one 29d. A solution of **48d** (149.1 mg, 0.47 mmol in 15 mol of THF) was cooled to –78 °C and LDA (5.2 mL, 0.1 M in THF, 0.52 mmol, 1.10 equiv) was added dropwise. The reaction was stirred for 1 h before allyl cyanoformate (60.2 mg, 0.54 mmol, 1.15 equiv) was added dropwise. After 12 h, the reaction was quenched with sat. NH_4Cl sol. and allowed to warm to room temperature. The reaction contents were transferred to a separatory funnel where the aqueous phase was extracted four times with CH_2Cl_2. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude mixture was purified by flash column chromatography (SiO_2, 15 x 3 cm, 50% EtOAc in hexanes) to afford 2,3-dihydropyridin-4-one **29d** (116.0 mg, 0.29 mmol, 62% yield) as a yellow solid; R_f = 0.40 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (s, 1H), 6.66 (s, 1H), 5.87 (ddt, J = 17.2, 10.3, 5.6 Hz, 1H), 5.59 (s, 1H), 5.30 (dq, J = 17.2, 1.6 Hz, 1H), 5.17 (dq, J = 10.4, 1.3 Hz, 1H), 4.61 (ddt, J = 5.6, 2.7, 1.4 Hz, 2H), 4.05 (d, J = 13.0 Hz, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.62 (d, J = 13.1 Hz, 1H), 3.55 (ddd, J = 12.1, 8.1, 5.7 Hz, 1H), 3.43 (ddd, J = 12.2, 6.9, 5.4 Hz, 1H), 3.00–2.77 (m, 2H), 2.23–2.06 (m, 1H), 1.79–1.60 (m, 2H), 0.96 (d, J = 6.2 Hz, 3H), 0.90 (d, J = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.1, 171.0, 155.7, 151.6, 148.0, 131.8, 129.0, 120.5, 118.3, 110.3, 108.4, 92.8, 65.7, 56.5, 56.0, 56.0, 54.5, 48.6, 40.4, 28.3, 25.0, 24.4, 23.5; IR (Neat Film NaCl) 2955, 1720, 1625, 1583, 1544, 1495, 1343, 1237, 1211, 1167, 11523, 1120, 1016

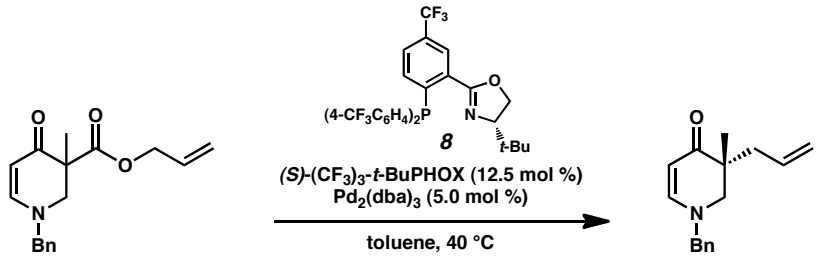
cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{23}H_{30}NO_5$ $[M+H]^+$: 400.2124, found 400.2110.

1.4.2.3.5 *2,3-Dihydropyridin-4-one Allylic Alkylation Products*



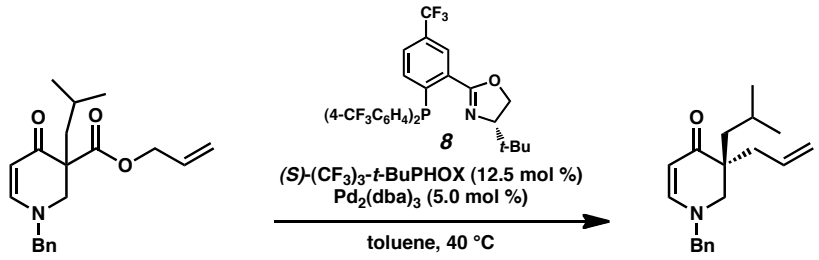
2,3-Dihydropyridin-4-one 30a. 2,3-Dihydropyridin-4-one **29a** (27.6 mg, 0.084 mmol, 1.0 equiv) was preloaded in a 1 dram vial and cycled into a glove box. A separate 1 dram vial was loaded with (S)-$(CF_3)_3$-*t*-Bu-PHOX (**8**, 4.1 mg, 10.5 µmol, 0.125 equiv), $Pd_2(dba)_3$ (3.9 mg, 4.20 µmol, 0.05 equiv), and a magnetic stir-bar. Toluene (1.6 mL) was added and the black suspension was stirred at 30 °C in a heating block for 30 min. 2,3-Dihydropyridin-4-one **29a** was dissolved in 1 mL of toluene and added to the orange catalyst solution, causing an immediate color change to olive green. The vial was capped with a Teflon screw cap and the reaction was stirred for 14 h at 40 °C in the glove box. Upon completion of the reaction, the vial was allowed to cool to room temperature and removed from the glove box. The reaction was concentrated under reduced pressure and the resulting brown oil was purified by flash-chromatography (1:1 Et_2O/hexanes) to afford 2,3-dihydropyridin-4-one **30a** (23.7 mg, 0.083 mmol, 98%) as a colorless oil; R_f = 0.73 (1:1 Et_2O/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.42–7.36 (m, 5H), 5.69 (td, J = 17.3, 7.5 Hz, 1H), 5.27 (d, J = 2.7 Hz, 3H), 5.05 (dd, J = 29.7, 13.4 Hz, 2H),

3.91 (d, J = 13.4 Hz, 1H), 3.58 (d, J = 11.8 Hz, 1H), 2.22 (ddd, J = 46.4, 13.8, 7.5 Hz, 2H), 1.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ198.3, 152.7, 141.7, 135.0, 132.6, 128.8, 128.7, 128.4, 119.2, 106.4, 69.1, 51.4, 43.4, 39.4, 19.5; IR (Neat Film, NaCl) 2922, 1728, 1673, 1602, 1498, 1453, 1416, 1381, 1342, 1305, 1232, 1200, 1144, 1119, 1088, 956, 913, 813, 761 cm^{-1}; HRMS (MM: ESI/APCI+) *m/z* calc'd for $C_{17}H_{20}NO_3$ $[M+H]^+$: 286.1443, found 286.1438; $[\alpha]_D^{25.0}$ +9.88 (*c* 1.15, $CHCl_3$, 84% ee); Thar SFC conditions: 10% MeOH in CO_2, 3 mL/min, Chiralpak AD-H column, λ = 254 nm, t_R (min): major = 2.80, minor = 3.13.



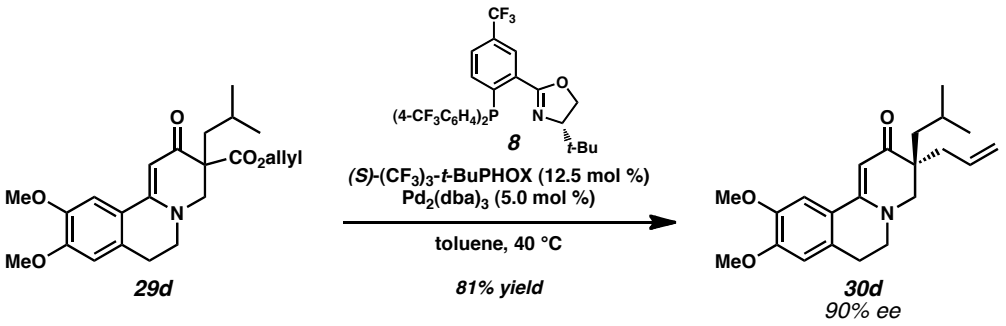
2,3-Dihydropyridin-4-one 30b. In a glove box, $Pd_2(dba)_3$ (2.3 mg, 0.0025 mmol, 5.0 mol %) and (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**, 3.7 mg, 0.00625 mmol, 12.5 mol %) were added to a scintillation vial equipped with a stir bar. The vial was charged with toluene (0.5 mL) and heated at 40 °C for 30 min. 2,3-Dihydropyridin-4-one **29b** (14.3 mg, 0.050 mmol, 1.00 equiv) and additional toluene (1.0 mL, total added = 1.5 mL, 0.033 M) were added, producing a green solution. The vial was sealed and stirred at 40 °C until the starting material was fully converted, determined by LCMS. The reaction was filtered through a celite pad, rinsed with EtOAc, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 5 x 1 cm, 30% EtOAc in hexanes) to afford

2,3-dihydropyridin-4-one **30b** (11.3 mg, 0.047 mmol, 94% yield) as a yellow oil; R_f = 0.30 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.25 (m, 3H), 7.24–7.14 (m, 2H), 7.03 (d, *J* = 7.4 Hz, 1H), 5.54 (ddt, *J* = 17.4, 10.1, 7.4 Hz, 1H), 4.94 (ddt, *J* = 9.9, 1.9, 0.9 Hz, 1H), 4.91–4.81 (m, 2H), 4.27 (d, *J* = 3.1 Hz, 2H), 3.07 (d, *J* = 13.0 Hz, 1H), 2.90 (d, *J* = 13.0 Hz, 1H), 2.22–1.97 (m, 2H), 0.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ196.5, 152.3, 135.6, 133.6, 129.0, 129.0, 129.0, 128.3, 128.0, 118.3, 96.9, 60.1, 55.9, 42.7, 39.7, 20.1, 20.0; IR (Neat Film NaCl) 3067, 3029, 2962, 2926, 1634, 1593, 1455, 1359, 1321, 1204, 1172, 1076, 1001, 916, 795 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{18}H_{20}NO$ $[M+H]^+$: 242.1545, found 242.1553; $[\alpha]_D^{25.0}$ +86.46 (c 1.16, $CHCl_3$, 86% ee); HPLC conditions: 10% IPA in hexanes, 1 mL/min, Chiralcel OJ column, λ = 210 nm, t_R (min): major = 18.77, minor = 21.21.



2,3-Dihydropyridin-4-one 30c. In a glove box, $Pd_2(dba)_3$ (1.4 mg, 0.0015 mmol, 5.0 mol %) and (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**, 2.2 mg, 0.00375 mmol, 12.5 mol %) were added to a scintillation vial equipped with a stir bar. The vial was charged with toluene (0.5 mL) and heated at 40 °C for 30 min. 2,3-Dihydropyridin-4-one **29c** (9.8 mg, 0.030 mmol, 1.00 equiv) and additional toluene (0.5 mL, total added = 1.0 mL, 0.030 M) were added, producing a green solution. The vial was sealed and stirred at 40 °C until the starting

material was fully converted, determined by TLC. The reaction was filtered through a celite pad, rinsed with EtOAc, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 5 x 1 cm, 30% EtOAc in hexanes) to afford 2,3-dihydropyridin-4-one **30c** (6.9 mg, 0.024 mmol, 81% yield) as a yellow oil; R_f = 0.40 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.32 (m, 3H), 7.29–7.22 (m, 2H), 7.05 (d, *J* = 7.4 Hz, 1H), 5.62 (dddd, *J* = 17.1, 10.1, 7.8, 7.0 Hz, 1H), 5.00 (ddt, *J* = 10.1, 2.1, 1.0 Hz, 1H), 4.97–4.91 (m, 2H), 4.33 (s, 2H), 3.13 (d, *J* = 3.2 Hz, 2H), 2.34–2.24 (m, 1H), 2.16 (ddt, *J* = 14.1, 7.8, 1.1 Hz, 1H), 1.61 (qd, *J* = 6.7, 5.6 Hz, 1H), 1.47 (dd, *J* = 14.2, 6.3 Hz, 1H), 1.33 (dd, *J* = 14.2, 5.5 Hz, 1H), 0.84 (d, *J* = 6.6 Hz, 3H), 0.82 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7, 152.4, 135.7, 133.7, 129.1, 128.5, 128.1, 118.4, 97.1, 60.2, 56.0, 42.8, 39.8, 20.2.; IR (Neat Film NaCl) 3072, 3029, 2954, 2867, 1633, 1593, 1494, 1455, 1385, 1361, 1296, 1205, 1173, 1105, 1076, 1028, 998, 793, 736 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{19}H_{26}NO$ $[M+H]^+$: 284.2014, found 284.2023; $[\alpha]_D^{25.0}$ +50.23 (c 0.65, $CHCl_3$, 88% ee); HPLC conditions: 7% IPA in hexanes, 1 mL/min, Chiralcel OJ column, λ = 210 nm, t_R (min): major = 11.44, minor = 14.80.

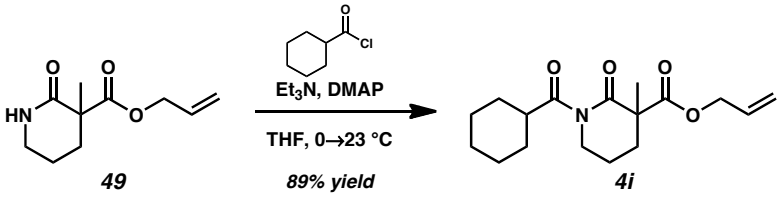


2,3-Dihydropyridin-4-one 30d. $Pd_2(dba)_3$ (1.4 mg, 0.0015 mmol, 5.0 mol %) and (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**, 2.2 mg, 0.00375 mmol, 12.5 mol %) were added to an oven-dried Schlenk tube equipped with a magnetic stir bar, and the tube was backfilled with argon 3 times. The tube was charged with toluene (1 mL) and heated at 40 °C for 30 min, generating a red/orange solution. 2,3-Dihydropyridin-4-one **29d** (11.9 mg, 0.03 mmol, 1.00 equiv) were added and the tube was lowered into a heating block (40 °C). After 3 h, TLC analysis indicated the reaction was complete. Consequently, the reaction was filtered through a silica gel plug, rinsed with EtOAc, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (SiO_2, 10 x 2 cm, 50% EtOAc in hexanes) to afford dihydropyridine-4-one **30d** (8.6 mg, 0.0242 mmol, 81% yield) as yellow oil; R_f = 0.50 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (s, 1H), 6.66 (s, 1H), 5.82 (ddt, J = 17.4, 10.2, 7.4 Hz, 1H), 5.62 (s, 1H), 5.10–5.03 (m, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 3.39 (s, 2H), 3.37 (td, J = 6.5, 1.5 Hz, 2H), 2.99–2.89 (m, 2H), 2.43 (ddt, J = 13.9, 7.2, 1.3 Hz, 1H), 2.25 (ddt, J = 14.0, 7.7, 1.1 Hz, 1H), 1.74 (hd, J = 6.6, 5.0 Hz, 1H), 1.66 (dd, J = 14.1, 6.5 Hz, 1H), 1.44 (dd, J = 14.1, 5.1 Hz, 1H), 0.94 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.3, 155.6, 151.4, 148.0, 134.7, 128.7, 120.8, 117.9, 110.4, 108.3, 94.3, 58.9, 56.0, 48.9, 46.1, 41.7, 39.2, 28.4, 25.1, 24.5, 24.1; IR (Neat Film NaCl) 2953, 1622, 1586,

1549, 1495, 1464, 1342, 1212, 1173, 1110, 1016, 913, 794 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{22}H_{30}NO_3$ $[M+H]^+$: 356.2147, found 356.2221; $[\alpha]_D^{25.0}$ +32.49 (c 0.71, $CHCl_3$, 90% ee); HPLC conditions: 30% IPA in hexanes, 1 mL/min, Chiralpak AD column, λ = 254 nm, t_R (min): major = 21.87, minor = 18.59.

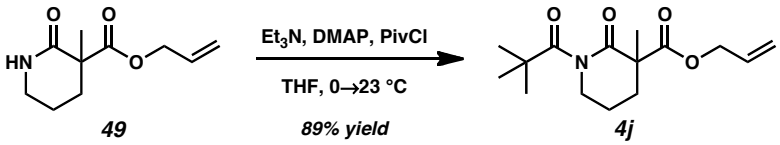
1.4.2.4 Preparation of Lactams

1.4.2.4.6 *Lactam Allylic Alkylation Precursors*



Lactam 4i. Lactam **49**[10] (117.8 mg, 0.597 mmol, 1.00 equiv) was transferred to a flame-dried 15 mL round-bottom flask using THF (4 x 0.5 mL + 1 x 0.4 mL rinses, total = 2.4 mL, 0.25 M). Et_3N (250 µL, 1.79 mmol, 3.00 equiv) and DMAP (9.3 mg, 0.0761 mmol, 13 mol%) were added and the flask was lowered into a 0 °C bath (ice/water). Cyclohexanecarbonyl chloride (160 µL, 1.20 mmol, 2.00 equiv) was added dropwise, and the reaction mixture transitioned from a solution to a white slurry. The ice bath expired gradually as the reaction was stirred overnight. After 15 h of stirring, no starting material remained by TLC analysis. The reaction was subsequently quenched with brine (15 mL) and transferred to a separatory funnel where the aqueous layer was extracted four times with EtOAc. The combined organics (100 mL) were rinsed twice with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 27.5 x 2 cm, 100%

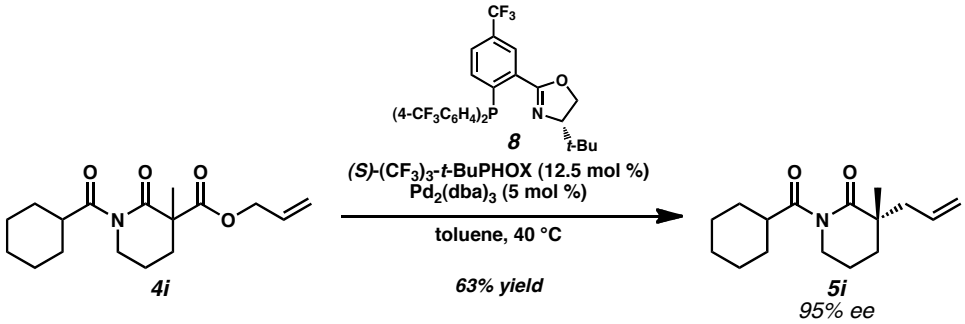
hexanes→10% EtOAc in hexanes) to afford lactam **4i** (163.5 mg, 0.532 mmol, 89% yield) as a yellow oil; R_f = 0.60 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (dddd, J = 17.1, 10.4, 5.8, 5.8 Hz, 1H), 5.32 (dq, J = 17.2, 1.5 Hz, 1H), 5.25 (dq, J = 10.4, 1.2 Hz, 1H), 4.64 (ddt, J = 5.8, 2.5, 1.3 Hz, 2H), 3.77 (ddd, J = 13.1, 7.7, 5.1 Hz, 1H), 3.58 (dddd, J = 13.4, 7.0, 5.0, 1.1 Hz, 1H), 3.27 (tt, J = 11.4, 3.2 Hz, 1H), 2.42 (dddd, J = 13.4, 6.0, 4.9, 0.9 Hz, 1H), 1.95 (dtd, J = 10.5, 3.5, 1.8 Hz, 1H), 1.92–1.80 (m, 3H), 1.79–1.70 (m, 3H), 1.67 (dtt, J = 10.8, 3.2, 1.5 Hz, 1H), 1.52 (s, 3H), 1.47–1.34 (m, 2H), 1.34–1.16 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.3, 173.5, 172.7, 131.4, 119.2, 66.4, 53.5, 45.7, 44.6, 33.1, 30.1, 29.6, 26.1, 25.9, 25.8, 23.0, 20.3; IR (Neat Film NaCl) 3086, 2931, 2855, 1738, 1694, 1652, 1479, 1451, 1378, 1330, 1301, 1249, 1218, 1196, 1159, 1134, 1073, 1053, 1032, 981, 957, 939, 896, 887, 842, 796, 773 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{26}O_4N$ $[M+H]^+$: 308.1856, found 308.1871.



Lactam 4j. Lactam **49**[9] (480 mg, 2.4 mmol, 1.0 equiv) in a 25 mL round-bottom flask equipped with a magnetic stir bar was taken up in THF (9.6 mL, 0.25 M). Et_3N (1.0 mL, 7.2 mmol, 3.0 equiv) and DMAP (29 mg, 0.24 mmol, 0.10 equiv) were added and the flask was lowered into a 0 °C bath (ice/water). Pivaloyl chloride (0.59 mL, 4.8 mmol, 2.0 equiv) was added dropwise and the reaction mixture transitioned from a solution to a white slurry. The ice bath expired gradually as the reaction was stirred overnight. After 24 h of stirring, TLC analysis indicated that conversion had ceased at approximately

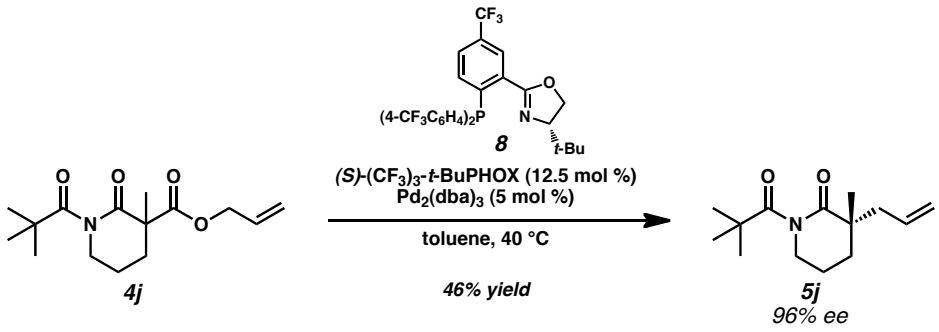
90%. The reaction was subsequently diluted with 20 mL EtOAc, quenched with brine (20 mL), and transferred to a separatory funnel where the aqueous layer was extracted three times with EtOAc (20 mL). The combined organics were washed twice with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 11 x 3 cm, 20% EtOAc in hexanes) to afford lactam **4j** (612 mg, 2.18 mmol, 89% yield) as a pale yellow oil; R_f = 0.37 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (ddt, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.33 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.25 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.70–4.59 (m, 2H), 3.62 (ddd, *J* = 12.8, 8.2, 4.9 Hz, 1H), 3.45 (dddd, *J* = 12.4, 6.2, 4.9, 1.0 Hz, 1H), 2.40 (dddd, *J* = 13.6, 7.1, 4.0, 1.0 Hz, 1H), 2.01–1.83 (m, 2H), 1.74 (ddd, *J* = 13.7, 9.5, 4.1 Hz, 1H), 1.52 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.8, 172.5, 131.7, 119.2, 66.4, 52.5, 47.9, 44.5, 33.6, 28.0, 22.8, 20.3; IR (Neat Film NaCl) 3434, 2090, 1650, 1257, 1125 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{24}NO_4$ $[M+H]^+$: 282.1700, found 282.1705.

1.4.2.4.7 *Lactam Allylic Alkylation Products*



Lactam 5i. $Pd_2(dba)_3$ (16.4 mg, 0.0150 mmol, 5.0 mol %) and (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**, 22.1 mg, 0.0374 mmol, 12.5 mol %) were added to an oven-dried scintillation vial equipped with a magnetic stir bar and the vial was cycled into a glove box. The vial was

charged with toluene (2.06 mL) and stirred at ambient temperature for 30 min, generating a red/orange solution. Lactam **4i** (91.9 mg, 0.299 mmol, 1.00 equiv) was transferred to the scintillation vial with toluene (3 x 2 mL + 1 x 1 mL rinses, total = 9.06 mL, 0.033 M) producing a green solution. The vial was sealed with a Teflon-lined cap, removed from the glove box, and lowered into a heating block (40 °C). After 7 days, the reaction was filtered through a silica gel plug, rinsed with EtOAc, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 27.5 x 2 cm, 100% hexanes→5%→10% EtOAc in hexanes) to afford recovered lactam **4i** (17.2 mg, 0.0560 mmol, 19% recovered) and lactam **5i** (49.8 mg, 0.189 mmol, 63% yield, 78% yield based on recovered lactam **4i**) as a yellow oil; R_f = 0.73 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (dddd, J = 16.6, 10.4, 7.8, 6.9 Hz, 1H), 5.13–5.06 (m, 2H), 3.76–3.67 (m, 1H), 3.57–3.49 (m, 1H), 3.18 (tt, J = 11.4, 3.3 Hz, 1H), 2.51 (ddt, J = 13.6, 6.9, 1.2 Hz, 1H), 2.27 (ddt, J = 13.6, 7.8, 1.1 Hz, 1H), 1.90 (dddd, J = 12.7, 5.5, 2.9, 1.4 Hz, 1H), 1.87–1.72 (m, 7H), 1.67 (dtt, J = 10.8, 3.5, 1.5 Hz, 1H), 1.62–1.56 (m, 1H), 1.42 (dtdd, J = 12.9, 12.0, 11.2, 3.2 Hz, 2H), 1.35–1.19 (m, 2H), 1.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.9, 179.5, 133.5, 118.9, 46.1, 45.8, 45.0, 44.5, 33.3, 30.0, 30.0, 26.1, 25.9, 25.9, 25.8, 19.8; IR (Neat Film NaCl) 3076, 2930, 2854, 1690, 1478, 1451, 1375, 1329, 1313, 1286, 1246, 1198, 1158, 1136, 1089, 1072, 1031, 996, 975, 919, 759 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{26}O_2N$ $[M+H]^+$: 264.1958, found 264.1945; $[\alpha]_D^{25.0}$ –96.13 (c 1.06, $CHCl_3$, 95% ee); JASCO SFC conditions: 1% IPA in CO_2, 5 mL/min, Chiralcel OJ-H column, λ = 222 nm, t_R (min): major = 2.53, minor = 2.13.

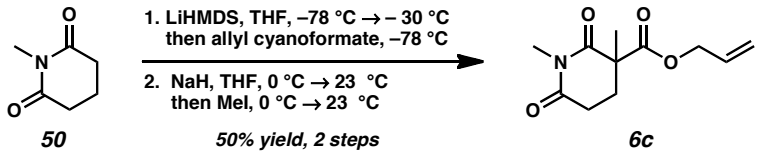


Lactam 5j. $Pd_2(pmdba)_3$ (27 mg, 25 μmol, 5.0 mol %) and (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**, 37 mg, 63 μmol, 12.5 mol %) were added to an oven-dried 20 mL scintillation vial equipped with a magnetic stir bar in a glove box. The vial was charged with toluene (12 mL) and stirred at ambient temperature (28 °C) for 30 min, resulting in a deep orange solution. Lactam **4j** (140 mg, 0.50 mmol, 1.0 equiv) was transferred to the scintillation vial with toluene (2 mL, total = 15 mL, 0.033 M), producing a light green solution. The vial was sealed with a Teflon-lined cap and lowered into a heating block (40 °C). After 16 days, TLC analysis indicated that conversion had ceased at approximately 50% and the vial was removed from the glove box and the reaction was filtered through a silica gel plug, rinsed with Et_2O, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 15 x 2.5 cm, 5% EtOAc in hexanes) to afford lactam **5j** (54 mg, 0.23 mmol, 46% yield) as a colorless oil; R_f = 0.58 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 (dddd, *J* = 17.1, 10.2, 7.8, 7.0 Hz, 1H), 5.16–5.05 (m, 2H), 3.53–3.38 (m, 2H), 2.51 (ddt, *J* = 13.7, 7.0, 1.3 Hz, 1H), 2.28 (ddt, *J* = 13.7, 7.7, 1.1 Hz, 1H), 1.92–1.80 (m, 3H), 1.61–1.58 (m, 1H), 1.27 (s, 9H), 1.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.5, 179.0, 133.7, 118.9, 48.5, 44.2, 43.4, 43.3, 33.4, 28.1, 25.0, 19.8; IR (Neat Film NaCl) 2963, 1684, 1482, 1457, 1391, 1282, 1259, 1156, 917 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{14}H_{24}NO_2$ $[M+H]^+$: 238.1802,

found 238.1809; $[\alpha]_D^{25.0}$ –7.13 (c 2.45, $CHCl_3$, 96% ee); HPLC conditions: 5% IPA in hexanes, 1 mL/min, Chiralcel OD-H column, λ = 210 nm, t_R (min): major = 7.95, minor = 6.52.

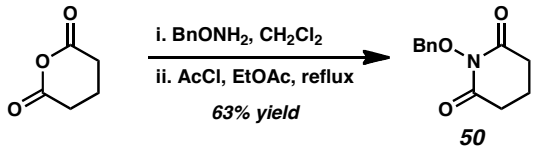
1.4.2.5 Preparation of Imides

1.4.2.5.8 *Imide Allylic Alkylation Precursors*



***N*-Methyl imide 6c.** A flame-dried 200 mL round-bottom flask containing a magnetic stir bar was cycled into a glove box and loaded with LiHMDS (5.69 g, 34.0 mmol, 1.7 equiv). The flask was removed from the glove box, reconnected to a manifold, and charged with THF (100 mL, 0.2 M) and lowered into a –78 °C bath. Imide **50**[48] (2.54 g, 20.0 mmol, 1.0 equiv) was added neat. After 1 h at –78 °C, the solution was warmed to 30 °C and stirred for 30 min before cooling back to –78 °C. Allyl cyanoformate (2.67 g, 24.0 mmol, 1.2 equiv) was added neat and the reaction was stirred for 1.5 h before TLC analysis indicated consumption of starting material. The reaction was subsequently quenched with brine and transferred to a separatory funnel where the aqueous layer was extracted with EtOAc (4 x 50 mL). The combined organics were rinsed twice with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 5 cm x 7 inches, 25%→30%→40% EtOAc in hexanes) to afford an intermediate oil (2.63 g, 0.45 mmol, 62% yield) that was moved on to the next step.

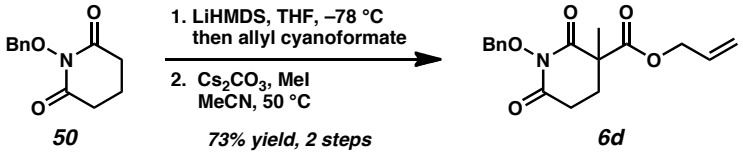
A flame-dried 200 mL flask equipped with a magnetic stir bar was charged with sodium hydride (60% in mineral oil, 312.5 mg, 7.81 mmol, 1.1 equiv) and THF (71 mL, 0.1 M) and cooled to 0 °C. A portion of the oil from the previous step (1.5 g, 7.10 mmol, 1.0 equiv) was added neat. After 1.5 h at 0 °C, the reaction was warmed to room temperature and stirred for 1 h before cooling back to 0 °C. Methyl iodide (886 μL, 14.20 mmol, 2.0 equiv) was added and the reaction was stirred for 2 h before warming to room temperature. After 15 h, the reaction was poured over a mixture of water and brine and transferred to a separatory funnel where the aqueous layer was extracted with EtOAc (4 x 50 mL). The combined organics were rinsed twice with aq. $Na_2S_2O_3$ (sat. solution half diluted) and twice with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 5 cm x 8 inches, 10% →20% EtOAc in hexanes) to afford imide **6c** (1.28 g, 5.69 mmol, 80% yield, 50% yield over two steps); R_f = 0.32 (35% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (ddt, J = 17.2, 10.5, 5.7 Hz, 1H), 5.29 (dq, J = 17.2, 1.5 Hz, 1H), 5.25 (dq, J = 10.5, 1.2 Hz, 1H), 4.63 (ddt, J = 5.6, 4.1, 1.4 Hz, 2H), 3.18 (s, 3H), 2.72 (ddd, J = 18.1, 5.4, 4.4 Hz, 1H), 2.64 (ddd, J = 17.9, 11.6, 5.4 Hz, 1H), 2.35 (ddd, J = 13.9, 5.4, 4.4 Hz, 1H), 1.89 (ddd, J = 13.9, 11.6, 5.4 Hz, 1H), 1.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 171.8, 171.3, 131.2, 119.3, 66.5, 50.9, 30.0, 28.7, 27.3, 21.9; IR (Neat Film NaCl) 2987, 2943, 1726, 1678, 1458, 1416, 1381, 1356, 1305, 1261, 1247, 1182, 1106, 1036, 993, 938 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{11}H_{18}NO_4$ $[M+H]^+$: 226.1074, found 226.1078.



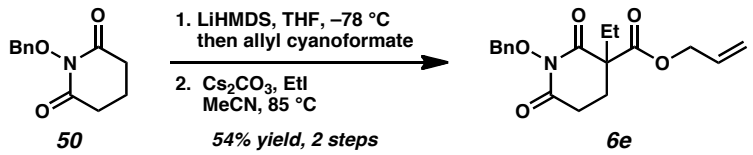
50

***N*-benzyloxyimide 50.** Benzyloxyamine hydrochloride (3.15 g, 19.7 mmol) in a 100 mL round-bottom flask was taken up in dichloromethane (30 mL) and saturated aqueous K_2CO_3 (30 mL) and stirred for 30 min. The mixture was transferred to a separatory funnel and the phases were separated. The aqueous phase was extracted twice with dichloromethane (30 mL), the combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. A portion of the resulting crude colorless oil (1.23 g, 10.0 mmol, 1.00 equiv) was diluted with dichloromethane (10 mL, 1.0 M) in a 50 mL round-bottom flask and glutaric anhydride (1.14 g, 10.0 mmol, 1.00 equiv) was added. An exotherm was observed, and the mixture was immediately concentrated under reduced pressure. The resulting residue was taken up in EtOAc (13 mL, 0.75 M) and acetyl chloride (2.00 mL, 2.81 mmol, 2.81 equiv) was added. A water condenser was affixed and the reaction was heated to a gentle reflux (oil bath, 85 °C) for 18 h. The reaction was diluted with EtOAc (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude solid was purified by flash column chromatography (SiO_2, 6 x 5 cm, 20% EtOAc in hexanes→50% Et_2O in dichloromethane) to afford *N*-benzyloxyimide **50** (1.37 g, 6.25 mmol, 63% yield) as a white solid; R_f = 0.64 (20% Et_2O in methylene chloride); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56–7.45 (m, 2H), 7.41–7.29 (m, 3H), 5.01 (s, 2H), 2.74–2.60 (m, 4H), 1.94–1.85 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.48 , 133.95 , 130.09 , 129.23 , 128.51 , 78.17 , 33.47 , 17.05; IR (Neat Film NaCl) 3033, 2957, 2902, 1689, 1457, 1381, 1350, 1331, 1251, 1175, 1134, 1087, 1056, 999,

968, 919, 893, 838, 759 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{12}H_{14}NO_3$ $[M+H]^+$: 220.0968, found 220.0971.

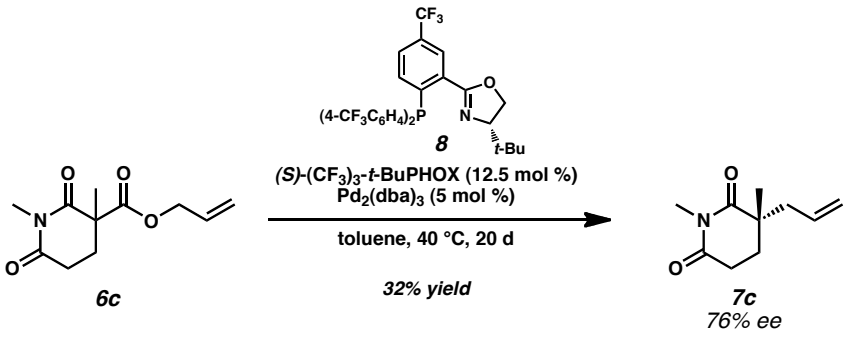


***N*-Benzyloxy imide 6d.** Acylation performed in manner analogous to *N*-methyl imide **6c** at –78 °C using *N*-benzyloxy imide **50** as starting material. Alkylation performed in manner analogous to β-ketoester **45a** at 50 °C. *N*-Benzyloxy imide **6d** was isolated after flash column chromatography (SiO_2, 17 to 25% EtOAc in hexanes) as a colorless oil (73% yield over two steps); R_f = 0.20 (20% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 (m, 2H), 7.37 (m, 3H), 5.87 (ddt, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.33 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.28 (dq, *J* = 10.4, 1.2 Hz, 1H), 5.01 (s, 2H), 4.66 (ddt, *J* = 13.0, 5.9, 1.3 Hz, 1H), 4.65 (ddt, *J* = 13.0, 5.9, 1.3 Hz, 1H), 2.72 (m, 2H), 2.30 (ddd, *J* = 14.1, 5.2, 4.0 Hz, 1H), 1.86 (ddd, *J* = 14.1, 11.8, 5.5 Hz, 1H), 1.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ170.7, 167.9, 167.4, 133.9, 130.9, 130.1, 129.2, 128.5, 119.9, 77.9, 66.9, 52.1, 30.5, 28.5, 21.6; IR (Neat Film NaCl) 2943, 1738, 1733, 1708, 1451, 1255, 1200, 1168, 976 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{20}NO_5$ $[M+H]^+$: 318.1336, found 318.1339.

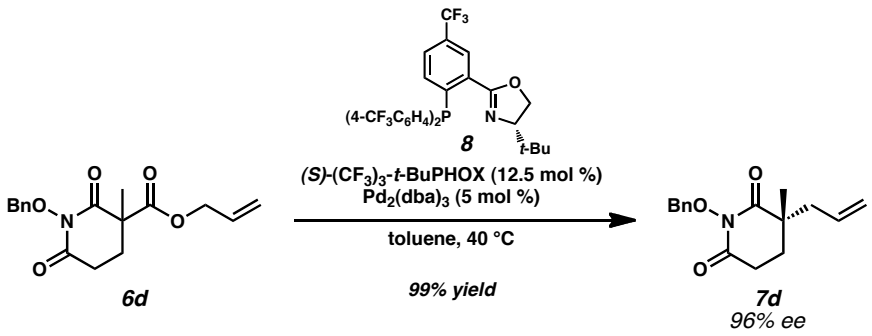


***N*-Benzyloxy imide 6e.** Acylation performed in manner analogous to *N*-methyl imide **6c** at –78 °C using *N*-benzyloxy imide **50** as starting material. Alkylation performed in manner analogous to β-ketoester **45a** at 85 °C using ethyl iodide. *N*-Benzyloxy imide **6e** was isolated after flash column chromatography (SiO_2, 14 to 20% EtOAc in hexanes) as a colorless oil (54% yield over two steps); R_f = 0.24 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (m, 2H), 7.37 (m, 3H), 5.87 (ddt, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.34 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.27 (dq, *J* = 10.4, 1.2 Hz, 1H), 5.0 (s, 2H), 4.66 (dt, *J* = 5.9, 1.3 Hz, 2H), 2.74 (m, 2H), 2.22 (ddd, *J* = 14.0, 5.2, 3.5 Hz, 1H), 2.05(m, 2H), 1.96 (ddd, *J* = 14.0, 12.3, 5.4 Hz, 1H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ170.2, 167.5, 167.1, 134.0, 131.0, 130.1, 129.3, 128.6, 120.0, 77.9, 66.8, 56.2, 30.4, 28.3, 24.8, 9.0; IR (Neat Film NaCl) 2943, 1733, 1713, 1648, 1454, 1237, 1190, 1168, 976, 752 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{18}H_{22}NO_5$ $[M+H]^+$: 332.1492, found 332.1493.

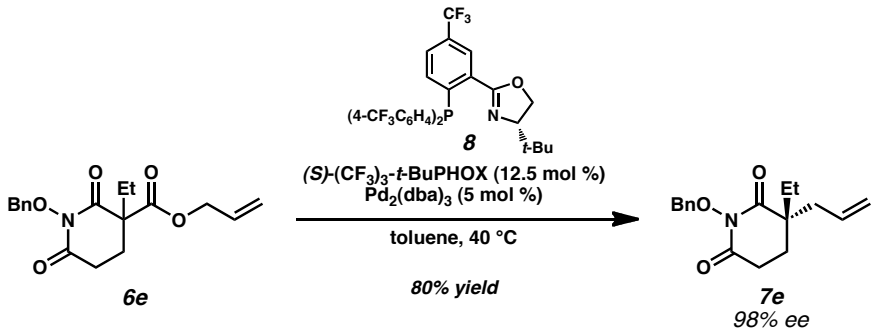
1.4.2.5.9 *Imide Allylic Alkylation Products*



***N*-Methyl imide 7c.** Prepared in a manner analogous to lactam **5h** using *N*-methyl imide **6c** as starting material. After 20 d, the reaction was filtered, concentrated, and *N*-Methyl imide **7c** was isolated following flash column chromatography (SiO_2, 3 cm x 10 inches, 5%→7%→9%→10% →12% EtOAc in hexanes) as an oil (32% yield); R_f = 0.36 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71 (dddd, J = 17.1, 10.2, 7.6, 7.1 Hz, 1H), 5.15–5.08 (m, 2H), 3.12 (s, 3H), 2.75–2.62 (m, 2H), 2.47 (ddt, J = 13.8, 7.1, 1.2 Hz, 1H), 2.29 (ddt, J = 13.8, 7.7, 1.1 Hz, 1H), 1.92 (ddd, J = 14.3, 8.6, 5.9 Hz, 1H), 1.66 (ddd, J = 14.0, 7.1, 5.8 Hz, 1H), 1.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.6, 172.5, 132.8, 119.5, 42.6, 41.7, 29.3, 27.8, 27.0, 23.4; IR (Neat Film NaCl) 2971, 2937, 2876, 1723, 1674, 1464, 1415, 1378, 1356, 1291, 1240, 1110, 1036, 998, 919 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{10}H_{16}NO_2$ $[M+H]^+$: 182.1176, found 182.1178; $[\alpha]_D^{25.0}$ –54.19 (c 1.64, $CHCl_3$, 76% ee); HPLC conditions: 3% IPA in hexanes, 1 mL/min, Chiralpak AD column, λ = 210 nm, t_R (min): major = 11.94, minor = 17.86.



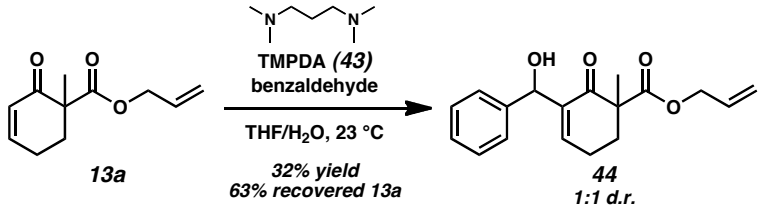
***N*-Benzyloxy imide 7d.** Prepared in a manner analogous to lactam **5h** using *N*-benzyloxy imide **6d** as starting material. *N*-Benzyloxy imide **7d** was isolated after flash column chromatography (SiO_2, 20% EtOAc in hexanes) as a colorless oil (99% yield); R_f = 0.29 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.36 (m, 3H), 5.64 (dddd, *J* = 17.2, 10.2, 7.7, 7.1 Hz, 1H), 5.09–5.15 (m, 2H), 5.0 (s, 2H), 2.66–2.77 (m, 2H), 2.43 (ddt, *J* = 13.9, 7.1, 1.2 Hz, 1H), 2.26 (ddt, *J* = 13.9, 7.7, 1.2 Hz, 1H), 1.87 (ddd, *J* = 14.3, 8.5, 5.9 Hz, 1H), 1.60 (ddd, *J* = 14.3, 7.0, 5.7 Hz, 1H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 168.1, 133.9, 132.3, 130.3, 129.2, 128.5, 119.9, 78.0, 43.1, 42.3, 29.7, 27.6, 23.1; IR (Neat Film NaCl) 3067, 2974, 2935, 1740, 1703, 1700, 1456, 1172, 978, 748 cm^{-1}; HRMS (MM: ESI-APCI) *m*/*z* calc'd for $C_{16}H_{20}NO_3$ $[M+H]^+$: 274.1438, found 274.1437; $[\alpha]_D^{25.0}$ –58.59 (c 1.26, $CHCl_3$, 96% ee); Thar SFC conditions: 5% MeOH in CO_2, 3 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R (min): major = 4.03, minor = 3.64.



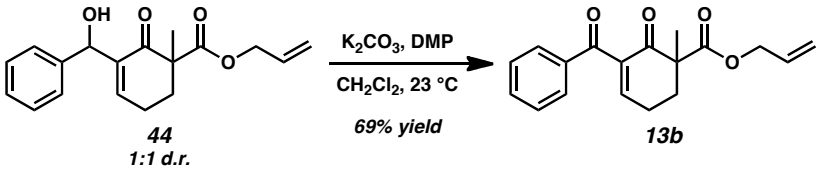
***N*-Benzyloxy imide 7e.** Prepared in a manner analogous to lactam **5h** using *N*-benzyloxy imide **6e** as starting material. *N*-Benzyloxy imide **7e** was isolated after flash column chromatography (SiO_2, 20% EtOAc in hexanes) as a colorless oil (80% yield); R_f = 0.20 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.36 (m, 3H), 5.63 (dddd, *J* = 17.3, 10.3, 7.7, 6.9 Hz, 1H), 5.08–5.10 (m, 2H), 4.99 (s, 2H), 2.67–2.76 (m, 2H), 2.46 (ddt, *J* = 14.0, 6.9, 1.3 Hz, 1H), 2.27 (ddt, *J* = 14.0, 7.7, 1.1 Hz, 1H), 1.80 (ddd, *J* = 14.2, 7.9, 6.4 Hz, 1H), 1.76–1.71 (m, 1H), 1.70 (dq, *J* = 14.2, 7.5 Hz, 1H), 1.62 (dq, *J* = 14.2, 7.5 Hz, 1H), 0.86 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 168.0, 134.0, 132.6, 130.2, 129.2, 128.5, 119.6, 78.0, 46.5, 40.0, 29.5, 28.6, 24.7, 8.2; IR (Neat Film NaCl) 3033, 2972, 1739, 1702, 1699, 1455, 1169, 977, 751 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{22}NO_3$ $[M+H]^+$: 288.1594, found 288.1591; $[\alpha]_D^{25.0}$ –35.98 (c 1.98, $CHCl_3$, 98% ee); Thar SFC conditions: 1% MeOH in CO_2, 2.5 mL/min, Chiralcel OB-H column, λ = 210 nm, t_R (min): major = 14.34, minor = 13.39.

1.4.2.6 Preparation of Enones and Diosphenol Ethers

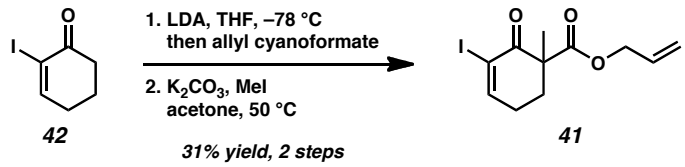
1.4.2.6.10 Enone and Diosphenol Ether Allylic Alkylation Precursors



Alcohol 44. Procedure adapted from the literature precedent of Kim.[44] A 15 mL round-bottom flask equipped with a stir bar was charged with enone **13a** (852.1 mg, 4.39 mmol, 1.94 equiv), THF (1.4 mL, 1.6 M), benzaldehyde (230 μL, 2.26 mmol, 1.00 equiv), H_2O (1.4 mL, 1.6 M), and TMPDA (**43**, 380 μL, 2.27 mmol, 1.00 equiv). The reaction mixture was a yellow suspension that transitioned to orange over time. After 6 days, the reaction was diluted with H_2O (10 mL) and transferred to a separatory funnel where the aqueous phase was extracted four times with CH_2Cl_2. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography (SiO_2, 25.5 x 3 cm, 100% hexanes→5%→10%→15%→20% EtOAc in hexanes) to afford recovered enone **13a** (536.0 mg, 2.76 mmol, 63% recovered) pale yellow oil and alcohol **44** (217.7 mg, 0.725 mmol, 32% yield, 45% yield based on recovered enone **13a**) as a yellow oil; R_f = 0.28 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) ~1:1 mixture of diastereomers, see Figure 1.42.1; IR (Neat Film NaCl) 3503 (broad), 3061, 3030, 2980 2934, 1735, 1672, 1492, 1452, 1424, 1379, 1291, 1246, 1187, 1165, 1111, 1018, 982, 936, 760 cm^{-1}; HRMS (EI+) calc'd for $C_{18}H_{20}O_4$ $[M+\bullet]^+$: 300.1362, found 300.1376.



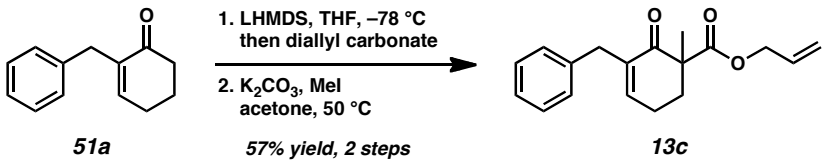
Enone 13b. A scintillation vial containing alcohol **44** (44.5 mg, 0.148 mmol, 1.00 equiv) was equipped with a stir bar, connected to a manifold, backfilled with Ar, and charged with CH_2Cl_2 (1 mL, 0.15 M). K_2CO_3 (62.5 mg, 0.452 mmol, 3.05 equiv) and DMP (96.3 mg, 0.227 mmol, 1.53 equiv) were added simultaneously to the vial. After 2 h of stirring, no starting material was detected by TLC analysis. Consequently, the reaction was diluted with CH_2Cl_2 (1 mL), filtered through a short celite plug rinsing with CH_2Cl_2, and concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography (SiO_2, 27 x 1 cm, 0.1% Et_3N in hexanes→0.1% Et_3N and 10% EtOAc in hexanes) to afford enone **13b** (30.4 mg, 0.102 mmol, 69% yield) as a yellow oil; Rf = 0.43 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 8.11–8.07 (m, 2H), 7.15–7.08 (m, 3H), 6.62 (ddd, J = 5.0, 2.9, 1.2 Hz, 1H), 5.61 (ddt, J = 17.1, 10.3, 5.7 Hz, 1H), 5.05 (dq, J = 17.2, 1.5 Hz, 1H), 4.92 (dq, J = 10.4, 1.3 Hz, 1H), 4.37 (dt, J = 5.7, 1.4 Hz, 2H), 2.11 (dddd, J = 13.5, 4.8, 3.4, 1.2 Hz, 1H), 2.04 (dddd, J = 20.1, 9.6, 5.1, 2.9 Hz, 1H), 1.59 (dtdd, J = 20.1, 5.1, 3.4, 1.4 Hz, 1H), 1.36–1.27 (m, 1H), 1.32 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 194.0, 193.6, 172.1, 150.9, 141.4, 137.6, 133.1, 132.0, 129.9, 128.5, 118.5, 65.9, 53.8, 33.5, 23.6, 20.6; IR (Neat Film NaCl) 3063, 3027, 2981, 2935, 2873, 2855, 2280, 1732, 1668, 1621, 1598, 1581, 1449, 1423, 1378, 1358, 1293, 1265, 1244, 1178, 1157, 1111, 988, 940, 814, 769, 712; HRMS (FAB+) cal'd for $C_{18}H_{18}O_4$ $[M+\bullet]^+$: 298.1205, found 298.1219.



α-Iodoenone 41. A 50 mL round-bottom flask equipped with a stir bar was charged with diisopropyl amine (450 μL, 3.21 mmol, 1.10 equiv) and THF (7 mL). The flask was lowered into a 0 °C bath (water/ice) and *n*-BuLi (1.26 mL, 2.43 M in hexanes, 3.06 mmol, 1.05 equiv) was added dropwise over several minutes. The reaction was stirred for 15 min before the ice bath was removed and replaced with a –78 °C bath (acetone/dry ice). α-Iodoenone **42** (641.3 mg, 2.91 mmol, 1.00 equiv) was transferred via cannula to the flask using several THF rinses (1 x 6 mL and 2 x 1 mL rinses, total added = 15 mL, 0.19 M), producing a yellow solution. The reaction was stirred for 1 h before allyl cyanoformate (330 μL, 3.06 mmol, 1.05 equiv) was added dropwise. After 2.5 h, no starting material was observed by ^{1}H NMR analysis and the reaction was subsequently quenched after an additional hour with sat. NH_4Cl solution (10 mL) and allowed to warm to room temperature. The reaction contents were transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (100 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography (SiO_2, 27.5 x 3 cm, 100% hexanes→5%→10% EtOAc in hexanes) to afford a yellow oil (R_f = 0.52, 30% EtOAc in hexanes) that was moved on to the next step.

The resulting yellow oil was transferred to an argon filled 25 mL Schlenk bomb (14/20 joint off of an 8 mm Kontes valve) equipped with a magnetic stir bar using several acetone rinses (ACS reagent grade, 5 x 2 mL). Additional acetone (3.2 mL, total added =

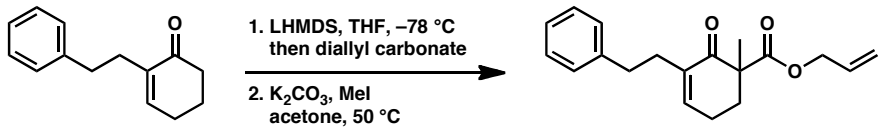
13.2 mL, 0.10 M), K_2CO_3 (367.6 mg, 2.66 mmol, 2.01 equiv), and MeI (170 μL, 2.73 mmol, 2.06 equiv) were added to the bomb. The Kontes valve was sealed, the bomb was lowered into a preheated oil bath (50 °C), and the reaction was stirred vigorously. After 18 h, ^{1}H NMR analysis indicated residual starting material, and consequently more MeI (90 μL, total added = 260 μL, 4.18 mmol, 3.15 equiv) was added. After an additional 21 h, no starting material remained by ^{1}H NMR analysis. Subsequently, the bomb was removed from the oil bath and allowed to cool to room temperature. The reaction contents were filtered through a celite plug rinsing with EtOAc and concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography (SiO_2, 28 x 2 cm, 100% hexanes→5% EtOAc in hexanes) to afford α-iodoenone **41** (277.8 mg, 0.868 mmol, 31% yield over two steps) as a pale yellow oil; R_f = 0.63 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (ddd, J = 4.7, 3.3, 1.0 Hz, 1H), 5.85 (dddd, J = 17.2, 10.8, 5.5, 5.5 Hz, 1H), 5.28 (dq, J = 17.2, 1.5 Hz, 1H), 5.22 (dm, J = 10.5 Hz, 1H), 4.64 (dddd, J = 11.5, 6.3, 4.8, 1.5 Hz, 1H), 4.57 (dddd, J = 11.4, 6.2, 4.7, 1.5 Hz, 1H), 2.60–2.51 (m, 2H), 2.42–2.33 (m, 1H), 2.02–1.95 (m, 1H), 1.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.4, 171.6, 158.1, 131.4, 118.7, 102.0, 66.1, 53.5, 33.3, 27.9, 21.3; IR (Neat Film NaCl) 3085, 2982, 2936, 2874, 2826, 1735, 1696, 1648, 1595, 1457, 1422, 1378, 1323, 1293, 1244, 1178, 1142, 1110, 1089, 1051, 966, 956, 930, 890, 864, 833, 782, 730 cm^{-1}; HRMS (FAB+) calc'd for $C_{11}H_{14}O_3I$ $[M+H]^+$: 320.9988, found 320.9993.



Enone 13c. A 25 mL round-bottom flask equipped with a magnetic stir bar was cycled into a glove box, loaded with LHMDS (527.6 mg, 3.15 mmol, 2.10 equiv), removed from the glove box, and connected to an Ar-filled manifold. The flask was charged with THF (1 mL) and lowered into a 0 °C bath (ice/water). Enone **51a**[49] (279.0 mg, 1.50 mmol, 1.00 equiv) was cannula transferred slowly from a scintillation vial to the flask using several THF rinses (1 x 4 mL + 2 x 0.5 mL, total added = 6 mL, 0.25 M), generating a bright red/pink solution. After the addition was complete, the 0 °C bath was removed and the reaction was allowed to warm to room temperature. After 30 min, the flask was lowered back into the 0 °C bath and diallyl carbonate (230 μL, 1.60 mmol, 1.07 equiv) was added dropwise, generating an orange solution. The bath was allowed to expire overnight. After 18 h, the reaction was quenched with sat. NH_4Cl sol. (10 mL) and transferred to a separatory funnel where the aqueous layer was extracted five times with Et_2O. The combined organics (75 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 21 x 2 cm, 100% hexanes→5%→10% EtOAc in hexanes) to afford a yellow oil.

The resulting yellow oil (285.8 mg, 1.06 mmol, 1.00 equiv) was transferred to an Ar-filled 25 mL Schlenk bomb (14/20 joint off of an 8 mm Kontes valve) equipped with a magnetic stir bar using several acetone rinses (1 x 1.5 mL + 3 x 0.5 mL, total added = 3 mL, 0.35 M). K_2CO_3 (292.7 mg, 2.12 mmol, 2.00 equiv) and methyl iodide (180 μL,

2.89 mmol, 2.73 equiv) were added to the bomb. The Kontes valve was sealed, the bomb was lowered into a preheated oil bath (50 °C), and the reaction was stirred vigorously. After 11 h, ^{1}H NMR analysis indicated residual starting material, and consequently more methyl iodide (130 μL, total added = 310 μL, 4.98 mmol, 4.71 equiv) was added. After an additional 8.5 h, no starting material remained by ^{1}H NMR analysis. Subsequently, the bomb was removed from the oil bath and allowed to cool to room temperature. The reaction contents were filtered through a celite plug rinsing with CH_2Cl_2 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 26.5 x 1.5 cm, 100% hexanes→5% EtOAc in hexanes) to afford enone **13c** (271.2 mg, 0.954 mmol, 64% yield over two steps, 90% purity) as a yellow oil. This yellow oil was diluted in EtOAc (50 mg/mL) and purified further by preparative HPLC (10% EtOAc in hexanes) to afford analytically pure enone **13c** (242.8 mg, 0.851 mmol, 57% yield over two steps) as a pale yellow oil; R_f = 0.59 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.25 (m, 2H), 7.21–7.14 (m, 3H), 6.50–6.45 (m, 1H), 5.78 (ddt, J = 17.2, 10.5, 5.6 Hz, 1H), 5.24 (dq, J = 17.2, 1.5 Hz, 1H), 5.19 (dq, J = 10.5, 1.1 Hz, 1H), 4.53 (dm, J = 5.6 Hz, 2H), 3.58 (dq, J = 15.7, 1.7 Hz, 1H), 3.51 (dq, J = 15.6, 1.7 Hz, 1H), 2.52–2.40 (m, 2H), 2.34–2.24 (m, 1H), 1.94–1.86 (m, 1H), 1.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.6, 172.6, 145.1, 139.5, 138.8, 131.8, 129.3, 128.5, 126.2, 118.4, 65.8, 53.6, 36.0, 33.7, 23.6, 20.6; IR (Neat Film NaCl) 3084, 3061, 3027, 2980, 2934, 1734, 1685, 1603, 1496, 1453, 1430, 1375, 1292, 1246, 1166, 1111, 1077, 1029, 984, 747 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{18}H_{21}O_3$ $[M+H]^+$: 285.1485, found 285.1482.

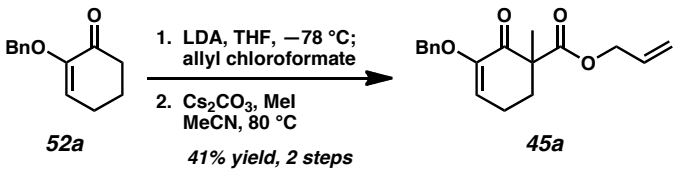


51b ***30% yield, 2 steps*** ***13d***

Enone 13d. A 25 mL round-bottom flask equipped with a magnetic stir bar was cycled into a glove box, loaded with LHMDS (215.6 mg, 1.29 mmol, 2.12 equiv), removed from the glove box, and connected to an Ar-filled manifold. The flask was charged with THF (0.5 mL) and lowered into a 0 °C bath (ice/water). Enone **51b**[49] (122.0 mg, 0.609 mmol, 1.00 equiv) was cannula transferred slowly from a scintillation vial to the flask using several THF rinses (1 x 1 mL + 2 x 0.5 mL, total added = 2.5 mL, 0.24 M), generating a bright pink solution. After the addition was complete, the 0 °C bath was removed and the reaction was allowed to warm to room temperature. After 30 min, the flask was lowered back into the 0 °C bath and diallyl carbonate (100 μL, 0.697 mmol, 1.14 equiv) was added dropwise. The bath was allowed to expire overnight. After 18 h, the reaction was quenched with sat. NH_4Cl sol. (5 mL) and transferred to a separatory funnel where the aqueous layer was extracted five times with Et_2O. The combined organics (70 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 27 x 1.5 cm, 100% hexanes→5% EtOAc in hexanes) to afford a yellow oil.

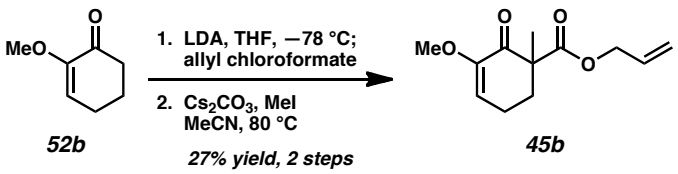
The resulting yellow oil (84.6 mg, 0.298 mmol, 1.00 equiv) was transferred to an Ar-filled 25 mL Schlenk bomb (14/20 joint off of an 8 mm Kontes valve) equipped with a magnetic stir bar using several acetone rinses (4 x 0.5 mL, total added = 2 mL, 0.15 M). K_2CO_3 (87.0 mg, 0.630 mmol, 2.12 equiv) and methyl iodide (100 μL, 1.61 mmol, 5.40 equiv) were added to the bomb. The Kontes valve was sealed, the bomb was lowered

into a preheated oil bath (50 °C), and the reaction was stirred vigorously. After 16 h, ^{1}H NMR analysis indicated residual starting material, and consequently more methyl iodide (130 μL, total added = 310 μL, 4.98 mmol, 4.71 equiv) was added. After an additional 8.5 h, no starting material remained by ^{1}H NMR analysis. Subsequently, the bomb was removed from the oil bath and allowed to cool to room temperature. The reaction contents were filtered through a celite plug rinsing with CH_2Cl_2 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 28 x 1.5 cm, 100% hexanes→2% EtOAc in hexanes) to afford enone **13d** (75.6 mg, 0.253 mmol, 42% yield over two steps, 80% purity) as a yellow oil. This yellow oil was diluted with EtOAc (50 mg/mL) and purified further by preparative HPLC (10% EtOAc in hexanes, 50 mL/min) to afford analytically pure enone **13d** (54.1 mg, 0.181 mmol, 30% yield over two steps) as a pale yellow oil; R_f = 0.67 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.24 (m, 2H), 7.20–7.15 (m, 3H), 6.53 (ddq, J = 4.6, 3.3, 1.0 Hz, 1H), 5.87 (ddt, J = 17.2, 10.5, 5.6 Hz, 1H), 5.29 (dq, J = 17.2, 1.5 Hz, 1H), 5.22 (dq, J = 10.5, 1.3 Hz, 1H), 4.65–4.57 (m, 2H), 2.74 (ddd, J = 13.4, 9.7, 6.1 Hz, 1H), 2.67 (ddd, J = 13.4, 9.3, 6.1 Hz, 1H), 2.57 (dddq, J = 13.8, 9.2, 6.4, 1.5 Hz, 1H), 2.52–2.37 (m, 2H), 2.29 (qt, J = 4.9, 1.3 Hz, 1H), 2.25 (ddt, J = 9.9, 4.8, 1.3 Hz, 1H), 1.88 (ddd, J = 13.4, 8.4, 5.3 Hz, 1H), 1.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.9, 172.7, 144.5, 142.0, 138.2, 131.8, 128.7, 128.4, 126.0, 118.5, 65.8, 53.6, 34.9, 33.6, 32.5, 23.5, 20.6; IR (Neat Film NaCl) 3026, 2930, 1733, 1683, 1603, 1495, 1456, 1377, 1244, 1167, 1109, 985, 931, 748 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{19}H_{23}O_3$ $[M+H]^+$: 299.1642, found 299.1638.



β-ketoester 45a. Diisopropylamine (390 μL, 2.78 mmol, 4.46 equiv) in a 10 mL round-bottom flask equipped with a magnetic stir bar was taken up in 2.0 mL THF and lowered into a 0 °C bath (ice/water). To the stirring solution was added *n*-butyl lithium (4.7 M solution in hexanes, 0.583 mL, 2.74 mmol, 4.40 equiv). This solution was stirred for 30 min before transferring the flask to a –78 °C bath (dry ice/acetone) and stirring the mixture for another 15 min. Benzyl diosphenol ether **52a**[50] (126 mg, 0.623 mmol, 1.00 equiv) in 1.1 mL THF (total = 3.1 mL, 0.2 M) was added dropwise by syringe, and the solution was stirred for 2 h. Allyl cyanoformate (270 μL, 2.49 mmol, 4.00 equiv) was added dropwise by syringe, and the reaction was stirred for 8 h until analysis by TLC showed complete consumption of starting material. The reaction was diluted with 2 mL EtOAc and quenched with 1.5 mL each saturated aqueous NH_4Cl and water. The –78 °C bath was removed and the biphasic mixture was warmed to room temperature. The mixture was transferred to a separatory funnel and the phases were separated. The aqueous phase was extracted twice with EtOAc (5 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude yellow oil was taken up in acetonitrile (2.0 mL, 0.3 M) in a flame-dried 2-dram vial equipped with a magnetic stir bar. Cs_2CO_3 (264 mg, 0.810 mmol, 1.30 equiv) and methyl iodide (116 μL, 1,86 mmol, 3.00 equiv) were added, and the reaction was blanketed under argon and sealed with a Teflon-lined cap. The vial was placed in a heating block (80 °C) and stirred for 8 h until analysis by TLC showed complete consumption of

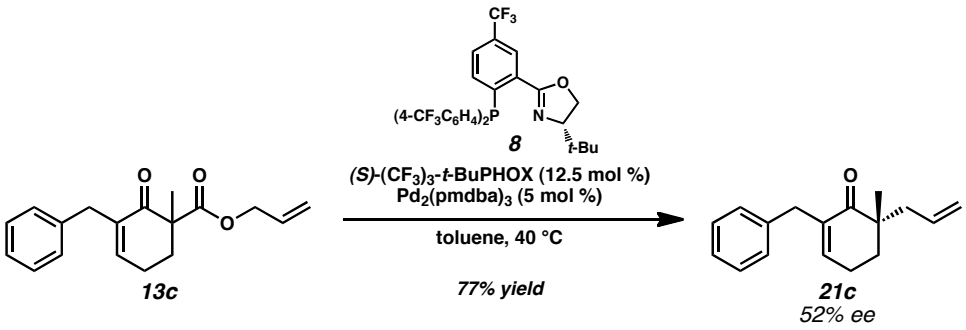
starting material. The reaction was diluted with 5 mL EtOAc, filtered and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 12 x 1.5 cm, 20% Et_2O in hexanes) to afford β-ketoester **45a** (77 mg, 0.26 mmol, 41% yield over two steps) as a colorless oil; R_f = 0.34 (40% Et_2O in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.29 (m, 5H), 5.93–5.79 (m, 2H), 5.30 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.23 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.95–4.83 (m, 2H), 4.67–4.52 (m, 2H), 2.50–2.41 (m, 2H), 2.39–2.27 (m, 1H), 1.96–1.83 (m, 1H), 1.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.0, 172.3, 149.7, 136.7, 131.7, 128.6, 128.0, 127.3, 118.8, 118.5, 70.1, 65.9, 54.3, 33.7, 21.7, 20.6; IR (Neat Film NaCl) 3394, 2916, 2167, 1996, 1692, 1627, 1455, 1251, 1153, 1110, 1056 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{18}H_{21}O_4$ $[M+H]^+$: 301.1434, found 301.1422.



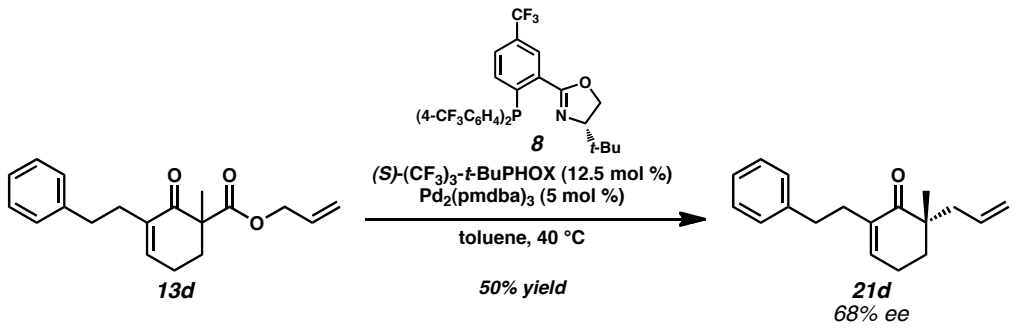
Diosphenol ether 45b. Prepared from **52b**[51] in an analogous manner to **45a**. Purified by flash chromatography (SiO_2, 15 x 3 cm, 20→40% Et_2O in hexanes) to afford diosphenol ether **45b** (57 mg, 0.25 mmol, 27% yield over two steps) as a colorless oil; R_f = 0.54 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.96–5.80 (m, 1H), 5.78 (d, *J* = 4.5 Hz, 1H), 5.27 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.20 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.67–4.55 (m, 2H), 3.60 (s, 3H), 2.56–2.43 (m, 2H), 2.42–2.32 (m, 1H), 1.95–1.85 (m, 1H), 1.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.0, 172.2, 150.7, 131.7, 118.4, 115.2, 65.9, 55.2, 54.3, 33.9, 21.5, 20.6; IR (Neat Film NaCl) 2936, 2839, 1734, 1696, 1631, 1455, 1378,

1365, 1252, 1231, 1174, 1110, 1081, 1064, 979, 935, 824 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{12}H_{17}O_4$ $[M+H]^+$: 225.1121, found 225.1122.

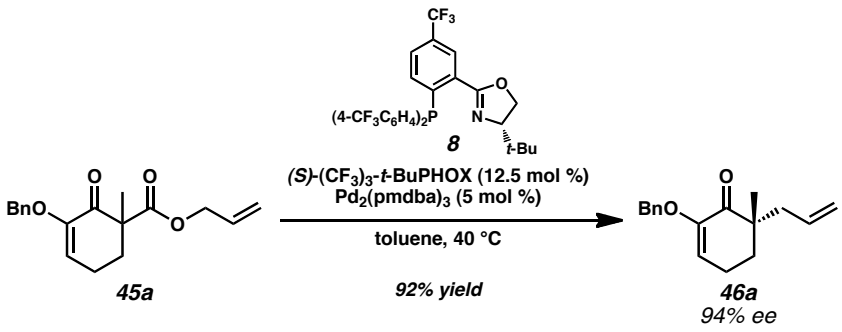
1.4.2.6.11 *Diosphenol Ether and Enone Allylic Alkylation Products*



Enone 21c. Prepared from **13c** in an analogous manner to **46a**. Purified by flash column chromatography (SiO_2, 12 x 2 cm, 10→20% Et_2O in hexanes) to afford enone **21c** (68 mg, 0.28 mmol, 77% yield) as a colorless oil and recovered enone **13c** (19 mg, 18% recovered); R_f = 0.70 (40% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.31–7.20 (m, 2H), 7.23 – 7.10 (m, 3H), 6.46 (d, *J* = 4.0 Hz, 1H), 5.75 – 5.60 (m, 1H), 5.08 – 4.93 (m, 2H), 3.50 (dq, *J* = 3.3, 1.6 Hz, 2H), 2.41 – 2.23 (m, 3H), 2.16 (ddt, *J* = 13.7, 7.6, 1.2 Hz, 1H), 1.89 (ddd, *J* = 13.7, 6.4, 5.5 Hz, 1H), 1.74 (ddd, *J* = 13.6, 6.9, 5.5 Hz, 1H), 1.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.06 , 144.55 , 140.04 , 137.98 , 134.25 , 129.19 , 128.45 , 126.11 , 118.09 , 44.49 , 41.21 , 36.03 , 33.41 , 23.03 , 21.90; IR (Neat Film NaCl) 3063, 3027, 2964, 2924, 1668, 1640, 1495, 1453, 1430, 1376, 1174, 1077, 996, 915, 749 cm^{-1}; $[\alpha]_D^{25.0}$ –200.23 (c 3.86, $CHCl_3$, 52% ee); HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{21}O$ $[M+H]^+$: 241.1587, found 241.1575; JASCO SFC conditions: 3% MeOH in CO_2, 5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R (min): major = 2.40, minor = 2.11.

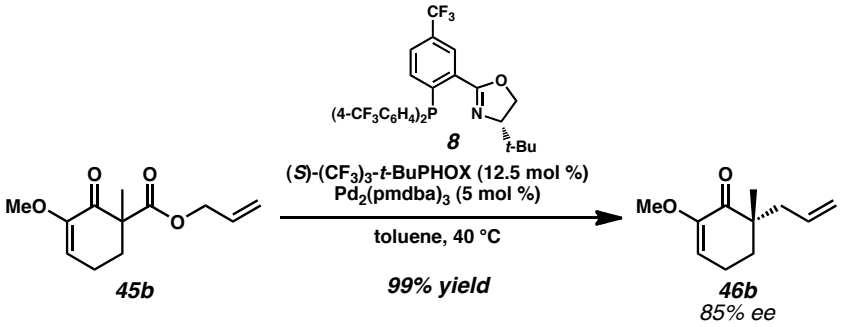


Enone 21d. Prepared from **13d** in an analogous manner to **46a**. Purified by flash column chromatography (SiO_2, 12 x 2 cm, 10→20% Et_2O in hexanes) to afford enone **13c** (17 mg, 67 μmol, 50% yield) as a colorless oil and recovered enone **13d** (8 mg, 20% recovered); R_f = 0.73 (40% Et_2O in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.21 (m, 2H), 7.22–7.13 (m, 3H), 6.50 (t, *J* = 4.1 Hz, 1H), 5.74 (ddt, *J* = 16.8, 10.3, 7.4 Hz, 1H), 5.12–5.00 (m, 2H), 2.76–2.62 (m, 2H), 2.59–2.41 (m, 2H), 2.40–2.12 (m, 4H), 1.89 (ddd, *J* = 13.6, 6.7, 5.5 Hz, 1H), 1.72 (ddd, *J* = 13.6, 6.7, 5.5 Hz, 1H), 1.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.4, 144.2, 142.1, 137.4, 134.4, 128.7, 128.3, 125.9, 118.1, 44.4, 41.3, 35.2, 33.4, 32.4, 23.0, 22.0; IR (Neat Film NaCl) 3062, 3026, 2962, 2924, 2855, 1669, 1639, 1496, 1453, 1430, 1377, 1175, 1078, 995, 914, 747 cm^{-1}; $[\alpha]_D^{25.0}$ –32.55 (c 1.24, $CHCl_3$, 68% ee); HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{18}H_{23}O$ $[M+H]^+$: 255.1743, found 255.1730; JASCO SFC conditions: 3% MeOH in CO_2, 5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R (min): major = 2.41, minor = 2.17.



Diosphenol ether 46a. $Pd_2(pmdba)_3$ (4.2 mg, 3.8 μmol, 5.0 mol %) and (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**, 5.7 mg, 9.6 μmol, 12.5 mol %) were added to an oven-dried 2-dram vial equipped with a magnetic stir bar in a glove box. The vial was charged with toluene (1.8 mL) and stirred at ambient temperature (28 °C) for 30 min, resulting in a deep orange solution. β-ketoester **45a** (23 mg, 77 μmol, 1.0 equiv) was transferred to the scintillation vial with toluene (0.5 mL, total = 2.3 mL, 0.033 M), producing a light green solution. The vial was sealed with a Teflon-lined cap and lowered into a heating block (40 °C). After 6 days, the reaction was complete by TLC and colorimetric analysis (the reaction mixture had reverted to an orange color) and was removed from the glove box. The reaction was filtered through a silica gel plug, rinsed with Et_2O, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 15 x 1.5 cm, 5%→10% Et_2O in hexanes) to afford diosphenol ether **46a** (18 mg, 70 μmol, 92% yield) as a colorless oil; R_f = 0.56 (40% Et_2O in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.26 (m, 5H), 5.83 (t, *J* = 4.5 Hz, 1H), 5.74 (ddt, *J* = 16.7, 10.3, 7.4 Hz, 1H), 5.12–5.03 (m, 2H), 4.85 (s, 2H), 2.42–2.33 (m, 3H), 2.21 (ddt, *J* = 13.8, 7.6, 1.2 Hz, 1H), 1.89 (ddd, *J* = 13.7, 6.7, 5.6 Hz, 1H), 1.71 (ddd, *J* = 13.7, 6.6, 5.4 Hz, 1H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5, 149.0, 136.8, 134.1, 128.6, 127.9, 127.4, 118.4, 118.0, 70.0, 45.4, 41.2, 33.1, 21.9, 20.9; IR (Neat Film NaCl) 2918, 2360, 1684,

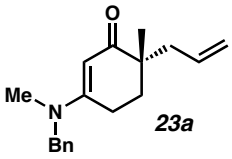
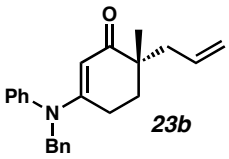
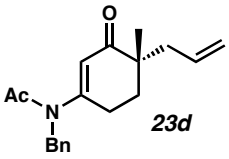
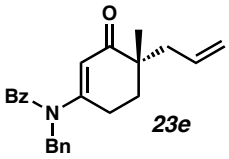
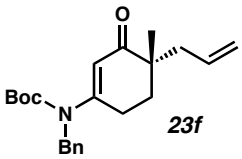
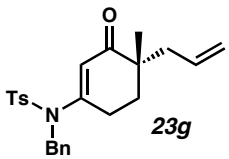
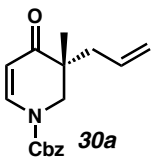
1628, 1457, 1220, 1204, 1094, 1050, 914, 736 cm^{-1}; $[\alpha]_D^{25.0}$ –12.01 (c 0.50, $CHCl_3$, 94% ee); HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{17}H_{21}O_2$ $[M+H]^+$: 257.1536, found 257.1529; HPLC conditions: 7% IPA in hexanes, 1 mL/min, Chiralcel OD-H column, λ = 254 nm, t_R (min): major = 7.24, minor = 8.27.

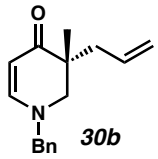
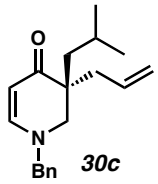
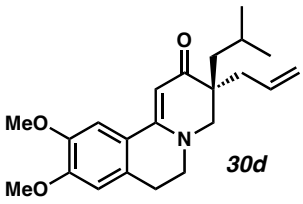
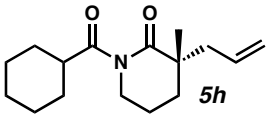
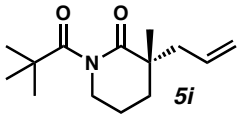
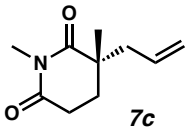
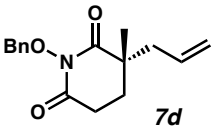
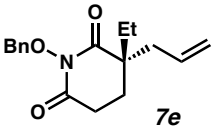


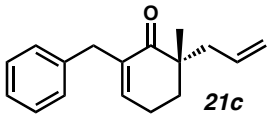
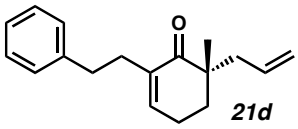
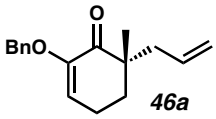
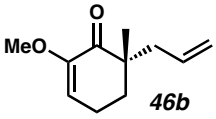
Diosphenol ether 46b. Prepared from **45b** in an analogous manner to **46a**. Purified by flash column chromatography (SiO_2, 10 x 3 cm, 5→10% Et_2O in hexanes) to afford diosphenol ether **45b** (111 mg, 0.616 mmol, 99% yield) as a colorless oil; R_f = 0.23 (40% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 5.79–5.65 (m, 2H), 5.12–5.01 (m, 2H), 3.58 (s, 3H), 2.47–2.34 (m, 3H), 2.20 (ddt, *J* = 13.7, 7.6, 1.1 Hz, 1H), 1.91 (ddd, *J* = 13.7, 6.8, 5.5 Hz, 1H), 1.72 (ddd, *J* = 13.7, 6.5, 5.4 Hz, 1H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.6, 150.0, 134.0, 118.4, 114.5, 55.1, 45.4, 41.2, 33.2, 21.9, 20.8; IR (Neat Film NaCl) 2929, 1687, 1631, 1455, 1375, 1225, 1095, 1056, 913 cm^{-1}; $[\alpha]_D^{25.0}$ –27.47 (c 6.00, $CHCl_3$, 85% ee); HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{11}H_{17}O_2$ $[M+H]^+$: 181.1223, found 181.1222; HPLC conditions: 2% IPA in hexanes, 1 mL/min, Chiralcel OD-H column, λ = 254 nm, t_R (min): major = 13.41, minor = 12.23.

1.4.2.7 Determination of Enantiomeric Excess

Table 1.5. Methods for the determination of enantiomeric excess (chiral HPLC and SFC).

entry	product	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
1	 *23a*	SFC Chiralcel OD-H 5% MeOH in CO_2 isocratic, 5.0 mL/min 210 nm	10.45	9.60	81
2	 *23b*	SFC Chiralpak AS-H 5% MeOH in CO_2 isocratic, 5.0 mL/min 254 nm	8.60	6.48	83
3	 *23d*	SFC Chiralpak AD-H 5% MeOH in CO_2 isocratic, 3.0 mL/min 254 nm	8.45	10.35	86
4	 *23e*	SFC Chiralpak AD-H 7% MeOH in CO_2 isocratic, 5.0 mL/min 210 nm	8.04	8.97	87
5	 *23f*	SFC Chiralpak AD-H 7% MeOH in CO_2 isocratic, 5.0 mL/min 210 nm	4.04	2.20	82
6	 *23g*	SFC Chiralpak AD-H 10% MeOH in CO_2 isocratic, 5.0 mL/min 210 nm	5.60	4.73	84
7	 *30a*	SFC Chiralpak AD-H 10% MeOH in CO_2 isocratic, 3.0 mL/min 254 nm	2.80	3.13	84

entry	product	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
8	 *30b*	HPLC Chiralcel OJ 10% IPA in hexanes isocratic, 1.0 mL/min 210 nm	18.77	21.21	86
9	 *30c*	HPLC Chiralcel OJ 7% IPA in hexanes isocratic, 1.0 mL/min 210 nm	11.44	14.80	88
10	 *30d*	HPLC Chiralpak AD 30% IPA in hexanes isocratic, 1.0 mL/min 254 nm	21.87	18.59	90
11	 *5h*	SFC Chiralcel OJ-H 1% IPA in CO_2 isocratic, 5.0 mL/min 222 nm	2.53	2.13	95
12	 *5i*	HPLC Chiralcel OD-H 5% IPA in hexanes isocratic, 1.0 mL/min 210 nm	7.95	6.52	96
13	 *7c*	HPLC Chiralpak AD 3% IPA in hexanes isocratic, 1.0 mL/min 210 nm	11.94	17.86	76
14	 *7d*	SFC Chiralcel OJ-H 1% MeOH in CO_2 isocratic, 3.0 mL/min 210 nm	4.03	3.64	96
15	 *7e*	SFC Chiralcel OB-H 1% MeOH in CO_2 isocratic, 2.5 mL/min 210 nm	14.34	13.39	98

entry	product	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
16	 ***21c***	SFC Chiralcel OJ-H 3% MeOH in CO_2 isocratic, 5.0 mL/min 210 nm	2.40	2.11	52
17	 ***21d***	SFC Chiralcel OJ-H 3% MeOH in CO_2 isocratic, 5.0 mL/min 210 nm	2.41	2.17	68
18	 ***46a***	HPLC Chiralcel OD-H 7% IPA in hexanes isocratic, 1.0 mL/min 254 nm	7.24	8.27	94
19	 ***46b***	HPLC Chiralcel OD-H 2% IPA in hexanes isocratic, 1.0 mL/min 254 nm	13.41	12.23	85

1.5 NOTES AND REFERENCE

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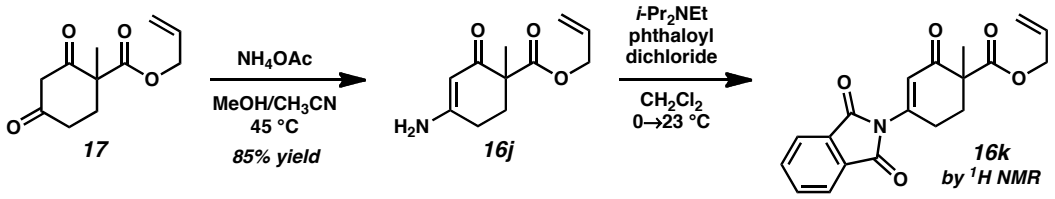
23a). ^{1}H NMR analysis suggests that the product was formed, but enaminone **16k** was not pursued further due to the results of the initial enaminone screen. See: Hansen, K. B.; Hsiao, Y.; Xu, F.; Rivera, N.; Clausen, A.; Kubryk, M.; Krska, S.; Rosner, T.; Simmons, B.; Balsells, J.; Ikemoto, N.; Sun, Y.; Spindler, F.; Malan, C.; Grabowski, E. J. J.; Armstrong, III , J. D. *J. Am. Chem. Soc.* **2009**, *131*, 8798–8804.



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(32) For another example of a screen performed with a Symyx core module, see: McDougal, N. T.; Virgil, S. C.; Stoltz, B. M. *Synlett* **2010**, 1712–1716.

(33) As mentioned previously, the corresponding electron-rich lactams (*N*-substituent = Me or Bn) exhibit little to no conversion to the desired products.

(34) For example, selectivities for lactam **5a** vary from 99% ee with (*S*)-**8** to 86% ee with (*S*)-**3** in toluene and to 96% ee with (*S*)-**8** in THF (Table 1.1).

(35) The distinction between *N*-substituents is most apparent when comparing benzoyl and tosyl lactams, which vary by ~40–80% ee depending on the conditions (see Table 1.1).

(36) Employing optimized conditions with (*S*)-**3** in Et_2O, enone **21a** has been isolated in 90% ee. See ref. 6b.

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(42) Interestingly, both groups found that Trost ligands failed to provide the desired α-quaternary products.

(43) The increase in steric bulk for substrates **4i** and **j** slows the reaction dramatically. Imide **7c** is also hampered by low reactivity. As such, these reactions with these substrates are often not run to completion and consequently have lower yields. See experimental section.

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APPENDIX 1

Spectra Relevant to Chapter 1:

Expanding Insight into the Asymmetric Palladium-Catalyzed

Allylic Alkylation of N-Heterocyclic Molecules and Cyclic Ketones

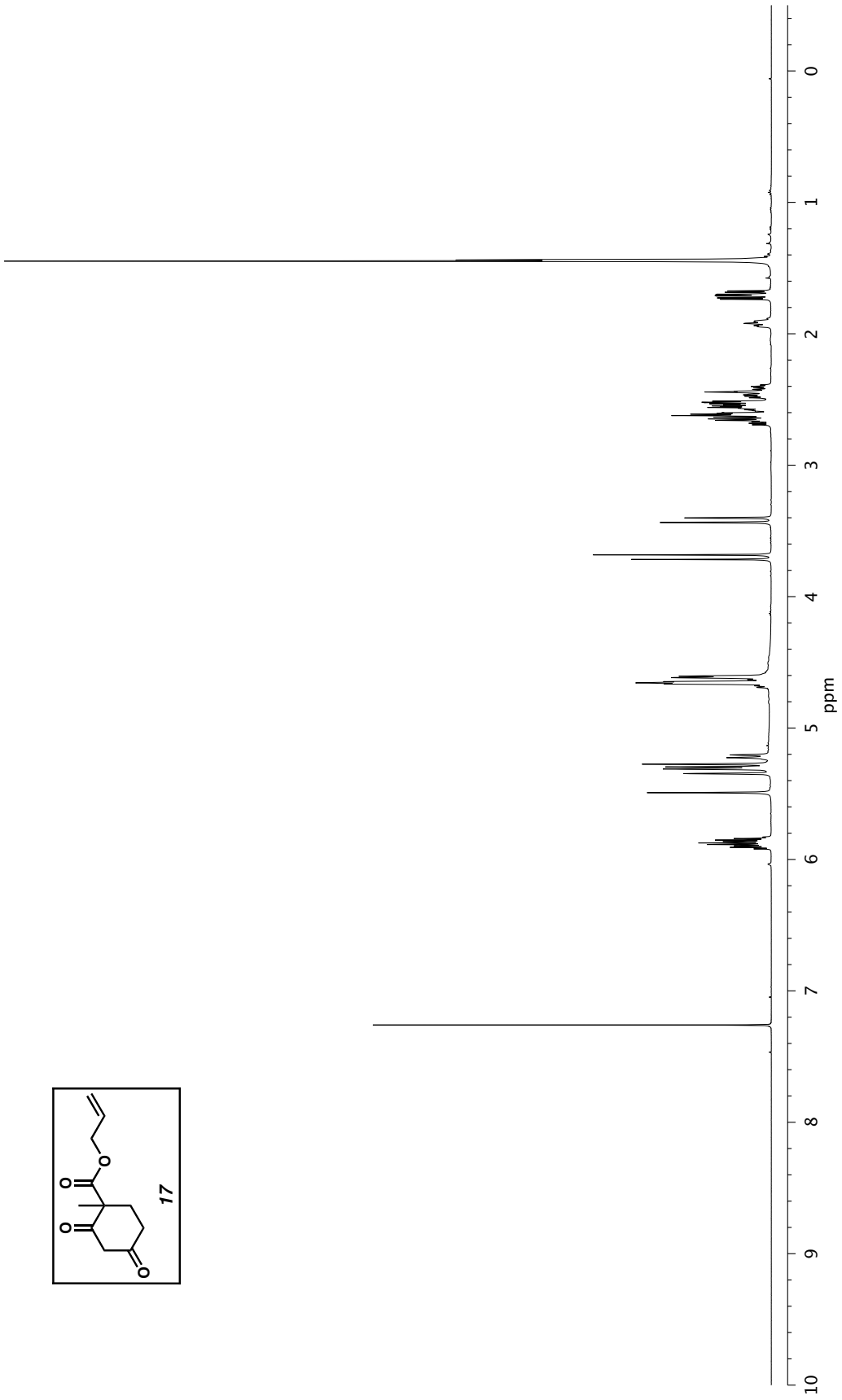


Figure A1.1.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **17**.

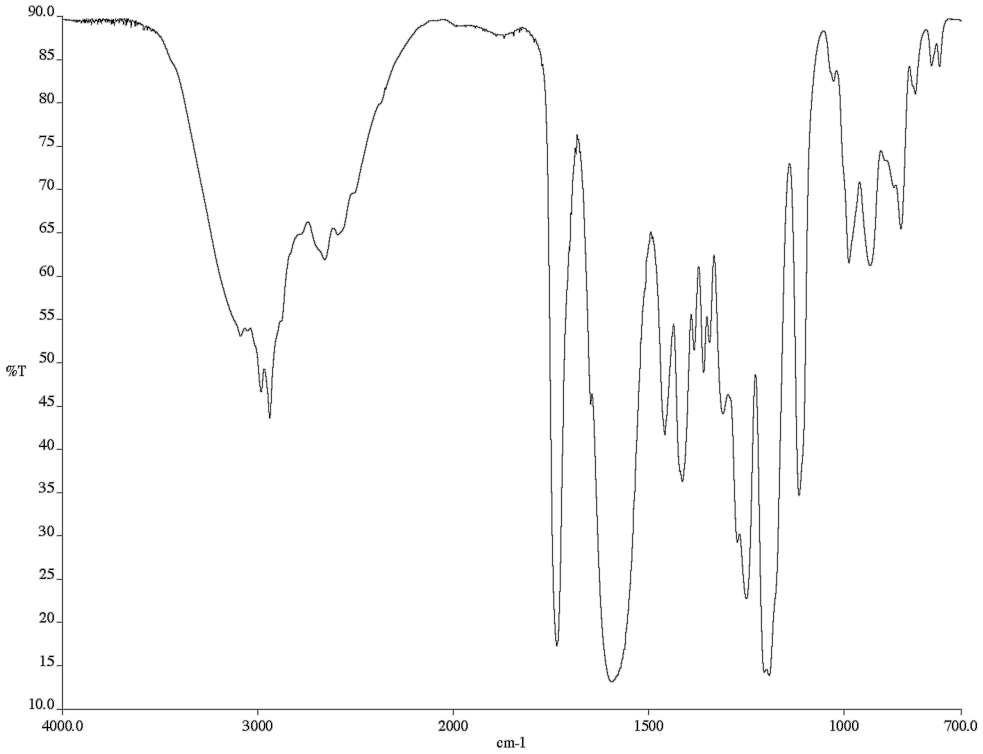


Figure A1.1.2. Infrared spectrum (thin film/NaCl) of compound **17**.

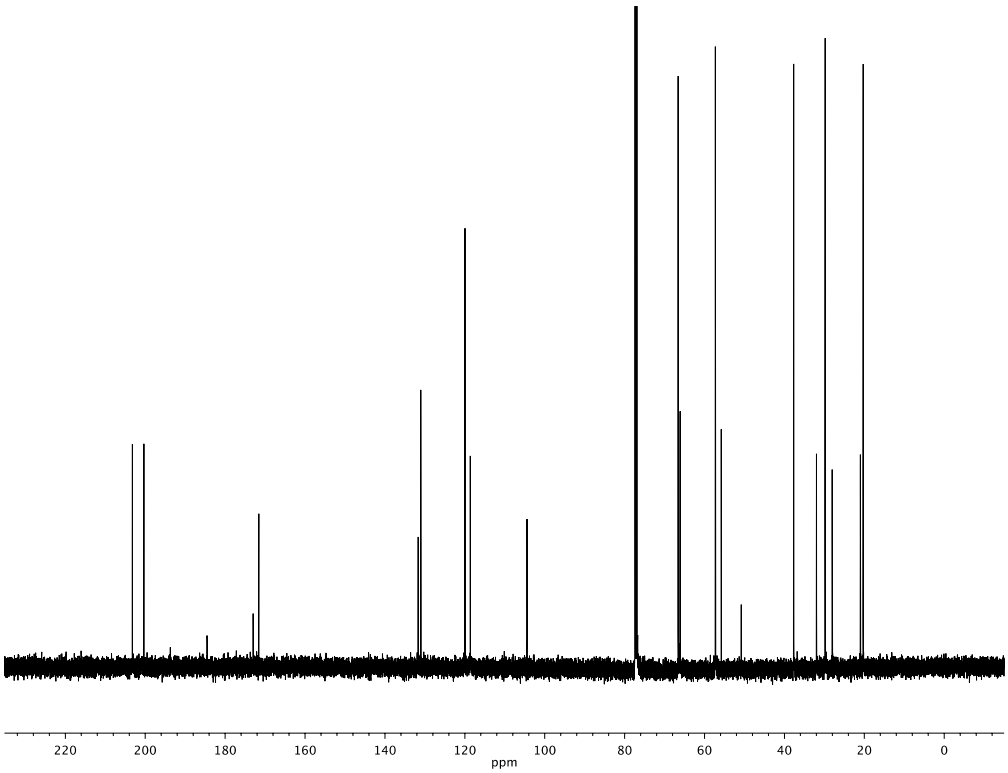


Figure A1.1.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **17**.

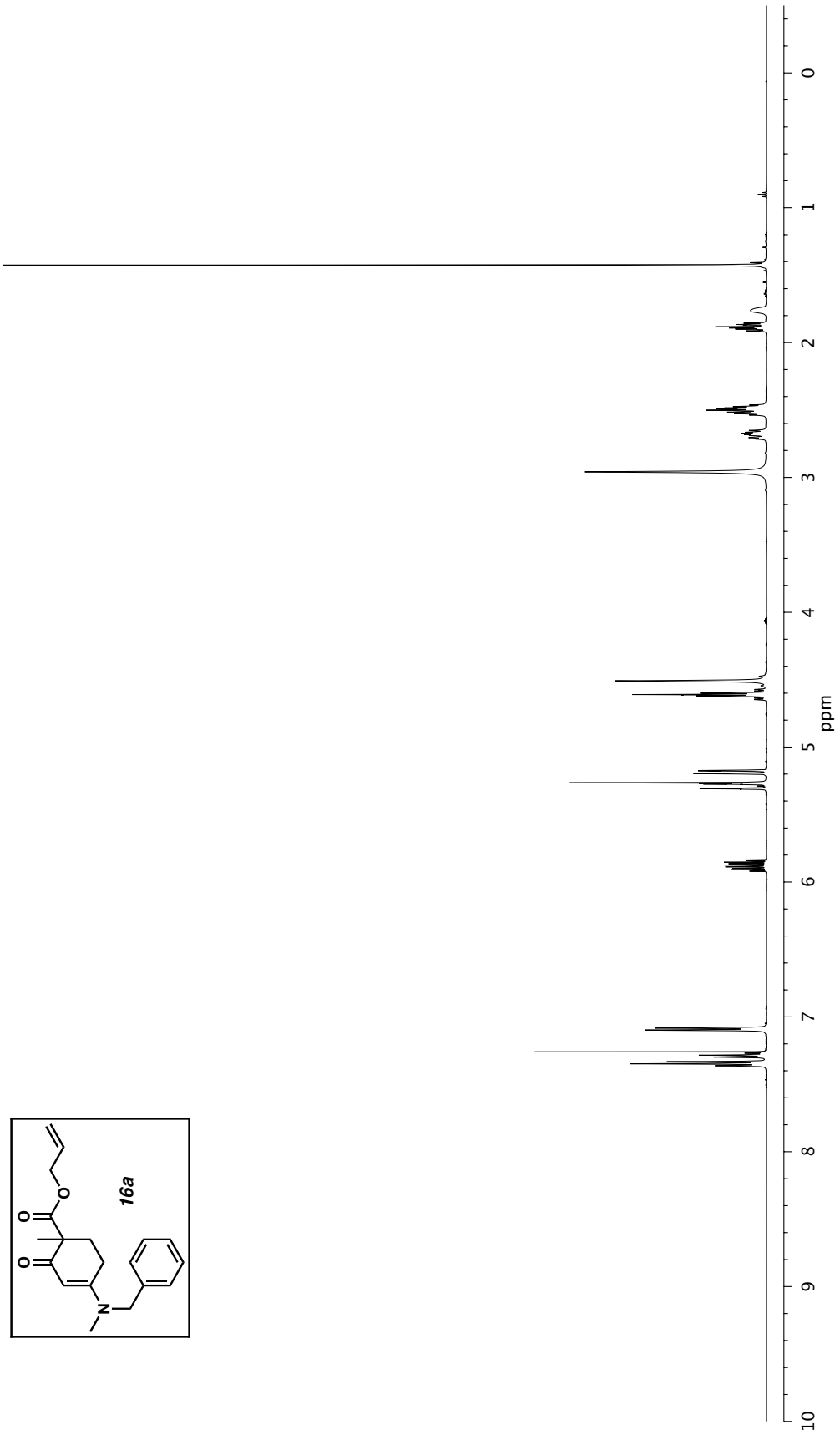


Figure A1.2.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **16a**.

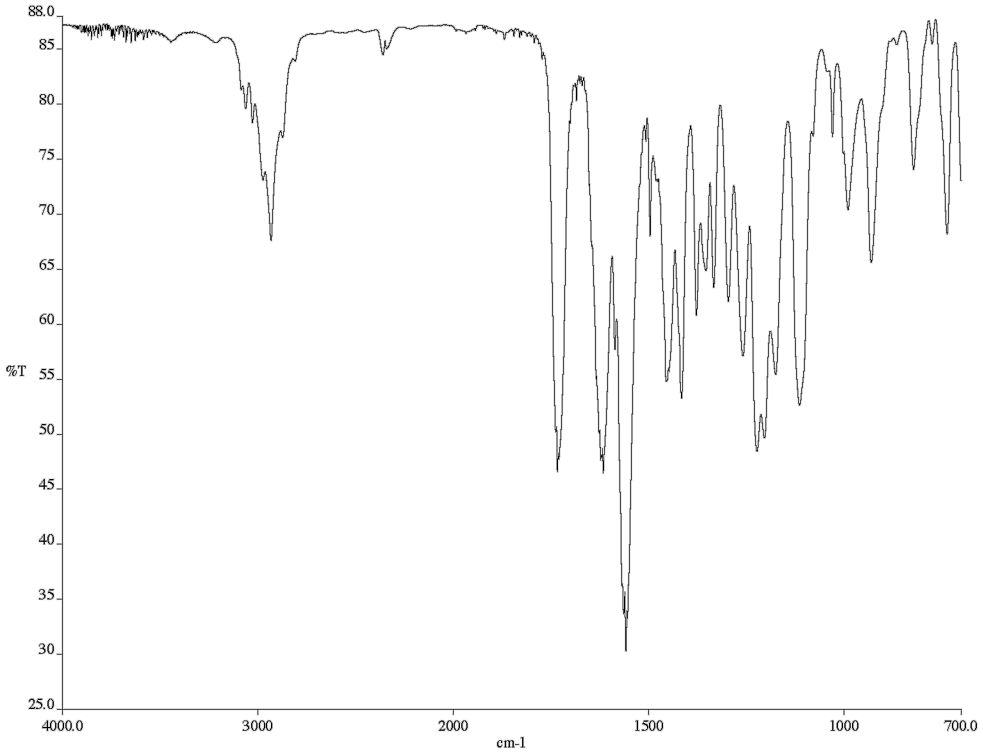


Figure A1.2.2. Infrared spectrum (thin film/NaCl) of compound **16a**.

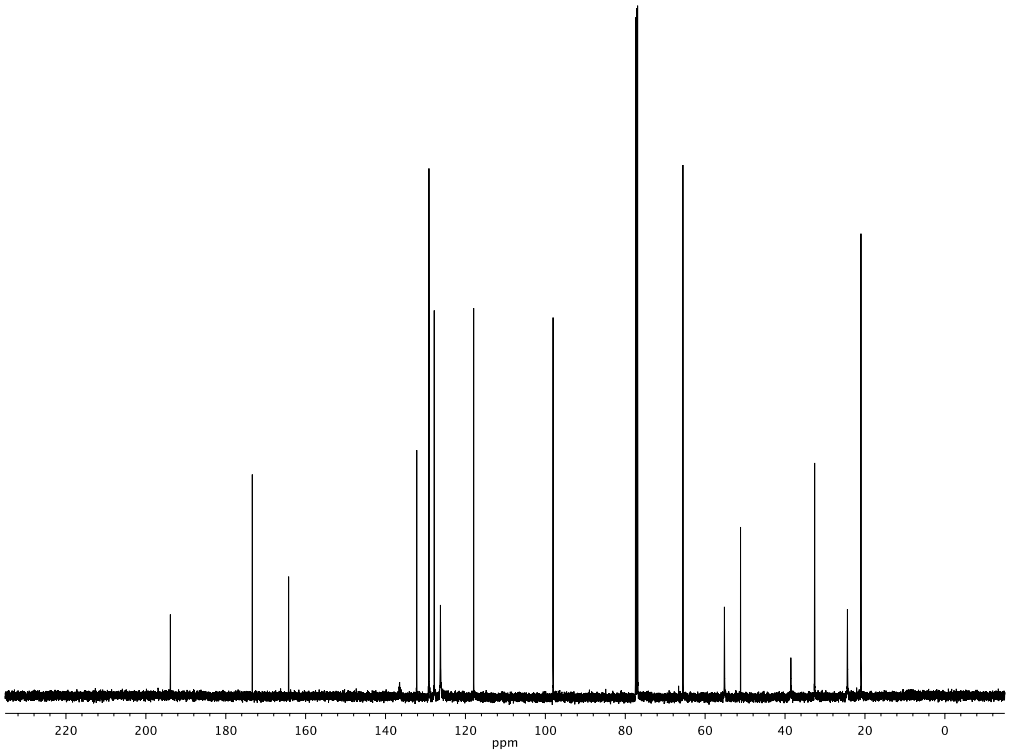


Figure A1.2.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **16a**.

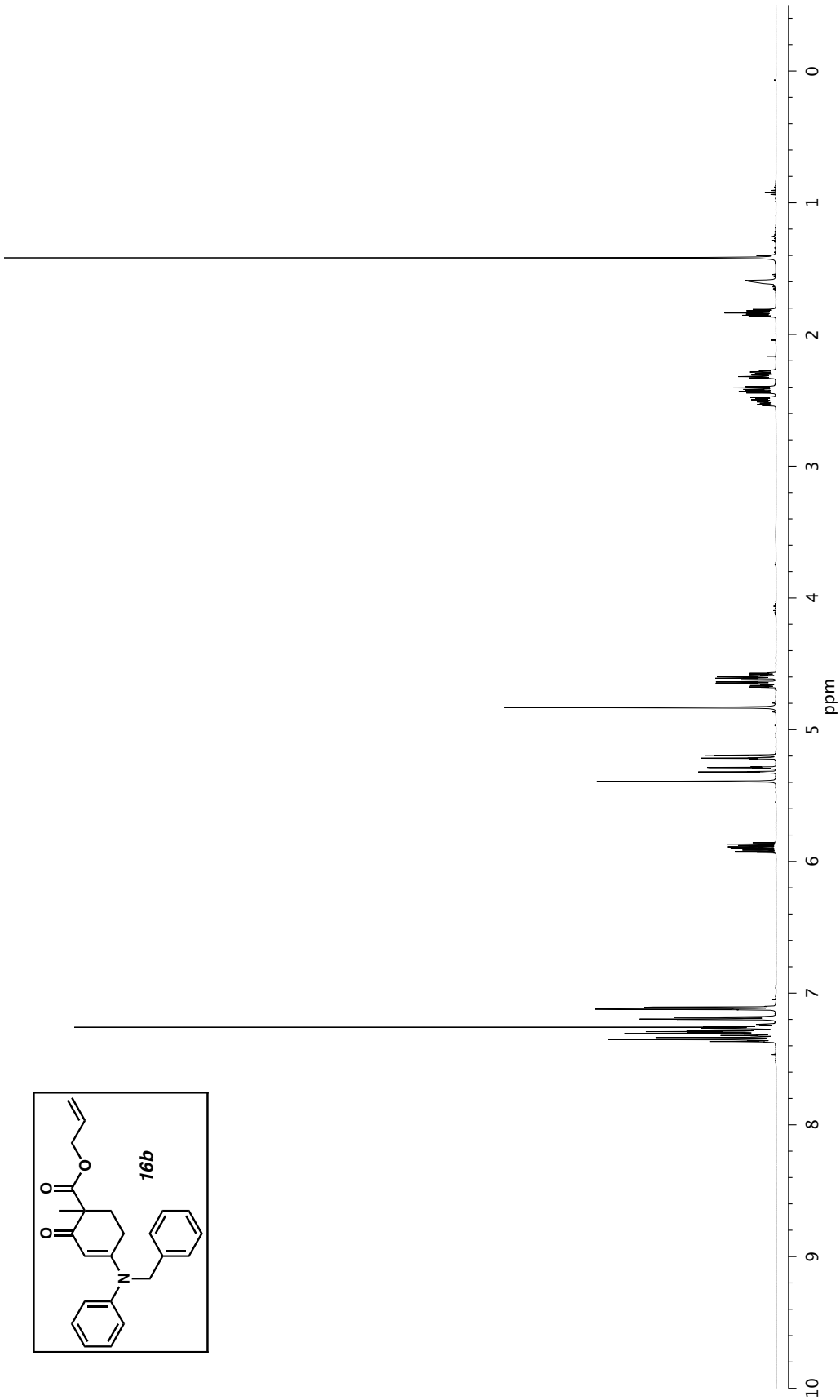


Figure A1.3.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **16b**.

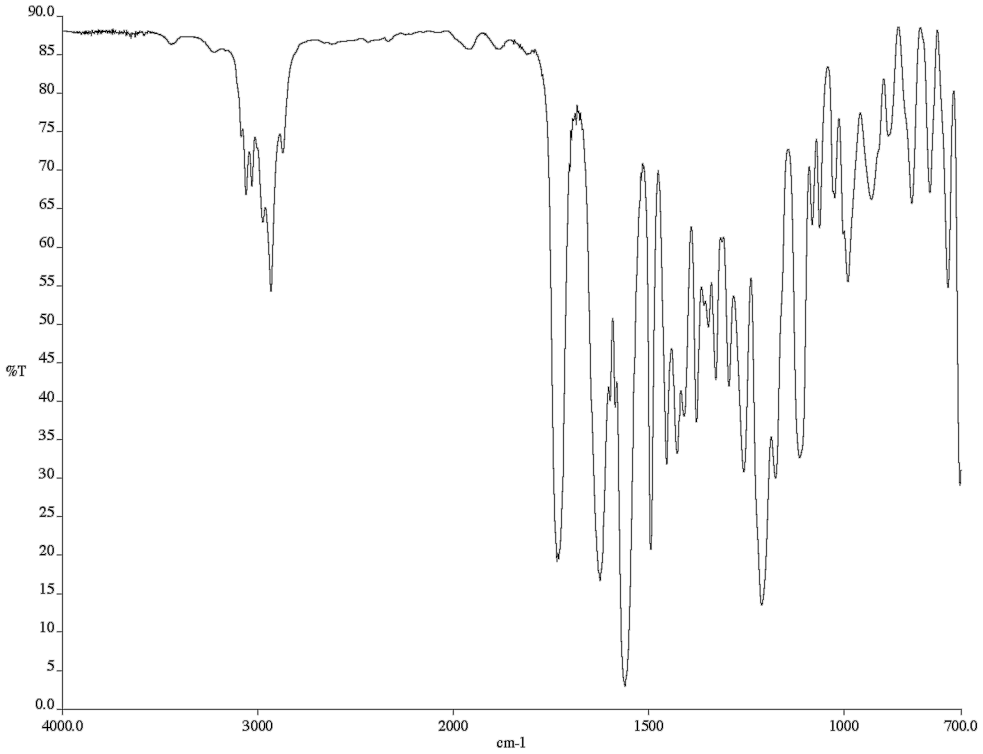


Figure A1.3.2. Infrared spectrum (thin film/NaCl) of compound **16b**.

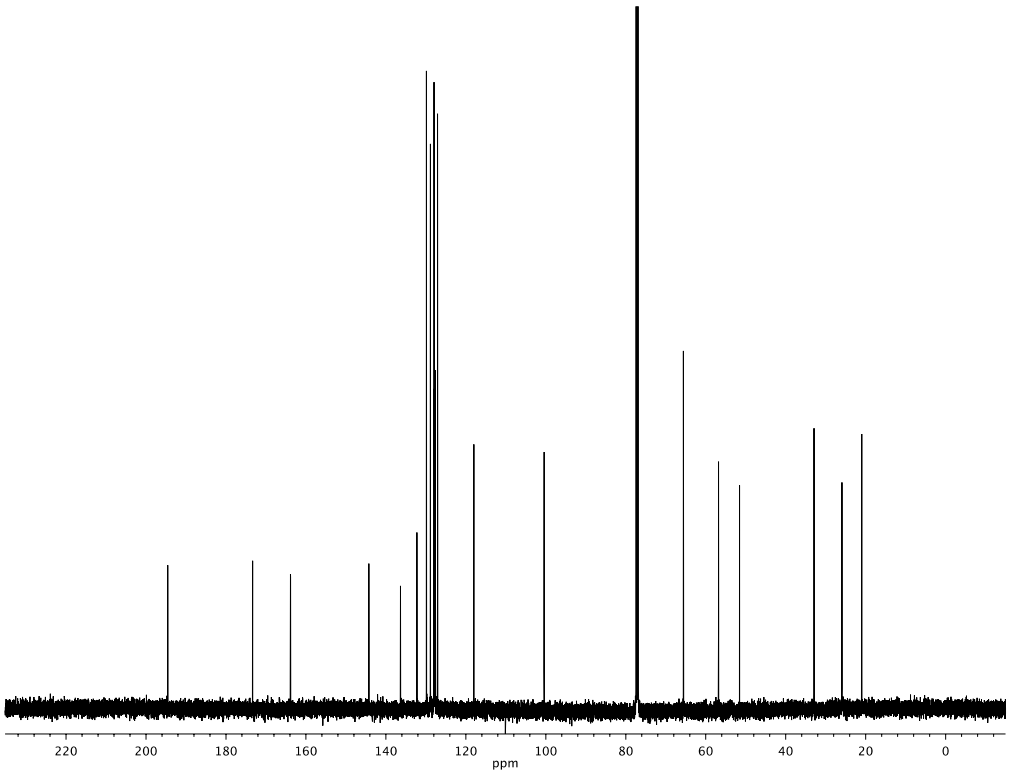


Figure A1.3.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **16b**.

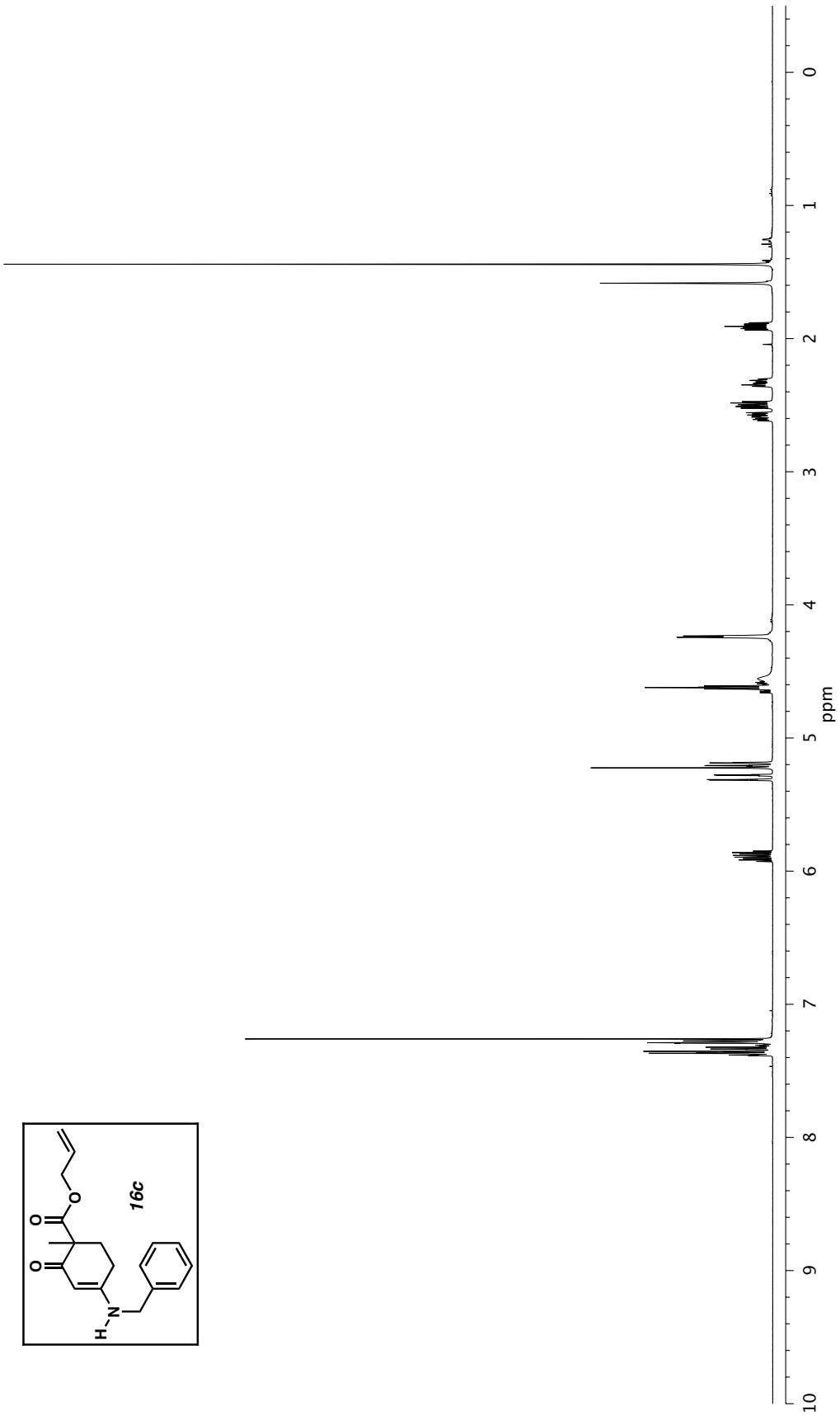


Figure A1.4.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **16c**.

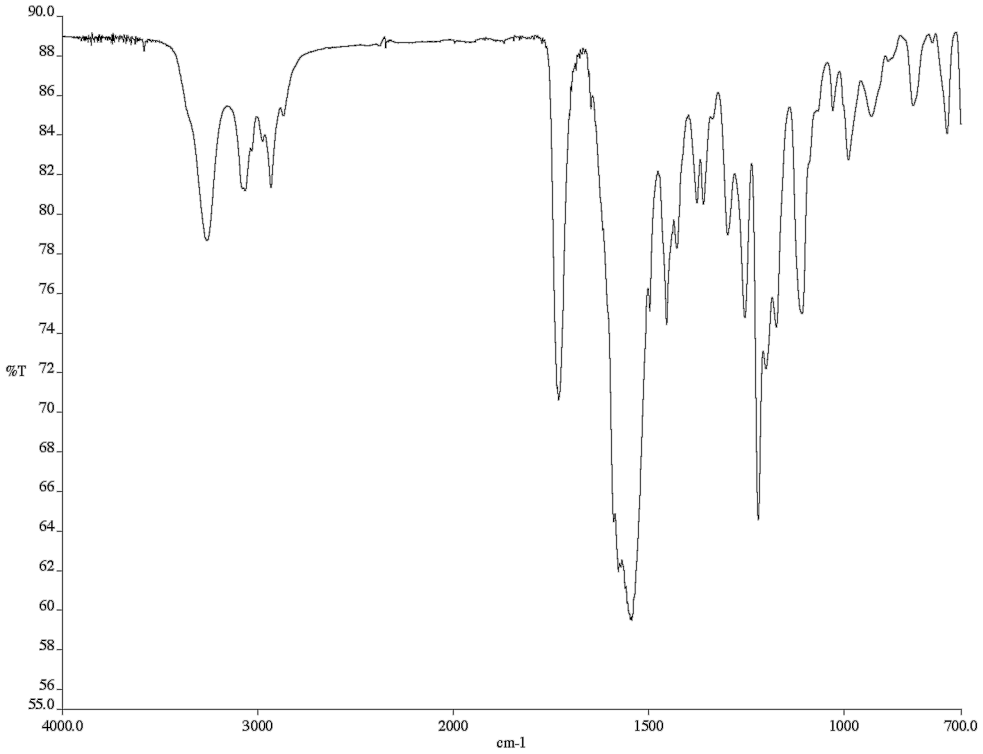


Figure A1.4.2. Infrared spectrum (thin film/NaCl) of compound **16c**.

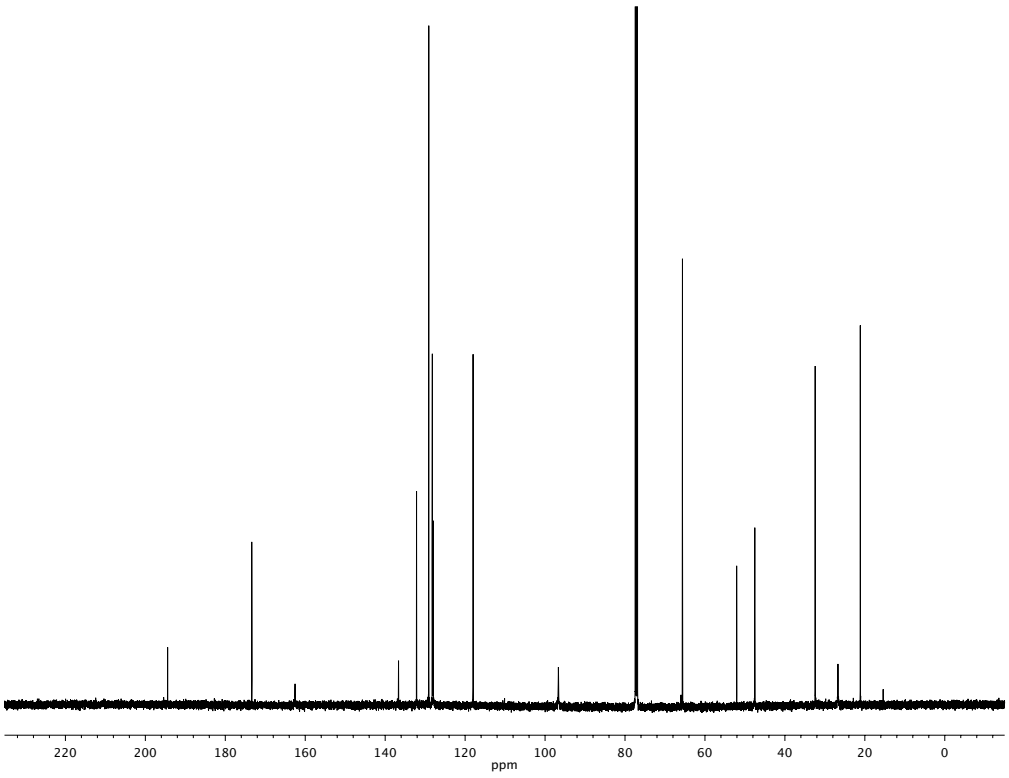


Figure A1.4.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **16c**.

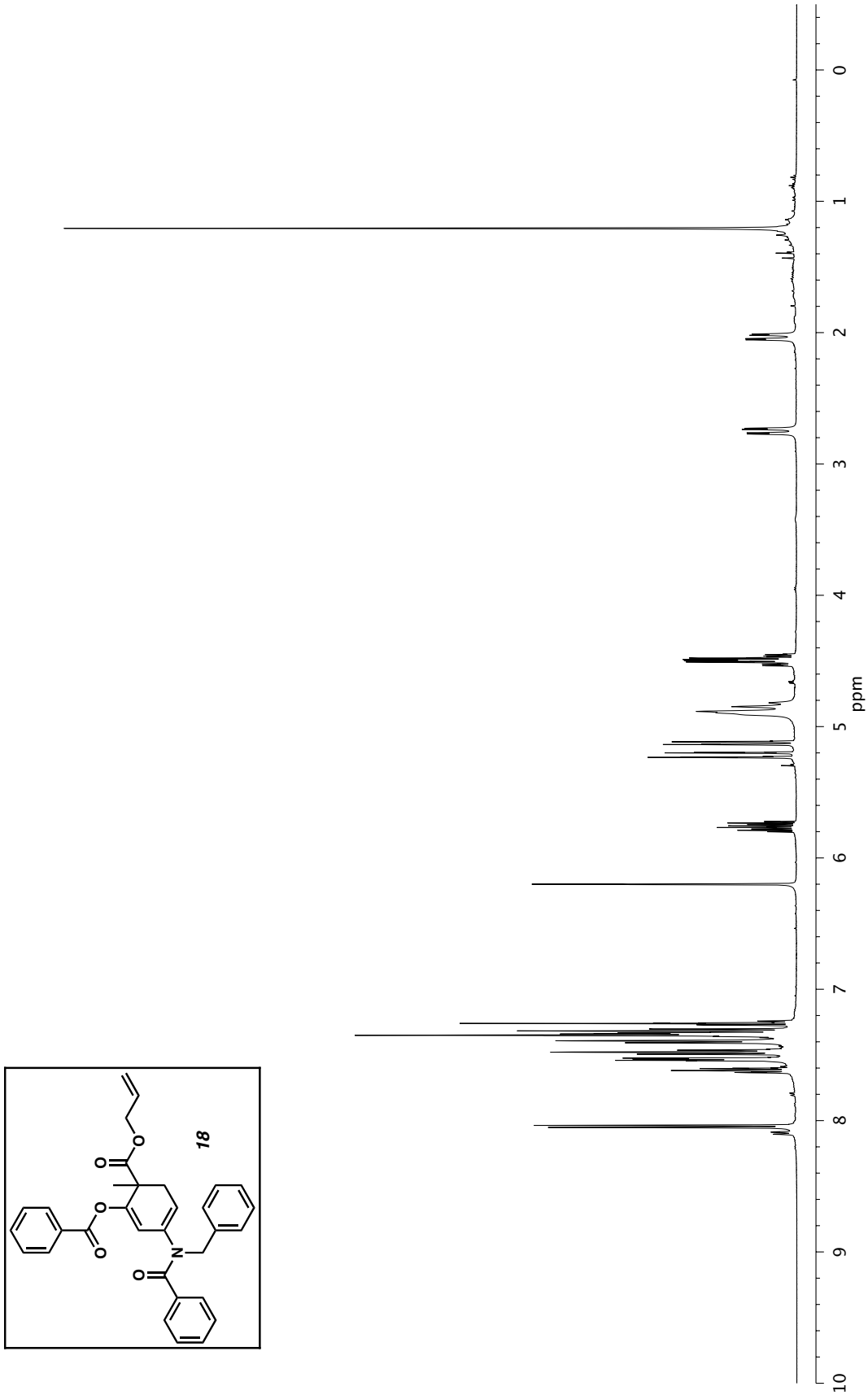


Figure A1.5.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **18**.

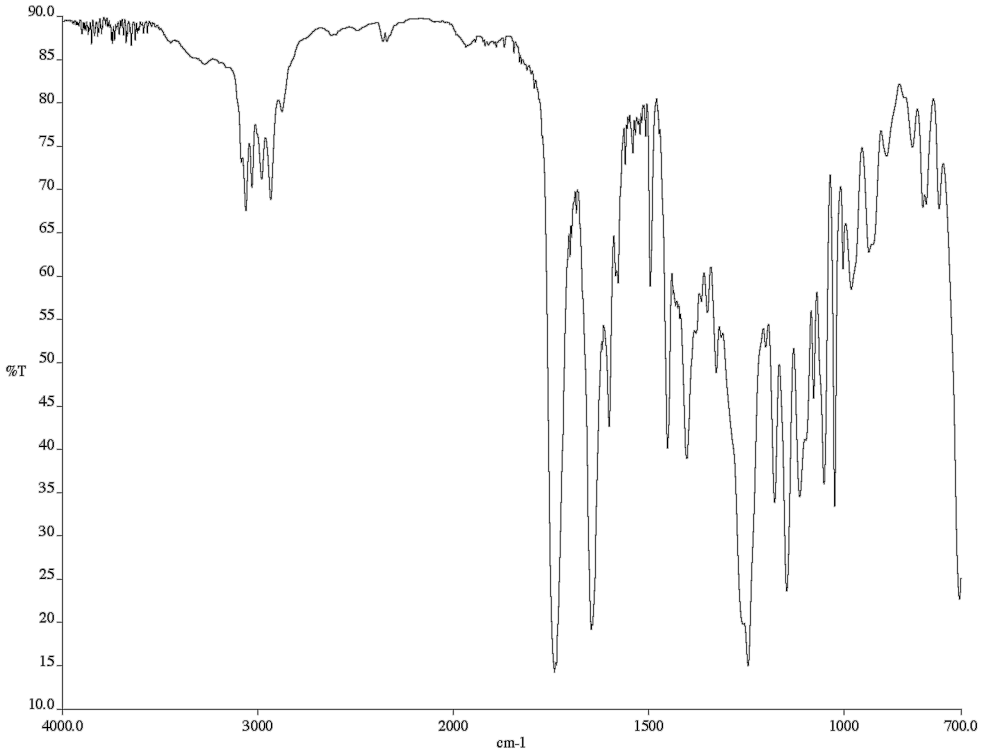


Figure A1.5.2. Infrared spectrum (thin film/NaCl) of compound **18**.

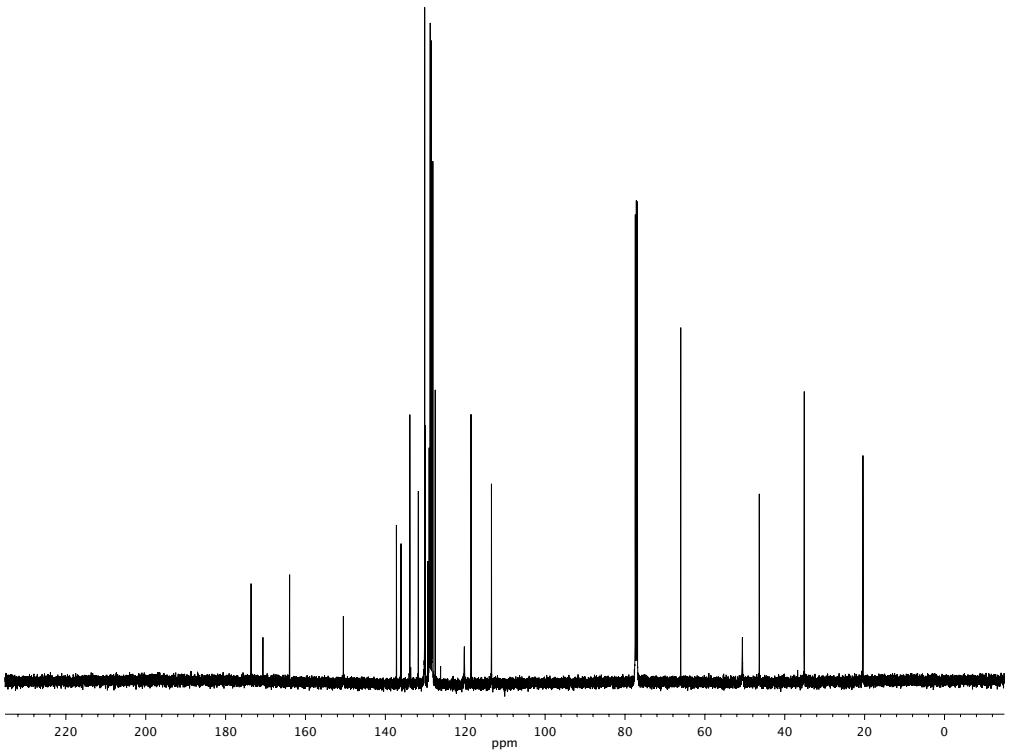


Figure A1.5.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **18**.

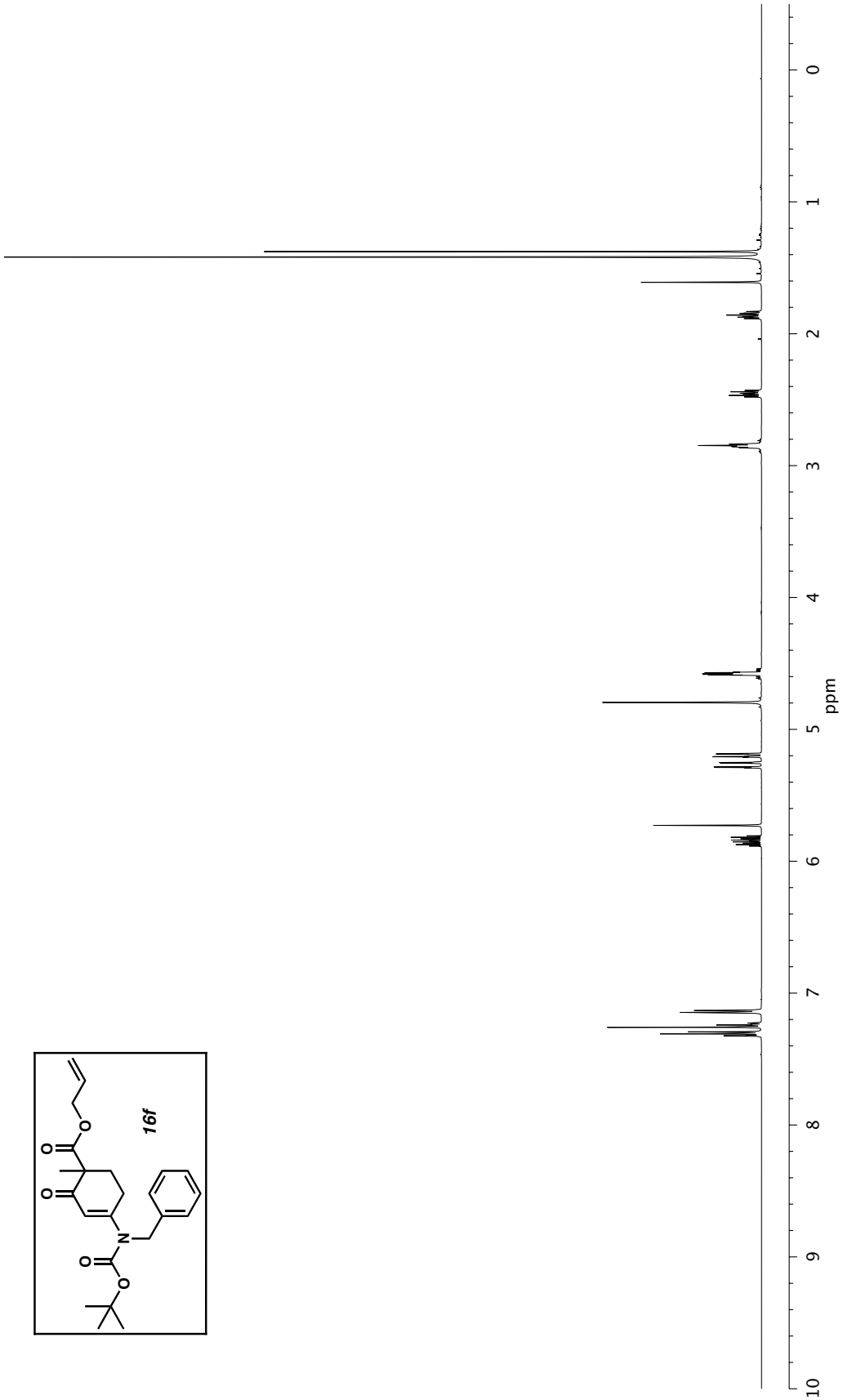


Figure A1.6.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **16f**.

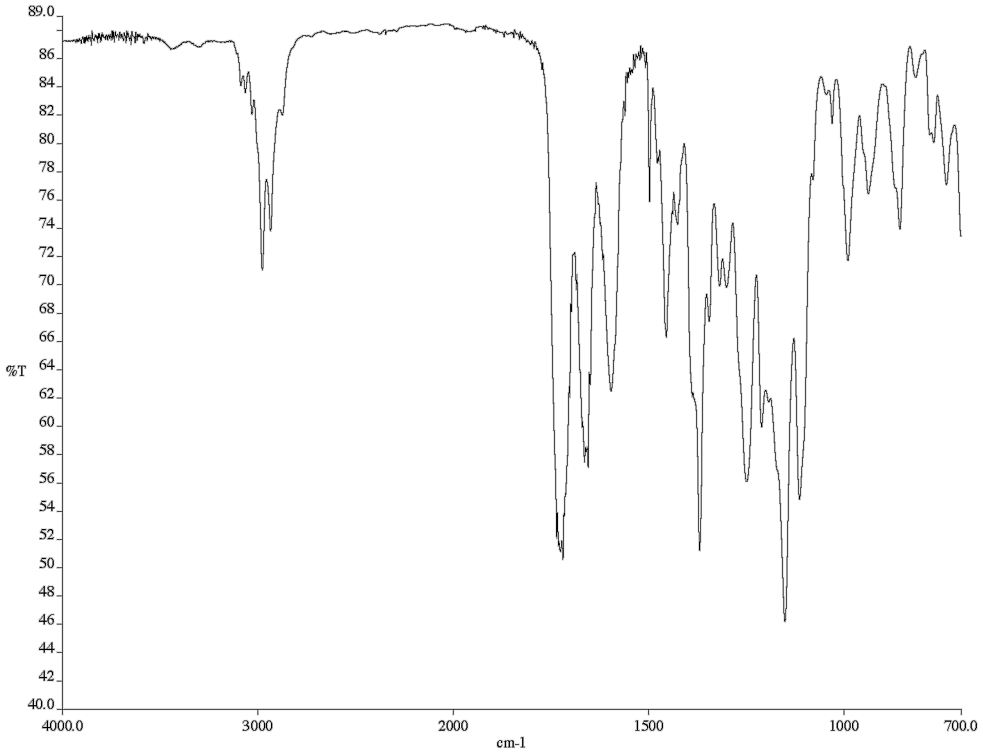


Figure A1.6.2. Infrared spectrum (thin film/NaCl) of compound **16f**.

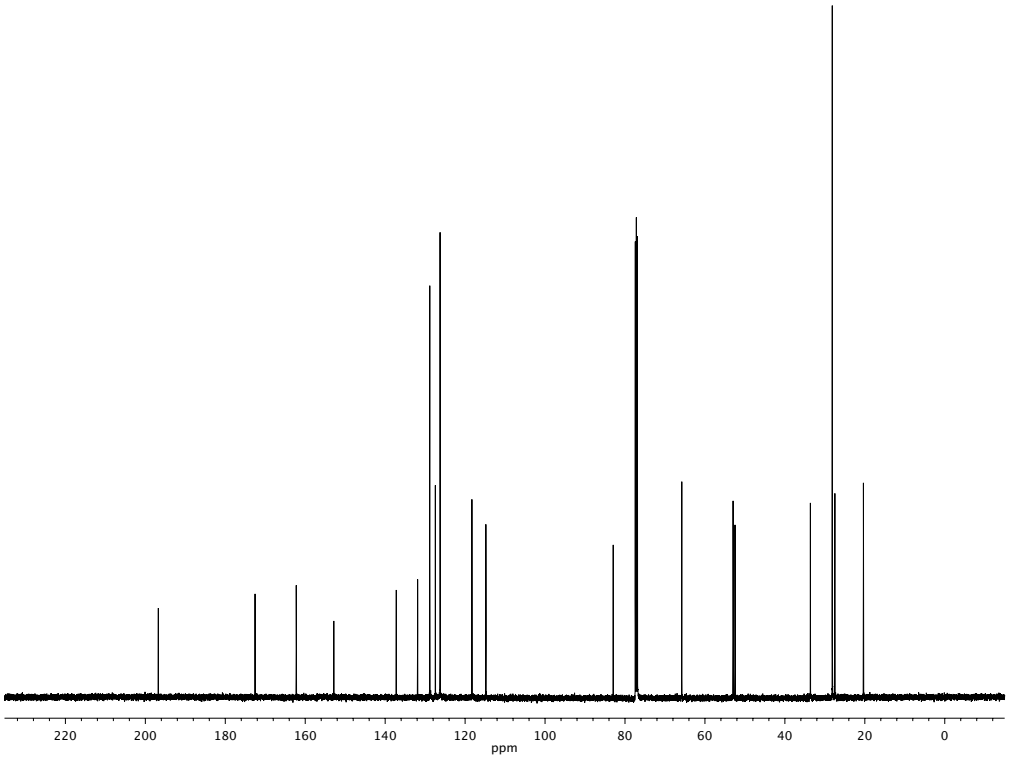


Figure A1.6.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **16f**.

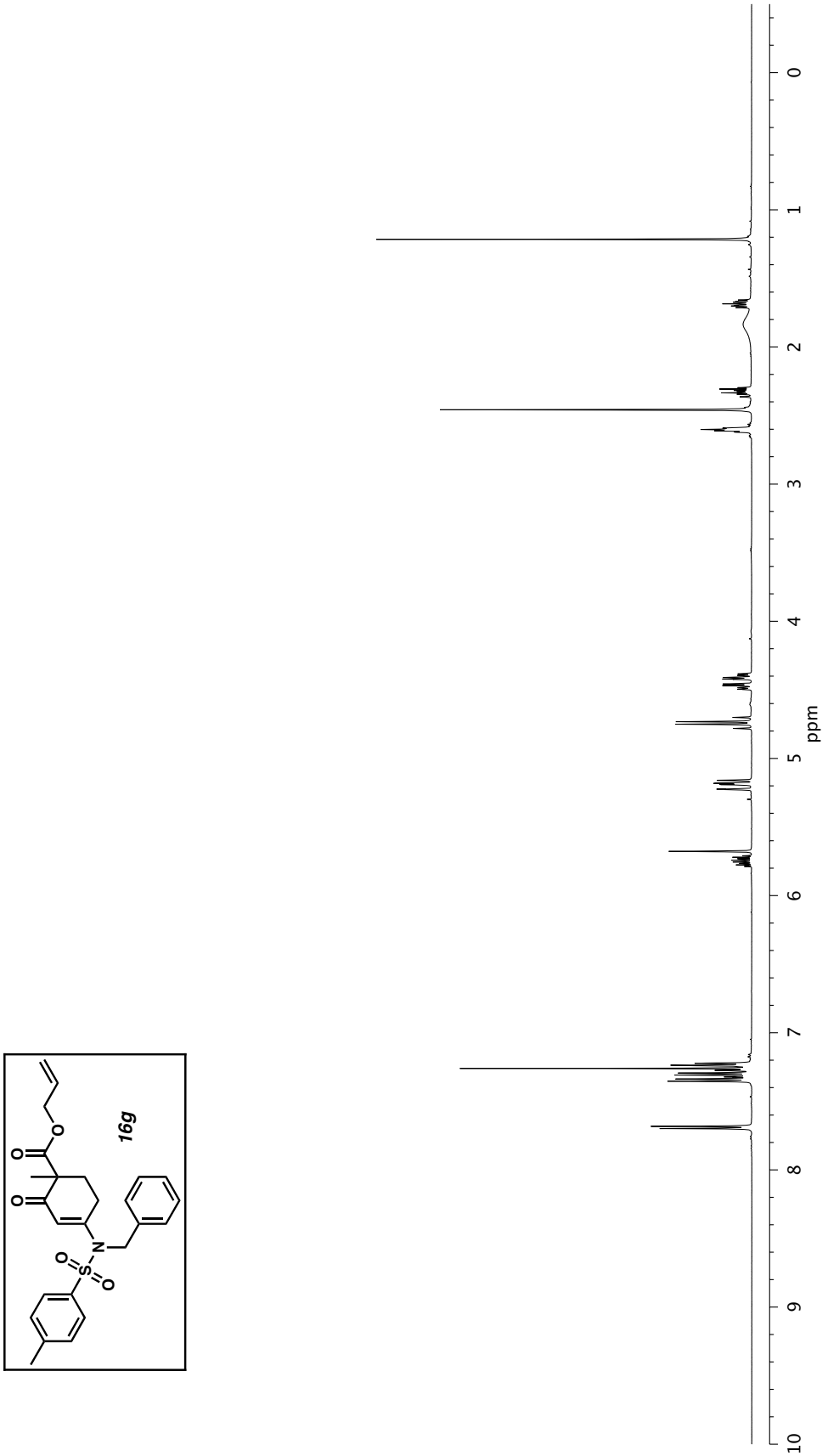


Figure A1.7.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **16g**.

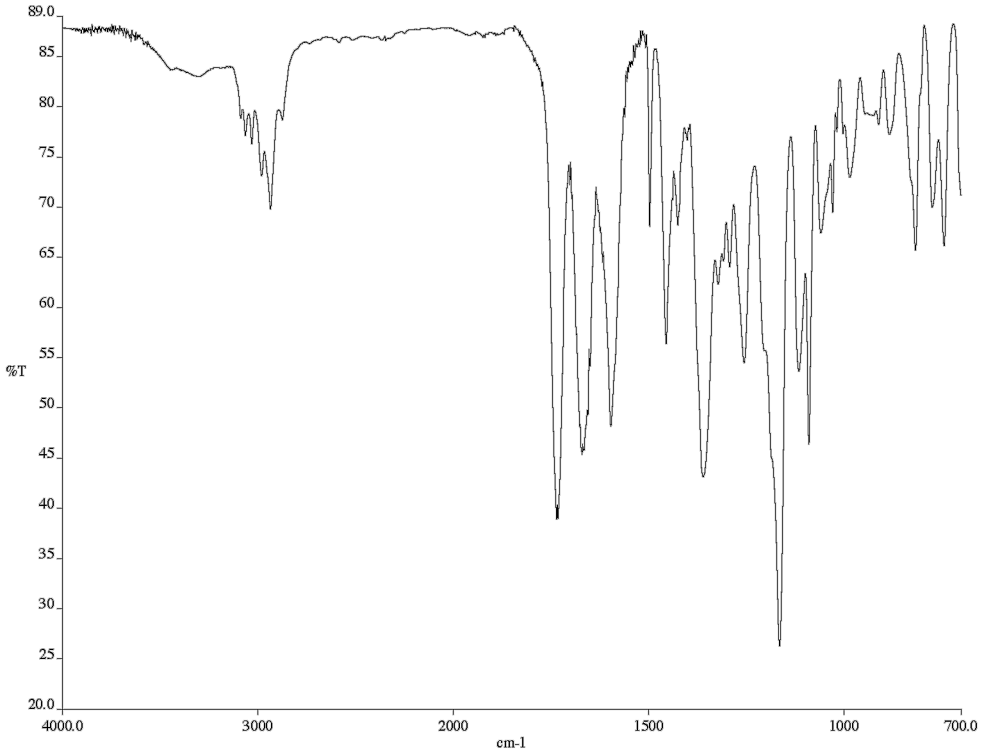


Figure A1.7.2. Infrared spectrum (thin film/NaCl) of compound **16g**.

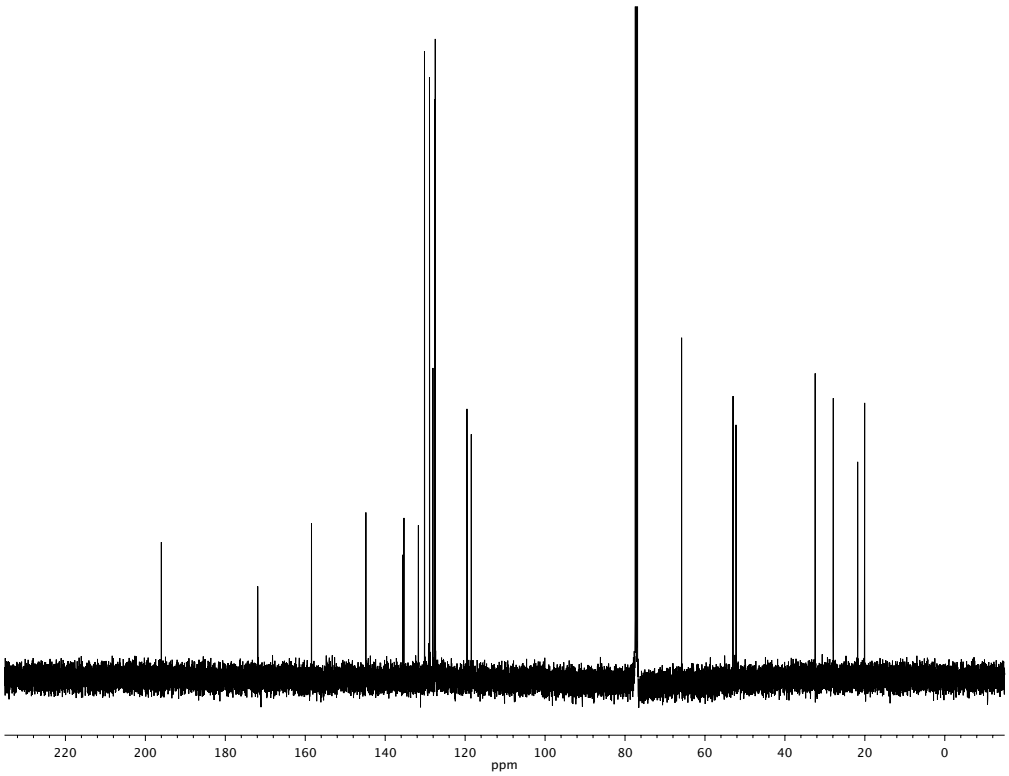


Figure A1.7.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **16g**.

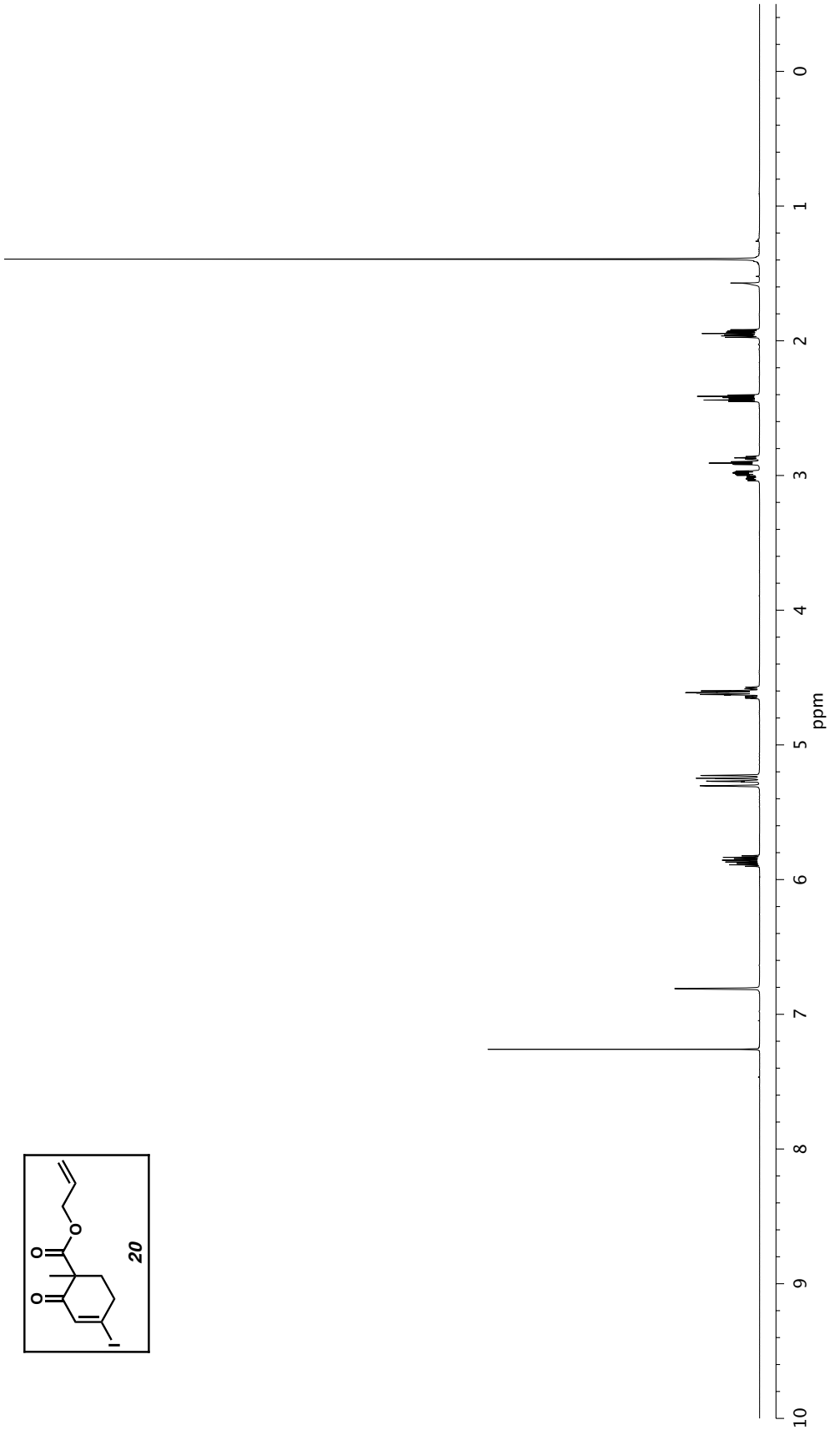


Figure A1.8.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **20**.

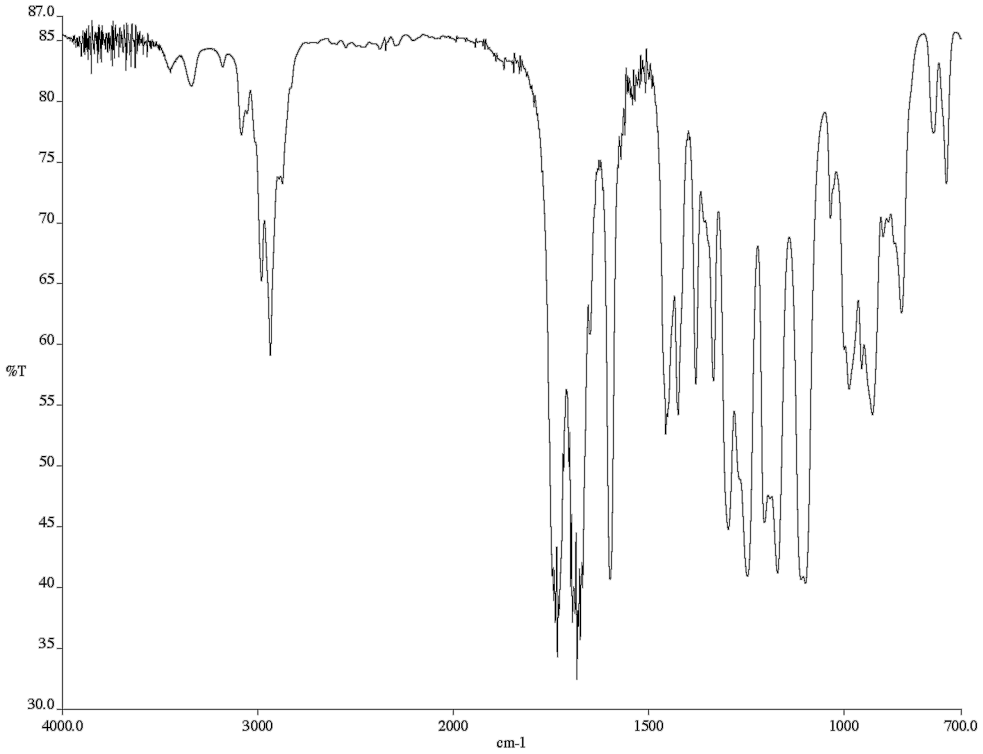


Figure A1.8.2. Infrared spectrum (thin film/NaCl) of compound **20**.

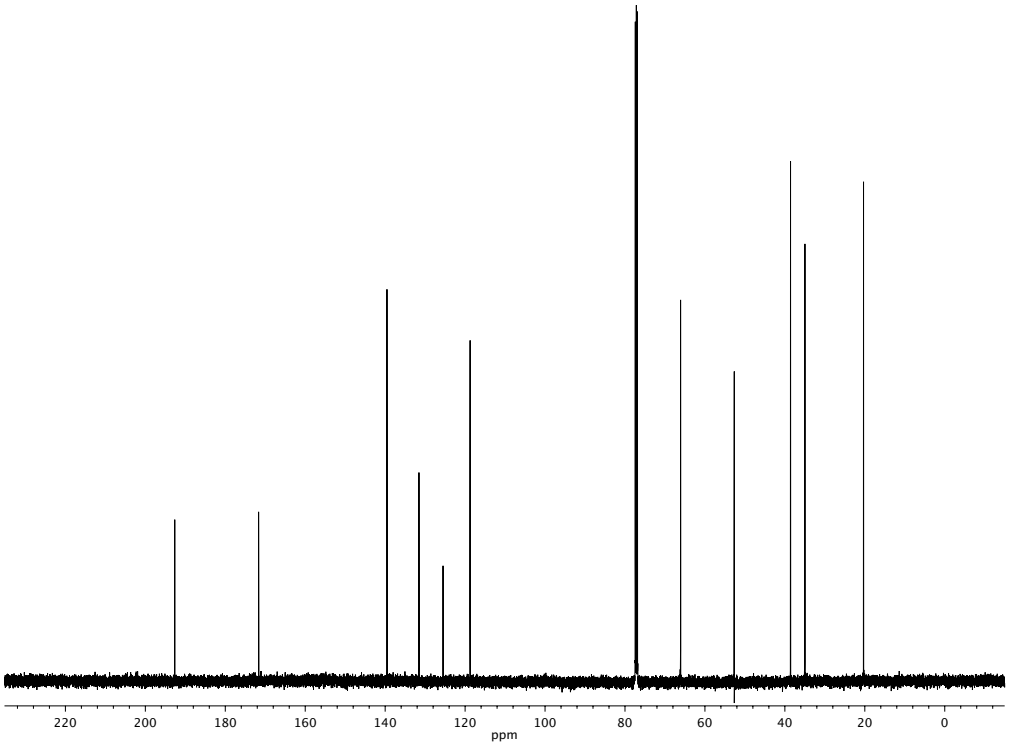


Figure A1.8.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **20**.

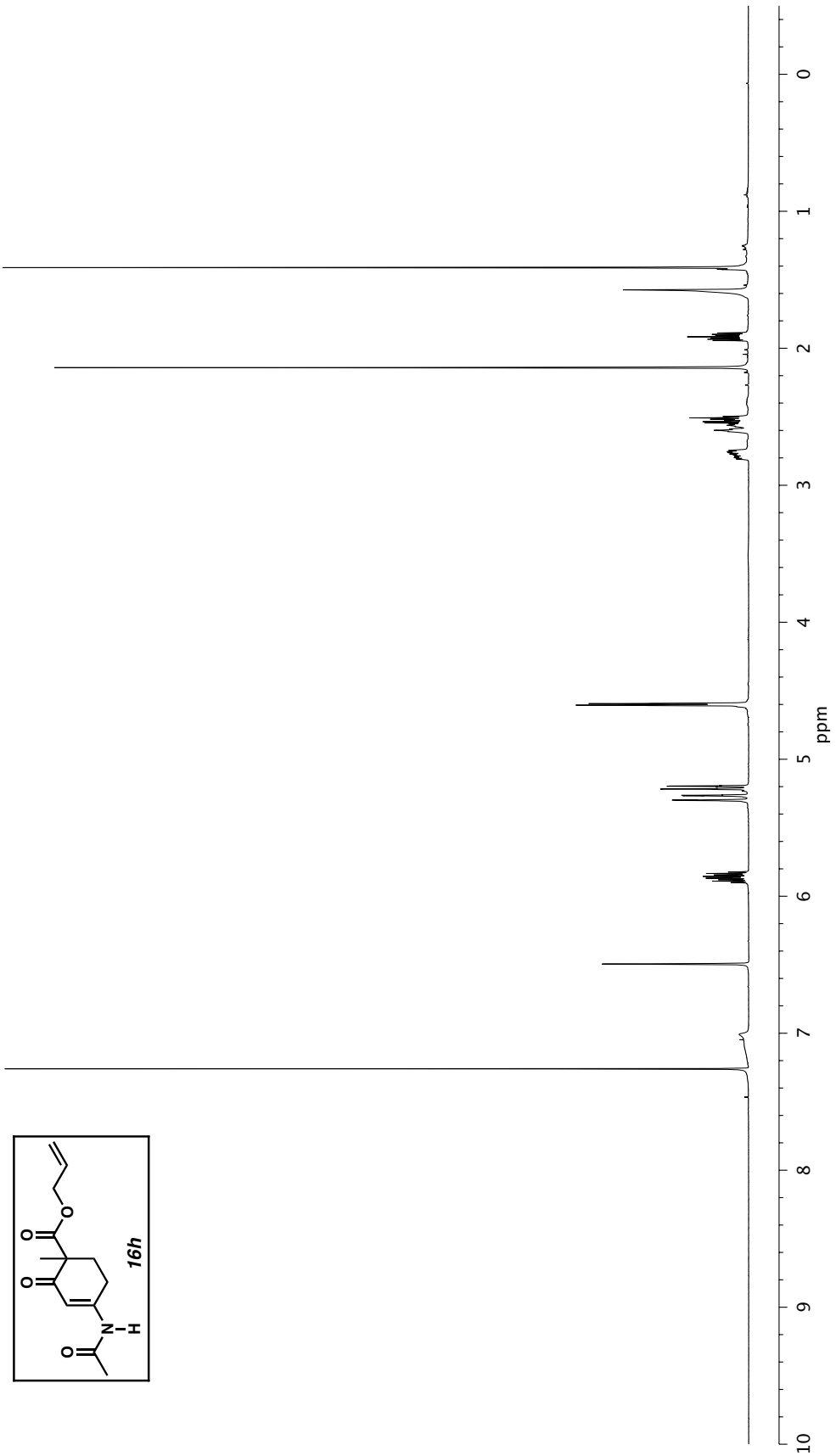


Figure A1.9.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **16h**.

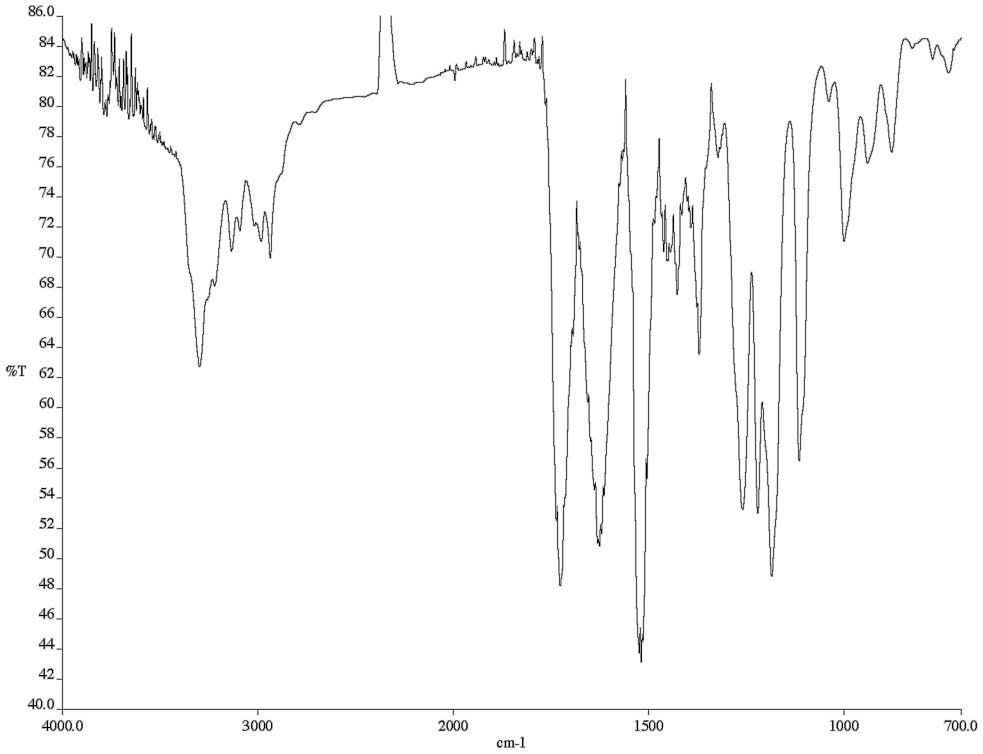


Figure A1.9.2. Infrared spectrum (thin film/NaCl) of compound **16h**.

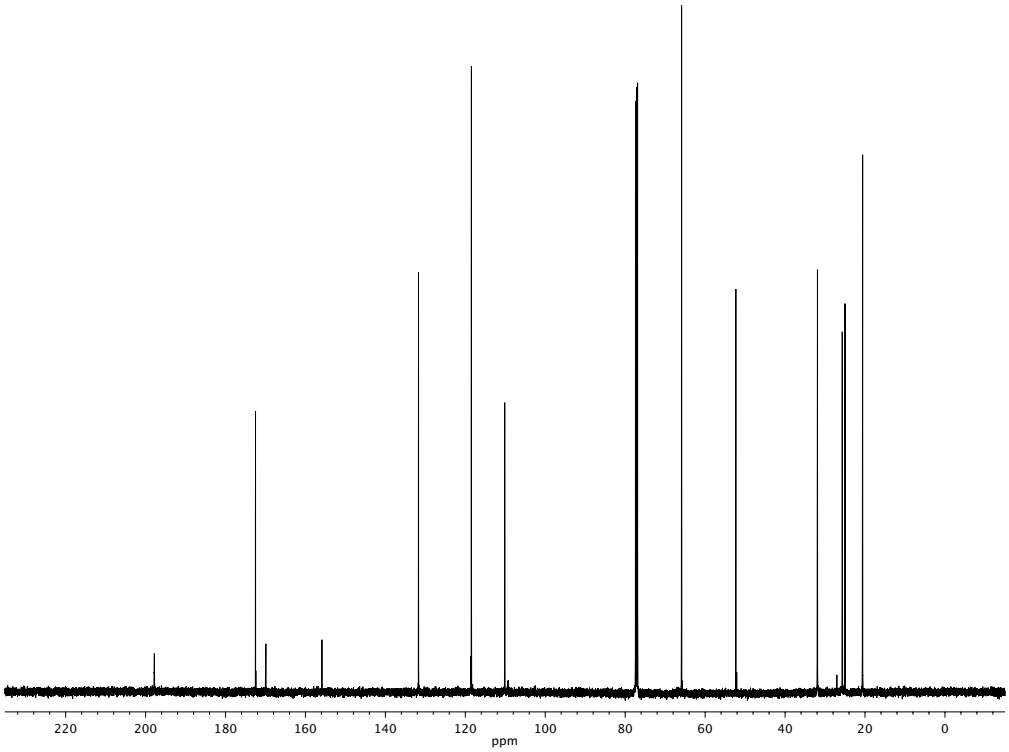


Figure A1.9.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **16h**.

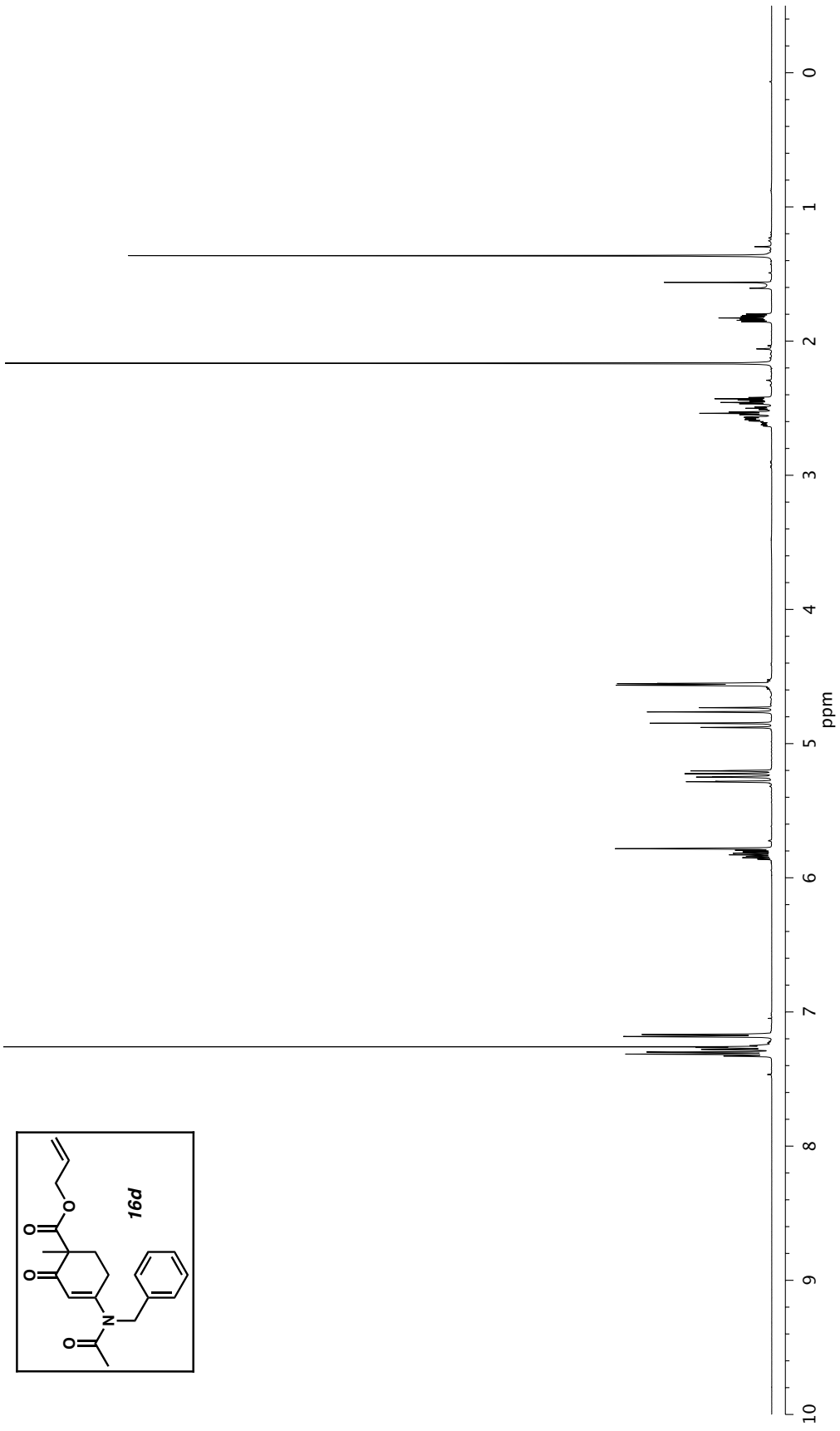


Figure A1.10.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **16d**.

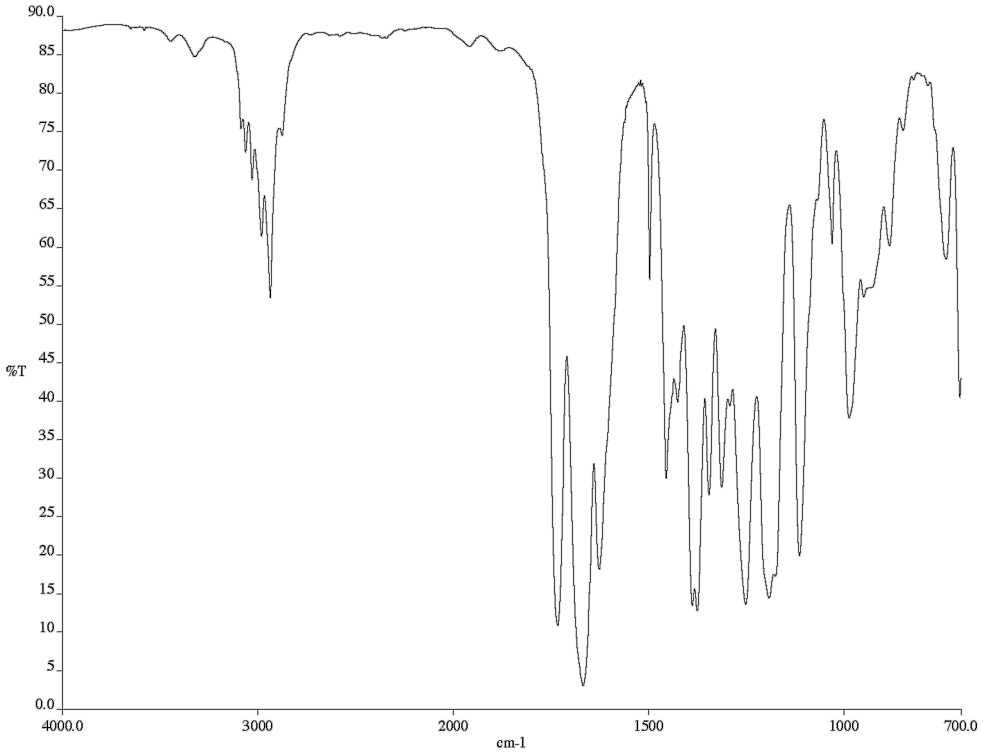


Figure A1.10.2. Infrared spectrum (thin film/NaCl) of compound **16d**.

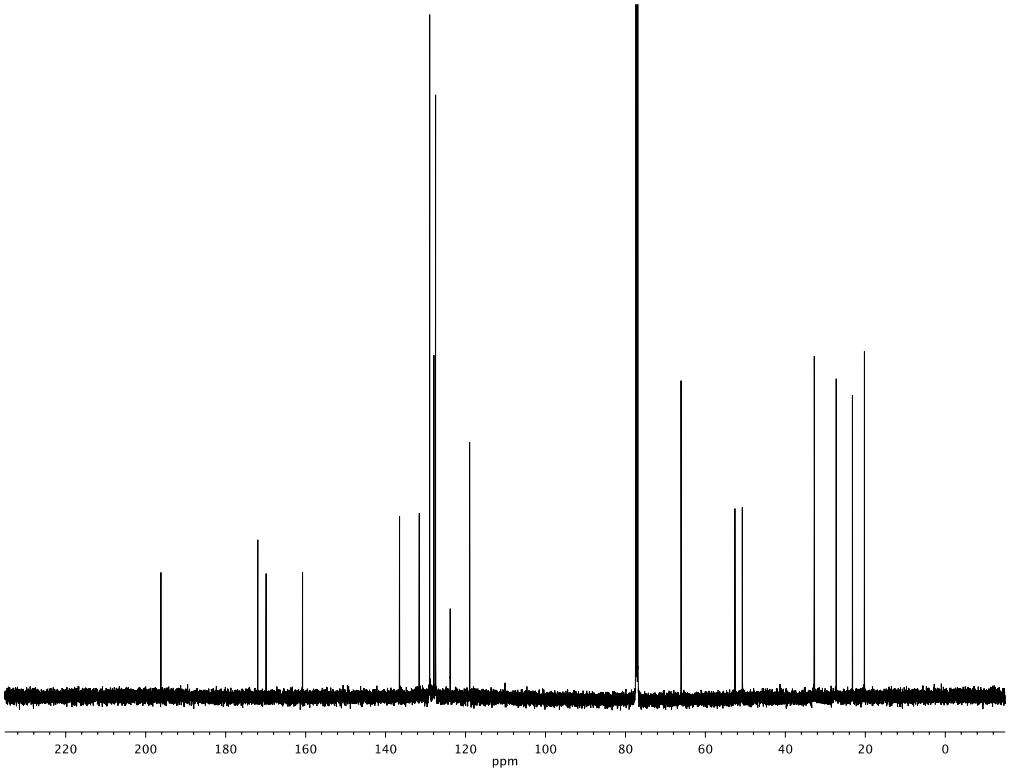


Figure A1.10.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **16d**.

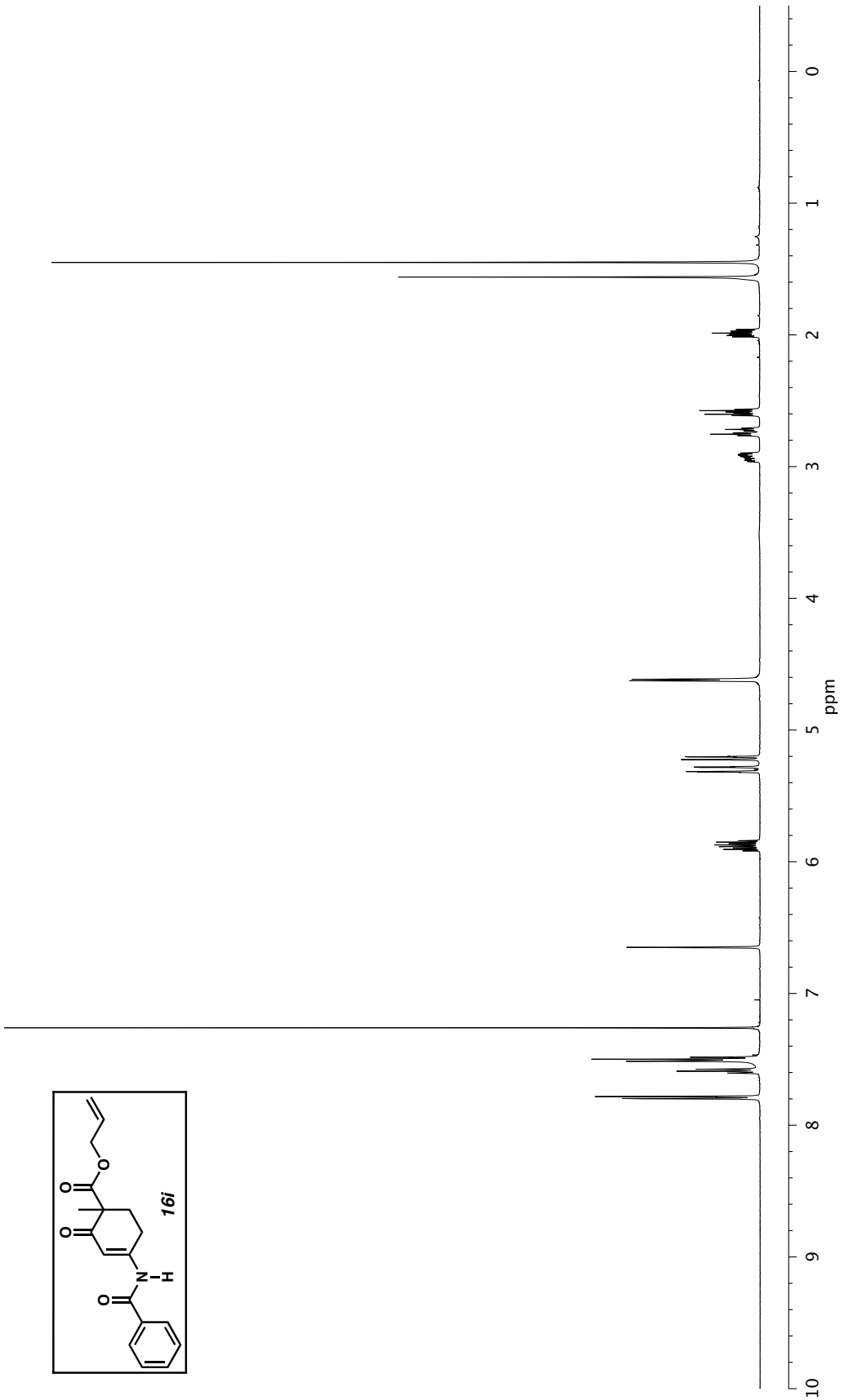


Figure A1.11.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **16i**.

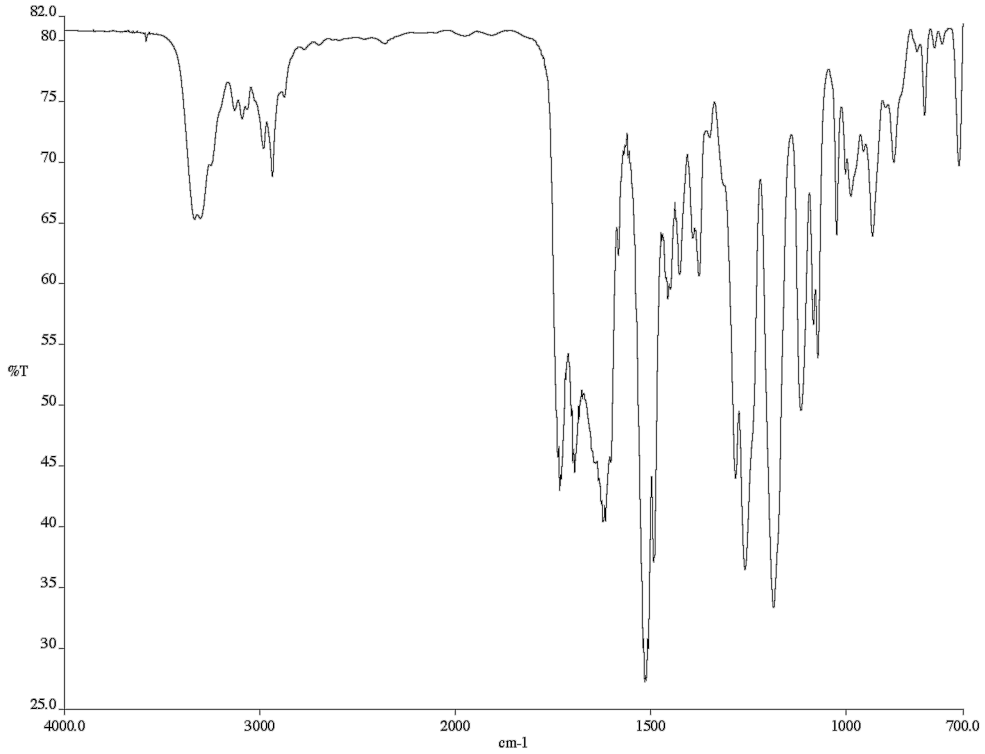


Figure A1.11.2. Infrared spectrum (thin film/NaCl) of compound **16i**.

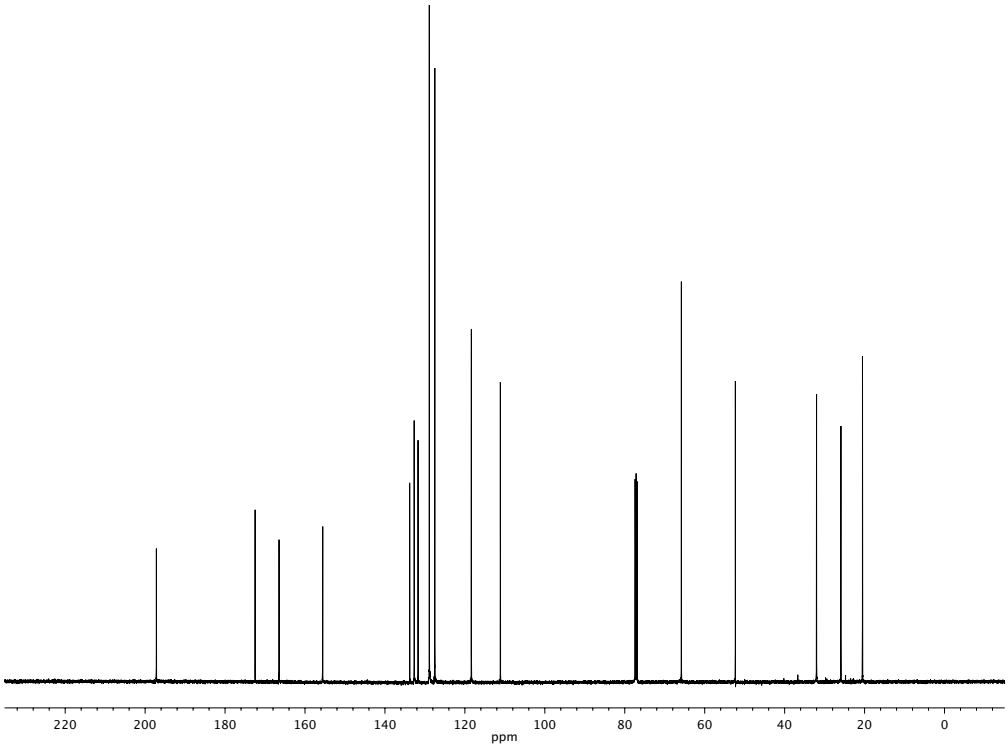


Figure A1.11.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **16i**.

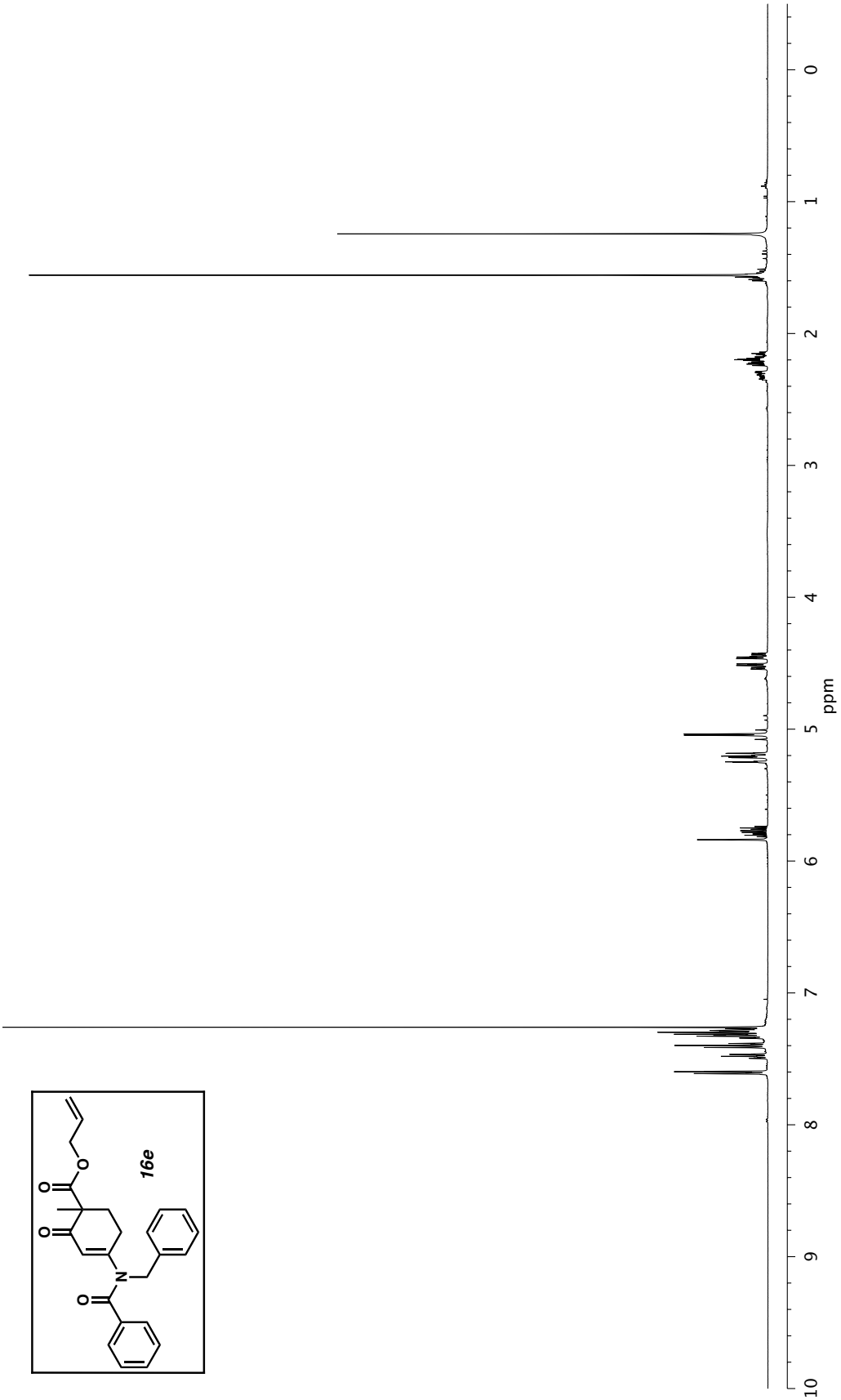


Figure A1.12.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **16e**.

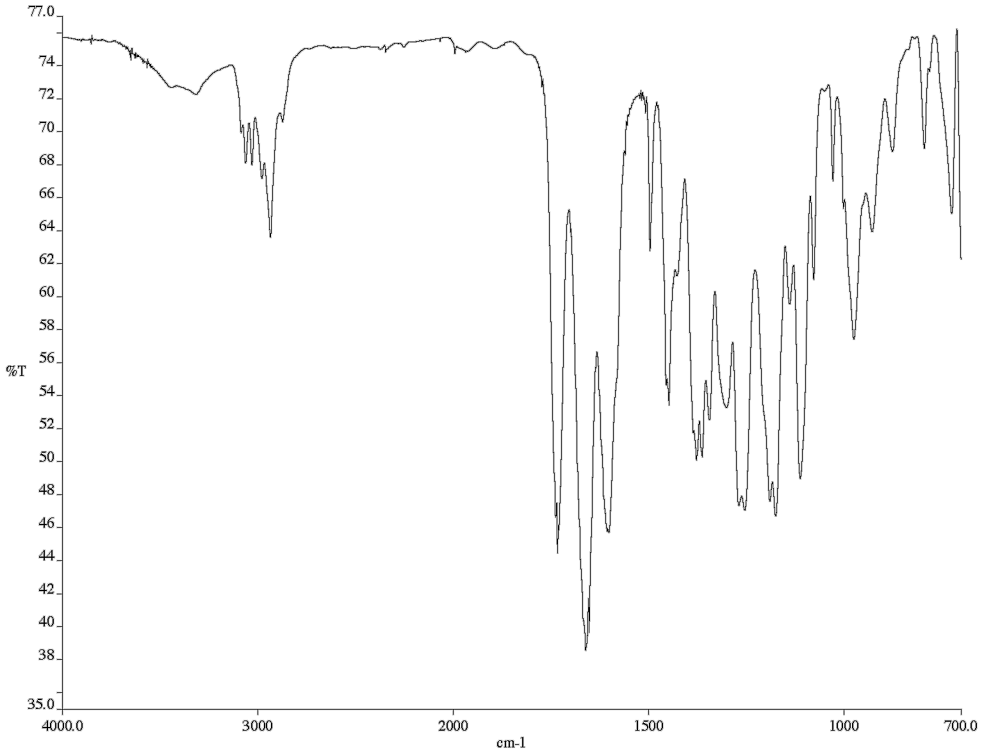


Figure A1.12.2. Infrared spectrum (thin film/NaCl) of compound **16e**.

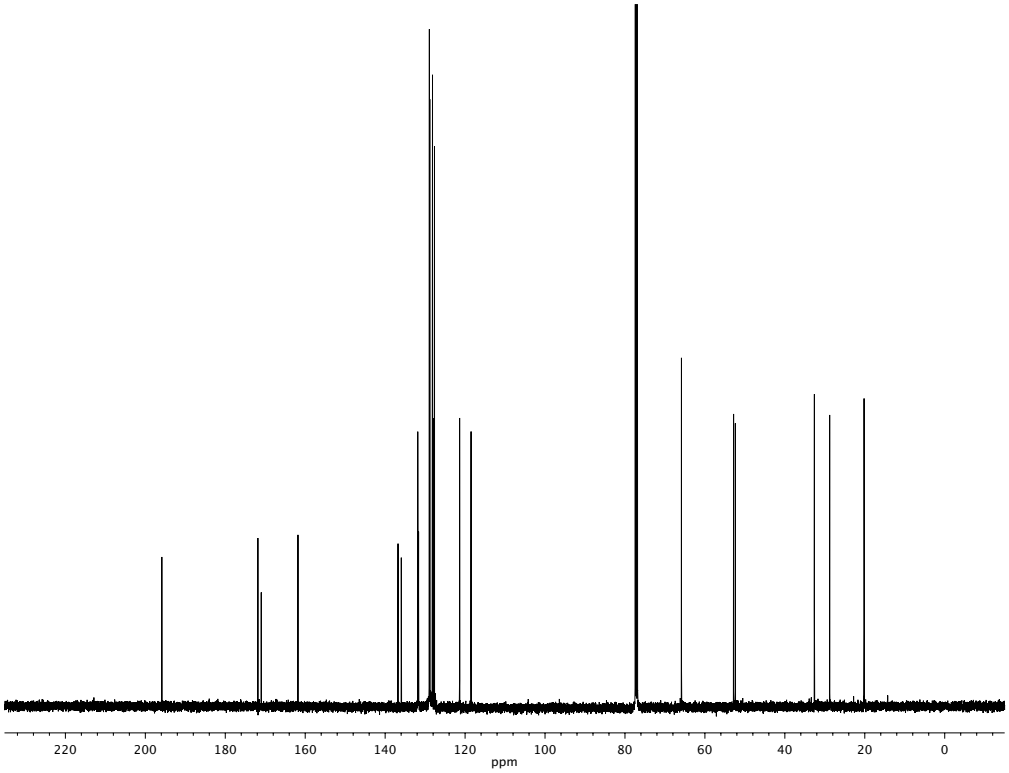


Figure A1.12.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **16e**.

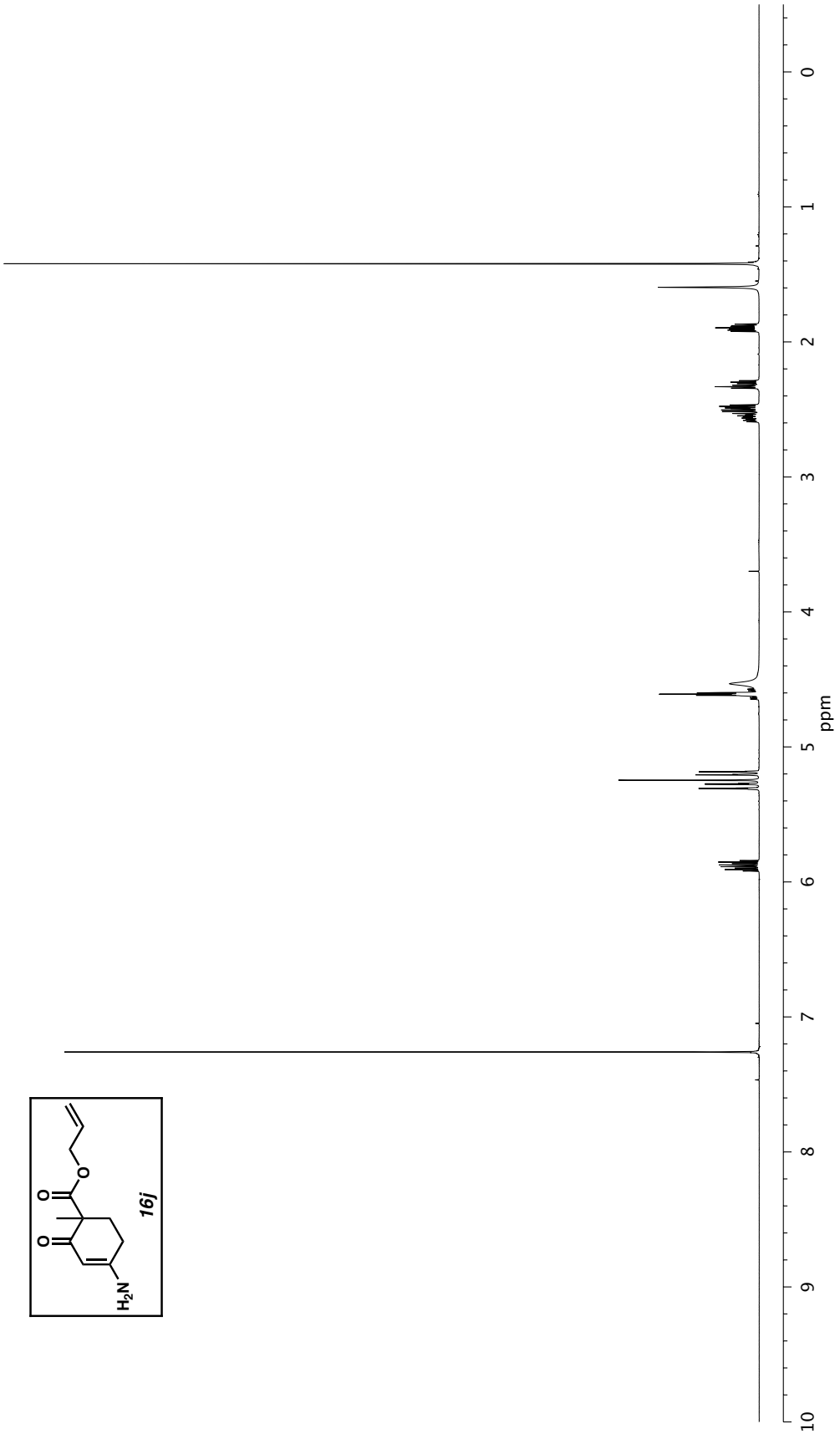


Figure A1.13.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **16j**.

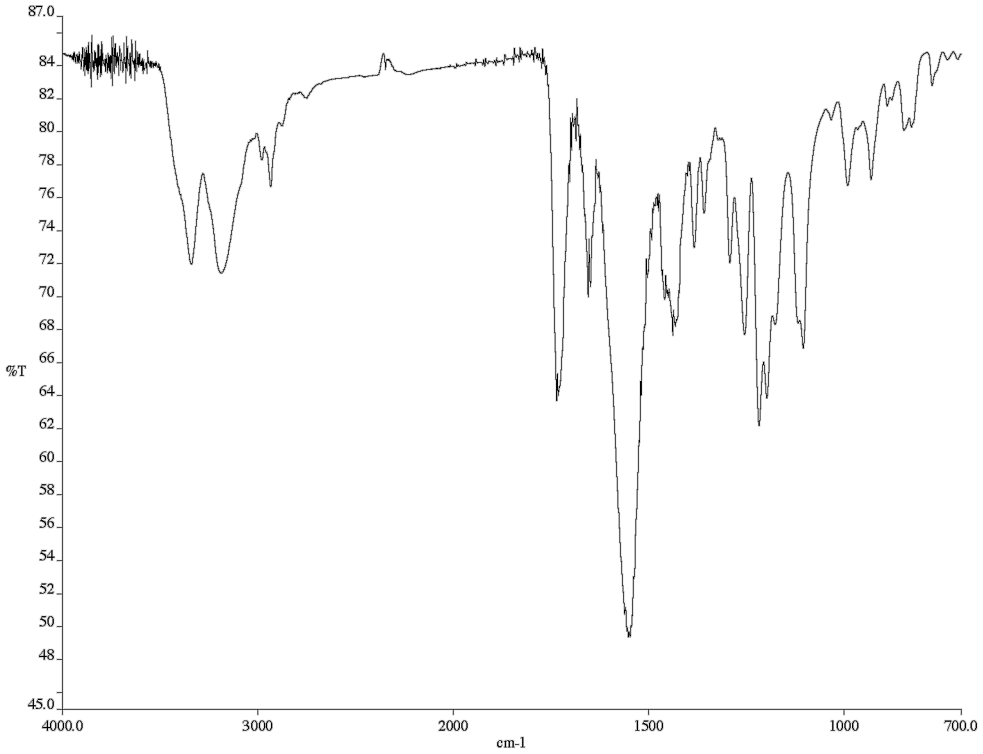


Figure A1.13.2. Infrared spectrum (thin film/NaCl) of compound **16j**.

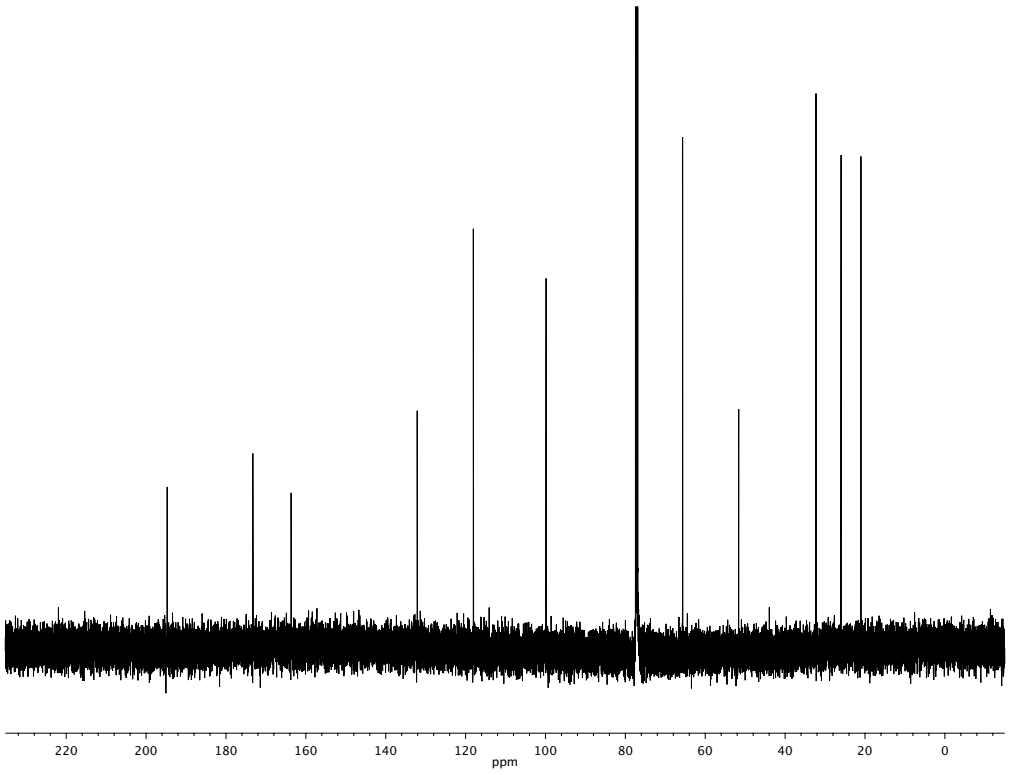


Figure A1.13.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **16j**.

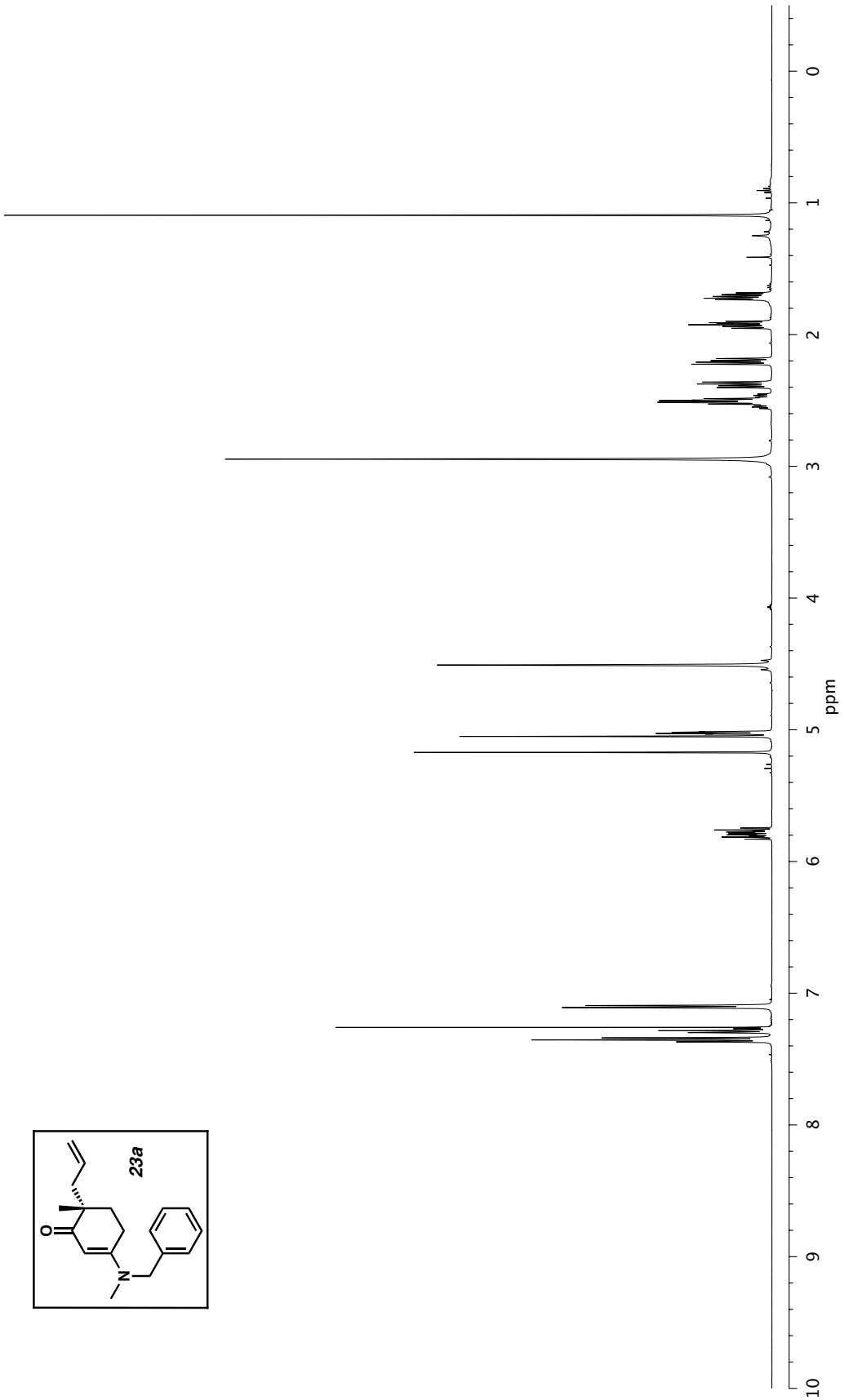


Figure A1.14.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **23a**.

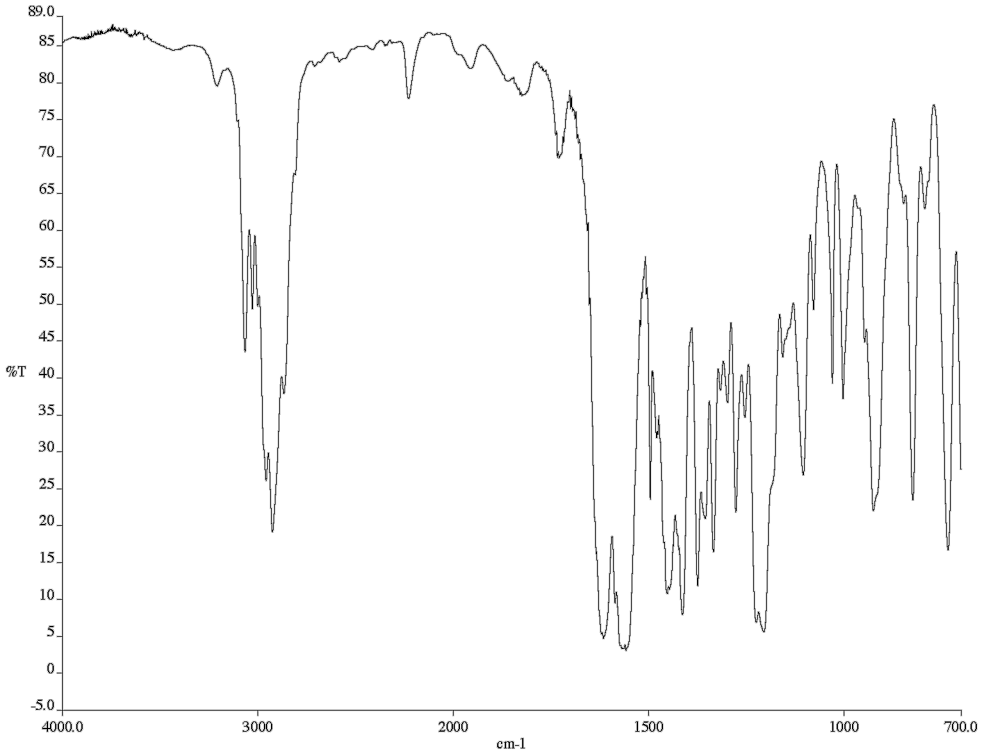


Figure A1.14.2. Infrared spectrum (thin film/NaCl) of compound **23a**.

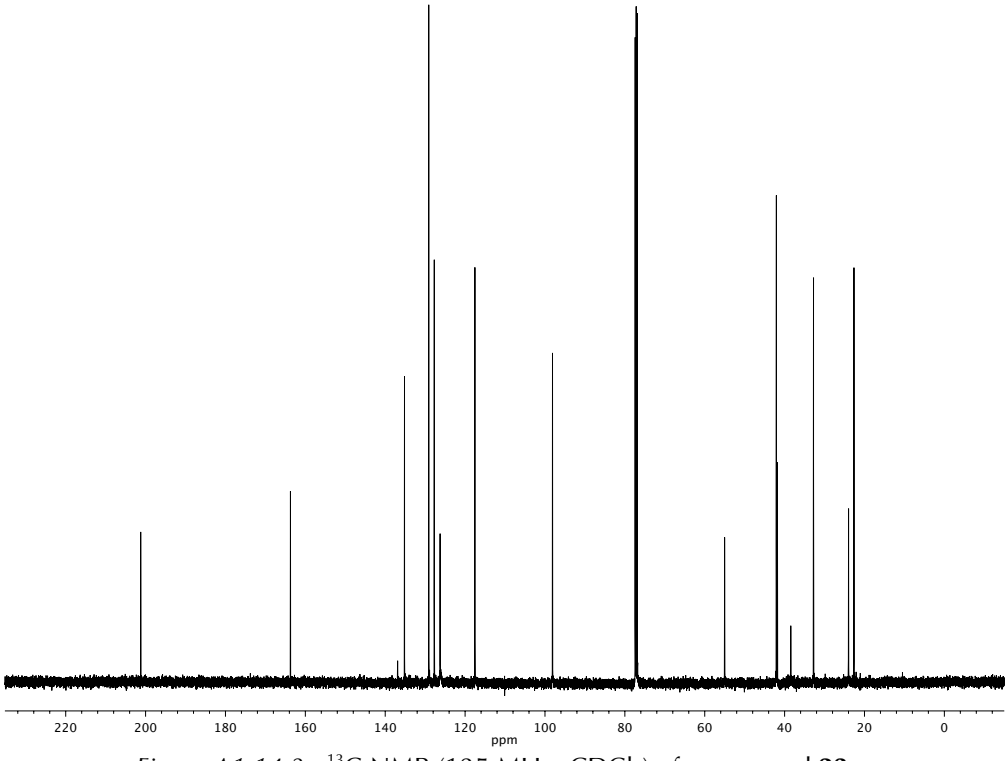


Figure A1.14.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **23a**.

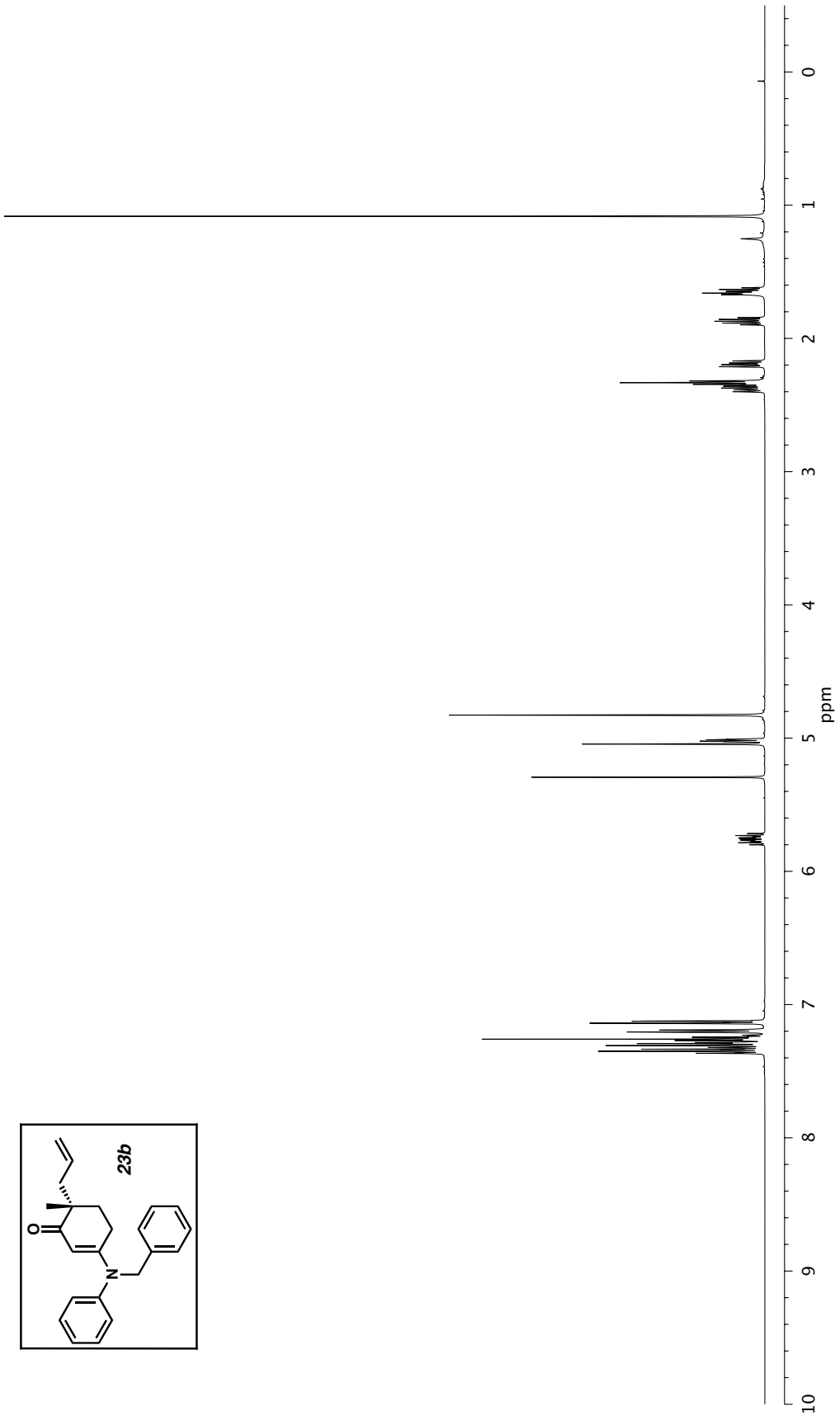


Figure A1.15.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **23b**.

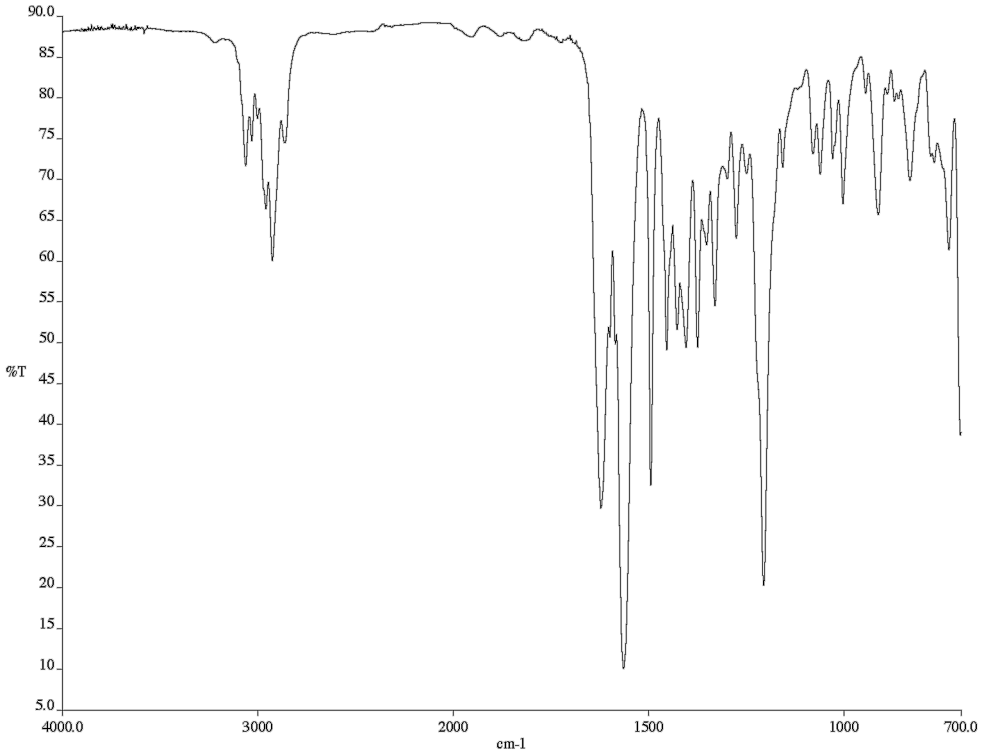


Figure A1.15.2. Infrared spectrum (thin film/NaCl) of compound **23b**.

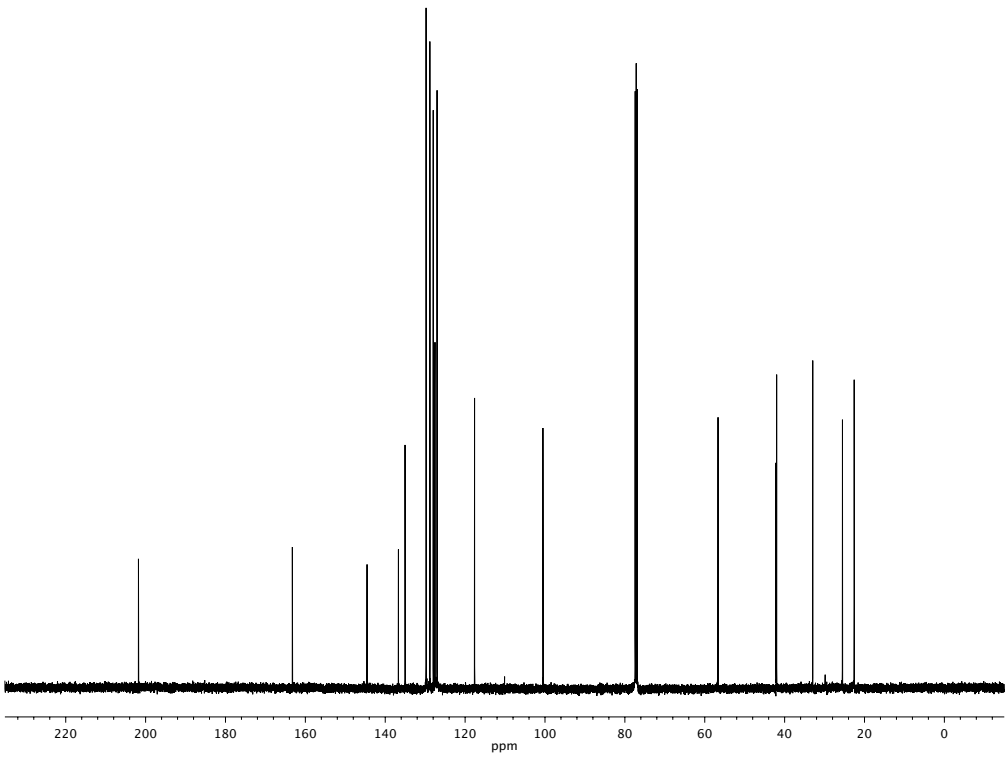


Figure A1.15.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **23b**.

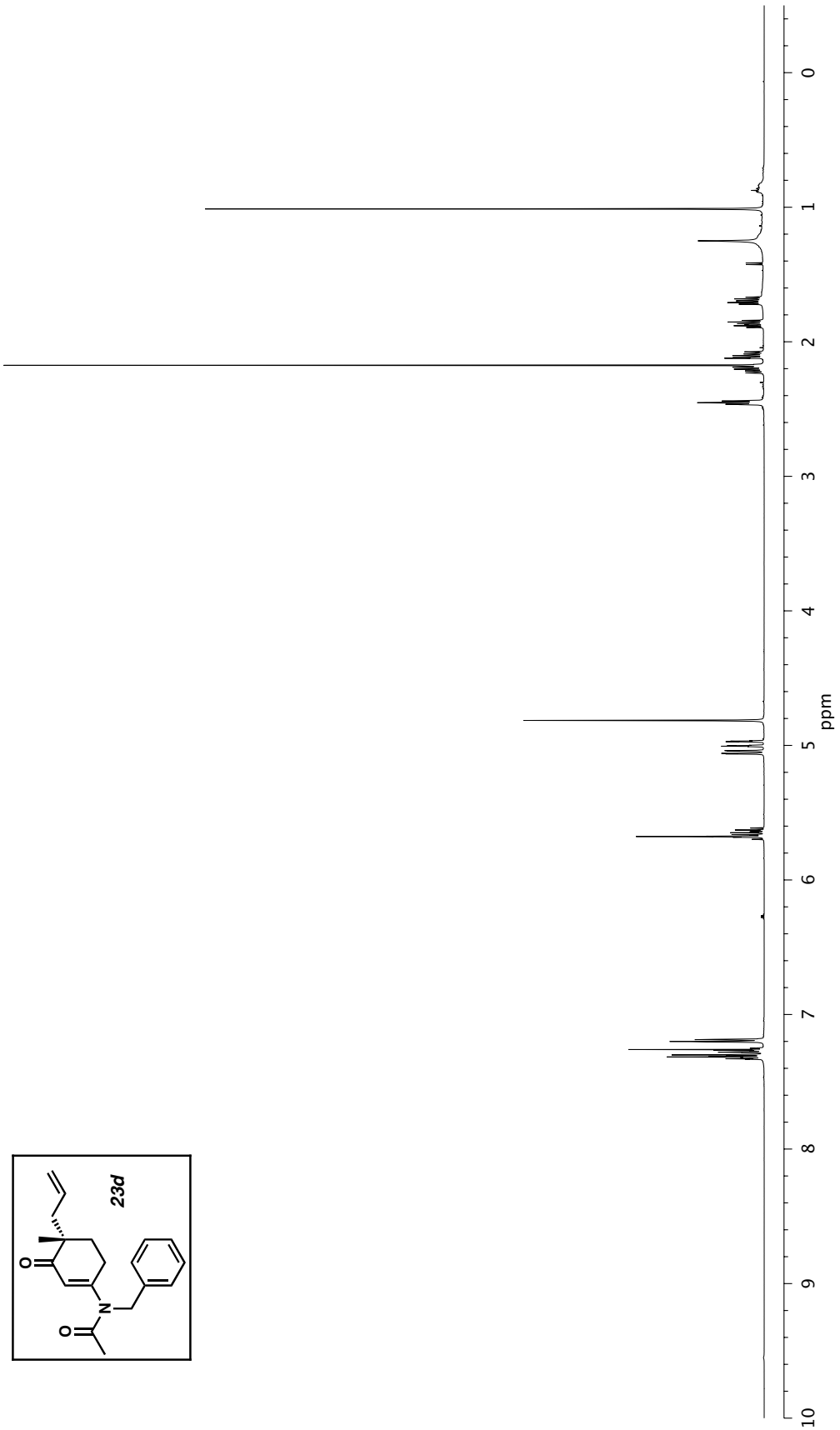


Figure A1.16.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **23d**.

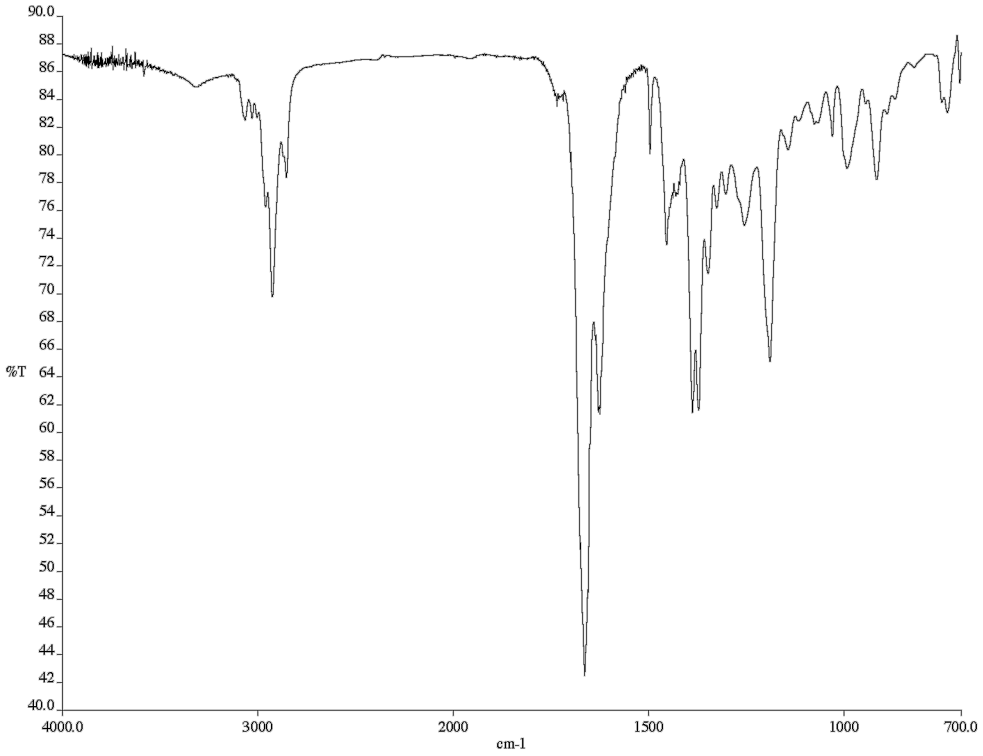


Figure A1.16.2. Infrared spectrum (thin film/NaCl) of compound **23d**.

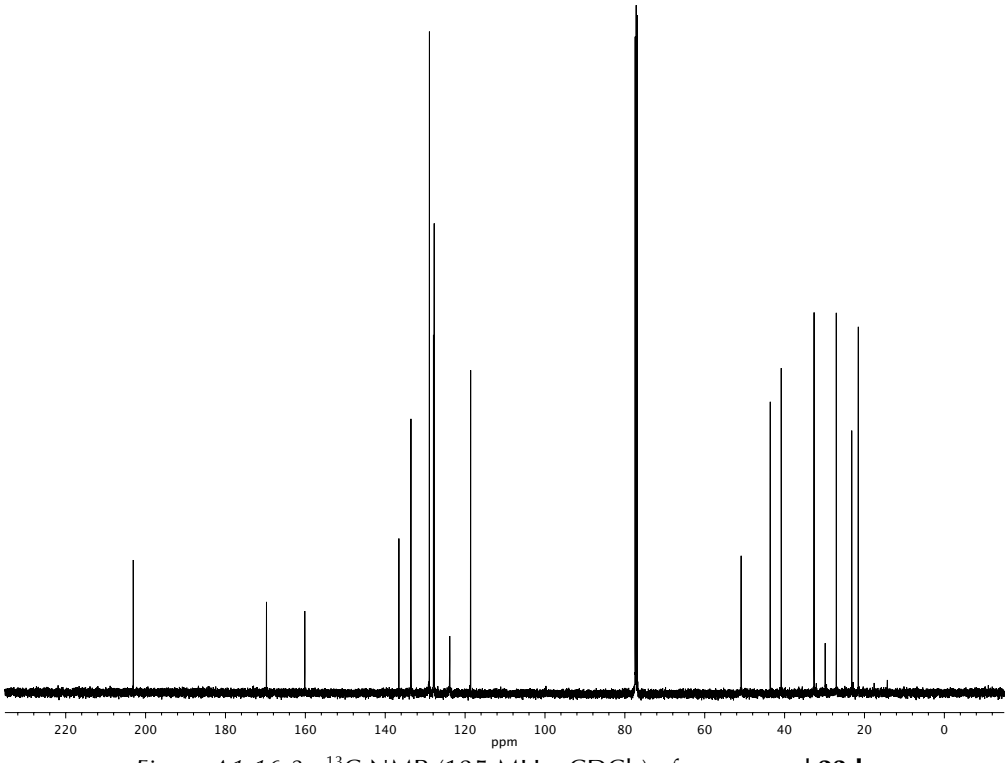


Figure A1.16.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **23d**.

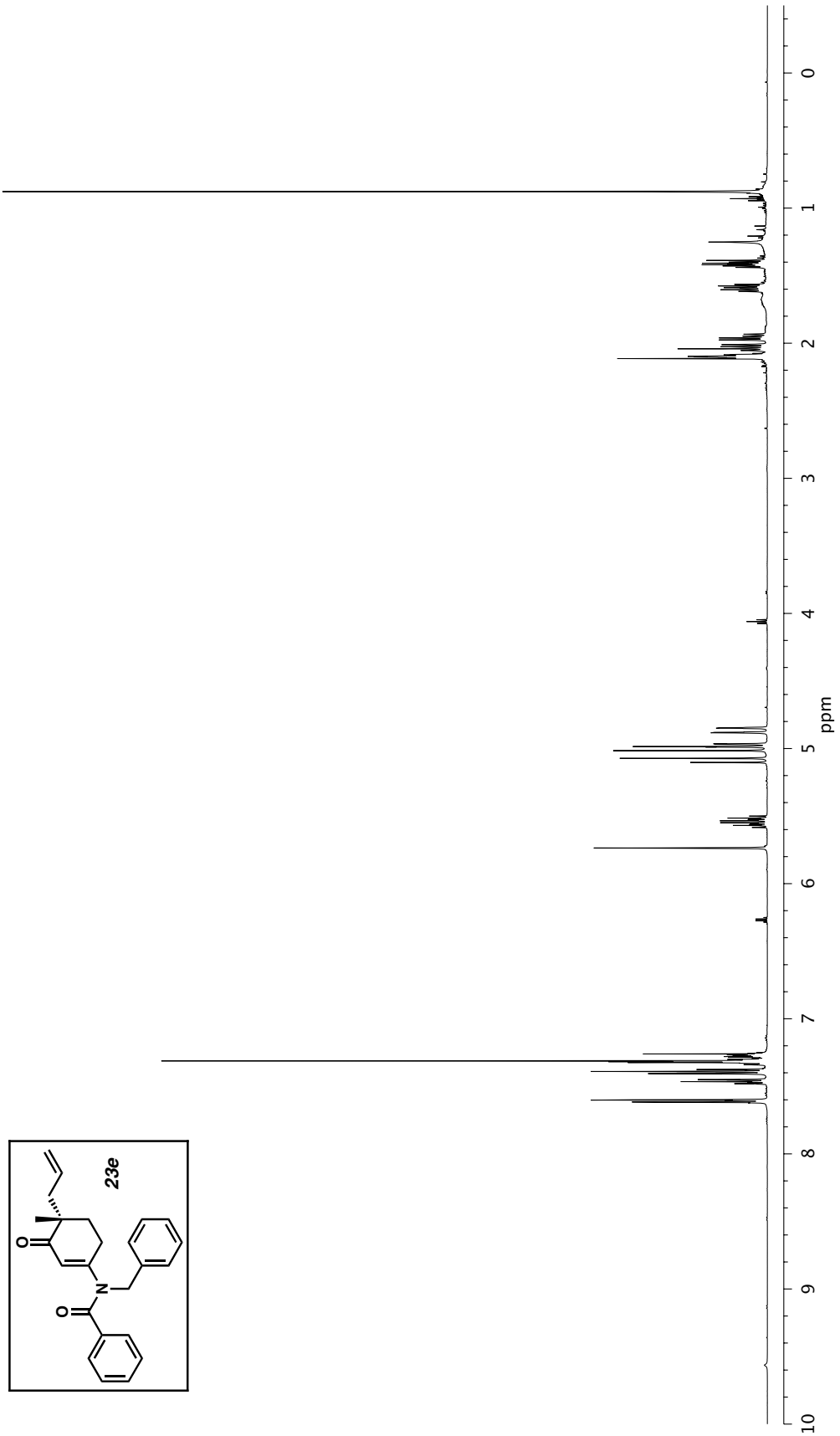


Figure A1.17.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **23e**.

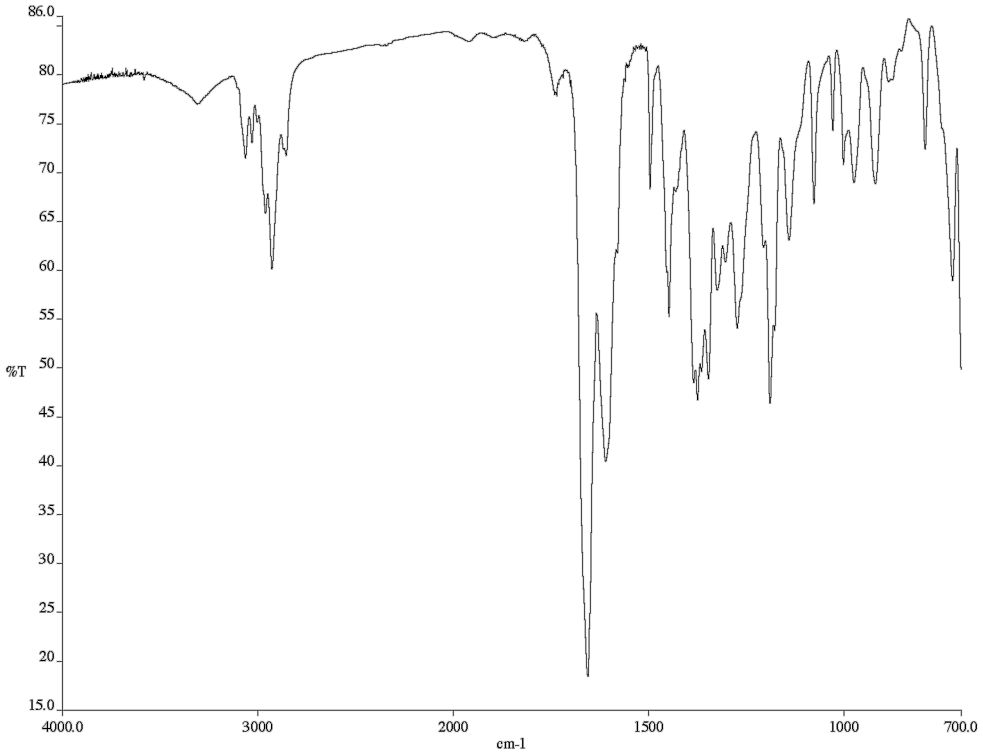


Figure A1.17.2. Infrared spectrum (thin film/NaCl) of compound **23e**.

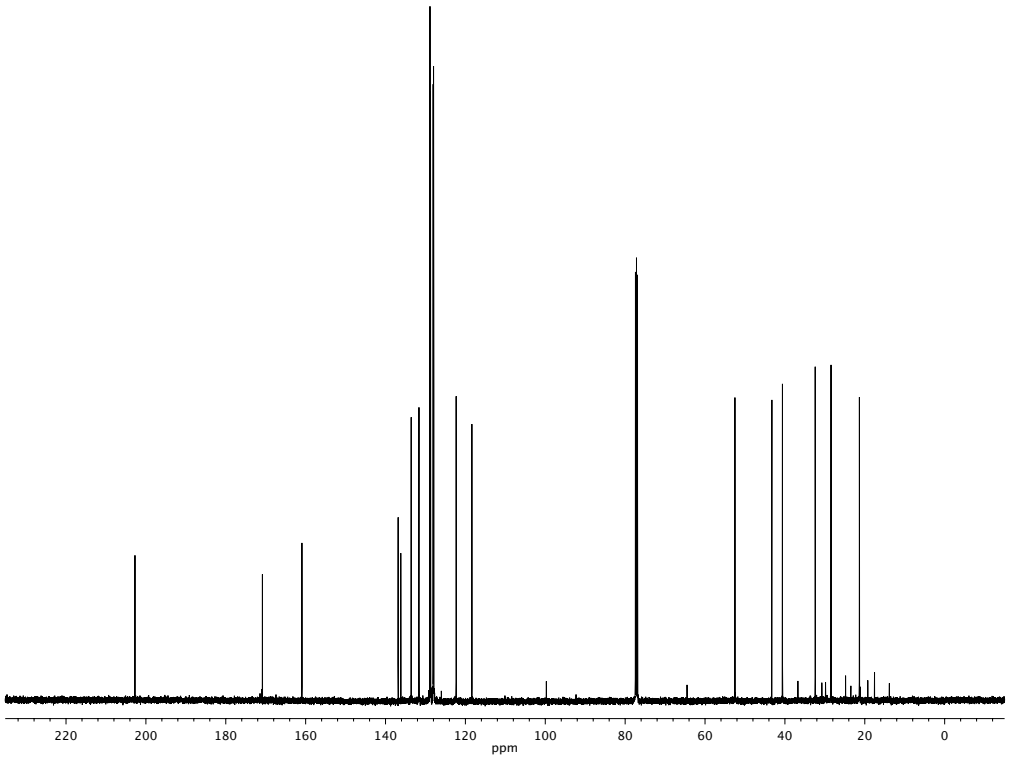


Figure A1.17.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **23e**.

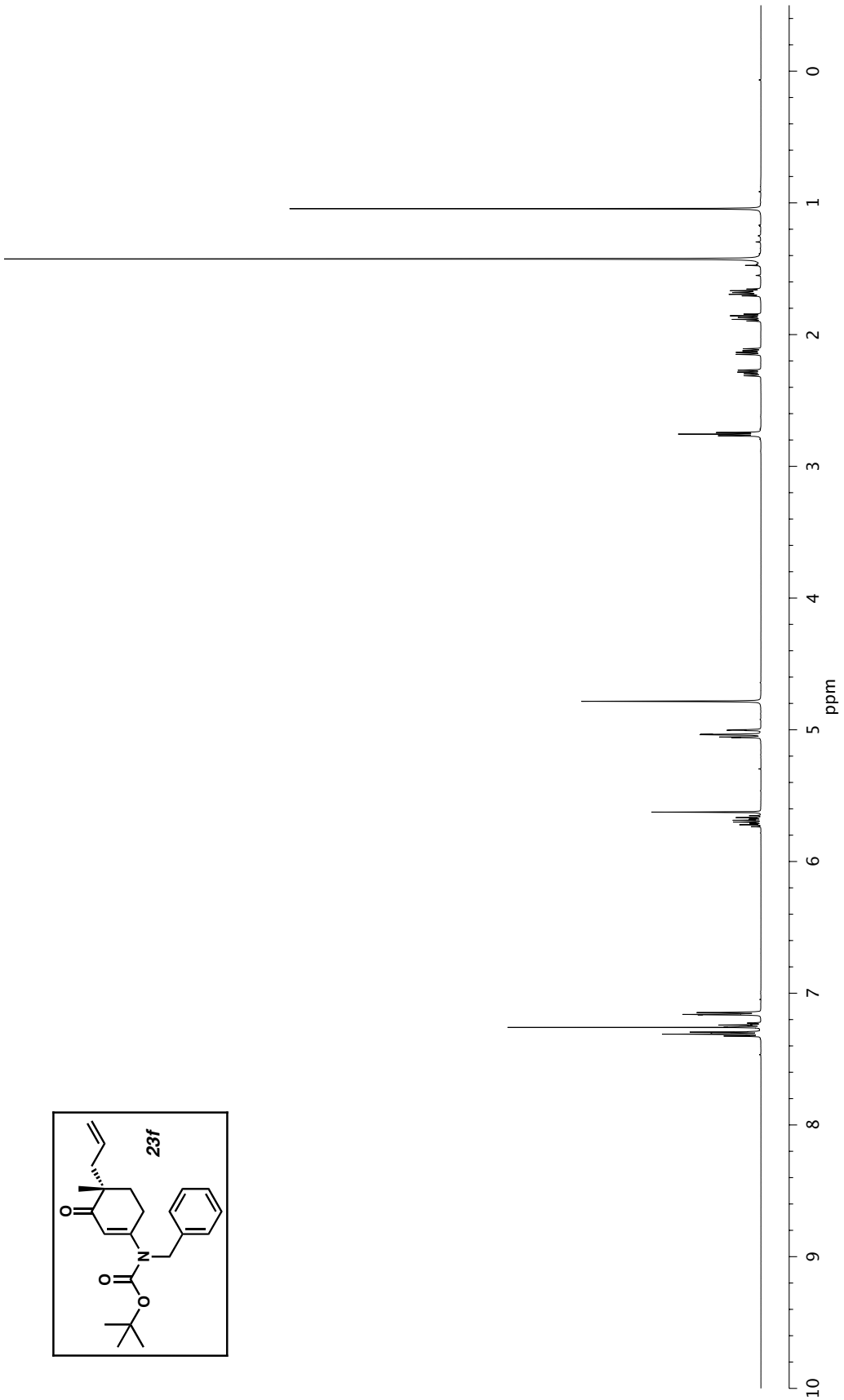


Figure A1.18.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **23f**.

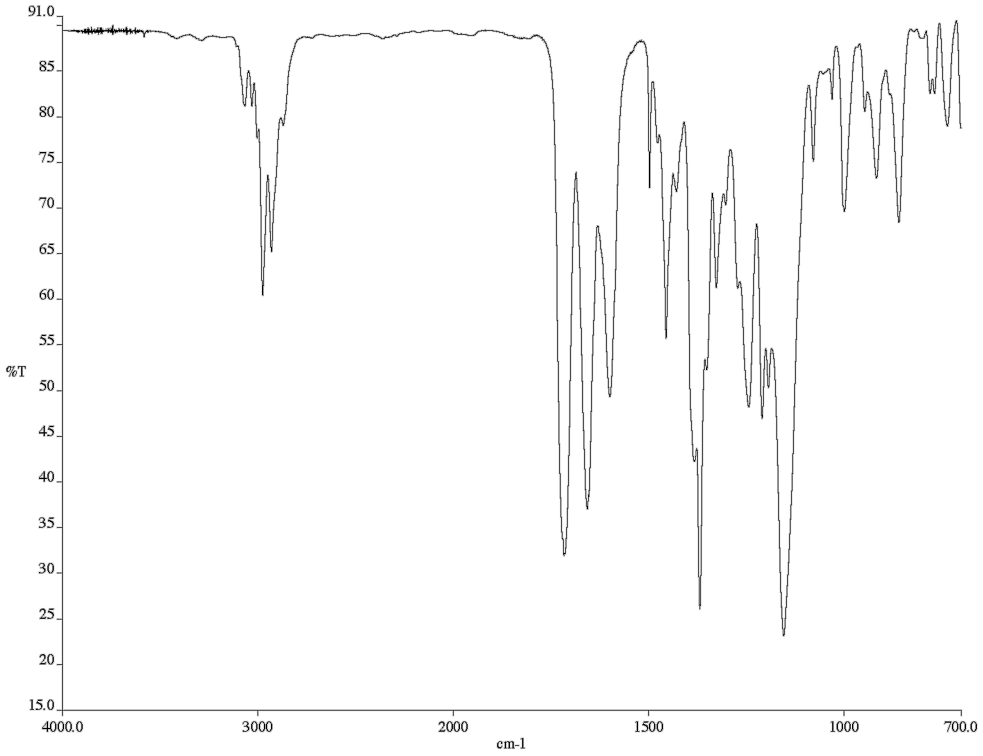


Figure A1.18.2. Infrared spectrum (thin film/NaCl) of compound **23f**.

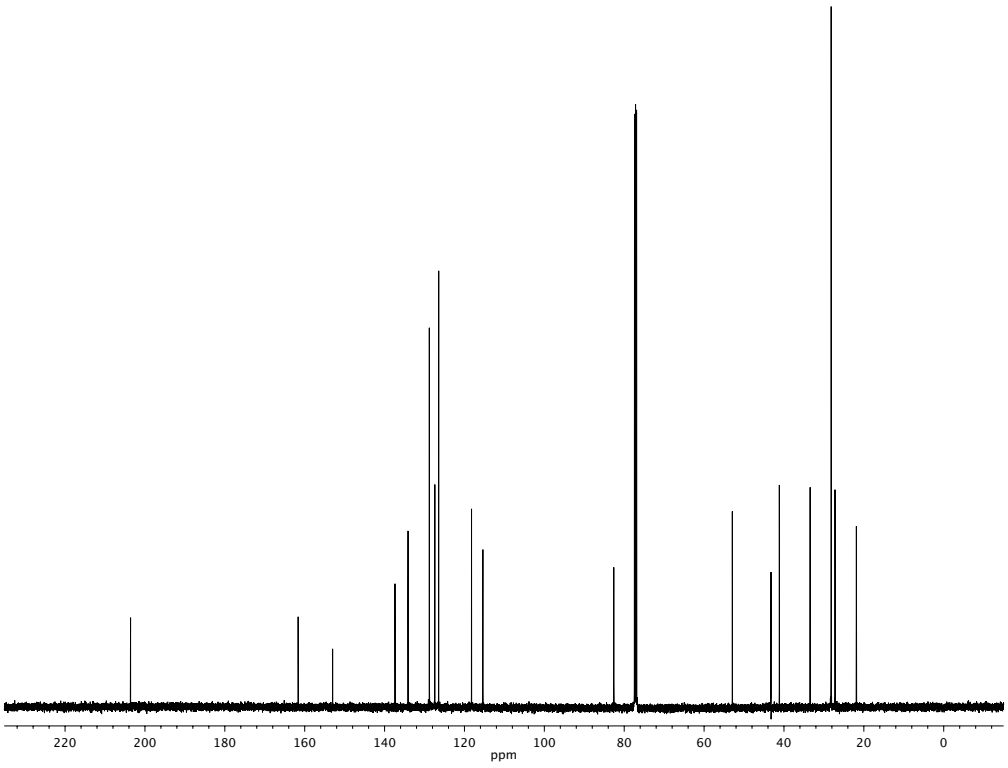


Figure A1.18.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **23f**.

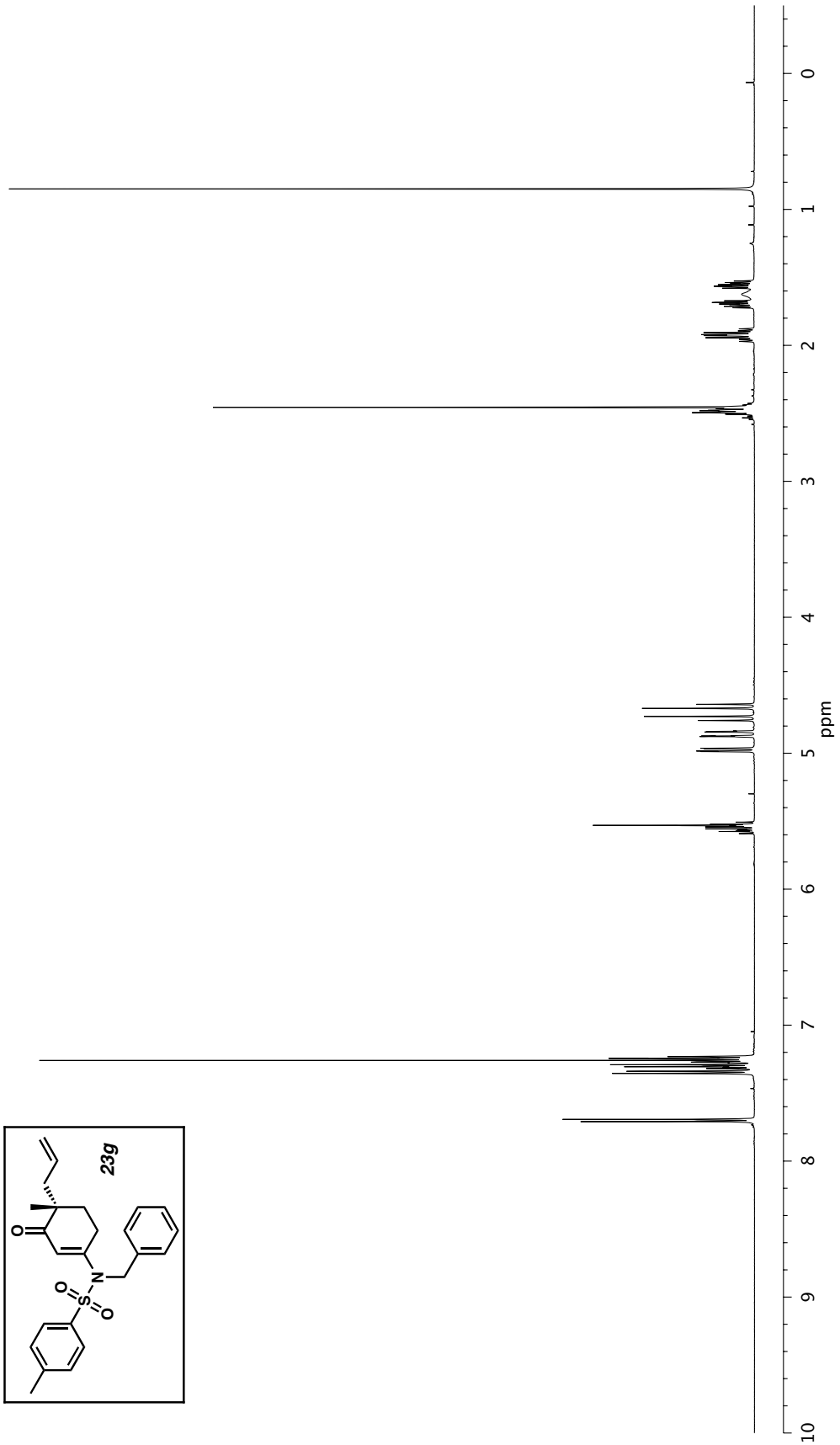


Figure A1.19.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **23g**.

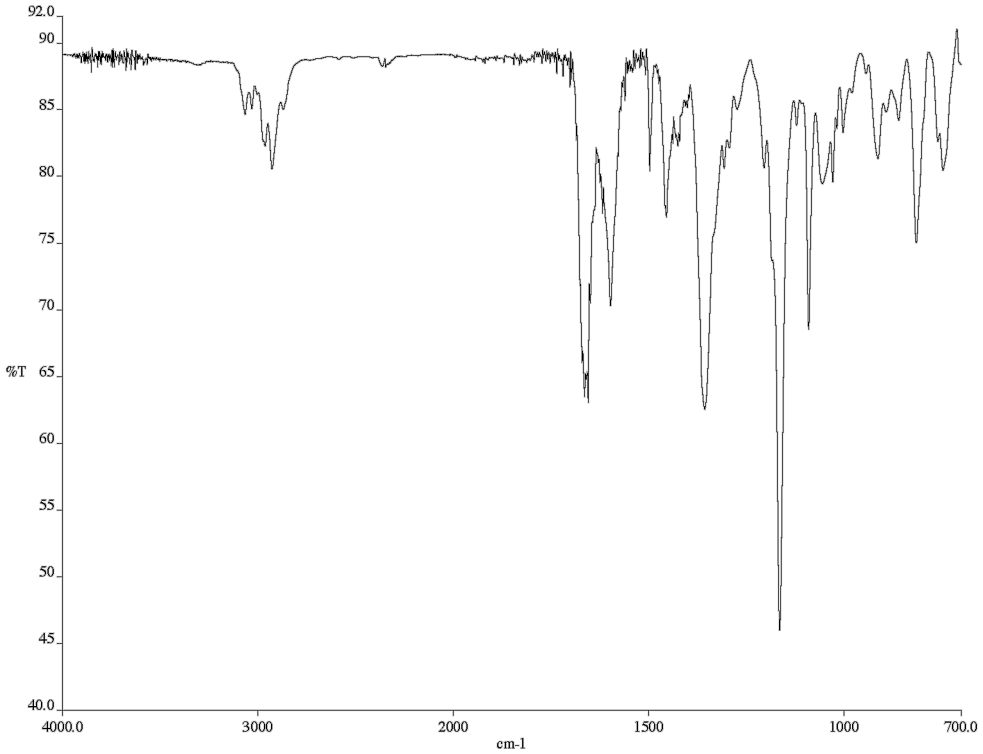


Figure A1.19.2. Infrared spectrum (thin film/NaCl) of compound **23g**.

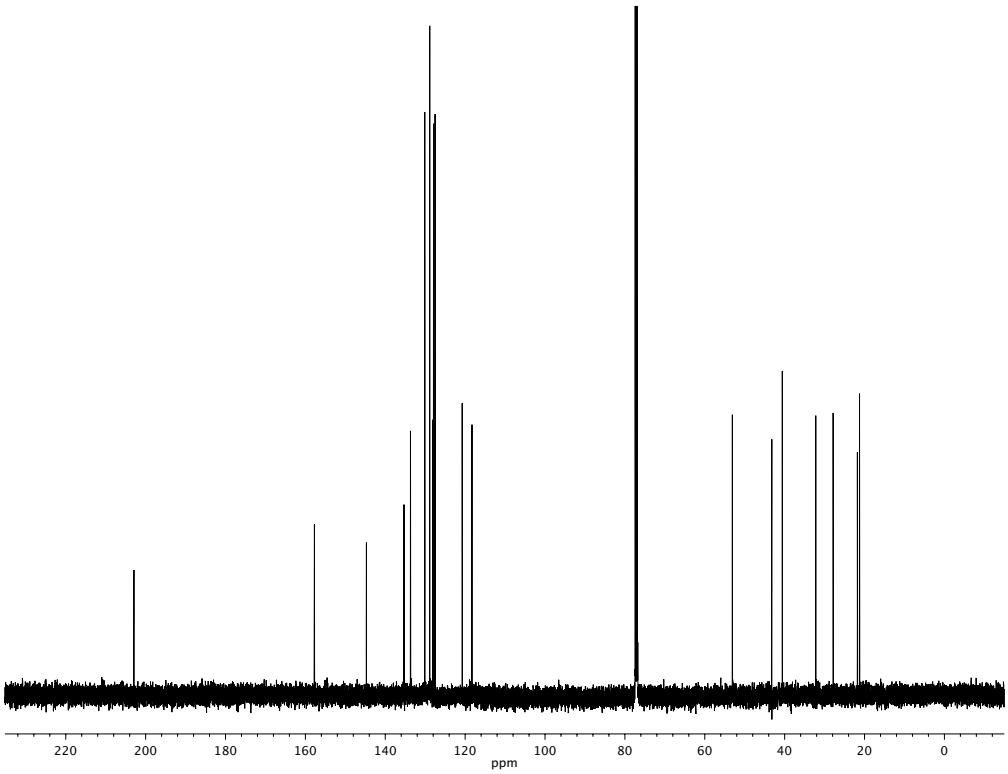


Figure A1.19.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **23g**.

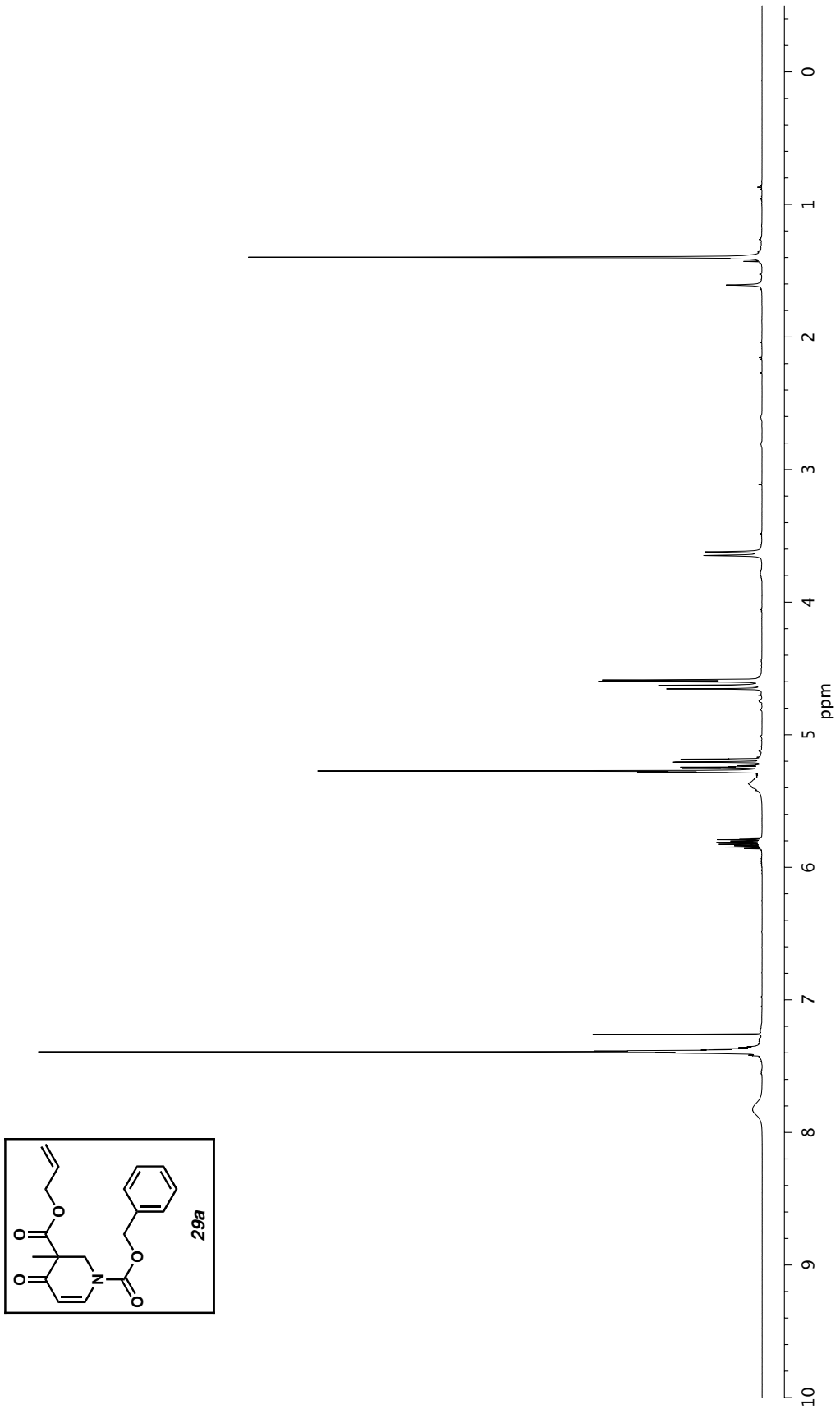


Figure A1.20.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **29a**.

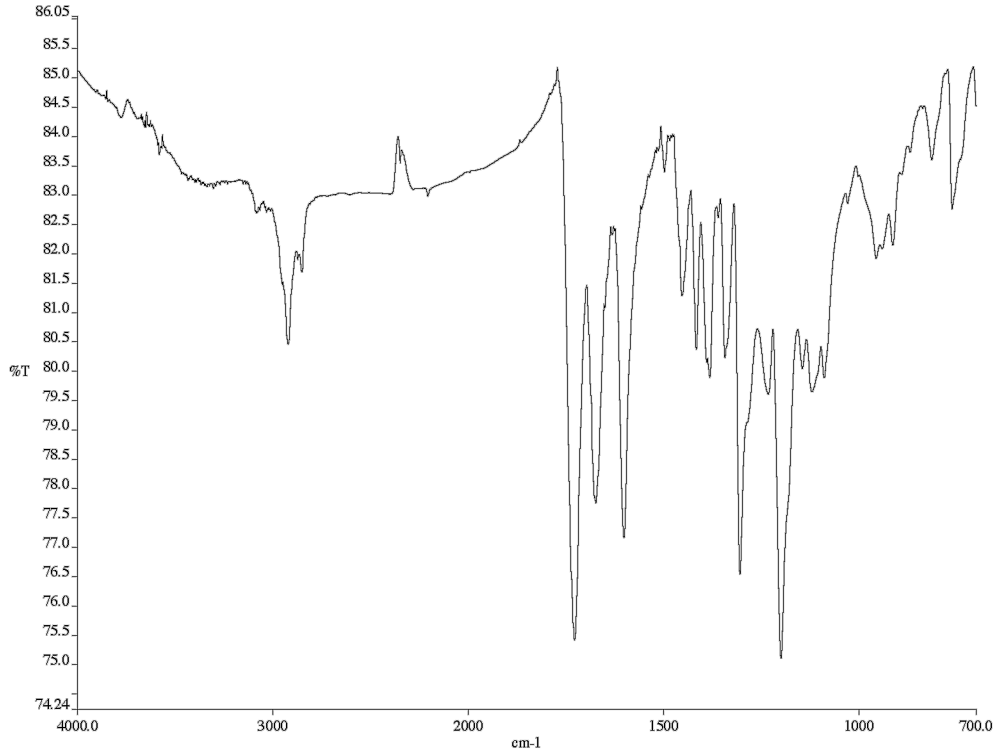


Figure A1.20.2. Infrared spectrum (thin film/NaCl) of compound **29a**.

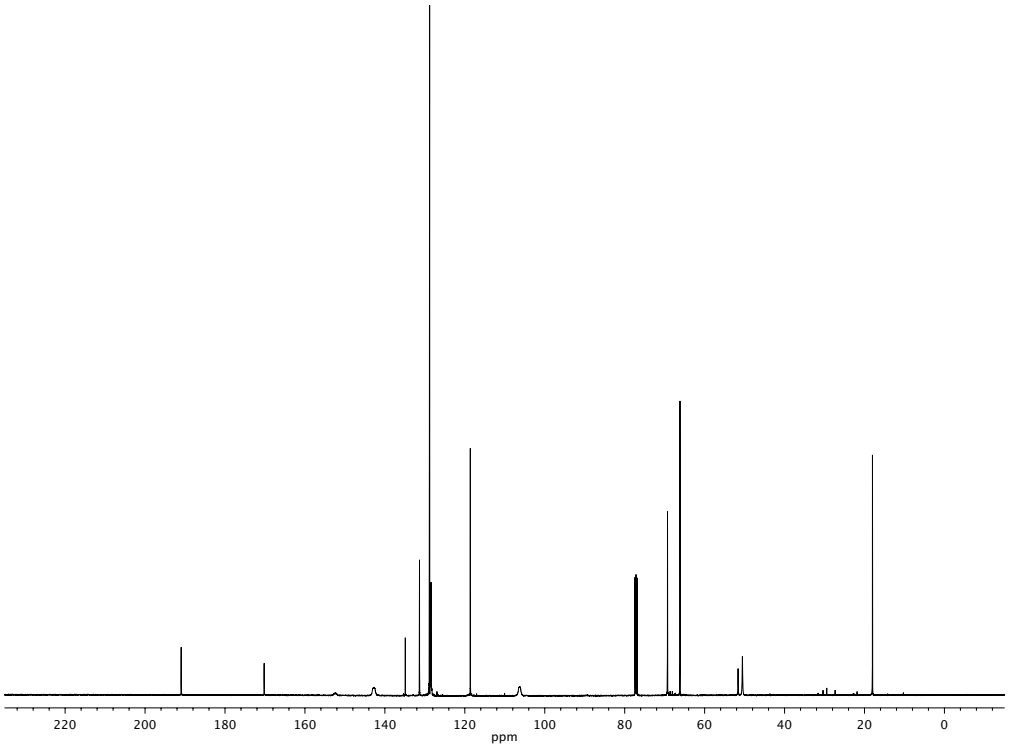


Figure A1.20.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **29a**.

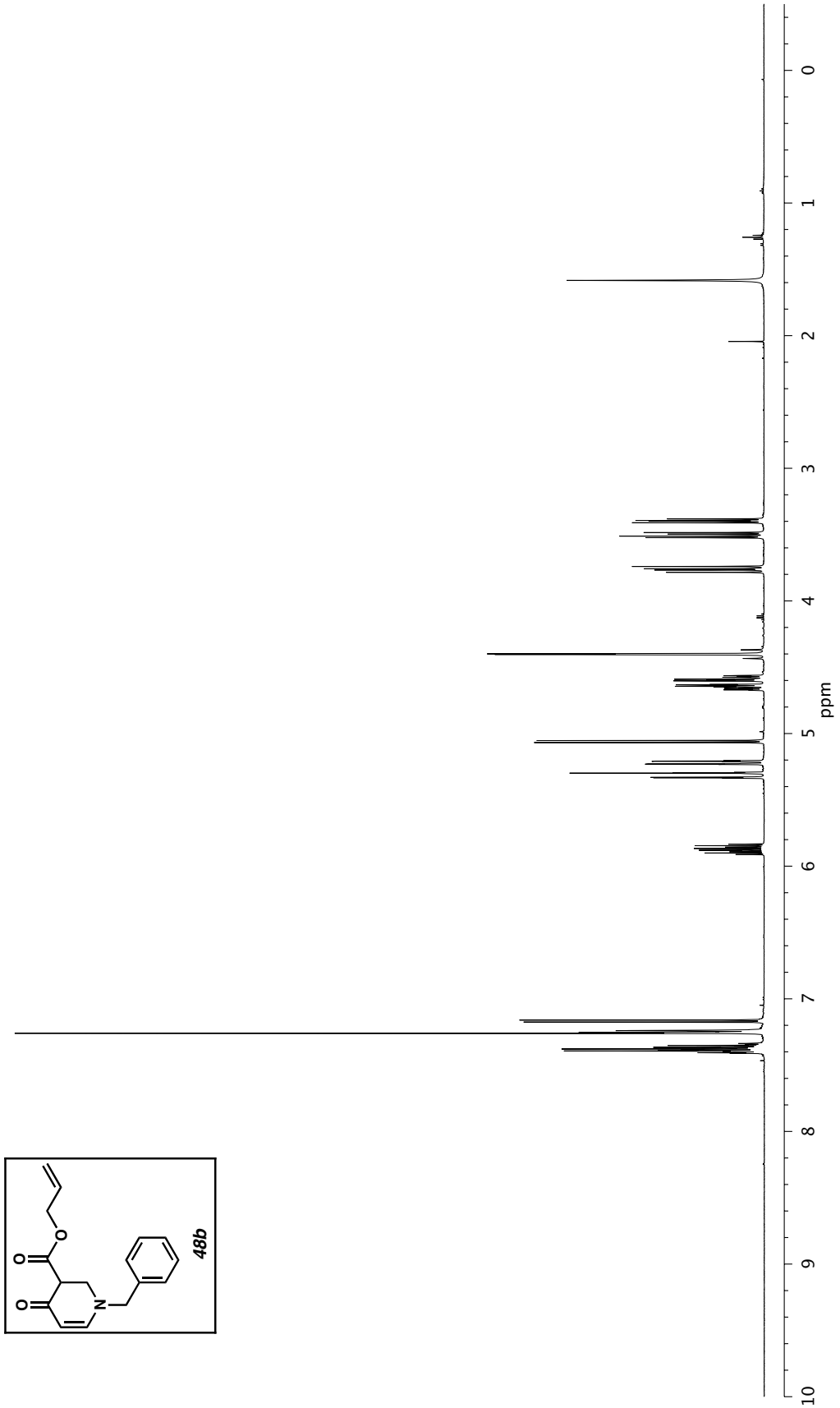


Figure A1.21.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **48b**.

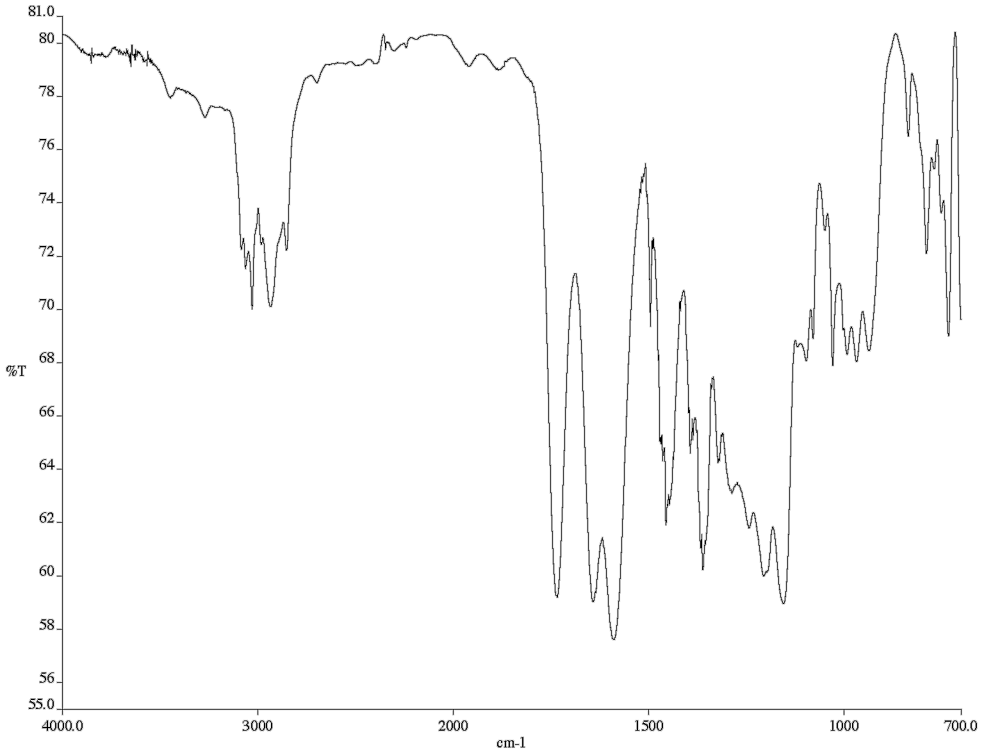


Figure A1.21.2. Infrared spectrum (thin film/NaCl) of compound **48b**.

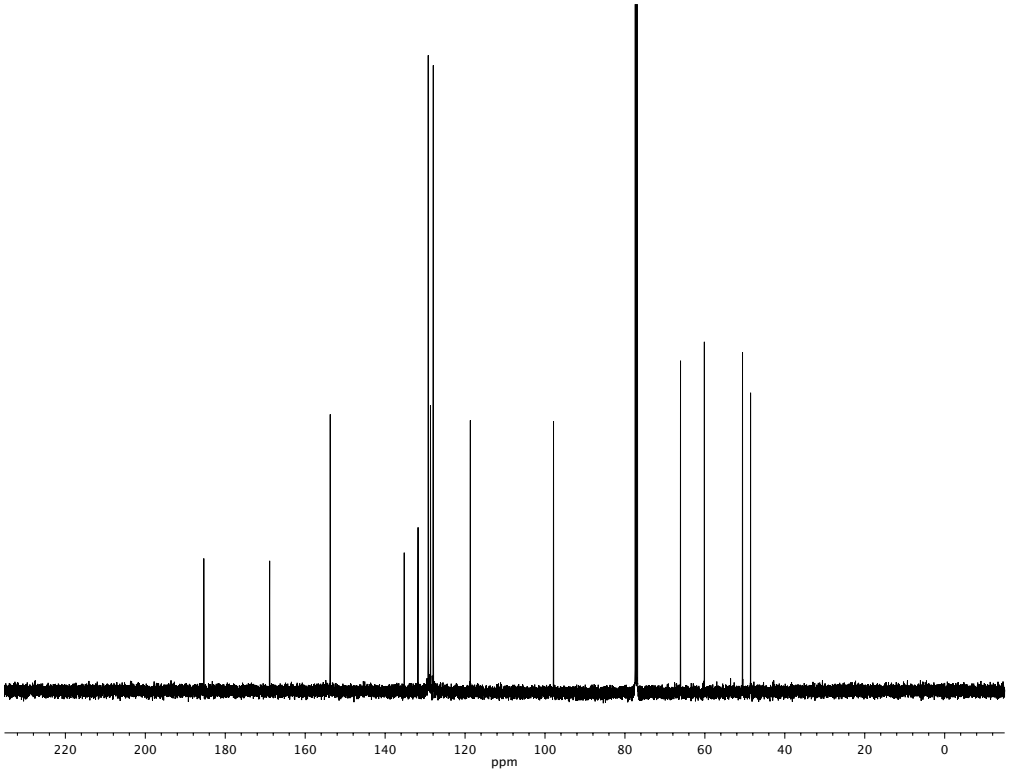


Figure A1.21.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **48b**.

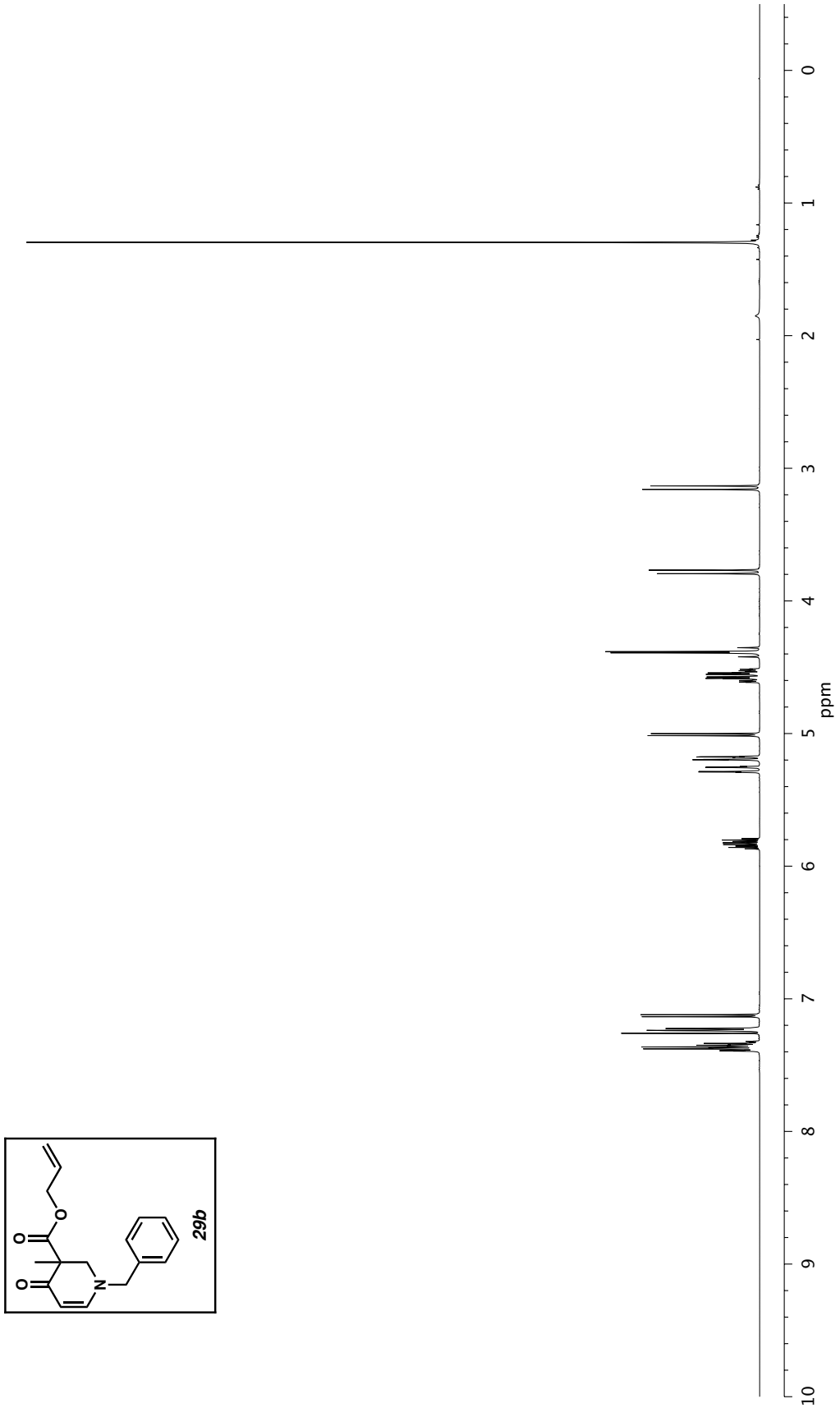


Figure A1.22.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **29b**.

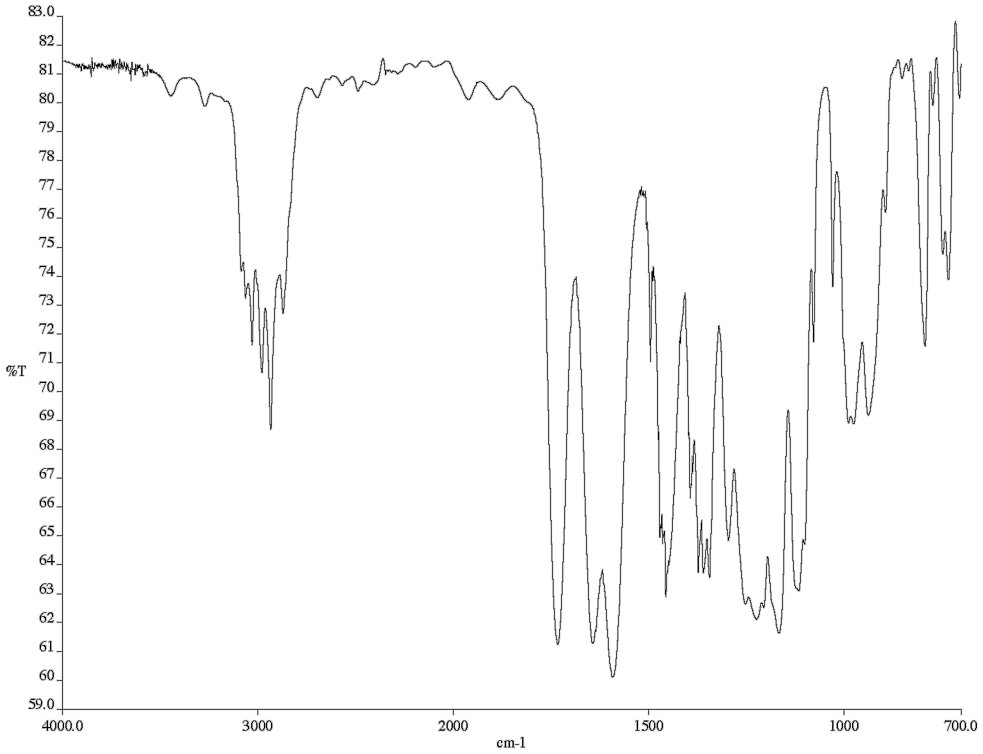


Figure A1.22.2. Infrared spectrum (thin film/NaCl) of compound **29b**.

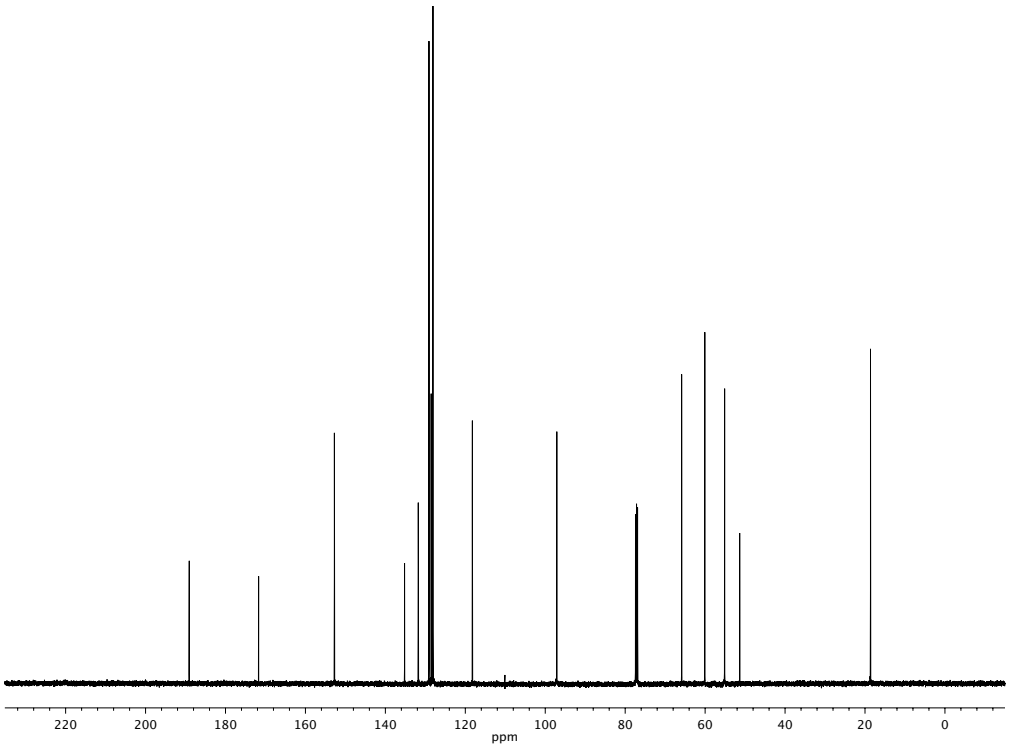


Figure A1.22.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **29b**.

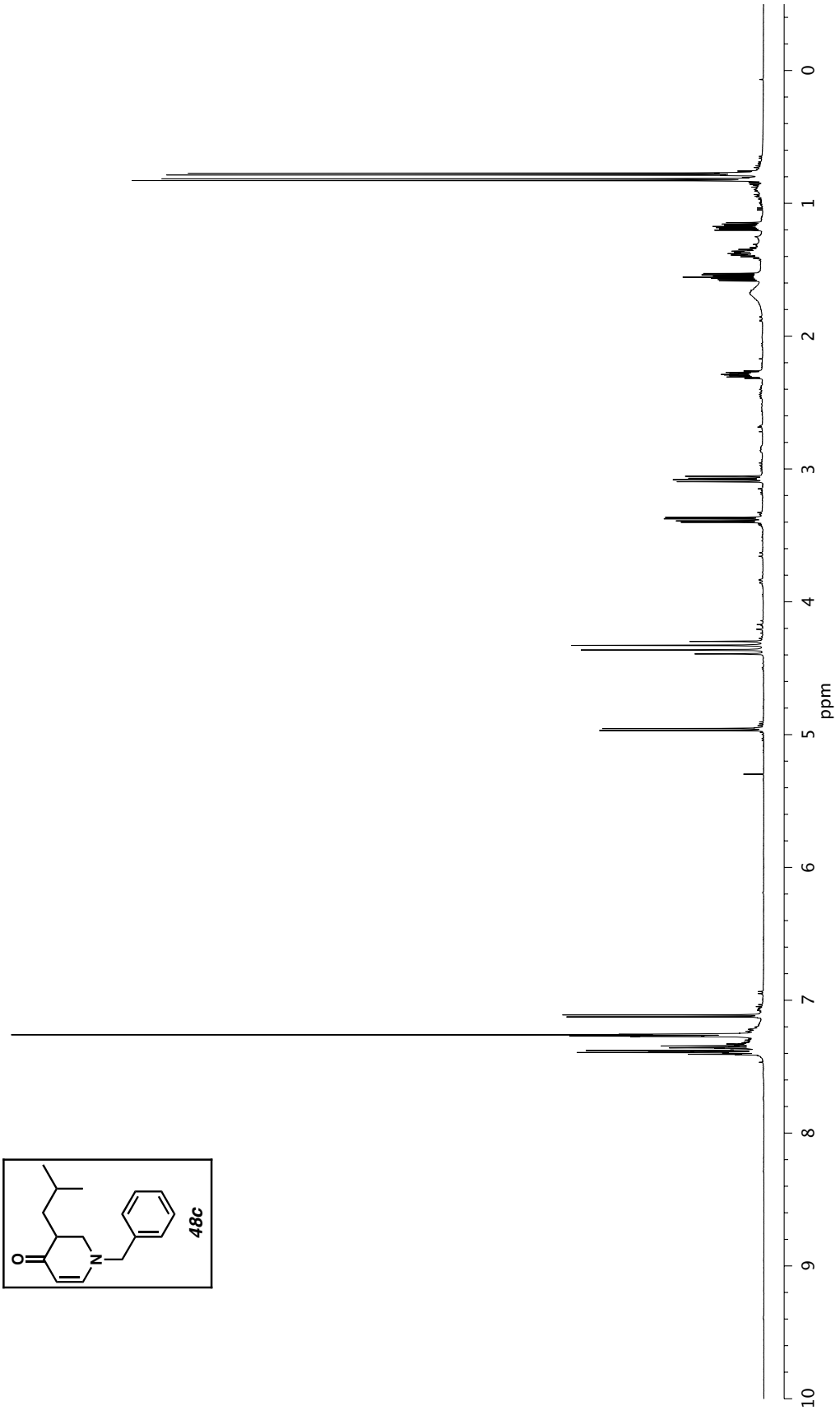


Figure A1.23.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **48c**.

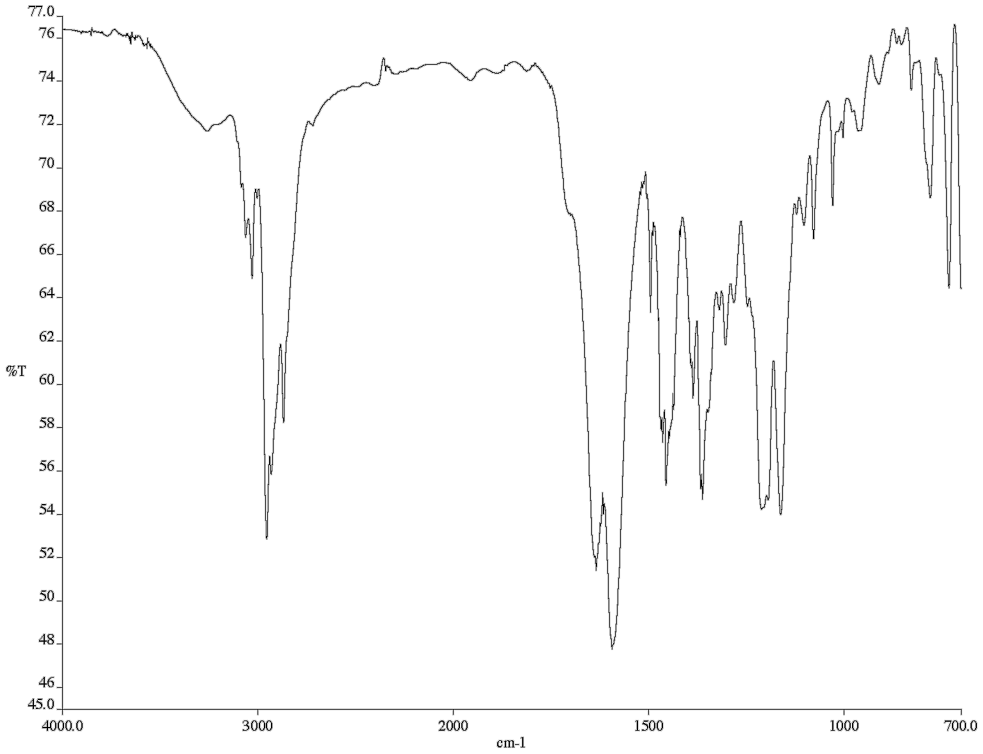


Figure A1.23.2. Infrared spectrum (thin film/NaCl) of compound **48c**.

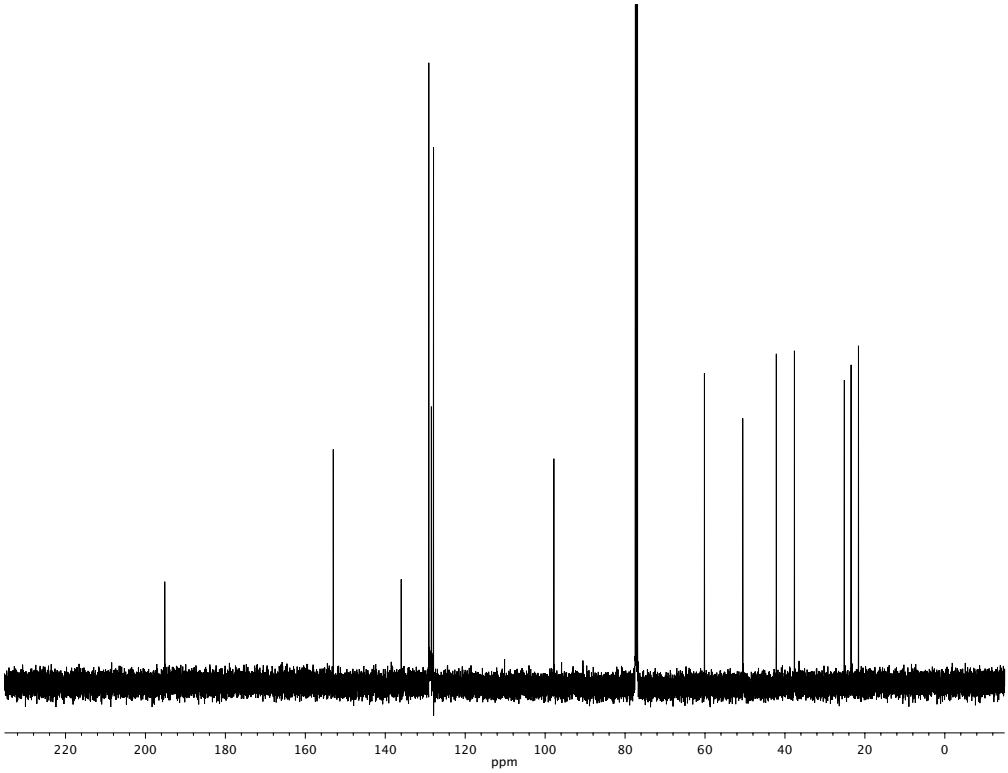


Figure A1.23.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **48c**.

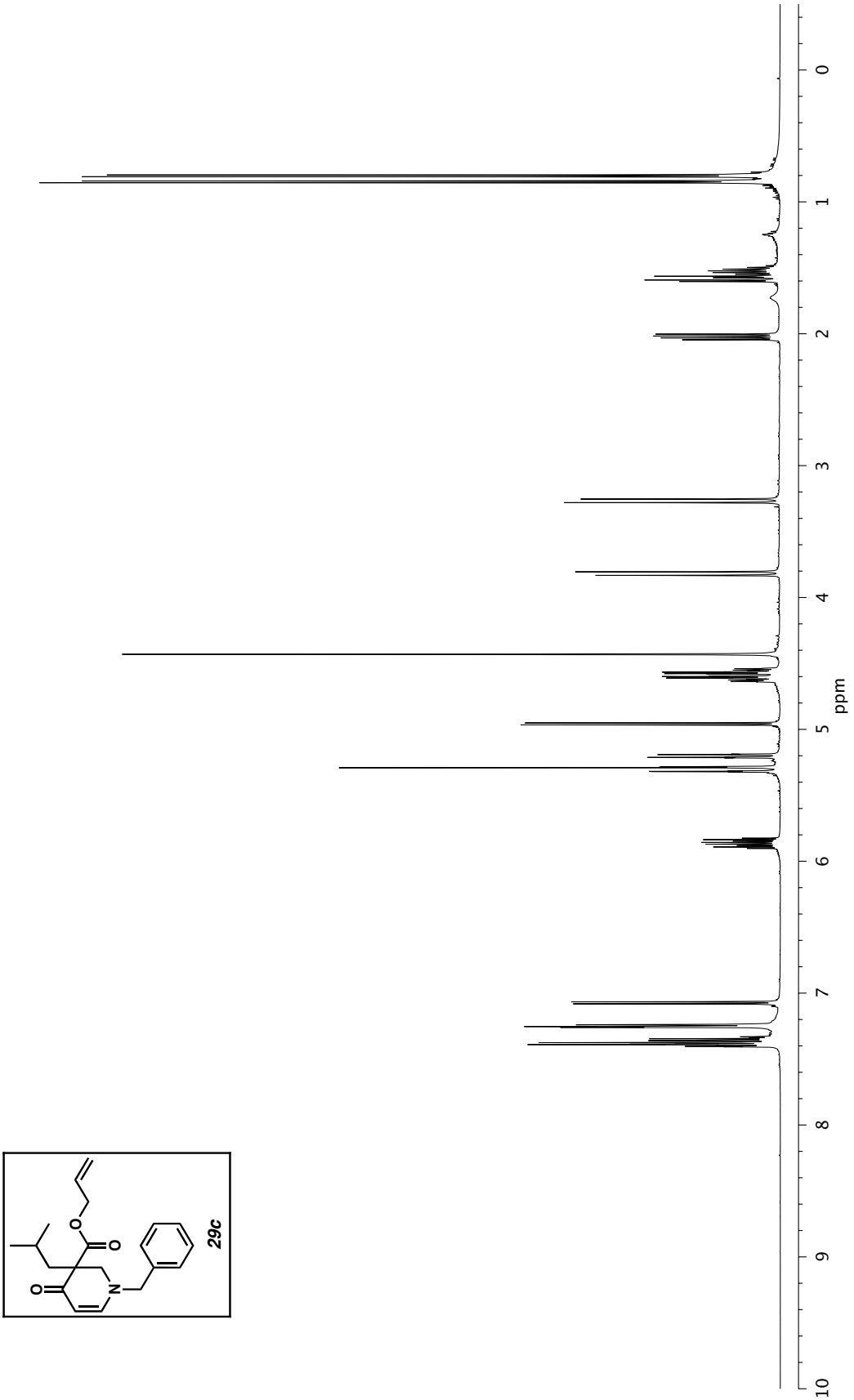


Figure A1.24.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **29c**.

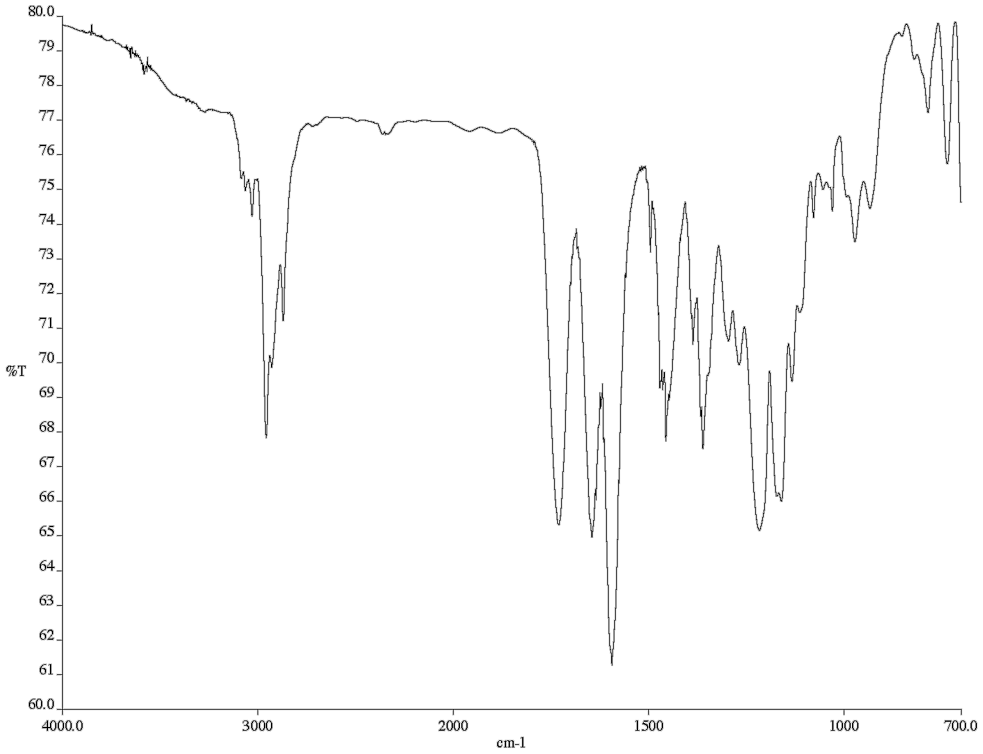


Figure A1.24.2. Infrared spectrum (thin film/NaCl) of compound **29c**.

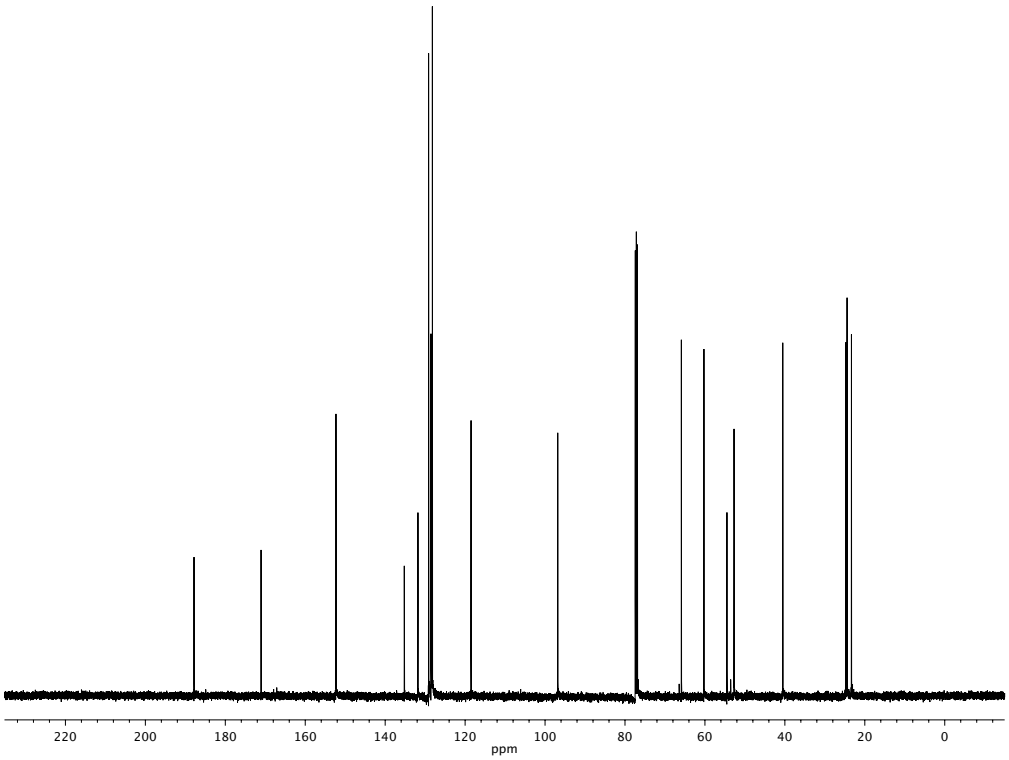


Figure A1.24.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **29c**.

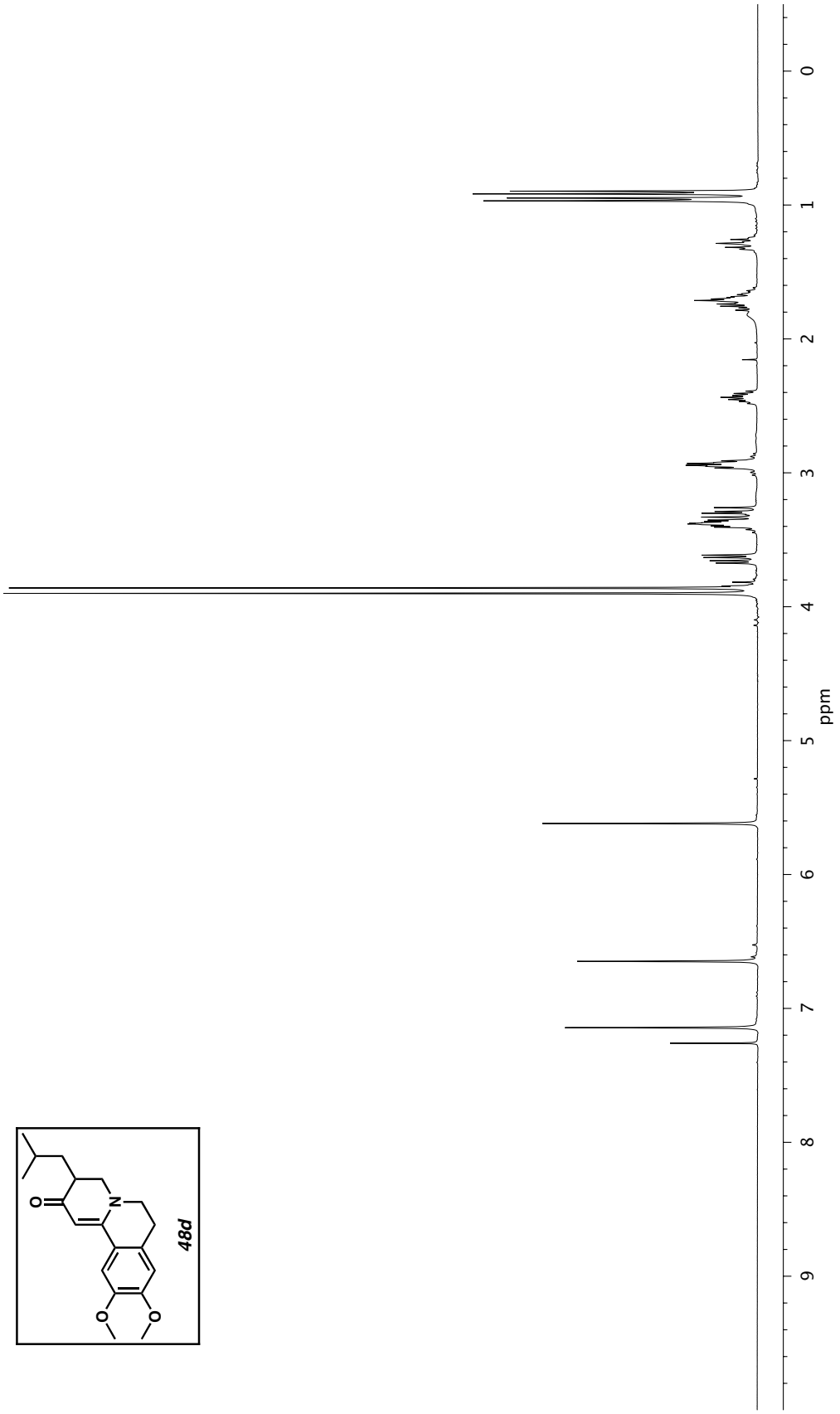


Figure A1.25.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **48d**.

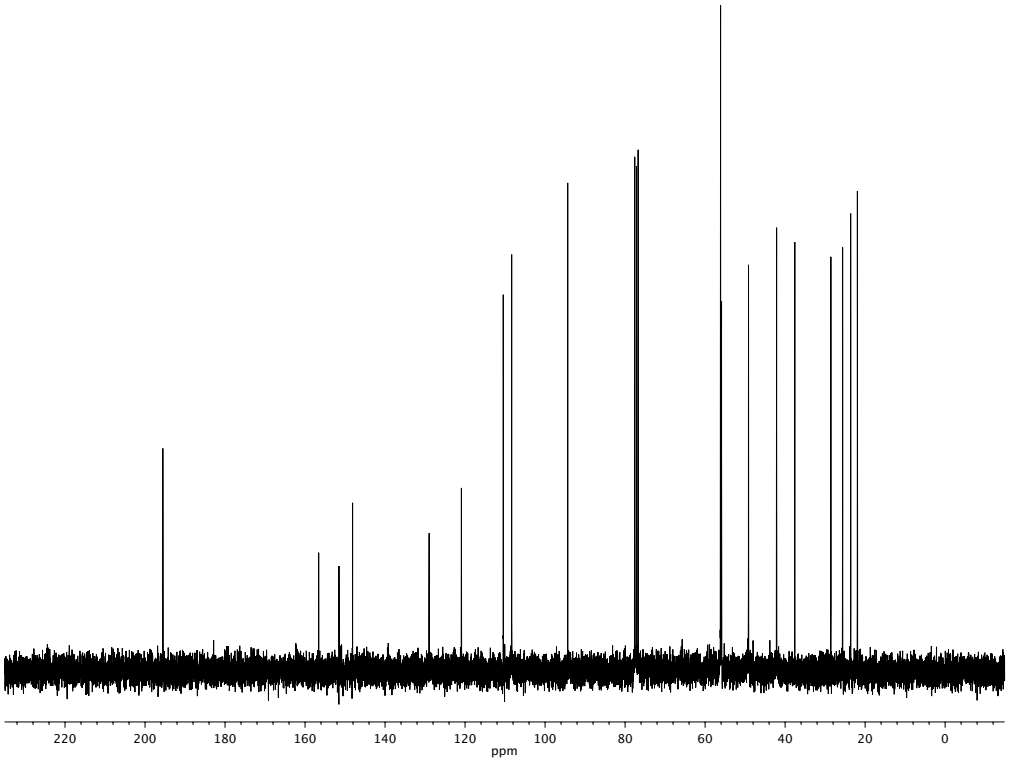


Figure A1.25.2. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **48d**.

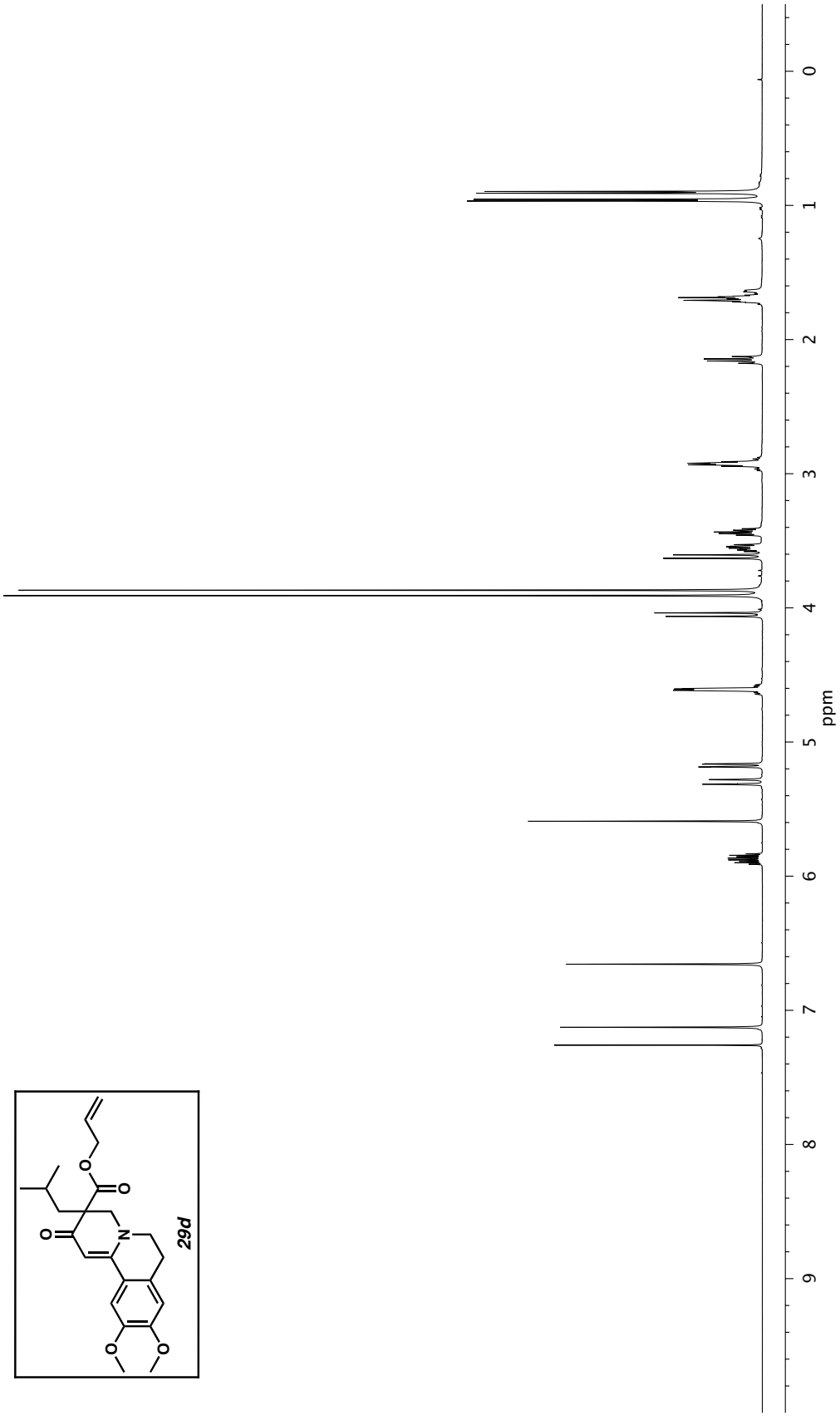


Figure A1.26.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **29d**.

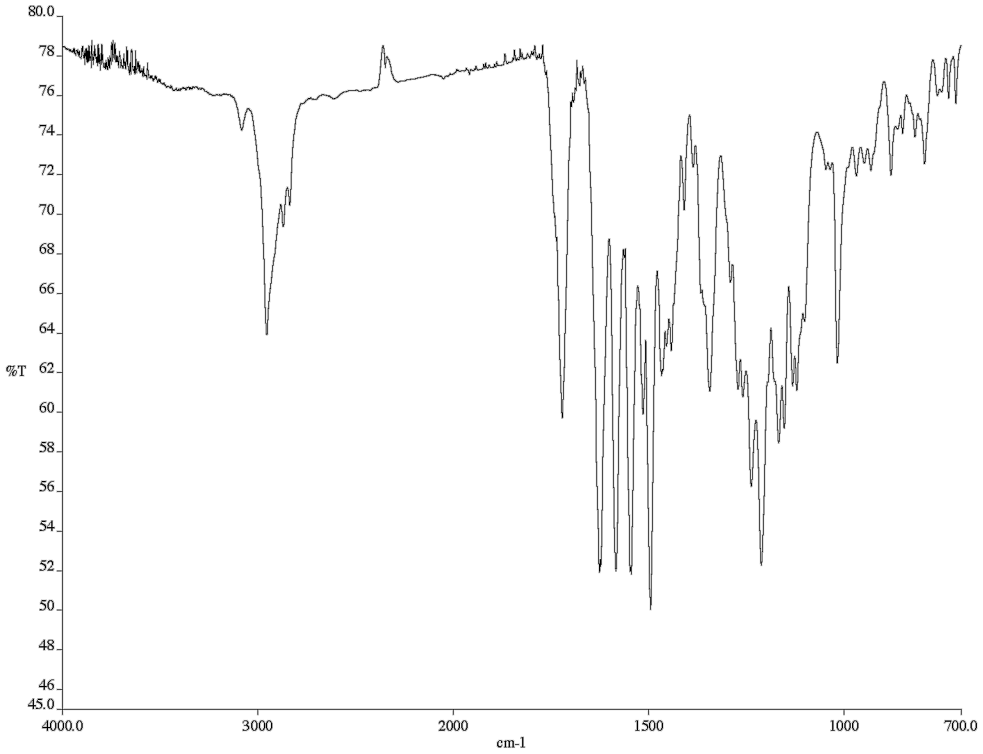


Figure A1.26.2. Infrared spectrum (thin film/NaCl) of compound **29d**.

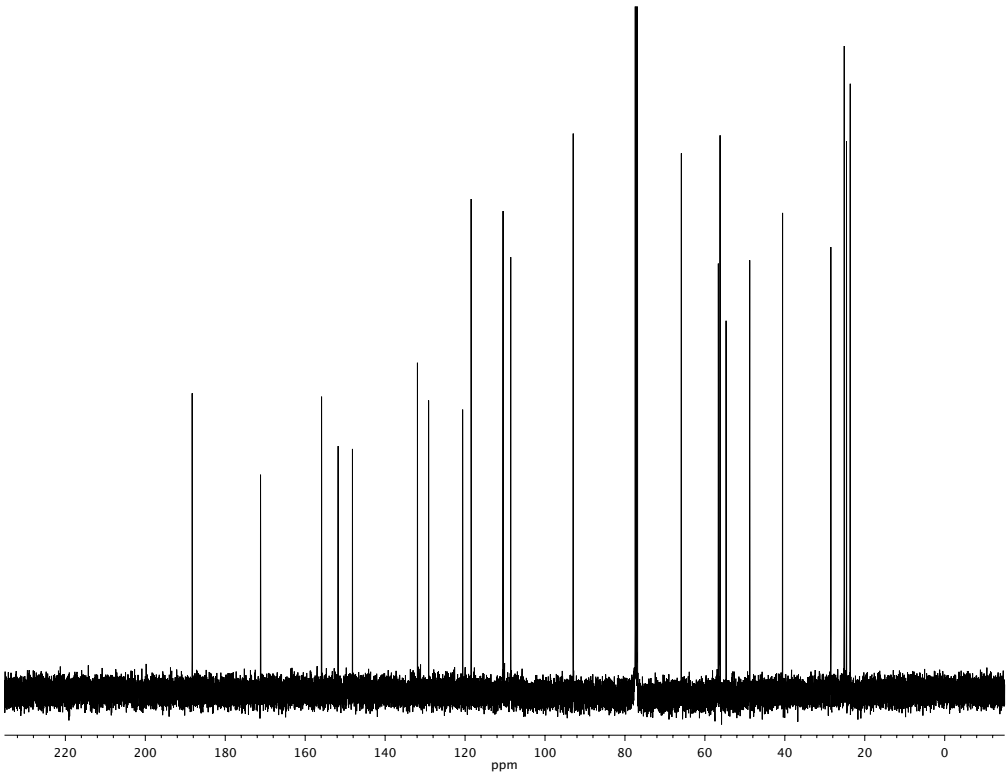


Figure A1.26.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **29d**.

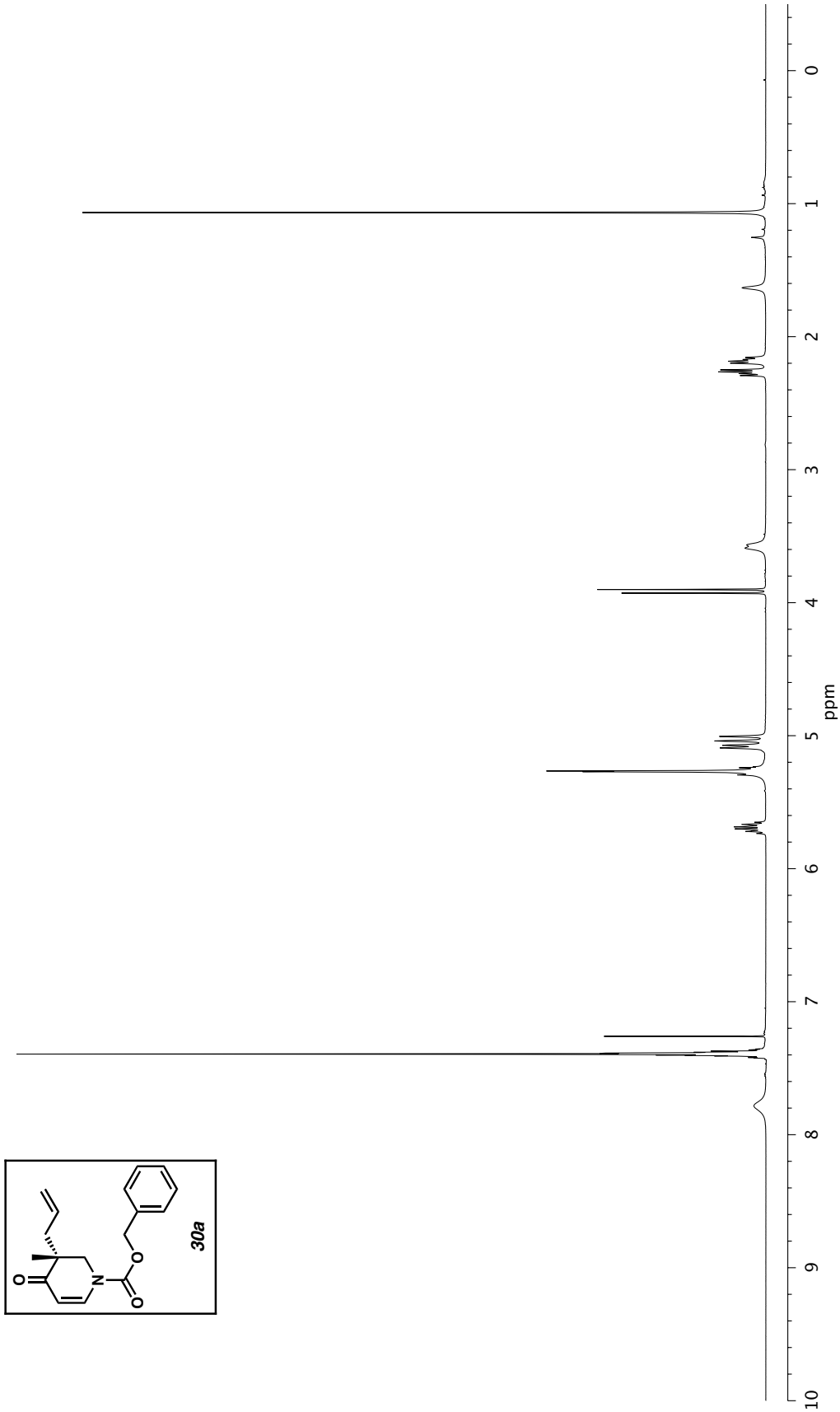


Figure A1.27.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **30a**.

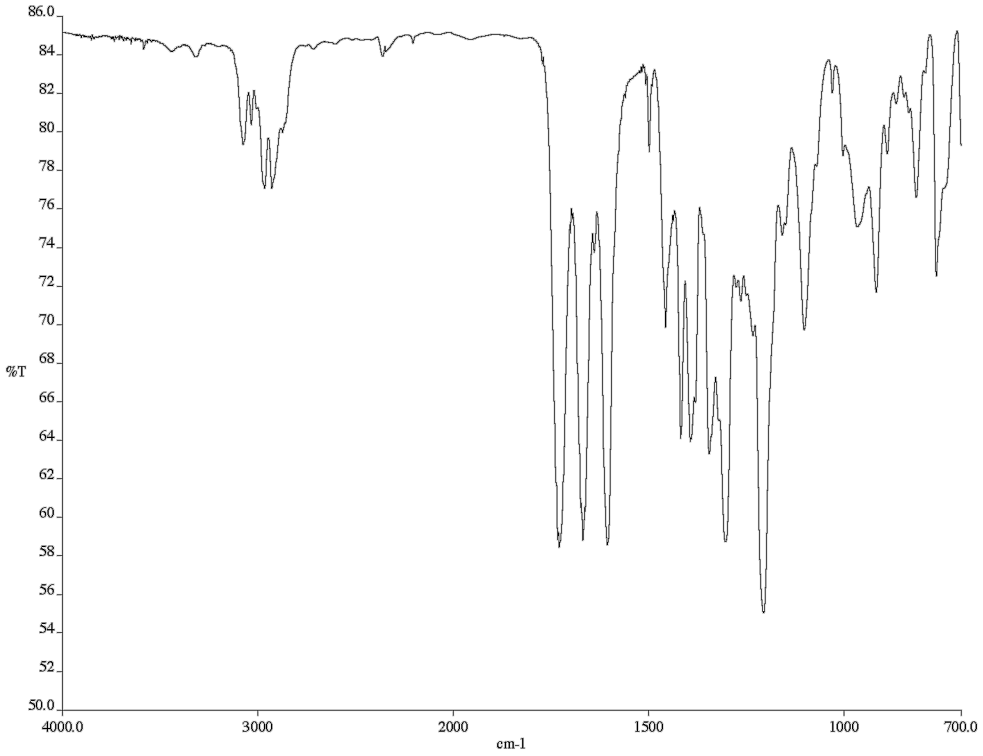


Figure A1.27.2. Infrared spectrum (thin film/NaCl) of compound **30a**.

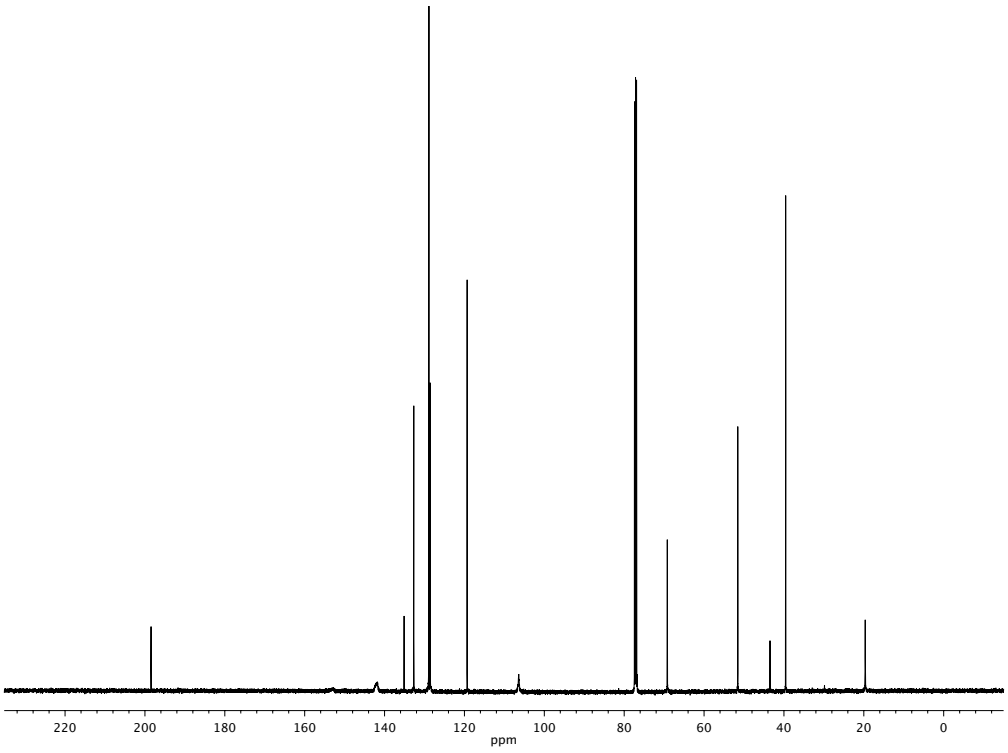


Figure A1.27.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **30a**.

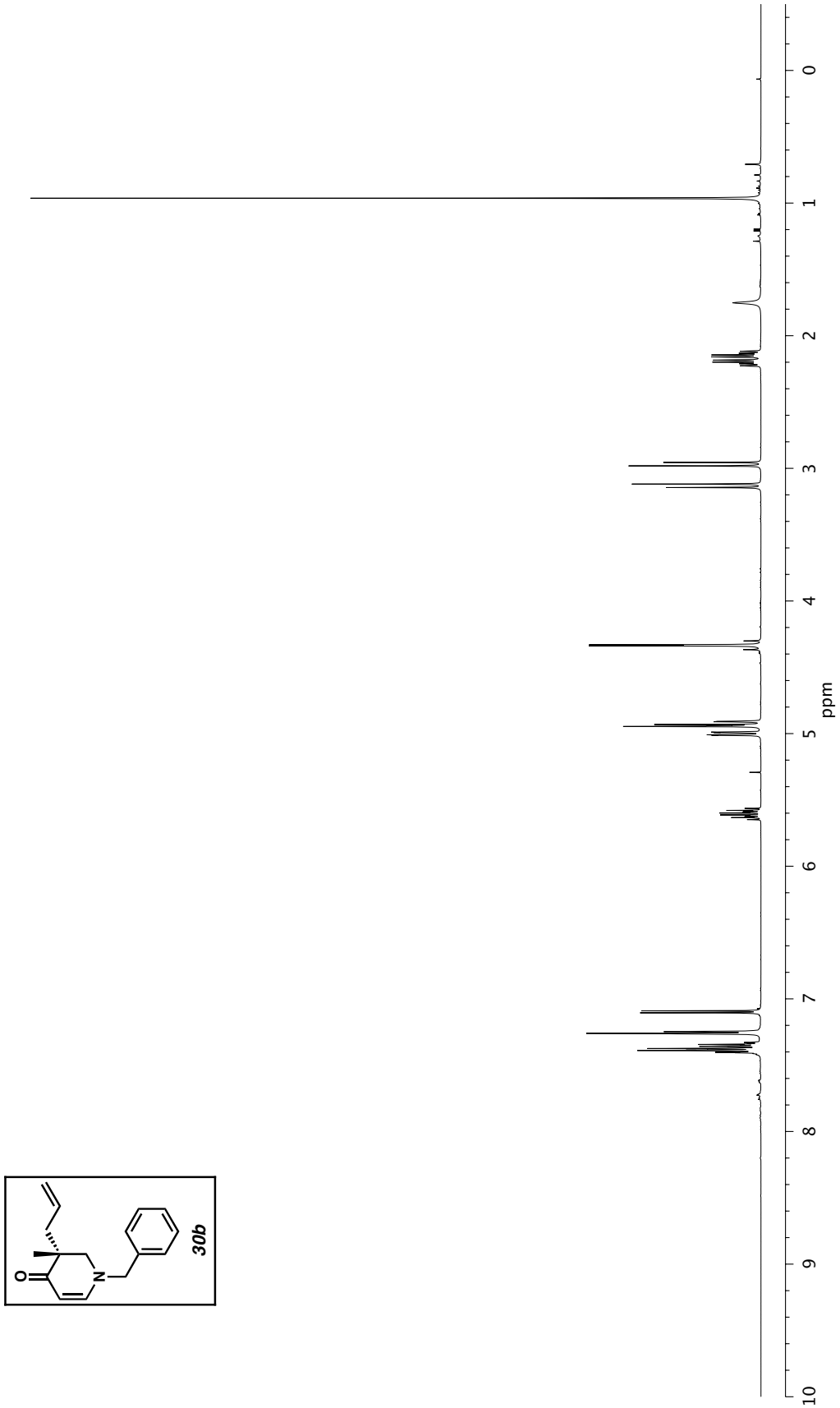


Figure A1.28.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **30b**.

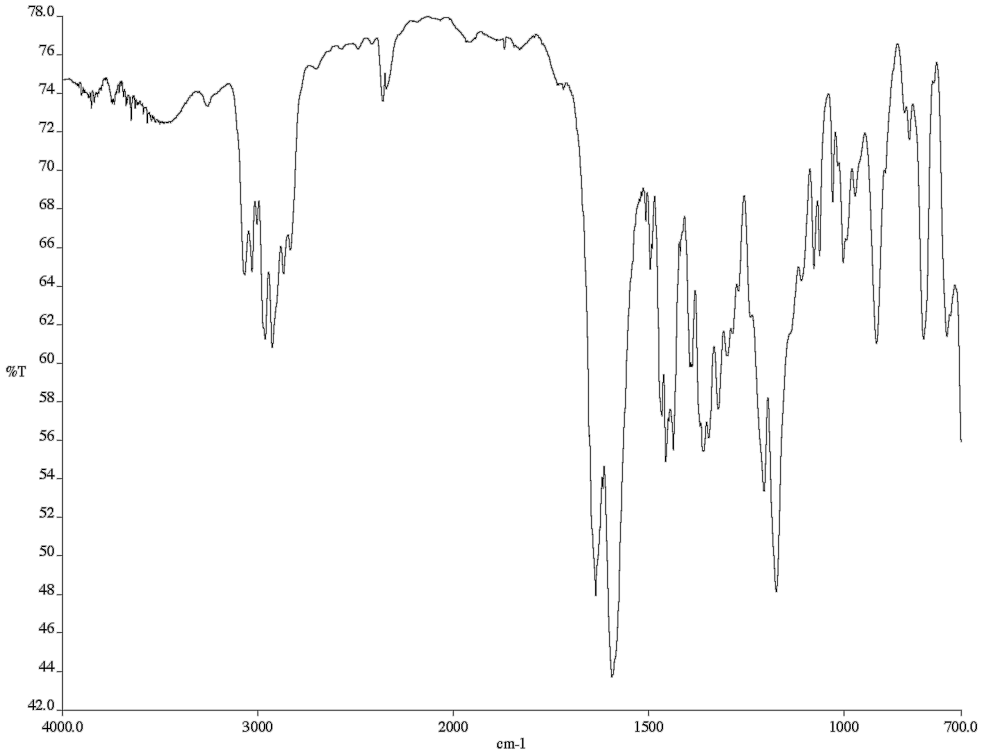


Figure A1.28.2. Infrared spectrum (thin film/NaCl) of compound **30b**.

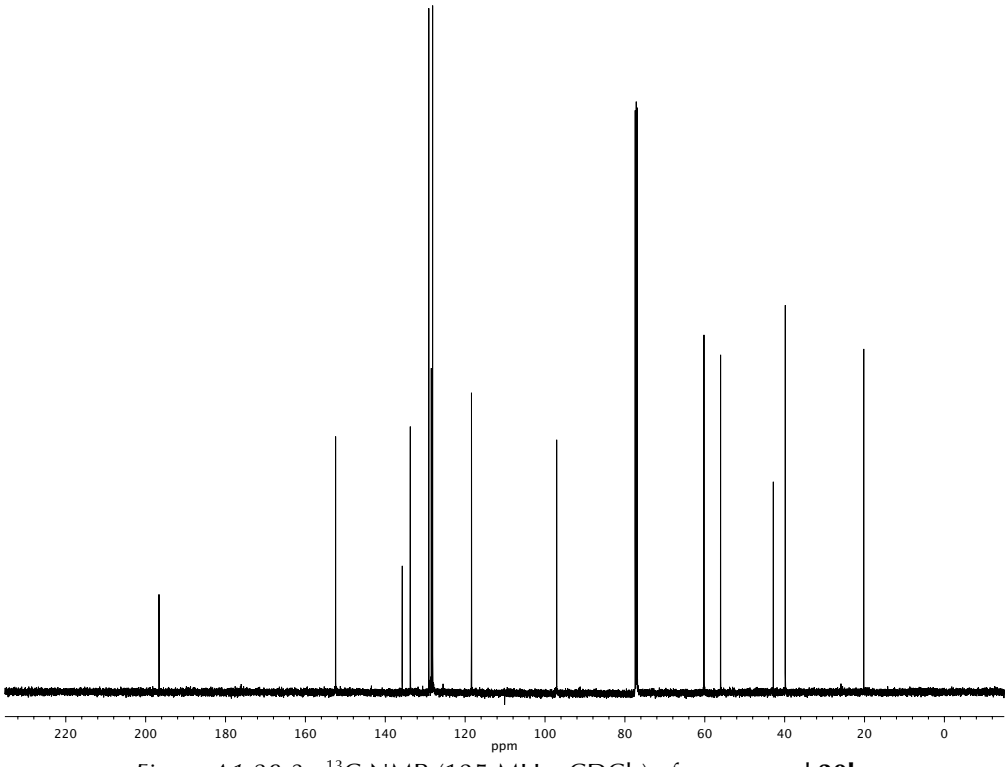


Figure A1.28.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **30b**.

