

SYNTHETIC APPLICATIONS AND METHODOLOGICAL DEVELOPMENTS OF
DONOR–ACCEPTOR CYCLOPROPANES

Thesis by

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To my teachers

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In Pirkei Avot, a prominent collection of Jewish ethics and morals, Shimon ben Zoma is quoted: “Who is wise? He who learns from all people.” This phrase has been somewhat of a guiding principle for me throughout my graduate studies, and throughout my time at Caltech I have been surrounded by an incredible group of people. These are the many students, professors and staff who have contributed toward my development as a scientist and have provided me with plenty of lessons in life and in Chemistry. I have resigned myself to the knowledge that this section will invariably be inadequate to address every manner in which I have been changed for the better by my interactions at this singular institution.

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Alex

ABSTRACT

Donor–acceptor cyclopropanes are a versatile class of synthetic intermediates, compatible in a broad range of ring-opening reactions and formal cycloadditions, and employed in numerous natural product syntheses. We have developed new Lewis acid mediated cycloadditions for the synthesis of five-membered heterocycles, and applied existing a transition metal catalyzed cyclopropane cycloaddition method toward the synthesis of complex alkaloids.

First, described is the development of a Lewis acid mediated (3 + 2) cycloaddition of donor–acceptor cyclopropanes with isocyanates, isothiocyanates and carbodiimides. This reaction was found in certain cases to proceed with excellent stereochemical fidelity, providing access to an array of enantioenriched thioimidates and amidines.

Second, we targeted the *Melodinus* alkaloids for total synthesis due to their unique structural features. Synthetic efforts toward scandine, the parent of the natural product family, are detailed herein. Our approach features a palladium catalyzed formal (3 + 2) cycloaddition of a vinyl cyclopropane and a β -nitrostyrene to rapidly assemble the central cyclopentane core of the natural product. Initial efforts focused on the synthesis and application of a 1,1-divinylcyclopropane to the formal (3 + 2) cycloaddition reaction, whereas later work entailed the use of a mono-vinylcyclopropane with the goal of installing the second requisite vinyl group at a later stage using modern C–H functionalization technologies.

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LIST OF ABBREVIATIONS

Å	Ångstrom
$[\alpha]_D$	specific rotation at wavelength of sodium D line
Ac	acetyl
Anal.	combustion elemental analysis
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
AIBN	2,2'-azobisisobutyronitrile
Ar	aryl
atm	atmosphere
BBN	borabicyclononane
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
bp	boiling point
br	broad
Bu	butyl
<i>i</i> -Bu	<i>iso</i> -butyl
<i>n</i> -Bu	butyl
<i>t</i> -Bu	<i>tert</i> -Butyl
Bz	benzoyl
<i>c</i>	concentration for specific rotation measurements
°C	degrees Celsius
ca.	about (Latin circa)
calc'd	calculated

CAN	ceric ammonium nitrate
cat	catalytic
Cbz	carbobenzyloxy
CCDC	Cambridge Crystallographic Data Centre
CDI	1,1'-carbonyldiimidazole
cf.	compare (Latin confer)
CI	chemical ionization
CID	collision-induced dissociation
cm ⁻¹	wavenumber(s)
comp	complex
Cy	cyclohexyl
d	doublet
D	deuterium
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
dec	decomposition
DIAD	diisopropyl azodicarboxylate
DMA	<i>N,N</i> -dimethylacetamide
DMAP	4-dimethylaminopyridine
dmdba	bis(3,5-dimethoxybenzylidene)acetone
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
DNA	(deoxy)ribonucleic acid
dppb	1,4-bis(diphenylphosphino)butane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio

E_A	activation energy
EC ₅₀	median effective concentration (50%)
EDC	<i>N</i> -(3-dimethylaminopropyl)- <i>N'</i> -ethylcarbodiimide
ee	enantiomeric excess
EI	electron impact
e.g.	for example (Latin <i>exempli gratia</i>)
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
FAB	fast atom bombardment
FID	flame ionization detector
g	gram(s)
GC	gas chromatography
gCOSY	gradient-selected correlation spectroscopy
GlyPHOX	2-(2-(diphenylphosphino)phenyl)oxazoline
h	hour(s)
HIV	human immunodeficiency virus
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoramide
HOBt	1-hydroxybenzotriazole
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectroscopy
HSV	herpes simplex virus
$h\nu$	light
Hz	hertz
IC ₅₀	median inhibition concentration (50%)
i.e.	that is (Latin <i>id est</i>)

IR	infrared (spectroscopy)
<i>J</i>	coupling constant
kcal	kilocalorie
KDA	potassium diisopropylamide
KHMDS	potassium hexamethyldisilazide
λ	wavelength
L	liter
LDA	lithium diisopropylamide
lit.	literature value
LTQ	linear trap quadrupole
m	multiplet; milli
<i>m</i>	meta
<i>m/z</i>	mass to charge ratio
M	metal; molar; molecular ion
Me	methyl
MHz	megahertz
μ	micro
μ waves	microwave irradiation
min	minute(s)
MM	mixed method
mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
n	nano
N	normal

nbd	norbornadiene
NBS	<i>N</i> -bromosuccinimide
NIST	National Institute of Standards and Technology
NMO	<i>N</i> -methylmorpholine <i>N</i> -oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
Nu	nucleophile
[O]	oxidation
<i>o</i>	ortho
<i>p</i>	para
PA	proton affinity
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
PhH	benzene
PhMe	toluene
PHOX	phosphinooxazoline
Piv	pivaloyl
<i>pK_a</i>	<i>pK</i> for association of an acid
PMB	<i>p</i> -methoxybenzyl
pmdba	bis(4-methoxybenzylidene)acetone
ppm	parts per million
PPTS	pyridinium <i>p</i> -toluenesulfonate
Pr	propyl
<i>i</i> -Pr	isopropyl

Py	pyridine
q	quartet
ref	reference
R	generic for any atom or functional group
R_f	retention factor
rt	room temperature
s	singlet or strong or selectivity factor
sat.	saturated
SET	single electron transfer
S _N 2	second-order nucleophilic substitution
sp.	species
t	triplet
TBAF	tetrabutylammonium fluoride
TBHP	<i>tert</i> -butyl hydroperoxide
TBS	<i>tert</i> -butyldimethylsilyl
TCDI	1,1'-thiocarbonyldiimidazole
TCNE	tetracyanoethylene
Tf	trifluoromethanesulfonyl (trifyl)
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMS	trimethylsilyl
TOF	time-of-flight
Tol	tolyl

TON	turnover number
t_R	retention time
Ts	<i>p</i> -toluenesulfonyl (tosyl)
UV	ultraviolet
v/v	volume to volume
w	weak
w/v	weight to volume
X	anionic ligand or halide

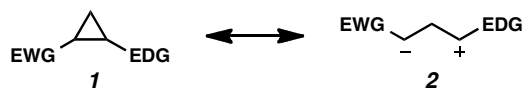
CHAPTER 1

Lewis Acid Mediated (3 + 2) Cycloadditions of Donor–Acceptor Cyclopropanes with Heterocumulenes[†]

1.1 INTRODUCTION

Donor–acceptor cyclopropanes (**1**) are those which bear an electron-donating group and an electron-withdrawing group with a vicinal relationship; these have found broad use as building-blocks in organic synthesis (Scheme 1.1.1).¹ Their reactivity is attributed to the electronic nature of these compounds, bearing substituents that polarize the cyclopropane C–C bond between them.

Scheme 1.1.1. Structural definition of donor–acceptor cyclopropanes

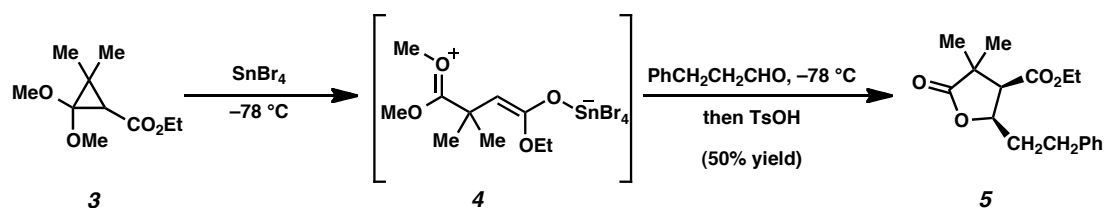


Historically, alkoxy or silyloxy substituents are among the most prevalent donor groups used in these systems. A typical example of such a system is Saigo's use of

[†] This work was performed in collaboration with Nicholas R. O'Connor and Robert A. Craig, II, graduate students in the Stoltz group. This work has been published. See: Goldberg, A. F. G.; O'Connor, N. R. O.; Craig, R. A., II; Stoltz, B. M. *Org. Lett.* **2012**, *14*, 5314–5317.

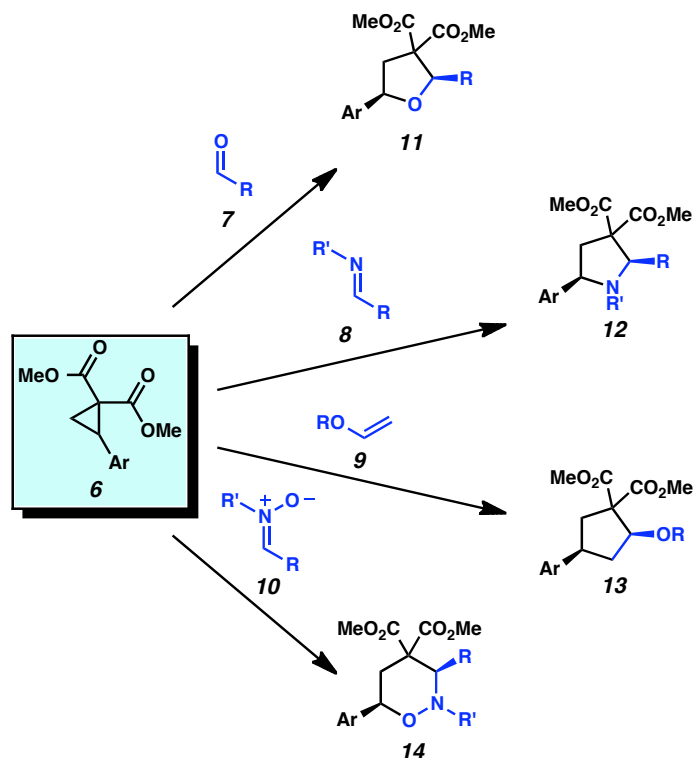
tin(IV) bromide to activate dimethoxycyclopropane **3**, which affords intermediate zwitterion **4** (Scheme 1.1.2).² Upon reaction with an aldehyde, followed by Brønsted acid catalyzed cyclization, lactones such as **5** are formed. In cases such as these, complete heterolysis of the reactive C–C bond results in loss of stereochemical information at those centers and any control of absolute stereochemistry must result from remote chiral centers or reagent control.

Scheme 1.1.2. Lewis acid activation of dimethoxycyclopropane **3**



More recently, aryl-substituted cyclopropane-1,1-diester (**6**) have proven valuable in Lewis acid promoted stereoselective 2, 3, or 4 atom ring-expansion reactions. By reaction with aldehydes (**7**),³ imines (**8**),⁴ enol ethers (**9**),⁵ and nitrones (**10**),⁶ an array of enantioenriched carbocycles and heterocycles (**11–14**) have been prepared (Scheme 1.1.3).

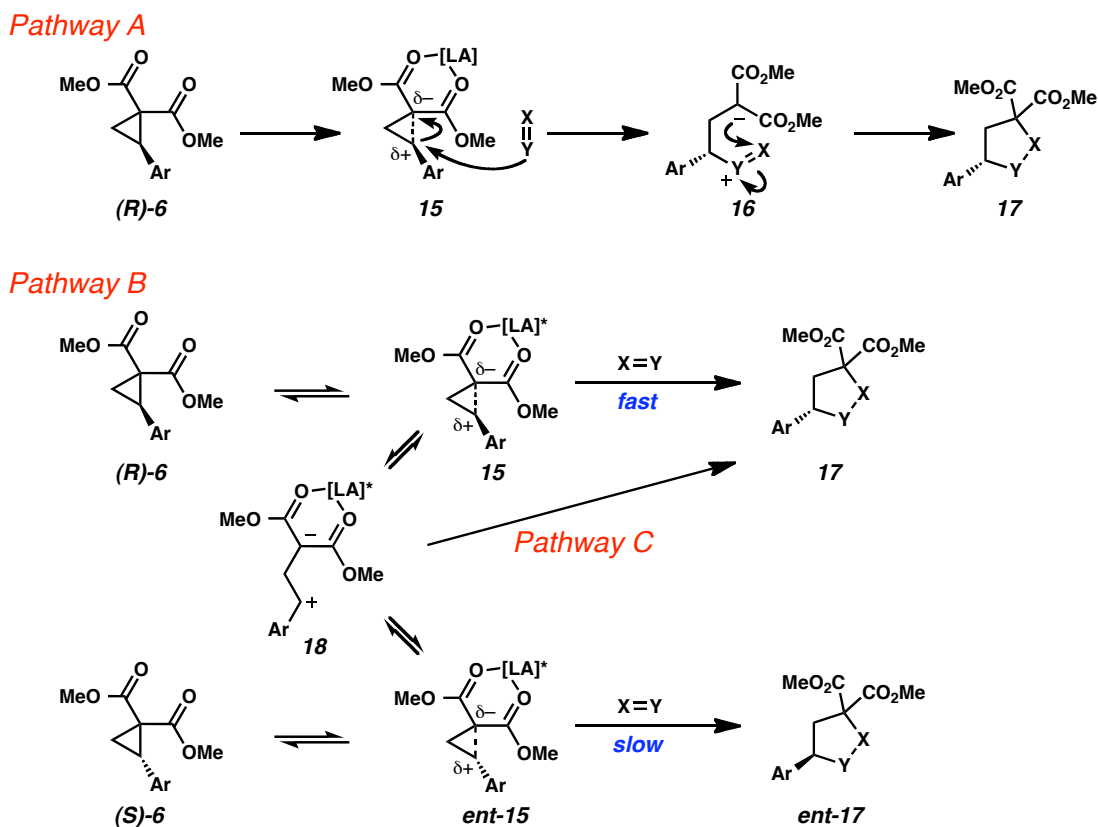
Scheme 1.1.3 Stereoselective (3 + 2) cycloadditions of donor–acceptor cyclopropanes.



There are two prevailing pathways toward enantioenriched products that have been studied in this system. First, enantioenriched starting materials have been converted stereospecifically to enantioenriched products with judicious choice of Lewis acid (Scheme 1.1.4, Pathway A). For these systems, it is generally believed that the Lewis acid activates the cyclopropane (**6**) toward nucleophilic attack without complete cleavage of the polarized C–C bond. The malonate zwitterion (**15**) then undergoes ring-closure to generate the product (**17**), with overall inversion of stereochemistry.^{3b,5a,6f} Alternatively, racemic cyclopropanes have been converted to enantioenriched products by means of a dynamic kinetic asymmetric transformation (DyKAT), wherein the starting material is racemized under the reaction conditions, and one enantiomer reacts faster with a chiral Lewis acid (Scheme 1.1.4, Pathway B).^{3d,4c,5b,6h} Finally, it is also possible that a discrete,

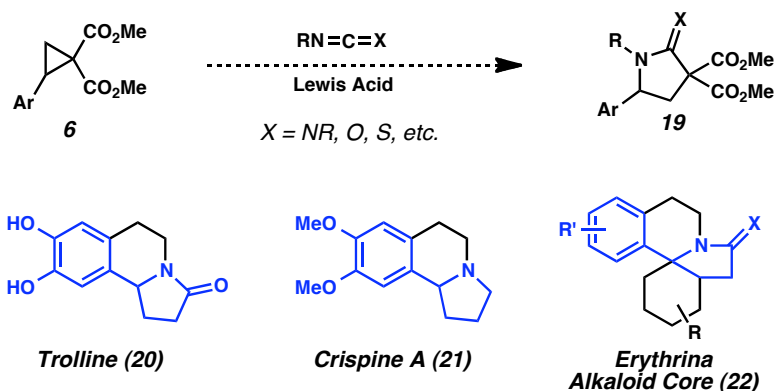
planarized zwitterion (**18**) can react with the dipolarophile in the presence of a chiral Lewis acid to effect facial selectivity.

Scheme 1.1.4. Prevailing pathways for stereoselective cyclopropane cycloadditions



Our research group has a long-standing interest in the asymmetric synthesis of chiral heterocycles.⁷ We were therefore interested in examining the use of heterocumulenes with this reaction platform toward the synthesis of chiral 5-aryl substituted lactam derivatives, a structural motif found in several natural products including trolline **20**,⁸ crispine A (**21**),⁹ and several of the *Erythrina* alkaloids (**22**).^{10,11}

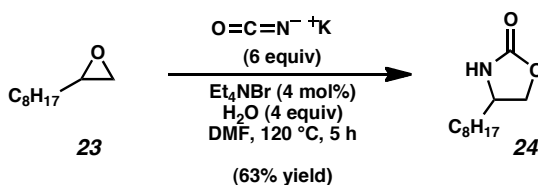
Scheme 1.1.5. Proposed (3 + 2) cycloaddition of heterocumulenes with cyclopropanes



1.2 INITIAL EFFORTS

Our initial attempts began with the investigation of potassium cyanate as a potential dipolarophile toward the synthesis of secondary γ -lactams. Swern reported the use of potassium cyanate in the synthesis of oxazolidinones from epoxides; heating of epoxides (i.e. **23**) with potassium cyanate, in the presence of a phase-transfer catalyst and water, affords oxazolidinones (i.e. **24**) in good yields (Scheme 1.2.1).¹² Notably, the inclusion of water was necessary for product formation; dimers were typically observed in the absence of water.

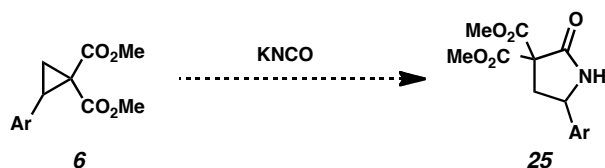
Scheme 1.2.1. Synthesis of oxazolidinones from epoxides



The use of potassium cyanate in reaction with cyclopropanes would bear certain advantages: it is readily available at low expense, and would provide direct access to γ -lactams (i.e. **25**, Scheme 1.2.2). Therefore, we began by studying the reactivity of donor–

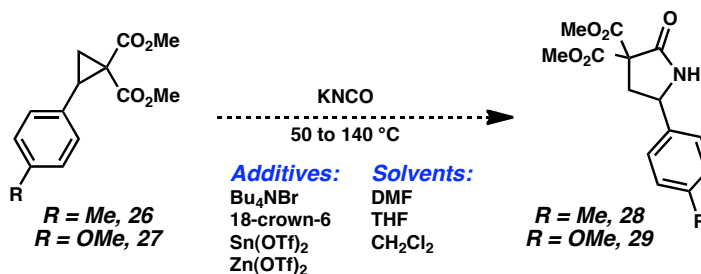
acceptor cyclopropanes with potassium cyanate under comparable conditions to those developed by Swern.

Scheme 1.2.2. Proposed synthesis of lactams using potassium cyanate

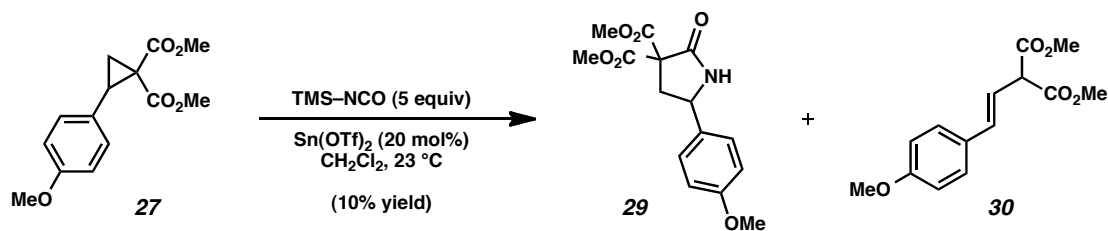


Our studies began by treatment of *para*-tolyl substituted cyclopropane **26** with potassium cyanate in several solvents in the presence of Lewis acids or phase-transfer catalysts (Scheme 1.2.3). Unfortunately, none of the desired product (**28**) was observed by LCMS. In our attempt to increase the reactivity of the cyclopropane, we examined *para*-methoxyphenyl cyclopropane **27**, and though the starting material was consumed in this case, no lactam formation was observed.

Scheme 1.2.3. Reactivity attempts of potassium cyanate with cyclopropanes **26** and **27**



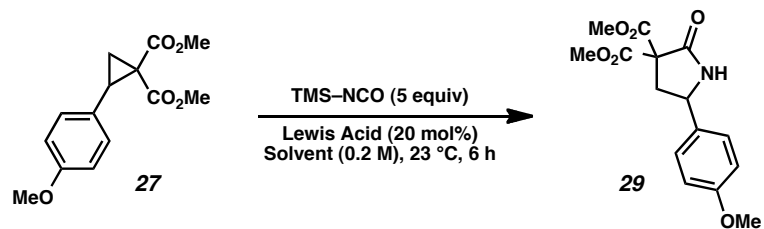
We considered that the cyclopropane may require Lewis acid activation, but the cyanate anion deactivated the Lewis acid by coordination. Therefore, we examined trimethylsilyl isocyanate as a potential alternative, using tin(II) triflate as a Lewis acid additive, and we were pleased to observe the formation of lactam **29** in 10% yield, with styrene **30** as the major side product. Having demonstrated proof-of-principle, we set out to optimize the cycloaddition reaction.

Scheme 1.2.4. Synthesis of lactam **29** from cyclopropane **27**

1.3 REACTION OPTIMIZATION OF ISOCYANATE CYCLOADDITION

Our first course of action was to examine an array of Lewis acids and solvents in the (3 + 2) cycloaddition reaction (Table 1.3.1). In several organic solvents, the yield of lactam **29** was unimproved (entries 1–6), and most of the starting material was isomerized to styrene **30**. The use of DMSO completely halted the reaction, likely due to deactivation of the Lewis acid by coordination of solvent (entry 7). With the use of unpurified ethyl acetate, we were pleased to observe a marked improvement to 56% yield (entry 7); upon repetition of this experiment with dry, distilled ethyl acetate, the yield fell to 18%, comparable to other dry organic solvents (entry 8), suggesting that water may play a role in the reaction.^{13,14} Finally, the examination of several other Lewis acids proved unfruitful in this exercise, either offering little reactivity (entries 10, 12) or complete isomerization of the cyclopropane (entry 11).

Table 1.3.1. Lewis acid and solvent screen for the (3 + 2) cycloaddition

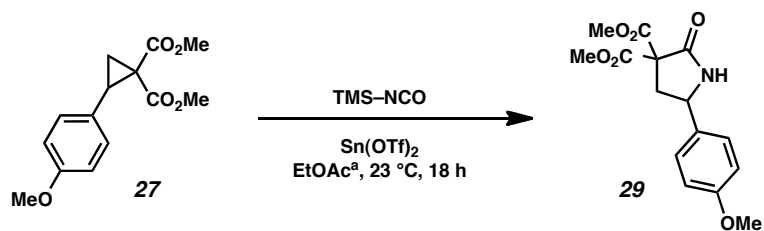


entry	Lewis Acid	Solvent	Conversion (%)	Yield of 29 (%) ^{a,b}
1	Sn(OTf) ₂	CH ₂ Cl ₂	100	23
2	Sn(OTf) ₂	THF	56	15
3	Sn(OTf) ₂	Et ₂ O	100 ^c	25
4	Sn(OTf) ₂	MeCN	97	20
5	Sn(OTf) ₂	PhMe	60	18
6	Sn(OTf) ₂	CHCl ₃ ^d	100	0
7	Sn(OTf) ₂	DMSO	0	0
8	Sn(OTf) ₂	EtOAc ^d	96 ^c	56
9	Sn(OTf) ₂	EtOAc	100 ^c	18
10	Zn(OTf) ₂ ^e	CH ₂ Cl ₂	0	0
11	Sc(OTf) ₃	CH ₂ Cl ₂	100	0
12	MgBr ₂ ·Et ₂ O	CH ₂ Cl ₂	40	15

^a Determined by LCMS, using 1,4-dichlorobenzene as an internal standard.^b The major side-product was typically styrene **30**. ^c 18 hour reaction time. ^dUndistilled. ^e Other unreactive Lewis acids include Mg(OTf)₂, Ni(OTf)₂, MnCl₂, Sm(OTf)₃.

We then sought to examine the effect of substrate concentration, isocyanate equivalence and Lewis acid equivalence on the outcome of the reaction (Table 1.3.2).¹⁵ We found that lowering the equivalence of isocyanate lowered the yield of lactam **29** slightly (entries 1–3). In addition, lowering the cyclopropane concentration decreased the yield (entry 4) and decreasing the Lewis acid loading to 5 mol% shut down reactivity entirely (entry 5). However, increasing the concentration to 0.6 M at this catalyst loading restored some measure of reactivity, providing lactam in 21% yield (entry 6). Increasing the quantity of tin from our original conditions improved the yield, to the point where we observed the highest yields with stoichiometric tin (entry 10).

Table 1.3.2. Equivalence and concentration optimization.

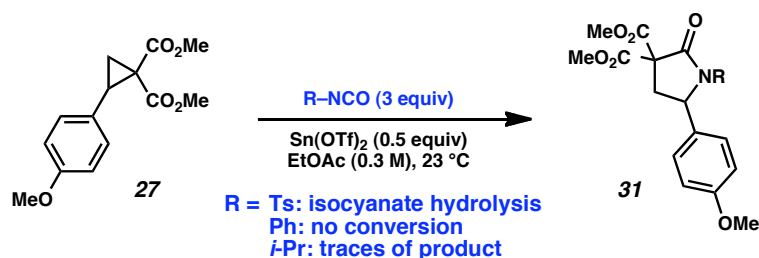


entry	Isocyanate equiv	Sn(OTf) ₂ equiv	[27]	Conversion (%)	Yield of 29 (%) ^{b,c}
1	5	0.2	0.2 M	63	64
2	4	0.2	0.2 M	59	56
3	3	0.2	0.2 M	59	54
4	3	0.2	0.1 M	31	21
5	3	0.05	0.3 M	3 ^d	0
6	3	0.05	0.6 M	23 ^d	21
7	3	0.1	0.6 M	64 ^d	61
8	3	0.2	0.6 M	100 ^d	85 (48) ^e
9	3	0.5	0.2 M	100	93
10	3	1.0	0.2 M	100	>99

^a Unpurified. ^b Determined by LCMS, using 1,4-dichlorobenzene as an internal standard. ^c The major side-product was typically styrene 30. ^d 24 hour reaction time. ^e Isolated yield.

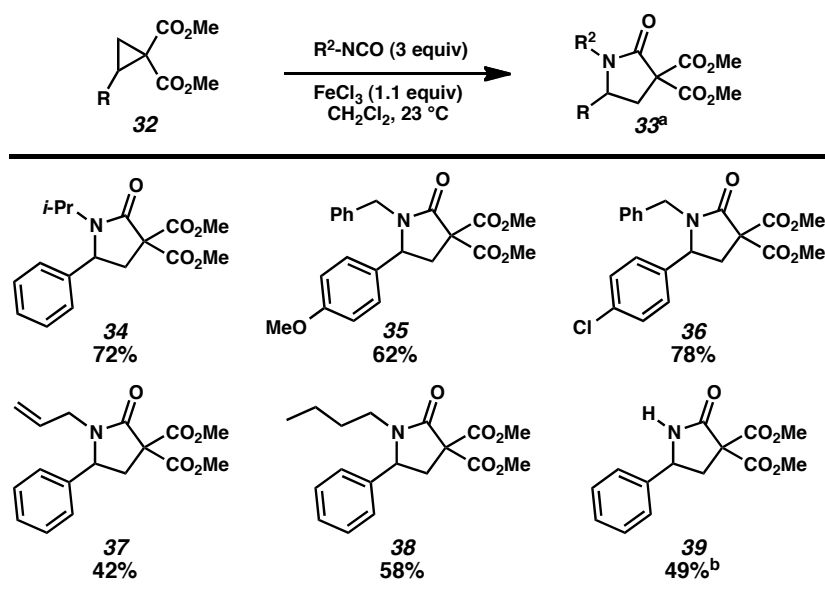
We were interested in ascertaining the compatibility of other heterocumulenes in this reaction; therefore we examined a breadth of substitution before further developing the reaction (Scheme 1.3.1). However, only with isopropyl isocyanate did we observe any trace of the desired product at room temperature. Phenyl isocyanate was found to be unreactive under the same conditions, and tosyl isocyanate was hydrolyzed quickly under the reaction conditions, presumably due to the presence of adventitious water in the unpurified solvent.

Scheme 1.3.1. Initial examination of alternative isocyanates.



The hydrolysis of tosyl isocyanate under the reaction conditions, while not surprising due to the highly electrophilic nature of the reagent, raised broader concerns about the presence of water in the reaction mixture. In addition, the poor reactivity for these substituted isocyanates prompted us to investigate stronger Lewis acids for this transformation; we sought to avoid biasing the system with an electron-rich arene. Furthermore, we returned to the use of dichloromethane, since the dry solvent was more readily accessible in our laboratory and provided comparable yields to those observed with dry ethyl acetate. A brief examination of several Lewis acids found that stoichiometric iron(III) chloride performed the desired transformation with several different alkyl-substituted isocyanates to afford lactams **34–39** (Scheme 1.3.2).¹⁶

Scheme 1.3.2. Scope of iron(III) chloride mediated (3 + 2) cycloadditions of isocyanates.

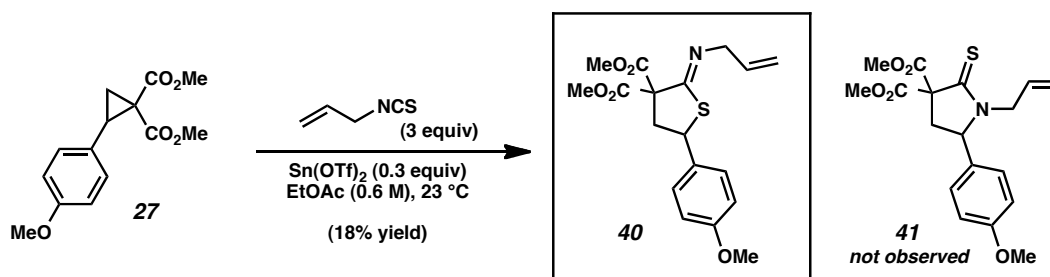


^a Isolated yields. ^b Trimethylsilylisocyanate was used and hydrolysis of the silyl group occurred upon workup.

1.4 ISOTHIOCYANATE (3 + 2) CYCLOADDITIONS

We also examined other classes of heterocumulenes under the same conditions. We had initially found that treatment of *para*-methoxyphenyl substituted cyclopropane (**27**) with allyl isothiocyanate in the presence of substoichiometric tin(II) triflate afforded a thioimide (**40**) in moderate yield; thiolactam **41** was not observed under these conditions (Scheme 1.4.1).

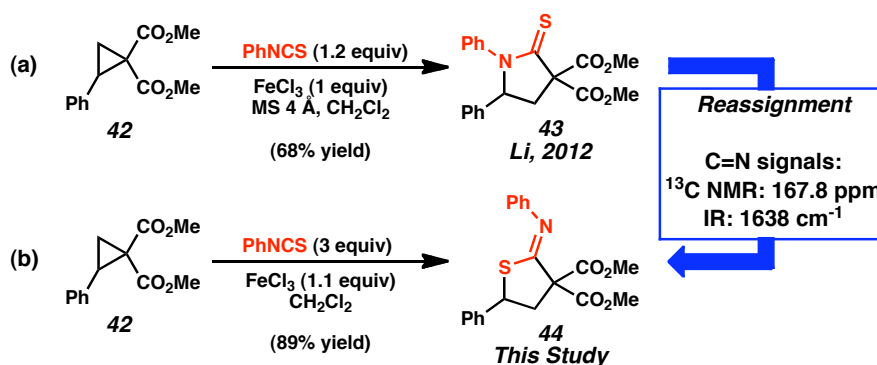
Scheme 1.4.1. Synthesis of thioimide **40** using allyl isothiocyanate



Concurrent with these studies, Li and coworkers disclosed an iron(III) chloride mediated (3 + 2) cycloaddition of aryl isothiocyanates with donor–acceptor cyclopropanes to form thiolactams (e.g. **44**) rather than thioimides (e.g. **43**, Scheme 1.4.2).¹⁷ We suspected that the products reported by Li may have been misassigned, and decided to investigate this further. Upon comparison of the ^{13}C NMR spectrum of allyl isothiocyanate adduct **40** to the spectra of the products reported by Li, we found similar shifts in the carbonyl range for these spectra; three signals were typically observed near 160 ppm—two corresponding to the ester functionalities—and the third is consistent with a thioimide. By contrast, a thioamide $\text{C}=\text{S}$ ^{13}C NMR signal is expected at approximately 200 ppm.¹⁸ Furthermore, the IR spectrum of **40** exhibited a $\text{C}=\text{N}$ stretch at 1638 cm^{-1} , and $\text{C}=\text{S}$ signals were not observed.¹⁹ Although no IR spectra were included

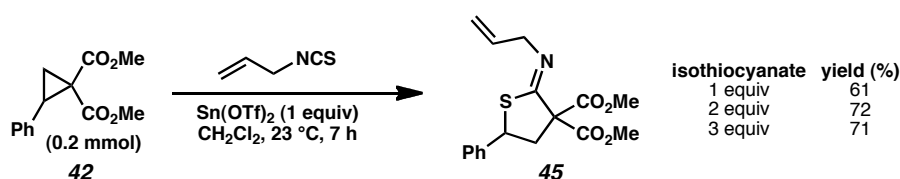
in Li's report, we reacted cyclopropane **42** with phenyl isothiocyanate under similar conditions to those reported by Li and obtained a compound with NMR spectra matching those reported (Scheme 2b). The product IR spectrum contained a C=N stretch at 1638 cm^{-1} while a C=S peak was not observed. Altogether, these data strongly support our assignment of compound **44** and Li's isothiocyanate (3 + 2) adducts as thioimides, not thiolactams.

Scheme 1.4.2. Structural reassignment of Li's arylisothiocyanate (3 + 2) products



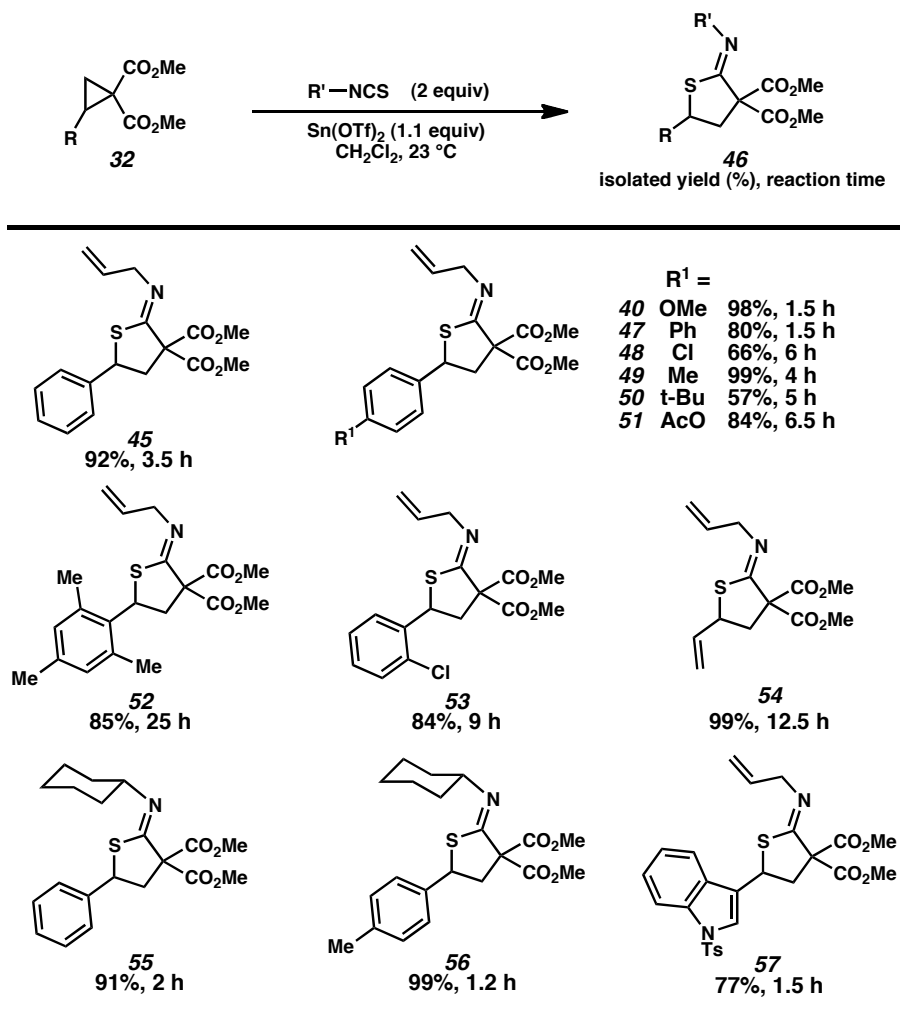
We ultimately found the use of stoichiometric Lewis acid was necessary to achieve complete conversion of the cyclopropane starting material. For the same reasons as before, we elected to perform the reaction in dry dichloromethane, and examined the necessary excess of isothiocyanate to achieve the good yields of thioimide (Scheme 1.4.3). We found that decreasing the equivalence of allylisothiocyanate from 3 to 2 with respect to cyclopropane had no measurable impact on the reaction yield, while the use of one equivalent of isothiocyanate resulted in a lower isolated yield.

Scheme 1.4.3. Study on isothiocyanate stoichiometry in (3 + 2) cycloadditions



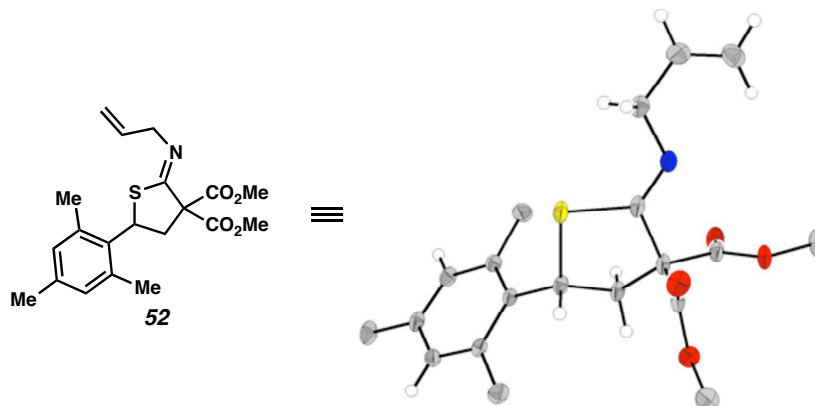
Eventually, we found that decreasing the reaction time—careful monitoring of the reaction and workup immediately upon completion—and increasing the reaction scale resulted in improved yields. Notably, the thioimide products slowly decompose at room temperature, as observed by discoloration of the material and new signals in their NMR spectra; storage in a –20 °C freezer is necessary for prolonged storage. We then examined the substrate scope of the reaction, and found that thioimides with electron-rich aryl substituents (**40**, **47**, **57**) were obtained with the shortest reaction times. Reactions leading to products with *ortho*- or electron-withdrawing arene substituents (**48**, **52**, **53**) were the slowest. Cyclopropanes were not limited to those with aryl substituents; a vinyl group could also be used as an electron-donating substituent, offering 5-vinylthioimide **54** in quantitative yield. In addition, cyclohexyl isothiocyanate was also compatible under these conditions, providing thioimides **55** and **56** in 91% and 99% yield respectively.

Scheme 1.4.4. Substrate scope of isothiocyanate (3 + 2) reaction



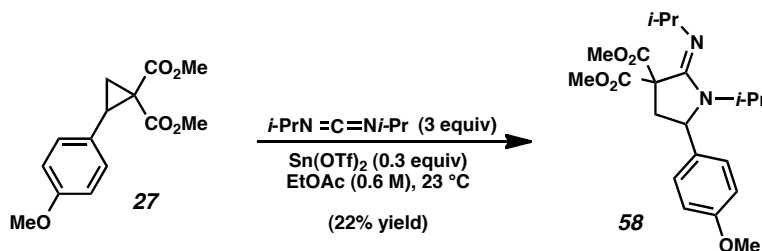
Notably, we were able to obtain x-ray quality crystals of mesityl-substituted product **52**, confirming our assignment of these products as thioimides. Furthermore, the geometry of the imide *N*-substituent was confirmed in this experiment, and the other thioimide products were assigned as such by analogy.

Scheme 1.4.5. Confirmation of thioimide structure by single crystal x-ray diffraction



1.5 CARBODIIMIDE (3 + 2) CYCLOADDITIONS

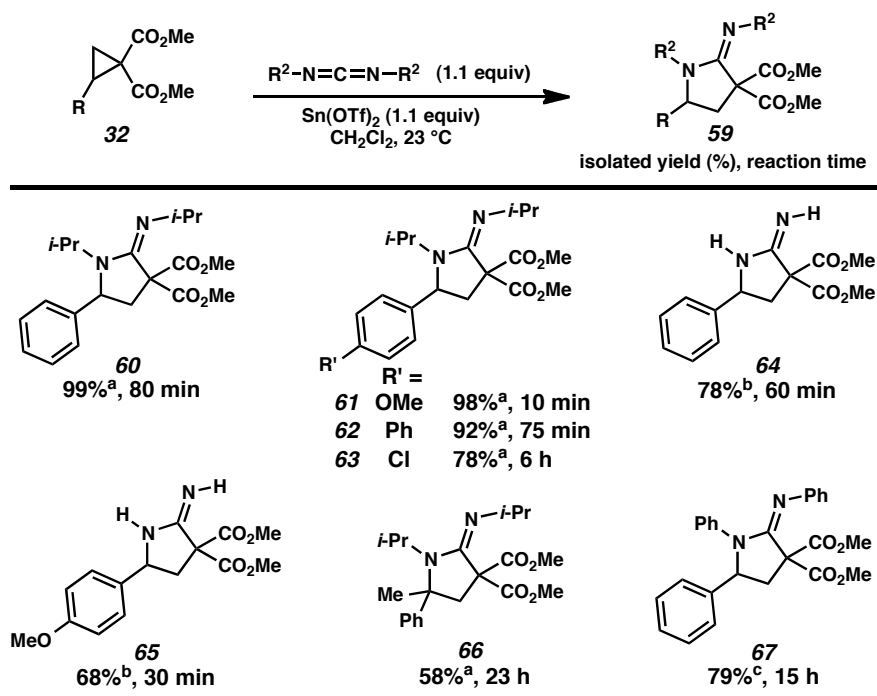
Finally, we turned our attention toward (3 + 2) cycloadditions with carbodiimides. In our initial studies, we found that treatment of cyclopropane **27** with diisopropylcarbodiimide in the presence of substoichiometric tin(II) triflate afforded amidine **58**, albeit in moderate yield (Scheme 1.5.1). Akin to our studies on isocyanates and isothiocyanates, we envisioned that the use of stoichiometric tin in dry dichloromethane would improve our initial results; using wet ethyl acetate, we observed by NMR conversion of carbodiimide to a urea side product. We sought to avoid this by excluding water from the reaction mixture and limiting the excess of carbodiimide.

Scheme 1.5.1. Synthesis of amidine **58** using diisopropylcarbodiimide

We were therefore pleased to find that with only a marginal excess of carbodiimide and tin(II) triflate, we observed quantitative formation of amidine **60** (Scheme 1.5.2). In

this case, the reaction was complete in only 80 minutes, and electron rich 5-para-methoxyphenyl amidine **58** was formed in 98% yield in less than 10 minutes. Primary amidines (**64** and **65**) could also be accessed using bis(trimethylsilyl)carbodiimide. Notably, (3 + 2) reactions were possible with cyclopropanes that are unreactive with isothiocyanates. For instance, a sterically congested 5,5-disubstituted amidine **66** could be generated in 58% yield. In addition, while aryl isothiocyanates were poorly reactive in the presence of tin(II) triflate, use of diphenylcarbodiimide resulted in the formation of the corresponding amidine (**67**) in 79% yield. Overall, the shorter reaction times indicate that carbodiimides are considerably more reactive dipolarophiles than comparable isothiocyanates in these reactions.

Scheme 1.5.2. Substrate scope of carbodiimide (3 + 2) cycloaddition.

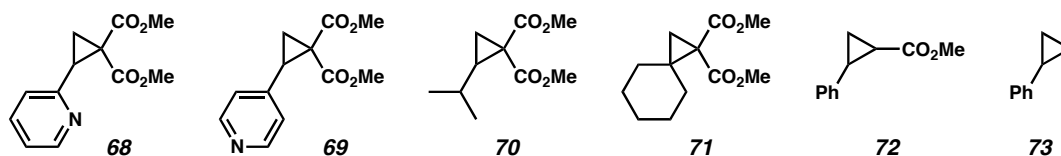


^a diisopropylcarbodiimide was used as the dipolarophile. ^b bis(trimethylsilyl)carbodiimide was used as the dipolarophile, the silyl groups are hydrolysed upon workup. ^c diphenylcarbodiimide was used as the dipolarophile.

1.6 UNREACTIVE AND PROBLEMATIC SUBSTRATES

We found several cyclopropanes to be unreactive in the Lewis acid mediated heterocumulene (3 + 2) reaction (Scheme 1.6.1). 2- and 4-pyridyl substituted cyclopropanes (**68** and **69**) were unreactive under standard reaction conditions. We considered that the pyridyl substituent inhibited the Lewis acid; although we thought that the use of an additional equivalent of Lewis acid may restore reactivity, efforts to this end failed to generate any desired (3 + 2) adduct. We also attempted to use alkyl substituted cyclopropanes **70** and **71**, since such substrates were known to be reactive under aldehyde (3 + 2) and nitron (3 + 3) cycloaddition conditions.^{3,6} Unfortunately, these substrates did not form (3 + 2) adducts under our standard conditions with heterocumulenes. Finally, application of a cyclopropane with one or no ester substituents (**72** and **73**) failed to afford (3 + 2) adducts, suggesting that the ester moieties are necessary for coordination to the Lewis acid.

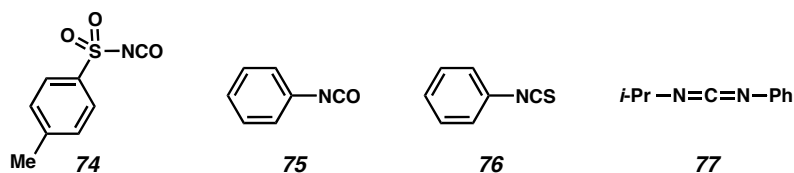
Scheme 1.6.1. Unreactive cyclopropanes in heterocumulene (3 + 2) cycloadditions



Certain heterocumulenes were also found to be unreactive under our standard conditions (Scheme 1.6.2). Tosylisocyanate (**74**) and phenylisocyanate (**75**) were unreactive under our standard conditions. Furthermore, while arylisothiocyanates (i.e. **76**) were unreactive using tin(II) triflate as the Lewis acid, these could participate in cyclopropane (3 + 2) cycloadditions with iron(III) chloride, as demonstrated by Li and coworkers.¹⁷ Finally, unsymmetrical carbodiimide **77** was attempted in the standard

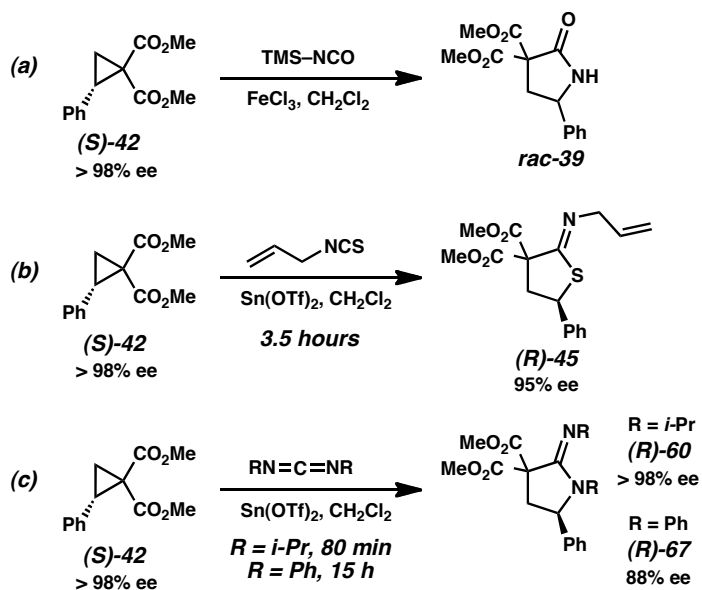
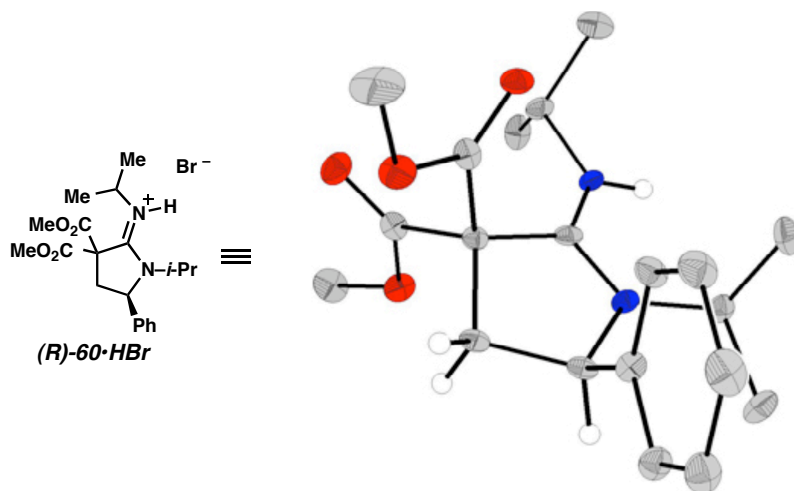
reaction conditions. We envisioned that the significant difference in reaction times between diisopropylcarbodiimide (80 min with cyclopropane **42**) and diphenylcarbodiimide (15 h) would proffer selectivity with a mixed carbodiimide (**77**), however, an inseparable mixture of constitutional isomers was produced.

Scheme 1.6.2. Problematic heterocumulenes in (3 + 2) cycloadditions



1.7 INVESTIGATIONS ON TRANSFER OF CHIRALITY

Finally, we sought to establish whether stereochemical information from the starting material is transferred to the product under the reaction conditions. We prepared enantioenriched cyclopropane (*S*)-**42** according to literature methods and subjected it to our standard reaction conditions (Scheme 1.7.1). Although treatment of this substrate with an isocyanate in the presence of iron(III) chloride resulted in complete racemization of the benzylic stereocenter (Scheme 1.7.1a), we observed transfer of chirality in the case of tin(II) triflate mediated (3 + 2) cycloadditions (Scheme 1.7.1b, c). Notably substrates that required longer reaction times resulted in increased erosion of optical activity. We were able to confirm the absolute stereochemistry of the HBr salt of (*R*)-**60** by single crystal x-ray diffraction, which revealed an inversion of configuration at the benzylic stereocenter through the course of the reaction, and also confirmed the geometry of the amidine substituent, notably it is inverted to that observed with the thioimides (Figure 1.7.1).

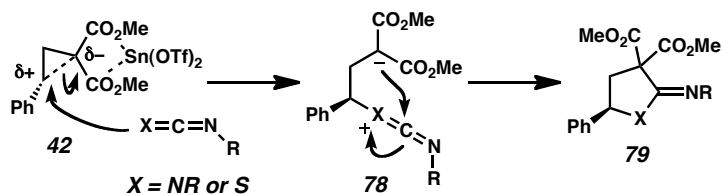
Scheme 1.7.1. Reactions of enantioenriched cyclopropane (**S**)-**42** with heterocumulenesFigure 1.7.1. Determination of absolute configuration by single crystal X-ray diffraction.²⁰

1.8 DISCUSSION OF MECHANISM

We propose that the mechanism of the isothiocyanate and carbodiimide reactions with tin(II) triflate involves a stereospecific intimate-ion pair mechanism analogous to that proposed for Johnson's (3 + 2) cycloadditions of aldehydes and donor–acceptor cyclopropanes (Scheme 1.8.1).^{3b,c,6e,f,g} Our observations, including stereochemical

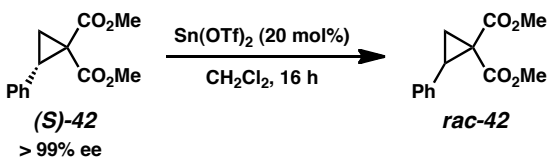
inversion at the benzylic position and greater reactivity of electron-rich dipolarophiles and of cyclopropanes with electron-rich aromatic substituents are all consistent with this mechanistic hypothesis.

Scheme 1.8.1. Mechanism of (3 + 2) cycloaddition with carbodiimides and isothiocyanates



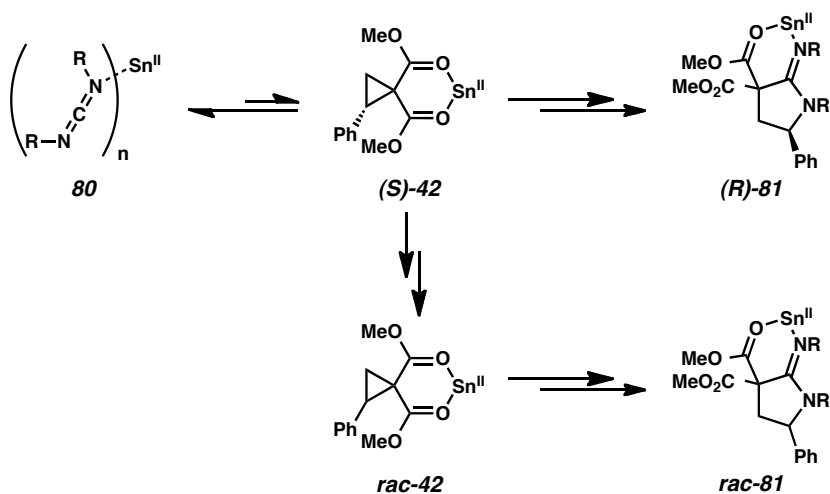
In the case of the iron-catalyzed isocyanate (3 + 2) cycloaddition, the dipolarophile likely reacts in a nucleophilic sense, which is corroborated by the lack of reactivity of the aryl- and sulfonyl-substituted isocyanates. However, the formation of a discrete carbocation intermediate in this case—as opposed to a contact-ion pair—is supported by the rapid racemization of the cyclopropane starting material.

Finally, the degree of interaction between the heterocumulene and the Lewis acid likely affects the course of the reaction. Whereas Johnson reported that in the presence of 0.2 equivalents of tin(II) triflate, enantioenriched cyclopropane (*S*)-**42** was completely racemized in 16 h, we found that amidine (*R*)-**67** was formed in 88% ee with a reaction time of 15 h with stoichiometric Lewis acid (*vide supra*, Scheme 1.7.1).^{3c} Although a direct comparison cannot be made since the cyclopropane is converted over time in the latter case, it is evident that cyclopropane racemization is attenuated in the presence of carbodiimide.

Scheme 1.8.2. Racemization of cyclopropane (*S*)-**42** with catalytic tin(II) triflate^{3c}

It is possible that an equilibrium exists between a tin–dipolarophile complex and a tin–cyclopropane complex, which would account for the mitigation of cyclopropane racemization over the extended reaction time ($R = \text{Ph}$, Scheme 1.8.3). Coordination of the product to the catalyst would minimize further racemization of the enantioenriched cyclopropane, and is consistent with the need for stoichiometric Lewis acid to achieve full conversion of starting material.

Scheme 1.8.3. Proposed mechanism accounting for attenuated racemization



1.9 FUTURE DIRECTIONS

We are currently examining the extensions of this methodology, and applications toward the synthesis of natural products. These aspects of the project are discussed in Appendix 1.

1.10 CONCLUSION

In summary, we have developed a method for the (3 + 2) cycloaddition of donor–acceptor cyclopropanes with heterocumulenes. We have demonstrated a novel mode of reactivity with isothiocyanates, complementary to that previously observed with alkoxy substituted cyclopropanes. Finally, we have shown that enantioenriched starting materials may be converted to enantioenriched 5-membered heterocycles by a stereospecific process. Investigations are ongoing to develop related methodologies and to apply this method to the synthesis of natural products.

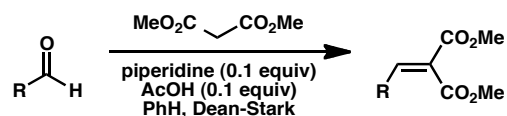
1.11 EXPERIMENTAL SECTION

1.11.1 MATERIALS AND METHODS

Unless stated otherwise, reactions were performed under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina).²¹ Commercially obtained reagents were used as received unless otherwise stated. Reaction temperatures were controlled by an IKAmag temperature modulator. Microwave reactions were performed with a Biotage Initiator Eight 400 W apparatus at 2.45 GHz. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, or potassium permanganate, iodine, or anisaldehyde staining. SiliaFlash P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. ¹H and ¹³C NMR spectra were recorded on a Varian Inova 500 (at 500 MHz and 126 MHz respectively), Varian 400 (at 400 MHz and 100 MHz, respectively) or on a Varian Mercury 300 (at 300 MHz) and are reported relative to CHCl₃ (δ 7.26 & 77.16 respectively). Data for ¹H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm⁻¹). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) or mixed (MM) ionization mode.

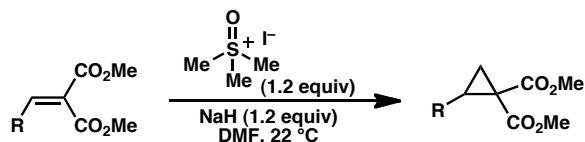
1.11.2 PREPARATIVE PROCEDURES

1.11.2.1 GENERAL AND MISCELLANEOUS EXPERIMENTAL PROCEDURES



General Procedure A. Knoevenagel condensation.

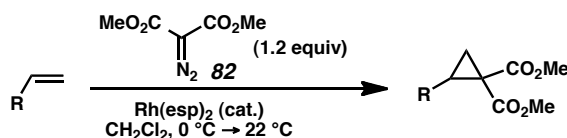
A round-bottom flask was charged with the appropriate aldehyde (14.4 mmol), followed by benzene (85 mL), dimethyl malonate (15.8 mmol), piperidine (1.44 mmol), and acetic acid (1.44 mmol). The flask was equipped with a Dean–Stark trap and condenser and the solution heated to reflux. Upon completion (as determined by TLC analysis), evaporation of the solvent gave the crude product, which was purified by silica gel column chromatography.



General Procedure B. Corey-Chaykovsky cyclopropanation.

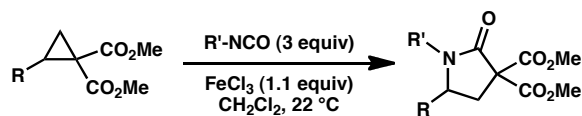
Sodium hydride (2.56 mmol, 60% dispersion in mineral oil) was suspended in anhydrous DMF (4 mL) in a flame-dried round-bottom flask under nitrogen. Trimethylsulfoxonium iodide (2.56 mmol) was added, and the solution stirred at ambient temperature for 1 hour. A solution of the appropriate benzylidene malonate (2.13 mmol) in anhydrous DMF (2 mL) was added, and the reaction mixture allowed to stir at room temperature. Upon completion (as determined by TLC analysis), the solution was poured

onto a mixture of ice and 2 M HCl_(aq) (10 mL) and extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed once with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the crude product, which was purified by silica gel column chromatography.



General Procedure C. Styrene cyclopropanation.

Rh(esp)₂ (0.3 mg) was added to a flame-dried round-bottom flask, which was then evacuated and backfilled with nitrogen three times. The appropriate styrene (5.0 mmol) and anhydrous dichloromethane (5 mL) were then added and the solution was stirred under nitrogen and cooled in an ice bath. A solution of diazodimethylmalonate (**82**) (6.0 mmol) in anhydrous dichloromethane (5 mL) was added dropwise over 20 minutes.²² The reaction solution was then allowed to warm to ambient temperature. Upon completion (as determined by TLC analysis), the crude product was adsorbed onto silica gel and purified by column chromatography. When traces of the rhodium catalyst remained after chromatography (as determined by a blue discoloration), the product was dissolved in anhydrous benzene (1.5 mL) in a flame-dried round-bottom flask. A solution of tetrakis(hydroxymethyl)phosphonium hydroxide (10 μ L, 1M in isopropanol) was added,²³ and the mixture was stirred at 60 °C for 12 hours. The solution was then cooled to room temperature, diluted with diethyl ether (20 mL), washed once with water and once with brine, dried over magnesium sulfate, filtered and concentrated to give the purified product.



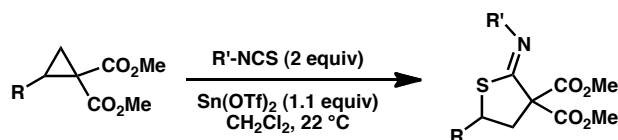
General Procedure D. *Isocyanate (3 + 2) reaction with D-A cyclopropanes.*

To a flame-dried 10 mL flask equipped with a magnetic stir bar was added iron(III) chloride (0.44 mmol) in an inert atmosphere glovebox. The flask was sealed with a Teflon septum, removed from the glovebox and placed under a nitrogen atmosphere. To an oven-dried 1 dram vial were added the appropriate cyclopropane (0.4 mmol) and isocyanate (1.2 mmol). The vial was sealed with a screw cap fitted with a Teflon septum, and this mixture was transferred to the reaction flask as a solution in anhydrous dichloromethane (1 mL + 0.33 mL rinse). The solution was then allowed to stir at ambient temperature under nitrogen. Upon consumption of the cyclopropane (as determined by TLC analysis), the reaction solution was diluted with dichloromethane, adsorbed onto Celite, and purified by silica gel column chromatography.

General Procedure E. *Isocyanate (3 + 2) reaction with D-A cyclopropanes.*

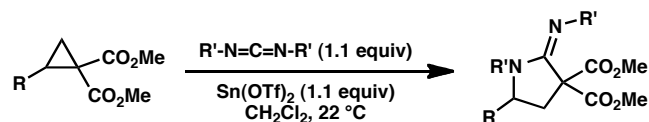
To an oven-dried 1 dram vial equipped with a magnetic stir bar was added iron (III) chloride (0.44 mmol) and oven-dried 4 Å molecular sieves (50 mg). The vial was sealed with a screw cap fitted with a rubber septum, and was placed under a nitrogen atmosphere. To a second oven-dried 1 dram vial was added the appropriate cyclopropane (0.4 mmol) and isocyanate (1.2 mmol). The vial was sealed with a screw cap fitted with a Teflon septum and this mixture was transferred to the first vial as a solution in anhydrous dichloromethane (1 mL + 0.33 mL rinse). The mixture was then allowed to

stir at ambient temperature under nitrogen. Upon consumption of the cyclopropane (as determined by TLC analysis), the reaction mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The layers were separated and the aqueous phase was washed twice with dichloromethane. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography.



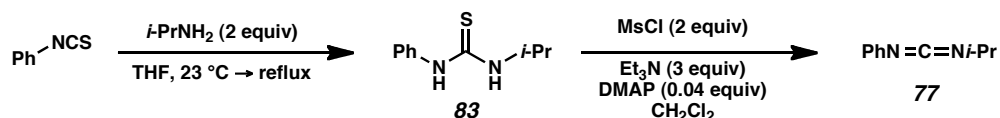
General Procedure F. Isothiocyanate (3 + 2) reaction with D-A cyclopropanes

To an oven-dried 1 dram vial equipped with a magnetic stir bar was added tin(II) trifluoromethanesulfonate (0.44 mmol) in an inert atmosphere glovebox. The vial was sealed with a screw cap fitted with a Teflon septum, removed from the glovebox and placed under a nitrogen atmosphere. To a separate, oven-dried 1 dram vial were added the appropriate cyclopropane (0.4 mmol) and isothiocyanate (0.8 mmol). The vial was sealed with a screw cap fitted with a Teflon septum, and the mixture was transferred to the first vial as a solution in anhydrous dichloromethane (1 mL + 0.33 mL rinse). The heterogeneous reaction mixture was then allowed to stir at ambient temperature under nitrogen. Upon consumption of the cyclopropane (as determined by TLC analysis), the reaction solution was diluted with dichloromethane (3 mL) and methanol (1 mL), adsorbed onto Celite, and purified by silica gel column chromatography. The products of this reaction were often found to be unstable during prolonged storage (~1 week) at ambient temperature; the decomposition products have not been identified.



General Procedure G. Carbodiimide (3 + 2) reaction with D–A cyclopropanes

To an oven-dried 1 dram vial equipped with a magnetic stir bar was added tin(II) trifluoromethanesulfonate (0.44 mmol) in an inert atmosphere glovebox. The vial was sealed with a screw cap fitted with a Teflon septum, removed from the glovebox and placed under a nitrogen atmosphere. To a separate, oven-dried 1 dram vial were added the appropriate cyclopropane (0.4 mmol) and carbodiimide (0.44 mmol). The vial was sealed with a screw cap fitted with a Teflon septum, and the mixture was transferred to the first vial as a solution in anhydrous dichloromethane (1 mL + 0.33 mL rinse). The heterogeneous reaction mixture was then allowed to stir at ambient temperature under nitrogen. Upon consumption of the cyclopropane (as determined by TLC analysis), the reaction solution was diluted with dichloromethane (3 mL) and methanol (1 mL), adsorbed onto Celite, and purified by silica gel column chromatography. The product obtained after column chromatography is an amidinium salt, which is dissolved in DCM, and washed with aqueous sodium hydroxide (0.1 M) and brine, then dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield the free amidine base.

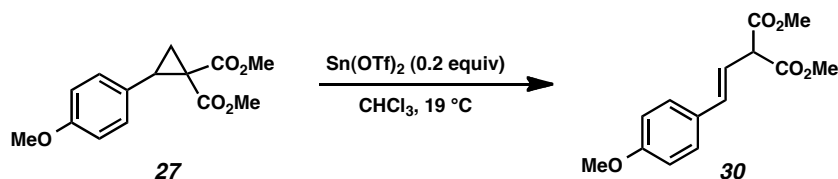


Thiourea 83. Prepared according to the method of Zhou and coworkers.²⁴ To a flame-dried round-bottom flask, equipped with a magnetic stir bar and fitted with a

rubber septum was added phenyl isothiocyanate (1.2 mL, 10 mmol, 1 equiv) and anhydrous THF (32 mL) under an inert atmosphere. To the stirring solution was added isopropylamine (1.64 mL, 20 mmol, 2 equiv) dropwise. The rubber septum was quickly replaced with a reflux condenser fitted with a hose adapter, connected to an inert atmosphere manifold. The resulting solution was heated to reflux with stirring for 40 min. The reaction mixture was then cooled to ambient temperature and the solvent was removed in vacuo. The residue was dissolved in ethyl acetate (60 mL) and washed with aqueous hydrochloric acid (10 mL, 1 N) and brine (10 mL), and the organic phase was dried over sodium sulfate, filtered, and concentrated in vacuo to afford crude thiourea **82** (1.89 g, 97%) as a white solid which was carried forward directly to the next step in the synthesis.

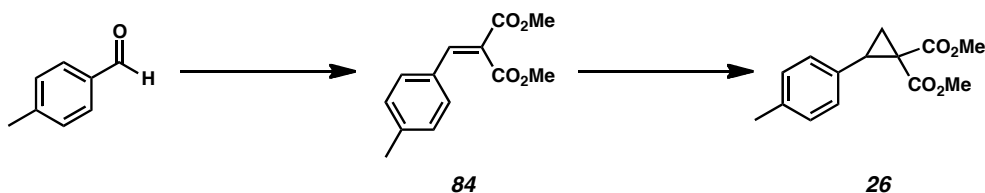
Carbodiimide 77. Prepared according to the method of Fell and Coppola.²⁵ To a flame-dried, round-bottom flask, equipped with a magnetic stir bar was added crude thiourea **82** (971 mg, 5 mmol, 1 equiv). The flask was sealed with a rubber septum and placed under an inert atmosphere. To the flask was added dry dichloromethane (50 mL, 0.1 M) and freshly distilled triethylamine (2.1 mL, 15 mmol, 3 equiv), followed by a dropwise addition of mesyl chloride (0.78 mL, 10 mmol, 2 equiv). Complete consumption of starting material was observed within 5 minutes, as determined by TLC. The volatiles were removed in vacuo, and a precipitate was observed. The mixture was filtered twice through SiO₂ (100 mL), eluting with dichloromethane, then purified by column chromatography on SiO₂ (10:1 hexanes:EtOAc) to afford carbodiimide **77** (332.2 mg, 41% yield) as a yellow oil: R_f = 0.81 (3:1 Hexanes:EtOAc eluent); ¹H NMR (300 MHz, CDCl₃) δ 7.38–7.20 (m, 2H), 7.21–7.02 (m, 3H), 3.80 (hept, J = 6.4 Hz, 1H), 1.35

(d, $J = 6.5$ Hz, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 140.9, 136.6, 129.4, 124.7, 123.4, 50.3, 24.9; IR (Neat Film, NaCl) 3419, 3067, 2973, 2129, 1637, 1592, 1501, 1454, 1367, 1320 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{10}\text{H}_{13}\text{N}_2$ $[\text{M}+\text{H}]^+$: 161.1073, found 161.1077.



Styrene 30. A 1 dram vial, equipped with a magnetic stir bar, was charged with tin(II) triflate (16.7 mg, 0.04 mmol, 0.2 equiv), then cyclopropane **27** (54.1 mg, 0.2 mmol, 1 equiv) was added as a solution in chloroform (1 mL). Stirring was initiated and a heterogeneous mixture with a yellow supernatant resulted. Consumption of starting material was observed by LCMS after 35 minutes. The reaction mixture was dry-loaded onto SiO_2 (~1 mL) and purified by column chromatography on SiO_2 (3:1 hexanes:EtOAc) to afford styrene **30** as a colorless solid: ^1H NMR (500 MHz, CDCl_3) δ 7.34 (d, $J = 7.7$ Hz, 2H), 6.85 (d, $J = 7.7$ Hz, 2H), 6.52 (d, $J = 16.0$ Hz, 1H), 6.31–6.21 (m, 1H), 4.19 (d, $J = 8.9$ Hz, 1H), 3.82 (s, 3H), 3.78 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.7, 159.7, 134.9, 128.9, 128.0, 118.4, 114.1, 55.8, 55.4, 53.0; IR (NaCl/film) 3002, 2953, 2834, 1736, 1607, 1513, 1251, 1177, 1029 cm^{-1} ; HRMS (MM: ESI-APCI) m/z calc'd for $\text{C}_{14}\text{H}_{16}\text{O}_5$ $[\text{M}+\text{H}]^+$: 265.1071, found 265.1076.

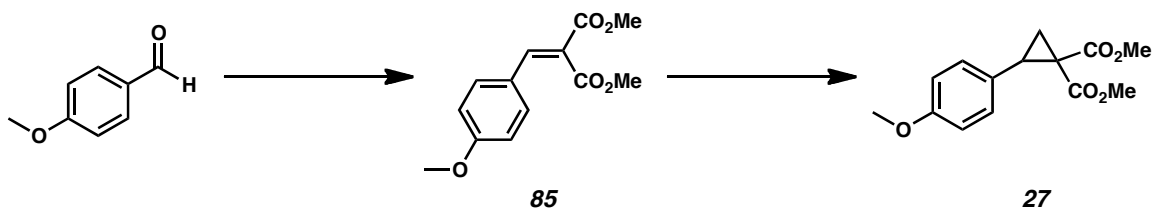
1.11.2.2 CYCLOPROPANE CHARACTERIZATION DATA



dimethyl 2-(*p*-tolyl)cyclopropane-1,1-dicarboxylate

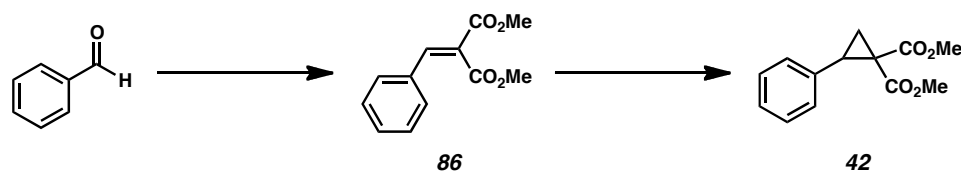
Benzylidene dimethylmalonate **84** was prepared according to General Method A: 30% yield. $R_f = 0.19$ (3:1 Hexanes:EtOAc eluent). Characterization data matches those reported in the literature.²⁶

Cyclopropane **26** was prepared according to General Method B: 77% yield. $R_f = 0.60$ (3:1 Hexanes:EtOAc). Characterization data matches those reported in the literature.²⁷

**dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate**

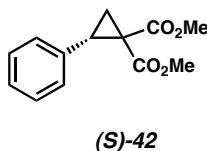
Benzylidene dimethylmalonate **85** was prepared according to General Method A: 92% yield. $R_f = 0.27$ (3:1 Hexanes:EtOAc eluent). Characterization data matches those reported in the literature.²⁸

Cyclopropane **27** was prepared according to General Method B: 95% yield. $R_f = 0.40$ (3:1 Hexanes:EtOAc eluent). Characterization data matches those reported in the literature.²⁹

**dimethyl 2-phenylcyclopropane-1,1-dicarboxylate**

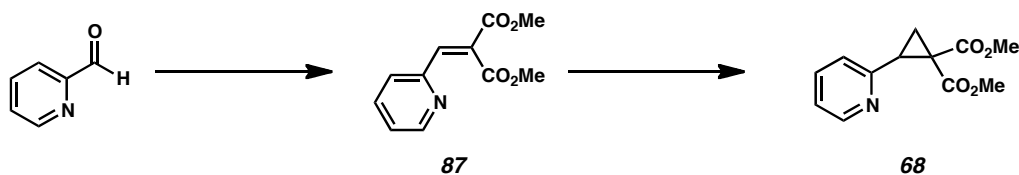
Benzylidene dimethylmalonate **86** was prepared according to General Method A: 99% yield. $R_f = 0.60$ (3:1 Hexanes:EtOAc eluent). Characterization data matches those reported in the literature.³⁰

Cyclopropane **42** was prepared according to General Method B: 66% yield. $R_f = 0.60$ (3:1 Hexanes:EtOAc eluent). Characterization data matches those reported in the literature.³¹



(S)-dimethyl 2-phenylcyclopropane-1,1-dicarboxylate

Cyclopropane (*S*)-**42** was prepared according to the method of Davies and coworkers.³² $[\alpha]_D^{25.0} -133.17^\circ$ (c 0.99, CHCl_3 , > 98% ee).

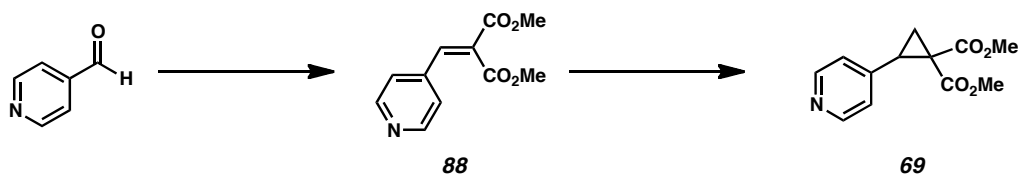


dimethyl 2-(pyridin-2-yl)cyclopropane-1,1-dicarboxylate

Benzylidene dimethylmalonate **87** was prepared according to General Method A: 97% yield. $R_f = 0.81$ (3:1 Hexanes:EtOAc eluent). Characterization data matches those reported in the literature.³³

Cyclopropane **68** was prepared according to General Method B, using saturated aqueous ammonium chloride in the workup instead of 2 M HCl: 95% yield. $R_f = 0.30$ (3:1 Hexanes:EtOAc eluent); ^1H NMR (500 MHz, CDCl_3) δ 8.45–8.34 (ddd, $J = 4.8, 1.9, 1.0$ Hz, 1H), 7.62–7.53 (tdd, $J = 7.3, 4.9, 1.1$ Hz, 1H), 7.29–7.26 (dt, $J = 7.9, 1.1$ Hz, 1H),

7.12–7.05 (ddt, $J = 7.3, 4.9, 1.1$ Hz, 1H), 3.82–3.68 (m, 3H), 3.53–3.43 (m, 3H), 3.12–3.06 (ddd, $J = 8.8, 7.4, 1.1$ Hz, 1H), 2.36–2.31 (ddd, $J = 7.4, 4.5, 1.1$ Hz, 1H), 1.84–1.78 (ddd, $J = 9.0, 4.5, 1.1$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 170.3, 167.3, 155.4, 149.0, 136.3, 124.0, 122.0, 53.0, 52.4, 38.0, 33.0, 20.5; IR (Neat Film, NaCl) 3011, 2952, 1734, 1593, 1570, 1477, 1437, 1379, 1334, 1301, 1275, 1210, 1132, 1085, 998, 970, 924, 878, 807, 759, 749 cm^{-1} ; HRMS (MM: ESI-APCI) m/z calc'd for $\text{C}_{12}\text{H}_{14}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 236.0917, found 236.0911.

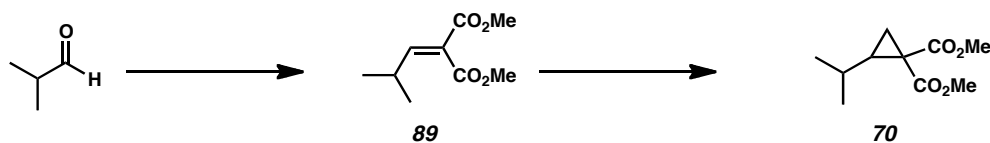


dimethyl 2-(pyridin-2-yl)cyclopropane-1,1-dicarboxylate

Benzylidene dimethylmalonate **88** was prepared according to General Method A: 76% yield. $R_f = 0.58$ (1:1 Hexanes:EtOAc eluent); ^1H NMR (400 MHz, CDCl_3) δ 8.72–8.60 (m, 2H), 7.68 (s, 1H), 7.29–7.21 (m, 2H), 3.87 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 166.0, 163.8, 150.7, 140.4, 140.0, 129.9, 122.8, 53.2, 53.1; IR (Neat Film, NaCl) 2954, 1732, 1638, 1596, 1437, 1374, 1269, 1225, 1067, 813 cm^{-1} ; HRMS (MM: ESI-APCI) m/z calc'd for $\text{C}_{11}\text{H}_{12}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 222.0761, found 222.0750.

Cyclopropane **69** was prepared according to General Method B: 81% yield. $R_f = 0.13$ (3:1 Hexanes:EtOAc eluent); ^1H NMR (500 MHz, CDCl_3) δ 8.42 (d, $J = 5.6$ Hz, 2H), 7.02 (dd, $J = 4.4, 1.7$ Hz, 2H), 3.73 (s, 3H), 3.35 (s, 3H), 3.07 (dd, $J = 9.1, 7.9$, 1H), 2.11 (dd, $J = 8.0, 5.4$ Hz, 1H), 1.71 (dd, $J = 9.1, 5.4$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 169.5, 166.4, 149.6, 144.1, 123.3, 53.0, 52.5, 37.7, 30.9, 18.7; IR (Neat Film, NaCl)

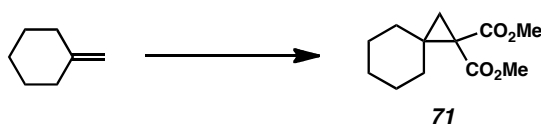
3029, 2954, 1732, 1601, 1437, 1335, 1282, 1212, 1133, 991, 836 cm^{-1} ; HRMS (MM: ESI-APCI) m/z calc'd for $\text{C}_{12}\text{H}_{14}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 236.0917, found 236.0908.



dimethyl 2-isopropylcyclopropane-1,1-dicarboxylate

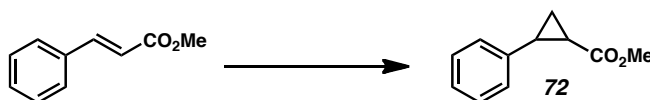
Isopropylidene dimethylmalonate **89** was prepared according to General Method A. 94% yield. $R_f = 0.30$ (9:1 Hexanes:EtOAc eluent). Characterization data matches those reported in the literature.³⁴

Cyclopropane **70** was prepared according to General Method B. 75% yield. $R_f = 0.40$ (9:1 Hexanes:EtOAc eluent). Characterization data matches those reported in the literature.³⁵



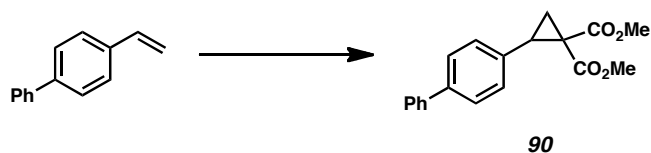
dimethyl spiro[2.5]octane-1,1-dicarboxylate

Cyclopropane **71** was prepared according to General Method C. 40% yield. $R_f = 0.20$ (9:1 Hexanes:EtOAc eluent). Characterization data matches those reported in the literature.³⁶



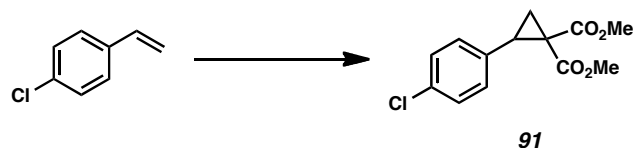
methyl 2-phenylcyclopropanecarboxylate

Cyclopropane **72** was prepared according to General Method B: 24% yield. $R_f = 0.6$ (3:1 Hexanes:EtOAc eluent). Characterization data matches those reported in the literature.³⁷



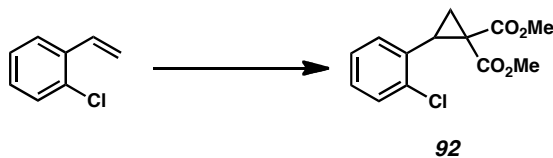
dimethyl 2-([1,1'-biphenyl]-4-yl)cyclopropane-1,1-dicarboxylate

Cyclopropane **90** was prepared according to General Method C: 99% yield. $R_f = 0.48$ (3:1 Hexanes:EtOAc eluent). Characterization data matches those reported in the literature.³⁸



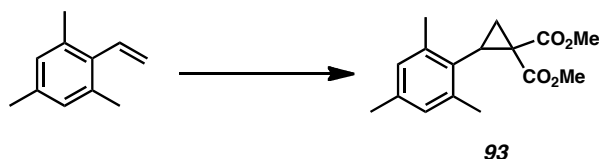
dimethyl 2-(4-chlorophenyl)cyclopropane-1,1-dicarboxylate

Cyclopropane **91** was prepared according to General Method C: 99% yield. $R_f = 0.53$ (3:1 Hexanes:EtOAc eluent). Characterization data matches those reported in the literature.²⁸



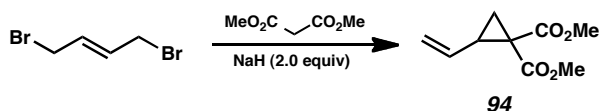
dimethyl 2-(2-chlorophenyl)cyclopropane-1,1-dicarboxylate

Cyclopropane **92** was prepared according to General Method C: 60% yield. $R_f = 0.50$ (3:1 Hexanes:EtOAc eluent); ^1H NMR (500 MHz, CDCl_3) δ 7.39–7.33 (m, 1H), 7.22–7.15 (m, 2H), 7.11–7.07 (m, 1H), 3.81 (s, 3H), 3.36 (s, 4H), 2.26 (dd, $J = 8.3, 5.2$ Hz, 1H), 1.79 (dd, $J = 9.1, 5.2$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 170.0, 167.1, 136.6, 132.8, 129.3, 129.0, 128.9, 126.5, 53.0, 52.4, 36.5, 31.3, 19.0; IR (Neat Film, NaCl) 3001, 2953, 1732, 1483, 1435, 1377, 1331, 1288, 1219, 1131, 1055, 894, 785, 754 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{13}\text{H}_{14}^{35}\text{ClO}_4$ $[\text{M}+\text{H}]^+$: 269.0575, found 269.0573.



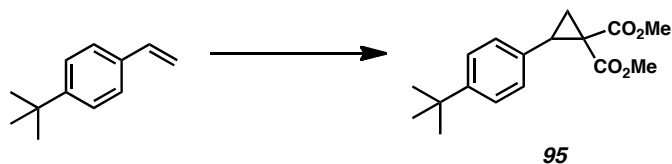
dimethyl 2-mesitylcyclopropane-1,1-dicarboxylate

Cyclopropane **93** was prepared according to General Method C: 71% yield. $R_f = 0.40$ (3:1 Hexanes:EtOAc eluent); ^1H NMR (500 MHz, CDCl_3) δ 6.81 (s, 2H), 3.83 (s, 3H), 3.34 (s, 3H), 3.10–3.02 (app t, $J = 9.3$ Hz, 1H), 2.42–2.36 (dd, $J = 8.9, 4.9$ Hz, 1H), 2.32 (s, 6H), 2.22 (s, 3H), 1.97–1.89 (dd, $J = 9.6, 4.9$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 170.8, 168.0, 136.6, 129.2, 128.5, 52.9, 52.2, 35.3, 32.0, 24.0, 21.0; IR (Neat Film, NaCl) 2953, 2921, 1728, 1612, 1437, 1372, 1328, 1287, 1224, 1196, 1128, 1096, 1032, 1015, 992, 894, 852, 782, 718 cm^{-1} ; HRMS (Low Voltage MM: ESI-APCI) m/z calc'd for $\text{C}_{16}\text{H}_{21}\text{O}_4$ $[\text{M}+\text{H}]^+$: 277.1434, found 277.1420.

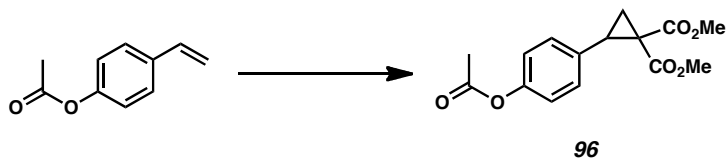


dimethyl 2-vinylcyclopropane-1,1-dicarboxylate

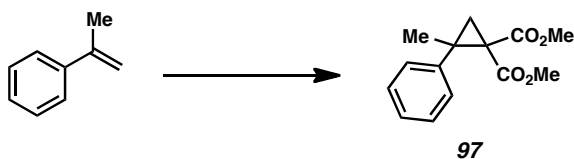
Cyclopropane **94** was prepared according to the method of Johnson and coworkers.³⁹

**dimethyl 2-(4-(tert-butyl)phenyl)cyclopropane-1,1-dicarboxylate**

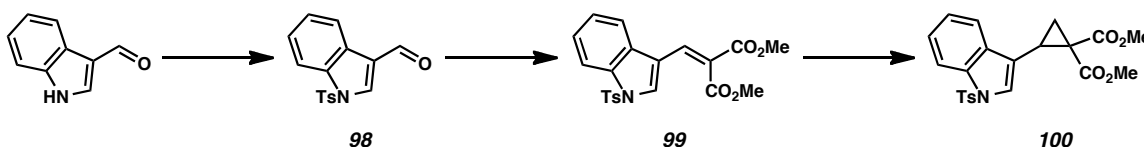
Cyclopropane **95** was prepared according to General Method C: 89% yield. $R_f = 0.50$ (3:1 Hexanes:EtOAc eluent). Characterization data matches those reported in the literature.⁴⁰

**dimethyl 2-(4-acetoxyphenyl)cyclopropane-1,1-dicarboxylate**

Cyclopropane **96** was prepared according to General Method C: 67% yield. $R_f = 0.30$ (3:1 Hexanes:EtOAc eluent). Characterization data matches those reported in the literature.^{3c}

**dimethyl 2-methyl-2-phenylcyclopropane-1,1-dicarboxylate**

Cyclopropane **97** was prepared according to General Method C: 41% yield. $R_f = 0.53$ (3:1 Hexanes:EtOAc eluent). Characterization data matches those reported in the literature.⁴¹



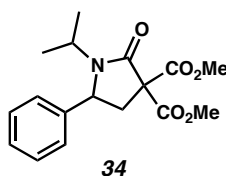
dimethyl 2-(1-tosyl-1*H*-indol-3-yl)cyclopropane-1,1-dicarboxylate

N-Tosylindole-3-carboxaldehyde (**98**) was prepared according to literature methods from indole-3-carboxaldehyde.⁴²

Benzylidene dimethylmalonate **99** was prepared according to General Method A: 75% yield. $R_f = 0.20$ (3:1 Hexanes:EtOAc eluent). Characterization data matches those reported in the literature.⁴³

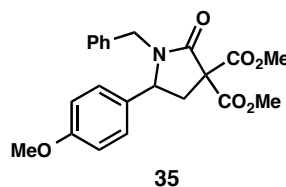
Cyclopropane **100** was prepared according to General Method B: 95% yield. $R_f = 0.30$ (3:1 Hexanes:EtOAc eluent).⁴³

1.11.2.3 CHARACTERIZATION DATA FOR LACTAMS



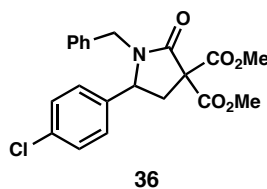
dimethyl 1-isopropyl-2-oxo-5-phenylpyrrolidine-3,3-dicarboxylate (34): Prepared according to General Method D. 72% yield. $R_f = 0.46$ (1:1 Hexanes:EtOAc eluent); ^1H NMR (500 MHz, CDCl_3) δ 7.39–7.26 (m, 5H), 4.64 (t, $J = 7.3$ Hz, 1H), 3.83 (s, 3H), 3.81

(s, 3H), 3.80–3.71 (m, 1H), 3.02 (dd, $J = 13.8, 7.7$ Hz, 1H), 2.59 (dd, $J = 13.8, 6.9$ Hz, 1H), 1.25 (d, $J = 6.9$ Hz, 3H), 1.01 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.3, 168.1, 167.2, 141.0, 129.0, 128.6, 127.2, 63.4, 59.7, 53.7, 53.5, 47.1, 38.4, 19.8, 19.7; IR (Neat Film, NaCl) 2954, 1735, 1703, 1495, 1457, 1434, 1367, 1342, 1259, 1218, 1130, 1090, 1065, 998, 966, 919, 894, 774 cm^{-1} ; HRMS (MM: ESI-APCI) m/z calc'd for $\text{C}_{17}\text{H}_{22}\text{NO}_5$ $[\text{M}+\text{H}]^+$: 320.1492, found 320.1490.



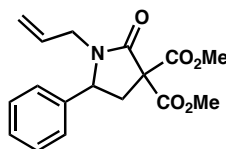
dimethyl 1-butyl-2-oxo-5-(4-methoxyphenyl)pyrrolidine-3,3-dicarboxylate (35):

Prepared according to General Method D. 62% yield. $R_f = 0.39$ (1:1 Hexanes:EtOAc eluent); ^1H NMR (500 MHz, CDCl_3) δ 7.30–7.23 (m, 3H), 7.08–7.02 (m, 4H), 6.94–6.87 (m, 2H), 5.11 (d, $J = 14.5$ Hz, 1H), 4.31 (t, $J = 7.6$ Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 3.46 (d, $J = 14.6$ Hz, 1H), 2.94 (dd, $J = 13.8, 7.2$ Hz, 1H), 2.65 (dd, $J = 13.8, 8.1$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.1, 167.9, 167.1, 160.0, 135.5, 130.4, 128.8, 128.7, 128.6, 127.9, 114.6, 63.4, 58.3, 55.5, 53.7, 53.6, 45.2, 38.1; IR (Neat Film, NaCl) 2953, 1735, 1705, 1513, 1434, 1281, 1247 cm^{-1} ; HRMS (MM: ESI-APCI) m/z calc'd for $\text{C}_{22}\text{H}_{24}\text{NO}_6$ $[\text{M}+\text{H}]^+$: 398.1598, found 398.1581.

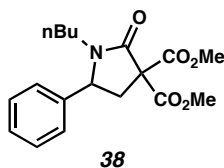


dimethyl 1-butyl-2-oxo-5-(4-chlorophenyl)pyrrolidine-3,3-dicarboxylate (36):

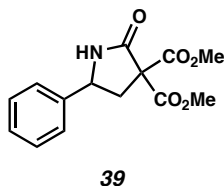
Prepared according to General Method D. 78% yield. $R_f = 0.41$ (1:1 Hexanes:EtOAc eluent); ^1H NMR (500 MHz, CDCl_3) δ 7.39–7.33 (m, 2H), 7.29–7.24 (m, 3H), 7.10–7.05 (m, 2H), 7.04–7.00 (m, 2H), 5.13 (d, $J = 14.6$ Hz, 1H), 4.33 (t, $J = 7.6$ Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.46 (d, $J = 14.6$ Hz, 1H), 2.97 (dd, $J = 13.9, 7.4$ Hz, 1H), 2.60 (dd, $J = 13.9, 7.8$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.9, 167.7, 167.2, 137.3, 135.1, 134.7, 129.5, 128.8, 128.7, 128.6, 128.0, 63.2, 58.1, 53.8, 53.7, 45.3, 37.9; IR (Neat Film, NaCl) 2953, 1736, 1708, 1435, 1242, 1204, 1090 cm^{-1} ; HRMS (MM: ESI-APCI) m/z calc'd for $\text{C}_{21}\text{H}_{21}^{35}\text{ClNO}_5$ $[\text{M}+\text{H}]^+$: 402.1103, found 402.1084.

**37****dimethyl 1-allyl-2-oxo-5-phenylpyrrolidine-3,3-dicarboxylate (37):**

Prepared according to General Method E. 42% yield. $R_f = 0.52$ (1:1 Hexanes:EtOAc eluent); ^1H NMR (500 MHz, CDCl_3) δ 7.42–7.29 (m, 3H), 7.24–7.18 (m, 2H), 5.71–5.52 (m, 1H), 5.12 (ddt, $J = 10.1, 1.3, 0.7$ Hz, 1H), 4.99–4.91 (m, 1H), 4.64 (t, $J = 7.5$ Hz, 1H), 4.40 (m, 1H), 3.90–3.84 (m, 3H), 3.82 (d, $J = 0.9$ Hz, 3H), 3.15–3.02 (m, 2H), 2.62 (dd, $J = 13.8, 7.4$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.0, 167.9, 166.8, 138.9, 131.0, 129.2, 128.8, 127.3, 118.9, 63.1, 59.1, 53.8, 53.6, 44.1, 38.0; IR (Neat Film, NaCl) 2953, 1735, 1707, 1433, 1245, 1214, 1070 cm^{-1} ; HRMS (FAB+) m/z calc'd for $\text{C}_{17}\text{H}_{20}\text{NO}_5$ $[\text{M}+\text{H}]^+$: 318.1341, found 318.1356.



dimethyl 1-butyl-2-oxo-5-phenylpyrrolidine-3,3-dicarboxylate (38): Prepared according to General Method E. 58% yield. $R_f = 0.10$ (4:1 Hexanes:EtOAc eluent); ^1H NMR (500 MHz, CDCl_3) δ 7.40–7.31 (m, 3H), 7.25–7.20 (m, 2H), 4.63 (t, $J = 7.5$ Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.70 (dt, $J = 13.7, 7.9$ Hz, 1H), 3.06 (dd, $J = 13.7, 7.3$ Hz, 1H), 2.57–2.53 (m, 2H), 1.43–1.30 (m, 2H), 1.29–1.10 (m, 2H), 0.82 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.1, 168.0, 166.9, 139.1, 129.2, 128.7, 127.1, 63.2, 59.5, 53.7, 53.6, 41.1, 38.3, 28.6, 19.8, 13.7; IR (Neat Film, NaCl) 2957, 2873, 1732, 1708, 1495, 1456, 1435, 1370, 1278, 1242, 1202, 1108, 1090, 1070, 893, 771 cm^{-1} ; HRMS (FAB+) m/z calc'd for $\text{C}_{18}\text{H}_{24}\text{NO}_5$ $[\text{M}+\text{H}]^+$: 334.1654, found 334.1646.

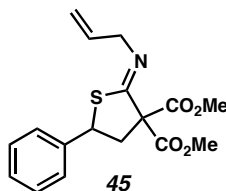


dimethyl 2-oxo-5-phenylpyrrolidine-3,3-dicarboxylate (39): Prepared according to General Method E. 49% yield. $R_f = 0.48$ (1:1 Hexanes:EtOAc eluent); ^1H NMR (500 MHz, CDCl_3) δ 7.40–7.33 (m, 2H), 7.33–7.28 (m, 3H), 6.93–6.69 (bs, 1H), 4.75 (t, $J = 7.4$ Hz, 1H), 3.85 (d, $J = 1.6$ Hz, 3H), 3.77 (dd, $J = 2.1, 0.9$ Hz, 3H), 3.18 (ddt, $J = 13.6, 7.2, 0.8$ Hz, 1H), 2.63 (ddd, $J = 13.5, 7.8, 1.8$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 169.5, 167.5, 167.4, 140.3, 129.0, 128.4, 126.0, 63.2, 55.4, 53.7, 53.6, 40.4; IR (Neat

Film, NaCl) 3251, 2955, 1729, 1435, 1250, 1208, 1060 cm^{-1} ; HRMS (FAB+) m/z calc'd for $\text{C}_{14}\text{H}_{16}\text{NO}_5$ $[\text{M}+\text{H}]^+$: 278.1028, found 278.1042.

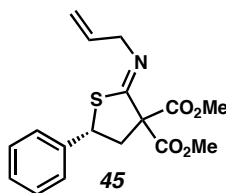
1.11.2.4 THIOIMIDATE CHARACTERIZATION DATA

Unless stated otherwise, all thioimides were prepared according to General Method F



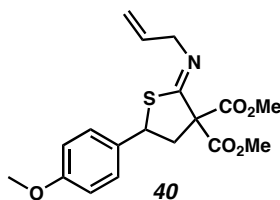
(Z)-dimethyl 2-(allylimino)-5-phenyldihydrothiophene-3,3(2H)-dicarboxylate

(45): 92% yield. R_f = 0.45 (7:3 Hexanes:EtOAc eluent); ^1H NMR (500 MHz, CDCl_3) δ 7.46–7.40 (m, 2H), 7.39–7.34 (m, 2H), 7.33–7.29 (m, 1H), 5.99 (ddt, J = 17.1, 10.4, 5.2 Hz, 1H), 5.26 (dq, J = 17.2, 1.8 Hz, 1H), 5.13 (dq, J = 10.4, 1.7 Hz, 1H), 4.73 (dd, J = 11.7, 4.9 Hz, 1H), 4.00 (dtd, J = 5.5, 1.8, 0.7 Hz, 2H), 3.88 (s, 3H), 3.81 (s, 3H), 3.12 (dd, J = 13.0, 4.9 Hz, 1H), 2.90 (dd, J = 13.0, 11.7 Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.4, 168.1, 166.0, 138.2, 134.0, 129.0, 128.5, 127.8, 116.0, 71.0, 59.8, 53.8, 53.6, 50.9, 44.3; IR (Neat Film, NaCl) 3010, 2952, 1738, 1652, 1495, 1435, 1269, 1227, 1169, 1098, 1064, 977, 921, 862, 842, 799, 765 cm^{-1} ; HRMS (MM: ESI-APCI) m/z calc'd for $\text{C}_{17}\text{H}_{20}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 334.1108, found 334.1113.

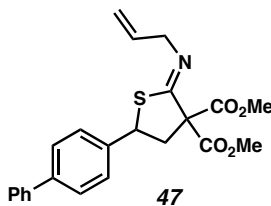


(*R,Z*)-dimethyl 2-(allylimino)-5-phenyldihydrothiophene-3,3(2*H*)-dicarboxylate

((*R*)-45): Characterization data is same as above; $[\alpha]_D^{25.0}$ 8.8° (*c* 0.445, CHCl₃, 95% ee).

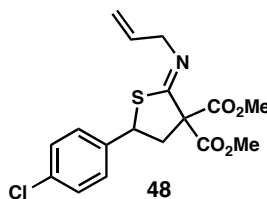
**dimethyl 1-allyl-5-(4-methoxyphenyl)-2-thioxopyrrolidine-3,3-dicarboxylate (40):**

98% yield. R_f = 0.49 (7:3 Hexanes:EtOAc eluent); ¹H NMR (500 MHz, CDCl₃) δ 7.38–7.32 (m, 2H), 6.90–6.85 (m, 2H), 6.03–5.92 (m, 1H), 5.24 (dq, *J* = 17.2, 1.8 Hz, 1H), 5.12 (dq, *J* = 10.4, 1.7 Hz, 1H), 4.71 (dd, *J* = 11.8, 4.8 Hz, 1H), 3.99 (dt, *J* = 5.2, 1.8 Hz, 2H), 3.87 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.07 (dd, *J* = 13.0, 4.9 Hz, 1H), 2.87 (dd, *J* = 13.0, 11.8 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 168.4, 168.1, 166.5, 159.7, 134.0, 130.0, 129.0, 116.0, 114.3, 71.1, 59.7, 55.5, 53.8, 53.6, 50.6, 44.5; IR (Neat Film, NaCl) 3003, 2953, 2837, 1736, 1638, 1610, 1513, 1435, 1305, 1250, 1175, 1098, 1070, 1032, 922, 831, 792 cm⁻¹; HRMS (Low Voltage MM: ESI-APCI) *m/z* calc'd for C₁₈H₂₂NO₅S [M+H]⁺: 364.1213, found 364.1193.

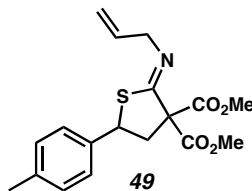
**(*Z*)-dimethyl 5-([1,1'-biphenyl]-4-yl)-2-(allylimino)dihydrothiophene-3,3(2*H*)-**

dicarboxylate (47): 80% yield. R_f = 0.53 (7:3 Hexanes:EtOAc eluent); ¹H NMR (500

MHz, CDCl₃) δ 7.62–7.56 (m, 4H), 7.53–7.49 (m, 2H), 7.48–7.42 (m, 2H), 7.39–7.33 (m, 1H), 6.00 (ddt, $J = 17.2, 10.4, 5.2$ Hz, 1H), 5.27 (dq, $J = 17.1, 1.8$ Hz, 1H), 5.14 (dq, $J = 10.3, 1.7$ Hz, 1H), 4.79 (dd, $J = 11.7, 4.9$ Hz, 1H), 4.02 (dt, $J = 5.2, 1.8$ Hz, 2H), 3.89 (s, 3H), 3.83 (s, 3H), 3.16 (dd, $J = 13.0, 4.9$ Hz, 1H), 2.94 (dd, $J = 13.0, 11.7$ Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 168.3, 168.0, 166.2, 141.4, 140.4, 137.0, 133.8, 128.9, 128.2, 127.6, 127.1, 116.0, 71.0, 59.6, 53.7, 53.5, 50.6, 44.2; IR (Neat Film, NaCl) 3029, 2952, 1736, 1651, 1639, 1487, 1435, 1412, 1279, 1263, 1226, 1168, 1099, 1070, 1008, 977, 920, 836, 799, 767, 738 cm⁻¹; HRMS (Low Voltage MM: ESI-APCI) m/z calc'd for C₂₃H₂₄NO₄S [M+H]⁺: 410.1421, found 410.1408.

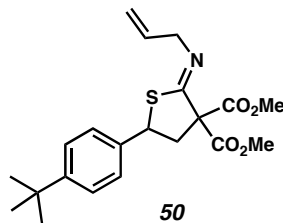


(Z)-dimethyl 2-(allylimino)-5-(4-chlorophenyl)dihydrothiophene-3,3(2H)-dicarboxylate (48): 66% yield. $R_f = 0.49$ (7:3 Hexanes:EtOAc eluent); ¹H NMR (400 MHz, CDCl₃) δ 7.42–7.19 (m, 4H), 5.97 (ddt, $J = 17.1, 10.4, 5.1$ Hz, 1H), 5.23 (dq, $J = 17.2, 1.9$ Hz, 1H), 5.12 (dq, $J = 10.4, 1.7$ Hz, 1H), 4.69 (dd, $J = 11.6, 4.9$ Hz, 1H), 3.98 (dt, $J = 5.1, 1.8$ Hz, 2H), 3.86 (s, 3H), 3.79 (s, 3H), 3.09 (dd, $J = 13.0, 5.0$ Hz, 1H), 2.82 (dd, $J = 13.0, 11.6$ Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 168.1, 167.8, 165.3, 136.7, 134.2, 133.8, 129.0, 129.0, 115.9, 70.8, 59.7, 53.7, 53.4, 50.0, 44.1; IR (Neat Film, NaCl) 2953, 1733, 1652, 1637, 1491, 1434, 1266, 1221, 1167, 1090, 1068, 1011 cm⁻¹; HRMS (MM: ESI-APCI) m/z calc'd for C₁₇H₁₉³⁵ClNO₄S [M+H]⁺: 368.0718, found 368.0729.