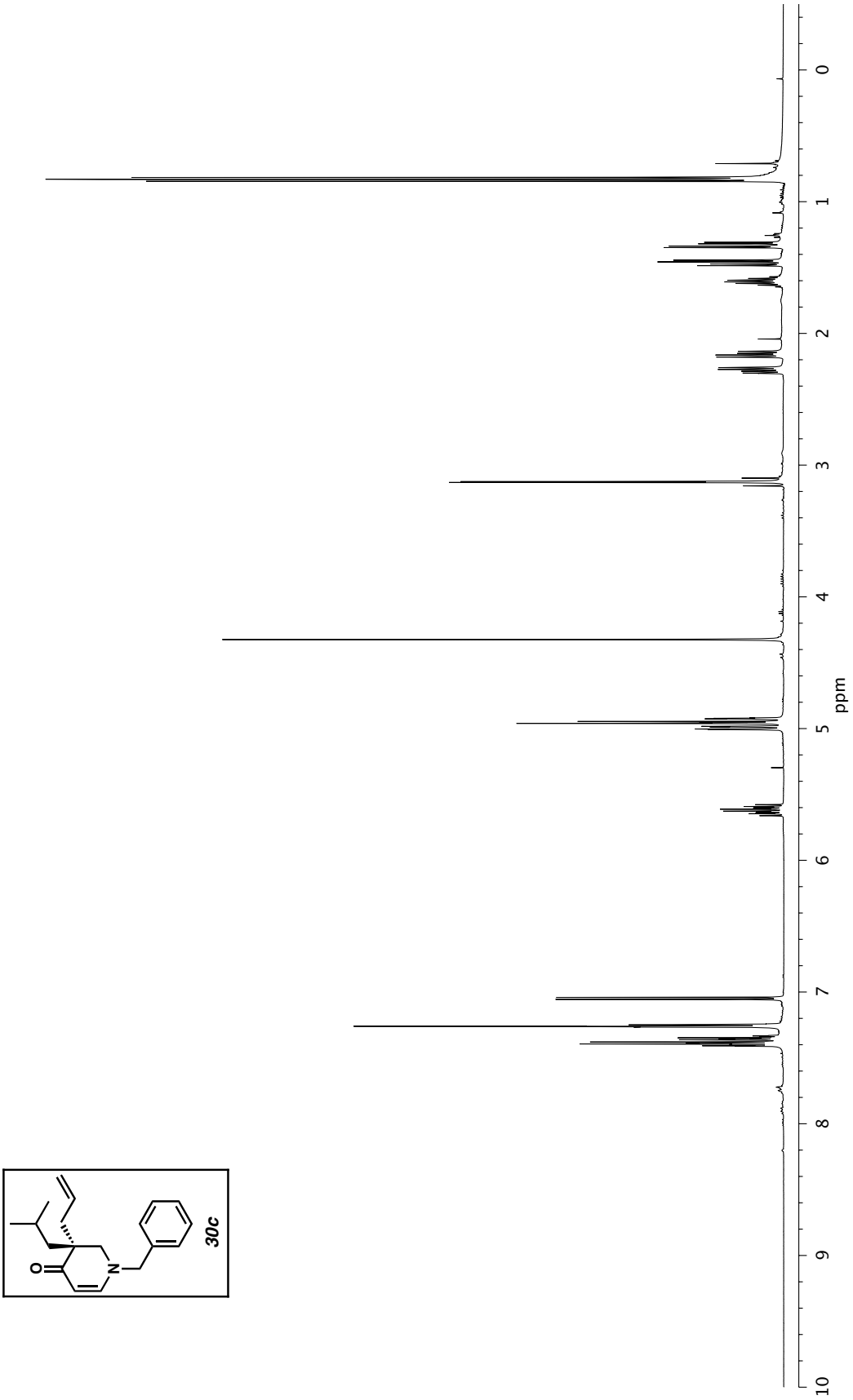


Figure A1.29.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **30c**.

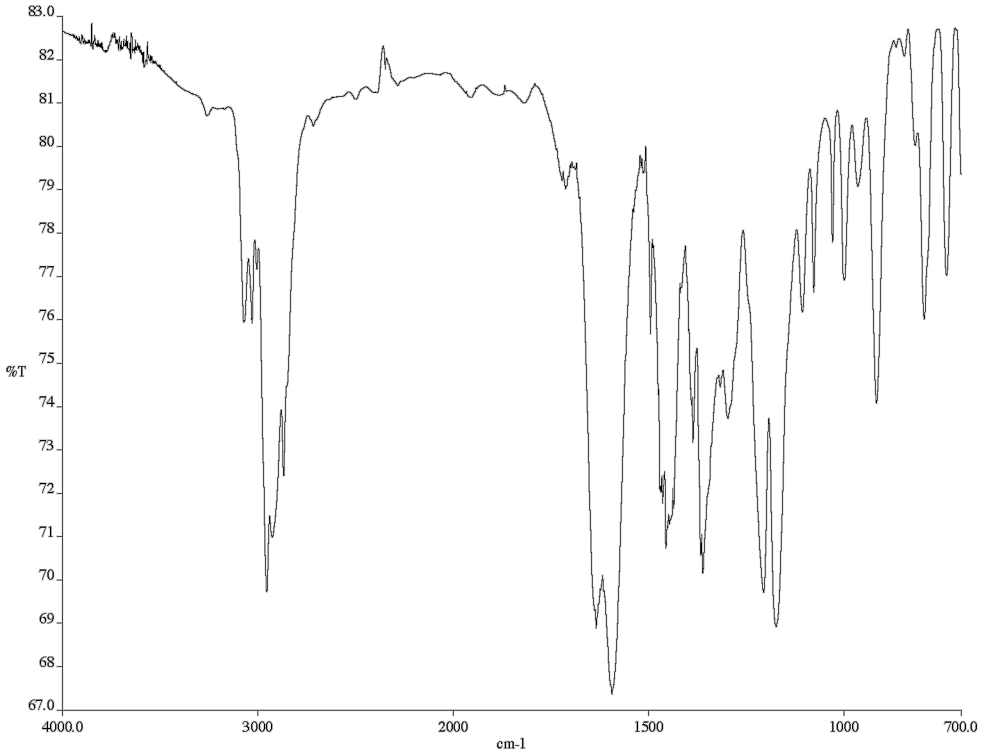


Figure A1.29.2. Infrared spectrum (thin film/NaCl) of compound **30c**.

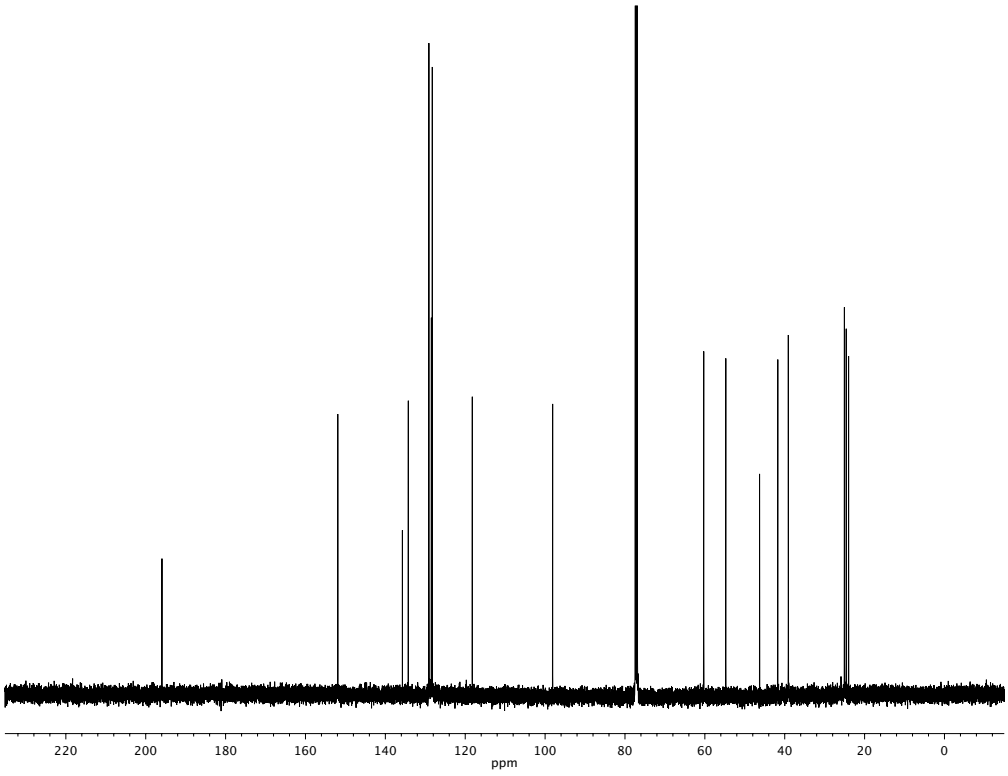


Figure A1.29.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **30c**.

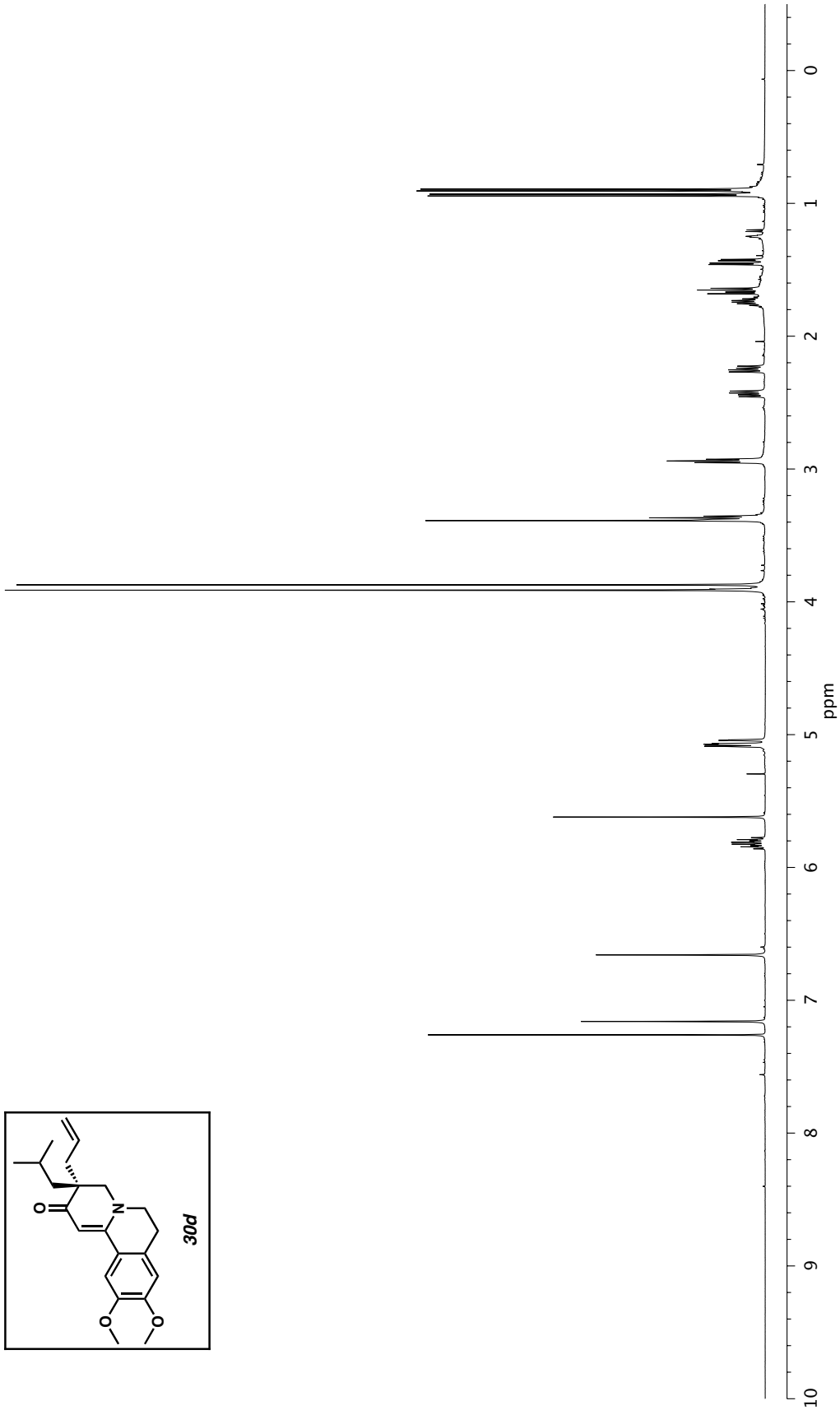


Figure A1.30.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **30d**.

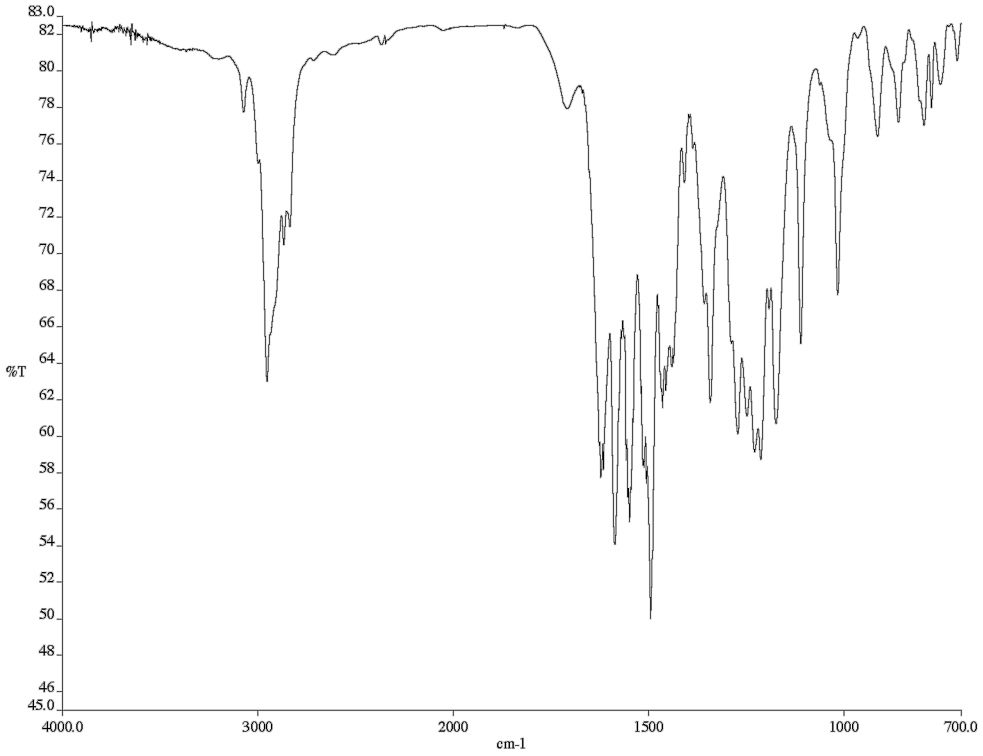


Figure A1.30.2. Infrared spectrum (thin film/NaCl) of compound **30d**.

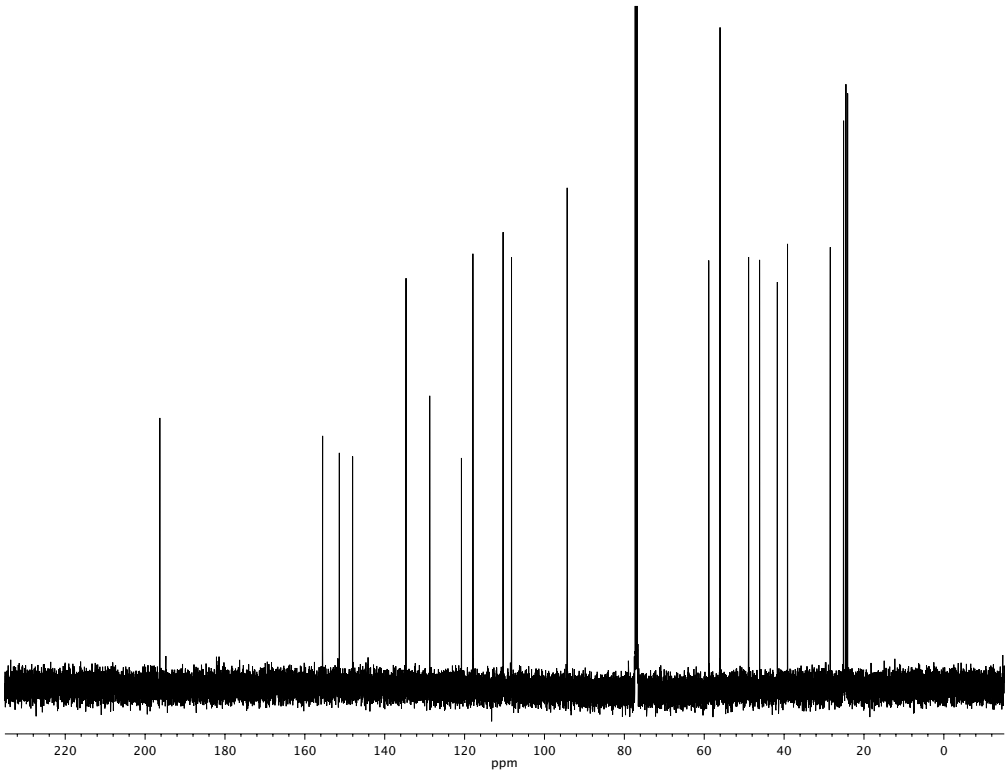


Figure A1.30.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **30d**.

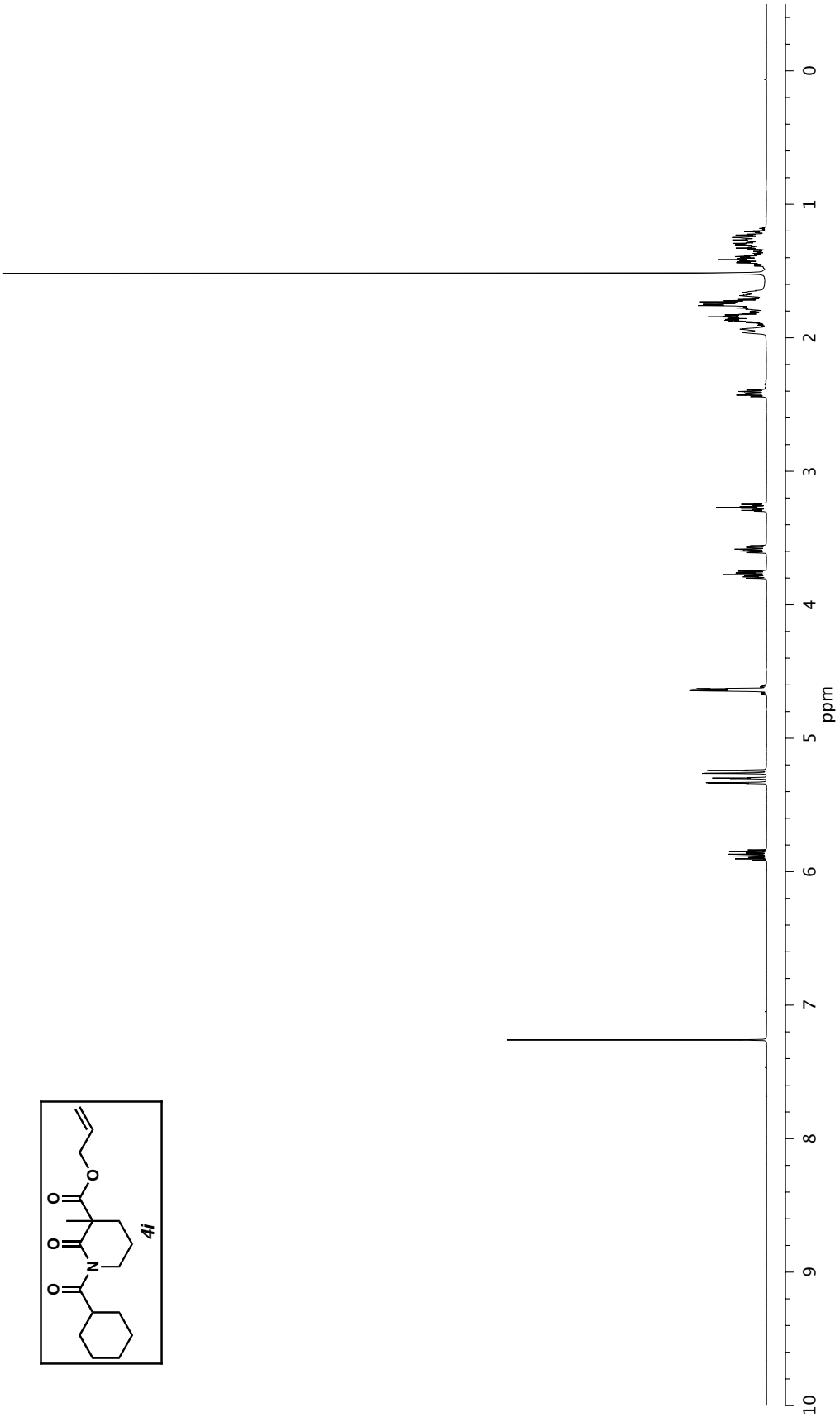


Figure A1.31.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4i**.

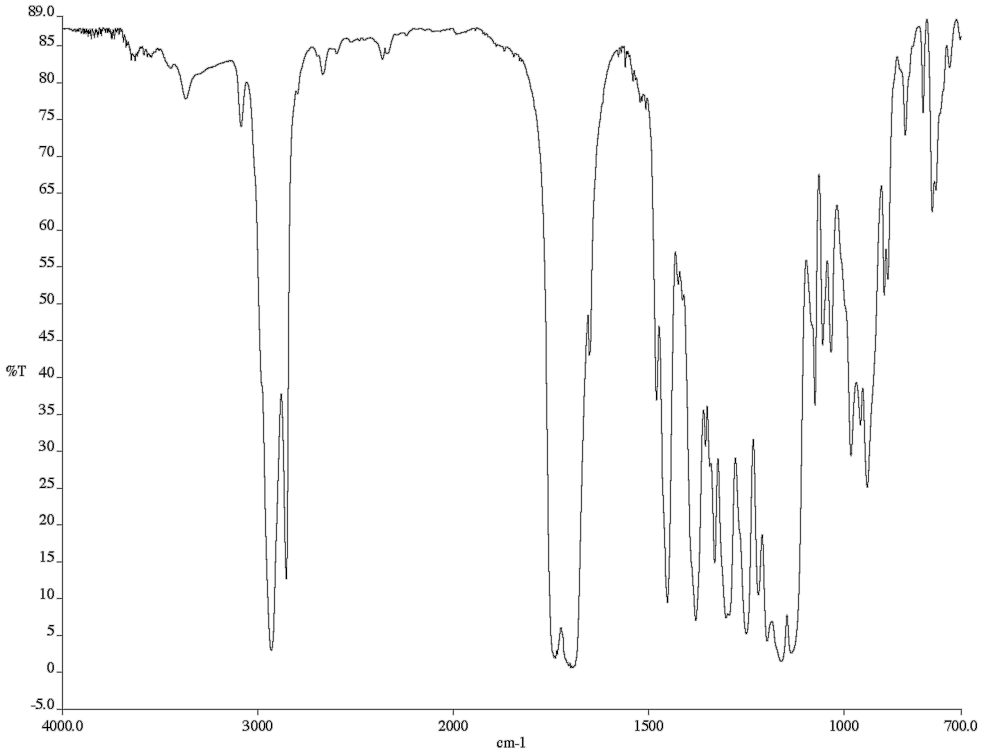


Figure A1.31.2. Infrared spectrum (thin film/NaCl) of compound **4i**.

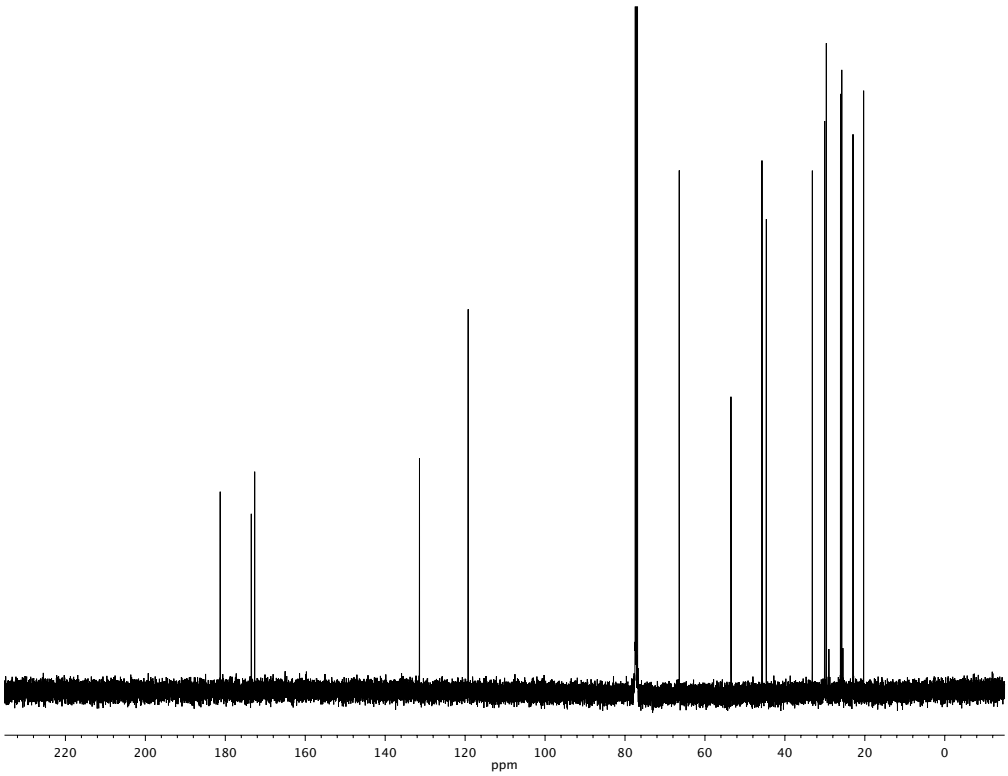


Figure A1.31.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4i**.

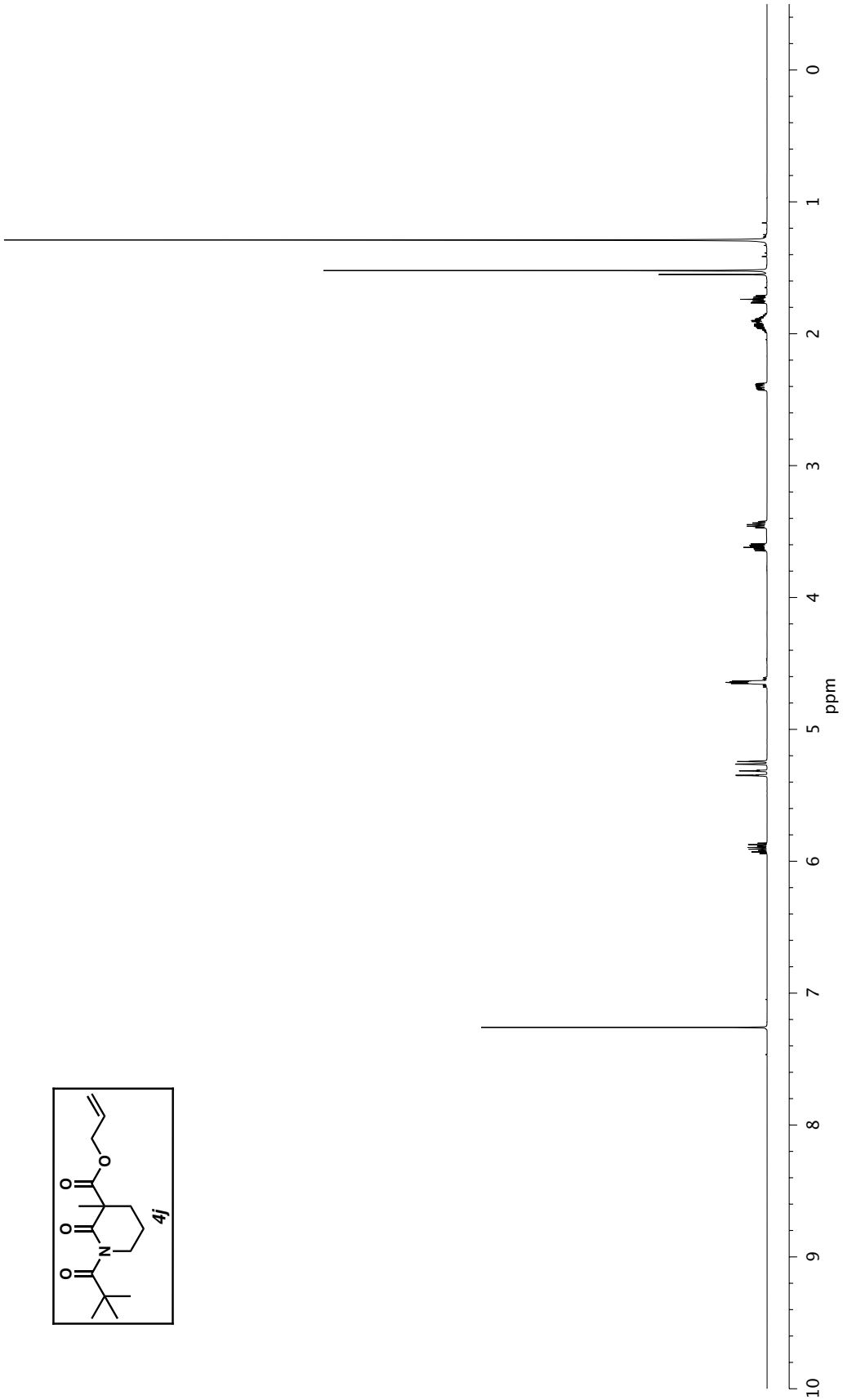


Figure A1.32.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4j**.

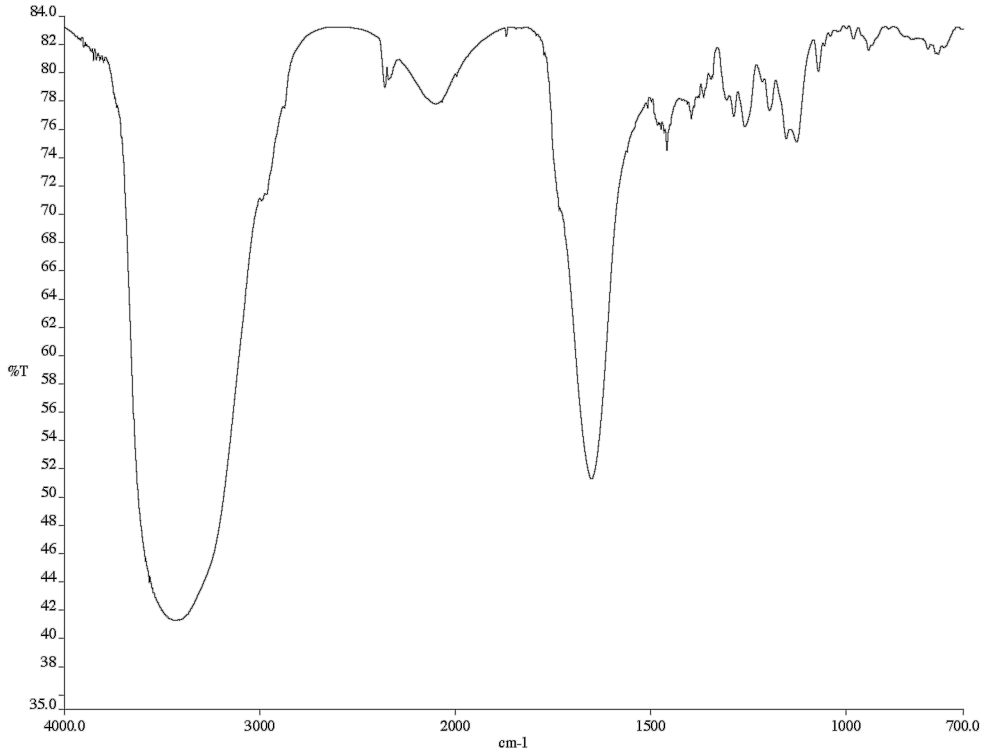


Figure A1.32.2. Infrared spectrum (thin film/NaCl) of compound **4j**.

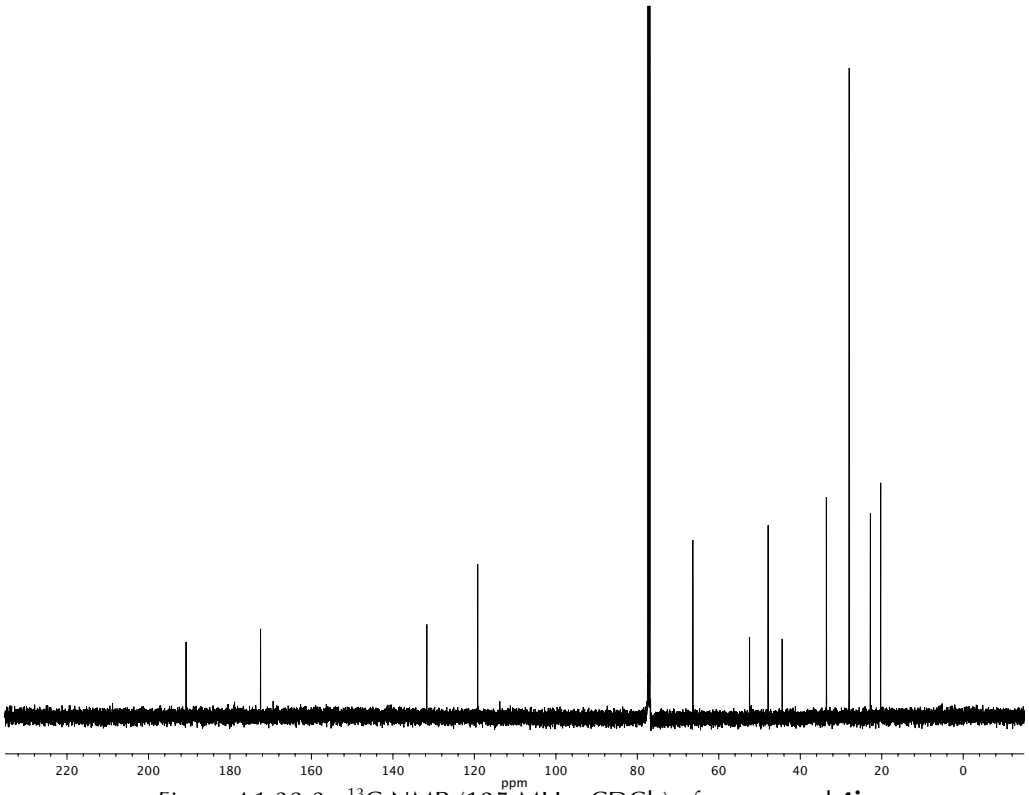


Figure A1.32.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **4j**.

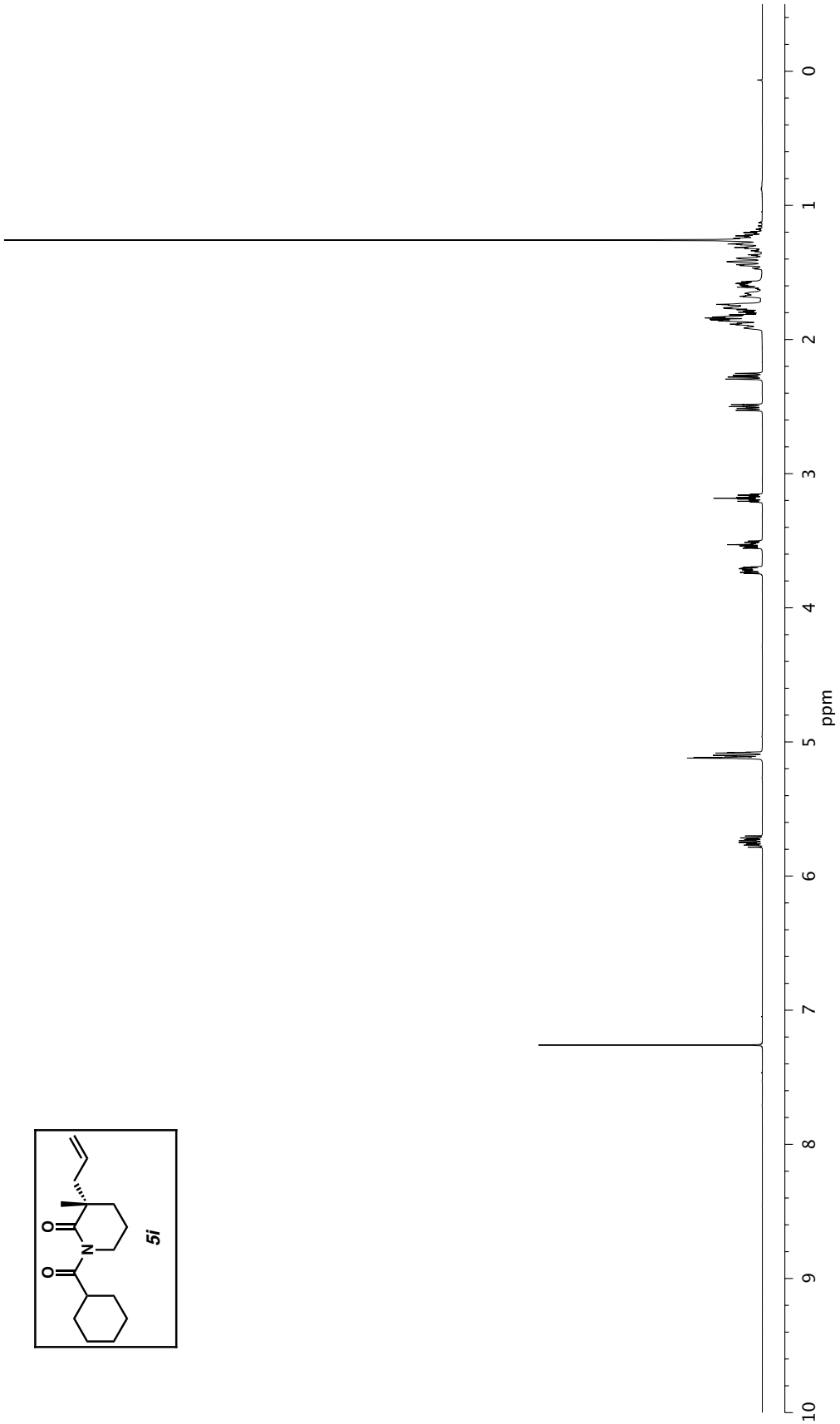


Figure A1.33.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5i**.

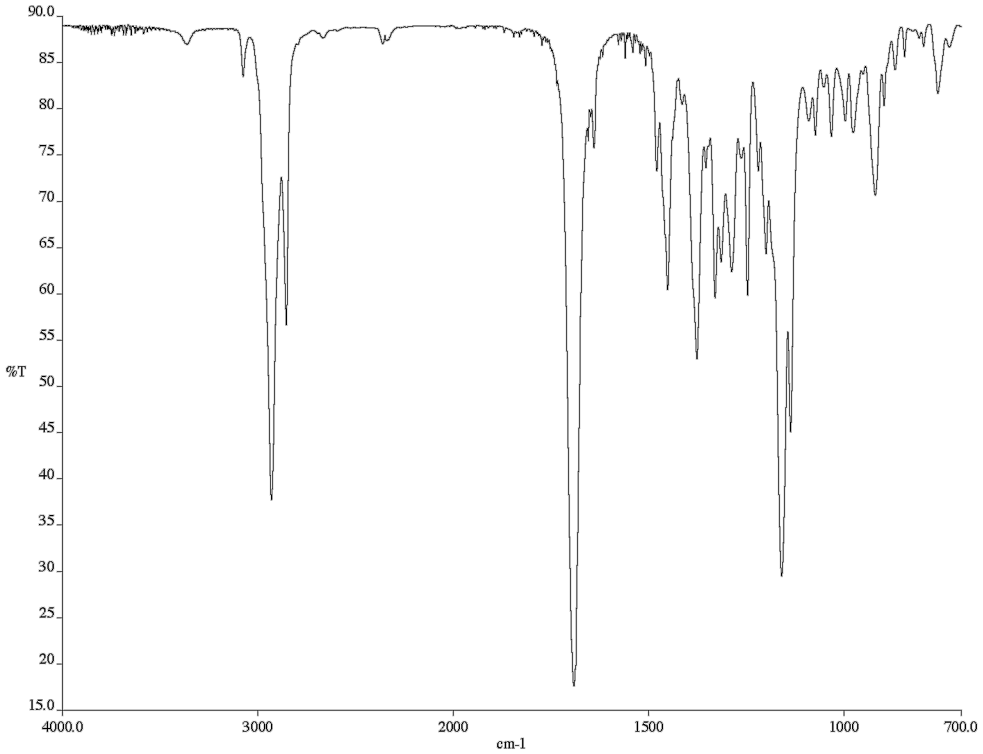


Figure A1.33.2. Infrared spectrum (thin film/NaCl) of compound **5i**.

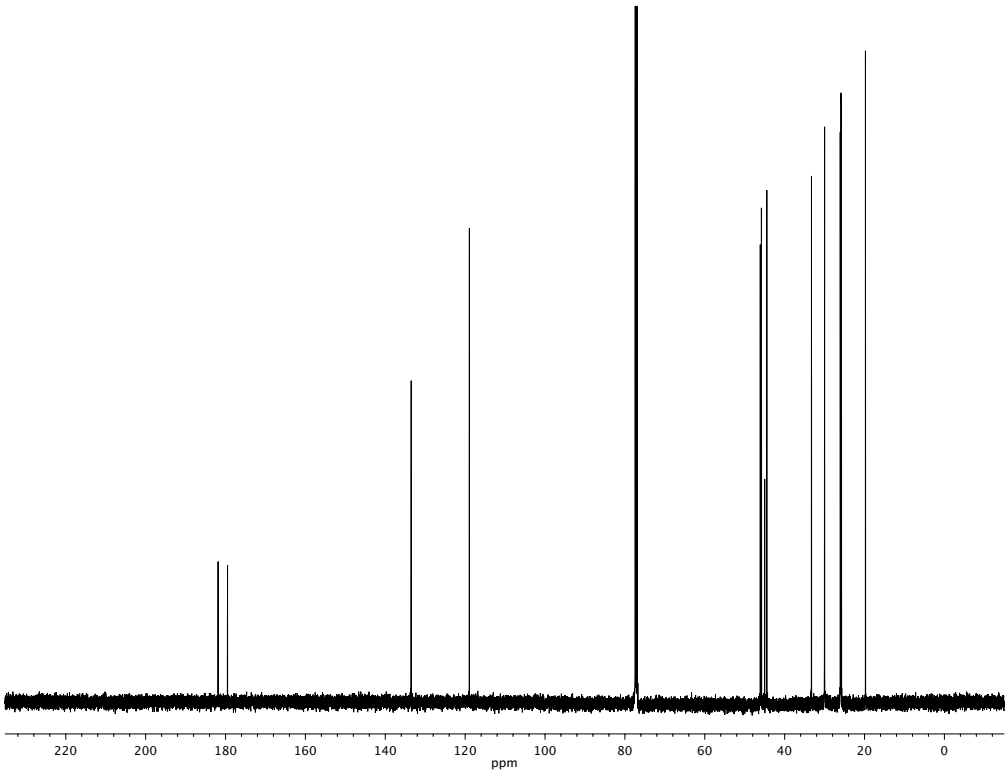


Figure A1.33.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **5i**.

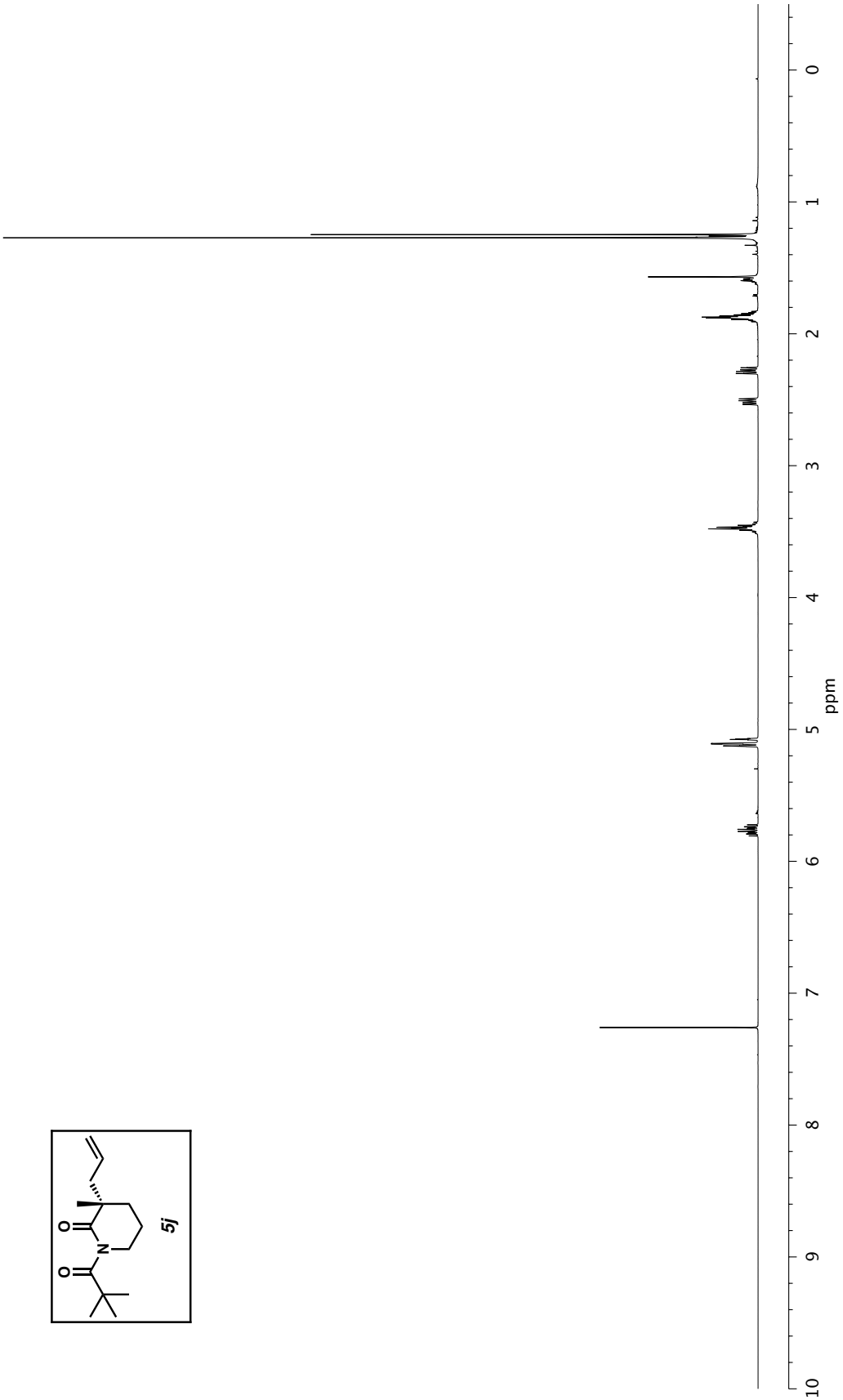


Figure A1.34.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **5j**.

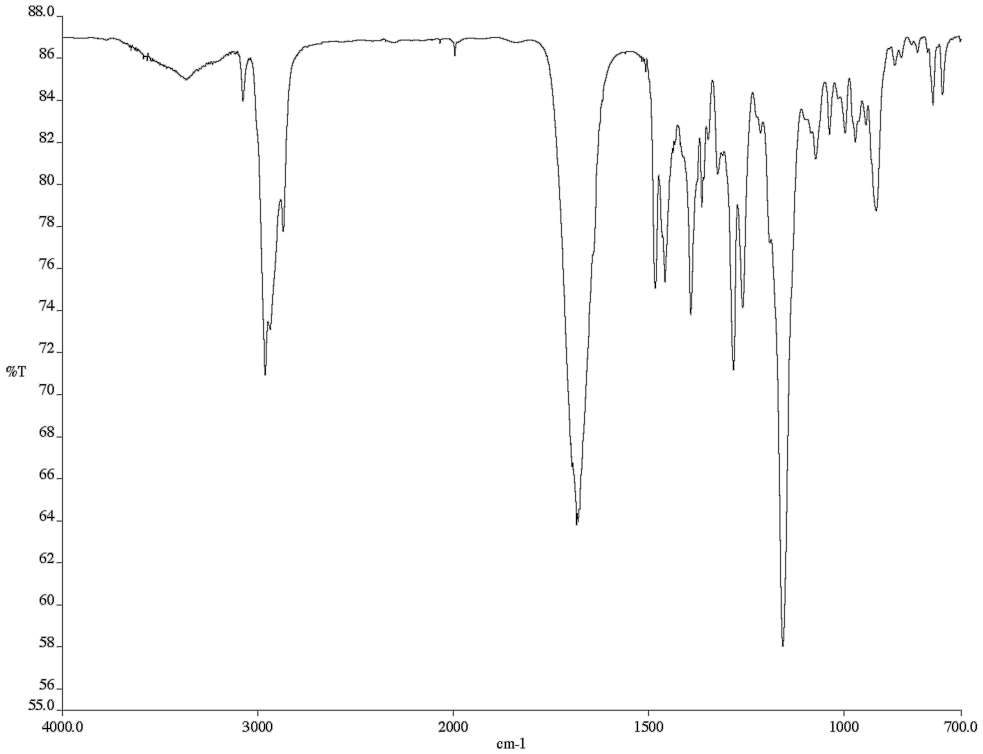


Figure A1.34.2. Infrared spectrum (thin film/NaCl) of compound **5j**.

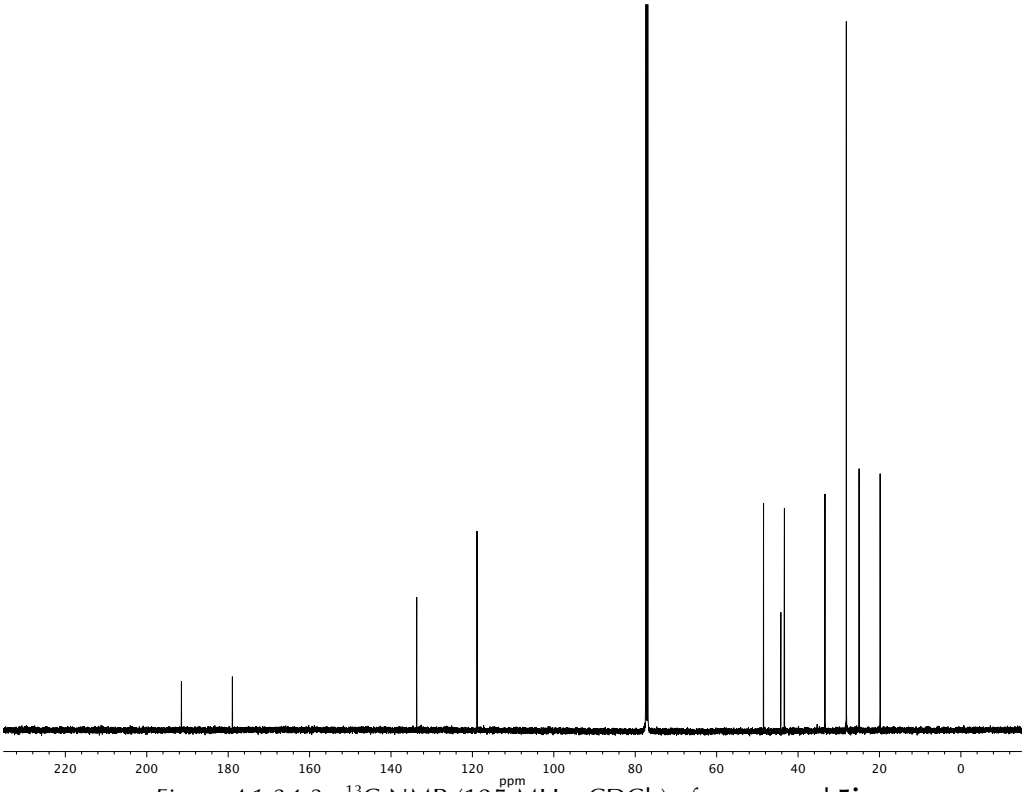


Figure A1.34.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **5j**.

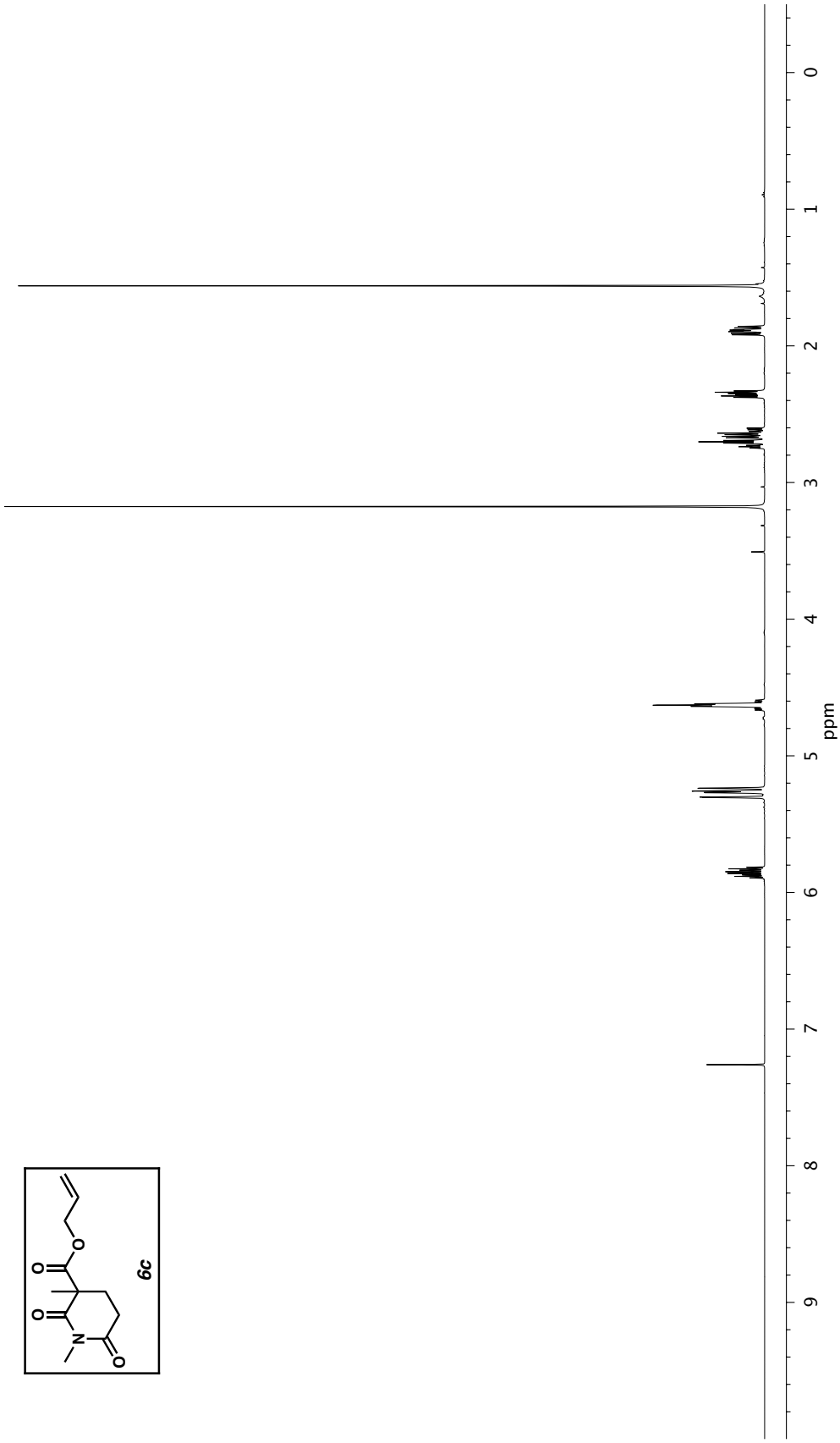


Figure A1.35.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **6c**.

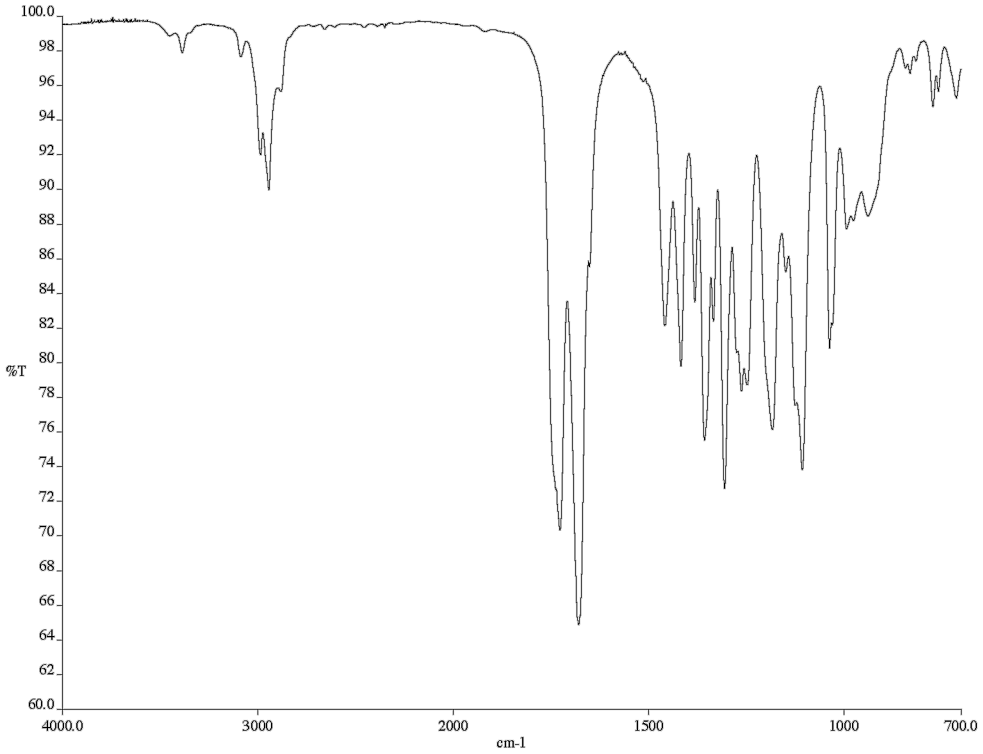


Figure A1.35.2. Infrared spectrum (thin film/NaCl) of compound **6c**.

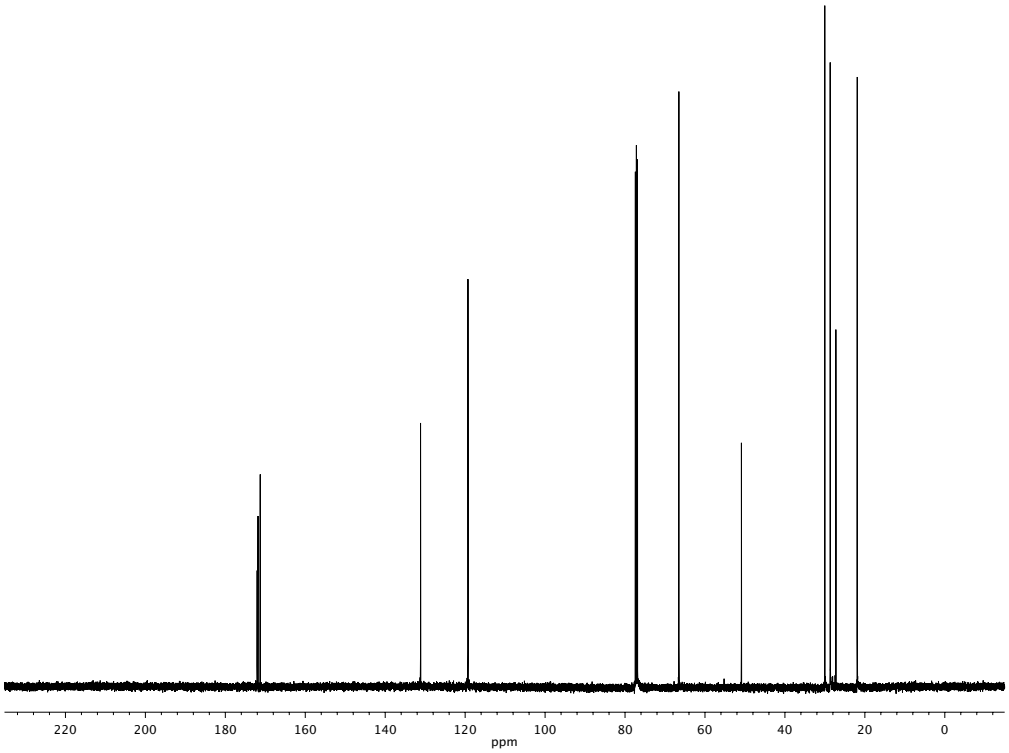


Figure A1.35.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **6c**.

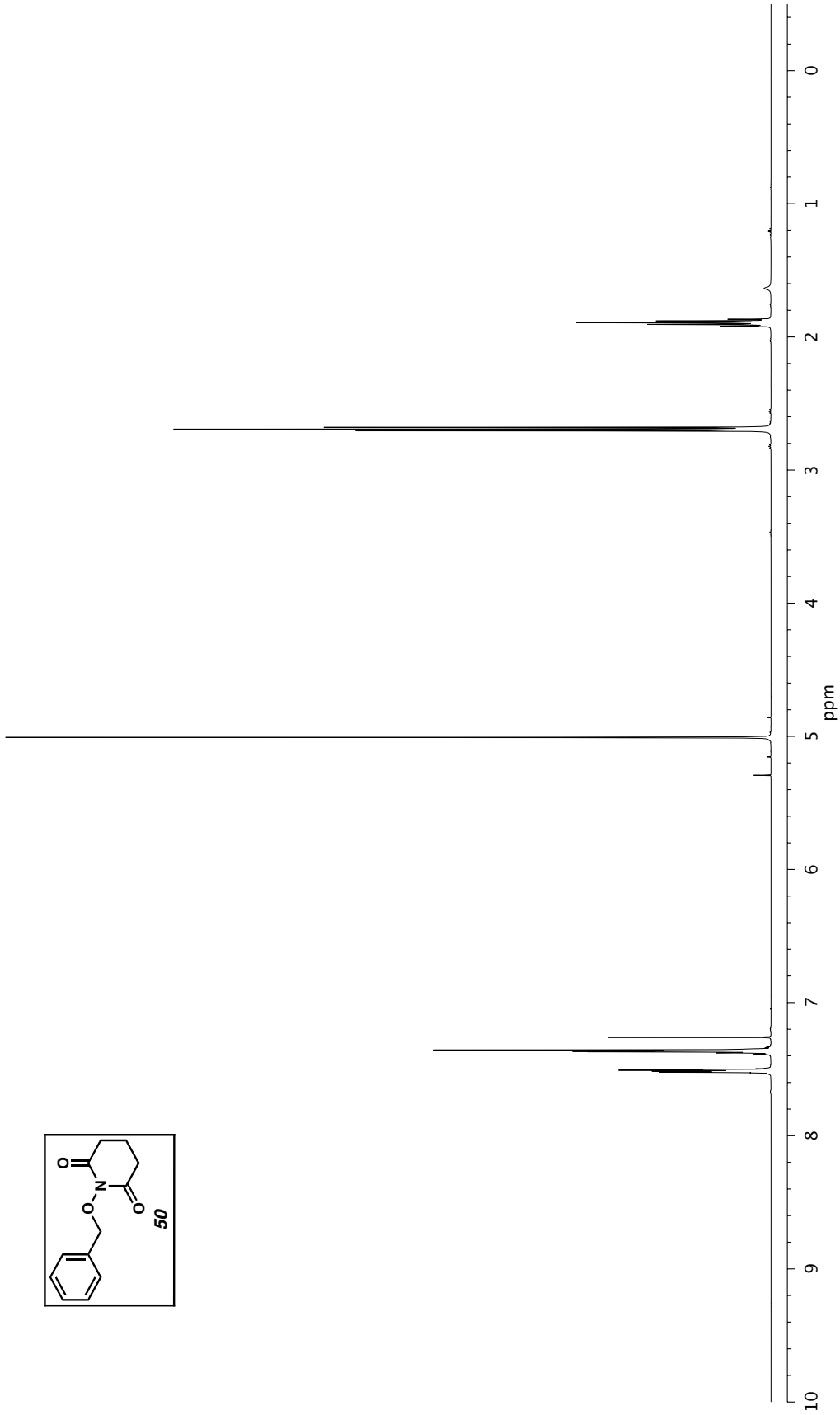


Figure A1.36.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **50**.

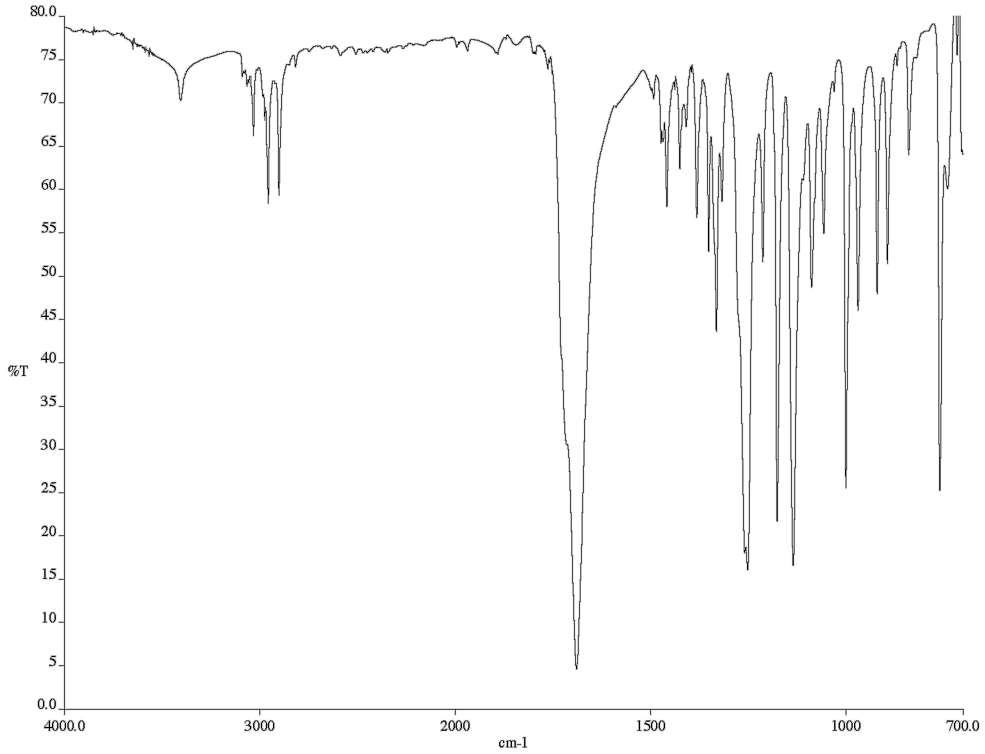


Figure A1.36.2. Infrared spectrum (thin film/NaCl) of compound **50**.

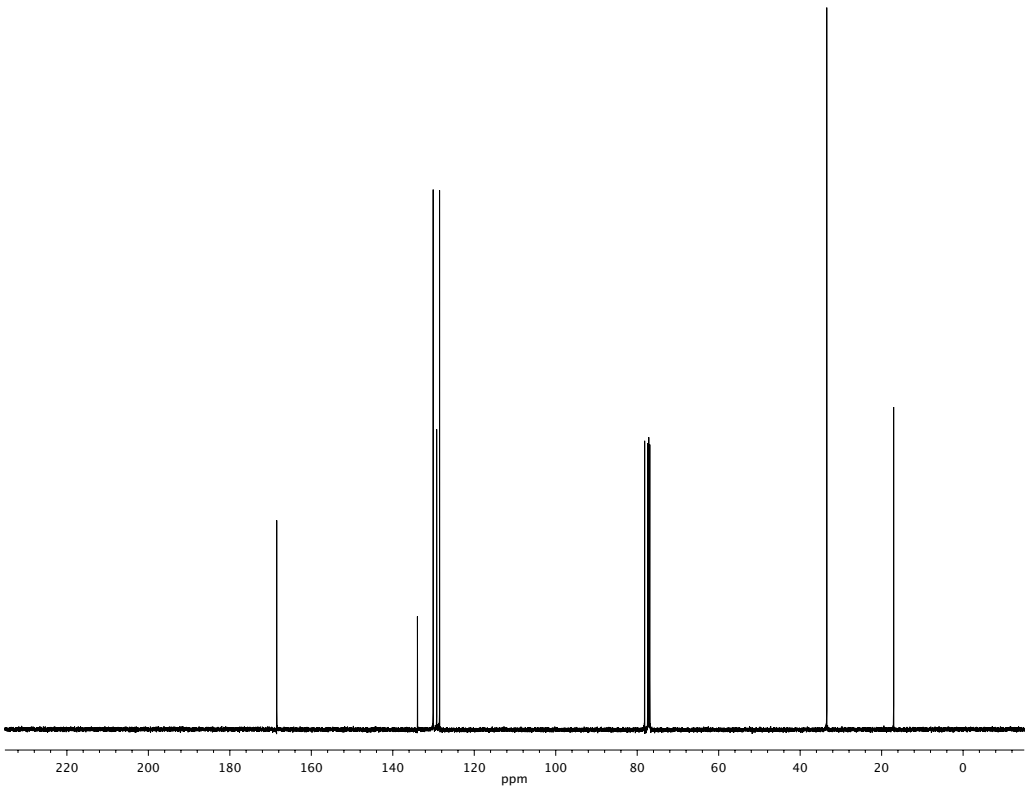


Figure A1.36.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **50**.

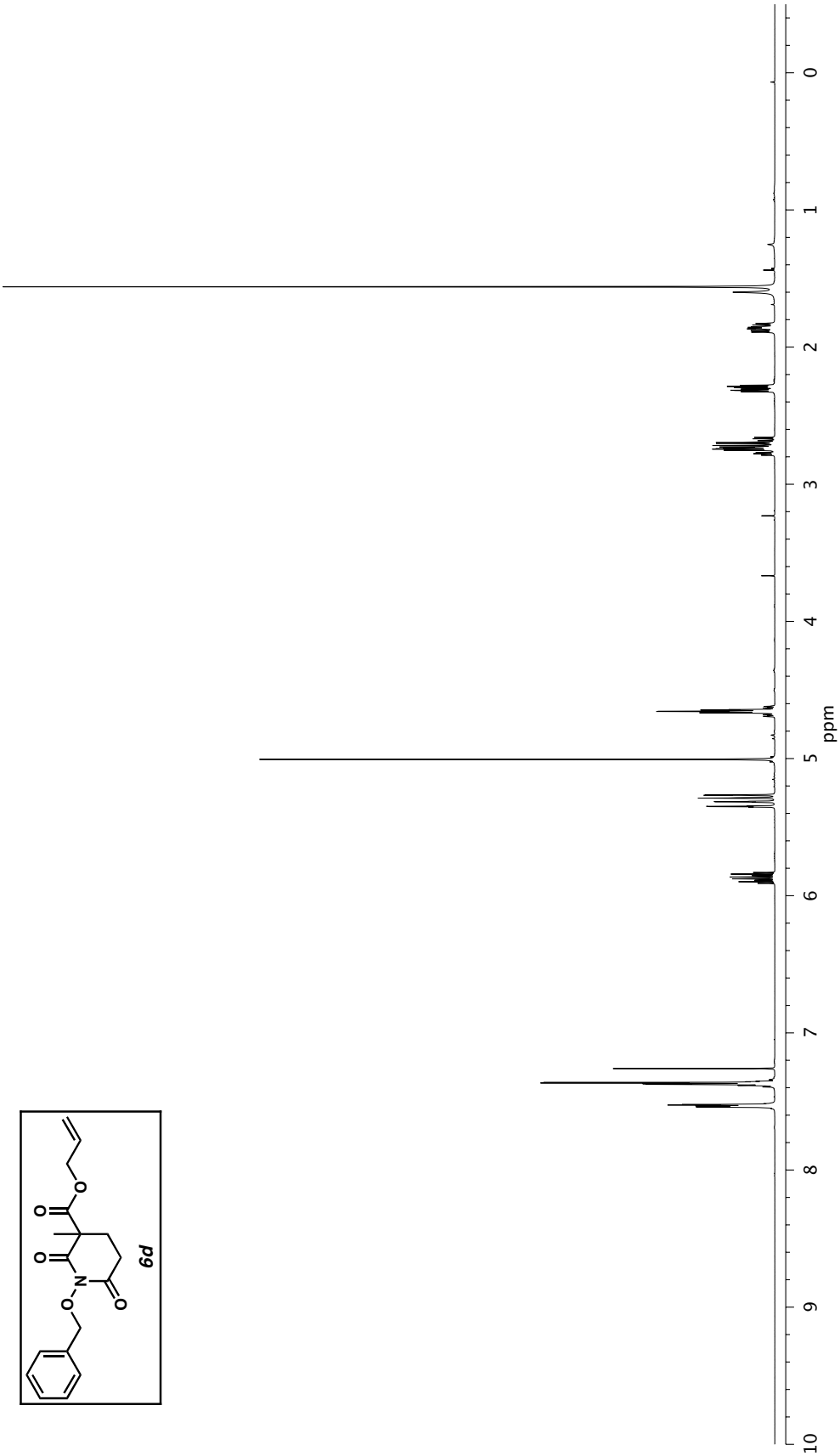


Figure A1.37.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **6d**.

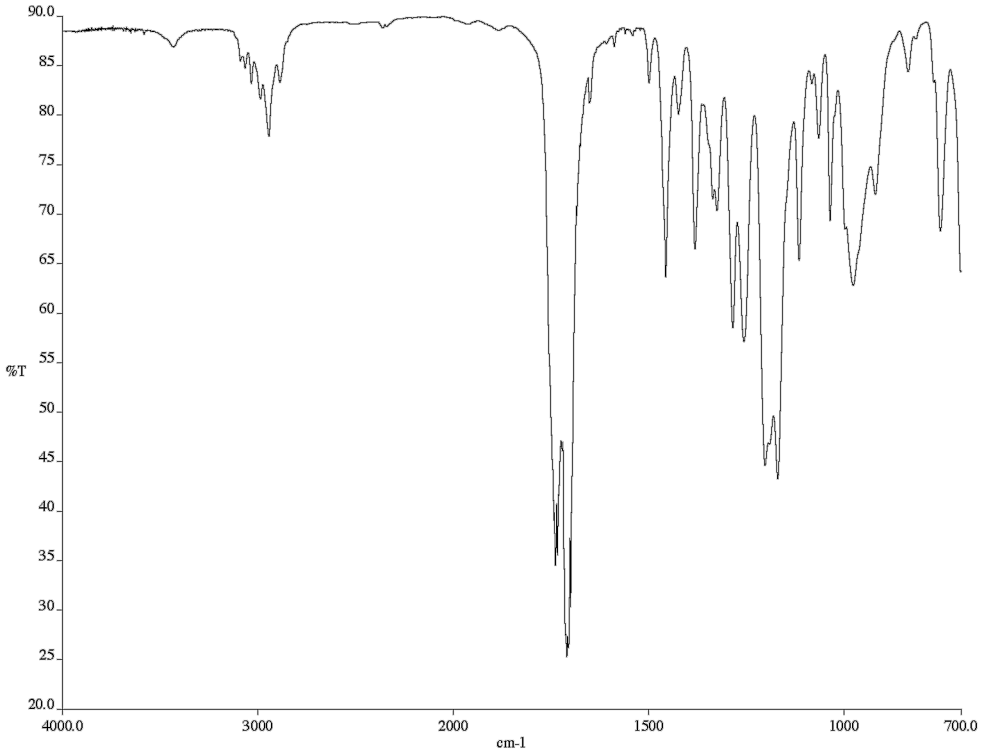


Figure A1.37.2. Infrared spectrum (thin film/NaCl) of compound **6d**.

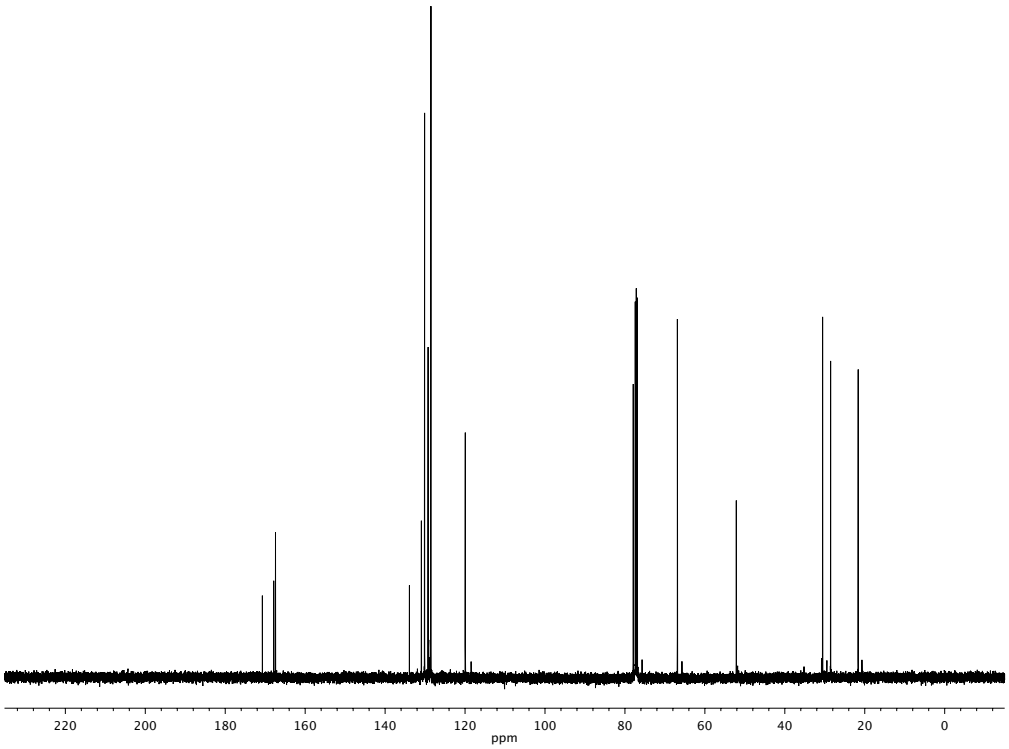


Figure A1.37.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **6d**.

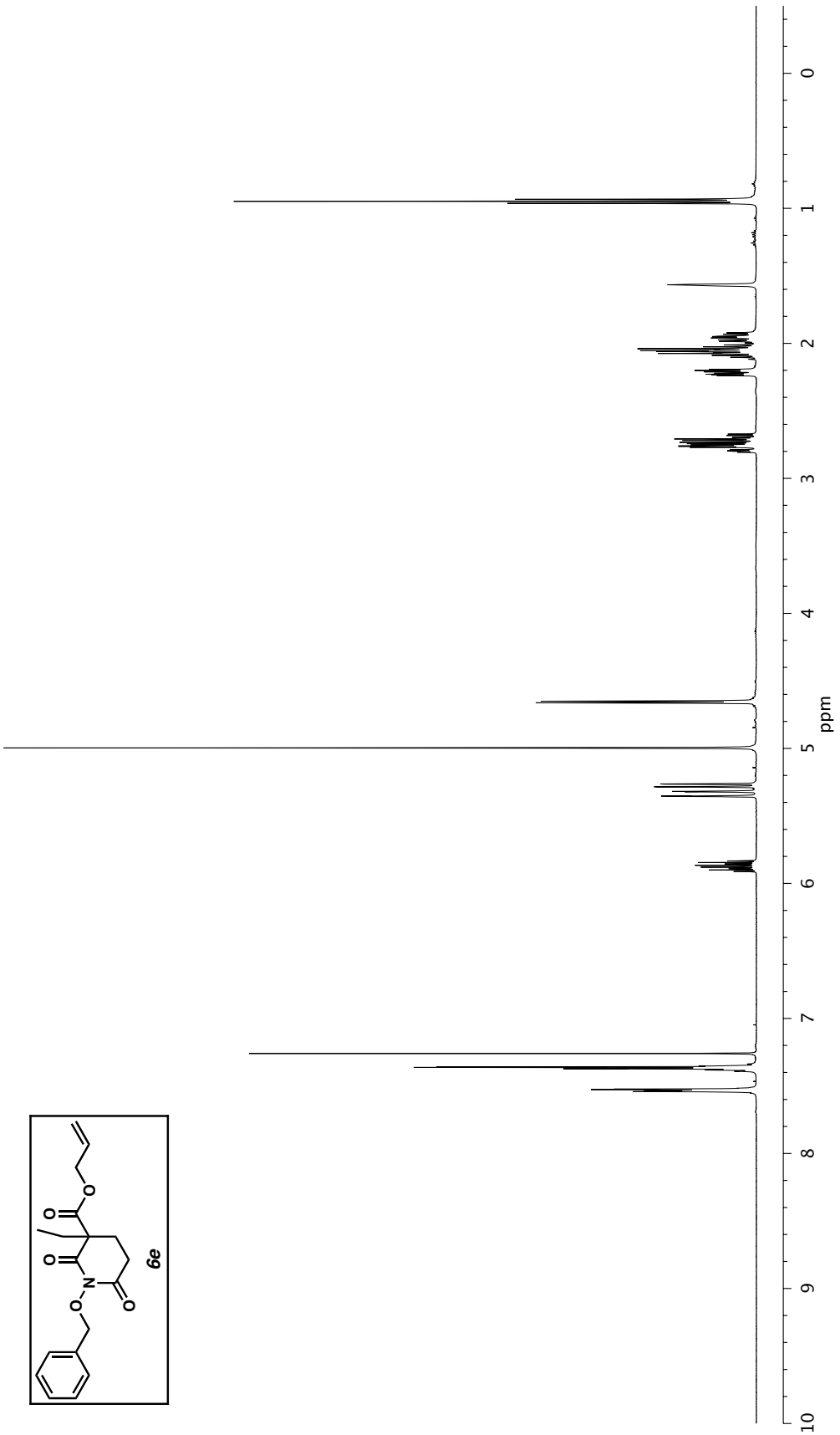


Figure A1.38.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **6e**.

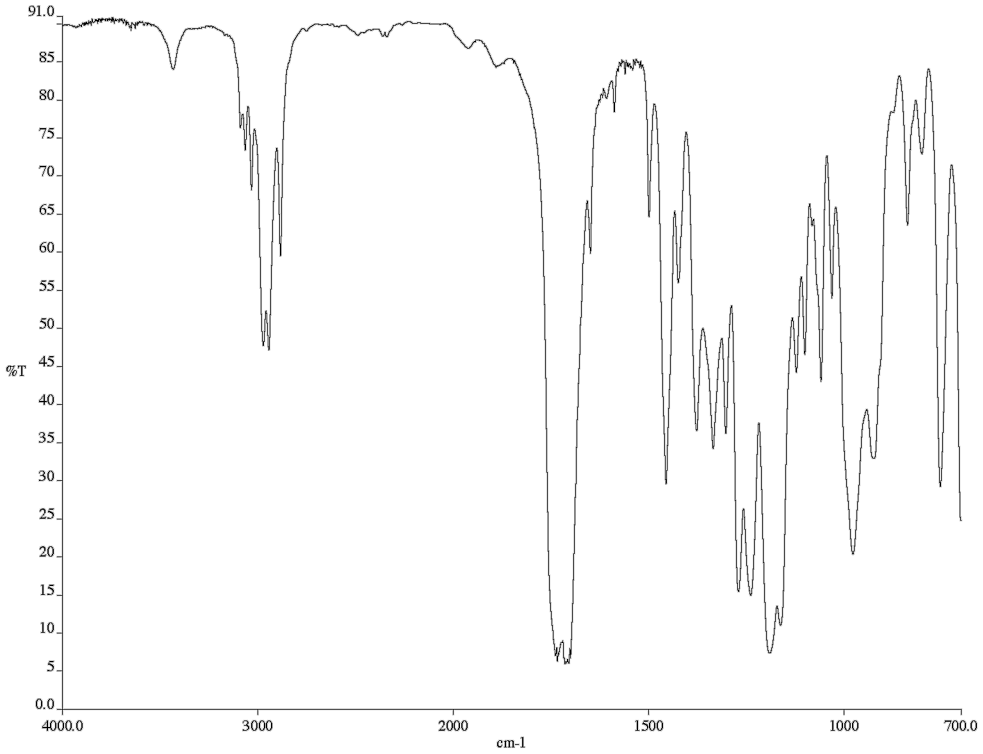


Figure A1.38.2. Infrared spectrum (thin film/NaCl) of compound **6e**.

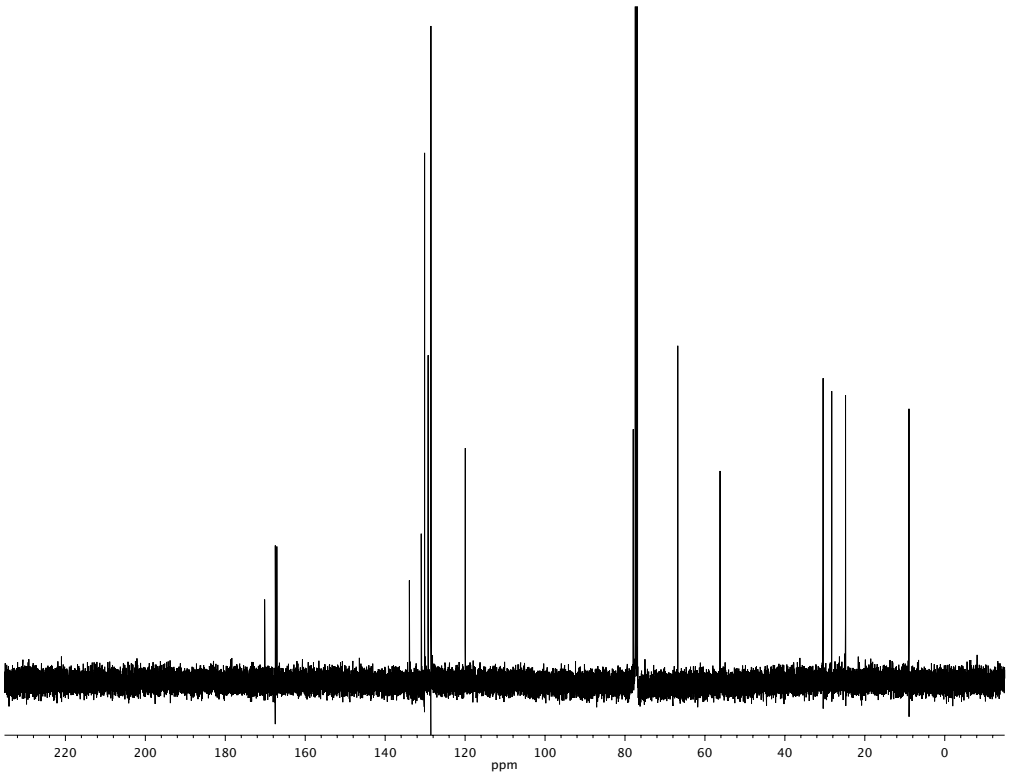


Figure A1.38.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **6e**.

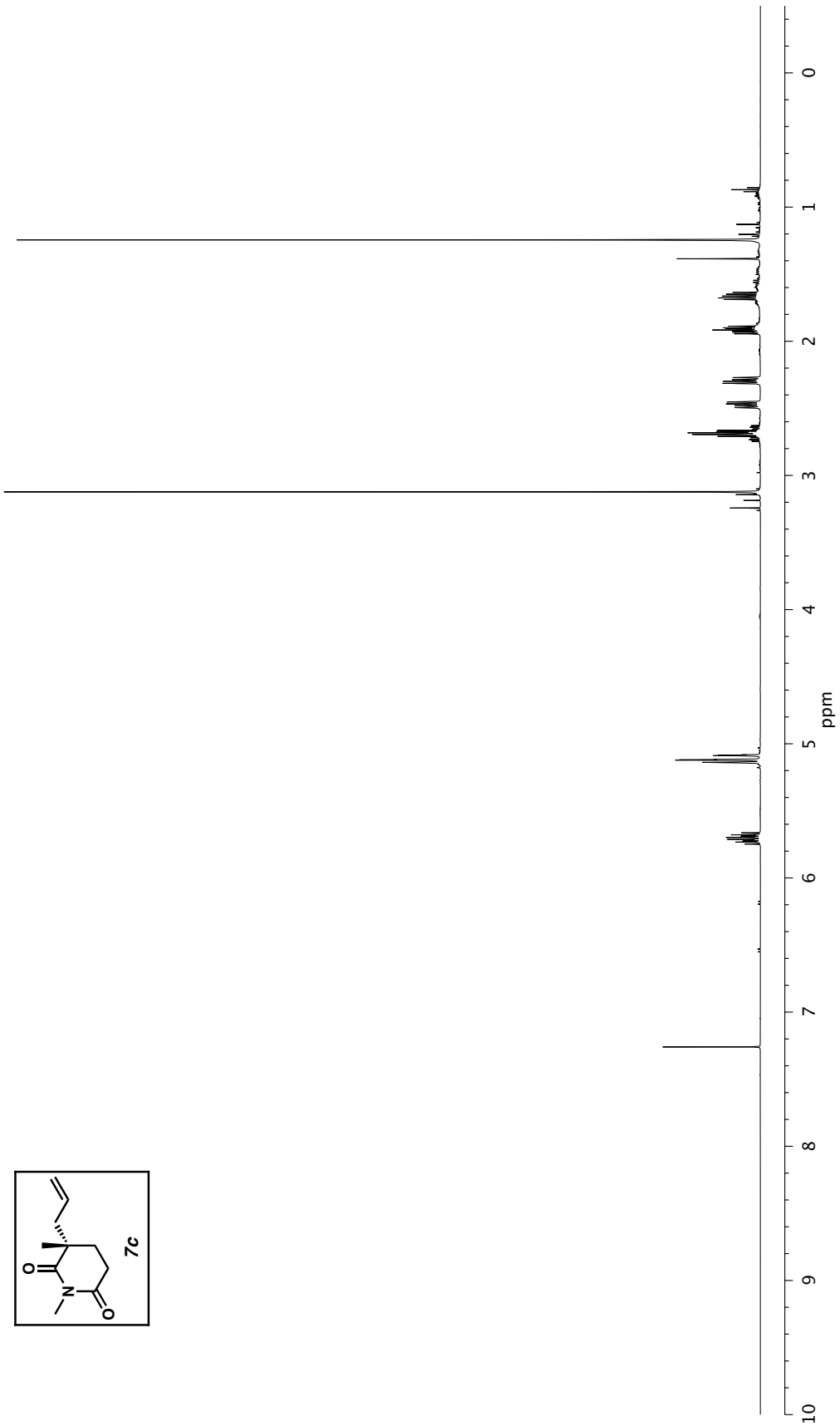


Figure A1.39.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **7c**.

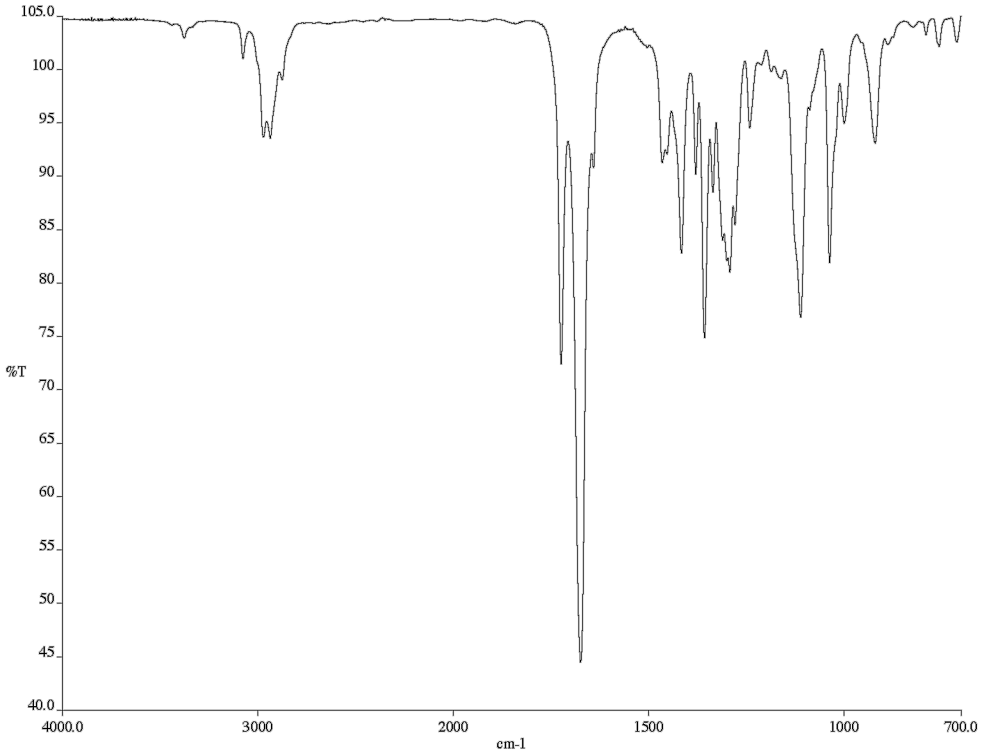


Figure A1.39.2. Infrared spectrum (thin film/NaCl) of compound **7c**.

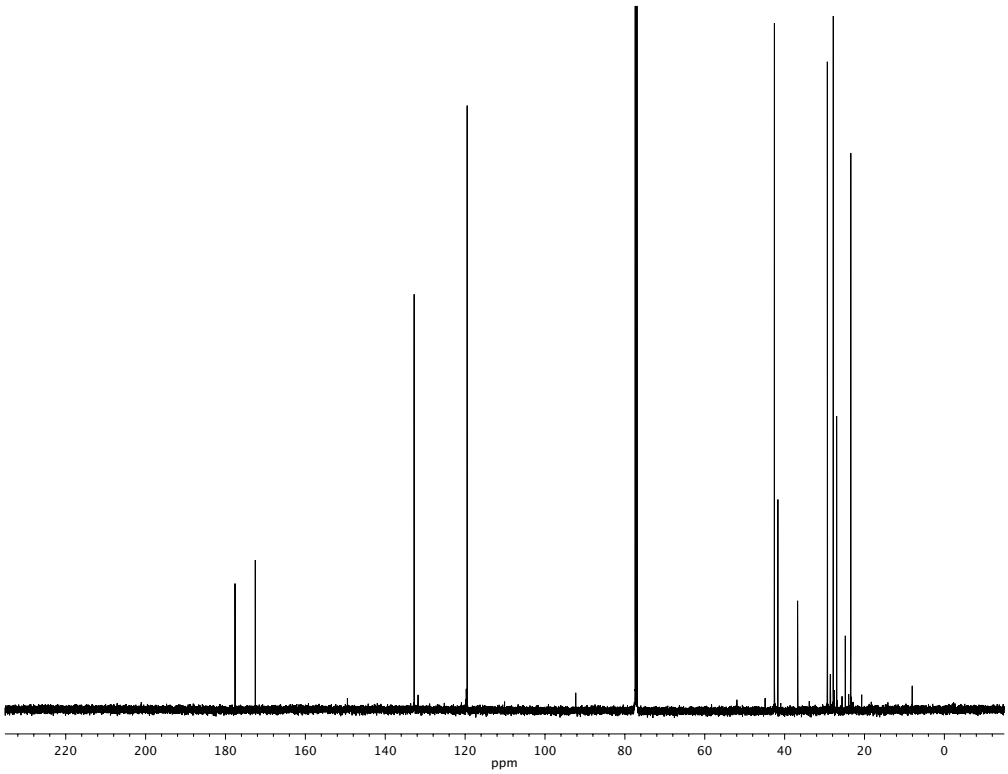


Figure A1.39.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **7c**.

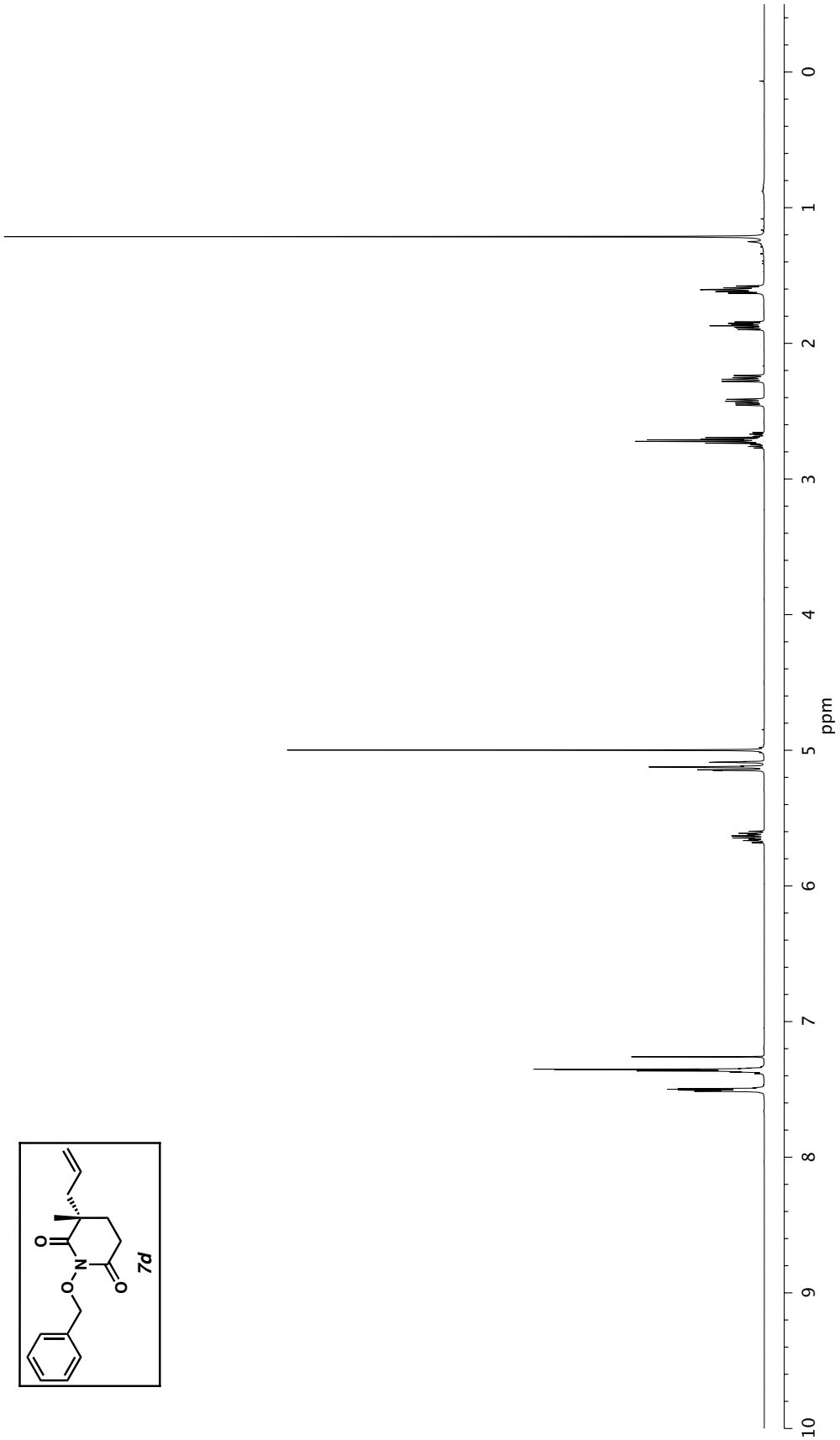


Figure A1.40.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **7d**.

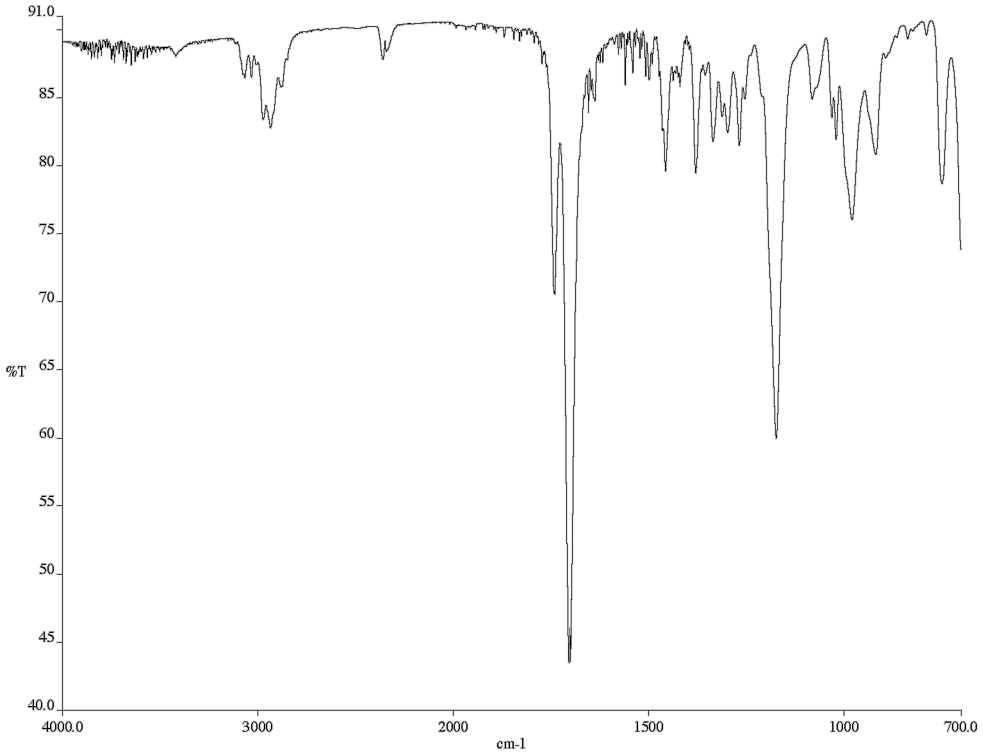


Figure A1.40.2. Infrared spectrum (thin film/NaCl) of compound **7d**.

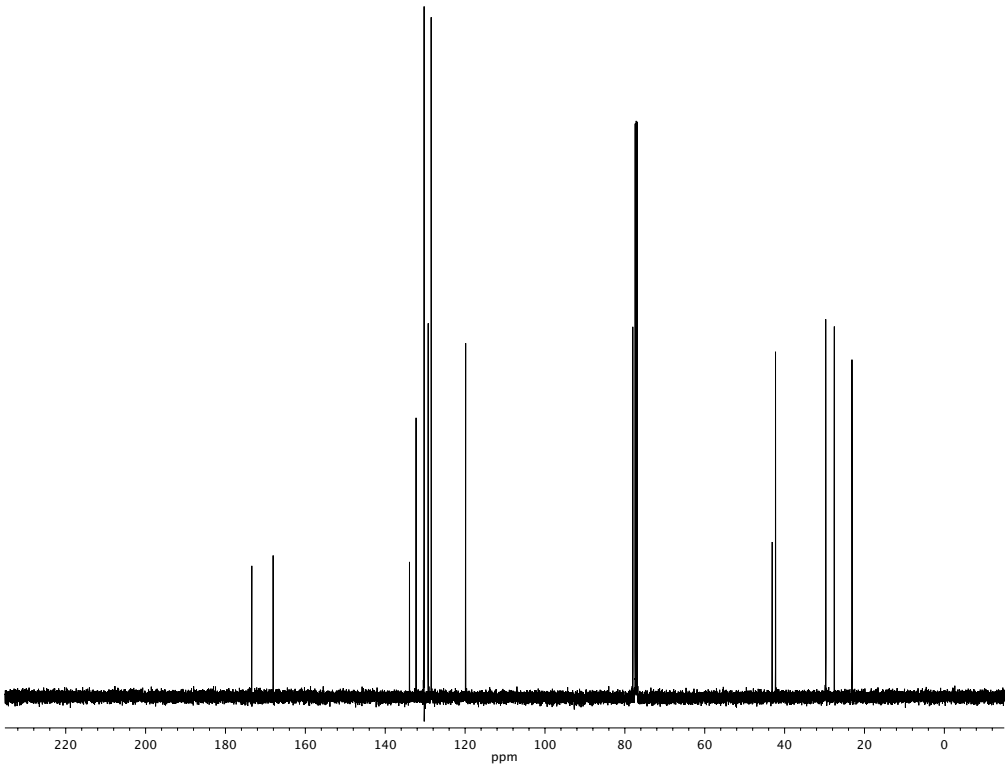


Figure A1.40.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **7d**.

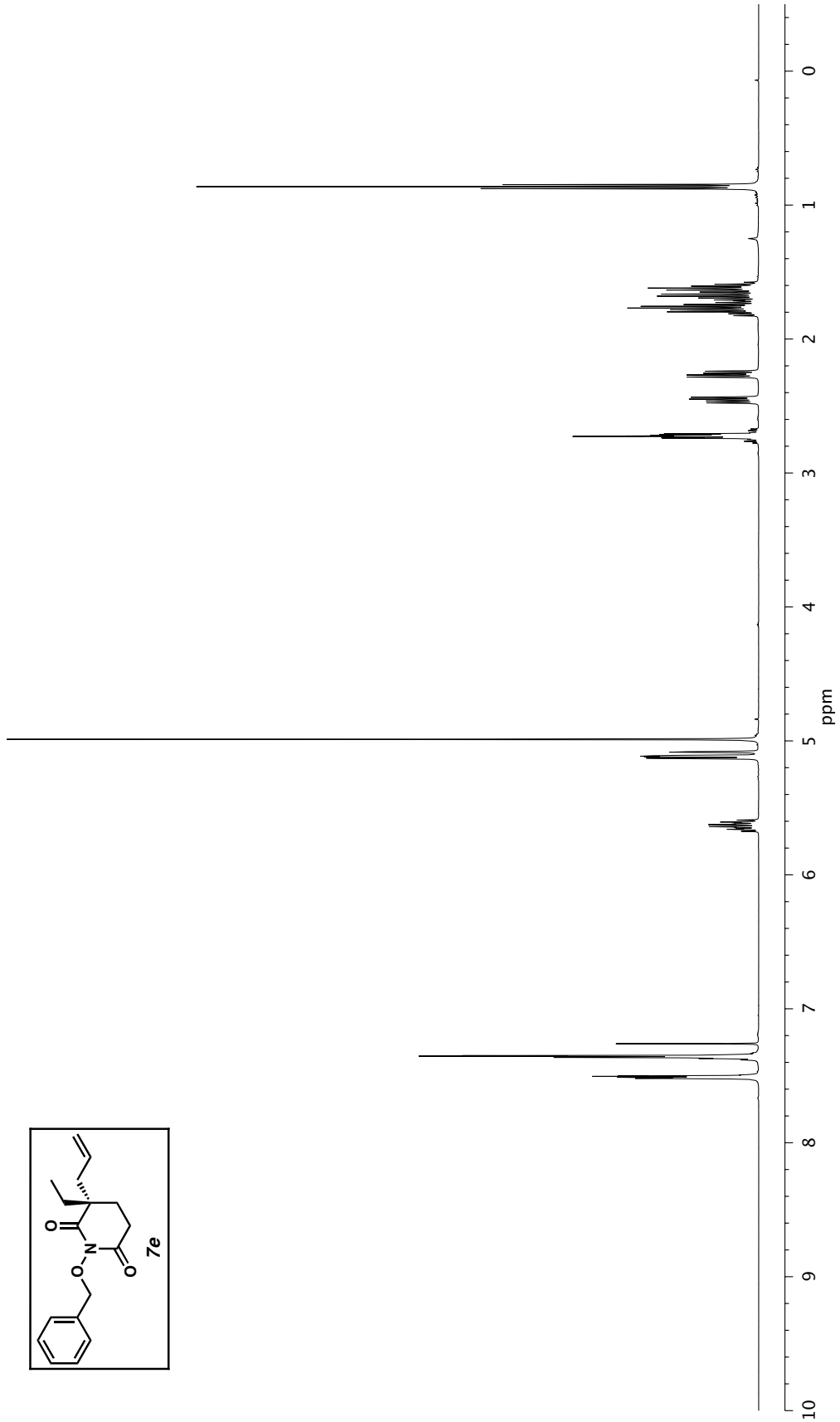


Figure A1.41.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **7e**.

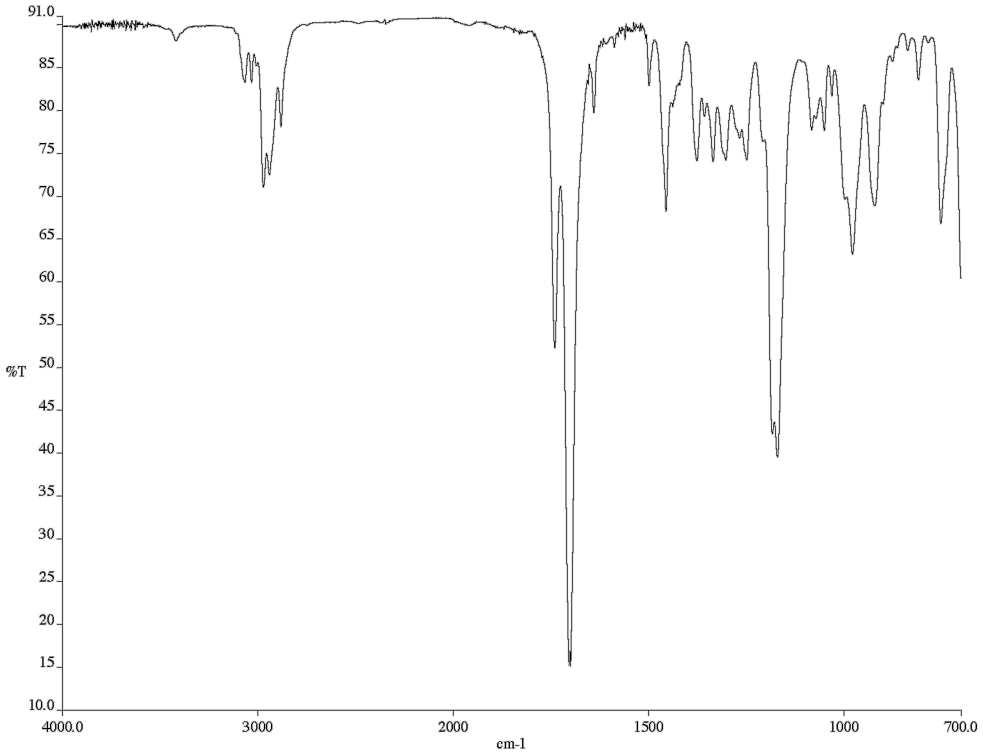


Figure A1.41.2. Infrared spectrum (thin film/NaCl) of compound **7e**.

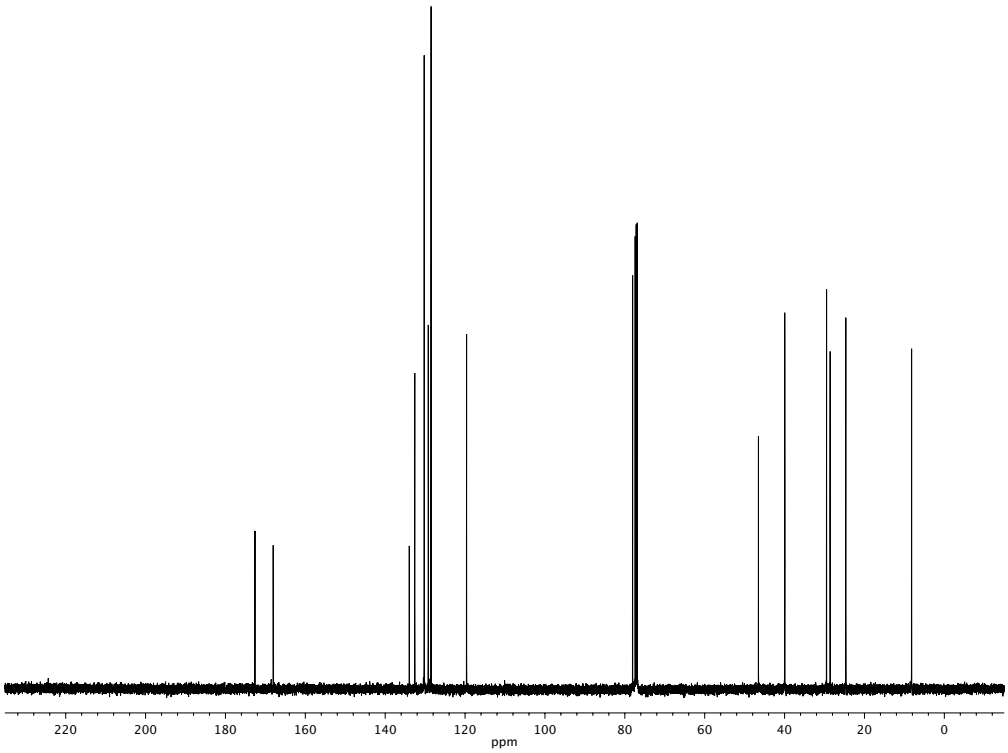


Figure A1.41.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **7e**.

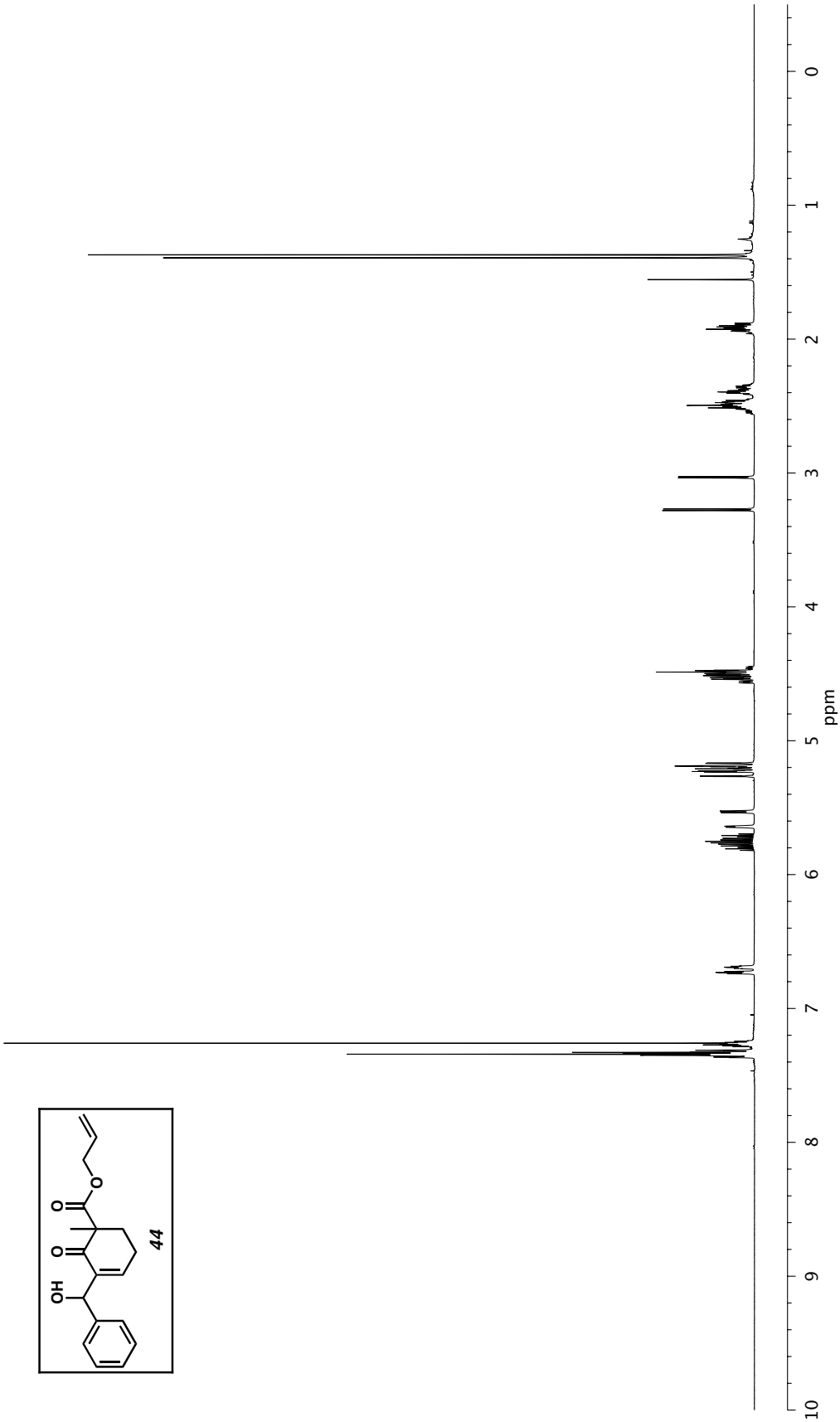


Figure A1.42.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **44**.

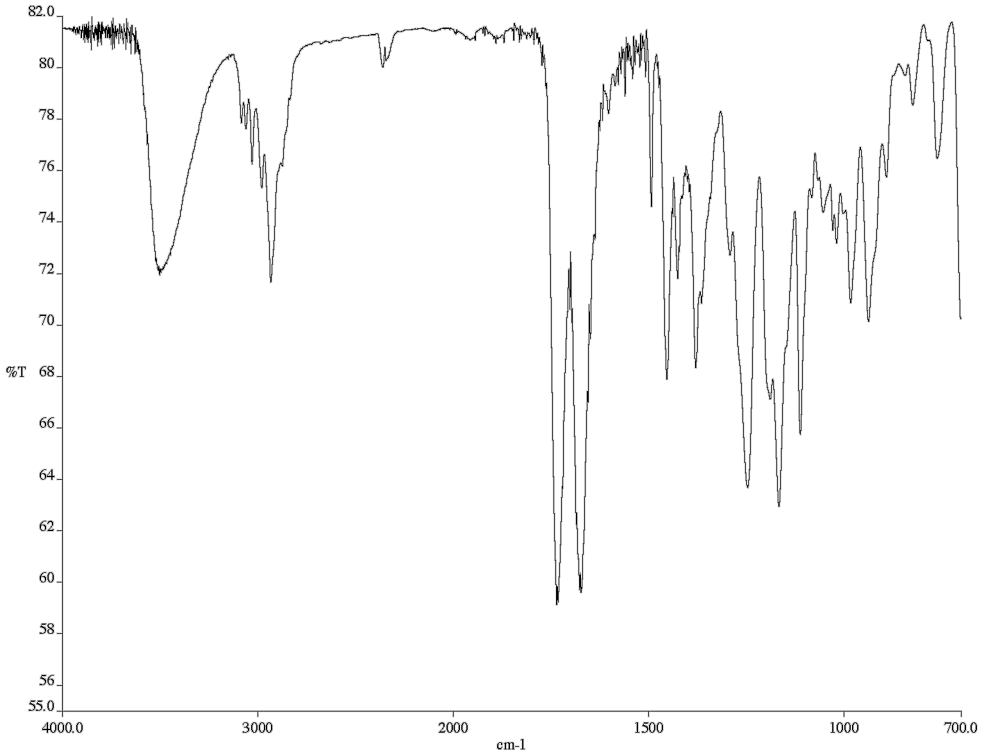


Figure A1.42.2. Infrared spectrum (thin film/NaCl) of compound **44**.

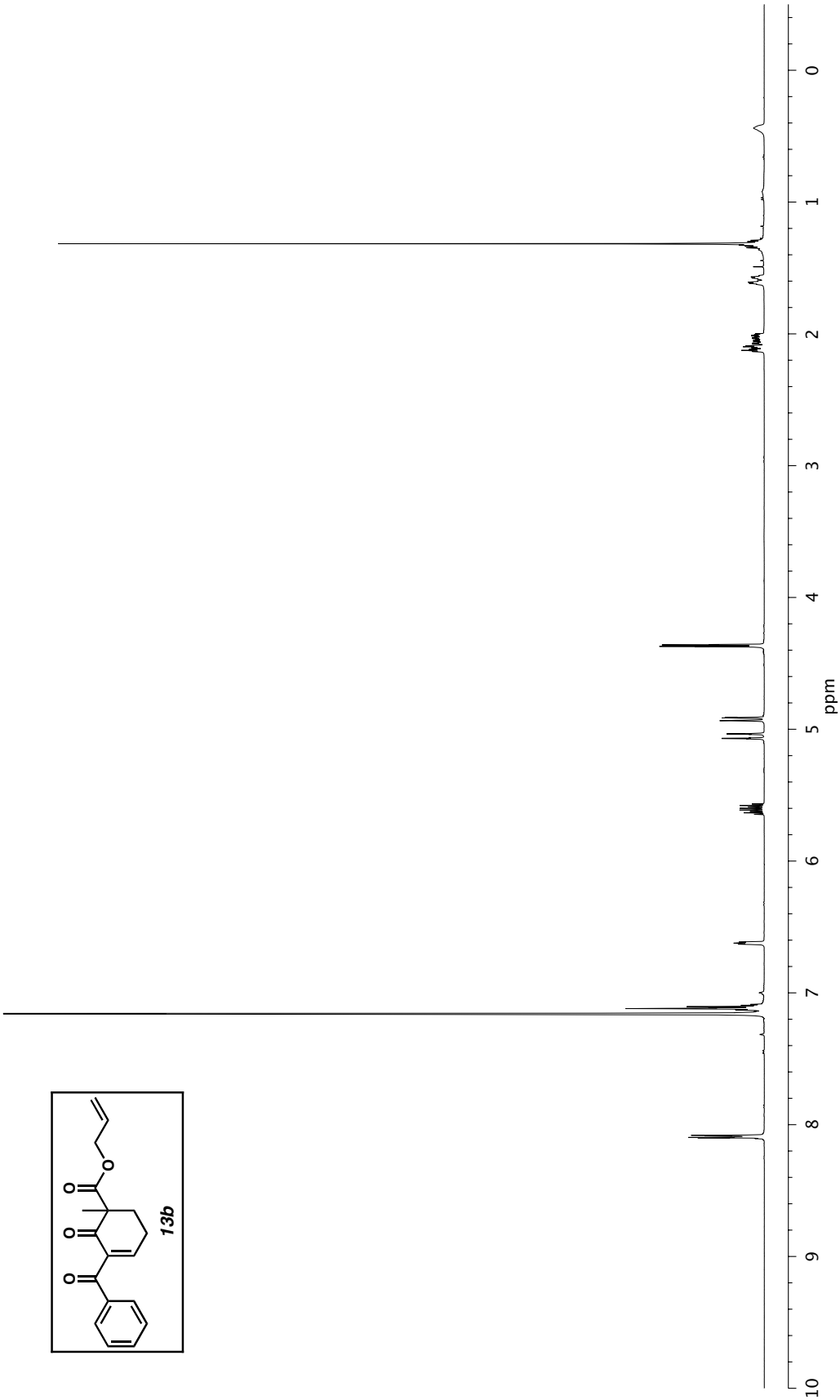


Figure A1.43.1. ^{1}H NMR (500 MHz, C_6D_6) of compound **13b**.

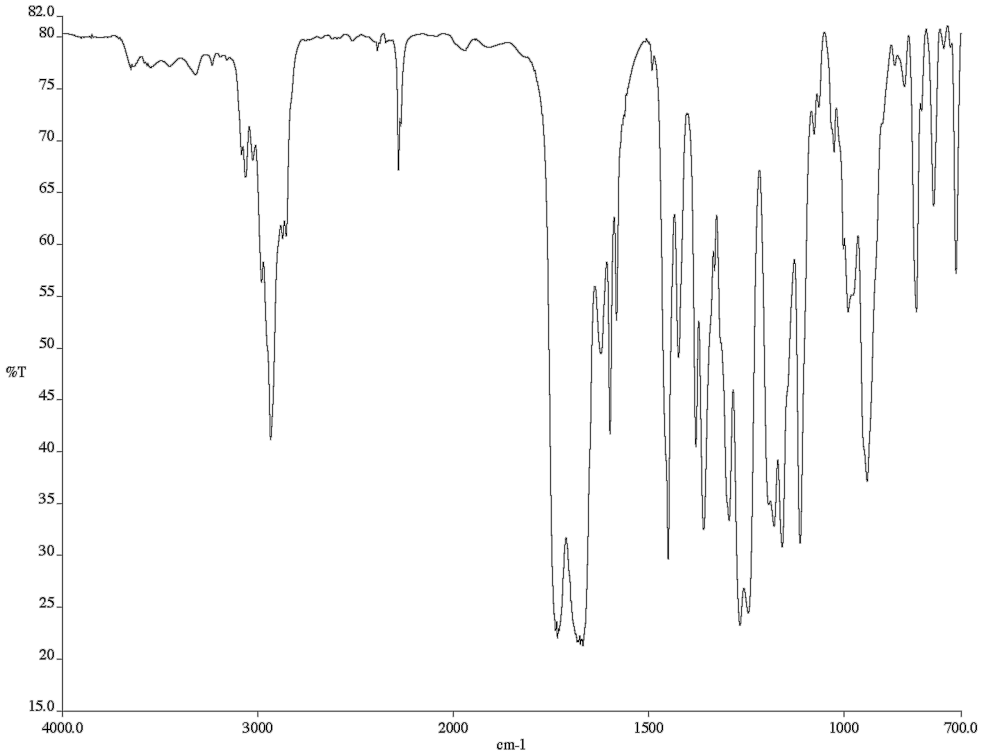


Figure A1.43.2. Infrared spectrum (thin film/NaCl) of compound **13b**.

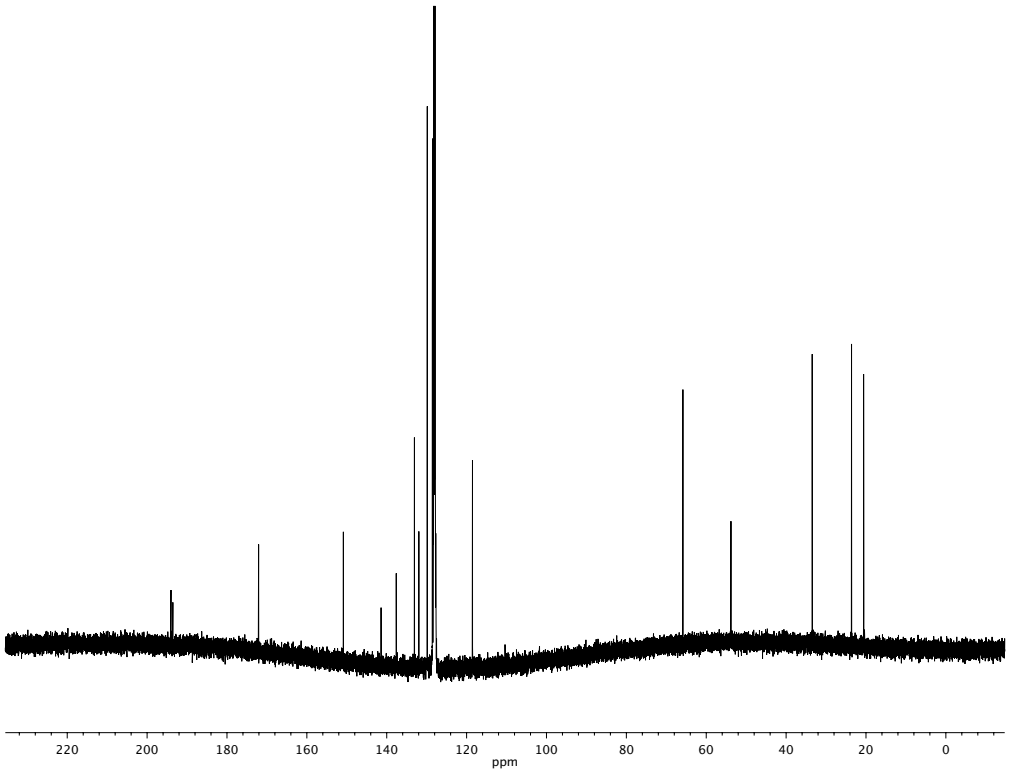


Figure A1.43.3. ^{13}C NMR (125 MHz, C_6D_6) of compound **13b**.

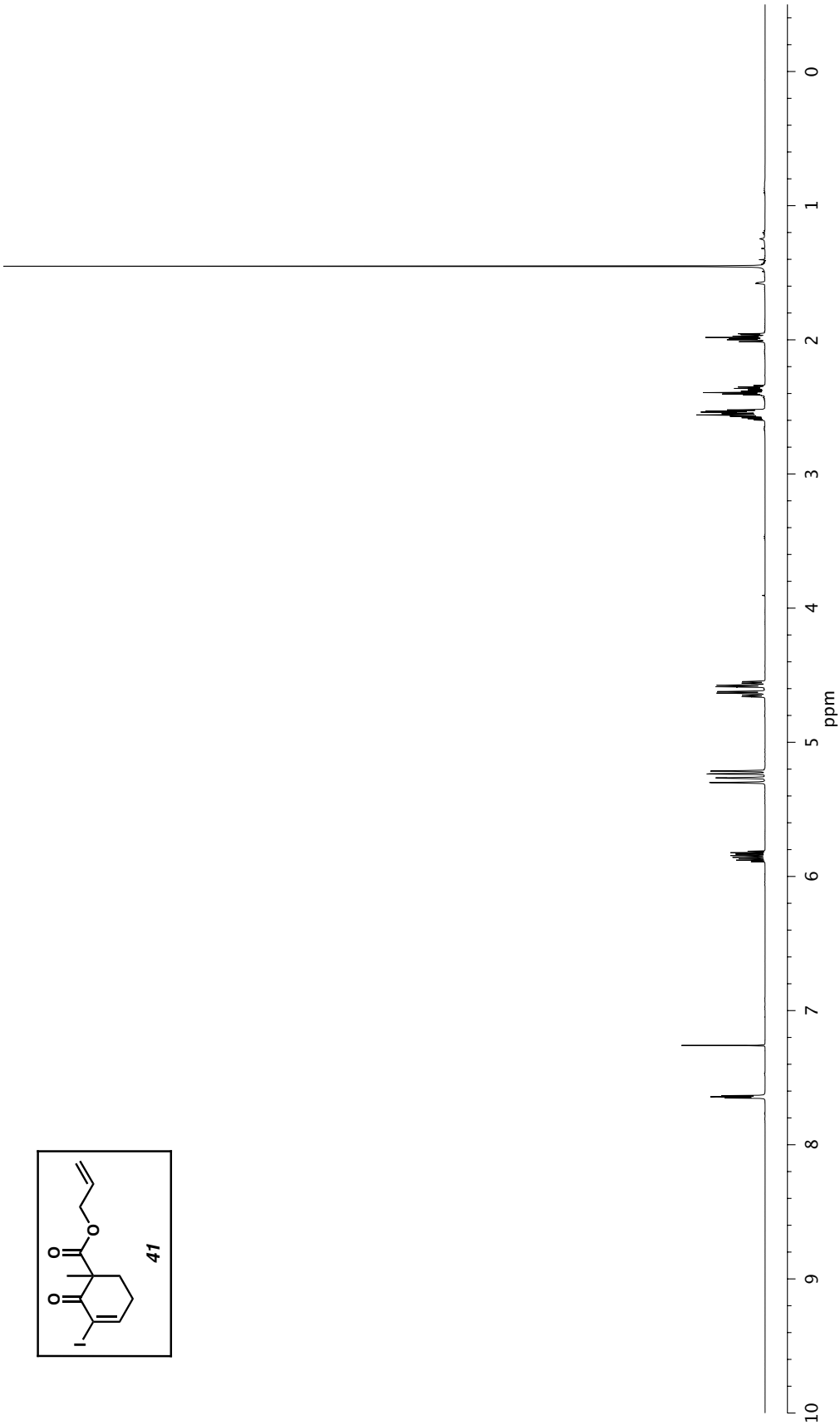


Figure A1.44.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **41**.

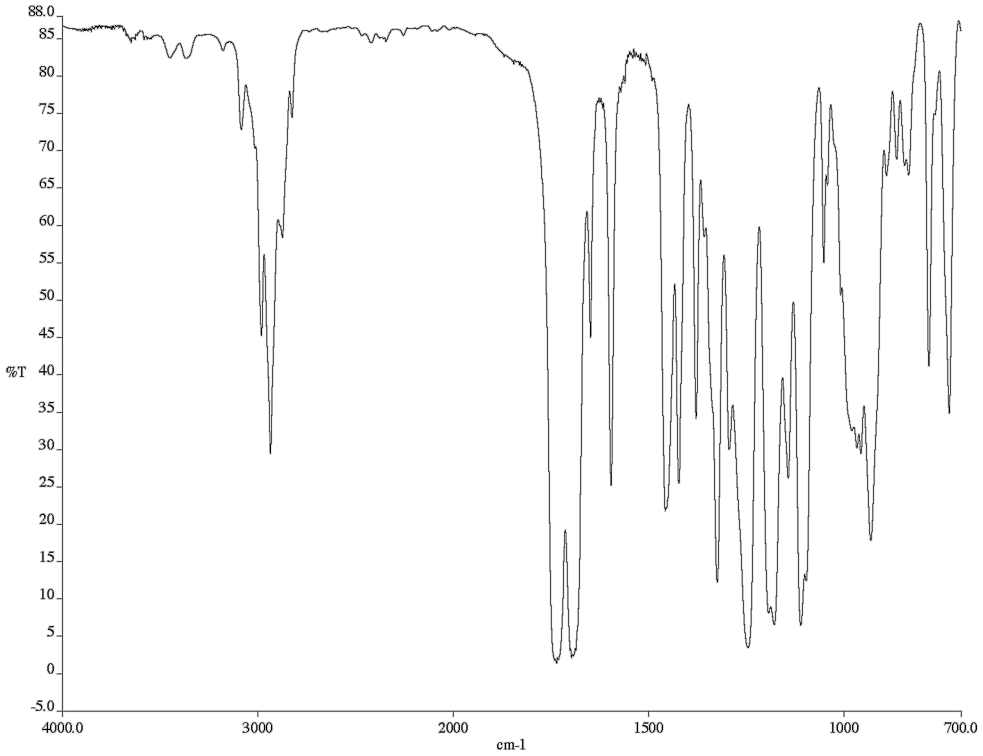


Figure A1.44.2. Infrared spectrum (thin film/NaCl) of compound **41**.

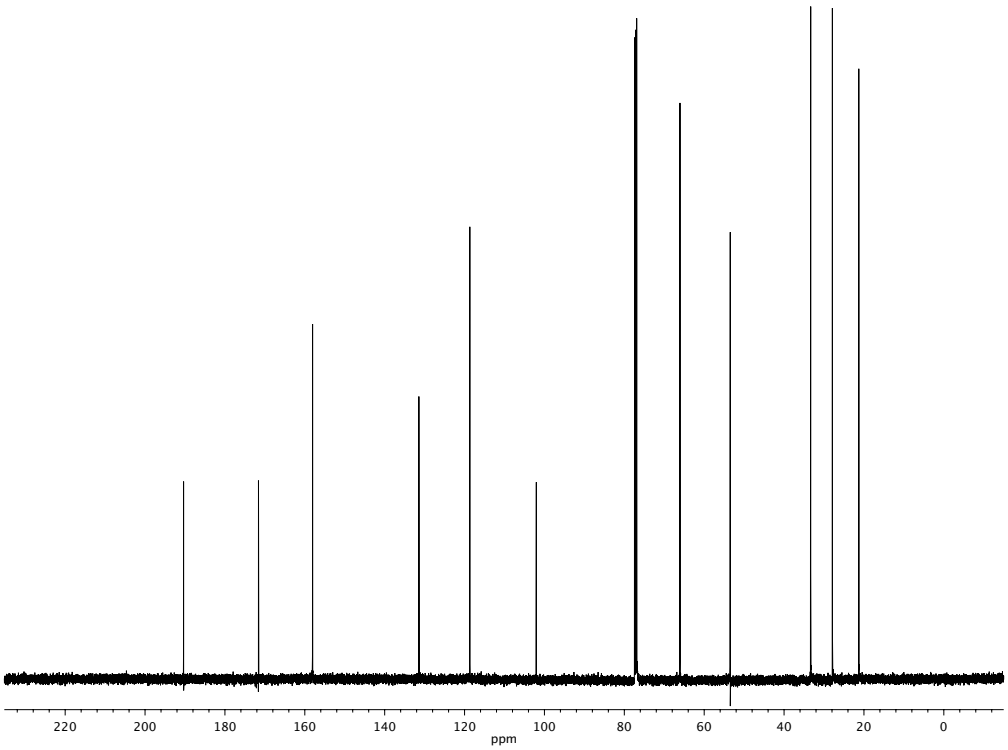


Figure A1.44.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **41**.

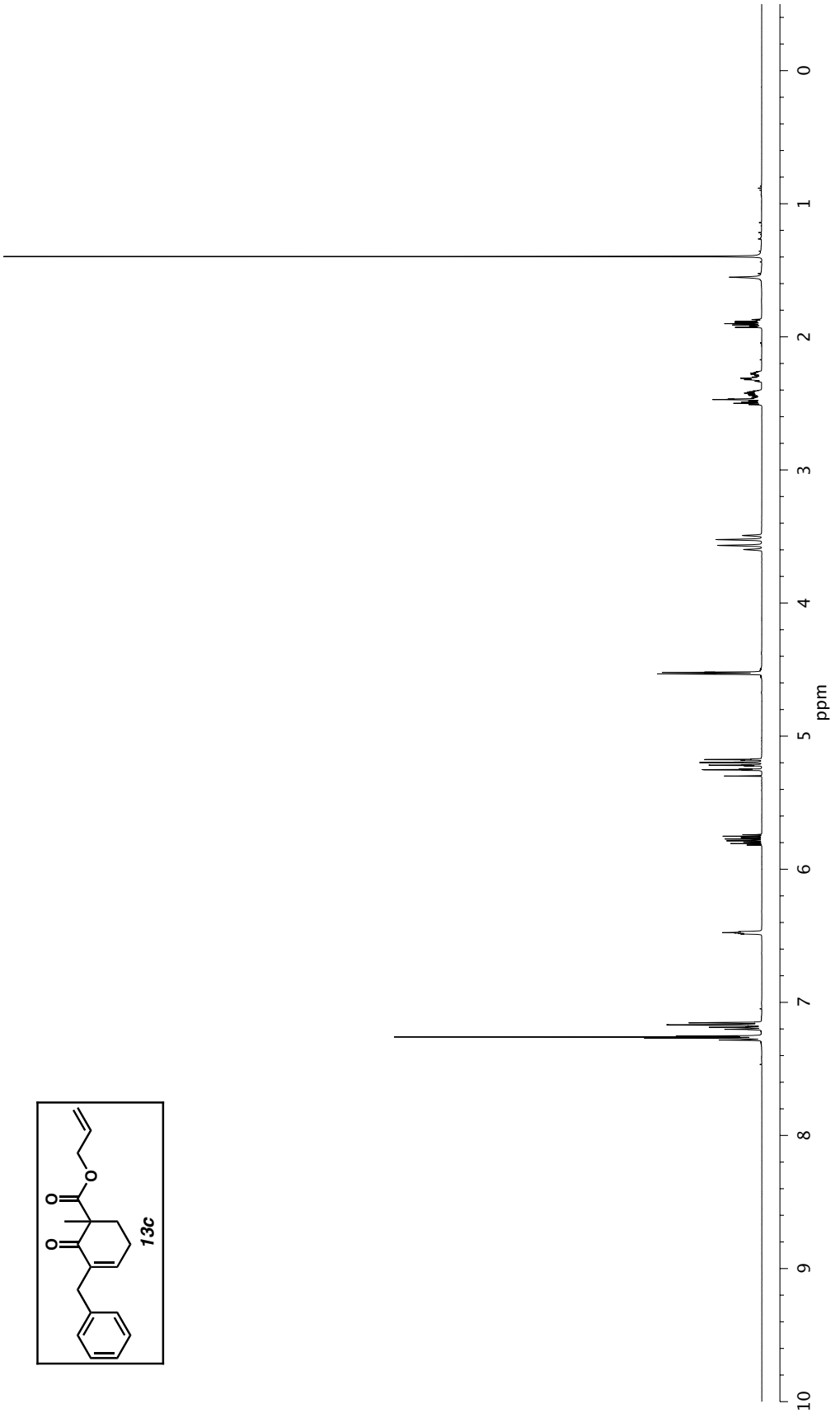


Figure A1.45.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **13c**.

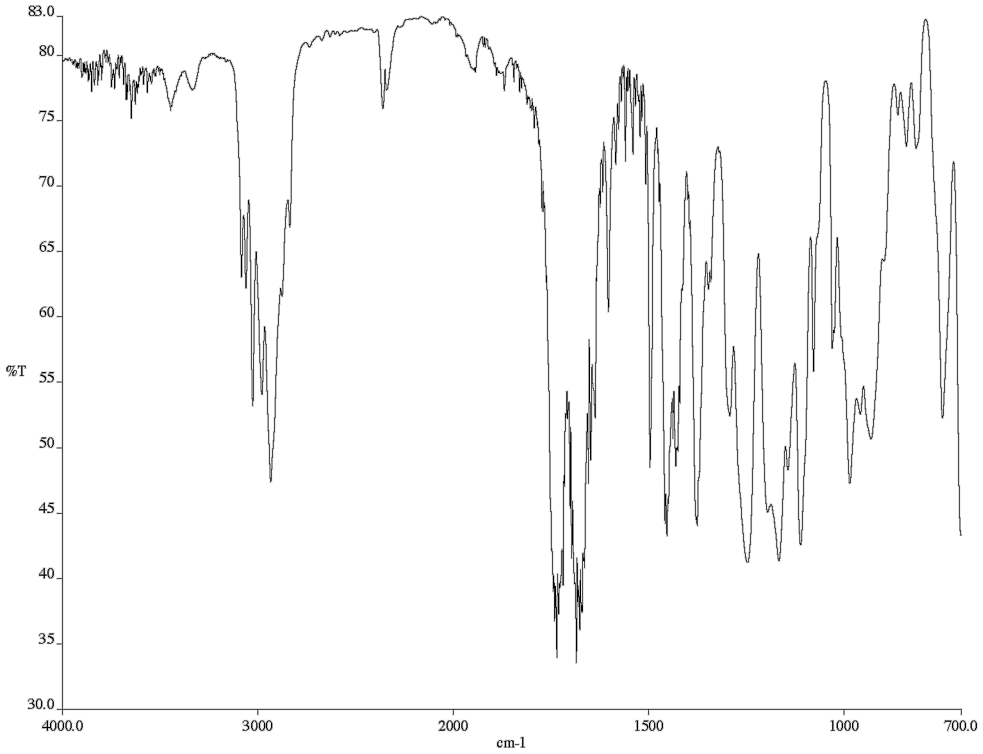


Figure A1.45.2. Infrared spectrum (thin film/NaCl) of compound **13c**.

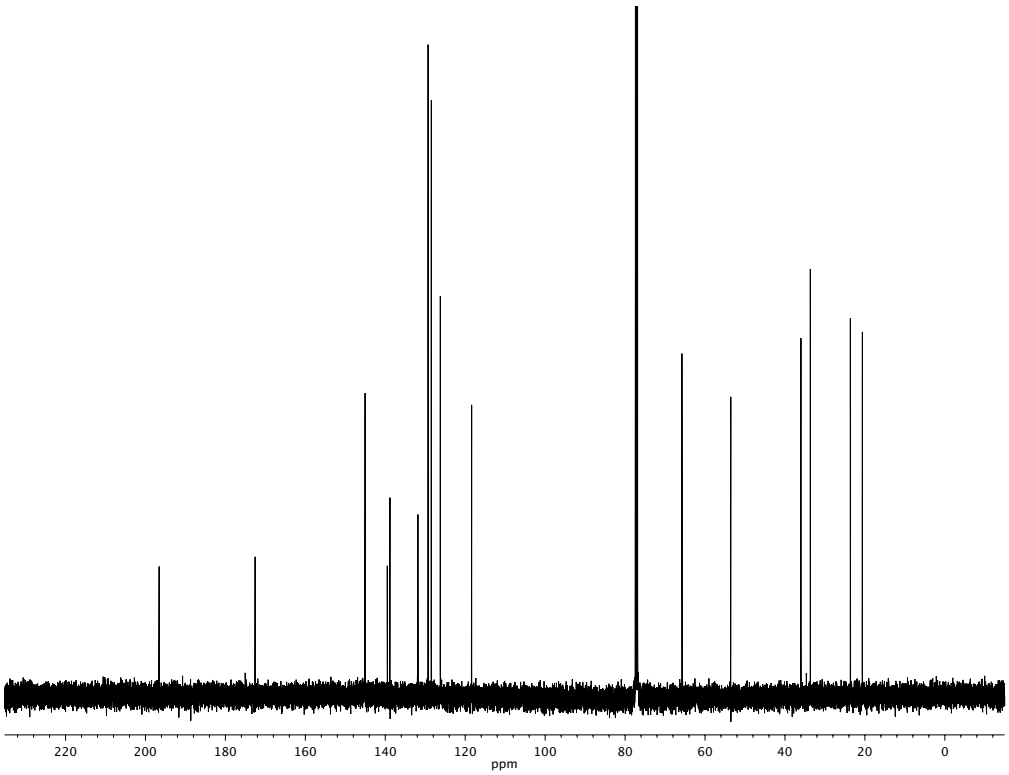


Figure A1.45.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **13c**.

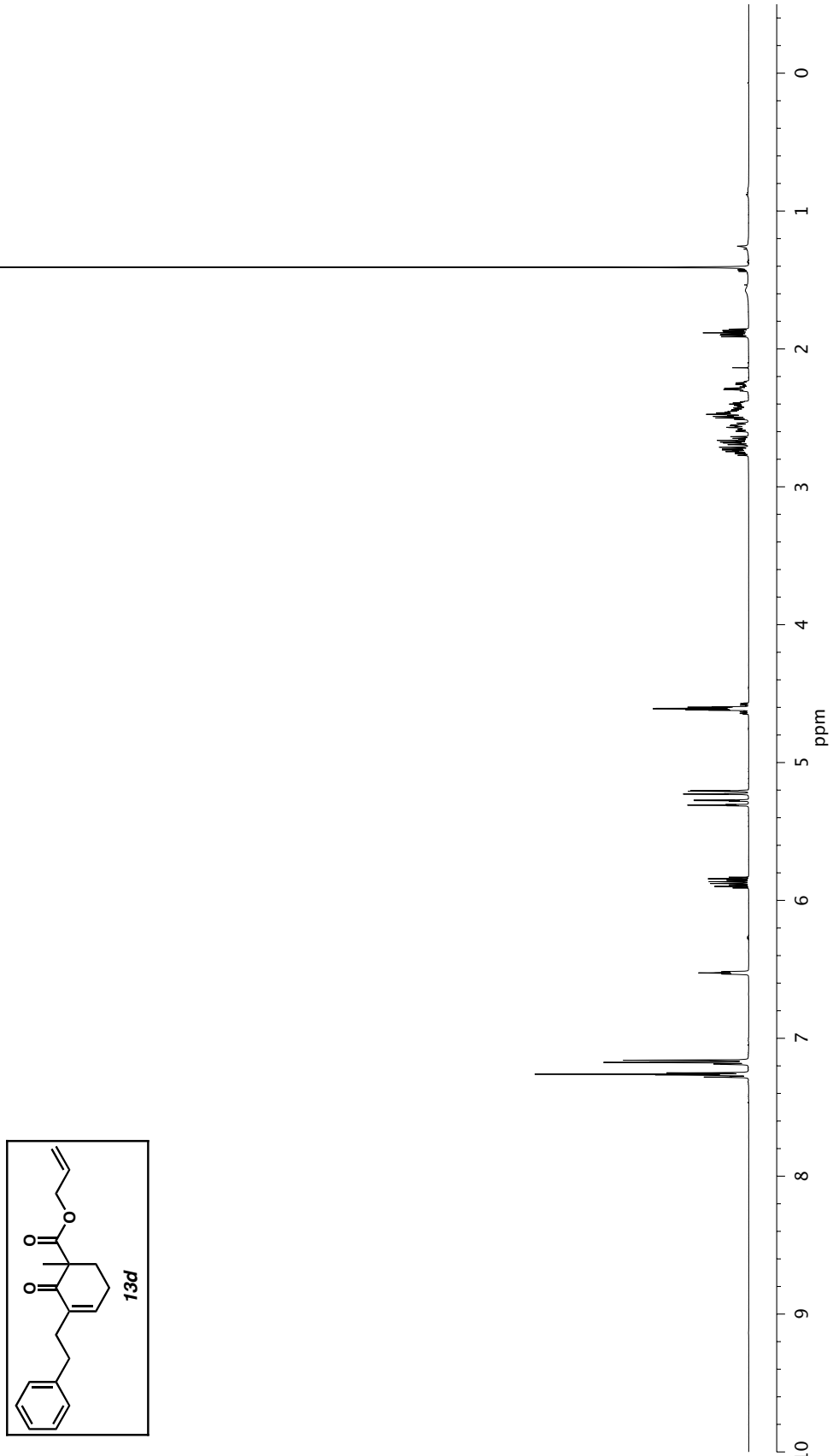


Figure A1.46.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **13d**.

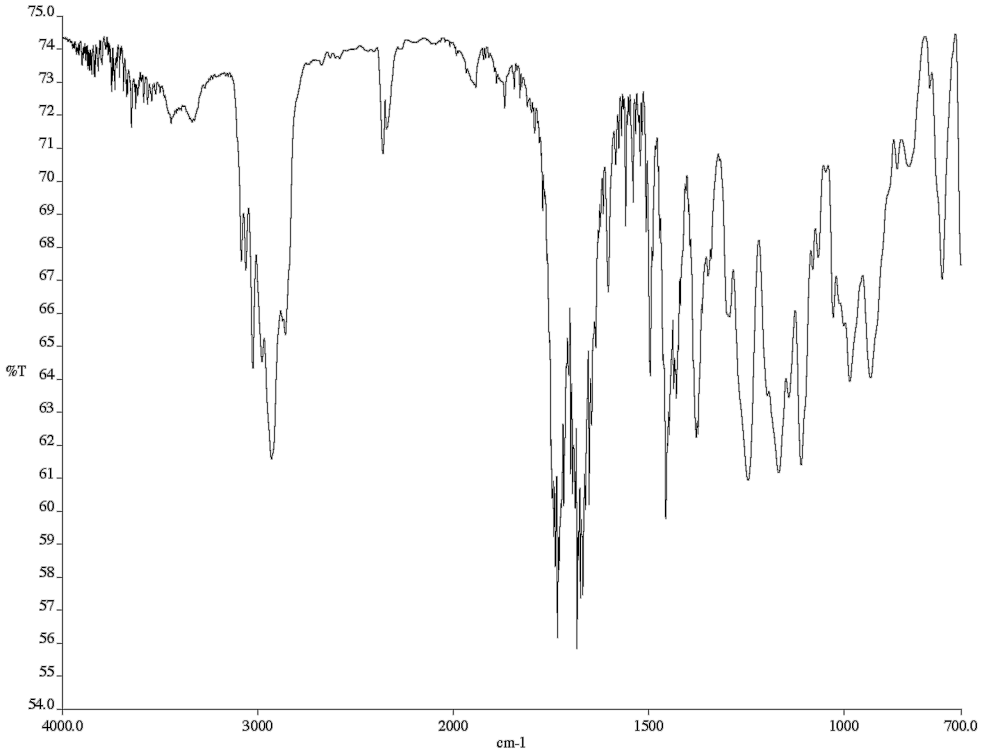


Figure A1.46.2. Infrared spectrum (thin film/NaCl) of compound **13d**.

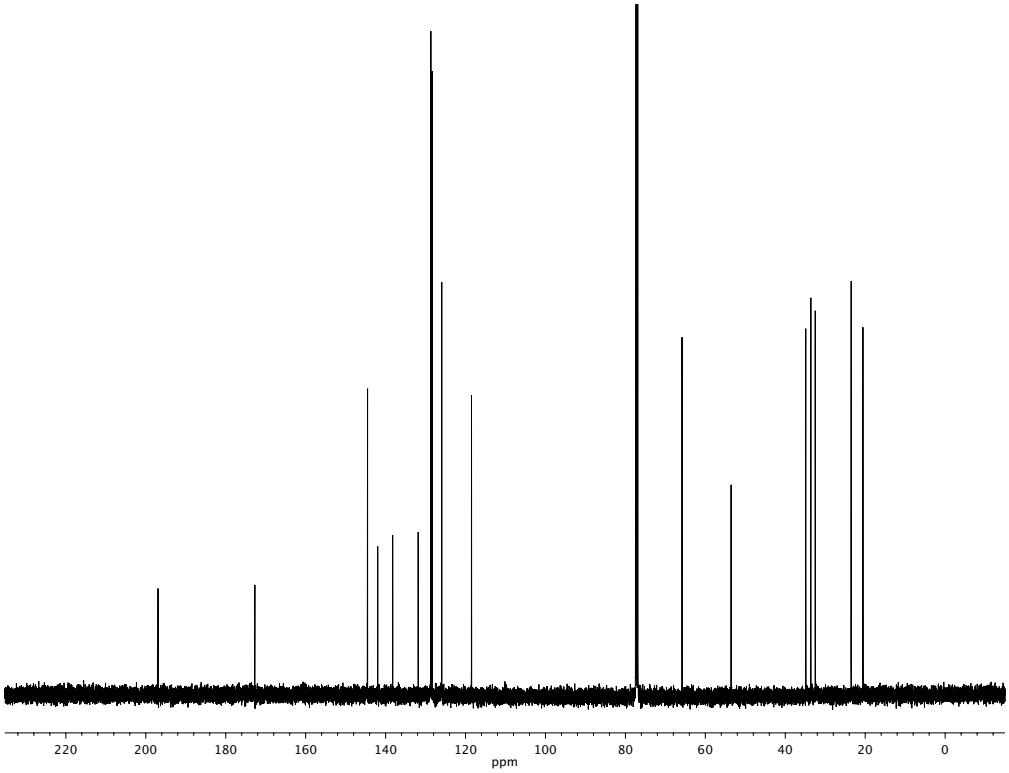


Figure A1.46.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **13d**.

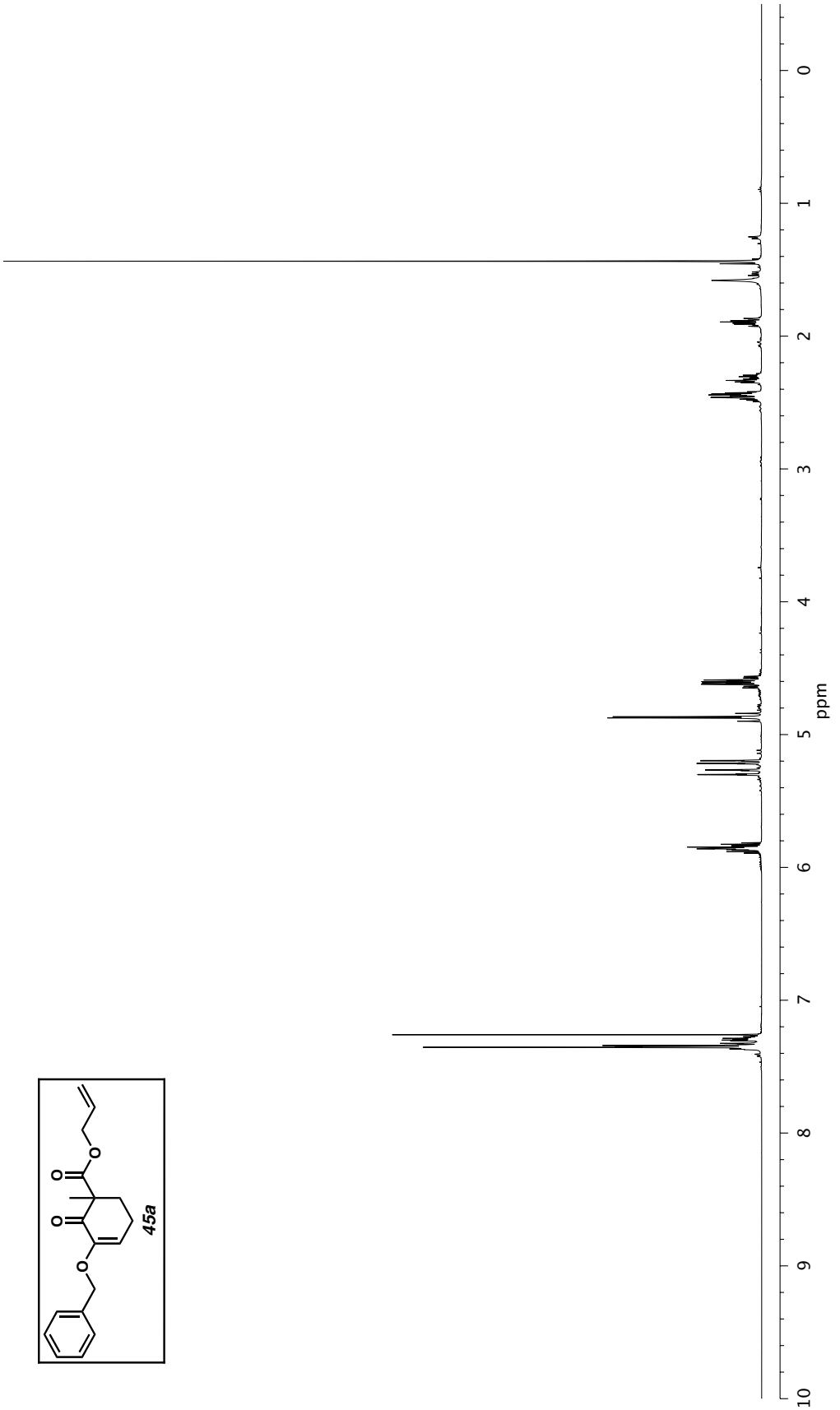


Figure A1.47.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **45a**.

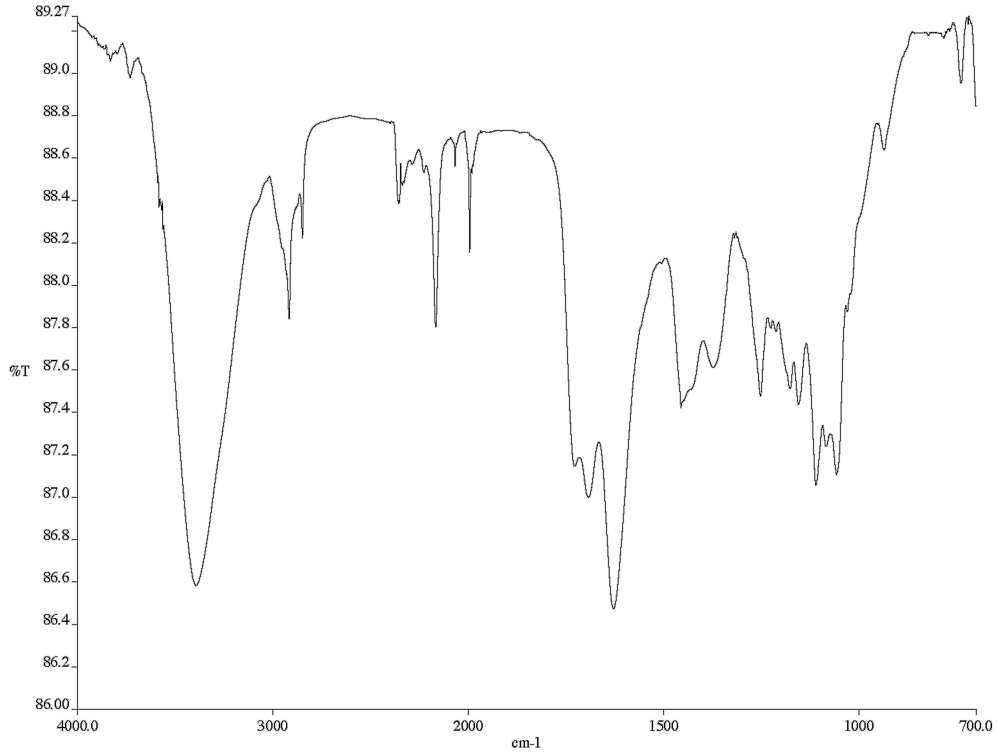


Figure A1.47.2. Infrared spectrum (thin film/NaCl) of compound **45a**.

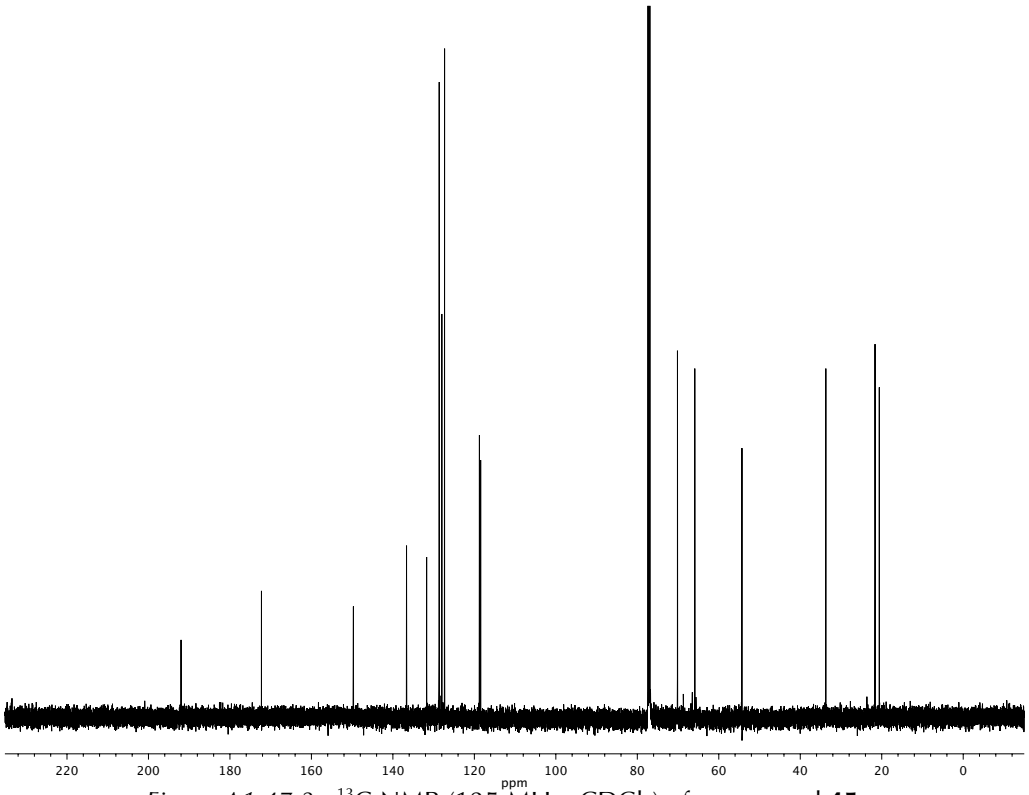


Figure A1.47.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **45a**.

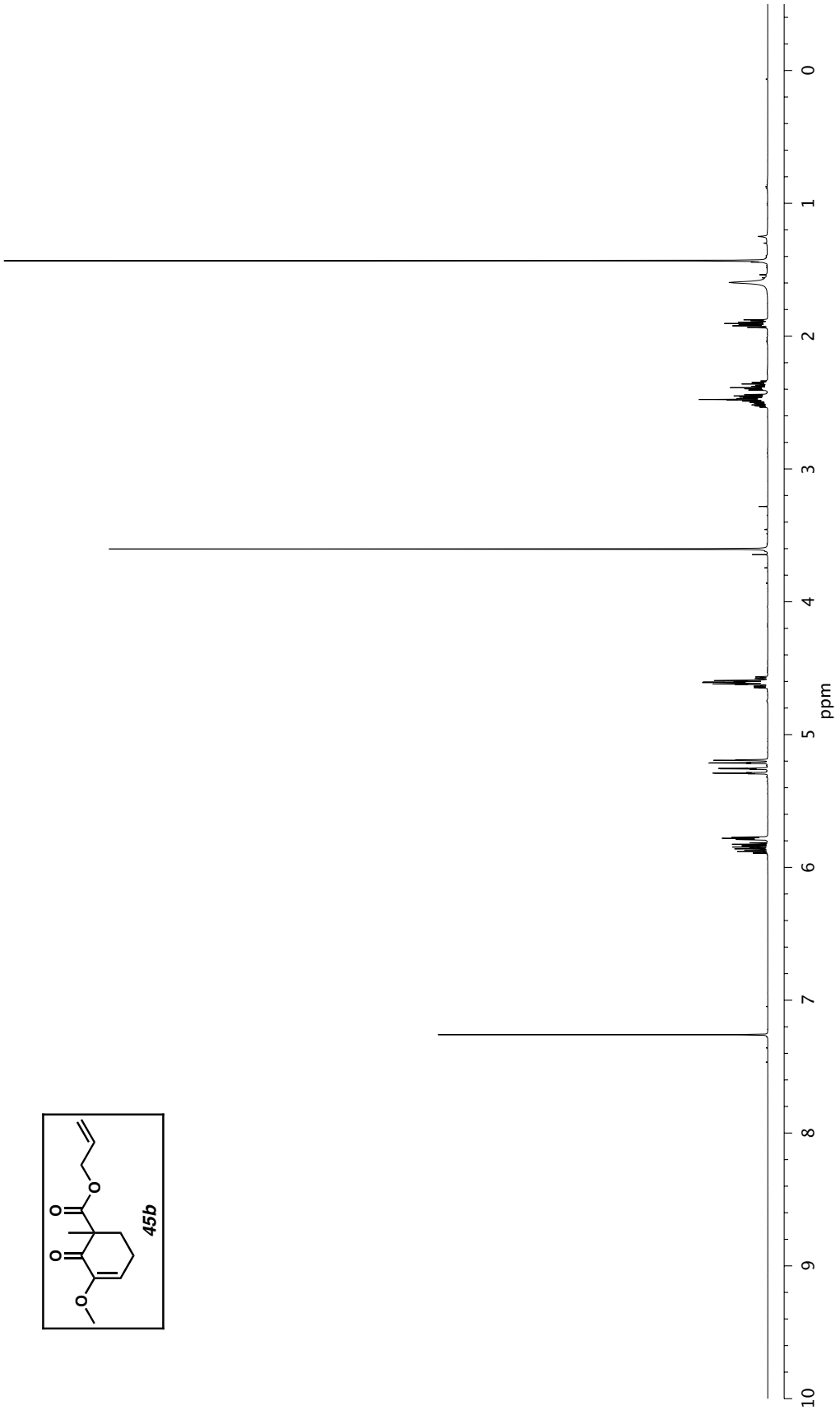


Figure A1.48.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **45b**.

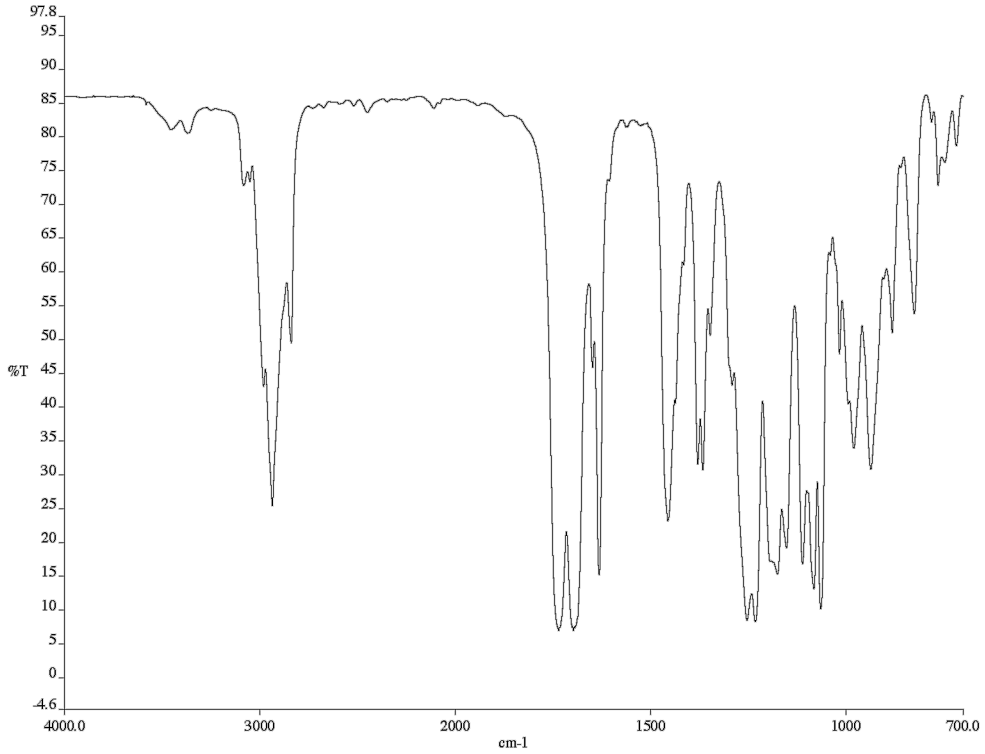


Figure A1.48.2. Infrared spectrum (thin film/NaCl) of compound **45b**.

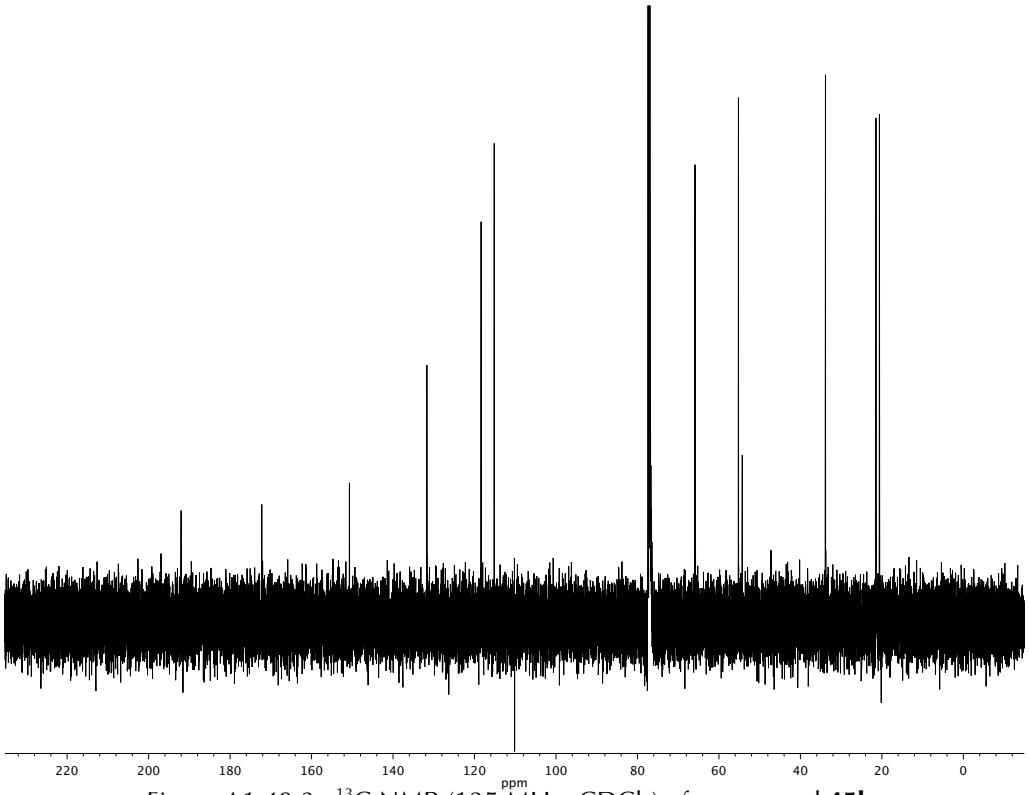


Figure A1.48.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **45b**.

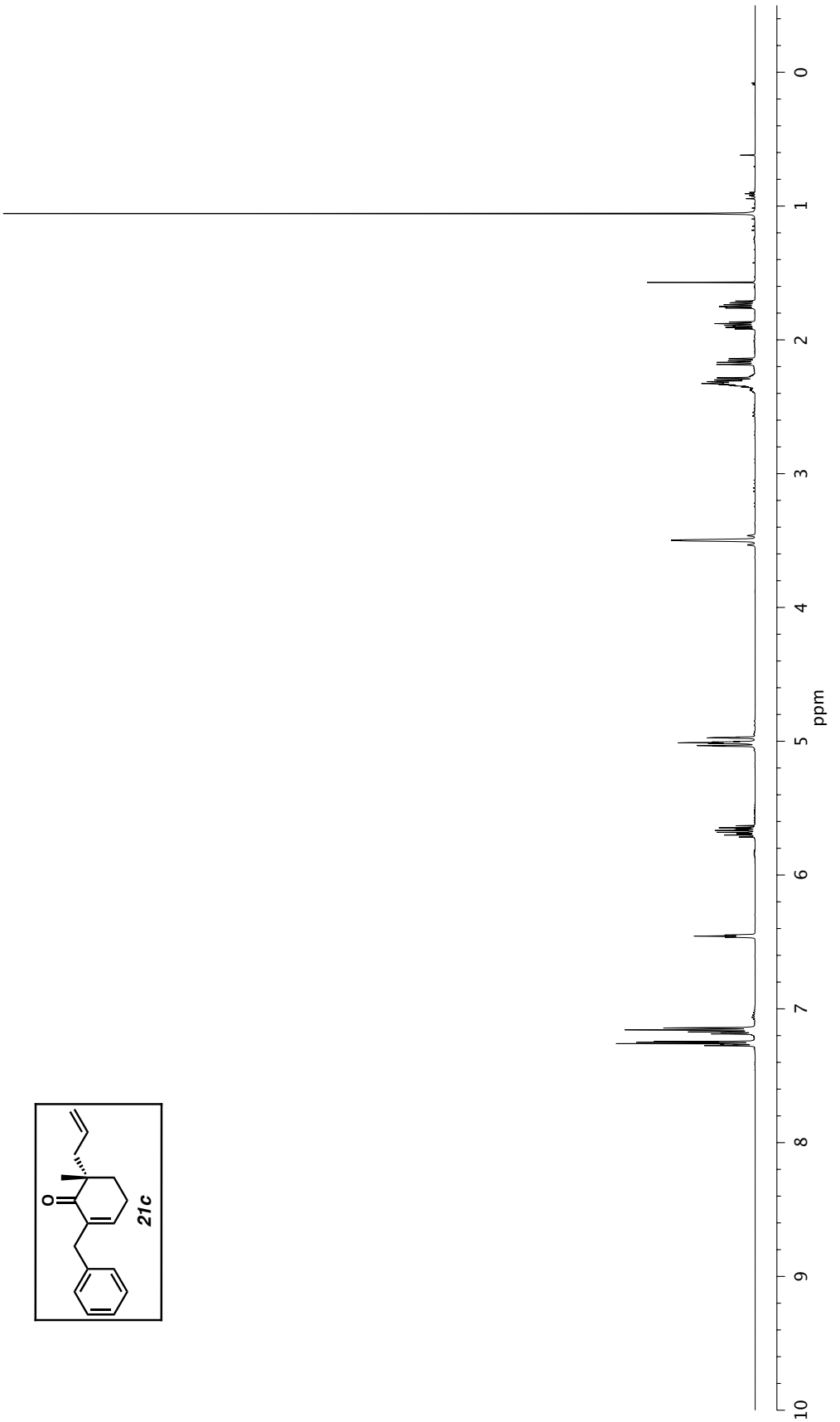


Figure A1.49.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **21c**.

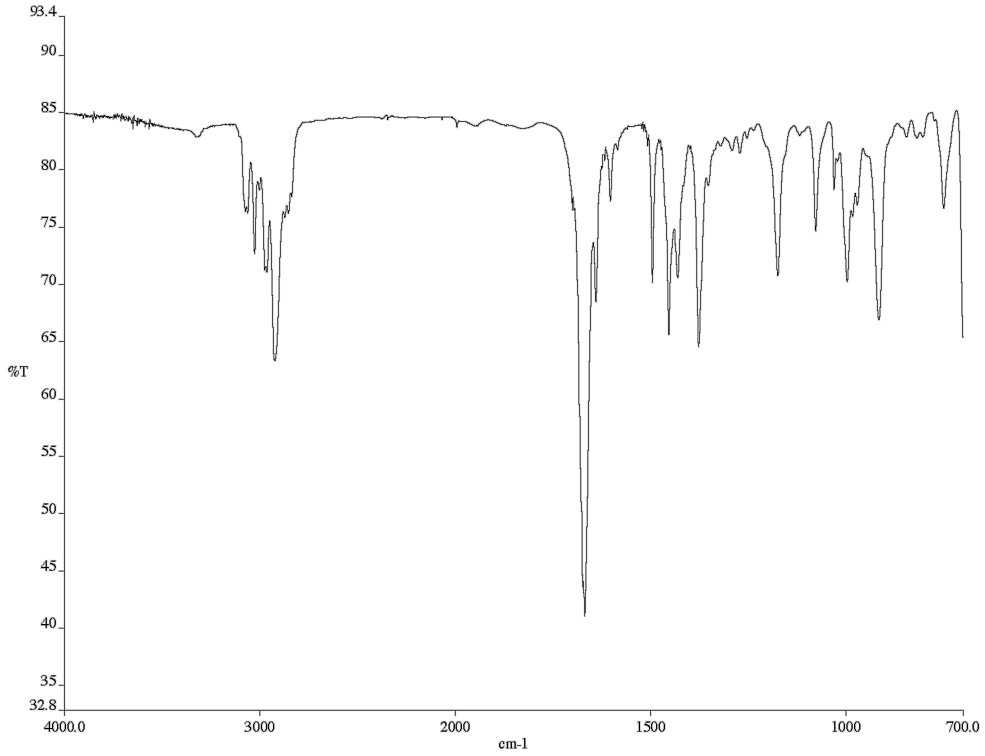


Figure A1.49.2. Infrared spectrum (thin film/NaCl) of compound **21c**.

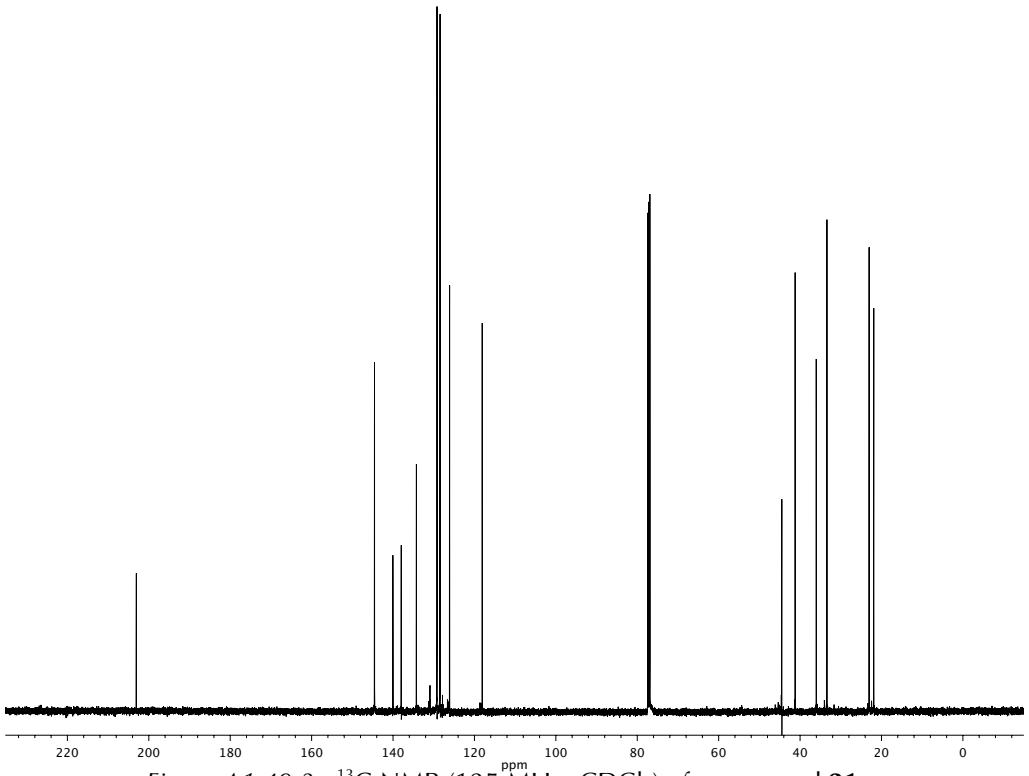


Figure A1.49.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **21c**.

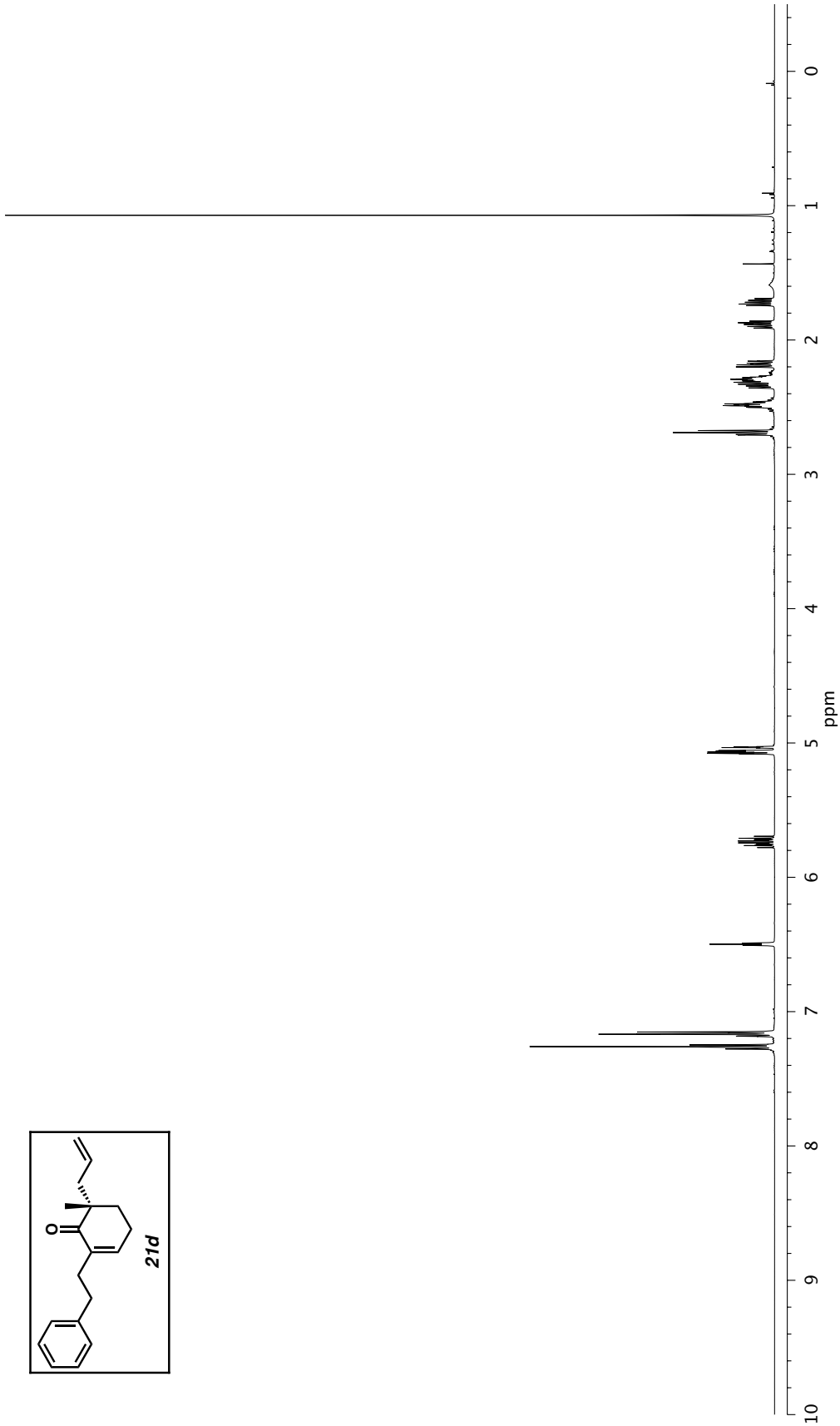


Figure A1.50.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **21d**.

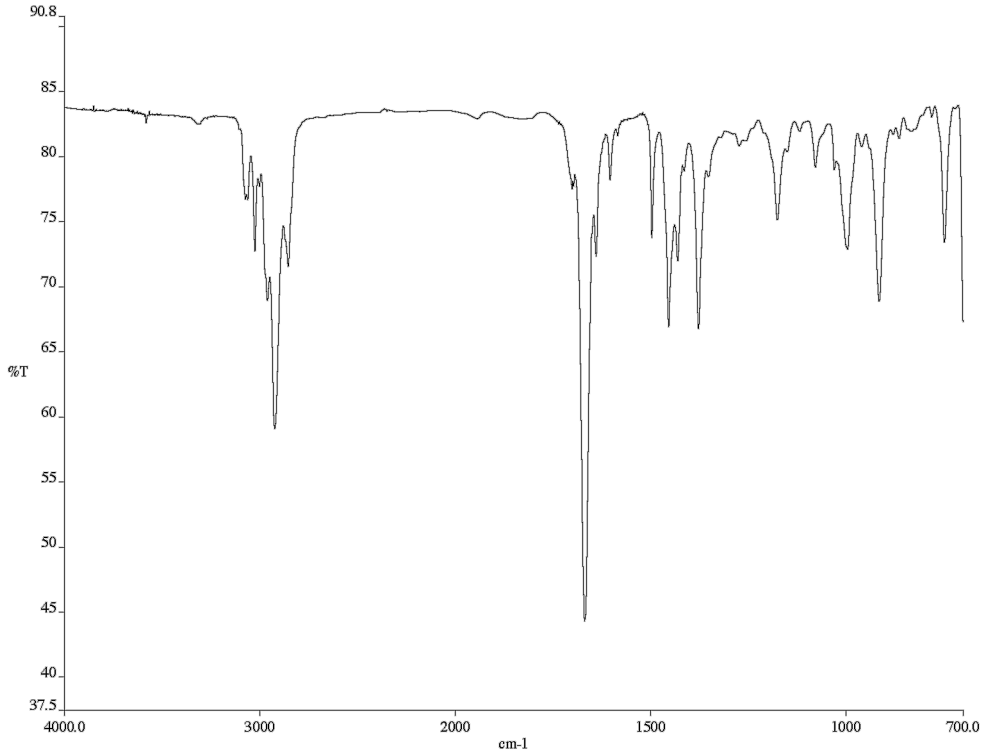


Figure A1.50.2. Infrared spectrum (thin film/NaCl) of compound **21d**.

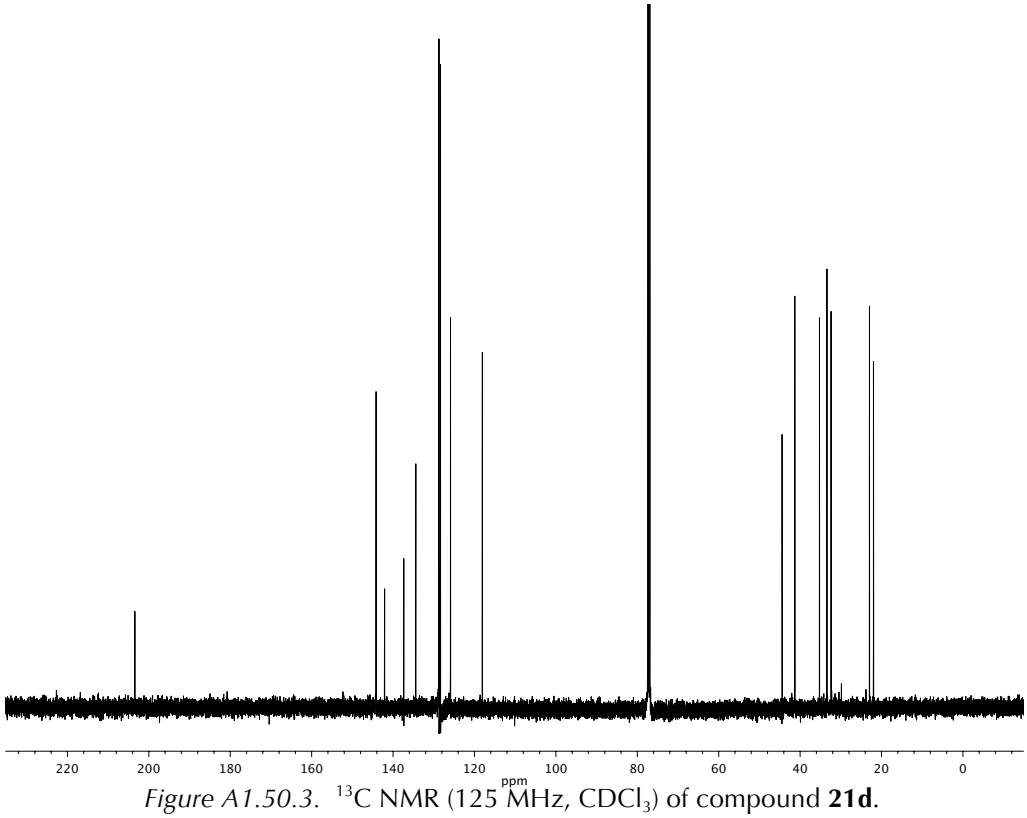


Figure A1.50.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **21d**.

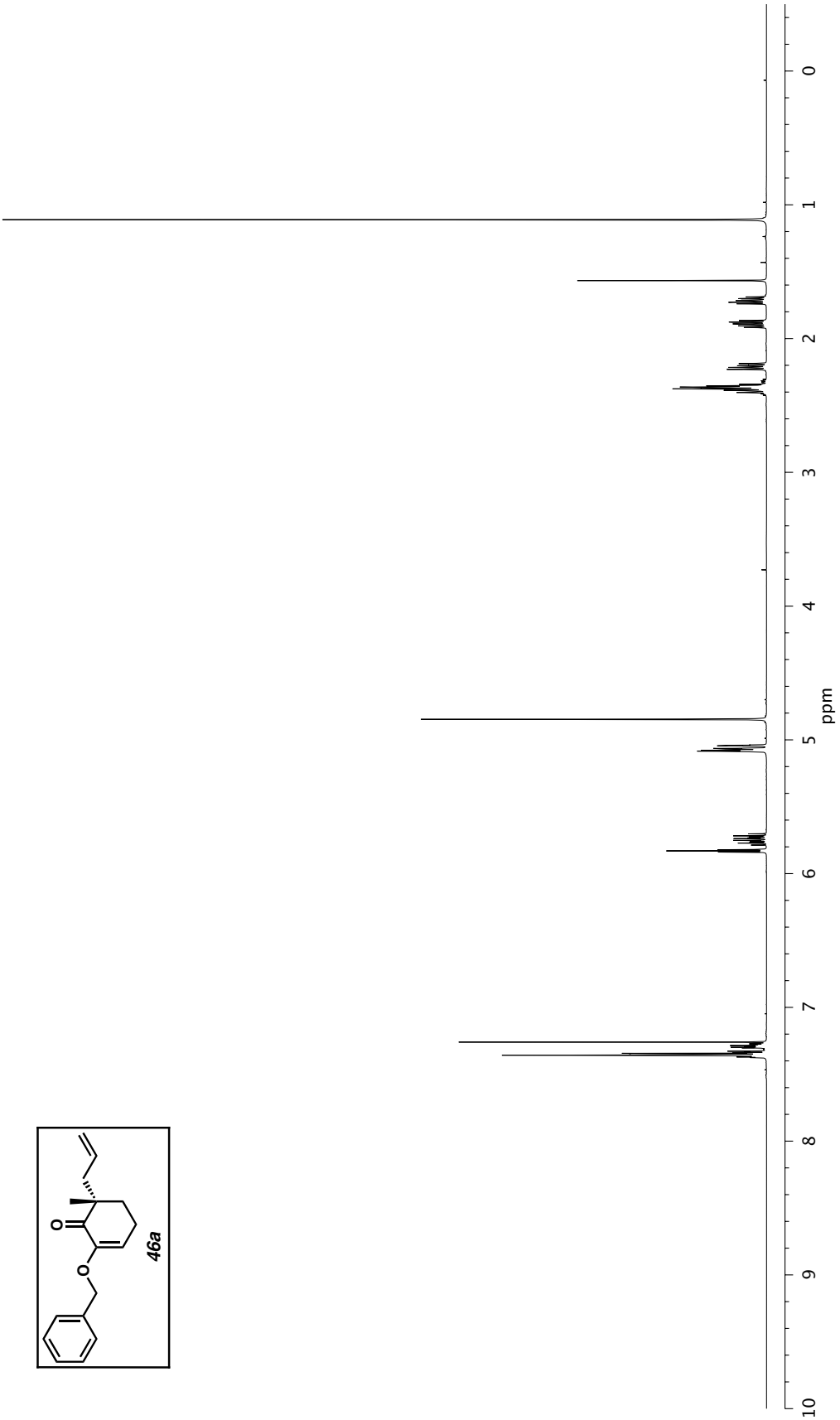


Figure A1.51.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **46a**.

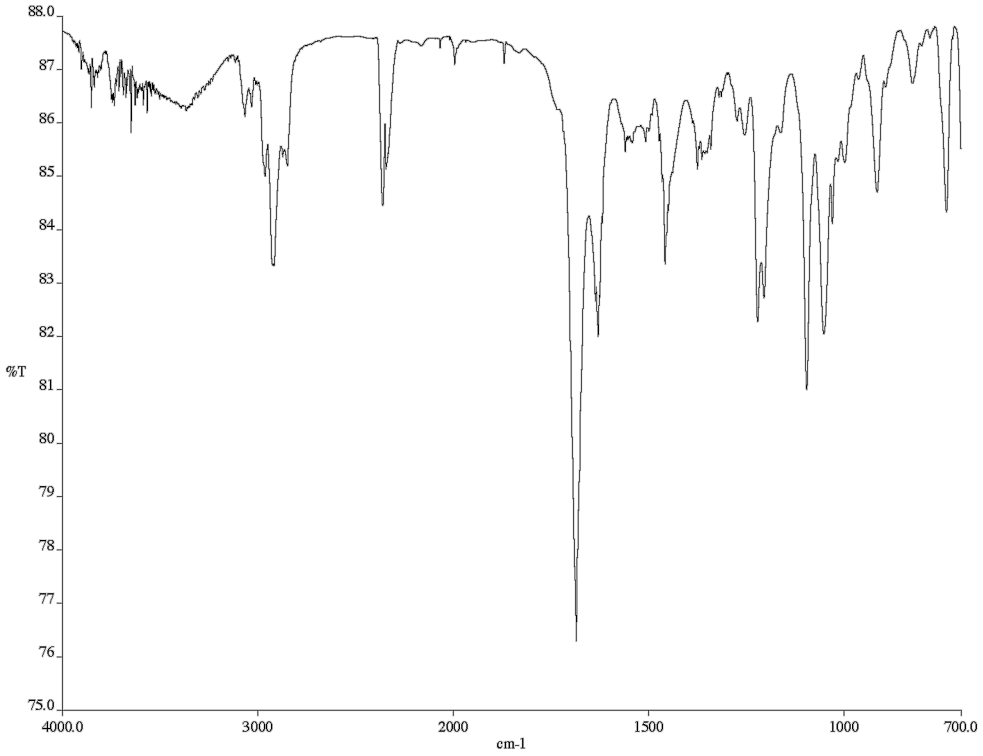


Figure A1.51.2. Infrared spectrum (thin film/NaCl) of compound **46a**.

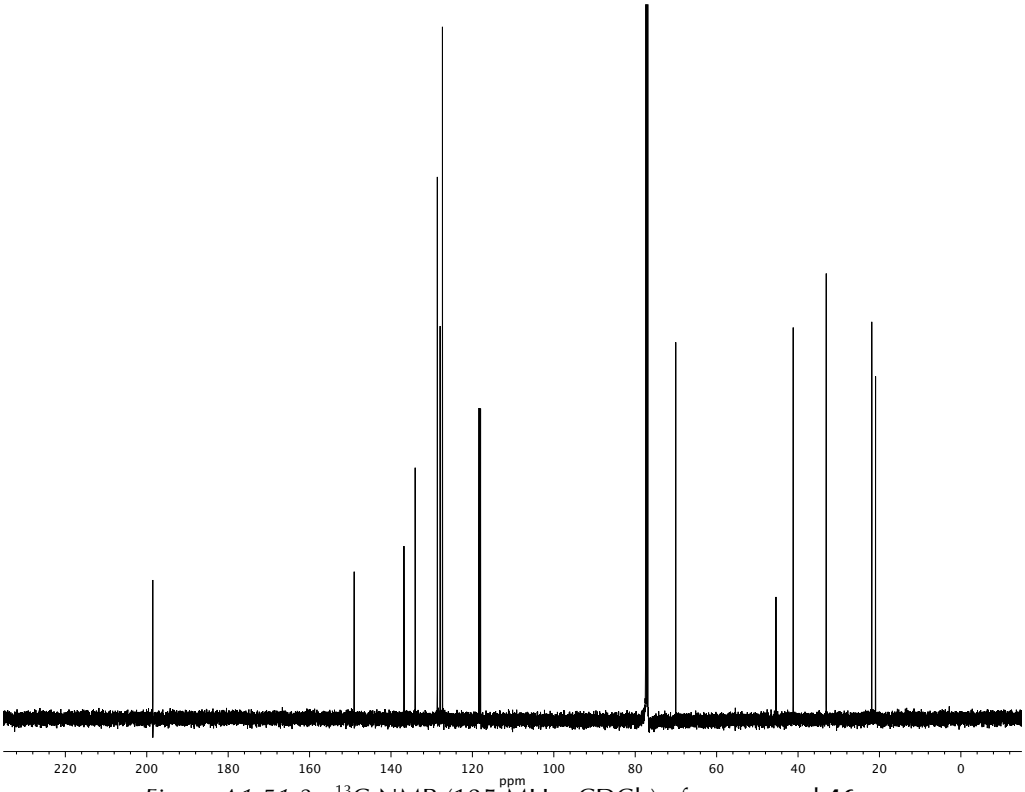


Figure A1.51.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **46a**.

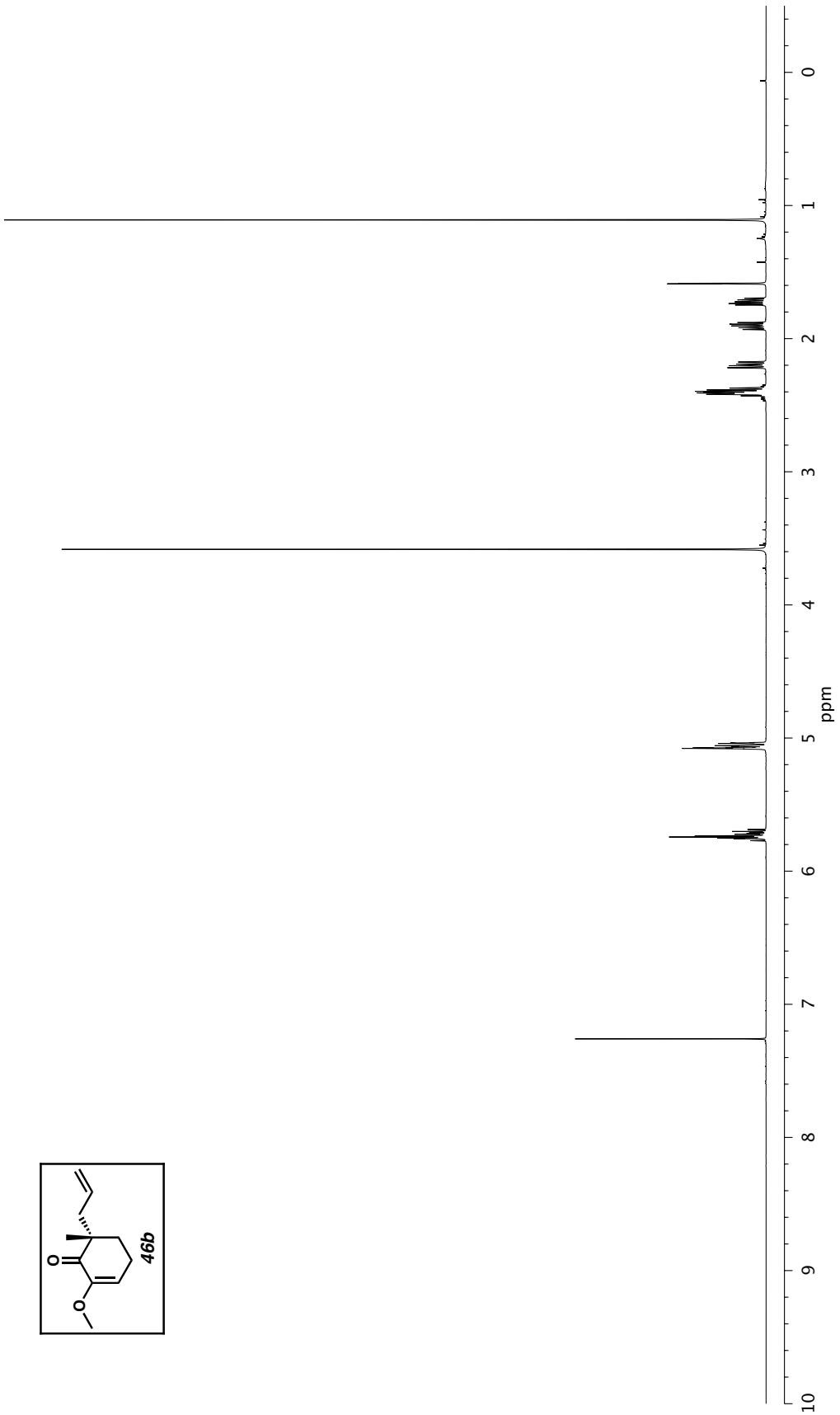


Figure A1.52.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **46b**.

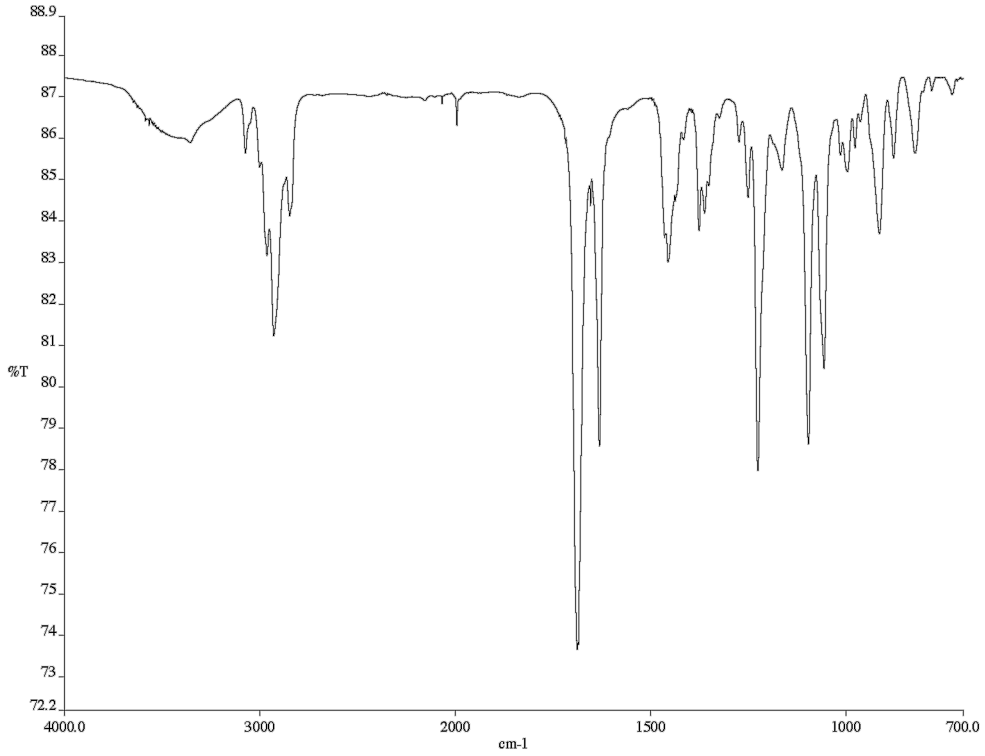


Figure A1.52.2. Infrared spectrum (thin film/NaCl) of compound **46b**.

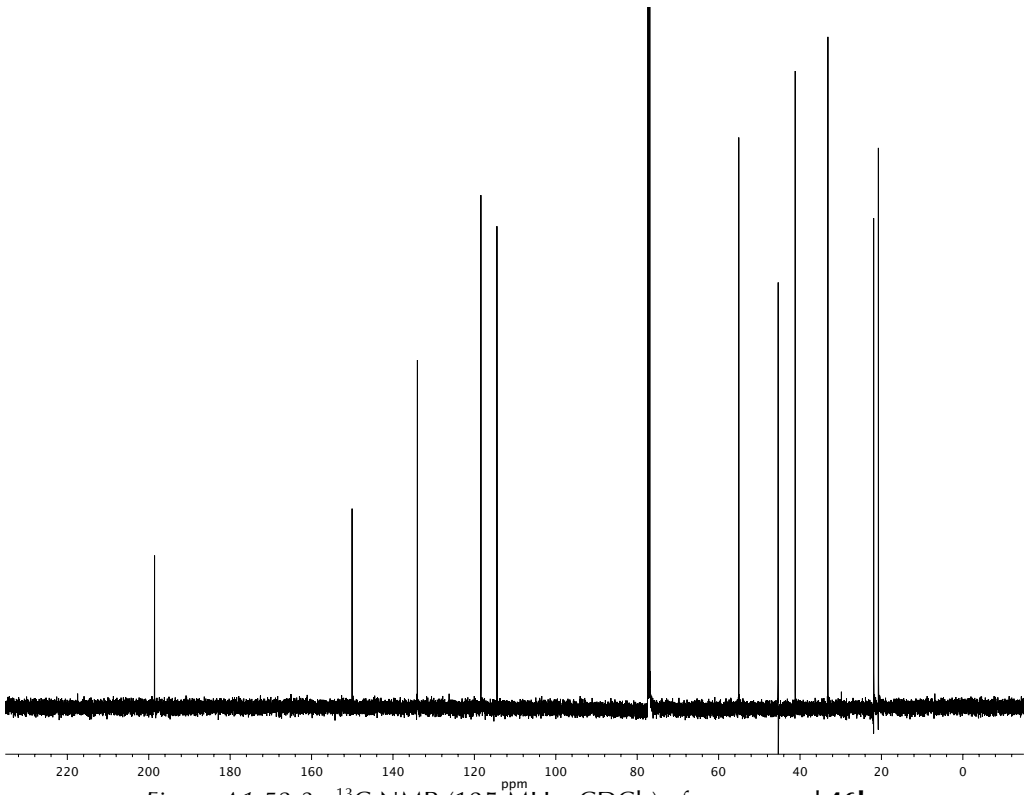


Figure A1.52.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **46b**.

CHAPTER 2

Palladium-Catalyzed Asymmetric Alkylation in the Synthesis of Cyclopentanoid and Cycloheptanoid Core Structures[†]

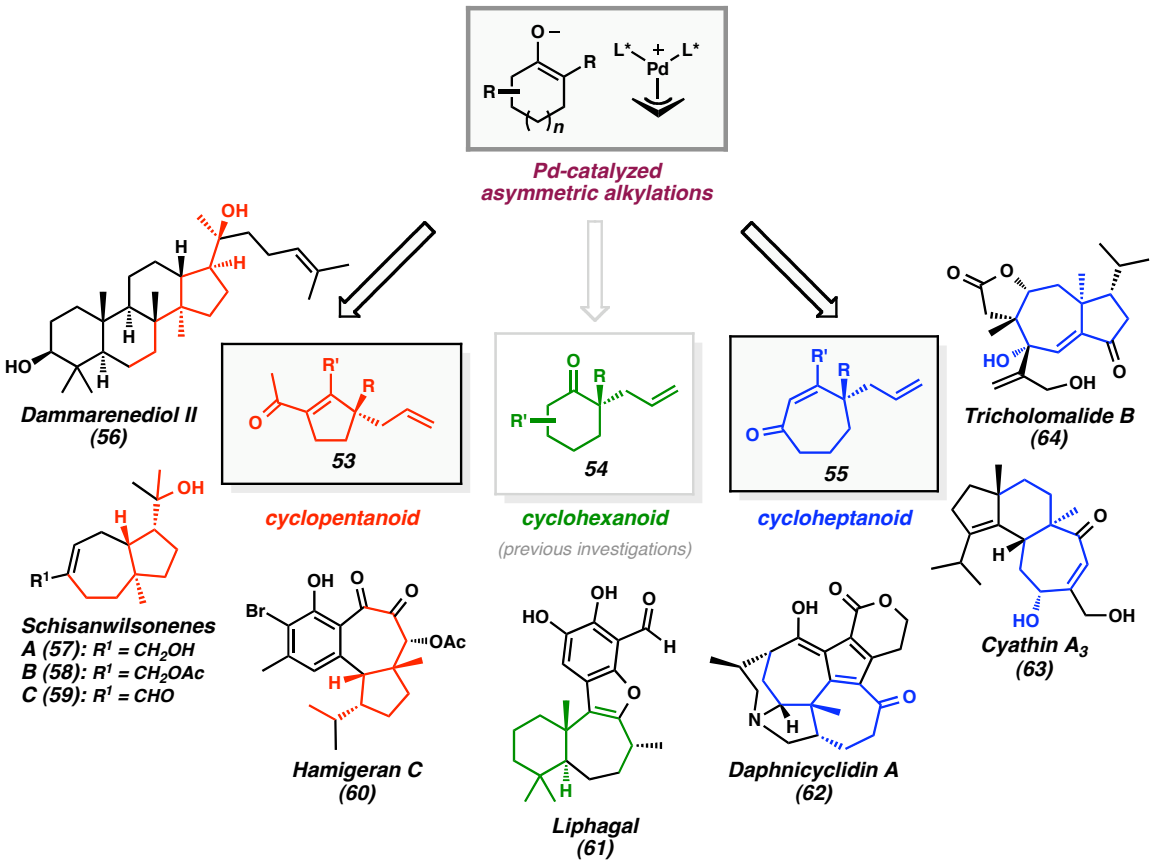
2.1 INTRODUCTION AND BACKGROUND

The stereoselective total synthesis of polycyclic natural products depends greatly on the available tools for the efficient preparation of small and medium sized rings in enantioenriched form.[1] Facile means to elaborate these monocyclic intermediates to fused, bridged, and spirocyclic architectures found within natural ring systems would significantly contribute to modern synthetic methods. While many strategies have been developed for the preparation of six-membered rings and their corresponding polycyclic derivatives, approaches toward the synthesis of five- and seven-membered rings would benefit from further development.

[†] This research was performed in collaboration with Drs. Allen Y. Hong, Michael R. Krout, Thomas Jensen, and Andrew M. Harned and has been published. This chapter was primarily derived from a published full paper (Ref. c). See: (a) Hong, A. Y.; Krout, M. R.; Jensen, T.; Bennett, N. B.; Harned, A. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 2756–2760. (b) Bennett, N. B.; Hong, A. Y.; Harned, A. M.; Stoltz, B. M. *Org. Biomol. Chem.* **2012**, *10*, 56–59. (c) Hong, A. Y.; Bennett, N. B.; Krout, M. R.; Jensen, T.; Harned, A. M.; Stoltz, B. M. *Tetrahedron* **2011**, *67*, 10234–10248.

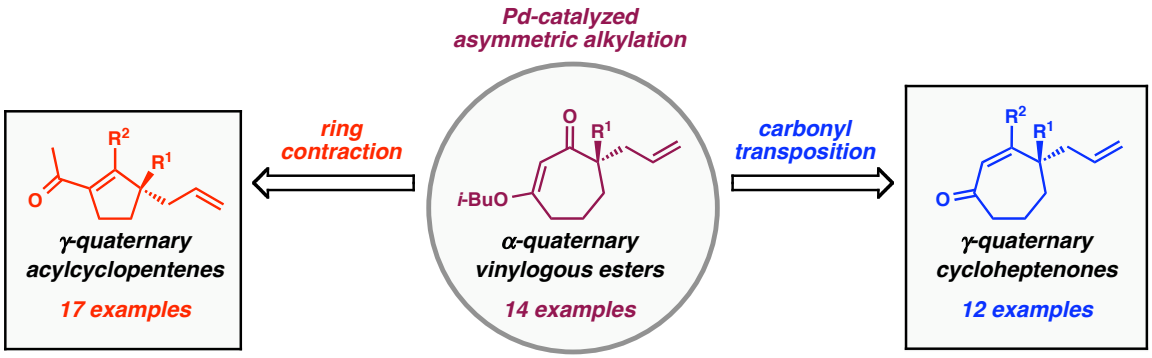
Guided by our continuing interest in the synthesis of polycyclic systems bearing all-carbon quaternary stereocenters using Pd-catalyzed asymmetric alkylation chemistry,[2,3,4,5,6] we sought to prepare various chiral cyclic ketone building blocks for total synthesis (Figure 2.1). Our investigation of six-membered ring substrates has previously enabeled the enantioselective total syntheses of a number of complex natural products (e.g., liphigal, **61**).[7] Given our earlier success, we aimed to generalize our approach to gain access to natural products containing chiral cyclopentanoid and cycloheptanoid ring systems as a part of a broader synthetic strategy.

Figure 2.1. Application of cyclopentanoid, cyclohexanoid, and cycloheptanoid cores toward stereoselective natural product synthesis.



Our efforts have led to the development of general strategies for the preparation of α-quaternary vinylogous esters and their conversion to γ-quaternary cycloheptenones using Stork–Danheiser transformations (Figure 2.2).[8] During the course of this work, we observed unusual reactivity with β-hydroxycycloheptanones and exploited a two-carbon ring contraction to provide a general synthesis of γ-quaternary acylcyclopentenes.[9] With access to the isomeric five- and seven-membered enones, we have prepared diverse synthetic derivatives and polycyclic systems that can potentially provide different entry points for synthetic routes toward complex natural products.

Figure 2.2. General access to enantioenriched cyclopentanoid and cyclohexanoid cores.

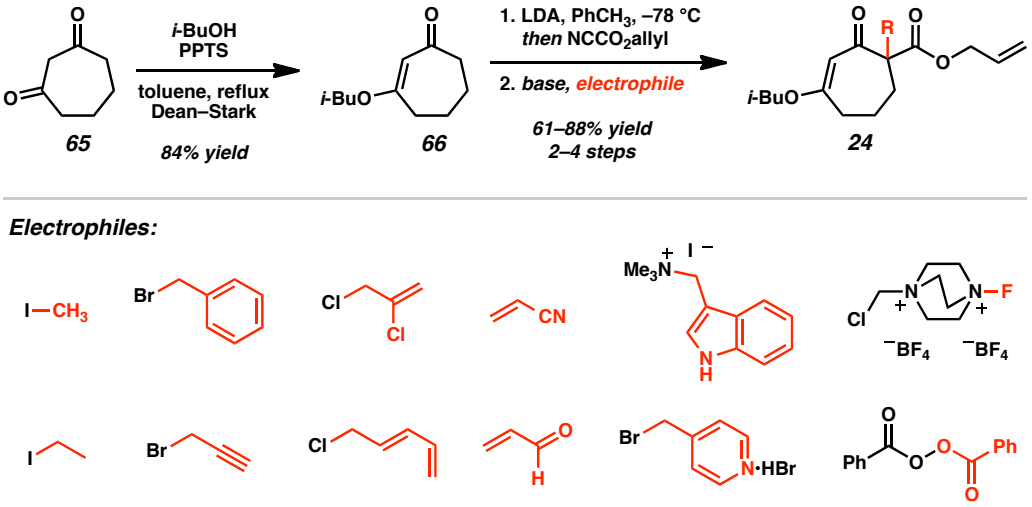


2.1 β-KETOESTER SYNTHESIS AND Pd-CATALYZED ASYMMETRIC ALKYLATION REACTIONS

Much of our past research on the asymmetric alkylation of cyclic ketones[2,3,7a,c,g–i,10d] and vinylogous esters[7b,d–f,10a–c,e] focused on six-membered rings, while transformations of larger rings were less thoroughly investigated. We hoped to expand our work by exploring asymmetric alkylations of seven-membered vinylogous esters.

The feasibility of various types of substrates for our asymmetric alkylation chemistry suggested that vinylogous ester **66** could be transformed into silyl enol ether, enol carbonate, or β-ketoester substrates, but we chose to prepare β-ketoesters due to their relative stability and ease of further functionalization. To access a variety of racemic α-quaternary β-ketoester substrates for Pd-catalyzed asymmetric alkylation reactions, we required multi-gram quantities of 1,3-cycloheptanedione (**65**). Dione **65** is commercially available,[11] but we typically prepare it from cyclopentanone by the route of Ragan and co-workers to facilitate large scale synthesis.[12] Treatment of **65** with *i*-BuOH and catalytic PPTS under Dean–Stark conditions produces vinylogous ester **66** (Scheme 2.1).[11] Acylation of **66** with allyl cyanoformate following deprotonation with LDA enables facile installation of the requisite allyl ester functionality. Subsequent enolate trapping with a variety of electrophiles under basic conditions provides substrates containing alkyl, alkyne, alkene, 1,3-diene, vinyl chloride, nitrile, heteroarene, aldehyde, fluoride, silyl ether, and ester functionalities in 61–88% yield over two to four steps (**24a**–**n**). With these quaternary β-ketoesters in hand, we evaluated the scope of Pd-catalyzed asymmetric alkylation reactions on seven-membered ring vinylogous ester substrates, focusing on methyl/allyl substituted **24a** for our initial optimization efforts.

Scheme 2.1. Synthesis of parent vinylogous ester ***66*** *and β-ketoester substrates* ***24****.*

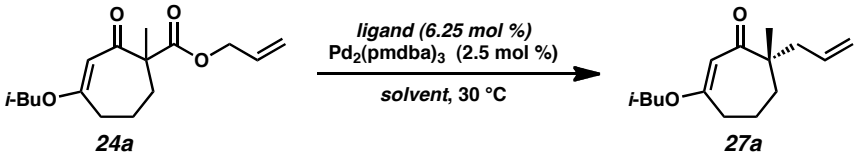


Optimal parameters for the asymmetric alkylation were identified with methyl-substituted β-ketoester **24a** by surveying several electronically differentiated PHOX ligands combined with $Pd_2(pmdba)_3$[13,14] in a number of solvents (Table 2.1). Our initial conditions employing (*S*)-*t*-BuPHOX[2,15] (**3**, 6.25 mol %) and $Pd_2(pmdba)_3$ (2.5 mol %) in THF give vinylogous ester **27a** in 94% yield and 84% ee (entry 1).[16] Application of the same catalyst system in other ethereal solvents, such as *p*-dioxane, 2-methyl THF, TBME, and Et_2O leads to only slight improvements in the enantioselectivity of the reaction to give the desired product in up to 86% ee (entries 2–5). Switching to aromatic solvents provides modest increases in asymmetric induction, furnishing **27a** in 91% yield and 88% ee in the case of toluene (entries 6 and 7).

We next examined the impact of other PHOX ligands (**8** and **67**) in this medium. Electron-deficient ligand **8**[7b,f,17] improves enantioselectivity at the cost of higher catalyst loading and lower yield (entry 8). Structural modification of the aryl phosphine

backbone was evaluated with ligand **67**, but this proved less effective, giving reduced yield and ee (entry 9). Of the three ligands, **3** furnishes the best overall results.

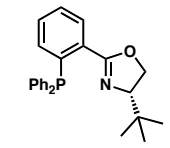
Table 2.1. Solvent and ligand effects on enantioselective decarboxylative allylation.[a]



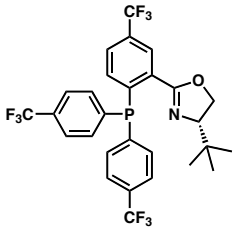
24a ***27a***

entry	ligand	solvent	yield (%)[b]	ee (%)[c]
1	*13*	THF[e]	94	84
2	*13*	*p*-dioxane	86	84
3	*13*	2-methyl THF[e]	75	85
4	*13*	TBME[e]	88	85
5	*13*	Et_2O	93	86
6	*13*	benzene	84	86
7	*13*	toluene	91	88
8[d]	*14*	toluene	57	90
9	*150*	toluene	77	72

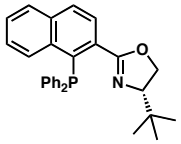
[a] *Conditions*: β-ketoester **24a** (1.0 equiv), $Pd_2(pmdba)_3$ (2.5 mol %), ligand (6.25 mol %) in solvent (0.1 M) at 30 °C; pmdba = 4,4'-methoxydibenzylideneacetone. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Increased catalyst loadings were required to achieve full conversion: $Pd_2(pmdba)_3$ (5 mol %), **8** (12.5 mol %). [e] THF = tetrahydrofuran, 2-methyl THF = 2-methyl tetrahydrofuran, TBME = *tert*-butyl methyl ether.



***(S)-t*-BuPHOX (*3*)**



(S)*-$(CF_3)_3$-*t*-BuPHOX *(8)

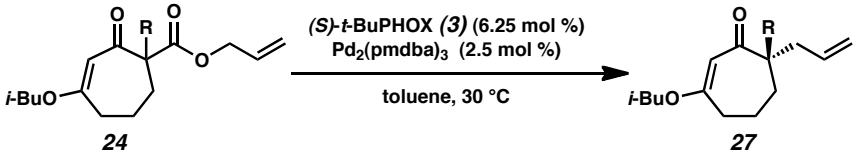


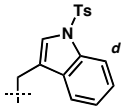
67

With optimal ligand and solvent conditions in hand, we explored asymmetric alkylation of a variety of α-substituted β-ketoesters (Table 2.2). Simple alkyl substitution perform well under our standard conditions (entries 1 and 2), as did a variety of aromatic and heteroaromatic groups (entries 3, 9–10). Additionally, unsaturated functionality such as alkynes, alkenes, and 1,3-dienes do not suffer from competitive reaction pathways (entries 4–6). In the case of vinyl chloride **24g**, no products derived from oxidative addition into the C–Cl bond are observed (entry 7). Gratifyingly, *N*-basic

functionality such as nitriles and pyridines can be carried through the reaction without noticeable catalyst poisoning (entries 8 and 9). Perhaps the most intriguing result is the observation that substrate **24k** with an unprotected aldehyde can be converted to the enantioenriched product **27k** in 90% yield and 80% ee, highlighting the essentially neutral character of the reaction conditions (entry 11). Tertiary fluoride products can also be obtained efficiently in 94% yield and 91% ee (entry 12). Although most β-ketoesters undergo smooth asymmetric alkylation, several products such as silyl ether **27m**[18] and benzoate ester **27n**[19] are not formed as efficiently due to unproductive side reactions (entries 13–14).

Table 2.2. Scope of the Pd-catalyzed enantioselective alkylation of cyclic vinylogous esters.[a]



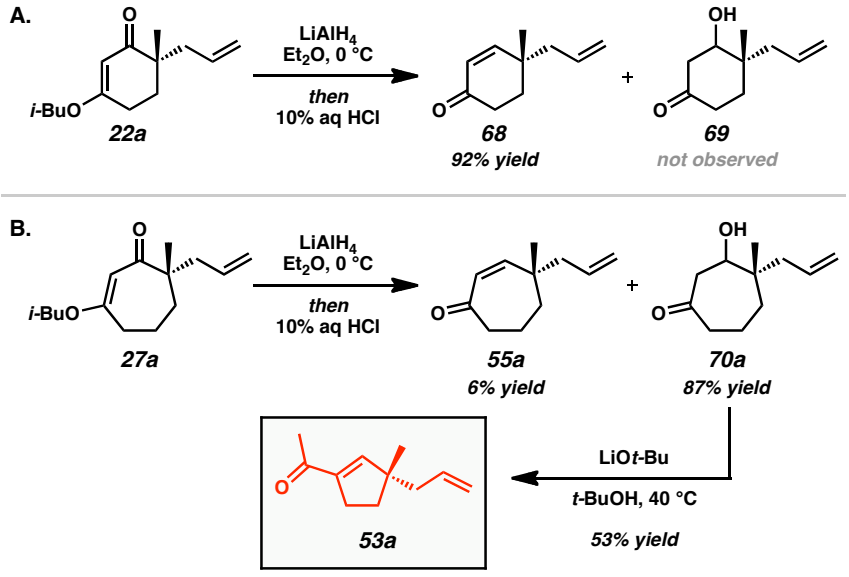
entry	substrate *24*	R	product *27*	yield (%)[b]	ee (%)[c]	entry	substrate *24*	R	product *27*	yield (%)[b]	ee (%)[c]
1	*24a*	$-CH_3$	*27a*	91	88	9	*24i*		*27i*	97	85
2	*24b*	$-CH_2CH_3$	*27b*	89	92						
3	*24c*	$-CH_2Ph$	*27c*	98	86	10	*24j*		*27j*	98	83
4	*24d*	$-CH_2C{\equiv}CH$	*27d*	88	89						
5	*24e*	$-CH_2CH_2CH{=}CH_2$	*27e*	95	87						
6	*24f*		*27f*	90	90	11	*24k*		*27k*	90	80
						12	*24l*	–F	*27l*	94	91
7	*24g*		*27g*	99	86	13	*24m*	$-CH_2OTBDPS$[d]	*27m*	66	58
8	*24h*	$-CH_2CH_2CN$	*27h*	96	87	14	*24n*		*27n*	75	57

[a] *Conditions*: β-ketoester **24** (1.0 equiv), $Pd_2(pmdba)_3$ (2.5 mol %), *(S)-t*-BuPHOX (**3**) (6.25 mol %) in toluene (0.1 M) at 30 °C; pmdba = 4,4'-methoxydibenzylideneacetone. [b] Isolated yield. [c] Determined by chiral HPLC or SFC. [d] Ts = 4-toluenesulfonyl, TBDPS = *tert*-butyldiphenylsilyl.

2.1 UNUSUAL REACTIVITY OF β-HYDROXYCYCLOHEPTANONES

With an assortment of asymmetric alkylation products in hand, we next sought to perform a carbonyl transposition using methods developed by Stork and Danheiser.[20] Hydride reduction of six-membered vinylogous ester **22a** with subsequent acid treatment gives enone **68** as expected (Scheme 2.2A). To our surprise, application of identical reaction conditions to the seven-membered analog (**27a**) provides poor yield of cycloheptenone **55a** (Scheme 2.2B). Only minor quantities of elimination product are observed even after prolonged stirring with 10% aqueous HCl. Closer inspection of the reaction mixture revealed β-hydroxyketone **70a** as the major product, suggesting that these seven-membered ring compounds display unique and unusual reactivity compared to their cyclohexyl counterparts.[21,22,23]

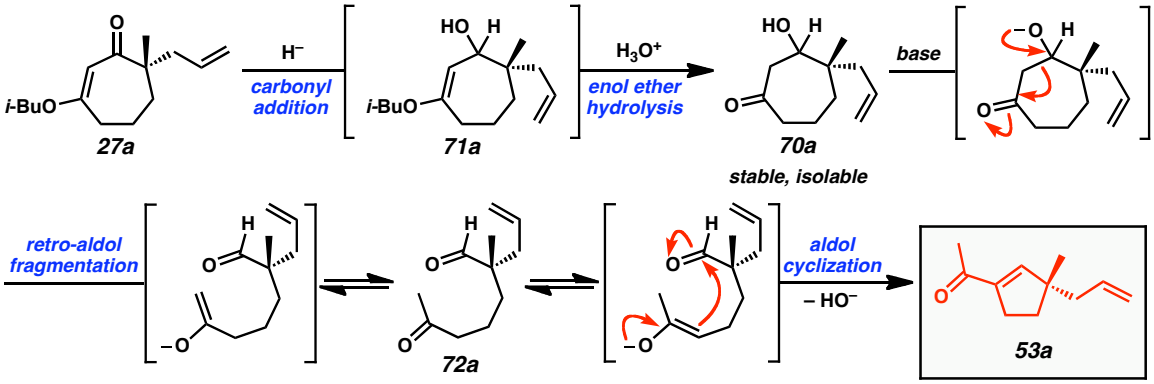
Scheme 2.2. Observation of the unusual reactivity of β-hydroxycycloheptanone ***70a****.*



Without initial success using acidic conditions, we reasoned that β-hydroxyketone **70a**[24] could potentially provide cycloheptenone **55a** under basic conditions through a β-elimination pathway (Scheme 2.2B). However, attempts in this regard did not produce enone **55a**, but instead generated isomeric enone **53a** that appeared to be formed through an unexpected ring contraction pathway. Notably, this transformation serves as a rare example of a two-carbon ring contraction.[22,25,26]

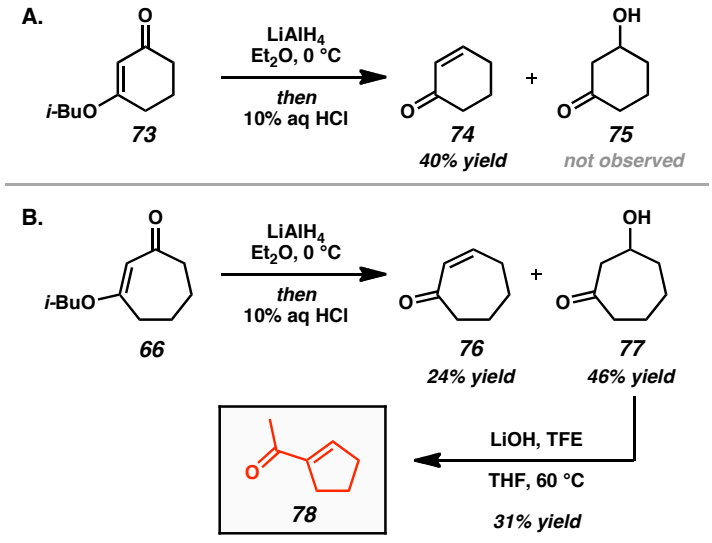
Upon consideration of the reaction mechanism, we believe this process occurs through an initial deprotonation of the hydroxy moiety, followed by retro-aldol ring fragmentation to a ketoaldehyde enolate (Scheme 2.3). Subsequent isomerization to the more substituted enolate and aldol cyclization could lead to the observed two-carbon ring contraction product **53a**. Attempts to isolate the intermediate ketoaldehyde **72a** were unsuccessful, but aldehyde peaks could be observed by ^{1}H NMR in reactions that did not proceed to full conversion. Subsequent experiments on more substituted β-hydroxyketones enabled isolation of linear uncyclized intermediates and provided additional support for this reaction mechanism (Scheme 2.6).

Scheme 2.3. Proposed ring contraction mechanism.



To explore the general stability and reactivity of β-hydroxycycloheptanones, we briefly examined simplified analogs that do not possess the α-quaternary stereocenter (Scheme 2.4). Following hydride reduction, elimination to cyclohexenone **74** is observed for the six-membered vinylogous ester **73**, while β-hydroxycycloheptanone **77** and volatile cycloheptenone **76** are observed for cycloheptyl analog **66**. In the seven-membered ring case, a higher proportion of elimination product is observed when compared to the substituted analog **27a**. A milder aqueous acid work-up may suffice to hydrolyze the isobutyl enol ether and enable isolation of the β-hydroxyketone in higher yield in this case. Ring contraction of β-hydroxycycloheptanone **77** under basic conditions proceeds smoothly to give volatile acylcyclopentene **78**. These observations suggest that the unusual two-carbon ring contraction appears to be a reactivity trend associated with seven-membered rings and motivated the development of the ring contraction methodology as a general approach to chiral acylcyclopentenes.

Scheme 2.4. Attempted Stork–Danheiser manipulations on unsubstituted rings.



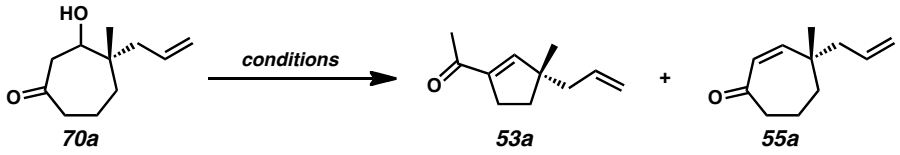
2.1 RING CONTRACTION STRATEGY FOR PREPARING γ-QUATERNARY ACYLCYCLOPENTENES

Intrigued by our findings, we sought to develop a robust route to γ-quaternary acylcyclopentenes with many substitution patterns. Exploration of a number of bases, additives, solvents, and temperatures for the ring contraction of β-hydroxyketone **70a** provided optimal parameters for the transformation (Table 2.3). Given our early result using LiO*t*-Bu, we examined a number of other aldol cyclization conditions with a variety of non-nucleophilic bases. We observed that several *tert*-butoxides in *t*-BuOH and THF provide conversion to the desired product (**53a**) in good yields (entries 1–4), but noted that the rate of product formation is comparatively slower with LiO*t*-Bu than with NaO*t*-Bu or KO*t*-Bu. The use of various hydroxides reveals a similar trend, where NaOH and KOH generate acylcyclopentene **53a** in 4 hours with improved yields over the respective *tert*-butoxides (entries 5 and 6). The relatively sluggish reactivity of LiOH may be due to the lower solubility of this base in THF, providing **53a** in low yield with the formation of various intermediates (entry 7).

To improve the yield of the reaction with LiOH as base, we investigated alcohol additives that facilitate the production of mild, organic-soluble bases under the reaction conditions. The combination of *t*-BuOH and LiOH in THF increases the yield of **53a** to a similar level as that observed with LiO*t*-Bu, although the reaction still proceeds slowly (entry 8). More acidic, non-nucleophilic alcohols such as hexafluoroisopropanol (HFIP) and 2,2,2-trifluoroethanol (TFE) demonstrate exceptional reactivity in combination with LiOH and efficiently afford **53a** in high yields (entries 9 and 10).[27] In particular, TFE enables the production of **53a** in 96% yield. Comparable results with preformed

$LiOCH_2CF_3$[28] suggest this alkoxide could be the active base under the LiOH/TFE ring contraction conditions (entry 11).

Table 2.3. Ring contraction optimization.[a]



70a ***53a*** ***55a*** ***not observed***

entry	base	additive	solvent	T (°C)	conversion (%)	time (h)	yield (%)[b]
1	LiO*t*-Bu	—	*t*-BuOH	40	100	9	71
2	LiO*t*-Bu	—	THF	40	100	8	60
3	NaO*t*-Bu	—	THF	40	100	5	81
4	KO*t*-Bu	—	THF	40	100	5	85
5	NaOH	—	THF	60	100	4	89
6	KOH	—	THF	60	100	4	87
7	LiOH	—	THF	60	78	24	19[d]
8	LiOH	*t*-BuOH	THF	60	98	24	78
9	LiOH	HFIP[c]	THF	60	99	12.5	87
10	LiOH	TFE[c]	THF	60	99	12.5	96
11	$LiOCH_2CF_3$	—	THF	60	—	10	90[e]
12	$CsOH{\cdot}H_2O$	—	THF	60	100	4	48
13	Cs_2CO_3	—	THF	60	67	24	61[f]
14	Cs_2CO_3	TFE[c]	THF	60	100	12.5	86
15	Cs_2CO_3	TFE[c]	CH_3CN	60	100	12.5	100
16	NaO*t*-Bu	*t*-BuOH	THF	40	100	8	52
17	KO*t*-Bu	*t*-BuOH	THF	40	100	8	57
18	LiOH	*t*-BuOH	THF	40	87	24	77
19	LiOH	TFE[c]	THF	40	73	24	73
20	LiOH	HFIP[c]	THF	40	84	24	81
21	CsF	—	CH_3CN	60	86	24	10

[a] *Conditions*: β-hydroxyketone **70a** (1.0 equiv), additive (1.5 equiv), base (1.5 equiv), solvent (0.1 M) at indicated temperature for 9–24 h. [b] GC yield using an internal standard at ≥ 98% conversion unless otherwise stated. [c] HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol; TFE = 2,2,2-trifluoroethanol. [d] Several reaction intermediates observed by TLC and GC analysis; proceeded to 78% conversion. [e] Isolated yield. [f] Reaction did not reach completion at 24 h; proceeded to 67% conversion.

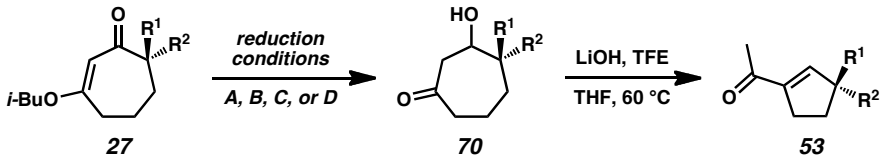
Concurrent investigation of cesium bases reinforced the importance of alcohol additives for the in situ formation of organic-soluble bases in the ring contraction transformation. With $CsOH{\cdot}H_2O$ and Cs_2CO_3, product formation is inefficient due to low

yield or sluggish reaction progress (entries 12 and 13). However, the addition of TFE affords acylcyclopentene **53a** in yields comparable to those of the LiOH/TFE conditions (entry 14). Notably, ring contraction with Cs_2CO_3/TFE can also be performed in acetonitrile as an alternative, non-ethereal solvent with high efficiency (entry 15). Additional combinations of bases, additives, solvents, and temperatures were evaluated, but these conditions were generally less effective (entries 16–21).[29]

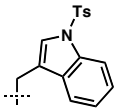
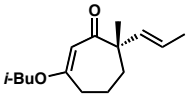
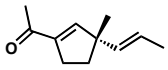
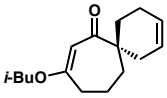
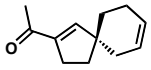
While a number of bases are effective for the production of **53a** in excellent yields, we selected the combination of LiOH/TFE as our standard conditions for reaction scope investigation due to the lower cost and greater availability of base. The data from our study further recognize the unique properties of these mild bases and suggest their application may be examined in a broader context.[30,31] Importantly, none of the conditions surveyed for the ring contraction studies generated the β-elimination product, cycloheptenone **55a**.

With optimal base-promoted conditions in hand, we investigated the scope of the ring contraction chemistry with a variety of substitution patterns[23] (Table 2.4). Simple alkyl, aromatic, and heteroaromatic functionalized substrates perform well under our standard parameters (Method A) in 84–95% yield (entries 1–6, 10). Additionally, vinyl chlorides, nitriles, and indoles can be incorporated into the target acylcyclopentenes in 85–92% yield (entries 7 and 8). Further studies revealed that DIBAL can alternatively be employed to generate the β-hydroxyketone by enabling more precise control of hydride stoichiometry. The use of these modified conditions followed by oxalic acid work-up in methanol (Method B) facilitates the preparation of pyridine-containing acylcyclopentene **53i** in higher yield compared to Method A (entry 9).

Table 2.4. Ring contraction substrate scope.[a–e]



27 ***70*** ***53***

entry	substrate *27*	reduction conditions	R^1	R^2	product *53*[e]	yield (%)[f]
1	***27a***	A	$-CH_3$	$-CH_2CH{=}CH_2$	***53a***	84
2	***27b***	A	$-CH_2CH_3$	$-CH_2CH{=}CH_2$	***53b***	90
3	***27c***	A	$-CH_2Ph$	$-CH_2CH{=}CH_2$	***53c***	86
4	***27d***	A	$-CH_2C{\equiv}CH$	$-CH_2CH{=}CH_2$	***53d***	95
5	***27e***	A	$-CH_2CH_2CH{=}CH_2$	$-CH_2CH{=}CH_2$	***53e***	87
6	***27f***	A		$-CH_2CH{=}CH_2$	***53f***	91
7	***27g***	A		$-CH_2CH{=}CH_2$	***53g***	92
8	***27h***	A	$-CH_2CH_2CN$	$-CH_2CH{=}CH_2$	***53h***	85
9	***27i***	B		$-CH_2CH{=}CH_2$	***53i***	80
10	***27j***	A		$-CH_2CH{=}CH_2$	***53j***	87
11	***27m***	C	$-CH_2OTBDPS$[i]	$-CH_2CH{=}CH_2$	***53m***	91
12	***27o***[g]	C	$-(CH_2)_3OTBDPS$[i]	$-CH_2CH{=}CH_2$	***53o***	85
13	***27p***[h]	A			***53p***	81
14	***27q***[g]	A			***53q***	87
15	***27n***	D	$-OH$	$-CH_2CH{=}CH_2$	***53n***	25
16	***27l***	A	$-F$	$-CH_2CH{=}CH_2$	***53l***	0

[a] *Reduction Conditions A*: vinylogous ester **27** (1.0 equiv), $LiAlH_4$ (0.55 equiv) in Et_2O (0.2 M) at 0 °C, then 10% aqueous HCl quench. [b] *Reduction Conditions B*: (1) vinylogous ester **27** (1.0 equiv), DIBAL (1.2 equiv) in $PhCH_3$ (0.03 M) at –78 °C; (2) oxalic acid·$2H_2O$ in MeOH (0.02 M). [c] *Reduction Conditions C*: vinylogous ester **27** (1.0 equiv), $CeCl_3{\cdot}7H_2O$ (1.0 equiv), $NaBH_4$ (3.0 equiv) in MeOH (0.02 M) at 0 °C, then 10% aqueous HCl in Et_2O at 0 °C. [d] *Reduction Conditions D*: (1) vinylogous ester **27** (1.0 equiv), DIBAL (3.3 equiv) in $PhCH_3$ (0.03 M) at –78 °C; (2) 10% aqueous HCl in Et_2O at 0 °C. [e] *Ring Contraction Conditions E*: β-hydroxyketone **70** (1.0 equiv), TFE (1.5 equiv), LiOH (1.5 equiv) in THF (0.1 M) at 60 °C. [f] Isolated yield over 2–3 steps. [g] Prepared from **27k**. See Experimental Section. [h] Prepared from **27a**. See Experimental Section. [i] Ts = 4-toluenesulfonyl, TBDPS = *tert*-butyldiphenylsilyl, DIBAL = diisobutylaluminum hydride.

While various compounds undergo the ring contraction sequence with high efficiency, other substrates with more sensitive functionality require modification of the reaction conditions. To this end, we investigated the use of milder reduction conditions developed by Luche[32] to further increase the reaction scope. Silyl ether substrate **27m**[33] can be converted to the corresponding acylcyclopentene **53m** in 86% yield using the $LiAlH_4$ protocol (Method A), but application of Luche reaction conditions using (Method C) enables improvement to 91% yield (entry 11). The same conditions provide the related silyl ether-containing acylcyclopentene **53o** with a longer carbon chain in 85% yield (entry 12).

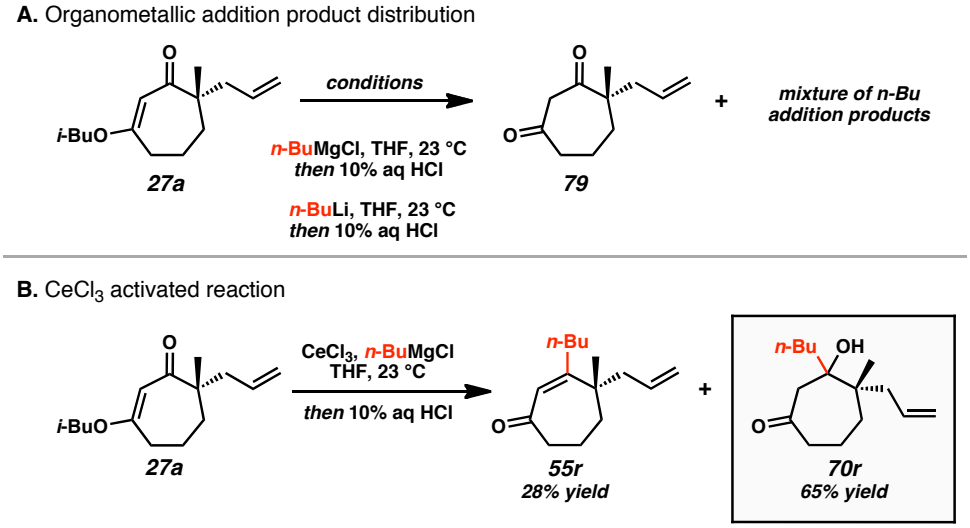
Our success in performing the ring contraction with a variety of substituents at the quaternary stereocenter encouraged studies aimed at determining whether additional substitution patterns could be introduced into the acylcyclopentene products. While most substrates involve a variable group and an allyl fragment positioned on the quaternary center, we were intrigued by the possibility of performing the ring contraction with other groups. Investigation of *trans*-propenyl substituted vinylogous ester **27p** using the standard LiOH/TFE conditions showed that the chemistry is unaffected by modification of the allyl fragment, generating product in 81% yield (entry 13). Additionally, the reaction of spirocycle **27q** also proceeds without complication and affords the desired acylcyclopentene in 87% yield (entry 14).

Although many compounds perform well in the ring contraction sequence, certain substrates pose significant challenges. DIBAL reduction with a 10% aqueous HCl work-up (Method D) and ensuing ring contraction of α-benzoate ester **27n** provides tertiary hydroxyl acylcyclopentene **53n**, but the yield is relatively low compared to other

substrates (entry 15). Attempts to prepare the corresponding tertiary fluoride **27l** were unsuccessful as no desired product was observed (entry 16). Under the reaction conditions, both vinylogous esters lead to more complex product mixtures from unproductive side reactions in contrast to the typically high yielding transformations observed for other substrates.

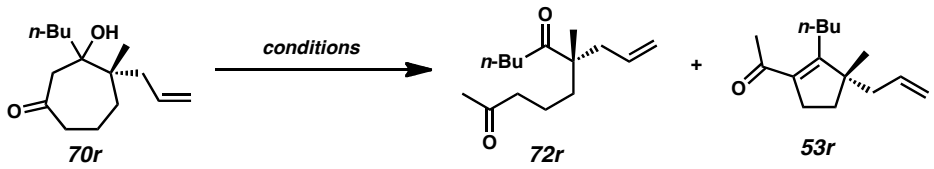
To obtain more functionalized acylcyclopentene products and extend our methodology, we sought access to β-substituted acylcyclopentenes by replacing the hydride reduction step with the addition of an organometallic reagent and applying the ring contraction chemistry on the resulting tertiary β-hydroxyketones. We selected a simple system for our initial investigations and evaluated the reaction of *n*-butyl nucleophiles with vinylogous ester **27a**. Unfortunately, the addition of *n*-BuMgCl or *n*-BuLi affords a complex mixture of products and proceeds slowly without reaching completion, consequently converting unreacted starting material to dione **79** upon work-up with strong acid (Scheme 2.5A).[34] This low reactivity can be understood from the electron-rich and sterically-crowded nature of the carbonyl electrophile. Gratifyingly, excellent reactivity is achieved by introducing $CeCl_3$ to the reaction with the Grignard reagent,[35] although a fair amount of the corresponding enone is produced in the transformation (Scheme 2.5B).[36] Nevertheless, the $CeCl_3$-supplemented addition furnishes a significantly improved overall yield of addition products with good selectivity for β-hydroxyketone **70r**.

Scheme 2.5. Organometallic addition to vinylogous ester ***27a***.



We next examined the ring contraction sequence with β-hydroxyketone **70r** (Scheme 2.6). Treatment of alcohol **70r** with the optimized ring contraction conditions using LiOH/TFE yields linear dione **72r** without any of the γ-substituted acylcyclopentene. Even though the conditions do not afford the desired product, the isolation of stable uncyclized intermediate **72r** supports our proposed retro-aldol fragmentation/aldol cyclization mechanism (Scheme 2.3). By employing a stronger base such as KO*t*-Bu, both steps of the rearrangement can be achieved to give acylcyclopentene **53r**. Furthermore, significantly higher yields and reduced reaction times are obtained with microwave irradiation.

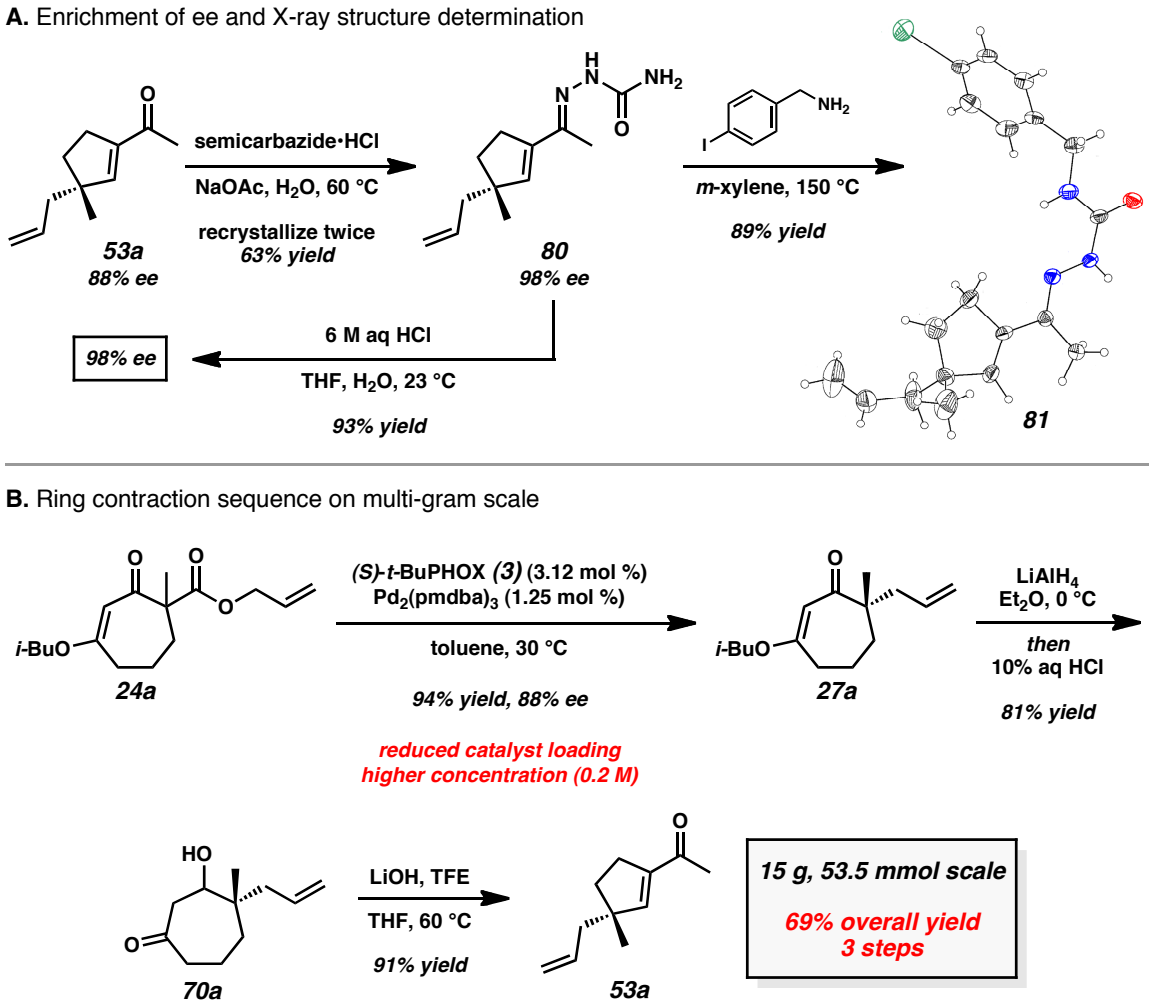
*Scheme 2.6. Ring contraction screen on β-hydroxyketone **70r**.*



LiOH, TFE, THF, 60 °C, 3 h	*71% yield*	*not observed*
KO*t*-Bu, THF, 60 °C, 22 h	*not observed*	*65% yield*
KO*t*-Bu, THF, 85 °C, μwaves, 5 min	*not observed*	*73% yield*

With a route to form a variety of acylcyclopentenes that possess different substitution patterns, we were interested in increasing the enantiopurity of these potentially useful intermediates. Formation of the corresponding semicarbazone **80** enables us to obtain material in 98% ee after two recrystallizations (Scheme 2.7A). A high yielding hydrolysis affords enantioenriched acylcyclopentene **53a**. Further functionalization of semicarbazone **80** with 4-iodobenzylamine provided crystals that allowed verification of absolute stereochemistry by X-ray crystallography.[37] To demonstrate the viability of our method for large-scale enantioselective synthesis, we performed the asymmetric alkylation and ring contraction transformations on multi-gram scale (Scheme 2.7B). Gratifyingly, our route proved to be robust and reliable. Using 50 mmol of substrate (15 g), we are able to achieve a 94% yield and 88% ee of our desired asymmetric alkylation product. Notably, the increased reaction scale permits reduced catalyst loadings (1.25 mol % $Pd_2(pmdba)_3$ and 3.12 mol % (*S*)-*t*-BuPHOX, **3**) and higher substrate concentrations (0.2 M). β-Ketoester **24a** undergoes the asymmetric alkylation and ring contraction protocol to furnish the desired acylcyclopentene in 69% overall yield over the three step sequence.

Scheme 2.7. Confirmation of absolute stereochemistry and multi-gram scale reactions.



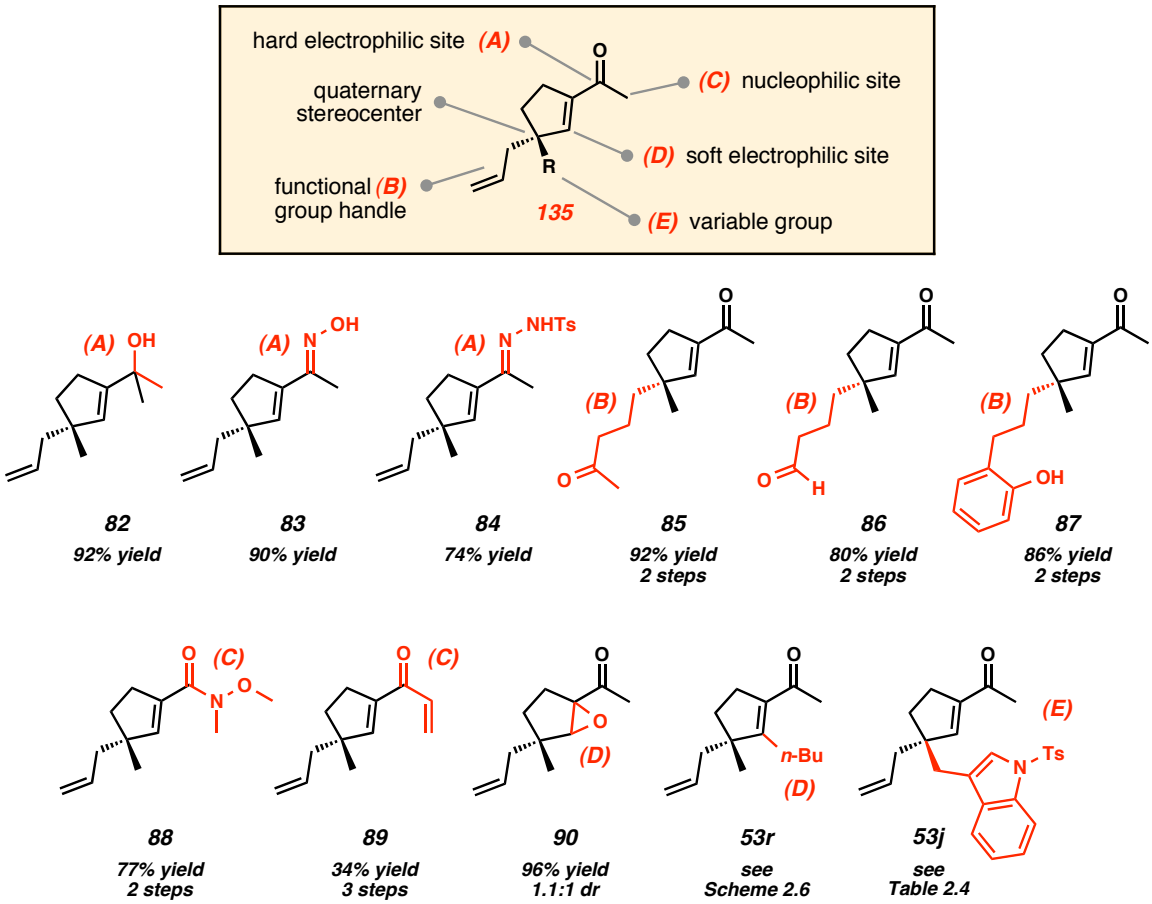
2.2 SYNTHESIS OF ACYLCYCLOPENTENE DERIVATIVES USING SITE-SELECTIVE TRANSFORMATIONS

With the ultimate goal of applying our methodology toward the total synthesis of complex natural products, we set out to probe the synthetic utility of various acylcyclopentenes prepared using our ring contraction strategy. While these acylcyclopentenes (**53**) are chiral fragments with low molecular weights, they possess an array of useful functionality that can be exploited for synthetic applications through site-

selective manipulations (Figure 2.3). Acylcyclopentene **53** contains hard and soft electrophilic sites, a nucleophilic site, a functional group handle in the form of an allyl group, and a variable group that is installed through asymmetric alkylation. Additionally, all of the acylcyclopentenes we have prepared bear an all-carbon quaternary stereocenter or a fully substituted tertiary center.

We aimed to perform site-selective functionalizations to demonstrate that a variety of derivatives could be prepared by recognizing the rich functionality present in acylcyclopentene **53** (Figure 2.3). Selective derivatization of site A enables access to tertiary alcohols, oximes, and hydrazones in 74–92% yield (**82**–**84**). Manipulation of site B through olefin methathesis with methyl vinyl ketone or crotonaldehyde provides intermediate bis-enone or enone-enal compounds in 90–95% yield as *trans* olefin isomers. Chemoselective hydrogenation with Wilkinson's catalyst reduces the less substituted and less sterically hindered olefin in these systems to form mono-enones **85** and **86** in 90–93% yield. Using the insights gathered from these manipulations, we performed chemoselective Heck and hydrogenation reactions to provide acylcyclopentene **87** bearing a pendant phenol in 86% yield over two steps. Through modification of site C, access to Weinreb amides and divinyl ketones can be achieved (**88**–**89**). Additionally, manipulation of site D gives rise to epoxide **90**. Functionalization of this site was also demonstrated with β-substituted acylcyclopentene **53r** (Scheme 2.6). Lastly, variations at site E are accomplished by installing the appropriate groups at an early stage during the asymmetric alkylation step (Scheme 2.1 and Table 2.2).

*Figure 2.3. Selective functionalizations on sites A–E of acylcyclopentenes (**53**).*

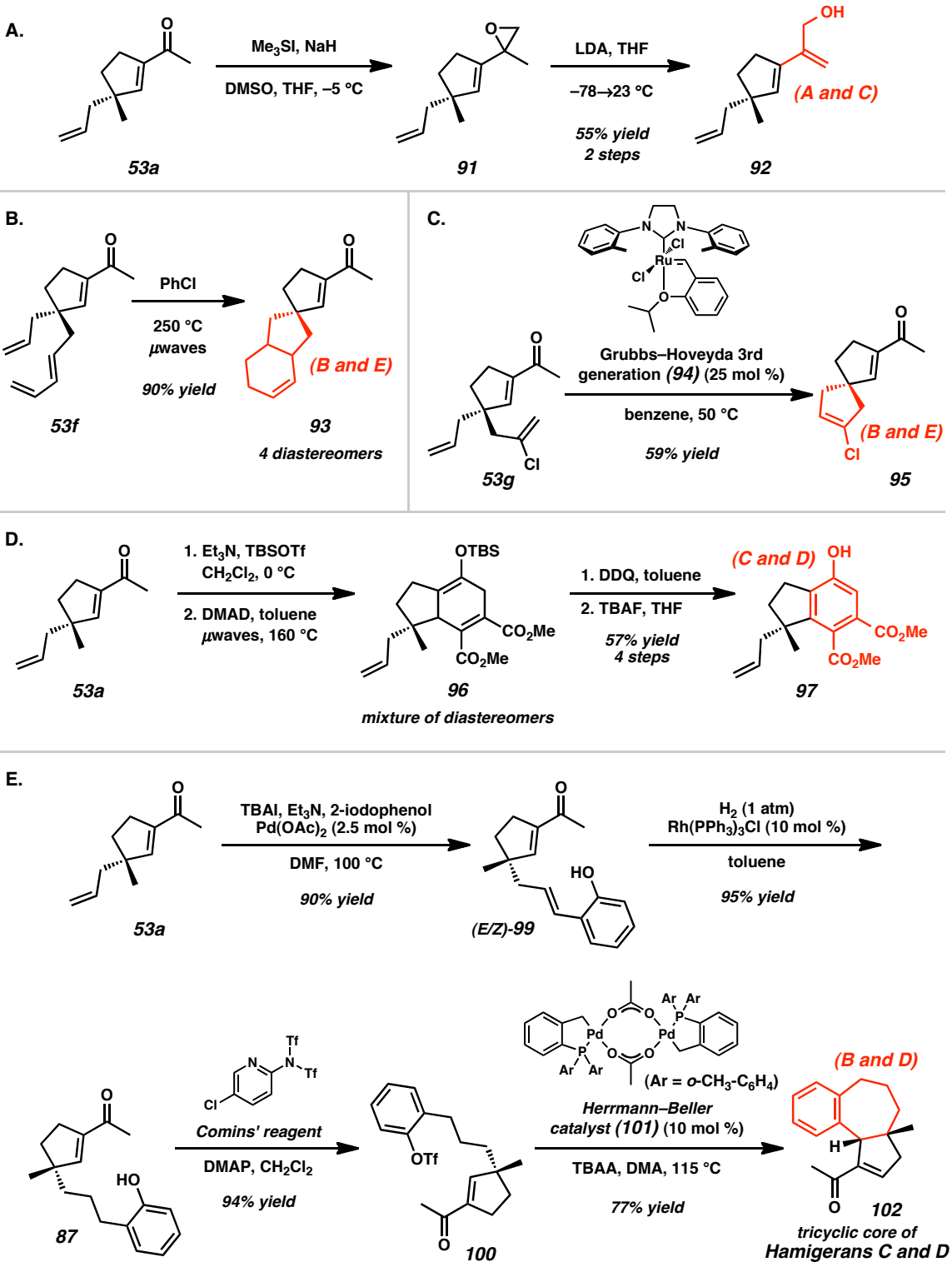


To further increase the potential of these chiral building blocks, we performed manipulations on a combination of reactive sites to arrive at more advanced synthetic intermediates (Scheme 2.8). Hydroxydiene **92** is obtained in 55% yield over two steps from acylcyclopentene **53a** by performing a carbonyl epoxidation followed by fragmentation (Scheme 2.8A). Spirocyclic systems such as enones **93** and **95** are obtained by performing an intramolecular Diels–Alder using **53f** or a ring-closing metathesis of **53g** using Grubbs–Hoveyda 3rd generation catalyst (Scheme 2.8B and Scheme 2.8C). Additionally, phenolic indane **97** is generated in 57% yield over four steps by exploiting an intermolecular Diels–Alder reaction with DMAD (Scheme 2.8D).

To arrive at intermediates that bear a stronger resemblance to natural products, we formed the triflate of Heck product **87** using Comins' reagent[38] and subjected the compound to a subsequent intramolecular Heck reaction using the Herrmann–Beller palladacycle **101**[39] to obtain tricycle **102** with the *cis*-ring fusion (Scheme 2.8E). This key tricycle contains all of the carbocyclic core of hamigerans C and D with the correct stereochemistry at the ring fusions.

Overall, our general strategy enables the synthesis of valuable chiral building blocks by taking advantage of the rich functional group content embedded in acylcyclopentenes (**53**). Site-selective manipulations at regions A–E produce monocyclic and polycyclic compounds with a large degree of structural variation. Our studies provide valuable insight into the nature of these compounds, and we aim to apply our knowledge of these promising intermediates in the total synthesis of complex natural products.

Scheme 2.8. Functionalization of multiple acylcyclopentene reactive sites.

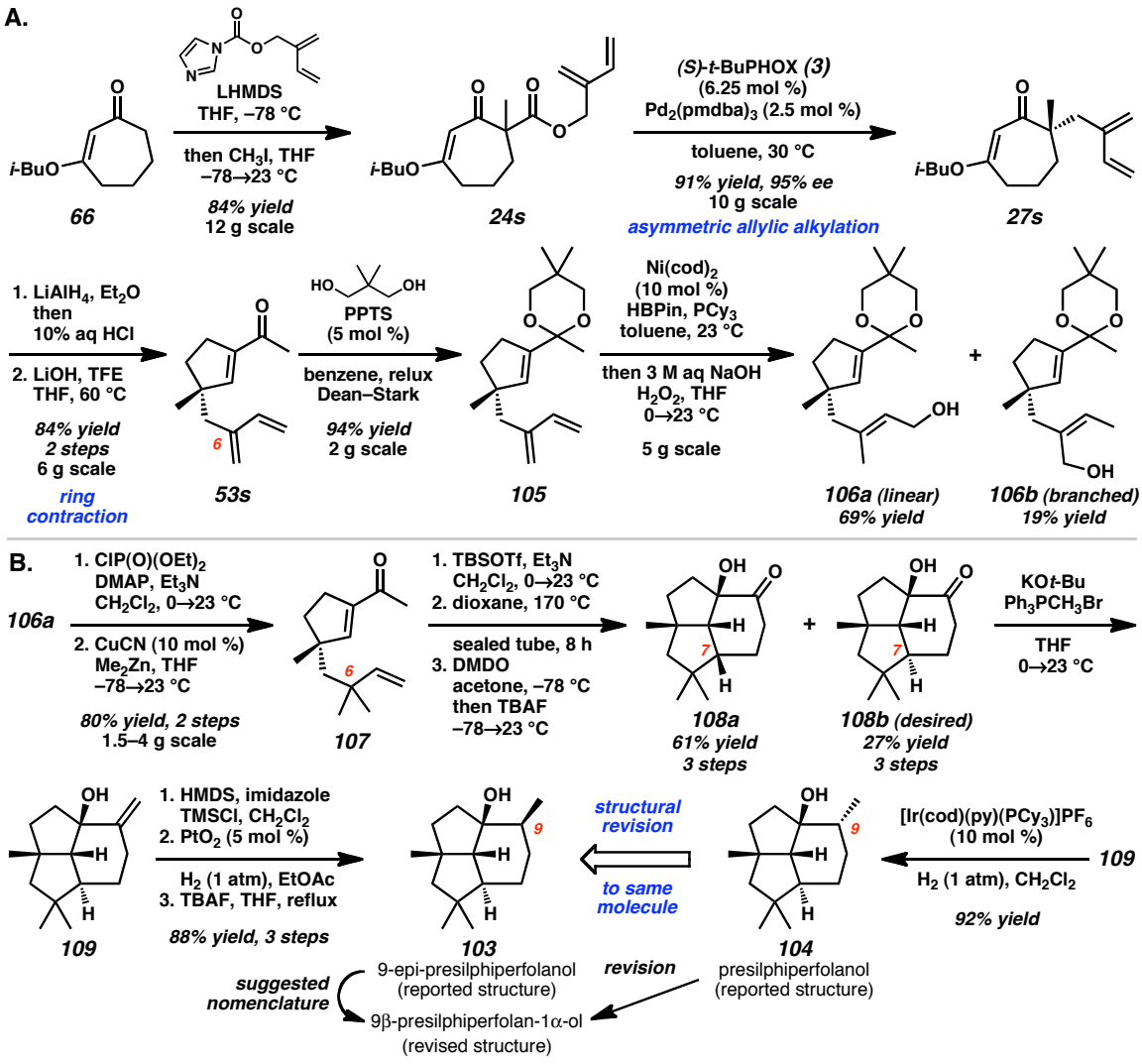


2.1.1 Application of Ring Contraction Toward (–)-9-epi-Presilphiperfolan-1-ol and (–)-Presilphiperfolan-1-ol[40]

In 2012, our group employed the ring contraction strategy toward the total synthesis of the reported structures of (–)-9-epi-presilphiperfolan-1-ol (**103**) and (–)-presilphiperfolan-1-ol (**104**).[41] In this route, vinylogous ester **66** is acylated and alkylated in a single step to afford vinylogous ester **24s** (Scheme 2.9A). Asymmetric allylic alkylation of this molecule under our standard Pd-catalyzed conditions affords α-quaternary vinylogous ester **27s** in excellent yield and 95% ee. Notably, no side products arising from a Heck or Diels–Alder pathway are observed in this transformation. The ring contraction process also proceeds well with this substrate, generating acylcyclopentene **53s** in 84% yield over two steps. A four step protection, hydroboration, phosphorylation, and S_N2' displacement sequence installs the geminal methyls at C(6) to furnish acylcyclopentene **107** (Scheme 2.9A and B). The tricyclic core of the natural product is assembled via a Diels–Alder cycloaddition, although a mixture of C(7) diastereomers is produced. Ensuing Rubottom oxidation selectivity forms the hydroxy group on the convex face of both diastereomeric tricycles to ultimately afford α-hydroxyketones **108a** and **b** (Scheme 2.9B). The desired ketone (**108b**) is olefinated with the standard Wittig ylide to give allylic alcohol **109**. Subsequent hydrogenation completes the synthesis by installing the C(9) methyl group selectively through either a steric (three step) or directing group (Crabtree's catalyst) approach. Analysis of the reported and synthetic structures of 9-epi-presilphiperfolan-1-ol (**103**) and presilphiperfolan-1-ol (**104**) suggest that the latter is not actually a natural product as the structure was originally misassigned. The spectral data of isolated **103** and **104** match

closely, and upon consideration of the biosynthetic pathway, we determined that isolated presilphiperfolan-1-ol (**104**) is actually 9-epi-presilphiperfolan-1-ol (**103**). To avoid future confusion, we propose that the name 9β-presilphiperfolan-1α-ol be used instead to describe this molecule.

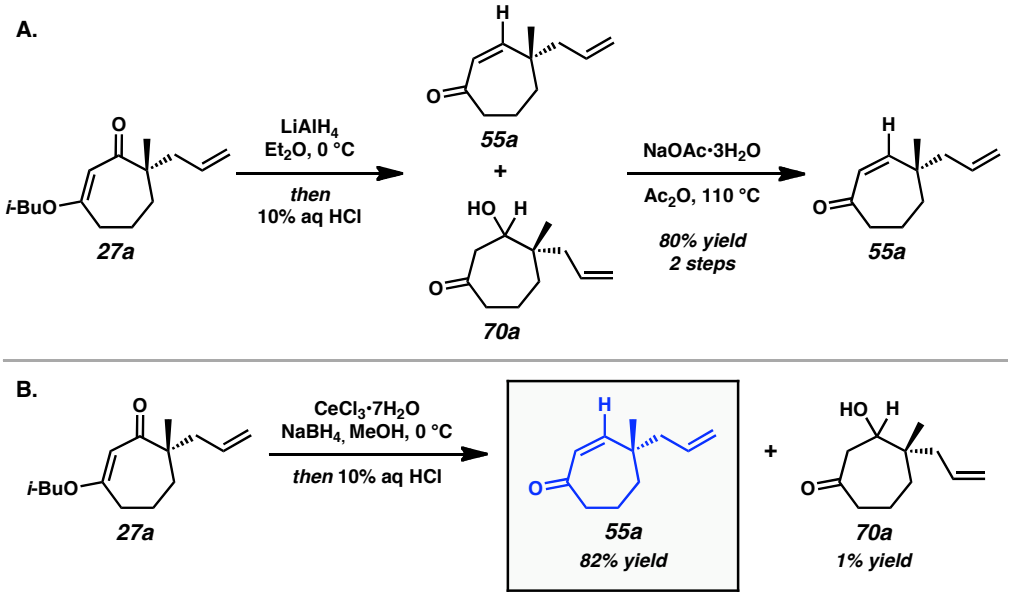
*Scheme 2.9. Route to (–)-9-epi-presilphiperfolan-1-ol (**103**) and (–)-presilphiperfolan-1-ol (**104**).*



2.3 CARBONYL TRANSPOSITION APPROACH TO γ-QUATERNARY CYCLOHEPTENONES

While pleased to discover the unusual reactivity of vinylogous esters **27** that led to the synthesis of various acylcyclopentenes, we maintained our original interest in preparing enantioenriched γ-quaternary cycloheptenones (**55**) and began reexamining reaction parameters to this end. Initially, we identified conditions to obtain cycloheptenone **55a** in two steps by activation and elimination of the hydroxy group at elevated temperatures, but ultimately desired a more direct route from vinylogous ester **27a** (Scheme 2.10A). After considerable experimentation, we fortuitously discovered that reduction and elimination using Luche conditions effectively furnished enone **55a** with minimal β-hydroxyketone **70a** (Scheme 2.10B). A number of factors may contribute to the reversed product distribution, with methanol as solvent likely playing a large role.[42] With an effective route to enone **55a**, we also sought to prepare β-substituted cycloheptenones through the 1,2-addition of organometallic reagents.

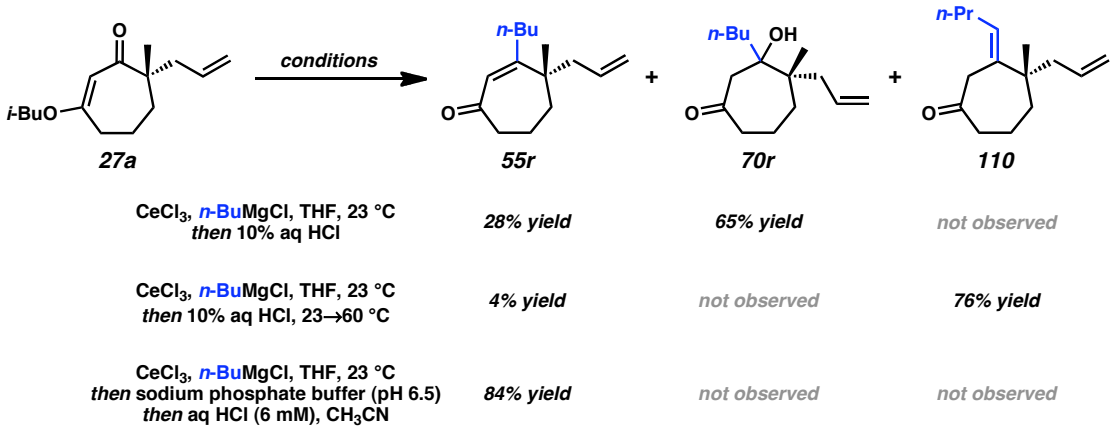
Scheme 2.10. Stepwise and one-pot formation of cycloheptenone ***55a****.*



We again investigated the addition of *n*-BuMgCl to vinylogous ester **27a** with $CeCl_3$ additive, focusing on the impact of various quenching parameters. While our previous studies showed that the formation of β-hydroxyketone **70r** is favored over cycloheptenone **55r** (Scheme 2.11, and Scheme 2.12, path a vs path b), we reasoned that elevated temperatures would promote dehydration of β-hydroxyketone **70** to form cycloheptenone **55** as the major product and simplify the product mixture (Scheme 2.12, path c). Subsequent heating of the reaction to 60 °C after acid quench leads to complete consumption of β-hydroxyketone (Scheme 2.11). However, the desired cycloheptenone **55r** is isolated as a minor product along with the non-conjugated enone **110** in 76% yield as a single olefin isomer. The prevalence of non-conjugated enone **110** again emphasizes the unusual reactivity of these seven-membered ring systems. To revise our approach, we extensively screened mild acidic work-up conditions to minimize the formation of

side products such as isomer **110**. We ultimately discovered that a sodium phosphate buffer quench followed by treatment of the crude enol ether[43] with dilute HCl in acetonitrile exclusively affords desired cycloheptenone **55r** (Scheme 2.11). Gratifyingly, a number of sp^3-hybridized carbon nucleophiles can be employed under these conditions, permitting the preparation of allyl,[44] homoallyl, and pentenyl substituted cycloheptenones (Table 2.5, entries 1–6, Method F).

Scheme 2.11. Synthesis of β-substituted cycloheptenones.



Scheme 2.12. General reaction mechanism for carbonyl transposition.

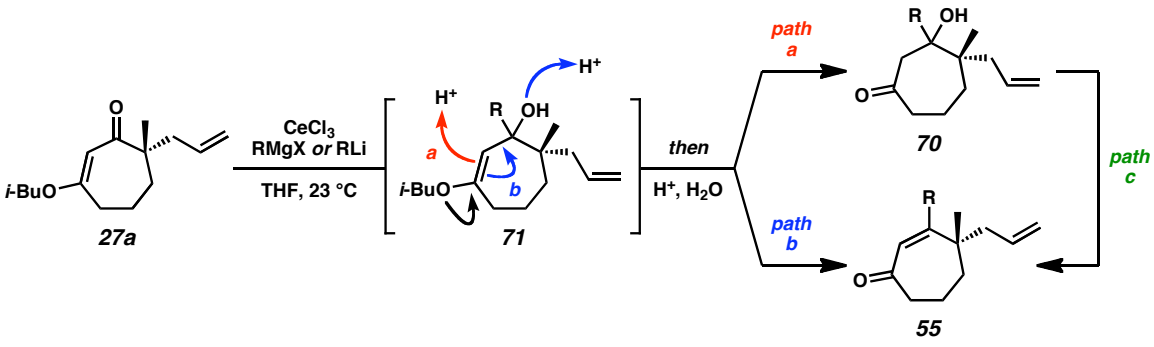
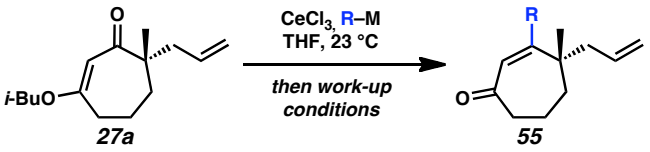
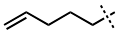


Table 2.5. Scope of organometallic addition/elimination.[a]



entry	R	M	work-up conditions[b]	product *55*	yield (%)[c]
1		–MgCl	F	*55r*	84
2		–MgBr	F	*55t*	73
3		–MgBr	F	*55u*	93
4		–MgBr	F	*55v*	90
5		–MgBr	F	*55w*	82
6		–MgBr	F	*55x*	92
7[d]		–Li	G	*55y*	84
8		–MgBr	H	*55z*	97
9[e]		–MgBr	H	*55aa*	66
10		–Li	G	*55ab*	72
11		–MgCl	G	*55ac*	84

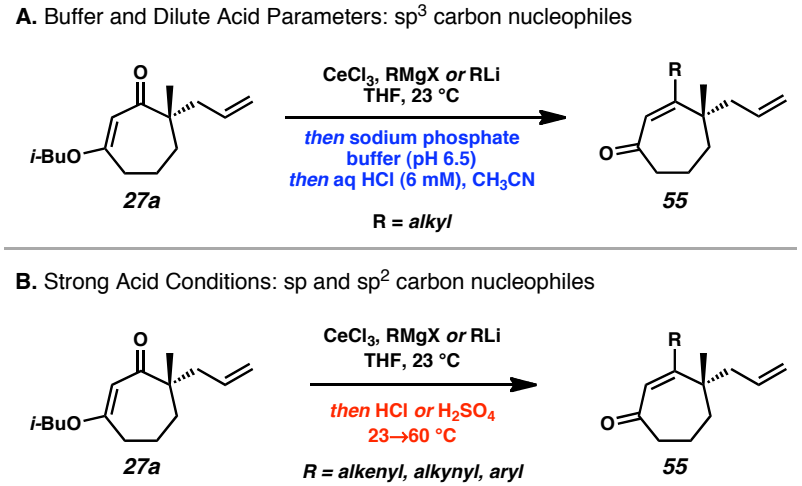
[a] *Conditions*: vinylogous ester **27a** (1.0 equiv), $CeCl_3$ (2.5 equiv), RMgX or RLi (3.0 equiv) in THF, 23 °C then work-up by Method F, G, or H. [b] *Method F*: (1) pH 6.5 sodium phosphate buffer; (2) 6 mM HCl, CH_3CN; *Method G*: 10% w/w aqueous HCl, 60 °C; Method H: 2 M H_2SO_4, 60 °C. [c] Yield of isolated product. [d] Performed without $CeCl_3$ additive. [e] Product was a 1.9:1 mixture of atropisomers.

We then turned our attention to sp- and sp^2-hybridized carbon nucleophiles as part of our goal to prepare variably substituted cycloheptenones (**55**). Attempts to apply the buffer and dilute acid quenching parameters provided poor selectivity and often led to complex mixtures of products. A thorough evaluation of work-up conditions revealed that the desired unsaturated β-substituted cycloheptenones could be obtained by quenching the reactions with concentrated strong acid followed by stirring at elevated

temperatures. Although investigated unsuccessfully for sp^3-hybridized carbon nucleophiles, the strong acid work-up conditions are more suitable for these reactions because the only possible elimination pathway leads to conjugated enone **55**. In this manner, the initial mixture of enone and β-hydroxyketone is funneled to the desired product (Scheme 2.12, paths b and c). By employing a HCl (Method G) or H_2SO_4 (Method H) quench, the synthesis of vinyl,[45] alkynyl,[46] aryl, and heteroaryl substituted enones was achieved in moderate to excellent yield (Table 2.5, entries 7–11). Particularly noteworthy is entry 9, where addition of an *ortho*-substituted Grignard reagent produces sterically congested cycloheptenone **55aa**.[47]

These results demonstrate that application of the appropriate quenching parameters based on the type of carbon nucleophile is required for successful carbonyl transposition to the cycloheptenone (Scheme 2.13). For sp^3-hybridized carbon nucleophiles, reaction work-up with buffer and dilute acid maximizes enone yield and minimizes formation of non-conjugated enone isomers. In contrast, reactions using sp- and sp^2-hybridized carbon nucleophiles require strong acidic work-up with heating for best results. Careful application of these general protocols (Methods F–H) provides access to diverse β-substituted γ-quaternary cycloheptenones (**55**).

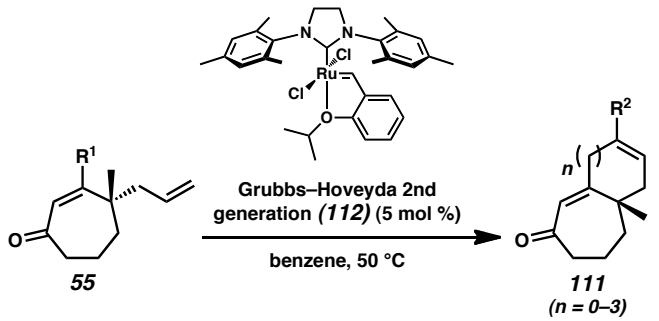
Scheme 2.13. Different work-up conditions for carbonyl transposition employing sp^3 versus sp/sp^2 carbon nucleophiles.



2.4 SYNTHESIS OF CYCLOHEPTENONE DERIVATIVES USING TRANSITION METAL-CATALYZED CYCLIZATIONS

Having produced a variety of cycloheptenones, we next turned our attention to the preparation of a series of bi- and tricyclic structures that would be valuable for total synthesis applications. The incorporation of alkene functionality at the β-position allows rapid access to a series of [7–*n*] fused ring systems through ring-closing metathesis with the γ-allyl fragment (Table 2.6). This transformation enables the formation of disubstituted bicycles (**111y**, **111t**, **111v**, and **111x**) from terminal alkenes in excellent yields (entries 1, 3, 5, and 8). Trisubstituted bicycles (**111z**, **111u**, and **111w**) are also accessible through enyne ring-forming metathesis (entry 2) and ring-closing metathesis with 1,1-disubstituted alkene β-substituents (entries 4 and 6). Additionally, both atropisomers of cycloheptenone **55aa** converge to the [7–7–6] tricyclic enone (**111aa**) under the reaction conditions (entry 7).

Table 2.6. Formation of bi- and tricyclic systems through ring-closing metathesis.[a]



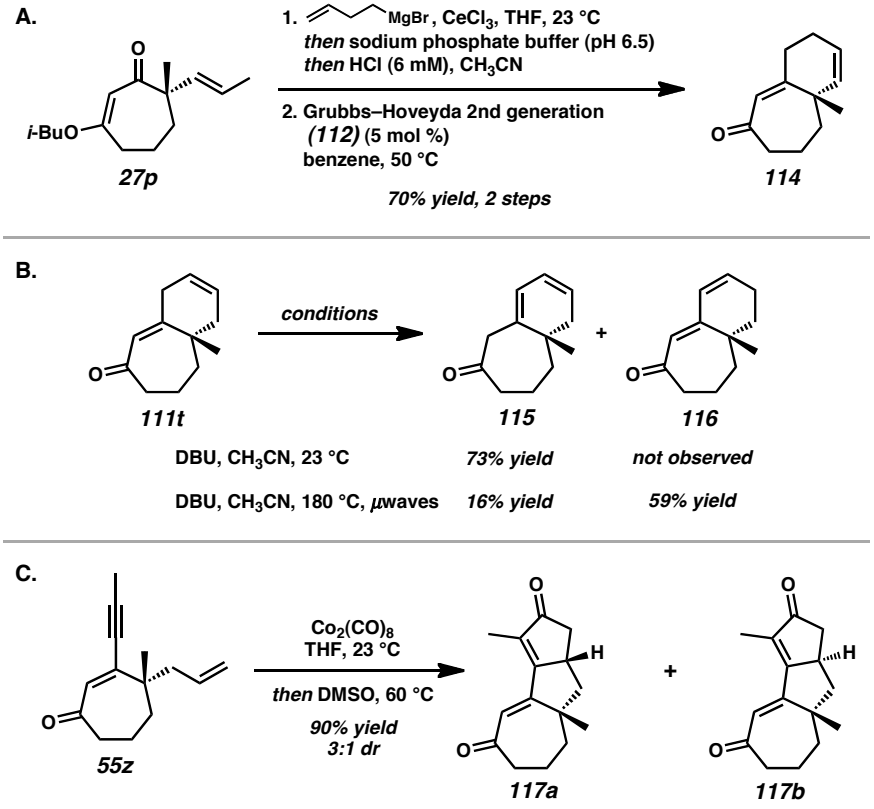
entry	substrate *55*	R^1	product *111*	R^2	yield (%)[b]
1[c]	*55y*	Ph	*111y*	R^2 = H	93
2	*55z*		*111z*	R^2 =	99
3[d]	*55t*		*111t*	R^2 = H	91
4[d]	*55u*		*111u*	R^2 = CH_3	90
5	*55v*		*111v*	R^2 = H	90
6	*55w*		*111w*	R^2 = CH_3	98
7[e]	*55aa*		*111aa*	—	96
8	*55x*		*111x*	—	99

[a] *Conditions*: cycloheptenone **55** (1.0 equiv) and Grubbs–Hoveyda 2nd generation catalyst (**112**, 5.0 mol %) in benzene, 50 °C. [b] Yield of isolated product. [c] *Conditions*: cycloheptenone **55** (1.0 equiv) and Grubbs 2nd generation catalyst (**113**, 0.2 mol %) in CH_2Cl_2, reflux. [d] 1,4-benzoquinone (10 mol %) added. [e] Performed in $PhCH_3$.

With two [7–6] bicyclic structures in hand, we next investigated the preparation of other such bicycles with variable olefin positions. Addition of 3-butenylmagnesium bromide to *trans*-propenyl vinylogous ester **27p** followed by ring-closing metathesis

furnishes bicycle **114** with the alkene adjacent to the quaternary stereocenter (Scheme 2.14A). Following the precedent of Fuchs,[48] we envisioned accessing bicycle **116** through a base-mediated migration from enone **111t**. However, treatment of skipped diene **111t** with an amine base at ambient temperature unexpectedly affords diene **115** instead (Scheme 2.14B). In the end, the alkene can be migrated in the desired direction to generate diene **116** by performing the reaction under microwave irradiation. Overall, these methods allow the preparation of a number of [7–6] bicycles with variable olefin substitution.

Scheme 2.14. Synthesis of additional [7–6] bicycles and [7–5–5] tricycles.



Recognition of the proximal enyne functionality of cycloheptenone **55z** prompted an investigation of a Pauson–Khand reaction to form more complex ring systems. Treatment of enone **55z** with dicobalt octacarbonyl in the presence of dimethylsulfoxide[49] generates the [7–5–5] tricycles **117a** to **117b** in a 3:1 diastereomeric ratio (Scheme 2.14C). Overall, our organometallic addition and elimination strategy combined with the appropriate work-up conditions facilitates the preparation of numerous bi- and tricyclic systems with a wide array of substitution patterns that may prove useful in the context of natural product synthesis.

2.5 UNIFIED STRATEGY FOR THE SYNTHESIS OF COMPLEX POLYCYCLIC NATURAL PRODUCTS

Our divergent approaches to the synthesis of acylcyclopentenes (**53**) and cycloheptenones (**55**) from enantioenriched vinylogous esters (**27**) have provided the foundation for the preparation of complex polycyclic molecules based on cyclopentanoid and cycloheptanoid core structures (Figure 2.4). Both [5–6] and [5–6–7] fused polycyclic molecules can be obtained from acylcyclopentenes. Synthetic elaboration of cycloheptenones provides access to [7–5], [7–6], [7–7], [7–8], [7–7–6], and [7–5–5] fused motifs. Additionally, [5–5], [5–6], and [7–6] spirocyclic structures can be prepared using our synthetic routes. These examples significantly add to the collection of polycyclic architectures accessible by elaboration of chiral six-membered ring carbocycles or heterocycles (**54**).[2,3] We have applied previously developed methodology toward a number of polycyclic cyclohexanoid natural products[7] (Figure 2.5) and similarly plan to exploit the ring contraction and ketone transposition methodology in future efforts

toward cyclopentanoid and cycloheptanoid natural products. The work presented in this chapter provides the foundation for future efforts and enables a broader synthetic approach to complex natural product targets.

Figure 2.4. Chiral fused and spirocyclic structures prepared by asymmetric allylic alkylation.

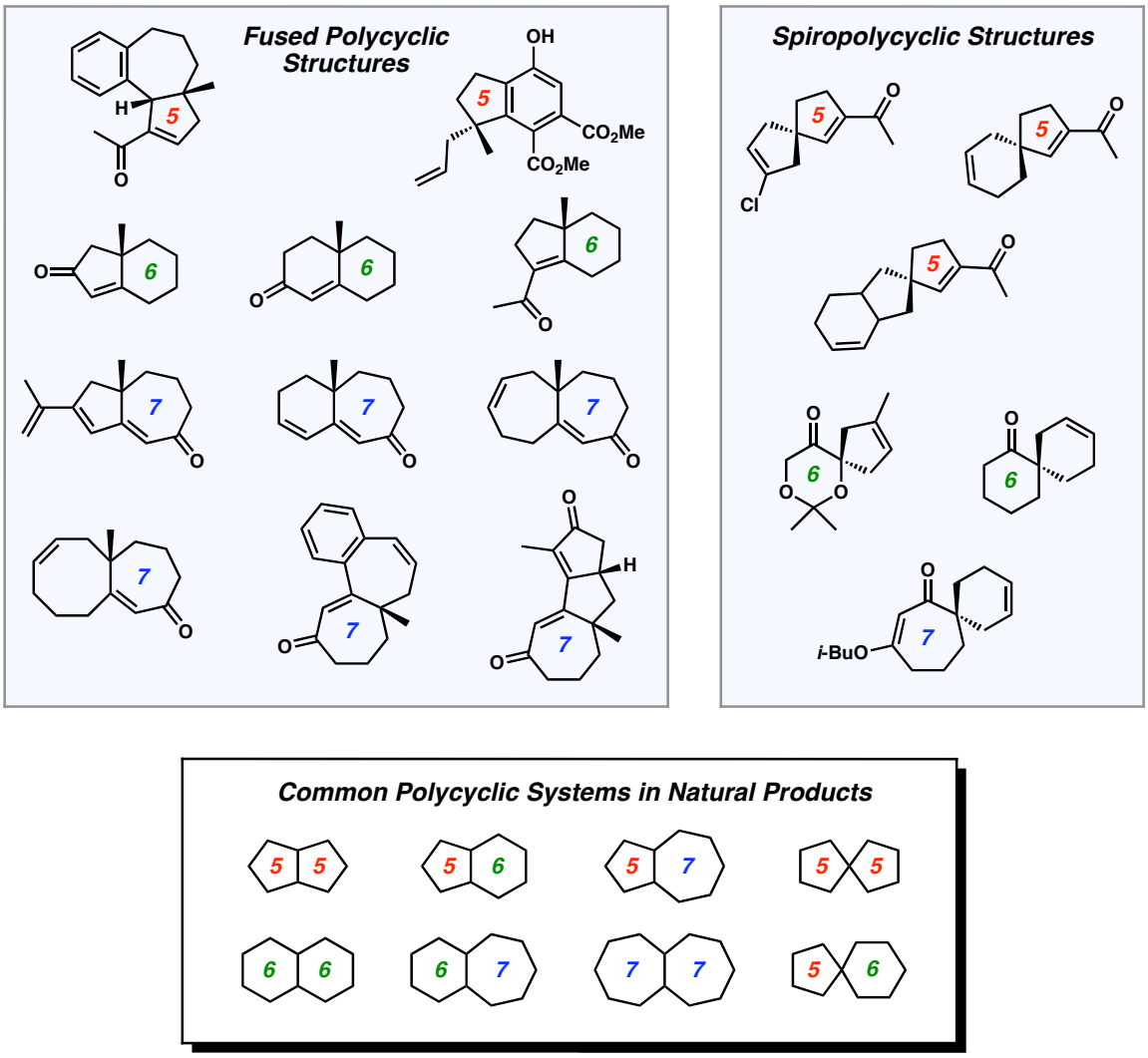
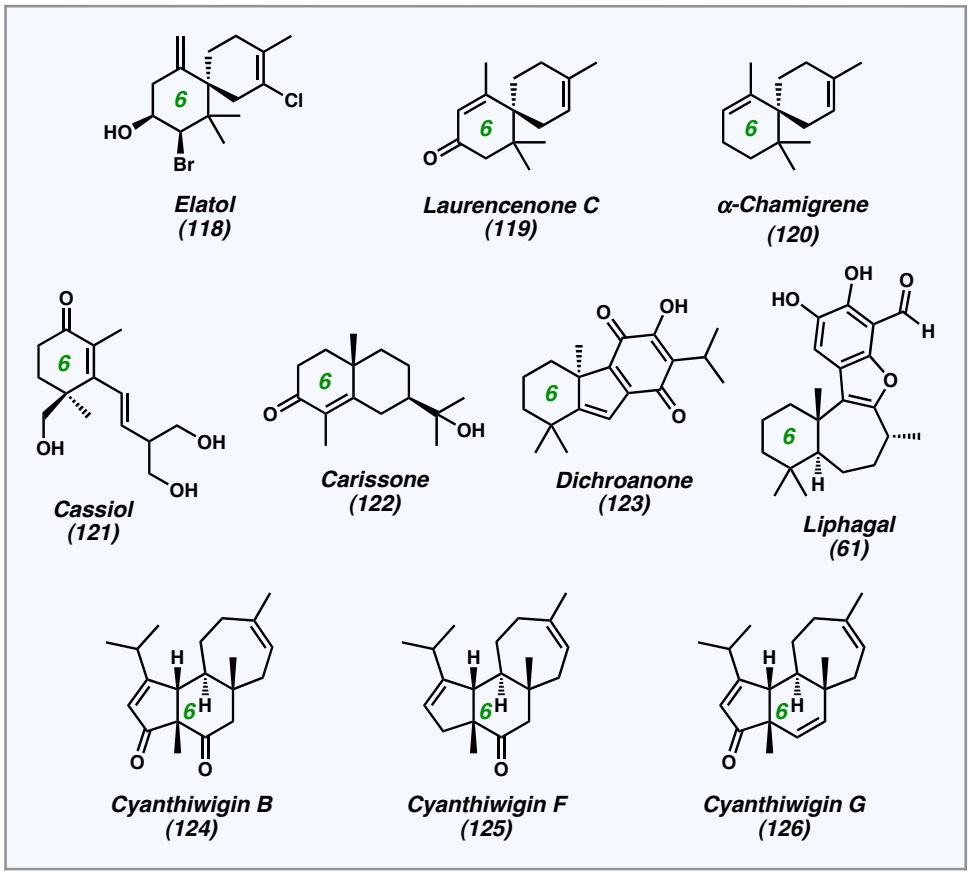


Figure 2.5. Pd-catalyzed asymmetric allylic alkylation in the total synthesis of cyclohexanoid natural products.



2.6 CONCLUDING REMARKS

We have successfully developed general, enantioselective synthetic routes toward γ-quaternary acylcyclopentenes (**53**) and cycloheptenones (**55**). The key stereoselective component unifying this chemistry is the Pd-catalyzed asymmetric alkylation of seven-membered vinylogous ester substrates to form α-quaternary vinylogous esters, for which we have demonstrated a broad substrate scope with a variety of all-carbon and heteroatom-containing functionality. These enantioenriched products were transformed in a divergent manner to either facilitate a two-carbon ring contraction to

acylcyclopentenes or a carbonyl transposition to cycloheptenones. Further synthetic elaboration of these products has enabled access to five- and seven-membered ring systems that are poised for further functionalization to bi- and tricyclic ring systems. Overall, the described strategies provide broader access to polycyclic ring systems and thus complement our previous work with six-membered ring building blocks. Efforts to expand the scope of these reactions, understand the key reaction mechanisms, and apply the chiral products to the total synthesis of natural products are the subject of future studies.

2.7 EXPERIMENTAL SECTION

2.7.1 MATERIALS AND METHODS

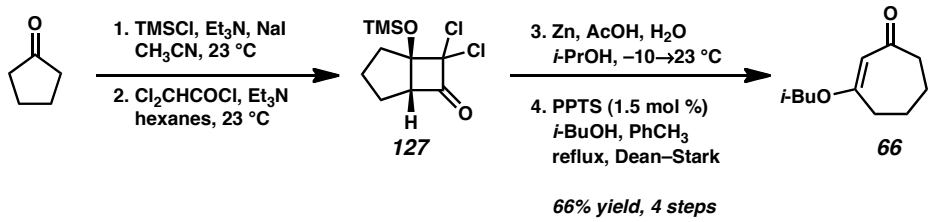
Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. THF was distilled over sodium/fluorenone or dried by passage through an activated alumina column under argon[50] prior to use. *p*-Dioxane was distilled over sodium or dried by passage through an activated alumina column under argon prior to use. Methanol was distilled over $Mg(OMe)_2$ prior to use. Other solvents were dried by passage through an activated alumina column under argon. Diisopropylamine and triethylamine were distilled over CaH_2 prior to use. Iodomethane, iodoethane, acrylonitrile, methyl vinyl ketone, and acrolein were distilled prior to use. Furan was distilled over KOH and hydroquinone prior to use. Purified water was obtained using a Barnstead NANOpure Infinity UV/UF system. Brine solutions are saturated aqueous solutions of sodium chloride. $MePh_3PBr$ was purchased from Sigma-Aldrich and stored in a glove box prior to use. NaH (60% wt. dispersion in mineral oil) was purchased from Sigma-Aldrich and purified by trituration with hexanes under a N_2 atmosphere and removal of residual solvent under vacuum. Grignard and organolithium reagents were purchased from Sigma-Aldrich unless otherwise stated and titrated according to the method of Love.[51] $LiOCH_2CF_3$ was prepared according to the method of Shreeve.[52] Allyl cyanoformate was prepared according to the method of Mander[53a] or Rattigan.[51b] Gramine methiodide was prepared according to the method of Armen.[54] The procedure of Maruyama and Naruta was used to prepare 1-chloro-2,4-pentadiene (92:8 *E*:*Z*).[55] Phosphinooxazoline (PHOX) ligands (*S*)-*t*-BuPHOX (**3**)[56] and (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**)[57] were prepared by methods described

in our previous work. Tris(4,4'-methoxydibenzylideneacetone)dipalladium(0) ($Pd_2(pmdba)_3$) was prepared according to the method of Ibers[58] or Fairlamb.[56b] Herrmann–Beller's catalyst (**101**) was prepared according to a literature procedure.[59] All other reagents were purchased from Sigma-Aldrich, Acros Organics, Strem, or Alfa Aesar and used as received unless otherwise stated. Reaction temperatures were controlled by an IKAmag temperature modulator. Microwave-assisted reactions were performed in a Biotage Initiator 2.5 microwave reactor. Glove box manipulations were performed under a N_2 atmosphere. Reaction progress was monitored by thin-layer chromatography (TLC). 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. Silia*Flash* P60 Academic Silica gel (particle size 0.040–0.063 mm) or ICN silica gel (particle size 0.032–0.0653 mm) was used for flash column chromatography. Automated flash column chromatography was performed on a Teledyne Isco CombiFlash R_f system. ^{1}H NMR spectra were recorded on a Varian Mercury 300 MHz, a Varian 400 MR 400 MHz, or a Varian Inova 500 MHz spectrometer and are reported relative to residual $CHCl_3$ (δ 7.26 ppm) or C_6H_6 (δ 7.16 ppm). Variable temperature ^{1}H NMR experiments were performed on a Varian Inova 500 MHz spectrometer and are reported relative to residual DMSO (δ 2.50 ppm). ^{13}C NMR spectra were recorded on a Varian Mercury 300 MHz, a Varian 400 MR 400 MHz, or a Varian Inova 500 MHz spectrometer (at 75 MHz, 100 MHz, and 125 MHz respectively) and are reported relative to $CHCl_3$ (δ 77.16 ppm) or C_6H_6 (δ 128.06 ppm). ^{19}F spectra were recorded on a Varian Mercury 300 MHz or a Varian Inova 500 MHz spectrometer (at 282 MHz and 470 MHz respectively) and are reported without the use of

a reference peak. 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, dm = doublet of multiplets, br s = broad singlet, br d = broad doublet, app = apparent. Data for ^{13}C and ^{19}F NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained using a Perkin Elmer Paragon 1000 or 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-1010 or Jasco P-2000 polarimeter operating on the sodium D-line (589 nm) using a 100 mm path-length cell and are reported as follows: $[\alpha]_D^T$ (concentration in g/100 mL, solvent, ee). Melting points were measured using a Thomas-Hoover capillary melting point apparatus and the reported values are uncorrected. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralcel AD or OD-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries Ltd. with visualization at 254 nm. Analytical chiral SFC was performed with a Mettler Toledo SFC supercritical CO_2 analytical chromatography system with a Chiralcel AD-H column (4.6 mm x 25 cm) with visualization at 254 nm/210 nm. Analytical chiral GC was performed with an Agilent 6850 GC utilizing a G-TA (30 m x 0.25 mm) column (1.0 mL/min carrier gas flow). High-resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility (EI+ or FAB+) or on 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+).

2.7.2 PREPARATIVE PROCEDURES

2.7.2.1 PREPARATION OF PARENT VINYLOGOUS ESTER 66



Vinylogous ester 66. NaI (157 g, 1.05 mol, 1.25 equiv) was placed in a 3 L 3-neck round-bottom flask, dried under high vacuum at 90 °C for 12 h, and allowed to cool to ambient temperature under N_2. CH_3CN (1.3 L) was added to dissolve the NaI. To the solution was added cyclopentanone (74.3 mL, 0.84 mol, 1.00 equiv), followed by Et_3N (146 mL, 1.05 mol, 1.25 equiv). The flask was fitted with an addition funnel, and the funnel was charged with TMSCl (122 mL, 0.96 mmol, 1.14 equiv), which was added dropwise over 30 min. The resulting suspension was stirred for an additional 1 h at ambient temperature. Pentane (1.0 L) was added, and the biphasic system was stirred vigorously for 10 min. The phases were separated and the CH_3CN layer was extracted with pentane (3 x 400 mL). The combined pentane phases were washed with H_2O (2 x 500 mL) and brine (500 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the desired product (131 g, quantitative) as a colorless oil.

A portion of the above trimethylsilyl ether (89.7 g, 0.57 mol, 1.00 equiv) was placed in a 3 L 3-neck round-bottom flask fitted with a stopper, an addition funnel, and an overhead stirrer. Hexanes (900 mL) was added, followed by Et_3N (111 mL, 0.80 mol, 1.39 equiv). Dichloroacetyl chloride (66.4 mL, 0.69 mol, 1.21 equiv) was dissolved in hexanes (400 mL) and added dropwise over 9.5 h. After 18 h of stirring at ambient

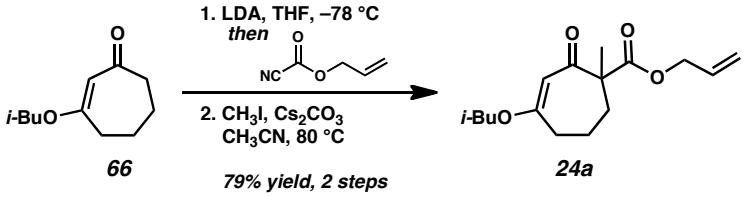
temperature, the brown suspension was filtered, rinsing with EtOAc (3 x 500 mL). The clear brown solution was concentrated under reduced pressure and then filtered through a pad of Al_2O_3 (7 x 18 cm, neutral) using EtOAc as eluent. The solution was concentrated under reduced pressure to afford the desired product (125 g, 0.47 mol, 82% yield) as a brown oil that crystallized in the freezer (–20 °C).

A portion of the above dichlorocyclobutanone (53.4 g, 0.20 mol, 1.00 equiv) was placed in a 3 L 3-neck round-bottom flask fitted with a thermometer, an addition funnel, and an overhead stirrer. Isopropyl alcohol and purified water (170 mL each) were added and the suspension was cooled to –10 °C (internal temperature) using a MeOH/ice bath. Zn dust (58.8 g, 0.90 mol, 4.50 equiv) was added in four portions (5 min between each) and AcOH (63 mL, 1.10 mol, 5.50 equiv) dissolved in H_2O (130 mL) was added dropwise while keeping the internal temperature below 0 °C (usually added over 1.5 h). The reaction was stirred for an additional 30 min at –10 °C (internal temperature) before the cooling bath was removed, and the reaction was allowed to warm to ambient temperature. After 8.5 h, the reaction was filtered, rinsing with isopropyl alcohol (100 mL). The mixture was cooled to 0 °C and neutralized by portionwise addition of K_2CO_3 (74.6 g, 0.54 mol, 5.50 equiv). The viscous suspension was filtered, rinsing with H_2O (100 mL) and EtOAc (300 mL). The biphasic system was concentrated under reduced pressure to ca. 200 mL and extracted with CH_2Cl_2. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the desired product (24.2 g, 0.19 mol, 96% yield) as a pale orange oil.

To a solution of 1,3-cycloheptanedione (35.8 g, 0.28 mol, 1.00 equiv) in toluene (280 mL) in a 1 L flask fitted with a reflux condenser and Dean–Stark trap was added

isobutanol (208 mL, 2.27 mol, 8.11 equiv) and pyridinium *p*-toluenesulfonate (1.07 g, 4.26 mmol, 1.50 mol %). The solution was immersed in an oil bath at 130 °C and monitored by TLC. When the starting material was consumed (typically within 4–6 h), the reaction was allowed to cool to ambient temperature. The resulting dark orange solution was washed with sat. aqueous $NaHCO_3$ (200 mL). The aqueous phase was extracted with EtOAc (3 x 150 mL) and the combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford a thick dark orange oil. The crude oil was flushed through a silica gel plug (SiO_2, 7 x 9 cm, 1:4→3:7→1:1 Et_2O-hexanes) to afford vinylogous ester **66** (43.5 g, 0.24 mol, 84% yield, 66% yield over 4 steps) as a pale orange oil; R_f = 0.22 (2:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.37 (s, 1H), 3.49 (d, *J* = 6.6 Hz, 2H), 2.60–2.56 (m, 4H), 2.00 (sept, *J* = 6.6 Hz, 1H), 1.88–1.77 (m, 4H), 0.96 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 176.6, 106.0, 75.0, 41.9, 33.1, 27.9, 23.7, 21.5, 19.3; IR (Neat Film NaCl) 2958, 2872, 1646, 1607, 1469, 1237, 1190, 1174 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{11}H_{18}O_2$ $[M]^{+\bullet}$: 182.1307; found 182.1310.

2.7.2.2 PREPARATION OF β-KETOESTERS 24

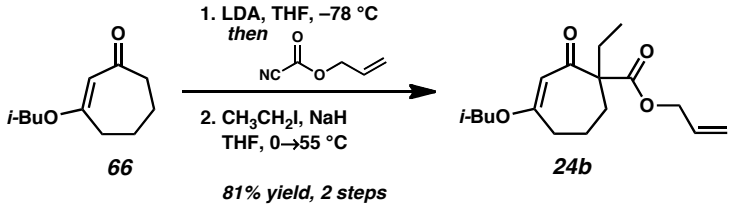


β-Ketoester 24a. To a solution of diisopropylamine (6.46 mL, 46.1 mmol, 1.20 equiv) in THF (180 mL) in a 500 mL round-bottom flask at 0 °C was added *n*-BuLi (17.2 mL, 44.2

mmol, 2.57 M in hexanes, 1.15 equiv) dropwise over 15 min using a syringe pump. After 15 min of stirring at 0 °C, the mixture was cooled to –78 °C using an acetone/CO_2(s) bath. A solution of vinylogous ester **66** (7.01 g, 38.4 mmol, 1.00 equiv) in THF (20 mL) was added dropwise over 20 min using a syringe pump. After an additional 1 h of stirring at –78 °C, allyl cyanoformate (4.60 mL, 42.2 mmol, 1.10 equiv) was added dropwise over 10 min. The mixture was stirred at –78 °C for 2.5 h, quenched by addition of sat. aqueous NH_4Cl and H_2O (30 mL each), and allowed to warm to ambient temperature. The reaction was diluted with Et_2O (100 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (2 x 100 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford a pale orange oil.

The crude oil was dissolved in CH_3CN (130 mL) in a 500 mL round-bottom flask and treated with CH_3I (7.2 mL, 115 mmol, 3.00 equiv) and Cs_2CO_3 (16.76 g, 49.9 mmol, 1.30 equiv). The flask was fitted with a condenser, immersed in an oil bath, and heated to 80 °C with vigorous stirring. After 12 h of stirring at 80 °C, the reaction was allowed to cool to ambient temperature, diluted with EtOAc (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford an orange oil. The crude product was purified by flash column chromatography (SiO_2, 5 x 15 cm, 19:1→9:1 hexanes:EtOAc, dry-loaded using Celite) to afford β-ketoester **24a** (8.51 g, 30.4 mmol, 79% yield over 2 steps) as a pale yellow oil; R_f = 0.43 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (dddd, *J* = 17.1, 10.7, 5.6, 5.6 Hz, 1H), 5.39 (s, 1H), 5.29 (app dq, *J* = 17.1, 1.5 Hz, 1H), 5.20 (app dq, *J* = 10.5, 1.4 Hz, 1H), 4.62 (dddd, *J* = 13.3, 5.6, 1.2, 1.2 Hz, 1H), 4.56 (dddd, *J* = 13.4, 5.6, 1.2, 1.2 Hz, 1H), 3.54–3.42 (m, 2H), 2.59

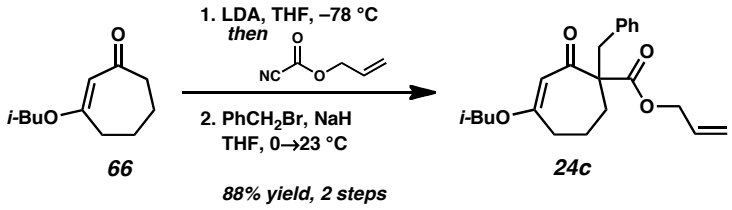
(ddd, J = 17.8, 9.8, 3.9 Hz, 1H), 2.45–2.38 (m, 2H), 2.02–1.94 (m, 2H), 1.84–1.75 (m, 1H), 1.70 (ddd, J = 14.4, 7.3, 4.4 Hz, 1H), 1.43 (s, 3H), 0.94 (d, J = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.1, 174.0, 173.5, 132.0, 118.4, 105.2, 74.8, 65.8, 59.1, 34.3, 33.9, 27.9, 24.2, 21.4, 19.3; IR (Neat Film NaCl) 2959, 2936, 2875, 1734, 1650, 1613, 1456, 1384, 1233, 1170, 1115, 994 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{16}H_{24}O_4$ $[M]^{+\bullet}$: 280.1675; found 280.1686.



β-Ketoester 24b. To a solution of diisopropylamine (0.92 mL, 6.58 mmol, 1.20 equiv) in THF (27 mL) in a 100 mL round-bottom flask at 0 °C was added *n*-BuLi (2.56 mL, 6.30 mmol, 2.46 M in hexanes, 1.15 equiv) dropwise over 10 min. After 15 min of stirring at 0 °C, the mixture was cooled to –78 °C using an acetone/CO_2(s) bath. A solution of vinylogous ester **66** (1.00 g, 5.48 mmol, 1.00 equiv) in THF (2 mL) was added dropwise using positive pressure cannulation. After an additional 1 h of stirring at –78 °C, allyl cyanoformate (0.67 mL, 6.02 mmol, 1.10 equiv) was added dropwise over 10 min. The mixture was stirred at –78 °C for 2.5 h, quenched by addition of 50% sat. aqueous NH_4Cl (8 mL), and allowed to warm to ambient temperature. The reaction was diluted with Et_2O (25 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 25 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a pale orange oil.

The crude oil was dissolved in THF (8 mL) in a 100 mL round-bottom flask, cooled to 0 °C, and stirred vigorously as hexane-washed NaH (158 mg, 6.58 mmol, 1.20 equiv) was added in one portion. Evolution of gas was observed and the reaction was stirred at 0 °C for 30 min to give a yellow-orange solution. CH_3CH_2I (1.31 mL, 16.4 mmol, 3.00 equiv) was added dropwise. The reaction was allowed to warm to ambient temperature and stirred for 4.5 h. The mixture was heated to 45 °C and stirred for 1.5 h. Additional CH_3CH_2I (0.65 mL, 8.22 mmol, 1.50 equiv) was added dropwise and the mixture was stirred at 45 °C for 6 h. A third portion of CH_3CH_2I (0.33 mL, 4.11 mmol, 0.75 equiv) was added dropwise and the reaction was warmed to 55 °C and stirred for 1.5 h. The flask was cooled to ambient temperature and quenched by addition of 50% sat. aqueous NH_4Cl (10 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 5 x 20 cm, 9:1→6:1→3:1→2:1 hexanes:EtOAc) to afford β-ketoester **24b** (1.31 g, 4.44 mmol, 81% yield over 2 steps) as a yellow oil; R_f = 0.53 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (dddd, *J* = 17.5, 10.2, 5.7, 5.7 Hz, 1H), 5.35 (s, 1H), 5.29 (app dq, *J* = 17.2, 1.5 Hz, 1H), 5.19 (app dq, *J* = 10.4, 1.3 Hz, 1H), 4.62 (dddd, *J* = 13.2, 5.7, 1.4, 1.4 Hz, 1H), 4.54 (dddd, *J* = 13.2, 5.7, 1.4, 1.4 Hz, 1H), 3.57–3.34 (m, 2H), 2.60 (dddd, *J* = 17.9, 9.9, 3.7, 1.2 Hz, 1H), 2.49–2.26 (m, 2H), 2.12–1.85 (m, 4H), 1.85–1.57 (m, 2H), 0.93 (d, *J* = 6.7 Hz, 6H), 0.84 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.7, 173.7, 173.2, 132.0, 118.5, 105.5, 74.7, 65.7, 63.1, 34.1, 31.0, 30.6, 27.9, 22.0, 19.3, 9.0; IR (Neat Film NaCl) 3085, 2960, 2937, 2876, 1731, 1663, 1613, 1471, 1461, 1453, 1424, 1383, 1369, 1328, 1304,

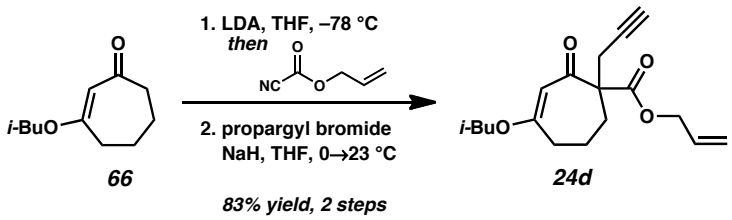
1278, 1229, 1199, 1170, 1121, 1006, 988, 931, 875, 858, 813 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{27}O_4$ $[M+H]^+$: 295.1904; found 295.1918.



β-Ketoester 24c. To a solution of diisopropylamine (0.92 mL, 6.58 mmol, 1.20 equiv) in THF (27 mL) in a 100 mL round-bottom flask at 0 °C was added *n*-BuLi (2.56 mL, 6.30 mmol, 2.46 M in hexanes, 1.15 equiv) dropwise over 10 min. After 15 min of stirring at 0 °C, the mixture was cooled to –78 °C using an acetone/CO_2(s) bath. A solution of vinylogous ester **66** (1.00 g, 5.48 mmol, 1.00 equiv) in THF (2 mL) was added dropwise using positive pressure cannulation. After an additional 1 h of stirring at –78 °C, allyl cyanoformate (0.67 mL, 6.02 mmol, 1.10 equiv) was added dropwise over 10 min. The mixture was stirred at –78 °C for 2.5 h, quenched by addition of 50% sat. aqueous NH_4Cl (8 mL), and allowed to warm to ambient temperature. The reaction was diluted with Et_2O (25 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 25 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a pale orange oil.

The crude oil was dissolved in THF (8 mL) in a 100 mL round-bottom flask, cooled to 0 °C, and stirred vigorously as hexane-washed NaH (197 mg, 8.22 mmol, 1.50 equiv) was added in one portion. Evolution of gas was observed and the reaction was stirred at 0 °C for 30 min to give a yellow-orange solution. Benzyl bromide (1.96 mL, 16.44 mmol, 3.00 equiv) was added dropwise. The reaction was allowed to warm to

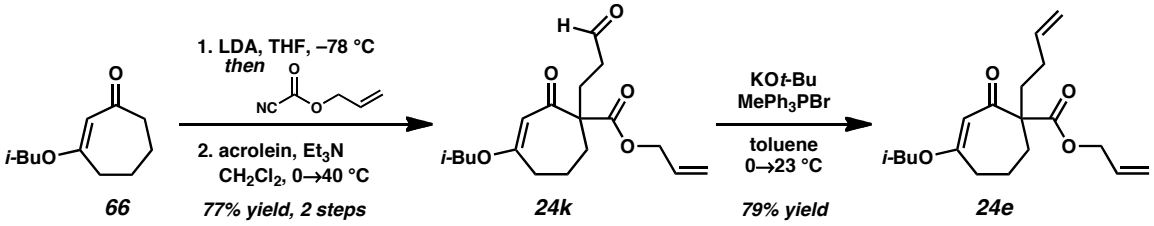
ambient temperature and stirred for 3 h. The reaction was quenched by addition of 50% sat. aqueous NH_4Cl (10 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 3 x 23 cm, hexanes→10:1 hexanes:EtOAc) to afford β-ketoester **24c** (1.72 g, 4.83 mmol, 88% yield over 2 steps) as a pale yellow oil; R_f = 0.26 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.15 (m, 3H), 7.15–7.06 (m, 2H), 5.85 (dddd, *J* = 17.1, 10.4, 5.8, 5.8 Hz, 1H), 5.36 (s, 1H), 5.30 (app dq, *J* = 17.2, 1.5 Hz, 1H), 5.21 (app dq, *J* = 10.4, 1.3 Hz, 1H), 4.63 (dddd, *J* = 13.2, 5.7, 1.3, 1.3 Hz, 1H), 4.52 (dddd, *J* = 13.2, 5.8, 1.3, 1.3 Hz, 1H), 3.42 (d, *J* = 6.5 Hz, 2H), 3.30 (d, *J* = 13.5 Hz, 1H), 3.23 (d, *J* = 13.5 Hz, 1H), 2.54 (ddd, *J* = 12.1, 10.0, 3.5 Hz, 1H), 2.38–2.18 (m, 2H), 2.04–1.83 (m, 2H), 1.81–1.64 (m, 2H), 0.92 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 174.0, 172.7, 137.0, 131.8, 130.7, 128.1, 126.8, 118.8, 105.7, 74.8, 66.0, 64.0, 43.1, 34.0, 31.3, 27.9, 22.0, 19.2; IR (Neat Film NaCl) 3085, 3062, 3029, 2959, 2934, 2873, 1736, 1732, 1661, 1652, 1611, 1495, 1471, 1454, 1423, 1383, 1368, 1270, 1235, 1173, 1088, 1007, 957, 992, 930, 862, 815, 741 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{22}H_{29}O_4$ $[M+H]^+$: 357.2060; found 357.2051.



β-Ketoester 24d. To a solution of diisopropylamine (0.92 mL, 6.58 mmol, 1.20 equiv) in THF (27 mL) in a 100 mL round-bottom flask at 0 °C was added *n*-BuLi (2.56 mL, 6.30 mmol, 2.46 M in hexanes, 1.15 equiv) dropwise over 10 min. After 15 min of stirring at 0 °C, the mixture was cooled to –78 °C using an acetone/CO_2(s) bath. A solution of vinylogous ester **66** (1.00 g, 5.48 mmol, 1.00 equiv) in THF (2 mL) was added dropwise using positive pressure cannulation. After an additional 1 h of stirring at –78 °C, allyl cyanoformate (0.67 mL, 6.02 mmol, 1.10 equiv) was added dropwise over 10 min. The mixture was stirred at –78 °C for 2.5 h, quenched by addition of 50% sat. aqueous NH_4Cl (8 mL), and then allowed to warm to ambient temperature. The reaction was diluted with Et_2O (25 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 25 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a pale orange oil.

The crude oil was dissolved in THF (8 mL) in a 100 mL round-bottom flask, cooled to 0 °C, and stirred vigorously as hexane-washed NaH (197 mg, 8.22 mmol, 1.5 equiv) was added in one portion. Evolution of gas was observed and the reaction was stirred at 0 °C for 30 min to give a yellow-orange solution. Propargyl bromide (1.22 mL, 10.96 mmol, 80% wt in toluene, 2.00 equiv) was added dropwise and the reaction was allowed to warm to ambient temperature and stirred for 5.5 h. The reaction was quenched by addition of 50% sat. aqueous NH_4Cl (10 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic

phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 3 x 24 cm, hexanes→20:1→15:1→10:1 hexanes:EtOAc) to afford β-ketoester **24d** (1.38 g, 4.53 mmol, 83% yield over 2 steps) as a pale yellow oil; R_f = 0.55 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (dddd, *J* = 17.2, 10.4, 5.7, 5.7 Hz, 1H), 5.38 (s, 1H), 5.29 (app dq, *J* = 17.2, 1.5 Hz, 1H), 5.19 (app dq, *J* = 10.4, 1.3 Hz, 1H), 4.63 (dddd, *J* = 13.2, 5.6, 1.4, 1.4 Hz, 1H), 4.56 (dddd, *J* = 13.2, 5.7, 1.4, 1.4 Hz, 1H), 3.56–3.38 (m, 2H), 2.79 (dd, *J* = 2.7, 0.6 Hz, 1H), 2.72–2.32 (m, 4H), 2.15–1.89 (m, 4H), 1.89–1.71 (m, 1H), 0.93 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.5, 174.8, 171.7, 131.7, 118.7, 105.0, 80.2, 74.9, 71.4, 66.1, 62.0, 34.3, 31.2, 27.9, 27.5, 21.7, 19.2; IR (Neat Film NaCl) 3289, 3085, 2959, 2933, 2874, 2120, 1740, 1735, 1654, 1649, 1470, 1452, 1424, 1402, 1384, 1369, 1309, 1291, 1272, 1232, 1187, 1173, 1133, 1085, 1066, 1007, 968, 930, 863, 820 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{18}H_{25}O_4$ $[M+H]^+$: 305.1753; found 305.1746.



β-Ketoester 24k. To a solution of diisopropylamine (1.49 mL, 10.63 mmol, 1.20 equiv) in THF (43 mL) in a 250 mL round-bottom flask at 0 °C was added *n*-BuLi (4.74 mL, 10.19 mmol, 2.51 M in hexanes, 1.15 equiv) dropwise over 10 min. After 15 min of stirring at 0 °C, the mixture was cooled to –78 °C using an acetone/CO_2(s) bath. A

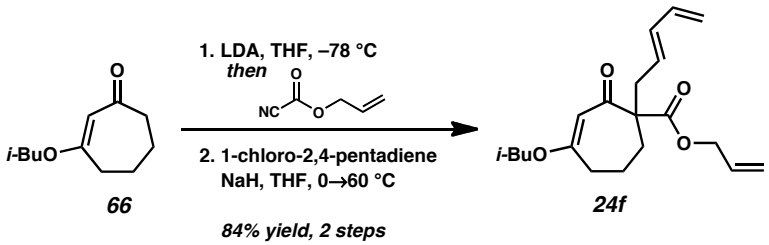
solution of vinylogous ester **66** (1.61 g, 8.86 mmol, 1.00 equiv) in THF (3 mL) was added dropwise using positive pressure cannulation. After an additional 1 h of stirring at –78 °C, allyl cyanoformate (1.06 mL, 9.74 mmol, 1.10 equiv) was added dropwise over 10 min. The mixture was stirred at –78 °C for 2.5 h, quenched by addition of 50% sat. aqueous NH_4Cl (12.9 mL), and then allowed to warm to ambient temperature. The reaction was diluted with Et_2O (50 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a pale orange oil. The crude oil was purified by automated flash column chromatography using a Teledyne Isco CombiFlash R_f (SiO_2, 25 g loading cartridge, 330 g column, hold 0% [3 min]→ramp to 20% [10 min]→hold 20% [10 min]→ramp to 50% [4 min]→hold 50% EtOAc in hexanes [5 min]) to afford the intermediate β-ketoester (2.02 g, 7.58 mmol, 86% yield).

A portion of the intermediate β-ketoester (990 mg, 3.72 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (10 mL) in a 100 mL round-bottom flask, cooled to 0 °C, and treated with Et_3N (0.518 mL, 3.72 mmol, 1.00 equiv). Acrolein (0.248 mL, 3.72 mmol, 1.00 equiv) was added dropwise and the reaction was allowed to warm to ambient temperature. After 51 h, the reaction was cooled to 0 °C and an additional portion of acrolein (0.125 mL, 1.86 mmol, 0.50 equiv) was added. After 100 h, the reaction was concentrated under reduced pressure, dissolved in Et_2O, and filtered through a cotton plug to remove salts. The filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography (SiO_2, 3 x 25 cm, 10:1→6:1→4:1 hexanes:EtOAc) to afford β-ketoester **24k** (1.07 g, 3.34 mmol, 90% yield, 77% yield over

2 steps) as a clear oil; R_f = 0.23, broad (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (t, *J* = 1.3 Hz, 1H), 5.86 (dddd, *J* = 17.1, 10.4, 5.8, 5.8 Hz, 1H), 5.36 (s, 1H), 5.30 (app dq, *J* = 17.2, 1.5 Hz, 1H), 5.22 (app dq, *J* = 10.4, 1.2 Hz, 1H), 4.63 (dddd, *J* = 13.1, 5.7, 1.3, 1.3 Hz, 1H), 4.55 (dddd, *J* = 13.2, 5.8, 1.3, 1.3 Hz, 1H), 3.55–3.40 (m, 2H), 2.66–2.29 (m, 5H), 2.29–2.08 (m, 2H), 2.08–1.89 (m, 2H), 1.89–1.59 (m, 2H), 0.94 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 197.9, 173.9, 172.7, 131.7, 119.0, 105.3, 74.9, 66.0, 61.8, 39.7, 34.2, 32.1, 29.6, 27.9, 21.5, 19.2; IR (Neat Film NaCl) 3084, 2960, 2936, 2875, 2829, 2723, 1727, 1649, 1611, 1471, 1454, 1422, 1403, 1385, 1369, 1306, 1270, 1234, 1191, 1173, 1104, 1004, 990, 931, 877, 862, 822 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{18}H_{27}O_5$ $[M+H]^+$: 323.1858; found 323.1860.

β-Ketoester 24e. $MePh_3PBr$ (1.33 g, 3.72 mmol, 1.26 equiv) was suspended in toluene (20 mL) in 100 mL round-bottom flask and cooled to 0 °C. KO*t*-Bu (0.348 g, 3.10 mmol, 1.05 equiv) was added in one portion and the bright yellow mixture was stirred at 0 °C for 30 min, warmed to ambient temperature, and stirred for an additional 2 h. The mixture was cooled to 0 °C and a solution of aldehyde **24k** (0.95 g, 2.94 mmol, 1.00 equiv) in toluene (2 mL) was added to the reaction using positive pressure cannulation. The mixture turned brown. The reaction was maintained at 0 °C for 1.5 h, warmed to ambient temperature, and stirred for 4 h. The reaction was quenched by addition of 50% sat. aqueous NH_4Cl (4 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 3 x 25 cm, 20:1→15:1 hexanes:EtOAc)

to afford β-ketoester **24e** (747 mg, 2.33 mmol, 79% yield) as a pale yellow oil; $R_f = 0.66$ (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (dddd, *J* = 17.2, 10.4, 5.7, 5.7 Hz, 1H), 5.84–5.69 (m, 1H), 5.35 (s, 1H), 5.29 (app dq, *J* = 17.2, 1.5 Hz, 1H), 5.20 (app dq, *J* = 10.4, 1.3 Hz, 1H), 5.08–4.96 (m, 1H), 4.96–4.87 (m, 1H), 4.62 (dddd, *J* = 13.1, 5.7, 1.4, 1.4 Hz, 1H), 4.54 (dddd, *J* = 13.1, 5.7, 1.4, 1.4 Hz, 1H), 3.53–3.38 (m, 2H), 2.59 (dddd, *J* = 17.9, 9.8, 3.7, 1.1 Hz, 1H), 2.51–2.29 (m, 2H), 2.09–1.87 (m, 6H), 1.87–1.66 (m, 2H), 0.94 (d, *J* = 6.7, 3H), 0.94 (d, *J* = 6.7, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.4, 173.7, 173.0, 138.2, 131.9, 118.6, 114.9, 105.4, 74.8, 65.8, 62.6, 36.8, 34.1, 31.5, 28.8, 27.9, 22.0, 19.3; IR (Neat Film NaCl) 3078, 2959, 2935, 2874, 1732, 1662, 1612, 1471, 1453, 1423, 1401, 1384, 1369, 1307, 1270, 1231, 1194, 1170, 1091, 993, 913, 874, 817, 766 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{19}H_{28}O_4$ $[M]^{+\bullet}$: 320.1988; found 320.1977.

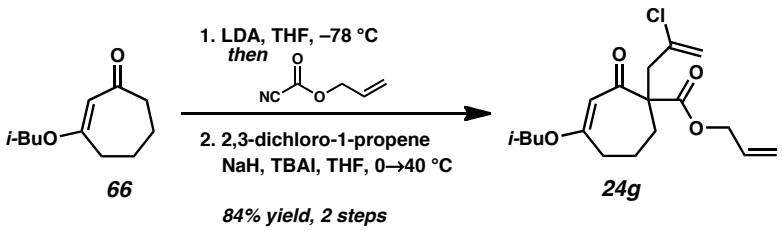


β-Ketoester 24f. To a solution of diisopropylamine (0.406 mL, 2.90 mmol, 1.20 equiv) in THF (12 mL) in a 50 mL round-bottom flask at 0 °C was added *n*-BuLi (1.10 mL, 2.77 mmol, 2.51 M in hexanes, 1.15 equiv) dropwise over 10 min. After 15 min of stirring at 0 °C, the mixture was cooled to –78 °C using an acetone/CO_2(s) bath. A solution of vinylogous ester **66** (0.44 g, 2.41 mmol, 1.00 equiv) in THF (2 mL) was added dropwise using positive pressure cannulation. After an additional 1 h of stirring at –78 °C, allyl cyanoformate (0.288 mL, 2.65 mmol, 1.10 equiv) was added dropwise over 10 min. The

mixture was stirred at –78 °C for 2.5 h, quenched by addition of 50% sat. aqueous NH_4Cl (4 mL), and then allowed to warm to ambient temperature. The reaction was diluted with Et_2O (15 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a pale orange oil. The crude oil was purified by automated flash column chromatography using a Teledyne Isco CombiFlash R_f (SiO_2, 5 g loading cartridge, 40 g column, hold 0% [1 min]→ramp to 20% [8 min]→hold 20% [5 min]→ramp to 50% [4 min]→50% EtOAc in hexanes [6 min]) to afford the intermediate β-ketoester (590 mg, 2.21 mmol, 92% yield).

A portion of the intermediate β-ketoester (250 mg, 0.94 mmol, 1.00 equiv) was dissolved in THF (5 mL) in a 50 mL round-bottom flask, cooled to 0 °C, and stirred vigorously as hexane-washed NaH (33.8 mg, 6.58 mmol, 1.50 equiv) was added in one portion. Evolution of gas was observed, and the reaction was stirred at 0 °C for 30 min to give a yellow-orange solution. 1-chloro-2,4-pentadiene[53] (144 mg, 1.41 mmol, 1.50 equiv) was added dropwise, and the reaction was allowed to warm to ambient temperature and then heated to 40 °C. After 10.5 h, an additional portion of 1-chloro-2,4-pentadiene (144 mg, 1.41 mmol, 1.50 equiv) was added, and the reaction was heated at 50 °C for 11.5 h. The flask was cooled to ambient temperature and the reaction was quenched by addition of 50% sat. aqueous NH_4Cl (2 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 3 x 25 cm, 20:1→15:1→10:1 hexanes:EtOAc) to afford β-ketoester **24f** (286 mg,

0.86 mmol, 91% yield, 84% yield over 2 steps) as a pale yellow oil; R_f = 0.59 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.25 (ddd, *J* = 16.7, 10.3, 10.3 Hz, 1H), 6.11–5.98 (m, 1H), 5.83 (dddd, *J* = 17.2, 10.4, 5.7, 5.7 Hz, 1H), 5.58 (ddd, *J* = 15.1, 7.7, 7.7 Hz, 1H), 5.36 (s, 1H), 5.27 (app dq, *J* = 17.2, 1.5 Hz, 1H), 5.18 (app dq, *J* = 10.4, 1.2 Hz, 1H), 5.08 (dd, *J* = 16.9, 1.6 Hz, 1H), 4.96 (dd, J = 16.9, 1.6 Hz, 1H), 4.60 (dddd, *J* = 13.2, 5.8, 1.4, 1.4 Hz, 1H), 4.52 (dddd, *J* = 13.2, 5.8, 1.4, 1.4 Hz, 1H), 3.57–3.35 (m, 2H), 2.65 (d, *J* = 7.7 Hz, 2H), 2.56 (ddd, *J* = 12.7, 6.8, 2.3 Hz, 1H), 2.48–2.19 (m, 2H), 2.10–1.85 (m, 2H), 1.85–1.63 (m, 2H), 0.92 (d, *J* = 6.7, 3H), 0.92 (d, *J* = 6.7, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9, 174.0, 172.7, 136.9, 134.6, 131.9, 129.7, 118.6, 116.1, 105.4, 74.8, 65.9, 62.9, 41.0, 34.1, 31.4, 27.9, 21.8, 19.2; IR (Neat Film NaCl) 3085, 2959, 2933, 2874, 1733, 1650, 1612, 1471, 1453, 1434, 1402, 1384, 1369, 1307, 1272, 1234, 1194, 1171, 1093, 1006, 968, 955, 929, 900, 864, 822, 761 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{20}H_{29}O_4$ $[M+H]^+$: 333.2066; found 333.2052.

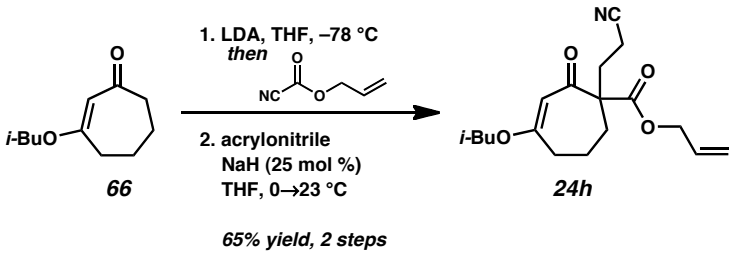


β-Ketoester 24g. To a solution of diisopropylamine (0.92 mL, 6.58 mmol, 1.20 equiv) in THF (27 mL) in a 100 mL round-bottom flask at 0 °C was added *n*-BuLi (2.56 mL, 6.30 mmol, 2.46 M in hexanes, 1.15 equiv) dropwise over 10 min. After 15 min of stirring at 0 °C, the mixture was cooled to –78 °C using an acetone/CO_2(s) bath. A solution of vinylogous ester **66** (1.00 g, 5.48 mmol, 1.00 equiv) in THF (2 mL) was added dropwise

using positive pressure cannulation. After an additional 1 h of stirring at –78 °C, allyl cyanoformate (0.67 mL, 6.02 mmol, 1.10 equiv) was added dropwise over 10 min. The mixture was stirred at –78 °C for 2.5 h, quenched by addition of 50% sat. aqueous NH_4Cl (8 mL), and allowed to warm to ambient temperature. The reaction was diluted with Et_2O (25 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 25 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a pale orange oil.

The crude oil was dissolved in THF (8 mL) in a 100 mL round-bottom flask, cooled to 0 °C, and stirred vigorously as hexane-washed NaH (197 mg, 8.22 mmol, 1.50 equiv) was added in one portion. Evolution of gas was observed, and the reaction was stirred at 0 °C for 30 min to give a yellow-orange solution. 2,3-dichloro-1-propene (1.00 mL, 10.96 mmol, 2.0 equiv) was added dropwise, and the reaction was allowed to warm to ambient temperature. After 10 h, TBAI (202 mg, 0.548 mmol, 0.10 equiv) was added, and the reaction was heated to 40 °C. After 41 h, the reaction was cooled to ambient temperature and quenched by addition of 50% sat. aqueous NH_4Cl (10 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 3 x 25 cm, 20:1→15:1 hexanes:EtOAc) to afford β-ketoester **24g** (1.57 g, 4.61 mmol, 84% yield over 2 steps) as a yellow oil; R_f = 0.60 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (dddd, *J* = 17.1, 10.4, 5.8, 5.8 Hz, 1H), 5.38–5.25 (m, 3H), 5.25–5.16 (m, 2H), 4.65 (dddd, *J* = 13.2, 5.8, 1.3, 1.3 Hz, 1H), 4.52 (dddd, *J* = 13.1, 5.8, 1.3, 1.3 Hz, 1H), 3.45 (ddd, *J* = 21.1, 9.3, 6.5 Hz, 2H), 3.04 (s,

2H), 2.71 (dddd, J = 18.2, 10.2, 3.0, 1.3 Hz, 1H), 2.62–2.47 (m, 1H), 2.39 (ddd, J = 17.2, 6.9, 2.6 Hz, 1H), 2.10–1.90 (m, 2H), 1.89–1.65 (m, 2H), 0.94 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.6, 174.8, 172.1, 138.1, 131.7, 118.8, 117.1, 104.9, 74.8, 66.2, 62.2, 46.1, 33.9, 30.7, 27.8, 22.6, 19.2; IR (Neat Film NaCl) 3085, 2960, 2935, 2875, 1737, 1662, 1610, 1471, 1452, 1427, 1384, 1369, 1298, 1272, 1229, 1198, 1171, 1153, 1079, 1008, 967, 930, 890, 862, 813 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{18}H_{25}O_4$ $[M–Cl]^+$: 305.1753; found 305.1742.

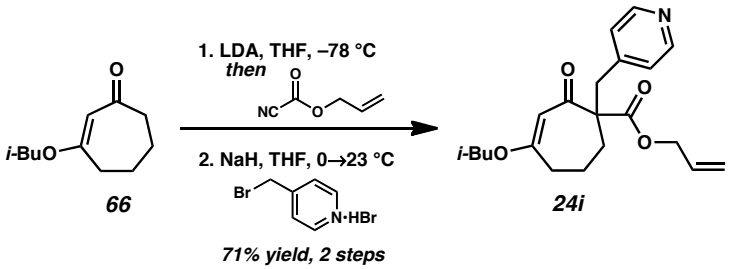


β-Ketoester 24h. To a solution of diisopropylamine (1.53 mL, 10.93 mmol, 1.20 equiv) in THF (45 mL) in a 250 mL round-bottom flask at 0 °C was added *n*-BuLi (4.17 mL, 10.47 mmol, 2.51 M in hexanes, 1.15 equiv) dropwise over 10 min. After 15 min of stirring at 0 °C, the mixture was cooled to –78 °C using an acetone/CO_2(s) bath. A solution of vinylogous ester **66** (1.66 g, 9.11 mmol, 1.00 equiv) in THF (2 mL) was added dropwise over 10 min. After an additional 1 h of stirring at –78 °C, allyl cyanoformate (1.09 mL, 10.0 mmol, 1.10 equiv) was added dropwise over 10 min. The mixture was stirred at –78 °C for 2.5 h, quenched by addition of 50% sat. aqueous NH_4Cl (13.5 mL), and then allowed to warm to ambient temperature. The reaction was diluted with Et_2O (50 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic phases were dried over Na_2SO_4, filtered, and

concentrated under reduced pressure to afford a pale orange oil. The crude oil was purified by automated flash column chromatography using a Teledyne Isco CombiFlash R_f (SiO_2, 25 g loading cartridge, 80 g column, multi-step gradient, hold 0% [2 min]→ramp to 20% [4 min]→hold 20% [15 min]→ramp to 50% [7 min]→hold 50% EtOAc in hexanes [5 min]) to afford the intermediate β-ketoester (2.08 g, 7.80 mmol, 86% yield).

One third of the intermediate β-ketoester (694 mg, 2.60 mmol, 1.00 equiv) was dissolved in THF (5 mL) in a 50 mL round-bottom flask, cooled to 0 °C, and stirred vigorously as hexane-washed NaH (15.6 mg, 0.65 mmol, 0.25 equiv) was added in one portion. Evolution of gas was observed, and the reaction was stirred at 0 °C for 30 min to give a yellow-orange solution. Acrylonitrile (0.256 mL, 3.90 mmol, 1.50 equiv) was added dropwise, and the reaction was allowed to warm to ambient temperature. After 40 h, the reaction was diluted with Et_2O (30 mL) and washed with H_2O (5 mL) and brine (5 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 3 x 25 cm, 10:1→6:1→4:1 hexanes:EtOAc) to afford β-ketoester **24h** (620 mg, 1.94 mmol, 75% yield, 65% yield over 2 steps) as a clear, colorless oil; R_f = 0.29 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (dddd, *J* = 16.2, 10.4, 5.8, 5.8 Hz, 1H), 5.38 (s, 1H), 5.32 (app dq, *J* = 17.2, 1.4 Hz, 1H), 5.25 (app dq, *J* = 10.4, 1.1 Hz, 1H), 4.67 (dddd, *J* = 13.0, 5.8, 1.2, 1.2 Hz, 1H), 4.58 (dddd, *J* = 13.1, 5.9, 1.2, 1.2 Hz, 1H), 3.57–3.39 (m, 2H), 2.58 (ddd, *J* = 13.1, 9.6, 3.9 Hz, 1H), 2.51–2.32 (m, 4H), 2.32–2.11 (m, 2H), 2.11–1.90 (m, 2H), 1.90–1.64 (m, 2H), 0.95 (d, *J* = 6.7 Hz, 6H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 196.9, 174.4, 172.0, 131.4, 119.7, 119.3, 105.1, 75.0, 66.3, 61.5, 34.1, 33.1, 32.0, 27.9, 21.4, 19.2, 13.3; IR (Neat Film NaCl) 3081, 2959, 2936, 2875, 2247, 1733, 1648, 1609, 1471, 1454, 1423, 1403, 1385, 1369, 1297, 1269, 1235, 1192, 1173, 1096, 996, 932, 874, 824, 764 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{18}H_{25}O_4N$ $[M]^{+\bullet}$: 319.1784; found 319.1777.

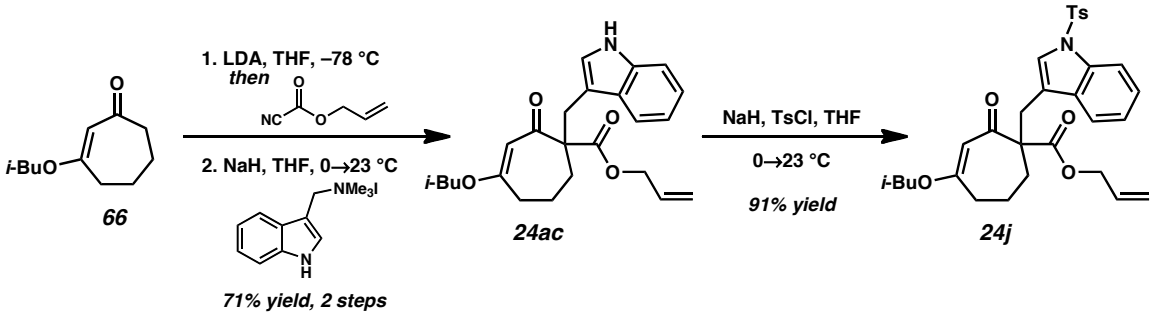


β-Ketoester 24i. To a solution of diisopropylamine (3.54 mL, 25.27 mmol, 1.20 equiv) in THF (108 mL) in a 250 mL round-bottom flask at 0 °C was added *n*-BuLi (10.26 mL, 24.22 mmol, 2.36 M in hexanes, 1.15 equiv) dropwise over 10 min. After 15 min of stirring at 0 °C, the mixture was cooled to –78 °C using an acetone/CO_2(s) bath. A solution of vinylogous ester **66** (3.84 g, 21.06 mmol, 1.00 equiv) in THF (10 mL) was added dropwise using positive pressure cannulation. After an additional 1 h of stirring at –78 °C, allyl cyanoformate (2.52 mL, 9.74 mmol, 1.10 equiv) was added dropwise over 10 min. The mixture was stirred at –78 °C for 2.5 h, quenched by addition of 50% sat. aqueous NH_4Cl (30.7 mL), and then allowed to warm to ambient temperature. The reaction was diluted with Et_2O (100 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a pale orange oil. The crude oil was purified by automated flash column chromatography using a

Teledyne Isco CombiFlash R_f (SiO_2, 32 g loading cartridge, 330 g column, multi-step gradient, hold 0% [2 min]→ramp to 20% [10 min]→hold 20% [6 min]→ramp to 50% [3 min]→hold 50% EtOAc in hexanes [11 min]) to afford the intermediate β-ketoester (4.66 g, 17.50 mmol, 83% yield) as a pale orange oil.

A portion of the intermediate β-ketoester (1.00 g, 3.75 mmol, 1.00 equiv) was dissolved in THF (25 mL) in a 100 mL round-bottom flask, cooled to 0 °C, and stirred vigorously as hexane-washed NaH (90 mg, 3.75 mmol, 1.00 equiv) was added in one portion. Evolution of gas was observed, and the reaction was stirred at 0 °C for 30 min to give a yellow-orange solution. Additional NaH (202 mg, 8.43 mmol, 2.25 equiv) was added, giving a thick yellow suspension. After 5 min, 4-(bromomethyl)pyridine hydrogen bromide (996 mg, 3.94 mmol, 1.05 equiv) was added portionwise, and the reaction was allowed to warm to ambient temperature. After 14 h, the reaction was quenched by addition of 50% sat. aqueous NH_4Cl (16 mL) to give a brown biphasic mixture. The phases were separated and the aqueous layer was extracted with Et_2O (3 x 25 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 3 x 25 cm, 1:1→1:4 hexanes:EtOAc→EtOAc) to afford β-ketoester **24i** (1.16 g, 3.23 mmol, 86% yield, 71% yield over 2 steps) as a yellow oil; R_f = 0.28, broad (1:2 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.06 (dd, *J* = 4.4, 1.6 Hz, 2H), 5.82 (dddd, *J* = 17.1, 10.4, 5.8, 5.8 Hz, 1H), 5.37 (s, 1H), 5.28 (app dq, *J* = 17.2, 1.5 Hz, 1H), 5.21 (app dq, *J* = 10.4, 1.2 Hz, 1H), 4.61 (dddd, *J* = 13.1, 5.9, 1.3, 1.3 Hz, 1H), 4.50 (dddd, *J* = 13.1, 5.9, 1.3, 1.3 Hz, 1H), 3.42 (d, *J* = 6.5 Hz, 2H), 3.27 (d, *J* = 13.3 Hz, 1H), 3.18 (d, *J* = 13.3 Hz, 1H), 2.54 (ddd, *J* = 17.2,

9.3, 3.0 Hz, 1H), 2.38–2.21 (m, 2H), 2.03–1.86 (m, 2H), 1.83–1.59 (m, 2H), 0.91 (d, J = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.0, 174.3, 172.3, 149.6, 146.1, 131.4, 126.0, 119.2, 105.6, 74.9, 66.1, 63.5, 42.4, 33.9, 31.5, 27.8, 21.8, 19.2; IR (Neat Film NaCl) 3072, 3026, 2959, 2935, 2874, 1733, 1660, 1608, 1557, 1496, 1470, 1452, 1415, 1384, 1369, 1293, 1272, 1232, 1201, 1172, 1095, 1074, 1005, 994, 956, 935, 862, 823, 773 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{21}H_{27}O_4N$ $[M]^{+\bullet}$: 357.1940; found 357.1945.



Indolyl β-Ketoester 24ac. To a solution of diisopropylamine (3.54 mL, 25.27 mmol, 1.20 equiv) in THF (108 mL) in a 250 mL round-bottom flask at 0 °C was added *n*-BuLi (10.26 mL, 24.22 mmol, 2.36 M in hexanes, 1.15 equiv) dropwise over 10 min. After 15 min of stirring at 0 °C, the mixture was cooled to –78 °C using an acetone/CO_2(s) bath. A solution of vinylogous ester **66** (3.84 g, 21.06 mmol, 1.00 equiv) in THF (10 mL) was added dropwise using positive pressure cannulation. After an additional 1 h of stirring at –78 °C, allyl cyanoformate (2.52 mL, 9.74 mmol, 1.10 equiv) was added dropwise over 10 min. The mixture was stirred at –78 °C for 2.5 h, quenched by addition of 50% sat. aqueous NH_4Cl (30.7 mL), and then allowed to warm to ambient temperature. The reaction was diluted with Et_2O (100 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic phases were dried

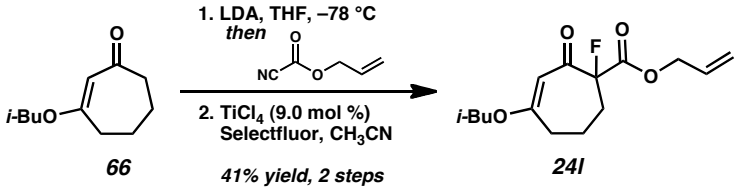
over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a pale orange oil. The crude oil was purified by automated flash column chromatography using a Teledyne Isco CombiFlash R_f (SiO_2, 32 g loading cartridge, 330 g column, multi-step gradient, hold 0% [2 min]→ramp to 20% [10 min]→hold 20% [6 min]→ramp to 50% [3 min]→hold 50% EtOAc in hexanes [11 min]) to afford the intermediate β-ketoester (4.66 g, 17.50 mmol, 83% yield) as a pale orange oil.

A portion of the intermediate β-ketoester (0.85 g, 3.19 mmol, 1.00 equiv) was dissolved in THF (32 mL) in a 100 mL round-bottom flask, cooled to 0 °C, and stirred vigorously as hexane-washed NaH (84 mg, 3.51 mmol, 1.10 equiv) was added in one portion. Evolution of gas was observed, and the reaction was stirred at 0 °C for 30 min to give a yellow-orange solution. Gramine methiodide[52] (1.06 g, 3.35 mmol, 1.05 equiv) was added portionwise to give a suspension. After 11.5 h, the reaction was a brown-orange solution. Additional gramine methiodide (212 mg, 0.67 mmol, 0.31 equiv) was added. After 30 min, the reaction was quenched by addition of 50% sat. aqueous NH_4Cl (4.3 mL) to give a brown biphasic mixture. Volatiles were removed under reduced pressure. The residue was extracted with EtOAc (3 x 40 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in a minimal amount of 1:1 hexanes:EtOAc and filtered through a silica gel pad (1.5 x 10 cm, 1:1 hexanes:EtOAc). The filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 5 x 20 cm, 6:1→4:1→2:1 hexanes:EtOAc) to afford β-ketoester **24ac** (1.09 g, 2.75 mmol, 86% yield, 71% yield over 2 steps) as an orange-brown semi-solid; R_f = 0.21 (4:1 hexanes:EtOAc); ^{1}H NMR

(300 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.67–7.54 (m, 1H), 7.38–7.29 (m, 1H), 7.21–7.04 (m, 2H), 7.00 (d, *J* = 2.4 Hz, 1H), 5.84 (dddd, *J* = 17.2, 10.4, 5.7, 5.7 Hz, 1H), 5.37 (s, 1H), 5.29 (app dq, *J* = 17.2, 1.5 Hz, 1H), 5.20 (app dq, *J* = 10.4, 1.3 Hz, 1H), 4.60 (dddd, *J* = 13.2, 5.6, 1.4, 1.4 Hz, 1H), 4.50 (dddd, *J* = 13.2, 5.8, 1.4, 1.4 Hz, 1H), 3.52 (dd, *J* = 14.3, 0.5 Hz, 1H), 3.47–3.31 (m, 3H), 2.63–2.34 (m, 2H), 2.28 (ddd, *J* = 17.8, 7.7, 4.0 Hz, 1H), 2.02–1.63 (m, 4H), 0.90 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.8, 173.7, 173.2, 135.8, 131.9, 128.8, 124.3, 121.8, 119.5, 119.2, 118.6, 111.1, 111.0, 106.0, 74.7, 65.9, 64.3, 34.0, 32.8, 31.6, 27.8, 21.7, 19.2; IR (Neat Film NaCl) 3785, 3584, 3392, 3079, 3057, 2958, 2930, 2874, 1729, 1641, 1607, 1457, 1457, 1433, 1423, 1384, 1368, 1341, 1233, 1191, 1174, 1127, 1085, 1010, 932, 879, 863, 822, 742 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{24}H_{29}O_4N$ $[M]^{+\bullet}$: 395.2097; found 395.2097.

Tosylindolyl β-Ketoester 24j. To a solution of indole **24ac** (250 mg, 0.63 mmol, 1.00 equiv) in THF (9 mL) in a 100 mL round-bottom flask was added TsCl (241 mg, 1.26 mmol, 2.00 equiv). The mixture was cooled to 0 °C and stirred vigorously as hexane-washed NaH (61 mg, 2.53 mmol, 4.00 equiv) was added in one portion. The reaction was maintained at 0 °C for 5 min before warming to ambient temperature. After 24 h, the white suspension was cooled to 0 °C and additional TsCl (241 mg, 1.26 mmol, 2.00 equiv) was added, followed by hexane-washed NaH (121 mg, 5.06 mmol, 8.00 equiv) in one portion. The reaction was allowed to warm to ambient temperature. After 46 h, the reaction was quenched by addition of 50% sat. aqueous NH_4Cl (3 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced

pressure. The crude product was purified by flash column chromatography (SiO_2, 3 x 25 cm, 10:1→6:1→4:1 hexanes:EtOAc) to afford β-ketoester **24j** (317 mg, 5.76 mmol, 91% yield) as a yellow foam; R_f = 0.40 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97–7.89 (m, 1H), 7.75–7.66 (m, 2H), 7.53–7.44 (m, 1H), 7.35 (s, 1H), 7.31–7.13 (m, 4H), 5.77 (dddd, *J* = 17.1, 10.4, 5.8 Hz, 1H), 5.39 (s, 1H), 5.25 (app dq, *J* = 17.2, 1.5 Hz, 1H), 5.18 (app dq, *J* = 10.4, 1.2 Hz, 1H), 4.52 (dddd, *J* = 13.1, 5.7, 1.3, 1.3 Hz, 1H), 4.42 (dddd, *J* = 13.2, 5.9, 1.3, 1.3 Hz, 1H), 3.48–3.32 (m, 3H), 3.26 (d, *J* = 14.4 Hz, 1H), 2.52 (ddd, *J* = 17.7, 9.2, 3.3 Hz, 1H), 2.41–2.19 (m, 5H), 2.02–1.82 (m, 2H), 1.78–1.58 (m, 2H), 0.92 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.8, 174.0, 172.8, 144.8, 135.4, 134.9, 132.1, 131.6, 129.9, 127.0, 125.8, 124.6, 123.2, 119.9, 118.9, 118.0, 113.7, 105.9, 74.8, 66.1, 63.6, 34.1, 32.2, 31.7, 27.9, 21.7, 21.6, 19.2; IR (Neat Film NaCl) 3854, 3401, 2959, 2931, 2874, 1731, 1657, 1650, 1609, 1448, 1368, 1279, 1233, 1188, 1173, 1121, 1098, 1087, 1019, 1007, 992, 976, 938, 864, 813, 748 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{31}H_{36}O_6N$ $[M+H]^+$: 550.2263; found 550.2250.

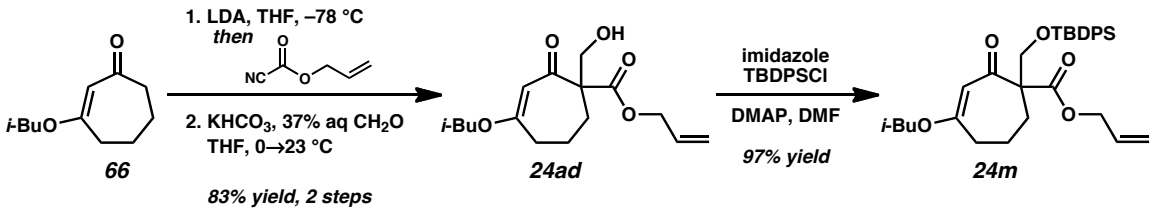


β-Ketoester 24l. To a solution of diisopropylamine (0.92 mL, 6.58 mmol, 1.20 equiv) in THF (27 mL) in a 100 mL round-bottomed flask at 0 °C in an ice/water bath was added *n*-BuLi (2.56 mL, 2.46 M in hexanes, 6.30 mmol, 1.15 equiv) dropwise over 10 min. After 15 min of stirring at 0 °C, the mixture was cooled to –78 °C using an acetone/CO_2(s) bath. A solution of vinylogous ester **66** (1.00 g, 5.48 mmol, 1.00 equiv)

in THF (2 mL) was added dropwise using positive pressure cannulation. After an additional 1 h of stirring at –78 °C, allyl cyanoformate (0.67 mL, 6.02 mmol, 1.10 equiv) was added dropwise over 10 min. The mixture was stirred at –78 °C for 2.5 h, quenched by addition of 50% sat. aqueous NH_4Cl (8 mL), and then allowed to warm to ambient temperature. The reaction was diluted with Et_2O (25 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a pale orange oil.

The crude oil was dissolved in CH_3CN (55 mL) in a 100 mL round-bottomed flask under N_2 and $TiCl_4$ (53.7 μL, 0.49 mmol, 9.0 mol %) was added dropwise, giving a dark purple-brown mixture. After 10 min, Selectfluor (2.33 g, 6.58 mmol, 1.20 equiv) was added in one portion. After 3.5 h, the reaction mixture was an orange suspension. The reaction was concentrated under reduced pressure and the orange residue was partitioned between water (25 mL) and Et_2O (25 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by automated flash column chromatography using Teledyne Isco CombiFlash R_f (SiO_2, 25 g loading cartridge, 120 g column, 10% EtOAc in hexanes) to afford β-ketoester **24l** (639 mg, 2.25 mmol, 41% yield over 2 steps) as a pale yellow oil; R_f = 0.44 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (dddd, *J* = 17.1, 10.7, 5.6, 5.6 Hz, 1H), 5.39 (s, 1H), 5.29 (ddd, *J* = 17.1, 2.9, 1.5 Hz, 1H), 5.20 (app d, *J* = 10.5 Hz, 1H), 4.59 (dddd, *J* = 19.0, 13.2, 5.6, 1.2 Hz, 2H), 3.50 (dd, *J* = 9.3, 6.8 Hz, 1H), 3.47 (dd, *J* = 9.3, 6.6 Hz, 1H), 2.59 (ddd, *J* = 17.8, 9.8, 3.9 Hz, 1H),

2.45–2.38 (m, 2H), 2.02–1.94 (m, 1H), 1.84–1.75 (m, 1H), 1.70 (ddd, J = 14.4, 7.3, 4.4 Hz, 1H), 1.43 (s, 3H), 0.94 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.1 (d, J_{CF} = 24.1 Hz), 178.0, 167.6 (d, J_{CF} = 25.4 Hz), 131.3, 119.0, 102.0 (d, J_{CF} = 1.1 Hz), 99.3 (d, J_{CF} = 193.5 Hz), 75.3, 66.6, 34.0 (d, J_{CF} = 2.1 Hz), 31.9 (d, J_{CF} = 22.5 Hz), 27.8, 20.7 (d, J_{CF} = 1.7 Hz), 19.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ –148.54 (dd, J = 35.4, 20.7 Hz); IR (Neat Film NaCl) 3086, 2960, 2938, 2876, 1752, 1654, 1649, 1603, 1471, 1453, 1422, 1403, 1385, 1369, 1282, 1249, 1229, 1204, 1176, 1137, 1095, 1045, 991, 953, 927, 874, 862, 843, 829, 795, 758 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{15}H_{21}O_4F$ $[M]^{+\bullet}$: 284.1425; found 284.1424.

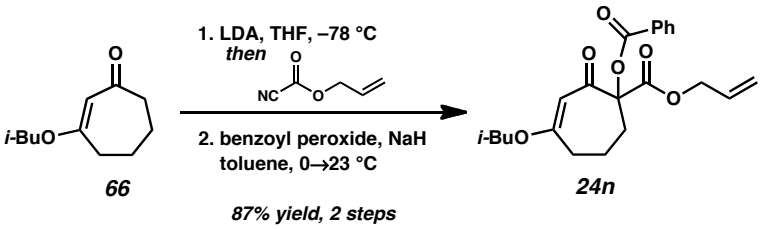


Hydroxy β-Ketoester 24ad. To a solution of diisopropylamine (1.84 mL, 13.15 mmol, 1.20 equiv) in THF (54 mL) in a 250 mL round-bottom flask at 0 °C was added *n*-BuLi (5.12 mL, 12.60 mmol, 2.51 M in hexanes, 1.15 equiv) dropwise over 10 min. After 15 min of stirring at 0 °C, the mixture was cooled to –78 °C using an acetone/CO_2(s) bath. A solution of vinylogous ester **66** (2.00 g, 10.96 mmol, 1.00 equiv) in THF (4 mL) was added dropwise using positive pressure cannulation. After an additional 1 h of stirring at –78 °C, allyl cyanoformate (1.34 mL, 12.06 mmol, 1.10 equiv) was added dropwise over 10 min. The mixture was stirred at –78 °C for 2.5 h, quenched by addition of 50% sat. aqueous NH_4Cl (16 mL), and then allowed to warm to ambient temperature. The reaction

was diluted with Et_2O (200 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a pale orange oil (2.92 g).

Half of the crude oil (1.46 g) was dissolved in THF (10 mL) in a 50 mL round-bottom flask and cooled to 0 °C. $KHCO_3$ (1.65 g, 16.44 mmol, 3.00 equiv) and 37% wt. aqueous formaldehyde (2.81 mL, 37.73 mmol, 6.9 equiv) were added. The reaction was allowed to warm to ambient temperature. After 11 h, the reaction was diluted with H_2O and CH_2Cl_2 (25 mL each). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 12 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 3 x 25 cm, 4:1→ 2:1→1:1 hexanes:EtOAc) to afford β-ketoester **24ad** (1.35 g, 4.55 mmol, 83% yield over 2 steps) as a pale yellow oil; R_f = 0.21 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89 (dddd, *J* = 17.2, 10.4, 5.7, 5.7 Hz, 1H), 5.43 (s, 1H), 5.32 (app dq, *J* = 17.2, 1.5 Hz, 1H), 5.23 (app dq, *J* = 10.4, 1.3 Hz, 1H), 4.76–4.54 (m, 2H), 3.93–3.72 (m, 2H), 3.51 (d, *J* = 6.5 Hz, 2H), 3.59–3.45 (m, 1H) 2.68–2.50 (m, 1H), 2.50–2.35 (m, 1H), 2.31–2.12 (m 1H), 2.10–1.91 (m, 2H), 1.91–1.71 (m, 2H), 0.96 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.2, 175.1, 171.9, 131.6, 118.9, 105.6, 75.1, 68.7, 66.1, 63.6, 33.7, 28.6, 27.9, 20.9, 19.2; IR (Neat Film NaCl) 3448, 3083, 2959, 2937, 2875, 1733, 1646, 1608, 1471, 1457, 1420, 1404, 1385, 1369, 1298, 1235, 1195, 1171, 1099, 1044, 998, 928, 869, 825 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{16}H_{25}O_5$ $[M+H]^+$: 297.1702; found 297.1715.

Siloxy β-Ketoester 24m. Alcohol **24ad** (895 mg, 3.02 mmol, 1.00 equiv), DMAP (553 mg, 4.53 mmol, 1.50 equiv), and imidazole (308 mg, 4.53 mmol, 1.50 equiv) were dissolved in DMF (11 mL) in a 20 mL scintillation vial with magnetic stir bar and septum fitted screw cap. TBDPSCl (0.942 mL, 3.62 mmol, 1.20 equiv) was added dropwise. The stirred mixture turned into a turbid white suspension within 5 min. After 54 h, the reaction was poured into H_2O (35 mL) and 2:1 CH_2Cl_2/hexanes (75 mL). The phases were separated and the aqueous layer was further extracted with 2:1 CH_2Cl_2/hexanes (4 x 35 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 5 x 25 cm, 40:1→20:1 hexanes:EtOAc) to afford siloxy β-ketoester **24m** (1.567 g, 2.93 mmol, 97% yield) as a clear, colorless oil; R_f = 0.58 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–7.61 (m, 4H), 7.47–7.32 (m, 6H), 5.86 (dddd, *J* = 17.1, 10.5, 5.7, 5.7 Hz, 1H), 5.39 (s, 1H), 5.29 (app dq, *J* = 17.2, 1.5 Hz, 1H), 5.19 (app dq, *J* = 10.4, 1.2 Hz, 1H), 4.65 (dddd, *J* = 13.2, 5.7, 1.3, 1.3 Hz, 1H), 4.52 (dddd, *J* = 13.3, 5.7, 1.3, 1.3 Hz, 1H), 4.15 (d, *J* = 9.6 Hz, 1H), 4.05 (d, *J* = 9.6 Hz, 1H), 3.47 (d, *J* = 6.5 Hz, 2H), 2.80–2.51 (m, 2H), 2.43 (ddd, *J* = 11.0, 7.4, 2.9 Hz, 1H), 2.17–1.89 (m, 3H), 1.89–1.68 (m, 1H), 1.04 (s, 9H), 0.95 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5, 174.8, 171.6, 135.8, 135.7, 133.3, 133.2, 131.89, 129.8, 129.7, 127.8, 127.7, 118.5, 105.8, 74.8, 69.0, 65.9, 65.1, 34.5, 30.0, 27.8, 26.8, 21.9, 19.4, 19.2; IR (Neat Film NaCl) 3460, 3071, 3049, 2958, 2931, 2890, 2857, 1738, 1650, 1609, 1472, 1429, 1384, 1362, 1299, 1236, 1200, 1173, 1113, 1007, 998, 936, 864, 822, 740 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{32}H_{43}O_5Si$ $[M+H]^+$: 535.2880; found 535.2880.



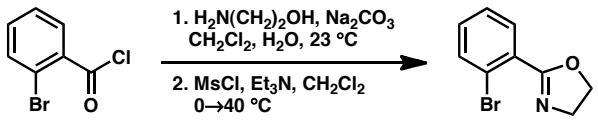
β-Ketoester 24n. To a solution of diisopropylamine (1.84 mL, 13.15 mmol, 1.20 equiv) in THF (54 mL) in a 250 mL round-bottomed flask at 0 °C in an ice/water bath was added *n*-BuLi (5.12 mL, 2.51 M in hexanes, 12.60 mmol, 1.15 equiv) dropwise over 10 min. After 15 min of stirring at 0 °C, the mixture was cooled to –78 °C using an acetone/CO_2(s) bath. A solution of vinylogous ester **66** (2.00 g, 10.96 mmol, 1.00 equiv) in THF (4 mL) was added dropwise using positive pressure cannulation. After an additional 1 h of stirring at –78 °C, allyl cyanoformate (1.34 mL, 12.06 mmol, 1.10 equiv) was added dropwise over 10 min. The mixture was stirred at –78 °C for 2.5 h, quenched by addition of 50% sat. aqueous NH_4Cl (16 mL), and then allowed to warm to ambient temperature. The reaction was diluted with Et_2O (20 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a pale orange oil (2.92 g).

Half of the crude oil (1.46 g) was dissolved in toluene (30 mL) in a 100 mL round-bottomed flask, cooled to 0 °C, and stirred vigorously as hexane-washed NaH (197 mg, 8.22 mmol, 1.50 equiv) was added in one portion. Evolution of gas was observed and the reaction was stirred at 0 °C for 30 min. Benzoyl peroxide (1.99 g, 8.22 mmol, 1.50 equiv) was added slowly portionwise, giving a thick, pasty suspension. The reaction was warmed to ambient temperature and diluted with toluene (20 mL) to give a more

freely stirring turbid yellow mixture. After 30 min, the reaction was diluted with toluene (50 mL) and washed with H_2O (2 x 5 mL) and brine (2 x 5 mL). The aqueous layers were combined and extracted with EtOAc (2 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 5 x 13 cm, 10:1 hexanes:EtOAc) to afford β-ketoester **24n** (1.85 g, 4.79 mmol, 87% yield over 2 steps) as a pale yellow oil; R_f = 0.46 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09–7.99 (m, 2H), 7.64–7.53 (m, 1H), 7.50–7.38 (m, 2H), 5.89 (dddd, *J* = 17.2, 10.5, 5.7, 5.7 Hz, 1H), 5.42 (s, 1H), 5.31 (app dq, *J* = 17.2, 1.5 Hz, 1H), 5.20 (app dq, *J* = 10.4, 1.3 Hz, 1H), 4.80–4.62 (m, 2H), 3.57 (d, *J* = 6.5 Hz, 2H), 2.87–2.46 (m, 4H), 2.12–1.85 (m, 3H), 0.96 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.1, 175.9, 168.0, 165.1, 133.6, 131.7, 130.0, 129.6, 128.6, 118.7, 102.2, 88.8, 75.2, 66.6, 33.8, 31.2, 27.9, 21.2, 19.2, 19.2; IR (Neat Film NaCl) 3070, 2960, 2937, 2875, 1753, 1727, 1661, 1605, 1471, 1452, 1423, 1384, 1369, 1315, 1280, 1222, 1206, 1175, 1107, 1097, 1070, 1044, 1026, 1002, 933, 849, 792 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{22}H_{26}O_6$ $[M]^{+\bullet}$: 386.1733; found 386.1729.

2.7.2.3 SYNTHESIS OF PHOX LIGANDS

Ligands (*S*)-*t*-BuPHOX (**3**)[54] and (*S*)-$(CF_3)_3$-*t*-BuPHOX (**8**)[55] were prepared according to previously reported procedures. The preparation of ligands **128** and **67** are described below.

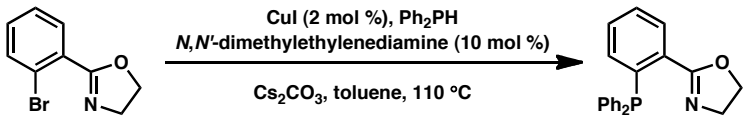


127

2-(2-Bromo-phenyl)-4,5-dihydrooxazole 127. To a solution of ethanolamine (1.32 mL, 21.9 mmol, 1.20 equiv) in CH_2Cl_2 (60 mL) in a 250 mL round-bottom flask was added a solution of Na_2CO_3 (5.80 g, 54.7 mmol, 3.00 equiv) in H_2O (45 mL). Neat 2-bromobenzoyl chloride (4.00 g, 2.38 mL, 18.2 mmol, 1.00 equiv) was added dropwise via syringe to the vigorously stirred biphasic system. The reaction flask was capped with a yellow plastic stopper and stirred for 7.5 h at 23 °C. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 25 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a white solid. The crude product was dissolved in CH_2Cl_2 (50 mL) and hexanes (10 mL) was added. The solution was concentrated to ca. 25 mL under reduced pressure resulting in precipitation of the intermediate amide (4.02 g, 16.4 mmol, 90% yield) as a white solid.

The intermediate amide (2.0 g, 8.2 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (62 mL) in a 100 mL round-bottom flask equipped with a reflux condenser. Et_3N (3.43 mL, 24.5 mmol, 3.00 equiv) was added, and the solution was cooled to 0 °C by use of an ice/water bath. Methanesulfonyl chloride (952 μL, 12.3 mmol, 1.50 equiv) was added dropwise. The reaction was stirred at 0 °C for 30 min and heated to 40 °C in an oil bath. After 5 h of stirring, the resulting yellow solution was allowed to cool to ambient temperature, diluted with CH_2Cl_2 (25 mL), and washed with H_2O (2 x 25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a thick, pale yellow oil. The crude oil was purified by flash

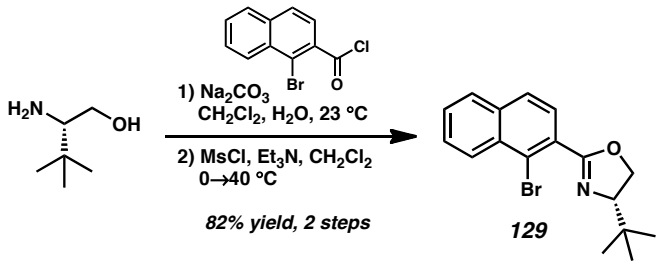
chromatography (SiO_2, 5 x 10 cm, 6:2:2 hexanes:EtOAc:toluene) to afford 2-(2-bromo-phenyl)-4,5-dihydrooxazole **127** (1.31 g, 5.79 mmol, 71% yield); R_f = 0.45 (9:1 $CHCl_3$:MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 7.8, 2.0 Hz, 1H), 7.65 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.35 (app dt, *J* = 7.6, 1.2 Hz, 1H), 7.29 (app dt, *J* = 7.6, 1.7 Hz, 1H), 4.46 (t, *J* = 9.6 Hz, 2H), 4.12 (t, *J* = 9.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 134.1, 131.8, 131.5, 129.8, 127.2, 122.0, 67.8, 55.5; IR (Neat Film NaCl) 3390, 3070, 2966, 2904, 2868, 1729, 1646, 1589, 1432, 1362, 1328, 1272, 1243, 1093, 1026, 938 cm^{-1}; HRMS (EI+) *m/z* calc'd for C_9H_8BrNO $[M]^{+\bullet}$: 224.9789; found 224.9779.



127 ***86% yield*** ***128***

PHOX Ligand 128. A 250 mL Schlenk flask was charged with CuI (66.7 mg, 0.35 mmol, 2 mol %), Ph_2PH (3.85 mL, 22.1 mmol, 1.25 equiv), *N,N'*-dimethylethylenediamine (191 mL, 1.77 mmol, 10 mol %), and toluene (18 mL). The solution was stirred at 23 °C for 20 min. 2-(2-Bromo-phenyl)-4,5-dihydrooxazole **127** (4.0 g, 17.7 mmol, 1.00 equiv) was azeotroped with toluene (2 x 5 mL) under reduced pressure, dissolved in toluene (18 mL), and transferred quantitatively to the Schlenk flask by use of positive pressure cannulation. Cs_2CO_3 (8.65 g, 26.5 mmol, 1.50 equiv) was added in one portion and the flask was evacuated/backfilled with Ar (three cycles). The teflon valve was sealed, and the yellow heterogeneous reaction mixture was stirred vigorously, immersed in an oil bath, and heated to 110 °C. After 20 h of stirring at 110 °C, the mixture was allowed to cool to ambient temperature and filtered through a pad of

Celite using CH_2Cl_2 (2 x 50 mL). The filtrate was concentrated under reduced pressure to afford a clear orange oil. The crude oil was flushed through a plug of silica gel (SiO_2, 5 x 10 cm, hexanes→9:1 CH_2Cl_2:Et_2O) to afford PHOX ligand **128** (5.03 g, 15.2 mmol, 86% yield) as a colorless viscous oil that crystallized upon standing; R_f = 0.50 (7:3 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 7.6, 3.4 Hz, 1H), 7.37–7.26 (comp. m, 12H), 6.89 (dd, *J* = 4.1, 7.6 Hz, 1H), 4.08 (t, *J* = 9.5 Hz, 2H), 3.78 (t, *J* = 9.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5 (d, J_{CP} = 2.8 Hz), 139.1 (d, J_{CP} = 24.9 Hz), 138.0 (d, J_{CP} = 11.5 Hz), 134.1 (d, J_{CP} = 20.7 Hz), 133.7 (d, J_{CP} = 1.8 Hz), 131.9 (d, J_{CP} = 18.9 Hz), 130.5, 129.9 (d, J_{CP} = 2.8 Hz), 128.7, 128.5 (d, J_{CP} = 7.4 Hz), 128.1, 67.2, 55.0; ^{31}P NMR (121 MHz, $CDCl_3$) δ –3.99 (s); IR (Neat Film NaCl) 3053, 3000, 2971, 2901, 2876, 1650, 1585, 1562, 1478, 1434, 1354, 1326, 1248, 1133, 1089, 1070, 1041, 974, 942, 898, 743 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{21}H_{19}NOP$ $[M+H]^+$: 332.1204; found 332.1218; mp = 99–101 °C.

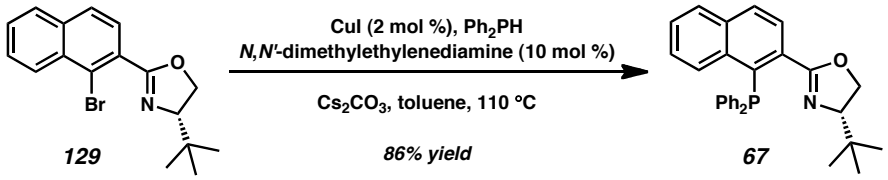


Dihydrooxazole 129. (*S*)-*tert*-Leucinol (1.02 g, 8.66 mmol, 1.00 equiv) was placed in a 250 mL round-bottom flask and dissolved in CH_2Cl_2 (14 mL). Na_2CO_3 (2.75 g, 26.0 mmol, 3.00 equiv) in H_2O (27.0 mL) was added dropwise via syringe to the vigorously stirred biphasic system. To the biphasic mixture was added a solution of 1-bromonaphthalene-2-carbonyl chloride (2.68 g, 9.96 mmol, 1.15 equiv) in CH_2Cl_2 (15

mL). The reaction was stirred vigorously at 23 °C for 9.5 h. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (4 x 50 mL). The combined organics were stirred with KOH (10 mL, 10 mmol, 1.0 N in MeOH) for 30 min and then transferred to a separatory funnel. H_2O (10 mL) was added and the mixture was neutralized with HCl (6.0 M in H_2O). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (4 x 50 mL). The combined organics were dried over $MgSO_4$ and concentrated under reduced pressure to afford the intermediate amide (3.03 g) as a pale yellow solid.

The intermediate amide (3.03 g) was dissolved in CH_2Cl_2 (43.3 mL) in a 100 mL 3-neck round-bottom flask fitted with a reflux condenser. The solution was cooled to 0 °C by use of an ice/water bath and Et_3N (2.90 mL, 20.8 mmol, 2.40 equiv) was added. Methanesulfonyl chloride (0.77 mL, 9.96 mmol, 1.15 equiv) was added dropwise. The reaction mixture was stirred at 0 °C for 30 min and heated to 40 °C in a water bath. After 21 h of stirring, the mixture was allowed to cool to ambient temperature and saturated aqueous $NaHCO_3$ was added. The biphasic system was stirred vigorously for 5 min and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organics were washed with brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure to afford a pale yellow oil. The crude oil was purified by flash chromatography (SiO_2, 3 x 15 cm, 9:1 hexanes:EtOAc) to afford **129** (2.36 g, 7.12 mmol, 82% yield over two steps) as a pale yellow oil that solidifies when placed in a –20 °C freezer; $R_f = 0.73$ (9:1 $CHCl_3$:MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (dd, *J* = 7.7, 0.5 Hz, 1H), 7.85–7.81 (m, 2H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.60 (app dt, *J* = 8.2, 1.3 Hz, 1H), 7.56 (app dt, *J* = 6.9, 1.3 Hz, 1H), 4.46 (dd, *J* = 10.4, 8.5 Hz, 1H),

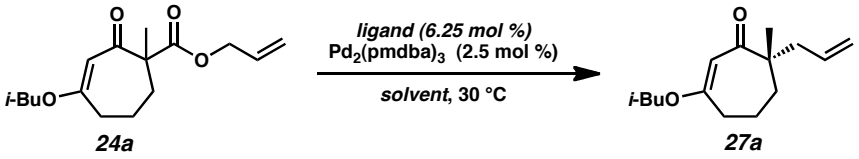
4.33 (dd, J = 8.5, 8.0 Hz, 1H), 4.17 (dd, J = 10.4, 8.2 Hz, 1H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8, 134.9, 132.3, 128.8, 128.3, 128.3, 128.0, 127.8, 127.7, 126.9, 123.2, 76.9, 69.2, 34.1, 26.1; IR (Neat Film NaCl) 3065, 2956, 2899, 2863, 1667, 1620, 1594, 1556, 1499, 1476, 1463, 1393, 1372, 1362, 1339, 1321, 1300, 1238, 1264, 1210, 1161, 1104, 1024, 977, 956, 920, 817, 752 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{17}H_{18}ONBr$ $[M]^{+\bullet}$: 331.0572; found 331.0583; $[\alpha]_D^{20.0}$ –64.0 (c 0.92, $CHCl_3$); mp = 66–68 °C.



PHOX Ligand 67. Prepared by the typical method as described for **128** above by employing **129** (830.6 mg, 2.50 mmol). After 24 h of stirring, the reaction mixture was filtered through a plug of Celite, eluted with CH_2Cl_2 (2 x 25 mL), and concentrated under reduced pressure. The crude oil was passed through a short plug of silica (SiO_2, 2.5 x 8 cm, hexanes→9:1 CH_2Cl_2:Et_2O) to afford a bright yellow oil. The crude oil was purified by flash chromatography (SiO_2, 2.5 x 25 cm, 19:1 hexanes:acetone and then 2.5 x 21 cm, 9:1→6:1 hexanes:EtOAc) to afford PHOX ligand **67** (950.8 mg, 2.17 mmol, 87% yield) as a bright yellow foam; R_f = 0.21 (9:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, J = 8.1 Hz, 1H), 7.96 (d, J = 8.0 Hz, 2H), 7.72 (dd, J = 8.3, 2.9 Hz, 1H), 7.45 (app dt, J = 7.8, 1.7 Hz, 2H), 7.41–7.38 (m, 3H), 7.29–7.22 (m, 6H), 7.16 (ddd, J = 8.3, 6.9, 1.0 Hz, 1H), 4.17–4.15 (m, 2H), 3.91 (dd, J = 9.8, 8.8 Hz, 1H), 0.97 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6 (d, J_{CP} = 5.1 Hz), 137.5 (d, J_{CP} = 33.1 Hz), 136.8, (d, J_{CP}

= 14.7 Hz), 136.5 (d, J_{CP} = 14.7), 134.9, 134.7 (d, J_{CP} = 33.6 Hz), 133.1 (d, J_{CP} = 26.7 Hz), 132.2 (d, J_{CP} = 17.5 Hz), 132.1 (d, J_{CP} = 17.5 Hz), 131.5 (d, J_{CP} = 0.9 Hz), 129.1 (d, J_{CP} = 7.4 Hz), 129.0, 128.4 (d, J_{CP} = 6.0 Hz), 127.8 (d, J_{CP} = 8.3 Hz), 126.6 (d, J_{CP} = 8.7 Hz), 126.4 (d, J_{CP} = 40.5 Hz), 76.8, 69.0, 34.1, 26.3; ^{31}P NMR (121 MHz, $CDCl_3$) δ –9.33 (s); IR (Neat Film NaCl) 3054, 2954, 2867, 1665, 1584, 1478, 1434, 1364, 1244, 1094, 1026, 986, 962, 922, 824 cm^{-1}; HRMS (FAB+) *m*/*z* calc'd for $C_{29}H_{28}NOP$ $[M]^{+\bullet}$: 437.1908; found 437.1908; $[\alpha]_D^{26.1}$ –38.2 (*c* 1.59, *n*-hexane).

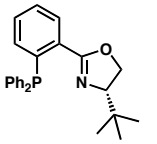
2.7.2.4 ENANTIOSELECTIVE Pd-CATALYZED DECARBOXYLATIVE ALKYLATION SCREENING PROTOCOL[a]



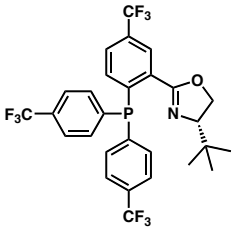
24a *27a*

entry	ligand	solvent	yield (%)[b]	ee (%)[c]
1	*13*	THF[e]	94	84
2	*13*	*p*-dioxane	86	84
3	*13*	2-methyl THF[e]	75	85
4	*13*	TBME[e]	88	85
5	*13*	Et_2O	93	86
6	*13*	benzene	84	86
7	*13*	toluene	91	88
8[d]	*14*	toluene	57	90
9	*150*	toluene	77	72

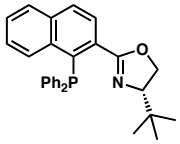
[a] *Conditions*: β-ketoester **24a** (1.0 equiv), $Pd_2(pmdba)_3$ (2.5 mol %), ligand (6.25 mol %) in solvent (0.1 M) at 30 °C; pmdba = 4,4'-methoxydibenzylideneacetone. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Increased catalyst loadings were required to achieve full conversion: $Pd_2(pmdba)_3$ (5 mol %), **8** (12.5 mol %). [e] THF = tetrahydrofuran, 2-methyl THF = 2-methyl tetrahydrofuran, TBME = *tert*-butyl methyl ether.



***(S)-t*-BuPHOX (*3*)**



(S)*-$(CF_3)_3$-*t*-BuPHOX *(8)



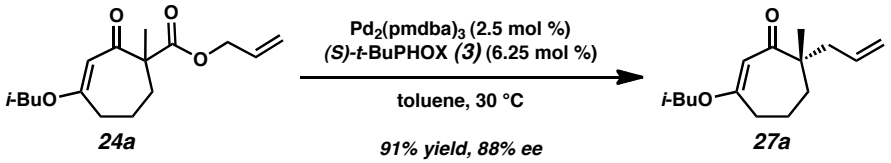
67

Enantioselective Allylation Screen to Produce Vinylogous Ester 27a *(0.20 mmol scale).* To a 25 mL flask was added $Pd_2(pmdba)_3$ (5.00 μmol, 2.5 mol %) and ligand (12.5 μmol, 6.25 mol %). The flask was evacuated/backfilled with N_2 (3 cycles, 5 min evacuation per cycle). Solvent (most of total volume, 0.1 M final concentration) was added and the black suspension was stirred for 30 min at 30 °C using an oil bath. A solution of β-ketoester **24a** (0.20 mmol, 1.00 equiv) in solvent (remainder of total volume) was transferred to the catalyst solution using positive pressure cannulation. When judged complete by TLC analysis, the reaction was filtered through a small plug of SiO_2, eluted with Et_2O, and concentrated under reduced pressure. Purification by flash

column chromatography (SiO_2, 1.5 x 15 cm, 9:1→6:1 hexanes:EtOAc) or preparative TLC (SiO_2, 2:1 hexanes:EtOAc) provided vinylogous ester **27a** for analysis. HPLC conditions: 1% IPA in hexanes, 1.0 mL/min, OD-H column, t_R (min): major = 6.30, minor = 7.26. (For characterization data, see p. 287)

2.7.2.5 PREPARATION OF CHIRAL VINYLOGOUS ESTERS 27

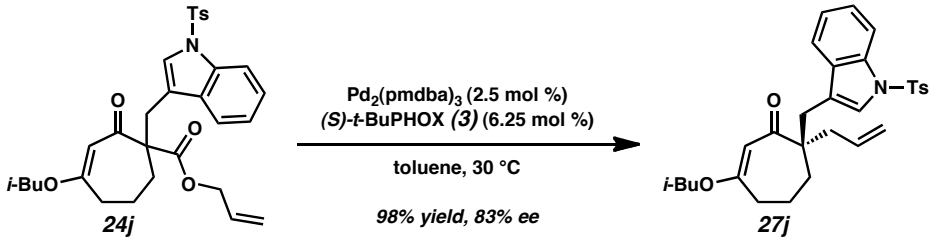
Non-enantioselective reactions were performed using $Pd(PPh_3)_4$ (5 mol %) or achiral PHOX ligand **128** (6.25 mol %) and $Pd_2(pmdba)_3$ (2.5 mol %) in toluene at 30 °C. For the synthesis of ligand **128**, see p. 277–283.



Schlenk Manifold Method: Asymmetric Allylic Alkylation

Vinylogous Ester 27a. $Pd_2(pmdba)_3$ (5.0 mg, 4.5 μmol, 2.5 mol %) and (*S*)-*t*-BuPHOX (4.4 mg, 11 μmol, 6.25 mol %) were placed in a 1 dram vial. The flask was evacuated/backfilled with N_2 (3 cycles, 10 min evacuation per cycle). Toluene (1.3 mL, sparged with N_2 for 1 h immediately before use) was added and the black suspension was immersed in an oil bath preheated to 30 °C. After 30 min of stirring, β-ketoester **24a** (50.7 mg, 0.181 mmol, 1.00 equiv) was added as a solution in toluene (0.5 mL, sparged with N_2 immediately before use) using positive pressure cannulation. The dark orange catalyst solution turned olive green immediately upon addition of β-ketoester **24a**. The

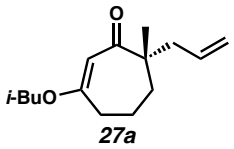
reaction was stirred at 30 °C for 21 h, allowed to cool to ambient temperature, filtered through a silica gel plug (2 x 2 cm, Et_2O), and concentrated under reduced pressure. The crude oil was purified by preparative TLC (SiO_2, 4:1 hexanes:EtOAc) to afford vinylogous ester **27a** (38.8 mg, 0.164 mmol, 91% yield, 88% ee) as a pale yellow oil. (For characterization data, see p. 287).



Glove Box Method: Asymmetric Allylic Alkylation

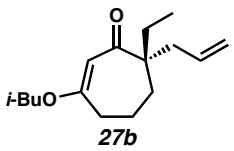
Vinylogous Ester 27j. A 20 mL scintillation vial was loaded with β-ketoester **24j** (447 mg, 0.81 mmol, 1.00 equiv). A separate 20 mL scintillation vial was loaded with $Pd_2(pmdba)_3$ (19.7 mg, 0.051 mmol, 6.25 mol %), (*S*)-*t*-BuPHOX (22.3 mg, 0.020 mmol, 2.5 mol %), and magnetic stir bar. The two vials and a teflon-lined hard cap were evacuated/backfilled with N_2 in a glove box antechamber (3 cycles, 5 min evacuation per cycle) before being trasnsferred into the glove box. Toluene (5 mL) was added to the vial containing $Pd_2(pmdba)_3$ and (*S*)-*t*-BuPHOX. The vial was capped and heated to 30 °C for 30 min. During this time, the mixture developed a dark orange color. β-Ketoester **24j** was dissolved in toluene (3 mL) and added to the catalyst solution dropwise, causing the solution to turn olive green. The solution was stirred at 30 °C in a heating block. The capped vial was removed from the glove box after 29 h of stirring. The crude product was concentrated under reduced pressure and purified by flash column chromatography

(SiO_2, 5 x 25 cm, 15:1→10:1→8:1→6:1 hexanes:EtOAc) to afford vinylogous ester **27j** (403 mg, 0.796 mmol, 98% yield, 82.9% ee) as a thick, white semi-solid. (For characterization data, see p. 294).



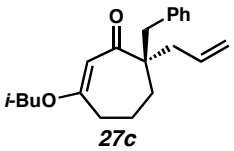
27a

Vinylogous Ester 27a ***(Table 2.1, entry 1).*** Prepared using Schlenk Manifold Method. 38.8 mg, 0.164 mmol, 91% yield. Preparative TLC (SiO_2, 4:1 hexanes:EtOAc). R_f = 0.31 (3:1 hexanes:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72 (dddd, *J* = 16.6, 10.5, 7.3, 7.3 Hz, 1H), 5.31 (s, 1H), 5.05–5.00 (m, 2H), 3.50 (dd, *J* = 9.3, 6.6 Hz, 1H), 3.47 (dd, *J* = 9.3, 6.6 Hz, 1H), 2.53–2.42 (m, 2H), 2.38 (dd, *J* = 13.7, 7.1 Hz, 1H), 2.20 (dd, *J* = 13.7, 7.8 Hz, 1H), 1.98 (app sept, *J* = 6.6 Hz, 1H), 1.86–1.70 (m, 3H), 1.62–1.56 (m, 1H), 1.14 (s, 3H), 0.95 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.7, 171.3, 134.6, 117.9, 105.0, 74.5, 51.5, 45.4, 36.1, 35.2, 28.0, 25.2, 19.9, 19.3, 19.3; IR (Neat Film NaCl) 2960, 2933, 2873, 1614, 1470, 1387, 1192, 1171, 998, 912 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{15}H_{24}O_2$ $[M]^{+\bullet}$: 236.1776; found 236.1767; $[\alpha]_D^{25.6}$ –69.04 (*c* 1.08, $CHCl_3$, 88.0% ee); HPLC conditions: 1% IPA in hexanes, 1.0 mL/min, OD-H column, t_R (min): major = 6.30, minor = 7.26.



27b

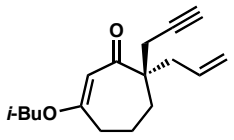
Vinylogous Ester 27b ***(Table 2.1, entry 2).*** Prepared using Schlenk Manifold Method. 226.3 mg, 0.90 mmol, 89% yield. Flash column chromatography (SiO_2, 3 x 24 cm, 20:1→15:1→10:1 hexanes:EtOAc). R_f = 0.43 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82–5.62 (m, 1H), 5.29 (s, 1H), 5.06–4.98 (m, 2H), 3.48 (dd, *J* = 11.1, 6.6 Hz, 1H), 3.45 (dd, *J* = 11.2, 6.6 Hz, 1H), 2.49–2.42 (m, 2H), 2.40 (dddd, *J* = 13.8, 7.1, 1.2 Hz, 1H), 2.23 (dddd, *J* = 13.8, 7.7, 1.1, 1.1 Hz, 1H), 1.97 (app sept, *J* = 6.7 Hz, 1H), 1.84–1.44 (m, 6H), 0.98–0.91 (d, *J* = 6.7 Hz, 6H), 0.79 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.2, 171.0, 135.1, 117.6, 105.5, 74.4, 54.8, 41.9, 36.1, 32.3, 31.3, 28.0, 20.0, 19.3, 8.6; IR (Neat Film NaCl) 3073, 2960, 2933, 2876, 1617, 1613, 1459, 1400, 1387, 1369, 1314, 1220, 1190, 1173, 996, 969, 954, 912, 883, 873, 856, 782 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{16}H_{26}O_2$ $[M]^{+\bullet}$: 250.1933; found 250.1909; $[\alpha]_D^{25.0}$ +25.83 (*c* 1.04, $CHCl_3$, 91.6% ee); HPLC conditions: 0.25% IPA in hexanes, 1.0 mL/min, AD column, t_R (min): minor = 16.23, major = 18.08.



27c

Vinylogous Ester 27c ***(Table 2.1, entry 3).*** Prepared using Schlenk Manifold Method. 172.5 mg, 0.552 mmol, 98% yield. Flash column chromatography (SiO_2, 3 x 24 cm, 20:1→15:1→10:1 hexanes:EtOAc). R_f = 0.50 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.14 (m, 3H), 7.14–7.08 (m, 2H), 5.85–5.68 (m, 1H), 5.31 (s, 1H),

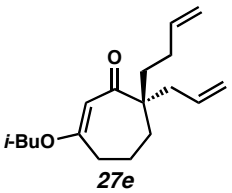
5.10–4.99 (m, 2H), 3.44 (dd, *J* = 14.7, 6.6 Hz, 1H), 3.41 (dd, *J* = 14.7, 6.6 Hz, 1H), 3.14 (d, *J* = 13.3 Hz, 1H), 2.71 (d, *J* = 13.3 Hz, 1H), 2.51 (dddd, *J* = 13.7, 6.8, 1.2, 1.2 Hz, 1H), 2.45–2.32 (m, 2H), 2.16 (dddd, *J* = 13.7, 7.9, 1.1, 1.1 Hz, 1H), 1.93 (app sept, *J* = 6.7 Hz, 1H), 1.83–1.56 (m, 4H), 0.92 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5, 171.4, 138.3, 134.5, 130.8, 128.0, 126.3, 118.2, 106.3, 74.5, 56.2, 44.1, 43.9, 36.3, 31.3, 27.9, 19.5, 19.3; IR (Neat Film NaCl) 3072, 3061, 3027, 3002, 2957, 2931, 2871, 1610, 1495, 1471, 1454, 1422, 1403, 1387, 1368, 1318, 1280, 1217, 1189, 1173, 1081, 1031, 1007, 969, 957, 913, 875, 856, 831, 760, 746, 733 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{21}H_{28}O_2$ $[M]^{+\bullet}$: 312.2089; found 312.2083; $[\alpha]_D^{25.0}$ +2.91 (*c* 0.98, $CHCl_3$, 86.3% ee); HPLC conditions: 0.5% IPA in hexanes, 1.0 mL/min, OD-H column, t_R (min): minor = 13.96, major = 15.70.



27d

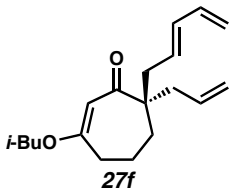
Vinylogous Ester 27d ***(Table 2.1, entry 4).*** Prepared using Schlenk Manifold Method. 224.7 mg, 0.86 mmol, 88% yield. Flash column chromatography (SiO_2, 3 x 25 cm, 20:1→15:1 hexanes:EtOAc). R_f = 0.44 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74–5.59 (m, 1H), 5.32 (s, 1H), 5.12–5.02 (m, 2H), 3.50 (dd, *J* = 14.9, 6.5 Hz, 1H), 3.47 (dd, *J* = 14.7, 6.6 Hz, 1H), 2.53–2.48 (m, 4H), 2.46 (dddd, *J* = 13.7, 7.3, 1.2, 1.2 Hz, 1H), 2.35 (dddd, *J* = 13.7, 7.6, 1.1, 1.1 Hz, 1H), 2.09–1.67 (m, 5H), 1.57 (s, 1H), 0.95 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.0, 171.7, 133.7, 118.5, 105.0, 81.7, 74.6, 70.8, 54.2, 42.9, 36.1, 32.5, 28.0, 27.1, 20.0, 19.3; IR (Neat Film NaCl) 3301,

3075, 2957, 2930, 2873, 2116, 1612, 1471, 1457, 1435, 1423, 1402, 1387, 1368, 1320, 1221, 1191, 1175, 995, 969, 916, 874, 845 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{24}O_2$ $[M]^{+\bullet}$: 260.1776; found 260.1737; $[\alpha]_D^{25.0}$ –26.51 (*c* 1.03, $CHCl_3$, 88.5% ee); HPLC conditions: 0.5% IPA in hexanes, 1.0 mL/min, OD-H column, t_R (min): major = 12.35, minor = 13.43.



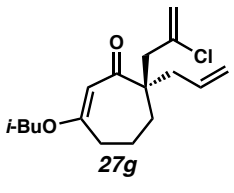
27e

Vinylogous Ester 27e ***(Table 2.1, entry 5).*** Prepared using Glove Box Method. 287.5 mg, 1.04 mmol, 95% yield. Flash column chromatography (SiO_2, 2 x 25 cm, 20:1 hexanes:EtOAc). R_f = 0.44 (10:1 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 5.84–5.64 (m, 2H), 5.30 (s, 1H), 5.09–4.87 (m, 4H), 3.49 (dd, *J* = 11.2, 6.6 Hz, 1H), 3.46 (dd, *J* = 11.1, 6.6 Hz, 1H), 2.54–2.37 (m, 3H), 2.27 (dddd, *J* = 13.8, 7.7, 1.2, 1.2 Hz, 1H), 2.07–1.89 (m, 3H), 1.86–1.45 (m, 6H), 0.95 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.8, 171.1, 138.9, 134.8, 117.9, 114.5, 105.5, 74.8, 54.4, 42.3, 38.0, 36.1, 32.7, 28.6, 28.0, 19.9, 19.3; IR (Neat Film NaCl) 3076, 2958, 2932, 2874, 1639, 1614, 1471, 1455, 1434, 1424, 1402, 1387, 1368, 1317, 1280, 1216, 1190, 1174, 1086, 996, 969, 955, 910, 878, 853, 829, 771 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{18}H_{28}O_2$ $[M]^{+\bullet}$: 276.2089; found 276.2060; $[\alpha]_D^{25.0}$ +15.28 (*c* 0.97, $CHCl_3$, 86.9% ee); HPLC conditions: 0.8% IPA in hexanes, 2.0 mL/min, AD column, t_R (min): major = 5.03, minor = 6.06.



27f

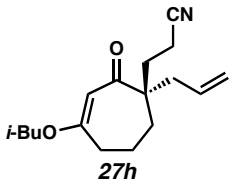
Vinylogous Ester 27f ***(Table 2.1, entry 6).*** Prepared using Schlenk Manifold Method. 232.9 mg, 0.81 mmol, 90% yield. Flash column chromatography (SiO_2, 3 x 25 cm, 20:1→15:1 hexanes:EtOAc). R_f = 0.45 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.30 (dt, *J* = 16.9, 10.3 Hz, 1H), 6.04 (dd, *J* = 15.1, 10.4 Hz, 1H), 5.82–5.53 (m, 2H), 5.31 (s, 1H), 5.15–4.92 (m, 4H), 3.48 (d, *J* = 6.5 Hz, 2H), 2.55–2.36 (m, 4H), 2.30–2.16 (m, 2H), 1.98 (app sept, *J* = 6.7 Hz, 1H), 1.84–1.67 (m, 4H), 0.95 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.3, 171.4, 137.2, 134.5, 134.1, 130.8, 118.0, 115.5, 105.5, 74.5, 55.1, 43.1, 41.6, 36.1, 32.5, 28.0, 19.9, 19.3; IR (Neat Film NaCl) 3075, 3036, 3007, 2958, 2931, 2873, 1726, 1635, 1611, 1471, 1456, 1436, 1402, 1387, 1368, 1312, 1277, 1219, 1190, 1173, 1085, 1005, 954, 911, 874, 831 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{29}O_2$ $[M+H]^+$: 289.2168; found 289.2172; $[\alpha]_D^{25.0}$ –20.62 (*c* 1.05, $CHCl_3$, 89.6% ee); SFC conditions: 5.0% IPA in hexanes, 2.5 mL/min, AD-H column, t_R (min): minor = 6.31, major = 6.99.



27g

Vinylogous Ester 27g ***(Table 2.1, entry 7).*** Prepared using Schlenk Manifold Method. 259.5 mg, 0.87 mmol, 99% yield. Flash column chromatography (SiO_2, 3 x 25 cm, 20:1→15:1 hexanes:EtOAc). R_f = 0.36 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz,

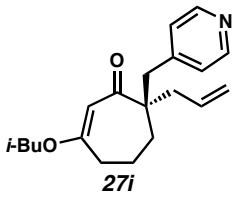
$CDCl_3$) δ 5.78–5.62 (m, 1H), 5.36 (s, 1H), 5.25 (s, 1H), 5.14 (s, 1H), 5.11–5.01 (m, 2H), 3.54–3.43 (m, 2H), 2.95 (dd, *J* = 14.4, 0.7 Hz, 1H), 2.54–2.41 (m, 4H), 2.25 (dddd, *J* = 13.9, 7.9, 1.1, 1.1 Hz, 1H), 2.07–1.89 (m, 2H), 1.88–1.70 (m, 3H), 0.95 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.3, 171.6, 139.4, 133.9, 118.7, 116.6, 105.9, 74.6, 54.7, 46.7, 43.7, 36.3, 31.5, 28.0, 19.6, 19.3; IR (Neat Film NaCl) 3075, 2958, 2934, 2874, 1612, 1471, 1458, 1424, 1403, 1388, 1368, 1339, 1321, 1297, 1222, 1192, 1175, 1082, 1010, 995, 968, 956, 916, 875, 847, 746 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{26}O_2Cl$ $[M+H]^+$: 297.1621; found 297.1623; $[\alpha]_D^{25.0}$ +4.20 (*c* 1.02, $CHCl_3$, 85.7% ee); HPLC conditions: 0.1% IPA in hexanes, 1.0 mL/min, OD-H column, t_R (min): minor = 24.19, major = 27.22.



27h

Vinylogous Ester 27h ***(Table 2.1, entry 8).*** Prepared using Schlenk Manifold Method. 292.8 mg, 1.06 mmol, 96% yield. Flash column chromatography (SiO_2, 3 x 25 cm, 20:1→10:1→8:1→6:1 hexanes:EtOAc). R_f = 0.39 broad (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75–5.58 (m, 1H), 5.31 (s, 1H), 5.15–5.04 (m, 2H), 3.48 (d, *J* = 6.5 Hz, 2H), 2.51 (t, *J* = 6.1 Hz, 2H), 2.40 (dddd, *J* = 14.0, 7.0, 1.2, 1.2 Hz, 1H), 2.35–2.22 (m, 3H), 2.11–1.93 (m, 2H), 1.93–1.62 (m, 5H), 0.96 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.9, 172.1, 133.1, 120.3, 119.2, 104.9, 74.7, 53.6, 41.8, 36.1, 33.9, 32.8, 28.0, 19.8, 19.3, 12.8; IR (Neat Film NaCl) 3076, 2958, 2933, 2874, 2246, 1635,

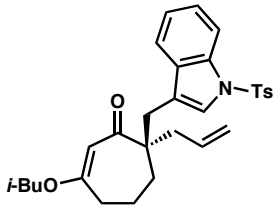
1609, 1472, 1458, 1420, 1404, 1388, 1368, 1319, 1281, 1214, 1192, 1175, 1084, 1003, 917, 880, 854, 827, 766 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{25}O_2N$ $[M]^{+\bullet}$: 275.1885; found 275.1893; $[\alpha]_D^{25.0}$ –20.97 (*c* 1.06, $CHCl_3$, 87.4% ee); HPLC conditions: 5.0% IPA in hexanes, 1.0 mL/min, OD-H column, t_R (min): major = 10.67, minor = 14.66.



27i

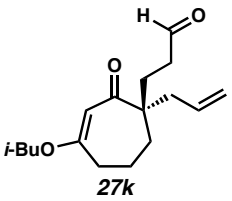
Vinylogous Ester 27i ***(Table 2.1, entry 9).*** Prepared using Glove Box Method. 339.6 mg, 1.08 mmol, 97% yield. Flash column chromatography (SiO_2, 3 x 20 cm, 1:1→1:4 hexanes:EtOAc→EtOAc). R_f = 0.28, broad (1:2 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 8.45 (dd, *J* = 4.5, 1.5 Hz, 2H), 7.05 (dd, *J* = 4.5, 1.6 Hz, 2H), 5.84–5.66 (m, 1H), 5.31 (s, 1H), 5.15–5.02 (m, 2H), 3.44 (dd, *J* = 15.1, 6.3 Hz, 1H), 3.41 (dd, *J* = 15.0, 6.3 Hz, 1H), 3.20 (d, *J* = 12.9 Hz, 1H), 2.60 (d, *J* = 12.9 Hz, 1H), 2.48 (dddd, *J* = 13.8, 6.9, 1.2, 1.2 Hz, 1H), 2.43–2.29 (m, 2H), 2.23 (dddd, *J* = 13.8, 7.8, 1.1, 1.1 Hz, 1H), 1.94 (app sept, *J* = 6.7 Hz, 1H), 1.84–1.67 (m, 2H), 1.67–1.51 (m, 2H), 0.92 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.4, 171.8, 149.5, 147.6, 133.7, 126.2, 118.9, 106.0, 74.6, 55.8, 43.8, 43.5, 36.2, 31.5, 27.9, 19.4, 19.3; IR (Neat Film NaCl) 3072, 3024, 2957, 2931, 2873, 1608, 1558, 1496, 1471, 1458, 1438, 1415, 1388, 1368, 1320, 1220, 1190, 1173, 1072, 994, 957, 916, 876, 844, 796 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{20}H_{27}O_2N$ $[M]^{+\bullet}$: 313.2042; found 313.2045; $[\alpha]_D^{25.0}$ +22.44 (*c* 1.16, $CHCl_3$, 84.6% ee);

HPLC conditions: 5.0% EtOH in hexanes, 1.0 mL/min, AD column, t_R (min): major = 13.22, minor = 15.13.



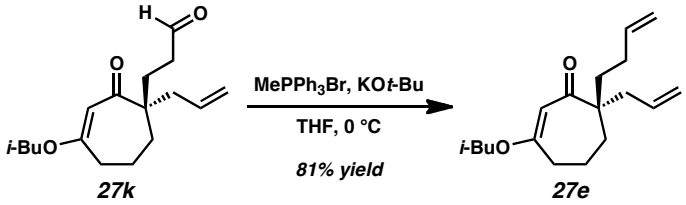
27j

Vinylogous Ester 27j ***(Table 2.1, entry 10).*** Prepared using Glove Box Method. 403 mg, 0.796 mmol, 98% yield. Flash column chromatography (SiO_2, 5 x 25 cm, 15:1→10:1→8:1→6:1 hexanes:EtOAc). R_f = 0.49 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (dm, *J* = 8.4 Hz, 1H), 7.70 (dm, *J* = 8.4 Hz, 2H), 7.48 (dm, *J* = 7.9 Hz, 1H), 7.31–7.13 (m, 5H), 5.86–5.68 (m, 1H), 5.32 (s, 1H), 5.13–5.00 (m, 2H), 3.42 (dd, *J* = 17.0, 7.7 Hz, 1H), 3.38 (dd, *J* = 17.0, 7.6 Hz, 1H), 3.20 (dd, *J* = 14.2, 0.7 Hz, 1H), 2.73 (d, *J* = 14.1 Hz, 1H), 2.51 (dddd, *J* = 13.7, 6.9, 1.3, 1.3 Hz, 1H), 2.44–2.15 (m, 6H), 1.92 (app sept, *J* = 6.7 Hz, 1H), 1.76–1.46 (m, 4H), 0.92 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.2, 171.7, 144.8, 135.4, 135.0, 134.1, 132.4, 129.8, 126.9, 125.4, 124.5, 123.2, 120.1, 119.6, 118.6, 113.8, 106.4, 74.6, 55.9, 44.1, 36.3, 33.0, 31.9, 27.9, 21.7, 19.5, 19.3; IR (Neat Film NaCl) 3584, 3401, 2068, 2958, 2930, 2873, 1609, 1494, 1470, 1448, 1422, 1402, 1368, 1306, 1279, 1215, 1188, 1174, 1120, 1097, 1020, 975, 916, 876, 813, 782, 747 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{30}H_{36}O_4NS$ $[M+H]^+$: 506.2365; found 506.2358; $[\alpha]_D^{25.0}$ +9.10 (*c* 1.00, $CHCl_3$, 82.9% ee); HPLC conditions: 5.0% EtOH in hexanes, 1.0 mL/min, AD column, t_R (min): major = 11.11, minor = 16.64.



27k

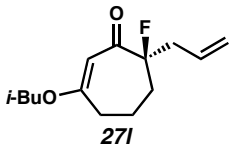
Vinylogous Ester 27k ***(Table 2.1, entry 11).*** Prepared using Glove Box Method. 77.3 mg, 0.278 mmol, 90% yield. Flash column chromatography (SiO_2, 2 x 25 cm, 6:1→4:1 hexanes:EtOAc). R_f = 0.35, broad (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (t, *J* = 1.5 Hz, 1H), 5.78–5.61 (m, 1H), 5.29 (s, 1H), 5.11–5.02 (m, 2H), 3.47 (m, 2H), 2.54–2.33 (m, 5H), 2.28 (dddd, *J* = 14.0, 7.6, 1.2, 1.2 Hz, 1H), 2.07–1.73 (m, 5H), 1.73–1.56 (m, 2H), 0.95 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.0, 202.3, 171.7, 134.0, 118.5, 105.2, 74.6, 53.6, 42.1, 39.4, 36.1, 33.1, 30.3, 28.0, 19.9, 19.3; IR (Neat Film NaCl) 3075, 2958, 2931, 2719, 1724, 1611, 1471, 1458, 1421, 1403, 1388, 1368, 1213, 1191, 1175, 998, 915, 878 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{27}O_3$ $[M+H]^+$: 279.1960; found 279.1969; $[\alpha]_D^{25.0}$ +15.37 (*c* 1.03, $CHCl_3$, 79.5% ee); Compound **27k** was derivatized using procedure below to determine ee using the corresponding chiral HPLC assay for vinylogous ester **27e**.



27k ***27e***

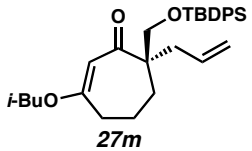
Vinylogous Ester 27e. To a solution of $MePh_3PBr$ (323.2 mg, 0.905 mmol, 0.84 equiv) in THF (14.0 mL) in a 50 mL round-bottom flask at 0 °C was added KO*t*-Bu (84.6 mg, 0.754 mmol, 0.699 equiv) to give a bright yellow suspension. Aldehyde **27k** (299.9 mg,

1.078 mmol, 1.00 equiv) in THF (2 mL) was added to the suspension using positive pressure cannulation and maintained at 0 °C. The reaction faded to an off-white suspension. After 1.5 h of stirring, an additional portion of Wittig reagent was prepared in a 20 mL scintillation vial. $MePPh_3Br$ (323.2 mg, 0.905 mmol, 0.84 equiv) was added to the vial. The vial was sealed with a septum, evacuated/backfilled with N_2 (3 cycles, 5 min evacuation per cycle). Anhydrous THF (3 mL) was added and the vial was cooled to 0 °C. KO*t*-Bu (84.6 mg, 0.754 mmol, 0.699 equiv) was added in one portion, giving a bright yellow suspension that was added to the reaction flask using positive pressure cannulation. The tan suspension was stirred at 0 °C for 1 h. An additional portion of Wittig reagent using $MePPh_3Br$ (323.2 mg, 0.905 mmol, 0.84 equiv), KO*t*-Bu (84.6 mg, 0.754 mmol, 0.699 equiv) and THF (3 mL) was prepared at 0 °C and added using positive pressure cannulation as previously described. The reaction showed a persistent yellow color. After 30 min of stirring at 0 °C, the reaction was quenched by addition of sat. aqueous NH_4Cl (5 mL) and stirred for 30 min while the mixture was allowed to warm to ambient temperature. The mixture was extracted with Et_2O (3 x 20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 3 x 25 cm, 1%→2%→3%→5% EtOAc in hexanes) to afford vinylogous ester **27e** (243.7 mg, 0.882 mmol, 81% yield) as a yellow liquid; HPLC conditions: 0.8% IPA in hexanes, 2.0 mL/min, AD column, t_R (min): major = 4.39, minor = 3.17. (For characterization data, see p. 290).



27l

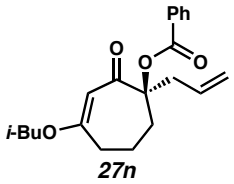
Vinylogous Ester 27l ***(Table 2.1, entry 12).*** Prepared using Schlenk Manifold Method. 172.5 mg, 0.552 mmol, 98% yield. Flash column chromatography (SiO_2, 3 x 24 cm, 20:1→15:1→10:1 hexanes:EtOAc). R_f = 0.59 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89–5.72 (m, 1H), 5.28 (s, 1H), 5.18–5.08 (m, 2H), 3.53 (dd, *J* = 10.6, 6.5 Hz, 1H), 3.50 (dd, *J* = 10.6, 6.6 Hz, 1H), 2.80–2.46 (m, 3H), 2.46–2.33 (m, 1H), 2.22–1.67 (m, 5H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2 (d, J_{CF} = 24.9 Hz), 176.9 (d, J_{CF} = 1.8 Hz), 131.9 (d, J_{CF} = 4.4 Hz), 119.3, 101.7, 101.2 (d, J_{CF} = 180.6 Hz), 75.0, 42.1 (d, J_{CF} = 23.2 Hz), 34.4 (d, J_{CF} = 23.2 Hz), 34.1 (d, J_{CF} = 2.4 Hz), 27.9, 21.7 (d, J_{CF} = 2.1 Hz), 19.3, 19.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ –145.81 (m); IR (Neat Film NaCl) 3086, 2960, 1752, 1654, 1649, 1603, 1471, 1453, 1422, 1403, 1385, 1369, 1282, 1249, 1229, 1204, 1176, 1137, 1095, 1066, 145, 991, 927, 873, 843, 795, 758 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{14}H_{21}O_2F$ $[M]^{+\bullet}$: 240.1526; found 240.1524; $[\alpha]_D^{25.0}$ +0.61 (*c* 1.02, $CHCl_3$, 91.2% ee); HPLC conditions: 1.0% IPA in hexanes, 1.0 mL/min, OD-H column, t_R (min): minor = 8.05, major = 8.80.



27m

Vinylogous Ester 27m ***(Table 2.1, entry 13).*** Prepared using Glove Box Method. 242.0 mg, 0.493 mmol, 66% yield. Flash column chromatography (SiO_2, 3 x 25 cm, 2%→5%→10% EtOAc in hexanes). R_f = 0.44 (10:1 hexanes:EtOAc); ^{1}H NMR (300

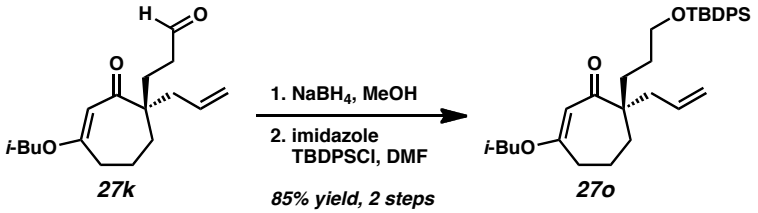
MHz, $CDCl_3$) δ 7.67–7.61 (m, 4H), 7.46–7.33 (m, 6H), 5.78–5.60 (m, 1H), 5.32 (s, 1H), 5.08–4.96 (m, 2H), 3.78 (d, *J* = 9.7 Hz, 1H), 3.67 (d, *J* = 9.7 Hz, 1H), 3.46 (dd, *J* = 14.7, 6.5 Hz, 1H), 3.43 (dd, *J* = 14.6, 6.5 Hz, 1H), 2.49 (dddd, *J* = 13.7, 6.6, 1.3, 1.3 Hz, 1H), 2.48–2.41 (m, 2H), 2.33 (dddd, *J* = 13.8, 7.8, 1.2, 1.2 Hz, 1H), 2.09–1.88 (m, 2H), 1.82–1.65 (m, 3H), 1.04 (s, 9H), 0.95 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.5, 171.5, 135.9, 135.8, 134.7, 133.7, 133.5, 129.7, 127.8, 127.7, 117.8, 106.1, 74.5, 69.0, 57.4, 41.0, 36.3, 30.3, 28.0, 27.0, 20.0, 19.5, 19.3; IR (Neat Film NaCl) 3071, 3050, 2957, 2930, 2857, 1731, 1614, 1472, 1428, 1402, 1388, 1368, 1315, 1261, 1222, 1190, 1174, 1112, 1007, 998, 969, 955, 938, 914, 880, 824, 810, 740 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{31}H_{43}O_3Si$ $[M+H]^+$: 491.2982; found 491.2993; $[\alpha]_D^{25.0}$ –6.72 (*c* 1.09, $CHCl_3$, 57.8% ee); HPLC conditions: 0.2% IPA in hexanes, 1.0 mL/min, OD-H column, t_R (min): major = 21.74, minor = 25.53.



27n

Vinylogous Ester 27n ***(Table 2.1, entry 14).*** Prepared using Schlenk Manifold Method. 589.8 mg, 1.72 mmol, 75% yield. Flash column chromatography (SiO_2, 5 x 13 cm, 20:1→15:1→10:1→6:1 hexanes:EtOAc). R_f = 0.57 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03–7.96 (m, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 5.96–5.78 (m, 1H), 5.27 (s, 1H), 5.19–5.08 (m, 2H), 3.42 (dd, *J* = 9.4, 6.6 Hz, 1H), 3.39 (dd, *J* = 9.4, 6.5 Hz, 1H), 3.06 (dddd, *J* = 14.8, 6.7, 1.4, 1.4 Hz, 1H), 2.83–2.67 (m, 2H), 2.55–2.34 (m, 2H), 2.10–1.74 (m, 4H), 0.80 (dd, *J* = 6.6, 4.7 Hz, 6H); ^{13}C NMR (75

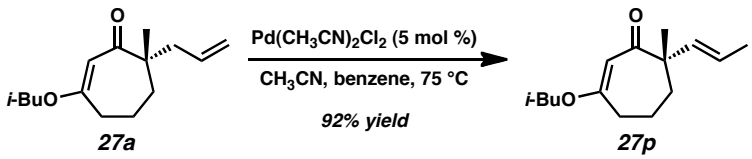
MHz, $CDCl_3$) δ 198.1, 174.3, 165.5, 133.1, 132.5, 130.6, 129.7, 128.5, 119.2, 102.1, 88.6, 74.9, 40.8, 34.0, 27.7, 21.9, 19.1, 19.0; IR (Neat Film NaCl) 3073, 2959, 2934, 2873, 1718, 1672, 1649, 1613, 1479, 1451, 1421, 1382, 1368, 1315, 1291, 1258, 1231, 1199, 1174, 1108, 1070, 1026, 1004, 919, 866, 820, 801, 762, 715 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{21}H_{26}O_4$ $[M]^{+\bullet}$: 342.1815; found 342.1831; $[\alpha]_D^{25.0}$ +79.72 (*c* 1.02, $CHCl_3$, 57.1% ee); HPLC conditions: 1.0% IPA in hexanes, 1.0 mL/min, OD-H column, t_R (min): major = 18.28, minor = 22.01.



Vinylogous Ester 27o. A round-bottom flask with magnetic stir bar was charged with aldehyde **27k** (40.2 mg, 0.14 mmol, 1.00 equiv) and MeOH (3.0 mL). The flask was cooled to 0 °C and $NaBH_4$ (5.5 mg, 0.14 mmol, 1.00 equiv) was added slowly portionwise. The mixture was stirred for 1 h at 0 °C. Sat. aqueous $NaHCO_3$ (3 mL) was added, followed by CH_2Cl_2 (10 mL). The mixture was stirred vigorously for 5 min. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). Combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude alcohol was used directly in the next step without further purification. R_f = 0.29 (2:1 hexanes:EtOAc).

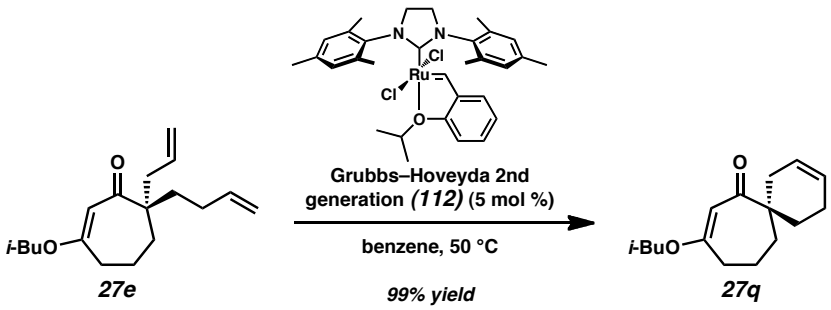
To a 2 dram vial with a solution of crude alcohol and imidazole (11.8 mg, 0.17 mmol, 1.20 equiv) in DMF (0.7 mL) at 0 °C was added TBDPSCl (39.6 μL, 0.14 mmol,

1.00 equiv) dropwise. After 2 h of stirring, the reaction was quenched by addition of H_2O (0.3 mL) and extracted with Et_2O (5 x 5 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by automated flash column chromatography using a Teledyne Isco CombiFlash R_f (SiO_2, 12 g loading cartridge, 80 g column, multi-step gradient, hold 2% [2 min]→ramp to 5% [10 min]→hold 5% [10 min]→ramp to 10% [32 min]→hold 10% Et_2O in hexanes [5 min]) to afford vinylogous ester **27o** (63.3 mg, 0.12 mmol, 85% yield over 2 steps) as a pale, white oil; R_f = 0.42 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69–7.62 (m, 4H), 7.46–7.33 (m, 6H), 5.82–5.62 (m, 1H), 5.29 (s, 1H), 5.08–4.96 (m, 2H), 3.61 (t, *J* = 6.1 Hz, 2H), 3.48 (dd, *J* = 13.7, 6.6 Hz, 1H), 3.45 (dd, *J* = 13.7, 6.6 Hz, 1H), 2.50–2.43 (m, 2H), 2.40 (dddd, *J* = 13.8, 7.0, 1.2 Hz, 1H), 2.25 (dddd, *J* = 13.9, 7.8, 1.1 Hz, 1H), 1.98 (app sept, *J* = 6.7 Hz, 1H), 1.86–1.38 (m, 8H), 1.04 (s, 9H), 0.95 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.0, 171.0, 135.7, 134.9, 134.1, 129.6, 127.7, 117.7, 105.2, 74.4, 64.4, 54.2, 42.1, 36.1, 34.8, 32.8, 28.0, 27.3, 27.0, 20.0, 19.3; IR (Neat Film NaCl) 3071, 3051, 3013, 2998, 2956, 2930, 2858, 1614, 1471, 1428, 1401, 1387, 1368, 1311, 1214, 1188, 1174, 1111, 1028, 1007, 998, 966, 913, 872, 823, 780, 740, 725 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{33}H_{47}O_3Si$ $[M+H]^+$: 519.3295; found 519.3275; $[\alpha]_D^{25.0}$ +9.06 (*c* 0.95, $CHCl_3$, 78.4% ee).



Vinylogous Ester 27p. $Pd(CH_3CN)_2Cl_2$ (49.1 mg, 0.189 mmol, 5 mol %) was placed in a 50 mL round-bottom Schlenk flask and evacuated/backfilled with N_2 (3 cycles, 5 min per cycle). Benzene (10 mL) was added, followed by acetonitrile (90 μL). A solution of vinylogous ester **27a** (895 mg, 3.79 mmol, 1.00 equiv) in benzene (5.0 mL) was added using positive pressure cannulation. The resulting orange solution was heated to 75 °C in an oil bath. After 11 h of stirring, the reaction was cooled to ambient temperature, filtered through a Celite plug (eluted with Et_2O), and concentrated carefully under reduced pressure, allowing for a film of ice to form on the outside of the flask, to afford a pale yellow oil. The crude oil was purified by automated flash column chromatography using a Teledyne Isco CombiFlash R_f (SiO_2, 25 g loading cartridge, 80 g column, linear gradient, 0→10% EtOAc in hexanes [33 min]) to afford vinylogous ester **27p** (823.6 mg, 3.48 mmol, 92% yield) in a 20:1 ratio to isomeric starting material **27a**. Analytically pure samples could be obtained using the above column conditions; R_f = 0.56 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.56 (dq, *J* = 15.7, 1.4 Hz, 1H), 5.41 (dq, *J* = 15.7, 6.2, Hz, 1H), 5.34 (s, 1H), 3.48 (d, *J* = 6.5 Hz, 2H), 2.63–2.33 (m, 2H), 2.04–1.91 (m, 1H), 1.90–1.70 (m, 4H), 1.67 (dd, *J* = 6.2, 1.4 Hz, 3H), 1.22 (s, 3H), 0.95 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.3, 171.6, 136.5, 123.9, 105.2, 74.5, 53.9, 36.2, 33.3, 28.0, 27.2, 20.2, 19.3, 18.4; IR (Neat Film NaCl) 3022, 2960, 2873, 1614, 1471, 1455, 1423, 1402, 1387, 1370, 1212, 1192, 1173, 1120, 967, 883, 858,

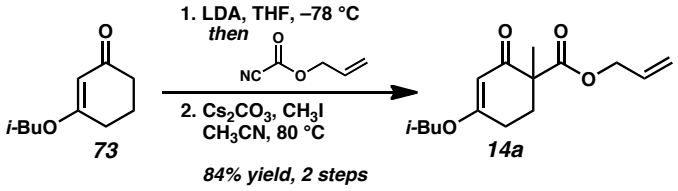
827 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{25}O_2$ $[M+H]^+$: 237.1849; found 237.1848; $[\alpha]_D^{25.0}$ +4.05 (*c* 1.39, $CHCl_3$, 88.0 % ee).



Vinylogous Ester 27q. Vinylogous ester **27e** (100 mg, 0.362 mmol, 1.00 equiv) was added to a 50 mL 2-neck flask fitted with a rubber septum and oven-dried reflux condenser. The flask was evacuated/backfilled with Ar (3 cycles, 5 min evacuation per cycle). Dry degassed benzene (36.2 mL, sparged with N_2 for 1 h immediately before use) was added. Grubbs–Hoveyda 2nd generation catalyst (11.3 mg, 18.1 μmol, 5 mol %) was added to the reaction, giving the solution an olive green color. The mixture was kept under Ar, stirred until homogeneous, and heated to 50 °C using an oil bath. After 30 min of stirring, the reaction was cooled to ambient temperature and several drops of ethyl vinyl ether were added. After 30 min, the reaction developed a deep brown color. The mixture was concentrated under reduced pressure and filtered through a silica gel plug (3 x 5 cm, 1:1 hexanes:Et_2O). The solvents were removed under reduced pressure and the residue was purified by flash column chromatography (SiO_2, 3 x 25 cm, 20:1→15:1→10:1 hexanes:EtOAc) to afford vinylogous ester **27q** (89.2 mg, 0.359 mmol, 99% yield) as a white solid. R_f = 0.39 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69–5.58 (m, 2H), 5.30 (s, 1H), 3.49 (dd, *J* = 14.4, 6.5 Hz, 1H), 3.46 (dd, *J* =

14.3, 6.5 Hz, 1H), 2.70–2.57 (m, 1H), 2.54–2.44 (m, 2H), 2.08–1.91 (m, 3H), 1.91–1.57 (m, 7H), 0.95 (d, J = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.2, 171.3, 125.6, 125.4, 104.0, 74.4, 50.5, 35.9, 33.9, 32.3, 32.2, 28.0, 22.4, 20.6, 19.3; IR (Neat Film NaCl) 3050, 3023, 2981, 2958, 2928, 2890, 2874, 2837, 1726, 1633, 1610, 1470, 1457, 1435, 1416, 1406, 1392, 1364, 1327, 1295, 1270, 1218, 1178, 1189, 1117, 1096, 1045, 1028, 1003, 953, 935, 917, 888, 850, 837, 807, 758, 731 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{16}H_{24}O_2$ $[M]^{+\bullet}$: 248.1776; found 248.1774; $[\alpha]_D^{25.0}$ –32.18 (c 0.97, $CHCl_3$, 78.4% ee).

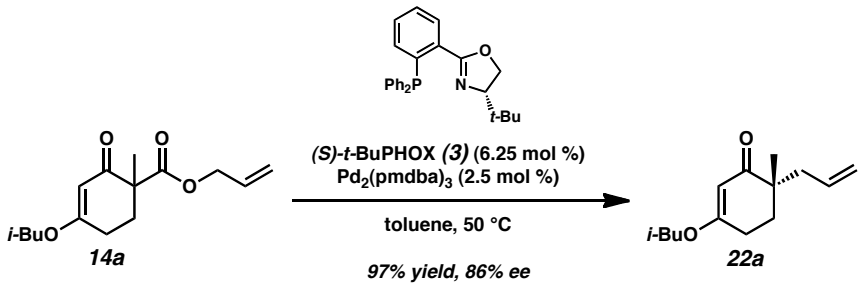
2.7.2.6 SYNTHETIC STUDIES ON THE REDUCTION/REARRANGEMENT OF SIX- AND SEVEN-MEMBERED VINYLOGOUS ESTERS



β-Ketoester 14a. To a solution of diisopropylamine (0.49 mL, 3.47 mmol, 1.17 equiv) in THF (10 mL) in a 50 mL round-bottom flask at 0 °C was added *n*-BuLi (1.70 mL, 3.40 mmol, 2.1 M in hexanes, 1.15 equiv) dropwise over 10 min. After 15 min of stirring at 0 °C, the reaction was cooled to –78 °C using an acetone/CO_2(s) bath. A solution of vinylogous ester **73**[60] (0.50 g, 2.97 mmol, 1.00 equiv) in THF (5.0 mL) was added dropwise using positive pressure cannulation. After an additional 1 h of stirring at –78 °C, allyl cyanoformate (0.37 mL, 3.40 mmol, 1.15 equiv) was added dropwise. The reaction was stirred at –78 °C for 2.5 h, quenched by addition of sat. aqueous NH_4Cl and H_2O (5 mL each), and then allowed to warm to ambient temperature. The reaction was

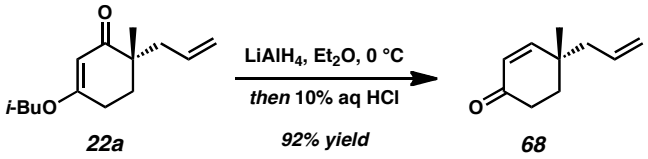
diluted with Et_2O (25 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (2 x 25 mL) and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford a pale red oil.

The crude oil was added to a 25 mL Schlenk flask and dissolved in CH_3CN (10 mL). CH_3I (0.56 mL, 8.90 mmol, 3.00 equiv) was added, followed by Cs_2CO_3 (1.26 g, 3.90 mmol, 1.30 equiv). The flask was sealed with a teflon valve, immersed in an oil bath, and heated to 80 °C. After 14 h of vigorous stirring, the suspension was allowed to cool to ambient temperature, diluted with EtOAc (25 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 3 x 20 cm, 19:1→9:1→4:1, hexanes:EtOAc) to afford β-ketoester **14a** (0.67 g, 2.52 mmol, 84% yield over 2 steps) as a pale yellow oil; $R_f = 0.36$ (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (dddd, *J* = 17.2, 10.7, 5.5, 5.5 Hz, 1H), 5.30 (s, 1H), 5.22 (app dq, *J* = 17.2, 1.5 Hz, 1H), 5.14 (app dq, *J* = 10.5, 1.3 Hz, 1H), 4.65–4.46 (m, 2H), 3.55 (d, *J* = 6.5 Hz, 2H), 2.60–2.23 (m, 3H), 1.97 (app sept, *J* = 6.6 Hz, 1H), 1.89–1.70 (m, 1H), 1.35 (s, 3H), 0.91 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.4, 176.7, 172.5, 131.9, 118.0, 101.7, 74.9, 65.5, 52.3, 31.7, 27.7, 26.3, 20.6, 19.0; IR (Neat Film NaCl) 2961, 2937, 2876, 1733, 1660, 1608, 1457, 1427, 1406, 1385, 1369, 1346, 1319, 1248, 1199, 1176, 1113, 1039, 991, 928, 837, 818, 772, 751 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{15}H_{22}O_4$ $[M]^{+\bullet}$: 266.1518; found 266.1510.



Vinylogous Ester 151. β-Ketoester **14a** (180 mg, 0.68 mmol, 1.00 equiv) in a 20 mL scintillation vial and a septum-fitted screw cap were evacuated/backfilled with N_2 (3 cycles, 5 min evacuation per cycle) in a glove box antechamber before being transferred into a glove box. A separate 20 mL scintillation vial in the glove box was loaded with (*S*)-*t*-BuPHOX (16.4 mg, 0.042 mmol, 6.25 mol %), $Pd_2(pmdba)_3$ (18.5 mg, 0.017 mmol, 2.5 mol %), and a magnetic stir bar. Toluene (4 mL) was added, and the black suspension was stirred at 30 °C in a heating block for 30 min. β-Ketoester **14a** was dissolved in toluene (2.8 mL) and added to the orange catalyst solution, causing an immediate color change to olive green. The vial was capped with the septum-fitted screw cap and the edges were sealed with electrical tape. The vial was removed from the glove box, connected to a N_2-filled Schlenk manifold, and immersed in a 50 °C oil bath. After 22 h, the reaction was an orange-brown solution. The mixture was concentrated under reduced pressure and purified by flash column chromatography (SiO_2, 2 x 25 cm, 20:1→10:1, hexanes:EtOAc) to afford vinylogous ester **22a** (146 mg, 0.66 mmol, 97% yield) as a clear, colorless oil; R_f = 0.57 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81–5.63 (m, 1H), 5.22 (s, 1H), 5.08–4.98 (m, 2H), 3.56 (d, *J* = 6.5 Hz, 2H), 2.40 (app t, *J* = 6.4 Hz, 2H), 2.33 (dddd, *J* = 13.8, 7.6, 1.0, 1.0 Hz, 1H), 2.16 (dddd, *J* = 13.8, 7.6, 1.0, 1.0 Hz, 1H), 2.00 (app sept, *J* = 6.7 Hz, 1H), 1.90 (ddd, *J* = 13.4, 6.6, 6.6

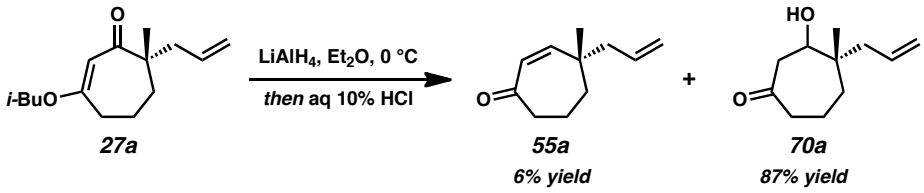
Hz, 1H), 1.68 (ddd, J = 13.6, 6.2, 6.2 Hz, 1H), 1.06 (s, 3H), 0.95 (d, J = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.5, 176.1, 134.4, 117.9, 101.4, 74.8, 43.3, 41.6, 31.9, 27.9, 26.0, 22.3, 19.2; IR (Neat Film NaCl) 3074, 2962, 2932, 2875, 1655, 1611, 1470, 1464, 1429, 1404, 1384, 1368, 1327, 1307, 1299, 1240, 1195, 1178, 1123, 1080, 1032, 996, 968, 951, 913, 862, 840, 806, 786, 736 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{14}H_{22}O_2$ $[M]^{+\bullet}$: 222.1620; found 222.1627; $[\alpha]_D^{25.0}$ –10.67 (c 0.98, $CHCl_3$, 86.3% ee); HPLC conditions: 5% IPA in hexanes, OD-H column, t_R (min): major = 5.80, minor = 6.53.



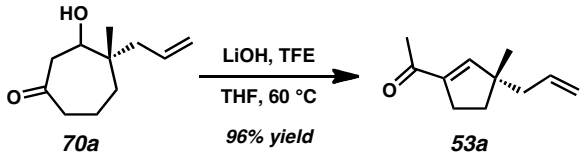
22a *68*

Cyclohexenone 68. A 50 mL round-bottom flask was charged with Et_2O (11.1 mL) and cooled to 0 °C in an ice/water bath. $LiAlH_4$ (13.6 mg, 0.36 mmol, 0.55 equiv) was added in one portion. After 10 min, a solution of vinylogous ester **22a** (146 mg, 0.66 mmol, 1.00 equiv) in Et_2O (2.0 mL) was added dropwise using positive pressure cannulation. After 30 min of stirring at 0 °C, an additional portion of $LiAlH_4$ (2.5 mg, 0.066 mmol, 0.10 equiv) was added. After 60 min of stirring, the reaction was quenched by slow addition of aqueous HCl (1.0 mL, 10% w/w). The resulting biphasic system was allowed to warm to ambient temperature and stirred vigorously for 8.5 h. The phases were separated and the aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified using flash column chromatography (SiO_2, 2 x 25 cm, 10:1→4:1→1:1→1:2 hexanes:Et_2O) to afford cyclohexenone **68** (90.5 mg, 0.60

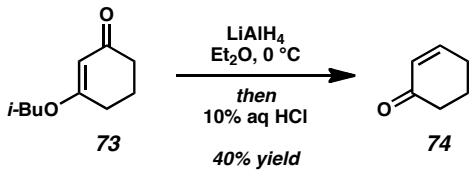
mmol, 92% yield) as a yellow oil; R_f = 0.51 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.67 (d, *J* = 10.2 Hz, 1H), 5.88 (d, *J* = 10.2 Hz, 1H), 5.79 (dddd, *J* = 16.8, 10.3, 7.4, 7.4 Hz, 1H), 5.20–5.01 (m, 2H), 2.54–2.36 (m, 2H), 2.29–2.10 (m, 2H), 2.05–1.89 (m, 1H), 1.85–1.69 (m, 1H), 1.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4, 158.4, 133.4, 127.6, 118.6, 45.2, 35.7, 34.1, 33.6, 24.7; IR (Neat Film NaCl) 3077, 3005, 2960, 2917, 2868, 2849, 1682, 1639, 1616, 1459, 1419, 1390, 1373, 1332, 1250, 1223, 1193, 1115, 996, 961, 918, 871, 803, 757 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{10}H_{14}O$ $[M]^{+\bullet}$: 150.1045; found 150.1056; $[\alpha]_D^{25.0}$ +26.72 (*c* 1.02, $CHCl_3$, 86.3% ee).



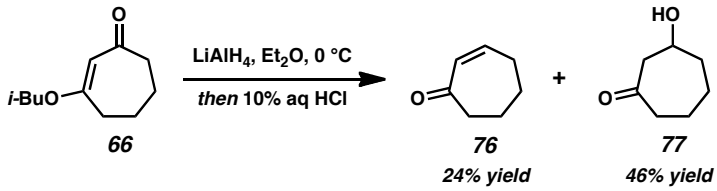
Cycloheptenone 55a and **β-Hydroxyketone 70a.** For procedure and characterization data, see General Method A (Section 2.10.2.8, p. 154–154).



Acylcyclopentene 53a. For procedure and characterization data, see General Method E (Section 2.10.2.8, p. 155).



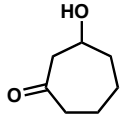
Cyclohexenone 74. A 25 mL round-bottom flask with magnetic stir bar and $LiAlH_4$ (22.8 mg, 0.60 mmol, 0.60 equiv) was charged with Et_2O (4 mL) and cooled to 0 °C in an ice/water bath. After 10 min, a solution of vinylogous ester **73** (168.23 mg, 1.00 mmol, 1.00 equiv) in Et_2O (1 mL) was added dropwise using positive pressure cannulation. After 30 min of stirring at 0 °C, the reaction was quenched by slow addition of aqueous HCl (2.60 mL, 10% w/w). The resulting biphasic system was allowed to warm to ambient temperature. The phases were separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated carefully under reduced pressure in an ice/water bath. The crude product purified using flash column chromatography (SiO_2, 2 x 25 cm, 5:1→4:1 hexanes:EtOAc) to afford cyclohexenone **74** (39.4 mg, 0.41 mmol, 40% yield) as a volatile pale yellow oil. Spectra for the compound match data for commercially available material.



Cycloheptenone 76 and β-Hydroxyketone 77. A 50 mL round-bottom flask with magnetic stir bar and $LiAlH_4$ (806 mg, 21.2 mmol, 0.60 equiv) was charged with Et_2O (8 mL) and cooled to 0 °C in an ice/water bath. After 10 min, a solution of vinylogous ester

66 (328.2 mg, 1.80 mmol, 1.00 equiv) in Et_2O (2 mL) was added dropwise using positive pressure cannulation. After 30 min of stirring at 0 °C, the reaction was quenched by slow addition of aqueous HCl (4.73 mL, 10% w/w). The resulting biphasic system was allowed to warm to ambient temperature. The phases were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated carefully under reduced pressure in an ice/water bath. The crude product purified using flash column chromatography (SiO_2, 2 x 25 cm, 6:1→4:1→2:1→1:1→1:2→1:4 hexanes:EtOAc) to afford β-hydroxyketone **77** (107.1 mg, 0.84 mmol, 46% yield) as a pale yellow oil and cycloheptenone **76** (47.9 mg, 0.44 mmol, 24% yield) as a colorless oil.

Cycloheptenone 76: Spectra for the compound match data for commercially available material.



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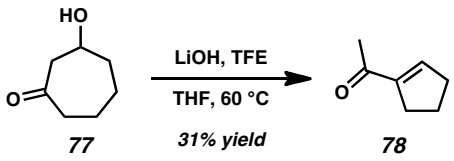
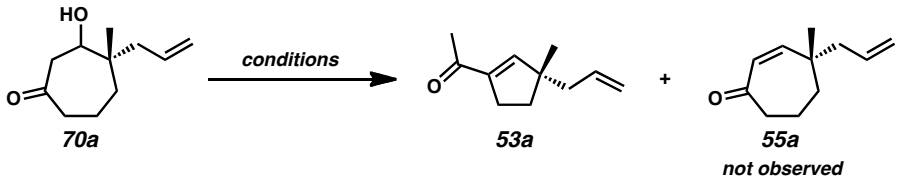
β-Hydroxyketone 77: R_f = 0.26 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.18–3.97 (m, 1H), 2.89–2.67 (m, 2H), 2.55–2.35 (m, 2H), 2.10 (br s, 1H), 1.95–1.69 (m, 5H), 1.65–1.49 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.6, 67.5, 51.8, 44.4, 38.8, 24.4, 23.8; IR (Neat Film NaCl) 3420, 2930, 2861, 1696, 1449, 1410, 1349, 1263, 1196, 1157, 1109, 1043, 1016, 929, 878, 829, 752, 710 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_7H_{12}O_2$ $[M]^{+\bullet}$: 128.0837; found 128.0828.



Acylcyclopentene 78. Alcohol **77** (101.3 mg, 0.79 mmol, 1.00 equiv) was dissolved in THF (7.9 mL) in a 20 mL scintillation vial with magnetic stir bar. The solution was treated with 2,2,2-trifluoroethanol (86.4 μL, 1.19 mmol, 1.50 equiv) and anhydrous LiOH (28.4 mg, 1.19 mmol, 1.50 equiv). The headspace of the vial was purged with N_2 and the vial was capped with a teflon-lined hard cap and stirred at 60 °C in a heating block. After 16 h of stirring, the suspension was allowed to cool to ambient temperature, diluted with Et_2O (150 mL), dried over Na_2SO_4 (30 min of stirring), filtered, and concentrated carefully under reduced pressure in an ice/water bath. The crude product was purified using flash column chromatography (SiO_2, 2 x 20 cm, 15:1→10:1 hexanes:Et_2O) to afford acylcyclopentene **78** (27 mg, 0.25 mmol, 31% yield) as a colorless fragrant oil. Spectra for the compound match data for commercially available material.

2.7.2.7 RING CONTRACTION SCREENING PROTOCOL[a]



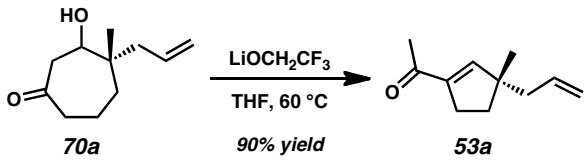
70a *53a* *55a* *not observed*

entry	base	additive	solvent	T (°C)	conversion (%)	time (h)	yield (%)[b]
1	LiO*t*-Bu	—	*t*-BuOH	40	100	9	71
2	LiO*t*-Bu	—	THF	40	100	8	60
3	NaO*t*-Bu	—	THF	40	100	5	81
4	KO*t*-Bu	—	THF	40	100	5	85
5	NaOH	—	THF	60	100	4	89
6	KOH	—	THF	60	100	4	87
7	LiOH	—	THF	60	78	24	19[d]
8	LiOH	*t*-BuOH	THF	60	98	24	78
9	LiOH	HFIP[c]	THF	60	99	12.5	87
10	LiOH	TFE[c]	THF	60	99	12.5	96
11	$LiOCH_2CF_3$	—	THF	60	—	10	90[e]
12	$CsOH{\cdot}H_2O$	—	THF	60	100	4	48
13	Cs_2CO_3	—	THF	60	67	24	61[f]
14	Cs_2CO_3	TFE[c]	THF	60	100	12.5	86
15	Cs_2CO_3	TFE[c]	CH_3CN	60	100	12.5	100
16	NaO*t*-Bu	*t*-BuOH	THF	40	100	8	52
17	KO*t*-Bu	*t*-BuOH	THF	40	100	8	57
18	LiOH	*t*-BuOH	THF	40	87	24	77
19	LiOH	TFE[c]	THF	40	73	24	73
20	LiOH	HFIP[c]	THF	40	84	24	81
21	CsF	—	CH_3CN	60	86	24	10

[a] *Conditions*: β-hydroxyketone **70a** (1.0 equiv), additive (1.5 equiv), base (1.5 equiv), solvent (0.1 M) at indicated temperature for 9–24 h. [b] GC yield using an internal standard at ≥ 98% conversion unless otherwise stated. [c] HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol; TFE = 2,2,2-trifluoroethanol. [d] Several reaction intermediates observed by TLC and GC analysis; proceeded to 78% conversion. [e] Isolated yield. [f] Reaction did not reach completion at 24 h; proceeded to 67% conversion.

Ring Contraction Screen to Produce Acylcyclopentene 53a *(0.10 mmol scale, Table 2.3, entries 1–15).* A benzene solution of β-hydroxyketone **70a** was transferred to a dry 1 dram vial and concentrated under reduced pressure to obtain a starting mass. To this vial was added a magnetic stir bar and 1,4-diisopropylbenzene (internal standard). The contents were solvated in either *t*-BuOH or THF (0.1 M). After complete solvation, an appropriate additive (*t*-BuOH, TFE, or HFIP; 1.50 equiv) was added, followed by base (1.50 equiv). The head space of the vial was purged with N_2 and the vial was capped

with a teflon-lined hard cap and stirred at the appropriate temperature (40 or 60 °C) in a heating block. Reaction progress was initially followed by TLC analysis, and when necessary, aliquots were removed and flushed through a small SiO_2 plug with EtOAc for GC analysis. GC conditions: 90 °C isothermal for 5 min, then ramp 10 °C/min to 250 °C, DB-WAX column, t_R (min): 1,4-diisopropylbenzene = 5.3, acylcyclopentene **53a** = 9.3, β-hydroxyketone **70a** = 17.1 and 17.2 (two diastereomers). (For characterization data, see p. 319–321).



Ring Contraction using $LiOCH_2CF_3$ *(Table 2.3, entry 11).* β-Hydroxyketone **70a** (30.0 mg, 0.16 mmol, 1.00 equiv) was measured into a 1 dram vial with magnetic stir bar with a septum-fitted screw cap. $LiOCH_2CF_3$[50] (26.0 mg, 0.25 mmol, 1.50 equiv) was measured into a separate 1 dram vial, capped with a septum, evacuated/backfilled with N_2 (3 cycles, 5 min evacuation per cycle), and dissolved in THF (0.5 mL). The solution was cannulated into the vial containing β-hydroxyketone along with additional THF rinses (2 x 0.5 mL). The yellow solution was stirred at 60 °C in a heating block. After 10 h, the reaction was cooled to ambient temperature. The turbid brown solution was diluted with Et_2O and stirred with Na_2SO_4 for 30 min. The reaction was filtered and concentrated under reduced pressure at 0 °C in an ice/water bath. The residue was purified by flash column chromatography (SiO_2, 1 x 20 cm, 15:1 hexanes:Et_2O) to afford acylcyclopentene

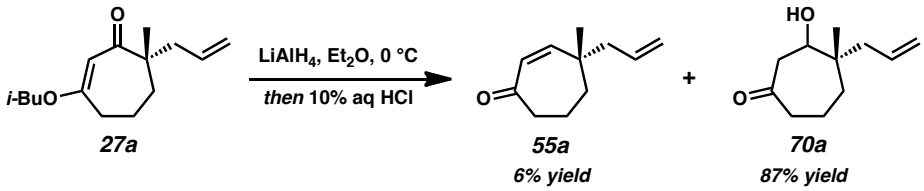
53a (24.4 mg, 0.149 mmol, 90% yield) as a clear, colorless oil. (For characterization data, see p. 320).

Additional Conditions. Additional reaction conditions are listed in Table 2.3, entries 16–21.

Unsuccessful Conditions. No reaction was observed using the following bases, with or without TFE additive: DBU, TMG, Na_2CO_3, K_2CO_3, $BaCO_3$, CaH_2. DBU = 1,8-diazabicyclo [5.4.0]undec-7-ene, TMG = 1,1,3,3-tetramethylguanidine.

2.7.2.8 PREPARATION OF β-HYDROXYKETONES AND ACYLCYCLOPENTENES

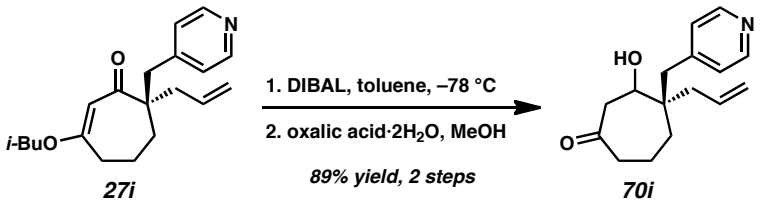
Full characterization data is reported for acylcyclopentenes **53**, cycloheptenone **55a**, and β-hydroxyketone intermediate **70a** (mixture of diastereomers). For all other β-hydroxyketone intermediates (**70b–j, l–o,** mixtures of diastereomers), R_f, IR, and HRMS data are reported and ^{1}H NMR and IR spectra are provided for reference in Figures A2.44–A2.58. For acylcyclopentenes **53a**, the ee value was unchanged from corresponding vinylogous ester **27a**. For all other acylcyclopentenes (**53**), ee values are assumed to be unchanged from the corresponding vinylogous esters (**27**). Representative procedures for General Methods A–E are described below.



27a *55a* *6% yield* *70a* *87% yield*

General Method A: $LiAlH_4$ Hydride Reduction / 10% Aq HCl Hydrolysis

Cycloheptenone 55a and **β-Hydroxyketone 70a.** A 500 mL round-bottom flask with magnetic stir bar was charged with Et_2O (150 mL) and cooled to 0 °C in an ice/water bath. $LiAlH_4$ (806 mg, 21.2 mmol, 0.55 equiv) was added in one portion. After 10 min, a solution of vinylogous ester **27a** (9.13 g, 38.6 mmol, 1.00 equiv) in Et_2O (43 mL) was added dropwise using positive pressure cannulation. The grey suspension was stirred for 40 min and additional $LiAlH_4$ (148 mg, 3.9 mmol, 0.10 equiv) was added in one portion. After an additional 30 min of stirring at 0 °C, the reaction was quenched by slow addition of aqueous HCl (110 mL, 10% w/w). The resulting biphasic system was allowed to warm to ambient temperature and stirred vigorously for 8.5 h. The phases were separated and the aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was azeotroped with toluene (3 x 20 mL) and purified using flash column chromatography (SiO_2, 5 x 15 cm, 9:1→3:1 hexanes:EtOAc, dry-loaded using Celite) to afford β-hydroxyketone **70a** (6.09 g, 33.41 mmol, 87% yield, 1.3:1 dr) as a colorless semi-solid and cycloheptenone **55a** (387 mg, 2.36 mmol, 6% yield) as a colorless oil. (For characterization data, see p. 319).

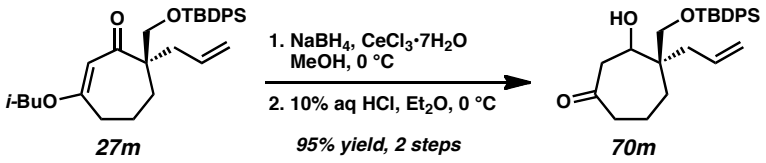


General Method B: DIBAL Reduction / Oxalic Acid Hydrolysis

β-Hydroxyketone 70i. A 25 mL pear-shaped flask was charged with vinylogous ester **27i** (29.4 mg, 0.094 mmol, 1.00 equiv) and toluene (3.0 mL). The solution was cooled to –78 °C using an acetone/CO_2(s) bath. A 1.0 M solution of DIBAL in toluene (112.6 μL, 0.113 mmol, 1.00 equiv) was added dropwise and the solution was stirred for 10 min. MeOH (180 μL), $Na_2SO_4 \cdot 10H_2O$ (1.08 g), and Celite (360 mg) were added. The reaction was stirred vigorously and allowed to warm slowly to ambient temperature. The mixture was filtered through a Celite plug (3 x 3 cm, EtOAc), and concentrated under reduced pressure. $R_f = 0.28$, broad (1:2 hexanes:EtOAc).

The crude hydroxy isobutyl enol ether was added to a 25 mL round-bottom flask and dissolved in MeOH (4.0 mL). Oxalic acid dihydrate (354.9 mg, 2.82 mmol, 30.0 equiv) was added in one portion. After 1 h of stirring, the reaction was neutralized to pH 7 with 1 M aqueous pH 7 NaH_2PO_4/Na_2HPO_4 buffer (6 mL). The biphasic mixture was stirred vigorously for 10 min and the phases were separated. The aqueous layer was extracted with Et_2O (4 x 15 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified using flash column chromatography (SiO_2, 1.5 x 25 cm, 4:1→2:1→1:2 hexanes:acetone) to afford β-hydroxyketone **70i** as a mixture of diastereomers (21.6 mg, 0.083 mmol, 89%

yield over 2 steps, 2.8:1 dr) as a clear, colorless residue which solidified upon standing. (For characterization data, see p. 329).

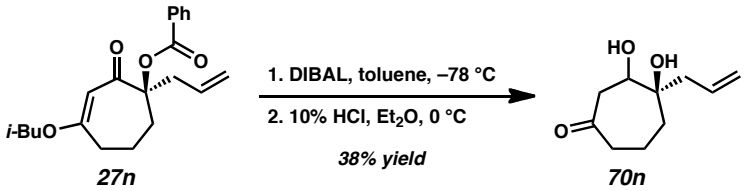


General Method C: Luche Reduction / 10% Aq HCl Hydrolysis

β-Hydroxyketone 70m. A 100 mL round-bottom flask with magnetic stir bar was charged with vinylogous ester **27m** (65.6 mg, 0.134 mmol, 1.00 equiv) and anhydrous MeOH (8.3 mL). The solution was cooled to 0 °C in an ice/water bath. $CeCl_3 \cdot 7H_2O$ (78.2 mg, 0.21 mmol, 1.56 equiv) was added in one portion and the mixture was stirred for 5 min. Addition of $NaBH_4$ (23.8 mg, 0.63 mmol, 4.70 equiv) led to the evolution of gas and a turbid solution that became clear after several minutes. The reaction was stirred at 0 °C. After 15 min, the reaction was diluted with CH_2Cl_2 (20 mL) until turbid, filtered through a Celite plug (3 x 3 cm, CH_2Cl_2), and concentrated under reduced pressure. The residue was taken up in CH_2Cl_2, filtered through a Celite plug (3 x 5 cm, CH_2Cl_2), and concentrated under reduced pressure a second time. R_f = 0.33 (10:1 hexanes:EtOAc).

The crude hydroxy isobutyl enol ether was added to a 25 mL round-bottom flask with a magnetic stir bar and dissolved in Et_2O (3.8 mL). The vigorously stirred solution was cooled to 0 °C and aqueous HCl (384 μL, 10% w/w) was added dropwise via syringe. After 30 min, the reaction was allowed to warm to ambient temperature and extracted with Et_2O (3 x 5 mL). The combined organic phases were dried over Na_2SO_4,

filtered, and concentrated under reduced pressure. The crude product was purified using flash column chromatography (SiO_2, 1.5 x 25 cm, 6:1→4:1 hexanes:EtOAc) to afford β-hydroxyketone **70m** as a mixture of diastereomers (55.6 mg, 0.13 mmol, 95% yield over 2 steps, 3.5:1 dr) as a colorless oil. (For characterization data, see p. 332).



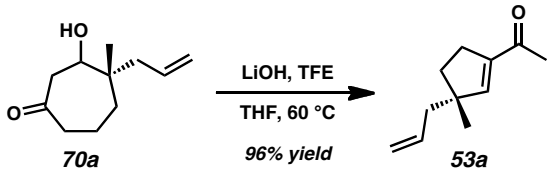
27n *70n*

General Method D: DIBAL Reduction / 10% Aq HCl Hydrolysis

β-Hydroxyketone 70n. A 50 mL pear-shaped flask was charged with vinylogous ester **27n** (100 mg, 0.292 mmol, 1.00 equiv) and toluene (9.5 mL). The solution was cooled to –78 °C using an acetone/CO_2(s) bath. A 1.0 M solution of DIBAL in toluene (963 μL, 0.963 mmol, 1.00 equiv) was added dropwise and the mixture was stirred for 15 min. MeOH (1.0 mL), $Na_2SO_4 \cdot 10\ H_2O$ (6.0 g), and Celite (1.2 g) were added, and the mixture was stirred vigorously and allowed to warm slowly to ambient temperature. The mixture was filtered through a Celite plug (3 x 3 cm, EtOAc), and concentrated under reduced pressure. $R_f = 0.30$ (2:1 hexanes:EtOAc).

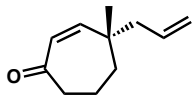
The crude hydroxy isobutyl enol ether was added to a 50 mL pear-shaped flask, dissolved in Et_2O (10 mL), and cooled to 0 °C in an ice/water bath. Aqueous HCl (0.835 mL, 10% w/w) was added dropwise and the biphasic mixture was stirred vigorously at 0 °C. After 40 min or stirring, additional aqueous HCl (0.835 mL, 10% w/w) was added. After 1.5 h, the layers were separated and the aqueous layer was extracted with Et_2O (5 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated

under reduced pressure. The crude product was purified using flash column chromatography (SiO_2, 1.5 x 25 cm, 10:1→6:1→4:1→2:1→1:1→1:2 hexanes:EtOAc) to afford β-hydroxyketone **70n** as a mixture of diastereomers (20.3 mg, 0.110 mmol, 38% yield over 2 steps) as a clear, colorless oil. (For characterization data, see p. 337).



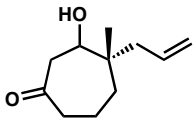
General Method E: β-Hydroxyketone Ring Contraction

Acylcyclopentene 53a. Alcohol **70a** (6.09 g, 33.4 mmol, 1.00 equiv) was dissolved in THF (334 mL) in a 500 mL round-bottom flask. The solution was treated with 2,2,2-trifluoroethanol (3.67 mL, 50.1 mmol, 1.50 equiv) and anhydrous LiOH (1.20 g, 50.1 mmol, 1.50 equiv). The flask was fitted with a condenser, purged with N_2, and heated to 60 °C using an oil bath. After 18 h of stirring, the suspension was allowed to cool to ambient temperature, diluted with Et_2O (150 mL), dried over Na_2SO_4 (30 min of stirring), filtered, and concentrated carefully under reduced pressure, allowing for a film of ice to form on the outside of the flask. The crude product was purified using flash column chromatography (SiO_2, 5 x 15 cm, 15:1 hexanes:Et_2O) to afford acylcyclopentene **53a** (5.29 g, 32.2 mmol, 96% yield) as a colorless fragrant oil. (For characterization data, see p. 320).



55a

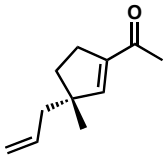
Cycloheptenone 55a. Prepared using General Method A. 387 mg, 2.36 mmol, 6% yield. Flash column chromatography (SiO_2, 5 x 15 cm, 9:1→3:1 hexanes:EtOAc, dry-loaded using Celite). R_f = 0.54 (7:3 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.04 (dd, *J* = 12.9, 0.7 Hz, 1H), 5.82 (d, *J* = 12.9 Hz, 1H), 5.75 (dddd, *J* = 17.1, 10.3, 7.8, 7.1 Hz, 1H), 5.10 (dddd, *J* = 10.3, 1.2, 1.2, 1.2 Hz, 1H), 5.08–5.03 (m, 1H), 2.65–2.52 (m, 2H), 2.19 (app dd, *J* = 13.7, 6.8 Hz, 1H), 2.11 (app dd, *J* = 13.7, 8.1 Hz, 1H), 1.84–1.76 (m, 3H), 1.68–1.63 (m, 1H), 1.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.7, 152.5, 133.8, 128.6, 118.6, 47.2, 45.1, 42.7, 38.2, 27.1, 18.4; IR (Neat Film NaCl) 3076, 3011, 2962, 2934, 2870, 1659, 1454, 1402, 1373, 1349, 1335, 1278, 1208, 1172, 997, 916, 874, 822, 772 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{11}H_{16}O$ $[M]^{+\bullet}$: 164.1201; found 164.1209; $[\alpha]_D^{21.0}$ –9.55 (*c* 1.07, $CHCl_3$, 88.0% ee).



70a

β-Hydroxyketone 70a ***(Table 2.4, entry 1).*** Prepared using General Method A. 6.09 g, 33.41 mmol, 87% yield, 1.3:1 dr. Flash column chromatography (SiO_2, 5 x 15 cm, 9:1→3:1 hexanes:EtOAc, dry-loaded using Celite). R_f = 0.23 (7:3 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ **major epimer**: 5.88 (dddd, *J* = 15.1, 9.0, 7.6, 7.6 Hz, 1H), 5.12–5.08 (m, 2H), 3.70 (dd, *J* = 4.9, 3.9 Hz, 1H), 2.86 (dd, *J* = 15.6, 1.7 Hz, 1H), 2.65

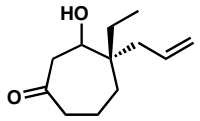
(dd, *J* = 15.6, 7.3 Hz, 1H), 2.54–2.43 (m, 2H), 2.24 (dd, *J* = 13.7, 7.8 Hz, 1H), 2.07 (dd, *J* = 13.4, 7.3 Hz, 1H), 1.99 (dd, *J* = 15.9, 4.4 Hz, 1H), 1.82–1.69 (m, 2H), 1.45–1.41 (m, 1H), 0.96 (s, 3H); **minor epimer:** 5.83 (dddd, *J* = 14.9, 10.3, 7.6, 7.6 Hz, 1H), 5.12–5.06 (m, 2H), 3.68 (dd, *J* = 4.1, 2.4 Hz, 1H) 2.80 (dd, *J* = 15.4, 2.4 Hz, 1H), 2.74 (dd, *J* = 15.4, 8.1 Hz 1H), 2.46–2.38 (m, 2H), 2.18 (dd, *J* = 13.9, 7.3 Hz, 1H), 2.09 (dd, *J* = 12.9, 7.8 Hz, 1H), 1.82–1.65 (m, 3H), 1.50–1.47 (m, 1H), 1.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ **major epimer**: 213.2, 135.0, 118.1, 72.9, 46.7, 44.9, 44.2, 41.0, 36.3, 21.9, 18.9; **minor epimer**: 212.6, 134.2, 118.3, 73.3, 47.2, 42.8, 41.0, 35.9, 22.6, 18.7; IR (Neat Film NaCl) 3436, 3074, 2932, 1692, 1638, 1443, 1403, 1380, 1352, 1318, 1246, 1168, 1106, 1069, 999, 913, 840 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{11}H_{18}O_2$ $[M]^{+\bullet}$: 182.1313; found 182.1307; $[\alpha]_D^{22.8}$ –57.10 (*c* 2.56, $CHCl_3$, 88.0% ee).



53a

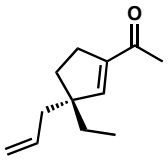
Acylcyclopentene 53a ***(Table 2.4, entry 1).*** Prepared using General Method E. 5.29 g, 32.2 mmol, 96% yield. Flash column chromatography (SiO_2, 5 x 15 cm, 15:1 hexanes:Et_2O). R_f = 0.67 (8:2 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.45 (app t, *J* = 1.7 Hz, 1H), 5.76 (dddd, *J* = 16.4, 10.7, 7.3, 7.3 Hz, 1H), 5.07–5.03 (m, 2H), 2.59–2.48 (m, 2H), 2.30 (s, 3H), 2.21–2.14 (m, 2H), 1.85 (ddd, *J* = 12.9, 8.3, 6.3 Hz, 1H), 1.64 (ddd, *J* = 12.9, 8.5, 6.1 Hz, 1H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.5, 151.9, 143.8, 134.9, 117.8, 50.0, 45.3, 36.0, 29.7, 26.8, 25.6; IR (Neat Film NaCl) 3077, 2956, 2863, 1668, 1635, 1616, 1454, 1435, 1372, 1366, 1309, 1265, 1213, 1177, 993,

914, 862 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{11}H_{17}O$ $[M+H]^{+\bullet}$: 165.1279; found 165.1281; $[\alpha]_D^{21.4}$ +17.30 (*c* 0.955, $CHCl_3$, 88.0% ee); GC conditions: 80 °C isothermal, GTA column, t_R (min): major = 54.7, minor = 60.2.



70b

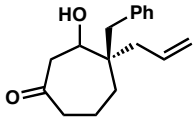
β-Hydroxyketone 70b ***(Table 2.4, entry 2).*** Prepared using General Method A. 111.5 mg, 0.57 mmol, 95% yield. Flash column chromatography (SiO_2, 2 x 25 cm, 10:1→3:1 hexanes:EtOAc). R_f = 0.36 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.45.1; IR (Neat Film NaCl) 3448, 3073, 2965, 2933, 1832, 1696, 1691, 1673, 1459, 1413, 1381, 1352, 1334, 1323, 1306, 1269, 1252, 1269, 1252, 1172, 1138, 1111, 1084, 1071, 1050, 997, 955, 930, 912, 876, 825, 777, 737 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{12}H_{20}O_2$ $[M]^{+\bullet}$: 196.1463; found 196.1480.



53b

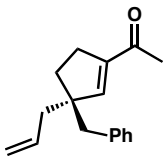
Acylcyclopentene 53b ***(Table 2.4, entry 2).*** Prepared using General Method E. 21.8 mg, 0.12 mmol, 95% yield. Flash column chromatography (SiO_2, 1 x 20 cm, 15:1 hexanes:Et_2O). R_f = 0.73 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.44 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.80–5.64 (m, 1H), 5.08–5.04 (m, 1H), 5.03–5.00 (m, 1H), 2.55–2.46 (m, 2H), 2.30 (s, 3H), 2.19–2.16 (m, 2H), 1.81–1.68 (m, 2H), 1.52–1.41 (m,

2H), 0.85 (dd, J = 7.5, 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 150.7, 144.6, 134.8, 117.7, 54.0, 43.1, 32.9, 31.3, 30.1, 26.9, 9.1; IR (Neat Film NaCl) 3075, 2962, 2922, 2878, 2855, 1669, 1639, 1617, 1459, 1437, 1372, 1319, 1266, 1207, 1052, 995, 913, 868, 784 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{12}H_{19}O$ $[M+H]^+$: 179.1436; found 179.1401; $[\alpha]_D^{25.0}$ +7.06 (*c* 0.98, $CHCl_3$, 91.6% ee).



70c

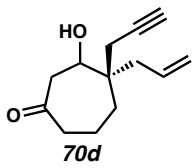
β-Hydroxyketone 70c ***(Table 2.4, entry 3).*** Prepared using General Method A. 109.9 mg, 0.43 mmol, 89% yield. Flash column chromatography (SiO_2, 2 x 25 cm, 10:1→3:1 hexanes:EtOAc). R_f = 0.11 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.46.1; IR (Neat Film NaCl) 3443, 3072, 3028, 3003, 2930, 2865, 1696, 1692, 1685, 1636, 1601, 1582, 1495, 1453, 1413, 1400, 1352, 1340, 1255, 1182, 1163, 1118, 1058, 1031, 995, 970, 916, 885, 848, 809, 754 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{17}H_{22}O_2$ $[M]^{+\bullet}$: 258.1620; found 258.1642.



53c

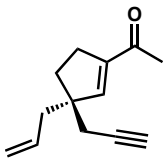
Acylcyclopentene 53c ***(Table 2.4, entry 3).*** Prepared using General Method E. 22.7 mg, 0.094 mmol, 97% yield. Flash column chromatography (SiO_2, 1 x 20 cm, 15:1 hexanes:Et_2O). R_f = 0.54 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.18

(m, 3H), 7.14–7.08 (m, 2H), 6.45 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.78 (dddd, *J* = 16.3, 10.8, 7.7, 7.0 Hz, 1H), 5.13–5.10 (m, 1H), 5.07 (dddd, *J* = 9.1, 2.2, 1.2, 1.2 Hz, 1H), 2.79 (d, *J* = 13.3 Hz, 1H), 2.73 (d, *J* = 13.3 Hz, 1H), 2.43 (dddd, *J* = 16.5, 8.6, 5.7, 1.7 Hz, 1H), 2.27–2.17 (m, 3H), 2.21 (s, 3H), 1.91–1.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.1, 150.1, 144.9, 138.2, 134.7, 130.4, 128.1, 126.4, 118.3, 54.6, 45.2, 43.3, 33.3, 30.0, 26.9; IR (Neat Film NaCl) 3061 3027, 3002, 2920, 2853, 1668, 1638. 1617, 1495, 1453, 1442, 1371, 1314, 1264, 1197, 1089, 1030, 995, 914, 861, 734 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{20}O$ $[M]^{+\bullet}$: 240.1514; found 240.1530; $[\alpha]_D^{25.0}$ –20.63 (*c* 0.83, $CHCl_3$, 86.3% ee).



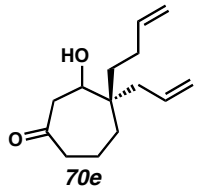
70d

β-Hydroxyketone 70d ***(Table 2.4, entry 4).*** Prepared using General Method A. 117 mg, 0.56 mmol, 98% yield. Flash column chromatography (SiO_2, 2 x 25 cm, 10:1→3:1 hexanes:EtOAc). R_f = 0.35 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.47.1; IR (Neat Film NaCl) 3434, 3295, 3074, 3002, 2932, 2114, 1690, 1684, 1637, 1447, 1354, 1252, 1166, 1124, 1064, 977, 917, 886, 838 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{18}O_2$ $[M]^{+\bullet}$: 206.1307; found 206.1311.



53d

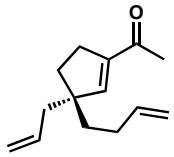
Acylcyclopentene 53d ***(Table 2.4, entry 4).*** Prepared using General Method E. 22.5 mg, 0.12 mmol, 97% yield. Flash column chromatography (SiO_2, 1 x 20 cm, 15:1 hexanes:Et_2O). R_f = 0.74 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.51 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.73 (dddd, *J* = 16.9, 10.2, 7.4, 7.4 Hz, 1H), 5.13 (dm, *J* = 10.2 Hz, 1H), 5.10–5.07 (m, 1H), 2.66–2.46 (m, 2H), 2.34–2.33 (m, 1H), 2.33–2.32 (m, 1H), 2.32 (s, 3H), 2.32–2.30 (m, 2H), 1.99 (dd, *J* = 2.7, 2.7 Hz, 1H), 1.93–1.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 197.3, 148.6, 145.2, 133.9, 118.6, 81.4, 70.3, 53.2, 42.4, 33.4, 30.0, 28.5, 26.9; IR (Neat Film NaCl) 3298, 3075, 3001, 2924, 2857, 2116, 1669, 1639, 1617, 1457, 1437, 1372, 1318, 1265, 1222, 1204, 996, 919, 867 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{16}O$ $[M]^{+\bullet}$: 188.1201; found 188.1211; $[\alpha]_D^{25.0}$ –58.65 (*c* 0.71, $CHCl_3$, 88.5% ee).



70e

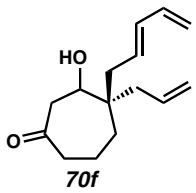
β-Hydroxyketone 70e ***(Table 2.4, entry 5).*** Prepared using General Method A. 116.7 mg, 0.52 mmol, 97% yield. Flash column chromatography (SiO_2, 2 x 25 cm, 10:1→3:1 hexanes:EtOAc). R_f = 0.15 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.48.1; IR (Neat Film NaCl) 3447, 3075, 3001, 2975, 2931, 2866, 1827, 1693, 1639, 1456, 1415, 1352, 1336, 1250, 1169, 1116, 1073, 995,

910, 855, 763, 714 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{18}H_{28}O_2$ $[M]^{+\bullet}$: 276.2089; found 276.2060.



53e

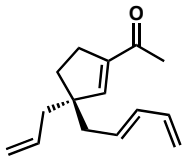
Acylcyclopentene 53e ***(Table 2.4, entry 5).*** Prepared using General Method E. 19.1 mg, 0.093 mmol, 90% yield. Flash column chromatography (SiO_2, 1 x 20 cm, 15:1 hexanes:Et_2O). R_f = 0.62 (4:1 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 6.45 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.79 (dddd, *J* = 16.8, 10.2, 6.5, 6.5 Hz, 1H), 5.72 (dddd, *J* = 16.8, 9.5, 7.3, 7.3 Hz, 1H), 5.09–5.07 (m, 1H), 5.05–4.97 (m, 2H), 4.94 (dm, *J* = 10.2 Hz, 1H), 2.56–2.49 (m, 2H), 2.30 (s, 3H), 2.23–2.17 (m, 2H), 2.15–1.91 (m, 2H), 1.85–1.70 (m, 2H), 1.58–1.50 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 150.4, 144.6, 138.8, 134.6, 117.9, 114.6, 53.5, 43.6, 38.1, 33.3, 30.1, 29.2, 26.9; IR (Neat Film NaCl) 3076, 3001, 2976, 2919, 2854, 1670, 1640, 1618, 1437, 1372, 1314, 1265, 1204, 995, 911, 865 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{14}H_{21}O$ $[M+H]^+$: 205.1592; found 205.1588; $[\alpha]_D^{25.0}$ –30.08 (*c* 0.92, $CHCl_3$, 86.9% ee).



70f

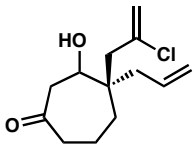
β-Hydroxyketone 70f ***(Table 2.4, entry 6).*** Prepared using General Method A. 117.5 mg, 0.50 mmol, 96% yield. Flash column chromatography (SiO_2, 2 x 25 cm, 10:1→3:1

hexanes:EtOAc). R_f = 0.19 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.49.1; IR (Neat Film NaCl) 3448, 3075, 3035, 3007, 2972, 2929, 2865, 1700, 1696, 1691, 1685, 1648, 1637, 1600, 1449, 1415, 1352, 1333, 1245, 1171, 1120, 1068, 1052, 1005, 969, 954, 912, 855, 838, 817, 720 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{15}H_{23}O_2$ $[M+H]^+$: 235.1698; found 235.1697.



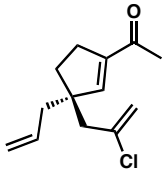
53f

Acylcyclopentene 53f ***(Table 2.4, entry 6).*** Prepared using General Method E. 25.2 mg, 0.12 mmol, 95% yield. Flash column chromatography (SiO_2, 1 x 20 cm, 15:1 hexanes:Et_2O). R_f = 0.65 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.45 (dd, *J* = 1.8, 1.8 Hz, 1H), 6.30 (ddd, *J* = 16.9, 10.2, 10.2 Hz, 1H), 6.08 (dd, *J* = 15.0, 10.4 Hz, 1H), 5.73 (dddd, *J* = 16.4, 11.6, 8.9, 7.5 Hz, 1H), 5.63 (ddd, *J* = 15.0, 7.6, 7.6 Hz, 1H), 5.14–5.09 (m, 2H), 5.06–5.02 (m, 1H), 5.00 (dm, *J* = 10.1 Hz, 1H), 2.54–2.46 (m, 2H), 2.30 (s, 3H), 2.25–2.17 (m, 4H), 1.80–1.74 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 150.0, 144.8, 137.0, 134.5, 134.3, 130.4, 118.1, 115.9, 54.0, 43.3, 42.0, 33.2, 30.0, 26.9; IR (Neat Film NaCl) 3079, 3006, 2929, 2857, 1735, 1670, 1640, 1617, 1439, 1371, 1318, 1267, 1201, 1175, 1084, 1004, 952, 912 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{15}H_{21}O$ $[M+H]^+$: 217.1592; found 217.1568; $[\alpha]_D^{25.0}$ –32.14 (*c* 1.26, $CHCl_3$, 89.6% ee).



70g

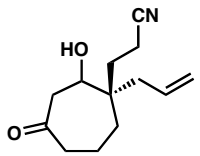
β-Hydroxyketone 70g ***(Table 2.4, entry 7).*** Prepared using General Method A. 114.9 mg, 0.47 mmol, 93% yield. Flash column chromatography (SiO_2, 2 x 25 cm, 10:1→3:1 hexanes:EtOAc). R_f = 0.15 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.50.1; IR (Neat Film NaCl) 3436, 3075, 2931, 2869, 1695, 1627, 1452, 1414, 1352, 1297, 1251, 1222, 1151, 1064, 1021, 997, 974, 915, 887, 839 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{19}O_2Cl$ $[M]^{+\bullet}$: 242.1074; found 242.1063.



53g

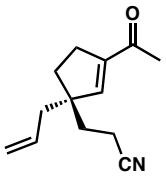
Acylcyclopentene 53g ***(Table 2.4, entry 7).*** Prepared using General Method E. 23.8 mg, 0.11 mmol, 99% yield. Flash column chromatography (SiO_2, 1 x 20 cm, 15:1 hexanes:Et_2O). R_f = 0.55 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.61 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.73 (dddd, *J* = 15.9, 11.1, 7.9, 7.3 Hz, 1H), 5.29 (d, *J* = 1.2 Hz, 1H), 5.15–5.14 (m, 1H), 5.11–5.10 (m, 1H), 5.08–5.04 (m, 1H), 2.56–2.48 (m, 4H), 2.31 (s, 3H), 2.28–2.25 (m, 2H), 1.93 (ddd, *J* = 13.3, 8.4, 6.6 Hz, 1H), 1.84 (ddd, *J* = 13.3, 8.1, 6.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 149.6, 144.4, 139.4, 134.0, 118.7, 116.4, 53.4, 48.0, 43.4, 33.3, 29.8, 26.9; IR (Neat Film NaCl) 3076, 2946, 2857, 1669, 1629, 1434, 1372, 1320, 1266, 1230, 1206, 1167, 996, 917, 886 cm^{-1}; HRMS (EI+) *m/z*

calc'd for $C_{13}H_{18}OCl$ $[M+H]^+$: 225.1046; found 225.1053; $[\alpha]_D^{25.0}$ +46.29 (*c* 1.06, $CHCl_3$, 85.7% ee).



70h

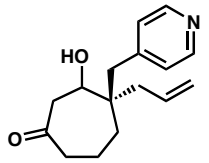
β-Hydroxyketone 70h ***(Table 2.4, entry 8).*** Prepared using General Method A. 72.4 mg, 0.33 mmol, 90% yield. Flash column chromatography (SiO_2, 2 x 25 cm, 4:1→2:1→1:1 hexanes:EtOAc). R_f = 0.40, broad (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.51.1; IR (Neat Film NaCl) 3468, 3075, 2932, 2871, 2247, 1696, 1458, 1437, 1420, 1352, 1319, 1252, 1169, 1122, 1070, 999, 921, 853, 754 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{19}O_2N$ $[M]^{+\bullet}$: 221.1416; found 221.1411.



53h

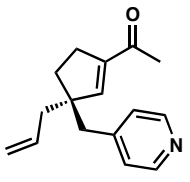
Acylcyclopentene 53h ***(Table 2.4, entry 8).*** Prepared using General Method E. 19.4 mg, 0.095 mmol, 94% yield. Flash column chromatography (SiO_2, 1 x 20 cm, 2:1→3:2→1:1 hexanes:Et_2O). R_f = 0.84, broad (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.42 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.70 (dddd, *J* = 16.4, 10.6, 7.4, 7.4 Hz, 1H), 5.15–5.12 (m, 1H), 5.15–5.06 (m, 1H), 2.60–2.52 (m, 2H), 2.37–2.22 (m, 2H), 2.32

(s, 3H), 2.23–2.20 (m, 2H), 1.93–1.82 (m, 3H), 1.73 (ddd, J = 13.6, 8.2, 7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.8, 147.2, 146.0, 133.3, 120.0, 119.0, 53.2, 43.5, 34.2, 32.7, 30.2, 27.0, 13.1; IR (Neat Film NaCl) 3074, 2923, 2857, 2245, 1667, 1640, 1618, 1423, 1373, 1308, 1264, 1202, 1090, 996, 918, 867 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{18}NO$ $[M+H]^+$: 204.1388; found 204.1385; $[\alpha]_D^{25.0}$ –31.11 (*c* 0.90, $CHCl_3$, 87.4% ee).



70i

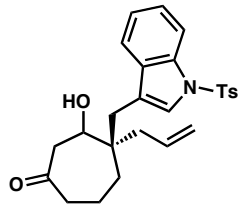
β-Hydroxyketone 70i ***(Table 2.4, entry 9).*** Prepared using General Method B. 21.6 mg, 0.083 mmol, 89% yield over 2 steps. Flash column chromatography (SiO_2, 1.5 x 25 cm, 4:1→2:1→1:2 hexanes:acetone). R_f = 0.10 (2:1 hexanes:acetone); ^{1}H NMR (300 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.52.1; IR (Neat Film NaCl) 3391, 3201, 3073, 2929, 2865, 1699, 1636, 1603, 1557, 1497, 1456, 1418, 1352, 1332, 1297, 1258, 1222, 1187, 1161, 1113, 1069, 1005, 995, 972, 915, 886, 851, 802, 735 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{16}H_{22}O_2N$ $[M+H]^+$: 260.1650; found 260.1649.



53i

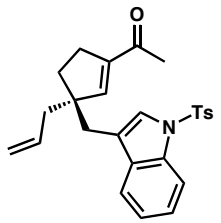
Acylcyclopentene 53i ***(Table 2.4, entry 9).*** Prepared using General Method E. 15.7 mg, 0.065 mmol, 90% yield. Flash column chromatography (SiO_2, 1.5 x 16 cm, 2:1→1:1

hexanes:acetone). R_f = 0.47 (2:1 hexanes:acetone); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (br d, *J* = 3.8 Hz, 2H), 7.04 (d, *J* = 5.7 Hz, 2H), 6.40 (dd, *J* = 1.7, 1.7 Hz, 1H), 5.75 (dddd, *J* = 17.3, 10.3, 7.3, 7.3 Hz, 1H), 5.16–5.04 (m, 2H), 2.77 (d, *J* = 13.0 Hz, 1H), 2.71 (d, *J* = 13.0 Hz, 1H), 2.52–2.39 (m, 1H), 2.33–2.35 (m, 1H), 2.28 (s, 3H), 2.24–2.20 (m, 2H), 1.85–1.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.8, 149.6, 148.6, 147.3, 145.4, 134.0, 125.7, 118.8, 54.2, 44.4, 43.3, 33.3, 30.0, 27.0; IR (Neat Film NaCl) 3401, 3071, 3025, 2922, 2856, 1668, 1640, 1618, 1600, 1557, 1495, 1441, 1415, 1373, 1318, 1277, 1265, 1220, 1194, 1071, 994, 917, 874, 844, 810, 763 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{16}H_{19}ON$ $[M]^{+\bullet}$: 176.1467; found 176.1458; $[\alpha]_D^{25.0}$ –8.58 (*c* 0.77, $CHCl_3$, 84.6% ee).



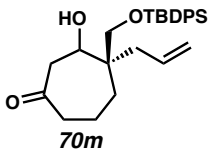
70j

β-Hydroxyketone 70j ***(Table 2.4, entry 10).*** Prepared using General Method A. 300.1 mg, 0.67 mmol, 94% yield. Flash column chromatography (SiO_2, 3 x 25 cm, 4:1→3:1→2:1→1:1 hexanes:EtOAc). R_f = 0.20, 0.26 (two diastereomers) (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.53.1; IR (Neat Film NaCl) 3436, 3068, 2930, 2873, 1693, 1639, 1597, 1494, 1447, 1365, 1402, 1365, 1279, 1211, 1188, 1172, 1133, 1121, 1095, 1063, 1020, 995, 975, 913, 813, 778, 747 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{26}H_{30}O_4NS$ $[M+H]^+$: 452.1896; found 452.1896.



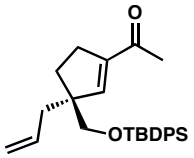
53j

Acylcyclopentene 53j ***(Table 2.4, entry 10).*** Prepared using General Method E. 55.7 mg, 0.10 mmol, 93% yield. Flash column chromatography (SiO_2, 2 x 25 cm, 10:1→8:1→6:1→4:1 hexanes:EtOAc). R_f = 0.67 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (br d, *J* = 8.2 Hz, 1H), 7.63 (dm, *J* = 8.4 Hz, 2H), 7.40 (dd, *J* = 7.3, 0.8 Hz, 1H), 7.33 (br s, 1H), 7.30 (ddd, *J* = 8.2, 8.2, 1.3 Hz, 1H), 7.21 (ddd, *J* = 7.5, 7.5, 1.1 Hz, 1H), 7.17 (dm, *J* = 8.2 Hz, 2H), 6.35 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.75 (dddd, *J* = 16.9, 10.3, 7.7, 6.9 Hz, 1H), 5.13–5.10 (m, 1H), 5.10–5.04 (m, 1H), 2.82 (s, 3H), 2.44 (dddd, *J* = 14.7, 8.8, 5.9, 1.7 Hz, 1H), 2.33 (br s, 2H), 2.31–2.18 (m, 3H), 2.16 (s, 3H), 1.86 (ddd, *J* = 14.6, 8.6, 6.1 Hz, 1H), 1.79 (ddd, *J* = 14.8, 7.6, 5.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.9, 149.9, 145.1, 144.9, 135.2, 135.1, 134.3, 131.9, 130.0, 126.7, 124.8, 124.7, 123.2, 119.9, 119.4, 118.5, 113.9, 54.5, 43.5, 33.8, 33.4, 30.0, 26.8, 21.7; IR (Neat Film NaCl) 3316, 3129, 3101, 3068, 3001, 2974, 2922, 2855, 1667, 1639, 1618, 1597, 1562, 1493, 1448, 1400, 1372, 1307, 1293, 1277, 1211, 1188, 1174, 1121, 1094, 1020, 978, 916, 853, 813, 747 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{26}H_{27}O_3NS$ $[M]^{+\bullet}$: 433.1712; found 433.1694; $[\alpha]_D^{25.0}$ +0.35 (*c* 1.09, $CHCl_3$, 82.9% ee).



70m

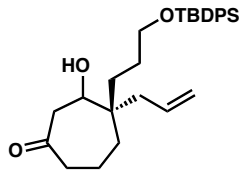
β-Hydroxyketone 70m ***(Table 2.4, entry 11).*** Prepared using General Method C. 55.6 mg, 0.13 mmol, 95% yield over 2 steps. Flash column chromatography (SiO_2, 1.5 x 25 cm, 6:1→4:1 hexanes:EtOAc). R_f = 0.22, 0.28 (two diastereomers) (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.54.1; IR (Neat Film NaCl) 3468, 3072, 3050, 2999, 3013, 2931, 2895, 2858, 2248, 1960, 1891, 1823, 1772, 1698, 1638, 1590, 1472, 1462, 1446, 1428, 1391, 1361, 1337, 1260, 1222, 1186, 1172, 1158, 1113, 1088, 1030, 1006, 999, 976, 914, 841, 823, 810, 740 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{27}H_{37}O_3Si$ $[M+H]^+$: 437.2512; found 437.2517.



53m

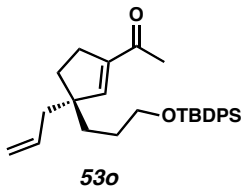
Acylcyclopentene 53m ***(Table 2.4, entry 11).*** Prepared using General Method E. 32.6 mg, 0.078 mmol, 96% yield. Flash column chromatography (SiO_2, 1 x 20 cm, 15:1 hexanes:Et_2O). R_f = 0.60 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67–7.60 (m, 4H), 7.47–7.34 (m, 6H), 6.50 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.71 (dddd, *J* = 17.0, 10.1, 7.8, 6.9 Hz, 1H), 5.12–5.08 (m, 1H), 5.06–5.02 (m, 1H), 3.57 (d, *J* = 9.8 Hz, 1H), 3.53 (d, *J* = 9.8 Hz, 1H), 2.54–2.48 (m, 2H), 2.38 (ddd, *J* = 13.8, 6.9, 1.1 Hz, 1H), 2.31–2.25 (m, 1H), 2.29 (s, 3H), 1.81–1.72 (m, 2H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.2, 148.5, 145.7, 135.8, 135.7, 134.5, 133.6, 133.6, 129.9, 129.9, 127.8, 118.0, 69.1, 56.5,

40.4, 30.7, 30.0, 27.0, 26.8, 19.5; IR (Neat Film NaCl) 3072, 3050, 2999, 2956, 2931, 2896, 2857, 1671, 1639, 1618, 1472, 1463, 1427, 1367, 1320, 1266, 1232, 1188, 1112, 998, 936, 915, 864, 824, 740 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{27}H_{34}O_2Si$ $[M]^{+\bullet}$: 433.1712; found 433.1694; $[\alpha]_D^{25.0}$ –17.58 (*c* 0.94, $CHCl_3$, 51.4% ee).



70o

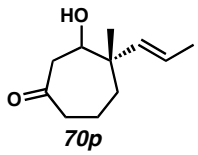
β-Hydroxyketone 70o ***(Table 2.4, entry 12).*** Prepared using General Method C. 110.6 mg, 0.24 mmol, 92% yield over 2 steps. Flash column chromatography (SiO_2, 2 x 25 cm, 6:1→4:1 hexanes:EtOAc). R_f = 0.15 (4:1 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.55.1; IR (Neat Film NaCl) 3436, 3071, 3050, 3013, 2999, 2931, 2896, 2859, 1960, 1891, 1826, 1694, 1638, 1589, 1472, 1461, 1428, 1390, 1360, 1325, 1307, 1251, 1218, 1188, 1168, 1111, 1092, 1007, 998, 973, 934, 914, 823, 798, 740 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{29}H_{41}O_3Si$ $[M+H]^+$: 465.2825; found 465.2810.



53o

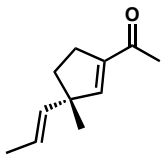
Acylcyclopentene 53o ***(Table 2.4, entry 12).*** Prepared using General Method E. 92.2 mg, 0.21 mmol, 92% yield. Flash column chromatography (SiO_2, 2 x 25 cm, 15:1 hexanes:Et_2O). R_f = 0.64 (4:1 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.71–7.64

(m, 4H), 7.48–7.35 (m, 6H), 6.44 (dd, J = 1.7, 1.7 Hz, 1H), 5.81–5.65 (m, 1H), 5.10–5.07 (m, 1H), 5.05–5.02 (m, 1H), 3.69–3.64 (m, 2H), 2.55–2.49 (m, 2H), 2.31 (s, 3H), 2.20–2.18 (m, 2H), 1.84–1.67 (m, 2H), 1.53–1.48 (m, 4H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 150.7, 144.4, 135.7, 134.7, 134.0, 129.7, 127.7, 117.8, 64.3, 53.3, 43.5, 34.8, 33.3, 30.0, 28.0, 27.0, 26.8, 19.3; IR (Neat Film NaCl) 3071, 3050, 3013, 2999, 2931, 2897, 2857, 1670, 638, 1618, 1589, 1472, 1461, 1448, 1428, 1388, 1372, 1316, 1263, 1201, 1157, 1111, 1093, 1030, 1008, 998, 937, 915, 865, 823, 803, 741, 726 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{25}H_{29}O_2Si$ $[M–C_4H_9]^+$: 389.1968; found 389.1958; $[\alpha]_D^{25.0}$ –14.19 (c 0.92, $CHCl_3$, 78.4% ee).



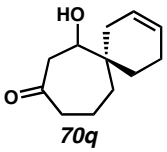
70p

β-Hydroxyketone 70p ***(Table 2.4, entry 13).*** Prepared using General Method A. 429.5 mg, 2.36 mmol, 87% yield. Flash column chromatography (SiO_2, 3 x 20 cm, 9:1→3:1 hexanes:EtOAc). R_f = 0.14 (4:1 hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.56.1; IR (Neat Film NaCl) 3449, 3027, 2963, 2928, 2873, 1694, 1454, 1404, 1350, 1320, 1251, 1170, 1066, 969 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{11}H_{19}O_2$ $[M+H]^+$: 165.1274; found 165.1278.



53p

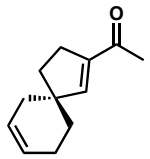
Acylcyclopentene 53p ***(Table 2.4, entry 13).*** Prepared using General Method E. Due to the volatility of acylcyclopentene **53p**, the work-up solvent (Et_2O) was removed using ambient pressure distillation (50→80 °C). 323.8 mg, 1.97 mmol, 93% yield. The crude oil was purified by automated flash column chromatography using a Teledyne Isco CombiFlash R_f (SiO_2, 32 g loading cartridge, 80 g column, linear gradient, 0→30% Et_2O in pentane [33 min]) and solvent was removed using ambient pressure distillation (60 °C). R_f = 0.55 (4:1 hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (dd, *J* = 1.7, 1.7 Hz, 1H), 5.50 (dq, *J* = 15.5, 1.3 Hz, 1H), 5.39 (dq, *J* = 15.6, 6.2 Hz, 1H), 2.58–2.52 (m, 2H), 2.31–2.28 (m, 1H), 2.30 (s, 3H), 1.91 (ddd, *J* = 12.8, 7.4, 7.4 Hz, 1H), 1.74 (ddd, *J* = 12.8, 7.2, 7.2 Hz, 1H), 1.68–1.64 (m, 2H), 1.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 151.4, 143.8, 137.5, 122.3, 51.5, 38.1, 29.6, 26.8, 25.4, 18.2; IR (Neat Film NaCl) 3022, 2958, 2859, 1674, 1617, 1451, 1377, 1365, 1310, 1271, 1229, 1165, 967 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{11}H_{17}O$ $[M+H]^+$: 165.1279; found 165.1278; $[\alpha]_D^{25.0}$ +89.82 (*c* 1.04, $CHCl_3$, 88.0 % ee).



70q

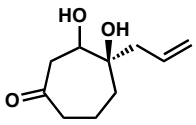
β-Hydroxyketone 70q ***(Table 2.4, entry 14).*** Prepared using General Method A. 29.1 mg, 0.150 mmol, 96% yield. Flash column chromatography (SiO_2, 2 x 20 cm, 9:1→3:1

hexanes:EtOAc). R_f = 0.09 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.57.1; IR (Neat Film NaCl) 3436, 3021, 2922, 2873, 2842, 2697, 1692, 1656, 1436, 1402, 1353, 1318, 1256, 1202, 1184, 1172, 1152, 1093, 1071, 1050, 1000, 981, 970, 949, 932, 876, 850, 834, 798, 750 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{12}H_{18}O_2$ $[M]^{+\bullet}$: 194.1307; found 194.1315.



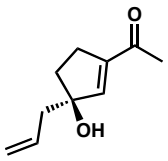
53q

Acylcyclopentene 53q ***(Table 2.4, entry 14).*** Prepared using General Method E. 21.7 mg, 0.123 mmol, 91% yield. Flash column chromatography (SiO_2, 1 x 20 cm, 15:1 hexanes:Et_2O). R_f = 0.65 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.72 (dm, *J* = 10.0 Hz, 1H), 5.65 (dm, *J* = 10.0 Hz, 1H), 2.59–2.52 (m, 2H), 2.30 (s, 3H), 2.13–2.04 (m, 2H), 2.02–1.98 (m, 2H), 1.77–1.70 (m, 2H), 1.69 (ddd, *J* = 12.8, 6.3, 6.3 Hz, 1H), 1.56 (ddd, *J* = 12.8, 6.5, 6.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.8, 151.4, 143.9, 127.0, 125.5, 48.7, 35.8, 35.8, 32.5, 28.9, 26.8, 23.1; IR (Neat Film NaCl) 3320, 3023, 2918, 2856, 1704, 1669, 1616, 1436, 1371, 1436, 1371, 1316, 1269, 1231, 11945, 1116, 1086, 1045, 1020, 980, 962, 935, 864, 763 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{12}H_{16}O$ $[M]^{+\bullet}$: 176.1201; found 176.1234; $[\alpha]_D^{25.0}$ –10.42 (*c* 1.08, $CHCl_3$, 78.4% ee).



70n

β-Hydroxyketone 70n ***(Table 2.4, entry 15).*** Prepared using General Method D. 20.3 mg, 0.110 mmol, 38% yield over 2 steps. Flash column chromatography (SiO_2, 1.5 x 25 cm, 10:1→6:1→4:1→2:1→1:1→1:2 hexanes:EtOAc). R_f = 0.19 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.58.1; IR (Neat Film NaCl) 3369, 3077, 3011, 2947, 2924, 1688, 1641, 1469, 1439, 1343, 1268, 1216, 1193, 1128, 1108, 1079, 1052, 1032, 1019, 999, 966, 909, 889, 808, 731 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{10}H_{15}O_2$ $[M–OH]^+$: 167.1067; found 167.1066.

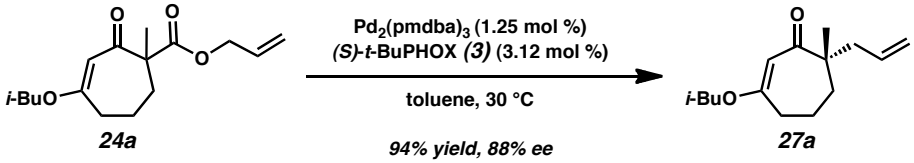


53n

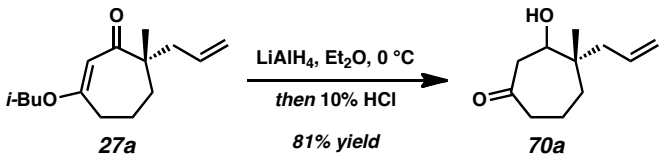
Acylcyclopentene 53n ***(Table 2.4, entry 15).*** Prepared using General Method E. 12.2 mg, 0.073 mmol, 67% yield. Flash column chromatography (SiO_2, 1.5 x 25 cm, 10:1→4:1→2:1→1:1 hexanes:EtOAc); R_f = 0.44 (1:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.48 (app t, *J* = 1.9 Hz, 1H), 5.91–5.77 (dddd, *J* = 16.5, 10.7, 7.4, 7.4 Hz, 1H), 5.23–5.15 (m, 2H), 2.67 (dddd, *J* = 17.0, 8.9, 4.1, 1.7 Hz, 1H), 2.50–2.40 (m, 3H), 2.33 (s, 3H), 2.14 (ddd, *J* = 13.7, 8.5, 4.1 Hz, 1H), 2.03 (br s, 1H), 1.91 (ddd, *J* = 13.7, 9.0, 5.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.5, 145.9, 145.5, 132.9, 119.8, 85.2, 44.9, 37.4, 29.1, 27.0; IR (Neat Film NaCl) 3400, 3077, 3004, 2961, 2929, 2856, 1841, 1668, 1622, 1428, 1372, 1295, 1267, 1228, 1205, 1173, 1070, 1057, 1016, 998,

966, 935, 917, 862, 831, 776 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{10}H_{13}O$ $[M–OH]^+$: 149.0961; found 149.0967; $[\alpha]_D^{25.0}$ –22.45 (*c* 1.22, $CHCl_3$, 57.1% ee).

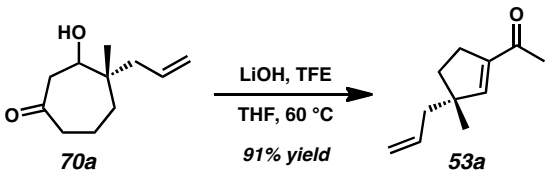
2.7.2.9 LARGE SCALE SYNTHESIS OF ACYLCYCLOPENTENE 53a



Vinylogous Ester 27a. $Pd_2(pmdba)_3$ (733.1 mg, 0.67 mmol, 0.0125) and (*S*)-*t*-BuPHOX (647.0 mg, 1.67 mmol, 0.0312 equiv) were placed in a 500 mL round-bottom flask. The flask was evacuated/backfilled with N_2 (3 cycles, 10 min evacuation per cycle). Toluene (222 mL, sparged with N_2 for 1 h immediately before use) was added and the black suspension was immersed in an oil bath preheated to 30 °C. After 30 min of stirring, β-ketoester **24a** (15.0 g, 53.5 mmol, 1.0 equiv) in toluene (46 mL, sparged with N_2 immediately before use) was added using positive pressure cannulation. The dark orange catalyst solution turned olive green immediately after the addition of β-ketoester **24a**. The solution was stirred at 30 °C for 32 h, allowed to cool to ambient temperature, filtered through a silica gel plug (2 x 5.5 cm SiO_2, Et_2O), and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (SiO_2, 8 x 12 cm, 19:1 hexanes:EtOAc, dry-loaded using SiO_2) to afford vinylogous ester **27a** (11.83 g, 50.1 mmol, 94% yield, 88% ee) as a pale yellow oil. (For characterization data, see p. 287).

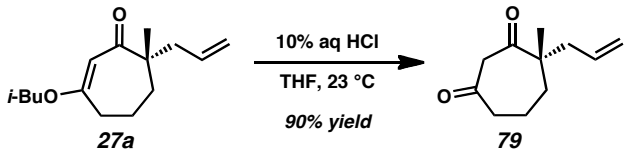


β-Hydroxyketone 70a. A 500 mL round-bottom flask with magnetic stir bar was charged with Et_2O (150 mL) and cooled to 0 °C. $LiAlH_4$ (1.04 g, 0.0275 mol, 0.55 equiv) was added in one portion. After 10 min, a solution of vinylogous ester **27a** (11.83 g, 50 mmol, 1.0 equiv) in Et_2O (50 and 25 mL for quantitative transfer) was added dropwise using positive pressure cannulation. The grey suspension was stirred for 60 min after which $LiAlH_4$ (190 mg, 5.0 mmol, 0.1 equiv) was added in one portion. After an additional 10 min of stirring at 0 °C, the reaction was quenched by slow addition of aqueous HCl (143 mL, 10% w/w). The resulting biphasic system was allowed to warm to ambient temperature and stirred vigorously for 10 h. The reaction was diluted with Et_2O, the phases were separated and the aqueous phase was extracted with Et_2O (3 x 150 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was azeotroped with toluene (50 mL) and purified using flash column chromatography (SiO_2, 8 x 13 cm, 9:1→3:1 hexanes:EtOAc, dry-loaded using Celite) to afford β-hydroxyketone **70a** (7.25 g, 39.8 mmol, 81% yield) as a colorless semi-solid. (For characterization data, see p. 319).



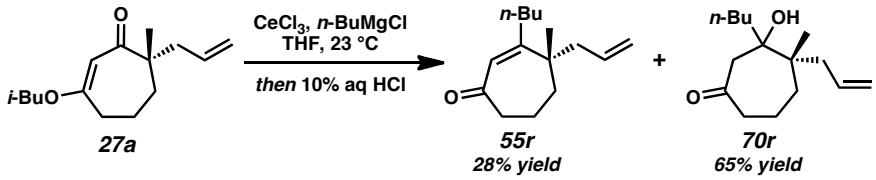
Acylcyclopentene 53a. Alcohol **70a** (7.25 g, 39.8 mmol, 1.0 equiv) was dissolved in THF (400 mL) in a 1 L round-bottom flask. The solution was treated with 2,2,2-trifluoroethanol (5.99 g, 4.36 mL, 59.7 mmol, 1.5 equiv) and LiOH (1.43 g, 59.7 mmol, 1.5 equiv). The flask was fitted with a reflux condenser, purged with N_2, and heated to 60 °C using an oil bath. After 18 h of stirring, the suspension was allowed to cool to ambient temperature, diluted with Et_2O (200 mL), stirred with Na_2SO_4 for 30 min, filtered, and concentrated carefully under reduced pressure, allowing for a film of ice to form on the outside of the flask. The crude product was purified using flash column chromatography (SiO_2, 8 x 12 cm, 15:1→9:1 pentane:Et_2O) to afford acylcyclopentene **53a** (5.93 g, 36.1 mmol, 91% yield) as a colorless fragrant oil. (For characterization data, see p. 320).

2.7.2.10 INITIAL SYNTHETIC STUDIES ON THE ORGANOMETALLIC ADDITION/REARRANGEMENT OF 27a



Cyclic Dione 79. A 20 mL scintillation vial equipped with a stir bar was charged with vinylogous ester **27a** (144.6 mg, 0.61 mmol, 1.00 equiv), THF (1 mL), and aqueous HCl (1 mL, 10% w/w, 2.87 mmol, 4.69 equiv). After 4.5 h of vigorous stirring, the solution

was diluted with H_2O (5 mL) and transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (70 mL) were dried over $MgSO_4$, filtered, and concentrated. The crude oil was purified by flash chromatography (SiO_2, 27.5 x 2 cm, 100% hexanes→10% EtOAc in hexanes) to afford cyclic dione **79** (99.4 mg, 0.55 mmol, 90% yield) as a pale yellow oil; R_f = 0.48 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.69 (d, J = 14.0 Hz, 1H), 5.12–5.04 (m, 2H), 3.72 (d, J = 14.0 Hz, 1H), 3.53 (d, J = 14.0 Hz, 1H), 2.48 (t, J = 6.6 Hz, 2H), 2.40 (dddd, J = 13.9, 7.1, 1.2, 1.2 Hz, 1H), 2.22 (dddd, J = 13.9, 7.7, 1.1, 1.1 Hz, 1H), 2.02–1.75 (m, 4H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.4, 203.7, 133.1, 119.1, 57.6, 50.9, 43.5, 42.9, 36.7, 21.9, 19.8; IR (Neat Film NaCl) 3076, 2972, 2935, 2871, 1719, 1695, 1639, 1463, 1417, 1378, 1337, 1210, 1160, 1112, 1059, 1026, 921 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{11}H_{16}O_2$ $[M]^{+\bullet}$: 180.1150; found 180.1165; $[\alpha]_D^{25.0}$ –19.38 (*c* 1.00, $CHCl_3$, 88.0% ee).

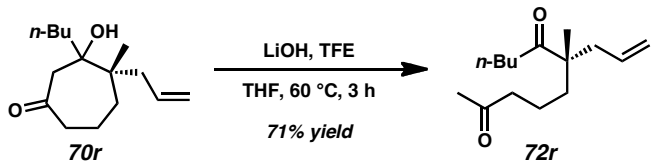


Cycloheptenone 55r and β-Hydroxyketone 70r. $CeCl_3 \cdot 7H_2O$ (419 mg, 1.13 mmol, 2.55 equiv) in a 100 mL round-bottom flask was immersed in a preheated oil bath at 150 °C and placed under vacuum for 4 h while stirring. The flask was cooled to ambient temperature, backfilled with N_2, and charged with THF (4 mL). After 15 h of stirring, additional THF (4 mL) and *n*-butylmagnesium chloride solution (1.2 mL, 1.86 M in THF, 2.23 mmol, 5.02 equiv) were added to the flask. The resulting slurry was stirred for 4.25

h before vinylogous ester **27a** (105 mg, 0.444 mmol, 1.00 equiv) dissolved in THF (1 mL) was added using positive pressure cannulation followed by two THF rinses (2 x 0.5 mL). After 45 min of stirring, the reaction was quenched by addition of 10% w/w HCl (10 mL). The phases were separated and the aqueous layer was extracted with ethyl acetate (3 x 15 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using a Teledyne Isco CombiFlash R_f system (SiO_2, 25 g loading cartridge, 12 g column, multi-step gradient, hold 0% [1 min]→ramp to 10% [5 min]→hold 10% [31 min]→100% EtOAc in hexanes [10 min]) to afford cycloheptenone **55r** (28 mg, 0.13 mmol, 28% yield) and β-hydroxyketone **70r** (69 mg, 0.29 mmol, 65% yield) as pale yellow oils.

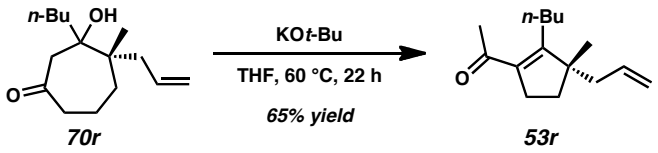
Cycloheptenone 55r. R_f = 0.68 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (s, 1H), 5.63 (dddd, *J* = 16.9, 10.3, 7.9, 6.7 Hz, 1H), 5.10–4.98 (m, 2H), 2.61–2.54 (m, 2H), 2.37 (dddd, *J* = 14.1, 6.7, 1.3, 1.3 Hz, 1H), 2.18–2.03 (m, 3H), 1.85–1.72 (m, 3H), 1.66–1.56 (m, 1H), 1.53–1.43 (m, 2H), 1.37 (app. septuplet, *J* = 7.3 Hz, 2H), 1.15 (s, 3H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.4, 163.0, 134.2, 128.7, 118.1, 45.7, 45.3, 44.4, 38.8, 34.0, 32.4, 25.7, 23.0, 17.6, 14.1; IR (Neat Film NaCl) 3076, 2957, 2933, 2872, 1652, 1611, 1467, 1414, 1379, 1342, 1263, 1218, 1178, 1109, 1072, 996, 962, 914, 841, 780, 713 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{25}O$ $[M+H]^+$: 221.1900; found 221.1905; $[\alpha]_D^{25.0}$ –33.17 (*c* 1.17, $CHCl_3$, 88.0% ee).

β-Hydroxyketone 70r. R_f = 0.48 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.76.1 (Neat Film NaCl) 3502, 3073, 2956, 2871, 1695, 1638, 1468, 1404, 1380, 1341, 1286, 1181, 1125, 1052, 1028, 998, 913, 868, 796, 732 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{27}O_2$ $[M+H]^+$: 239.2006; found 239.2013.



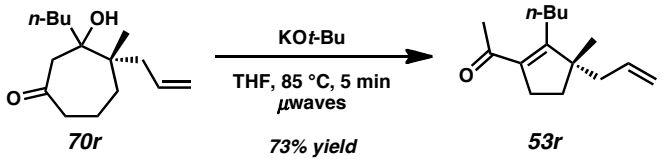
Linear Dione 72r. A 50 mL round-bottom flask equipped with a magnetic stir and fitted with a water condenser was charged with β-hydroxyketone **70r** (56.9 mg, 0.24 mmol, 1.00 equiv), THF (3 mL), TFE (60 μL, 0.83 mmol, 3.50 equiv), and LiOH (17.3 mg, 0.72 mmol, 3.03 equiv). The flask was backfilled with argon and lowered into a preheated oil bath (60 °C). After 3 h, the reaction was removed from the bath, allowed to cool to room temperature, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 3 x 21 cm, 10%→20%→30% EtOAc in hexanes) to afford linear dione **72r** (40.1 mg, 0.17 mmol, 71% yield) as a pale yellow oil; R_f = 0.57 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68–5.57 (m, 1H), 5.06–4.98 (m, 2H), 2.43 (t, *J* = 7.3 Hz, 2H), 2.39 (t, *J* = 6.4 Hz, 2H), 2.31 (dddd, J = 14.0, 7.3, 1.2, 1.2 Hz, 1H), 2.18 (dddd, *J* = 14.0, 7.7, 1.2, 1.2 Hz, 1H), 2.11 (s, 3H), 1.63–1.34 (m, 6H), 1.33–1.24 (m, 2H), 1.10 (s, 3H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.9, 208.6, 133.9, 118.1, 50.9, 44.0, 42.6, 37.4, 37.4, 30.1, 25.9, 22.6, 21.1, 18.7, 14.1; IR (Neat Film NaCl) 3076, 2958, 2933, 2873, 1718, 1701, 1639,

1465, 1409, 1378, 1360, 1256, 1230, 1174, 1142, 1120, 1029, 994, 916, 766, 728 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{27}O_2$ $[M+H]^+$: 239.2006; found 239.2005; $[\alpha]_D^{25.0}$ +5.57 (*c* 1.17, $CHCl_3$, 88.0% ee).



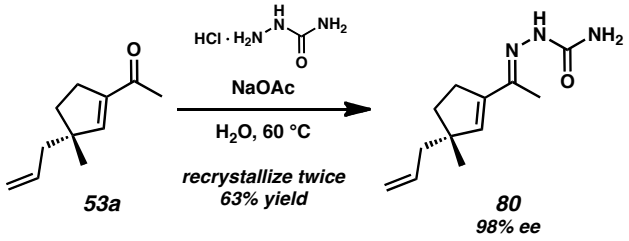
Acylcyclopentene 53r. A 25 mL round-bottom flask equipped with a stir bar and fitted with a water condenser was charged with β-hydroxyketone **70r** (91.5 mg, 0.38 mmol, 1.00 equiv), THF (4 mL), and KO*t*-Bu (66.5 mg, 0.59 mmol, 1.55 equiv). The flask was lowered into a preheated oil bath (60 °C) and stirred overnight. Additional THF (4 mL) was added after 19 h of heating. After an additional 3 h, the reaction was removed from the bath, allowed to cool to room temperature, dried over Na_2SO_4, filtered through a silica gel plug, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 3 x 27 cm, 100% pentane→2%→5%→10% Et_2O in pentane) to afford acylcyclopentene **53r** (55.1 mg, 0.25 mmol, 65% yield) as a pale yellow oil; R_f = 0.81 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77–5.65 (m, 1H), 5.08–5.00 (m, 2H), 2.60–2.49 (m, 2H), 2.45–2.37 (m, 1H), 2.24–2.17 (m, 4H), 2.15–2.10 (m, 2H), 1.85 (ddd, *J* = 12.8, 7.7, 6.2 Hz, 1H), 1.60–1.51 (m, 1H), 1.47–1.34 (m, 4H), 1.06 (s, 3H), 0.93 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 164.2, 135.0, 134.7, 117.6, 52.6, 43.8, 35.0, 32.1, 31.5, 30.4, 27.6, 24.7, 23.8, 14.0; IR (Neat film NaCl) 3075, 3002, 2957, 2930, 2870, 2859, 1677, 1653, 1639, 1602, 1456, 1432, 1373, 1355, 1311, 1275, 1258, 1188, 1141, 1089, 995, 959, 913, 848, 801, 726 cm^{-1};

HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{25}O$ $[M+H]^+$: 221.1900; found 221.1900; $[\alpha]_D^{25.0}$ –1.44 (*c* 1.35, $CHCl_3$, 88.0% ee).



Acylcyclopentene 53r. KO*t*-Bu (32 mg, 0.283 mmol, 1.62 equiv), THF (1.75 mL), and β-hydroxyketone mmol, 1.00 equiv) were added to a 0.5–2.0 mL microwave vial with a magnetic spin vane. The pale yellow solution was subjected to microwave irradiation in a Biotage Initiator microwave reactor (temperature: 85 °C, sensitivity: normal). After 5 min of irradiation, the crimp cap was removed and Na_2SO_4 was added to the vial. The contents were filtered through a silica gel plug with Et_2O, concentrated under reduced pressure, and purified by flash column chromatography (5% Et_2O in pentane) to yield acylcyclopentene **53r** (31 mg, 0.14 mmol, 73% yield) as a pale yellow oil.

2.7.2.11 PREPARATION OF ACYLCYCLOPENTENE DERIVATIVES

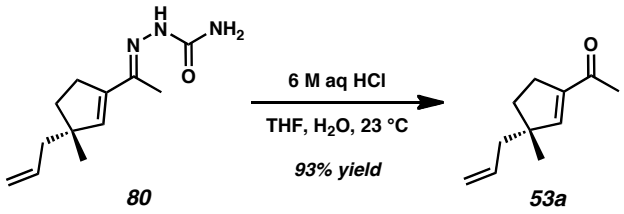


Semicarbazone 80. A 15 mL round-bottom flask was charged with sodium acetate (150 mg, 1.83 mmol, 1.20 equiv), semicarbazide hydrochloride (204 mg, 1.83 mmol, 1.20 equiv), and a magnetic stir bar. Purified water (1.7 mL) was added and the mixture was

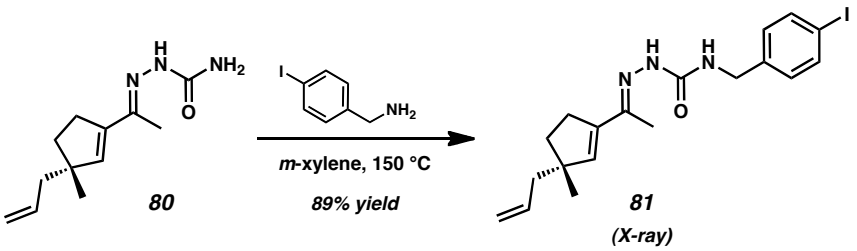
stirred until all the solids had dissolved. Acylcyclopentene **53a** (250 mg, 1.52 mmol, 1.00 equiv) was added neat and the mixture was heated to 60 °C for 4 h. The slurry was allowed to cool to ambient temperature while stirring and was then vacuum filtered (water aspirator). The white solid was dried under reduced pressure to afford semicarbazone **15** (311 mg, 1.40 mmol, 92% yield). The ee of the semicarbazone at this point was found to be 91% (measured by hydrolysis to ketone **53a,** GC conditions: 80 °C isothermal for 90 min, G-TA column, t_R (min): acylcyclopentene **53a** = 54.98).

The semicarbazone **80** (300 mg, 1.36 mmol) was transferred to a round-bottom flask, the solids were suspended in toluene-hexanes (50:50), and the mixture was heated to 90 °C while stirring. After a few minutes of stirring, the solids had dissolved completely to afford a clear, colorless solution. Heating was discontinued, and the stirring mixture was allowed to cool to ambient temperature while still immersed in the oil bath. After 10 h had elapsed, the slurry was vacuum filtered to afford **80** (246 mg, 1.11 mmol, 82% yield, 63% overall yield after recrystallizing twice). The ee at this point was found to be 94.5% (measured by hydrolysis to ketone **53a**). A second recrystallization following the above procedure employing **80** (241 mg, 1.09 mmol) afforded **80** (201 mg, 0.91 mmol, 83% yield). The ee at this point was found to be 97.9% (measured by hydrolysis to ketone **53a**); R_f = 0.30 (9:1 $CHCl_3$-MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (br s, 1H), 6.06 (br s, 1H), 5.85 (app t, *J* = 1.6 Hz, 1H), 5.76 (dddd, *J* = 16.7, 9.3, 7.4, 7.4 Hz, 1H), 5.47 (br s, 1H), 5.06–4.98 (m, 2H), 2.67–2.49 (m, 2H), 2.15–2.12 (m, 2H), 1.98 (s, 3H), 1.82 (ddd, *J* = 12.8, 8.2, 6.9 Hz, 1H), 1.62 (ddd, *J* = 12.8, 8.5, 6.4 Hz, 1H), 1.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 145.0, 141.7, 141.2, 135.6, 117.2, 49.2, 45.9, 36.2, 30.8, 26.3, 12.8; IR (Neat Film NaCl) 3473, 3266,

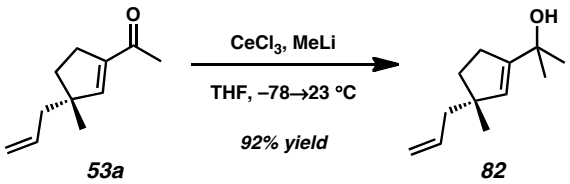
3189, 2946, 2858, 1698, 1579, 1478, 1437, 1377, 1349, 1321, 1130, 1109, 993, 910, 845, 768 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{12}H_{20}N_3O$ $[M+H]^+$: 222.1606; found 222.1610; $[\alpha]_D^{22.6}$ +39.80 (*c* 0.84, $CHCl_3$, 97.9% ee); mp = 145–146 °C (1:1 toluene-hexanes).



Acylcyclopentene 53a. A solution of semicarbazone **80** (191.8 mg, 0.867 mmol, 1.00 equiv) in THF (1.92 mL) was treated with aqueous HCl (3.84 mL, 6.0 M, in H_2O) was added. The resulting biphasic mixture was stirred vigorously at ambient temperature for 30 h. The reaction was diluted with Et_2O (10 mL), the phases were separated, and the aqueous phase was extracted with Et_2O (2 x 10 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated carefully under reduced pressure, allowing for a film of ice to form on the outside of the flask. The residue was filtered through a short silica gel plug (1 x 10 cm SiO_2, 4:1 hexanes:Et_2O) to afford acylcyclopentene **53a** (132.6 mg, 0.81 mmol, 93% yield); $[\alpha]_D^{22.6}$ +39.80 (*c* 0.84, $CHCl_3$, 97.9% ee). (For characterization data, see p. 320).

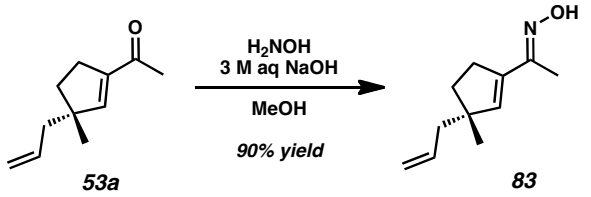


Iodoarene 81. To a solution of semicarbazone **80** (50 mg, 0.23 mmol, 1.00 equiv) in *m*-xylene (2.2 mL) was added 4-iodo-benzylamine (63 mg, 0.27 mmol, 1.17 equiv). The resulting pale yellow solution was immersed in an oil bath and heated to 150 °C. After 9 h of stirring at 150 °C, the reaction was allowed to cool to ambient temperature and concentrated under reduced pressure to afford a pale yellow solid. The crude solid was purified by flash column chromatography (1.0 x 15 cm SiO_2, 9:1→7:3 hexanes:EtOAc) to afford iodoarene **81** (88 mg, 0.20 mmol, 89% yield) as a white solid. X-ray quality crystals were obtained by slow vapor diffusion of pentane into a chloroform solution of **81**; R_f = 0.52 (9:1 $CHCl_3$-MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.66–7.64 (m, 2H), 7.08 (d, *J* = 8.5 Hz, 2H), 6.50 (t, *J* = 6.1 Hz, 1H), 5.86 (app t, *J* = 1.5 Hz, 1H), 5.76 (dddd, *J* = 16.9, 9.0, 7.6, 7.6 Hz, 1H), 5.04–5.01 (m, 2H), 4.46 (d, *J* = 6.3 Hz, 2H), 2.60–2.49 (m, 2H), 2.18–2.10 (m, 2H); 1.95 (s, 3H), 1.82 (ddd, *J* = 12.9, 8.5, 6.3 Hz, 1H), 1.62 (ddd, *J* = 12.9, 8.5, 6.1 Hz, 1H), 1.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3, 144.5, 141.5, 141.4, 139.2, 137.8, 135.6, 129.4, 117.2, 92.6, 49.3, 45.9, 43.2, 36.2, 30.9, 26.3, 12.5; IR (Neat Film NaCl) 3411, 3194, 3075, 2946, 2920, 2863, 1677, 1528, 1486, 1401, 1323, 1259, 1142, 1114, 1057, 1000, 913, 845 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{25}N_3OI$ $[M+H]^+$: 438.1043; found 438.1036; $[\alpha]_D^{22.2}$ +31.43 (*c* 0.36, $CHCl_3$, 91.0% ee); mp = 123–124 °C ($CHCl_3$-*n*-pentane).



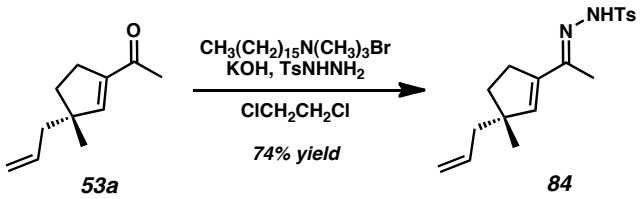
Alcohol 82. $CeCl_3$ (187 mg, 0.759 mmol, 2.50 equiv) was weighed out in a glove box and placed in a 25 mL round-bottom flask. The flask was sealed with a septum and removed from the glove box. THF (3 mL) was added to the flask, the suspension was cooled to –78 °C using an acetone/CO_2(s) bath, and MeLi (326 μL, 0.912 mmol, 2.80 M in DME, 3.00 equiv) was added in a dropwise manner. The resulting pale brown suspension was stirred at –78 °C for 30 min. Acylcyclopentene **53a** (50.0 mg, 0.304 mmol, 1.00 equiv) was added neat to the reaction in a dropwise manner. After 30 min of stirring at –78 °C, the reaction was quenched by dropwise addition of sat. aqueous NH_4Cl (1.0 mL), the cooling bath was removed, and the reaction was allowed to warm to ambient temperature. The reaction was diluted with Et_2O (10 mL) and H_2O (10 mL), and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 15 mL), and the combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by automated flash column chromatography using a Teledyne Isco CombiFlash R_f (SiO_2, 5 g loading cartridge, 12 g column, multi-step gradient, 5% [5 min]→10% Et_2O in pentane) to afford alcohol **82** (50.4 mg, 0.280 mmol, 92% yield) as a pale yellow oil; R_f = 0.31 (4:1 hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (dddd, *J* = 14.7, 11.8, 9.3, 7.4 Hz, 1H), 5.34 (dd, *J* = 1.8, 1.8 Hz, 1H), 5.04–5.00 (m, 1H), 5.00–4.97 (m, 1H), 2.45–2.29 (m, 2H), 2.18–2.00 (m, 2H), 1.81 (ddd, *J* = 12.7, 8.3, 6.0 Hz, 1H), 1.60 (ddd, *J* = 12.7, 8.5, 6.1 Hz, 1H), 1.44 (br s, 1H), 1.34 (s, 6H), 1.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 149.7, 136.21, 131.6, 116.7, 70.9, 48.2, 46.2, 36.9, 30.9, 29.3, 29.3, 26.5; IR (Neat Film NaCl) 3370, 3077, 2973, 2943, 2859, 1637, 1454, 1412, 1367, 1328, 1254, 1212, 1162, 1137, 997, 960, 940, 910, 853, 806 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{12}H_{19}$ $[M\text{-}OH]^+$: 163.1481; found 163.1482; $[\alpha]_D^{25.0}$ +5.34 (*c* 1.16, $CHCl_3$, 88.0 % ee).



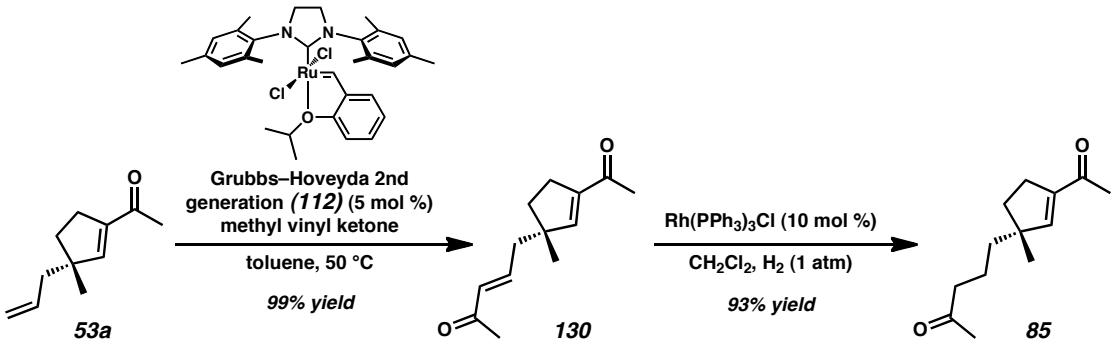
Oxime 83. A 1 dram vial with magnetic stir bar was charged with acylcyclopentene **53a** (40.0 mg, 0.24 mmol, 1.00 equiv), MeOH (0.24 mL), 50% wt aqueous hydroxylamine (47 μL, 0.76 mmol, 3.13 equiv), and 3 M aqueous NaOH (125 μL, 0.376 mmol, 0.51 equiv). After 9 d, the reaction was diluted with Et_2O (10 mL) and H_2O (2 mL) and stirred vigorously for several minutes. The layers were separated and the aqueous layer was extracted with Et_2O (5 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was taken up in CH_2Cl_2, filtered through a cotton plug, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 1.5 x 20 cm, 20:1→ 15:1 hexanes:EtOAc) to afford oxime **83** (39.3 mg, 0.21 mmol, 90% yield) as a clear oil; R_f = 0.52 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (br s, 1H), 5.90 (br t, *J* = 1.5 Hz, 1H), 5.85–5.66 (m, 1H), 5.02 (m, 2H), 2.70–2.45 (m, 2H), 2.14 (m, 2H), 2.05 (s, 3H), 1.85 (ddd, *J* = 12.9, 8.1, 6.6 Hz, 1H), 1.65 (ddd, *J* = 12.8, 8.3, 6.3 Hz, 1H), 1.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 141.8, 139.1, 135.6, 117.2, 48.9, 45.9, 36.3,

30.6, 26.2, 11.3; IR (Neat Film NaCl) 3272, 3233, 3075, 3003, 2952, 2925, 2864, 1639, 1455, 1437, 1414, 1379, 1322, 1280, 1103, 1010, 995, 913, 850, 828, 756, 715 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_8H_{12}NO$ $[M–C_3H_5]^+$: 138.0919; found 138.0960; $[\alpha]_D^{25.0}$ +21.34 (*c* 1.57, $CHCl_3$, 88.0% ee).



Tosylhydrazone 84. A 25 mL flask with magnetic stir bar was charged with acylcyclopentene **53a** (40.0 mg, 0.24 mmol, 1.00 equiv), 1,2-dichloroethane (2.7 mL), cetyltrimethylammonium bromide (26.6 mg, 0.073 mmol, 0.30 equiv), KOH (136.7 mg, 2.44 mmol, 10.0 equiv), and $TsHNNH_2$ (271.9 mg, 1.46 mmol, 6.00 equiv), forming a thick white suspension. After 43 h, the reaction was quenched by the addition of sat. aqueous NH_4Cl (5 mL). The mixture was extracted with CH_2Cl_2 (5 x 10 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using a Teledyne Isco CombiFlash R_f system (SiO_2, 3 x 25 cm, 4:1→3:1 hexanes:EtOAc) to afford tosylhydrazone **84** (196.7 mg, 0.94 mmol, 74% yield) as a clear oil; R_f = 0.41 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.3 Hz, 2H), 7.54 (br s, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 5.85 (app t, *J* = 1.6 Hz, 1H), 5.81–5.62 (m, 1H), 5.06–4.92 (m, 2H), 2.58–2.48 (m, 2H), 2.43 (s, 3H), 2.19–2.00 (m, 2H), 1.89 (s, 3H), 1.85–1.71 (m, 1H), 1.71–1.50 (m, 1H), 1.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.5, 144.1, 142.4, 141.6, 135.5, 135.4, 129.5, 128.3, 117.2, 49.3, 45.8, 36.2, 30.7, 26.1, 21.7, 12.9; IR (Neat

Film NaCl) 3217, 3072, 2953, 2924, 2864, 1706, 1639, 1618, 1598, 1495, 1454, 1401, 1337, 1307, 1292, 1212, 1185, 1168, 1094, 1059, 1029, 996, 914, 870, 850, 830, 813, 706 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{15}H_{19}O_2N_2S$ $[M–C_3H_5]^+$: 291.1167; found 291.1181; $[\_]_D^{25.0}$ +34.25 (*c* 1.05, $CHCl_3$, 88.0% ee).

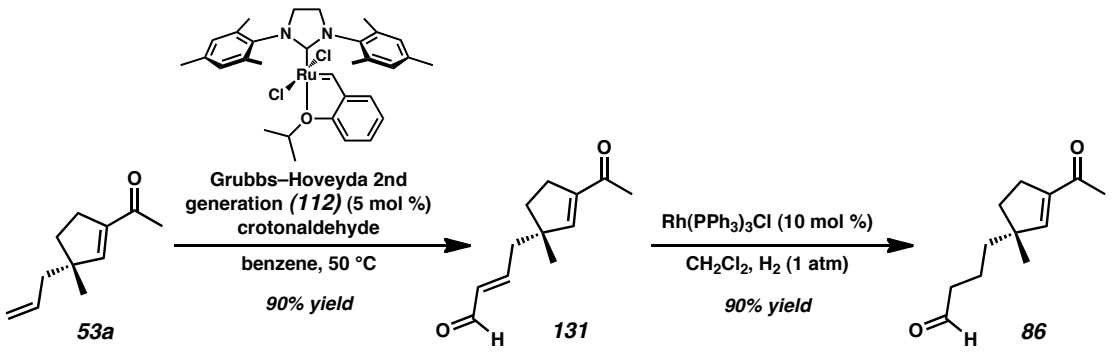


Bis-enone 130. To an oven-dried reaction tube with magnetic stir bar was added acylcyclopentene **53a** (50 mg, 0.304 mmol, 1.00 equiv). The headspace was purged with N_2 and dry degassed toluene (2.0 mL, sparged with N_2 for 1 h immediately before use) was added, followed by methyl vinyl ketone (124 μL, 1.53 mmol, 5.03 equiv). Grubbs–Hoveyda 2nd generation catalyst (9.5 mg, 15.2 μmol, 5 mol %) was quickly added to the reaction, giving the solution an olive green color. A reflux condenser was attached and the reaction was inserted into a 50 °C heating block. The solution quickly developed a dark brown color. After 2 h, the reaction was cooled to ambient temperature. The solution was filtered through a short silica gel plug (2 x 4 cm, Et_2O). The filtrate was concentrated under reduced pressure and the brown residue was purified by flash column chromatography (SiO_2, 2 x 25 cm, 10:1→4:1→2:1→1:1 hexanes:EtOAc) to afford bis-enone **130** (62.3 mg, 0.30 mmol, 99% yield) as a brown liquid; R_f = 0.31 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.71 (ddd, *J* = 15.5, 7.6, 7.6 Hz, 1H),

6.42 (s, 1H), 6.10 (d, J = 15.8 Hz, 1H), 2.68–2.40 (m, 2H), 2.33 (dd, J = 7.6, 0.9 Hz, 2H), 2.28 (s, 3H), 2.22 (s, 3H), 1.84 (ddd, J = 14.7, 8.2, 6.6 Hz, 1H), 1.70 (ddd, J = 13.1, 8.4, 6.1 Hz, 1H), 1.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 197.1, 150.2, 144.3, 143.8, 133.8, 50.1, 43.7, 36.2, 29.8, 27.3, 26.8, 25.7; IR (Neat Film NaCl) 3584, 3318, 2956, 2866, 1697, 1669, 1626, 1454, 1429, 1365, 1308, 1254, 1182, 1098, 1021, 982, 937, 867 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{13}H_{18}O_2$ $[M]^{+\bullet}$: 206.1307; found 206.1303; $[\alpha]_D^{25.0}$ +47.61 (c 1.02, $CHCl_3$, 88.0% ee).

Mono-enone 85. An oven-dried 2-neck flask fitted with a magnetic stir bar, rubber septum, and glass T-joint with 14/20 adapter was charged with bis-enone **130** (50.0 mg, 0.24 mmol, 1.00 equiv) and evacuated/backfilled with N_2 in a glove box antechamber (3 cycles, 5 min evacuation per cycle) before being transferred into the glove box. CH_2Cl_2 (2.5 mL) and $Rh(PPh_3)_3Cl$ (22.4 mg, 0.024 mmol, 10 mol %) were added to the flask, giving a red solution. The flask was sealed with a septum on one neck and T-joint (set to the closed position) on the other neck and carefully brought out of the glove box. A H_2 balloon was attached to the T-joint and the flask was gently evacuated/backfilled with H_2 (3 cycles, 2 min evacuation per cycle). After 10 h of stirring, the brown reaction mixture was filtered through a short silica gel plug (2 x 4 cm, Et_2O) and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 2 x 25 cm, 10:1→4:1→2:1 hexanes:Et_2O) to afford enone **85** (46.8 mg, 0.23 mmol, 93% yield) as an orange liquid; R_f = 0.40 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.43 (app t, J = 1.7 Hz, 1H), 2.65–2.46 (m, 2H), 2.40 (t, J = 7.1 Hz, 2H), 2.27 (s, 3H), 2.11 (s, 3H), 1.88–1.72 (m, 1H), 1.71–1.46 (m, 3H), 1.46–1.29 (m, 2H), 1.08 (s, 3H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 208.8, 197.5, 152.0, 143.6, 50.0, 44.2, 40.4, 36.1, 30.1, 29.7, 26.8, 25.6, 19.4; IR (Neat Film NaCl) 2998, 2953, 2866, 1716, 1667, 1616, 1456, 1427, 1367, 1308, 1270, 1225, 1190, 1170, 1103, 1058, 1021, 841, 871, 726 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{20}O_2$ $[M]^{+\bullet}$: 208.1463; found 208.1460; $[\alpha]_D^{25.0}$ +25.55 (*c* 1.46, $CHCl_3$, 88.0% ee).

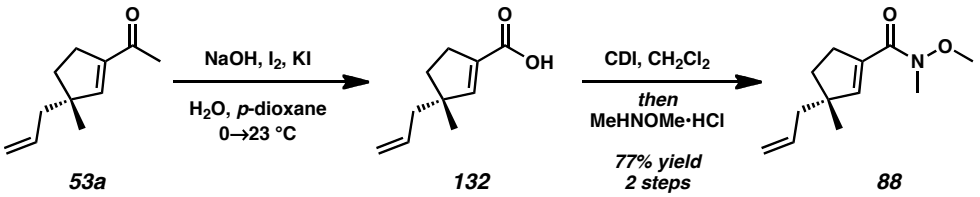


Bis-enone 131. To a 2-neck round-bottomed flask with magnetic stir bar and attached reflux condenser was added acylcyclopentene **53a** (100 mg, 0.608 mmol, 1.00 equiv). The flask was evacuated/backfilled with N_2 (3 cycles, 30 s evacuation per cycle). Dry degassed benzene (8.0 mL, sparged with N_2 for 1 h immediately before use) was added, followed by crotonaldehyde (251 μL, 3.06 mmol, 5.03 equiv). Grubbs–Hoveyda 2nd generation catalyst (19.0 mg, 30.4 μmol, 5 mol %) was quickly added to the reaction, giving the solution an olive green color. The flask was immersed in a 50 °C oil bath. The solution quickly developed a dark brown color. After 2 h, the reaction was cooled to ambient temperature. Several drops of ethyl vinyl ether were added and the reaction mixture was stirred for 5 min. The mixture was concentrated under reduced pressure and the brown residue was purified by flash column chromatography (SiO_2, 2 x 25 cm,

10:1→4:1→2:1 hexanes:EtOAc) to afford bis-enone **131** (105.4 mg, 0.55 mmol, 90% yield) as a brown oil; R_f = 0.38 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.50 (d, *J* = 7.8 Hz, 1H), 6.76 (app dt, *J* = 15.4, 7.6 Hz, 1H), 6.42 (app t, *J* = 1.8 Hz, 1H), 6.13 (app ddt, *J* = 15.5, 7.8, 1.3 Hz, 1H), 2.68–2.50 (m, 2H), 2.45 (dd, *J* = 7.6, 1.3 Hz, 2H), 2.28 (s, 3H), 1.85 (ddd, *J* = 13.1, 8.4, 6.5 Hz, 1H), 1.72 (ddd, *J* = 13.1, 8.5, 6.0 Hz, 1H), 1.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.0, 193.5, 154.0, 149.7, 144.5, 135.6, 50.1, 43.9, 36.1, 29.8, 26.8, 25.8; IR (Neat Film NaCl) 3359, 3317, 3041, 2957, 2928, 2867, 2820, 2743, 2708, 1691, 1668, 1636, 1618, 1456, 1431, 1378, 1369, 1341, 1308, 1269, 1203, 1162, 1149, 1109, 1093, 1036, 1013, 978, 936, 893, 868 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{12}H_{17}O_2$ $[M+H]^+$: 193.1229; found 193.1224; $[\alpha]_D^{25.0}$ +46.07 (*c* 1.13, $CHCl_3$, 88.0% ee).

Mono-enone 86. An oven-dried 2-neck flask fitted with a magnetic stir bar, rubber septum, and a glass T-joint with 14/20 adapter was charged with and bis-enone **131** (42.8 mg, 0.22 mmol, 1.00 equiv) and evacuated/backfilled with N_2 in a glove box antechamber (3 cycles, 5 min evacuation per cycle) before being transferred into the glove box. CH_2Cl_2 (2.5 mL) and $Rh(PPh_3)_3Cl$ (10.3 mg, 0.011 mmol, 5 mol %) were added to the flask, giving a red solution. The flask was sealed with a septum on one neck and T-joint (set to the closed position) on the other neck and carefully brought out of the glove box. A H_2 balloon was attached to the T-joint and the flask was gently evacuated/backfilled with H_2 (five cycles, 2 min evacuation per cycle). After 20 h of stirring, an additional portion of $Rh(PPh_3)_3Cl$ (10.3 mg, 0.011 mmol, 5 mol %) in CH_2Cl_2 (0.5 mL) was added to the reaction using positive pressure cannulation. After 1.5 h of stirring, the reaction

was diluted with Et_2O, filtered through a short silica gel plug (2 x 4 cm, Et_2O), and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 2 x 25 cm, 10:1→4:1 hexanes:Et_2O) to afford enone **86** (39.2 mg, 0.20 mmol, 90% yield) as an pale colorless oil; R_f = 0.48 (2:1 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (t, *J* = 1.5 Hz, 1H), 6.44 (app t, *J* = 1.7 Hz, 1H), 2.59–2.48 (m, 2H), 2.43 (td, *J* = 7.1, 1.4 Hz, 2H), 2.28 (s, 3H), 1.88–1.73 (m, 1H), 1.73–1.51 (m, 3H), 1.51–1.33 (m, 2H), 1.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 197.5, 151.7, 143.8, 50.0, 44.5, 40.4, 36.1, 29.8, 26.8, 25.6, 17.8; IR (Neat Film NaCl) 3427, 3314, 3042, 2951, 2865, 2721, 1723, 1665, 1616, 1457, 1411, 1378, 1367, 1340, 1308, 1269, 1193, 1156, 1105, 1060, 1034, 1020, 970, 942, 867, 801 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{12}H_{18}O_2$ $[M]^{+\bullet}$: 194.1307; found 194.1321; $[\alpha]_D^{25.0}$ +32.50 (*c* 0.69, $CHCl_3$, 88.0% ee).

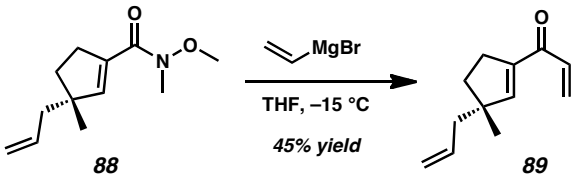


Carboxylic acid 132. A 50 mL round-bottom flask with magnetic stir bar was charged with acylcyclopentene **53a** (200 mg, 1.22 mmol, 1.00 equiv) and *p*-dioxane (10 mL). The solution was cooled to 0 °C and 5 M aqueous NaOH (10 mL) was added dropwise. The white suspension was stirred for 5 min at 0 °C. A dark brown solution of I_2 (1.37 g, 5.40 mmol, 4.40 equiv) and KI (2.09 g, 12.59 mmol, 10.50 equiv) in purified H_2O (10 mL) was added to the reaction dropwise, causing the reaction to become a yellow suspension. After 6.5 h of stirring at 0 °C, an additional portion of I_2 (343 mg, 1.35

mmol, 1.11 equiv) in *p*-dioxane (2 mL) was added to the reaction. After 30 min of stirring at 0 °C, the reaction was acidified to pH 2 using 2 M aqueous HCl. The reaction was extracted with Et_2O (3 x 30 mL) until the organic layer was clear. The combined organic phases were washed with sat. aqueous $K_2S_2O_3$ (2 x 10 mL), H_2O (2 x 10 mL), and brine (2 x 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a yellow semi-solid. The residue was taken up in EtOAc, filtered through a silica gel plug (3 x 3 cm, EtOAc), and concentrated to give carboxylic acid **132** as a pale yellow oil which was used directly in the next step; R_f = 0.35, broad (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.69 (app t, *J* = 1.9 Hz, 1H), 5.89–5.62 (m, 1H), 5.11–4.99 (m, 2H), 2.68–2.47 (m, 2H), 2.26–2.09 (m, 2H), 1.91 (ddd, *J* = 13.0, 8.2, 7.0 Hz, 1H), 1.69 (ddd, *J* = 13.0, 8.2, 6.2 Hz, 1H), 1.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 154.3, 134.8, 133.9, 117.8, 49.8, 45.2, 36.3, 30.3, 25.5; IR (Neat Film NaCl) 3076, 3004, 2956, 2926, 2865, 2610, 1687, 1634, 1454, 1424, 1374, 1348, 1306, 1280, 1216, 1180, 1083, 995, 915, 745, 720 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_7H_9O_2$ $[M–C_3H_5]^+$: 125.0603; found 125.0629; $[\alpha]_D^{25.0}$ +1.43 (*c* 0.80, $CHCl_3$, 88.0% ee).

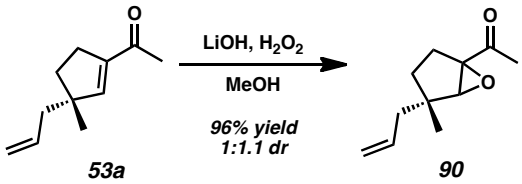
Amide 88. A 50 mL flask with magnetic stir bar was charged with carboxylic acid **132** (202.7 mg, 1.22 mmol, 1.00 equiv) and anhydrous CH_2Cl_2 (4.0 mL). To the vigorously stirred reaction was added 1,1'-carbonyldiimidazole (217 mg, 1.34 mmol, 1.10 equiv) in a portionwise manner. After 15 min, anhydrous *N*,*O*-dimethylhydroxylamine hydrochloride (143 mg, 1.46 mmol, 1.20 equiv) was added portionwise. The reaction became turbid after several min. After 21 h, an additional portion of *N*,*O*-

dimethylhydroxylamine hydrochloride (14.3 mg, 0.146 mmol, 0.12 equiv) was added. At 23.5 h, the reaction was transferred to a separatory funnel, washed with 0.25 M HCl (2 x 2 mL), sat. aqueous $NaHCO_3$, and brine. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 3 x 25 cm, 4:1→3:1 hexanes:EtOAc) to afford amide **88** as a clear oil (196.7 mg, 0.94 mmol, 77% yield over 2 steps); R_f = 0.41 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.26 (app t, *J* = 1.9 Hz, 1H), 5.87–5.68 (m, 1H), 5.09–4.97 (m, 2H), 3.63 (s, 3H), 3.23 (s, 3H), 2.77–2.55 (m, 2H), 2.21–2.11 (m, 2H), 1.83 (ddd, *J* = 12.8, 8.3, 6.4 Hz, 1H), 1.62 (ddd, *J* = 12.7, 8.4, 6.0 Hz, 1H), 1.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 147.0, 135.4, 135.3, 117.4, 61.2, 49.4, 45.4, 35.9, 33.3, 32.9, 25.6; IR (Neat Film NaCl) 3584, 3401, 3078, 2954, 2930, 2864, 1641, 1609, 1454, 1441, 1414, 1378, 1329, 1198, 1177, 1152, 1105, 1043, 997, 969, 914, 812, 723 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{12}H_{20}NO_2$ $[M+H]^+$: 210.1494; found 210.1498; $[\alpha]_D^{25.0}$ +1.41 (*c* 0.98, $CHCl_3$, 88.0% ee).



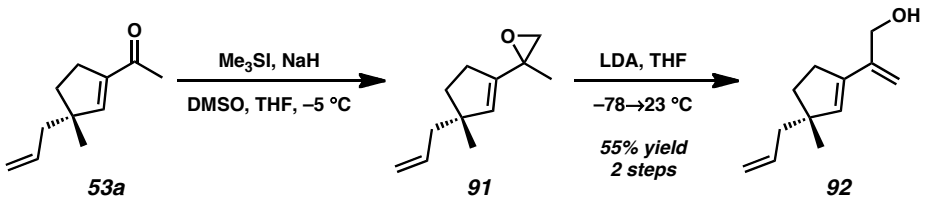
Divinylketone 89. A 25 mL round-bottomed flask with magnetic stir bar was charged with amide **88** (97.0 mg, 0.46 mmol, 1.00 equiv), evacuated/backfilled with N_2 (3 cycles, 5 min evacuation per cycle), dissolved in THF (3.0 mL), and cooled to –15 °C using an ethylene glycol/CO_2(s) bath. The yellow solution became cloudy. Vinylmagnesium bromide solution (1.38 mL, 1.0 M in THF, 1.38 mmol, 3.00 equiv) was added dropwise.

The solution was maintained at –15 °C for 20 min before the flask was allowed to warm to ambient temperature. The reaction was quenched by addition into sat. aqueous NH_4Cl (2.0 mL) using positive pressure cannulation. The mixture was extracted with Et_2O (3 x 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 2 x 25 cm, 0%→1%→2%→3% Et_2O in hexanes) to afford divinylketone **89** (36.2 mg, 0.21 mmol, 45% yield) as a pale yellow liquid; R_f = 0.68 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (dd, *J* = 17.1, 10.5 Hz, 1H), 6.53 (app t, *J* = 1.7 Hz, 1H), 6.28 (dd, *J* = 17.1, 1.9 Hz, 1H), 5.85–5.65 (m, 1H), 5.69 (dd, *J* = 10.5, 1.9 Hz, 1H), 5.11–4.99 (m, 2H), 2.76–2.50 (m, 2H), 2.29–2.09 (m, 2H), 1.87 (ddd, *J* = 12.9, 8.2, 6.8 Hz, 1H), 1.67 (ddd, *J* = 12.9, 8.3, 6.3 Hz, 1H), 1.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.9, 152.1, 143.7, 134.8, 132.6, 127.7, 117.8, 50.3, 45.3, 35.8, 30.1, 25.5; IR (Neat Film NaCl) 3584, 3400, 3078, 2955, 2927, 2866, 1622, 1606, 1453, 1440, 1408, 1374, 1348, 1308, 1255, 1204, 1169, 1059, 981, 956, 915, 783 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_9H_{11}O$ $[M–C_3H_5]^+$: 135.0846; found 135.0810; $[\alpha]_D^{25.0}$ +0.84 (*c* 0.81, $CHCl_3$, 88.0% ee).



Epoxide 90. A solution of acylcyclopentene **53a** (100 mg, 0.609 mmol, 1.00 equiv) in MeOH (6.1 mL) in a 25 mL round-bottom flask was treated with LiOH (7.3 mg, 0.30 mmol, 0.50 equiv) in one portion. Aqueous H_2O_2 (75.0 μL, 83.3 mg, 2.00 equiv, 50% in H_2O) was added dropwise. After 12 h of stirring at ambient temperature additional

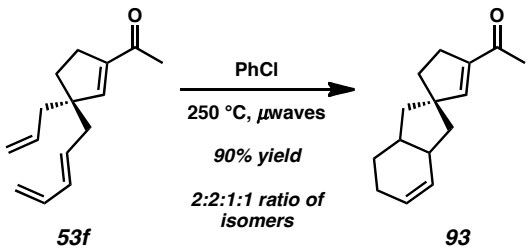
aqueous H_2O_2 (75.0 μL, 83.3 mg, 2.00 equiv, 50% in H_2O) was added. The reaction was stirred for an additional 8 h, diluted with CH_2Cl_2 (10 mL), sat. aqueous $NaHCO_3$ (1.0 mL), and water (1.0 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over Mg_2SO_4, filtered, and concentrated carefully under reduced pressure. The crude product was purified by automated flash column chromatography using a Teledyne Isco CombiFlash R_f (SiO_2, 12 g loading cartridge, 25 g column, linear gradient, 5%→30% Et_2O in pentane [15 min]) to afford epoxide **90** (106 mg, 0.588 mmol, 96% yield) as a colorless fragrant oil and as a 1.1:1 mixture of diastereomers; R_f = 0.54 (4:1 hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90–5.68 (m, 2H), 5.14–5.01 (m, 4H), 3.32 (s, 1H), 3.30 (s, 1H), 2.35–2.21 (m, 4H), 2.07 (s, 3H), 2.07 (s, 3H), 2.05–1.99 (m, 2H), 1.96–1.85 (m, 2H), 1.54–1.49 (m, 1H), 1.33–1.29 (m, 2H), 1.20–1.16 (m, 1H), 1.13 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.8, 205.6, 134.7, 133.6, 118.4, 117.8, 70.3, 70.2, 69.4, 69.3, 42.7, 42.7, 42.4, 42.3, 41.3, 31.9, 31.4, 25.0, 24.8, 24.1, 21.7, 20.5; IR (Neat Film NaCl) 3072, 3002, 2958, 2878, 1706, 1642, 1459, 1444, 1419, 1397, 1360, 1325, 1286, 1261, 1115, 922, 856, 831 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{11}H_{17}$ $[M+H]^+$: 181.1223; found 181.1226; $[\alpha]_D^{25.0}$ –6.94 (*c* 1.40, $CHCl_3$, 88.0 % ee).



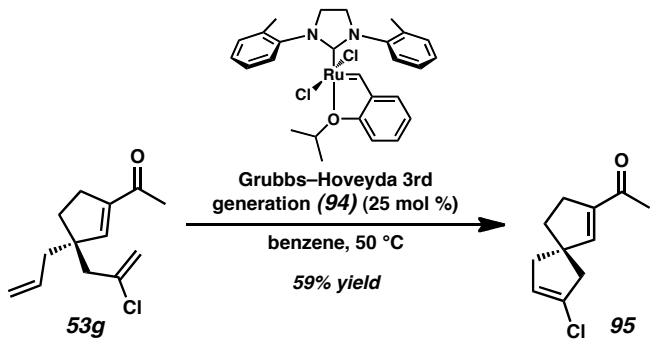
Allylic alcohol 92. NaH (36.5 mg, 0.91 mmol, 3.0 equiv, 60% w/w in mineral oil) was suspended in DMSO (1.2 mL) in a 25 mL round-bottom flask. After 20 min of stirring at ambient temperature, THF (3.7 mL) was added and the resulting mixture was cooled to –5 °C using a water/NaCl/ice bath. Me_3SI (192.3 mg, 0.95 mmol, 3.1 equiv) was dissolved in DMSO (1.2 mL) and added dropwise to the stirred reaction. After an additional 5 min of stirring, acylcyclopentene **53a** (50 mg, 0.30 mmol, 1.0 equiv) was added neat dropwise. After 1.5 h of stirring at –5 °C, the reaction was diluted with Et_2O (15 mL) and quenched by pouring the reaction over 10 g of ice. The phases were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated carefully under reduced pressure, allowing for a film of ice to form on the outside of the flask, to give the volatile crude epoxide **91** as a colorless oil; R_f = 0.60 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.92.1; ^{13}C NMR (100 MHz, $CDCl_3$) mixture of two diastereomers, see Figure A2.92.3; IR (Neat Film NaCl) 3072, 3037, 2953, 2923, 2864, 1637, 1451, 1437, 1385, 1370, 1338, 1259, 1140, 1105, 1066, 994, 910, 856, 846, 806, 730 cm^{-1}; HRMS (APCI+) *m/z* calc'd for $C_{12}H_{19}O$ $[M+H]^+$: 179.1435; found 179.1430.

To a solution of diisopropylamine (0.11 mL, 0.76 mmol, 2.5 equiv) in THF (2.0 mL) in a 10 mL round-bottom flask at 0 °C was added *n*-BuLi (370 µL, 0.76 mmol, 2.05 M in cyclohexane, 2.5 equiv) dropwise over 10 min. After 15 min of stirring, the

reaction was cooled to –78 °C using an acetone/CO_2(s) bath and crude epoxide **91** in THF (1.0 mL) was added dropwise using positive pressure cannulation. The cooling bath was allowed to warm to ambient temperature and the reaction was stirred for 18 h. The reaction was diluted with Et_2O (10 mL) and quenched by addition of a 50:50 (v/v) mixture of sat. aqueous NH_4Cl and water (2.0 mL each). The phases were separated and the aqueous phase was extracted with Et_2O (2 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated carefully under reduced pressure, allowing for a film of ice to form on the outside of the flask, to afford a pale yellow oil. The residue was purified by flash column chromatography (SiO_2, 1 x 22 cm, 20% Et_2O in pentane) to afford allylic alcohol **92** (29.9 mg, 0.17 mmol, 55% yield over 2 steps) as a colorless oil; R_f = 0.25 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82–5.72 (m, 1H), 5.60 (dd, *J* = 1.7, 1.7 Hz, 1H), 5.22 (app q, *J* = 1.4 Hz, 1H), 5.05–5.04 (m, 1H), 5.04–5.01 (m, 1H), 5.01–4.99 (m, 1H), 4.33 (br s, 2H), 2.58–2.45 (m, 2H), 2.17–2.08 (m, 2H), 1.82 (ddd, *J* = 12.7, 8.8, 5.9 Hz, 1H), 1.62 (ddd, *J* = 12.7, 8.8, 5.8 Hz, 1H), 1.51 (br s, 1H), 1.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 139.1, 136.0, 135.9, 116.9, 111.9, 64.3, 49.3, 46.2, 35.9, 32.0, 26.4; IR (Neat Film NaCl) 3325, 3071, 3032, 2948, 2859, 1639, 1600, 1451, 1437, 1414, 1370, 1320, 1226, 1194, 1078, 1029, 994, 910, 848 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{12}H_{17}$ $[M–OH]^+$: 161.1325; found 161.1324; $[\alpha]_D^{25.0}$ +17.59 (c 1.38, $CHCl_3$, 88.0% ee).

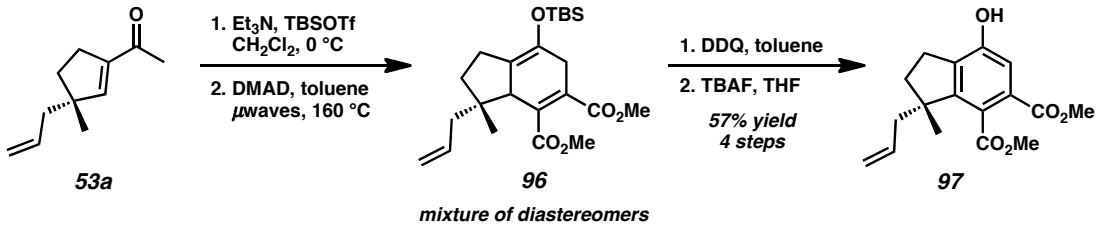


Cyclohexene 93. Acylcyclopentene **53f** (25.2 mg, 0.12 mmol, 1.00 equiv) was added to a 2.0–5.0 mL microwave vial with magnetic stir bar and sealed with a septum-fitted crimp cap. Chlorobenzene (5 mL) was added via syringe. The clear, colorless solution was subjected to microwave irradiation in a Biotage Initiator microwave reactor (temperature: 250 °C, sensitivity: low). After 2 h of irradiation, the vial was uncapped and the solvent was removed under reduced pressure. The yellow residue was purified by flash column chromatography (SiO_2, 1.5 x 15 cm, 15:1 hexanes:Et_2O) to afford cyclohexene **93** as a yellow oil (22.5 mg, 0.104 mmol, 90% yield); R_f = 0.65 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) mixture of four diastereomers (2:2:1:1), see Figure A2.94.1; ^{13}C NMR (125 MHz, $CDCl_3$) mixture of four diastereomers, see Figure A2.94.3; IR (Neat Film NaCl) 3014, 2921, 2855, 1666, 1611, 1448, 1437, 1369, 1339, 1303, 1268, 1190, 1093, 1075, 1051, 1037, 1024, 935, 868, 798, 733, 703 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{15}H_{20}O$ $[M]^{+\bullet}$: 216.1514; found 216.1518; $[\alpha]_D^{25.0}$ –15.57 (*c* 1.01, $CHCl_3$, 88.0% ee).



Spirocycle 95. A 2-neck flask fitted with rubber septum and reflux condenser under N_2 was charged with Grubbs–Hoveyda 3rd generation catalyst (2.2 mg, 0.035 mmol, 6.1 mol %). Dry degassed benzene (4 mL, sparged with N_2 for 1 h immediately before use) was added to give a pale green solution. The flask was evacuated/backfilled with N_2 (3 cycles, 5 min evacuation per cycle). Acylcyclopentene **53g** (14.2 mg, 0.063 mmol, 1.0 equiv) in dry, degassed benzene (4 mL) under N_2 was added to the catalyst solution using positive pressure cannulation. The flask was rinsed with benzene (2 mL) and washes were added into the catalyst solution. The reaction was immersed in a preheated 50 °C oil bath and stirred for 44 h. An additional portion of Grubbs–Hoveyda 3rd generation catalyst (4.4 mg, 0.070 mmol, 12.2 mol %) in degassed benzene (2 mL) was added into the reaction using positive pressure cannulation. After stirring for an additional 15 h, a third portion of Grubbs–Hoveyda 3rd generation catalyst (2.2 mg, 0.035 mmol, 6.1 mol %) in degassed benzene (2 mL) was added into the reaction using positive pressure cannulation. After 31 h, the reaction was treated with several drops of ethyl vinyl ether and allowed to cool to ambient temperature. The solution was diluted with Et_2O (15 mL) and filtered through a short silica gel plug (2 x 10 cm, Et_2O). The orange filtrate was purified by flash column chromatography (SiO_2, 2 x 25 cm, 1%→3%→5%→6.5% Et_2O in hexanes) to give volatile spirocycle **95** (7.3 mg, 0.0376 mmol, 59% yield); R_f = 0.49

(4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 (app t, *J* = 1.7 Hz, 1H), 5.64 (app p, *J* = 2.2 Hz, 1H), 2.66 (ddd, *J* = 16.2, 4.5, 2.1 Hz, 1H), 2.62–2.53 (m, 3H), 2.51 (ddd, *J* = 16.2, 4.6, 2.4 Hz, 1H), 2.43 (ddd, *J* = 16.3, 4.6, 2.4 Hz, 1H), 2.31 (s, 3H), 2.09–1.95 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.3, 150.2, 144.2, 130.7, 125.2, 56.2, 49.7, 44.3, 39.4, 29.6, 26.8; IR (Neat Film NaCl) 2929, 2845, 1726, 1668, 1616, 1436, 1370, 1340, 1314, 1276, 1193, 1079, 1052, 990, 966, 936, 905, 866, 822, 804 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{11}H_{13}OCl$ $[M]^{+\bullet}$: 196.0655; found 196.0655; $[\alpha]_D^{25.0}$ –19.80 (*c* 0.53, $CHCl_3$, 88.0% ee).



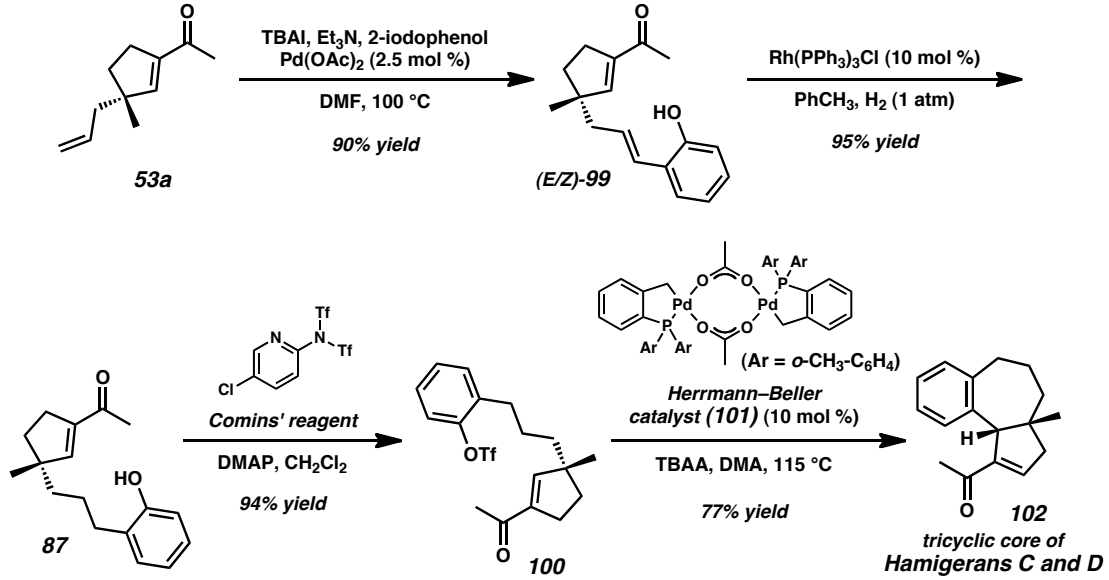
Phenol 97. A 15 mL flask with magnetic stir bar was charged with acylcyclopentene **53a** (50 mg, 0.274 mmol, 1.00 equiv) and anhydrous CH_2Cl_2 (3.0 mL). The flask was cooled to 0 °C and Et_3N (152.8 μL, 1.096 mmol, 4.00 equiv) was added, followed by dropwise addition of TBSOTf (125.8 μL, 0.548 mmol, 2.00 equiv). The reaction became a pale yellow solution. After 1 h of stirring at 0 °C, the reaction was quenched by the addition of sat. aqueous $NaHCO_3$ and slowly allowed to warm to ambient temperature. The mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was filtered through a silica gel plug (2 x 3 cm, 5:1 H:Et_2O) and concentrated under reduced pressure to give crude silyl enol ether as a pale yellow oil. R_f = 0.79 (10:1 hexanes:EtOAc).

The silyl enol ether was added to a 2.0–5.0 mL microwave vial with magnetic stir bar and sealed with a septum-fitted crimp cap. Toluene (5 mL) was added, followed by dimethyl acetylenedicarboxylate (101 μL, 0.822 mmol, 3.00 equiv). The clear, colorless solution was subjected to microwave irradiation in a Biotage Initiator microwave reactor (temperature: 160 °C, sensitivity: low). After 2.5 h of irradiation, the vial was uncapped and solvent was removed under reduced pressure. The yellow residue was purified by flash column chromatography (SiO_2, 3 x 25 cm, 15:1→10:1→4:1→2:1 hexanes:EtOAc) to afford siloxydiene **96** as a mixture of diastereomers. R_f = 0.31 (10:1 hexanes:EtOAc).

A 20 mL scintillation vial with magnetic stir bar was charged with siloxydiene **96** and toluene (3.0 mL). DDQ (63.5 mg, 0.280 mmol, 1.02 equiv) was added portionwise. Upon complete addition, the solution became a turbid red suspension. After 2 h, the reaction was diluted with CH_2Cl_2 and filtered through a Celite plug (2 x 3 cm, CH_2Cl_2). The clear yellow solution was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 2 x 25 cm, 20:1→15:1→10:1→4:1→2:1 hexanes:EtOAc) to afford the intermediate silyl aryl ether. R_f = 0.31 (10:1 hexanes:EtOAc).

A 20 mL scintillation vial with magnetic stir bar was charged with silyl aryl ether. The vial was evacuated, and backfilled with N_2. Anhydrous THF (3 mL) was added and a TBAF solution (300 μL, 1.0 M in THF) was added dropwise, giving a bright red solution. After 10 min, the reaction was quenched by the addition of sat. aqueous NH_4Cl (600 μL) and H_2O (600 μL). The mixture was stirred vigorously for 20 min and extracted with Et_2O (3 x 5 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column

chromatography (SiO_2, 2 x 25 cm, 5:1→4:1 hexanes:EtOAc) to afford phenol **97** as a pale yellow oil (52.6 mg, 0.173 mmol, 57% yield over 4 steps); R_f = 0.11 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (s, 1H), 5.89 (br s, *J* = 1.9 Hz, 1H), 5.66 (dddd, *J* = 17.3, 10.2, 7.9, 7.9 Hz, 1H), 5.09–4.91 (m, 2H), 3.88 (s, 3H), 3.83 (s, 3H), 2.76 (t, *J* = 7.3 Hz, 2H), 2.47–2.26 (m, 2H), 2.24–2.08 (ddd, *J* = 12.0, 7.0, 7.0 Hz, 1H), 1.85–1.70 (ddd, *J* = 12.7, 7.6, 7.6 Hz, 1H), 1.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 166.7, 152.5, 150.0, 135.8, 135.3, 128.3, 124.0, 117.7, 115.4, 52.7, 52.5, 49.4, 44.1, 38.3, 26.1, 25.6; IR (Neat Film NaCl) 3401, 3075, 2953, 2871, 1723, 1639, 1588, 1435, 1418, 1376, 1330, 1311, 1258, 1192, 1175, 1142, 1047, 995, 964, 916, 884, 857, 794, 769, 738, 719 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{20}O_5$ $[M]^{+\bullet}$: 304.1311; found 304.1317; $[\alpha]_D^{25.0}$ –45.63 (*c* 0.91, $CHCl_3$, 88.0% ee).



Phenol 87. DMF (1.52 mL) was sparged with N_2 in a 25 mL Schlenk flask for 1 h. Et_3N (0.849 mL, 6.09 mmol, 5.0 equiv), TBAI (450 mg, 1.22 mmol, 1.0 equiv) and 2-

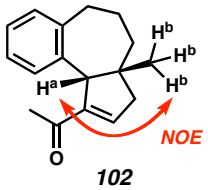
iodophenol (282.2 mg, 1.28 mmol, 1.05 equiv) were added, followed by $Pd(OAc)_2$ (6.84 mg, 0.030 mmol, 2.5 mol %). The flask was carefully evacuated/backfilled with N_2 (3 cycles, 1 min evacuation per cycle) followed by addition of acylcyclopentene **53a** (200 mg, 1.22 mmol, 1.0 equiv). The suspension was immersed in an oil bath at 100 °C. The reaction turned orange within 15 min of stirring. After 5 h of stirring, the reaction was allowed to cool to ambient temperature, diluted with EtOAc (10 mL), and poured into aqueous HCl (10 mL, 1.0 M). The phases were separated and the aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography using a Teledyne Isco CombiFlash R_f system (SiO_2, 12 g loading cartridge, 40 g column, linear gradient, 5%→30% EtOAc in hexanes [25 min]) to afford styrenyl phenol **99** as a mixture of olefin isomers (283.0 mg, 1.10 mmol, 90% yield) as a colorless oil. R_f = 0.17 (4:1 hexanes:EtOAc).

$Rh(PPh_3)_3Cl$ (22.2 mg, 0.024 mmol, 0.10 equiv) was weighed out in a glove box and added to a long reaction tube with magnetic stir bar. Styrenyl phenol **99** (61.5 mg, 0.240 mmol, 1.0 equiv) was dissolved in toluene (4.8 mL) and added to the reaction tube using positive pressure cannulation. H_2 was bubbled through the suspension for 5 min and the reaction tube was fitted with a balloon containing H_2 (1 atm). The reaction was stirred for an additional 6 h at which point TLC analysis indicated complete conversion of the starting material. The resulting clear orange reaction mixture was adsorbed onto a 12 g Isco loading cartridge and purified by flash column chromatography using a Teledyne Isco CombiFlash R_f system (SiO_2, 12 g loading cartridge, 24 g column, linear

gradient, 5%→50% Et_2O in hexanes [40 min]) to afford phenol **87** (58.9 mg, 0.228 mmol, 95% yield) as a pale yellow oil; R_f = 0.18 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13–7.04 (m, 2H), 6.87 (t, *J* = 7.4 Hz, 1H), 6.75 (d, *J* = 7.9 Hz, 1H), 6.46 (app t, *J* = 1.7 Hz, 1H), 4.82 (bs, 1H), 2.60 (t, *J* = 7.3 Hz, 2H), 2.56–2.50 (m, 2H), 2.29 (s, 3H), 1.87–1.75 (m, 1H), 1.71–1.42 (m, 5H), 1.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.9, 153.6, 152.8, 143.4, 130.4, 128.4, 127.3, 120.9, 115.3, 50.1, 40.8, 36.2, 30.8, 29.7, 26.8, 25.8, 25.5; IR (Neat Film NaCl) 3344, 3054, 3039, 2951, 2863, 1651, 1610, 1592, 1507, 1455, 1377, 1365, 1313, 1272, 1238, 1179, 1155, 1127, 1106, 1042, 907, 853, 752 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{23}O_2$ $[M+H]^+$: 259.1693; found 259.1691; $[\alpha]_D^{25.0}$ +28.73 (c 0.74, $CHCl_3$, 88.0% ee).

Triflate 100. To a solution of phenol **87** (104.2 mg, 0.40 mmol, 1.00 equiv) in CH_2Cl_2 (8.0 mL) in a 20 mL vial was added DMAP (97.8 mg, 0.80 mmol, 2.0 equiv) in one portion, followed by *N*,*N*-Bis(trifluoromethylsulfonyl)-5-chloro-2-pyridylamine (172.8 mg, 0.44 mmol, 1.1 equiv). After 15 min of stirring at ambient temperature, TLC revealed full conversion of phenol **87**. The reaction mixture was adsorbed onto a 12 g Isco loading cartridge and purified by flash column chromatography using a Teledyne Isco CombiFlash R_f system (SiO_2, 12 g loading cartridge, 40 g column, linear gradient, 5→20% EtOAc in hexanes [25 min]) to afford triflate **100** (146.2 mg, 0.374 mmol, 94% yield) as a clear, colorless oil; R_f = 0.44. (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.30 (m, 2H), 7.28 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.24 (dm, *J* = 7.8 Hz, 1H), 6.44 (app t, *J* = 1.8 Hz, 1H), 2.69 (t, *J* = 7.7 Hz, 2H), 2.61–2.46 (m, 2H), 2.29 (s, 3H),

1.80 (ddd, J = 13.0, 8.7, 6.5 Hz, 1H), 1.66 (ddd, J = 11.8, 8.0, 5.2 Hz, 1H), 1.64–1.45 (m, 3H), 1.50 (ddd, J = 11.4, 7.5, 5.1 Hz, 1H), 1.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.6, 152.0, 148.1, 143.7, 135.1, 131.3, 128.5, 128.0, 121.5, 118.7 (q, J = 320 Hz, 1C), 50.0, 40.7, 36.1, 30.8, 29.8, 26.8, 25.8, 25.7; IR (Neat Film NaCl) 3032, 2958, 2868, 1671, 1617, 1486, 1454, 1420, 1365, 1303, 1251, 1217, 1140, 1100, 1073, 893, 814, 767 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{18}H_{22}F_3O_4S$ $[M+H]^+$: 391.1188; found 391.1193; $[\alpha]_D^{25.0}$ +22.00 (c 1.31, $CHCl_3$, 88.0% ee).

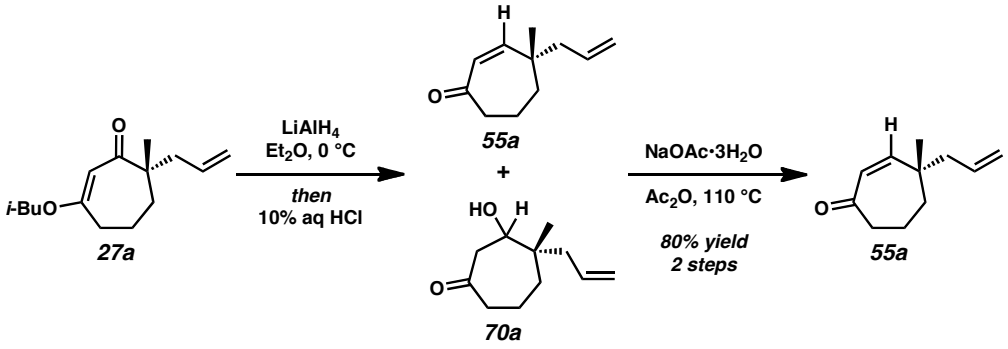


102

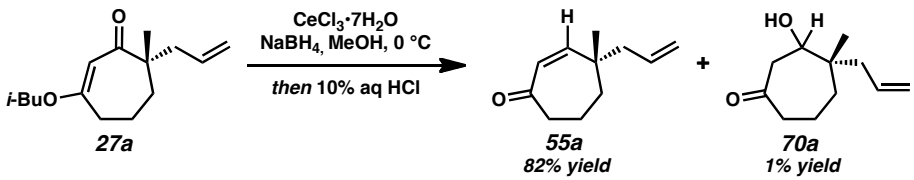
Acylcyclopentene 102. To a solution of triflate **100** (30.0 mg, 0.077 mmol, 1.0 equiv) in dry DMA (1.54 mL) in a 4 dram vial was added TBAA (57.9 mg, 0.19 mmol, 2.5 equiv, stored and weighed out in a glove box). The resulting clear, colorless solution was degassed by bubbling Ar though the solution for 1 h. Herrmann's catalyst[57] (7.2 mg, 7.7 μmol, 0.10 equiv) was placed in a reaction tube which was subsequently evacuated/backfilled with Ar (3 cycles, 1 min evacuation per cycle). The solution containing triflate **100** was added to the catalyst using positive pressure cannulation. The resulting pale green-yellow solution was immersed in an oil bath at ambient temperature and heated to 115 °C. After 2 h of stirring, the reaction was allowed to cool to ambient temperature, diluted with EtOAc (10 mL), and poured into aqueous HCl (1.0 M, 5.0 mL). The phases were separated and the aqueous phase was extracted with EtOAc (10 mL). The combined organics were washed with brine (5.0 mL), dried over $MgSO_4$, filtered,

and concentrated under reduced pressure. The crude product was purified by flash column chromatography using a Teledyne Isco CombiFlash R_f system (SiO_2, 2.5 g loading cartridge, 4 g column, multi-step gradient, hold 5% [10 min]→hold 10% [4 min]→hold 20% [3 min]→ hold 60% EtOAc in hexanes [3 min]) to afford acylcyclopentene **102** (14.3 mg, 0.0595 mmol, 77% yield, 62% yield over 4 steps) as a pale yellow solid. The relative stereochemistry was assigned based on strong NOE interaction between H^a and H^b; R_f = 0.46 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17–7.06 (m, 3H), 6.95 (app t, *J* = 2.4 Hz, 1H), 6.63 (bd, *J* = 6.2 Hz, 1H), 3.86 (s, 1H), 2.92–2.84 (m, 1H), 2.66 (app dd, *J* = 13.5, 7.9 Hz, 1H), 2.41 (s, 3H), 2.32–2.18 (m, 2H) 1.84 (app ddt, *J* = 13.5, 7.7, 5.6 Hz, 1H), 1.58–1.43 (m, 1H), 1.30 (ddd, *J* = 14.0, 5.1, 2.3 Hz, 1H), 1.18 (s, 3H), 0.85 (app dt, *J* = 13.5, 5.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7, 146.2, 144.6, 139.6, 139.2, 128.5, 126.7, 126.2, 125.0, 55.5, 48.4, 43.9, 34.1, 30.6, 26.9, 25.9, 21.4; IR (Neat Film NaCl) 3062, 3012, 2933, 2893, 2859, 1659, 1617, 1476, 1456, 1446, 1370, 1278, 1266, 1244, 1199, 1123, 997, 935, 794, 757, 752, 730 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{21}O$ $[M+H]^+$: 241.1587; found 241.1591; $[\alpha]_D^{25.0}$ +3.88 (*c* 1.43, $CHCl_3$, 88.0% ee).

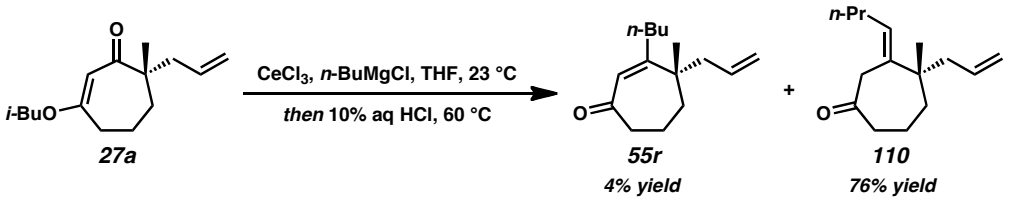
2.1.1.12 REVISED APPROACH TO THE REDUCTION/REARRANGEMENT AND ORGANOMETALLIC ADDITION/REARRANGEMENT OF 27a



Cycloheptenone 55a. A round-bottom flask charged with vinylogous ester **27a** (367.0 mg, 1.55 mmol, 1.00 equiv) and THF (5 mL, 0.3 M) was cooled in a 0 °C ice/water bath and $LiAlH_4$ (34.0 mg, 0.90 mmol, 0.58 equiv) was added. After 25 min of stirring, the reaction was quenched at 0 °C with the addition of aqueous HCl (10 mL, 10% w/w) and transferred to a separatory funnel where the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. To the resulting crude oil was added Ac_2O (3.8 mL) and $NaOAc{\cdot}3H_2O$ (1.28 g, 9.43 mmol, 6.08 equiv) and the mixture was lowered into a preheated oil bath (110 °C). After 15 h of heating, the reaction was allowed to cool to ambient temperature and quenched with K_2CO_3 (5.59 g, 40.5 mmol) and water (10 mL). After an addition 30 min of stirring, the solution was transferred to a separatory funnel where the aqueous phase was extracted with EtOAc (4 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 2 x 16 cm, 20:1 hexanes:EtOAc) to afford cycloheptenone **55a** (203.9 mg, 1.24 mmol, 80% yield) as a pale yellow oil. (For characterization data, see p. 319).

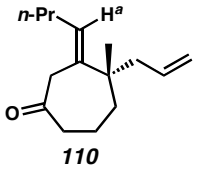


Cycloheptenone 55a and β-Hydroxyketone 70a. A 100 mL round-bottom flask with magnetic stir bar was charged with vinylogous ester **27a** (186.8 mg, 0.79 mmol, 1.00 equiv) and anhydrous MeOH (14 mL). The solution was cooled to 0 °C (water/ice bath). $CeCl_3 \cdot 7H_2O$ (294.5 mg, 0.79 mmol, 1.56 equiv) was added in one portion and the mixture was stirred for 5 min. Portionwise addition of $NaBH_4$ (89.7 mg, 2.37 mmol, 3.00 equiv) at 0 °C led to the evolution of gas and a turbid solution that became clearer after several minutes. TLC analysis indicated that no starting material remained after 2 min. Consequently, the reaction was quenched by dropwise addition of aqueous HCl (2 mL, 10% w/w) at 0 °C. After an additional 10 min of stirring, the reaction was diluted with CH_2Cl_2 (60 mL) and H_2O (2 mL). The layers were separated. The aqueous layer was extracted with CH_2Cl_2 (6 x 5 mL). The combined organic layers were washed with sat. aqueous $NaHCO_3$ (2 x 5 mL) and brine (2 x 5 mL), dried over Na_2SO_4, filtered, and evaporated to give a pale yellow oil. The crude mixture was purified using flash chromatography (SiO_2, 2 x 25 cm, 20:1→15:1→3:1 hexanes:EtOAc) to afford volatile enone **55a** (106.9 mg, 0.645 mmol, 82% yield) as a pale yellow oil and β-hydroxyketone **70a** as a mixture of diastereomers (1.4 mg, 0.0077 mmol, 1% yield, 3.5:1 dr) as a colorless oil. (For characterization data of **55a** and **70a**, see p. 319–320).



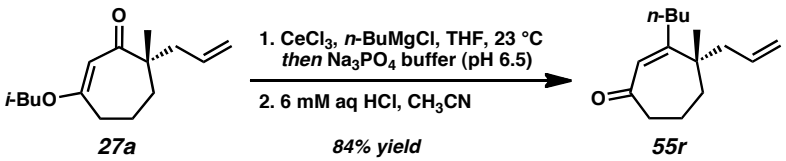
Cycloheptenone 55r and Cycloheptenone Isomer 110. An oven dried 15 mL round-bottom flask equipped with a magnetic stir bar was cycled into a glove box. The flask was loaded with anhydrous cerium chloride (130.4 mg, 0.53 mmol, 2.49 equiv), fitted with a septum, removed from the glove box, and connected to an argon-filled Schlenk manifold. A portion of THF (5.5 mL) was added, rinsing the cerium chloride to the bottom of the flask. As the resulting thick white slurry was stirred, a solution of *n*-butylmagnesium chloride (340 μL, 1.89 M in THF, 0.64 mmol, 3.03 equiv) was added and the mixture turned pale yellow. After 45 min of stirring, neat vinylogous ester **27a** (50.2 mg, 0.21 mmol, 1.00 equiv) was added to the flask. The slurry maintained the yellow color with the addition. TLC analysis indicated that no starting material remained after 5 min. After an additional 10 min of stirring, the reaction was quenched with aqueous HCl (1 mL, 10% w/w) and lowered into a preheated oil bath (60 °C). After 17 h, the yellow suspension was removed from the bath, cooled to ambient temperature, and transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (75 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 1 x 27 cm, 100% hexanes→2%→10% EtOAc in hexanes) to afford moderately contaminated cycloheptenone **55r** and pure alkene isomer **110** (35.4 mg, 0.16 mmol, 76% yield) as an orange oil. Additional purification by flash chromatography (SiO_2, 1 x 27 cm, 100% hexanes→2%→5% EtOAc in hexanes)

furnished cycloheptenone **55r** (1.7 mg at 95% purity, 0.0076 mmol, 4% yield) as a yellow oil. (For characterization data of **55r**, see p. 342).



110

Cycloheptenone Isomer 110. R_f = 0.76 (30% EtOAc in hexanes); The relative alkene stereochemistry was assigned based on NOE interactions of H^a proton; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.66 (dddd, J = 16.9, 10.6, 7.9, 6.6 Hz, 1H), 5.43 (t, J = 7.1 Hz, 1H), 5.03–4.97 (m, 2H), 3.20 (d, J = 14.6 Hz, 1H), 3.13 (d, J = 14.6 Hz, 1H), 2.47–2.38 (m, 1H), 2.36–2.26 (m, 2H), 2.15–1.95 (m, 3H), 1.82–1.69 (m, 2H), 1.66–1.58 (m, 1H), 1.58–1.50 (m, 1H), 1.40–1.32 (m, 2H), 1.07 (s, 3H), 0.88 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.0, 136.2, 135.1, 130.0, 117.2, 44.8, 43.3, 43.3, 41.8, 41.1, 30.2, 25.0, 22.9, 19.6, 13.9; IR (Neat Film NaCl) 3074, 3042, 2959, 2929, 2871, 1706, 1638, 1457, 1436, 1378, 1351, 1302, 1262, 1231, 1163, 1098, 1069, 996, 953, 912, 805, 776, 729 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{15}H_{24}O_2$ $[M]^{+\bullet}$: 220.1827; found 220.1780; $[\alpha]_D^{25.0}$ –10.92 (*c* 0.76, $CHCl_3$, 88.0% ee).



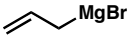
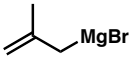
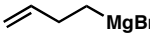
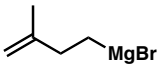
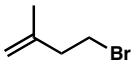
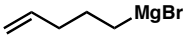
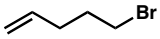
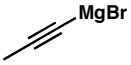
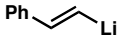
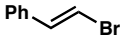
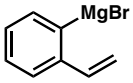
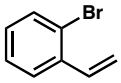
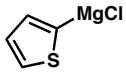
27a ***84% yield*** ***55r***

Cycloheptenone 55r. A 50 mL round-bottom flask equipped with a magnetic stir bar was cycled into a glove box. The flask was loaded with anhydrous cerium chloride

(260.8 mg, 1.06 mmol, 2.50 equiv), fitted with a septum, removed from the glove box, and connected to an argon-filled Schlenk manifold. A portion of THF (8.5 mL) was added, rinsing the cerium chloride to the bottom of the flask. As the resulting thick white slurry was stirred, a solution of *n*-butylmagnesium bromide (680 μL, 1.87 M in THF, 1.27 mmol, 3.00 equiv) was added and the mixture turned grey. After 30 min of stirring, vinylogous ester **27a** (100.0 mg, 0.42 mmol, 1.00 equiv) was added neat from a Hamilton syringe and the needle was rinsed with a small portion of THF (2 mL; total THF added = 10.5 mL, 0.04 M). The color of the slurry initially transitioned to yellow with the vinylogous ester addition before turning back to grey. TLC analysis indicated that no starting material remained after 15 min. After an additional 10 min of stirring, the reaction was quenched with pH 6.5 Na_3PO_4 buffer (8 mL). A thick grey emulsion formed. The mixture was transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (125 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was transferred to a 20 mL scintillation vial and concentrated under reduced pressure. A stir bar, CH_3CN (1.0 mL), and 6 mM aqueous HCl (1.0 mL) were added to the vial. The resulting cloudy solution was stirred vigorously for 5 min before being transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (100 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 3 x 30 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **55r** (82.4 mg, 0.35 mmol, 84% yield) as a pale yellow oil. (For characterization data of **55r**, see p. 342).

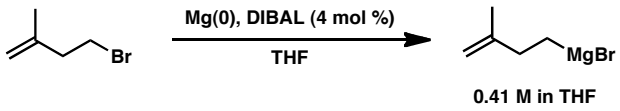
2.1.1.13 GRIGNARD AND ORGANOLITHIUM REAGENTS

Table 2.7. Sources of Grignard and organolithium reagents.[a]

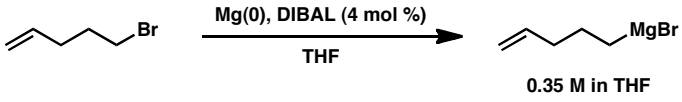
entry	reagent	molarity (M)	obtained from
1		0.86 M in Et_2O	Sigma-Aldrich
2		0.39 M in THF	Sigma-Aldrich
3		0.44 M in THF	Sigma-Aldrich
4		0.41 M in THF	
5		0.35 M in THF	
6		0.25 M in THF	Sigma-Aldrich
7		n/a[b]	
8		0.40 M in THF	
9		n/a[b]	
10		0.44 M in THF	

[a] *Titrated using method of Love (see ref. 49).* [b] *Not titrated.*

Grignard and Organolithium Reagents. Reagents were purchased from Sigma-Aldrich or prepared according to procedures listed below. Reagents were titrated according to the method of Love.[49]

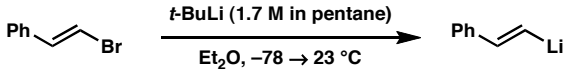


(3-Methylbut-3-enyl)magnesium bromide ***(Table 2.7, entry 4).*** A 250 mL Schlenk bomb (14/20 joint off of a 12 mm Kontes valve) equipped with a magnetic stir bar, fitted with a rubber septum, and connected to a Schlenk manifold was flame-dried three times, backfilling with argon after each drying cycle. Once cool, magnesium metal (2.04 g, 83.79 mmol, 2.50 equiv) was added. After three argon backfilling cycles, the flask was charged with THF (50 mL, 0.7 M) and neat DIBAL[61] (150 μL, 1.29 mmol, 4 mol %) and stirring was initiated. The stirring was stopped after 10 min, and 4-bromo-2-methylbut-1-ene[62] (5.00 g, 33.57 mmol, 1.00 equiv) was added via syringe with the needle in the solution directly above the magnesium. The mixture was heated to reflux, sealed by closing the Schlenk valve, and stirred vigorously. The flask was occasionally heated back to reflux and then allowed to cool to room temperature (23 °C). The reaction color became amber over time. After 30 min, an aliquot was removed and titrated following the procedure of Love (0.41 M in THF).[49] See p. 392 for use of this reagent.

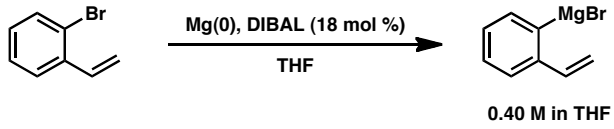


Pent-4-enylmagnesium bromide ***(Table 2.7, entry 5).*** A 250 mL Schlenk bomb (14/20 joint off of a 12 mm Kontes valve) equipped with a magnetic stir bar, fitted with a rubber septum, and connected to a Schlenk manifold was flame-dried three times, backfilling with argon after each drying cycle. Once cool, magnesium metal (614.4 mg, 25.27 mmol, 2.53 equiv) was added. After three argon backfilling cycles, the flask was charged

with THF (20 mL, 0.5 M) and neat DIBAL[59] (50 μL, 0.43 mmol, 4 mol %) and stirring was initiated. The stirring was stopped after 10 min and 5-bromopent-1-ene (1.18 mL, 9.98 mmol, 1.00 equiv) was added via a syringe, with the needle in the solution directly above the magnesium. The mixture was heated to reflux, sealed by closing the Schlenk valve, and stirred vigorously. The flask was occasionally heated back to reflux and then allowed to cool to room temperature (23 °C). The reaction color became amber over time. After 30 min, an aliquot was removed and titrated following the procedure of Love (0.35 M in THF).[49] See p. 381 and p. 393 for use of this reagent.

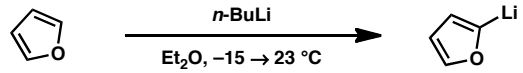


(*E*)-Styryllithium ***(Table 2.7, entry 7).*** See p. 394 for the synthesis and use of this reagent.

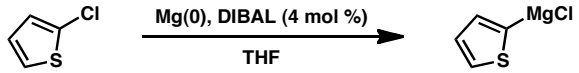


(2-Vinylphenyl)magnesium bromide ***(Table 2.7, entry 8).*** A 250 mL Schlenk round-bottom flask (14/20 joint off of a 12 mm Kontes valve) equipped with a magnetic stir bar, fitted with a rubber septum, and connected to a Schlenk manifold was flame-dried three times, backfilling with argon after each drying cycle. Once cool, magnesium metal (491.3 mg, 20.21 mmol, 2.53 equiv) was added. After three argon backfilling cycles, the flask was charged with THF (16 mL, 0.5 M) and neat DIBAL[59] (170 μL, 1.46 mmol, 18 mol %) and stirring was initiated. The stirring was stopped after 10 min and *o*-

bromostyrene (1.00 mL, 7.98 mmol, 1.00 equiv) was added with the needle in the solution directly above the magnesium. The mixture was heated to reflux, sealed by closing the Schlenk valve, and stirred vigorously. The flask was occasionally heated back to reflux and then allowed to cool to room temperature (23 °C). The reaction became amber over time. After 2 h, a small portion of the reaction was removed and titrated following the procedure of Love.[49] See p. 396 for use of this reagent.



Furan-2-yllithium ***(Table 2.7, entry 9).*** Prepared following a procedure similar to Sauers and Hagedorn.[63] See p. 398 for the synthesis and use of this reagent.



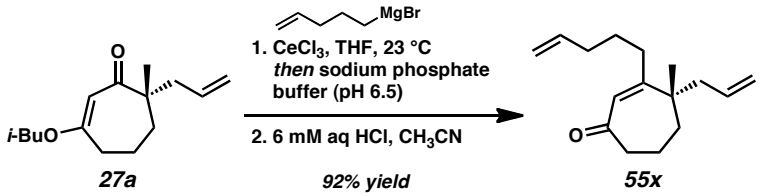
0.44 M in THF

Thiophen-2-ylmagnesium chloride ***(Table 2.7, entry 10).*** A two-neck 50 mL round-bottom flask equipped with a magnetic stir bar, fitted with a rubber septum on one neck and a water condenser on the other neck, and connected to a Schlenk manifold (through the condenser) was flame-dried three times, backfilling with argon after each drying cycle. Once cool, magnesium metal (635.0 mg, 26.12 mmol, 2.60 equiv) was added. After two argon backfilling cycles, the flask was charged with THF (20 mL) and neat DIBAL[59] (50 μL, 0.43 mmol, 4 mol %) and stirring was initiated. The stirring was stopped after 10 min and 2-chlorothiophene (930 μL, 10.04 mmol, 1.00 equiv) was added via a syringe, with the needle in the solution directly above the magnesium. The mixture

was heated to reflux. A small piece of I_2 (size of a spatula tip) dissolved in THF (1 mL) was cannula-transferred into the mixture after 12 h and 13.5 h. The flask was allowed to cool to room temperature (23 °C). After 15 h, an aliquot was removed and titrated following the procedure of Love (0.44 M in THF).[49] See p. 382 and p. 400 for use this reagent.

2.1.1.14 CARBONYL TRANSPOSITION TO γ-QUATERNARY CYCLOHEPTENONES

Representative procedures for General Methods F–H are described below.

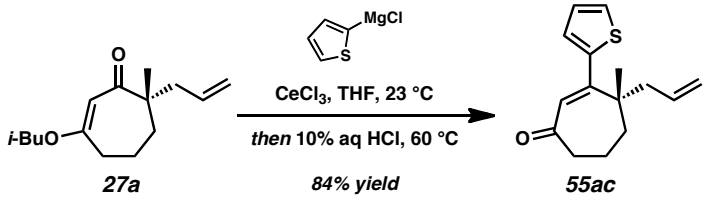


General Method F:

Organometallic Addition / Na_3PO_4 Buffer Quench / Dilute HCl Workup

Cycloheptenone 55x. A 100 mL round-bottom flask equipped with a magnetic stir bar was cycled into a glove box. The flask was loaded with anhydrous cerium chloride (616.2 mg, 2.50 mmol, 2.50 equiv), fitted with a septum, removed from the glove box, and connected to an argon-filled Schlenk manifold. A portion of THF (13 mL) was added, rinsing the cerium chloride to the bottom of the flask. As the resulting thick white slurry was stirred, a solution of pent-4-enylmagnesium bromide (8.6 mL, 0.35 M in THF, 3.01 mmol, 3.01 equiv) was added and the mixture turned grey. After 30 min of stirring,

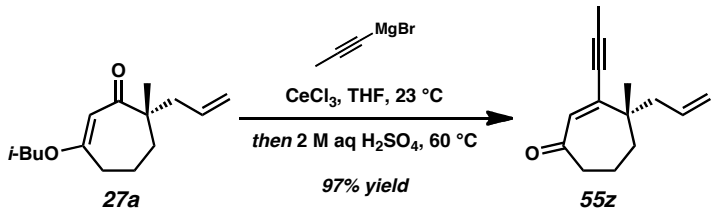
vinylogous ester **27a** (236.3 mg, 1.00 mmol, 1.00 equiv) was cannula-transferred to the slurry from a flame-dried 10 mL conical flask using several THF rinses (3 x 4 mL; total THF added = 25 mL, 0.04 M). TLC analysis indicated that no starting material remained after 5 min. After an additional 10 min of stirring, the reaction was quenched with pH 6.5 Na_3PO_4 buffer (20 mL). A thick grey emulsion formed. The mixture was transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organic (150 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was transferred to a 20 mL scintillation vial and concentrated under reduced pressure. A stir bar, CH_3CN (2.0 mL), and aqueous HCl (2.0 mL, 6 mM) were added to the vial. The resulting cloudy solution was stirred vigorously for 30 min before being transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (75 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 3 x 30 cm, 100% hexanes→1%→2%→5% EtOAc in hexanes) to afford cycloheptenone **55x** (214.2 mg, 0.92 mmol, 92% yield) as a clear colorless oil.



General Method G: Organometallic Addition / Aq HCl Quench

Cycloheptenone 55ab. A 100 mL round-bottom flask equipped with a magnetic stir bar was cycled into a glove box. The flask was loaded with anhydrous cerium chloride (616.2 mg, 2.50 mmol, 2.50 equiv), fitted with a septum, removed from the glove box,

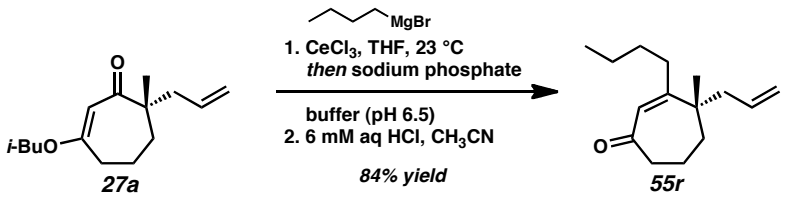
and connected to an argon-filled Schlenk manifold. A portion of THF (13 mL) was added, rinsing the cerium chloride to the bottom of the flask. As the resulting thick white slurry was stirred, a solution of thiophen-2-ylmagnesium chloride (6.8 mL, 0.44 M in THF, 2.99 mmol, 2.99 equiv) was added and the mixture turned dark grey. After 30 min of stirring, vinylogous ester **27a** (236.4 mg, 1.00 mmol, 1.00 equiv) was cannula-transferred to the slurry from a flame-dried 10 mL conical flask using several THF rinses (3 x 4 mL; total THF added = 25 mL, 0.04 M). TLC analysis indicated that no starting material remained after 25 min. After an additional 5 min of stirring, the reaction was quenched with aqueous HCl (5 mL, 10% w/w) and lowered into a preheated oil bath (60 °C). After 20 h, additional aqueous HCl (5 mL, 10% w/w) was added. After 26 h, the yellow solution was removed from the bath, cooled to ambient temperature, treated with sat. aqueous $NaHCO_3$ solution (25 mL), and transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (150 mL) were rinsed once with sat. aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 3 x 30 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **55ac** (206.1 mg, 0.84 mmol, 84% yield) as a yellow/orange oil.



General Method H: Organometallic Addition / Aq H_2SO_4 Quench

Cycloheptenone 55z. A 100 mL round-bottom flask equipped with a magnetic stir bar was cycled into a glove box. The flask was loaded with anhydrous cerium chloride (616.2 mg, 2.50 mmol, 2.50 equiv), fitted with a septum, removed from the glove box, and connected to an argon-filled Schlenk manifold. A portion of THF (13 mL) was added, rinsing the cerium chloride to the bottom of the flask. As the resulting thick white slurry was stirred, a solution of prop-1-ynylmagnesium bromide (12 mL, 0.25 M in THF, 3.00 mmol, 3.00 equiv) was added and the mixture turned yellow. After 30 min of stirring, vinylogous ester **27a** (236.4 mg, 1.00 mmol, 1.00 equiv) was cannula-transferred to the slurry from a flame-dried 10 mL conical flask using several THF rinses (3 x 4 mL; total THF added = 25 mL, 0.04 M). The slurry maintained the yellow color with the addition. TLC analysis indicated that no starting material remained after 5 min. After an additional 10 min of stirring, the reaction was quenched with 2 M H_2SO_4 (5 mL) and lowered into a preheated oil bath (60 °C). A white precipitate formed within several minutes. After 12 h, the yellow suspension was removed from the bath, cooled to ambient temperature, treated with sat. aqueous $NaHCO_3$ solution (50 mL), and transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (175 mL) were rinsed once with sat. aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was

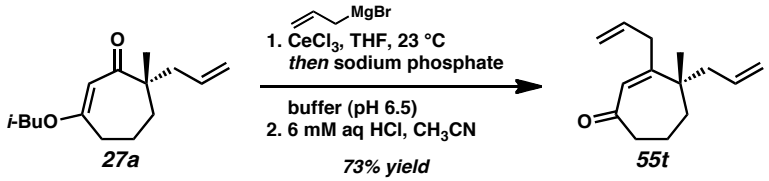
purified by flash chromatography (SiO_2, 3 x 30 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **55z** (195.4 mg, 0.97 mmol, 97% yield) as a yellow oil.



Cycloheptenone 55r ***(Table 2.5, entry 1).*** Prepared using General Method F. A 50 mL round-bottom flask equipped with a magnetic stir bar, fitted with a rubber septum, and connected to a Schlenk manifold was flame-dried three times, backfilling with argon after each drying cycle. The hot flask was placed into a glove box antechamber, which was evacuated/backfilled with N_2 (3 cycles, 5 min evacuation per cycle) before the flask was brought into the glove box. The flask was loaded with anhydrous cerium chloride (260.8 mg, 1.06 mmol, 2.50 equiv), refitted with the septum, removed from the glove box, and reconnected to the argon-filled Schlenk manifold. A portion of THF (8.5 mL) was added, rinsing the cerium chloride to the bottom of the flask. As the resulting thick white slurry was stirred, a solution of *n*-butylmagnesium bromide (680 μL, 1.87 M in THF, 1.27 mmol, 3.00 equiv) was added and the mixture turned grey. After 30 min of stirring, vinylogous ester **27a** (100.0 mg, 0.42 mmol, 1.00 equiv) was added neat from a Hamilton syringe and the needle was rinsed with a small portion of THF (2 mL; total THF added = 10.5 mL, 0.04 M). The color of the slurry initially transitioned to yellow with the vinylogous ester addition before turning back to grey.

TLC analysis indicated that no starting material remained after 15 min. After an additional 10 min of stirring, the reaction was quenched with pH 6.5 Na_3PO_4 buffer (8

mL). A thick grey emulsion formed. The mixture was transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (125 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was transferred to a 20 mL scintillation vial and concentrated under reduced pressure. A stir bar, CH_3CN (1.0 mL), and 6 mM aqueous HCl (1.0 mL) were added to the vial. The resulting cloudy solution was stirred vigorously for 5 min before being transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (100 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 3 x 30 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **55r** (82.4 mg, 0.35 mmol, 84% yield) as a pale yellow oil. (For characterization data, see p. 342).

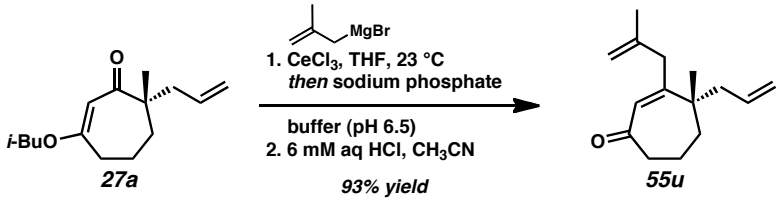


Cycloheptenone 55t ***(Table 2.5, entry 2).*** Prepared using General Method F. A 100 mL round-bottom flask equipped with a magnetic stir bar, fitted with a rubber septum, and connected to a Schlenk manifold was flame-dried three times, backfilling with argon after each drying cycle. The hot flask was placed into a glove box antechamber, which was evacuated/backfilled with N_2 (3 cycles, 5 min evacuation per cycle) before the flask was brought into the glove box. The flask was loaded with anhydrous cerium chloride (616.3 mg, 2.50 mmol, 2.50 equiv), refitted with the septum, removed from the glove

box, and reconnected to the argon-filled Schlenk manifold. A portion of THF (13 mL) was added, rinsing the cerium chloride to the bottom of the flask. As the resulting thick white slurry was stirred, a solution of allylmagnesium bromide (3.49 mL, 0.86 M in Et_2O, 3.00 mmol, 3.00 equiv) was added and the mixture turned initially orange, then red over time. After 30 min of stirring, vinylogous ester **27a** (236.6 mg, 1.00 mmol, 1.00 equiv) was cannula-transferred to the slurry from a flame-dried 10 mL conical flask using several THF rinses (3 x 4 mL; total THF added = 25 mL, 0.04 M). The mixture faded back to orange with the addition.

TLC analysis indicated that no starting material remained after 5 min. After an additional 10 min of stirring, the reaction was quenched with pH 6.5 Na_3PO_4 buffer (20 mL). A thick grey emulsion formed. The mixture was transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (250 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was transferred to a 20 mL scintillation vial and concentrated under reduced pressure. A stir bar, CH_3CN (2.0 mL), and 6 mM aqueous HCl (2.0 mL) were added to the vial. The resulting cloudy solution was stirred vigorously for 30 min before being transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (75 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 3 x 30 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **55t** (148.6 mg, 0.73 mmol, 73% yield) as a pale yellow oil; R_f = 0.68 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (s, 1H), 5.75 (dddd, *J* = 16.9, 10.1, 6.8, 6.8 Hz, 1H), 5.64 (dddd, *J* = 17.0, 10.3, 7.8, 6.8 Hz, 1H), 5.14–5.00 (m,

4H), 2.96–2.84 (m, 2H), 2.62–2.54 (m, 2H), 2.38 (dddd, J = 14.2, 6.8, 1.3, 1.3 Hz, 1H), 2.10 (dddd, J = 14.2, 7.8, 1.1, 1.1 Hz, 1H), 1.84–1.76 (m, 3H), 1.67–1.57 (m, 1H), 1.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.2, 160.3, 136.0, 134.0, 130.0, 118.3, 117.9, 45.5, 45.2, 44.4, 38.8, 38.5, 25.7, 17.6; IR (Neat Film NaCl) 3077, 2976, 2939, 2872, 1654, 1612, 1458, 1412, 1380. 1342, 1290, 1250, 1217, 1177, 1106, 996, 916 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{14}H_{21}O$ $[M+H]^+$: 205.1587; found 205.1587; $[\alpha]_D^{25.0}$ –34.64 (*c* 1.55, $CHCl_3$, 88% ee).

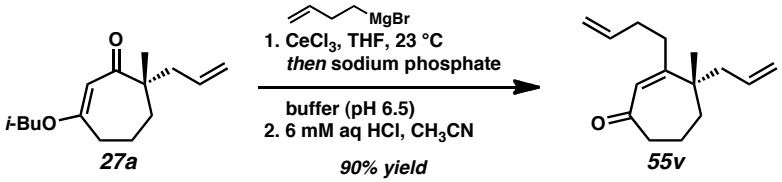


Cycloheptenone 55u ***(Table 2.5, entry 3).*** Prepared using General Method F. A 100 mL round-bottom flask equipped with a magnetic stir bar, fitted with a rubber septum, and connected to a Schlenk manifold was flame-dried three times, backfilling with argon after each drying cycle. The hot flask was placed into a glove box antechamber, which was evacuated/backfilled with N_2 (3 cycles, 5 min evacuation per cycle) before the flask was brought into the glove box. The flask was loaded with anhydrous cerium chloride (616.2 mg, 2.50 mmol, 2.50 equiv), refitted with the septum, removed from the glove box, and reconnected to the argon-filled Schlenk manifold. A portion of THF (13 mL) was added, rinsing the cerium chloride to the bottom of the flask. As the resulting thick white slurry was stirred, a solution of (2-methylallyl)magnesium bromide (7.7 mL, 0.39 M in THF, 3.00 mmol, 3.00 equiv) was added and the mixture turned initially yellow and eventually orange with time. After 30 min of stirring, vinylogous ester **27a** (236.2 mg,

1.00 mmol, 1.00 equiv) was cannula-transferred to the slurry from a flame-dried 10 mL conical flask using several THF rinses (3 x 4 mL; total THF added = 25 mL, 0.04 M).

TLC analysis indicated that no starting material remained after 5 min. After an additional 15 min of stirring, the reaction was quenched with pH 6.5 Na_3PO_4 buffer (20 mL). A thick grey emulsion formed. The mixture was transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (150 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was transferred to a 20 mL scintillation vial and concentrated under reduced pressure. A stir bar, CH_3CN (2.0 mL), and 6 mM aqueous HCl (2.0 mL) were added to the vial. The resulting cloudy solution was stirred vigorously for 30 min before being transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (75 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 3 x 30 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **55u** (202.9 mg, 0.93 mmol, 93% yield) as a pale yellow oil; R_f = 0.65 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (s, 1H), 5.65 (dddd, *J* = 16.9, 10.3, 7.8, 6.8 Hz, 1H), 5.09–5.01 (m, 2H), 4.94–4.91 (m, 1H), 4.78 (dd, *J* = 1.9, 0.9 Hz, 1H), 2.85 (q, *J* = 16.2 Hz, 2H), 2.63–2.55 (m, 2H), 2.37 (dddd, *J* = 14.1, 6.8, 1.3, 1.3 Hz, 1H), 2.10 (dddd, *J* = 14.2, 7.8, 1.1, 1.1 Hz, 1H), 1.85–1.75 (m, 3H), 1.68 (s, 3H), 1.66–1.59 (m, 1H), 1.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.3, 159.1, 142.8, 134.0, 129.5, 118.3, 115.2, 45.4, 45.0, 44.4, 42.7, 38.8, 25.6, 22.2, 17.6; IR (Neat Film NaCl) 3075, 2970, 2939, 2872, 1661, 1652, 1612, 1455, 1376, 1342, 1309, 1249, 1218,

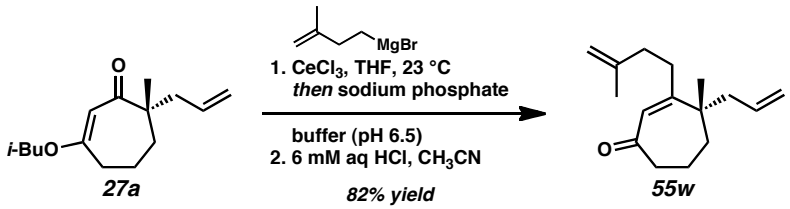
996, 914, 893 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{23}O$ $[M+H]^+$: 219.1743; found 219.1740; $[\alpha]_D^{25.0}$ –35.09 (*c* 0.95, $CHCl_3$, 88% ee).



Cycloheptenone 55v ***(Table 2.5, entry 4).*** Prepared using General Method F. A 100 mL round-bottom flask equipped with a magnetic stir bar, fitted with a rubber septum, and connected to a Schlenk manifold was flame-dried three times, backfilling with argon after each drying cycle. The hot flask was placed into a glove box antechamber, which was evacuated/backfilled with N_2 (3 cycles, 5 min evacuation per cycle) before the flask was brought into the glove box. The flask was loaded with anhydrous cerium chloride (616.2 mg, 2.50 mmol, 2.50 equiv), refitted with the septum, removed from the glove box, and reconnected to the argon-filled Schlenk manifold. A portion of THF (13 mL) was added, rinsing the cerium chloride to the bottom of the flask. As the resulting white mixture was stirred, a solution of but-3-enylmagnesium bromide (6.82 mL, 0.44 M in THF, 3.00 mmol, 3.00 equiv) was added, generating a thick grey slurry. After 30 min of stirring, vinylogous ester **27a** (236.4 mg, 1.00 mmol, 1.00 equiv) was cannula-transferred to the slurry from a flame-dried 10 mL conical flask using several THF rinses (3 x 4 mL; total THF added = 25 mL, 0.04 M).

After 20 min, the reaction was quenched with pH 6.5 Na_3PO_4 buffer (20 mL). A thick grey emulsion formed. The mixture was transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organic (150 mL)

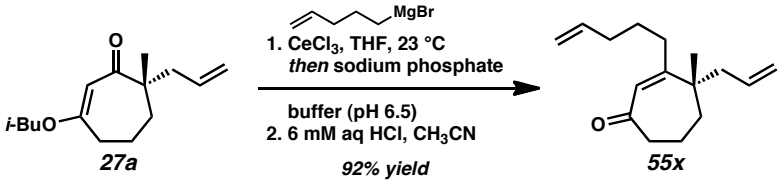
were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was transferred to a 20 mL scintillation vial and concentrated under reduced pressure. A stir bar, CH_3CN (2.0 mL), and 6 mM aqueous HCl (2.0 mL) were added to the vial. The resulting cloudy solution was stirred vigorously for 5 min before being transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (80 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 3 x 30 cm, 100% hexanes→2%→5%→10% EtOAc in hexanes) to afford cycloheptenone **55v** (196.6 mg, 0.90 mmol, 90% yield) as a yellow oil; R_f = 0.67 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (s, 1H), 5.86–5.77 (m, 1H), 5.63 (dddd, *J* = 16.9, 10.3, 7.8, 6.8 Hz, 1H), 5.08–4.96 (m, 4H), 2.59–2.54 (m, 2H), 2.36 (dddd, *J* = 14.1, 6.7, 1.3, 1.3 Hz, 1H), 2.28–2.17 (m, 4H), 2.08 (dddd, *J* = 14.1, 7.9, 2.1, 1.0 Hz, 1H), 1.83–1.73 (m, 3H), 1.65–1.57 (m, 1H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.2, 161.6, 137.7, 134.0, 128.9, 118.2, 115.4, 45.7, 45.2, 44.3, 38.7, 34.0, 33.4, 25.7, 17.6; IR (Neat Film NaCl) 3076, 2975, 2938, 2872, 1652, 1611, 1465, 1452, 1415, 1379, 1342, 1263, 1218, 1177, 1109, 1069, 996, 914, 877, 841, 764, 714 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{23}O$ $[M+H]^+$: 219.1743; found 219.1742; $[\alpha]_D^{25.0}$ –34.11 (*c* 1.21, $CHCl_3$, 88% ee).



Cycloheptenone 55w ***(Table 2.5, entry 5).*** Prepared using General Method F. A 100 mL round-bottom flask equipped with a magnetic stir bar, fitted with a rubber septum, and connected to a Schlenk manifold was flame-dried three times, backfilling with argon after each drying cycle. The hot flask was placed into a glove box antechamber, which was evacuated/backfilled with N_2 (3 cycles, 5 min evacuation per cycle) before the flask was brought into the glove box. The flask was loaded with anhydrous cerium chloride (616.2 mg, 2.50 mmol, 2.50 equiv), refitted with the septum, removed from the glove box, and reconnected to the argon-filled Schlenk manifold. A portion of THF (13 mL) was added, rinsing the cerium chloride to the bottom of the flask. As the resulting thick white slurry was stirred, a solution of (3-methylbut-3-enyl)magnesium bromide (7.3 mL, 0.41 M in THF, 2.99 mmol, 2.99 equiv) was added and the mixture turned yellow. After 30 min of stirring, vinylogous ester **27a** (236.4 mg, 1.00 mmol, 1.00 equiv) was cannula-transferred to the slurry from a flame-dried 10 mL conical flask using several THF rinses (3 x 4 mL; total THF added = 25 mL, 0.04 M).

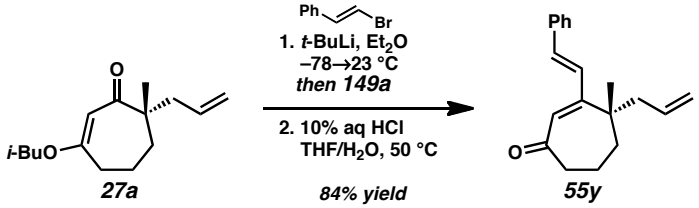
TLC analysis indicated that no starting material remained after 5 min. After an additional 10 min of stirring, the reaction was quenched with pH 6.5 Na_3PO_4 buffer (20 mL). A thick grey emulsion formed. The mixture was transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organic (150 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was transferred to a 20 mL scintillation vial and concentrated under

reduced pressure. A stir bar, CH_3CN (2.0 mL), and 6 mM aqueous HCl (2.0 mL) were added to the vial. The resulting cloudy solution was stirred vigorously for 5 min before being transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (75 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 3 x 30 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **55w** (191.1 mg, 0.82 mmol, 82% yield) as a clear colorless oil; R_f = 0.69 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (s, 1H), 5.64 (dddd, *J* = 16.9, 10.3, 7.8, 6.8 Hz, 1H), 5.09–4.99 (m, 2H), 4.77–4.73 (m, 1H), 4.72–4.69 (m, 1H), 2.59–2.56 (m, 2H), 2.38 (dddd, *J* = 14.1, 6.7, 1.3, 1.3 Hz, 1H), 2.31–2.14 (m, 4H), 2.10 (dddd, *J* = 14.1, 7.8, 1.1, 1.1 Hz, 1H), 1.83–1.75 (m, 3H), 1.75–1.74 (m, 3H), 1.66–1.57 (m, 1H), 1.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.3, 162.1, 145.1, 134.0, 129.0, 118.3, 110.6, 45.8, 45.3, 44.3, 38.8, 38.3, 32.5, 25.7, 22.7, 17.6; IR (Neat Film NaCl) 3075, 2968, 2938, 2873, 1652, 1611, 1455, 1415, 1377, 1342, 1262, 1218, 1181, 1109, 1069, 996, 915, 887 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{25}O$ $[M+H]^+$: 233.1900; found 233.1896; $[\alpha]_D^{25.0}$ –32.57 (*c* 1.32, $CHCl_3$, 88% ee).



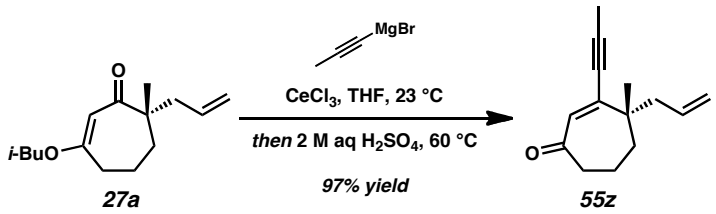
Cycloheptenone 55x ***(Table 2.5, entry 6).*** Prepared using General Method F. See procedure described above. R_f = 0.65 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (s, 1H), 5.79 (dddd, *J* = 16.9, 10.2, 6.7, 6.7 Hz, 1H), 5.67–5.57 (m, 1H),

5.07–4.96 (m, 4H), 2.60–2.53 (m, 2H), 2.35 (dddd, J = 14.1, 6.7, 2.5, 1.2 Hz, 1H), 2.20–2.04 (m, 5H), 1.83–1.73 (m, 3H), 1.66–1.53 (m, 3H), 1.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.3, 162.6, 138.2, 134.1, 128.8, 118.2, 115.3, 45.7, 45.2, 44.3, 38.7, 33.8, 33.5, 29.3, 25.7, 17.6; IR (Neat Film NaCl) 3076, 2975, 2937, 2870, 1652, 1611, 1456, 1415, 1380, 1343, 1257, 1218, 1179, 1110, 1071, 994, 913 cm^{-1}; HRMS (MM: ESI-APCI+) m/z calc'd for $C_{16}H_{25}O$ $[M+H]^+$: 233.1900; found 233.1900; $[\alpha]_D^{25.0}$ –34.96 (*c* 1.46, $CHCl_3$, 88% ee).

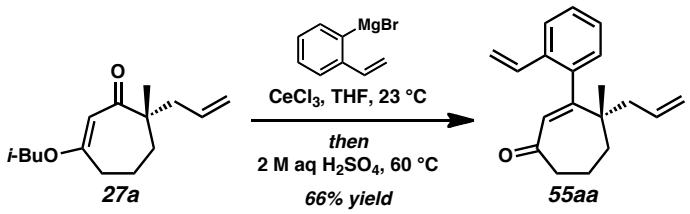


Cycloheptenone 55y ***(Table 2.5, entry 7).*** Prepared using General Method G. A flame-dried round-bottom flask equipped with a magnetic stir bar and fitted with a rubber septum was connected to a Schlenk manifold. The flask was charged with (*E*)-β-bromostyrene (1.5 mL, 11.69 mmol, 1.98 equiv) and Et_2O (13 mL) and lowered into a dry ice/acetone bath (–78 °C). After dropwise addition of *t*-butyllithium (13.5 mL, 1.7 M in pentane, 22.95 mmol, 3.88 equiv), the solution was stirred for 2 h (at –78 °C), warmed to room temperature (30 min stir at 23 °C), and placed back into the dry ice/acetone bath. Vinylogous ester **27a** (1.40 g, 5.92 mmol, 1.00 equiv) was transferred to the round-bottom flask by two Et_2O rinses (2 x 3 mL, total Et_2O added = 19 mL, 0.3 M). The flask was stirred at –78 °C for 25 min before being transferred to an ice/water bath (0 °C).

TLC analysis indicated that no starting material remained after 2 h. Consequently, the reaction was quenched with 10% w/w aqueous HCl (10 mL). After 20 min of stirring, the mixture was transferred to a separatory funnel where the aqueous phase was extracted three times with Et_2O. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. A round-bottom flask was charged with the crude oil, THF (20 mL), and 10% w/w aqueous HCl (0.5 mL) and lowered into a preheated oil bath (50 °C). After 2 h, the reaction allowed to cool to room temperature, concentrated under reduced pressure, diluted with water (10 mL) and Et_2O (20 mL), and transferred to a separatory funnel where the aqueous layer was extracted twice with Et_2O (2 x 20 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 3 x 23 cm, 20:1→ 15:1→10:1 hexanes:EtOAc) to afford cycloheptenone **55y** (1.33 g, 4.99 mmol, 84% yield) as a yellow oil; R_f = 0.67 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.3 Hz, 2H), 7.35 (d, *J* = 7.4 Hz, 2H), 7.28 (d, *J* = 7.3 Hz, 1H), 6.90 (s, 2H), 6.30 (s, 1H), 5.67 (dddd, *J* = 16.8, 10.3, 8.1, 6.5 Hz, 1H), 5.09–5.02 (m, 2H), 2.71–2.57 (m, 2H), 2.46 (dddd, *J* = 14.1, 6.5, 1.3, 1.3 Hz, 1H), 2.14 (dddd, *J* = 14.1, 8.1, 1.1, 1.1 Hz, 1H), 1.92–1.79 (m, 3H), 1.72–1.64 (m, 1H), 1.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7, 158.5, 136.7, 133.9, 133.3, 129.2, 128.9, 128.5, 127.1, 127.1, 118.4, 46.2, 44.5, 44.4, 38.7, 26.8, 17.6; IR (Neat Film NaCl) 3075, 3059, 3002, 2966, 2936, 2869, 1640, 1581, 1573, 1495, 1449, 1414, 1379. 1343, 1303, 12.77, 1250, 1217, 1178, 1109, 1082, 1028, 996, 963, 916, 839, 799, 752, 718 cm^{-1}; HRMS (MM: ESI-APCI+) *m*/*z* calc'd for $C_{19}H_{23}O$ $[M+H]^+$: 267.1743; found 267.1755; $[\alpha]_D^{25.0}$ –44.99 (*c* 0.81, $CHCl_3$, 88% ee).



Cycloheptenone 55z ***(Table 2.5, entry 8).*** Prepared using General Method H. See procedure described above. R_f = 0.65 (30% EtoAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (s, 1H), 5.70 (dddd, *J* = 16.8, 10.5, 8.2, 6.6 Hz, 1H), 5.10–5.01 (m, 2H), 2.65–2.49 (m, 3H), 2.16 (dddd, *J* = 13.8, 8.2, 1.0, 1.0 Hz, 1H), 2.01 (s, 3H), 1.83–1.75 (m, 3H), 1.66–1.59 (m, 1H), 1.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.5, 145.6, 135.0, 134.3, 118.3, 92.9, 80.7, 46.5, 45.4, 44.6, 37.3, 27.0, 17.6, 4.7; IR (Neat Film NaCl) 3076, 2969, 2937, 2219, 1652, 1580, 1455, 1415, 1377, 1346, 1255, 1225, 1184, 1110, 998, 916, 893, 866, 813, 784, 716 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{14}H_{19}O$ $[M+H]^+$: 203.1430; found 203.1428; $[\alpha]_D^{25.0}$ –49.25 (*c* 1.21, $CHCl_3$, 88% ee).

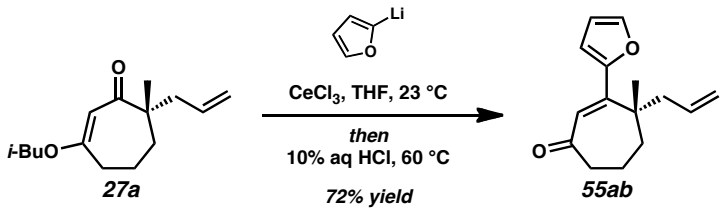


Cycloheptenone 55aa ***(Table 2.5, entry 9).*** Prepared using General Method H. A 100 mL round-bottom flask equipped with a magnetic stir bar, fitted with a rubber septum, and connected to a Schlenk manifold was flame-dried three times, backfilling with argon after each drying cycle. The hot flask was placed into a glove box antechamber, which was evacuated/backfilled with N_2 (4 cycles, 1 min evacuation per cycle) before the flask was brought into the glove box. The flask was loaded with anhydrous cerium chloride

(616.4 mg, 2.50 mmol, 2.50 equiv), refitted with the septum, removed from the glove box, and reconnected to the argon-filled Schlenk manifold. A portion of THF (13 mL) was added, rinsing the cerium chloride to the bottom of the flask. As the resulting thick white slurry was stirred, a solution of (2-vinylphenyl)magnesium bromide (7.5 mL, 0.40 M in THF, 3.00 mmol, 3.00 equiv) was added and the mixture turned yellow and green over time. After 30 min of stirring, vinylogous ester **27a** (236.3 mg, 1.00 mmol, 1.00 equiv) was cannula-transferred to the slurry from a flame-dried 10 mL conical flask using several THF rinses (3 x 4 mL; total THF added = 25 mL, 0.04 M). The reaction color returned to yellow with addition of vinylogous ester **27a**.

TLC analysis indicated that no starting material remained after 40 min. After an additional 30 min of stirring, the reaction was quenched with 2 M H_2SO_4 (5 mL) and lowered into a preheated oil bath (60 °C). A grey precipitate formed within several minutes. After 26 h, the yellow suspension was removed from the bath, cooled to room temperature (23 °C), treated with sat. aqueous $NaHCO_3$ solution (50 mL), and transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (175 mL) were rinsed once with sat. aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified first by flash chromatography (SiO_2, 3 x 30 cm, 100% hexanes→2%→5% EtOAc in hexanes) and then by flash chromatography using a Teledyne Isco CombiFlash R*f* system (SiO_2, 12 g loading cartridge, 40 g column, multi-step gradient, hold 0% [2 min]→ramp to 85% [17 min]→hold 85% CH_2Cl_2 in hexanes [2.5 min]→ramp to 100% [3 min]→hold 100% CH_2Cl_2 [5 min]) to afford cycloheptenone **55aa** (176.7 mg, 0.66 mmol, 66% yield) as a pale yellow oil; R_f = 0.74 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$)

and ^{13}C NMR (125 MHz, $CDCl_3$) mixture of two atropisomers isomers (1.9 : 1 ratio), see Figure A1.307 for ^{1}H NMR (in $CDCl_3$) and Figure A1.308 for variable temperature ^{1}H NMR data (in DMSO-d_6 at 25, 50, 75, and 100 °C); IR (Neat Film NaCl) 3060, 3007, 2973, 2936, 2936, 1669, 1626, 1604, 1594, 1476, 1464, 1443, 1413, 1379, 1356, 1338, 1307, 1281, 1251, 1214, 1177, 1136, 1109, 1095, 1057, 1020, 996, 915, 864, 818, 769, 743 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{19}H_{23}O$ $[M+H]^+$: 267.1743; found 267.1751.



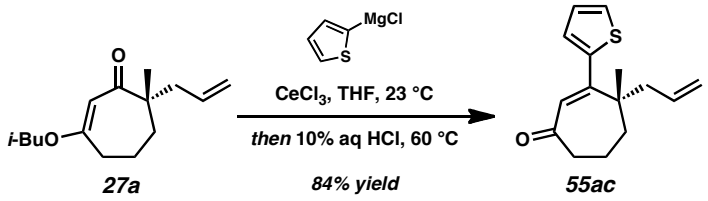
Cycloheptenone 55ab ***(Table 2.5, entry 10).*** Prepared using General Method G. A 100 and a 25 mL round-bottom flask each equipped with a magnetic stir bar, fitted with a rubber septum, and connected to a Schlenk manifold were flame-dried three times, backfilling with argon after each drying cycle. The hot 100 mL flask was placed into a glove box antechamber, which was evacuated/backfilled with N_2 (3 cycles, 5 min evacuation per cycle) before the flask was brought into the glove box. The flask was loaded with anhydrous cerium chloride (616.2 mg, 2.50 mmol, 2.50 equiv), refitted with the septum, removed from the glove box, and reconnected to the argon-filled Schlenk manifold.

Once cool, the 25 mL flask was charged with furan (230 μL, 3.16 mmol, 1.05 equiv) and Et_2O (3 mL, 1 M) and lowered into an ethylene glycol/dry ice bath (–15 °C). To the cooled solution was added *n*-BuLi (1.42 mL, 2.12 M in hexanes, 3.01 mmol, 1.00

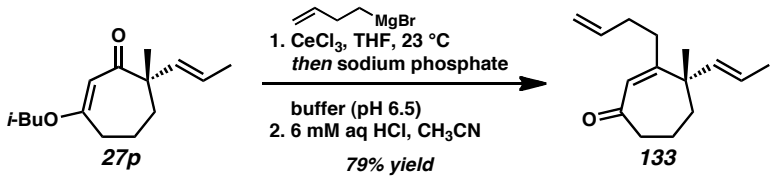
equiv) dropwise and the flask was warmed to room temperature (23 °C). The reaction became cloudy and white with time. After 1 h, a portion of THF (13 mL) was added to the 100 mL flask before the contents of the 25 mL flask were cannula-transferred to the 100 mL flask. After 30 min of stirring, vinylogous ester **27a** (236.4 mg, 1.00 mmol, 1.00 equiv) was cannula-transferred to the 100 mL flask from a flame-dried 10 mL conical flask using several THF rinses (3 x 4 mL; total THF added = 25 mL, 0.04 M).

After 35 min, the reaction was quenched with 10% w/w aqueous HCl (5 mL) and lowered into a preheated oil bath (60 °C). After 17 h, the solution was removed from the bath, cooled to room temperature (23 °C), treated with sat. aqueous $NaHCO_3$ solution (50 mL), and transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (250 mL) were rinsed once with sat. aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 3 x 30 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **55ab** (164.7 mg, 0.72 mmol, 72% yield) as a yellow oil; R_f = 0.70 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 1.8, 0.6 Hz, 1H), 6.56 (dd, *J* = 3.4, 0.7 Hz, 1H), 6.43 (s, 1H), 6.41 (dd, *J* = 3.4, 1.8 Hz, 1H), 5.65 (dddd, *J* = 16.9, 10.2, 8.1, 6.6 Hz, 1H), 5.01 (dddd, *J* = 10.2, 2.0, 0.9, 0.9 Hz, 1H), 4.97 (dddd, *J* = 16.9, 2.3, 1.4, 1.4 Hz, 1H), 2.71–2.60 (m, 3H), 2.24 (dddd, *J* = 14.1, 8.1, 1.1, 1.1 Hz, 1H), 1.97–1.81 (m, 3H), 1.72–1.64 (m, 1H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7, 155.3, 149.2, 142.9, 134.3, 129.3, 118.1, 111.4, 111.2, 45.9, 44.7, 44.3, 39.8, 26.3, 17.4; IR (Neat Film NaCl) 3118, 3075, 2941, 2871, 1661, 1652, 1645, 1581, 1557, 1455, 1415, 1380, 1341, 1258, 1215, 1173, 1152, 1106, 1080, 1029, 997, 956, 917, 898, 886, 858, 812, 742 cm^{-1};

HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{19}O_2$ $[M+H]^+$: 231.1380; found 231.1374; $[\alpha]_D^{25.0}$ –26.90 (*c* 1.18, $CHCl_3$, 88% ee).



Cycloheptenone 55ac ***(Table 2.5, entry 11).*** Prepared using General Method G. See procedure described above. R_f = 0.70 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.00–6.95 (m, 2H), 6.17 (s, 1H), 5.69 (dddd, *J* = 16.7, 10.2, 8.1, 6.4 Hz, 1H), 5.06 (dddd, *J* = 10.2, 2.0, 1.0, 1.0 Hz, 1H), 5.01 (ddd, *J* = 16.9, 3.4, 1.5 Hz, 1H), 2.74–2.59 (m, 2H), 2.50 (dddd, *J* = 14.1, 6.4, 1.4, 1.4 Hz, 1H), 2.12 (dddd, *J* = 14.1, 8.1, 1.1, 1.1 Hz, 1H), 1.96–1.84 (m, 3H), 1.77–1.68 (m, 1H), 1.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.2, 154.6, 143.8, 134.0, 133.7, 127.0, 126.7, 125.5, 118.5, 45.6, 45.1, 44.2, 38.8, 26.4, 17.7; IR (Neat Film NaCl) 3103, 3075, 2964, 2938, 2871, 1671, 1655, 1590, 1519, 1454, 1438, 1415, 1378, 1341, 1251, 1234, 1218, 1178, 1134, 1107, 1077, 1045, 996, 917, 849, 836, 761, 708 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{19}OS$ $[M+H]^+$: 247.1151; found 247.1152; $[\alpha]_D^{25.0}$ –3.65 (*c* 1.31, $CHCl_3$, 88% ee).

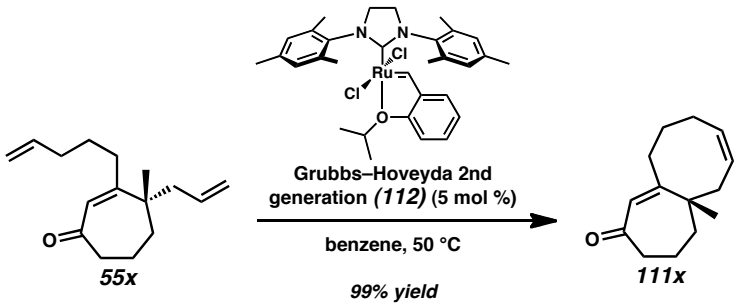


Cycloheptenone 133. Prepared using General Method F. A 100 mL round-bottom flask equipped with a magnetic stir bar, fitted with a rubber septum, and connected to a Schlenk manifold was flame-dried three times, backfilling with argon after each drying cycle. The hot flask was placed into a glove box antechamber, which was evacuated/backfilled with N_2 (4 cycles, 1 min evacuation per cycle) before the flask was brought into the glove box. The flask was loaded with anhydrous cerium chloride (591.6 mg, 2.40 mmol, 2.50 equiv), refitted with the septum, removed from the glove box, and reconnected to the argon-filled Schlenk manifold. A portion of THF (12 mL) was added, rinsing the cerium chloride to the bottom of the flask. As the resulting thick white slurry was stirred, a solution of but-3-enylmagnesium bromide (6.55 mL, 0.44 M in THF, 2.88 mmol, 3.00 equiv) was added and the mixture turned pale yellow. After 40 min of stirring, vinylogous ester **27p** (226.9 mg, 0.96 mmol, 1.00 equiv) was cannula-transferred to the slurry from a 20 mL scintillation vial using several THF rinses (3 x 4 mL; total THF added = 24 mL, 0.04 M).

TLC analysis indicated that no starting material remained after 5 min. After an additional 10 min, the reaction was quenched with pH 6.5 Na_3PO_4 buffer (20 mL). A thick grey emulsion formed. The mixture was transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organic (125 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was transferred to a 20 mL scintillation vial and concentrated under reduced pressure. A

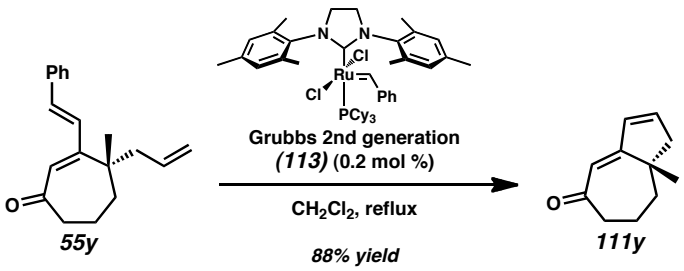
stir bar, CH_3CN (2.0 mL), and 6 mM aqueous HCl (2.0 mL) were added to the vial. The resulting cloudy solution was stirred vigorously for 5 min before being transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (75 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 3 x 30.5 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **133** (165.0 mg, 0.76 mmol, 79% yield) as a pale yellow oil; R_f = 0.74 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (s, 1H), 5.83–5.74 (m, 1H), 5.43–5.32 (m, 2H), 5.02 (dm, *J* = 17.2 Hz, 1H), 4.97 (dm, *J* = 10.2 Hz, 1H), 2.66–2.50 (m, 2H), 2.27–2.12 (m, 4H), 1.84–1.71 (m, 4H), 1.69 (dd, *J* = 4.8, 0.7 Hz, 3H), 1.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.8, 161.7, 137.8, 137.2, 129.3, 124.4, 115.2, 48.6, 44.1, 41.3, 34.8, 34.1, 26.0, 18.2, 18.0; IR (Neat Film NaCl) 3077, 2962, 2937, 2874, 2856, 1650, 1614, 1451, 1414, 1378, 1342, 1273, 1251, 1224, 1198, 1126, 1069, 974, 911 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{23}O$ $[M+H]^+$: 219.1743; found 219.1741; $[\alpha]_D^{20.0}$ +123.43 (*c* 1.10, $CHCl_3$, 88% ee).

2.1.1.15 PREPARATION OF POLYCYCLIC CYCLOHEPTENONE DERIVATIVES BY RING-CLOSING METATHESIS



General Method I: Ring-Closing Metathesis

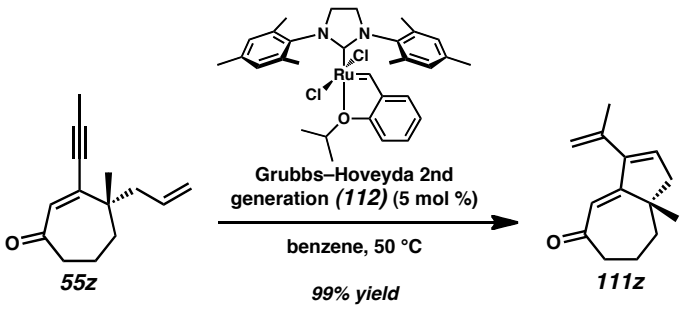
Enone 111x. A 100 mL round-bottom flask equipped with a magnetic stir bar, fitted with a water condenser, and connected to a Schlenk manifold (through the condenser) was flame-dried three times, backfilling with argon after each drying cycle. Once cool, the flask was loaded with neat cycloheptenone **55x** (50.0 mg, 0.22 mmol, 1.00 equiv) and backfilled with argon twice. Benzene (1 h argon sparge before use, 43 mL, 0.005 M) was added to the flask, followed by Grubbs–Hoveyda 2nd generation catalyst (6.7 mg, 0.011 mmol, 5 mol %). The solution color turned pale green with addition of catalyst. The flask was lowered into a preheated oil bath (50 °C). The reaction was removed from the oil bath after 30 min, cooled to room temperature (23 °C), and quenched with ethyl vinyl ether (1 mL). The reaction was filtered through a short silica gel plug rinsing with Et_2O and concentrated under reduced pressure. The crude oil was purified twice by flash chromatography (SiO_2, both columns 2 x 28 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **111x** (43.5 mg, 0.21 mmol, 99% yield) as a yellow oil.



Enone 111y ***(Table 2.6, entry 1).*** A 100 mL round-bottom flask equipped with a magnetic stir bar, fitted with a water condenser, and connected to a Schlenk manifold (through the condenser) was flame-dried three times, backfilling with argon after each drying cycle. Once cool, the flask was loaded with neat cycloheptenone **55y** (452.8 mg, 1.70 mmol, 1.00 equiv) and dichloromethane (60 mL, 0.03 M) and the resulting solution was sparged with Ar. After 30 min of degassing, Grubbs 2nd generation catalyst (3.4 mg, 0.0040 mmol, 0.2 mol %) was added to the flask. The solution color turned pale red with addition of catalyst. The flask was lowered into a preheated oil bath (50 °C).

The flask was removed from oil bath after 1 h, cooled to room temperature (23 °C), and charged with DMSO (50 μL) and silica gel (70 mg). The resulting mixture was concentrated the reaction under reduced pressure and purified by flash chromatography (SiO_2, 2 x 17 cm, 15:1 hexanes:EtOAc) to afford cycloheptenone **111y** (242.9 mg, 1.50 mmol, 88% yield) as a yellow oil; R_f = 0.52 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.35–6.32 (m, 1H), 6.14 (dddd, *J* = 5.6, 2.5, 1.7, 0.7 Hz, 1H), 5.87 (app s, 1H), 2.70 (dddt, *J* = 15.1, 6.4, 3.5, 0.9 Hz, 1H), 2.59–2.51 (m, 2H), 2.41 (ddd, *J* = 17.9, 2.9, 1.6 Hz, 1H), 2.11–2.02 (m, 1H), 2.00–1.82 (m, 3H), 1.23 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.8, 169.2, 142.7, 134.4, 121.7, 51.6, 46.7, 45.1, 37.9, 29.7, 21.2; IR (Neat Film NaCl) 3056, 2930, 2867, 2841, 1651, 1615, 1580, 1449, 1372, 1352, 1293, 1261, 1211, 1190, 1159, 1080, 968, 951, 862, 844, 801, 811, 723 cm^{-1}; HRMS (MM:

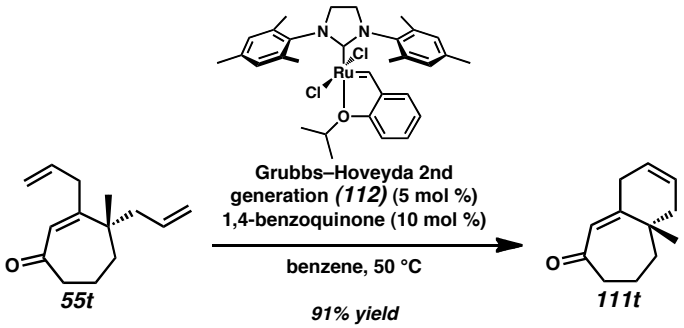
ESI–APCI+) *m/z* calc'd for $C_{11}H_{15}O$ $[M+H]^+$: 163.1117; found 163.1120; $[\alpha]_D^{26.0}$ –48.88 (*c* 1.83, $CHCl_3$, 88% ee).



Enone 111z ***(Table 2.6, entry 2)***. Prepared using General Method I. A two-neck 100 mL round-bottom flask equipped with a magnetic stir bar, fitted with rubber septa and a water condenser, and connected to a Schlenk manifold (through the condenser) was flame-dried three times, backfilling with argon after each drying cycle. Once cool, the flask was loaded with neat cycloheptenone **55z** (50.0 mg, 0.25 mmol, 1.00 equiv) and backfilled with argon. Benzene (1 h argon sparge before use, 39 mL) was added to the flask, followed by Grubbs–Hoveyda 2nd generation catalyst (7.8 mg, 0.012 mmol, 5 mol %). The solution color turned pale green with addition of catalyst. The flask was rinsed with more benzene (10 mL; total benzene added = 49 mL, 0.005 M) and lowered into a preheated oil bath (50 °C).

TLC analysis indicated no starting material remained after 3 h. Consequently, the reaction was removed from oil bath, cooled to room temperature (23 °C), and quenched with ethyl vinyl ether (1 mL). The reaction was filtered through a short silica gel plug rinsing with Et_2O and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 2 x 28.5 cm, 100% hexanes→2%→5% EtOAc in

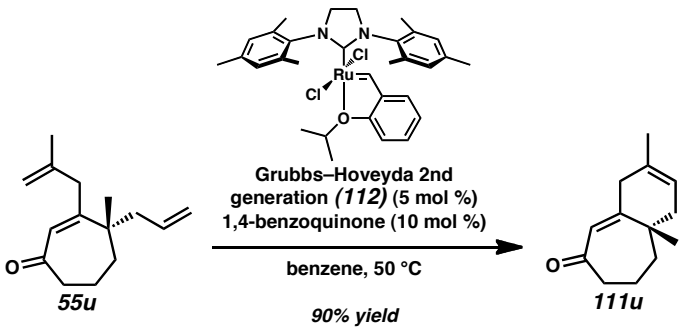
hexanes) to afford cycloheptenone **111z** (50 mg, 0.25 mmol, 99% yield) as a yellow oil; R_f = 0.64 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.16 (t, *J* = 2.8 Hz, 1H), 6.02 (s, 1H), 5.13–5.11 (m, 1H), 4.97 (s, 1H), 2.76 (ddd, *J* = 14.7, 6.7, 4.7 Hz, 1H), 2.56 (ddd, *J* = 14.7, 9.8, 5.1 Hz, 1H), 2.48 (dd, *J* = 17.8, 2.0 Hz, 1H), 2.33 (dd, *J* = 17.8, 3.1 Hz, 1H), 2.09–1.99 (m, 1H), 1.94 (dd, *J* = 9.9, 4.0 Hz, 2H), 1.91–1.89 (m, 3H), 1.89–1.83 (m, 1H), 1.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7, 167.2, 146.8, 138.4, 137.5, 122.0, 115.9, 49.5, 48.3, 45.0, 38.2, 28.4, 23.1, 20.9; IR (Neat Film NaCl) 3084, 3052, 2918, 2868, 2845, 1652, 1607, 1450, 1374, 1352, 1311, 1290, 1259, 1210, 1190, 1164, 1117, 1082, 1004, 982, 944, 898, 881, 848, 811, 771, 746 cm^{-1}; HRMS (MM: ESI–APCI+) *m/z* calc'd for $C_{14}H_{19}O$ $[M+H]^+$: 203.1430; found 203.11428; $[\alpha]_D^{25.0}$ –55.41 (*c* 1.61, $CHCl_3$, 88% ee).