(Z)-dimethyl 2-(allylimino)-5-(p-tolyl)dihydrothiophene-3,3(2H)-dicarboxylate

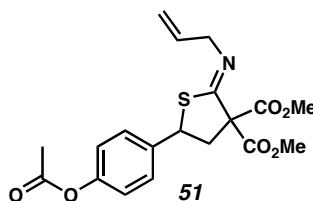
(49): 99% yield. R_f = 0.47 (7:3 Hexanes:EtOAc eluent); ^1H NMR (500 MHz, CDCl_3) δ 7.33–7.29 (m, 2H), 7.19–7.15 (m, 2H), 5.98 (ddt, J = 17.2, 10.4, 5.2 Hz, 1H), 5.25 (dq, J = 17.2, 1.8 Hz, 1H), 5.14 (dq, J = 10.4, 1.7 Hz, 1H), 4.72 (dd, J = 11.8, 4.8 Hz, 1H), 4.01 (dt, J = 5.2, 1.8 Hz, 2H), 3.88 (s, 3H), 3.82 (s, 3H), 3.10 (dd, J = 13.1, 4.9 Hz, 1H), 2.88 (dd, J = 13.0, 11.8 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.2, 168.0, 138.5, 134.9, 133.7, 129.7, 127.7, 116.3, 71.1, 59.5, 53.9, 53.7, 51.1, 44.5, 21.3; IR (Neat Film, NaCl) 3011, 2952, 1737, 1652, 1639, 1515, 1435, 1278, 1269, 1257, 1228, 1169, 1071, 1018, 978, 921, 864, 848, 818, 790 cm^{-1} ; HRMS (Low Voltage MM: ESI-APCI) m/z calc'd for $\text{C}_{18}\text{H}_{22}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 348.1264, found 348.1254.



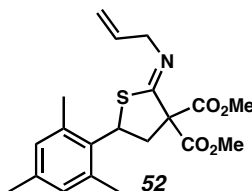
(Z)-dimethyl 2-(allylimino)-5-(4-(tert-butyl)phenyl)dihydrothiophene-3,3(2H)-

dicarboxylate (50): 41% yield. R_f = 0.30 (3:1 Hexanes:EtOAc eluent); ^1H NMR (500 MHz, CDCl_3) δ 7.41–7.32 (m, 4H), 5.98 (ddt, J = 17.1, 10.4, 5.2 Hz, 1H), 5.25 (dq, J = 17.2, 1.8 Hz, 1H), 5.13 (dq, J = 10.4, 1.7 Hz, 1H), 4.71 (dd, J = 11.8, 4.9 Hz, 1H), 3.99 (dt, J = 5.1, 1.7 Hz, 2H), 3.88 (s, 3H), 3.81 (s, 3H), 3.07 (dd, J = 13.0, 4.9 Hz, 1H), 2.90

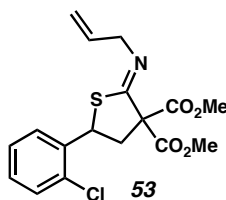
(dd, $J = 13.0, 11.8$ Hz, 1H) 1.31 (s, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.5, 168.2, 166.3, 151.6, 135.1, 134.1, 127.5, 125.9, 116.0, 71.1, 59.8, 53.8, 53.6, 50.7, 44.3, 34.8, 31.4; IR (Neat Film, NaCl) 2955, 2904, 2868, 1737, 1652, 1639, 1509, 1435, 1363, 1280, 1267, 1227, 1168, 1111, 1070, 1016, 978, 920, 828 cm^{-1} ; HRMS (Low Voltage MM: ESI-APCI) m/z calc'd for $\text{C}_{21}\text{H}_{28}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 390.1734, found 390.1726.



(Z)-dimethyl 5-(4-acetoxyphenyl)-2-(allylimino)dihydrothiophene-3,3(2H)-dicarboxylate (51): 84% yield. $R_f = 0.20$ (3:1 Hexanes:EtOAc eluent); ^1H NMR (500 MHz, CDCl_3) δ 7.49–7.41 (m, 2H), 7.12–7.05 (m, 2H), 5.97 (ddt, $J = 17.2, 10.3, 5.2$ Hz, 1H), 5.25 (dq, $J = 17.2, 1.8$ Hz, 1H), 5.13 (dq, $J = 10.4, 1.7$ Hz, 1H), 4.72 (dd, $J = 11.6, 4.9$ Hz, 1H), 3.99 (ddd, $J = 7.0, 1.7, 1.0$ Hz, 2H), 3.87 (s, 3H), 3.80 (s, 3H), 3.11 (dd, $J = 13.1, 4.9$ Hz, 1H), 2.85 (dd, $J = 13.1, 11.6$ Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 169.5, 168.4, 168.0, 165.8, 150.6, 135.8, 134.0, 129.0, 122.2, 116.0, 71.0, 59.8, 53.8, 53.6, 50.3, 44.5, 21.3; IR (Neat Film, NaCl) 2953, 1736, 1649, 1639, 1507, 1436, 1370, 1280, 1257, 1194, 1167, 1099, 1016, 911, 851 cm^{-1} ; HRMS (Low Voltage MM: ESI-APCI) m/z calc'd for $\text{C}_{19}\text{H}_{22}\text{NO}_6\text{S}$ $[\text{M}+\text{H}]^+$: 392.1162, found 392.1159.

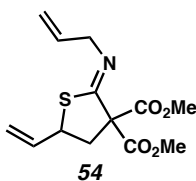


(Z)-dimethyl 2-(allylimino)-5-mesityldihydrothiophene-3,3(2H)-dicarboxylate (52): 85% yield. White, translucent crystals were obtained by slow diffusion of 1% benzene in heptane into a solution of thioimide **52** in ethyl acetate, M.P.: 89–91 °C; R_f = 0.52 (7:3 Hexanes:EtOAc eluent); ^1H NMR (500 MHz, CDCl_3) δ 6.87–6.84 (m, 2H), 5.99 (ddt, J = 17.2, 10.4, 5.2 Hz, 1H), 5.32 (dd, J = 12.5, 5.3 Hz, 1H), 5.24 (dq, J = 17.2, 1.8 Hz, 1H), 5.13 (dq, J = 10.4, 1.7 Hz, 1H), 4.02 (dtd, J = 5.2, 1.8, 0.8 Hz, 2H), 3.90 (s, 3H), 3.84 (s, 3H), 3.24 (dd, J = 13.3, 12.5 Hz, 1H), 2.93 (dd, J = 13.3, 5.3 Hz, 1H), 2.46 (s, 6H), 2.25 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.5, 168.3, 166.8, 137.9, 134.0, 130.9, 129.2, 116.0, 71.1, 59.8, 53.8, 53.6, 46.2, 40.0, 21.3, 20.9; IR (Neat Film, NaCl) 3010, 2952, 2918, 1737, 1649, 1638, 1611, 1435, 1267, 1230, 1203, 1167, 1097, 1073, 1015, 976, 921, 954, 822, 799, 774, 739 cm^{-1} ; HRMS (Low Voltage MM: ESI-APCI) m/z calc'd for $\text{C}_{20}\text{H}_{26}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 376.1577, found 376.1563.



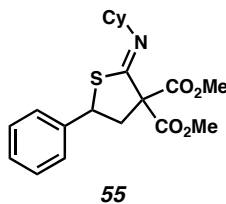
(Z)-dimethyl 2-(allylimino)-5-(2-chlorophenyl)dihydrothiophene-3,3(2H)-dicarboxylate (53): 84% yield. R_f = 0.48 (7:3 Hexanes:EtOAc eluent); ^1H NMR (500 MHz, CDCl_3) δ 7.65 (dd, J = 7.8, 1.7 Hz, 1H), 7.38 (dd, J = 7.9, 1.4 Hz, 1H), 7.31 (td, J = 7.6, 1.4 Hz, 1H), 7.23 (td, J = 7.6, 1.7, 1H), 5.98 (ddt, J = 17.2, 10.4, 5.2 Hz, 1H), 5.30–5.22 (m, 2H), 5.14 (dq, J = 10.4, 1.7 Hz, 1H), 4.03 (td, J = 4.4, 2.0 Hz, 2H), 3.88 (s, 3H), 3.77 (s, 3H), 3.19 (dd, J = 13.0, 5.1 Hz, 1H), 2.84 (dd, J = 13.0, 11.0 Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.1, 168.0, 165.7, 135.8, 134.0, 133.9, 130.0, 129.5, 128.5,

127.5, 116.1, 70.6, 59.7, 53.8, 53.6, 47.0, 42.6; IR (Neat Film, NaCl) 3011, 2953, 1737, 1651, 1639, 1435, 1279, 1256, 1228, 1171, 1130, 1100, 1069, 1051, 1038, 977, 921, 760 cm^{-1} ; HRMS (Low Voltage MM: ESI-APCI) m/z calc'd for $\text{C}_{17}\text{H}_{19}^{35}\text{ClNO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 368.0718, found 368.0700.

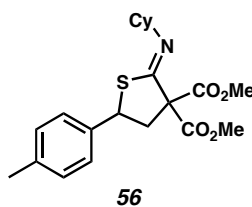


(Z)-dimethyl 2-(allylimino)-5-vinyldihydrothiophene-3,3(2H)-dicarboxylate (54):

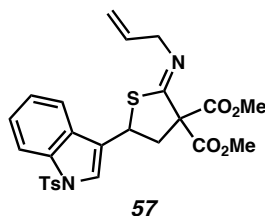
99% yield. $R_f = 0.45$ (7:3 Hexanes:EtOAc eluent); ^1H NMR (500 MHz, CDCl_3) δ 5.95 (ddt, $J = 17.2, 10.4, 5.2$ Hz, 1H), 5.80 (ddd, $J = 16.9, 10.0, 8.4$ Hz, 1H), 5.33 (dq, $J = 16.9, 0.8$ Hz, 1H), 5.23 (ddd, $J = 17.3, 1.8, 0.6$ Hz, 1H), 5.19 (d, $J = 10.1$, 1H), 5.13 (ddd, $J = 10.4, 1.7, 0.7$ Hz, 1H), 4.22 (m, 1H), 3.98 (dd, $J = 5.2, 2.0$ Hz, 2H), 3.84 (s, 3H), 3.81 (d, $J = 0.6$ Hz, 3H), 2.97 (ddd, $J = 13.1, 5.1, 0.8$ Hz, 1H), 2.61 (dd, $J = 13.1, 10.6$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.1, 168.0, 135.7, 133.6, 118.9, 116.3, 70.5, 59.4, 53.8, 53.7, 50.3, 42.2; IR (Neat Film, NaCl) 2952, 1735, 1649, 1638, 1434, 1328, 1272, 1254, 1169, 1139, 1097, 1068, 987, 923, 859, 787, 728 cm^{-1} ; HRMS (Low Voltage MM: ESI-APCI) m/z calc'd for $\text{C}_{13}\text{H}_{18}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 284.0951, found 284.0962.



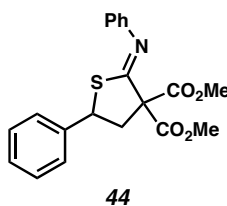
(Z)-dimethyl 2-(cyclohexylimino)-5-phenyldihydrothiophene-3,3(2H)-dicarboxylate (55): 91% yield. R_f = 0.40 (3:1 Hexanes:EtOAc eluent); ^1H NMR (500 MHz, CDCl_3) δ 7.46–7.42 (m, 2H), 7.36 (ddd, J = 8.2, 7.1, 0.9 Hz, 2H), 7.30 (m, 1H), 4.69 (dd, J = 11.7, 4.9 Hz, 1H), 3.87 (s, 3H), 3.78 (s, 3H), 3.08 (dd, J = 13.0, 4.9 Hz, 1H), 2.98 (tt, J = 10.1, 3.6 Hz, 1H), 2.85 (dd, J = 13.0, 11.7 Hz, 1H), 1.85–1.72 (m, 4H), 1.65–1.57 (m, 1H), 1.57–1.44 (m, 2H), 1.37–1.20 (m, 4H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.6, 168.3, 161.5, 138.6, 128.9, 128.4, 127.8, 70.8, 67.1, 53.7, 53.4, 50.6, 44.0, 32.8, 31.7, 25.8, 24.7, 24.6; IR (Neat Film, NaCl) 2930, 2854, 1738, 1651, 1435, 1168, 1067, 973, 912, 764 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{20}\text{H}_{26}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 376.1577, found 356.1589.



(Z)-dimethyl 2-(cyclohexylimino)-5-(p-tolyl)dihydrothiophene-3,3(2H)-dicarboxylate (56): 99% yield. R_f = 0.63 (2:1 Hexanes: EtOAc eluent); ^1H NMR (500 MHz, CDCl_3) δ 7.35–7.29 (m, 2H), 7.18–7.14 (m, 2H), 4.67 (dd, J = 11.8, 4.8 Hz, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 3.05 (dd, J = 13.0, 4.9 Hz, 1H), 2.98 (tt, J = 10.1, 3.6 Hz, 1H), 2.83 (dd, J = 13.0, 11.8 Hz, 1H), 2.35 (s, 3H), 1.83–1.72 (m, 4H), 1.65–1.57 (m, 1H), 1.56–1.44 (m, 2H), 1.38–1.21 (m, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.7, 168.3, 161.5, 138.2, 135.5, 129.6, 127.6, 70.9, 67.0, 53.6, 53.4, 50.4, 44.0, 32.8, 31.7, 25.8, 24.7, 24.5, 21.2; IR (Neat Film, NaCl) 2929, 2853, 1735, 1648, 1434, 1255, 1167, 1071, 973, 818 cm^{-1} ; HRMS (APCI) m/z calc'd for $\text{C}_{21}\text{H}_{28}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 390.1734, found 390.1738.



(Z)-dimethyl 2-(allylimino)-5-(1-tosyl-1H-indol-3-yl)dihydrothiophene-3,3(2H)-dicarboxylate (57): 77% yield. R_f = 0.80 (1:1 Hexanes:EtOAc eluent); ^1H NMR (500 MHz, CDCl_3) δ 168.1, 167.9, 166.2, 145.4, 135.5, 135.1, 133.6, 130.2, 128.9, 127.1, 125.5, 123.9, 123.5, 119.9, 116.3, 114.0, 77.4, 70.5, 59.7, 53.9, 53.7, 42.7, 41.7, 21.7; ^{13}C NMR (126 MHz, CDCl_3) δ 168.1, 167.9, 166.2, 145.4, 135.5, 135.1, 133.6, 130.2, 128.9, 127.1, 125.5, 123.9, 123.5, 119.9, 116.3, 114.0, 77.4, 70.5, 59.7, 53.9, 53.7, 42.7, 41.7, 21.7; IR (Neat Film, NaCl) 2953, 1738, 1639, 1447, 1372, 1275, 1175, 1126, 1095, 974, 912, 733 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{26}\text{H}_{27}\text{N}_2\text{O}_6\text{S}_2$ $[\text{M}+\text{H}]^+$: 527.1305, found 527.1298.

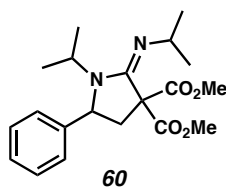


(Z)-dimethyl 5-phenyl-2-(phenylimino)dihydrothiophene-3,3(2H)-dicarboxylate (44): Prepared using General Method D, using phenylisothiocyanate. 89% yield. R_f = 0.60 (3:1 Hexanes:EtOAc eluent); ^1H NMR (500 MHz, CDCl_3) δ 7.41–7.37 (m, 2H), 7.36–7.31 (m, 4H), 7.30–7.27 (m, 1H), 7.16–7.11 (m, 1H), 7.05–7.01 (m, 2H), 4.76 (dd, J = 11.7, 4.9 Hz, 1H), 3.97 (s, 3H), 3.87 (s, 3H), 3.19 (dd, J = 13.1, 4.9 Hz, 1H), 2.99 (dd, J = 13.1, 11.7 Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.3, 167.9, 167.8, 151.0, 137.8,

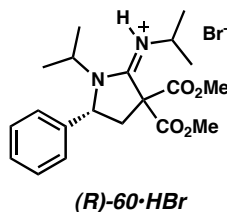
129.1, 129.0, 128.5, 127.8, 125.3, 120.2, 71.4, 54.0, 53.8, 51.2, 43.9; IR (Neat Film, NaCl) 3030, 2952, 1735, 1638, 1593, 1486, 1434, 1268, 1224, 1170, 1063, 973, 763 cm^{-1} ; HRMS (ESI) m/z calc'd for $\text{C}_{20}\text{H}_{20}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 370.1108, found 370.1098.

1.11.2.5 CHARACTERIZATION DATA FOR AMIDINES

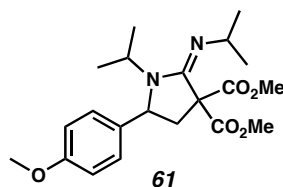
All amidines were synthesized according to General Method G.



(E)-dimethyl 1-isopropyl-2-(isopropylimino)-5-phenylpyrrolidine-3,3-dicarboxylate (60): 98% yield. R_f = 0.39 (9:1 CH_2Cl_2 :MeOH eluent); ^1H NMR (400 MHz, CDCl_3) δ 7.37–7.18 (m, 5H), 4.52 (t, J = 7.1 Hz, 1H), 3.99 (p, J = 6.8 Hz, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 3.50 (hept, J = 6.0 Hz, 1H), 2.95 (dd, J = 12.8, 7.0 Hz, 1H), 2.33 (dd, J = 12.8, 7.2 Hz, 1H), 1.15 (d, J = 6.8 Hz, 3H), 1.11 (d, J = 6.0 Hz, 3H), 1.05 (d, J = 5.9 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H).; ^{13}C NMR (101 MHz, CDCl_3) δ 169.7, 169.2, 151.3, 143.8, 128.5, 127.8, 127.0, 60.5, 59.8, 53.1, 52.9, 51.4, 47.3, 43.4, 24.7, 24.3, 19.6, 19.2; IR (Neat Film, NaCl) 2963, 1731, 1659, 1436, 1261, 1212, 1063, 969 cm^{-1} ; HRMS (MM: ESI-APCI) m/z calc'd for $\text{C}_{20}\text{H}_{29}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 361.2122, found 361.2018.

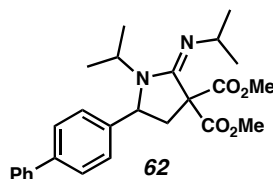


(R,E)-dimethyl 1-isopropyl-2-(isopropylimino)-5-phenylpyrrolidine-3,3-dicarboxylate ((R)-60•HBr): Acetyl bromide (22 μ L, 0.3 mmol) was dissolved in dichloromethane (3 mL) in a 10 mL round-bottom flask. Methanol (41 μ L, 1 mmol) was added to the solution and this mixture was transferred into a second flask containing a solution of amidine (R)-**60** (72 mg, 0.2 mmol) in dichloromethane (3 mL), prepared by the above procedure. The mixture was concentrated in vacuo and crystallized by vapor diffusion of diethyl ether into dichloromethane to produce fine colorless needles suitable for x-ray crystallography. $[\alpha]_D^{25.0}$ 8.8° (*c* 0.445, CHCl₃, > 98% ee).

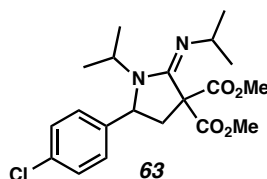


(E)-dimethyl 1-isopropyl-2-(isopropylimino)-5-(4-methoxyphenyl)pyrrolidine-3,3-dicarboxylate (61): 98% yield. R_f = 0.42 (9:1 CH₂Cl₂:MeOH eluent); ¹H NMR (400 MHz, CDCl₃) δ 7.25–7.16 (m, 2H), 6.89–6.79 (m, 2H), 4.50 (br t, *J* = 6.9 Hz, 1H), 4.07–3.95 (br m, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.72 (s, 3H), 3.49 (p, *J* = 6.0 Hz, 1H), 2.93 (br dd, *J* = 12.8, 6.9 Hz, 1H), 2.30 (br dd, *J* = 12.9, 7.3 Hz, 1H), 1.14 (br d, *J* = 6.9 Hz, 4H), 1.11 (d, *J* = 4.3 Hz, 2H), 1.05 (d, *J* = 6.0 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 3H).; ¹³C NMR (101 MHz, CDCl₃) δ 169.5, 169.0, 159.3, 151.6, 135.2, 128.2, 113.9, 60.7, 59.6, 55.3, 53.2, 53.0, 51.4, 47.4, 43.4, 24.5, 24.1, 19.7, 19.2.; IR (Neat Film, NaCl) 2963, 2928,

1736, 1654, 1612, 1513, 1249, 1214, 1172, 1081 cm^{-1} ; HRMS (MM: ESI-APCI) m/z calc'd for $\text{C}_{21}\text{H}_{31}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$: 391.2227, found 391.2208.

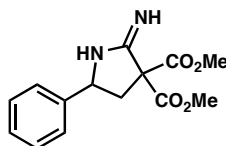


(E)-dimethyl 5-([1,1'-biphenyl]-4-yl)-1-isopropyl-2-(isopropylimino)pyrrolidine-3,3-dicarboxylate (62): 92% yield. R_f = 0.42 (9:1 CH_2Cl_2 :MeOH eluent); ^1H NMR (500 MHz, CDCl_3) δ 7.63–7.53 (m, 4H), 7.47–7.38 (m, 4H), 7.37–7.32 (m, 1H), 4.59 (t, J = 7.1 Hz, 1H), 4.04 (hept, J = 6.9 Hz, 1H), 3.83 (s, 3H), 3.74 (s, 3H), 3.53 (hept, J = 5.9 Hz, 1H), 3.00 (dd, J = 12.8, 7.0 Hz, 1H), 2.37 (dd, J = 12.8, 7.3 Hz, 1H), 1.20 (d, J = 6.8 Hz, 3H), 1.15 (d, J = 6.0 Hz, 3H), 1.08 (d, J = 5.9 Hz, 3H), 0.95 (d, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 169.7, 169.2, 151.4, 142.9, 140.8, 140.7, 128.9, 127.5, 127.4, 127.2, 127.1, 60.6, 59.6, 53.2, 53.0, 51.5, 47.4, 43.4, 24.7, 24.4, 19.8, 19.2; IR (Neat Film, NaCl) 2964, 1733, 1658, 1486, 1435, 1375, 1358, 1264, 1216, 1165, 1126, 1076, 1008, 973, 841, 767, 733 cm^{-1} ; HRMS (MM: ESI-APCI) m/z calc'd for $\text{C}_{26}\text{H}_{33}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 437.2435, found 437.2411.



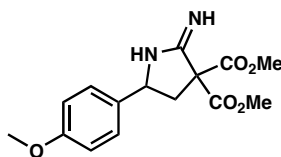
(E)-dimethyl 5-(4-chlorophenyl)-1-isopropyl-2-(isopropylimino)pyrrolidine-3,3-dicarboxylate (63): 78% yield. R_f = 0.40 (9:1 CH_2Cl_2 :MeOH eluent); ^1H NMR (500

MHz, CDCl₃) δ 7.30–7.23 (m, 4H), 4.50 (t, J = 7.1 Hz, 1H), 4.00 (hept, J = 6.9 Hz, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 3.48 (hept, J = 5.9 Hz, 1H), 2.95 (dd, J = 12.8, 7.1 Hz, 1H), 2.27 (dd, J = 12.9, 7.1 Hz, 1H), 1.13 (d, J = 6.7 Hz, 3H), 1.09 (d, J = 6.0 Hz, 3H), 1.04 (d, J = 5.9 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 169.6, 169.1, 151.2, 142.6, 133.4, 128.7, 128.3, 60.4, 59.1, 53.2, 53.0, 51.5, 47.3, 43.3, 24.7, 24.3, 19.9, 19.1; IR (Neat Film, NaCl) 2965, 1733, 1658, 1489, 1435, 1376, 1359, 1269, 1214, 1165, 1126, 1088, 1014, 974, 831 cm⁻¹; HRMS (MM: ESI-APCI) m/z calc'd for C₂₀H₂₈³⁵ClN₂O₄ [M+H]⁺: 395.1732, found 395.1755.



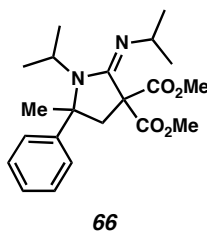
64

dimethyl 2-imino-5-phenylpyrrolidine-3,3-dicarboxylate (64): 78% yield. R_f = 0.45 (9:1 CH₂Cl₂:MeOH eluent); ¹H NMR (500 MHz, CDCl₃) δ 7.34–7.27 (m, 3H), 7.25–7.21 (m, 2H), 4.99 (dd, J = 8.2, 6.9 Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.10 (dd, J = 13.6, 7.0 Hz, 1H), 2.37 (dd, J = 13.6, 8.1 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 168.9, 168.3, 160.2, 144.2, 128.6, 127.1, 126.4, 68.4, 67.4, 53.6, 53.4, 42.8; IR (Neat Film, NaCl) 3449, 3028, 1729, 1665, 1600, 1435, 1386, 1354, 1279, 1243, 1201, 1154, 1114, 1075, 765 cm⁻¹; HRMS (FAB+) m/z calc'd for C₁₄H₁₇N₂O₄ [M+H]⁺: 277.1188, found 277.1176.

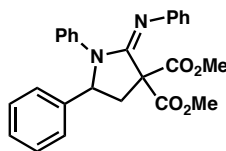


65

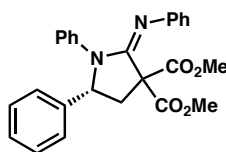
dimethyl 2-imino-5-(4-methoxyphenyl)pyrrolidine-3,3-dicarboxylate (65): 68% yield. $R_f = 0.47$ (9:1 CH_2Cl_2 :MeOH eluent); ^1H NMR (500 MHz, CDCl_3) δ 7.23–7.16 (m, 2H), 6.84 (dd, $J = 6.8, 1.9$ Hz, 2H), 4.97–4.88 (m, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.76 (s, 3H), 3.06 (dd, $J = 13.6, 6.9$ Hz, 1H) 2.34 (dd, $J = 13.6, 8.1$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.9, 168.3, 160.1, 158.7, 136.3, 127.5, 113.9, 113.9, 67.8, 67.4, 55.4, 53.6, 53.4, 42.9; IR (Neat Film, NaCl) 3464, 3374, 3102, 2955, 2838, 1738, 1662, 1612, 1514, 1439, 1351, 1247, 1213, 1175, 1105, 1077, 1034, 831, 733 cm^{-1} ; HRMS (FAB+) m/z calc'd for $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$: 307.1294, found 307.1287.



(E)-dimethyl 1-isopropyl-2-(isopropylimino)-5-methyl-5-phenylpyrrolidine-3,3-dicarboxylate (66): 58% yield. $R_f = 0.35$ (10:1 CHCl_3 :MeOH eluent); ^1H NMR (500 MHz, CDCl_3) δ 7.48–7.44 (m, 2H), 7.38–7.33 (m, 2H), 7.29–7.24 (m, 1H), 3.85 (s, 3H), 3.71 (s, 3H), 3.44 (dt, $J = 11.8, 5.9$ Hz, 1H), 3.09–2.99 (hept, $J = 6.7$ Hz, 1H), 2.83–2.72 (m, 2H), 1.61 (s, 3H), 1.35 (dd, $J = 17.2, 6.7$ Hz, 6H), 1.10 (dd, $J = 18.8, 5.9$ Hz, 6H); ^{13}C NMR (126 MHz, CDCl_3) δ 170.5, 170.2, 148.5, 146.8, 128.3, 127.2, 126.7, 64.8, 60.3, 53.2, 53.1, 51.4, 50.5, 47.1, 24.9, 24.8, 24.5, 19.9, 19.1; IR (Neat Film, NaCl) 2963, 1731, 1654, 1375, 1251, 1217, 1090 cm^{-1} ; HRMS (MM: ESI-APCI) m/z calc'd for $\text{C}_{21}\text{H}_{31}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 375.2278, found 375.2297.

**67****(*E*)-dimethyl 1,5-diphenyl-2-(phenylimino)pyrrolidine-3,3-dicarboxylate (**67**):**

79% yield. R_f =0.32 (10:1 CH_2Cl_2 :MeOH eluent); ^1H NMR (400 MHz, DMSO- d_6 , 80 °C) δ 7.34 – 7.16 (m, 8H), 7.10 (dt, J = 15.2, 7.6 Hz, 5H), 6.95 (t, J = 7.4 Hz, 1H), 6.80 (t, J = 7.3 Hz, 1H), 6.71 (d, J = 7.7 Hz, 2H), 5.28 (t, J = 7.0 Hz, 1H), 3.66 (s, 3H) 3.45 (s, 3H), 3.17 (dd, J = 13.0, 7.2 Hz, 1H), 3.05 (s, 1H), 2.71 (dd, J = 13.0, 6.9 Hz, 1H); ^{13}C NMR (101 MHz, DMSO- d_6 , 100 °C) δ 168.5, 168.2, 152.0, 148.4, 148.3, 140.9, 129.6, 129.5, 129.4, 129.3, 129.2, 129.1, 129.0, 128.9, 128.8, 128.7, 128.2, 128.2, 128.1, 128.0, 127.7, 127.5, 127.4, 127.3, 127.2, 126.6, 125.9, 124.6, 122.0, 121.9, 120.9, 64.1, 63.1, 62.7, 55.3, 54.5, 54.3, 53.4, 52.6, 52.4, 51.9, 43.0; IR (Neat Film, NaCl) 3062, 3027, 2948, 1730, 1661, 1592, 1493, 1372, 1263, 1051 cm^{-1} ; HRMS (MM: ESI-APCI) m/z calc'd for $\text{C}_{26}\text{H}_{25}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 429.1809, found 429.1825.

**(*R*)-67****(*R,E*)-dimethyl 1,5-diphenyl-2-(phenylimino)pyrrolidine-3,3-dicarboxylate ((*R*)-**67**):**

Characterization data same as above; $[\alpha]_{\text{D}}^{25.0}$ 36.7° (c 0.805, CHCl_3 , 88% ee).

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- (14) We have evidence to suggest the role of water is not to hydrolyze the trimethylsilylisocyanate to cyanic acid: in situ treatment of potassium cyanate with mild acids does not afford the desired lactam.
- (15) The yields, as determined by LCMS, are inflated, likely as a result of the volatility of the internal standard. We believe the yields to be self-consistent within each

optimization table, but are not compared easily to other tables due to minor differences in experimental setup.

- (16) Other Lewis acids examined included aluminum trichloride, tin(IV) chloride, indium trichloride. We also attempted to use tin(II) chloride with microwave heating, but complex reaction mixtures resulted.
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APPENDIX 1

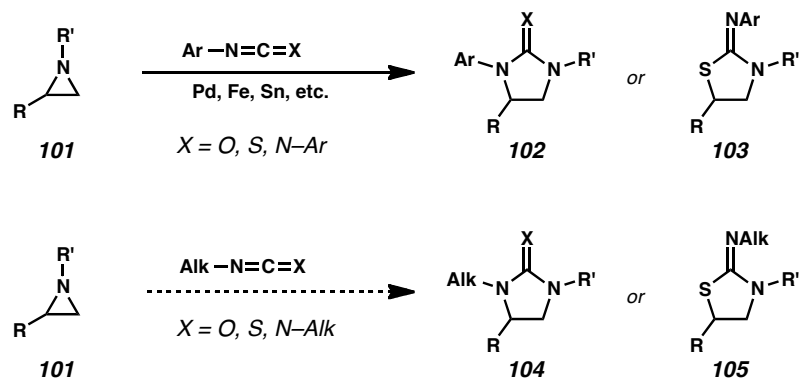
Future Directions for Lewis Acid Mediated (3 + 2) Cyclopropane Cycloadditions[†]

A1.1 RING-EXPANSION REACTIONS OF AZIRIDINES

Aziridines (**101**) are an important class of nitrogen containing heterocycles.¹ Ring expansion reactions of these compounds with aryl-substituted heterocumulenes is well-documented, using palladium and iron catalysts to promote (3 + 2) cycloadditions (Scheme A1.1.1).² However, none of the known methods are capable of incorporating alkyl-substituted heterocumulenes into corresponding 5-membered ring products (e.g. **104** and **105**).

[†] This work was performed in collaboration with Nicholas R. O'Connor and Robert A. Craig, II, graduate students in the Stoltz group.

Scheme A1.1.1. (3 + 2) Cycloadditions of aziridines and carbodiimides



We have found in preliminary work that stoichiometric zinc triflate is a competent Lewis acid for converting enantioenriched aziridines to guanidine products with good retention of stereochemical information (Table A1.1.1). Efforts are ongoing to improve the enantiomeric excess of the products, and to examine the substrate scope of the reaction.

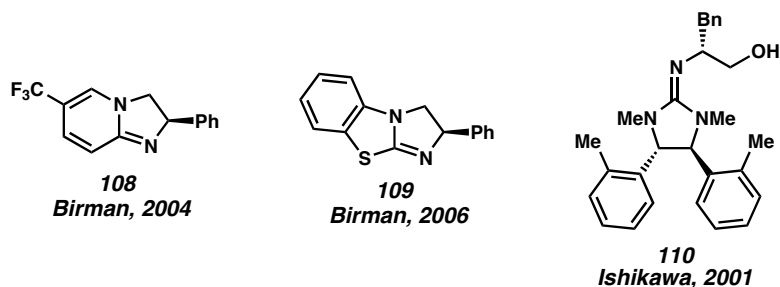
Table A1.1.1. Preliminary Lewis acid optimization for guanidine synthesis

Entry	Lewis Acid	Time (h)	Yield (%)	ee (%)
1	Sn(OTf) ₂ (Sigma)	7	59	24
2	Sn(OTf) ₂ (Strem)	7	63	36
3	SnCl ₂	48	>99	42
4	FeCl ₃	8	80	1
5	Cu(OTf) ₂	72	>99	55
6	Zn(OTf) ₂	72	73	82
7	ZnCl ₂	72	>99	17
8	ZnBr ₂	24	83	10
9	ZnI ₂	72	71	2

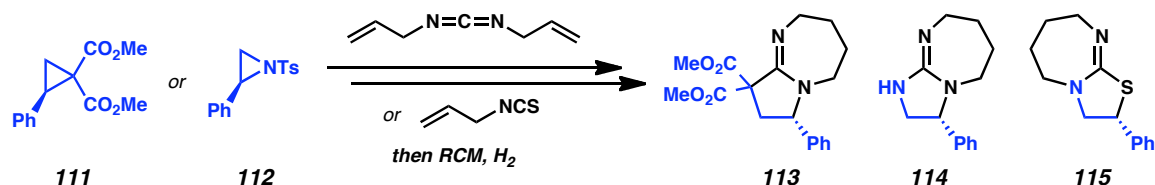
A1.1.1 AMIDINE AND GUANIDINE CATALYSIS

Chiral amidines, guanidines, and isothioureas have been shown to be useful nucleophilic catalysts for an array of asymmetric transformations, including acylations, aldol reactions, among others.³ Examples of these include Birman's amidine (**108**) and isothiourea (**109**) catalysts,^{4,5} and guanidine **110** developed by Ishikawa (Figure A1.1.1).⁶ We envision that Lewis acid (3 + 2) cycloadditions of appropriately substituted heterocumulenes could afford access to an array of chiral nucleophilic catalysts (e.g. **113–114**) from readily available enantioenriched aziridines (**112**) or cyclopropanes (**111**, Scheme A1.1.2).

Figure A1.1.1. Examples of chiral nucleophilic catalysts.



Scheme A1.1.2. Potential nucleophilic catalysts accessible via Lewis acid (3 + 2) cycloaddition

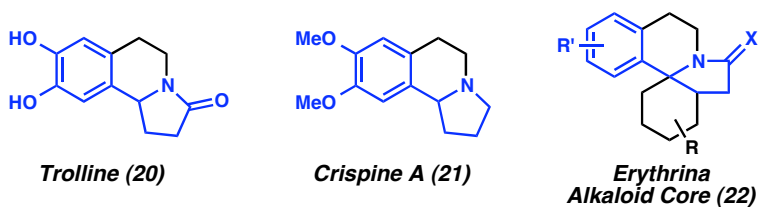


A1.2 NATURAL PRODUCT SYNTHESIS

Several natural products contain the 5-aryl substituted γ -lactam motif accessible via cyclopropane/heterocumulene (3 + 2) cycloaddition, including trolline (**20**), crispine A

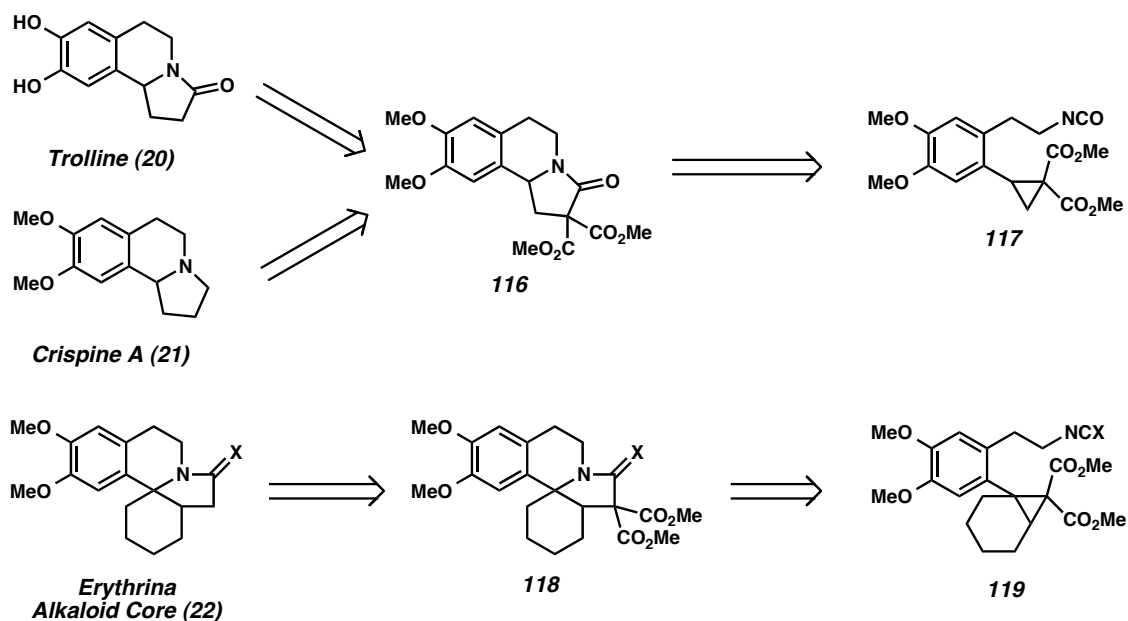
(**21**), and several of the *Erythrina* alkaloids (i.e., **22**, Figure A1.2.1). To demonstrate the utility of the (3 + 2) cycloaddition methodology, proposed is a general route toward this series of natural products.

Figure A1.2.1. Natural products accessible via cyclopropane (3 + 2) cycloadditions



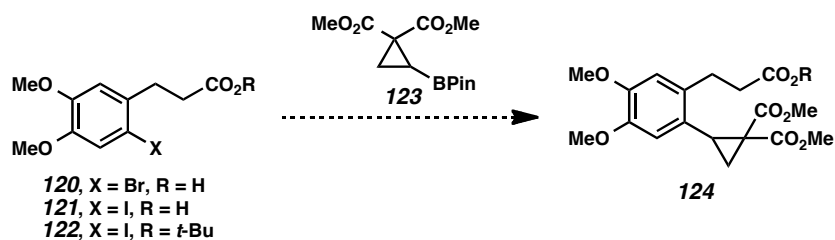
We envisioned that trolline (**20**) and crispine A (**21**) could be derived from common intermediate **116** via decarboxylation followed by demethylation or lactam reduction, respectively (Scheme A1.2.1). The key synthetic intermediate could arise from intramolecular (3 + 2) cycloaddition of isocyanate **117**. The tetracyclic core of the *Erythrina* alkaloids could be rapidly assembled in a similar fashion via intramolecular (3 + 2) cycloaddition of a heterocumulene moiety with a bicyclo[4.1.0]heptane unit (**119**).

Scheme A1.2.1. Retrosynthetic analysis of alkaloid natural products **20**, **21**, **22**

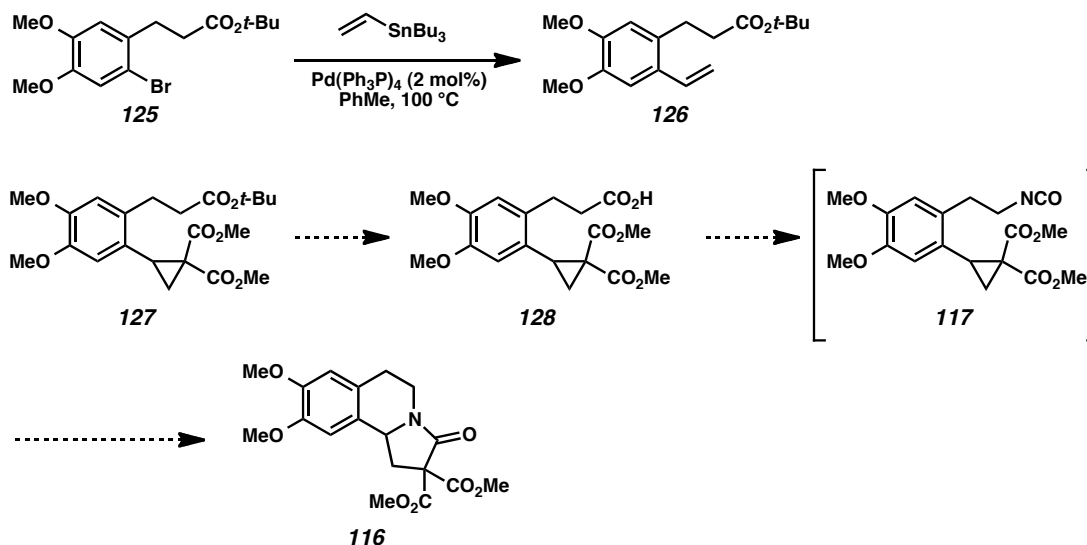


Preliminary work toward the (3 + 2) substrate has been carried out. Our initial efforts focused on a Suzuki cross coupling of cyclopropyl boronate ester (**123**) with haloarenes **120–122** (Scheme A1.2.2). The cyclopropane fragment (**123**) has previously been synthesized in enantiopure form by Gevorgyan and coworkers, and would provide an entry point to asymmetric synthesis.⁷ However, under numerous conditions, we failed to observe any cross-coupled product (**124**).

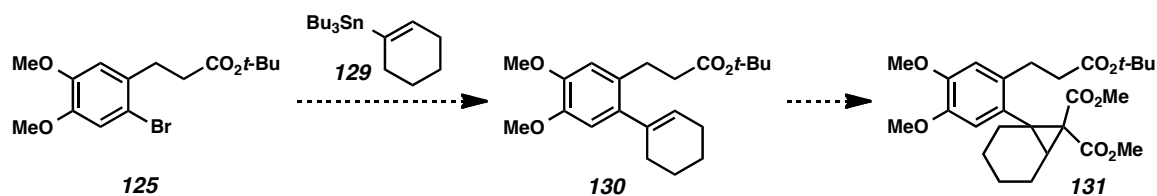
Scheme A1.2.2. Failed Suzuki cross coupling with cyclopropyl boronate ester **XX**



Fortunately, Stille cross-coupling of aryl bromide **125** afforded a styrene derivative (**126**) which may, in future work, be cyclopropanated with diazodimethylmalonate (Scheme A1.2.3). Cleavage of the *tert*-butyl ester followed by a Curtius rearrangement would provide an isocyanate (**117**) that may be treated directly with Lewis acid to afford the desired tricycle **116**.

Scheme A1.2.3. Stille coupling of bromide **125** and proposed conversion to tricycle **116**

We envision that an appropriate cyclopropane precursor (**131**) to the *Erythrina* alkaloid core would be accessible by a similar route. Stille coupling of aryl bromide **125** with known cyclohexenyl tributyltin (**129**) followed by cyclopropanation would afford a suitable isocyanate precursor for (3 + 2) cycloaddition (Scheme A1.2.4).⁸

Scheme A1.2.4. Proposed synthesis of cyclopropane **131** via Stille coupling.

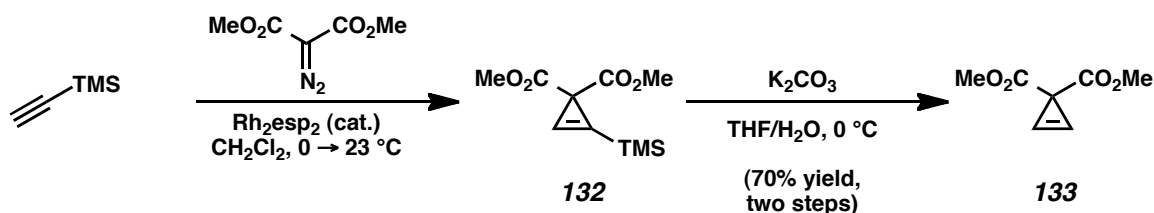
A1.3 CONCLUSION

In summary, a variety of methodological and synthetic applications are envisioned based on our original discovery, including guanidine synthesis from chiral aziridines, synthesis of novel chiral nucleophilic catalysts, and total synthesis of polycyclic alkaloids. Efforts are currently ongoing to realize these goals.

A1.4 EXPERIMENTAL SECTION

A1.4.1 MATERIALS AND METHODS

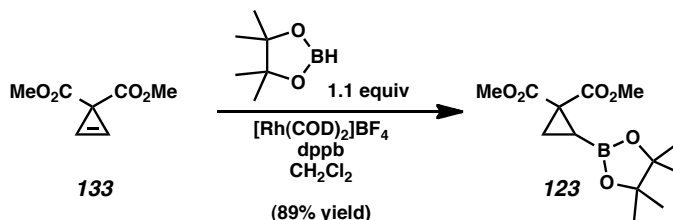
Unless stated otherwise, reactions were performed under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina).⁹ Commercially obtained reagents were used as received unless otherwise stated. Reaction temperatures were controlled by an IKAmag temperature modulator. Microwave reactions were performed with a Biotage Initiator Eight 400 W apparatus at 2.45 GHz. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, or potassium permanganate, iodine, or anisaldehyde staining. SiliaFlash P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. ¹H and ¹³C NMR spectra were recorded on a Varian Inova 500 (at 500 MHz and 126 MHz respectively), Varian 400 (at 400 MHz and 100 MHz, respectively) or on a Varian Mercury 300 (at 300 MHz) and are reported relative to CHCl₃ (δ 7.26 & 77.16 respectively). Data for ¹H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm⁻¹). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) or mixed (MM) ionization mode.

A1.4.2 PREPARATIVE PROCEDURES

Cyclopropene 133. Prepared by an improved procedure based on that reported by Gevorgyan and coworkers.⁷ To a flame-dried round-bottom flask equipped with a magnetic stir bar was added bis[rhodium($\alpha,\alpha,\alpha',\alpha'$ -tetramethyl-1,3-benzenedipropionic acid)] (0.7 mg, 0.9 μ mol, 0.016 mol%) and trimethylsilylacetylene (0.82 mL, 5.75 mmol, 1 equiv). The flask was sealed with a rubber septum, then evacuated and backfilled with argon three times. Dichloromethane was then added (10 mL, 0.6 M) and the flask was cooled in an ice-water bath with stirring. Diazodimethylmalonate (0.9982 g, 6.3 mmol, 1.1 equiv) was added dropwise, then the flask was removed from the bath and allowed to warm to ambient temperature, stirring overnight (13 h). Complete consumption of the starting material was observed (TLC), and the solvent was evaporated in vacuo. The residue was purified by column chromatography on SiO₂ (20:1 $\rightarrow$ 6:1 hexanes:EtOAc) to afford cyclopropene **132** as a blue oil which was carried forward directly to the next stage.

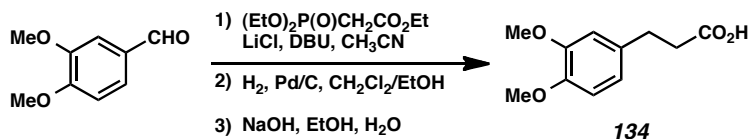
Cyclopropene **132** was dissolved in tetrahydrofuran (30 mL) in a round-bottom flask, and the solution was cooled in an ice-water bath. To this solution was added K₂CO₃ (10 mL, 10% in water) with stirring. After 10 minutes, TLC indicated complete consumption of starting material (3:1 hexanes:EtOAc, SM = 0.62, prod = 0.21). The phases were separated and the organic phase was concentrated to an approximate volume

of 5 mL. The aqueous and organic phases were recombined and diluted with water (10 mL) and diethyl ether (25 mL). The phases were separated and the aqueous layer was extracted with additional diethyl ether (25 mL). The combined organics were dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography to afford cyclopropene **133** (634.1 mg, 70% yield) as an amorphous white solid. The characterization data matched those reported by Gevorgyan and coworkers.⁷

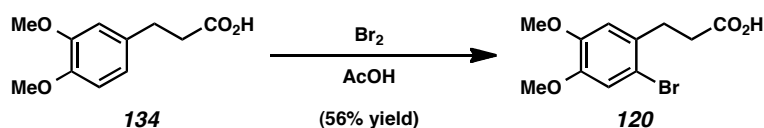


Cyclopropane 123. In a nitrogen filled glove-box, an oven-dried scintillation vial was charged with bis(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate (5.2 mg, 0.013 mmol, 0.02 equiv) and dppb (6.0 mg, 0.014 mmol, 0.022 equiv), and the solids were dissolved in dichloromethane, affording an orange solution. A separate one dram vial was charged with cyclopropene **133** (99.5 mg, 0.64 mmol, 1 equiv) and pinacolborane (0.1 mL, 0.7 mmol, 1.1 equiv). The mixture was dissolved in dichloromethane (0.5 mL) and transferred into the first vial; the second vial was then washed with additional dichloromethane (0.3 mL) and transferred into the first vial. The reaction was stirred for 17 h and complete conversion of the starting material was observed (TLC: 3:1 hexanes:EtOAc, R_f : SM = 0.21, product: 0.46). The reaction mixture was dry-loaded onto SiO_2 (~1 mL) and purified by column chromatography on SiO_2 (8:1 hexanes:EtOAc)

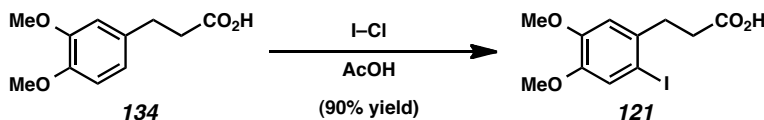
to afford cyclopropane **123** (160.7 mg, 89% yield). The characterization data matched those reported by Gevorgyan.⁷



3-(3,4-Dimethoxyphenyl)propionic acid 134. Prepared according to the method of Lebel and coworkers without modification.¹⁰

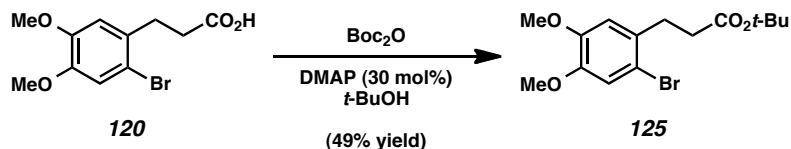


3-(2-bromo-3,4-dimethoxyphenyl)propionic acid 120. Prepared according to the method of Lebel and coworkers with minor modifications:¹⁰ pre-cooling the acetic acid solution in an ice-water bath resulted in a frozen mixture; therefore, the solution was cooled until it began to freeze, and bromine was added thereafter, with continued cooling in the ice-water bath.

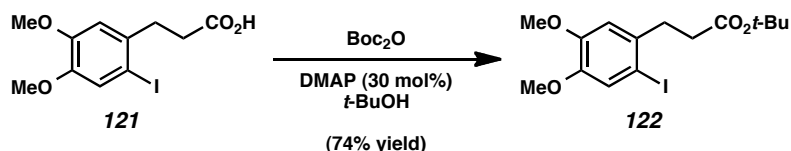


3-(2-iodo-3,4-dimethoxyphenyl)propionic acid 121. Carboxylic acid **134** (1.0812 g, 5.14 mmol, 1 equiv) was dissolved in acetic acid (6 mL) in a round-bottom flask. Iodine monochloride (1.1370 g, 6.94 mmol, 1.35 equiv) was added in portions at ambient temperature to afford an orange solution. After at least 20 minutes, a precipitate was observed. After 85 minutes, the suspension was poured over water (10 mL) and a

saturated solution of aqueous sodium thiosulfate was slowly added until the orange color disappeared. The suspension was filtered, washed with water, and air-dried to afford iodide **121** (1.5503 g, 90% yield) as a white amorphous solid: ^1H NMR (300 MHz, CDCl_3) δ 7.21 (s, 1H), 6.80 (s, 1H), 3.85 (s, 6H), 3.00 (t, $J = 7.8$ Hz, 2H), 2.66 (t, $J = 7.8$ Hz, 2H).

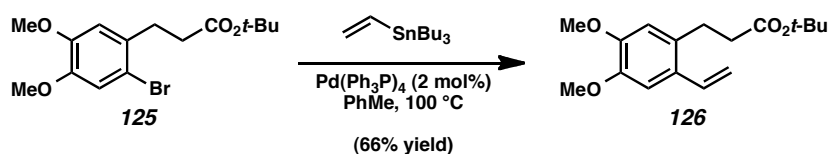


***tert*-butyl ester 125.** According to the procedure of Takeda and coworkers.¹¹ To a suspension of acid **120** (1.0007 g, 3.4 mmol, 1 equiv) and di-*tert*-butyl dicarbonate (2.2544 g, 10.4 mmol, 3 equiv) in *tert*-butanol (8.5 mL, 0.4 M) was added 4-(*N,N*-dimethylamino)pyridine (127.3 mg, 1.02 mmol, 0.3 equiv). Vigorous bubbling was observed and the solution became yellow. After one hour, the reaction mixture was dry-loaded directly onto SiO_2 (~10 mL) and purified by column chromatography on SiO_2 (20:1 $\rightarrow$ 10:1 hexanes:EtOAc) to afford *tert*-butyl ester **125** (581.6 mg, 49% yield): ^1H NMR (300 MHz, Chloroform-*d*) δ 6.99 (s, 1H), 6.77 (s, 1H), 3.85 (s, 6H), 2.95 (t, $J = 7.7$ Hz, 2H), 2.52 (t, $J = 7.7$ Hz, 2H), 1.43 (s, 9H).



***tert*-butyl ester 122.** According to the procedure of Takeda and coworkers.¹¹ To a suspension of acid **121** (340 mg, 1 mmol, 1 equiv) and di-*tert*-butyl dicarbonate (652 mg,

3 mmol, 3 equiv) in *tert*-butanol (2.5 mL, 0.4 M) was added 4-(*N,N*-dimethylamino)pyridine (36.6 mg, 0.3 mmol, 0.3 equiv). Vigorous bubbling was observed and the solution becomes yellow. After one hour, the reaction mixture was dry-loaded directly onto SiO₂ and purified by column chromatography on SiO₂ (hexanes → 10:1 hexanes:EtOAc) to afford *tert*-butyl ester **122**.



Styrene 126. In a nitrogen-filled glovebox, a flame-dried Schlenk bomb was charged with tetrakis(triphenylphosphine) palladium(0) (30 mg, 0.03 mmol, 0.02 equiv). The bomb was sealed, removed from the glovebox, and placed under an atmosphere of argon. To a vial containing bromide **125** (455.1 mg, 1.30 mmol, 1 equiv) was added dry toluene, which was then removed in vacuo; this procedure was repeated twice to remove traces of water from the substrate. Under an atmosphere of argon, the bromide was dissolved in toluene (3 mL) and transferred to the Schlenk bomb under a high flow of argon. Finally, vinyl tributyltin (0.4 mL, 1.37 mmol, 1.05 equiv) was added as a neat oil to the Schlenk bomb under a high flow of argon. The bomb was sealed and lowered into an oil bath which was preheated to 100 °C. After 17 hours, the bomb was cooled to ambient temperature, and a crude product was obtained by a workup procedure that was not properly recorded. The crude product was purified by column chromatography to afford styrene **126** as a yellow solid (253.1 mg, 66% yield). ¹H NMR of the crude material showed complete consumption of the starting material and clean signals corresponding to the vinyl group: 5.87 (dd, *J* = 17.2, 10.5 Hz, 1H), 5.09 (d, *J* = 10.5 Hz, 1H), 5.04 (d, *J* =

17.2 Hz, 1 H). ^1H NMR of the purified product was poorly shimmed or had paramagnetic impurities.

A1.5 NOTES AND REFERENCES

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APPENDIX 2

Spectra Relevant to Chapter 1:

Lewis Acid Mediated (3 + 2) Cycloadditions of

Donor–Acceptor Cyclopropanes with Heterocumulenes

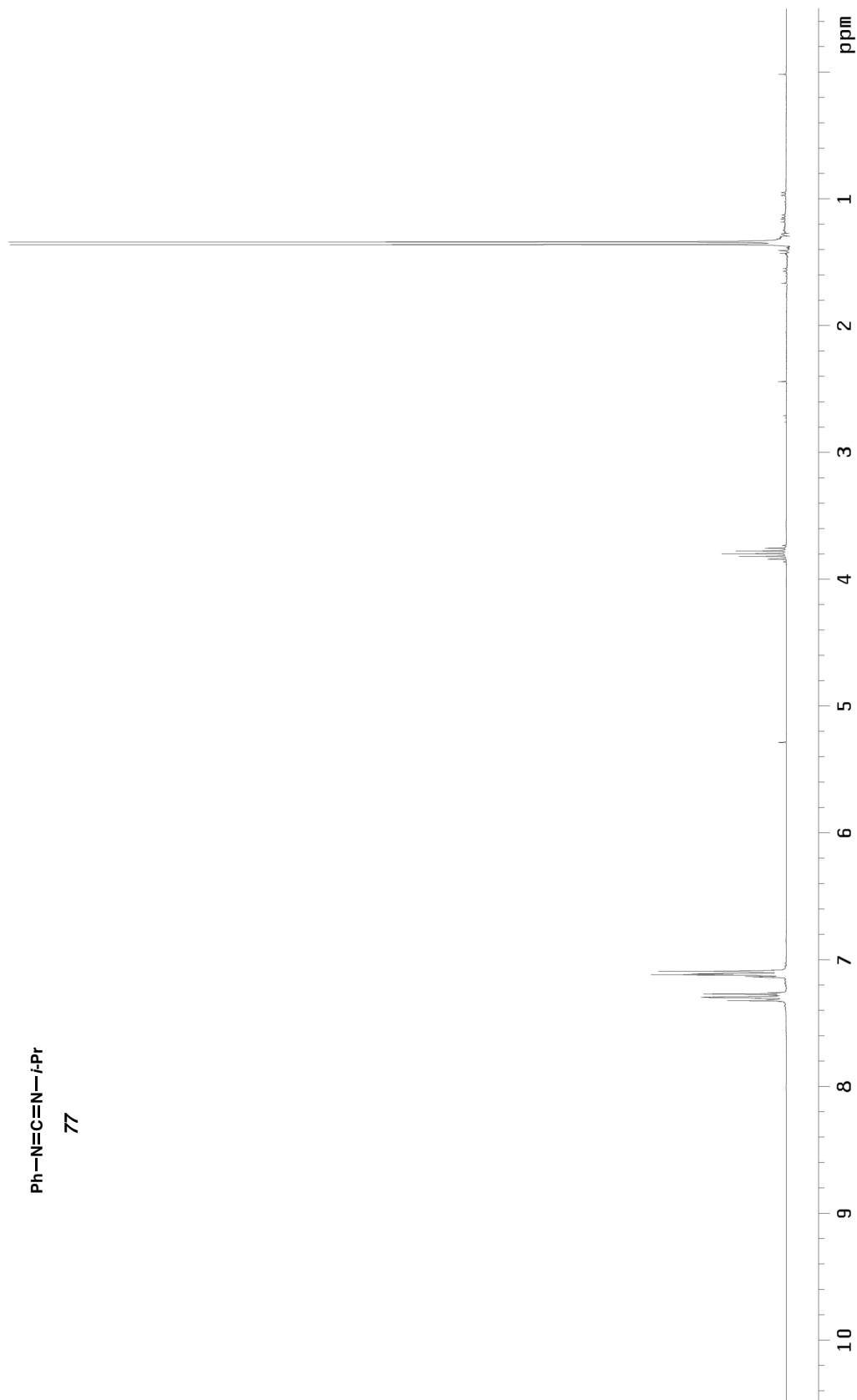


Figure A2.1 ^1H NMR (300 MHz, CDCl_3) of compound 77

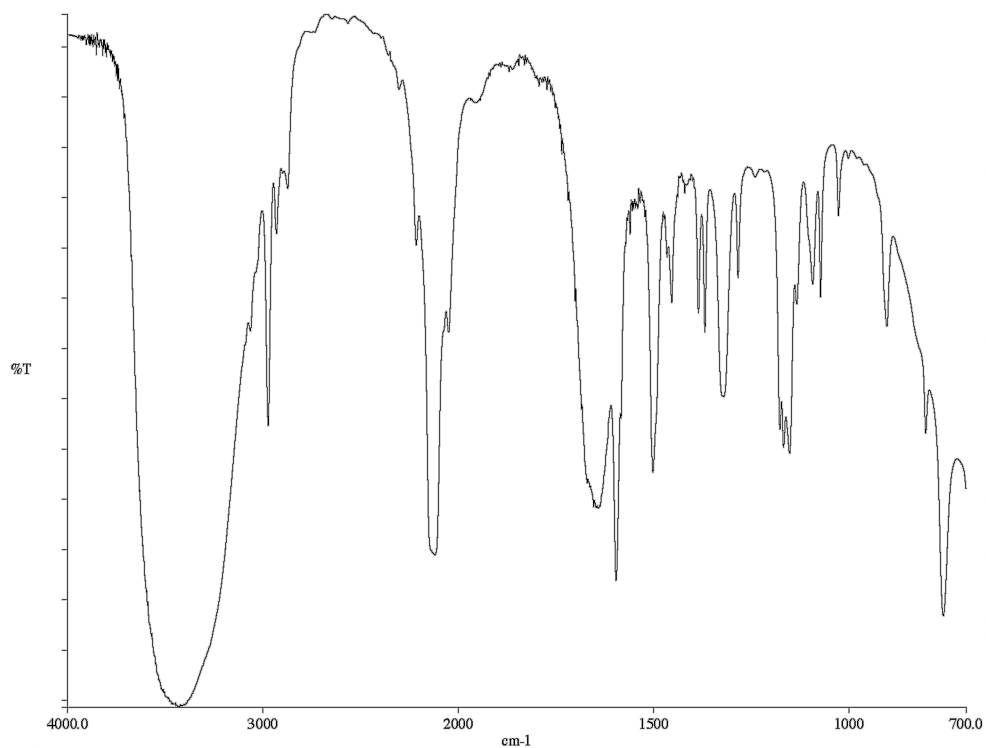


Figure A2.2 Infrared spectrum (thin film/NaCl) of compound **77**

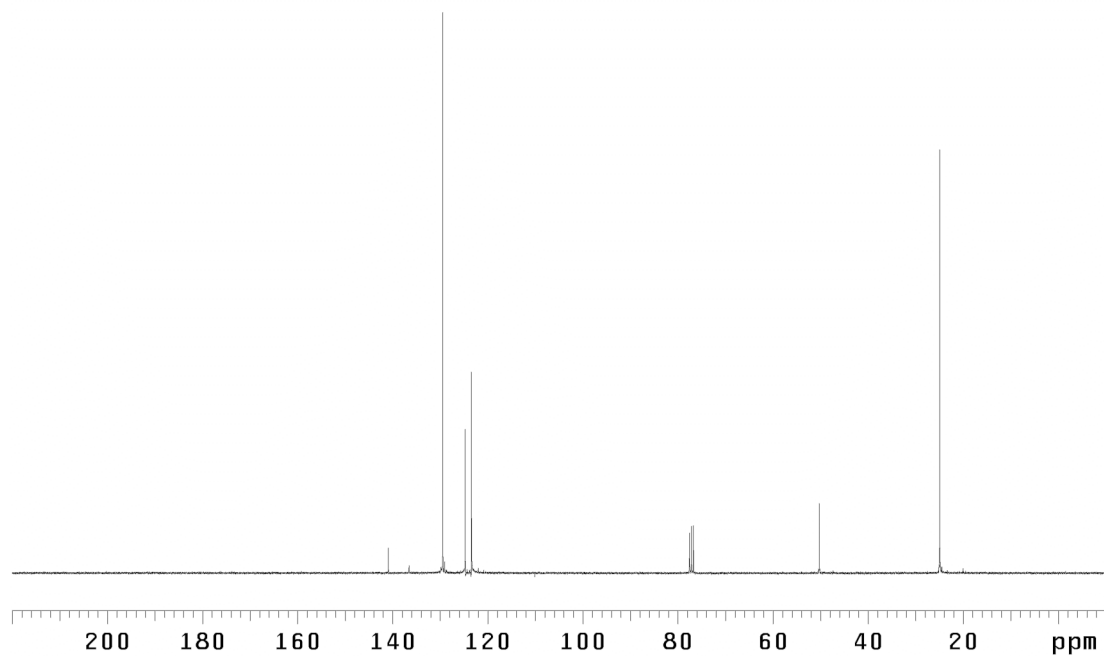


Figure A2.3 ¹³C NMR (75 MHz, CDCl₃) of compound **77**

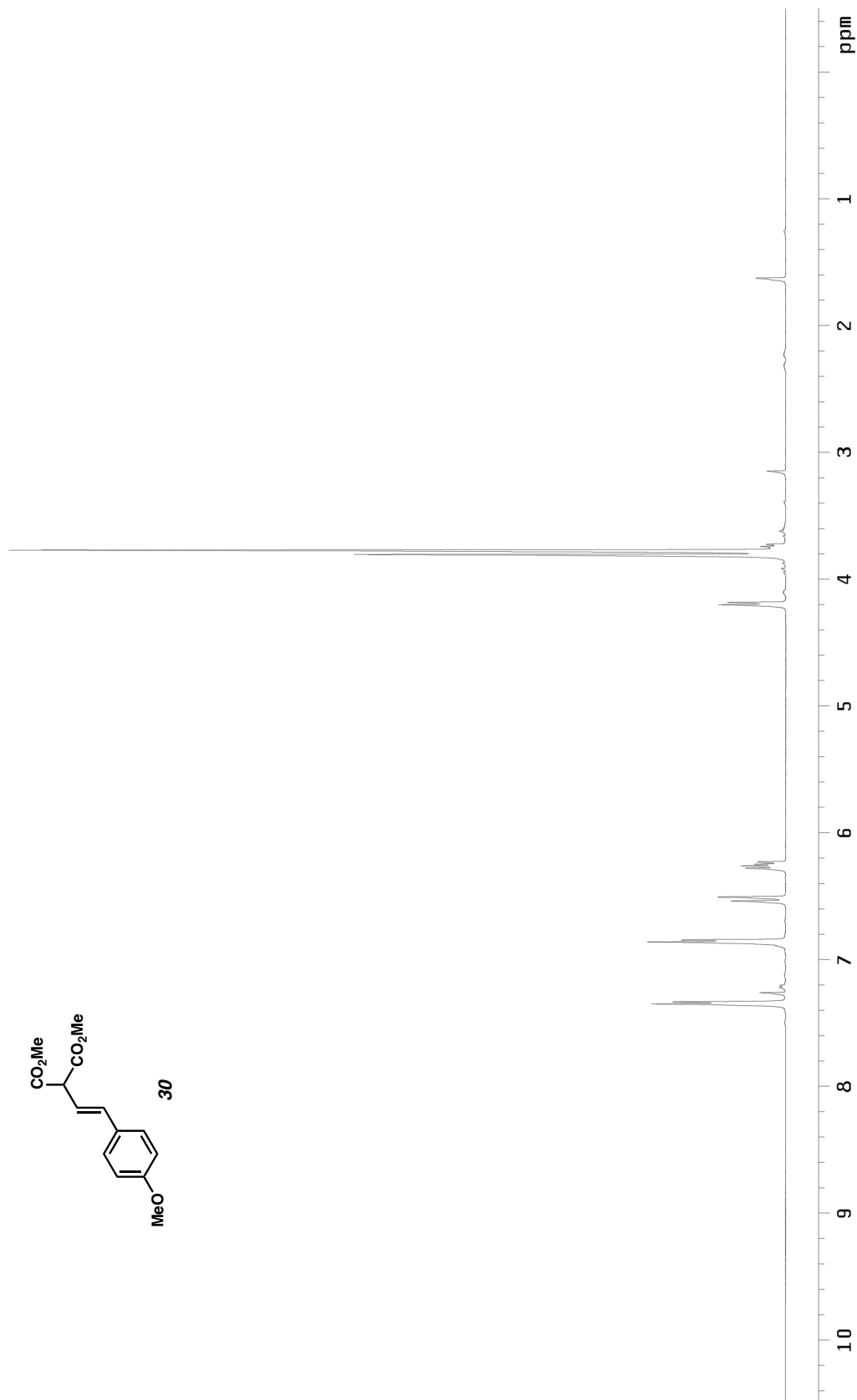


Figure A2.4 ¹H NMR (500 MHz, CDCl₃) of compound **30**

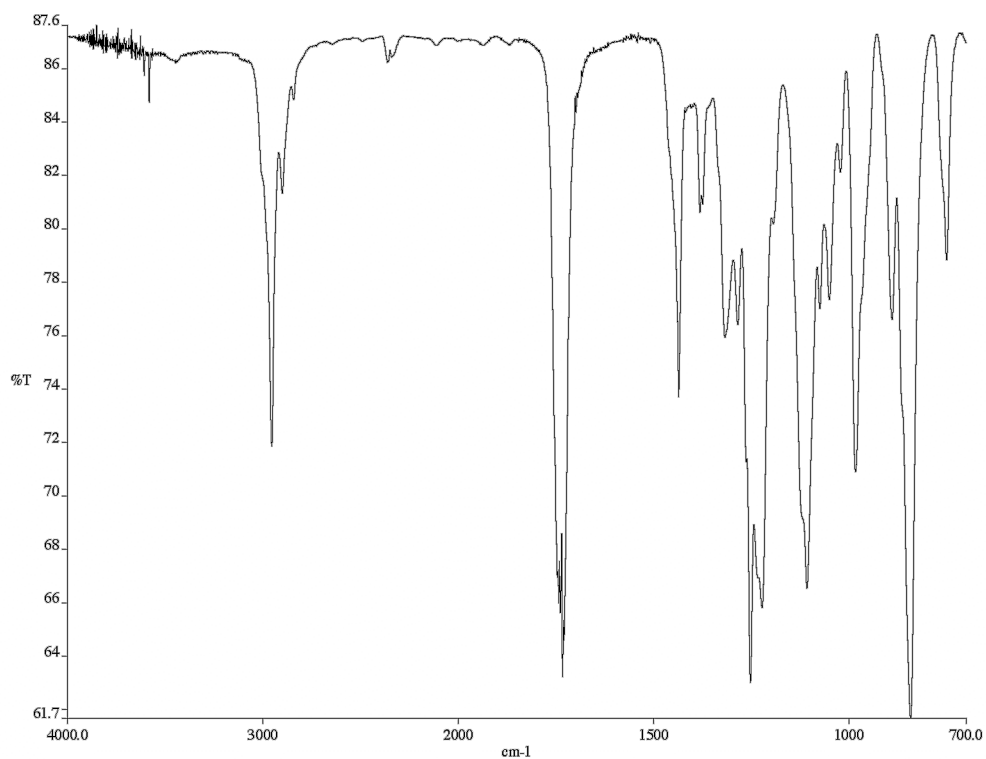


Figure A2.5 Infrared spectrum (thin film/NaCl) of compound **30**

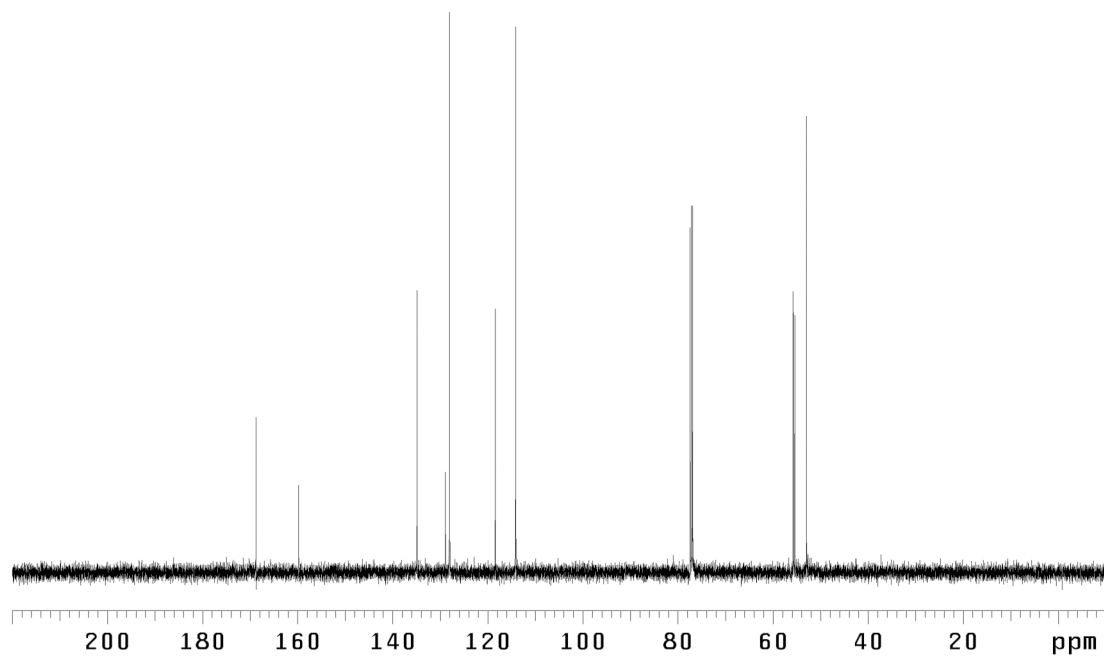


Figure A2.6 ¹³C NMR (126 MHz, CDCl₃) of compound **30**

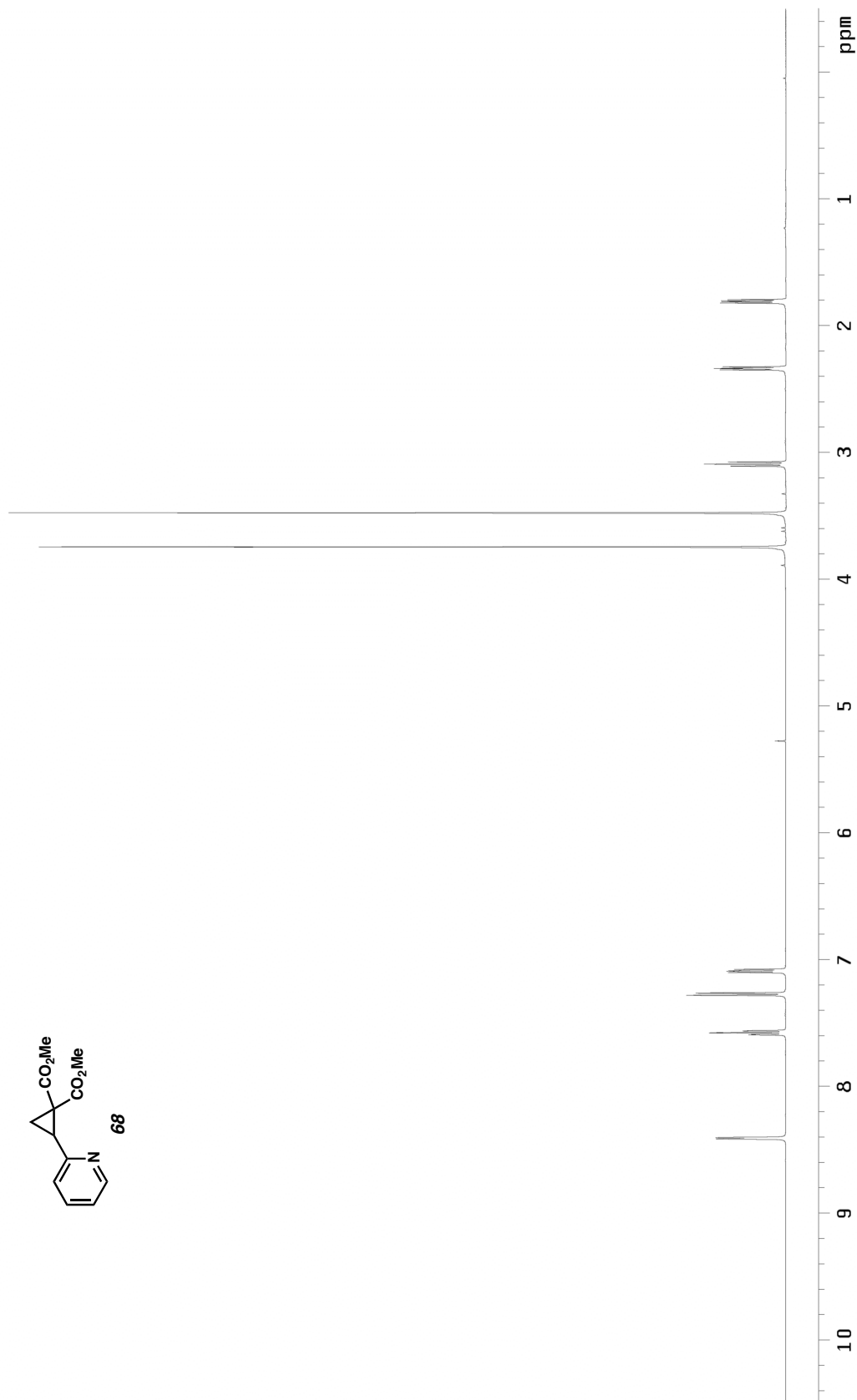


Figure A2.7 ¹H NMR (500 MHz, CDCl₃) of compound **68**

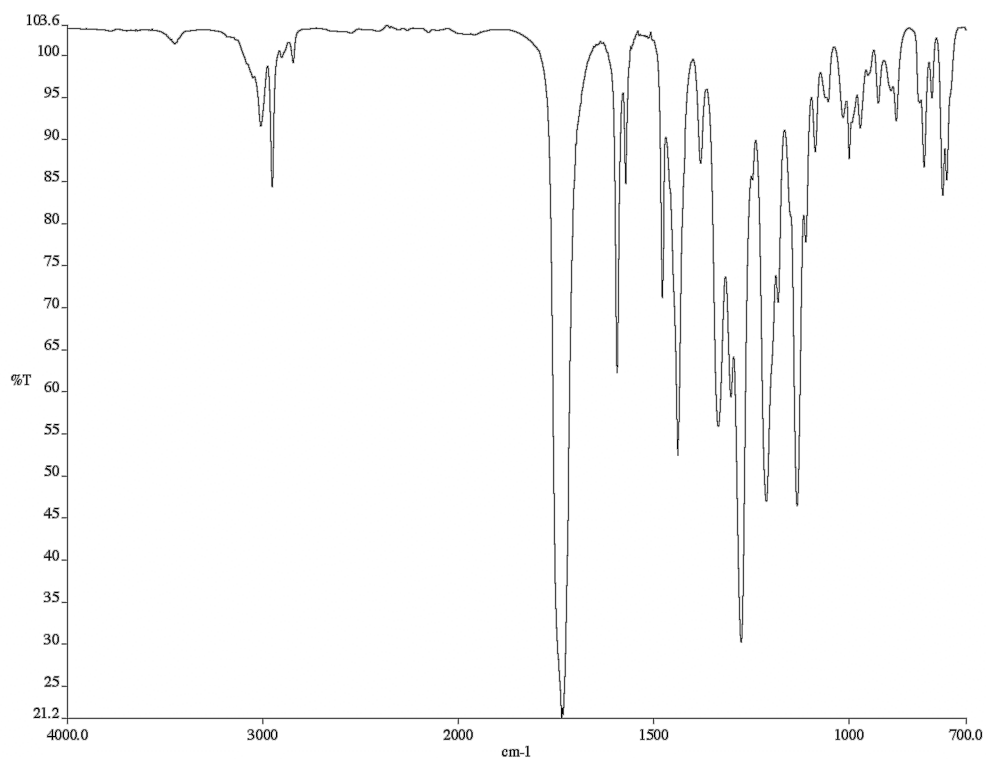


Figure A2.8 Infrared spectrum (thin film/NaCl) of compound **68**

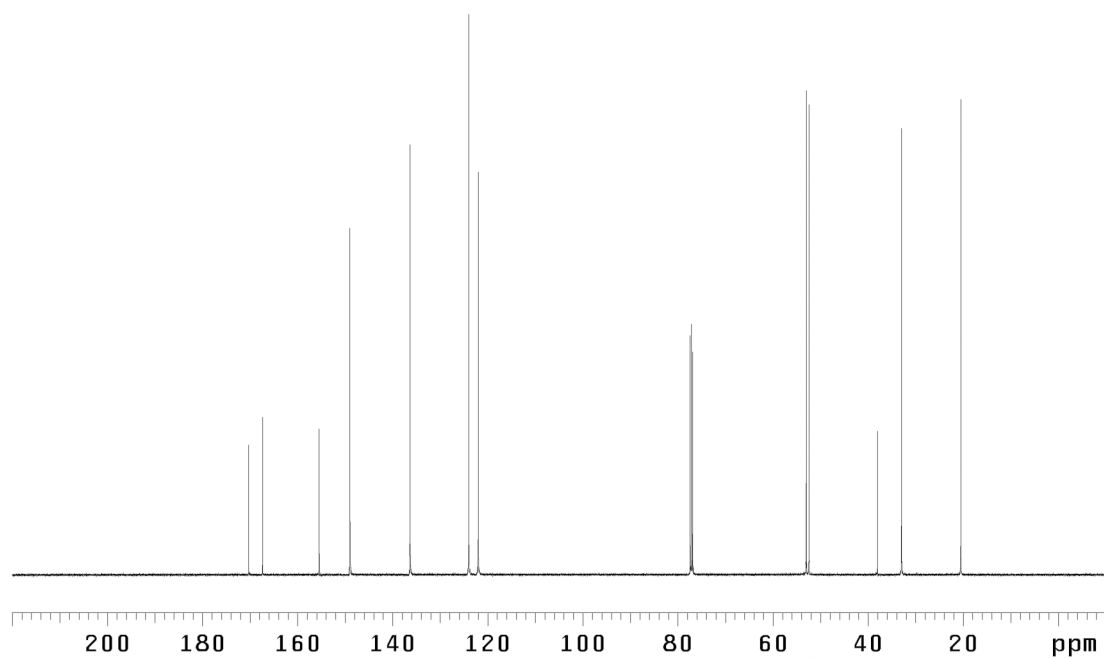


Figure A2.9 ¹³C NMR (126 MHz, CDCl₃) of compound **68**

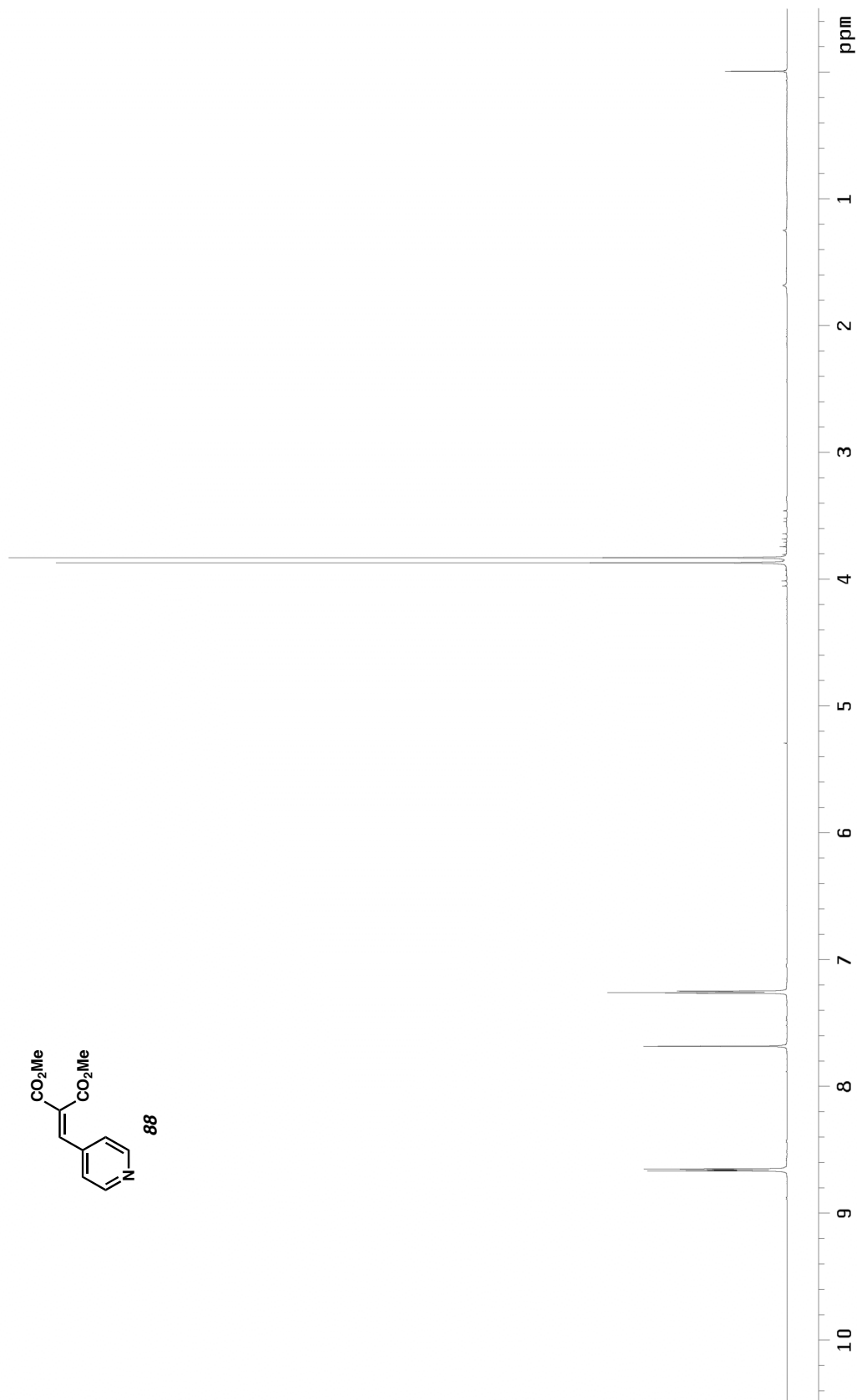


Figure A2.10 ^1H NMR (500 MHz, CDCl_3) of compound **88**

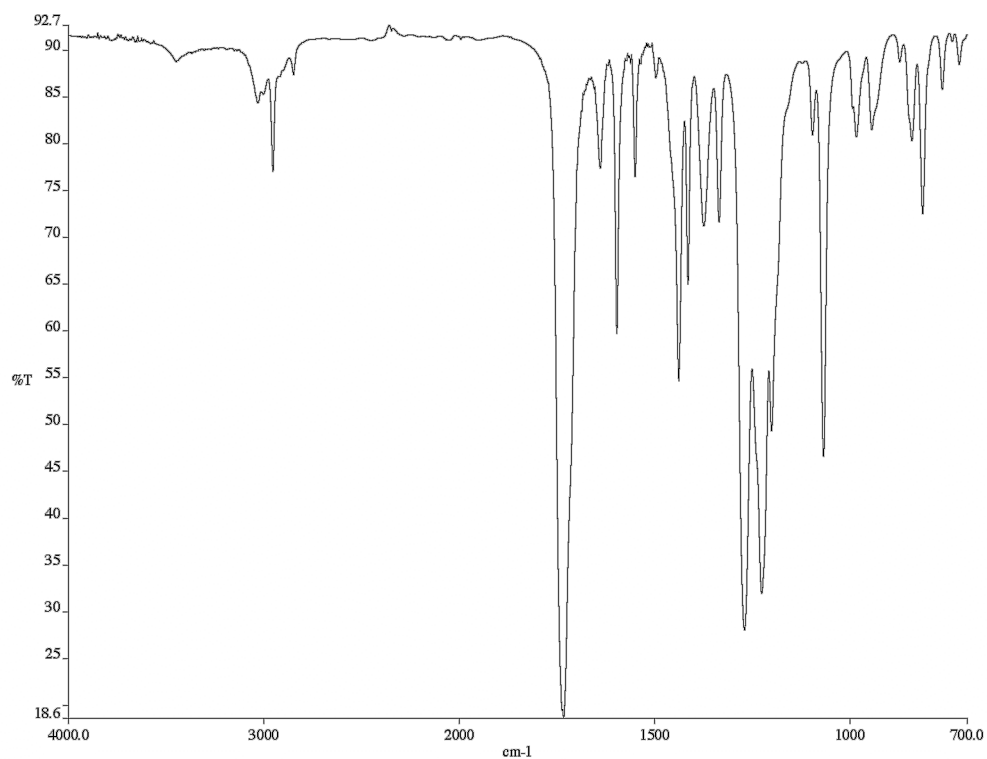


Figure A2.11 Infrared spectrum (thin film/NaCl) of compound **88**

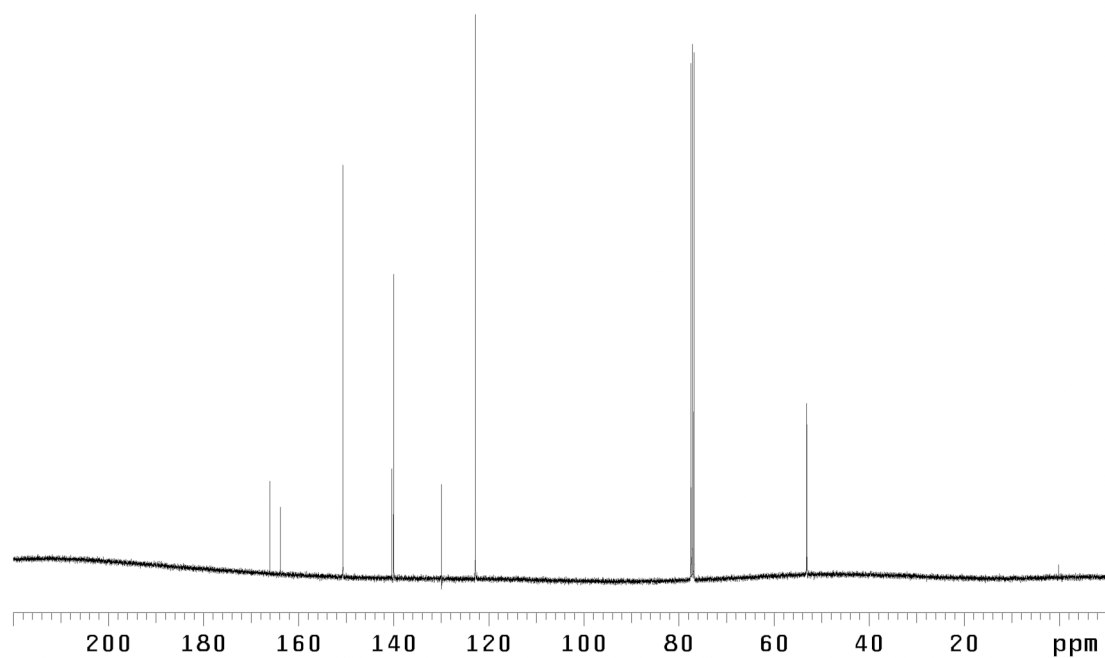


Figure A2.12 ¹³C NMR (126 MHz, CDCl₃) of compound **88**

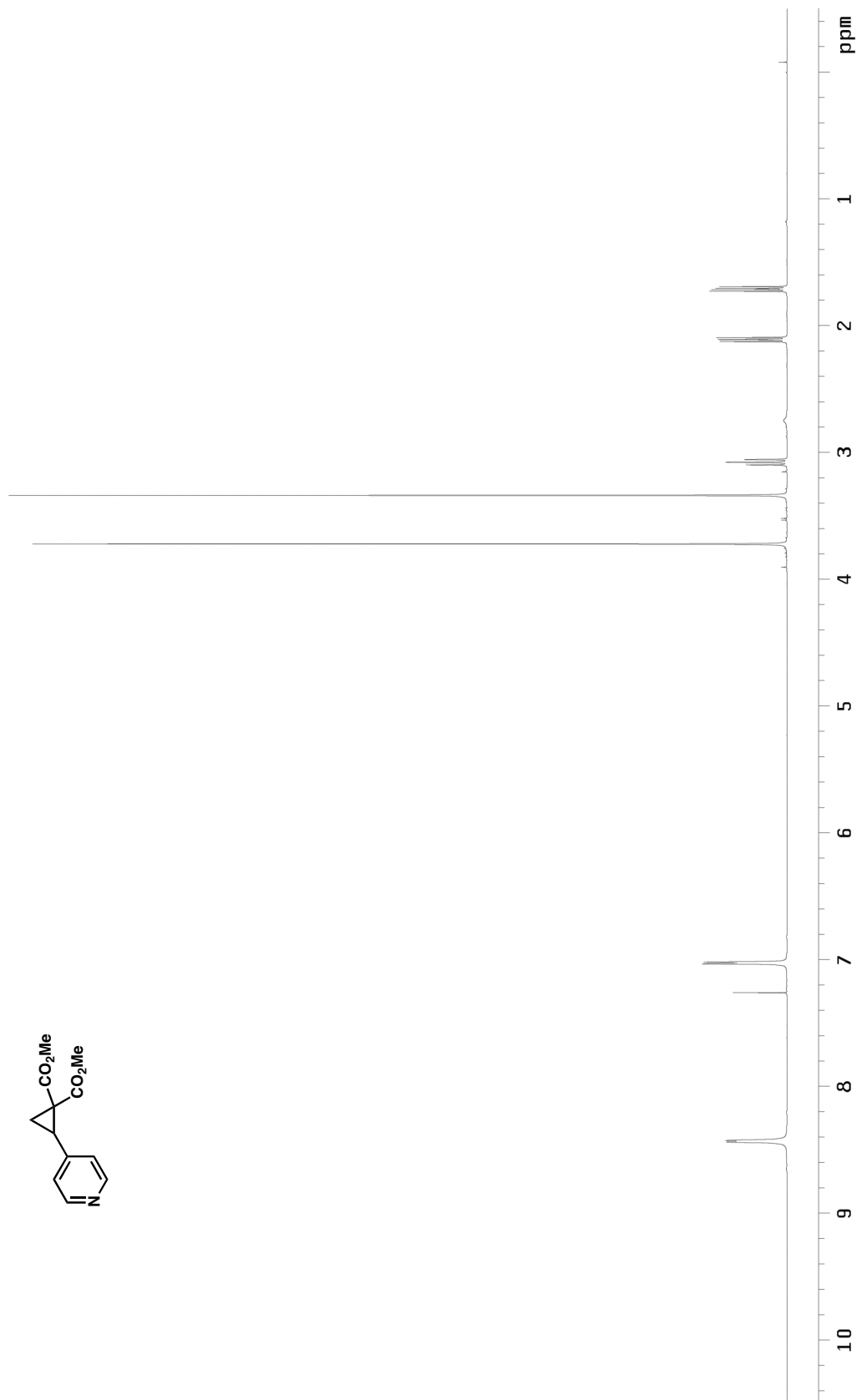


Figure A2.13 ¹H NMR (500 MHz, CDCl₃) of compound **69**

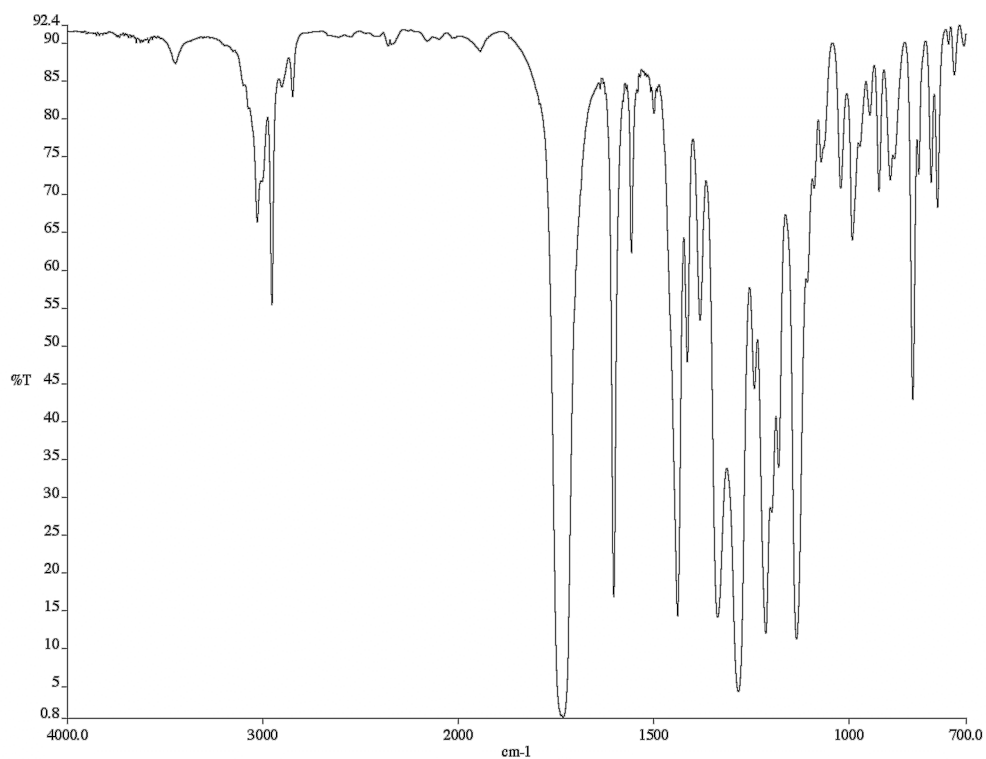


Figure A2.14 Infrared spectrum (thin film/NaCl) of compound **69**

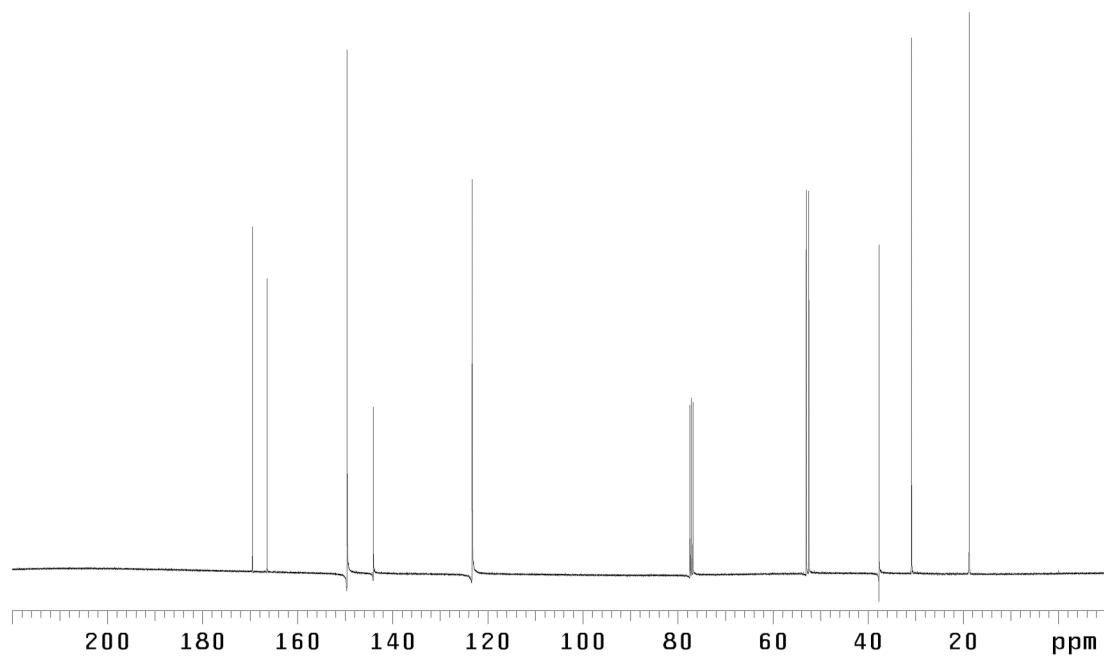


Figure A2.15 ¹³C NMR (126 MHz, CDCl₃) of compound **69**

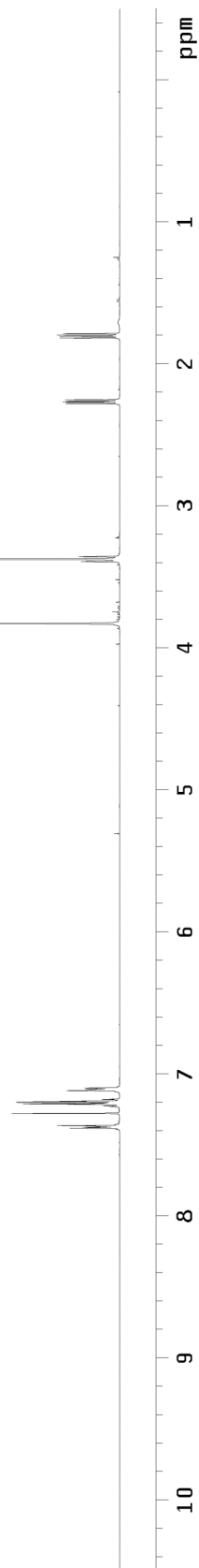
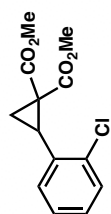