Enone 111t ***(Table 2.6, entry 3)***. Prepared using General Method I. A 250 mL round-bottom flask equipped with a magnetic stir bar, fitted with a water condenser, and connected to a Schlenk manifold (through the condenser) was flame-dried three times, backfilling with argon after each drying cycle. Once cool, cycloheptenone **55t** (174.6 mg, 0.85 mmol, 1.00 equiv) was cannula-transferred from a 20 mL scintillation vial to the 250 mL flask using several benzene rinses (1.5 h argon sparge before use, 5 x 4 mL).

Additional benzene (141 mL) was added to the flask followed by 1,4-benzoquinone (9.2 mg, 0.085 mmol, 10 mol %) and Grubbs–Hoveyda 2nd generation catalyst (26.8 mg, 0.043 mmol, 5 mol %). The solution color turned pale green with addition of catalyst. The flask was rinsed with more benzene (10 mL; total benzene added = 171 mL, 0.005 M) and lowered into a preheated oil bath (50 °C).

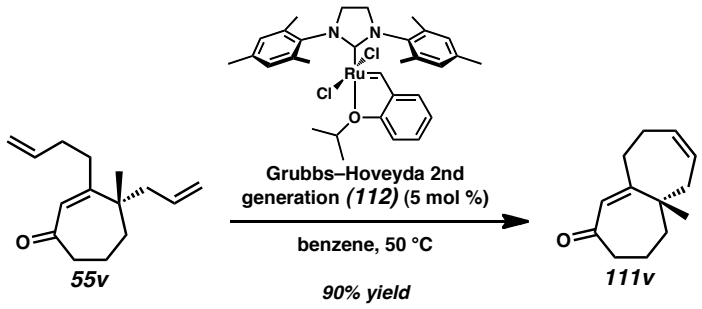
The reaction was removed from oil bath after 2.5 h, cooled to room temperature (23 °C), and quenched with ethyl vinyl ether (2 mL). The reaction color turned dark green with the ethyl vinyl ether addition. The reaction was filtered through a short silica gel plug rinsing with Et_2O and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 3 x 25 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **111t** (47.7 mg, 0.27 mmol, 91% yield) as a yellow oil; R_f = 0.58 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 5.95 (d, *J* = 2.1 Hz, 1H), 5.46–5.41 (m, 1H), 5.34 (ddddd, *J* = 9.9, 4.4, 2.8, 2.8, 1.0 Hz, 1H), 2.72 (dm, *J* = 20.2 Hz, 1H), 2.44–2.33 (m, 2H), 2.27 (dm, *J* = 20.2 Hz, 1H), 1.97 (dm, *J* = 17.6 Hz, 1H), 1.44 (ddd, *J* = 17.5, 5.2, 0.9 Hz, 1H), 1.33–1.19 (m, 4H), 0.86 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 202.2, 156.0, 127.2, 125.1, 125.0, 44.3, 41.8, 41.4, 41.2, 36.3, 26.1, 17.6; IR (Neat Film NaCl) 3274, 3029, 2933, 2833, 1720, 1650, 1619, 1452, 1420, 1381, 1345, 1306, 1264, 1239, 1219, 1185, 1125, 1105, 1082, 1004, 976, 952, 938, 924, 892, 884, 871, 836, 775, 733 cm^{-1}; HRMS (MM: ESI–APCI+) *m*/*z* calc'd for $C_{12}H_{17}O$ $[M+H]^+$: 177.1274; found 177.1277; $[\alpha]_D^{25.0}$ –49.94 (*c* 0.86, $CHCl_3$, 88% ee).



Enone 111u ***(Table 2.6, entry 4)***. Prepared using General Method I. A three-neck 100 mL round-bottom flask equipped with a magnetic stir bar and fitted with rubber septa and a water condenser was connected to a Schlenk manifold (through the condenser). The flask was flame-dried three times, backfilling with argon after each drying cycle. Once cool, the flask was loaded with neat cycloheptenone **55u** (50.0 mg, 0.23 mmol, 1.00 equiv), benzene (1 h argon sparge before use, 46 mL, 0.005 M), 1,4-benzoquinone (2.5 mg, 0.023 mmol, 10 mol %), and Grubbs–Hoveyda 2nd generation catalyst (7.2 mg, 0.011 mmol, 5 mol %). The solution color turned pale green with addition of catalyst. The flask was lowered into a preheated oil bath (50 °C).

The reaction was removed from oil bath after 1 h, cooled to room temperature (23 °C), and quenched with ethyl vinyl ether (1.5 mL). The reaction color turned dark green with the ethyl vinyl ether addition. The reaction was filtered through a short silica gel plug rinsing with Et_2O and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 2 x 28 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **111u** (39.0 mg, 0.21 mmol, 90% yield) as a yellow oil; R_f = 0.56 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (d, *J* = 2.0 Hz, 1H), 5.38–5.34 (m, 1H), 3.06 (dm, *J* = 19.7 Hz, 1H), 2.63–2.49 (m, 3H), 2.28 (dm, *J* = 17.2 Hz, 1H), 1.85 (dd, *J* = 17.2, 5.3 Hz, 1H), 1.81–1.75 (m, 2H), 1.74–1.65 (m, 2H),

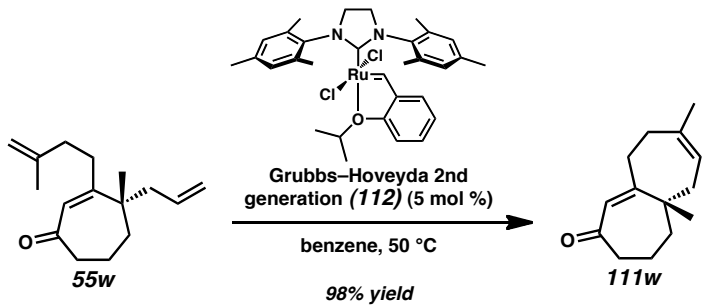
1.68 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.1, 159.4, 131.8, 126.3, 119.5, 44.3, 41.6, 41.5, 41.3, 41.3, 26.6, 22.5, 17.6; IR (Neat Film NaCl) 3273, 3017, 2963, 2930, 1720, 1656, 1651, 1645, 1619, 1616, 1450, 1418, 1378, 1363, 1345, 1268, 1239, 1220, 1191, 1151, 1134, 1104, 1072, 1038, 989, 972, 962, 944, 931, 897, 877, 854, 827, 784, 732 cm^{-1}; HRMS (MM: ESI–APCI+) *m*/*z* calc'd for $C_{13}H_{19}O$ $[M+H]^+$: 191.1430; found 191.1436; $[\alpha]_D^{25.0}$ +9.09 (*c* 0.86, $CHCl_3$, 88% ee).



Enone 111v ***(Table 2.6, entry 5)***. Prepared using General Method I. A two-neck 100 mL round-bottom flask equipped with a magnetic stir bar, fitted with rubber septa and a water condenser, and connected to a Schlenk manifold (through the condenser) was flame-dried three times, backfilling with argon after each drying cycle. Once cool, the flask was loaded with neat cycloheptenone **55v** (50.0 mg, 0.23 mmol, 1.00 equiv), Grubbs–Hoveyda 2nd generation catalyst (7.2 mg, 0.011 mmol, 5 mol %), benzene (1 h argon sparge before use, 46 mL, 0.005 M). The solution color turned pale green with addition of catalyst. The flask was lowered into a preheated oil bath (50 °C).

TLC analysis indicated no starting material remained after 15 min. Consequently, the reaction was removed from the oil bath, cooled to room temperature (23 °C), and quenched with ethyl vinyl ether (1 mL). The reaction color turned amber with the ethyl

vinyl ether addition. The reaction was filtered through a short silica gel plug rinsing with Et_2O and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 2 x 27.5 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **111v** (39.4 mg, 0.21 mmol, 90% yield) as a yellow oil; R_f = 0.58 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (s, 1H), 5.65–5.58 (m, 1H), 5.54–5.49 (m, 1H), 2.81–2.74 (m, 1H), 2.66–2.59 (m, 2H), 2.56–2.46 (m, 2H), 2.24–2.13 (m, 2H), 2.07 (ddd, *J* = 14.1, 11.1, 3.1 Hz, 1H), 1.93 (ddddd, *J* = 14.1, 11.0, 9.3, 4.8, 2.9 Hz, 1H), 1.85–1.79 (m, 1H), 1.76 (dd, *J* = 14.9, 7.9 Hz, 1H), 1.66 (ddd, *J* = 14.0, 6.9, 2.8 Hz, 1H), 1.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.8, 165.3, 129.9, 129.7, 126.2, 47.8, 43.9, 40.7, 40.3, 34.5, 32.2, 27.8, 19.6; IR (Neat Film NaCl) 3287, 3017, 2930, 2833, 1652, 1616, 1481, 1450, 1380, 1352, 1342, 1291, 1279, 1262, 1243, 1224, 1204, 1184, 1162, 1084, 1075, 1047, 1021, 984, 963, 921, 896, 877, 846, 834, 788, 755 cm^{-1}; HRMS (MM: ESI–APCI+) *m/z* calc'd for $C_{13}H_{19}O$ $[M+H]^+$: 191.1430; found 191.1430; $[\alpha]_D^{25.0}$ –92.01 (*c* 0.82, $CHCl_3$, 88% ee).

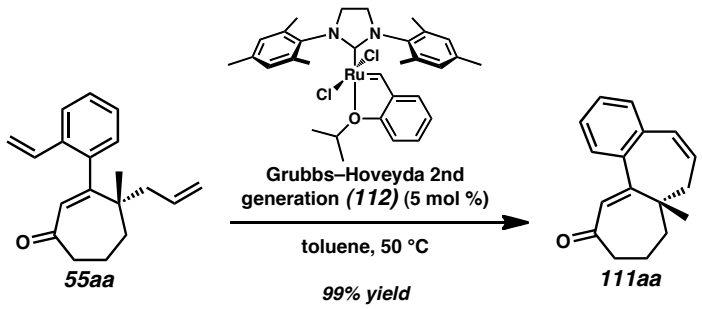


Enone 111w ***(Table 2.6, entry 6)***. Prepared using General Method I. A two-neck 100 mL round-bottom flask equipped with a magnetic stir bar, fitted with rubber septa and a water condenser, and connected to a Schlenk manifold (through the condenser) was

flame-dried three times, backfilling with argon after each drying cycle. Once cool, the flask was loaded with neat cycloheptenone **55w** (50.0 mg, 0.22 mmol, 1.00 equiv) and backfilled with argon. Benzene (1 h argon sparge before use, 33 mL) was added to the flask, followed by Grubbs–Hoveyda 2nd generation catalyst (6.7 mg, 0.011 mmol, 5 mol %). The solution color turned pale green with addition of catalyst. The flask was rinsed with more benzene (10 mL; total benzene added = 43 mL, 0.005 M) and lowered into a preheated oil bath (50 °C).

TLC analysis indicated no starting material remained after 30 min. After an additional 10 min of stirring, the reaction was removed from the oil bath, cooled to room temperature (23 °C), and quenched with ethyl vinyl ether (1 mL). The reaction color turned dark brown with the ethyl vinyl ether addition. The reaction was filtered through a short silica gel plug rinsing with Et_2O and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 2 x 28.5 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **111w** (43.2 mg, 0.21 mmol, 98% yield) as a clear colorless oil; R_f = 0.63 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (s, 1H), 5.41–5.34 (m, 1H), 2.79 (td, *J* = 12.3, 5.3 Hz, 1H), 2.66–2.55 (m, 2H), 2.54–2.42 (m, 2H), 2.19 (ddd, *J* = 12.5, 6.0, 3.3 Hz, 1H), 2.14–2.02 (m, 2H), 1.98–1.88 (m, 1H), 1.85–1.76 (m, 1H), 1.71–1.63 (m, 2H), 1.62 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.9, 165.8, 136.9, 129.5, 120.7, 47.7, 43.9, 40.6, 40.2, 36.9, 34.3, 27.5, 25.3, 19.7; IR (Neat Film NaCl) 3300, 3014, 2928, 2828, 1657, 1617, 1480, 1450, 1379, 1353, 1342, 1292, 1259, 1216, 1171, 1131, 1106, 1082, 1050, 1009, 982, 962, 916, 897, 874, 833, 814, 795, 765 cm^{-1}; HRMS (MM: ESI–APCI+) *m/z*

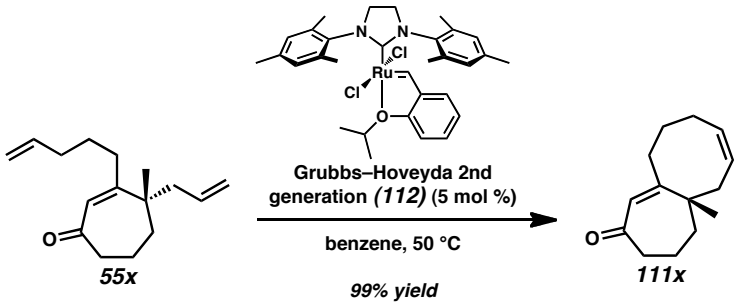
calc'd for $C_{14}H_{21}O_2$ $[M+H]^+$: 205.1587; found 205.1582; $[\alpha]_D^{25.0}$ –73.66 (*c* 0.95, $CHCl_3$, 88% ee).



Enone 111aa ***(Table 2.6, entry 7)***. Prepared using General Method I. A three-neck 100 mL round-bottom flask equipped with a magnetic stir bar, fitted with rubber septa and a water condenser, and connected to a Schlenk manifold (through the condenser) was flame-dried three times, backfilling with argon after each drying cycle. Once cool, cycloheptenone **55aa** (65.8 mg, 0.25 mmol, 1.00 equiv) was cannula-transferred from a 20 mL scintillation vial to the 100 mL flask using several toluene rinses (1.5 h argon sparge before use, 5 x 4 mL). Additional toluene (20 mL) was added to the flask followed by Grubbs–Hoveyda 2nd generation catalyst (7.7 mg, 0.012 mmol, 5 mol %). The solution color turned pale green with addition of catalyst. The flask was rinsed with more toluene (9 mL; total toluene added = 49 mL, 0.005 M) and lowered into a preheated oil bath (50 °C).

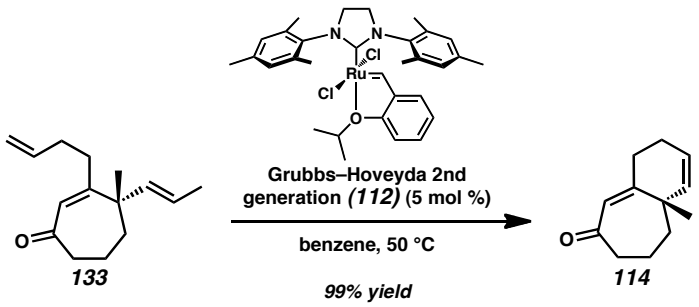
The reaction was removed from the oil bath after 6.5 h, cooled to room temperature (23 °C), and quenched with ethyl vinyl ether (0.5 mL). The reaction color turned dark brown with the ethyl vinyl ether addition. The reaction was filtered through a short silica gel plug rinsing with EtOAc and concentrated under reduced pressure. The

crude oil was purified by flash chromatography (SiO_2, 2 x 24.5 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **111aa** (56.7 mg, 0.23 mmol, 96% yield) as a yellow oil; R_f = 0.64 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.26 (m, 1H), 7.22–7.19 (m, 2H), 7.10 (d, *J* = 7.4 Hz, 1H), 6.53 (dm, *J* = 11.1 Hz, 1H), 6.03 (dt, *J* = 11.2, 6.0 Hz, 1H), 5.82 (s, 1H), 2.71–2.60 (m, 2H), 2.30 (ddd, *J* = 15.6, 5.8, 0.8 Hz, 1H), 2.21 (ddd, *J* = 15.6, 6.3, 1.8 Hz, 1H), 2.15 (ddd, *J* = 13.9, 7.5, 4.5 Hz, 1H), 2.01–1.85 (m, 3H), 1.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.3, 162.5, 142.5, 135.5, 132.0, 130.8, 130.0, 128.8, 128.8, 127.9, 127.3, 50.6, 44.2, 42.4, 40.1, 27.8, 19.3; IR (Neat Film NaCl) 3057, 3017, 2933, 2870, 1718, 1665, 1601, 1481, 1445, 1417, 1383, 1354, 1340, 1286, 1258, 1228, 1180, 1125, 996, 984, 936, 890, 828, 780, 757 cm^{-1}; HRMS (MM: ESI–APCI+) *m*/*z* calc'd for $C_{17}H_{19}O$ $[M+H]^+$: 239.1430; found 239.1432; $[\alpha]_D^{20.0}$ –86.75 (*c* 0.70, $CHCl_3$, 88% ee).



Enone 185w ***(Table 2.6, entry 8)***. Prepared using General Method I. See procedure described above. R_f = 0.56 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77–5.70 (m, 1H), 5.65 (tdt, *J* = 10.4, 6.4, 1.3 Hz, 1H), 2.68–2.55 (m, 2H), 2.54–2.44 (m, 1H), 2.30–2.24 (m, 2H), 2.24–2.15 (m, 1H), 2.13–2.04 (m, 1H), 1.94–1.69 (m, 7H), 1.52–1.41 (m, 1H), 1.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.2, 165.6, 132.2,

131.9, 128.5, 49.0, 44.2, 39.8, 39.5, 35.5, 31.1, 27.0, 26.5, 17.8; IR (Neat Film NaCl) 3018, 2928, 2859, 1645, 1608, 1468, 1448, 1411, 1380, 1343, 1327, 1279, 1253, 1214, 1178, 1131, 1102, 1088, 1051, 1015, 987, 965, 937, 920, 899, 880, 845, 796, 777, 747 cm^{-1}; HRMS (MM: ESI–APCI+) *m/z* calc'd for $C_{14}H_{21}O$ $[M+H]^+$: 205.1587; found 205.1587; $[\alpha]_D^{25.0}$ –141.99 (*c* 1.01, $CHCl_3$, 88% ee).

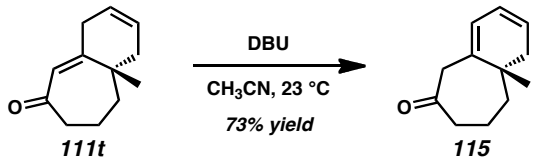


Enone 114. Prepared using General Method I. A 100 mL round-bottom flask equipped with a magnetic stir bar, fitted with a water condenser, and connected to a Schlenk manifold (through the condenser) was flame-dried three times, backfilling with argon after each drying cycle. Once cool, the flask was loaded with neat cycloheptenone **133** (50.0 mg, 0.23 mmol, 1.00 equiv) and backfilled with argon twice. Benzene (1 h argon sparge before use, 44 mL) was added to the flask, followed by Grubbs–Hoveyda 2nd generation catalyst (7.2 mg, 0.011 mmol, 5 mol %). The flask was rinsed with more benzene (2 mL; total benzene added = 46 mL, 0.005 M) and lowered into a preheated oil bath (50 °C). The solution color turned pale green with addition of catalyst and amber over time.

The reaction was removed from the oil bath after 50 min, cooled to room temperature (23 °C), and quenched with ethyl vinyl ether (0.5 mL). The reaction was

filtered through a short silica gel plug rinsing with Et_2O and concentrated under reduced pressure. The crude oil was purified twice by flash chromatography (SiO_2, both columns 2 x 27.5 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford cycloheptenone **114** (35.8 mg, 0.23 mmol, 89% yield, 70% yield from vinylogous ester **27p**) as a pale yellow oil; R_f = 0.62 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (s, 1H), 5.72–5.67 (m, 1H), 5.28 (dd, *J* = 9.7, 2.4 Hz, 1H), 2.71–2.64 (m, 1H), 2.62–2.54 (m, 1H), 2.53–2.46 (m, 1H), 2.31–2.11 (m, 3H), 1.92–1.74 (m, 3H), 1.70 (ddd, *J* = 14.0, 6.6, 2.4 Hz, 1H), 1.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.5, 161.3, 137.8, 126.9, 125.3, 44.6, 43.6, 40.6, 33.8, 28.1, 27.7, 18.6; IR (Neat Film NaCl) 3019, 2934, 2866, 2845, 1665, 1653, 1621, 1450, 1414, 1350, 1309, 1281, 1258, 1217, 1181, 1171, 1132, 1087, 1074, 1024, 1013, 973, 938, 902, 881, 865, 783, 767, 716 cm^{-1}; HRMS (MM: ESI–APCI+) *m/z* calc'd for $C_{12}H_{17}O$ $[M+H]^+$: 177.1274; found 177.1274; $[\alpha]_D^{20.0}$ –188.35 (*c* 0.72, $CHCl_3$, 88% ee).

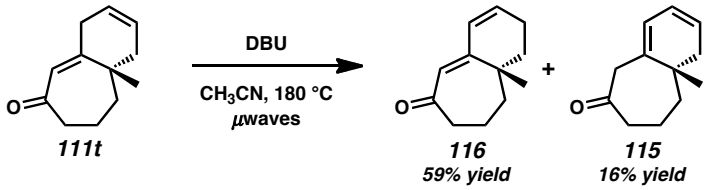
2.1.1.16 PREPARATION OF POLYCYCLIC CYCLOHEPTENONE DERIVATIVES BY OTHER METHODS



111t *115*

Diene 115. A 20 mL scintillation vial containing enone **111t** (31.5 mg, 0.18 mmol, 1.00 equiv) was equipped with a stir bar and sealed with a screw cap containing a teflon septum. The vial was connected to a Schlenk manifold and backfilled with argon three

times. Acetonitrile (1.8 mL, 0.1 M) was added to the vial followed by DBU (30 μL, 0.20 mmol, 1.12 equiv). The solution was stirred at room temperature (23 °C) until no starting material remained by TLC analysis (4 h). The reaction was passed through a short silica gel plug, rinsed with water, dried over $MgSO_4$, filtered through another short silica gel plug, and concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography (SiO_2, 1 x 28.5 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford diene **115** (23.1 mg, 0.13 mmol, 73% yield) as a pale yellow oil; R_f = 0.63 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (ddt, *J* = 9.0, 5.3, 1.7 Hz, 1H), 5.79–5.73 (m, 2H), 3.27 (d, *J* = 16.3 Hz, 1H), 2.93 (d, *J* = 16.3 Hz, 1H), 2.73 (ddd, *J* = 12.4, 10.0, 4.7 Hz, 1H), 2.33–2.23 (m, 2H), 2.08–2.00 (m, 1H), 1.89–1.67 (m, 3H), 1.49–1.41 (m, 1H), 0.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.0, 138.6, 125.4, 123.9, 123.6, 49.5, 42.7, 37.6, 37.5, 36.5, 24.1, 20.9; IR (Neat Film NaCl) 3039, 2929, 2865, 2817, 1708, 1645, 1587, 1453, 1424, 1403, 1371, 1356, 1319, 1286, 1263, 1235, 1211, 1143, 1105, 1082, 1039, 987, 969, 940, 925, 851, 817, 761, 704 cm^{-1}; HRMS (GC-EI+) *m/z* calc'd for $C_{12}H_{16}O$ [M+·]$^+$: 176.1201; found 176.1219; $[\alpha]_D^{25.0}$ –205.54 (*c* 0.71, $CHCl_3$, 88% ee).

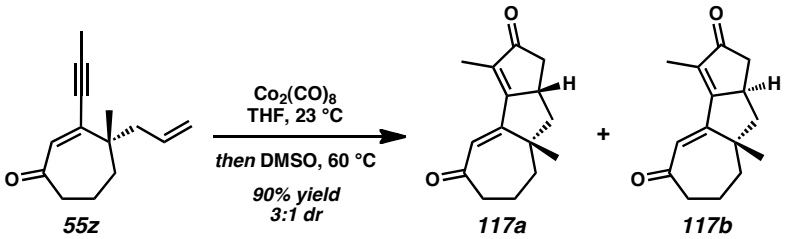


Diene 115 and Diene 116. A 2.0–5.0 mL μwave vial fitted with a stir bar and sealed with a screw cap containing a teflon septum was flame-dried three times, backfilling with

argon after each drying cycle. Once cool, diene **111t** (66.7 mg, 0.38 mmol, 1.00 equiv) was cannula-transferred to the vial with several acetonitrile rinses (4 x 1 mL, 0.09 M) and the flask was charged with DBU (66 μL, 0.44 mmol, 1.17 equiv). The pale yellow solution was subjected to microwave irradiation in a Biotage Initiator microwave reactor (temperature: 180 °C, sensitivity: normal). After 5 h of irradiation, the crimp cap was removed and the reaction was filtered through a silica gel plug. The resulting solution was concentrated under reduced pressure and purified by flash chromatography (SiO_2, 2 x 29 cm, 100% hexanes→10%→30%→50%→80% CH_2Cl_2 in hexanes) to yield diene **116** (39.5 mg, 0.22 mmol, 59% yield) as a yellow oil and diene **115 (**10.4 mg, 0.059 mmol, 16% yield) as a pale yellow oil.

Diene 115: Characterization data is identical to that described above.

Diene 116: R_f = 0.56 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.13–6.07 (m, 1H), 6.02 (dd, *J* = 9.9, 2.8 Hz, 1H), 5.76 (s, 1H), 2.75 (dddt, *J* = 15.6, 6.6, 5.0, 0.9 Hz, 1H), 2.52 (ddd, *J* = 15.4, 9.5, 5.6 Hz, 1H), 2.38–2.27 (m, 1H), 2.19 (dtt, *J* = 19.3, 5.6, 1.3 Hz, 1H), 2.05–1.93 (m, 1H), 1.87–1.77 (m, 2H), 1.74–1.62 (m, 2H), 1.44 (ddt, *J* = 13.2, 5.4, 1.5 Hz, 1H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.1, 156.2, 135.1, 131.4, 129.1, 44.6, 42.2, 38.9, 37.6, 23.1, 22.9, 18.8; IR (Neat Film NaCl) 3026, 2967, 2922, 2868, 2849, 1650, 1621, 1583, 1449, 1428, 1383, 1353, 1338, 1284, 1244, 1225, 1207, 1173, 1163, 1130, 1114, 1090, 1077, 1023, 978, 954, 935, 911, 881, 866, 840, 777, 727 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{12}H_{17}O$ $[M+H]^+$: 177.1274; found 177.1278; $[\alpha]_D^{25.0}$ –298.04 (*c* 1.24, $CHCl_3$, 88% ee).



Enones 117a and 117b. A 20 mL scintillation vial containing cycloheptenone **55z** (185.6 mg, 0.92 mmol, 1.00 equiv) was equipped with a stir bar and sealed with a screw cap containing a teflon septum. The vial was connected to a Schlenk manifold and backfilled with argon three times. The vial was charged with THF (5.0 mL, 0.2 M) and dicobalt octacarbonyl (388.5 mg, 1.14 mmol, 1.24 equiv), generating a dark brown solution. After 12 h of stirring at room temperature (23 °C), DMSO (380 μL, 5.35 mmol, 5.83 equiv) was added and the vial was lowered into a preheated oil bath (60 °C). Reaction turned dark red over time. The vial was removed from the oil bath after 14 h and cooled to room temperature. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography using a Teledyne Isco CombiFlash R_f system (SiO_2, 25 g loading cartridge, 40 g column, multi-step gradient, hold 0% [5 min]→ramp to 5% [5 min]→hold 5% [50 min]→ramp to 10% [5 min]→hold 10% [15 min]→ramp to 15% [1 min]→hold 15% [7 min]→ramp to 20% [1 min]→hold 20% EtOAc in hexanes [27 min]) to afford a 3:1 diastereomeric mixture of cycloheptenones **117a**:**117b** (190.2 mg, 0.83 mmol, 90% yield). Analytically pure samples of **117a** and **117b** could be obtained using the above column conditions.

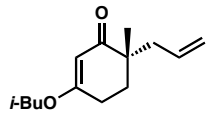
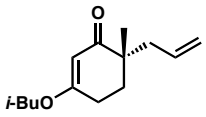
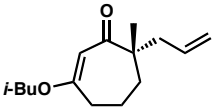
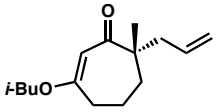
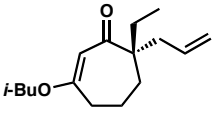
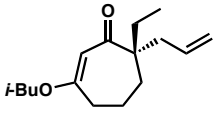
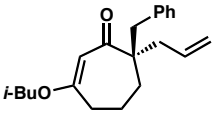
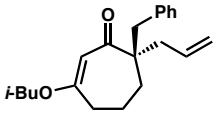
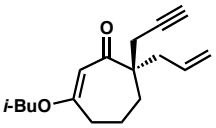
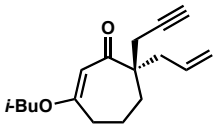
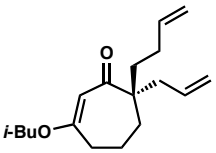
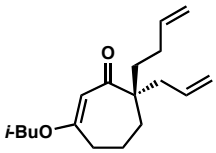
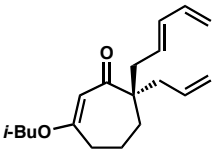
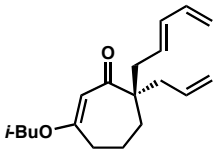
Major diastereomer (117a): yellow oil that solidified upon cooling; R_f = 0.32 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.38 (s, 1H), 3.21–3.12 (m, 1H),

2.81–2.75 (m, 1H), 2.75 (dd, *J* = 17.8, 6.3 Hz, 1H), 2.62 (ddd, *J* = 14.0, 11.4, 4.6 Hz, 1H), 2.19–2.09 (m, 1H), 2.11 (dd, *J* = 17.8, 3.7 Hz, 1H), 2.01 (dd, *J* = 11.6, 6.9 Hz, 1H), 1.99–1.90 (m, 2H), 1.89 (d, *J* = 2.6 Hz, 3H), 1.88–1.81 (m, 1H), 1.32 (s, 3H), 1.28 (t, *J* = 11.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.5, 204.8, 172.4, 155.0, 135.6, 128.8, 50.9, 47.2, 45.6, 42.3, 40.5, 39.5, 26.8, 20.9, 9.0; For NOESY correlation data, see Figure A1.351; IR (Neat Film NaCl) 2945, 2917, 2867, 1701, 1662, 1446, 1375, 1332, 1304, 1258, 1219, 1196, 1148, 1099, 1054, 978, 945, 895, 869, 852, 830, 802, 706 cm^{-1}; HRMS (GC-EI+) *m/z* calc'd for $C_{15}H_{19}O_2$ $[M+H]^+$: 231.1380; found 231.1381; $[\alpha]_D^{20.0}$ +150.77 (*c* 1.01, $CHCl_3$, 88% ee).

Minor diastereomer (117b): orange oil that solidified upon cooling; R_f = 0.25 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.27 (s, 1H), 3.09–2.98 (m, 1H), 2.70 (dd, *J* = 18.1, 6.4 Hz, 1H), 2.71–2.64 (m, 1H), 2.63–2.56 (m, 1H), 2.16 (dd, *J* = 12.5, 8.5 Hz, 1H), 2.11 (dd, *J* = 18.1, 3.3 Hz, 1H), 2.12–1.96 (m, 2H), 1.95–1.87 (m, 2H), 1.87 (d, *J* = 2.5 Hz, 3H), 1.28 (dd, *J* = 12.4, 11.6 Hz, 1H), 1.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.7, 206.4, 173.0, 154.6, 133.7, 127.4, 48.9, 48.3, 42.4, 42.3, 41.3, 37.5, 31.9, 22.2, 8.5; For NOESY correlation data, see Figure A1.355; IR (Neat Film NaCl) 2928, 2867, 1703, 1668, 1453, 1410, 1377, 1305, 1285, 1236, 1208, 1157, 1094, 1054, 996, 949, 891, 874, 859, 791, 720 cm^{-1}; HRMS (GC-EI+) *m/z* calc'd for $C_{15}H_{19}O_2$ $[M+H]^+$: 231.1380; found 231.1372; $[\alpha]_D^{20.0}$ –407.06 (*c* 1.65, $CHCl_3$, 88% ee).

2.1.1.17 DETERMINATION OF ENANTIOMERIC EXCESS

Table 2.8. Methods for the determination of enantiomeric excess (Chiral HPLC and SFC).

entry	product	compound assayed	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
1	 **22a**	 **22a**	HPLC Chiralcel OD-H 5% IPA in hexane isocratic, 1.0 mL/min	5.80	6.53	86
2	 **27a**	 **27a**	HPLC Chiralcel OD-H 1% IPA in hexane isocratic, 1.0 mL/min	6.30	7.26	88
3	 **27b**	 **27b**	HPLC Chiralcel AD 0.25% IPA in hexane isocratic, 1.0 mL/min	18.08	16.23	92
4	 **27c**	 **27c**	HPLC Chiralcel OD-H 0.5% IPA in hexane isocratic, 1.0 mL/min	15.70	13.96	86
5	 **27d**	 **27d**	HPLC Chiralcel OD-H 0.5% IPA in hexane isocratic, 1.0 mL/min	12.35	13.43	89
6	 **27e**	 **27e**	HPLC Chiralcel AD 0.8% IPA in hexane isocratic, 2.0 mL/min	5.03	6.06	87
7	 **27f**	 **27f**	SFC Chiralcel AD-H 5% IPA in hexane isocratic, 2.5 mL/min	6.99	6.31	90

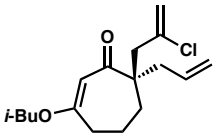
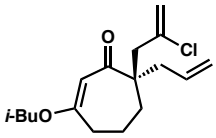
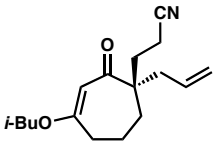
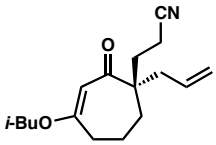
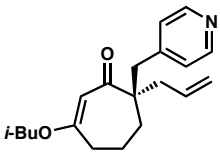
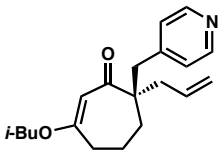
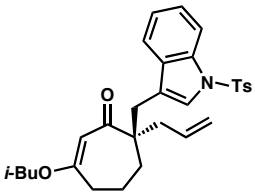
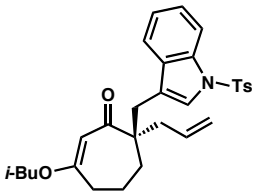
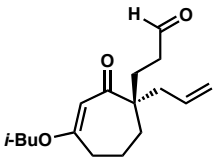
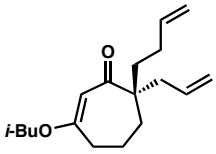
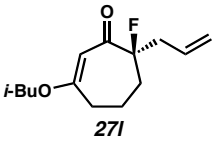
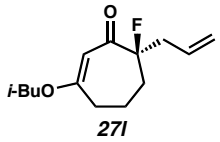
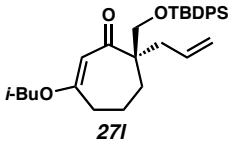
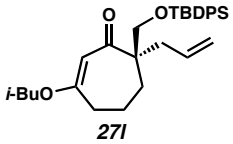
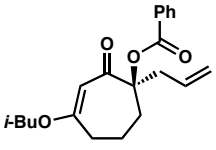
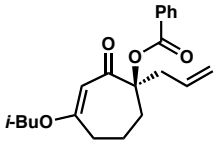
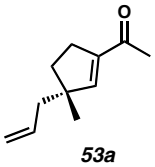
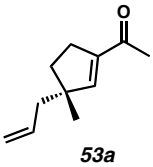
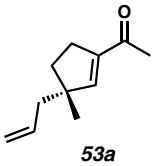
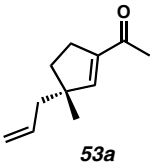
entry	product	compound assayed	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
8	 ***27g***	 ***27g***	HPLC Chiralcel OD-H 0.1% IPA in hexane isocratic, 1.0 mL/min	27.22	24.19	86
9	 ***27h***	 ***27h***	HPLC Chiralcel OD-H 5% IPA in hexane isocratic, 1.0 mL/min	10.67	14.66	87
10	 ***27i***	 ***27i***	HPLC Chiralcel AD 5% EtOH in hexane isocratic, 1.0 mL/min	13.22	15.13	85
11	 ***27j***	 ***27j***	HPLC Chiralcel AD 5% EtOH in hexane isocratic, 1.0 mL/min	11.11	16.64	83
12	 ***27k***	 ***27e***	HPLC Chiralcel AD 0.8% IPA in hexane isocratic, 2.0 mL/min	4.39	5.17	80
13	 ***27l***	 ***27l***	HPLC Chiralcel OD-H 1% IPA in hexane isocratic, 1.0 mL/min	8.80	8.05	91
14	 ***27l***	 ***27l***	HPLC Chiralcel OD-H 0.2% IPA in hexane isocratic, 1.0 mL/min	21.74	25.53	58
15	 ***27n***	 ***27n***	HPLC Chiralcel OD-H 1% IPA in hexane isocratic, 1.0 mL/min	18.28	22.01	57

Table 2.9. Methods for the determination of enantiomeric excess (Chiral GC).

entry	product	compound assayed	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
1	 ***53a***	 ***53a***	GC G-TA 80 °C isotherm	54.98	61.35	88
2	 ***53a***	 ***53a***	GC G-TA 80 °C isotherm	54.74	60.24	98

2.2 NOTES AND REFERENCES

(1) For a review discussing our strategy of using natural product structures to drive the development of enantioselective catalysis, see: Mohr, J. T.; Krout, M. R.; Stoltz, B. M. *Nature* **2008**, *455*, 323–332.

(2) For examples of asymmetric palladium-catalyzed allylic alkylation reactions of carbocyclic ketone enolates developed by our group, see: (a) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045. (b) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924–6927. (c) Behenna, D. C.; Mohr, J. T.; Sherden, N. H.; Marinescu, S. C.; Harned, A. M.; Tani, K.; Seto, M.; Ma, S.; Novák, Z.; Krout, M. R.; McFadden, R. M.; Roizen, J. L.; Enquist, Jr., J. A.; White, D. E.; Levine, S. R.; Petrova, K. V.; Iwashita, A.; Virgil, S. C.; Stoltz, B. M. *Chem.—Eur. J.* **2011**, *17*, 14199–14223.

(3) For examples of asymmetric palladium-catalyzed allylic alkylation reactions of heterocyclic ketone enolates (such as those derived from dioxanones and lactams) developed by our group, see: (a) Seto, M.; Roizen, J. L.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6873–6876. (b) Behenna, D. C.; Liu, Y.; Yurino, T.; Kim, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nature Chem.* **2012**, *4*, 130–133.

(4) For examples of asymmetric palladium-catalyzed protonation reactions of cyclic ketone enolates, see: (a) Mohr, J. T.; Nishimata, T.; Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 11348–11349. (b) Marinescu, S. C.; Nishimata, T.; Mohr, J. T.; Stoltz, B. M. *Org. Lett.* **2008**, *10*, 1039–1042.

(5) For an example of an asymmetric palladium-catalyzed conjugate addition/enolate alkylation cascade reaction of cyclic ketone enolates, see: Streuff, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nature Chem.* **2010**, *2*, 192–196.

(6) For studies on the computational and experimental studies on the mechanism of palladium-catalyzed asymmetric alkylation using the PHOX ligand scaffold, see: (a) Keith, J. A.; Behenna, D. C.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Oxgaard, J.; Stoltz, B. M.; Goddard, III, W. A. *J. Am. Chem. Soc.* **2007**, *129*, 11876–11877. (b) Sherden, N. H.; Behenna, D. C.; Virgil, S. C.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6840–6843. (c) Keith, J. A.; Behenna, D. C.; Sherden, N.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Nielsen, R. J.; Oxgaard, J.; Stoltz, B. M.; Goddard, III, W. A. *J. Am. Chem. Soc.* **2012**, *134*, 19050–19060.

(7) For examples of the asymmetric alkylation of cyclic ketone, vinylogous ester, or vinylogous thioester-derived enolates in the context of natural product synthesis, see: (a) Dichroanone: McFadden, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 7738–7739. (b) Elatol: White, D. E.; Stewart, I. C.; Grubbs, R. H.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 810–811. (c) Cyanthiwigin F: Enquist, Jr., J. A.; Stoltz, B. M. *Nature* **2008**, *453*, 1228–1231. (d) Carissone: Levine, S. R.; Krout, M. R.; Stoltz, B. M. *Org. Lett.* **2009**, *11*, 289–292. (e) Cassiol: Petrova, K. V.; Mohr, J. T.; Stoltz, B. M. *Org. Lett.* **2009**, *11*, 293–295. (f) Elatol, Laurencenone C, α-Chamigrene, and the Proposed Structure of Laurencenone B: White, D. E.; Stewart, I. C.; Seashore-Ludlow, B. A.; Grubbs, R. H.; Stoltz, B. M. *Tetrahedron* **2010**, *66*, 4668–4686. (g) Hamigeran B: Mukherjee, H. McDougal, N. T.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* **2011**, *13*, 825–827. (h) Liphagal: Day, J. J.; McFadden, R. M.; Virgil, S. C.; Kolding, H.; Alleva, J. L.; Stoltz, B.

M. *Angew. Chem., Int. Ed.* **2011**, *50*, 6814–6818. (i) Cyanthiwigins B, F, and G: Enquist, Jr., J. A.; Virgil, S. C.; Stoltz, B. M. *Chem.—Eur. J.* **2011**, *17*, 9957–9969.

(8) For our initial communication on the addition of organometallic reagents to chiral vinylogous esters to form γ-quaternary cycloheptenones, see: Bennett, N. B.; Hong, A. Y.; Harned, A. M.; Stoltz, B. M. *Org. Biomol. Chem.* **2012**, *10*, 56–59.

(9) For our initial communication on the palladium catalyzed asymmetric alkylation and ring contraction studies in the synthesis of γ-quaternary acylcyclopentenes, see: Hong, A. Y.; Krout, M. R.; Jensen, T.; Bennett, N. B.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 2756–2760.

(10) Concurrent with our efforts, palladium–catalyzed asymmetric allylic alkylations reactions of unstabilized enolates for the synthesis of enantioenriched α-quaternary cyclic ketones, vinylogous esters, and vinylogous thioesters were reported by Trost. See: (a) Trost, B. M.; Pissot-Soldermann, C.; Chen, I.; Schroeder, G. M. *J. Am. Chem. Soc.* **2004**, *126*, 4480–4481. (b) Trost, B. M.; Schroeder, G. M. *Chem.—Eur. J.* **2005**, *11*, 174–184. (c) Trost, B. M.; Pissot-Soldermann, C.; Chen, I. *Chem.—Eur. J.* **2005**, *11*, 951–959. (d) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846–2847. (e) Trost, B. M.; Bream, R. N.; Xu, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3109–3112.

(11) 1,3-Cycloheptanedione (catalog #515981) and 3-isobutoxy-2-cyclohepten-1-one (catalog #T271322) are commercially available from Sigma-Aldrich. The price of 1,3-cycloheptanedione is $40,000/mol. Adopted from Aldrich August 28th, 2011.

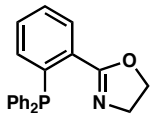
(12) (a) Ragan, J. A.; Makowski, T. W.; am Ende, D. J.; Clifford, P. J.; Young, G. R.; Conrad, A. K.; Eisenbeis, S. A. *Org. Process Res. Dev.* **1998**, *2*, 379–381. (b) Ragan, J. A.; Murry, J. A.; Castaldi, M. J.; Conrad, A. K.; Jones, B. P.; Li, B.; Makowski, T. W.; McDermott, R.; Sitter, B. J.; White, T. D.; Young, G. R. *Org. Process. Res. Dev.* **2001**, *5*, 498–507. (c) Do, N.; McDermott, R. E.; Ragan, J. A. *Org. Synth.* **2008**, *85*, 138–146.

(13) (a) Ukai, T.; Kawazura, H.; Ishii, Y.; Bonnet, J. J.; Ibers, J. A. *J. Organomet. Chem.* **1974**, 65, 253–266. (b) Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F. *Org. Lett.* **2004**, *6*, 4435–4438.

(14) $Pd_2(pmdba)_3$ is preferable to $Pd_2(dba)_3$ in this reaction for ease of separation of pmdba from the reaction products during purification. pmdba = 4,4'-methoxydibenzylideneacetone.

(15) Our group has made improvements to the synthetic route toward PHOX ligands and developed procedures for large-scale synthesis. See: (a) Tani, K.; Behenna, D. C.; McFadden, R. M.; Stoltz, B. M. *Org. Lett.* **2007**, *9*, 2529–2531. (b) Krout, M. R.; Mohr, J. T.; Stoltz, B. M. *Org. Synth.* **2009**, *86*, 181–193.

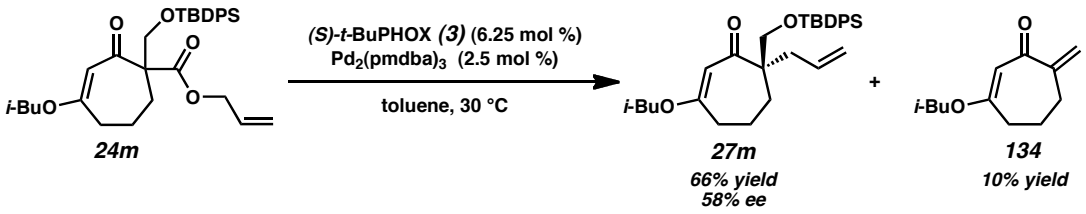
(16) Racemic products were obtained using $Pd(PPh_3)_4$ (5 mol %) or achiral PHOX ligand **128** (6.25 mol %) and $Pd_2(pmdba)_3$ (2.5 mol %) in toluene at 30 °C.



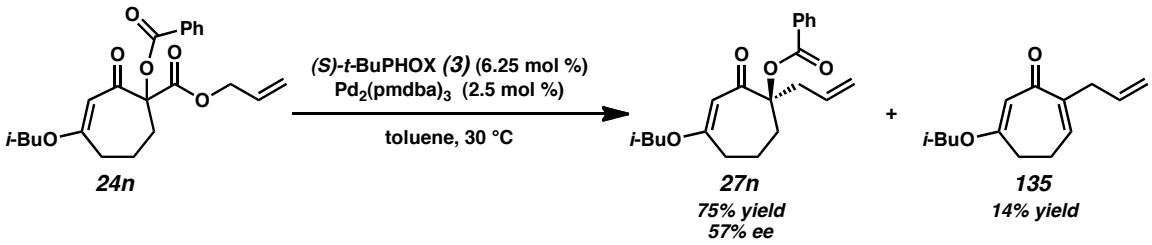
128

(17) For a preparation of electron-deficient PHOX ligand **8** ((*S*)-$(CF_3)_3$-*t*-BuPHOX), see: (a) McDougal, N. T.; Streuff, J.; Mukherjee, H.; Virgil, S. C.; Stoltz, B. M. *Tetrahedron Lett*. **2010**, *51*, 5550–5554. (b) Also see ref. 7b and 7f.

(18) The reaction with silyl-protected alcohol **24m** afforded alkylation product **27m** and exocyclic enone **134** in 10% yield. A related silyl-protected alcohol substrate did not display this type of elimination during an asymmetric decarboxylative alkylation reaction on a six-membered ring β-ketoester substrate. See ref. 2b.



(19) The reaction with benzoate ester **24n** afforded alkylation product **27n** and endocyclic enone **135** in 14% yield.



(20) Stork, G.; Danheiser, R. L. *J. Org. Chem*. **1973**, *38*, 1775–1776.

(21) Differences in ring conformational preferences can also be observed in the ^{1}H NMR spectra of 1,3-cyclohexadione (exclusively ketoenol form) and 1,3-cycloheptadione (exclusively diketo form). See ref. 12c.

(22) For selected examples of the two-carbon ring contraction of seven-membered carbocycles, see: (a) Frankel, J. J.; Julia, S.; Richard-Neuville, C. *Bull. Soc.*

Chim. Fr. **1968**, 4870–4875. (b) Jun, C.-H.; Moon, C. W.; Lim, S.-G.; Lee, H. *Org. Lett.* **2002**, *4*, 1595–1597.

(23) Notably, **70a** and related β-hydroxyketones appear to undergo minimal decomposition after several months of storage at room temperature by TLC and ^{1}H NMR analysis, and immediate conversion to acylcyclopentenes **53a** is not necessary to achieve high yields.

(24) While a recent report shows a single example of a similar β-hydroxyketone, we believe the unusual reactivity and synthetic potential of these compounds has not been fully explored. See: Rinderhagen, H.; Mattay, J. *Chem.—Eur. J.* **2004**, *10*, 851–874.

(25) For an example of a photochemical two-carbon ring contraction of a macrocycle, see: Yang, Z.; Li, Y.; Pattenden, G. *Tetrahedron* **2010**, *66*, 6546–6549.

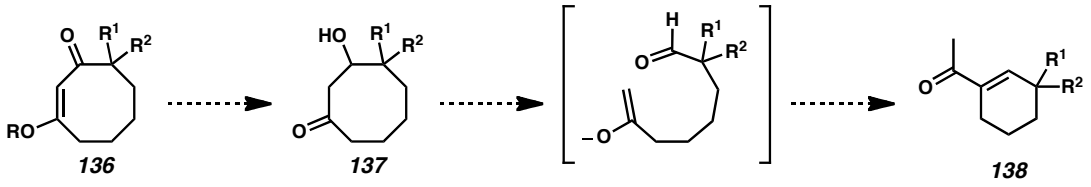
(26) For examples of ring contractions of medium-sized ring heterocycles, see: (a) Nasveschuk, C. G.; Rovis, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3264–3267. (b) Nasveschuk, C. G.; Rovis, T. *J. Org. Chem.* **2008**, *73*, 612–617. (c) Nasveschuk, C. G.; Rovis, T. *Org. Biomol. Chem.* **2008**, *6*, 240–254. (d) Baktharaman, S.; Afagh, N.; Vandersteen, A.; Yudin A. K. *Org. Lett.* **2010**, *12*, 240–243. (e) Dubovyk, I.; Pichugin, D.; Yudin, A. K. *Angew. Chem., Int. Ed.* **2011**, *50*, 5924–5926. (f) Volchkov, I.; Park, S.; Lee, D. *Org. Lett.* **2011**, *13*, 3530–3533. (g) Dubinina, G. G.; Chain, W. J. *Tetrahedron Lett.* **2011**, *52*, 939–942.

(27) For a discussion of the properties of fluorinated alcohols and their use, see: Begue, J.-P.; Bonnet-Delpon, D.; Crousse, B. *Synlett* **2004**, 18–29.

(28) A lithium alkoxide species is presumably generated in situ based on the following pK_a values: (H_2O = 15.7, TFE = 12.5, HFIP = 9.3 [water]; H_2O = 31.2, TFE = 23.5, HFIP = 18.2 [DMSO]); Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.

(29) No reaction was observed with the following bases (with or without TFE additive): DBU, TMG, Na_2CO_3, $BaCO_3$, and CaH_2. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TMG = 1,1,3,3-tetramethylguanidine.

(30) The two-carbon ring contraction strategy can potentially be extended to β-hydroxyketones of other medium sized rings to provide other useful cyclic enone products. These possibilities are the subject of current investigations.

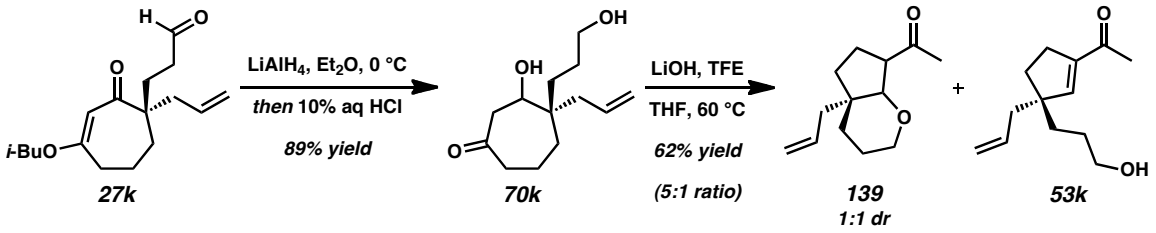


(31) Fluorinated lithium alkoxides were recently used to promote Horner–Wadsworth–Emmons olefinations of sensitive substrates, demonstrating their mild reactivity. See: Blasdel, L. K.; Myers, A. G. *Org. Lett.* **2005**, *7*, 4281–4283.

(32) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.

(33) Although we had success in preparing silyloxy acylcyclopentene **53p** from vinylogous ester **27p**, we wondered whether it would be possible to perform a ring contraction on aldehyde **27k**. Under our standard conditions, the intermediate ketodiol **70k** can be obtained in 89% yield, however the subsequent

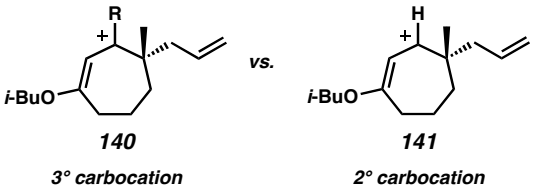
ring contraction proceeded in 62% yield to afford a complex mixture of pyran diastereomers **139** and uncyclized acylcyclopentene **53k**.



(34) Analytically pure samples of dione **79** can be obtained from vinylogous ester **27a** by treatment with acid. See Experimental Section (Section 2.7.2.10) for details.

(35) The addition of cerium chloride to reactions with organolithium or Grignard reagents has been shown to increase reactivity and reduce side reactions with vinylogous ester systems, see: Crimmins, M. T.; Dedopoulou, D. *Synth. Commun.* **1992**, *22*, 1953–1958.

(36) The increase in enone formation with the organometallic addition relative to the hydride reduction is likely due to the higher stability of the tertiary carbocation (**140**) compared to the secondary carbocation (**141**) formed along the reduction pathway.



(37) CCDC 686849 (**81**) contains the supplementary crystallographic data for this chapter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The data can also be viewed in Appendix 3.

(38) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299–6302.

(39) Herrmann, W. A.; Brossmer, C.; Öfele, K.; Reisinger, C.-P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1845–1848.

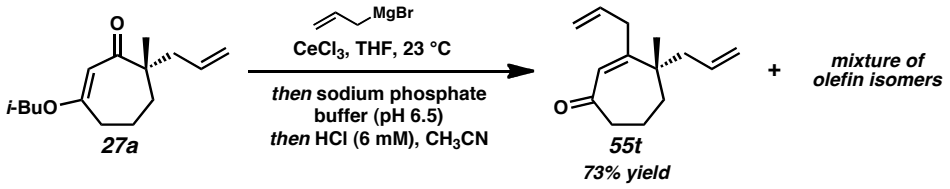
(40) Another application of the ring contraction methodology toward daucane sesquiterpenes is presented in Chapter 3.

(41) Hong, A. Y.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 9674–9678.

(42) Preferential β-hydroxyketone formation is observed when the acidification of the intermediate isobutyl enol ether is performed in diethyl ether instead of methanol. See Table 2.4.

(43) Attempts to purify the crude enol ether were challenging due to decomposition to enone **55r** and β-hydroxyketone **70r**.

(44) The yield of cycloheptenone **55t** is lower than many related enones due to the formation of several side products presumed to be non-conjugated alkene isomers.



(45) Synthesis of the simple β-vinyl substituted enone proved challenging due to the formation of a complex product mixture.

(46) Quenching the alkynyl nucleophile addition with hydrochloric acid provided a complex mixture of products, most notably one with an equivalent of HCl added into the molecule. This issue was resolved by instead using sulfuric acid.

(47) Cycloheptenone **55aa** is formed as a 1.9:1 mixture of atropisomers whose isomeric peaks coalesce in a variable temperature ^{1}H NMR study. See Figure A2.108.4.

(48) Jin, Z.; Fuchs, P. L. *J. Am. Chem. Soc.* **1994**, *116*, 5995–5996.

(49) Chung, Y. K.; Lee, B. Y.; Jeong, N.; Hudecek, M.; Pauson, P. L. *Organometallics* **1993**, *12*, 220–223.

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APPENDIX 2

Spectra Relevant to Chapter 2:

Catalytic Asymmetric Synthesis of Cyclopentanoid and Cycloheptanoid

Core Structures Using Pd-Catalyzed Asymmetric Alkylation

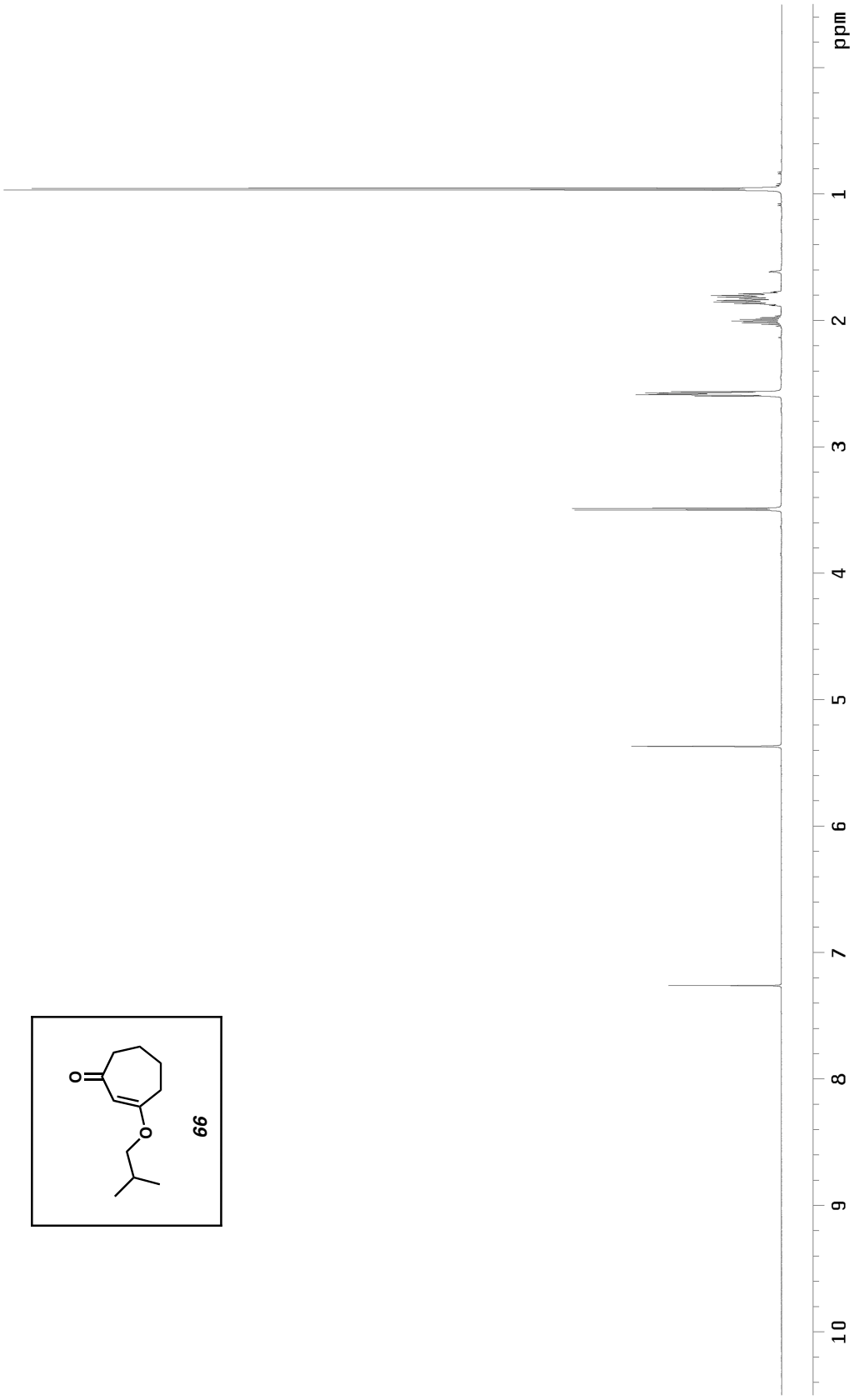


Figure A2.1.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **66**.

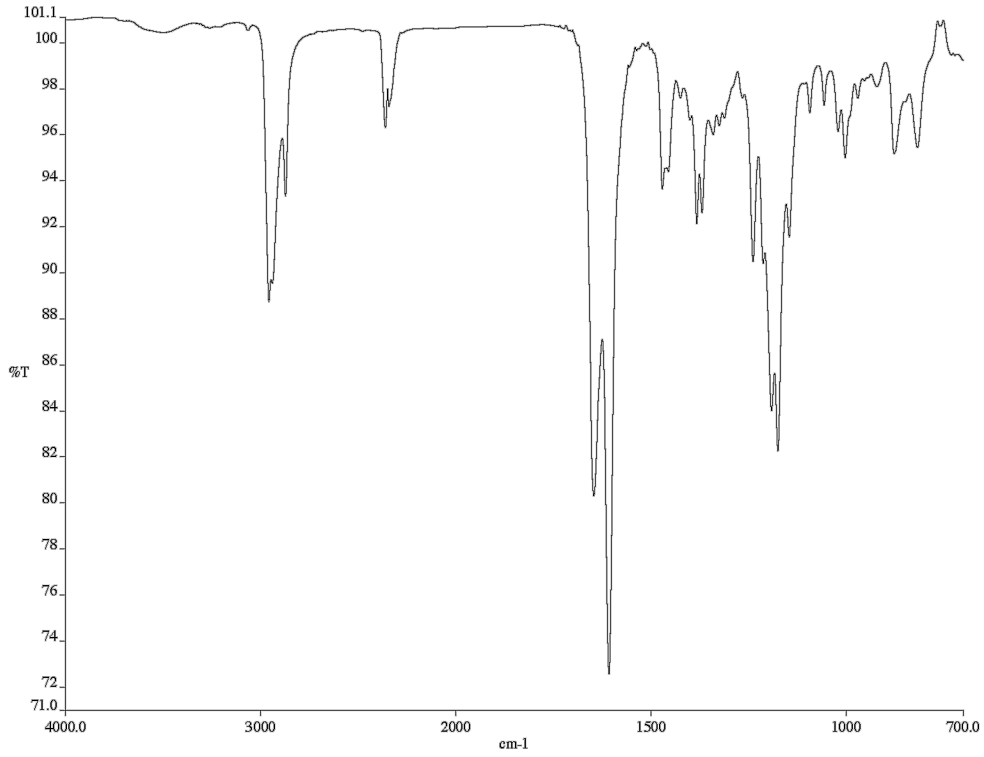


Figure A2.1.2. Infrared spectrum (thin film/NaCl) of compound **66**.

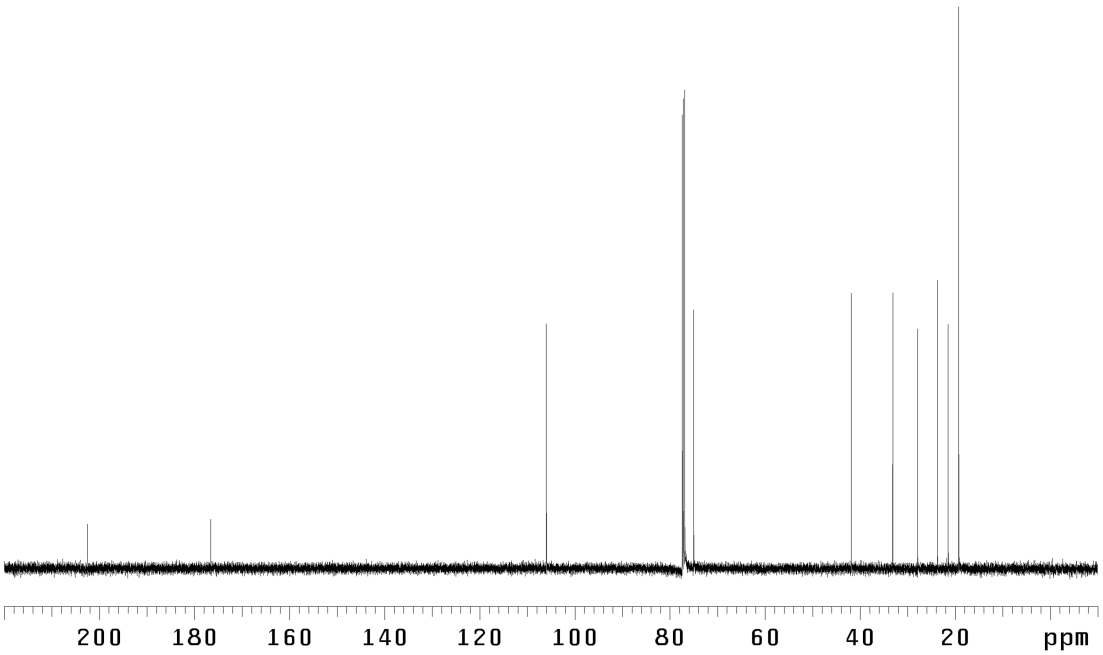


Figure A2.1.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **66**.

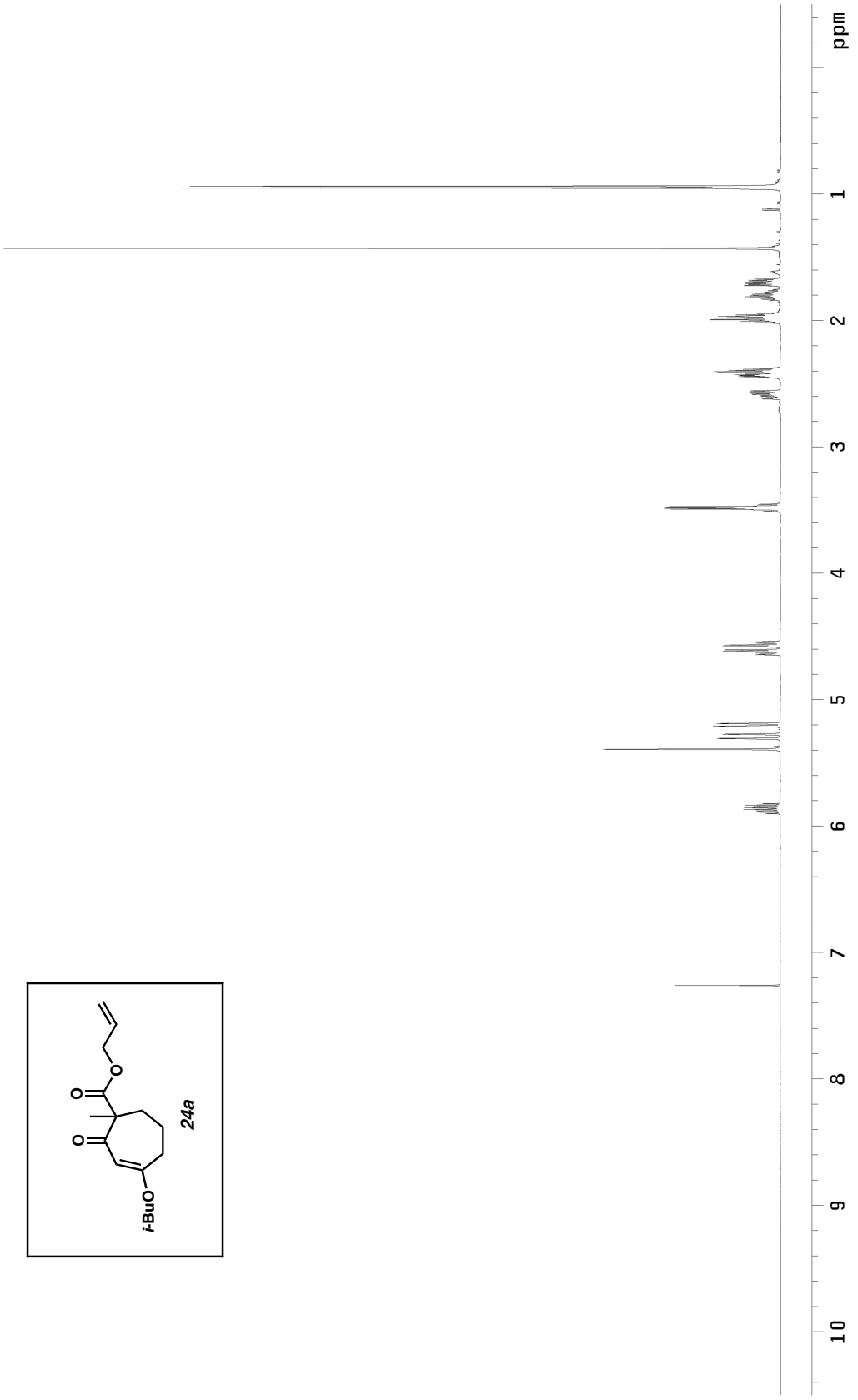


Figure A2.2.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **24a**.

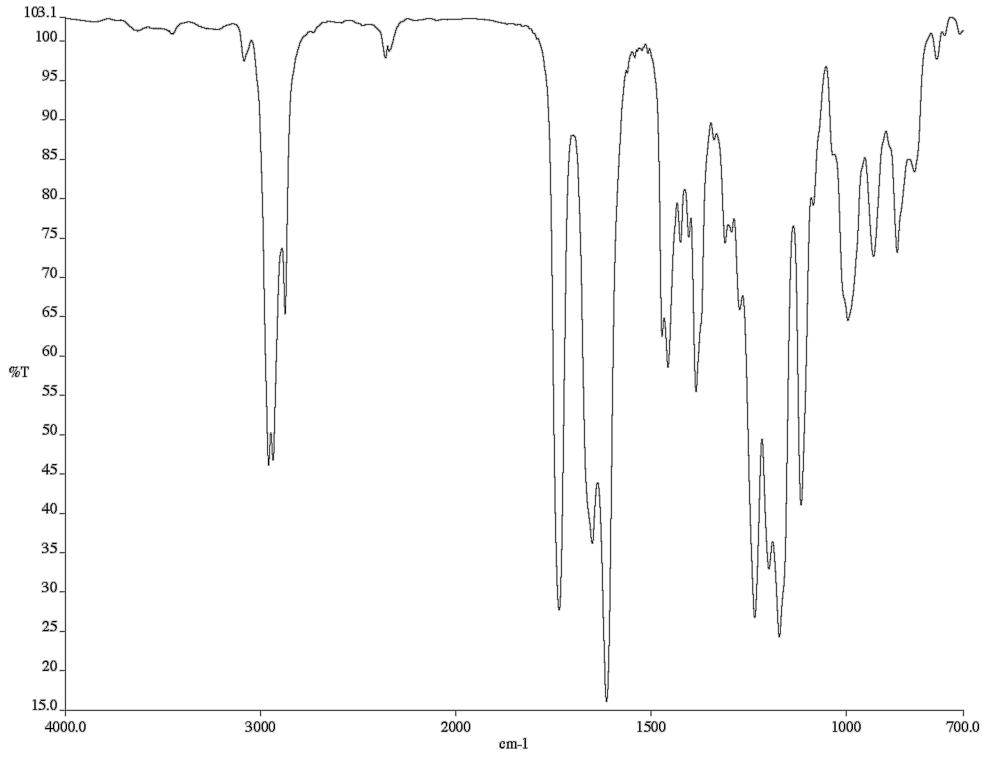


Figure A2.2.2. Infrared spectrum (thin film/NaCl) of compound **24a**.

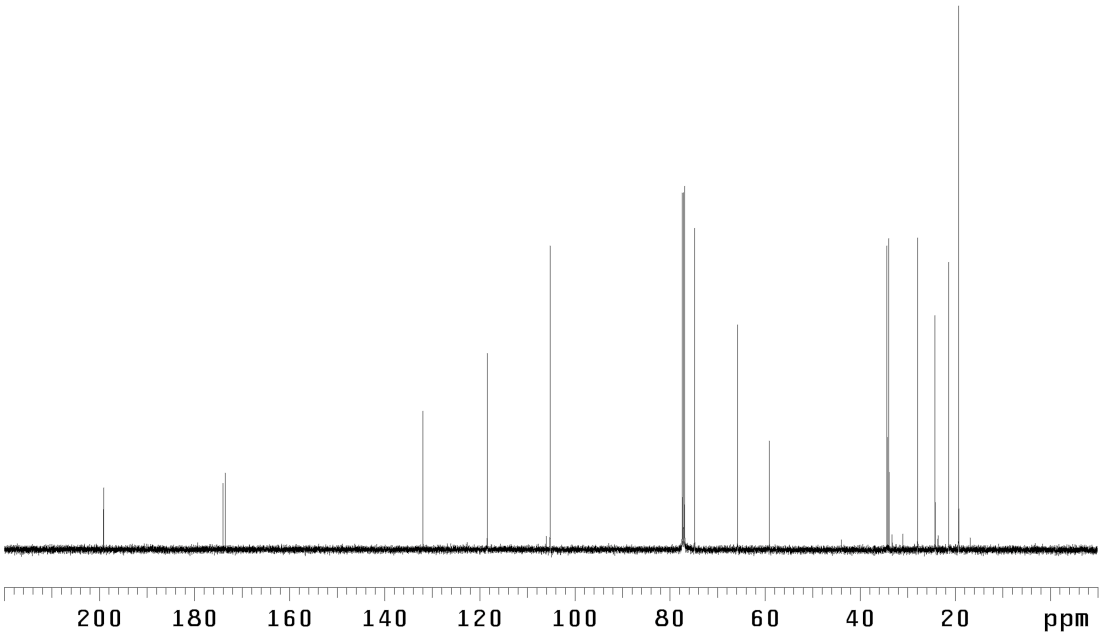


Figure A2.2.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **24a**.

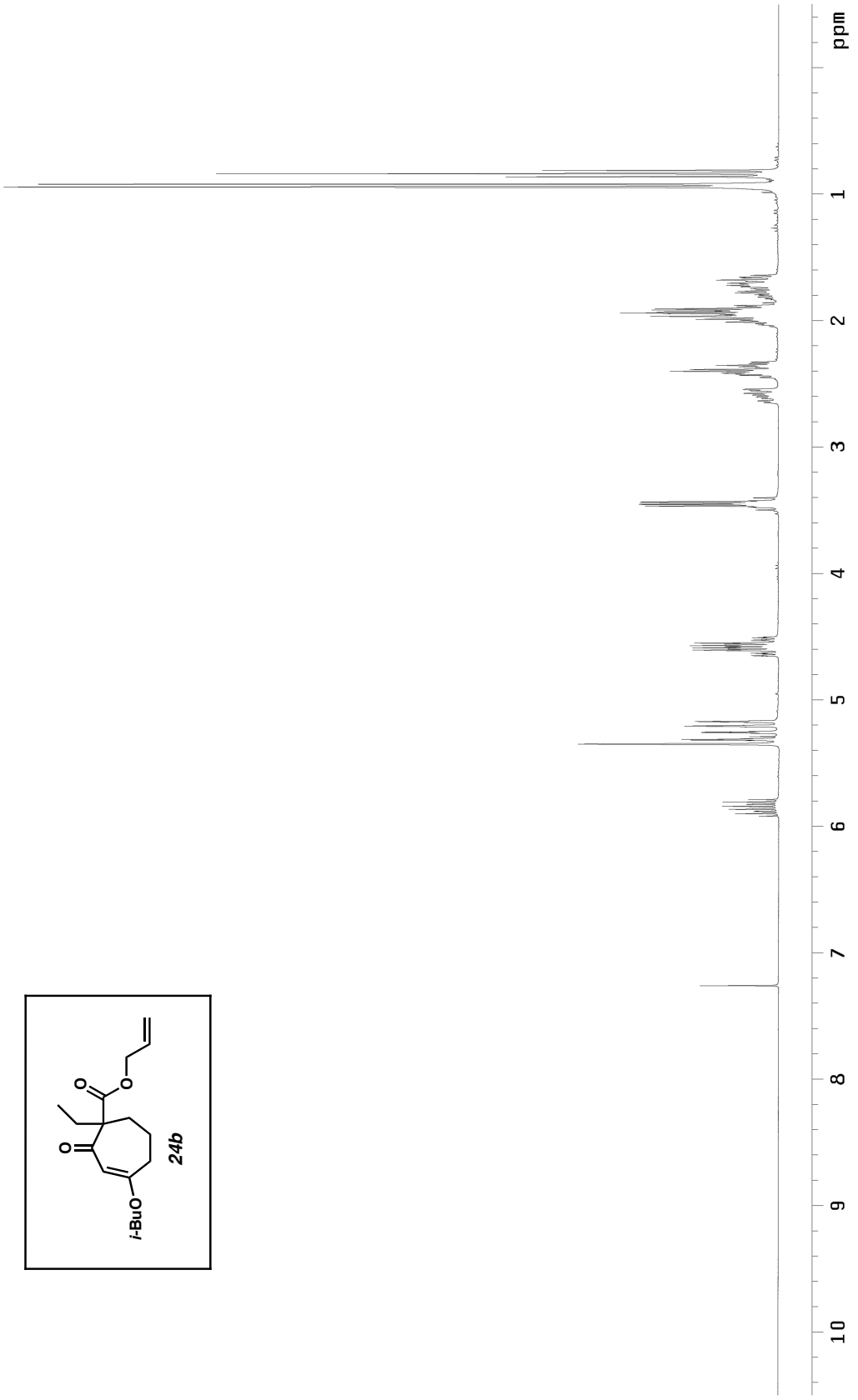


Figure A2.3.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **24b**.

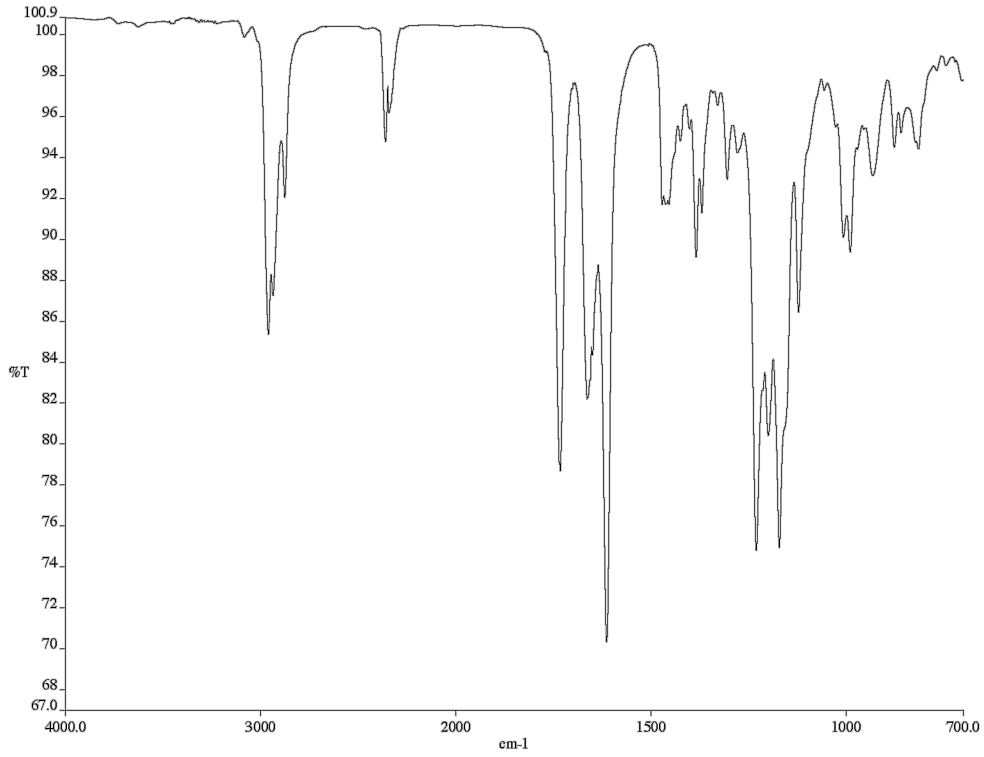


Figure A2.3.2. Infrared spectrum (thin film/NaCl) of compound **24b**.

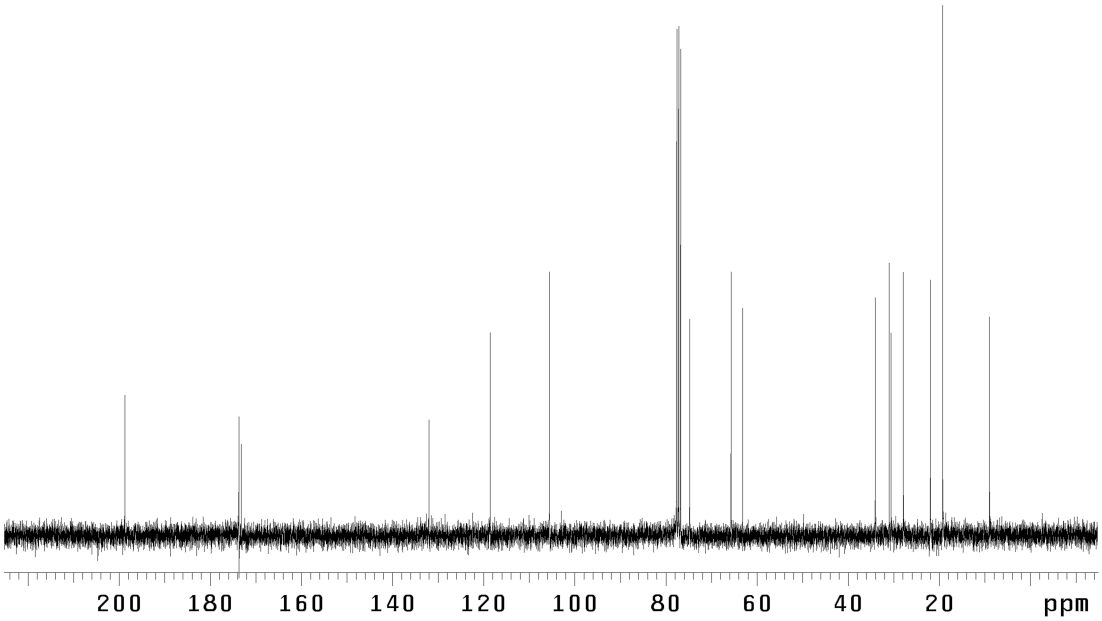


Figure A2.3.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **24b**.

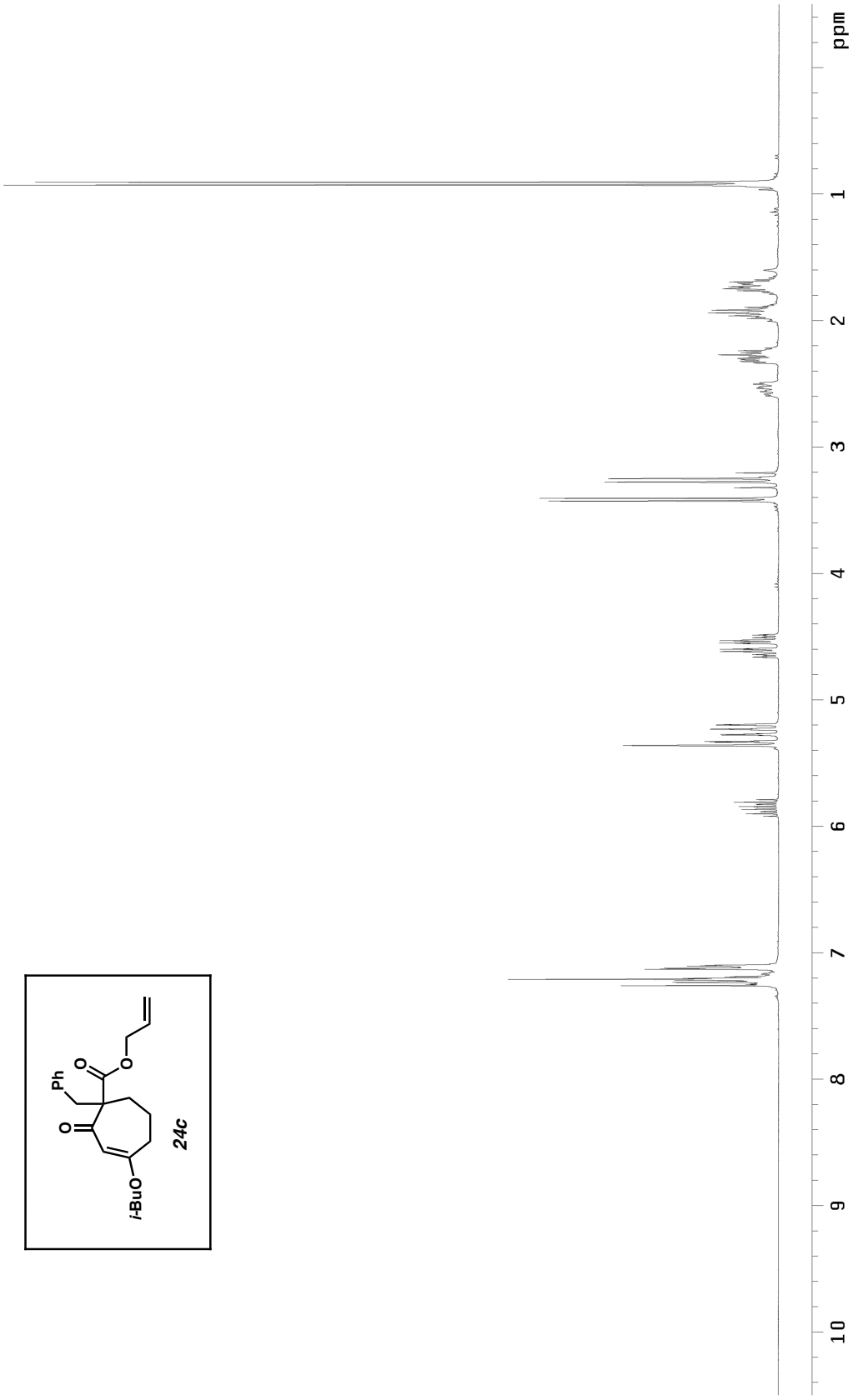


Figure A2.4.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **24c**.

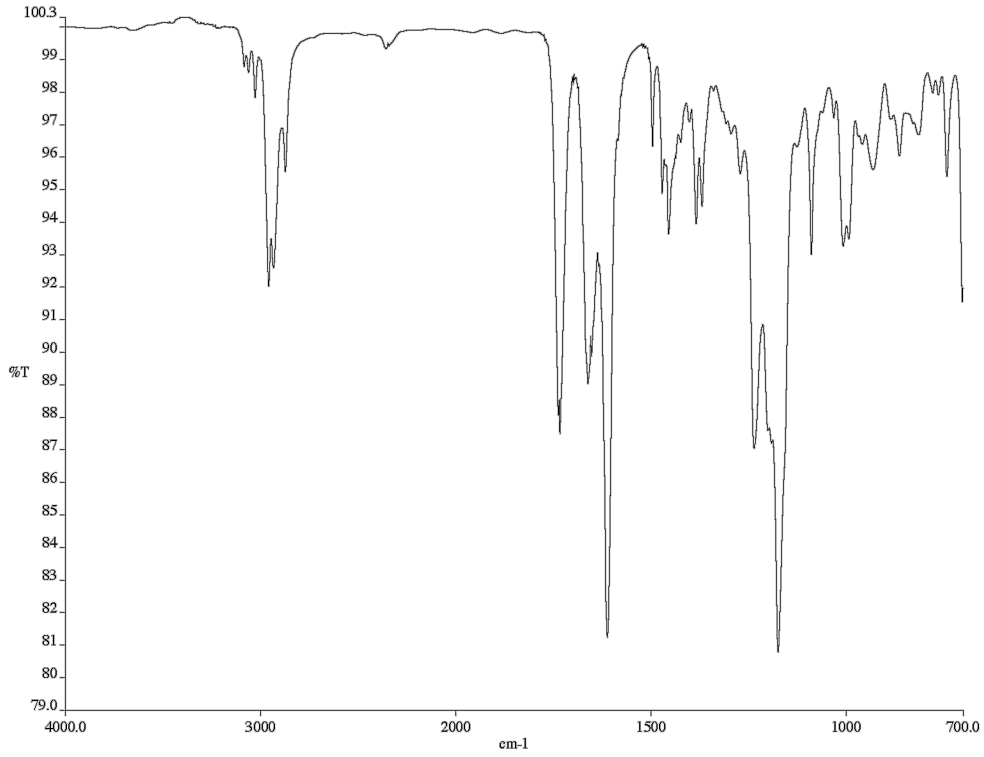


Figure A2.4.2. Infrared spectrum (thin film/NaCl) of compound **24c**.

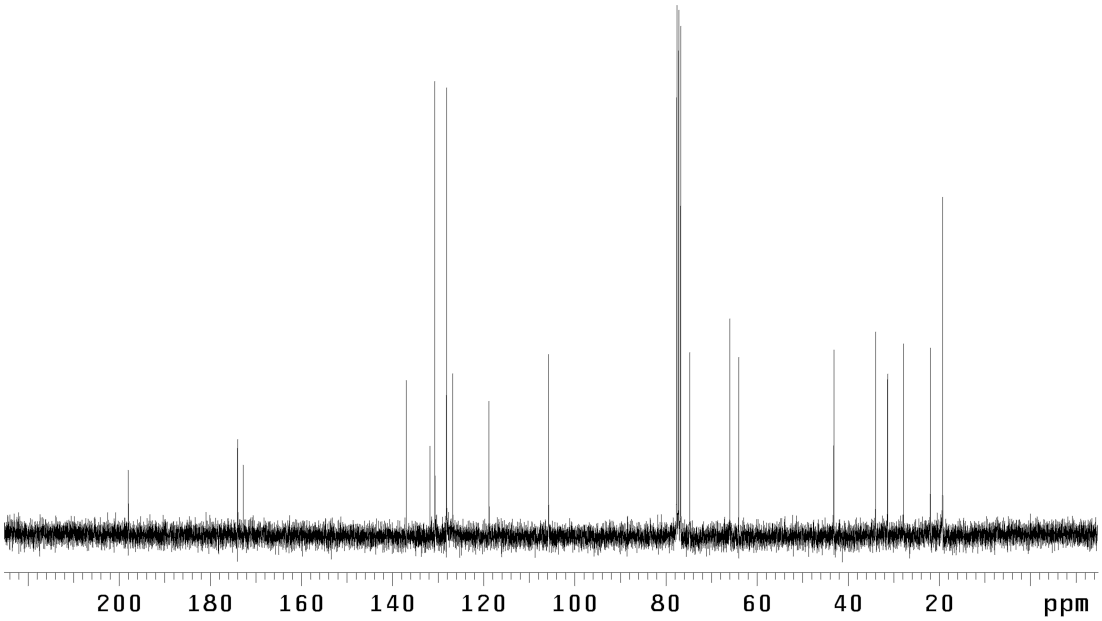


Figure A2.4.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **24c**.

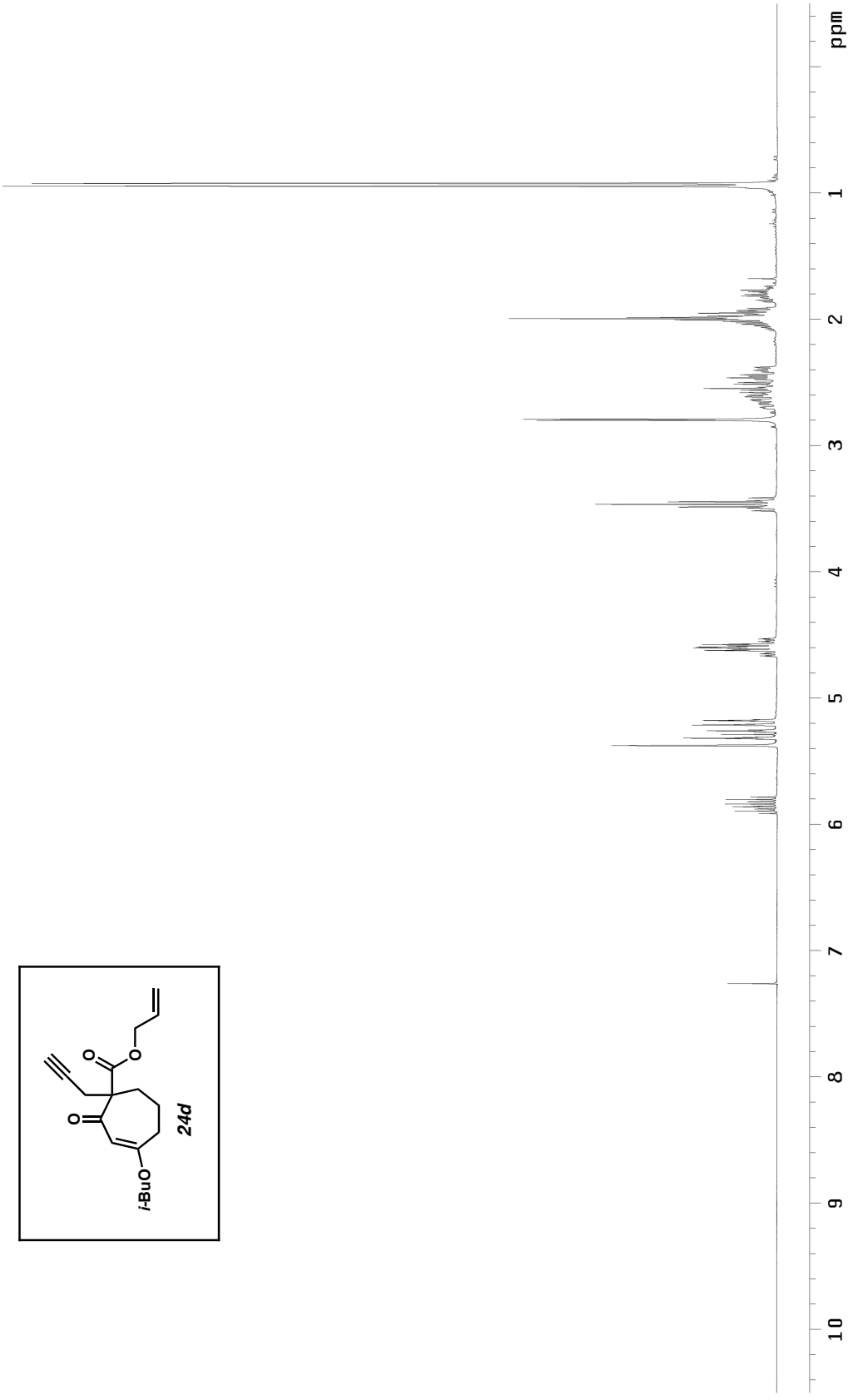


Figure A2.5.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **24d**.

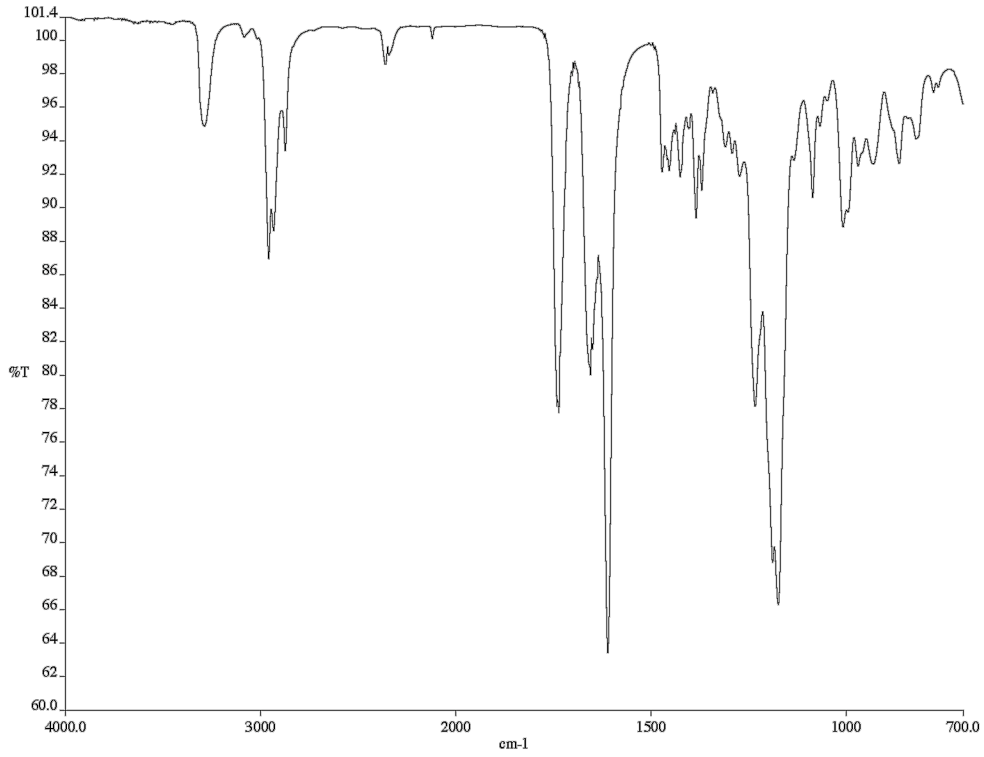


Figure A2.5.2. Infrared spectrum (thin film/NaCl) of compound **24d**.

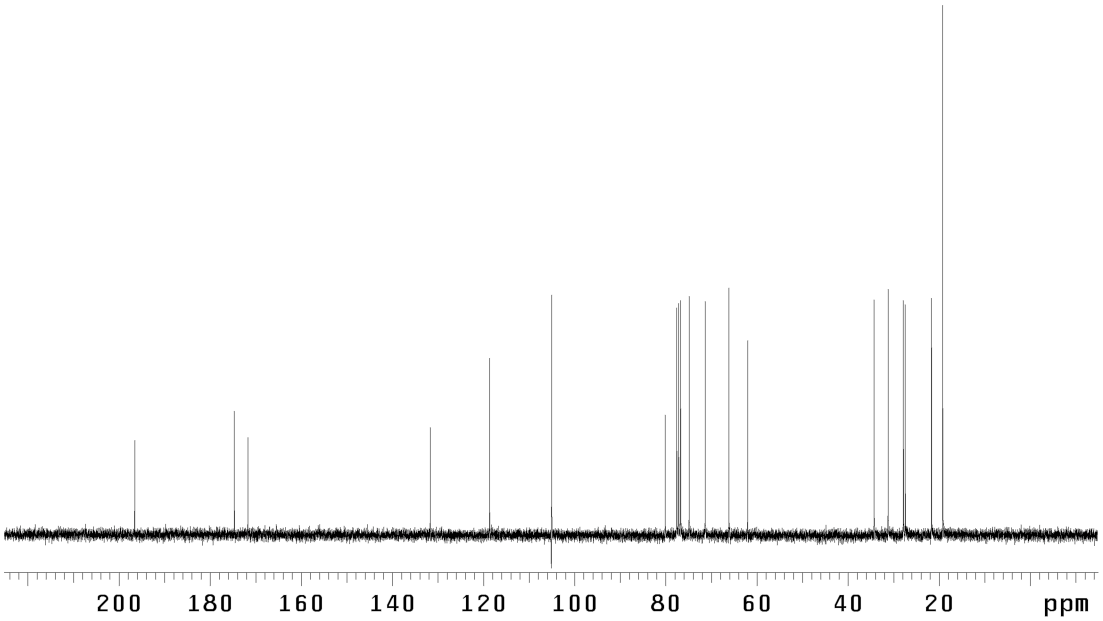


Figure A2.5.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **24d**.

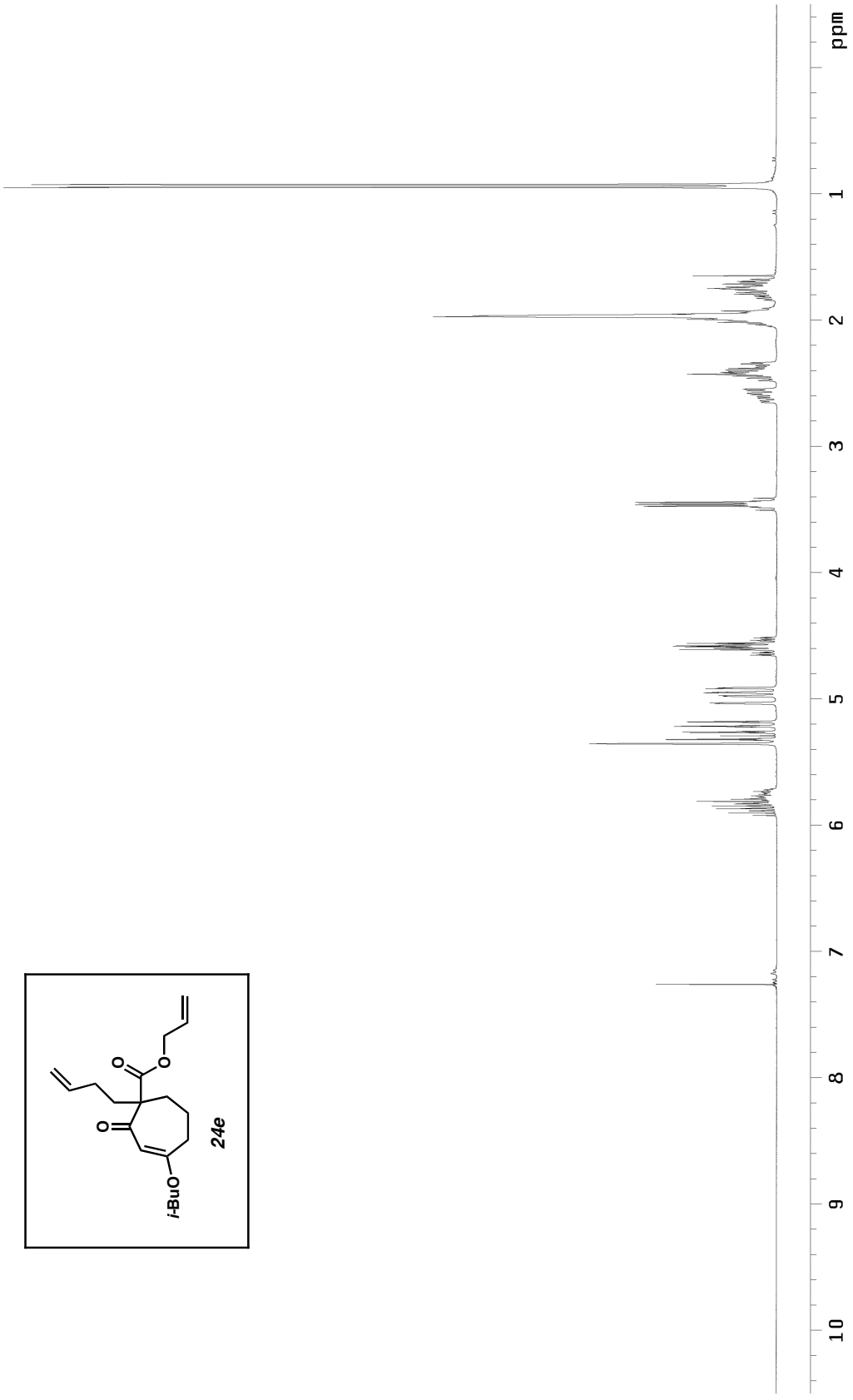


Figure A2.6.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **24e**.

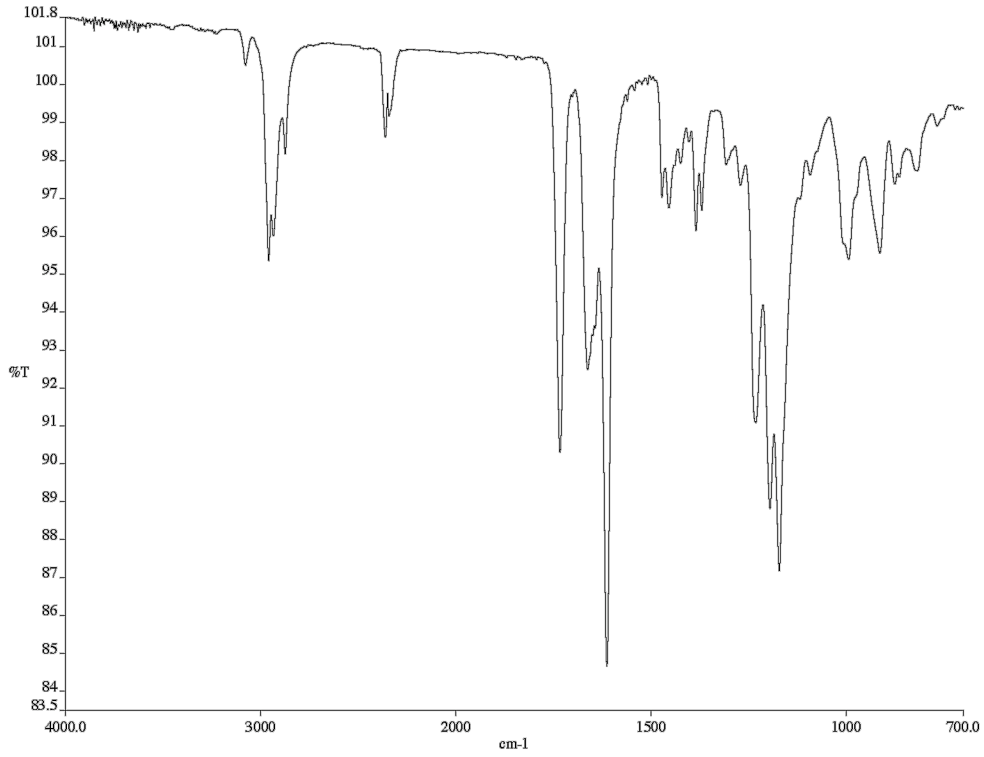


Figure A2.6.2. Infrared spectrum (thin film/NaCl) of compound **24e**.

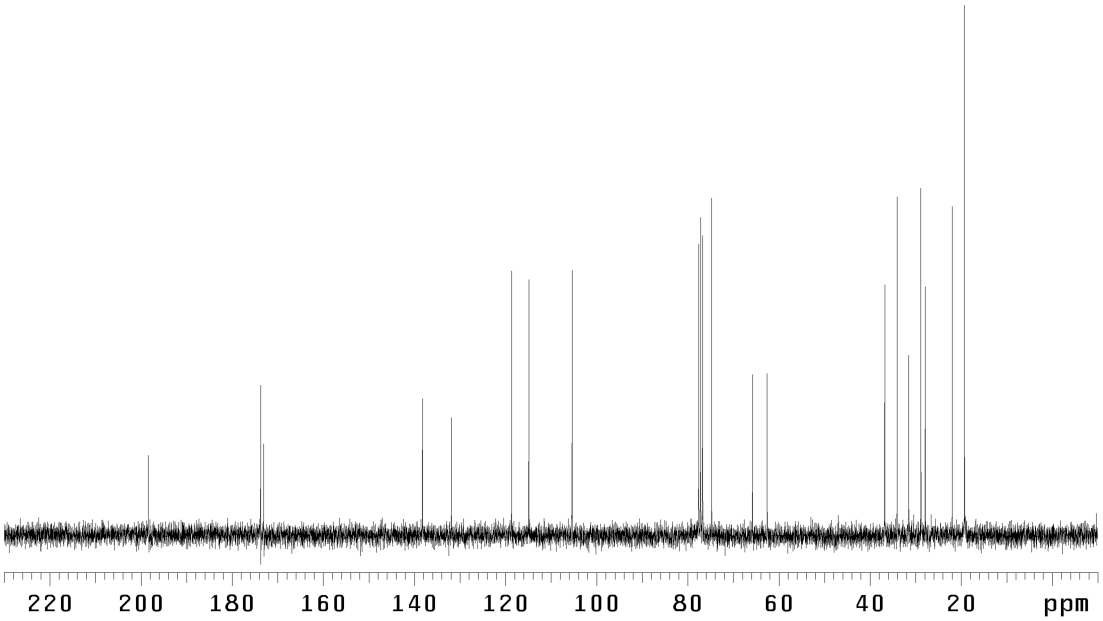


Figure A2.6.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **24e**.

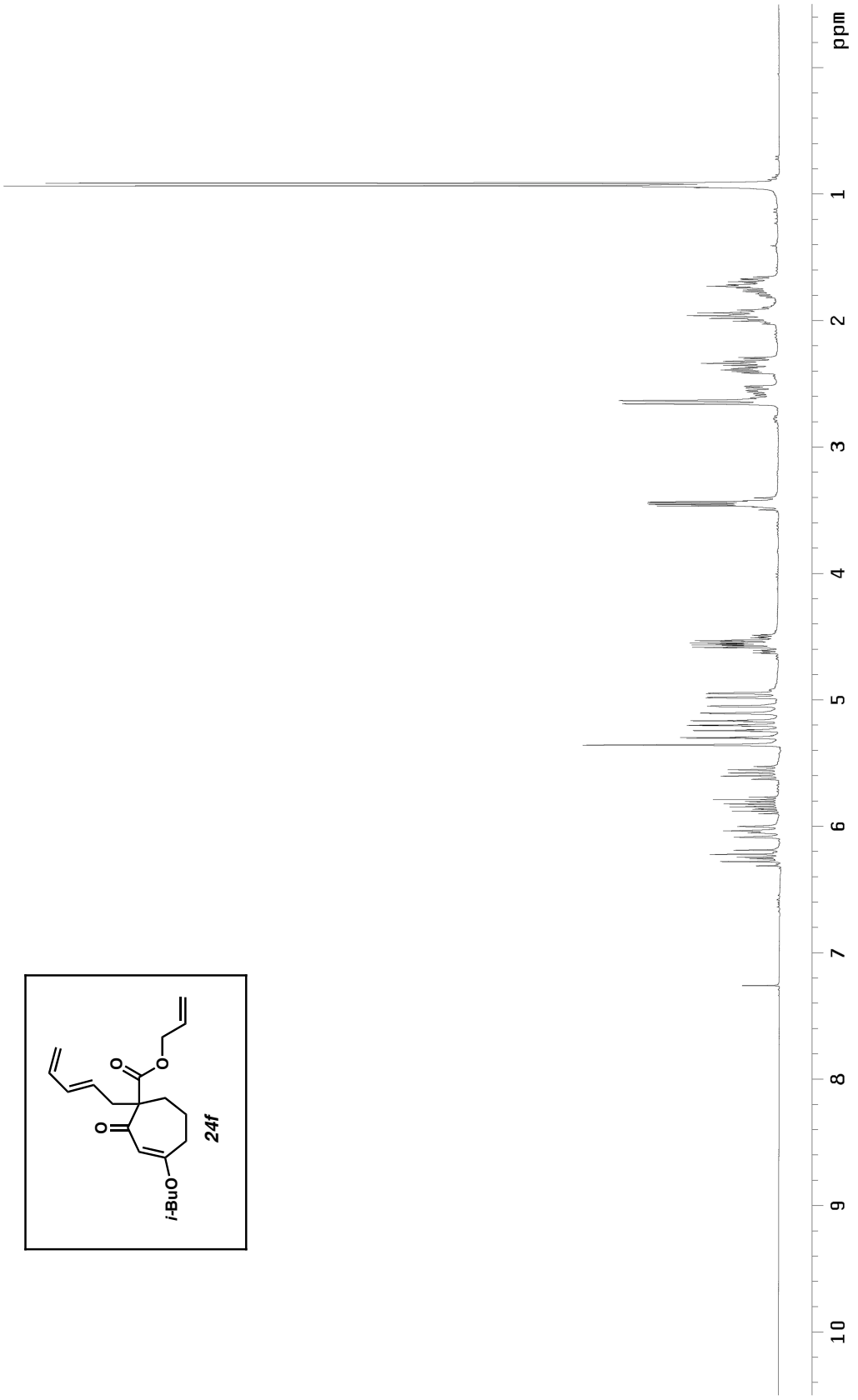


Figure A2.7.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **24f**.

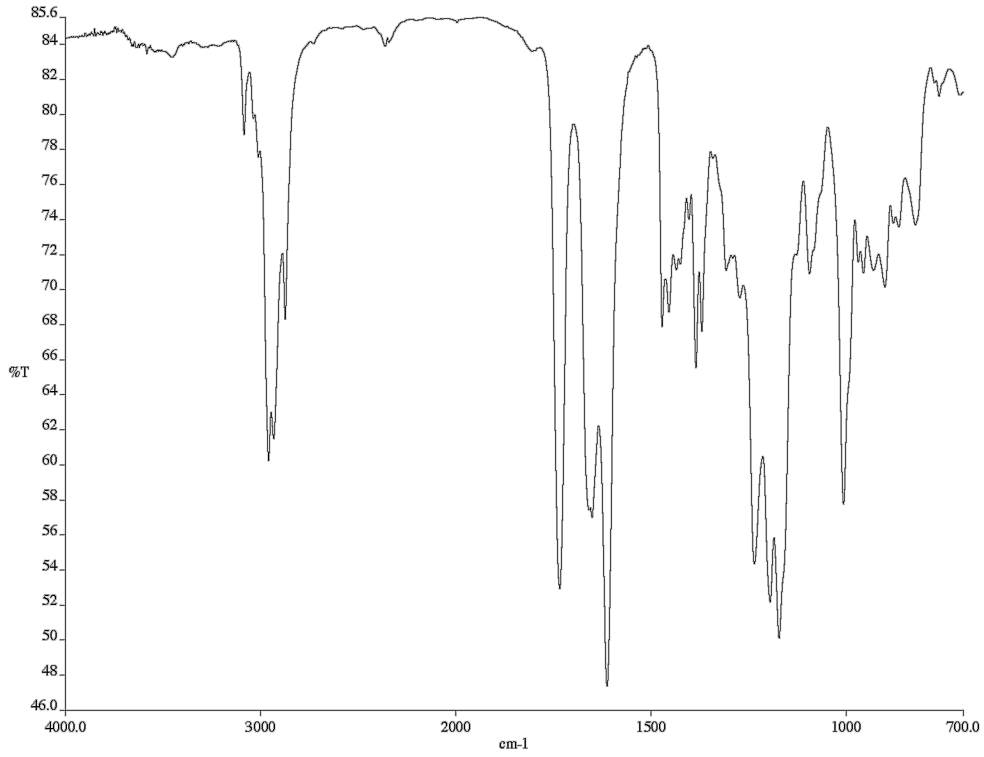


Figure A2.7.2. Infrared spectrum (thin film/NaCl) of compound **24f**.

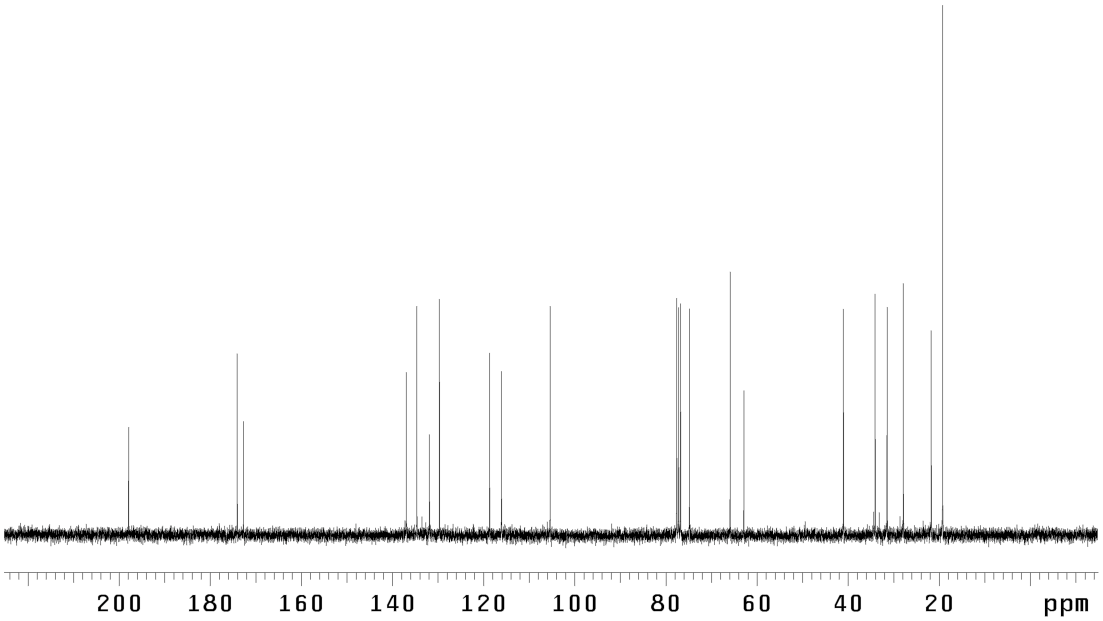


Figure A2.7.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **24f**.

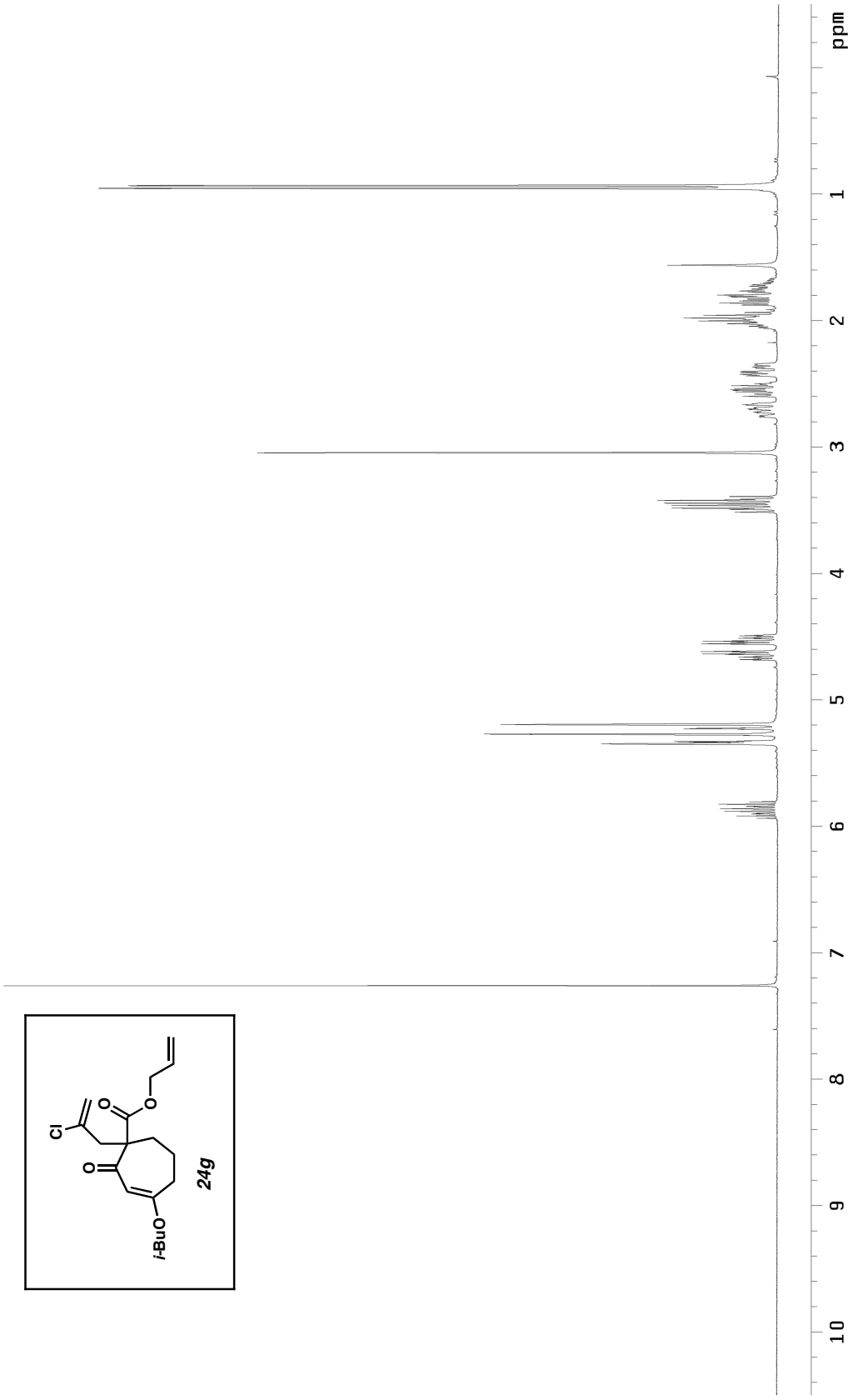


Figure A2.8.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **24g**.

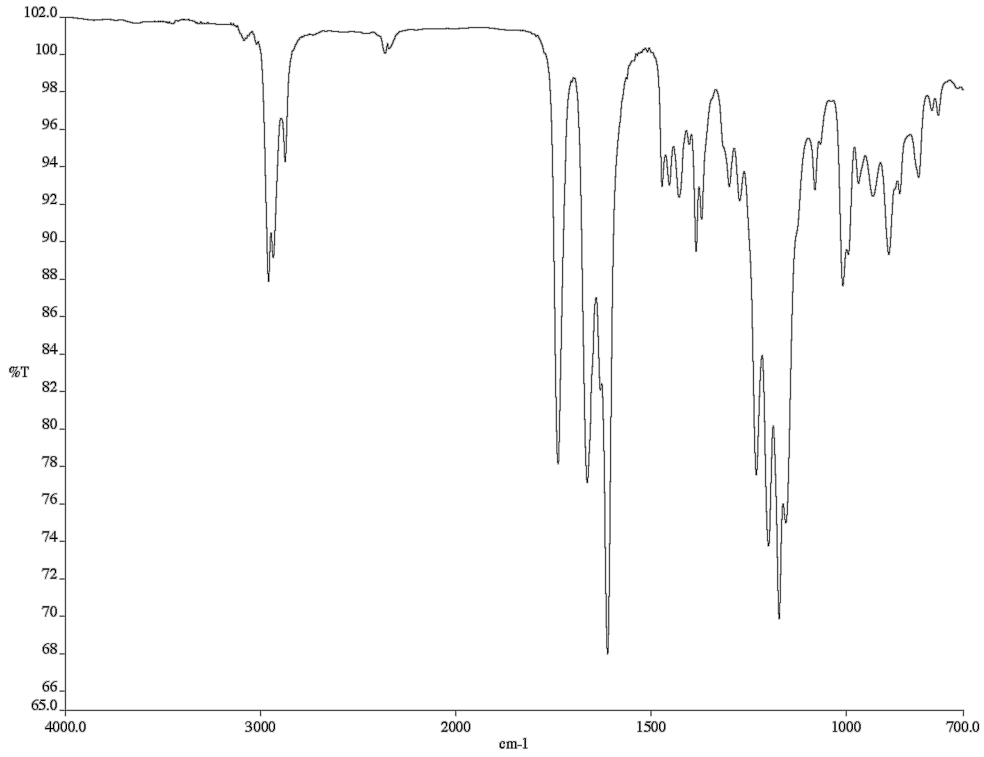


Figure A2.8.2. Infrared spectrum (thin film/NaCl) of compound **24g**.

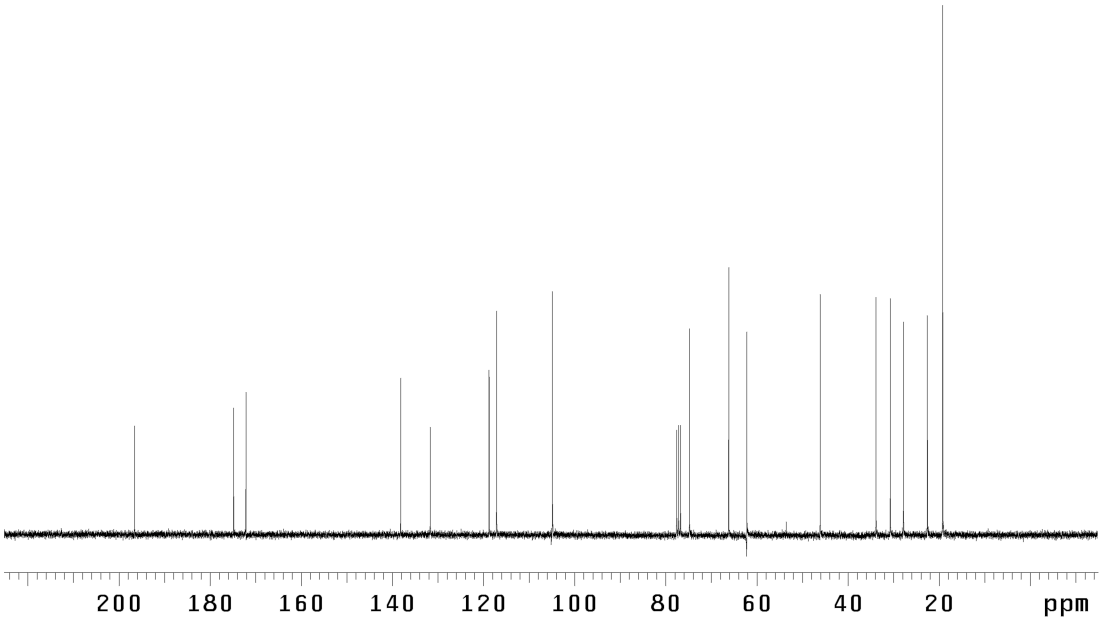


Figure A2.8.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **24g**.

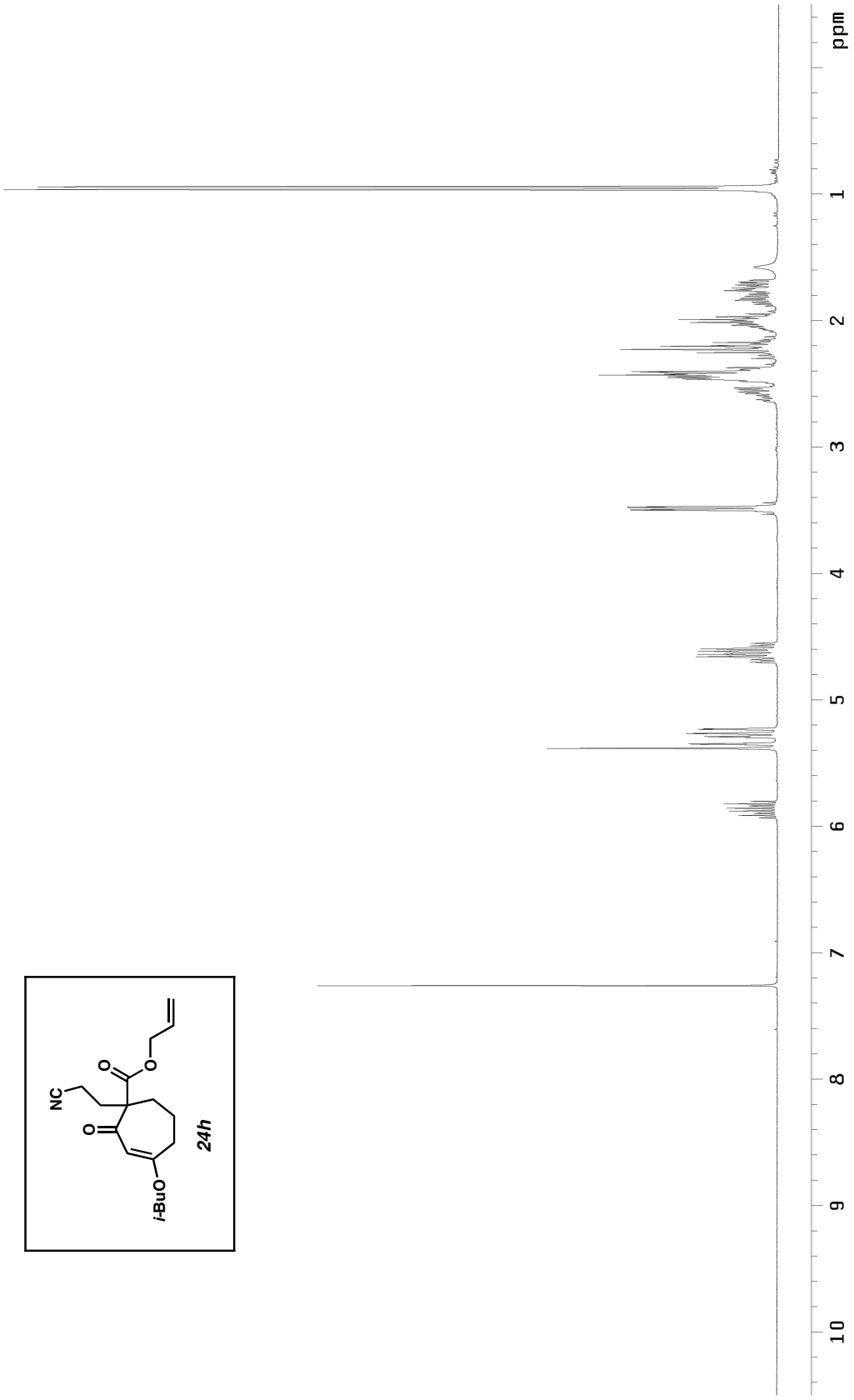


Figure A2.9.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **24h**.

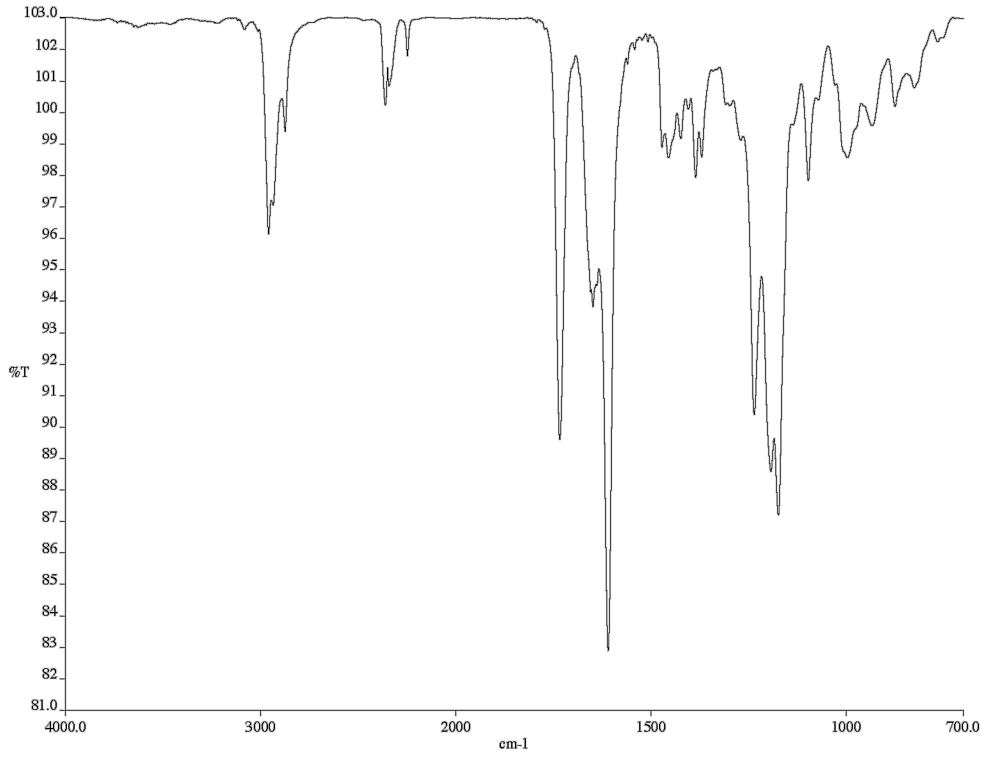


Figure A2.9.2. Infrared spectrum (thin film/NaCl) of compound **24h**.

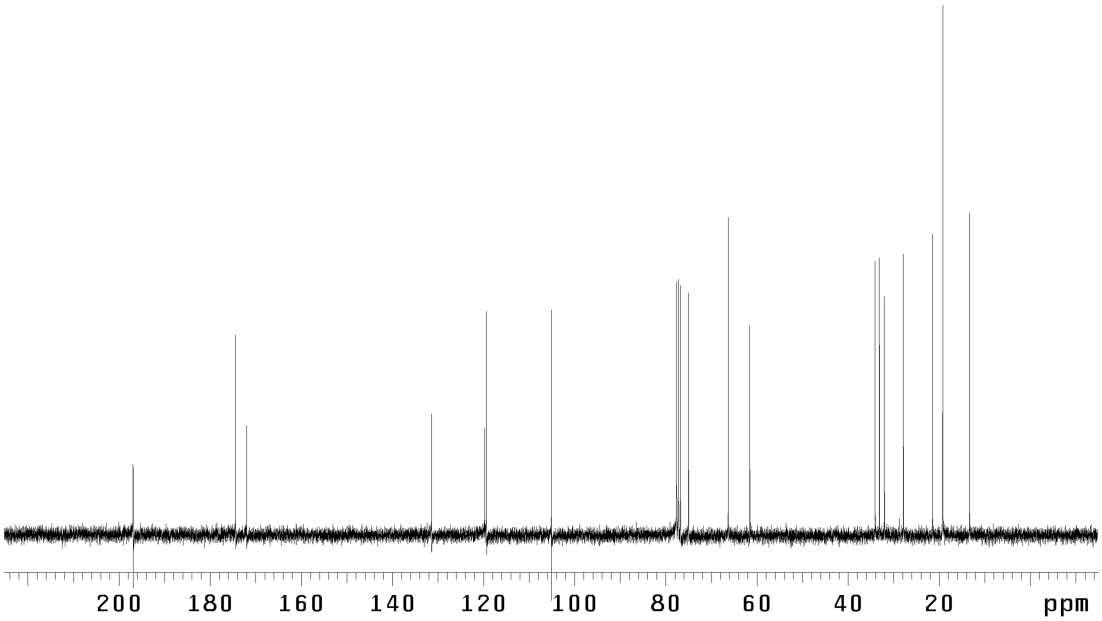


Figure A2.9.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **24h**.

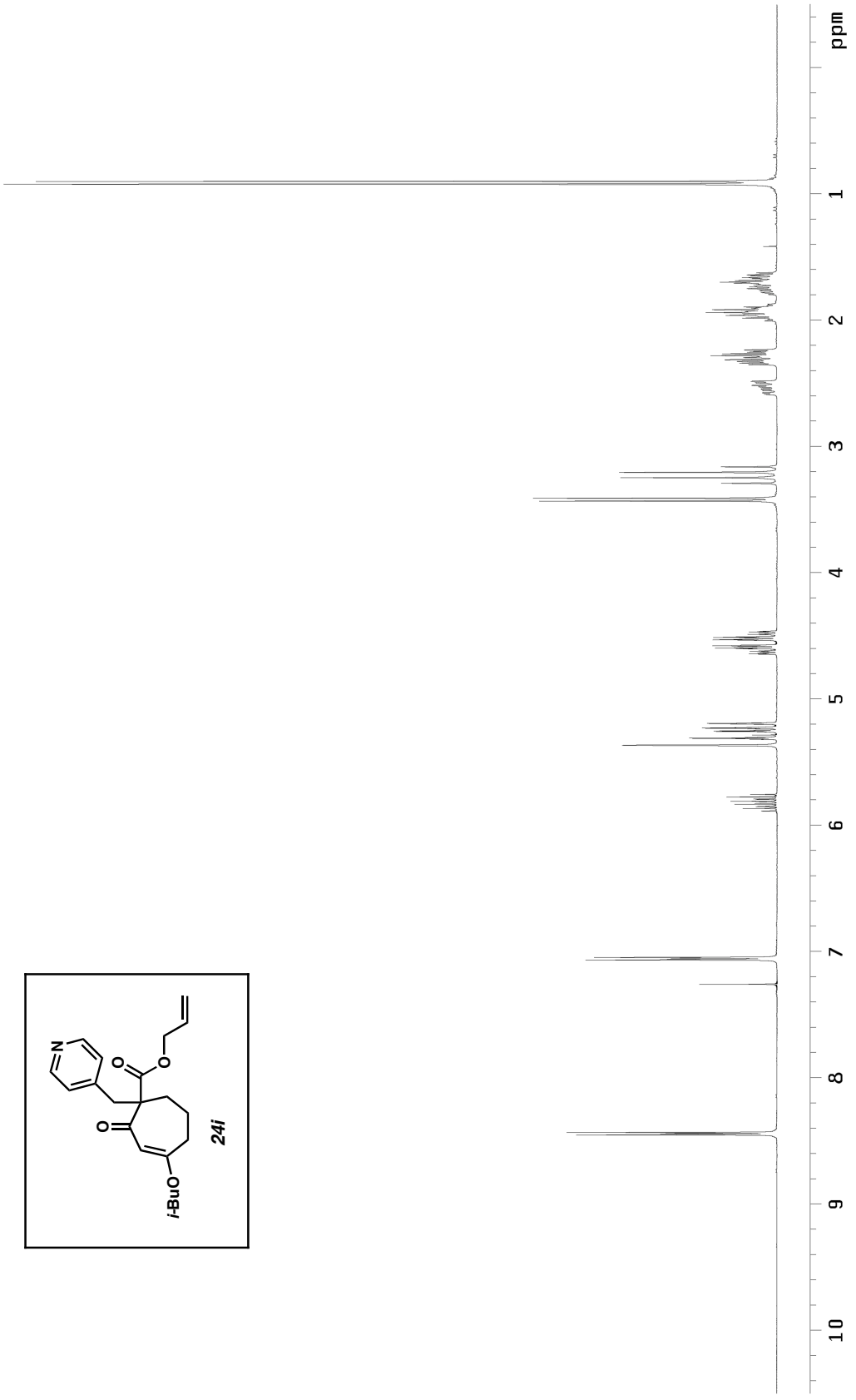


Figure A2.10.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **24i**.

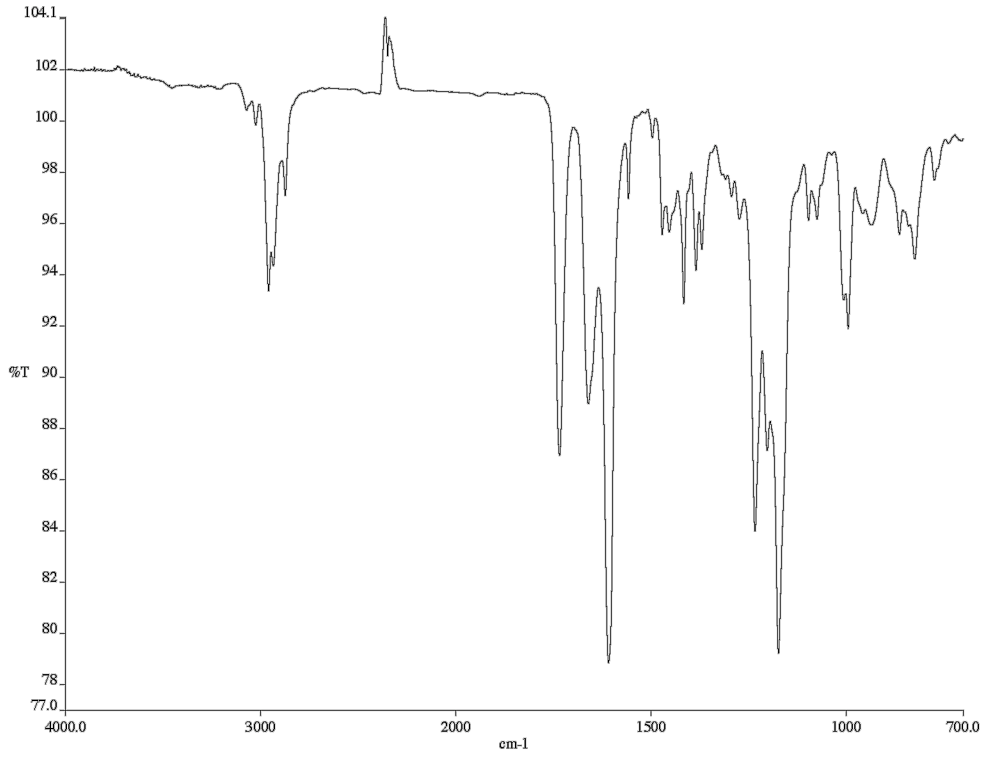


Figure A2.10.2. Infrared spectrum (thin film/NaCl) of compound **24i**.

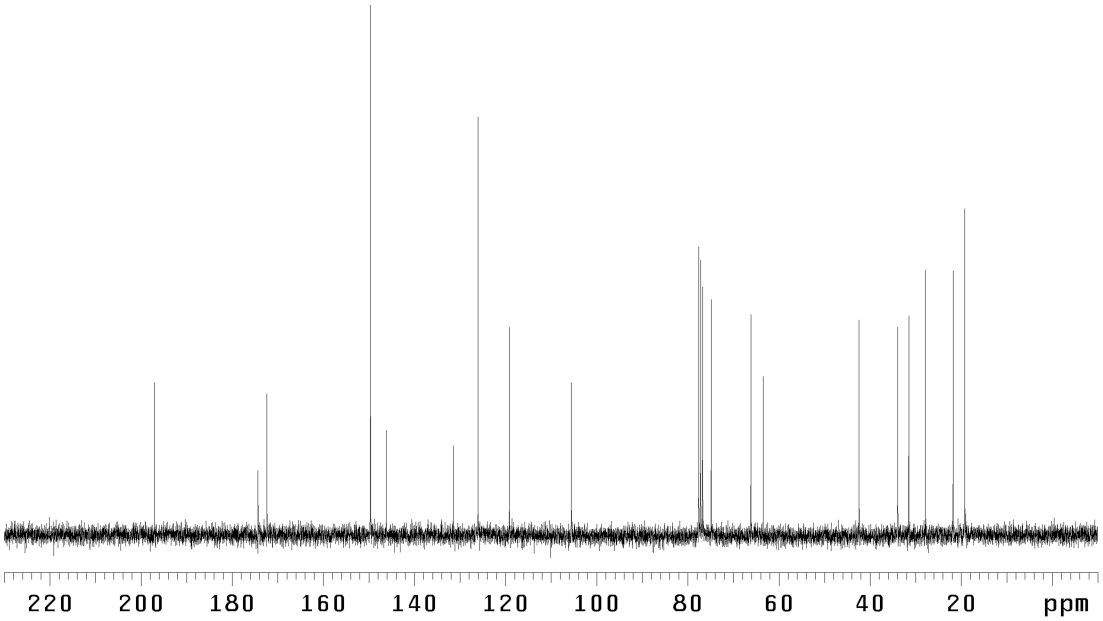


Figure A2.10.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **24i**.

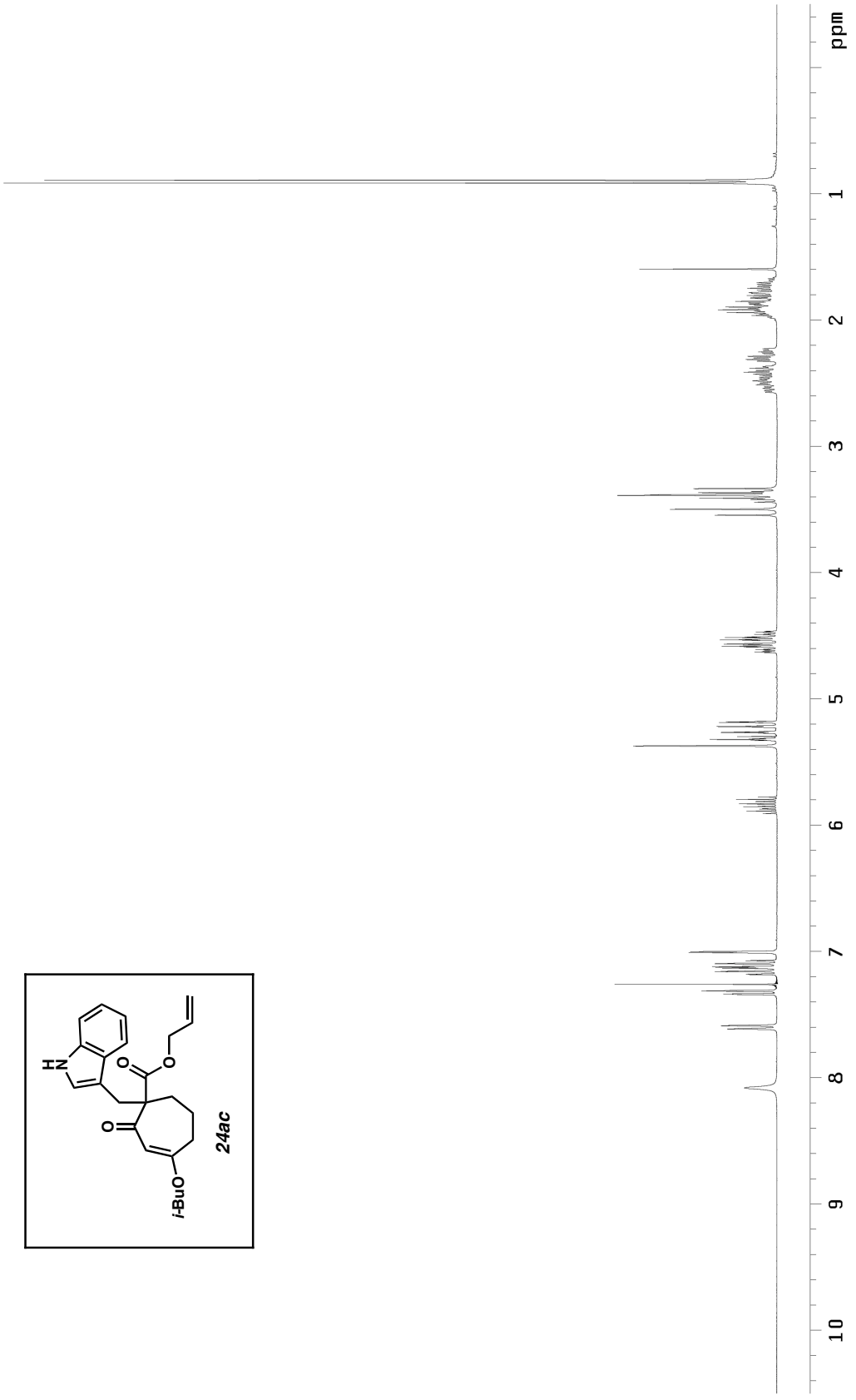


Figure A2.11.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **24ac**.

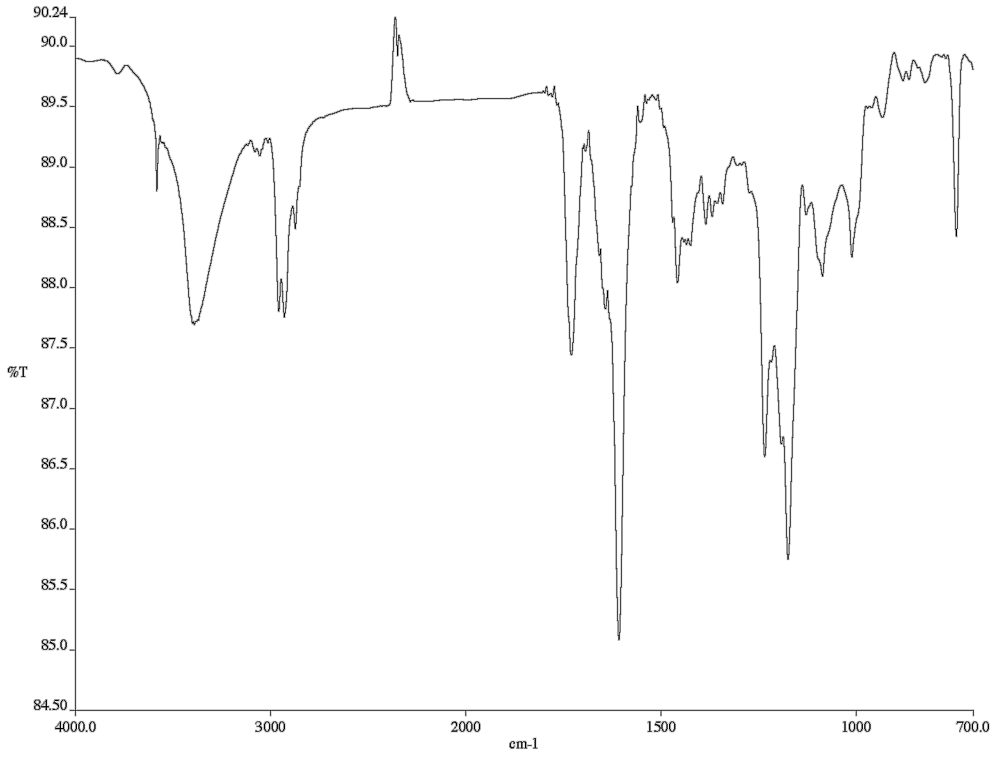


Figure A2.11.2. Infrared spectrum (thin film/NaCl) of compound **24ac**.

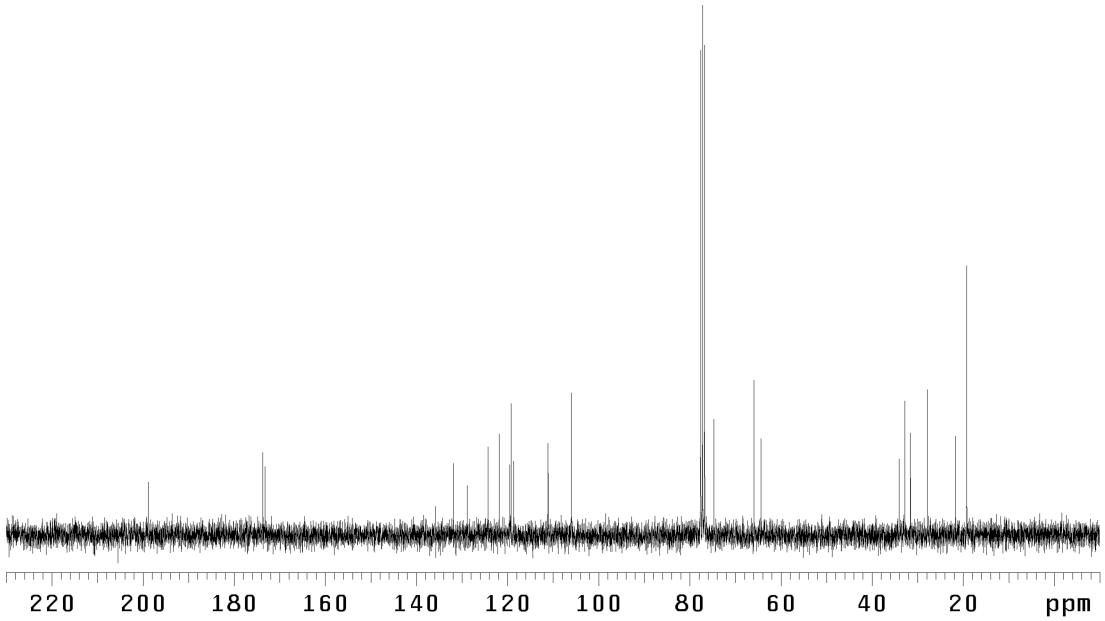


Figure A2.11.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **24ac**.

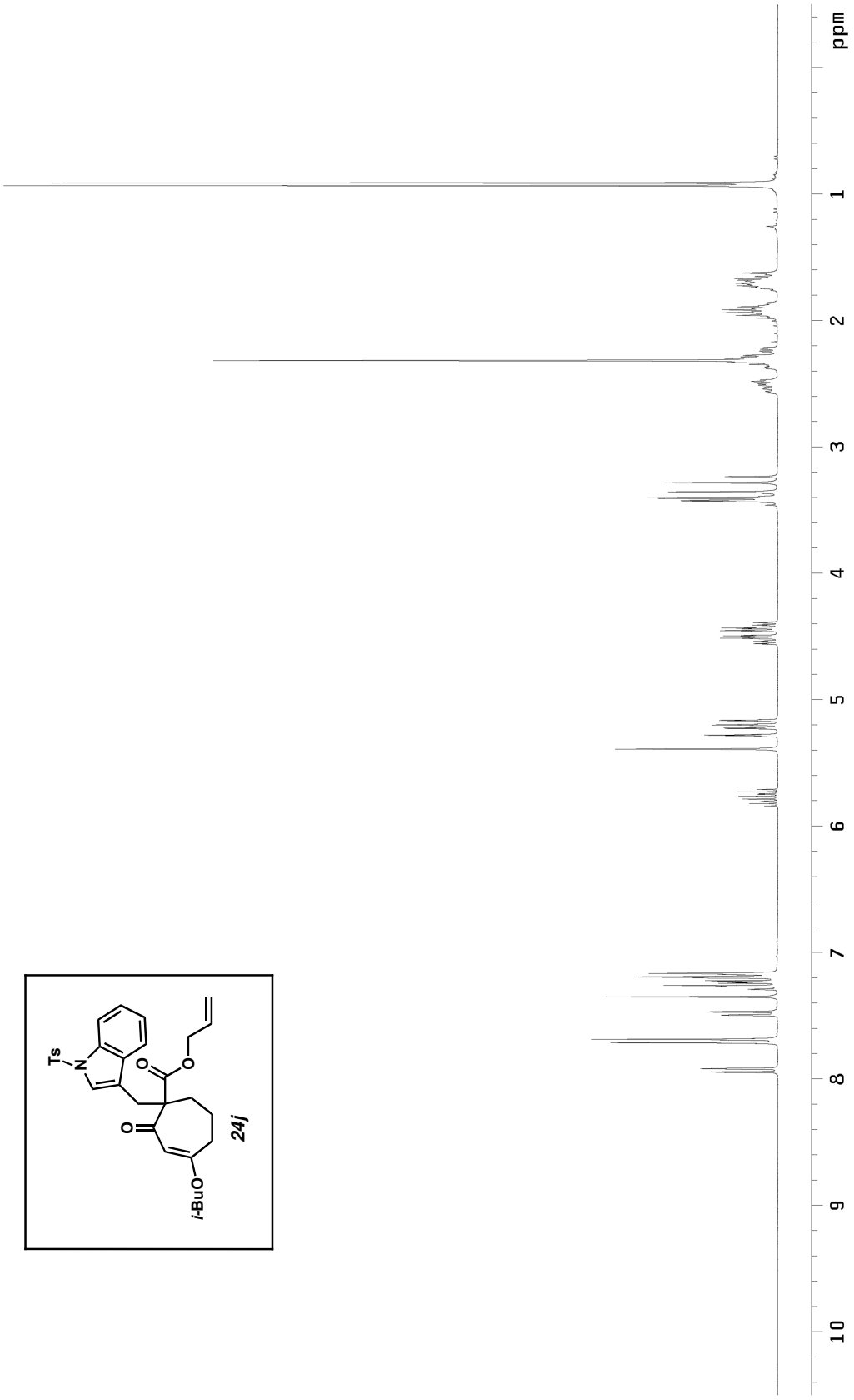


Figure A2.12.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **24j**.

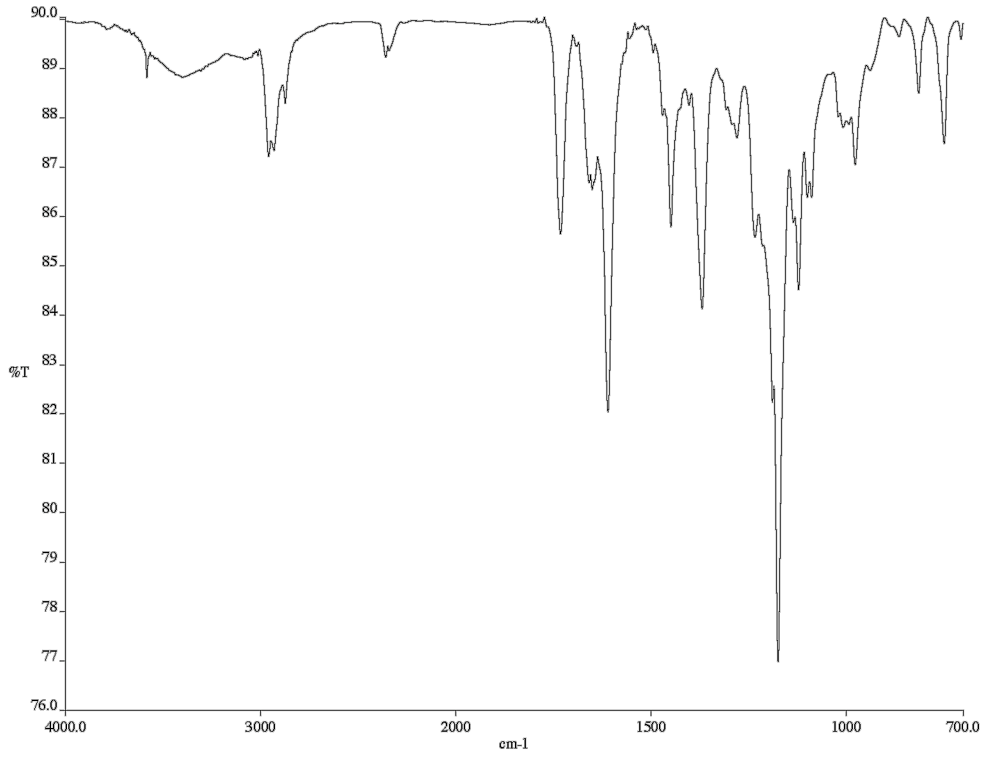


Figure A2.12.2. Infrared spectrum (thin film/NaCl) of compound **24j**.

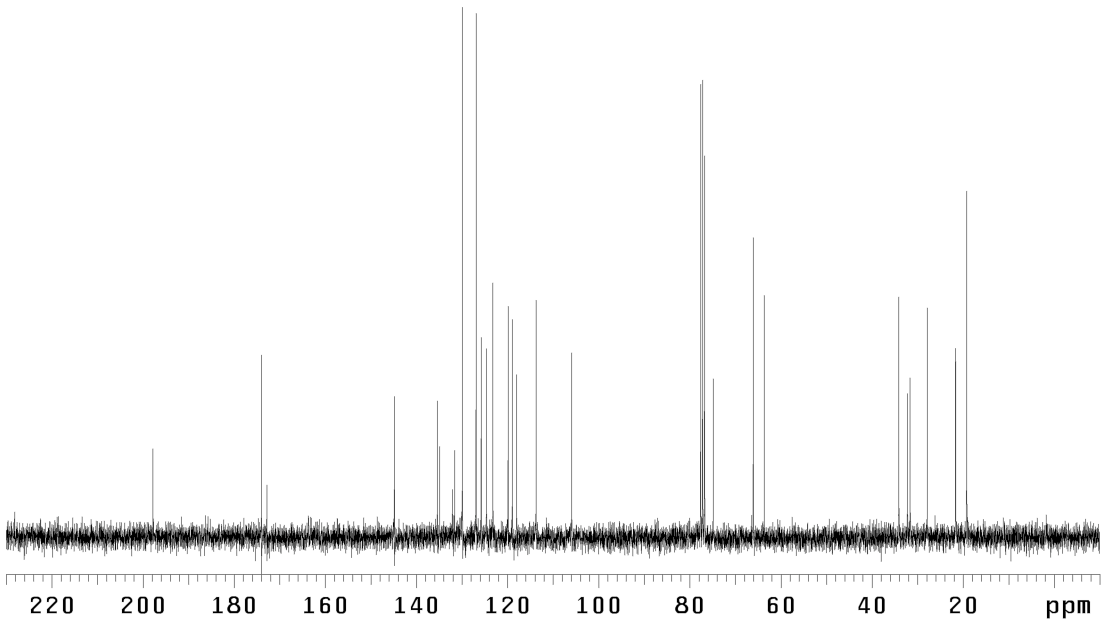


Figure A2.12.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **24j**.

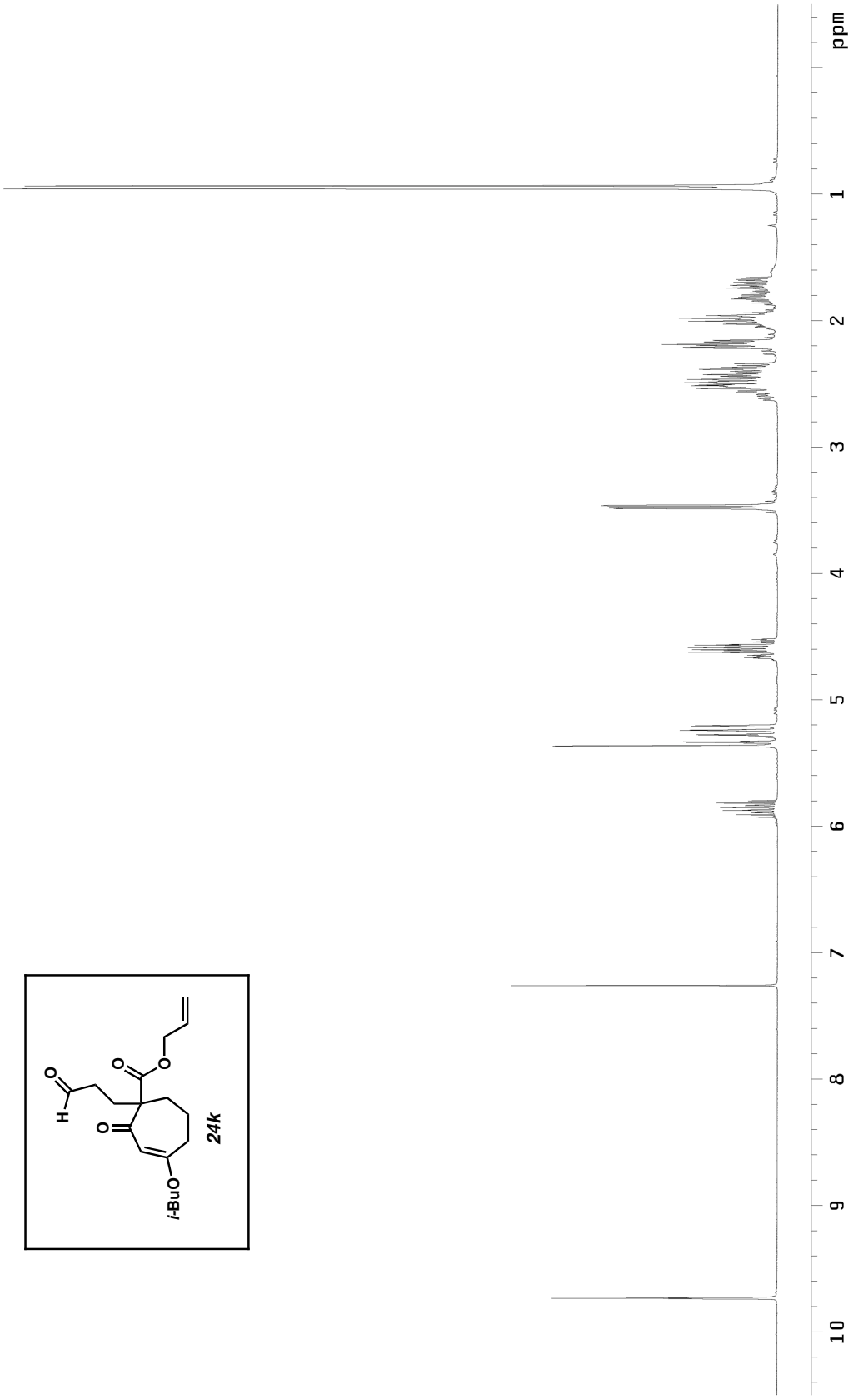


Figure A2.13.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **24k**.

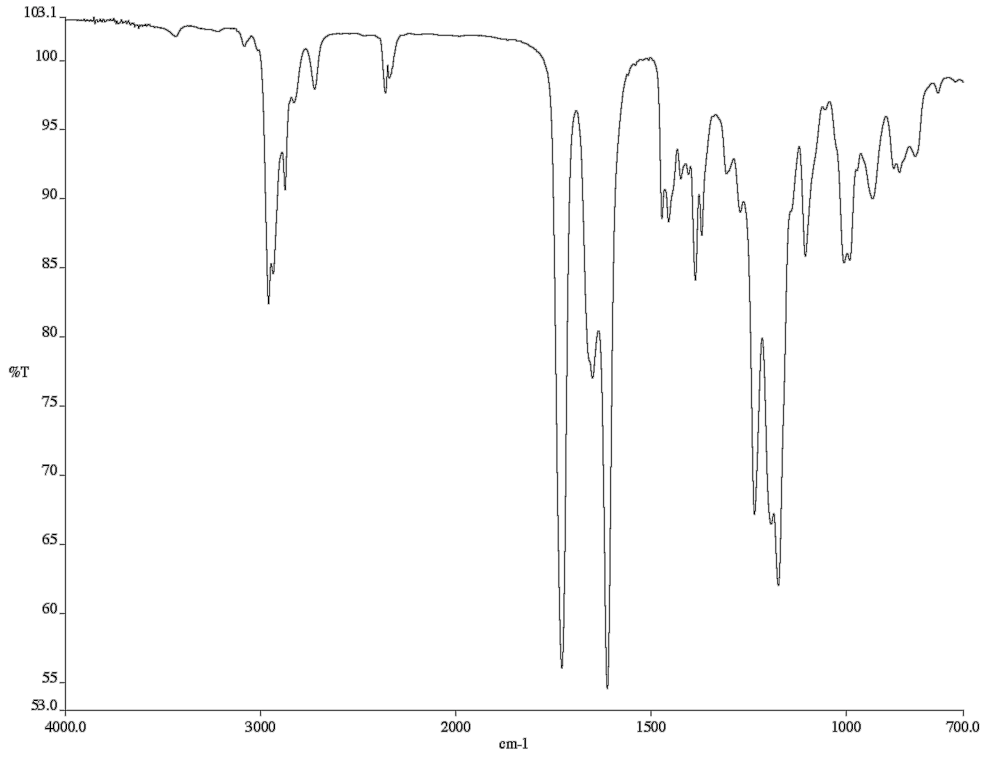


Figure A2.13.2. Infrared spectrum (thin film/NaCl) of compound **24k**.

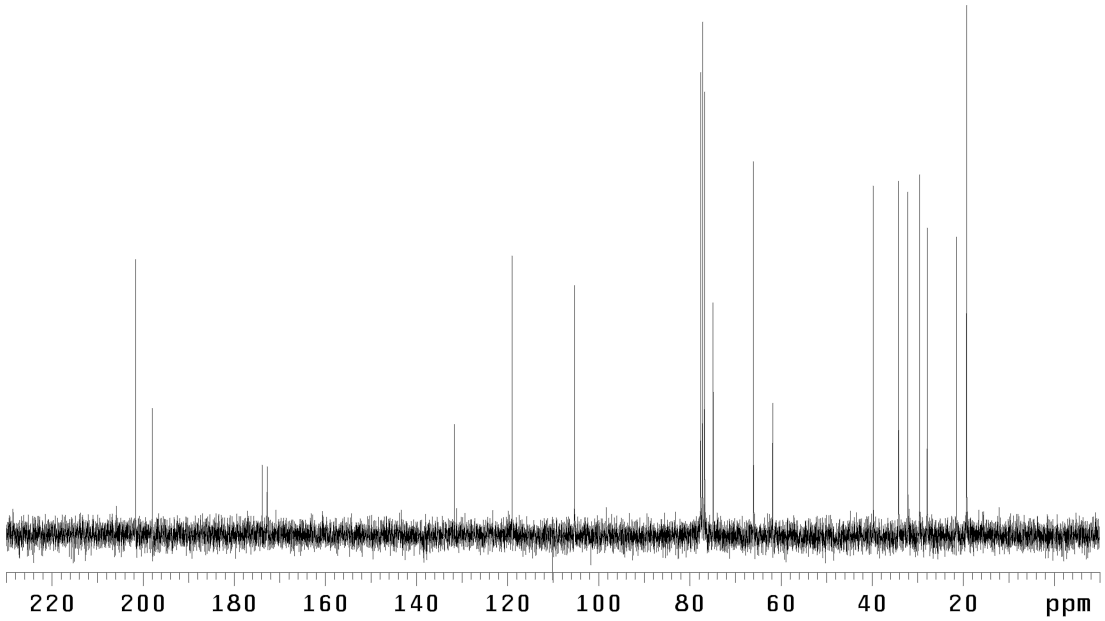


Figure A2.13.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **24k**.

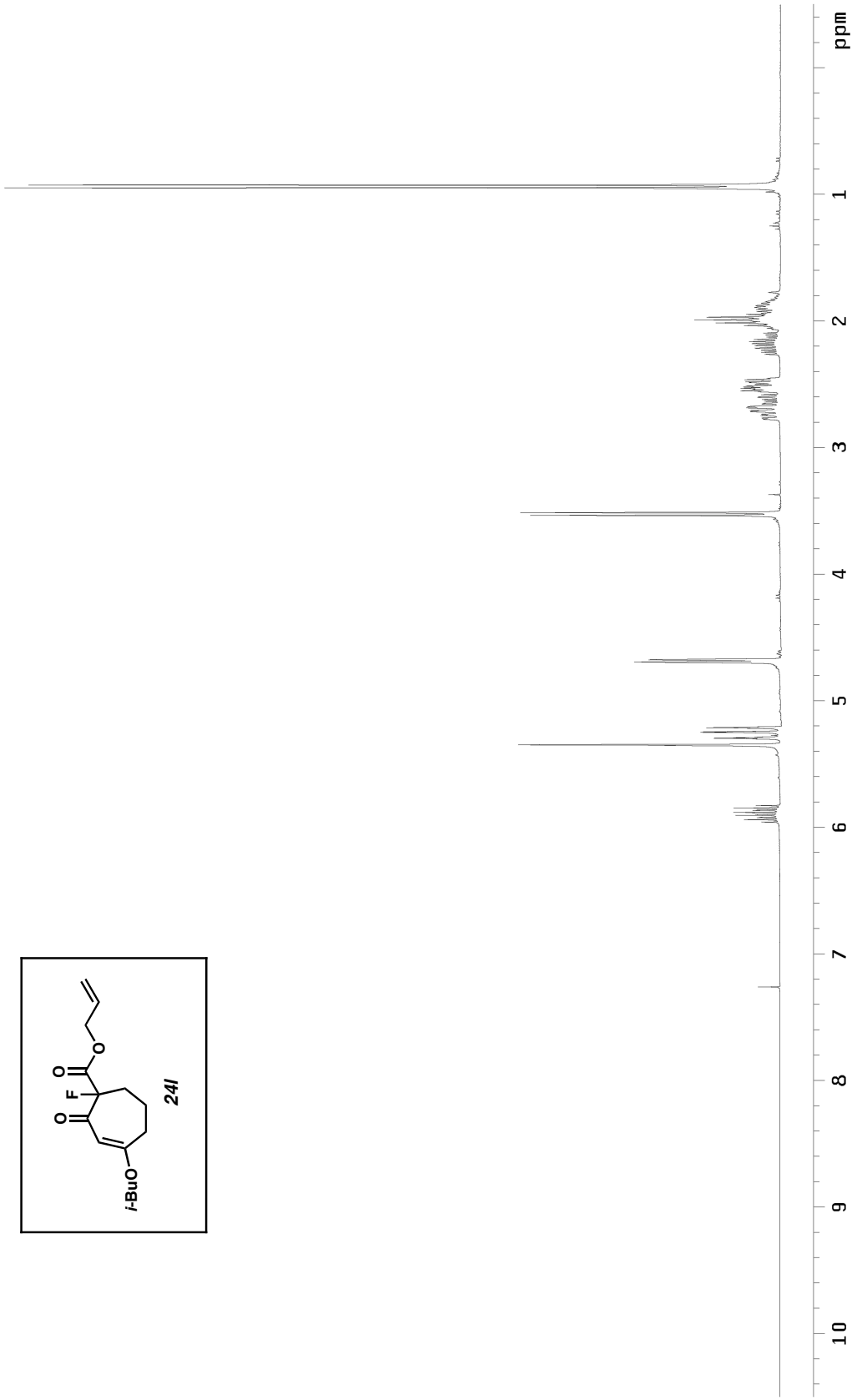


Figure A2.14.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **24l**.

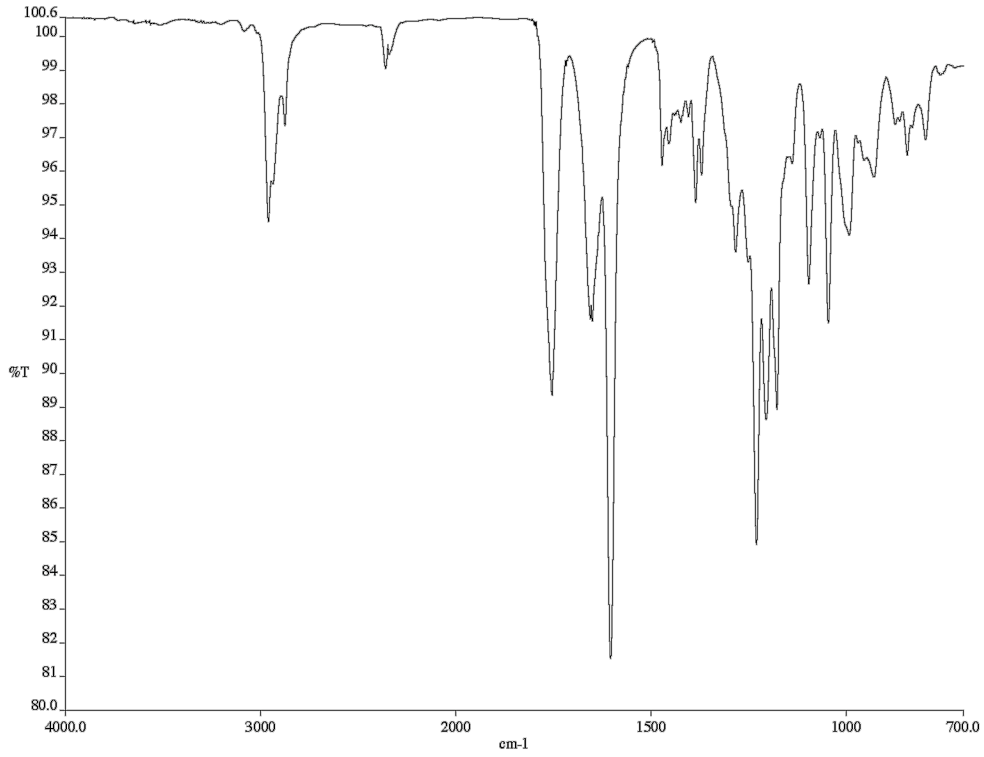


Figure A2.14.2. Infrared spectrum (thin film/NaCl) of compound **24l**.

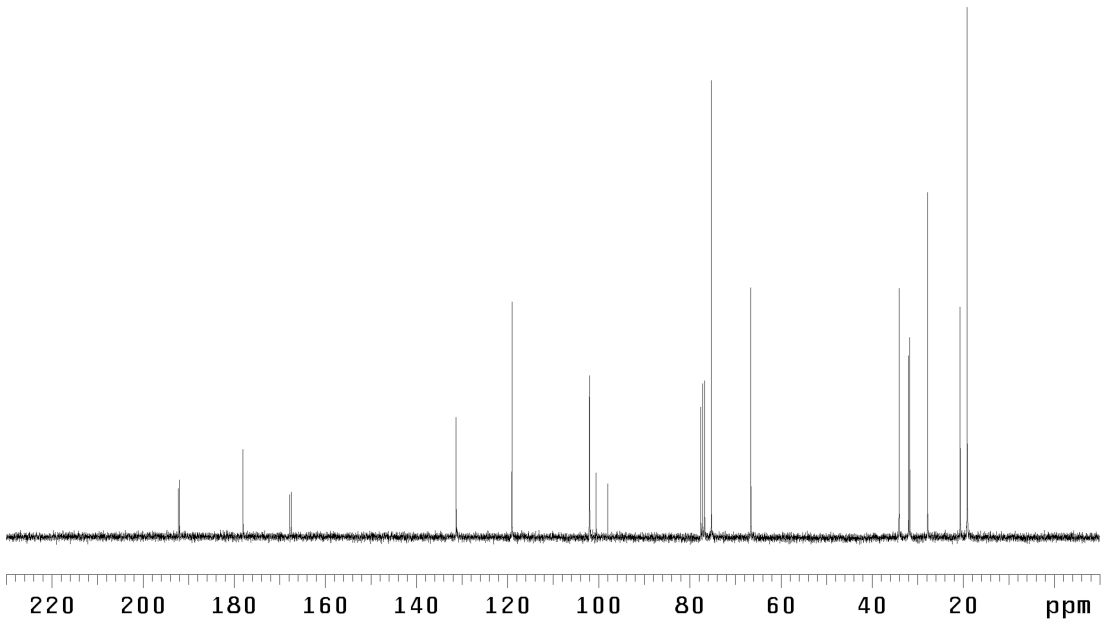


Figure A2.14.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **24l**.

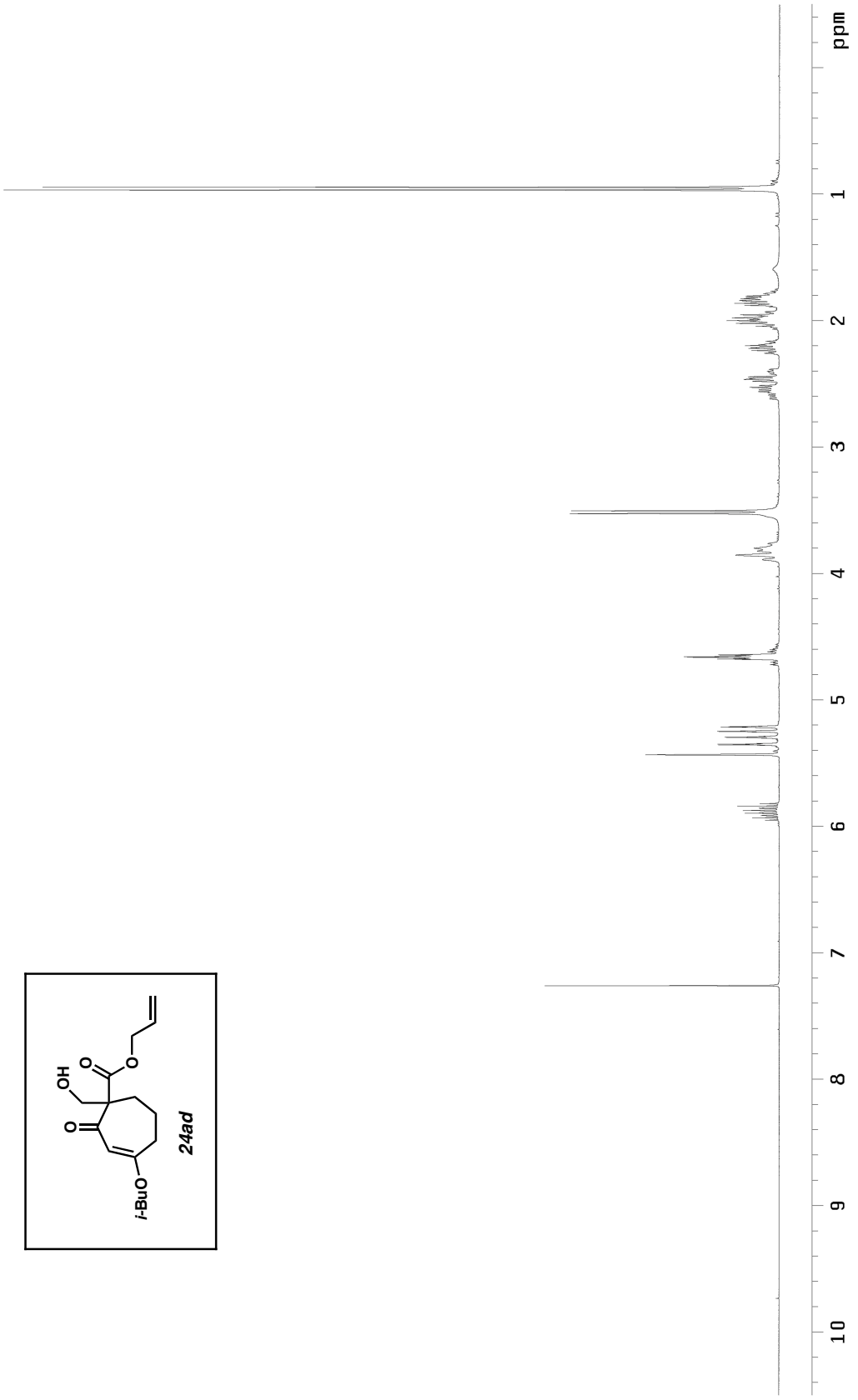


Figure A2.15.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **24ad**.

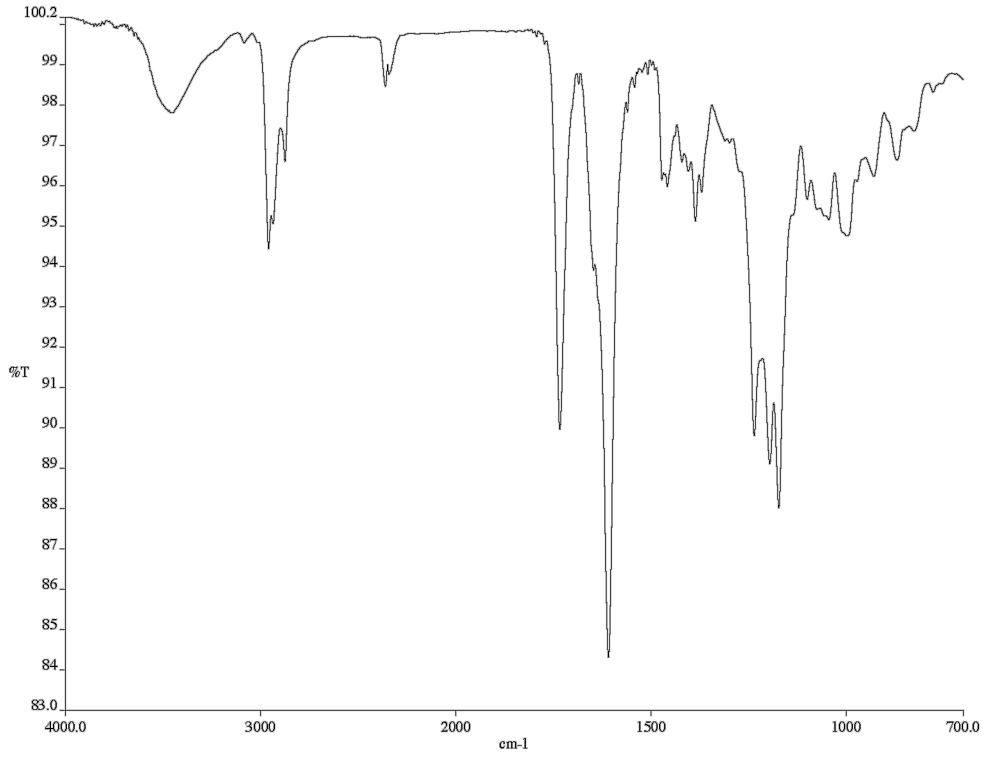


Figure A2.15.2. Infrared spectrum (thin film/NaCl) of compound **24ad**.

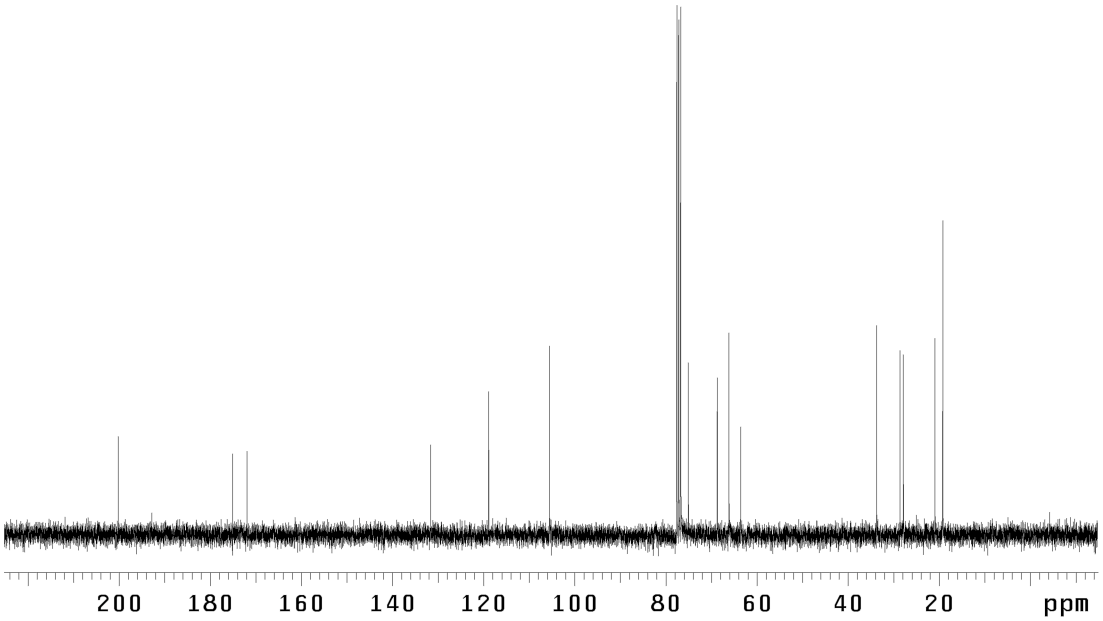


Figure A2.15.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **24ad**.

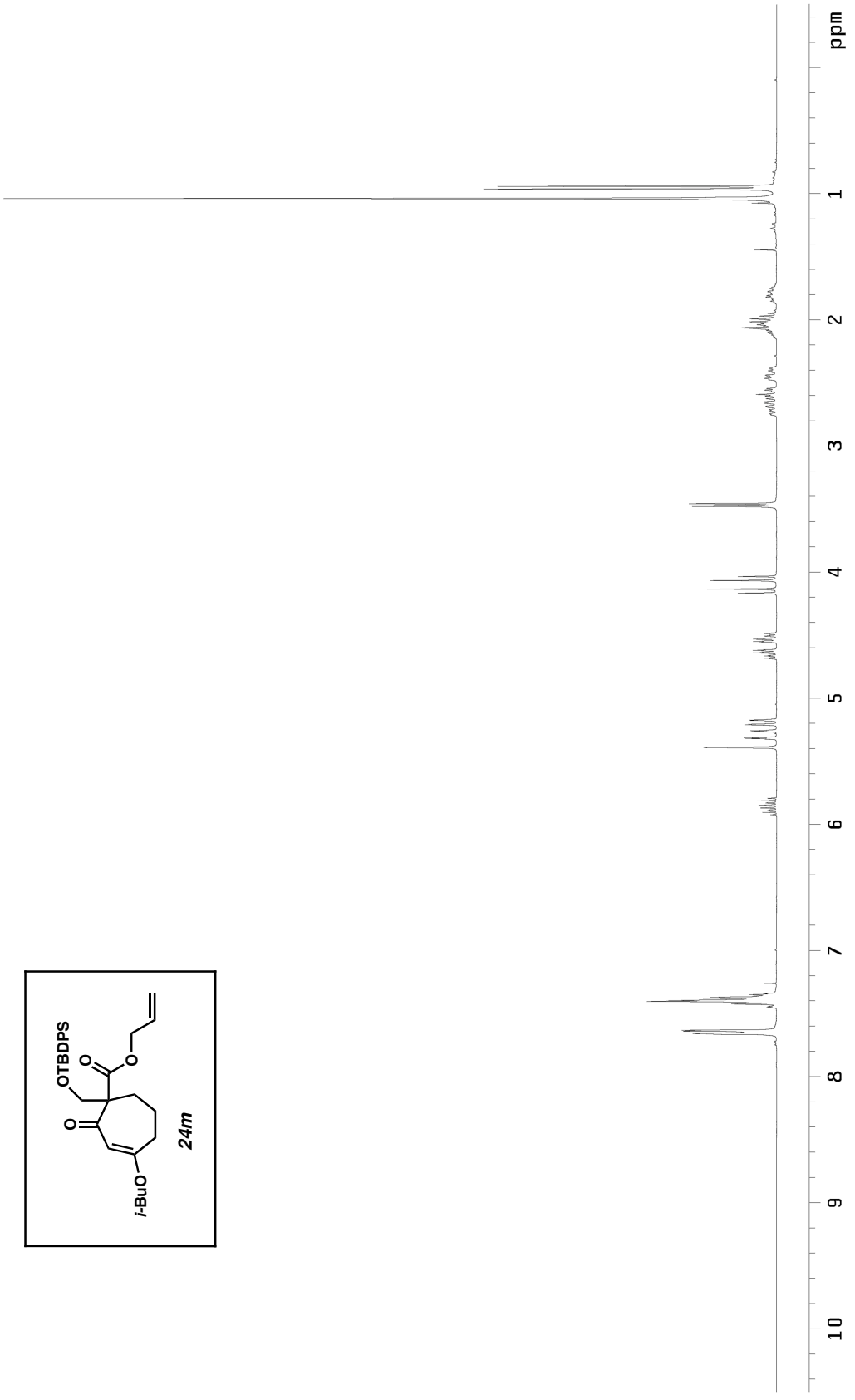


Figure A2.16.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **24m**.

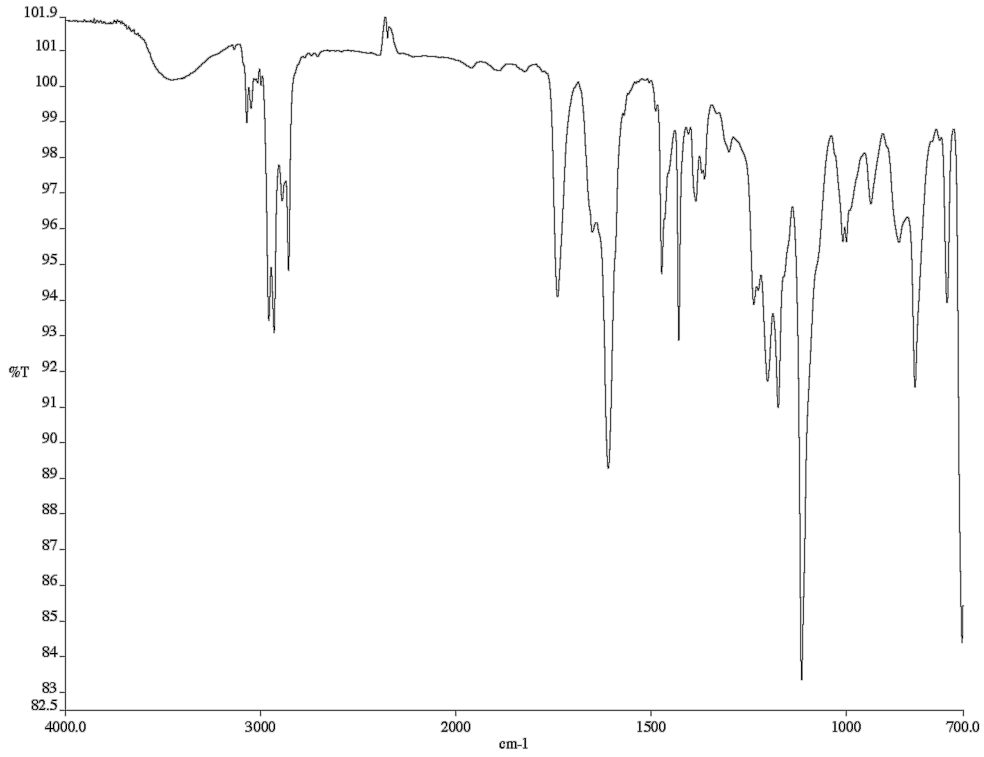


Figure A2.16.2. Infrared spectrum (thin film/NaCl) of compound **24m**.

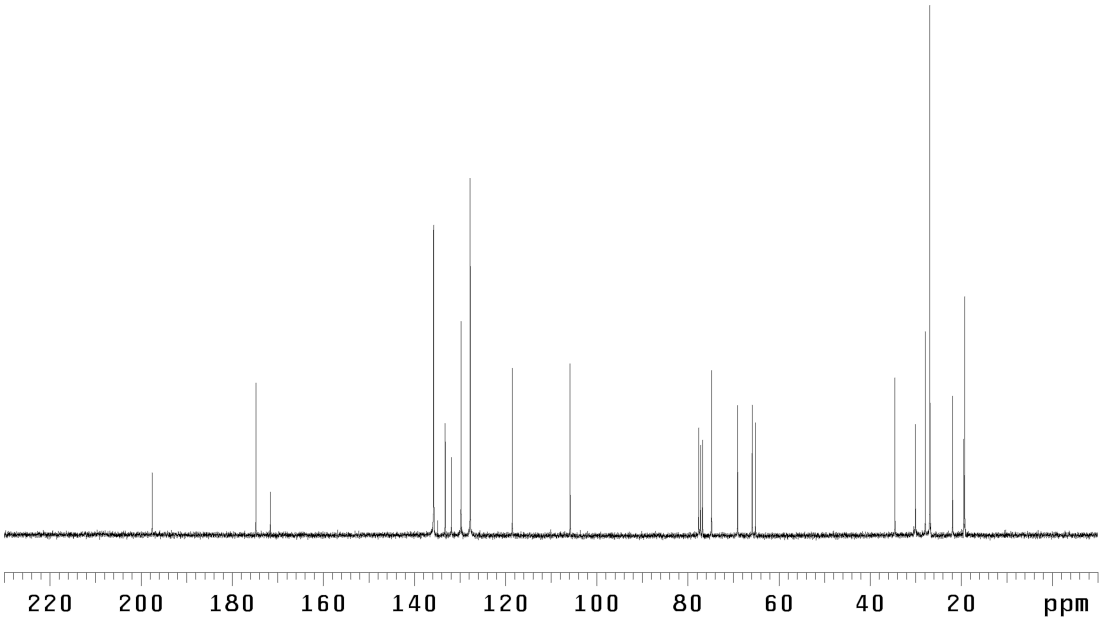


Figure A2.16.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **24m**.

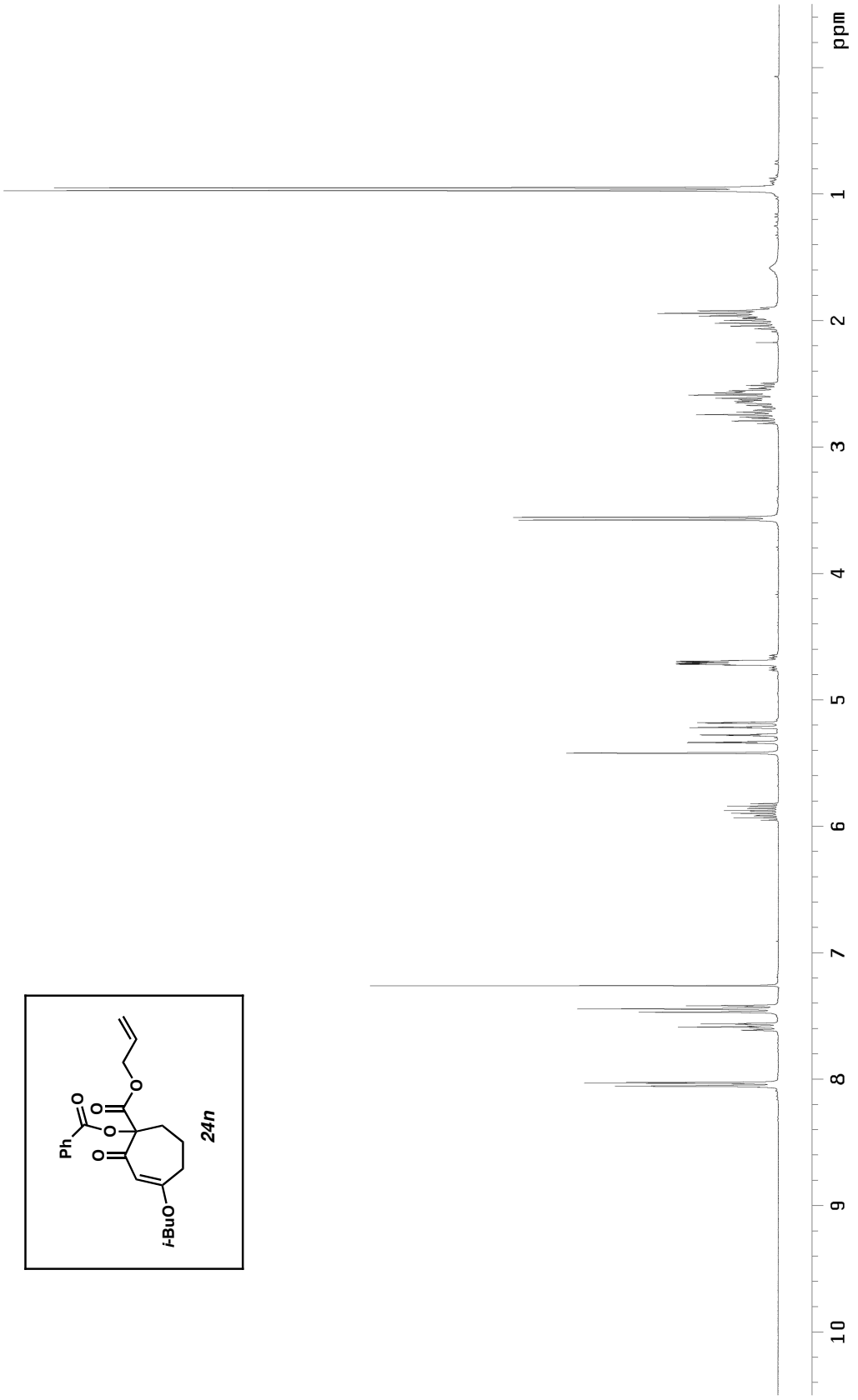


Figure A2.17.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **24n**.

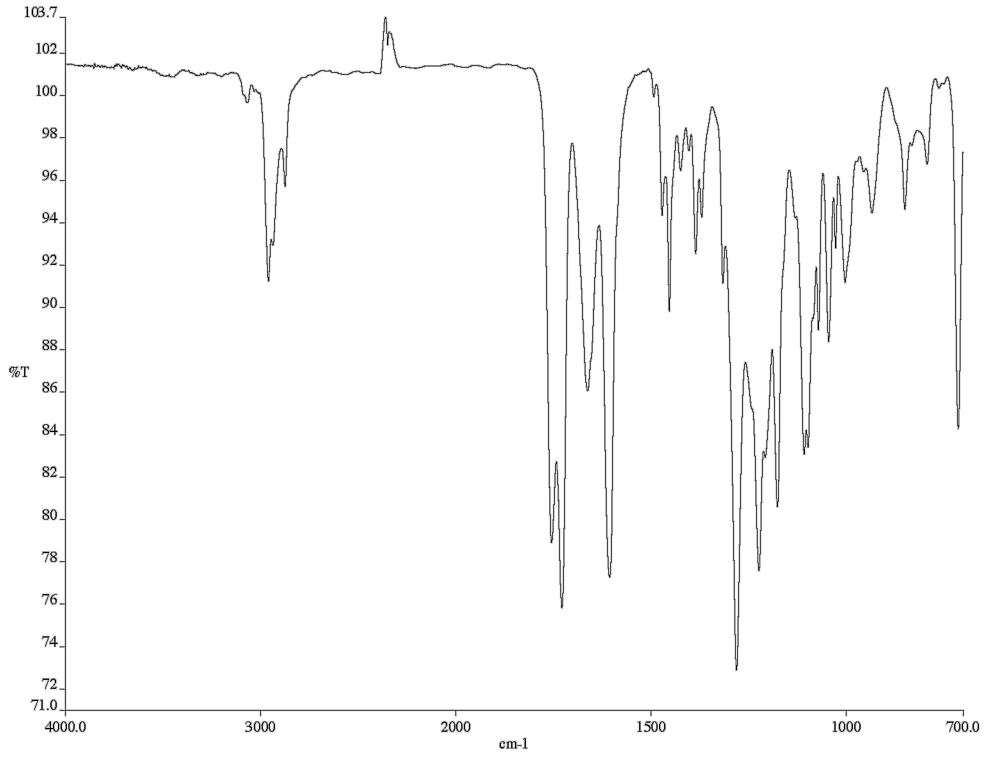


Figure A2.17.2. Infrared spectrum (thin film/NaCl) of compound **24n**.

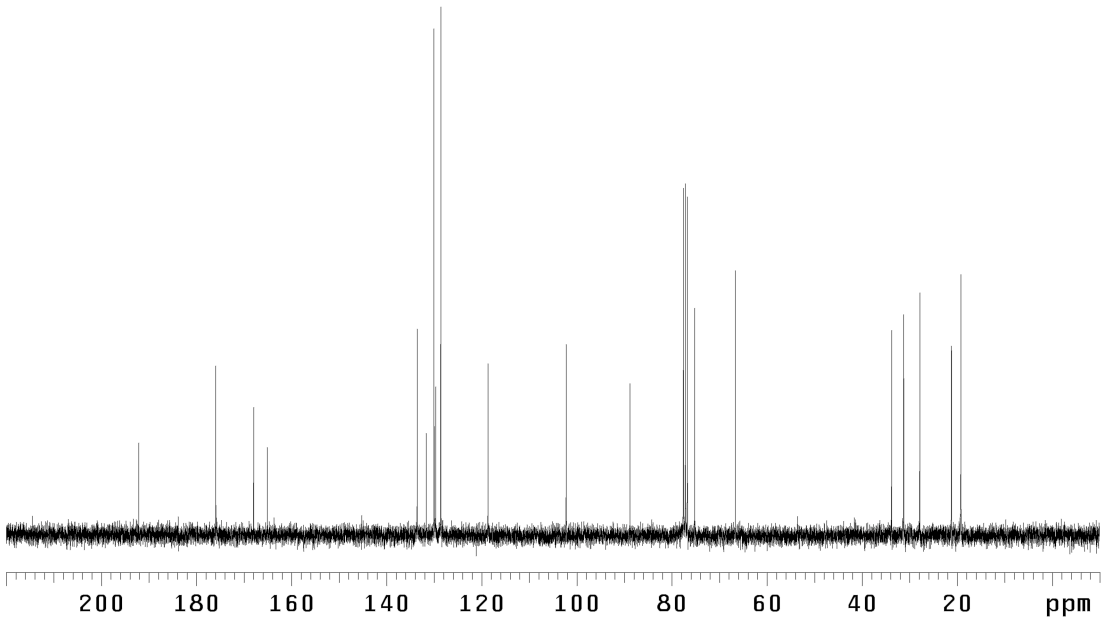


Figure A2.17.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **24n**.

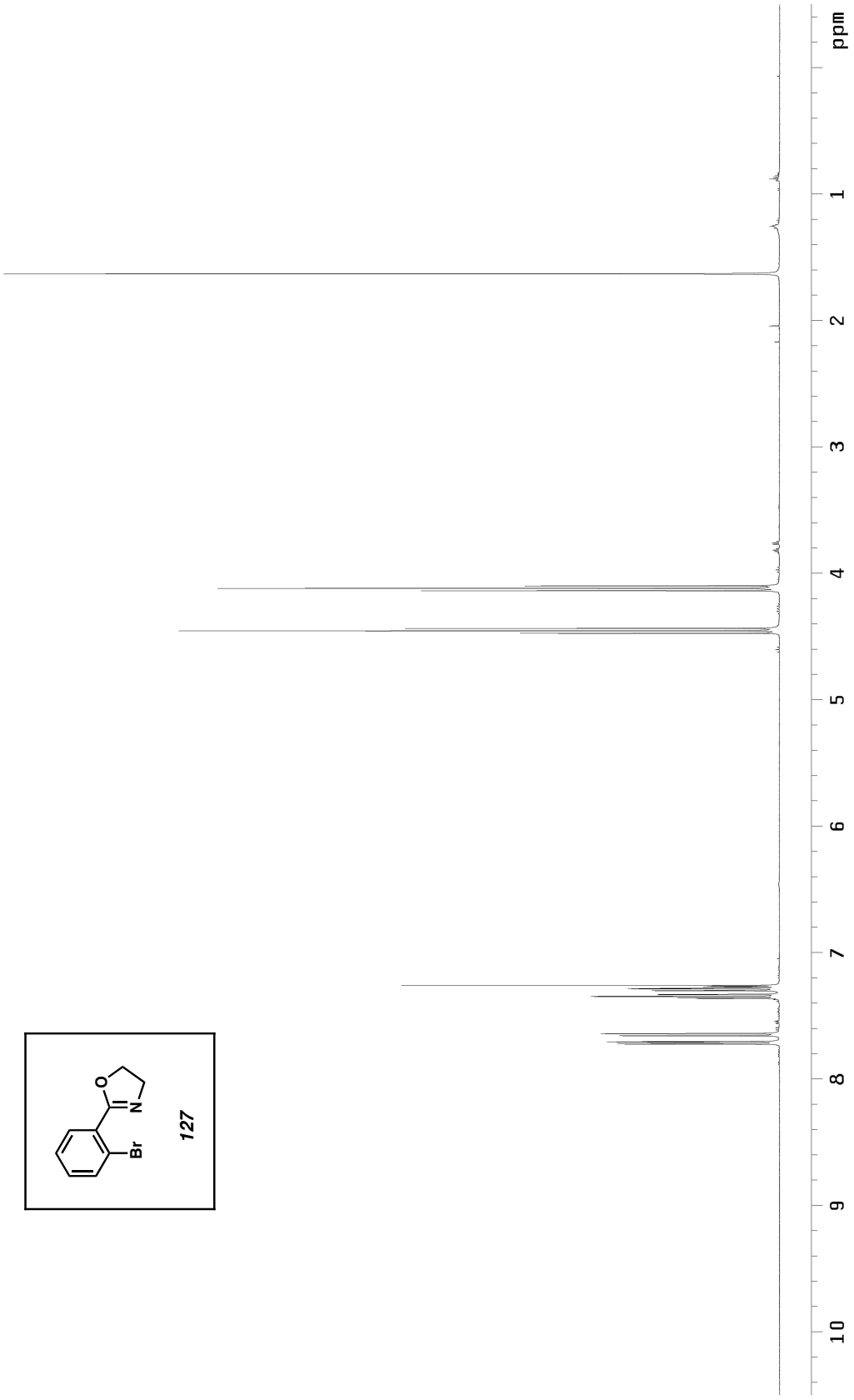


Figure A2.18.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **127**.

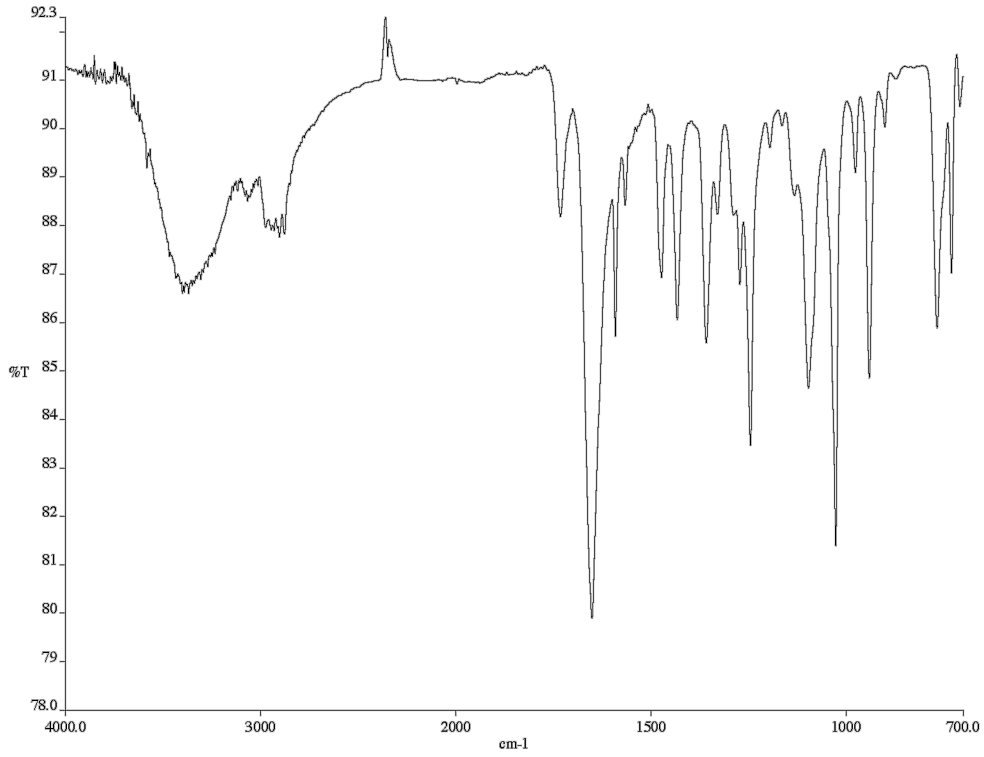


Figure A2.18.2. Infrared spectrum (thin film/NaCl) of compound **127**.

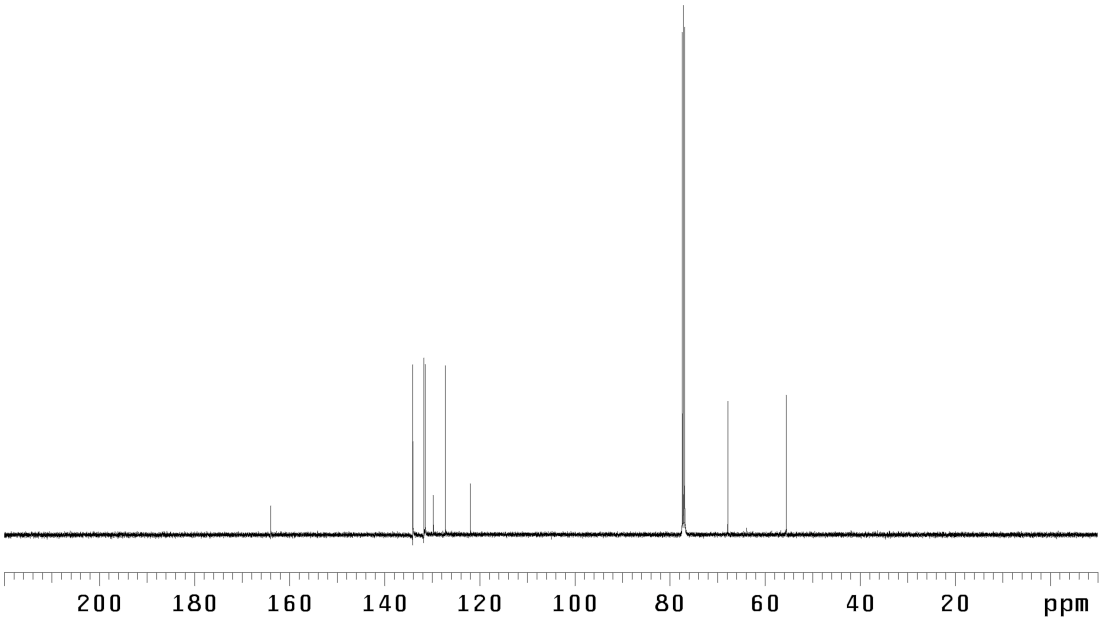


Figure A2.18.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **127**.

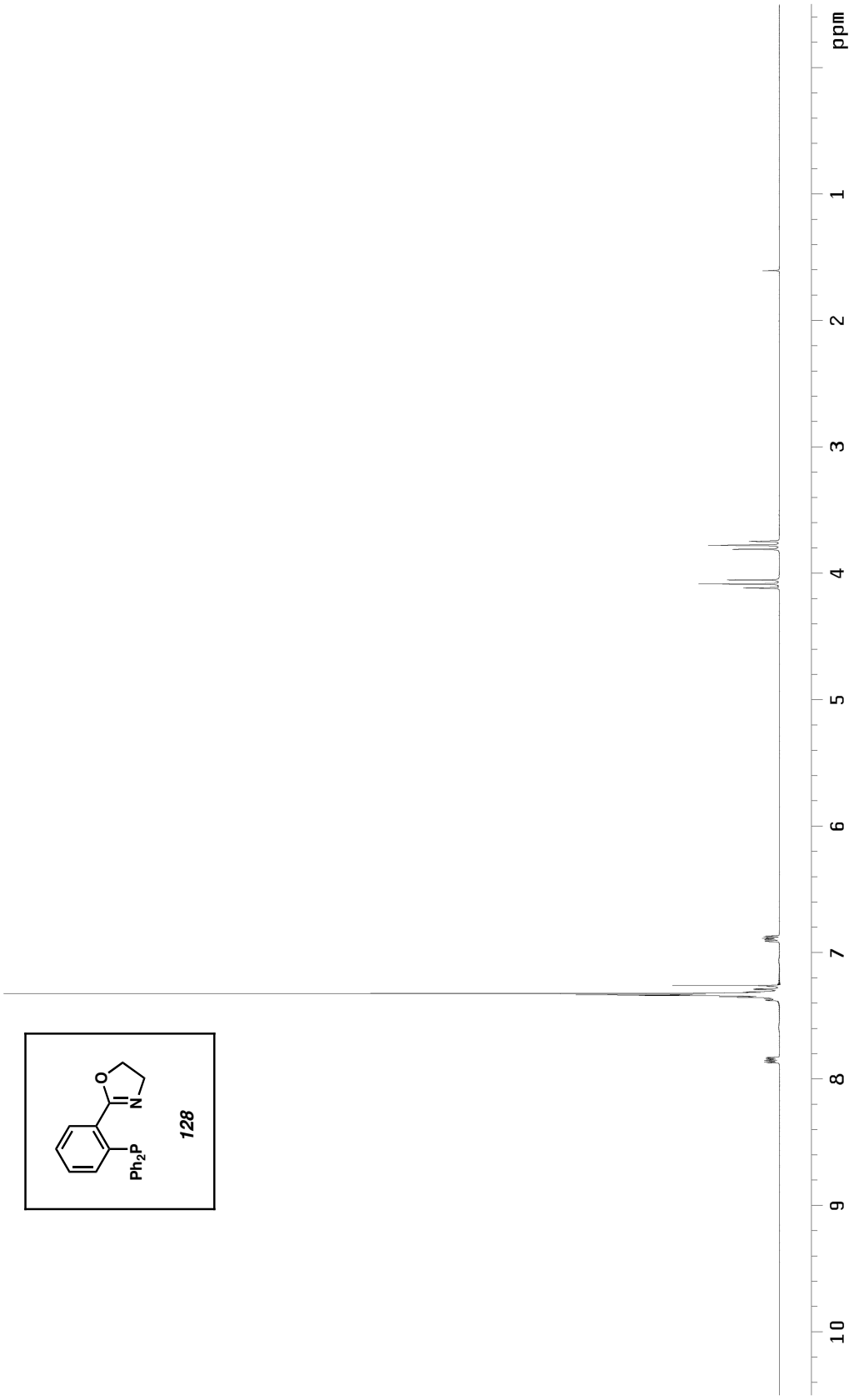


Figure A2.19.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **128**.

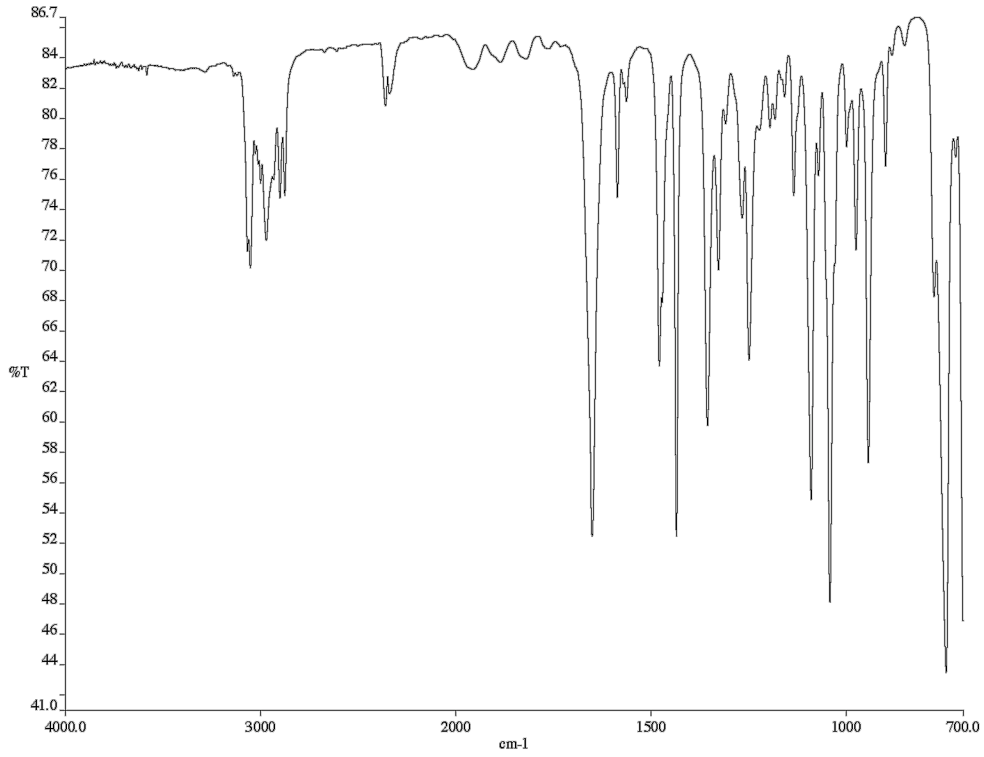


Figure A2.19.2. Infrared spectrum (thin film/NaCl) of compound **128**.

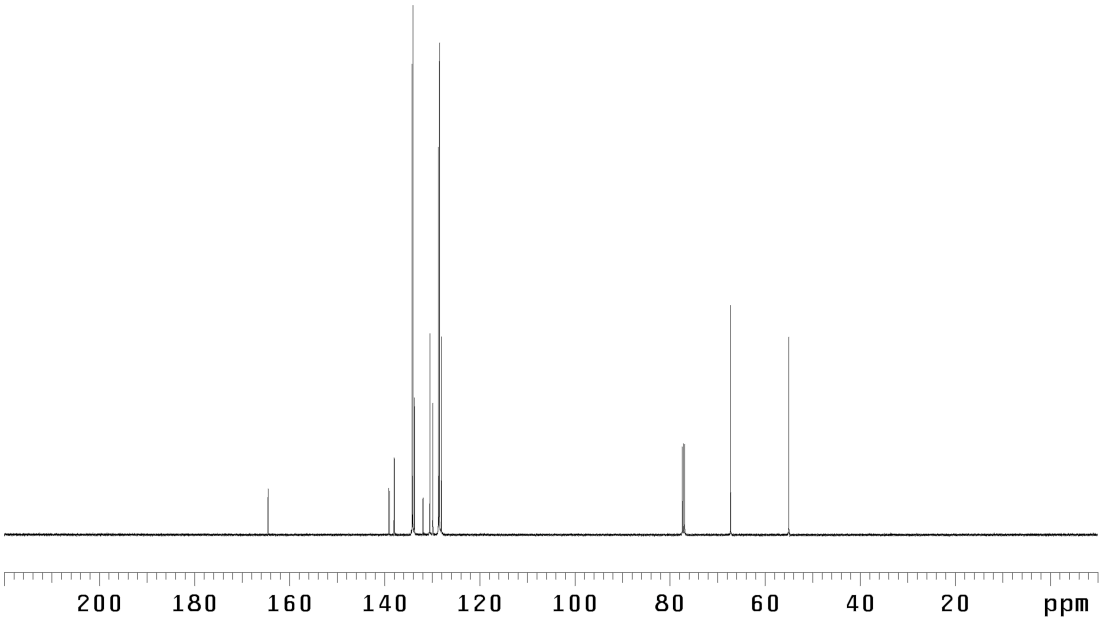


Figure A2.19.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **128**.

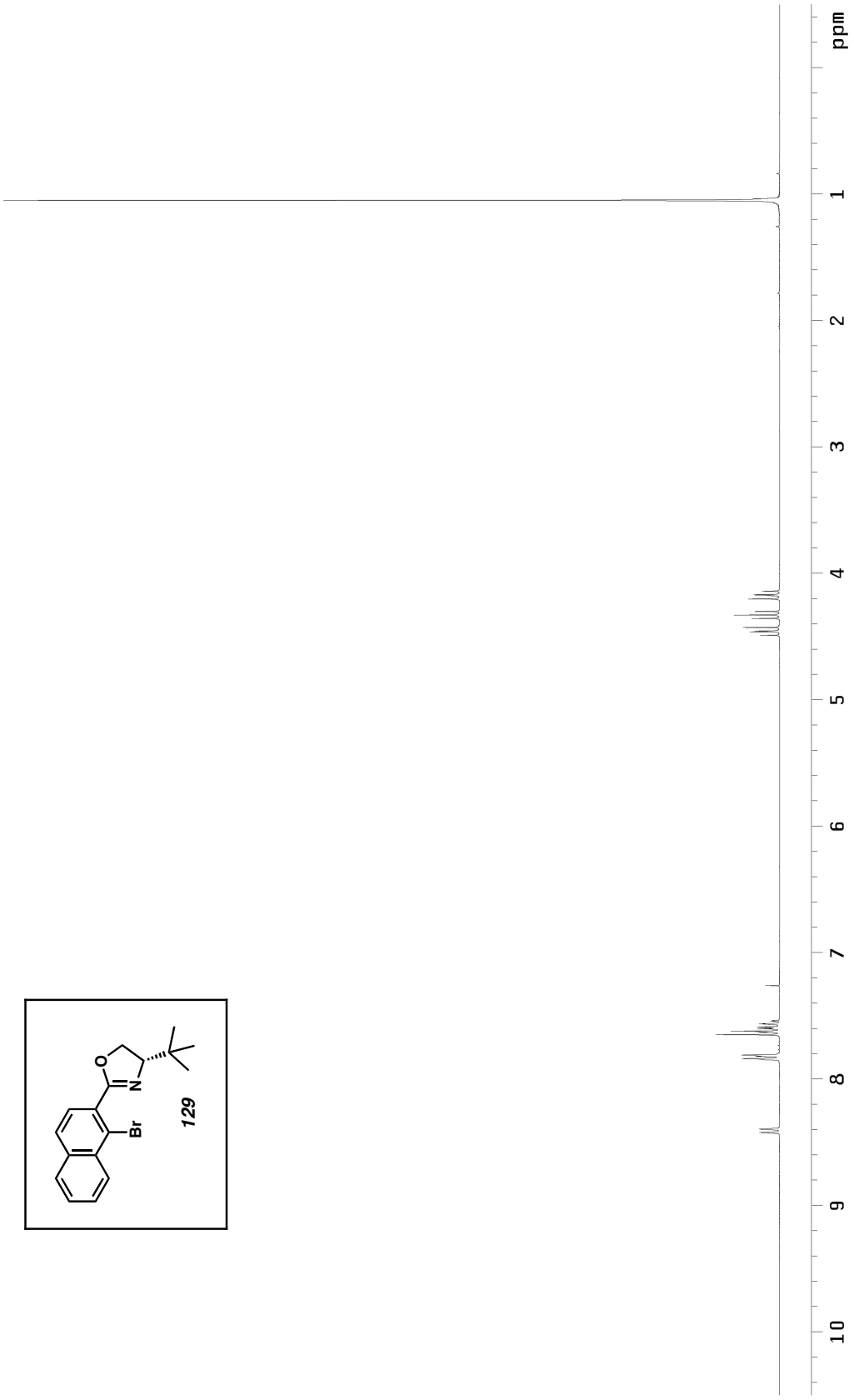


Figure A2.20.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **129**.

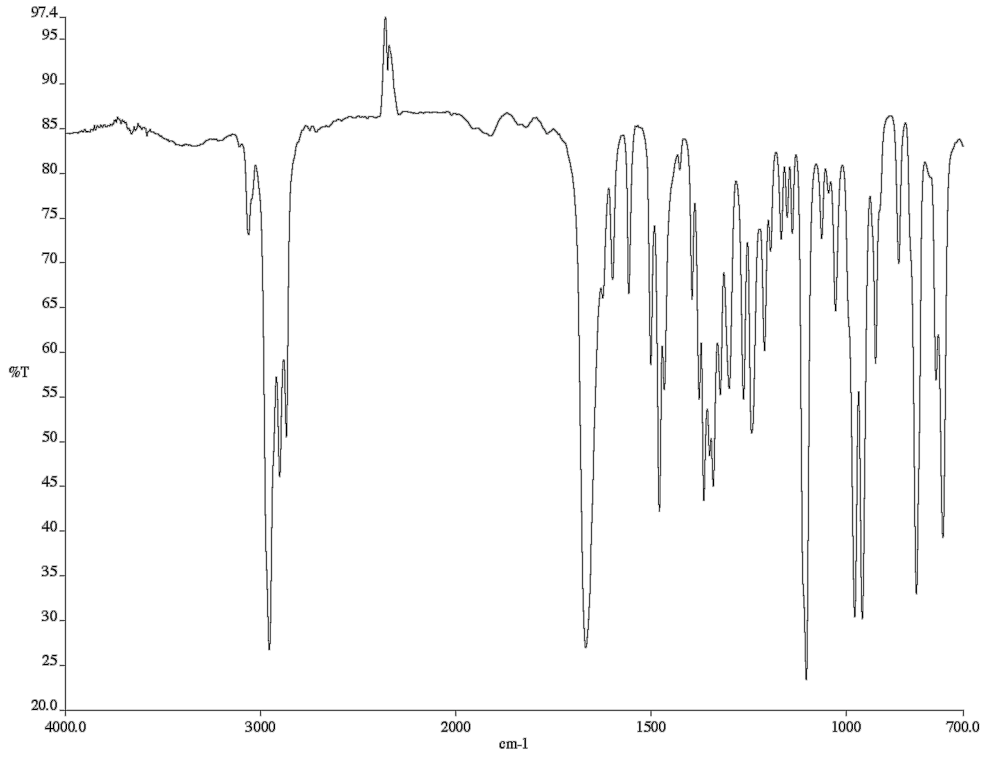


Figure A2.20.2. Infrared spectrum (thin film/NaCl) of compound **129**.

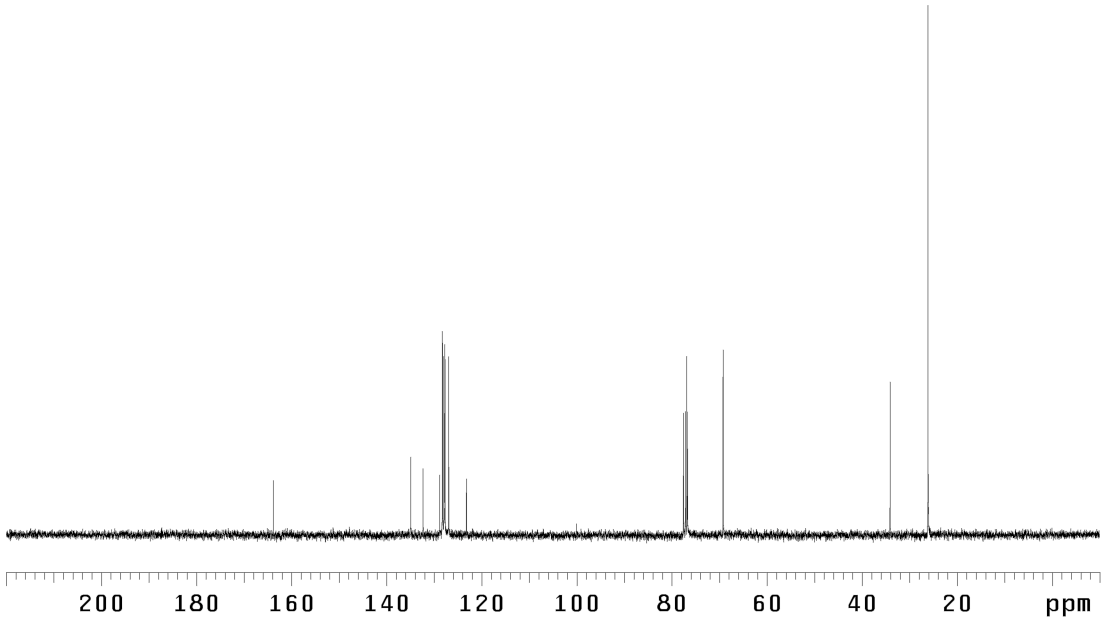


Figure A2.20.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **129**.

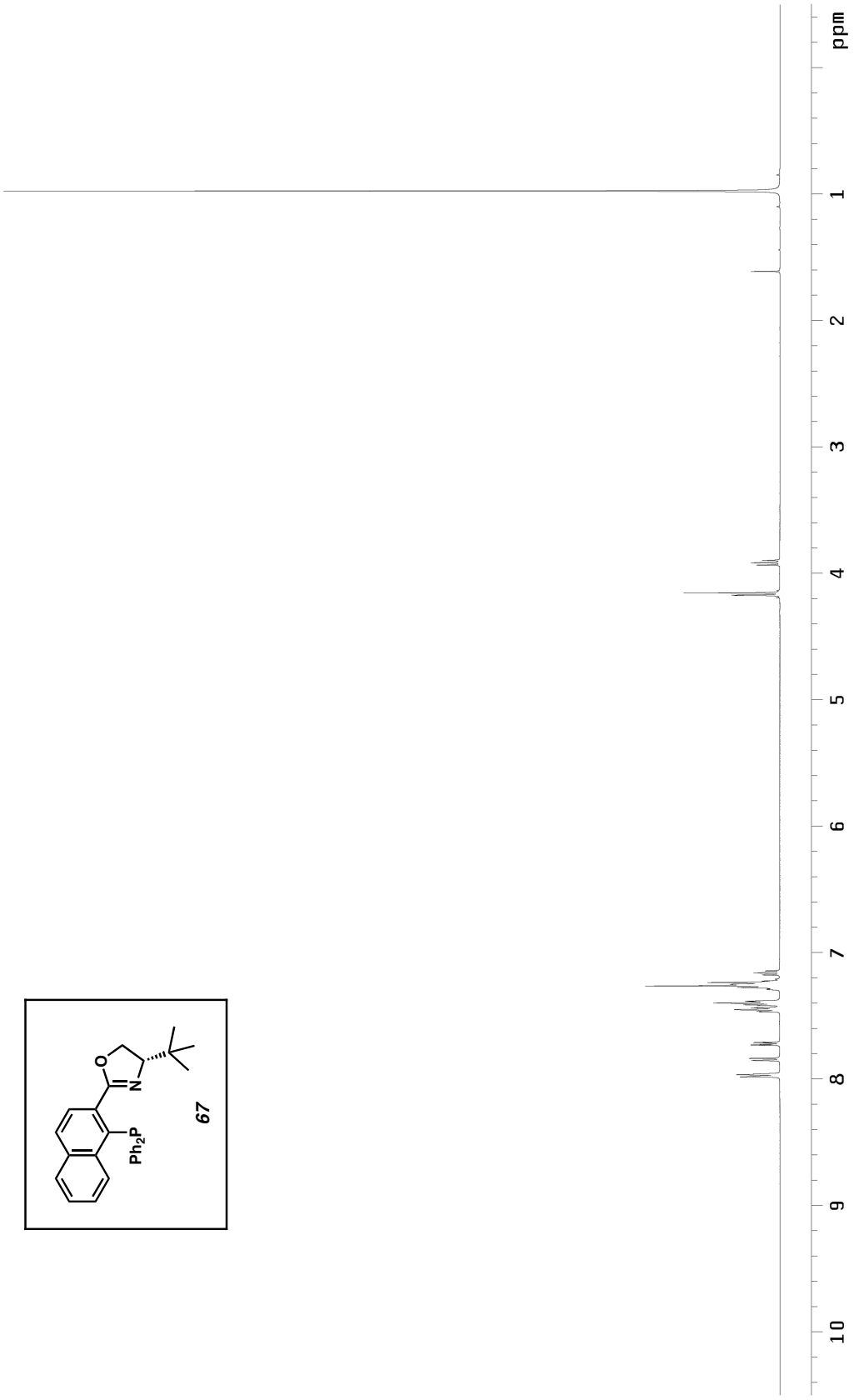


Figure A2.21.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **67**.

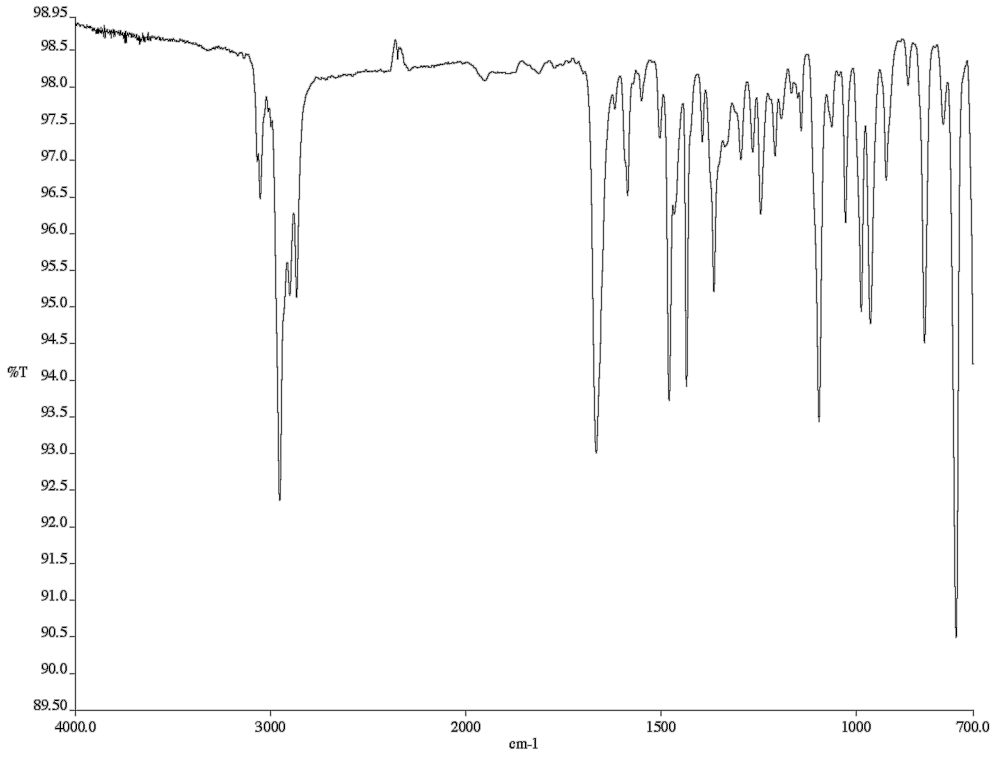


Figure A2.21.2. Infrared spectrum (thin film/NaCl) of compound **67**.

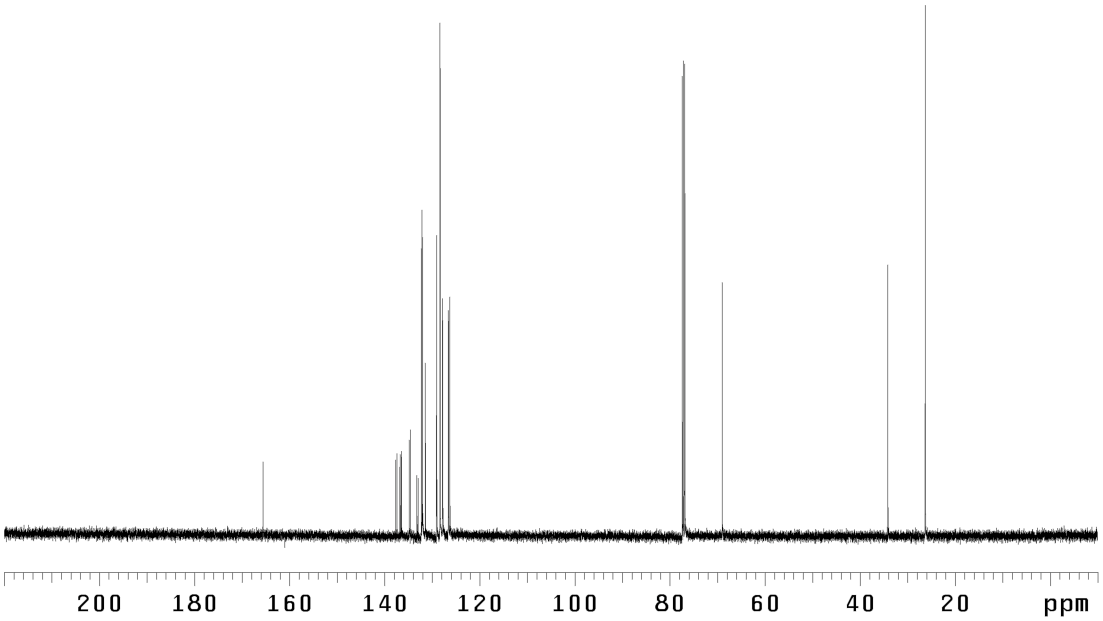


Figure A2.21.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **67**.

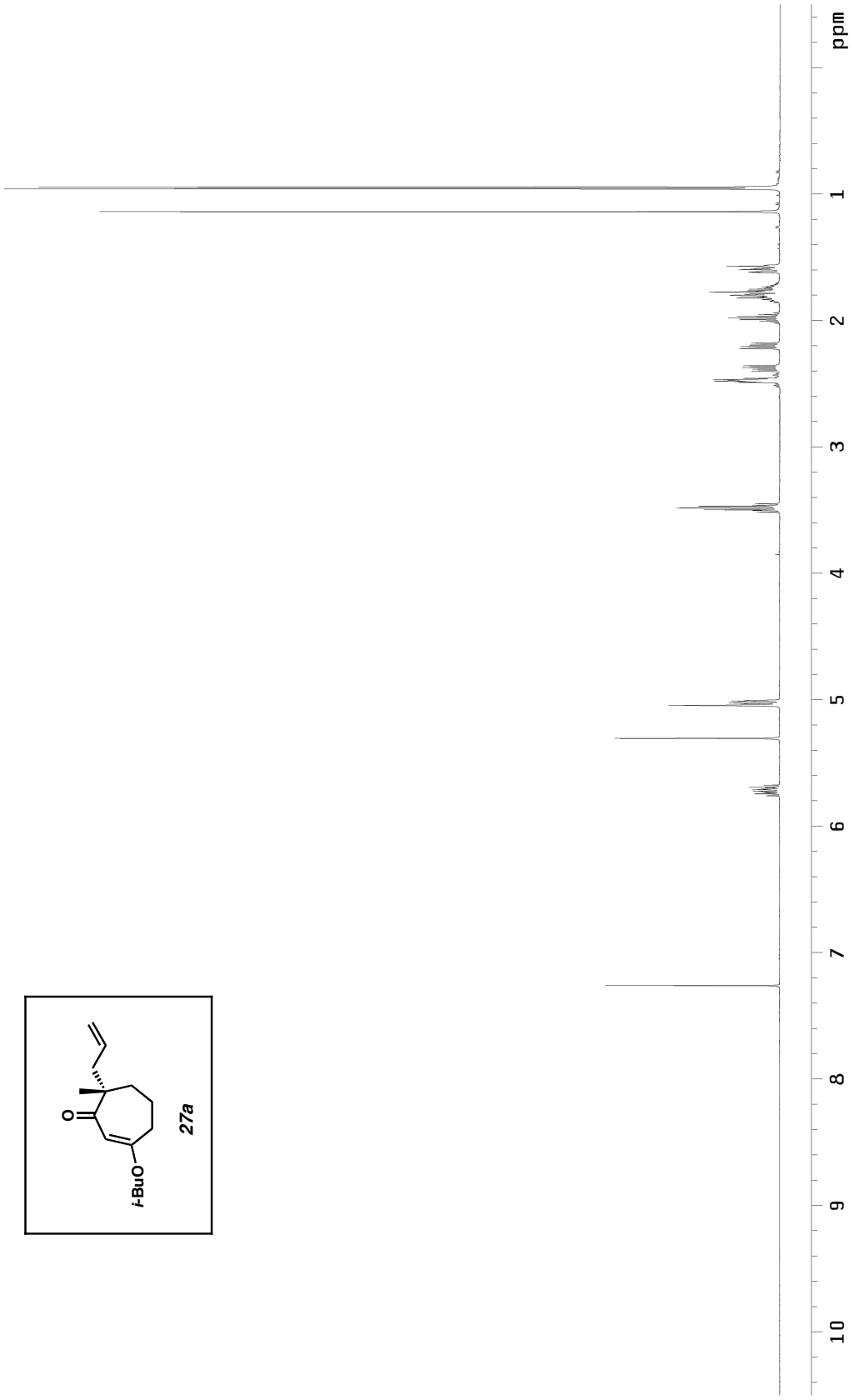


Figure A2.22.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **27a**.

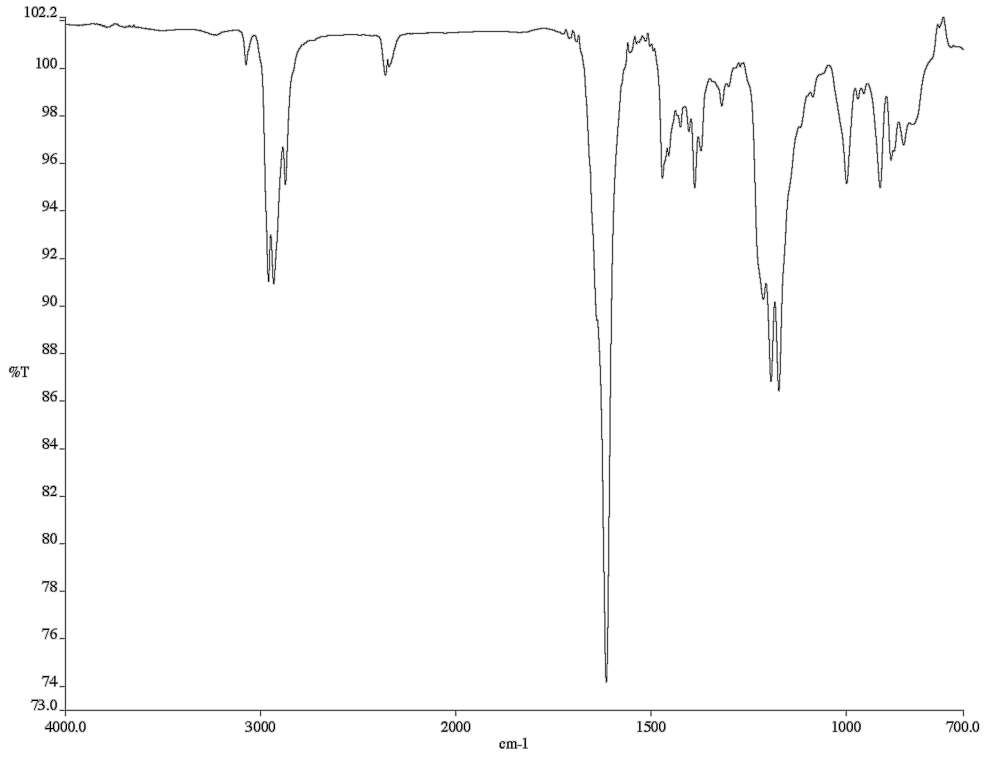


Figure A2.22.2. Infrared spectrum (thin film/NaCl) of compound **27a**.

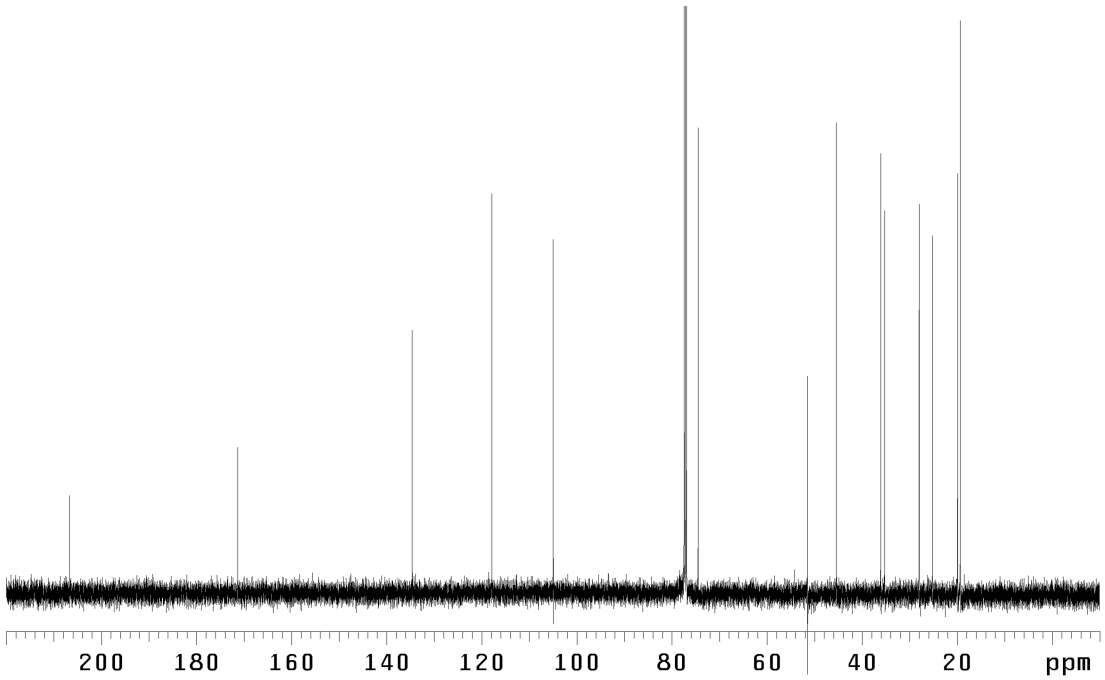


Figure A2.22.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **27a**.

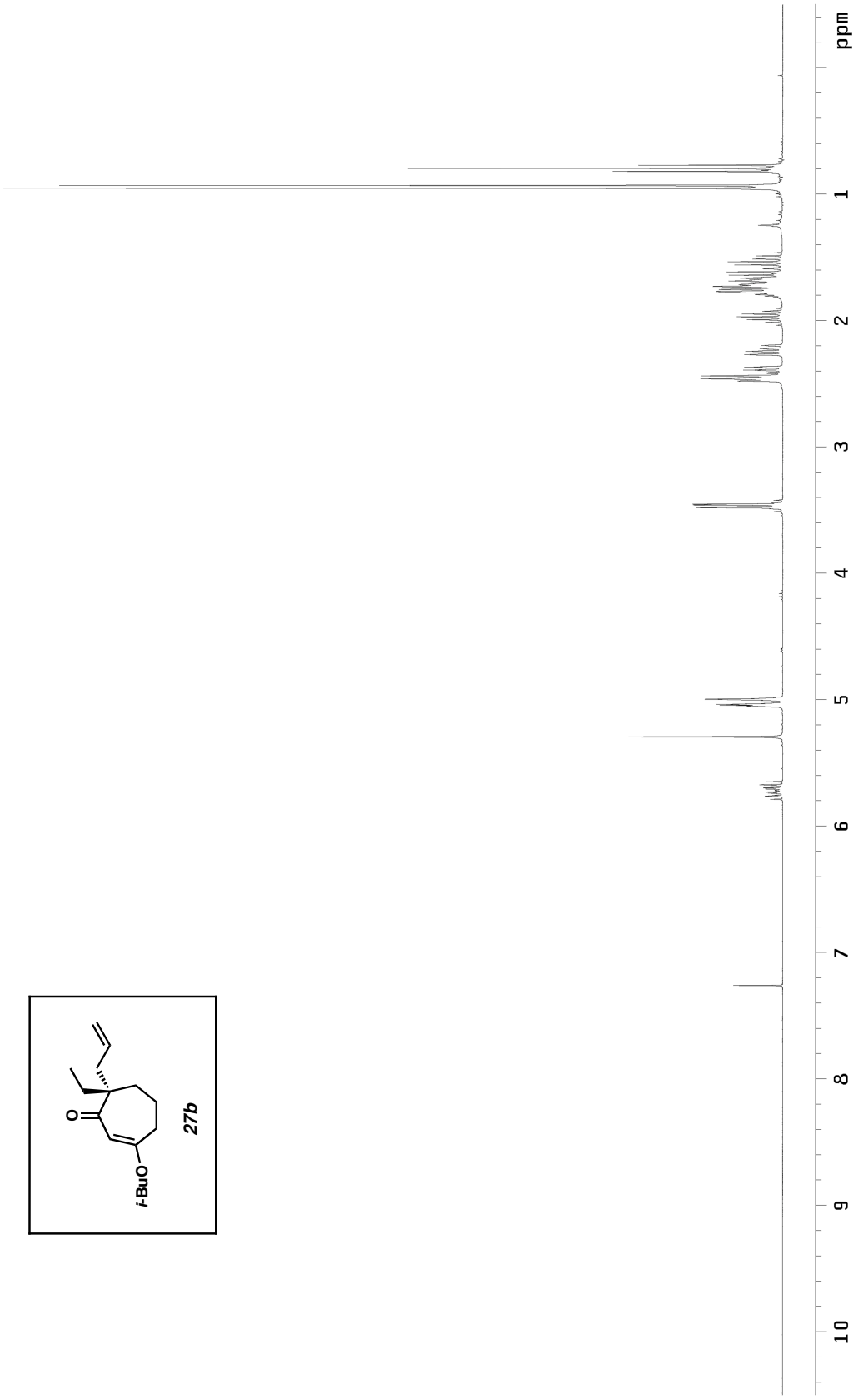


Figure A2.23.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **27b**.

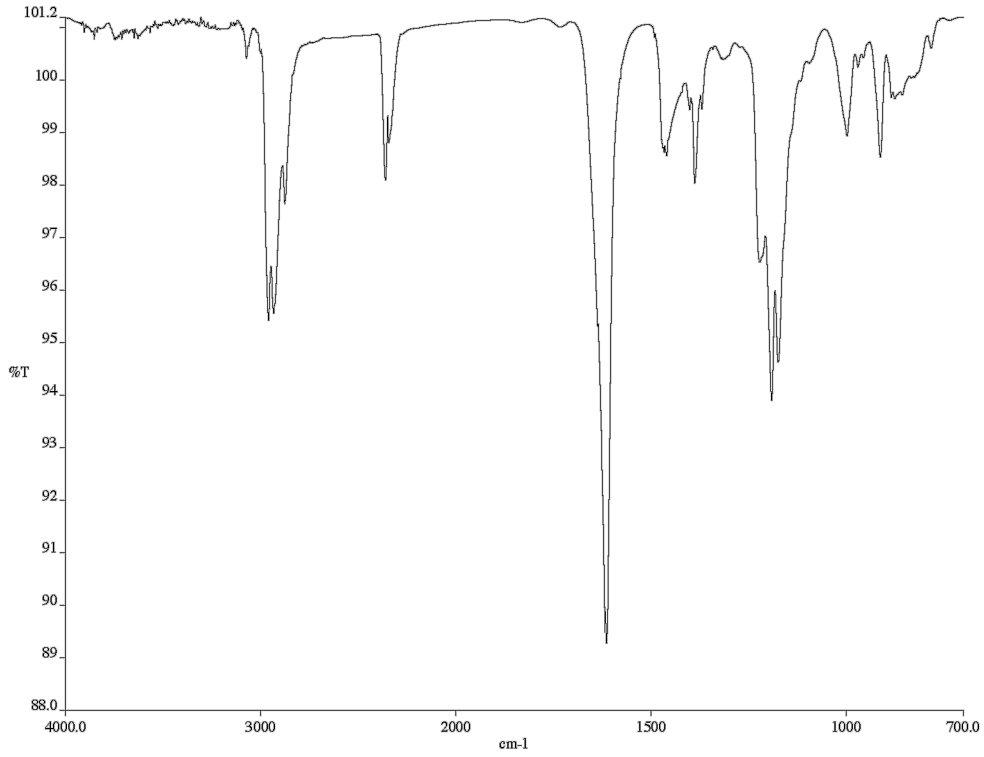


Figure A2.23.2. Infrared spectrum (thin film/NaCl) of compound **27b**.

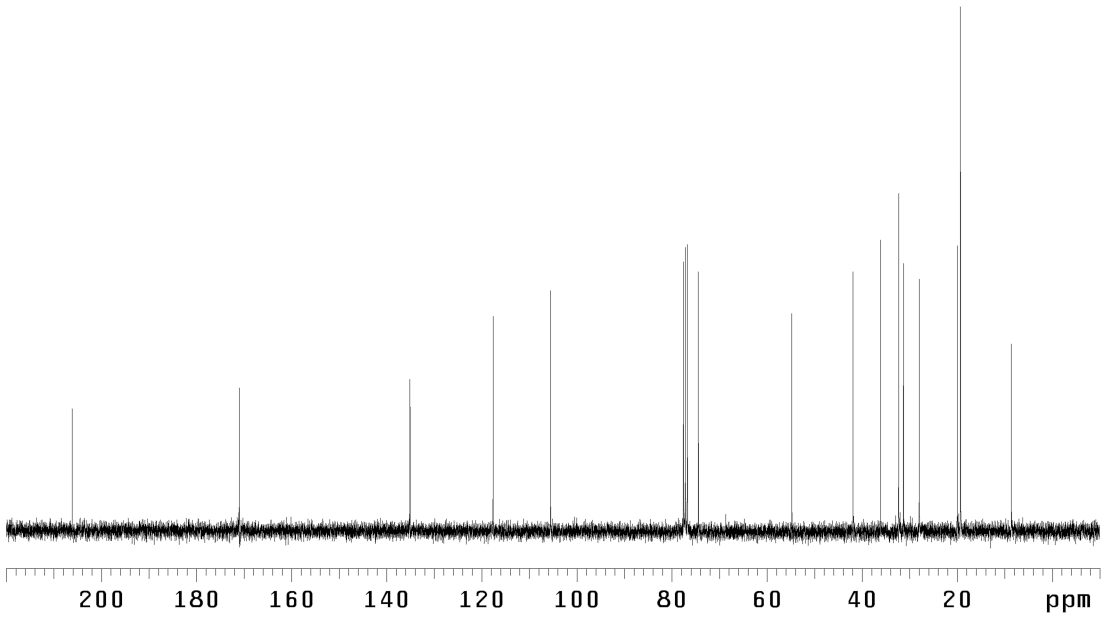


Figure A2.23.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **27b**.

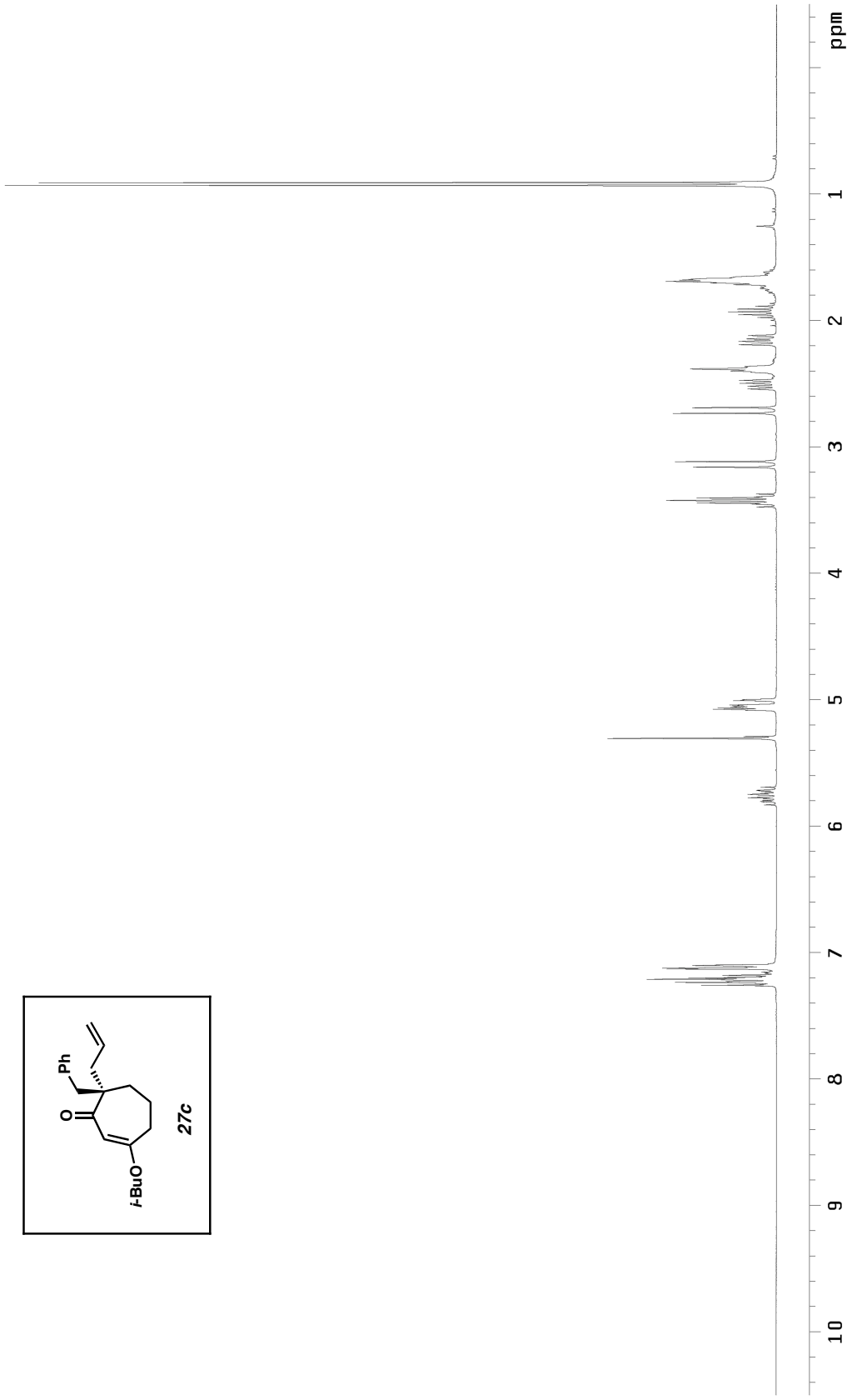


Figure A2.24.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **27c**.

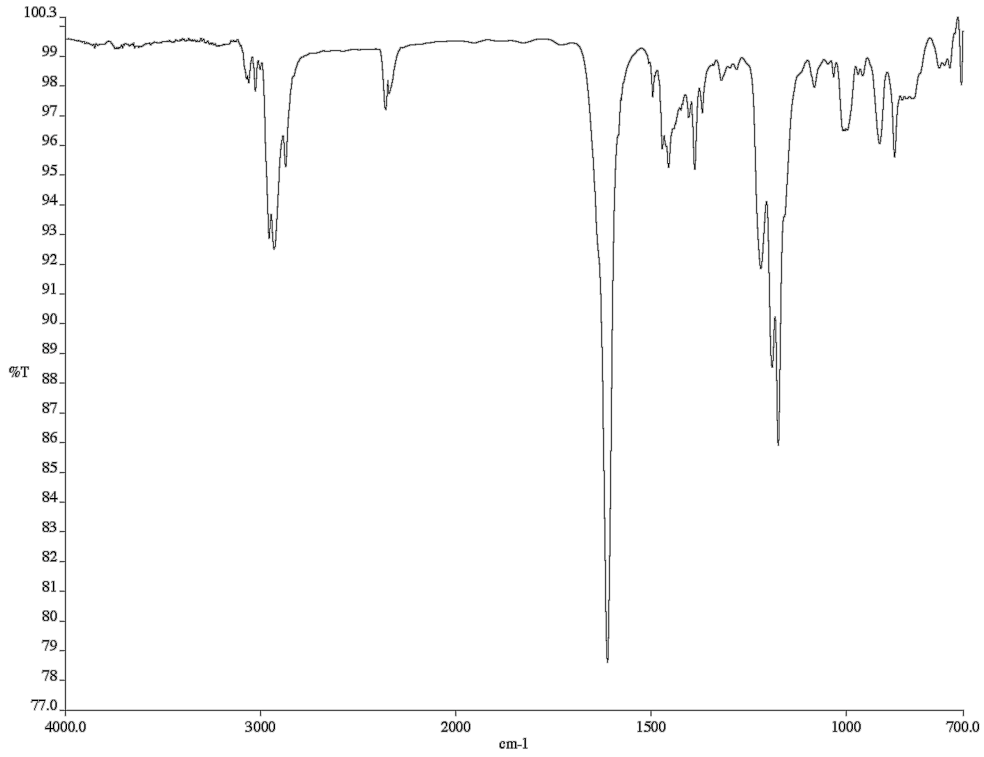


Figure A2.24.2. Infrared spectrum (thin film/NaCl) of compound **27c**.

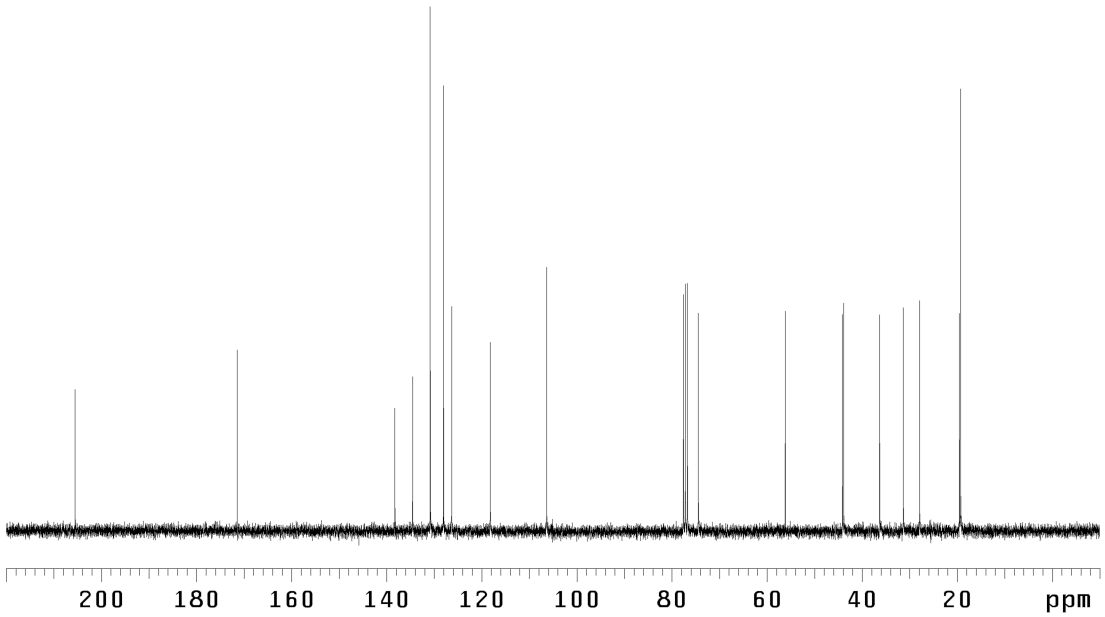


Figure A2.24.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **27c**.

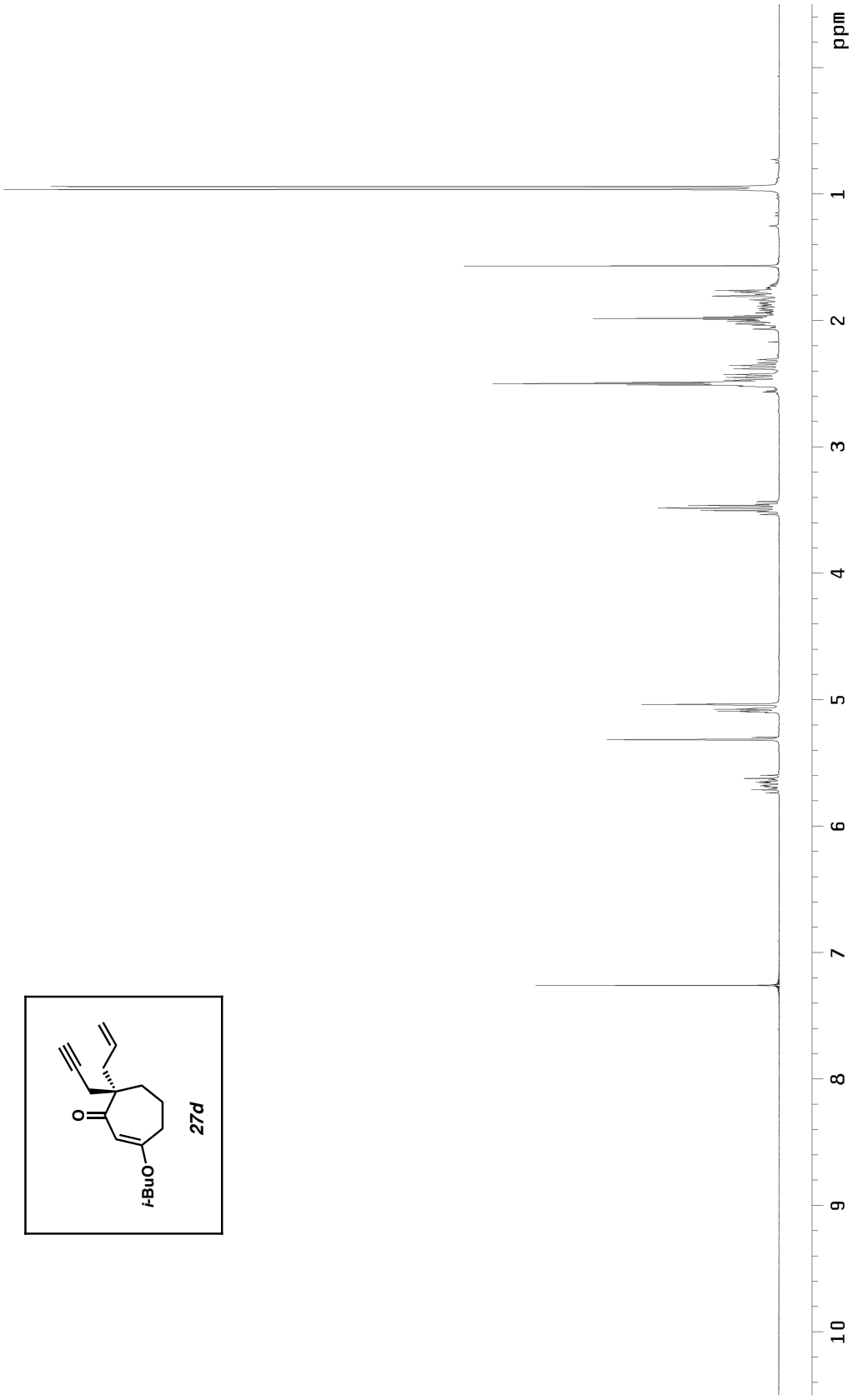


Figure A2.25.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **27d**.

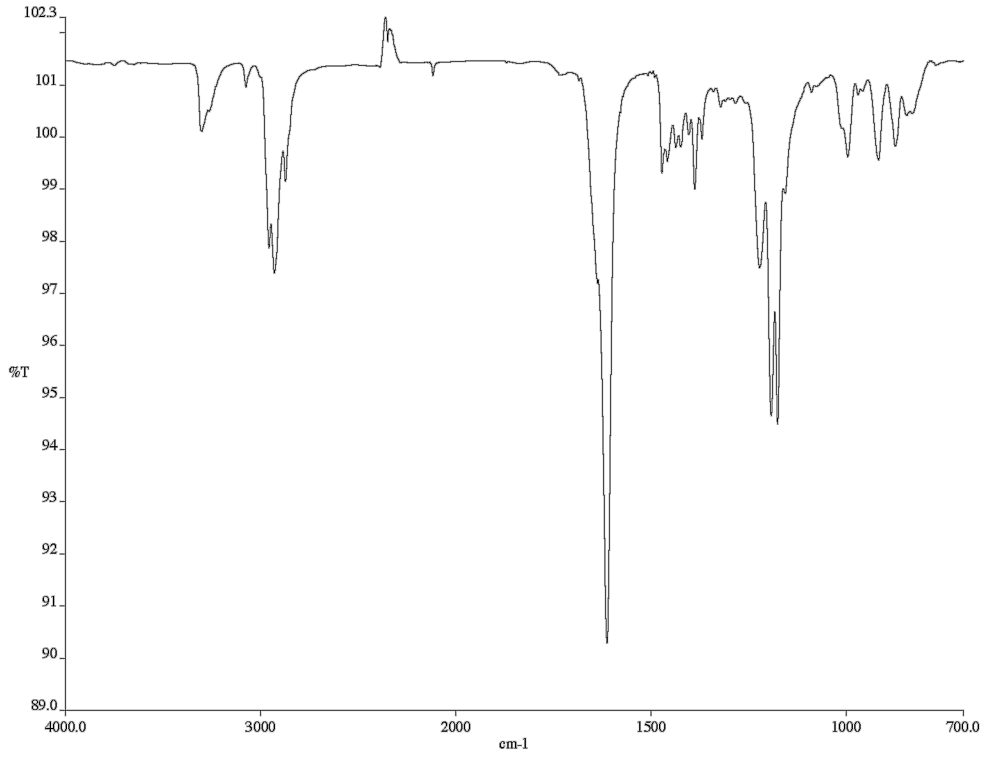


Figure A2.25.2. Infrared spectrum (thin film/NaCl) of compound **27d**.

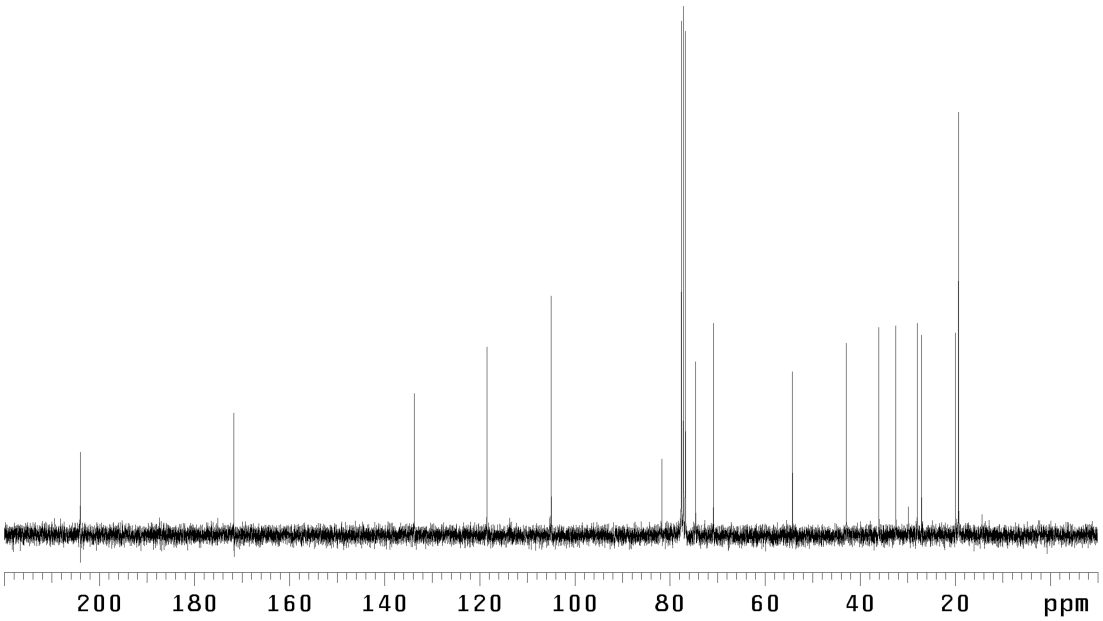


Figure A2.25.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **27d**.

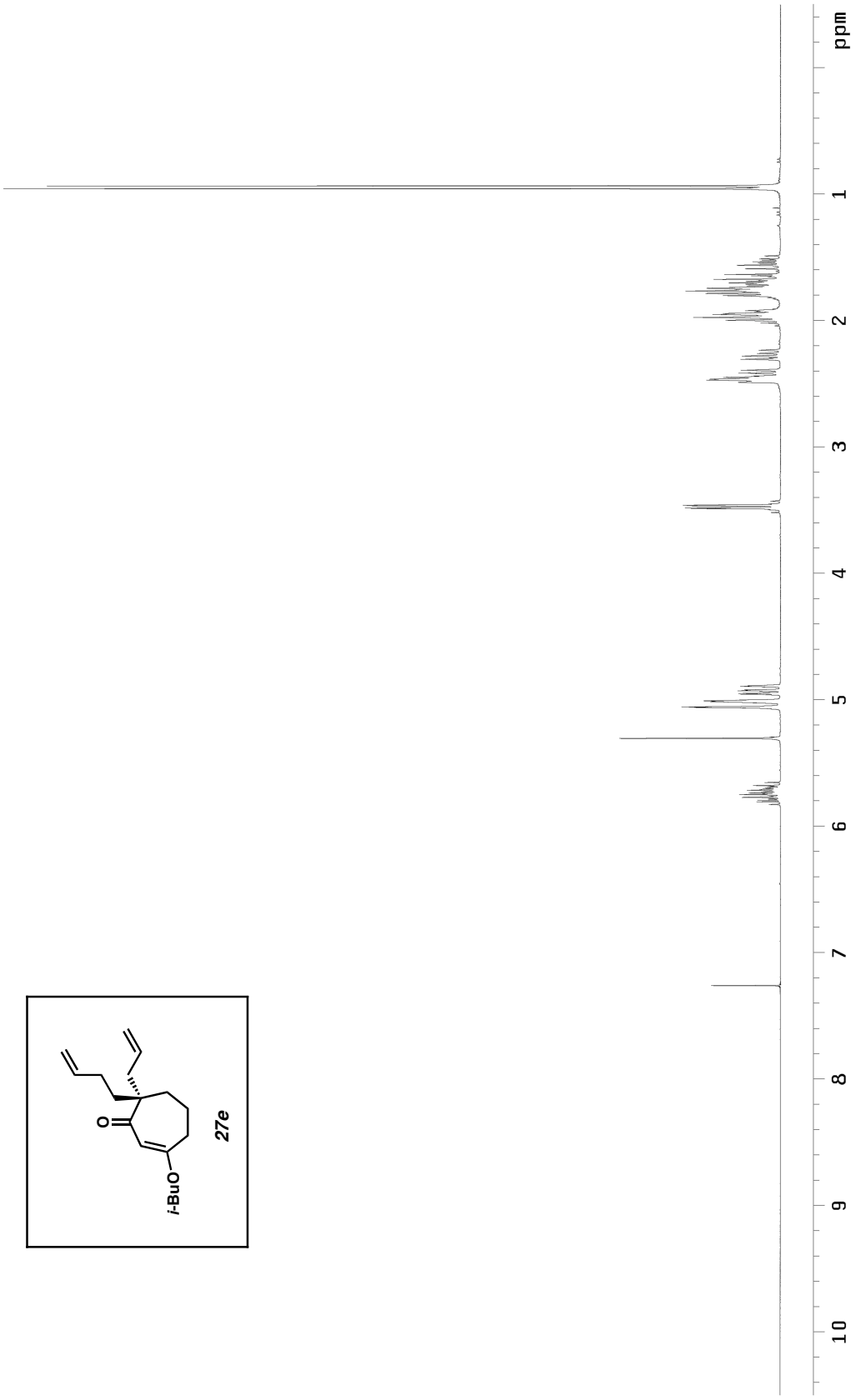


Figure A2.26.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **27e**.

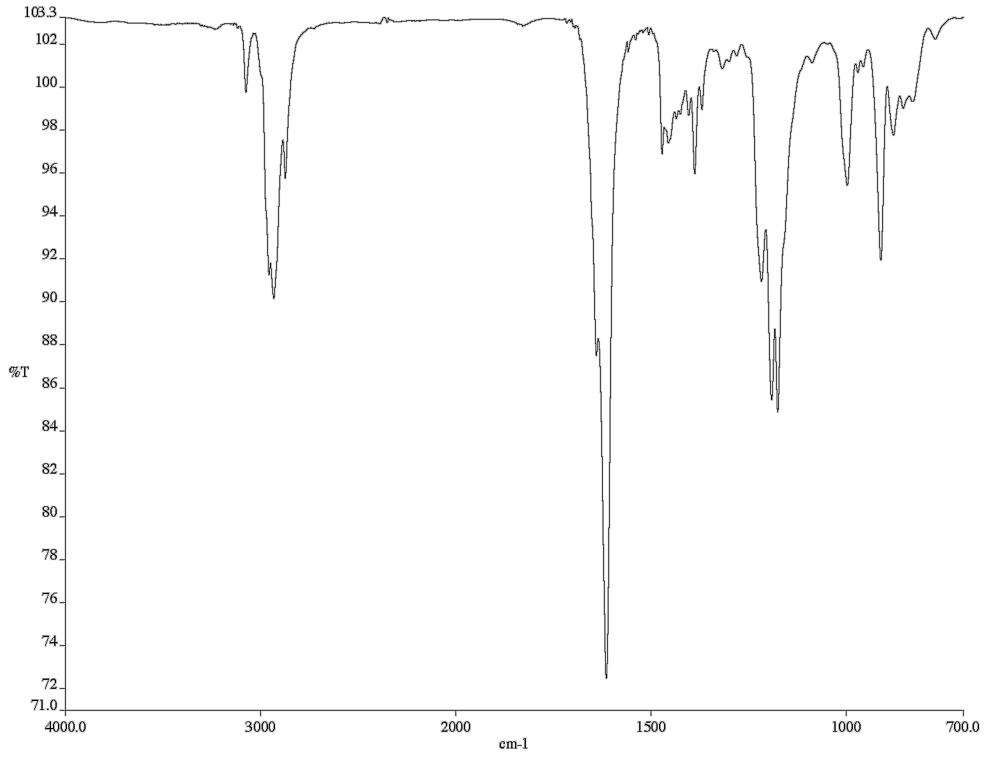


Figure A2.26.2. Infrared spectrum (thin film/NaCl) of compound **27e**.

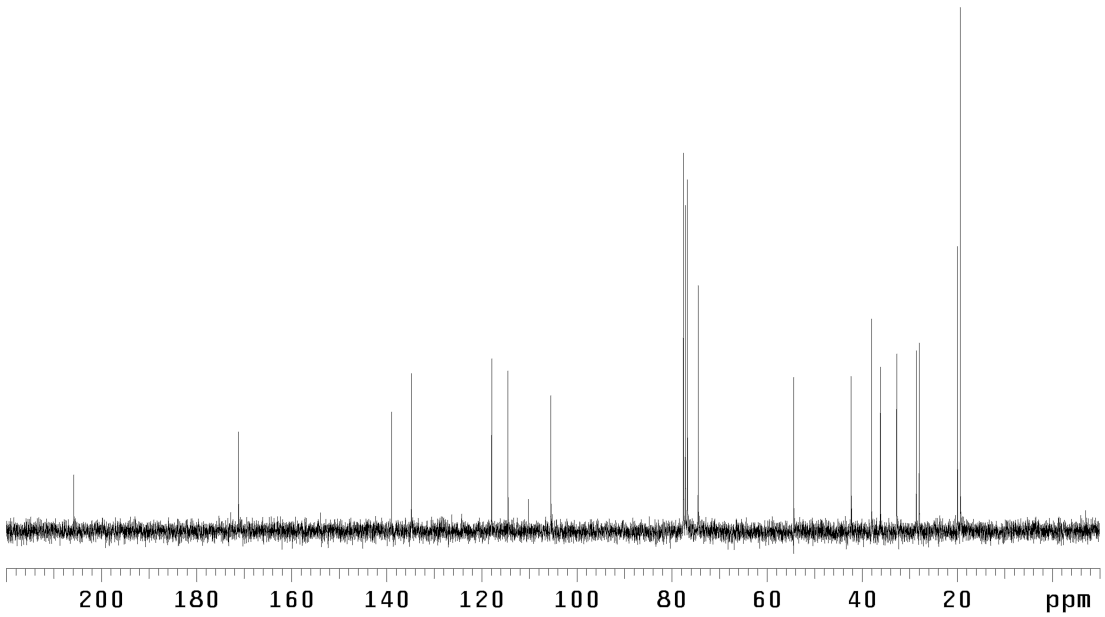


Figure A2.26.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **27e**.

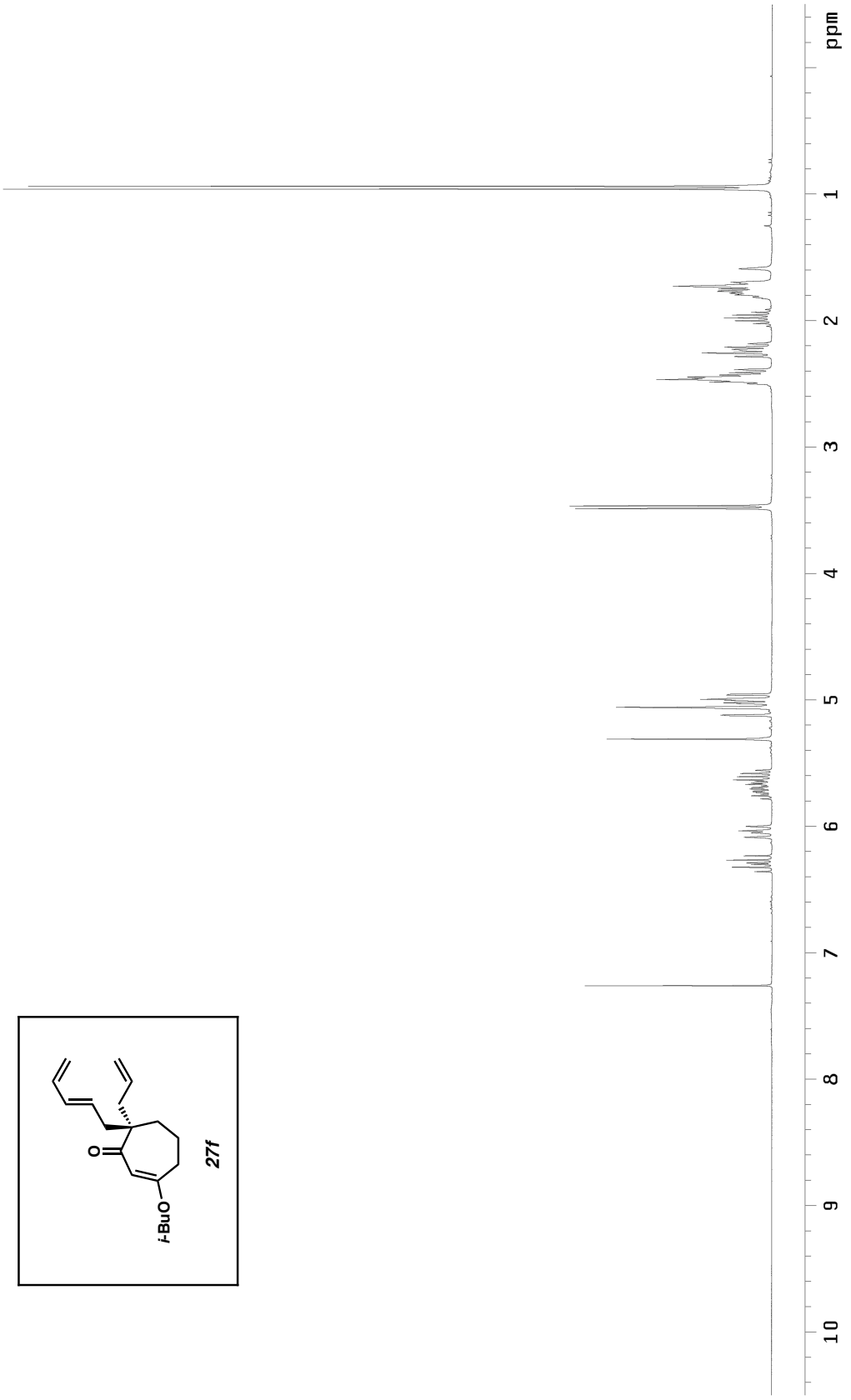


Figure A2.27.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **27f**.

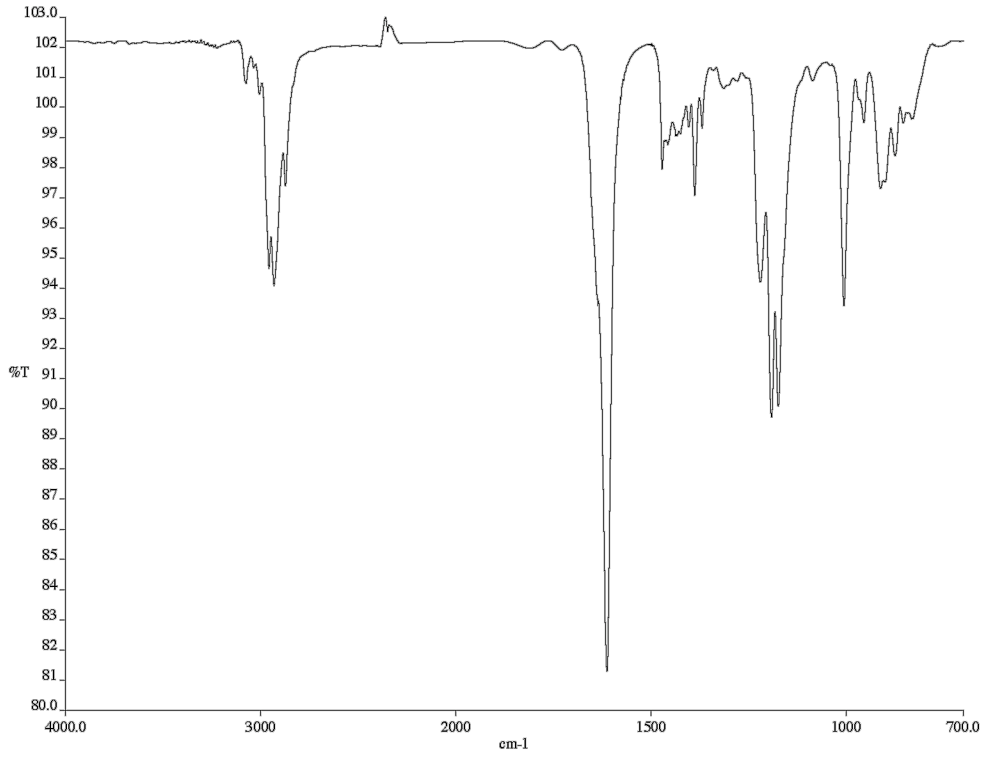


Figure A2.27.2. Infrared spectrum (thin film/NaCl) of compound **27f**.

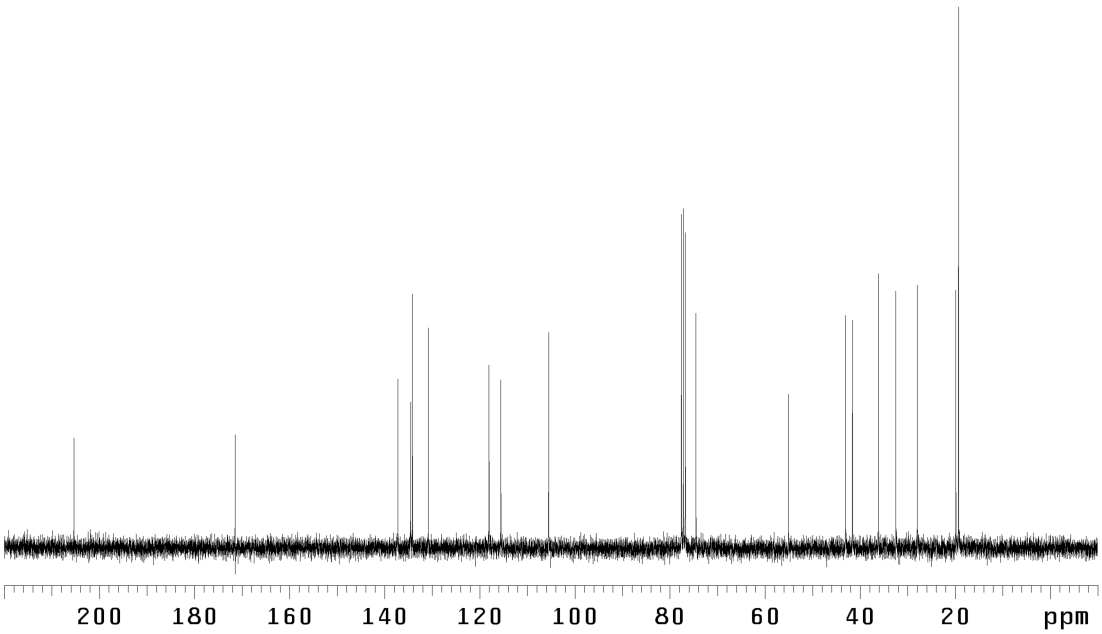


Figure A2.27.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **27f**.

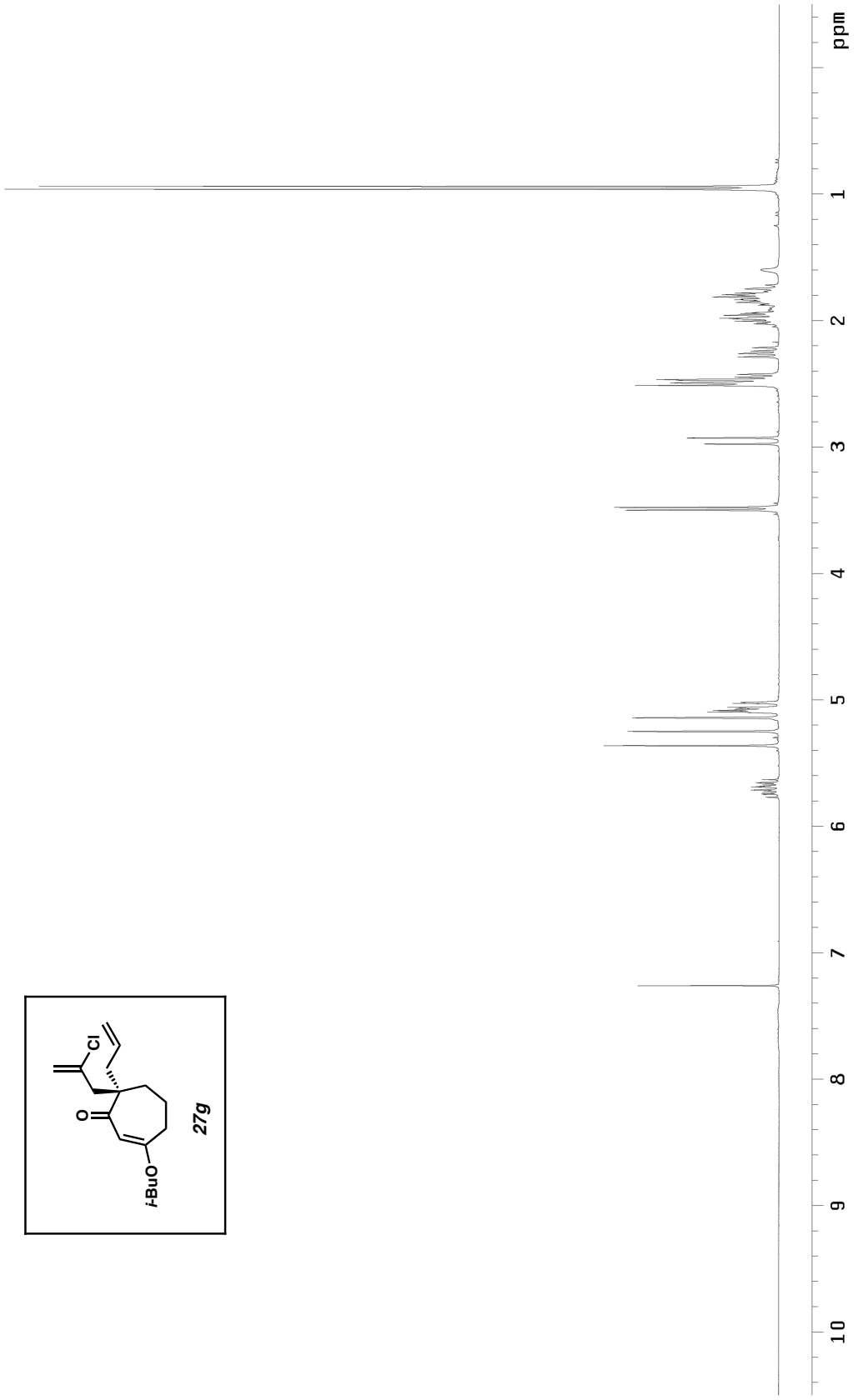


Figure A2.28.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **27g**.

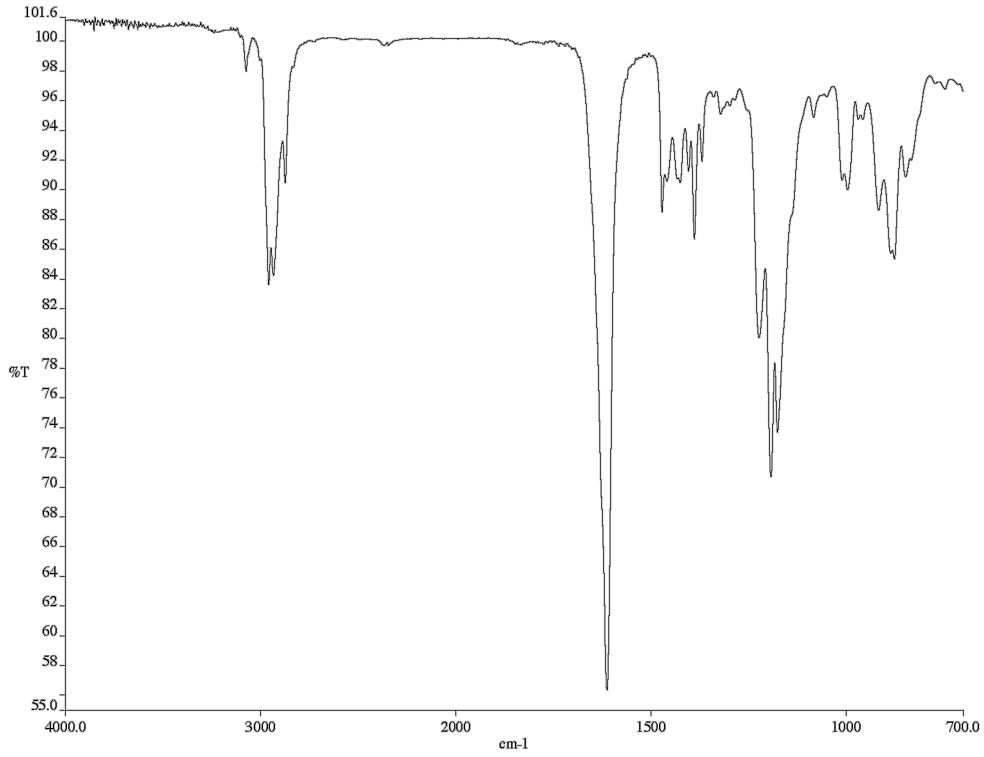


Figure A2.28.2. Infrared spectrum (thin film/NaCl) of compound **27g**.

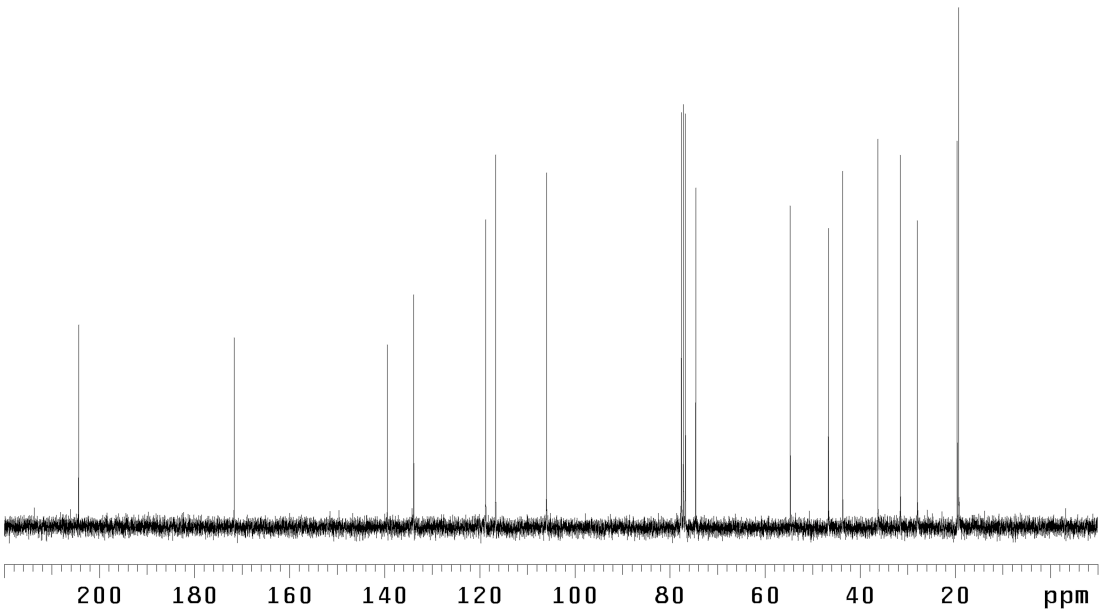


Figure A2.28.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **27g**.

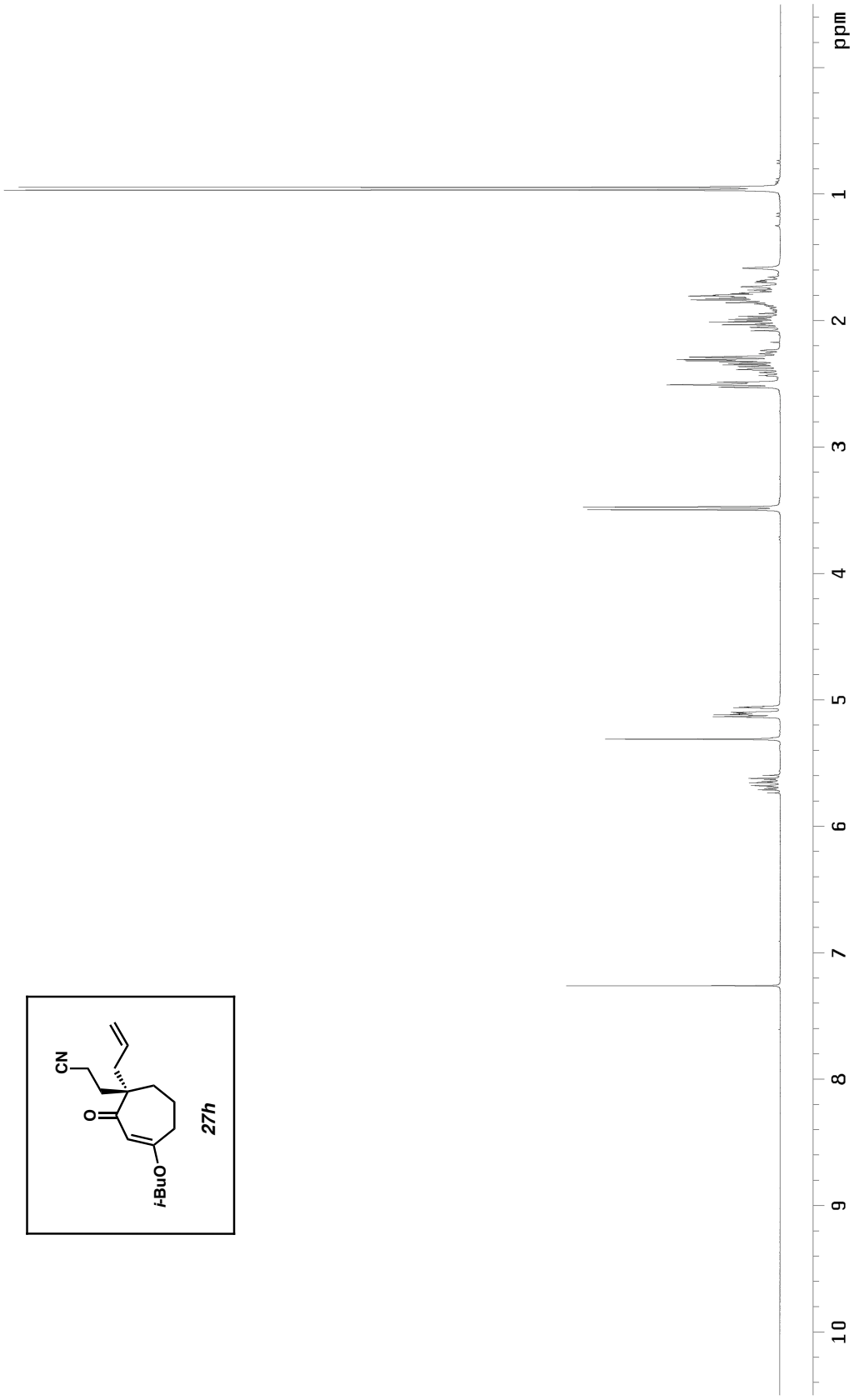


Figure A2.29.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **27h**.

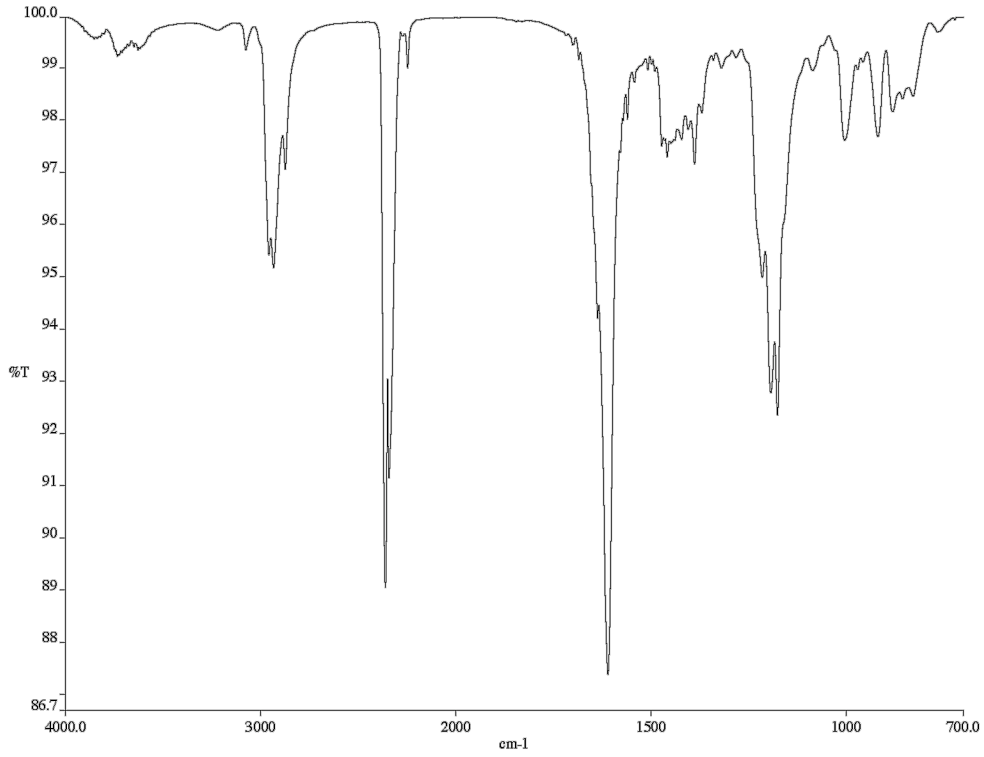


Figure A2.29.2. Infrared spectrum (thin film/NaCl) of compound **27h**.

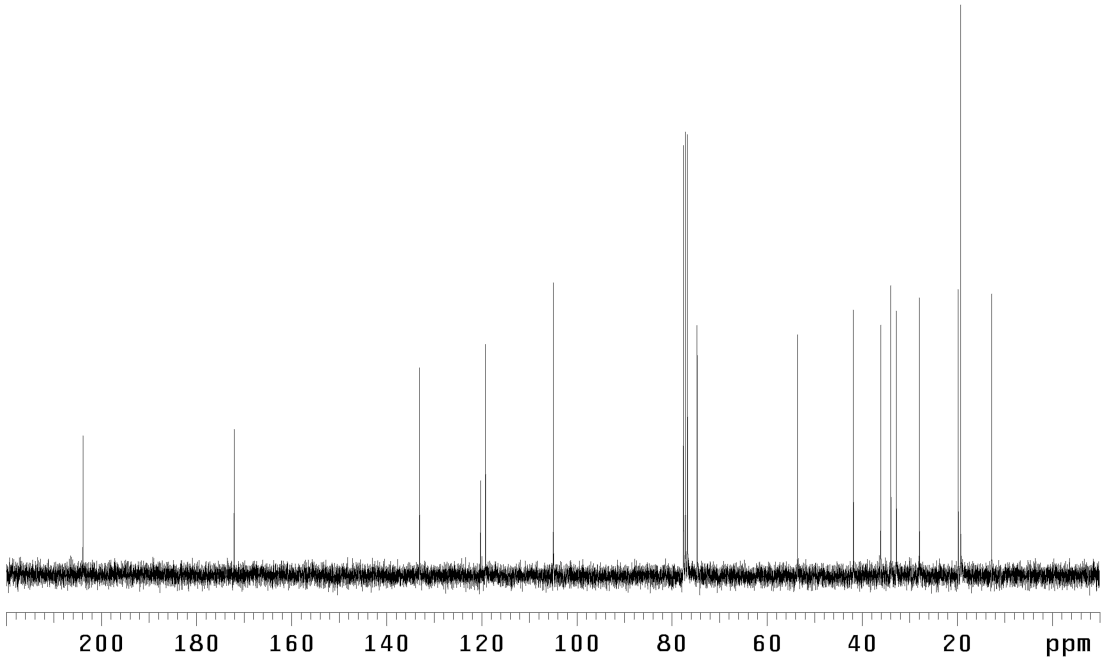


Figure A2.29.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **27h**.

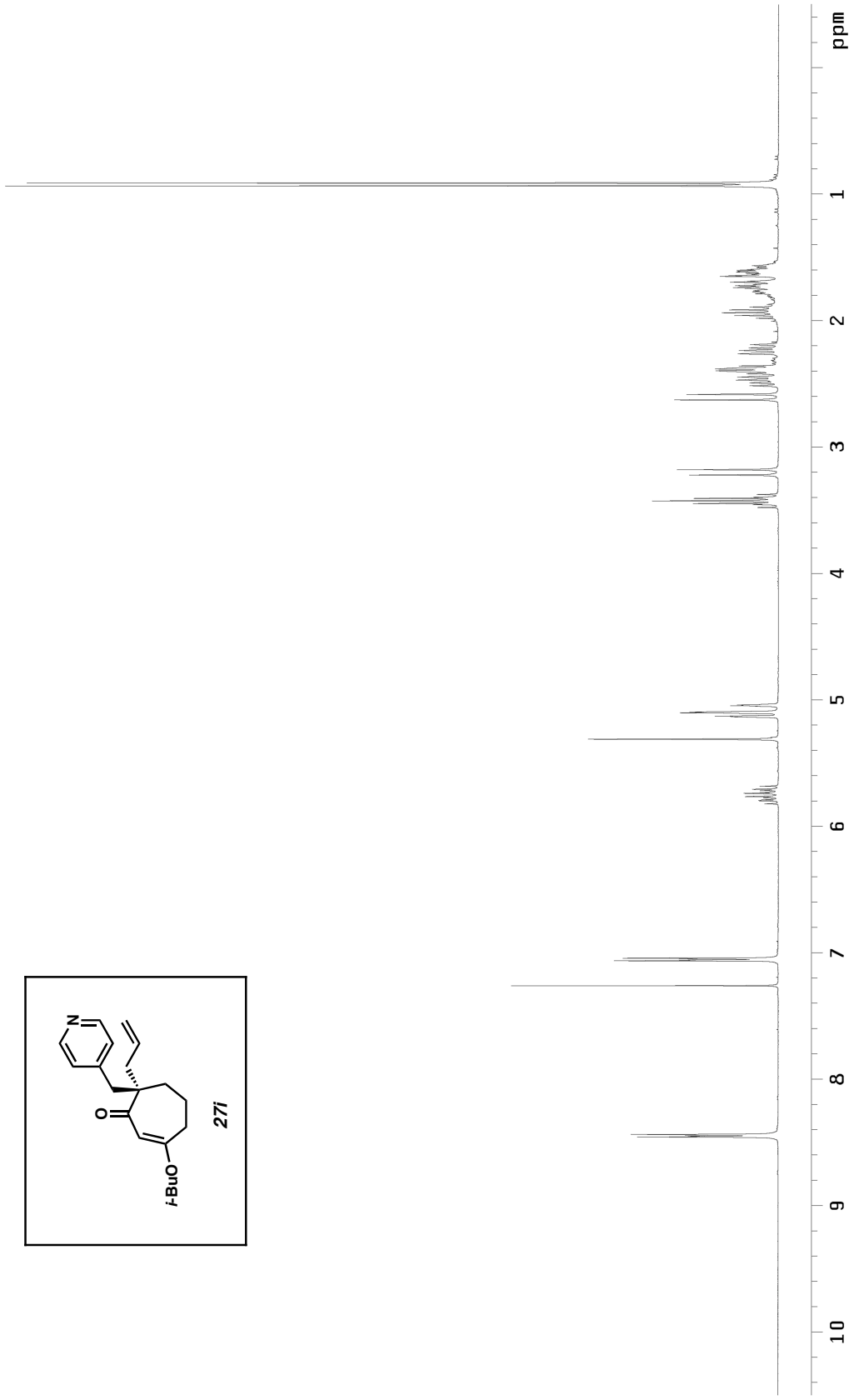


Figure A2.30.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **27i**.

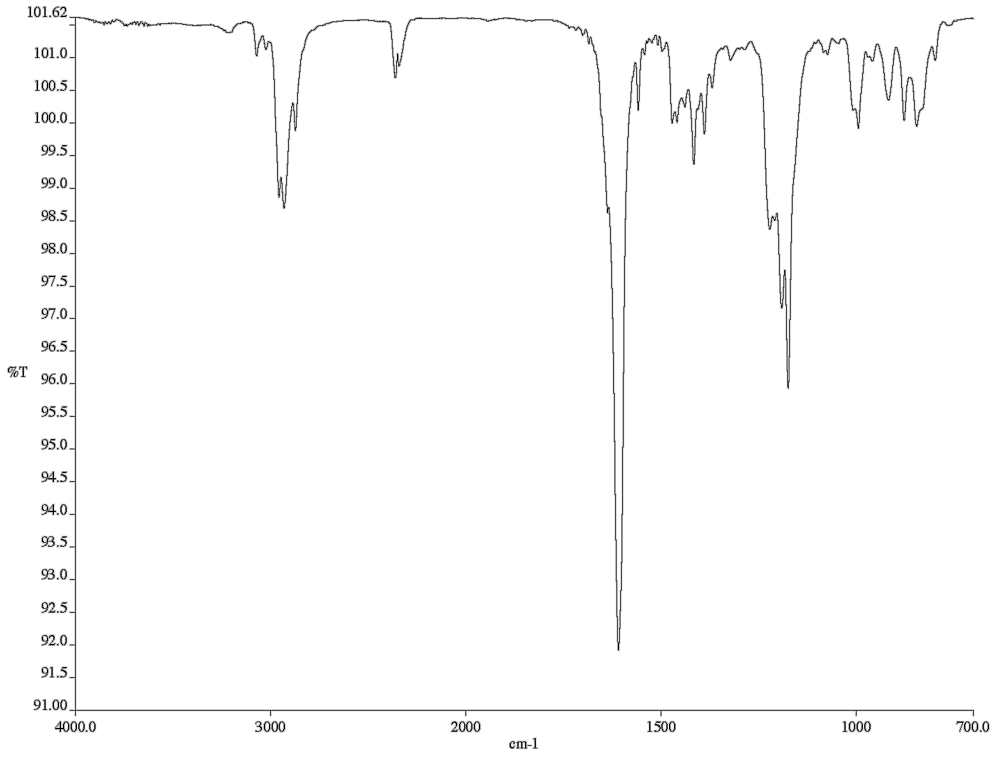


Figure A2.30.2. Infrared spectrum (thin film/NaCl) of compound **27i**.

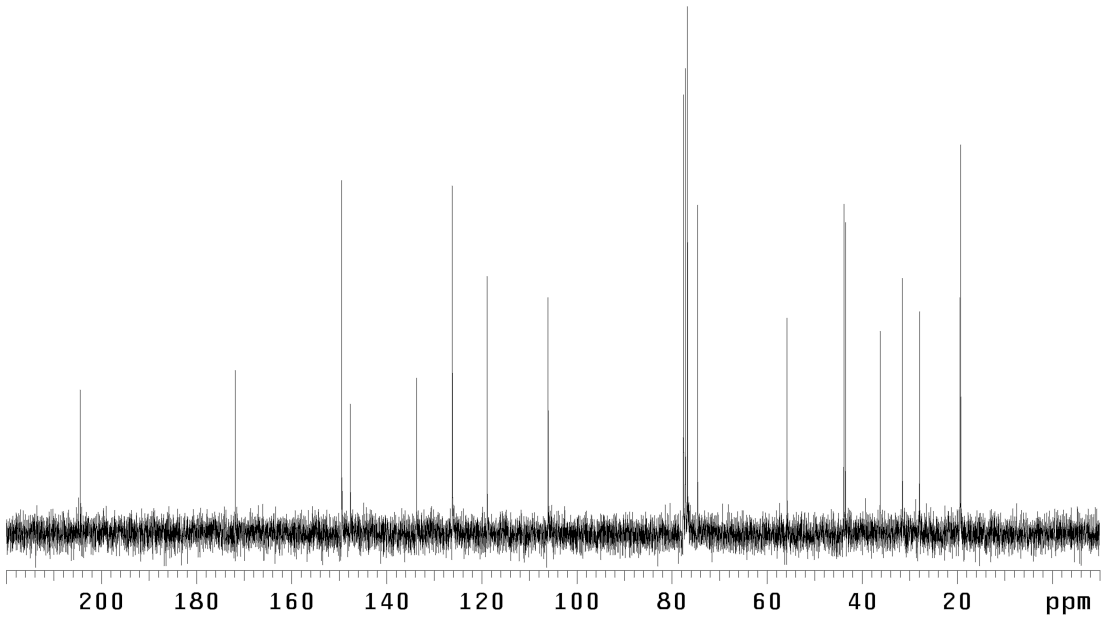


Figure A2.30.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **27i**.

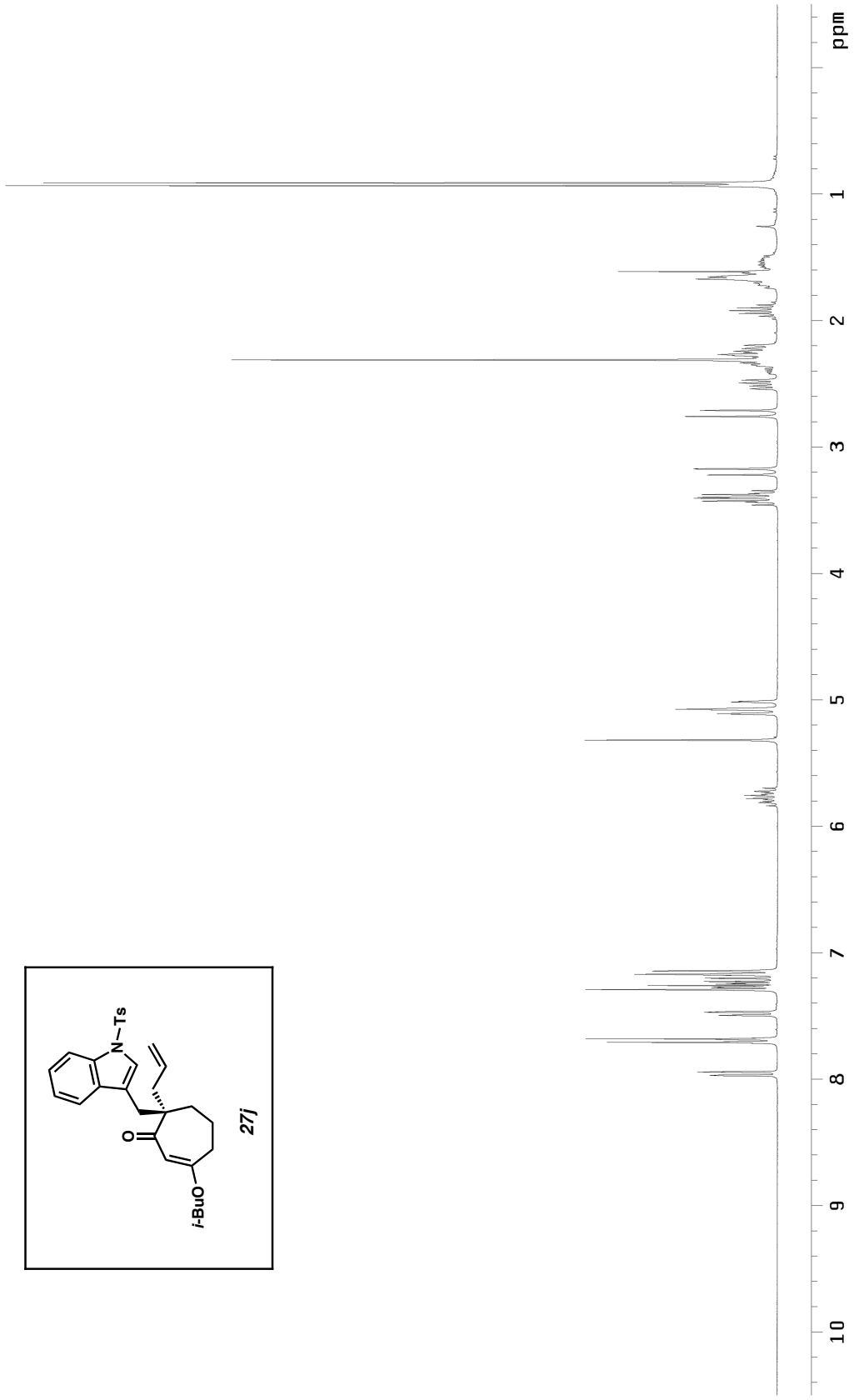


Figure A2.31.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **27j**.

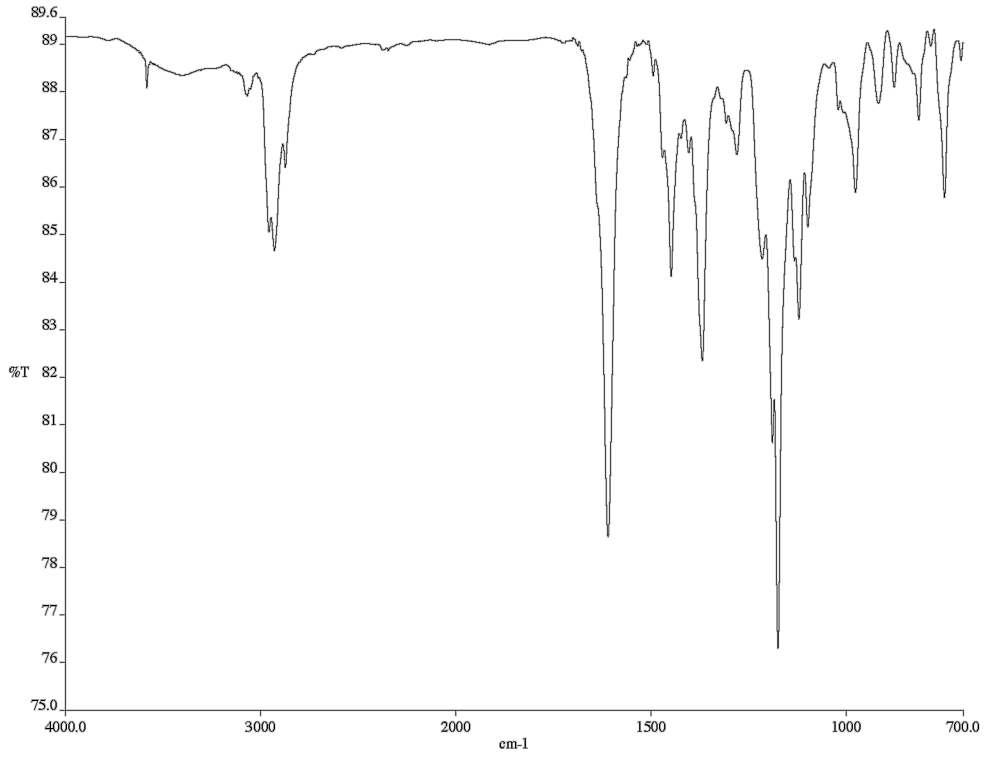


Figure A2.31.2. Infrared spectrum (thin film/NaCl) of compound **27j**.

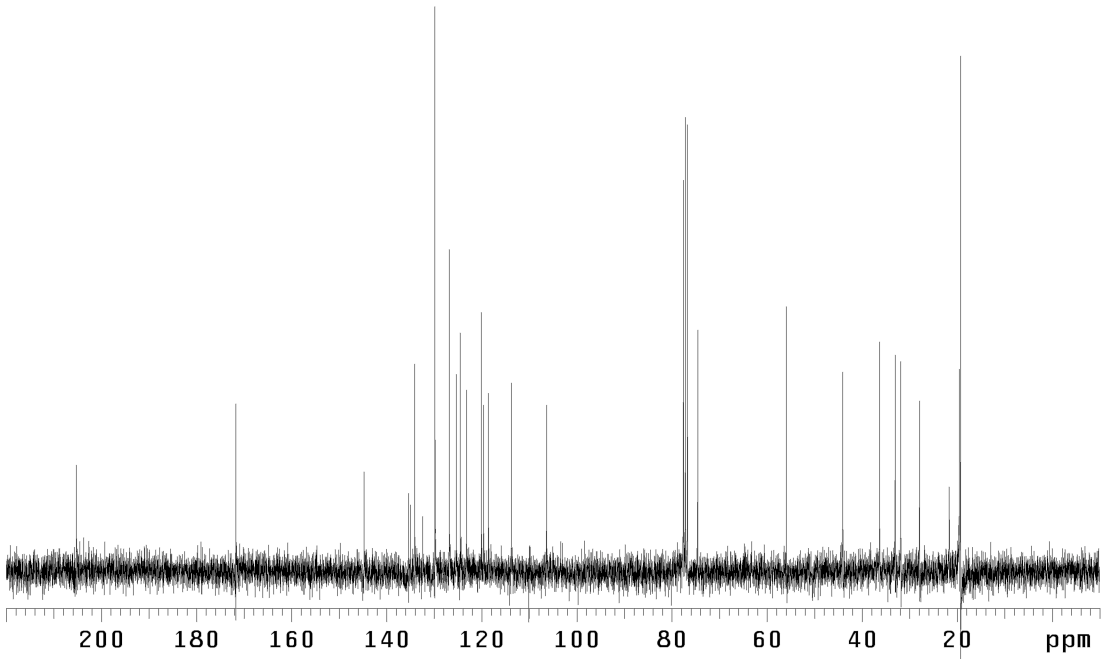


Figure A2.31.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **27j**.

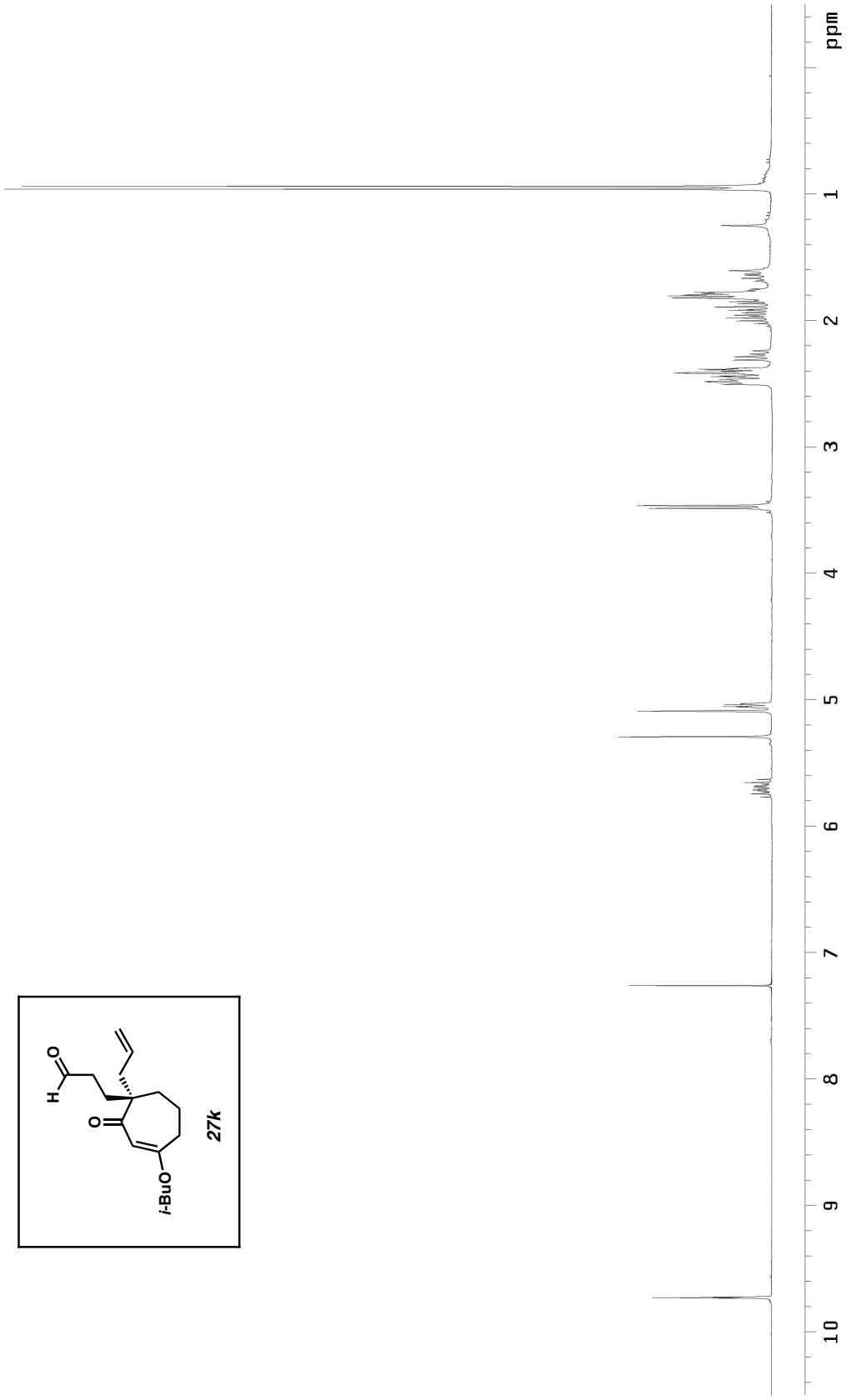


Figure A2.32.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **27k**.

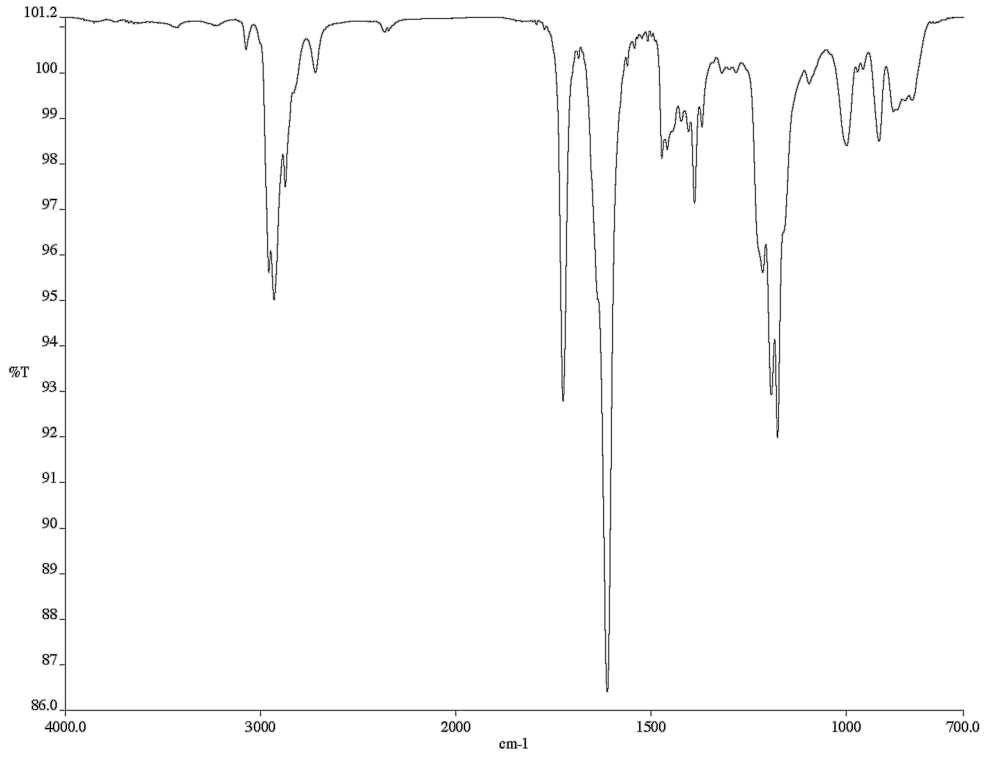


Figure A2.32.2. Infrared spectrum (thin film/NaCl) of compound **27k**.

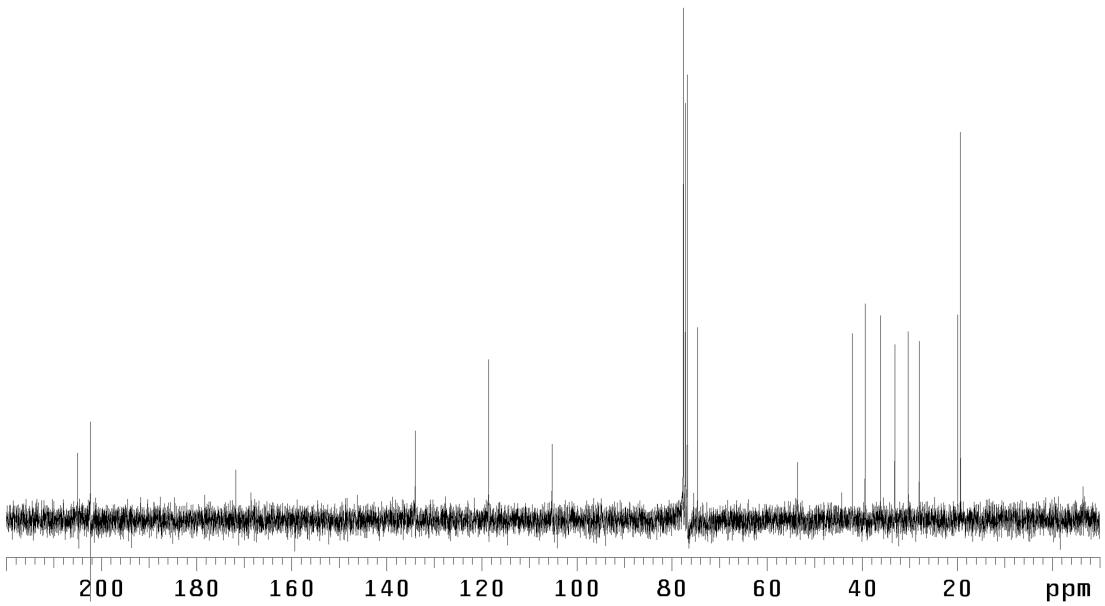


Figure A2.32.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **27k**.

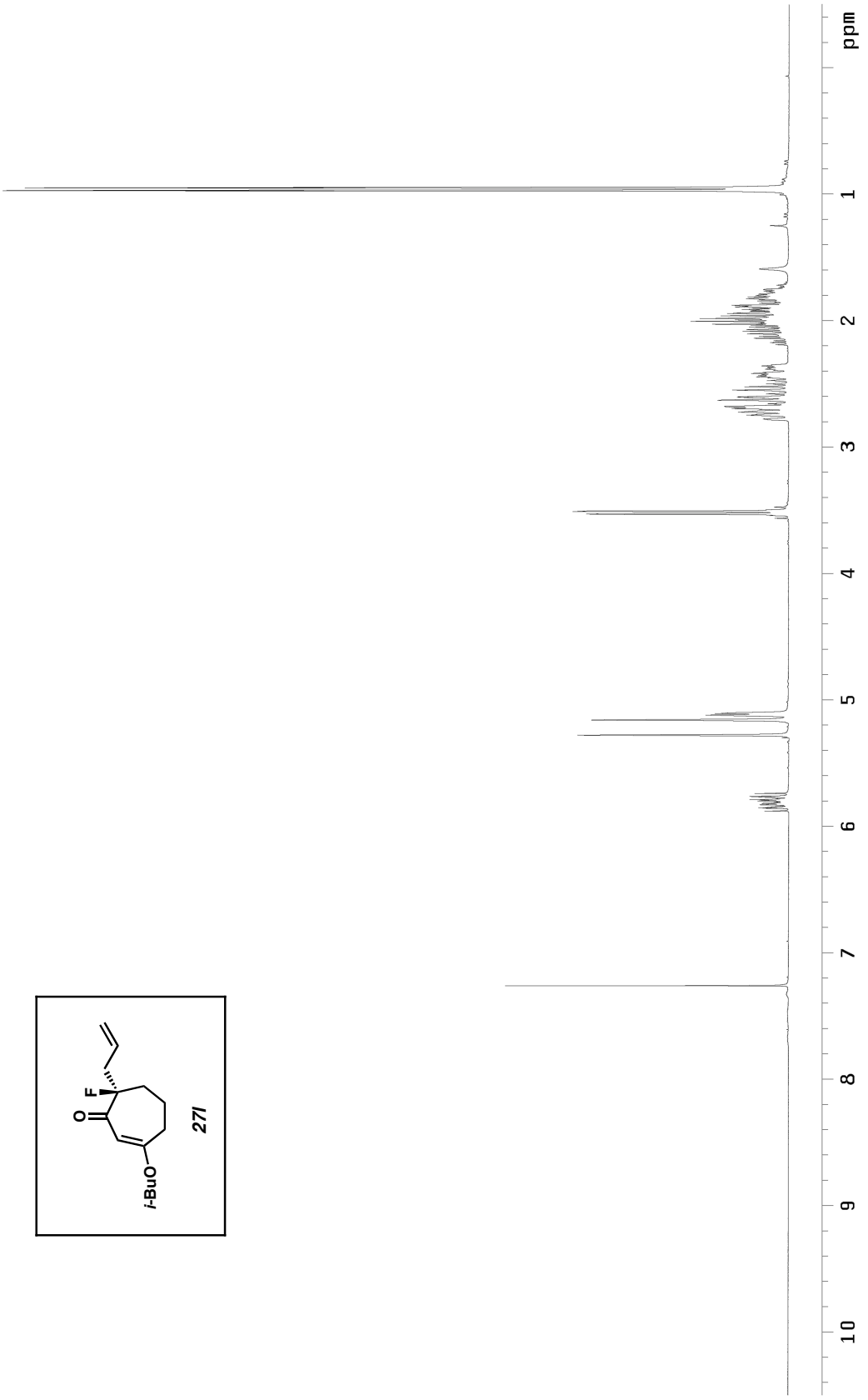


Figure A2.33.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **27l**.

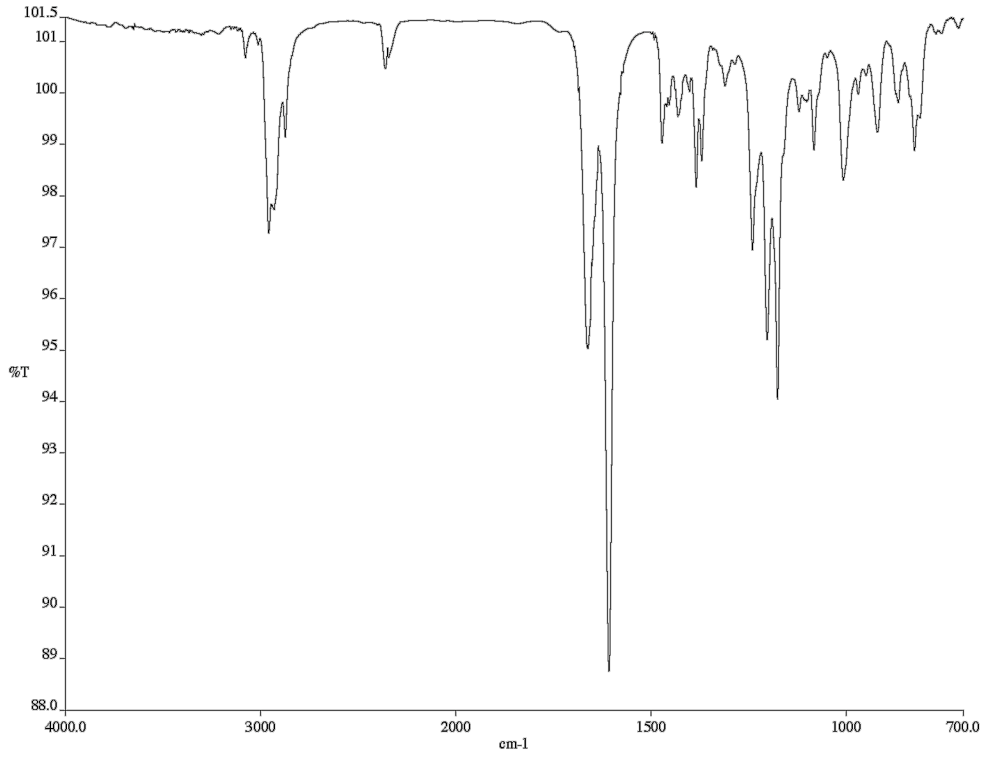


Figure A2.33.2. Infrared spectrum (thin film/NaCl) of compound **27l**.

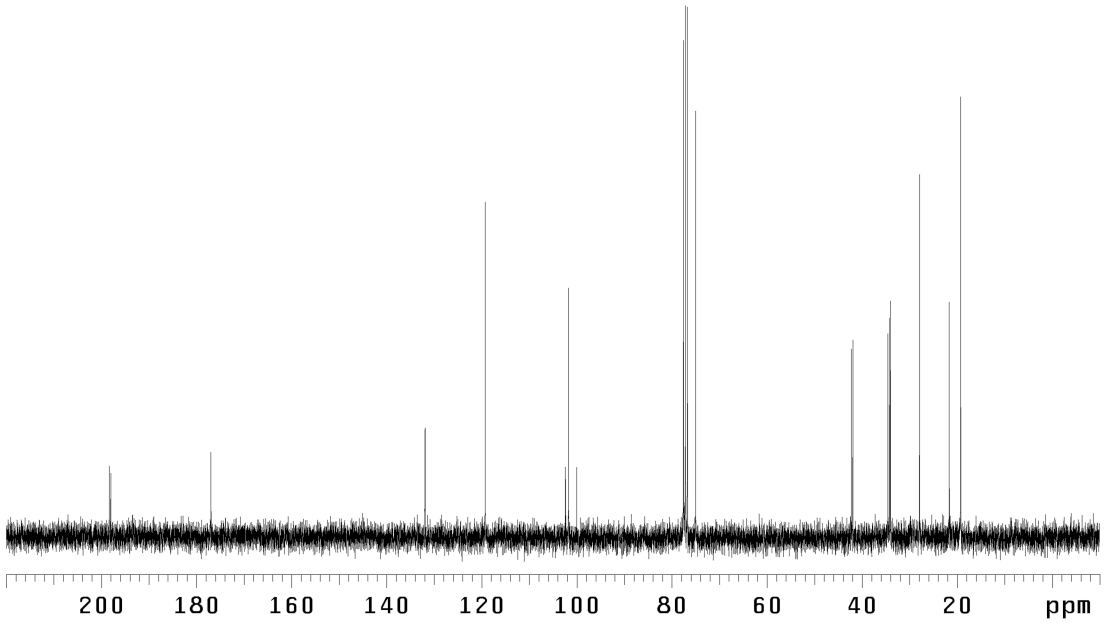


Figure A2.33.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **27l**.

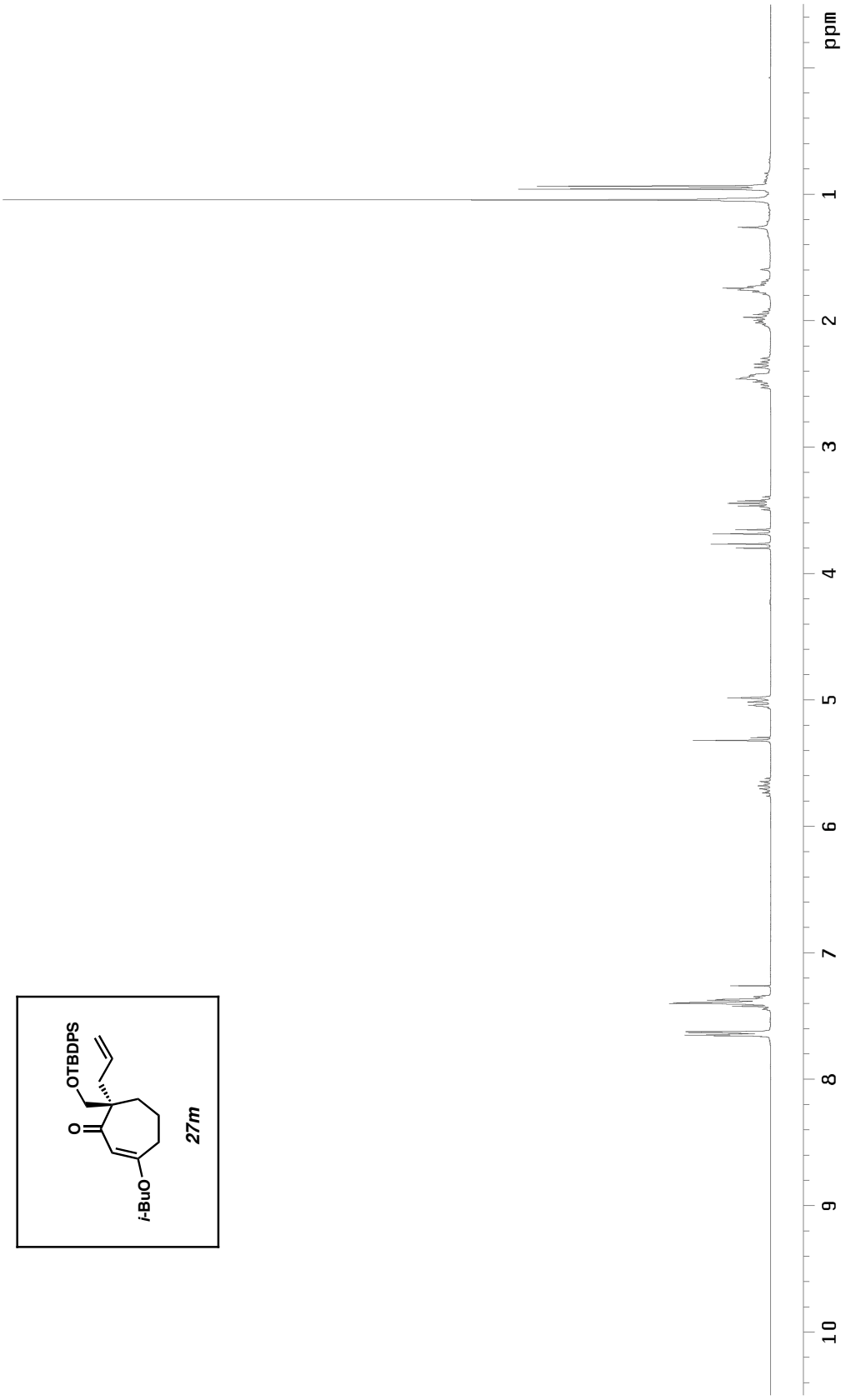


Figure A2.34.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **27m**.

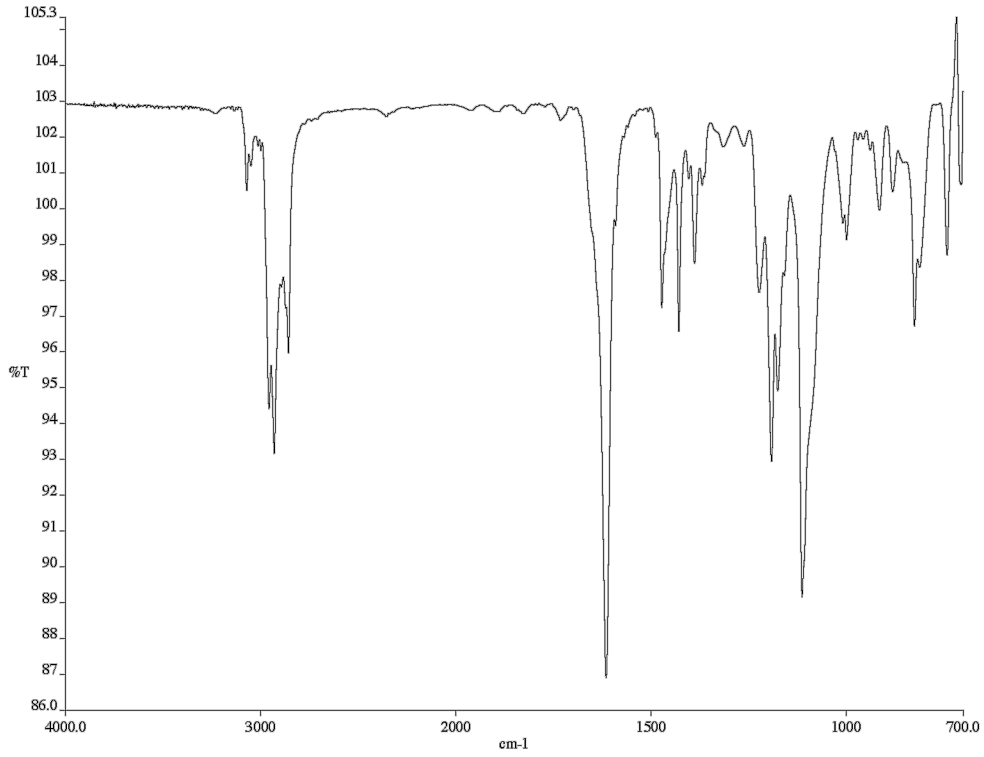


Figure A2.34.2. Infrared spectrum (thin film/NaCl) of compound **27m**.

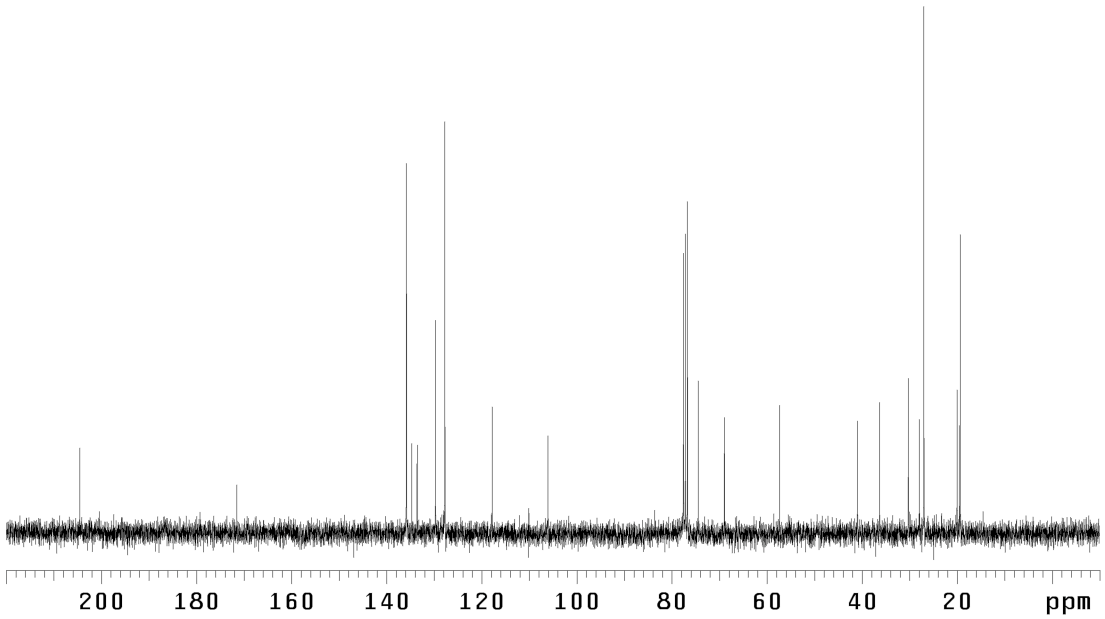


Figure A2.34.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **27m**.

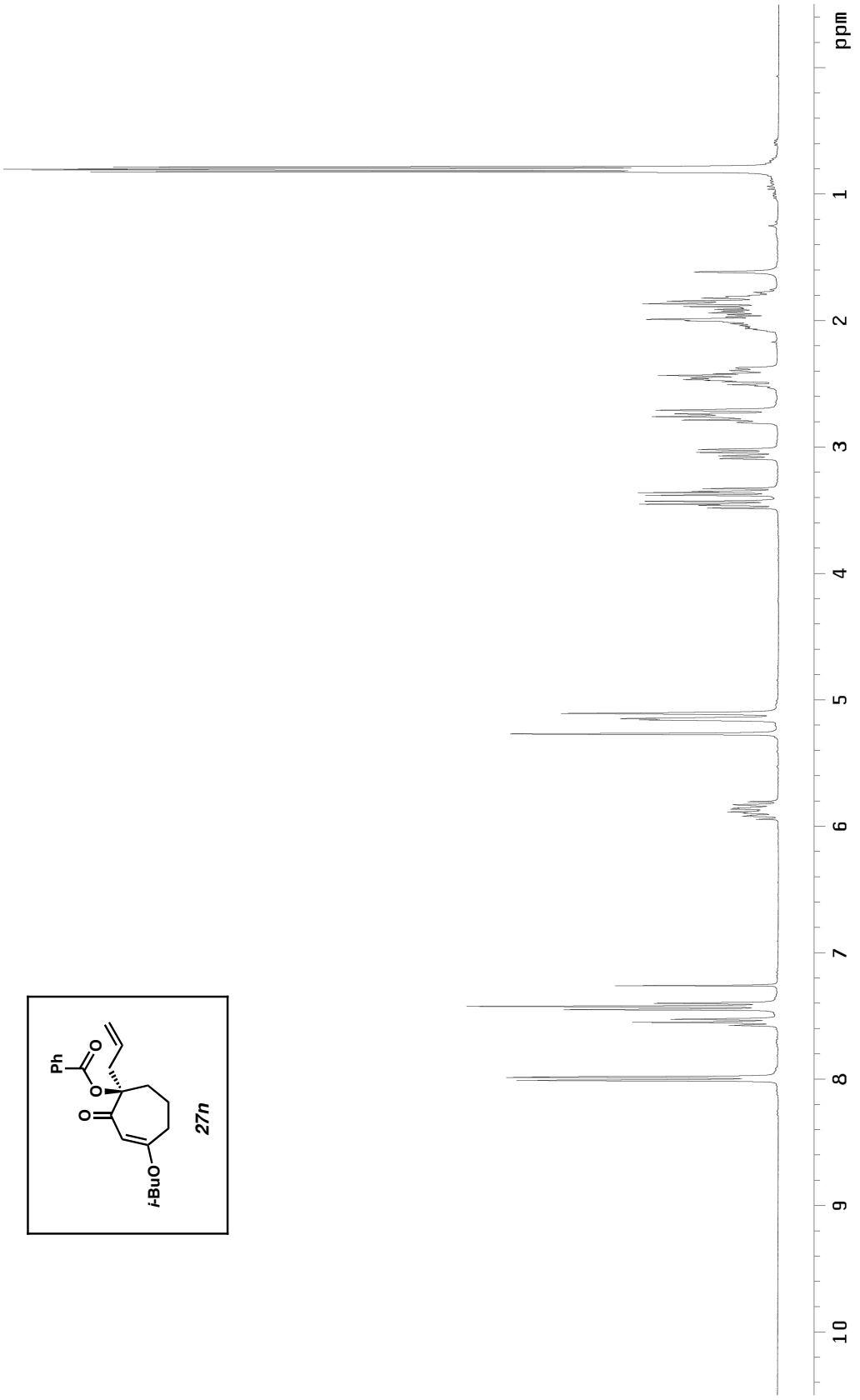


Figure A2.35.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **27n**.

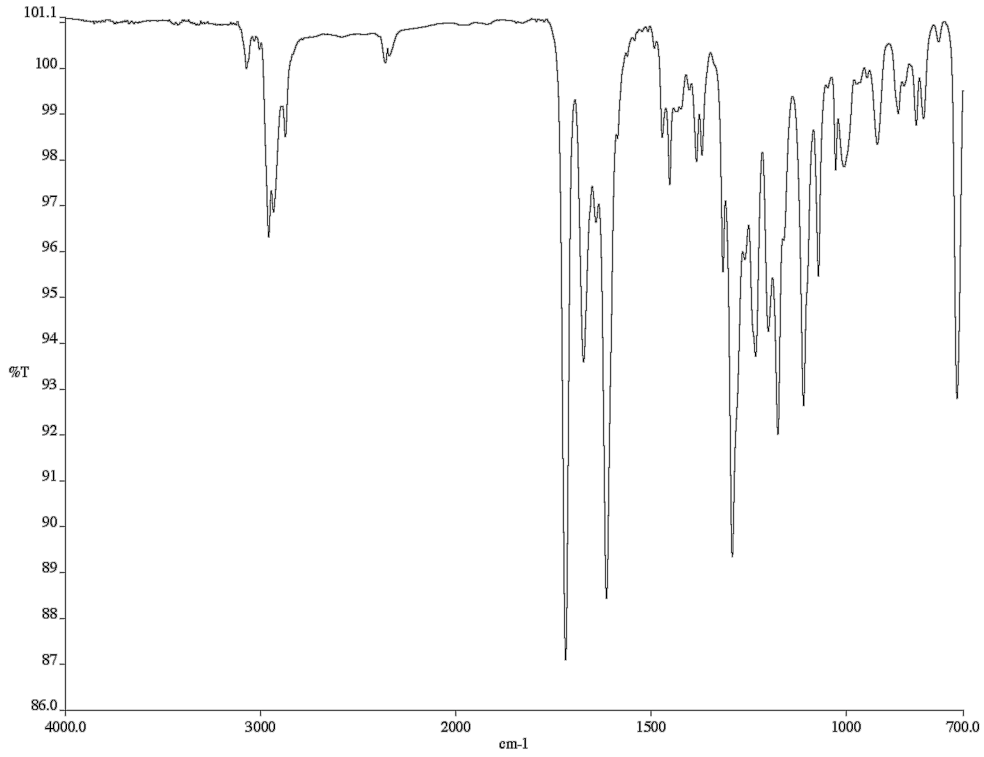


Figure A2.35.2. Infrared spectrum (thin film/NaCl) of compound **27n**.

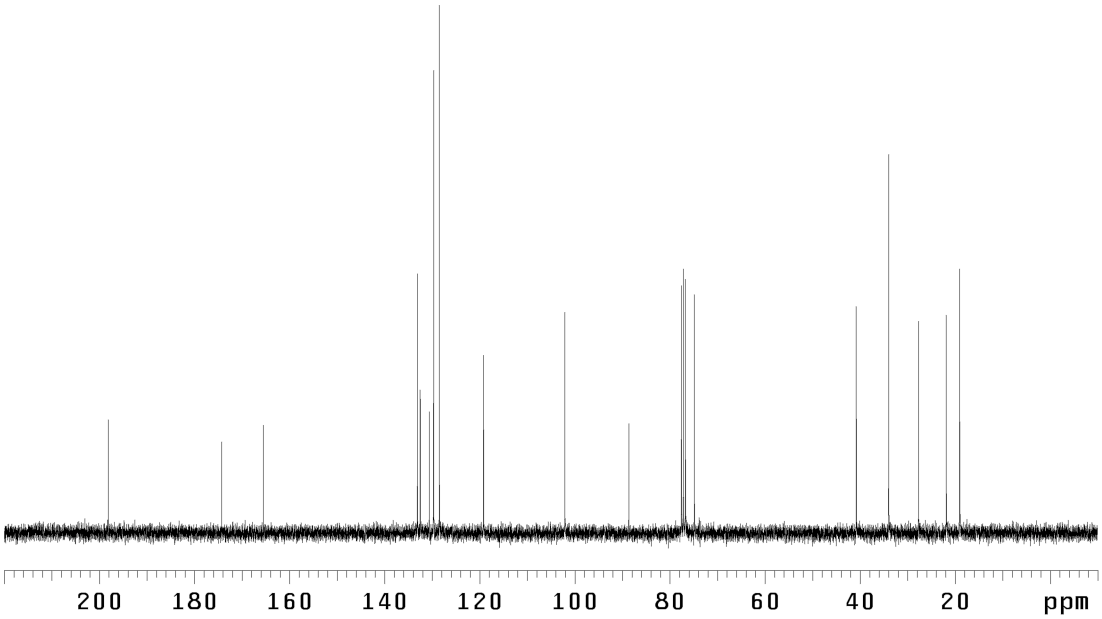


Figure A2.35.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **27n**.

Figure A2.36.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **27o**.

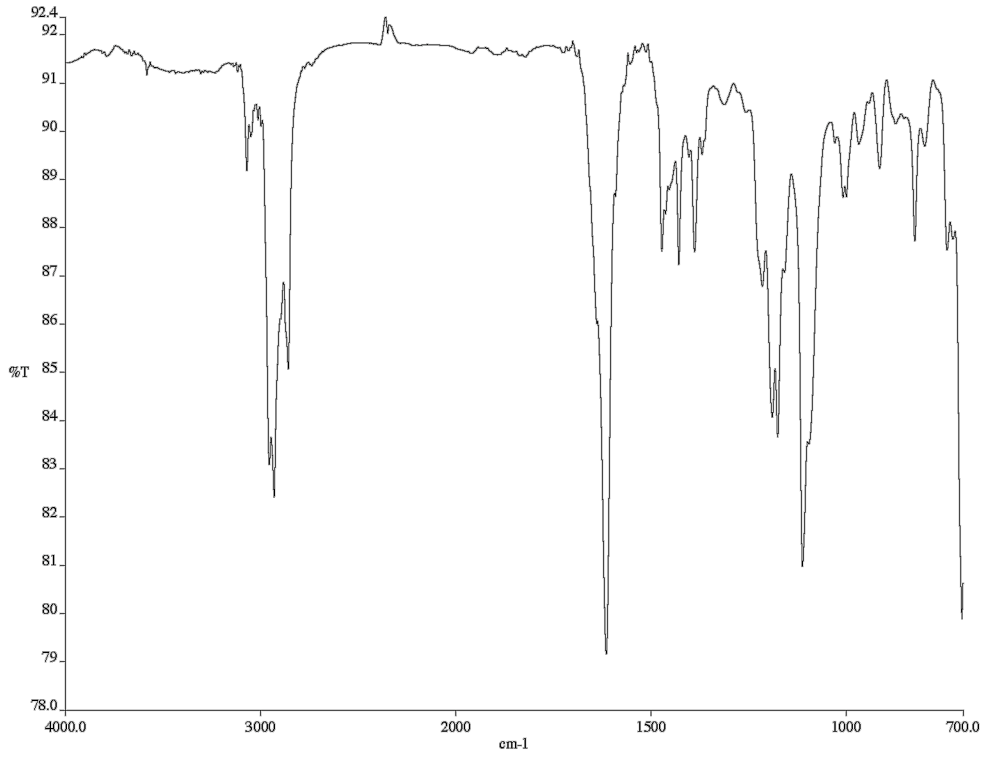


Figure A2.36.2. Infrared spectrum (thin film/NaCl) of compound **27o**.

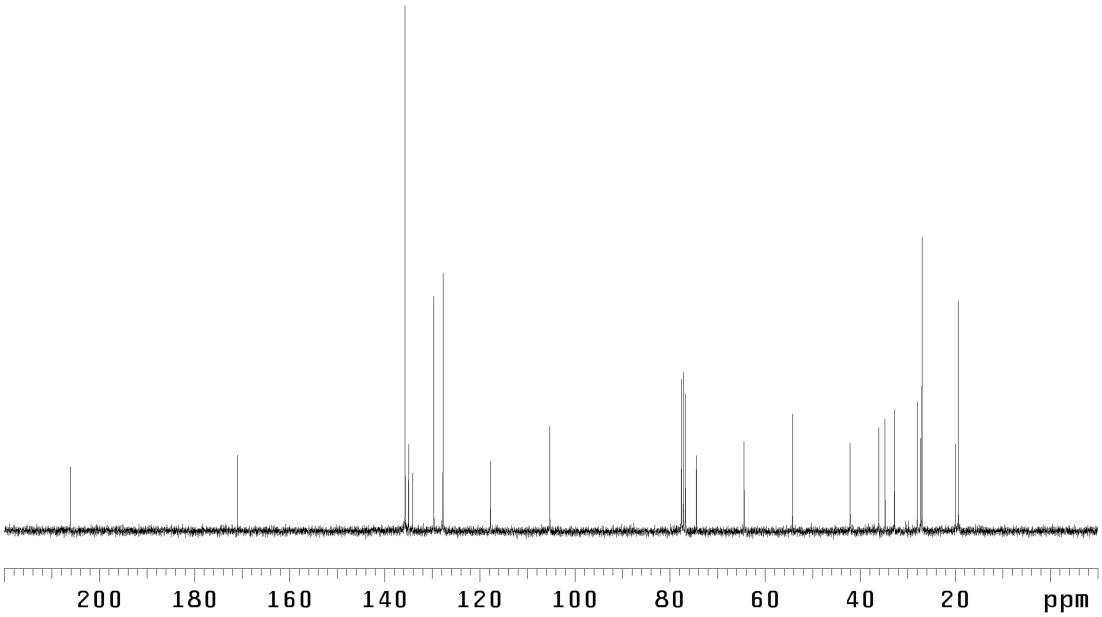


Figure A2.36.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **27o**.

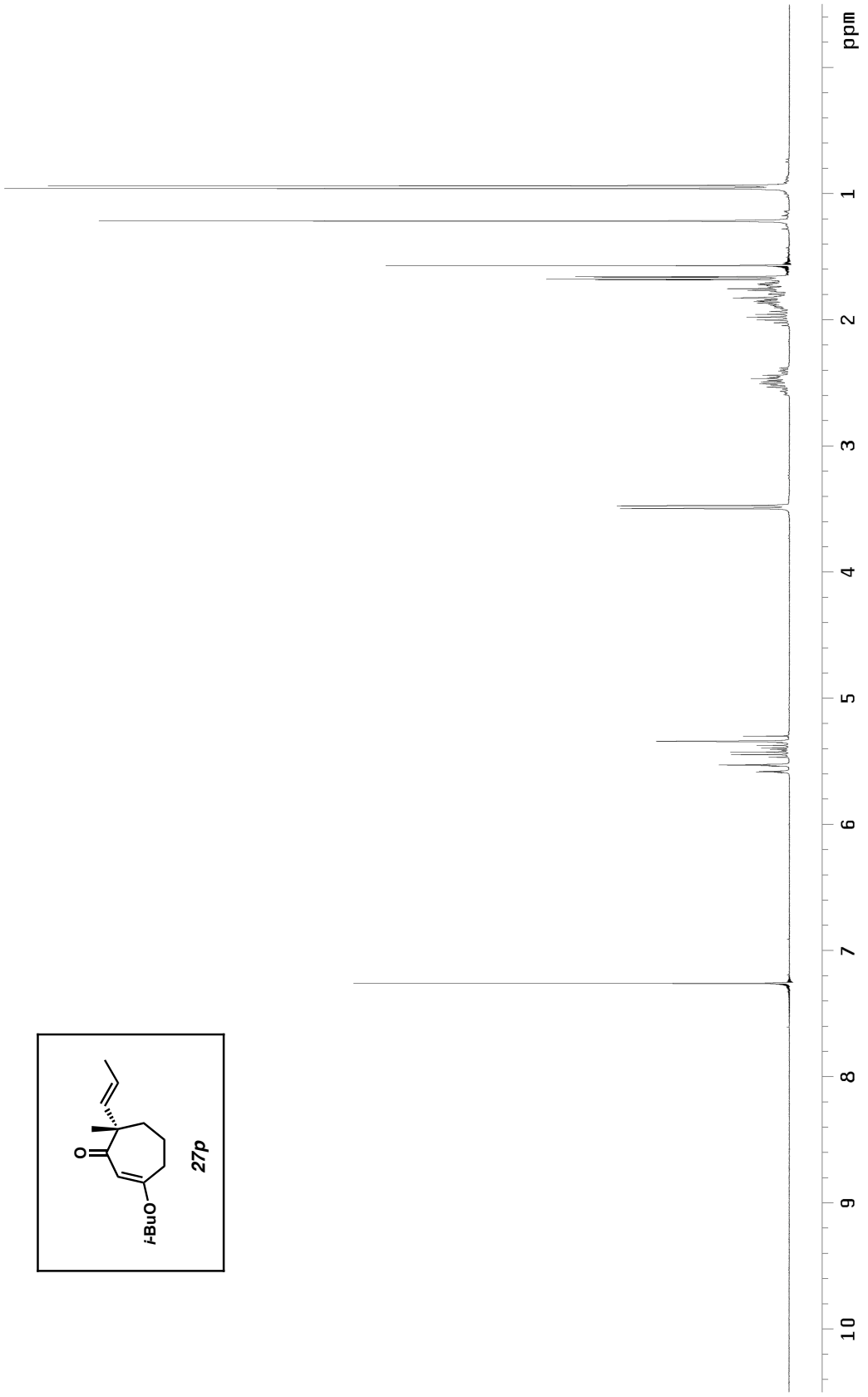


Figure A2.37.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **27p**.

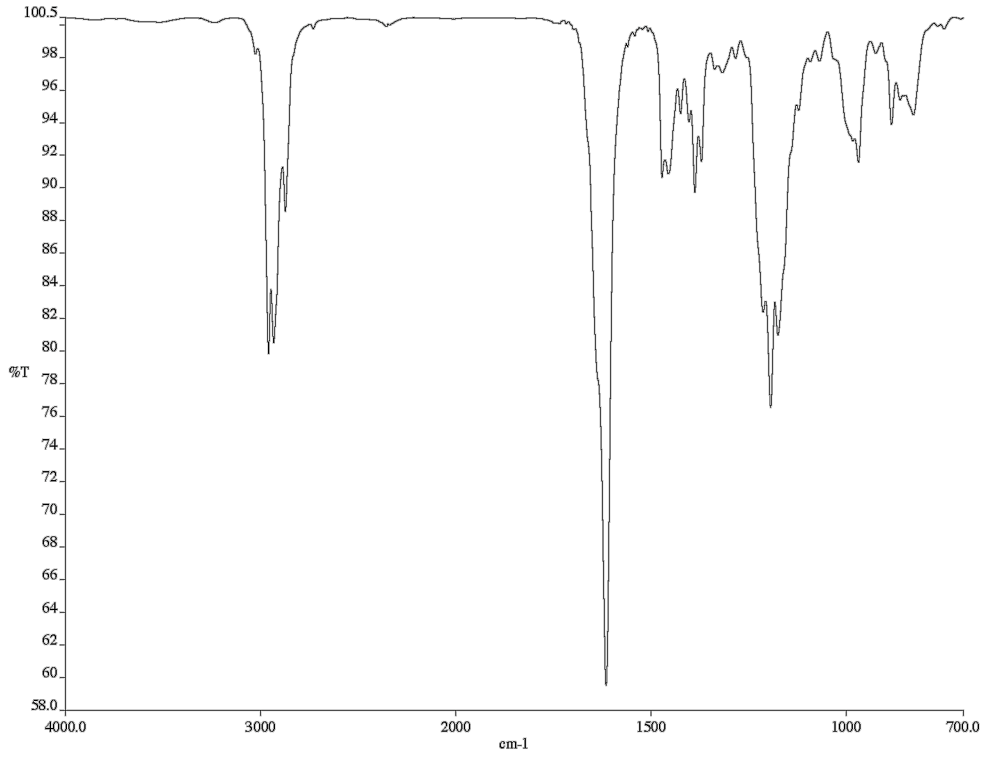


Figure A2.37.2. Infrared spectrum (thin film/NaCl) of compound **27p**.

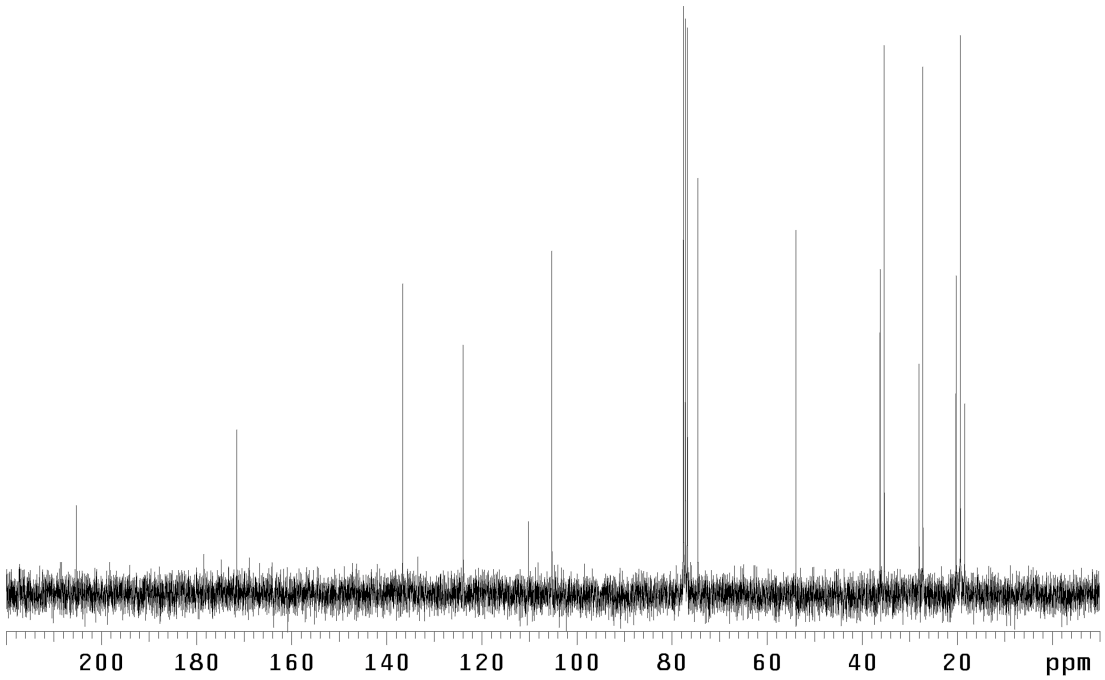


Figure A2.37.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **27p**.

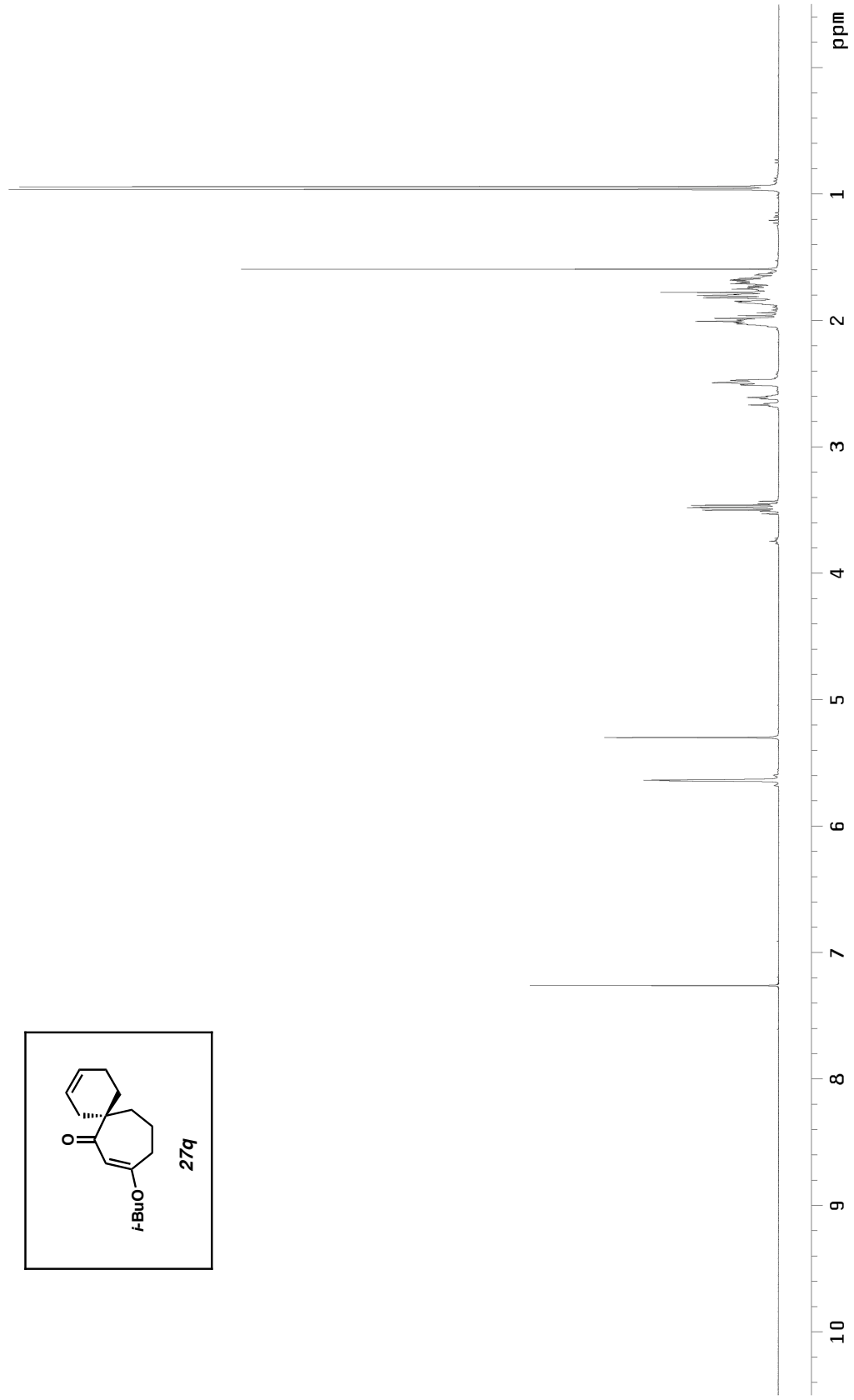


Figure A2.38.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **27q**.

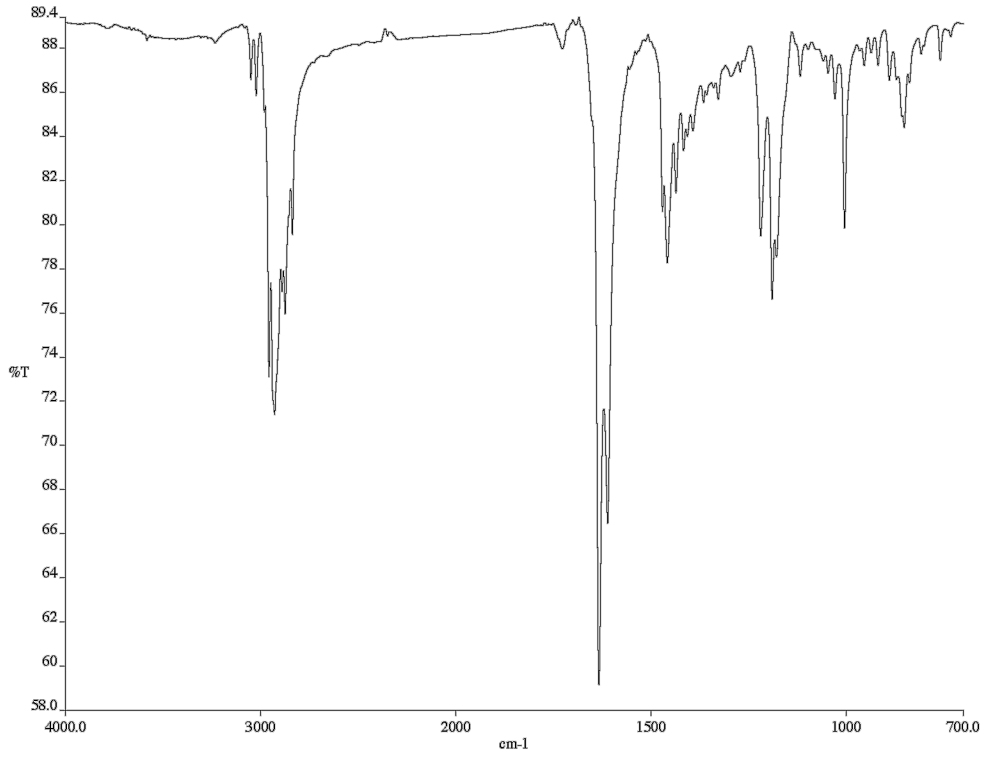


Figure A2.38.2. Infrared spectrum (thin film/NaCl) of compound **27q**.

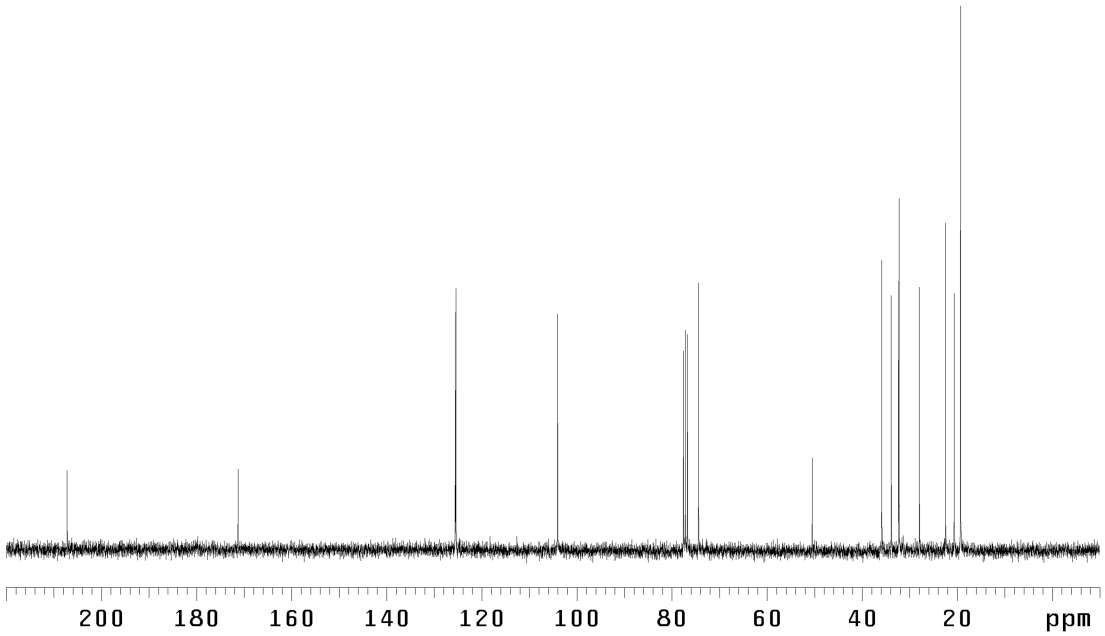


Figure A2.38.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **27q**.

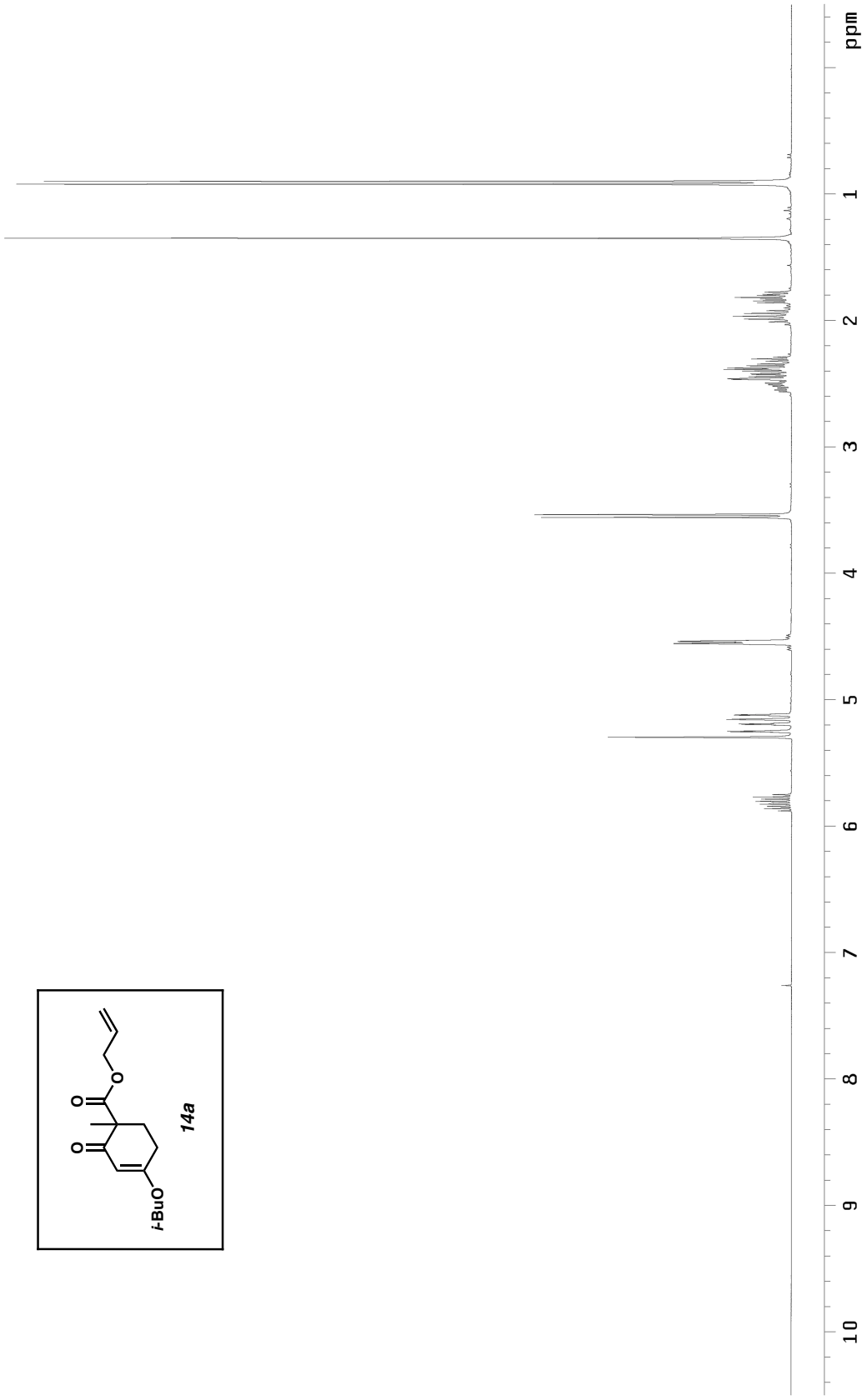


Figure A2.39.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **14a**.

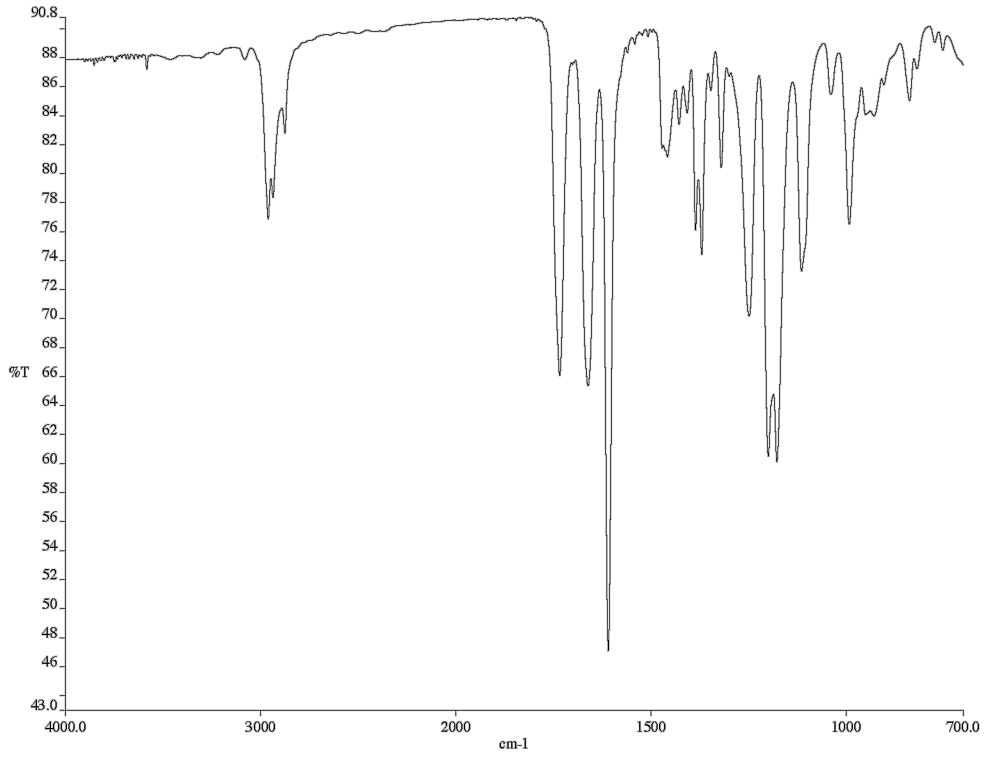


Figure A2.39.2. Infrared spectrum (thin film/NaCl) of compound **14a**.

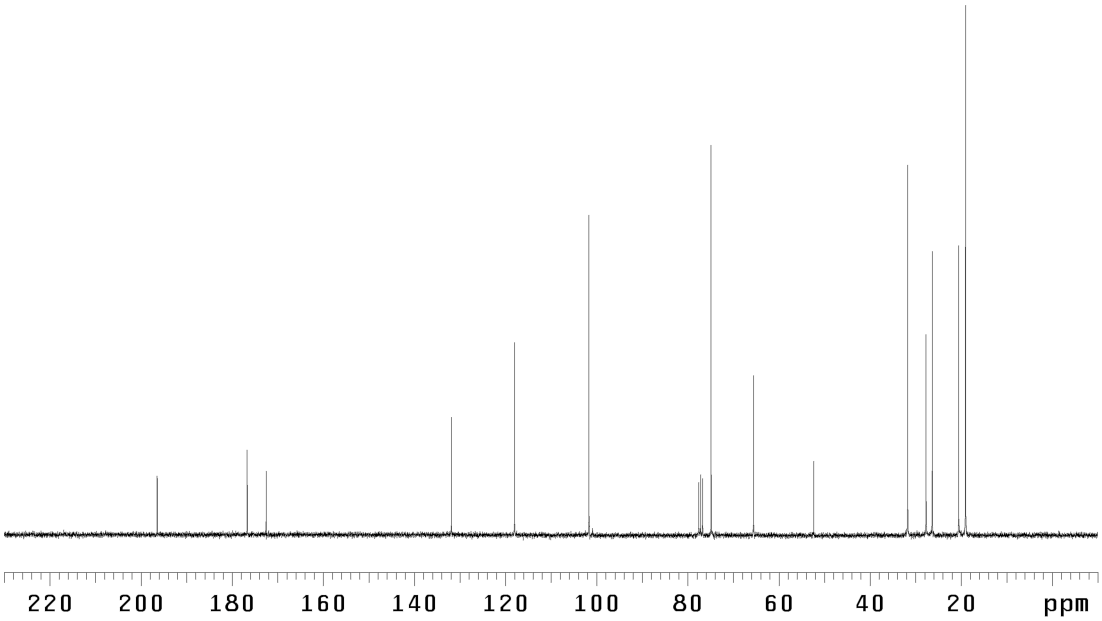


Figure A2.39.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **14a**.

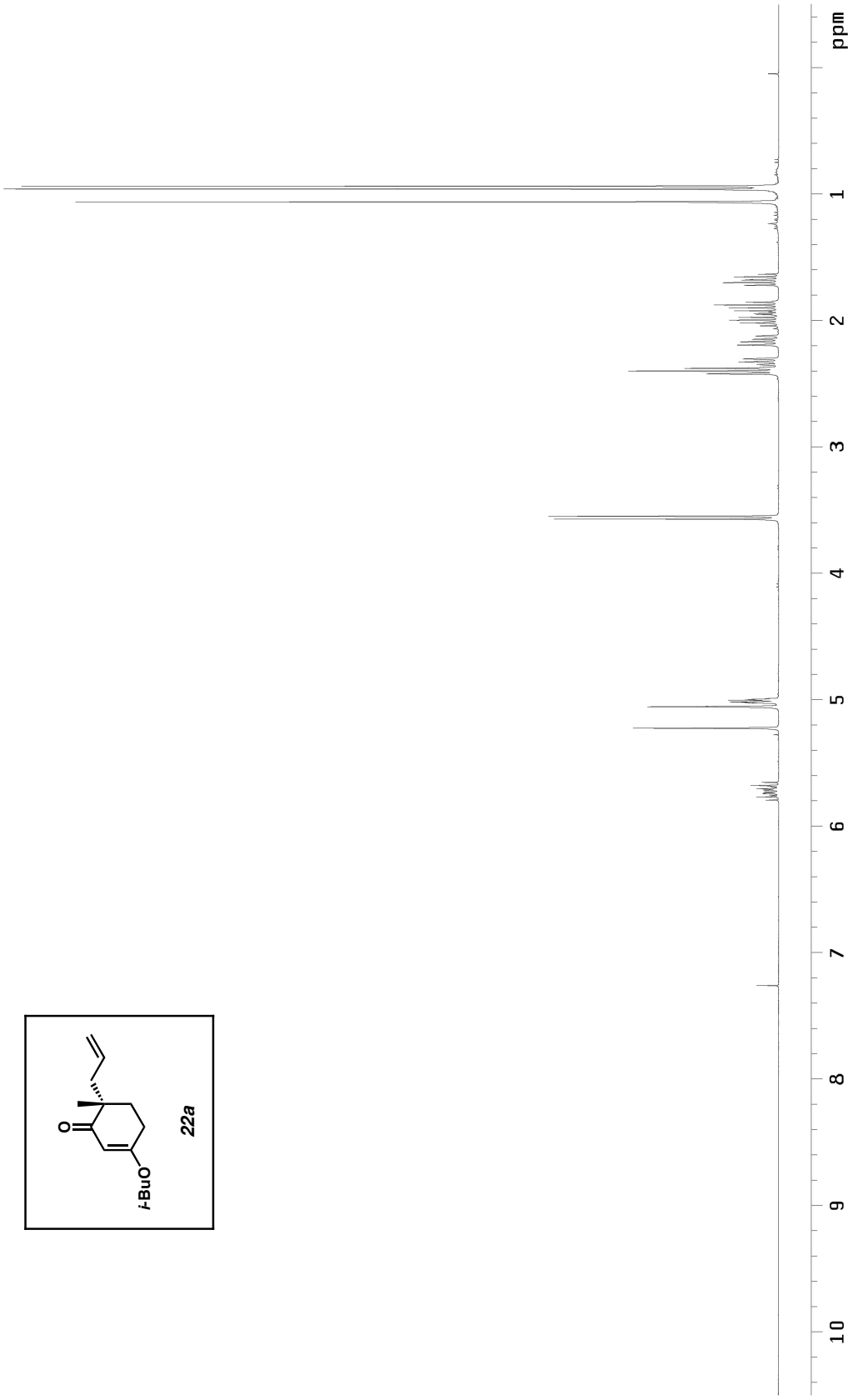


Figure A2.40.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **22a**.

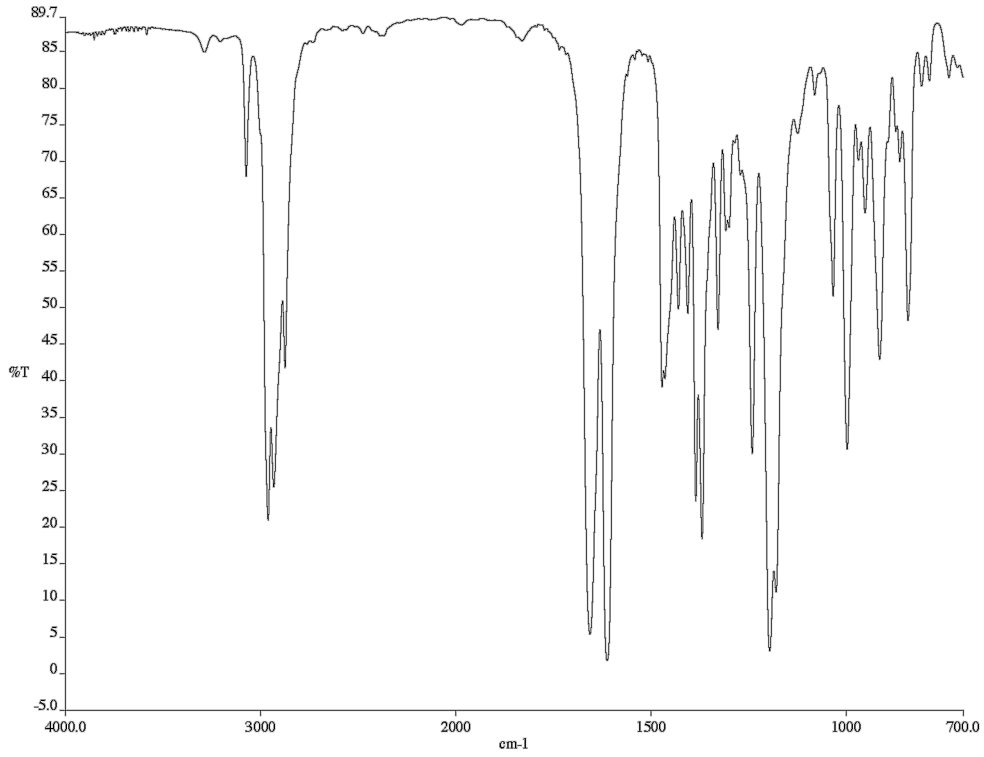


Figure A2.40.2. Infrared spectrum (thin film/NaCl) of compound **22a**.

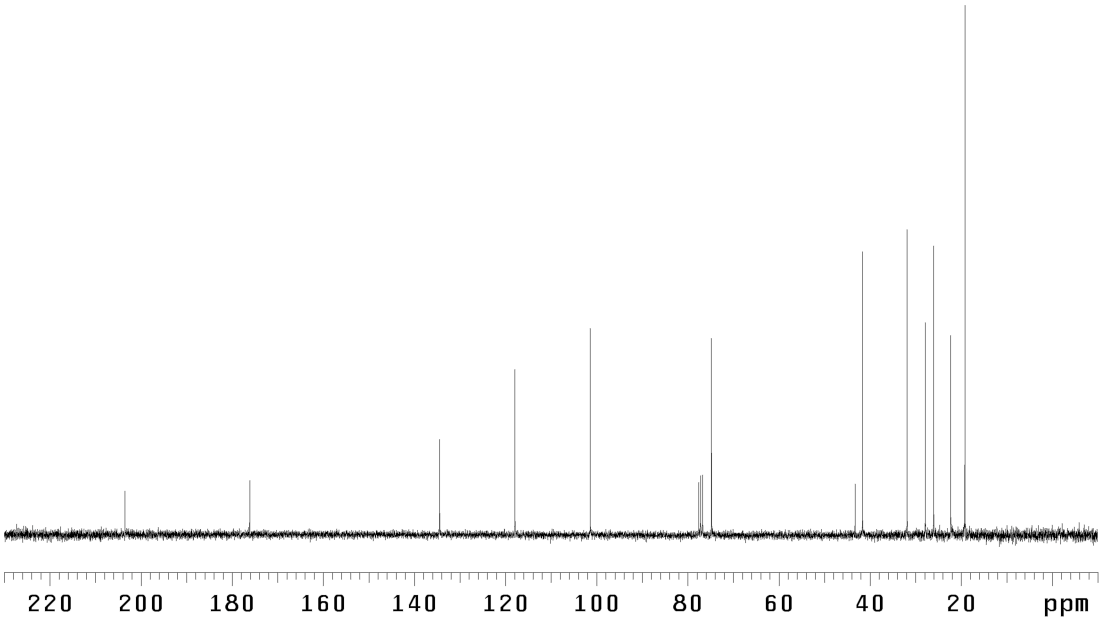


Figure A2.40.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **22a**.

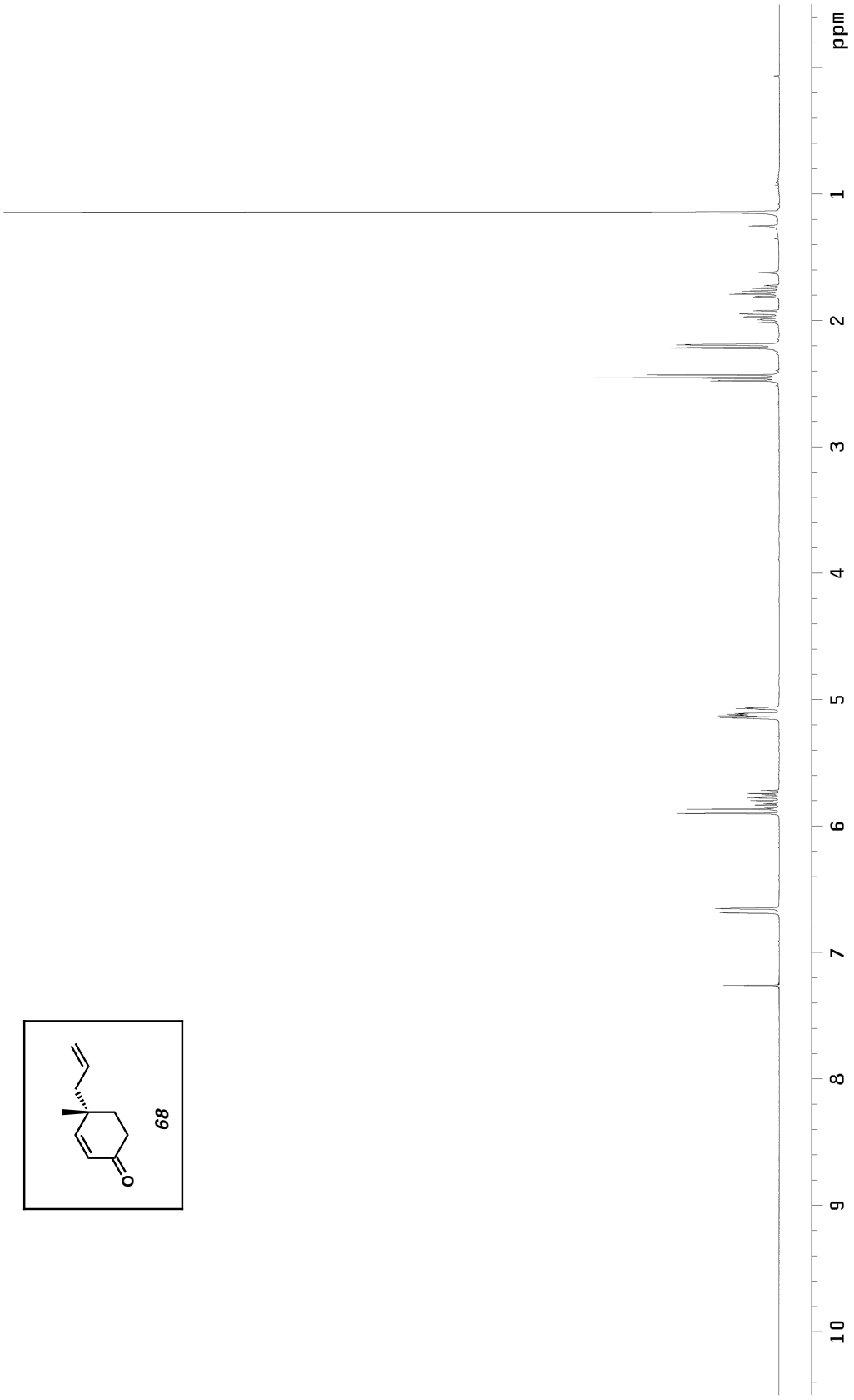


Figure A2.41.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **68**.

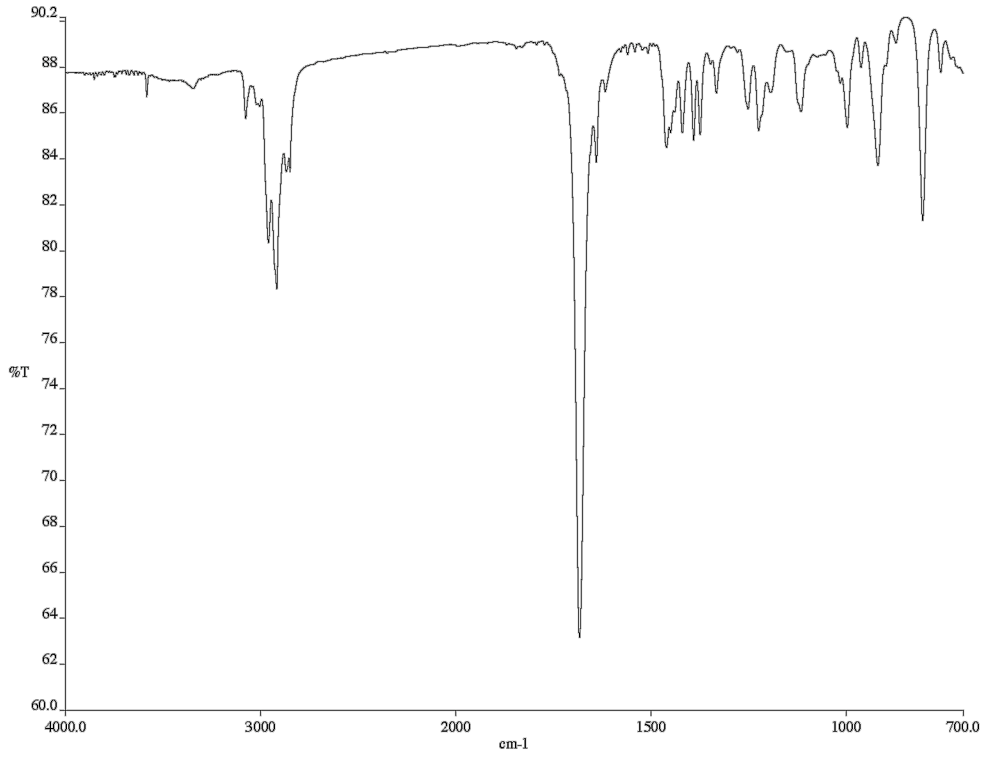


Figure A2.41.2. Infrared spectrum (thin film/NaCl) of compound **68**.

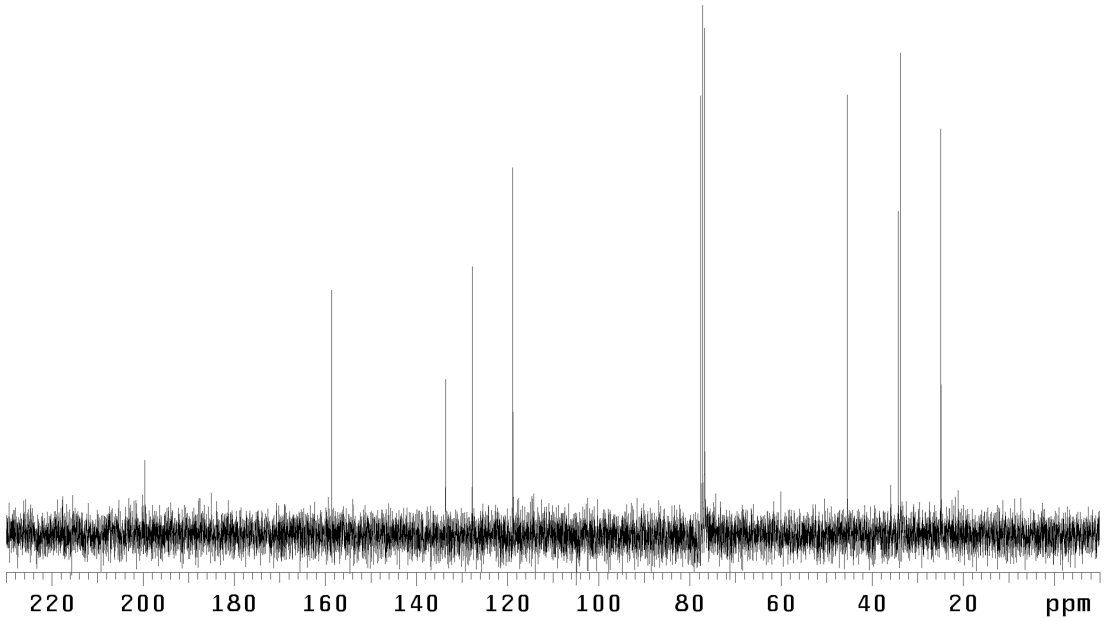


Figure A2.41.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **68**.

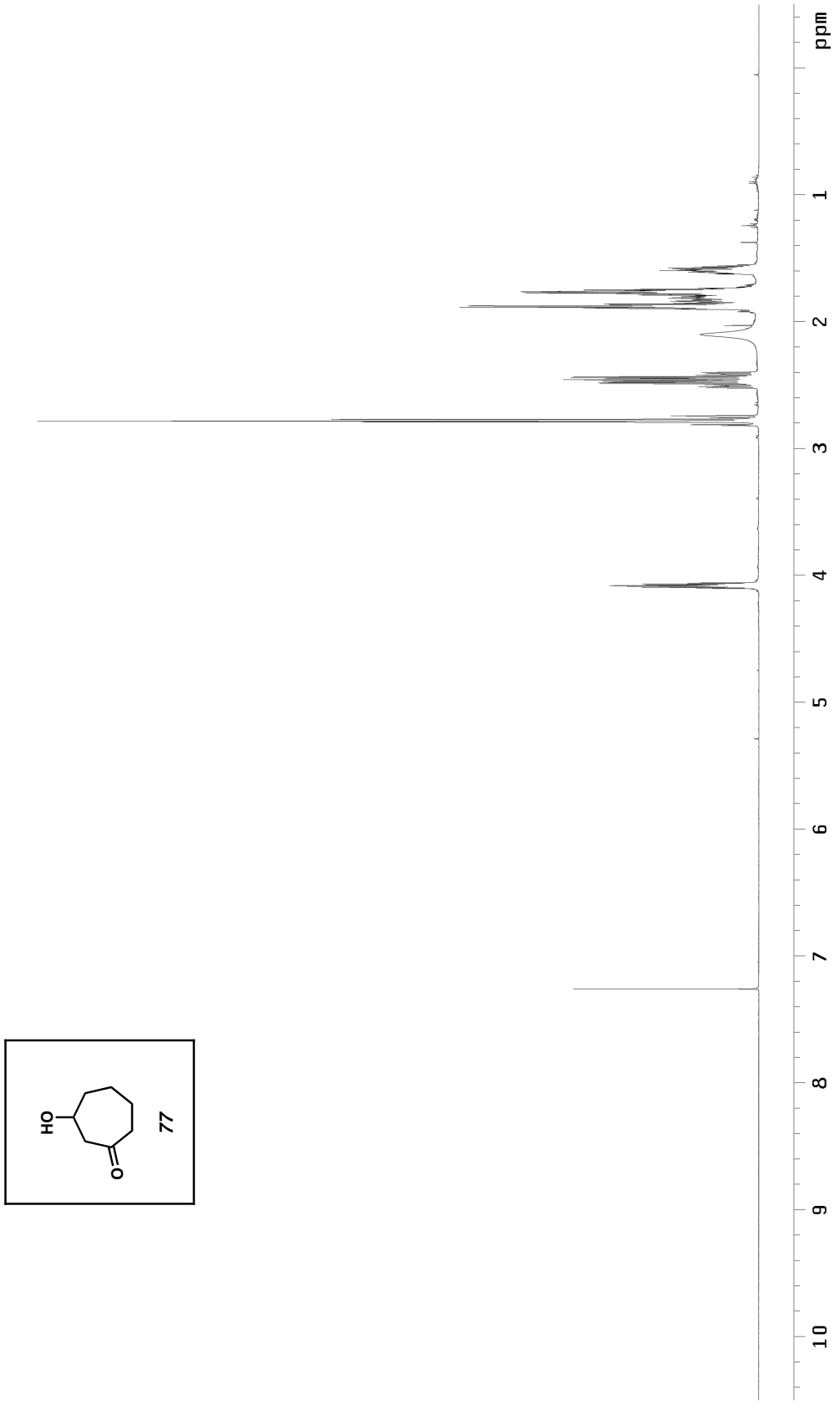


Figure A2.42.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **77**.

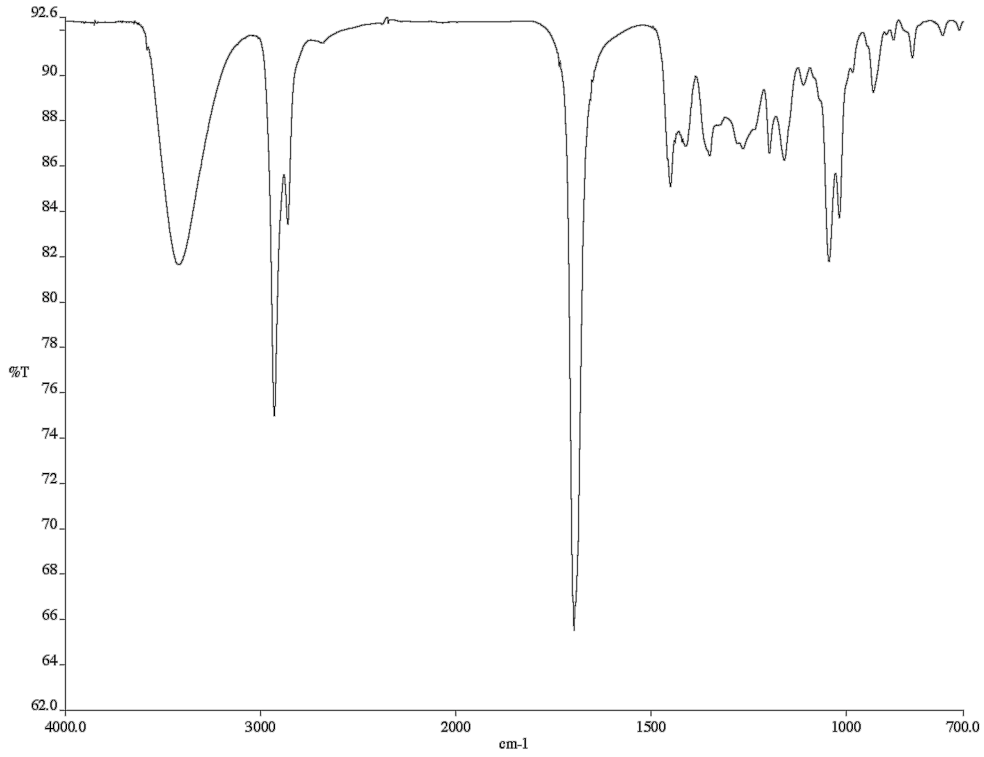


Figure A2.42.2. Infrared spectrum (thin film/NaCl) of compound **77**.

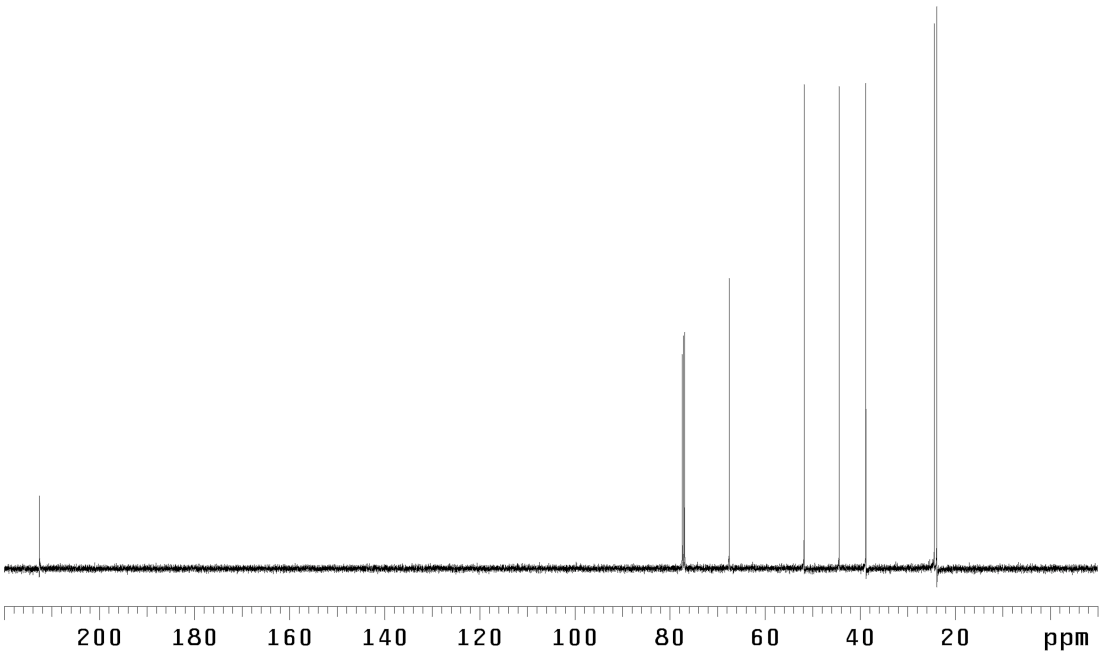


Figure A2.42.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **77**.

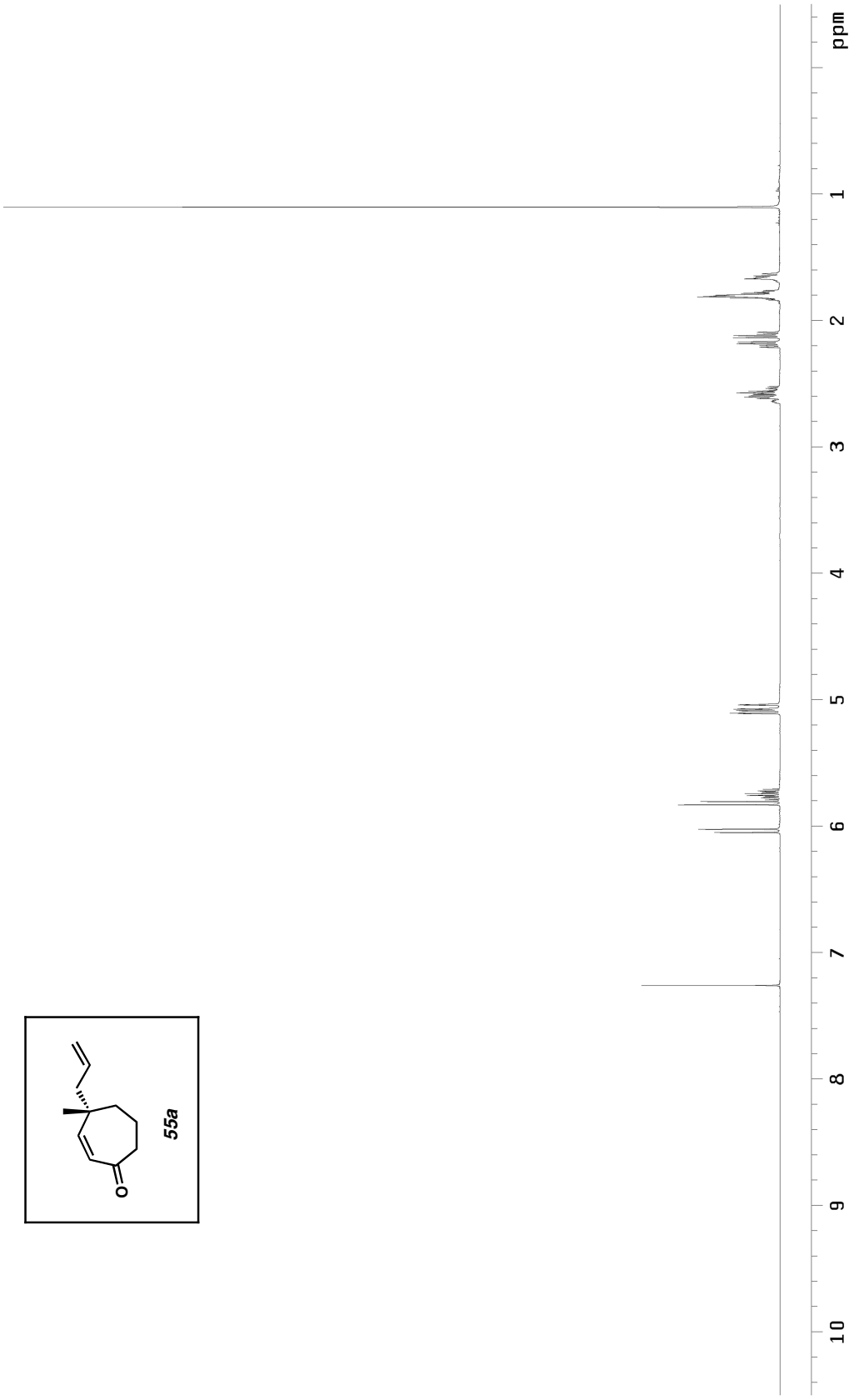


Figure A2.43.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **55a**.

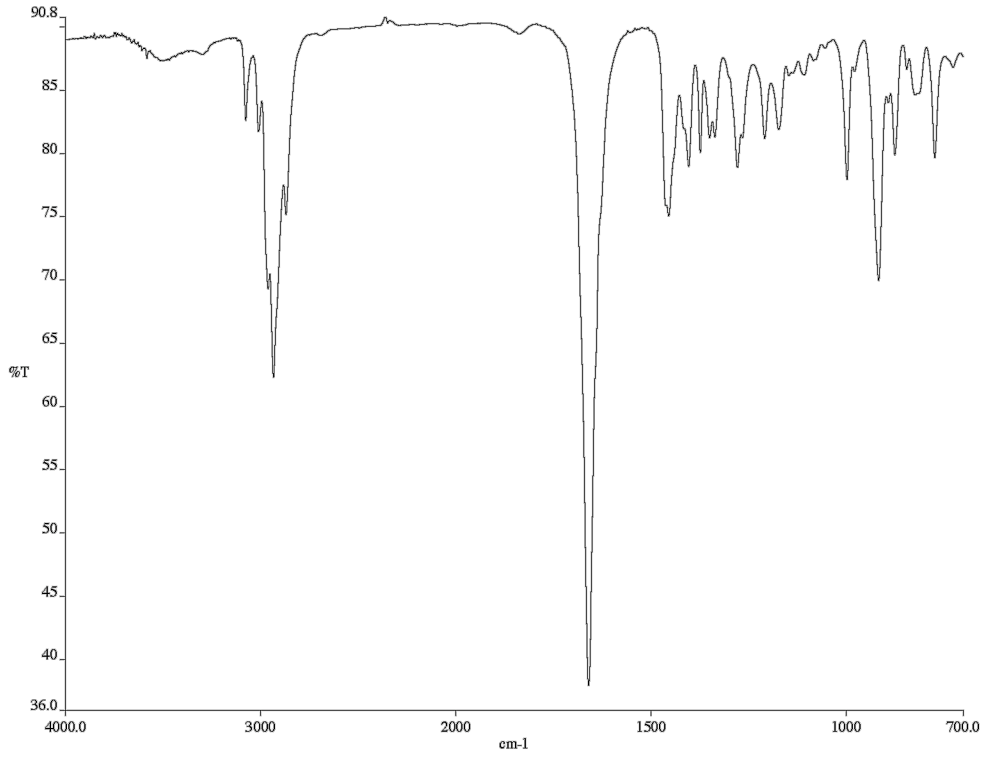


Figure A2.43.2. Infrared spectrum (thin film/NaCl) of compound **55a**.

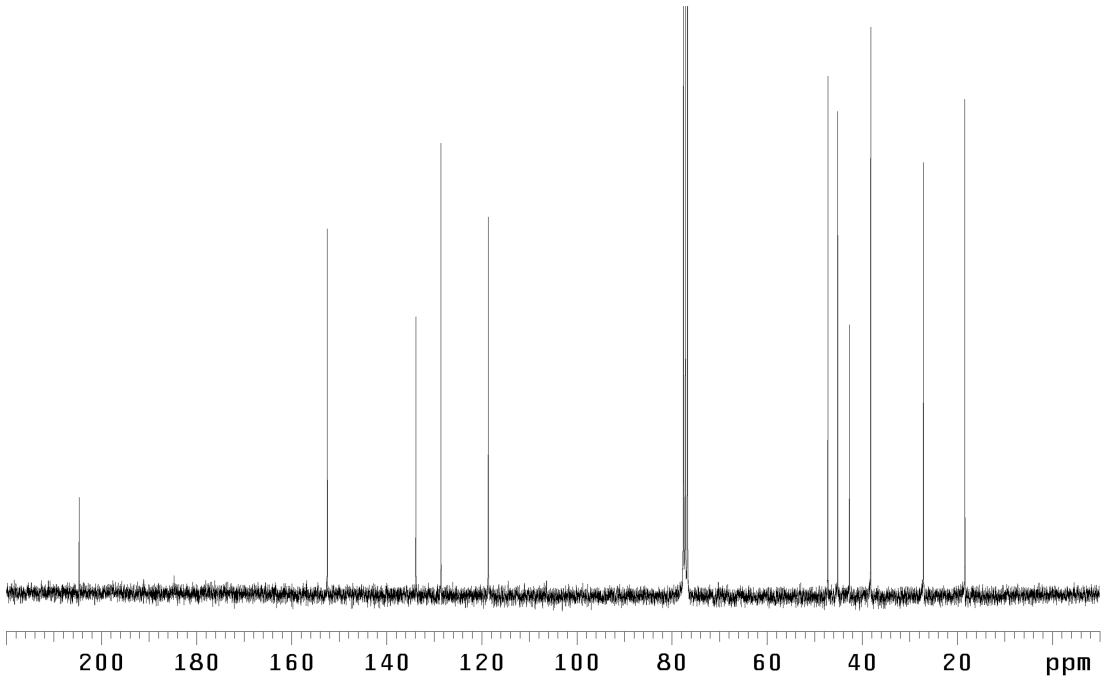


Figure A2.43.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **55a**.

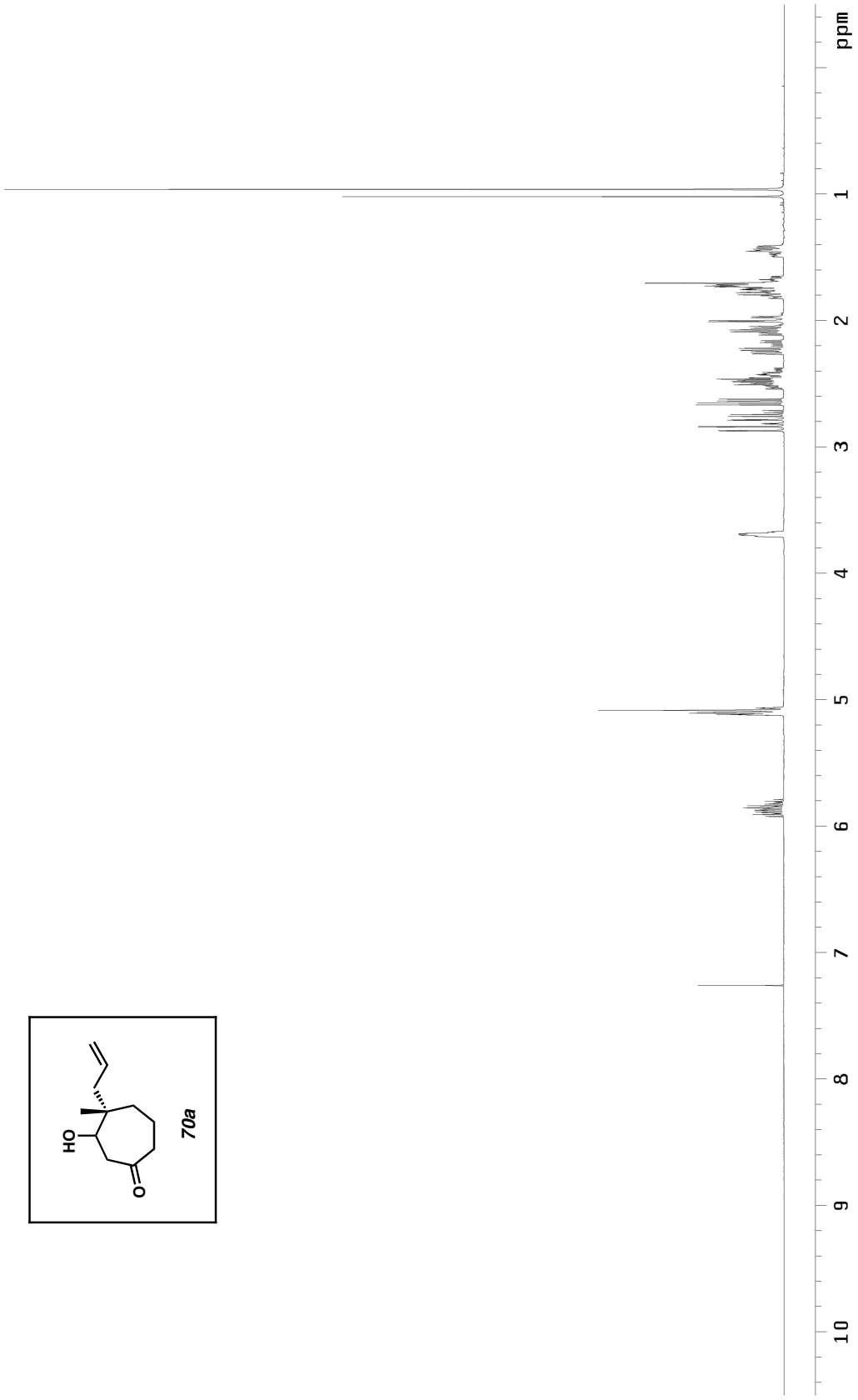


Figure A2.44.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **70a**.

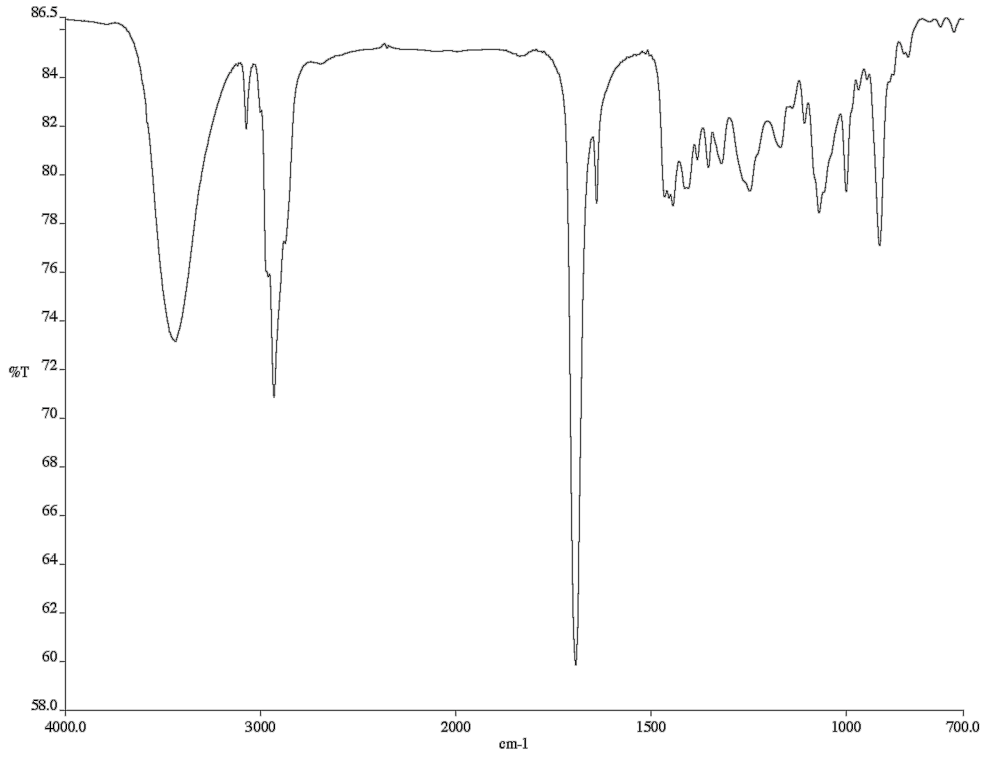


Figure A2.44.2. Infrared spectrum (thin film/NaCl) of compound **70a**.

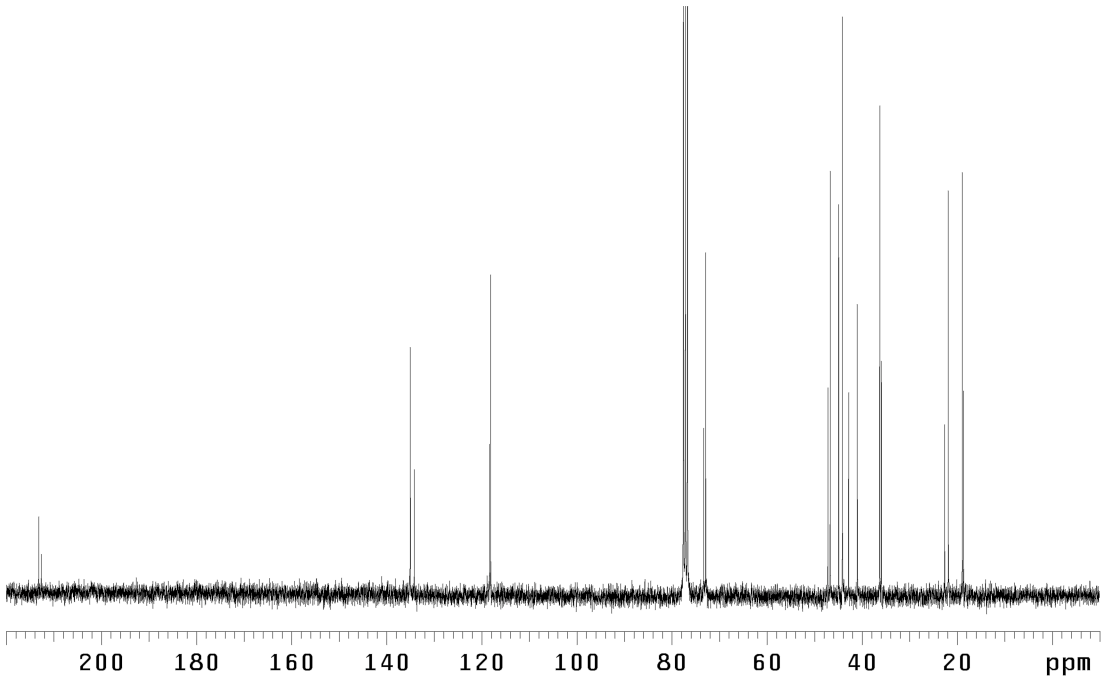


Figure A2.44.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **70a**.

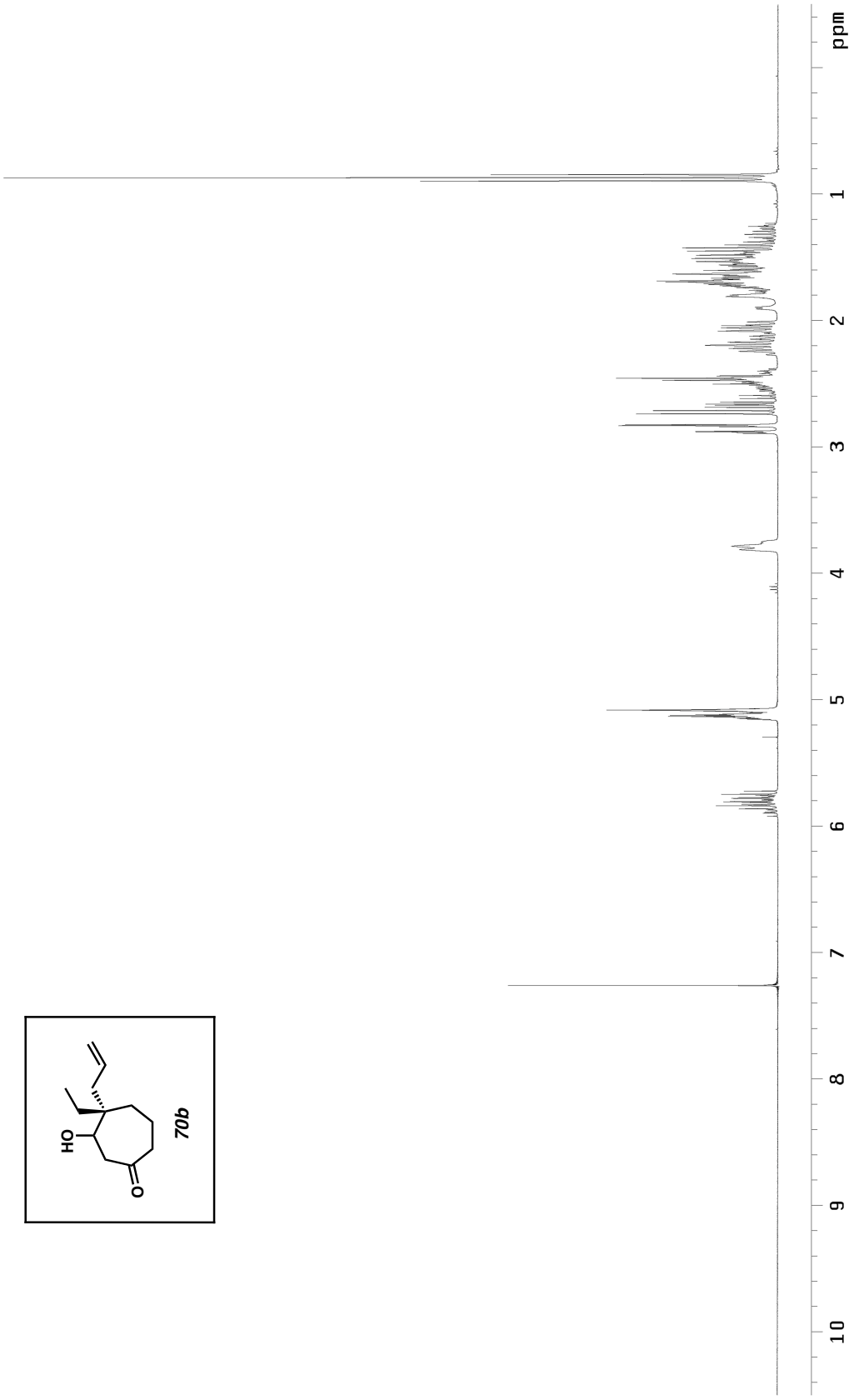


Figure A2.45.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **70b**.

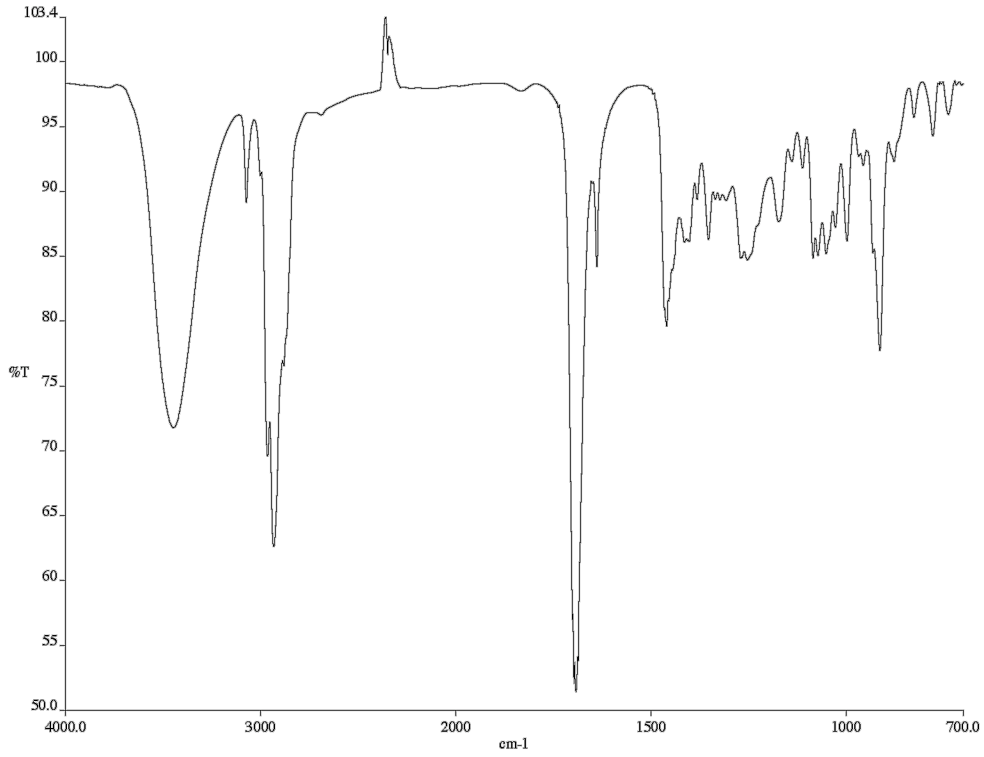


Figure A2.45.2. Infrared spectrum (thin film/NaCl) of compound **70b**.

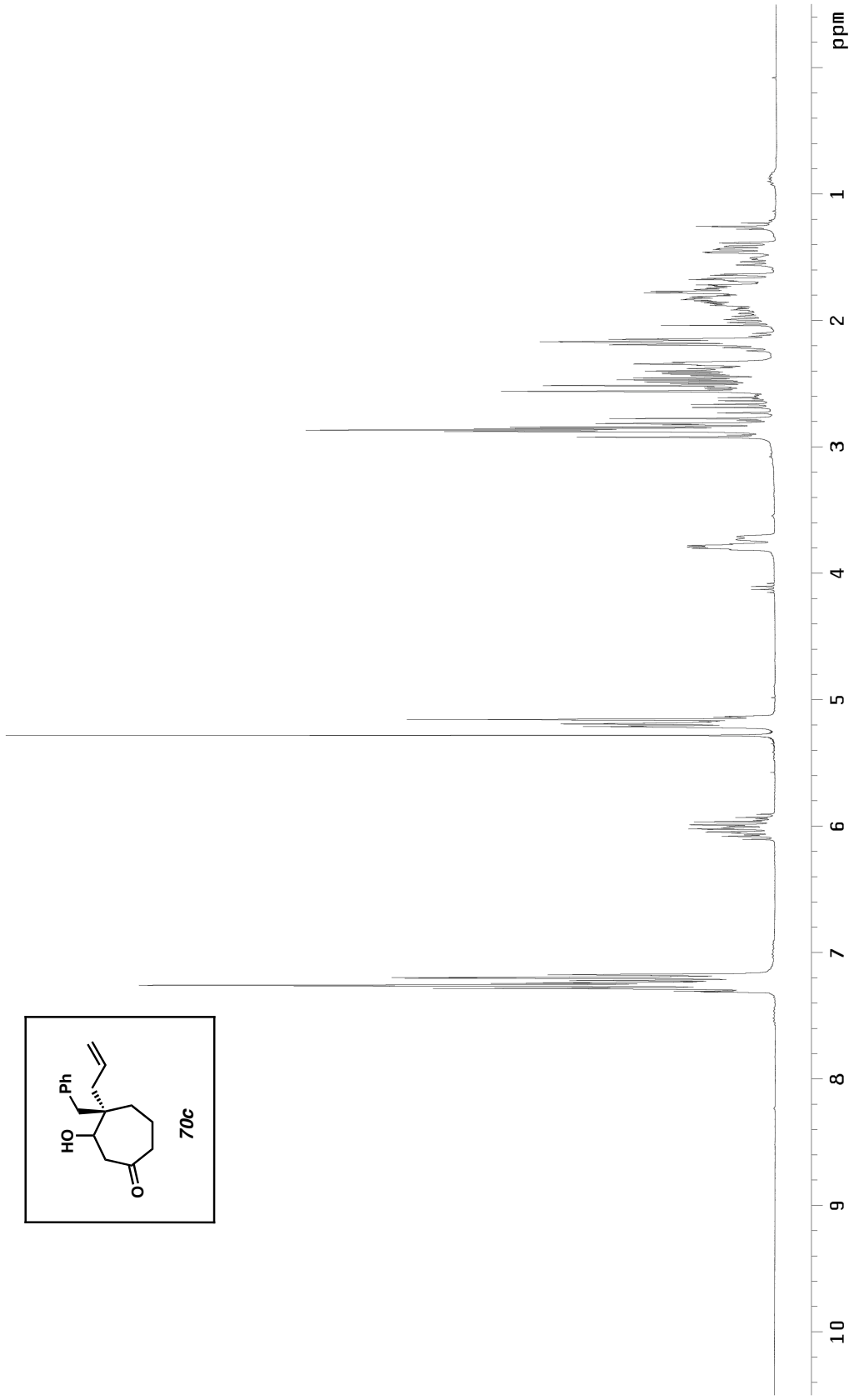


Figure A2.46.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **70c**.

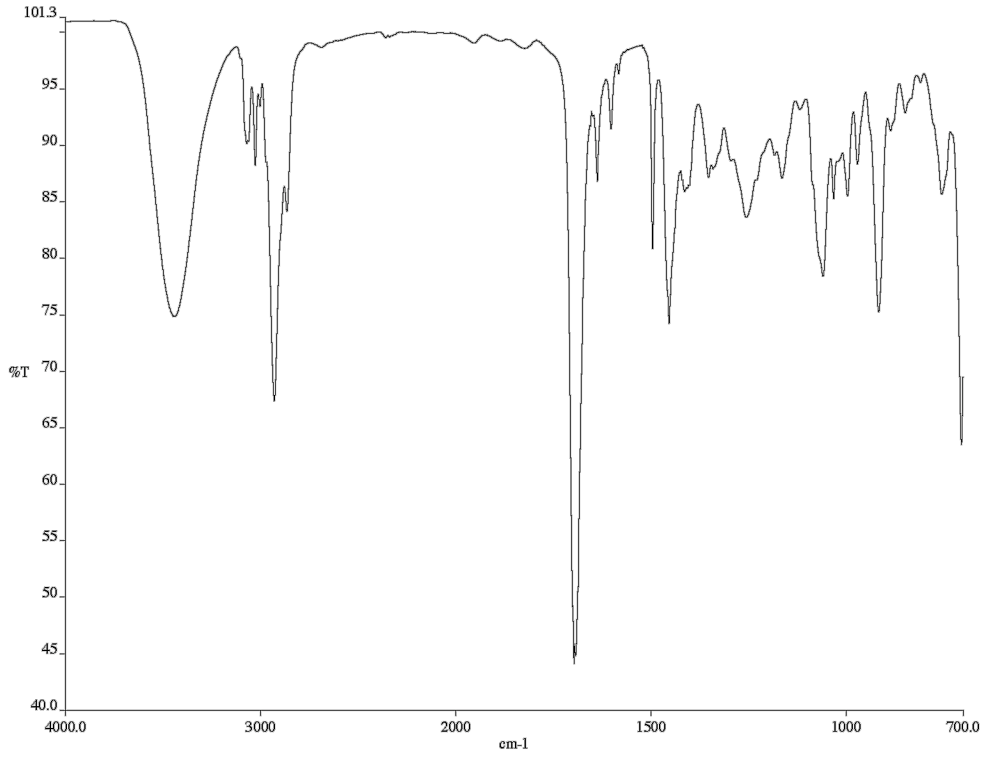


Figure A2.46.2. Infrared spectrum (thin film/NaCl) of compound **70c**.

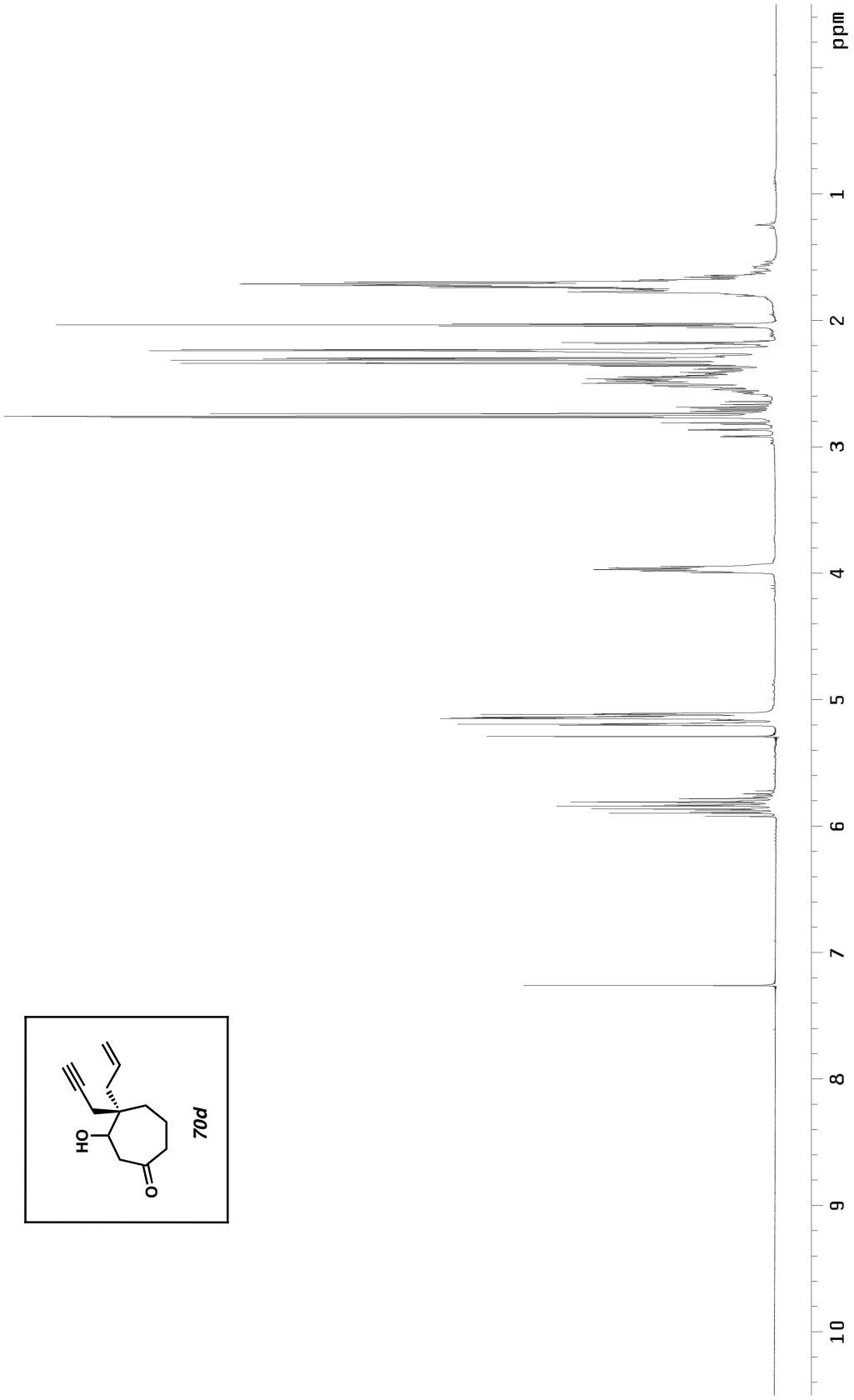


Figure A2.47.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **70d**.

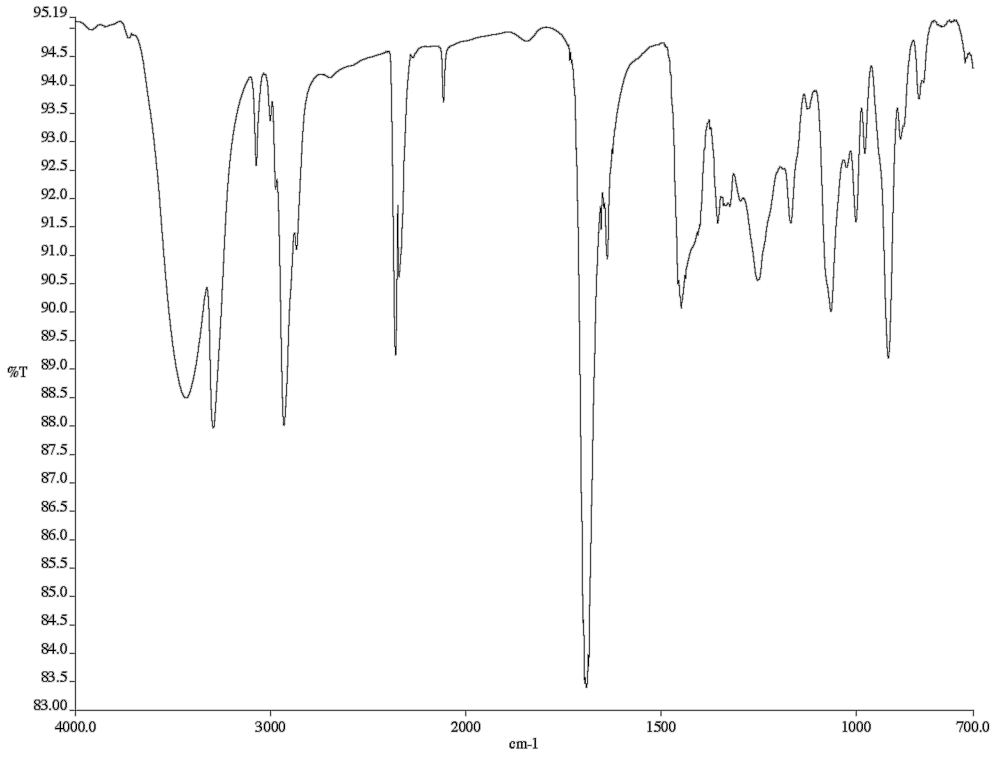


Figure A2.47.2. Infrared spectrum (thin film/NaCl) of compound **70d**.

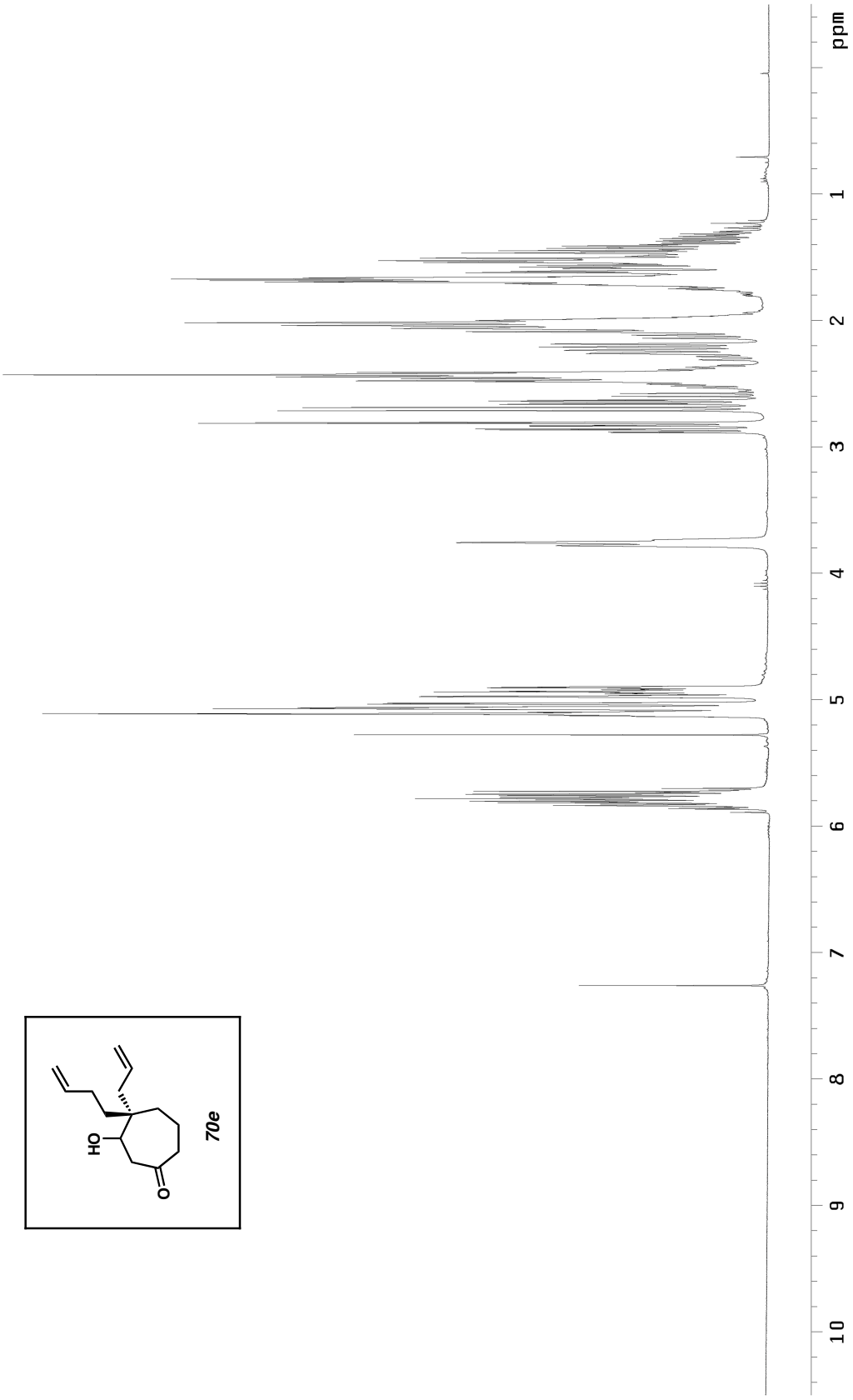


Figure A2.48.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **70e**.

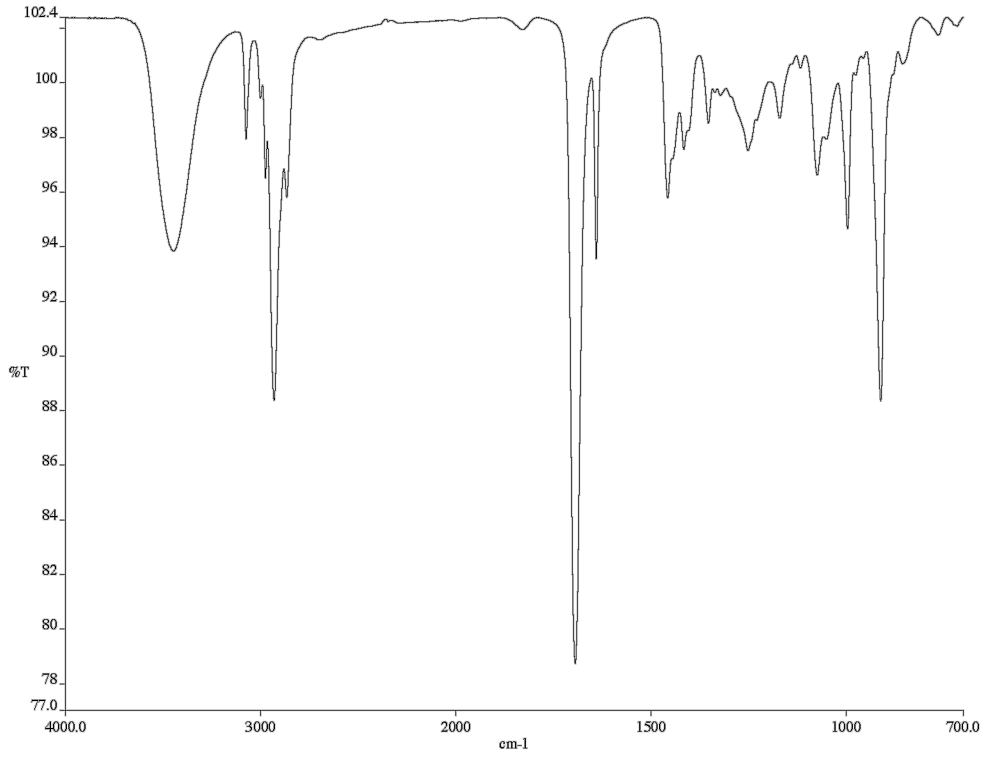


Figure A2.48.2. Infrared spectrum (thin film/NaCl) of compound **70e**.

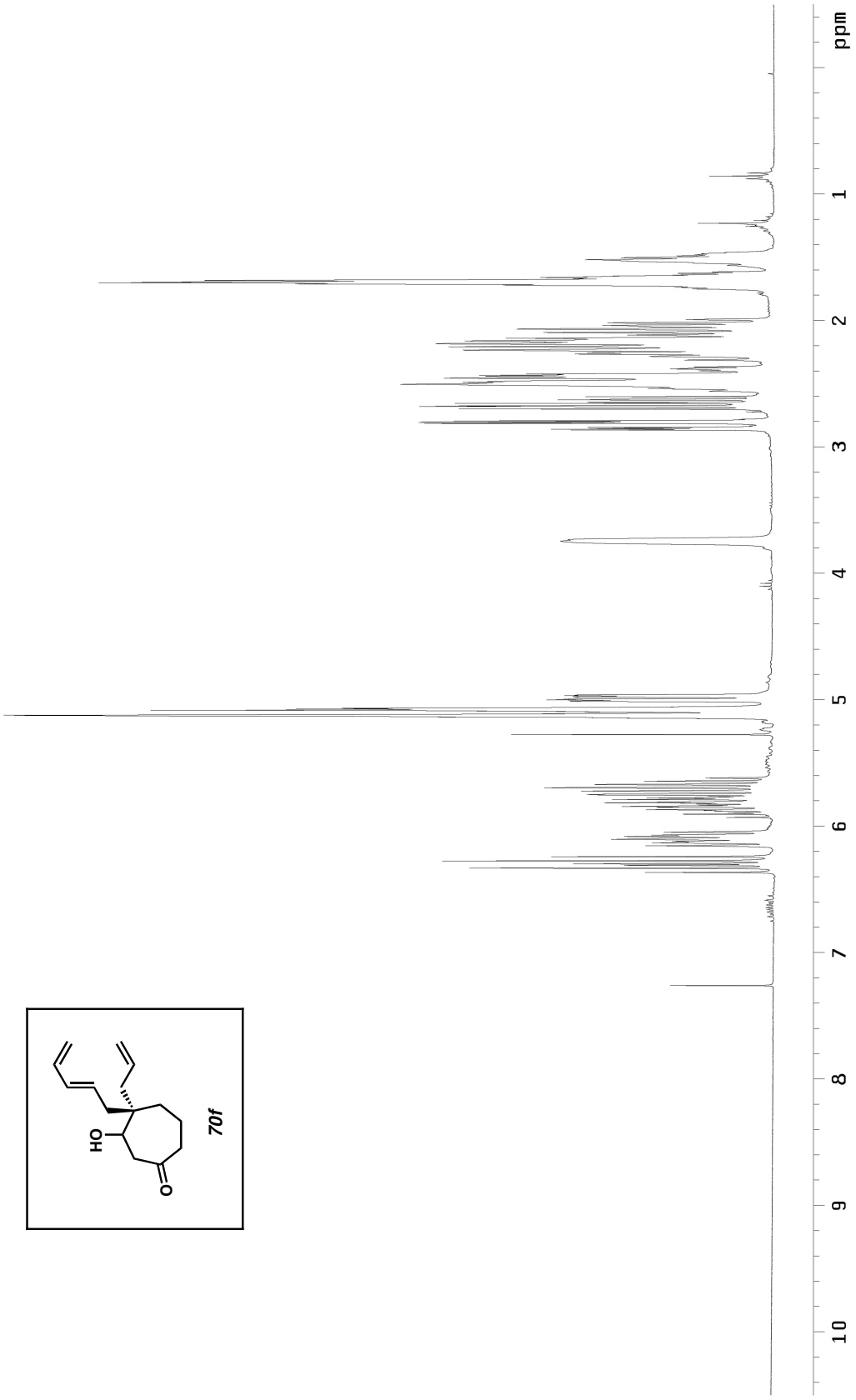


Figure A2.49.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **70f**.

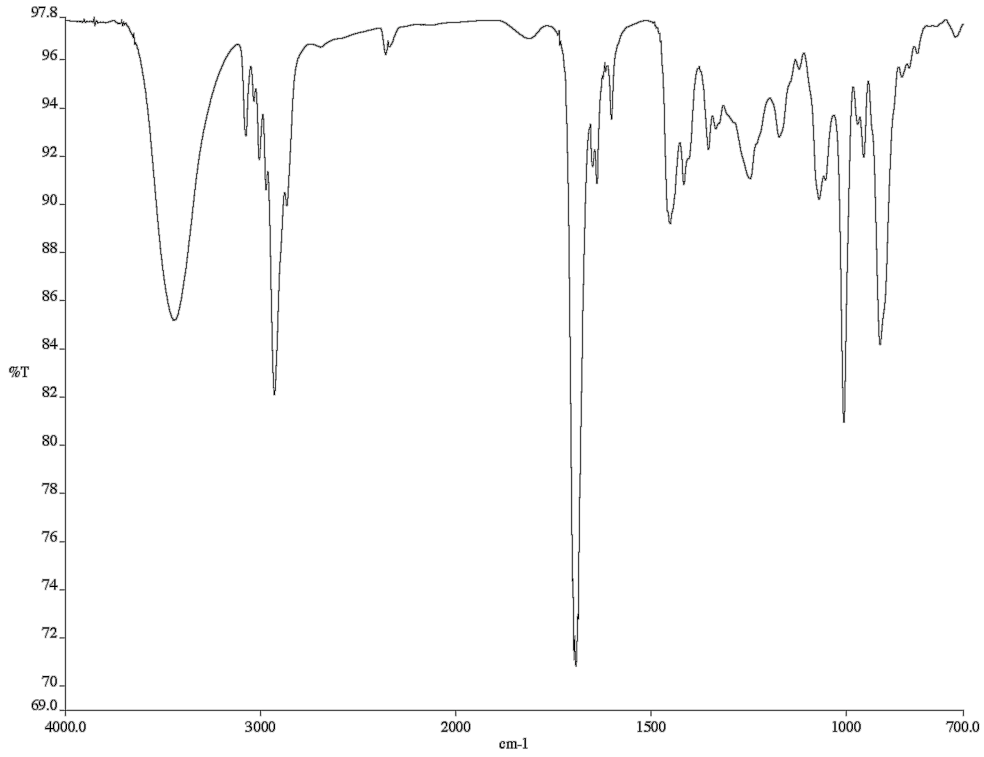


Figure A2.49.2. Infrared spectrum (thin film/NaCl) of compound **70f**.

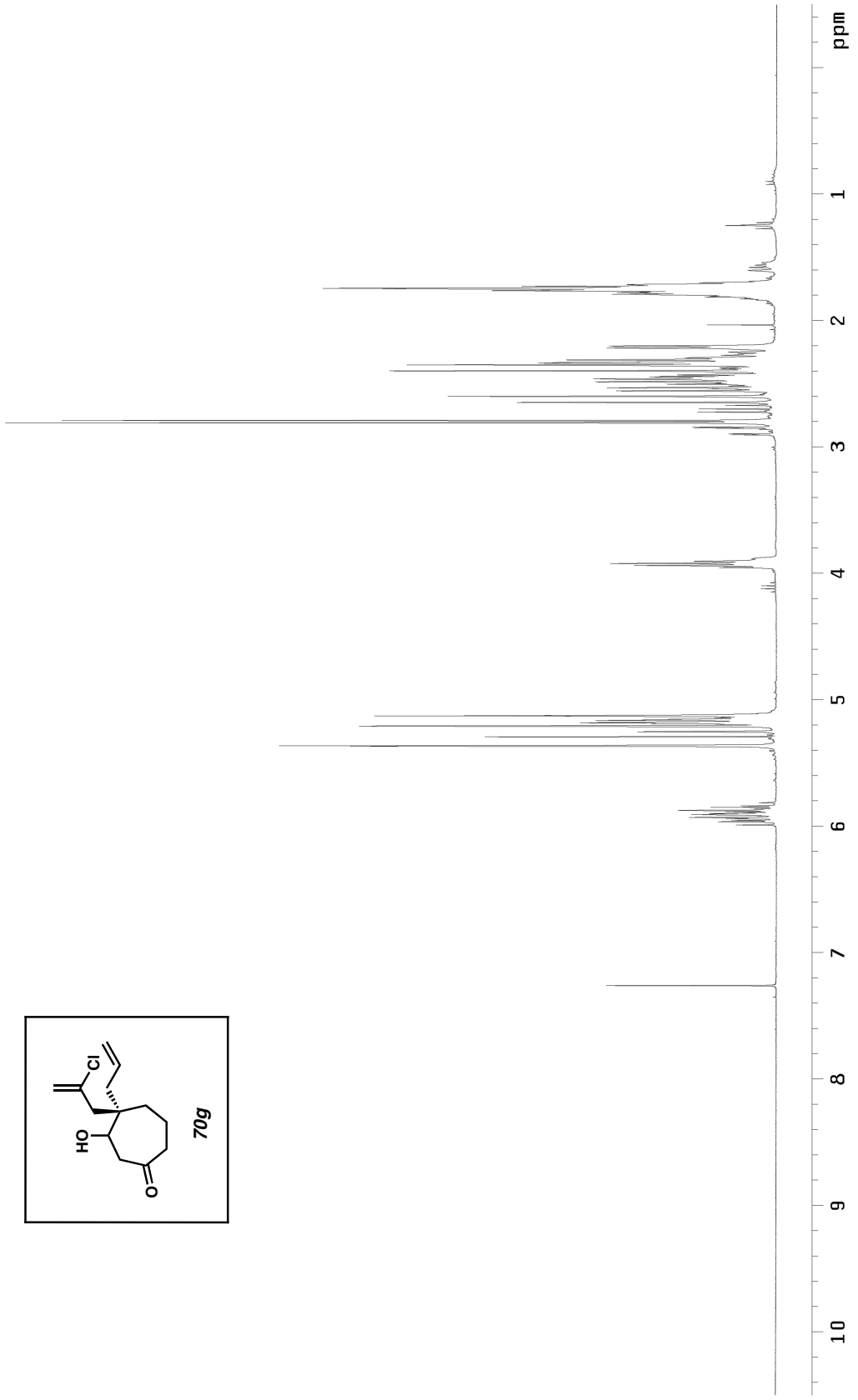


Figure A2.50.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **70g**.

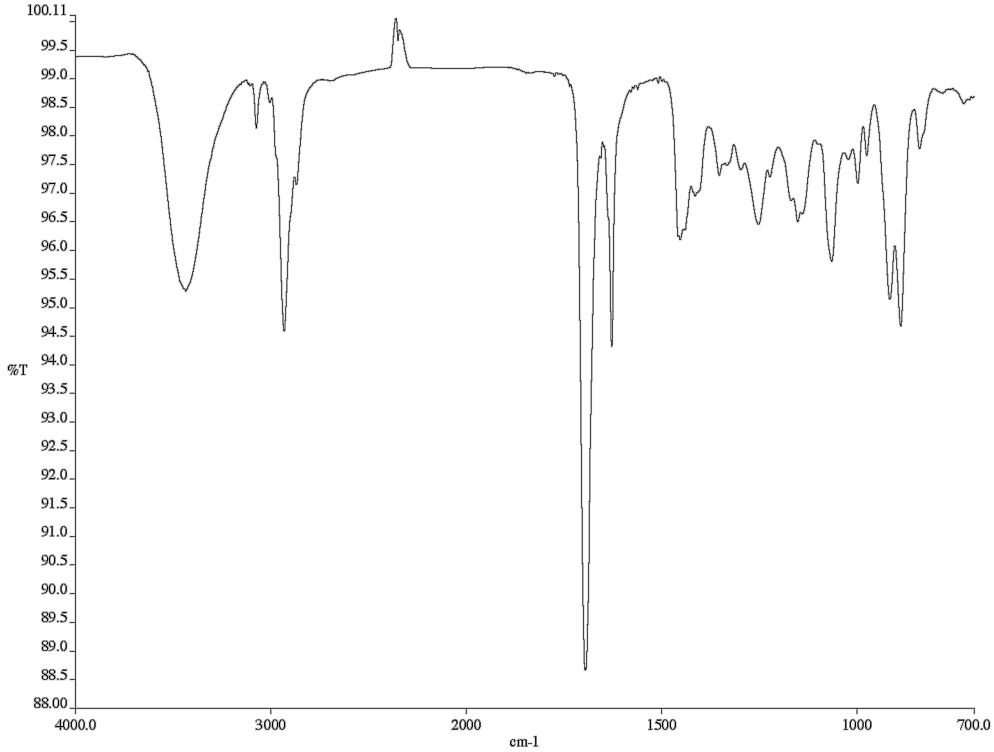


Figure A2.50.2. Infrared spectrum (thin film/NaCl) of compound **70g**.

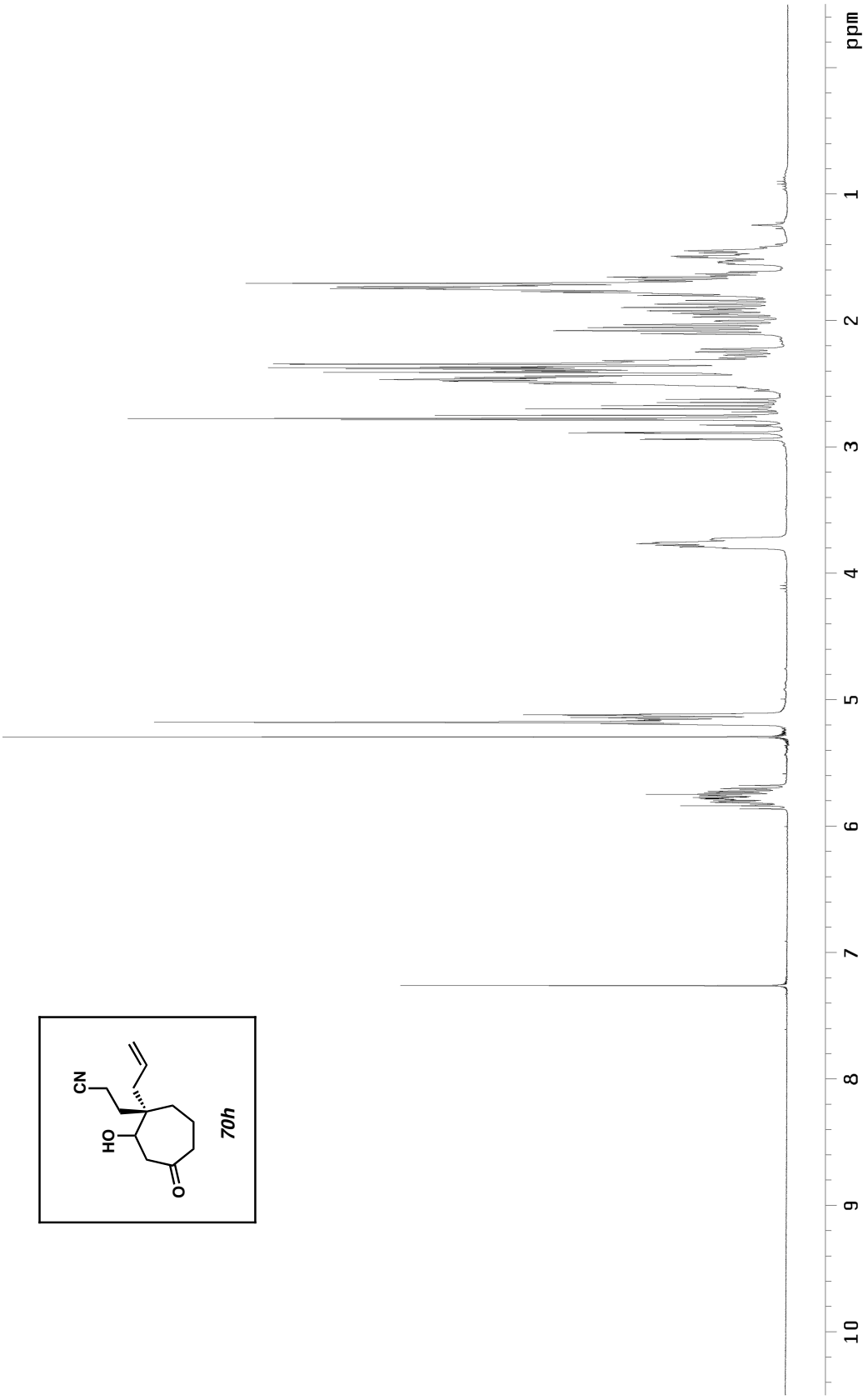


Figure A2.51.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **70h**.

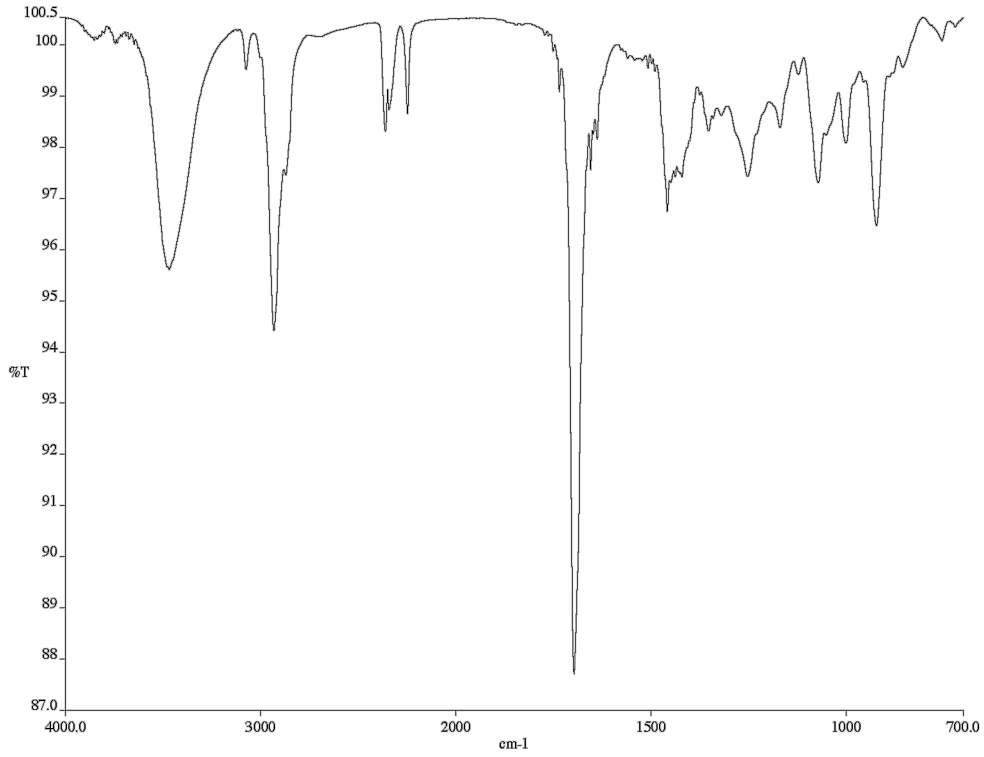


Figure A2.51.2. Infrared spectrum (thin film/NaCl) of compound **70h**.

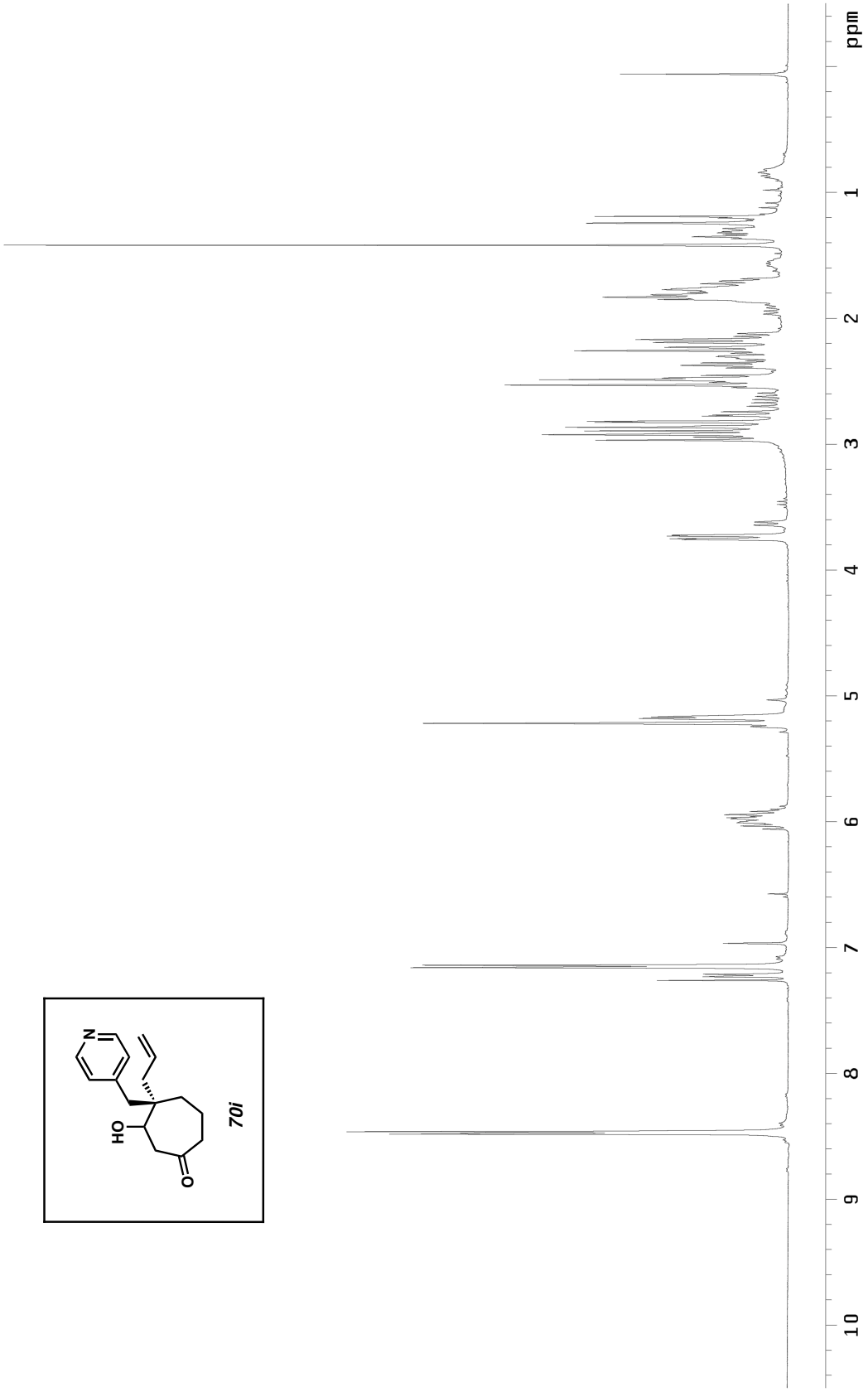


Figure A2.52.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **70i**.

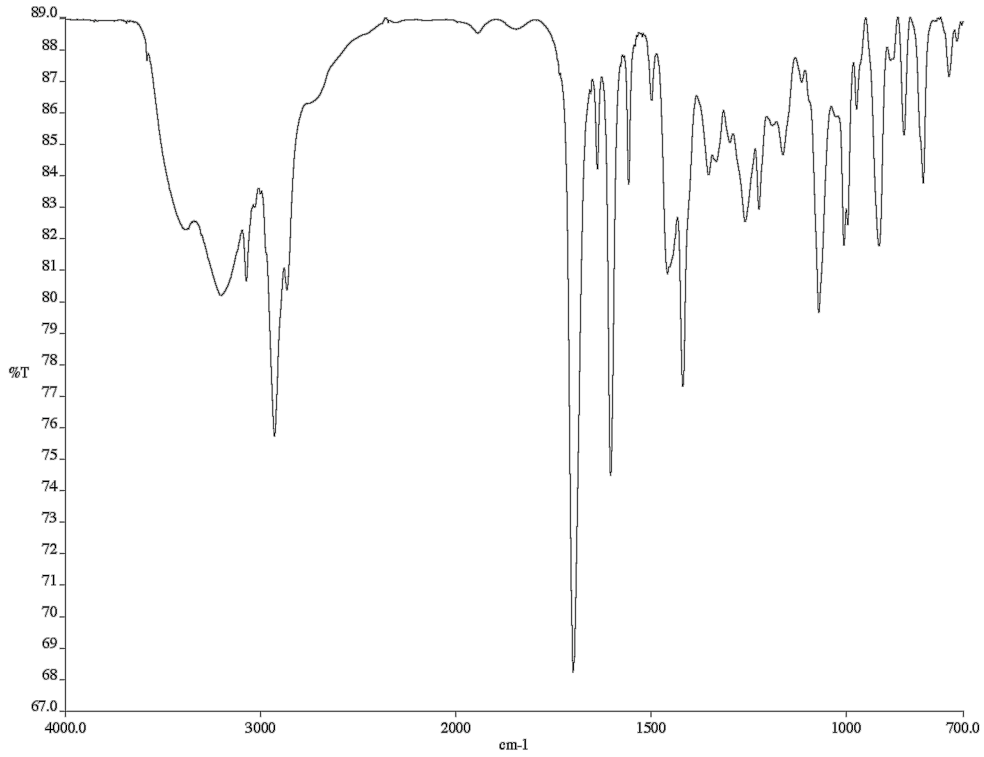


Figure A2.52.2. Infrared spectrum (thin film/NaCl) of compound **70i**.

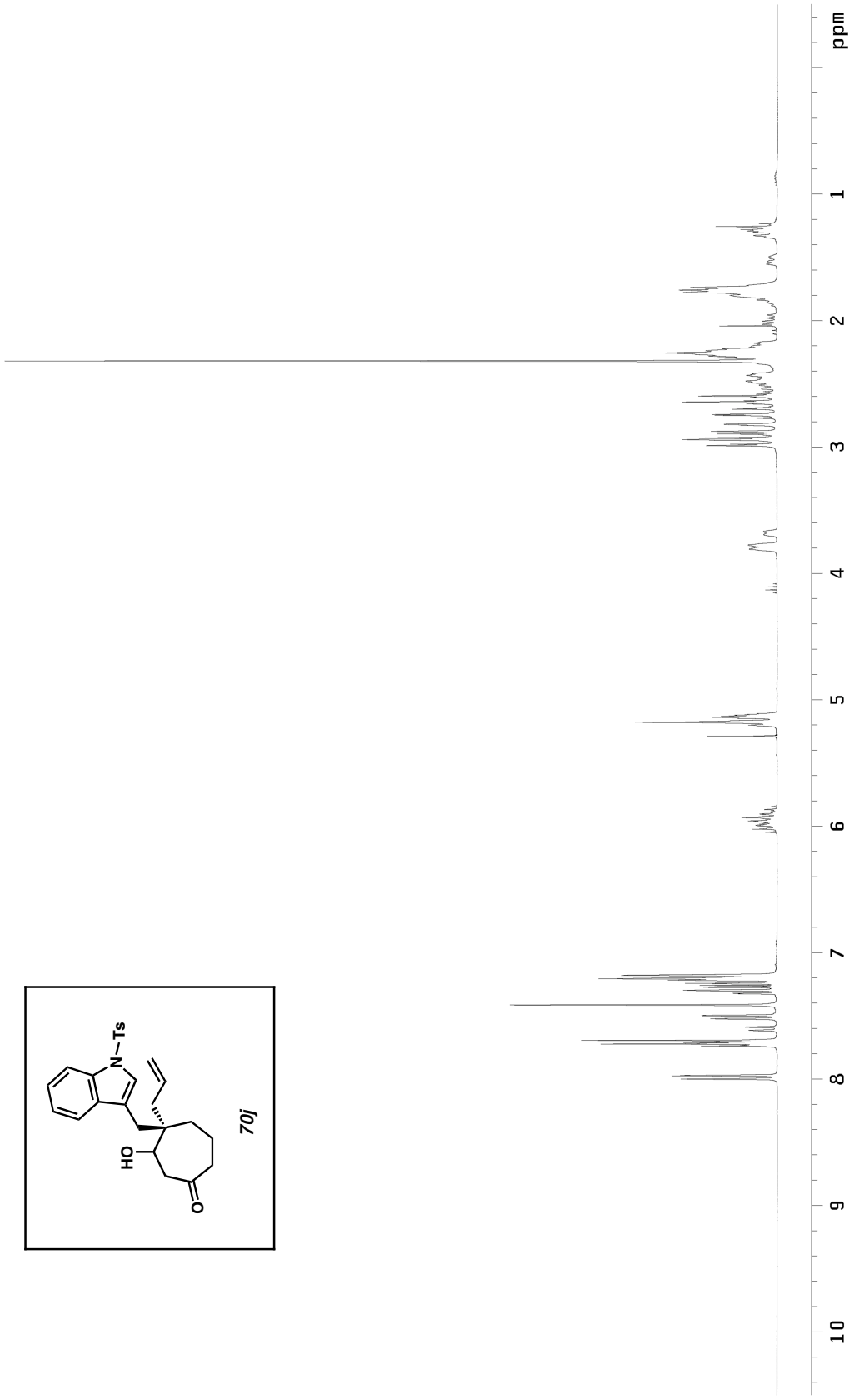


Figure A2.53.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **70j**.

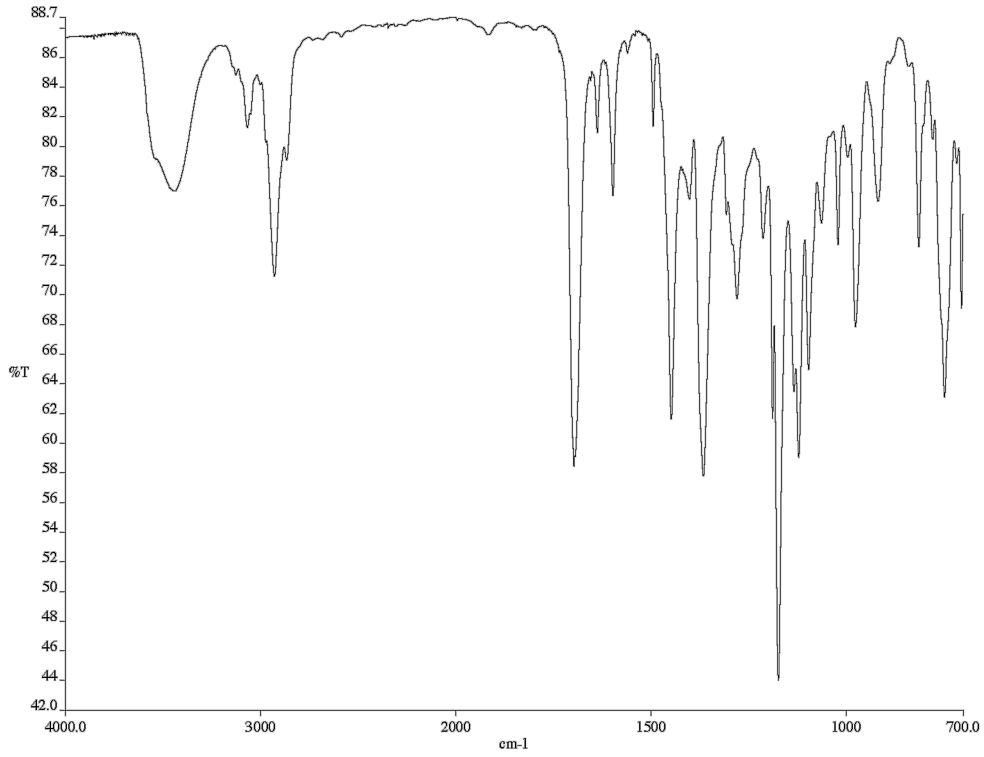


Figure A2.53.2. Infrared spectrum (thin film/NaCl) of compound **70j**.

Figure A2.54.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **70m**.

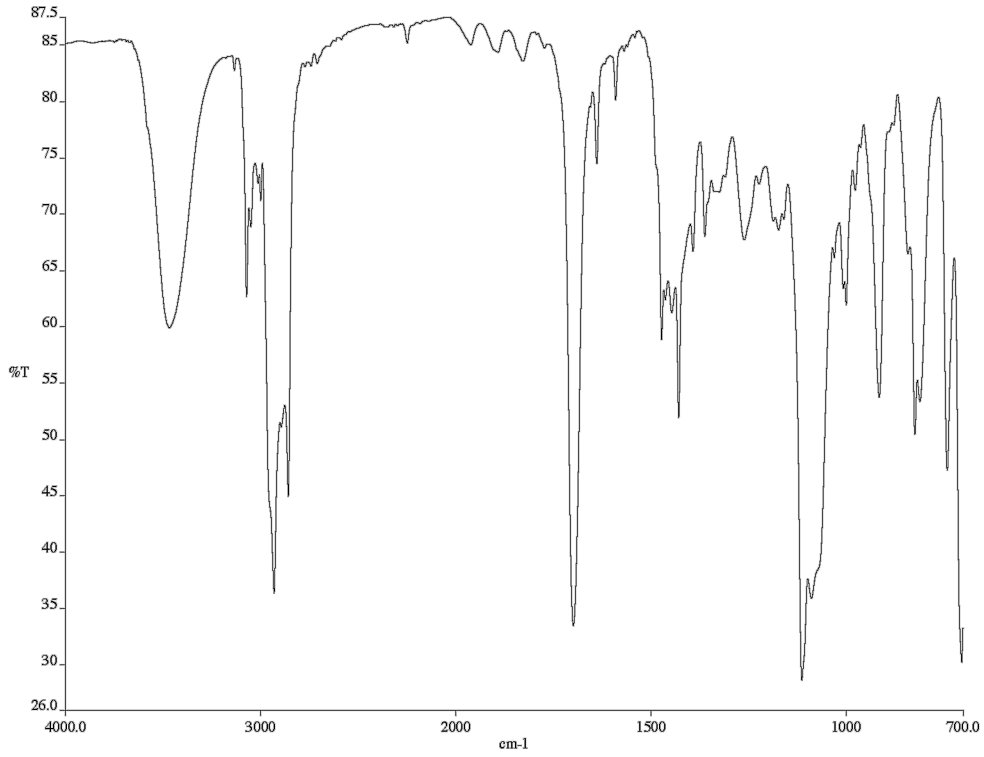


Figure A2.54.2. Infrared spectrum (thin film/NaCl) of compound **70m**.

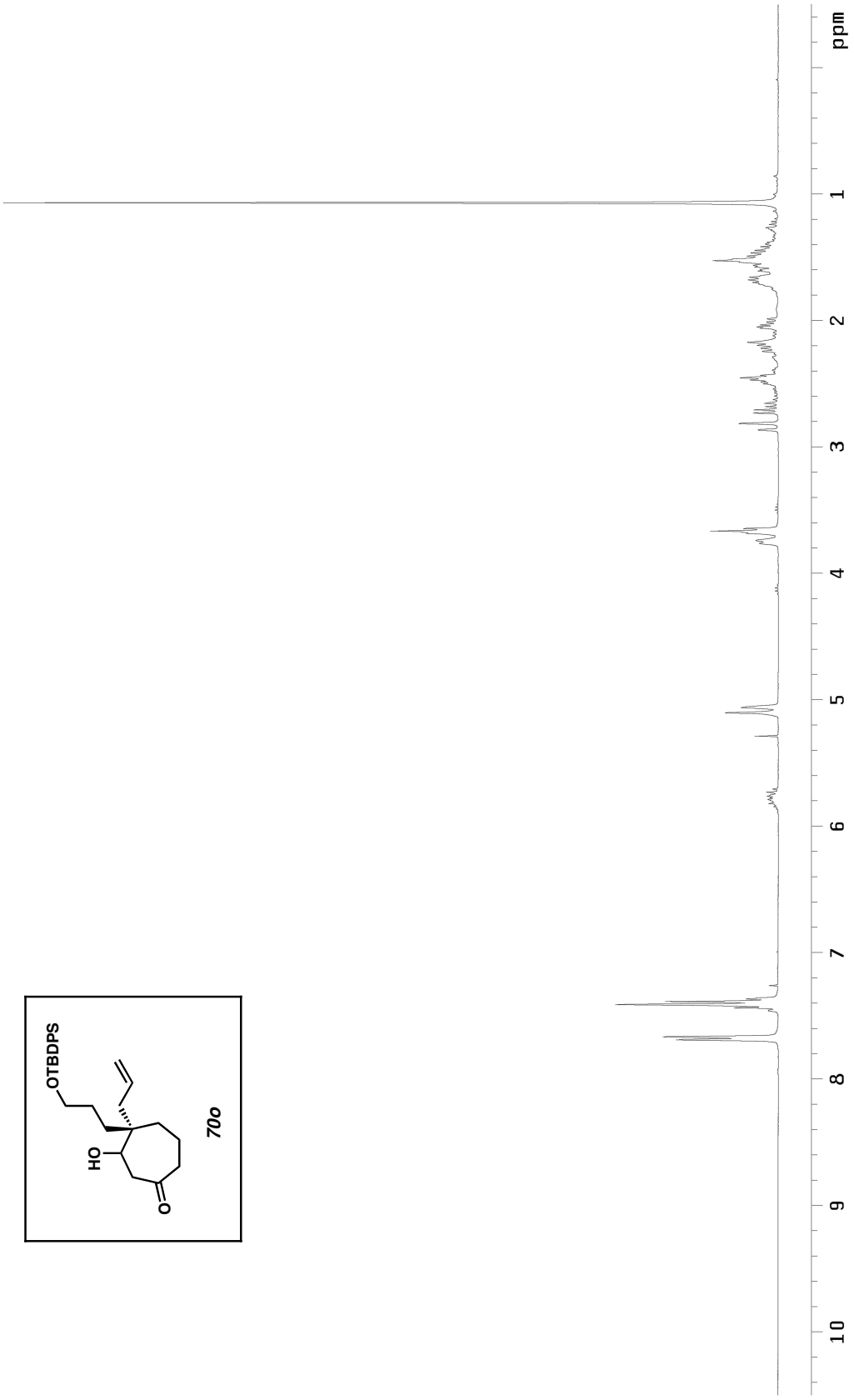


Figure A2.55.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **70o**.

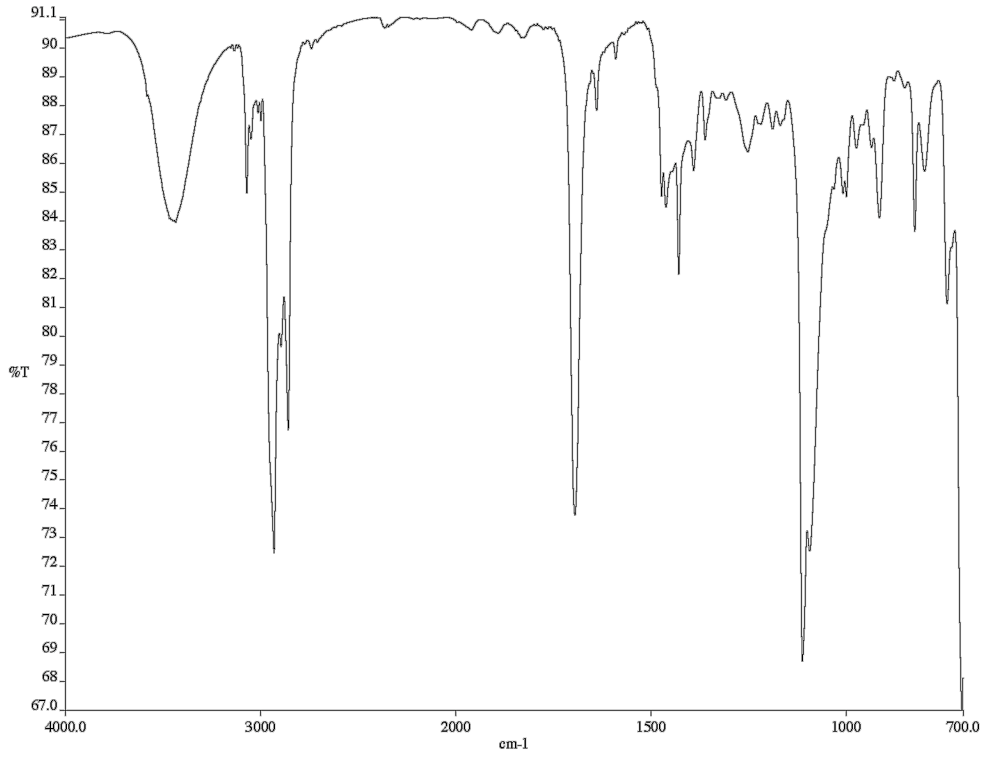


Figure A2.55.2. Infrared spectrum (thin film/NaCl) of compound **70o**.

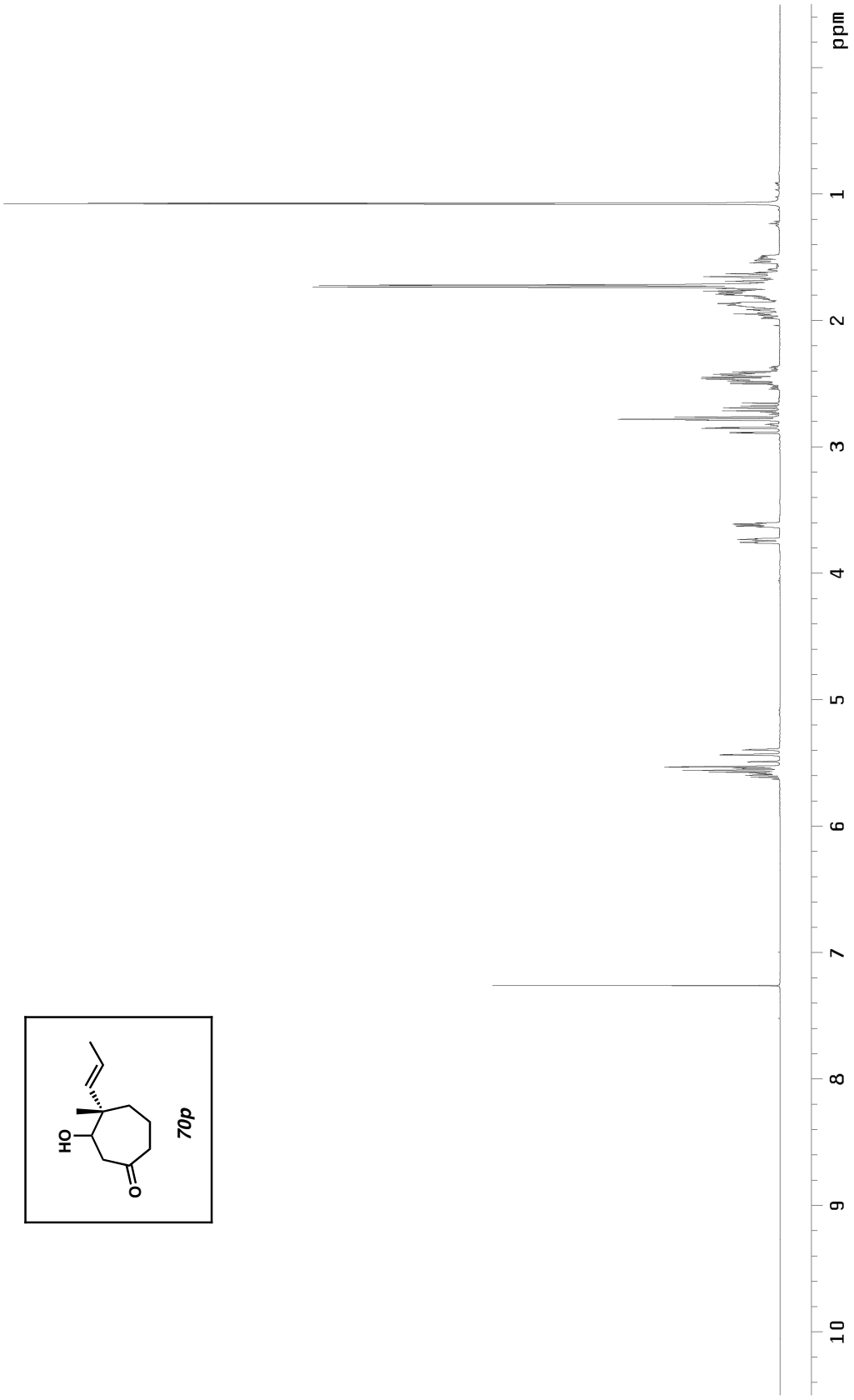


Figure A2.56.1. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **70p**.

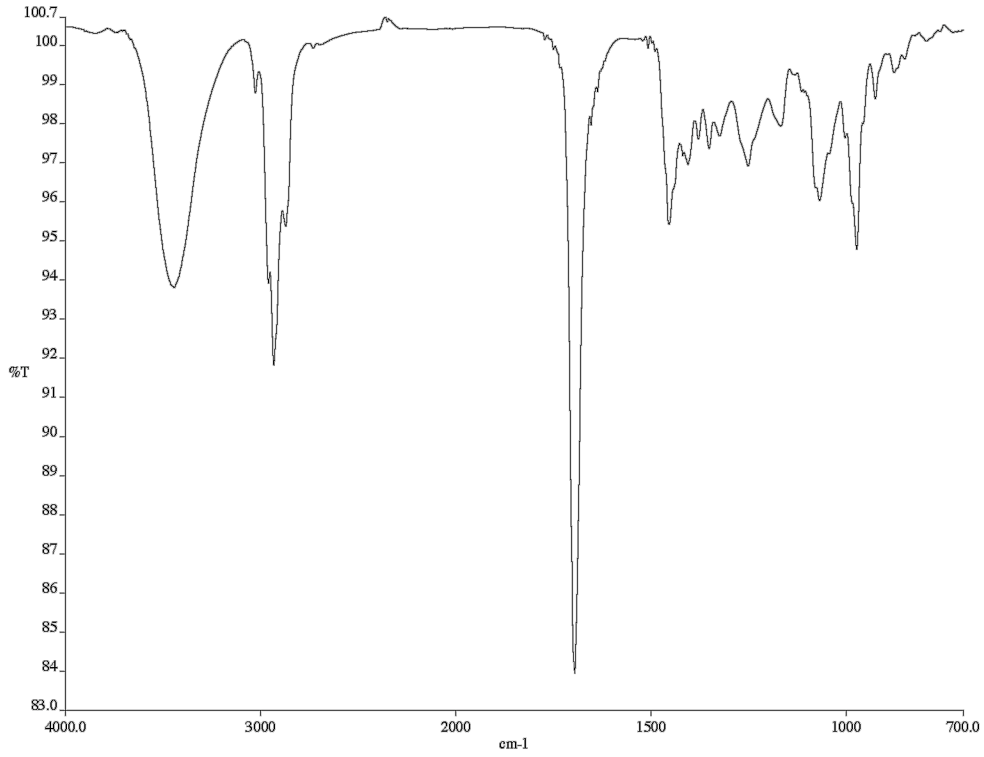


Figure A2.56.2. Infrared spectrum (thin film/NaCl) of compound **70p**.

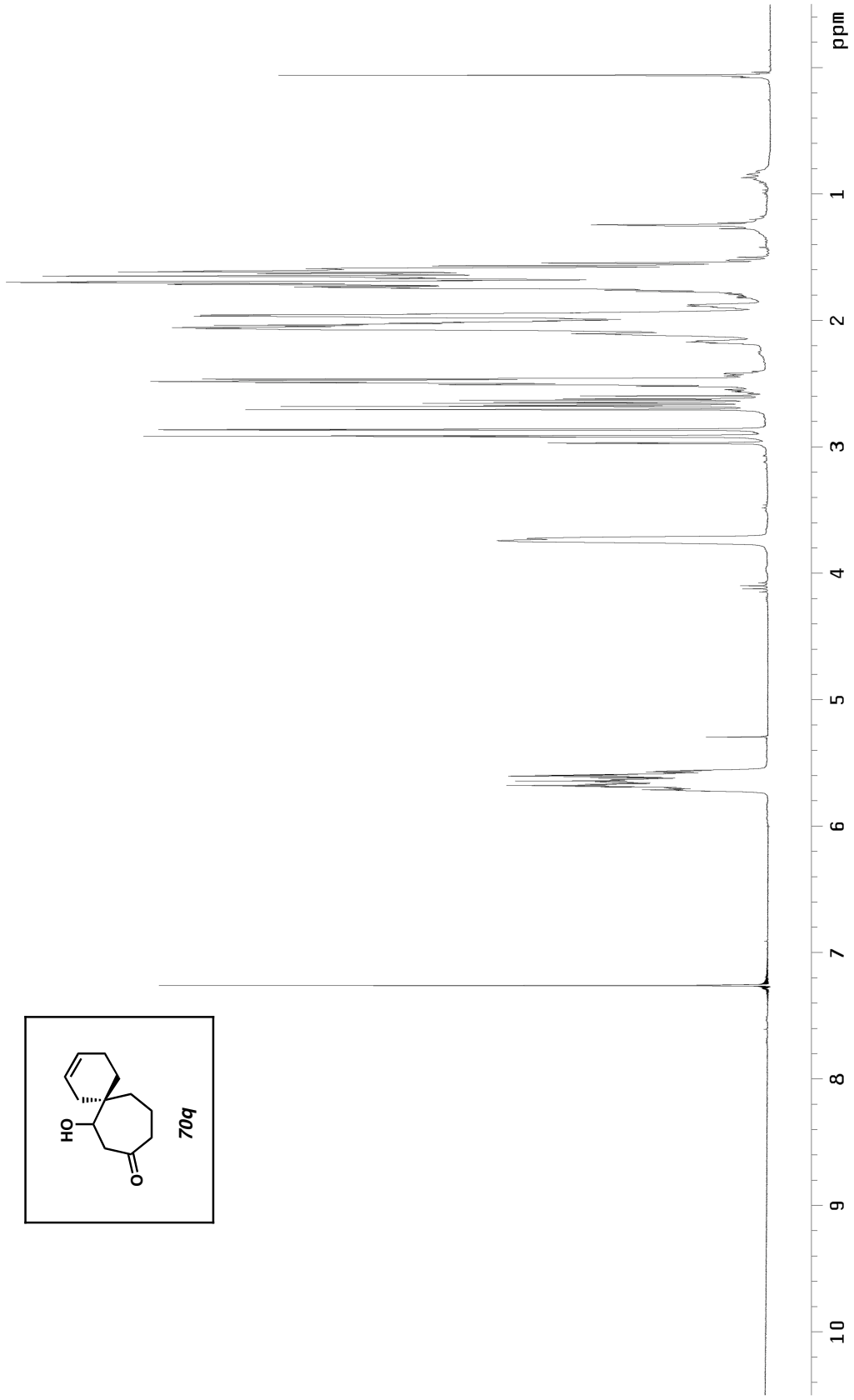


Figure A2.57.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **70q**.

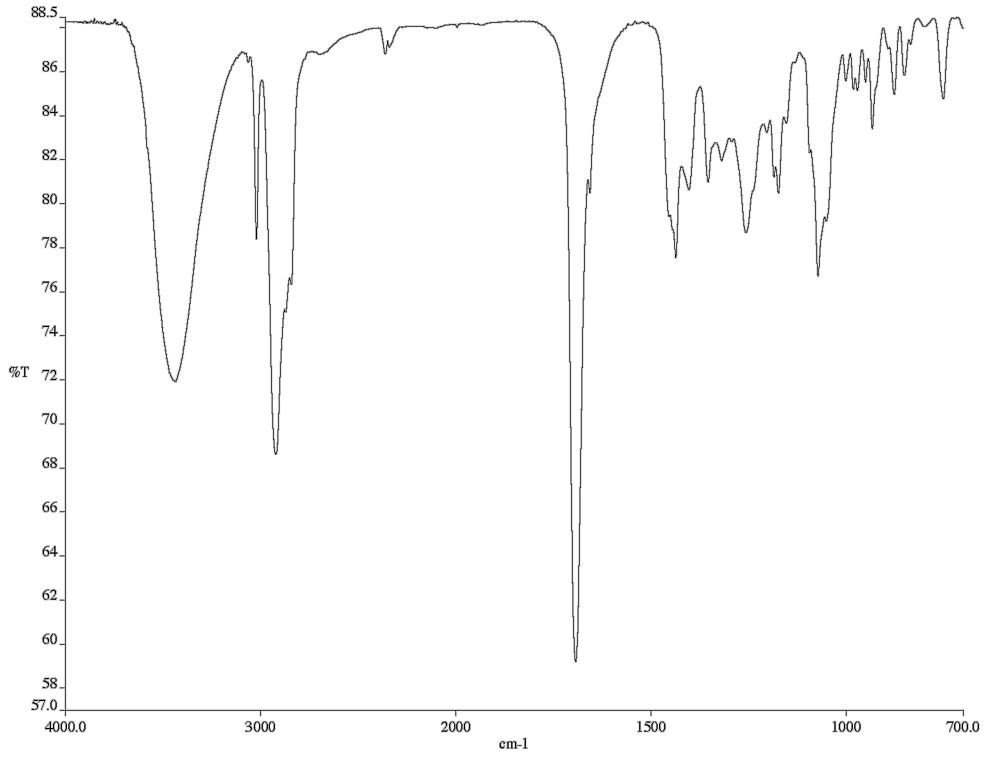


Figure A2.57.2. Infrared spectrum (thin film/NaCl) of compound **70q**.

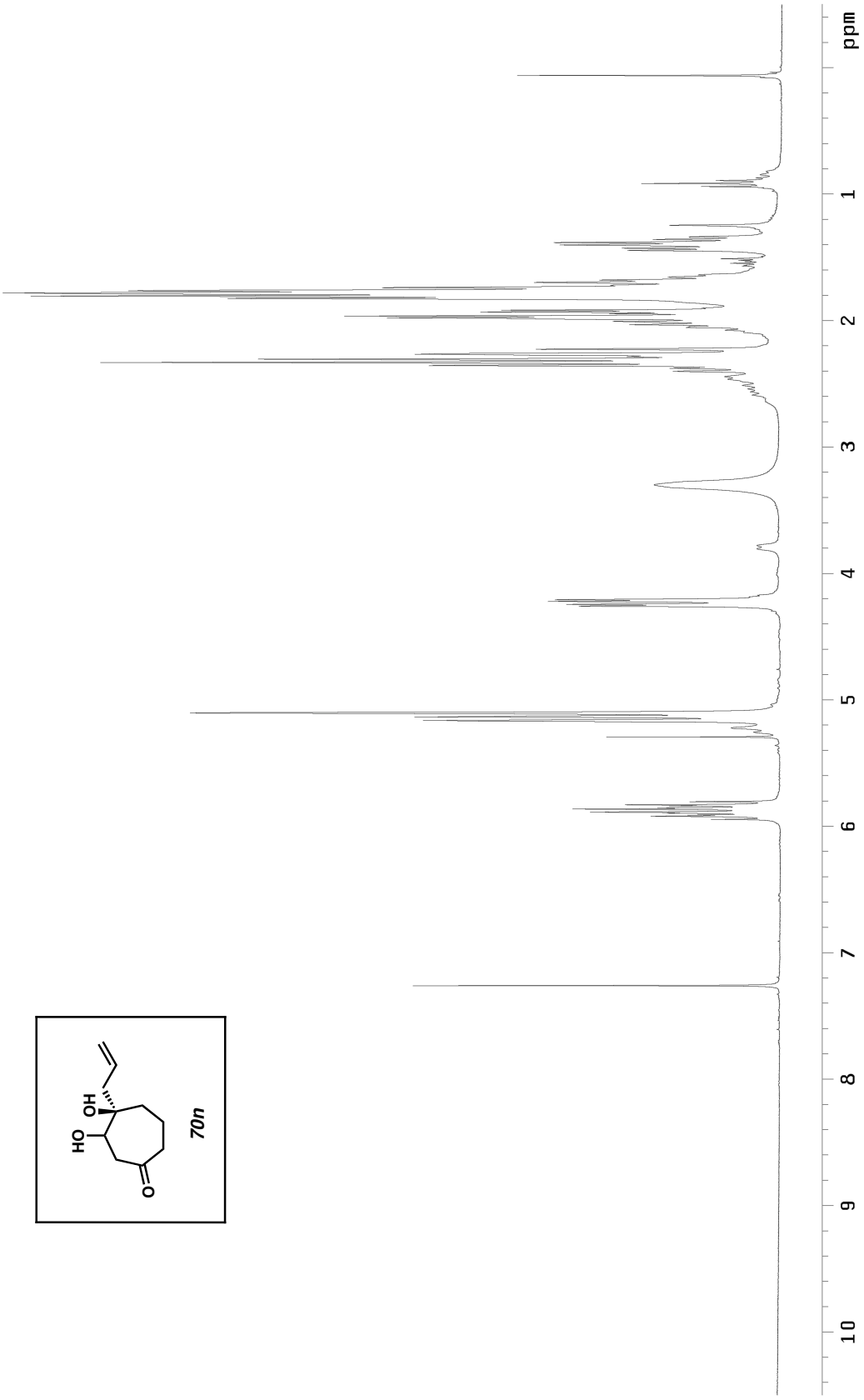


Figure A2.58.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **70n**.

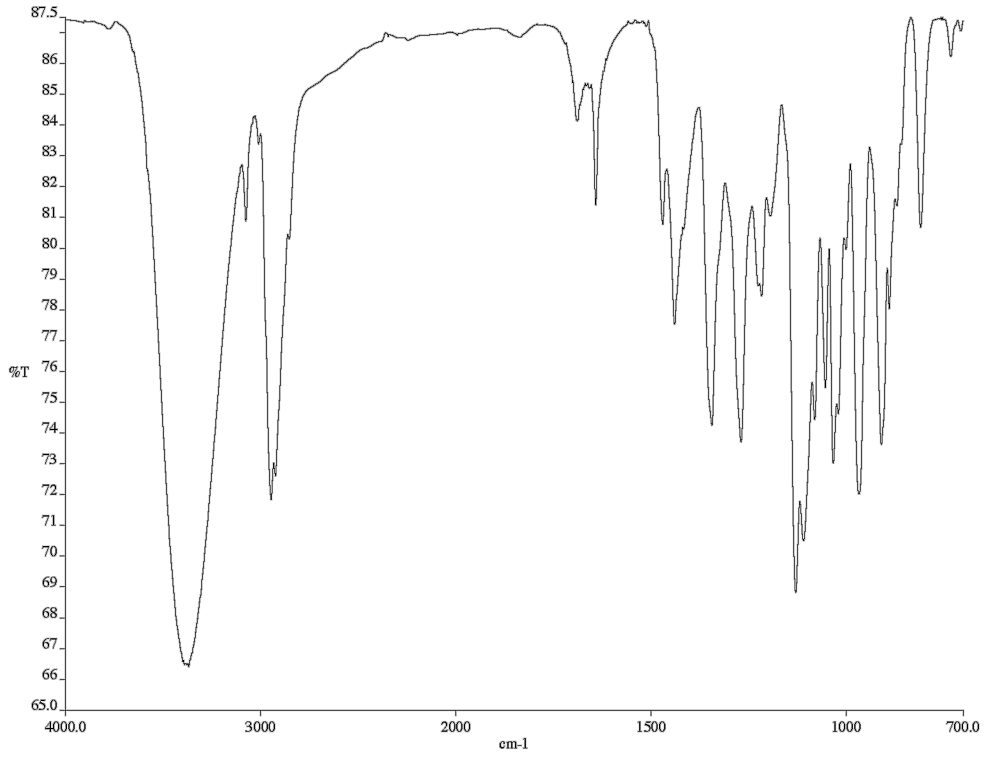


Figure A2.58.2. Infrared spectrum (thin film/NaCl) of compound **70n**.

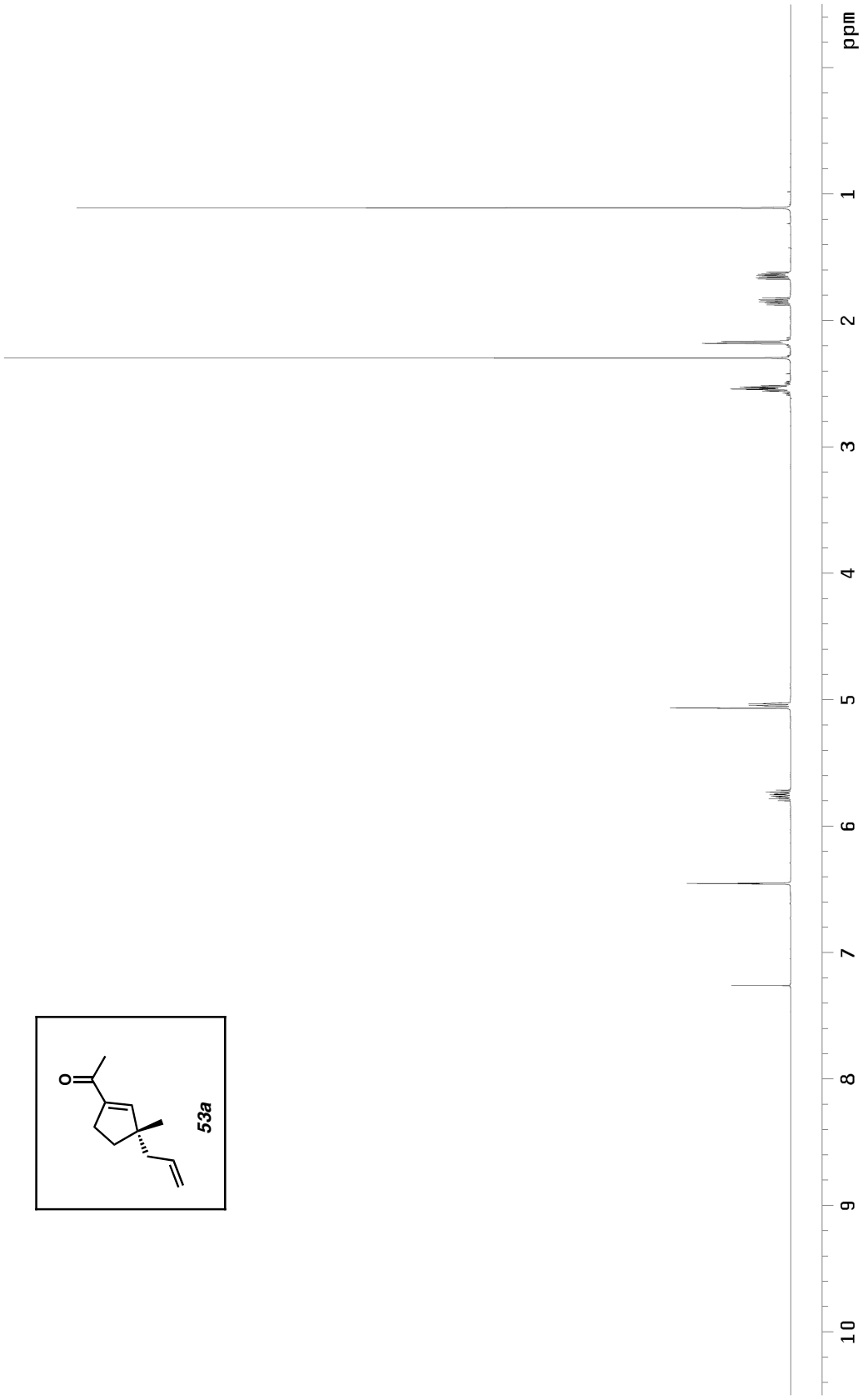


Figure A2.59.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **53a**.

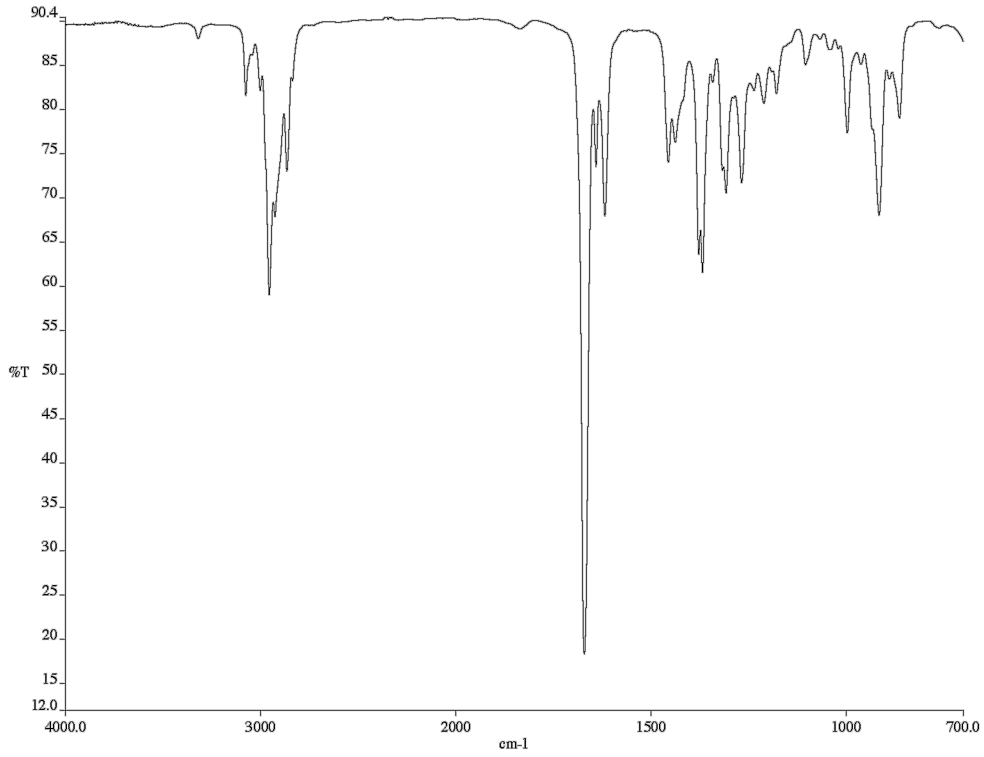


Figure A2.59.2. Infrared spectrum (thin film/NaCl) of compound **53a**.

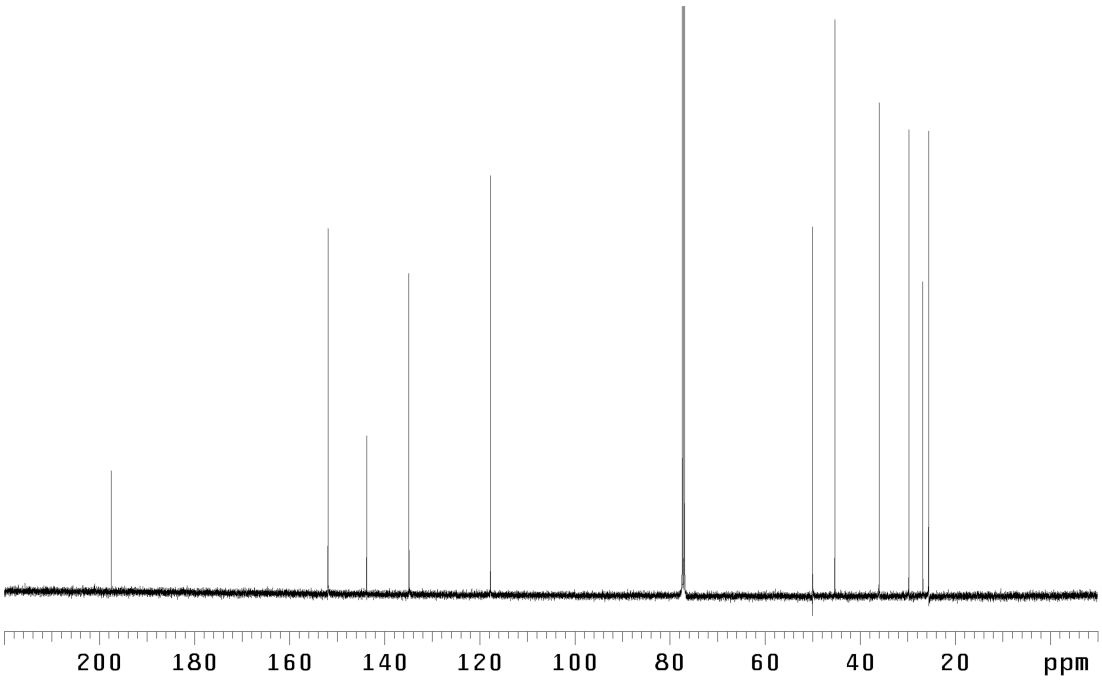


Figure A2.59.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **53a**.

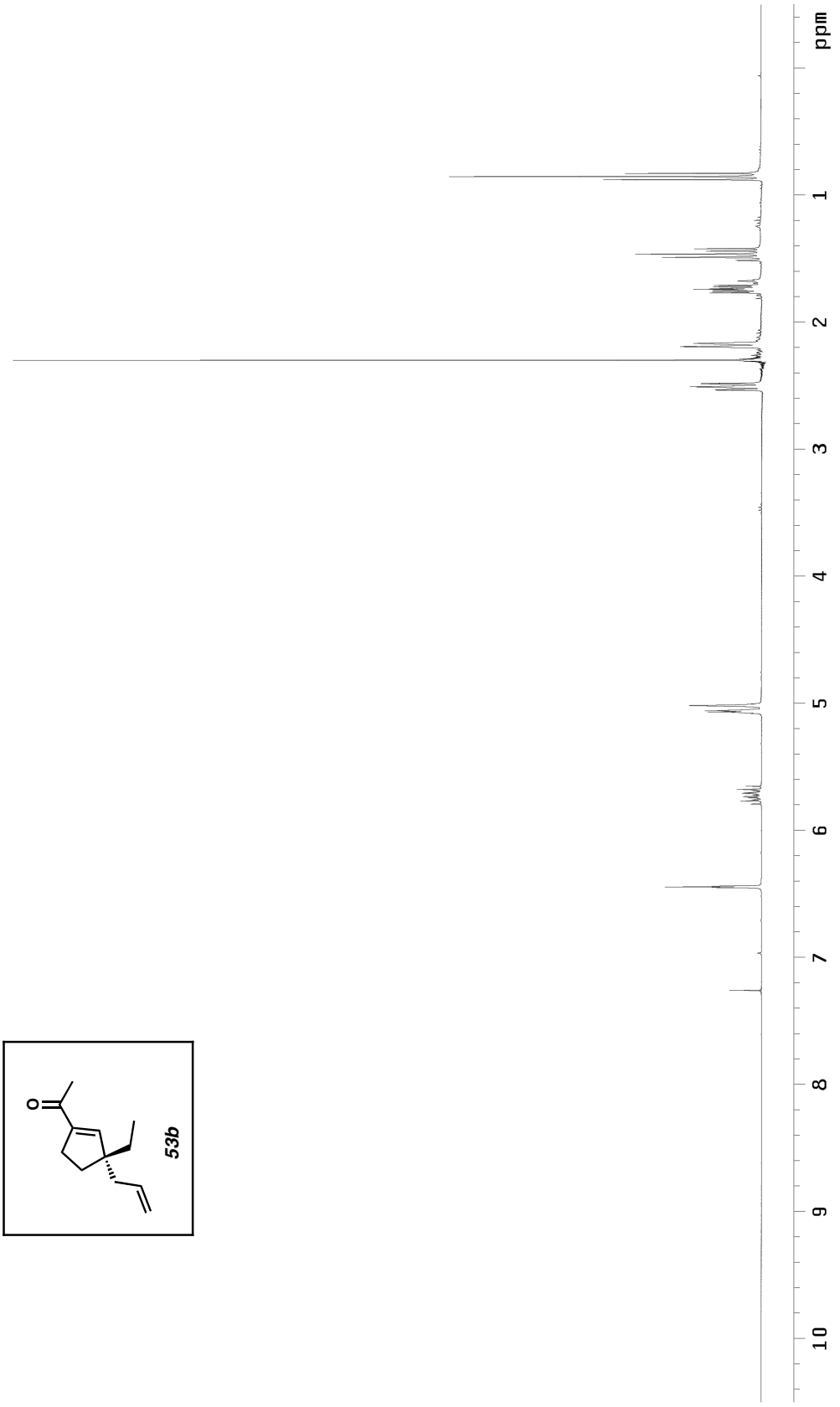


Figure A2.60.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **53b**.

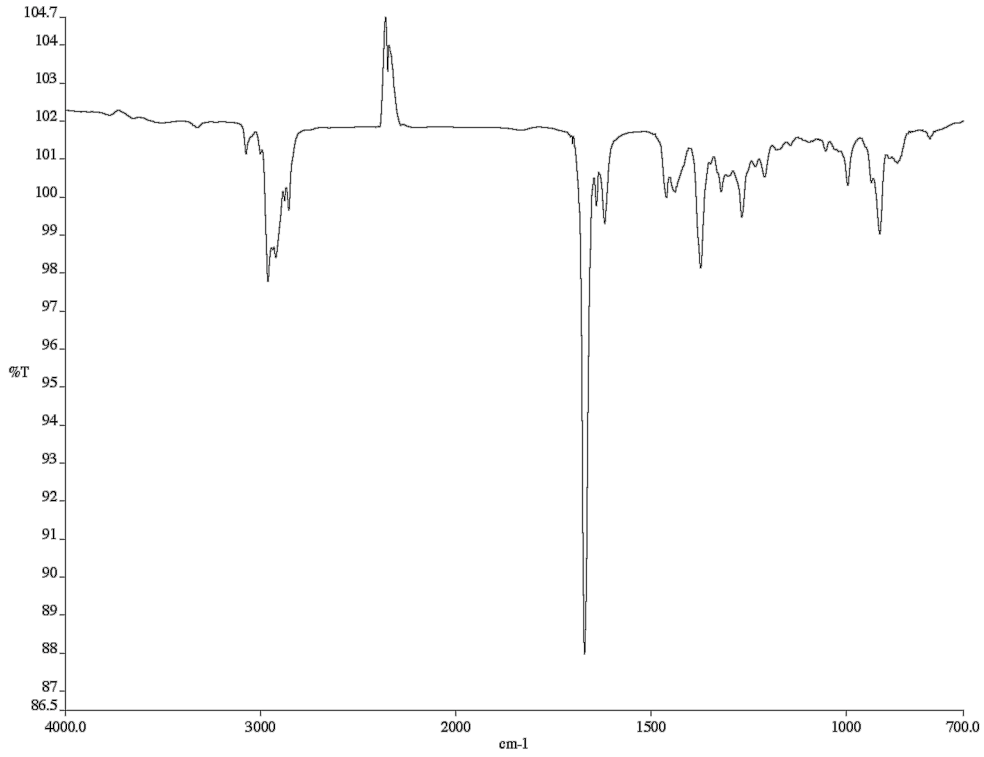


Figure A2.60.2. Infrared spectrum (thin film/NaCl) of compound **53b**.

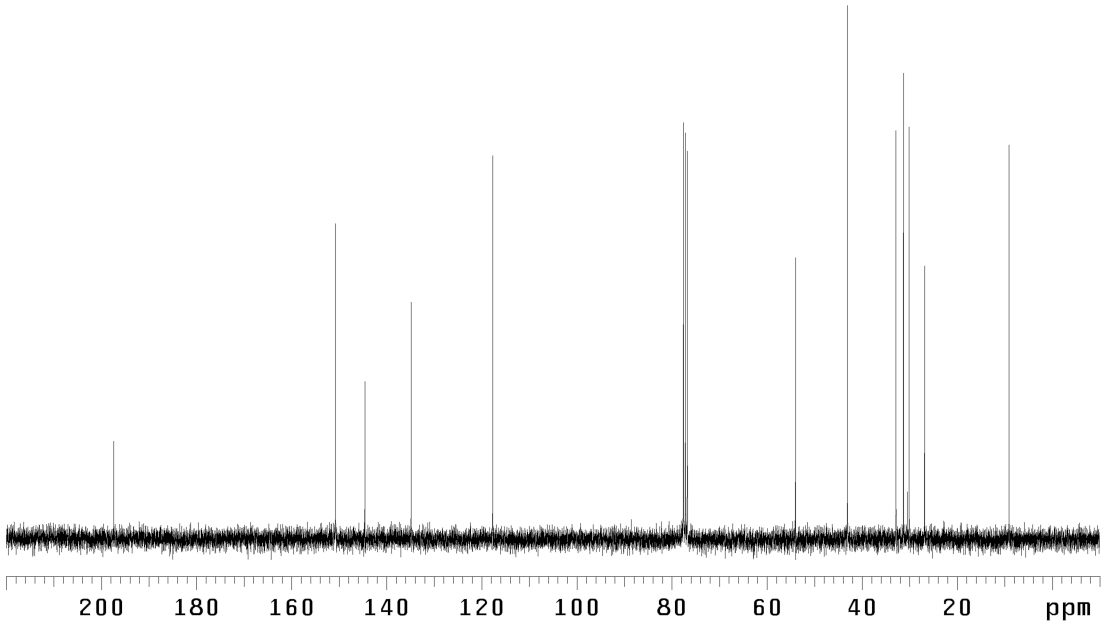


Figure A2.60.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **53b**.

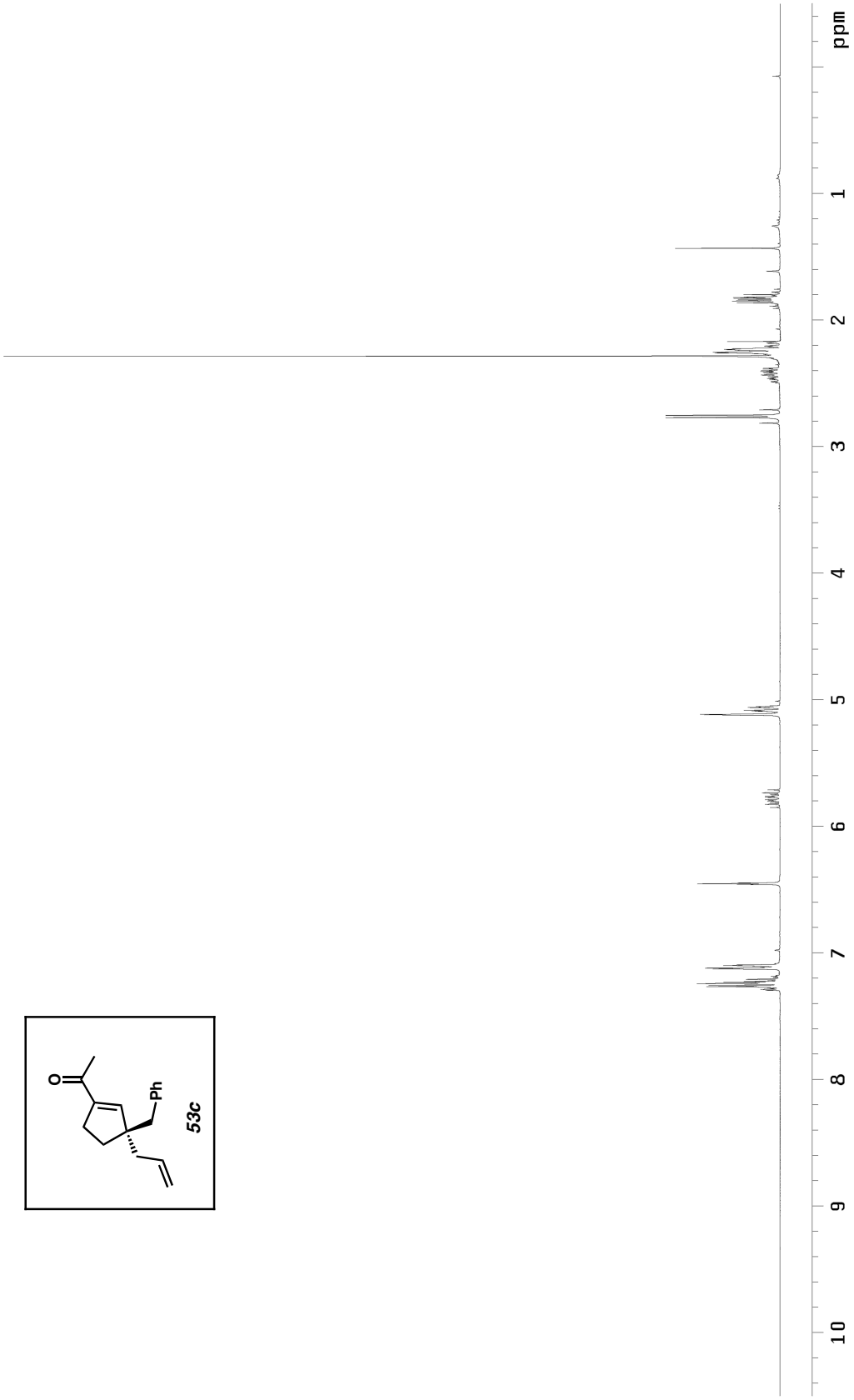


Figure A2.61.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **53c**.

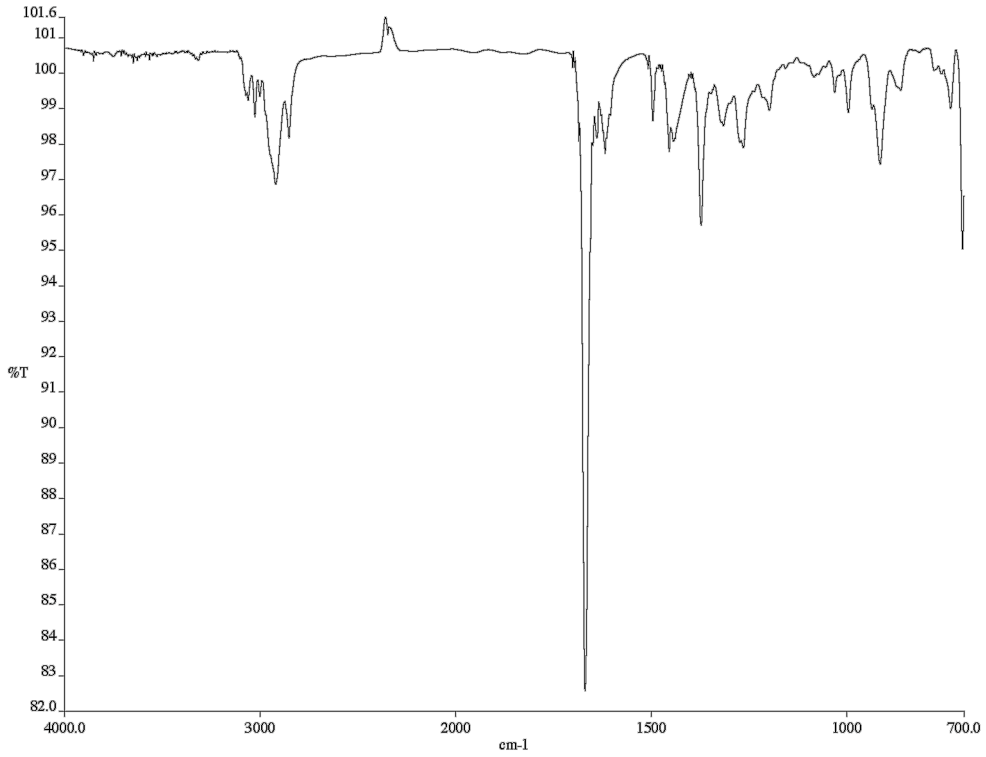


Figure A2.61.2. Infrared spectrum (thin film/NaCl) of compound **53c**.

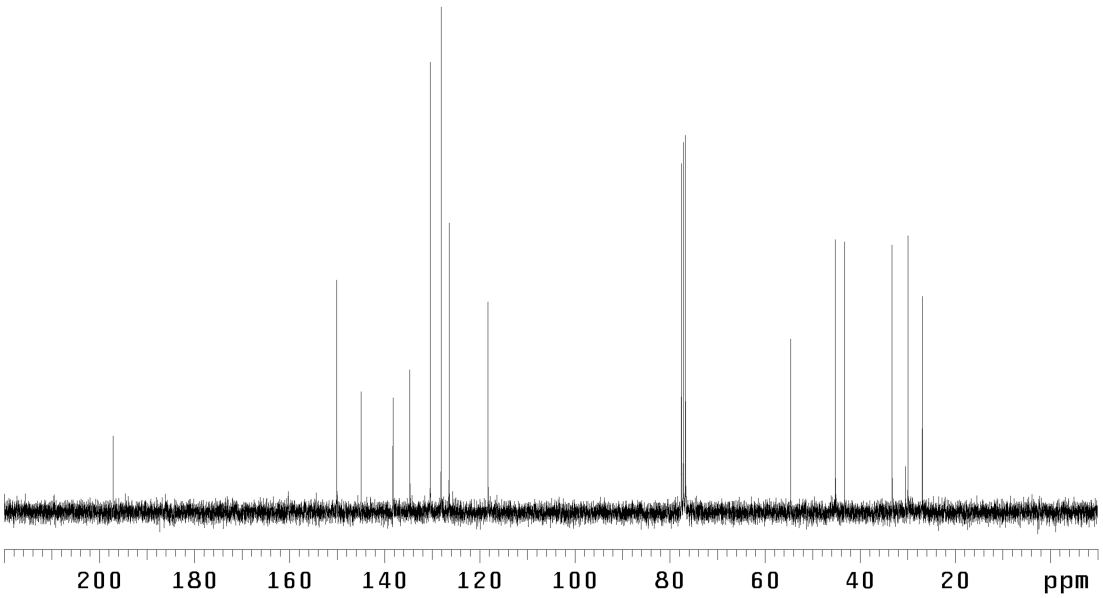


Figure A2.61.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **53c**.

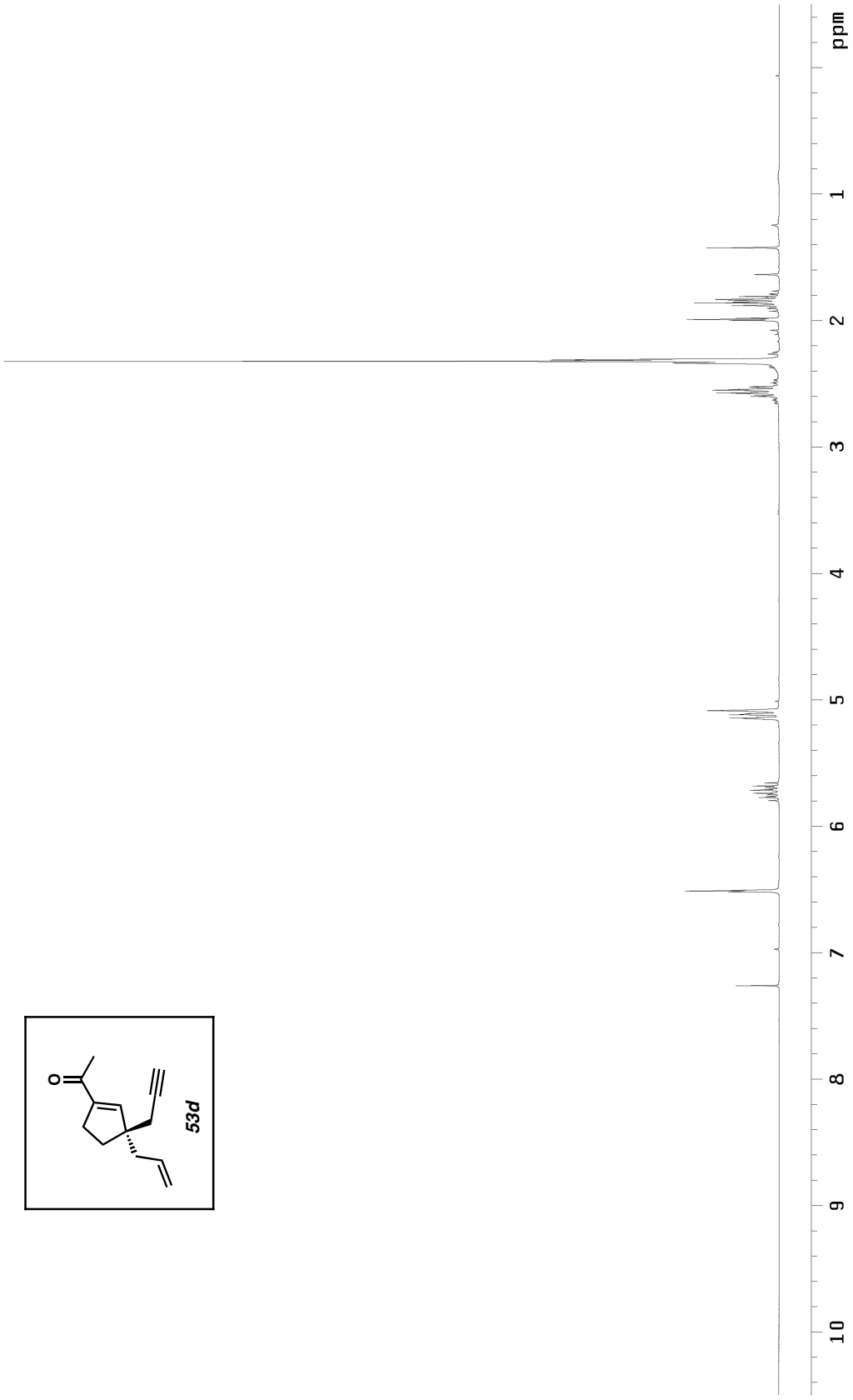


Figure A2.62.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **53d**.

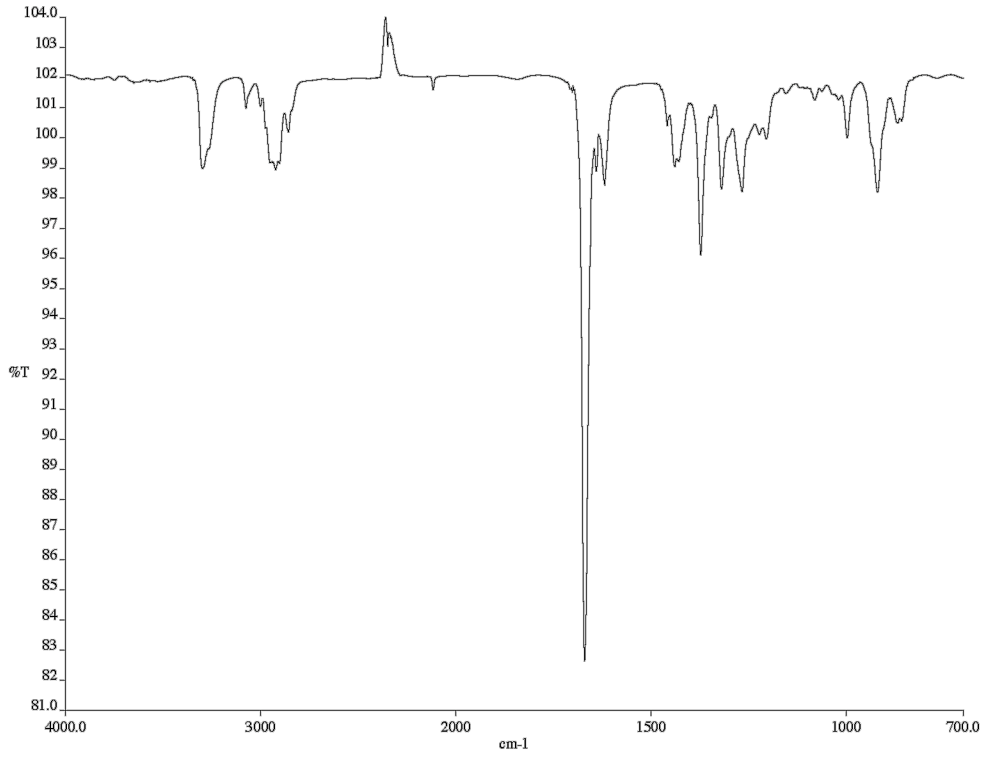


Figure A2.62.2. Infrared spectrum (thin film/NaCl) of compound **53d**.

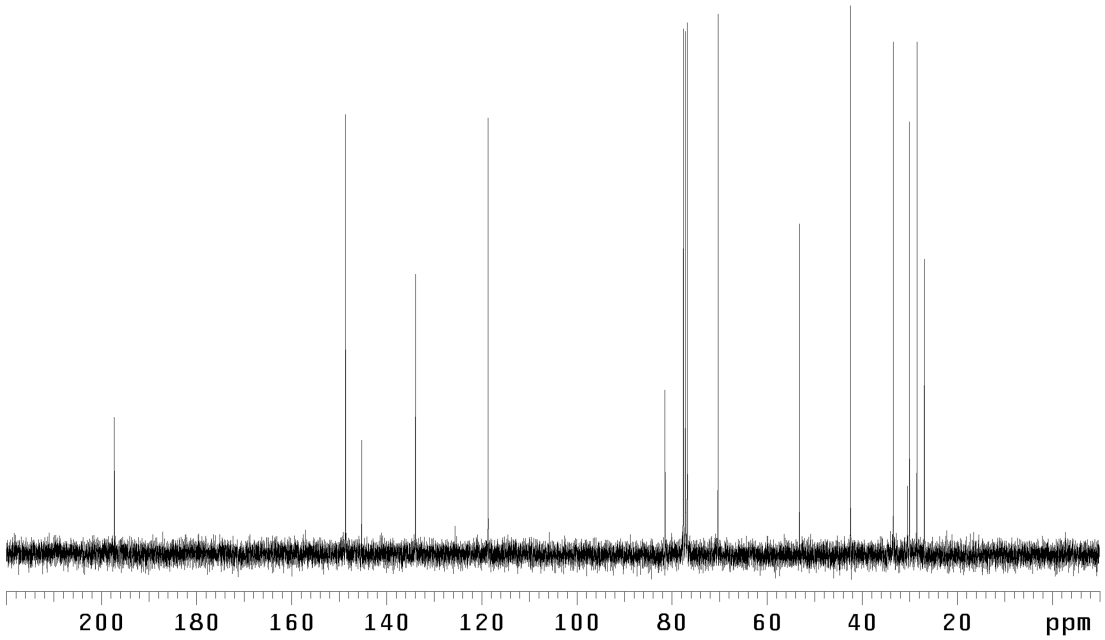


Figure A2.62.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **53d**.

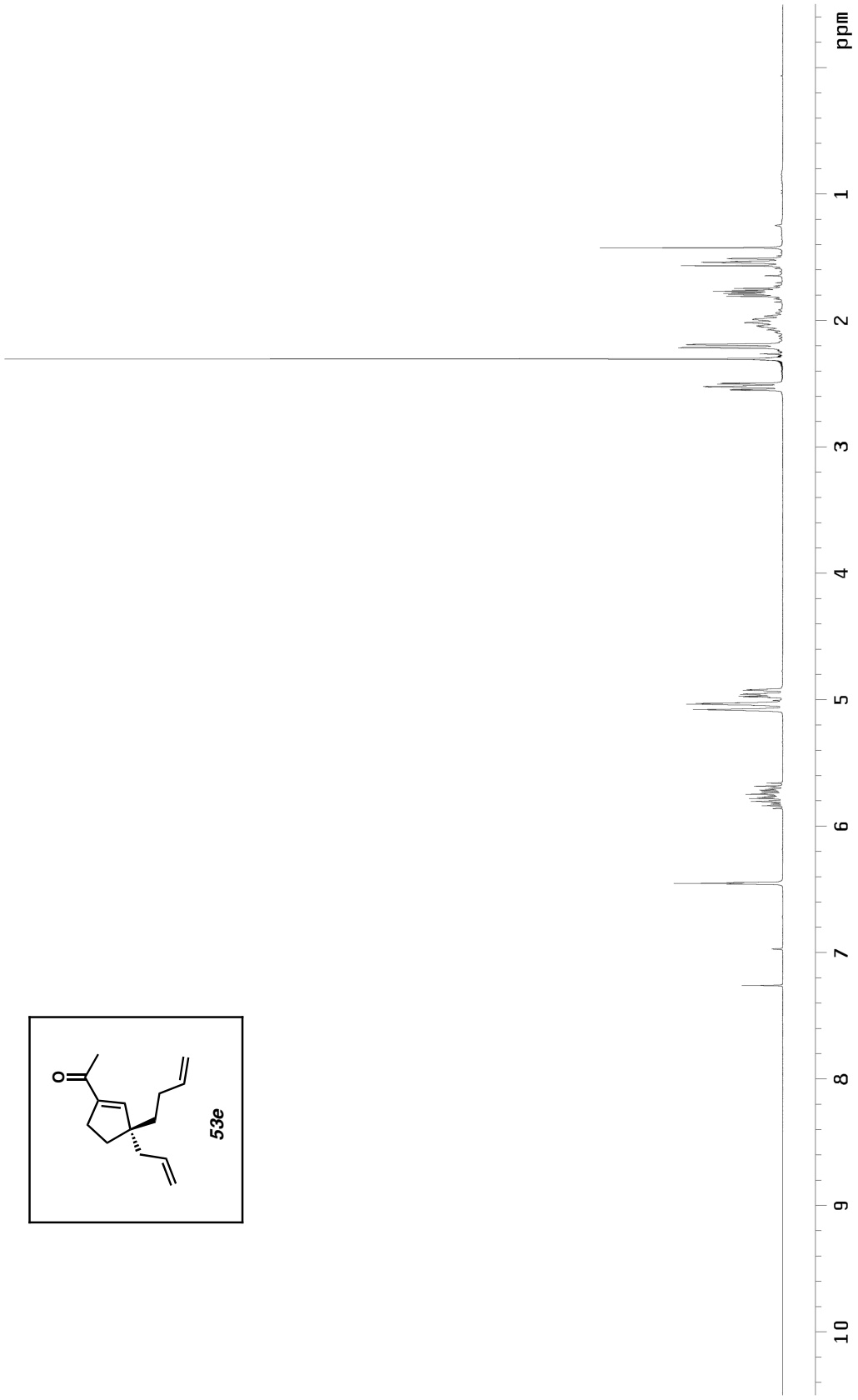


Figure A2.63.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **53e**.

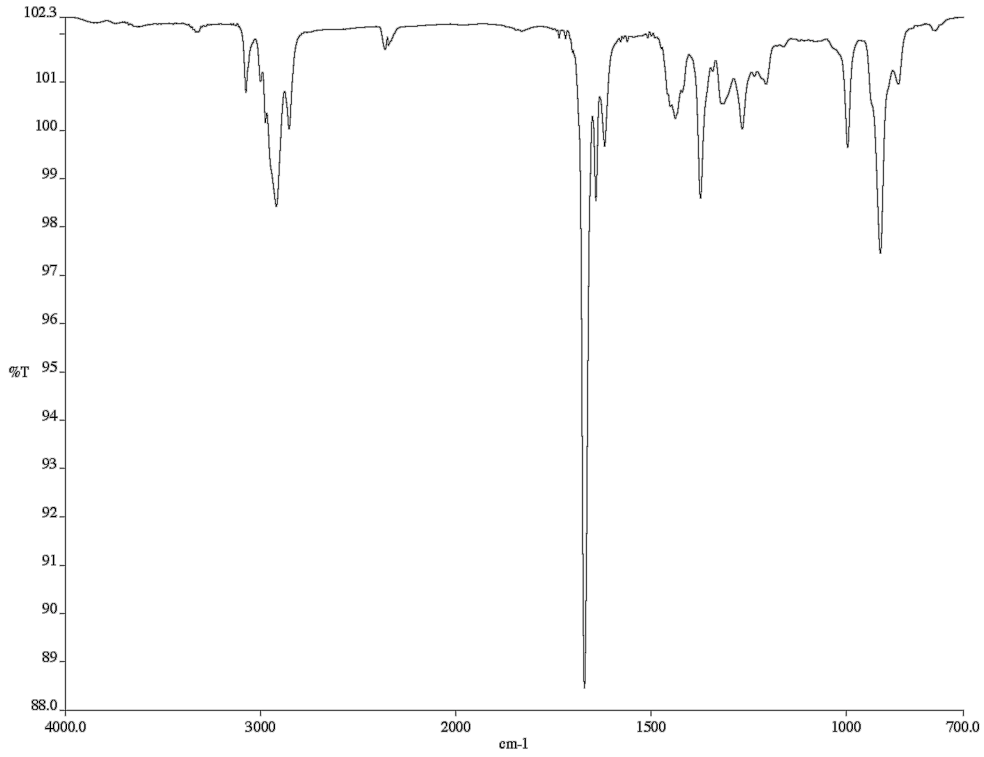


Figure A2.63.2. Infrared spectrum (thin film/NaCl) of compound **53e**.

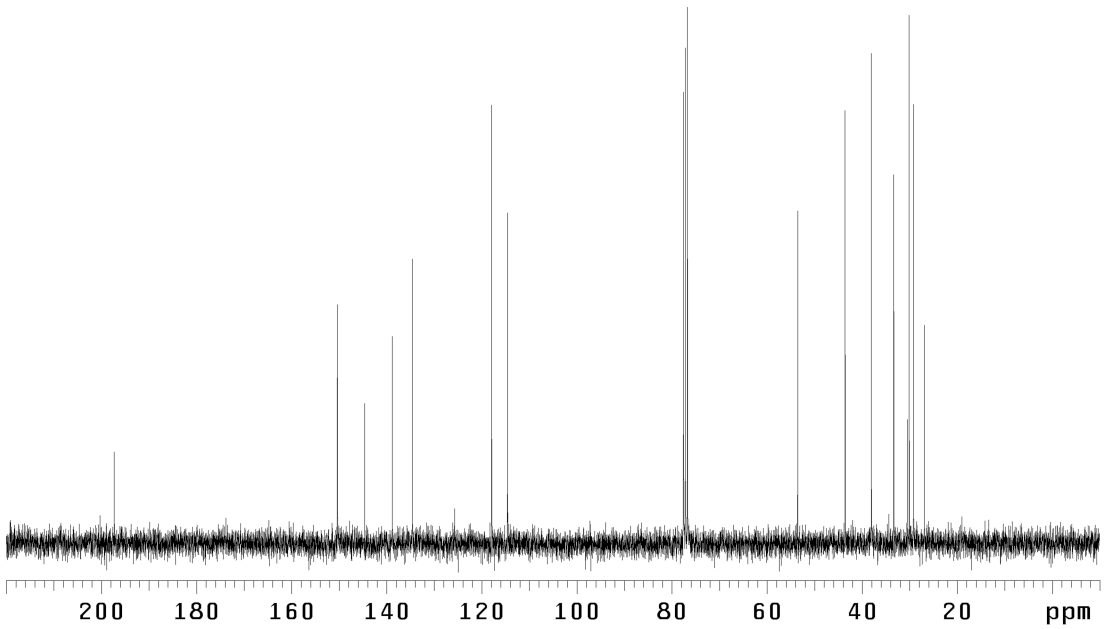


Figure A2.63.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **53e**.

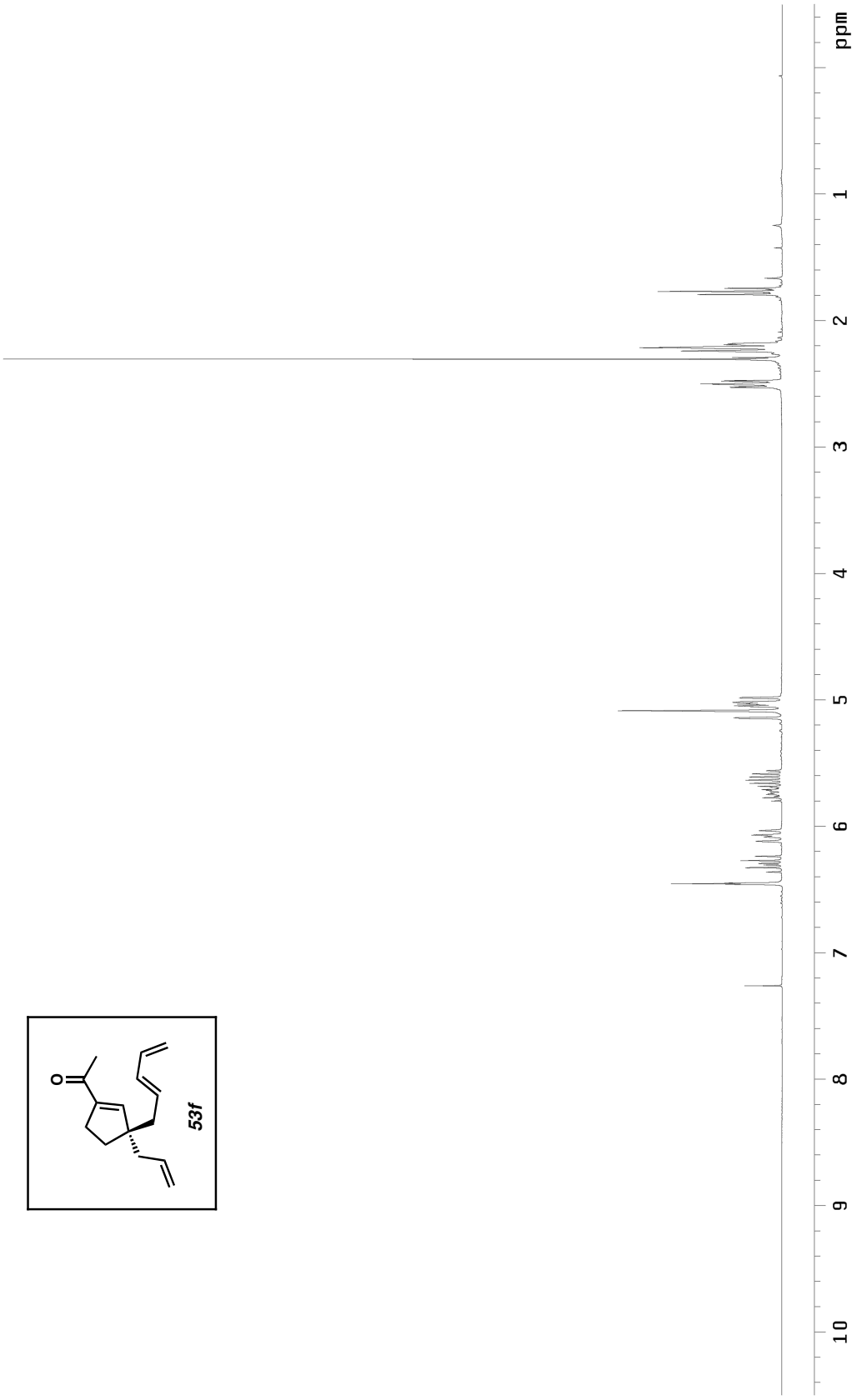


Figure A2.64.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **53f**.

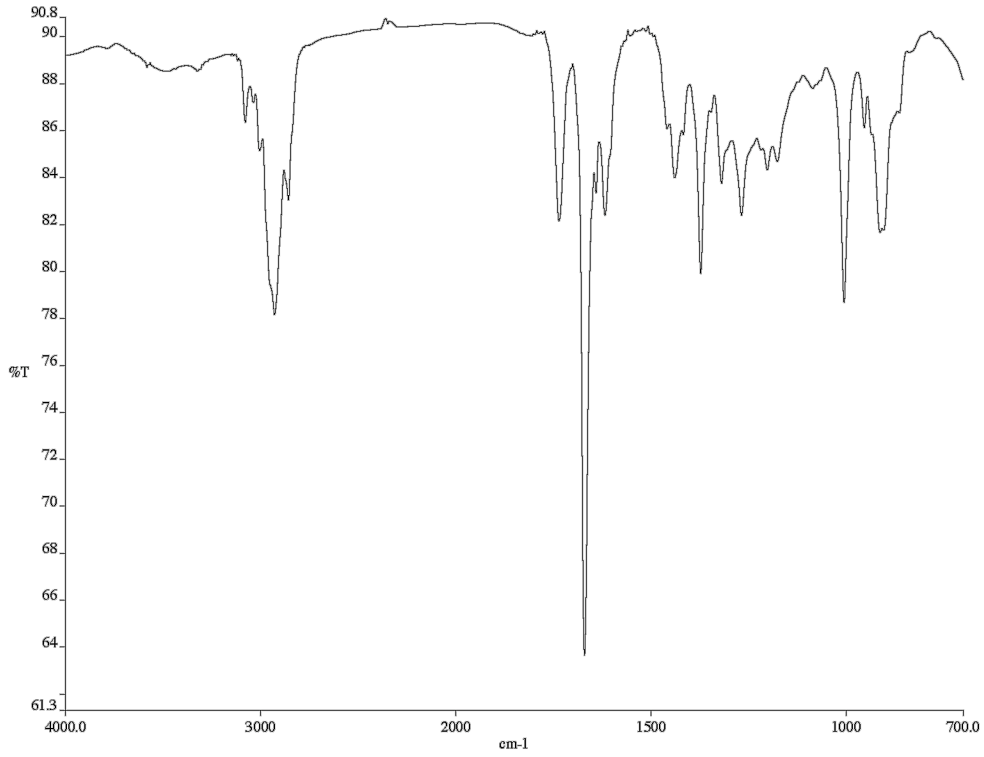


Figure A2.64.2. Infrared spectrum (thin film/NaCl) of compound **53f**.

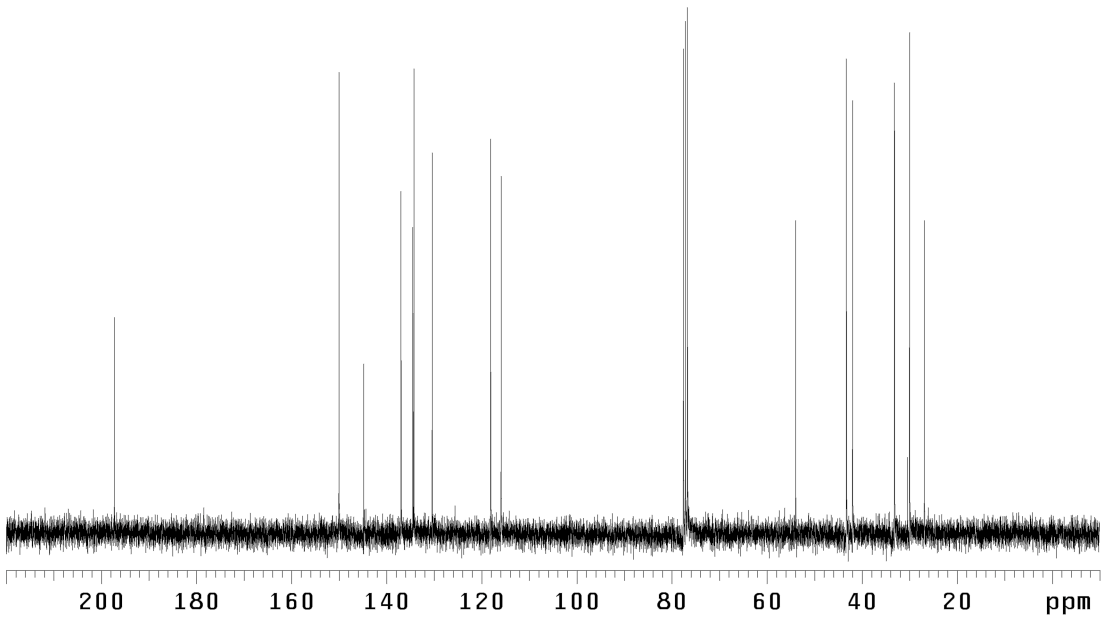


Figure A2.64.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **53f**.

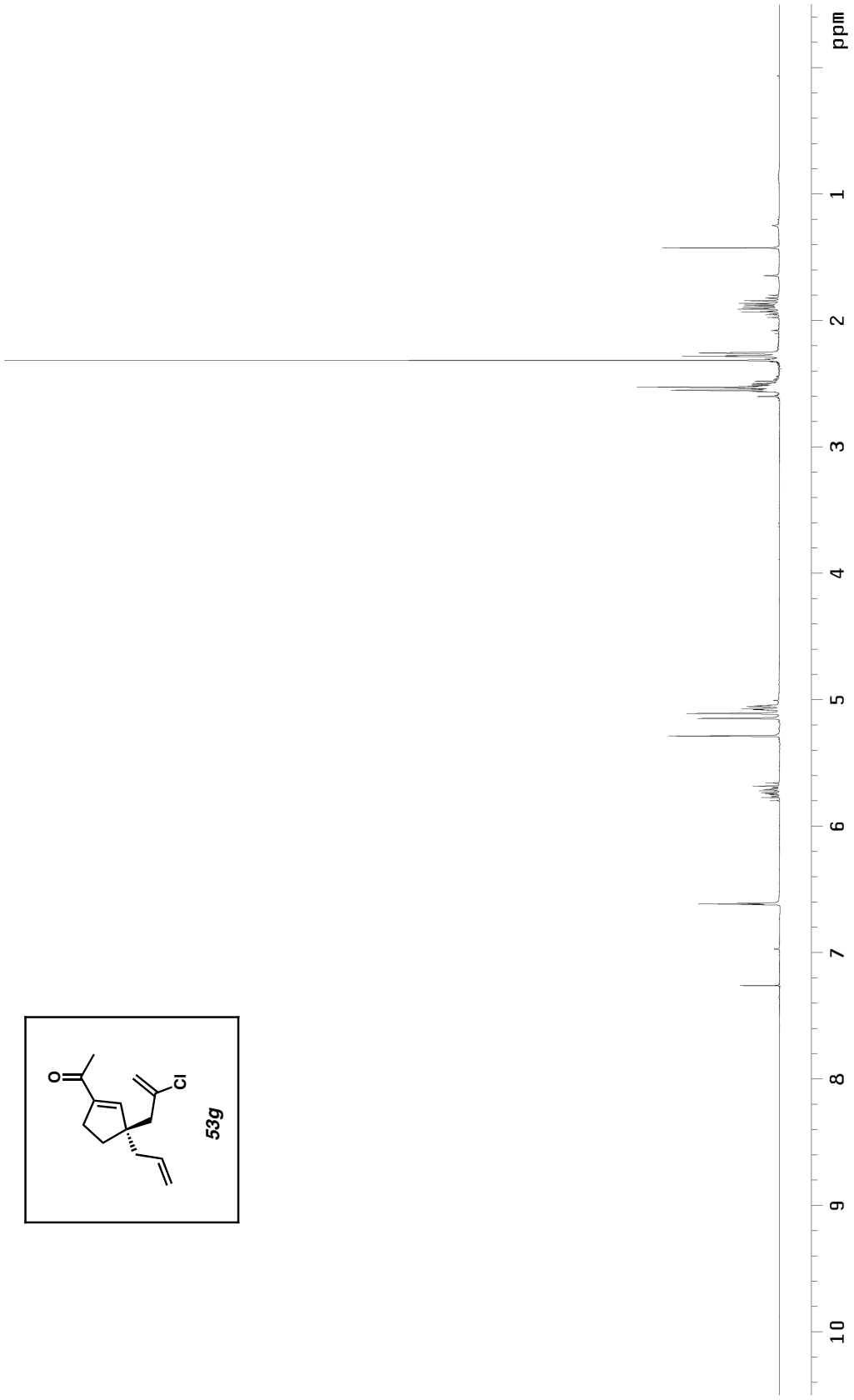


Figure A2.65.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **53g**.

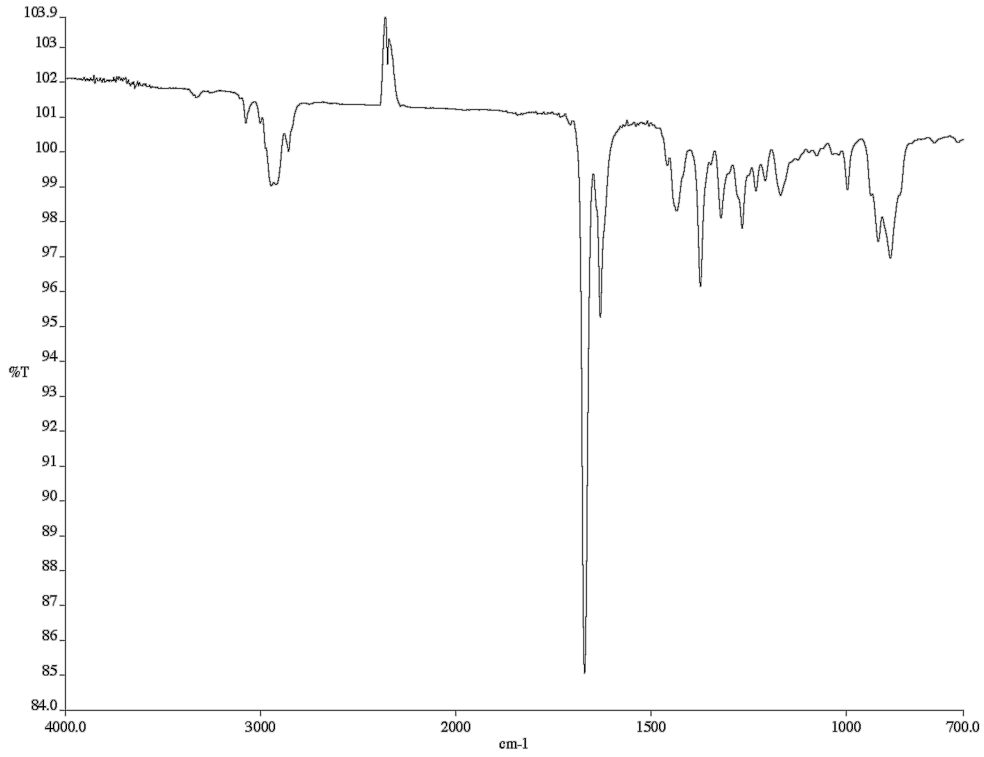


Figure A2.65.2. Infrared spectrum (thin film/NaCl) of compound **53g**.

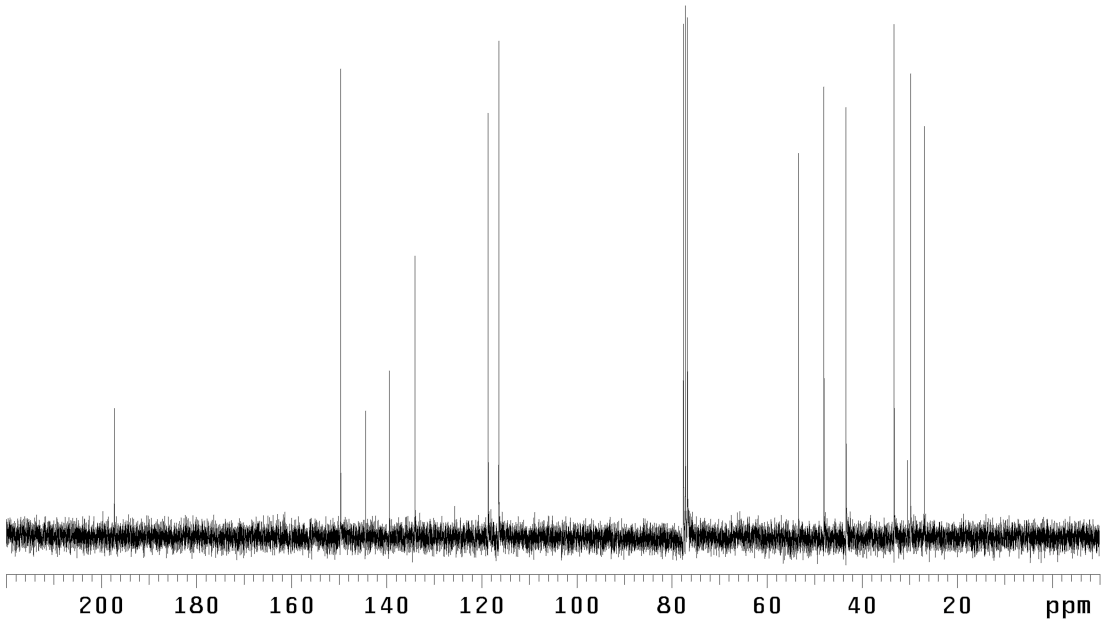


Figure A2.65.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **53g**.

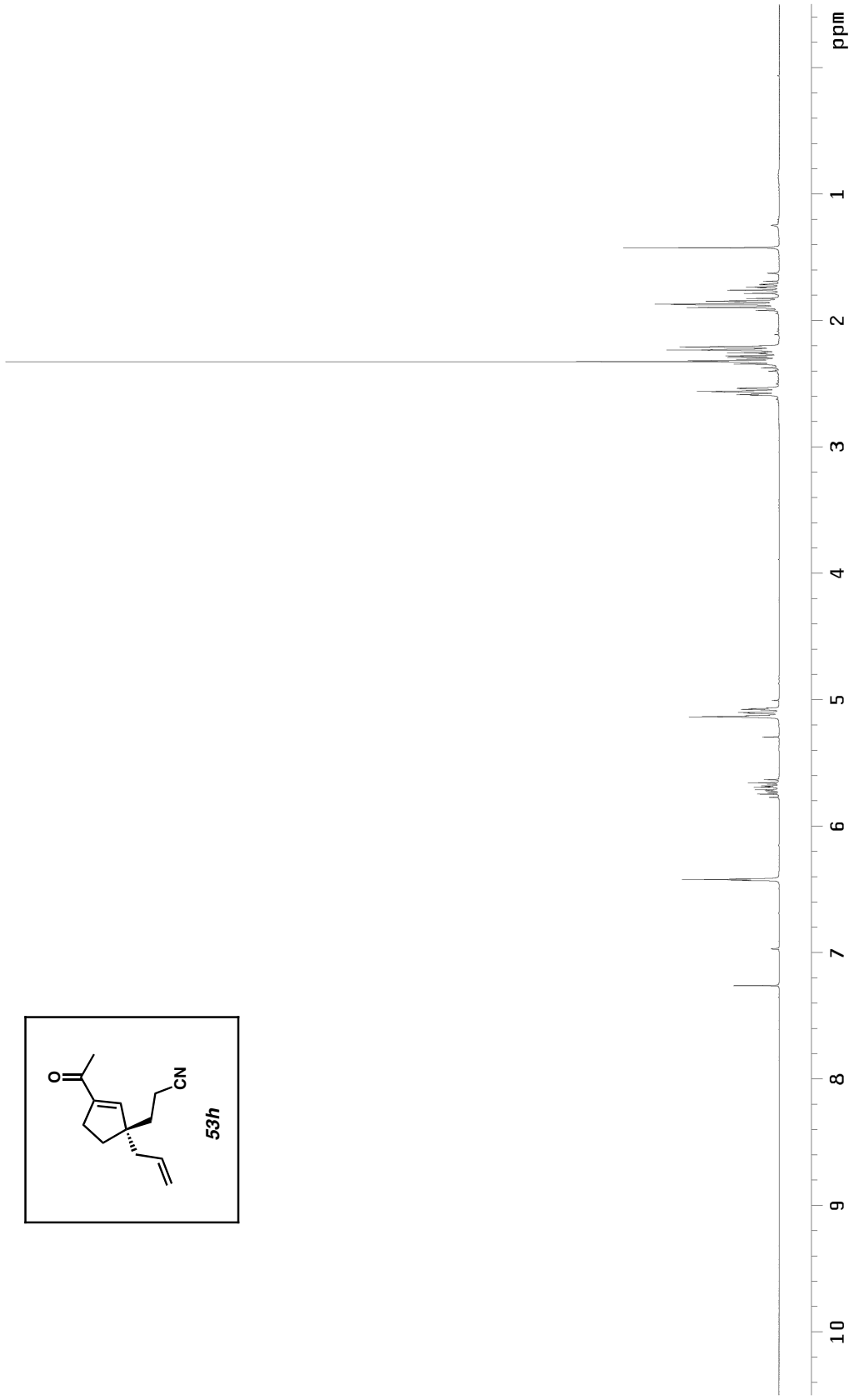


Figure A2.66.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **53h**.

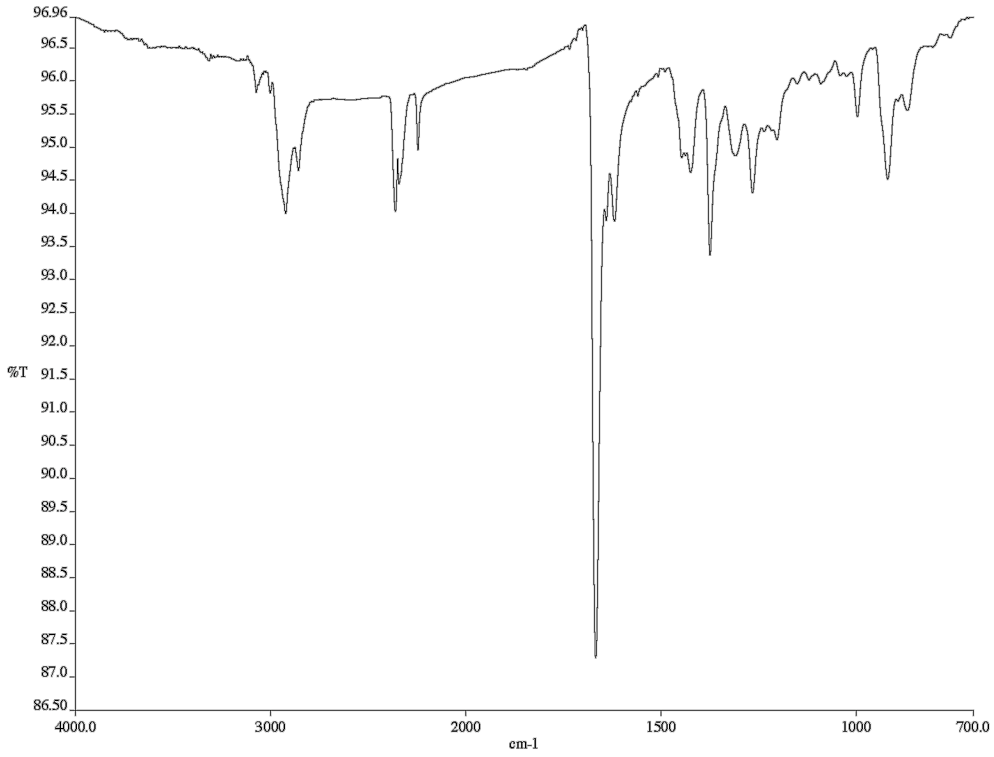


Figure A2.66.2. Infrared spectrum (thin film/NaCl) of compound **53h**.

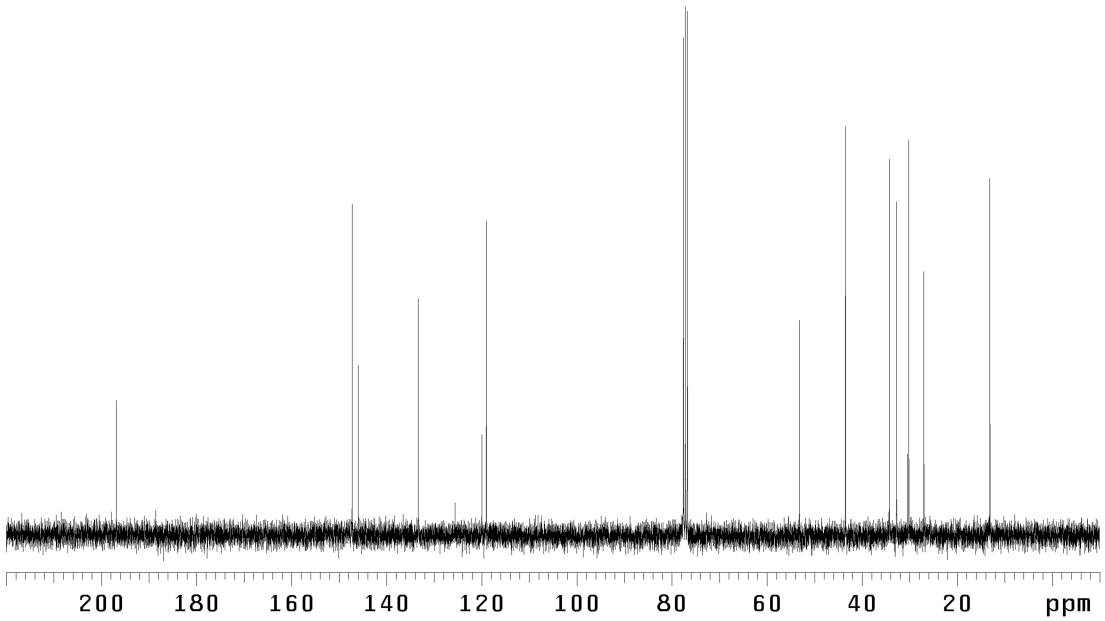


Figure A2.66.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **53h**.

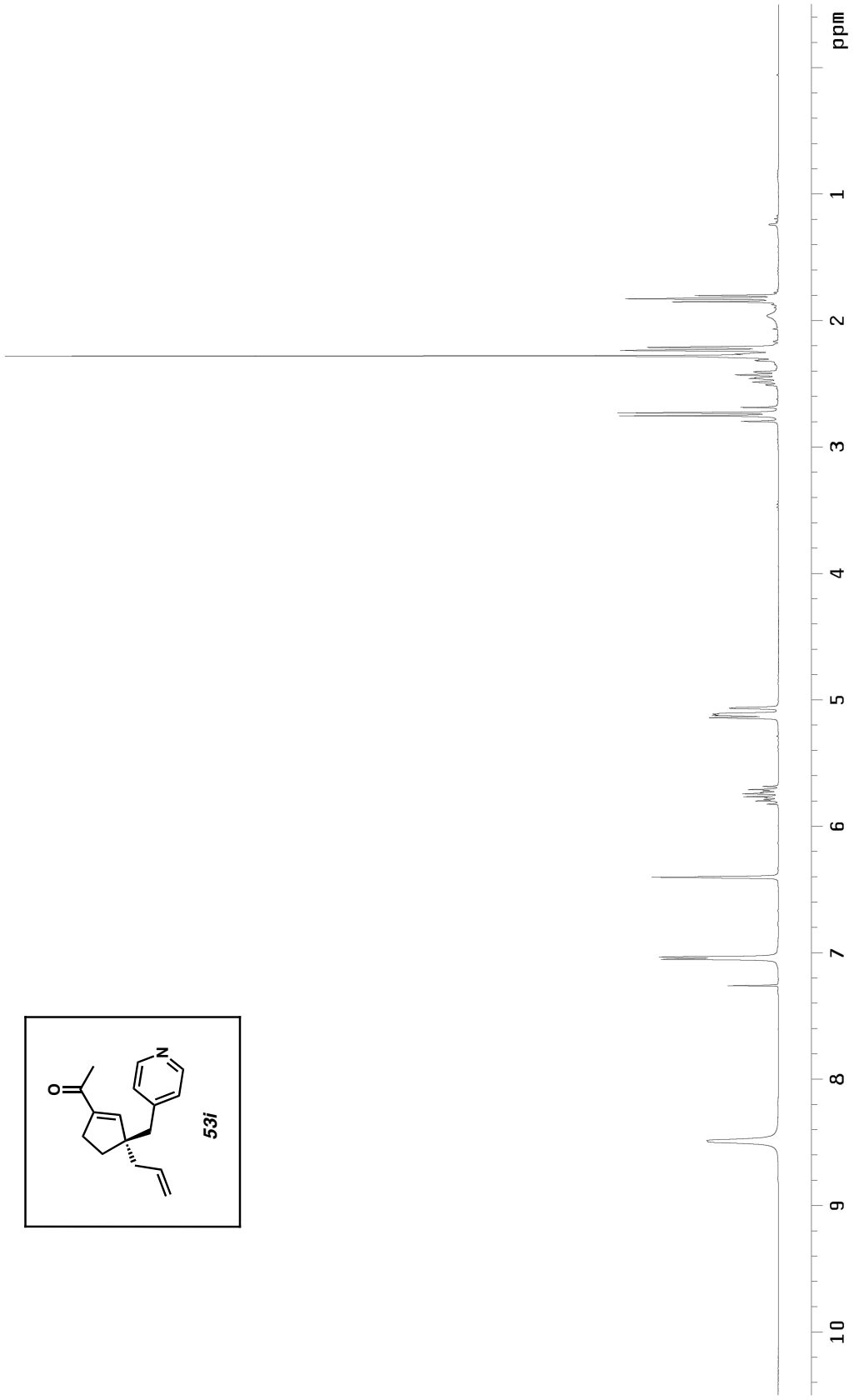


Figure A2.67.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **53i**.

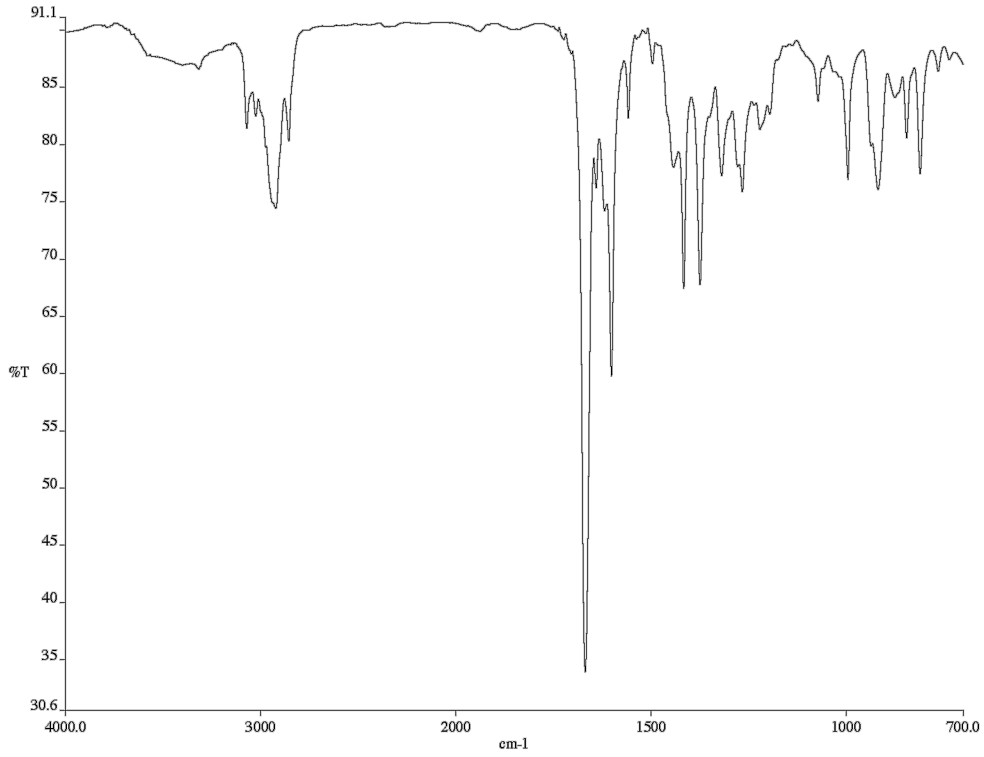


Figure A2.67.2. Infrared spectrum (thin film/NaCl) of compound **53i**.

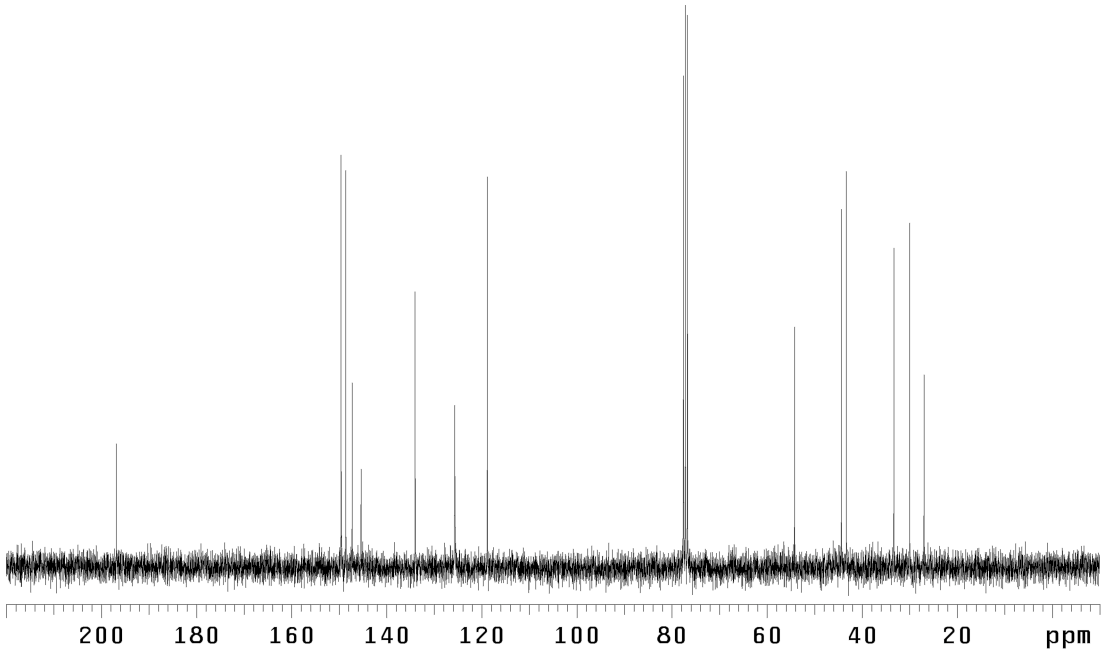


Figure A2.67.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **53i**.

Figure A2.68.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **53j**.

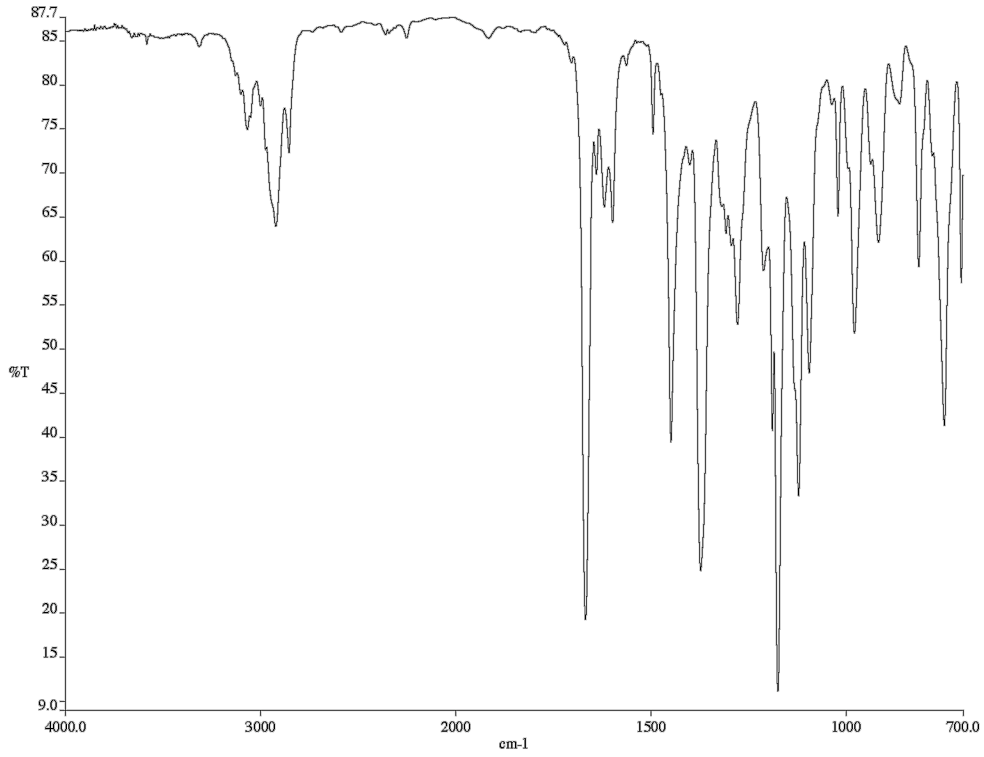


Figure A2.68.2. Infrared spectrum (thin film/NaCl) of compound **53j**.

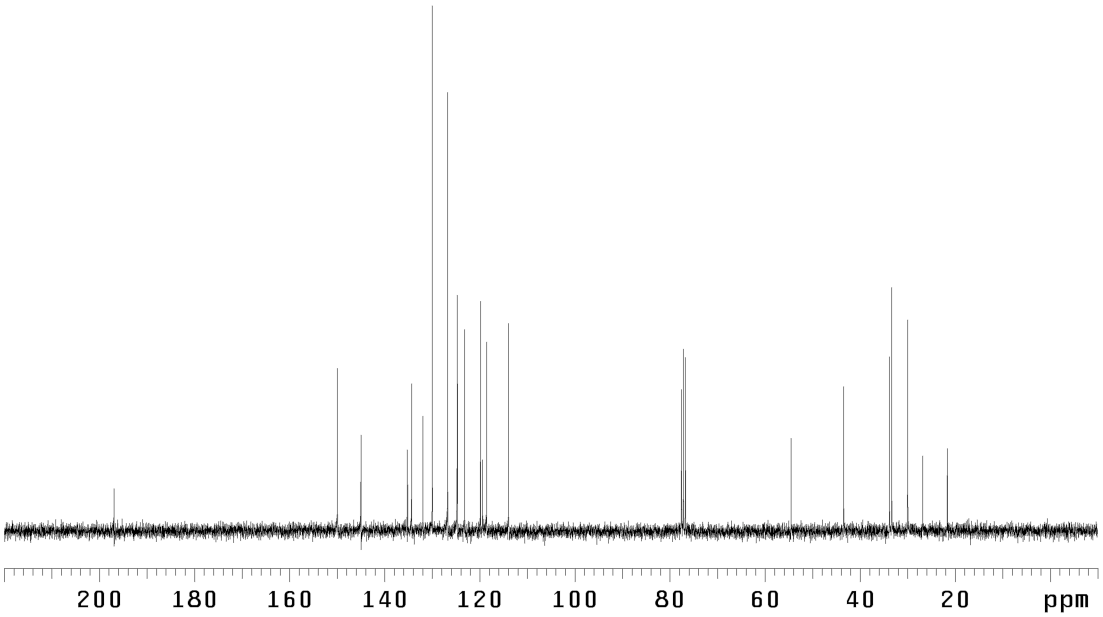


Figure A2.68.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **53j**.

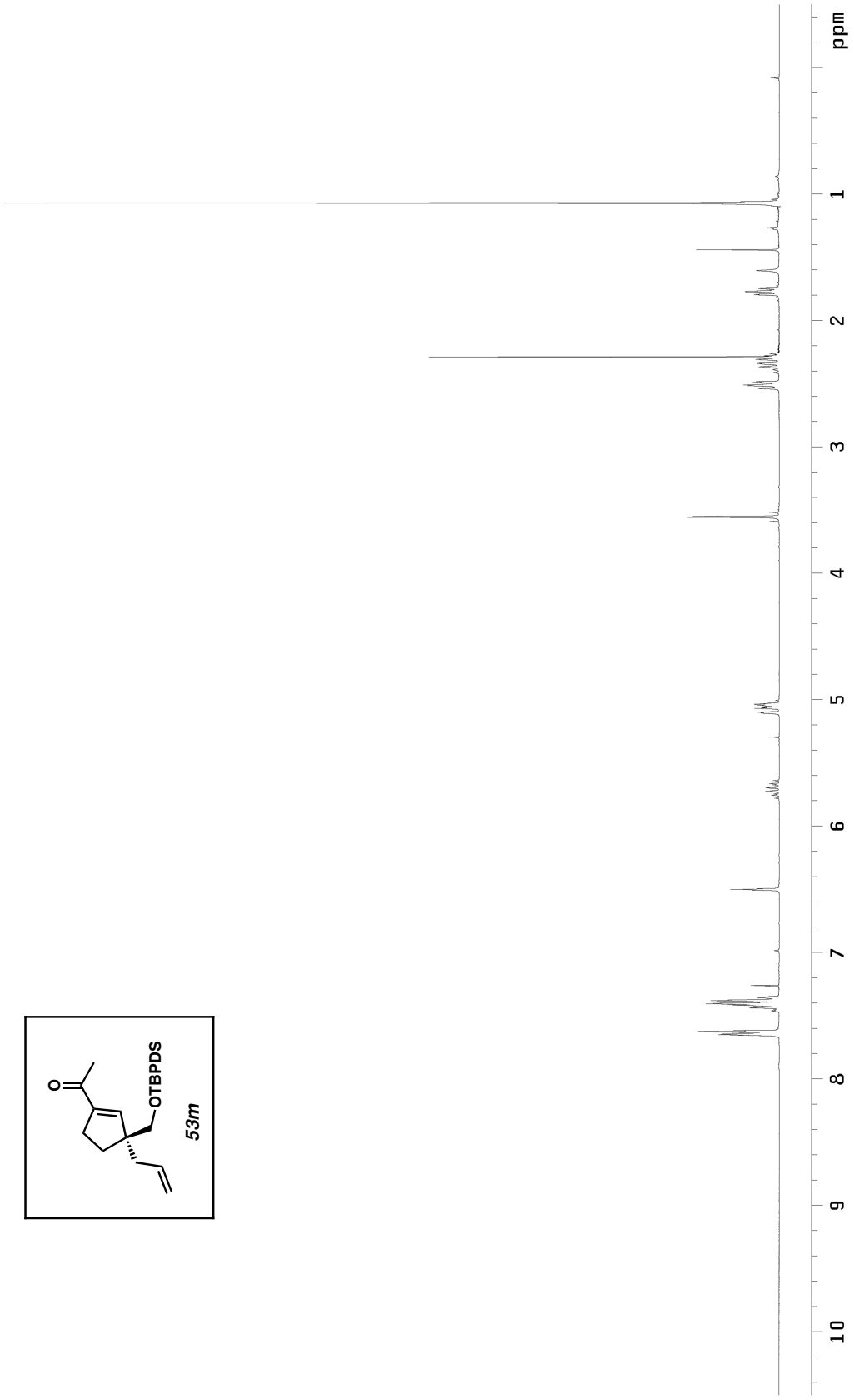


Figure A2.69.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **53m**.

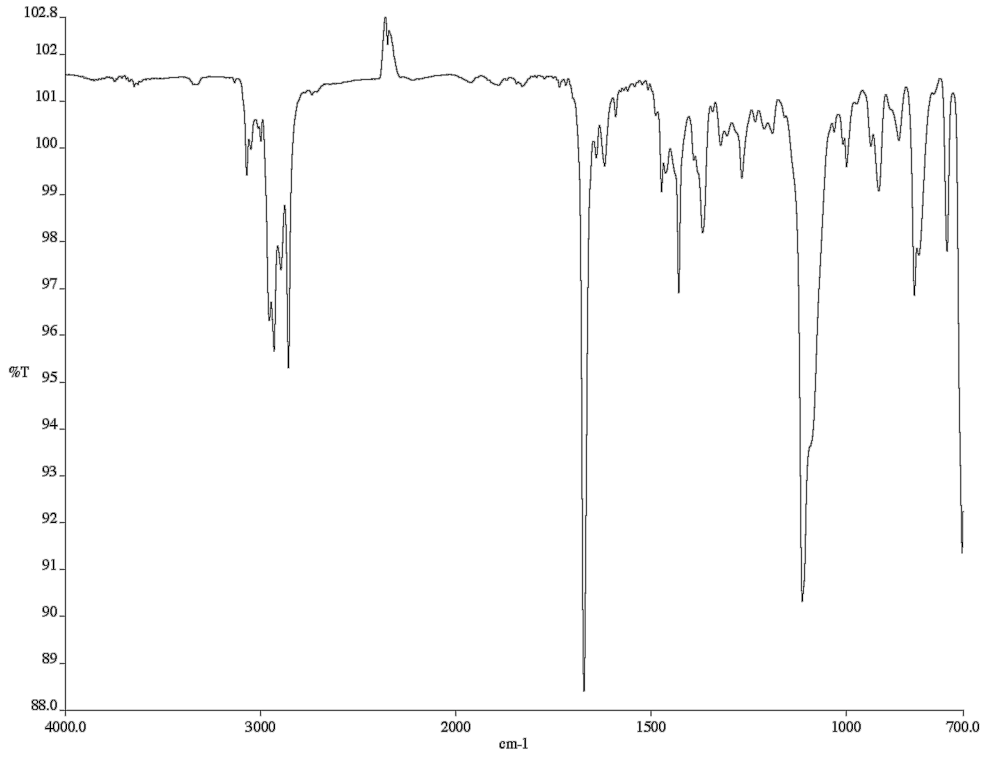


Figure A2.69.2. Infrared spectrum (thin film/NaCl) of compound **53m**.

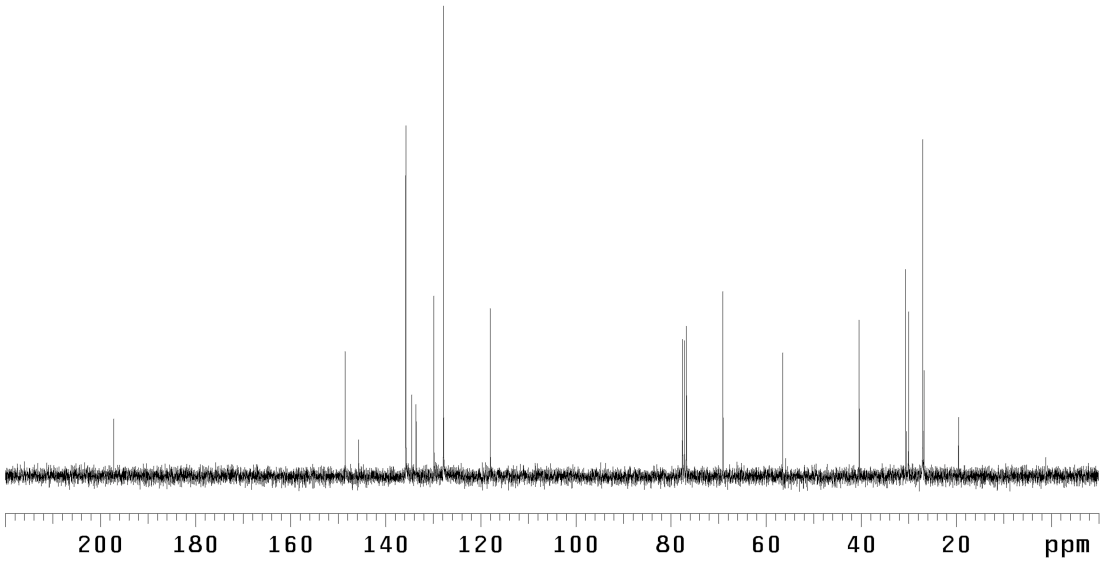


Figure A2.69.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **53m**.

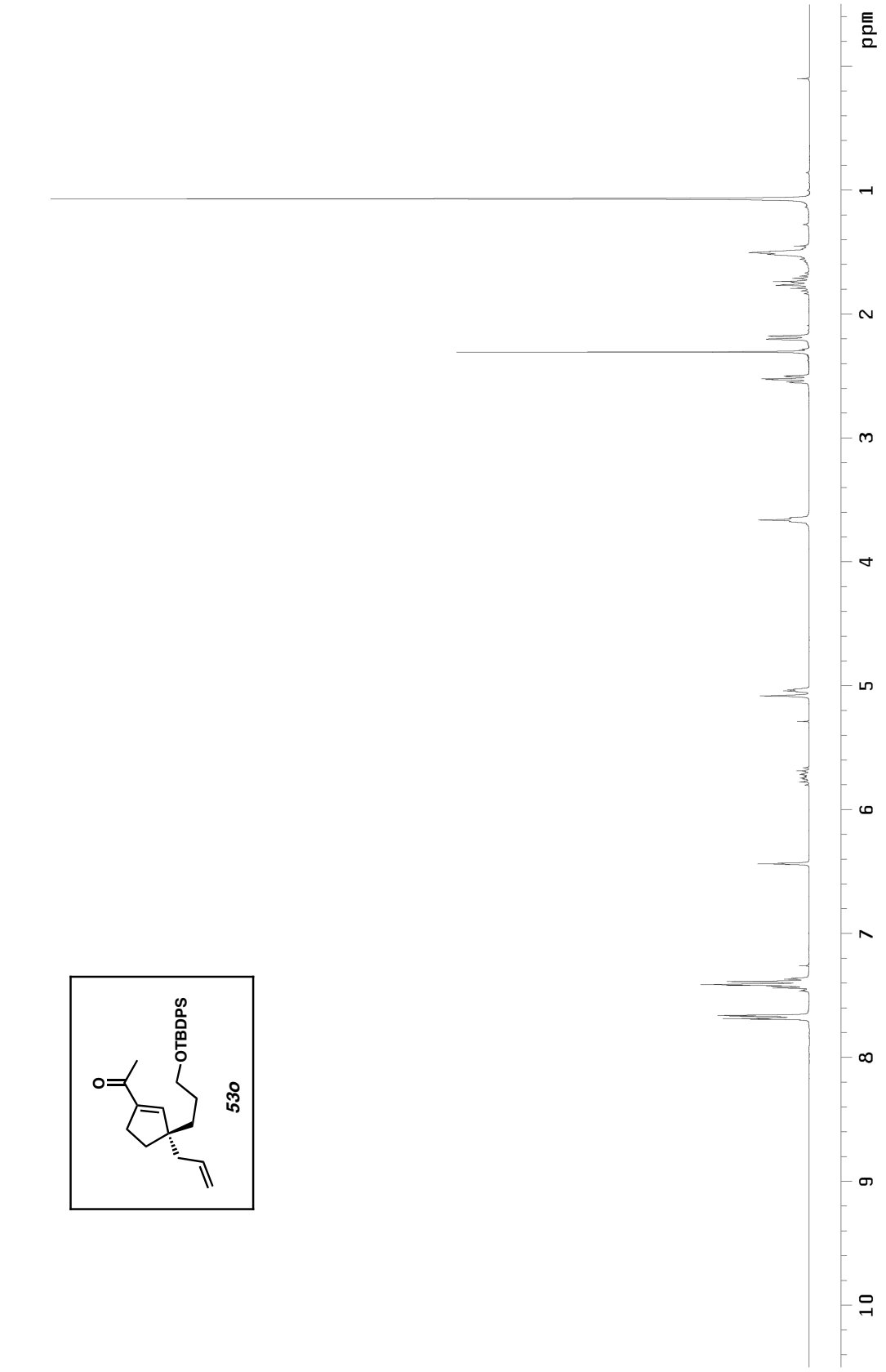


Figure A2.70.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **53o**.

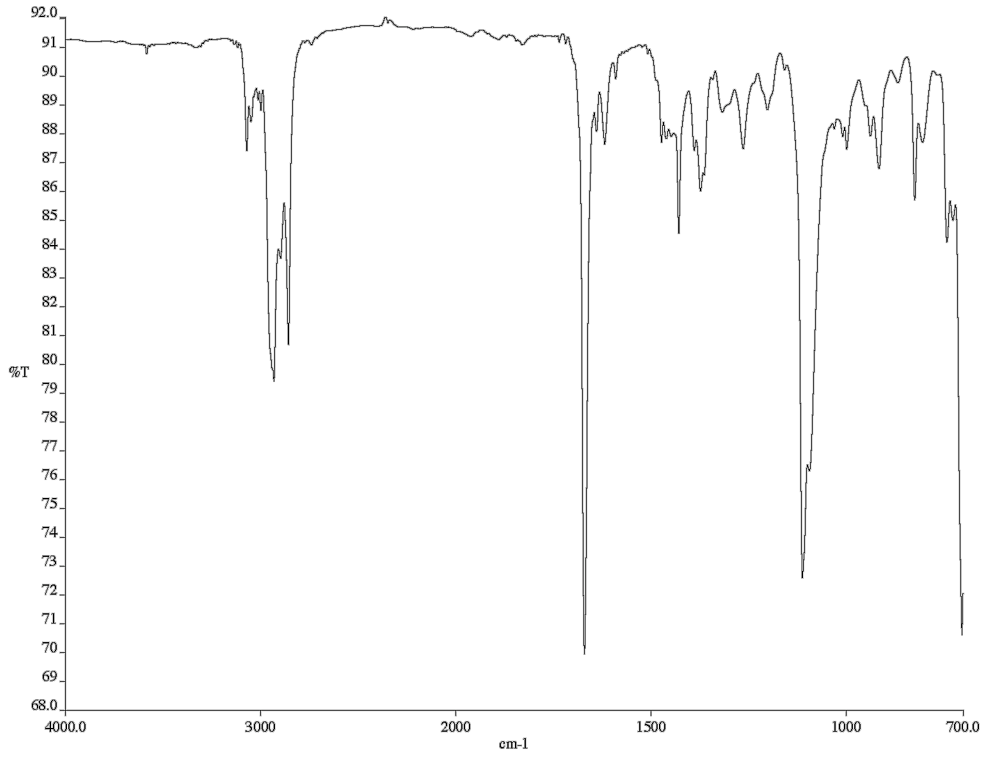


Figure A2.70.2. Infrared spectrum (thin film/NaCl) of compound **53o**.

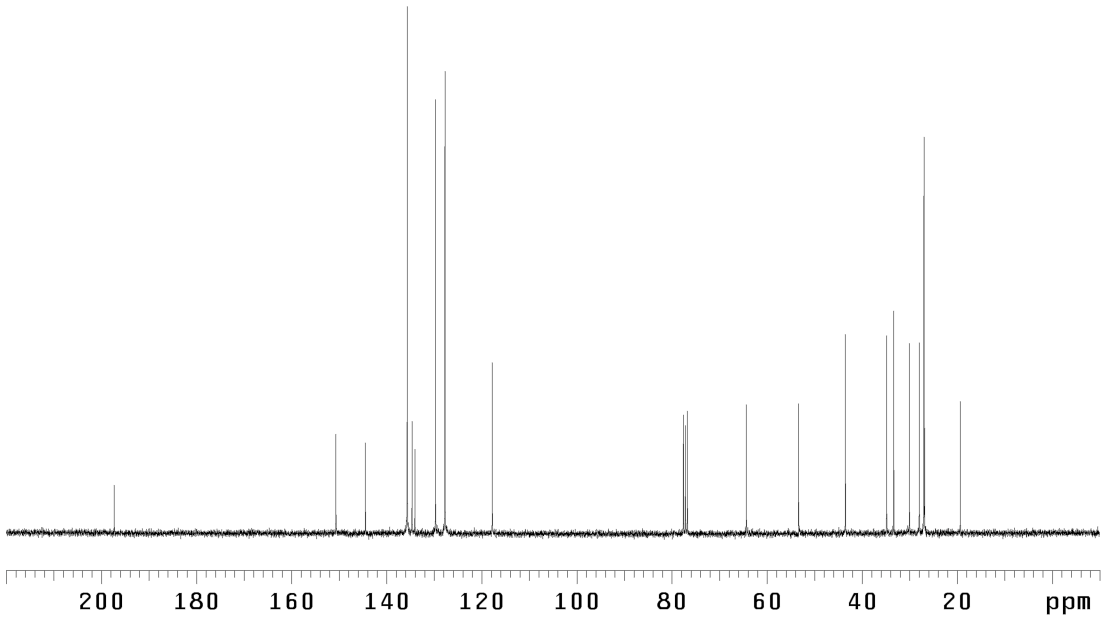


Figure A2.70.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **53o**.

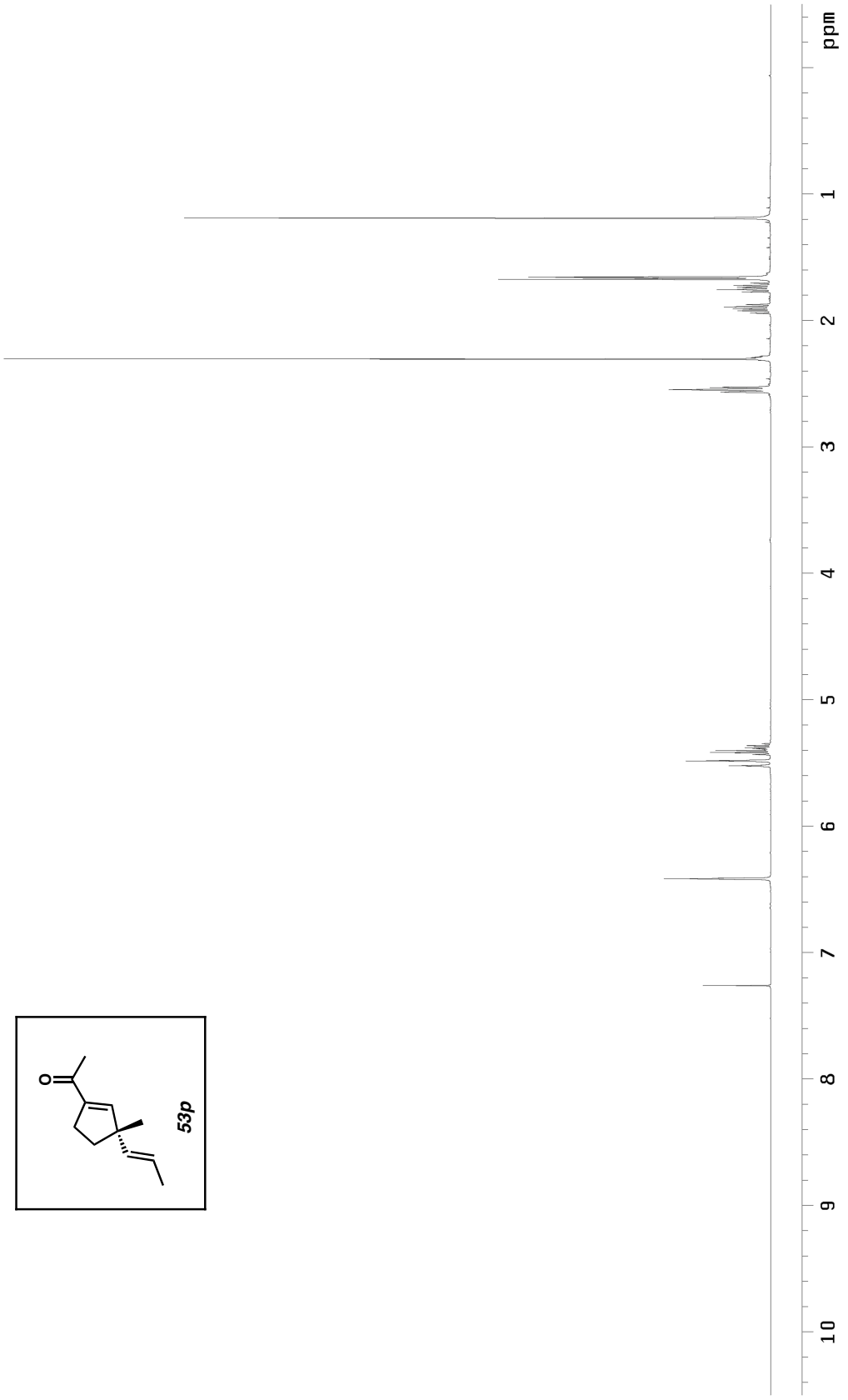


Figure A2.71.1. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **53p**.

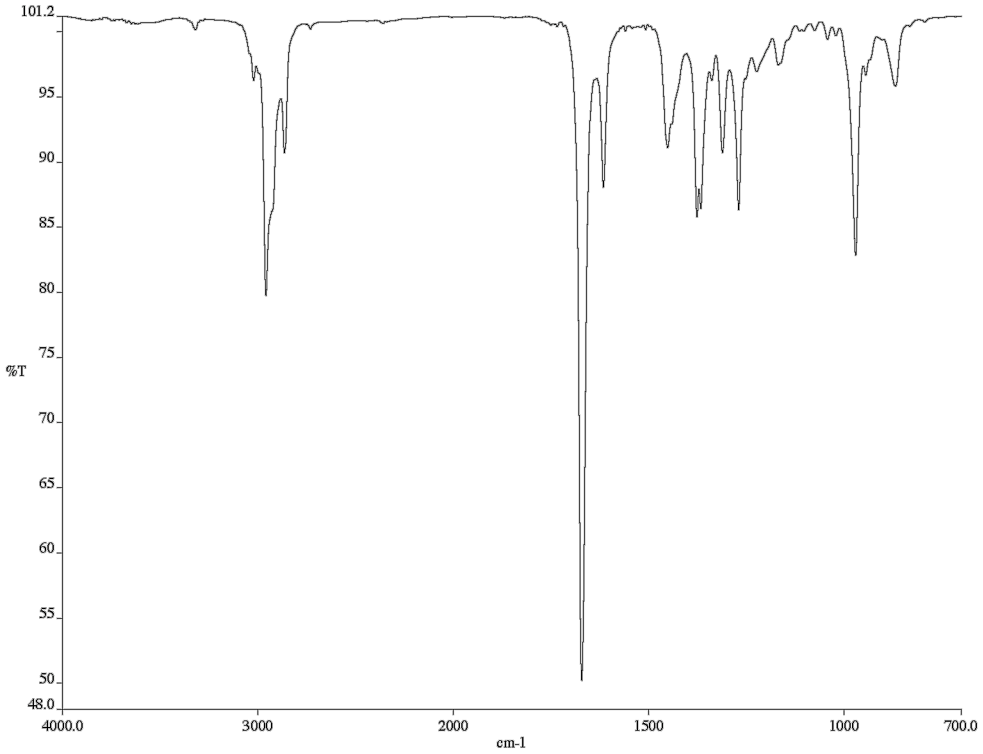


Figure A2.71.2. Infrared spectrum (thin film/NaCl) of compound **53p**.

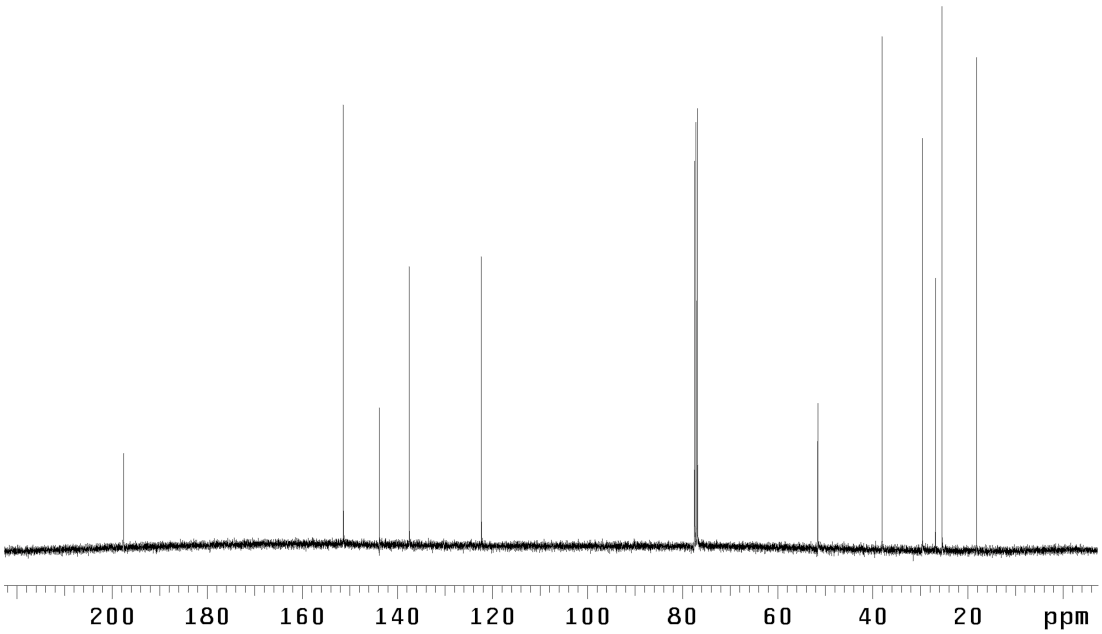


Figure A2.71.3. ^{13}C NMR (100 MHz, $CDCl_3$) of compound **53p**.

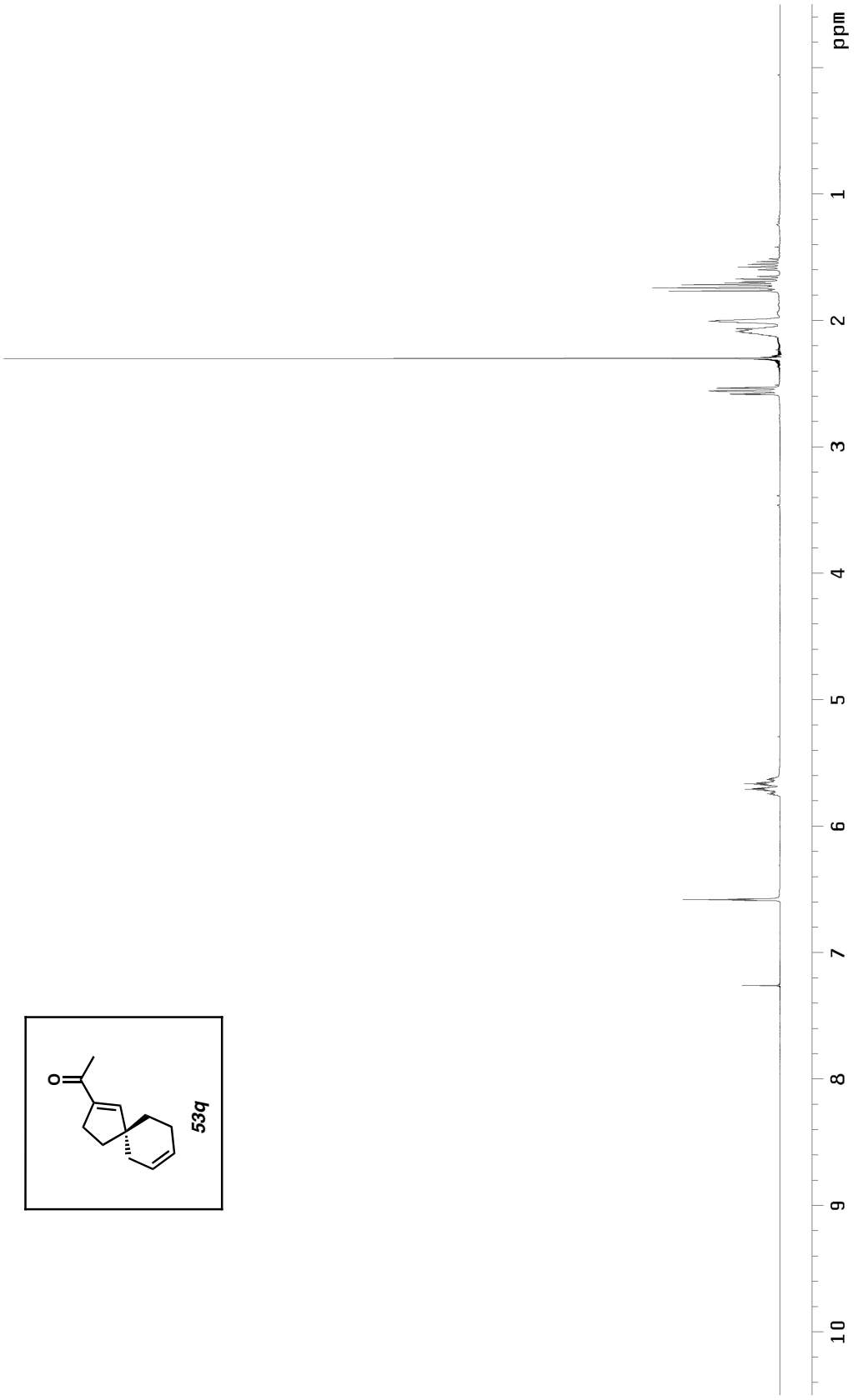


Figure A2.72.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **53q**.

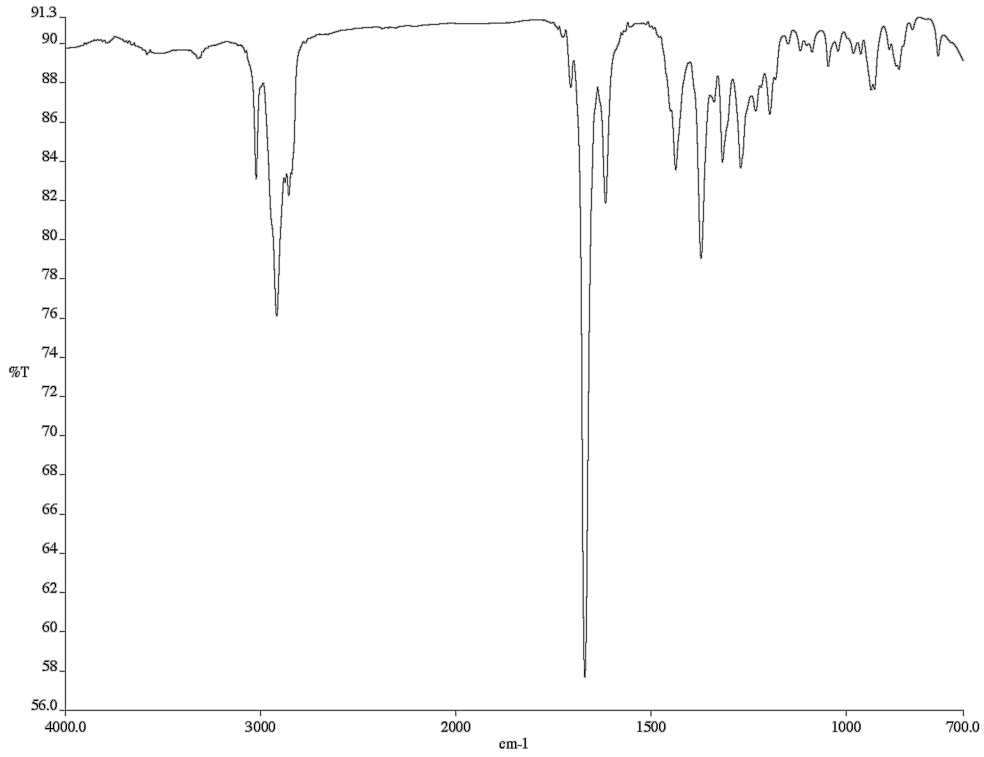


Figure A2.72.2. Infrared spectrum (thin film/NaCl) of compound **53q**.

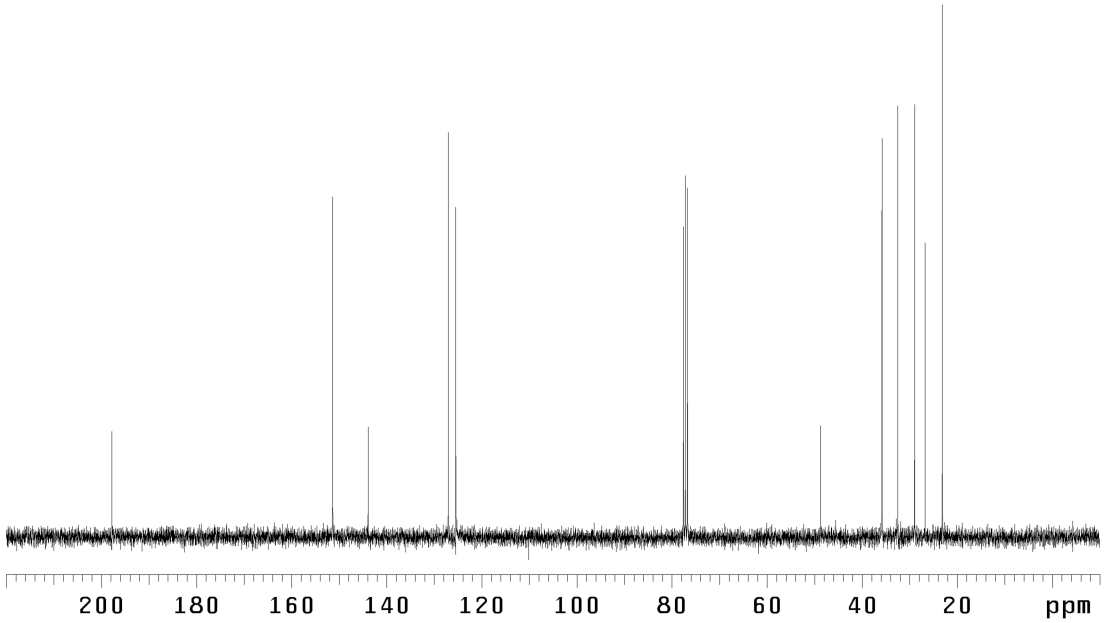


Figure A2.72.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **53q**.

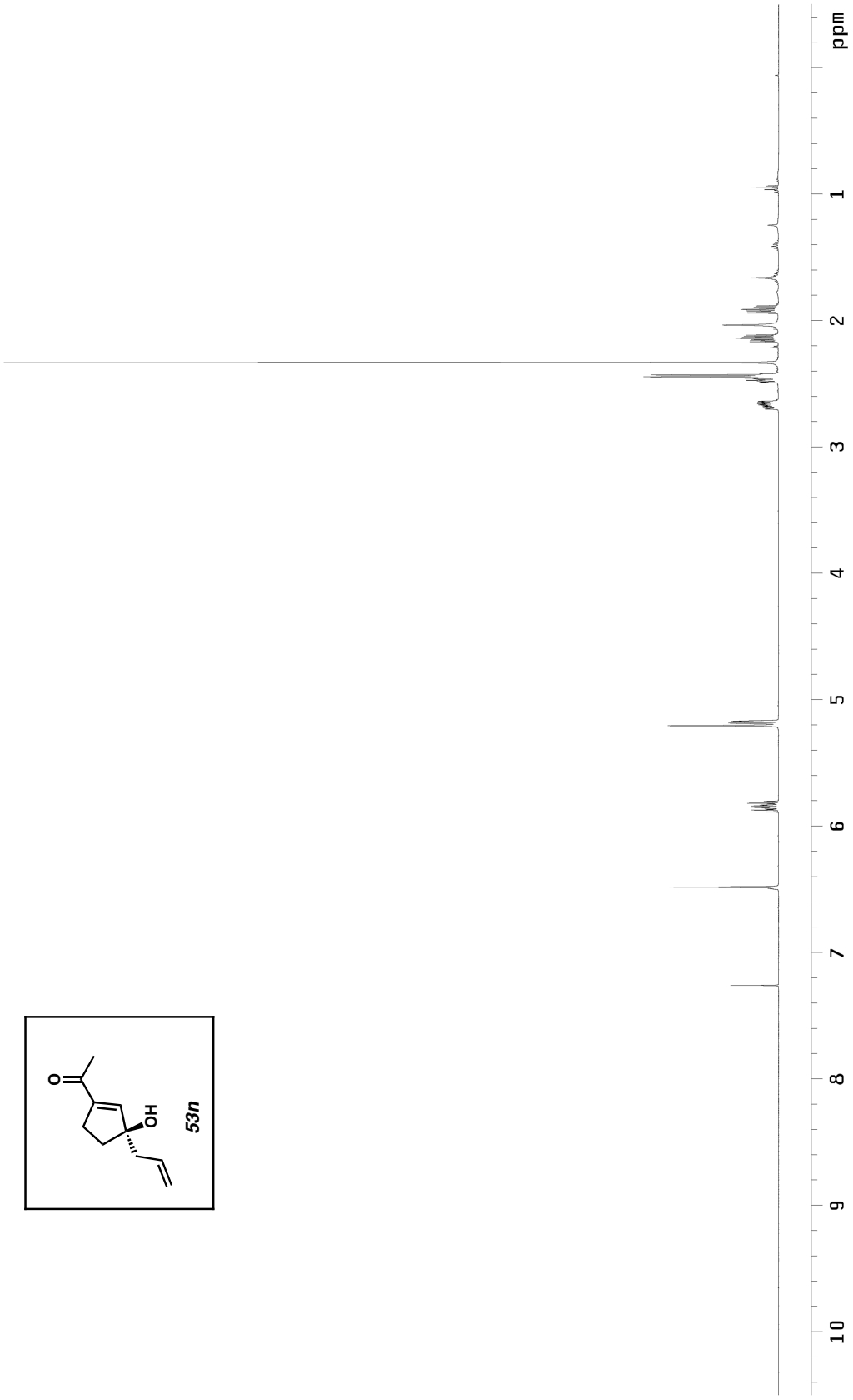


Figure A2.73.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **53n**.

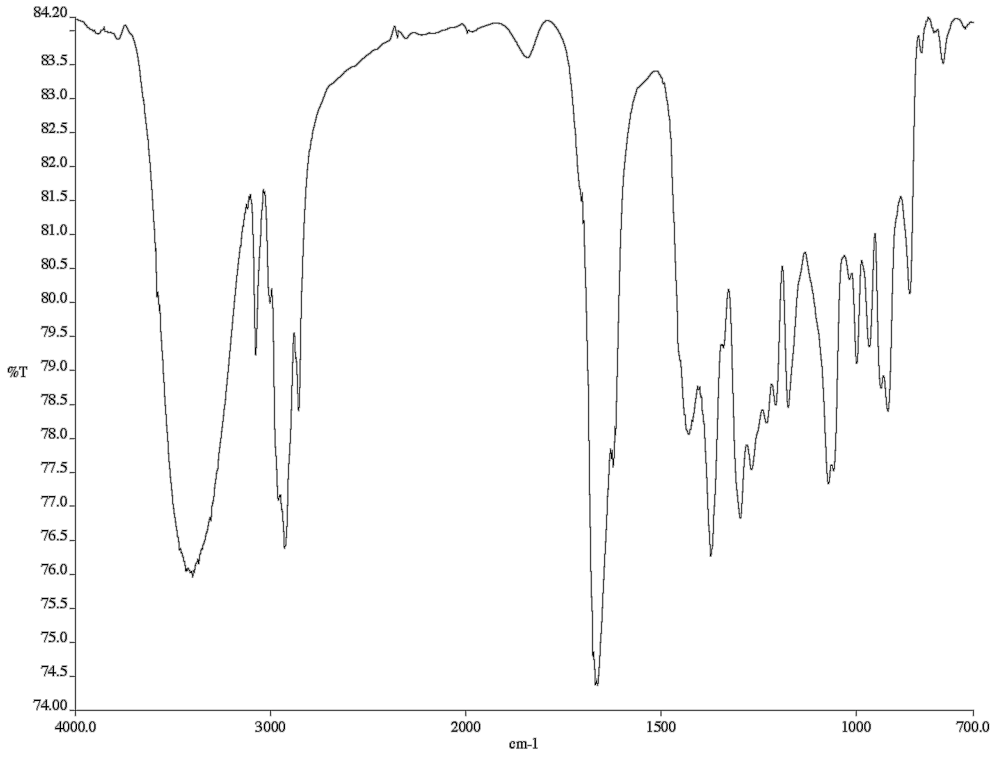


Figure A2.73.2. Infrared spectrum (thin film/NaCl) of compound **53n**.

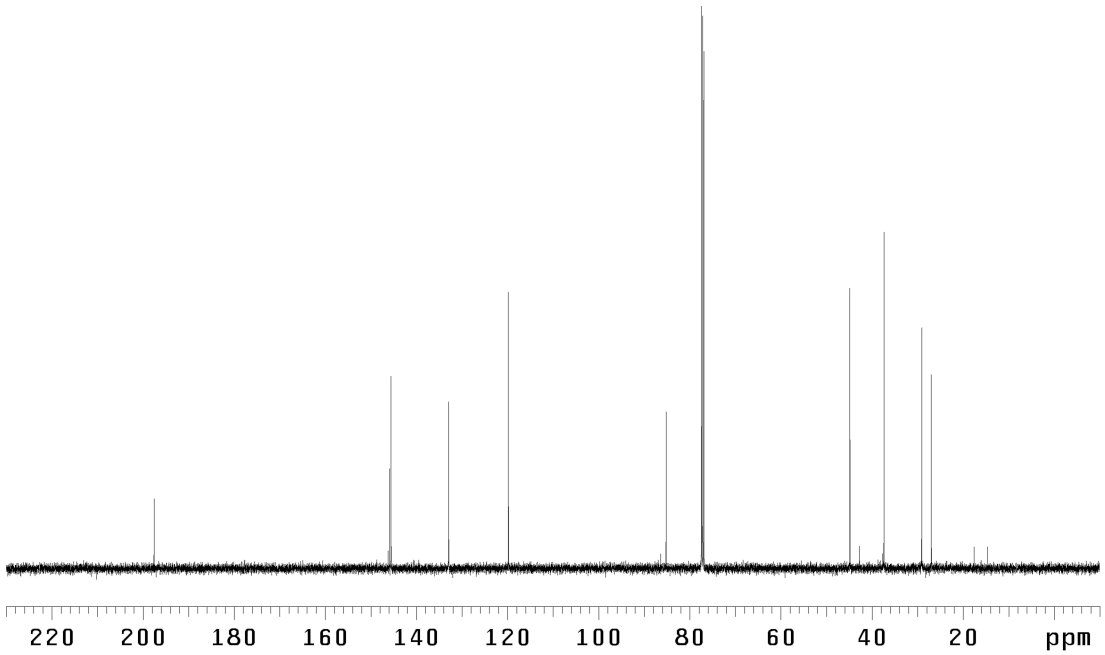


Figure A2.73.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **53n**.

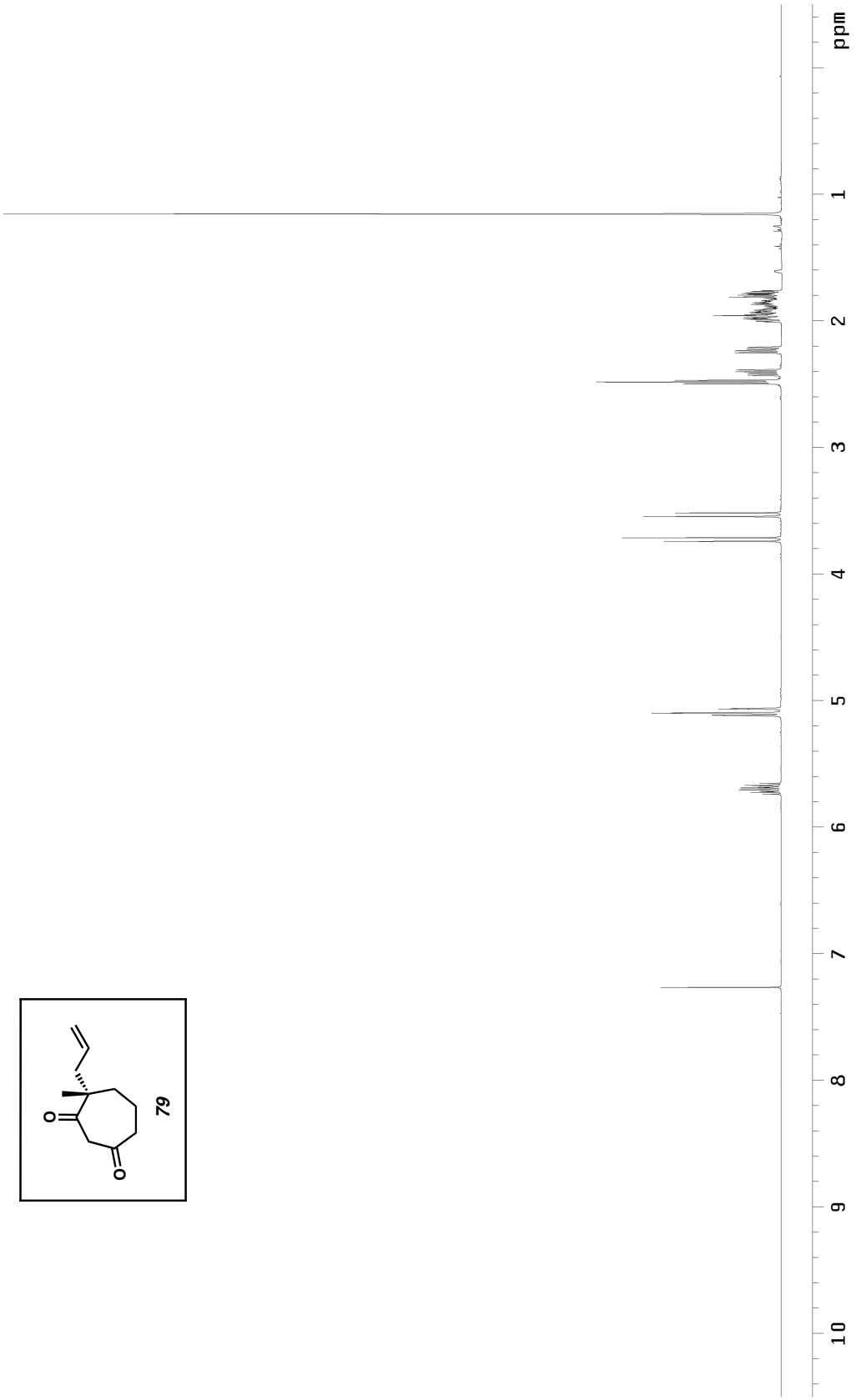


Figure A2.74.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **79**.

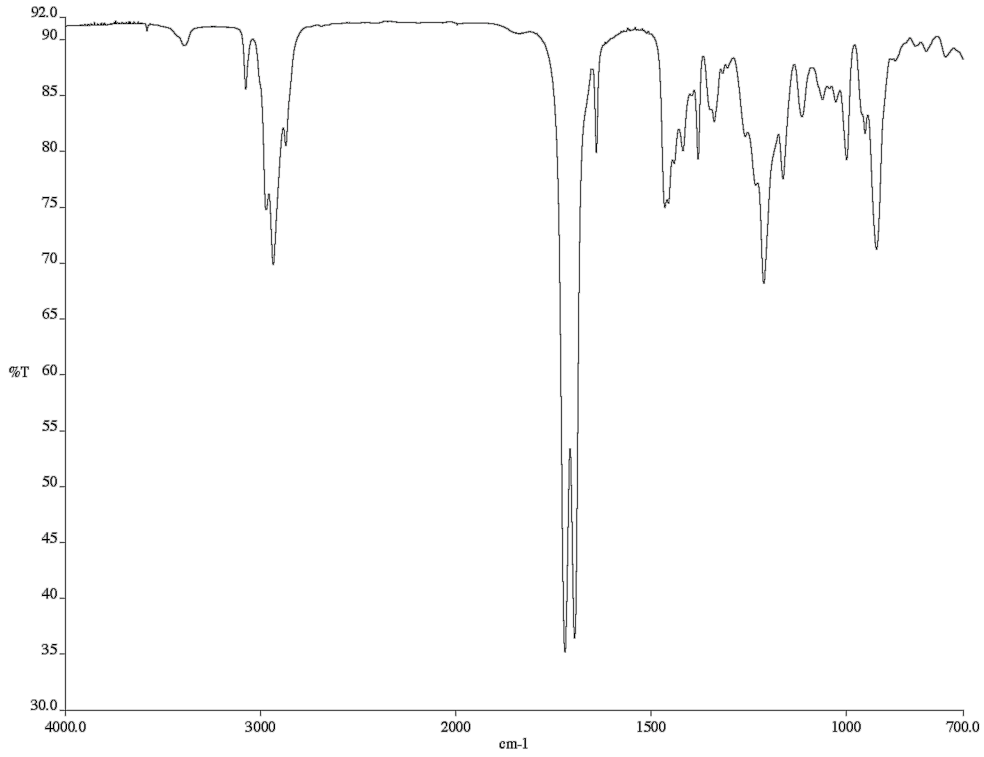


Figure A2.74.2. Infrared spectrum (thin film/NaCl) of compound **79**.

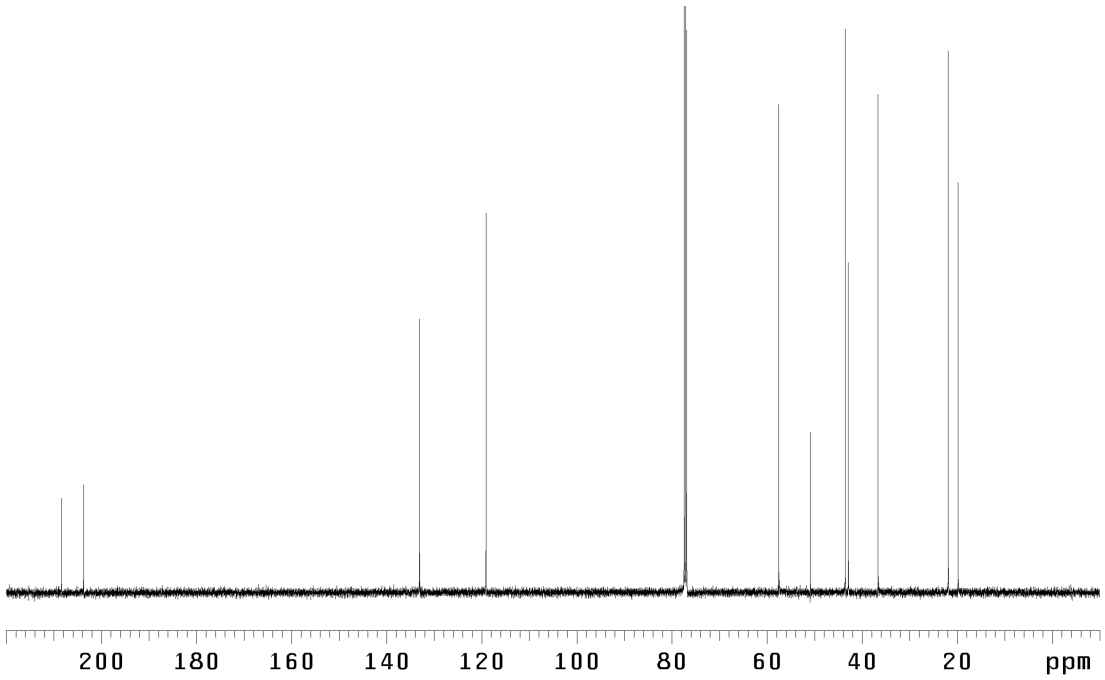


Figure A2.74.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **79**.

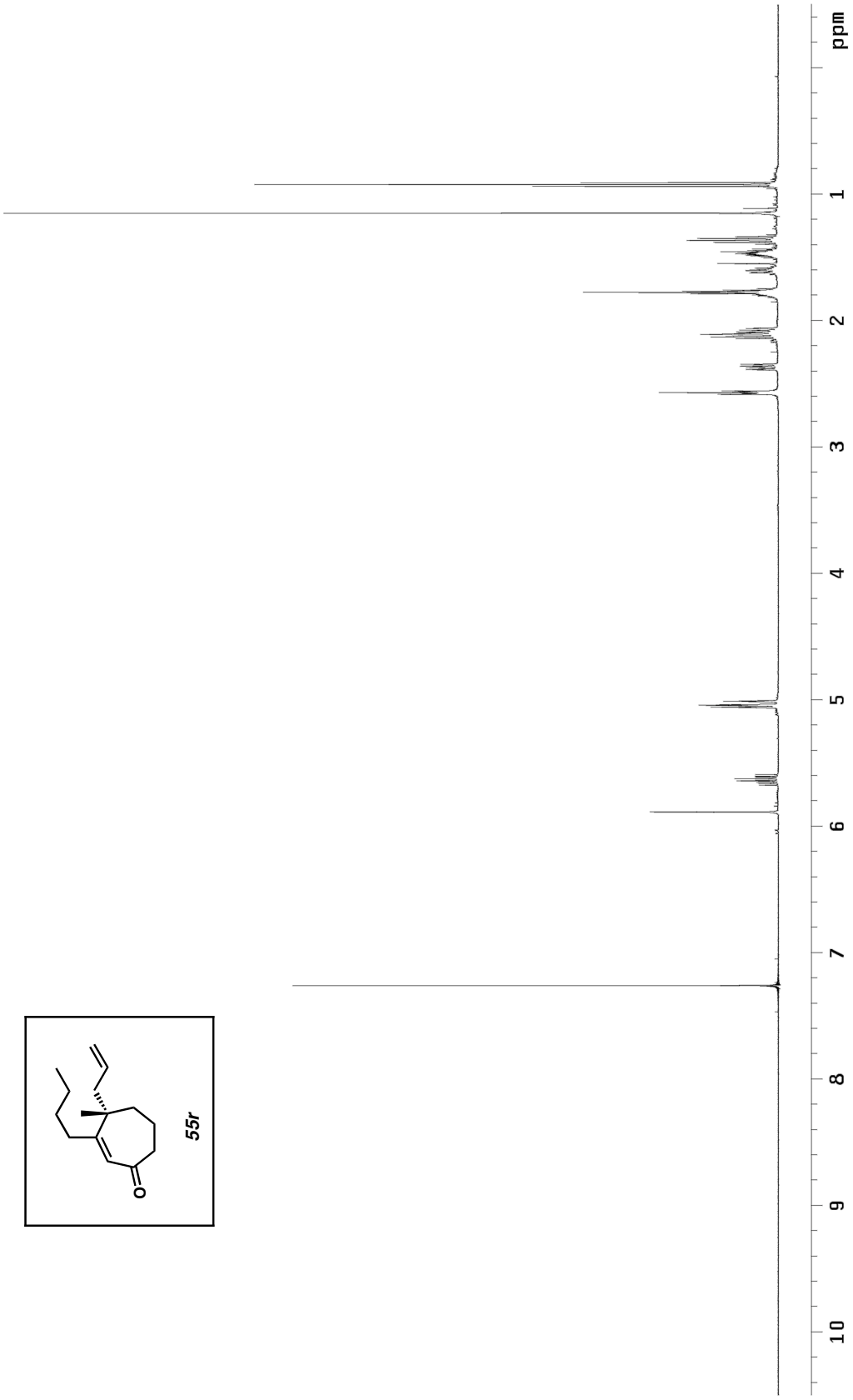


Figure A2.75.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **55r**.