Figure A2.16 ^1H NMR (500 MHz, CDCl_3) of compound **92**

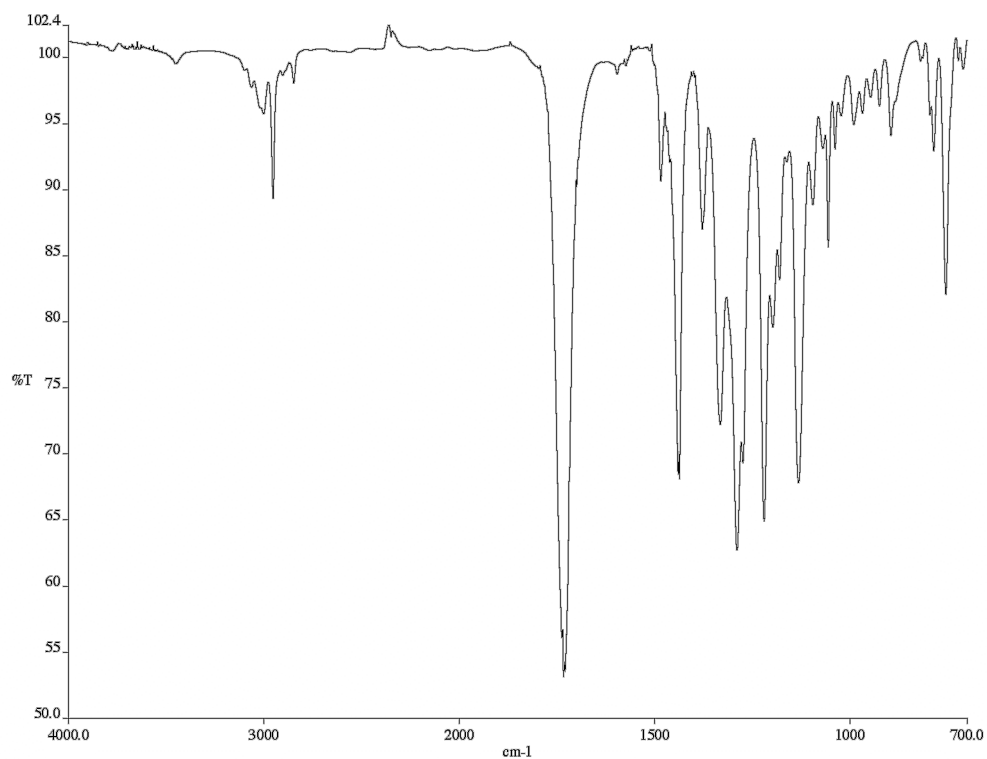


Figure A2.17 Infrared spectrum (thin film/NaCl) of compound **92**

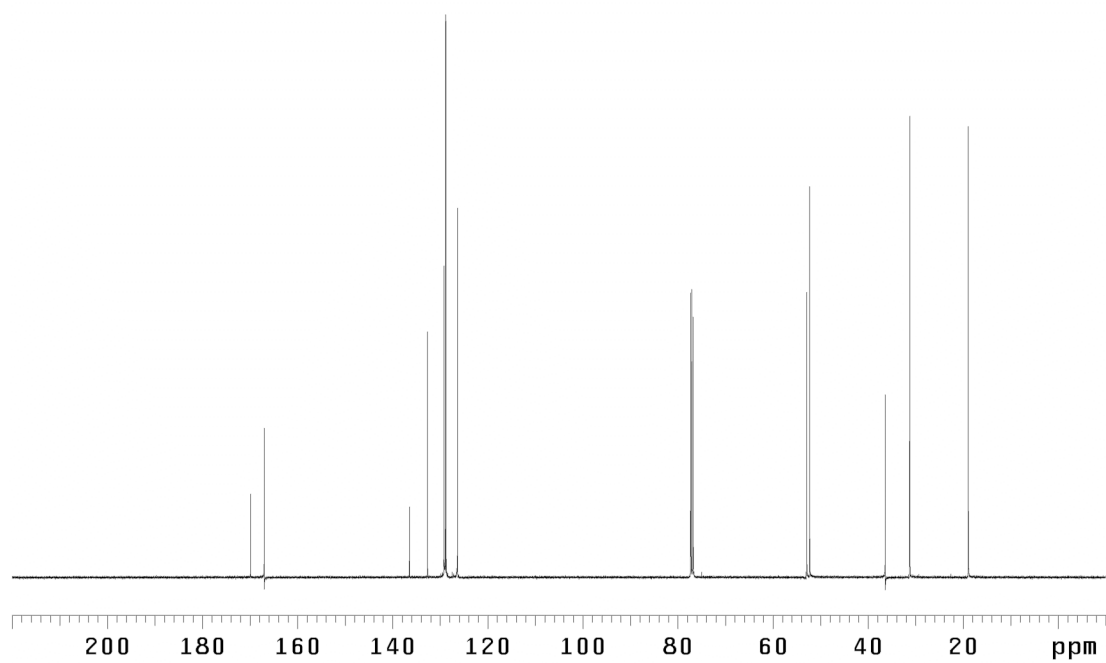


Figure A2.18 ¹³C NMR (126 MHz, CDCl₃) of compound **92**

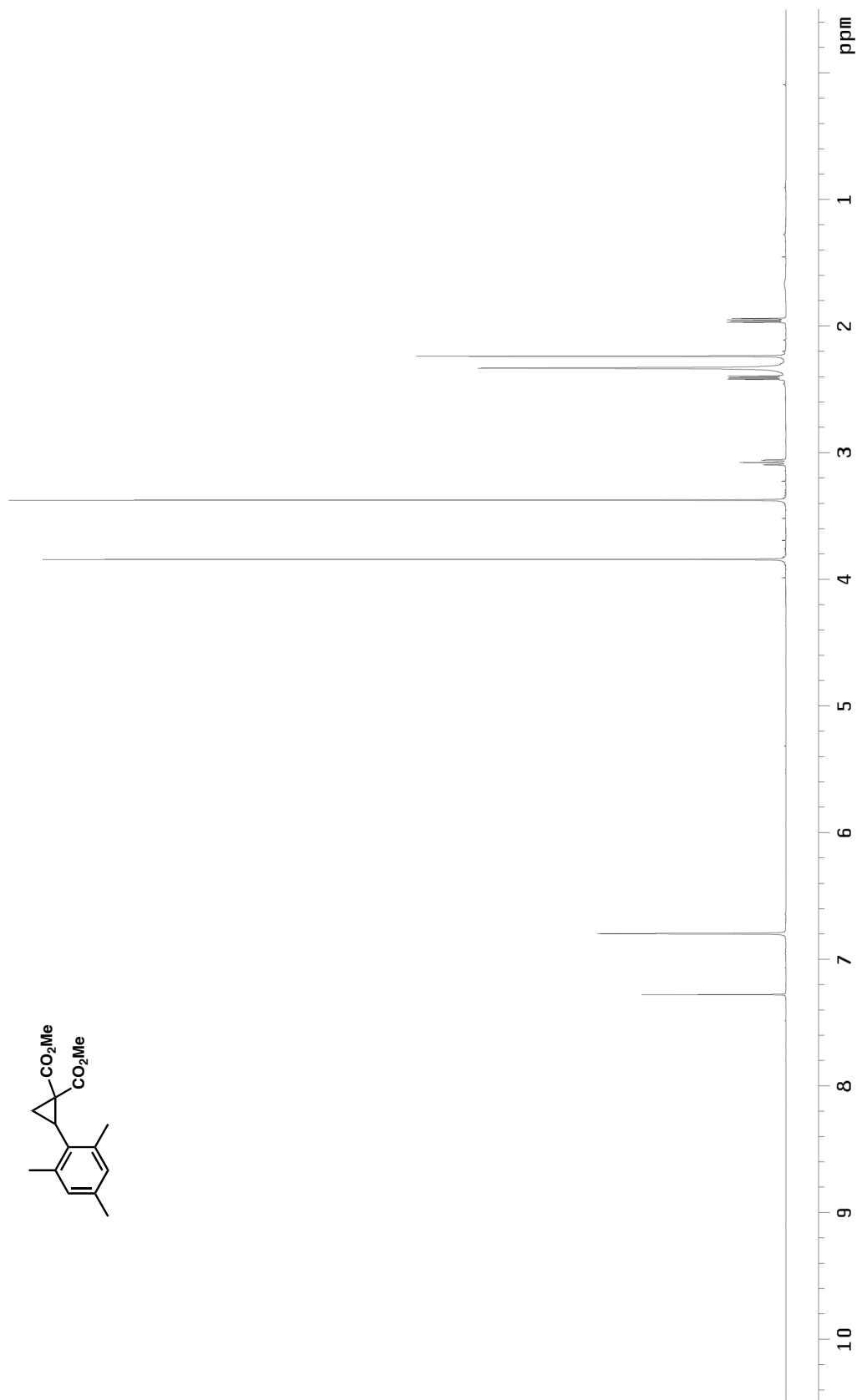


Figure A2.19. ^1H NMR (500 MHz, CDCl_3) of compound **93**

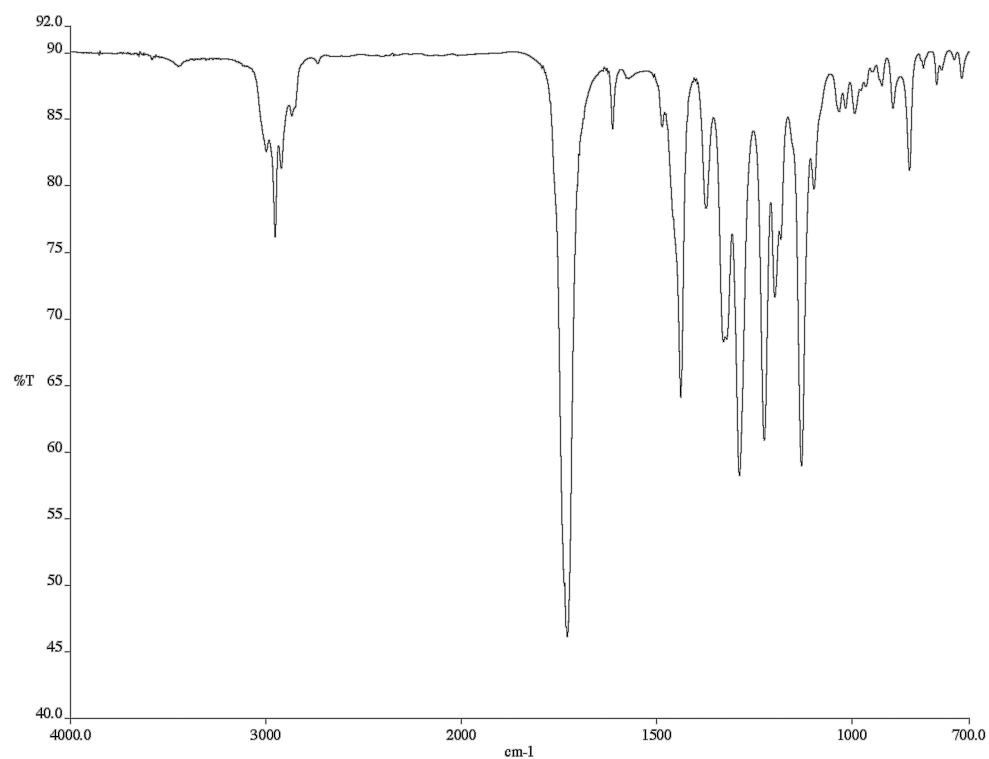


Figure A2.20 Infrared spectrum (thin film/NaCl) of compound **93**

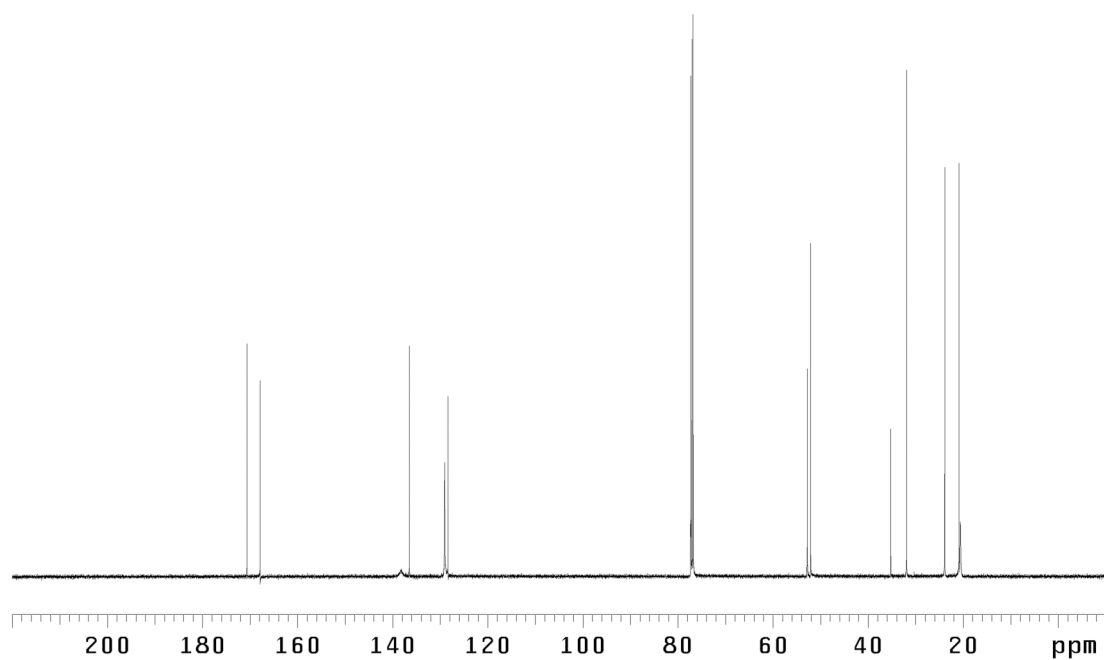


Figure A2.21 ¹³C NMR (126 MHz, CDCl₃) of compound **93**

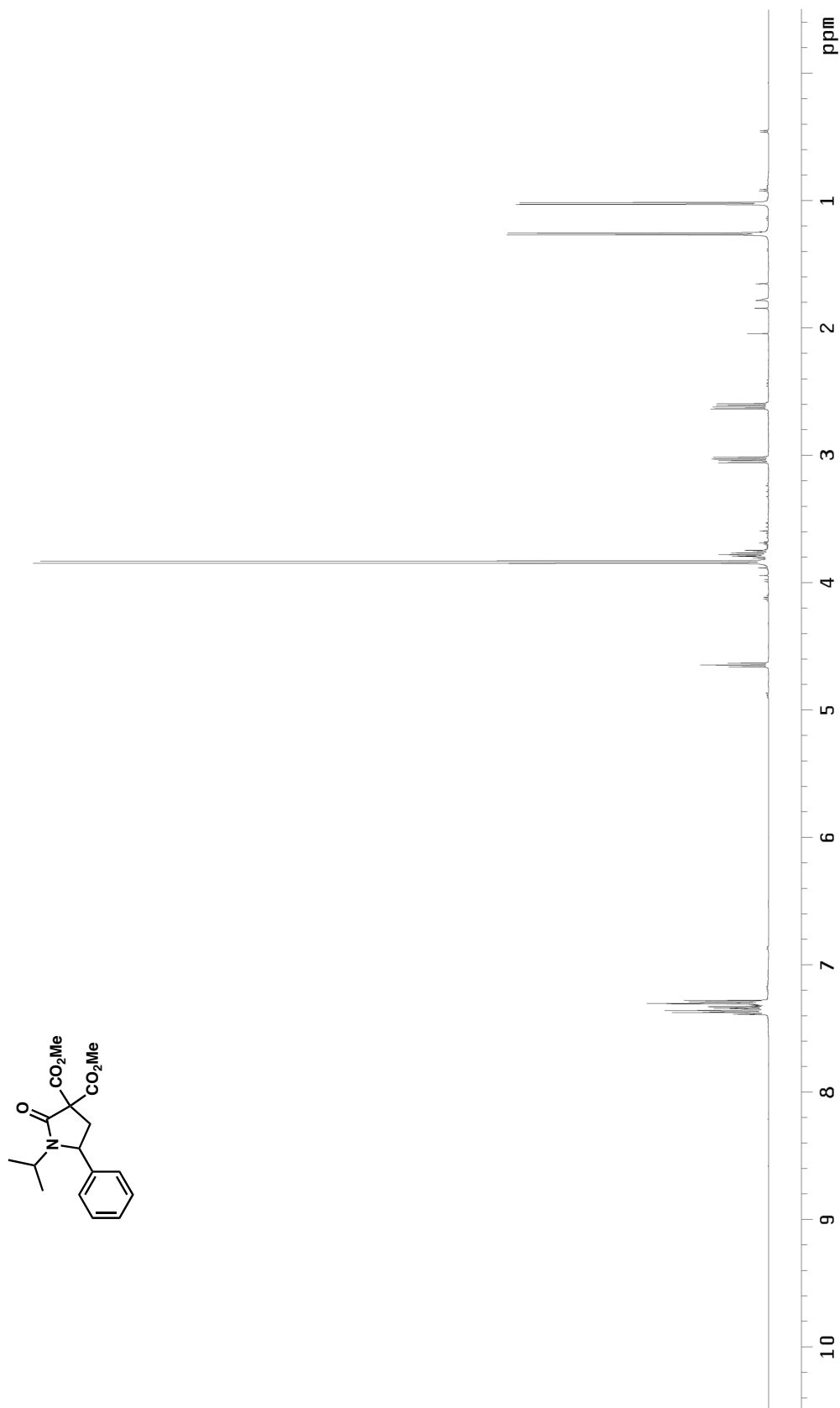


Figure A2.22 ¹H NMR (500 MHz, CDCl₃) of compound **34**

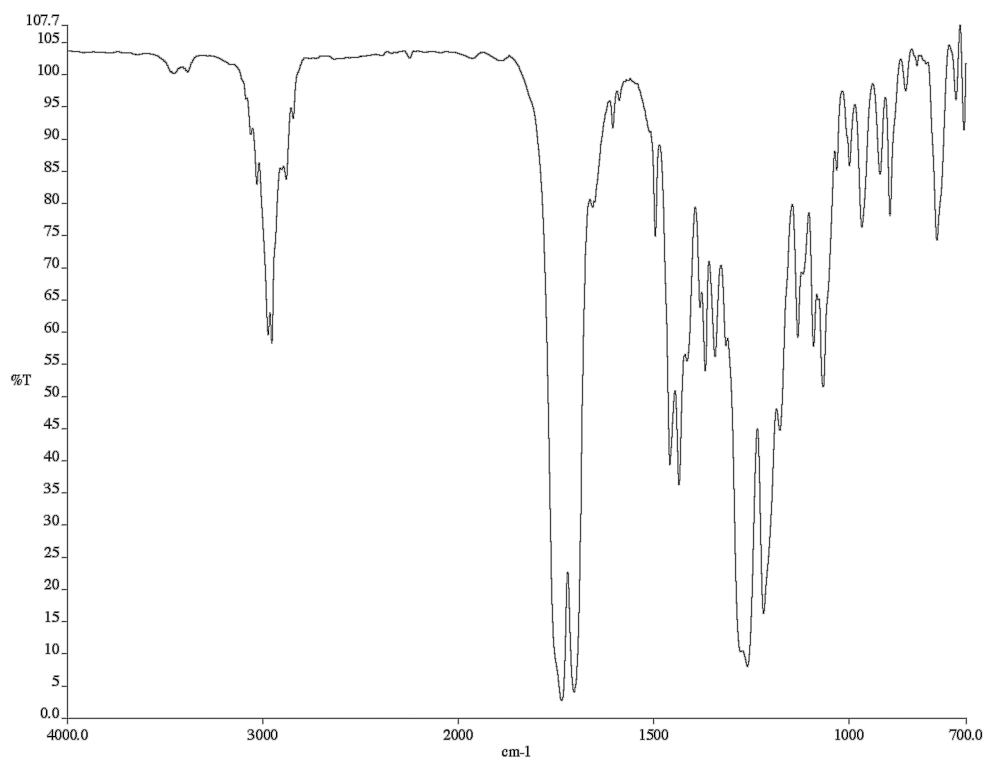


Figure A2.23 Infrared spectrum (thin film/NaCl) of compound **34**

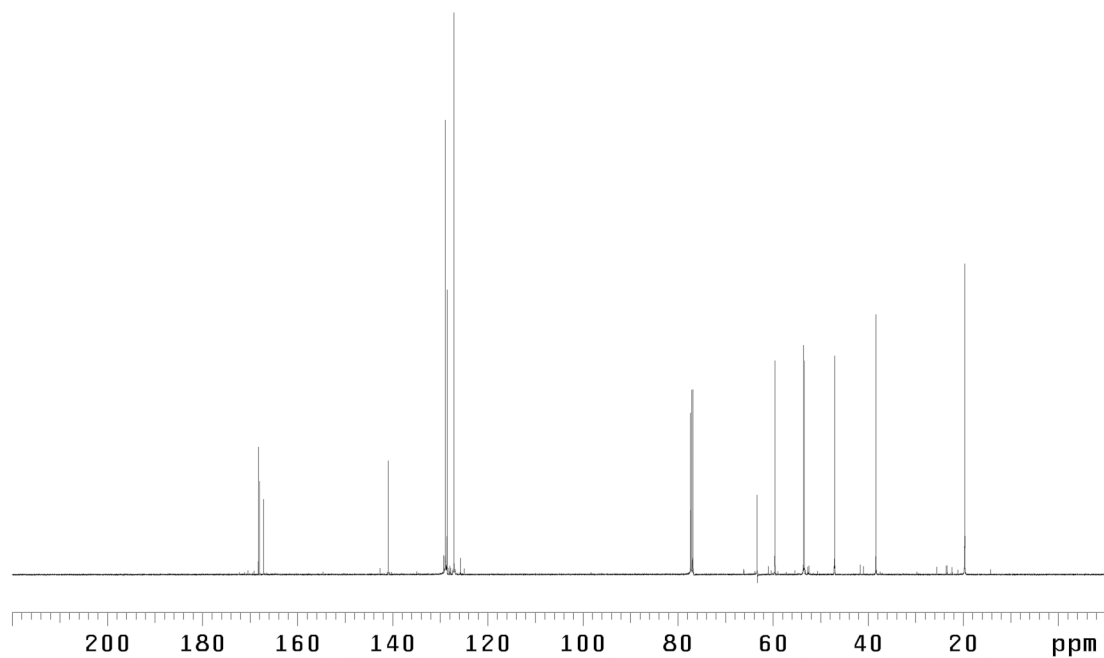


Figure A2.24 ¹³C NMR (126 MHz, CDCl₃) of compound **34**

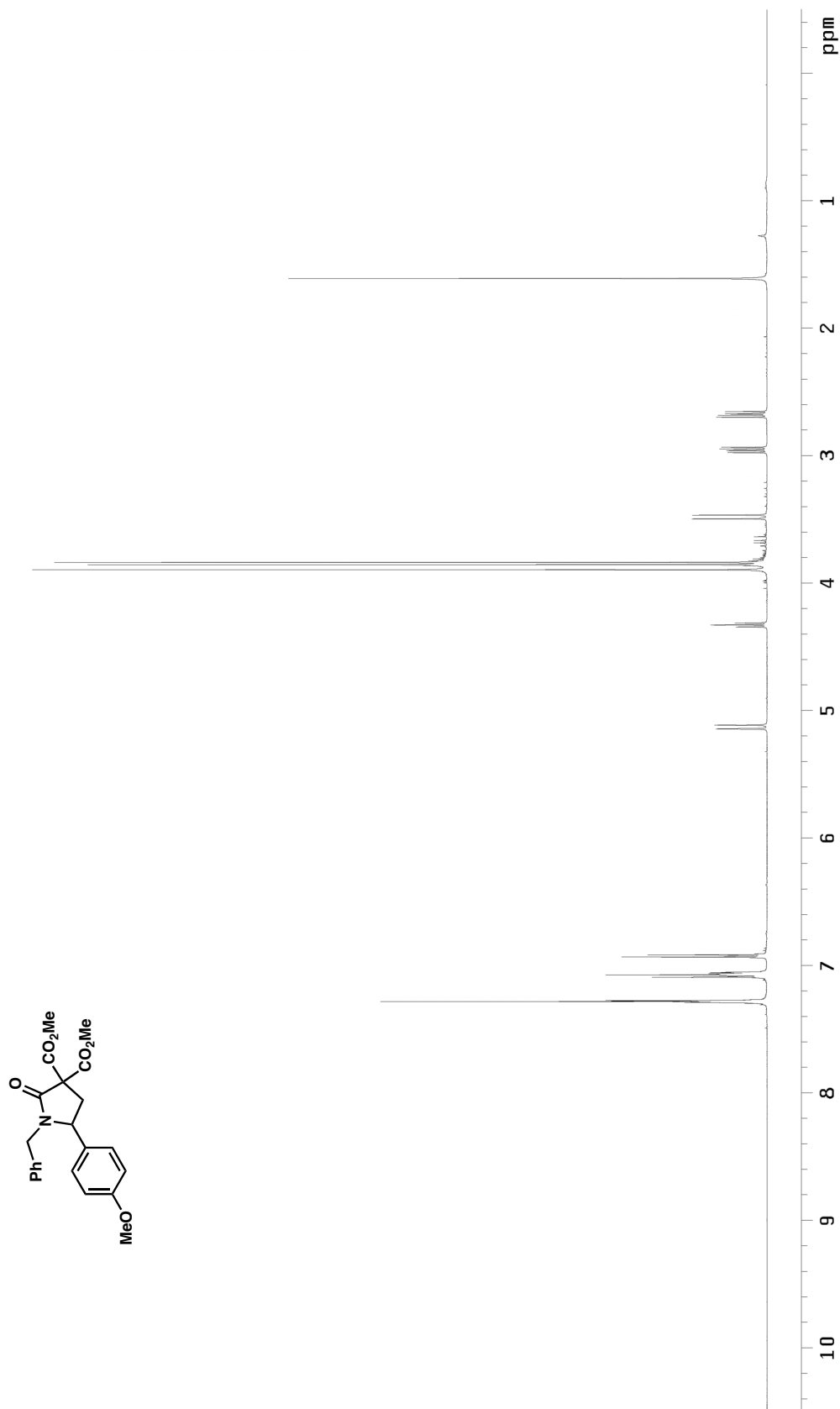


Figure A2.25 ¹H NMR (500 MHz, CDCl₃) of compound **35**

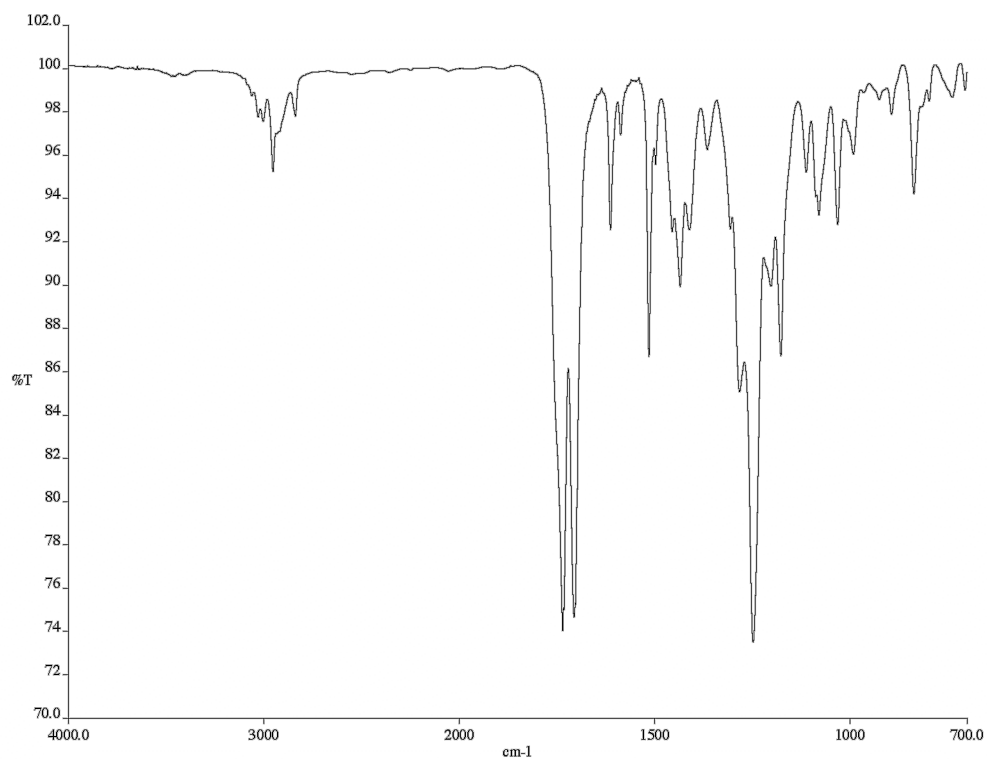


Figure A2.26 Infrared spectrum (thin film/NaCl) of compound **35**

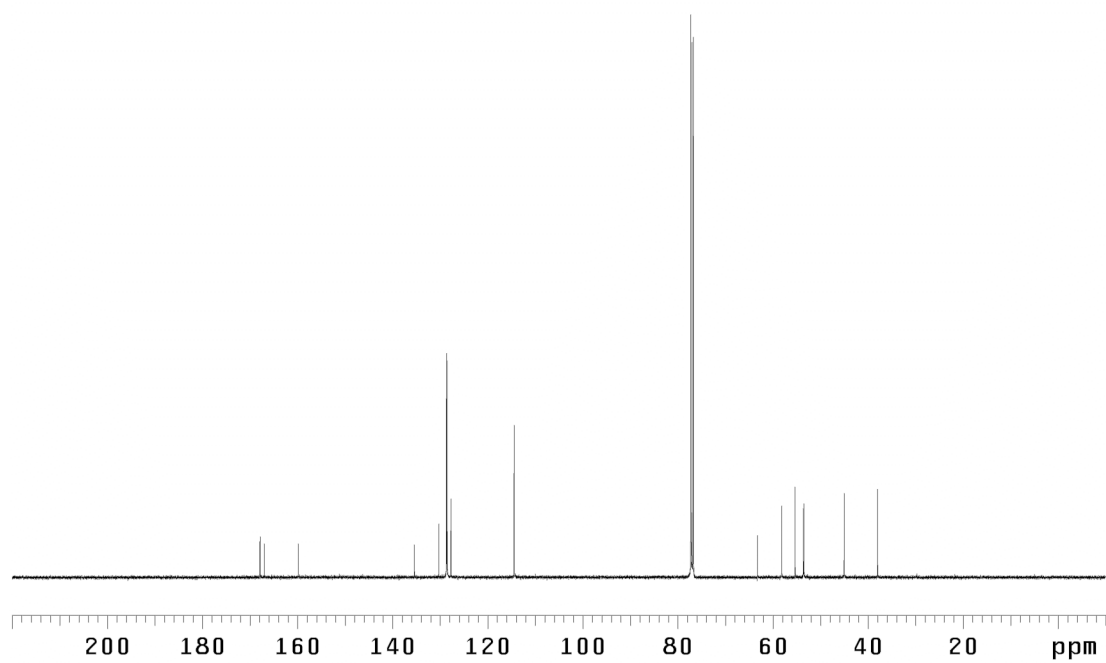


Figure A2.27 ¹³C NMR (126 MHz, CDCl₃) of compound **35**

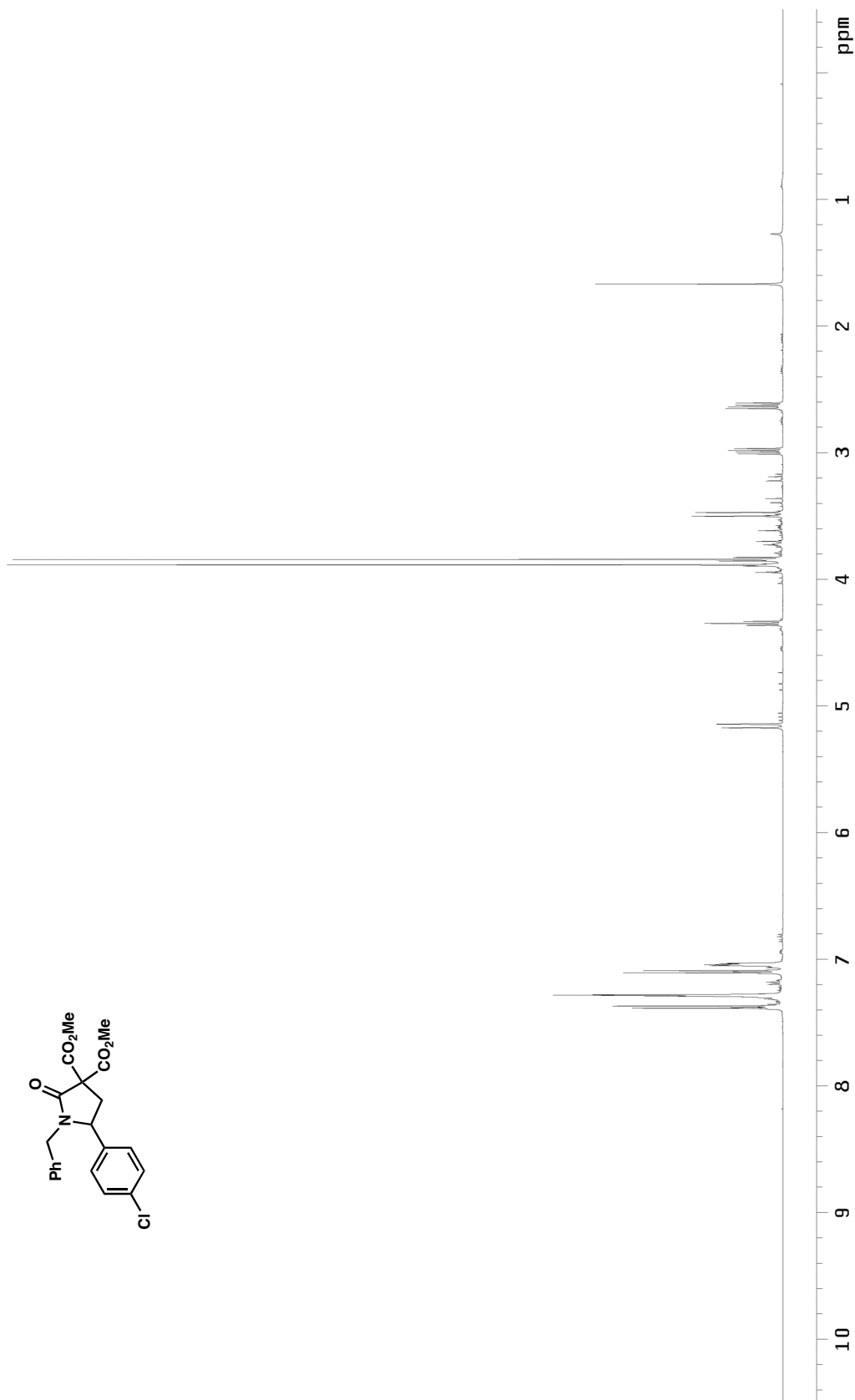


Figure A2.28 ¹H NMR (500 MHz, CDCl₃) of compound **36**

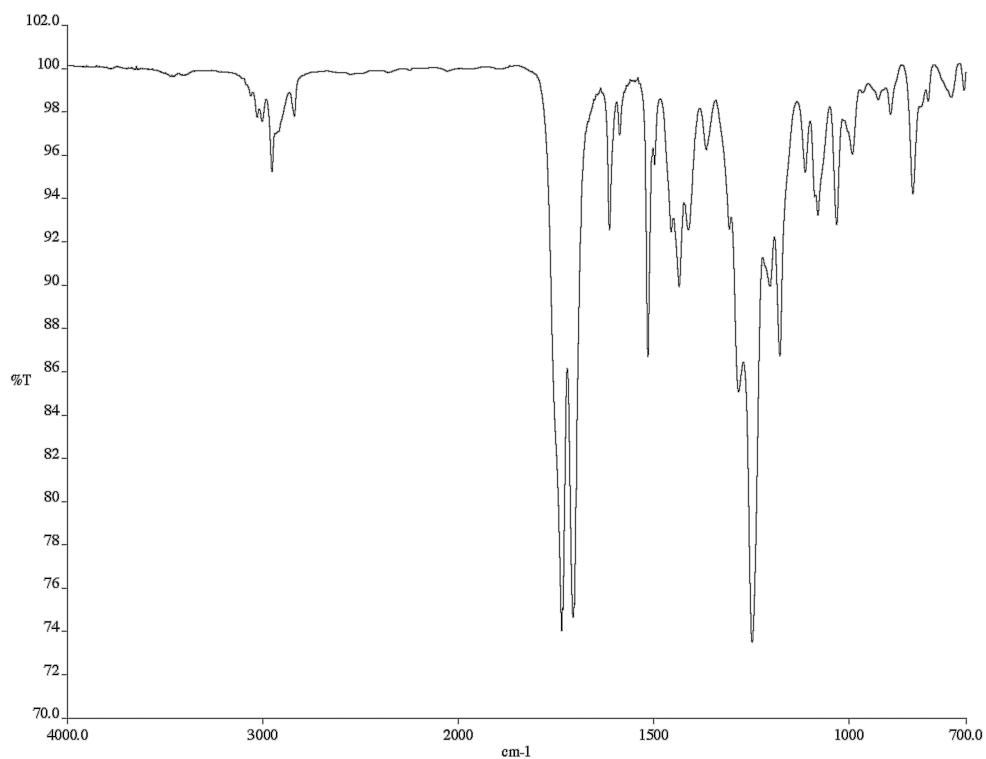


Figure A2.29 Infrared spectrum (thin film/NaCl) of compound **36**

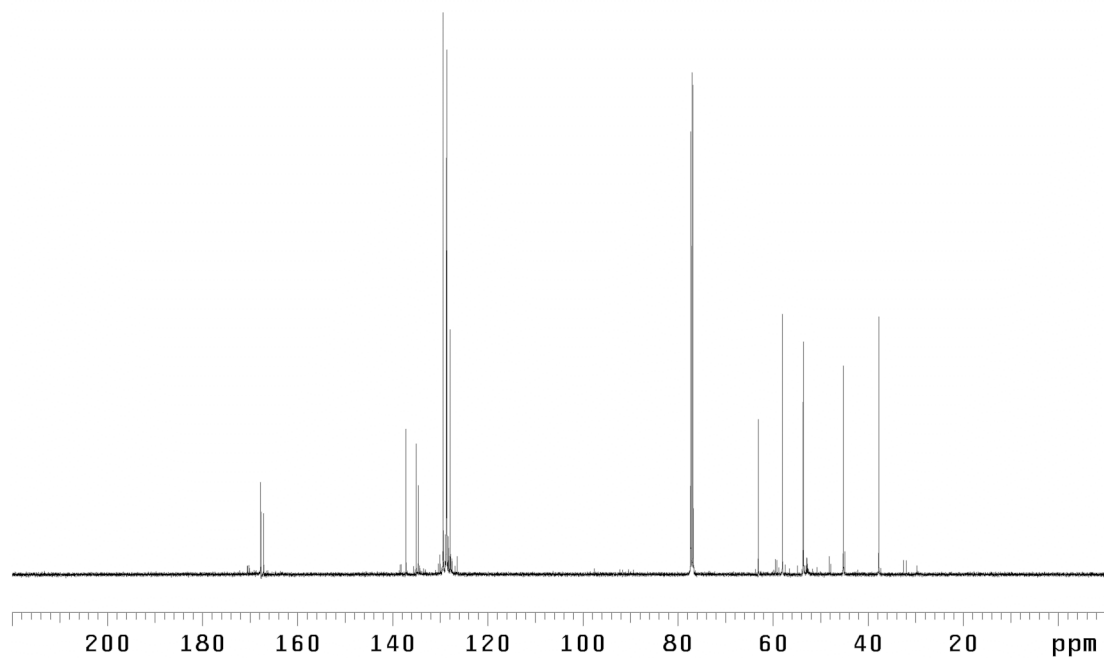


Figure A2.30 ¹³C NMR (126 MHz, CDCl₃) of compound **36**

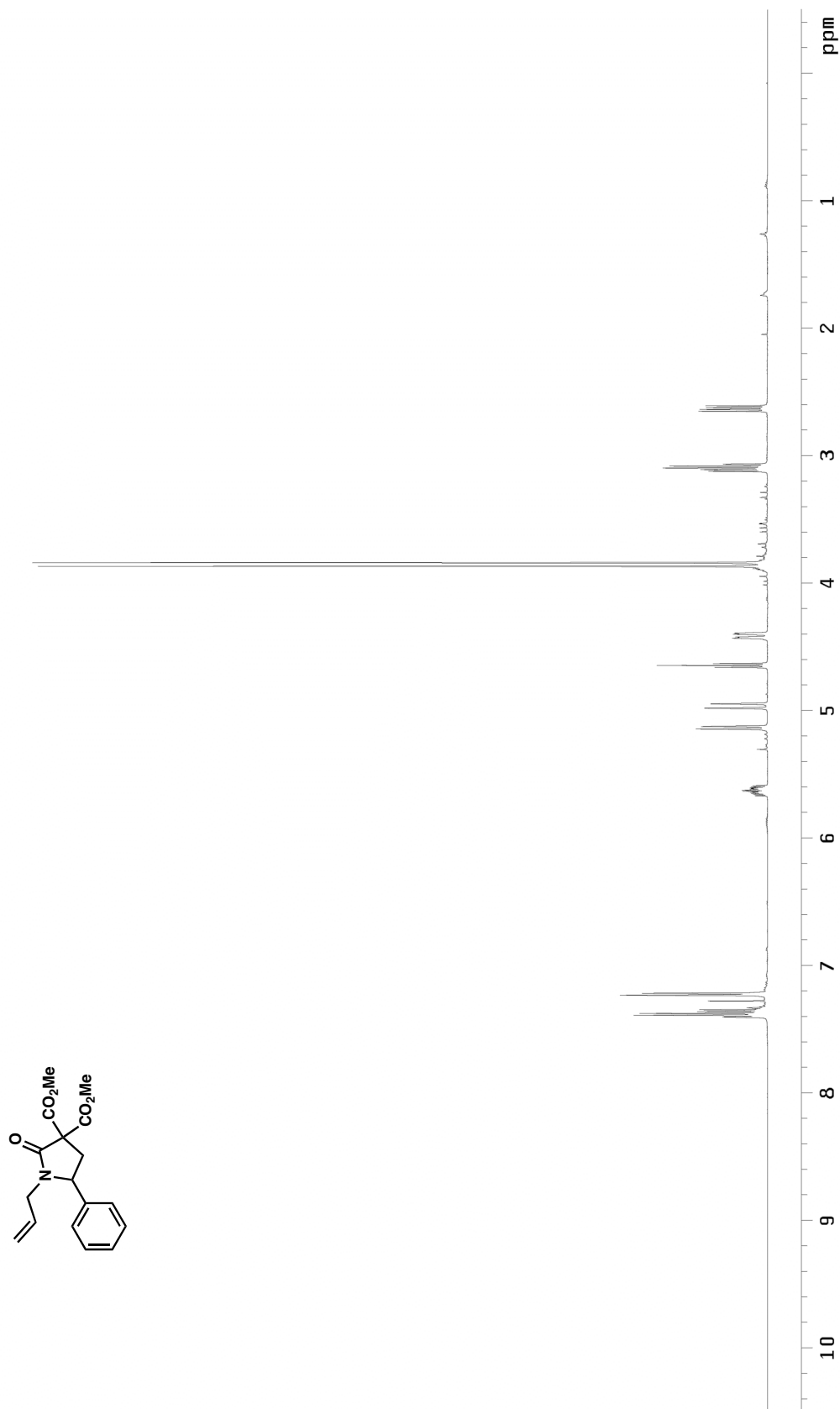


Figure A2.31 ¹H NMR (500 MHz, CDCl₃) of compound **37**

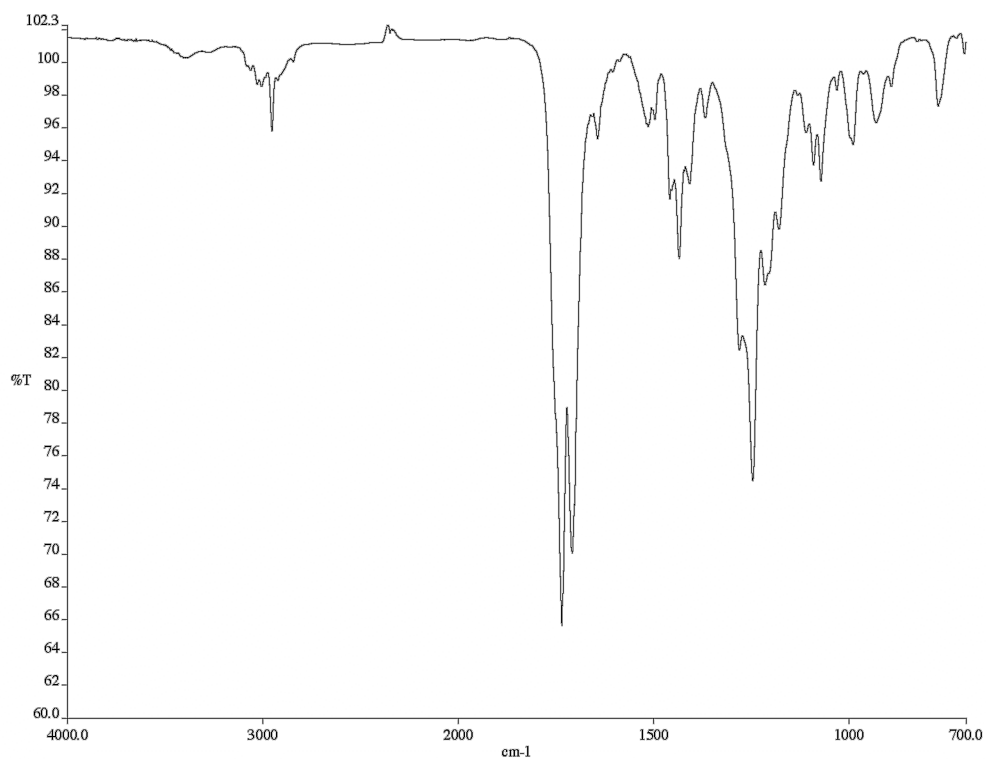


Figure A2.32 Infrared spectrum (thin film/NaCl) of compound **37**

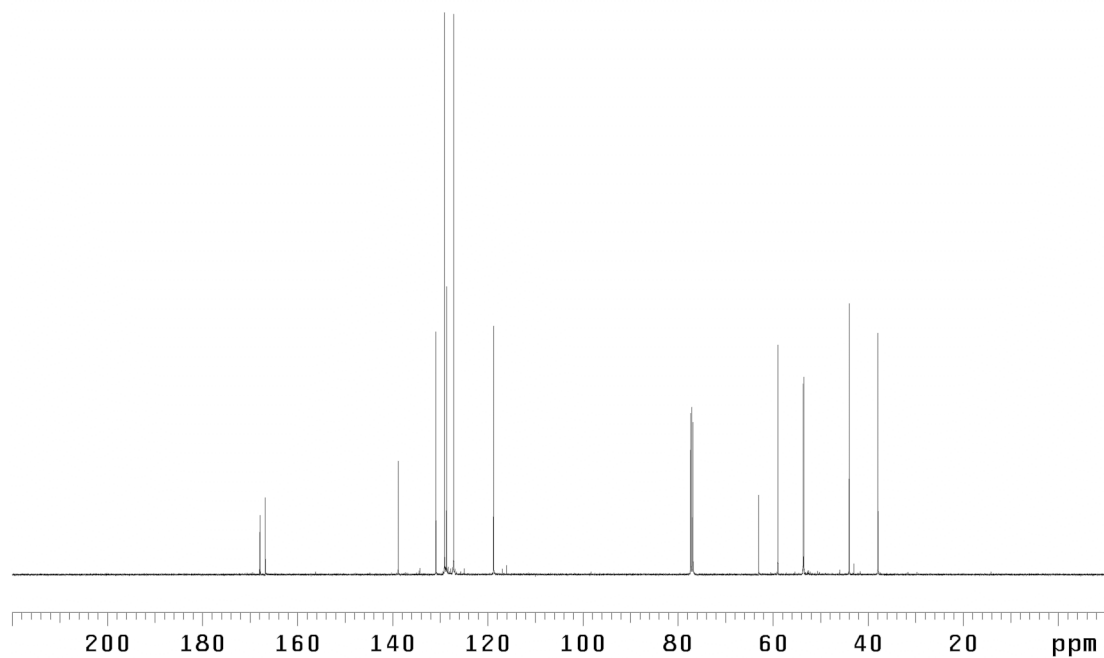


Figure A2.33 ¹³C NMR (126 MHz, CDCl₃) of compound **37**

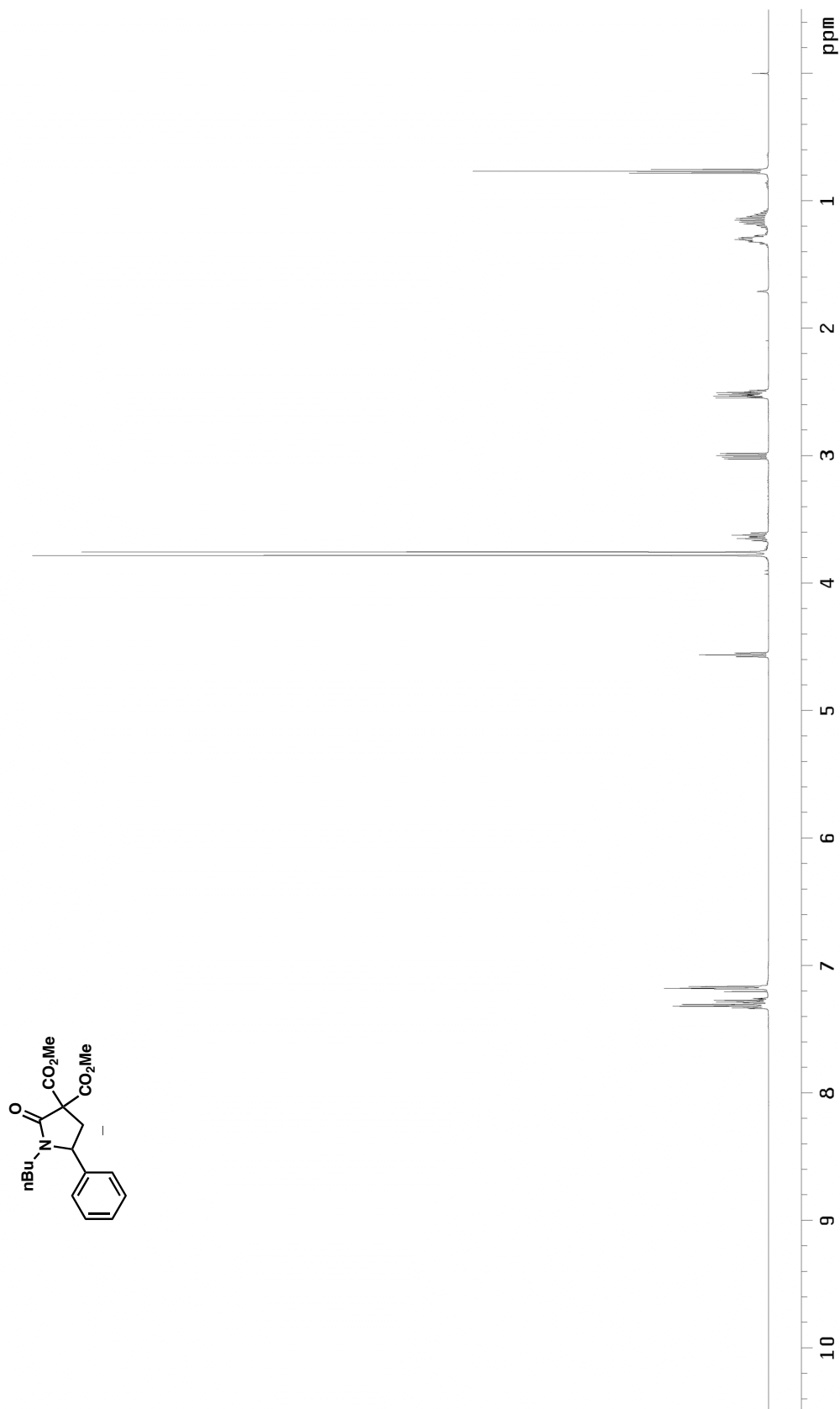


Figure A2.34 ^1H NMR (500 MHz, CDCl_3) of compound **38**

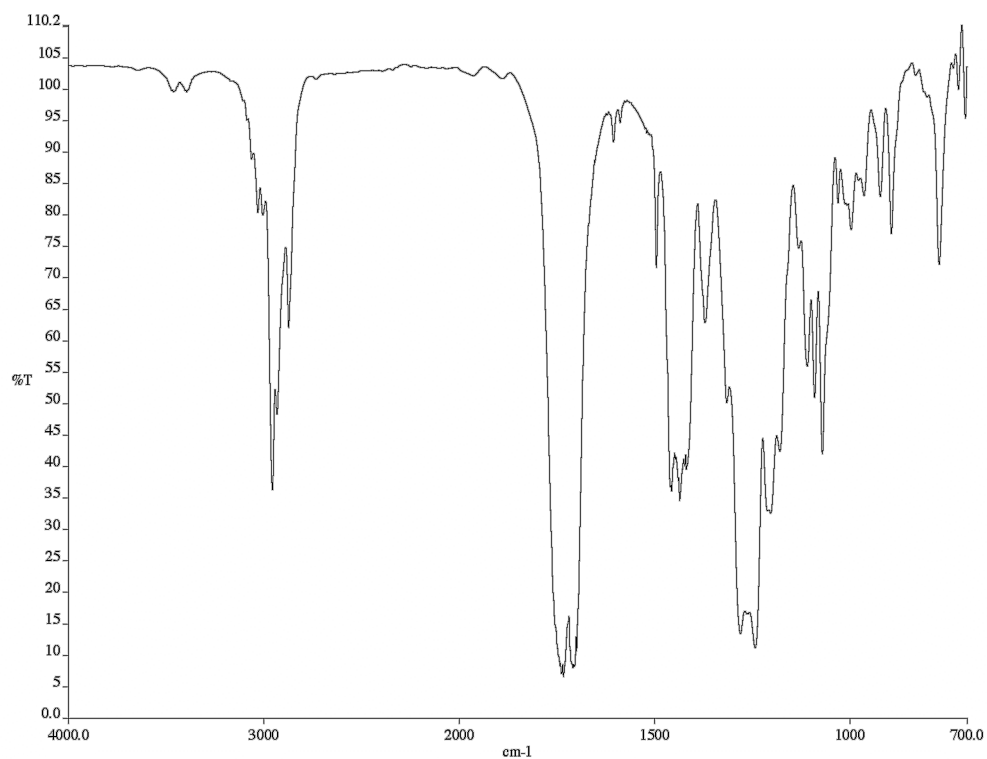


Figure A2.35 Infrared spectrum (thin film/NaCl) of compound **38**

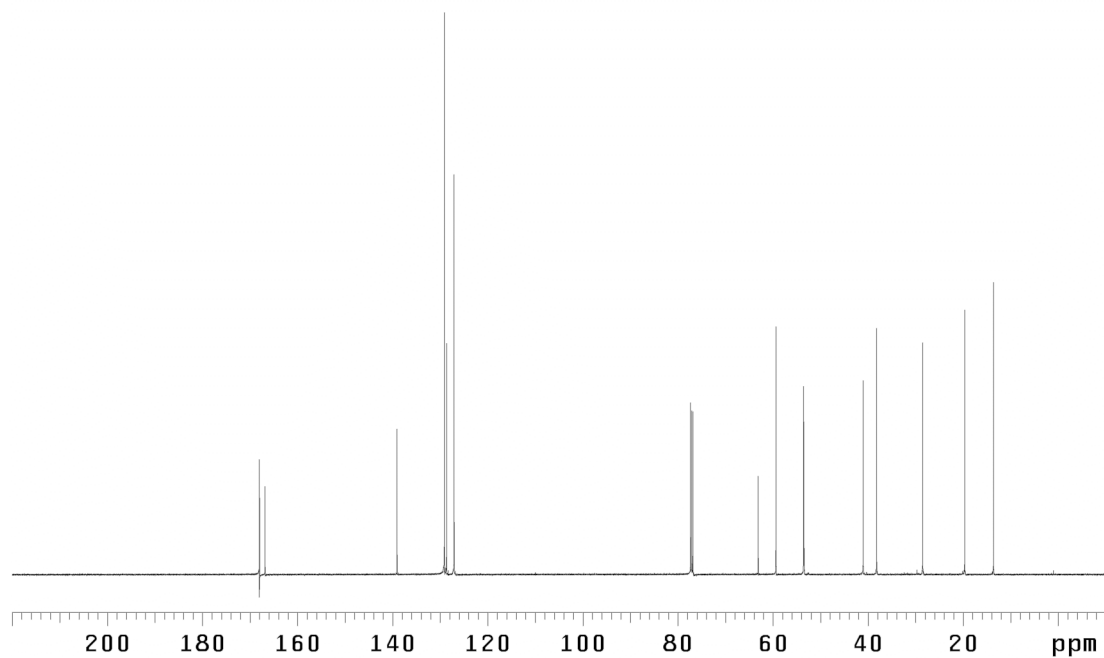


Figure A2.36 ¹³C NMR (126 MHz, CDCl₃) of compound **38**

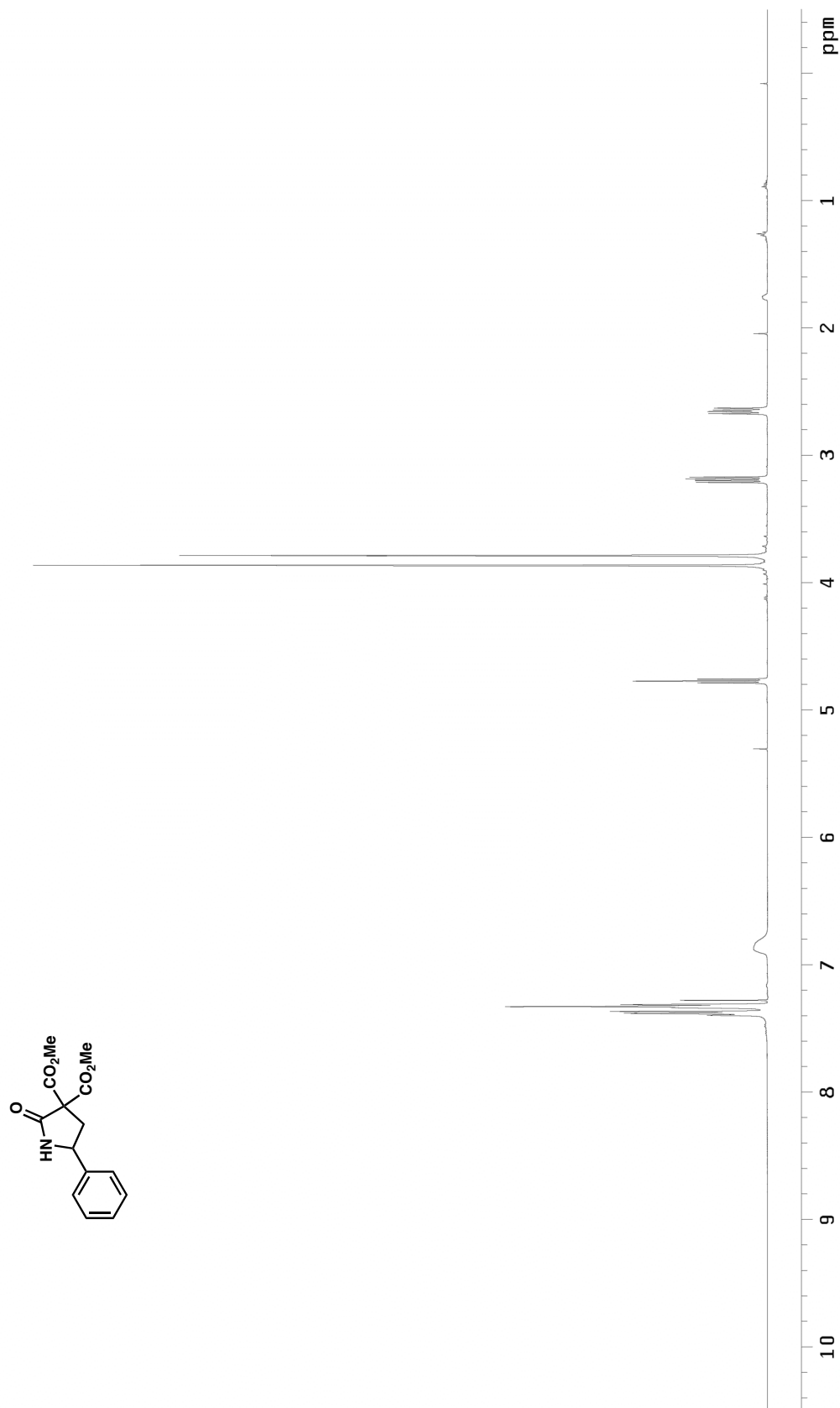


Figure A2.37 ^1H NMR (500 MHz, CDCl_3) of compound **39**

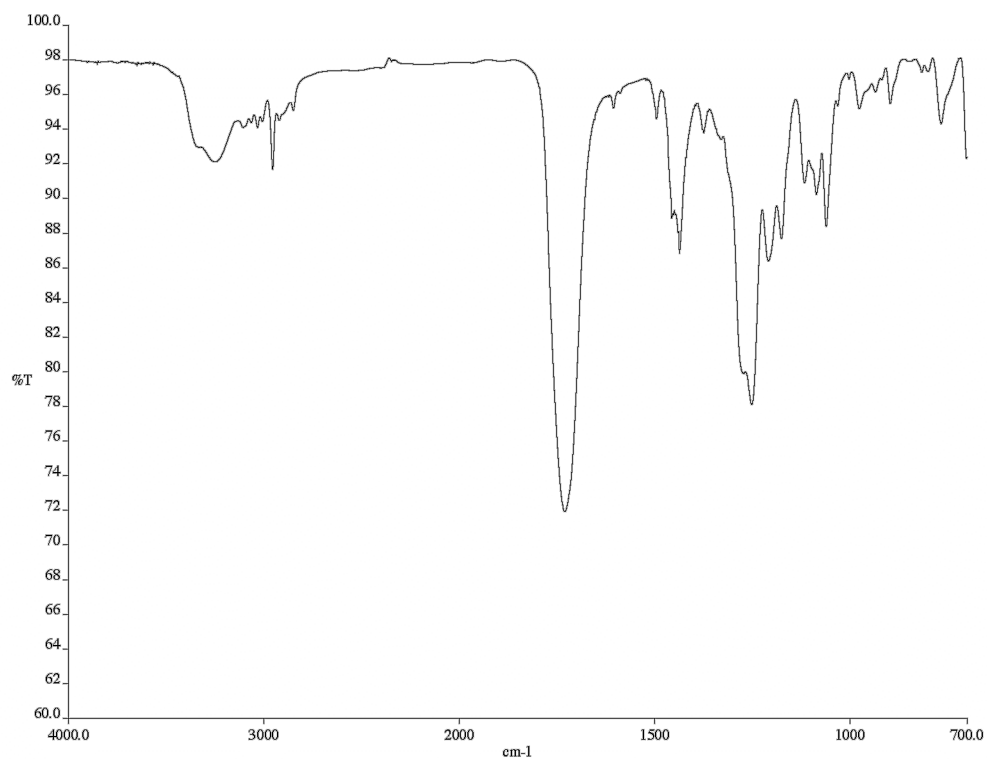


Figure A2.38 Infrared spectrum (thin film/NaCl) of compound **39**

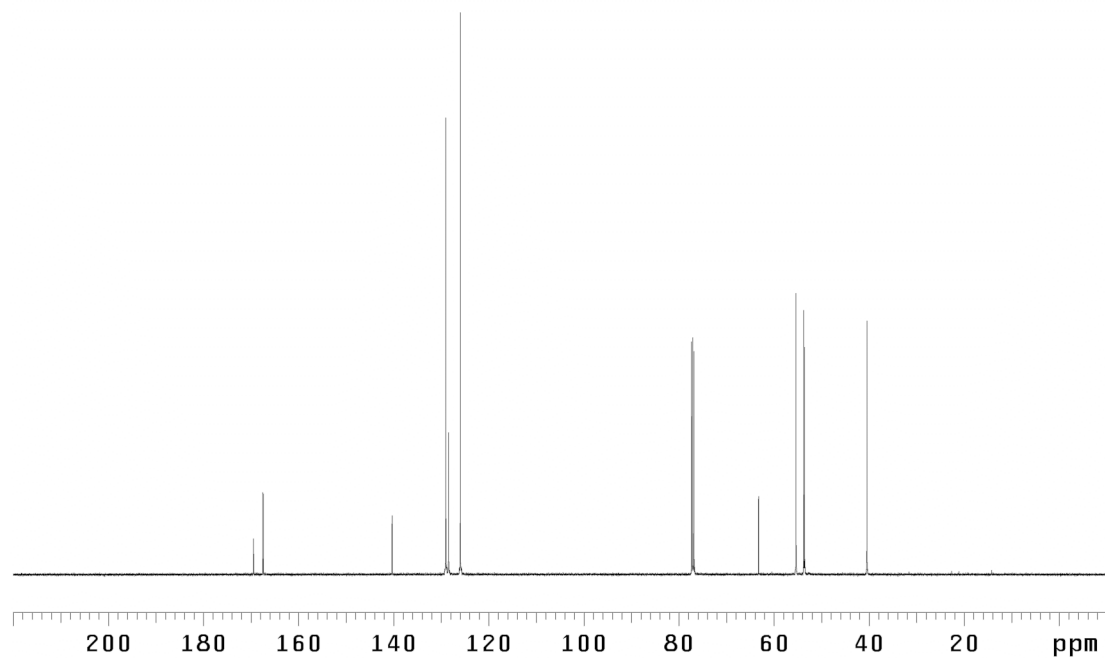


Figure A2.39 ¹³C NMR (126 MHz, CDCl₃) of compound **39**

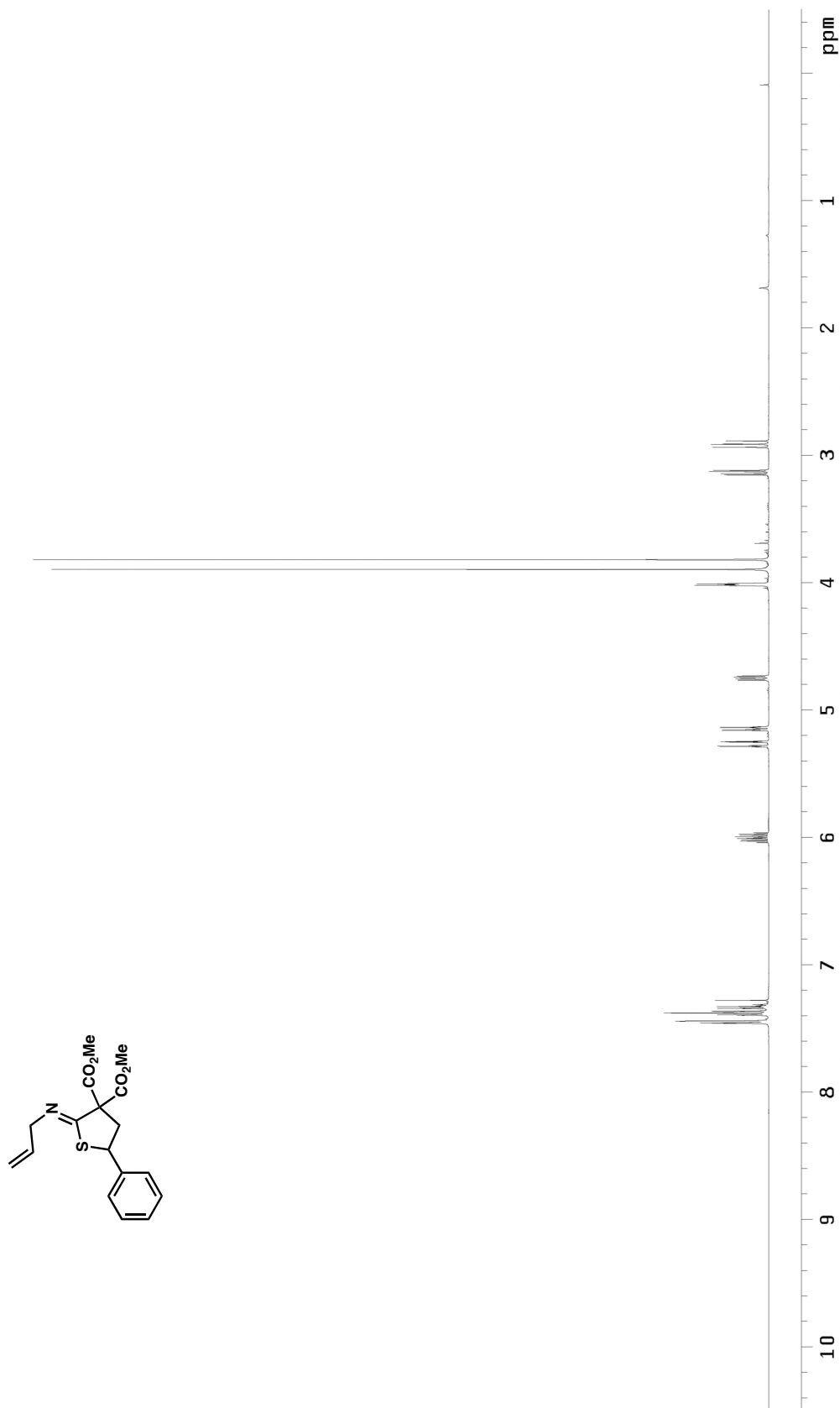


Figure A2.40 ¹H NMR (500 MHz, CDCl₃) of compound **45**

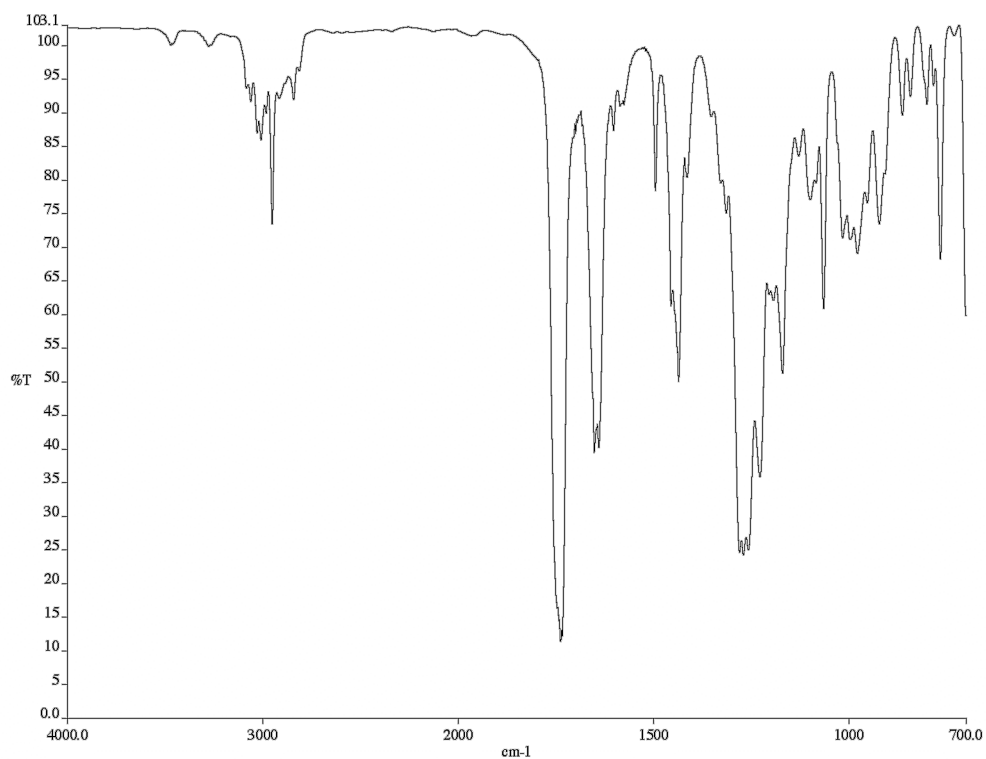


Figure A2.41 Infrared spectrum (thin film/NaCl) of compound **45**

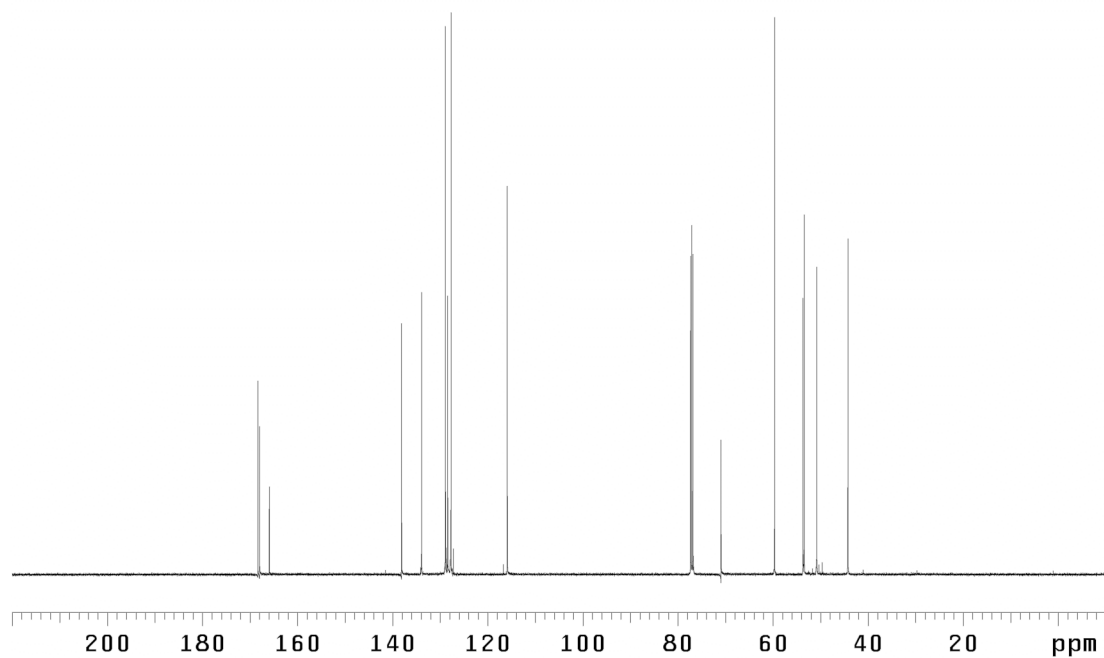


Figure A2.42 ¹³C NMR (126 MHz, CDCl₃) of compound **45**

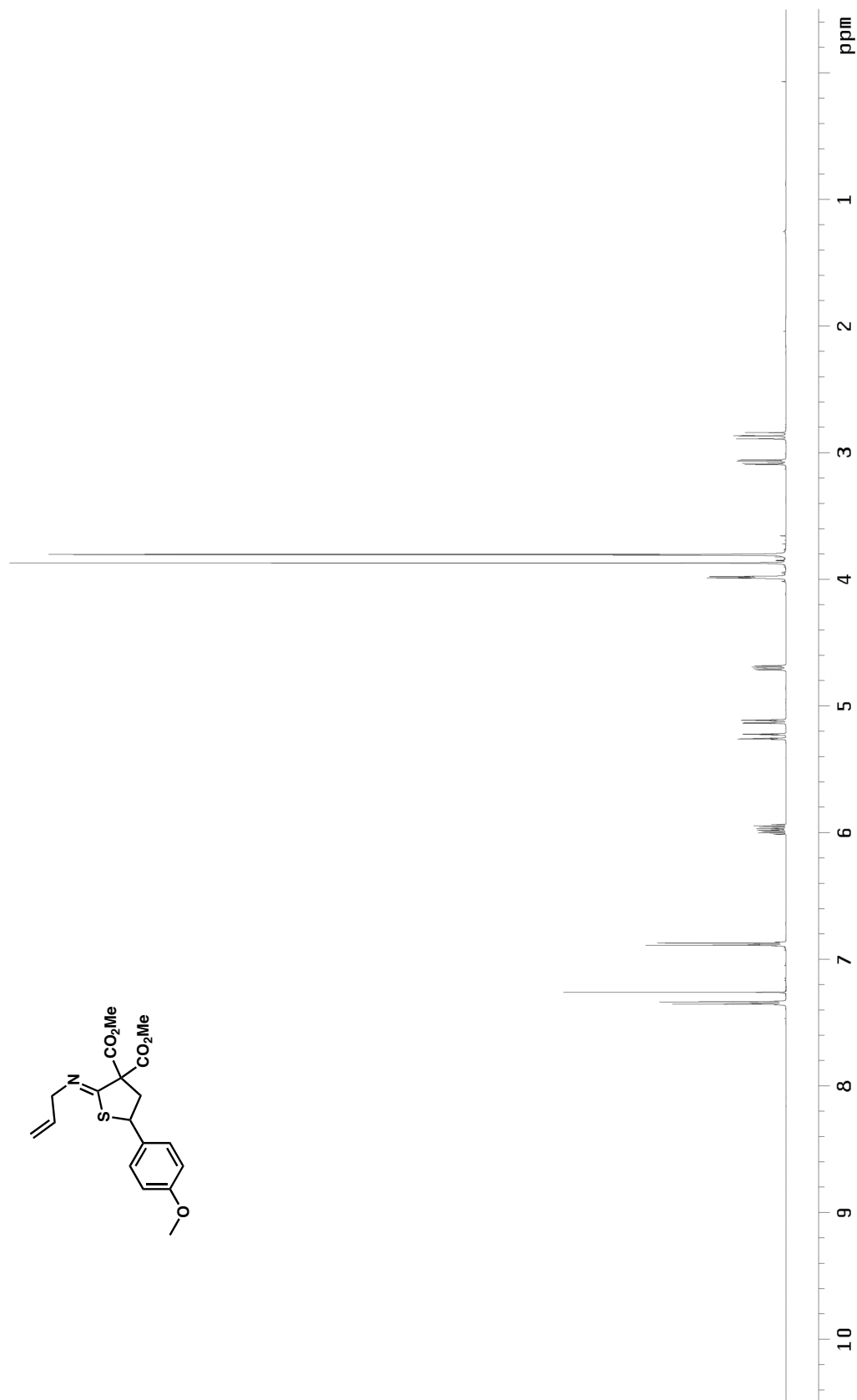


Figure A2.43 ¹H NMR (500 MHz, CDCl₃) of compound **40**

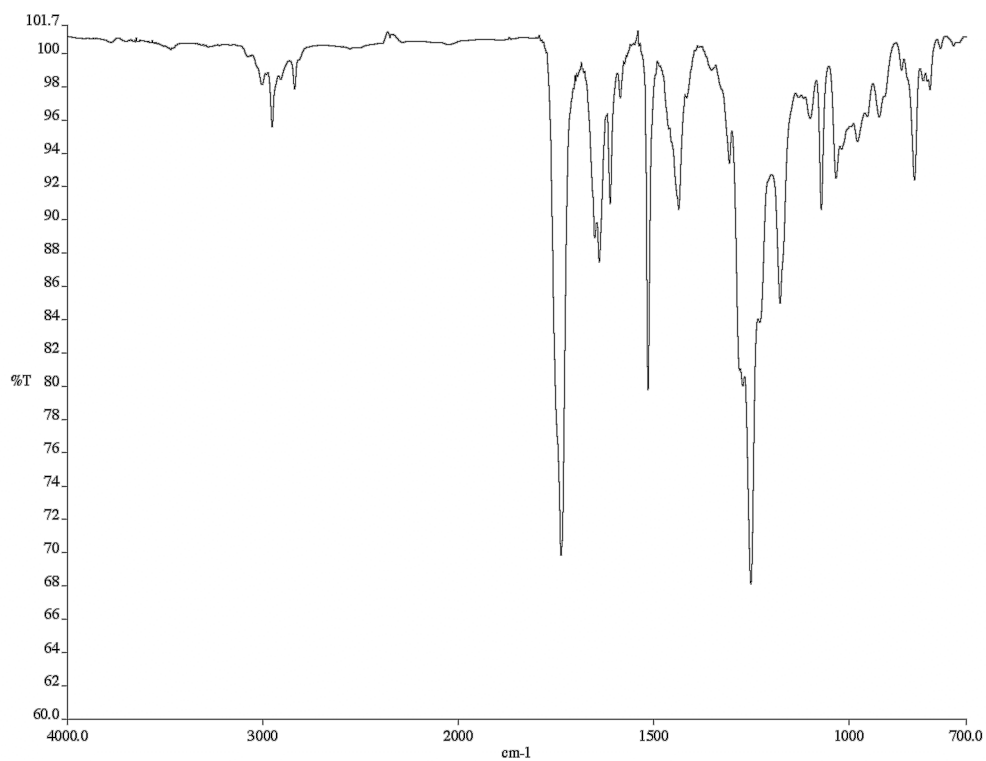


Figure A2.44 Infrared spectrum (thin film/NaCl) of compound **40**

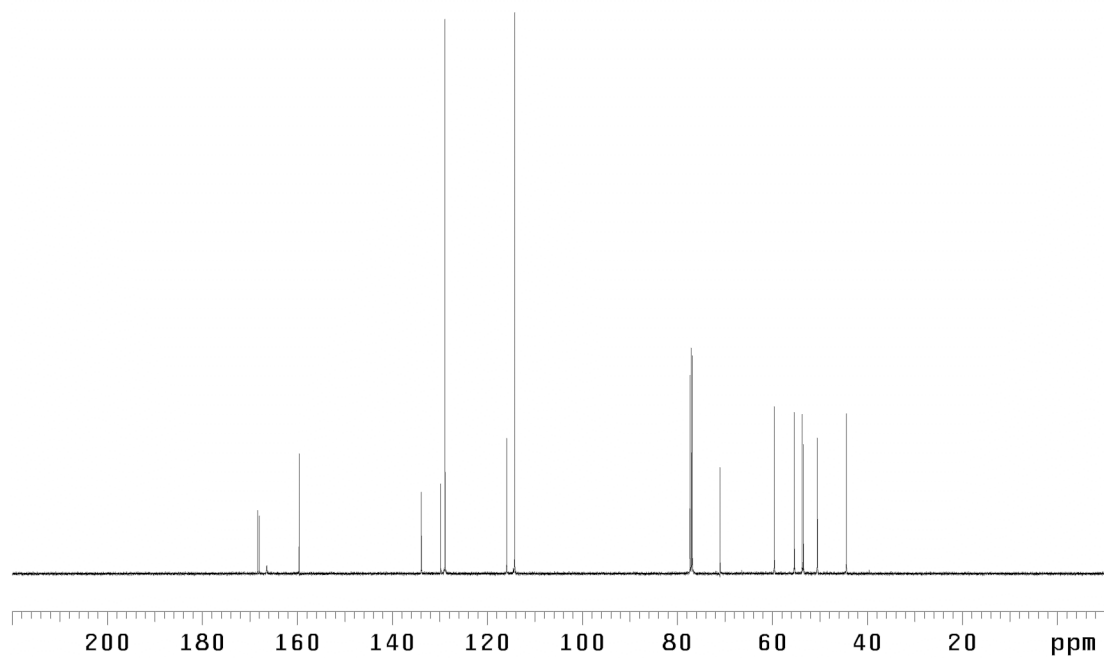


Figure A2.45 ¹³C NMR (126 MHz, CDCl₃) of compound **40**

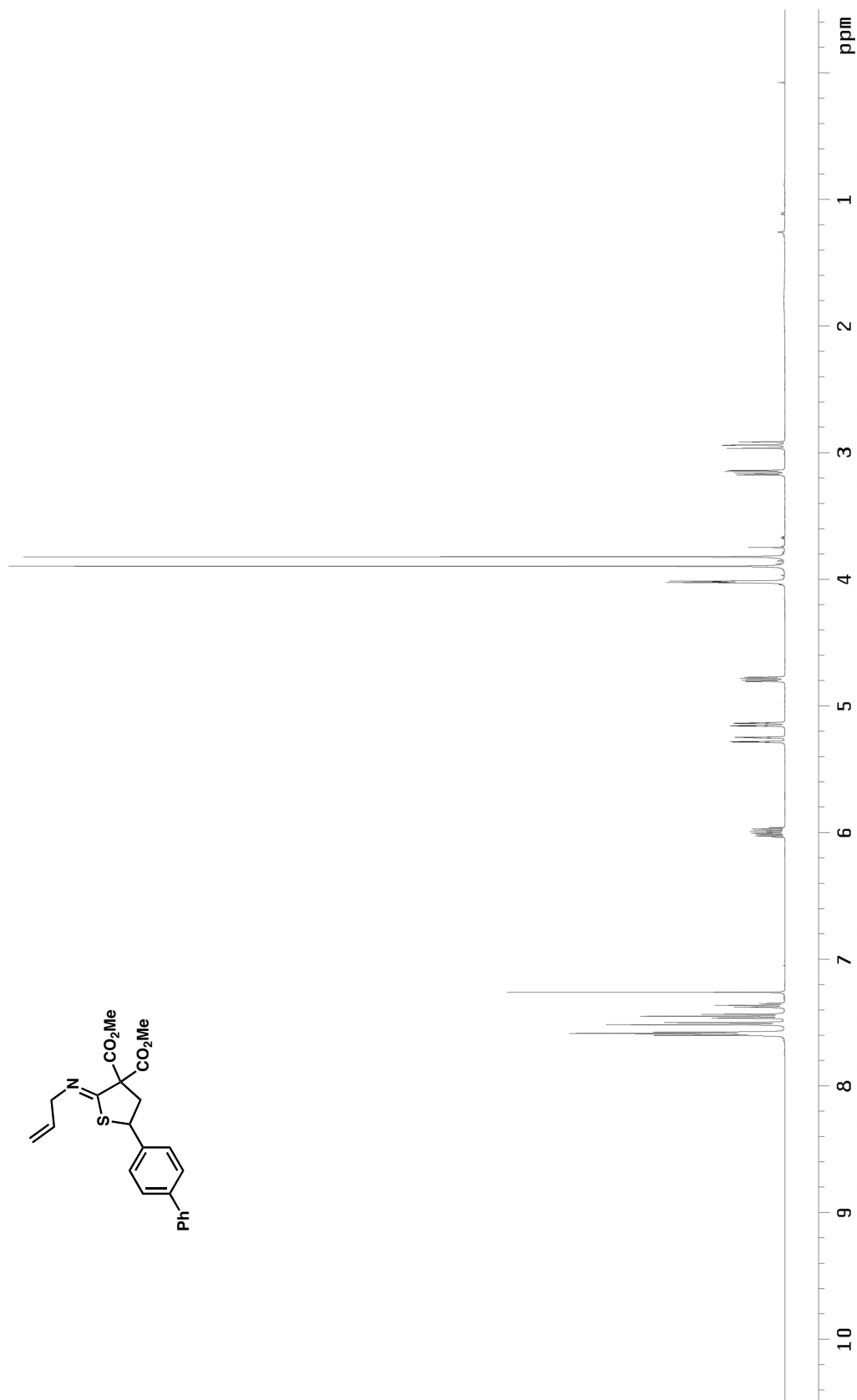


Figure A2.46 ¹H NMR (500 MHz, CDCl₃) of compound 47

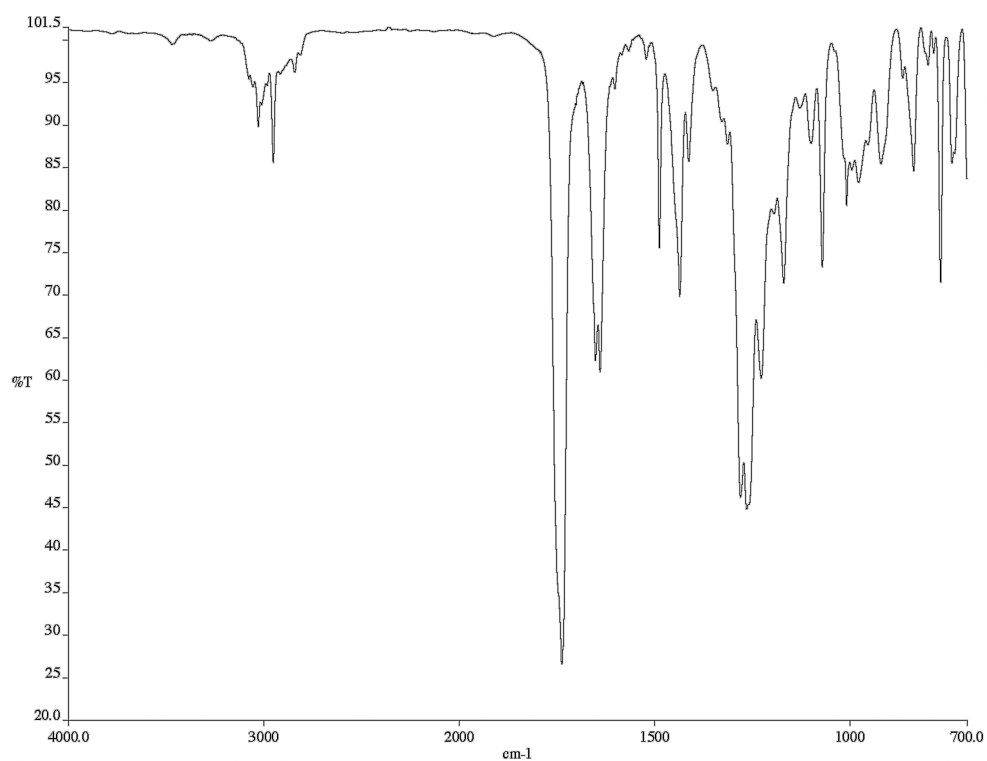


Figure A2.47 Infrared spectrum (thin film/NaCl) of compound **47**

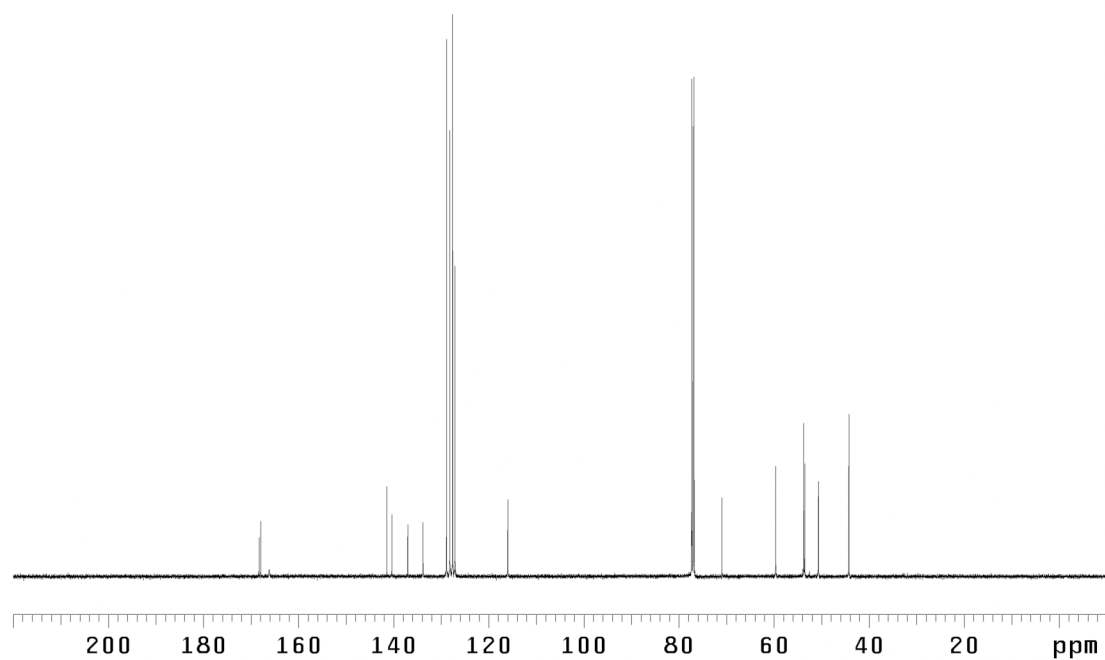


Figure A2.48 ¹³C NMR (126 MHz, CDCl₃) of compound **47**

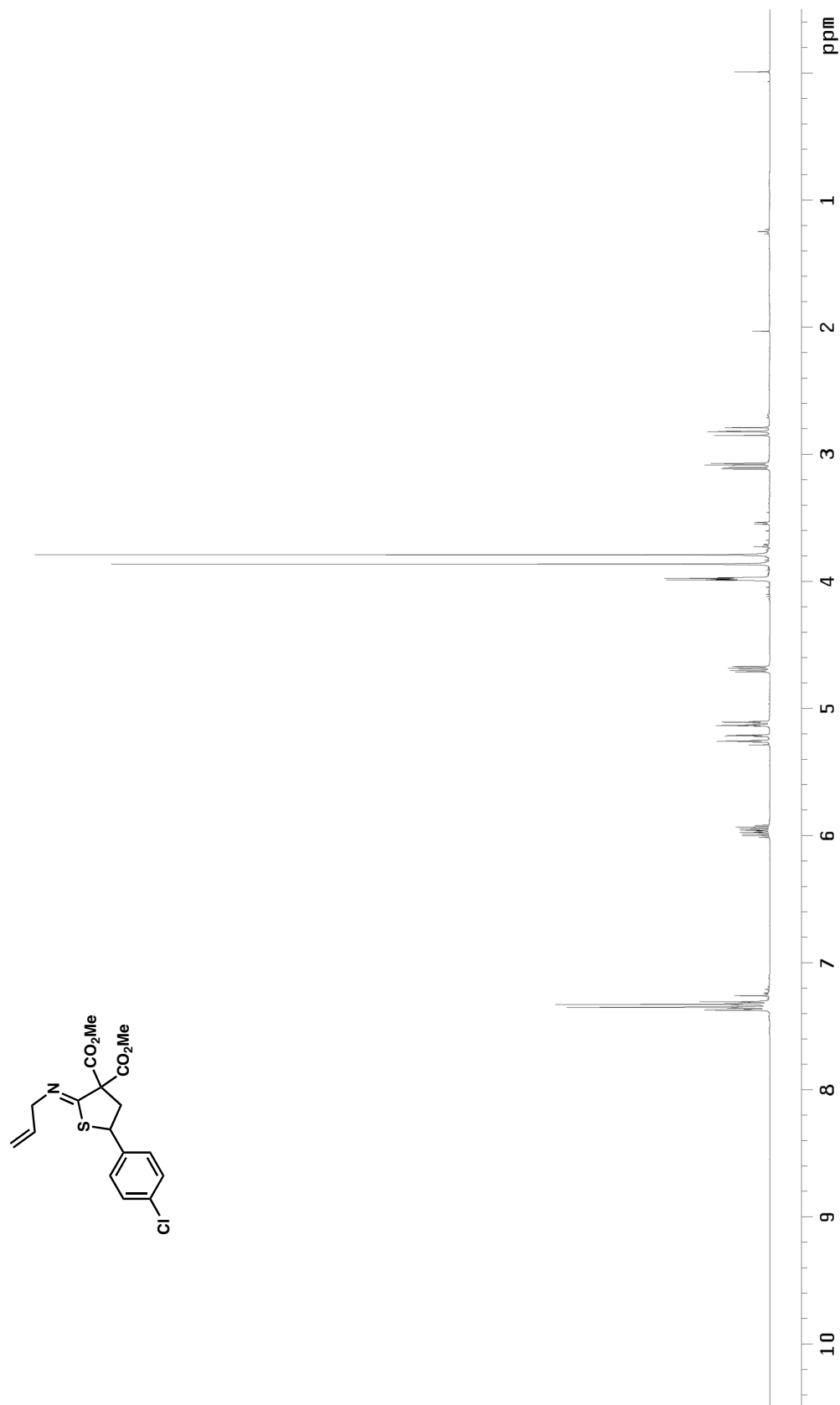


Figure A2.49 ^1H NMR (500 MHz, CDCl_3) of compound **48**

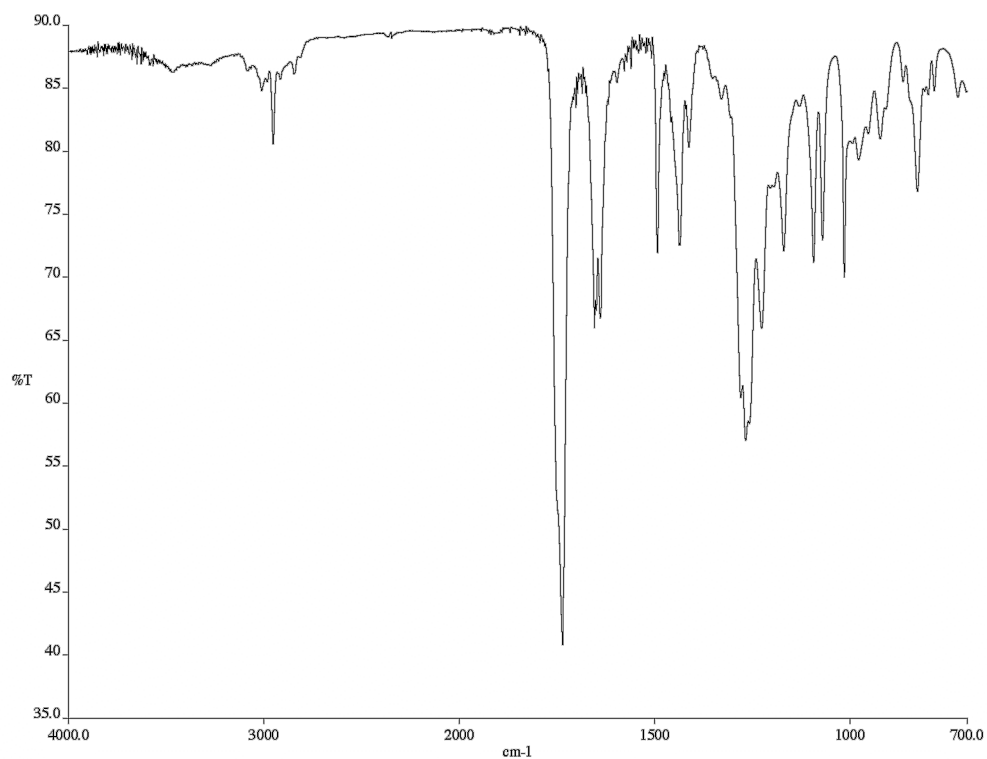


Figure A2.50 Infrared spectrum (thin film/NaCl) of compound **48**

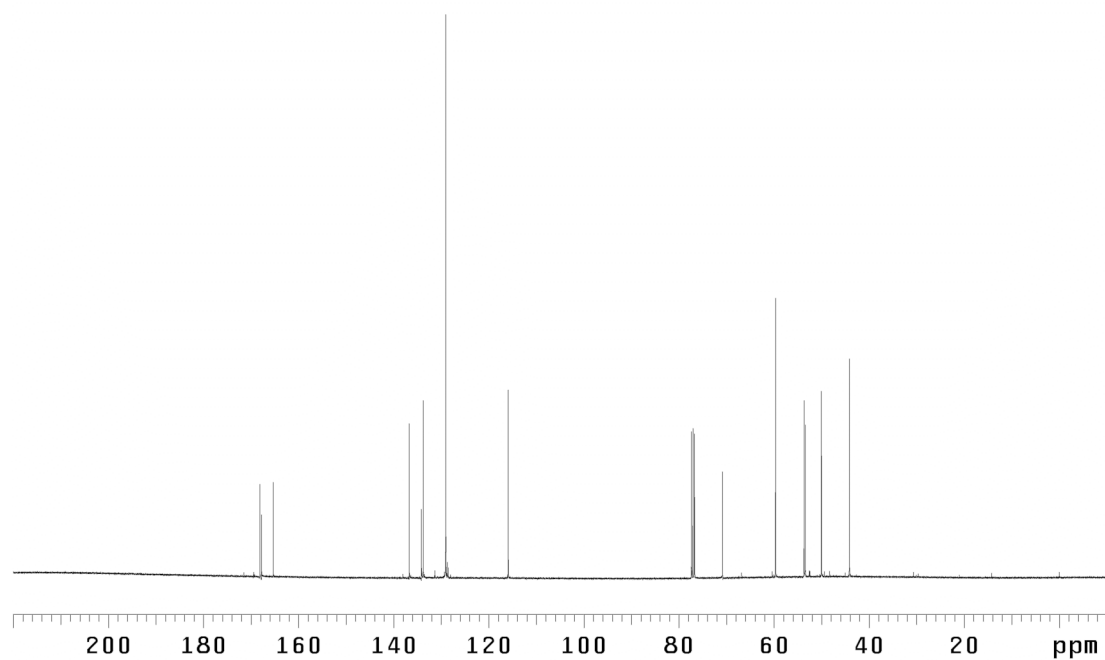


Figure A2.51 ¹³C NMR (126 MHz, CDCl₃) of compound **48**

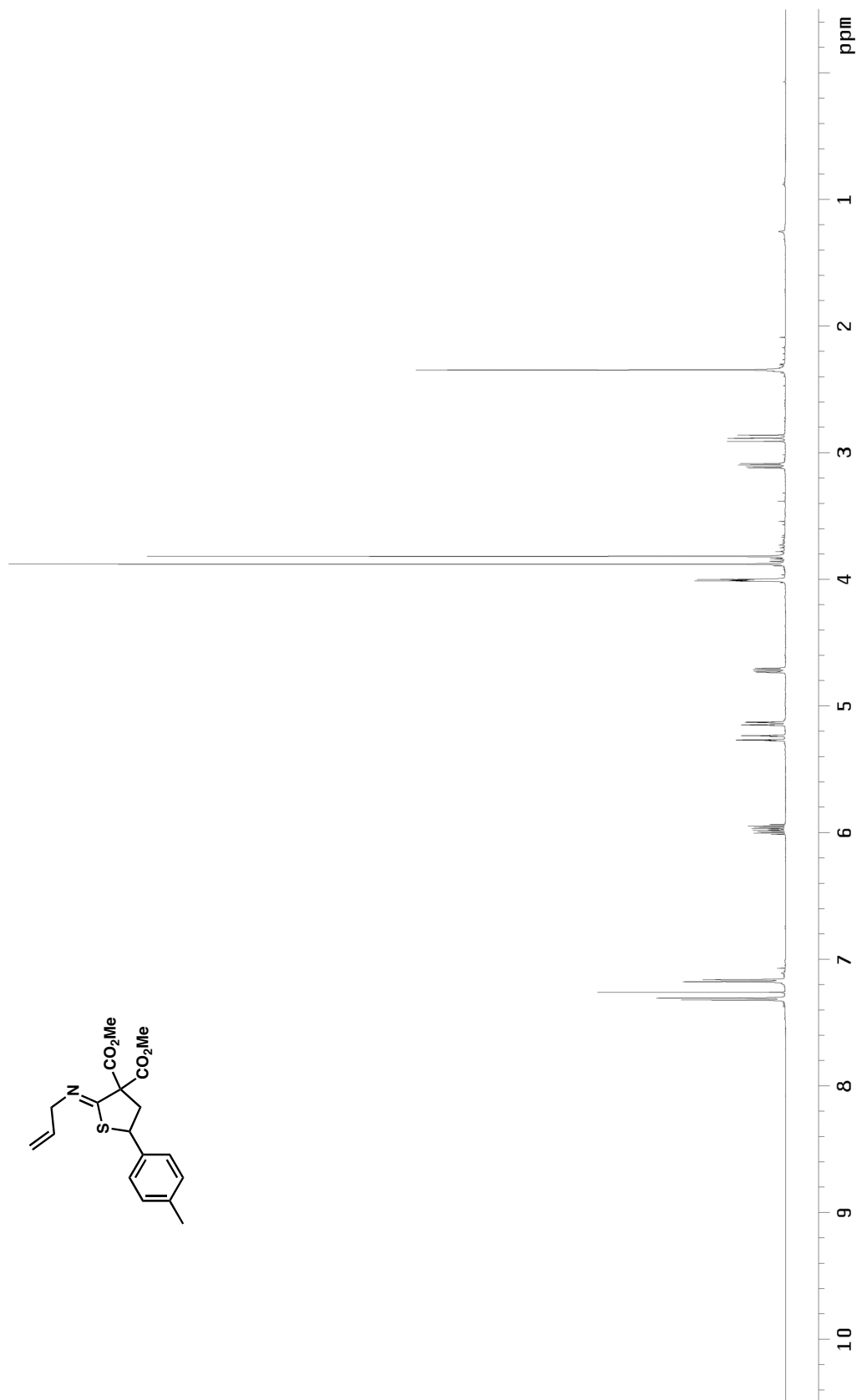


Figure A2.52 ¹H NMR (500 MHz, CDCl₃) of compound 49

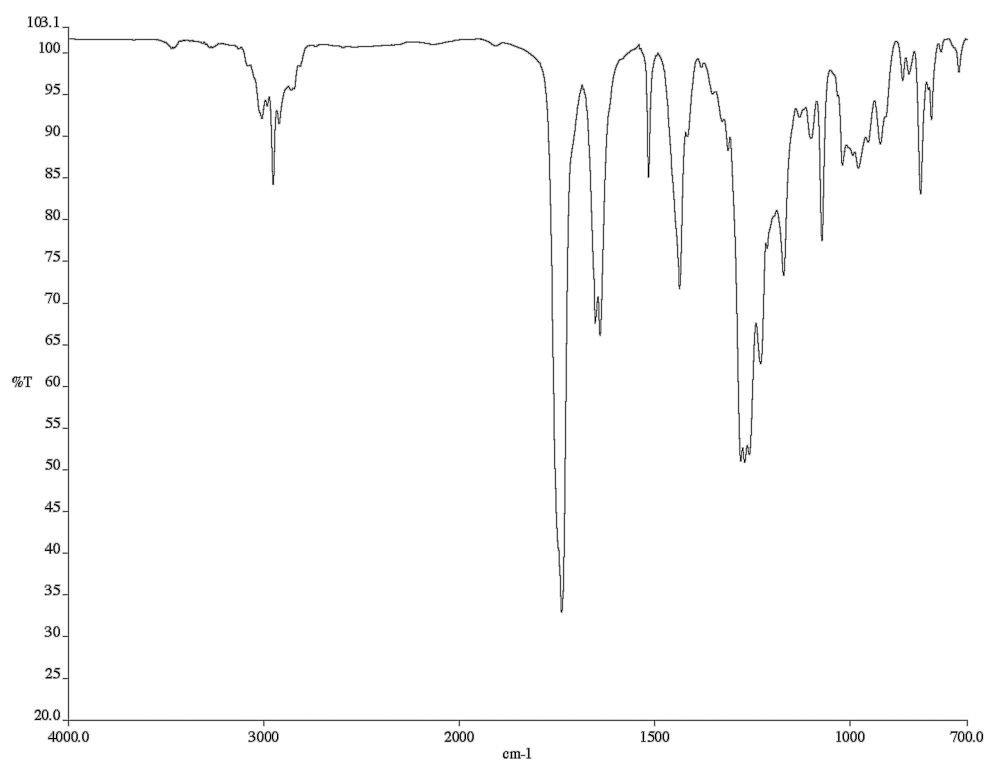


Figure A2.53 Infrared spectrum (thin film/NaCl) of compound **49**

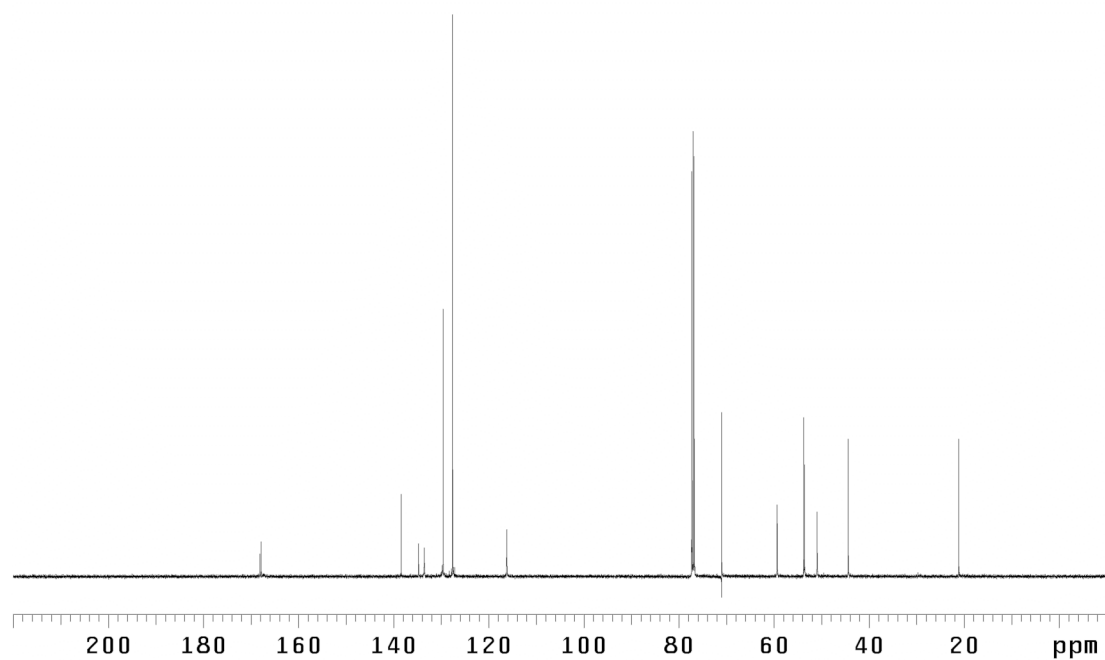


Figure A2.54 ^{13}C NMR (126 MHz, CDCl_3) of compound **49**

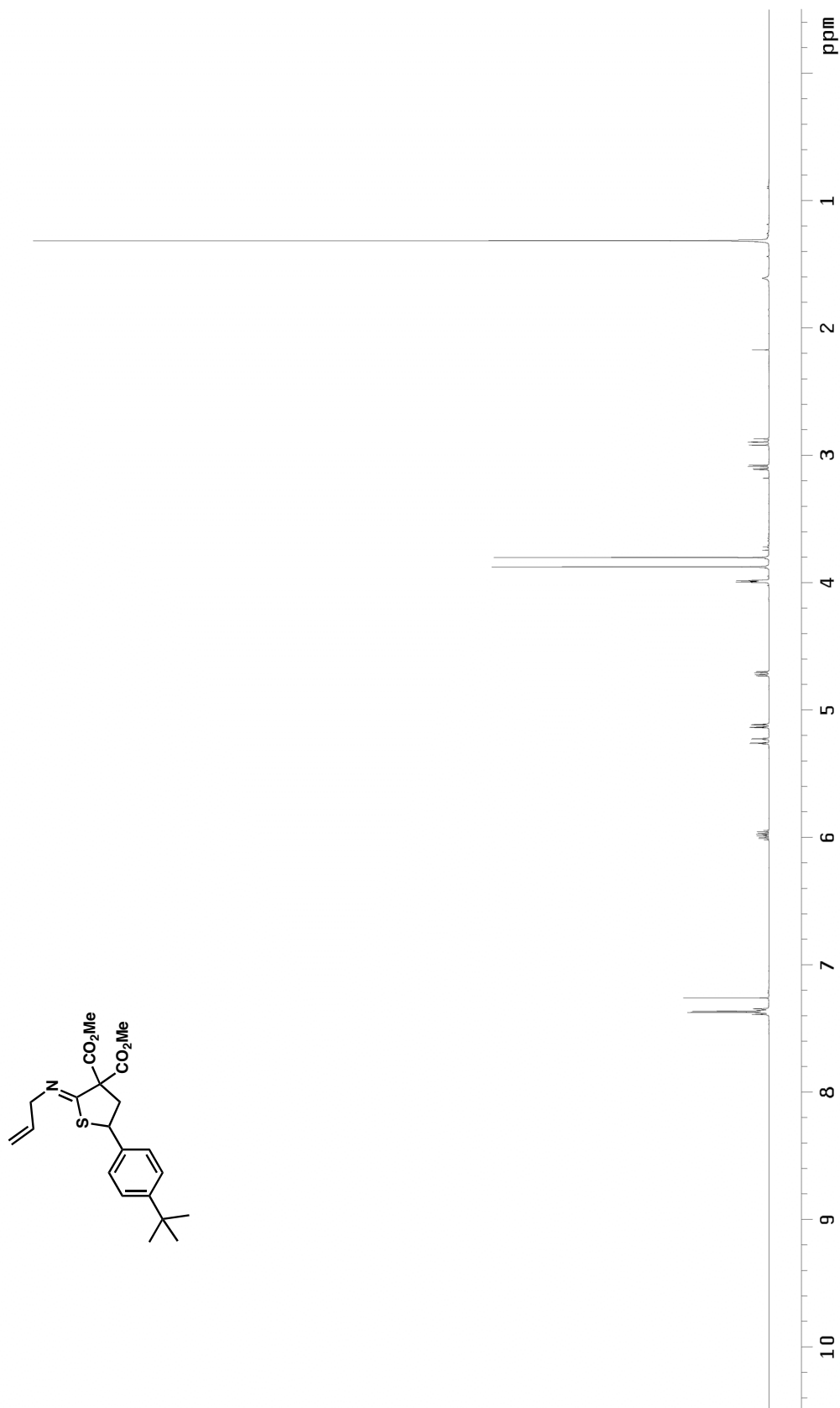


Figure A2.55 ¹H NMR (500 MHz, CDCl₃) of compound **50**

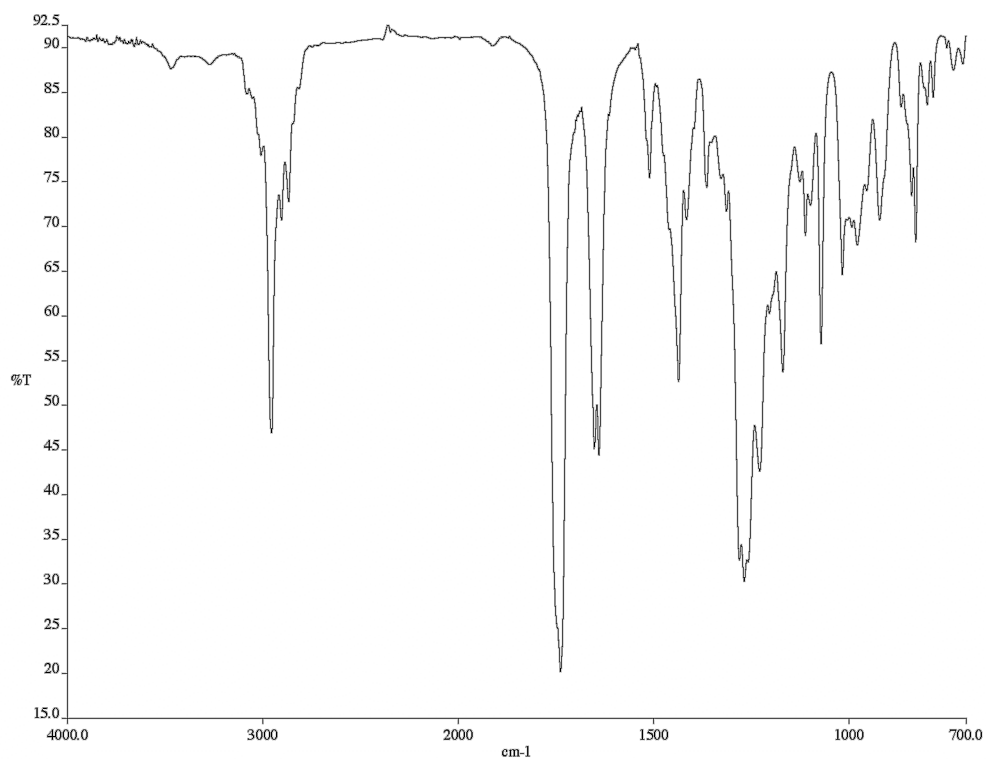


Figure A2.56 Infrared spectrum (thin film/NaCl) of compound **50**

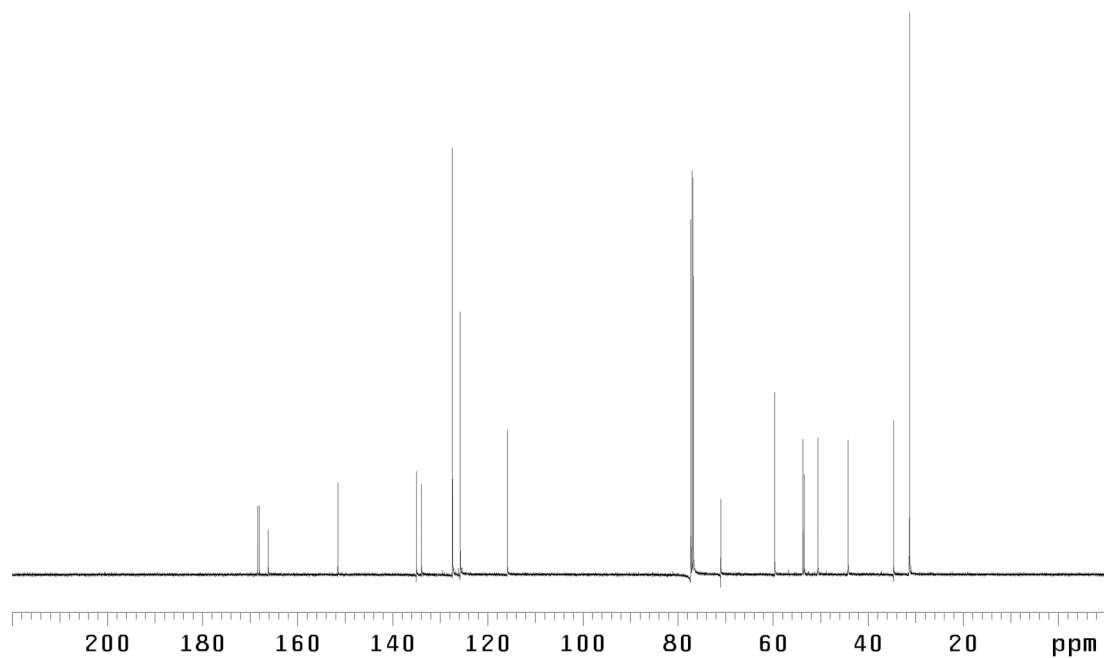


Figure A2.57 ¹³C NMR (126 MHz, CDCl₃) of compound **50**

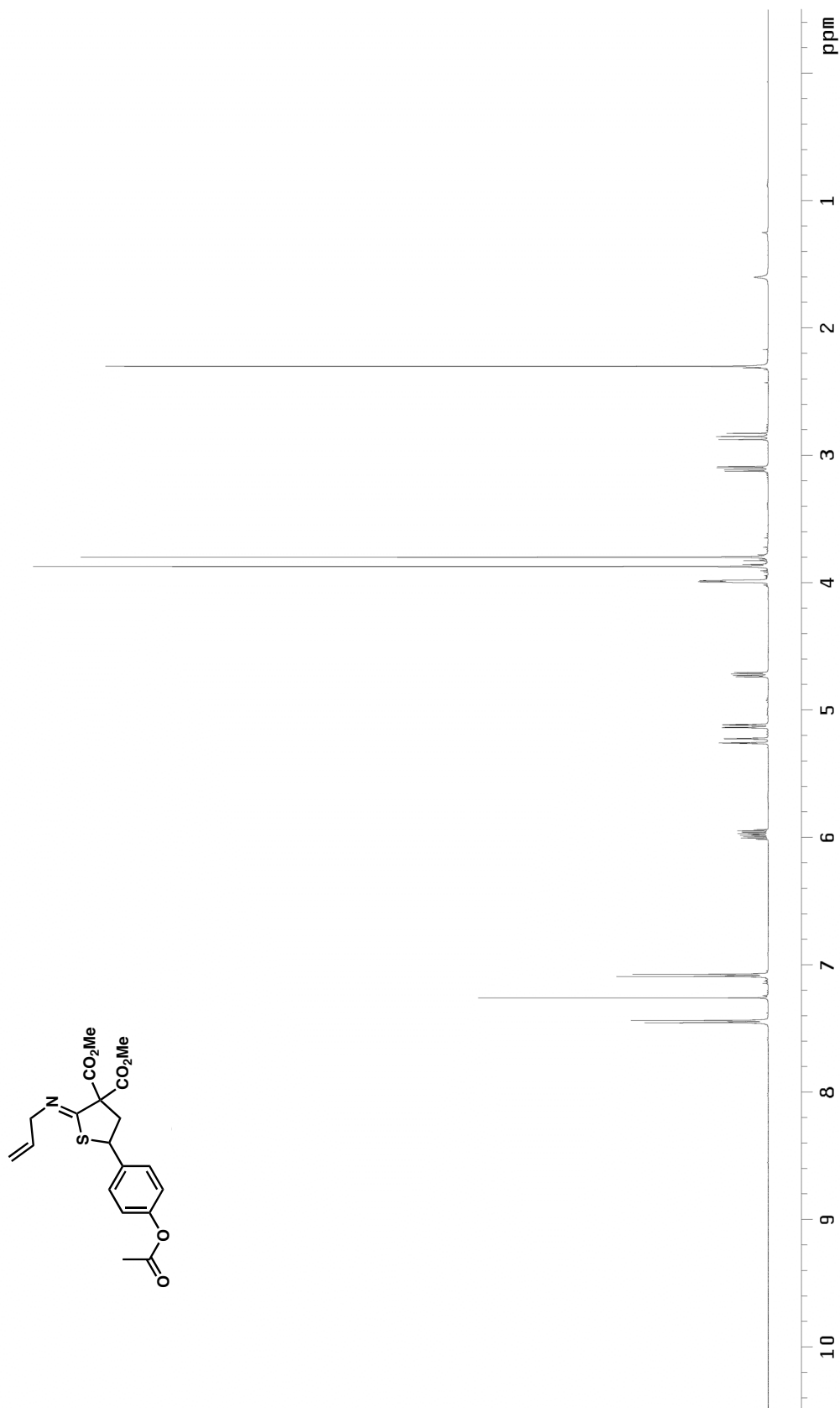


Figure A2.58 ¹H NMR (500 MHz, CDCl₃) of compound **51**

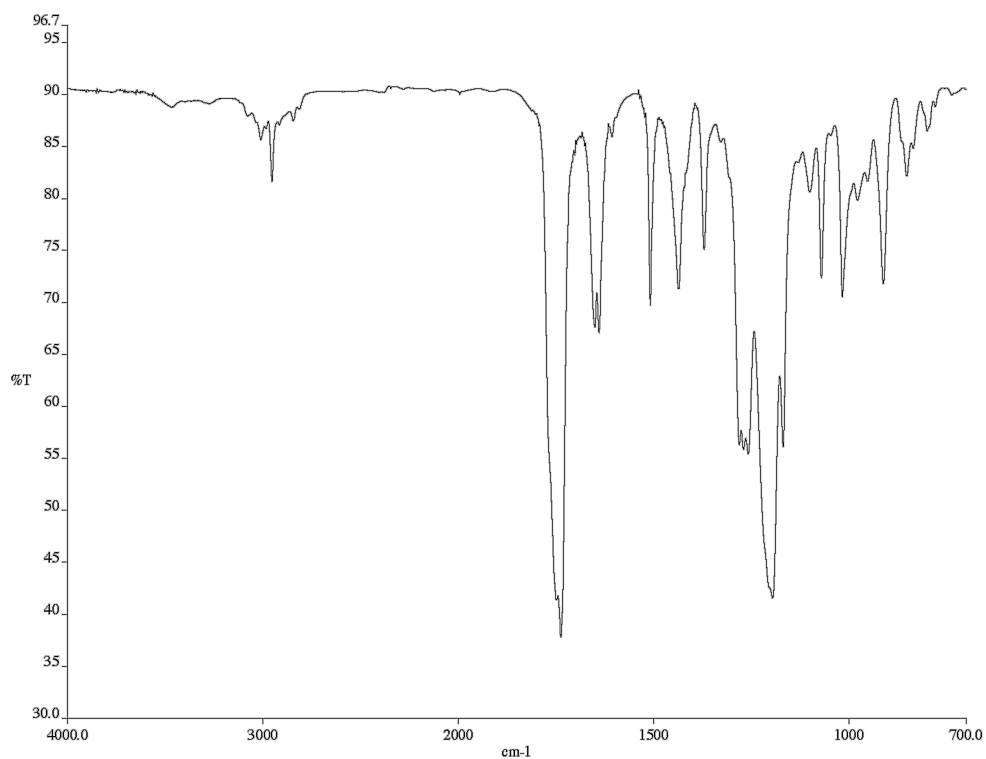


Figure A2.59 Infrared spectrum (thin film/NaCl) of compound **51**

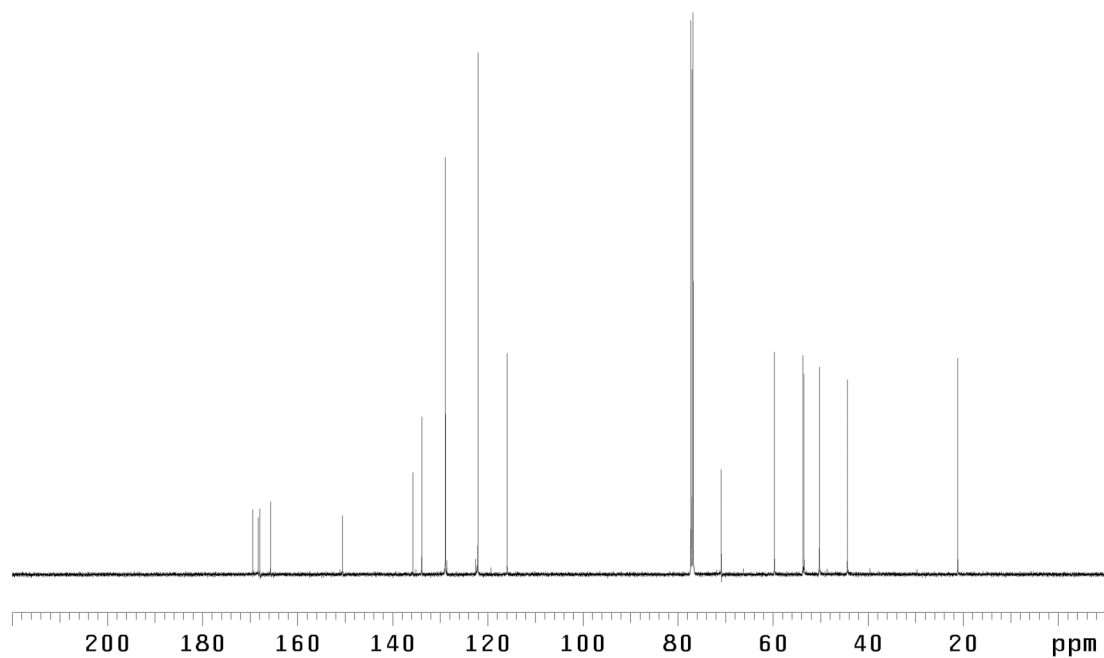


Figure A2.60 ¹³C NMR (126 MHz, CDCl₃) of compound **51**

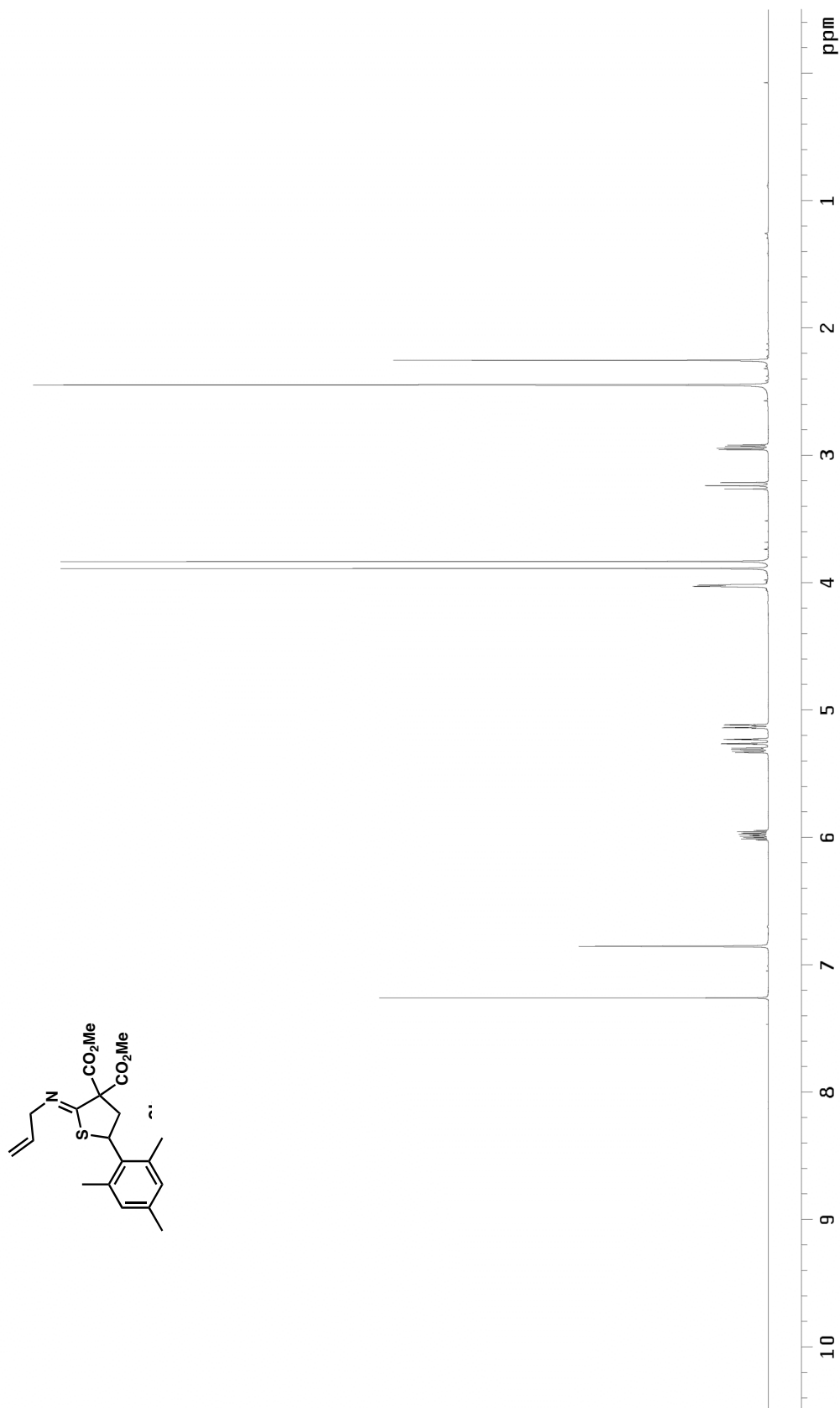


Figure A2.61 ^1H NMR (500 MHz, CDCl_3) of compound **52**

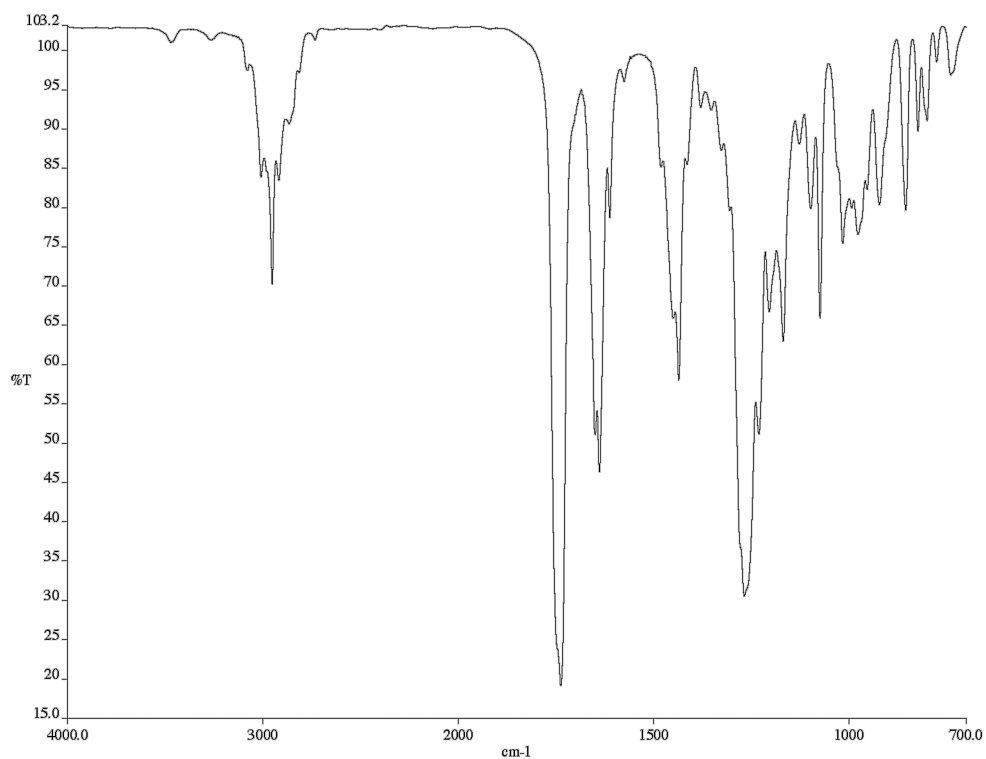


Figure A2.62 Infrared spectrum (thin film/NaCl) of compound **52**

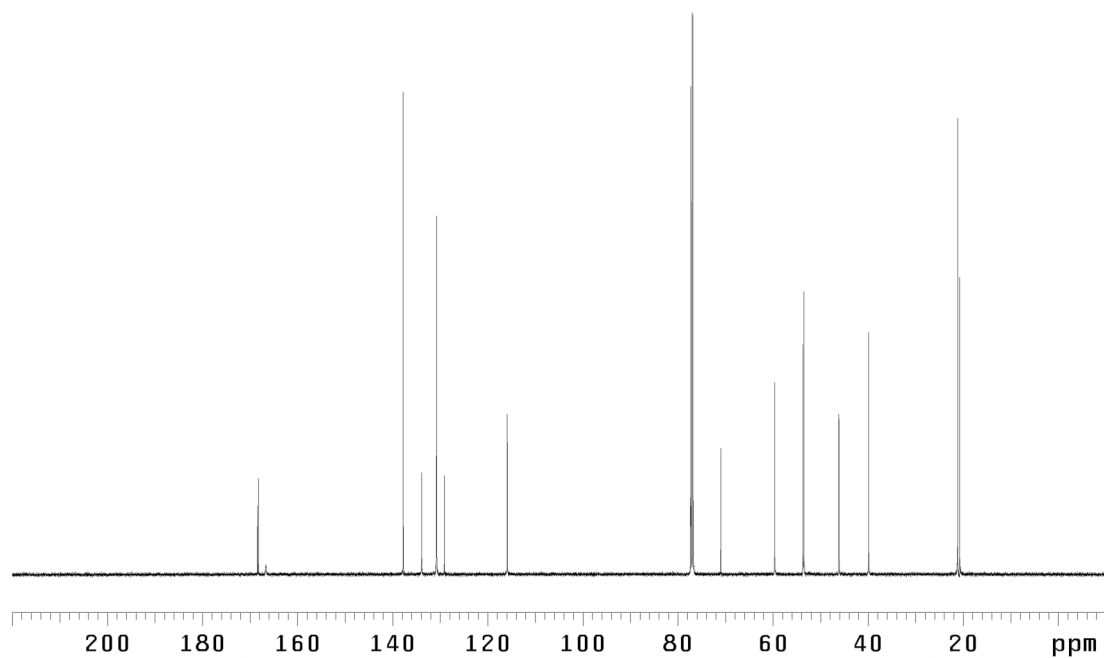


Figure A2.63 ^{13}C NMR (126 MHz, CDCl_3) of compound **52**

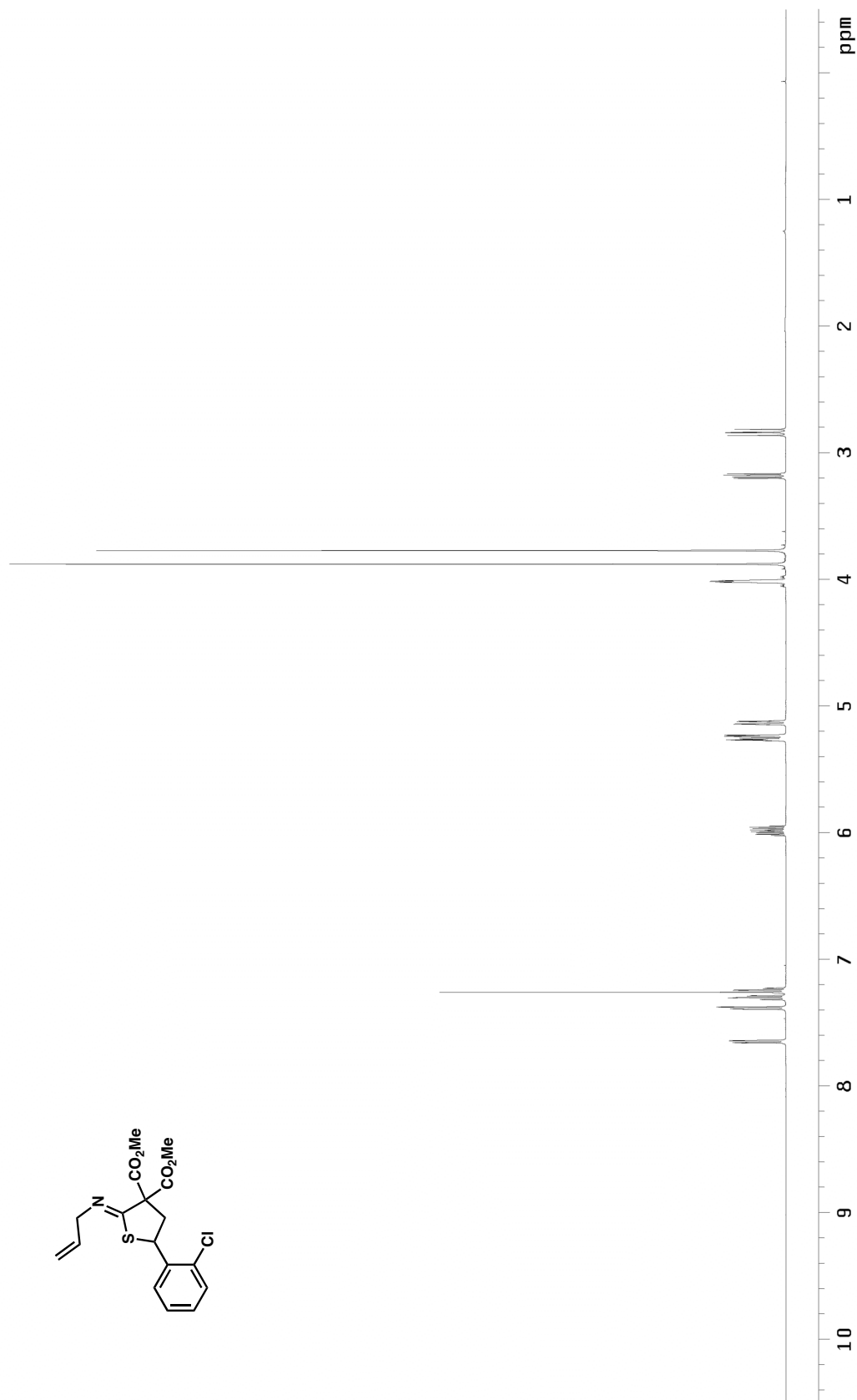


Figure A2.64 ¹H NMR (500 MHz, CDCl₃) of compound **53**

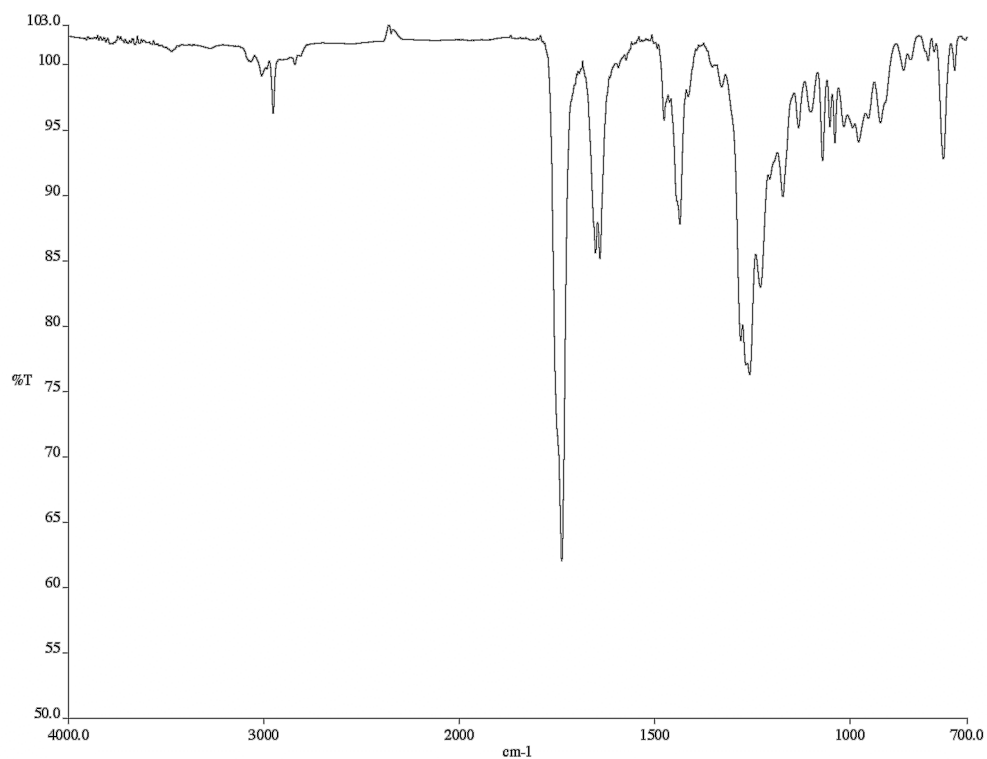


Figure A2.65 Infrared spectrum (thin film/NaCl) of compound **53**

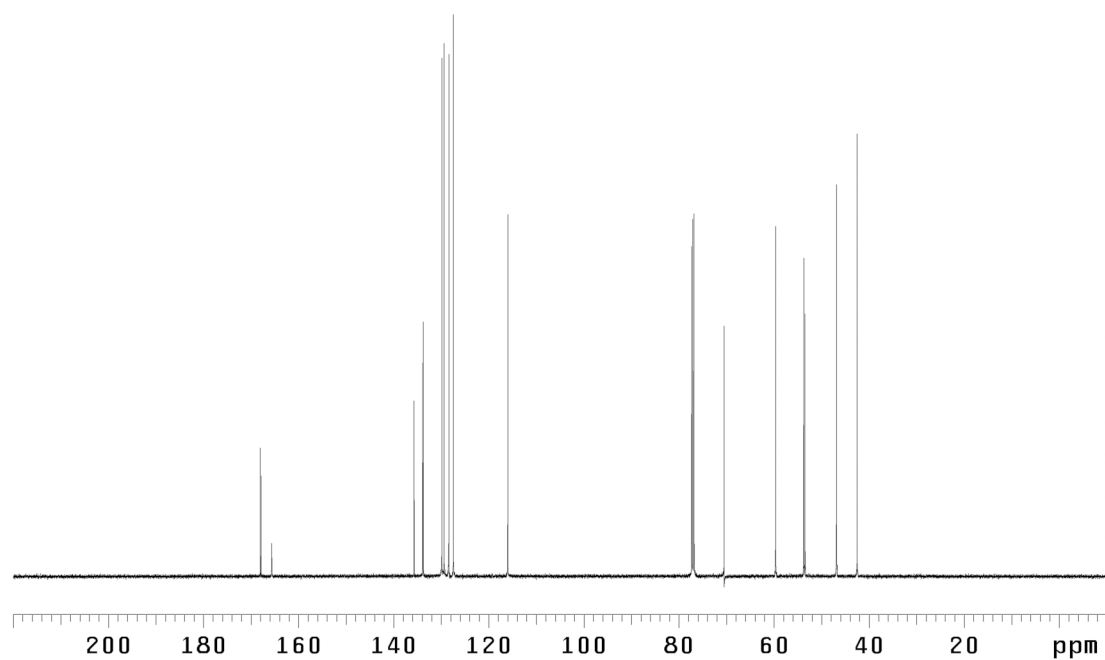


Figure A2.66 ¹³C NMR (126 MHz, CDCl₃) of compound **53**

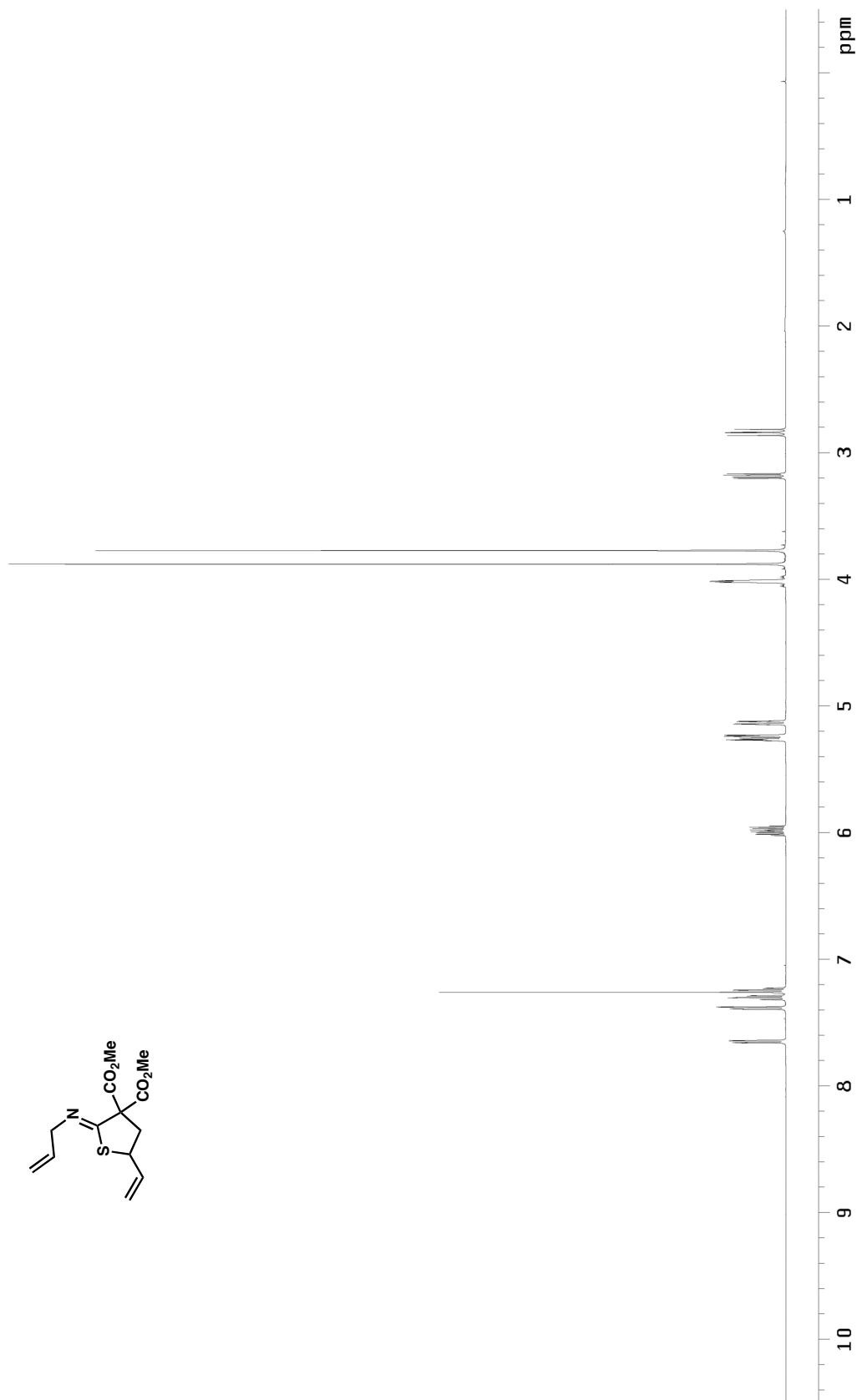


Figure A2.67 ¹H NMR (500 MHz, CDCl₃) of compound **54**

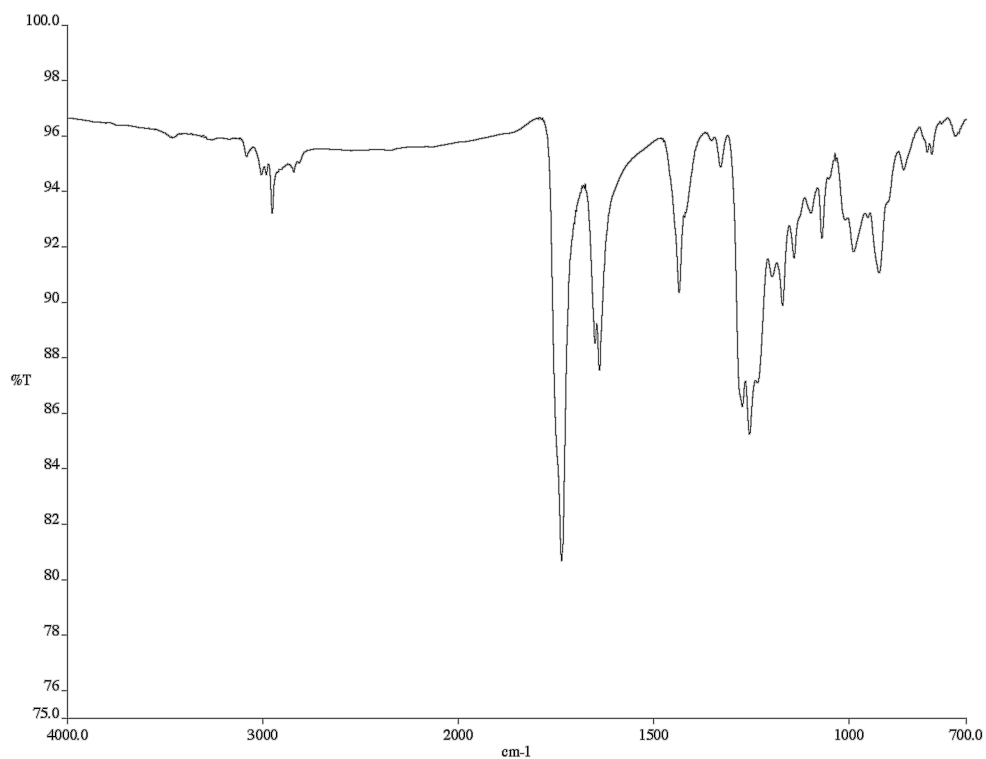


Figure A2.68 Infrared spectrum (thin film/NaCl) of compound **54**

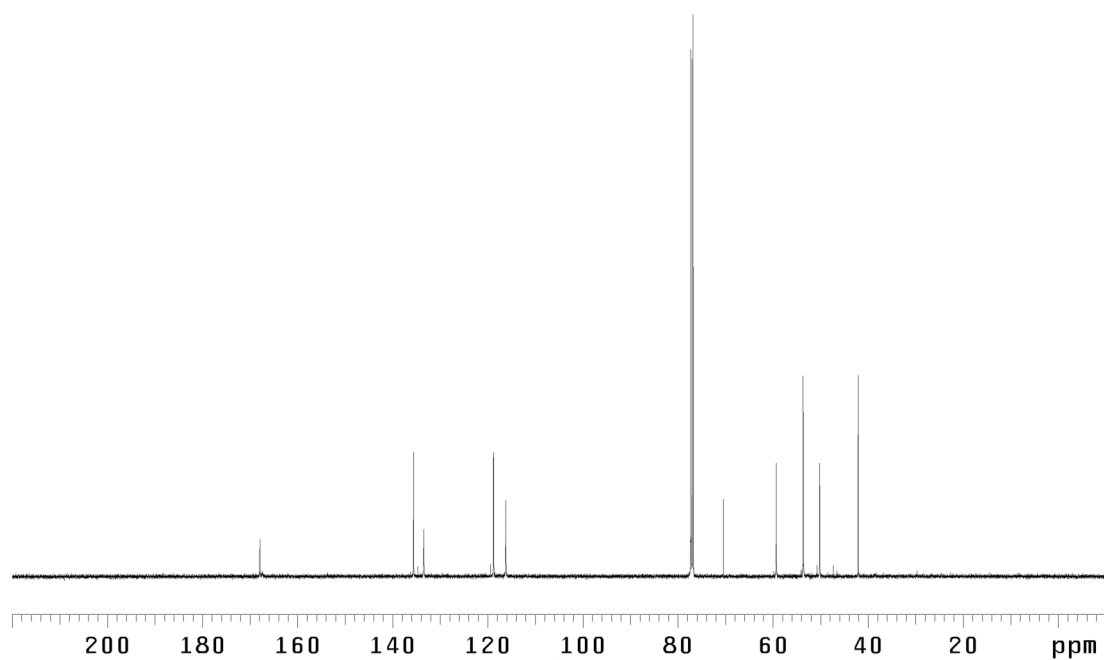


Figure A2.69 ^{13}C NMR (126 MHz, CDCl_3) of compound **54**

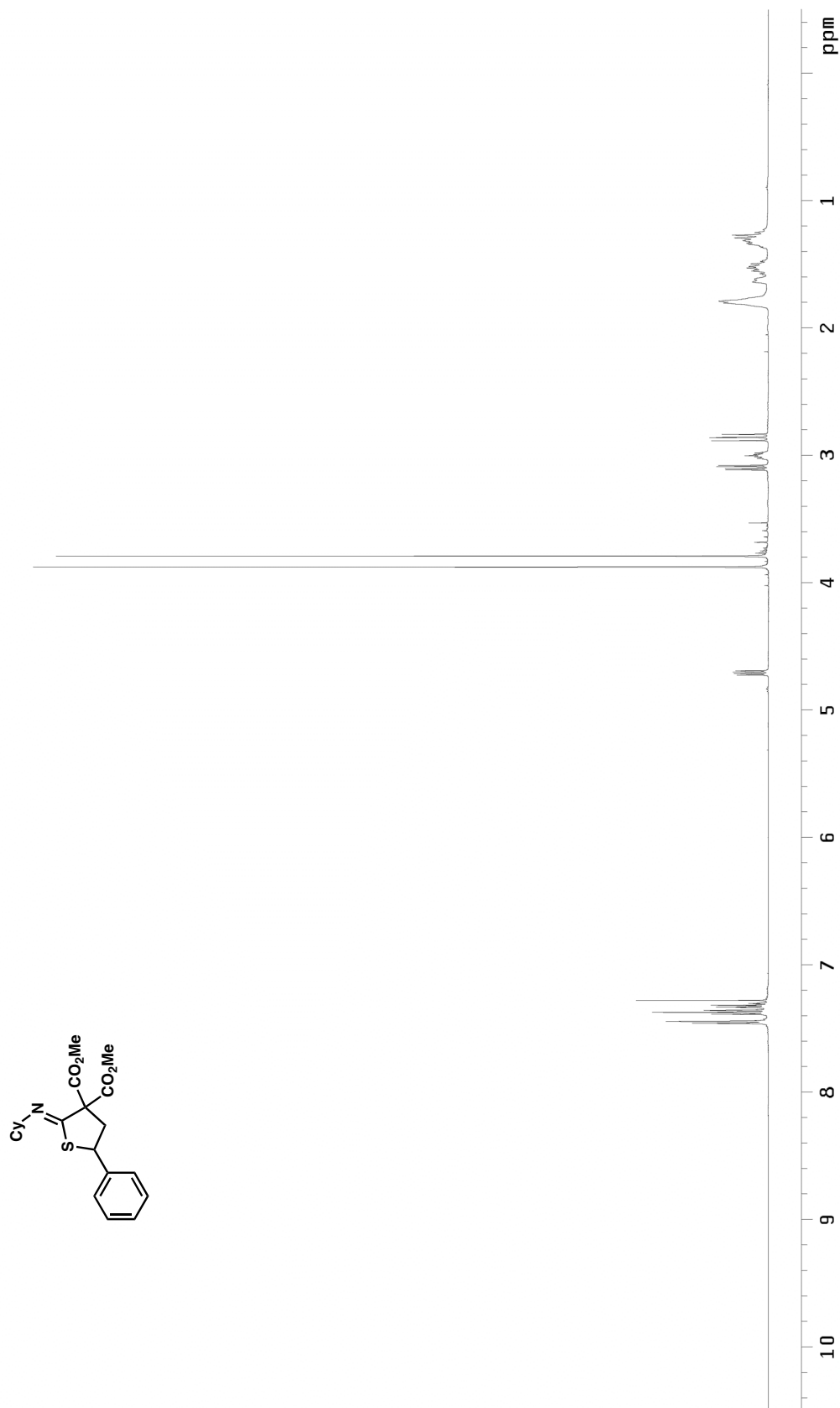


Figure A2.70 ¹H NMR (500 MHz, CDCl₃) of compound **55**

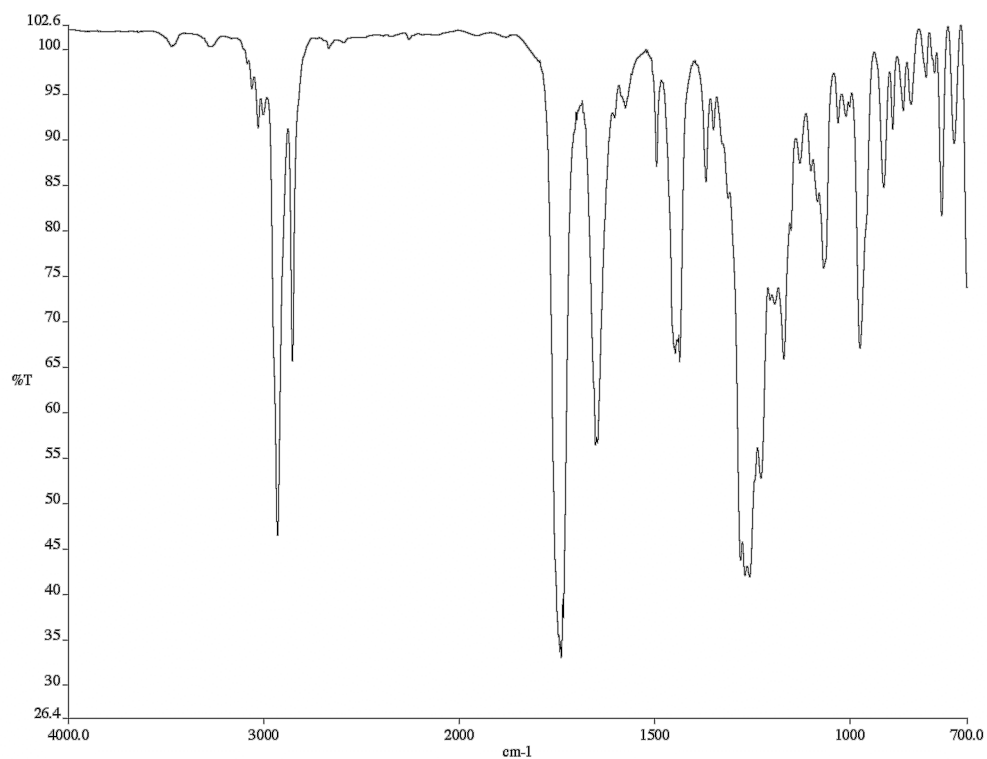


Figure A2.71 Infrared spectrum (thin film/NaCl) of compound **55**

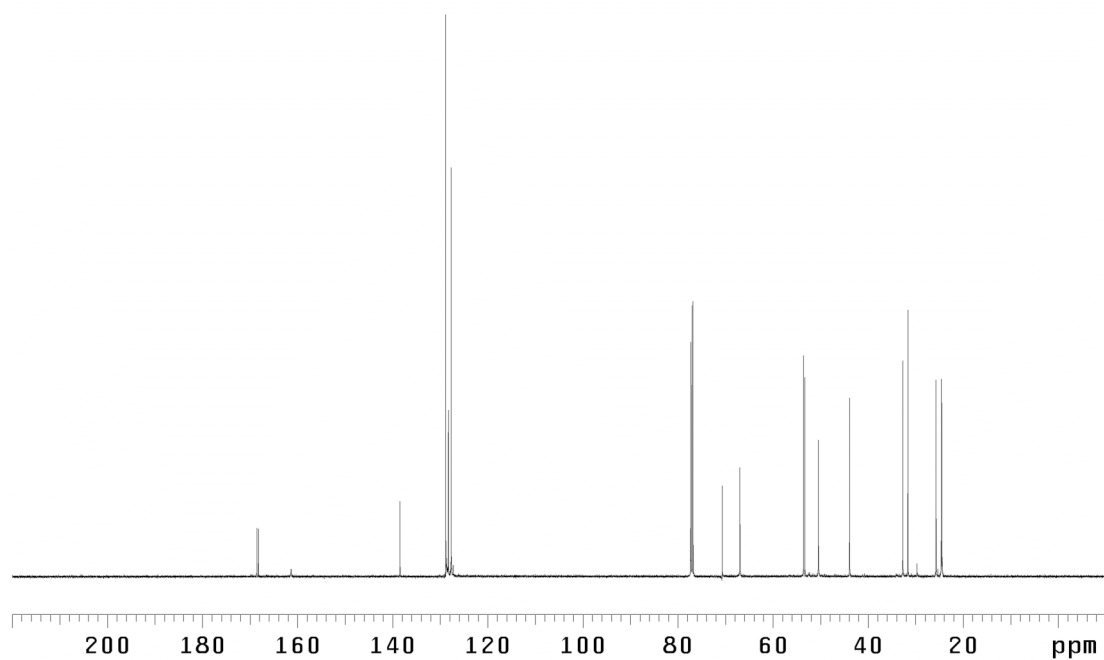


Figure A2.72 ¹³C NMR (126 MHz, CDCl₃) of compound **55**

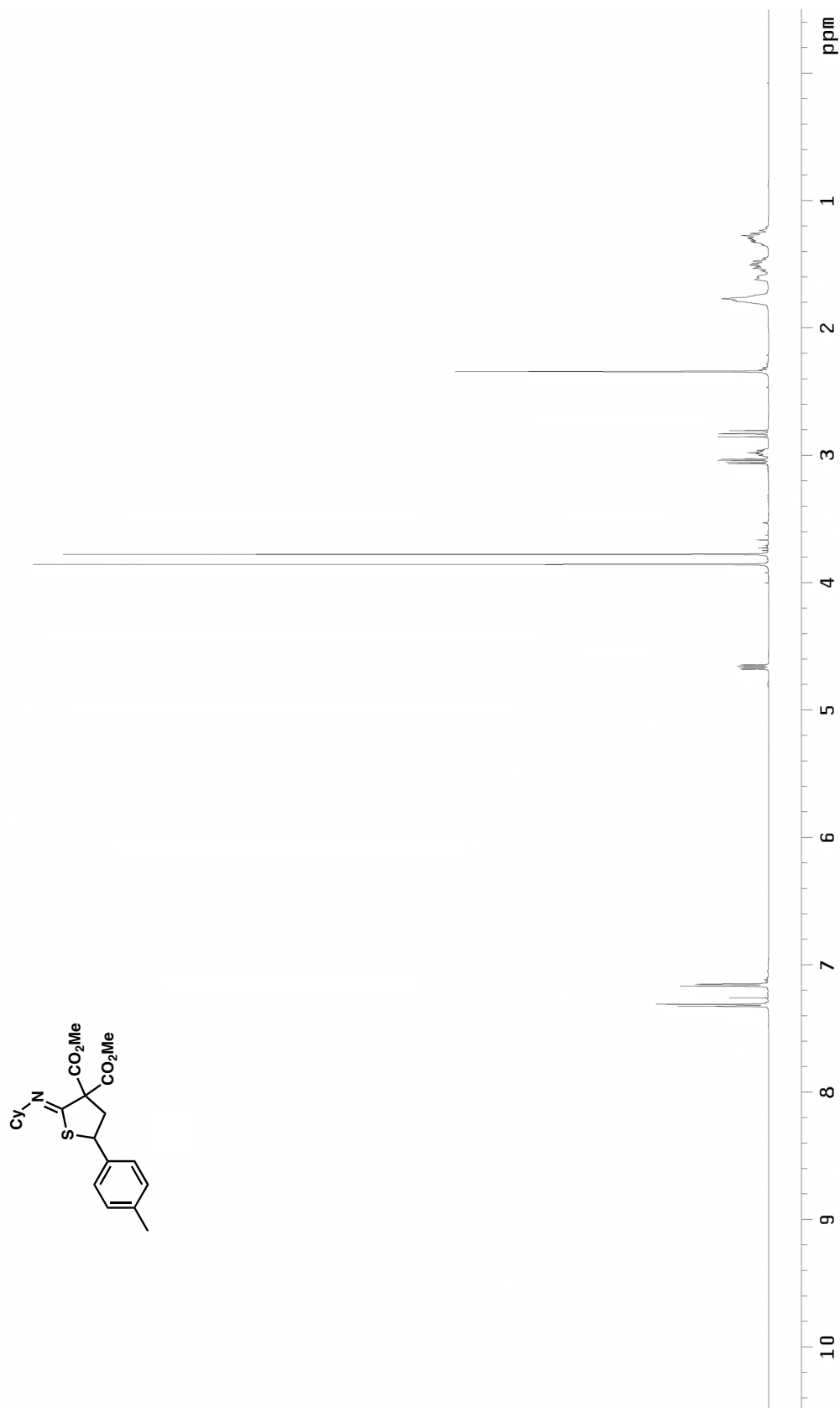


Figure A2.73 ^1H NMR (500 MHz, CDCl_3) of compound **56**

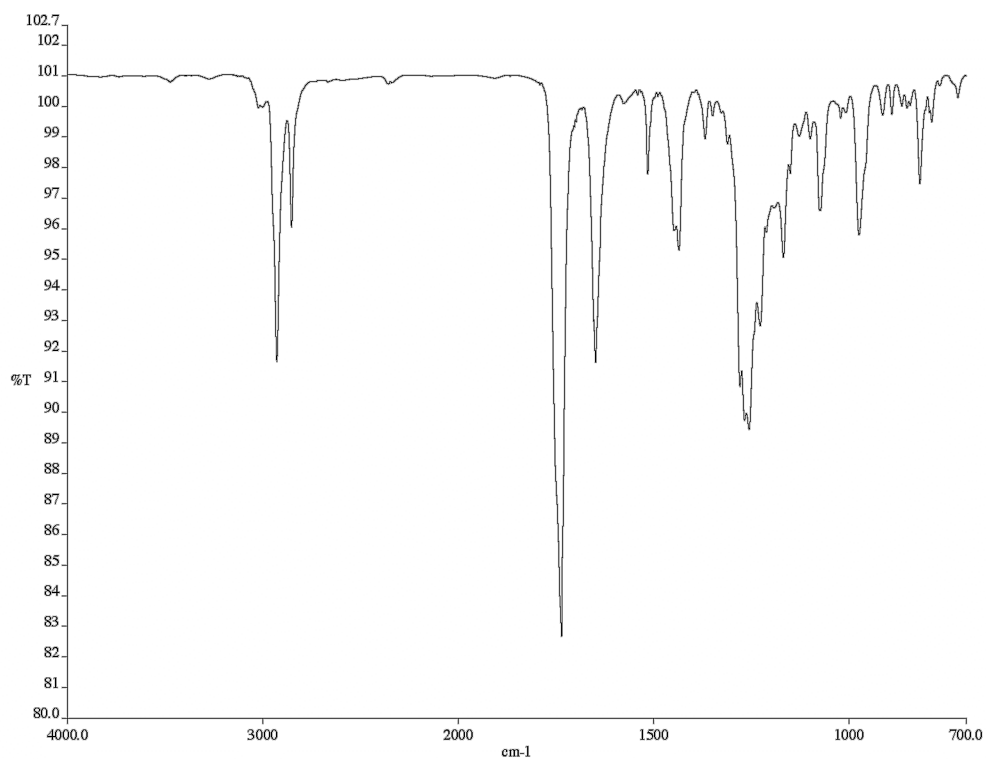


Figure A2.74 Infrared spectrum (thin film/NaCl) of compound **56**

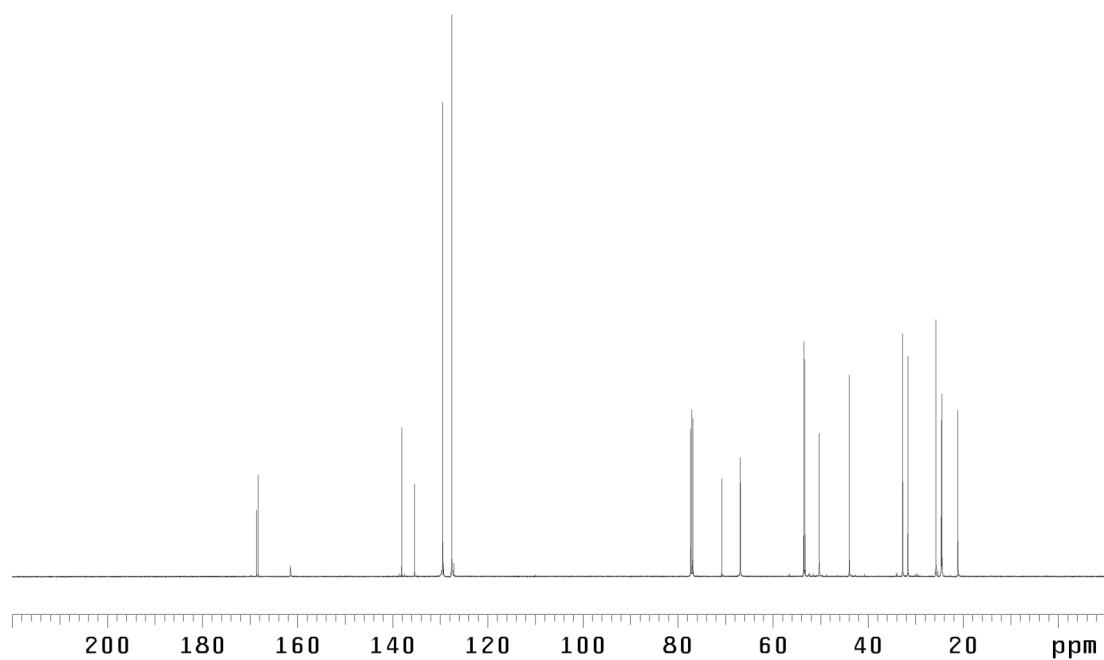


Figure A2.75 ¹³C NMR (126 MHz, CDCl₃) of compound **56**

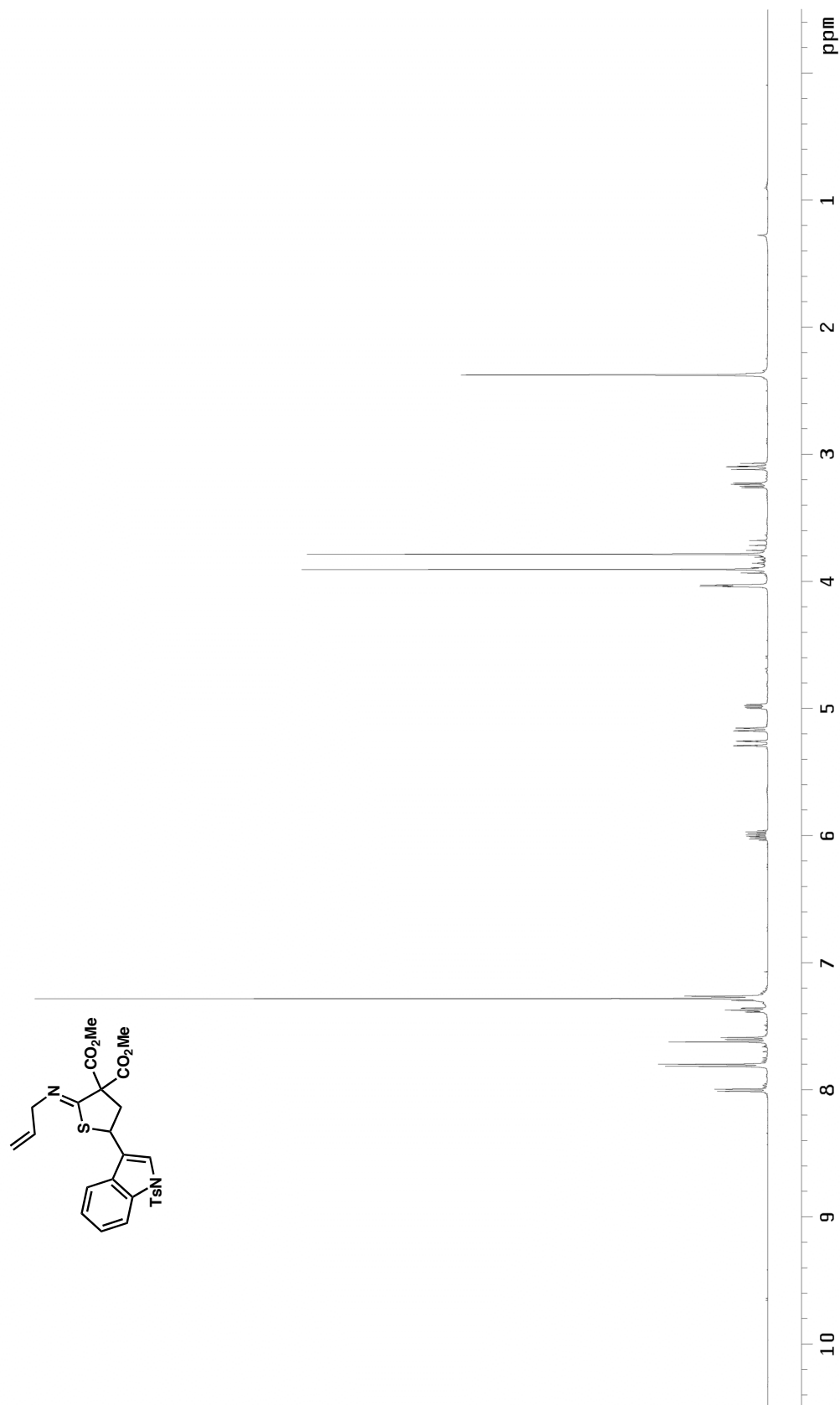


Figure A2.76 ¹H NMR (500 MHz, CDCl₃) of compound **57**

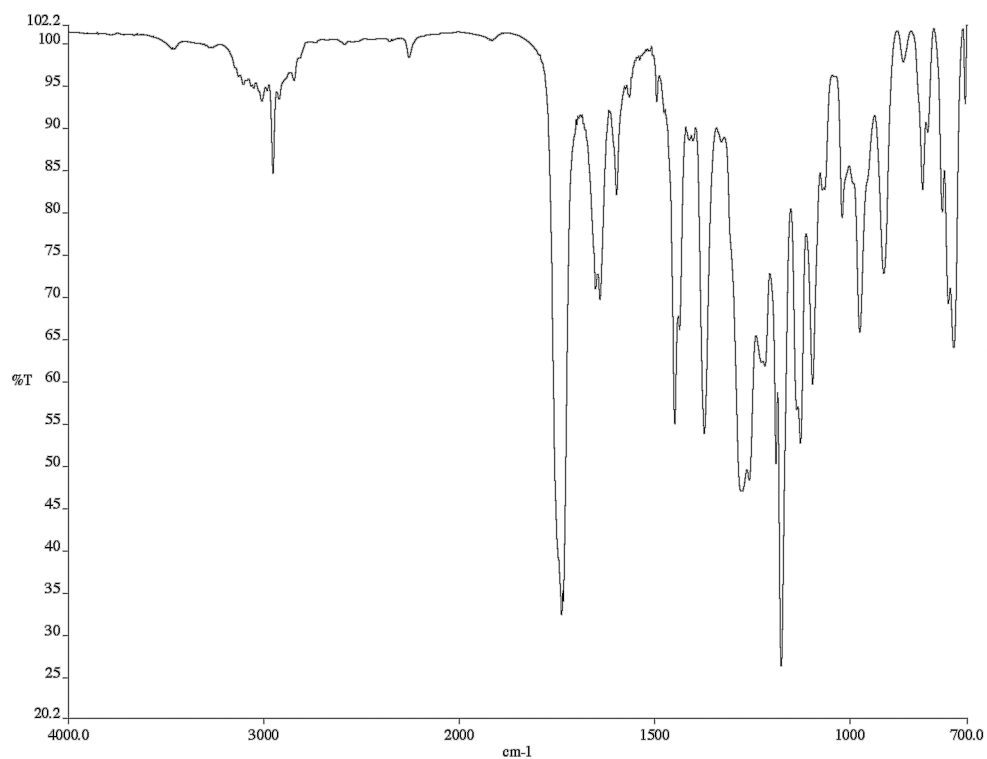


Figure A2.77 Infrared spectrum (thin film/NaCl) of compound **57**

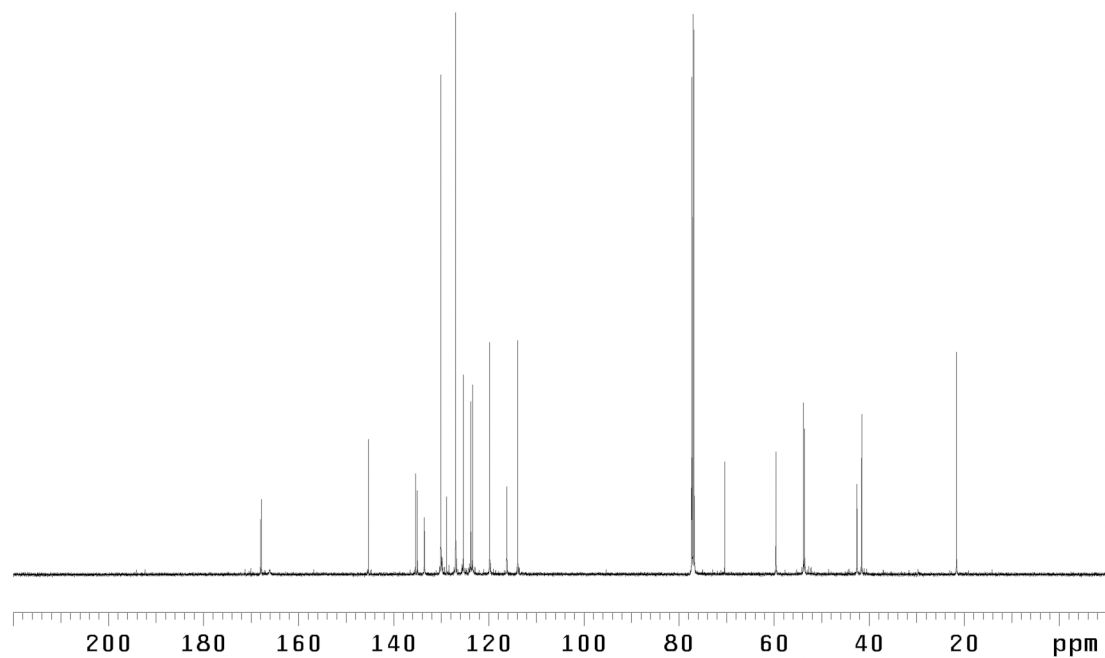


Figure A2.78 ¹³C NMR (126 MHz, CDCl₃) of compound **57**

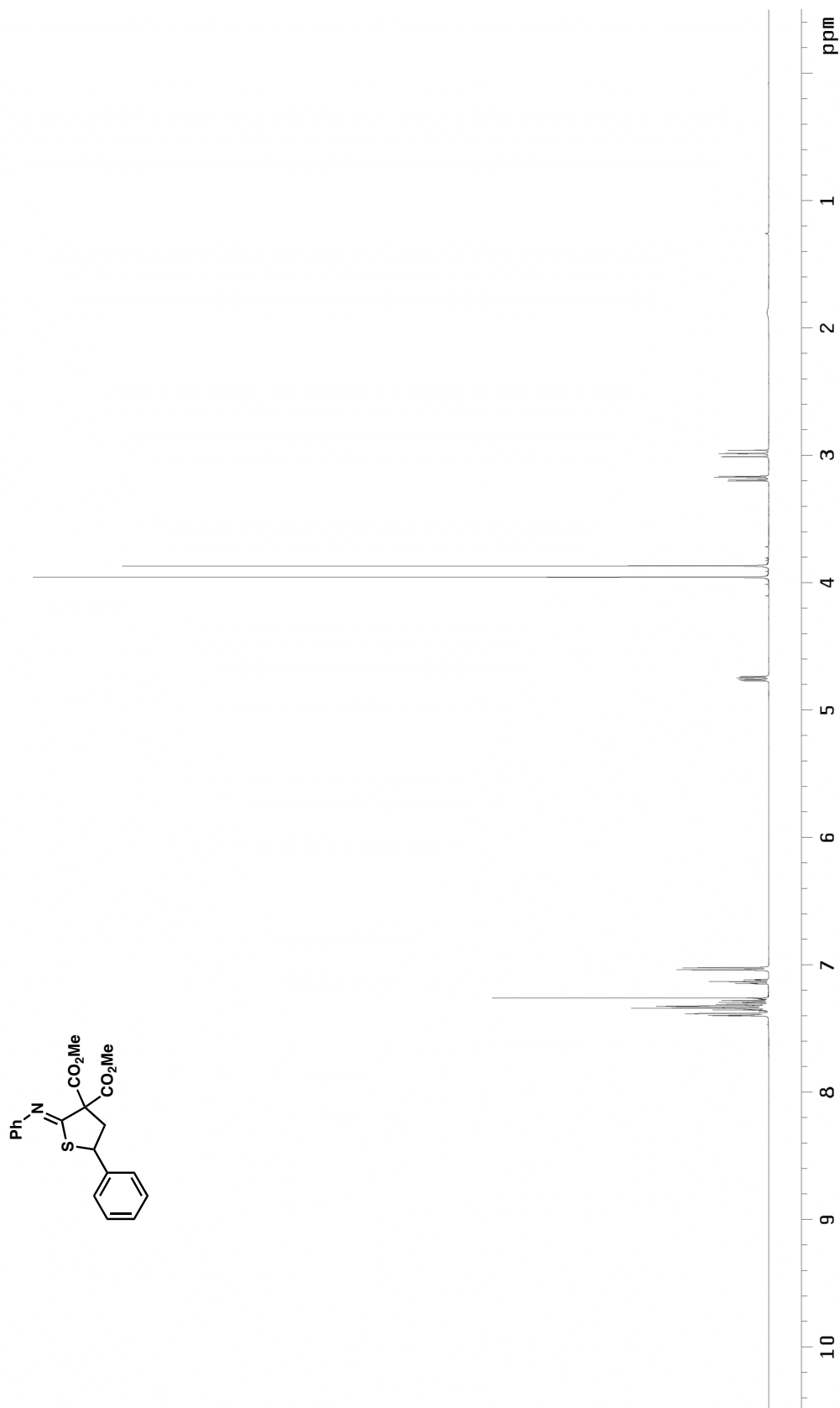


Figure A2.79 ¹H NMR (500 MHz, CDCl₃) of compound **44**

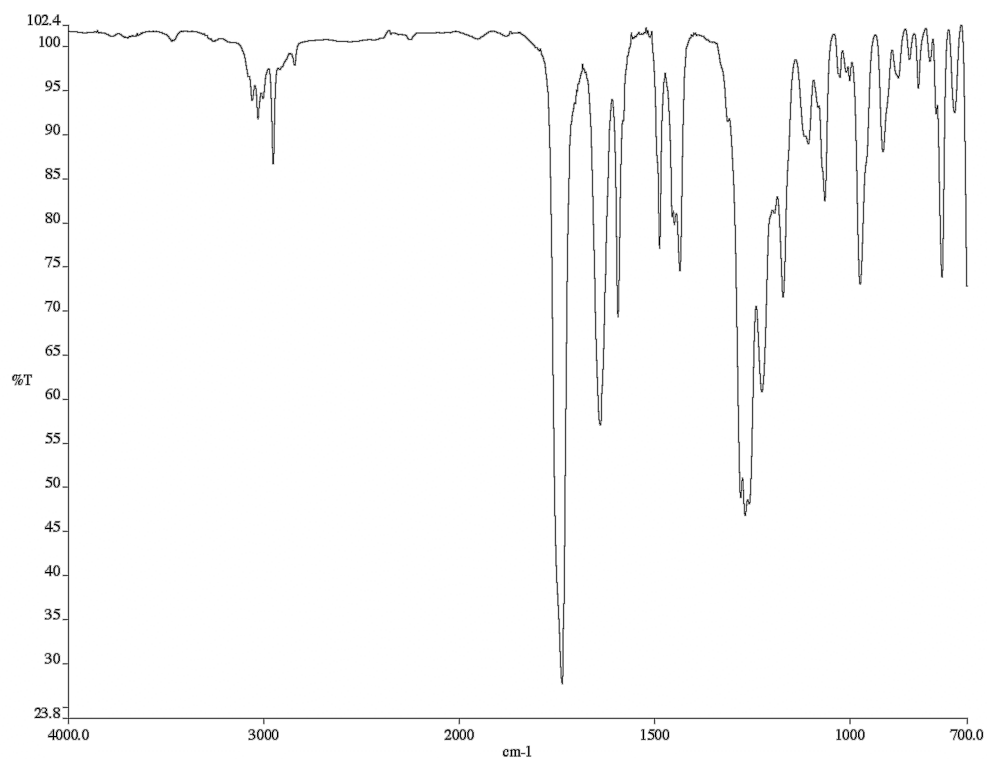


Figure A2.80 Infrared spectrum (thin film/NaCl) of compound **44**

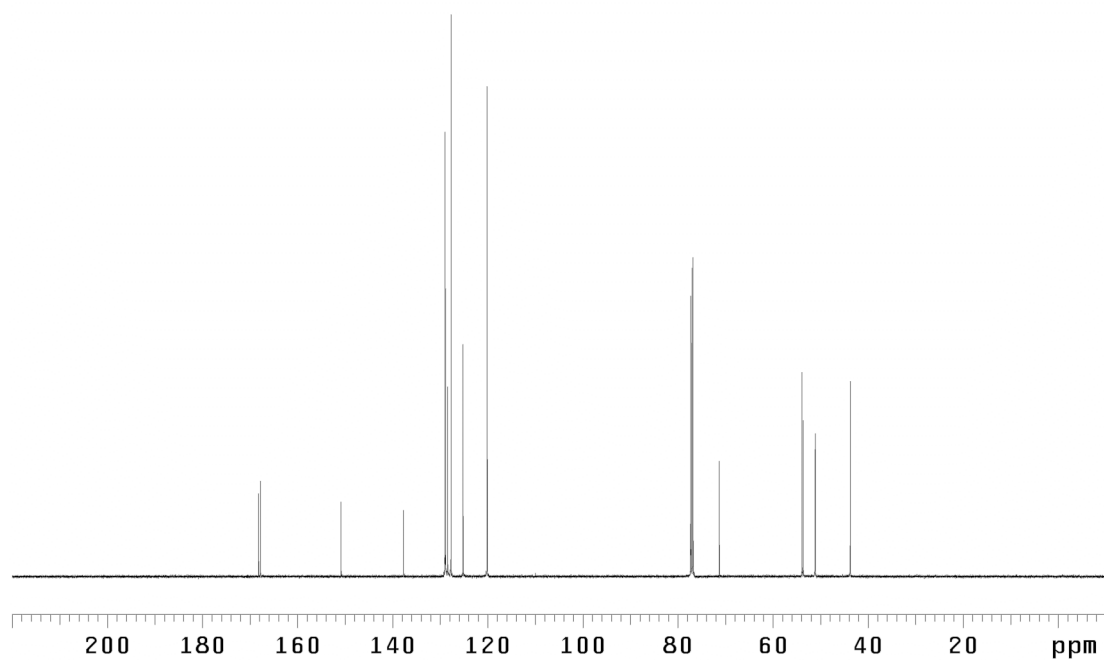


Figure A2.81 ¹³C NMR (126 MHz, CDCl₃) of compound **44**

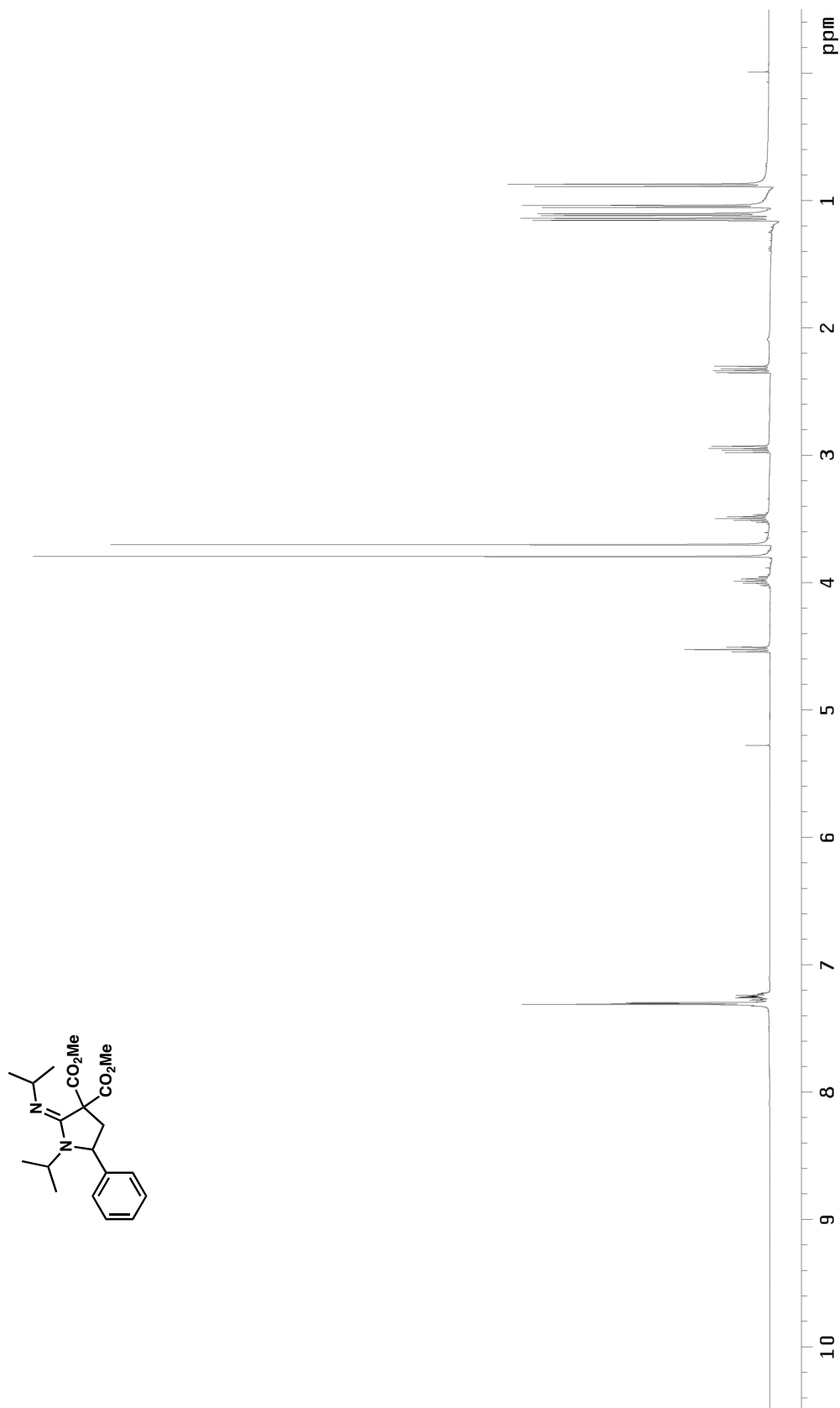


Figure A2.82 ^1H NMR (400 MHz, CDCl_3) of compound **60**

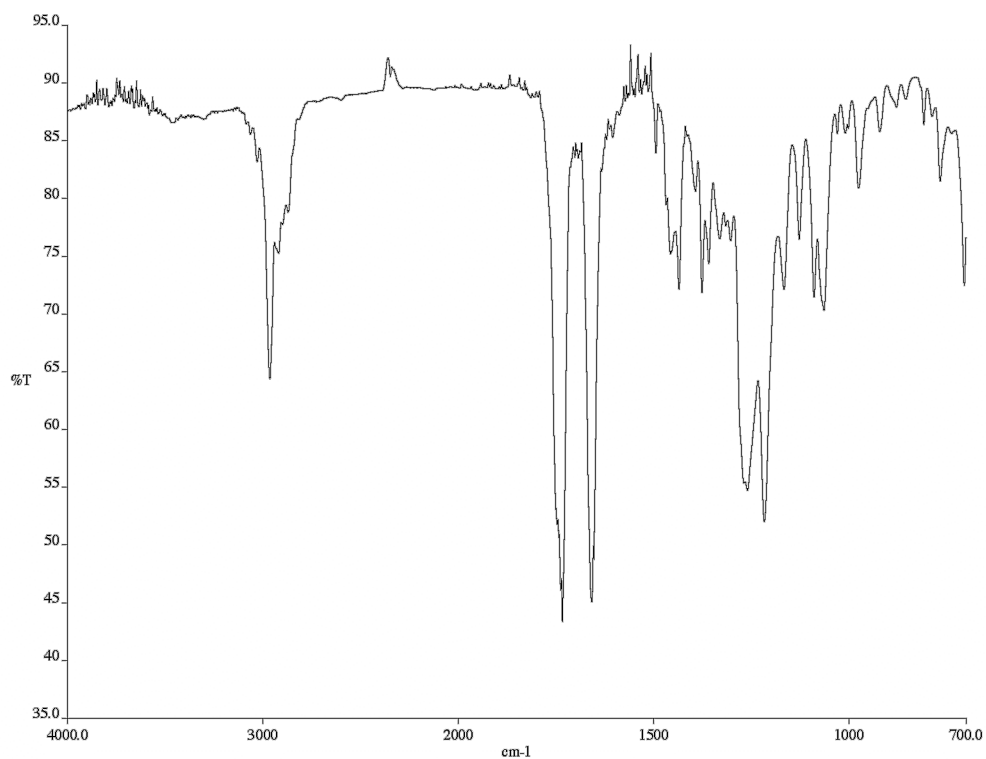


Figure A2.83 Infrared spectrum (thin film/NaCl) of compound **60**

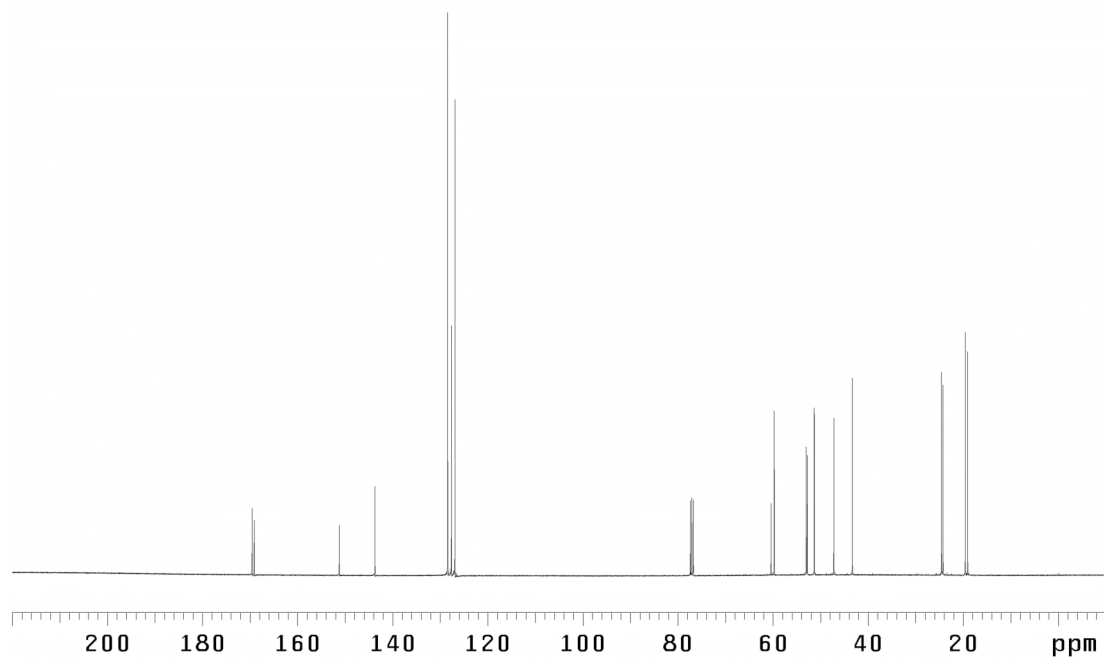


Figure A2.84 ¹³C NMR (101 MHz, CDCl₃) of compound **60**

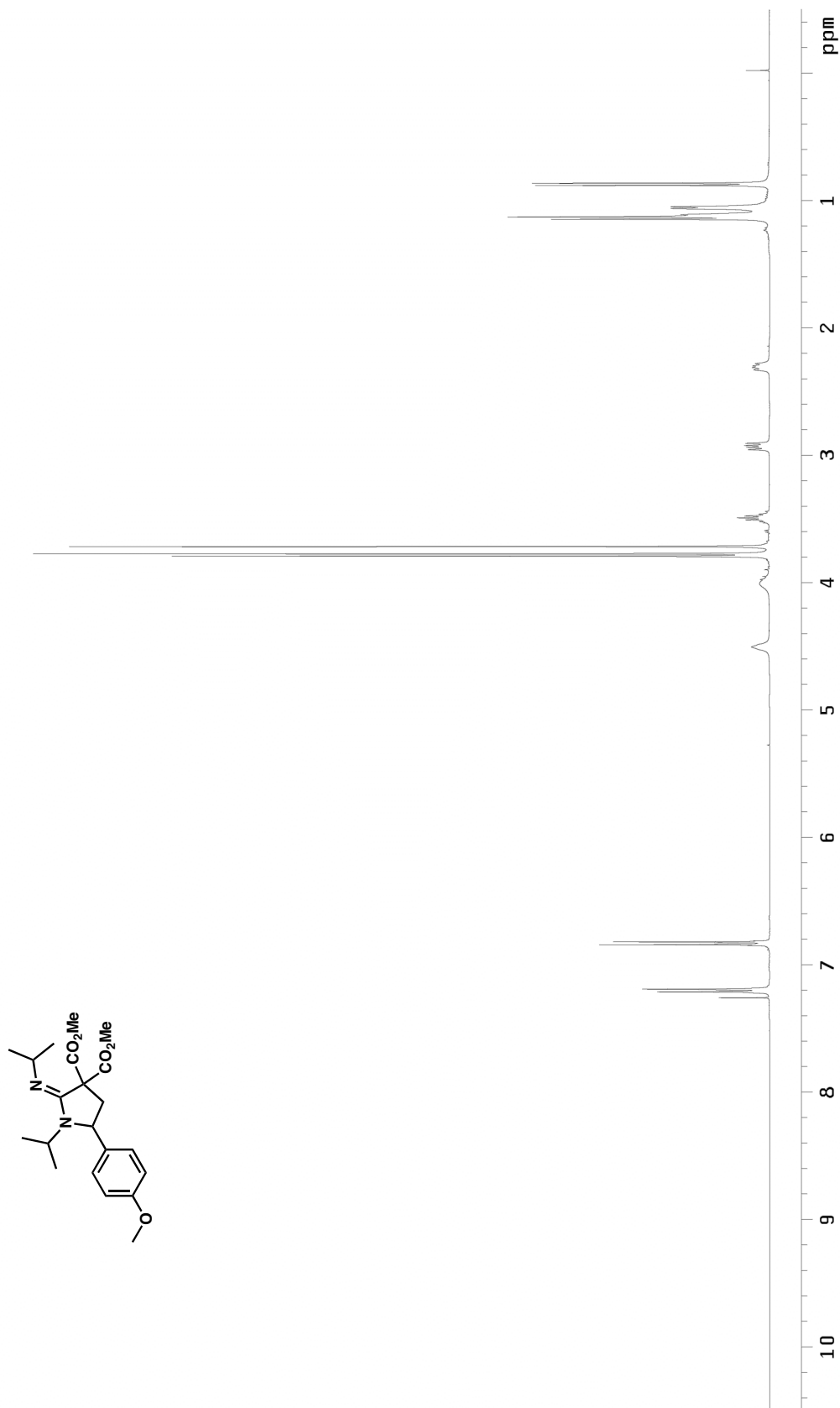


Figure A2.85 ^1H NMR (400 MHz, CDCl_3) of compound **61**

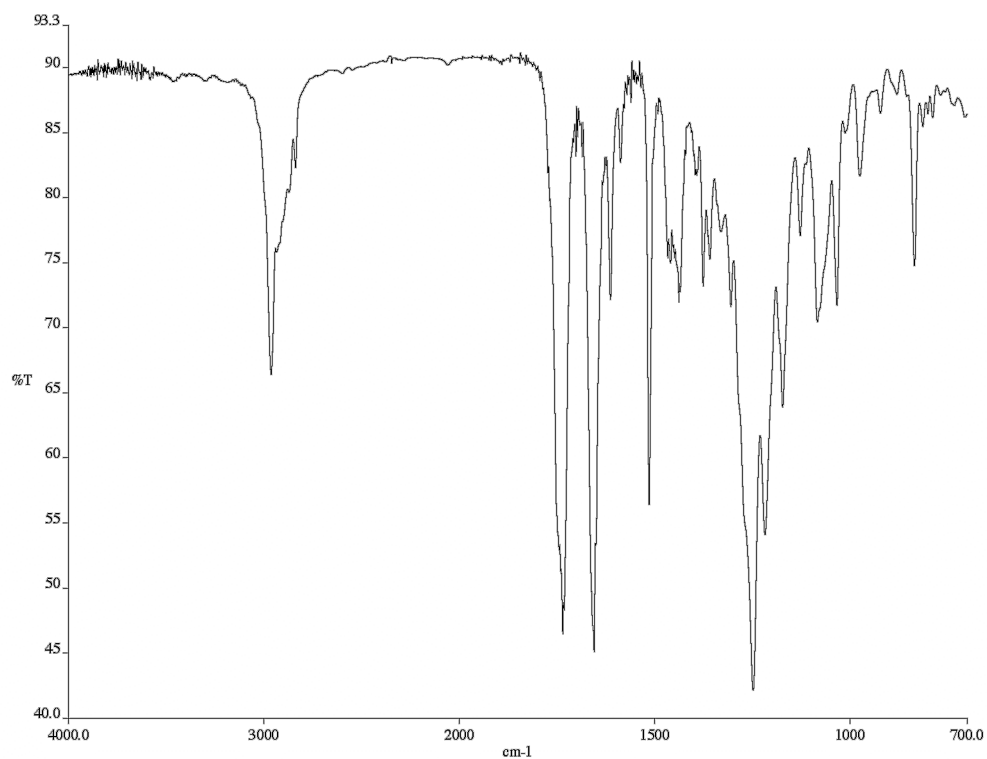


Figure A2.86 Infrared spectrum (thin film/NaCl) of compound **61**

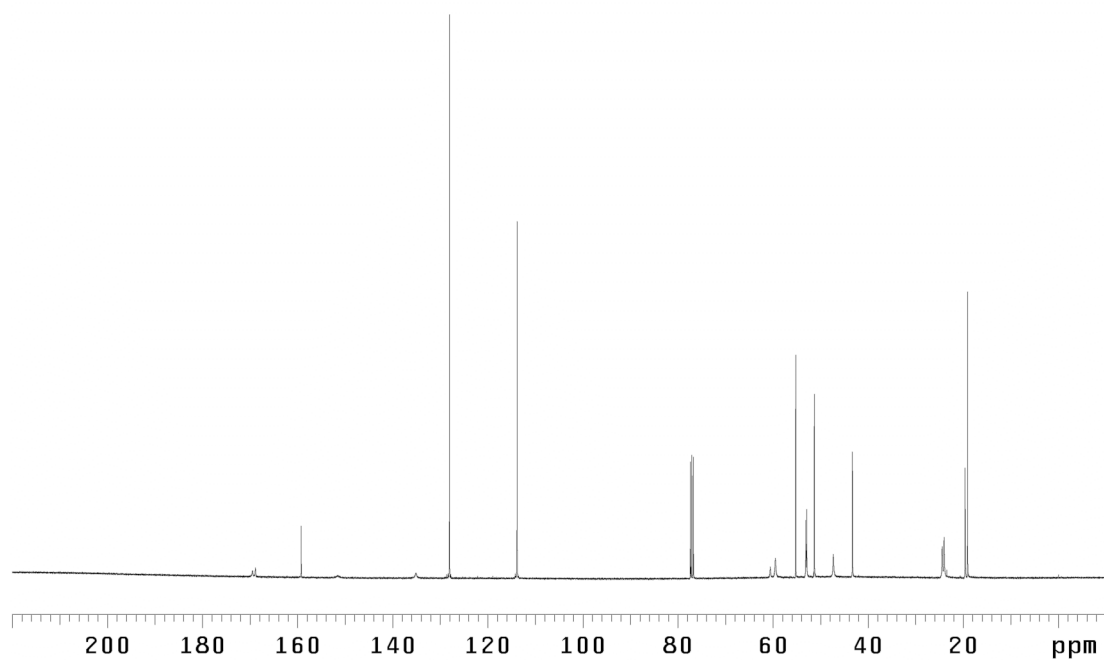


Figure A2.87 ¹³C NMR (101 MHz, CDCl₃) of compound **61**

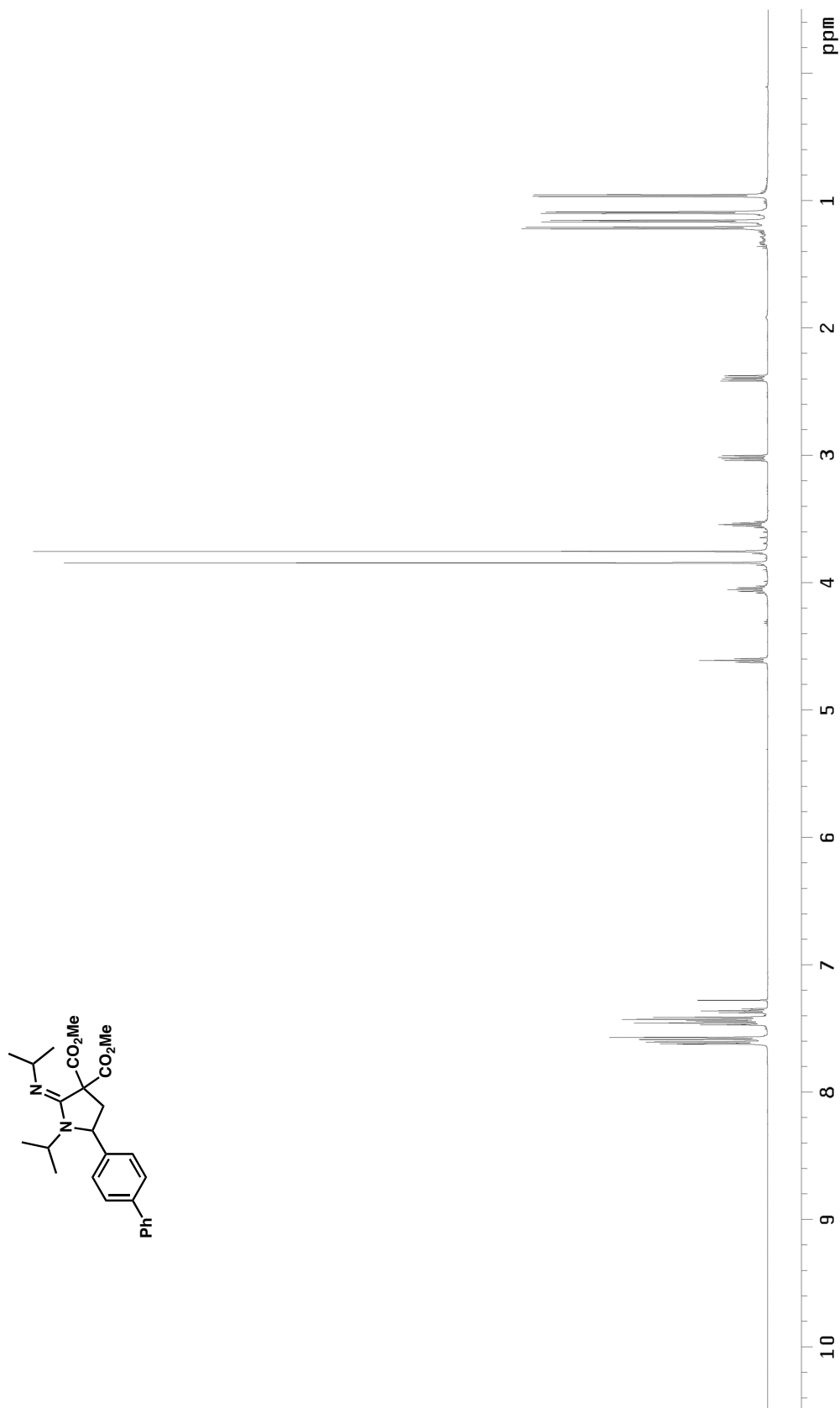


Figure A2.88 ¹H NMR (500 MHz, CDCl₃) of compound **62**

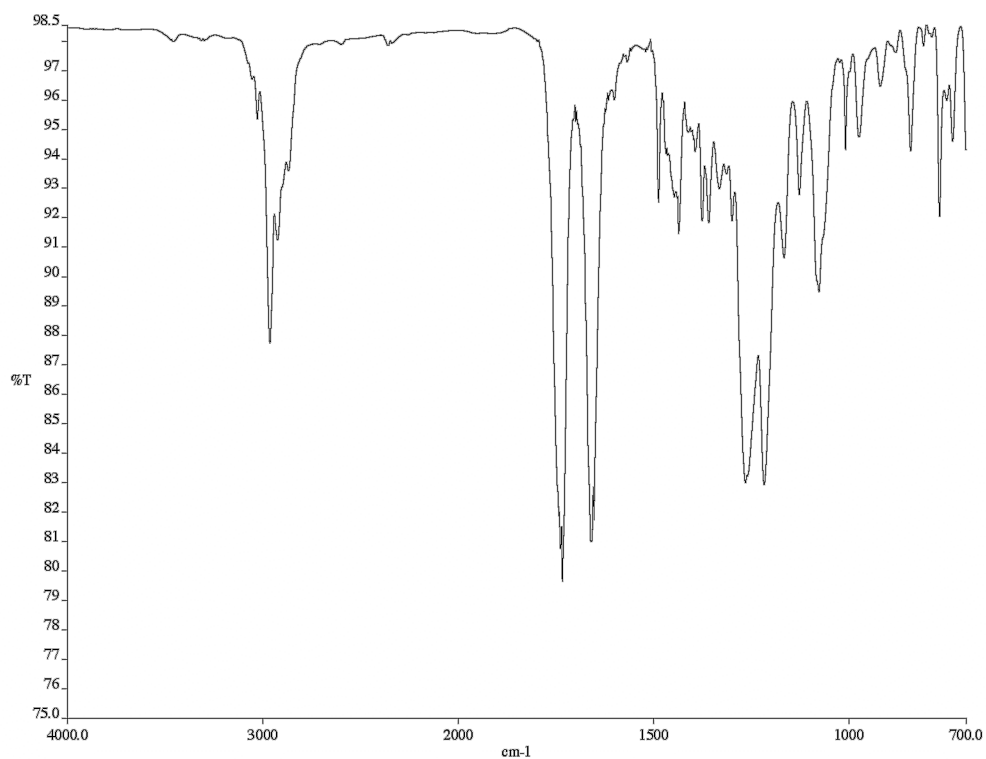


Figure A2.89 Infrared spectrum (thin film/NaCl) of compound **62**

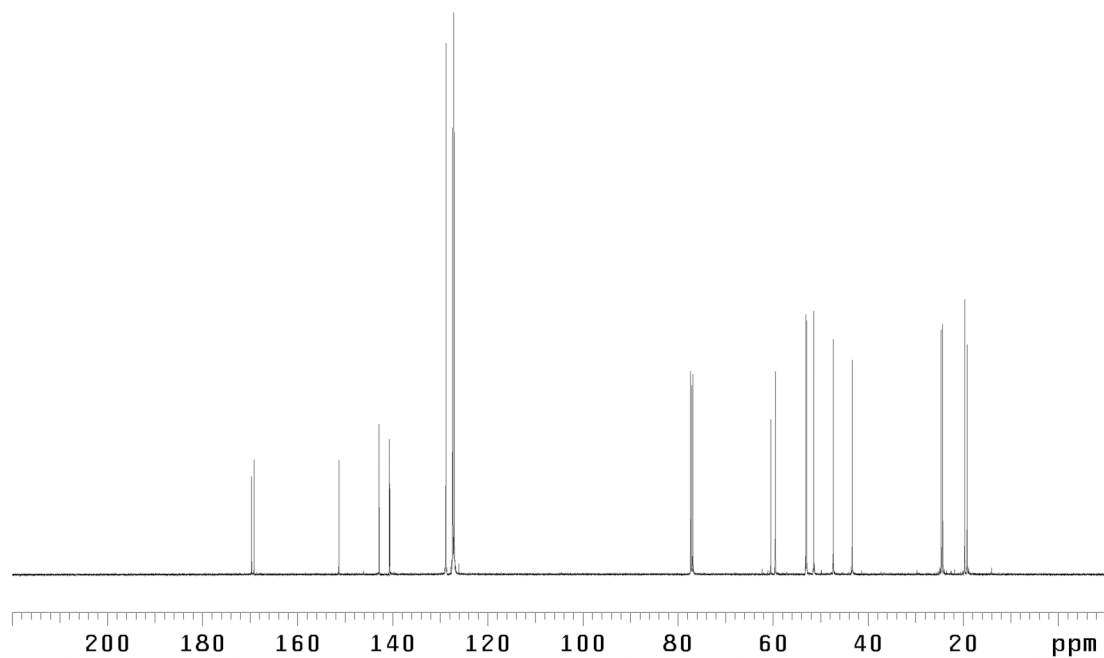


Figure A2.90 ¹³C NMR (126 MHz, CDCl₃) of compound **62**

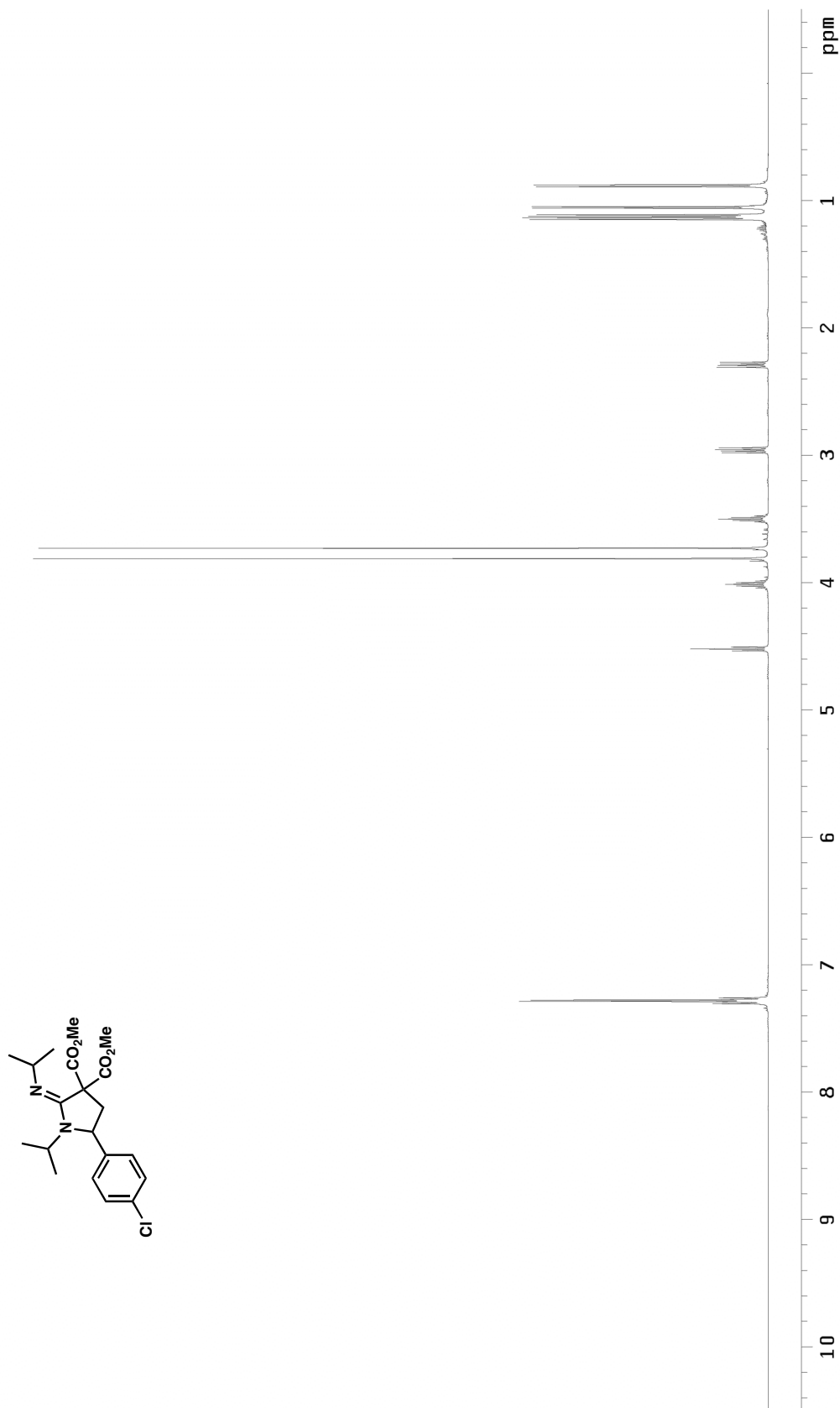


Figure A2.91 ¹H NMR (500 MHz, CDCl₃) of compound **63**

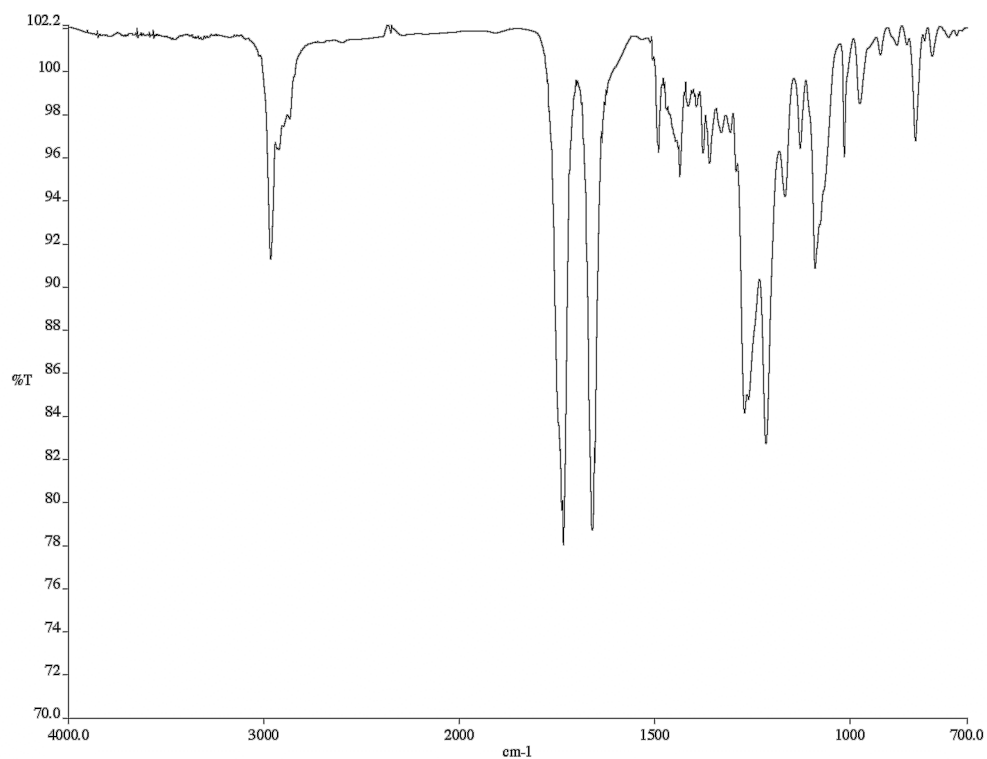


Figure A2.92 Infrared spectrum (thin film/NaCl) of compound **63**

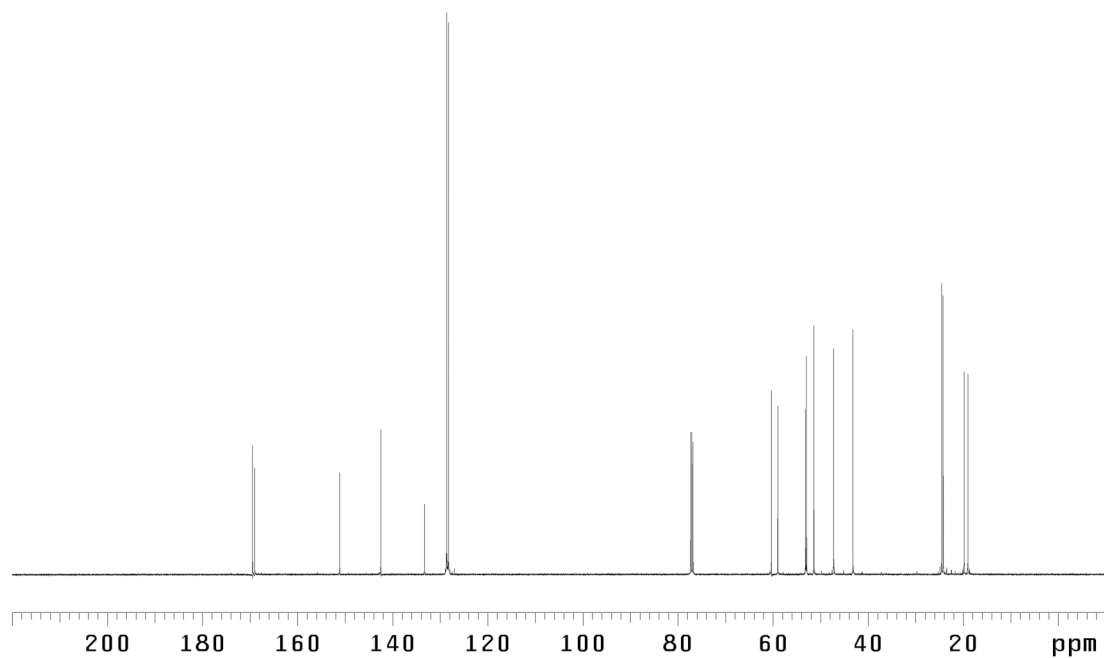


Figure A2.93 ¹³C NMR (126 MHz, CDCl₃) of compound **63**

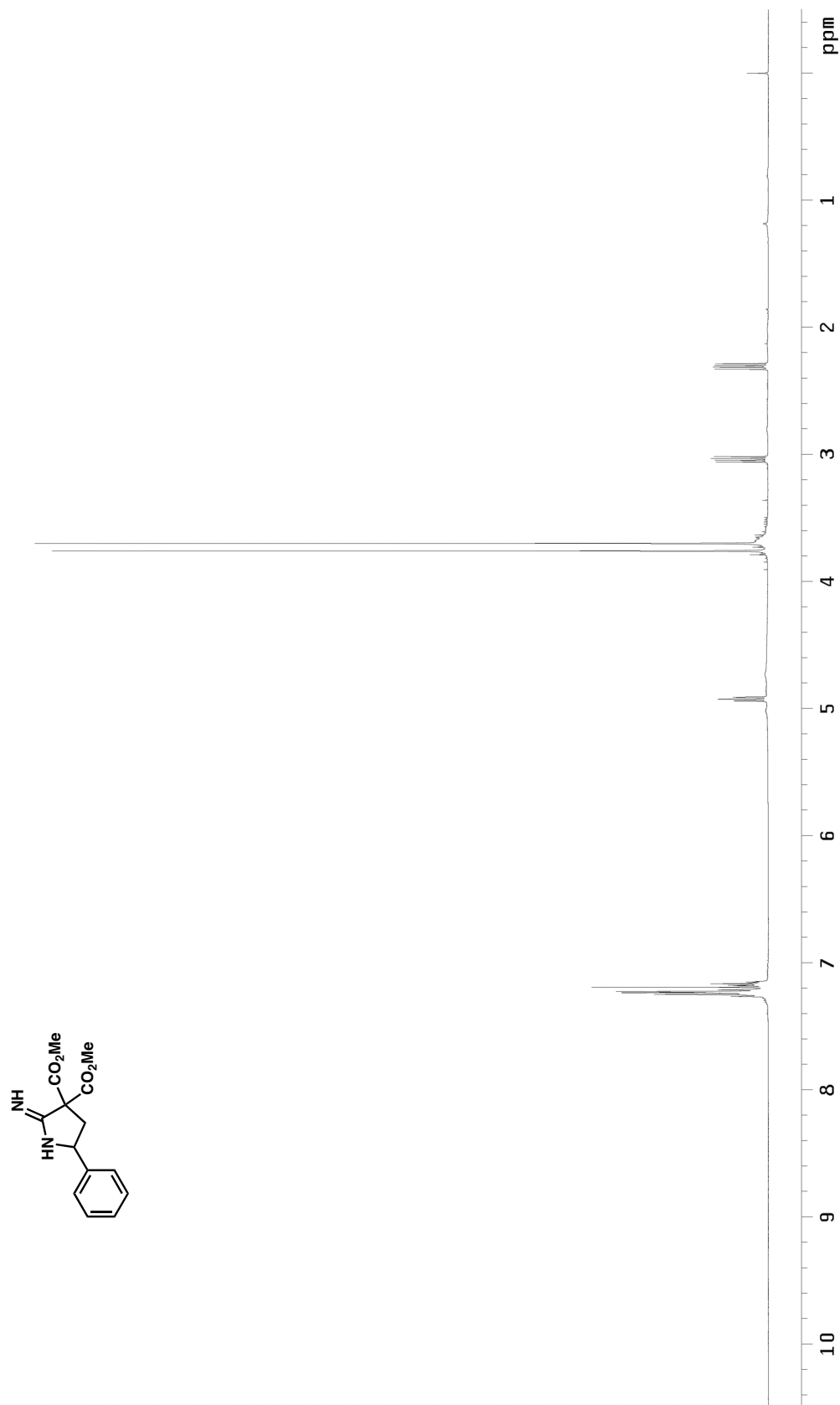


Figure A2.94 ¹H NMR (500 MHz, CDCl₃) of compound **64**

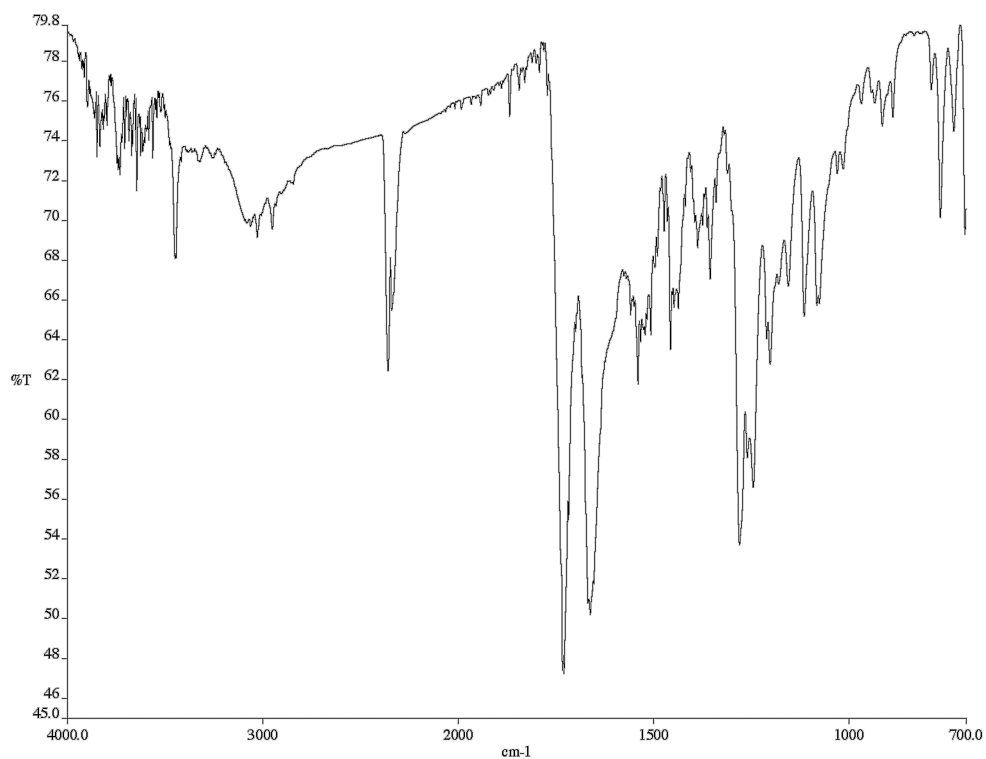


Figure A2.95 Infrared spectrum (thin film/NaCl) of compound **64**

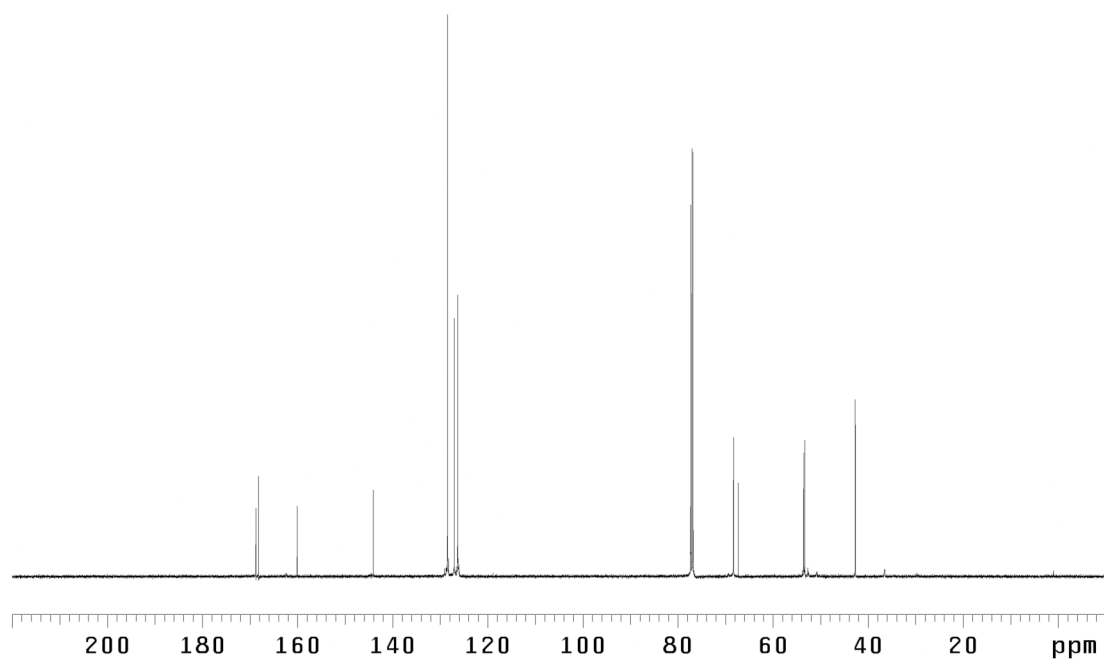


Figure A2.96 ¹³C NMR (126 MHz, CDCl₃) of compound **64**

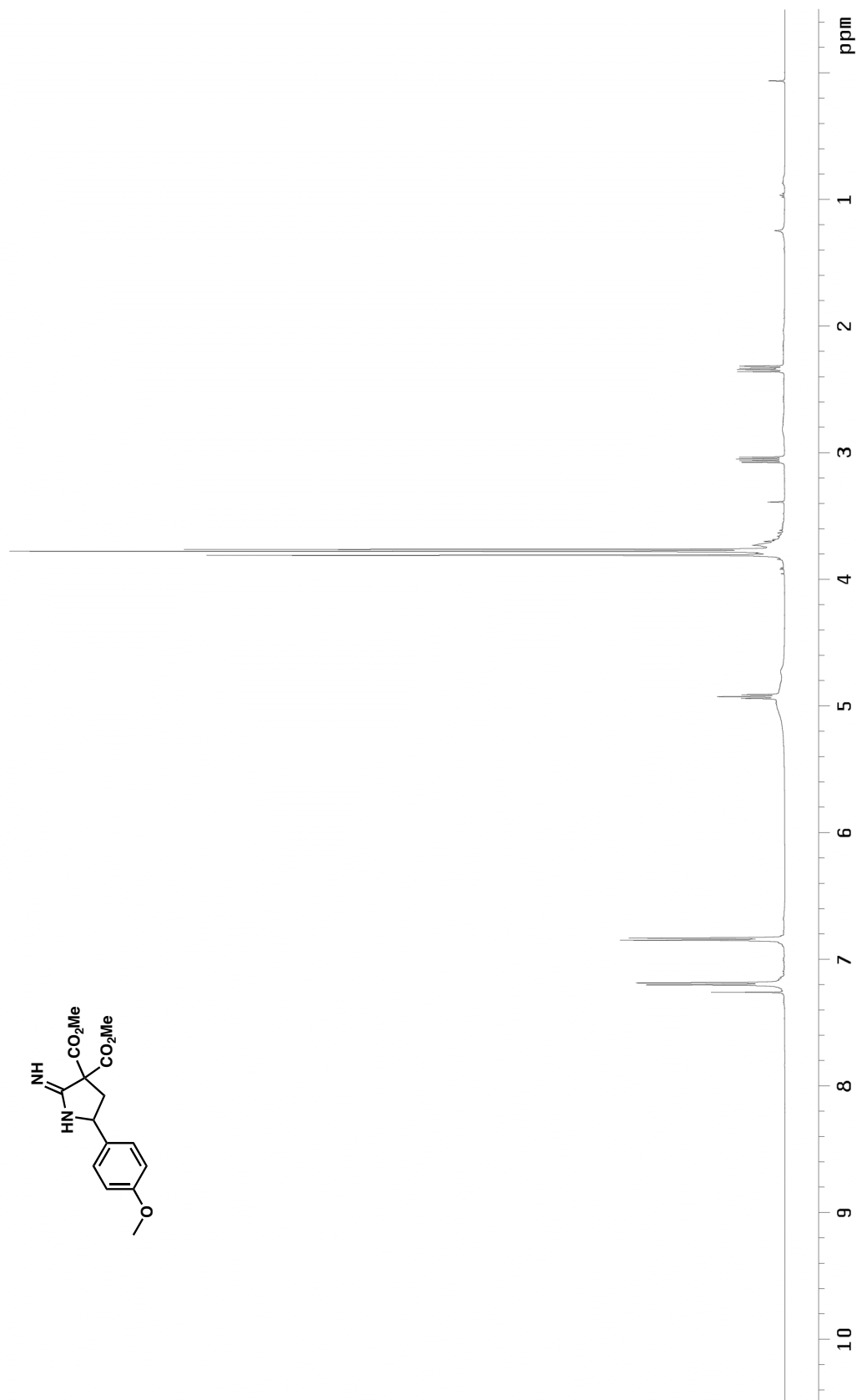


Figure A2.97 ¹H NMR (500 MHz, CDCl₃) of compound **65**

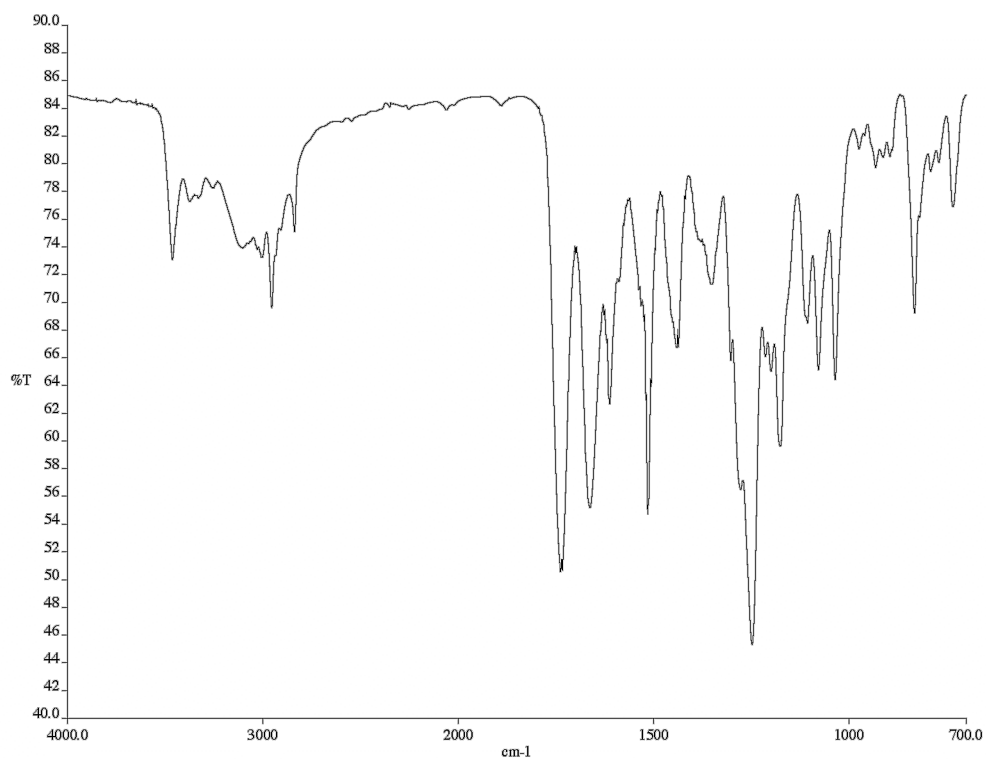


Figure A2.98 Infrared spectrum (thin film/NaCl) of compound **65**

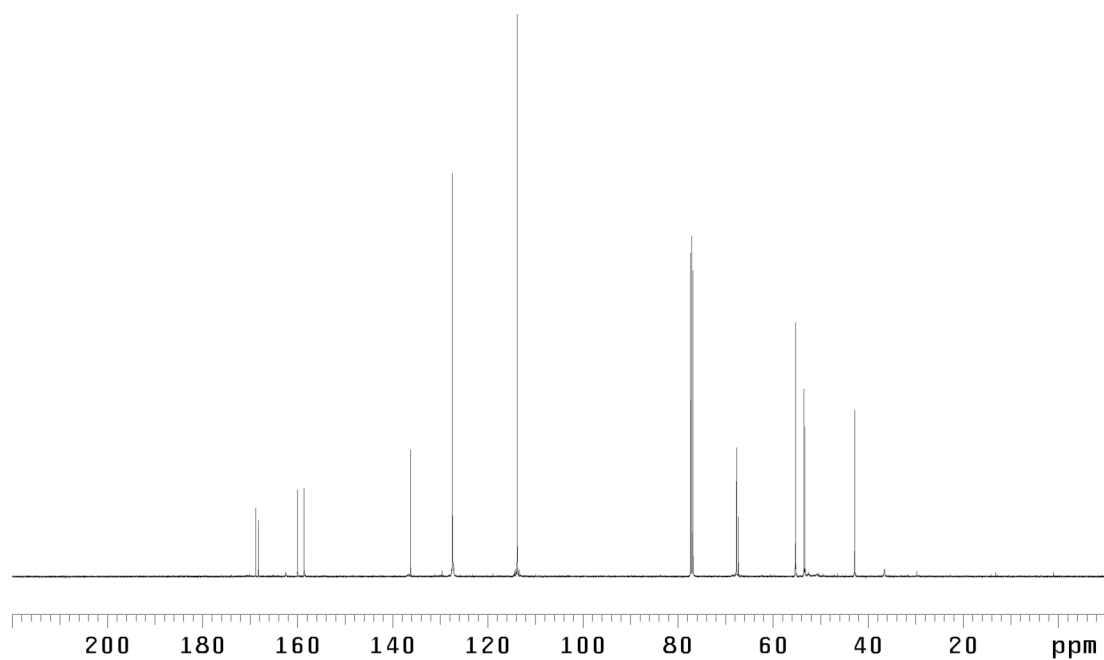


Figure A2.99 ¹³C NMR (126 MHz, CDCl₃) of compound **65**

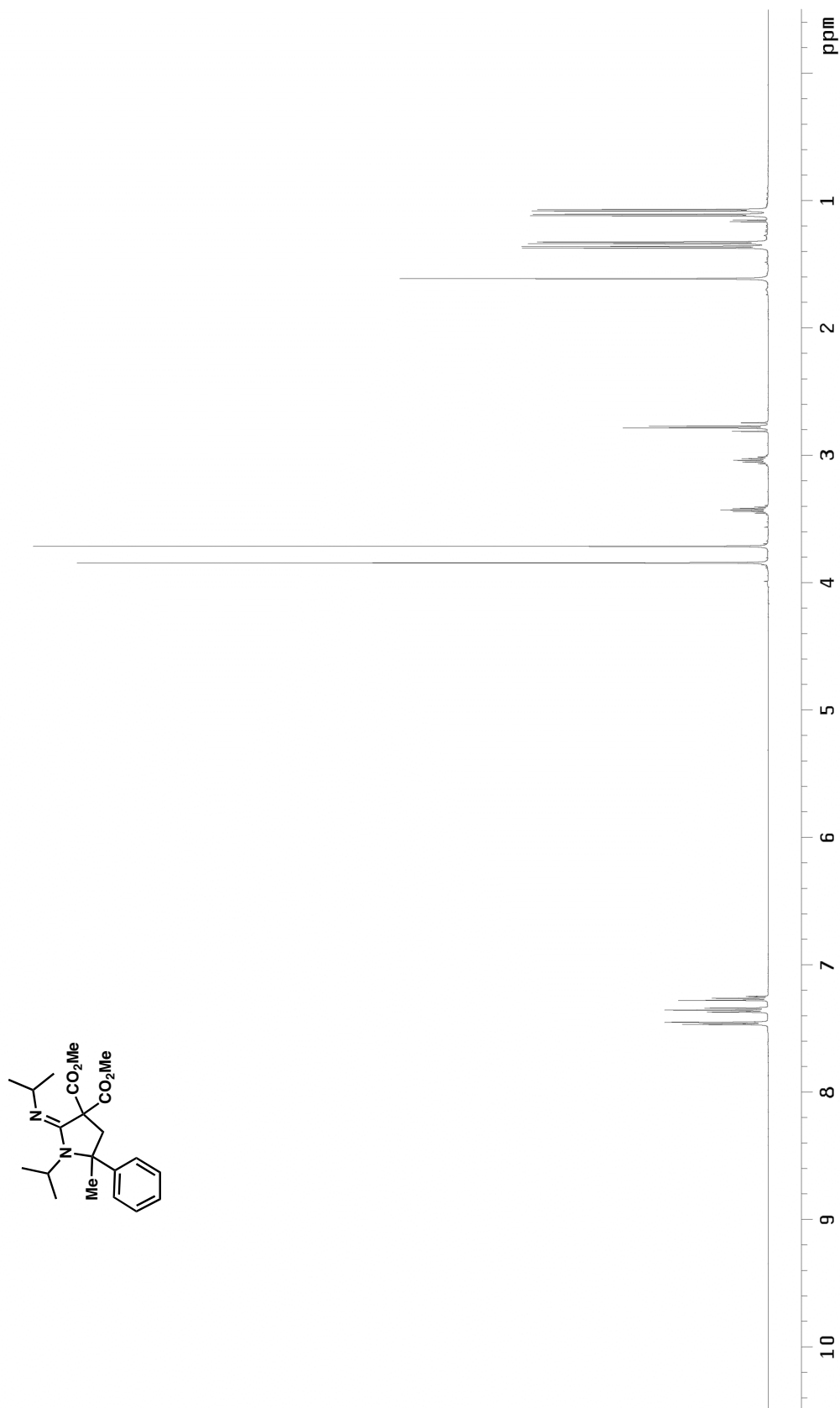


Figure A2.100 ¹H NMR (500 MHz, CDCl₃) of compound **66**

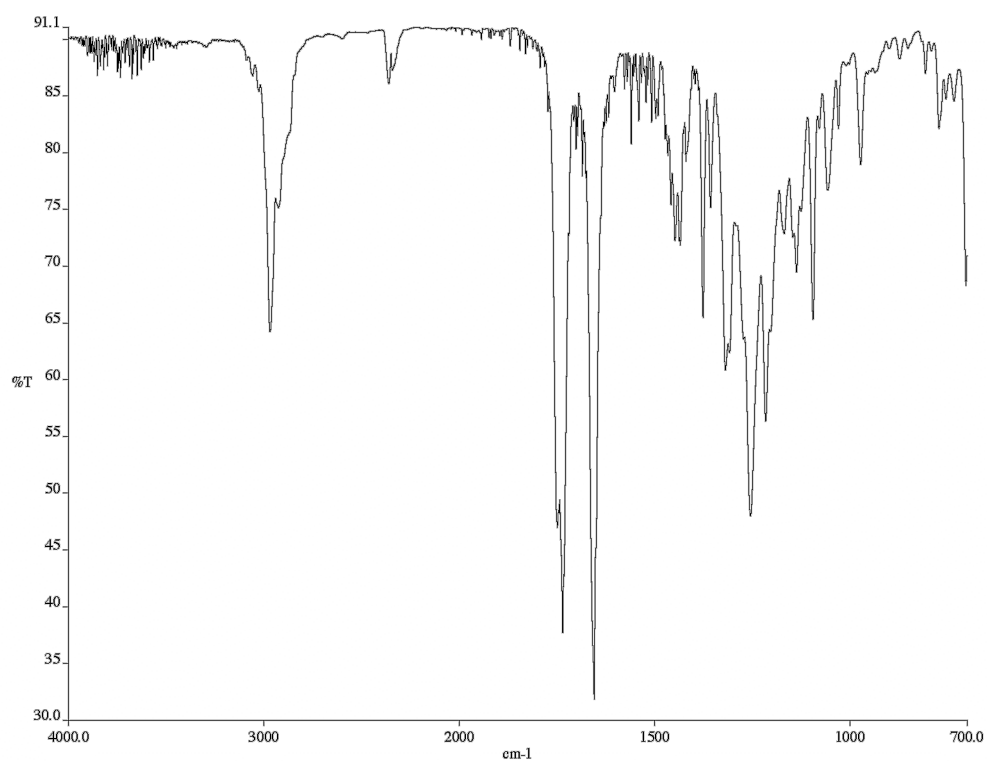


Figure A2.101 Infrared spectrum (thin film/NaCl) of compound **66**

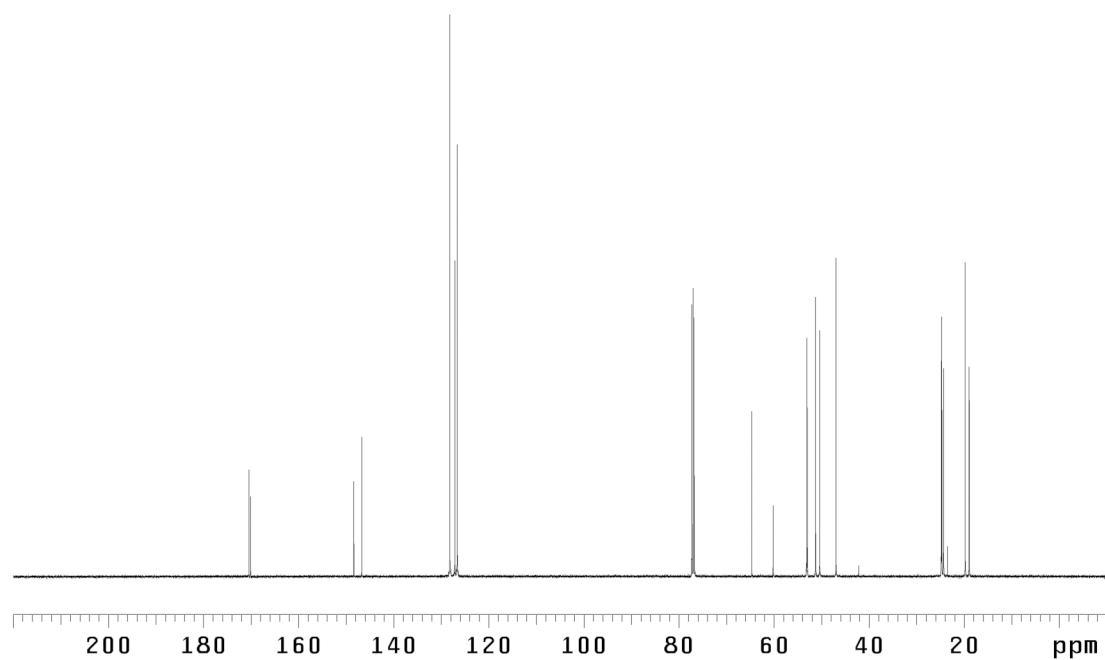


Figure A2.102 ¹³C NMR (126 MHz, CDCl₃) of compound **66**

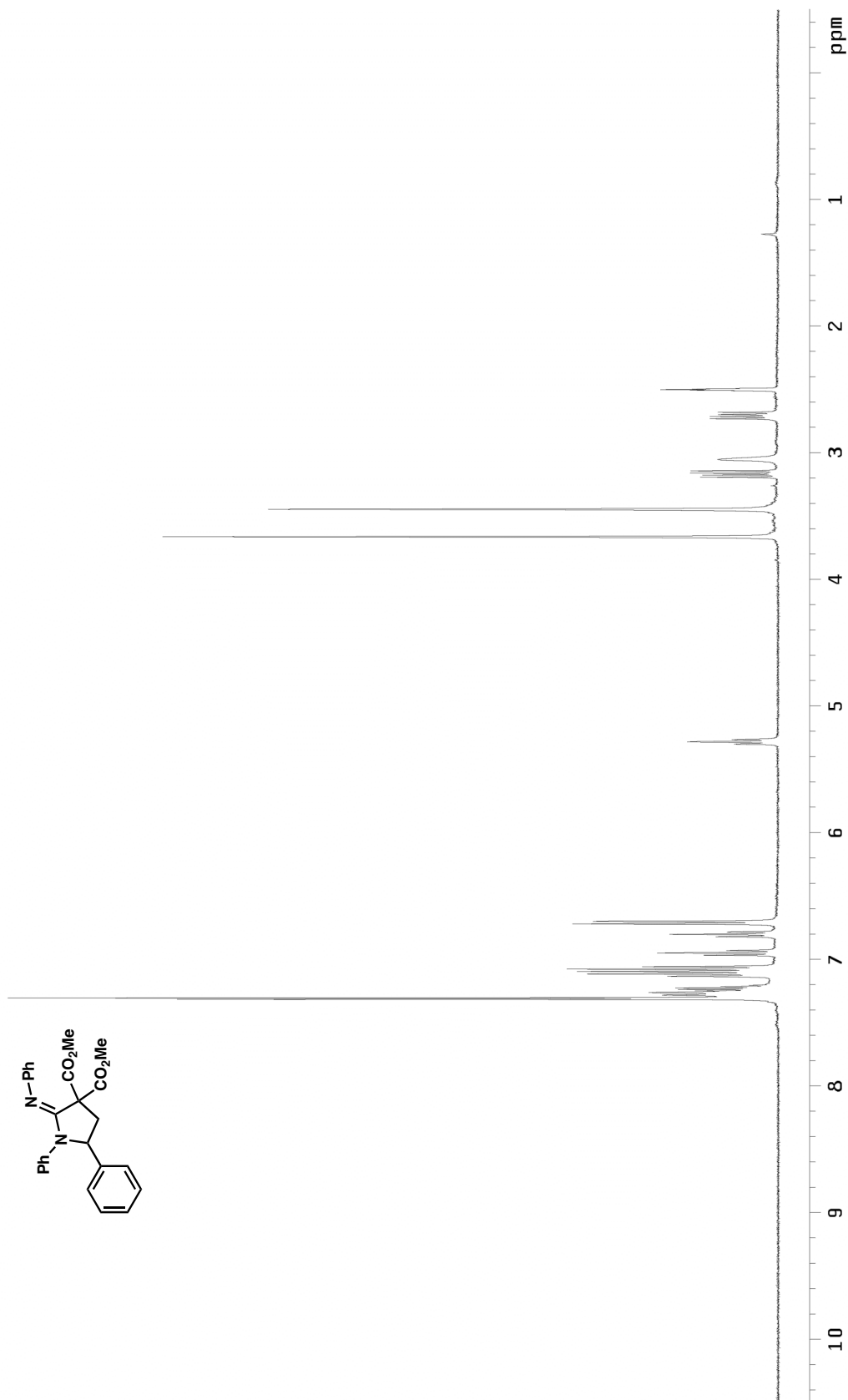


Figure A2.103 ¹H NMR (400 MHz, DMSO-d₆, 80 °C) of compound **67**

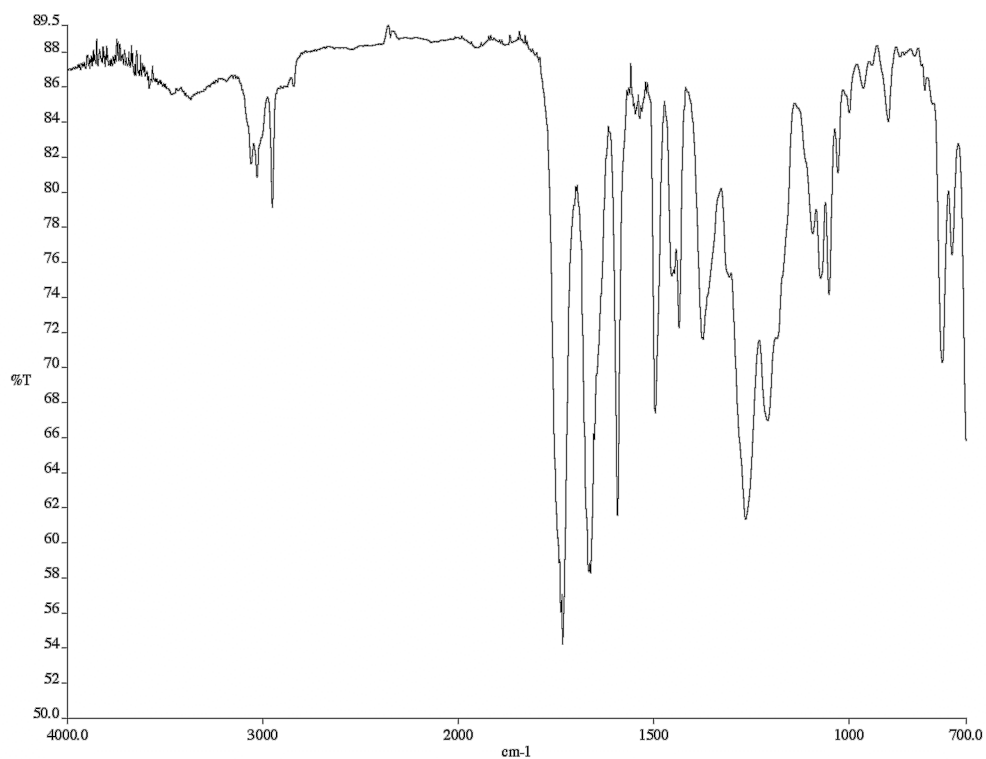


Figure A2.104 Infrared spectrum (thin film/NaCl) of compound **67**

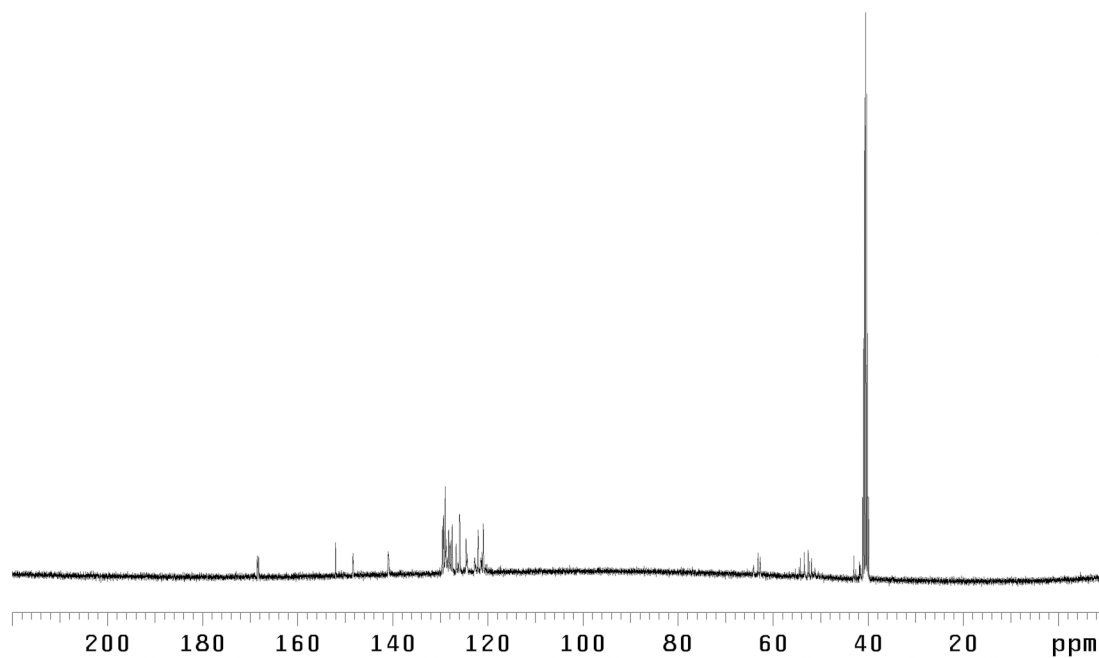


Figure A2.105 ¹³C NMR (101 MHz, DMSO-d₆, 100 °C) of compound **67**

APPENDIX 3

X-ray Crystallography Reports

Relevant to Chapter 1

A3.1

CRYSTAL STRUCTURE ANALYSIS FOR COMPOUND 52

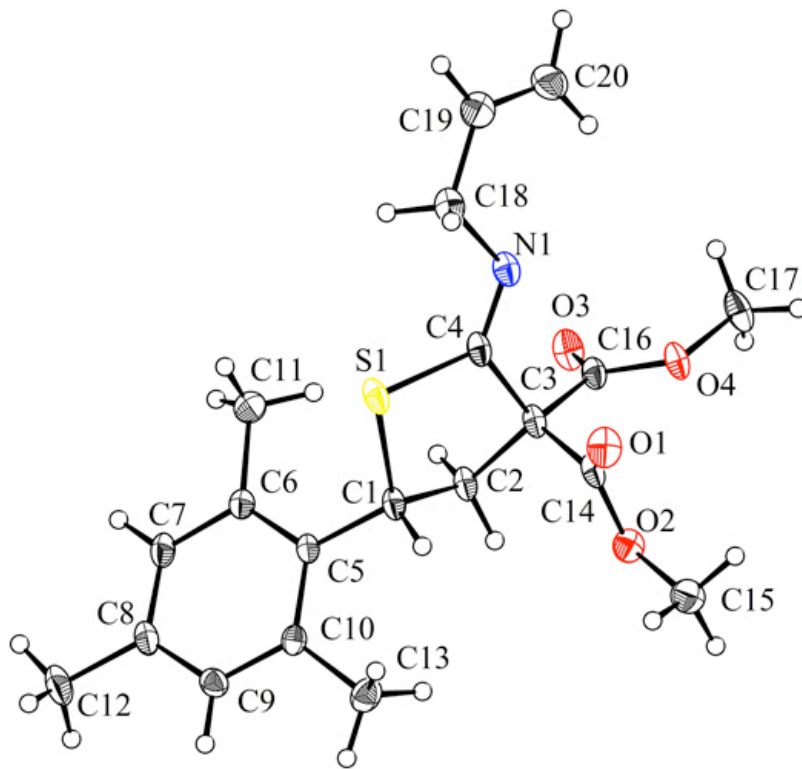


Table A3.1.1. Crystal data and structure analysis details for **52**.

Empirical formula	C ₂₀ H ₂₅ N O ₄ S
Formula weight	375.47
Crystallization solvent	Benzene/Heptane/Ethyl Acetate
Crystal shape	?
Crystal color	colourless
Crystal size	0.08 x 0.19 x 0.46 mm

Data Collection

Preliminary photograph(s)	rotation
Type of diffractometer	Bruker KAPPA APEX II
Wavelength	0.71073 $\approx$ MO K
Data collection temperature	100.15 K
Theta range for 5787 reflections used in lattice determination	2.521 to 31.600 $^\circ$
Unit cell dimensions	a = 14.5982(10) $\approx$ $\alpha = 90^\circ$ b = 16.1620(12) $\approx$ $\beta = 92.145(4)^\circ$ c = 8.2014(6) $\approx$ $\gamma = 90^\circ$
Volume	1933.7(2) $\approx^3$
Z	4
Crystal system	monoclinic
Space group	P 1 2 ₁ /c 1 (# 14)
Density (calculated)	1.290 g/cm ³
F(000)	800
Theta range for data collection	1.4 to 37.4 $^\circ$
Completeness to theta = 25.00 $^\circ$	100.0%
Index ranges	-24 $\leq$ h $\leq$ 24, 0 $\leq$ k $\leq$ 27, 0 $\leq$ l $\leq$ 13
Data collection scan type	narrow and scans
Reflections collected	15085
Independent reflections	15085 [$R_{\text{int}} = 0.0000$]
Reflections > 2 σ (I)	10418
Average σ (I)/(net I)	0.0676
Absorption coefficient	0.19 mm ⁻¹
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9848 and 0.9170

Reflections monitored for decay	0
Decay of standards	0%

Structure Solution and Refinement

Primary solution method	direct
Secondary solution method	difmap
Hydrogen placement	geom
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	15085 / 0 / 241
Treatment of hydrogen atoms	constr
Goodness-of-fit on F^2	1.06
Final R indices [$I > 2\sigma(I)$, 10418 reflections]	$R1 = 0.0592$, $wR2 = 0.1221$
R indices (all data)	$R1 = 0.1034$, $wR2 = 0.1431$
Type of weighting scheme used	calc
Weighting scheme used	calc
$w = 1 / [\sigma^2(F_o^2) + (0.0645P)^2 + 0.3700P]$ where $P = (F_o^2 + 2F_c^2) / 3$	
Max shift/error	0.001
Average shift/error	0.000
Largest diff. peak and hole	0.49 and -0.37 $e\text{\AA}^{-3}$

Programs Used

Cell refinement	SAINT V8.18C (Bruker-AXS, 2007)
Data collection	APEX2 2012.2-0 (Bruker-AXS, 2007)
Data reduction	SAINT V8.18C (Bruker-AXS, 2007)
Structure solution	SHELXS-97 (Sheldrick, 1990)
Structure refinement	SHELXL-97 (Sheldrick, 1997)
Graphics	DIAMOND 3 (Crystal Impact, 1999)

Table A3.1.2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\approx^2 \times 10^3$) for rac13. $U(eq)$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
S(1)	7001(1)	6892(1)	2895(1)	22(1)
O(1)	8360(1)	6282(1)	6404(1)	27(1)
O(2)	7480(1)	5212(1)	7100(1)	22(1)
O(3)	7866(1)	4219(1)	2706(1)	26(1)
O(4)	8857(1)	4560(1)	4768(1)	22(1)
N(1)	8660(1)	6157(1)	2476(1)	20(1)
C(1)	6183(1)	6259(1)	4018(2)	18(1)
C(2)	6567(1)	5375(1)	4014(2)	18(1)
C(3)	7607(1)	5456(1)	4275(2)	17(1)
C(4)	7894(1)	6152(1)	3131(2)	18(1)
C(5)	5192(1)	6358(1)	3430(1)	15(1)
C(6)	4890(1)	6274(1)	1789(1)	18(1)
C(7)	3969(1)	6418(1)	1363(2)	20(1)
C(8)	3336(1)	6643(1)	2493(2)	20(1)
C(9)	3634(1)	6687(1)	4121(2)	19(1)
C(10)	4541(1)	6543(1)	4608(1)	17(1)
C(11)	5514(1)	6056(1)	420(2)	26(1)