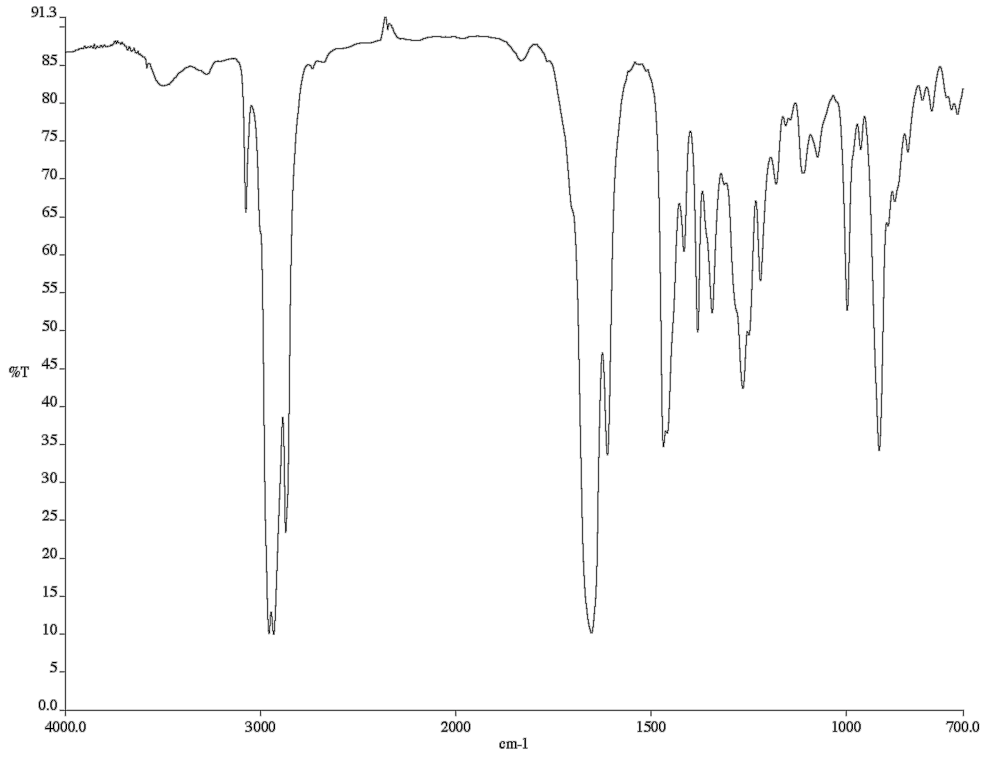


Figure A2.75.2. Infrared spectrum (thin film/NaCl) of compound **55r**.

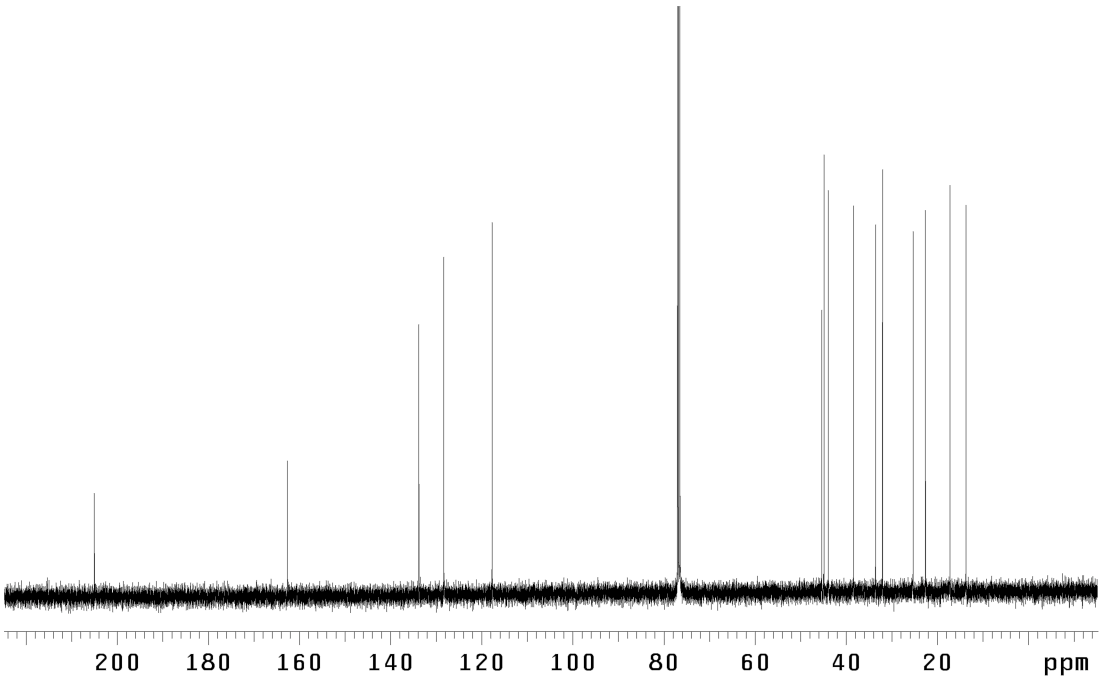


Figure A2.75.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **55r**.

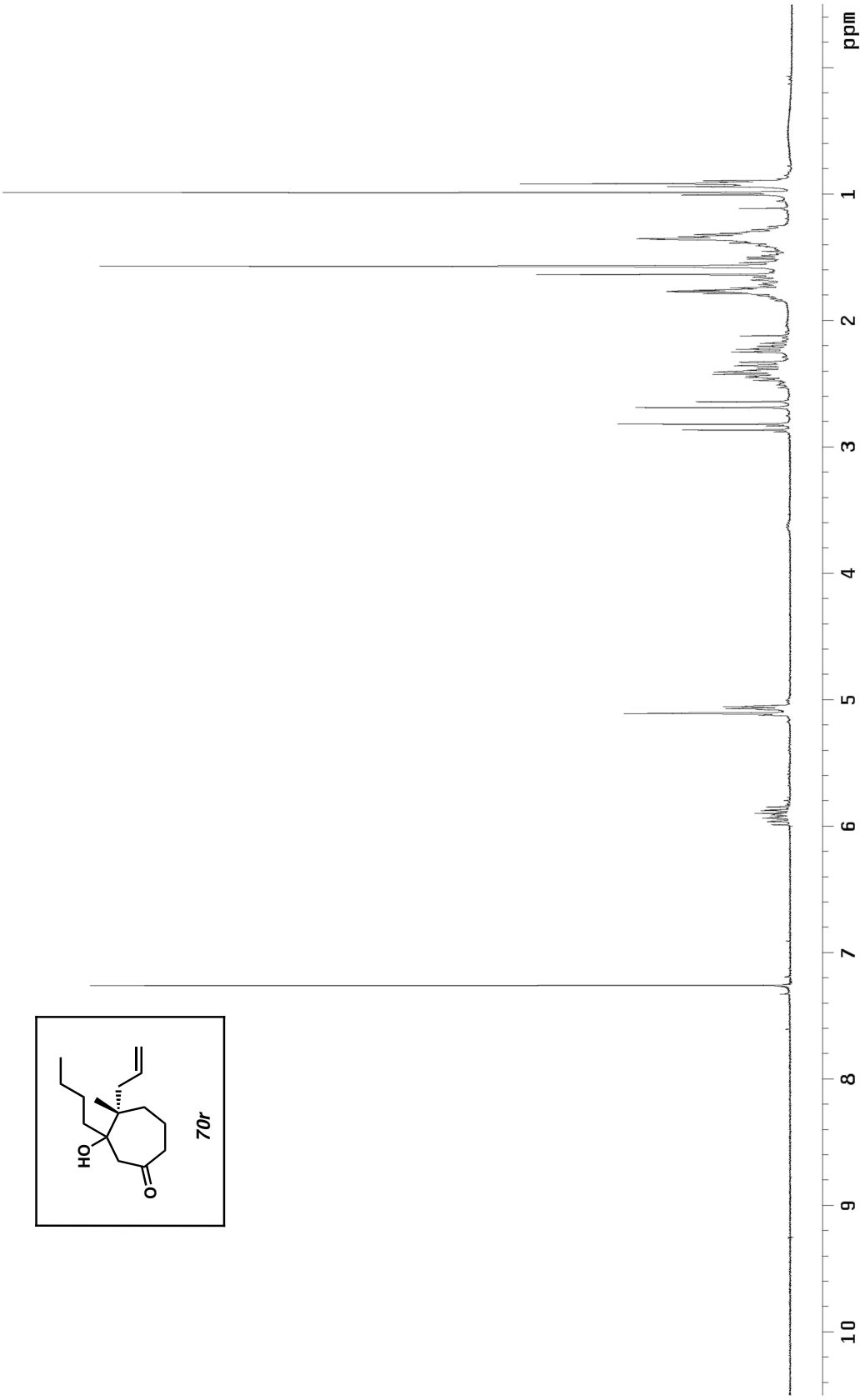


Figure A2.76.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **70r**.

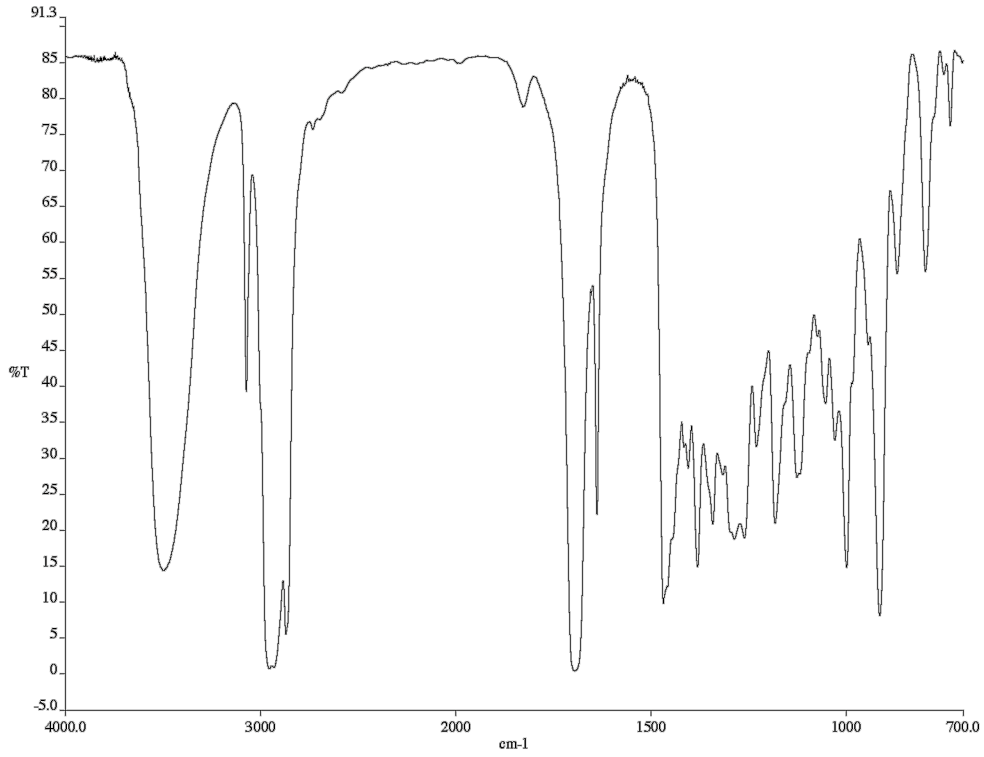


Figure A2.76.2. Infrared spectrum (thin film/NaCl) of compound **70r**.

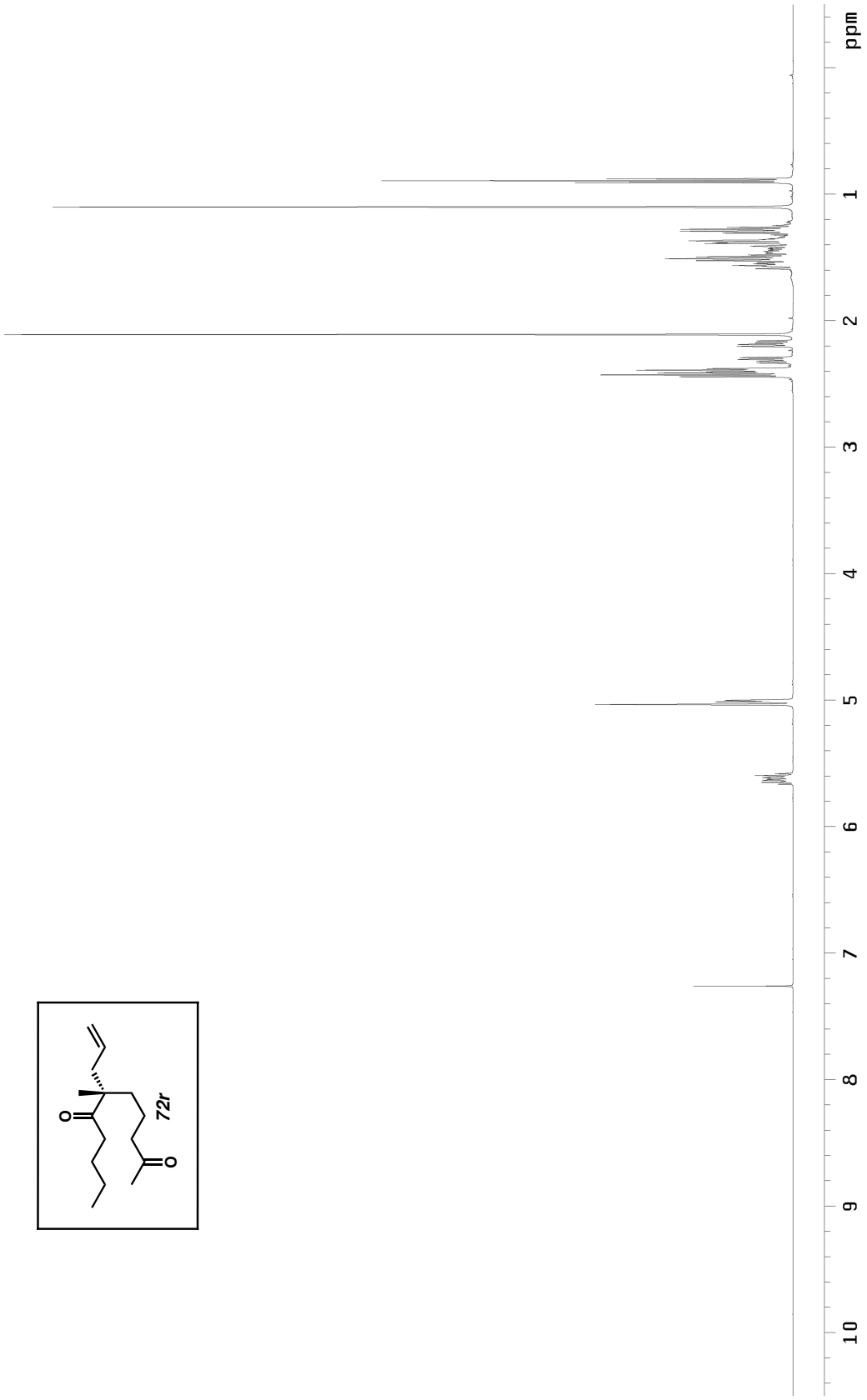


Figure A2.77.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **72r**.

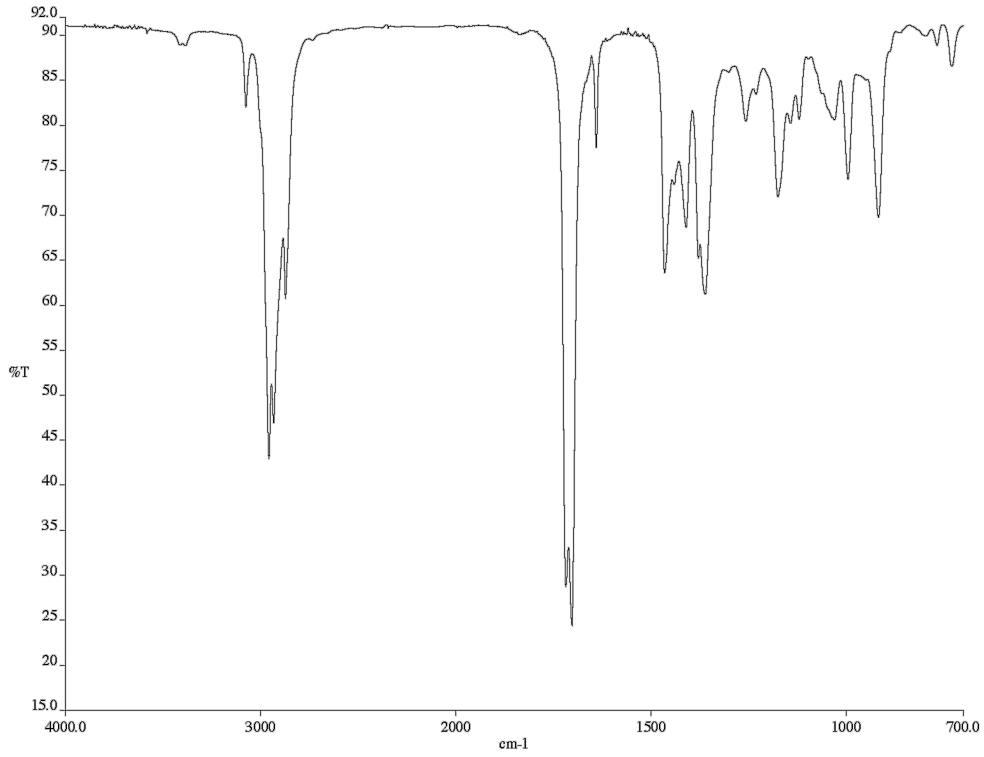


Figure A2.77.2. Infrared spectrum (thin film/NaCl) of compound **72r**.

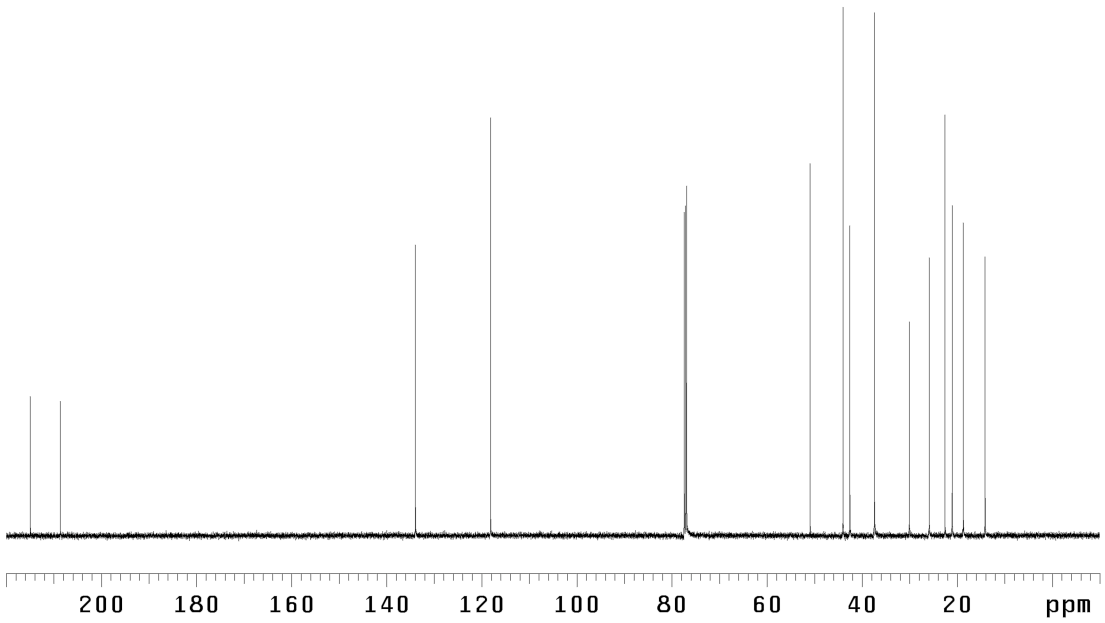


Figure A2.77.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **72r**.

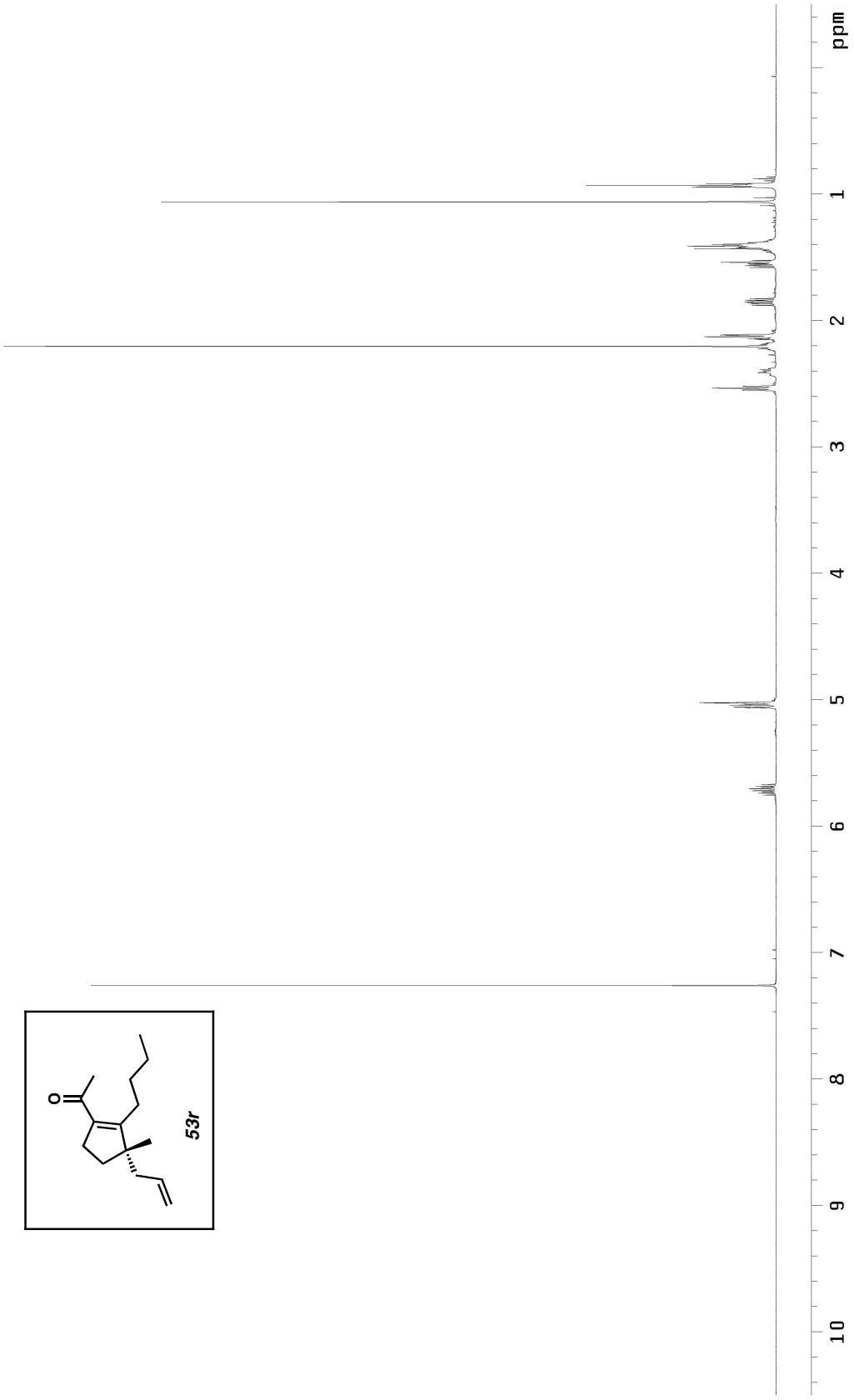


Figure A2.78.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **53r**.

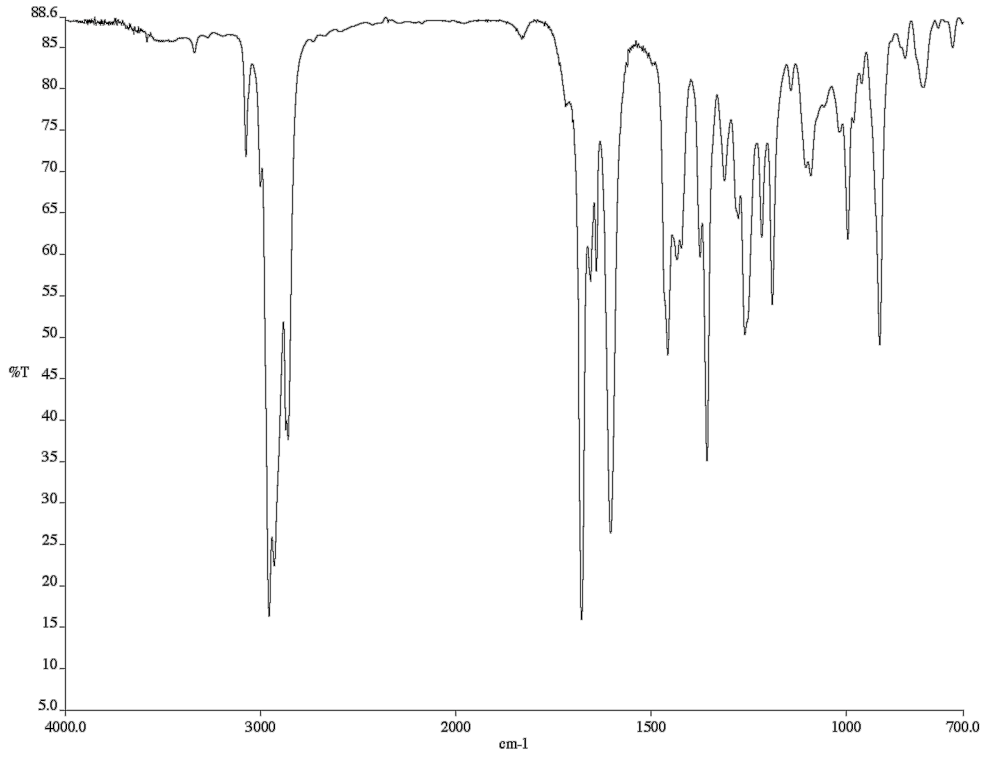


Figure A2.78.2. Infrared spectrum (thin film/NaCl) of compound **53r**.

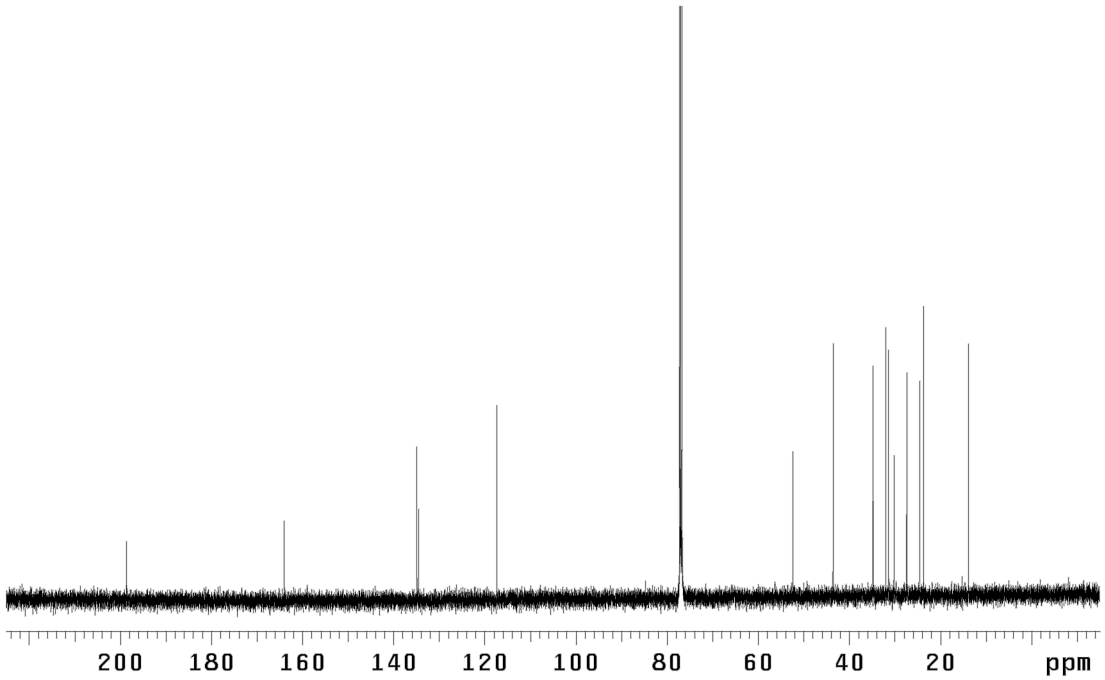


Figure A2.78.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **53r**.

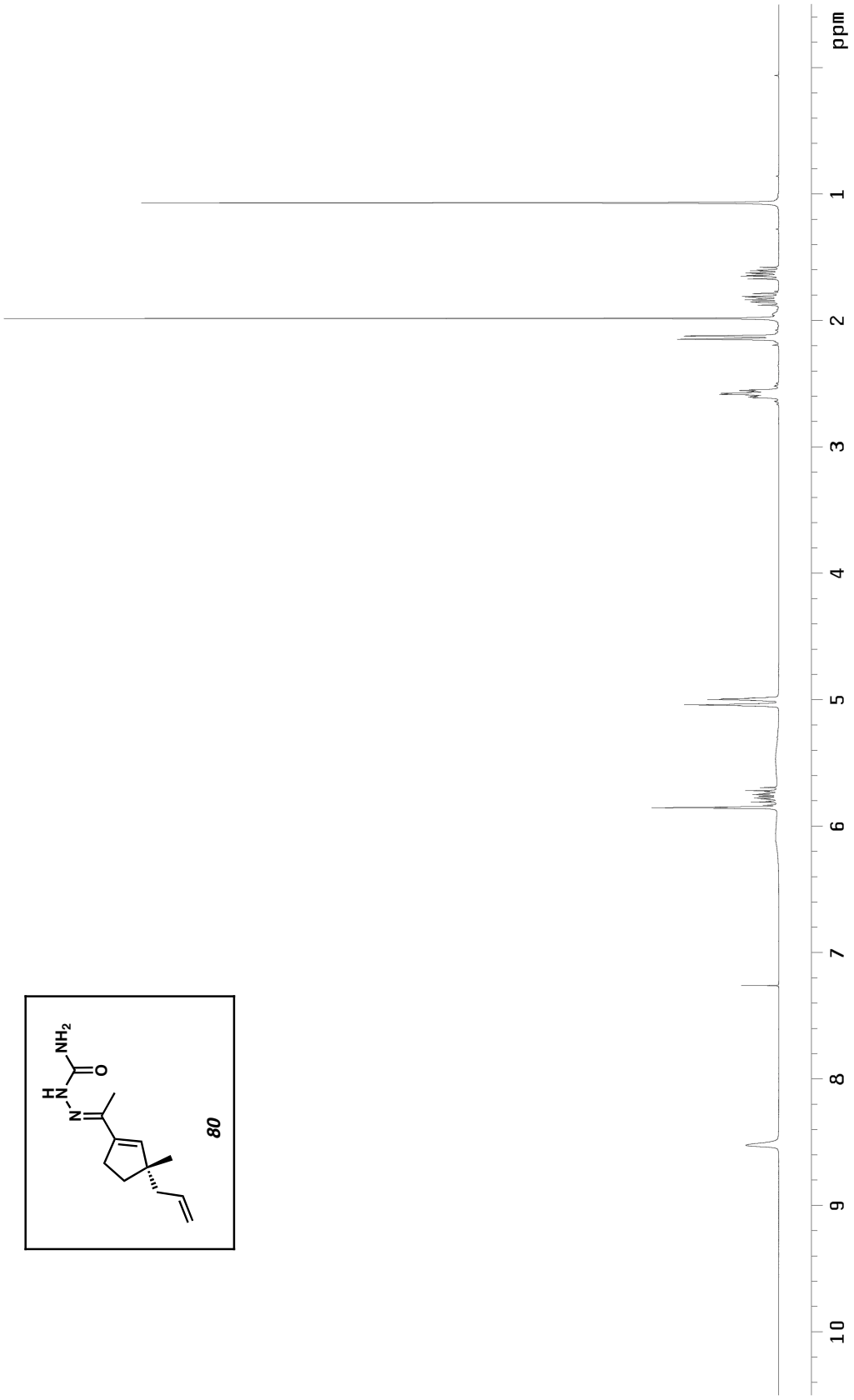


Figure A2.79.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **80**.

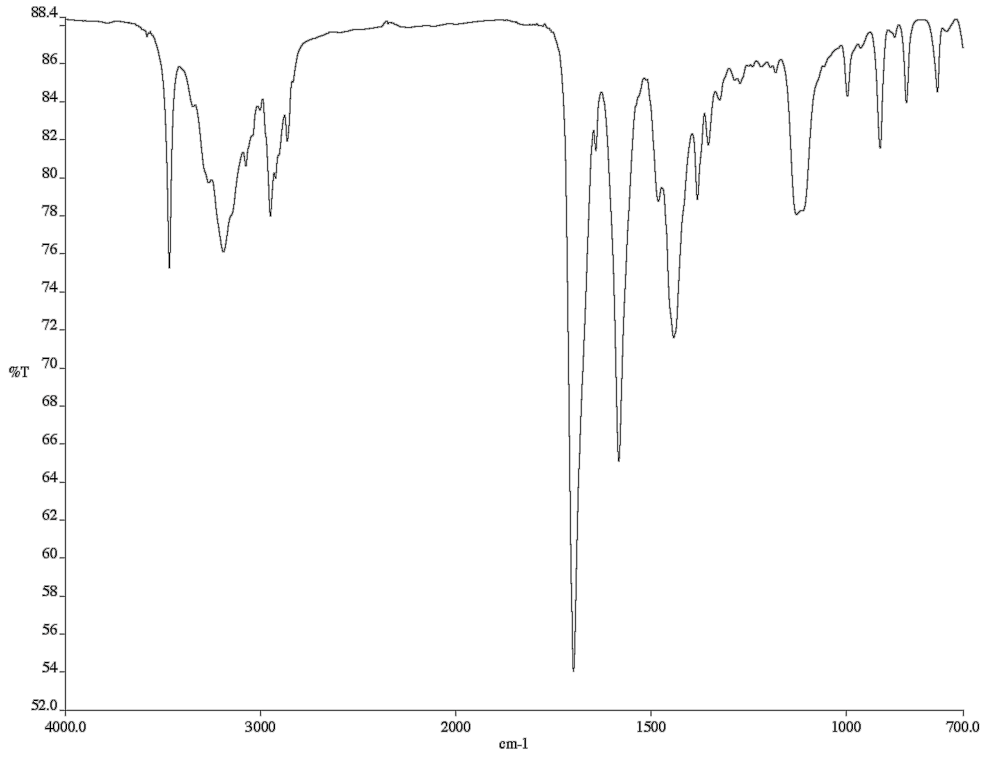


Figure A2.79.2. Infrared spectrum (thin film/NaCl) of compound **80**.

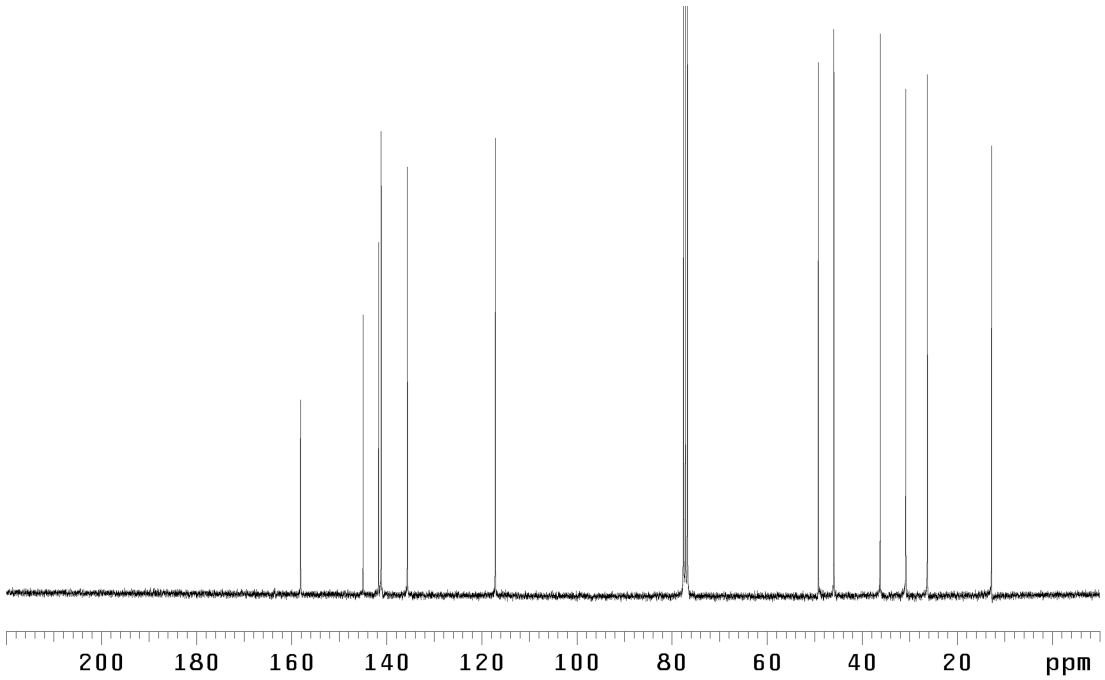


Figure A2.79.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **80**.

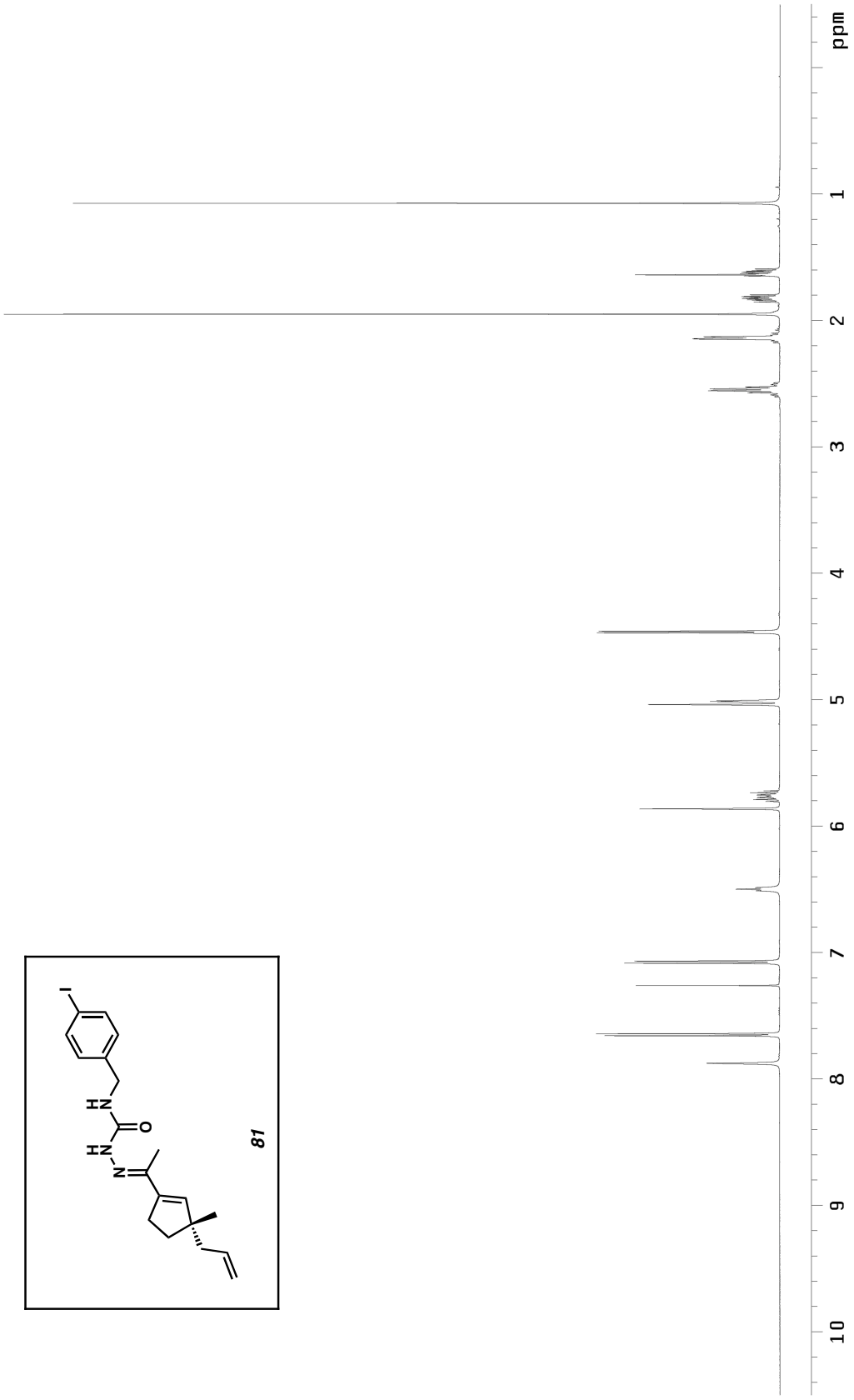


Figure A2.80.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **81**.

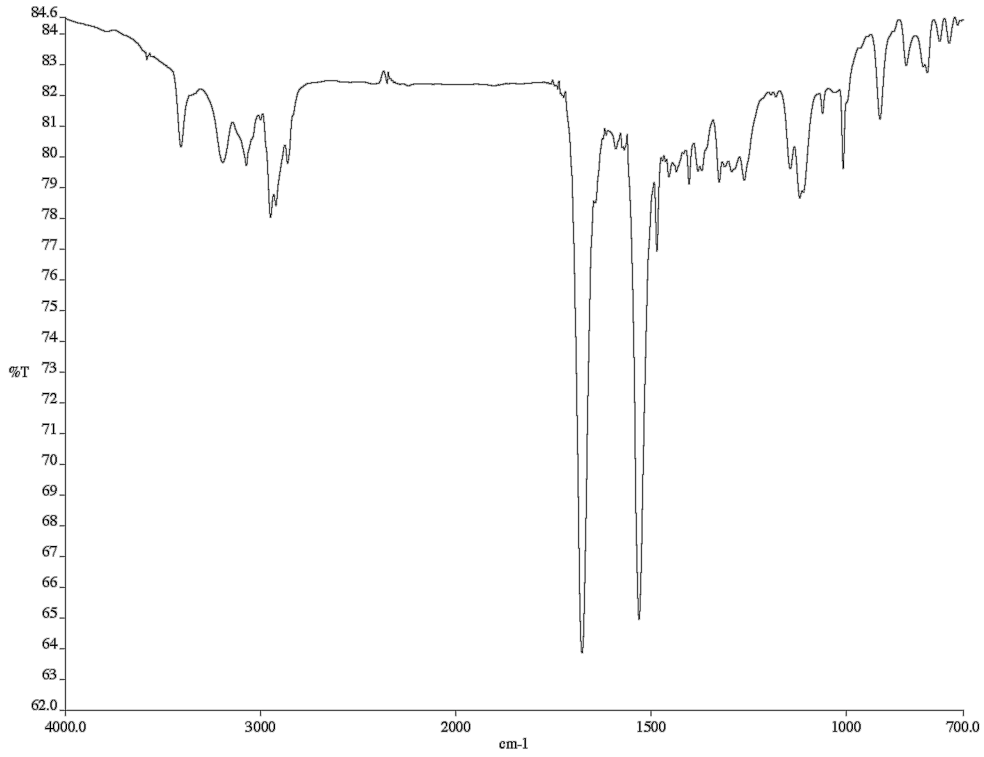


Figure A2.80.2. Infrared spectrum (thin film/NaCl) of compound **81**.

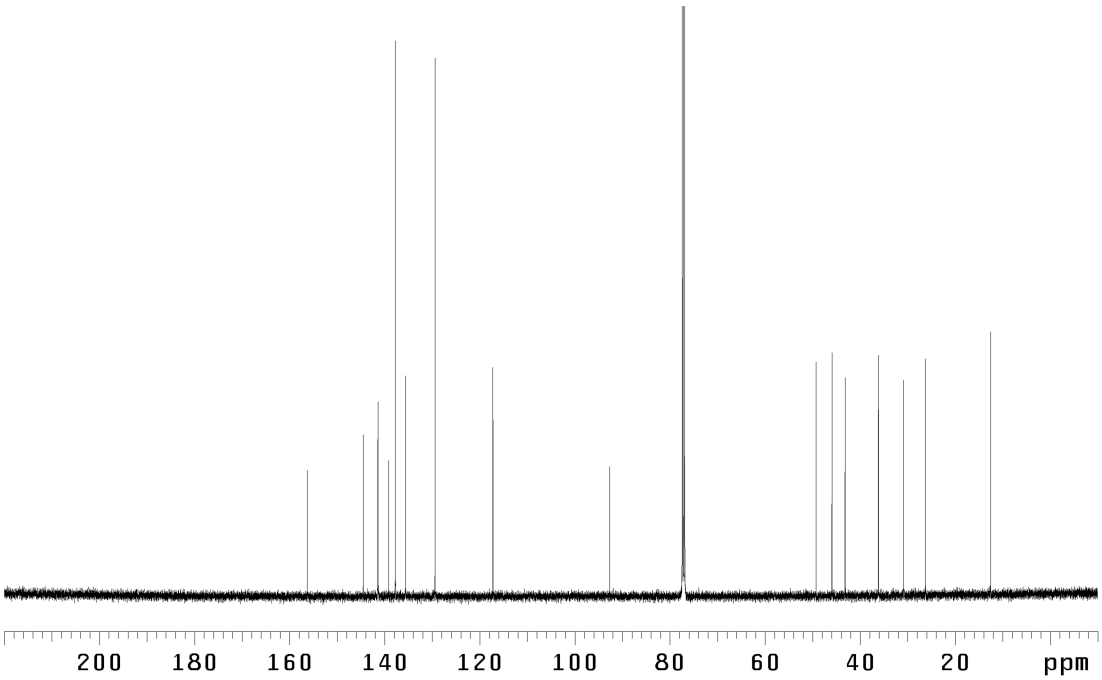


Figure A2.80.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **81**.

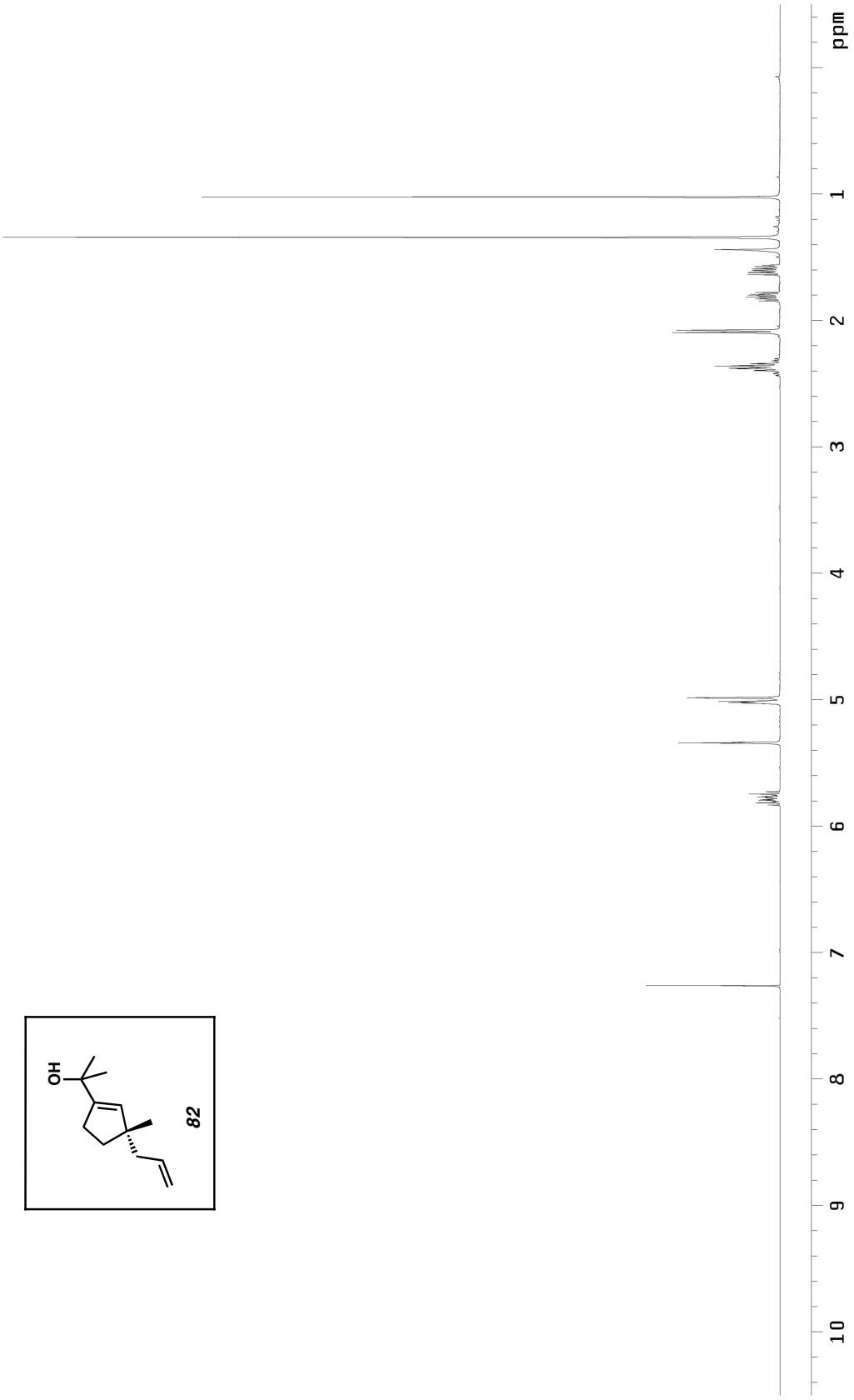


Figure A2.81.1. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **82**.

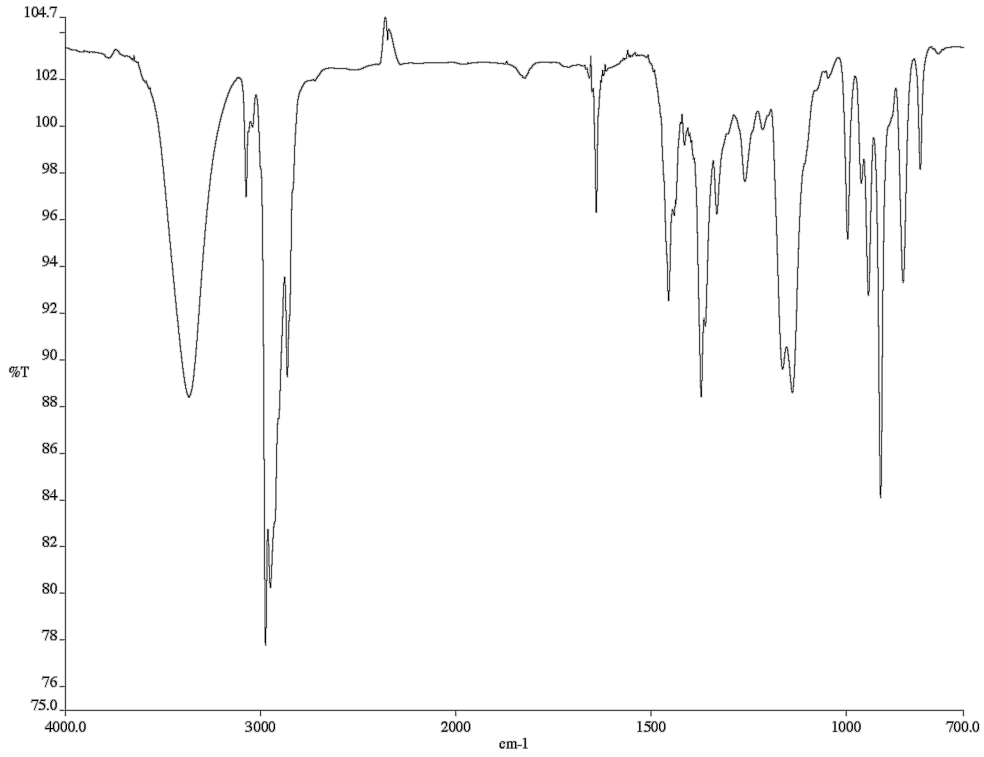


Figure A2.81.2. Infrared spectrum (thin film/NaCl) of compound **82**.

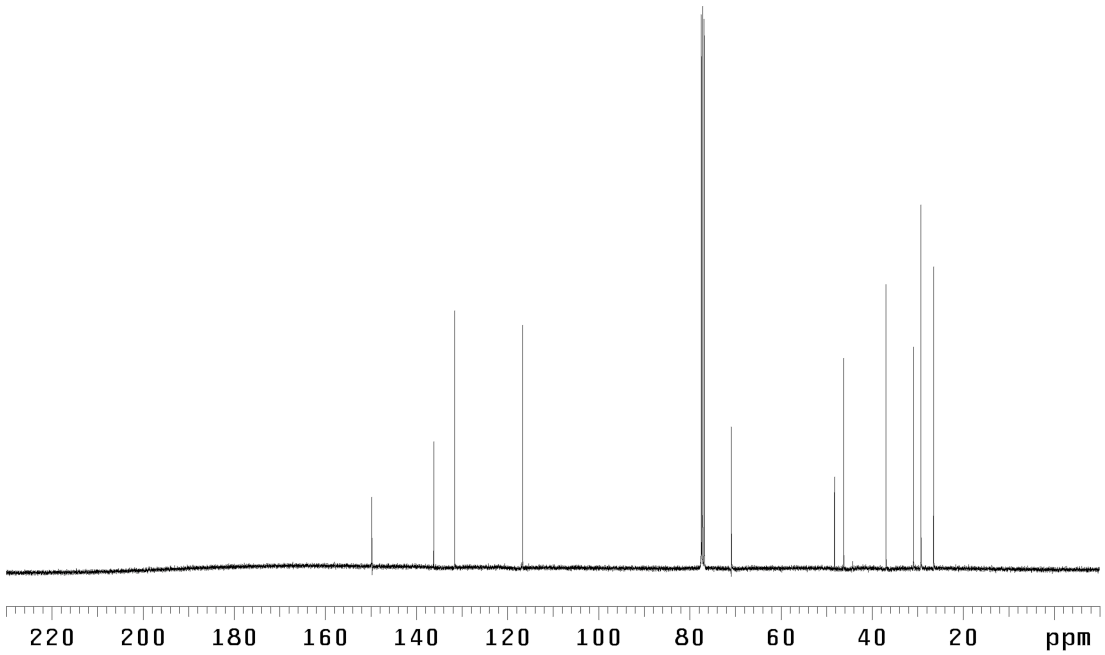


Figure A2.81.3. ^{13}C NMR (100 MHz, $CDCl_3$) of compound **82**.

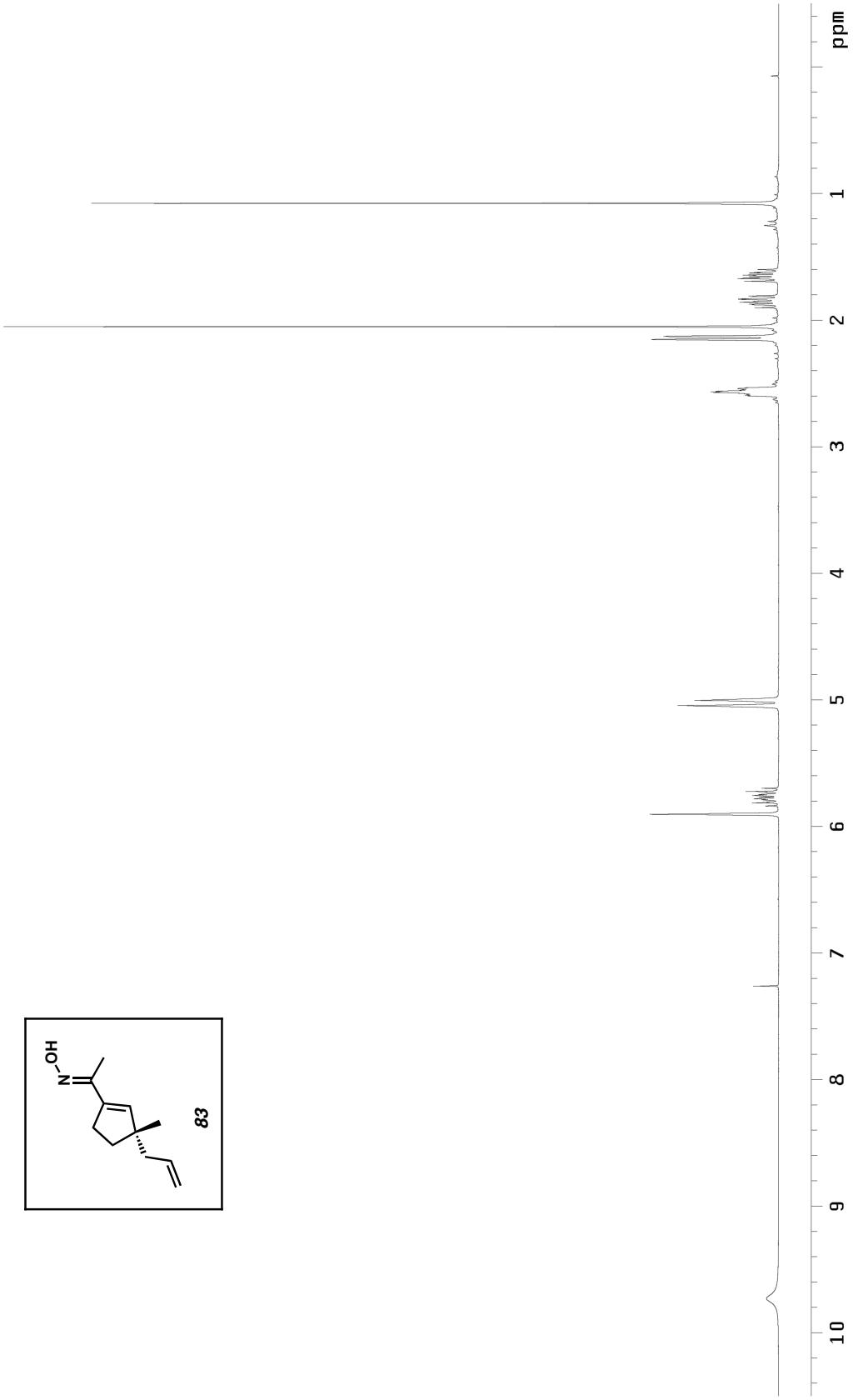


Figure A2.82.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **83**.

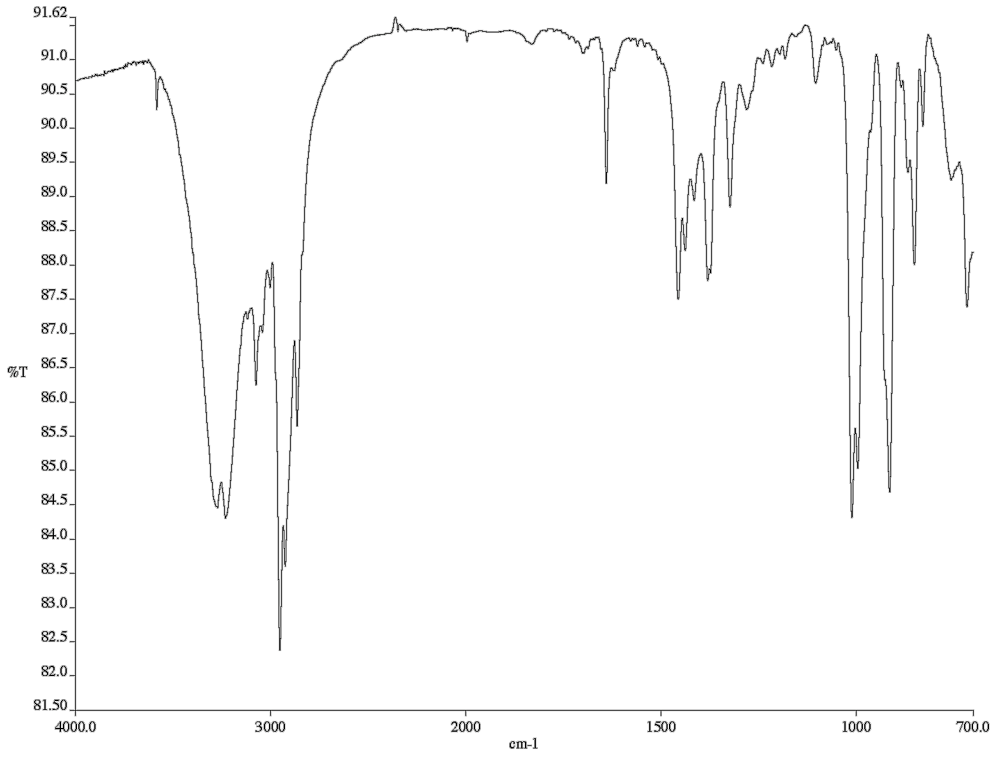


Figure A2.82.2. Infrared spectrum (thin film/NaCl) of compound **83**.

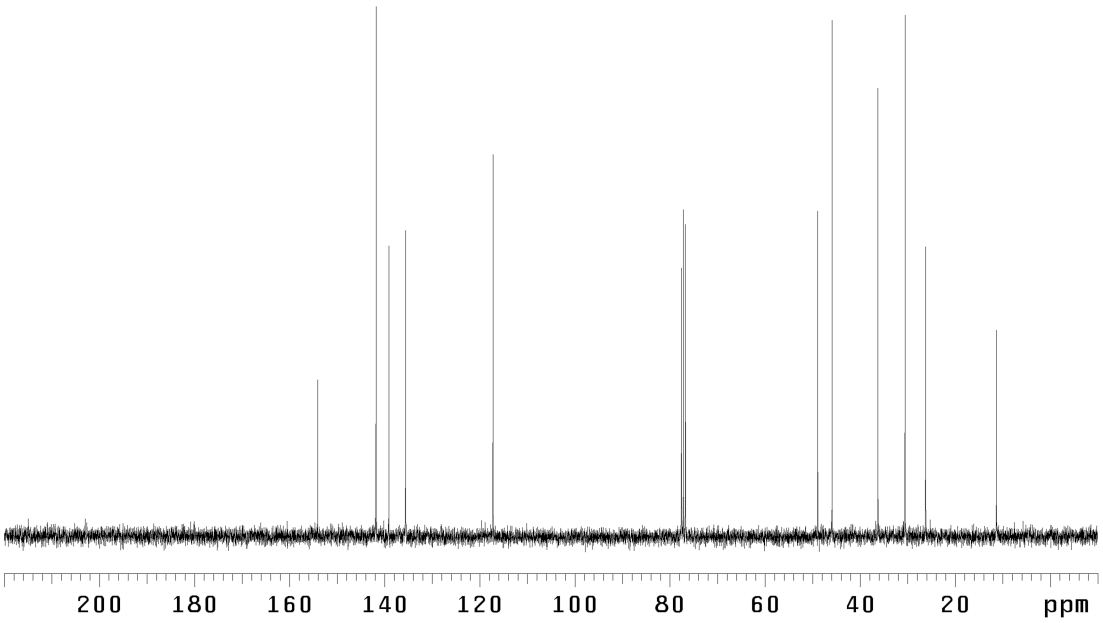


Figure A2.82.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **83**.

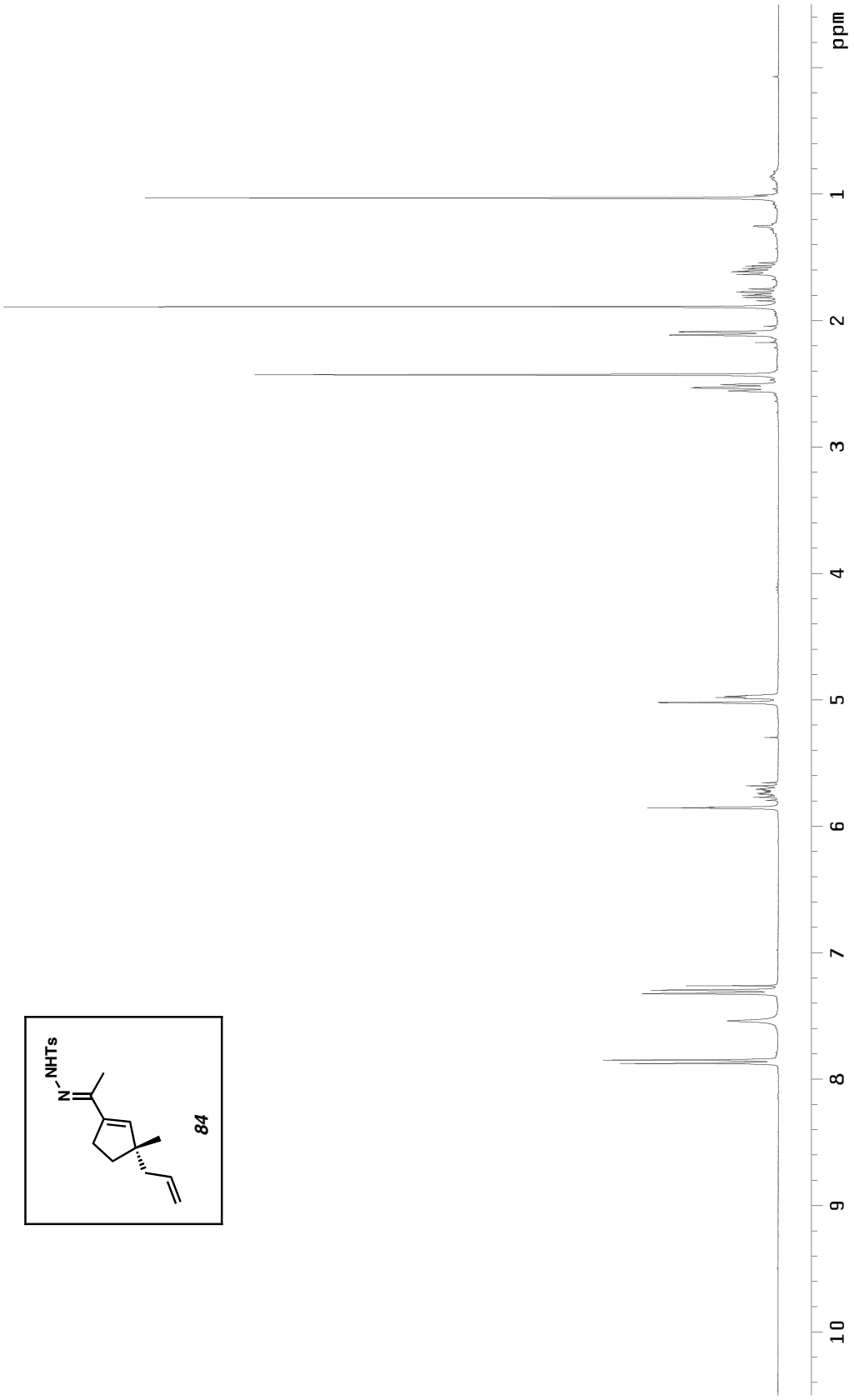


Figure A2.83.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **84**.

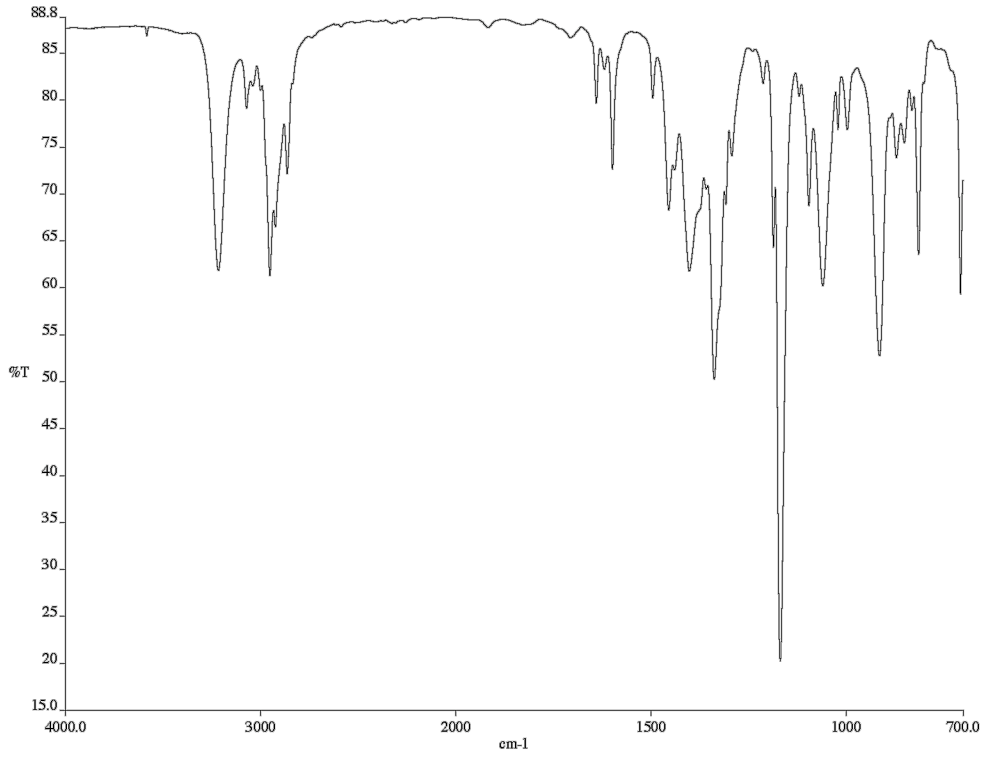


Figure A2.83.2. Infrared spectrum (thin film/NaCl) of compound **84**.

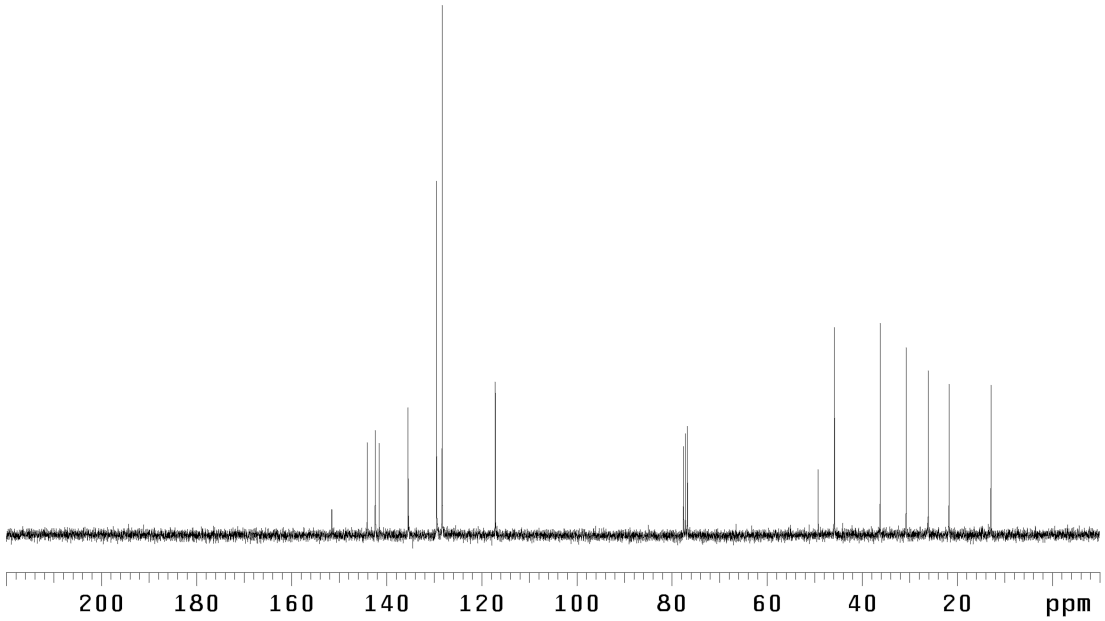


Figure A2.83.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **84**.

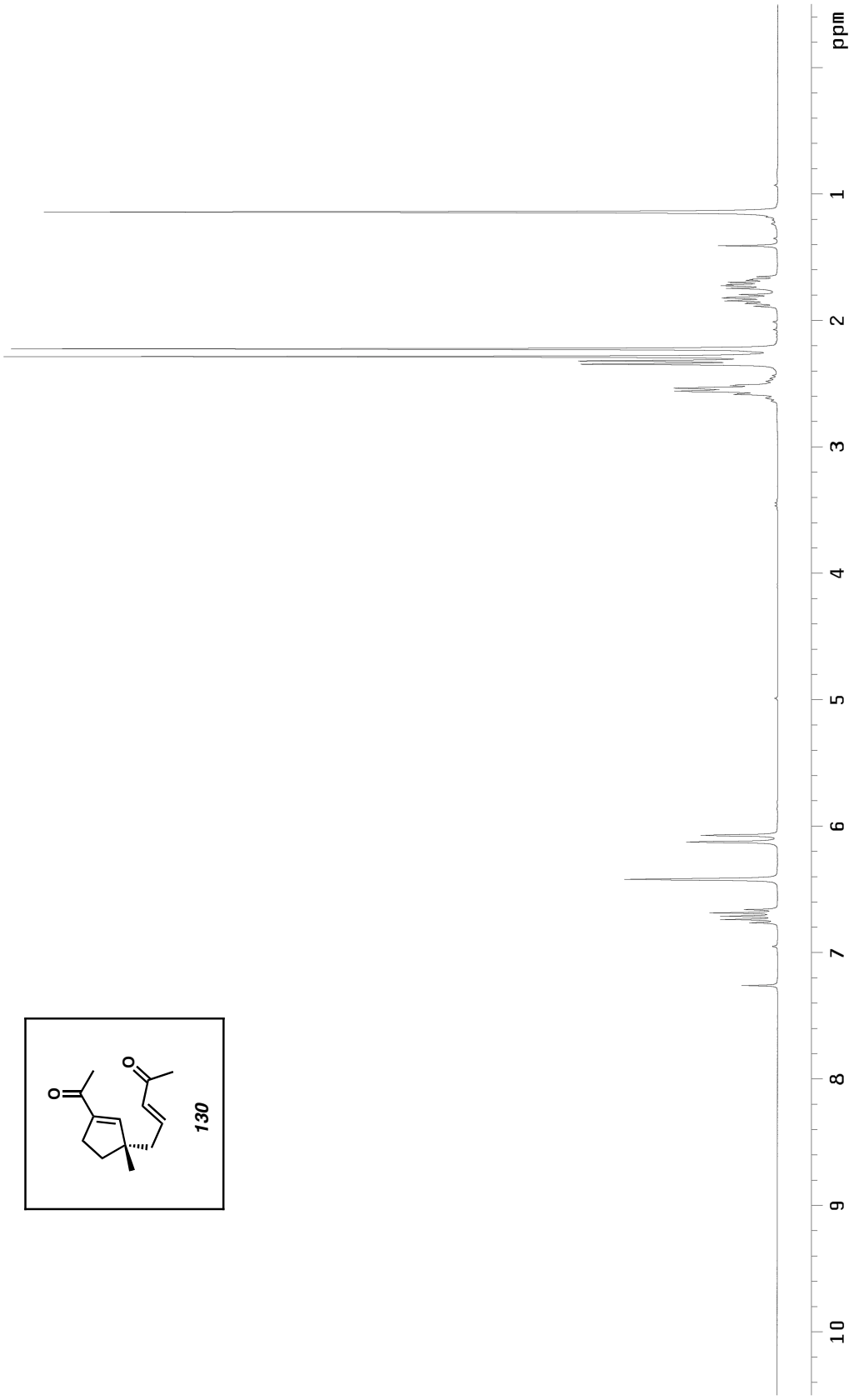


Figure A2.84.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **130**.

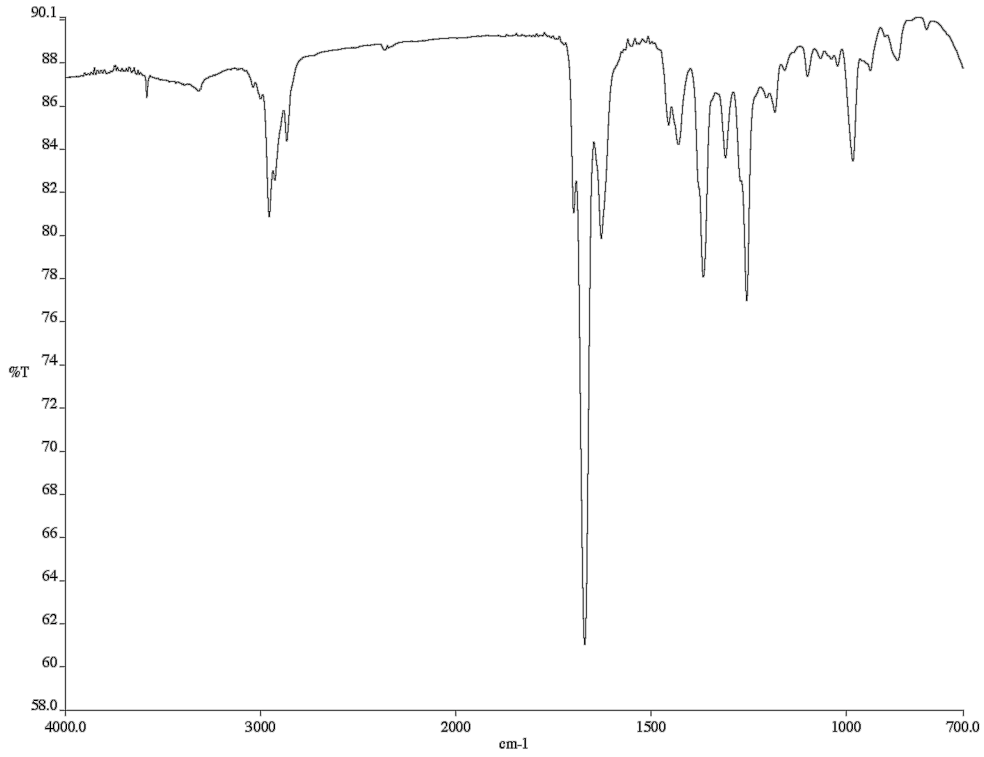


Figure A2.84.2. Infrared spectrum (thin film/NaCl) of compound **130**.

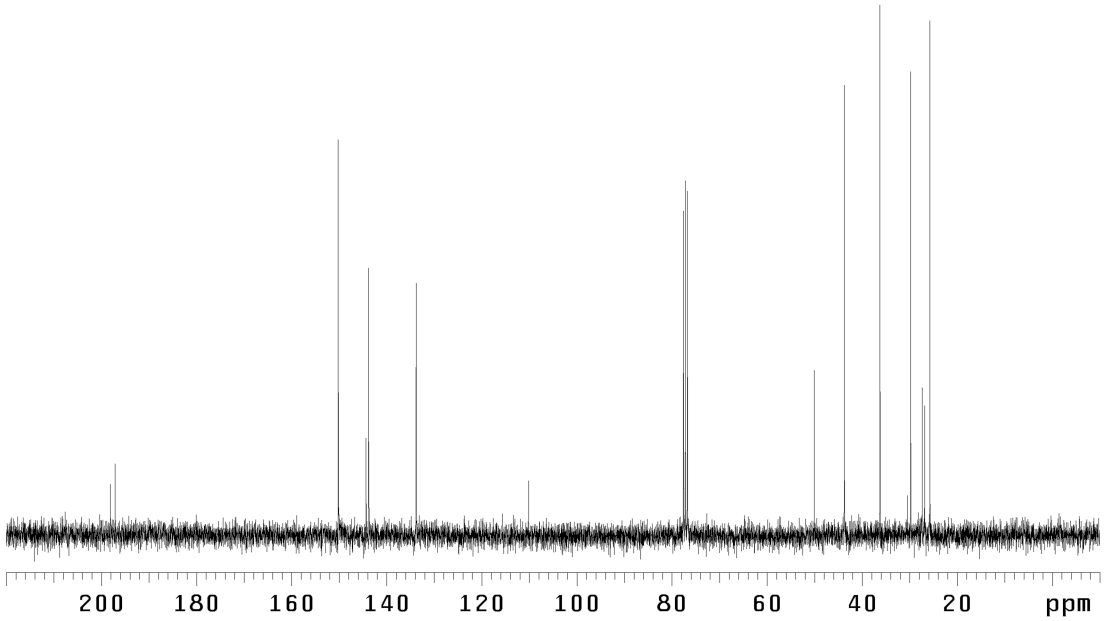


Figure A2.84.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **130**.

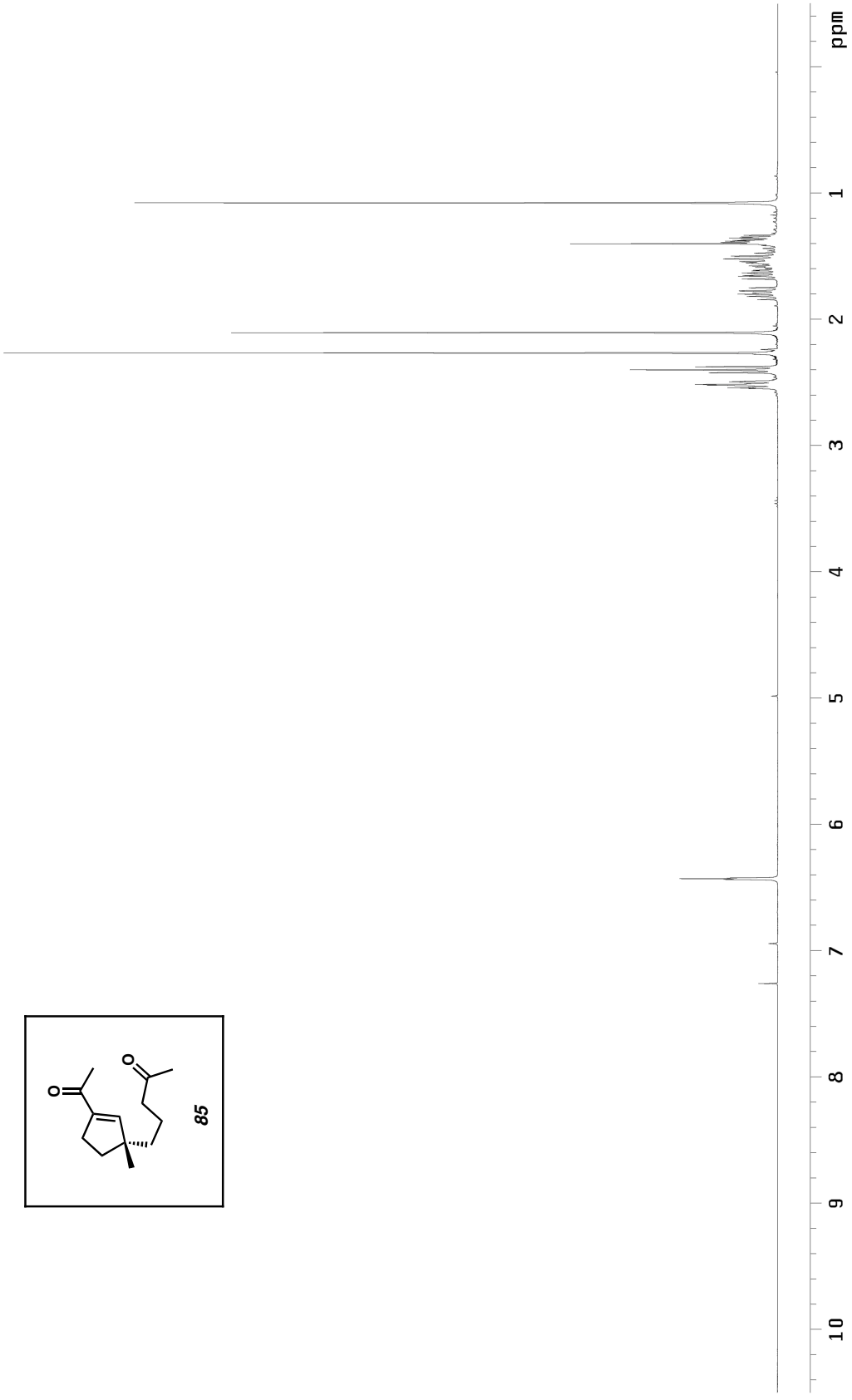


Figure A2.85.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **85**.

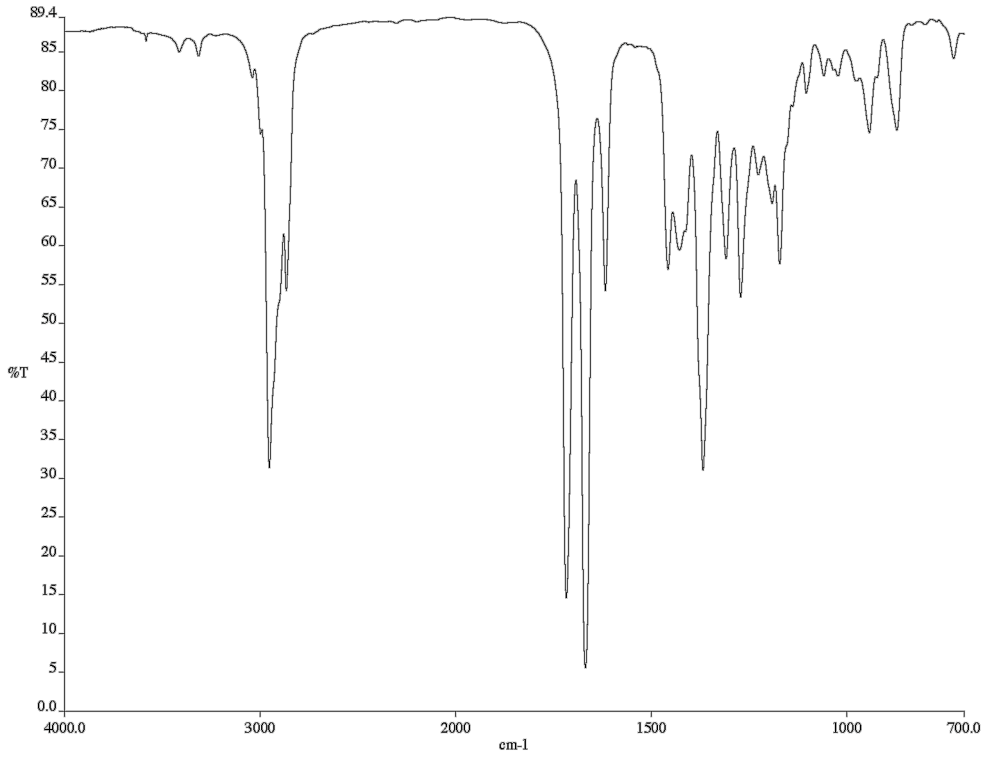


Figure A2.85.2. Infrared spectrum (thin film/NaCl) of compound **85**.

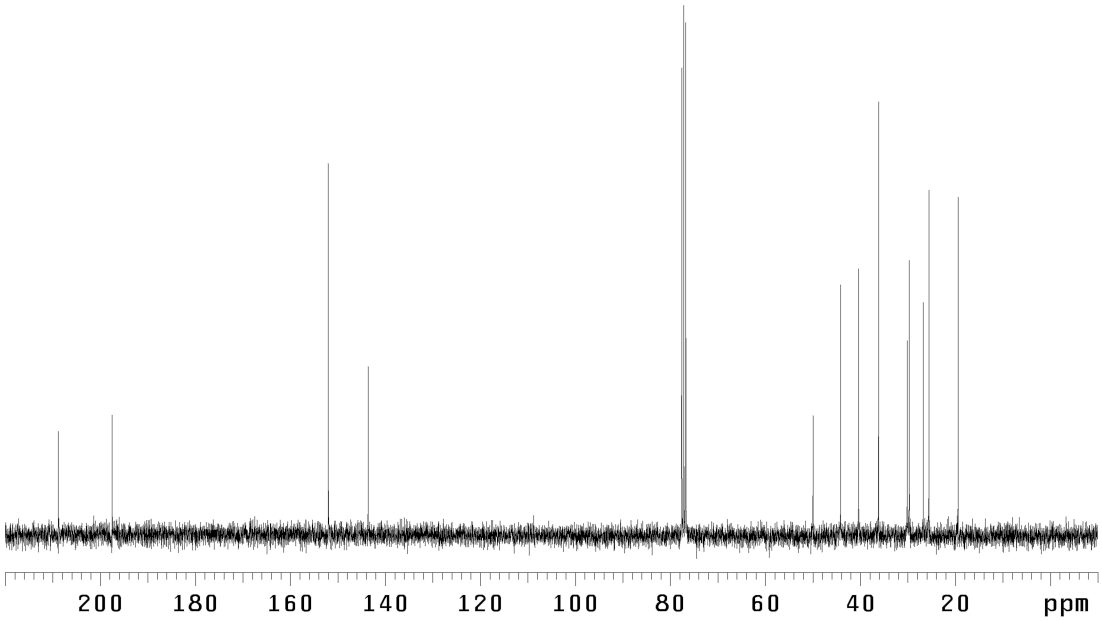


Figure A2.85.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **85**.

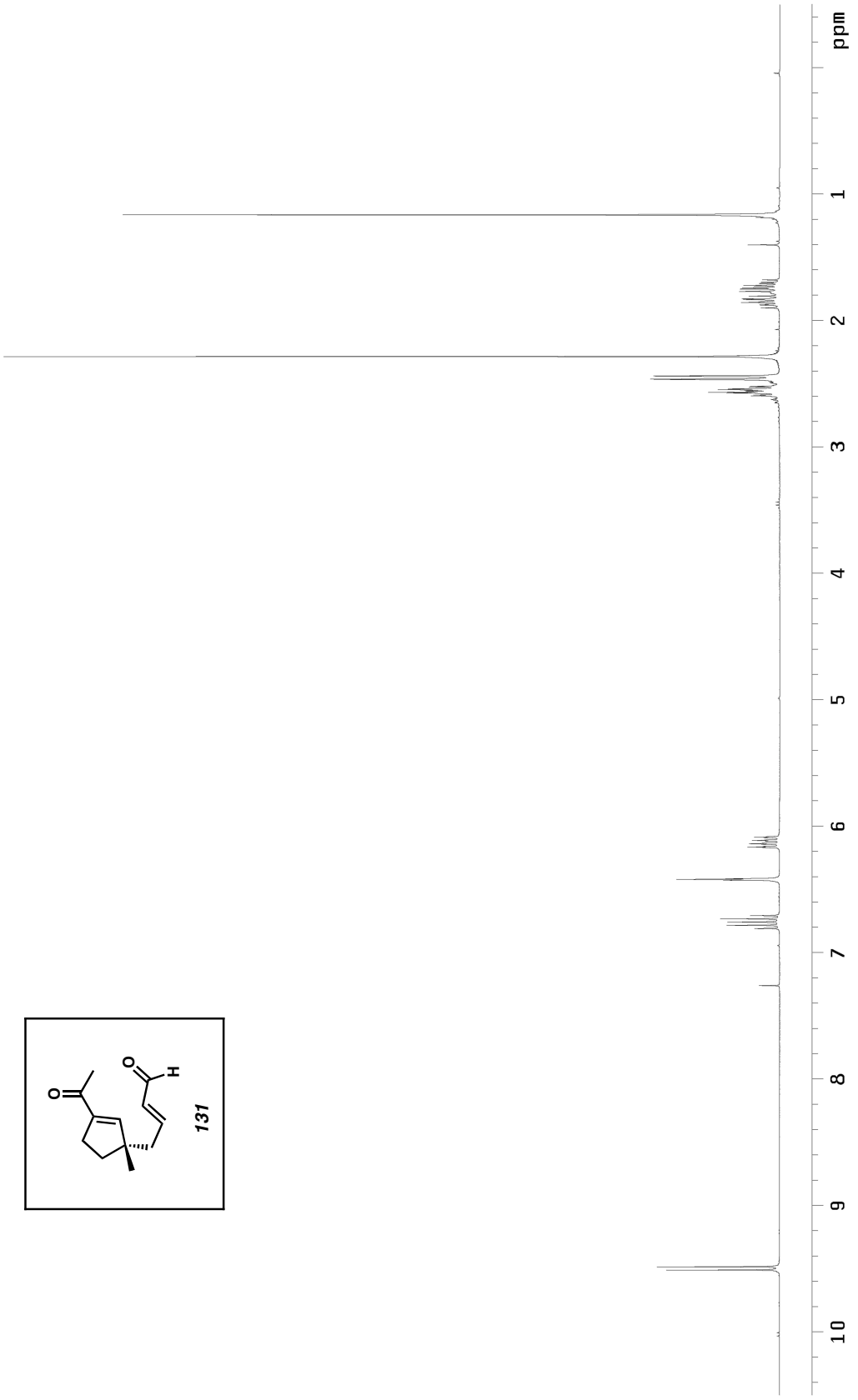


Figure A2.86.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **131**.

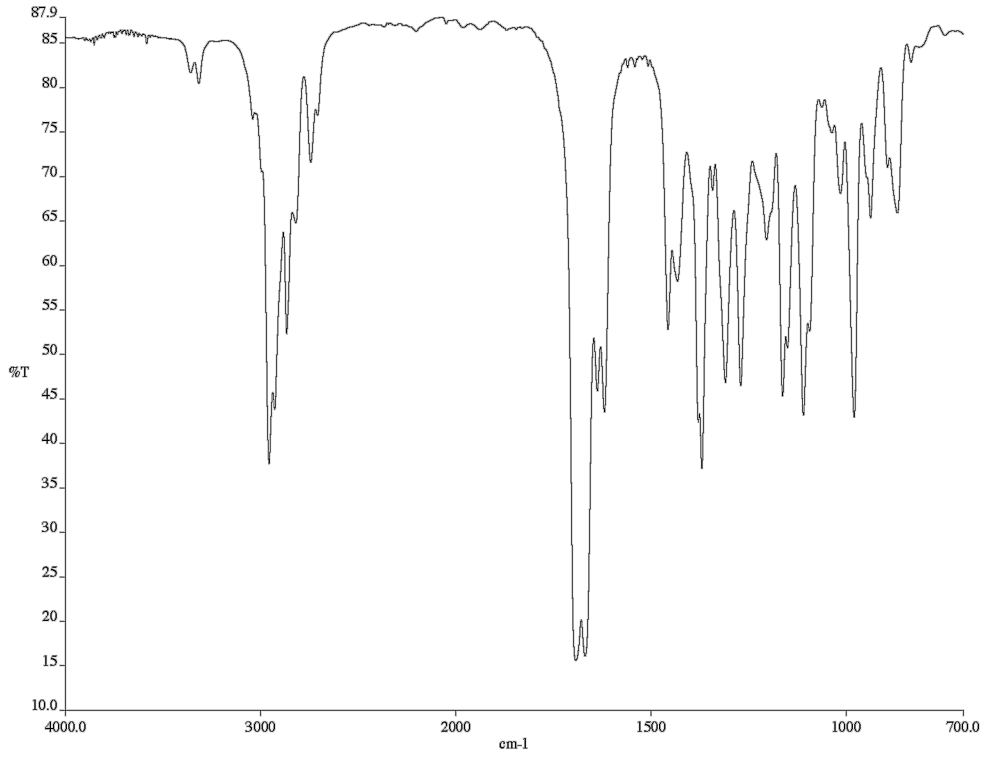


Figure A2.86.2. Infrared spectrum (thin film/NaCl) of compound **131**.

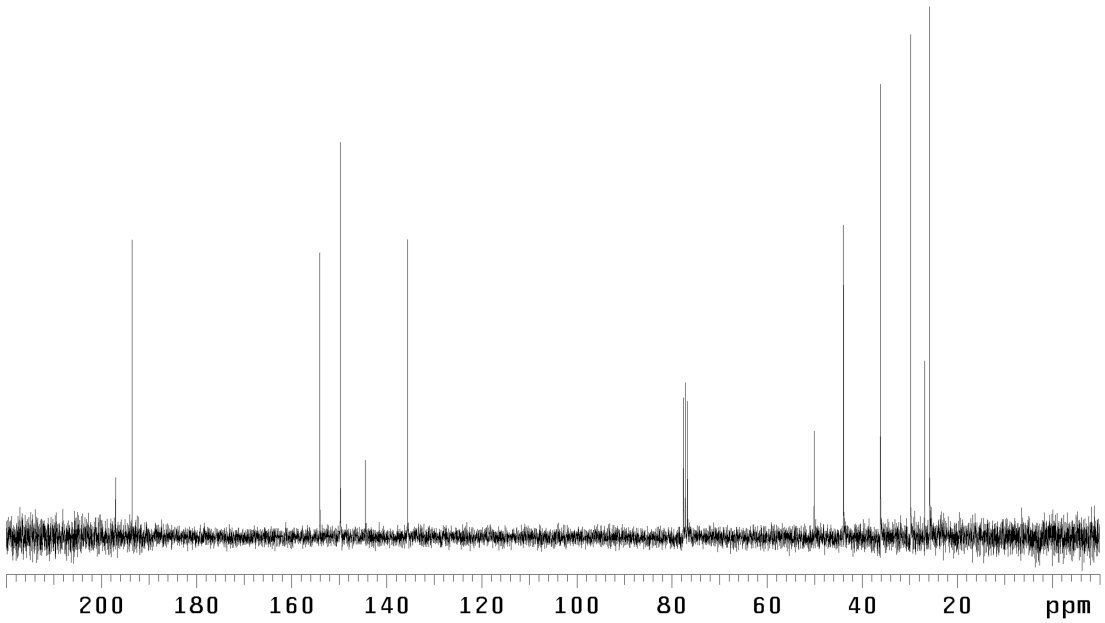


Figure A2.86.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **131**.

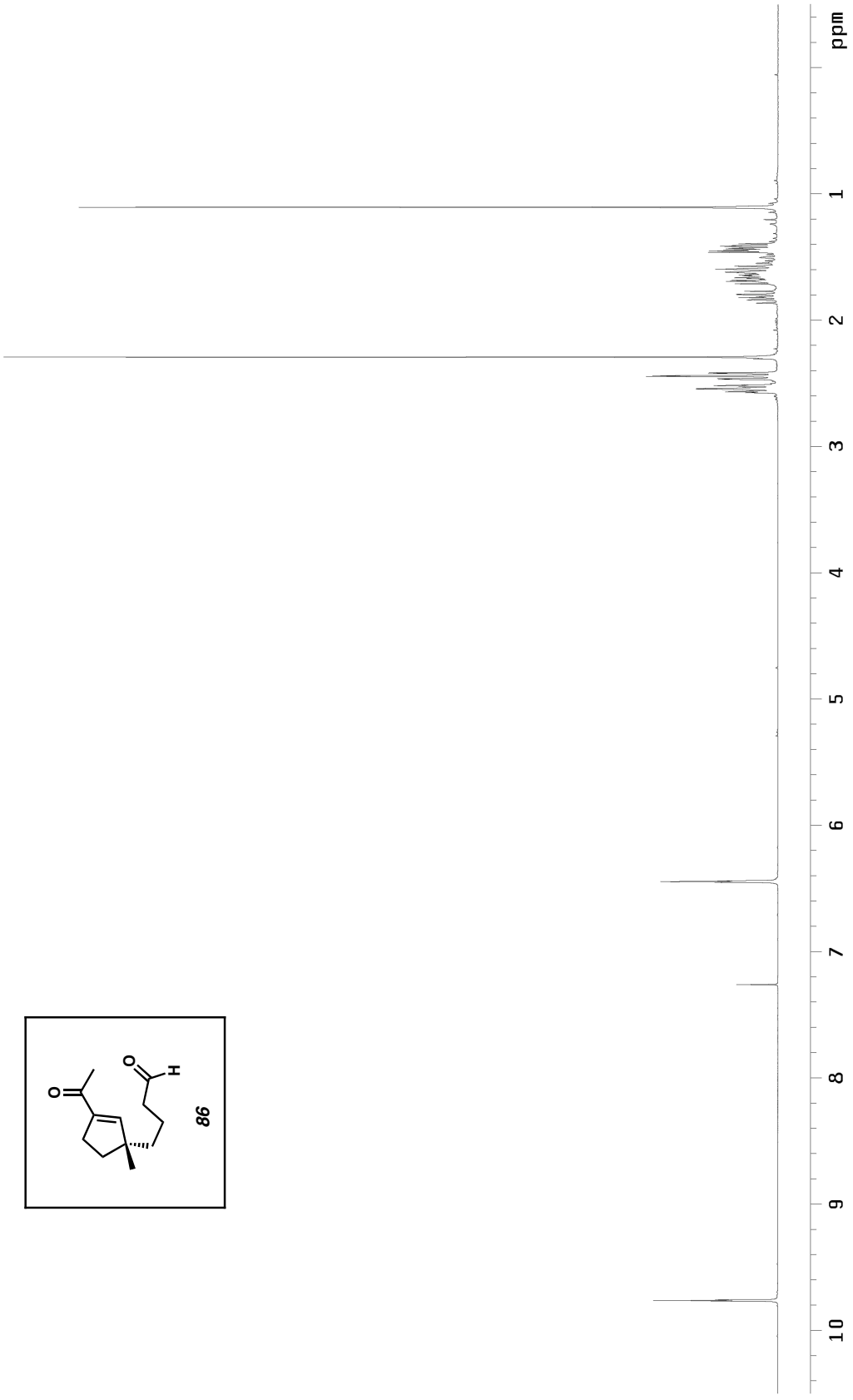


Figure A2.87.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **86**.

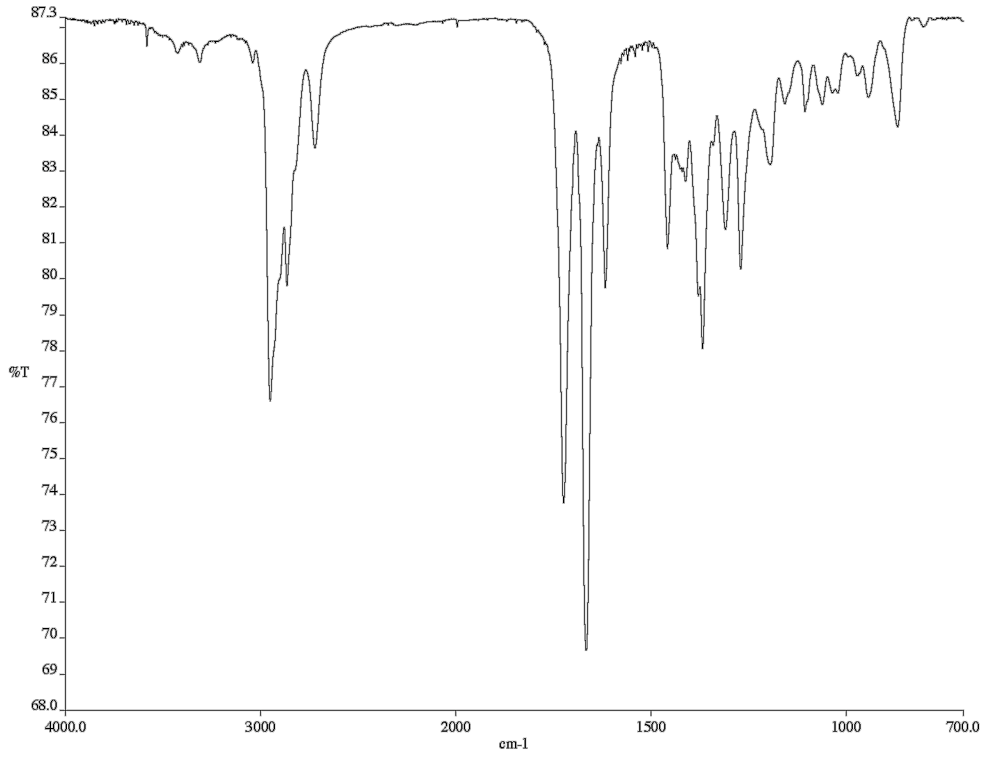


Figure A2.87.2. Infrared spectrum (thin film/NaCl) of compound **86**.

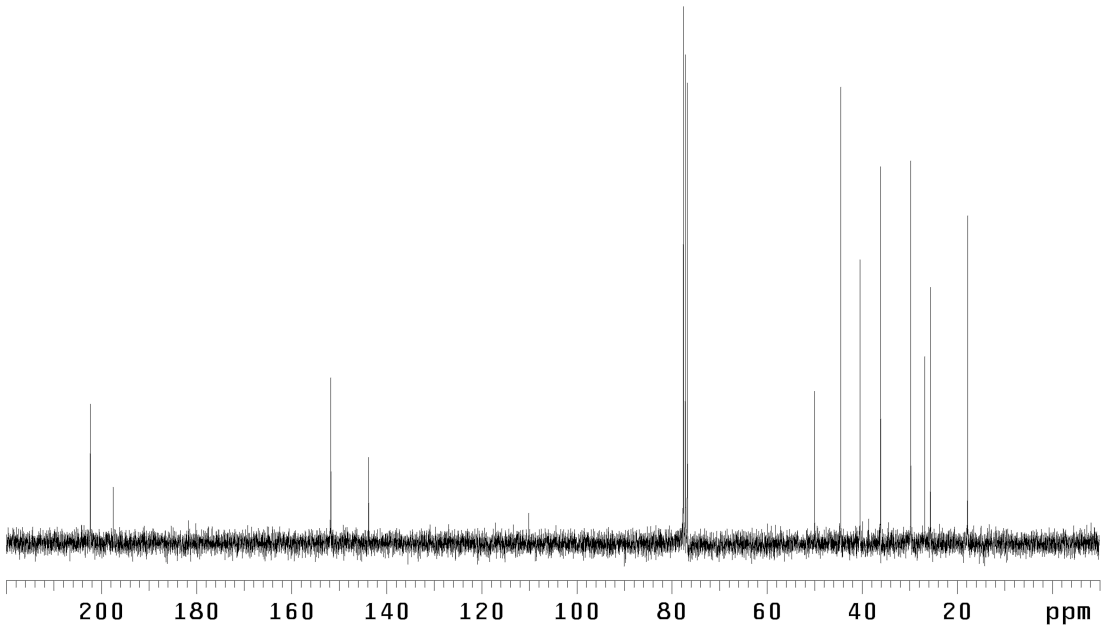


Figure A2.87.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **86**.

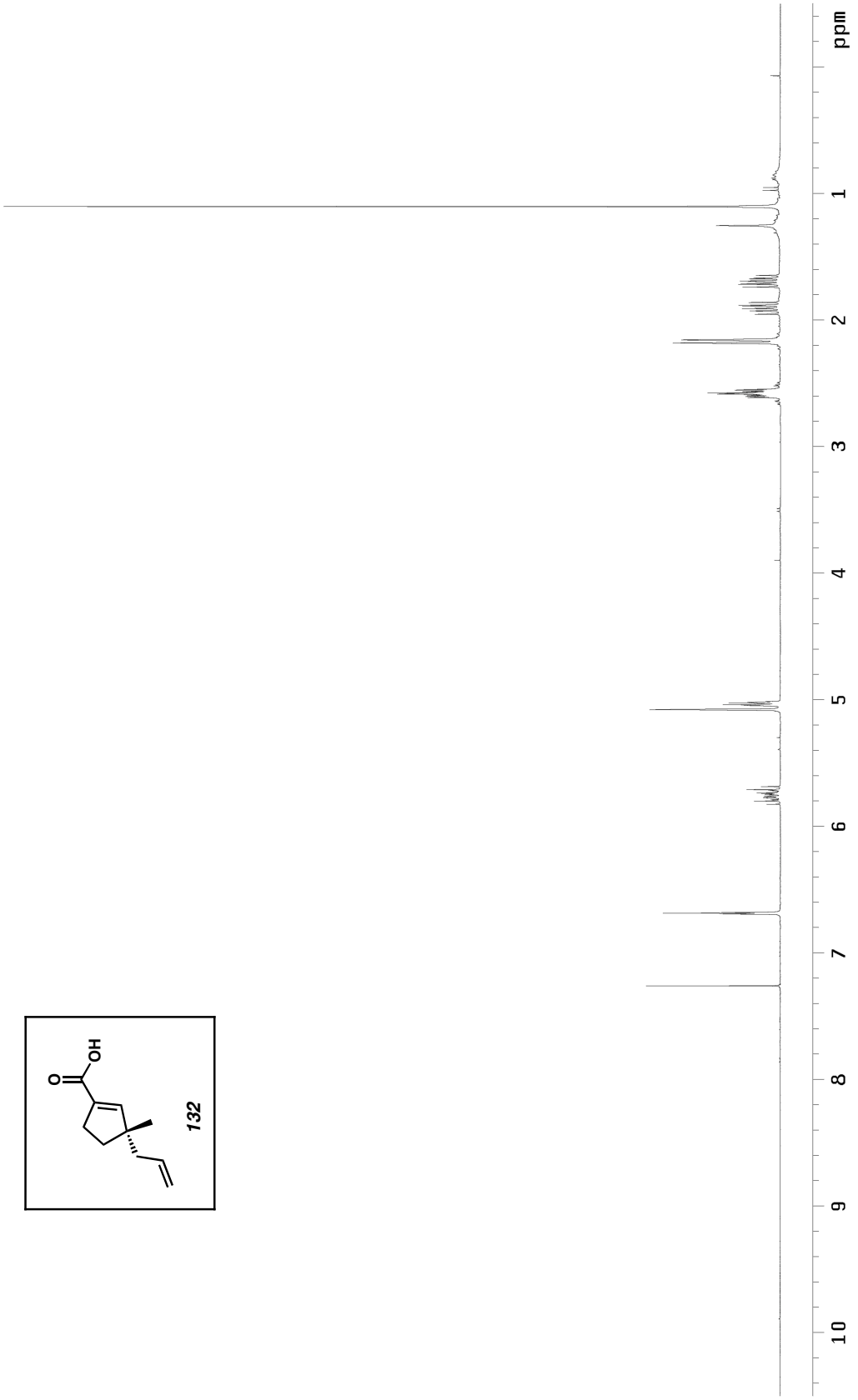


Figure A2.88.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **132**.

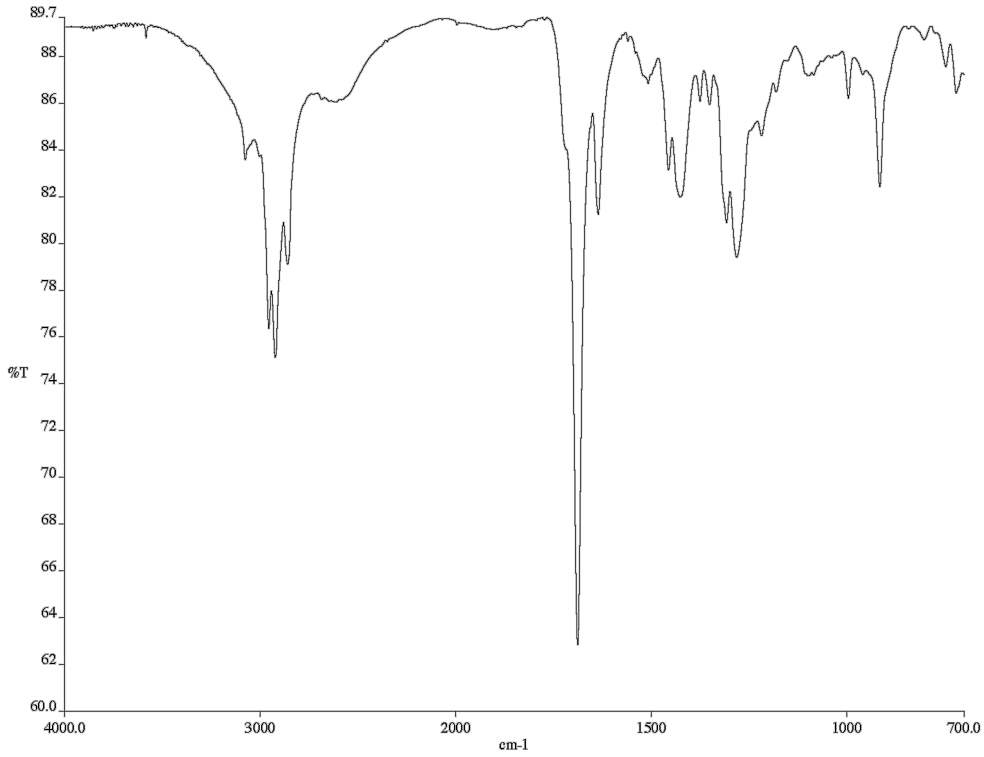


Figure A2.88.2. Infrared spectrum (thin film/NaCl) of compound **132**.

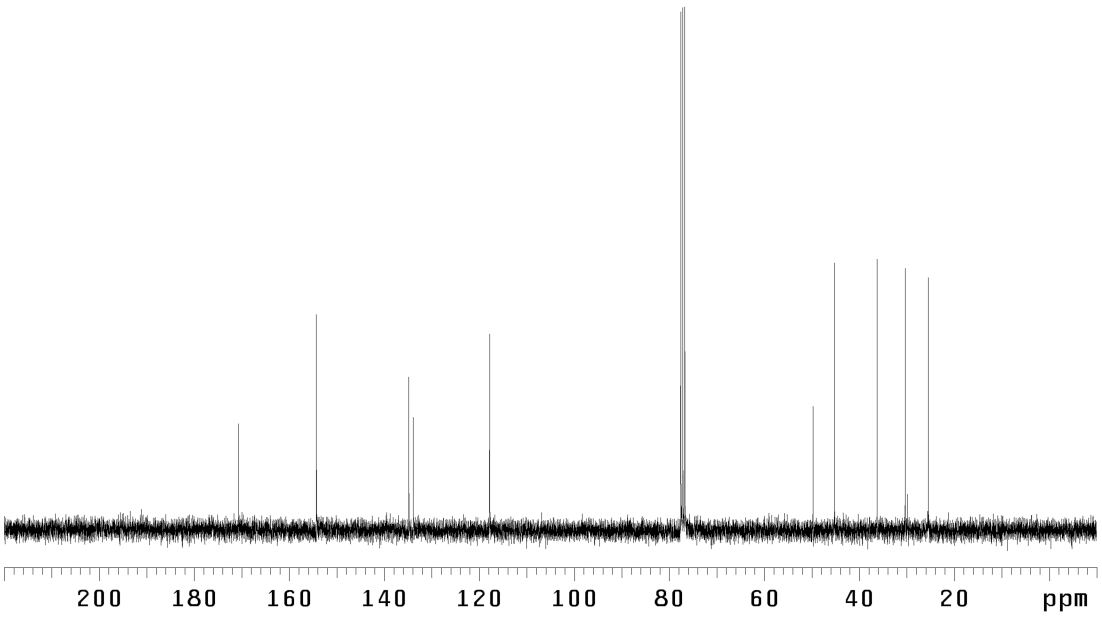


Figure A2.88.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **132**.

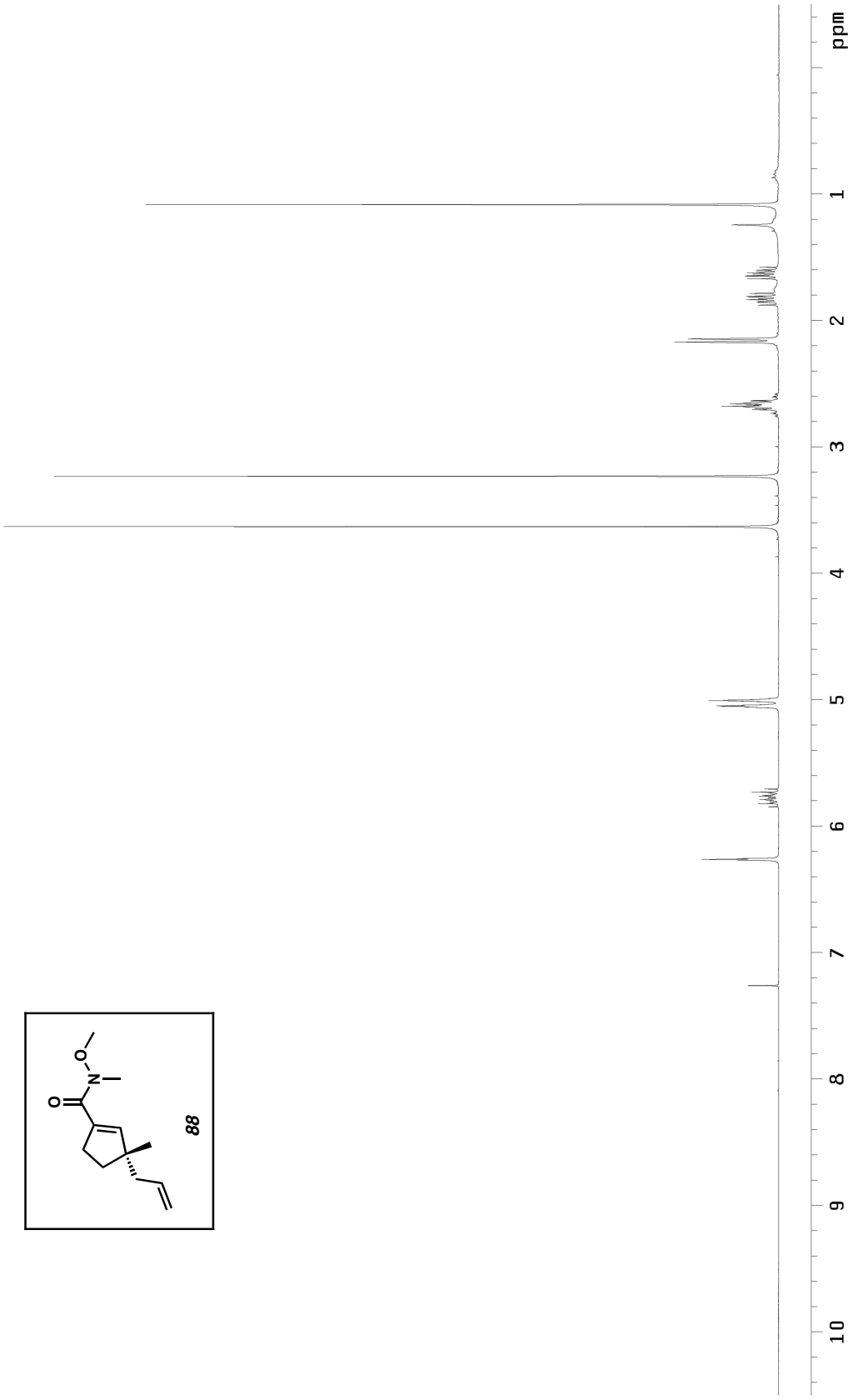


Figure A2.89.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **88**.

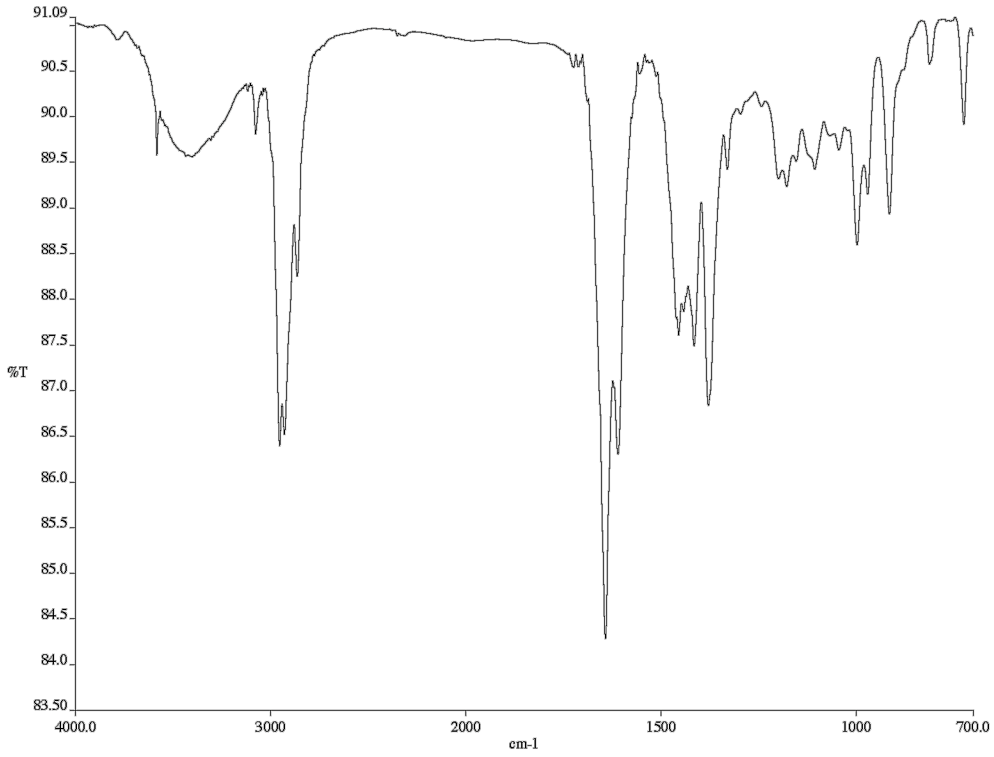


Figure A2.89.2. Infrared spectrum (thin film/NaCl) of compound **88**.

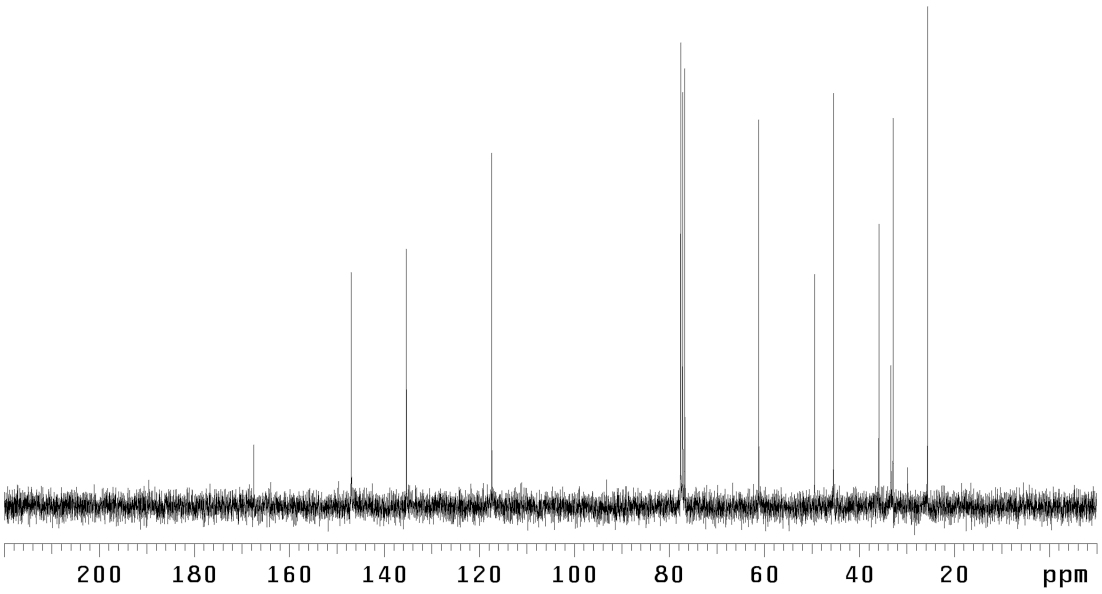


Figure A2.89.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **88**.

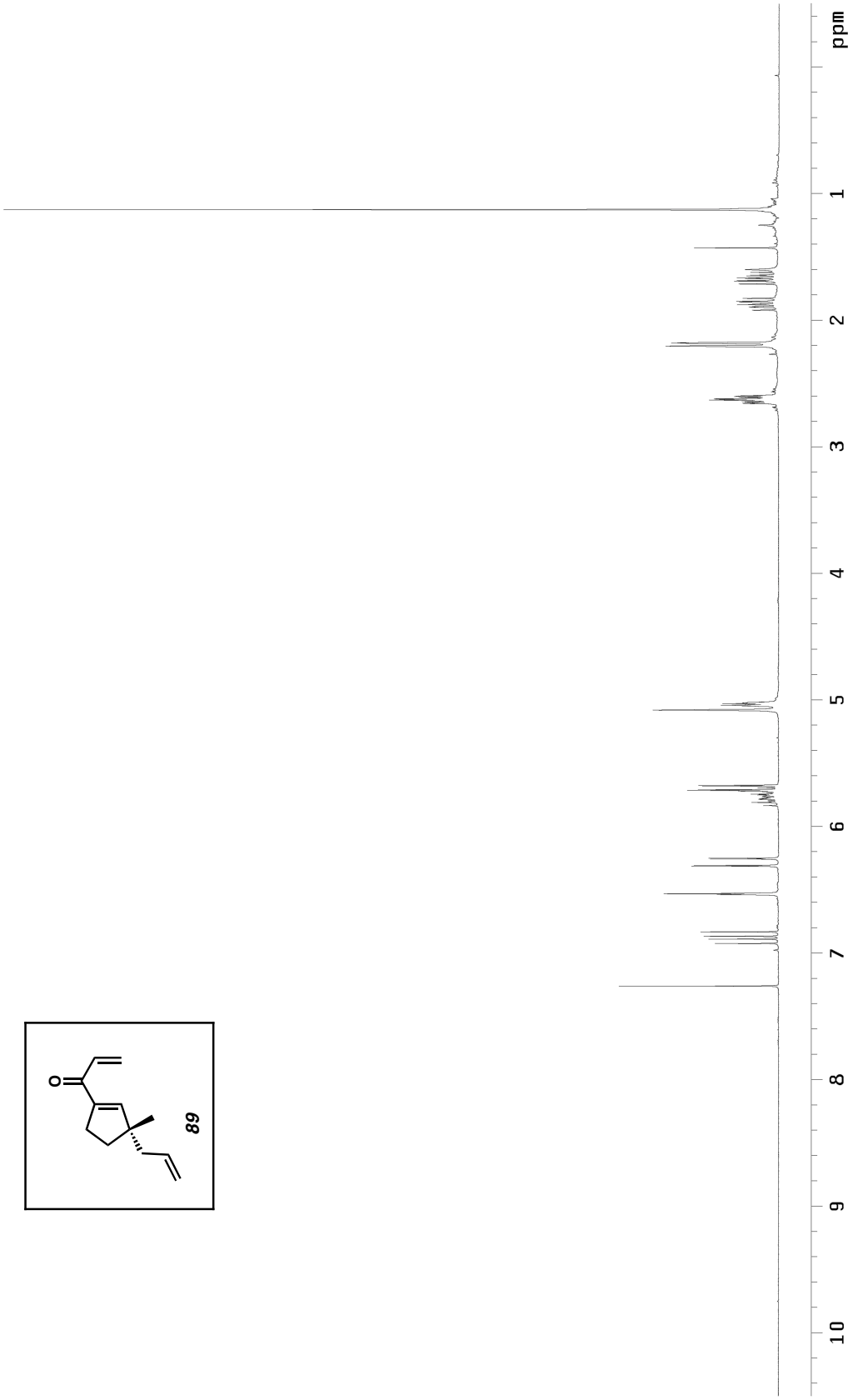


Figure A2.90.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **89**.

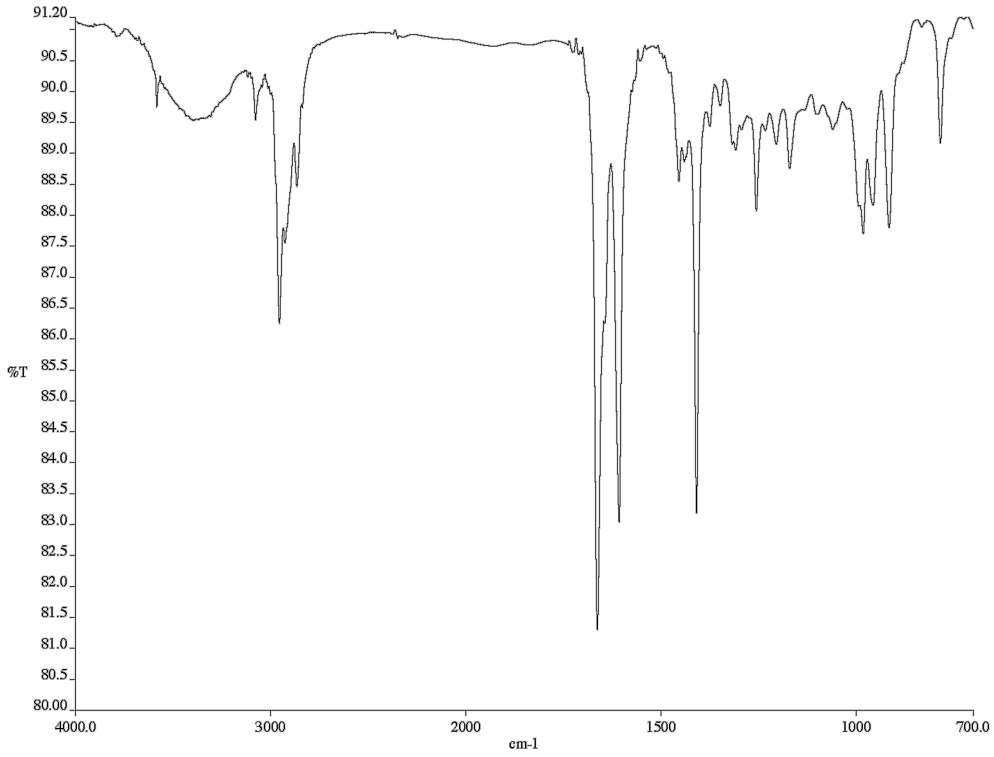


Figure A2.90.2. Infrared spectrum (thin film/NaCl) of compound **89**.

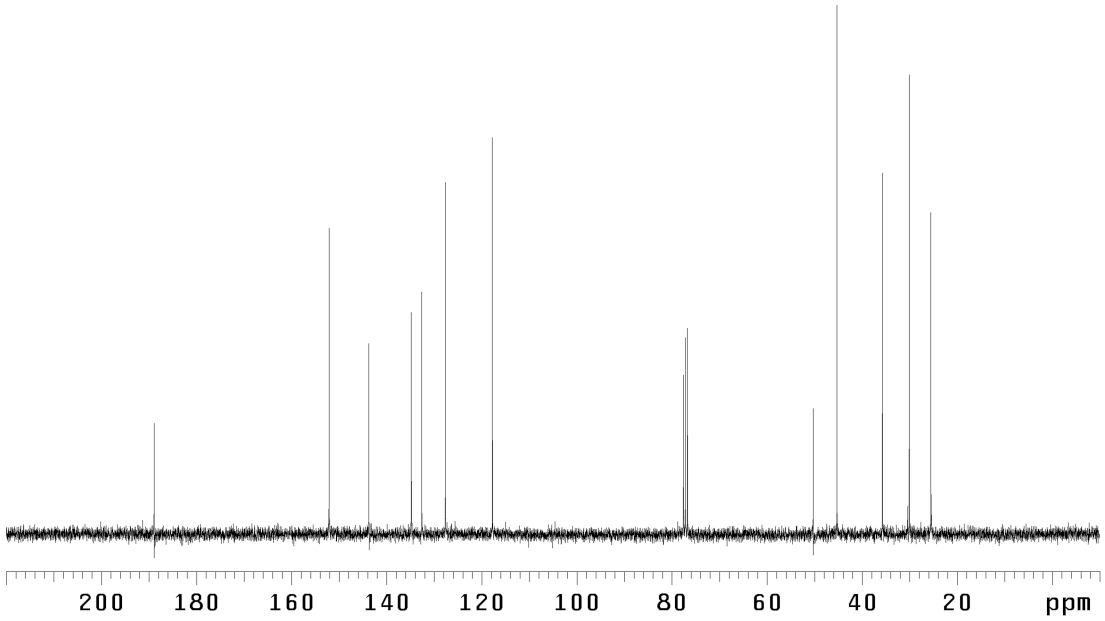


Figure A2.90.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **89**.

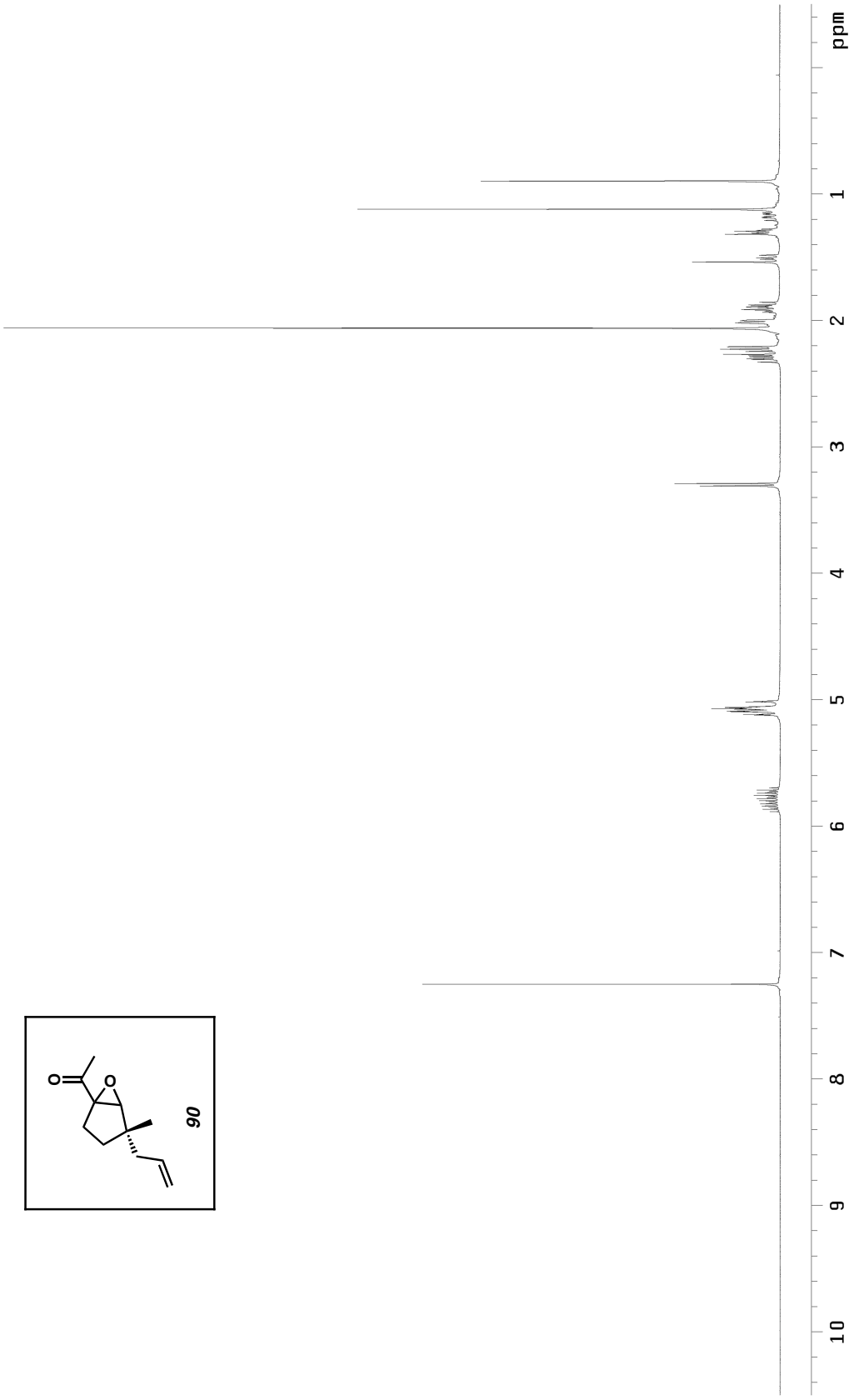


Figure A2.91.1. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **90**.

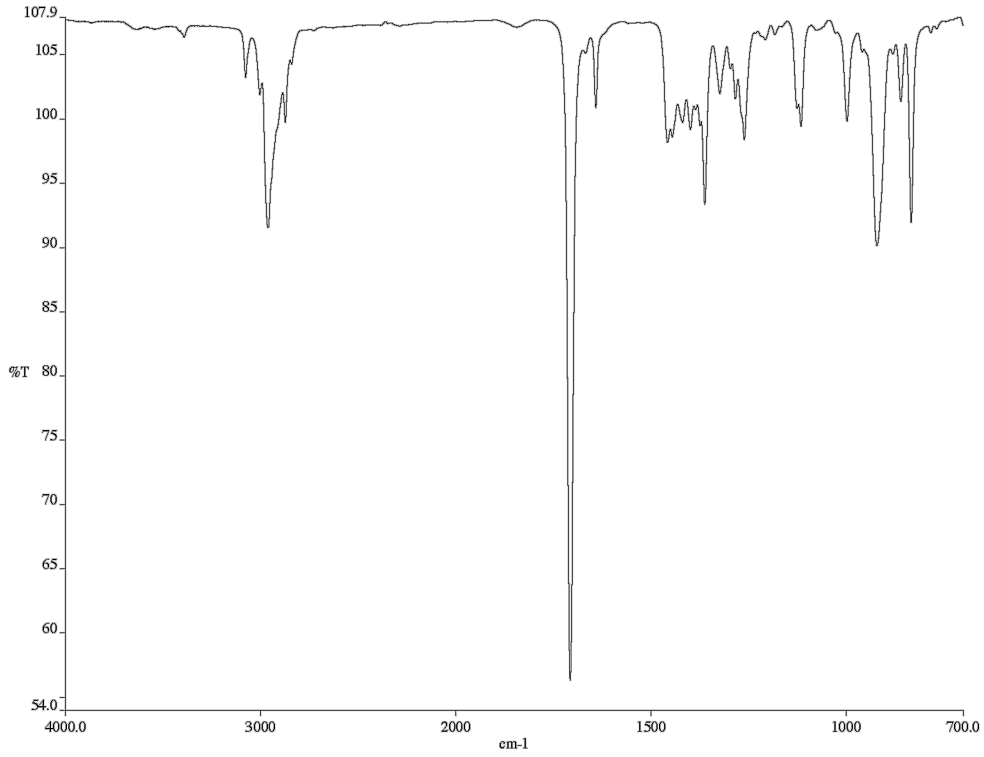


Figure A2.91.2. Infrared spectrum (thin film/NaCl) of compound **90**.

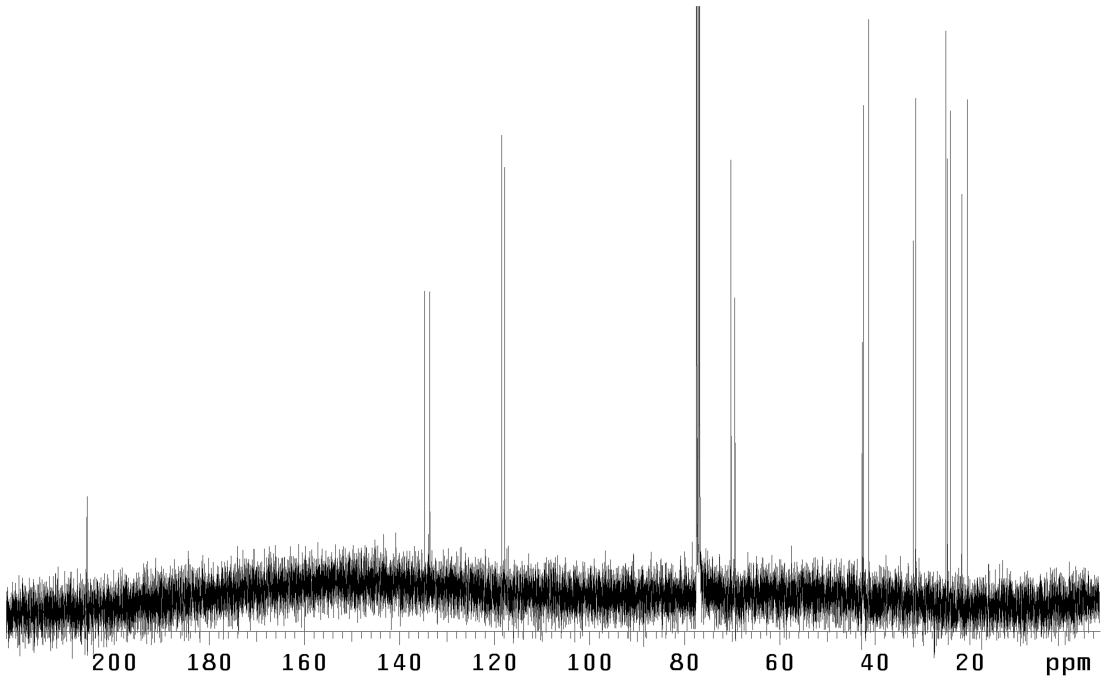


Figure A2.91.3. ^{13}C NMR (100 MHz, $CDCl_3$) of compound **90**.

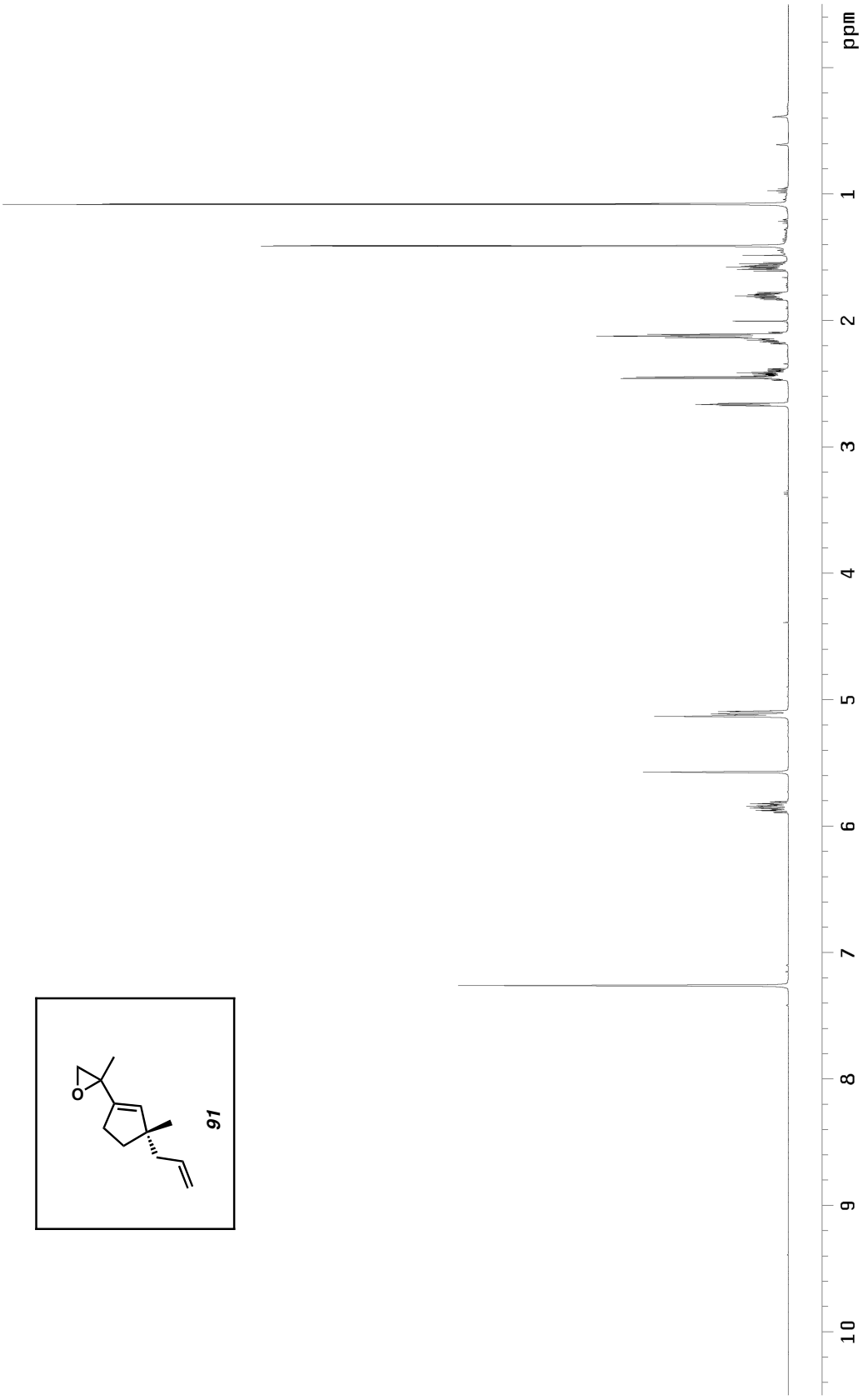


Figure A2.92.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **91**.

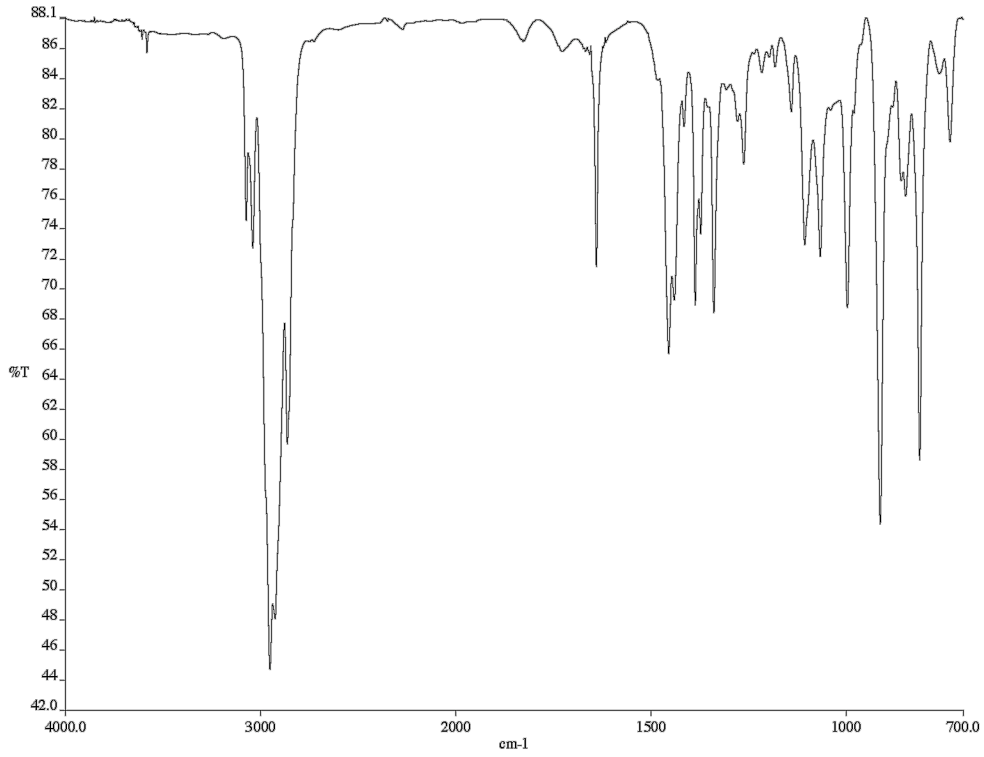


Figure A2.92.2. Infrared spectrum (thin film/NaCl) of compound **91**.

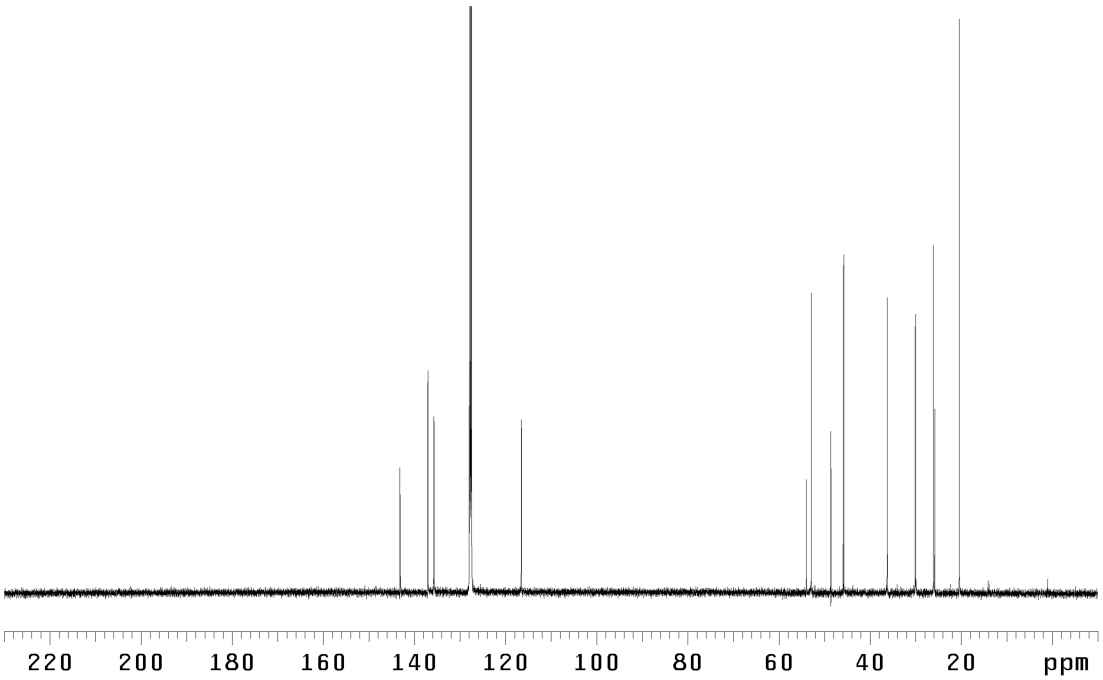


Figure A2.92.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **91**.

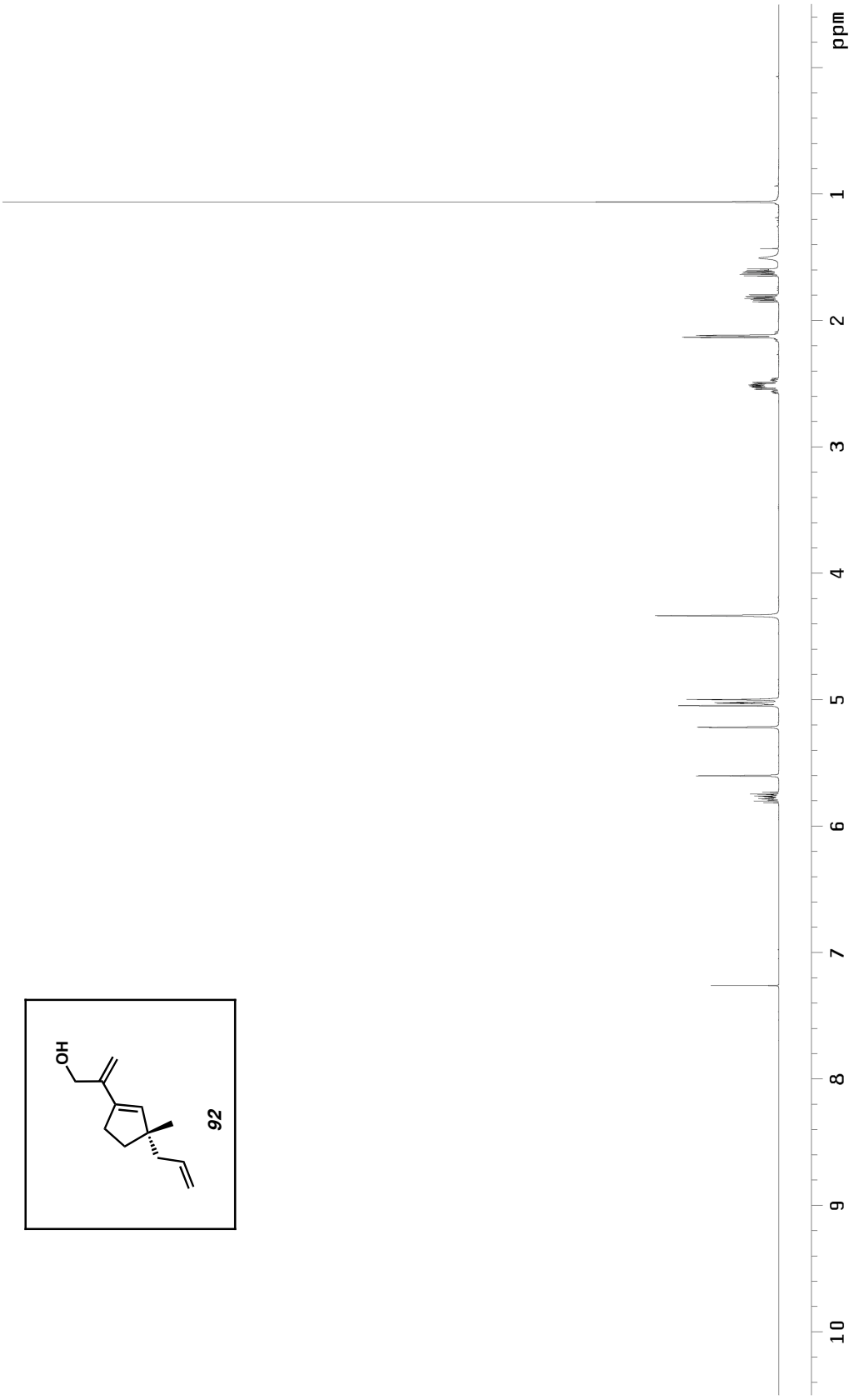


Figure A2.93.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **92**.

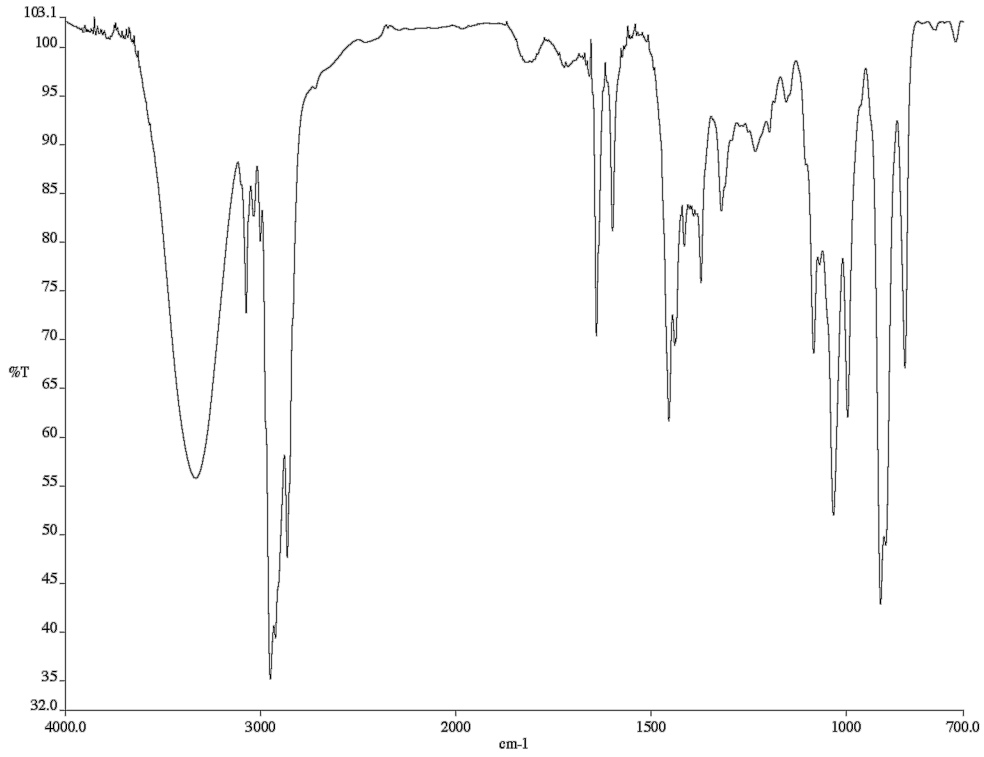


Figure A2.93.2. Infrared spectrum (thin film/NaCl) of compound **92**.

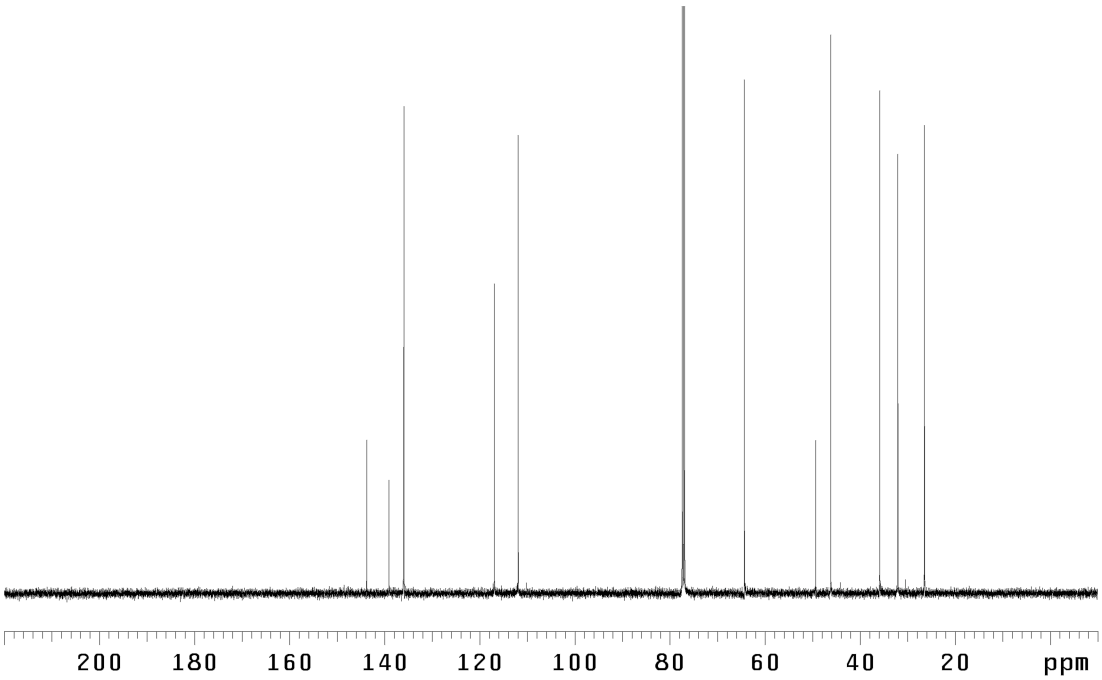


Figure A2.93.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **92**.

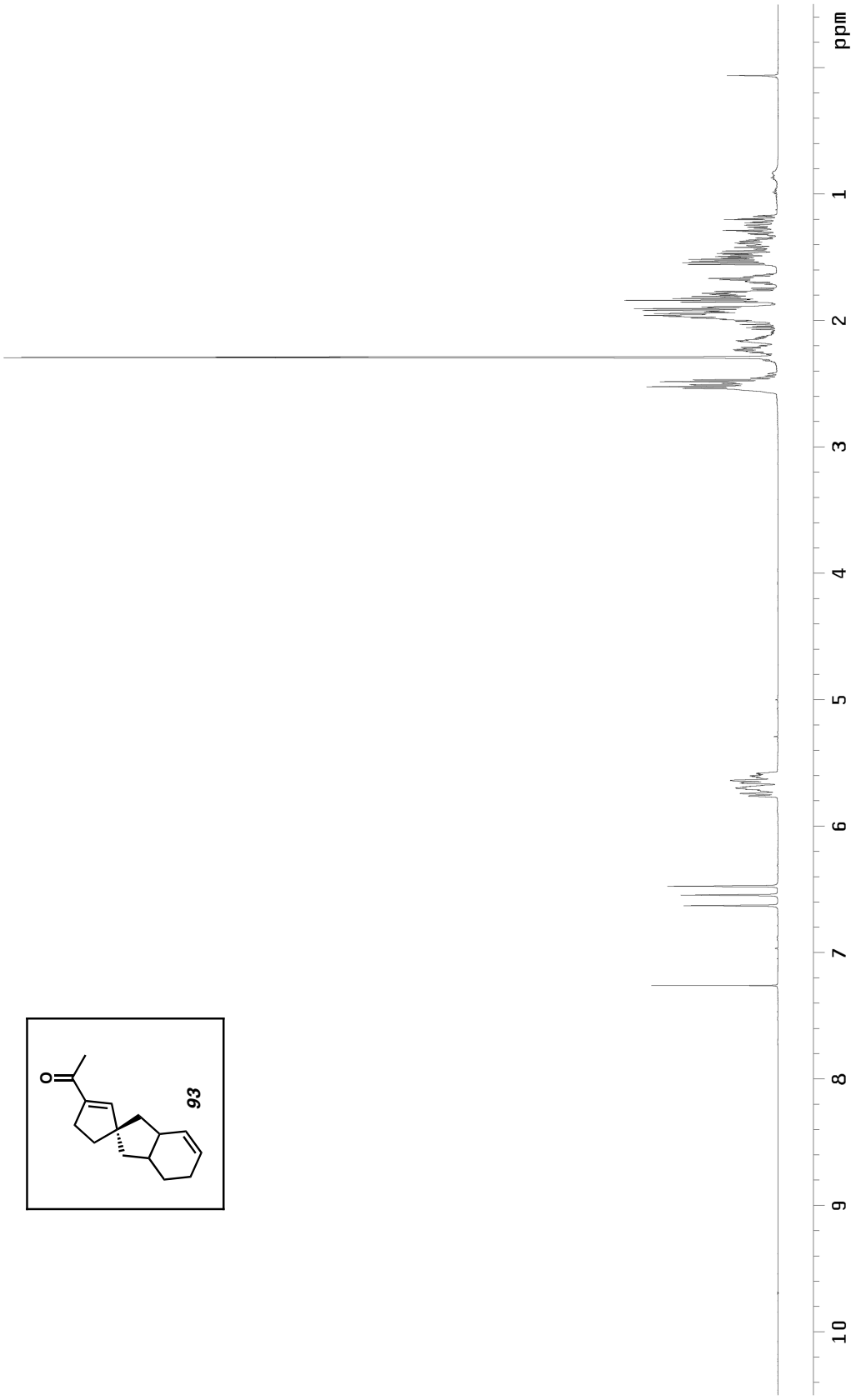


Figure A2.94.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **93**.

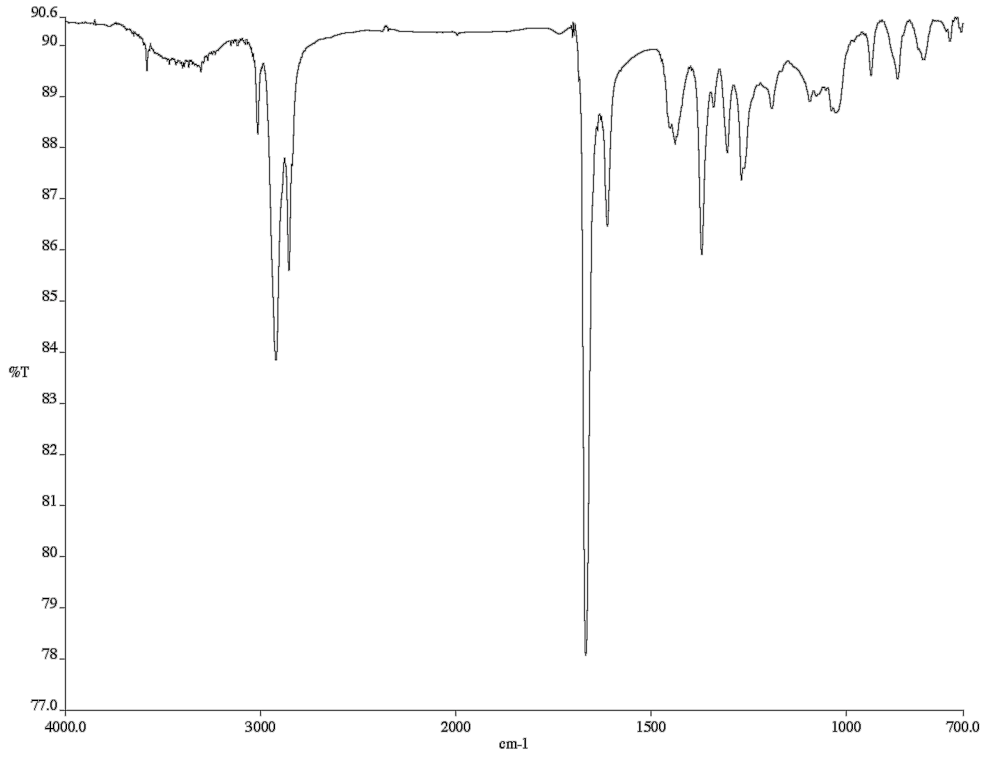


Figure A2.94.2. Infrared spectrum (thin film/NaCl) of compound **93**.

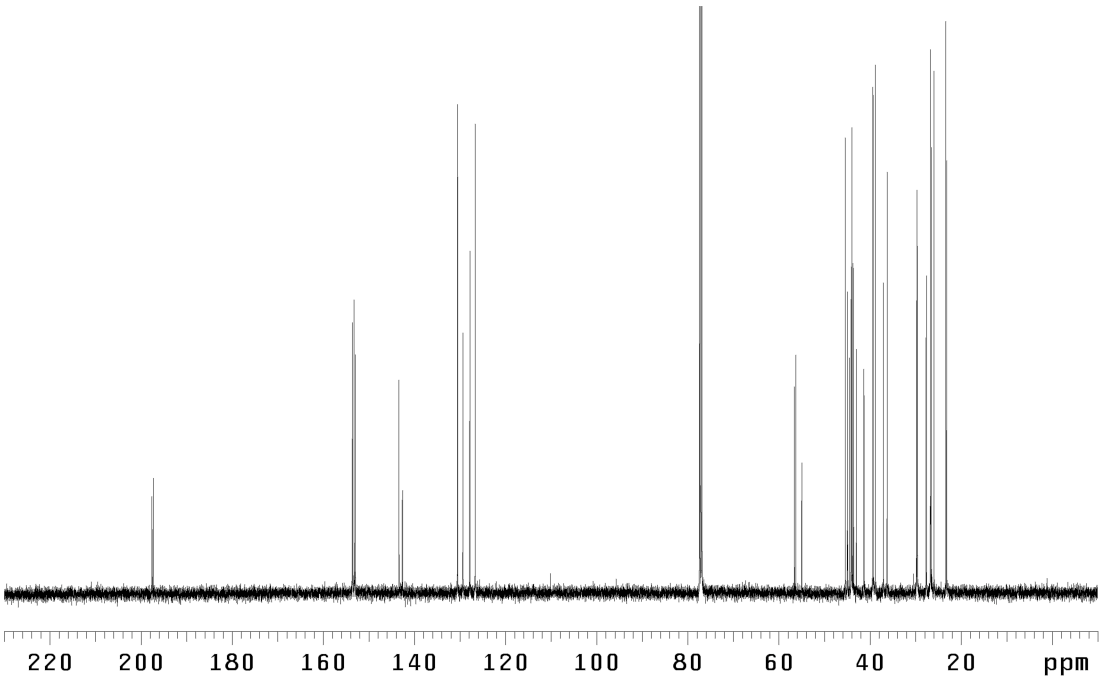


Figure A2.94.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **93**.

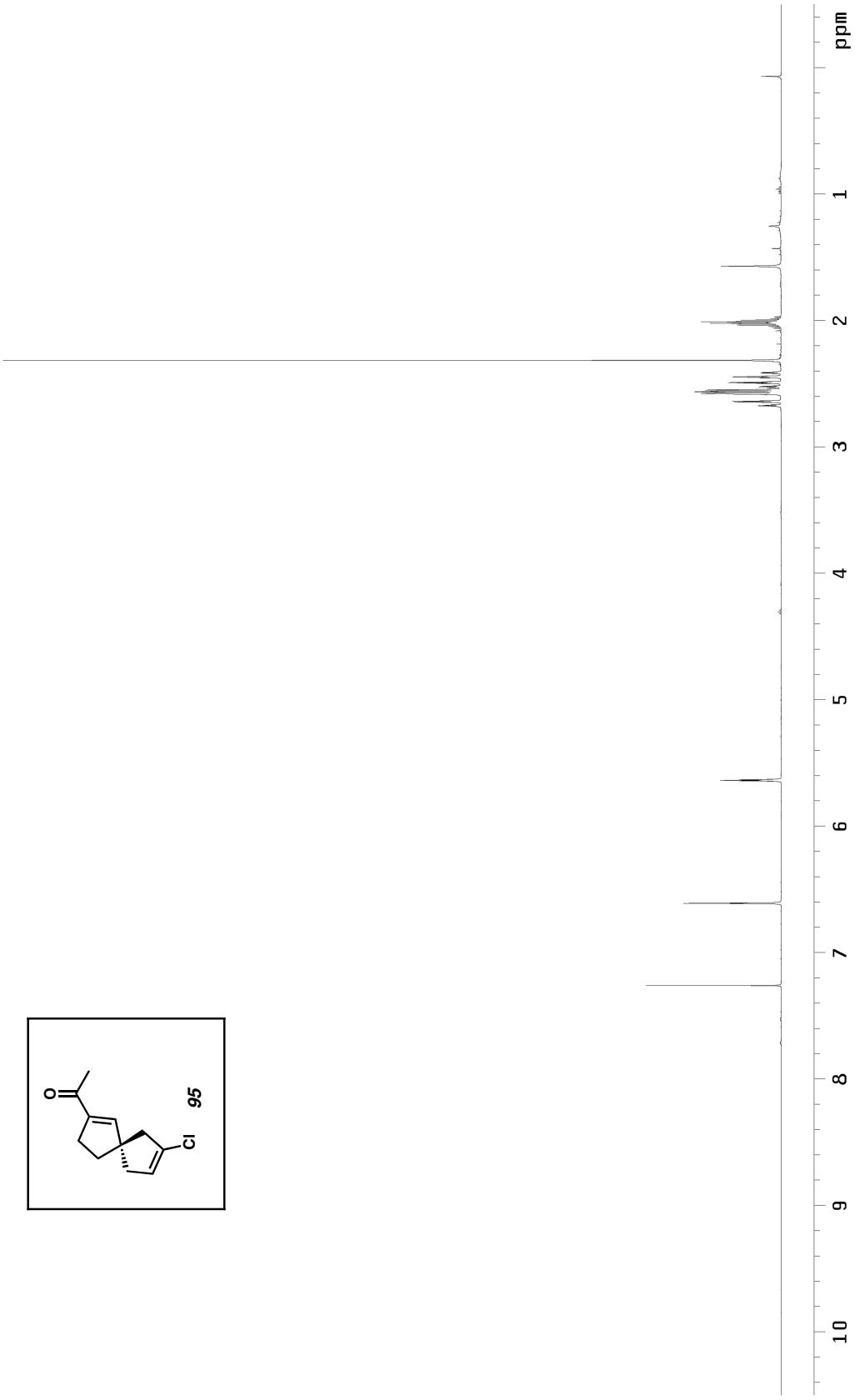


Figure A2.95.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **95**.

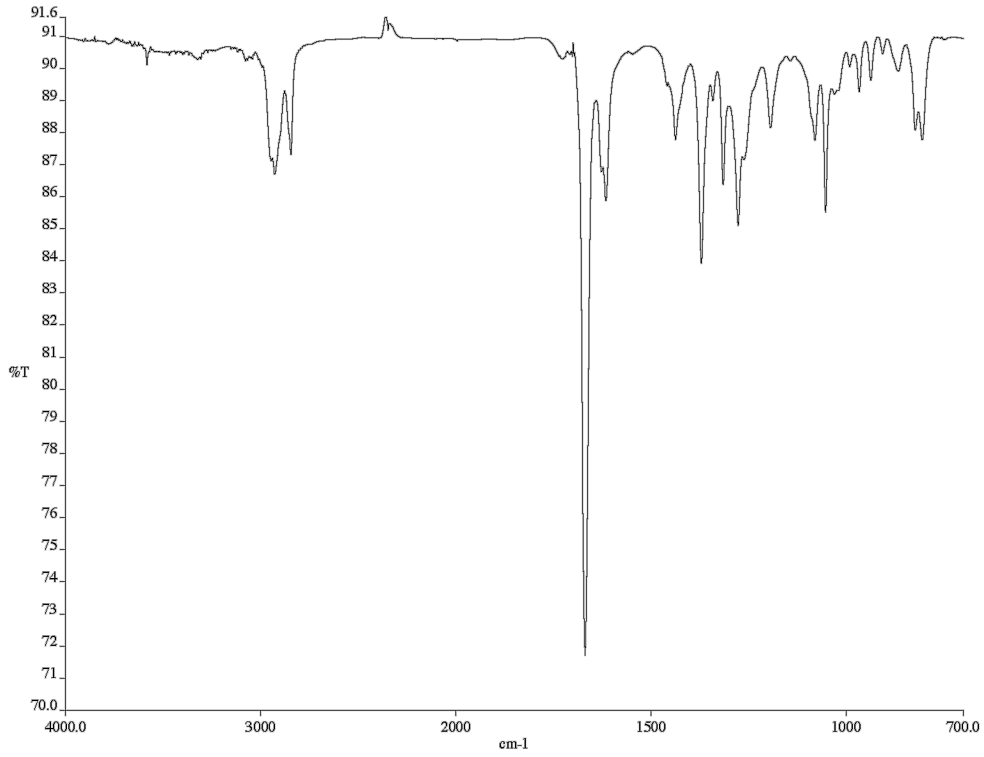


Figure A2.95.2. Infrared spectrum (thin film/NaCl) of compound **95**.

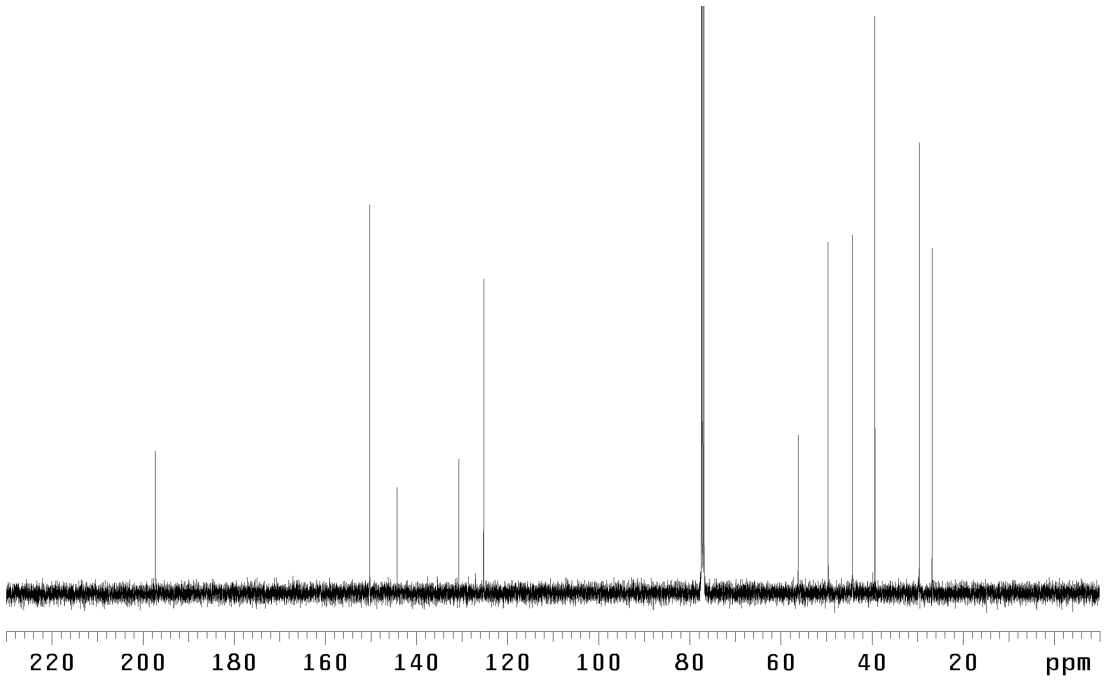


Figure A2.95.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **95**.

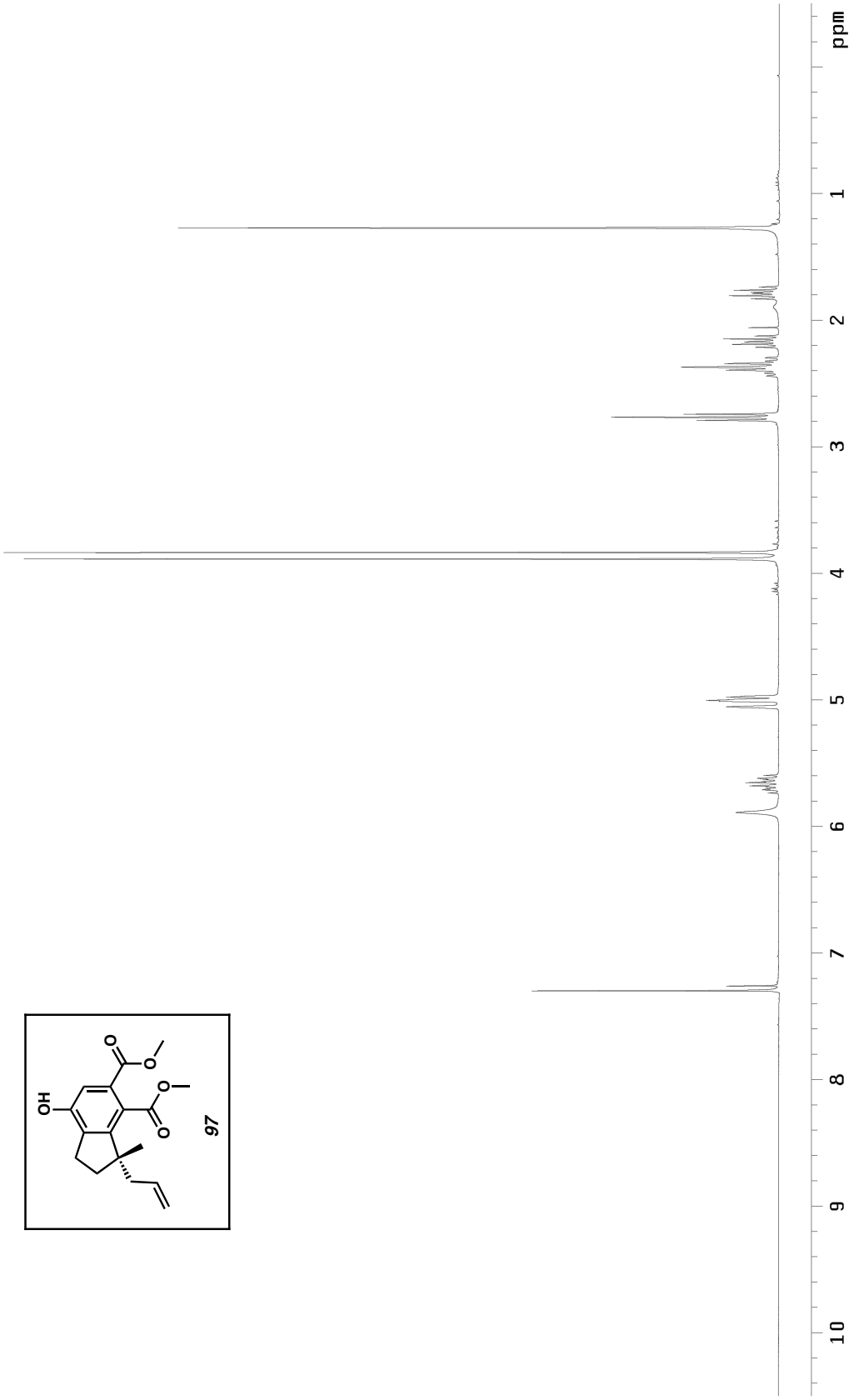


Figure A2.96.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **97**.

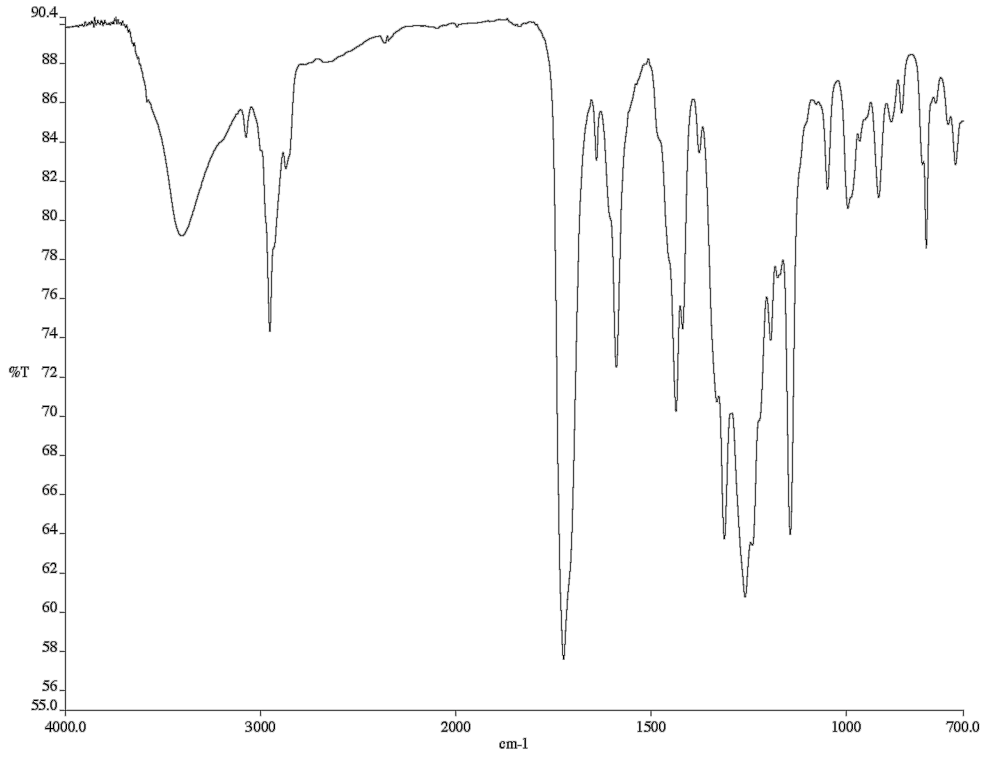


Figure A2.96.2. Infrared spectrum (thin film/NaCl) of compound **97**.

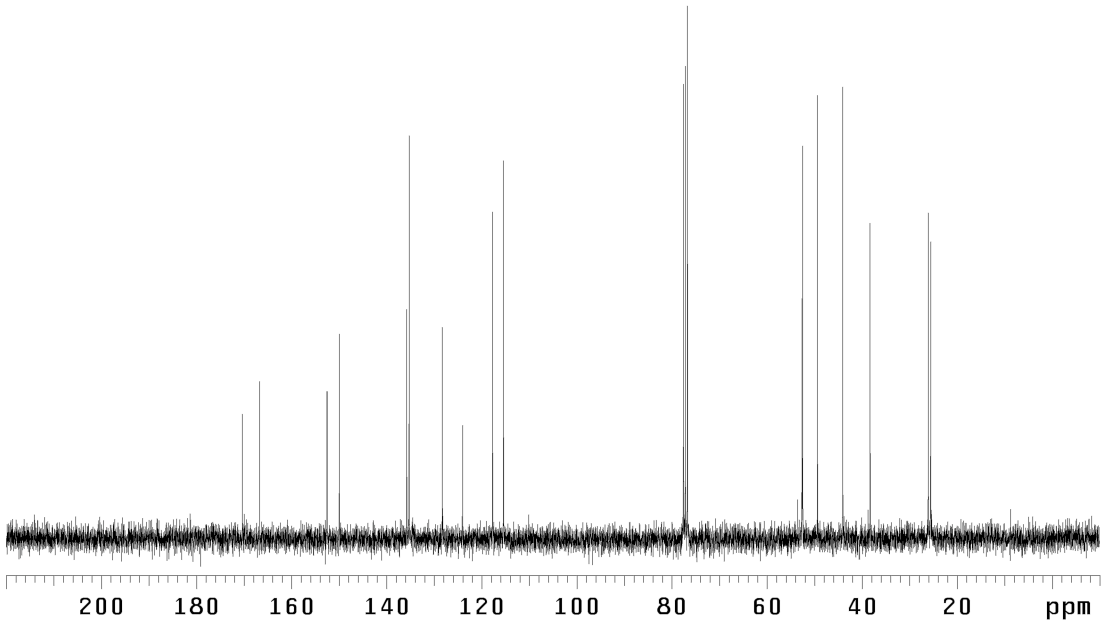


Figure A2.96.3. ^{13}C NMR (75 MHz, $CDCl_3$) of compound **97**.

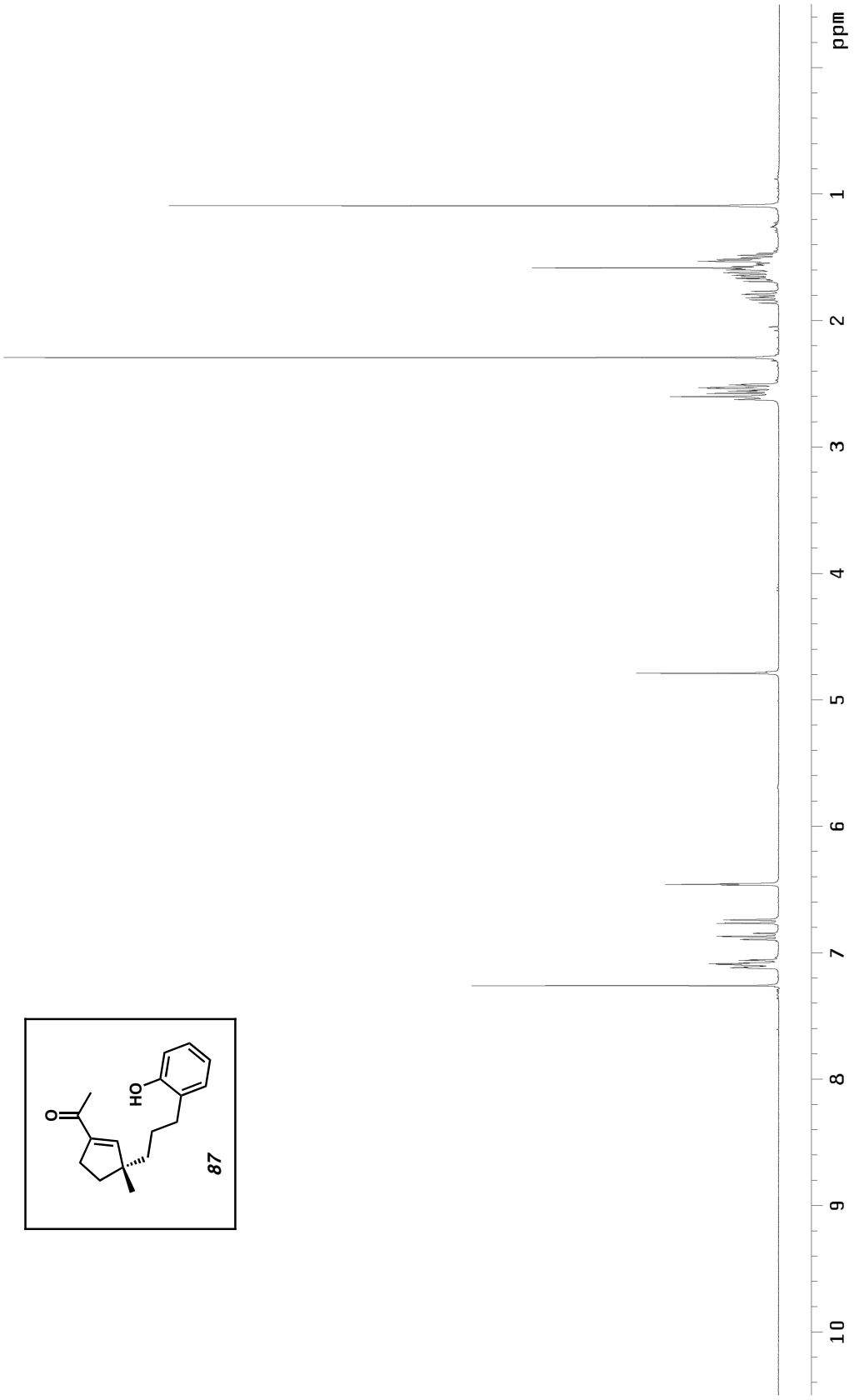


Figure A2.97.1. ^{1}H NMR (300 MHz, $CDCl_3$) of compound **87**.

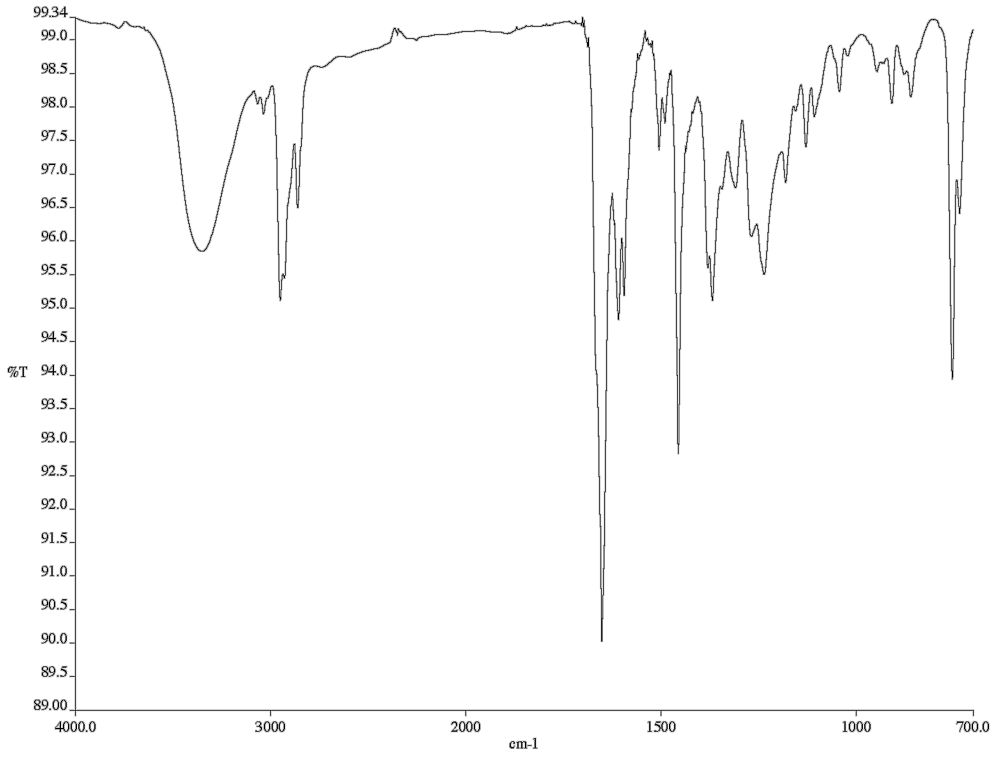


Figure A2.97.2. Infrared spectrum (thin film/NaCl) of compound **87**.

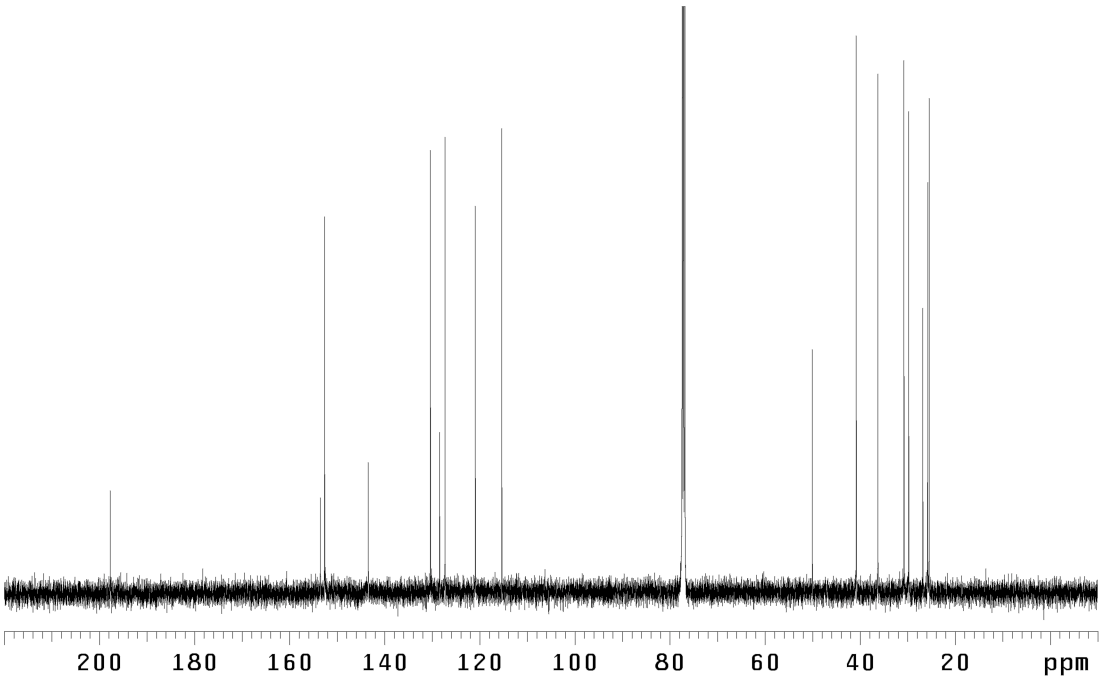


Figure A2.97.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **87**.

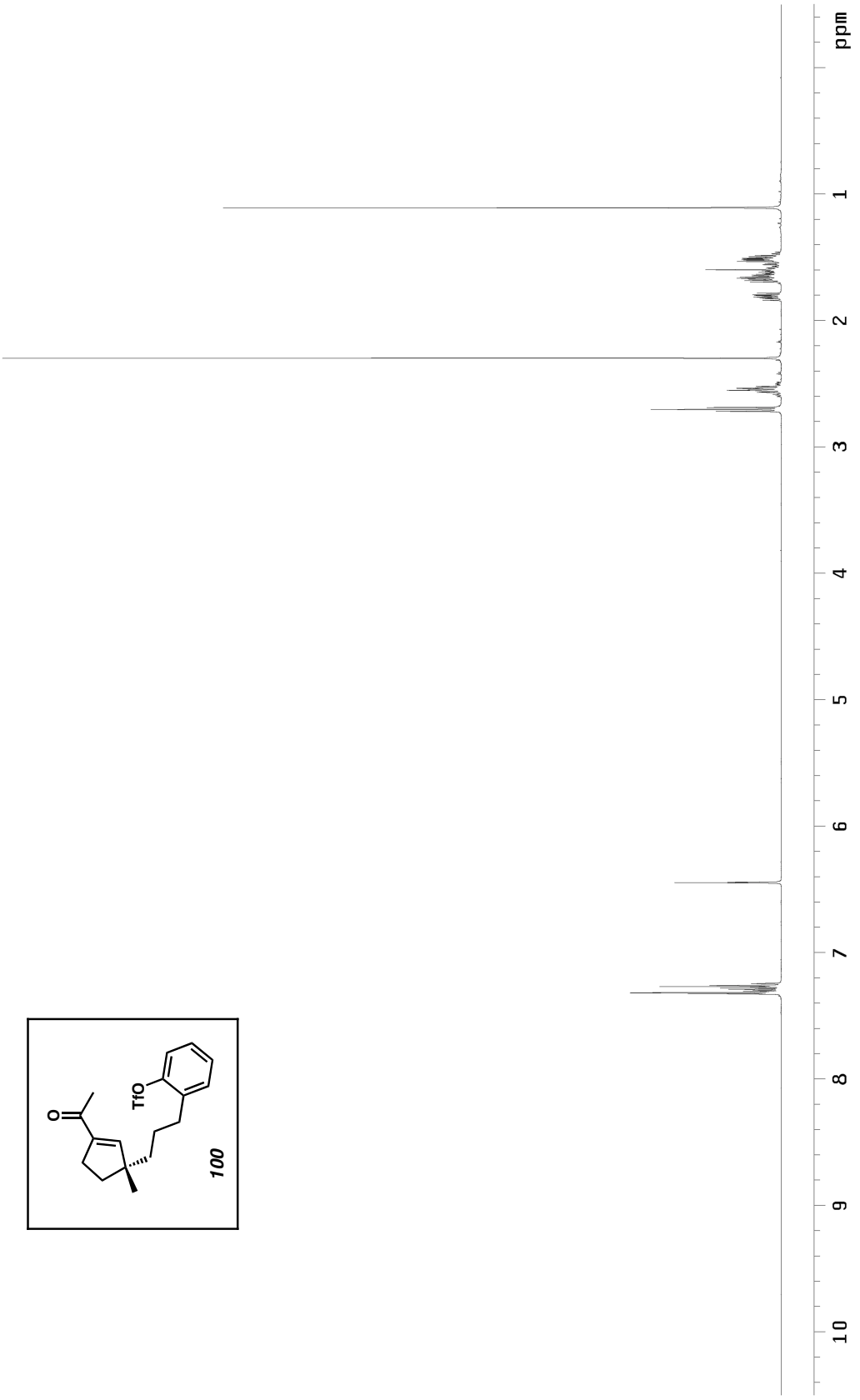


Figure A2.98.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **100**.

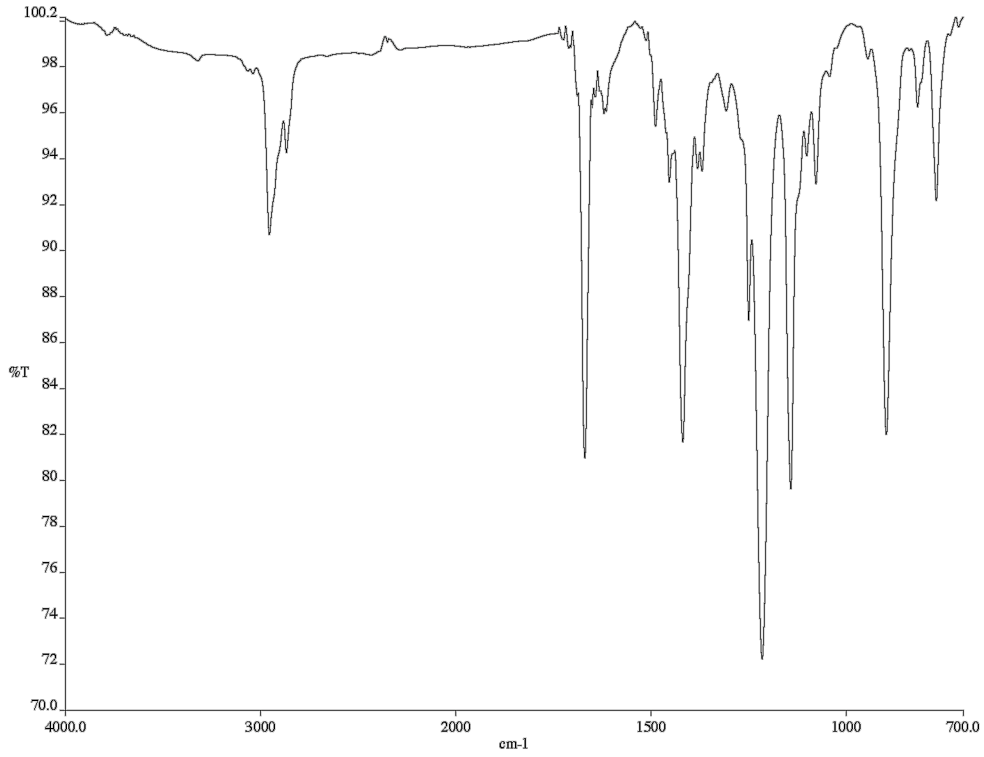


Figure A2.98.2. Infrared spectrum (thin film/NaCl) of compound **100**.

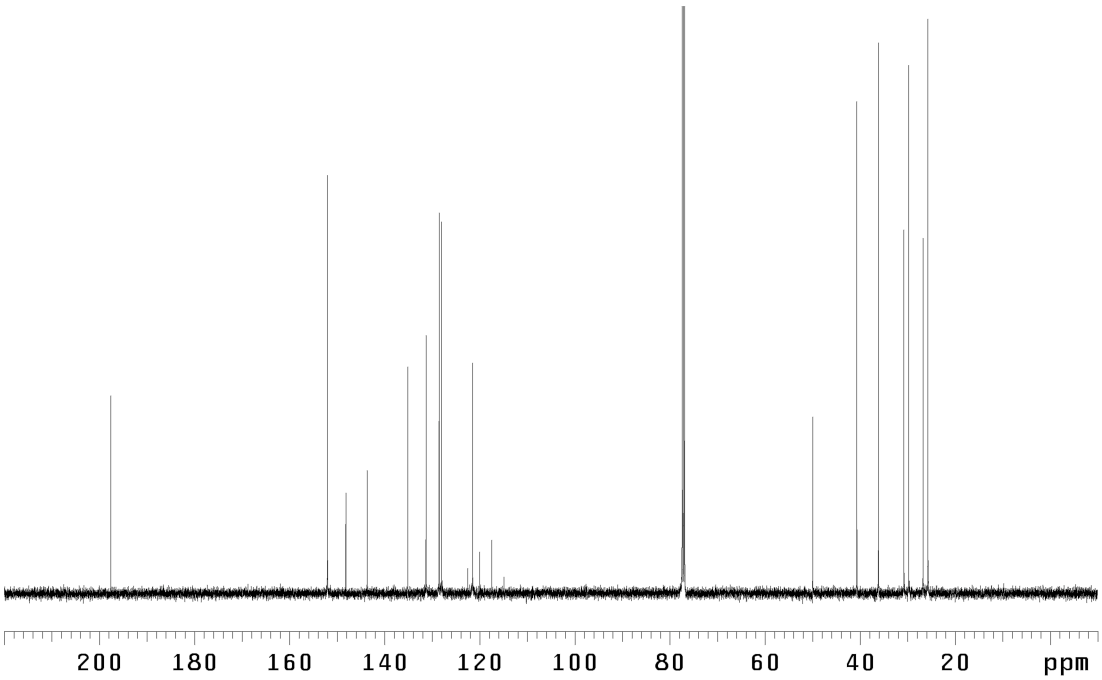


Figure A2.98.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **100**.

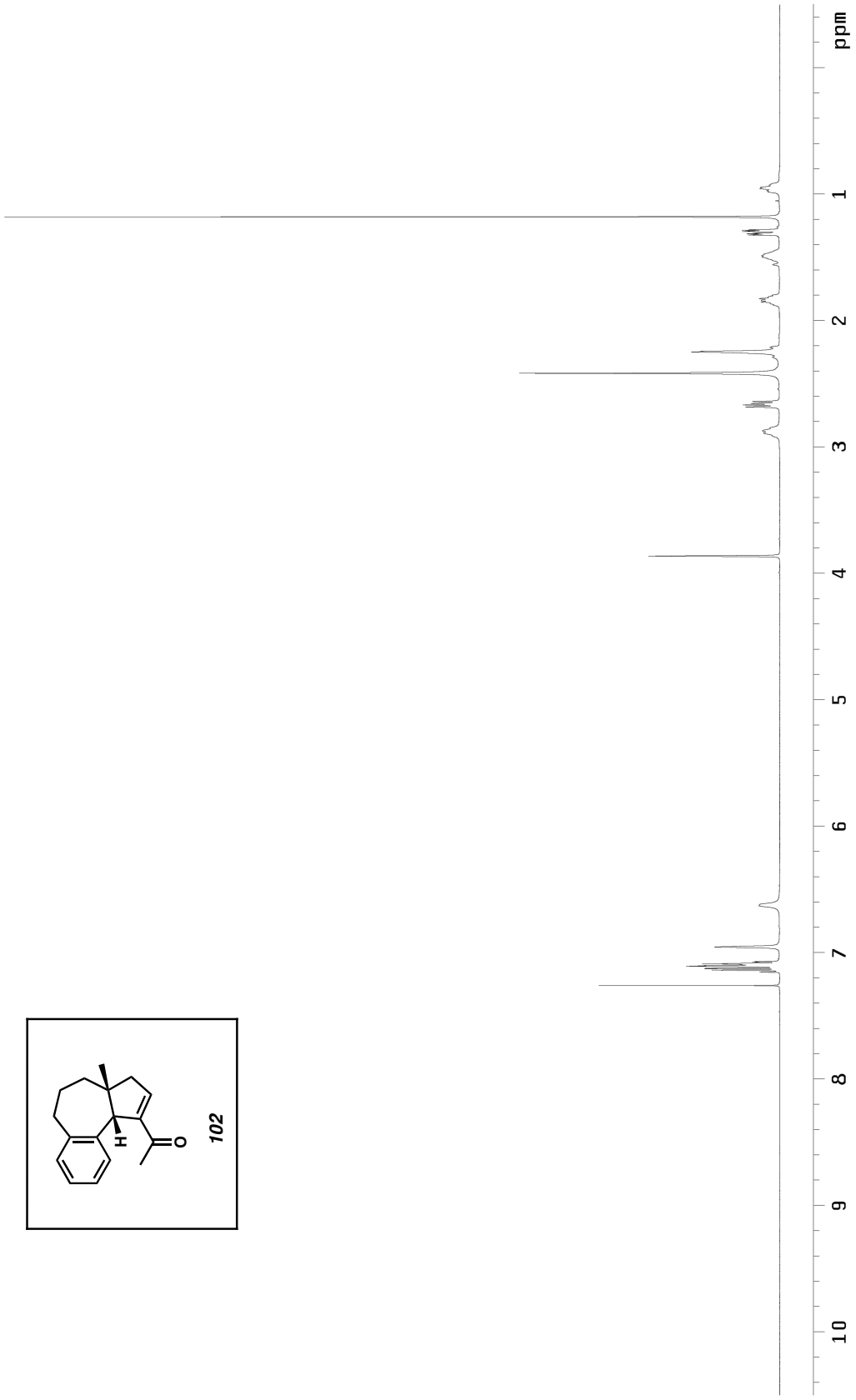


Figure A2.99.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **102**.

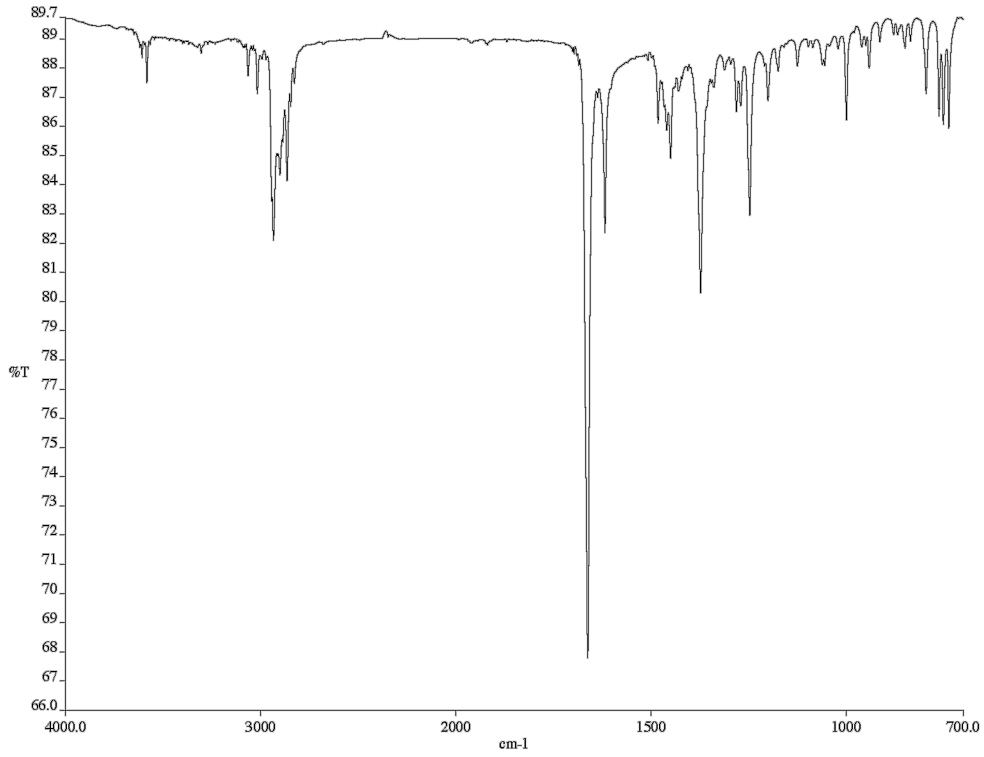


Figure A2.99.2. Infrared spectrum (thin film/NaCl) of compound **102**.

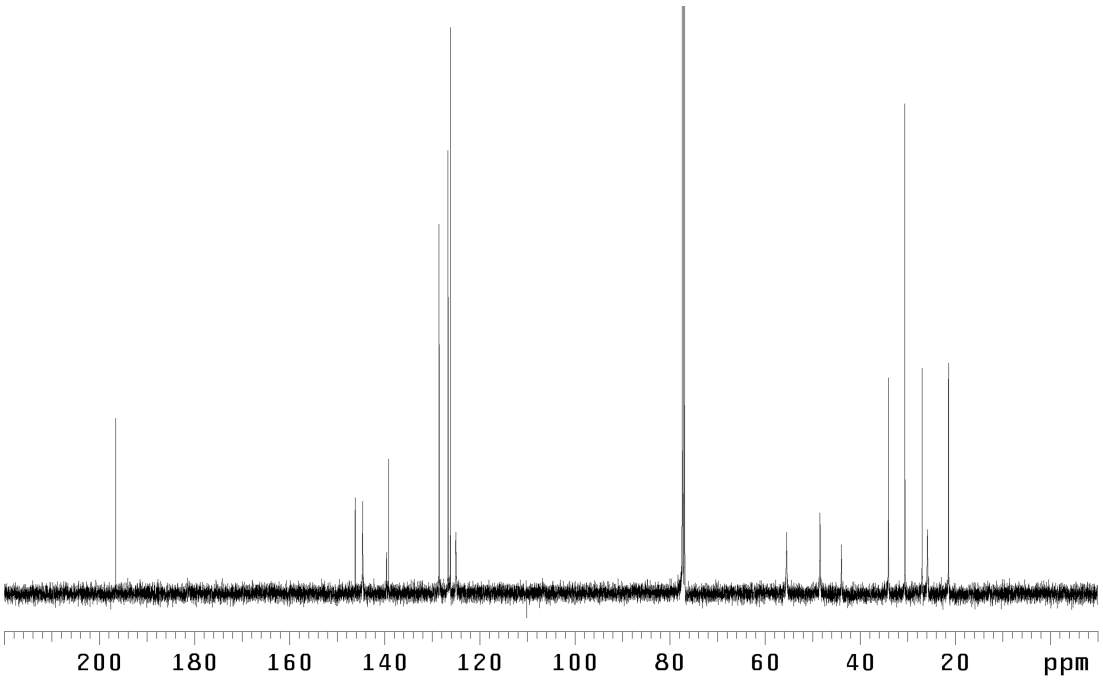


Figure A2.99.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **102**.

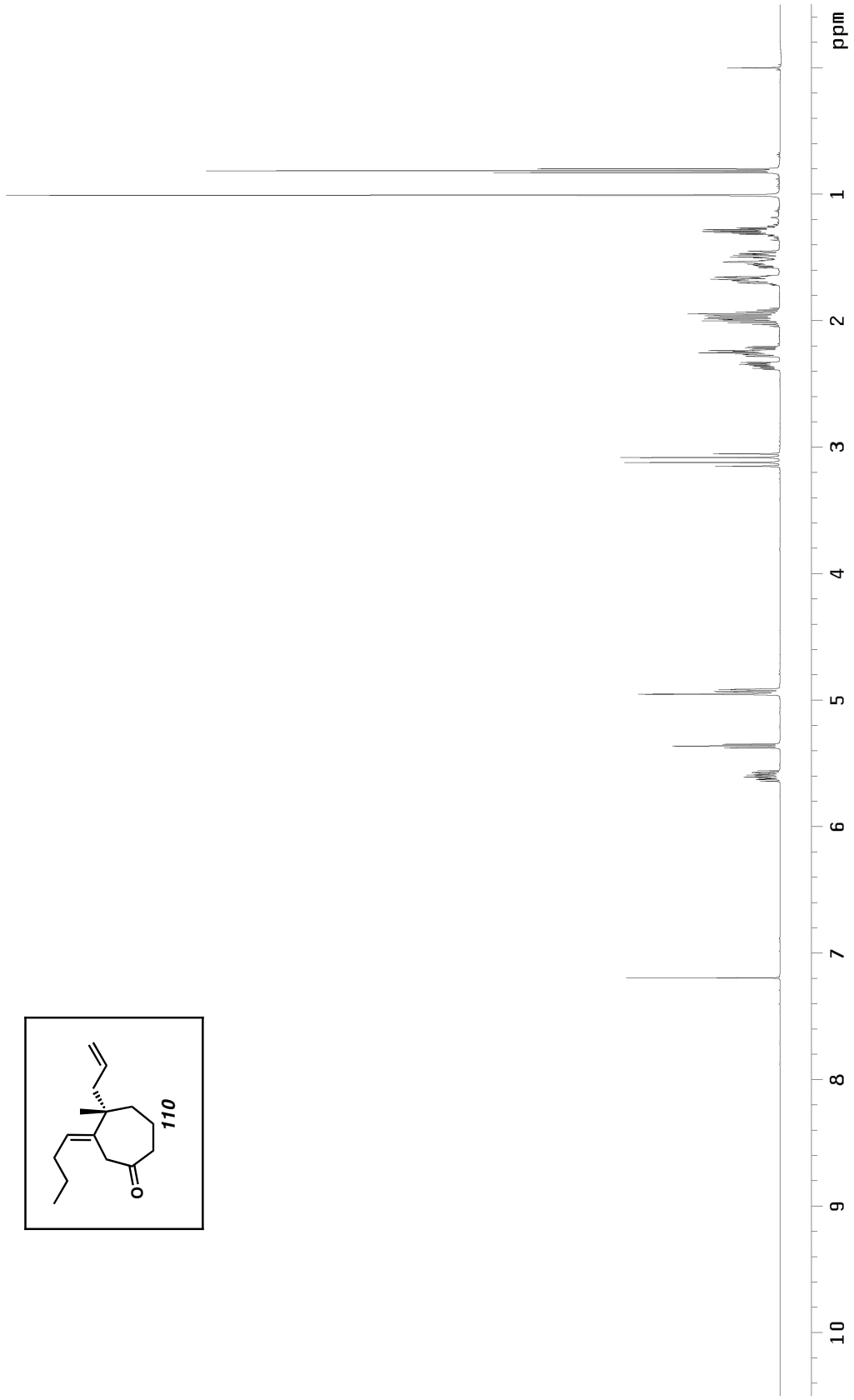


Figure A2.100.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **110**.

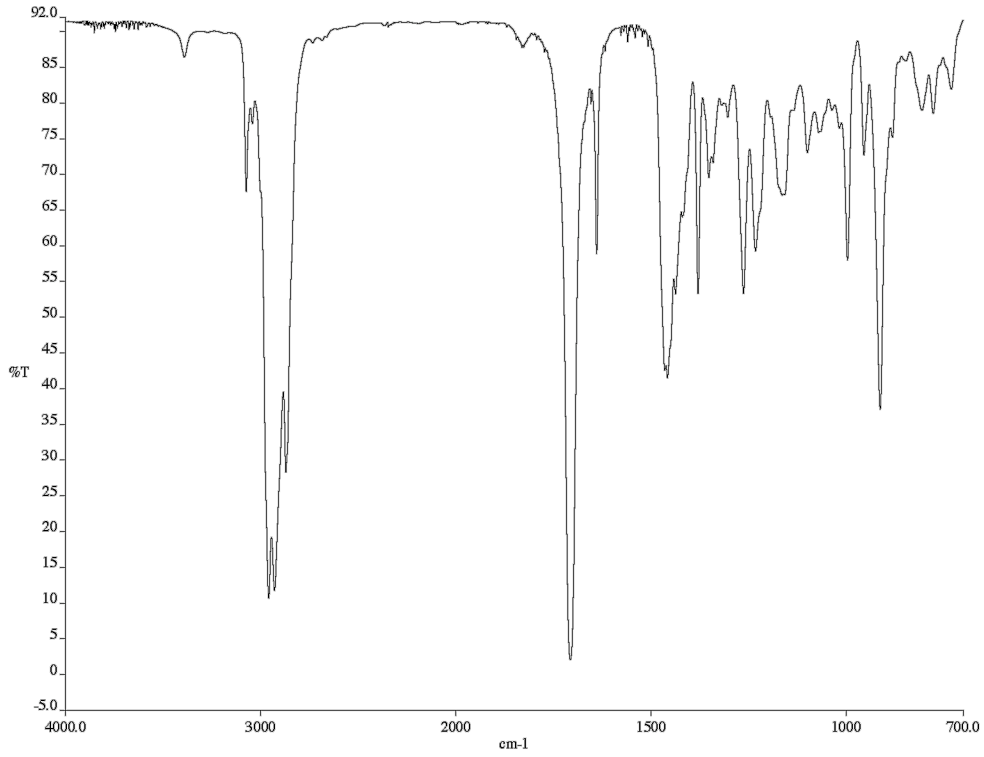


Figure A2.100.2. Infrared spectrum (thin film/NaCl) of compound **110**.

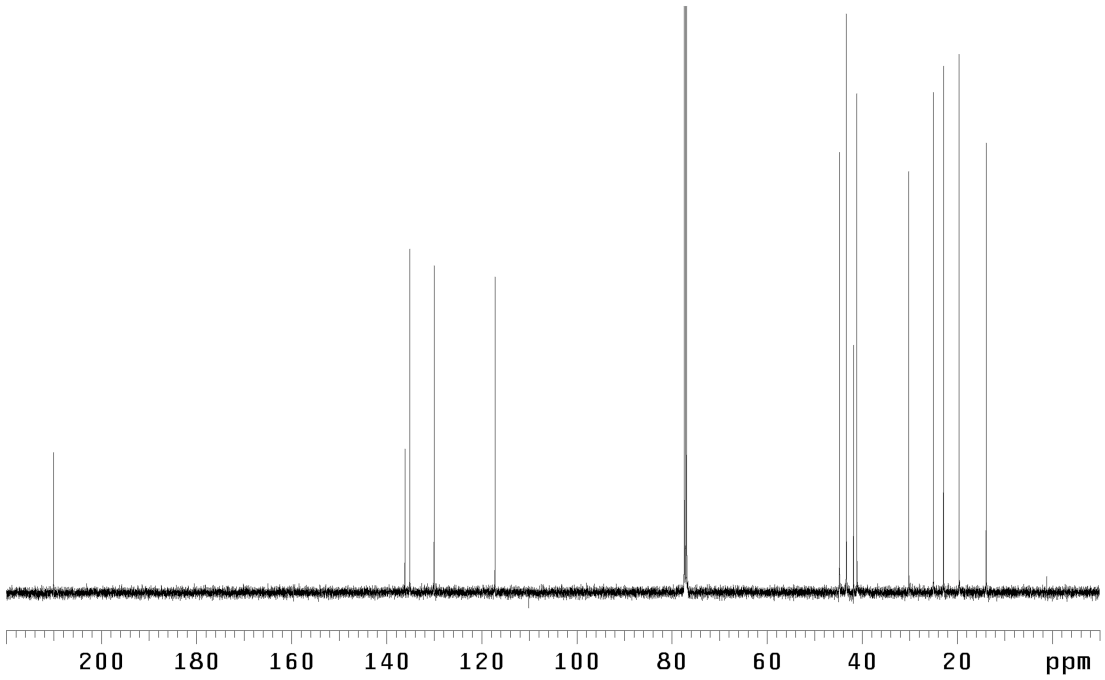


Figure A2.100.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **110**.

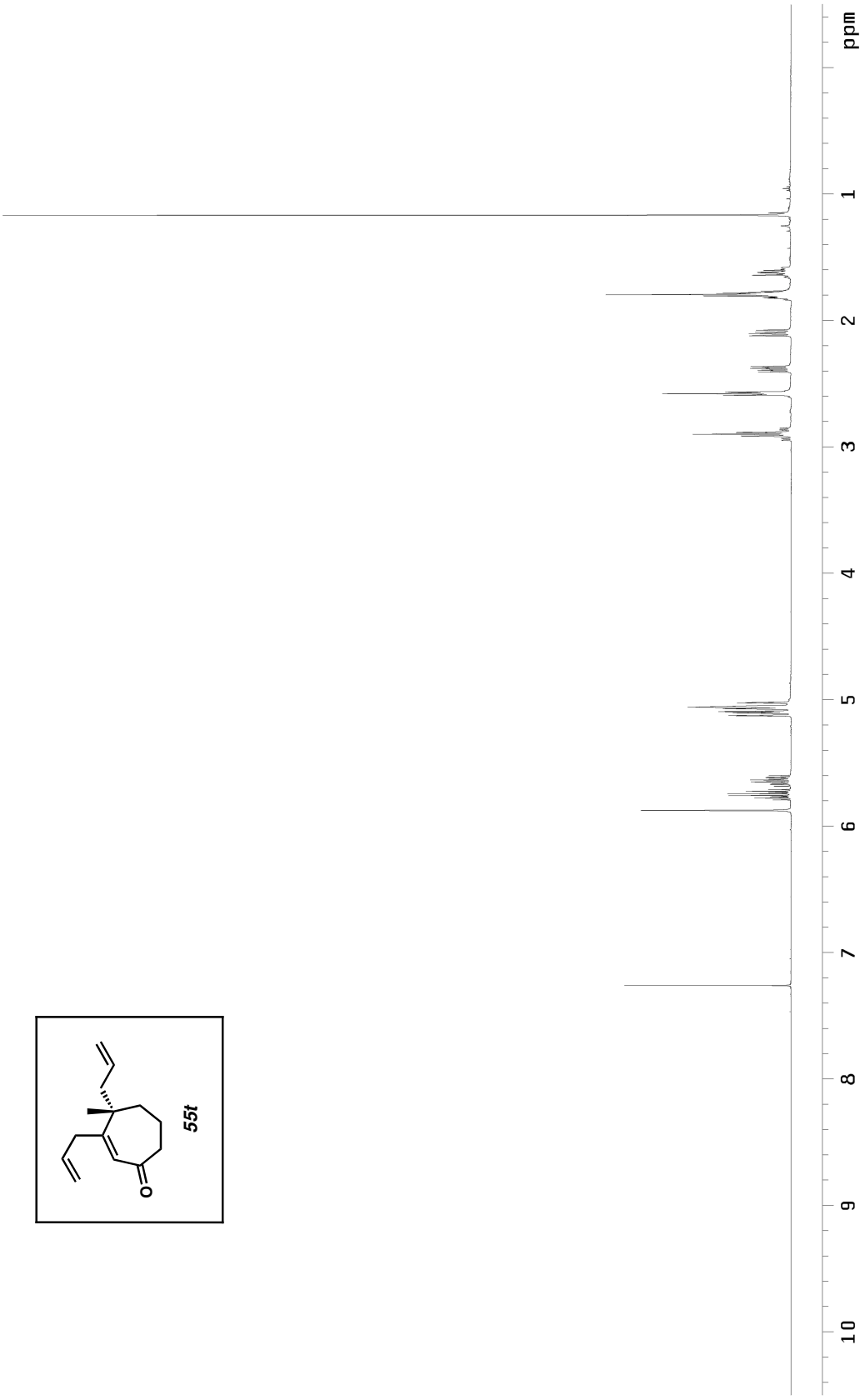


Figure A2.101.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **55t**.

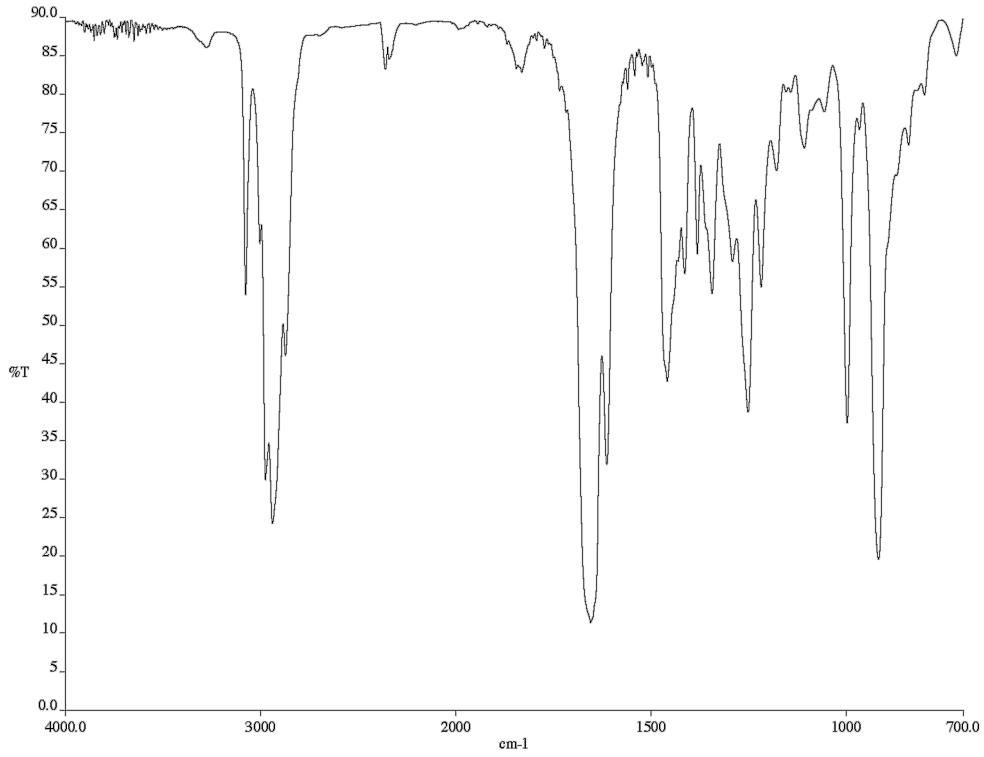


Figure A2.101.2. Infrared spectrum (thin film/NaCl) of compound **55t**.

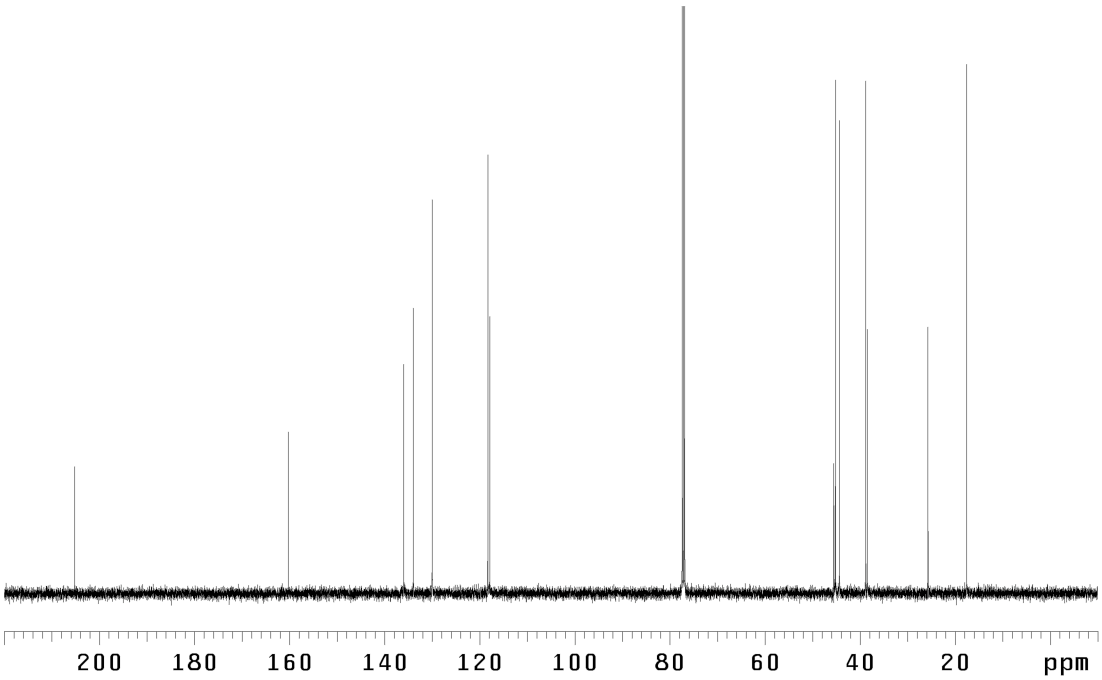


Figure A2.101.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **55t**.

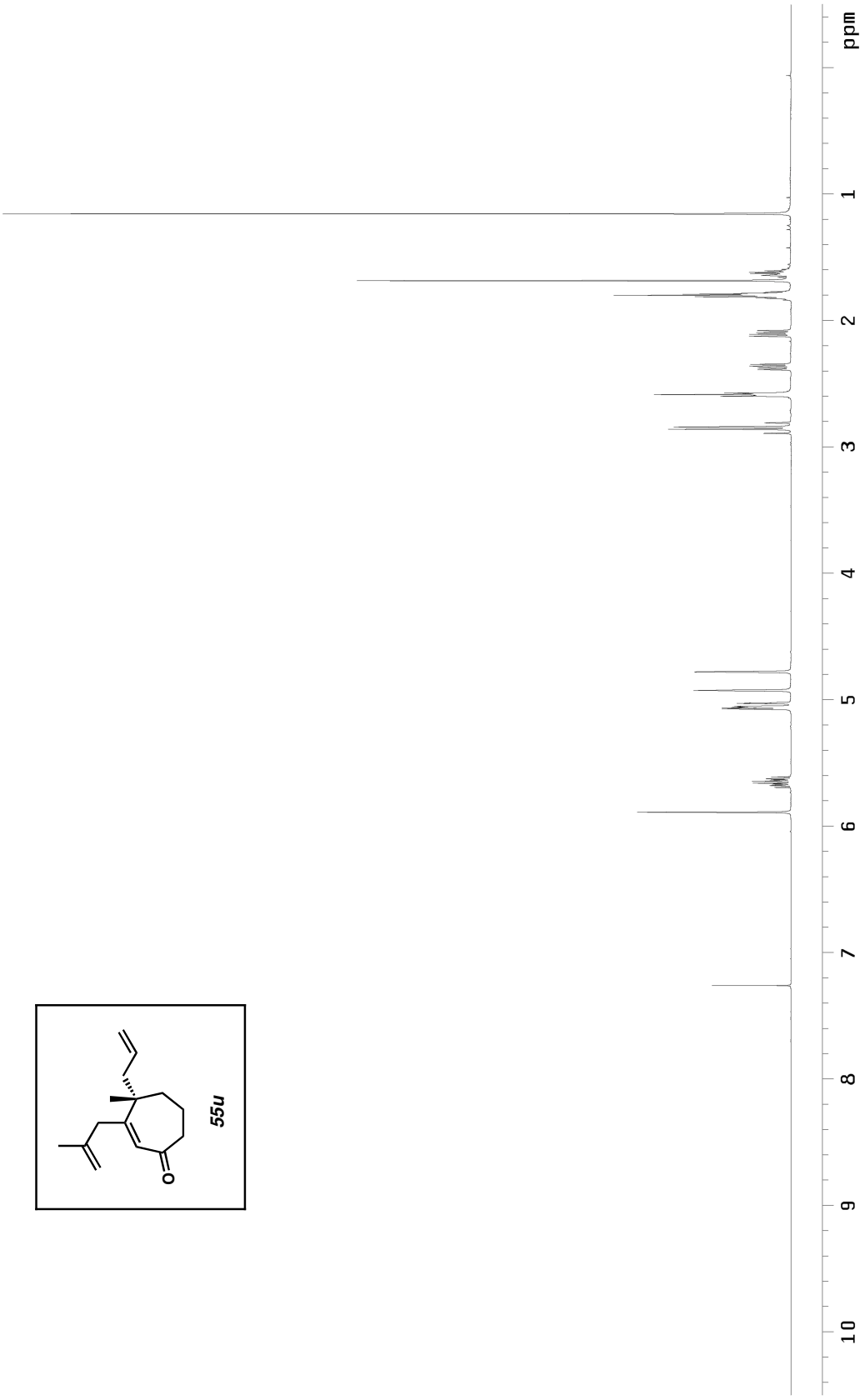


Figure A2.102.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **55u**.

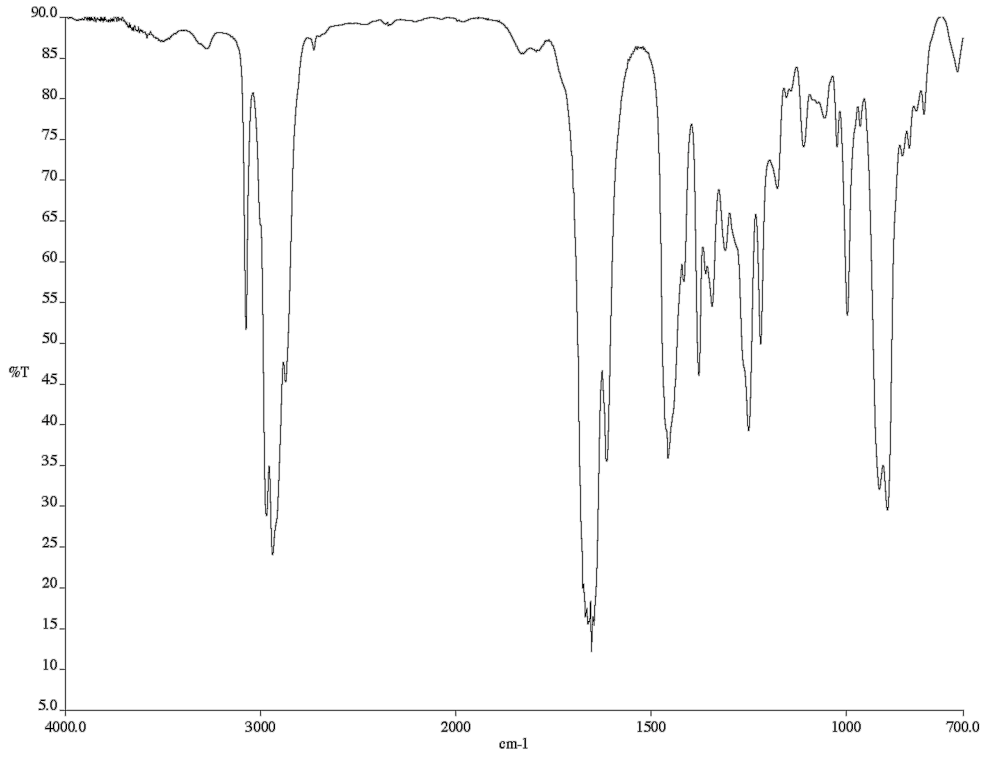


Figure A2.102.2. Infrared spectrum (thin film/NaCl) of compound **55u**.

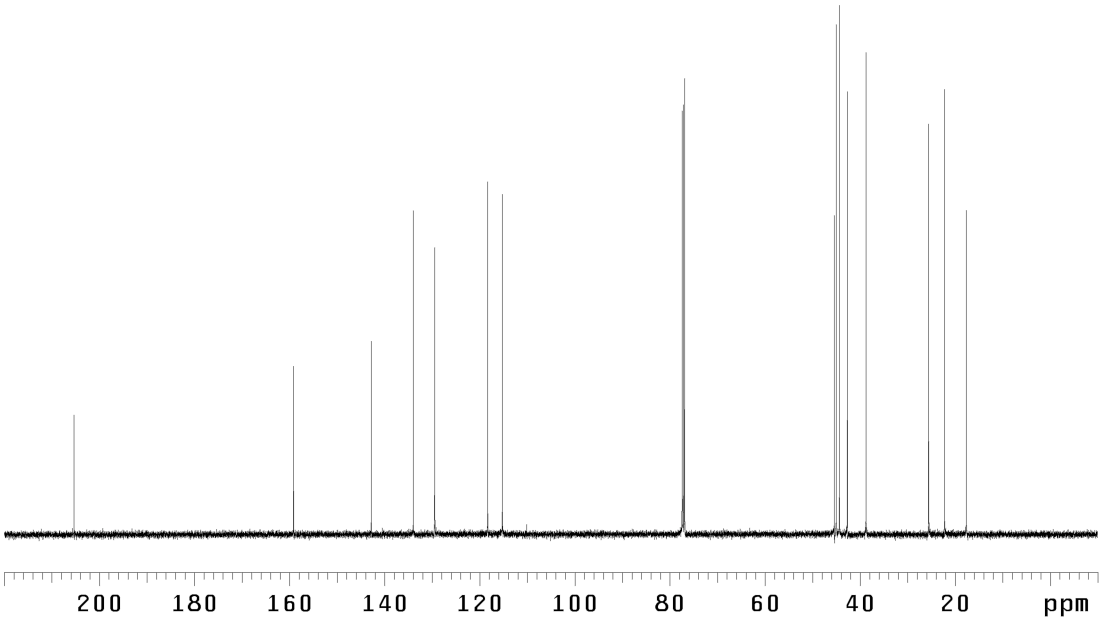


Figure A2.102.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **55u**.

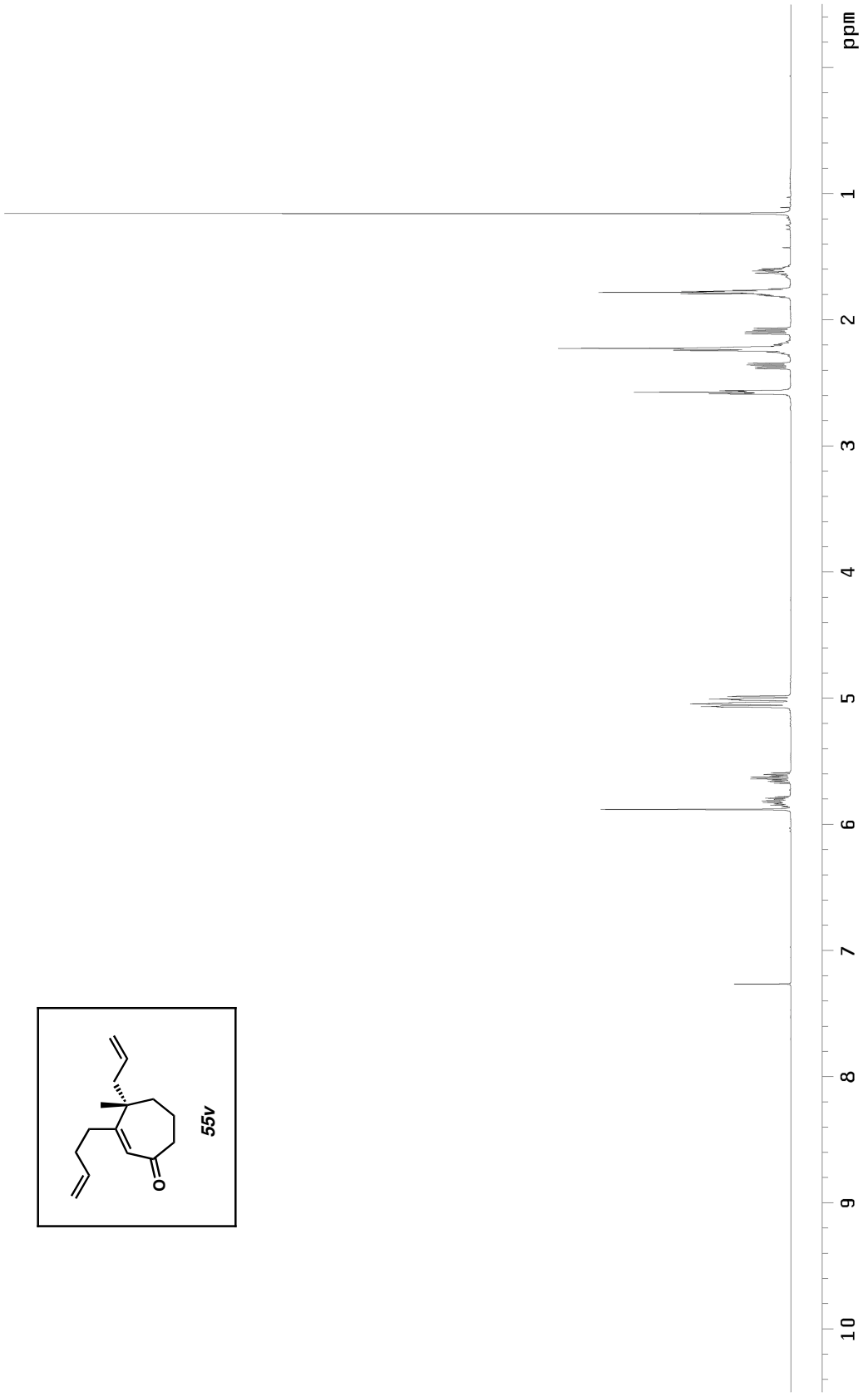


Figure A2.103.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **55v**.

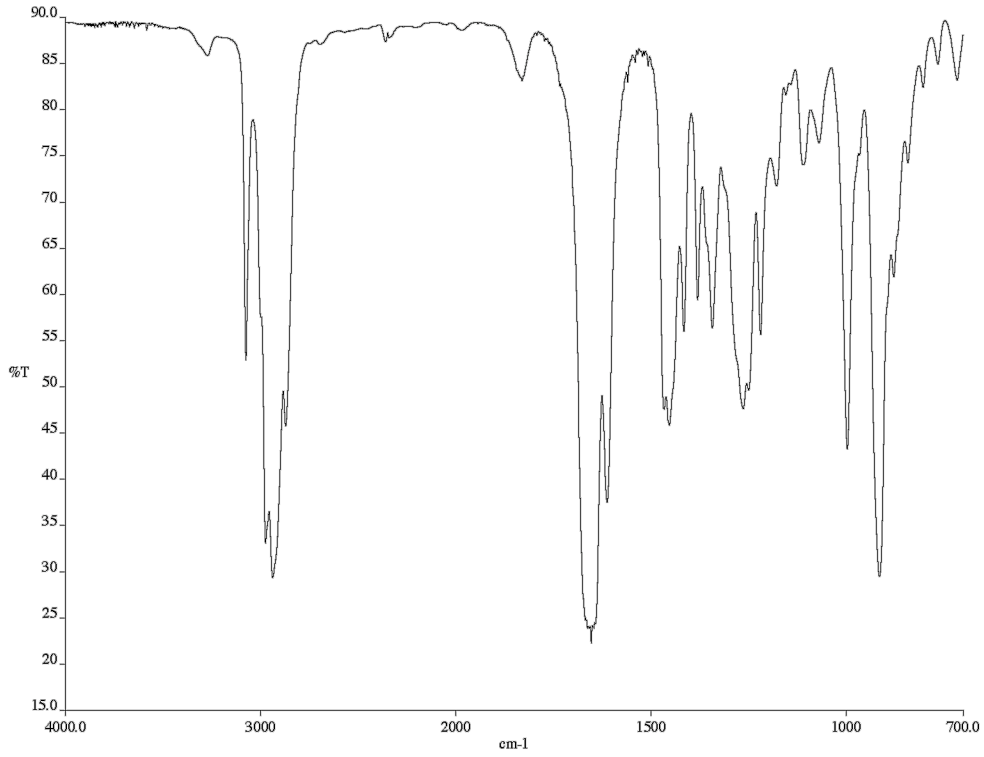


Figure A2.103.2. Infrared spectrum (thin film/NaCl) of compound **55v**.

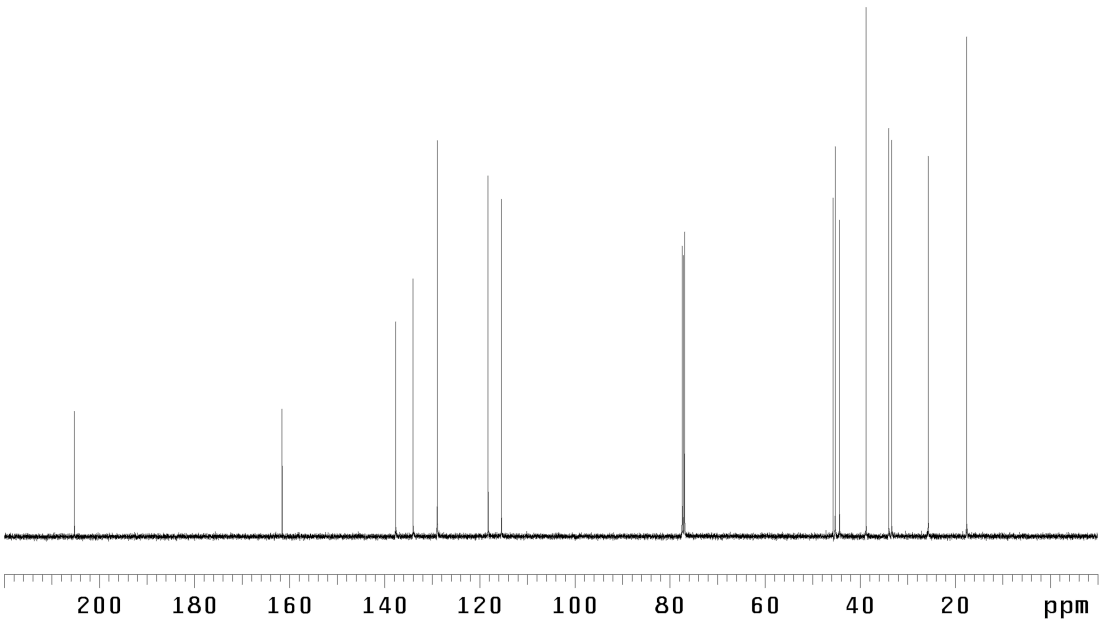


Figure A2.103.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **55v**.

Figure A2.104.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **55w**.

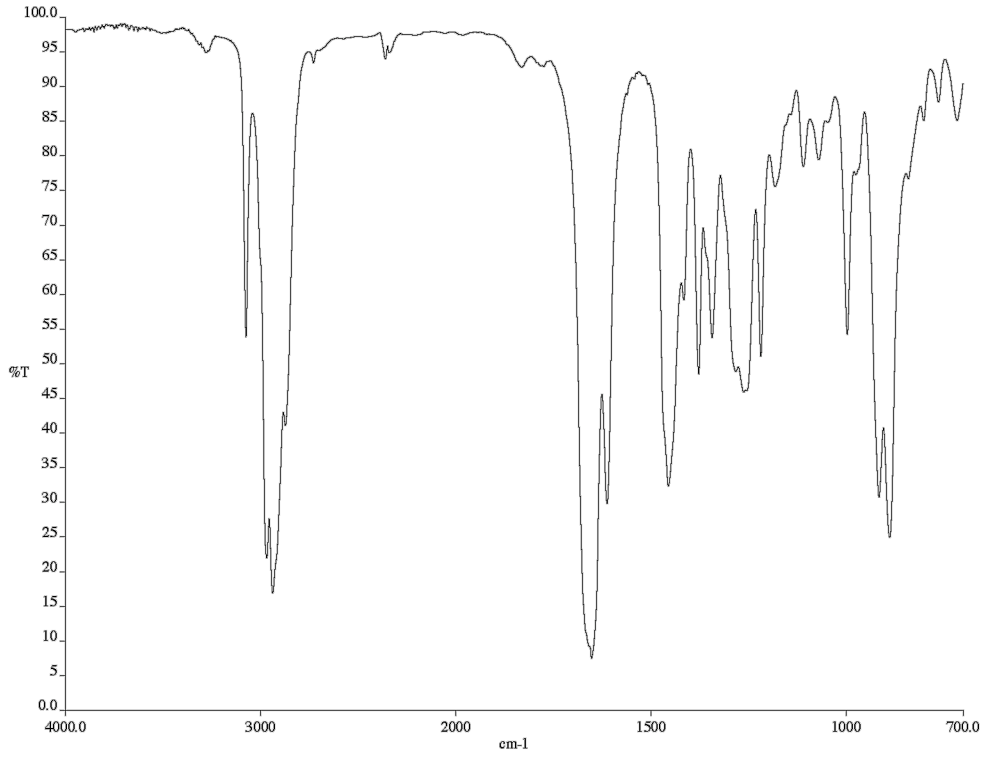


Figure A2.104.2. Infrared spectrum (thin film/NaCl) of compound **55w**.

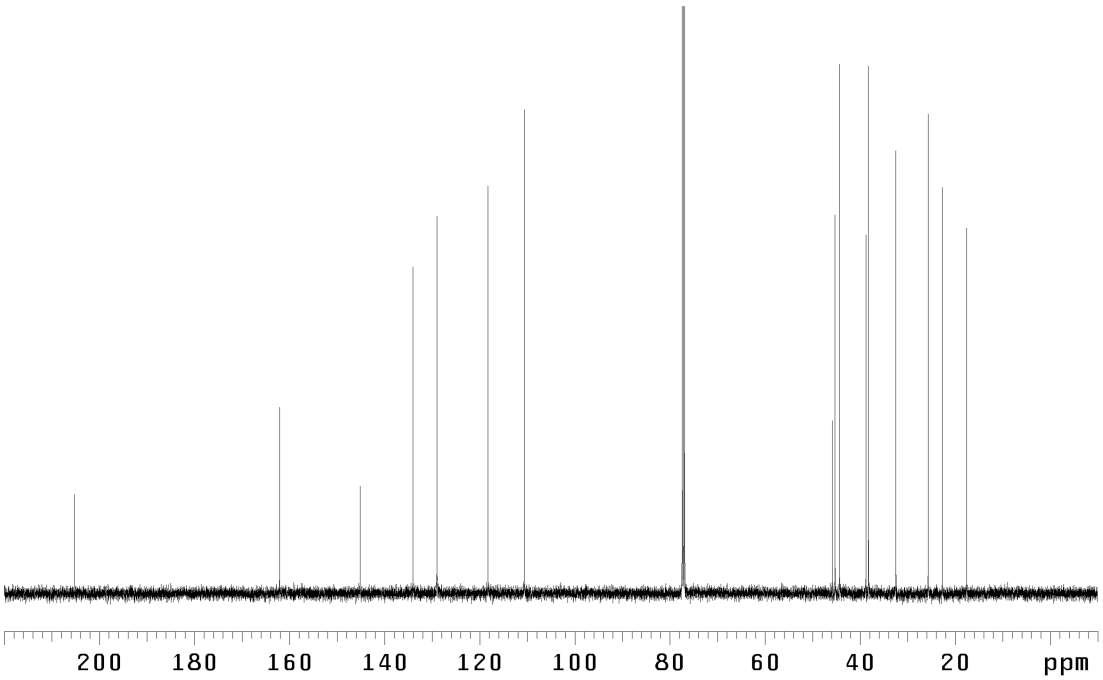


Figure A2.104.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **55w**.

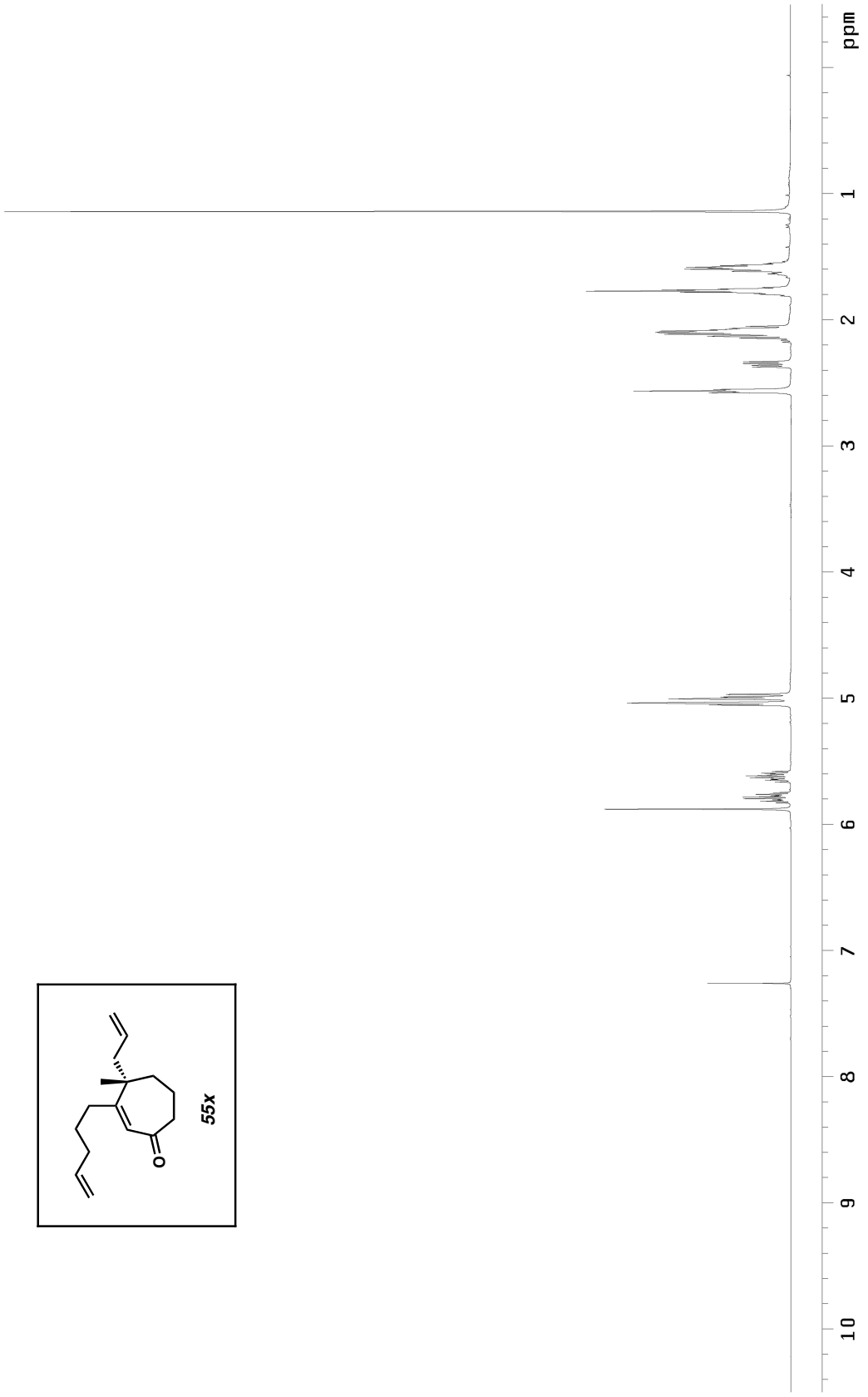


Figure A2.105.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **55x**.

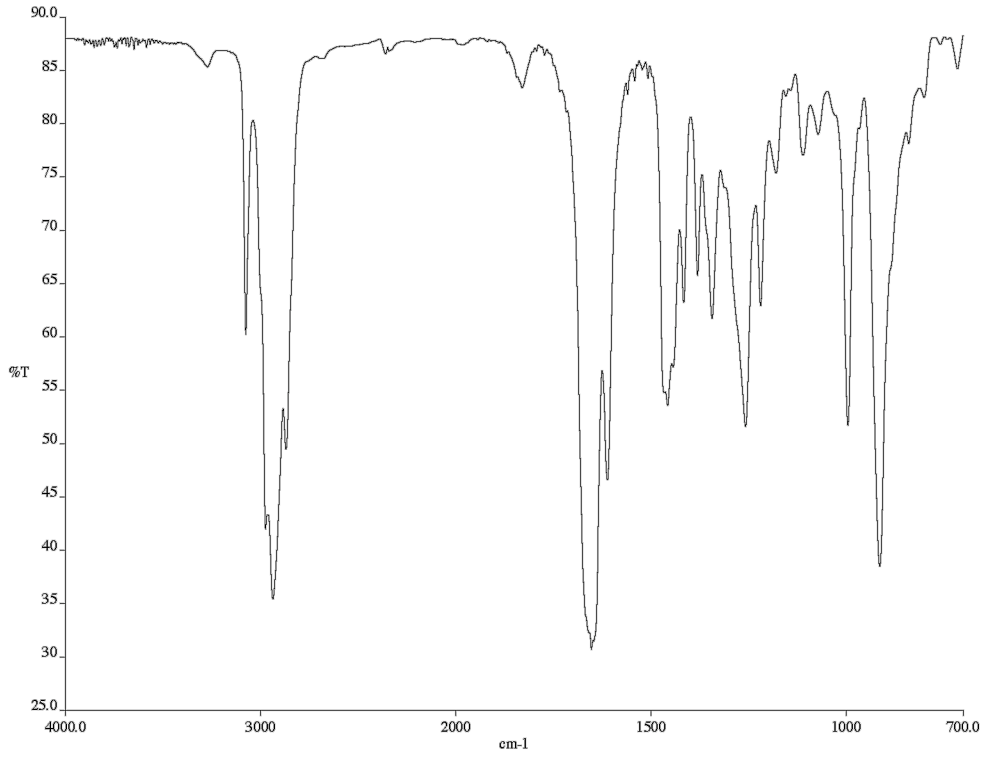


Figure A2.105.2. Infrared spectrum (thin film/NaCl) of compound **55x**.

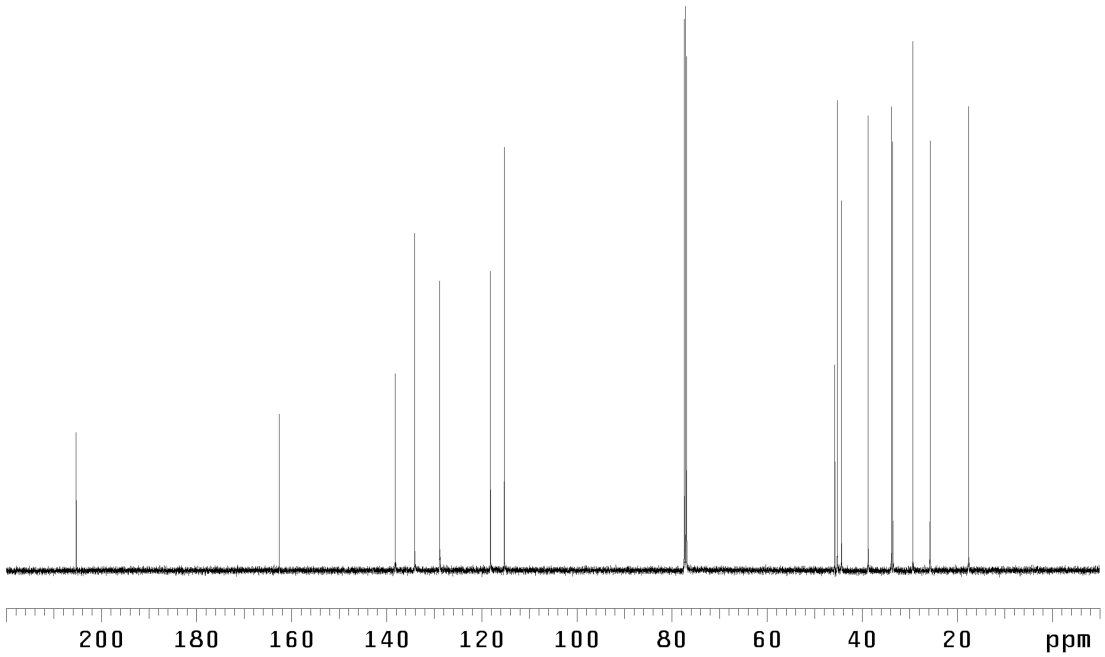


Figure A2.105.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **55x**.

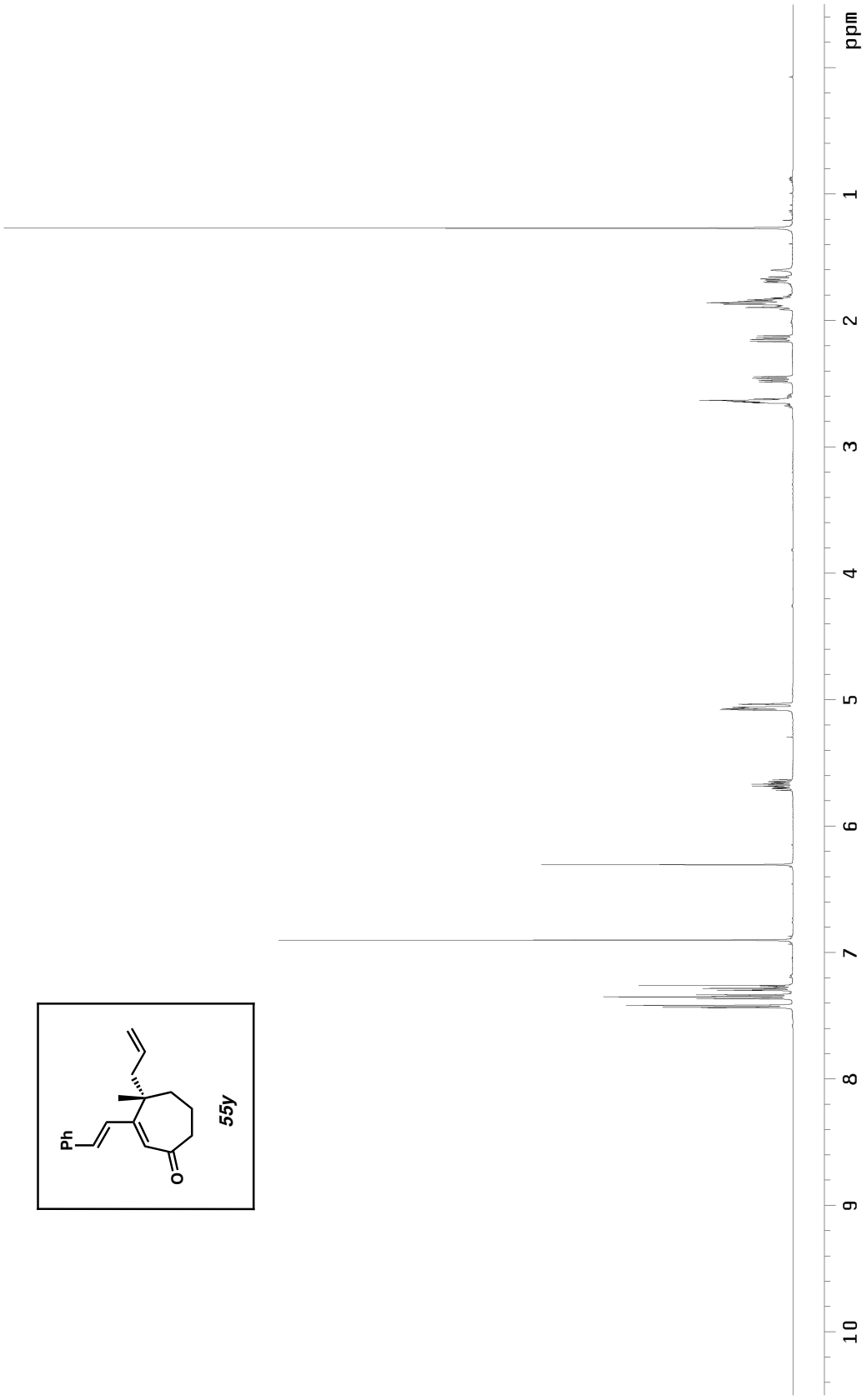


Figure A2.106.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **55y**.

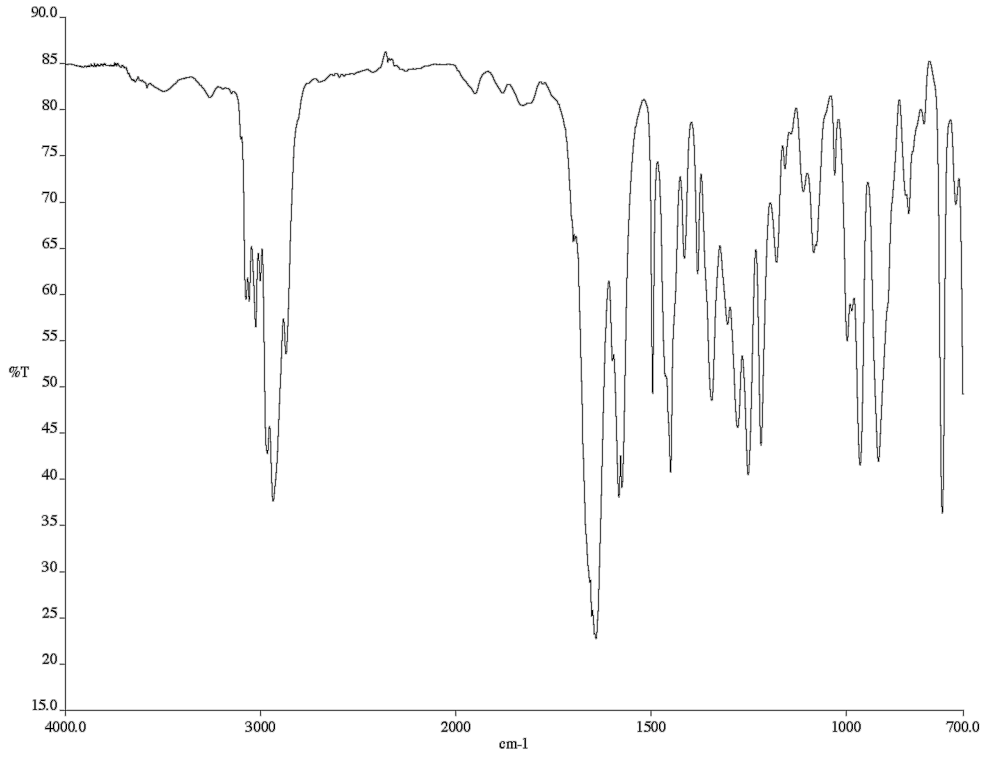


Figure A2.106.2. Infrared spectrum (thin film/NaCl) of compound **55y**.

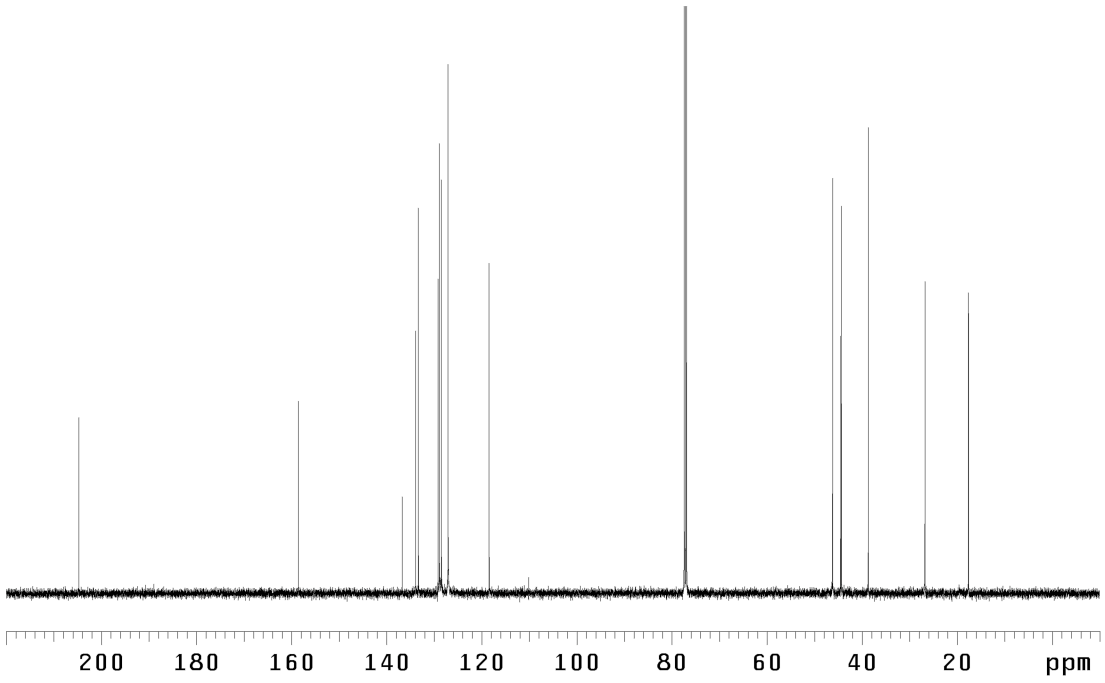


Figure A2.106.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **55y**.

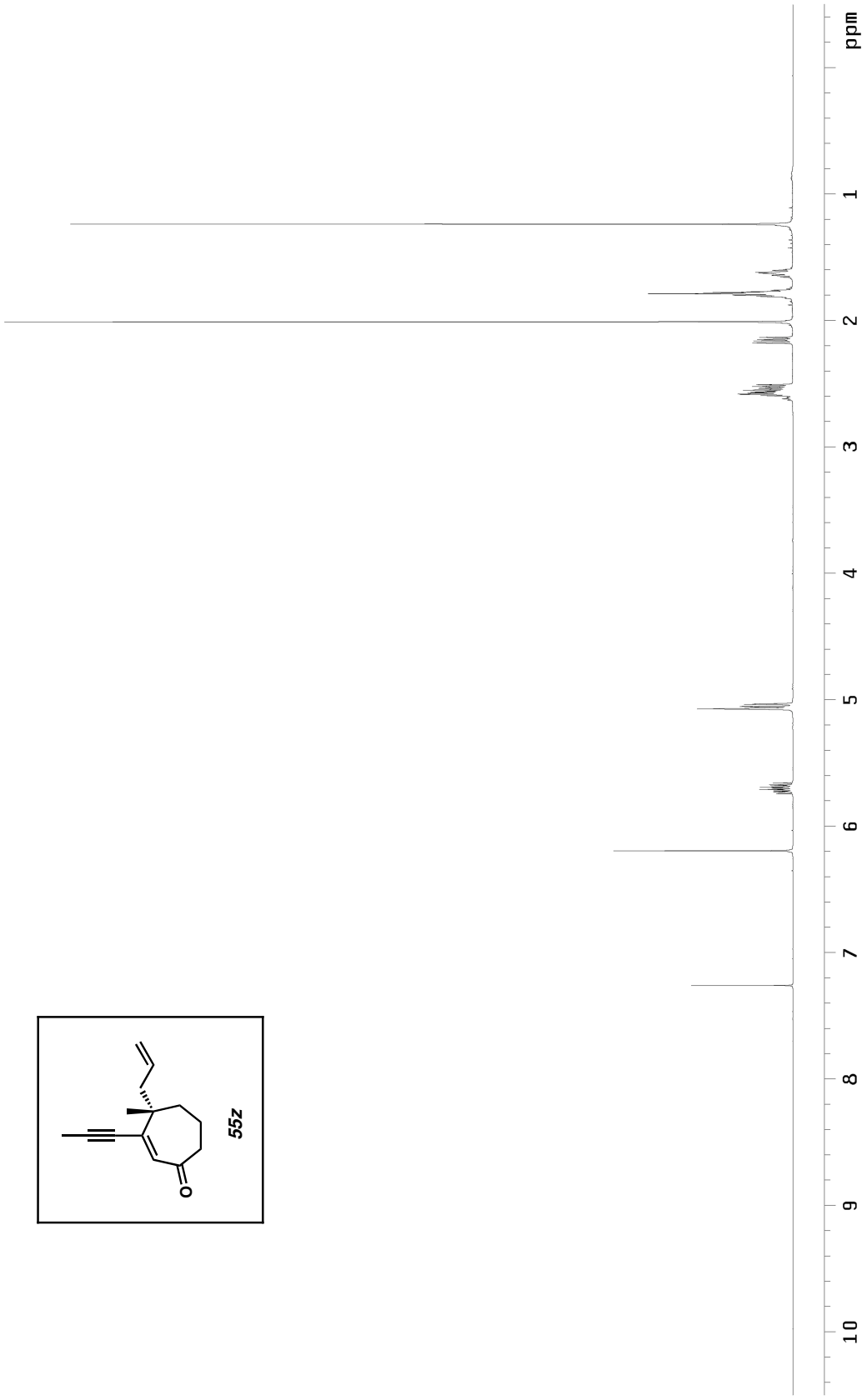


Figure A2.107.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **55z**.

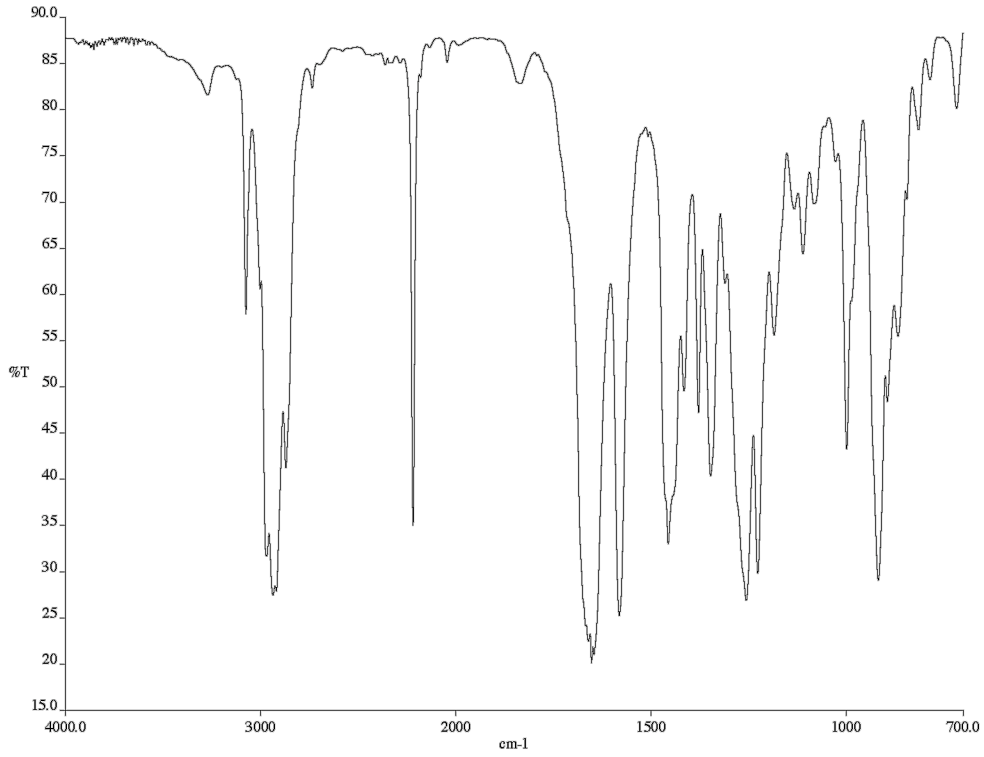


Figure A2.107.2. Infrared spectrum (thin film/NaCl) of compound **55z**.

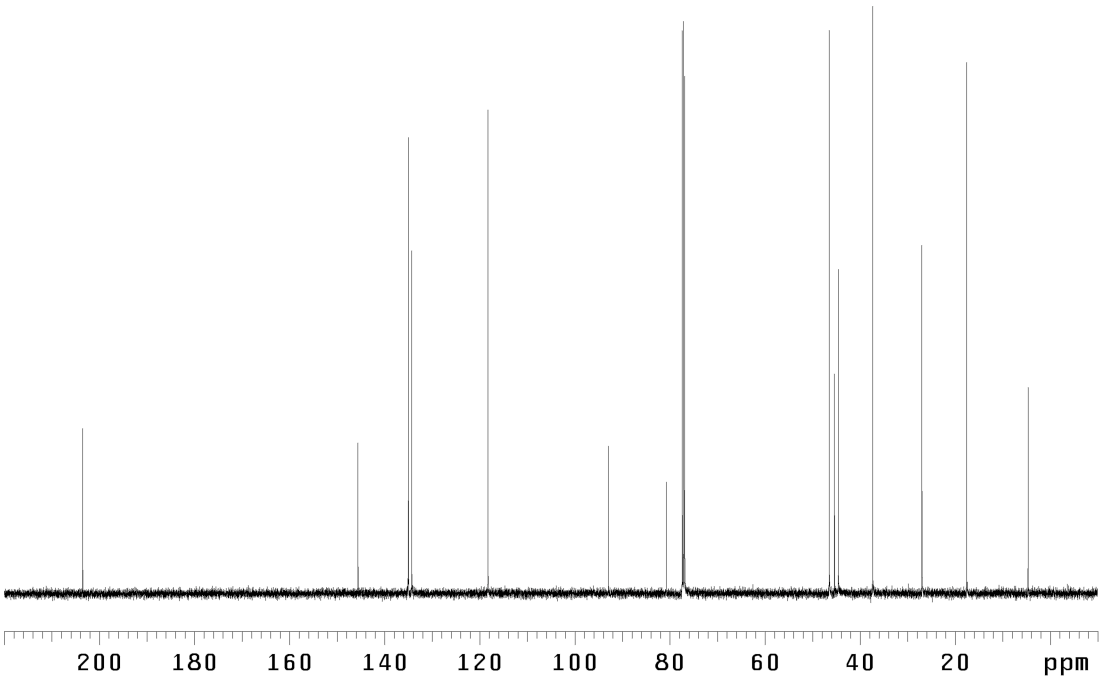


Figure A2.107.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **55z**.

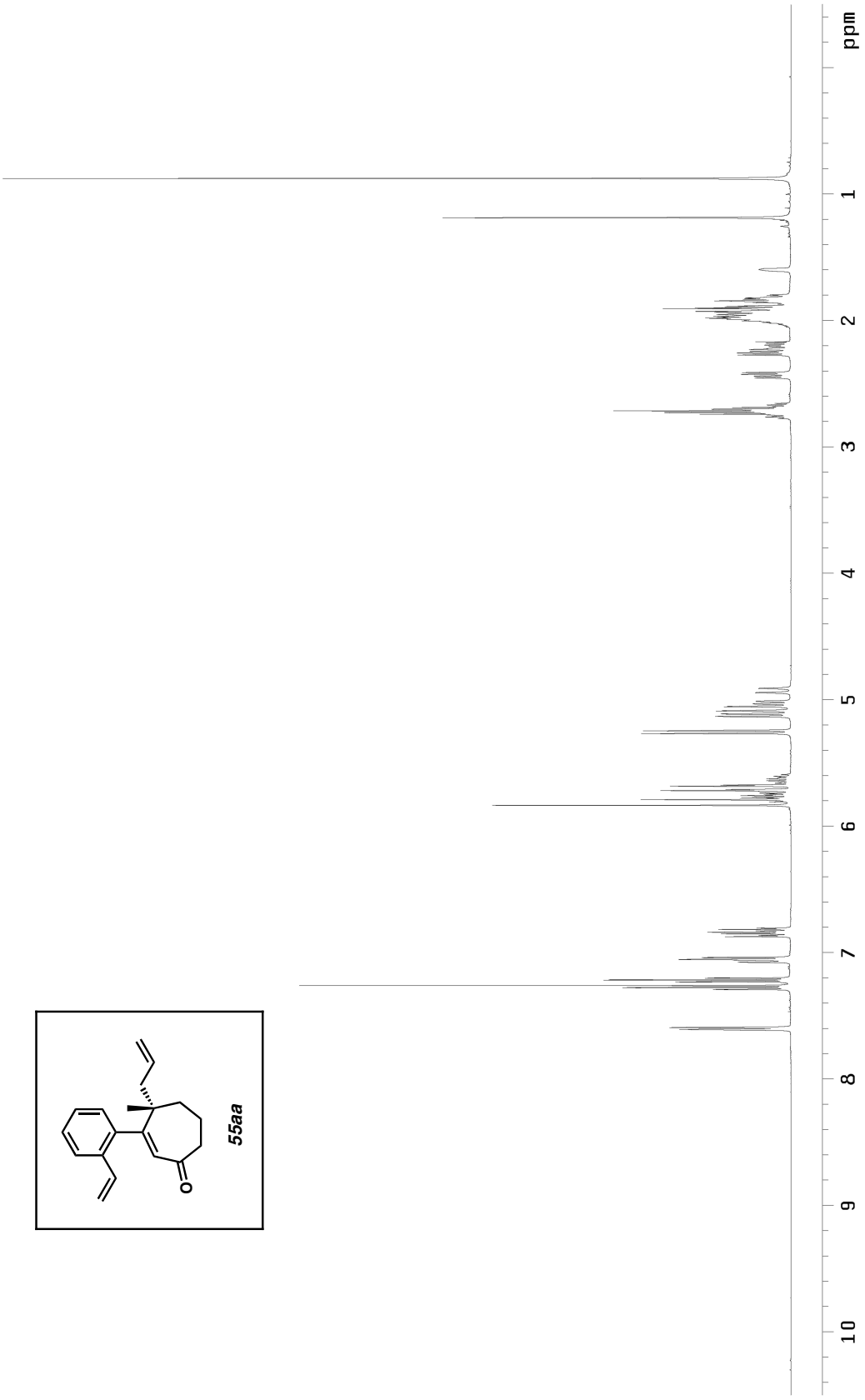


Figure A2.108.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **55aa**.

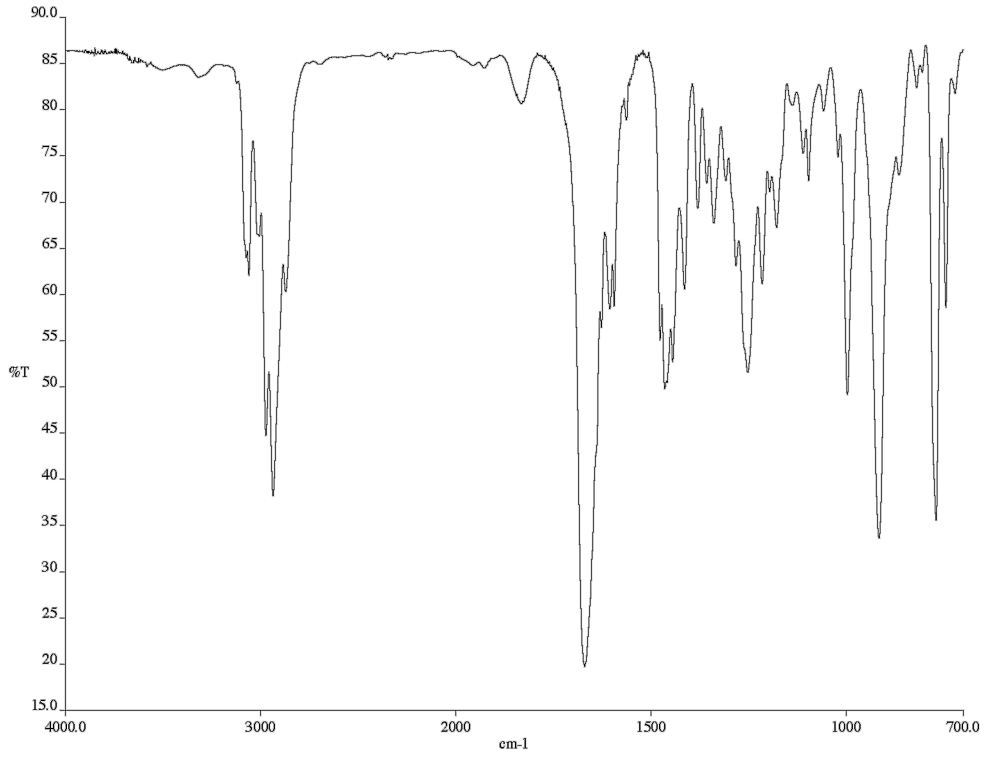


Figure A2.108.2. Infrared spectrum (thin film/NaCl) of compound **55aa**.

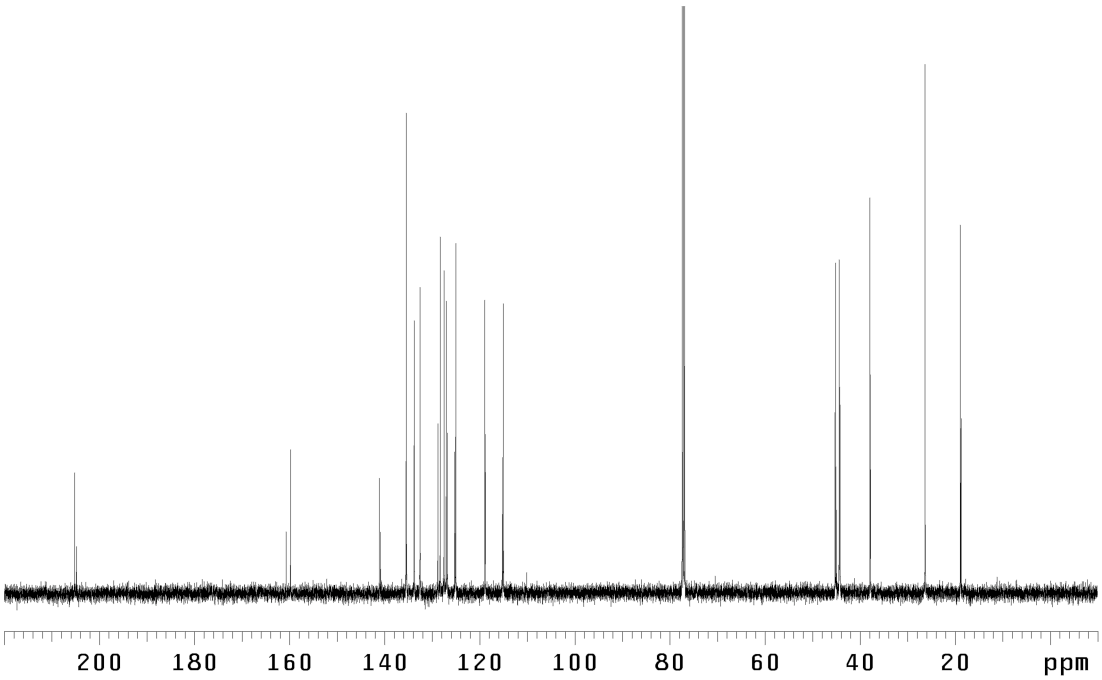


Figure A2.108.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **55aa**.

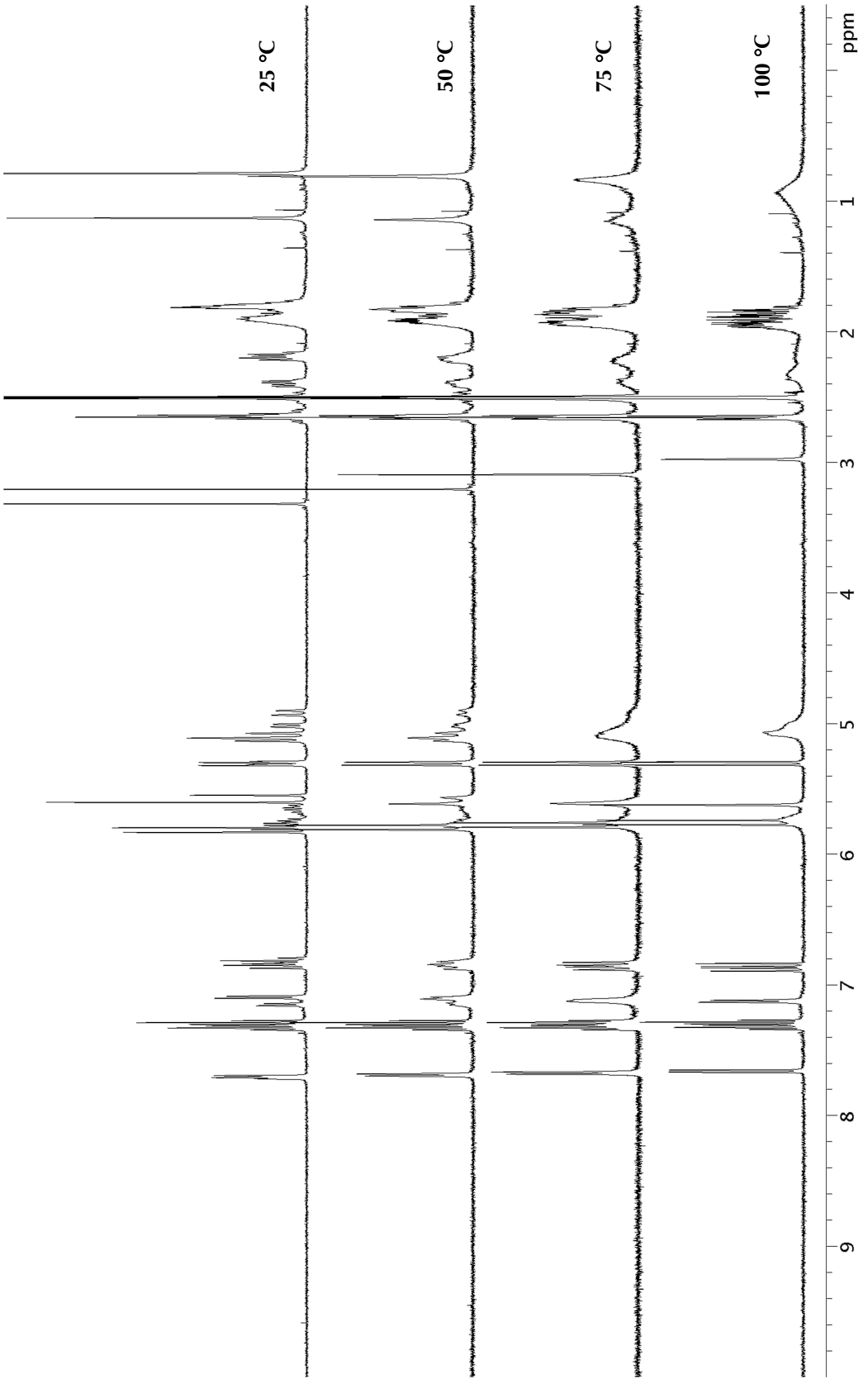


Figure A2.108.4. Variable Temperature ^{1}H NMR (500 MHz, DMSO-d_6) of compound **55aa**.

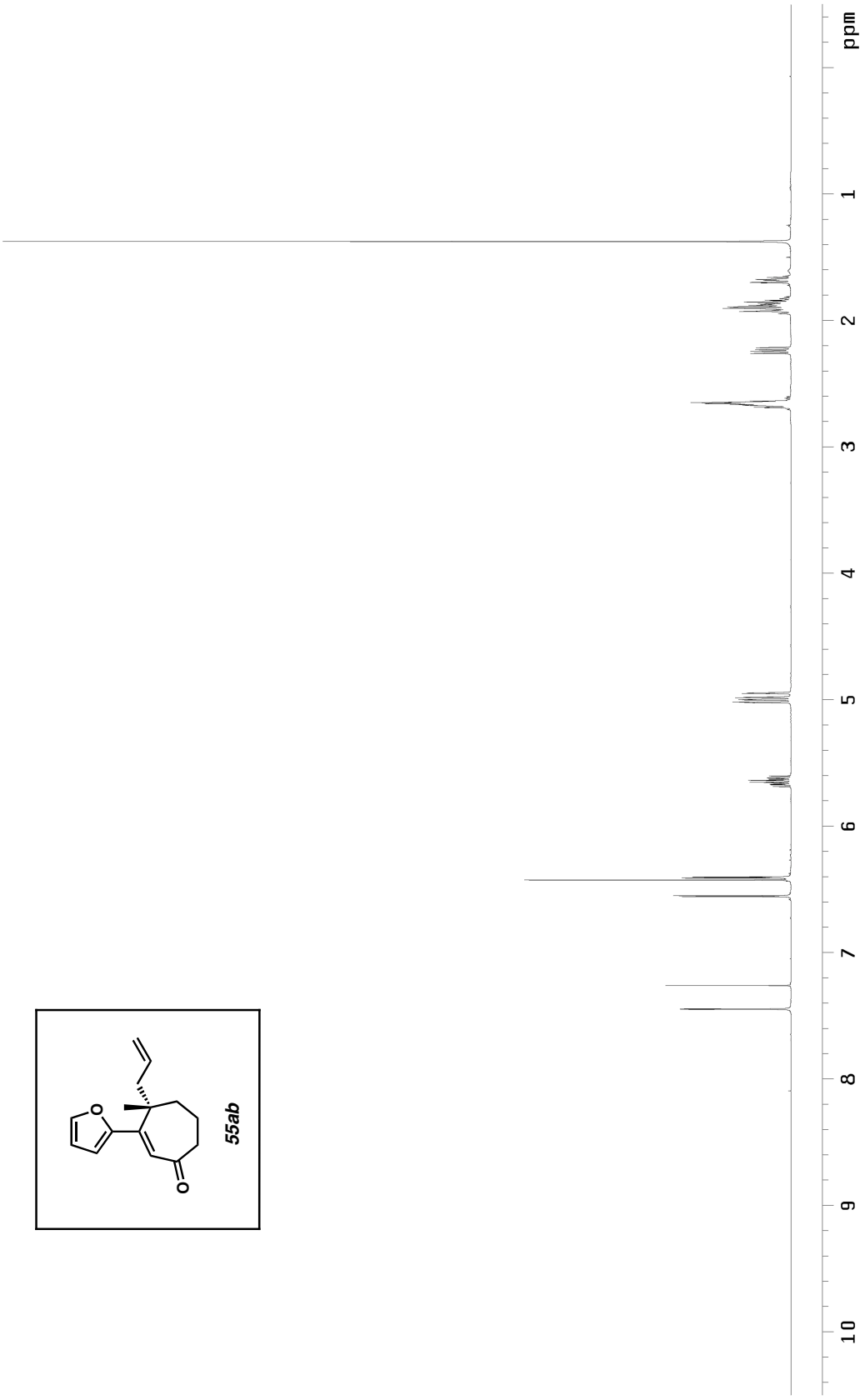


Figure A2.109.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **55ab**.

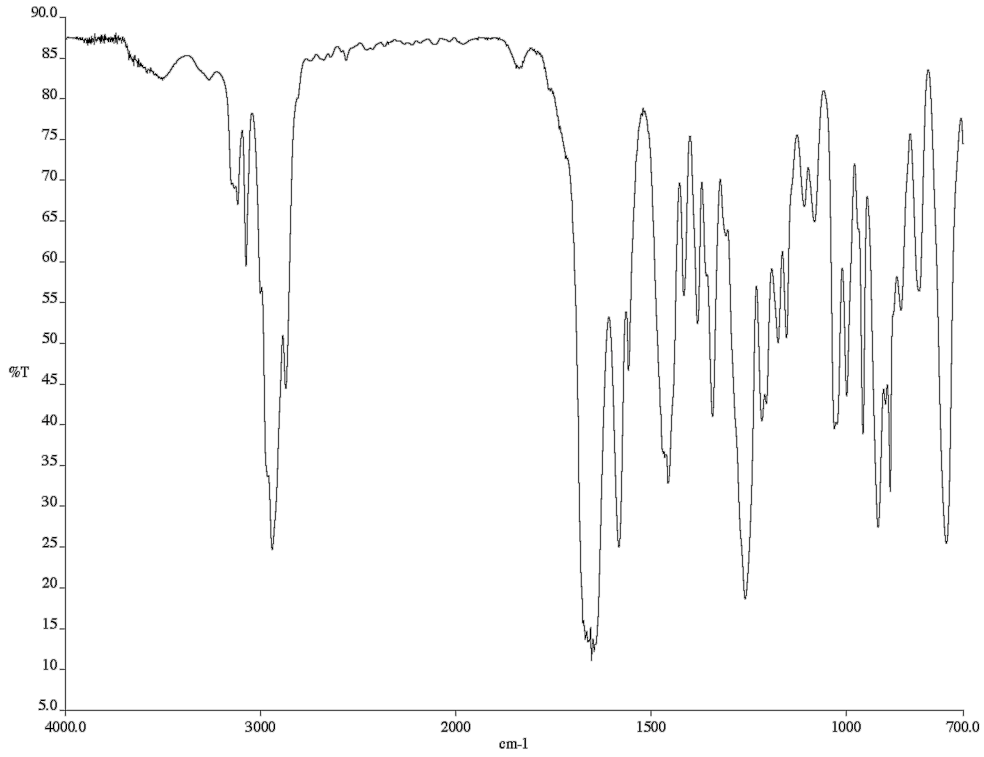


Figure A2.109.2. Infrared spectrum (thin film/NaCl) of compound **55ab**.

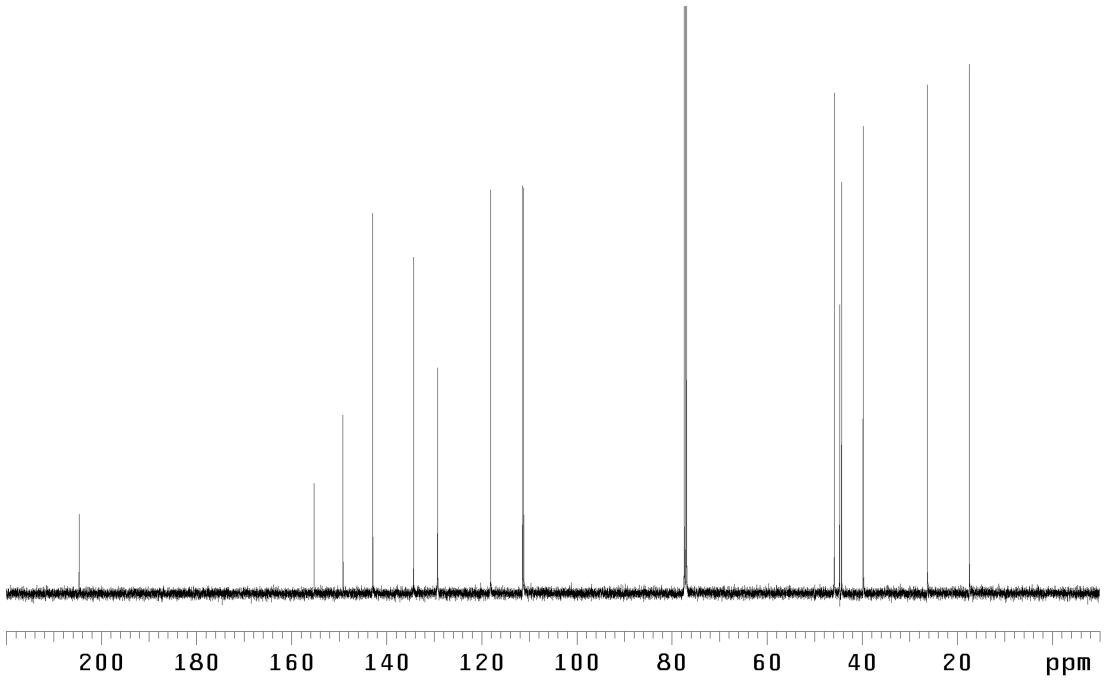


Figure A2.109.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **55ab**.

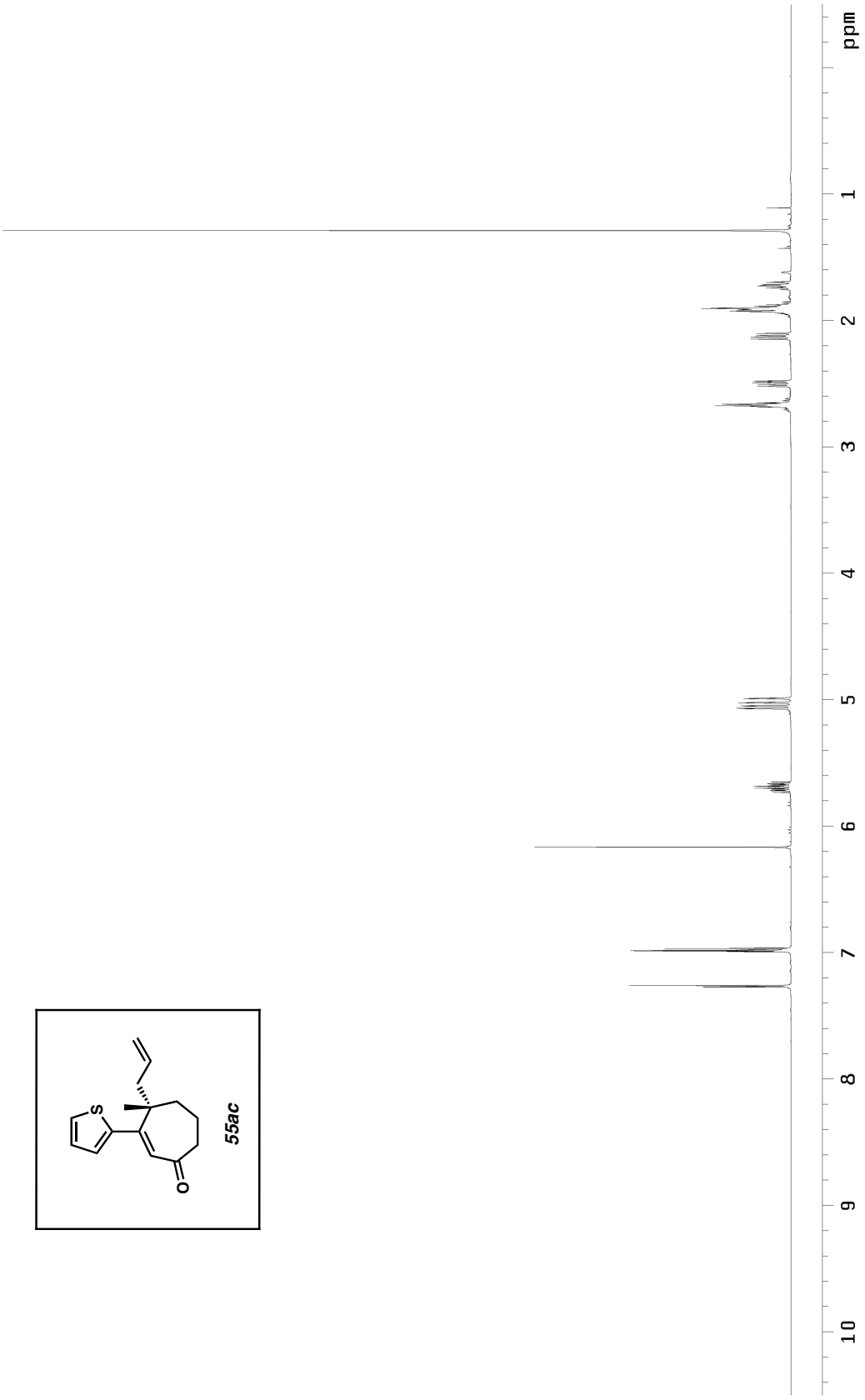


Figure A2.110.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **55ac**.

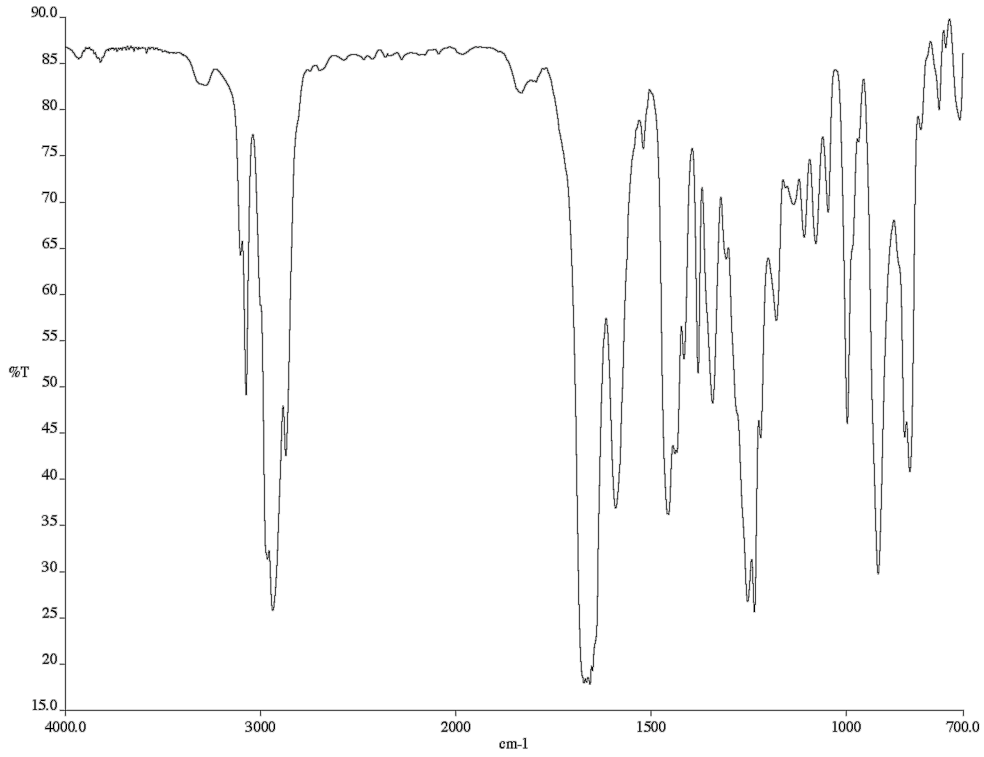


Figure A2.110.2. Infrared spectrum (thin film/NaCl) of compound **55ac**.

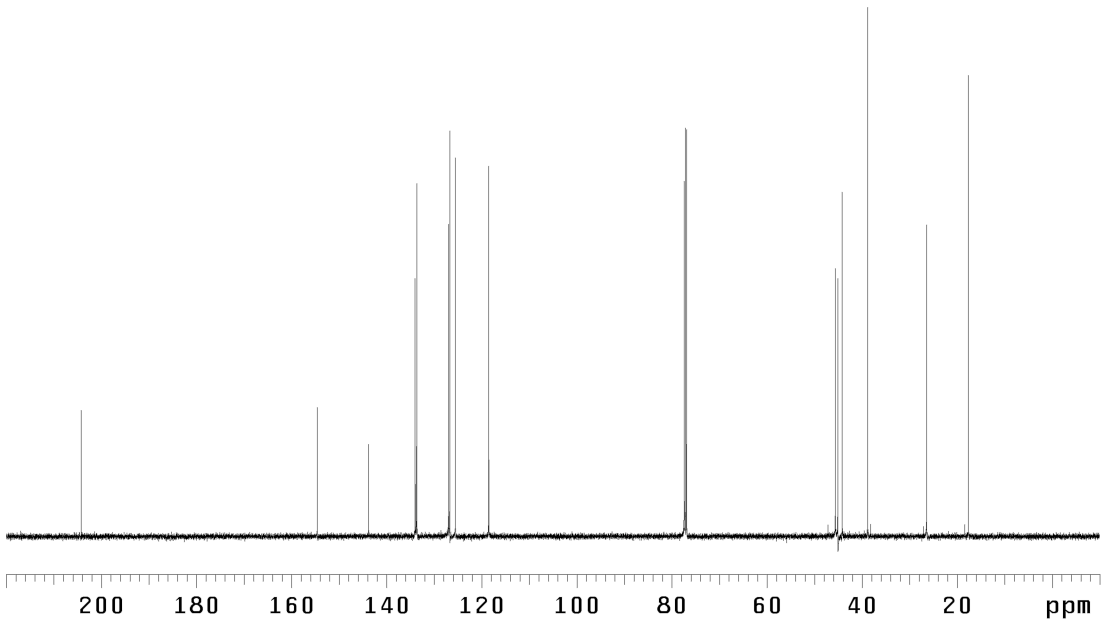


Figure A2.110.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **55ac**.

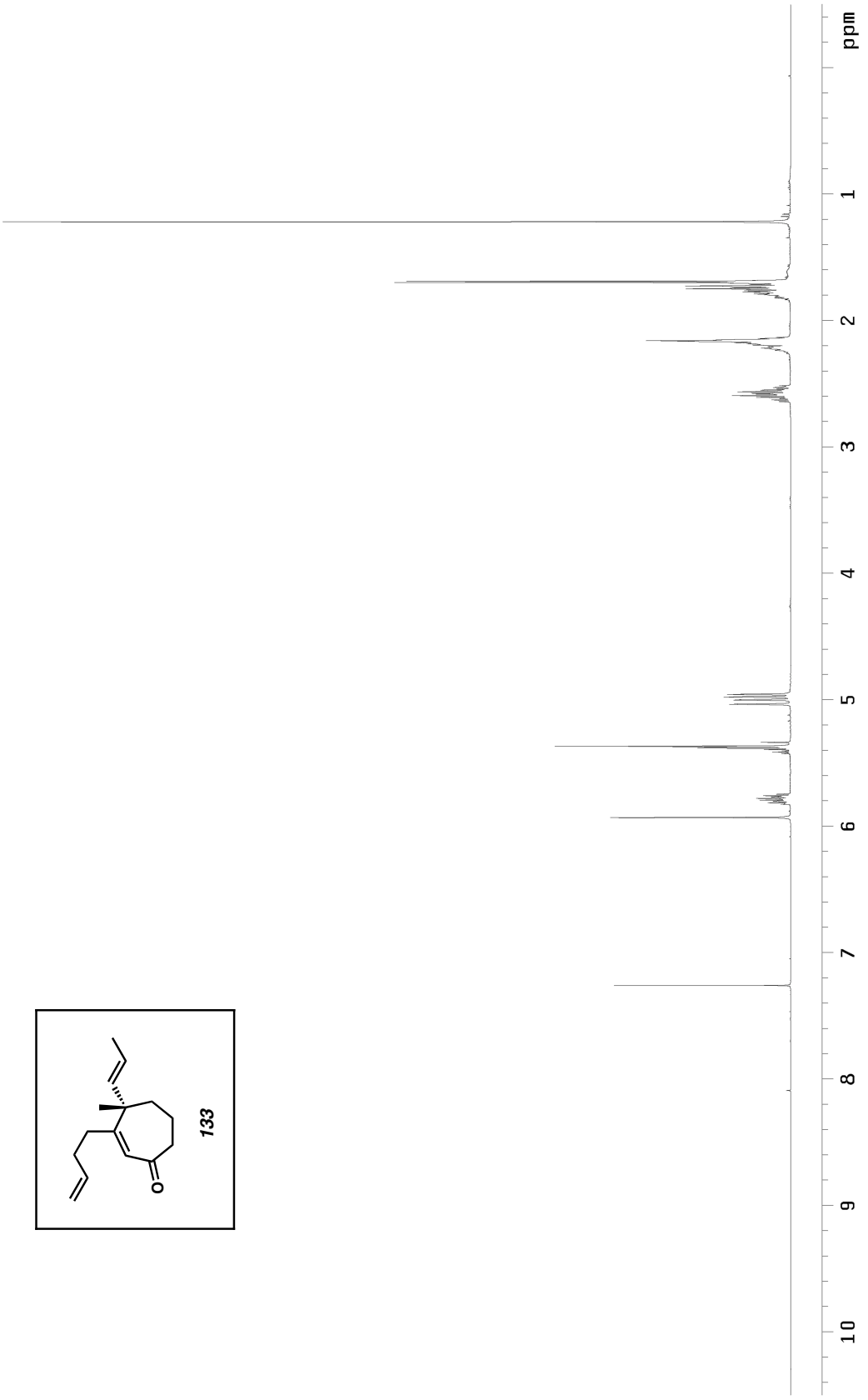


Figure A2.111.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **133**.

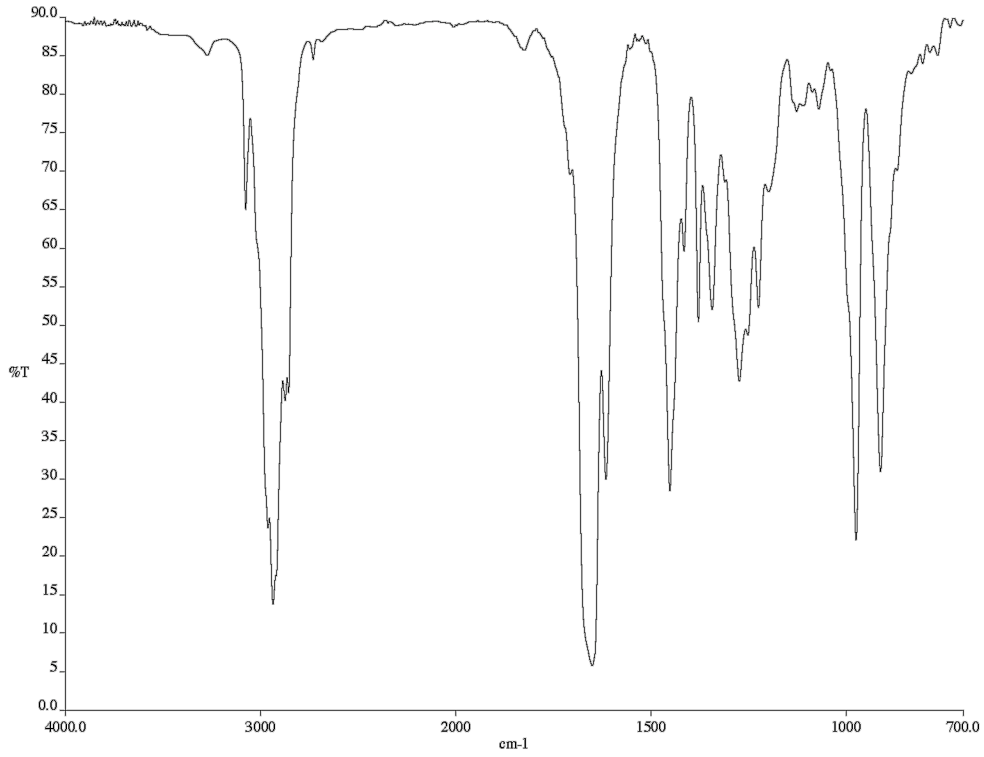


Figure A2.111.2. Infrared spectrum (thin film/NaCl) of compound **133**.

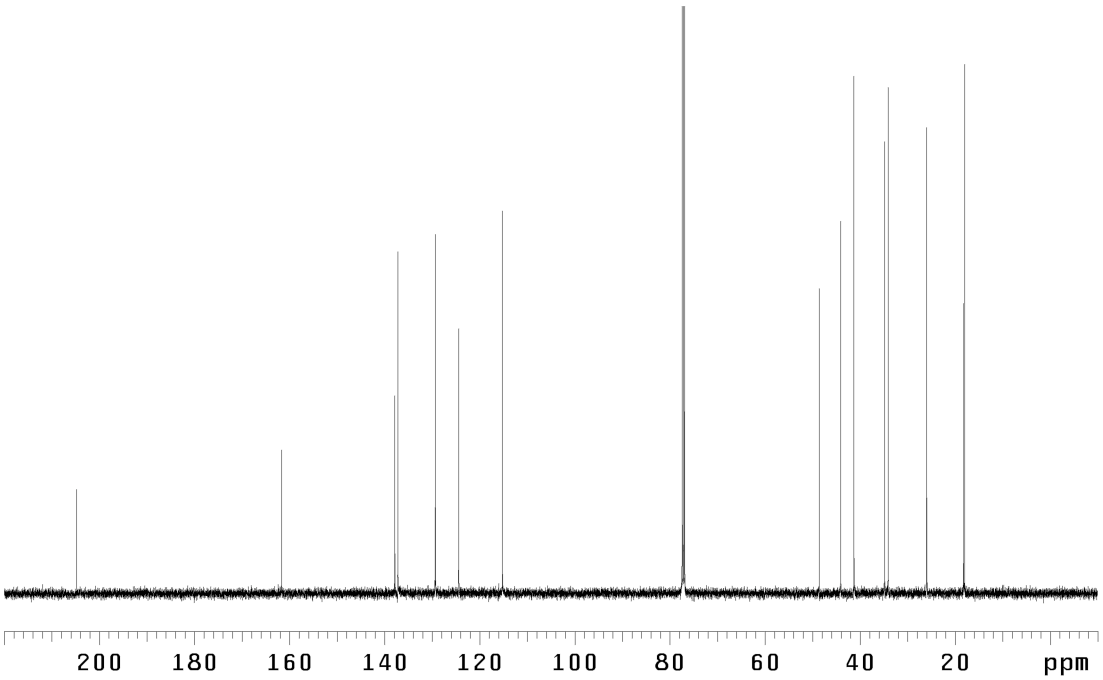


Figure A2.111.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **133**.

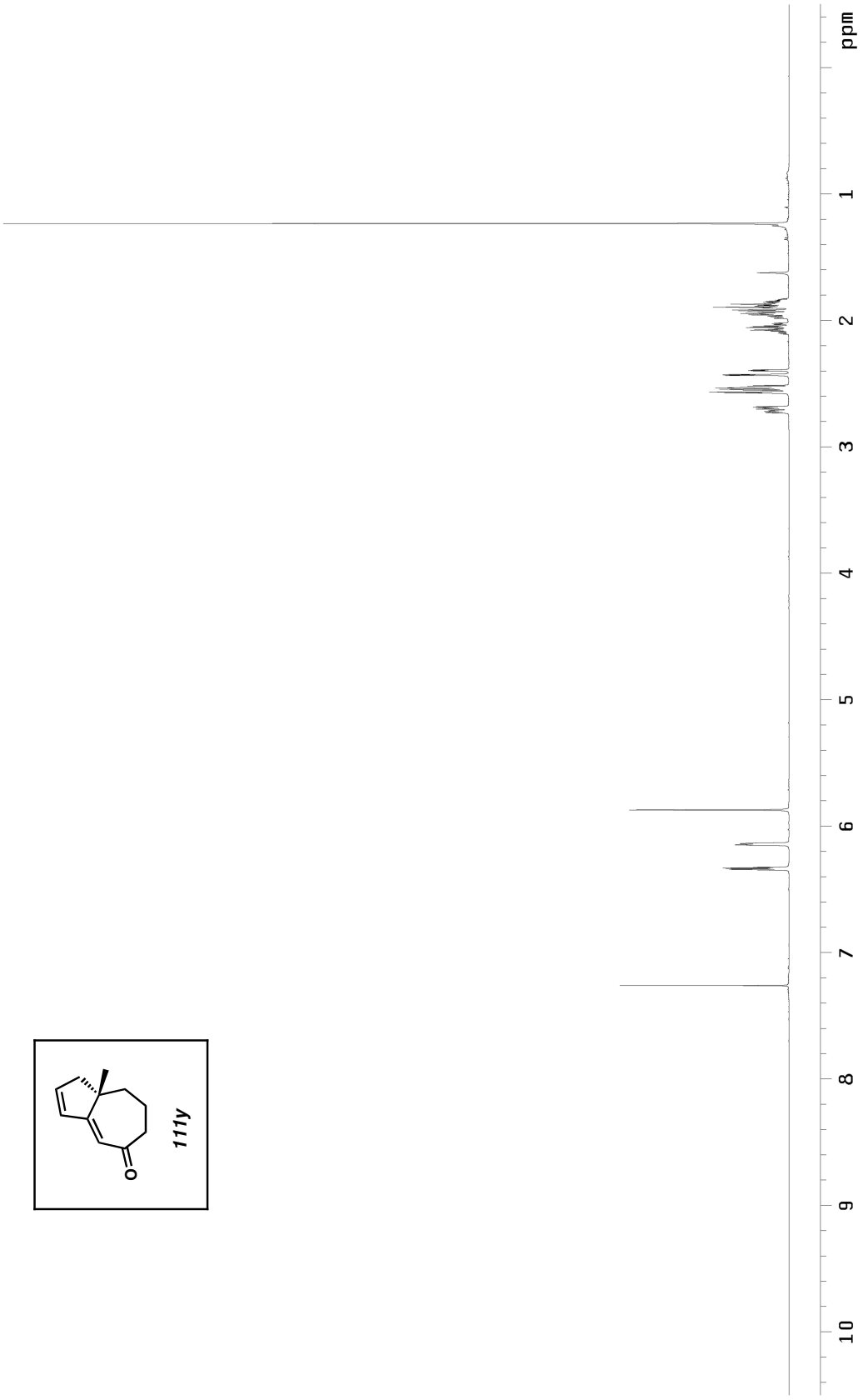


Figure A2.112.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **111y**.

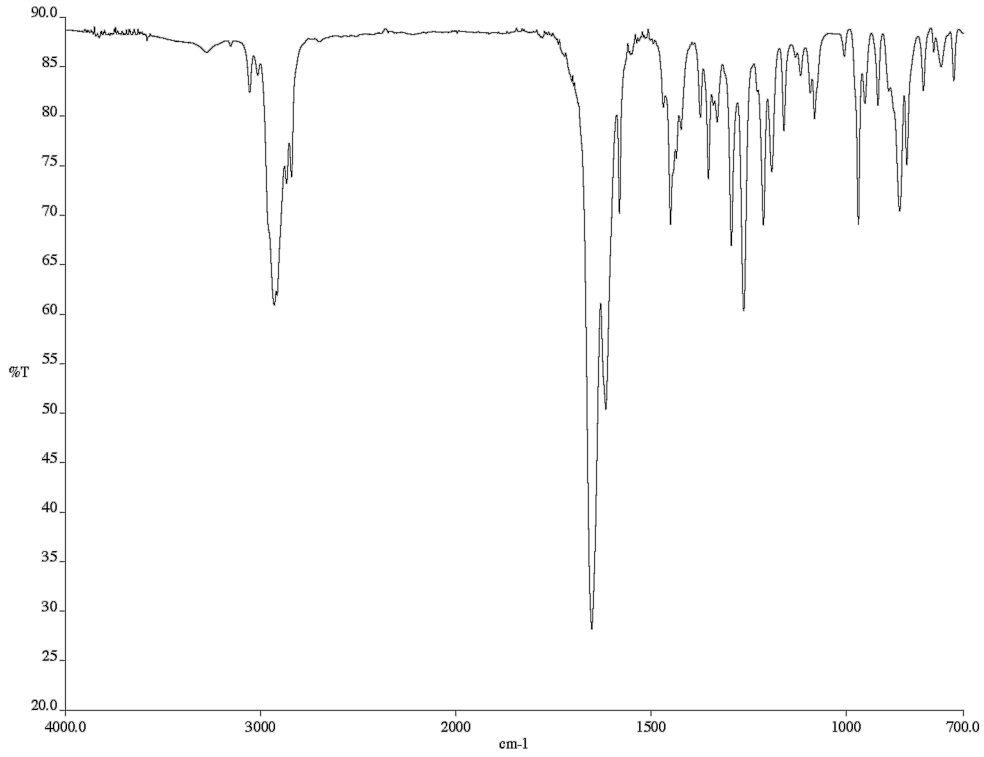


Figure A2.112.2. Infrared spectrum (thin film/NaCl) of compound **111y**.

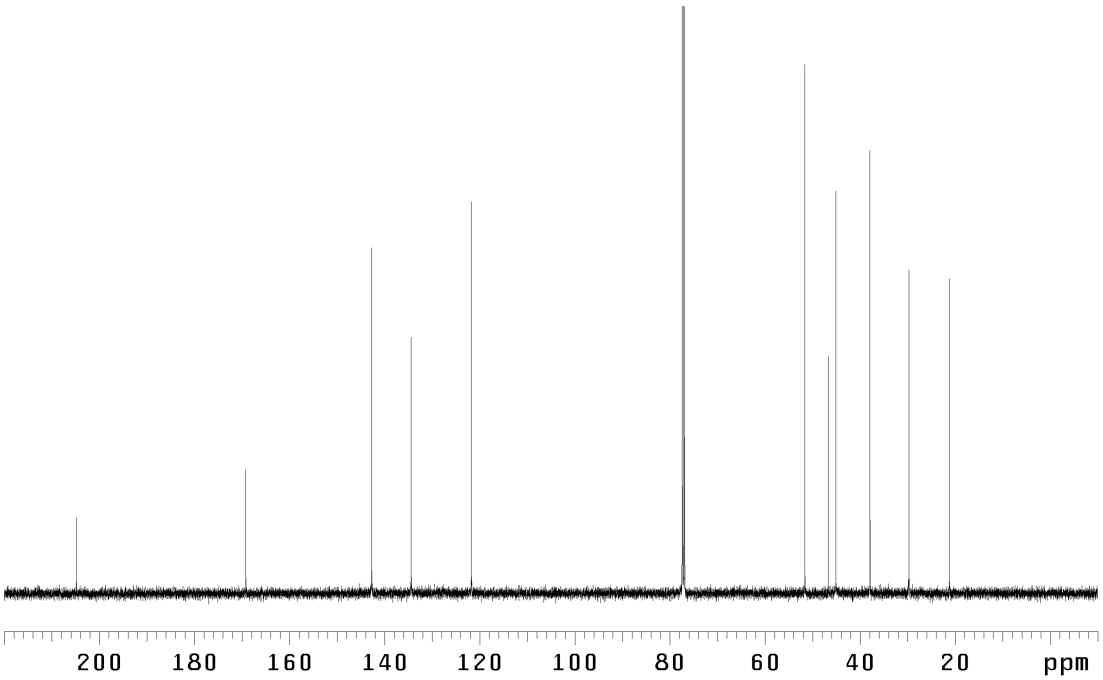


Figure A2.112.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **111y**.

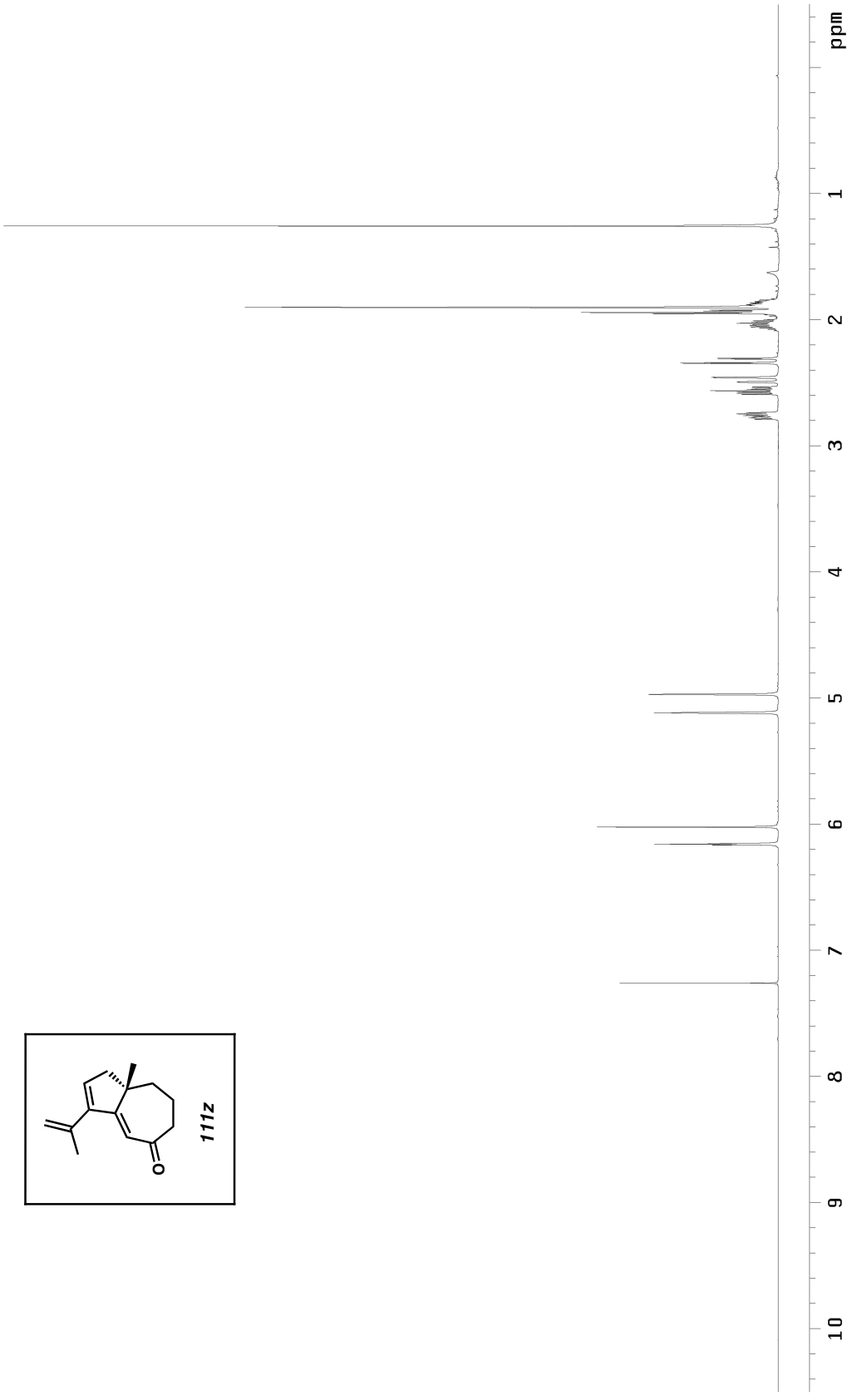


Figure A2.113.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **111z**.