C(12)	2354(1)	6831(1)	1995(2)	29(1)
C(13)	4795(1)	6554(1)	6414(1)	24(1)
C(14)	7874(1)	5710(1)	6034(2)	18(1)
C(15)	7719(1)	5383(1)	8800(2)	26(1)
C(16)	8111(1)	4667(1)	3805(2)	18(1)
C(17)	9433(1)	3862(1)	4390(2)	29(1)
C(18)	8876(1)	6851(1)	1424(2)	23(1)
C(19)	9690(1)	6694(1)	428(2)	27(1)
C(20)	10218(1)	6036(1)	521(2)	31(1)

Table A3.1.3. Bond lengths [$\approx$] and angles [∞] for **52**.

S(1)-C(1)	1.8457(13)
S(1)-C(4)	1.7750(12)
O(1)-C(14)	1.1975(14)
O(2)-C(14)	1.3343(15)
O(2)-C(15)	1.4511(15)
O(3)-C(16)	1.1997(14)
O(4)-C(16)	1.3320(15)
O(4)-C(17)	1.4486(16)
N(1)-C(4)	1.2587(17)
N(1)-C(18)	1.4571(16)
C(1)-H(1)	1.0000
C(1)-C(2)	1.5343(16)
C(1)-C(5)	1.5167(17)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(2)-C(3)	1.5308(17)
C(3)-C(4)	1.5333(17)
C(3)-C(14)	1.5361(17)
C(3)-C(16)	1.5297(16)
C(5)-C(6)	1.4066(16)
C(5)-C(10)	1.4121(18)
C(6)-C(7)	1.3959(18)
C(6)-C(11)	1.5136(19)
C(7)-H(7)	0.9500
C(7)-C(8)	1.3812(19)
C(8)-C(9)	1.3904(17)
C(8)-C(12)	1.5075(18)
C(9)-H(9)	0.9500
C(9)-C(10)	1.3892(17)
C(10)-C(13)	1.5126(16)
C(11)-H(11A)	0.9800
C(11)-H(11B)	0.9800
C(11)-H(11C)	0.9800
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800
C(13)-H(13A)	0.9800
C(13)-H(13B)	0.9800

C(13)-H(13C)	0.9800
C(15)-H(15A)	0.9800
C(15)-H(15B)	0.9800
C(15)-H(15C)	0.9800
C(17)-H(17A)	0.9800
C(17)-H(17B)	0.9800
C(17)-H(17C)	0.9800
C(18)-H(18A)	0.9900
C(18)-H(18B)	0.9900
C(18)-C(19)	1.489(2)
C(19)-H(19)	0.9500
C(19)-C(20)	1.313(2)
C(20)-H(20A)	0.9500
C(20)-H(20B)	0.9500
C(4)-S(1)-C(1)	93.31(6)
C(14)-O(2)-C(15)	114.91(10)
C(16)-O(4)-C(17)	116.24(10)
C(4)-N(1)-C(18)	118.20(11)
S(1)-C(1)-H(1)	106.7
C(2)-C(1)-S(1)	105.80(9)
C(2)-C(1)-H(1)	106.7
C(5)-C(1)-S(1)	114.20(8)
C(5)-C(1)-H(1)	106.7
C(5)-C(1)-C(2)	116.22(10)
C(1)-C(2)-H(2A)	110.5
C(1)-C(2)-H(2B)	110.5
H(2A)-C(2)-H(2B)	108.7
C(3)-C(2)-C(1)	106.28(9)
C(3)-C(2)-H(2A)	110.5
C(3)-C(2)-H(2B)	110.5
C(2)-C(3)-C(4)	105.66(9)
C(2)-C(3)-C(14)	111.69(10)
C(4)-C(3)-C(14)	108.25(9)
C(16)-C(3)-C(2)	112.20(10)
C(16)-C(3)-C(4)	108.18(10)
C(16)-C(3)-C(14)	110.60(9)
N(1)-C(4)-S(1)	127.60(9)
N(1)-C(4)-C(3)	122.25(10)
C(3)-C(4)-S(1)	110.15(9)
C(6)-C(5)-C(1)	123.69(11)
C(6)-C(5)-C(10)	118.76(11)
C(10)-C(5)-C(1)	117.55(10)

C(5)-C(6)-C(11)	123.86(11)
C(7)-C(6)-C(5)	119.14(11)
C(7)-C(6)-C(11)	116.99(11)
C(6)-C(7)-H(7)	118.7
C(8)-C(7)-C(6)	122.59(11)
C(8)-C(7)-H(7)	118.7
C(7)-C(8)-C(9)	117.69(11)
C(7)-C(8)-C(12)	121.68(12)
C(9)-C(8)-C(12)	120.63(12)
C(8)-C(9)-H(9)	119.1
C(10)-C(9)-C(8)	121.88(11)
C(10)-C(9)-H(9)	119.1
C(5)-C(10)-C(13)	121.74(11)
C(9)-C(10)-C(5)	119.79(11)
C(9)-C(10)-C(13)	118.41(11)
C(6)-C(11)-H(11A)	109.5
C(6)-C(11)-H(11B)	109.5
C(6)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5
C(8)-C(12)-H(12A)	109.5
C(8)-C(12)-H(12B)	109.5
C(8)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
C(10)-C(13)-H(13A)	109.5
C(10)-C(13)-H(13B)	109.5
C(10)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5
O(1)-C(14)-O(2)	124.42(11)
O(1)-C(14)-C(3)	124.85(12)
O(2)-C(14)-C(3)	110.72(10)
O(2)-C(15)-H(15A)	109.5
O(2)-C(15)-H(15B)	109.5
O(2)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5
O(3)-C(16)-O(4)	125.53(11)

O(3)-C(16)-C(3)	124.03(11)
O(4)-C(16)-C(3)	110.43(10)
O(4)-C(17)-H(17A)	109.5
O(4)-C(17)-H(17B)	109.5
O(4)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5
N(1)-C(18)-H(18A)	109.0
N(1)-C(18)-H(18B)	109.0
N(1)-C(18)-C(19)	112.84(11)
H(18A)-C(18)-H(18B)	107.8
C(19)-C(18)-H(18A)	109.0
C(19)-C(18)-H(18B)	109.0
C(18)-C(19)-H(19)	117.1
C(20)-C(19)-C(18)	125.79(13)
C(20)-C(19)-H(19)	117.1
C(19)-C(20)-H(20A)	120.0
C(19)-C(20)-H(20B)	120.0
H(20A)-C(20)-H(20B)	120.0

Symmetry transformations used to generate equivalent atoms:

Table A3.1.4. Anisotropic displacement parameters ($\approx \times 10^4$) for **52**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	146(1)	147(1)	372(2)	67(1)	-20(1)	19(1)
O(1)	275(6)	192(4)	326(5)	-16(4)	-66(4)	-65(4)
O(2)	204(5)	218(4)	232(4)	-6(3)	-28(3)	-45(3)
O(3)	261(5)	201(4)	313(5)	-57(4)	-71(4)	32(4)
O(4)	175(5)	176(4)	300(5)	-10(3)	-55(3)	60(3)
N(1)	170(5)	157(4)	275(5)	8(4)	-34(4)	-1(4)
C(1)	140(6)	152(5)	228(5)	21(4)	-52(4)	-1(4)
C(2)	142(6)	134(5)	259(6)	23(4)	-55(4)	-3(4)
C(3)	136(6)	125(5)	245(5)	10(4)	-47(4)	5(4)
C(4)	160(6)	127(5)	256(6)	6(4)	-50(5)	11(4)
C(5)	138(5)	139(5)	181(5)	20(4)	-28(4)	4(4)
C(6)	174(6)	184(5)	173(5)	13(4)	-19(4)	7(4)
C(7)	185(6)	211(6)	210(5)	35(4)	-70(5)	-12(5)
C(8)	145(6)	157(5)	286(6)	54(4)	-41(5)	-6(4)
C(9)	177(6)	168(5)	237(5)	19(4)	25(5)	20(4)
C(10)	192(6)	127(5)	180(5)	16(4)	-14(4)	13(4)
C(11)	258(7)	331(7)	186(5)	-2(5)	10(5)	35(6)
C(12)	152(6)	289(7)	436(8)	87(6)	-65(6)	12(5)
C(13)	311(8)	249(6)	171(5)	-12(5)	-13(5)	31(5)
C(14)	130(6)	132(5)	272(6)	0(4)	-39(4)	27(4)
C(15)	236(7)	302(7)	241(6)	-38(5)	-11(5)	-12(5)
C(16)	158(6)	137(5)	248(6)	31(4)	-22(5)	14(4)
C(17)	232(7)	237(7)	401(8)	-37(6)	-48(6)	116(5)
C(18)	207(7)	182(5)	301(6)	22(5)	-30(5)	-21(5)
C(19)	219(7)	292(7)	309(7)	32(5)	-34(5)	-87(5)
C(20)	211(7)	391(8)	323(7)	-5(6)	2(6)	-20(6)

Table A3.1.5. Hydrogen coordinates ($\times 10^3$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **52**.

	x	y	z	U _{iso}
H(1)	622	645	518	21
H(2A)	631	504	490	22
H(2B)	641	510	296	22
H(7)	377	636	25	24
H(9)	320	682	492	23
H(11A)	516	576	-44	39
H(11B)	601	570	84	39
H(11C)	578	656	-2	39
H(12A)	227	677	81	44
H(12B)	221	740	230	44
H(12C)	195	645	255	44
H(13A)	424	663	704	37
H(13B)	522	701	665	37
H(13C)	509	603	672	37
H(15A)	839	538	896	39
H(15B)	745	496	949	39
H(15C)	748	593	910	39
H(17A)	907	335	441	44
H(17B)	994	382	520	44
H(17C)	968	394	330	44
H(18A)	899	735	211	28
H(18B)	834	697	68	28
H(19)	984	711	-34	33
H(20A)	1009	561	128	37
H(20B)	1072	599	-17	37

A3.2 CRYSTAL STRUCTURE ANALYSIS FOR COMPOUND (R)-60•HBr

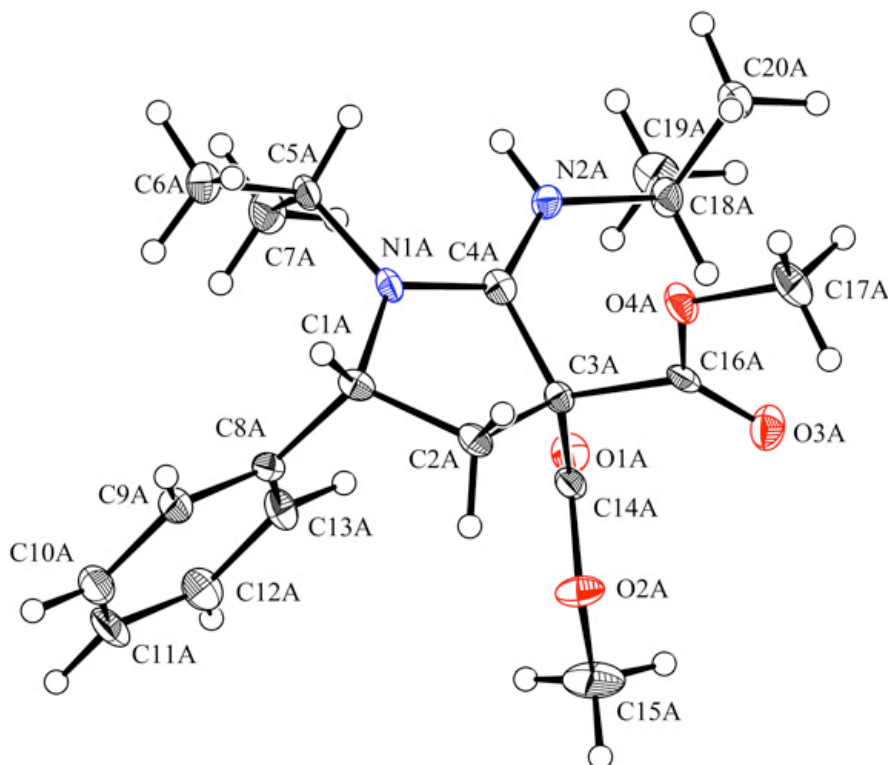


Table A3.2.1. Crystal data and structure analysis details for (R)-60•HBr.

Empirical formula	C ₂₀ H ₃₁ Br N ₂ O ₅
Formula weight	459.38
Crystallization solvent	diethyl ether / dichloromethane
Crystal shape	prism
Crystal color	colourless
Crystal size	0.17 x 0.18 x 0.47 mm

Data Collection

Preliminary photograph(s)	rotation
Type of diffractometer	Bruker KAPPA APEX II
Wavelength	0.71073 $\approx$ MO K

Data collection temperature	100.15 K	
Theta range for 9397 reflections used in lattice determination	2.620 to 31.334°	
Unit cell dimensions	a = 8.0748(6) Å b = 15.1323(12) Å c = 29.190(2) Å	$\alpha = 98.815(5)^\circ$ $\beta = 92.189(5)^\circ$ $\gamma = 105.250(4)^\circ$
Volume	3388.9(5) Å ³	
Z	6	
Crystal system	triclinic	
Space group	P 1 (# 1)	
Density (calculated)	1.351 g/cm ³	
F(000)	1440	
Theta range for data collection	1.7 to 35.3°	
Completeness to theta = 25.00°	99.7%	
Index ranges	-12 ≤ h ≤ 12, -24 ≤ k ≤ 24, -46 ≤ l ≤ 45	
Data collection scan type	narrow and scans	
Reflections collected	161414	
Independent reflections	54469 [R _{int} = 0.0430]	
Reflections > 2σ(I)	44420	
Average σ(I)/(net I)	0.0781	
Absorption coefficient	1.85 mm ⁻¹	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.0000 and 0.8047	
Reflections monitored for decay	0	
Decay of standards	0%	

Structure Solution and Refinement

Primary solution method	direct
Secondary solution method	difmap
Hydrogen placement	geom
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	54469 / 21 / 1585
Treatment of hydrogen atoms	mixed
Goodness-of-fit on F ²	1.65
Final R indices [I > 2σ(I), 44420 reflections]	R1 = 0.0568, wR2 = 0.1138
R indices (all data)	R1 = 0.0743, wR2 = 0.1159
Type of weighting scheme used	calc
Weighting scheme used	calc $w = 1/[\sigma^2(F_o^2) + (0.0000P)^2 + 0.0000P]$ where

$$P=(F_o^2+2F_c^2)/3$$

Max shift/error	0.001
Average shift/error	0.000
Absolute structure parameter	0.029(3)
Largest diff. peak and hole	3.05 and -1.34 e Σ ³

Programs Used

Cell refinement	SAINT V8.18C (Bruker-AXS, 2007)
Data collection	APEX2_2011.2-3 (Bruker-AXS, 2007)
Data reduction	SAINT V8.18C (Bruker-AXS, 2007)
Structure solution	SHELXS-97 (Sheldrick, 1990)
Structure refinement	
Graphics	

Table A3.2.2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\approx^2 \times 10^3$) for (R)-**60**•HBr. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U_{eq}
O(1A)	5205(3)	3297(1)	8553(1)	18(1)
O(2A)	8042(3)	3464(1)	8523(1)	23(1)
O(3A)	7013(3)	1830(2)	9013(1)	23(1)
O(4A)	6394(3)	573(1)	8452(1)	19(1)
N(1A)	4511(3)	1542(2)	7520(1)	13(1)
N(2A)	2967(3)	1288(2)	8164(1)	14(1)
C(1A)	6285(4)	1836(2)	7379(1)	14(1)
C(2A)	7391(4)	1877(2)	7827(1)	14(1)
C(3A)	6203(4)	1976(2)	8227(1)	12(1)
C(4A)	4428(4)	1573(2)	7975(1)	14(1)
C(5A)	2951(4)	1256(2)	7188(1)	16(1)
C(6A)	3358(5)	925(2)	6694(1)	24(1)
C(7A)	2076(4)	2039(2)	7207(1)	23(1)
C(8A)	6672(4)	2728(2)	7175(1)	15(1)
C(9A)	7542(4)	2761(2)	6775(1)	18(1)
C(10A)	8003(4)	3575(2)	6590(1)	21(1)
C(11A)	7600(4)	4364(2)	6807(1)	23(1)
C(12A)	6731(4)	4340(2)	7206(1)	22(1)
C(13A)	6259(4)	3527(2)	7390(1)	18(1)
C(14A)	6408(4)	2992(2)	8455(1)	14(1)
C(15A)	8393(5)	4430(2)	8746(1)	34(1)

C(16A)	6583(4)	1461(2)	8621(1)	14(1)
C(17A)	6827(5)	27(2)	8784(1)	25(1)
C(18A)	2705(4)	1332(2)	8666(1)	18(1)
C(19A)	1333(5)	1853(2)	8773(1)	26(1)
C(20A)	2143(4)	350(2)	8781(1)	23(1)
O(1B)	2761(3)	3136(1)	5141(1)	17(1)
O(2B)	5580(3)	3478(1)	5045(1)	21(1)
O(3B)	5020(3)	2039(1)	5691(1)	20(1)
O(4B)	4388(3)	642(1)	5224(1)	15(1)
N(1B)	2497(3)	1144(2)	4168(1)	13(1)
N(2B)	861(3)	1029(2)	4810(1)	13(1)
C(1B)	4227(4)	1579(2)	4036(1)	12(1)
C(2B)	5323(4)	1771(2)	4507(1)	14(1)
C(3B)	4061(4)	1890(2)	4879(1)	11(1)
C(4B)	2345(4)	1315(2)	4624(1)	10(1)
C(5B)	1134(4)	495(2)	3828(1)	16(1)
C(6B)	1108(6)	-489(2)	3872(1)	34(1)
C(7B)	1377(5)	664(2)	3331(1)	25(1)
C(8B)	4279(4)	2426(2)	3819(1)	16(1)
C(9B)	5329(4)	2597(2)	3455(1)	20(1)
C(10B)	5427(5)	3384(2)	3252(1)	27(1)
C(11B)	4507(5)	4012(2)	3411(1)	27(1)
C(12B)	3444(5)	3838(2)	3769(1)	29(1)
C(13B)	3321(4)	3048(2)	3970(1)	21(1)
C(14B)	4016(4)	2910(2)	5039(1)	14(1)
C(15B)	5731(5)	4454(2)	5218(1)	35(1)
C(16B)	4545(4)	1538(2)	5321(1)	11(1)
C(17B)	4834(4)	217(2)	5610(1)	19(1)
C(18B)	562(4)	1128(2)	5308(1)	16(1)
C(19B)	-769(4)	1662(2)	5395(1)	24(1)
C(20B)	24(5)	159(2)	5438(1)	23(1)
O(1C)	7414(3)	3248(1)	1843(1)	18(1)
O(2C)	10170(3)	3462(1)	1676(1)	20(1)
O(3C)	9486(3)	1908(1)	2270(1)	18(1)
O(4C)	8375(3)	559(1)	1779(1)	17(1)
N(1C)	6577(3)	1420(2)	803(1)	12(1)
N(2C)	5107(3)	1248(2)	1469(1)	14(1)
C(1C)	8322(4)	1713(2)	645(1)	14(1)
C(2C)	9463(4)	1764(2)	1090(1)	14(1)
C(3C)	8351(4)	1926(2)	1498(1)	12(1)
C(4C)	6541(4)	1503(2)	1260(1)	12(1)
C(5C)	4995(4)	1095(2)	474(1)	16(1)
C(6C)	5401(5)	735(2)	-8(1)	25(1)
C(7C)	4090(4)	1873(2)	480(1)	23(1)
C(8C)	8674(4)	2610(2)	448(1)	14(1)
C(9C)	9607(4)	2662(2)	57(1)	17(1)
C(10C)	10051(4)	3492(2)	-124(1)	22(1)
C(11C)	9592(4)	4260(2)	85(1)	21(1)
C(12C)	8658(4)	4211(2)	475(1)	19(1)
C(13C)	8190(4)	3389(2)	650(1)	17(1)
C(14C)	8566(4)	2959(2)	1696(1)	15(1)
C(15C)	10528(5)	4459(2)	1838(1)	28(1)
C(16C)	8817(4)	1481(2)	1902(1)	13(1)
C(17C)	8809(5)	56(2)	2138(1)	24(1)

C(18C)	4905(4)	1339(2)	1975(1)	15(1)
C(19C)	3653(5)	1915(2)	2094(1)	24(1)
C(20C)	4316(4)	374(2)	2103(1)	20(1)
O(1D)	1240(3)	5108(1)	6240(1)	20(1)
O(2D)	3700(3)	4743(1)	6402(1)	20(1)
O(3D)	4660(3)	6149(1)	5724(1)	18(1)
O(4D)	5282(3)	7583(1)	6158(1)	16(1)
N(1D)	3160(3)	7177(2)	7194(1)	15(1)
N(2D)	1547(3)	7222(2)	6524(1)	14(1)
C(1D)	4426(4)	6735(2)	7354(1)	16(1)
C(2D)	5261(4)	6488(2)	6909(1)	15(1)
C(3D)	3823(4)	6343(2)	6516(1)	13(1)
C(4D)	2718(4)	6949(2)	6737(1)	12(1)
C(5D)	2529(5)	7876(2)	7495(1)	21(1)
C(6D)	3492(7)	8846(2)	7419(1)	44(1)
C(7D)	2737(6)	7782(3)	8001(1)	40(1)
C(8D)	3631(4)	5924(2)	7600(1)	16(1)
C(9D)	4577(4)	5780(2)	7978(1)	19(1)
C(10D)	3931(5)	5037(2)	8204(1)	24(1)
C(11D)	2319(5)	4419(2)	8048(1)	24(1)
C(12D)	1365(4)	4564(2)	7676(1)	24(1)
C(13D)	2023(4)	5321(2)	7453(1)	19(1)
C(14D)	2742(4)	5328(2)	6366(1)	14(1)
C(15D)	2805(5)	3759(2)	6283(1)	26(1)
C(16D)	4603(4)	6663(2)	6069(1)	18(1)
C(17D)	6055(4)	7985(2)	5766(1)	20(1)
C(18D)	1059(4)	7056(2)	6019(1)	16(1)
C(19D)	-850(4)	6519(2)	5928(1)	22(1)
C(20D)	1460(5)	7990(2)	5849(1)	23(1)
O(1E)	8189(3)	5002(1)	2884(1)	17(1)
O(2E)	10789(3)	4812(1)	3084(1)	20(1)
O(3E)	11510(3)	6349(1)	2459(1)	19(1)
O(4E)	11784(3)	7706(1)	2936(1)	16(1)
N(1E)	9306(3)	6863(2)	3901(1)	14(1)
N(2E)	7912(3)	7004(2)	3214(1)	13(1)
C(1E)	10840(4)	6612(2)	4078(1)	15(1)
C(2E)	11850(4)	6544(2)	3643(1)	16(1)
C(3E)	10485(4)	6346(2)	3224(1)	13(1)
C(4E)	9125(4)	6767(2)	3441(1)	12(1)
C(5E)	8093(4)	7202(2)	4207(1)	17(1)
C(6E)	8924(5)	7597(2)	4695(1)	24(1)
C(7E)	6434(4)	6429(2)	4205(1)	25(1)
C(8E)	10401(4)	5743(2)	4298(1)	14(1)
C(9E)	11448(4)	5716(2)	4684(1)	18(1)
C(10E)	11196(5)	4923(2)	4890(1)	24(1)
C(11E)	9887(4)	4130(2)	4696(1)	25(1)
C(12E)	8829(4)	4150(2)	4313(1)	22(1)
C(13E)	9087(4)	4951(2)	4113(1)	20(1)
C(14E)	9677(4)	5308(2)	3044(1)	13(1)
C(15E)	10098(5)	3806(2)	2945(1)	28(1)
C(16E)	11305(4)	6788(2)	2820(1)	13(1)
C(17E)	12685(5)	8211(2)	2588(1)	22(1)
C(18E)	7528(4)	6881(2)	2704(1)	14(1)
C(19E)	5668(4)	6298(2)	2585(1)	19(1)

C(20E)	7882(4)	7829(2)	2556(1)	20(1)
O(1F)	3235(3)	5134(1)	-412(1)	19(1)
O(2F)	5671(3)	4755(1)	-225(1)	18(1)
O(3F)	6672(3)	6143(1)	-899(1)	18(1)
O(4F)	7152(3)	7587(1)	-500(1)	16(1)
N(1F)	5150(3)	7135(2)	573(1)	13(1)
N(2F)	3519(3)	7236(2)	-81(1)	12(1)
C(1F)	6479(4)	6698(2)	719(1)	14(1)
C(2F)	7291(4)	6503(2)	261(1)	14(1)
C(3F)	5819(4)	6356(2)	-119(1)	12(1)
C(4F)	4727(4)	6948(2)	117(1)	12(1)
C(5F)	4508(5)	7803(2)	905(1)	21(1)
C(6F)	5459(6)	8792(2)	852(1)	36(1)
C(7F)	4692(5)	7654(2)	1401(1)	27(1)
C(8F)	5722(4)	5850(2)	939(1)	16(1)
C(9F)	6733(5)	5676(2)	1296(1)	21(1)
C(10F)	6146(5)	4885(2)	1498(1)	26(1)
C(11F)	4527(5)	4264(2)	1334(1)	32(1)
C(12F)	3517(5)	4448(2)	988(1)	30(1)
C(13F)	4112(4)	5250(2)	793(1)	22(1)
C(14F)	4735(4)	5344(2)	-269(1)	14(1)
C(15F)	4757(5)	3776(2)	-342(1)	23(1)
C(16F)	6572(4)	6673(2)	-552(1)	11(1)
C(17F)	7860(4)	7967(2)	-903(1)	20(1)
C(18F)	3033(4)	7127(2)	-582(1)	15(1)
C(19F)	1129(4)	6619(2)	-683(1)	21(1)
C(20F)	3407(5)	8094(2)	-714(1)	23(1)
Br(1A)	8079(1)	123(1)	6649(1)	21(1)
Br(1B)	6474(1)	134(1)	3290(1)	18(1)
Br(1C)	137(1)	-30(1)	-14(1)	21(1)
Br(1D)	8418(1)	8234(1)	7949(1)	23(1)
Br(1E)	4521(1)	8396(1)	4618(1)	20(1)
Br(1F)	358(1)	8210(1)	1391(1)	21(1)
O(5A)	9657(3)	349(1)	7734(1)	19(1)
O(5B)	7574(3)	112(2)	4381(1)	21(1)
O(5C)	1767(3)	255(2)	1077(1)	20(1)
O(5D)	9265(3)	8257(2)	6859(1)	25(1)
O(5E)	5655(3)	8046(1)	3544(1)	18(1)
O(5F)	1187(3)	8178(2)	296(1)	24(1)

Table A3.2.3. Bond lengths [$\approx$] and angles [∞] for (R)-**60**•HBr.

O(1A)-C(14A)	1.207(4)
O(2A)-C(14A)	1.316(4)
O(2A)-C(15A)	1.456(3)
O(3A)-C(16A)	1.189(3)
O(4A)-C(16A)	1.326(3)
O(4A)-C(17A)	1.454(4)
N(1A)-C(1A)	1.479(4)
N(1A)-C(4A)	1.327(3)
N(1A)-C(5A)	1.483(4)
N(2A)-H(2A)	0.8800
N(2A)-C(4A)	1.319(4)
N(2A)-C(18A)	1.482(4)
C(1A)-H(1A)	1.0000
C(1A)-C(2A)	1.539(4)
C(1A)-C(8A)	1.521(4)
C(2A)-H(2AA)	0.9900
C(2A)-H(2AB)	0.9900
C(2A)-C(3A)	1.555(4)
C(3A)-C(4A)	1.513(4)
C(3A)-C(14A)	1.541(4)
C(3A)-C(16A)	1.548(4)
C(5A)-H(5A)	1.0000
C(5A)-C(6A)	1.531(4)
C(5A)-C(7A)	1.527(4)
C(6A)-H(6AA)	0.9800
C(6A)-H(6AB)	0.9800
C(6A)-H(6AC)	0.9800
C(7A)-H(7AA)	0.9800
C(7A)-H(7AB)	0.9800
C(7A)-H(7AC)	0.9800
C(8A)-C(9A)	1.386(4)
C(8A)-C(13A)	1.401(4)
C(9A)-H(9A)	0.9500
C(9A)-C(10A)	1.388(4)
C(10A)-H(10A)	0.9500
C(10A)-C(11A)	1.386(5)
C(11A)-H(11A)	0.9500
C(11A)-C(12A)	1.382(4)
C(12A)-H(12A)	0.9500
C(12A)-C(13A)	1.385(4)
C(13A)-H(13A)	0.9500
C(15A)-H(15G)	0.9800
C(15A)-H(15H)	0.9800
C(15A)-H(15I)	0.9800
C(17A)-H(17G)	0.9800
C(17A)-H(17H)	0.9800
C(17A)-H(17I)	0.9800
C(18A)-H(18A)	1.0000
C(18A)-C(19A)	1.535(5)
C(18A)-C(20A)	1.529(4)

C(19A)-H(19G)	0.9800
C(19A)-H(19H)	0.9800
C(19A)-H(19I)	0.9800
C(20A)-H(20G)	0.9800
C(20A)-H(20H)	0.9800
C(20A)-H(20I)	0.9800
O(1B)-C(14B)	1.186(4)
O(2B)-C(14B)	1.325(3)
O(2B)-C(15B)	1.456(4)
O(3B)-C(16B)	1.204(3)
O(4B)-C(16B)	1.314(3)
O(4B)-C(17B)	1.458(3)
N(1B)-C(1B)	1.473(4)
N(1B)-C(4B)	1.332(3)
N(1B)-C(5B)	1.485(3)
N(2B)-H(2B)	0.8800
N(2B)-C(4B)	1.330(4)
N(2B)-C(18B)	1.473(3)
C(1B)-H(1B)	1.0000
C(1B)-C(2B)	1.552(4)
C(1B)-C(8B)	1.505(4)
C(2B)-H(2BA)	0.9900
C(2B)-H(2BB)	0.9900
C(2B)-C(3B)	1.540(4)
C(3B)-C(4B)	1.524(4)
C(3B)-C(14B)	1.552(4)
C(3B)-C(16B)	1.544(4)
C(5B)-H(5B)	1.0000
C(5B)-C(6B)	1.509(5)
C(5B)-C(7B)	1.523(4)
C(6B)-H(6BA)	0.9800
C(6B)-H(6BB)	0.9800
C(6B)-H(6BC)	0.9800
C(7B)-H(7BA)	0.9800
C(7B)-H(7BB)	0.9800
C(7B)-H(7BC)	0.9800
C(8B)-C(9B)	1.398(4)
C(8B)-C(13B)	1.401(4)
C(9B)-H(9B)	0.9500
C(9B)-C(10B)	1.395(4)
C(10B)-H(10B)	0.9500
C(10B)-C(11B)	1.391(5)
C(11B)-H(11B)	0.9500
C(11B)-C(12B)	1.391(5)
C(12B)-H(12B)	0.9500
C(12B)-C(13B)	1.393(4)
C(13B)-H(13B)	0.9500
C(15B)-H(15D)	0.9800
C(15B)-H(15E)	0.9800
C(15B)-H(15F)	0.9800
C(17B)-H(17D)	0.9800
C(17B)-H(17E)	0.9800
C(17B)-H(17F)	0.9800
C(18B)-H(18B)	1.0000

C(18B)-C(19B)	1.513(5)
C(18B)-C(20B)	1.527(4)
C(19B)-H(19D)	0.9800
C(19B)-H(19E)	0.9800
C(19B)-H(19F)	0.9800
C(20B)-H(20D)	0.9800
C(20B)-H(20E)	0.9800
C(20B)-H(20F)	0.9800
O(1C)-C(14C)	1.194(4)
O(2C)-C(14C)	1.327(4)
O(2C)-C(15C)	1.457(3)
O(3C)-C(16C)	1.192(3)
O(4C)-C(16C)	1.334(3)
O(4C)-C(17C)	1.470(4)
N(1C)-C(1C)	1.476(4)
N(1C)-C(4C)	1.322(3)
N(1C)-C(5C)	1.492(4)
N(2C)-H(2C)	0.8800
N(2C)-C(4C)	1.324(4)
N(2C)-C(18C)	1.481(3)
C(1C)-H(1C)	1.0000
C(1C)-C(2C)	1.544(4)
C(1C)-C(8C)	1.517(4)
C(2C)-H(2CA)	0.9900
C(2C)-H(2CB)	0.9900
C(2C)-C(3C)	1.546(4)
C(3C)-C(4C)	1.524(4)
C(3C)-C(14C)	1.544(4)
C(3C)-C(16C)	1.525(4)
C(5C)-H(5C)	1.0000
C(5C)-C(6C)	1.510(4)
C(5C)-C(7C)	1.539(4)
C(6C)-H(6CA)	0.9800
C(6C)-H(6CB)	0.9800
C(6C)-H(6CC)	0.9800
C(7C)-H(7CA)	0.9800
C(7C)-H(7CB)	0.9800
C(7C)-H(7CC)	0.9800
C(8C)-C(9C)	1.392(4)
C(8C)-C(13C)	1.391(4)
C(9C)-H(9C)	0.9500
C(9C)-C(10C)	1.403(4)
C(10C)-H(10C)	0.9500
C(10C)-C(11C)	1.373(5)
C(11C)-H(11C)	0.9500
C(11C)-C(12C)	1.390(4)
C(12C)-H(12C)	0.9500
C(12C)-C(13C)	1.383(4)
C(13C)-H(13C)	0.9500
C(15C)-H(15A)	0.9800
C(15C)-H(15B)	0.9800
C(15C)-H(15C)	0.9800
C(17C)-H(17A)	0.9800
C(17C)-H(17B)	0.9800

C(17C)-H(17C)	0.9800
C(18C)-H(18C)	1.0000
C(18C)-C(19C)	1.516(5)
C(18C)-C(20C)	1.522(4)
C(19C)-H(19A)	0.9800
C(19C)-H(19B)	0.9800
C(19C)-H(19C)	0.9800
C(20C)-H(20A)	0.9800
C(20C)-H(20B)	0.9800
C(20C)-H(20C)	0.9800
O(1D)-C(14D)	1.197(4)
O(2D)-C(14D)	1.333(4)
O(2D)-C(15D)	1.454(3)
O(3D)-C(16D)	1.184(4)
O(4D)-C(16D)	1.335(3)
O(4D)-C(17D)	1.462(3)
N(1D)-C(1D)	1.460(4)
N(1D)-C(4D)	1.335(3)
N(1D)-C(5D)	1.478(4)
N(2D)-H(2D)	0.8800
N(2D)-C(4D)	1.300(4)
N(2D)-C(18D)	1.477(4)
C(1D)-H(1D)	1.0000
C(1D)-C(2D)	1.529(4)
C(1D)-C(8D)	1.525(4)
C(2D)-H(2DA)	0.9900
C(2D)-H(2DB)	0.9900
C(2D)-C(3D)	1.549(4)
C(3D)-C(4D)	1.531(4)
C(3D)-C(14D)	1.541(4)
C(3D)-C(16D)	1.559(4)
C(5D)-H(5D)	1.0000
C(5D)-C(6D)	1.523(5)
C(5D)-C(7D)	1.514(4)
C(6D)-H(6DA)	0.9800
C(6D)-H(6DB)	0.9800
C(6D)-H(6DC)	0.9800
C(7D)-H(7DA)	0.9800
C(7D)-H(7DB)	0.9800
C(7D)-H(7DC)	0.9800
C(8D)-C(9D)	1.394(4)
C(8D)-C(13D)	1.384(4)
C(9D)-H(9D)	0.9500
C(9D)-C(10D)	1.385(4)
C(10D)-H(10D)	0.9500
C(10D)-C(11D)	1.400(5)
C(11D)-H(11D)	0.9500
C(11D)-C(12D)	1.384(5)
C(12D)-H(12D)	0.9500
C(12D)-C(13D)	1.397(4)
C(13D)-H(13D)	0.9500
C(15D)-H(15P)	0.9800
C(15D)-H(15Q)	0.9800
C(15D)-H(15R)	0.9800

C(17D)-H(17P)	0.9800
C(17D)-H(17Q)	0.9800
C(17D)-H(17R)	0.9800
C(18D)-H(18D)	1.0000
C(18D)-C(19D)	1.533(4)
C(18D)-C(20D)	1.527(4)
C(19D)-H(19P)	0.9800
C(19D)-H(19Q)	0.9800
C(19D)-H(19R)	0.9800
C(20D)-H(20P)	0.9800
C(20D)-H(20Q)	0.9800
C(20D)-H(20R)	0.9800
O(1E)-C(14E)	1.215(4)
O(2E)-C(14E)	1.325(4)
O(2E)-C(15E)	1.462(3)
O(3E)-C(16E)	1.200(3)
O(4E)-C(16E)	1.325(3)
O(4E)-C(17E)	1.465(3)
N(1E)-C(1E)	1.485(4)
N(1E)-C(4E)	1.327(3)
N(1E)-C(5E)	1.486(4)
N(2E)-H(2E)	0.8800
N(2E)-C(4E)	1.317(4)
N(2E)-C(18E)	1.481(4)
C(1E)-H(1E)	1.0000
C(1E)-C(2E)	1.541(4)
C(1E)-C(8E)	1.515(4)
C(2E)-H(2EA)	0.9900
C(2E)-H(2EB)	0.9900
C(2E)-C(3E)	1.553(4)
C(3E)-C(4E)	1.520(4)
C(3E)-C(14E)	1.533(4)
C(3E)-C(16E)	1.532(4)
C(5E)-H(5E)	1.0000
C(5E)-C(6E)	1.514(4)
C(5E)-C(7E)	1.528(4)
C(6E)-H(6EA)	0.9800
C(6E)-H(6EB)	0.9800
C(6E)-H(6EC)	0.9800
C(7E)-H(7EA)	0.9800
C(7E)-H(7EB)	0.9800
C(7E)-H(7EC)	0.9800
C(8E)-C(9E)	1.394(4)
C(8E)-C(13E)	1.394(4)
C(9E)-H(9E)	0.9500
C(9E)-C(10E)	1.396(4)
C(10E)-H(10E)	0.9500
C(10E)-C(11E)	1.398(5)
C(11E)-H(11E)	0.9500
C(11E)-C(12E)	1.390(5)
C(12E)-H(12E)	0.9500
C(12E)-C(13E)	1.396(4)
C(13E)-H(13E)	0.9500
C(15E)-H(15M)	0.9800

C(15E)-H(15N)	0.9800
C(15E)-H(15O)	0.9800
C(17E)-H(17M)	0.9800
C(17E)-H(17N)	0.9800
C(17E)-H(17O)	0.9800
C(18E)-H(18E)	1.0000
C(18E)-C(19E)	1.525(4)
C(18E)-C(20E)	1.520(4)
C(19E)-H(19M)	0.9800
C(19E)-H(19N)	0.9800
C(19E)-H(19O)	0.9800
C(20E)-H(20M)	0.9800
C(20E)-H(20N)	0.9800
C(20E)-H(20O)	0.9800
O(1F)-C(14F)	1.209(4)
O(2F)-C(14F)	1.328(4)
O(2F)-C(15F)	1.451(3)
O(3F)-C(16F)	1.212(3)
O(4F)-C(16F)	1.321(3)
O(4F)-C(17F)	1.459(3)
N(1F)-C(1F)	1.481(4)
N(1F)-C(4F)	1.329(3)
N(1F)-C(5F)	1.497(4)
N(2F)-H(2F)	0.8800
N(2F)-C(4F)	1.316(4)
N(2F)-C(18F)	1.473(3)
C(1F)-H(1F)	1.0000
C(1F)-C(2F)	1.533(4)
C(1F)-C(8F)	1.517(4)
C(2F)-H(2FA)	0.9900
C(2F)-H(2FB)	0.9900
C(2F)-C(3F)	1.542(4)
C(3F)-C(4F)	1.526(4)
C(3F)-C(14F)	1.537(4)
C(3F)-C(16F)	1.513(4)
C(5F)-H(5F)	1.0000
C(5F)-C(6F)	1.526(5)
C(5F)-C(7F)	1.506(4)
C(6F)-H(6FA)	0.9800
C(6F)-H(6FB)	0.9800
C(6F)-H(6FC)	0.9800
C(7F)-H(7FA)	0.9800
C(7F)-H(7FB)	0.9800
C(7F)-H(7FC)	0.9800
C(8F)-C(9F)	1.398(4)
C(8F)-C(13F)	1.383(4)
C(9F)-H(9F)	0.9500
C(9F)-C(10F)	1.394(4)
C(10F)-H(10F)	0.9500
C(10F)-C(11F)	1.410(5)
C(11F)-H(11F)	0.9500
C(11F)-C(12F)	1.381(6)
C(12F)-H(12F)	0.9500
C(12F)-C(13F)	1.397(4)

C(13F)-H(13F)	0.9500
C(15F)-H(15J)	0.9800
C(15F)-H(15K)	0.9800
C(15F)-H(15L)	0.9800
C(17F)-H(17J)	0.9800
C(17F)-H(17K)	0.9800
C(17F)-H(17L)	0.9800
C(18F)-H(18F)	1.0000
C(18F)-C(19F)	1.521(4)
C(18F)-C(20F)	1.527(4)
C(19F)-H(19J)	0.9800
C(19F)-H(19K)	0.9800
C(19F)-H(19L)	0.9800
C(20F)-H(20J)	0.9800
C(20F)-H(20K)	0.9800
C(20F)-H(20L)	0.9800
O(5A)-H(5AA)	0.846(17)
O(5A)-H(5AB)	0.830(17)
O(5B)-H(5BA)	0.863(17)
O(5B)-H(5BB)	0.845(17)
O(5C)-H(5CA)	0.882(17)
O(5C)-H(5CB)	0.850(17)
O(5D)-H(5DA)	0.874(18)
O(5D)-H(5DB)	0.895(17)
O(5E)-H(5EA)	0.857(17)
O(5E)-H(5EB)	0.891(17)
O(5F)-H(5FA)	0.866(19)
O(5F)-H(5FB)	0.896(18)

C(14A)-O(2A)-C(15A)	115.9(3)
C(16A)-O(4A)-C(17A)	115.2(2)
C(1A)-N(1A)-C(5A)	123.7(2)
C(4A)-N(1A)-C(1A)	113.8(2)
C(4A)-N(1A)-C(5A)	122.5(2)
C(4A)-N(2A)-H(2A)	116.3
C(4A)-N(2A)-C(18A)	127.4(3)
C(18A)-N(2A)-H(2A)	116.3
N(1A)-C(1A)-H(1A)	108.2
N(1A)-C(1A)-C(2A)	102.6(2)
N(1A)-C(1A)-C(8A)	113.9(2)
C(2A)-C(1A)-H(1A)	108.2
C(8A)-C(1A)-H(1A)	108.2
C(8A)-C(1A)-C(2A)	115.3(2)
C(1A)-C(2A)-H(2AA)	110.7
C(1A)-C(2A)-H(2AB)	110.7
C(1A)-C(2A)-C(3A)	105.2(2)
H(2AA)-C(2A)-H(2AB)	108.8
C(3A)-C(2A)-H(2AA)	110.7
C(3A)-C(2A)-H(2AB)	110.7
C(4A)-C(3A)-C(2A)	101.9(2)
C(4A)-C(3A)-C(14A)	109.6(2)
C(4A)-C(3A)-C(16A)	114.3(2)
C(14A)-C(3A)-C(2A)	113.6(2)
C(14A)-C(3A)-C(16A)	106.5(2)

C(16A)-C(3A)-C(2A)	111.1(2)
N(1A)-C(4A)-C(3A)	110.6(2)
N(2A)-C(4A)-N(1A)	122.7(3)
N(2A)-C(4A)-C(3A)	126.8(2)
N(1A)-C(5A)-H(5A)	107.5
N(1A)-C(5A)-C(6A)	111.8(3)
N(1A)-C(5A)-C(7A)	110.5(2)
C(6A)-C(5A)-H(5A)	107.5
C(7A)-C(5A)-H(5A)	107.5
C(7A)-C(5A)-C(6A)	111.9(3)
C(5A)-C(6A)-H(6AA)	109.5
C(5A)-C(6A)-H(6AB)	109.5
C(5A)-C(6A)-H(6AC)	109.5
H(6AA)-C(6A)-H(6AB)	109.5
H(6AA)-C(6A)-H(6AC)	109.5
H(6AB)-C(6A)-H(6AC)	109.5
C(5A)-C(7A)-H(7AA)	109.5
C(5A)-C(7A)-H(7AB)	109.5
C(5A)-C(7A)-H(7AC)	109.5
H(7AA)-C(7A)-H(7AB)	109.5
H(7AA)-C(7A)-H(7AC)	109.5
H(7AB)-C(7A)-H(7AC)	109.5
C(9A)-C(8A)-C(1A)	118.4(3)
C(9A)-C(8A)-C(13A)	119.2(3)
C(13A)-C(8A)-C(1A)	122.3(3)
C(8A)-C(9A)-H(9A)	119.8
C(8A)-C(9A)-C(10A)	120.4(3)
C(10A)-C(9A)-H(9A)	119.8
C(9A)-C(10A)-H(10A)	120.0
C(11A)-C(10A)-C(9A)	120.0(3)
C(11A)-C(10A)-H(10A)	120.0
C(10A)-C(11A)-H(11A)	119.9
C(12A)-C(11A)-C(10A)	120.1(3)
C(12A)-C(11A)-H(11A)	119.9
C(11A)-C(12A)-H(12A)	119.9
C(11A)-C(12A)-C(13A)	120.1(3)
C(13A)-C(12A)-H(12A)	119.9
C(8A)-C(13A)-H(13A)	119.9
C(12A)-C(13A)-C(8A)	120.1(3)
C(12A)-C(13A)-H(13A)	119.9
O(1A)-C(14A)-O(2A)	125.7(3)
O(1A)-C(14A)-C(3A)	123.3(3)
O(2A)-C(14A)-C(3A)	111.1(2)
O(2A)-C(15A)-H(15G)	109.5
O(2A)-C(15A)-H(15H)	109.5
O(2A)-C(15A)-H(15I)	109.5
H(15G)-C(15A)-H(15H)	109.5
H(15G)-C(15A)-H(15I)	109.5
H(15H)-C(15A)-H(15I)	109.5
O(3A)-C(16A)-O(4A)	126.2(3)
O(3A)-C(16A)-C(3A)	123.8(2)
O(4A)-C(16A)-C(3A)	110.0(2)
O(4A)-C(17A)-H(17G)	109.5
O(4A)-C(17A)-H(17H)	109.5

O(4A)-C(17A)-H(17I)	109.5
H(17G)-C(17A)-H(17H)	109.5
H(17G)-C(17A)-H(17I)	109.5
H(17H)-C(17A)-H(17I)	109.5
N(2A)-C(18A)-H(18A)	109.3
N(2A)-C(18A)-C(19A)	107.7(3)
N(2A)-C(18A)-C(20A)	109.9(2)
C(19A)-C(18A)-H(18A)	109.3
C(20A)-C(18A)-H(18A)	109.3
C(20A)-C(18A)-C(19A)	111.3(3)
C(18A)-C(19A)-H(19G)	109.5
C(18A)-C(19A)-H(19H)	109.5
C(18A)-C(19A)-H(19I)	109.5
H(19G)-C(19A)-H(19H)	109.5
H(19G)-C(19A)-H(19I)	109.5
H(19H)-C(19A)-H(19I)	109.5
C(18A)-C(20A)-H(20G)	109.5
C(18A)-C(20A)-H(20H)	109.5
C(18A)-C(20A)-H(20I)	109.5
H(20G)-C(20A)-H(20H)	109.5
H(20G)-C(20A)-H(20I)	109.5
H(20H)-C(20A)-H(20I)	109.5
C(14B)-O(2B)-C(15B)	115.1(3)
C(16B)-O(4B)-C(17B)	115.6(2)
C(1B)-N(1B)-C(5B)	122.4(2)
C(4B)-N(1B)-C(1B)	113.4(2)
C(4B)-N(1B)-C(5B)	123.9(2)
C(4B)-N(2B)-H(2B)	116.3
C(4B)-N(2B)-C(18B)	127.4(2)
C(18B)-N(2B)-H(2B)	116.3
N(1B)-C(1B)-H(1B)	109.3
N(1B)-C(1B)-C(2B)	101.5(2)
N(1B)-C(1B)-C(8B)	112.3(2)
C(2B)-C(1B)-H(1B)	109.3
C(8B)-C(1B)-H(1B)	109.3
C(8B)-C(1B)-C(2B)	114.9(2)
C(1B)-C(2B)-H(2BA)	110.8
C(1B)-C(2B)-H(2BB)	110.8
H(2BA)-C(2B)-H(2BB)	108.9
C(3B)-C(2B)-C(1B)	104.9(2)
C(3B)-C(2B)-H(2BA)	110.8
C(3B)-C(2B)-H(2BB)	110.8
C(2B)-C(3B)-C(14B)	114.4(2)
C(2B)-C(3B)-C(16B)	110.6(2)
C(4B)-C(3B)-C(2B)	101.5(2)
C(4B)-C(3B)-C(14B)	110.4(2)
C(4B)-C(3B)-C(16B)	113.9(2)
C(16B)-C(3B)-C(14B)	106.2(2)
N(1B)-C(4B)-C(3B)	110.4(2)
N(2B)-C(4B)-N(1B)	122.7(2)
N(2B)-C(4B)-C(3B)	126.9(2)
N(1B)-C(5B)-H(5B)	108.1
N(1B)-C(5B)-C(6B)	108.7(3)
N(1B)-C(5B)-C(7B)	112.4(2)