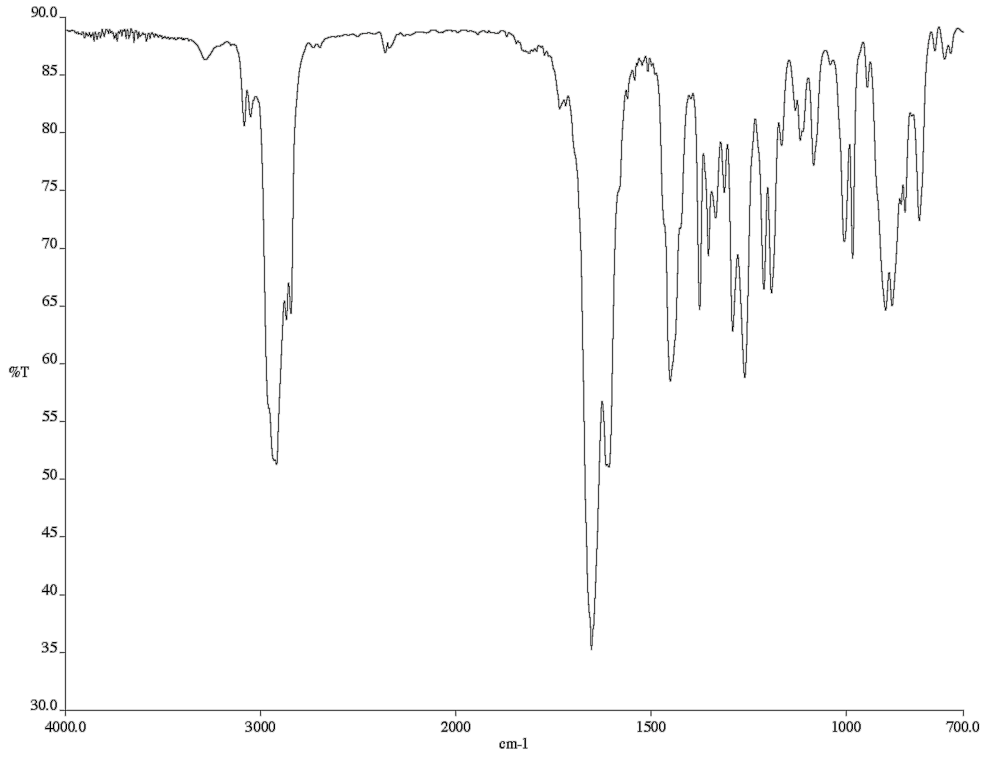


Figure A2.113.2. Infrared spectrum (thin film/NaCl) of compound **111z**.

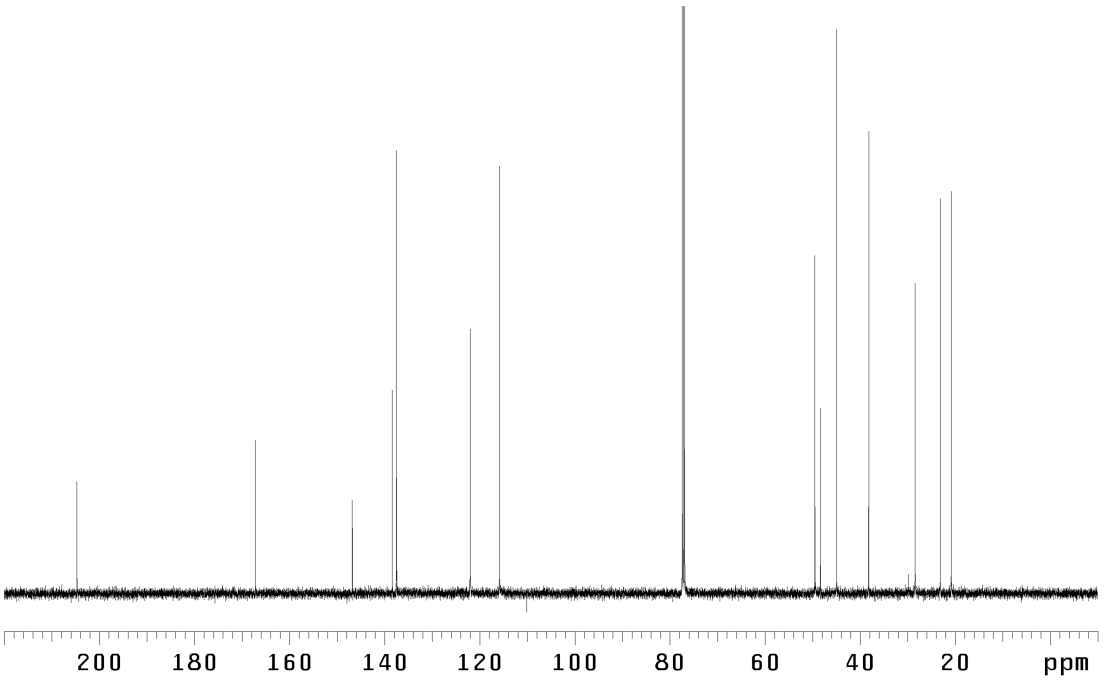


Figure A2.113.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **111z**.

Figure A2.114.1. ^{1}H NMR (500 MHz, C_6D_6) of compound **111t**.

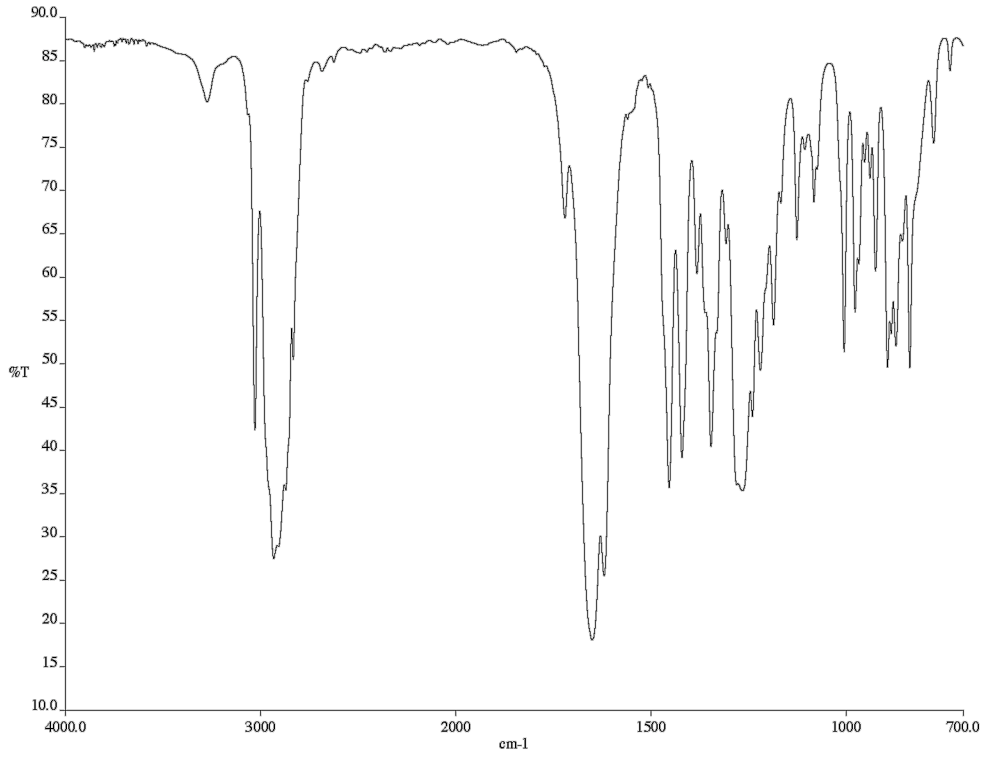


Figure A2.114.2. Infrared spectrum (thin film/NaCl) of compound **111t**.

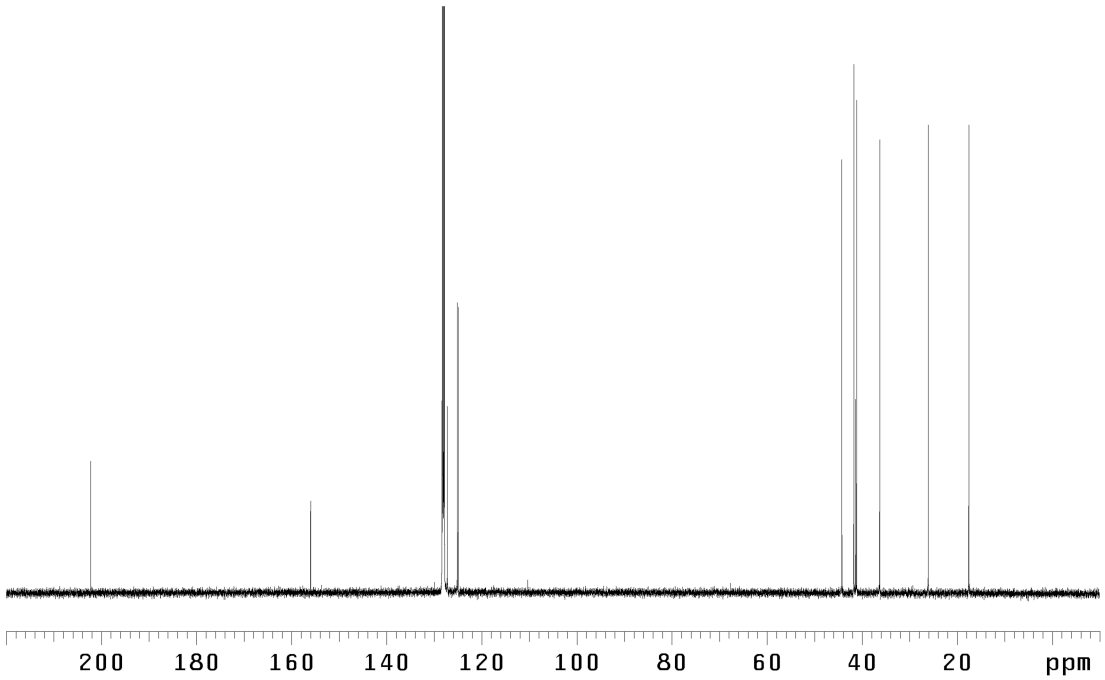


Figure A2.114.3. ^{13}C NMR (125 MHz, C_6D_6) of compound **111t**.

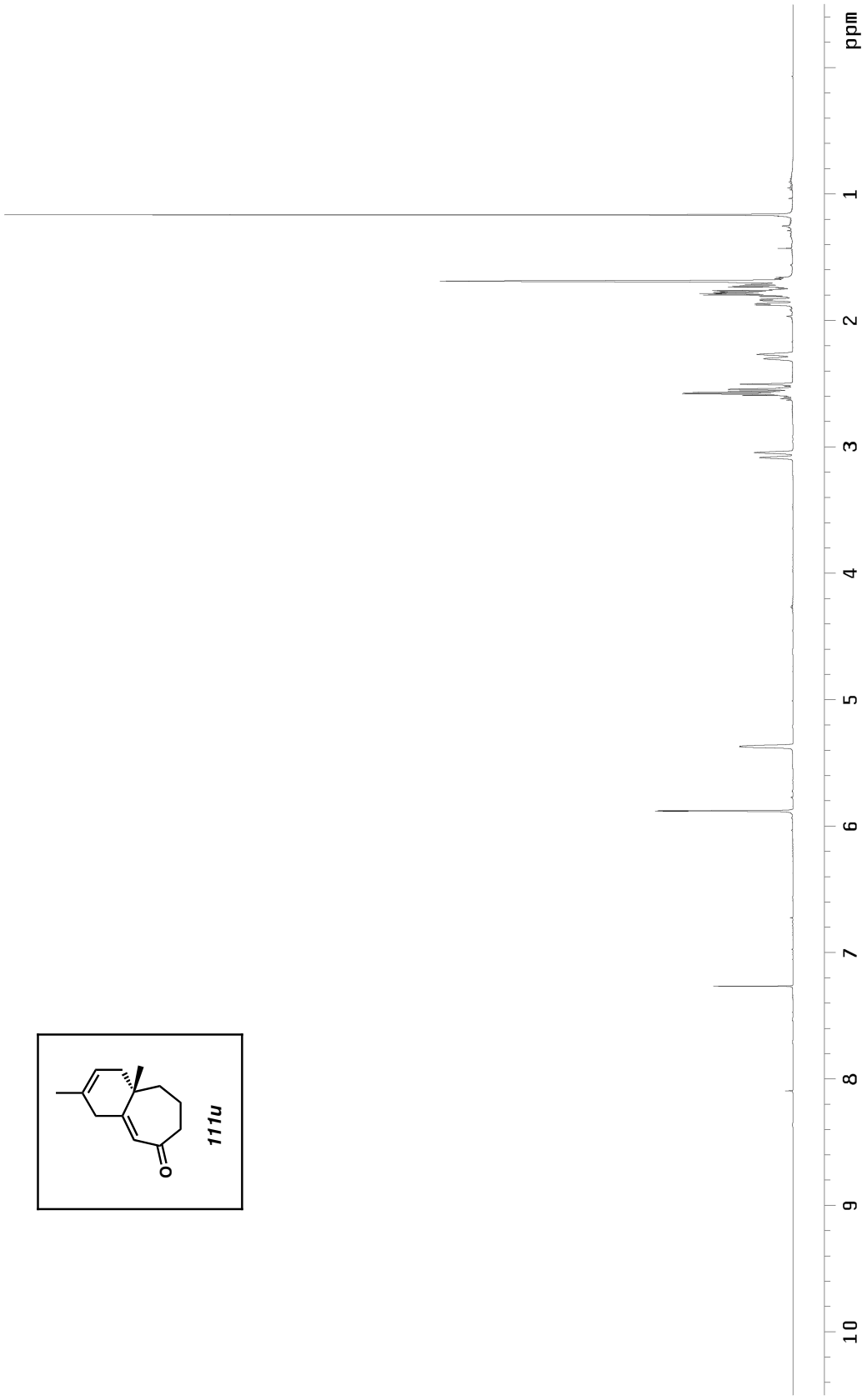


Figure A2.115.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **111u**.

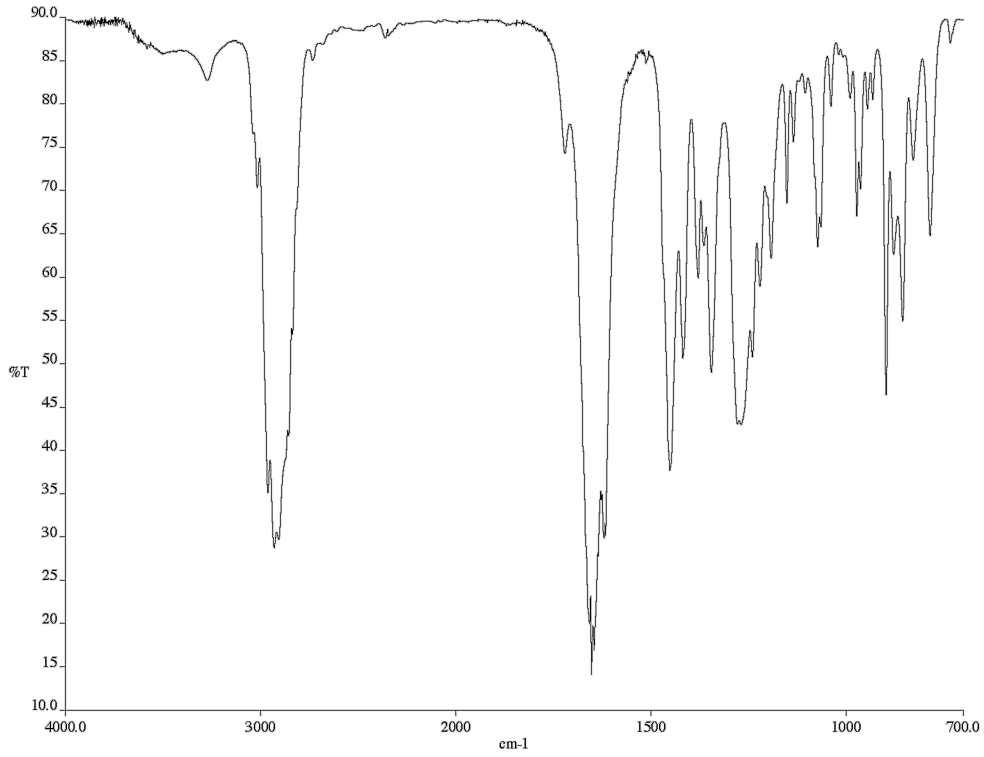


Figure A2.115.2. Infrared spectrum (thin film/NaCl) of compound **111u**.

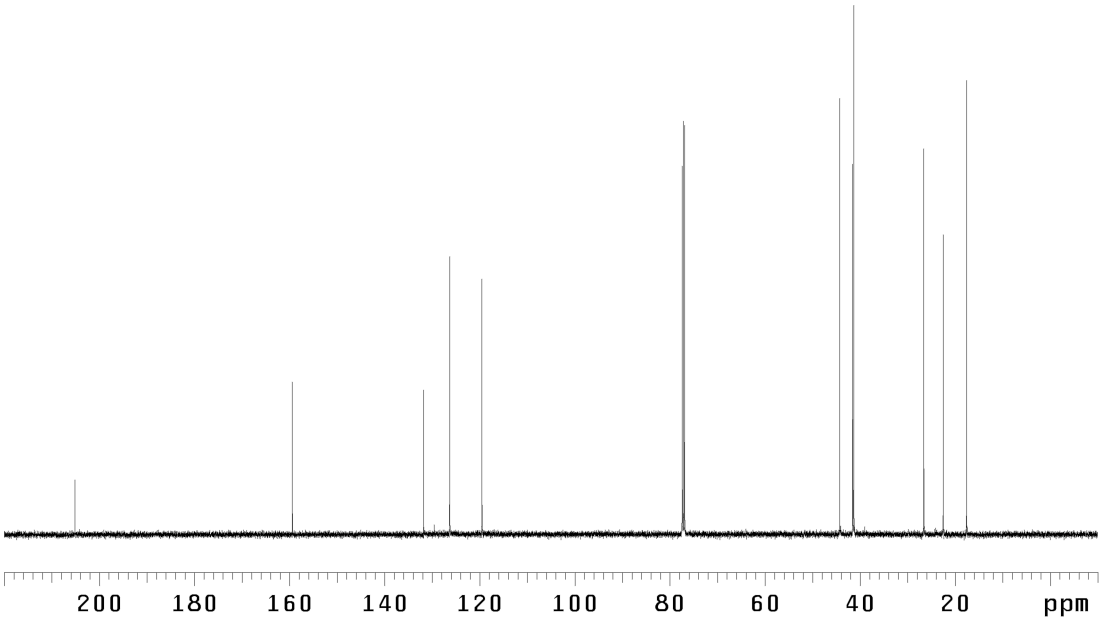


Figure A2.115.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **111u**.

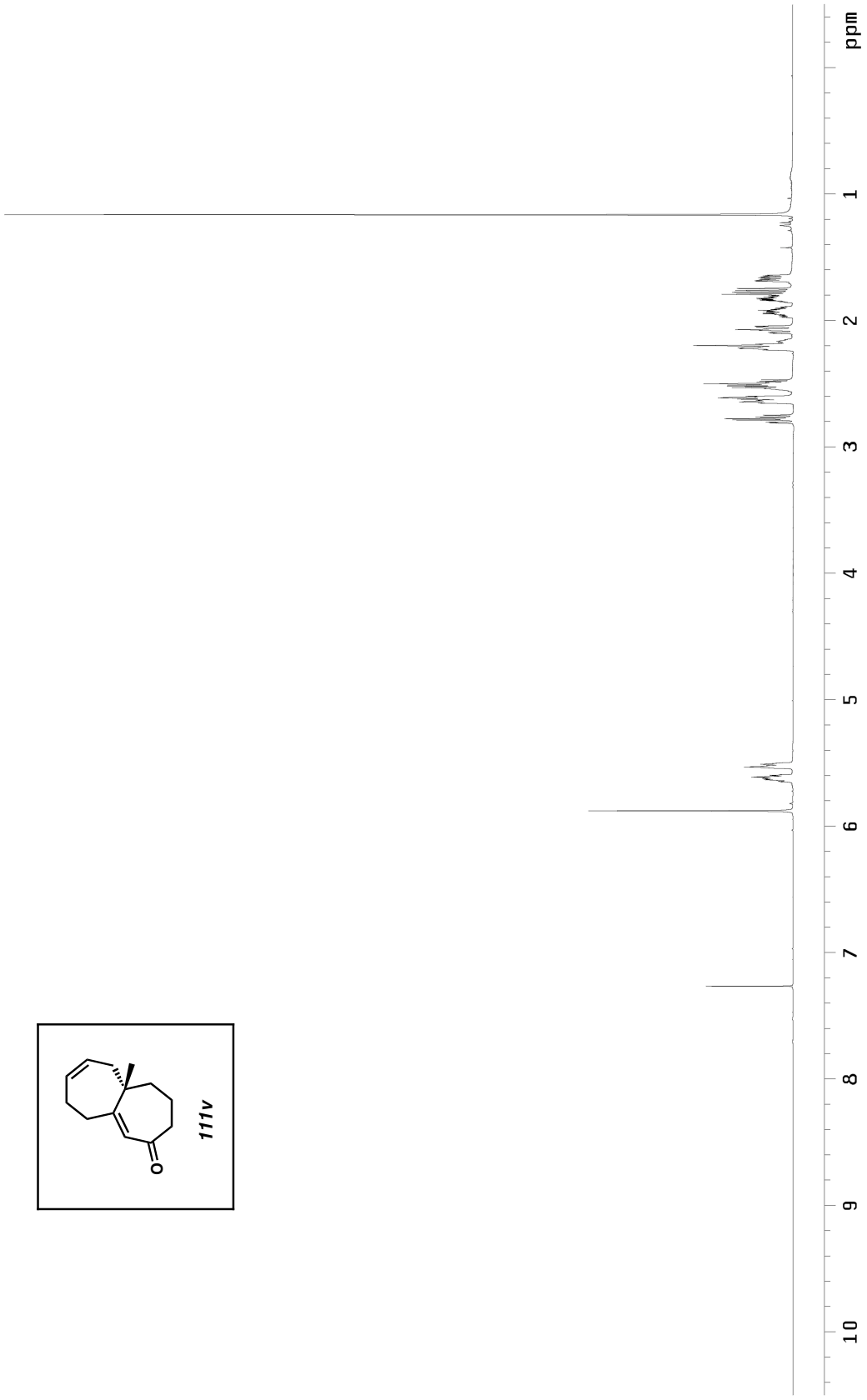


Figure A2.116.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **111v**.

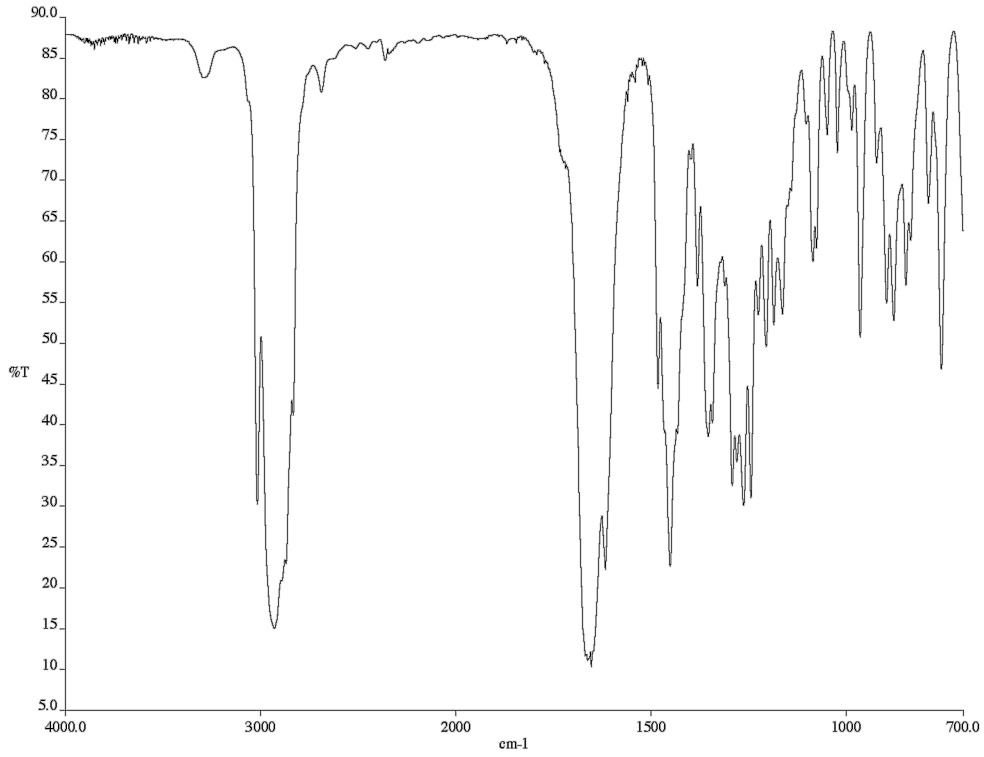


Figure A2.116.2. Infrared spectrum (thin film/NaCl) of compound **111v**.

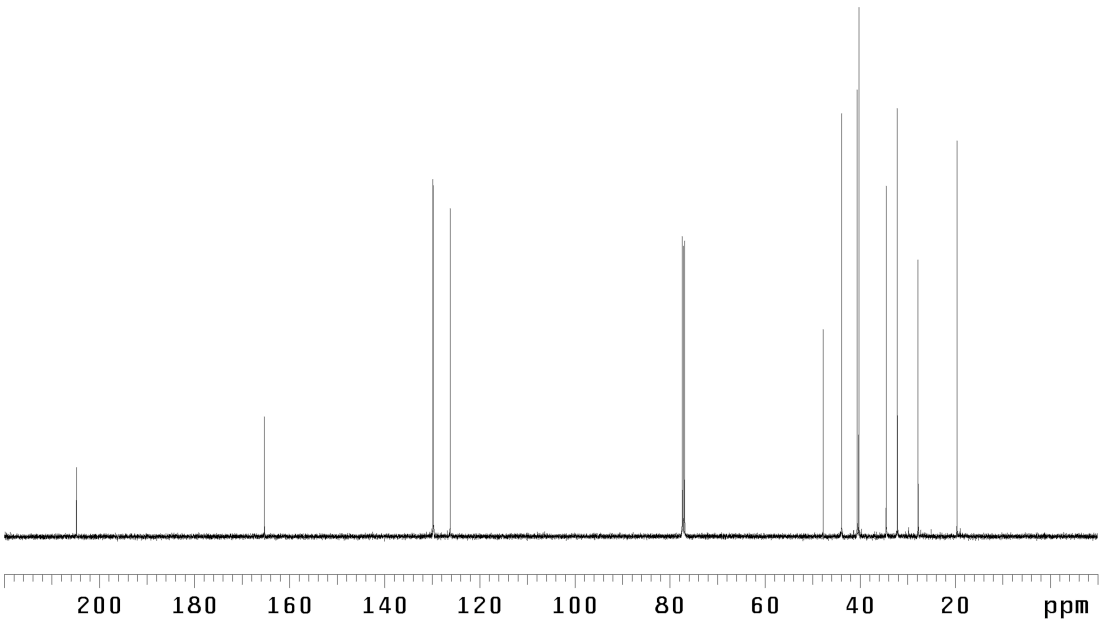


Figure A2.116.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **111v**.

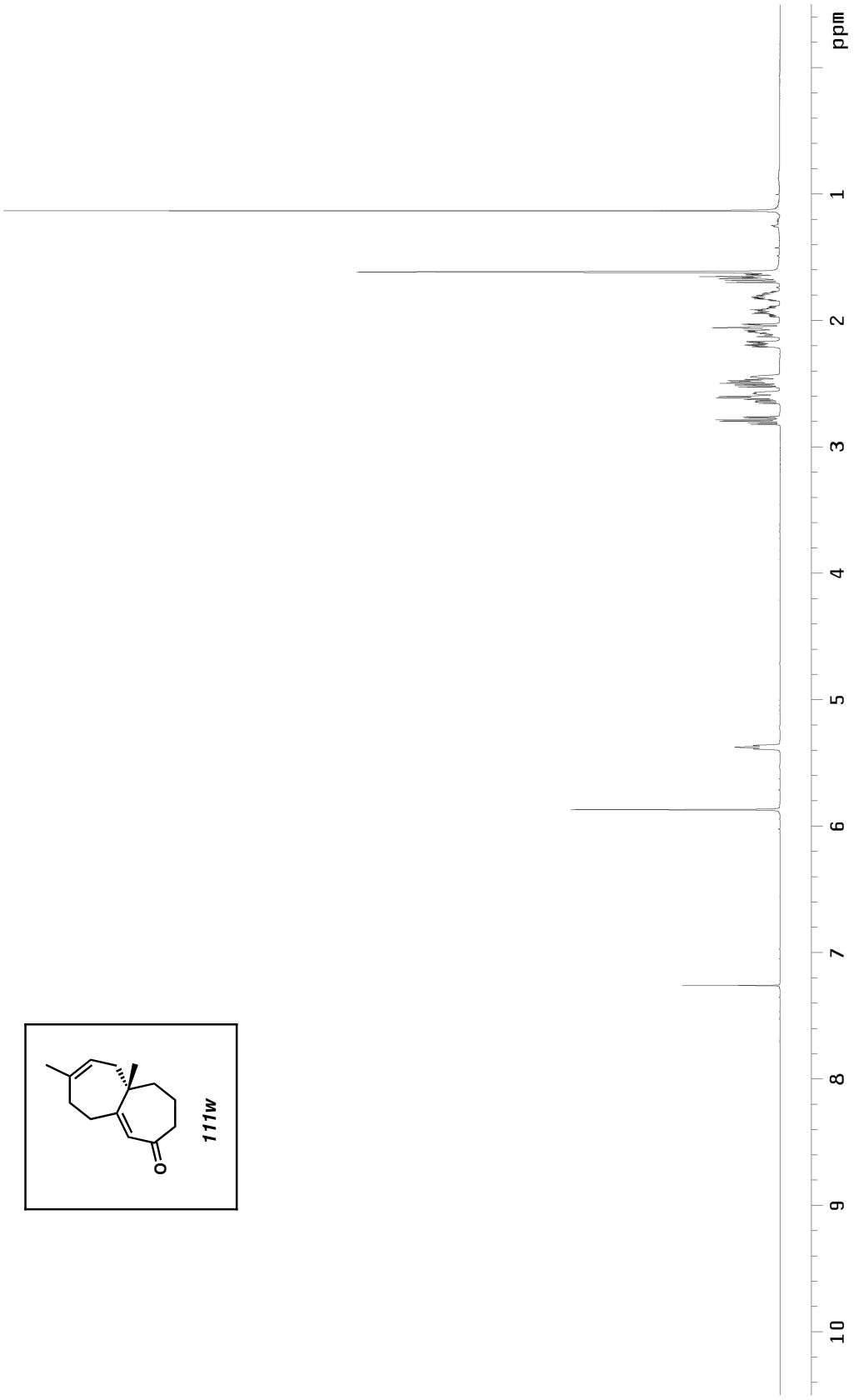


Figure A2.117.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **111w**.

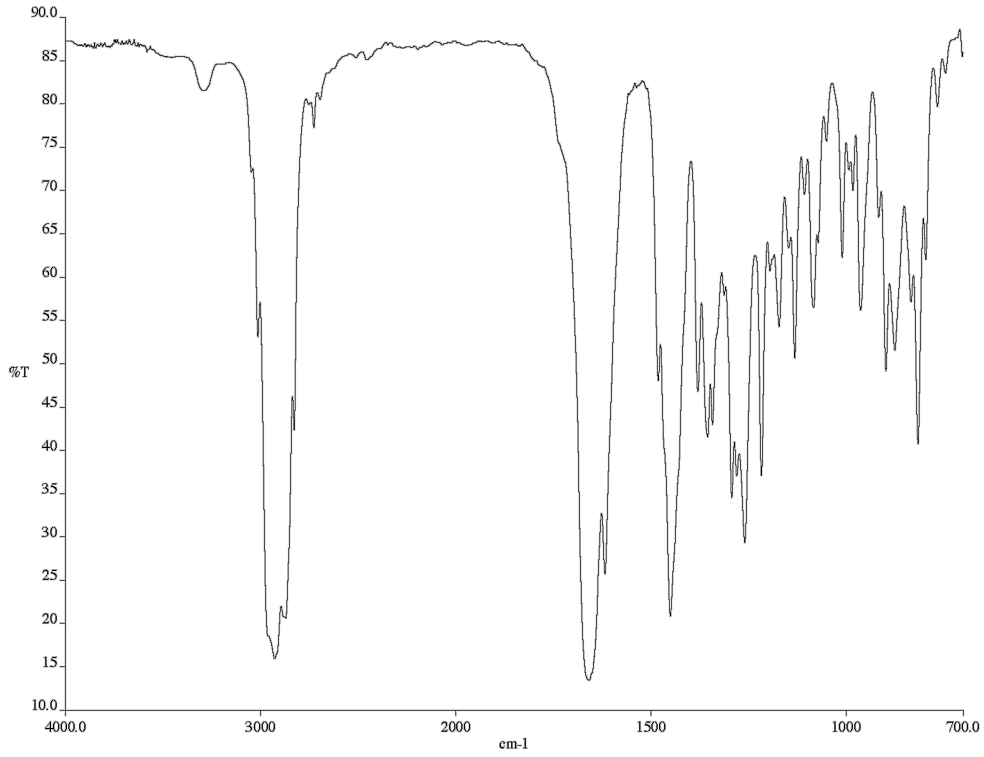


Figure A2.117.2. Infrared spectrum (thin film/NaCl) of compound **111w**.

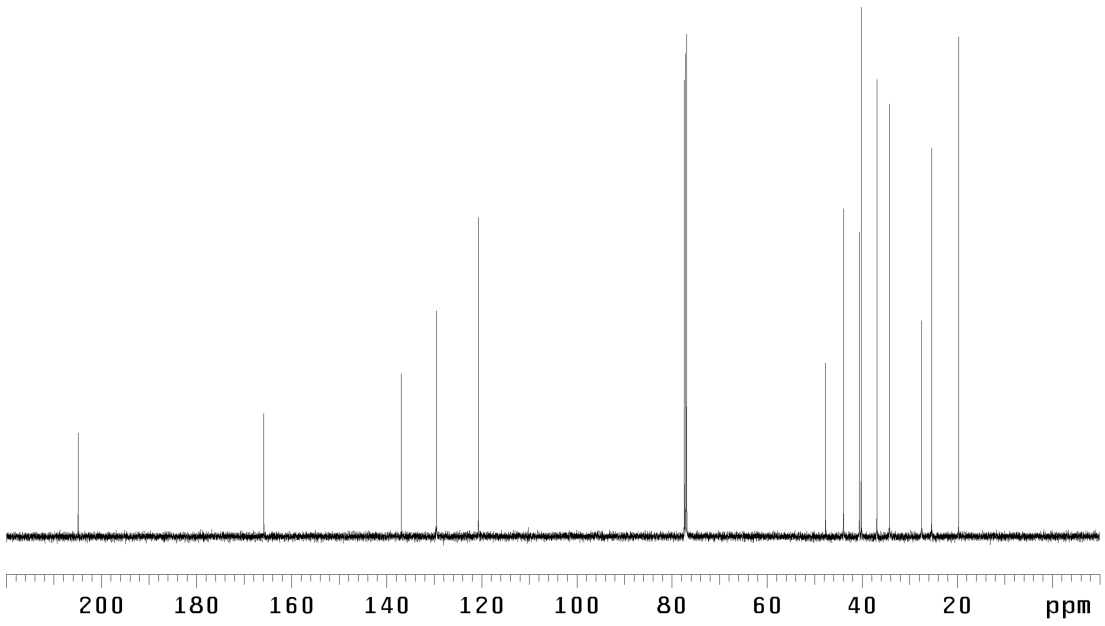


Figure A2.117.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **111w**.

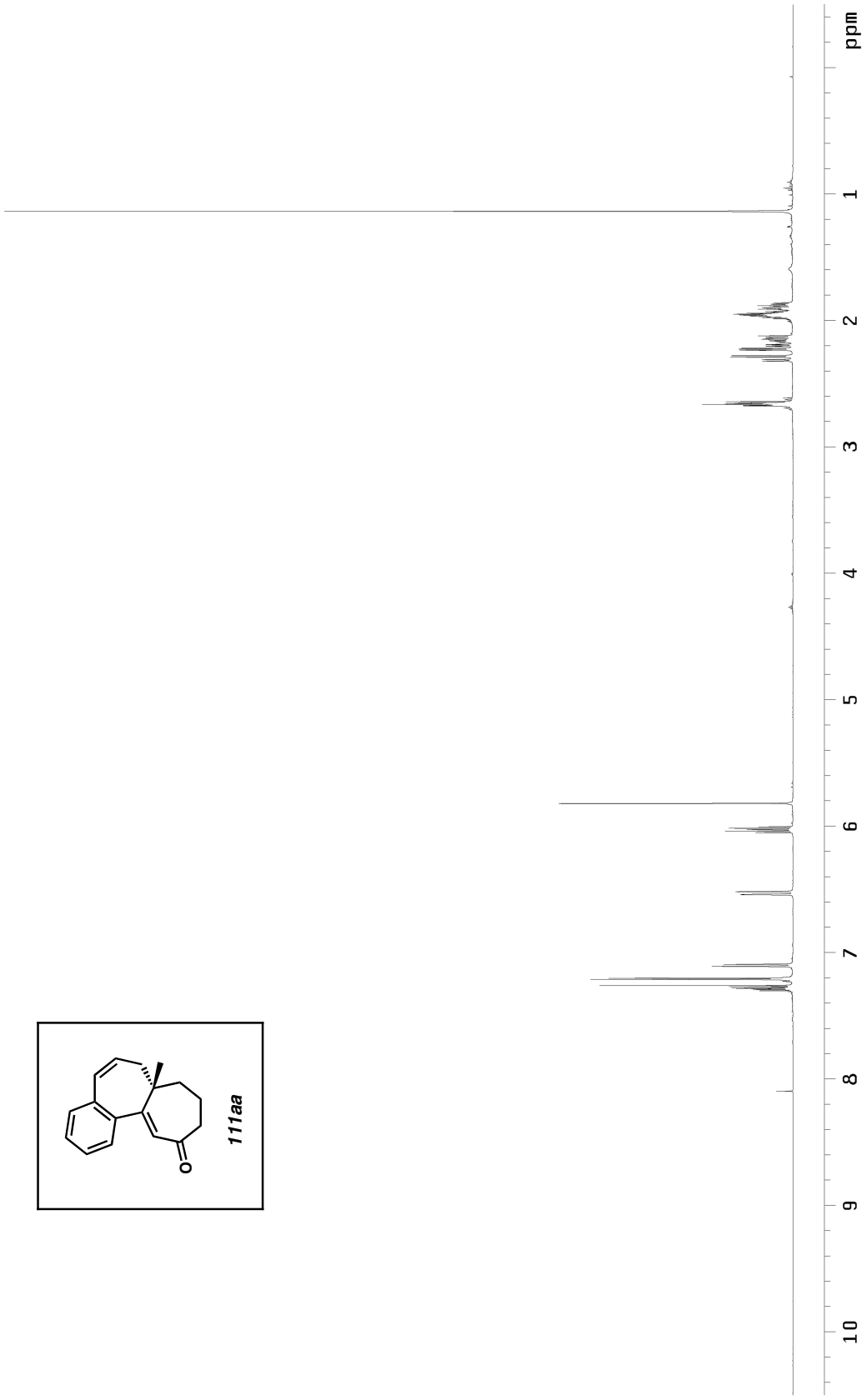


Figure A2.118.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **111aa**.

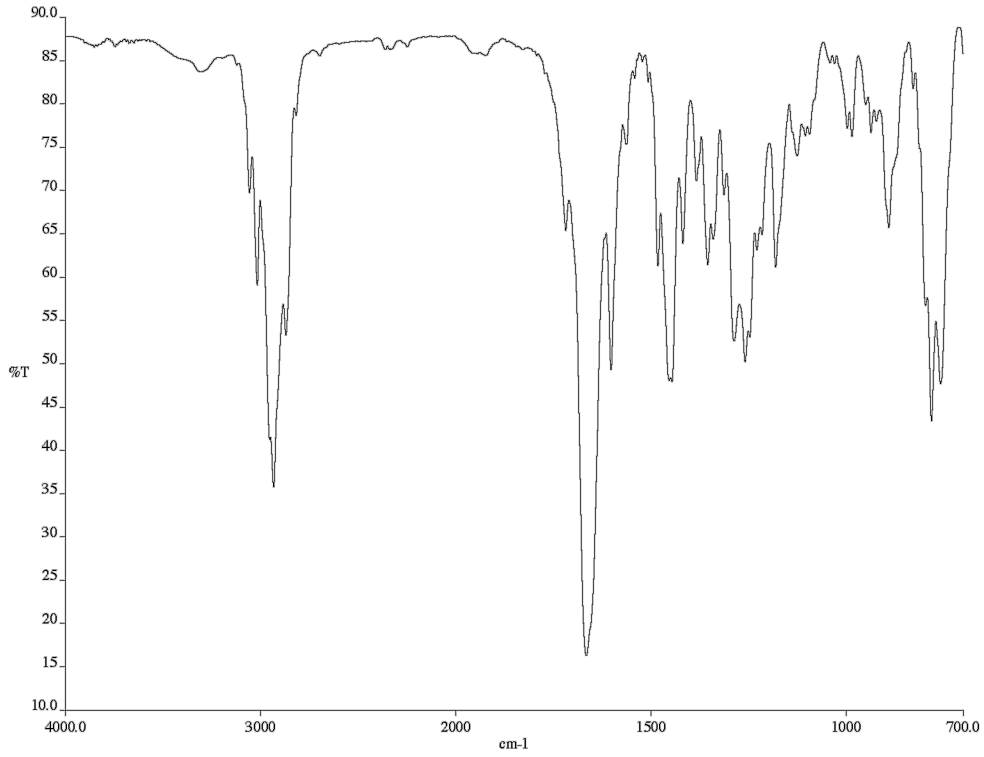


Figure A2.118.2. Infrared spectrum (thin film/NaCl) of compound **111aa**.

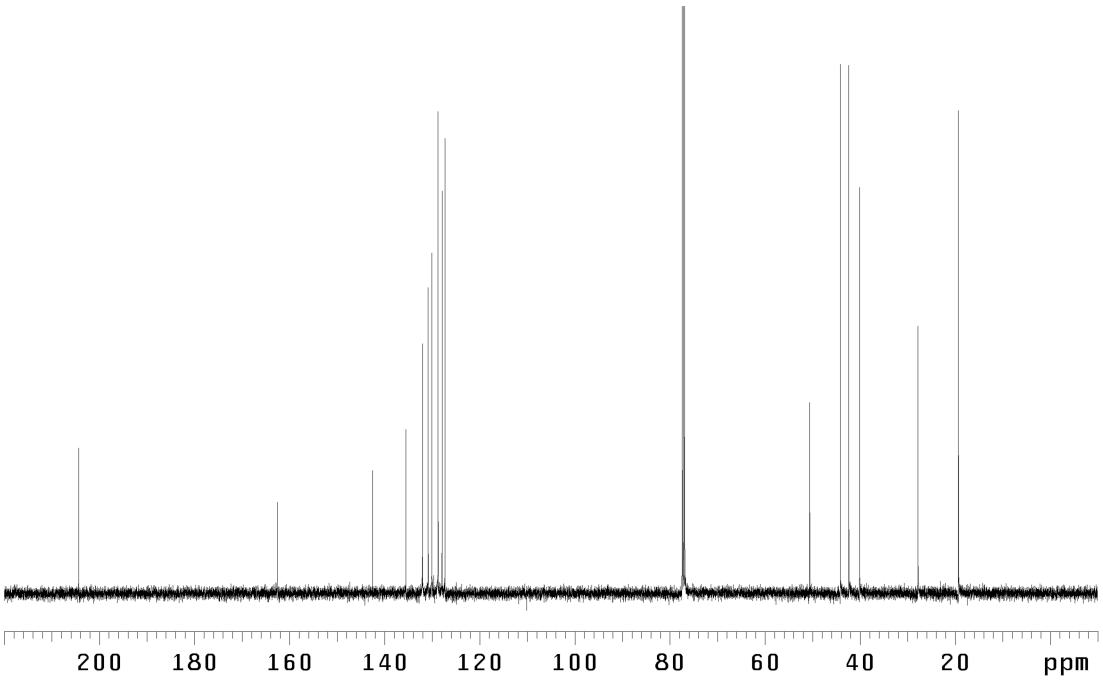


Figure A2.118.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **111aa**.

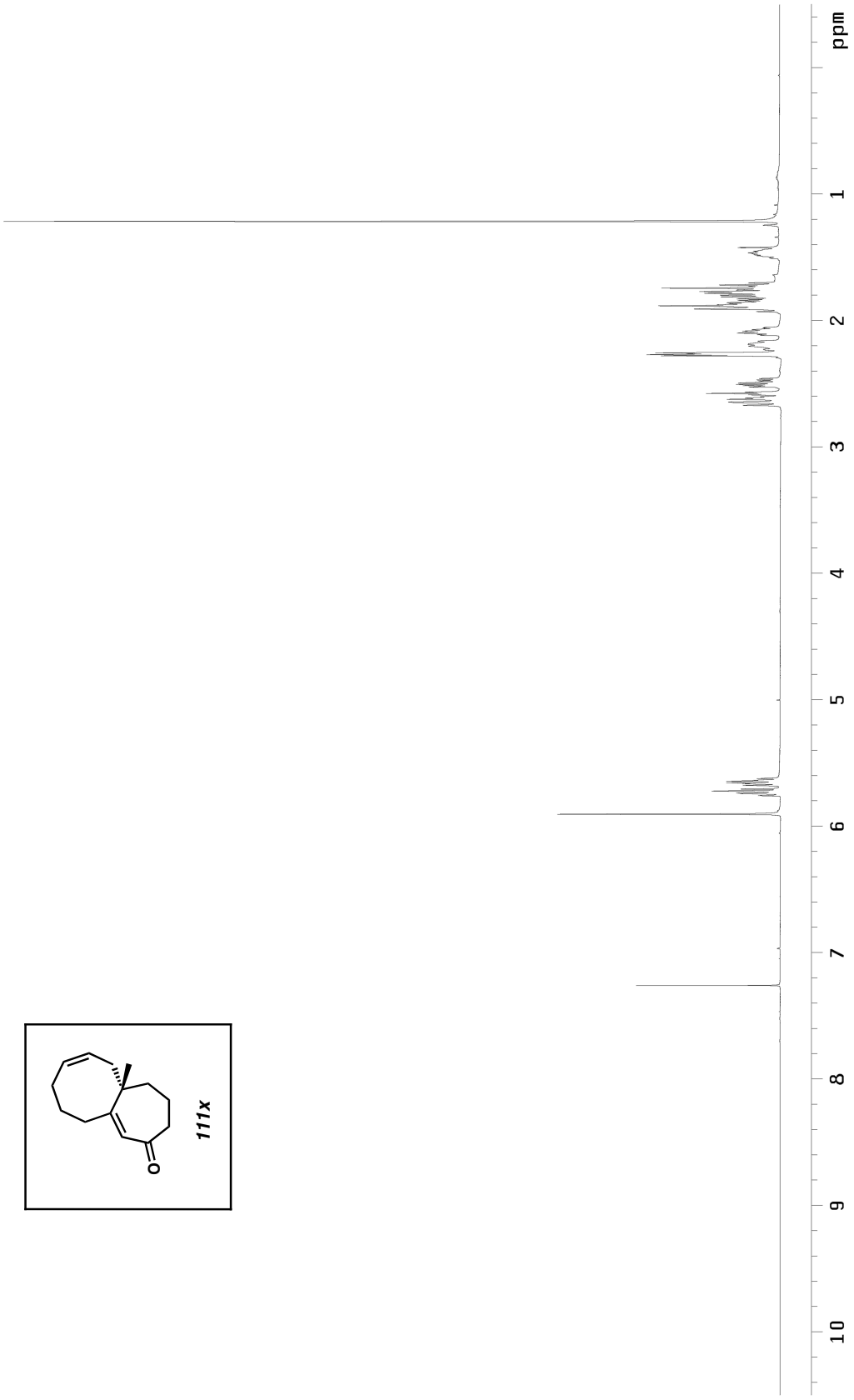


Figure A2.119.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **111x**.

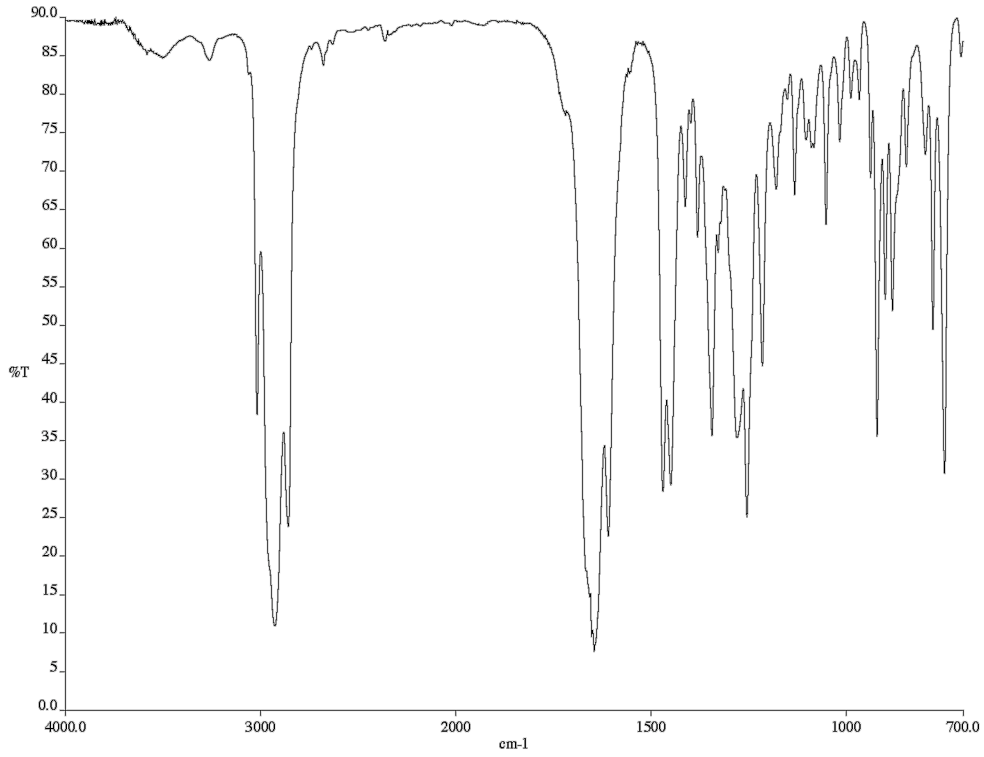


Figure A2.119.2. Infrared spectrum (thin film/NaCl) of compound **111x**.

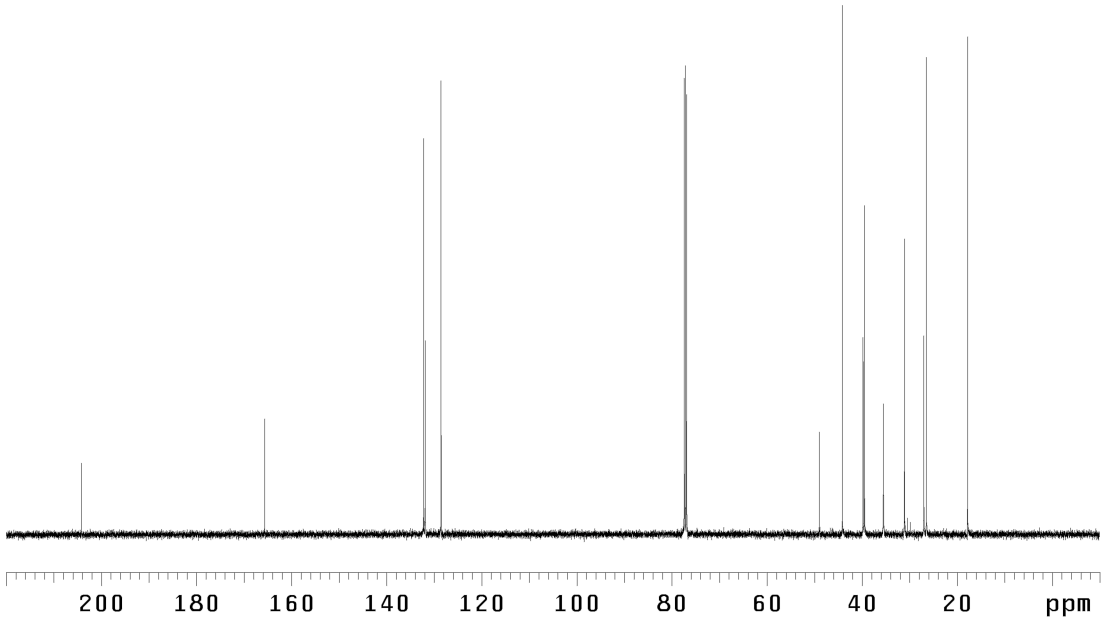


Figure A2.119.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **111x**.

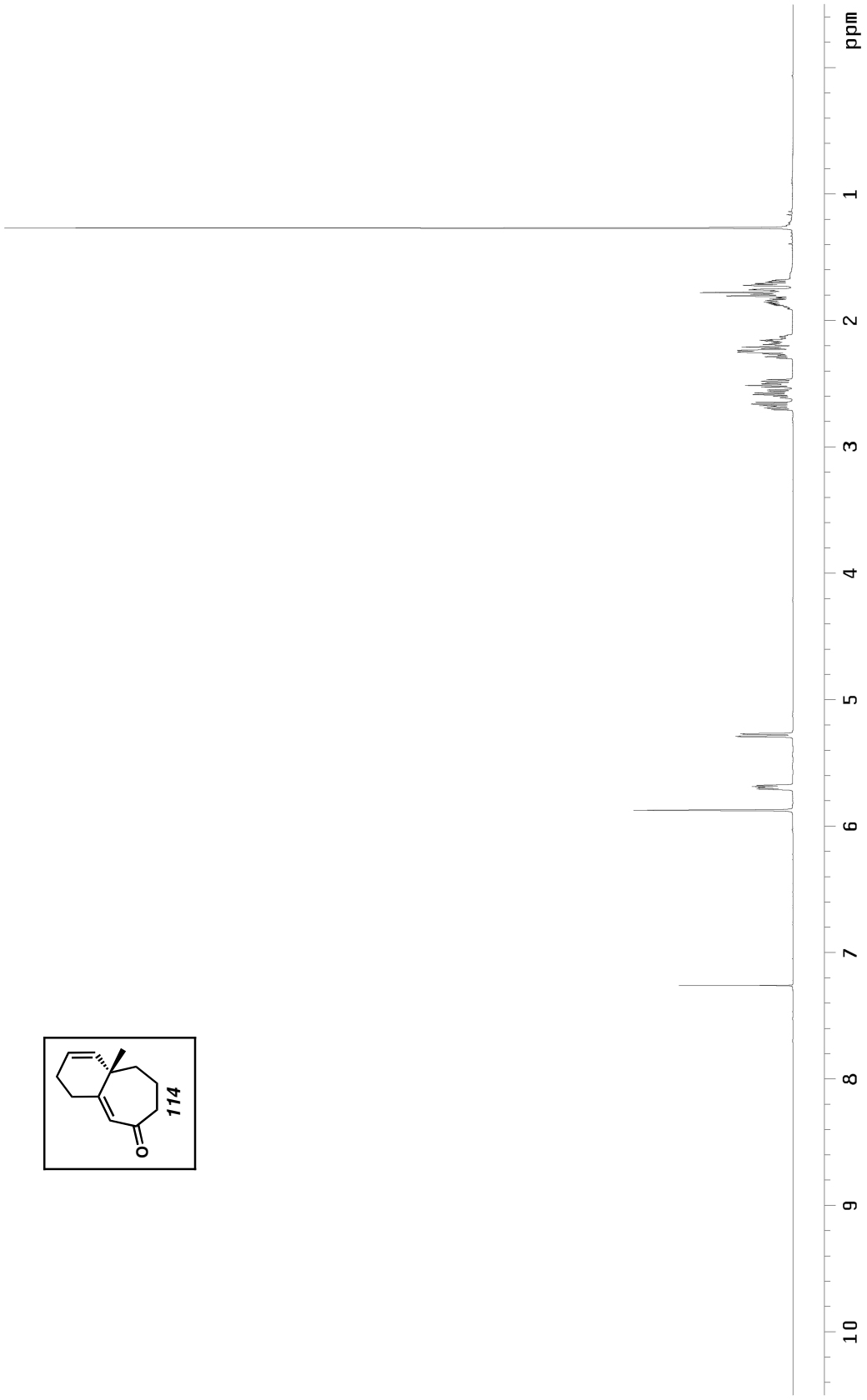


Figure A2.120.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **114**.

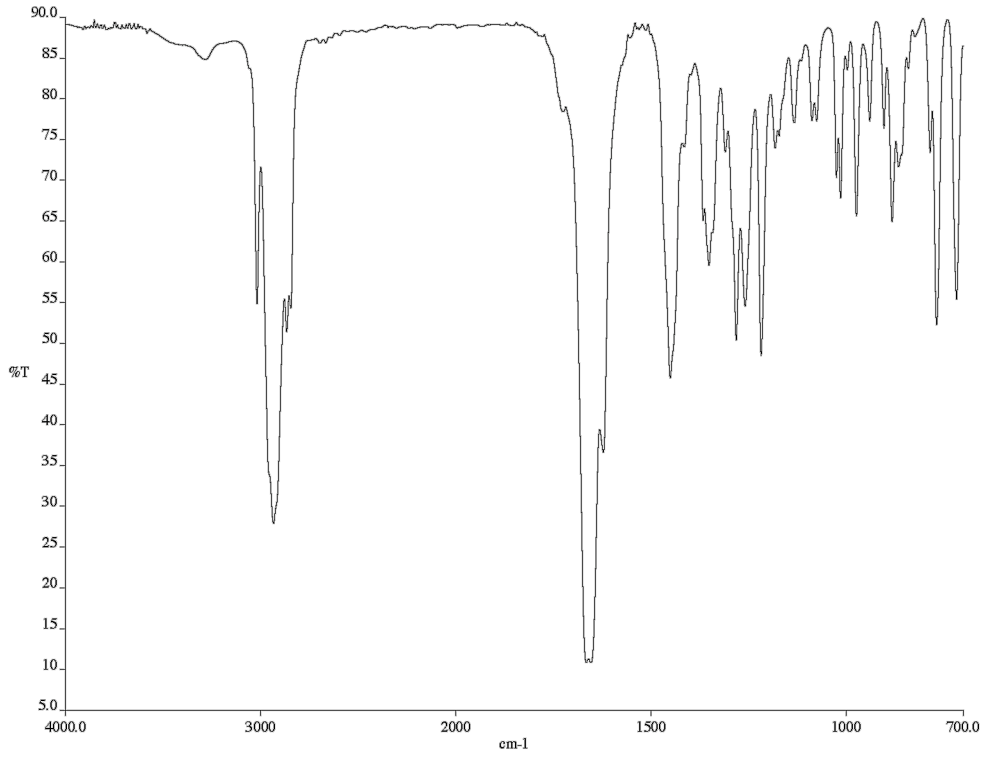


Figure A2.120.2. Infrared spectrum (thin film/NaCl) of compound **114**.

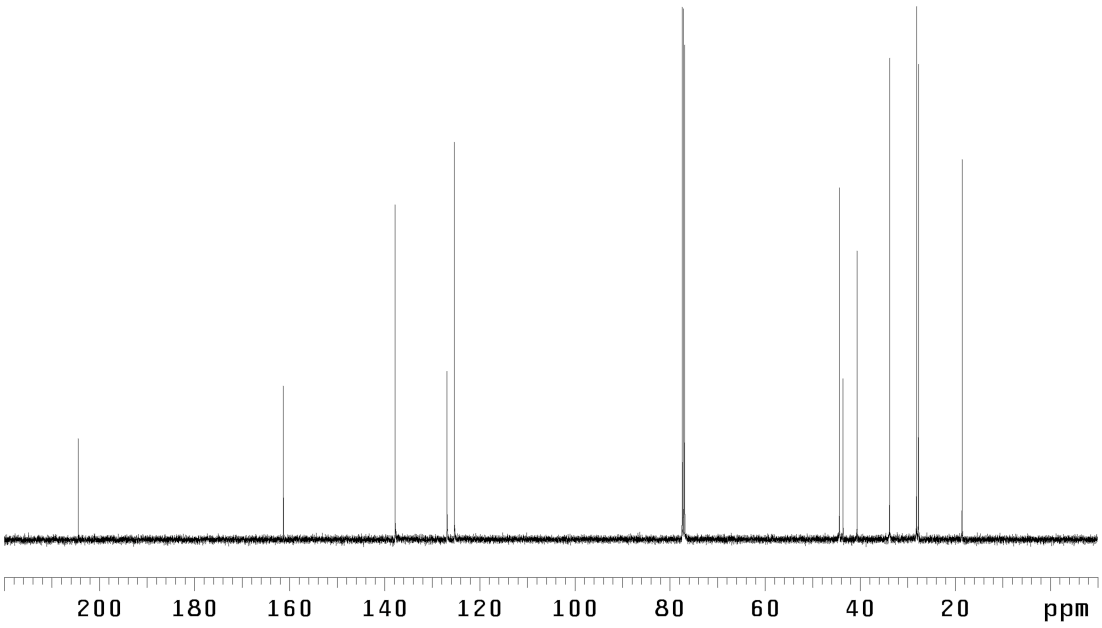


Figure A2.120.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **114**.

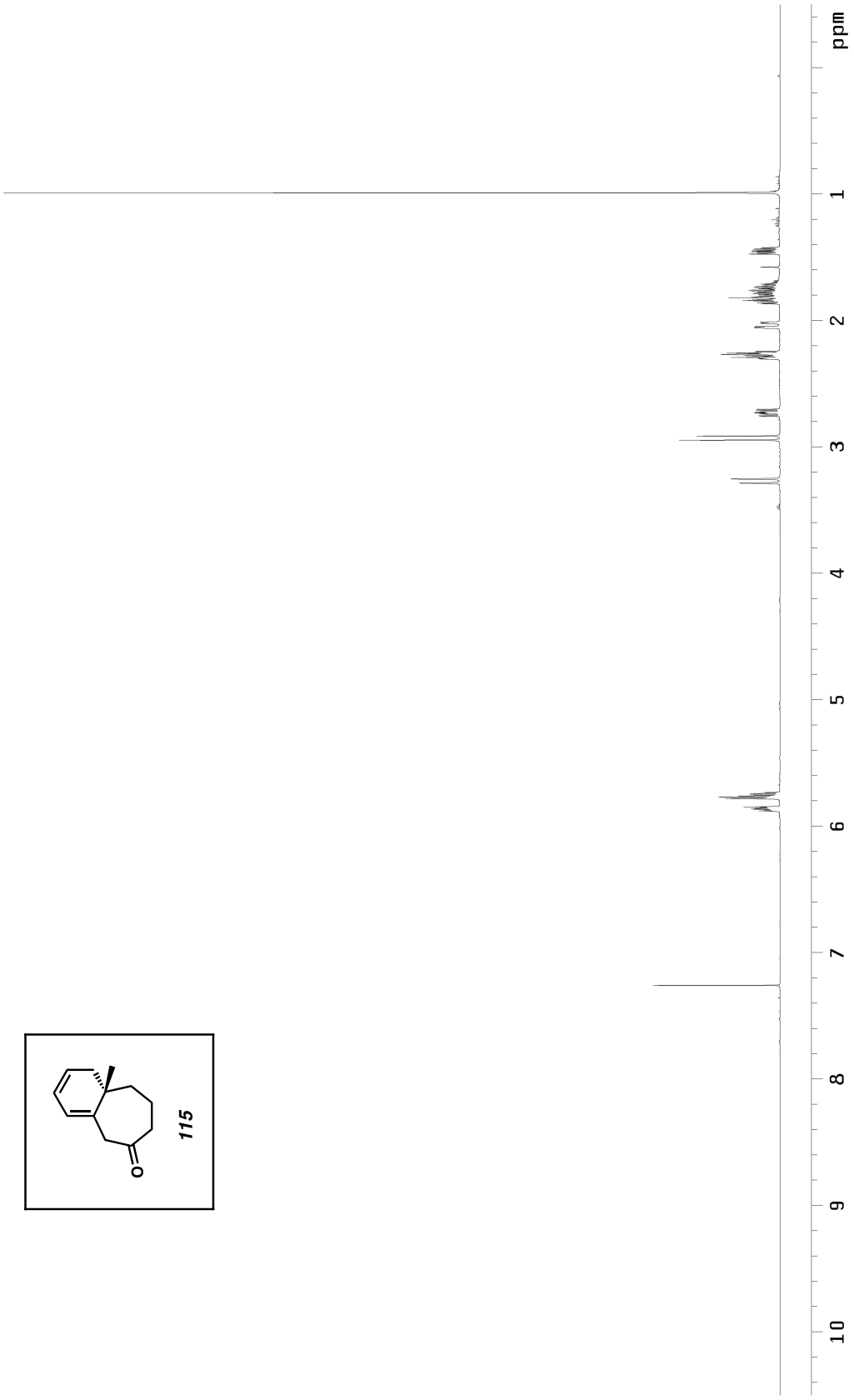


Figure A2.121.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **115**.

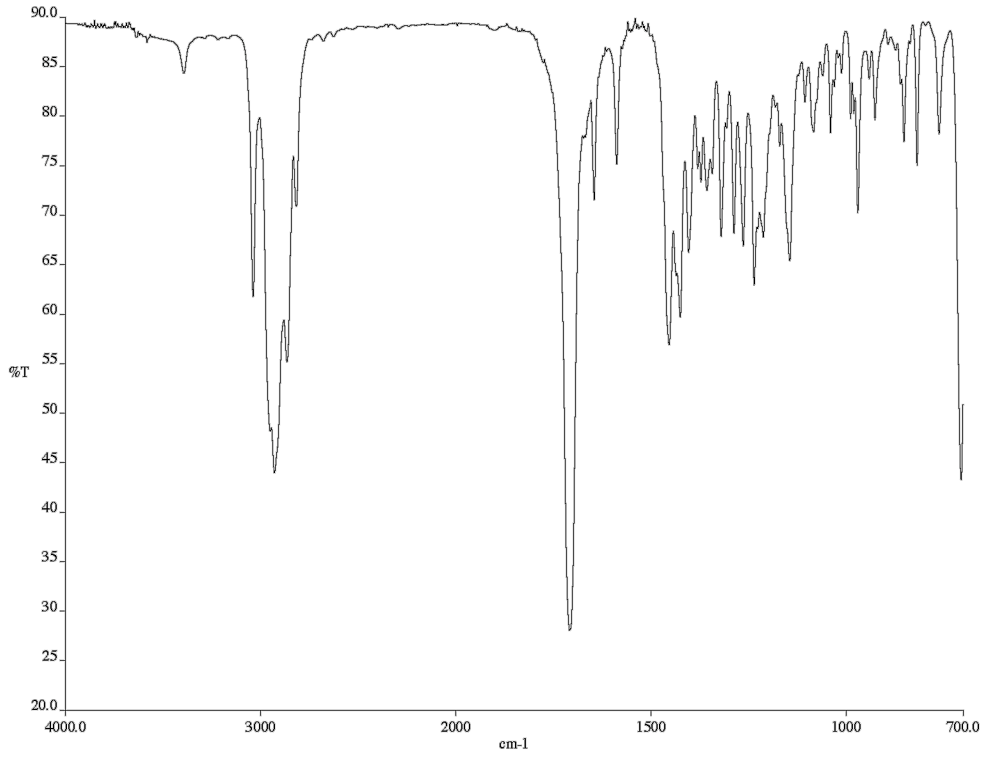


Figure A2.121.2. Infrared spectrum (thin film/NaCl) of compound **115**.

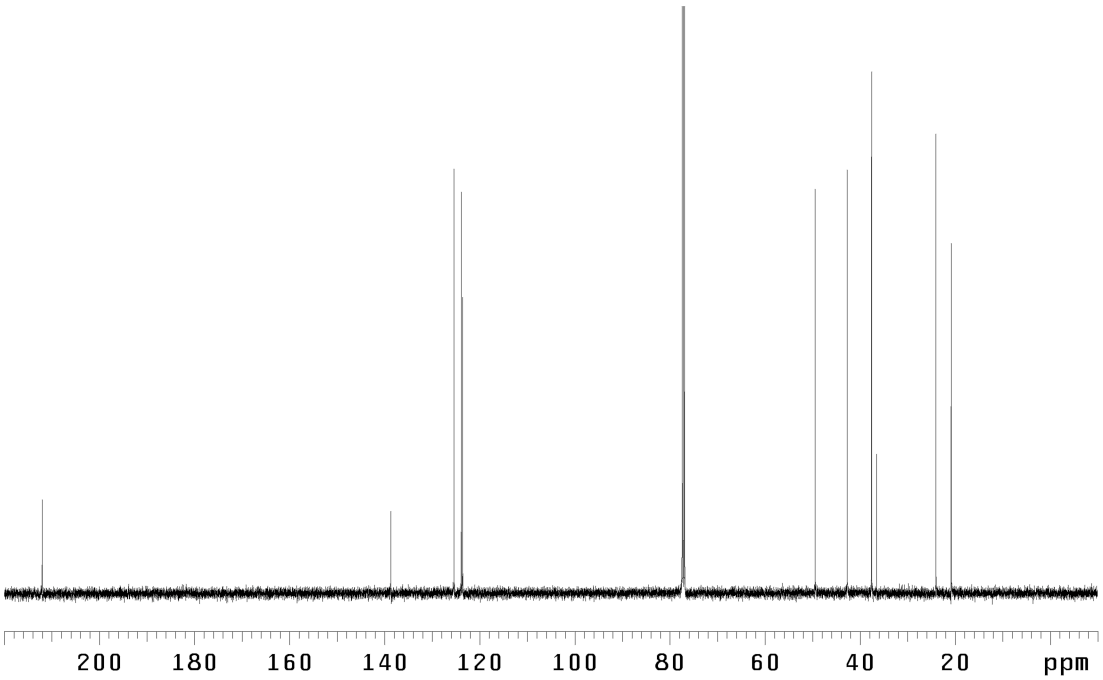


Figure A2.121.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **115**.

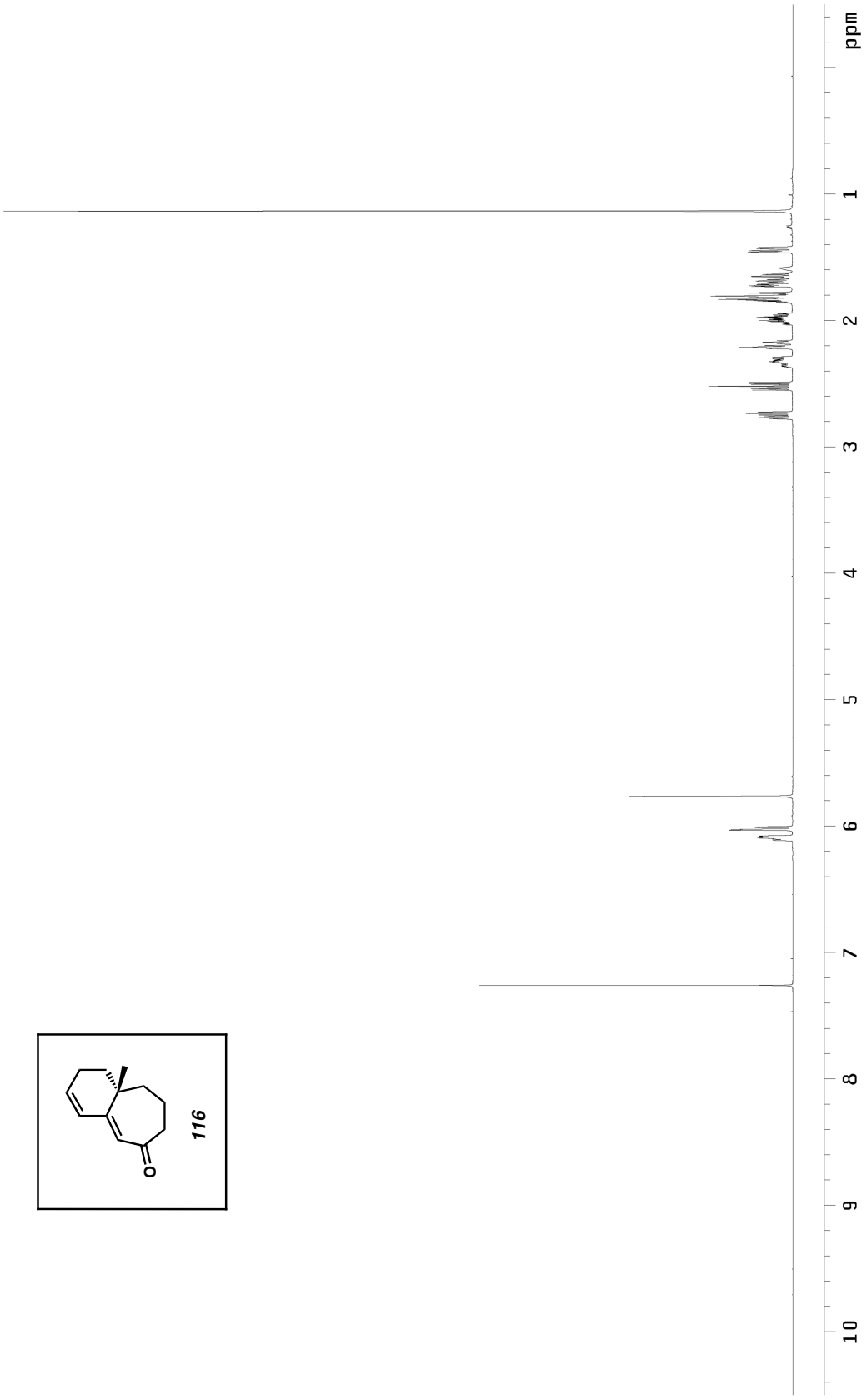


Figure A2.122.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **116**.

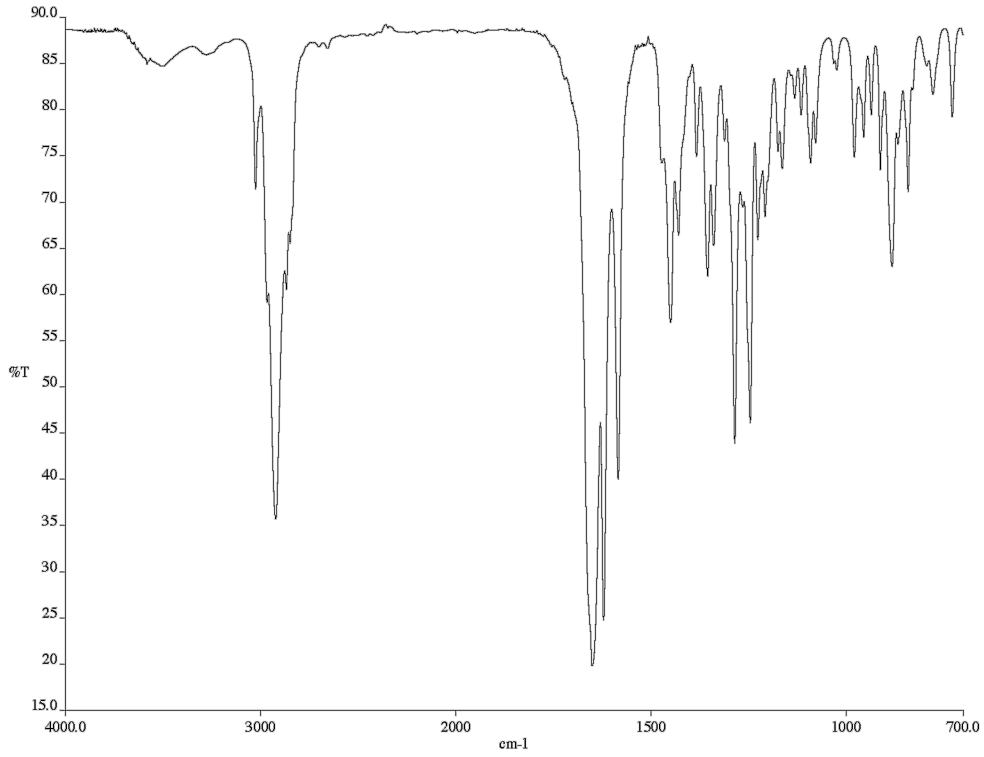


Figure A2.122.2. Infrared spectrum (thin film/NaCl) of compound **116**.

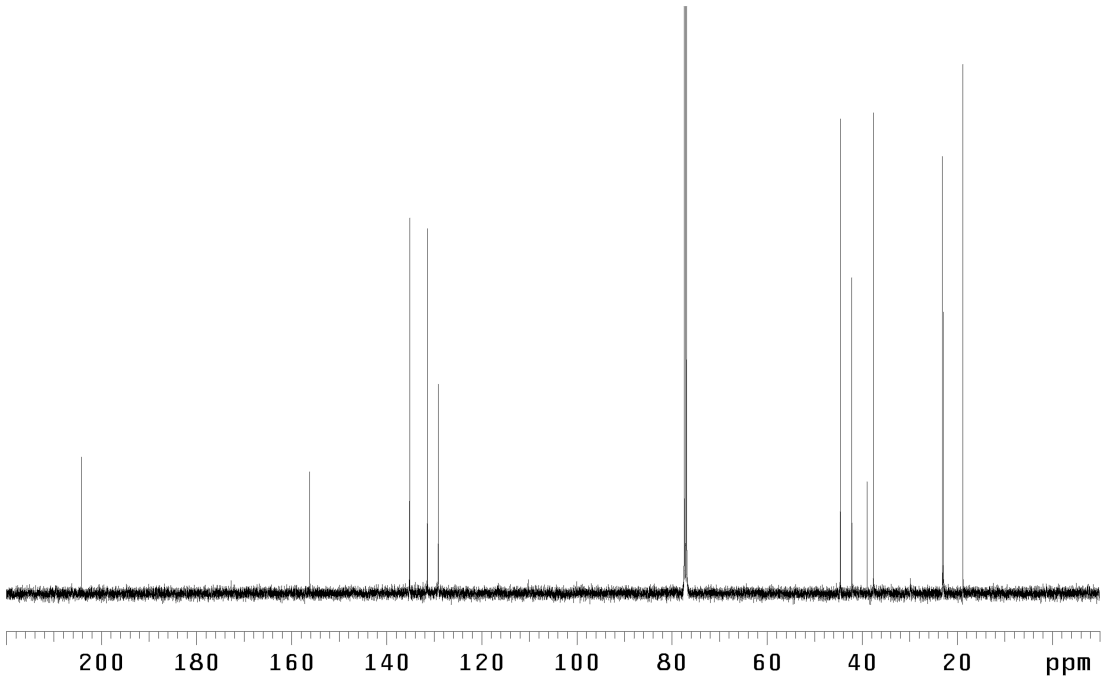


Figure A2.122.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **116**.

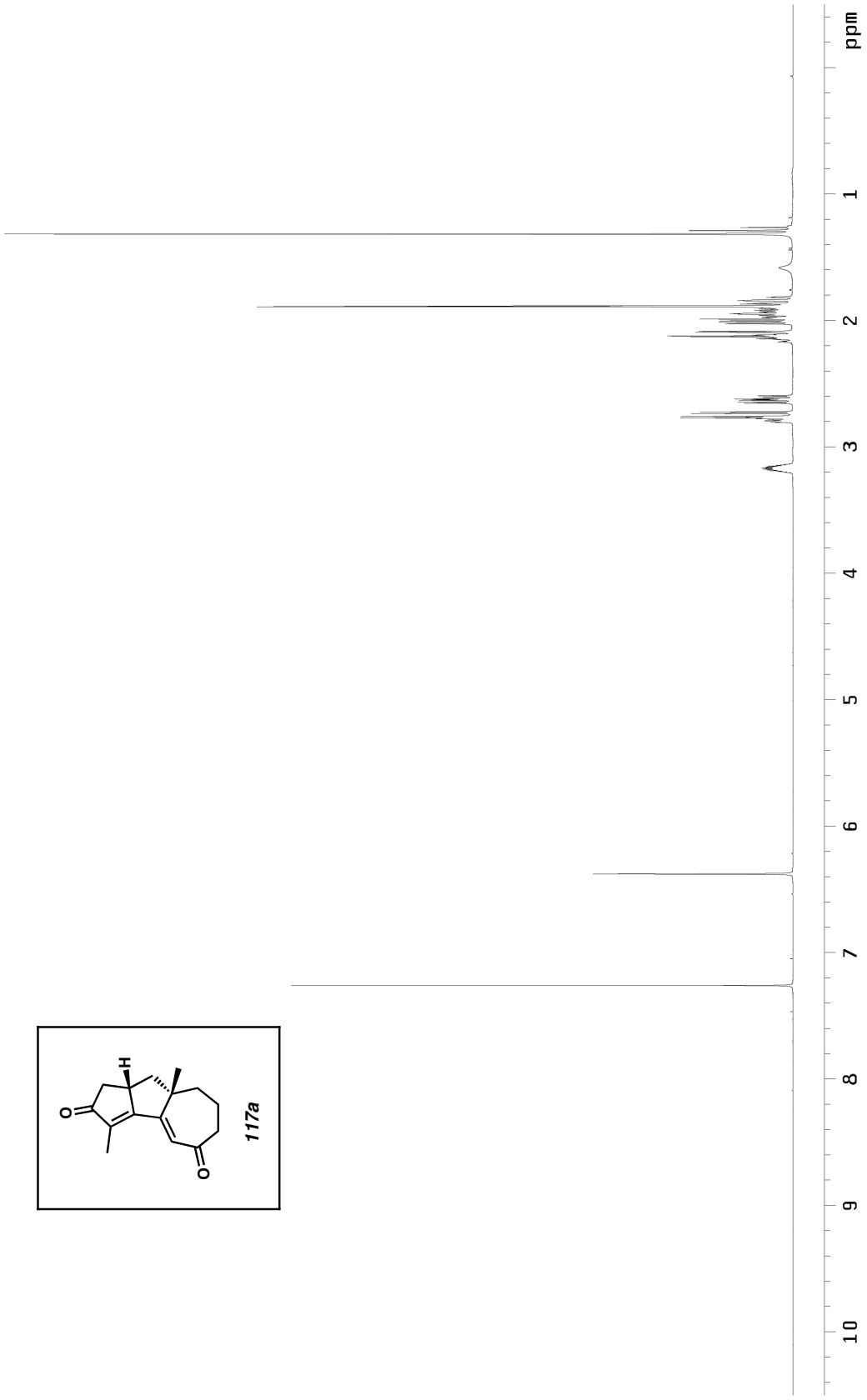


Figure A2.123.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **117a**.

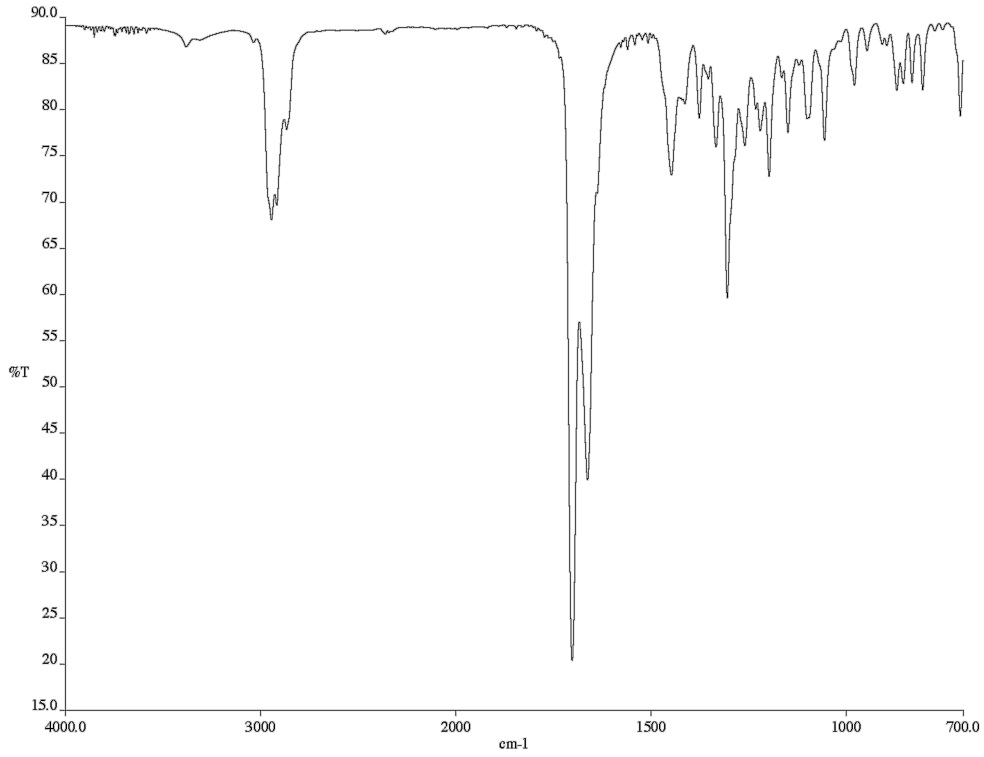


Figure A2.123.2. Infrared spectrum (thin film/NaCl) of compound **117a**.

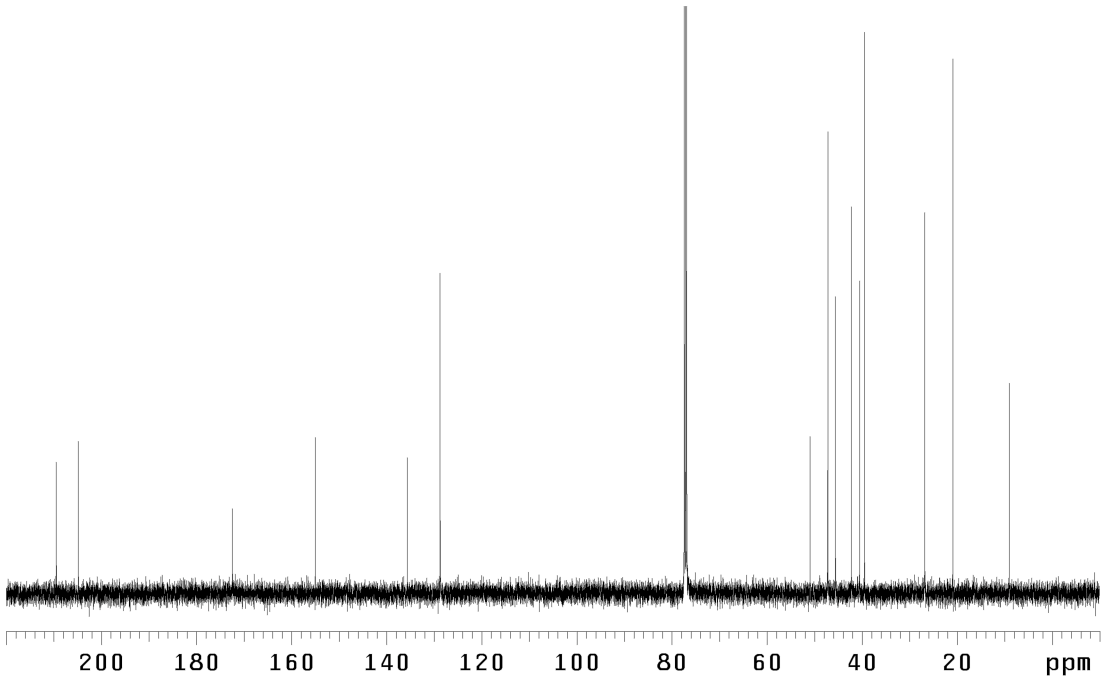


Figure A2.123.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **117a**.

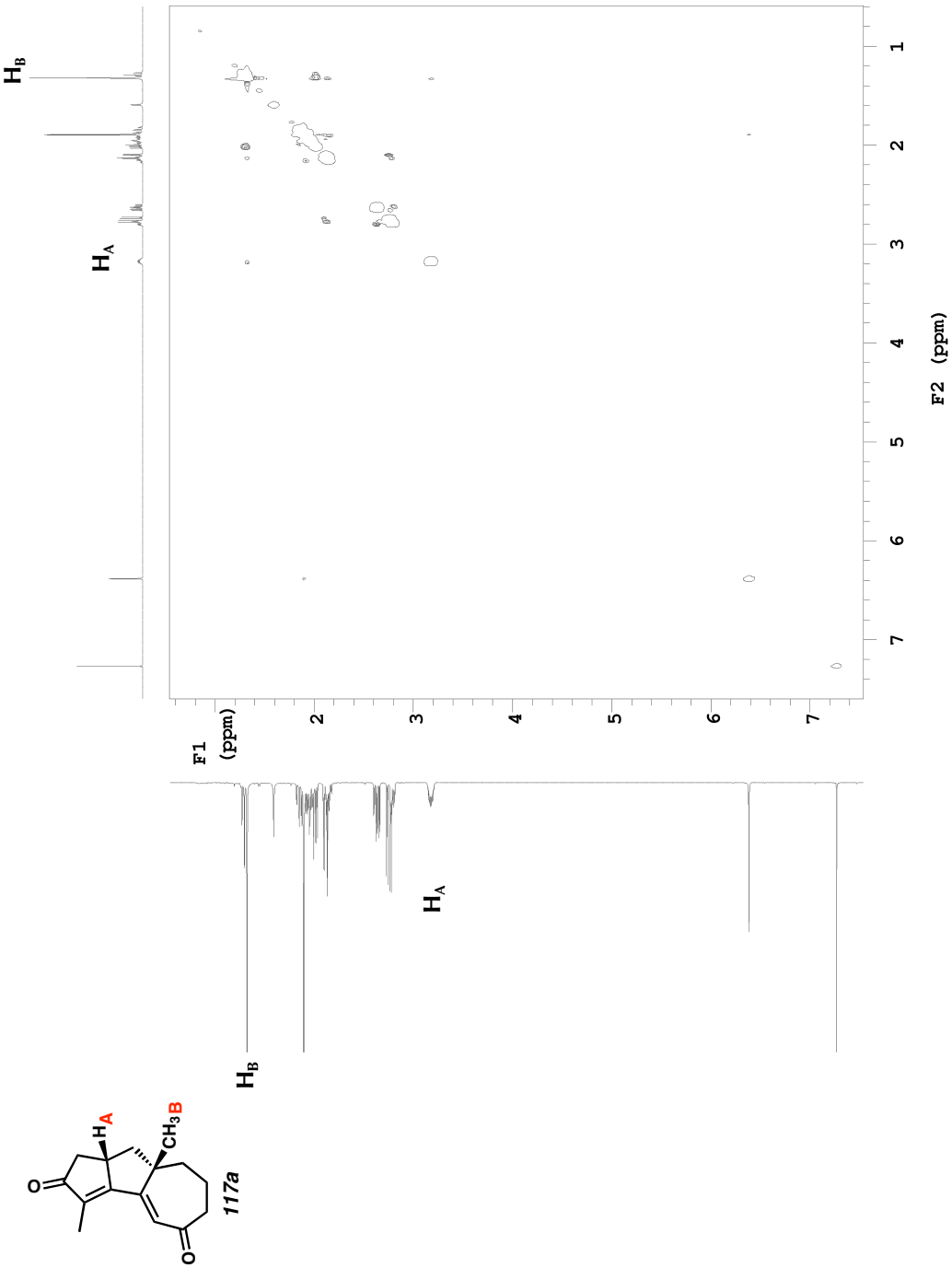


Figure A2.123.4. NOESY (500 MHz, $CDCl_3$) of compound **117a**.

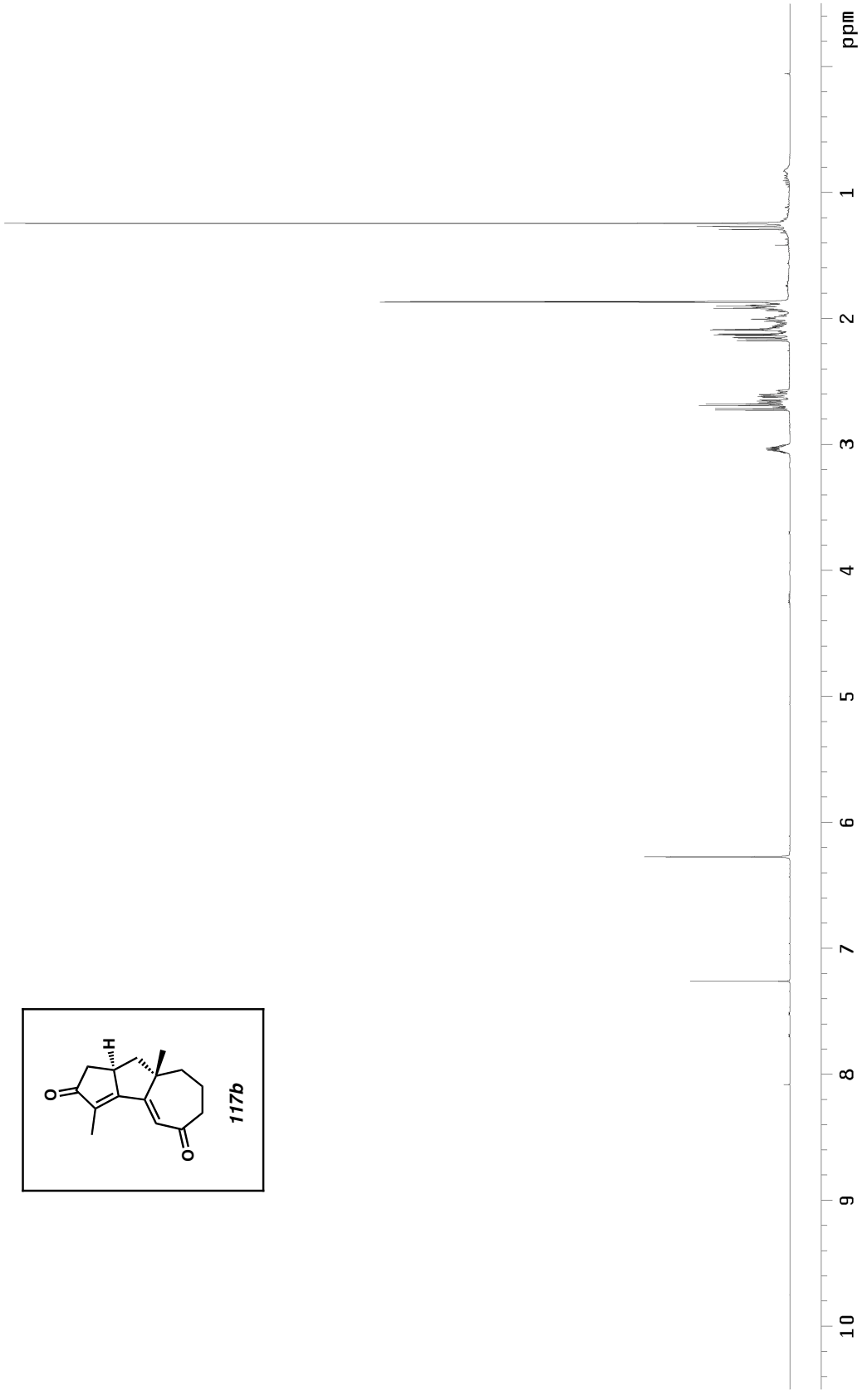


Figure A2.124.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **117b**.

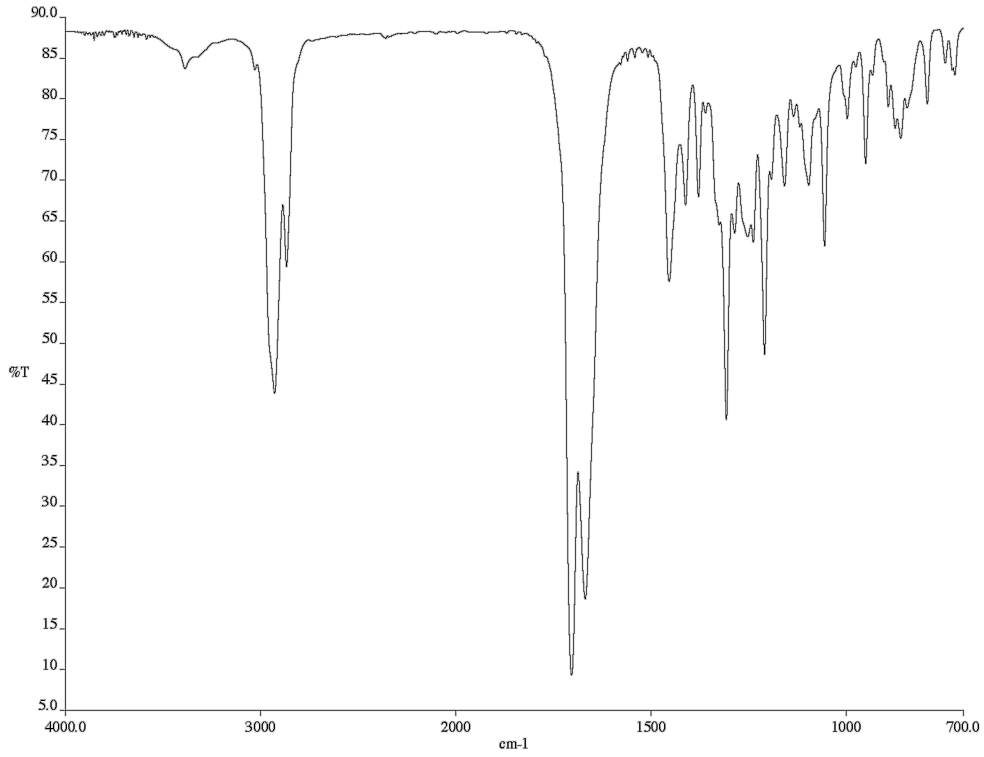


Figure A2.124.2. Infrared spectrum (thin film/NaCl) of compound **117b**.

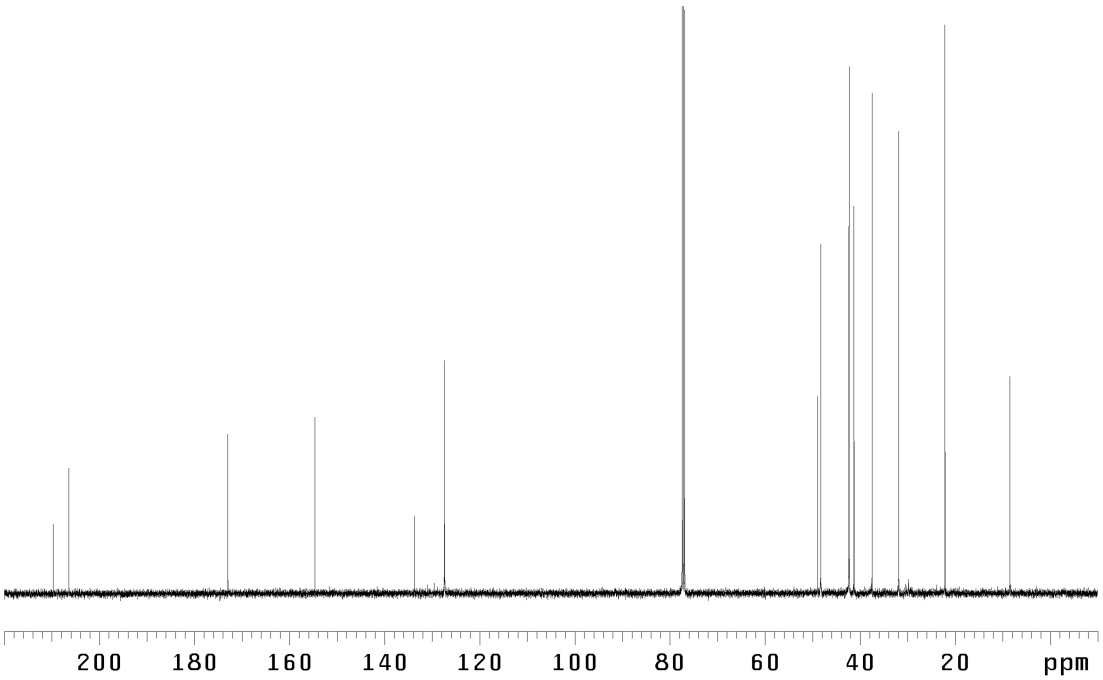


Figure A2.124.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **117b**.

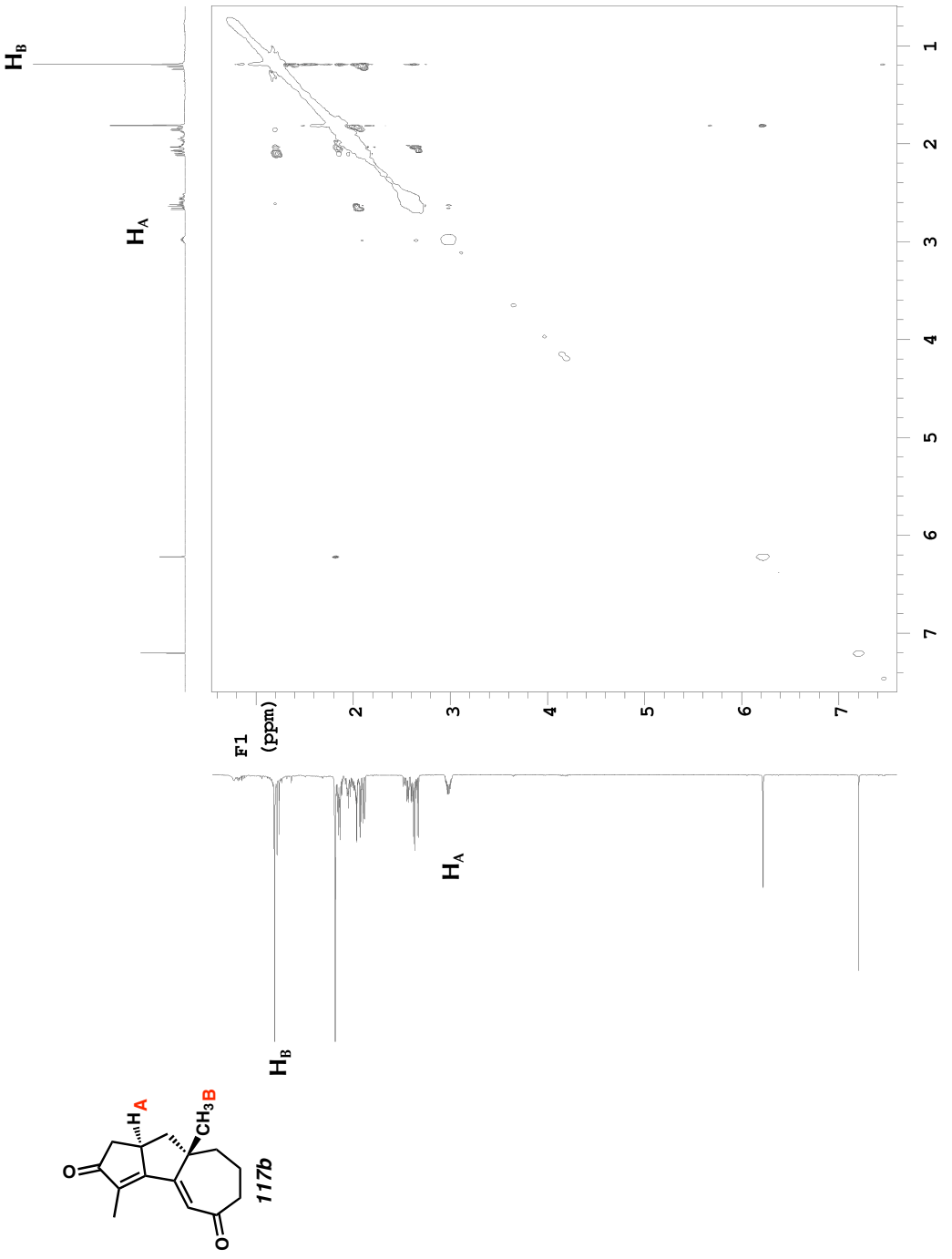


Figure A2.124.4. NOESY (500 MHz, $CDCl_3$) of compound **117b**.

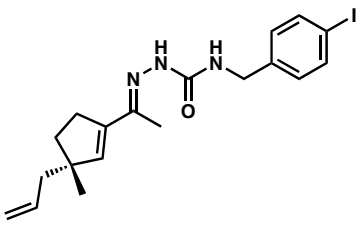
APPENDIX 3

X-Ray Crystallography Reports Relevant to Chapter 2:

Palladium-Catalyzed Asymmetric Alkylation in the Synthesis of

Cyclopentanoid and Cycloheptanoid Core Structures

A3.1 CRYSTAL STRUCTURE ANALYSIS OF 81

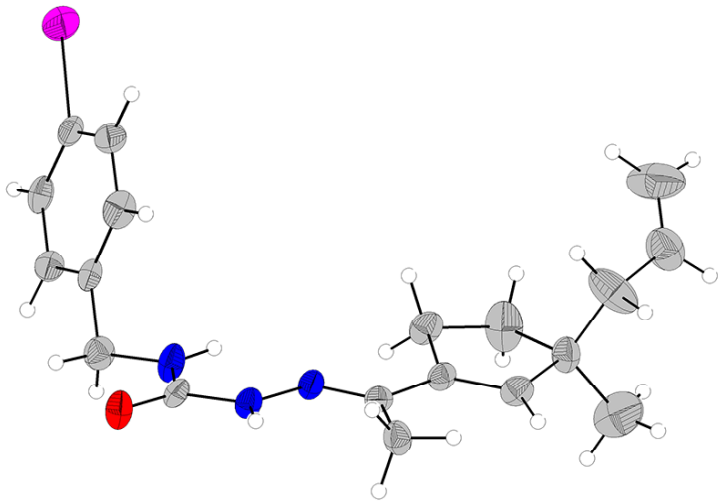


Compound **81**

(AYH02) (CCDC 686849)

Contents

*Figure A3.1. Semicarbazone **81** is shown with 50% probability ellipsoids.*



*CCDC 686849 (**81**) contains the supplementary crystallographic data for this appendix. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.*

*Table A3.1. Crystal data and structure refinement for semicarbazone **81** (CCDC 686849).*

Empirical formula	$C_{19}H_{24}N_3OI$
Formula weight	437.31
Crystallization solvent	Dichloromethane/pentane
Crystal habit	Needle
Crystal size	0.28 x 0.11 x 0.07 mm^3
Crystal color	Colorless

Data Collection

Type of diffractometer	Bruker KAPPA APEX II
Wavelength	0.71073 Å MoKα
Data collection temperature	100(2) K
θ range for 9911 reflections used in lattice determination	2.57 to 28.78°
Unit cell dimensions	a = 17.160(4) Å b = 5.5921(14) Å β = 90.689(6)° c = 19.984(5) Å
Volume	1917.6(8) $Å^3$
Z	4
Crystal system	Monoclinic
Space group	$P2_1$
Density (calculated)	1.515 Mg/m^3
F(000)	880
Data collection program	Bruker APEX2 v2.1-0
θ range for data collection	1.55 to 29.84°
Completeness to θ = 29.84°	88.9 %
Index ranges	$-23 \le h \le 23, -7 \le k \le 7, -26 \le l \le 25$
Data collection scan type	ω scans; 16 settings
Data reduction program	Bruker SAINT-Plus v7.34A
Reflections collected	8962
Independent reflections	8962 [R_{int} = 0.0000]
Absorption coefficient	1.680 mm^{-1}
Absorption correction	Semi-empirical from equivalents (TWNABS)
Max. and min. transmission	0.7460 and 0.5010

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 2008)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Geometric positions
Structure refinement program	SHELXL-97 (Sheldrick, 2008)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	8962 / 1 / 437
Treatment of hydrogen atoms	Riding
Goodness-of-fit on F^2	1.609
Final R indices [I>2σ(I), 7203 reflections]	R1 = 0.0409, *w*R2 = 0.0481
R indices (all data)	R1 = 0.0619, *w*R2 = 0.0493
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.002
Average shift/error	0.000
Absolute structure determination	Anomalous differences
Absolute structure parameter	0.003(11)
Largest diff. peak and hole	0.807 and –0.967 e.Å^{-3}

Special Refinement Details

The structure was refined as a single component, although the crystals were twins, using an HKLF4 format reflection file prepared with TWINABS (see below). The two orientations were separated using CELL_NOW as follows.

Rotated from first domain by 178.9 degrees about reciprocal axis –0.032 1.000 0.104 and real axis –0.001 1.000 0.007. Twin law to convert hkl from first to this domain (SHELXL TWIN matrix):

-1.000 -0.065 0.016

-0.003 0.998 0.014

-0.022 0.207 -0.999

From Saint integration; Twin Law, Sample 1 of 1 transforms h1.1(1)->h1.2(2)

-0.99897 -0.07583 0.01646

-0.00750 0.99693 0.01538

-0.02464 0.19596 -0.99910

Twinabs;

PART 1 - Refinement of parameters to model systematic errors

18757 data (4443 unique) involve domain 1 only, mean I/sigma 13.7

18551 data (4364 unique) involve domain 2 only, mean I/sigma 7.1

10342 data (4106 unique) involve 2 domains, mean I/sigma 19.2

HKLF 4 dataset constructed from all observations involving domains 1..2

8970 Corrected reflections written to file twin4.hkl

Reflections merged according to point-group 2

Minimum and maximum apparent transmission: 0.501007 0.745969

Additional spherical absorption correction applied with mu*r = 0.2000

Crystals were mounted on a glass fiber using Paratone oil then placed on the diffractometer under a nitrogen stream at 100 K.

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

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

*Figure A3.2. Semicarbazone **81** (CCDC 686849).*

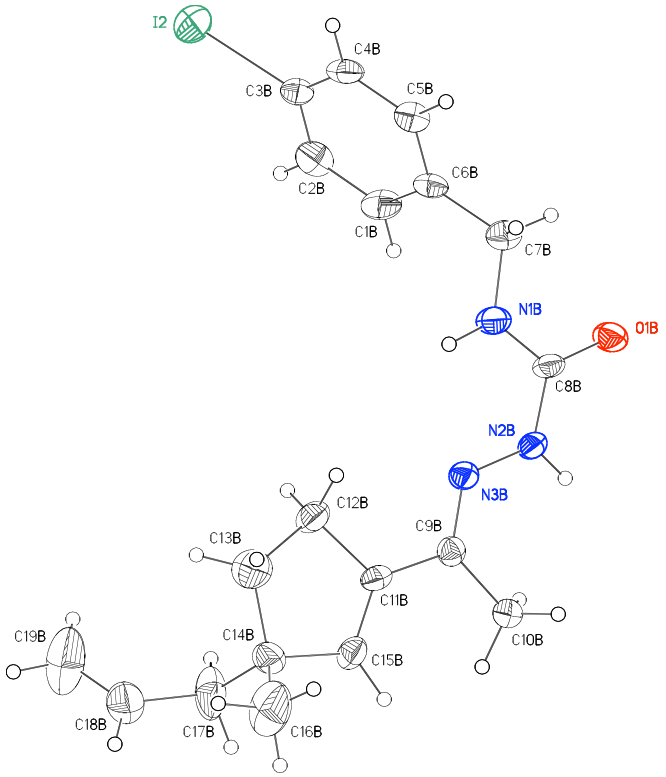


*Table A3.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for semicarbazone **81** (CCDC 686849). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.*

	x	y	z	U_{eq}
I(1)	9525(1)	8297(1)	6590(1)	36(1)
O(1A)	7955(1)	941(3)	3051(1)	30(1)
N(1A)	7500(2)	3872(4)	3727(1)	30(1)
N(2A)	6670(2)	1070(4)	3270(1)	28(1)
N(3A)	6059(2)	2296(4)	3562(1)	28(1)
C(1A)	8489(2)	4383(5)	4938(2)	26(1)
C(2A)	8786(2)	5006(6)	5555(2)	27(1)
C(3A)	9158(2)	7186(5)	5637(2)	24(1)
C(4A)	9240(2)	8700(6)	5094(2)	23(1)
C(5A)	8934(2)	8049(6)	4481(2)	24(1)
C(6A)	8541(2)	5886(5)	4389(2)	21(1)
C(7A)	8214(2)	5251(6)	3716(2)	29(1)
C(8A)	7411(2)	1915(5)	3335(2)	24(1)
C(9A)	5356(2)	1676(5)	3411(2)	25(1)
C(10A)	5153(2)	-221(5)	2912(2)	34(1)

Table A3.2 (cont.)

C(11A)	4738(2)	3016(6)	3736(2)	25(1)
C(12A)	4902(2)	5012(5)	4229(2)	30(1)
C(13A)	4096(2)	6199(5)	4302(2)	34(1)
C(14A)	3501(2)	4222(5)	4130(2)	33(1)
C(15A)	3985(2)	2625(5)	3693(2)	32(1)
C(16A)	3271(2)	2838(6)	4771(2)	47(1)
C(17A)	2751(2)	5160(6)	3793(2)	36(1)
C(18A)	2864(2)	6198(6)	3116(2)	39(1)
C(19A)	2612(2)	8233(8)	2900(2)	51(1)
I(2)	5760(1)	351(1)	-1541(1)	52(1)
O(1B)	6661(1)	7118(3)	2275(1)	34(1)
N(1B)	7173(2)	4167(4)	1625(1)	34(1)
N(2B)	7955(2)	7040(4)	2098(1)	27(1)
N(3B)	8578(2)	5882(4)	1807(1)	26(1)
C(1B)	6496(2)	3858(5)	289(2)	33(1)
C(2B)	6341(2)	3322(8)	-374(2)	35(1)
C(3B)	5958(2)	1240(6)	-534(2)	29(1)
C(4B)	5742(2)	-303(6)	-40(2)	31(1)
C(5B)	5895(2)	235(6)	618(2)	28(1)
C(6B)	6287(2)	2329(5)	795(2)	26(1)
C(7B)	6454(2)	2863(6)	1519(2)	32(1)
C(8B)	7233(2)	6143(5)	2016(2)	25(1)
C(9B)	9266(2)	6619(5)	1925(2)	24(1)
C(10B)	9471(2)	8670(6)	2382(2)	33(1)
C(11B)	9892(2)	5325(6)	1586(2)	25(1)
C(12B)	9704(2)	3469(7)	1051(2)	34(1)
C(13B)	10499(2)	2401(6)	903(2)	54(1)
C(14B)	11131(2)	4019(5)	1204(2)	33(1)
C(15B)	10659(2)	5558(6)	1666(2)	30(1)
C(16B)	11736(3)	2543(7)	1600(2)	67(2)
C(17B)	11522(2)	5571(7)	690(2)	58(1)
C(18B)	12017(3)	4302(6)	194(2)	52(1)
C(19B)	11859(3)	3982(7)	-416(2)	77(2)

*Table A3.3. Bond lengths [Å] and angles [°] for semicarbazone **81** (CCDC 686849).*

I(1)-C(3A)	2.092(3)		
O(1A)-C(8A)	1.226(4)	C(8A)-N(1A)-C(7A)	120.7(3)
N(1A)-C(8A)	1.354(4)	C(8A)-N(2A)-N(3A)	119.8(3)
N(1A)-C(7A)	1.449(4)	C(9A)-N(3A)-N(2A)	118.6(3)
N(2A)-C(8A)	1.361(4)	C(2A)-C(1A)-C(6A)	122.1(3)
N(2A)-N(3A)	1.388(3)	C(1A)-C(2A)-C(3A)	119.6(3)
N(3A)-C(9A)	1.289(4)	C(2A)-C(3A)-C(4A)	119.8(3)
C(1A)-C(2A)	1.375(5)	C(2A)-C(3A)-I(1)	120.1(2)
C(1A)-C(6A)	1.386(4)	C(4A)-C(3A)-I(1)	119.9(2)
C(2A)-C(3A)	1.385(4)	C(5A)-C(4A)-C(3A)	119.7(3)
C(3A)-C(4A)	1.384(4)	C(4A)-C(5A)-C(6A)	121.7(3)
C(4A)-C(5A)	1.376(4)	C(1A)-C(6A)-C(5A)	117.2(3)
C(5A)-C(6A)	1.397(5)	C(1A)-C(6A)-C(7A)	122.8(3)
C(6A)-C(7A)	1.494(4)	C(5A)-C(6A)-C(7A)	120.1(3)
C(9A)-C(11A)	1.457(4)	N(1A)-C(7A)-C(6A)	115.0(3)
C(9A)-C(10A)	1.494(4)	O(1A)-C(8A)-N(1A)	123.1(3)
C(11A)-C(15A)	1.312(4)	O(1A)-C(8A)-N(2A)	121.2(3)
C(11A)-C(12A)	1.514(5)	N(1A)-C(8A)-N(2A)	115.8(3)
C(12A)-C(13A)	1.542(4)	N(3A)-C(9A)-C(11A)	116.2(3)
C(13A)-C(14A)	1.542(5)	N(3A)-C(9A)-C(10A)	123.9(3)
C(14A)-C(15A)	1.505(4)	C(11A)-C(9A)-C(10A)	119.8(3)
C(14A)-C(17A)	1.538(5)	C(15A)-C(11A)-C(9A)	127.4(3)
C(14A)-C(16A)	1.552(5)	C(15A)-C(11A)-C(12A)	109.9(3)
C(17A)-C(18A)	1.487(5)	C(9A)-C(11A)-C(12A)	122.6(3)
C(18A)-C(19A)	1.290(5)	C(11A)-C(12A)-C(13A)	102.6(3)
I(2)-C(3B)	2.096(3)	C(12A)-C(13A)-C(14A)	105.2(2)
O(1B)-C(8B)	1.242(4)	C(15A)-C(14A)-C(17A)	114.4(3)
N(1B)-C(8B)	1.356(4)	C(15A)-C(14A)-C(13A)	100.7(3)
N(1B)-C(7B)	1.447(4)	C(17A)-C(14A)-C(13A)	113.7(3)
N(2B)-C(8B)	1.346(4)	C(15A)-C(14A)-C(16A)	109.3(3)
N(2B)-N(3B)	1.383(3)	C(17A)-C(14A)-C(16A)	108.2(3)
N(3B)-C(9B)	1.270(4)	C(13A)-C(14A)-C(16A)	110.3(3)
C(1B)-C(6B)	1.376(4)	C(11A)-C(15A)-C(14A)	114.4(3)
C(1B)-C(2B)	1.380(5)	C(18A)-C(17A)-C(14A)	114.4(3)
C(2B)-C(3B)	1.373(5)	C(19A)-C(18A)-C(17A)	127.0(3)
C(3B)-C(4B)	1.366(4)	C(8B)-N(1B)-C(7B)	123.6(3)
C(4B)-C(5B)	1.372(4)	C(8B)-N(2B)-N(3B)	119.3(3)
C(5B)-C(6B)	1.394(5)	C(9B)-N(3B)-N(2B)	119.4(3)
C(6B)-C(7B)	1.501(5)	C(6B)-C(1B)-C(2B)	121.4(3)
C(9B)-C(11B)	1.467(4)	C(3B)-C(2B)-C(1B)	119.6(3)
C(9B)-C(10B)	1.504(4)	C(4B)-C(3B)-C(2B)	120.0(3)
C(11B)-C(15B)	1.330(4)	C(4B)-C(3B)-I(2)	120.1(3)
C(11B)-C(12B)	1.522(4)	C(2B)-C(3B)-I(2)	119.8(2)
C(12B)-C(13B)	1.521(5)	C(3B)-C(4B)-C(5B)	120.3(3)
C(13B)-C(14B)	1.530(5)	C(4B)-C(5B)-C(6B)	120.9(3)
C(14B)-C(15B)	1.505(4)	C(1B)-C(6B)-C(5B)	117.7(3)
C(14B)-C(17B)	1.509(5)	C(1B)-C(6B)-C(7B)	122.4(3)
C(14B)-C(16B)	1.537(6)	C(5B)-C(6B)-C(7B)	119.8(3)
C(17B)-C(18B)	1.493(5)	N(1B)-C(7B)-C(6B)	113.3(3)
C(18B)-C(19B)	1.260(5)	O(1B)-C(8B)-N(2B)	121.1(3)

Table A3.3 (cont.)

O(1B)-C(8B)-N(1B)	123.0(3)	C(12B)-C(13B)-C(14B)	108.9(3)
N(2B)-C(8B)-N(1B)	115.9(3)	C(15B)-C(14B)-C(17B)	109.6(3)
N(3B)-C(9B)-C(11B)	116.0(3)	C(15B)-C(14B)-C(13B)	101.3(3)
N(3B)-C(9B)-C(10B)	124.7(3)	C(17B)-C(14B)-C(13B)	112.9(3)
C(11B)-C(9B)-C(10B)	119.3(3)	C(15B)-C(14B)-C(16B)	110.9(3)
C(15B)-C(11B)-C(9B)	128.7(3)	C(17B)-C(14B)-C(16B)	110.8(3)
C(15B)-C(11B)-C(12B)	110.6(3)	C(13B)-C(14B)-C(16B)	110.9(3)
C(9B)-C(11B)-C(12B)	120.7(3)	C(11B)-C(15B)-C(14B)	114.2(3)
C(13B)-C(12B)-C(11B)	102.9(3)	C(18B)-C(17B)-C(14B)	116.1(3)
		C(19B)-C(18B)-C(17B)	126.3(5)

Table A3.4. Anisotropic displacement parameters ($Å^2$ x 10^4) for semicarbazone ***81*** *(CCDC 686849). The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$.*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
I(1)	340(2)	433(1)	310(1)	1(1)	-116(1)	-2(1)
O(1A)	177(14)	294(13)	431(15)	-131(10)	-15(11)	35(10)
N(1A)	166(17)	377(19)	352(17)	-168(12)	3(13)	-6(12)
N(2A)	150(17)	315(15)	378(18)	-133(12)	-22(13)	22(12)
N(3A)	186(19)	310(15)	328(18)	-35(12)	-35(15)	38(13)
C(1A)	190(20)	176(16)	420(20)	13(15)	-22(18)	9(13)
C(2A)	250(20)	237(18)	320(20)	88(15)	-7(16)	-4(16)
C(3A)	170(20)	261(17)	270(20)	-18(14)	-7(16)	69(14)
C(4A)	180(20)	200(20)	310(20)	-23(14)	-29(15)	-13(14)
C(5A)	240(20)	201(19)	275(19)	26(16)	5(15)	34(16)
C(6A)	171(19)	195(18)	269(19)	-26(14)	-8(15)	64(14)
C(7A)	260(20)	280(18)	330(20)	-40(17)	-16(16)	-38(18)
C(8A)	200(20)	257(18)	260(20)	-33(14)	-61(17)	19(16)
C(9A)	200(20)	231(17)	330(20)	-9(14)	-9(18)	-26(15)
C(10A)	200(20)	410(20)	430(20)	-69(17)	3(18)	-44(17)
C(11A)	190(20)	240(20)	330(20)	21(16)	-31(15)	-26(17)
C(12A)	250(20)	283(18)	360(20)	-23(16)	-60(16)	-30(16)
C(13A)	260(20)	305(19)	440(20)	-99(15)	-50(18)	42(16)
C(14A)	190(20)	305(19)	490(30)	-7(15)	9(19)	19(15)
C(15A)	260(20)	240(20)	460(20)	-48(14)	-26(19)	-18(15)
C(16A)	360(30)	500(30)	540(30)	114(18)	30(20)	88(19)
C(17A)	250(20)	390(20)	450(20)	-34(18)	9(18)	40(20)
C(18A)	270(20)	480(20)	420(30)	-75(18)	-70(20)	77(18)
C(19A)	410(30)	600(20)	510(20)	40(20)	-88(19)	120(30)
I(2)	431(2)	791(2)	333(2)	-69(1)	-57(1)	-30(2)
O(1B)	227(16)	346(12)	447(16)	-105(10)	2(13)	9(11)
N(1B)	220(19)	350(17)	440(20)	-151(12)	-38(16)	9(12)
N(2B)	230(20)	301(15)	272(17)	-106(12)	-29(14)	3(13)
N(3B)	208(18)	309(16)	277(16)	-57(12)	-23(14)	26(14)
C(1B)	340(30)	190(20)	470(30)	-9(15)	-50(20)	-62(15)
C(2B)	310(20)	404(19)	350(20)	130(20)	-22(16)	20(20)
C(3B)	190(20)	370(20)	310(20)	-17(16)	-51(17)	17(16)
C(4B)	200(20)	270(20)	450(30)	-58(16)	-50(18)	-39(15)
C(5B)	270(20)	236(18)	340(20)	71(16)	-20(16)	-10(17)
C(6B)	170(20)	246(18)	350(20)	8(15)	-46(17)	-2(14)
C(7B)	300(20)	310(20)	360(20)	-12(15)	-23(17)	-59(16)
C(8B)	200(20)	282(19)	270(20)	-34(14)	-76(16)	-6(16)
C(9B)	250(20)	257(18)	220(20)	11(14)	2(17)	11(16)
C(10B)	260(20)	400(20)	330(20)	-104(16)	37(16)	-60(18)
C(11B)	250(20)	241(17)	253(19)	-25(16)	-45(15)	-52(18)
C(12B)	340(20)	341(18)	330(20)	-105(19)	-60(16)	10(20)
C(13B)	450(30)	450(20)	730(30)	-310(20)	70(30)	-4(19)
C(14B)	250(20)	350(20)	390(20)	-54(15)	20(19)	25(15)

Table A3.4 (cont.)

C(15B)	340(20)	290(18)	266(19)	-75(16)	-25(16)	33(18)
C(16B)	720(40)	680(30)	610(30)	-170(20)	-50(30)	380(30)
C(17B)	840(30)	400(20)	510(30)	-150(20)	330(20)	-90(20)
C(18B)	500(30)	540(30)	520(30)	-104(19)	110(30)	-49(19)
C(19B)	1060(50)	830(40)	420(30)	40(20)	60(30)	500(30)

*Table A3.5. Hydrogen bonds for semicarbazone **81** (CCDC 686849) [Å and °].*

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(2A)-H(2A)...O(1B)#1	0.88	2.13	2.972(3)	159.7
N(2B)-H(2B)...O(1A)#2	0.88	2.04	2.895(3)	163.1

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

CHAPTER 3

Unified Approach to Daucane and Sphenolobane Bicyclo[5.3.0]decane core: Enantioselective Synthesis of Four Daucane Sesquiterpenes and Related Molecules[†]

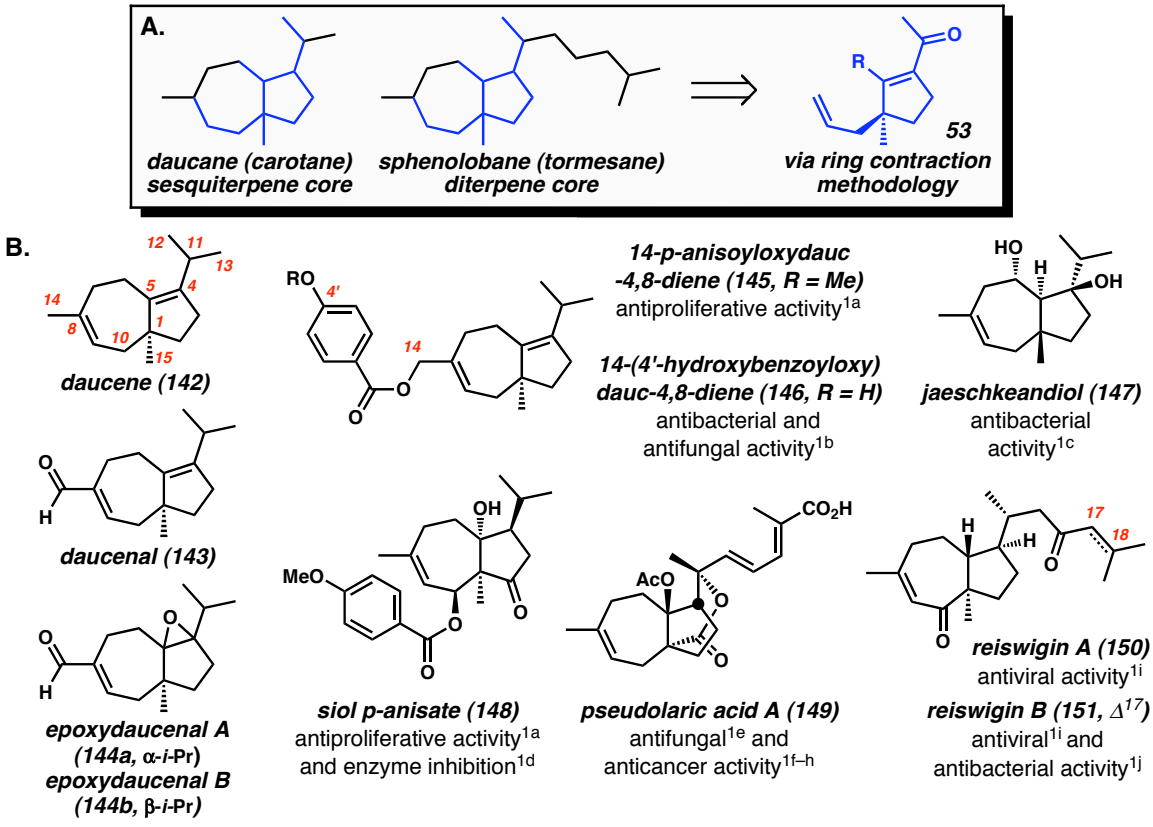
3.1 INTRODUCTION AND BACKGROUND

The daucane (carotane) sesquiterpenes and sphenolobane (tormesane) diterpenes are two structurally related families of natural products that share a hydroazulene (i.e., bicyclo[5.3.0]decane) core (Figure 3.1A). These terpenoids feature varied degrees of oxidation with diverse peripheral functionality and, as a group, exhibit a wide range of biological activity (Figure 3.1B).[1] As such, the synthetic community has reported several studies[2] and total syntheses[1i,3] of a number of these natural products. Central to our interest in these molecules is the cyclopentane motif, which we envisioned accessing from a γ-quaternary acylcyclopentene (**53**) generated by a combination of the palladium-catalyzed asymmetric enolate alkylation[4,5,6] and ring contraction chemistry that is

[†] The research has been submitted for publication.

discussed in the preceding chapter (Figure 3.1A).[7] As part of our ongoing efforts to apply this methodology,[8] we have developed a route to the sesquiterpene and diterpene carbocyclic scaffolds, explored functionalization of the hydroazulene skeleton to oxidized compounds including epoxydaucenal B (**144b**), and completed the first total syntheses of 14-*p*-anisoyloxydauc-4,8-diene (**145**) and daucenal (**143**) via the archetypal daucane sesquiterpene, daucene (**142**).

*Figure 3.1. Bicyclo[5.3.0]decane skeletons linked to acylcyclopentene **53** and examples of hydroazulene natural products.*



3.1.1 Isolation, Structural Determination, and Bioactivity of Relevant Daucane Sesquiterpenes

Feldmann reported the earliest study on a daucane sesquiterpene in 1865,[9] and since that time, numerous molecules in this class have been identified and investigated. The majority of the research on this family of natural products was performed in the 1950s–1970s, and an excellent review by Ghisalberti details the isolation, characterization, bioactivity, and biosynthesis of these sesquiterpenes.[10] The following section focuses on the daucane sesquiterpenes associated with our synthetic efforts and the reader is directed to the aforementioned review for further information.

The structurally simplest daucane we have prepared is daucene (**142**), which has been isolated from several sources[11] and is postulated to be the biosynthetic precursor to more functionalized derivatives.[11a,12] This natural product was originally obtained from *Daucus carotoa*[11a] in 1961 by Pigulevskii and has also more recently been found as a constituent of extracts from *Piptoporus betulinus*,[11b] *Gleophyllum odoratum*,[11b] x*Cupressocyparis leylandii*,[11c] *Ferula hermonis*,[11d] and *Matricaria chamomilla*.[11e] Interestingly, both enantiomers of daucene occur naturally. Pigulevskii first analyzed daucene with Raman and infrared (IR) spectroscopy, which suggested a hydroazulene structure with tri- and tetrasubstituted double bonds. A series of hydrogenation experiments were performed and the resulting reduced molecules were also examined. The structure of daucene was ultimately confirmed by several total syntheses, which are discussed in Section 3.2.

In 1991, Hashidoko et al. isolated daucenal (**143**) and epoxydaucenal A and B (**144a** and **b**) from the leaves of *Rosa rugosa*.[13] Initial analysis of daucenal by EI mass

spectrometry and $^{1}H/^{13}C$ NMR suggested the molecule contained either a [7–5] or [4–8] bicyclic skeleton. The bicyclo[5.3.0]decane structure that is characteristic of the daucane sesquiterpenes was ultimately confirmed by Correlation through Long-Range Coupling (COLOC) NMR.[14] The NMR spectra of epoxydaucenal A and B (**144a** and **b**) shared several related signals to daucenal, and mass spectrometry indicated each molecule contained an additional oxygen. The structural similarity was confirmed as daucenal (**143**) was oxidized with 3-chloroperbenzoic acid to provide a 70:30 mixture of the epoxidized molecules (**144a**:**144b**) in 58% yield. The relative stereochemistry of epoxy and isopropyl groups was determined by NOE experiments.

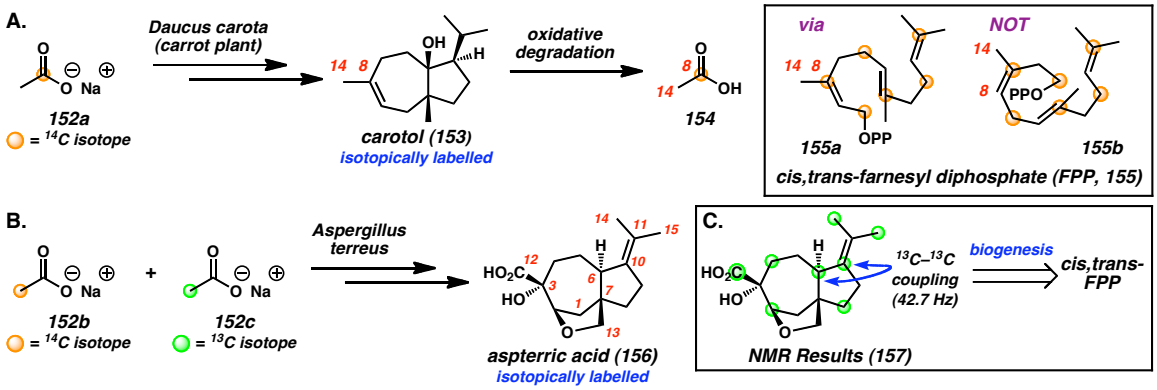
14-*p*-anisoyloxydauc-4,8-diene (**145**) was first isolated by Miski et al.[15] in 1986 from the roots of *Ferula tingitana*. The molecular structure of this sesquiterpene was elucidated by mass spectrometry and IR, ultraviolet (UV), and NMR spectroscopy. Viola and co-workers[1a] later isolated ester **145** from *Ferula communis* and found this molecule displays antiproliferative activity against HL-60, Jurkat, K562, RS 4;11, and SEM human tumor cells with IC_{50} values comparable or superior to many of the more oxygenated and complex daucane sesquiterpenes screened. Interestingly, the related 14-(4'-hydroxybenzoyloxy)dauc-4,8-diene (**146**), which was isolated from *Ferula hermonis*, displays antibacterial and antifungal activity.[1b]

Despite the earliest isolation occurring over twenty five years ago and this bioactivity, to our knowledge no total syntheses have been reported for any of these C(14) oxidized sesquiterpenes.

3.1.2 Biosynthetic Studies

Two main experiments have been performed to explore the biogenesis of the daucane sesquiterpene skeleton.[16] In 1962, Soucek fed ^{14}C-labeled sodium acetate (**152a**) to *Daucus carota* (carrot plant) to determine the positions of isotope incorporation in carotol (**153**, Scheme 3.1A).[17] The resulting ^{14}C-enriched carotol was oxidatively degraded to generate acetic acid (**154**) from the C(8) and C(14) positions of the molecule. The acetic acid formed through this process contained the ^{14}C-isotope, suggesting that the carbocyclic core arises through folding of *cis,trans*-farnesyl diphosphate (FPP, **155**) as depicted in intermediate **155a** instead of conformation **155b**. The latter arrangement would necessitate an additional methyl shift to obtain the carbon skeleton and consequently occlude ^{14}C-incorporation in the degradation product.

Scheme 3.1. ^{14}C- and ^{13}C-labeled sodium acetate feeding experiments.



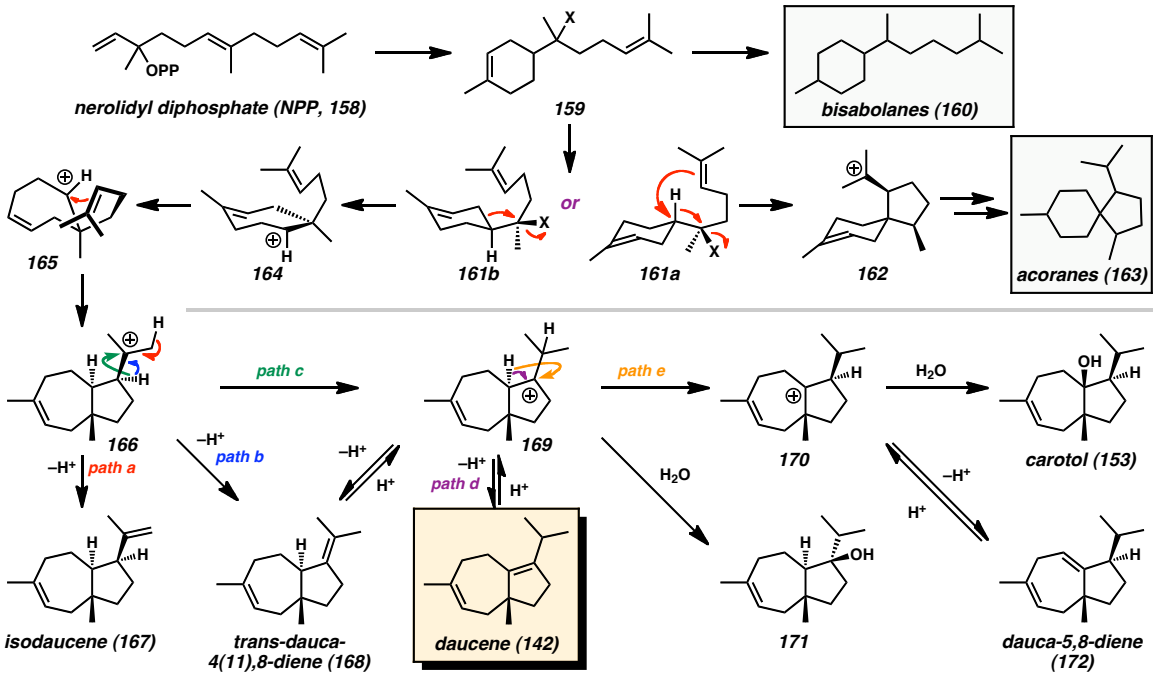
A second isotope study was performed by Tsuda et al. in 1976.[18] This publication details the first isolation of a daucane sesquiterpene from a source outside the Umbelliferae (Apiaceae) family. To gain insight into the biosynthetic pathway in the

fungus *Aspergillus terreus*, they simultaneously fed ^{14}C- and ^{13}C-labeled sodium acetate (**152b** and **152c**) to the organism and analyzed the resulting enriched aspterric acid (**156**, Scheme 3.1B). The mass of the enriched aspterric acid was obtained, and the extent of isotope incorporation was determined from the ^{14}C-isotope to be 1.32%. Analysis of the ^{13}C isotope by NMR revealed enrichment at multiple positions and a ^{13}C–^{13}C coupling between C(6) and C(10) (see **157**, Scheme 3.1C). Given these results, Tsuda and co-workers proposed that aspterric acid (**156**) also arises through a concerted cyclization of *cis,trans*-FPP (**155**) through a conformation like that described by Soucek.

Ghisalberti argues in his 1994 review that a concerted cyclization mechanism is plausible, but not necessarily operable, as such a pathway does not rationalize the formation of other sesquiterpenes that are co-isolated with daucanes.[10] To resolve this issue, he proposes an alternative stepwise biosynthesis that explains the co-occurrence of bisabolane (**160**)[19] and acorane (**163**)[11c,13,19] natural products (Scheme 3.2). Initial cyclization of nerolidyl diphosphate (NPP, **158**) generates carbocation **159**, which may be funneled to the bisabolanes directly or undergo a subsequent cyclization/1,2-hydride shift (**161a**) to afford the acorane sesquiterpenes. Alternatively, ring expansion of cyclohexane **161** and subsequent cyclization reveals daucane carbocation **166**, which may be converted to other cations through various 1,2-hydride shifts. Ultimately these carbocations may be neutralized through an elimination reaction or quenching with water. Ghisalberti's pathway is reasonable, but speculative. The only justification for this route beyond co-isolation is the observation of interconversion between the daucane and acorane scaffolds in synthetic efforts[20] and Naegeli and Kaiser's 1962 synthesis of daucene that also forms acoradiene (**173**) in the final acid-promoted cyclization (see

Section 3.2).[21] Further biological experiments are necessary to confirm the validity of this biosynthetic proposal.

*Scheme 3.2. Biosynthetic route that rationalizes co-isolation of bisabolane (**160**), acorane (**163**), and daucane sesquiterpenes.*

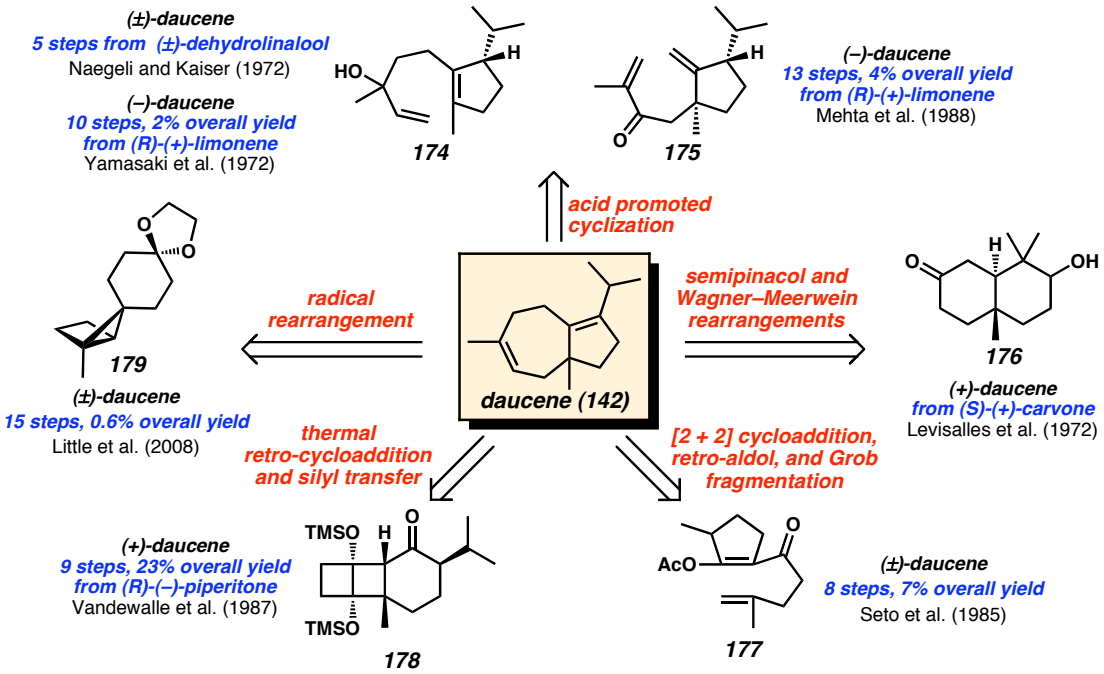


3.2 PREVIOUS TOTAL SYNTHESES OF DAUCENE

Of the daucane molecules we selected to target, only daucene (**142**) has been synthesized previously. Five main strategies have been employed to construct the [7–5] bicyclic core of this natural product (Scheme 3.3). Early efforts by Naegeli and Kaiser,[21] Yamasaki,[22] and Mehta[12,23] focus on acid-promoted cyclizations that append the seven-membered ring onto an existing cyclopentane scaffold. Around the same time, Levisalles reported a semipinacol and Wagner–Meerwein rearrangement sequence on *trans*-decalin **176** that expands the left half of the molecule to the cycloheptyl ring and contracts the

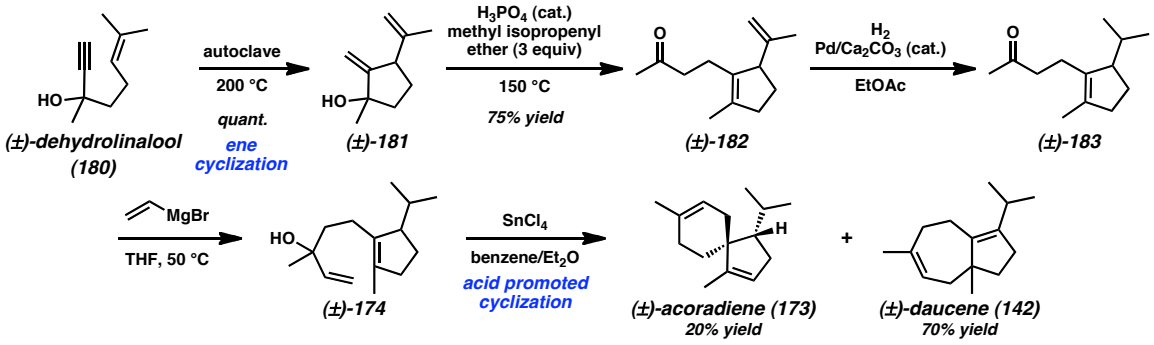
right portion to the isopropyl-accessorized cyclopentene motif.[24] In the 1980s, Seto[25] and Vandewalle[26] independently reported syntheses of daucene that include a [2 + 2] cycloaddition to prepare the bicyclic core. Seto cleaves the resulting cyclobutane with a retro-aldol fragmentation, while Vandewalle employs a thermally promoted retro-cycloaddition that triggers a silyl transfer reaction in situ. Most recently, Little has disclosed an electrochemically-induced radical ring expansion on cyclohexane **179**.[27] Overall, these past routes can only produce daucene racemically or rely on enantioenriched, naturally occurring starting materials to obtain the sesquiterpene asymmetrically. These approaches also suffer from low yields, poor enantiopurity, and/or extended preparation times (e.g., >30 days). Many of these syntheses also incorporate similar steps or strategies to arrive at key intermediates.

Scheme 3.3. Retrosynthetic analysis of previous routes to daucene.



Naegeli and Kaiser accomplished the first total synthesis of daucene (**142**) in 1972 (Scheme 3.4).[21] In their route, racemic dehydrolinalool (**180**) is cyclized to allylic alcohol **181** and subsequently treated with acid and methyl isopropenyl ether at elevated temperature to initiate a Claisen rearrangement that affords ketone **182**. Ketone **182** is hydrogenated with Lindlar's catalyst and converted to allylic alcohol **174** with vinylmagnesium bromide. Finally, a Lewis acid-induced cyclization with tin(IV) chloride completes the synthesis of daucene (**142**) and also produces the natural product acoradiene (**173**). This approach furnishes daucene quickly (5 steps), but prepares the racemic product, and does not indicate yields for several steps in the sequence.

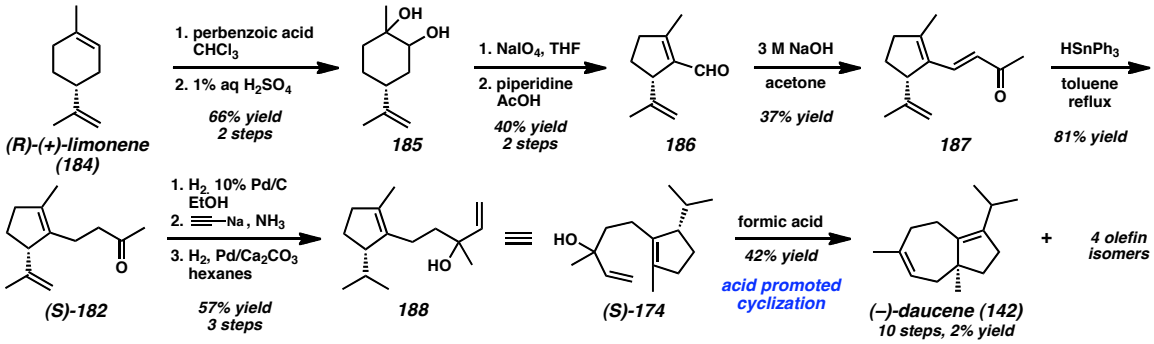
Scheme 3.4. First total synthesis by Naegeli and Kaiser in 1972.



Yamasaki and co-worker's synthesis also invokes an acid-promoted cyclization on allylic alcohol **174**, but affords the natural product in enantiopure form (Scheme 3.5).[22] Their approach starts with (*R*)-(+)-limonene (**184**), which is oxidized with perbenzoic acid to generate an epoxide that is opened with acid to furnish diol **185**. Diol **185** is contracted to acylcyclopentene **186** by sequential treatment with sodium periodate and piperidine in acetic acid. An aldol condensation on acylcyclopentene **186** produces

enone **187**, which is reduced to the corresponding ketone ((*S*)-**182**) with triphenyltin hydride. Conversion of ketone (*S*)-**182** to allylic alcohol **188** is accomplished through a three-step hydrogenation, acetylene addition, and Lindlar reduction sequence. It is unclear why the authors selected a two-step installation of the vinyl group instead of employing a vinyl organometallic reagent. Nevertheless, treatment of allylic alcohol (*S*)-**174** with formic acid results in the formation of five compounds, of which (–)-daucene (**142**) is isolated in 42% yield. The key disadvantage of Yamasaki's route is that several steps perform poorly and consequently provide the natural product in diminished overall yield.

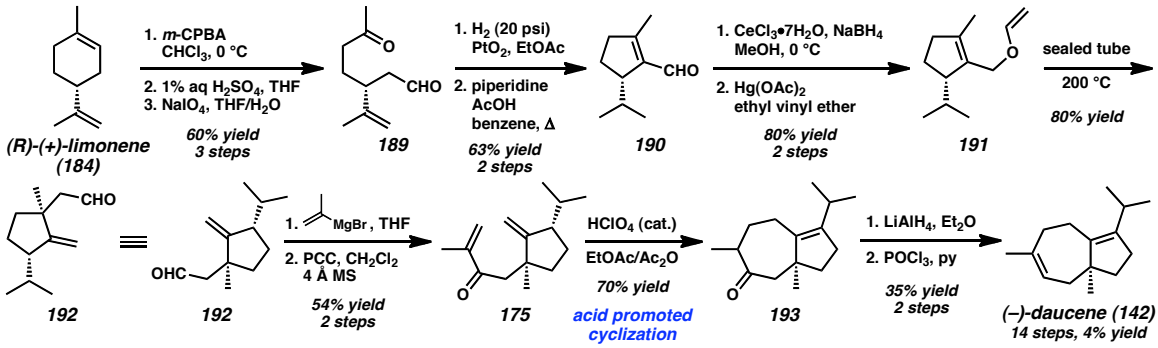
*Scheme 3.5. Yamasaki's 1972 route to enantioenriched allylic alcohol **182** and (–)-daucene (**142**).*



Mehta's synthesis[12,23] not only incorporates an acid-promoted cyclization, but also follows the same initial ring opening sequence from (*R*)-(+)-limonene (**184**) employed by Yamasaki. However, Mehta opts to hydrogenate the isopropenyl group earlier in the synthetic route, arriving at enal **190** instead of the dehydrated analog (**186**, Scheme 3.5). Luche reduction of enal **190** generates an allylic alcohol that is treated with mercury(II) acetate and ethyl vinyl ether to produce vinyl ether **191** (Scheme 3.6). Vinyl ether **191** is

heated in a sealed tube to initiate a Claisen rearrangement that affords aldehyde **192**, which is converted to enone **175** through Grignard addition and oxidation. Acid-catalyzed cyclization of enone **175** completes the cycloheptyl ring and furnishes ketone **193** as an inconsequential mixture of diastereomers. To install the remaining olefin and complete the synthesis, ketone **193** is reduced and the resulting alcohol is eliminated. However, the elimination step suffers from low yield due to the formation of other olefin isomers. In summary, Mehta's synthesis parallels Yamaski's efforts closely and again produces daucene in low overall yield.

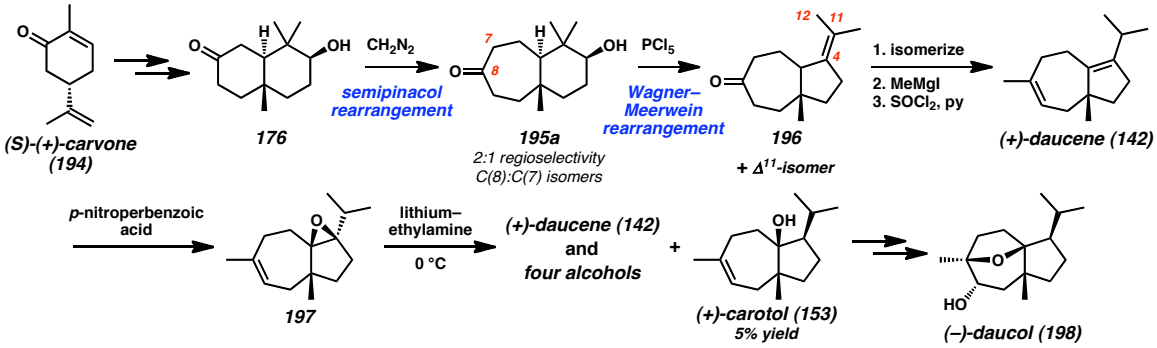
*Scheme 3.6. Mehta's 1988 acid-promoted cyclization approach to (–)-daucene (**142**).*



Shortly after the disclosure of Naegeli and Kaiser,[21] Levisalles et al. reported a route to daucene starting from (*S*)-(+)-carvone (**194**, Scheme 3.7).[24] Unfortunately, their report is vague and does not include yields for almost every transformation described, making it challenging to compare this work to other efforts in the area. The key sequence starts from the carvone-derived ketone **176**,[24] which is treated with diazomethane to effect a semipinacol rearrangement that generates a 2:1 inseparable mixture of ketone **195a** and the corresponding C(7) isomer. Purification of these alcohols is accomplished by

chromatographic separation of the corresponding acetates, after which hydrolysis again affords alcohol **195a**. A phosphorus pentachloride-initiated Wagner–Meerwein 1,2-rearrangement of alcohol **195a** produces alkene **196** as well as the Δ^{11}-isomer. (+)-Daucene (**142**) is subsequently obtained through isomerization of the C(4) olefin (conditions unspecified), Grignard addition to the ketone, and elimination of the resulting alcohol. Interestingly, Levisalle and co-workers also convert daucene to (+)-carotol (**153**) and (–)-daucol (**198**), although the process is extremely low yielding. Overall, this route is less desirable as several steps in the sequence have either poor regioselectivity or diastereoselectivity.

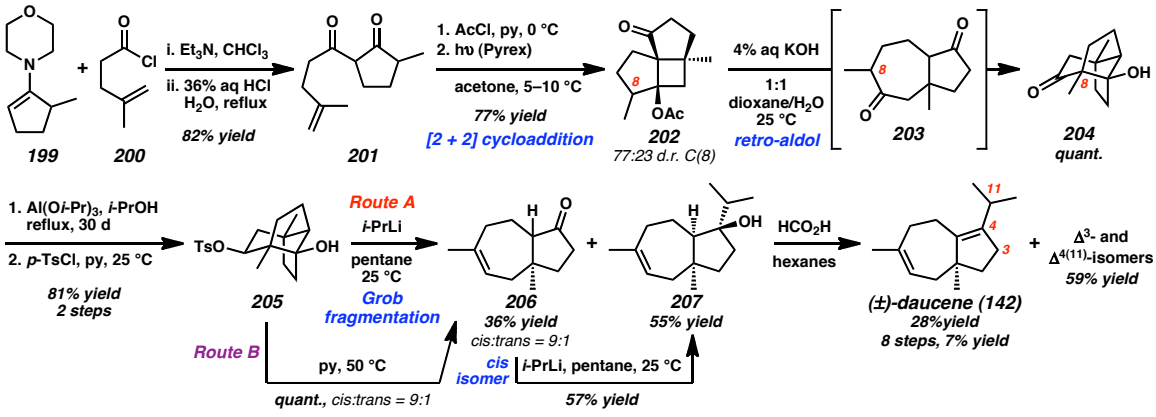
*Scheme 3.7. Synthesis of (+)-daucene (**142**), (+)-carotol (**153**), and (–)-daucol (**198**) by Levisalles in 1972.*



Seto and co-workers published an alternative strategy to racemic daucene in 1985.[25] In their route, enamine **199** is first treated with acid chloride **200** to afford dione **201**. Dione **201** is converted to the acetoxy enone and subsequently irradiated to furnish the [2 + 2] cycloaddition product, cyclobutane **202**. Fragmentation of cyclobutane **202** is accomplished through a base-mediated retro-aldol process that initially generates bicycle

203 en route to tricyclic ketone **204**. A Meerwein–Ponndorf–Verley reduction of ketone **204** forms the equatorial alcohol preferentially, although the process requires 30 days to complete. The resulting diol is selectively tosylated at the secondary position to afford sulfonic ester **205**. Isopropyllithium initiates Grob fragmentation of alcohol **205** and also diastereoselectively adds to the resulting ketone to produce a mixture of ketone **206** and alcohol **207** (Route A). Alternatively, a two-step sequence can be employed to obtain alcohol **207** (Route B). Elimination of the alcohol functionality with formic acid generates daucene (**142**) in low yield in conjunction with other olefin products. The early steps in Seto's synthesis proceed with good to excellent yields and install the necessary C(8)-C(9) olefin selectively due to the Grob fragmentation. However, the final steps in the sequence are low yielding and result in multiple isomers.

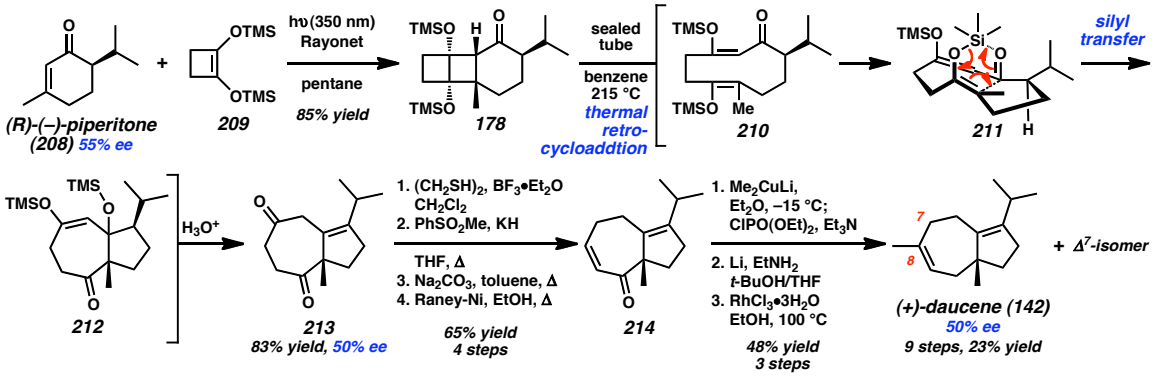
*Scheme 3.8. Seto's 1985 total synthesis of racemic daucene (**142**).*



Vandewalle's 1987 synthesis of (+)-daucene also incorporates a [2 + 2] cycloaddition, but arrives at the bicyclic core by fragmenting cyclobutane **178** through a thermally promoted retro-cycloaddition that initially generates siloxyenone **210** (Scheme

3.9).[26] Siloxyenone **210** is conformationally oriented such that a silyl transfer is triggered in situ. The resulting silyl ether (**212**) is hydrolyzed during work-up to reveal dione **213**. Vandewalle protects the more accessible ketone of dione **213** with ethane-1,2-dithiol, converts the sterically hindered ketone to the enone, and then removes the thioacetal functionality with Raney-Ni. Cuprate addition to enone **214** installs the C(14) methyl group and the reaction is quenched with diethyl phosphorochloridate to furnish a vinyl phosphate. Lithium reduction of this phosphate provides an alkene that is isomerized to (+)-daucene (**142**) and the Δ^7-isomer with Grieco's rhodium conditions.[28] Vandewalle's approach is elegant and produces daucene in good overall yield, but in poor enantiopurity due to the low natural enantioenrichment of the starting material.

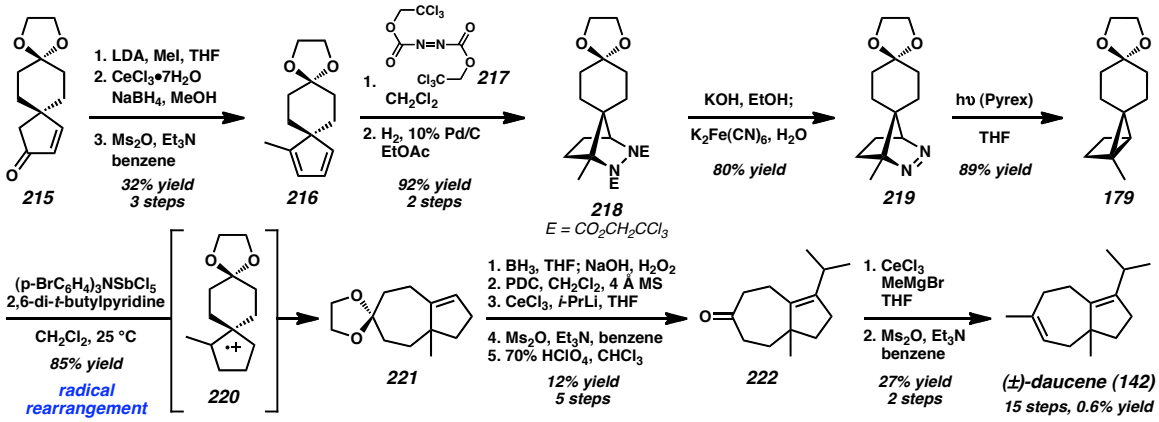
Scheme 3.9. Retro-cycloaddition/aldol approach to (+)-daucene by Vandewalle in 1987.



Twenty years elapsed following Vandewalle's and Mehta's 1980s syntheses before another approach to daucene was disclosed by Little and co-workers. Their publication focuses primarily on the development of an electrochemically-induced radical rearrangement, but also includes a low yielding synthesis of racemic daucene to

demonstrate application of the methodology. To this end, enone **215** is transformed into diene **216** through an alkylation, reduction, and elimination pathway. A [4 + 2] cycloaddition between diene **216** and azodicarboxylate **217** and ensuing reduction produce hydrazine **218**. The ester groups of hydrazine **218** are removed to generate diazene **219**, which is irradiated to liberate nitrogen and form cyclobutane **179**. Radical cleavage of the cyclobutane generates intermediate **220**, which undergoes a ring expansion rearrangement to ultimately afford alkene **221**. Alkene **221** is converted to a ketone, treated with isopropyllithium, and the resulting alcohol is eliminated to arrive at ketone **222**. Another organometallic addition and elimination sequence completes the synthesis, producing daucene in 15 steps and 0.6% overall yield. The middle portion of Little's synthesis is robust and well developed, but the early and late steps are low yielding. In particular, installation of the remaining functionality following the radical rearrangement is cumbersome. While the radical process provides an interesting and powerful alternative to previous approaches, Little's route needs optimization and could potentially also be improved by incorporating more of the necessary functionality earlier in the synthesis.

Scheme 3.10. Little's 2008 synthesis of racemic daucene.



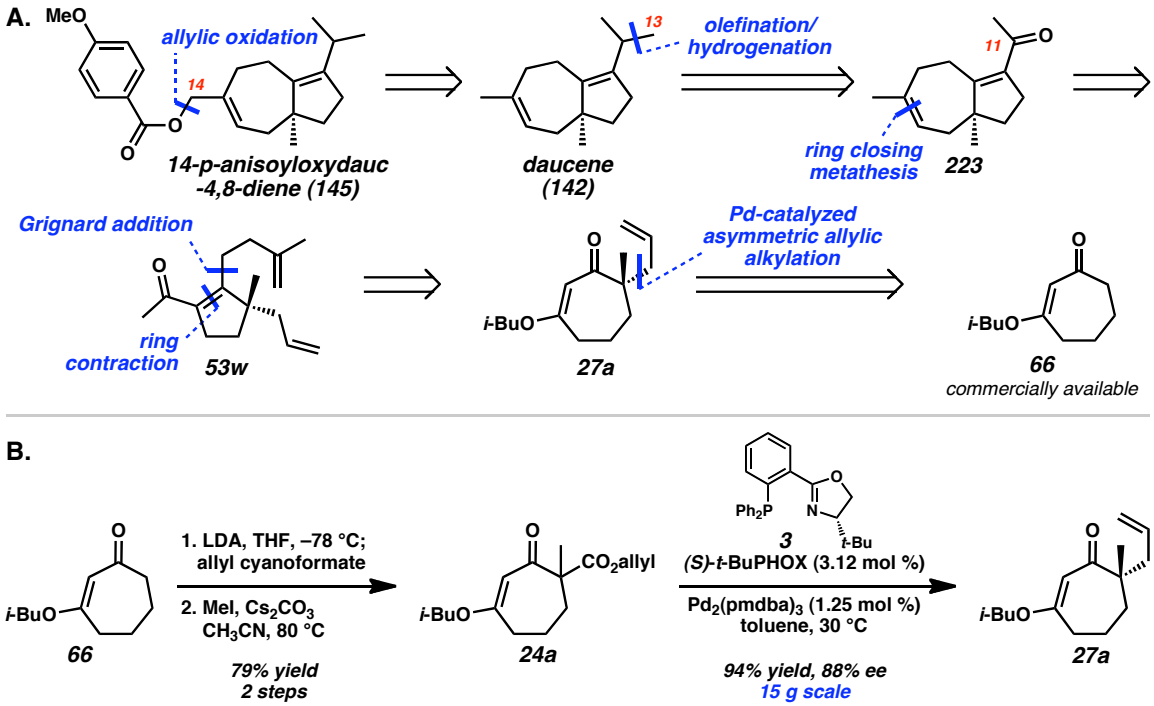
3.3 ENANTIOSELECTIVE SYNTHESIS OF BICYCLO[5.3.0]DECANE CARBOCYCLIC CORE AND DAUCANE SESQUITERPENES

3.3.1 Retrosynthetic Analysis

Our initial target was the biologically active sesquiterpene 14-*p*-anisoyloxydauc-4,8-diene (**145**). We retrosynthetically envisioned preparing this natural product via an allylic oxidation at the C(14) position of daucene (**142**, Scheme 3.11A). In contrast to previous efforts, we sought to access daucene by implementation of enantioselective catalysis in a manner that would avoid the formation of multiple olefin isomers. To this end, we planned a late-stage installation of the C(13) methyl group through olefination and hydrogenation of enone **223**. This key intermediate possesses the [7–5] bicyclic core and could potentially allow entry to either terpenoid series through incorporation of the appropriate sesquiterpene or diterpene chain at the C(11) position. We also anticipated that enone **223** may be converted to more oxidized members of the daucane family. Retrosynthetically, the cycloheptenyl portion of enone **223** would be formed through

ring-closing metathesis of acylcyclopentene **53w**, which could be generated by employing our retro-aldol/aldol ring contraction sequence[7] after Grignard addition to vinylogous ester **27a**. As described in Chapter 2, we have previously prepared vinylogous ester **27a**[7a] enantioselectively from vinylogous ester **66** using our palladium-catalyzed allylic alkylation methodology (Scheme 3.11B).[4]

*Scheme 3.11. (a) Retrosynthetic analysis and (b) synthesis of enantioenriched vinylogous ester **27a**.*

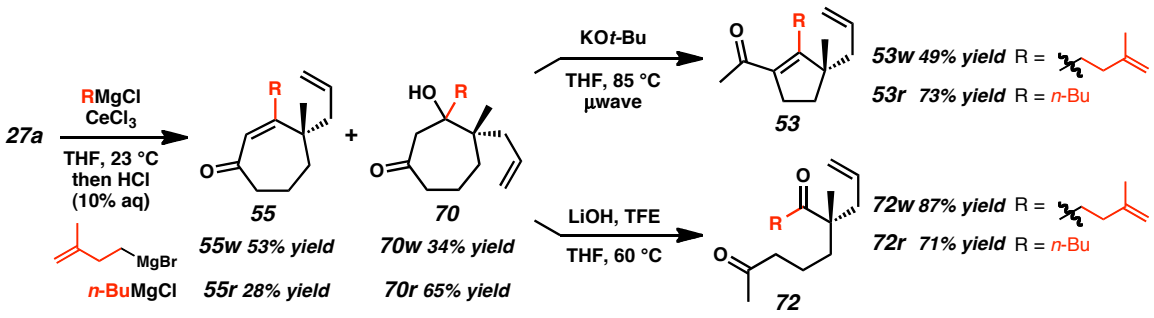


3.3.2 Challenges with Initial Approach

As we pursued this approach, we encountered two challenges. First, $CeCl_3$ assisted addition of (3-methylbut-3-en-1-yl)magnesium bromide to vinylogous ester **27a** results in poor selectivity for the desired β-hydroxyketone (**70w**), favoring formation of

cycloheptenone **55w** (Scheme 3). This product distribution contrasts with our previous work with *n*-butylmagnesium chloride,[7] where β-hydroxyketone **70r** is generated preferentially. Ultimately, this result directs considerable material to a less productive compound (vide infra), thus limiting our synthetic route. In addition, our optimized microwave-assisted ring contraction conditions proceed poorly to furnish acylcyclopentene **53w** also in diminished yield compared to the *n*-butyl analogue (**53r**, Scheme 3B). Alternatively, treatment of β-hydroxyketone **70w** with lithium hydroxide and trifluoroethanol (TFE) provides an excellent yield of acyclic dione **72w**, from which we envisioned installing the necessary cyclopentene ring in a later aldol reaction (see below). With an acceptable solution for the second issue, we turned our attention to resolve the first.

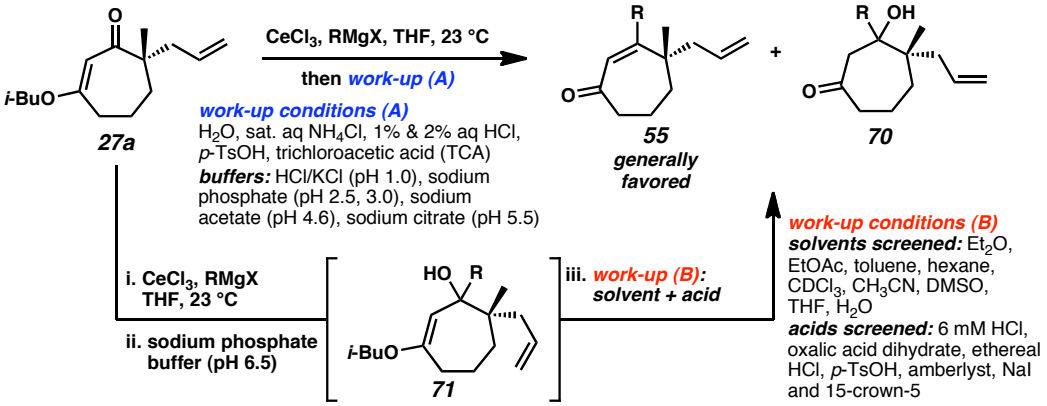
Scheme 3.12. Challenges with early steps.



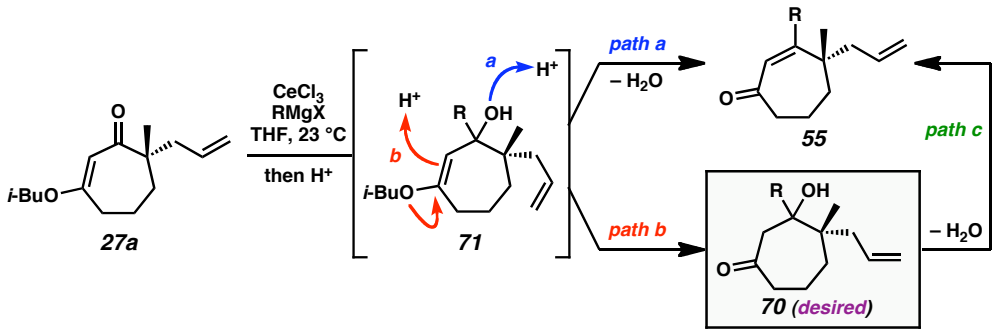
3.3.3 Efforts to Resolve Grignard Addition Selectivity and Siloxyenone Solution

In attempting to alter the Grignard addition product ratios, we first screened a series of work-up parameters.[29] Unfortunately, all other acidic quenching conditions investigated favor the cycloheptenone (**55**) or at best preferentially afford the β-hydroxyketone (**70**), but in lower yield (Scheme 3.13). We also examined several buffer solutions comprising a range of acidic pH, but the majority of these conditions provide similar results. The main exception is a sodium phosphate buffer (pH 6.5) quench, which leads to the transient formation of enol ether **71**.[30] A number of solvents and acids were probed for the selective hydrolysis of enol ether **71**, but the same trends were observed with this substrate. The propensity of elimination under a variety of acidic conditions is likely due to the stability of the carbocations generated with hydrolysis of tertiary alcohol **71** or **70** (i.e., path a/c favored over path b, Scheme 3.14). Although not necessarily the desired outcome, these efforts did identify conditions that enabled the development of our ketone transposition methodology toward γ-quaternary cycloheptenones (see Chapter 2, Section 2.6).[7b,30]

Scheme 3.13. Acidic work-up screen.



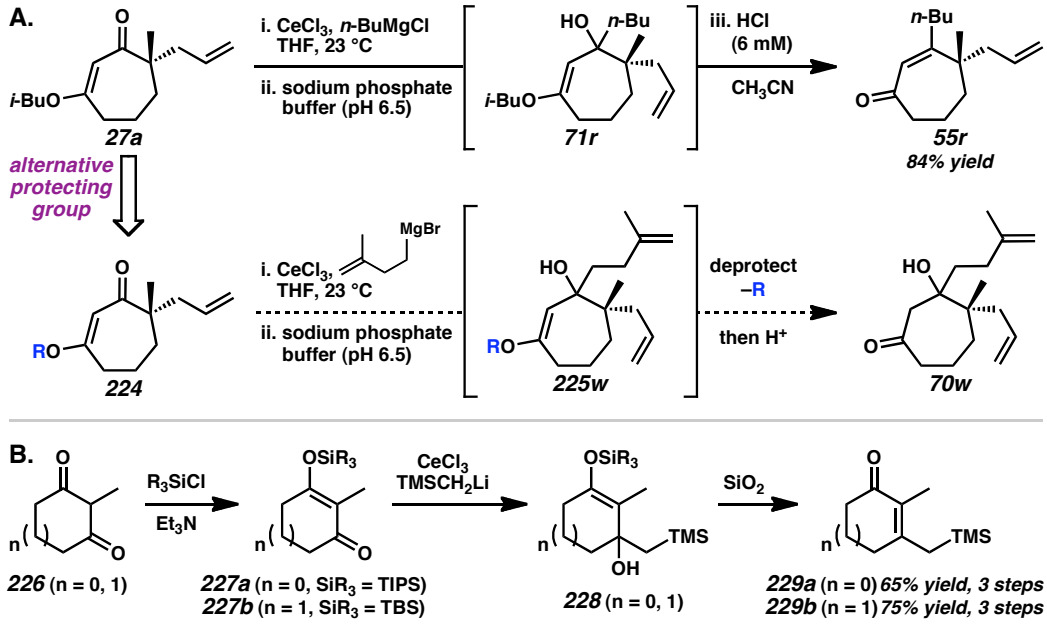
*Scheme 3.14. Elimination pathways to undesired product, cycloheptenone **55**.*



As varying the work-up parameters appeared ineffective at resolving this issue, we decided to redesign our electrophile and began examining alternative vinylogous systems. As mentioned above, our previous screening had indicated that a sodium phosphate buffer quench transiently provides enol ether **71** en route to cycloheptenone **55r** (Scheme 3.15A). We hypothesized that a related vinylogous molecule (**224**) with a more labile alkoxy group could be orthogonally removed after Grignard addition to afford β-hydroxyketone **70w** preferentially. Kuwajima has reported that the addition of lithium and cerium nucleophiles to five- and six-membered ring siloxyenones temporarily generates an α-hydroxy silyl enol ether (**228**) that eliminates to form β-substituted enones

(**229**) upon exposure to silica gel (Scheme 3.15B).[31,32] The initial lack of desilylation or Peterson olefination with these siloxyenone substrates suggests that the transformation is fairly mild. We consequently envisioned that the silyl enol ether analogue of intermediate **225w** (R = SiR_3) could be cleaved prior to chromatography with a fluoride source, prompting us to pursue siloxyenones as an alternative approach.

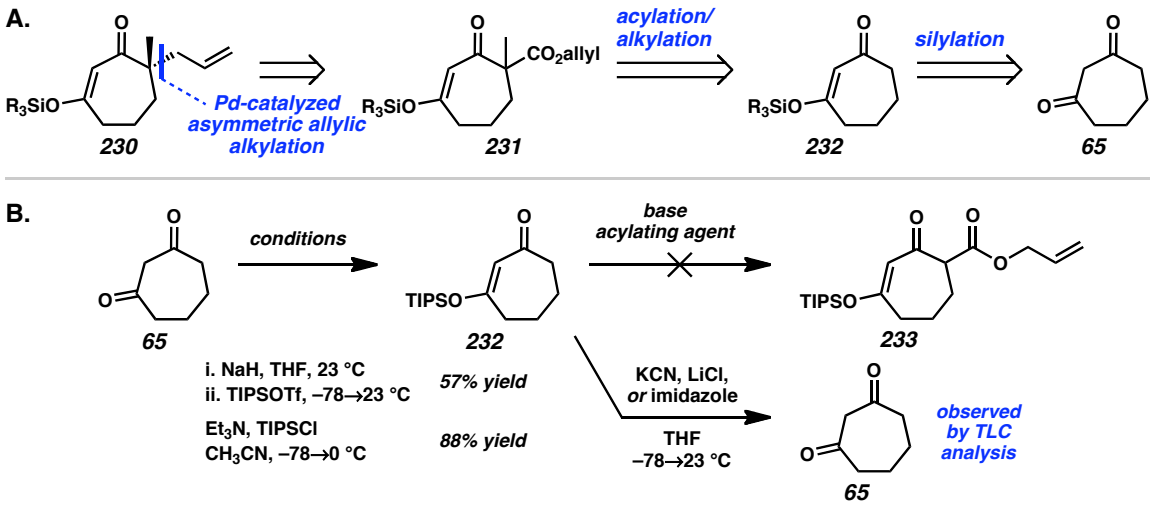
Scheme 3.15. Siloxyenone inspiration based on (a) previous results and (b) Kuwajima's precedence with Grignard addition to five- and six-membered siloxyenones.



Retrosynthetically, we planned to synthesize enantioenriched siloxyenone **230** through Pd-catalyzed asymmetric alkylation of β-ketoester **231** (Scheme 3.16A). β-Ketoester **231** would be derived from siloxyenone **232** through an acylation/alkylation pathway, as Kuwajima has shown that siloxyenones may be alkylated under standard LDA conditions.[31] Siloxyenone **232** can be obtained from dione **65** by treatment with

either sodium hydride[33] or Et_3N and a silylating agent (Scheme 3.16B), and we selected the TIPS substituted siloxyenone as it is amenable to flash column chromatography.[34] Although the silylation reaction proved effective, unfunctionalized siloxyenone **232** was unstable to a variety of acylating conditions. We screened several combinations of bases (LDA and LHMDS) and acylating agents (allyl cyanoformate, allyl chloroformate, allyl 1H-imidazole-1-carboxylate), but could never isolate β-ketoester **233**. A simple TLC experiment indicated that treatment of siloxyenone **232** with the acylating agent counterions results in loss of the silyl group (CN^- and imadazole > Cl^-) and production of dione **65** (Scheme 3.16B).

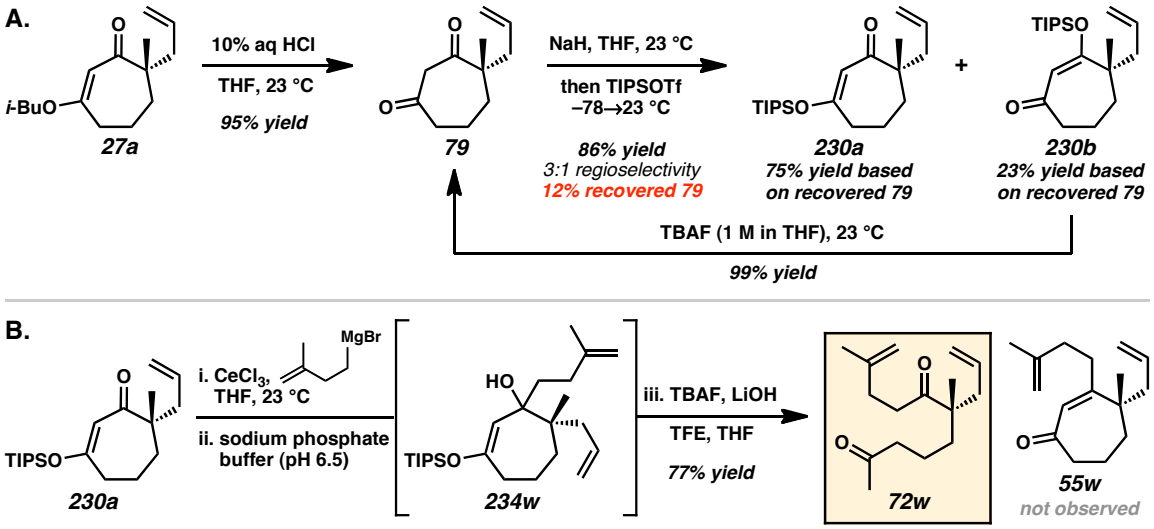
*Scheme 3.16. New retrosynthetic analysis and challenges with acylation of siloxyenone **232**.*



As such, we devised another approach from vinylogous ester **27a** that avoids these issues as the quaternary stereocenter is already incorporated in the molecule. To this end, vinylogous ester **27a** was hydrolyzed and the resulting dione (**79**) was treated with sodium hydride and triisopropylsilyl triflate[33] to produce siloxyenone **230a** in good

yield with 3:1 regioselectivity (Scheme 3.17). A number of other conditions were examined for the silylation; unfortunately, no improvements in reaction conversion or regioselectivity were observed with an amine base, multiple equivalents of reagents, other additives (i.e., 18-crown-6), or incremental warming of the reaction. However, siloxyenone **230b** can be converted to the desired isomer through iterative fluoride deprotection and silylation.

*Scheme 3.17. Synthesis and reactivity of siloxyenone **230a**.*



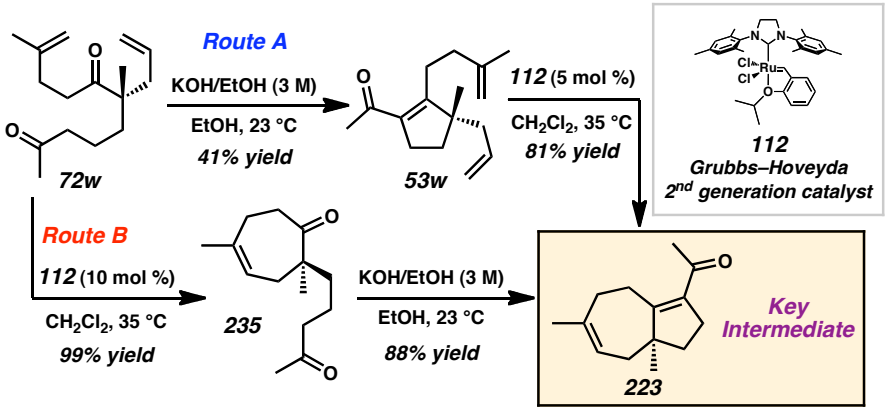
With this new vinylogous electrophile in hand, we tested our hypothesis by exposing siloxyenone **230a** to $CeCl_3$ promoted Grignard conditions with a buffer and fluoride quench. We were pleased to find that no cycloheptenone **55w** is observed and the reaction also incorporates the ring-opening step by directly producing acyclic dione **72w**. TLC analysis of the reaction after the fluoride quench indicates initial formation of both acyclic dione **72w** and β-hydroxyketone **70w**. The latter is converted to the dione

over time and the addition of LiOH/TFE expedites this retro-aldol process. A screen of other fluoride sources revealed that a TBAT quench only produces β-hydroketone **70w** even over extended exposure (determined by TLC analysis), [35] while a cesium fluoride and LiOH work-up also generates dione **72w**, albeit in a lower 70% yield. Overall, this new approach resolves the Grignard addition selectivity issues and provides the first example of interrupting the standard Stork-Danheiser ketone transposition process with a siloxyenone.

3.3.4 Completion of Key Intermediate Enone 223

Having developed an improved route to acyclic dione **72w**, we pursued preparation of our key intermediate, enone **223** (Scheme 3.18). Although this molecule can be synthesized from dione **72w** via acylcyclopentene **53w** (Route A), the sequence proceeds in higher yield when the ring-closing metathesis is performed first (Route B). Racemic dione **235** has previously been prepared from nerolidol by Urones and co-workers along several synthetic routes in 7–10 steps (13–33% yield), and these efforts are discussed in detail in the following section (Section 3.3.5).[36] By comparison, our route proceeding via enantioselective catalysis affords dione **235** in 7 steps with 40% overall yield. Applying Urones' potassium hydroxide aldol conditions generates enone **223** from dione **235** as reported.

Scheme 3.18. Two paths to [7–5] bicyclic enone ***223****.*

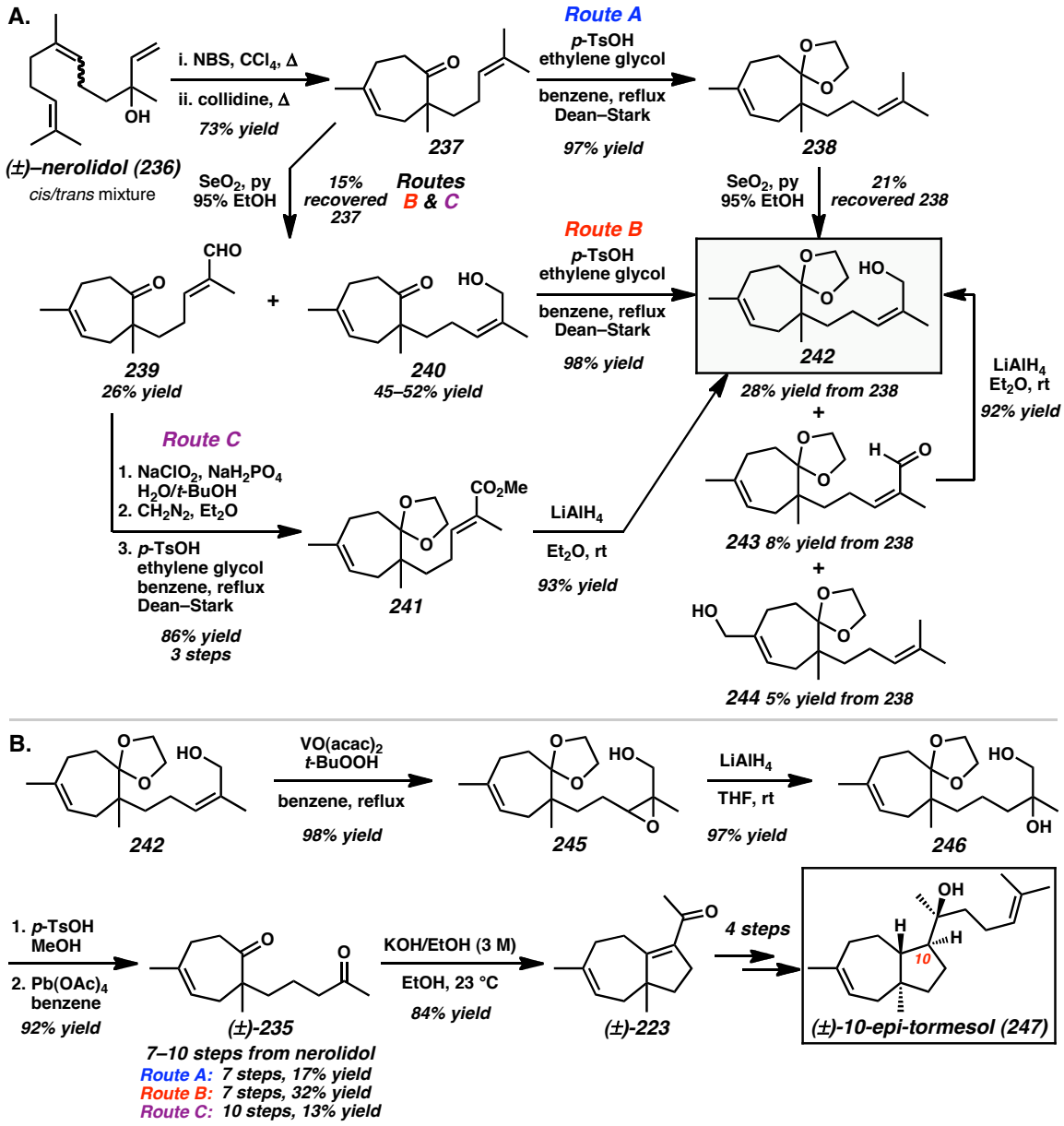


3.3.5 *Urones' Synthetic Route to Dione 235 and Enone 223*

During the 1990s, Urones and co-workers reported two papers on synthetic efforts toward tormesol (**248**) that incorporate dione (±)-**235** and enone (±)-**223** as key intermediates.[36] Their first publication investigates selenium oxidation of several cyclohepentyl molecules derived from nerolidol (**236**), including ketone **237** and ketal **238** (Scheme 3.19A).[36a] These oxidations generate a range of products in low to moderate yield that are sequentially moved on to alcohol **242**. The allylic olefin of alcohol **242** is selectively oxidized under vanadium-promoted conditions, and the resulting epoxide (**245**) is reduced to diol **246** with lithium aluminum hydride ($LiAlH_4$, Scheme 3.19B). Hydrolysis of ketal **246** reveals the ketone functionality and ensuing oxidative cleavage with $Pb(OAc)_4$ affords dione **235**. Along these routes, dione **235** is prepared in 7–10 steps and 13–33% overall yield. Urones' second report details efforts to obtain tormesol from enone **223**, which is derived from dione **235** as discussed previously.[36b] Ultimately, their approach is incapable of producing the desired diterpene

due to epimerization issues, but allows preparation of the non-natural isomer 10-epi-tormesol (**247**) from enone **223** in 4 steps.

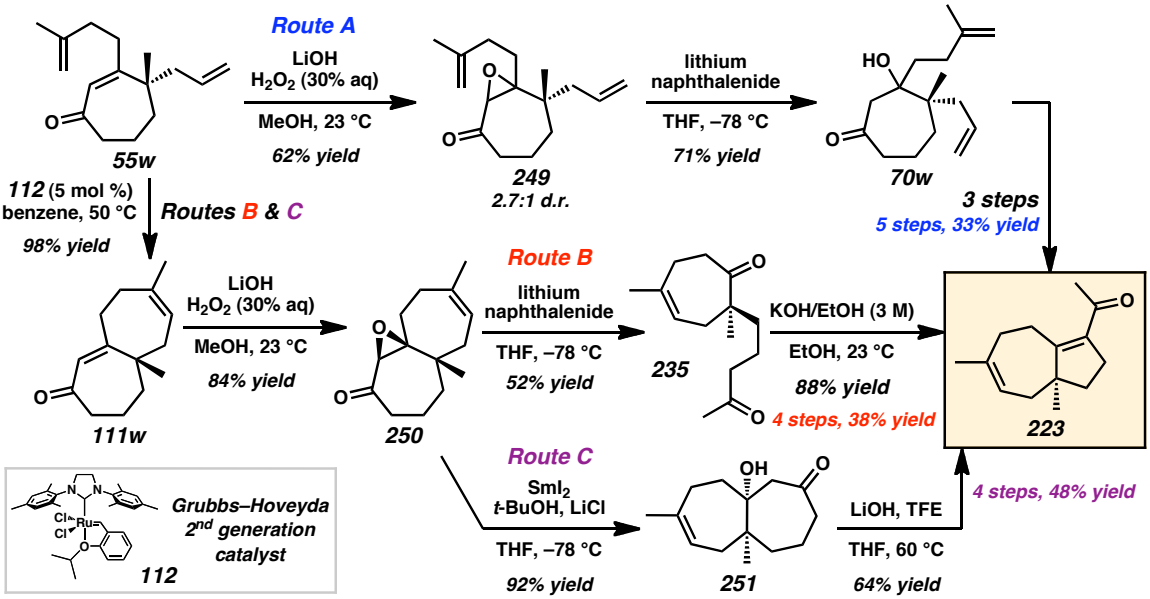
*Scheme 3.19. Urones' various routes to dione (±)-**235** and enone (±)-**223**.*



3.3.6 Alternative Routes to Enone 223 from Cycloheptenone 55w

As our early research on the addition of (3-methylbut-3-en-1-yl)magnesium bromide to vinylogous ester **27a** had generated a significant quantity of cycloheptenone **55w** (Scheme 3.12), we investigated means to direct this material back into our synthetic efforts. To this end, oxidation of cycloheptenone **55w** with lithium hydroxide and hydrogen peroxide generates epoxide **249** as an inconsequential 2.7:1 mixture of diastereomers (Route A, Scheme 3.20). Subsequent lithium naphthalenide reduction affords β-hydroxyketone **70w**, which may be conveyed onto enone **223** in 3 steps as discussed previously (Section 3.3.4). Unfortunately, the epoxidation step proceeds moderately, prompting us to examine alternative routes.

*Scheme 3.20. Epoxidation routes to key intermediate enone **223**.*



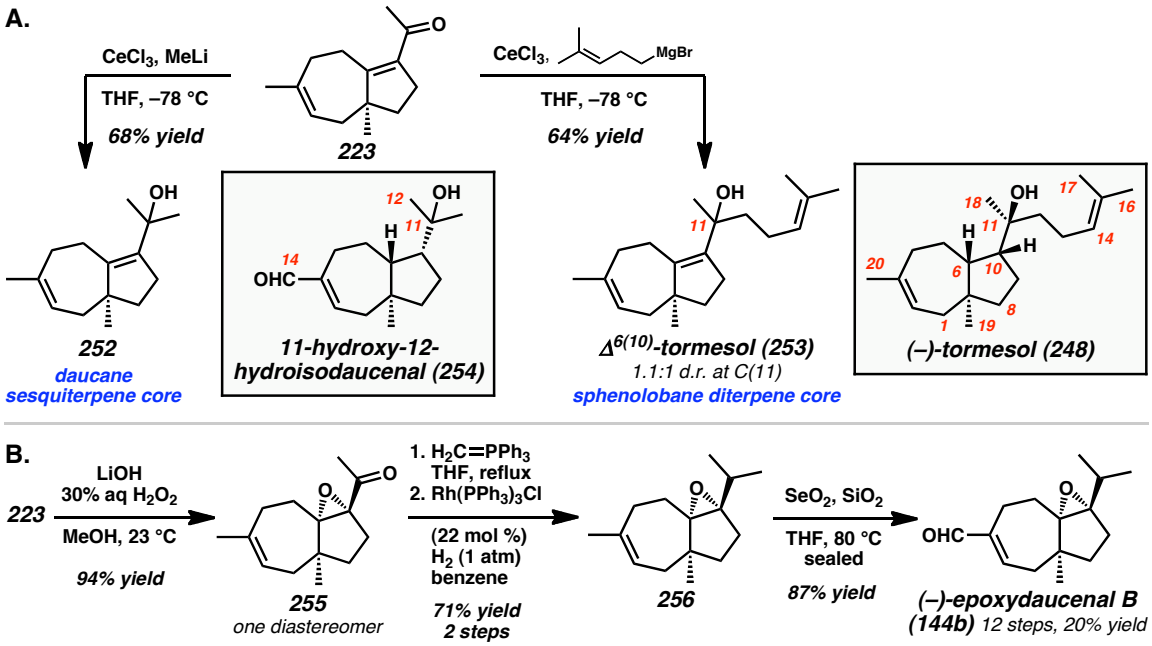
We consequently pursued two other approaches through bicyclic enone **111w** (Routes B and C), which can be formed from cycloheptenone **55w** via a nearly quantitative ring-closing metathesis. Gratifyingly, oxidation of enone **111w** under the same hydrogen peroxide conditions furnishes epoxide **250** in 84% yield. Reduction of epoxide **250** with lithium naphthalenide interestingly also promotes an in situ retro-aldol reaction that produces dione **235**, albeit in low yield (Route B). Dione **235** may be converted to enone **223** with Urones' aldol conditions (vide supra). Alternatively, reduction of epoxide **250** under milder samarium diiodide conditions with lithium chloride as an additive gives β-hydroxyketone **251** in 92% yield. Samarium diiodide reduction without lithium chloride or with HMPA as an additive also provides β-hydroxyketone **251**, but in lower yield or with additional side products.[37] Use of our standard ring contraction conditions (LiOH, TFE, THF, 65 °C) initiates both retro-aldol fragmentation of β-hydroxyketone **251** and ensuing aldol condensation to form enone **223**. Overall, route C provides enone **223** from cycloheptenone **55w** in the shortest sequence with the greatest overall yield.

As cycloheptenone **55w** may alternatively be prepared from vinylogous ester **27a** in 82% yield by a buffer quench (Chapter 2, Section 2.6), we also considered the relative merit of pursuing our daucane targets via this cycloheptyl molecule. Along this approach, the key intermediate enone **223** is produced in 8 steps from vinylogous ester **37a** with 29% overall yield. By comparison, our siloxyenone route also proceeds to enone **223** in 8 steps, but with a higher 35% overall yield. Further large-scale optimization of the cycloheptenone route may allow this alternative approach to become more competitive.

3.3.7 Derivatization of Enone 223 and Pursuit of Oxygenated Molecules

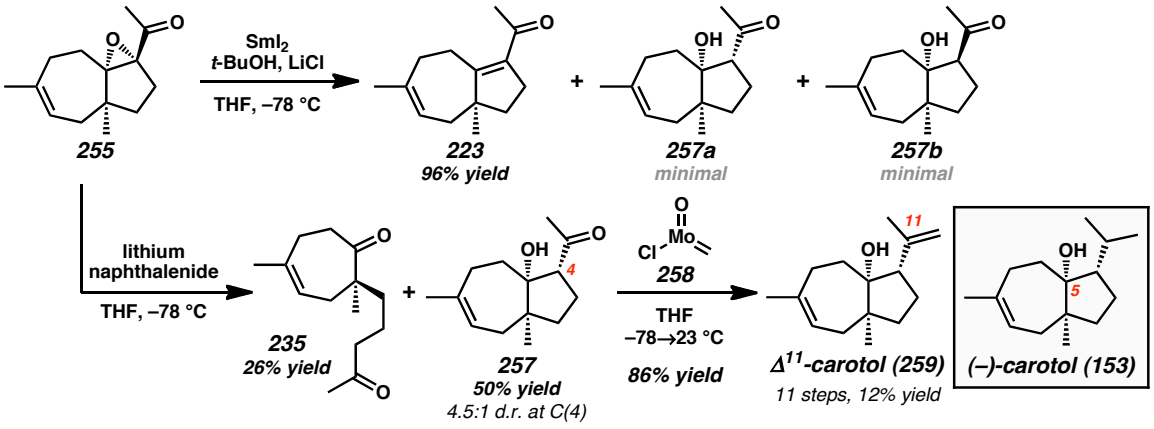
With several routes to enone **223** in hand, we converted this key intermediate to both terpenoid scaffolds and other oxygenated daucane molecules as part of our initial goals. Treatment of enone **223** with methyllithium or (4-methylpent-3-en-1-yl)magnesium bromide results in the formation of alcohols **23** and **24**, which contain the daucane and sphenolobane carbocyclic cores, respectively (Scheme 6A). This tertiary alcohol motif is present in natural products in both the daucane[38] and sphenolobane series, and alcohol **24** is the $\Delta^{6(10)}$-analogue of the diterpene (–)-tormesol (**25**).[39] Enone **223** can also be selectively epoxidized with lithium hydroxide and hydrogen peroxide to provide epoxyketone **255** in excellent yield as a single diastereomer (Scheme 3.21B). A few daucane sesquiterpenes incorporate an epoxide at this position, and of these, we decided to pursue epoxydaucenal B (**144b**).[13] Toward this target, Wittig olefination of epoxyketone **255** furnishes a diene that is selectively hydrogenated at the terminal alkene with Wilkinson's catalyst. The resulting isopropyl accessorized epoxide (**256**) is heated in a sealed vessel with selenium dioxide[40] to generate epoxydaucenal B (**144b**) in 12 steps and 20% overall yield from vinylogous ester **13** (longest linear sequence).

Scheme 3.21. Derivatization of enone ***223*** *to sesquiterpene/diterpene cores and conversion to (–)-epoxydaucenal B (****144b****).*



Having completed this natural product, we turned our attention to the carotol series, which contains a tertiary alcohol at C(5) (Scheme 3.22). We first explored samarium diiodide reduction of ketoepoxide **255** based on the previous success with epoxide **250** (Scheme 3.20), but surprisingly isolated enone **223** in 96% yield. The preference for elimination in the cyclopentyl, but not cycloheptyl system again suggests that the conformation of seven-membered ring compounds imparts unique reactivity to these molecules (see Chapter 2). Alternatively, lithium naphthalenide reduction opens ketoepoxide **255** to furnish tertiary alcohol **257** in 50% yield, favoring the desired C(4) isomer (**257a**) in 4.5:1 diastereoselectivity. Unfortunately, the reduction also produces dione **235** likely through an in situ retro-aldol process, but this material can be recycled through our route.

*Scheme 3.22. Efforts toward Δ^{11}-carotol (**259**).*



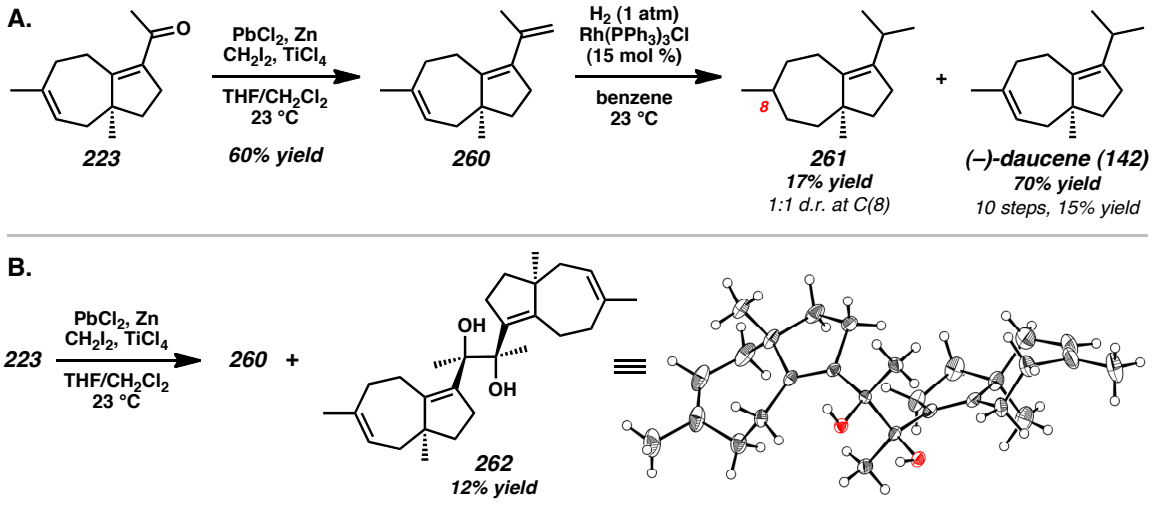
When considering olefination conditions for the installation of the C(13) carbon, we were drawn to the work of Kauffmann and co-workers,[41] who observed that methylene(oxo)molybdenum(V) chloride (**258**)[42] preferentially methylenates α- and β-hydroxyketones.[41c] Surprisingly, only the reports by Kauffmann on this molybdenum alkylidene exist and no synthetic applications with this system have been reported. Treatment of sterically hindered β-hydroxyketone **257a** with complex **258** proceeds in good yield to generate Δ^{11}-carotol (**259**), the dehydro analogue of (–)-carotol (**153**).

3.3.8 Endgame for Total Syntheses of Daucene, Daucenal, and 14-p-Anisoyloxydauc-4,8-diene

In addition to these transformations, we investigated conversion of enone **223** to daucene (**142**) and related C(14) oxidized natural products (Scheme 3.23A). Following our retrosynthetic plan, we attempted to olefinate enone **223** with the standard Wittig ylide, but unfortunately recovered starting material and observed poor conversion to triene **260**. Alternatively, methylenation with Lombardo conditions[43] generates triene

260 in moderate yield in conjunction with a number of more polar products. One of these polar molecules provided crystals suitable for X-ray analysis and was subsequently identified as diol **262** (Scheme 3.23B). Diol **262** likely arises under the reaction conditions from a titanium-mediated McMurry coupling.[44] With triene **260** in hand, we screened a series of hydrogenation conditions and found that Wilkinson's catalyst again preferentially reduces the terminal olefin to afford (–)-daucene (**142**) in 10 steps and 15% overall yield. Over hydrogenation to alkene **261** is also observed, especially with extended exposure to H_2.

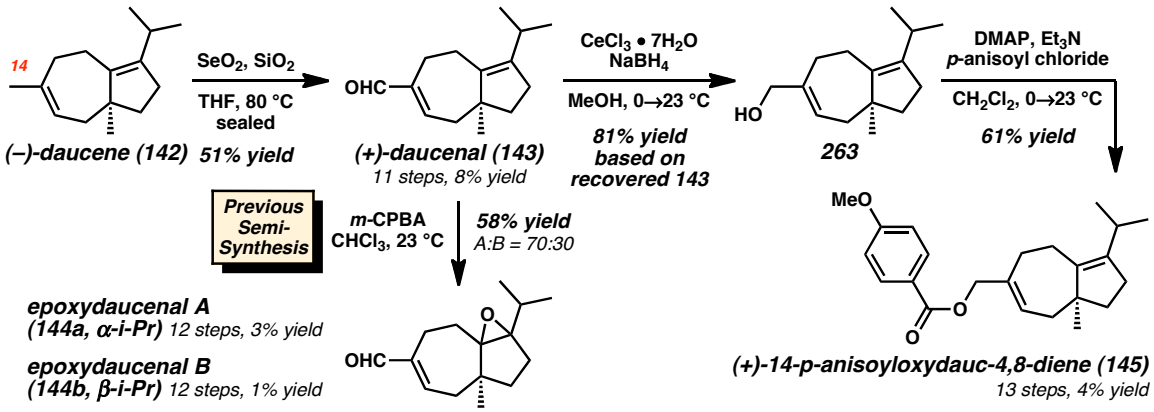
*Scheme 3.23. Olefination and hydrogenation steps toward (–)-daucene (**142**).*



We next examined allylic oxidation of daucene to access C(14) functionalized sesquiterpenes (Scheme 3.24). Gratifyingly, the selenium dioxide conditions employed previously also proved effective in the oxidation of daucene to generate (+)-daucenal (**143**) in 8% overall yield over 11 steps. As mentioned previously, Hashidoko completed a semi-synthesis of epoxydaucenal A and B (**144a** and **144b**) from daucenal as part of

their isolation efforts to confirm the structures of these epoxidized sesquiterpenes.[13] By comparison to our previous route, this formal synthesis of epoxydaucenal B (**144b**) also produces the natural product in 12 steps, albeit in much lower overall yield (1%). Continuing toward our initial goal, Luche reduction of daucenal (**143**) provides allylic alcohol **263**, which can be treated with base and *p*-anisoyl chloride to afford (+)-14-*p*-anisoyloxydauc-4,8-diene (**145**) in 13 steps with 4% overall yield. Given the bioactivity observed for esters **145** and **146** (Figure 3.1),[1a,b] we envision that exploration of other unnatural ester derivatives prepared from alcohol **263** may prove promising in structure-activity relationship studies and enable the subsequent preparation of more potent analogues.

*Scheme 3.24. Endgame for (+)-daucenal (**143**) and (+)-14-p-anisoyloxydauc-4,8-diene (**145**) and formal syntheses of epoxydaucenal A and B (**144a** and **144b**).*



3.4 CONCLUDING REMARKS

In summary, we have completed the first catalytic enantioselective total syntheses of epoxydaucenal B (**144b**), daucene (**142**), daucenal (**143**), and 14-*p*-anisoyloxydauc-

4,8-diene (**145**) in 10–13 steps with 20%, 15%, 8%, and 4% overall yields, respectively. Our route overcomes the challenge of accessing β-substituted acylcyclopentene **53w** by employing a siloxyenone to effect the Grignard addition and ring opening in a single step. Subsequent ring-closing metathesis and aldol reactions form the bicyclo[5.3.0]decane core. Derivatization of the key intermediate, enone **223**, allows access to either the daucane sesquiterpene or sphenobolane diterpene carbon skeletons, as well as other oxygenated scaffolds. Our efforts feature several olefination methods to install the C(13) carbon, including the underutilized molybdenum alkylidene developed by Kauffmann. Future directions are focused on biological evaluation of the molecules reported herein and application of the developed synthetic strategy to other daucane sesquiterpenes and sphenolobane diterpenes.

3.5 EXPERIMENTAL SECTION

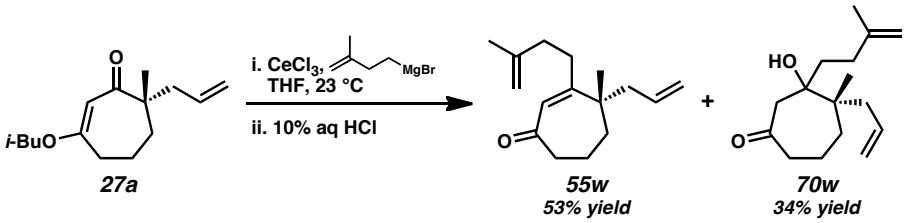
3.5.1 MATERIALS AND METHODS

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.[45] Methanol (MeOH) was distilled over Mg and I_2 according to the procedure of Lund and Bjerrum.[46] Brine solutions are saturated aqueous solutions of sodium chloride. Vinylogous ester **27a** was prepared following the method found in our previous report.[7a] Triisopropylsilyl triflate was distilled immediately before use. Oxotrischlorobis(tetrahydrofuran)molybdenum(V) was prepared according to the procedure of McUliffe.[42] All other reagents were purchased from Sigma-Aldrich, Acros Organics, Strem, Alfa Aesar, or TCI America and used as received unless otherwise stated. Reaction temperatures were controlled by an IKAmag temperature modulator. Microwave-assisted reactions were performed in a Biotage Initiator 2.5 microwave reactor. Glove box manipulations were performed under a N_2 atmosphere. Reaction progress was monitored by thin-layer chromatography (TLC). TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde staining, and/or $KMnO_4$ staining. ICN silica gel (particle size 0.032-0.0653 mm) or Silicycle Silia*Flash* P60 Academic silica gel (particle size 0.040-0.063 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on a Varian Inova 500 MHz spectrometer and are reported relative to residual $CHCl_3$ (δ 7.26 ppm) or benzene-d_6 (C_6D_6, δ 7.16 ppm). ^{13}C NMR spectra are recorded on a Varian Inova 500 MHz

spectrometer (125 MHz) and are reported relative to $CDCl_3$ (δ 77.16 ppm) or benzene-d_6 (C_6D_6, δ 128.06 ppm). 2D NMR experiments were performed on a Varian Inova 400 MHz or Varian Inova 500 MHz spectrometer and are reported relative to residual solvent. 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, dm = doublet of multiplets, br = broad (e.g., br s = broad singlet), app = apparent. Data for ^{13}C are reported in terms of chemical shifts (δ ppm). IR spectra were obtained by a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility (EI+, GC-EI+, FAB+) or on 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+). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell and are reported as: $[\alpha]_D^T$ (concentration in g/100 mL, solvent, *ee*).

3.5.2 Preparative Procedures

3.5.2.1 Procedures Associated with Initial Approach

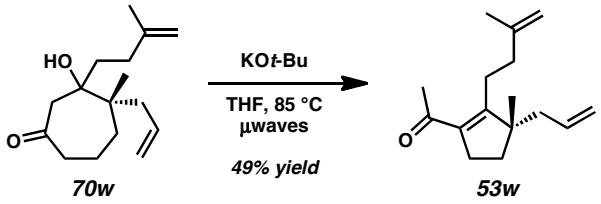


Cycloheptenone 55w and β-Hydroxyketone 70w. A flame-dried 250 mL round-bottom flask equipped with a stir bar was cycled into a glove box where the flask was loaded with anhydrous cerium chloride (2.66 g, 10.79 mmol, 2.54 equiv). The flask was removed from the glove box, connected to an Ar-filled manifold, and charged with THF (50 mL). After 24 h of stirring, (3-methylbut-3-en-1-yl)magnesium bromide[47] (0.24 M in THF, 52.85 mL, 12.69 mmol, 2.99 equiv) was added to the flask, causing the slurry to initially turn yellow and orange over time. After 3 h, the flask was charged with additional THF (20 mL), and vinylogous ester **27a** (1.00 g, 4.25 mmol, 1.00 equiv) was transferred from a conical flask to the round-bottom flask using several THF rinses (3 x 10 mL, total added = 106 mL, 0.04 M). TLC analysis indicated no starting material remained after 5 min. After 40 min, the reaction was quenched with HCl (10% w/w aq, 50 mL) and transferred to a separatory funnel where the aqueous layer was extracted five times with EtOAc. The combined organics were rinsed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 28 x 3 cm, 100% hexanes→5%→10%→20% EtOAc in hexanes) to afford cycloheptenone **55w** (473.0 mg, 2.04 mmol, 53% yield) as a

pale yellow oil and β-hydroxyketone **70w** (325.3 mg, 1.30 mmol, 34% yield) as a pale yellow oil.

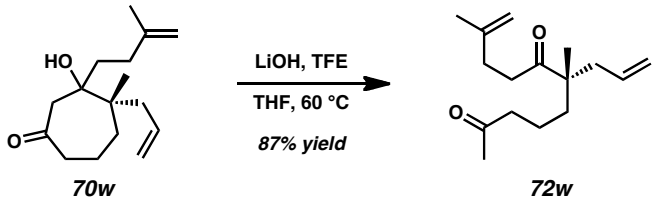
Cycloheptenone 55w. Characterization data matches that previously reported.[30]

β-hydroxyketone 70w. R_f = 0.55 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) mixture of two diastereomers, see Figure SI-1A; IR (Neat Film NaCl) 3464, 3072, 2965, 2936, 2866, 1694, 1647, 1638, 1452, 1375, 1342, 1299, 1229, 1186, 1110, 1073, 1029, 997, 967, 917, 884, 793 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{27}O_2$ $[M+H]^+$: 251.2006, found 251.2007.



Acylcyclopentene 53w. KO*t*-Bu (269.4 mg, 2.40 mmol, 1.65 equiv) and THF (10 mL, 0.10 M), were added to a flame-dried 20 mL microwave vial with a stir bar. β-hydroxyketone **70w** (364.9 mg, 1.46 mmol, 1.00 equiv) was transferred to the vial using benzene (200 μL) and THF (2 x 1 mL). Another portion of THF (3 mL, total added = 15 mL, 0.10 M) was added to the vial. The pale yellow solution was subjected to microwave irradiation in a Biotage Initiator microwave reactor (temperature: 85 °C, sensitivity: normal). After 5 min of irradiation, the crimp cap was removed and Na_2SO_4 was added to the vial. The reaction contents were transferred to a separatory funnel,

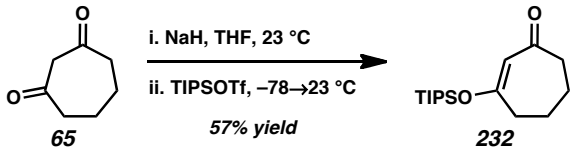
quenched with HCl (10% w/w aq, 10 mL), and extracted four times with Et_2O. The combined organics (300 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 28.5 x 3 cm, 100% pentane→5%→10%→15%→20% Et_2O in pentane) to afford acylcyclopentene **53w** (164.3 mg, 0.71 mmol, 49% yield) as a yellow oil; R_f = 0.75 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71 (dddd, J = 16.8, 10.3, 7.6, 7.0 Hz, 1H), 5.08–5.01 (m, 2H), 4.74 (dq, J = 2.2, 1.1 Hz, 1H), 4.73 (td, J = 1.4, 0.7 Hz, 1H), 2.61–2.52 (m, 3H), 2.33 (tdt, J = 12.2, 5.0, 1.1 Hz, 1H), 2.21 (s, 3H), 2.20–2.04 (m, 4H), 1.88 (ddd, J = 12.9, 7.5, 6.3 Hz, 1H), 1.80 (dd, J = 1.4, 1.0 Hz, 3H), 1.61–1.53 (m, 1H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.7, 163.5, 146.3, 135.0, 134.9, 117.7, 109.9, 52.6, 43.7, 37.5, 35.0, 31.6, 30.4, 26.6, 24.7, 22.5; IR (Neat Film NaCl) 3074, 2957, 2929, 2864, 1676, 1648, 1602, 1453, 1373, 1355, 1313, 1273, 1252, 1208, 1113, 995, 960, 913, 885 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{25}O$ $[M+H]^+$: 233.1900, found 233.1903; $[\alpha]_D^{25.0}$ –7.12 (c 1.53, $CHCl_3$, 88% ee).



Dione 72w. β-Hydroxyketone **70w** (50.6 mg, 0.20 mmol, 1.00 equiv) was transferred to a flame-dried 15 mL round-bottom flask equipped with a stir bar and water condenser using several THF rinses (4 x 1 mL, total = 4 mL, 0.05 M). TFE (58 μL, 0.81 mmol, 4.00 equiv) and LiOH (14.2 mg, 0.59 mmol, 2.93 equiv) were added, generating a pale

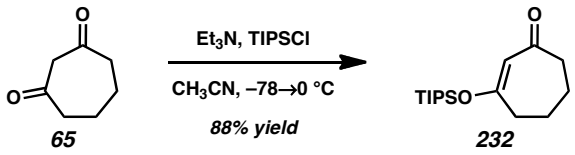
yellow solution. The flask was lowered into a preheated oil bath (60 °C) and heated for 2 h. After cooling to room temperature, the reaction was filtered through a short silica gel plug (2 x 10 cm) rinsing with Et_2O. The combined organics were concentrated under reduced pressure at 0 °C (ice/water) and purified by flash column chromatography (SiO_2, 25 x 2 cm, 100% pentane→2%→5%→10%→15% Et_2O in pentane) to afford dione **72w** (44.1 mg, 0.81 mmol, 87% yield) as a yellow oil; R_f = 0.56 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68–5.59 (m, 1H), 5.06–5.01 (m, 2H), 4.72 (dqt, J = 2.2, 1.5, 0.8 Hz, 1H), 4.67 (qq, J = 1.3, 0.8 Hz, 1H), 2.61–2.57 (m, 2H), 2.40 (dd, J = 7.3, 6.0 Hz, 2H), 2.33 (ddt, J = 14.0, 7.2, 1.2 Hz, 1H), 2.24 (t, J = 7.9 Hz, 2H), 2.21 (ddt, J = 14.0, 7.5, 1.2 Hz, 1H), 2.12 (s, 3H), 1.74 (dd, J = 1.4, 0.8 Hz, 3H), 1.63–1.54 (m, 1H), 1.52–1.33 (m, 3H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.2, 208.6, 145.2, 133.9, 118.3, 110.2, 51.1, 44.0, 42.6, 37.4, 36.1, 31.5, 30.1, 22.9, 21.1, 18.7; IR (Neat Film NaCl) 3076, 2968, 2935, 1717, 1703, 1648, 1640, 1458, 1437, 1410, 1358, 1271, 1229, 1174, 1076, 996, 917, 889, 725 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{27}O_2$ $[M+H]^+$: 251.2006, found 251.2006; $[\alpha]_D^{25.0}$ 6.64 (c 0.96, $CHCl_3$, 88% ee).

3.5.2.2 Siloxyenone Efforts Toward Acyclic Dione 72w



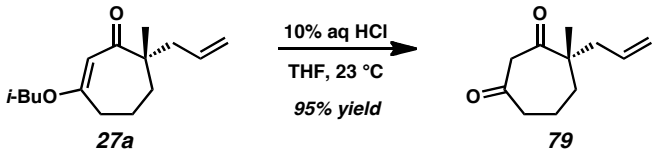
Siloxyenone 232. A flame-dried 50 mL round-bottom flask equipped with a stir bar was cycled into a glove box where the flask was loaded with sodium hydride (148.3 mg, 3.71 mmol, 1.06 equiv). The flask was removed from the glove box, connected to an Ar-filled manifold, and charged with THF (13 mL). Dione **65** (442.4 mg, 3.51 mmol, 1.00 equiv)

was transferred to the flask using several THF rinses (3 x 3 mL, total added = 22 mL, 0.16 M). The addition caused the reaction mixture to bubble vigorously and develop into an orange slurry. After 30 min, the flask was lowered into a –78 °C bath and TIPSOTf (990 μL, 3.68 mmol, 1.05 equiv) was added dropwise over several minutes. TLC analysis indicated no starting material remained after 1.5 h. Consequently, the reaction was transferred to a separatory funnel containing sat. aq $NaHCO_3$ and Et_2O and the aqueous layer was extracted three times with Et_2O. The combined organics (150 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 25.5 x 5 cm, 100% hexanes→5%→10% EtOAc in hexanes) to afford siloxyenone **232** (561.1 mg, 1.99 mmol, 57% yield) as an orange oil. Characterization data matches that reported previously by Corey et al.[48]



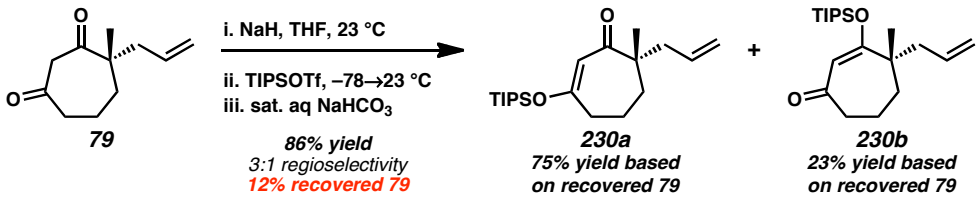
Siloxyenone 232. A flame-dried 50 mL round-bottom flask equipped with a stir bar and dione **65** (1.00 g, 7.93 mmol, 1.00 equiv) was charged with CH_3CN (79 mL, 0.10 M) and Et_3N (1.16 mL, 8.32 mmol, 1.05 equiv) and lowered into a –78 °C bath (dry ice/acetone). TIPSCl (1.87 mL, 8.74 mmol, 1.10 equiv) was added dropwise over 10 min and the reaction was moved to a 0 °C bath (ice/water). TLC analysis indicated no starting material remained after 2.5 h. Consequently, the reaction was quenched with sat. aq $NaHCO_3$ (10 mL) and transferred to a separatory funnel where the aqueous layer was

extracted three times with pentane. The combined organics (250 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. ^1H NMR analysis indicated that the resulting crude oil was sufficiently pure, affording siloxyenone **232** (1.96 g, 6.94 mmol, 88% yield) as an orange oil. Characterization data matches that reported previously by Corey et al.[48]



27a *79*

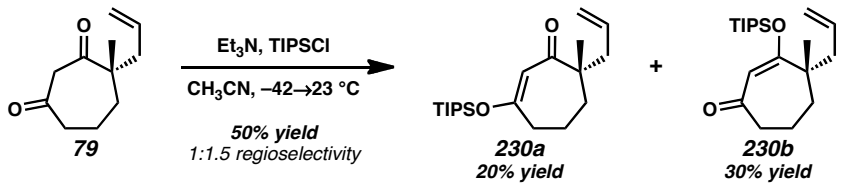
Dione 79. The following procedure affords a higher yield than our previous report.[7b] A flame-dried 50 mL round-bottom flask equipped with a stir bar was charged with vinylogous ester **27a** (1.83 g, 7.73 mmol, 1.00 equiv), THF (12.5 mL, 0.6 M), and hydrochloric acid (10% w/w aq = 2.87 M, 12.5 mL, 35.9 mmol, 4.64 equiv). The reaction mixture was initially a cloudy suspension that became a colorless solution over time. TLC analysis indicated no starting material remained after 4.5 h. Consequently, the reaction was transferred to a separatory funnel, diluted with water, and extracted six times with CH_2Cl_2. The combined organics (150 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 27 x 3 cm, 100% hexanes→15% EtOAc in hexanes) to afford dione **79** (1.33 g, 7.37 mmol, 95% yield) as a yellow oil. Characterization data matches that previously reported.[7b]



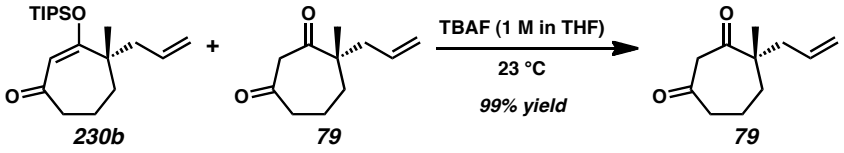
Siloxyenones 230a and 230b. A flame-dried 50 mL round-bottom flask equipped with a stir bar was cycled into a glove box where the flask was loaded with NaH (80.9 mg, 3.20 mmol, 1.05 equiv). The flask was removed from the glove box, connected to an Ar-filled manifold, and charged with THF (9 mL). Dione **79** (547.3 mg, 3.04 mmol, 1.00 equiv) was transferred via cannula from a scintillation vial to the round-bottom flask using several THF rinses (1 x 5 mL + 5 x 1 mL, total added = 19 mL, 0.16 M). The reaction was stirred at room temperature for 30 min before the flask was lowered into a –78 °C bath (dry ice/acetone) and TIPSOTf (850 μL, 3.16 mmol, 1.04 equiv) was added dropwise over 20 min. After the addition was complete, the bath was removed and the reaction was allowed to warm to room temperature. After 13 h of stirring, the reaction was poured into a separatory funnel containing Et_2O (20 mL), sat. aq $NaHCO_3$ (20 mL), and water (10 mL). The aqueous layer was extracted once with Et_2O and four times with CH_2Cl_2. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 26 x 3 cm, 100% hexanes→2%→15% EtOAc in hexanes) to afford siloxyenone **230a** (669.9 mg, 1.99 mmol, 66% yield, 75% yield based on recovered dione **79**) as a yellow oil, a mixed fraction of siloxyenone **230b** with dione **79** (206.5 mg total, 50:1 = **230b**:**79**, siloxyenone **230b**: 204.3 mg, 0.6069 mmol, 20% yield, 23% yield based on recovered dione **79**) as a yellow oil, and recovered dione **79** (66.0 mg, 0.366 mmol, 12% recovered) as a yellow oil.

Siloxyenone 230a. R_f = 0.76 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 5.87–5.74 (m, 1H), 5.78 (s, 1H), 5.06–5.00 (m, 2H), 2.51 (ddt, J = 13.5, 7.1, 1.3 Hz, 1H), 2.25 (ddt, J = 13.5, 7.7, 1.1 Hz, 1H), 2.21–2.16 (m, 2H), 1.67–1.59 (m, 1H), 1.44–1.37 (m, 2H), 1.34–1.28 (m, 1H), 1.20 (s, 3H), 1.13–1.00 (m, 21H); ^{13}C NMR (125 MHz, C_6D_6) δ 204.3, 167.5, 135.1, 117.8, 113.9, 51.8, 46.0, 38.2, 35.1, 25.4, 19.98, 18.1, 18.1, 12.9; IR (Neat Film NaCl) 3075, 2944, 2893, 2867, 1700, 1613, 1464, 1419, 1385, 1301, 1249, 1204, 1137, 1109, 1070, 1016, 996, 917, 883, 823, 782, 741 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{20}H_{37}O_2Si$ $[M+H]^+$: 337.2557, found 337.2566; $[\alpha]_D^{25.0}$ –60.52 (c 1.01, $CHCl_3$, 88% ee).

Siloxyenone 230b. R_f = 0.64 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 5.72 (s, 1H), 5.78–5.65 (m, 1H), 5.06–4.98 (m, 2H), 2.54 (ddt, J = 13.6, 6.5, 1.5 Hz, 1H), 2.49 (dm, J = 18.0 Hz, 1H), 2.42 (ddd, J = 17.9, 9.4, 5.1 Hz, 1H), 2.05 (ddt, J = 13.6, 8.1, 1.1 Hz, 1H), 1.62 (ddd, J = 14.4, 9.9, 1.4 Hz, 1H), 1.44 (dtdd, J = 14.6, 9.8, 4.7, 1.4 Hz, 1H), 1.41–1.30 (m, 1H), 1.26 (ddt, J = 14.4, 9.0, 1.2 Hz, 1H), 1.19–1.06 (m, 3H), 1.11 (s, 3H), 1.04 (d, J = 3.1 Hz, 9H), 1.02 (d, J = 3.0 Hz, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 199.3, 172.1, 134.6, 118.1, 113.9, 46.3, 45.3, 44.5, 37.0, 25.9, 18.3, 18.3, 17.9, 13.1; IR (Neat Film NaCl) 2944, 2892, 2867, 1636, 1592, 1464, 1378, 1351, 1283, 1249, 1207, 1170, 1071, 1016, 996, 917, 883, 855, 782 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{20}H_{37}O_2Si$ $[M+H]^+$: 337.2557, found 337.2559; $[\alpha]_D^{25.0}$ –46.35 (c 1.35, $CHCl_3$, 88% ee).

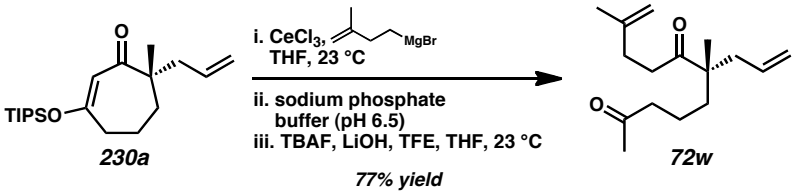


Siloxyenones 230a and 230b. A flame-dried 15 mL round-bottom flask equipped with a stir bar was charged with dione **79** (50.5 mg, 0.280 mmol, 1.00 equiv) and CH_3CN (2.8 mL, 0.1 M) and lowered into a –42 °C (dry ice/CH_3CN). Et_3N (40 μL, 0.287 mmol, 1.02 equiv) and TIPSCl (70 μL, 0.327 mmol, 1.17 equiv) were added dropwise to the reaction and the bath was allowed to expire over time. After 2 h, the reaction was quenched with water (5 mL) and transferred to a separatory funnel where the aqueous layer was extracted six times with hexanes. The combined organics (100 mL) were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 27 x 1.5 cm, 100% hexanes→2%→15% EtOAc in hexanes) to afford siloxyenone **230a** (19.2 mg, 0.0570 mmol, 20% yield) as a yellow oil and a mixed fraction of siloxyenone **230b** with dione **79** (31.0 mg total, 5.6:1 = **230b**:**79**, siloxyenone **230b**: 28.3 mg, 0.0840 mmol, 30% yield) as a yellow oil. (For characterization of siloxyenones **230a** and **230b**, see p. 739).



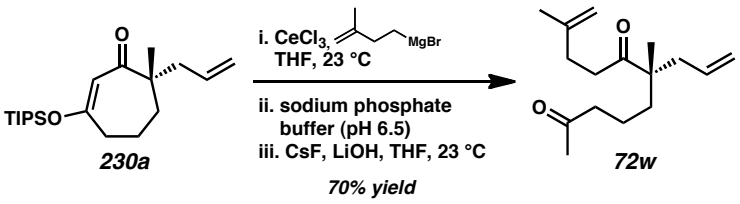
Dione 79. To a scintillation vial containing a mixed fraction of siloxyenone **230b** (262.6 mg, 0.780 mmol, 1.00 equiv) and dione **79** (12.0 mg, 0.0666 mmol) was added a stir bar and TBAF (1.0 M in THF, 2 mL, 2.00 mmol, 2.56 equiv). After 4 h, no siloxyenone

230b was observed by TLC. Consequently, the reaction was quenched with water (10 mL) and transferred to a separatory funnel where the aqueous layer was extracted six times with CH_2Cl_2. The combined organics (75 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 27.5 x 5 cm, 100% hexanes→5%→15% EtOAc in hexanes) to afford dione **79** (151.7 mg, 0.842 mmol, 99% yield) as a yellow oil. Characterization data matches that previously reported.[7b]



Dione 72w. A flame-dried 50 mL round-bottom flask equipped with a stir bar was cycled into a glove box where the flask was loaded with anhydrous cerium chloride (589.5 mg, 2.39 mmol, 2.50 equiv). The flask was removed from the glove box, connected to an Ar-filled manifold, placed under full vacuum, and lowered into an oil bath set to 140 °C. After 12.5 h, the flask was removed from the bath, allowed to cool to room temperature, and charged with THF (12 mL). After 3 h of stirring, (3-methylbut-3-en-1-yl)magnesium bromide[47] (0.59 M in THF, 4.86 mL, 2.87 mmol, 3.00 equiv) was added and the slurry initially turned yellow and then orange over time. After 40 min, siloxyenone **230a** (321.8 mg, 0.956 mmol, 1.00 equiv) was transferred from a scintillation vial to the round-bottom flask using several THF rinses (1 x 6 mL + 3 x 2 mL, total added = 24 mL, 0.04 M). TLC analysis indicated no starting material remained after 10 min. Consequently, the reaction was quenched with sodium phosphate buffer

(20 mM, pH 6.5, 20 mL) and transferred to a separatory funnel where the aqueous layer was extracted four times with Et_2O. The combined organics (150 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was transferred to a scintillation vial equipped with a stir bar and backfilled with Ar. The vial was charged with TBAF (1.0 M in THF, 1.43 mL, 1.43 mmol, 1.50 equiv), TFE (210 μL, 2.88 mmol, 3.01 equiv), and LiOH (34.4 mg, 1.44 mmol, 1.50 equiv). After 4 h, the reaction was quenched with water (10 mL) and transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified twice by flash column chromatography (SiO_2, 27.5 x 2 cm, 100% hexanes→5%→10% TBME in hexanes ***then*** SiO_2, 28 x 2 cm, 100% hexanes→2%→5%→20% TBME in hexanes) to afford dione **72w** (185.0 mg, 0.739 mmol, 77% yield) as a pale yellow oil. (For characterization data, see p. 734).

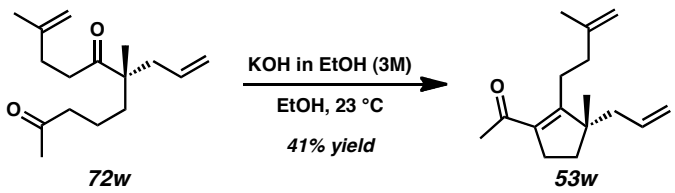


Dione 72w. A flame-dried 15 mL round-bottom flask equipped with a stir bar was cycled into a glove box where the flask was loaded with anhydrous cerium chloride (141.7 mg, 0.575 mmol, 2.50 equiv). The flask was removed from the glove box, connected to an Ar-filled manifold, placed under full vacuum, and lowered into an oil bath set to 140 °C. After 12 h, the flask was removed from the bath, allowed to cool to

room temperature, and charged with THF (1.7 mL). After 2 h of stirring, (3-methylbut-3-en-1-yl)magnesium bromide[47] (0.59 M in THF, 1.17 mL, 0.690 mmol, 3.01 equiv) was added and the slurry initially turned yellow and then orange over time. After 30 min, siloxyenone **230a** (77.3 mg, 0.230 mmol, 1.00 equiv) was transferred from a scintillation vial to the round-bottom flask using several THF rinses (1 x 2 mL + 2 x 1 mL, total added = 5.7 mL, 0.04 M). TLC analysis indicated no starting material remained after 5 min. Consequently, the reaction was quenched with sodium phosphate buffer (20 mM, pH 6.5, 5 mL) and transferred to a separatory funnel where the aqueous layer was extracted four times with Et_2O. The combined organics (75 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

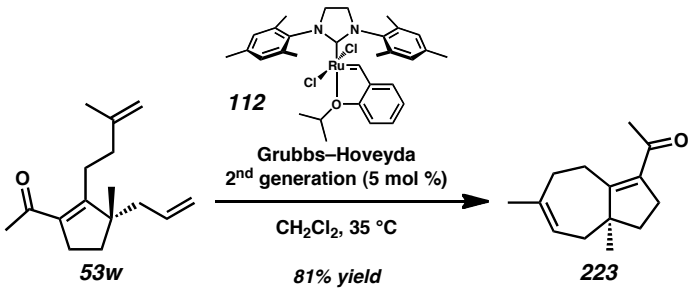
A separate flame-dried 10 mL round-bottom flask equipped with a stir bar was loaded with CsF (145.2 mg, 0.956 mmol, 4.16 equiv) and flame-dried again. Upon cooling, the crude oil from the previous step was transferred to the flask using several THF rinses (3 x 1 mL, total added = 3 mL, 0.08 M). As the reaction failed to progress by TLC analysis after 1 h, LiOH (18.5 mg, 0.772 mmol, 3.36 equiv) was added. TLC analysis indicated the desired product was mainly present after an additional 13 h. Consequently, the reaction was quenched with water (10 mL) and transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (75 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 28 x 1.5 cm, 100% hexanes→2%→5%→10% TBME in hexanes) to afford dione **72w** (40.4 mg, 0.161 mmol, 70% yield) as a pale yellow oil. (For characterization data, see p. 734).

3.5.2.3 Routes to Key Intermediate Enone 53w



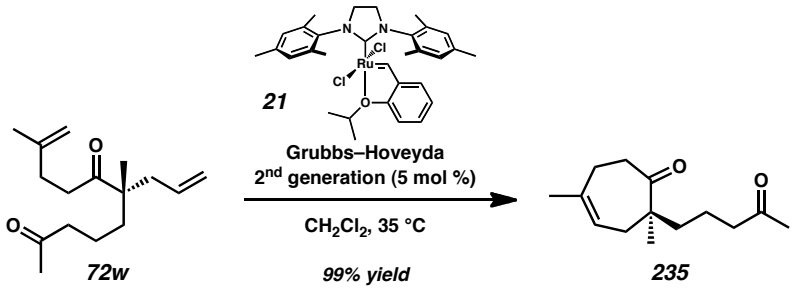
72w *53w*

Enone 53w. A scintillation vial equipped with a stir bar and dione **72w** (40.4 mg, 0.161 mmol, 1.00 equiv) was charged with EtOH (950 µL, 0.17 M) and KOH solution (3 M in EtOH, 140 µL, 0.420 mmol, 2.60 equiv). The resulting yellow solution was stirred vigorously. Over the course of the reaction, an additional portion of the KOH solution (2 d = 140 µL, 3 d = 280 µL, 4 d = 1.4 mL, 5 d = 5.0 mL, total added = 7.66 mL, 23.0 mmol, 142 equiv) was added. After 6 days, the reaction was quenched with water (10 mL) and transferred to a separatory funnel where the aqueous layer was extracted four times with Et_2O. The combined organics (75 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 28 x 1.5 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford enone **53w** (15.3 mg, 0.0660 mmol, 41% yield) as a yellow oil. (For characterization data, see p. 733).



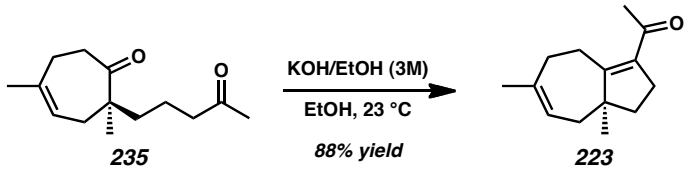
Enone 223. A flame-dried 25 mL round-bottom flask equipped with a stir bar and water condenser was charged with acylcyclopentene **53w** (1.0 M in benzene, 100 μL, 0.100 mmol, 1.00 equiv), CH_2Cl_2 (20 mL, 0.005 M, 30 min Ar sparge before use), and Grubbs–Hoveyda 2nd generation catalyst (**112**, 3.2 mg, 0.00511 mmol, 5 mol %), generating a pale green solution. The flask was lowered into a preheated oil bath (35 °C) and stirred for 5 h before the reaction was cooled to room temperature and quenched with ethyl vinyl ether. The reaction was filtered through a short silica gel plug rinsing with Et_2O and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 21.5 x 1.3 cm, 100% hexanes→2% Et_2O in pentane) to afford enone **223** (16.5 mg, 0.081 mmol, 81% yield) as a yellow oil. Spectral data for enone **223** matches that previously reported by Urones[36]: R_f = 0.73 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.36 (ddt, J = 7.9, 6.7, 1.4 Hz, 1H), 3.21 (dt, J = 11.1, 5.9 Hz, 1H), 2.66–2.56 (m, 1H), 2.50 (ddd, J = 15.3, 8.7, 2.8 Hz, 1H), 2.29–2.16 (m, 1H), 2.21 (s, 3H), 2.17–2.11 (m, 3H), 2.02 (ddd, J = 14.4, 6.6, 1.2 Hz, 1H), 1.75–1.69 (m, 1H), 1.69 (d, J = 1.4 Hz, 3H), 1.64 (ddd, J = 12.3, 7.7, 2.8 Hz, 1H), 0.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.5, 165.0, 139.4, 133.4, 121.1, 52.7, 37.8, 37.3, 33.2, 30.8, 30.4, 26.1, 24.2, 23.7; IR (Neat Film NaCl) 2926, 2852, 1675, 1653, 1612, 1437, 1356,

1301, 1262, 1204, 945, 825 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{14}H_{20}O$ $[M+\bullet]^+$: 204.1514, found 204.1530; $[\alpha]_D^{25.0}$ –146.03 (c 0.98, $CHCl_3$, 88% ee).



Dione 235. To a flame-dried 250 mL Schlenk flask equipped with a stir bar and water condenser was added dione **72w** (422.6 mg, 1.69 mmol, 1.00 equiv) via several CH_2Cl_2 rinses (5 x 6 mL, 30 min Ar sparge before use). The flask was charged with additional CH_2Cl_2 (130 mL) and Hoveyda–Grubbs 2nd generation catalyst (**21**, 53.0 mg, 0.0846 mmol, 5.0 mol %), generating a pale green solution. The flask was rinsed with CH_2Cl_2 (10 mL, total added = 170 mL, 0.01 M) and lowered into a preheated oil bath (35 °C). After 22 h, the reaction was quenched with ethyl vinyl ether (3 mL), removed from the oil bath, and allowed to cool to room temperature. The reaction contents were filtered through a short silica gel plug, rinsing with TBME, and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 27.5 x 2 cm, 100% hexanes→5%→10%→15%→20%→30% TBME in hexanes) to afford dione **235** (370.5 mg, 1.67 mmol, 99% yield) as a yellow oil. Spectral data for dione **235** matches that previously reported by Urones[36a]: R_f = 0.39 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.45 (dddd, J = 7.7, 6.2, 3.0, 1.5 Hz, 1H), 2.88 (ddd, J = 11.5, 9.5, 5.7 Hz, 1H), 2.59 (ddd, J = 11.5, 6.9, 5.4 Hz, 1H), 2.43

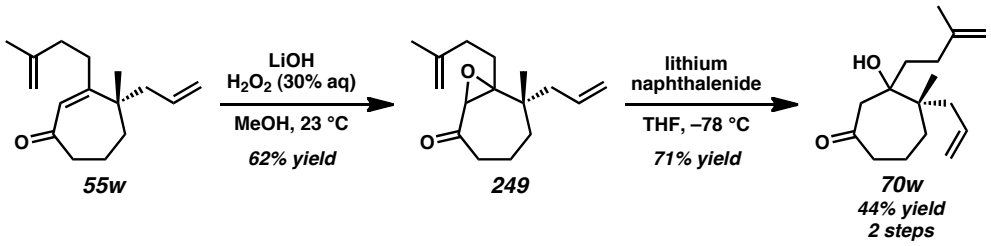
(dddd, J = 15.2, 6.1, 2.7, 1.3 Hz, 1H), 2.38 (t, J = 6.9 Hz, 2H), 2.34–2.20 (m, 2H), 2.11 (s, 3H), 2.08 (ddq, J = 15.4, 7.3, 1.0 Hz, 1H), 1.66 (q, J = 1.1 Hz, 3H), 1.56–1.38 (m, 4H), 1.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.0, 208.8, 137.0, 121.5, 53.8, 44.2, 38.0, 37.9, 34.7, 32.1, 30.1, 25.4, 22.4, 18.7; IR (Neat Film NaCl) 2963, 2931, 1714, 1705, 1436, 1360, 1314, 1215, 1173, 1123, 1071, 1011, 894, 826 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{14}H_{23}O_2$ $[M+H]^+$: 223.1693, found 223.1696; $[\alpha]_D^{25.0}$ 52.49 (c 0.93, $CHCl_3$, 88% ee).



Enone 223. Procedure adapted from report by Urones.[36a] A flame-dried 25 mL round-bottom flask equipped with a stir bar was charged with dione **235** (255.6 mg, 1.15 mmol, 1.00 equiv), EtOH (6.74 mL, 0.17 M), and KOH solution (3 M in EtOH, 1.02 mL, 3.06 mmol, 2.66 equiv), generating a yellow solution that transitioned to orange over time. After 9 h, an additional portion of KOH (3 M in EtOH, 0.90 mL, total added = 1.92 mL, 5.76 mmol, 5.01 equiv) was added. After 22 h, no starting material remained by TLC. Consequently, the reaction was diluted with water (15 mL) and transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (100 mL) were rinsed with HCl (0.5 M, 15 mL) and water (15 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 26 x 2 cm, 100% hexanes→5% TBME in hexanes) to afford enone **223** (205.6 mg, 1.01 mmol, 88% yield)

as a yellow oil. Spectral data for enone **223** matches that previously reported by Urones.[36a] (For characterization data, see p. 745).

3.5.2.4 Routes to Reincorporate Cycloheptenone 55w into Synthetic Efforts

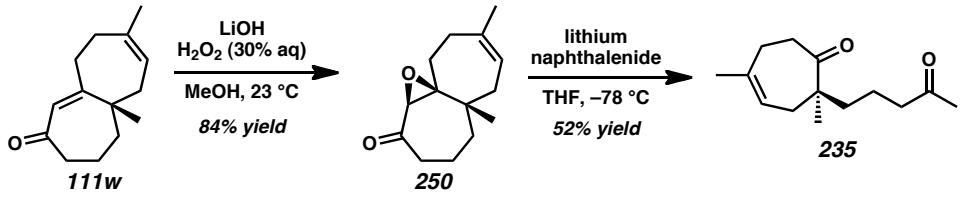


Epoxide 249. Procedure adapted from report by Stoltz.[7a] To a scintillation vial containing a stir bar and cycloheptenone **55w** (216.6 mg, 0.932 mmol, 1.00 equiv) was added MeOH (3.6 mL), LiOH (56.1 mg, 2.34 mmol, 2.51 equiv), H_2O_2 (30% w/w aq, 950 µL, 9.30 mmol, 9.98 equiv), and additional MeOH (1.0 mL, total added = 4.6 mL, 0.2 M). During the course of the reaction, additional LiOH (7 h = 56.5 mg, 22 h = 55.8 mg, 31 h = 56.0 mg, 95.5 h = 55.9 mg, 142 h = 56.2 mg, total added = 336.5 mg, 14.0 mmol, 15.0 equiv) and H_2O_2 (950 µL more at 7 h, 22 h, 31 h, 71.5 h, 142 h, 151 h, total added = 7.6 mL, 74.4 mmol, 80 equiv) were added to the flask. The solvent level decreased over time and so more MeOH (47.5 h = 3 mL, 71.5 h = 2 mL, 77.5 h = 3 mL) was added when appropriate. After 10 days, TLC analysis indicated minor starting material remaining. Consequently, the reaction was diluted with CH_2Cl_2 (10 mL) and water (20 mL), quenched with sat. $NaHCO_3$ solution (10 mL), and transferred to a separatory funnel where the aqueous layer was extracted six times with CH_2Cl_2. The combined organics (125 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 28 x 2 cm,

100% hexanes→2%→5%→10%→20% EtOAc in hexanes) to afford recovered cycloheptenone **55w** (22.1 mg, 0.0951 mmol, 10% recovered) and epoxide **249** (142.8 mg, 0.575 mmol, 62% yield, 69% yield based on recovered cycloheptenone **55w**) as a cloudy yellow oil; R_f = 0.75 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) mixture of two diastereomers, see Figure SI-2A; IR (Neat Film NaCl) 3075, 2970, 2936, 1703, 1649, 1639, 1457, 1395, 1376, 1339, 1291, 1261, 1206, 1169, 1121, 996, 919, 890, 848 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{16}H_{25}O_2$ $[M+H]^+$: 249.1855, found 249.1851.

β-Hydroxyketone 70w. Procedure adapted from report by Liu.[49] A flame-dried 25 mL round-bottom flask equipped with a stir bar was loaded with epoxide **249** (50.0 mg, 0.201 mmol, 1.00 equiv) and THF (5.8 mL, 0.10 M) and lowered into a –78 °C bath (dry ice/acetone). A lithium naphthalenide solution[50] (1.0 M in THF, 3.6 mL, 3.60 mmol, 6.26 equiv) was added dropwise to the flask, generating a dark green solution. During the course of the reaction, an additional portion of lithium naphthalenide (1.0 M in THF, 1 h = 1.0 mL, 5 h = 2.0 mL, 2.5 h = 0.58 mL, total added = 6.60 mL, 6.60 mmol, 11.5 equiv) was added. After 9 h, the reaction was quenched with water (10 mL), diluted with EtOAc, and stirred for 12 h. The reaction contents were transferred to a separatory funnel where the aqueous layer was extracted four times with CH_2Cl_2. The combined organics (125 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified twice by flash column chromatography (SiO_2, 27.5 x 2 cm, 100% hexanes→5%→10%→20% EtOAc in hexanes ***then*** SiO_2, 27.5 x 2 cm, 100% hexanes→2%→5%→10%→15% EtOAc in hexanes) to afford β-

hydroxyketone **70w** (102.6 mg, 0.410 mmol, 71% yield) as a yellow oil. (For characterization data, see p. 733).

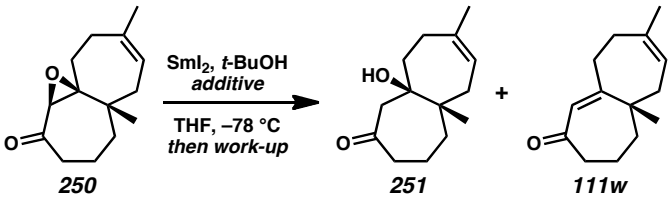


Epoxide 250. A flame-dried 25 round-bottom flask equipped with a stir bar was charged with enone **111w** (110.3 mg, 0.540 mmol, 1.00 equiv), MeOH (4.8 mL, 0.11 M), LiOH (32.4 mg, 1.35 mmol, 2.50 equiv), and H_2O_2 (30% w/w aq, 550 μL, 5.38 mmol, 10.0 equiv). After 30.5 h, no starting material remained by TLC analysis. Consequently, the reaction was quenched with sat. aq $NaHCO_3$ (10 mL) and water (10 mL) and was transferred to a separatory funnel where the aqueous layer was extracted five times with CH_2Cl_2. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 28 x 1.5 cm, 100% hexanes→2%→5%→20% EtOAc in hexanes) to afford epoxide **250** (99.5 mg, 0.452 mmol, 84% yield) as a yellow oil that solidified upon freezing; R_f = 0.68 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 5.20 (ddt, J = 8.6, 5.1, 1.8 Hz, 1H), 3.18 (d, J = 1.3 Hz, 1H), 2.45 (td, J = 11.5, 5.3 Hz, 1H), 2.24–2.14 (m, 1H), 2.07 (ddd, J = 13.3, 12.4, 2.9 Hz, 1H), 2.00–1.89 (m, 1H), 1.82 (ddt, J = 14.9, 4.9, 1.8 Hz, 1H), 1.68 (ddd, J = 15.7, 5.6, 2.9 Hz, 1H), 1.67–1.58 (m, 1H), 1.56 (q, J = 1.4 Hz, 3H), 1.46 (dd, J = 14.8, 8.6 Hz, 1H), 1.29–1.20 (m, 1H), 1.13–1.04 (m, 2H), 0.97 (s, 3H), 0.78 (ddd, J = 13.3, 5.5, 3.2 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 207.8, 138.0, 121.7, 72.0, 67.5, 40.6, 40.6, 40.1, 36.3, 33.8, 31.2, 26.1, 25.7, 18.1; IR

(Neat Film NaCl) 2961, 2928, 2843, 1698, 1452, 1437, 1330, 1270, 841 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{14}H_{20}O_2$ $[M+\bullet]^+$: 220.1463, found 220.1496; $[\alpha]_D^{25.0}$ –78.43 (c 1.06, $CHCl_3$, 88% ee).

Dione 235. To a 15 mL round-bottom flask equipped with a stir bar was loaded with epoxide **250** (35.6 mg, 0.162 mmol, 1.00 equiv) and THF (1.6 mL, 0.10 M) and lowered into a –78 °C bath (dry ice/acetone). A lithium naphthalenide solution[50] (1.0 M in THF, 680 μL, 0.680 mmol, 4.2 equiv) was added dropwise to the flask, generating a dark green solution. After 1.5 h, the reaction was quenched with water (5 mL), allowed to warm to room temperature, and transferred to a separatory funnel where the aqueous layer was extracted six times with CH_2Cl_2. The combined organics (75 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified twice by flash column chromatography (SiO_2, 29 x 1.5 cm, 100% hexanes→5%→10%→15%→20%→50% EtOAc in hexanes ***then*** SiO_2, 25.5 x 1.5 cm, 100% hexanes→10%→15% EtOAc in hexanes) to afford enone **235** (18.7 mg, 0.0842 mmol, 52% yield) as a yellow oil. (For characterization data, see p. 746).

Table 3.1. Samarium diiodide reduction of epoxide ***250****.*



250 ***251*** ***111w***

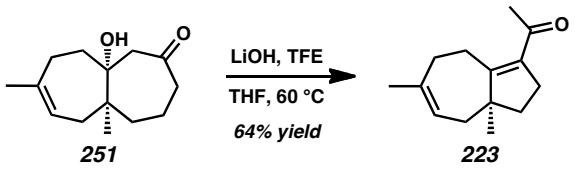
entry	additive	equiv.	work-up	yield (%)[b] *251*	*111w*
1	–	–	sat. aq. NH_4Cl	75[c]	–
2	HMPA	5.7	sat. aq. NH_4Cl	90[d]	8
3	LiCl	7.1	sat. aq. NH_4Cl	76	–
4	LiCl	8.6	H_2O	92	–[e]

[a] *Conditions*: epoxide **250** (1.0 equiv), SmI_2 (1.8–2.1 equiv.), *t*-BuOH (1.1–1.4 equiv.), and additive in THF (0.1 M) at –78 °C. [b] Isolated yield. [c] 95% purity. [d] 86% purity. [e] Observed, but not isolated.

Samarium Diiodide Reduction Screen on Epoxide 250. A series of samarium diiodide conditions were investigated in the reduction of epoxide **250**. A general procedure is provided below and related reactions were performed analogously with appropriate changes in additive and work-up conditions.

β-Hydroxyketone 251 (*LiCl Additive and H_2O quench*: Table 3.1, entry 4). A flame-dried 10 mL round-bottom flask equipped with a stir bar was cycled into a glove box where the flask was loaded with lithium chloride (52.6 mg, 1.24 mmol, 8.57 equiv). The flask was removed from the glove box and connected to an Ar-filled manifold. Epoxide **250** (31.9 mg, 0.145 mmol, 1.00 equiv) was transferred to the flask using several THF rinses (30 min Ar sparge before use, 3 x 0.5 mL, total added = 1.5 mL), *t*-BuOH (20 μL, 0.209 mmol, 1.44 equiv) was added, and the flask was lowered into a –78 °C bath (dry ice/acetone). A samarium diiodide solution[51] (0.1 M in THF, 3.04 mL, 0.304 mmol, 2.10

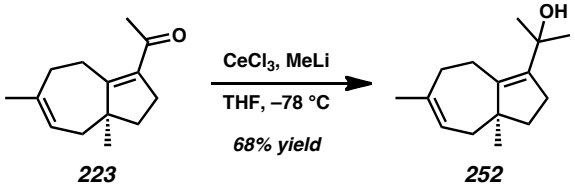
equiv) was added dropwise over 5 min down the side of the flask, generating a dark blue solution. TLC analysis indicated that no starting material remained after 5 min. After an additional 5 min, the reaction was quenched with water (2 mL), allowed to warm to room temperature, and transferred to a separatory funnel where the aqueous layer was extracted four times with EtOAc. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 25 x 1.5 cm, 100% hexanes→20% EtOAc in hexanes) to afford β-hydroxyketone **251** (29.7 mg, 0.133 mmol, 92% yield) as a yellow oil that solidified upon freezing; R_f = 0.26 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38 (tdd, J = 6.2, 2.6, 1.4 Hz, 1H), 3.10 (br s, 1H), 2.67 (br m, 1H), 2.43–2.32 (m, 2H), 2.20 (br m, 1H), 2.13 (br m, 1H), 2.04 (br m, 1H), 1.90 (dd, J = 15.4, 10.7 Hz, 1H), 1.84–1.76 (m, 2H), 1.73 (d, J = 1.3 Hz, 3H), 1.77–1.67 (m, 2H), 1.62 (br s, 1H), 1.57 (dd, J = 14.3, 10.5 Hz, 1H), 1.47 (ddd, J = 13.8, 8.9, 1.8 Hz, 1H), 1.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.0, 140.0, 122.5, 77.3, 54.2, 43.1, 42.4, 40.1, 38.3, 36.4, 28.0, 25.4, 23.0, 18.2; IR (Neat Film NaCl) 3510, 2958, 2926, 2859, 1692, 1445, 1402, 1284, 1023, 903, 851, 828 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{14}H_{22}O_2$ $[M+\bullet]^+$: 222.1620, found 222.1629; $[\alpha]_D^{25.0}$ –39.67 (c 0.85, $CHCl_3$, 86% ee).



251 *223*

Enone 223. A 20 mL scintillation vial equipped with a stir bar and β-hydroxyketone **251** (13.6 mg, 0.0612 mmol, 1.00 equiv) was connected to an Ar-filled manifold and flushed with Ar. The vial was loaded with THF (1.5 mL, 0.04 M), TFE (10 μL, 0.137 mmol, 2.24 equiv), and LiOH (2.2 mg, 0.0919 mmol, 1.50 equiv) and lowered into a preheated oil bath (60 °C). After 72 h, the solvent had evaporated, and so the vial was charged with additional THF (1.5 mL). TLC analysis of the reaction after 75 h indicated no starting material or dione **235**. Consequently, the reaction was removed from the oil bath, allowed to cool to room temperature, filtered through a celite plug rinsing with Et_2O, and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO2, 23 x 1.5 cm, 100% hexanes hexanes→5% TBME in hexanes) to afford enone **223** (8.0 mg, 0.0392 mmol, 64% yield) as a yellow oil. (For characterization data, see p. 745).

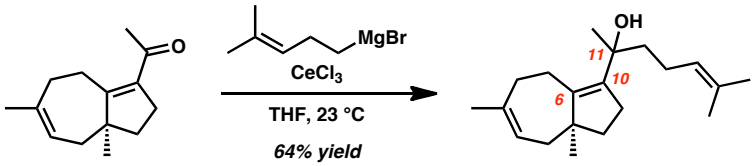
3.5.2.5 Derivatization of Enone 223 and Synthesis of (–)-Epoxydaucenal B (144b) and Δ[11]-Carotol (259)



223 *252*

Alcohol 252. A flame-dried 15 mL round-bottom flask equipped with a stir bar was cycled into a glove box where the flask was loaded with anhydrous cerium chloride (76.4

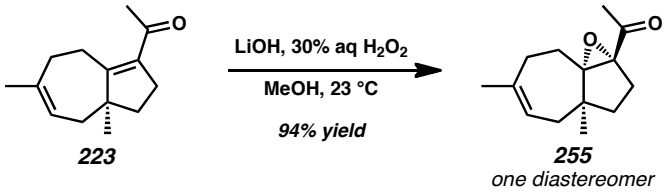
mg, 0.310 mmol, 2.53 equiv). The flask was removed from the glove box, connected to an Ar-filled manifold, placed under full vacuum, and lowered into an oil bath set to 140 °C. After 13 h, the flask was removed from the bath, allowed to cool to room temperature, and charged with THF (3 mL). After 3 h of stirring, methyllithium (1.6 M in pentane, 310 μL, 0.496 mmol, 4.05 equiv) was added and the flask was lowered into a –78 °C bath (dry ice/acetone). The resulting slurry initially turned yellow and then orange over time. After 10 min, enone **223** (25.0 mg, 0.122 mmol, 1.00 equiv) was added neat. TLC analysis indicated no starting material remained after 5 min. Consequently, the reaction was quenched after 10 min with sat. NH_4Cl solution (20 mL) and transferred to a separatory funnel where the aqueous layer was extracted four times with Et_2O. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 27.5 x 2 cm, 100% hexanes→5% TBME in hexanes) to afford alcohol **252** (18.3 mg, 0.0829 mmol, 68% yield) as a pale yellow oil; R_f = 0.65 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38 (tp, J = 6.5, 1.5 Hz, 1H), 3.00 (ddd, J = 13.6, 4.9, 3.9 Hz, 1H), 2.37–2.26 (m, 1H), 2.21 (dddd, J = 15.6, 8.6, 3.4, 1.2 Hz, 1H), 2.14 (dt, J = 15.2, 4.6 Hz, 1H), 2.11–2.04 (m, 1H), 2.01 (dt, J = 7.0, 1.1 Hz, 2H), 1.99–1.94 (m, 1H), 1.71 (t, J = 1.3 Hz, 4H), 1.62–1.51 (m, 2H), 1.36 (s, 3H), 1.34 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 139.3, 139.0, 122.0, 72.5, 51.3, 39.3, 37.8, 34.1, 31.2, 30.7, 30.5, 26.1, 24.1, 23.3; IR (Neat Film NaCl) 3373, 2965, 2924, 2850, 1455, 1367, 1331, 1259, 1172, 1138, 1083, 1043, 1012, 984, 945, 887, 822 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{15}H_{23}O$ $[(M+H)–H_2]^+$: 219.1749, found 219.1743; $[\alpha]_D^{25.0}$ –33.73 (c 1.83, $CHCl_3$, 88% ee).



223 ***Δ$^{6(10)}$-tormesol (253)***
1:1 d.r. at C11

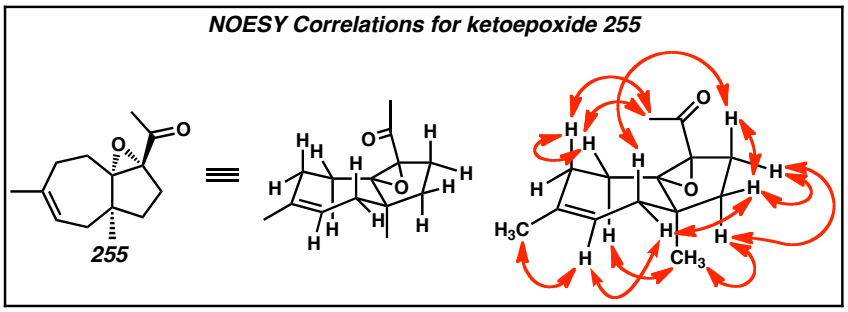
Δ$^{6(10)}$-tormesol (253). A flame-dried 15 mL round-bottom flask equipped with a stir bar was cycled into a glove box where the flask was loaded with anhydrous cerium chloride (91.2 mg, 0.370 mmol, 2.52 equiv). The flask was removed from the glove box, connected to an Ar-filled manifold, placed under full vacuum, and lowered into an oil bath set to 140 °C. After 12 h, the flask was removed from the bath, allowed to cool to room temperature, and charged with THF (1.6 mL). After 3 h of stirring, (4-methylpent-3-en-1-yl)magnesium bromide (0.39 M in THF, 1.13 mL, 0.441 mmol, 3.00 equiv) was added and the slurry turned yellow. After 45 min, enone **223** (30.0 mg, 0.147 mmol, 1.00 equiv) was transferred from a scintillation vial to the round-bottom flask using several THF rinses (1 x 1.5 mL + 3 x 0.5 mL, total added = 4.6 mL, 0.03 M). TLC analysis indicated no starting material remained after 5 min. Consequently, the reaction was quenched with sat. NH_4Cl solution (3 mL) at –78 °C and allowed to warm to room temperature. The reaction contents were transferred to a separatory funnel where the aqueous layer was extracted four times with CH_2Cl_2 and three times with Et_2O. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 28 x 1.5 cm, 5% TBME in hexanes) to afford Δ$^{6(10)}$-tormesol (**253**, 27.1 mg, 0.0941 mmol, 64% yield) as a yellow oil; R_f = 0.75 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) mixture of two diastereomers, see Figure SI-10A; IR (Neat

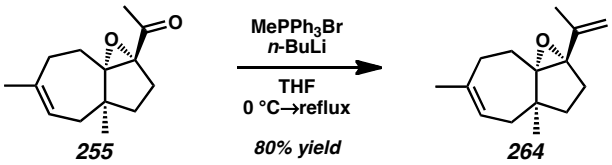
Film NaCl) 3460, 2964, 2925, 2853, 1668, 1645, 1449, 1375, 1330, 1310, 1261, 1238, 1192, 1111, 1063, 1006, 983, 924, 825 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{20}H_{32}O$ $[M+\bullet]^+$: 288.2453, found 288.2451.



Ketoepoxide 255. Procedure adapted from report by Stoltz.[7a] A flame-dried 25 mL round-bottom flask equipped with a stir bar and enone **223** (100.4 mg, 0.491 mmol, 1.00 equiv) was backfilled with Ar and charged with MeOH (3 mL), LiOH (29.5 mg, 1.23 mmol, 2.50 equiv), and H_2O_2 (30% w/w aq, 500 μL, 4.90 mmol, 10.0 equiv). Over the course of the reaction, additional LiOH (29.5 mg at 33 h, 46 h, 73 h and 29.6 mg at 80.5 h, total added = 147.6 mg, 6.15 mmol, 12.5 equiv) and H_2O_2 (500 μL at 33 h, 46 h, 73 h, 80.5 h, total added = 2.5 mL, 24.5 mmol, 50 equiv) were added. After 4 days, no starting material remained by TLC analysis. Consequently, CH_2Cl_2 (10 mL), water (10 mL), and sat. $NaHCO_3$ solution (10 mL) was added. The reaction contents were transferred to a separatory funnel where the aqueous layer was extracted four times with CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 28.5 x 1.5 cm, 100% hexanes→2%→5% TBME in hexanes) to afford ketoepoxide **255** (101.8 mg, 0.462 mmol, 94% yield) as a yellow oil; R_f = 0.70 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 5.31 (ddq, J = 8.7, 5.2, 1.7 Hz, 1H), 2.22 (ddd, J = 13.8, 11.1, 8.2 Hz, 1H), 2.07 (dddd, J = 13.6, 3.8, 1.9, 1.0 Hz, 1H), 2.03–1.93 (m, 1H), 1.97 (s,

3H), 1.77 (tdd, J = 12.8, 2.0, 1.1 Hz, 1H), 1.73 (ddt, J = 13.8, 8.2, 0.9 Hz, 1H), 1.56 (td, J = 1.8, 0.7 Hz, 3H), 1.52 (dddd, J = 14.4, 6.6, 2.0, 1.2 Hz, 1H), 1.47 (dd, J = 14.4, 8.6 Hz, 1H), 1.41 (dddd, J = 12.4, 6.2, 5.5, 0.7 Hz, 1H), 1.37 (ddd, J = 12.4, 11.1, 8.2 Hz, 1H), 1.00 (ddt, J = 12.4, 8.2, 0.8 Hz, 1H), 0.96 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 204.9, 139.9, 122.8, 78.3, 74.7, 44.5, 35.9, 35.8, 29.1, 27.9, 26.8, 26.1, 25.2, 19.4; IR (Neat Film NaCl) 2962, 2930, 2868, 1701, 1446, 1354, 1266, 1178, 1136, 1128, 1079, 1020, 994, 975, 954, 934, 882, 833 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{14}H_{21}O_2$ $[M+H]^+$: 221.1536, found 221.1530; $[\alpha]_D^{25.0}$ –50.64 (c 1.24, $CHCl_3$, 88% ee).

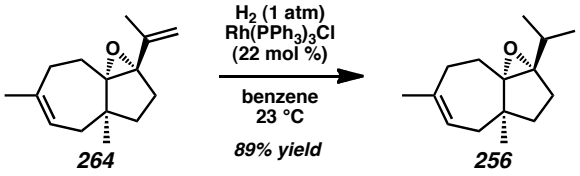




Diene 264. A flame-dried 25 mL round-bottom flask equipped with a stir bar was cycled into a glove box and loaded with methyltriphenylphosphonium bromide (121.1 mg, 0.339 mmol, 1.54 equiv). The flask was removed from the glove box, connected to an Ar-filled manifold, charged with THF (1.4 mL), and lowered into a 0 °C bath (ice/water). *n*-BuLi (2.5 M in hexanes, 110 µL, 0.275 mmol, 1.25 equiv) was added dropwise to the flask, generating a bright yellow solution. After 15 min, ketoepoxide **255** (48.5 mg, 0.220

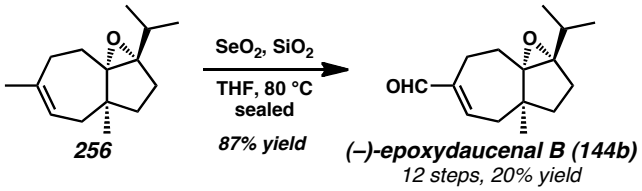
mmol, 1.00 equiv) was transferred via cannula to the flask using several THF rinses (3 x 1 mL, total added = 4.4 mL, 0.05 M) and the bath was allowed to warm to room temperature over time. After 1 h, significant starting material persisted by TLC analysis. Consequently, an additional solution (15 min prestir at 0 °C) of methyltriphenylphosphonium bromide (353.5 mg, 0.990 mmol, 4.50 equiv) and *n*-BuLi (2.5 M in hexanes, 330 μL, 0.275 mmol, 1.25 equiv) in THF (2 mL) was prepared and cannula transferred to the 25 mL flask. After 17 h, starting material was still present by TLC analysis, so a water condenser was attached to the flask and the reaction was heated to reflux. After 45 h, starting material was still observed by TLC analysis. Consequently, another solution (15 min prestir at 0 °C) of methyltriphenylphosphonium bromide (356.7 mg, 0.999 mmol, 4.53 equiv) and *n*-BuLi (2.5 M in hexanes, 330 μL, 0.275 mmol, 1.25 equiv) in THF (2 mL) was prepared and cannula transferred to the 25 mL flask. The solvent level decreased over time and more THF (2 mL at 47 h and 65 h) was added when appropriate. After 4 days, no starting material was observed by TLC analysis. Consequently, the reaction was quenched with H_2O (5 mL) and transferred to a separatory funnel where the aqueous layer was extracted four times with Et_2O. The combined organics (75 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 26.5 x 1.5 cm, 100% hexanes→2%→10% TBME in hexanes) to afford diene **264** (38.5 mg, 0.176 mmol, 80% yield) as a yellow oil; R_f = 0.76 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.47 (ddp, J = 8.6, 5.1, 1.6 Hz, 1H), 4.98 (q, J = 1.2 Hz, 2H), 2.14 (dddt, J = 14.2, 4.5, 1.8, 0.9 Hz, 1H), 2.06 (ddd, J = 13.7, 10.8, 8.3 Hz, 1H), 2.00 (br t, J = 13.8 Hz, 1H), 1.87 (t, J = 1.2 Hz, 3H), 1.87–1.83

(m, 1H), 1.82 (ddt, J = 13.8, 8.3, 1.0 Hz, 1H), 1.80–1.72 (m, 1H), 1.76 (td, J = 1.8, 0.6 Hz, 3H), 1.67 (dddd, J = 14.0, 13.0, 2.1, 1.1 Hz, 1H), 1.41 (ddd, J = 12.7, 10.8, 8.3 Hz, 1H), 1.39 (dddd, J = 13.7, 6.5, 1.9, 0.6 Hz, 1H), 1.23 (dd, J = 12.4, 8.2 Hz, 1H), 0.99 (d, J = 0.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.4, 139.9, 123.0, 112.9, 78.6, 74.1, 43.9, 36.2, 36.1, 29.9, 28.4, 25.4, 24.6, 20.8, 19.7; IR (Neat Film NaCl) 2962, 2929, 2868, 2851, 1646, 1444, 1373, 960, 903, 831 cm^{-1}; HRMS (GC-EI+) *m/z* calc'd for $C_{15}H_{22}O$ $[M+\bullet]^+$: 218.1671, found 218.1672; $[\alpha]_D^{25.0}$ –55.99 (c 1.11, $CHCl_3$, 88% ee).



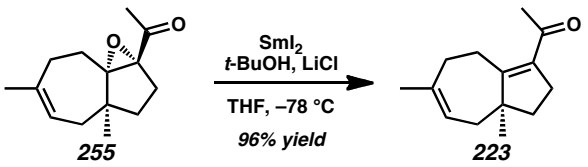
Epoxide 256. A flame-dried 10 mL round-bottom flask equipped with a stir bar was cycled into a glove box and loaded with Wilkinson's catalyst (13.1 mg, 0.0142 mmol, 15.0 mol %). The flask was removed from the glove box, connected to an Ar-filled manifold, and charged with benzene (30 min Ar sparge before use, 0.15 mL). Diene **264** (20.6 mg, 0.0944 mmol, 1.00 equiv) was transferred to the flask via a cannula using several benzene rinses (3 x 1 mL, total added = 3.15 mL, 0.03 M). The reaction was disconnected from the manifold, connected to a hydrogen balloon, and flushed with hydrogen, generating an orange solution. After 4 h, no starting material was observed by TLC, so the stir bar was removed and rinsed with CH_2Cl_2, and the reaction was concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 24.5 x 1.5 cm, 100% hexanes→1% TBME in hexanes) to afford an oil that contained both epoxide **256** and residual starting

material (~10%). The reaction was set up again following the above procedure (Wilkinson's catalyst: 6.3 mg, 0.00681 mmol, 7 mol %; benzene: 3.15 mL, 0.03 M). After 3 h, a reaction aliquot was removed and ^{1}H NMR analysis revealed no starting material. Consequently, the stir bar was removed and rinsed with CH_2Cl_2, and the reaction was concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 27 x 1.5 cm, 100% hexanes→1% TBME in hexanes) to afford epoxide **256** (18.4 mg, 0.0835 mmol, 89% yield) as a yellow oil; R_f = 0.69 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.46 (ddq, J = 8.7, 5.3, 1.7 Hz, 1H), 2.17 (ttt, J = 13.3, 1.8, 0.8 Hz, 1H), 2.08 (dd, J = 14.7, 4.5 Hz, 1H), 1.94 (dddd, J = 14.4, 6.6, 1.9, 1.3 Hz, 1H), 1.82–1.74 (m, 1H), 1.77 (td, J = 1.8, 0.7 Hz, 3H), 1.76–1.66 (m, 4H), 1.43 (ddd, J = 14.1, 6.6, 1.9 Hz, 1H), 1.31 (ddd, J = 12.5, 10.5, 8.6 Hz, 1H), 1.15 (ddd, J = 12.3, 8.0, 1.0 Hz, 1H), 1.07 (d, J = 6.9 Hz, 6H), 0.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.6, 123.2, 77.5, 76.3, 44.1, 36.2, 35.4, 30.1, 28.6, 25.5, 25.4, 22.9, 19.7, 19.5, 19.0; IR (Neat Film NaCl) 2961, 2930, 2869, 1709, 1454, 1368, 1022, 964, 828 cm^{-1}; HRMS (GC-EI+) *m/z* calc'd for $C_{15}H_{24}O$ $[M+\bullet]^+$: 220.1827, found 220.1820; $[\alpha]_D^{25.0}$ –50.57 (c 1.25, $CHCl_3$, 88% ee).

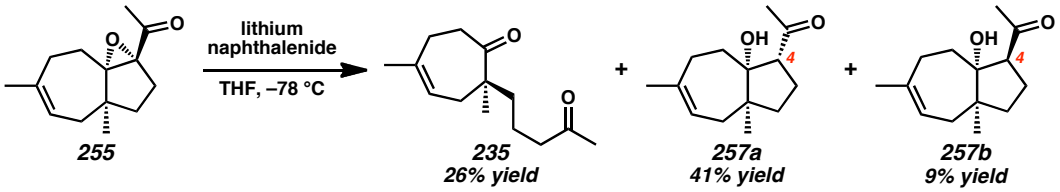


(–)-Epoxydaucenal B (144b). Adapted from a procedure by Wood.[40] A 20 mL scintillation vial equipped with a stir bar and epoxide **256** (10.8 mg, 0.0490 mmol, 1.00 equiv) was connected to an Ar-filled manifold and flushed with Ar. The vial was charged

with THF (5.13 mL) and premixed selenium dioxide (10.9 mg, 0.0982 mmol, 2.00 equiv) and silica gel (117.8 mg, 1.96 mmol, 40.0 equiv). The vial was rinsed with THF (1 mL, total added = 6.13 mL, 0.008 M), sealed with a teflon cap, and lowered into a preheated sand bath (80 °C). After 30 min, starting material persisted by TLC analysis, so the vial was resealed and lowered back into the sand bath. After an additional 15 min, no starting material remained by TLC analysis. Consequently, the reaction was filtered through a short celite pad rinsing with Et_2O and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 26 x 1.5 cm, 100% hexanes$\rightarrow$2%$\rightarrow$5%$\rightarrow$10% TBME in hexanes) to afford epoxydaucenal B (**144b**, 10.0 mg, 0.0427 mmol, 87% yield) as a yellow oil; R_f = 0.58 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 9.22 (s, 1H), 6.03 (dddd, J = 8.7, 5.1, 2.2, 1.2 Hz, 1H), 3.11–3.03 (m, 1H), 1.85 (ddtd, J = 14.0, 5.1, 1.5, 0.8 Hz, 1H), 1.69–1.60 (m, 1H), 1.62–1.52 (m, 3H), 1.51 (sept, J = 7.0 Hz, 1H), 1.44–1.40 (m, 1H), 1.41–1.33 (m, 2H), 1.03 (d, J = 6.8 Hz, 3H), 0.96–0.86 (m, 1H), 0.83 (s, 3H), 0.77 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 191.9, 152.5, 146.3, 75.7, 75.1, 44.3, 37.1, 35.7, 28.5, 25.4, 22.9, 20.1, 19.8, 19.6, 19.0; IR (Neat Film NaCl) 2961, 2931, 2869, 1687, 1683, 1644, 1455, 1444, 1378, 1229, 1149, 1023, 1003, 965, 876 cm^{-1}; HRMS (GC-EI+) *m/z* calc'd for $C_{15}H_{22}O_2$ $[M+\bullet]^+$: 234.1620, found 234.1630; $[\alpha]_D^{25.0}$ –20.52 (c 1.00, $CHCl_3$, 88% ee).



Enone 223. A flame-dried 10 mL round-bottom flask equipped with a stir bar was cycled into a glove box where the flask was loaded with lithium chloride (77.0 mg, 1.82 mmol, 8.59 equiv). The flask was removed from the glove box and connected to an Ar-filled manifold. Epoxide **255** (46.6 mg, 0.212 mmol, 1.00 equiv) was transferred to the flask using several THF rinses (60 min Ar sparge before use, 1 x 0.6 mL + 3 x 0.5 mL, total added = 2.1 mL, 0.1 M), *t*-BuOH (20 μL, 0.209 mmol, 0.99 equiv) was added, and the flask was lowered into a –78 °C bath (dry ice/acetone). A samarium diiodide solution[51] (0.1 M in THF, 4.5 mL, 0.450 mmol, 2.13 equiv) was added dropwise over 5 min down the side of the flask, generating a dark blue solution. TLC analysis indicated that no starting material remained after 8 min. Consequently, the reaction was quenched with sat. NH_4Cl solution (2 mL), allowed to warm to room temperature, and transferred to a separatory funnel where the aqueous layer was extracted four times with Et_2O. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 26 x 1.5 cm, 100% hexanes→5%→10%→15%→30%→50% TBME in hexanes) to afford enone **223** (41.5 mg, 0.203 mmol, 96% yield) as a yellow oil. (For characterization data, see p. 745).

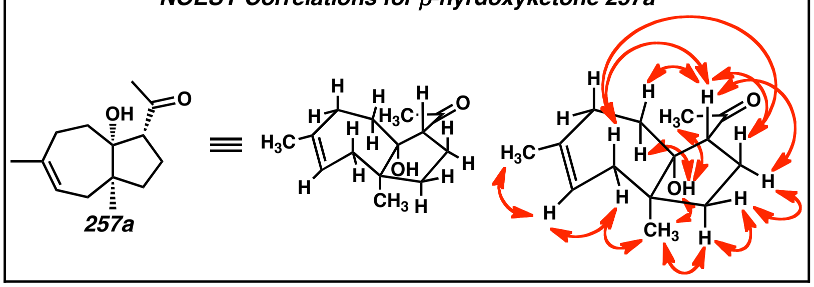


β-hydroxyketone 257a and b. Procedure adapted from report by Liu.[49] A flame-dried 15 mL round-bottom flask equipped with a glass stir bar and ketoepoxide **255** (50.2 mg, 0.228 mmol, 1.00 equiv) was charged with THF (2.3 mL, 0.1 M) and lowered into a –78 °C bath (acetone/dry ice). A lithium naphthalenide solution[50] (1.0 M, 680 μL, 0.680 mmol, 2.98 equiv) was added dropwise and the reaction mixture turned dark green. Over the course of the reaction, an additional portion of lithium naphthalenide was added (680 μL at 1.5 h, 3 h, 4.5 h, total added = 2.72 mL, 2.72 mmol, 11.9 equiv). After 9 h, the reaction was quenched with H_2O and allowed to warm to room temperature. The reaction was transferred to a separatory funnel where the aqueous layer was extracted six times with CH_2Cl_2. The combined organics (50 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 28 x 1.5 cm, 100% hexanes→2%→5%→10%→20%→40% TBME in hexanes) to afford dione **235** (13.1 mg, 0.0588 mmol, 26% yield), β-hydroxyketone **257a** (20.7 mg, 0.0933 mmol, 41% yield) as a yellow oil, and β-hydroxyketone **257b** (4.6 mg, 0.0206 mmol, 9% yield) as a yellow oil. (For characterization data of dione **235**, see p. 746).

β-hydroxyketone 257a. R_f = 0.57 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 5.34 (ddt, J = 8.5, 4.5, 1.5 Hz, 1H), 3.95 (s, 1H), 2.77 (dd, J = 10.2, 9.1 Hz, 1H), 2.00

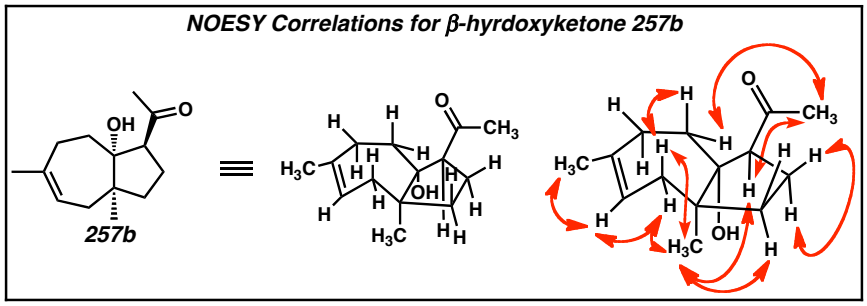
(dddd, J = 12.2, 3.4, 1.7, 0.9 Hz, 1H), 1.96 (dt, J = 8.6, 1.6 Hz, 1H), 1.90 (ddd, J = 12.3, 10.1, 5.1 Hz, 1H), 1.87–1.74 (m, 3H), 1.69 (ddd, J = 14.4, 10.7, 1.9 Hz, 1H), 1.68 (s, 3H), 1.63 (t, J = 1.7 Hz, 3H), 1.53 (ddd, J = 17.5, 12.4, 5.1 Hz, 1H), 1.57–1.47 (m, 1H), 1.24–1.15 (m, 1H), 1.19 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 212.8, 139.5, 122.6, 84.1, 56.3, 48.7, 40.4, 38.3, 34.2, 31.0, 29.4, 25.4, 25.3, 20.5; IR (Neat Film NaCl) 3479, 2959, 2925, 2853, 1694, 1446, 1394, 1362, 1307, 1260, 1243, 1175, 1105, 1077, 1051, 1010, 832 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{14}H_{23}O_2$ [M+H]$^+$: 223.1693, found 223.1692; $[\alpha]_D^{25.0}$ –193.24 (c 0.57, $CHCl_3$, 88% ee).

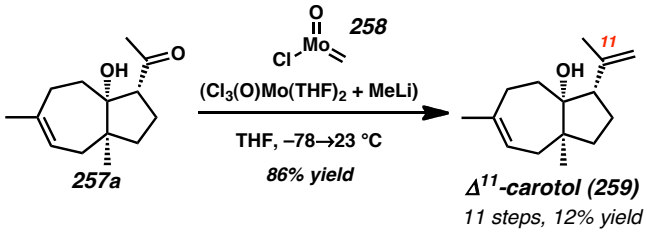
NOESY Correlations for β-hyrdoxyketone 257a



β-hydroxyketone 257b. R_f = 0.36 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 5.21 (dddd, J = 8.6, 6.4, 3.2, 1.6 Hz, 1H), 2.83 (t, J = 9.6 Hz, 1H), 2.24 (br t, J = 14.2 Hz, 1H), 2.18 (dddd, J = 13.7, 10.5, 9.7, 5.4 Hz, 1H), 2.04 (dd, J = 15.1, 6.4 Hz, 1H), 1.98 (s, 3H), 1.85 (dd, J = 15.0, 7.4 Hz, 1H), 1.69–1.57 (m, 4H), 1.53 (dt, J = 1.7, 0.8 Hz, 3H), 1.45 (dtd, J = 13.7, 9.4, 6.1 Hz, 1H), 1.26 (ddd, J = 14.9, 6.5, 2.6 Hz, 1H), 1.15 (ddd, J = 13.0, 9.3, 5.4 Hz, 1H), 0.87 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 208.2, 140.4, 122.2, 84.2, 62.7, 47.5, 35.6, 34.2, 31.5, 31.1, 28.1, 25.2, 24.8, 20.6; IR (Neat Film NaCl) 3501, 2962, 2927, 2874, 1694, 1457, 1363, 1213, 1069, 1027, 833, 819 cm^{-1}; HRMS (EI+) *m/z*

calc'd for $C_{14}H_{22}O_2$ $[M+\bullet]^+$: 222.1620, found 222.1623; $[\alpha]_D^{25.0}$ 67.43 (c 0.46, $CHCl_3$, 88% ee).

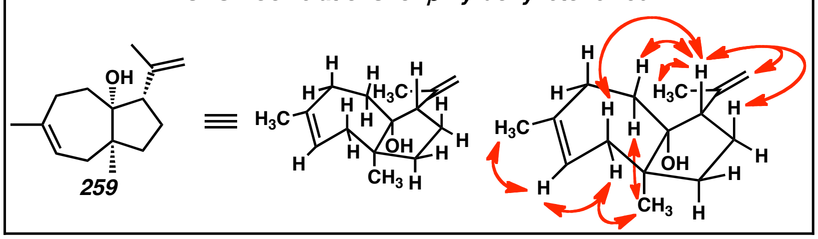




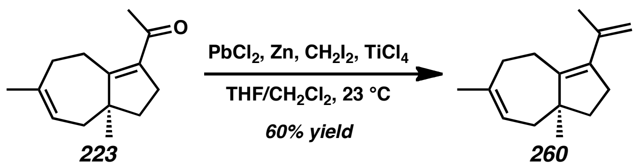
Δ^{11}-carotol (259). A flame-dried 25 mL round-bottom flask equipped with a stir bar was cycled into a glove box, loaded with oxotrischlorobis(tetrahydrofuran)molybdenum(V)[42] (139.0 mg, 0.383 mmol, 4.11 equiv), removed from the glove box, and connected to an Ar-filled manifold. The flask was charged with THF (2 mL) and lowered into a –78 °C bath (dry ice/acetone). Methyllithium (1.58 M in Et_2O, 240 µL, 0.379 mmol, 4.06 equiv) was added dropwise to the flask causing the reaction mixture to transition from a bright green solution to a dark red/purple solution. After 1 h, β-hydroxyketone **257a** (20.7 mg, 0.0933 mmol, 1.00 equiv) was transferred to the flask via cannula using several THF rinses (2 x 1.5 mL + 1 mL, total added = 6 mL), and the bath was allowed to expire over time. After 29 h, starting material persisted by TLC analysis. Consequently, an additional solution (1 h prestir at –78 °C) of oxotrischlorobis(tetrahydrofuran)-

molybdenum(V) (138.7 mg, 0.383 mmol, 4.10 equiv) and methyllithium (1.58 M in Et_2O, 240 μL, 0.275 mmol, 1.25 equiv) in THF (1 mL) was prepared and transferred via cannula to the 25 mL flask at –78 °C. The bath was once again allowed to expire over time. As starting material was still observed by TLC analysis after 40 h and 53 h, two additional solutions (*vide supra*) were prepared at –78 °C and transferred via cannula to the 25 mL flask at these times ($Cl_3(O)Mo(THF)_2$ total added = 556.1 mg, 1.52 mmol, 16.4 equiv; MeLi total added = 0.96 mL, 1.52 mmol, 16.3 equiv; THF total added = 9 mL). After 65 h, starting material was completely consumed by TLC analysis. The reaction was subsequently quenched with water (5 mL) and transferred to a separatory funnel where the aqueous layer was extracted four times with Et_2O. The combined organics (50 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 25.5 x 1.5 cm, 100% hexanes→2% TBME in hexanes) to afford Δ^{11}-carotol (**259**, 17.6 mg, 0.0799 mmol, 86% yield) as a yellow oil; R_f = 0.75 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.32 (ddp, J = 8.8, 4.5, 1.5 Hz, 1H), 5.04 (p, J = 1.5 Hz, 1H), 4.86 (dq, J = 1.7, 0.9 Hz, 1H), 2.77 (dd, J = 11.0, 7.7 Hz, 1H), 2.32 (ddd, J = 15.7, 4.3, 2.1 Hz, 1H), 2.18–2.01 (m, 2H), 1.84 (dd, J = 1.5, 0.8 Hz, 3H), 1.87–1.75 (m, 2H), 1.76–1.62 (m, 3H), 1.69 (t, J = 1.7 Hz, 3H), 1.51 (ddd, J = 14.2, 9.1, 2.5 Hz, 1H), 1.47 (br s, 1H), 1.35 (dd, J = 12.3, 8.0 Hz, 1H), 1.01 (d, J = 0.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.8, 139.0, 122.2, 113.3, 83.2, 53.4, 48.3, 40.4, 39.3, 34.6, 29.5, 26.8, 25.4, 25.2, 21.9; IR (Neat Film NaCl) 3545, 3069, 2963, 2924, 2867, 1636, 1448, 1374, 1006, 898, 825 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{15}H_{24}O$ $[M+\bullet]^+$: 220.1827, found 220.1834; $[\alpha]_D^{25.0}$ 17.49 (c 1.05, $CHCl_3$, 88% ee).

NOESY Correlations for β-hyrdoxyketone 259

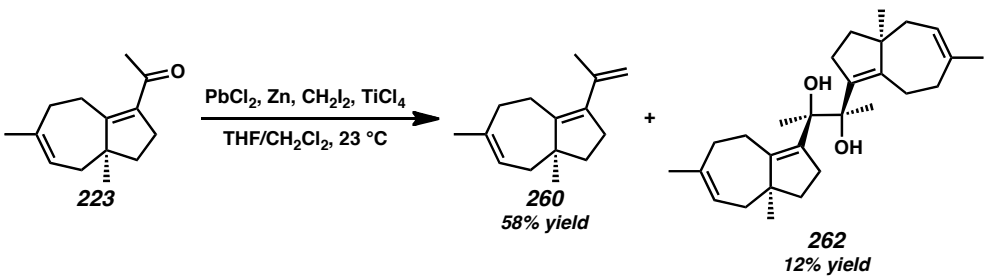


3.5.2.6 Synthesis of (–)-Daucene (142), (+)-Daucenal (143), and (+)-14-p-Anisoyloxydauc-4,8-diene (145)



Triene 260. A flame-dried two-neck 25 mL round-bottom flask equipped with a stir bar and water condenser was loaded with lead(II) chloride (20.6 mg, 0.0740 mmol, 0.16 equiv) and zinc dust (437.5 mg, 6.69 mmol, 14.4 equiv) and backfilled with argon. The flask was charged with THF (6.5 mL) and diiodomethane (300 μL, 3.72 mmol, 8.02 equiv) and lowered into a preheated oil bath (70 °C). After 15 min, the bath was removed, the reaction was cooled to room temperature over 15 min and then lowered into a 0 °C bath (ice/water). Premixed titanium(IV) chloride (100 μL, 0.912 mmol, 1.96 equiv) and CH_2Cl_2 (830 μL) were added quickly, the bath was removed, and the reaction was allowed to warm to room temperature. After 1 h, enone **223** (94.9 mg, 0.464 mmol, 1.00 equiv) was transferred to the flask via cannula using several THF rinses (3 x 1 mL, total added = 9.5 mL, 0.05 M). No starting material remained after 1.5 h by TLC analysis, so the reaction was quenched with a sat. $NaHCO_3$ solution (10 mL) and filtered

through a celite plug into a separatory funnel rinsing with Et_2O. The aqueous layer was extracted four times with Et_2O. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 28 x 1.5 cm, 100% hexanes) to afford triene **260** (56.5 mg, 0.279 mmol, 60% yield) as a pale yellow oil; R_f = 0.73 (0.3% Et_2O in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43 (ddp, J = 7.4, 5.9, 1.5 Hz, 1H), 4.90 (dq, J = 2.9, 1.5 Hz, 1H), 4.71 (dq, J = 2.5, 0.8 Hz, 1H), 2.65 (ddd, J = 13.8, 5.1, 3.6 Hz, 1H), 2.40 (dtd, J = 15.2, 8.3, 2.9 Hz, 1H), 2.29 (dddd, J = 15.4, 7.4, 4.7, 1.3 Hz, 1H), 2.11–2.04 (m, 3H), 2.01 (dd, J = 13.9, 7.6 Hz, 1H), 1.92 (ddddd, J = 16.7, 10.6, 4.7, 2.9, 1.4 Hz, 1H), 1.85 (dd, J = 1.5, 0.8 Hz, 3H), 1.74 (t, J = 1.5 Hz, 3H), 1.64–1.60 (m, 2H), 0.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.4, 142.6, 139.9, 135.2, 122.4, 112.8, 50.5, 40.1, 38.4, 33.7, 32.6, 26.1, 23.7, 23.6, 22.8; IR (Neat Film NaCl) 3078, 2962, 2924, 2846, 1627, 1443, 1368, 891, 829 cm^{-1}; HRMS (GC-EI+) *m/z* calc'd for $C_{15}H_{22}$ $[M+\bullet]^+$: 202.1721, found 202.1703; $[\alpha]_D^{25.0}$ –76.62 (c 0.94, $CHCl_3$, 88% ee).



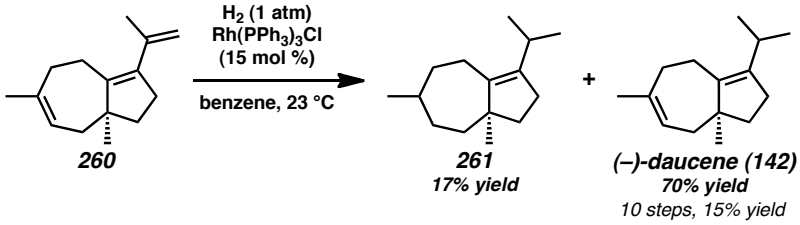
Triene 260 and Diol 262. A flame-dried two-neck 50 mL round-bottom flask equipped with a stir bar and water condenser was loaded with lead(II) chloride (30.9 mg, 0.111 mmol, 0.16 equiv) and zinc dust (640.0 mg, 9.79 mmol, 14.4 equiv) and backfilled with argon. The flask was charged with THF (10 mL) and diiodomethane (440 µL, 5.46

mmol, 8.04 equiv) and lowered into a preheated oil bath (80 °C). After 20 min, the bath was removed, the reaction was cooled to room temperature over 10 min, and then lowered into a 0 °C bath (ice/water). Premixed titanium(IV) chloride (150 μL, 1.37 mmol, 2.01 equiv) and dichloromethane (1.22 mL) were added quickly, the bath was removed, and the reaction was allowed to warm to room temperature. After 50 min, enone **223** (138.9 mg, 0.680 mmol, 1.00 equiv) was transferred to the flask via cannula using several THF rinses (1 x 1.6 mL + 2 x 1 mL, total added = 13.6 mL, 0.05 M). TLC analysis indicated no starting material remained after 1.5 h. Consequently, the reaction was quenched with a sat. aq $NaHCO_3$ (13 mL) and filtered through a celite plug into a separatory funnel rinsing with Et_2O. The aqueous layer was extracted four times with Et_2O. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 29 x 1.5 cm, 100% hexanes) to afford triene **260** (79.9 mg, 0.395 mmol, 58% yield) as a pale yellow oil, diol **262** (15.3 mg, 0.03735 mmol, 12% yield) as a white solid, and several other polar organics.

Triene 260. For characterization data, see p. 768.

Diol 262. R_f = 0.57 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.42 (ddt, J = 7.5, 4.5, 1.3 Hz, 2H), 3.30–3.20 (m, 2H), 2.36 (dddd, J = 15.6, 10.5, 7.5, 3.1 Hz, 2H), 2.17–2.00 (m, 12H), 1.98 (dd, J = 14.3, 7.5 Hz, 2H), 1.73 (t, J = 1.3 Hz, 6H), 1.52 (ddd, J = 12.0, 7.5, 1.7 Hz, 2H), 1.46 (ddd, J = 12.1, 10.3, 8.4 Hz, 2H), 1.40 (s, 6H), 0.93 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.1, 140.4, 135.7, 122.2, 80.2, 50.1, 40.0, 38.4, 33.2,

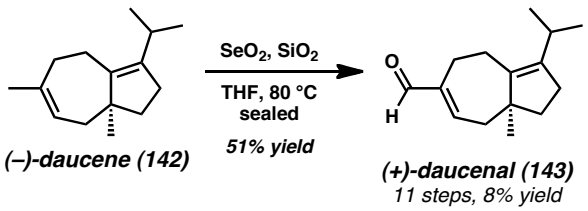
31.9, 25.5, 25.5, 24.1, 23.1; IR (Neat Film NaCl) 3339, 2965, 2942, 2924, 2849, 1439, 1368, 1184, 1097, 1057, 977, 914, 828 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{28}H_{41}O$ $[M–OH]^+$: 393.3152, found 393.3029; $[\alpha]_D^{25.0}$ –58.15 (c 1.53, $CHCl_3$, 88% ee).



(–)-Daucene (142). A flame-dried 25 mL round-bottom flask equipped with a stir bar was cycled into a glove box and loaded with Wilkinson's catalyst (48.0 mg, 0.0519 mmol, 15.0 mol %). The flask was removed from the glove box, connected to an Ar-filled manifold, and charged with benzene (30 min Ar sparge before use, 3 mL). Triene **260** (70.0 mg, 0.346 mmol, 1.00 equiv) was transferred to the flask via cannula using several benzene rinses (1 x 2.5 mL + 3 x 2 mL, total added = 11.5 mL, 0.03 M). The flask was disconnected from the manifold, connected to a hydrogen balloon, and flushed with hydrogen, generating an orange solution. After 8 h, minimal starting material remained by TLC, so the stir bar was removed and rinsed with CH_2Cl_2 and the reaction was concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was loaded onto a silica gel column[52] using hexanes and minimal CH_2Cl_2 and purified by flash column chromatography (SiO_2, 27.5 x 2 cm, 100% hexanes) to afford alkene **261** (11.9 mg, 0.0576 mmol, 17% yield) as a clear colorless oil and daucene (**142**, 49.5 mg, 0.242 mmol, 70% yield) as a clear colorless oil.

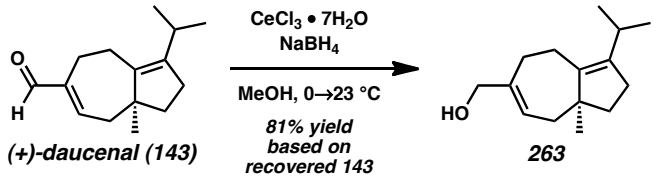
Alkene 261. R_f = 0.92 (0.3% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) mixture of two diastereomers, see Figure SI-19A; IR (Neat Film NaCl) 2955, 2923, 2856, 1457, 1379, 1369, 1360 cm^{-1}; HRMS (GC-EI+) *m/z* calc'd for $C_{15}H_{26}$ $[M+\bullet]^+$: 206.2034, found 206.2040.

(–)-Daucene (142). R_f = 0.84 (0.3% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 5.42 (ddt, J = 9.2, 5.6, 1.5 Hz, 1H), 2.66 (sept, J = 6.8 Hz, 1H), 2.44–2.36 (m, 1H), 2.17 (ddt, J = 8.7, 6.7, 2.2 Hz, 2H), 2.08–2.03 (m, 1H), 2.05–1.99 (m, 2H), 1.94 (dd, J = 14.1, 7.8 Hz, 1H), 1.86–1.78 (m, 1H), 1.74 (t, J = 1.6 Hz, 3H), 1.62–1.48 (m, 2H), 0.98 (d, J = 6.9 Hz, 3H), 0.92 (d, J = 6.9 Hz, 3H), 0.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.0, 139.9, 138.8, 122.8, 49.7, 40.5, 38.7, 33.7, 27.3, 26.6, 26.1, 23.7, 22.7, 22.0, 21.4; IR (Neat Film NaCl) 2959, 2932, 2845, 1444, 1366, 1330, 1303, 1202, 828 cm^{-1}; HRMS (GC-EI+) *m/z* calc'd for $C_{15}H_{24}$ $[M+\bullet]^+$: 204.1878, found 204.1878; $[\alpha]_D^{25.0}$ –24.95 (c 1.37, $CHCl_3$, 86% ee).



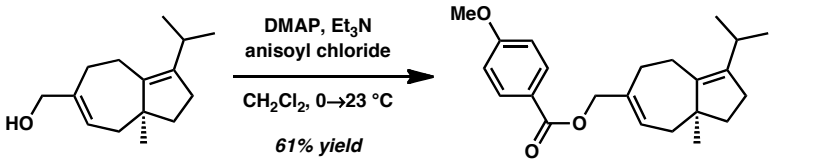
(+)-Daucenal (143). Adapted from a procedure by Wood.[40] A 20 mL scintillation vial equipped with a stir bar and daucene (**142**, 9.6 mg, 0.047 mmol, 1.00 equiv) was connected to an Ar-filled manifold and flushed with Ar. The vial was charged with THF (4.87 mL) and premixed selenium dioxide (10.4 mg, 0.0937 mmol, 2.00 equiv) and silica gel (113.9 mg, 1.896 mmol, 40.4 equiv). The vial was sealed with a teflon cap and

lowered into a preheated sand bath (80 °C). After 20 min, starting material persisted by TLC analysis, so the vial was resealed and lowered back into the sand bath. After an additional 10 min, no starting material remained by TLC analysis. Consequently, the reaction was filtered through a short celite pad rinsing with Et_2O and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 27.5 x 1.5 cm, 100% hexanes→5%→10%→ 20% TBME in hexanes) to afford daucenal (**143**, 5.2 mg, 0.0238 mmol, 51% yield) as a yellow oil; R_f = 0.77 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.26 (d, J = 1.1 Hz, 1H), 6.10 (dddd, J = 8.4, 5.2, 2.0, 1.1 Hz, 1H), 3.05 (ddd, J = 15.2, 5.4, 2.7 Hz, 1H), 2.51 (sept, J = 6.7 Hz, 1H), 2.33 (ddd, J = 14.1, 5.5, 3.1 Hz, 1H), 2.13 (ddd, J = 8.5, 5.1, 1.9 Hz, 2H), 2.05 (dd, J = 14.3, 5.2 Hz, 1H), 1.94 (ddd, J = 14.3, 8.2, 1.1 Hz, 1H), 1.76 (br tdd, J = 14.2, 3.4, 1.6 Hz, 1H), 1.62 (br ddt, J = 14.5, 10.1, 2.4 Hz, 1H), 1.55 (dtd, J = 12.6, 6.8, 1.2 Hz, 1H), 1.47 (dtd, J = 12.4, 7.7, 1.1 Hz, 1H), 0.90 (dd, J = 6.9, 1.1 Hz, 3H), 0.88 (dd, J = 6.9, 1.1 Hz, 3H), 0.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.0, 152.8, 146.8, 141.0, 140.3, 49.8, 41.7, 39.2, 27.4, 26.7, 24.2, 24.0, 22.4, 21.9, 21.3; IR (Neat Film NaCl) 2956, 2930, 2863, 1685, 1636, 1453, 1378, 1245, 1144, 929 cm^{-1}; HRMS (GC-EI+) *m/z* calc'd for $C_{15}H_{22}O$ $[M+\bullet]^+$: 218.1671, found 218.1680; $[\alpha]_D^{25.0}$ 33.65 (c 0.50, $CHCl_3$, 86% ee).



Allylic Alcohol 263. A 20 mL scintillation vial equipped with a stir bar and daucenal (**143**, 10.2 mg, 0.0467 mmol, 1.00 equiv) was connected to an Ar-filled manifold and flushed with Ar. The vial was charged with MeOH (930 μL) and cerium chloride heptahydrate (20.9 mg, 0.0561 mmol, 1.20 equiv). After 10 min of stirring, the cerium chloride heptahydrate had dissolved, generating a yellow solution. The vial was subsequently lowered into a 0 °C bath (ice/water) and sodium borohydride (4.1 mg, 0.108 mmol, 2.32 equiv) was added. The bath was allowed to expire over time. Additional sodium borohydride (35 min = 11.9 mg, 2 h 25 min = 12.3 mg, 6 h = 12.9 mg, 8 h = 50.2 mg; total added = 91.5 mg, 2.42 mmol, 51.8 equiv) and cerium chloride heptahydrate (8 h = 22.7 mg; total added = 43.6 mg, 0.117 mmol, 2.51 equiv) were added. After 20 h, the reaction was quenched with a sat. NH_4Cl solution (5 mL) and transferred to a separatory funnel where the aqueous layer was extracted four times with Et_2O. The combined organics were rinsed with 5% w/w HCl (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 29 x 1.5 cm, 100% hexanes→5%→10%→20% TBME in hexanes) to afford recovered daucenal (**143**, 3.4 mg, 0.0156 mmol, 33% recovered) and alcohol **263** (5.6 mg, 0.0253 mmol, 54% yield, 81% yield based on recovered **143**) as a yellow oil; R_f = 0.42 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70 (ddtd, J = 8.0, 5.2, 2.0, 0.9 Hz, 1H), 4.03 (t, J = 1.5 Hz, 2H), 2.68 (sept, J = 6.8 Hz, 1H), 2.48 (ddd, J = 13.9, 5.7, 2.9 Hz, 1H), 2.22–2.16 (m,

4H), 2.14 (dd, J = 14.1, 5.3 Hz, 1H), 2.04 (dd, J = 14.1, 8.0 Hz, 1H), 2.05–1.95 (m, 1H), 1.86–1.77 (m, 1H), 1.62 (dt, J = 12.3, 6.2 Hz, 1H), 1.55 (dt, J = 12.3, 8.2 Hz, 1H), 0.98 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2, 141.6, 139.4, 124.7, 68.9, 49.4, 40.4, 38.8, 29.6, 27.3, 26.6, 23.8, 23.2, 22.0, 21.3; IR (Neat Film NaCl) 3325, 2957, 2930, 2859, 1710, 1455, 1380, 1367, 1360, 1261, 1055, 997, 841, 803 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{15}H_{24}O$ $[M+\bullet]^+$: 220.1827, found 220.1830; $[\alpha]_D^{25.0}$ –13.28 (c 0.56, $CHCl_3$, 86% ee).



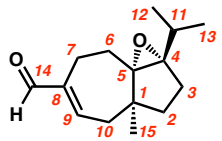
263 ***(+)-14-p-anisoyloxydauc-4,8-diene (145)***
13 steps, 4% yield

14-*p*-Anisoyloxydauc-4,8-diene (145). A scintillation vial equipped with allylic alcohol **263** (5.6 mg, 0.0253 mmol, 1.00 equiv), a stir bar, and a Teflon cap was flushed with Ar and connected to an Ar-filled manifold. The vial was charged with CH_2Cl_2 (2 mL, 0.01 M) and lowered into a 0 °C bath (ice/water). DMAP (0.5 mg, 0.0041 mmol, 16 mol %), Et_3N (10 μL, 0.072 mmol, 2.8 equiv), and *p*-anisoyl chloride (10 μL, 0.074 mmol, 2.9 equiv) were added to the vial and the bath was allowed to expire over time. TLC analysis indicated starting material remained after 4 h, so additional Et_3N (10 μL, total added = 20 μL, 0.14 mmol, 5.7 equiv) and *p*-anisoyl chloride (10 μL, total added = 20 μL, 0.15 mmol, 5.8 equiv) were added. TLC analysis indicated no residual starting material after 18 h, so the reaction was loaded directly onto a column, and the crude material was purified by flash column chromatography (SiO_2, 28.5 x 2 cm, 100% hexanes→2% TBME

in hexanes) to afford 14-p-anisoyloxydauc-4,8-diene (**145**, 5.5 mg, 0.0155 mmol, 61% yield) as a yellow oil that solidified upon freezing; R_f = 0.70 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (dm, J = 8.9 Hz, 2H), 6.92 (dm, J = 8.9 Hz, 2H), 5.85 (ddp, J = 7.3, 5.0, 1.1 Hz, 1H), 4.70 (d, J = 1.1 Hz, 2H), 3.86 (s, 3H), 2.67 (sept, J = 6.9 Hz, 1H), 2.49 (ddd, J = 13.9, 5.7, 2.8 Hz, 1H), 2.25 (ddd, J = 14.6, 5.8, 2.8 Hz, 1H), 2.19 (ddd, J = 8.2, 6.0, 2.2 Hz, 2H), 2.20–2.14 (m, 1H), 2.07 (dd, J = 14.1, 8.1 Hz, 1H), 2.07 (tm, J = 13.5 Hz, 1H), 1.88 (dddd, J = 14.6, 12.3, 5.0, 2.5 Hz, 1H), 1.64 (dt, J = 12.3, 6.1 Hz, 1H), 1.56 (dt, J = 12.4, 8.3 Hz, 1H), 0.98 (d, J = 6.9 Hz, 3H), 0.95 (s, 3H), 0.93 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 163.4, 141.5, 139.5, 138.6, 131.8, 128.4, 123.0, 113.7, 70.3, 55.6, 49.4, 40.5, 38.8, 29.9, 27.3, 26.6, 23.8, 23.0, 22.0, 21.3; IR (Neat Film NaCl) 2956, 2928, 2854, 1716, 1607, 1582, 1456, 1421, 1368, 1315, 1271, 1256, 1167, 1100, 1032, 846, 770 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{23}H_{30}O_3$ $[M+\bullet]^+$: 354.2195, found 354.2193; $[\alpha]_D^{25.0}$ 2.27 (c 0.55, $CHCl_3$, 86% ee).

3.5.3 Comparison of Data for Synthetic and Reported Natural Products

Spectral data for synthetic (–)-epoxydaucenal B (**144b**), (–)-daucene (**142**), (+)-daucenal (**143**), and (+)-14-*p*-anisoyloxydauc-4,8-diene (**145**) (^{1}H NMR, ^{13}C NMR, $[\alpha]_D^T$) were compared with available reported spectral data for either natural or synthetic samples. Tables comparing compound data are shown in Tables 3.2–3.9.

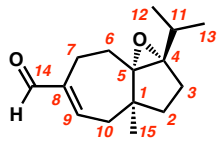


(–)-epoxydaucenal B (144b)

*Table 3.2. Comparison of ^{1}H NMR data for synthetic and natural epoxydaucenal B (**144b**).[a–b]*

Assignment	Synthetic 144b (ppm)[c]	Multiplicity, *J* (Hz)	Natural[13] 144b (ppm)[d]	Multiplicity, *J* (Hz)
C1	—	—	—	—
C2	1.41–1.33	m		
	0.96–0.86	m		
C3	1.69–1.60	m		
	1.41–1.33	m		
C4	—	—	—	—
C5	—	—	—	—
C6	1.62–1.52	m		
	1.44–1.40	m		
C7	3.11–3.03	m	3.068	m
	1.62–1.52	m		
C8	—	—	—	—
C9	6.03	dddd, 8.7, 5.1, 2.2, 1.2	6.028	m
C10	1.85	ddtd, 14.0, 5.1, 1.5, 0.8	1.840	dd, 14.1, 5.0
	1.62–1.52	m		
C11	1.51	sept, 7.0	1.522	sept, 6.9
C12	1.03	d, 6.8	1.028	d, 6.9
C13	0.77	d, 7.0	0.763	d, 6.9
C14	9.22	s	9.211	s
C15	0.83	s	0.828	s

[a] See Figure 5.16.1 for ^{1}H NMR spectra. [b] Blank spaces in table represent neglected or unreported signals. [c] ^{1}H NMR spectra was obtained at 500 MHz in C_6D_6 and standardized to residual C_6H_6. [d] ^{1}H NMR spectra was obtained at 500 MHz in C_6D_6 and standardized to TMS.

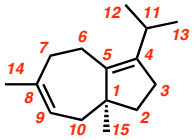


(–)-epoxydaucenal B (144b)

*Table 3.3. Comparison of ^{13}C NMR data for synthetic and natural epoxydaucenal B (**144b**).*[a]

Assignment	**Synthetic 144b** (ppm)[b]	**Natural**[13] **144b** (ppm)[c]
C1	44.3	44.2
C2	35.7	35.7
C3	22.9	22.8[d]
C4	75.1	75.0
C5	75.7	75.7
C6	25.4	25.4[d]
C7	20.1	20.1
C8	146.3	146.3
C9	152.5	152.3
C10	37.1	37.1
C11	28.5	28.5
C12	19.0	18.9[e]
C13	19.6	19.5[e]
C14	191.9	191.8
C15	19.8	19.7

[a] See Figure 5.16.3 for ^{13}C NMR spectra. [b] ^{13}C NMR spectra was obtained at 125 MHz in C_6D_6 and standardized to residual C_6H_6. [c] ^{13}C NMR spectra was obtained at 125 MHz in C_6D_6 and standardized to TMS. [d] C(3) and C(6) were misassigned, see HSQC spectra, Figure SI-14D. [e] C(12) and C(13) were misassigned, see HSQC spectra, Figure 5.16.4.

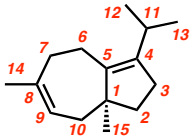


(–)-daucene (142)

*Table 3.4, Part 1. Comparison of ^{1}H NMR Data for synthetic and reported[53] daucene (**142**).[a–b]*

Assignment	**Synthetic 142** (ppm)[b]	**Multiplicity, *J*** (Hz)	**Little[27] 142** (ppm)[d]	**Multiplicity, *J*** (Hz)	**Seto[25] 142** (ppm)[e]	**Multiplicity, *J*** (Hz)
C1	—	—	—	—	—	—
C2	1.59	ddd, 11.9, 6.7, 5.1	1.65–1.48[f]	m		
	1.52	dt, 12.2, 8.5				
C3	2.17	ddt, 8.7, 6.7, 2.2	2.21–2.12	m		
C4	—	—	—	—	—	—
C5	—	—	—	—	—	—
C6	2.44–2.36	m	2.39	m		
	1.86–1.78	m	1.81	m		
C7	2.05–1.99	m	2.05–1.90	m		
C8	—	—	—	—	—	—
C9	5.42	ddt, 9.2, 5.6, 1.5	5.42	m	5.43	br t, 6.6
C10	2.08–2.03	m	2.05–1.90	m		
	1.94	dd, 14.1, 7.8				
C11	2.66	sept, 6.8	2.66	sept, 6.75	2.67	sept, 6.8
C12	0.98	d, 6.9	0.98	d, 6.75	0.98	d, 6.8
C13	0.92	d, 6.9	0.93	d, 6.75	0.92	d, 6.8
C14	1.74	t, 1.6	1.74	s	1.74	br s
C15	0.91	s	0.91	s	0.91	s

[a] See Figure 5.22.1 for ^{1}H NMR spectra. [b] Blank spaces in table represent neglected or unreported signals. [c] ^{1}H NMR spectra was obtained at 500 MHz in $CDCl_3$ and standardized to residual $CHCl_3$. [d] ^{1}H NMR spectra was obtained at 400 MHz in $CDCl_3$ and standardized to residual $CHCl_3$. [e] ^{1}H NMR was obtained in $CDCl_3$ at unknown MHz. [f] Little reports this signal as 3H, however HSQC data indicates only 2H for this range (see Figure 5.22.4).

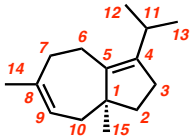


(–)-daucene (142)

*Table 3.4, Part 2. Comparison of ^{1}H NMR Data for synthetic and reported[53] daucene (**2**).[a–b]*

Assignment	Synthetic **142** (ppm)[b]	Multiplicity, ***J*** (Hz)	Yamasaki[22] **142** (ppm)[e]	Multiplicity, ***J*** (Hz)	Naegeli[21] **142** (ppm)[e]	Multiplicity, ***J*** (Hz)
C1	—	—	—	—	—	—
C2	1.59	ddd, 11.9, 6.7, 5.1				
	1.52	dt, 12.2, 8.5				
C3	2.17	ddt, 8.7, 6.7, 2.2				
C4	—	—	—	—	—	—
C5	—	—	—	—	—	—
C6	2.44–2.36	m				
	1.86–1.78	m				
C7	2.05–1.99	m				
C8	—	—	—	—	—	—
C9	5.42	ddt, 9.2, 5.6, 1.5	5.37	t, 5	5.44	t, 6.5
C10	2.08–2.03	m				
	1.94	dd, 14.1, 7.8				
C11	2.66	sept, 6.8				
C12	0.98	d, 6.9	0.99	d, 5	1.00	d, 6.5
C13	0.92	d, 6.9	0.92	d, 5	0.92	d, 6.5
C14	1.74	t, 1.6	1.73	s	1.75	br s
C15	0.91	s	0.94	s	0.91	s

[a] See Figure 5.22.1 for ^{1}H NMR spectra. [b] Blank spaces in table represent neglected or unreported signals. [c] ^{1}H NMR spectra was obtained at 500 MHz in $CDCl_3$ and standardized to residual $CHCl_3$. [d] ^{1}H NMR spectra was obtained at 400 MHz in $CDCl_3$ and standardized to residual $CHCl_3$. [e] ^{1}H NMR was obtained in $CDCl_3$ at unknown MHz.

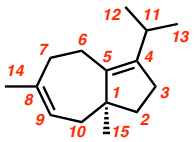


(–)-daucene (142)

*Table 3.5. Comparison of ^{13}C NMR data for synthetic and reported daucene (**142**).*[a]

Assignment	**Synthetic 142** (ppm)[b]	**Little[27] 142** (ppm)[c]	**Seto[25] 142** (ppm)[d]
C1	49.7	49.7	49.7
C2	38.7	38.7	38.7
C3	27.3	27.3	27.3
C4	138.8	138.9	138.8
C5	142.0	142.1	142.0
C6	22.7	22.7	22.6
C7	33.7	33.7	33.6
C8	139.9	140.0	139.7
C9	122.8	122.9	122.8
C10	40.5	40.6	40.5
C11	26.6	26.6	26.5
C12	22.0	22.1	21.9
C13	21.4	21.4	21.2
C14	26.1	26.2	25.9
C15	23.7	23.7	23.6

[a] See Figure 5.22.3 for ^{13}C NMR spectra. [b] ^{13}C NMR spectra was obtained at 125 MHz in $CDCl_3$ and standardized to residual $CHCl_3$. [c] ^{13}C NMR spectra was obtained at 100 MHz in $CDCl_3$ and standardized to residual $CHCl_3$. [d] ^{13}C NMR was obtained in $CDCl_3$ at unknown MHz

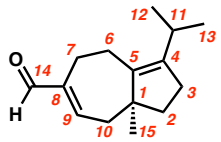


(–)-daucene (142)

*Table 3.6. Comparison of optical rotation data for synthetic and reported daucene (**142**).*[a]

Synthetic 142	**(+)-Natural[11a] 142**	**Yamasaki[22] 142**	**Mehta[23] 142**
$[\alpha]_D^{25} = -24.95$ (c 1.37, $CHCl_3$, 86% ee)	$[\alpha]_D^{25} = +23.32$ (c unspecified)	$[\alpha]_D^{25} = -21.5$ (c 0.8, EtOH)	$[\alpha]_D^{25} = -20$ (c 1.00)

[a] Daucene has been isolated from a number of sources.[11] Both (+)-[11] and (–)-daucene[11b–c] have been isolated from nature, however the optical rotation has only been determined for natural (+)-daucene. Yamasaki and Mehta, though, have reported rotations for synthetic (–)-daucene.

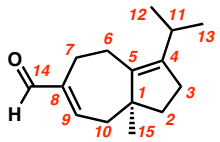


(+)-daucenal (143)

*Table 3.7. Comparison of ^{1}H NMR data for synthetic and natural daucenal (**143**).*[a]

Assignment	**Synthetic 143** (ppm)[b]	**Multiplicity, *J*** (Hz)	**Natural**[13] **143** (ppm)[c]	**Multiplicity, *J*** (Hz)
C1	—	—	—	—
C2	1.55	dtd, 12.6, 6.8, 1.2	1.550	dd, 12.4, 7.4
	1.47	dtd,12.4, 7.7, 1.1	1.471	dd, 12.4, 7.4
C3	2.13	ddd, 8.5, 5.1, 1.9	2.125	br ddd, 7.7, 7.4, 2.9
C4	—	—	—	—
C5	—	—	—	—
C6	2.33	ddd, 14.1, 5.5, 3.1	2.330	ddd, 14.0, 5.4, 3.0
	1.62	br ddt, 14.5, 10.1, 2.4	1.616	br ddd, 14.5, 14.0, 2.9
C7	3.06	ddd, 15.2, 5.4, 2.7	3.049	ddd, 14.9, 15.4, 2.9
	1.76	br tdd, 14.2, 3.4, 1.6	1.763	br dddd, 14.9, 14.5, 3.0, 2.0
C8	—	—	—	—
C9	6.10	dddd, 8.4, 5.2, 2.0, 1.1	6.101	ddd, 8.2, 5.2, 2.0
C10	2.05	dd, 14.3, 5.2	2.053	br dd, 14.3, 5.2
	1.94	ddd, 14.3, 8.2, 1.1	1.935	dd, 14.3, 8.2
C11	2.51	sept, 6.7	2.512	sept, 6.9
C12	0.90	dd, 6.9, 1.1	0.897	d, 6.9
C13	0.88	dd, 6.9, 1.1	0.869	d, 6.9
C14	9.26	d, 1.1	9.263	s
C15	0.81	s	0.811	s

[a] See Figure 5.24.1 for ^{1}H NMR spectra. [b] ^{1}H NMR spectra was obtained at 500 MHz in C_6D_6 and standardized to residual C_6H_6. [c] ^{1}H NMR spectra was obtained at 500 MHz in C_6D_6 and standardized to TMS.