C(6B)-C(5B)-H(5B)	108.1
C(6B)-C(5B)-C(7B)	111.1(3)
C(7B)-C(5B)-H(5B)	108.1
C(5B)-C(6B)-H(6BA)	109.5
C(5B)-C(6B)-H(6BB)	109.5
C(5B)-C(6B)-H(6BC)	109.5
H(6BA)-C(6B)-H(6BB)	109.5
H(6BA)-C(6B)-H(6BC)	109.5
H(6BB)-C(6B)-H(6BC)	109.5
C(5B)-C(7B)-H(7BA)	109.5
C(5B)-C(7B)-H(7BB)	109.5
C(5B)-C(7B)-H(7BC)	109.5
H(7BA)-C(7B)-H(7BB)	109.5
H(7BA)-C(7B)-H(7BC)	109.5
H(7BB)-C(7B)-H(7BC)	109.5
C(9B)-C(8B)-C(1B)	118.6(3)
C(9B)-C(8B)-C(13B)	118.9(3)
C(13B)-C(8B)-C(1B)	122.4(3)
C(8B)-C(9B)-H(9B)	120.0
C(10B)-C(9B)-C(8B)	120.0(3)
C(10B)-C(9B)-H(9B)	120.0
C(9B)-C(10B)-H(10B)	119.6
C(11B)-C(10B)-C(9B)	120.8(3)
C(11B)-C(10B)-H(10B)	119.6
C(10B)-C(11B)-H(11B)	120.3
C(10B)-C(11B)-C(12B)	119.3(3)
C(12B)-C(11B)-H(11B)	120.3
C(11B)-C(12B)-H(12B)	119.9
C(11B)-C(12B)-C(13B)	120.2(3)
C(13B)-C(12B)-H(12B)	119.9
C(8B)-C(13B)-H(13B)	119.7
C(12B)-C(13B)-C(8B)	120.6(3)
C(12B)-C(13B)-H(13B)	119.7
O(1B)-C(14B)-O(2B)	125.7(3)
O(1B)-C(14B)-C(3B)	124.5(2)
O(2B)-C(14B)-C(3B)	109.8(2)
O(2B)-C(15B)-H(15D)	109.5
O(2B)-C(15B)-H(15E)	109.5
O(2B)-C(15B)-H(15F)	109.5
H(15D)-C(15B)-H(15E)	109.5
H(15D)-C(15B)-H(15F)	109.5
H(15E)-C(15B)-H(15F)	109.5
O(3B)-C(16B)-O(4B)	127.1(3)
O(3B)-C(16B)-C(3B)	123.2(2)
O(4B)-C(16B)-C(3B)	109.7(2)
O(4B)-C(17B)-H(17D)	109.5
O(4B)-C(17B)-H(17E)	109.5
O(4B)-C(17B)-H(17F)	109.5
H(17D)-C(17B)-H(17E)	109.5
H(17D)-C(17B)-H(17F)	109.5
H(17E)-C(17B)-H(17F)	109.5
N(2B)-C(18B)-H(18B)	108.8
N(2B)-C(18B)-C(19B)	108.8(3)
N(2B)-C(18B)-C(20B)	108.3(2)

C(19B)-C(18B)-H(18B)	108.8
C(19B)-C(18B)-C(20B)	113.3(3)
C(20B)-C(18B)-H(18B)	108.8
C(18B)-C(19B)-H(19D)	109.5
C(18B)-C(19B)-H(19E)	109.5
C(18B)-C(19B)-H(19F)	109.5
H(19D)-C(19B)-H(19E)	109.5
H(19D)-C(19B)-H(19F)	109.5
H(19E)-C(19B)-H(19F)	109.5
C(18B)-C(20B)-H(20D)	109.5
C(18B)-C(20B)-H(20E)	109.5
C(18B)-C(20B)-H(20F)	109.5
H(20D)-C(20B)-H(20E)	109.5
H(20D)-C(20B)-H(20F)	109.5
H(20E)-C(20B)-H(20F)	109.5
C(14C)-O(2C)-C(15C)	116.4(2)
C(16C)-O(4C)-C(17C)	114.6(2)
C(1C)-N(1C)-C(5C)	122.5(2)
C(4C)-N(1C)-C(1C)	114.1(2)
C(4C)-N(1C)-C(5C)	123.3(2)
C(4C)-N(2C)-H(2C)	116.0
C(4C)-N(2C)-C(18C)	128.0(2)
C(18C)-N(2C)-H(2C)	116.0
N(1C)-C(1C)-H(1C)	108.9
N(1C)-C(1C)-C(2C)	101.6(2)
N(1C)-C(1C)-C(8C)	113.8(2)
C(2C)-C(1C)-H(1C)	108.9
C(8C)-C(1C)-H(1C)	108.9
C(8C)-C(1C)-C(2C)	114.5(2)
C(1C)-C(2C)-H(2CA)	110.6
C(1C)-C(2C)-H(2CB)	110.6
C(1C)-C(2C)-C(3C)	105.5(2)
H(2CA)-C(2C)-H(2CB)	108.8
C(3C)-C(2C)-H(2CA)	110.6
C(3C)-C(2C)-H(2CB)	110.6
C(4C)-C(3C)-C(2C)	101.2(2)
C(4C)-C(3C)-C(14C)	109.0(2)
C(4C)-C(3C)-C(16C)	115.9(2)
C(14C)-C(3C)-C(2C)	114.2(2)
C(16C)-C(3C)-C(2C)	110.4(2)
C(16C)-C(3C)-C(14C)	106.4(2)
N(1C)-C(4C)-N(2C)	123.3(3)
N(1C)-C(4C)-C(3C)	110.4(2)
N(2C)-C(4C)-C(3C)	126.3(2)
N(1C)-C(5C)-H(5C)	107.5
N(1C)-C(5C)-C(6C)	111.3(3)
N(1C)-C(5C)-C(7C)	110.1(2)
C(6C)-C(5C)-H(5C)	107.5
C(6C)-C(5C)-C(7C)	112.6(3)
C(7C)-C(5C)-H(5C)	107.5
C(5C)-C(6C)-H(6CA)	109.5
C(5C)-C(6C)-H(6CB)	109.5
C(5C)-C(6C)-H(6CC)	109.5
H(6CA)-C(6C)-H(6CB)	109.5

H(6CA)-C(6C)-H(6CC)	109.5
H(6CB)-C(6C)-H(6CC)	109.5
C(5C)-C(7C)-H(7CA)	109.5
C(5C)-C(7C)-H(7CB)	109.5
C(5C)-C(7C)-H(7CC)	109.5
H(7CA)-C(7C)-H(7CB)	109.5
H(7CA)-C(7C)-H(7CC)	109.5
H(7CB)-C(7C)-H(7CC)	109.5
C(9C)-C(8C)-C(1C)	117.5(2)
C(13C)-C(8C)-C(1C)	123.6(2)
C(13C)-C(8C)-C(9C)	118.8(3)
C(8C)-C(9C)-H(9C)	120.0
C(8C)-C(9C)-C(10C)	119.9(3)
C(10C)-C(9C)-H(9C)	120.0
C(9C)-C(10C)-H(10C)	119.8
C(11C)-C(10C)-C(9C)	120.4(3)
C(11C)-C(10C)-H(10C)	119.8
C(10C)-C(11C)-H(11C)	120.0
C(10C)-C(11C)-C(12C)	119.9(3)
C(12C)-C(11C)-H(11C)	120.0
C(11C)-C(12C)-H(12C)	120.1
C(13C)-C(12C)-C(11C)	119.8(3)
C(13C)-C(12C)-H(12C)	120.1
C(8C)-C(13C)-H(13C)	119.4
C(12C)-C(13C)-C(8C)	121.1(3)
C(12C)-C(13C)-H(13C)	119.4
O(1C)-C(14C)-O(2C)	125.9(3)
O(1C)-C(14C)-C(3C)	123.2(3)
O(2C)-C(14C)-C(3C)	110.9(2)
O(2C)-C(15C)-H(15A)	109.5
O(2C)-C(15C)-H(15B)	109.5
O(2C)-C(15C)-H(15C)	109.5
H(15A)-C(15C)-H(15B)	109.5
H(15A)-C(15C)-H(15C)	109.5
H(15B)-C(15C)-H(15C)	109.5
O(3C)-C(16C)-O(4C)	126.0(3)
O(3C)-C(16C)-C(3C)	124.1(2)
O(4C)-C(16C)-C(3C)	109.9(2)
O(4C)-C(17C)-H(17A)	109.5
O(4C)-C(17C)-H(17B)	109.5
O(4C)-C(17C)-H(17C)	109.5
H(17A)-C(17C)-H(17B)	109.5
H(17A)-C(17C)-H(17C)	109.5
H(17B)-C(17C)-H(17C)	109.5
N(2C)-C(18C)-H(18C)	108.7
N(2C)-C(18C)-C(19C)	109.0(2)
N(2C)-C(18C)-C(20C)	109.0(2)
C(19C)-C(18C)-H(18C)	108.7
C(19C)-C(18C)-C(20C)	112.7(3)
C(20C)-C(18C)-H(18C)	108.7
C(18C)-C(19C)-H(19A)	109.5
C(18C)-C(19C)-H(19B)	109.5
C(18C)-C(19C)-H(19C)	109.5
H(19A)-C(19C)-H(19B)	109.5

H(19A)-C(19C)-H(19C)	109.5
H(19B)-C(19C)-H(19C)	109.5
C(18C)-C(20C)-H(20A)	109.5
C(18C)-C(20C)-H(20B)	109.5
C(18C)-C(20C)-H(20C)	109.5
H(20A)-C(20C)-H(20B)	109.5
H(20A)-C(20C)-H(20C)	109.5
H(20B)-C(20C)-H(20C)	109.5
C(14D)-O(2D)-C(15D)	115.9(3)
C(16D)-O(4D)-C(17D)	114.6(2)
C(1D)-N(1D)-C(5D)	123.8(2)
C(4D)-N(1D)-C(1D)	113.7(2)
C(4D)-N(1D)-C(5D)	122.3(2)
C(4D)-N(2D)-H(2D)	116.2
C(4D)-N(2D)-C(18D)	127.6(3)
C(18D)-N(2D)-H(2D)	116.2
N(1D)-C(1D)-H(1D)	108.5
N(1D)-C(1D)-C(2D)	102.4(2)
N(1D)-C(1D)-C(8D)	112.9(2)
C(2D)-C(1D)-H(1D)	108.5
C(8D)-C(1D)-H(1D)	108.5
C(8D)-C(1D)-C(2D)	115.6(2)
C(1D)-C(2D)-H(2DA)	110.9
C(1D)-C(2D)-H(2DB)	110.9
C(1D)-C(2D)-C(3D)	104.1(2)
H(2DA)-C(2D)-H(2DB)	109.0
C(3D)-C(2D)-H(2DA)	110.9
C(3D)-C(2D)-H(2DB)	110.9
C(2D)-C(3D)-C(16D)	110.7(2)
C(4D)-C(3D)-C(2D)	102.1(2)
C(4D)-C(3D)-C(14D)	111.0(2)
C(4D)-C(3D)-C(16D)	112.7(2)
C(14D)-C(3D)-C(2D)	114.5(2)
C(14D)-C(3D)-C(16D)	106.1(2)
N(1D)-C(4D)-C(3D)	109.1(2)
N(2D)-C(4D)-N(1D)	124.0(3)
N(2D)-C(4D)-C(3D)	126.9(2)
N(1D)-C(5D)-H(5D)	108.5
N(1D)-C(5D)-C(6D)	109.5(3)
N(1D)-C(5D)-C(7D)	111.0(3)
C(6D)-C(5D)-H(5D)	108.5
C(7D)-C(5D)-H(5D)	108.5
C(7D)-C(5D)-C(6D)	110.9(3)
C(5D)-C(6D)-H(6DA)	109.5
C(5D)-C(6D)-H(6DB)	109.5
C(5D)-C(6D)-H(6DC)	109.5
H(6DA)-C(6D)-H(6DB)	109.5
H(6DA)-C(6D)-H(6DC)	109.5
H(6DB)-C(6D)-H(6DC)	109.5
C(5D)-C(7D)-H(7DA)	109.5
C(5D)-C(7D)-H(7DB)	109.5
C(5D)-C(7D)-H(7DC)	109.5
H(7DA)-C(7D)-H(7DB)	109.5
H(7DA)-C(7D)-H(7DC)	109.5

H(7DB)-C(7D)-H(7DC)	109.5
C(9D)-C(8D)-C(1D)	118.6(3)
C(13D)-C(8D)-C(1D)	121.9(3)
C(13D)-C(8D)-C(9D)	119.5(3)
C(8D)-C(9D)-H(9D)	119.7
C(10D)-C(9D)-C(8D)	120.7(3)
C(10D)-C(9D)-H(9D)	119.7
C(9D)-C(10D)-H(10D)	120.3
C(9D)-C(10D)-C(11D)	119.5(3)
C(11D)-C(10D)-H(10D)	120.3
C(10D)-C(11D)-H(11D)	119.9
C(12D)-C(11D)-C(10D)	120.1(3)
C(12D)-C(11D)-H(11D)	119.9
C(11D)-C(12D)-H(12D)	120.1
C(11D)-C(12D)-C(13D)	119.9(3)
C(13D)-C(12D)-H(12D)	120.1
C(8D)-C(13D)-C(12D)	120.3(3)
C(8D)-C(13D)-H(13D)	119.9
C(12D)-C(13D)-H(13D)	119.9
O(1D)-C(14D)-O(2D)	125.5(3)
O(1D)-C(14D)-C(3D)	123.7(3)
O(2D)-C(14D)-C(3D)	110.8(2)
O(2D)-C(15D)-H(15P)	109.5
O(2D)-C(15D)-H(15Q)	109.5
O(2D)-C(15D)-H(15R)	109.5
H(15P)-C(15D)-H(15Q)	109.5
H(15P)-C(15D)-H(15R)	109.5
H(15Q)-C(15D)-H(15R)	109.5
O(3D)-C(16D)-O(4D)	127.4(3)
O(3D)-C(16D)-C(3D)	124.0(3)
O(4D)-C(16D)-C(3D)	108.5(2)
O(4D)-C(17D)-H(17P)	109.5
O(4D)-C(17D)-H(17Q)	109.5
O(4D)-C(17D)-H(17R)	109.5
H(17P)-C(17D)-H(17Q)	109.5
H(17P)-C(17D)-H(17R)	109.5
H(17Q)-C(17D)-H(17R)	109.5
N(2D)-C(18D)-H(18D)	108.8
N(2D)-C(18D)-C(19D)	108.8(2)
N(2D)-C(18D)-C(20D)	108.8(2)
C(19D)-C(18D)-H(18D)	108.8
C(20D)-C(18D)-H(18D)	108.8
C(20D)-C(18D)-C(19D)	112.7(3)
C(18D)-C(19D)-H(19P)	109.5
C(18D)-C(19D)-H(19Q)	109.5
C(18D)-C(19D)-H(19R)	109.5
H(19P)-C(19D)-H(19Q)	109.5
H(19P)-C(19D)-H(19R)	109.5
H(19Q)-C(19D)-H(19R)	109.5
C(18D)-C(20D)-H(20P)	109.5
C(18D)-C(20D)-H(20Q)	109.5
C(18D)-C(20D)-H(20R)	109.5
H(20P)-C(20D)-H(20Q)	109.5
H(20P)-C(20D)-H(20R)	109.5

H(20Q)-C(20D)-H(20R)	109.5
C(14E)-O(2E)-C(15E)	115.7(2)
C(16E)-O(4E)-C(17E)	115.6(2)
C(1E)-N(1E)-C(5E)	123.7(2)
C(4E)-N(1E)-C(1E)	113.6(2)
C(4E)-N(1E)-C(5E)	122.7(3)
C(4E)-N(2E)-H(2E)	116.0
C(4E)-N(2E)-C(18E)	128.1(3)
C(18E)-N(2E)-H(2E)	116.0
N(1E)-C(1E)-H(1E)	108.6
N(1E)-C(1E)-C(2E)	102.3(2)
N(1E)-C(1E)-C(8E)	113.7(2)
C(2E)-C(1E)-H(1E)	108.6
C(8E)-C(1E)-H(1E)	108.6
C(8E)-C(1E)-C(2E)	114.8(2)
C(1E)-C(2E)-H(2EA)	110.7
C(1E)-C(2E)-H(2EB)	110.7
C(1E)-C(2E)-C(3E)	105.2(2)
H(2EA)-C(2E)-H(2EB)	108.8
C(3E)-C(2E)-H(2EA)	110.7
C(3E)-C(2E)-H(2EB)	110.7
C(4E)-C(3E)-C(2E)	101.4(2)
C(4E)-C(3E)-C(14E)	109.2(2)
C(4E)-C(3E)-C(16E)	114.9(2)
C(14E)-C(3E)-C(2E)	113.6(2)
C(16E)-C(3E)-C(2E)	109.9(2)
C(16E)-C(3E)-C(14E)	107.9(2)
N(1E)-C(4E)-C(3E)	110.5(2)
N(2E)-C(4E)-N(1E)	123.4(3)
N(2E)-C(4E)-C(3E)	126.1(2)
N(1E)-C(5E)-H(5E)	107.7
N(1E)-C(5E)-C(6E)	111.4(3)
N(1E)-C(5E)-C(7E)	110.5(2)
C(6E)-C(5E)-H(5E)	107.7
C(6E)-C(5E)-C(7E)	111.8(3)
C(7E)-C(5E)-H(5E)	107.7
C(5E)-C(6E)-H(6EA)	109.5
C(5E)-C(6E)-H(6EB)	109.5
C(5E)-C(6E)-H(6EC)	109.5
H(6EA)-C(6E)-H(6EB)	109.5
H(6EA)-C(6E)-H(6EC)	109.5
H(6EB)-C(6E)-H(6EC)	109.5
C(5E)-C(7E)-H(7EA)	109.5
C(5E)-C(7E)-H(7EB)	109.5
C(5E)-C(7E)-H(7EC)	109.5
H(7EA)-C(7E)-H(7EB)	109.5
H(7EA)-C(7E)-H(7EC)	109.5
H(7EB)-C(7E)-H(7EC)	109.5
C(9E)-C(8E)-C(1E)	117.9(2)
C(13E)-C(8E)-C(1E)	123.2(3)
C(13E)-C(8E)-C(9E)	118.8(3)
C(8E)-C(9E)-H(9E)	119.2
C(8E)-C(9E)-C(10E)	121.6(3)
C(10E)-C(9E)-H(9E)	119.2

C(9E)-C(10E)-H(10E)	120.6
C(9E)-C(10E)-C(11E)	118.8(3)
C(11E)-C(10E)-H(10E)	120.6
C(10E)-C(11E)-H(11E)	120.0
C(12E)-C(11E)-C(10E)	120.0(3)
C(12E)-C(11E)-H(11E)	120.0
C(11E)-C(12E)-H(12E)	119.8
C(11E)-C(12E)-C(13E)	120.5(3)
C(13E)-C(12E)-H(12E)	119.8
C(8E)-C(13E)-C(12E)	120.2(3)
C(8E)-C(13E)-H(13E)	119.9
C(12E)-C(13E)-H(13E)	119.9
O(1E)-C(14E)-O(2E)	125.6(2)
O(1E)-C(14E)-C(3E)	122.3(3)
O(2E)-C(14E)-C(3E)	112.1(2)
O(2E)-C(15E)-H(15M)	109.5
O(2E)-C(15E)-H(15N)	109.5
O(2E)-C(15E)-H(15O)	109.5
H(15M)-C(15E)-H(15N)	109.5
H(15M)-C(15E)-H(15O)	109.5
H(15N)-C(15E)-H(15O)	109.5
O(3E)-C(16E)-O(4E)	126.0(3)
O(3E)-C(16E)-C(3E)	123.6(2)
O(4E)-C(16E)-C(3E)	110.3(2)
O(4E)-C(17E)-H(17M)	109.5
O(4E)-C(17E)-H(17N)	109.5
O(4E)-C(17E)-H(17O)	109.5
H(17M)-C(17E)-H(17N)	109.5
H(17M)-C(17E)-H(17O)	109.5
H(17N)-C(17E)-H(17O)	109.5
N(2E)-C(18E)-H(18E)	108.7
N(2E)-C(18E)-C(19E)	108.1(2)
N(2E)-C(18E)-C(20E)	109.4(2)
C(19E)-C(18E)-H(18E)	108.7
C(20E)-C(18E)-H(18E)	108.7
C(20E)-C(18E)-C(19E)	113.2(3)
C(18E)-C(19E)-H(19M)	109.5
C(18E)-C(19E)-H(19N)	109.5
C(18E)-C(19E)-H(19O)	109.5
H(19M)-C(19E)-H(19N)	109.5
H(19M)-C(19E)-H(19O)	109.5
H(19N)-C(19E)-H(19O)	109.5
C(18E)-C(20E)-H(20M)	109.5
C(18E)-C(20E)-H(20N)	109.5
C(18E)-C(20E)-H(20O)	109.5
H(20M)-C(20E)-H(20N)	109.5
H(20M)-C(20E)-H(20O)	109.5
H(20N)-C(20E)-H(20O)	109.5
C(14F)-O(2F)-C(15F)	115.7(2)
C(16F)-O(4F)-C(17F)	116.4(2)
C(1F)-N(1F)-C(5F)	122.3(2)
C(4F)-N(1F)-C(1F)	113.4(2)
C(4F)-N(1F)-C(5F)	123.9(2)
C(4F)-N(2F)-H(2F)	116.3

C(4F)-N(2F)-C(18F)	127.5(2)
C(18F)-N(2F)-H(2F)	116.3
N(1F)-C(1F)-H(1F)	109.2
N(1F)-C(1F)-C(2F)	101.6(2)
N(1F)-C(1F)-C(8F)	112.3(2)
C(2F)-C(1F)-H(1F)	109.2
C(8F)-C(1F)-H(1F)	109.2
C(8F)-C(1F)-C(2F)	115.1(2)
C(1F)-C(2F)-H(2FA)	110.9
C(1F)-C(2F)-H(2FB)	110.9
C(1F)-C(2F)-C(3F)	104.4(2)
H(2FA)-C(2F)-H(2FB)	108.9
C(3F)-C(2F)-H(2FA)	110.9
C(3F)-C(2F)-H(2FB)	110.9
C(4F)-C(3F)-C(2F)	101.8(2)
C(4F)-C(3F)-C(14F)	110.5(2)
C(14F)-C(3F)-C(2F)	115.0(2)
C(16F)-C(3F)-C(2F)	109.2(2)
C(16F)-C(3F)-C(4F)	114.2(2)
C(16F)-C(3F)-C(14F)	106.4(2)
N(1F)-C(4F)-C(3F)	109.5(2)
N(2F)-C(4F)-N(1F)	123.0(3)
N(2F)-C(4F)-C(3F)	127.5(2)
N(1F)-C(5F)-H(5F)	108.0
N(1F)-C(5F)-C(6F)	108.8(3)
N(1F)-C(5F)-C(7F)	112.4(3)
C(6F)-C(5F)-H(5F)	108.0
C(7F)-C(5F)-H(5F)	108.0
C(7F)-C(5F)-C(6F)	111.4(3)
C(5F)-C(6F)-H(6FA)	109.5
C(5F)-C(6F)-H(6FB)	109.5
C(5F)-C(6F)-H(6FC)	109.5
H(6FA)-C(6F)-H(6FB)	109.5
H(6FA)-C(6F)-H(6FC)	109.5
H(6FB)-C(6F)-H(6FC)	109.5
C(5F)-C(7F)-H(7FA)	109.5
C(5F)-C(7F)-H(7FB)	109.5
C(5F)-C(7F)-H(7FC)	109.5
H(7FA)-C(7F)-H(7FB)	109.5
H(7FA)-C(7F)-H(7FC)	109.5
H(7FB)-C(7F)-H(7FC)	109.5
C(9F)-C(8F)-C(1F)	117.4(3)
C(13F)-C(8F)-C(1F)	122.6(3)
C(13F)-C(8F)-C(9F)	120.0(3)
C(8F)-C(9F)-H(9F)	119.9
C(10F)-C(9F)-C(8F)	120.3(3)
C(10F)-C(9F)-H(9F)	119.9
C(9F)-C(10F)-H(10F)	120.5
C(9F)-C(10F)-C(11F)	119.0(3)
C(11F)-C(10F)-H(10F)	120.5
C(10F)-C(11F)-H(11F)	119.7
C(12F)-C(11F)-C(10F)	120.6(3)
C(12F)-C(11F)-H(11F)	119.7
C(11F)-C(12F)-H(12F)	120.1

C(11F)-C(12F)-C(13F)	119.8(3)
C(13F)-C(12F)-H(12F)	120.1
C(8F)-C(13F)-C(12F)	120.3(3)
C(8F)-C(13F)-H(13F)	119.8
C(12F)-C(13F)-H(13F)	119.8
O(1F)-C(14F)-O(2F)	125.8(2)
O(1F)-C(14F)-C(3F)	123.1(3)
O(2F)-C(14F)-C(3F)	111.1(2)
O(2F)-C(15F)-H(15J)	109.5
O(2F)-C(15F)-H(15K)	109.5
O(2F)-C(15F)-H(15L)	109.5
H(15J)-C(15F)-H(15K)	109.5
H(15J)-C(15F)-H(15L)	109.5
H(15K)-C(15F)-H(15L)	109.5
O(3F)-C(16F)-O(4F)	124.5(2)
O(3F)-C(16F)-C(3F)	123.4(2)
O(4F)-C(16F)-C(3F)	112.0(2)
O(4F)-C(17F)-H(17J)	109.5
O(4F)-C(17F)-H(17K)	109.5
O(4F)-C(17F)-H(17L)	109.5
H(17J)-C(17F)-H(17K)	109.5
H(17J)-C(17F)-H(17L)	109.5
H(17K)-C(17F)-H(17L)	109.5
N(2F)-C(18F)-H(18F)	109.5
N(2F)-C(18F)-C(19F)	109.5(2)
N(2F)-C(18F)-C(20F)	108.1(2)
C(19F)-C(18F)-H(18F)	109.5
C(19F)-C(18F)-C(20F)	110.7(3)
C(20F)-C(18F)-H(18F)	109.5
C(18F)-C(19F)-H(19J)	109.5
C(18F)-C(19F)-H(19K)	109.5
C(18F)-C(19F)-H(19L)	109.5
H(19J)-C(19F)-H(19K)	109.5
H(19J)-C(19F)-H(19L)	109.5
H(19K)-C(19F)-H(19L)	109.5
C(18F)-C(20F)-H(20J)	109.5
C(18F)-C(20F)-H(20K)	109.5
C(18F)-C(20F)-H(20L)	109.5
H(20J)-C(20F)-H(20K)	109.5
H(20J)-C(20F)-H(20L)	109.5
H(20K)-C(20F)-H(20L)	109.5
H(5AA)-O(5A)-H(5AB)	117(3)
H(5BA)-O(5B)-H(5BB)	113(3)
H(5CA)-O(5C)-H(5CB)	109(2)
H(5DA)-O(5D)-H(5DB)	105(2)
H(5EA)-O(5E)-H(5EB)	107(2)
H(5FA)-O(5F)-H(5FB)	107(4)

Symmetry transformations used to generate equivalent atoms:

Table A3.2.4. Anisotropic displacement parameters ($\approx \times 10^4$) for (R)-**60•HBr**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1A)	246(12)	132(9)	182(10)	11(8)	35(9)	80(8)
O(2A)	202(12)	132(9)	284(12)	-45(8)	-6(10)	-9(8)
O(3A)	331(14)	195(10)	173(11)	39(8)	-26(9)	90(9)
O(4A)	285(12)	137(9)	176(10)	71(8)	42(9)	65(8)
N(1A)	177(13)	123(10)	105(10)	40(8)	46(9)	41(9)
N(2A)	155(12)	152(11)	102(10)	1(8)	21(9)	42(9)
C(1A)	149(14)	90(11)	175(13)	15(9)	50(11)	44(10)
C(2A)	140(14)	140(12)	166(13)	42(10)	68(11)	49(10)
C(3A)	147(14)	99(11)	127(12)	30(9)	28(10)	48(9)
C(4A)	192(15)	94(11)	134(12)	6(9)	48(11)	67(10)
C(5A)	163(15)	194(13)	128(13)	75(10)	35(11)	34(11)
C(6A)	268(18)	294(16)	135(14)	33(12)	30(13)	16(14)
C(7A)	220(17)	257(16)	255(16)	115(13)	-14(13)	95(13)
C(8A)	149(14)	127(12)	145(13)	25(10)	14(11)	4(10)
C(9A)	168(15)	212(14)	163(13)	51(11)	30(11)	29(11)
C(10A)	199(16)	235(15)	212(15)	95(12)	31(12)	45(12)
C(11A)	228(17)	202(14)	290(17)	162(12)	62(14)	43(12)
C(12A)	259(17)	168(13)	260(16)	73(11)	35(13)	94(12)
C(13A)	190(16)	203(13)	187(14)	96(11)	63(12)	100(11)
C(14A)	140(14)	141(12)	161(13)	67(10)	21(11)	28(10)
C(15A)	360(20)	110(13)	450(20)	-96(14)	49(18)	-22(13)
C(16A)	117(14)	129(12)	180(13)	69(10)	40(11)	3(10)
C(17A)	302(19)	203(14)	296(17)	153(13)	75(14)	93(13)
C(18A)	193(16)	232(14)	115(13)	25(11)	59(11)	65(12)
C(19A)	259(18)	254(16)	277(17)	30(13)	97(14)	104(14)
C(20A)	185(16)	288(16)	213(16)	120(12)	7(13)	4(13)
O(1B)	177(11)	139(9)	201(11)	-4(8)	21(9)	82(8)
O(2B)	154(11)	78(8)	366(13)	-25(8)	34(10)	-8(7)
O(3B)	257(12)	180(10)	138(10)	-21(8)	-66(9)	43(9)
O(4B)	246(12)	108(8)	107(9)	31(7)	-2(8)	55(8)
N(1B)	116(12)	124(10)	121(10)	30(8)	7(9)	-3(8)
N(2B)	113(12)	158(11)	100(10)	4(8)	13(9)	1(9)
C(1B)	119(13)	108(11)	130(12)	20(9)	38(10)	4(9)
C(2B)	114(13)	121(11)	168(13)	28(10)	7(11)	21(10)
C(3B)	104(13)	107(11)	104(11)	5(9)	-30(10)	13(9)
C(4B)	115(13)	72(10)	113(12)	21(9)	9(10)	35(9)
C(5B)	144(14)	199(13)	96(12)	-27(10)	6(10)	-10(11)
C(6B)	490(20)	151(14)	245(17)	-70(12)	-74(17)	-43(15)
C(7B)	207(17)	349(18)	140(14)	29(12)	38(12)	-12(14)
C(8B)	162(15)	128(12)	167(13)	19(10)	-22(11)	-9(10)
C(9B)	205(16)	190(14)	179(14)	59(11)	19(12)	-31(12)
C(10B)	277(19)	219(15)	241(16)	117(12)	7(14)	-80(13)

C(11B)	350(20)	161(14)	267(17)	92(12)	-67(15)	-32(13)
C(12B)	400(20)	211(15)	274(18)	68(13)	-41(15)	112(14)
C(13B)	270(18)	165(13)	208(15)	52(11)	16(13)	69(12)
C(14B)	155(14)	87(11)	158(13)	29(9)	11(11)	16(10)
C(15B)	340(20)	73(13)	550(20)	-81(14)	87(18)	-24(13)
C(16B)	122(13)	81(11)	116(12)	1(9)	15(10)	-4(9)
C(17B)	277(17)	193(13)	122(13)	67(10)	20(12)	100(12)
C(18B)	198(16)	172(13)	74(12)	-18(10)	23(11)	7(11)
C(19B)	122(15)	279(16)	282(17)	-48(13)	56(13)	44(12)
C(20B)	232(17)	285(16)	180(15)	103(12)	63(13)	32(13)
O(1C)	224(12)	106(9)	222(11)	35(8)	32(9)	54(8)
O(2C)	191(12)	114(9)	264(11)	14(8)	58(9)	-16(8)
O(3C)	211(12)	148(9)	152(10)	8(7)	-45(8)	31(8)
O(4C)	276(12)	117(9)	126(9)	37(7)	7(8)	61(8)
N(1C)	160(12)	110(10)	107(10)	28(8)	49(9)	39(9)
N(2C)	150(12)	162(11)	83(10)	17(8)	14(9)	30(9)
C(1C)	205(15)	133(12)	116(12)	57(10)	76(11)	71(11)
C(2C)	175(15)	139(12)	130(12)	40(9)	53(11)	63(10)
C(3C)	117(13)	100(11)	131(12)	9(9)	13(10)	27(9)
C(4C)	156(14)	80(11)	120(12)	33(9)	20(10)	37(10)
C(5C)	183(15)	176(13)	95(12)	27(10)	4(11)	27(11)
C(6C)	291(19)	258(16)	136(14)	-22(12)	0(13)	3(13)
C(7C)	197(17)	208(14)	280(17)	79(12)	-25(13)	51(12)
C(8C)	176(15)	122(12)	119(12)	32(9)	19(11)	39(10)
C(9C)	222(16)	183(13)	124(13)	54(10)	83(11)	51(11)
C(10C)	269(18)	221(14)	201(15)	137(12)	107(13)	49(13)
C(11C)	280(18)	154(13)	213(15)	108(11)	56(13)	43(12)
C(12C)	275(17)	124(12)	199(14)	51(10)	31(12)	73(11)
C(13C)	246(17)	155(13)	161(13)	49(10)	98(12)	102(11)
C(14C)	205(15)	111(12)	96(12)	29(9)	1(11)	-5(10)
C(15C)	320(20)	139(13)	348(19)	12(12)	154(16)	-19(13)
C(16C)	98(14)	131(12)	192(14)	64(10)	31(11)	54(10)
C(17C)	350(20)	200(14)	228(15)	150(12)	56(14)	115(13)
C(18C)	160(15)	214(13)	83(12)	53(10)	0(10)	29(11)
C(19C)	311(19)	283(16)	89(13)	-87(11)	12(12)	92(14)
C(20C)	206(16)	223(15)	157(14)	76(11)	13(12)	10(12)
O(1D)	206(12)	167(10)	223(11)	30(8)	2(9)	26(8)
O(2D)	223(12)	110(9)	280(12)	53(8)	49(9)	69(8)
O(3D)	225(12)	131(9)	181(10)	15(8)	12(9)	35(8)
O(4D)	216(11)	87(8)	170(10)	36(7)	16(8)	4(8)
N(1D)	224(14)	153(11)	80(10)	19(8)	-16(9)	79(9)
N(2D)	181(13)	132(10)	105(10)	19(8)	5(9)	63(9)
C(1D)	184(15)	166(13)	128(13)	35(10)	-17(11)	64(11)
C(2D)	134(14)	177(13)	175(13)	64(10)	-15(11)	77(11)
C(3D)	118(13)	113(11)	148(13)	17(9)	2(10)	22(10)
C(4D)	167(14)	70(10)	127(12)	23(9)	-21(10)	26(10)
C(5D)	310(18)	229(14)	132(13)	-30(11)	-18(12)	167(13)
C(6D)	750(30)	164(15)	360(20)	-54(14)	0(20)	124(18)
C(7D)	780(30)	490(20)	120(15)	39(14)	63(17)	510(20)
C(8D)	174(15)	148(12)	171(13)	43(10)	-12(11)	77(11)
C(9D)	209(16)	158(13)	192(14)	28(11)	-26(12)	59(11)
C(10D)	312(19)	235(15)	202(15)	74(12)	-17(14)	108(13)
C(11D)	308(19)	221(15)	211(15)	116(12)	57(14)	76(13)
C(12D)	223(17)	249(15)	206(15)	93(12)	-12(13)	-12(13)

C(13D)	159(15)	240(14)	152(14)	86(11)	-33(11)	2(12)
C(14D)	174(15)	132(12)	115(12)	57(9)	36(11)	20(10)
C(15D)	330(20)	115(13)	308(18)	33(12)	31(15)	43(12)
C(16D)	137(15)	141(13)	296(17)	48(12)	79(13)	57(11)
C(17D)	227(17)	170(13)	199(15)	86(11)	30(12)	31(12)
C(18D)	166(15)	187(13)	120(13)	29(10)	-25(11)	64(11)
C(19D)	229(17)	246(15)	180(15)	49(12)	-67(13)	67(13)
C(20D)	274(18)	202(14)	207(15)	74(12)	-23(13)	51(12)
O(1E)	127(11)	105(9)	242(11)	17(8)	-31(9)	-22(7)
O(2E)	186(11)	130(9)	271(12)	11(8)	-32(9)	54(8)
O(3E)	205(12)	141(9)	192(10)	5(8)	50(9)	13(8)
O(4E)	206(11)	121(9)	142(9)	41(7)	-18(8)	-3(8)
N(1E)	182(13)	111(10)	108(11)	17(8)	-20(9)	32(9)
N(2E)	147(12)	147(11)	117(11)	22(8)	4(9)	62(9)
C(1E)	146(14)	134(12)	139(13)	24(10)	-37(11)	-6(10)
C(2E)	113(14)	146(12)	192(14)	63(10)	-21(11)	-20(10)
C(3E)	118(13)	97(11)	149(12)	26(9)	-8(10)	-6(9)
C(4E)	113(13)	91(11)	131(12)	15(9)	-13(10)	-22(9)
C(5E)	233(16)	159(13)	131(13)	39(10)	28(11)	78(11)
C(6E)	330(20)	286(16)	104(13)	37(11)	-32(13)	89(14)
C(7E)	231(18)	286(17)	260(17)	79(13)	89(14)	70(13)
C(8E)	150(14)	136(12)	139(12)	34(10)	-17(10)	33(10)
C(9E)	159(15)	203(13)	176(14)	60(11)	-20(11)	35(11)
C(10E)	284(19)	223(15)	235(16)	93(12)	-43(13)	83(13)
C(11E)	278(18)	203(14)	275(17)	115(12)	-25(14)	54(13)
C(12E)	209(17)	175(13)	258(16)	114(12)	-28(13)	-8(12)
C(13E)	185(16)	198(14)	208(15)	85(11)	-32(12)	43(12)
C(14E)	168(14)	113(11)	108(12)	32(9)	3(10)	30(10)
C(15E)	330(20)	83(12)	420(20)	14(12)	-59(16)	79(12)
C(16E)	115(13)	116(11)	167(13)	44(10)	15(11)	15(10)
C(17E)	259(18)	179(14)	194(15)	105(11)	14(13)	-8(12)
C(18E)	173(15)	177(13)	87(12)	35(10)	-15(10)	75(11)
C(19E)	150(15)	196(14)	222(15)	-15(11)	-45(12)	65(11)
C(20E)	226(17)	224(14)	194(15)	100(12)	23(12)	93(12)
O(1F)	190(12)	151(10)	243(11)	61(8)	13(9)	47(8)
O(2F)	231(12)	101(9)	213(11)	20(8)	15(9)	35(8)
O(3F)	243(12)	163(9)	150(10)	-4(8)	55(9)	67(8)
O(4F)	257(12)	107(8)	99(9)	34(7)	29(8)	12(8)
N(1F)	168(13)	136(10)	110(10)	33(8)	-17(9)	80(9)
N(2F)	141(12)	133(10)	98(10)	20(8)	-12(9)	52(9)
C(1F)	147(14)	163(12)	135(12)	46(10)	1(11)	71(10)
C(2F)	167(14)	134(12)	121(12)	35(9)	7(11)	39(10)
C(3F)	126(13)	91(11)	132(12)	27(9)	-2(10)	16(9)
C(4F)	140(14)	81(11)	132(12)	26(9)	10(10)	17(9)
C(5F)	326(18)	192(14)	160(14)	0(11)	9(13)	160(13)
C(6F)	630(30)	219(16)	240(17)	2(13)	13(18)	172(17)
C(7F)	380(20)	330(17)	125(14)	-28(12)	-34(14)	192(15)
C(8F)	225(16)	146(12)	131(13)	35(10)	39(11)	85(11)
C(9F)	310(18)	229(15)	174(14)	68(11)	42(13)	174(13)
C(10F)	430(20)	278(16)	180(15)	111(12)	94(14)	237(15)
C(11F)	550(30)	199(15)	261(17)	104(13)	208(17)	145(15)
C(12F)	430(20)	203(15)	258(17)	91(13)	153(16)	59(15)
C(13F)	246(18)	229(15)	183(15)	69(12)	45(13)	60(13)
C(14F)	157(14)	123(12)	128(12)	21(9)	13(11)	24(10)

C(15F)	350(20)	72(11)	238(15)	8(10)	62(14)	23(12)
C(16F)	132(14)	155(12)	50(11)	17(9)	-21(10)	62(10)
C(17F)	238(17)	216(14)	155(14)	107(11)	27(12)	22(12)
C(18F)	177(15)	168(12)	99(12)	22(10)	-28(11)	61(11)
C(19F)	215(17)	139(13)	200(15)	-5(11)	-47(13)	-39(11)
C(20F)	351(19)	240(15)	129(13)	76(11)	-9(13)	130(13)
Br(1A)	265(2)	205(1)	172(1)	6(1)	-6(1)	118(1)
Br(1B)	212(2)	209(1)	143(1)	38(1)	18(1)	89(1)
Br(1C)	286(2)	173(1)	186(2)	-11(1)	-24(1)	92(1)
Br(1D)	242(2)	223(2)	175(2)	45(1)	22(1)	-12(1)
Br(1E)	225(2)	166(1)	142(1)	0(1)	31(1)	-40(1)
Br(1F)	212(2)	228(2)	157(1)	45(1)	-2(1)	10(1)
O(5A)	202(12)	160(10)	207(11)	8(8)	11(9)	47(8)
O(5B)	155(11)	210(10)	200(11)	29(8)	-5(9)	-74(9)
O(5C)	189(12)	159(10)	246(12)	43(8)	21(9)	55(9)
O(5D)	342(15)	272(12)	219(12)	50(9)	23(10)	202(11)
O(5E)	200(12)	176(10)	162(10)	29(8)	54(9)	63(8)
O(5F)	253(13)	291(12)	214(12)	35(9)	37(10)	159(10)

Table A3.2.5. Hydrogen coordinates ($\times 10^3$) and isotropic displacement parameters ($\approx^2 \times 10^3$) for (R)-**60**•HBr.

	x	y	z	U _{iso}
H(2A)	204	104	797	17
H(1A)	646	133	714	16
H(2AA)	842	242	787	17
H(2AB)	776	130	782	17
H(5A)	213	72	729	19
H(6AA)	404	146	657	37
H(6AB)	228	64	650	37
H(6AC)	402	47	670	37
H(7AA)	186	224	753	35
H(7AB)	98	182	702	35
H(7AC)	282	256	709	35
H(9A)	782	222	663	22
H(10A)	859	359	632	25
H(11A)	792	492	668	27
H(12A)	646	488	735	26
H(13A)	565	351	766	21
H(15G)	784	477	855	51
H(15H)	964	472	878	51
H(15I)	794	446	905	51
H(17G)	691	-57	862	37
H(17H)	593	-8	900	37
H(17I)	793	36	896	37
H(18A)	381	168	885	21
H(19G)	173	248	870	38
H(19H)	114	190	910	38
H(19I)	25	151	859	38
H(20G)	99	3	863	35
H(20H)	211	38	912	35
H(20I)	296	1	867	35
H(2B)	-4	75	461	16
H(1B)	460	112	381	15
H(2BA)	580	124	454	16
H(2BB)	628	234	453	16
H(5B)	0	59	391	20
H(6BA)	226	-58	383	50
H(6BB)	27	-92	363	50
H(6BC)	78	-61	418	50
H(7BA)	134	130	331	37
H(7BB)	45	22	312	37
H(7BC)	249	58	324	37
H(9B)	598	218	334	25
H(10B)	613	349	300	32

H(11B)	460	456	328	33
H(12B)	280	426	388	35
H(13B)	258	293	421	25
H(15D)	494	467	503	53
H(15E)	692	482	520	53
H(15F)	543	453	554	53
H(17D)	488	-42	549	28
H(17E)	396	20	584	28
H(17F)	596	58	576	28
H(18B)	166	149	549	19
H(19D)	-33	229	532	36
H(19E)	-101	171	572	36
H(19F)	-183	134	520	36
H(20D)	-108	-19	527	35
H(20E)	-10	21	577	35
H(20F)	90	-16	536	35
H(2C)	416	99	128	16
H(1C)	849	121	40	17
H(2CA)	1052	228	112	17
H(2CB)	979	118	109	17
H(5C)	419	57	59	19
H(6CA)	606	125	-15	37
H(6CB)	432	43	-20	37
H(6CC)	608	29	1	37
H(7CA)	386	208	80	34
H(7CB)	300	164	28	34
H(7CC)	483	240	36	34
H(9C)	994	214	-9	21
H(10C)	1067	352	-39	26
H(11C)	991	482	-4	25
H(12C)	834	474	62	23
H(13C)	753	336	91	21
H(15A)	1026	476	158	42
H(15B)	1175	471	195	42
H(15C)	982	457	209	42
H(17A)	855	-61	201	36
H(17B)	813	14	240	36
H(17C)	1004	30	224	36
H(18C)	605	167	215	18
H(19A)	412	254	202	36
H(19B)	349	197	243	36
H(19C)	254	161	192	36
H(20A)	317	5	195	30
H(20B)	427	43	244	30
H(20C)	513	2	200	30
H(2D)	98	754	670	16
H(1D)	531	721	758	19
H(2DA)	563	591	691	18
H(2DB)	628	700	687	18
H(5D)	128	777	740	26
H(6DA)	471	898	753	65
H(6DB)	300	931	760	65
H(6DC)	339	888	709	65
H(7DA)	236	712	803	60

H(7DB)	204	812	818	60
H(7DC)	395	804	812	60
H(9D)	568	620	808	22
H(10D)	458	495	846	29
H(11D)	188	390	820	28
H(12D)	26	415	757	28
H(13D)	136	542	720	23
H(15P)	229	362	596	38
H(15Q)	190	360	649	38
H(15R)	363	339	631	38
H(17P)	515	793	552	30
H(17Q)	688	765	564	30
H(17R)	665	864	587	30
H(18D)	176	667	586	19
H(19P)	-101	589	600	33
H(19Q)	-123	649	560	33
H(19R)	-153	684	613	33
H(20P)	67	834	598	34
H(20Q)	132	788	551	34
H(20R)	265	834	596	34
H(2E)	725	727	339	16
H(1E)	1153	714	432	18
H(2EA)	1241	603	363	19
H(2EB)	1274	713	364	19
H(5E)	778	772	408	20
H(6EA)	909	709	485	36
H(6EB)	818	791	487	36
H(6EC)	1004	804	468	36
H(7EA)	600	615	388	38
H(7EB)	557	669	436	38
H(7EC)	667	595	437	38
H(9E)	1236	625	481	22
H(10E)	1190	492	516	29
H(11E)	972	358	483	30
H(12E)	792	362	419	26
H(13E)	836	496	385	23
H(15M)	935	367	266	42
H(15N)	943	355	319	42
H(15O)	1105	352	290	42
H(17M)	1192	808	230	32
H(17N)	1372	801	252	32
H(17O)	1302	888	271	32
H(18E)	830	654	255	17
H(19M)	557	566	263	29
H(19N)	533	629	226	29
H(19O)	491	656	279	29
H(20M)	708	816	269	30
H(20N)	772	775	222	30
H(20O)	907	819	266	30
H(2F)	294	753	11	15
H(1F)	736	716	95	17
H(2FA)	771	594	25	17
H(2FB)	827	704	23	17
H(5F)	326	770	82	25

H(6FA)	669	891	94	54
H(6FB)	499	923	105	54
H(6FC)	530	887	53	54
H(7FA)	413	700	142	40
H(7FB)	415	806	160	40
H(7FC)	592	780	150	40
H(9F)	782	610	140	26
H(10F)	683	477	174	31
H(11F)	413	372	146	38
H(12F)	242	403	88	35
H(13F)	341	538	56	26
H(15J)	426	364	-66	34
H(15K)	383	363	-14	34
H(15L)	556	340	-30	34
H(17J)	696	780	-116	30
H(17K)	882	771	-100	30
H(17L)	828	864	-82	30
H(18F)	373	676	-76	18
H(19J)	93	599	-62	31
H(19K)	78	660	-101	31
H(19L)	45	695	-49	31
H(20J)	267	844	-55	34
H(20K)	318	804	-105	34
H(20L)	462	843	-62	34
H(5AA)	998(5)	-14(2)	771(1)	29
H(5AB)	915(5)	48(2)	797(1)	29
H(5BA)	681(4)	-35(2)	445(1)	32
H(5BB)	758(5)	62(1)	454(1)	32
H(5CA)	145(5)	-29(1)	117(1)	29
H(5CB)	114(4)	59(2)	119(1)	29
H(5DA)	897(5)	875(2)	681(1)	38
H(5DB)	901(5)	820(2)	715(1)	38
H(5EA)	601(5)	860(2)	349(1)	26
H(5EB)	528(5)	808(2)	383(1)	26
H(5FA)	230(2)	832(3)	35(1)	35
H(5FB)	75(5)	820(3)	57(1)	35

CHAPTER 2

Progress toward the Total Synthesis of Scandine and the Melodinus Alkaloids[†]

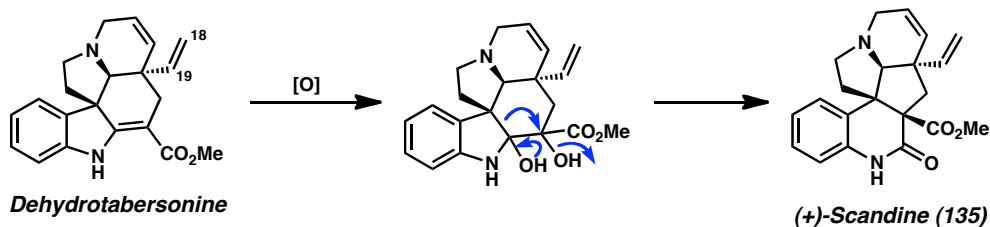
2.1 INTRODUCTION AND SYNTHETIC STRATEGY

2.1.1 INTRODUCTION

The *Melodinus* alkaloids are a family of dihydroquinolinone natural products originally isolated over 40 years ago from *Melodinus scandens* Forst and are structurally related to the *Aspidosperma* alkaloids by means of an oxidative rearrangement of 18,19-dehydrotabersonine (Scheme 2.1.1).^{1,2} Although no biological activity has been directly attributed to any member of this class of compounds to date, some species of the *Melodinus* genus are used in Chinese folk medicine to treat meningitis in children and rheumatic disease.^{3,4}

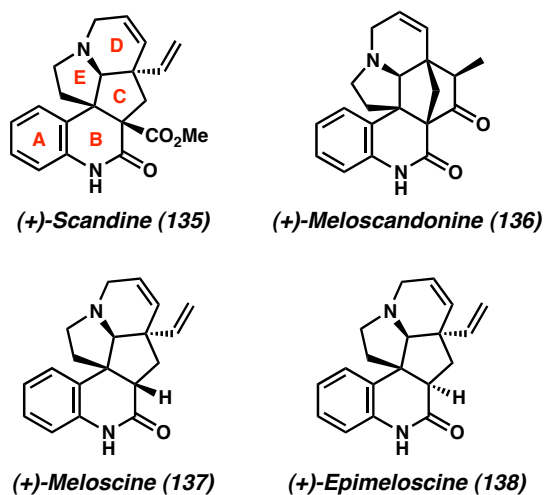
[†] Later aspects of this work were performed in collaboration with Nicholas R. O'Connor, a graduate student in the Stoltz group. A portion of this work was published. See: Goldberg, A. F. G.; Stoltz, B. M. *Org. Lett.* **2011**, *13*, 4474–4476.

Scheme 2.1.1. Proposed Biosynthesis of the Melodinus Alkaloids.



Despite the lack of known biological activity, we were intrigued by their structural complexity and interested in the prospects of preparing non-natural derivatives for biological evaluation (Figure 2.1.1). The *Melodinus* alkaloids feature a congested cyclopentane core, bearing four contiguous stereocenters; in the case of (+)-scandine (**135**),¹ (+)-meloscandonine (**136**),⁵ and others,⁶ three of these are quaternary stereocenters. Indeed, construction of this highly substituted C ring constitutes a formidable challenge, and the only members of the family to have been synthesized to date are meloscine (**137**) and its C(16) epimer, epimeloscine (**138**).^{7,8,9}

Figure 2.1.1. Representative examples of the Melodinus Alkaloids

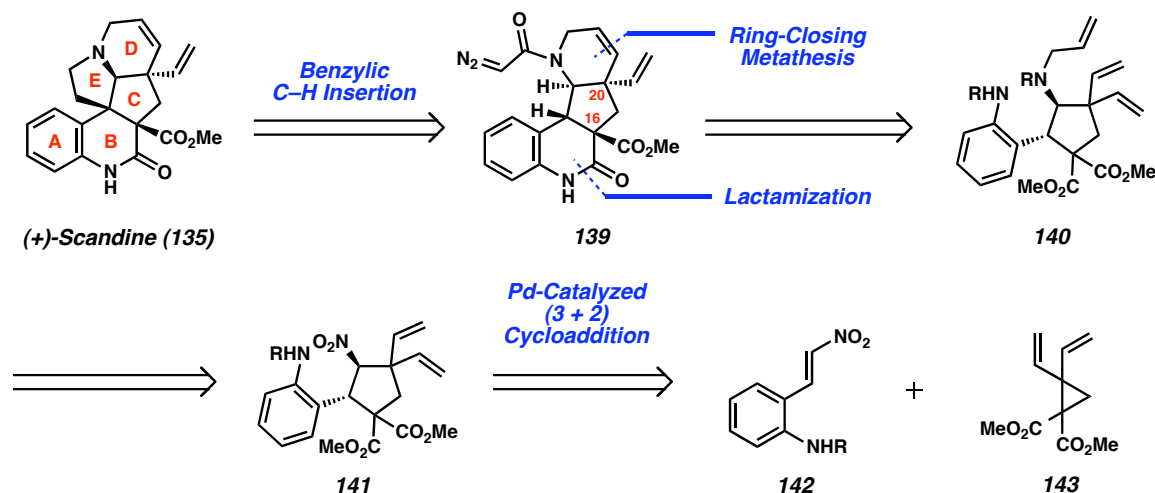


2.1.2 ORIGINAL RETROSYNTHETIC ANALYSIS

The parent of the natural product family, (+)-scandine (**135**), is believed to be the biosynthetic precursor to the 13 other known members of the family. In the long-term interest of a general route to the Melodinus alkaloids, we sought a strategy for the rapid assembly of scandine (**135**); other members of the *Melodinus* alkaloids would then be prepared from this natural product, or by a similar approach.

Through our synthetic strategy, we chose to exploit elements of symmetry found within the target natural product. In particular, the quaternary stereocenter at C(20) bears two olefinic substituents, and C(16) bears two carbon substituents in the carboxylic acid oxidation state.

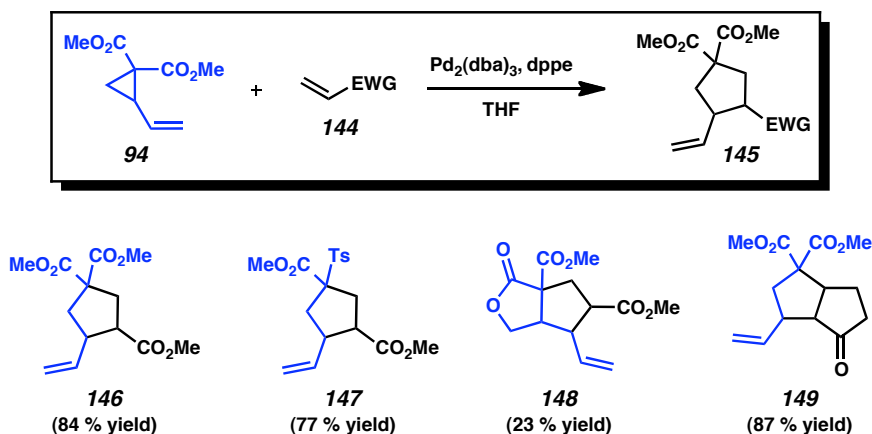
Accordingly, after disconnection of the E ring via benzylic C–H insertion, we envisioned that the D and B rings of **139** could be formed by ring-closing metathesis (RCM) and lactamization respectively of divinylcyclopentane **140** (Scheme 2.1.2). Notably, the C(20) and C(16) quaternary carbons in this proposed intermediate are not stereogenic; the vinyl groups and the methyl esters are diastereotopic, and the stereochemistry at these carbons would be set by the RCM and lactamization steps, controlled by the neighboring stereocenters. This intermediate could arise, in turn, from nitrocyclopentane (**141**), the product of a transition metal catalyzed, intermolecular formal (3 + 2) cycloaddition between a *trans*- β -nitrostyrene (**142**) and divinylcyclopropane **143**.¹⁰

Scheme 2.1.2. Retrosynthetic analysis of scandine (**135**).

2.1.2.1 METAL-CATALYZED CYCLOPROPANE (3 + 2) CYCLOADDITIONS

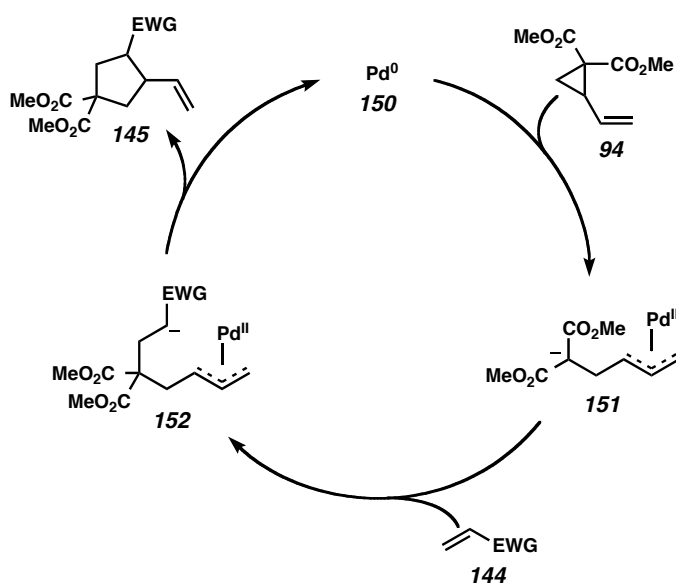
In 1985, Tsuji and coworkers reported a palladium-catalyzed (3 + 2) cycloaddition of vinylcyclopropane-1,1-diester with a range of conjugate acceptors. In particular, α,β -unsaturated ketones and esters afforded cyclopentane products (**146–149**, Scheme 2.1.3). All of the products were isolated as mixtures of diastereomers.¹⁰

Scheme 2.1.3. Tsuji's palladium-catalyzed (3 + 2) cycloaddition of vinylcyclopropanes



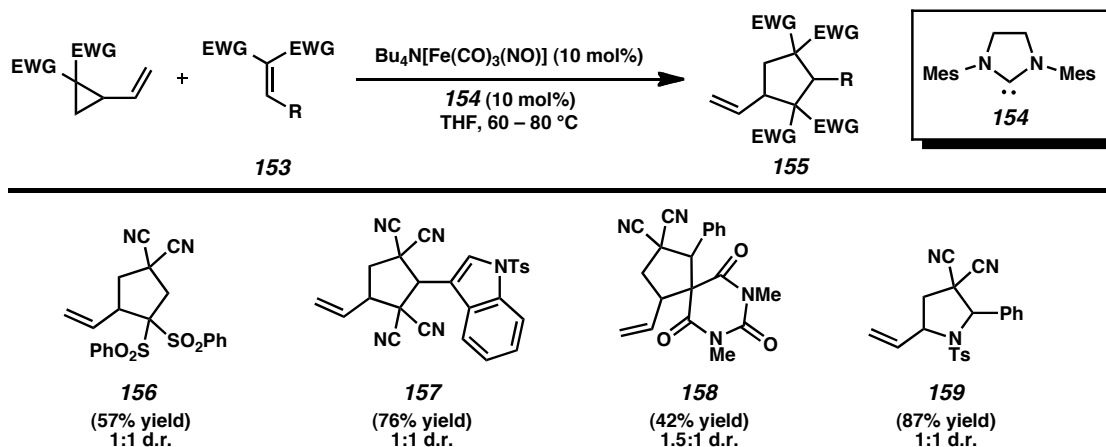
The mechanism of the reaction is believed to proceed via palladium mediated C–C bond cleavage of vinylcyclopropane **94** to form a palladium(II) allyl species with a pendent malonate anion (**151**, Scheme 2.1.4). The malonate moiety then reacts with the conjugate acceptor (**144**) to form anion **152**, which undergoes a 5-exo ring-closure to generate the vinylcyclopentane product **145** and regenerate the palladium(0) catalyst.

Scheme 2.1.4. Proposed mechanism of the palladium-catalyzed (3 + 2) cycloaddition



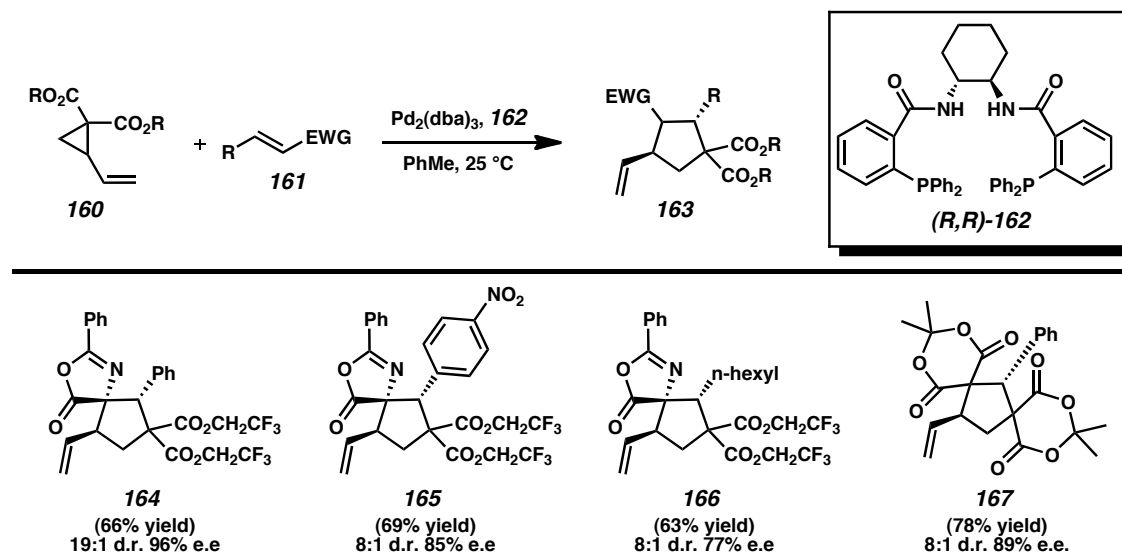
More recently, an iron-catalyzed variant of this reaction was reported by Plietker in 2012, which expanded the substrate scope to some degree, but suffered from the same problems with diastereoselectivity as the original system (Scheme 2.1.5).¹¹ Notably, the reaction was amenable to the use of nitrogen-containing cyclopropanes and conjugate acceptors.

Scheme 2.1.5. Iron-catalyzed (3 + 2) cycloaddition of vinylcyclopropanes



During the course of our studies, in 2011, Trost and coworkers disclosed the enantio- and diastereoselective variant of this reaction (Scheme 2.1.6).¹² In this case, vinylcyclopropanes with highly electron-deficient ester groups were reacted with conjugate acceptors to afford cyclopentanes (**155**) with high stereoselectivity. The electron-deficiency of the cyclopropane diester functionality was critical to the enantioselectivity, as it rendered reversible the non-stereoselective conjugate addition step of the reaction mechanism (*vide supra*, Scheme 2.1.4).

Scheme 2.1.6. Enantio- and diastereoselective palladium-catalyzed (3 + 2) cycloaddition

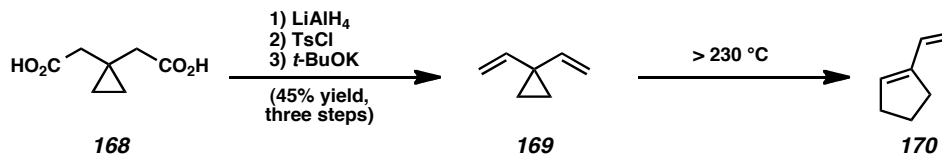


From the literature precedent, it was not clear whether this reaction would be compatible with vinylcyclopropanes bearing quaternary centers. We therefore began a research program to synthesize and examine the reactivity of such a cyclopropane toward the ultimate goal of applying it to the synthesis of the *Melodinus* alkaloids.

2.1.2.2 KNOWN 1,1-DIVINYLCYCLOPROPANES

At the outset of this project, only two 1,1-divinylcyclopropanes were known in the literature,^{13,14} prompting some concern that the desired cyclopropane would be too unstable to isolate. First, in 1972, Dolbier and Alonso reported the synthesis of 1,1-divinylcyclopropane (**169**), by a three-step procedure from diacid **168** (Scheme 2.1.7).¹³ In their studies, they found that this compound underwent quantitative rearrangement to cyclopentene **170** at 230 °C; notably, the activation barrier was 12–13 kcal/mol lower than the corresponding monovinylcyclopropane. The proposed mechanism is concerted or biradical in nature, so while this example is illustrative of potential stability issues that may arise in the synthesis of the desired diester analogue (**143**), that cyclopropane would likely react via a polar mechanism.

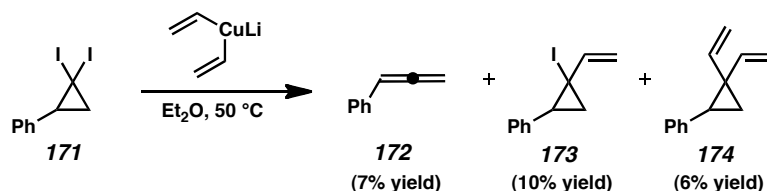
Scheme 2.1.7. Synthesis and properties of 1,1-divinylcyclopropane (**169**)



The other 1,1-divinylcyclopropane known at the time was prepared by Mathias and Weyerstahl through vinylation of a 1,1-dihalocyclopropane (**171**, Scheme 2.1.8).¹⁴ Treatment of this cyclopropane with divinyl cuprate afforded a low-yielding mixture of

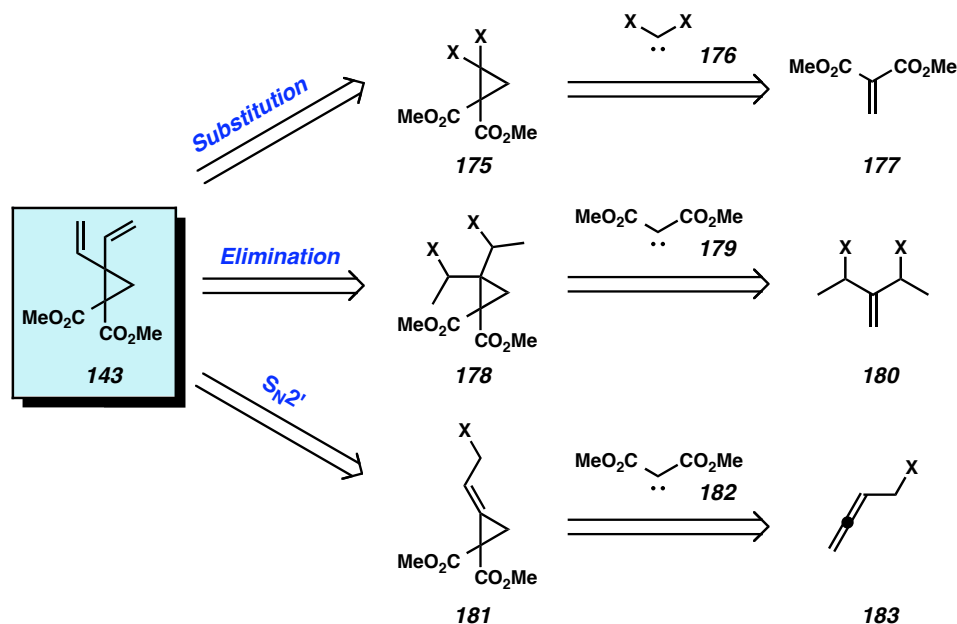
three compounds, including phenylallene (**172**), a monovinylated cyclopropane (**173**) and the divinylcyclopropane of interest (**174**).

Scheme 2.1.8. Synthesis of 2-phenyl-1,1-divinylcyclopropane (**174**)



2.1.2.3 DIVINYLCYCLOPROPANE RETROSYNTHESIS

We examined several possible approaches toward the synthesis of the desired divinylcyclopropane (**143**, Scheme 2.1.9). First, a substitution approach analogous to Weyerstahl's may be possible from a 1,1-dihalocyclopropane (**175**), which would be generated in turn from methyldiene dimethylmalonate (**177**).¹⁵ Alternatively, the two vinyl groups could be formed by elimination of cyclopropane **178**, synthesized by cyclopropanation with a malonate-derived carbenoid (**179**). Finally, the last route that we studied involved $\text{S}_{\text{N}}2'$ displacement of alkylidene cyclopropane **181** with a vinyl nucleophile. This cyclopropane could be derived by cyclopropanation of allene **183**.

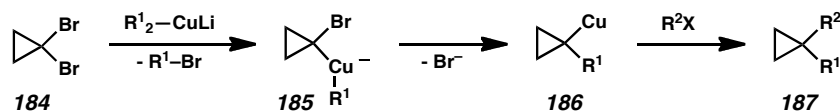
Scheme 2.1.9. Retrosynthesis of divinylcyclopropane **143**

2.2 TOWARD THE SYNTHESIS OF A DIVINYLCYCLOPROPANE

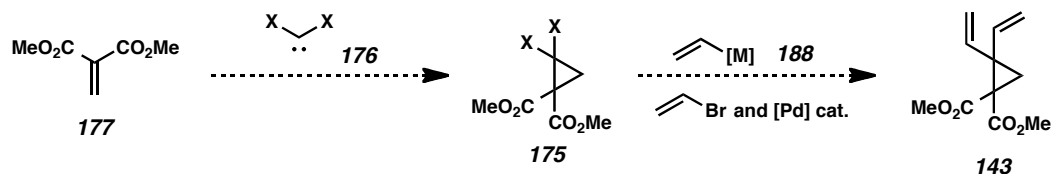
2.2.1 GEM-DIHALOCYCLOPROPANE SUBSTITUTION ROUTE

We first examined the use of a 1,1-dihalocyclopropane toward the desired divinylcyclopropane (**143**). The synthesis and reactions of 1,1-dihalocyclopropanes has been extensively researched and an excellent literature review on this topic was published by Fedorynski in 2003.¹⁵ Fedorynski describes reactions of 1,1-dihalocyclopropanes with dialkyl cuprates,¹⁶ trialkyl zincates,¹⁷ manganates,¹⁸ or magnesates¹⁹ that yield alkylated cyclopropylmetals (**186**), which can react with an electrophile to deliver products with geminal substitution (**187**, Scheme 2.2.1). Furthermore, the cyclopropylmetal intermediates can be used in metal-catalyzed cross-coupling reactions with vinyl halides to deliver vinylcyclopropanes.

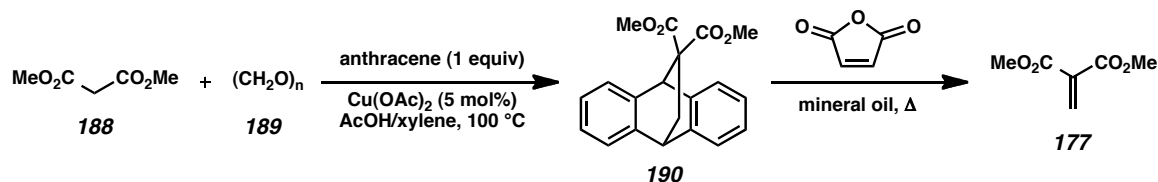
Scheme 2.2.1. Dialkylation of dihalocyclopropanes with dialkylcuprates



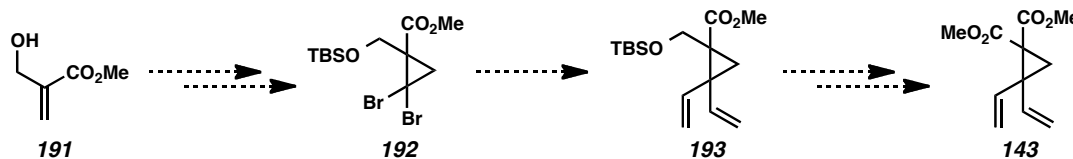
Accordingly, cyclopropanation of methyldiene dimethylmalonate (**177**) followed by substitution could conceivably provide a rapid route to the desired 1,1-divinylcyclopropane (**143**, Scheme 2.2.2)

Scheme 2.2.2. Proposed gem-dihalocyclopropane route toward 1,1-divinylcyclopropane **143**

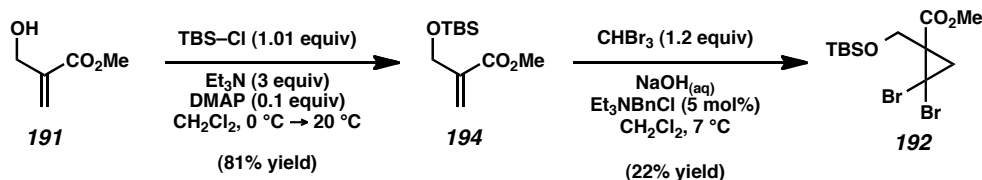
Methyldiene dimethylmalonate (**177**), from a technical standpoint, is notoriously difficult to synthesize and handle.²⁰ It is particularly prone to anionic polymerization, which can easily occur under the reaction conditions by which it is synthesized, typically by condensation of dimethylmalonate (**188**) and formaldehyde (**189**). De Keyser and coworkers succeeded in the development of a scalable route to its synthesis (Scheme 2.2.3).²⁰ Their method involves an in situ trapping of the condensation product via a Diels–Alder reaction with anthracene to afford a crystalline adduct (**190**), which can easily be separated without chromatography from the reaction mixture. Following recrystallization, the anthracene adduct (**190**) is thermolyzed in the presence of maleic anhydride—used to trap the anthracene and drive the reaction forward—and the methyldiene dimethylmalonate (**177**) is purified by distillation.

Scheme 2.2.3. De Keyser's synthesis of methylene dimethylmalonate (**177**)

Due to the highly reactive nature of methylenedimethylmalonate (**177**), we sought to first examine the vinylation of *gem*-dihalocyclopropanes using a model substrate (**192**). Acrylate **191** was chosen as a suitable cyclopropane precursor because of its relative ease of preparation, its structural resemblance to the desired acrylate, and the potential for conversion to the 1,1-diester following successful vinylation (Scheme 2.2.4). Studies on this substrate could later be applied to methylenedimethylmalonate (**177**) to shorten the synthetic sequence.

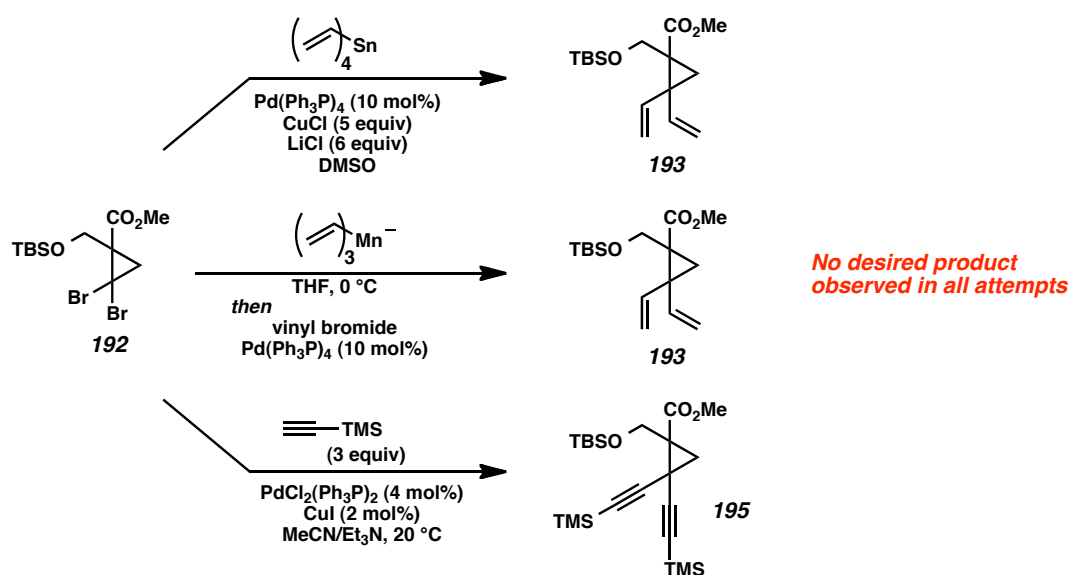
Scheme 2.2.4. Proposed conversion of model cyclopropane **192** to desired (3 + 2) substrate **143**

Accordingly, acrylate derivative **191** was prepared by a known procedure, and protected as a silyl ether (**194**, Scheme 2.2.5).²¹ The product (**194**) was then cyclopropanated by phase-transfer catalysis to afford the *gem*-dibromocyclopropane (**192**).

Scheme 2.2.5. Synthesis of a model *gem*-dihalocyclopropane (**192**)

Unfortunately, efforts to doubly substitute cyclopropane **192** failed (Scheme 2.2.6). Attempted procedures included Stille and Sonogashira cross-couplings, as well as a substitution with a trialkylmanganate with in situ palladium-catalyzed cross coupling to vinyl bromide.^{18b} Since no desired substitution products observed with this substrate, we did not pursue this route further and we shifted our focus to an alternative approach.

Scheme 2.2.6. Efforts to vinylate dibromocyclopropane **192**

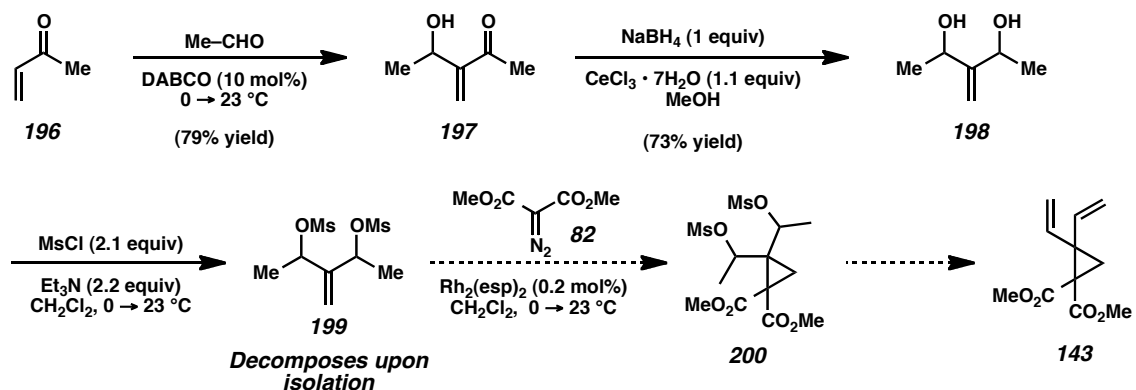


2.2.2 DOUBLE ELIMINATION ROUTE

We turned our attention toward the formation of the desired vinyl groups by elimination of two leaving groups. In this vein, we set out to prepare dimesylate **200** as a divinyl cyclopropane precursor (Scheme 2.2.7). Baylis–Hilman reaction of methyl vinyl ketone (**19**) with acetaldehyde by a known procedure furnished adduct **197** which was then reduced to afford diol **198** as a mixture of diastereomers.²² Although this substrate underwent mesylation cleanly, the product (**199**) was unstable as a neat oil, and underwent spontaneous, violent decomposition.²³ Furthermore, when the dimesylate was

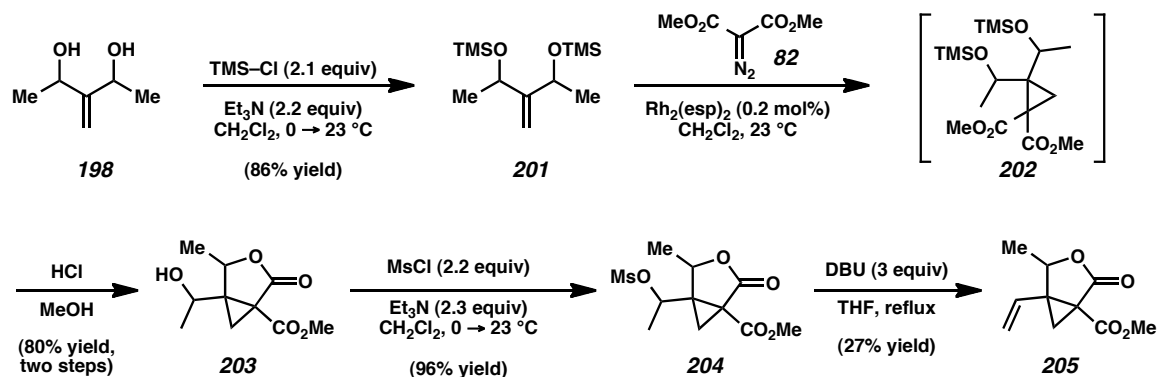
subjected as a solution in dichloromethane directly to cyclopropanation with diazodimethylmalonate, a complex reaction mixture was observed and no desired cyclopropane product (**200**) could be isolated.

Scheme 2.2.7. Synthetic approach to elimination substrate precursor



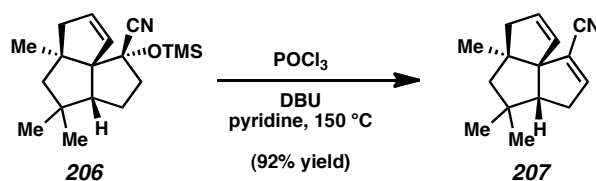
To avoid problems of substrate stability, we opted to protect diol **198** as a disilyl ether (**201**), and this substrate was cyclopropanated efficiently using Du Bois' catalyst to give cyclopropane **202**, which was immediately subjected to alcohol deprotection under acidic conditions.²⁴ In the event, one free hydroxyl underwent an undesired, in situ lactonization to give bicyclic lactone **203**. This product could however be mesylated and eliminated to yield a vinylcyclopropane (**205**).

Scheme 2.2.8. Vinylcyclopropane synthesis via a protected diol (**201**).



We attempted to avoid the undesired lactonization by directly eliminating the silyl ethers under an array of conditions. In particular, a report by Paquette and coworkers detailed the elimination of a silylated cyanohydrin (**206**) to give an unsaturated nitrile (**207**, Scheme 2.2.9).²⁵ The stability of the unsaturated nitrile (**207**) likely aided the elimination of the silyl ether in Paquette's system. Unfortunately, our efforts with this and numerous other methods to directly convert silyl ethers to olefins were unsuccessful.

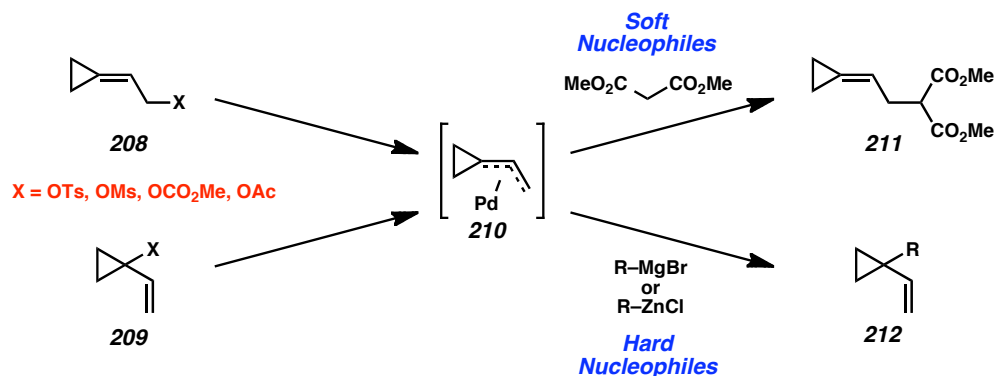
Scheme 2.2.9. Direct elimination of a silyl ether (**206**) to form an unsaturated nitrile (**207**)



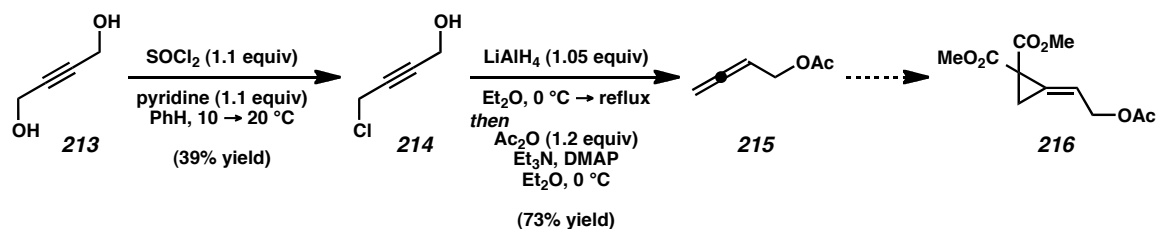
2.2.3 ALKYLIDENECYCLOPROPANE ROUTE

Finally, we examined a route to the divinylcyclopropane by $\text{S}_{\text{N}}2'$ displacement of a substituted alkylidenecyclopropane. De Meijere and coworkers have studied the allylic alkylation of cyclopropane derivatives with carbon nucleophiles under palladium catalysis.²⁶ In their study, they demonstrated that both vinylcyclopropanes (**209**) and methylenecyclopropanes (**208**) with allylic leaving groups will react with the palladium catalyst to form a common palladium allyl intermediate (**210**), which is then alkylated by soft nucleophiles (*i.e.* malonates) at the terminal position or by hard nucleophiles (*i.e.* organozinc or Grignard reagents) at the branched position to afford substituted methylene cyclopropanes (**211**) or vinyl cyclopropanes (**212**) respectively.

Scheme 2.2.10. Allylic alkylation of cyclopropane derivatives



We sought to prepare an analogous alkylidenecyclopropane bearing the necessary methyl ester functionalities, and envisioned its preparation using a known homoallenyl acetate (**215**, Scheme 2.2.11).²⁷

Scheme 2.2.11. Synthetic approach to alkylidenecyclopropane **216**

Conditions were screened for cyclopropanation of allene **215** with diazodimethylmalonate (**82**), examining several catalysts, carbenoid precursor equivalents, and addition times (Table 2.2.1). On our first attempt (entry 1), we were able to isolate the desired alkylidenecyclopropane (**216**) in 42% yield; however, this required an excess of the allene starting material (**215**), which required several steps to prepare. When the excess reagent was inverted, the yield decreased (entry 2), however, increasing the catalyst loading and the diazo equivalence improved the yield to 58% (entry 3). Increasing or decreasing the slow addition time of the diazo reagent had a detrimental effect on the yield (entries 4-5). Changing the catalyst ligand to electron poor

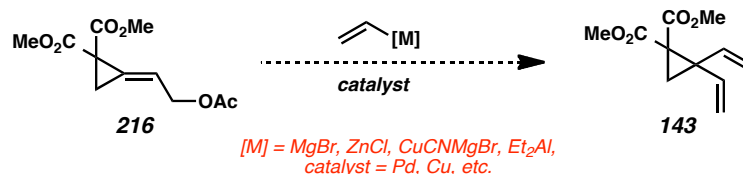
trifluoroacetate resulted in a complex product mixture (entry 6), and electron-rich caprolactam was poorly reactive under similar conditions (entry 7). Microwave heating of a neat mixture of the reaction components (entry 8) afforded considerably shortened reaction times, however, the yield was not improved. Finally, the use of Du Bois' catalyst gave the highest isolated yield, with a short reaction time, low catalyst loading, and no need for slow addition of the diazodimethylmalonate (**82**).²⁸

Table 2.2.1. Optimization of allene cyclopropanation

entry	diazo equiv	catalyst	temperature	addition time	yield (%) ^a
1	0.3	Rh ₂ (OAc) ₄ (0.25 mol%)	reflux	8 h	42 ^b
2	2	Rh ₂ (OAc) ₄ (0.25 mol%)	reflux	6 h	28 ^b
3	3	Rh ₂ (OAc) ₄ (1 mol%)	reflux	6 h	58
4	3	Rh ₂ (OAc) ₄ (1 mol%)	reflux	12 h	37
5	3	Rh ₂ (OAc) ₄ (1 mol%)	reflux	3 h	38
6	3	Rh ₂ (tfa) ₄ (1 mol%)	reflux	3 h	18
7	3	Rh ₂ (cap) ₄ (1 mol%)	reflux	3 h	22 ^c
8	1.3	Rh ₂ (OAc) ₄ (0.4 mol%)	100 °C ^d	3 h	51
9	1.3	Rh ₂ (esp) ₂ (0.1 mol%)	0 → 23 °C	—	80 ^b

^a ¹H NMR yield (pentachlorobenzene as internal standard). ^b Isolated yield. ^c 55% recovered starting material. ^d Microwave heating, solvent-free, 15 minute reaction time.

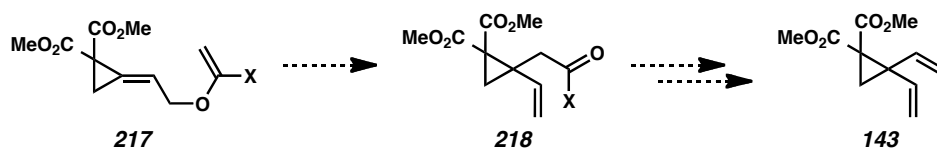
With the desired alkylidene cyclopropane (**216**) in hand, we examined an array of allylic substitution conditions with vinyl nucleophiles, including those reported by de Meijere, as well as other catalytic systems with vinyl alanes, and cuprates (Scheme 2.2.12). Unfortunately, in all cases, none of the desired divinylcyclopropane **143** was observed, and only ring-opened products could be observed.^{29,30} It is possible that the diester functionality on the methylenecyclopropane serves to weaken the distal bond of the methylenecyclopropane, favoring ring-opening rather than substitution.

Scheme 2.2.12. Attempted S_N2' displacement with vinyl nucleophiles

It is possible that a broader screen may find a compatible leaving group for this transformation to out-compete the ring-opening process; however, we turned our attention at this point to other possible approaches to install the necessary vinyl group from this alkylidenecyclopropane substrate.

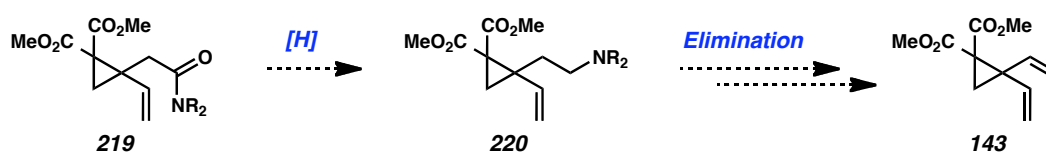
2.2.4 CLAISEN REARRANGEMENT ROUTE

At this stage, we considered that the use of a Claisen rearrangement may offer an alternative pathway to install the desired quaternary carbon on the cyclopropane (Scheme 2.2.13).³¹ The use of Claisen rearrangements to install vicinal quaternary centers is well precedented, and the intramolecular nature of the reaction could aid the efficiency of the carbon-carbon bond formation. However, we envisioned potential chemoselectivity and side-reactivity problems in the conversion of the Claisen product (**218**) to the desired divinylcyclopropane (**143**). Particularly, conditions would be necessary that could reduce the product carbonyl in the presence of the methyl esters, and lactonization of any intermediate alcohol with the ester functionalities would also present a challenge.

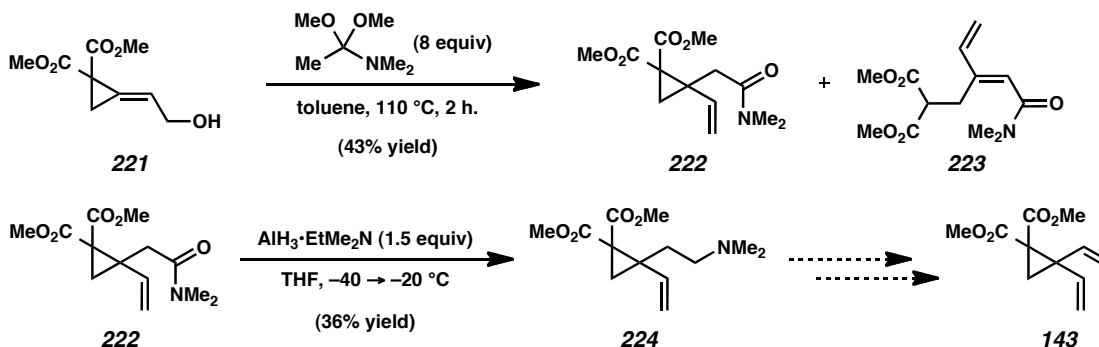
Scheme 2.2.13. Proposed Claisen-rearrangement approach to cyclopropane **143**

Accordingly, we turned to the Eschenmoser–Claisen reaction variant, since numerous examples exist in the literature for chemoselective reduction of amides in the presence of esters,³² the product tertiary amines (**220**) would not be expected to react with the pendent ester functionalities and can be eliminated to form olefins by means of the Cope³³ or Hofmann³⁴ elimination (Scheme 2.2.14).

Scheme 2.2.14. Proposed selective derivatization of an Eschenmoser–Claisen product (**219**)



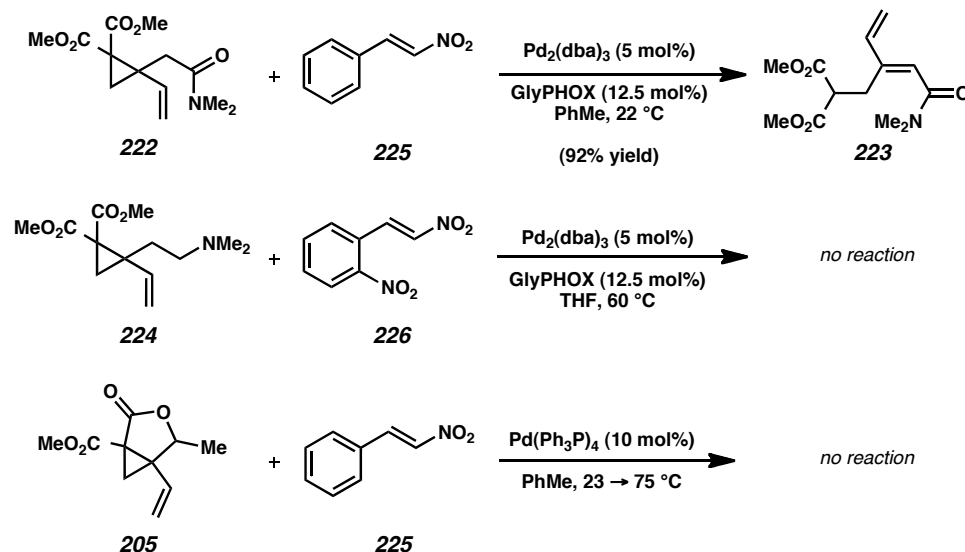
We therefore treated alcohol **221** under typical reaction conditions with dimethylacetamide dimethyl acetal, and observed the formation of amide **222** in moderate yield (Scheme 2.2.15).³⁵ The main side product of the reaction was conjugated amide (**223**), likely formed by base-promoted ring opening of the desired product. Unfortunately, extensive screening of reaction temperatures and times could not improve the yield of the desired vinylcyclopropane (**222**); nevertheless, sufficient material could be rendered to examine the later stages of the synthesis. Therefore, the amide (**222**) was reduced in 36% yield to the dimethylamine (**224**) using alane. Efforts to eliminate the amine (**224**) to form the desired divinylcyclopropane (**143**) have been unsuccessful to date. Fortunately, our efforts to this point provided three unique vinylcyclopropanes (**205**, **222**, and **224**) which we could examine in the palladium-catalyzed (3 + 2) reaction.

Scheme 2.2.15. Eschenmoser–Claisen rearrangement of alkylidenecyclopropane **221**

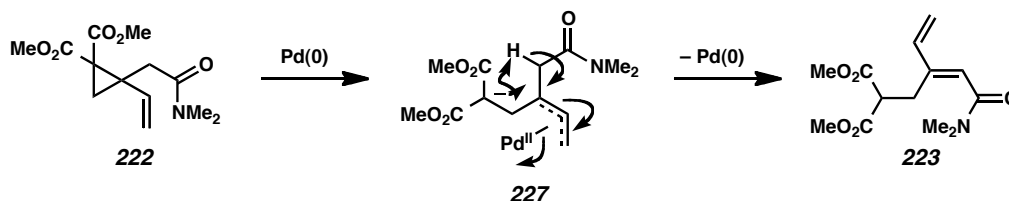
2.3 INVESTIGATION OF (3 + 2) CYCLOADDITION

With three functionalized vinyl cyclopropanes in hand, we set out to determine their compatibility with palladium-catalyzed (3 + 2) cycloaddition conditions originally developed by Tsuji. Under an array of conditions, no cyclopentane products could be isolated (Scheme 2.3.1). In the case of the dimethylamide substituted cyclopropane (**222**), the starting material was isomerized in high yield to conjugated amide **223** as a mixture of olefin isomers. With the dimethylamine analogue (**224**) and bicyclic vinylcyclopropane **205**, the starting material remained unreacted, even at elevated temperatures.

Scheme 2.3.1. Attempted (3 + 2) cycloadditions of vinyl cyclopropanes with nitrostyrenes



The isomerization of dimethylamide **222** is attributed to the presence of acidic protons on the substrate: upon formation of the palladium(II) allyl species (**227**), the pendant malonate acts as a base, eliminating Pd(0) via deprotonation of the α -proton of the dimethylamide to give conjugated amide **223** (Scheme 2.3.2).

Scheme 2.3.2. Mechanism for cyclopropane ring-opening isomerization of dimethylamide **222**

As for vinylcyclopropanes **205** and **224**, we propose that the lack of reactivity results from a demanding allylation step of the mechanistic cycle (Scheme 2.3.3). Whereas hard nucleophiles such as Grignard reagents will typically react under palladium catalysis via an inner-sphere mechanism, at the allyl terminus with greater substitution, soft-nucleophiles often proceed by outer-sphere attack at the least-substituted position. In the case of an unsubstituted vinyl cyclopropane (3 + 2) cycloaddition (*i.e.* **228**, R = H,

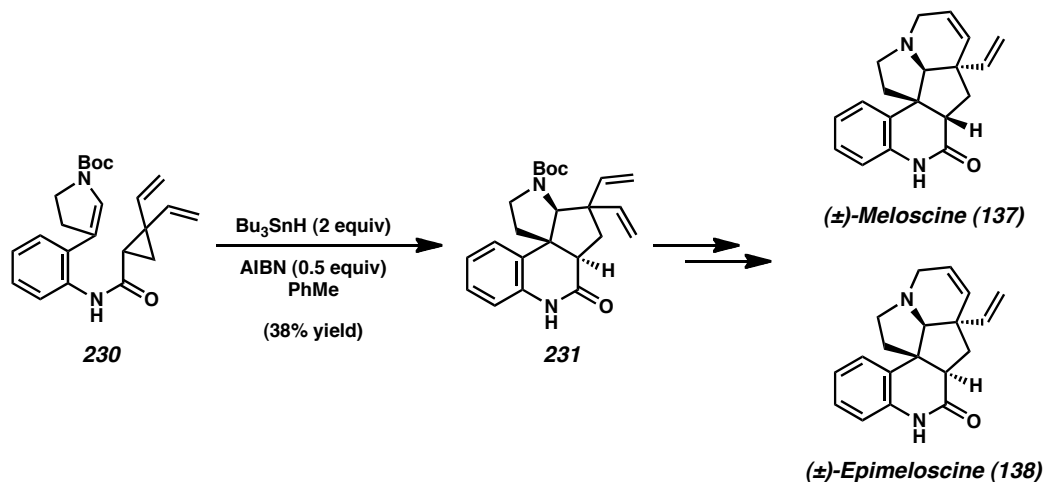
Scheme 2.3.3), conformational effects in the ring-closure presumably override the innate selectivity for terminal vs. branched alkylation; however, in the case of our substituted vinylcyclopropanes (*i.e.* $R \neq H$), the steric demand is likely too high to form the desired cyclopentane ring (**229**).

Scheme 2.3.3. Mechanistic reasoning for cycloaddition failure

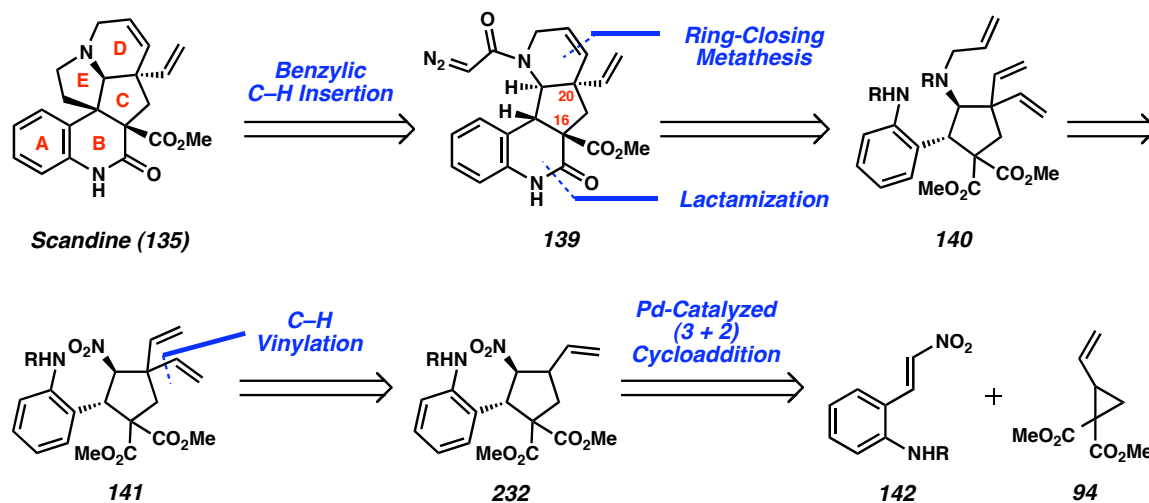


2.4 REVISED RETROSYNTHESIS

In the course of our studies, Curran and Zhang reported the total syntheses of ($\pm$)-meloscine (**137**) and ($\pm$)-epimeloscine (**138**) by a similar route to our own original proposed synthesis (Scheme 2.4.1).^{7d} Their synthesis relied on an intramolecular, radical-mediated cycloaddition of a divinylcyclopropane with a pendent dihydropyrrole to provide tetracycle **231** which was quickly advanced to both natural products, using a diastereoselective ring-closing metathesis to complete the final ring. Scandine (**135**), the parent of the natural product family, was not accessed via this route, and the radical-mediated cycloaddition offered no obvious pathway for an enantioselective total synthesis; nevertheless, the similarity of their route to our own original pathway, as well as the challenges we faced in effecting a transition metal catalyzed intermolecular (3 + 2) cycloaddition encouraged us to modify our synthetic plan.

Scheme 2.4.1. Summary of Curran's synthesis of ($\pm$)-meloscine (**137**) and ($\pm$)-epimeloscine (**138**)

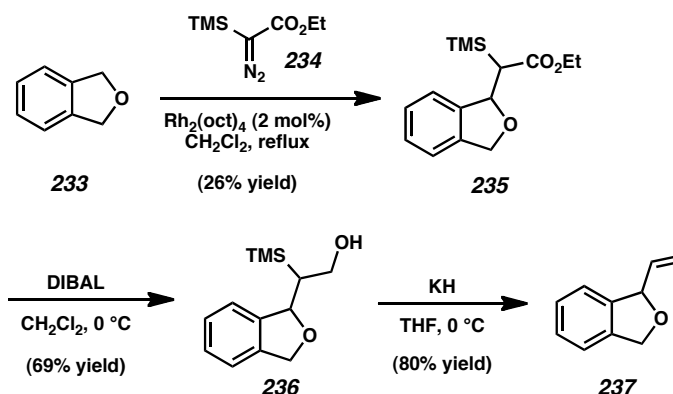
The primary revision to our synthetic plan involves using a monovinylcyclopropane (**94**) in the palladium-catalyzed (3 + 2) cycloaddition, and appending the second vinyl group at a later stage by C–H functionalization. While the (3 + 2) cycloaddition step is better supported by literature precedent, no published approach to direct C–H vinylation exists to date.