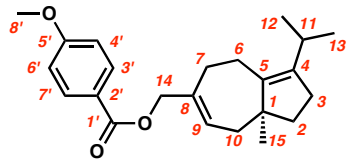


(+)-daucenal (143)

*Table 3.8. Comparison of ^{13}C NMR data for synthetic and natural daucenal (**143**).*[a]

Assignment	**Synthetic 143** (ppm)[b]	**Natural[13] 143** (ppm)[c]
C1	49.8	49.8
C2	39.2	41.7[d]
C3	27.4	27.4
C4	140.3	141.0
C5	141.0	146.7[e]
C6	22.4	24.0
C7	24.0	22.4
C8	146.8	140.2[e]
C9	152.8	152.8
C10	41.7	39.2[d]
C11	26.7	26.7
C12	21.9	21.7
C13	21.3	21.2
C14	193.0	193.0
C15	24.2	24.2

[a] See Figure 5.24.3 for ^{13}C NMR spectra. [b] ^{13}C NMR spectra was obtained at 125 MHz in C_6D_6 and standardized to residual C_6H_6. [c] ^{13}C NMR spectra was obtained at 125 MHz in C_6D_6 and standardized to TMS. [d] C2 and C10 were misassigned, see 2D NMR spectra, Figures 5.24.4–6. [e] C5 and C8 were misassigned, see 2D NMR spectra, Figures 5.24.4–6.



(+)-14-p-anisoyloxydauc-4,8-diene (145)

*Table 3.9. Comparison of ^{1}H NMR data for synthetic and natural[15,1a] 14-p-anisoyloxydauc-4,8-diene (**145**).[a–b]*

Assignment	Synthetic **145** (ppm)[c]	Multiplicity, ***J*** (Hz)	Natural[15] **145** (ppm)[d]	Multiplicity, ***J*** (Hz)
C1	—	—	—	—
C2	1.64	dt, 12.3, 6.1		
	1.56	dt, 12.4, 8.3		
C3	2.19	ddd, 8.2, 6.0, 2.2		
C4	—	—	—	—
C5	—	—	—	—
C6	2.49	ddd, 13.9, 5.7, 2.8		
	1.88	dddd, 14.6, 12.3, 5.0, 2.5		
C7	2.25	ddd, 14.6, 5.8, 2.8		
	2.07	tm, 13.5		
C8	—	—	—	—
C9	5.85	ddp, 7.3, 5.0, 1.1	5.86	br t, 6.5
C10	2.20–2.14	m		
	2.07	dd, 14.1, 8.1		
C11	2.67	sept, 6.9	2.69	sept
C12	0.98	d, 6.9	0.98	d, 7.2
C13	0.93	d, 6.8	0.93	d, 7.2
C14	4.70	d, 1.1	4.70	br s
C15	0.95	s	0.95	s
C1'	—	—	—	—
C2'	—	—	—	—
C3'/ C7'	6.92	dm, 8.9	6.93	d, 9.1
C4'/C6’	8.01	dm, 8.9	8.01	d, 9.1
C5'	—	—	—	—
C8'	3.86	s	3.86	s

[a] See Figure 5.26.1 for ^{1}H NMR spectra. [b] Blank spaces in table represent neglected or unreported signals. [c] ^{1}H NMR spectra was obtained at 500 MHz in $CDCl_3$ and standardized to residual $CDCl_3$. [d] ^{1}H NMR spectra was obtained at 200 MHz in $CDCl_3$ and standardized to TMS.

3.6 NOTES AND REFERENCES

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(51) Example procedure for the preparation of a samarium diiodide solution: A flame-dried 50 mL Schlenk tube equipped with a stir bar was connected to an Ar-filled manifold, loaded with samarium metal (311.3 mg, 2.07 mmol, 1.45 equiv), and backfilled with Ar three times. The flask was charged with THF (1 h Ar sparge before use, 14.3 mL, 0.1 M) and lowered into a 0 °C bath (ice/water). 1,2-Diiodoethane was added in two portions (203.0 mg and 30 min = 200.2 mg, total added = 403.2 mg, 1.43 mmol, 1.00 equiv), the ice bath was removed, and the reaction was allowed to warm to room temperature. After 1 h of vigorous stirring, the reaction had developed into a dark blue solution and was administered as a 0.1 M solution.

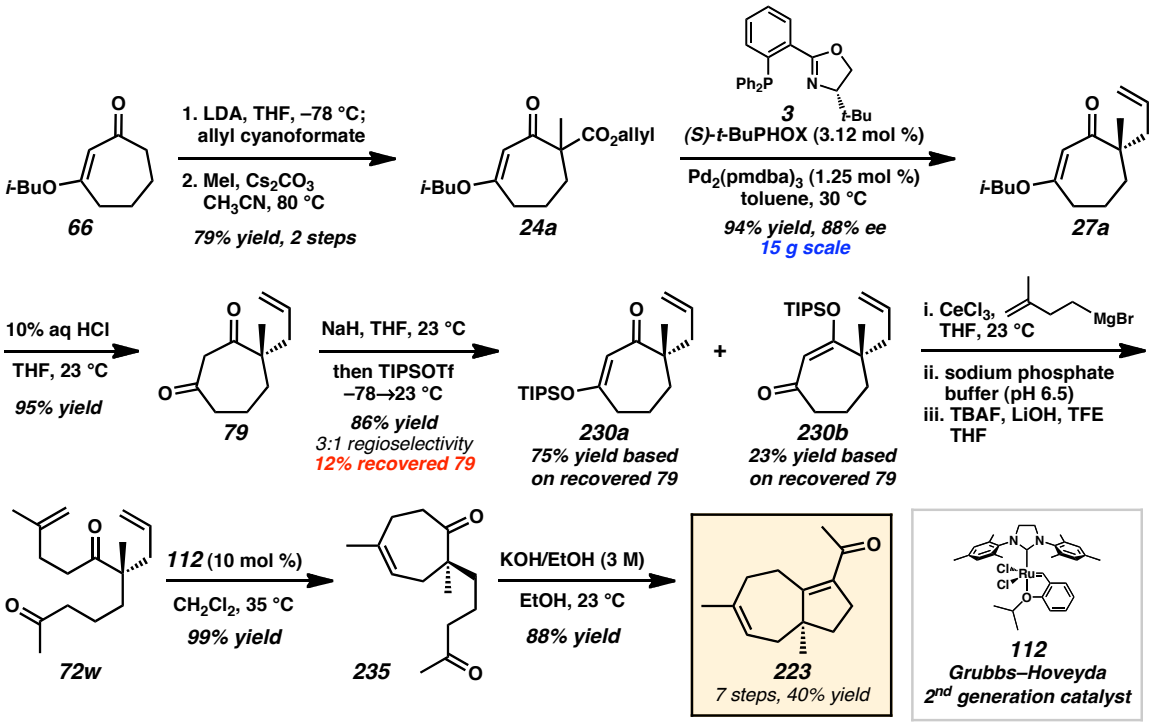
(52) Use of benzene to load the crude oil onto the column prohibits clean separation of the nonpolar products (i.e., alkene **261** and daucene (**142**)).

(53) Mehta also reports several ^{1}H NMR signals for daucene, but neglects to include J values for most signals (Ref. 23). Mehta indicates that they compared data with an authentic sample provided by the Seto group (Ref. 25). Consequently, Mehta's data has been neglected from the table.

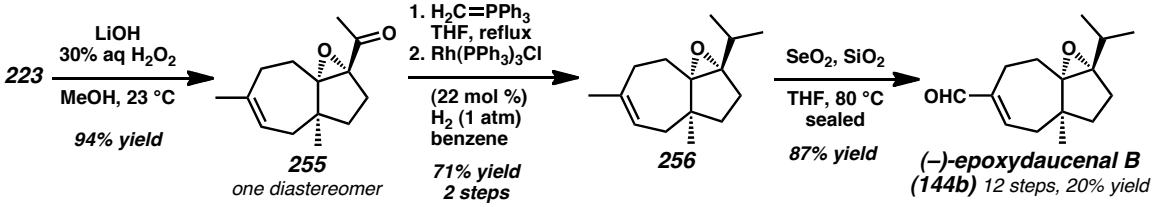
APPENDIX 4

Synthetic Summary for Daucane Natural Products

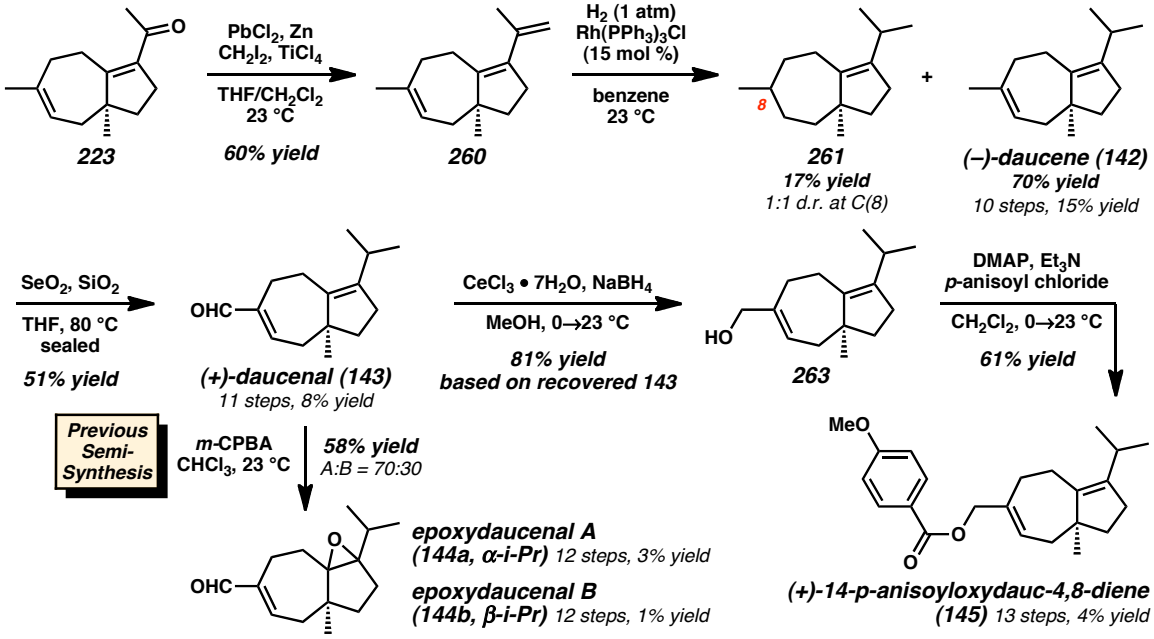
Scheme A4.1. Route to key intermediate enone ***223***.



*Scheme A4.2. Synthesis of (–)-epoxydaucenal B (****144b****).*



*Scheme A4.3. Synthesis of (–)-daucene (**142**), (+)-daucenal (**143**), and (+)-14-p-anisoyloxydauc-4,8-diene (**145**) and formal syntheses of epoxydaucenal A and B (**144a** and **144b**).*



APPENDIX 5

Spectra Relevant to Chapter 3:

Unified Approach to Daucane and Sphenolobane

Bicyclo[5.3.0]decane core: Enantioselective Synthesis of

Four Daucane Sesquiterpenes and Related Molecules

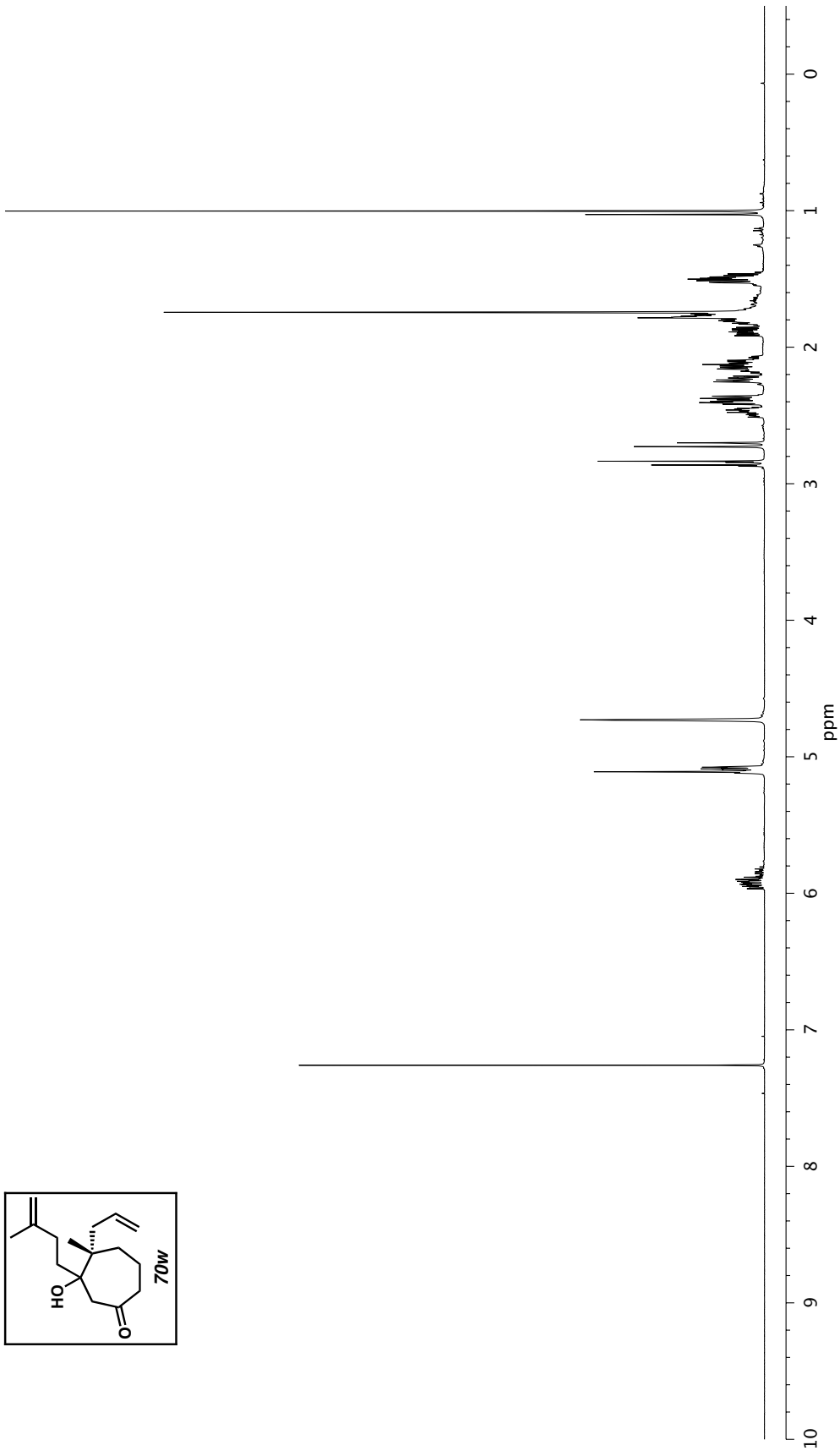


Figure A5.1.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **70w**.

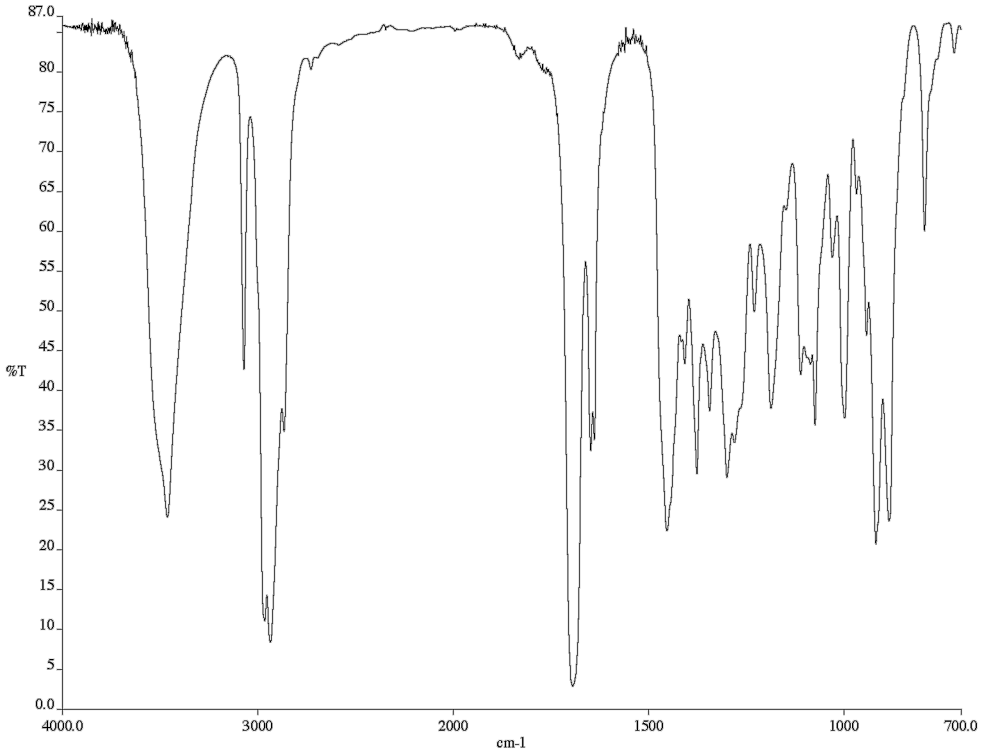


Figure A5.1.2. Infrared spectrum (thin film/NaCl) of compound **70w**.

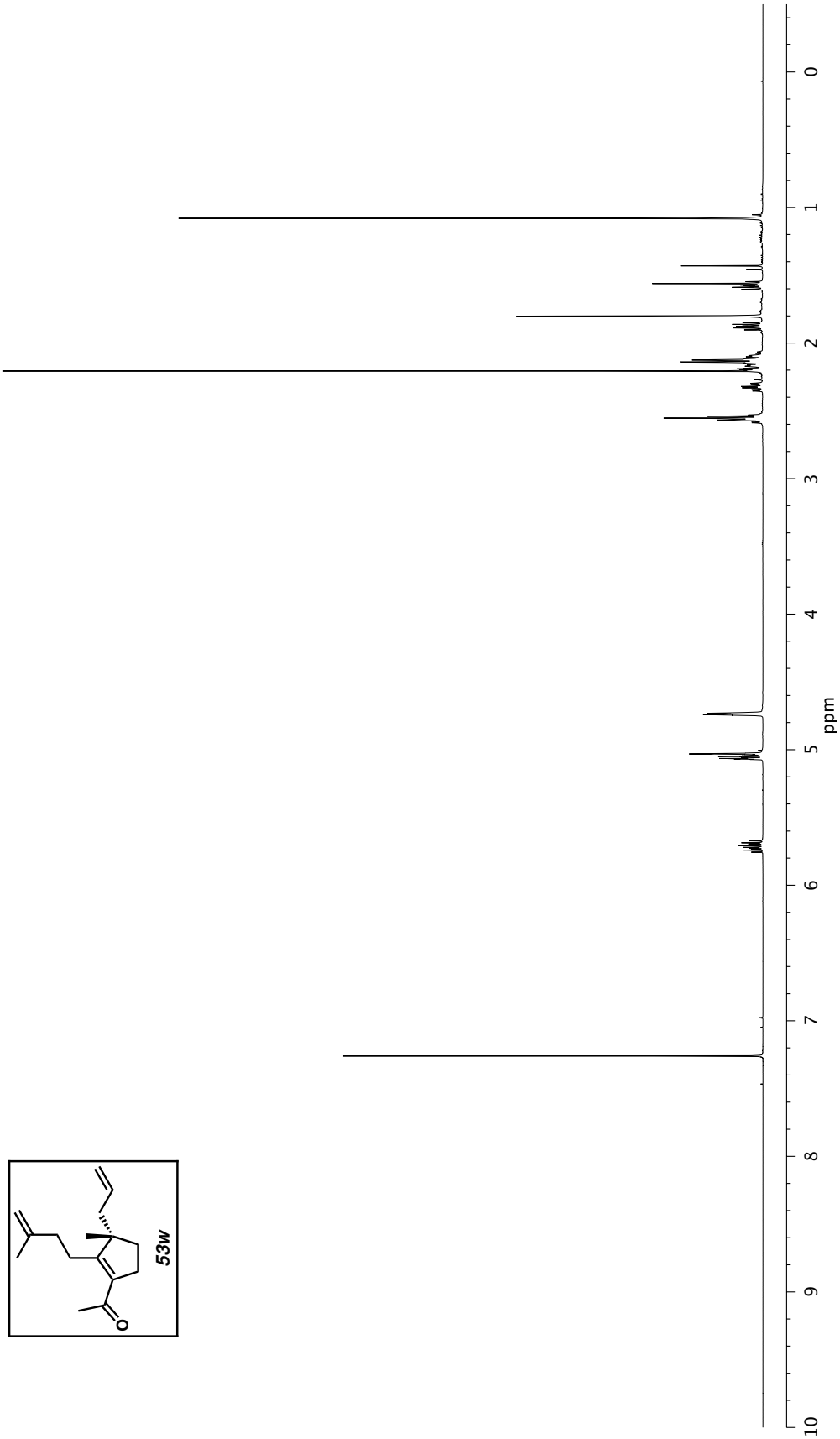


Figure A5.2.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **53w**.

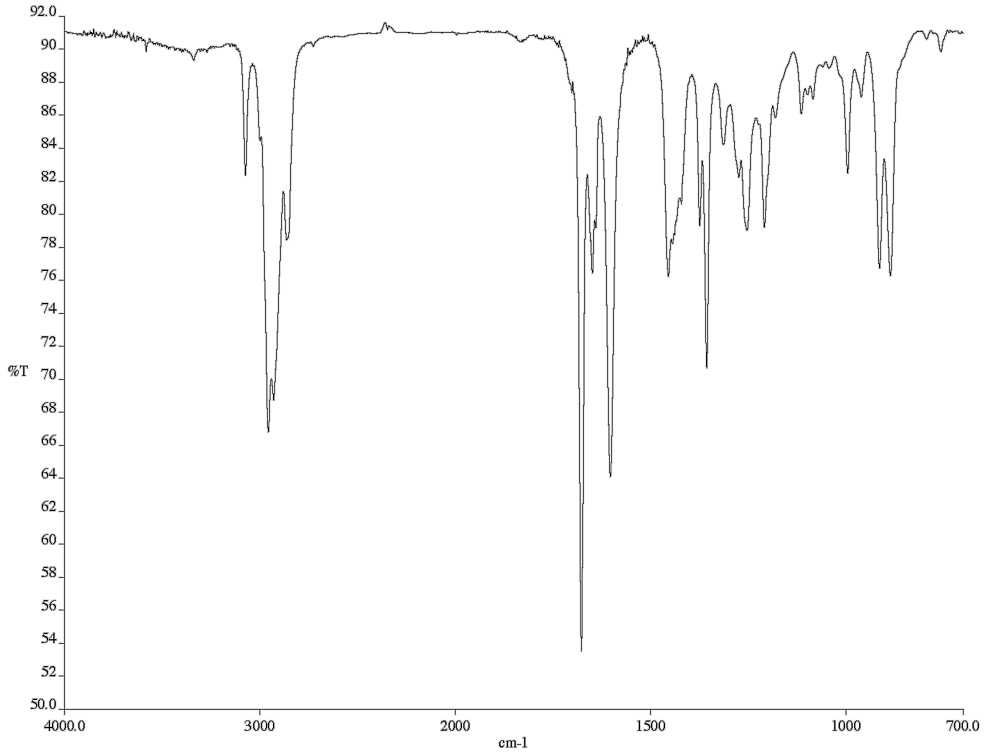


Figure A5.2.2. Infrared spectrum (thin film/NaCl) of compound **53w**.

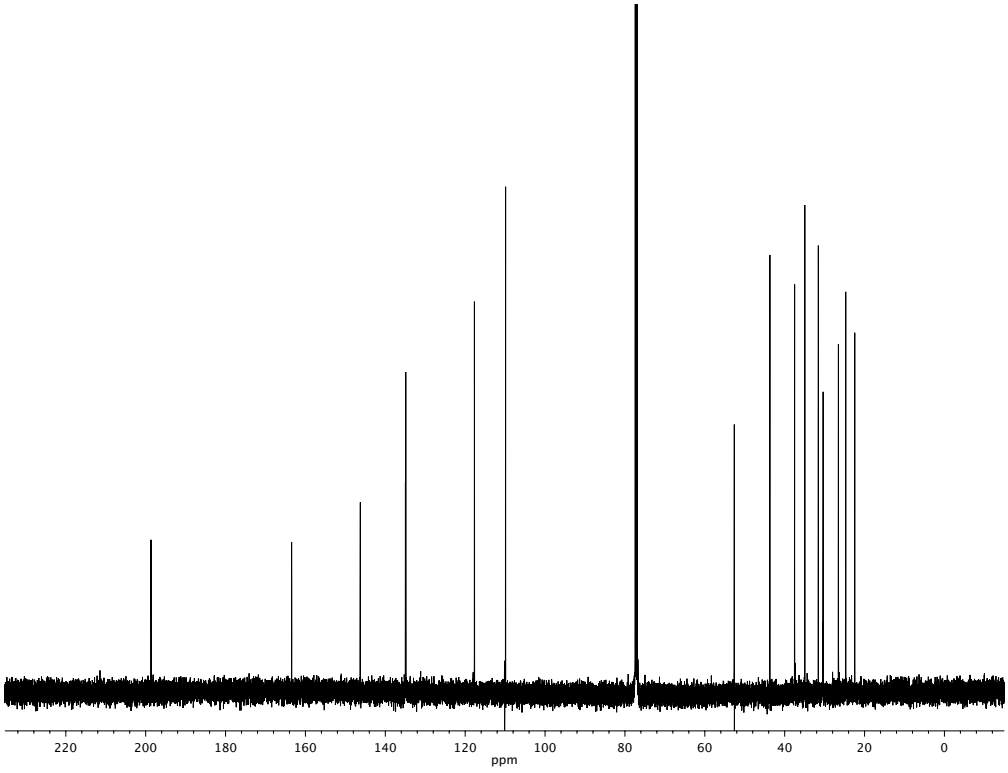


Figure A5.2.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **53w**.

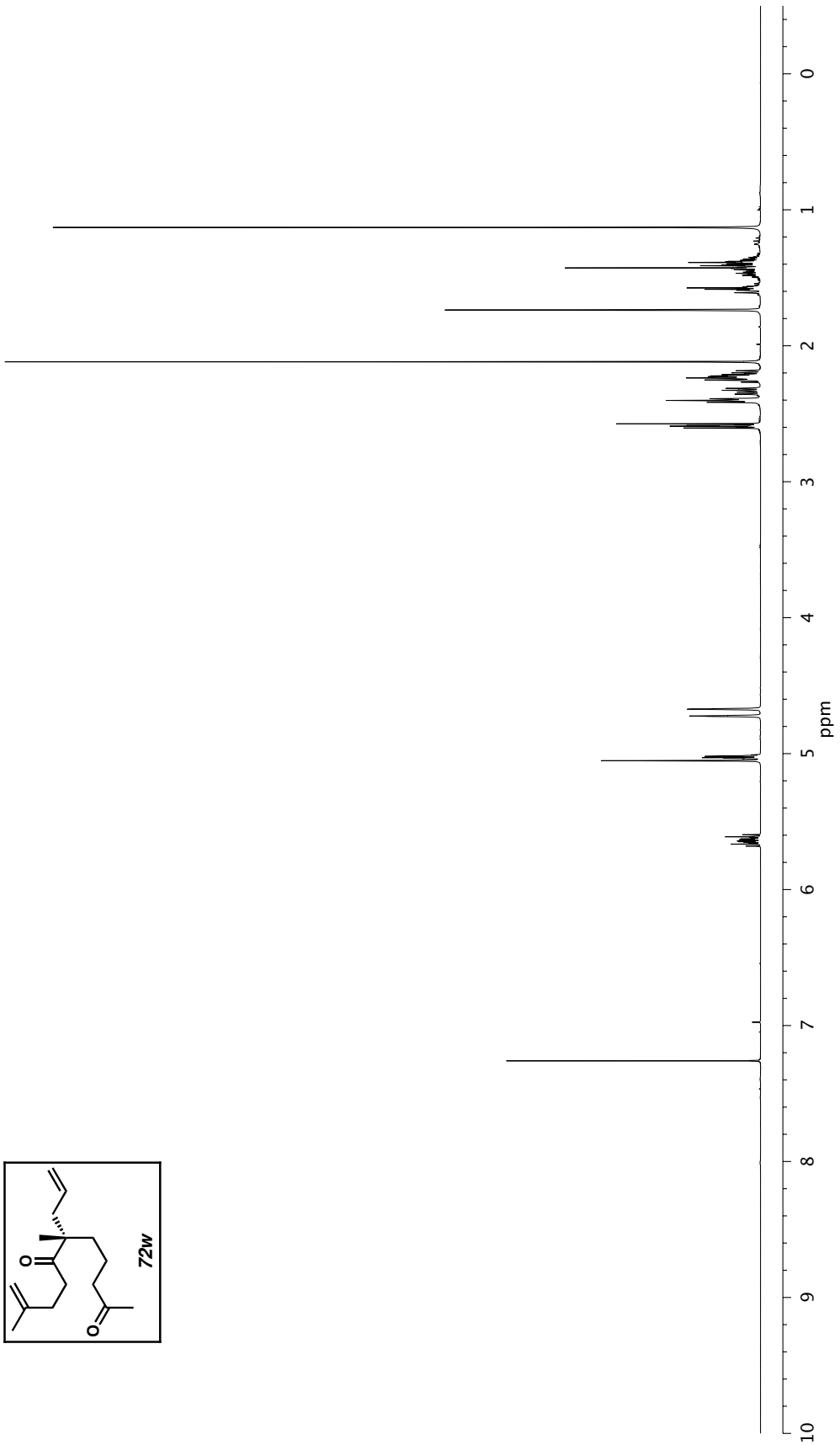


Figure A5.3.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **72w**.

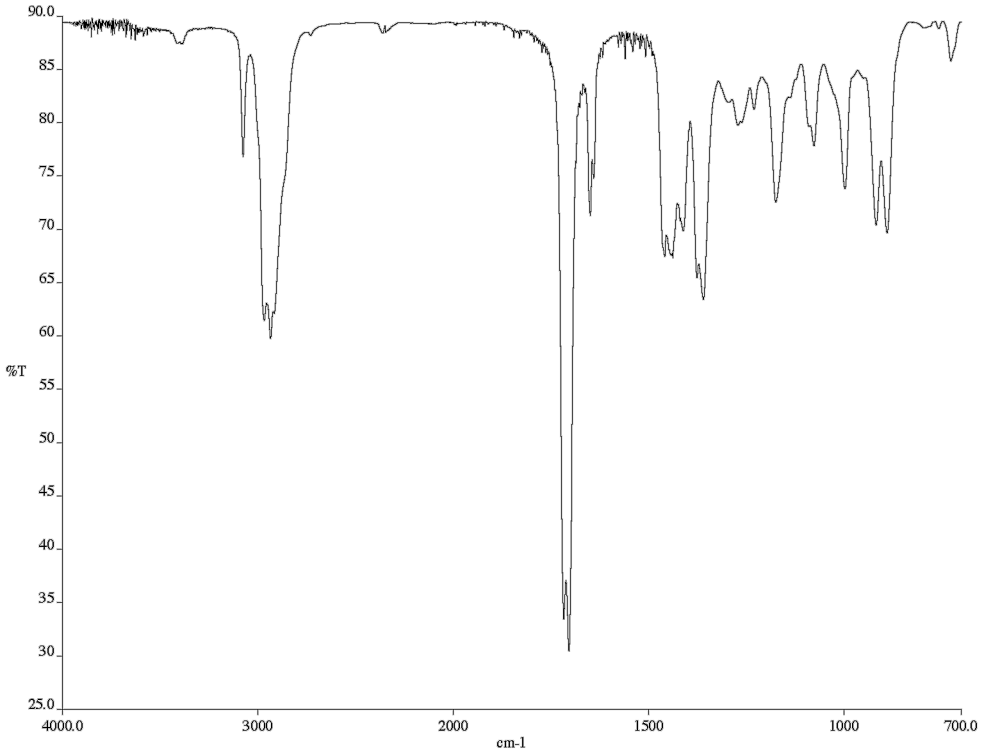


Figure A5.3.2. Infrared spectrum (thin film/NaCl) of compound **72w**.

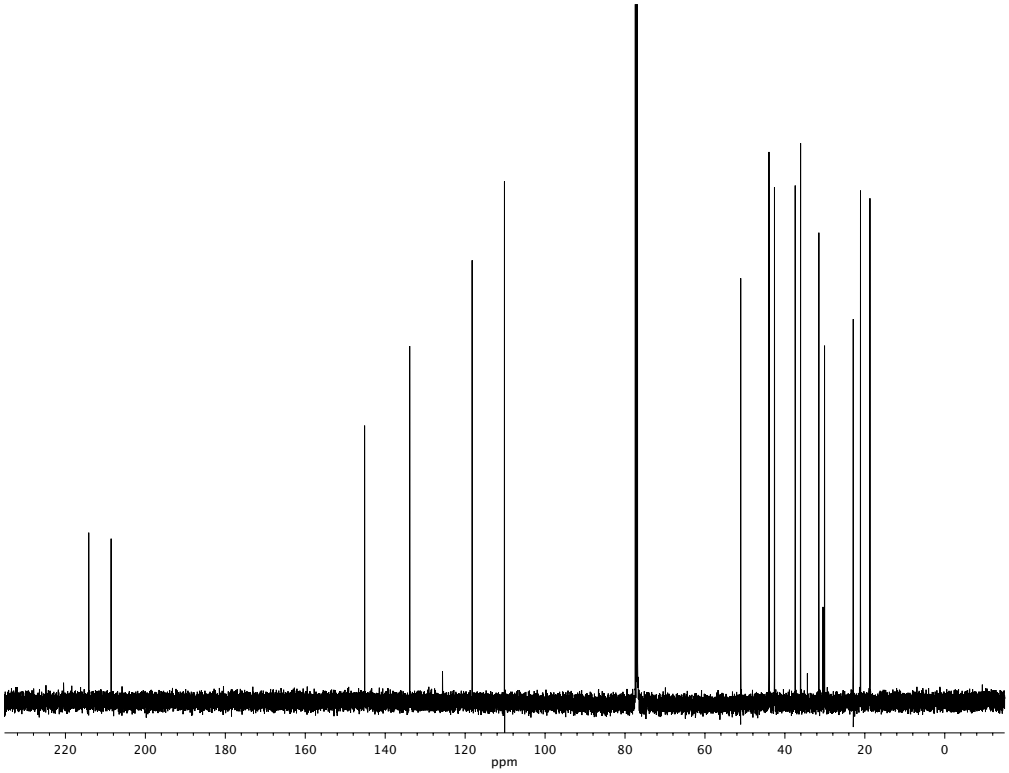


Figure A5.3.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **72w**.

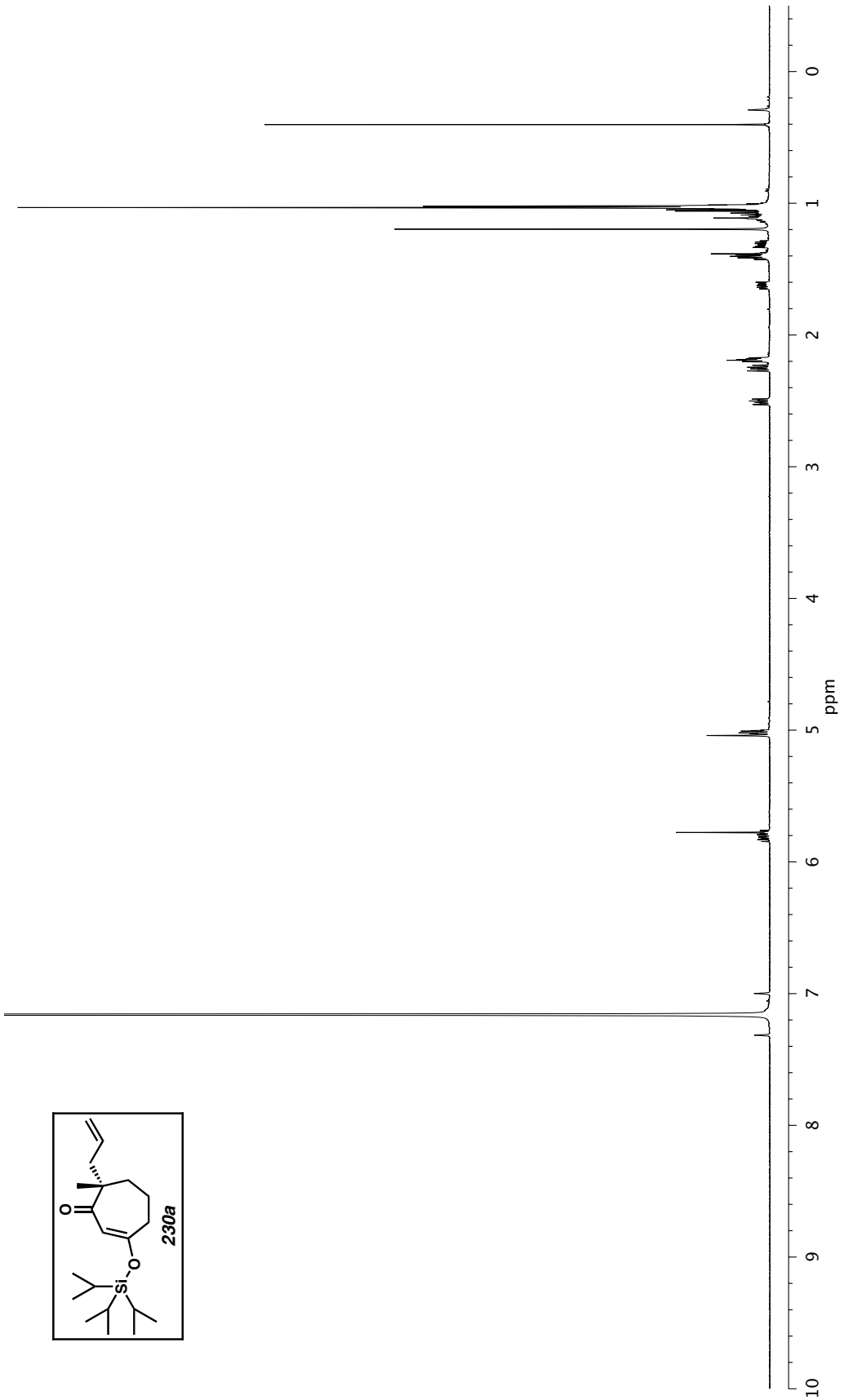


Figure A5.4.1. ^{1}H NMR (500 MHz, C_6D_6) of compound **230a**.

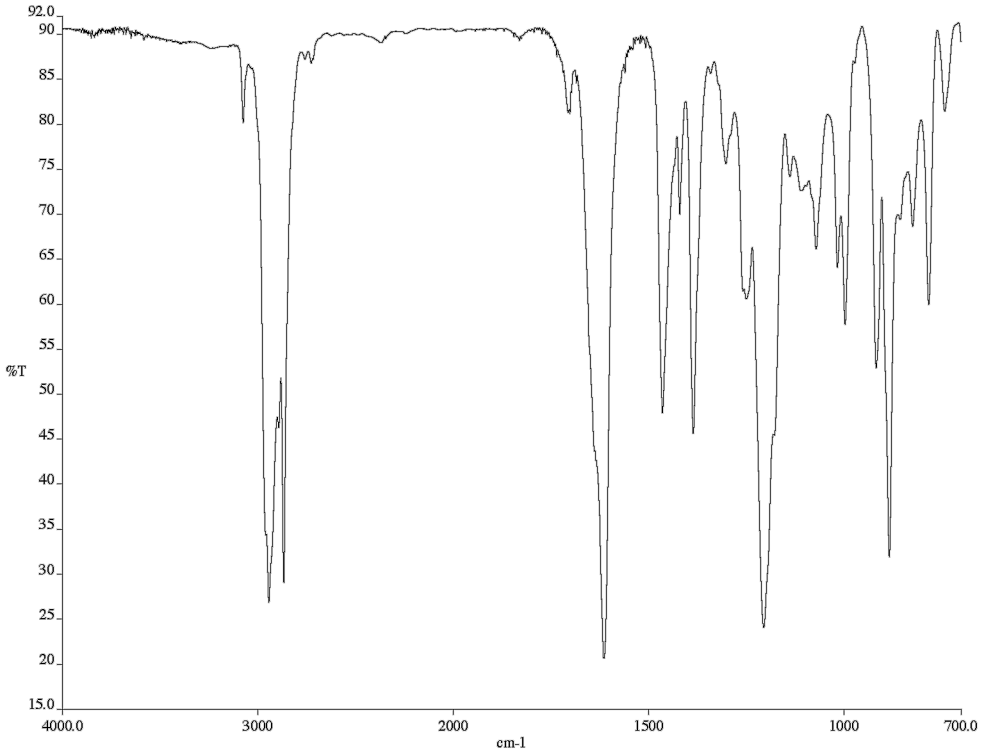


Figure A5.4.2. Infrared spectrum (thin film/NaCl) of compound **230a**.

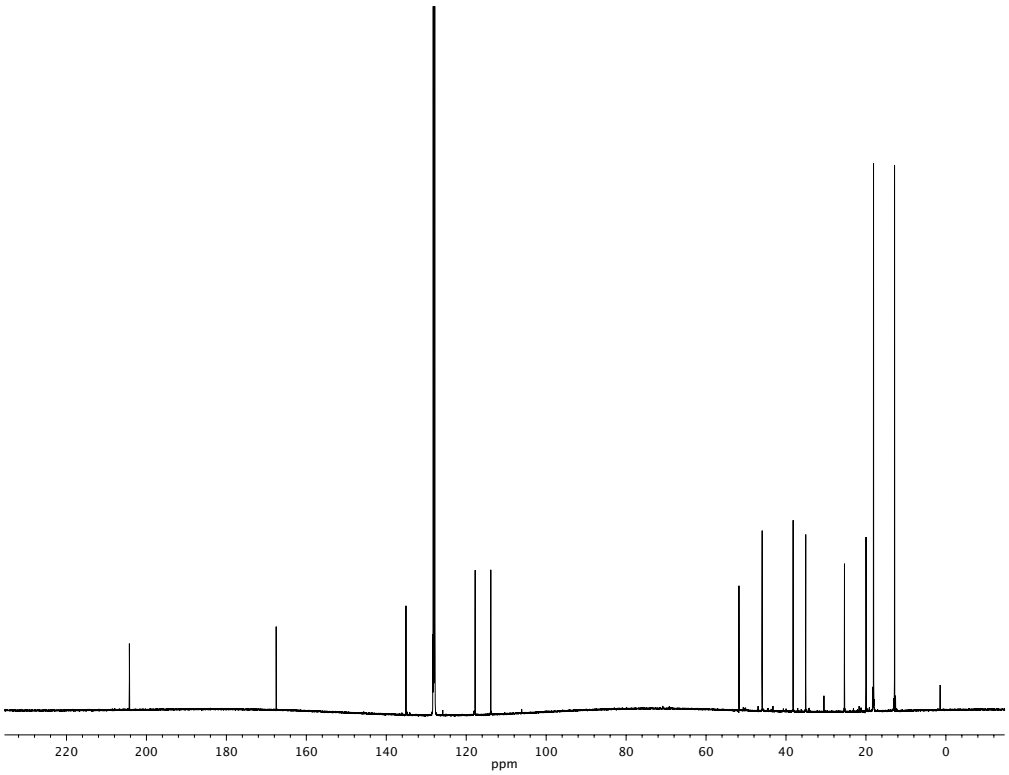


Figure A5.4.3. ^{13}C NMR (125 MHz, C_6D_6) of compound **230a**.

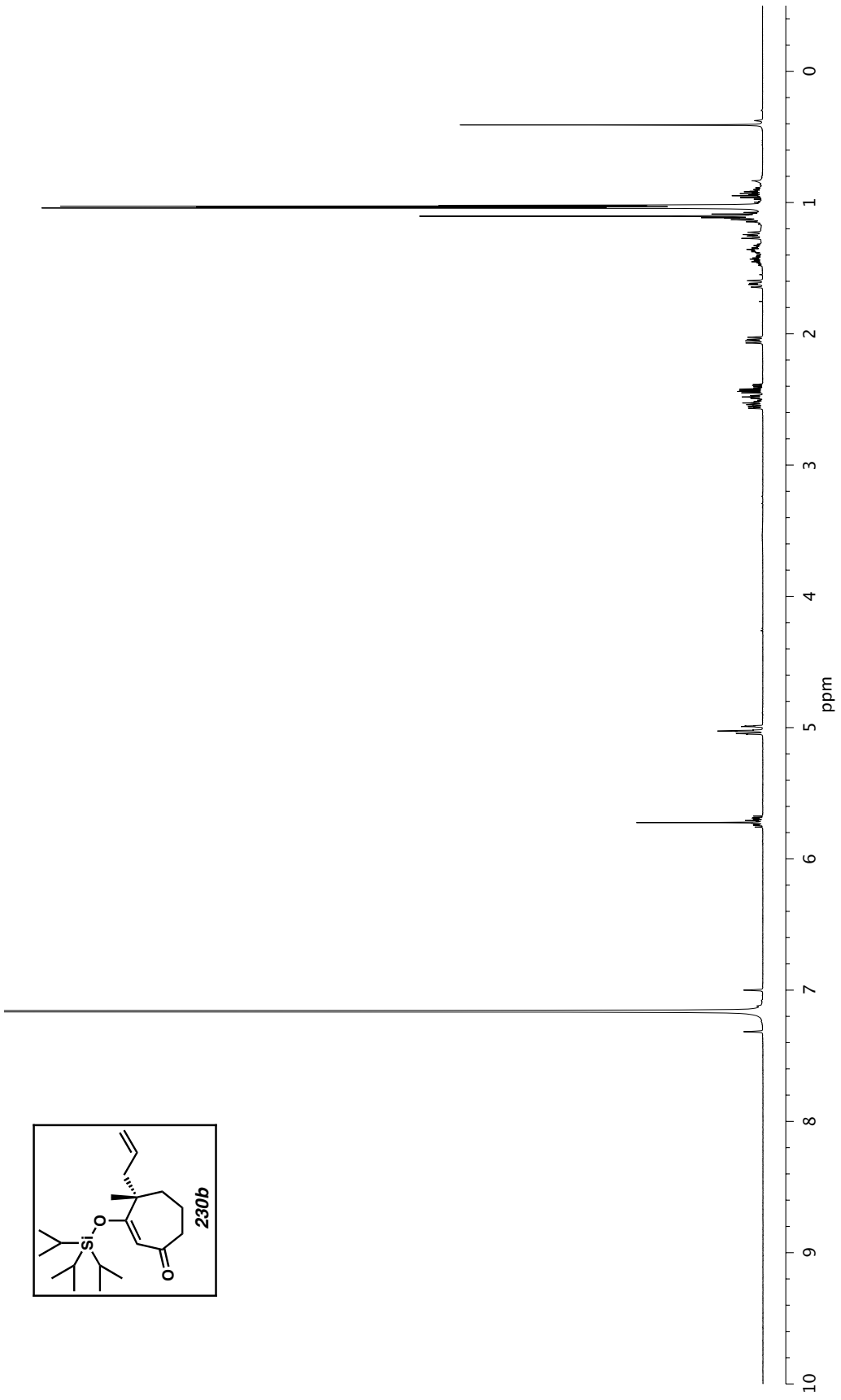


Figure A5.5.1. ^{1}H NMR (500 MHz, C_6D_6) of compound **230b**.

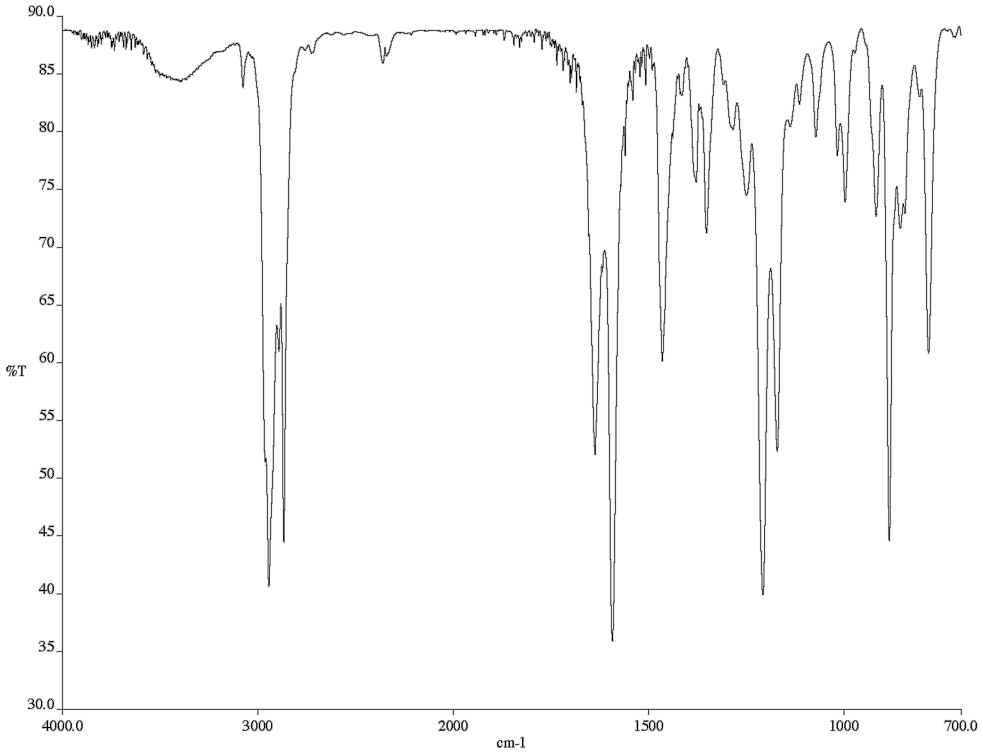


Figure A5.5.2. Infrared spectrum (thin film/NaCl) of compound **230b**.

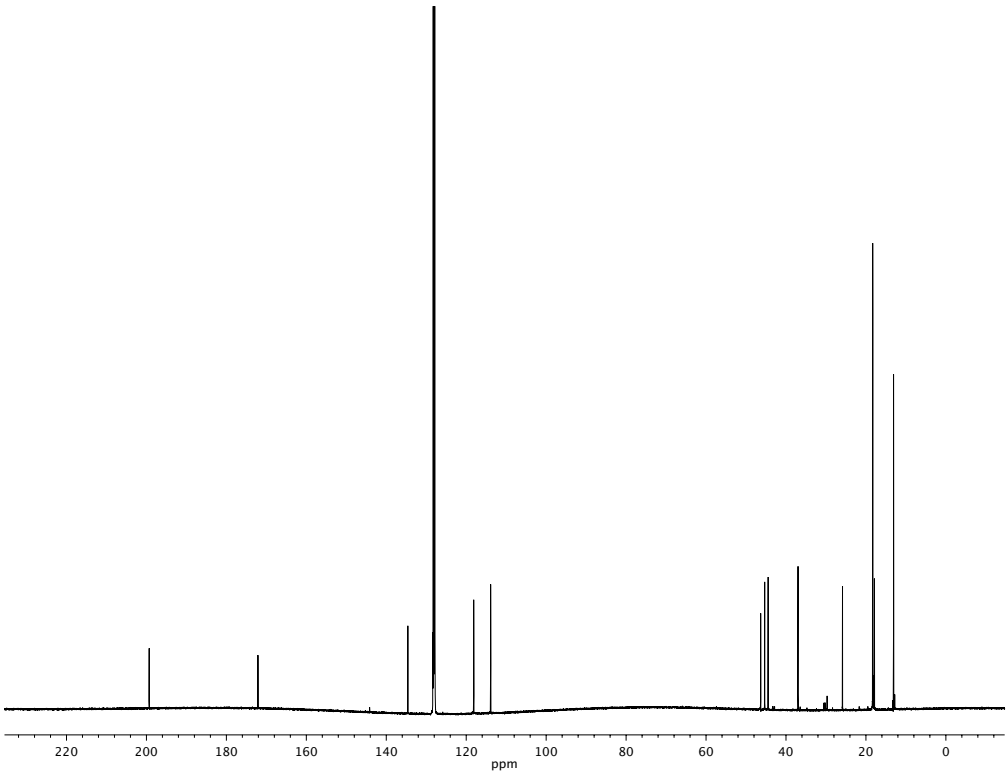


Figure A5.5.3. ^{13}C NMR (125 MHz, C_6D_6) of compound **230b**.

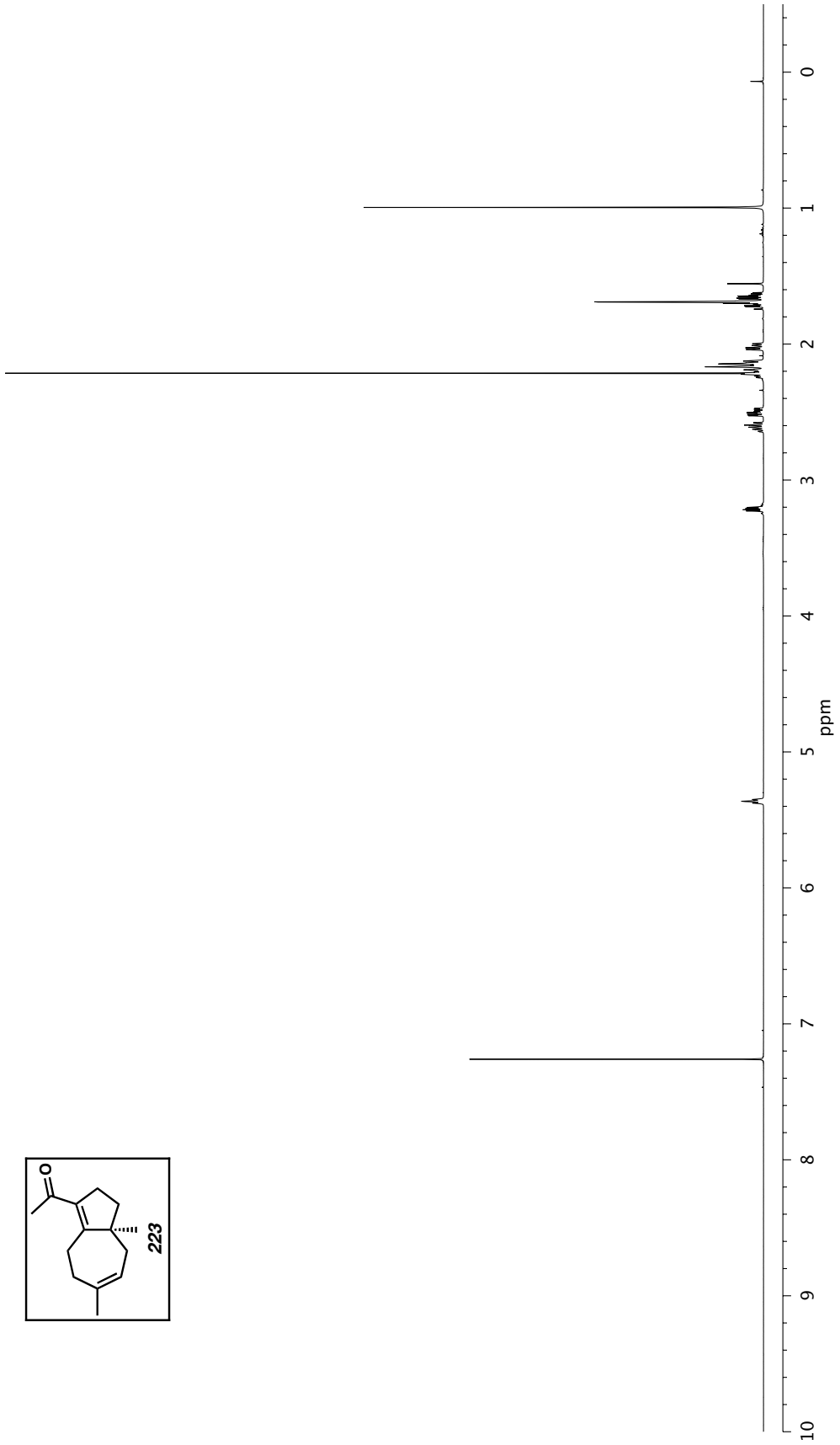


Figure A5.6.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **223**.

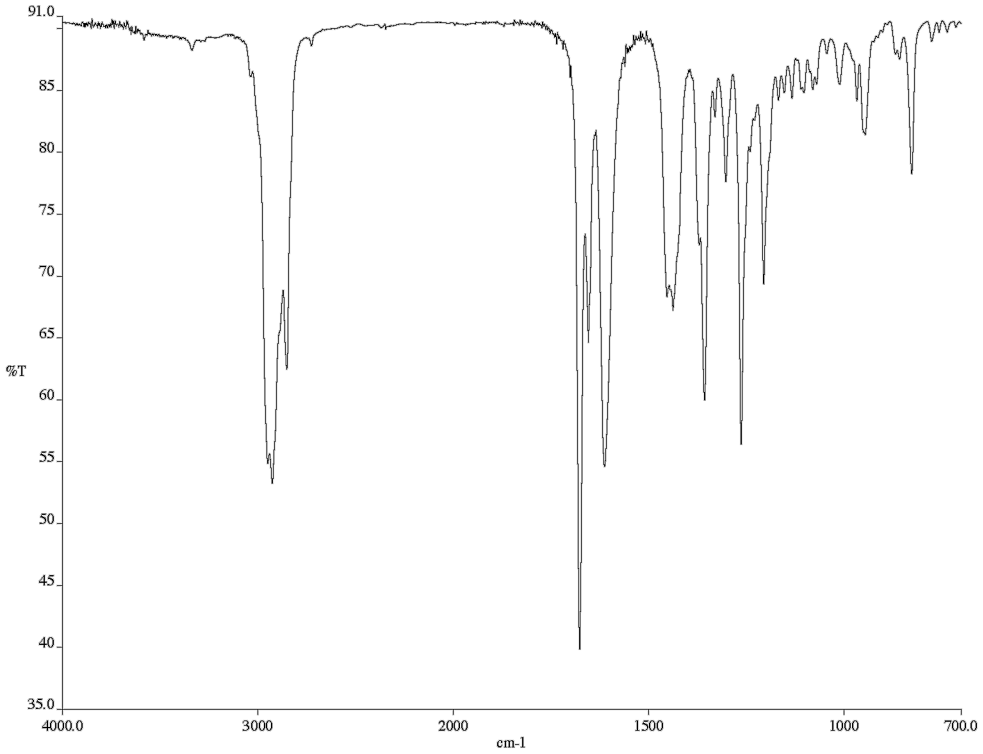


Figure A5.6.2. Infrared spectrum (thin film/NaCl) of compound **223**.

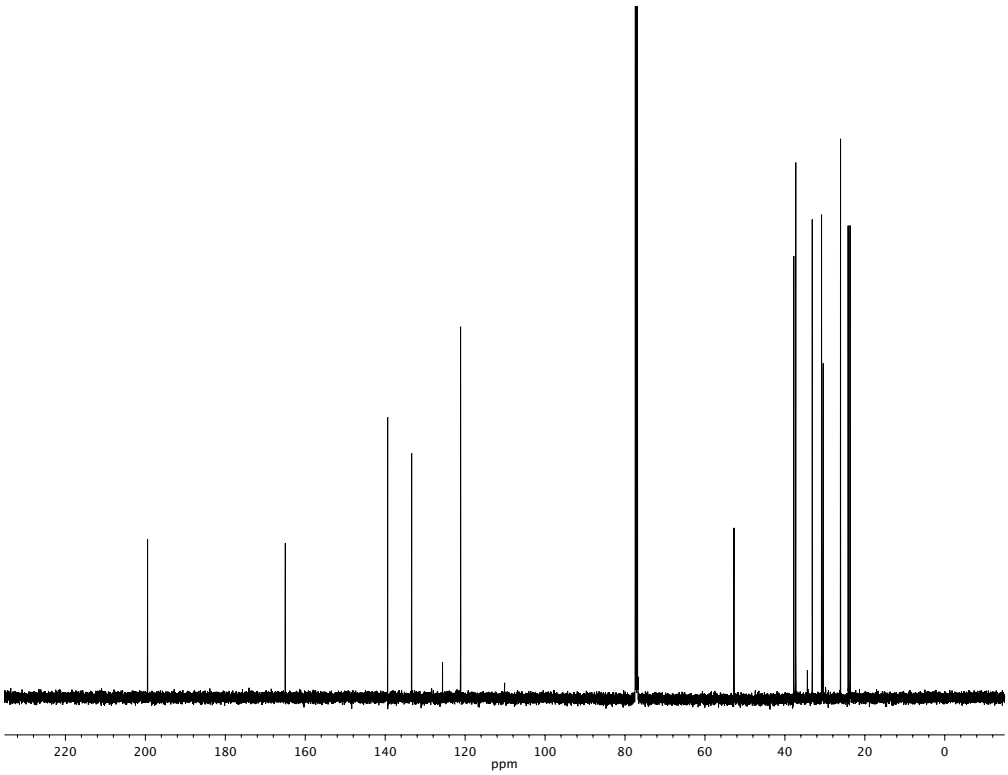


Figure A5.6.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **223**.

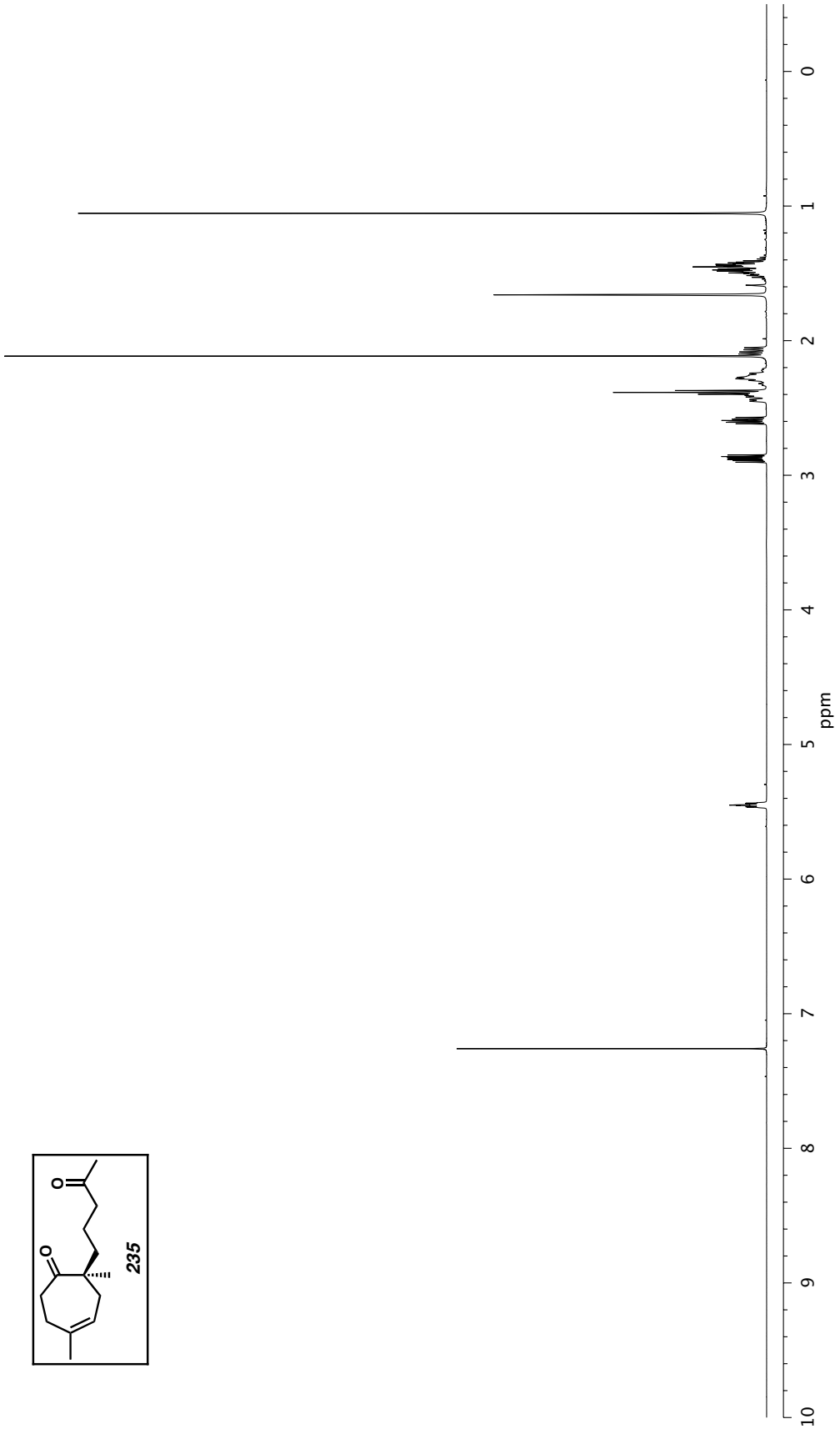


Figure A5.7.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **235**.

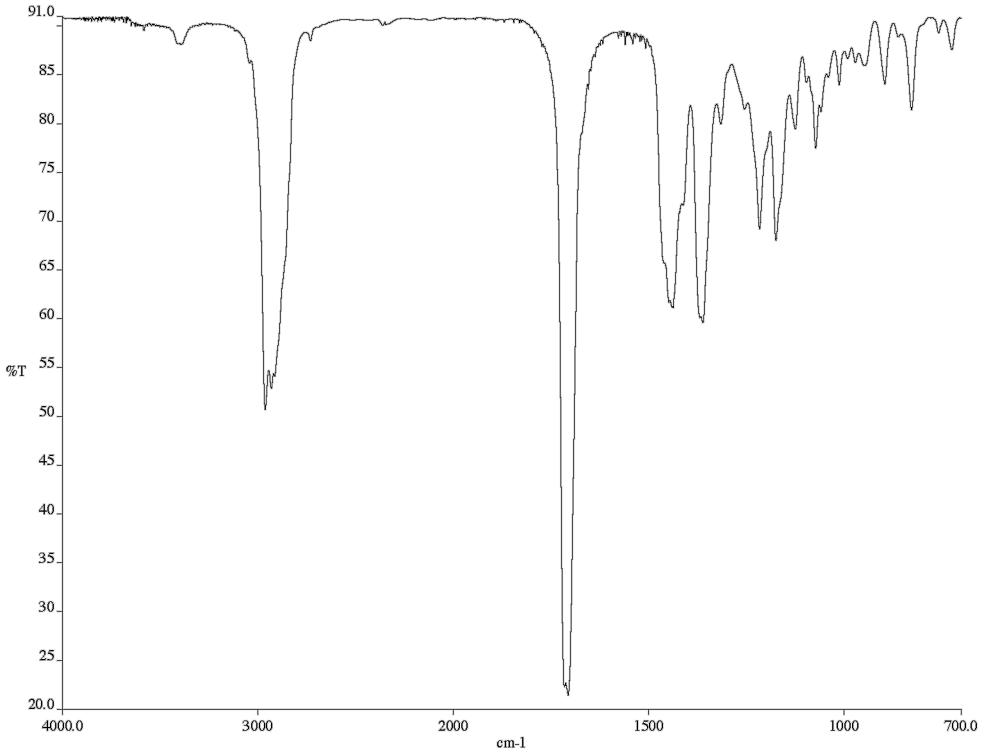


Figure A5.7.2. Infrared spectrum (thin film/NaCl) of compound **235**.

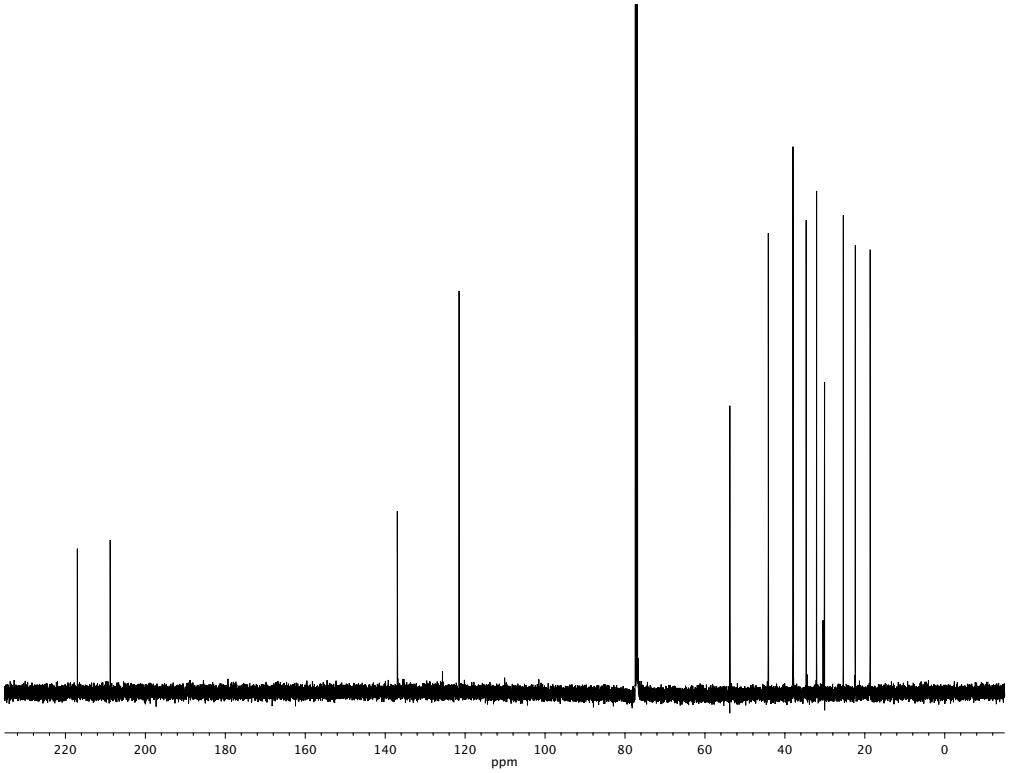


Figure A5.7.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **235**.

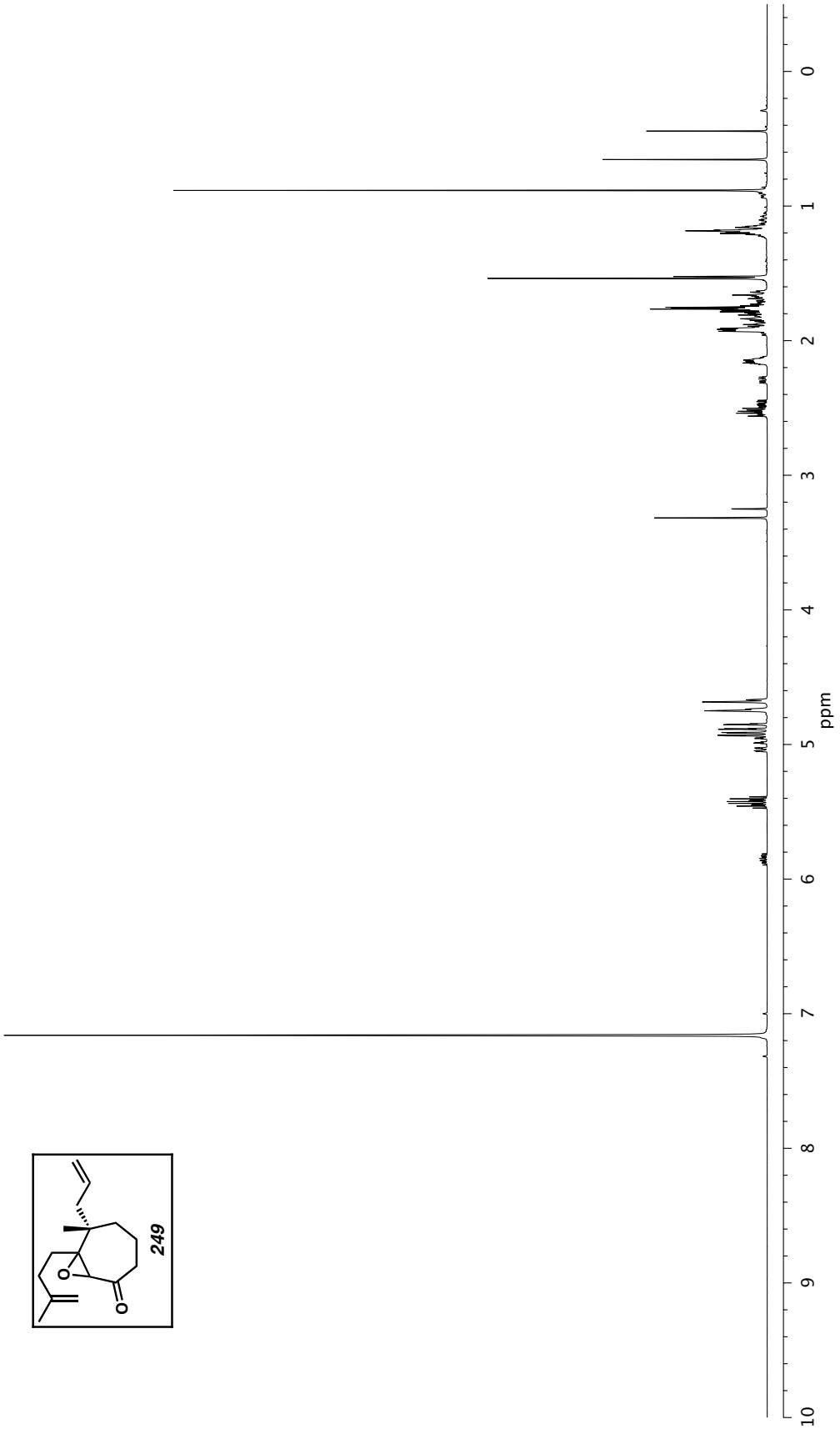


Figure A5.8.1. ^{1}H NMR (500 MHz, C_6D_6) of compound **249**.

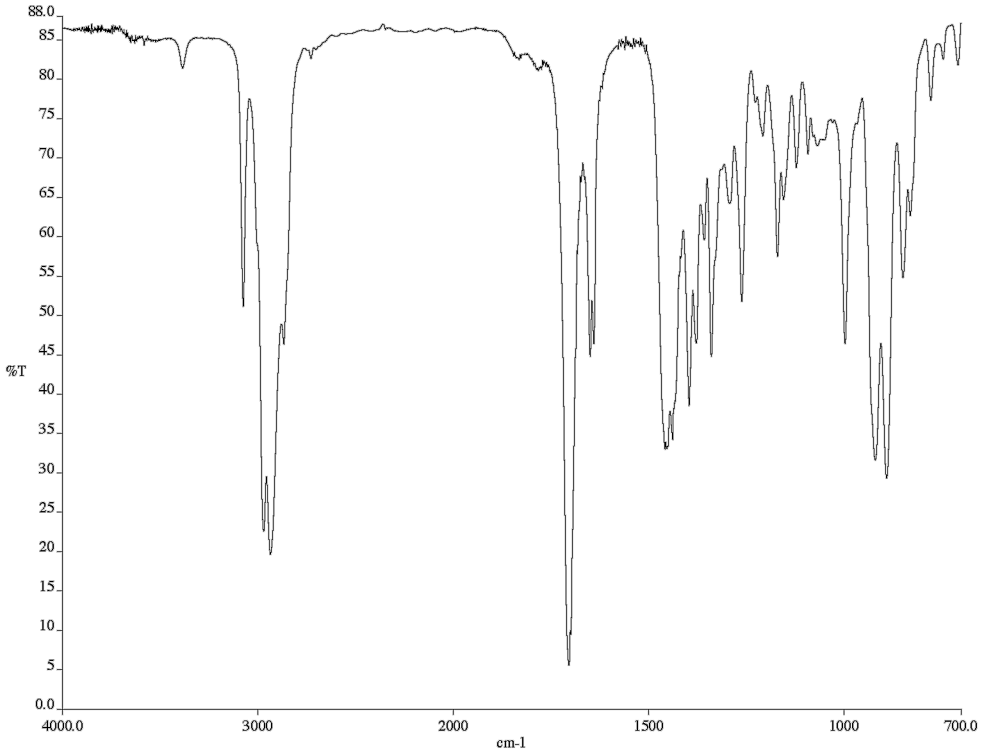


Figure A5.8.2. Infrared spectrum (thin film/NaCl) of compound **249**.

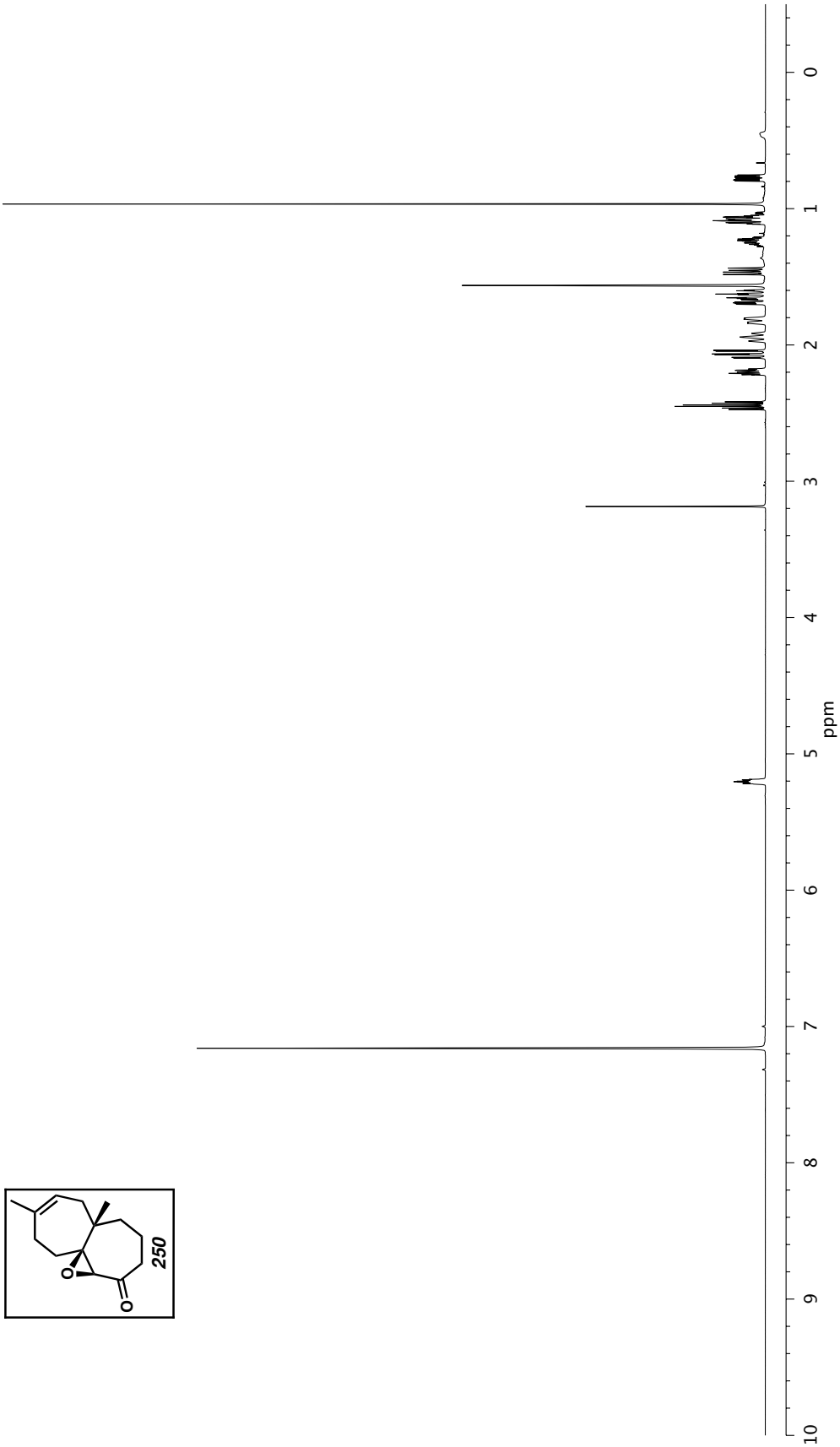


Figure A5.9.1. ^{1}H NMR (500 MHz, C_6D_6) of compound **250**.

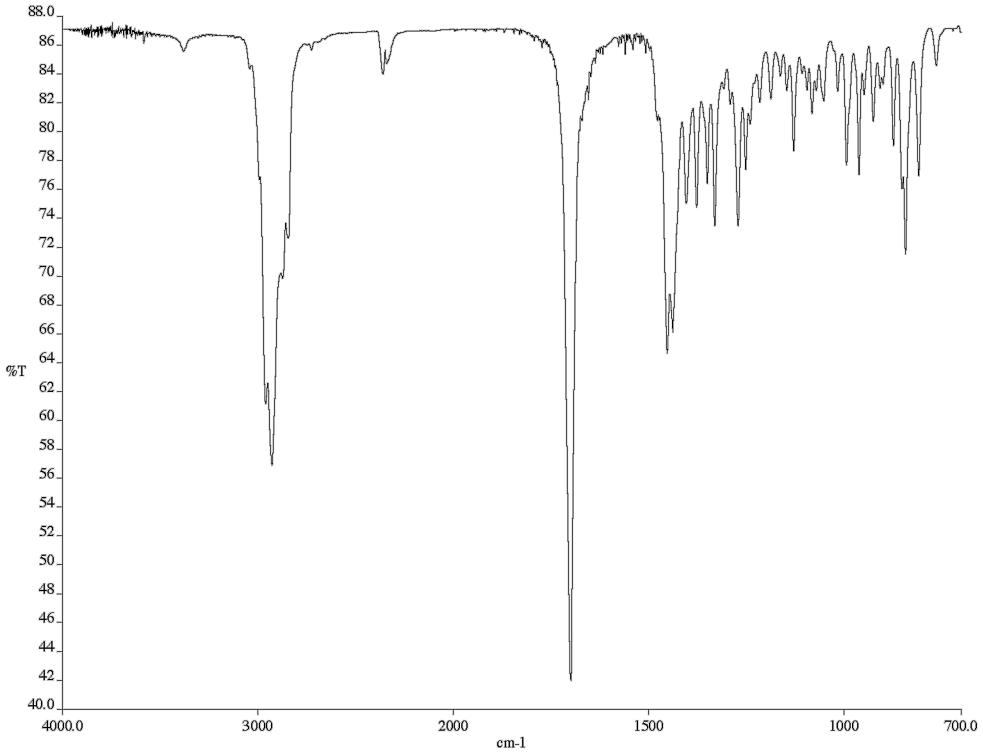


Figure A5.9.2. Infrared spectrum (thin film/NaCl) of compound **250**.

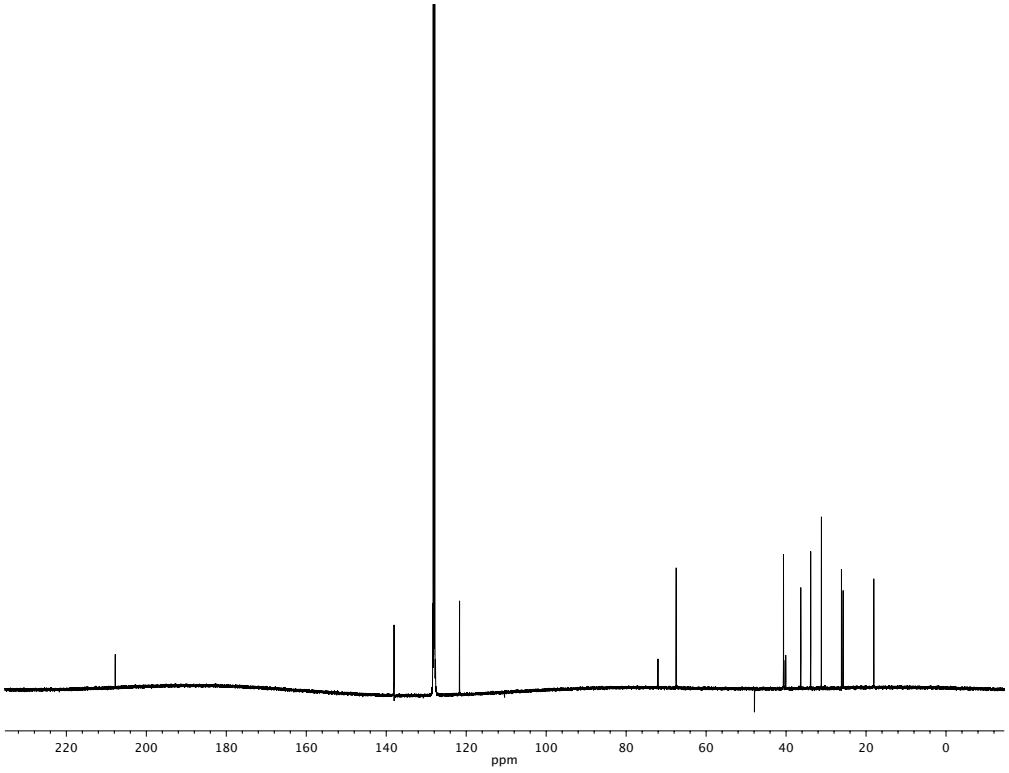


Figure A5.9.3. ^{13}C NMR (125 MHz, C_6D_6) of compound **250**.

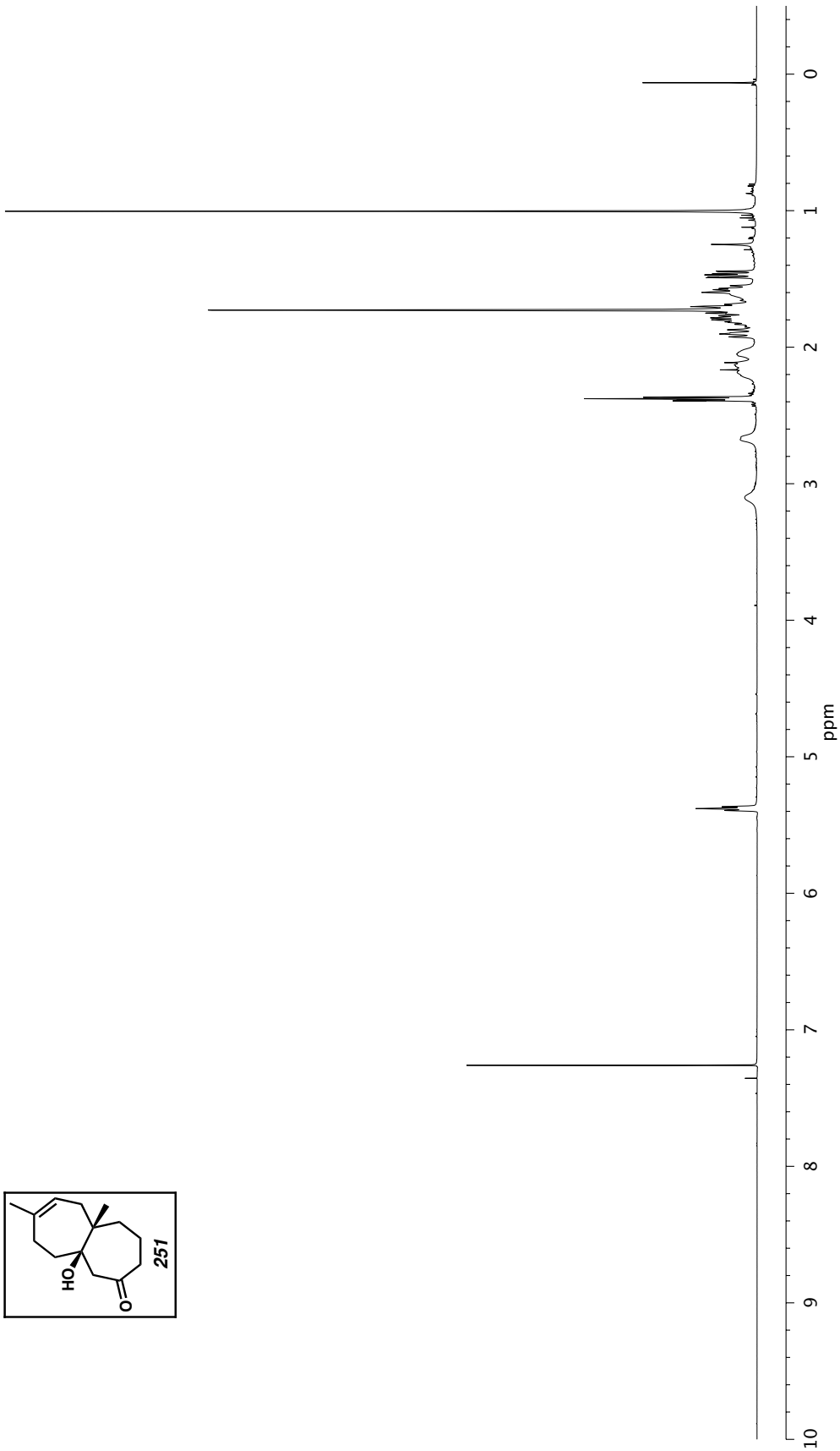


Figure A5.10.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **251**.

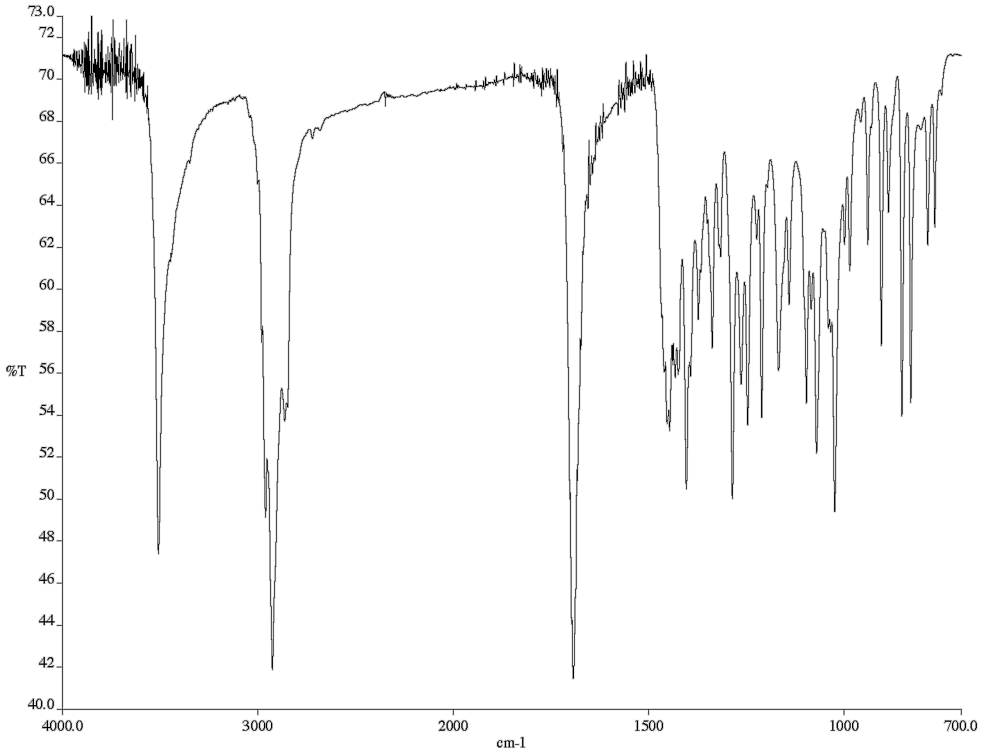


Figure A5.10.2. Infrared spectrum (thin film/NaCl) of compound **251**.

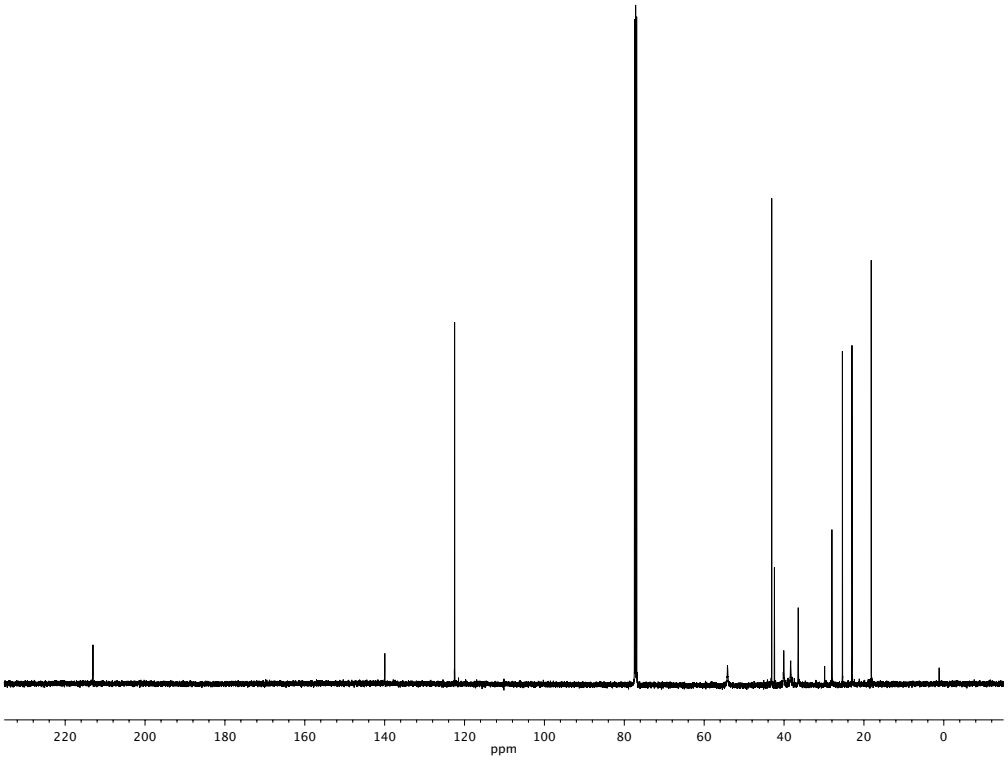


Figure A5.10.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **251**.

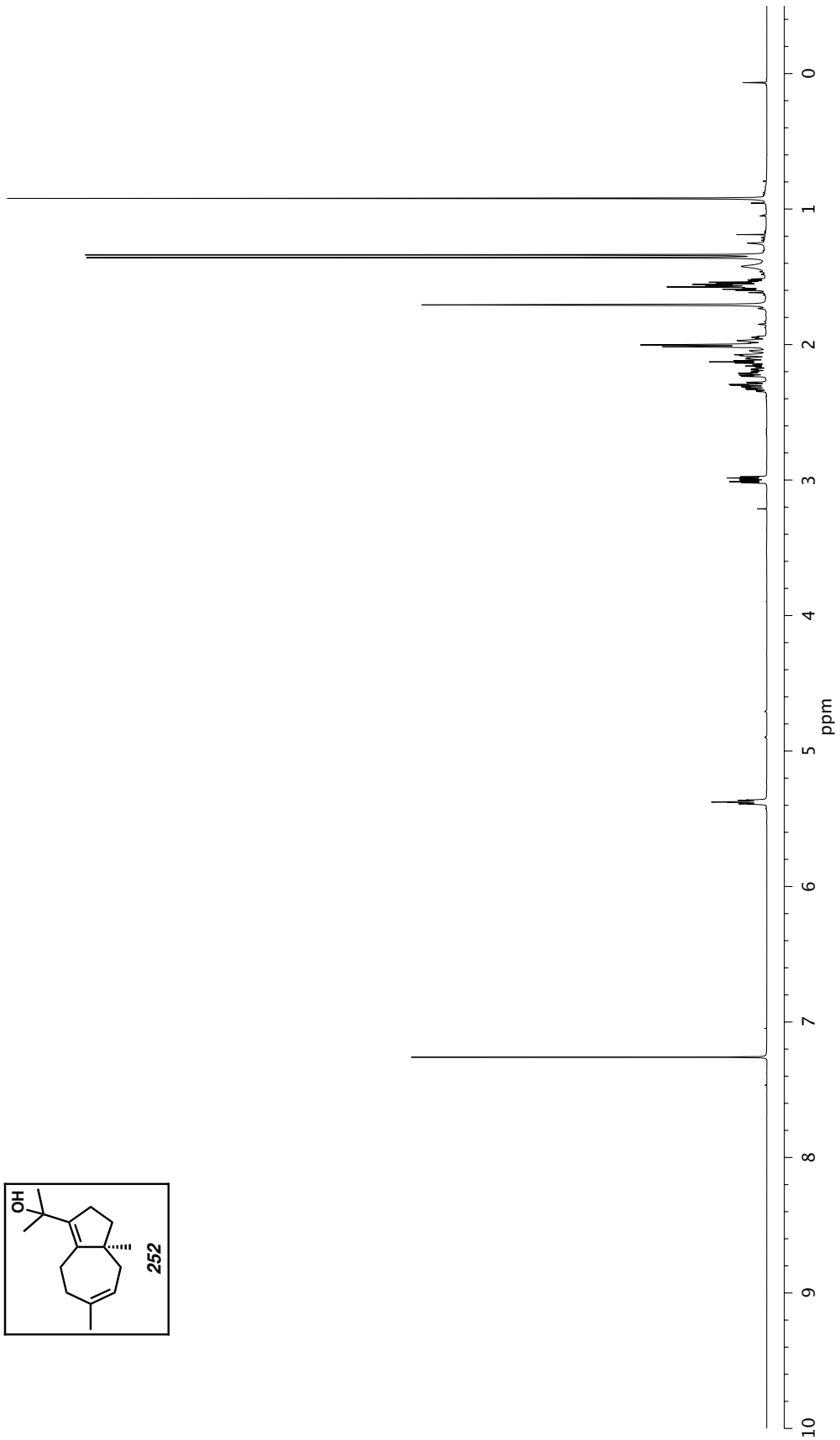


Figure A5.11.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **252**.

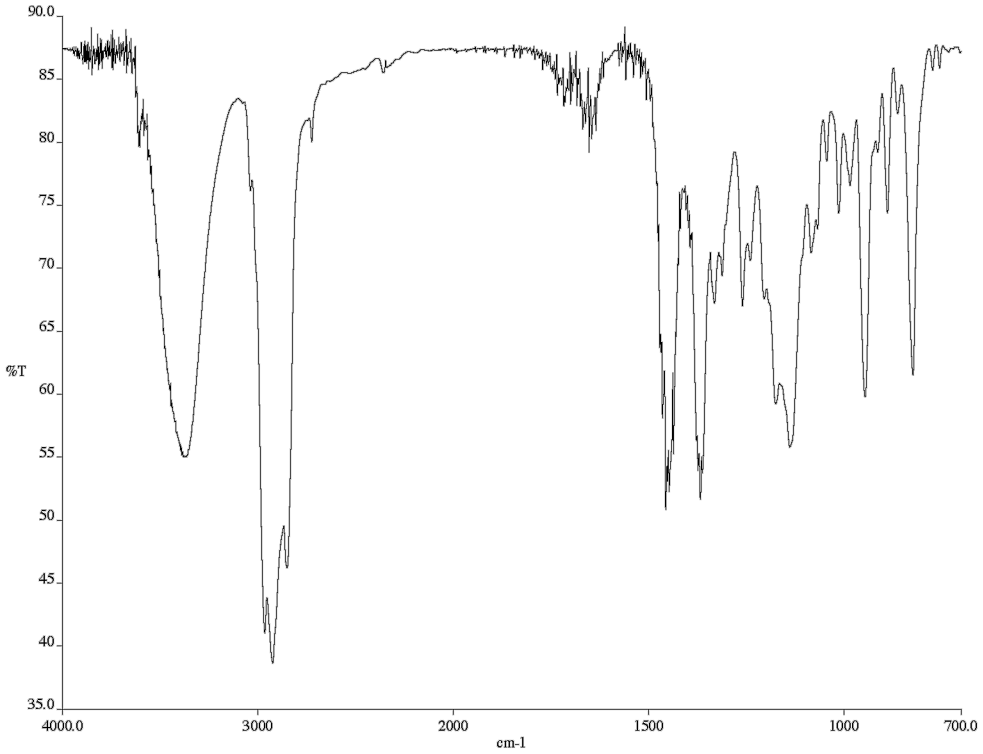


Figure A5.11.2. Infrared spectrum (thin film/NaCl) of compound **252**.

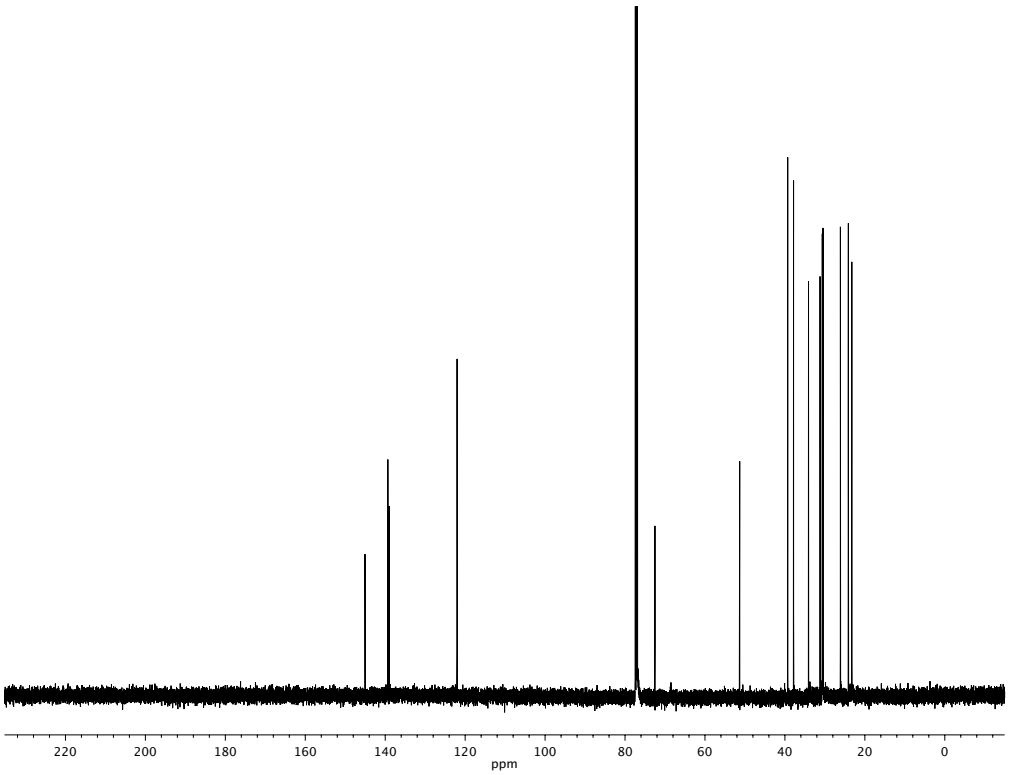


Figure A5.11.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **252**.

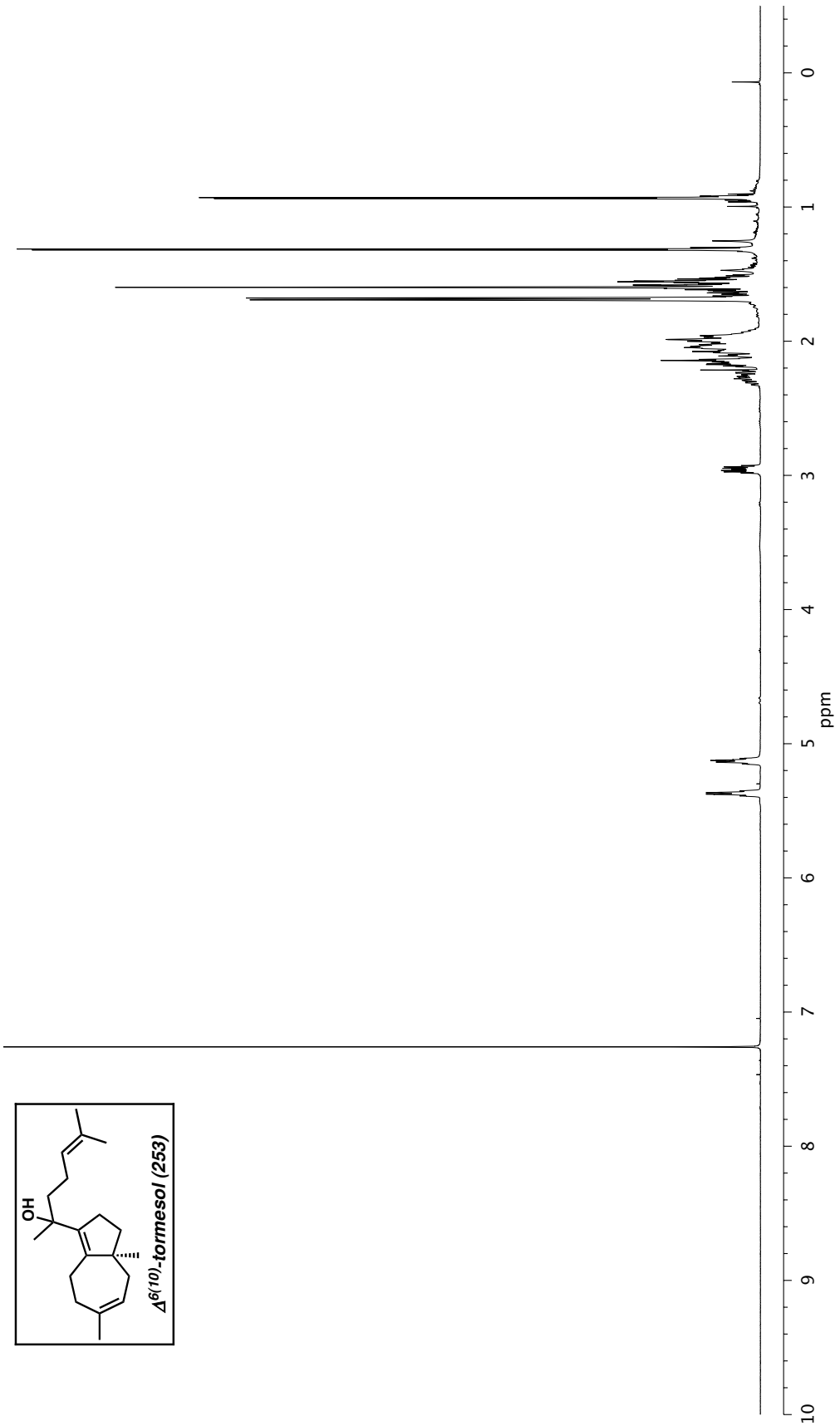


Figure A5.12.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **253**.

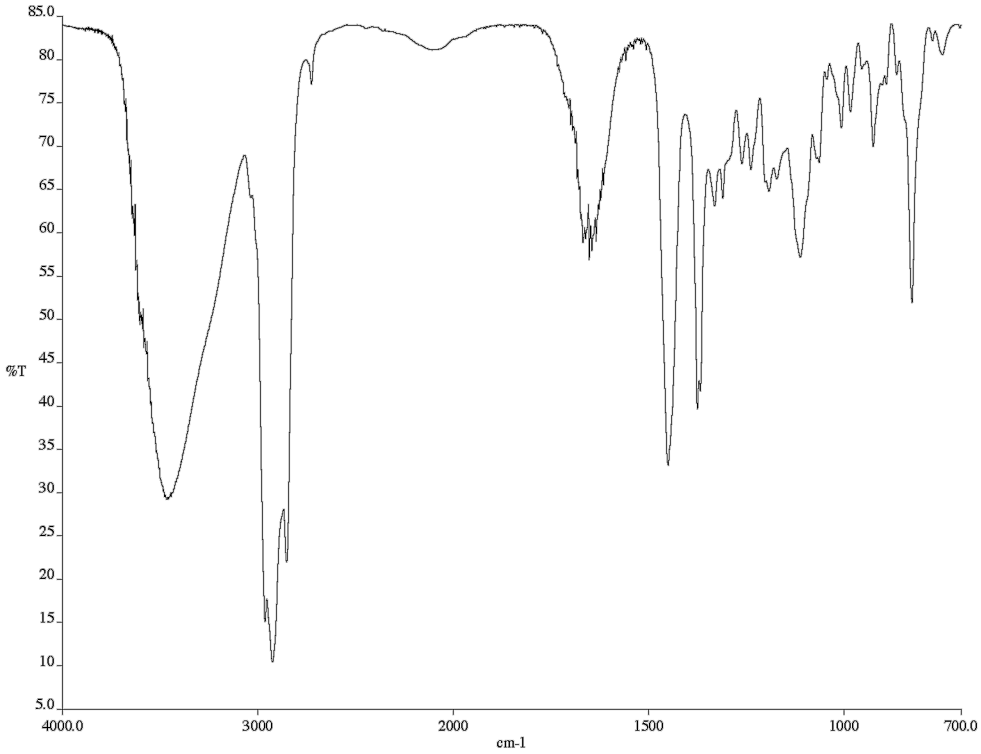


Figure A5.12.2. Infrared spectrum (thin film/NaCl) of compound **253**.

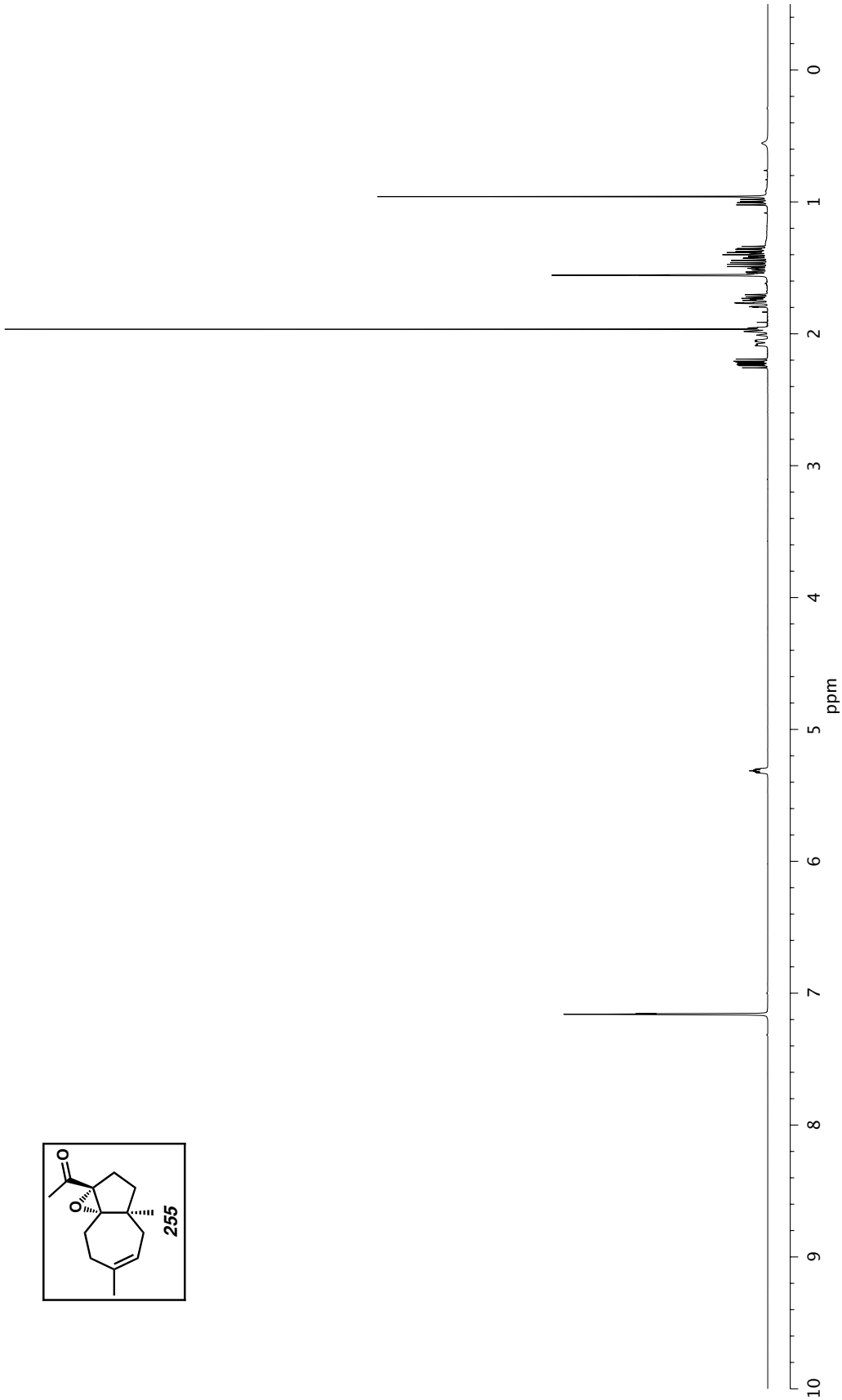


Figure A5.13.1. ^{1}H NMR (500 MHz, C_6D_6) of compound **255**.

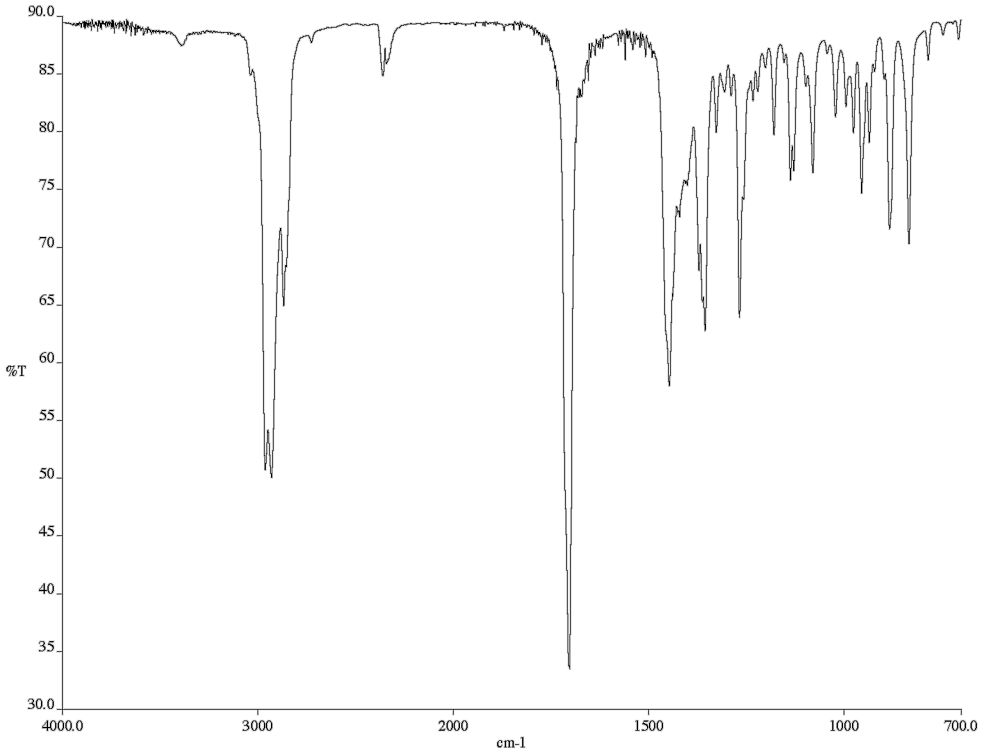


Figure A5.13.2. Infrared spectrum (thin film/NaCl) of compound **255**.

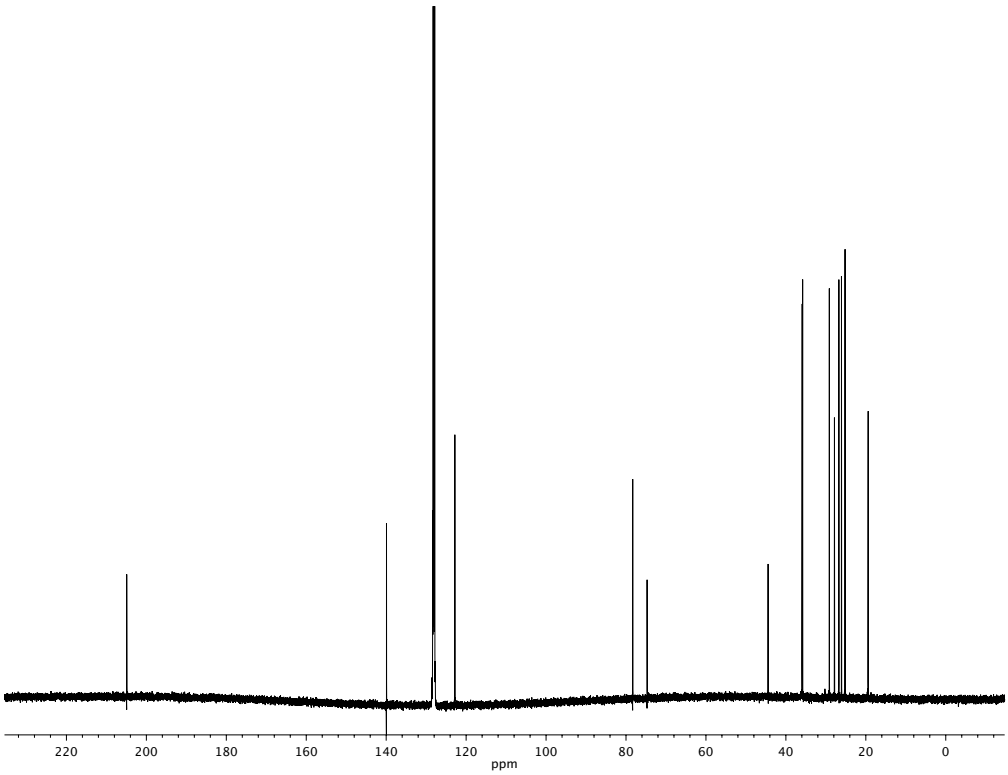


Figure A5.13.3. ^{13}C NMR (125 MHz, C_6D_6) of compound **255**.

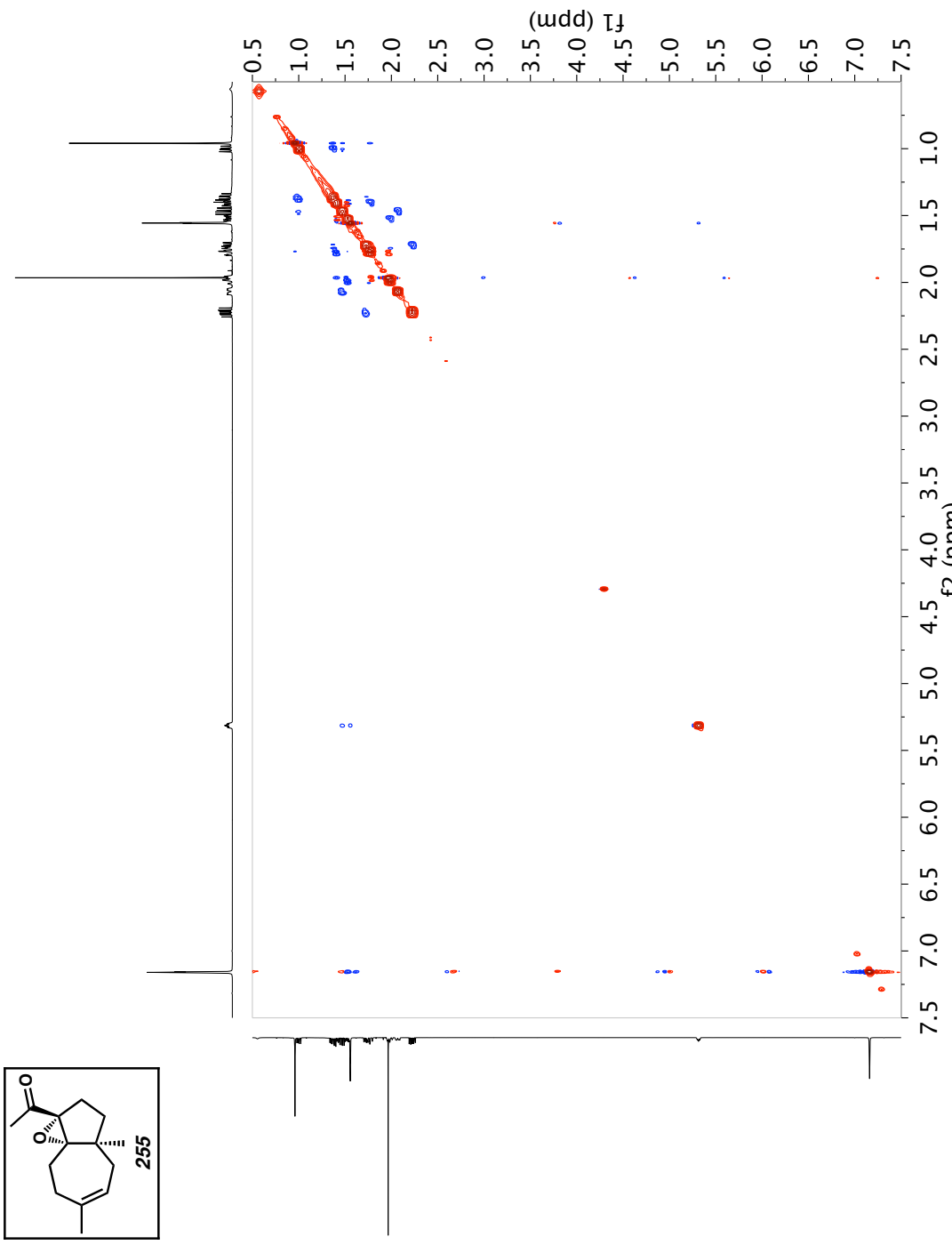


Figure A5.13.4. NOESY NMR (500 MHz, C_6D_6) of compound **255**.

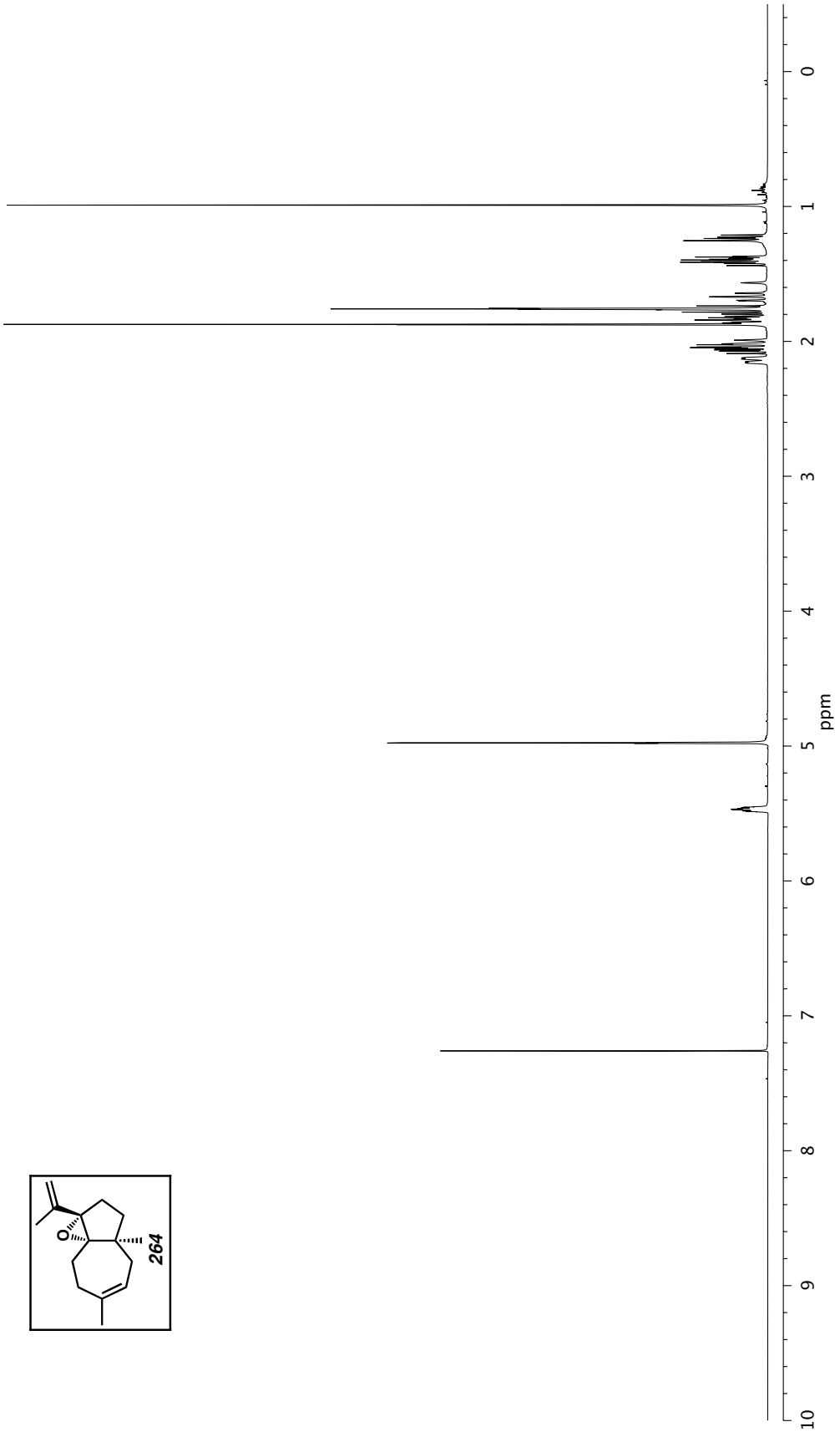


Figure A5.14.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **264**.

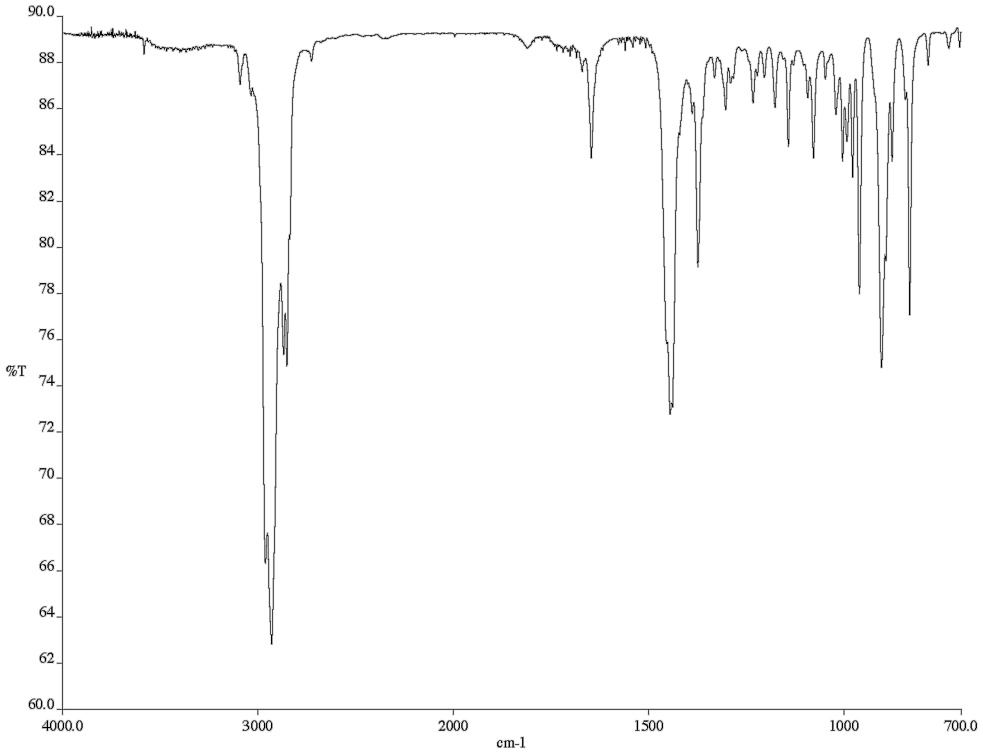


Figure A5.14.2. Infrared spectrum (thin film/NaCl) of compound **264**.

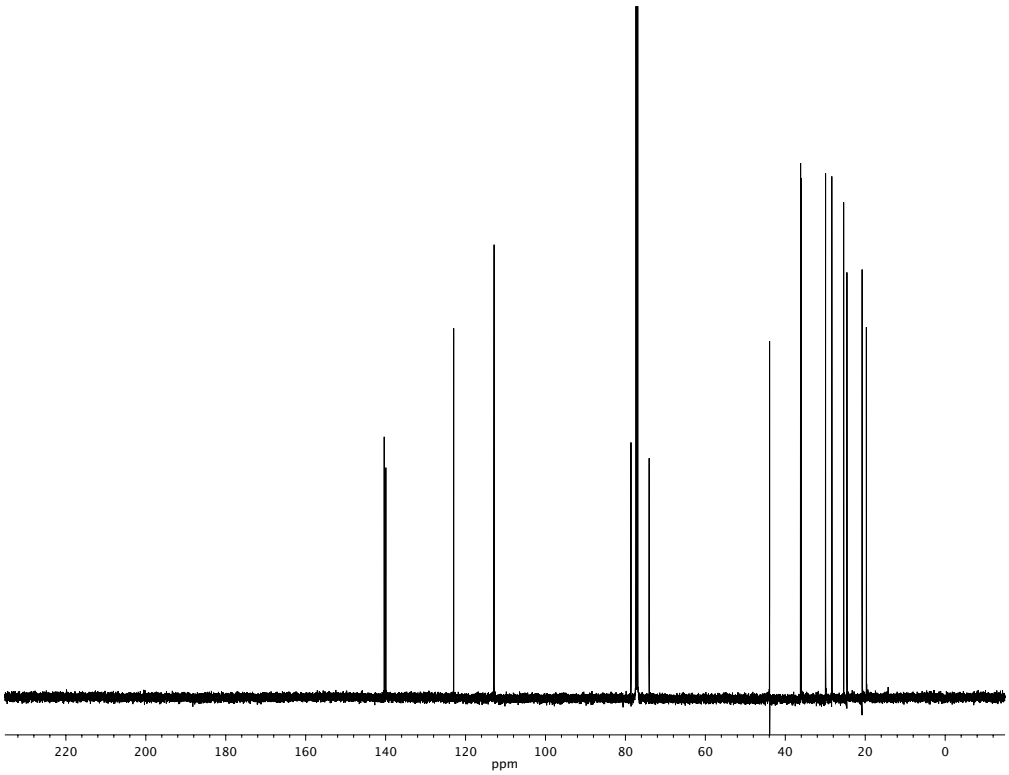


Figure A5.14.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **264**.

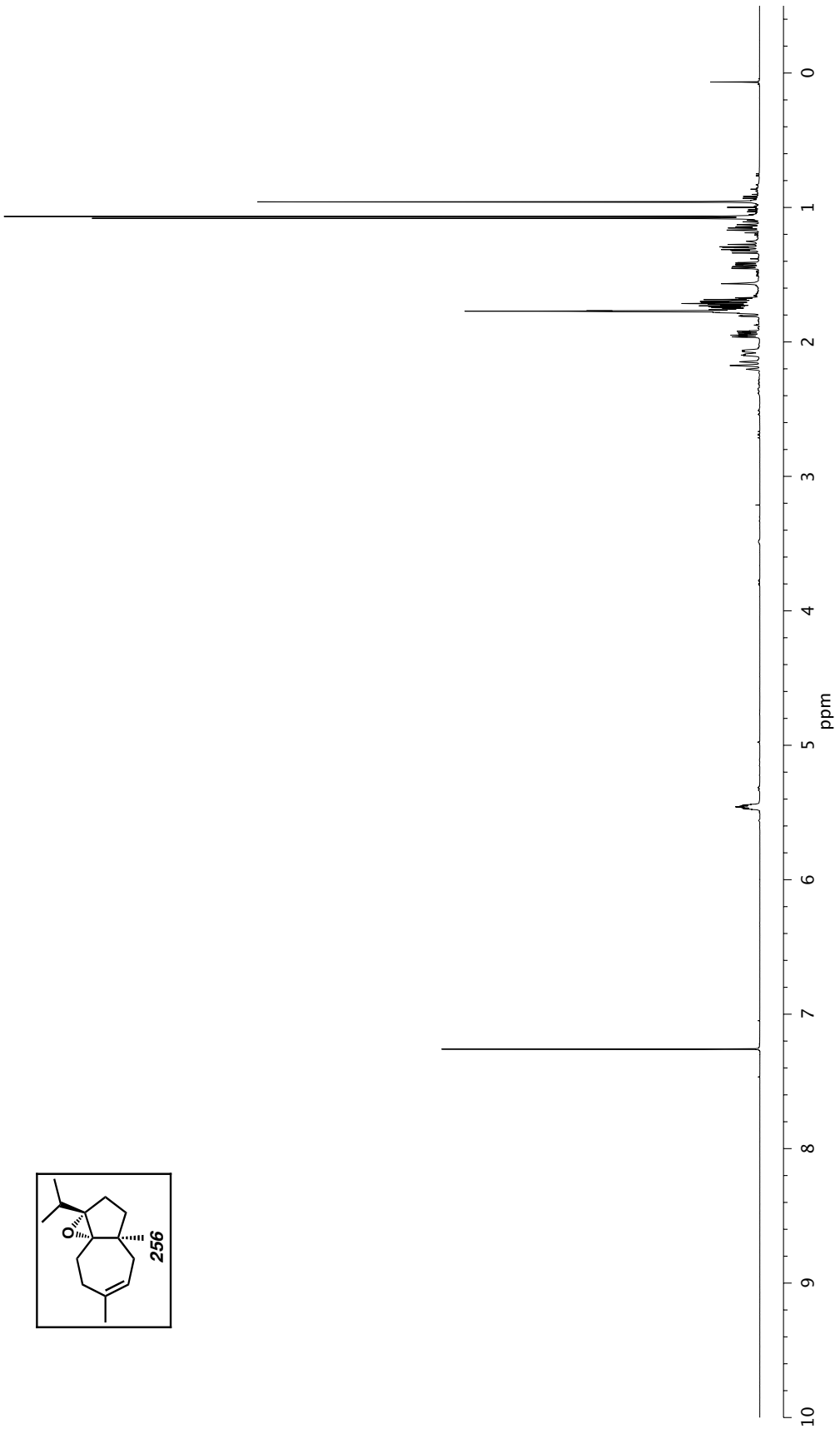


Figure A5.15.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **256**.

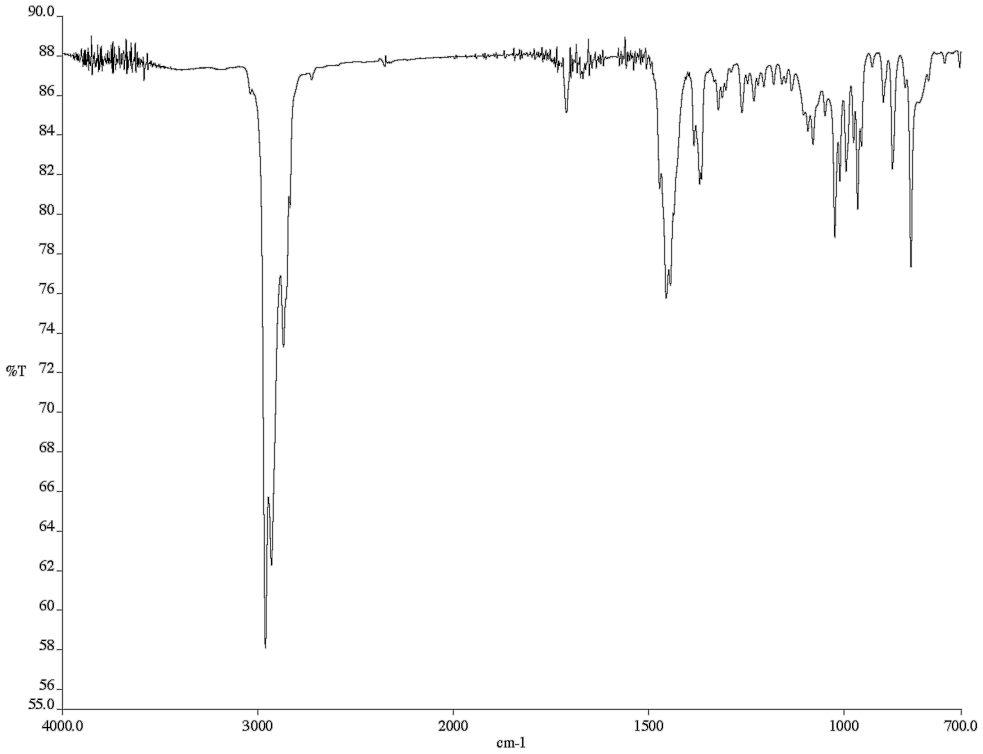


Figure A5.15.2. Infrared spectrum (thin film/NaCl) of compound **256**.

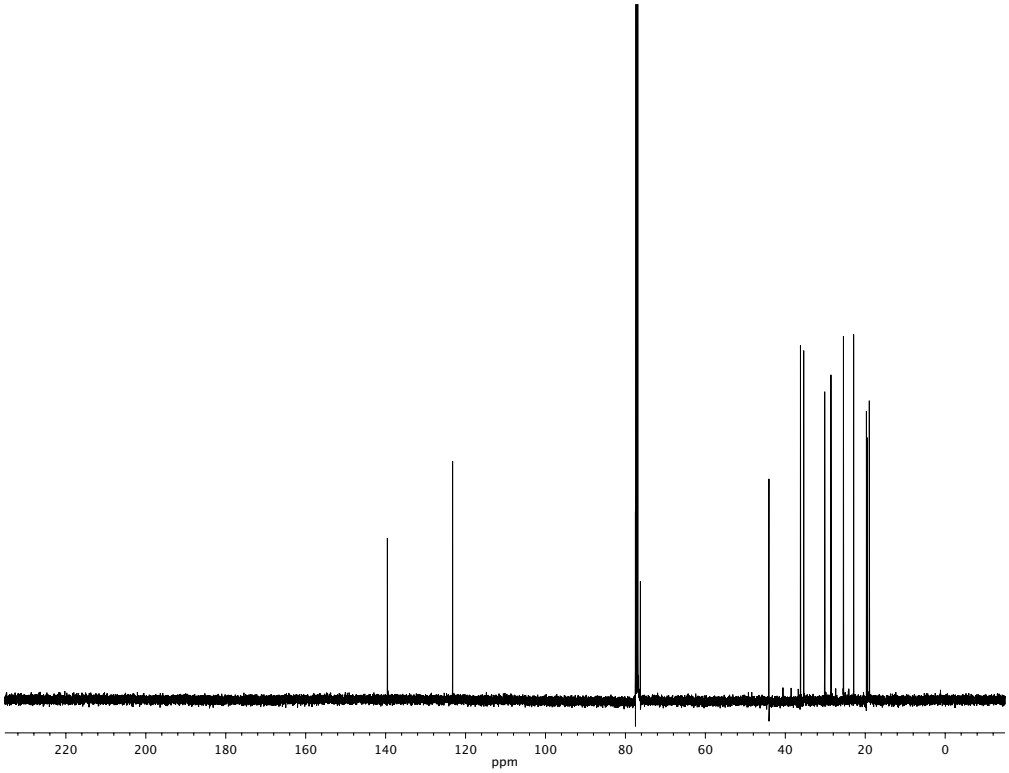


Figure A5.15.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **256**.

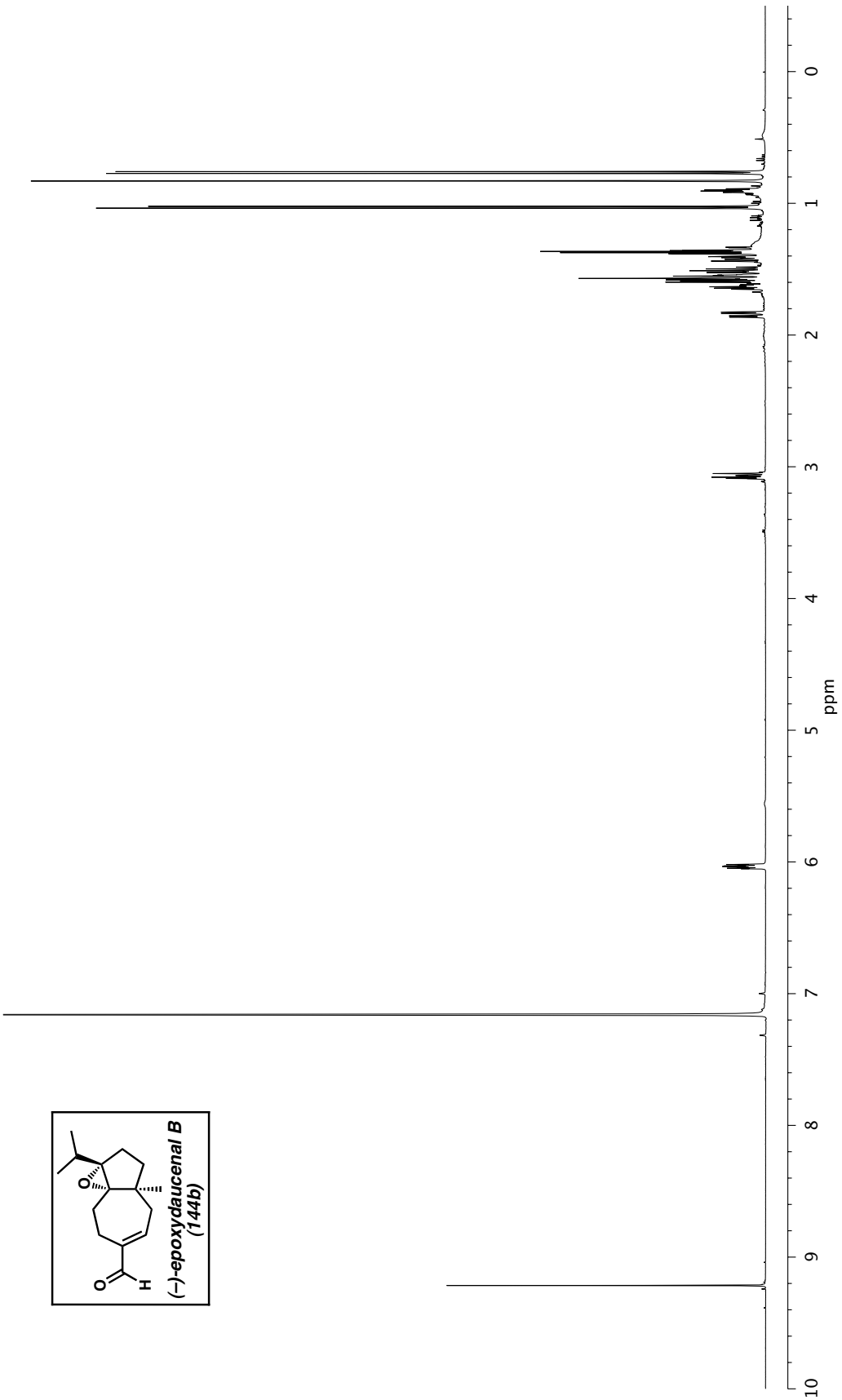


Figure A5.16.1. ^{1}H NMR (500 MHz, C_6D_6) of compound **144b**.

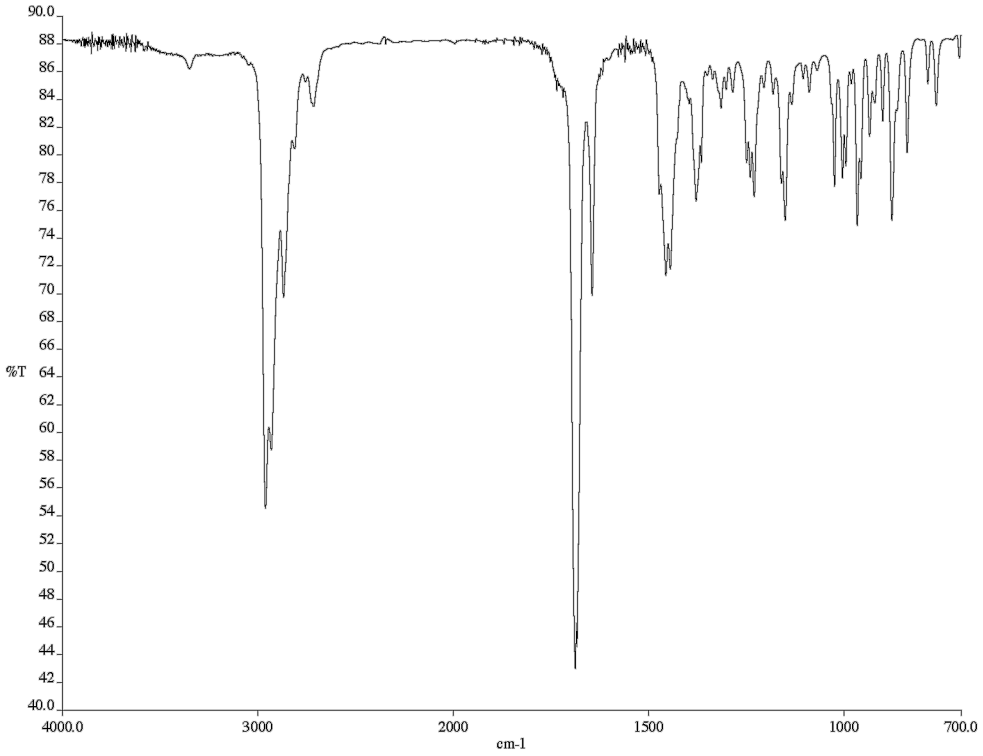


Figure A5.16.2. Infrared spectrum (thin film/NaCl) of compound **144b**.

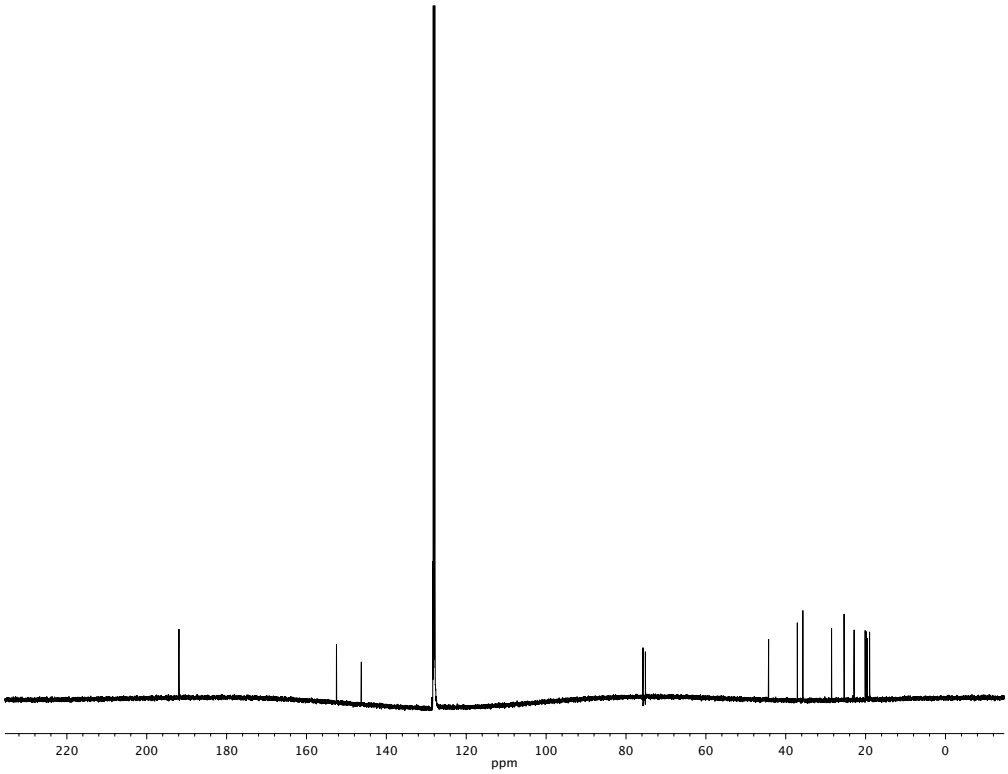


Figure A5.16.3. ^{13}C NMR (125 MHz, C_6D_6) of compound **144b**.

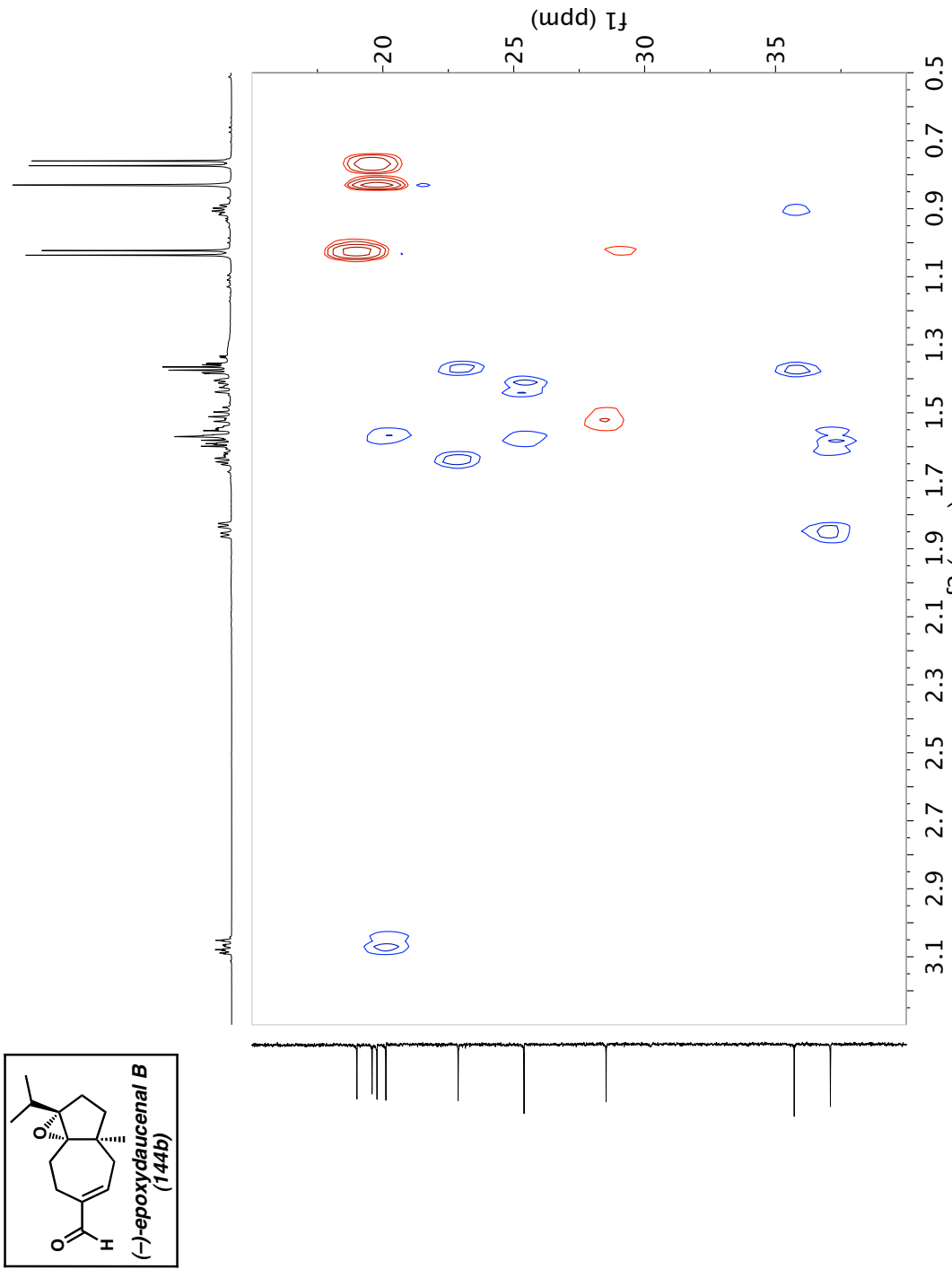


Figure A5.16.4. HSQC NMR (400 MHz, C_6D_6) of compound **144b**.

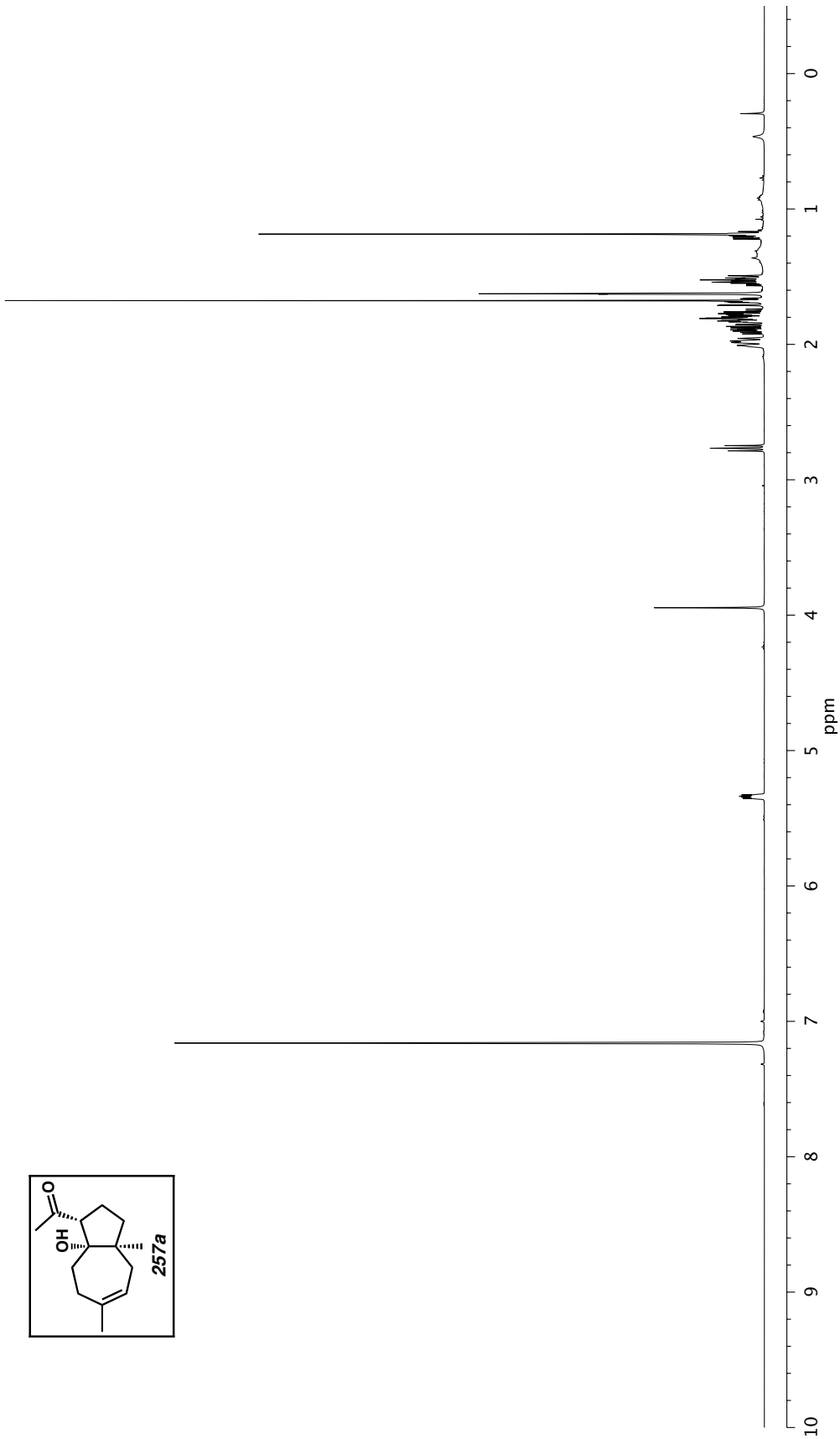


Figure A5.17.1. ^{1}H NMR (500 MHz, C_6D_6) of compound **257a**.

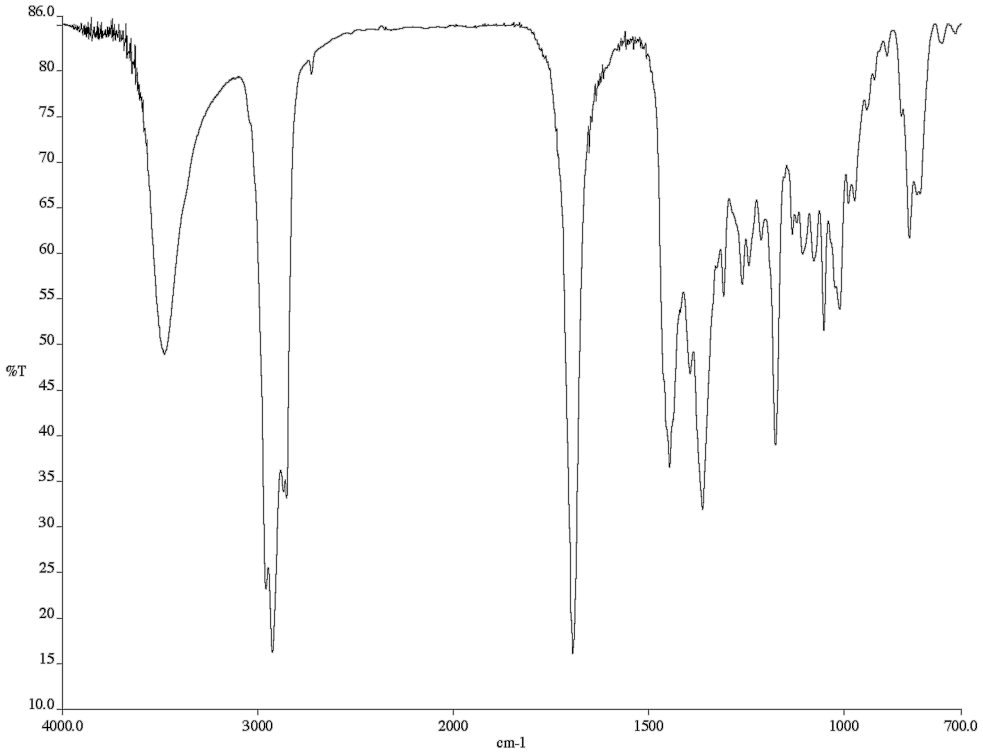


Figure A5.17.2. Infrared spectrum (thin film/NaCl) of compound **257a**.

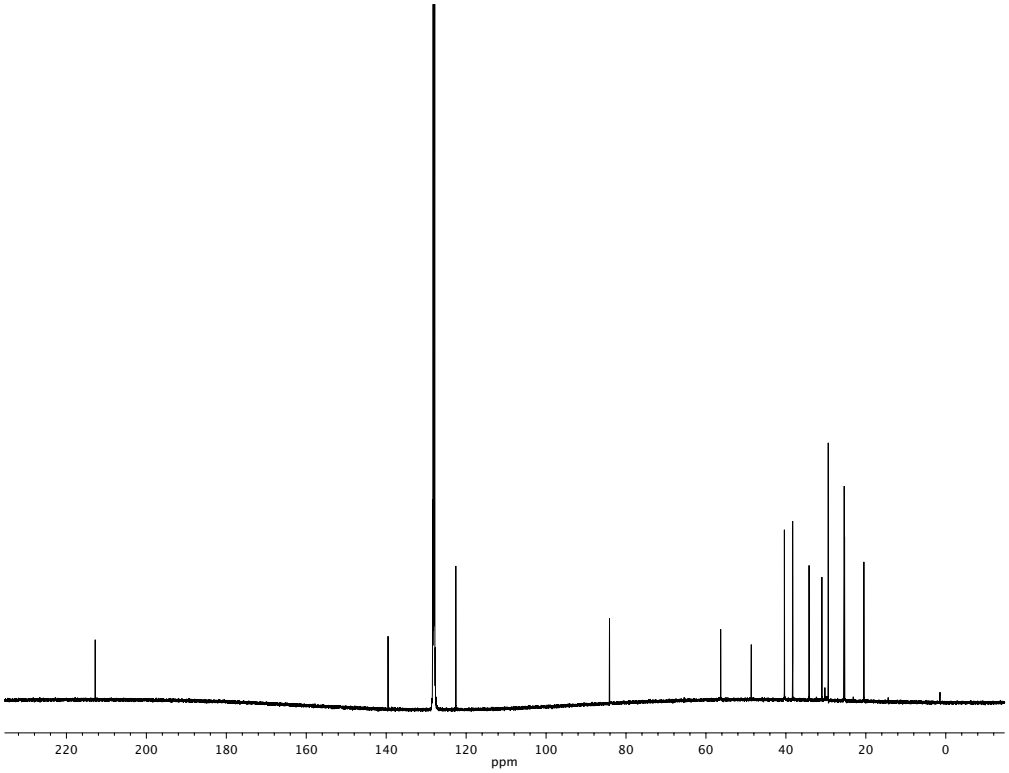


Figure A5.17.3. ^{13}C NMR (125 MHz, C_6D_6) of compound **257a**.

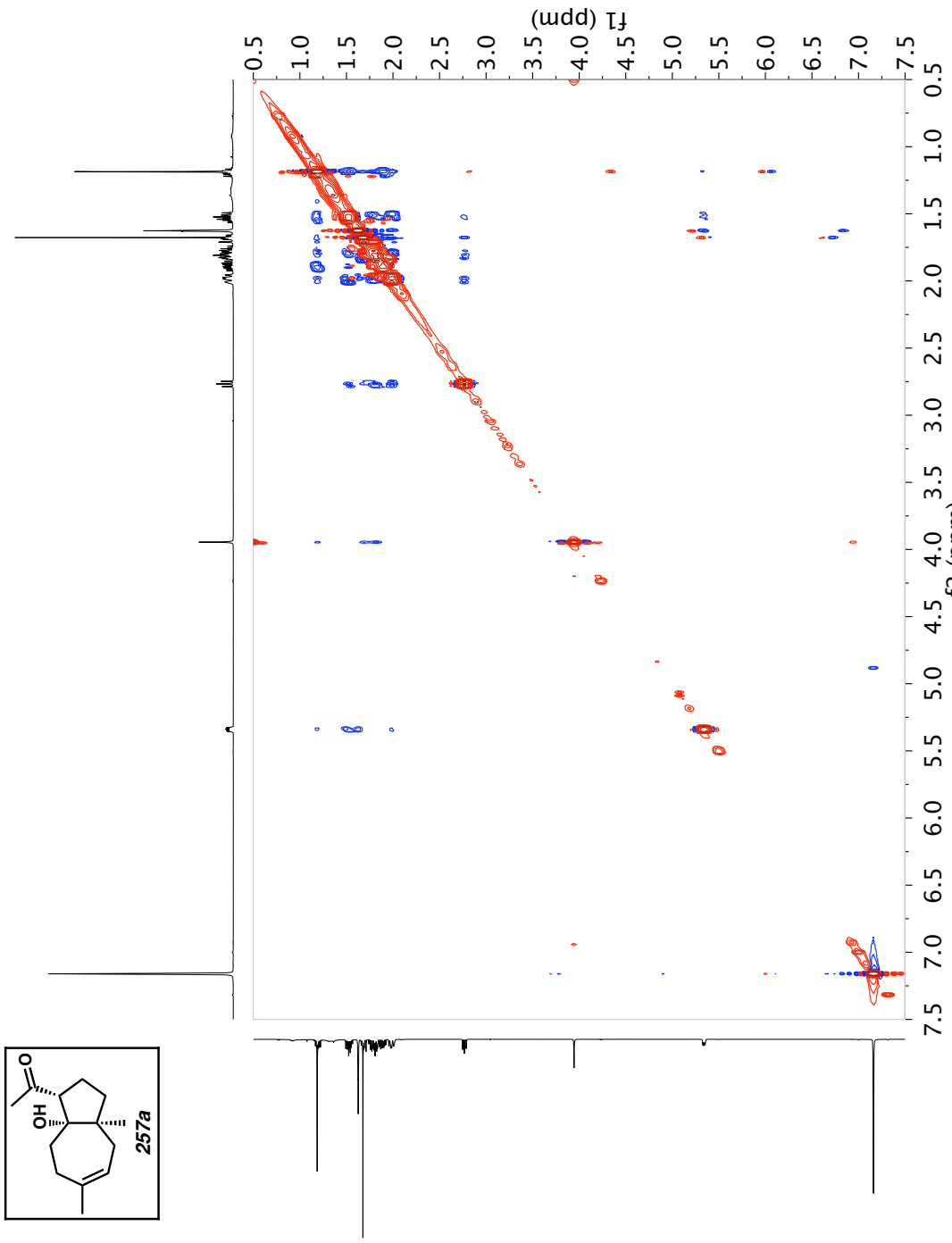


Figure A5.17.4. NOESY NMR (500 MHz, C_6D_6) of compound **257a**.

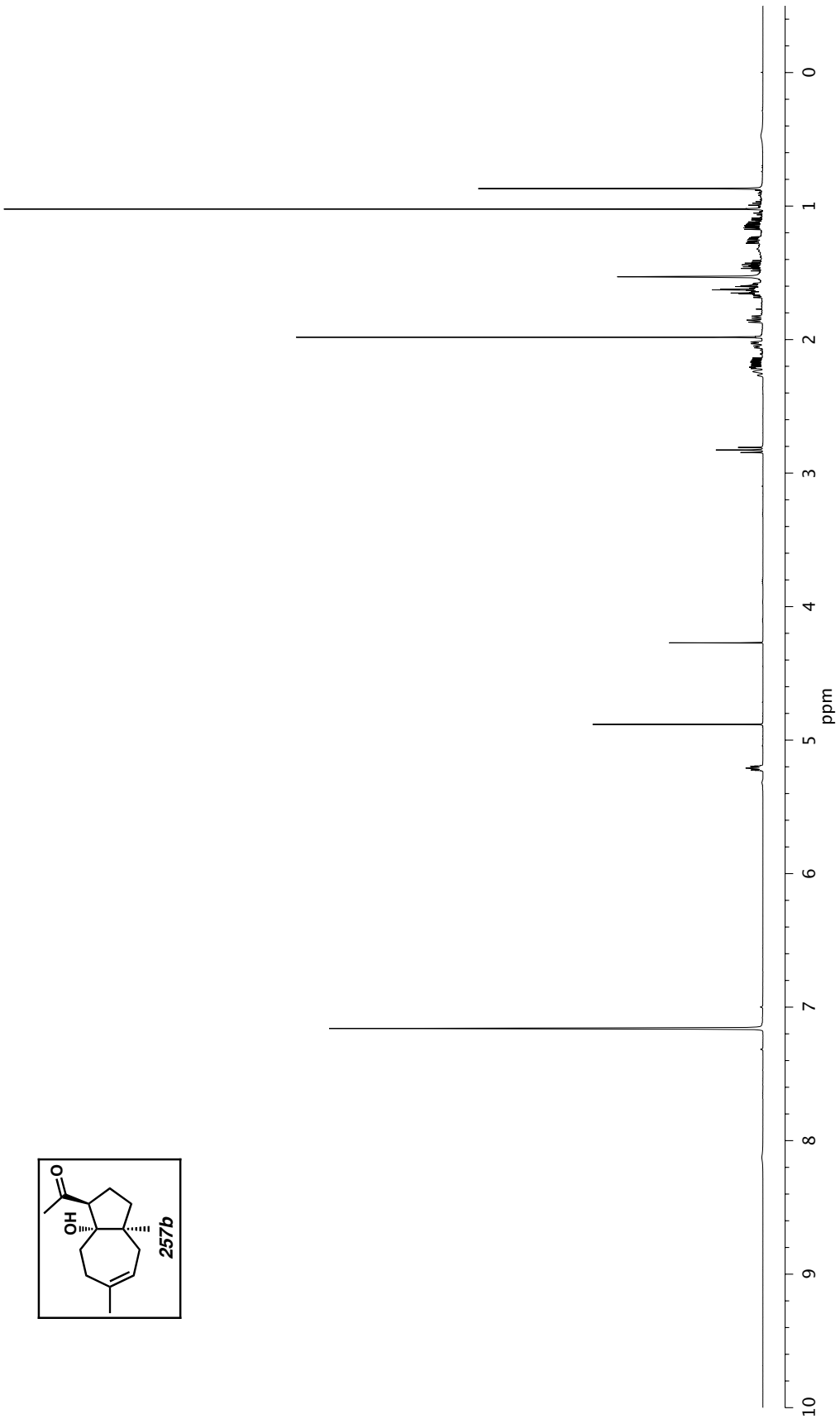


Figure A5.18.1. ^{1}H NMR (500 MHz, C_6D_6) of compound **257b**.

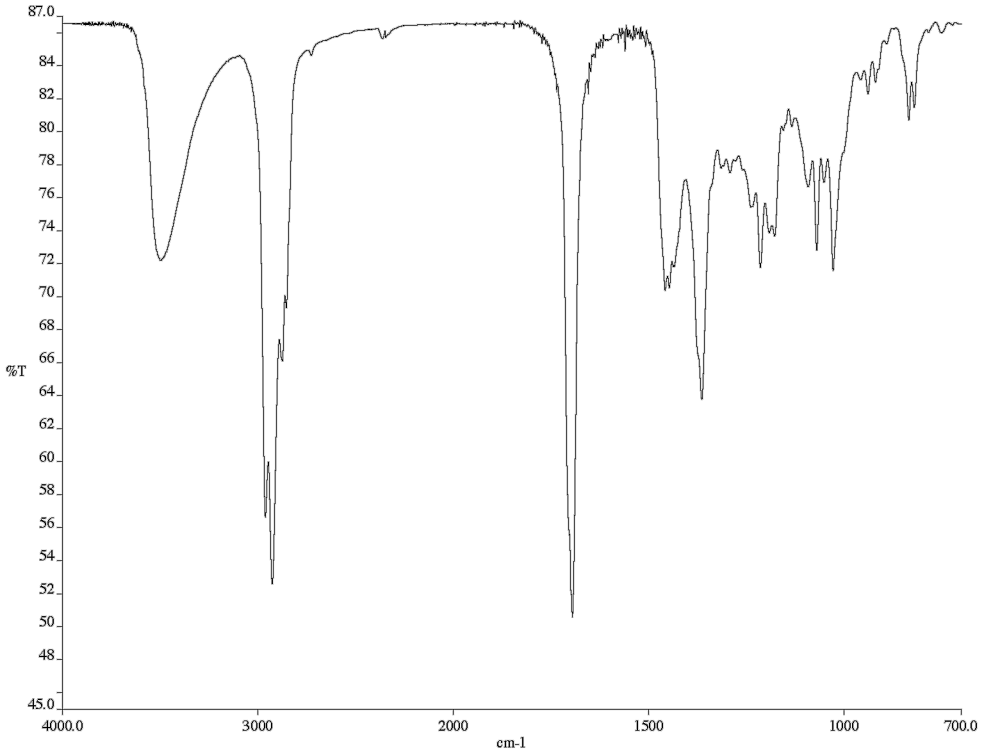


Figure A5.18.2. Infrared spectrum (thin film/NaCl) of compound **257b**.

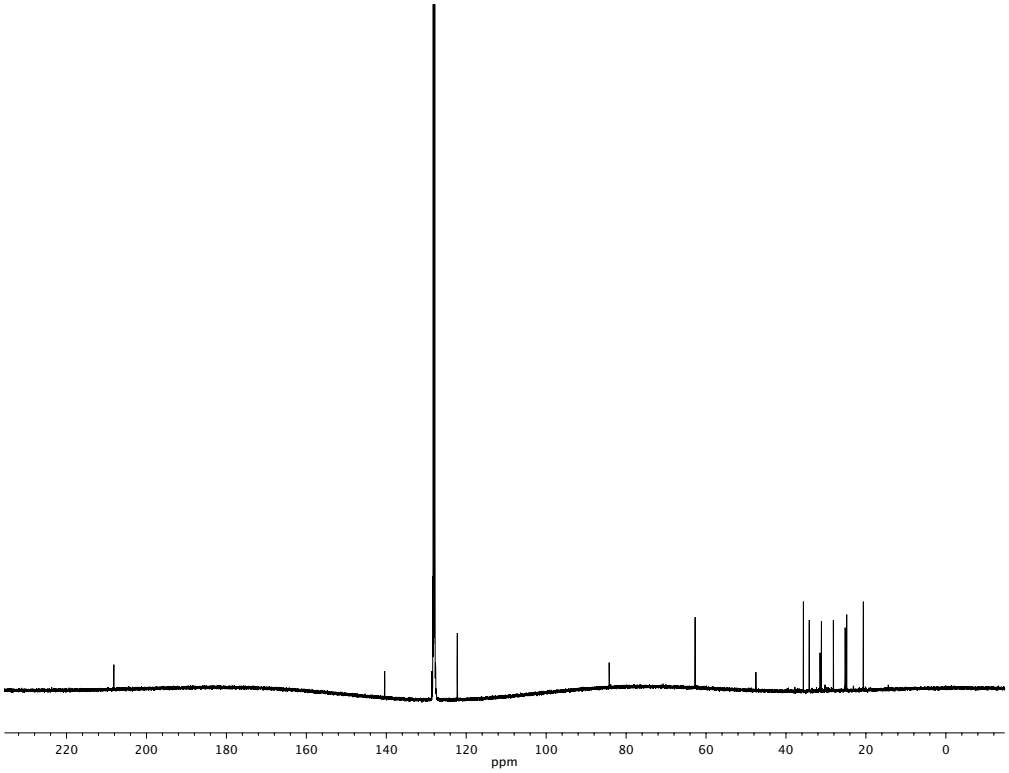


Figure A5.18.3. ^{13}C NMR (125 MHz, C_6D_6) of compound **257b**.

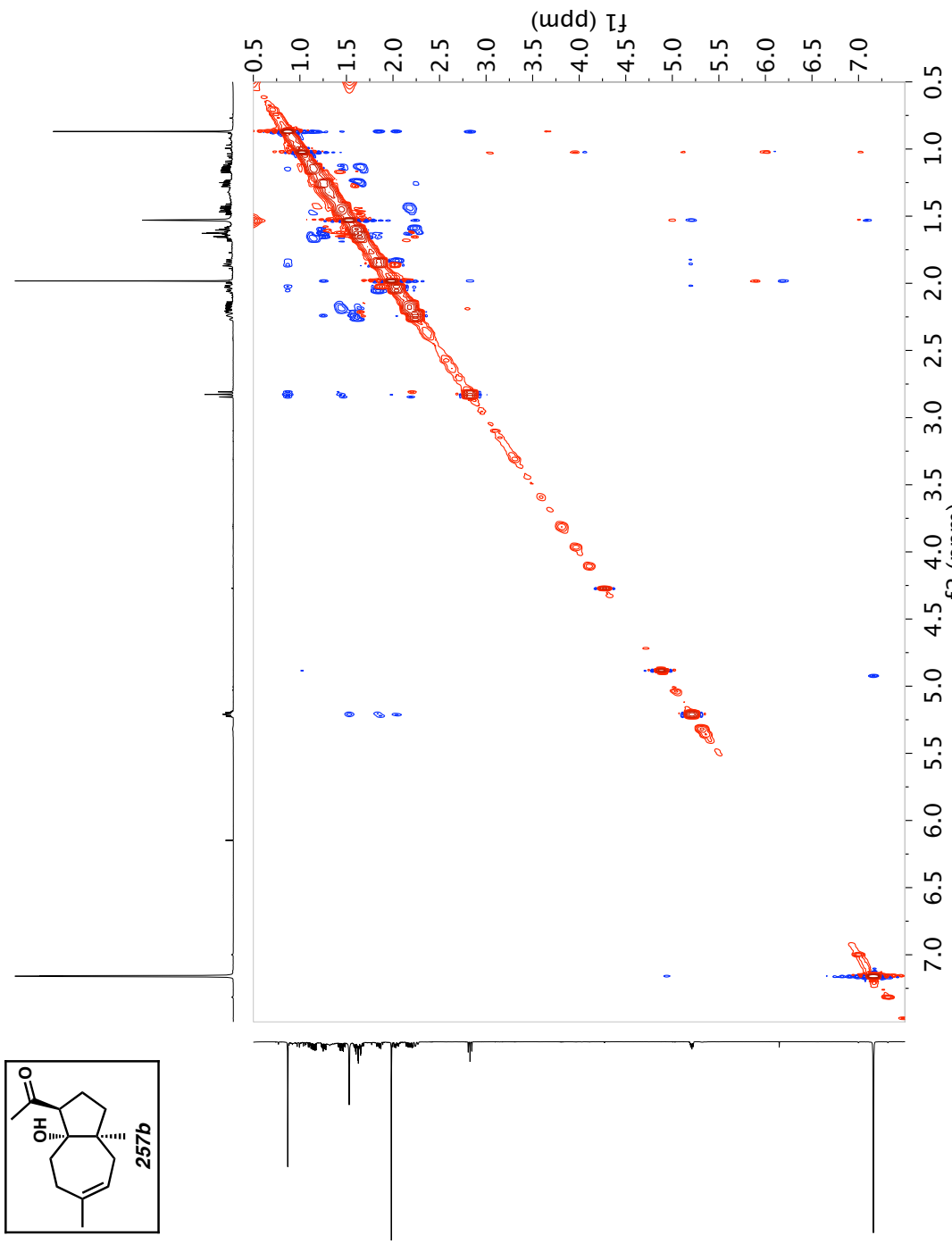


Figure A5.18.4. NOESY NMR (500 MHz, C_6D_6) of compound **257b**.

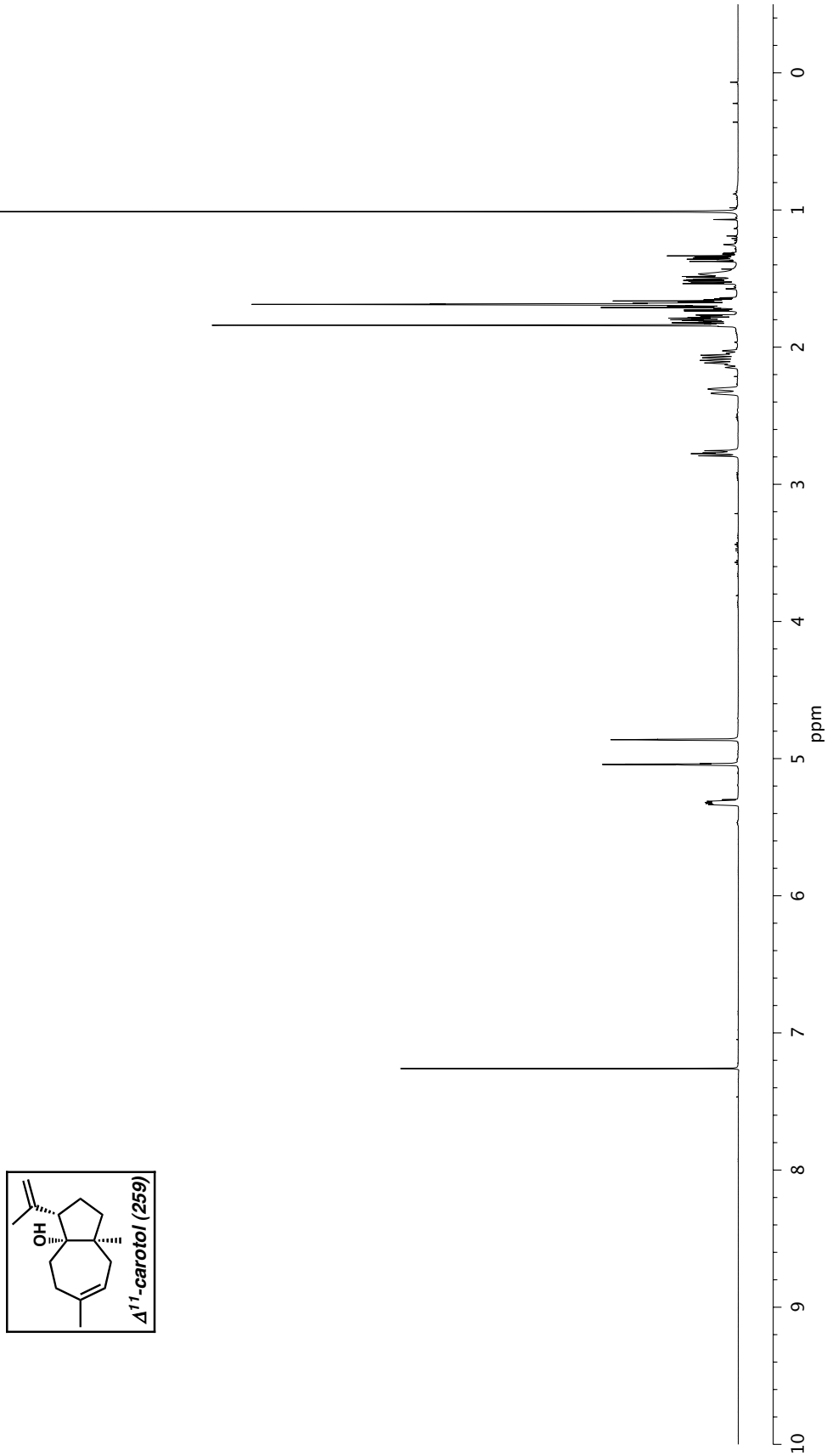


Figure A5.19.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **259**.

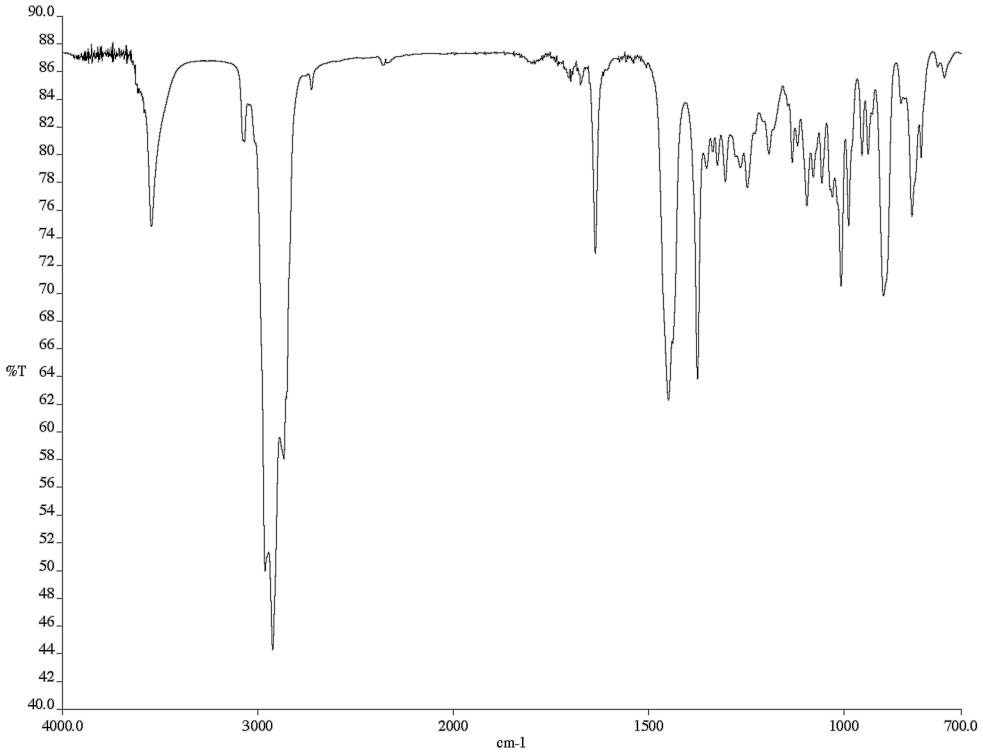


Figure A5.19.2. Infrared spectrum (thin film/NaCl) of compound **259**.

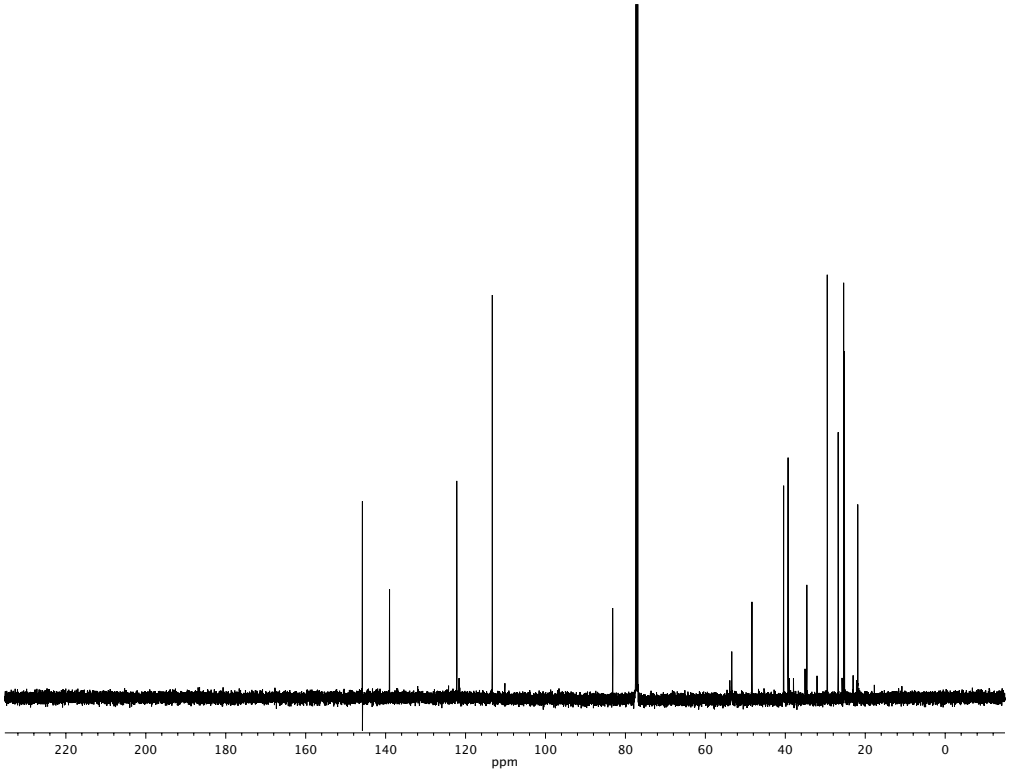


Figure A5.19.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **259**.

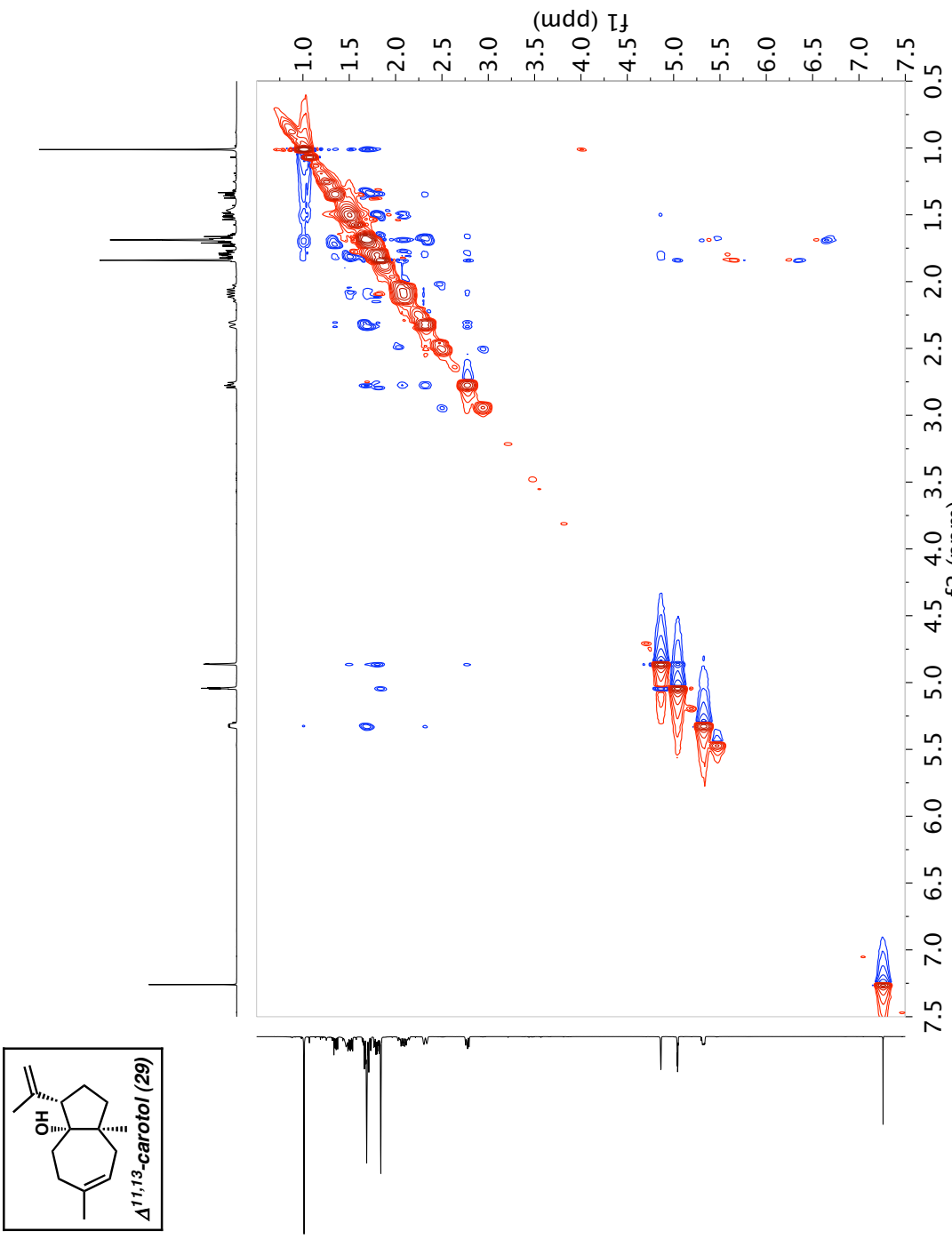


Figure A5.19.4. NOESY NMR (500 MHz, $CDCl_3$) of compound **259**.

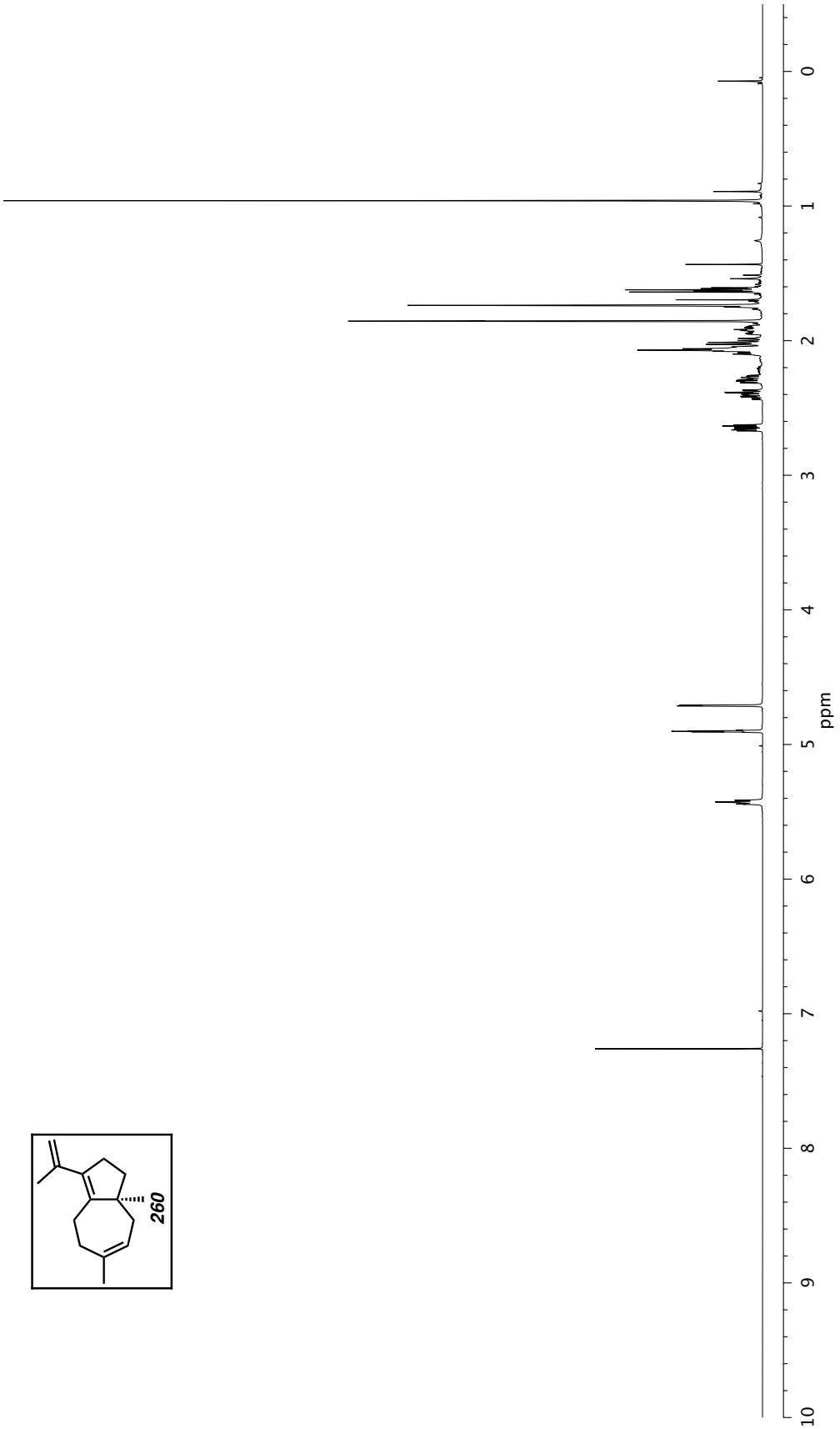


Figure A5.20.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **260**.

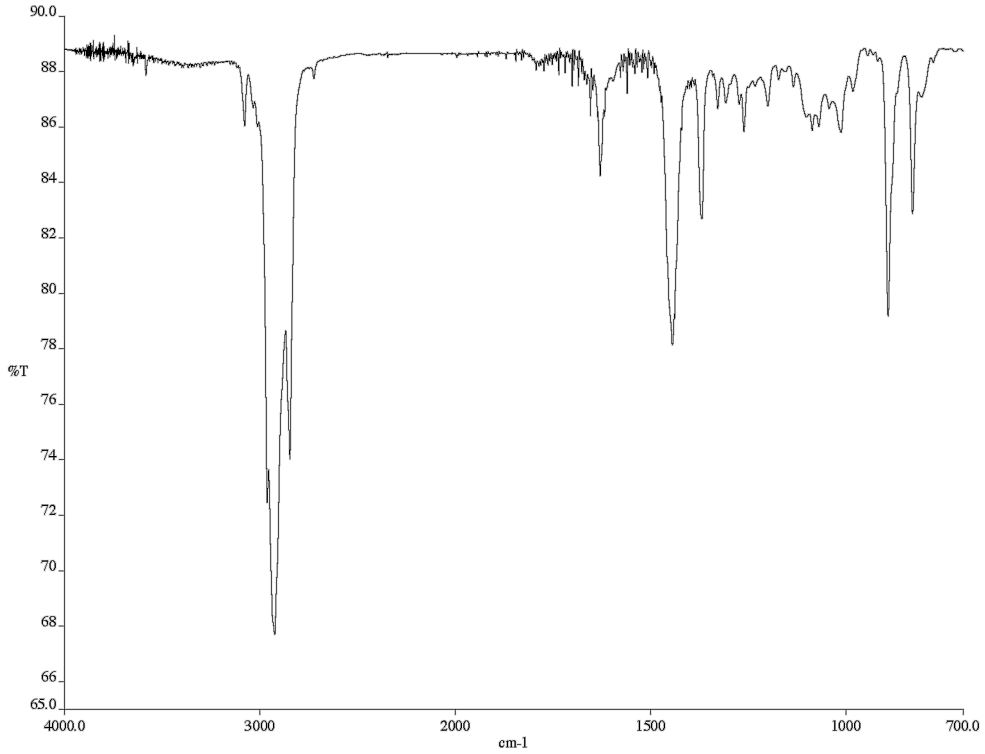


Figure A5.20.2. Infrared spectrum (thin film/NaCl) of compound **260**.

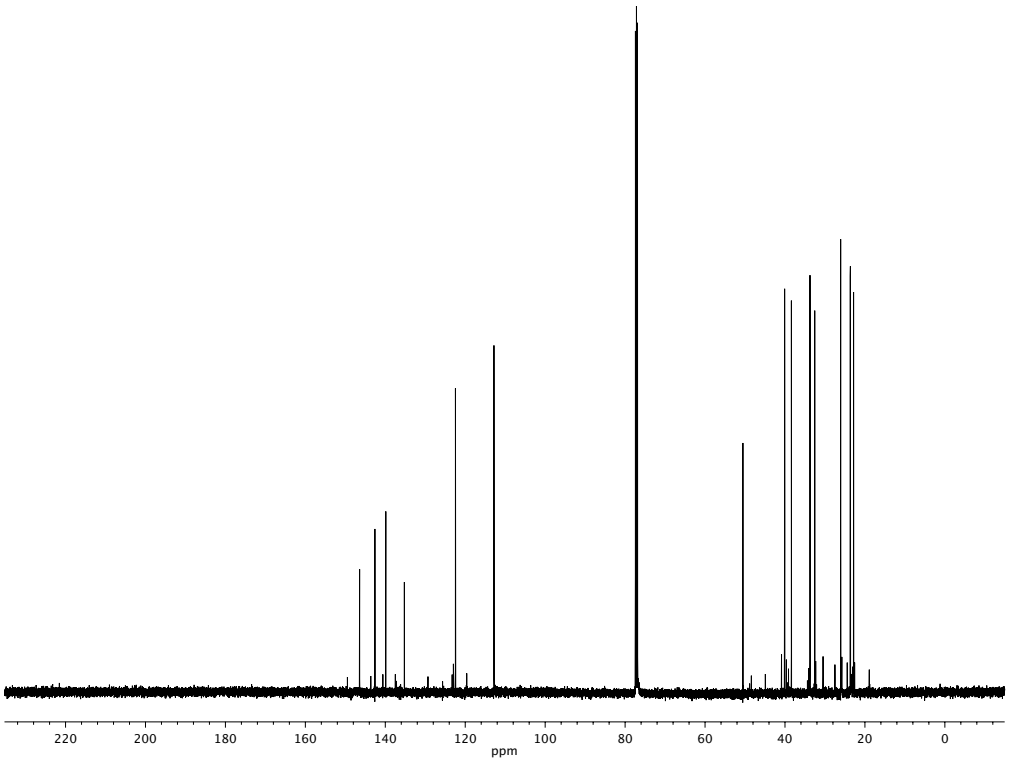


Figure A5.20.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **260**.

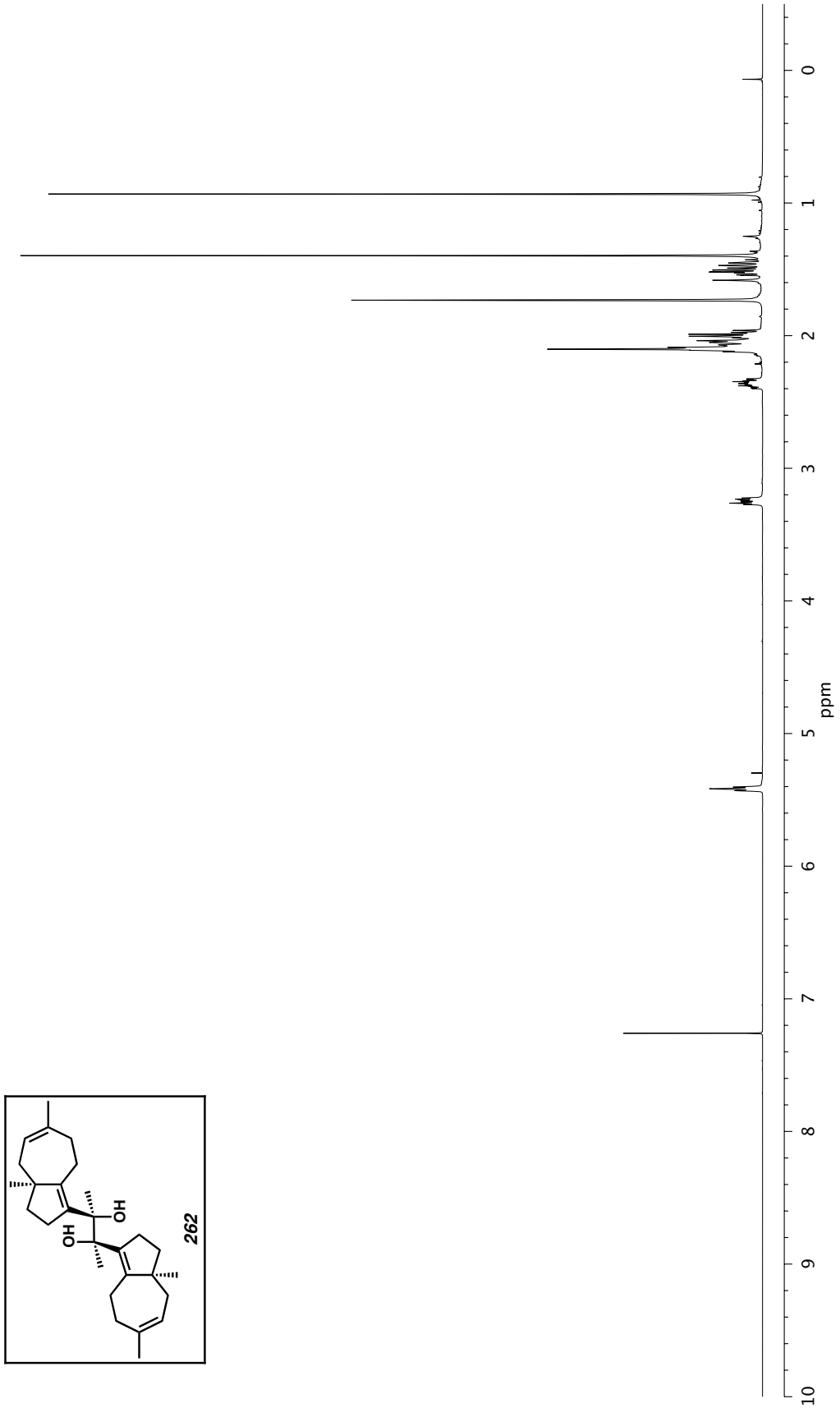


Figure A5.21.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **262**.

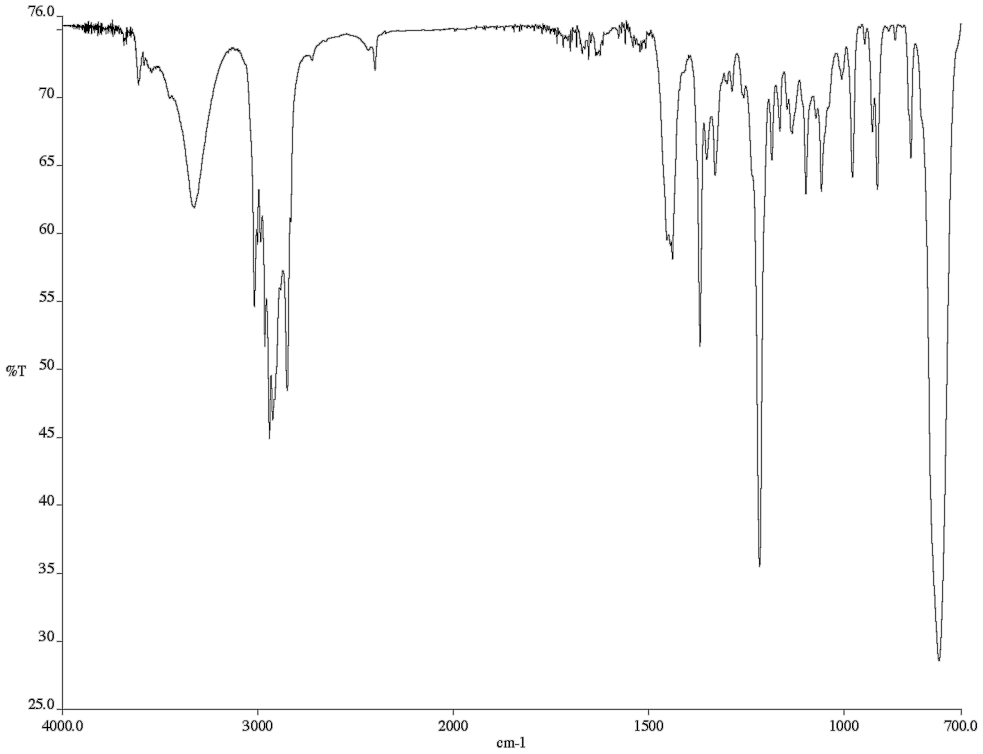


Figure A5.21.2. Infrared spectrum (thin film/NaCl) of compound **262**.

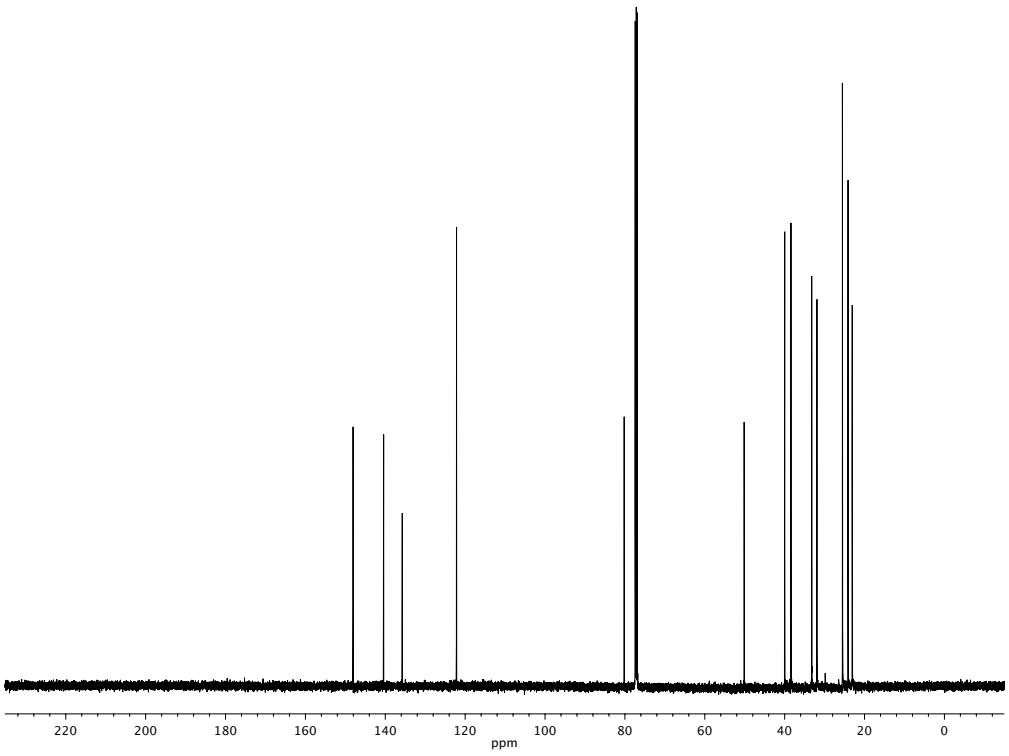


Figure A5.21.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **262**.

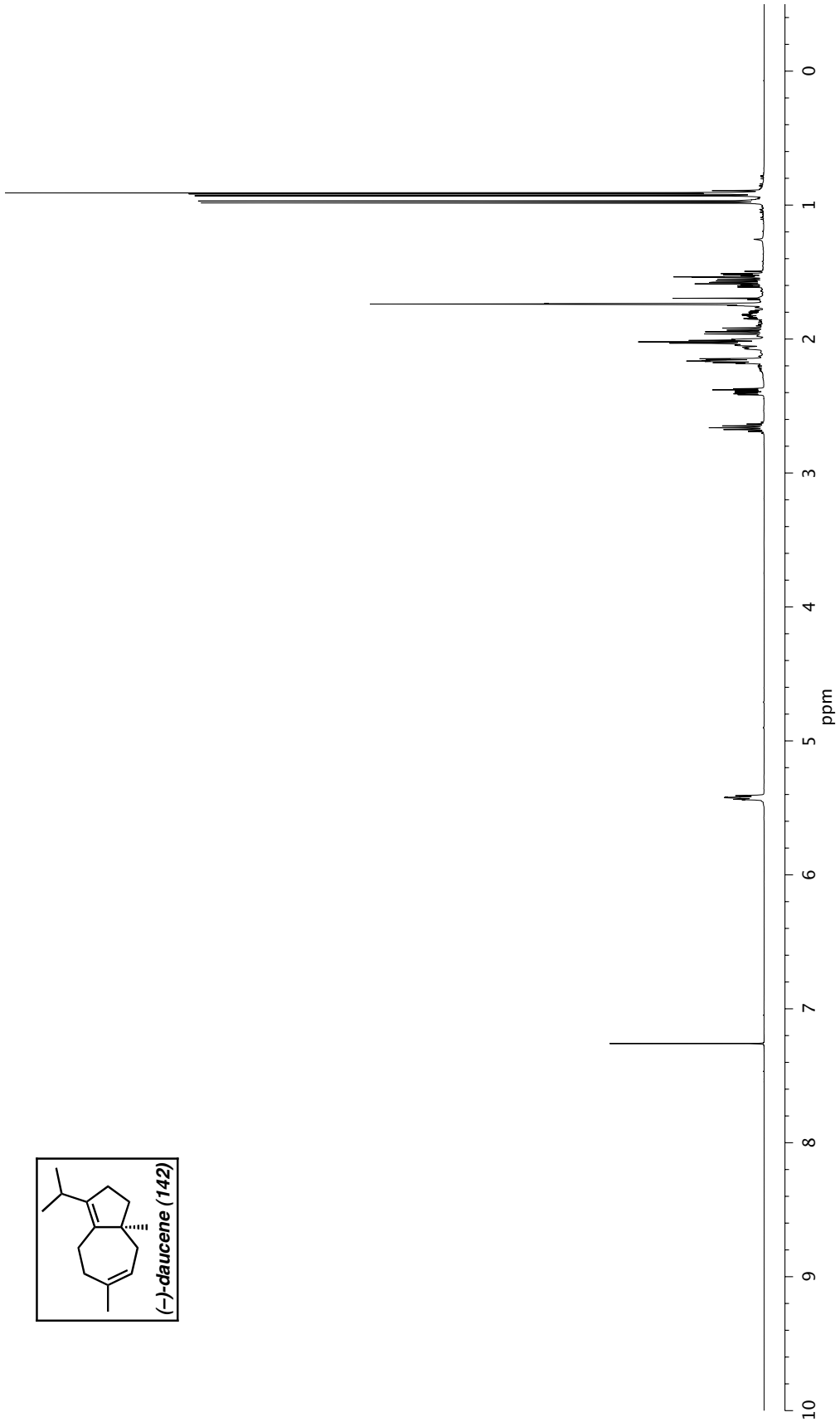


Figure A5.22.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **142**.

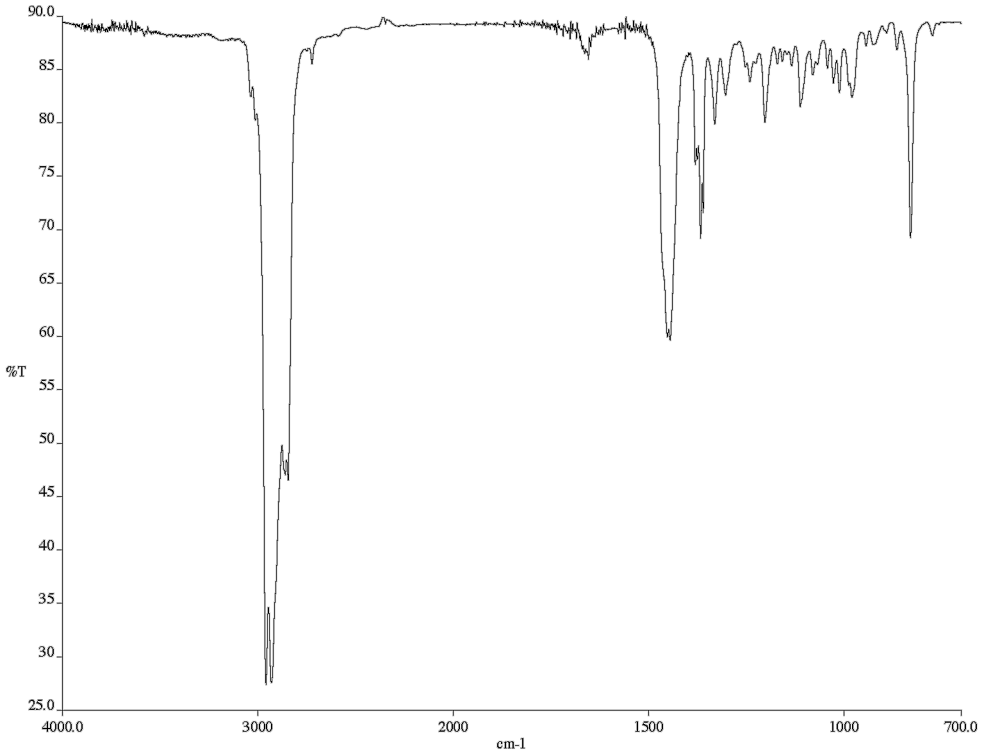


Figure A5.22.2. Infrared spectrum (thin film/NaCl) of compound **142**.

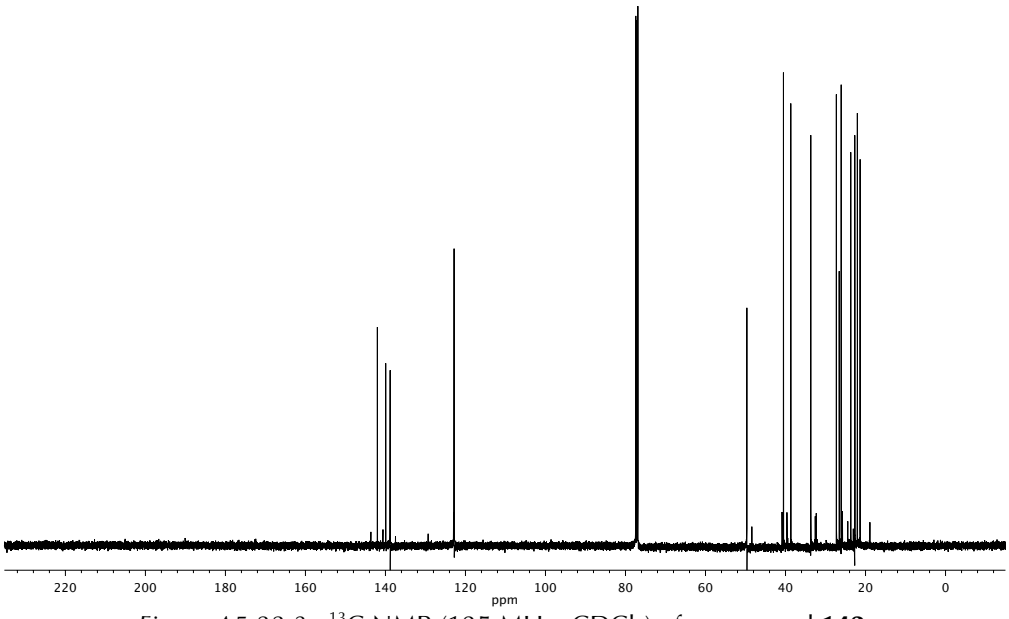


Figure A5.22.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **142**.

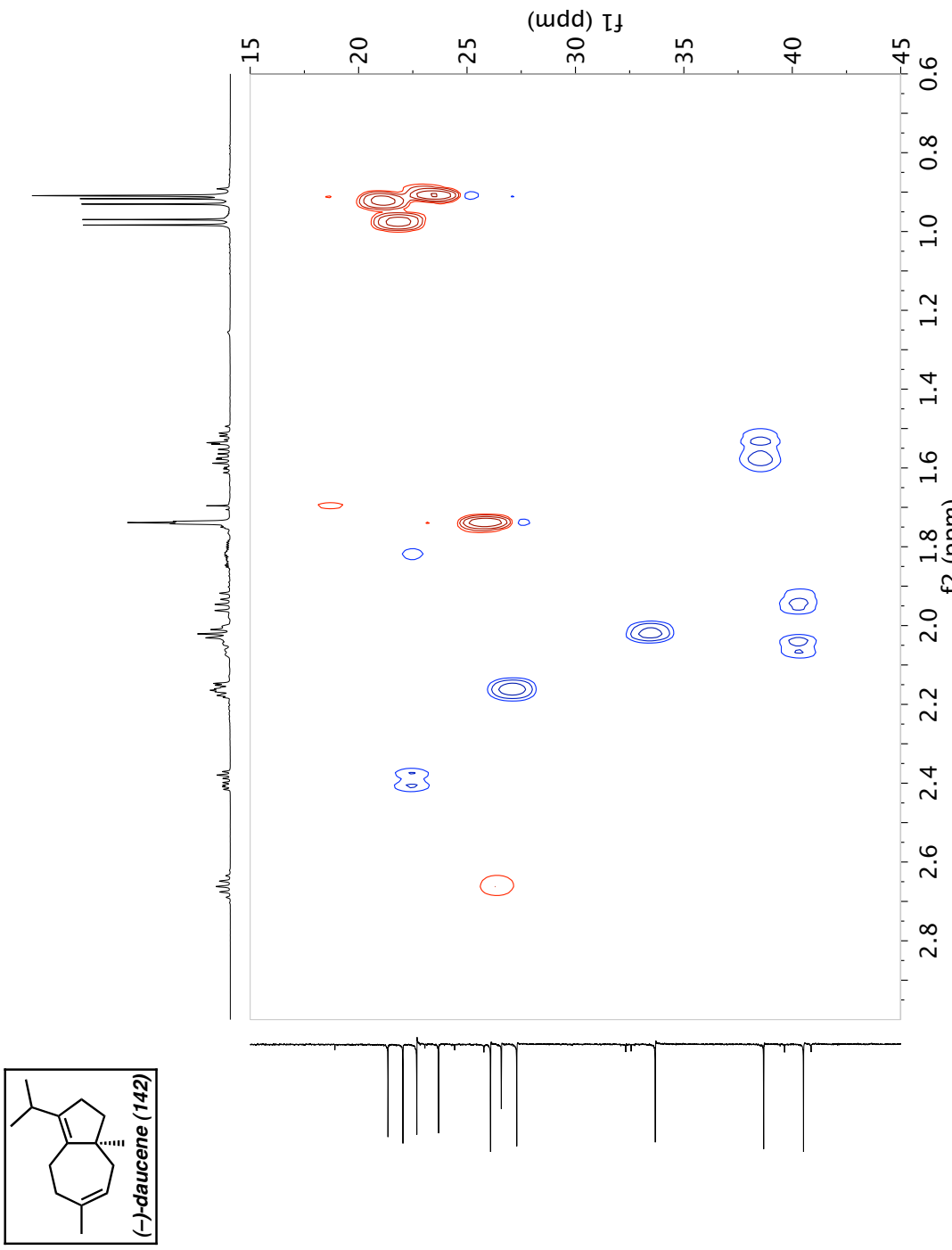


Figure A5.22.4. HSQC NMR (500 MHz, $CDCl_3$) of compound **142**.

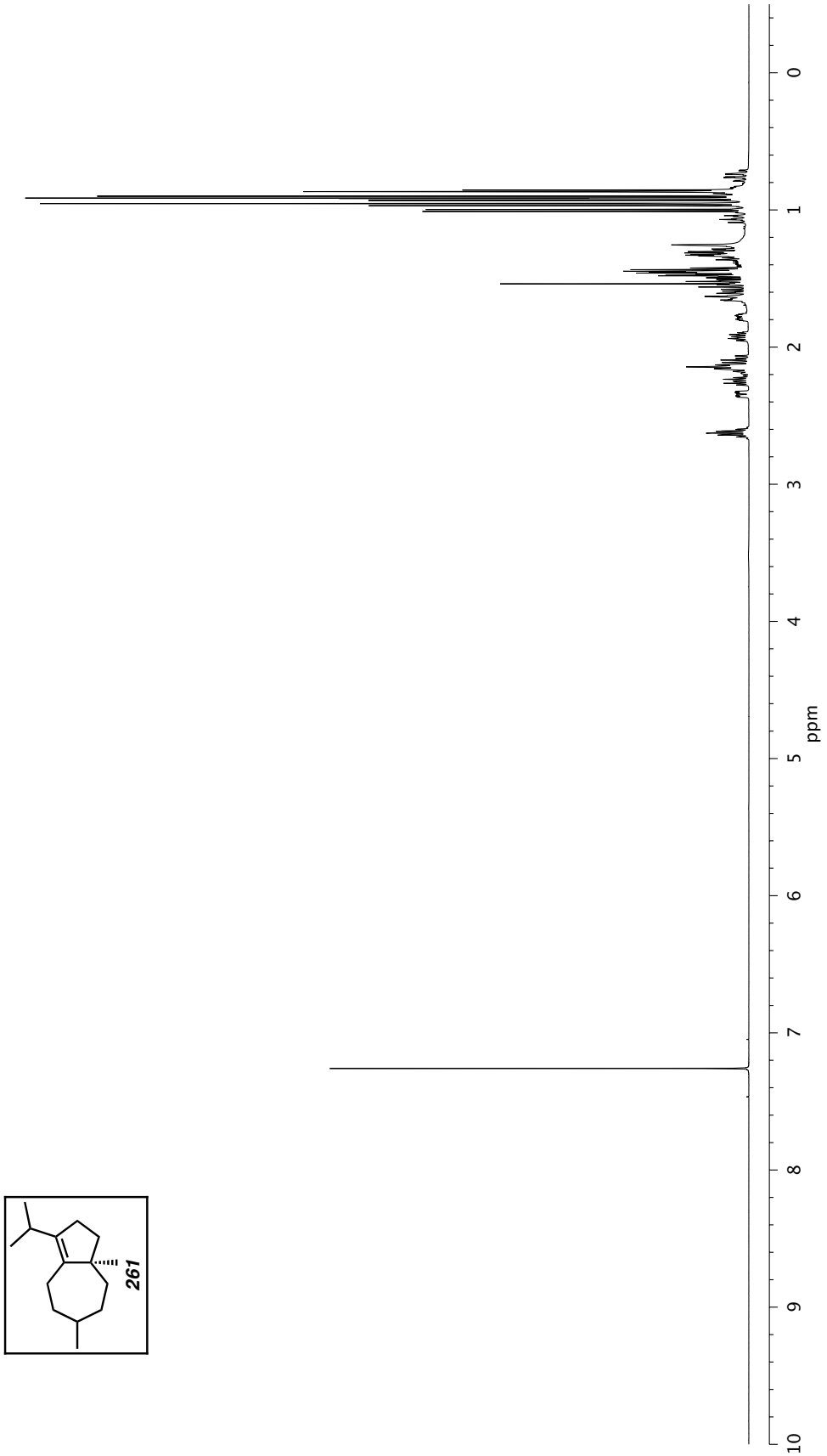


Figure A5.23.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **261**.

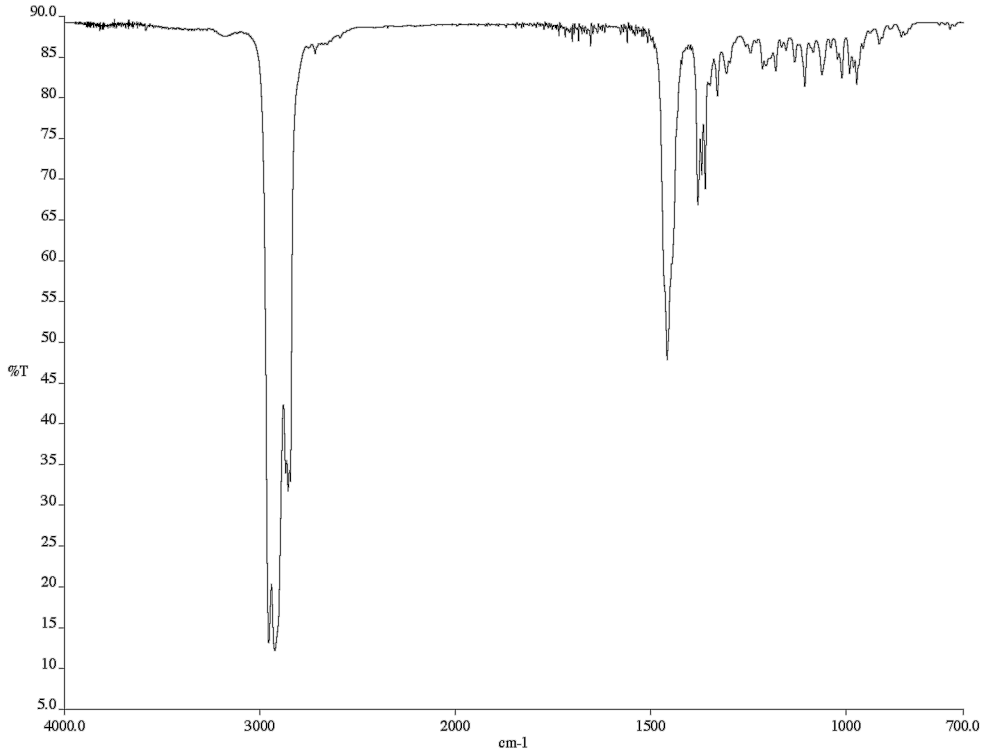


Figure A5.23.2. Infrared spectrum (thin film/NaCl) of compound **261**.

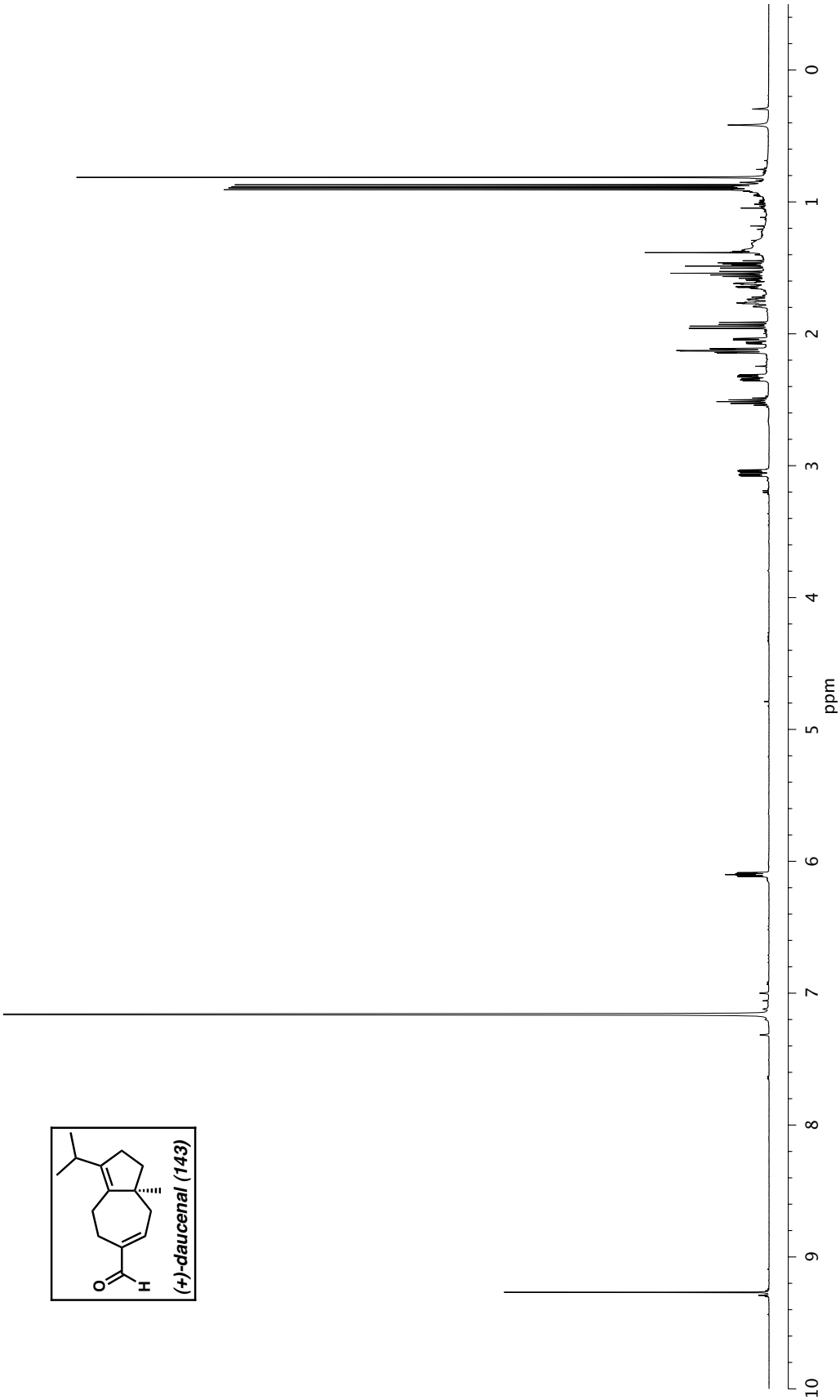


Figure A5.24.1. ^{1}H NMR (500 MHz, C_6D_6) of compound **143**.

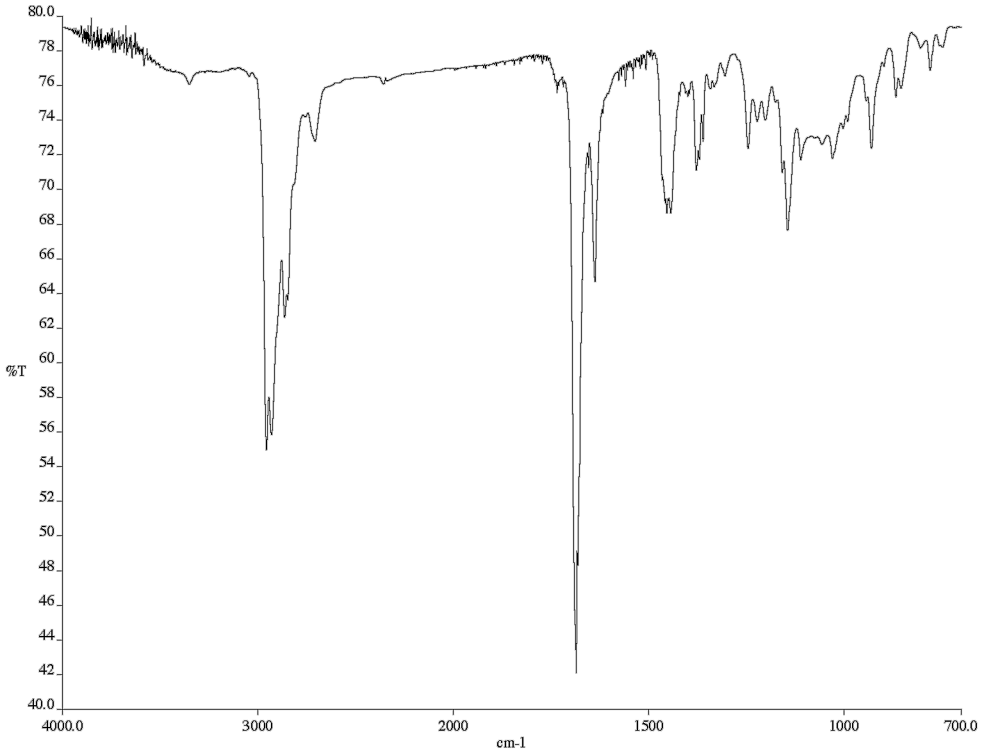


Figure A5.24.2. Infrared spectrum (thin film/NaCl) of compound **143**.

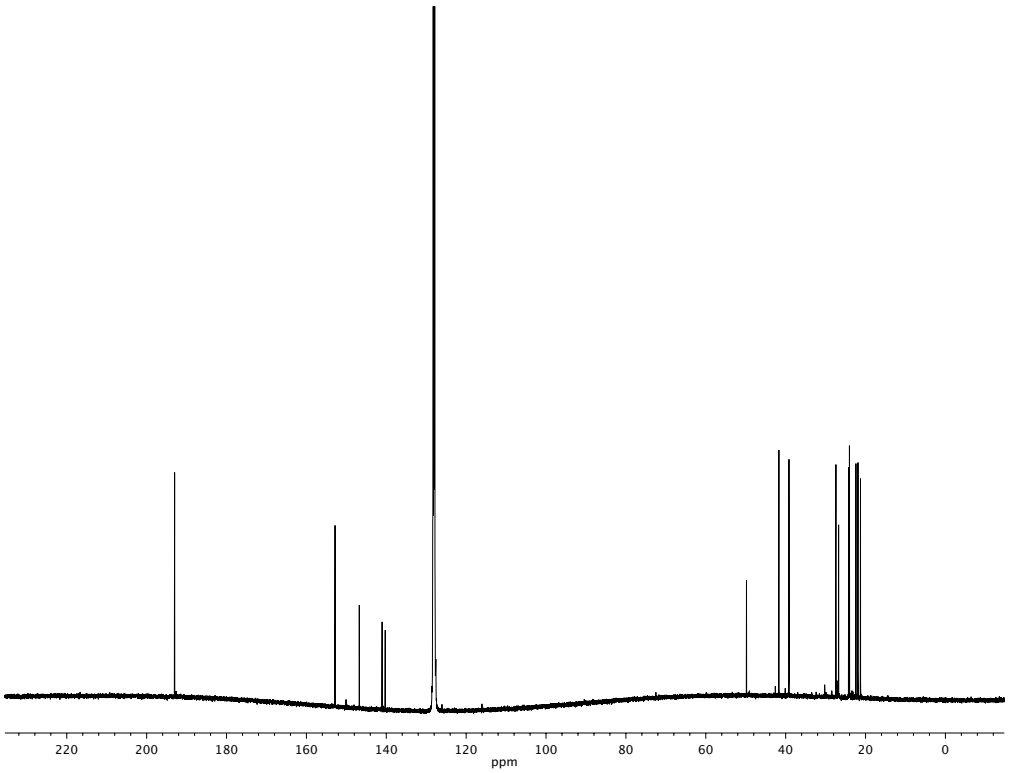


Figure A5.24.3. ^{13}C NMR (125 MHz, C_6D_6) of compound **143**.

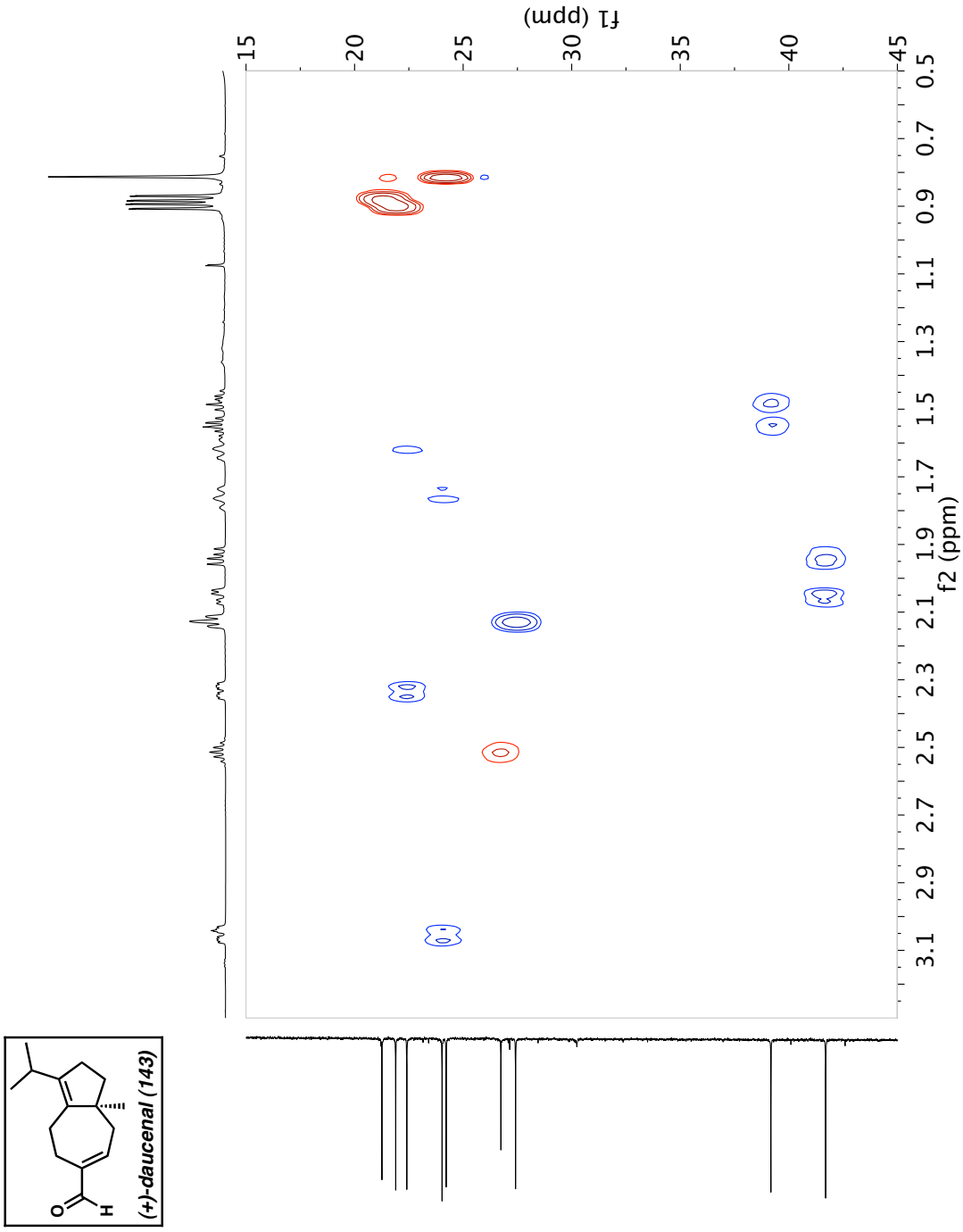


Figure A5.24.4. HSQC NMR (500 MHz, C_6D_6) of compound **143**.

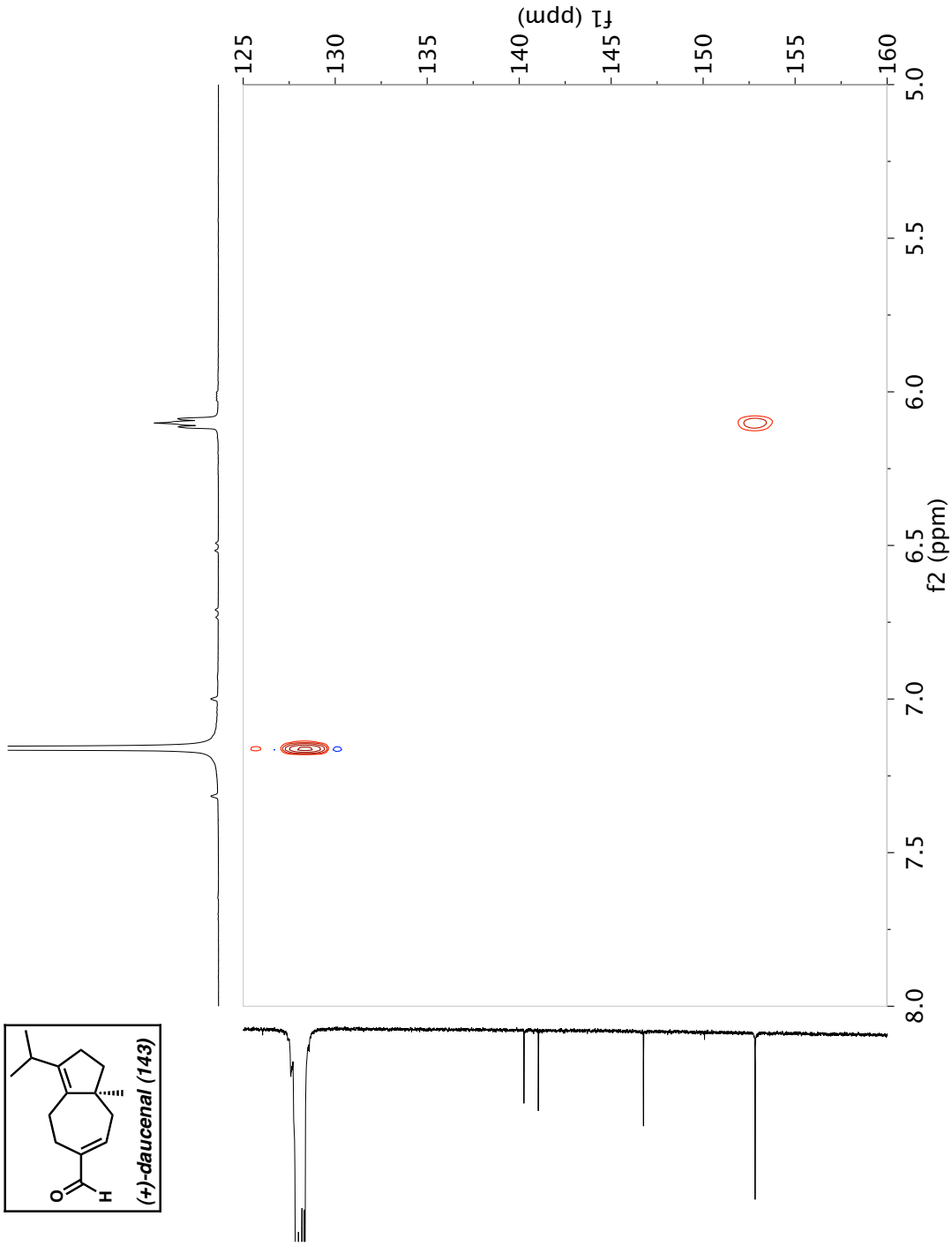


Figure A5.24.5. HSQC NMR (500 MHz, C_6D_6) of compound **143**.

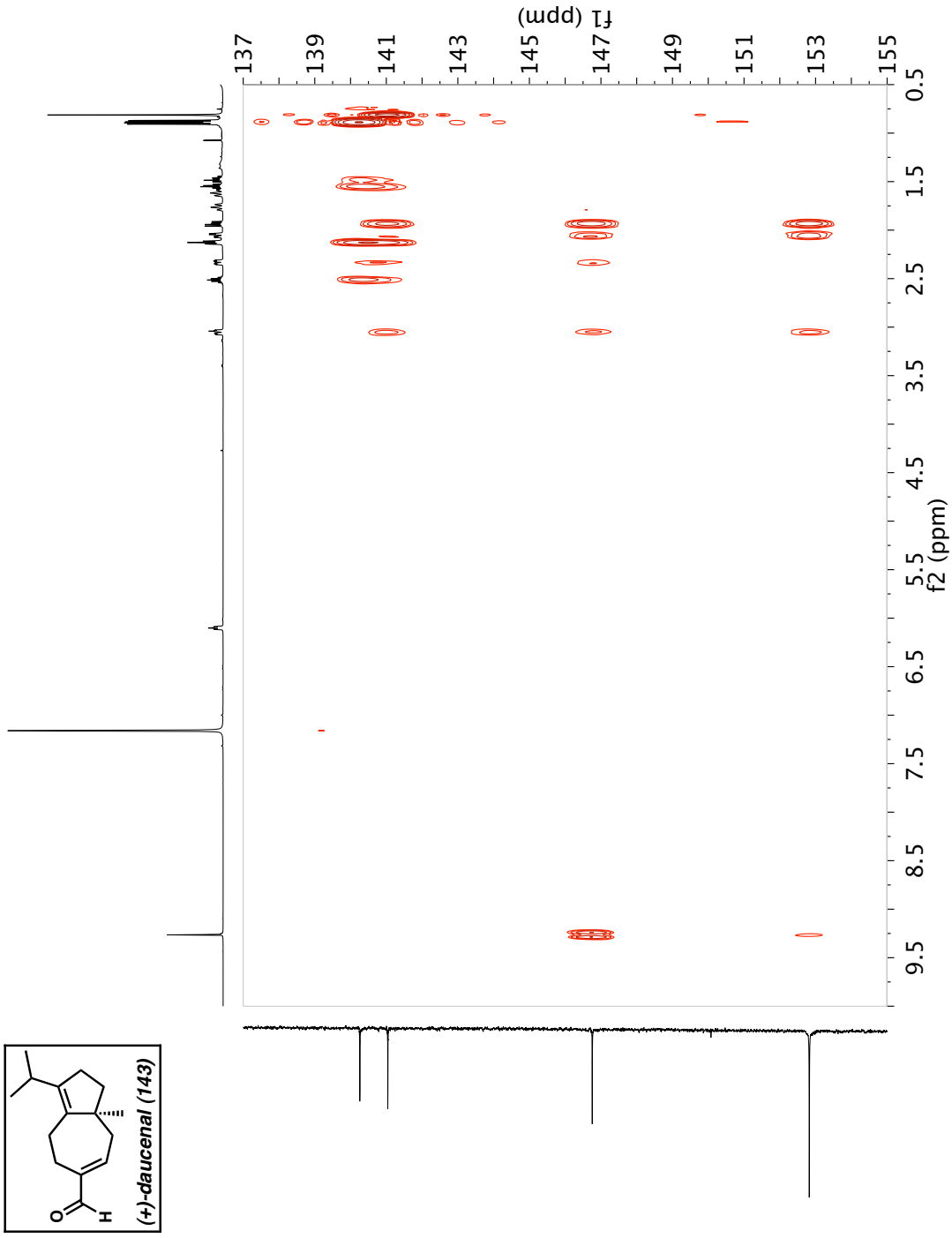


Figure A5.24.6. HMBC NMR (500 MHz, C_6D_6) of compound **143**.

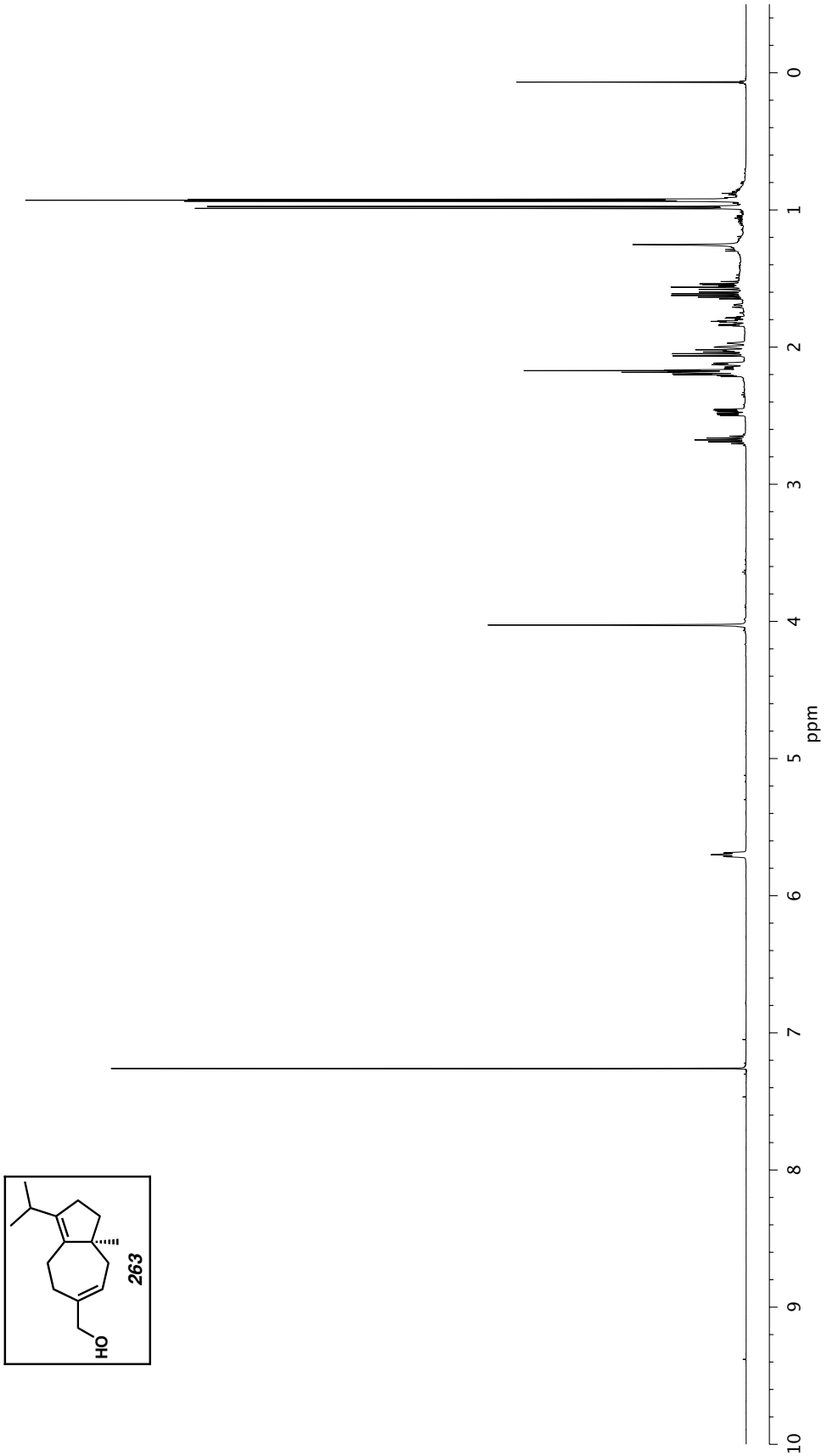


Figure A5.25.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **263**.

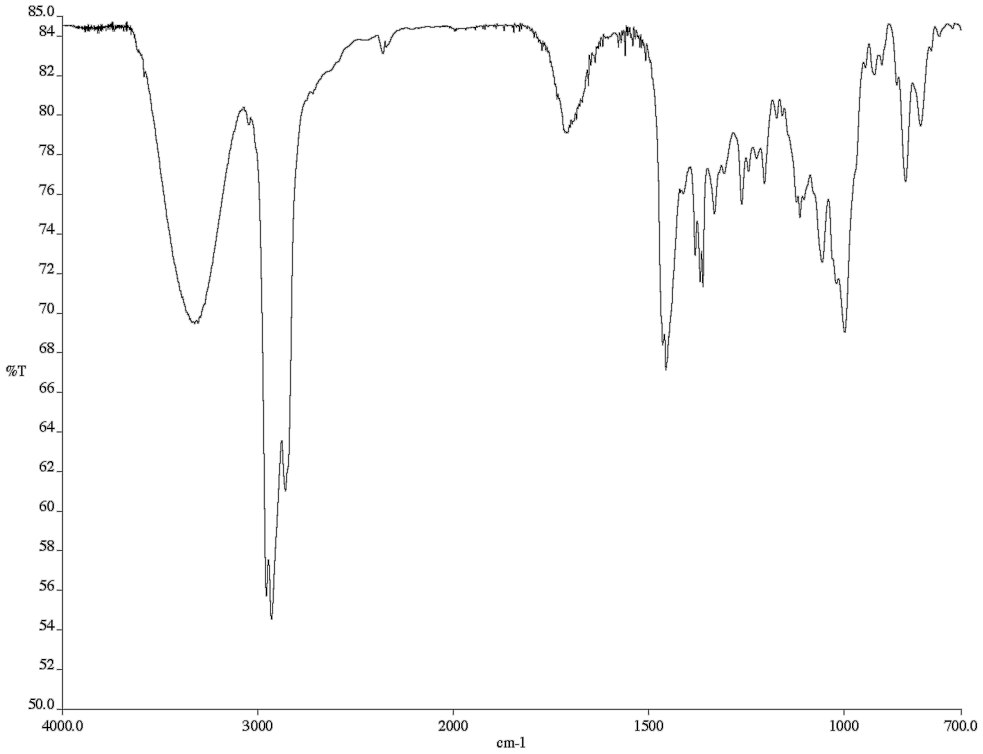


Figure A5.25.2. Infrared spectrum (thin film/NaCl) of compound **263**.

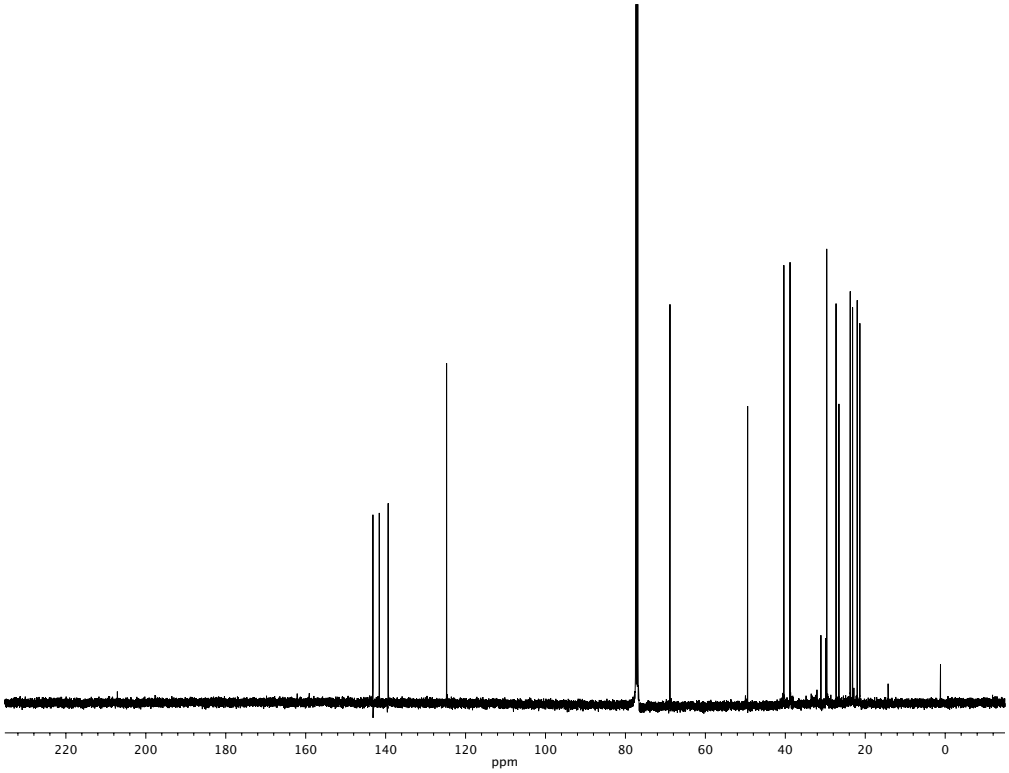


Figure A5.25.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **263**.

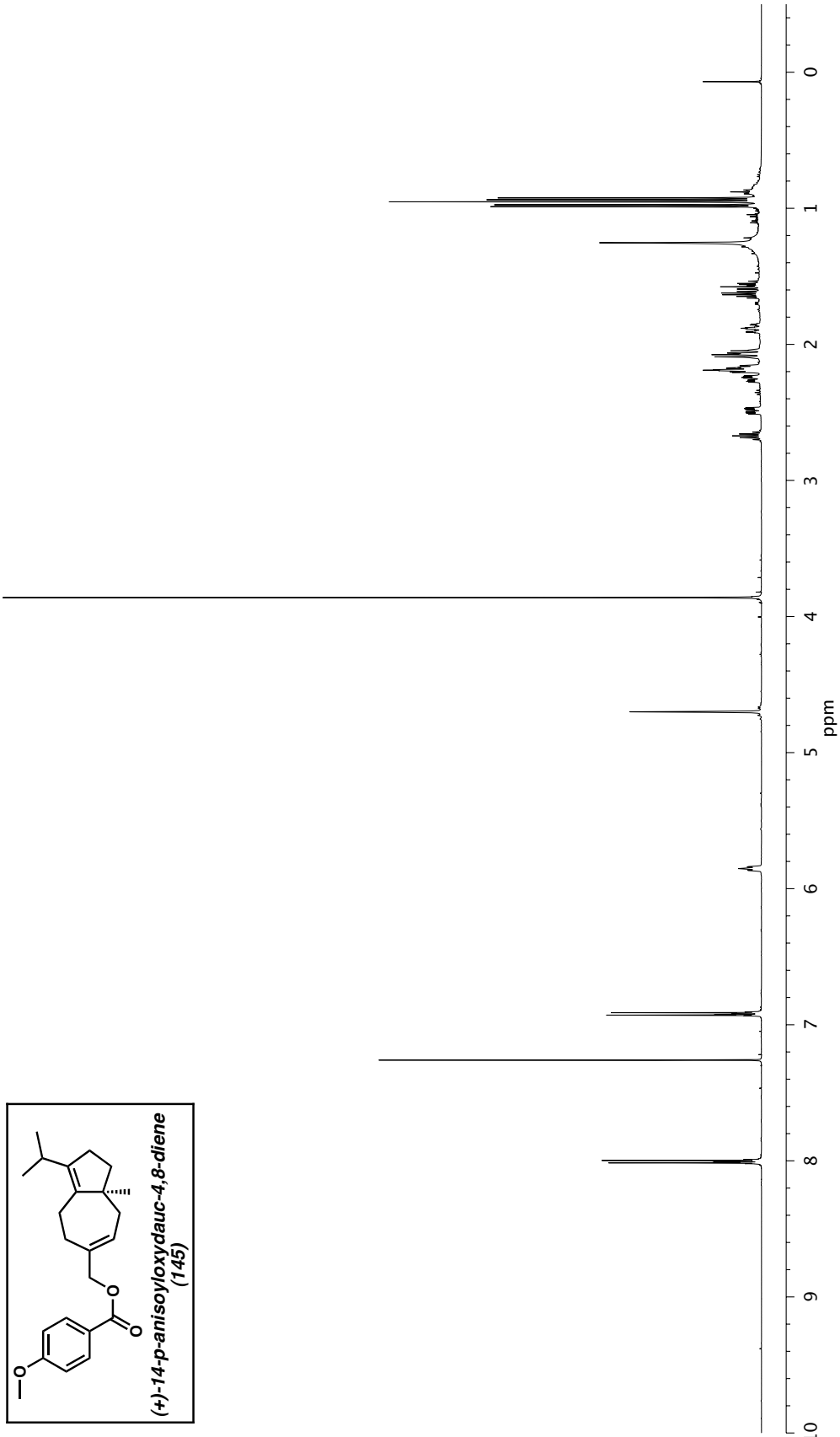


Figure A5.26.1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **145**.

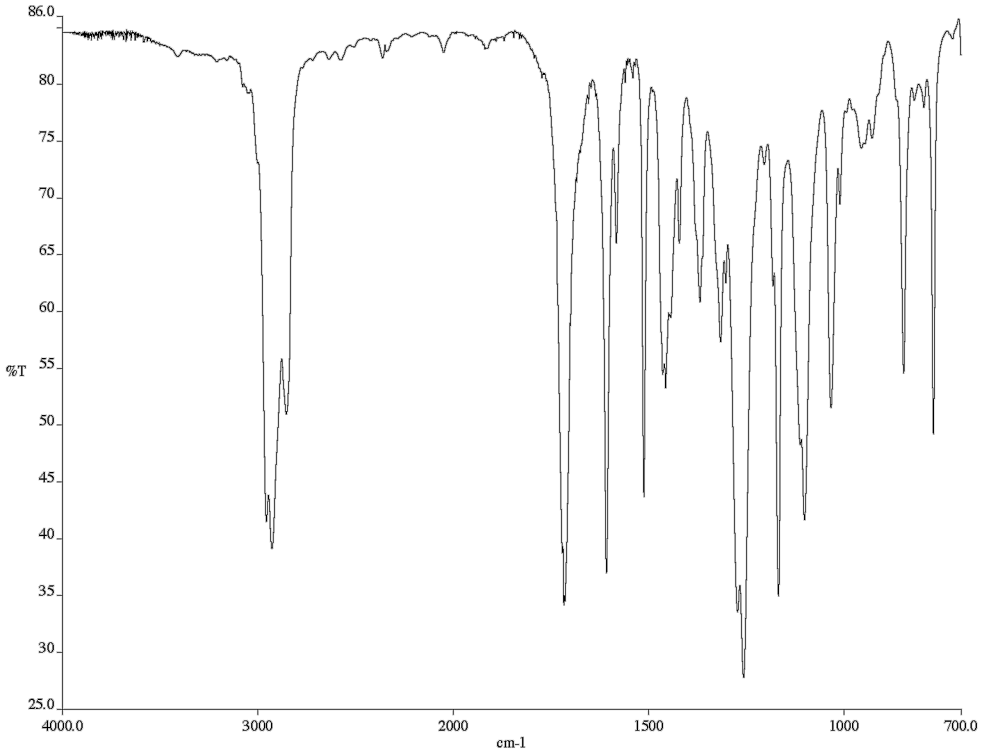


Figure A5.26.2. Infrared spectrum (thin film/NaCl) of compound **145**.

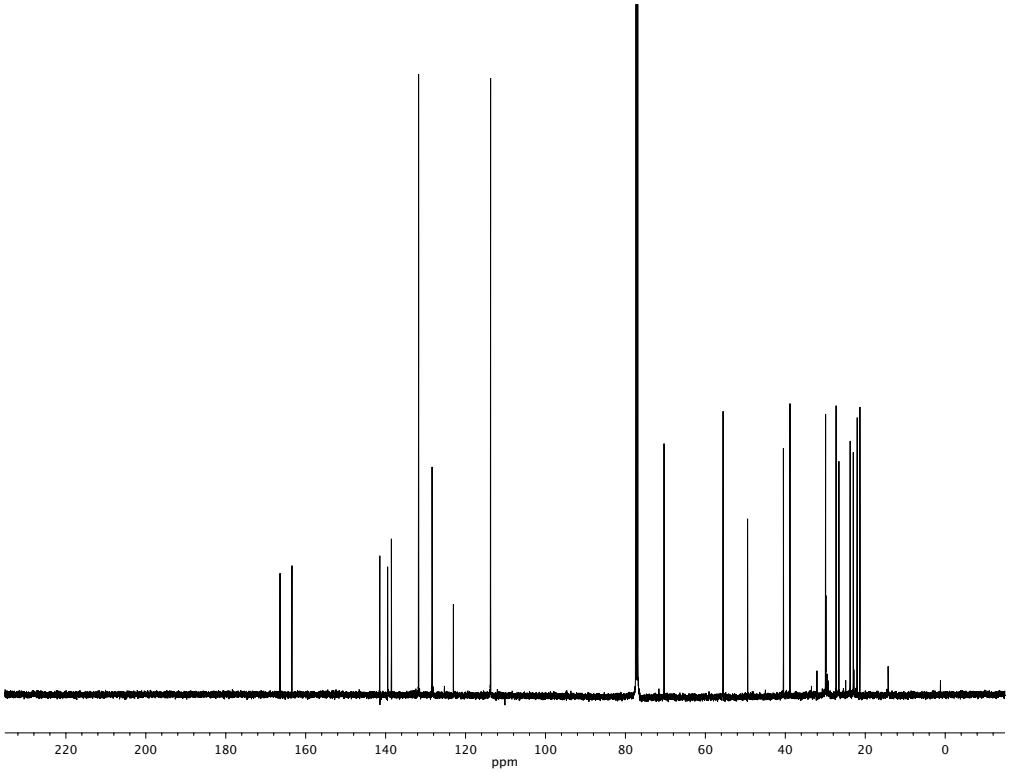


Figure A5.26.3. ^{13}C NMR (125 MHz, $CDCl_3$) of compound **145**.

APPENDIX 6

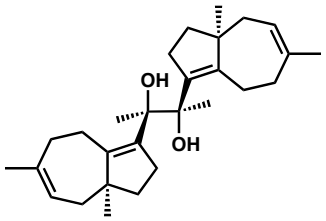
X-Ray Crystallography Reports Relevant to Chapter 3:

Unified Approach to Daucane and Sphenolobane

Bicyclo[5.3.0]decane core: Enantioselective Synthesis of

Four Daucane Sesquiterpenes and Related Molecules

A6.1 CRYSTAL STRUCTURE ANALYSIS OF 262



Compound **262**

(NBB04)

Contents

*Figure A6.1. Diol **262**.*

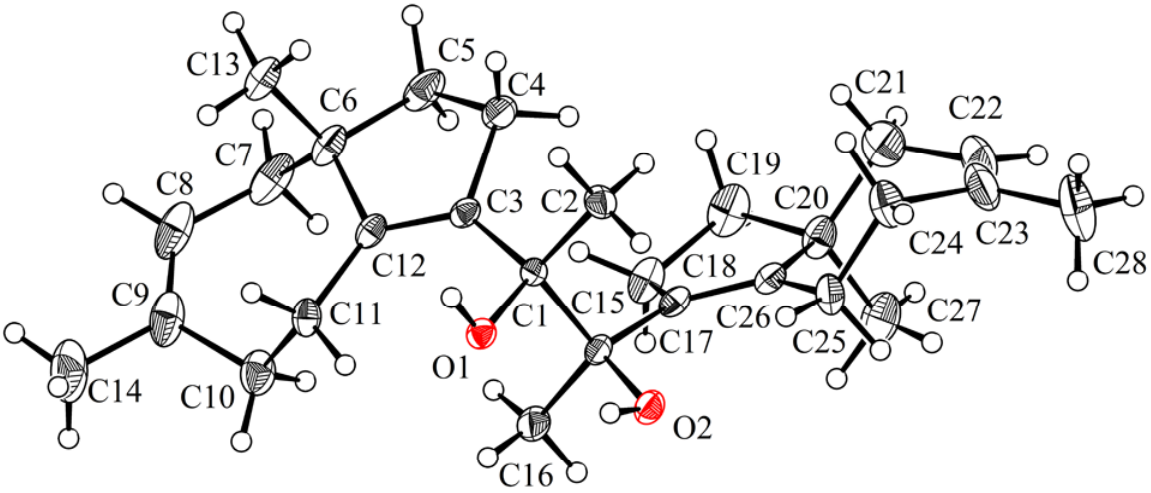


Table A6.1. Crystal data and structure analysis details for diol ***262****.*

Empirical formula	C28 H42 O2
Formula weight	410.61
Crystallization solvent	CH_2Cl_2/hexanes
Crystal shape	blade
Crystal color	colourless
Crystal size	0.09 x 0.25 x 0.48 mm

Data Collection

Preliminary photograph(s)	rotation	
Type of diffractometer	Bruker APEX-II CCD	
Wavelength	0.71073 ≈ MoK	
Data collection temperature	100 K	
Theta range for 9010 reflections used in lattice determination	2.71 to 27.56∞	
Unit cell dimensions	a = 9.7419(3) ≈ b = 10.9851(4) ≈ c = 23.6134(8) ≈	α= 90∞ β= 90∞ γ = 90∞
Volume	2527.01(15) $≈^3$	
Z	4	
Crystal system	orthorhombic	
Space group	P 21 21 21 (# 19)	
Density (calculated)	1.079 g/cm^3	
F(000)	904	
Theta range for data collection	2.0 to 37.4∞	
Completeness to theta = 25.000∞	100.0%	
Index ranges	-14 ≤ h ≤ 16, -17 ≤ k ≤ 17, -37 ≤ l ≤ 40	
Data collection scan type	and scans	
Reflections collected	61255	
Independent reflections	11770 [R_{int}= 0.0700]	
Reflections > 2σ(I)	8166	
Average σ(I)/(net I)	0.0702	
Absorption coefficient	0.06 mm^{-1}	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.0000 and 0.9369	

Table A6.1 (cont.)

Structure Solution and Refinement

Primary solution method	dual
Secondary solution method	?
Hydrogen placement	difmap
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	11770 / 0 / 439
Treatment of hydrogen atoms	refall
Goodness-of-fit on F^2	1.53
Final R indices [$I>2\sigma(I)$, 8166 reflections]	R1 = 0.0571, wR2 = 0.0678
R indices (all data)	R1 = 0.1007, wR2 = 0.0719
Type of weighting scheme used	calc
Weighting scheme used	
Max shift/error	0.000
Average shift/error	0.000
Absolute structure parameter	0.4(4)
Extinction coefficient	0
Largest diff. peak and hole	0.35 and -0.31 e$\approx^{-3}$

Programs Used

Cell refinement	SAINT V8.18C (Bruker-AXS, 2007)
Data collection	APEX2_2012.4-3 (Bruker-AXS, 2007)
Data reduction	SAINT V8.18C (Bruker-AXS, 2007)
Structure solution	SHELXT (Sheldrick, 2012)
Structure refinement	SHELXL-2012 (Sheldrick, 2012)
Graphics	DIAMOND 3 (Crystal Impact, 1999)

Table A6.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for diol ***262****. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.*

	x	y	z	U_{eq}
O(1)	7807(1)	6932(1)	5090(1)	17(1)
O(2)	5443(1)	7868(1)	5280(1)	21(1)
C(1)	7808(1)	7750(1)	5565(1)	15(1)
C(2)	8110(2)	9030(1)	5338(1)	21(1)
C(3)	8843(1)	7404(1)	6018(1)	17(1)
C(4)	9476(2)	8399(1)	6383(1)	26(1)
C(5)	10151(2)	7684(2)	6859(1)	32(1)
C(6)	10488(1)	6435(1)	6606(1)	24(1)
C(7)	10388(2)	5445(2)	7068(1)	35(1)
C(8)	10753(2)	4178(2)	6892(1)	37(1)
C(9)	10009(2)	3526(2)	6538(1)	36(1)
C(10)	8761(2)	4065(2)	6255(1)	30(1)
C(11)	9140(2)	5120(1)	5853(1)	21(1)
C(12)	9400(1)	6320(1)	6138(1)	17(1)
C(13)	11929(2)	6439(2)	6345(1)	29(1)
C(14)	10366(3)	2243(2)	6373(1)	53(1)
C(15)	6276(1)	7657(1)	5776(1)	16(1)
C(16)	5932(2)	6374(1)	5986(1)	25(1)
C(17)	5928(1)	8596(1)	6225(1)	17(1)
C(18)	6114(2)	8266(1)	6844(1)	27(1)
C(19)	6028(2)	9496(2)	7140(1)	35(1)
C(20)	5128(1)	10286(1)	6756(1)	26(1)
C(21)	5581(2)	11630(2)	6799(1)	37(1)
C(22)	4725(2)	12522(2)	6476(1)	42(1)
C(23)	4670(2)	12550(1)	5919(1)	38(1)
C(24)	5474(2)	11644(1)	5572(1)	31(1)
C(25)	4939(2)	10347(1)	5641(1)	24(1)
C(26)	5380(1)	9708(1)	6175(1)	18(1)
C(27)	3610(2)	10146(2)	6918(1)	39(1)
C(28)	3765(3)	13405(2)	5594(1)	58(1)

Table A6.3. Bond lengths [Å] and angles [°] for diol ***262***.

O(1)-H(1)	0.805(16)	C(19)-H(19A)	0.965(18)
O(1)-C(1)	1.4370(15)	C(19)-H(19B)	1.018(17)
O(2)-H(2)	0.785(18)	C(19)-C(20)	1.532(2)
O(2)-C(15)	1.4447(16)	C(20)-C(21)	1.544(2)
C(1)-C(2)	1.5345(18)	C(20)-C(26)	1.5297(19)
C(1)-C(3)	1.5172(18)	C(20)-C(27)	1.536(2)
C(1)-C(15)	1.5763(18)	C(21)-H(21A)	0.977(16)
C(2)-H(2A)	0.985(16)	C(21)-H(21B)	0.985(19)
C(2)-H(2B)	0.971(14)	C(21)-C(22)	1.496(3)
C(2)-H(2C)	0.961(15)	C(22)-H(22)	0.912(16)
C(3)-C(4)	1.5230(18)	C(22)-C(23)	1.317(2)
C(3)-C(12)	1.3393(17)	C(23)-C(24)	1.508(2)
C(4)-H(4A)	0.989(15)	C(23)-C(28)	1.500(3)
C(4)-H(4B)	1.009(16)	C(24)-H(24A)	1.005(18)
C(4)-C(5)	1.521(2)	C(24)-H(24B)	0.989(17)
C(5)-H(5A)	1.017(17)	C(24)-C(25)	1.526(2)
C(5)-H(5B)	0.992(16)	C(25)-H(25A)	0.956(14)
C(5)-C(6)	1.532(2)	C(25)-H(25B)	1.020(16)
C(6)-C(7)	1.543(2)	C(25)-C(26)	1.5056(19)
C(6)-C(12)	1.5371(19)	C(27)-H(27A)	1.034(18)
C(6)-C(13)	1.534(2)	C(27)-H(27B)	0.963(19)
C(7)-H(7A)	1.008(15)	C(27)-H(27C)	0.952(18)
C(7)-H(7B)	0.975(16)	C(28)-H(28A)	0.96(2)
C(7)-C(8)	1.496(2)	C(28)-H(28B)	0.97(2)
C(8)-H(8)	0.989(16)	C(28)-H(28C)	1.03(2)
C(8)-C(9)	1.318(2)		
C(9)-C(10)	1.508(2)	C(1)-O(1)-H(1)	106.8(11)
C(9)-C(14)	1.503(3)	C(15)-O(2)-H(2)	104.6(14)
C(10)-H(10A)	0.978(15)	O(1)-C(1)-C(2)	107.47(11)
C(10)-H(10B)	0.962(16)	O(1)-C(1)-C(3)	113.13(10)
C(10)-C(11)	1.544(2)	O(1)-C(1)-C(15)	101.87(10)
C(11)-H(11A)	0.969(14)	C(2)-C(1)-C(15)	110.59(11)
C(11)-H(11B)	0.999(13)	C(3)-C(1)-C(2)	110.41(11)
C(11)-C(12)	1.5015(19)	C(3)-C(1)-C(15)	112.98(10)
C(13)-H(13A)	0.948(16)	C(1)-C(2)-H(2A)	107.8(9)
C(13)-H(13B)	0.955(16)	C(1)-C(2)-H(2B)	111.5(8)
C(13)-H(13C)	0.997(17)	C(1)-C(2)-H(2C)	108.5(8)
C(14)-H(14A)	1.013(19)	H(2A)-C(2)-H(2B)	109.6(12)
C(14)-H(14B)	0.99(2)	H(2A)-C(2)-H(2C)	111.1(12)
C(14)-H(14C)	0.96(2)	H(2B)-C(2)-H(2C)	108.4(11)
C(15)-C(16)	1.5310(19)	C(1)-C(3)-C(4)	119.21(11)
C(15)-C(17)	1.5181(19)	C(12)-C(3)-C(1)	129.90(11)
C(16)-H(16A)	1.011(16)	C(12)-C(3)-C(4)	110.74(11)
C(16)-H(16B)	0.986(15)	C(3)-C(4)-H(4A)	111.0(9)
C(16)-H(16C)	0.969(15)	C(3)-C(4)-H(4B)	109.0(9)
C(17)-C(18)	1.5160(19)	H(4A)-C(4)-H(4B)	109.5(12)
C(17)-C(26)	1.3383(17)	C(5)-C(4)-C(3)	102.85(12)
C(18)-H(18A)	0.987(15)	C(5)-C(4)-H(4A)	112.8(9)
C(18)-H(18B)	0.984(16)	C(5)-C(4)-H(4B)	111.5(9)
C(18)-C(19)	1.524(2)	C(4)-C(5)-H(5A)	113.1(9)

Table A6.3 (cont.)

C(4)-C(5)-H(5B)	108.3(9)	O(2)-C(15)-C(16)	106.67(11)
C(4)-C(5)-C(6)	105.53(12)	O(2)-C(15)-C(17)	109.40(10)
H(5A)-C(5)-H(5B)	109.5(13)	C(16)-C(15)-C(1)	111.65(10)
C(6)-C(5)-H(5A)	112.6(9)	C(17)-C(15)-C(1)	112.85(10)
C(6)-C(5)-H(5B)	107.7(8)	C(17)-C(15)-C(16)	110.57(11)
C(5)-C(6)-C(7)	110.03(12)	C(15)-C(16)-H(16A)	107.9(8)
C(5)-C(6)-C(12)	101.88(11)	C(15)-C(16)-H(16B)	112.2(9)
C(5)-C(6)-C(13)	110.53(14)	C(15)-C(16)-H(16C)	108.1(9)
C(12)-C(6)-C(7)	114.03(13)	H(16A)-C(16)-H(16B)	109.2(12)
C(13)-C(6)-C(7)	110.13(12)	H(16A)-C(16)-H(16C)	109.2(13)
C(13)-C(6)-C(12)	109.99(12)	H(16B)-C(16)-H(16C)	110.2(13)
C(6)-C(7)-H(7A)	107.2(8)	C(18)-C(17)-C(15)	118.92(11)
C(6)-C(7)-H(7B)	105.2(9)	C(26)-C(17)-C(15)	130.37(12)
H(7A)-C(7)-H(7B)	106.7(12)	C(26)-C(17)-C(18)	110.58(12)
C(8)-C(7)-C(6)	116.39(13)	C(17)-C(18)-H(18A)	114.0(9)
C(8)-C(7)-H(7A)	109.7(8)	C(17)-C(18)-H(18B)	109.2(9)
C(8)-C(7)-H(7B)	111.2(9)	C(17)-C(18)-C(19)	102.90(12)
C(7)-C(8)-H(8)	117.3(9)	H(18A)-C(18)-H(18B)	105.4(12)
C(9)-C(8)-C(7)	123.48(16)	C(19)-C(18)-H(18A)	112.9(9)
C(9)-C(8)-H(8)	119.1(9)	C(19)-C(18)-H(18B)	112.6(8)
C(8)-C(9)-C(10)	120.73(15)	C(18)-C(19)-H(19A)	112.8(10)
C(8)-C(9)-C(14)	123.12(17)	C(18)-C(19)-H(19B)	107.9(10)
C(14)-C(9)-C(10)	116.11(18)	C(18)-C(19)-C(20)	105.16(13)
C(9)-C(10)-H(10A)	110.7(8)	H(19A)-C(19)-H(19B)	108.5(14)
C(9)-C(10)-H(10B)	110.0(9)	C(20)-C(19)-H(19A)	111.8(10)
C(9)-C(10)-C(11)	111.99(13)	C(20)-C(19)-H(19B)	110.5(10)
H(10A)-C(10)-H(10B)	103.8(13)	C(19)-C(20)-C(21)	109.76(13)
C(11)-C(10)-H(10A)	109.9(9)	C(19)-C(20)-C(27)	110.28(14)
C(11)-C(10)-H(10B)	110.1(9)	C(26)-C(20)-C(19)	101.77(11)
C(10)-C(11)-H(11A)	108.6(8)	C(26)-C(20)-C(21)	114.20(12)
C(10)-C(11)-H(11B)	107.2(8)	C(26)-C(20)-C(27)	109.69(13)
H(11A)-C(11)-H(11B)	107.9(11)	C(27)-C(20)-C(21)	110.79(13)
C(12)-C(11)-C(10)	115.05(13)	C(20)-C(21)-H(21A)	107.1(9)
C(12)-C(11)-H(11A)	109.8(8)	C(20)-C(21)-H(21B)	105.3(10)
C(12)-C(11)-H(11B)	108.1(8)	H(21A)-C(21)-H(21B)	104.7(14)
C(3)-C(12)-C(6)	111.04(12)	C(22)-C(21)-C(20)	115.65(14)
C(3)-C(12)-C(11)	128.09(12)	C(22)-C(21)-H(21A)	112.5(9)
C(11)-C(12)-C(6)	120.75(11)	C(22)-C(21)-H(21B)	110.7(10)
C(6)-C(13)-H(13A)	111.1(10)	C(21)-C(22)-H(22)	118.4(11)
C(6)-C(13)-H(13B)	110.5(9)	C(23)-C(22)-C(21)	123.13(16)
C(6)-C(13)-H(13C)	111.6(9)	C(23)-C(22)-H(22)	118.4(11)
H(13A)-C(13)-H(13B)	109.9(13)	C(22)-C(23)-C(24)	120.46(16)
H(13A)-C(13)-H(13C)	105.9(12)	C(22)-C(23)-C(28)	123.33(18)
H(13B)-C(13)-H(13C)	107.7(12)	C(28)-C(23)-C(24)	116.10(17)
C(9)-C(14)-H(14A)	110.7(10)	C(23)-C(24)-H(24A)	109.3(10)
C(9)-C(14)-H(14B)	110.9(11)	C(23)-C(24)-H(24B)	109.6(10)
C(9)-C(14)-H(14C)	111.9(12)	C(23)-C(24)-C(25)	112.35(14)
H(14A)-C(14)-H(14B)	105.5(15)	H(24A)-C(24)-H(24B)	104.7(14)
H(14A)-C(14)-H(14C)	107.3(15)	C(25)-C(24)-H(24A)	112.1(10)
H(14B)-C(14)-H(14C)	110.3(16)	C(25)-C(24)-H(24B)	108.4(9)
O(2)-C(15)-C(1)	105.36(10)	C(24)-C(25)-H(25A)	109.1(8)

Table A6.3 (cont.)

		C(20)-C(27)-H(27C)	111.4(10)
C(24)-C(25)-H(25B)	107.3(8)	H(27A)-C(27)-H(27B)	109.9(15)
H(25A)-C(25)-H(25B)	105.6(13)	H(27A)-C(27)-H(27C)	108.5(15)
C(26)-C(25)-C(24)	115.28(13)	H(27B)-C(27)-H(27C)	104.9(15)
C(26)-C(25)-H(25A)	108.5(8)	C(23)-C(28)-H(28A)	109.4(14)
C(26)-C(25)-H(25B)	110.6(9)	C(23)-C(28)-H(28B)	106.8(11)
C(17)-C(26)-C(20)	111.30(11)	C(23)-C(28)-H(28C)	109.9(10)
C(17)-C(26)-C(25)	127.83(12)	H(28A)-C(28)-H(28B)	111.7(16)
C(25)-C(26)-C(20)	120.72(11)	H(28A)-C(28)-H(28C)	110.4(17)
C(20)-C(27)-H(27A)	112.1(10)	H(28B)-C(28)-H(28C)	108.6(16)
C(20)-C(27)-H(27B)	109.8(11)		

Table A6.4. Anisotropic displacement parameters ($Å^2$ x 10^4) for diol ***262****. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$.*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	148(5)	184(5)	165(5)	-13(4)	16(4)	7(4)
O(2)	170(5)	245(5)	208(5)	-55(4)	-40(4)	47(4)
C(1)	133(6)	143(6)	169(6)	-7(5)	9(5)	4(5)
C(2)	201(8)	170(7)	251(8)	14(6)	48(7)	-10(6)
C(3)	123(6)	219(7)	161(6)	-31(5)	18(5)	7(5)
C(4)	186(7)	299(8)	292(8)	-123(6)	-23(6)	25(7)
C(5)	210(8)	520(10)	242(8)	-139(7)	-71(7)	72(8)
C(6)	167(7)	396(8)	164(7)	-14(6)	-15(6)	79(7)
C(7)	234(9)	631(12)	173(7)	81(7)	-1(7)	102(8)
C(8)	284(9)	541(11)	288(9)	234(8)	46(8)	158(8)
C(9)	337(9)	365(9)	366(9)	216(8)	109(8)	137(8)
C(10)	289(9)	277(8)	330(9)	98(7)	26(8)	55(7)
C(11)	226(8)	205(7)	187(7)	34(6)	-11(6)	61(6)
C(12)	130(6)	261(7)	131(6)	2(5)	21(5)	34(5)
C(13)	182(8)	415(10)	264(8)	0(8)	-20(6)	79(7)
C(14)	528(13)	376(11)	696(16)	219(10)	35(12)	193(10)
C(15)	119(6)	178(6)	194(7)	26(5)	-3(5)	16(5)
C(16)	157(8)	215(8)	391(9)	55(7)	63(7)	-13(6)
C(17)	114(6)	236(7)	160(6)	30(5)	14(5)	3(5)
C(18)	240(8)	375(9)	186(7)	84(6)	36(6)	79(7)
C(19)	361(10)	525(11)	153(7)	-13(7)	-4(7)	130(9)
C(20)	235(8)	346(8)	183(7)	-45(6)	24(6)	89(7)
C(21)	397(10)	425(10)	284(9)	-176(8)	-9(8)	63(8)
C(22)	486(11)	288(9)	487(11)	-176(8)	3(10)	115(8)
C(23)	470(11)	200(8)	466(11)	-64(7)	-14(9)	82(7)
C(24)	408(10)	235(8)	289(9)	31(6)	16(8)	68(7)
C(25)	297(9)	216(7)	203(7)	-30(6)	-45(6)	100(7)
C(26)	133(6)	244(7)	159(6)	-15(5)	-12(5)	14(6)
C(27)	309(10)	506(12)	366(11)	-18(9)	117(8)	128(9)
C(28)	779(17)	299(10)	669(16)	27(11)	5(14)	248(12)

Table A6.5. Hydrogen coordinates (x 10^3) and isotropic displacement parameters ($Å^2$ x 10^3) for diol ***262***.

	x	y	z	U_{iso}
H(1)	854(2)	700(1)	494(1)	29(5)
H(2)	584(2)	754(2)	503(1)	43(6)
H(2A)	745(2)	920(1)	503(1)	28(4)
H(2B)	802(1)	964(1)	563(1)	21(4)
H(2C)	904(2)	905(1)	520(1)	19(4)
H(4A)	877(2)	897(1)	652(1)	28(4)
H(4B)	1018(2)	886(1)	615(1)	30(4)
H(5A)	1099(2)	811(1)	702(1)	45(5)
H(5B)	946(2)	756(1)	716(1)	30(4)
H(7A)	942(2)	546(1)	722(1)	26(4)
H(7B)	1098(2)	573(1)	737(1)	34(5)
H(8)	1163(2)	384(1)	704(1)	36(4)
H(10A)	825(2)	344(1)	605(1)	25(4)
H(10B)	812(2)	434(1)	654(1)	28(4)
H(11A)	842(1)	521(1)	557(1)	18(4)
H(11B)	1000(1)	488(1)	565(1)	15(3)
H(13A)	1210(2)	570(1)	615(1)	30(4)
H(13B)	1204(2)	712(1)	610(1)	29(4)
H(13C)	1266(2)	650(1)	664(1)	36(5)
H(14A)	959(2)	167(2)	647(1)	59(6)
H(14B)	1049(2)	217(2)	596(1)	54(6)
H(14C)	1117(2)	196(2)	657(1)	61(6)
H(16A)	611(2)	579(1)	566(1)	29(4)
H(16B)	649(2)	614(1)	632(1)	25(4)
H(16C)	496(2)	635(1)	608(1)	31(4)
H(18A)	698(2)	783(1)	692(1)	29(4)
H(18B)	538(2)	771(1)	696(1)	26(4)
H(19A)	566(2)	944(1)	752(1)	45(5)
H(19B)	700(2)	984(2)	716(1)	44(5)
H(21A)	655(2)	1166(1)	669(1)	26(4)
H(21B)	557(2)	1182(2)	721(1)	49(5)
H(22)	418(2)	1304(1)	668(1)	40(5)
H(24A)	648(2)	1171(2)	567(1)	44(5)
H(24B)	542(2)	1187(1)	517(1)	40(5)
H(25A)	522(1)	987(1)	532(1)	21(4)
H(25B)	389(2)	1038(1)	562(1)	37(5)
H(27A)	332(2)	924(2)	694(1)	56(6)
H(27B)	344(2)	1055(2)	727(1)	52(6)
H(27C)	303(2)	1054(2)	665(1)	40(5)
H(28A)	328(2)	1393(2)	586(1)	79(7)
H(28B)	436(2)	1386(2)	534(1)	50(6)
H(28C)	307(2)	1292(2)	535(1)	58(6)

Table A6.6. Hydrogen bonds for diol ***262*** *[Å and °].*

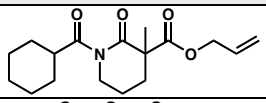
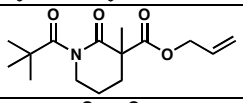
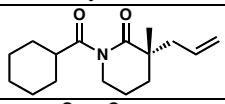
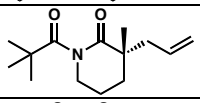
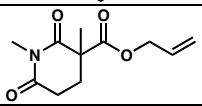
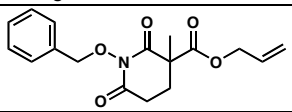
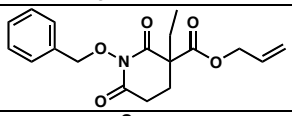
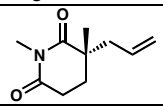
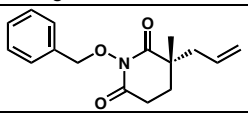
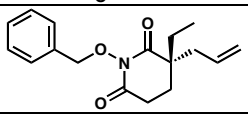
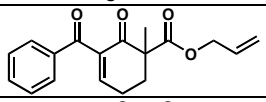
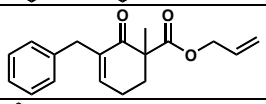
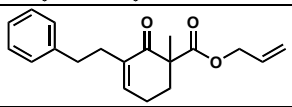
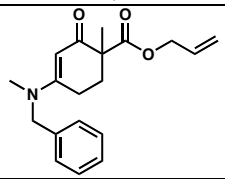
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1)...O(2)#1	0.805(16)	1.927(17)	2.7217(14)	169.1(16)
O(2)-H(2)...O(1)	0.785(18)	2.035(17)	2.5617(14)	124.4(17)

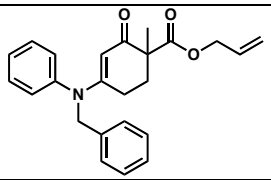
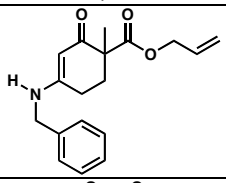
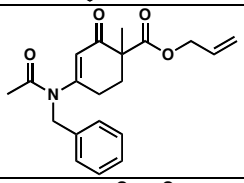
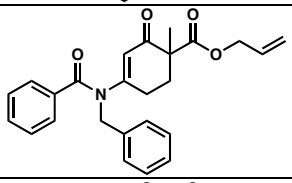
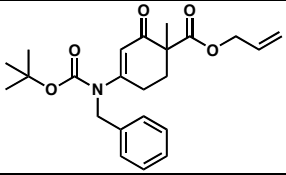
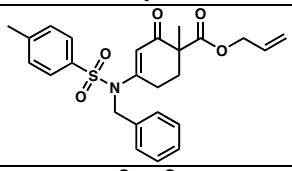
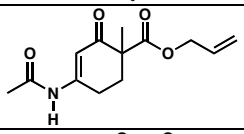
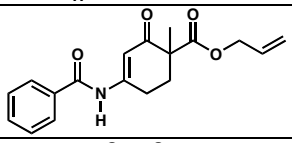
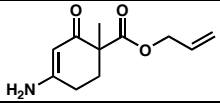
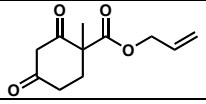
APPENDIX 7

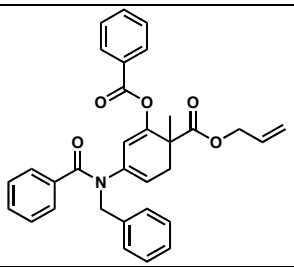
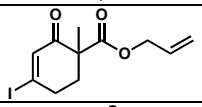
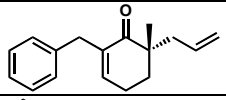
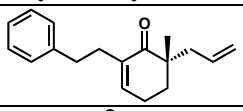
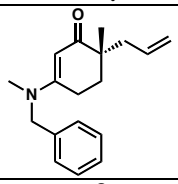
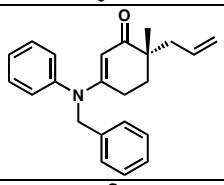
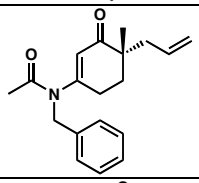
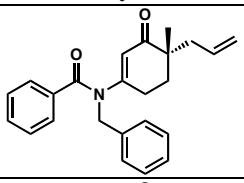
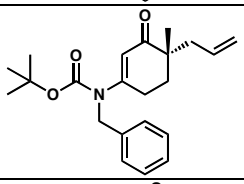
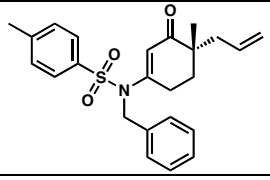
Notebook Cross-Reference

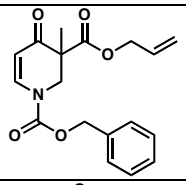
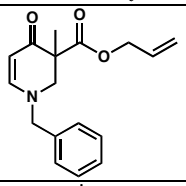
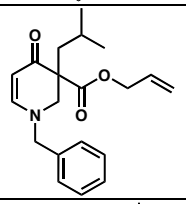
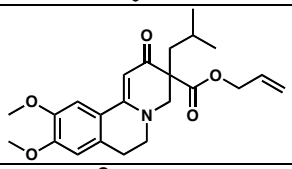
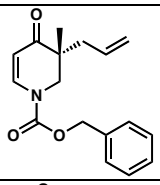
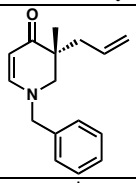
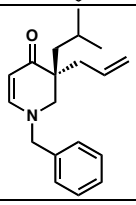
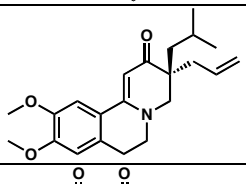
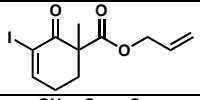
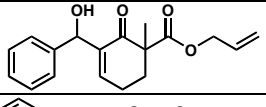
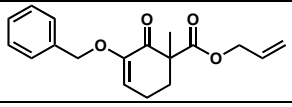
The following notebook cross-reference has been included to facilitate access to the original spectroscopic data obtained for the compounds presented in this thesis. For each compound, both hard copy and electronic characterization folders have been created that contain copies of the original ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, ^{31}P NMR, ^{2}H NMR, COSY, HSQC, HMBC, NOESY, IR spectra. Additionally, HRMS and X-ray data can also be found in these files. All notebooks and spectral data are stored in the Stoltz Group archives.

Table A7.1. Notebook cross-reference for compounds in Chapter 1.

compound	chemical structure	^{1}H NMR	^{13}C NMR	IR
4i		NBB-IX-63A	NBB-IX-63A	NBB-IX-63A
4j		DCD-IV-067	DCD-IV-067	DCD-IV-067
5i		NBB-IX-83A	NBB-IX-83A	NBB-IX-83A
5j		DCD-IV-103	DCD-IV-103	DCD-IV-103
6c		DCBIII_123	DCBIII_123	DCBIII_123
6d		JK-V-81	JK-V-81	JK-V-81
6e		JK-V-91	JK-V-91	JK-V-91
7c		DCBIII_127_final	DCBIII_127_final	DCBIII_127
7d		JK-V-83-chiral	JK-V-83-chiral	JK-V-83-chiral
7e		JK-V-93-chiral	JK-V-93-chiral	JK-V-93-chiral
13b		NBB-VIII-281A	NBB-VIII-281A	NBB-VIII-281A
13c		NBB-IX-301-2B	NBB-IX-301-2B	NBB-IX-301-2B
13d		NBB-X-15-2B	NBB-X-15-2B	NBB-X-15-2B
16a		NBB-VII-203A	NBB-VII-203A	NBB-VII-203A

16b		NBB-VII-205-2C	NBB-VII-205-2C	NBB-VII-205-2B
16c		NBB-VI-289A	NBB-VI-289A	NBB-VI-289A
16d		NBB-VII-227&241 Frac 10–21	NBB-VII-227&241 Frac 10–21	NBB-VII-227&241 Frac 10–21
16e		DCD-IV-217	DCD-IV-217	DCD-IV-217
16f		NBB-VII-221A	NBB-VII-221A	NBB-VII-221A
16g		NBB-VII-189A	NBB-VII-189A	NBB-VII-189A
16h		DCD-IV-215	DCD-IV-215	DCD-IV-215
16i		DCD-IV-213	DCD-IV-213	DCD-IV-213
16j		NBB-VII-299 Crystal 1	NBB-VII-299 Crystal 1	NBB-VII-299 Crystal 1
17		NBB-VII-235A	NBB-VII-235A	NBB-VII-235A

18		NBB-VII-81B	NBB-VII-81B	NBB-VII-81B
20		NBB-VII-289B	NBB-VII-289B	NBB-VII-289B
21c		DCD-V-057	DCD-V-057	DCD-V-057
21d		DCD-V-059	DCD-V-059	DCD-V-059
23a		NBB-VIII-83-2A	NBB-VIII-83-2A	NBB-VIII-83-2A
23b		NBB-VIII-85-2A	NBB-VIII-85-2A	NBB-VIII-85-2A
23d		NBB-IX-257A	NBB-IX-257A	NBB-IX-257A
23e		NBB-IX-259-3A	NBB-IX-259-3A	NBB-IX-259-3A
23f		NBB-VIII-87A	NBB-VIII-87A	NBB-VIII-87A
23g		NBB-VIII-89A	NBB-VIII-89A	NBB-VIII-89A

29a		ANM-I-105	ANM-I-105	ANM-I-130
29b		WBL-III-083C-H	WBL-III-083C-H	WBL-III-083
29c		WBL-III-073-C-H	WBL-III-073-C-H	WBL-III-073
29d		WBL-II-253	WBL-II-253	WBL-II-253
30a		ANM-I-110	ANM-I-110	ANM-I-109
30b		WBL-III-085-C-H	WBL-III-085-C-H	WBL-III-085
30c		WBL-III-077-C-H	WBL-III-077-C-H	WBL-III-077
30d		WBL-II-267-H_C	WBL-II-267-H_C	WBL-II-267
41		NBB-VIII-153A	NBB-VIII-153A	NBB-VIII-153A
44		NBB-VIII-247B	—	NBB-VIII-247B
45a		char_DCD-III_251	char_DCD-III_251	char_DCD-III_251

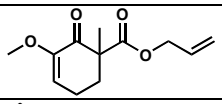
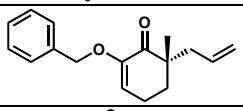
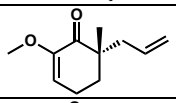
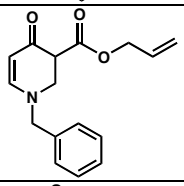
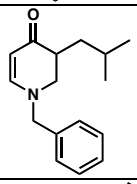
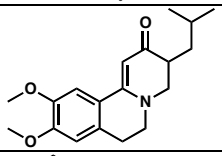
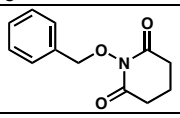
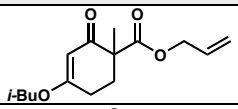
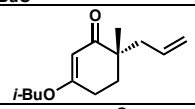
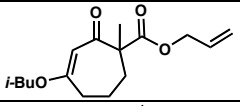
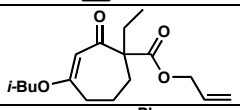
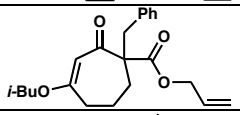
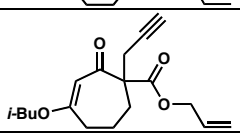
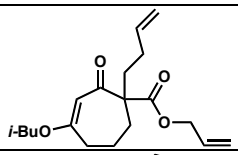
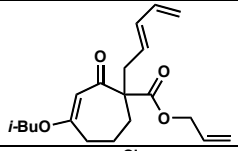
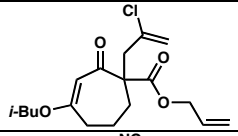
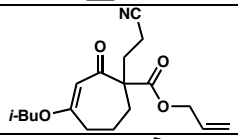
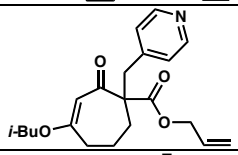
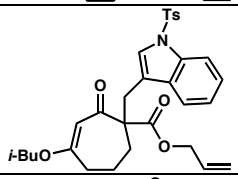
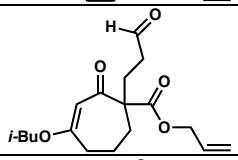
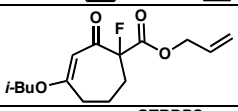
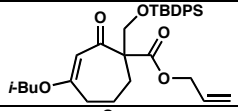
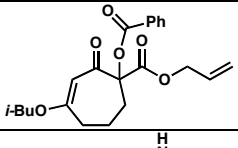
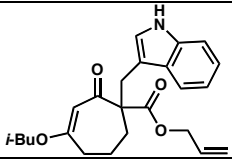
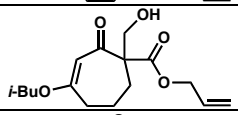
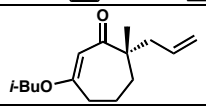
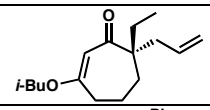
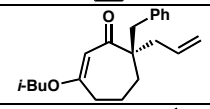
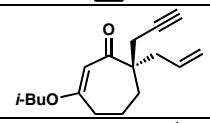
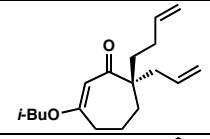
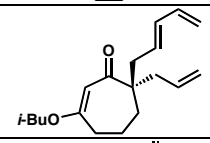
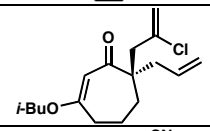
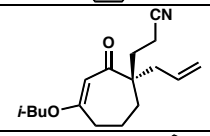
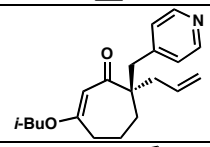
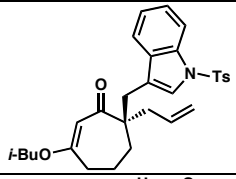
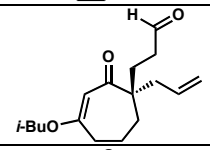
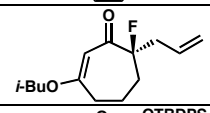
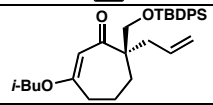
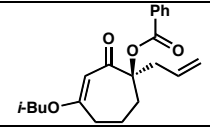
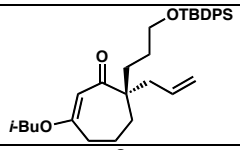
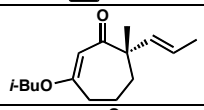
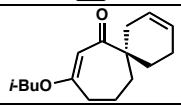
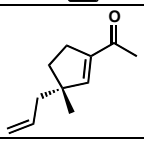
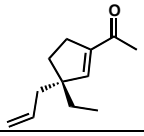
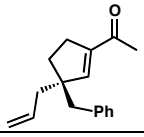
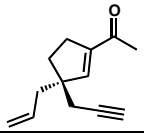
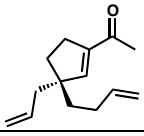
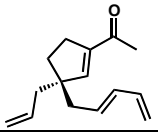
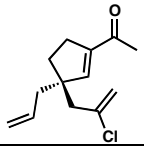
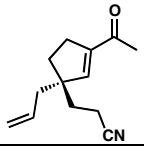
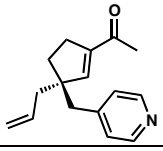
45b		DCD-III-253	DCD-III-253	DCD-III-253-2
46a		char_DCD-IV-021	char_DCD-IV-021	char_DCD-IV-021
46b		DCD-IV-201	DCD-IV-201	DCD-IV-201
48b		WBL-III-075-2	WBL-III-041H-C	WBL-III-041
48c		WBL-III-065-1-C-H	WBL-III-065-1-C-H	WBL-III-065-1
48d		WBL-II-249-2	WBL-II-249-2	—
50		DCD-III-281	DCD-III-281	DCD-III-281

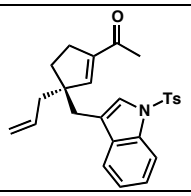
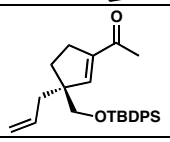
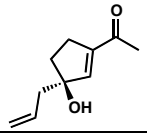
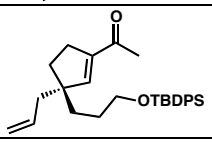
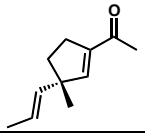
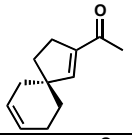
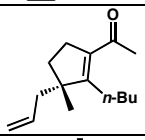
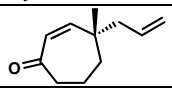
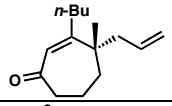
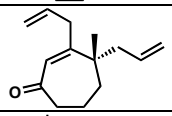
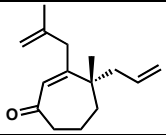
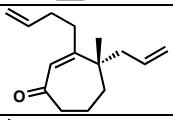
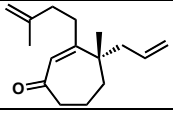
Table A7.2. Notebook cross-reference for compounds in Chapter 2.

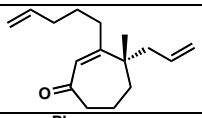
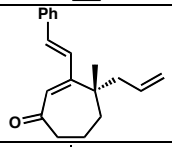
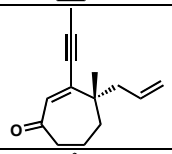
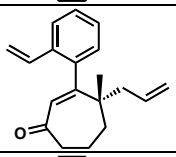
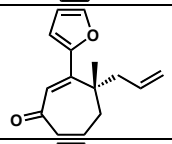
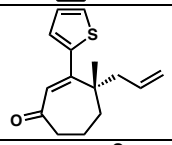
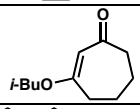
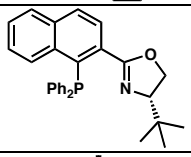
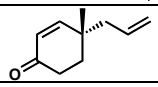
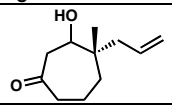
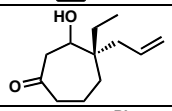
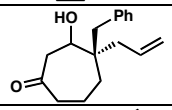
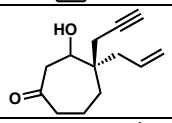
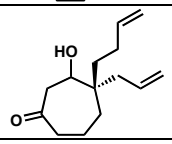
compound	chemical structure	^{1}H NMR	^{13}C NMR	IR
14a		AYH-VIII-137A	AYH-VIII-137A	AYH-VIII-137A
22a		AYH-VIII-139A	AYH-VIII-139A	AYH-VIII-139A
24a		MRK_VI_227B_1H	MRK_VI_227B_13C	IBuOTsujiSub2
24b		AYH-V-285A	AYH-V-285A	AYH-V-285A
24c		AYH-V-293Bnew	AYH-V-293B	AYH-V-293B
24d		AYH-VI-71B	AYH-VI-71B	AYH-VI-71B

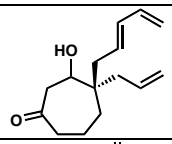
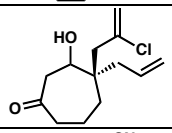
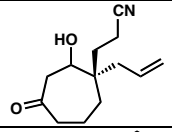
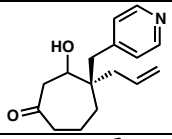
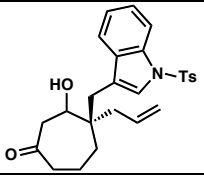
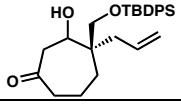
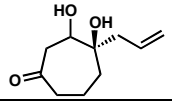
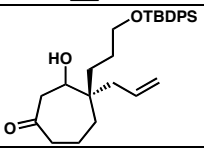
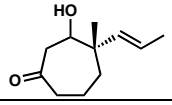
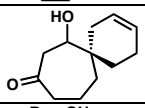
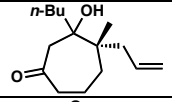
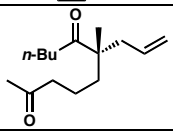
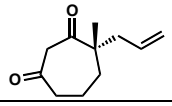
24e		AYH-VI-273A	AYH-VI-273A	AYH-VI-273A
24f		AYH-VI-105Anew	AYH-VI-105A	AYH-VI-105A
24g		AYH-VI-151Anew	AYH-VI-151A	AYH-VI-151A
24h		AYH-VI-183Bnew	AYH-VI-147D	AYH-VI-147D
24i		AYH-VII-49B2	AYH-VII-49B2	AYH-VII-49B2
24j		AYH-VII-127B	AYH-VII-127B	AYH-VII-127B
24k		AYH-VI-257Bnew	AYH-VI-257B	AYH-VI-257B
24l		AYH-VI-37Ax	AYH-VI-37A	AYH-VI-37A
24m		AYH-VI-251Bx3	AYH-VI-251Bx3	AYH-VI-237B
24n		AYH-VI-225Bnew	AYH-VI-225B	AYH-VI-225B
24ac		AYH-VII-117B	AYH-VII-117B	AYH-VII-117B
24ad		AYH-VI-233Bnew	AYH-VI-233B	AYH-VI-233B2
27a		MRK_VII_ 33B_1H	MRK_VII_ 33B_13C	MRK_VII_33B

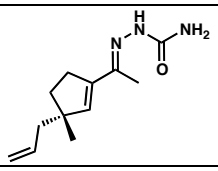
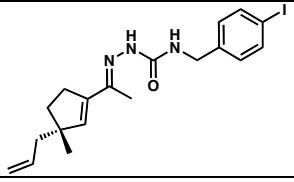
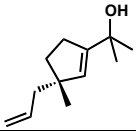
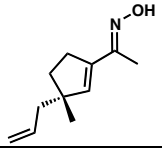
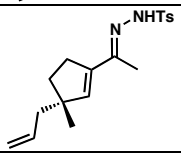
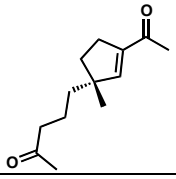
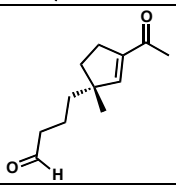
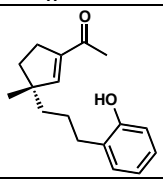
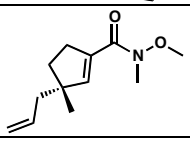
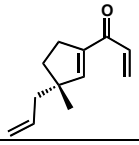
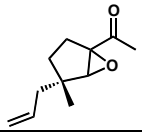
27b		AYH-VI-29A	AYH-VI-29A	AYH-VI-29A
27c		AYH-VI-27A	AYH-VI-27A	AYH-VI-27A
27d		AYH-VI-101A	AYH-VI-73A	AYH-VI-73A
27e		AYH-VI-279A	AYH-VI-279A	AYH-VI-279A
27f		AYH-VI-125A	AYH-VI-121A	AYH-VI-121A
27g		AYH-VI-165Anew	AYH-VI-165A	AYH-VI-165A
27h		AYH-VI-155Bnew	AYH-VI-157B	AYH-VI-157B
27i		AYH-VII-57Cnew	AYH-VII-53C	AYH-VII-53C
27j		AYH-VII-135Bx	AYH-VII-135Bx	AYH-VII-135Bx
27k		AYH-VI-269A	AYH-VI-269A	AYH-VI-269A
27l		AYH-VI-61Anew	AYH-VI-43A	AYH-VI-43A
27m		AYH-VI-255A	AYH-VI-255A	AYH-VI-255A
27n		AYH-VI-229Bnew	AYH-VI-229B	AYH-VI-229B

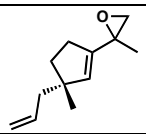
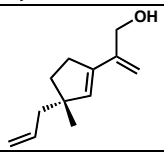
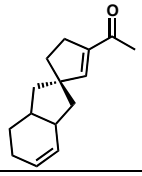
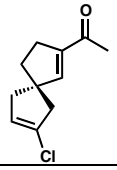
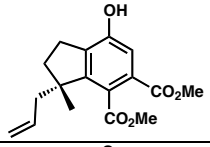
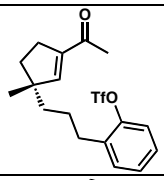
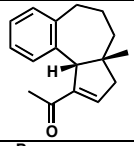
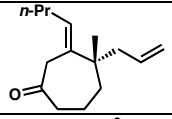
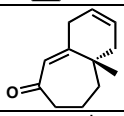
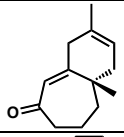
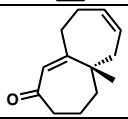
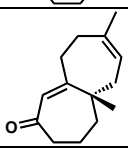
27o		AYH-VIII-295Ax	AYH-VIII-295Ax	AYH-VIII-207A
27p		TJ-VII-127B	TJ-VII-101	TJ-VII-101
27q		AYH-VIII-233A	AYH-VIII-219B	AYH-VIII-219B
53a		TJ_III_67_1H	TJ_III_67_13C	TJ_III_67
53b		AYH-VI-99A	AYH-VI-99A	AYH-VI-99A
53c		AYH-VI-59A	AYH-VI-59A	AYH-VI-59A
53d		AYH-VI-113Ax	AYH-VI-113A	AYH-VI-113A
53e		AYH-VI-291A	AYH-VI-291A	AYH-VI-291A
53f		AYH-VIII-293A	AYH-VI-133A	AYH-VI-133A
53g		AYH-VI-169A	AYH-VI-169A	AYH-VI-169A
53h		AYH-VI-163A	AYH-VI-163A	AYH-VI-163A
53i		AYH-VIII-303A	AYH-VIII-303A	AYH-VIII-277Ax

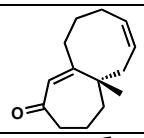
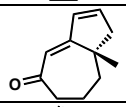
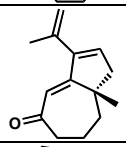
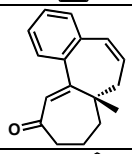
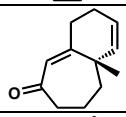
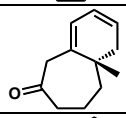
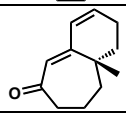
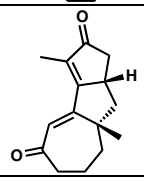
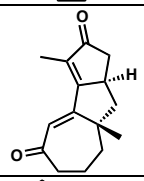
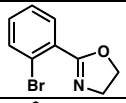
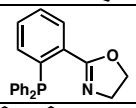
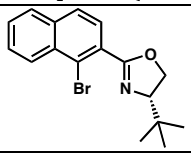
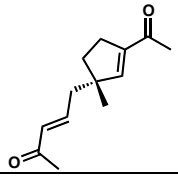
53j		AYH-VII-141A	AYH-VII-141A	AYH-VII-141A
53m		AYH-VIII-163A	AYH-VIII-163A	AYH-VI-289A
53n		AYH-IX-107B	AYH-IX-107B	AYH-IX-107B
53o		AYH-VIII-215A	AYH-VIII-215A	AYH-VIII-215A
53p		TJ-VII-141	TJ-VII-141	TJ-VII-141
53q		AYH-VIII-223A	AYH-VIII-223A	AYH-VIII-223A
53r		NBB-V-227A	NBB-V-227A	NBB-V-227A
55a		TJ-III-55A	TJ-III-55A	TJ-III-55A
55r		NBB-II-57B	NBB-I-161	NBB-II-227B
55t		NBB-VI-51B	NBB-VI-51B	NBB-VI-41B
55u		NBB-VI-79B	NBB-VI-79B	NBB-VI-79B
55v		NBB-VI-97C	NBB-VI-97C	NBB-VI-97C
55w		NBB-V-301B	NBB-V-301B	NBB-V-301B

55x		NBB-VI-85A	NBB-VI-85A	NBB-VI-85A
55y		NBB-VI-245-2B	NBB-VI-245-2B	NBB-VI-245-2B
55z		NBB-VI-69-2A	NBB-VI-69-2A	NBB-VI-69-2A
55aa		NBB-VI-223-2B	NBB-VI-223-2B	NBB-VI-223-2B
55ab		NBB-VI-123-2A	NBB-VI-123-2A	NBB-VI-123-2A
55ac		NBB-VI-63B	NBB-VI-63B	NBB-VI-63B
66		MRK_VI_ 201B_1H	MRK_VI_ 201B_13C	MRK_VII_135B
67		MRK-XI-133 flash again	MRK-XI-133 flash again	MRK-XI-133 flash
68		AYH-VIII-141A	AYH-VIII-141A	AYH-VIII-141A
70a		TJ-III-55B	TJ-III-55B	TJ-III-55B
70b		AYH-VI-97B	AYH-VI-97B	AYH-VI-97B
70c		AYH-VI-57B	AYH-VI-57B	AYH-VI-57B
70d		AYH-VI-111B	AYH-VI-111B	AYH-VI-111B
70e		AYH-VI-287B	AYH-VI-287B	AYH-VI-287B

70f		AYH-VI-131B	AYH-VI-131B	AYH-VI-131B
70g		AYH-VI-167B	AYH-VI-167B	AYH-VI-167B
70h		AYH-VI-161C	AYH-VI-161C	AYH-VI-161C
70i		AYH-IX-53C	AYH-IX-53C	AYH-IX-53C
70j		AYH-VII-137AB	AYH-VII-137AB	AYH-VII-137AB
70m		AYH-VI-161BC	AYH-VI-161BC	AYH-VI-161BC
70n		AYH-IX-105F	AYH-IX-105F	AYH-IX-105F
70o		AYH-VIII-213A	AYH-VIII-213A	AYH-VIII-213A
70p		TJ-VII-133B	TJ-VII-133B	TJ-VII-103B
70q		AYH-VIII-221B	AYH-VIII-221B	AYH-VIII-221B
70r		NBB-II-41C	NBB-II-61B	NBB-II-61B
72r		NBB-VII-39A	NBB-VII-39A	NBB-VII-39A
77		AYH-X-245E	AYH-X-245E2	AYH-X-245E2
79		NBB-VI-281A	NBB-VI-281A	NBB-VI-281A

80		TJ-III-83E	TJ-III-83E	TJ-III-83E
81		TJ-III-135B	TJ-III-135B	TJ-III-135B
82		TJ-VIII-249	TJ-VIII-249	TJ-VIII-249
83		AYH-VIII-157C	AYH-VIII-157C	AYH-VIII-157C
84		AYH-VIII-151Cx	AYH-VIII-151C	AYH-VIII-151C
85		AYH-VIII-75A	AYH-VIII-75Ax2	AYH-VIII-75A
86		AYH-VIII-111Bx	AYH-VIII-111B	AYH-VIII-111Bx2
87		TJ-VII-303A	TJ-VII-303A	TJ-VII-303A
88		AYH-VII-119A	AYH-VII-119A	AYH-VII-119A
89		AYH-VIII-79A	AYH-VII-173C	AYH-VII-173Cx
90		TJ-VII-177	TJ-VII-177	TJ-VII-177

91		TJ-VIII-225	TJ-VIII-225	TJ-VIII-225
92		TJ-VIII-87	TJ-VIII-87	TJ-VIII-87
93		AYH-IX-59B	AYH-IX-59B	AYH-IX-59B
95		AYH-IX-93B	AYH-IX-93B	AYH-IX-93B
97		AYH-VIII-253D	AYH-VIII-253D	AYH-VIII-253D
100		TJ-VIII-101B	TJ-VIII-101B	TJ-VII-41
102		TJ-VIII-181	TJ-VIII-181	TJ-VIII-181
110		NBB-VI-299A	NBB-VI-299A	NBB-VI-299A
111t		NBB-VI-167B	NBB-VI-167B	NBB-VI-167B
111u		NBB-VI-113A	NBB-VI-113A	NBB-VI-113A
111v		NBB-VI-101A	NBB-VI-101A	NBB-VI-101A
111w		NBB-VI-65A	NBB-VI-65A	NBB-VI-65A

111x		NBB-VI-93-2B	NBB-VI-93-2B	NBB-VI-93-2B
111y		NBB-VI-255C	NBB-VI-255C	NBB-VI-255B
111z		NBB-VI-89A	NBB-VI-89A	NBB-VI-89A
111aa		NBB-VI-199A	NBB-VI-199A	NBB-VI-199A
114		NBB-VI-215A	NBB-VI-215A	NBB-VI-215A
115		NBB-VI-187-2A	NBB-VI-187A	NBB-VI-187A
116		NBB-VI-249B	NBB-VI-243-2B	NBB-VI-249B
117a		NBB-VI-213B	NBB-VI-213B	NBB-VI-213B
117b		NBB-VI-213F	NBB-VI-213F	NBB-VI-213F
127		TJ-I-91	TJ-I-91	TJ-I-91-3
128		TJ-PHOX	TJ-PHOX	TJ-I-263A
129		TJ-III-143A	TJ-III-143	TJ-III-143
130		AYH-VII-293F	AYH-VII-293F	AYH-VII-293F

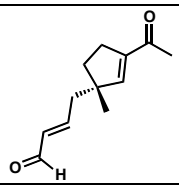
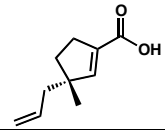
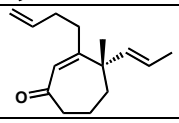
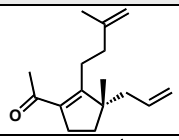
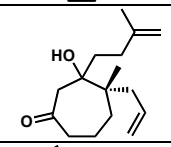
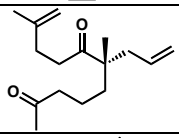
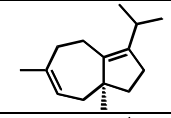
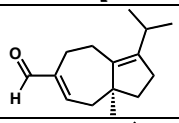
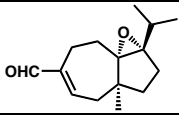
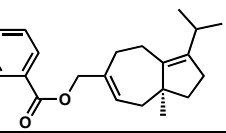
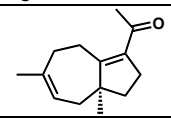
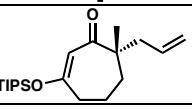
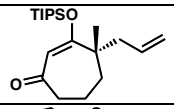
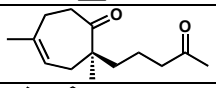
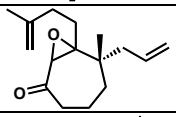
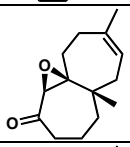
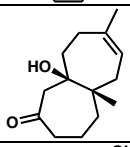
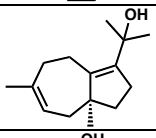
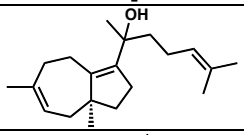
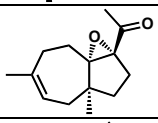
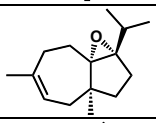
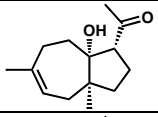
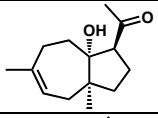
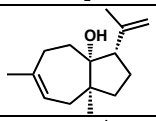
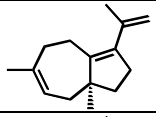
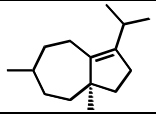
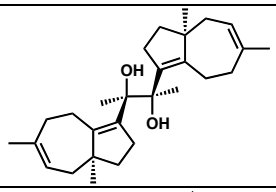
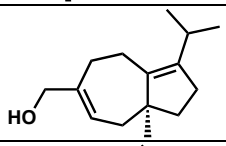
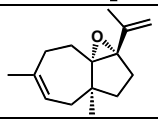
131		AYH-VIII-109C	AYH-VIII-109C	AYH-VIII-109C
132		AYH-VI-191B	AYH-VI-191B	AYH-VI-191B
133		NBB-VI-207B	NBB-VI-207B	NBB-VI-207B

Table A7.3. Notebook cross-reference for compounds in Chapter 3.

compound	chemical structure	^{1}H NMR	^{13}C NMR	IR
53w		NBB-IV-125B	NBB-IV-125B	NBB-IV-125B
70w		NBB-V-67-2B	—	NBB-V-67-2B
72w		NBB-VIII-243-3A	NBB-VIII-243-3A	NBB-VIII-243-3A
142		NBB-IX-231D	NBB-IX-231D	NBB-IX-231D
143		NBB-IX-275A	NBB-IX-261-2A	NBB-IX-261-2A
144b		NBB-X-149B	NBB-X-149B	NBB-X-149B
145		NBB-X-29A	NBB-X-29A	NBB-X-29A
223		NBB-IX-139B	NBB-VIII-257A	NBB-VIII-257A
230a		NBB-V-221A	NBB-V-221A	NBB-V-221A

230b		NBB-IX-65C	NBB-V-221C	NBB-IX-65C
235		NBB-IX-137B	NBB-VIII-255B	NBB-VIII-255B
249		NBB-IX-113A	—	NBB-IX-113A
250		NBB-X-25-2A	NBB-X-25-2A	NBB-X-25-2A
251		NBB-X-77C	NBB-X-77C	NBB-X-77C
252		NBB-IX-161B	NBB-IX-161B	NBB-IX-161B
253		NBB-IX-229D	—	NBB-IX-229D
255		NBB-IX-177A	NBB-IX-177A	NBB-IX-177A
256		NBB-X-147A	NBB-X-147A	NBB-X-147A
257a		NBB-IX-235C	NBB-IX-235C	NBB-IX-235C
257b		NBB-X-63G	NBB-X-63G	NBB-X-63G
259		NBB-X-127A	NBB-X-127A	NBB-X-127A
260		NBB-IX-233A	NBB-IX-233A	NBB-IX-233A
261		NBB-IX-231B	NBB-IX-231B	NBB-IX-231B

262		NBB-IX-233E	NBB-IX-233E	NBB-IX-233E
263		NBB-IX-275C_D	NBB-IX-275C_D	NBB-IX-275C+D
264		NBB-X-97A	NBB-X-97A	NBB-X-97A

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ABOUT THE AUTHOR

Nathan Bruce Bennett was born in Arlington, VA to Dr. Bruce and Karen Bennett and is the oldest of four children. His family moved to California when he was eight. From a young age, Nathan loved school and learning and decided to study chemistry while a student at Moorpark High School.

Nathan attended Brigham Young University (BYU) for his undergraduate education. Following his freshman year, he took a two-year hiatus to volunteer as a full time missionary for his church in Arizona. Upon returning to BYU, he began research in the lab of Profs. Noel Owen and Steven Wood where he isolated bioactive metabolites generated by endophytic fungi and bacteria found in a poisonous plant (Black Henbane). With the retirement of Prof. Owen and the completion of the sophomore organic series, he transitioned to Prof. Steven Fleming's group and investigated a photochemical rearrangement of cinnamyl acetate. This project introduced him to organic synthesis and mechanistic studies as he prepared an isotopically labeled compound that was analyzed by NMR spectroscopy. Together, these research experiences fostered a connection between bioactive natural products and organic synthesis, ultimately directing his graduate emphasis of study. Nathan graduated magna cum laude with a B.S. in Chemistry from BYU in 2008.

Upon completion of his bachelor's degree, Nathan moved to the California Institute of Technology where he pursued his Ph.D. under the guidance of Professor Brian M. Stoltz. His graduate research focused on the development of new palladium-catalyzed allylic alkylation methodology and application of these methods toward various molecular architectures and the total synthesis of several daucane sesquiterpenes. While at Caltech, Nathan met and married his wife, Chanel, and their son Eli was born a few years later. In July 2013, Nathan will begin a postdoctoral position in the laboratories of Prof. Vy Dong at UC Irvine.