Scheme 2.4.2. Revised retrosynthesis for scandine (**135**)

Inspired by our synthetic proposal, Davies and coworkers have set out to develop conditions for C–H vinylation, based on their vast expertise with donor–acceptor

carbenoids.³⁶ In preliminary efforts, Davies found that a trimethylsilyl group on diazo **234** can serve as a moderately effective electron-donating group for C–H insertion with phthalan (**233**).³⁷ After reduction of the ethyl ester (**235**) with DIBAL, Peterson-type elimination of silyl alcohol **236** delivers the vinylated product (**237**) in a moderate overall yield. Efforts are currently ongoing to improve the yield of this process and apply it to more complex and synthetically relevant structures; application of this method to the natural product synthesis will require an orthogonal approach for formation of the β -hydroxysilane in the presence of the ester functionalities on the natural product.³⁸

Scheme 2.4.3. Davies' preliminary C–H vinylation results

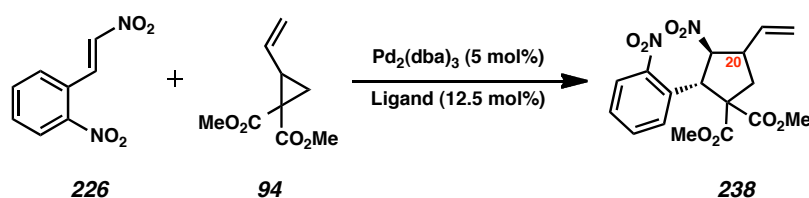


2.5 CONSTRUCTION OF THE ABCD RING SYSTEM

Our initial efforts via this route focused on examining the palladium catalyzed (3 + 2) cycloaddition with commercially available β -2-dinitrostyrene **226** and we examined several ligands, solvents and reaction temperatures (Table 2.5.1). In particular, the conservation of the *trans* relationship between the aryl ring and the styrenyl nitro group was critical, whereas the diastereoselectivity at the allylic position could prove inconsequential, upon installation of the second vinyl group at a later stage. Indeed, in all cases, we observed the formation of only two product diastereomers, and the relative

stereochemistry of each was established after reduction of the nitro groups (*vide infra*); the two products formed were differentiated only by the stereochemistry at C(20). In the course of our optimizations, we found that elevated reaction temperatures improved the reaction yield (entries 1–2). A screen of several solvents (entries 2–5) revealed THF to be optimal. The use of monodentate triphenylphosphine provided poor yields of the cyclopentane product (entry 6) and the use of dppe, a ligand originally used in Tsuji's study, offered comparable yields to GlyPHOX (entry 7). Finally, reducing the temperature from 60 °C to 40 °C proved beneficial (entry 8). Unfortunately, the catalyst loading could not be reduced without lowering the yield (entry 9), potentially due to catalyst oxidation by the nitro functionalities on the starting material and product.

Table 2.5.1. Optimization of (3 + 2) cycloaddition

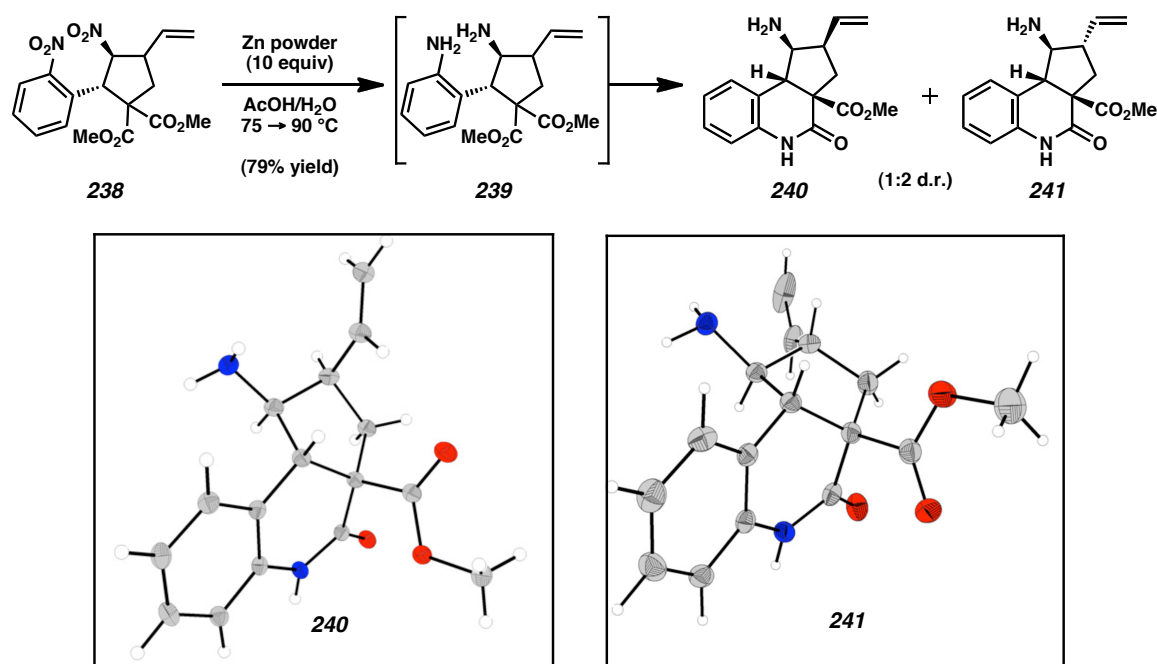


entry ^a	solvent	ligand	temperature	yield (%) ^b
1	PhMe	GlyPHOX	23 °C	21 ^c
2	PhMe	GlyPHOX	60 °C	38
3	dioxane	GlyPHOX	60 °C	58
4	EtOAc	GlyPHOX	60 °C	60
5	THF	GlyPHOX	60 °C	73
6	THF	PPh ₃ ^d	60 °C	26
7	THF	dppe	60 °C	70
8	THF	dppe	40 °C	81 (60°)
9	THF	dppe ^e	40 °C	19 ^c

^a 1 equiv of **226** and **94** used in each reaction. ^b ¹H NMR yield (hexamethylcyclotrisiloxane as internal standard). ^c Isolated yield. ^d 22.5 mol% of ligand used. ^e 2.5 mol% Pd and 6.25 mol% ligand used.

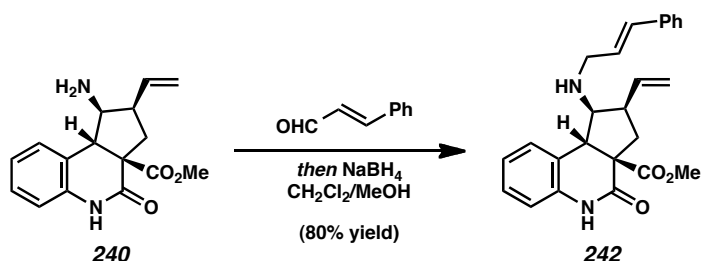
Having developed an effective method to prepare vinylcyclopentane **238**, we next examined the reduction of the nitro functionalities on the molecule. Treatment of the diastereomeric mixture of vinylcyclopentanes (**238**) with zinc in acetic acid performed the desired transformation, and the nascent aniline underwent diastereoselective lactamization to generate tricycles **240** and **241**; their structures were confirmed unambiguously by single crystal X-ray diffraction (Scheme 2.5.1).

Scheme 2.5.1. Reduction of cyclopentane **238** to diastereomeric tricyclic lactams **240** and **241**

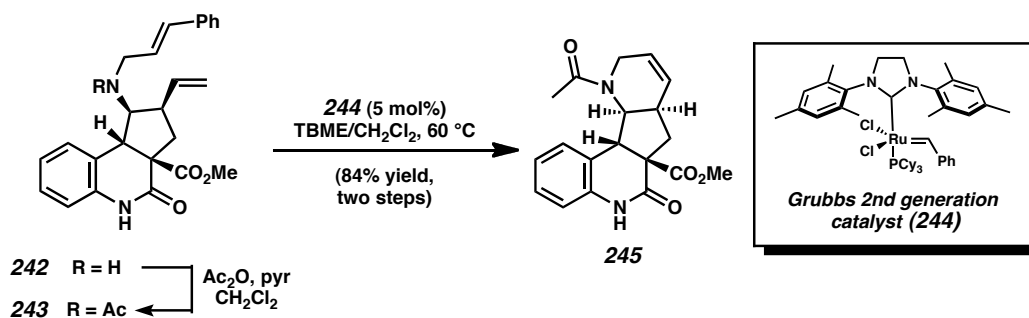


Following construction of the ABC ring system, we turned our attention to the installation of the D ring by ring-closing metathesis, using tricyclic primary amine **240** to this end. Monoalkylation of the primary amine proved non-trivial, yielding mixtures of bisalkylated product when treated with allylic electrophiles or under standard reductive amination conditions. Fortunately, preforming the cinnamaldimine, followed by dilution

and reduction with sodium borohydride yielded secondary cinnamyl amine **242** exclusively (Scheme 2.5.2).

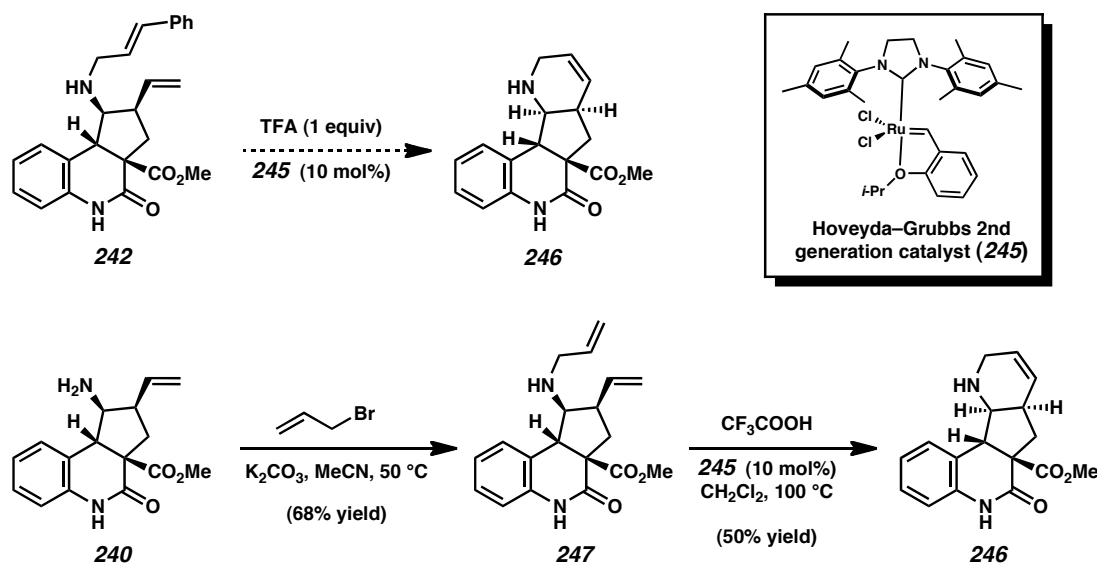
Scheme 2.5.2. Reductive amination of primary amine **240**

Secondary amine **242** was treated with acetic anhydride to generate acetamide **243**, which precipitated cleanly from the reaction mixture and could be advanced to the ring-closing metathesis step without additional purification. We encountered solubility issues in the following stage; acetamide **243** was found to be insoluble in several organic solvents commonly employed in olefin metathesis. Conveniently, we found that at elevated temperatures, acetamide **243** was soluble in a 1:1 mixture of *tert*-butyl methyl ether and dichloromethane. Therefore, a suspension of the metathesis substrate in a solution of Grubbs 2nd generation catalyst (**244**) in this solvent system became homogeneous at the desired reaction temperature; upon cooling, the metathesis product (**245**) precipitated from the reaction mixture with > 95% purity based on NMR analysis.

Scheme 2.5.3. Ring-closing metathesis of cinnamyl amine **242**

Efforts are ongoing to complete the pentacyclic framework of the *Melodinus* alkaloids by benzylic C–H activation. Attempts to directly diazotize acetamide **245** were unsuccessful, as were our efforts to cleave the acetate, so we turned instead to examining the ring-closing metathesis on an unprotected secondary amine, then appending the diazoacetamide fragment separately. It has previously been demonstrated that protonation of secondary amines can serve to prevent their coordination to metathesis catalysts, allowing for an in situ protection of the amine.³⁹ This approach was unsuccessful for conversion of cinnamyl amine **242** to the desired tetracyclic secondary amine (246). Nevertheless, allyl amine **247** was a competent substrate for this transformation albeit in low overall yield (Scheme 2.5.4).⁴⁰

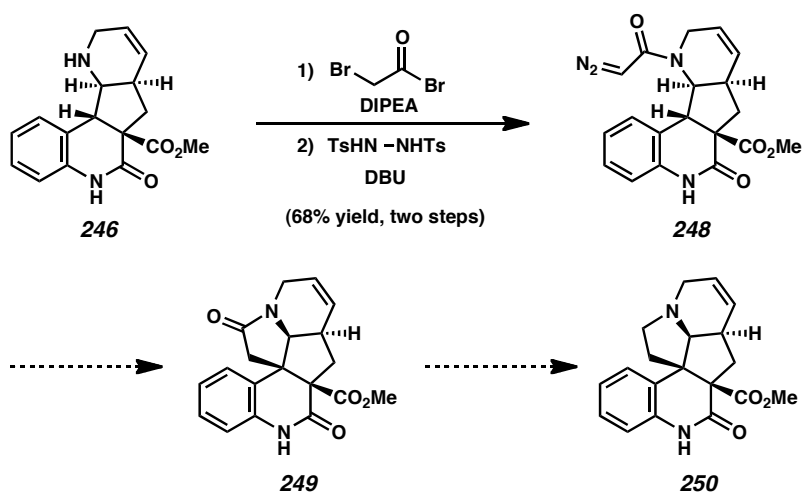
Scheme 2.5.4. Synthesis of tetracyclic secondary amine **246**



The free tetracyclic secondary amine (**246**) could then be converted to the diazoacetamide (**248**) by a two-step procedure reported by Fukuyama.⁴¹ Unfortunately, efforts to date to perform the desired benzylic C–H insertion have produced only complex product mixtures, and we have not isolated the desired pentacyclic core (**249**) of

the natural product family to date. When this transformation is accomplished, reduction of the tertiary lactam in the presence of the methyl ester and quinolinone moieties will afford the pentacyclic skeleton of scandine (**250**), absent the C(20) vinyl group. We predict that the presence of two alkyl substituents on the tertiary lactam will improve its reactivity with Lewis acidic reductants, compared to the secondary, quinolinone lactam, which is also adjacent to a quaternary center.⁴²

Scheme 2.5.5. Synthesis of diazoacetamide (**248**), proposed C–H insertion and lactam reduction



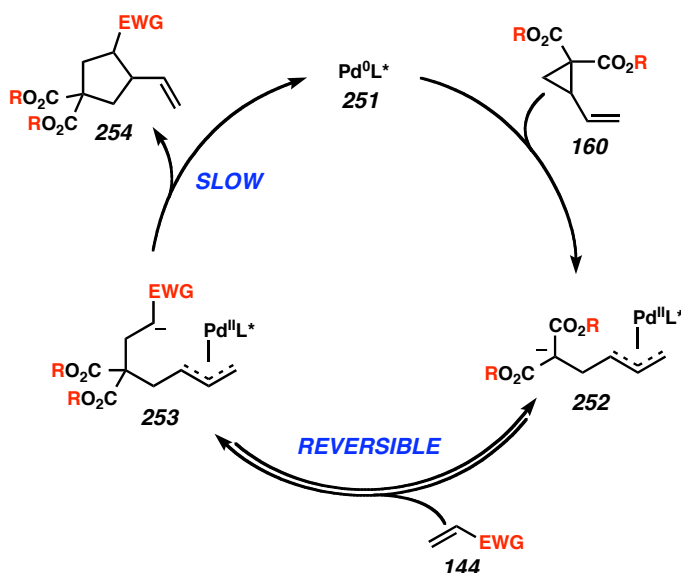
2.6 OUTLOOK

The remaining challenges to overcome in the synthesis of the scandine (**135**) include the benzylic C–H insertion of diazoacetamide **248**, installation of the C(20) vinyl group, and rendering the synthesis enantioselective. Finally, the derivatization of scandine (**135**) to other members of the natural product family will be examined; a strategy to this end will be discussed in this section.

2.6.1 ENANTIOSELECTIVE TOTAL SYNTHESIS

With the goal of rendering the synthesis of the *Melodinus* alkaloids enantioselective, we will draw on the studies by Trost and co-workers on the enantioselective vinylcyclopropane (3 + 2) cycloaddition.¹² The unifying feature of their system is the use of an electron-withdrawing diester component on the cyclopropane (**160**), and an electron-poor conjugate acceptor (**144**, Scheme 2.6.1). These two components, together, contribute to the reversibility of the conjugate addition step of the catalytic cycle; an electron-poor diester makes for a good leaving group in the retro-Michael reaction, and an electron-poor conjugate acceptor likely slows the ring-closing allylation step.

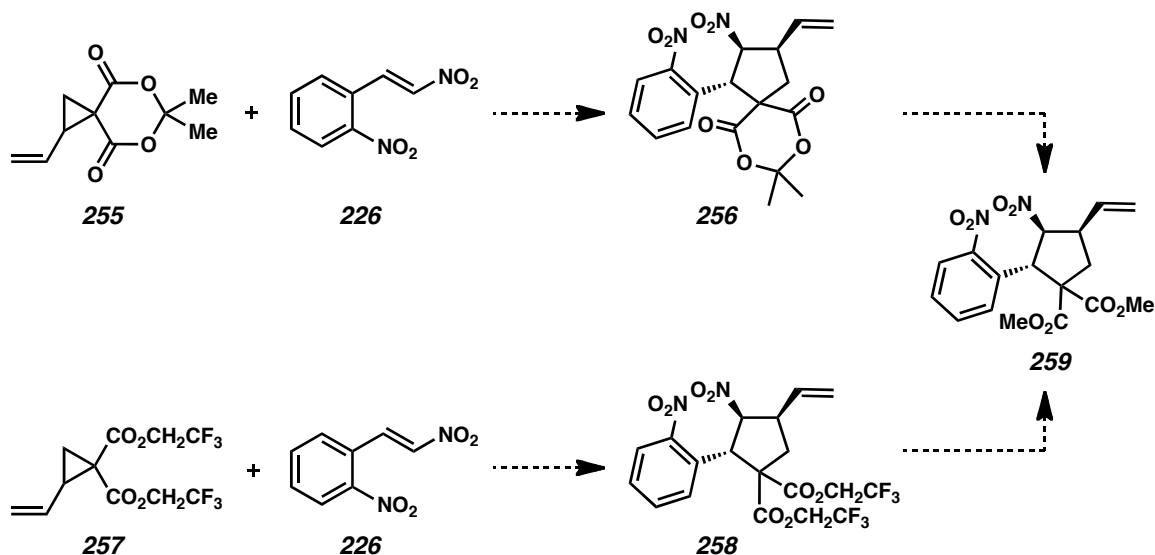
Scheme 2.6.1. Mechanism of Trost's enantioselective (3 + 2) cycloaddition.



We envision that nitrostyrene **226** may be a suitable partner in an enantioselective (3 + 2) cycloaddition with Meldrum's acid derived cyclopropane **255** or bis(trifluoroethyl)malonate derivative **257** (Scheme 2.6.2). Although the pK_a of a nitroalkane (~ 10)⁴³ is higher than that of a Meldrum's acid derivative (~ 5)⁴⁴ or an azlactone (~ 9),⁴⁵ it is conceivable that the reversibility of the conjugate addition will be

aided by the extended conjugation of the dinitrostyrene conjugate acceptor (**226**). The cyclopentane product of either (3 + 2) cycloaddition could be converted to dimethyl ester **259** using procedures reported by Trost in the same account.

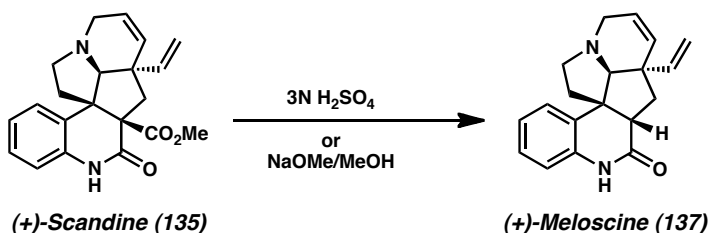
Scheme 2.6.2. Proposed enantioselective (3 + 2) cycloaddition with nitrostyrene (**226**)



2.6.2 DERIVATIZATION OF SCANDINE TO OTHER NATURAL PRODUCTS

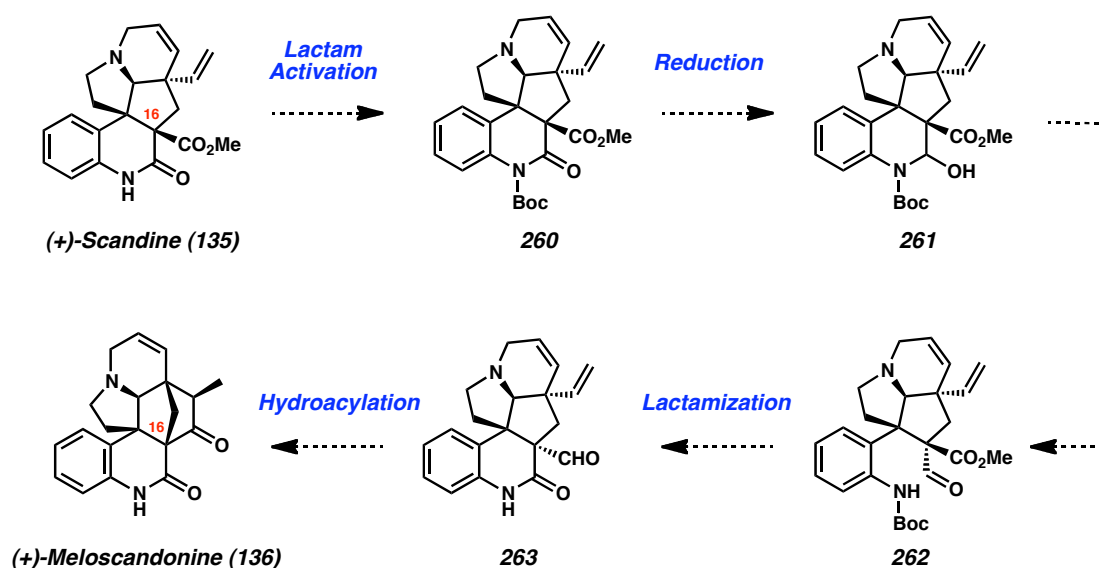
The conversion of scandine (**135**) to meloscine (**137**) was demonstrated by Bernauer and coworkers in 1969 (Scheme 2.6.3).^{1b} However, the synthesis of any other member of the natural product family from scandine has not been accomplished to our knowledge.

Scheme 2.6.3. Conversion of scandine (**135**) to meloscine (**137**)



We propose the synthesis of meloscandonine (**136**) from scandine (**135**) by means of an inversion of the stereochemistry at C(16), followed by C–C bond formation with the C(20) vinyl group (Scheme 2.6.4). Envisioned is an activation of the quinolinone carbonyl by forming Boc imide **260** followed by reduction to hemiaminal **261**. The stereochemistry at C(16) could be inverted by reversible ring-opening of the hemiaminal, followed by irreversible lactamization with the methyl ester, with loss of methanol, to form aldehyde **263**. Finally, intramolecular hydroacylation of the C(20) vinyl group would complete the synthesis of meloscandonine (**136**).⁴⁶

Scheme 2.6.4. Proposed synthesis of meloscandonine (**136**) from scandine (**135**)



2.7 CONCLUSION

In summary, efforts to synthesize and apply a 1,1-divinylcyclopropane toward the total synthesis of scandine are described. Furthermore, we have applied a monovinylcyclopropane toward the preparation of a tetracyclic precursor to scandine

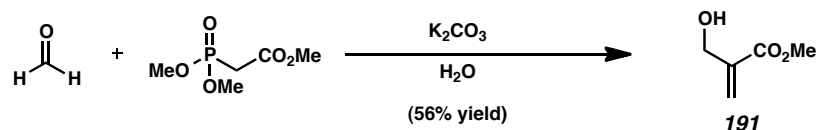
(**135**) via palladium-catalyzed (3 + 2) cycloaddition with a nitrostyrene (**226**) followed by ring-closing metathesis. Efforts are currently underway to complete the total synthesis by sequential C–H activation of the benzylic and allylic positions.

2.8 EXPERIMENTAL SECTION

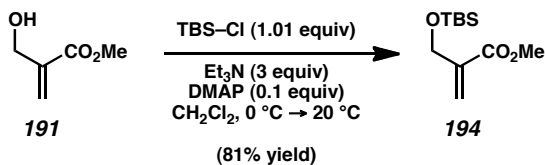
2.8.1 MATERIALS AND METHODS

Unless stated otherwise, reactions were performed under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina).⁴⁷ Commercially obtained reagents were used as received unless otherwise stated. Reaction temperatures were controlled by an IKAmag temperature modulator. Microwave reactions were performed with a Biotage Initiator Eight 400 W apparatus at 2.45 GHz. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, or potassium permanganate, iodine, or anisaldehyde staining. SiliaFlash P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. ¹H and ¹³C NMR spectra were recorded on a Varian Inova 500 (at 500 MHz and 126 MHz respectively), Varian 400 (at 400 MHz and 100 MHz, respectively) or on a Varian Mercury 300 (at 300 MHz) and are reported relative to CHCl₃ (δ 7.26 & 77.16 respectively). Data for ¹H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm⁻¹). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) or mixed (MM) ionization mode.

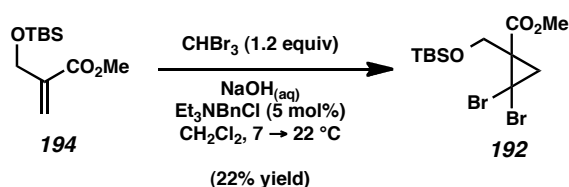
2.8.2 PREPARATIVE PROCEDURES



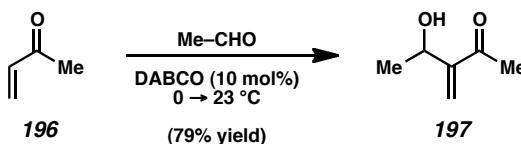
Acrylate 191. Synthesized by a method adapted from Villieras and Rambaud.²¹ To a round-bottom flask were added trimethyl phosphonoacetate (9.1 mL, 63 mmol, 1 equiv) and formaldehyde (20.5 g, 37% in water, 252 mmol, 4 equiv). The flask was lowered into a room-temperature water bath. To the mixture was added a saturated solution of potassium carbonate in water (15.3 g, 110 mmol, 1.75 equiv) dropwise via addition funnel over the course of one hour, and stirring was continued for an additional hour. The reaction mixture was quenched by addition of saturated aqueous ammonium chloride (30 mL), then extracted three times with diethyl ether. The combined organics were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Methyl acrylate, produced as a side-product, was mostly removed by azeotropic distillation with methanol. The residue was purified by vacuum distillation (~0.5 torr, 44 °C) to afford acrylate **191** as a clear oil (4.07 g, 56% yield) with minor impurities which were carried forward to the next reaction. The characterization data matched those reported in the literature.⁴⁸



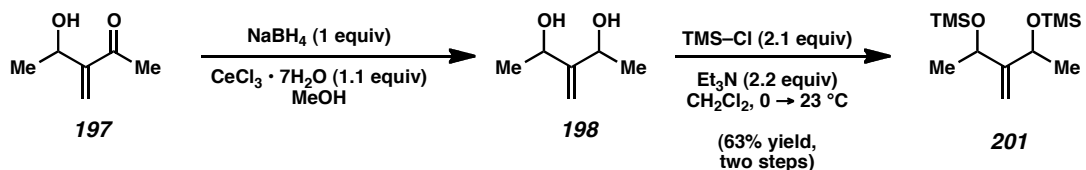
Silyl ether 194. To a flame-dried round-bottom flask equipped with a stir bar were added *tert*-butyl dimethyl silyl chloride (5.34 g, 35.4 mmol, 1.01 equiv), 4-(*N,N*-dimethylamino)pyridine (430 mg, 3.5 mmol, 0.1 equiv), and the flask was sealed with a rubber septum and placed under an inert atmosphere. Dichloromethane (75 mL, 0.48 M) was added and the solution was cooled in an ice-water bath. Acrylate **191** (4.0711 g, 35.0 mmol, 1 equiv) was added to the solution, followed by a dropwise addition of triethylamine (15 mL, 105.2 mmol, 3 equiv) to give a cloudy suspension. The reaction mixture was allowed to warm slowly to ambient temperature (23 °C) and TLC analysis showed complete conversion after 11 hours. The reaction mixture was vacuum filtered through a fritted funnel to remove ammonium salts, and washed with cold, aqueous hydrochloric acid (1N, 75 mL). The aqueous layer was back-extracted with dichloromethane (3 x 10 mL, 1 x 20 mL). The combined organics were washed with saturated aqueous sodium bicarbonate (70 mL) and the aqueous layer was back-extracted with dichloromethane (3 x 10 mL). The combined organics were washed with brine (40 mL) and the aqueous layer was back-extracted with dichloromethane (2 x 10 mL). The combined organics were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on SiO₂ (30:1 hexanes:EtOAc) to afford silyl ether **194** (6.5294 g, 81% yield) as a clear oil. The characterization data matched those reported in the literature.⁴⁹



Cyclopropane 192. To a round-bottom flask were added silyl ether **194** (2.0 g, 8.7 mmol, 1 equiv), bromoform (0.91 mL, 10.4 mmol, 1.2 equiv), and triethylbenzylammonium chloride (100 mg, 0.43 mmol, 0.05 equiv). The reaction mixture was cooled in a 7 °C bath, and sodium hydroxide (1.6 mL, 50% in water) was added dropwise; a brown precipitate was observed upon addition of base. The reaction mixture was slowly warmed to ambient temperature (22 °C) and stirred for 18 hours. The reaction mixture was quenched by addition of sulfuric acid (7 mL, 5% in water), diluted with water (20 mL), and extracted with dichloromethane (3 x 30 mL); on the second wash, an emulsion formed, and was homogenized by addition of brine (15 mL). The combined organics were washed with brine (20 mL). The combined aqueous layers was acidified with sulfuric acid (20 mL, 5% in water) and extracted with ethyl acetate (2 x 50 mL). The combined organics were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on SiO₂ (30:1 → 5:1 hexanes:EtOAc) to afford dibromocyclopropane **192**: ¹H NMR (300 MHz, CDCl₃) δ 4.54 (d, *J* = 10.5 Hz, 1H), 3.79 (s, 3H), 3.56 (d, *J* = 10.4 Hz, 1H), 2.40 (d, *J* = 8.0 Hz, 1H), 1.87 (d, *J* = 8.1 Hz, 1H), 0.86 (s, 9H), 0.05 (s, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 168.5, 66.5, 52.9, 40.7, 30.7, 25.8, 18.3, -5.2, -5.4; IR (NaCl/film) 2953, 2859, 1748, 1434, 1251, 1160, 1100, 836, 777 cm⁻¹; HRMS (MM: ESI-APCI) *m/z* calc'd for C₁₂H₂₃O₃Si⁷⁹Br₂ [M+H]⁺: 400.9778, found 400.9776.



Hydroxyketone 197. Prepared according to the procedure of Koert et al.²² 1,4-Diazabicyclo[2.2.2]octane (5.98 g, 50 mmol, 0.1 equiv) and acetaldehyde (27.40 mL, 465 mmol, 1 equiv) were added to a round-bottom flask, which was cooled in an ice-water bath. Methyl vinyl ketone (40 mL, 480 mmol, 1 equiv) was added dropwise via addition funnel over 8 hours with stirring, and the resulting solution was stirred at this temperature for an additional 2 hours, then warmed to ambient temperature (23 °C), and stirred for an additional 11 hours. The reaction mixture was partitioned between diethyl ether (300 mL) and aqueous hydrochloric acid (50 mL, 1N), and the resulting biphasic mixture was separated. The aqueous layer was extracted with diethyl ether (2 x 100 mL). The combined organics were washed with saturated aqueous sodium bicarbonate, and the aqueous layer was back-extracted with diethyl ether (2 x 100 mL). The combined organics were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by vacuum distillation (5.4 torr, 71 °C; lit: 6 torr, 80 °C) to afford hydroxyketone **197** (42.18 g, 79% yield) as a colorless oil. The spectral data matched those reported by Koert et al.

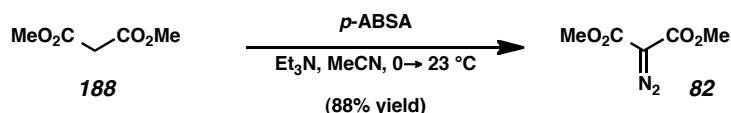


Disilylether 201. To a round-bottom flask, equipped with a magnetic stir bar, were added hydroxyketone **197** (5.00 g, 43.8 mmol, 1 equiv), cerium trichloride heptahydrate (18.0 g, 48.2 mmol, 1.1 equiv) and undistilled methanol (220 mL, 0.2 M). The flask was lowered into an ice-water bath, and sodium borohydride (1.66 g, 43.8 mmol, 1 equiv) was

added in portions. Upon consumption of starting material, as observed by TLC, acetone (10 mL) was added, and the reaction mixture was concentrated in vacuo. The residue was partitioned between ethyl acetate (150 mL) and a saturated solution of sodium potassium tartrate (150 mL), and stirred overnight; the aqueous phase became a creamy yellow suspension. To the biphasic mixture was added saturated aqueous ammonium chloride (50 mL) and deionized water (100 mL), and the phases were separated. The aqueous layer was extracted with dichloromethane (150 mL); a emulsion resulted, which was clarified by addition of brine (50 mL). The combined organics were dried over sodium sulfate, filtered and concentrated in vacuo to afford crude diol **198** (3.7031 g, 73% yield).

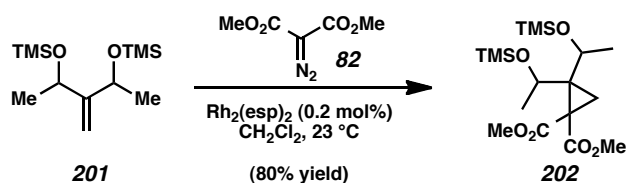
To a flame-dried round-bottom flask was added crude diol **198** (1.000 g, 8.61 mmol, 1 equiv). The flask was sealed with a rubber septum and placed under an inert atmosphere. Dichloromethane (86 mL, 0.1 M) and freshly distilled triethylamine (2.7 mL, 18.9 mmol, 2.2 equiv) were added, and the flask was cooled in an ice-water bath with stirring. To the stirring solution was added freshly distilled trimethylsilyl chloride (2.3 mL, 18.1 mmol, 2.1 equiv) dropwise over 15 minutes, and the reaction mixture was warmed to ambient temperature. Upon consumption of starting material, as observed by TLC, the reaction mixture was poured into an aqueous solution of sodium bicarbonate (100 mL, 10%), and the phases were separated. The aqueous layer was extracted with dichloromethane (50 mL). The combined organics were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on SiO₂ (2:1 hexanes:diethyl ether) to afford a mixture of diastereomeric silyl ethers **201** (1.9228 g, 86%, 63% over two steps) as a

clear oil: R_f = 0.56 (9:1 hexanes:EtOAc); ^1H NMR (400 MHz, CDCl_3 , major diastereomer) δ 5.11 (t, J = 1.1 Hz, 2H), 4.28 (qt, J = 6.4, 1.1 Hz, 2H), 1.27 (d, J = 6.4 Hz, 6H), 0.11 (s, 18H); ^1H NMR (400 MHz, CDCl_3 , minor diastereomer) δ 5.07 (t, J = 0.8 Hz, 2H), 4.37 (q, J = 6.3 Hz, 2H), 1.28 (d, J = 6.6 Hz, 6H), 0.11 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3 , major diastereomer) δ 157.0, 107.7, 68.5, 25.0, 0.2; ^{13}C NMR (101 MHz, CDCl_3 , minor diastereomer) δ 156.5, 108.5, 68.4, 24.4, 0.3; IR (NaCl/film) 2963, 1652, 1449, 1370, 1249, 1100, 972, 838 cm^{-1} ; HRMS (MM: ESI-APCI) m/z calc'd for $\text{C}_{12}\text{H}_{29}\text{O}_2\text{Si}_2$ $[\text{M}+\text{H}]^+$: 261.1701, found 261.1703.



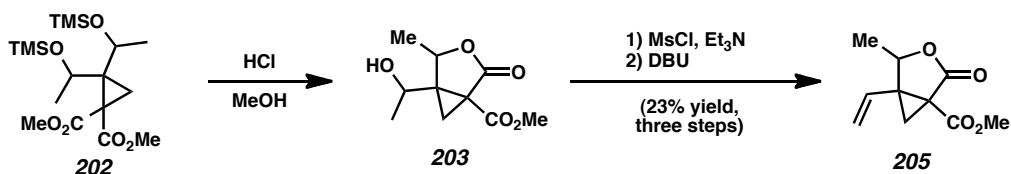
Diazodimethylmalonate 82. According to the method of Tullis and Helquist, with minor modifications.⁵⁰ To a flame-dried round-bottom flask were sequentially added *p*-acetamidobenzenesulfonyl azide⁵¹ (34.72 g, 144.6 mmol, 1.01 equiv), acetonitrile (500 mL), and freshly distilled triethylamine (21.4 mL, 153.6 mmol, 1.07 equiv), and the resulting homogeneous mixture was cooled in an ice-water bath. To the stirring solution was added dimethylmalonate (16.4 mL, 143.4 mmol, 1 equiv) dropwise over approximately 5 minutes; over the course of the addition, the solution became yellow. The ice-water bath was removed and the reaction mixture was stirred for 17 hours. After this time, a thick slurry was observed, which was vacuum-filtered through a fritted funnel, washing the filter cake with 1:1 hexanes:diethyl ether (400 mL). The solution was concentrated in vacuo, and a thick slurry resulted. The slurry was passed through the same filter cake, washing with 1:1 hexanes:diethyl ether (> 500 mL, the yellow color was

mostly removed from the filter cake). The solution was concentrated in vacuo and the residue was purified by vacuum distillation (62 °C, 1.84 torr, *CAUTION*)⁵² to afford diazodimethylmalonate **82** (19.9 g, 88% yield) as a yellow oil.



Cyclopropane 202. To a flame-dried round-bottom flask, equipped with a magnetic stir bar, were added olefin **201** (689.0 mg, 2.6 mmol, 1 equiv), bis[rhodium($\alpha,\alpha,\alpha',\alpha'$ -tetramethyl-1,3-benzenedipropionic acid)] (2.0 mg, 2.5 μmol , 0.001 equiv), and dichloromethane (2.5 mL). The flask was sealed and placed under an inert atmosphere. To a separate, flame-dried flask was added diazodimethylmalonate (0.33 mL, 2.6 mmol, 1 equiv) and dichloromethane (2.5 mL) under an inert atmosphere. This mixture was taken up in a syringe and transferred by syringe pump to the first flask, over 3 hours. The reaction mixture was concentrated in vacuo, and filtered through a short plug of SiO_2 (3:1 hexanes:EtOAc). The crude product was then purified by column chromatography on SiO_2 (25:1 hexanes:EtOAc) to afford cyclopropane **202** (458.8 mg, 80% yield) as a 20:12:3 mixture of diastereomers: $R_f = 0.41$ (9:1 hexanes:EtOAc); ^1H NMR (400 MHz, CDCl_3 , integration referenced to major diastereomer) δ 4.24 (q, $J = 6.5$ Hz, 1H) 4.20 (q, $J = 6.4$ Hz, 1.2H), 4.04 (q, $J = 6.4$ Hz, 0.37H), 3.92 (q, $J = 6.5$ Hz, 1H), 3.73 – 3.64 (m, 10.7H), 1.67 – 1.59 (m, 1.5H), 1.45 – 1.33 (m, 8.3H), 1.29 – 1.20 (m, 3.5H); ^{13}C NMR (101 MHz, CDCl_3) δ 169.9, 169.3, 168.9, 168.5, 70.3, 68.2, 66.9, 66.9, 52.8, 52.5, 52.4, 52.3, 46.1, 45.2, 38.2, 37.3, 23.1, 23.0, 22.3, 22.2, 21.5, 21.4, 20.6, 0.7, 0.4, 0.3, 0.2; IR

(NaCl/film) 2958, 2903, 1733, 1434, 1251, 1100, 982, 841 cm^{-1} ; HRMS (MM: ESI-APCI) m/z calc'd for $\text{C}_{17}\text{H}_{34}\text{O}_6\text{Si}_2$ $[\text{M}+\text{H}]^+$: 391.1967, found 391.1981.

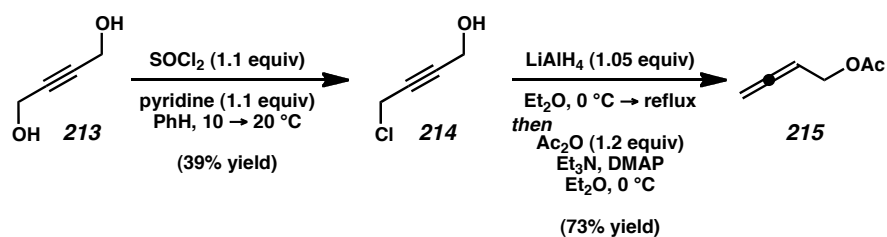


Vinylcyclopropane 205. To a solution of silyl ether **202** (249.3 mg, 0.64 mmol, 1 equiv) in methanol (6.4 mL) was added a drop of aqueous hydrochloric acid (1 N). After 15 minutes, the reaction mixture was diluted with deionized water (30 mL) and dichloromethane (10 mL). The phases were separated and the aqueous phase was washed with dichloromethane (4 x 20 mL). The combined organics were washed with brine (20 mL) and the aqueous phase was back-extracted with dichloromethane (20 mL). The combined organics were dried over magnesium sulfate, filtered and concentrated to afford crude alcohol **203** (157.5 mg, 99% yield) as a complex mixture of diastereomers which was carried forward without further purification.

A flame-dried round-bottom flask was charged with alcohol **203** (385.4 mg, 1.8 mmol, 1 equiv), sealed with a rubber septum, and placed under an inert atmosphere. To the flask were added dichloromethane (10 mL, 0.2 M) and mesyl chloride (155 μL , 1.98 mmol, 1.1 equiv), then the flask was cooled in an ice bath and stirred. Triethylamine (0.38 mL, 2.16 mmol, 1.2 equiv) was added dropwise to the stirring solution and warmed to room temperature. The reaction was quenched after 10 minutes with water (3 mL) and saturated aqueous ammonium chloride (3 mL), the phases were separated, and the aqueous layer was extracted with additional dichloromethane (10 mL). The combined

organics were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO₂ (1:1 hexanes:EtOAc) to afford mesylate **204** as a complex mixture of diastereomers.

A round-bottom flask was charged with mesylate **204**, THF (6 mL, 0.25 M) and DBU (0.67 mL, 4.5 mmol, 3 equiv), and fitted with a reflux condenser. The solution was heated in an oil bath to reflux, and stirred for 15 hours. Upon completion, the solvent was evaporated and the residue was purified by column chromatography (5:1 hexanes:EtOAc) to afford vinylcyclopropane **205** (82.9 mg, 23% yield over two steps): ¹H NMR (300 MHz, CDCl₃, major diastereomer) δ 5.78 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.42 – 5.26 (m, 2H), 4.83 (q, *J* = 6.3 Hz, 1H), 3.79 (s, 3H), 2.19 (d, *J* = 5.3 Hz, 1H), 1.59 (d, *J* = 5.4 Hz, 1H), 1.36 (d, *J* = 6.3 Hz, 3H); ¹H NMR (300 MHz, CDCl₃, minor diastereomer) δ 5.96 (dd, *J* = 17.1, 10.1 Hz, 1H), 5.45 – 5.37 (m, 2H), 4.52 (q, *J* = 6.5 Hz, 1H), 3.78 (s, 3H), 2.32 (d, *J* = 5.0 Hz, 1H), 1.51 (d, *J* = 4.8 Hz, 1H), 1.47 (d, *J* = 6.5 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃, major diastereomer) δ 170.3, 165.5, 130.2, 119.7, 76.1, 53.1, 45.0, 38.1, 21.1, 16.3; IR (NaCl/film) 3087, 2993, 2948, 1780, 1731, 1441, 1365, 1221, 1098, 1041, 940 cm⁻¹; HRMS (MM: ESI-APCI) *m/z* calc'd for C₁₀H₁₂O₄Na [M+Na]⁺: 219.0628, found 219.0631.

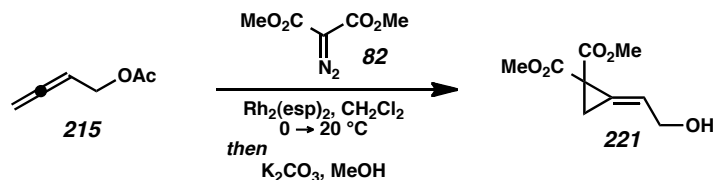


Allene 215. Synthesized by a procedure adapted from the literature.²⁷ A round-bottom flask containing 2-butyne-1,4-diol (86.0 g, 1.00 mol, 1 equiv), pyridine (89.0 mL, 1.1 mol, 1.1 equiv) and benzene (100 mL) was cooled in a 10 °C bath and stirred. Thionyl chloride (80.2 g, 1.1 mol, 1.1 equiv) was added dropwise by addition funnel over 4.5 hours, and the reaction mixture was allowed to warm slowly to ambient temperature (20 °C), and stirred overnight. Throughout the addition, a biphasic mixture was observed as well as a precipitate. The reaction mixture was poured into ice-cold water (250 mL) and the phases were separated. The aqueous layer was extracted with diethyl ether (4 x 100 mL). The combined organics were washed with water (100 mL), saturated aqueous sodium bicarbonate (100 mL), and brine (100 mL), then dried over magnesium sulfate, filtered, and concentrated in vacuo to afford a brown oil. The residue was purified by fractional distillation (1.30–1.05 torr, 47–57 °C), and redistilled (1.3 torr, 56–60 °C) to afford alkyne **214** as a clear oil (41.0 g, 39% yield). Spectral data matched those reported in the literature.^{27a}

To a 1 L, 3-neck flask, equipped with a reflux condenser, addition funnel, and a magnetic stirrer was added lithium aluminum hydride (8.39 g, 210 mmol, 1.05 equiv). The system was then sealed with rubber septa, purged with inert gas, freshly distilled diethyl ether (250 mL) was added, and the flask was cooled in an ice-water bath. Alkyne **214** (20.89 g, 200 mmol, 1 equiv) and diethyl ether (150 mL) were added to the addition funnel, and the resulting solution was added at such a rate to allow the receiving solution to reflux and evolve hydrogen gas gently; the alkyne addition proceeded over 1.25 hours. Complete consumption of starting material was observed after an additional 1 hour of stirring. The reaction was quenched by careful, dropwise addition of water (8.4 mL) via

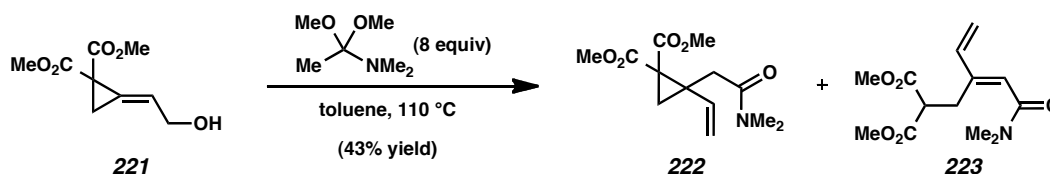
the addition funnel, followed by aqueous sodium hydroxide (8.4 mL, 15%), then additional water (25.2 mL). Finally, anhydrous magnesium sulfate was added to the stirring mixture, and the entire suspension was vacuum filtered through a plug of celite on a fritted filter, directly into a second 1 L flask, washing with diethyl ether.

To the resulting solution were added 4-(*N,N*-dimethylamino)pyridine (2.45 g, 20 mmol, 0.1 equiv) and freshly distilled triethylamine (36 mL, 260 mmol, 1.3 equiv), and the flask was sealed with a rubber septum, placed under an inert atmosphere and cooled in an ice-water bath. Acetic anhydride (22.6 mL, 240 mmol, 1.2 equiv) was added dropwise to the solution, and TLC analysis following the addition revealed complete conversion to the desired acetate. The reaction mixture was diluted to a volume of approximately 500 mL with diethyl ether, and was washed with 10% aqueous hydrochloric acid (4 x 75 mL). The combined aqueous layers were washed once with diethyl ether (75 mL). The combined organics were washed with brine and dried over magnesium sulfate, filtered, and concentrated carefully in vacuo (*volatile product!*). The residue was purified by vacuum distillation (110–85 torr, 90 °C) to afford allene **215** as a colorless oil (22.4 g, 73% yield), which should be kept in a –20 °C freezer for prolonged storage—becomes discolored over time at room temperature: ¹H NMR (300 MHz, CDCl₃) δ 5.29 (app p, *J* = 6.8 Hz, 1H), 4.85 (d, *J* = 6.6 Hz, 2H), 4.57 (d, *J* = 7.0 Hz, 2H); 2.07 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 209.8, 170.8, 86.4, 76.6, 62.2, 20.9; IR (NaCl/film) 2948, 1956, 1736, 1436, 1377, 1362, 1229, 1029, 853 cm^{–1}; HRMS (EI+) *m/z* calc'd for C₆H₈O₂ [M+H]⁺: 112.0524, found 112.0517.



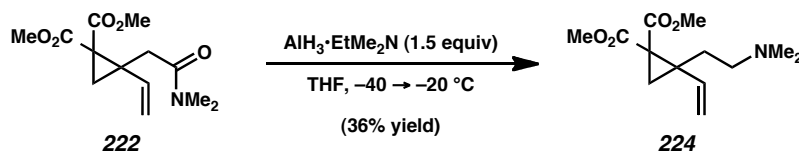
Alkylidenecyclopropane 221. A flame-dried 250 mL round-bottom flask, equipped with a magnetic stir bar, was charged with bis[rhodium($\alpha,\alpha,\alpha',\alpha'$ -tetramethyl-1,3-benzenedipropionic acid)] (6.4 mg, 8.4 μmol , 0.0002 equiv) and sealed with a rubber septum. The flask was evacuated and backfilled with argon three times, then charged with dichloromethane (30 mL) and allene **215** (4.00 mL, 34.8 mmol, 1 equiv), and cooled in an ice-water bath. To a separate, flame-dried flask was added diazodimethylmalonate **82** (5.66 mL, 45.2 mmol, 1.3 equiv) and dichloromethane (30 mL). The diazo solution was transferred to the first flask by syringe over 10 minutes. The resulting mixture was stirred for ten minutes, then warmed to ambient temperature with continued stirring. After 4.5 hours, the solvent was evaporated *in vacuo*, and redissolved in methanol (150 mL). To the resulting solution was added potassium carbonate (500 mg, 3.6 mmol, 0.1 equiv), and this mixture was stirred for 1 hour. At this time, additional potassium carbonate (400 mg, 2.9 mmol) was added, and the mixture was stirred for an additional hour. The mixture was then poured into a 1 L round-bottom flask containing water (75 mL) and saturated aqueous ammonium chloride (75 mL). Methanol was evaporated *in vacuo*, then the remaining aqueous solution was extracted with ethyl acetate (3 x 50 mL). The combined organics were washed with brine (75 mL) and dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (6:5 hexanes/EtOAc) to provide alkylidenecyclopropane **221** (5.97 g, 94% yield). $R_f = 0.28$ (1:1 hexanes/Et₂O); ^1H NMR (300 MHz, CDCl_3 , major

diastereomer) δ 6.21 (tt, J = 5.6, 2.7 Hz, 1H), 4.36 (d, J = 5.6 Hz, 2H), 3.74 (s, 6H), 2.29 – 2.21 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.3, 123.1, 120.3, 61.9, 52.9, 30.7, 18.0; IR (Neat Film/NaCl) 3469, 2953, 1731, 1439, 1315, 1266, 1105 cm^{-1} ; HRMS (MM: ESI-APCI) m/z calc'd for $\text{C}_9\text{H}_{12}\text{O}_5\text{Na}$ $[\text{M}]^+$: 223.0577; found 223.0586.



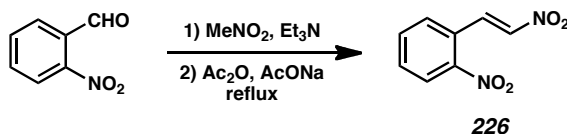
Vinylcyclopropane 222. A flame-dried 250 mL round-bottom flask, equipped with a magnetic stir bar, was charged with alcohol **221** (801.8 mg, 4 mmol, 1 equiv), toluene (50 mL), and dimethylacetamide dimethyl acetal (5 mL, 34 mmol, 8.5 equiv). The flask was then fitted with a reflux condenser and a rubber septum, placed under a positive pressure of nitrogen gas, and heated to reflux in a preheated oil bath. The reaction was stirred for two hours, then cooled to room temperature. The solvent was removed *in vacuo*, and the residue was purified by column chromatography (3:2 $\rightarrow$ 1:1 $\rightarrow$ 2:3 hexanes:EtOAc) to afford vinylcyclopropane **222** (460.0 mg, 43% yield) and conjugated amide **223** (as a mixture of olefin isomers). **222**: ^1H NMR (400 MHz, CDCl_3) δ 5.88 (dd, J = 17.2, 10.5 Hz, 1H), 5.10 (d, J = 10.5 Hz, 1H), 5.06 (d, J = 17.2 Hz, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 3.01 (d, J = 16.7 Hz, 1H), 2.98 (s, 3H), 2.93 (s, 3H), 2.83 (d, J = 16.5 Hz, 1H), 1.99 (d, J = 5.6 Hz, 1H), 1.64 (d, J = 5.6 Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 170.0, 169.7, 168.1, 137.1, 116.3, 52.9, 52.8, 39.7, 37.2, 35.5, 35.5, 35.2, 24.4; IR (NaCl/film) 3474, 2948, 1728, 1652, 1434, 1301, 1263, 1224, 1110 cm^{-1} ; HRMS (MM: ESI-APCI) m/z calc'd for $\text{C}_{13}\text{H}_{20}\text{NO}_5$ $[\text{M}+\text{H}]^+$: 270.1336, found 270.1363. **223**: ^1H NMR (400 MHz,

CDCl₃, olefin isomer 1) δ 6.30 (dd, $J = 17.5, 10.9$ Hz, 1H), 6.10 (s, 1H), 5.47 (d, $J = 17.5$ Hz, 1H), 5.27 (d, $J = 10.9$, 1H), 3.81 (t, $J = 7.6$ Hz, 1H), 3.68 (s, 6H), 3.17 (d, $J = 7.7$ Hz, 2H), 3.01 (s, 3H), 2.98 (s, 3H); ¹H NMR (400 MHz, CDCl₃, olefin isomer 2) δ 6.83 (dd, $J = 17.8, 11.1$ Hz, 1H), 5.97 (s, 1H), 5.45 (d, $J = 18.1$ Hz, 1H), 5.31 (d, $J = 11.1$ Hz, 1H), 3.73 (s, 6H), 3.67 (t, $J = 7.5$ Hz, 1H), 2.98 – 2.90 (app m, 8H).

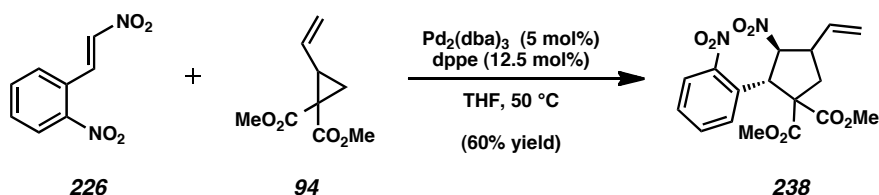


Amine 224. A flame-dried round-bottom flask, equipped with a magnetic stir bar, was charged with amide **222** (53.3 mg, 0.2 mmol, 1 equiv), sealed with a rubber septum, and placed under an inert atmosphere. THF (3 mL, 0.2 M) was added, and the reaction mixture was cooled to $-40\text{ }^\circ\text{C}$. Alane was added dropwise as a 0.5 M solution in toluene (0.4 mL, 0.2 mmol, 1 equiv), and the solution was stirred for one hour, slowly allowing the cooling bath to warm to $-20\text{ }^\circ\text{C}$. Upon completion, methanol (100 μL) was added to quench unreacted alane, and the reaction mixture was partitioned between ethyl acetate and water. The phases were separated and the aqueous phase was extracted with ethyl acetate (3x). The combined organics were washed with brine, dried over anhydrous sodium sulfate, decanted, and concentrated in vacuo. The residue was purified by column chromatography (20:1 CHCl₃:MeOH with 0.1% Et₃N) to afford dimethyl amine **224** (18.3 mg, 36% yield): ¹H NMR (500 MHz, CDCl₃) δ 5.73 (dd, $J = 17.2, 10.5$ Hz, 1H), 5.18 (dd, $J = 10.5, 0.9$ Hz, 1H), 5.14 (d, $J = 17.2$ Hz, 1H), 3.75 (s, 3H), 3.67 (s, 3H), 2.43 (ddd, $J = 9.9, 5.7, 3.8$ Hz, 2H), 2.28 (s, 6H), 2.04 (ddd, $J = 13.9, 10.5, 6.0$ Hz, 1H),

1.85 (d, $J = 5.5$ Hz, 1H), 1.80 (ddd, $J = 13.5, 10.0, 6.4$ Hz, 1H), 1.58 (d, $J = 5.6$ Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.8, 167.8, 135.9, 117.6, 57.0, 52.9, 52.7, 45.2, 40.7, 37.2, 29.2, 23.7; IR (NaCl/film) 2953, 2764, 1731, 1437, 1298, 1224, 1108 cm^{-1} ; HRMS (MM: ESI-APCI) m/z calc'd for $\text{C}_{13}\text{H}_{22}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 256.1543, found 256.1548.

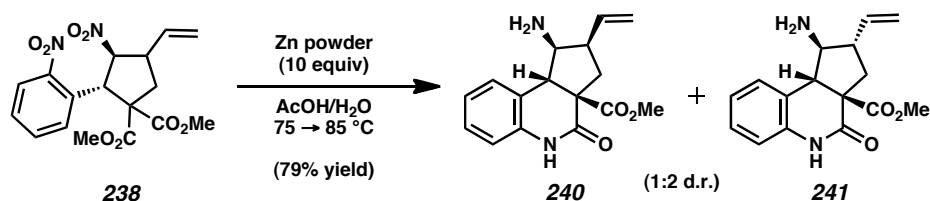


β -2-dinitrostyrene 226. Prepared by a modified procedure from Solomonovici et al.⁵³ To a round-bottom flask equipped with a magnetic stir bar were added 2-nitrobenzaldehyde (40.00 g, 265 mmol, 1 equiv), nitromethane (22 mL, 406.0 mmol, 1.6 equiv) and triethylamine (0.24 mL, 1.7 mmol, 0.006 equiv), and the resulting homogeneous mixture was stirred for 24 hours. At this point, acetic anhydride (240 mL) and sodium acetate (12.8 g, 156 mmol, 0.6 equiv) were added, and the mixture was heated to reflux and stirred for an hour. The reaction mixture was then poured into deionized water (2.4 L) and stirred until the red oil became a crystalline orange solid. The orange solid was filtered through a Büchner funnel, washed with additional deionized water, and air-dried on the funnel. The crude solid was purified by recrystallization from toluene to afford β -2-dinitrostyrene **226** (37.46 g, 73% yield) as gold-colored crystals.



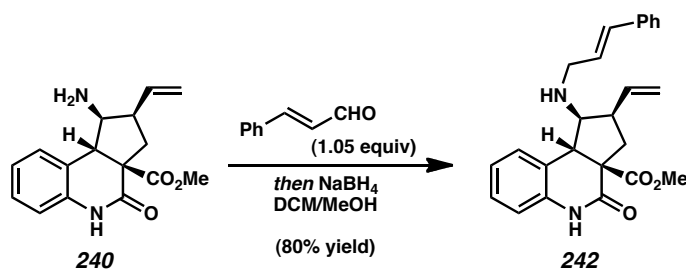
Cyclopentane 238. To a flame-dried schlenk-tube was added $\text{Pd}_2(\text{dba})_3$ (147 mg, 0.160 mmol) and dppe (147 mg, 0.369 mmol). The Schlenk tube was evacuated and backfilled twice with argon. In a separate, flame-dried, conical flask, THF was sparged with argon for 20 minutes. After this period, THF (25 mL) was added to the Schlenk tube, and the resulting purple solution was heated at 40 °C until the solution became bright orange, at which point, it was allowed to cool to ambient temperature. To a separate, flame-dried conical flask was added β -2-dinitrostyrene (**226**) (575 mg, 2.96 mmol, 1 equiv), THF (5 mL) and vinylcyclopropane **94** (500 μL , 2.96 mmol, 1 equiv). The latter solution was transferred via cannula to the Schlenk tube, and the reaction mixture became red. The solution was heated to 40 °C and stirred for 14 hours. Upon completion, the reaction mixture was concentrated in vacuo and purified by flash chromatography (100 mL SiO_2 , 10:1 $\rightarrow$ 5:1 hexanes:ethyl acetate), yielding a yellow solid which was further purified by trituration with diethyl ether to afford **238** (670.9 mg, 60% yield), a white solid, as a mixture of diastereomers: R_f = 0.17 (3:1 hexanes:ethyl acetate); ^1H NMR (400 MHz, CDCl_3 , major diastereomer) δ 7.89–7.84 (m, 1H), 7.60–7.52 (m, 1H), 7.49–7.41 (m, 1H), 7.40–7.35 (m, 1H), 5.90 (dtd, J = 18.2, 8.8, 8.0 Hz, 1.4 Hz, 1H), 5.53 (d, J = 10.7 Hz, 1H), 5.33–5.19 (m, 2H), 5.10 (td, J = 10.5, 1.4 Hz, 1H), 3.85–3.76 (m, 1H) 3.75 (app d, J = 1.4 Hz, 3H), 3.27 (app d, J = 1.5 Hz, 3H), 2.76–2.67 (m, 1H), 2.65–2.56 (m, 1H); ^1H NMR (400 MHz, CDCl_3 , minor diastereomer) δ 7.89–7.84 (m, 1H), 7.60–7.52 (m, 1H), 7.49–7.41 (m, 1H), 7.40–7.35 (m, 1H), 5.76–5.61 (m, 2H), 5.43 (ddd, J = 8.7, 7.1, 1.3 Hz, 1H), 5.33–5.19 (m, 2H), 3.71 (app d, J = 1.6 Hz, 3H), 3.42–3.30 (m, 1H), 3.34 (app d, J = 1.4 Hz, 3H), 2.79 (ddd, J = 13.7, 6.9, 1.3 Hz, 1H), 2.39 (ddd, J = 13.8, 10.6, 1.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.5, 170.4, 170.0,

169.9, 134.7, 132.9, 132.5, 132.4, 130.6, 129.5, 129.4, 129.2, 125.4, 125.4, 120.3, 119.4, 94.9, 93.4, 64.7, 62.9, 53.7, 53.5, 52.9, 52.8, 48.2, 46.6, 46.3, 38.6, 37.4; IR (NaCl/film) 3002, 2955, 1733, 1557, 1532, 1436, 1358, 1282, 1263, 1219, 1173, 932 cm^{-1} ; HRMS (MM: ESI-APCI) m/z calc'd for $\text{C}_{17}\text{H}_{19}\text{N}_2\text{O}_8$ $[\text{M}+\text{H}]^+$: 379.1136, found 379.1144.



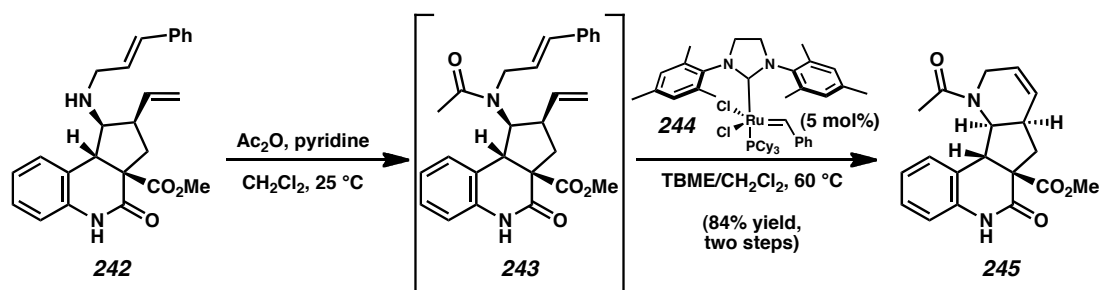
Lactams 240 and 241. A suspension of cyclopentane **238** (5.2206 g, 13.8 mmol, 1 equiv) in acetic acid (85% in H_2O , 70 mL, 0.2 M) was stirred in an open flask, heated in a 75 $^\circ\text{C}$ oil bath until completely homogeneous. Zinc powder (9.0130 g, 138 mmol, 10 equiv) was added to the heated solution in portions, maintaining an internal temperature lower than 90 $^\circ\text{C}$. Vigorous bubbling was observed over the course of the zinc addition. Upon completion of the addition, the temperature was allowed to stabilize at 75 $^\circ\text{C}$ and the reaction progress was monitored by TLC. Upon consumption of starting material, the flask was removed from the oil bath and allowed to cool to room temperature, during which time, white solids precipitated from solution. The heterogeneous mixture was filtered through celite, and washed with 100 mL of ethyl acetate. The solution was basified with saturated $\text{NaHCO}_3(\text{aq})$ and solid Na_2CO_3 . The phases were separated and the aqueous phase was extracted exhaustively with ethyl acetate. The combined organics were washed with saturated $\text{NaHCO}_3(\text{aq})$ and brine, dried over sodium sulfate, filtered and evaporated in vacuo. The crude product was purified by flash chromatography (800 mL SiO_2 , 150:1:0.25 CHCl_3 : MeOH : Et_3N) to afford **240** (1.7434 g, 44% yield) as a white

solid and a 3.5:1 mixture of **241**:**240** (1.3768g, 35% yield) which could be repurified under the same conditions to yield **241** as a single diastereomer. **240**: R_f = 0.30 (10:1 chloroform:methanol); ^1H NMR (500 MHz, CDCl_3) δ 9.12 (s, 1H), 7.22–7.11 (m, 2H), 7.01–6.95 (m, 1H), 6.81 (d, J = 8.3 Hz, 1H), 5.59 (ddd, J = 16.8, 10.0, 8.4 Hz, 1H), 5.15–4.98 (m, 2H), 3.54 (s, 3H), 3.05 (d, J = 10.8 Hz, 1H), 2.77 (dd, J = 14.3, 9.8, 1H), 2.67 (t, J = 10.4 Hz, 1H), 2.50 (dd, J = 14.3, 9.2 Hz), 2.44–2.31 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.4, 169.2, 138.2, 134.4, 121.7, 127.4, 122.5, 120.6, 116.0, 114.8, 61.2, 54.6, 54.6, 52.2, 50.0, 36.33; IR (NaCl/film) 3233, 1734, 1675, 1595, 1496, 1383, 1248, 919, 758 cm^{-1} ; HRMS (MM: ESI-APCI) m/z calc'd for $\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 287.1390, found 287.1392. **241**: R_f = 0.26 (10:1 chloroform:methanol); ^1H NMR (500 MHz, CDCl_3) δ 8.89 (s, 1H), 7.23–7.04 (m, 2H), 6.97 (t, J = 7.5 Hz, 1H), 6.80 (d, J = 7.9 Hz, 1H), 5.86 (dt, J = 18.1, 9.5 Hz, 1H), 5.21–5.08 (m, 2H), 3.55 (s, 3H), 3.03 (m, 3H), 2.76 (dt, J = 14.3, 7.6 Hz, 1H), 2.37 (dd, J = 13.9, 4.8 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.2, 169.5, 137.5, 135.6, 128.8, 128.3, 123.5, 122.4, 117.9, 115.8, 60.3, 56.5, 54.8, 53.2, 45.2, 37.2; IR (NaCl/film) 3210, 3074, 1730, 1672, 1595, 1496, 1384, 1272, 1250, 1213, 924, 758 cm^{-1} ; HRMS (MM: ESI-APCI) m/z calc'd for $\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 287.1390, found 287.1393.



Cinnamyl amine 242. A flame-dried Schlenk tube was charged with primary amine **240** (200.6 mg, 0.70 mmol, 1 equiv), and CH₂Cl₂ (1.4 mL, 0.5M). To this suspension, at ambient temperature (21 °C) was added freshly distilled *trans*-cinnamaldehyde (92 µL, 0.73 mmol, 1.05 equiv). After three minutes, the mixture becomes completely homogeneous. The progress of the reaction was monitored by TLC (imine R_f = 0.47, 10:1 chloroform:methanol), and after consumption of the primary amine was observed (approximately one hour), the solution was cooled to 0 °C in an ice bath, and methanol (7 mL) was added. The solution was stirred for one minute, sodium borohydride (34.9 mg, 0.91 mmol, 1.3 equiv) was added in one portion under high flow of argon, and vigorous bubbling was observed. The Schlenk tube was removed from the ice bath, and after 5 minutes, LCMS indicated complete consumption of the imine. After an additional 10 minutes of stirring, the solution was cooled again to 0 °C, and water (1 mL) was added dropwise. The reaction mixture was concentrated *in vacuo*, partitioned between diethyl ether (20 mL) and water (5 mL), and the phases were separated. The aqueous phase was extracted with diethyl ether (2 x 15 mL), then the combined organics were washed with brine (5 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (30 mL SiO₂, 3:1 → 1:1 hexanes:ethyl acetate) to afford **242** (225.2 mg, 80% yield) as a white solid: R_f = 0.46 (1:1 hexanes:ethyl acetate); ¹H NMR (400 MHz, CDCl₃) δ 8.87 (s, 1H), 7.23–7.06 (m, 7H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.77 (d, *J* = 7.7 Hz, 1H), 6.20 (d, *J* = 15.9 Hz, 1H), 6.02–5.88 (m, 2H), 5.18–5.08 (m, 2H), 3.53 (s, 3H), 3.34 (d, *J* = 10.5 Hz, 1H), 3.26 (dd, *J* = 13.7, 6.5 Hz, 1H), 3.06 (dd, *J* = 14.2, 6.2 Hz, 1H), 3.01–2.92 (m, 2H), 2.89–2.76 (m, 1H), 2.38 (dd, *J* = 14.2, 4.6 Hz, 1H), 1.30 (br s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 172.2, 169.6, 137.8, 137.1, 135.6, 131.0,

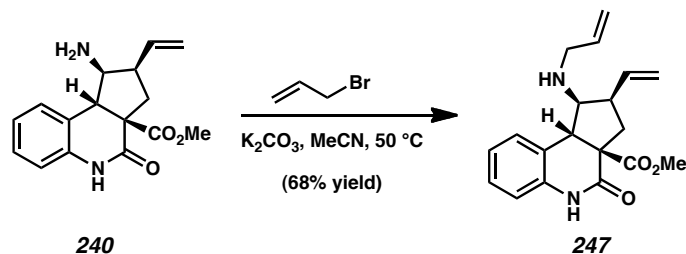
129.4, 128.6, 128.3, 128.2, 127.4, 126.3, 123.5, 122.4, 117.1, 115.7, 65.6, 56.5, 53.2, 52.2, 50.0, 43.8, 37.5; IR (NaCl/film) 3207, 3060, 1733, 1677, 1596, 1494, 1384, 1247, 1104, 753 cm^{-1} ; HRMS (MM: ESI-APCI) m/z calc'd for $\text{C}_{25}\text{H}_{27}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 403.2016, found 403.2018.



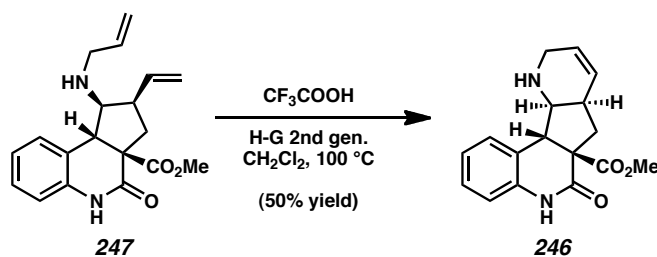
Tetracycle 245. An oven-dried scintillation vial was charged with secondary amine **242** (60.3 mg, 0.150 mmol, 1 equiv) and sealed with a screw-cap fitted with a teflon septum. Dichloromethane (0.3 mL) was added, followed by acetic anhydride (71 μL , 77 mg, 0.75 mmol, 5 equiv), then pyridine (0.12 mL, 118 mg, 1.5 mmol, 10 equiv). The vial was lowered into a 25 $^{\circ}\text{C}$ oil bath and stirred for 14 hours. Over the course of the reaction, a white precipitate formed. Upon completion, the reaction mixture was diluted with diethyl ether (2 mL) and the precipitate was collected by filtration, washed further with diethyl ether and air-dried to afford crude acetamide **243** (58.9 mg, 88% crude yield) which was used without further purification in the next reaction.

A flame-dried Schlenk bomb was charged with crude **243** (58.9 mg, 0.133 mmol, 1 equiv) and Grubbs 2nd generation catalyst (**244**) (5.8 mg, 0.0068 mmol, 0.05 equiv). The bomb was evacuated and backfilled with argon three times. In a separate, flame-dried conical flask, a 1:1 mixture of dichloromethane and *tert*-butyl methyl ether was degassed

by sparging with argon for 20 minutes, then 2.7 mL of this solvent mixture was added to the schlenk bomb under high argon flow. The bomb was sealed and heated in a 60 °C oil bath, and the heterogeneous mixture was stirred for 100 minutes, monitoring by LCMS. Upon completion, the reaction mixture was concentrated in vacuo, and the residue was triturated with toluene to yield tetracycle **245** (45.1 mg, 95% yield, 84% over two steps), in greater than 95% purity, as a grey solid which exists as a 3:1 mixture of rotamers in chloroform: R_f = 0.26 (10:1 CHCl_3 :MeOH); ^1H NMR (300 MHz, CDCl_3) δ 8.32 (br s, 0.33H), 8.19 (br s, 1H), 7.29–7.23 (m, 1H), 7.23–7.17 (m, 0.33H), 7.03 (td, J = 7.5, 1.2 Hz, 1H), 6.98–6.91 (m, 1.33H), 6.87–6.77 (m, 1.66H), 5.83–5.70 (m, 2.66H), 5.16 (dd, J = 11.9, 7.8 Hz, 0.33H), 4.75–4.66 (m, 1H), 4.16–3.98 (m, 1.66H), 3.64–3.56 (m, 5.66H), 3.48 (d, J = 11.9 Hz, 0.33H), 3.23–3.13 (m, 1.33H), 2.89 (br s, 1H), 2.80 (br s, 0.33 H), 2.35 (dd, J = 14.4, 3.3 Hz, 1H), 2.27 (dd, J = 14.3, 3.3 Hz, 0.33 H), 1.99 (s, 1H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 172.1, 171.5, 170.3, 169.8, 169.0, 168.8, 135.7, 135.4, 130.6, 129.2, 128.9, 128.5, 128.4, 127.9, 124.2, 123.2, 121.8, 121.1, 120.6, 120.4, 116.0, 115.6, 60.9, 55.6, 55.5, 54.7, 53.5, 53.3, 47.3, 46.7, 41.6, 38.0, 37.1, 34.6, 33.8, 34.6, 33.8, 22.1, 20.7; IR (NaCl/film) 3215, 2917, 1734, 1680, 1639, 1624, 1597, 1493, 1430, 1372, 1271, 1246, 1214, 1115, 758 cm^{-1} ; HRMS (MM: ESI-APCI) m/z calc'd for $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 341.1496, found 341.1498.

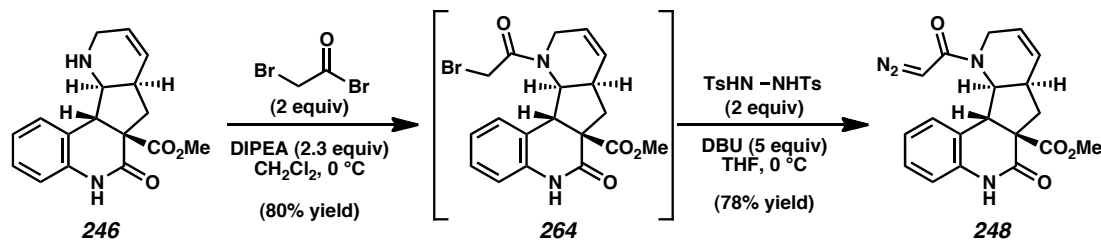


Allylamine 247. A flame-dried flask was charged with amine **240** (51.5 mg, 0.17 mmol, 1 equiv) and potassium carbonate (27.2 mg, 0.19 mmol, 1 equiv), then sealed with a rubber septum and placed under inert atmosphere. Acetonitrile (0.6 mL) was added, followed by allyl bromide (0.017 mL, 0.19 mmol, 1.1 equiv), and the mixture was stirred at ambient temperature for one hour, 40 °C for 3 hours, and 50 °C for 5 hours. At this stage additional allyl bromide (0.005 mL, 0.058 mmol, 0.34 equiv) was added, and the reaction mixture was stirred at 50 °C for an additional 14 hours. The reaction mixture was filtered through celite, and volatiles were removed in vacuo. The residue was purified by column chromatography (150:1 → 50:1 CHCl₃:MeOH) to afford allylamine **247** (40.2 mg, 68% yield) as a white powder after lyophilization from benzene, with minor impurities detected by NMR: ¹H NMR (500 MHz, CDCl₃) δ 8.52 (s, 1H), 7.24 – 7.19 (m, 2H), 7.03 (td, *J* = 7.5, 1.2 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 5.99 (ddd, *J* = 17.0, 10.2, 8.9 Hz, 1H), 5.72 – 5.60 (m, 1H), 5.24 – 5.13 (m, 2H), 4.99 – 4.91 (m, 2H), 3.61 (s, 3H), 3.40 (d, *J* = 10.4 Hz, 1H), 3.20 – 3.12 (m, 1H), 3.06 – 2.94 (m, 3H), 2.88 (qd, *J* = 8.4, 4.7 Hz, 1H), 2.44 (dd, *J* = 14.3, 4.7 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 172.2, 169.5, 136.6, 135.5, 129.4, 128.3, 123.5, 122.4, 117.1, 115.8, 115.5, 65.4, 56.6, 53.2, 52.1, 50.5, 43.7, 37.5; IR (NaCl/film) 3225, 3082, 2978, 1731, 1676, 1597, 1496, 1382, 1246, 915 cm⁻¹; HRMS (MM: ESI-APCI) *m/z* calc'd for C₁₉H₂₃N₂O₃ [M+H]⁺: 327.1703, found 327.1713.



Tetracycle 246. A flame-dried microwave vial (2–5 mL capacity), equipped with a magnetic stir bar, was charged with allylamine **247** (21.3 mg, 0.065 mmol, 1 equiv), then sealed with a microwave cap and evacuated and back-filled with argon. Dichloromethane was degassed by sparging with argon in a separate flame-dried conical flask, and added (3 mL) to the microwave vial. To the resulting solution was added neat trifluoroacetic acid (0.005 mL, 0.065 mmol, 1 equiv). A separate, flame-dried conical flask was charged with Hoveyda-Grubbs 2nd generation catalyst (4 mg, 0.064 mmol, 0.1 equiv), sealed with a rubber septum, and evacuated and backfilled with argon. To this flask was added degassed dichloromethane (1–2 mL), and the resulting solution was transferred to the microwave vial via syringe. The reaction mixture was heated to 100 °C for 1 hour. Upon cooling, saturated aqueous sodium bicarbonate (2 mL) was added and the phases were separated. The aqueous layer was extracted with dichloromethane (2 x 2 mL) and the combined organics were dried over anhydrous sodium sulfate, decanted and concentrated in vacuo. The residue was purified by column chromatography on SiO₂ (150:1 → 30:1 CHCl₃:MeOH) to afford tetracycle **246** (9.8 mg, 50% yield): ¹H NMR (500 MHz, CDCl₃) δ 8.24 (s, 1H), 7.22 (t, *J* = 7.7 Hz, 1H), 7.17 (d, *J* = 7.2 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 5.85 (d, *J* = 10.5 Hz, 1H), 5.76 (d, *J* = 10.4 Hz, 1H), 3.61 (s, 3H), 3.55 (d, *J* = 9.8 Hz, 1H), 3.51 (d, *J* = 17.4 Hz, 1H), 3.31 (d, *J* = 17.3 Hz, 1H), 3.23 (dd, *J* = 9.7, 7.8 Hz, 1H), 3.09 (dd, *J* = 13.6, 8.8 Hz, 1H), 2.71 – 2.64 (br

m, 1H), 2.15 (dd, $J = 13.6, 6.7$ Hz, 1H), 1.70 (br s, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 171.8, 168.7, 135.3, 129.1, 128.7, 128.0, 125.4, 123.6, 123.0, 115.4, 61.8, 56.6, 53.1, 48.2, 40.2, 37.7, 34.7; IR (NaCl/film) 3211, 3062, 2913, 1733, 1676, 1597, 1491, 1432, 1377, 1244, 1105, 912 cm^{-1} ; HRMS (MM: ESI-APCI) m/z calc'd for $\text{C}_{17}\text{H}_{19}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 299.1390, found 299.1401.



Diazoacetamide 248. A flame-dried round-bottom flask, fitted with a magnetic stir bar, was charged with secondary amine **246** (51.3 mg, 0.172 mmol, 1 equiv) and sealed with a rubber septum. Dichloromethane (2 mL, 0.1 M) and Diisopropylethylamine (0.070 mL, 0.395 mmol, 2.3 equiv) were added, the flask was lowered into an ice-water bath, and stirring was initiated. Bromoacetyl bromide (30 μL , 3.44 mmol, 2 equiv) was added dropwise, and the starting material was consumed within 5 minutes (LCMS). The reaction mixture was directly dry-loaded onto silica gel (~ 1.5 mL) and purified by column chromatography on SiO_2 (1:1 hexanes:EtOAc) to afford bromoacetamide **264** (57.8 mg, 80%) which was carried forward directly to the next step.

A flame-dried round-bottom flask, fitted with a magnetic stir bar, was charged with bromoacetamide **264** (57.8 mg, 0.138 mmol, 1 equiv), and $\text{N,N}'$ -ditosylhydrazide (95.3 mg, 0.276 mmol, 2 equiv). The flask was sealed with a rubber septum, and THF (0.4 mL, 0.4 M) was added. The flask was lowered into an ice-water bath, and stirring

was initiated. 1,8-Diazabicycloundec-7-ene (100 μ L, 0.689 mmol, 5 equiv) was then added dropwise, and the reaction was monitored by LCMS. Upon completion, the reaction mixture was dry-loaded onto SiO₂ and purified by column chromatography (2:1 $\rightarrow$ 4:1 $\rightarrow$ 1:0 EtOAc:hexanes), and repurified (35:1 CH₂Cl₂:MeOH) to afford diazoacetamide **248** (39.3 mg, 78% yield) as a yellow solid, and observed to be a mixture of rotamers by NMR: ¹H NMR (500 MHz, d₆-DMSO, 80 °C) δ 10.32 (s, 1H), 7.17 (t, J = 7.7 Hz, 1H), 6.98 – 6.92 (m, 2H), 6.92 – 6.87 (m, 1H), 5.77 (d, J = 11.9 Hz, 1H), 5.72 (d, J = 10.3 Hz, 1H), 5.41 (br s, 1H), 3.82 (d, J = 18.3 Hz, 1H), 3.56 – 3.49 (m, 4H), 3.45 (d, J = 11.5 Hz, 1H), 2.96 (dd, J = 14.2, 9.4 Hz, 1H), 2.74 (br s, 2H), 2.19 (d, J = 14.4 Hz, 1H); ¹³C NMR (126 MHz, d₆-DMSO, 80 °C) δ 188.4, 187.2, 171.6, 171.3, 167.5, 167.1, 163.8, 137.4, 137.0, 129.0, 122.8, 121.0, 120.0, 115.7, 58.3, 55.3, 53.3, 47.5, 46.7, 46.2, 41.4, 41.2, 38.0, 36.8, 33.8. IR (NaCl/film) 3216, 3092, 2918, 2104, 1733, 1681, 1597, 1493, 1427, 1377, 1241, 1209, 1167, 1110 cm⁻¹; HRMS (MM: ESI-APCI) m/z calc'd for C₁₉H₁₉N₄O₄ [M+H]⁺: 367.1401, found 367.1414.

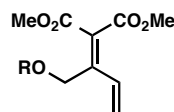
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- (39) Woodward, C. P.; Spiccia, N. D.; Jackson, W. R.; Robinson, A. J. *Chem. Commun.* **2011**, 47, 779–781.
- (40) Control experiments have since found that comparable yields can be obtained without the use of trifluoroacetic acid. For additional discussion of approaches toward the D-ring closure, see Appendix 4.
- (41) Toma, T.; Shimokawa, J.; Fukuyama, T. *Org. Lett.* **2007**, 9, 3195–3197.

- (42) Examples include: (a) Park, S.; Brookhart, M. *J. Am. Chem. Soc.* **2012**, *134*, 640–653. (b) Barbe, G.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 18–19. (c) Collins, C. J.; Lanz, M.; Singaram, B. *Tetrahedron Lett.* **1999**, *40*, 3673–3676. (d) Brown, H. C.; Heim, P. *J. Org. Chem.* **1973**, *38*, 912–916. Also, see ref 32b.
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- (49) Stueckler, C.; Winkler, C. K.; Bonnekessel, M.; Faber, K. *Adv. Synth. Catal.* **2010**, *352*, 2663–2666.
- (50) Tullis, J. S.; Helquist, P. Rhodium-Catalyzed Heterocyclization of a Diazomalonate and a Nitrile: 4-Carbomethoxy-5-Methoxy-2-Phenyl-1,3-Oxazole. In *Organic Syntheses*; Wiley & Sons: New York, 1998; IX, pp 155.

- (51) Prepared by the method of Davies, omitting the recrystallization from toluene: Davies, H. M. L.; Cantrell, W. R., Jr.; Romines, K. R.; Baum, J. S. Synthesis of Furans via Rhodium(II) Acetate-Catalyzed Reaction of Acetylenes with α -Diazocarbonyls: Ethyl 2-Methyl-5-Phenyl-3-Furancarboxylate. In *Organic Syntheses*; Wiley & Sons: New York, 1998; IX, pp 422.
- (52) Diazo compounds are known to be explosive; this distillation has been repeated numerous times without incident, heating to at least 88 °C, nevertheless, proper precautions should be taken, including the use of a blast-shield.
- (53) Solomonovici, A.; Blumberg, S. *Tetrahedron* **1966**, 22, 2505–2509.

APPENDIX 4

Additional Studies Related to Chapter 2:

Progress toward the Total Synthesis of Scandine and the Melodinus Alkaloids

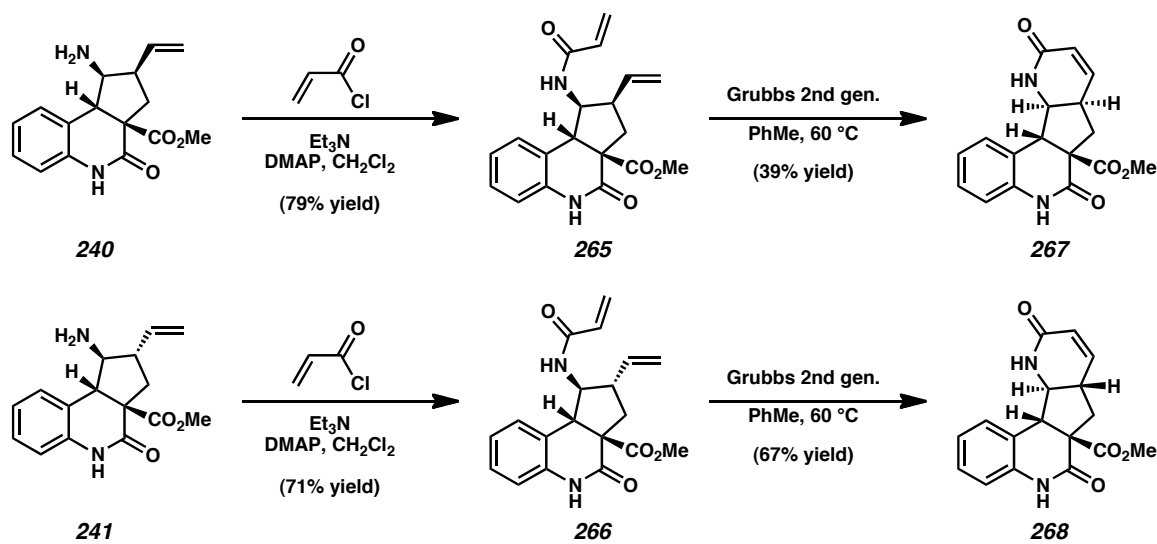
A4.1 ALTERNATIVE APPROACHES TO D-RING RCM

A4.1.1 ACRYLAMIDE RING-CLOSING METATHESIS APPROACH

Our initial approach to the D-ring of the *Melodinus* alkaloids involved conversion of primary amine **240** to the acrylamide followed by ring-closing metathesis (Scheme A4.1.1). In the event, treatment of either diastereomer (**240** or **241**) of the primary amine with acryloyl chloride resulted in clean conversion to the corresponding acrylamides (**265** and **266**). Although Grubbs' first-generation catalyst did not successfully accomplish ring-closure in refluxing dichloromethane, the use of the second-generation catalyst at higher temperatures in toluene afforded tetracycles **267** and **268** in moderate yield. Notably, under the unoptimized conditions, the 5-6 *trans* system was formed in a higher yield than the corresponding *cis* compound. This route offers the possibility of γ -

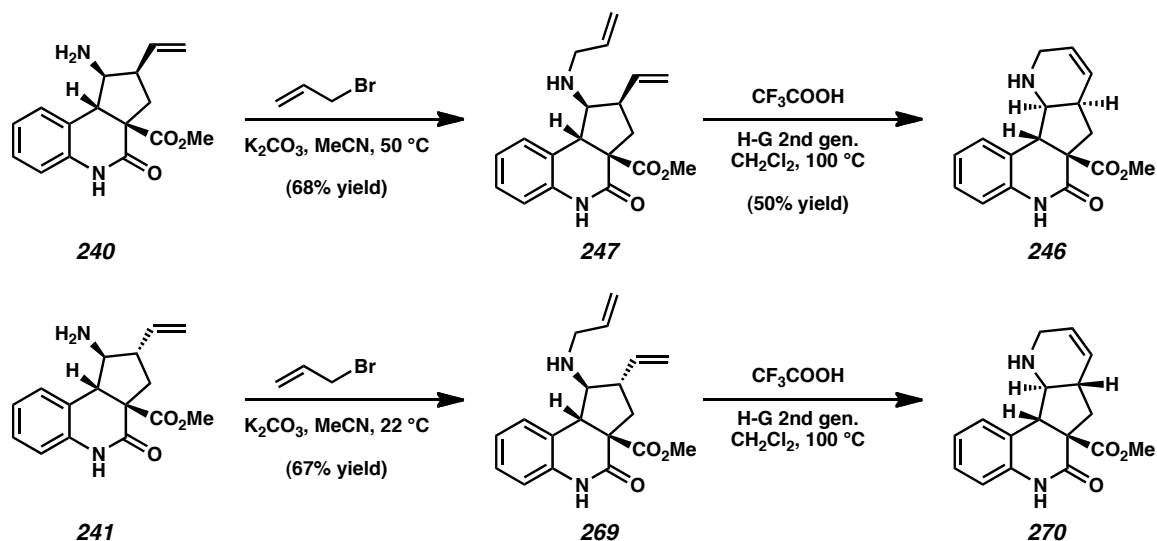
alkylation of the α,β -unsaturated lactam, which could provide an avenue for epimerizing the undesired diastereomer; however, selective reduction of the lactam to the dehydropiperidine system would be necessary in this case.

Scheme A4.1.1. Acylation/RCM sequence for D-ring synthesis.



A4.1.2 ALLYLAMINE RING-CLOSING METATHESIS APPROACH

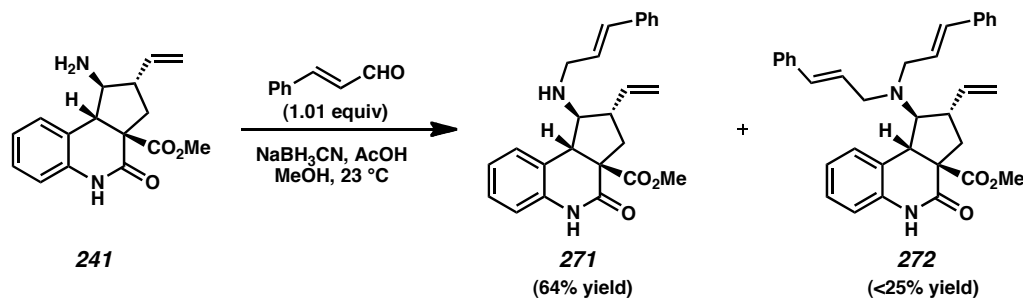
We also examined an analogous approach to the tetracyclic framework of the natural product family using an amine allylation approach to install the D-ring in the correct oxidation state. Whereas reductive amination with acrolein could not be accomplished, we found that either diastereomer of the tricyclic primary amine (**240** or **241**) could be monoalkylated in moderate yield with allyl bromide (Scheme A4.1.2). Ring-closing metathesis could then be accomplished by treatment of the secondary amines (**247** or **269**) with trifluoroacetic acid followed by reaction with Hoveyda–Grubbs second generation catalyst. In the event, free secondary amines **246** and **270** were formed, though further optimization is necessary.

Scheme A4.1.2. Allylation and RCM of primary amines **240** and **241**.

A4.1.3 DEVELOPMENT OF REDUCTIVE AMINATION CONDITIONS

In our effort to improve the yield of the amine alkylation/ring-closing metathesis sequence, we examined the reductive amination of amine **241** with cinnamaldehyde (Scheme A4.1.3). Using an excess of aldehyde (1.6 equiv), we observed mixtures of mono- and bis-cinnamylated amine by LCMS (**271** and **272** respectively), and reducing the quantity of aldehyde under these conditions still resulted in mixtures.

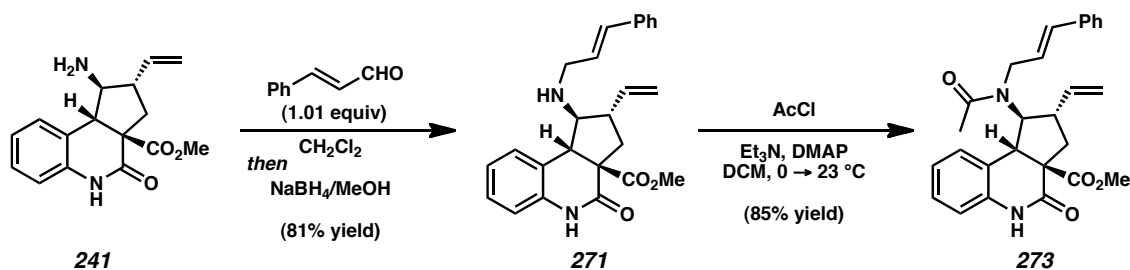
Scheme A4.1.3. Initial reductive amination attempt with cinnamaldehyde



Gratifyingly, we found that preforming the imine followed by reduction with sodium borohydride afforded the desired cinnamylamine (**271**) in 81% yield, and acetylation of

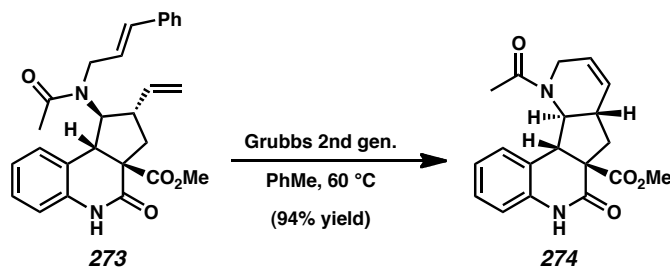
the secondary amine proceeded cleanly (Scheme A4.1.4). Notably, the conditions that were effective in the RCM of free allylamines **247** and **269** surprisingly gave no product when applied to secondary cinnamylamine **271**.

Scheme A4.1.4. Reductive amination and acetylation of amine **241**



Ring-closing metathesis of the protected secondary amine (**273**) was successful, and the tetracyclic product (**274**) precipitated from the reaction mixture with excellent purity (Scheme A4.1.5). It is worth noting that both the acetylation and RCM steps of the reaction needed re-optimization for the *cis* diastereomer (**242**). Under the same acetylation conditions as above, a doubly acetylated compound was formed as a side product.¹ Furthermore, the corresponding RCM substrate (**243**, Chapter 2) was insoluble in toluene and the desired reaction did not proceed under the same conditions; the conditions described in Chapter 2 were effective for this transformation.

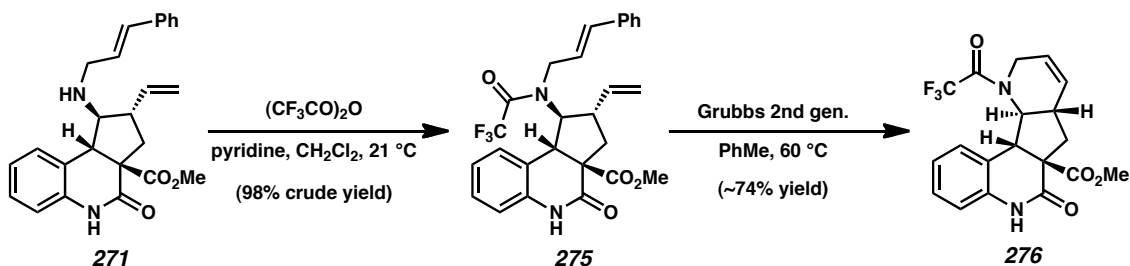
Scheme A4.1.5. Ring-closing metathesis of cinnamylamine **273**



A4.1.4 TRIFLUOROACETAMIDE-PROTECTED RCM SUBSTRATE

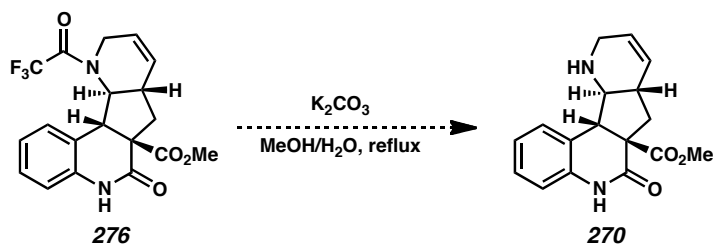
Due to the difficulty in directly converting the tetracyclic acetamide (**245**, Chapter 2) to the desired diazoacetamide, we considered the use of a trifluoroacetamide as an easily cleaved nitrogen protecting group toward the free tetracyclic secondary amine. We first investigated this sequence with **242**; the protection step proceeded cleanly, providing trifluoroacetamide **275** in 98% crude yield, and ring-closing metathesis provided tetracycle **276** (Scheme A4.1.6).

Scheme A4.1.6. Ring-closing metathesis of TFA protected amine

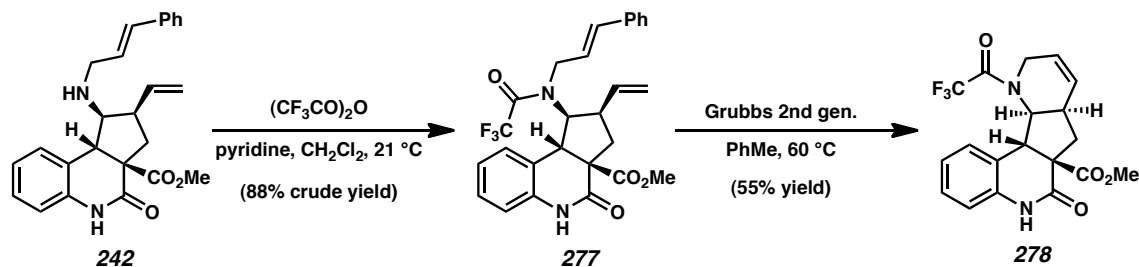


Only a single attempt has been made to cleave the trifluoroacetamide group from tetracycle **276** (Scheme A4.1.7). While promising by LCMS, the product (**270**) was not successfully isolated.

Scheme A4.1.7. Attempt to cleave TFA group from tetracycle **276**

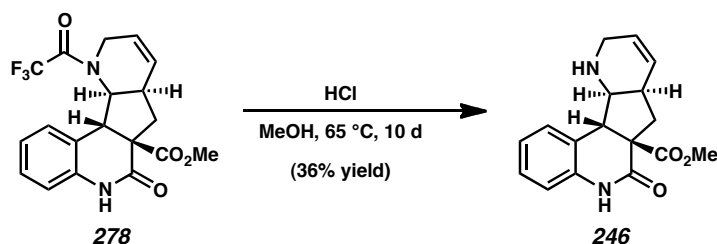


Application of the same protection/RCM sequence to the *cis* cinnamylamine diastereomer was equally effective, but lower yielding, likely due to loss of material during a filtration step (Scheme A4.1.8).

Scheme A4.1.8. TFA protection/RCM Sequence with *cis*-diastereomer **242**

Cleavage of the trifluoroacetate group from tetracycle **278** under the conditions attempted with the *trans*-[5,6] tetracycle (**276**) was ineffective, and only methyl ester hydrolysis and decarboxylation was observed by LCMS. Several other conditions were attempted, including sodium borohydride reduction, and lithium hydroxide mediated hydrolysis failed to cleanly convert the trifluoroacetamide **278** to the free secondary amine **246**. However, preliminary efforts using methanolic hydrochloric acid performed the desired amine deprotection cleanly, albeit slowly (Scheme A4.1.9). Starting material could be recovered, however further optimization may be necessary improve the efficiency of this transformation.

Scheme A4.1.9. Amine deprotection under acidic conditions



A4.1.5 SUMMARY

Our studies on the assembly of the *Melodinus* alkaloid D-ring revealed that the chemistry of the *trans*-5,6-fused system typically was well-behaved compared to the *cis*-5,6-fused system that is found in the natural product. Firstly, the reactivity of the *trans*

system did not always translate well to the *cis* system, and often required reoptimization. Direct conversion of the secondary cinnamyl amine (**242**) to the corresponding tetracycle by RCM would shorten the synthetic sequence by avoiding protection and deprotection steps. However, the most reliable approach would likely be via the trifluoroacetamide, if the deprotection step can be optimized.

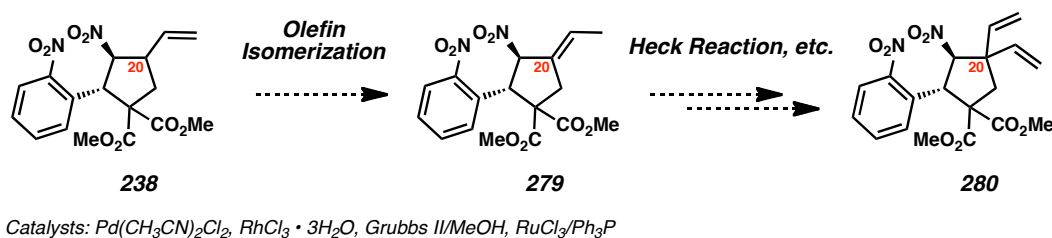
A4.2 INITIAL EFFORTS FOR C(20) FUNCTIONALIZATION

Prior to our collaborative efforts with the Davies group, we examined several methods to functionalize the C(20) position of the natural product scaffold.

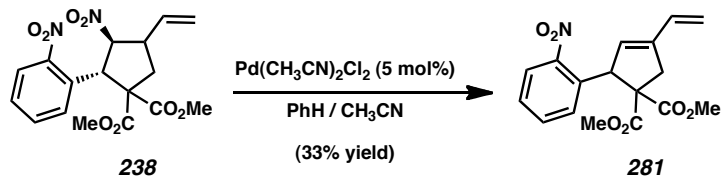
A4.2.1 OLEFIN ISOMERIZATION

We examined the reactivity of the (3 + 2) cycloaddition adduct (**238**) with an array of catalysts known to perform olefin isomerization, envisioning the formation of trisubstituted olefin **279**, which could be used as a handle for installing the quaternary center at C(20) by a Heck reaction.² Unfortunately under none of these conditions did we observe the desired transformation (Scheme A4.2.1).

Scheme A4.2.1. Olefin Isomerization approach to C(20) functionalization.



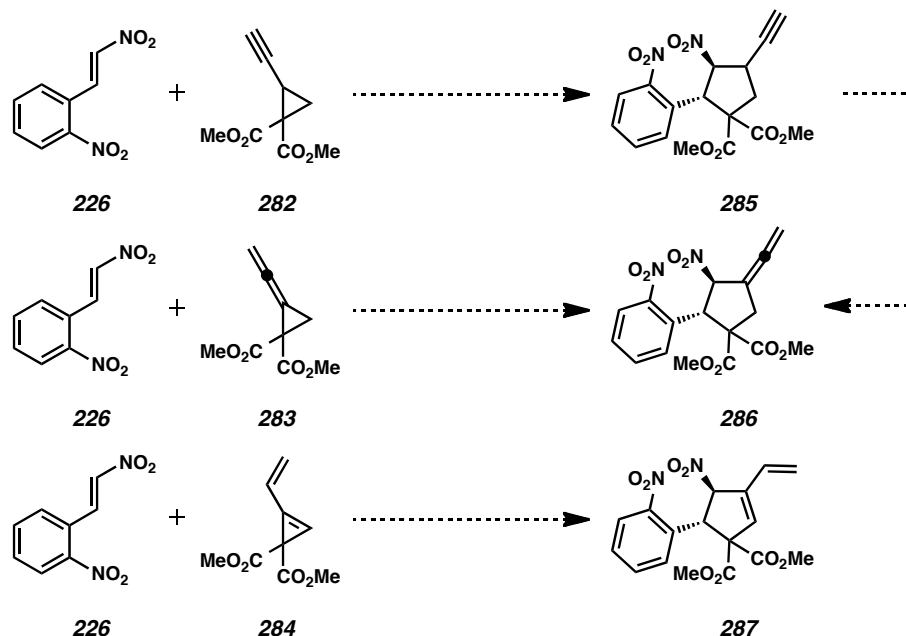
Interestingly, with bis(acetonitrile)dichloropalladium(II), we observed an elimination of nitrous acid to form diene **281** (Scheme A4.2.2).

Scheme A4.2.2. Unexpected elimination of HNO_2 to form diene **281**

A4.2.2 ALTERNATIVE CYCLOPROPANES

We also considered installing an additional unit of unsaturation on the cyclopropane, prior to (3 + 2) cycloaddition (Scheme A4.2.3). Accordingly application of an alkynyl- or vinylidenecyclopropane (**282** and **283** respectively) or a vinylcyclopropene (**284**) would provide access to cyclopentane derivatives (**285**, **286**, **287**) with an additional functional handle.

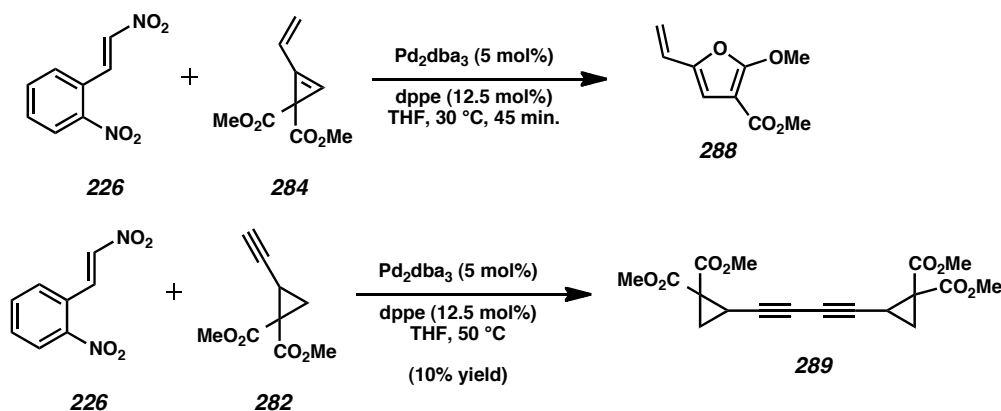
Scheme A4.2.3. Proposed application of doubly unsaturated cyclopropanes



Unfortunately, none of these cyclopropane derivatives underwent the desired (3 + 2) cycloaddition with nitrostyrene **226**. Vinylidenecyclopropane **283** was unreactive under

standard conditions, alkynylcyclopropane **282** underwent a Glaser-type coupling in low yield, and vinylcyclopropene **284** isomerized rapidly to furan **288**.

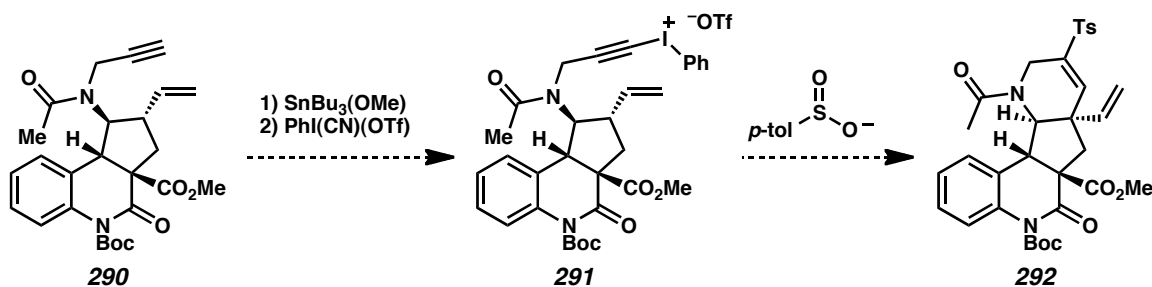
Scheme A4.2.4. Reactions of cyclopropane derivatives **282** and **284**

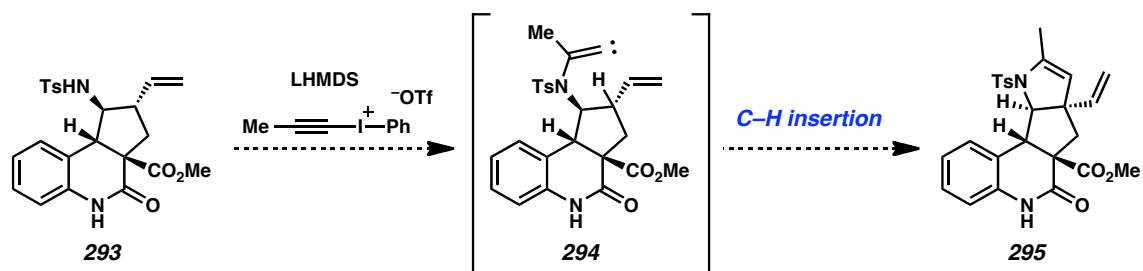


A4.3 C(20) FUNCTIONALIZATION VIA C–H INSERTION

Prior to the preliminary studies on intermolecular C–H vinylation, we examined an approach to the D-ring by means of an intramolecular alkylidene carbene or vinylidene carbenoid C–H insertion reaction.³ Preliminary examinations of this approach were unsuccessful. Two methods examined involved reaction of alkynyl iodonium triflate **291** with *para*-toluene sulfinate (Scheme A4.3.1) and reaction of toluenesulfonamide **293** with propynyl iodonium triflate (Scheme A4.3.2).

Scheme A4.3.1. Attempted formation and reaction of alkynyliodonium triflate **291**.



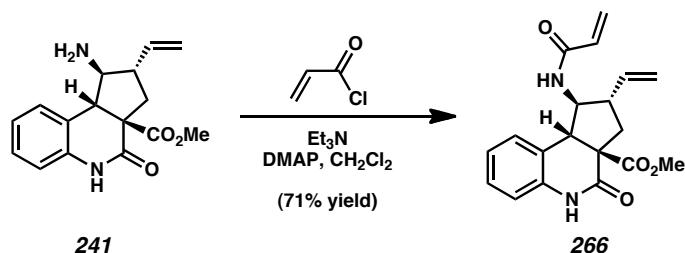
Scheme A4.3.2. Attempted formal (3 + 2) cycloaddition of toluenesulfonamide **293**

A4.4 EXPERIMENTAL SECTION

A4.4.1 MATERIALS AND METHODS

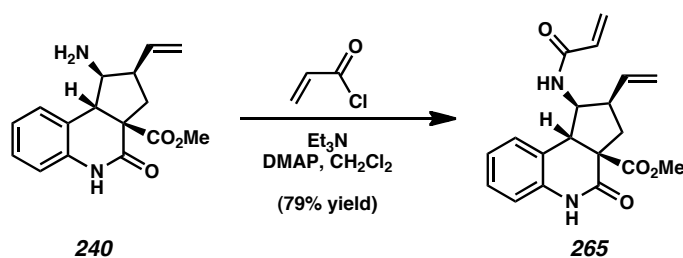
Unless stated otherwise, reactions were performed under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina).⁴ Commercially obtained reagents were used as received unless otherwise stated. Reaction temperatures were controlled by an IKAmag temperature modulator. Microwave reactions were performed with a Biotage Initiator Eight 400 W apparatus at 2.45 GHz. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, or potassium permanganate, iodine, or anisaldehyde staining. SiliaFlash P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. ¹H and ¹³C NMR spectra were recorded on a Varian Inova 500 (at 500 MHz and 126 MHz respectively), Varian 400 (at 400 MHz and 100 MHz, respectively) or on a Varian Mercury 300 (at 300 MHz) and are reported relative to CHCl₃ (δ 7.26 & 77.16 respectively). Data for ¹H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm⁻¹). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) or mixed (MM) ionization mode.

A4.4.2 PREPARATIVE PROCEDURES

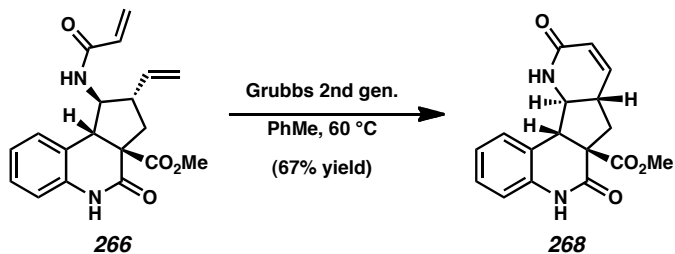


Acrylamide 266. To a flame-dried round-bottom flask were added amine **241** (53.9 mg, 0.19 mmol, 1 equiv) and 4-(*N,N*-dimethylamino)pyridine (1.9 mg, 0.02 mmol, 0.1 equiv). The flask was sealed with a rubber septum and placed under an inert atmosphere. The flask was charged with dichloromethane (1 mL, 0.2 M) and upon dissolution of the solids with stirring, the flask was cooled in an ice-water bath. To the cooled solution was added triethylamine (0.034 mL, 0.24 mmol, 1.3 equiv) followed by acryloyl chloride (0.018 mL, 0.22 mmol, 1.2 equiv). The cooling bath was removed and the reaction mixture was allowed to warm to ambient temperature. After 5 hours, complete conversion was observed by LCMS. The volatiles were removed in vacuo and the residue was purified by column chromatography on SiO₂ (20:1 CHCl₃:MeOH) to afford acrylamide **266** (45.4 mg, 71% yield) as an off-white powder: ¹H NMR (500 MHz, 1:1 CD₃OD:CDCl₃, referenced to residual CHD₂OD peak at 3.31 ppm) δ 8.19 (d, *J* = 9.3 Hz, 1H), 7.15 (td, *J* = 7.7, 1.5 Hz, 1H), 7.04 (dd, *J* = 7.7, 1.4 Hz, 1H), 6.90 (td, *J* = 7.5, 1.2 Hz, 1H), 6.85 (dd, *J* = 8.0, 1.1 Hz, 1H), 6.19–6.05 (m, 2H), 5.66 (ddd, *J* = 17.0, 10.2, 7.8 Hz, 1H), 5.59 (dd, *J* = 9.9, 1.9 Hz, 1H), 5.06 (dt, *J* = 17.1, 1.2 Hz, 1H), 5.02–4.94 (m, 1H), 4.02–3.94 (m, 1H), 3.61 (s, 4H), 3.40 (dd, *J* = 11.4, 1.8 Hz, 1H), 2.77 (dd, *J* = 13.7, 9.7 Hz, 1H), 2.69 (p, *J* = 9.1 Hz, 1H), 2.46 (dd, *J* = 13.7, 8.8 Hz, 1H); ¹³C NMR (126 MHz, 1:1 CD₃OD:CDCl₃, referenced to ¹³CD₃OD peak at 49.0 ppm) δ 173.1, 170.0,

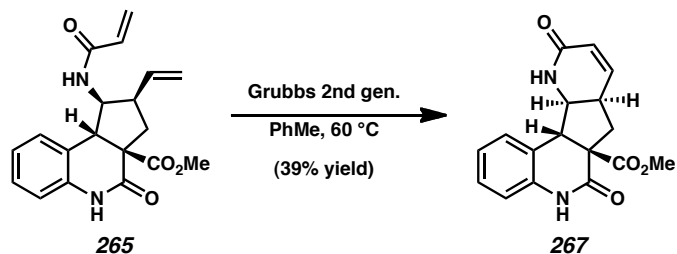
138.6, 136.1, 131.1, 131.0, 128.9, 126.9, 123.7, 121.2, 116.7, 116.1, 60.5, 55.7, 53.4, 52.3, 52.2, 37.4; HRMS (MM: ESI-APCI) m/z calc'd for $C_{19}H_{21}N_2O_4$ $[M+H]^+$: 341.1496, found 341.1479.



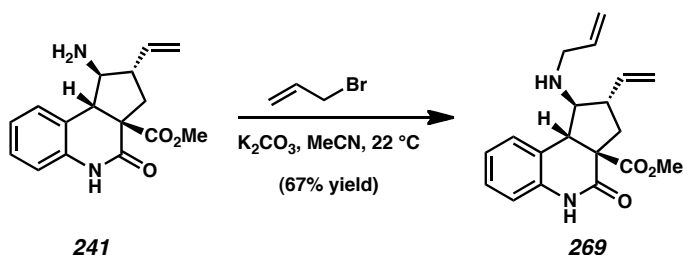
Acrylamide 265. Prepared according to the same procedure as above. Full conversion was observed by LCMS after 5 hours, and after similar purification, acrylamide **265** (49.8 mg, 79% yield) was obtained: 1H NMR (500 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.21 (td, $J = 7.7, 1.5$ Hz, 1H), 7.17 (dd, $J = 7.8, 1.3$ Hz, 1H), 6.99 (td, $J = 7.5, 1.1$ Hz, 1H), 6.76 (d, $J = 7.6$ Hz, 1H), 6.20 (dd, $J = 17.0, 1.3$ Hz, 1H), 6.06 (dd, $J = 17.0, 10.3$ Hz, 1H), 5.85 (ddd, $J = 17.7, 10.4, 7.8$ Hz, 1H), 5.70–5.61 (m, 2H), 5.29–5.15 (m, 1H), 4.51–4.41 (m, 1H), 3.66 (s, 3H), 3.53–3.42 (m, 2H), 3.05 (dd, $J = 13.8, 8.0$ Hz, 1H), 2.98 (dt, $J = 15.4, 7.9$ Hz, 1H), 2.51 (dd, $J = 13.8, 6.7$ Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 168.0, 165.1, 136.3, 135.3, 130.6, 128.7, 127.1, 123.8, 121.1, 118.7, 115.6, 115.4, 57.9, 56.5, 53.5, 52.5, 43.3, 37.4.



Tetracycle 268. A flame-dried 5 mL conical flask was charged with acrylamide **266** (20.7 mg, 0.059 mmol, 1 equiv) and Grubbs' first-generation catalyst (2.4 mg, 0.003 mmol, 0.05 equiv). The flask was sealed with a septum, evacuated, and back-filled with argon. A separate flame-dried flask was charged with dichloromethane and sparged with argon gas. Dichloromethane (1.2 mL) was transferred into the first flask, and the septum was quickly swapped for a cold-finger water condenser. The solution was heated to reflux for 10 hours, and little conversion was observed by LCMS. The reaction mixture was concentrated in vacuo, and Grubbs second-generation catalyst (4.2 mg, 0.005 mmol, 0.1 equiv) was added, followed by degassed (sparging with Ar_(g)) toluene. The resulting solution was heated to 60 °C and monitored by LCMS for conversion. Upon complete consumption of starting material, the reaction mixture was concentrated in vacuo, and the residue was purified by column chromatography on SiO₂ (30:1 CHCl₃:MeOH) to afford tetracycle **268** (12.7 mg, 67% yield) as a maroon-brown solid. Trituration with d₆-acetone affords a white solid. ¹H NMR (500 MHz, 1:1 CD₃OD:CDCl₃, referenced to residual CHD₂OD peak at 3.31 ppm) δ 7.56 (s, 1H), 7.30–7.22 (m, 2H), 7.08 (td, *J* = 7.5, 1.2 Hz, 1H), 6.93 (d, *J* = 7.3 Hz, 1H), 6.87 (dd, *J* = 9.6, 1.9 Hz, 1H), 5.87 (dd, *J* = 9.6, 2.9 Hz, 1H), 3.65 (s, 3H), 3.39 (d, *J* = 11.5 Hz, 1H), 3.27 (d, *J* = 11.5 Hz, 1H), 2.98 (dd, *J* = 13.6, 8.3 Hz, 1H), 2.90–2.78 (m, 1H), 2.26 (dd, *J* = 13.6, 12.2 Hz, 1H); ¹³C NMR (126 MHz, 1:1 CD₃OD:CDCl₃, referenced to ¹³CD₃OD peak at 49.0 ppm) δ 172.5, 170.0, 169.7, 145.0, 136.1, 129.6, 129.0, 126.0, 124.3, 119.3, 116.7, 62.4, 57.1, 53.7, 51.2, 42.1, 34.6.

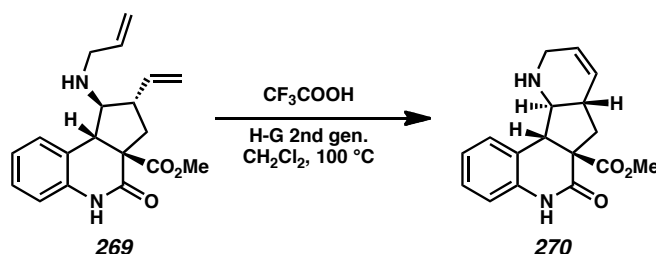


Tetracycle 267. Prepared according to the above procedure: Grubbs first-generation catalyst gave no conversion in dichloromethane, the solution was filtered through celite prior to resubjecting the material with Grubbs second-generation catalyst in toluene (full conversion was observed by LCMS after 13 hours). No trituration after the chromatographic purification was recorded, and tetracycle **267** (7.3 mg, 39% yield) was obtained. ^1H NMR (300 MHz, 1:1 $\text{CD}_3\text{OD}:\text{CDCl}_3$, referenced to residual CHD_2OD peak at 3.31 ppm) δ 7.24 (td, $J = 7.7, 1.6$ Hz, 1H), 7.17 (dd, $J = 7.5, 1.5$ Hz, 1H), 7.04 (td, $J = 7.5, 1.2$ Hz, 1H), 6.92 (dd, $J = 7.9, 1.2$ Hz, 1H), 6.54 (ddd, $J = 10.1, 2.6, 1.0$ Hz, 1H), 5.87 (dd, $J = 10.0, 2.4$ Hz, 1H), 3.66–3.50 (app m, 5H), 3.26 (d, $J = 9.8$ Hz, 1H), 3.19 – 3.08 (m, 1H), 2.45 (dd, $J = 13.4, 4.7$ Hz, 1H); HRMS (MM: ESI-APCI) m/z calc'd for $\text{C}_{17}\text{H}_{17}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 313.1183, found 313.1175.



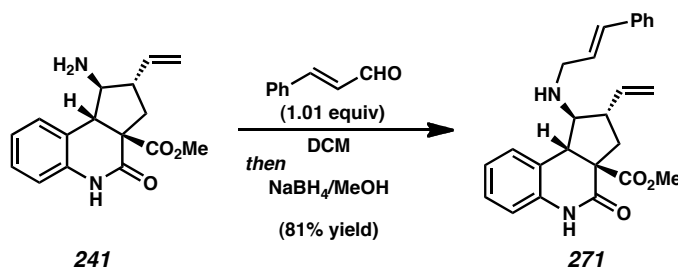
Allylamine 269. A flame-dried flask was charged with amine **241** (67.1 mg, 0.23 mmol, 1 equiv) and potassium carbonate (33 mg, 0.24, 1.02 equiv), then sealed with a rubber septum and placed under an inert atmosphere. Acetonitrile (2 mL) was added,

followed by allyl bromide (0.021 mL, 0.24 mmol, 1.04 equiv), and the mixture was stirred at ambient temperature overnight. The reaction mixture was filtered through celite, washing with dichloromethane, and the volatiles were removed in vacuo. The residue was purified by column chromatography on SiO₂ (150:1 CHCl₃:MeOH) to afford allylamine **269** (51.3 mg, 67% yield): ¹H NMR (300 MHz, CDCl₃) δ 7.82 (br s, 1H), 7.31–7.15 (m, 2H), 7.04 (td, *J* = 7.5, 1.2 Hz, 1H), 6.78 (d, *J* = 7.9 Hz, 1H), 5.79–5.58 (m, 2H), 5.19–4.87 (m, 4H), 3.61 (s, 3H), 3.34 (d, *J* = 10.7 Hz, 1H), 3.27–3.07 (m, 1H), 3.06–2.95 (m, 1H), 2.81–2.48 (m, 4H). HRMS (MM: ESI-APCI) *m/z* calc'd for C₁₉H₂₃N₂O₃ [M+H]⁺: 327.1703, found 327.1692.

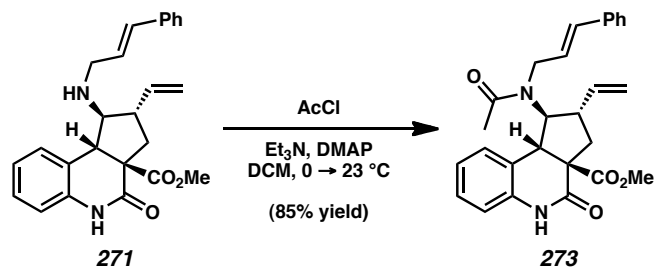


Tetracycle 270. A flame-dried microwave vial (2-5 mL capacity), equipped with a magnetic stir bar, was charged with allylamine **269** (11.5 mg, 0.035 mmol, 1 equiv) then sealed with a rubber septum, placed under an inert atmosphere and charged with dichloromethane (4.5 mL). To a flame-dried flask was added trifluoroacetic acid (0.1 mL) and toluene (0.9 mL), and 0.027 mL of this solution was added to the microwave vial. Finally, the septum was removed and Hoveyda-Grubbs second-generation catalyst (2.2 mg, 0.0035 mmol, 0.1 equiv) was added quickly, and the microwave vial was sealed with a microwave cap. The reaction mixture was heated to 100 °C in a microwave reactor for 1 hour. Additional catalyst (1.0 mg) was added to the reaction mixture and the

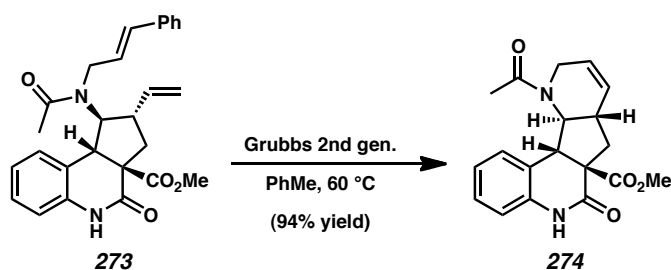
vial was re-sealed and subjected to microwave heating for an additional hour. The volatiles were removed in vacuo and the residue was purified by preparatory TLC (10:1 CHCl₃:MeOH; R_F SM = 0.44, Prod: 0.50) to afford tetracycle **270** (yield was not recorded). ¹H NMR (300 MHz, CDCl₃) δ 7.61 (s, 1H), 7.18–7.08 (m, 2H), 7.00 (t, *J* = 7.9 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 5.84 (d, *J* = 11.1 Hz, 1H), 5.55 (ddd, *J* = 10.2, 6.0, 3.1 Hz, 1H), 3.60 (s, 3H), 3.47 (ddd, *J* = 17.6, 5.3, 2.6 Hz, 1H), 3.34 (ddd, *J* = 17.2, 6.0, 2.5 Hz, 1H), 3.13 (d, *J* = 11.1 Hz, 1H), 2.85 (dd, *J* = 13.4, 7.6 Hz, 1H), 2.53–2.28 (m, 1H), 2.07–1.91 (m, 1H).



Cinnamylamine 271. Prepared by an analogous method as that reported for the synthesis of **242**, Chapter 2, using amine **241** (302.4 mg, 1.04 mmol, 1 equiv), cinnamaldehyde (0.138 mL, 1.10 mmol, 1.05 equiv) and sodium borohydride (47 mg, 1.25 mmol, 1.2 equiv) to obtain cinnamylamine **271** (343.1 mg, 81% yield): ¹H NMR (400 MHz, CDCl₃) δ 7.96 (s, 1H), 7.35–7.17 (m, 9H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.78 (dd, *J* = 7.9, 1.1 Hz, 1H), 6.26 (d, *J* = 16.0 Hz, 1H), 6.01 (dt, *J* = 15.9, 6.2 Hz, 1H), 5.73 (ddd, *J* = 16.9, 10.0, 8.3 Hz, 1H), 5.16 (d, *J* = 17.0 Hz, 1H), 5.07 (dd, *J* = 10.1, 1.6 Hz, 1H), 3.61 (s, 3H), 3.40–3.27 (m, 2H), 3.19 (dd, *J* = 14.4, 6.4 Hz, 1H), 2.83–2.73 (m, 2H), 2.67 (dt, *J* = 16.9, 8.6 Hz, 1H), 2.58 (dd, *J* = 13.2, 7.3 Hz, 1H).

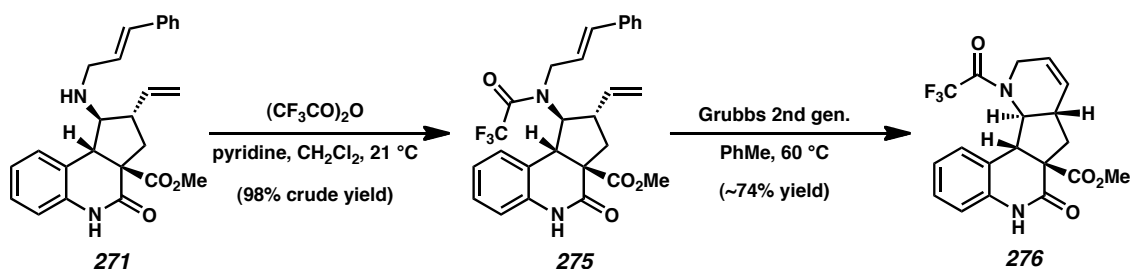


Acetamide 273. A flame-dried round-bottom flask, equipped with a magnetic stir bar, was charged with amine **271** (149.8 mg, 0.37 mmol, 1 equiv) and 4-(*N,N*-dimethylamino)pyridine (4.9 mg, 0.037 mmol, 0.1 equiv), sealed with a rubber septum and placed under an inert atmosphere. To the flask was added dichloromethane (3 mL) and triethylamine (0.065 mL, 0.45 mmol, 1.2 equiv). The flask was cooled in an ice-water bath, then acetyl chloride (0.030 mL, 0.41 mmol, 1.1 equiv) was added. The cooling bath was removed, and the reaction was monitored by LCMS. Upon complete consumption of starting material, the reaction mixture was dry-loaded onto SiO₂ (~2 mL) and purified by column chromatography on SiO₂ (2:1 → 1:1 hexanes:EtOAc) to afford acetamide **273** (140.7 mg, 85% yield).



Tetracycle 274. A flame-dried Schlenk tube, equipped with a stir bar, was charged with Grubbs' second-generation catalyst (3.8 mg, 0.0045 mmol, 0.1 equiv), then sealed with a rubber septum, and evacuated and backfilled with argon. In a separate flame-dried flask, acetamide **273** (20 mg, 0.045 mmol, 1 equiv) was dissolved in toluene (0.9 mL)

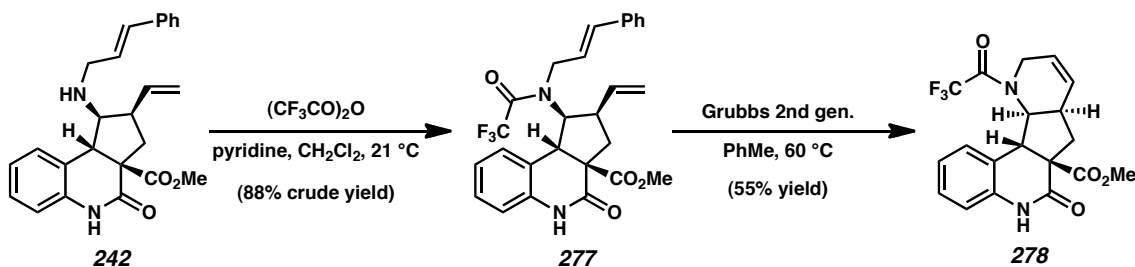
which was degassed by sparging with argon gas. The acetamide solution was transferred via syringe to the Schlenk tube, and the resulting solution was heated to 60 °C in an oil bath. After one hour, a brown suspension was observed, and after five hours (total), the suspension was filtered, washing with a small amount of toluene (ambient temperature) to afford tetracycle **274** (14.4 mg, 94% yield) as a white solid: ^1H NMR (300 MHz, CDCl_3) δ 7.78 (s, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.27–7.13 (m, 1H), 7.02 (td, J = 7.5, 1.2 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 5.98 (d, J = 9.6 Hz, 1H), 5.62 (d, J = 9.7 Hz, 1H), 5.13 (d, J = 12.0 Hz, 1H), 4.05 (d, J = 18.0 Hz, 1H), 3.74 (d, J = 17.5 Hz, 1H), 3.64 (s, 3H), 2.98 (q, J = 8.4 Hz, 2H), 2.79 (t, J = 11.0 Hz, 1H), 2.10 (app m, 4H).



Trifluoroacetamide 276. An oven-dried vial, equipped with a magnetic stir bar, was charged with amine **271** (141.3 mg, 0.35 mmol, 1 equiv), sealed with a cap fitted with a Teflon septum, and placed under an inert atmosphere. To the vial were added sequentially dichloromethane (0.72 mL), trifluoroacetic anhydride (0.250 mL, 1.76 mmol, 5 equiv), and freshly distilled pyridine (0.18 mL, 2.23 mmol, 6.4 equiv). The reaction was allowed to stir at ambient temperature for 6 hours, then was quenched by addition of saturated aqueous copper(II) sulfate (exothermic!). The biphasic mixture was extracted with dichloromethane, then the combined organics were dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was filtered through a short plug

of SiO₂ (1:1 hexanes:EtOAc), and concentrated in vacuo to afford crude acetamide **275** (172.0 mg, 98% yield) as a yellow-ish foam after concentrating from hexanes. The material was found to be clean by LCMS and was carried forward directly to the next stage of the sequence.

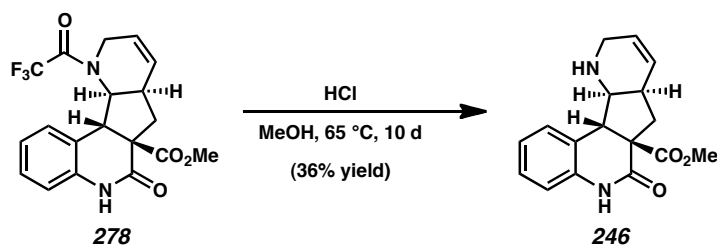
A flame-dried Schlenk flask, equipped with a magnetic stir bar, was charged with Grubbs' second generation catalyst (29.8 mg, 0.035 mmol, 0.1 equiv), then sealed with a rubber septum, evacuated and backfilled with argon. To the flask was then added benzene (4 mL). Crude acetamide **275** (172.0 mg, 0.345 mmol, 1 equiv) was then added to the Schlenk flask as a solution in benzene (3 mL). The reaction mixture was heated to 60 °C in an oil bath with stirring for 17 hours, then dry-loaded onto SiO₂ and purified by column chromatography (3:1 hexanes:EtOAc) to afford trifluoroacetamide **276** (102.9 mg, 74% yield): ¹H NMR (500 MHz, CDCl₃) δ 8.16 (s, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.25 (t, *J* = 7.7 Hz, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 6.04 (d, *J* = 8.9 Hz, 1H), 5.67 (d, *J* = 10.6 Hz, 1H), 5.03 (d, *J* = 11.9 Hz, 1H), 4.29 (d, *J* = 18.7 Hz, 1H), 3.82 (d, *J* = 16.8 Hz, 1H), 3.68 (s, 3H), 3.15 – 2.93 (m, 3H), 2.20 (dd, *J* = 12.9, 10.2 Hz, 1H).



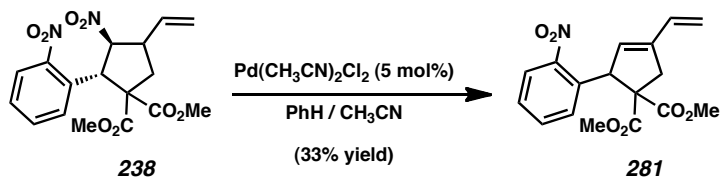
Trifluoroacetamide 277. Acylation of secondary amine **242** (506.1 mg, 1.26 mmol, 1 equiv) was performed exactly as above, using trifluoroacetic anhydride (0.89 mL, 6.29

mmol, 5 equiv), pyridine (0.63 mL), and dichloromethane (2.5 mL) to afford crude trifluoroacetamide **278** (548.9 mg, 88% yield) as a yellow-brown foam which was carried forward without further purification.

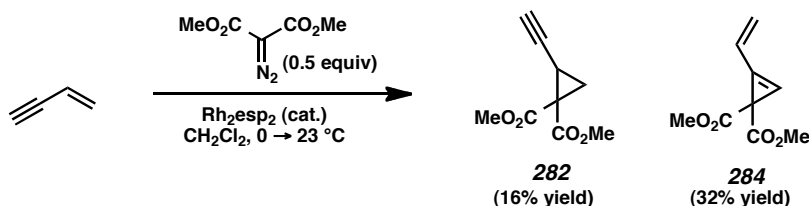
Ring-closing metathesis of crude trifluoroacetamide **278** (548.9 mg, 1.1 mmol, 1 equiv) was performed as above, using Grubbs' second generation catalyst (93 mg, 0.11 mmol, 0.1 equiv) and benzene (22 mL, 0.05 M), with modifications: after 16 hours, additional catalyst (50 mg, 0.059 mmol) was added, and complete consumption of starting material was observed by LCMS after an additional 2 hours. The volatiles were removed in vacuo, and the solid residue was triturated with diethyl ether—some material was likely lost in this stage—to afford trifluoroacetate **278** (240.8 mg, 55% yield). ^1H NMR (300 MHz, CDCl_3 , ~ 1:1 mixture of amide bond rotamers) δ 8.22 (s, 0.45H), 8.11 (s, 0.55H), 7.30–7.18 (m, 1H), 7.01 (app qd, J = 8.4, 8.0, 1.1 Hz, 1H), 6.92 (t, J = 6.1 Hz, 1H), 6.81 (dd, J = 7.9, 5.3 Hz, 1H), 5.89–5.82 (m, 1H), 5.78 – 5.70 (m, 1H), 5.00 (dd, J = 11.9, 7.9 Hz, 0.45H), 4.79–4.65 (m, 0.55H), 4.35 (d, J = 17.9 Hz, 0.55H), 4.24–4.05 (m, 1H), 3.89–3.69 (m, 1H), 3.64–3.61 (m, 3H), 3.58 (d, J = 11.9 Hz, 0.45H), 3.22 (ddd, J = 19.7, 14.4, 9.6 Hz, 1H), 2.93 (s, 1H), 2.33 (td, J = 14.9, 3.3 Hz, 1H); ^{19}F NMR (282 MHz, CDCl_3) δ -68.6, -69.8.



Secondary amine 246. A flame-dried round-bottom flask, equipped with a stir-bar, sealed with a rubber septum, and under an inert atmosphere, was charged with methanol (10 mL), which was freshly distilled from $\text{Mg}(\text{OMe})_2$, and cooled in an ice-water bath. Acetyl chloride (0.25 mL, 3.5 mmol, 6.7 equiv) was added to the flask, dropwise, then the cooling bath was removed. The rubber septum was removed, acetamide **278** (206.7 mg, 0.524 mmol, 1 equiv) was added quickly, and the septum was replaced. The flask was heated to 65 °C in an oil bath with stirring. After heating for 4 days, the reaction flask was cooled to room temperature, additional acetyl chloride (0.05 mL) was added, and the flask was reheated to 65 °C for 4 days. The flask was cooled to ambient temperature, and stirred for an additional 2 days. The volatiles were removed in vacuo and the residue was partitioned between water and diethyl ether, with a small amount of acetone to solubilize remaining solids. The phases were separated, and the aqueous layer was extracted once with diethyl ether and twice with ethyl acetate. The aqueous layer was then basified to $\text{pH} = \sim 11$ with aqueous sodium hydroxide (3 M, 1 mL) and extracted with an unrecorded solvent. Upon concentration of the combined basic extracts, the residue was purified by column chromatography (30:1 $\rightarrow$ 15:1 CHCl_3 :MeOH) to afford secondary amine **246** (56.8 mg, 36% yield). The characterization data matches those reported in Chapter 2.

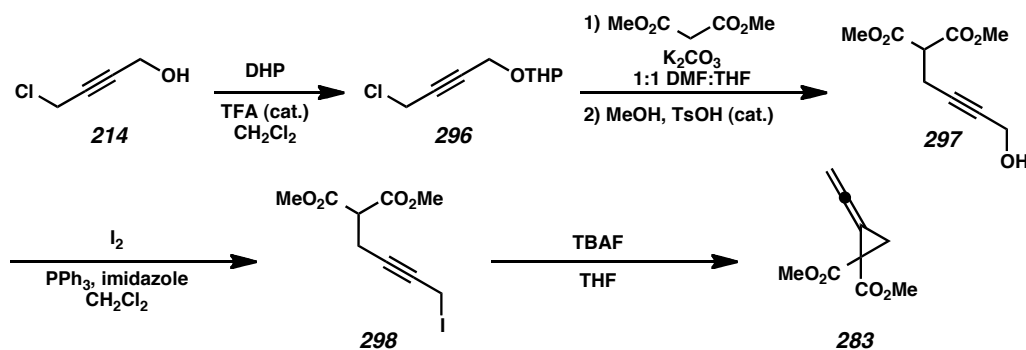


Diene 281. A flame-dried Schlenk tube, equipped with a magnetic stir bar, was charged with cyclopentane **238** (50 mg, 0.13 mmol, 1 equiv) and bis(acetonitrile)dichloropalladium(II) (2.1 mg, 0.007 mmol, 0.05 equiv). The tube was sealed with a rubber septum, and evacuated and backfilled with argon. To the Schlenk were added toluene (1.3 mL, 0.1 M) and acetonitrile (0.020 mL). The reaction mixture was heated, with stirring, at 75 °C in an oil bath for 12 hours. The volatiles were removed and the residue was purified by column chromatography on SiO₂ (6:1 → 3:1 hexanes:EtOAc) to afford diene **281** (14.4 mg, 33% yield) and recovered starting material (23.0 mg, 46% recovery). **281**: ¹H NMR (500 MHz, CDCl₃) δ 7.76 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.46 (td, *J* = 7.6, 1.4 Hz, 1H), 7.38–7.32 (m, 1H), 7.19 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.60 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.70 (d, *J* = 45.0 Hz, 1H), 5.27 (d, *J* = 5.7 Hz, 1H), 5.24 (s, 1H), 3.76 (s, 3H), 3.64 (d, *J* = 17.1 Hz, 1H), 3.17 (s, 3H), 2.93 (d, *J* = 17.1 Hz, 1H).

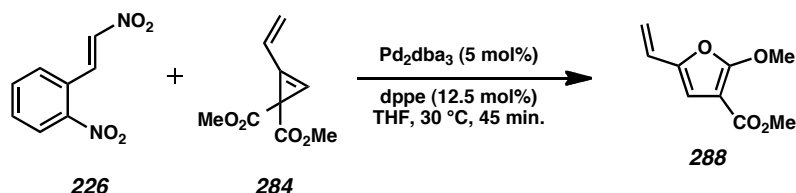


Alkynylcyclopropane 282 and Vinylcyclopropene 284. A 25 mL conical side-arm flask—with a line drawn with a marker indicating 1 mL volume—was fitted with a magnetic stir bar and a dry-ice cold-finger condenser. The joints on the condensor and flask side-arm were sealed with rubber septa, the system was flame-dried under vacuum, and allowed to cool under a positive pressure of nitrogen. The conical flask was charged with bis[rhodium(α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid)] (2.2 mg, 0.0029 mmol, 0.04 mol%) and after reattaching the condenser, the entire system was evacuated

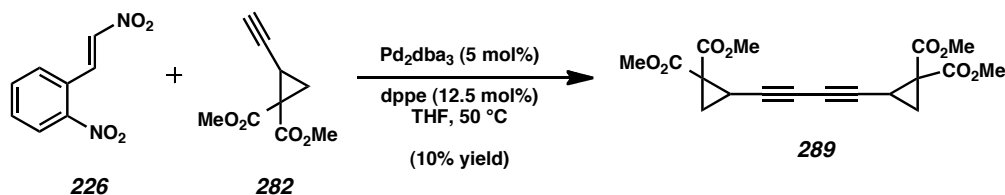
and backfilled with argon. The condenser was charged with dry ice and acetone and the conical flask was lowered into an ice-water bath, then gaseous vinylacetylene (b.p. = 0–6 °C) was introduced into the system with a needle, through the condenser septum until the condensate reached the 1 mL line drawn on the side-arm flask (15 mmol, ~ 2 equiv). The flask was then charged, via the side-arm, with dichloromethane (8.0 mL, 1 M) and diazodimethylmalonate (1.00 mL, 7.98 mmol, 1 equiv), and the cooling bath was removed. After 3.5 hours, a spatula tip of catalyst was added quickly via the side-arm and additional bubbling was observed. After complete conversion of the diazomalonate, the volatiles were removed and the residue was purified by column chromatography on SiO₂ (6:1 → 3:1 hexanes:Et₂O) to afford alkynylcyclopropane **282** (239.7 mg, 16% yield) as a clear oil and vinylcyclopropene **284** (468.0 mg, 32% yield) as an oil which solidifies upon refrigeration. **282**: ¹H NMR (400 MHz, CDCl₃) δ 3.81 (s, 3H), 3.75 (s, 3H), 2.47 (ddd, *J* = 9.4, 7.3, 2.2 Hz, 1H), 1.97 (d, *J* = 2.2 Hz, 1H), 1.86 (dd, *J* = 7.3, 4.7 Hz, 1H), 1.59 (dd, *J* = 9.3, 4.7 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 168.9, 79.6, 68.6, 53.0, 52.9, 35.8, 21.9, 16.3. **284**: ¹H NMR (400 MHz, CDCl₃) δ 6.68–6.66 (m, 1H), 6.47 (dd, *J* = 17.0, 10.3 Hz, 1H), 5.82–5.71 (m, 2H), 3.66 (s, 6H).



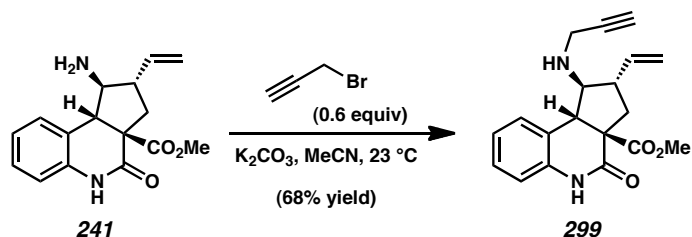
Vinylidenecyclopropane 283. Prepared according to the method of Johnson and coworkers.⁵



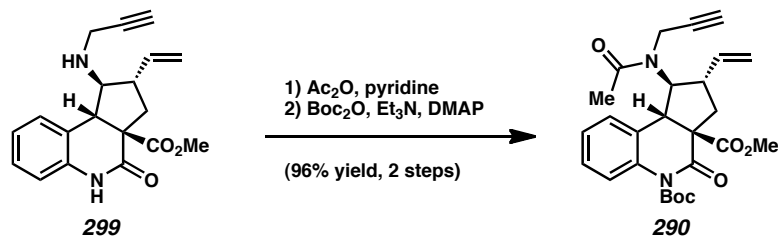
Furan 288. Set up under standard (3 + 2) conditions (see compound **238**, chapter 2). Complete conversion of the cyclopropane was observed in less than 45 minutes. The reaction mixture was dry-loaded onto SiO₂ and purified by column chromatography (20:1 → 10:1 hexanes:EtOAc) to afford furan **288** (no yield was obtained): ¹H NMR (500 MHz, CDCl₃) δ 6.44 (d, *J* = 1.4 Hz, 1H), 6.32 (ddd, *J* = 17.4, 11.4, 1.4 Hz, 1H), 5.47 (d, *J* = 17.5 Hz, 1H), 5.09 (d, *J* = 11.3 Hz, 1H), 4.15 (s, 3H), 3.79 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 163.3, 161.6, 143.0, 124.0, 110.9, 109.6, 92.6, 58.0, 51.3.



Diyne 289. Setup under standard (3 + 2) conditions (see compound **238**, chapter 2). No conversion was observed at 30 °C over 3 hours. Heated to 50 °C for an additional 1.5 hours. Reaction halted and purified by column chromatography in spite of incomplete conversion of cyclopropane to afford diyne **289**: ¹H NMR (300 MHz, CDCl₃) δ 3.81 (s, 6H), 3.75 (s, 6H), 2.49 (dd, *J* = 9.2, 7.2 Hz, 2H), 1.87 (dd, *J* = 7.2, 4.8 Hz, 2H), 1.61 (dd, *J* = 9.2, 4.7 Hz, 2H).

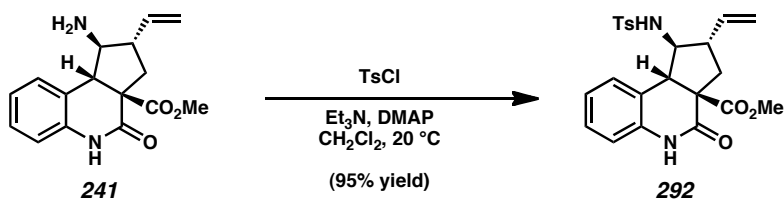


Propargylamine 299. An oven-dried vial equipped with a magnetic stir bar was charged with amine **241** (100.7 mg, 0.35 mmol, 1.67 equiv) and potassium carbonate (49.3 mg, 0.35 mmol, 1.67 equiv). The vial was sealed with a cap lined with a Teflon septum, and placed under an inert atmosphere. Acetonitrile (0.70 mL) was added, followed by propargyl bromide (0.024 mL, 80 wt% in toluene, 0.21 mmol, 1 equiv), and the resulting reaction mixture was stirred at ambient temperature for 5.5 hours. The reaction mixture was filtered through Celite, dry-loaded onto SiO₂ (~1 mL), and purified by column chromatography on SiO₂ (5:3 hexanes:EtOAc until product eluted, then 20:1 CHCl₃) to afford recovered amine **241** (53.6 mg, 53% rsm) and propargyl amine **299** (46.9 mg, 68% yield, 41% of **241**): ¹H NMR (400 MHz, CDCl₃) δ 9.04 (d, *J* = 2.8 Hz, 1H), 7.21–7.13 (m, 2H), 6.96 (td, *J* = 7.5, 1.2 Hz, 1H), 6.81 (dd, *J* = 7.9, 1.2 Hz, 1H), 5.68 (ddd, *J* = 16.9, 10.0, 8.5 Hz, 1H), 5.10 (dd, *J* = 17.0, 1.2 Hz, 1H), 4.99 (dd, *J* = 10.1, 1.6 Hz, 1H), 3.52 (s, 3H), 3.27 (d, *J* = 10.5 Hz, 1H), 3.21 (dd, *J* = 17.1, 2.4 Hz, 1H), 3.11 (dd, *J* = 17.1, 2.4 Hz, 1H), 2.83 (dd, *J* = 10.5, 9.1 Hz, 1H), 2.77–2.67 (m, 1H), 2.60–2.48 (m, 2H), 1.99 (t, *J* = 2.4 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 172.0, 170.1, 140.1, 135.6, 129.0, 128.6, 123.6, 121.8, 116.7, 115.9, 82.1, 71.6, 66.4, 56.0, 54.0, 53.2, 49.1, 37.6, 37.0.



Propargyl acetamide 290. An oven-dried vial equipped with a magnetic stir bar was charged with propargyl amine **299** (14.7 mg, 0.046 mmol, 1 equiv), sealed with a cap lined with a Teflon septum, and placed under an inert atmosphere. To the vial were added dichloromethane (0.100 mL), pyridine (0.037 mL, 0.46 mmol, 10 equiv), and acetic anhydride (0.022 mL, 0.23 mmol, 5 equiv). After 24 hours of stirring, toluene was added to and evaporated from the solution twice to remove excess pyridine. Hexanes was added, and a white precipitate was observed. The solvent was then removed in vacuo to afford a crude acetate which was carried forward without further purification.

A vial was charged with the crude acetate, di-*tert*-butyl dicarbonate (14.3 mg, 0.054 mmol, 1.2 equiv), 4-(*N,N*-dimethylamino)pyridine (unspecified), dichloromethane (0.200 mL), and triethylamine (0.012 mL, 0.068 mmol, 1.5 equiv). Complete consumption of starting material was observed after 90 minutes, and the reaction mixture was dry-loaded onto SiO₂ and purified by column chromatography (3:1 hexanes:EtOAc) to afford propargyl acetamide **290** (20.3 mg, 96% yield, two steps).



Toluenesulfonamide 292. An oven-dried 1 dram vial, equipped with a magnetic stir bar, was charged with amine **241** (100.4 mg, 0.35 mmol, 1 equiv), tosyl chloride (79.8 mg, 0.38 mmol, 1.1 equiv) and 4-(*N,N*-dimethylamino)pyridine (4.5 mg, 0.038 mmol, 0.1 equiv). The vial was sealed with a cap lined with a Teflon septum, and placed under nitrogen atmosphere. Dichloromethane (1.8 mL) was added to the vial, followed by freshly distilled triethylamine (0.08 mL, 0.5 mmol, 1.5 equiv), and the reaction mixture was stirred for 6.5 hours. The reaction mixture was dry-loaded onto SiO₂ (~1.5 mL) and purified by column chromatography on SiO₂ (3:1 hexanes:EtOAc until excess TsCl eluted, then 1:1 hexanes:EtOAc) to afford toluenesulfonamide **292** (146.2 mg, 95% yield): ¹H NMR (500 MHz, CDCl₃) δ 7.86 (s, 1H), 7.46 (d, *J* = 8.3 Hz, 3H), 7.20 (td, *J* = 7.7, 1.4 Hz, 1H), 7.14–7.08 (m, 2H), 6.87 (td, *J* = 7.5, 1.1 Hz, 1H), 6.75 (d, *J* = 7.9 Hz, 1H), 5.39 (ddd, *J* = 17.2, 9.9, 7.3 Hz, 1H), 4.92 (d, *J* = 17.0 Hz, 1H), 4.82–4.72 (m, 2H), 3.63 (s, 3H), 3.43–3.36 (m, 1H), 3.32 (d, *J* = 11.0 Hz, 1H), 2.77–2.67 (m, 1H), 2.62–2.51 (m, 2H), 2.39 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 171.7, 168.4, 143.1, 138.2, 136.8, 134.8, 129.8, 129.4, 128.5, 126.8, 123.7, 119.7, 117.0, 115.0, 64.2, 54.9, 53.3, 53.2, 49.0, 36.0, 21.5.

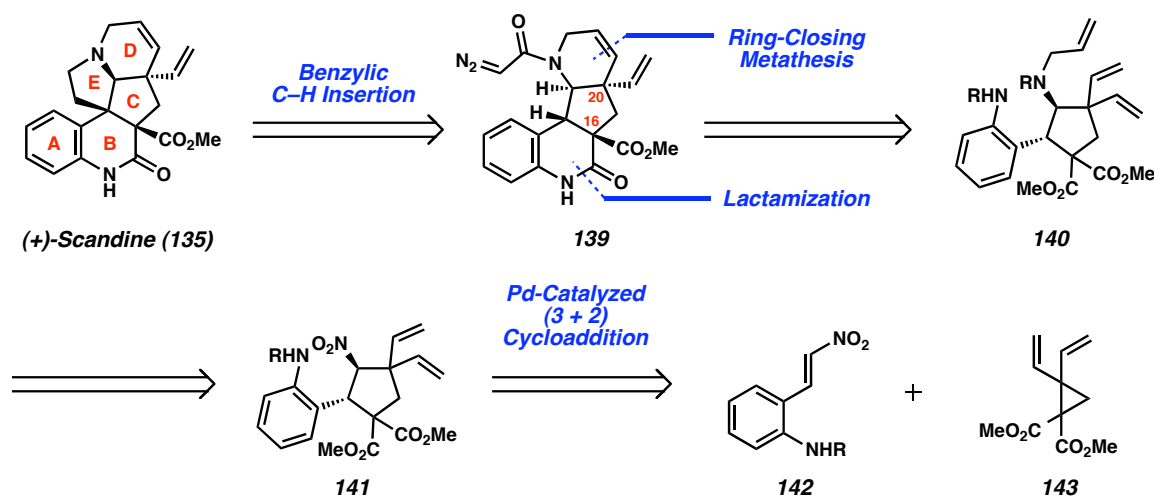
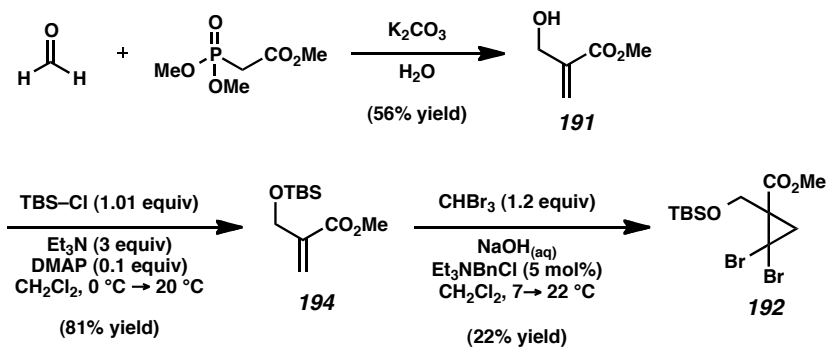
A4.5 NOTES AND REFERENCES

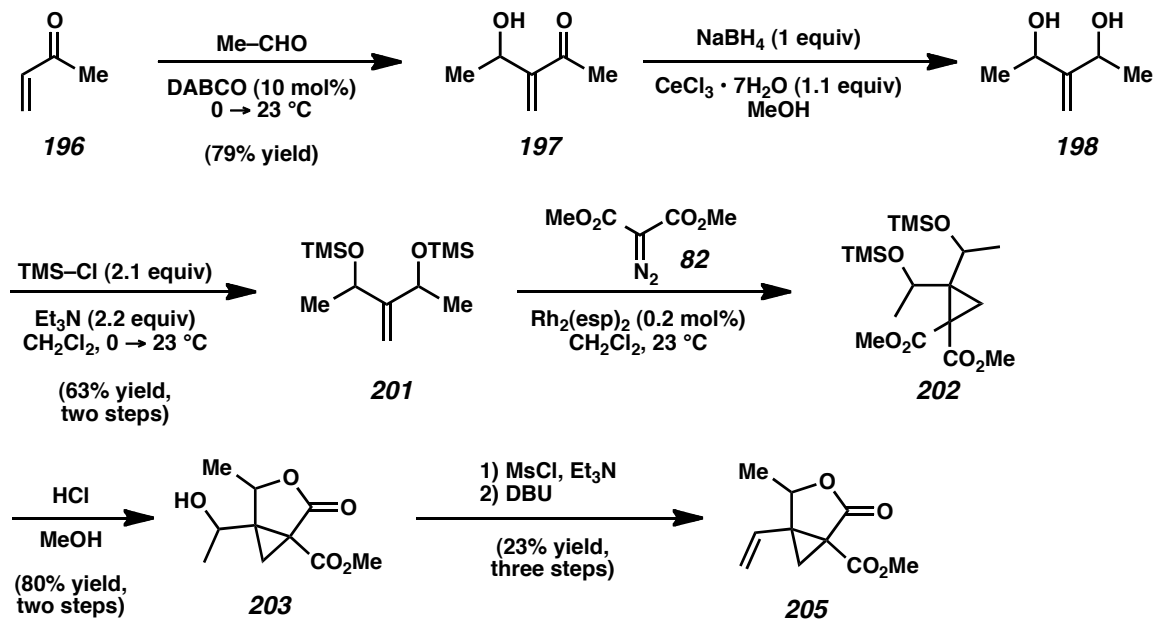
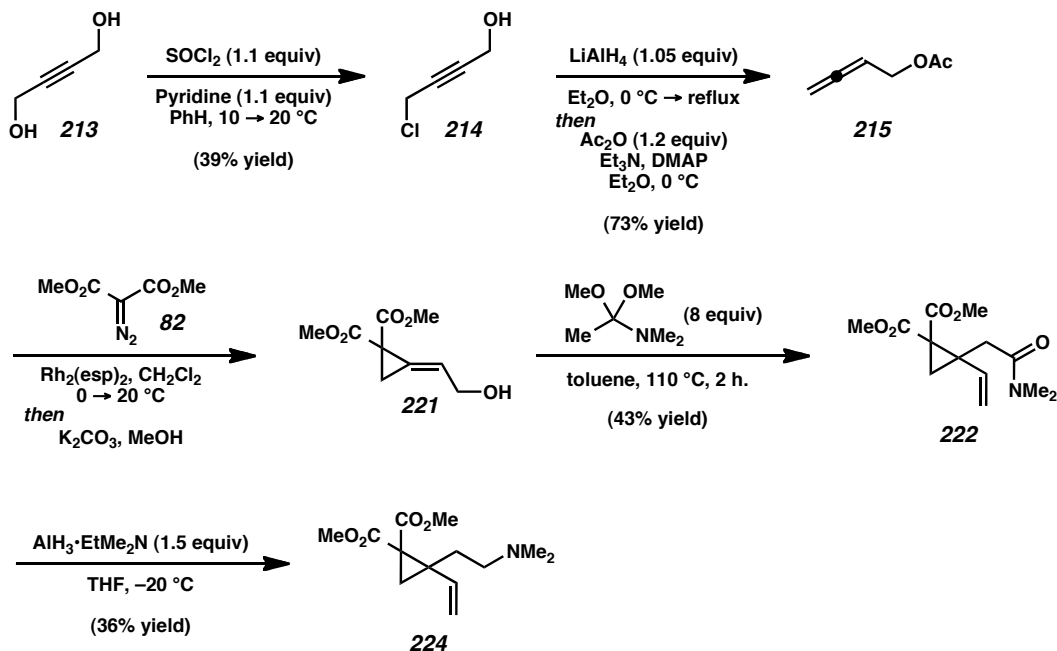
- (1) Observed via LCMS
- (2) An intramolecular Heck reaction would be the most likely method to successfully install the quaternary center at this position. This approach has been employed in several natural product syntheses. See: (a) Overman, L. E. *Pure & Appl. Chem.* **1994**, *66*, 1423–1430. (b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2963. MacMillan used a similar intramolecular Heck reaction in the total synthesis of aspidospermidine: (c) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183–188.
- (3) (a) Knorr, R. *Chem. Rev.* **2004**, *104*, 3795–3849. (b) Stang, P. J. *Acc. Chem. Res.* **1982**, *15*, 348–354. (c) Stang, P. J. *Acc. Chem. Res.* **1978**, *11*, 107–114. (d) Stang, P. J. *Chem. Rev.* **1978**, *78*, 383–405. (d) Barluenga, J.; Sigüeiro, R.; Vicente, R.; Ballesteros, A.; Tomás, M.; Rodríguez, M. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 10377–10381. (e) Vadola, P. A.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 16525–16528. (f) Feldman, K. S.; Bruendl, M. M.; Schildknecht, K.; Bohnstedt, A. C. *J. Org. Chem.* **1996**, *61*, 5440–5452. (g) Feldman, K. S.; Wroblewski, M. L. *Org. Lett.* **2000**, *2*, 2603–2605.
- (4) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.
- (5) Campbell, M. J.; Pohlhaus, P. D.; Min, G.; Ohmatsu, K.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 9180–9181. (b) THP protected precursor to **297** was

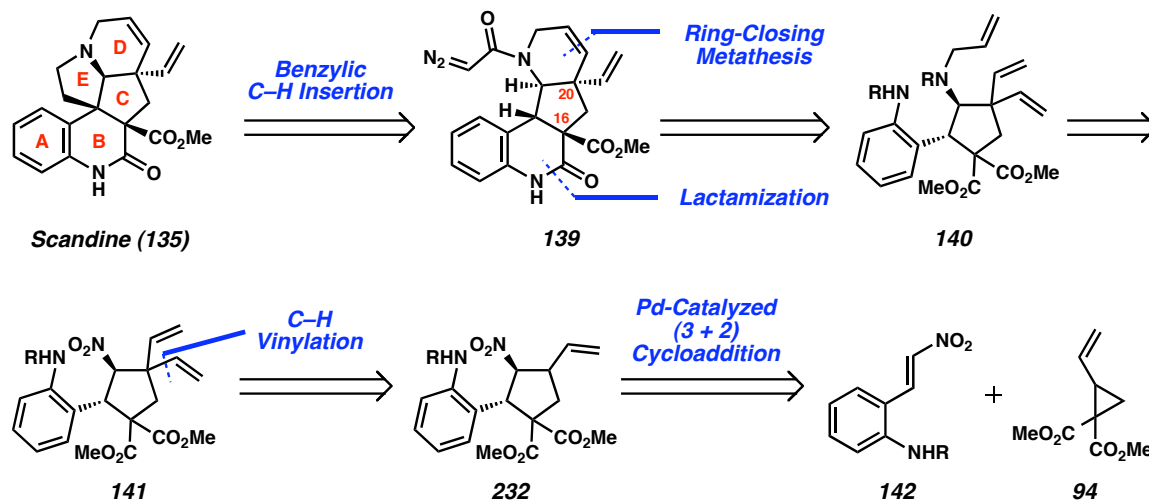
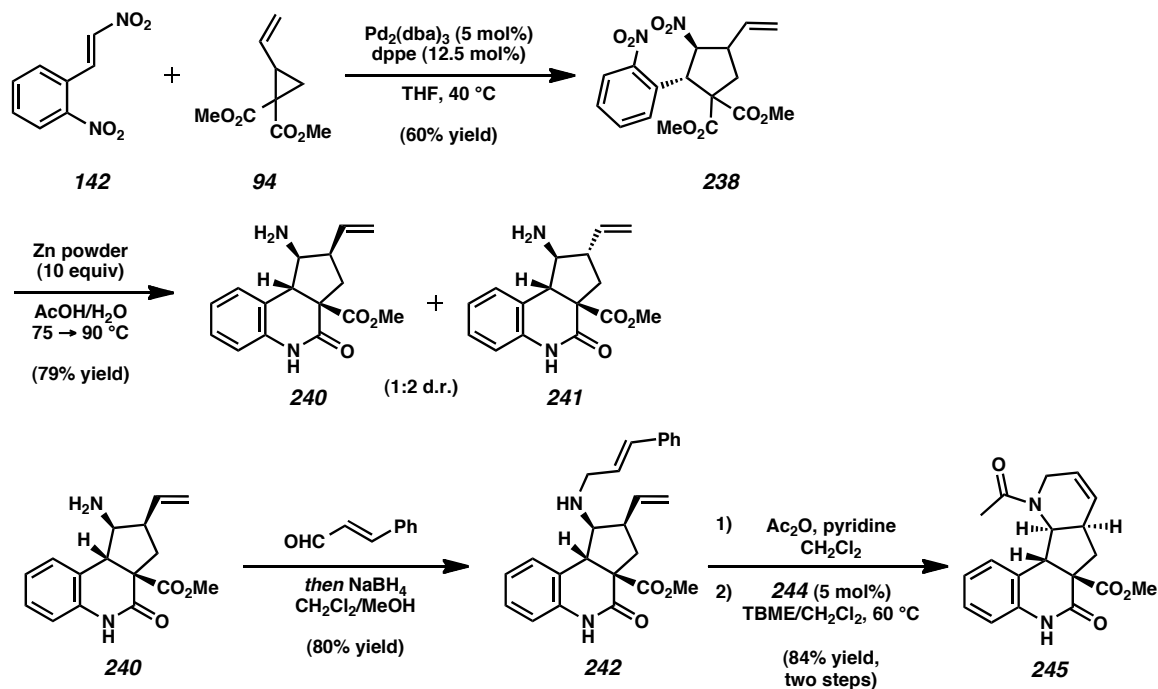
prepared according to the method described in: Deslongchamps, P.; Lamothe, S.; Lin, H.-S. *Can. J. Chem.* **1984**, 62, 2395–2398.

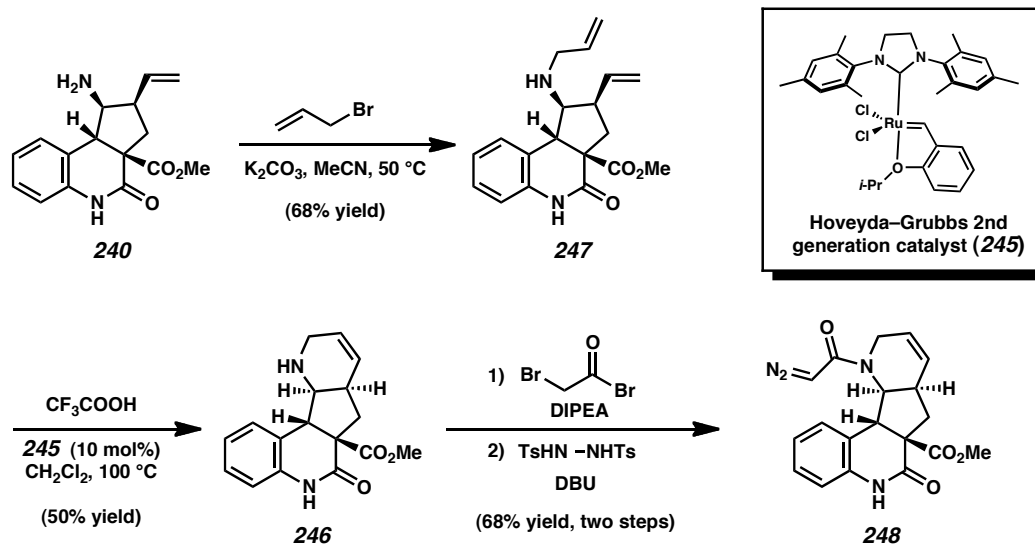
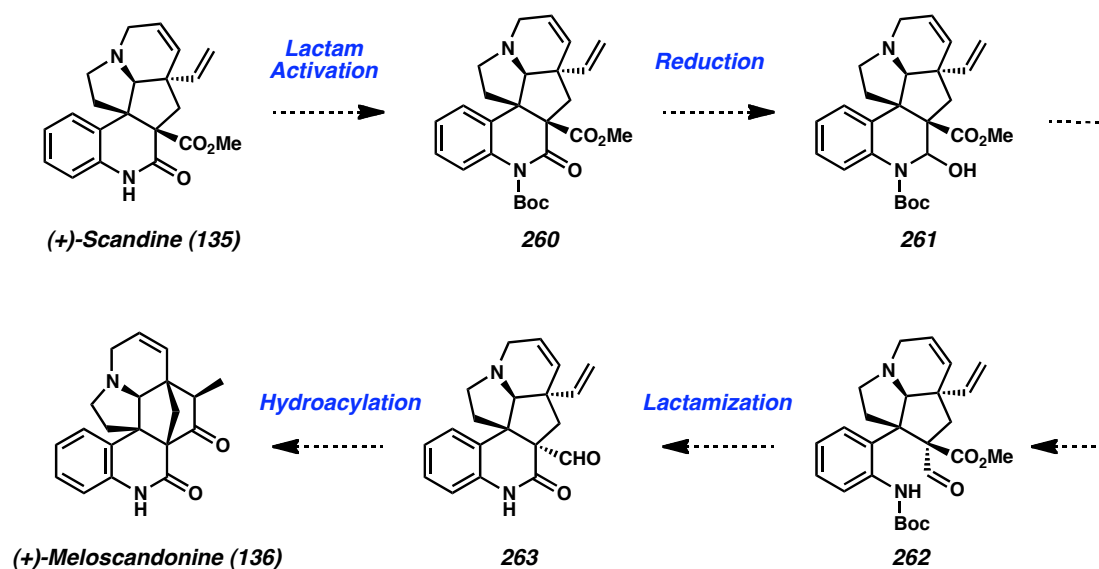
APPENDIX 5

*Synthetic Summary toward the Total Synthesis of
Scandine and the Melodinus Alkaloids*

Scheme A5.1 Original retrosynthetic analysis of scandine (**135**)Scheme A5.2 Synthesis of dibromocyclopropane **192**

Scheme A5.3. Synthesis of bicyclic vinylcyclopropane **205**Scheme A5.4. Synthesis of vinylcyclopropane **224**

Scheme A5.5. Revised retrosynthesis of scandine (**135**)Scheme A5.6. Synthesis of tetracycle **245**

Scheme A5.7. Synthesis of diazoacetamide **248**Scheme A5.8. Proposed conversion of scandine (**135**) to meloscandonine (**136**)

APPENDIX 6

Spectra Relevant to Chapter 2:

*Progress toward the Total Synthesis of
Scandine and the Melodinus Alkaloids*

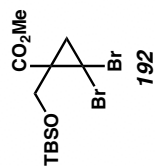


Figure A6.1 ^1H NMR (300 MHz, CDCl_3) of compound **192**

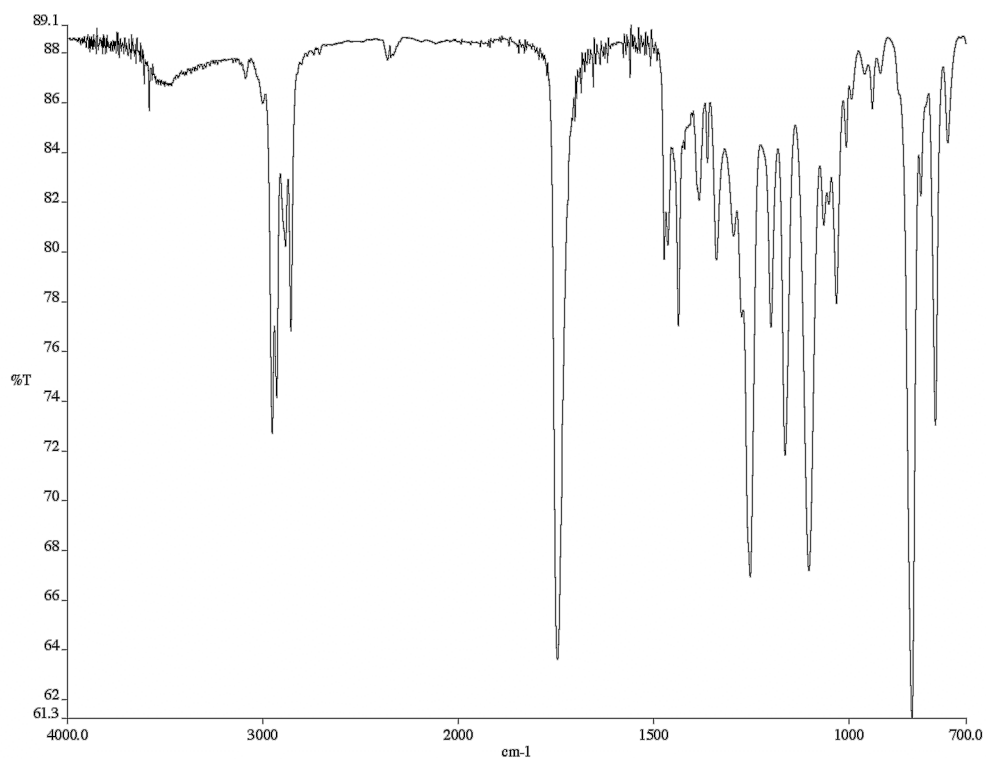


Figure A6.2 Infrared spectrum (thin film/NaCl) of compound **192**

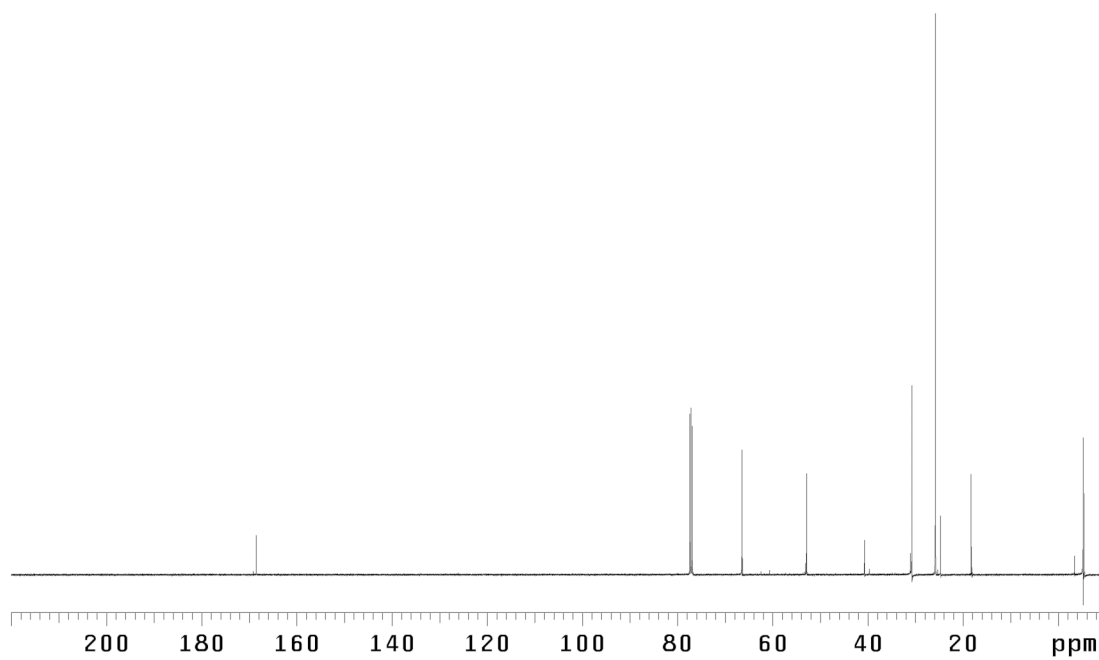


Figure A6.3 ¹³C NMR (126 MHz, CDCl₃) of compound **192**

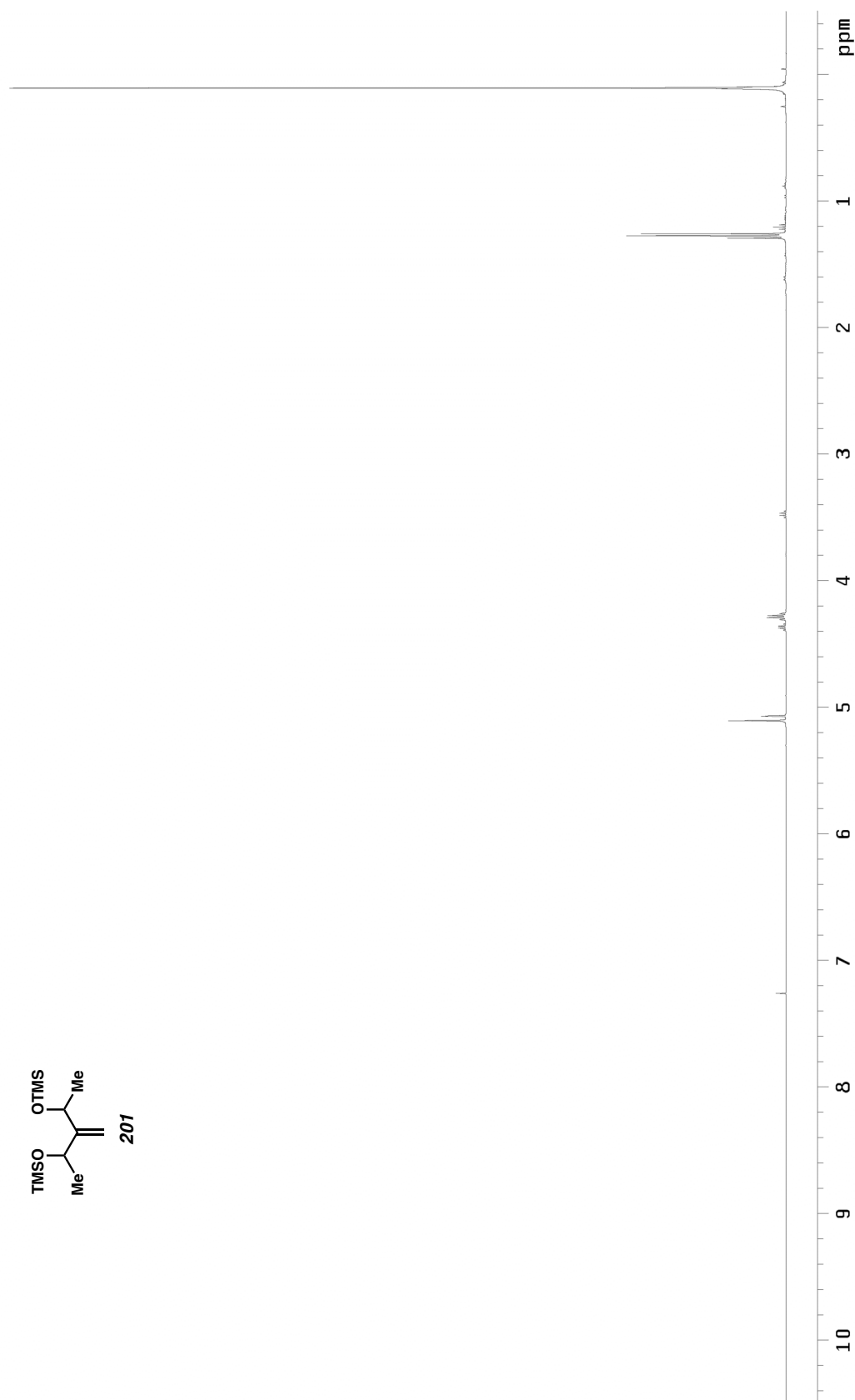


Figure A6.4 ¹H NMR (400 MHz, CDCl₃) of compound **201**

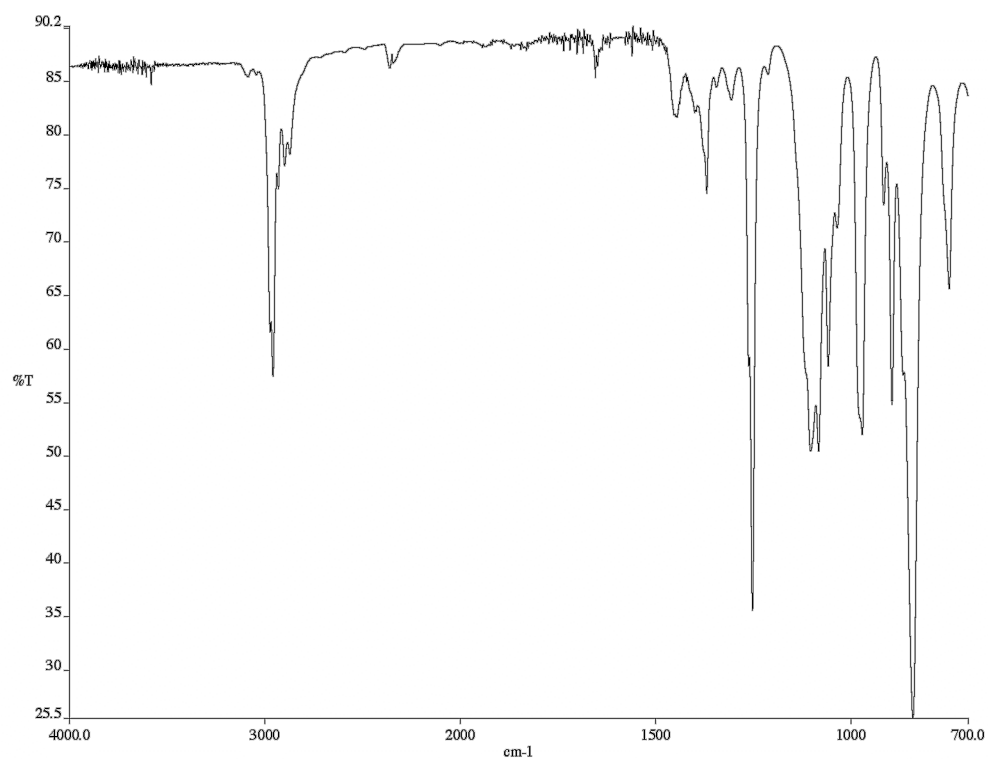


Figure A6.5 Infrared spectrum (thin film/NaCl) of compound **201**

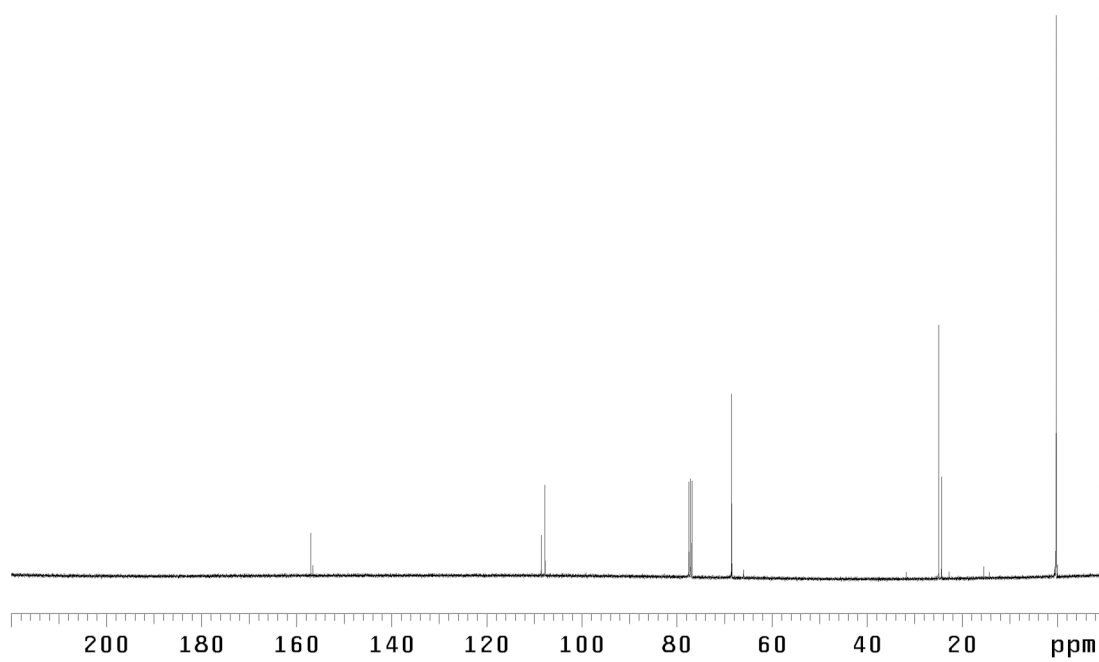


Figure A6.6 ¹³C NMR (100 MHz, CDCl₃) of compound **201**

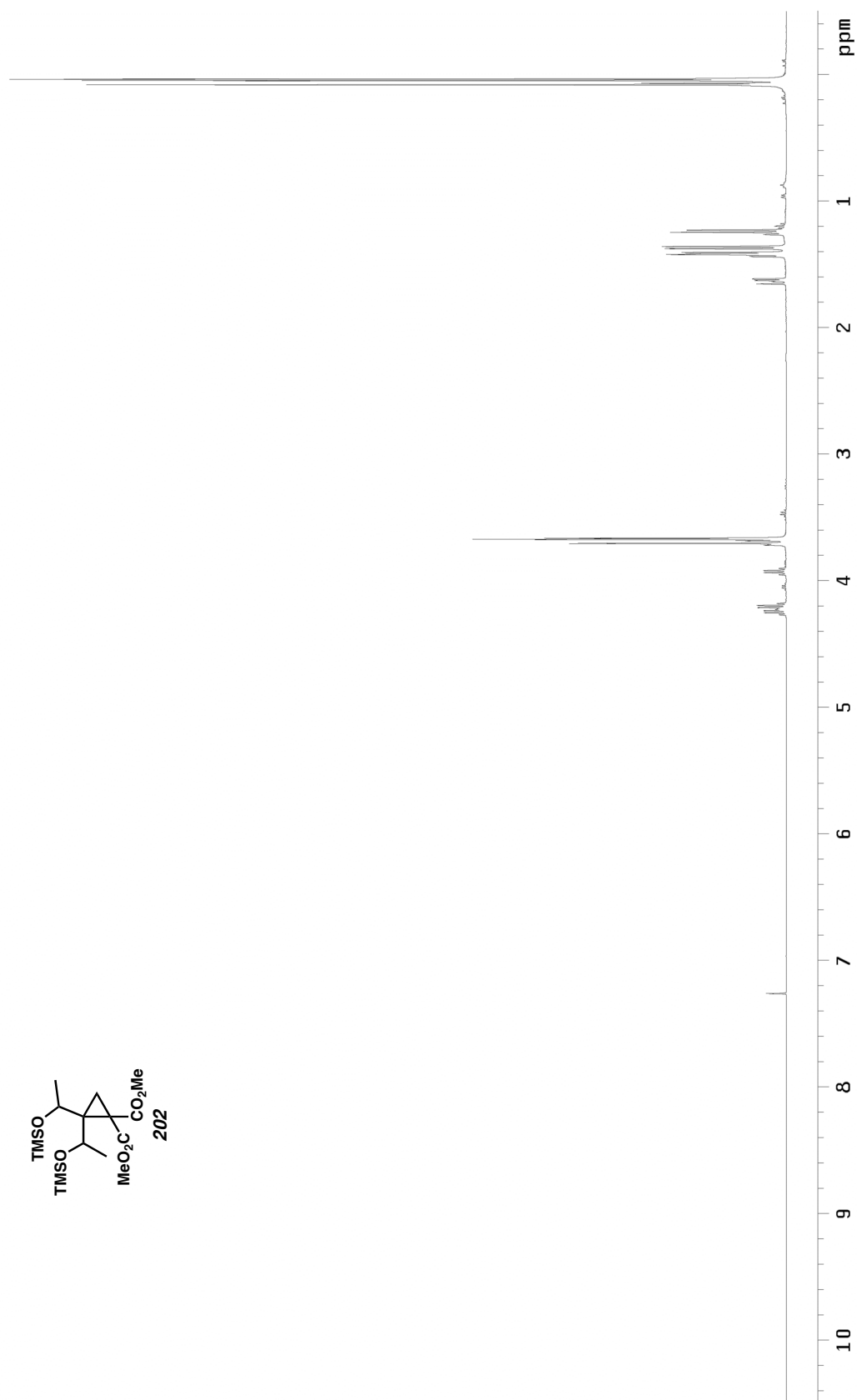


Figure A6.7 ^1H NMR (400 MHz, CDCl_3) of compound **202**

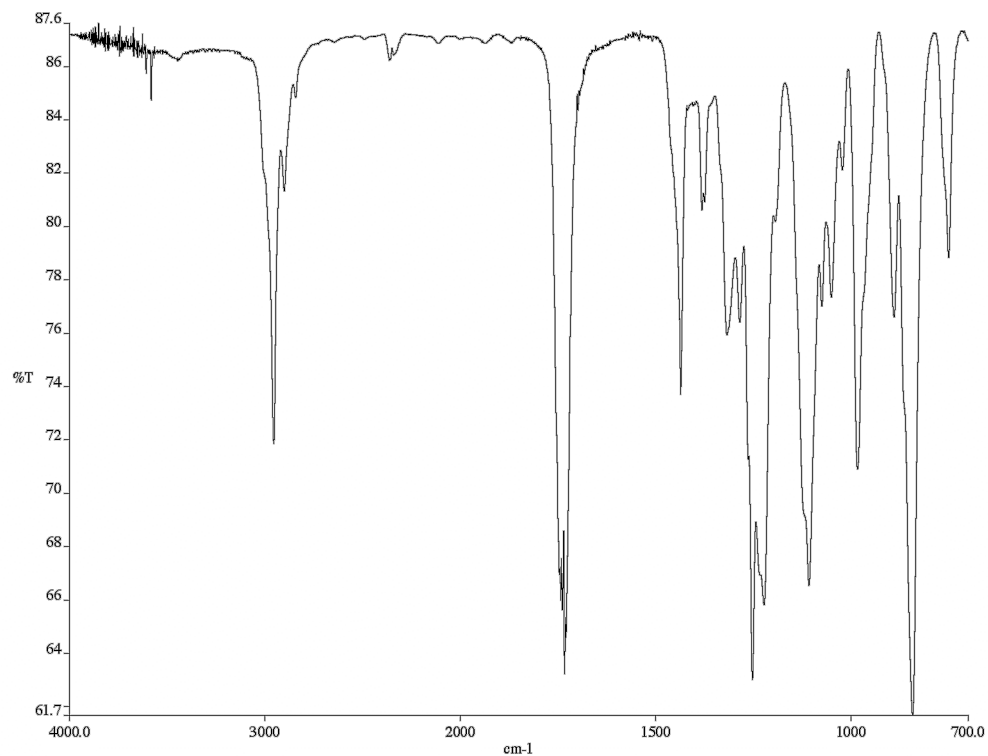


Figure A6.8 Infrared spectrum (thin film/NaCl) of compound **202**

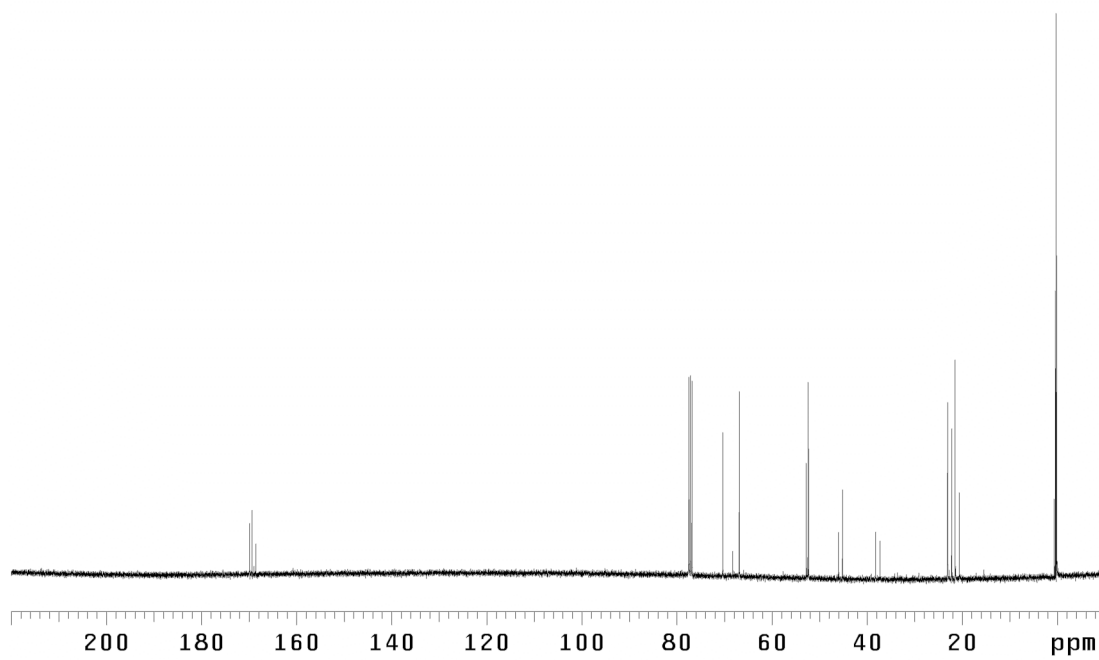


Figure A6.9 ¹³C NMR (100 MHz, CDCl₃) of compound **202**

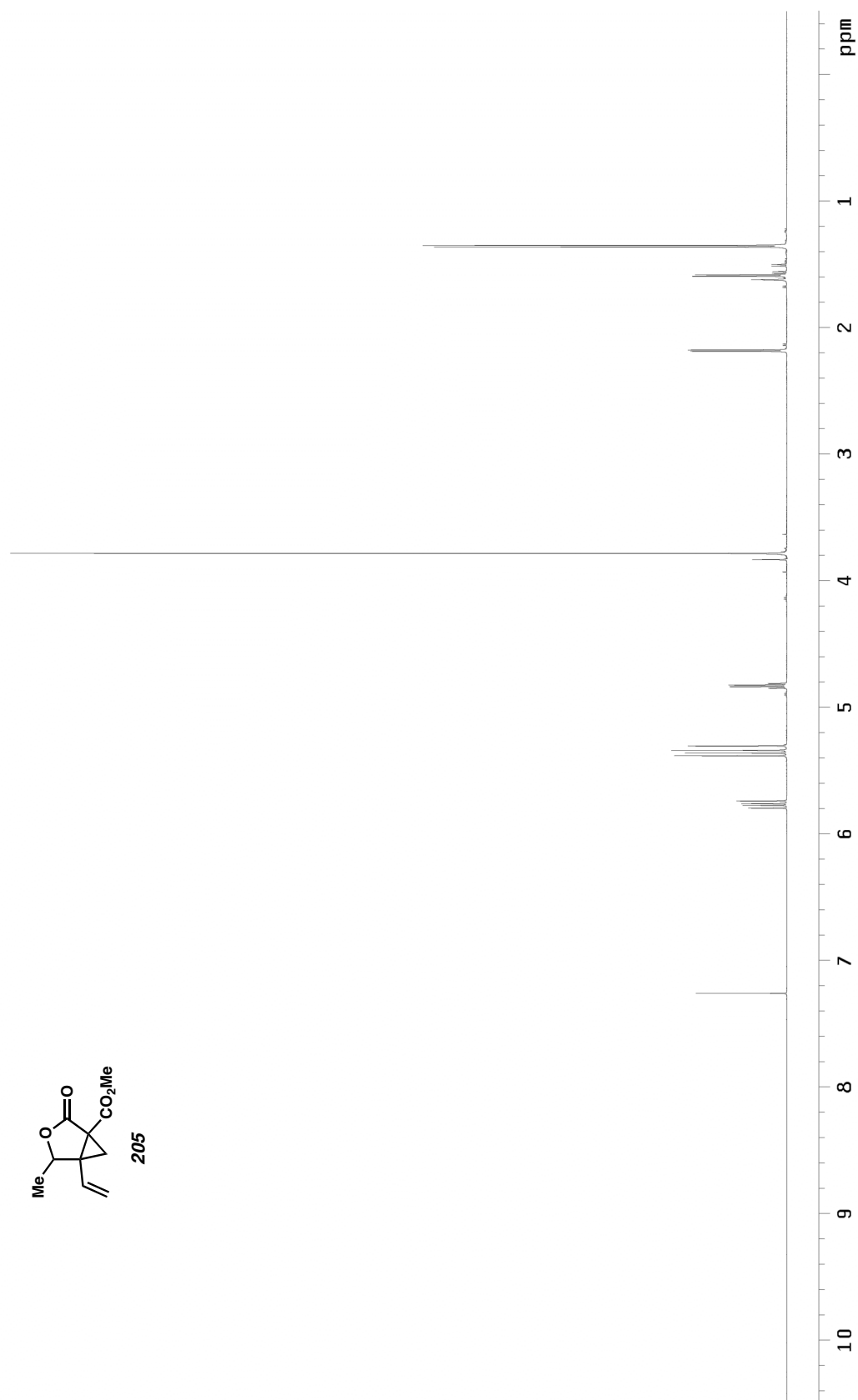


Figure A6.10 ^1H NMR (500 MHz, CDCl_3) of compound **205**

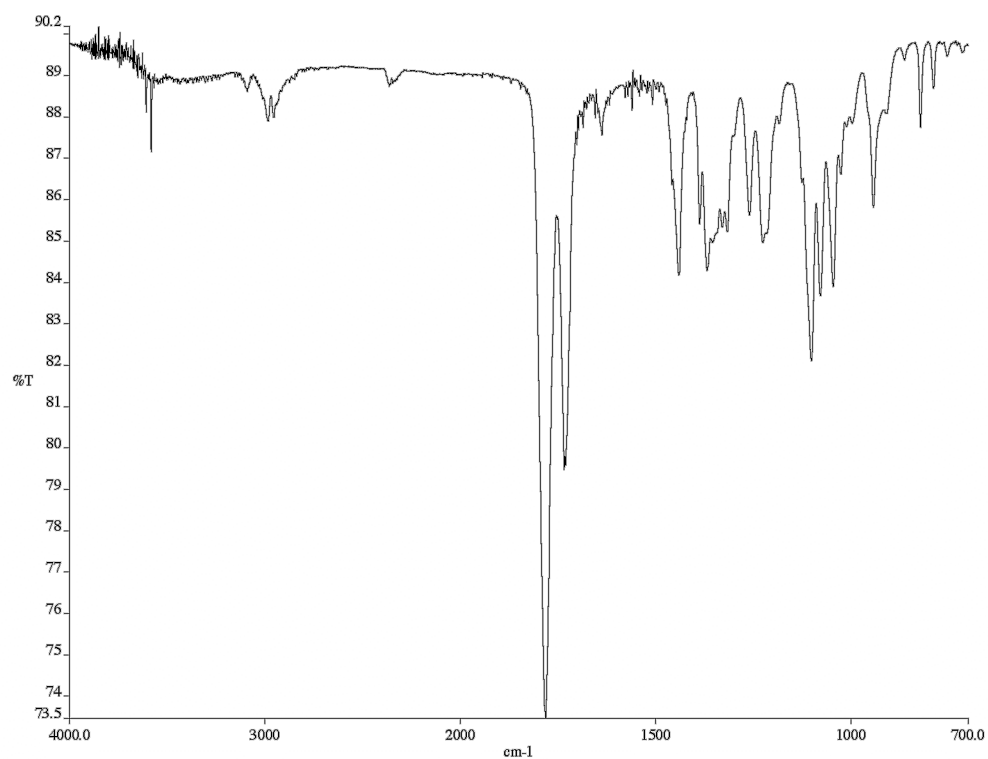


Figure A6.11 Infrared spectrum (thin film/NaCl) of compound **205**

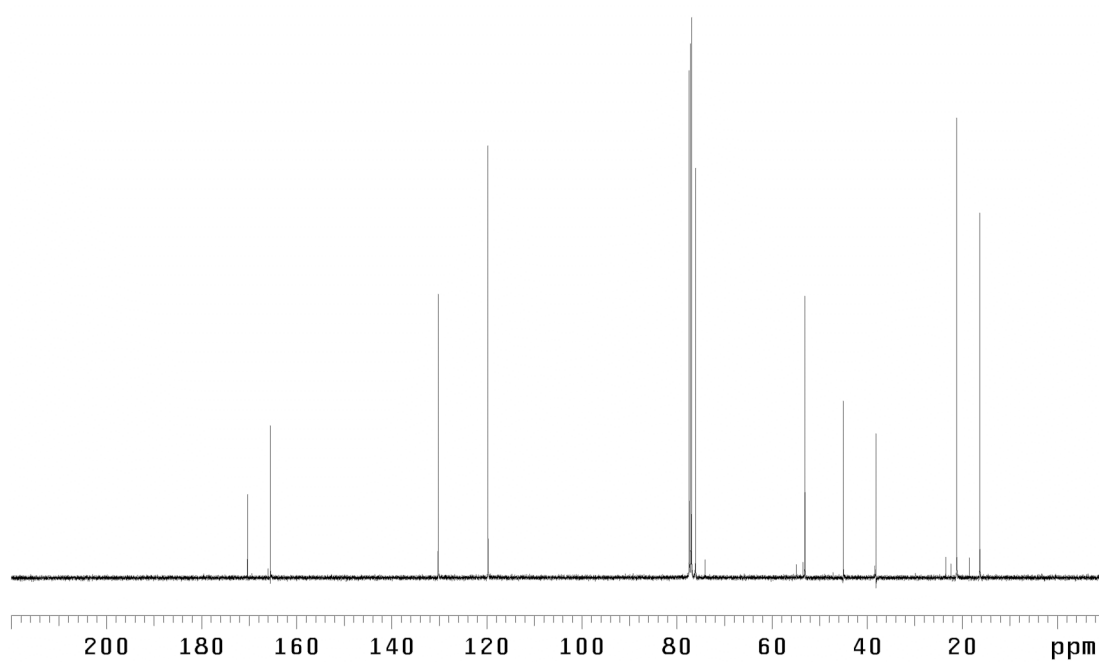


Figure A6.12 ¹³C NMR (126 MHz, CDCl₃) of compound **205**

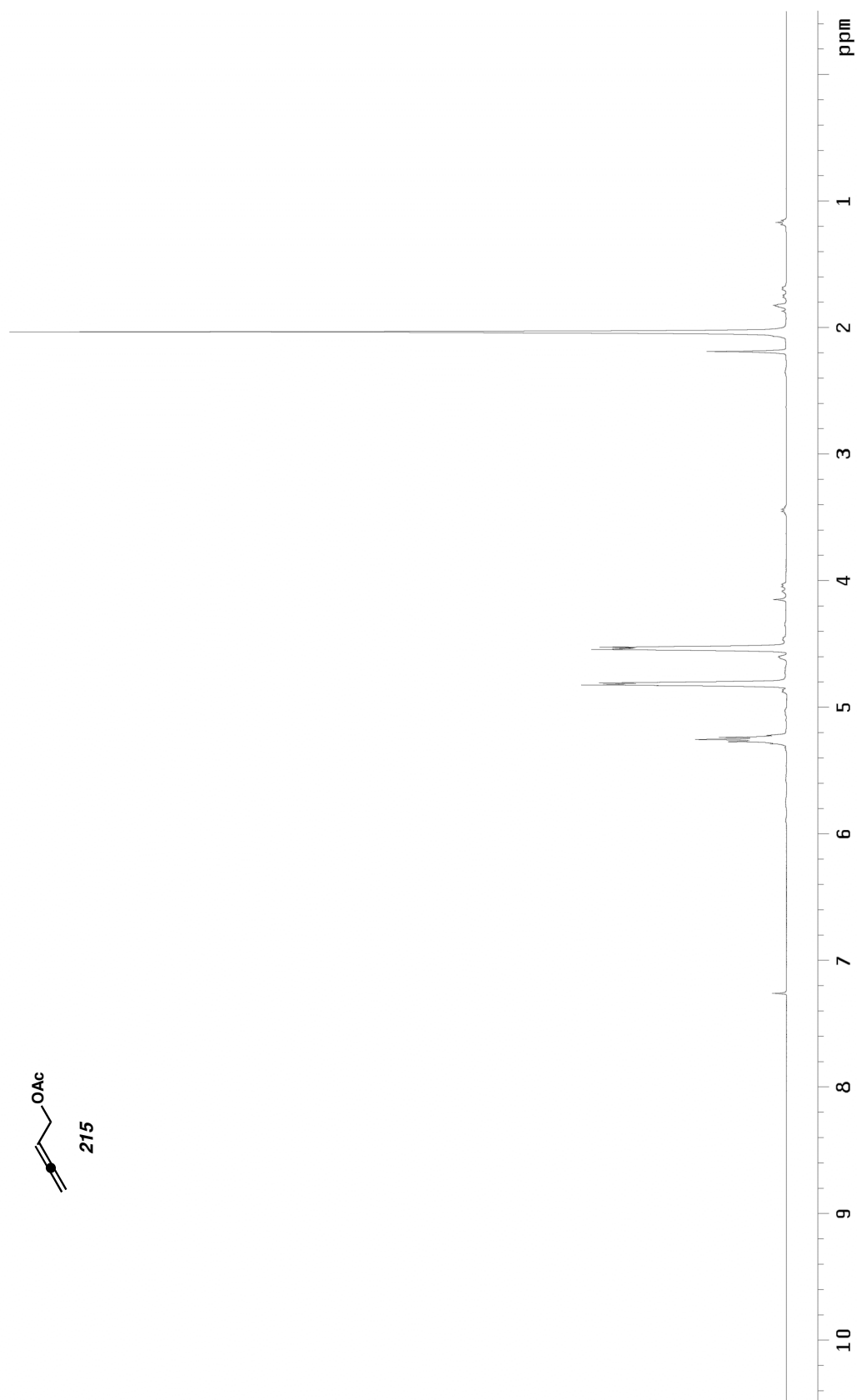


Figure A6.13 ^1H NMR (400 MHz, CDCl_3) of compound **215**

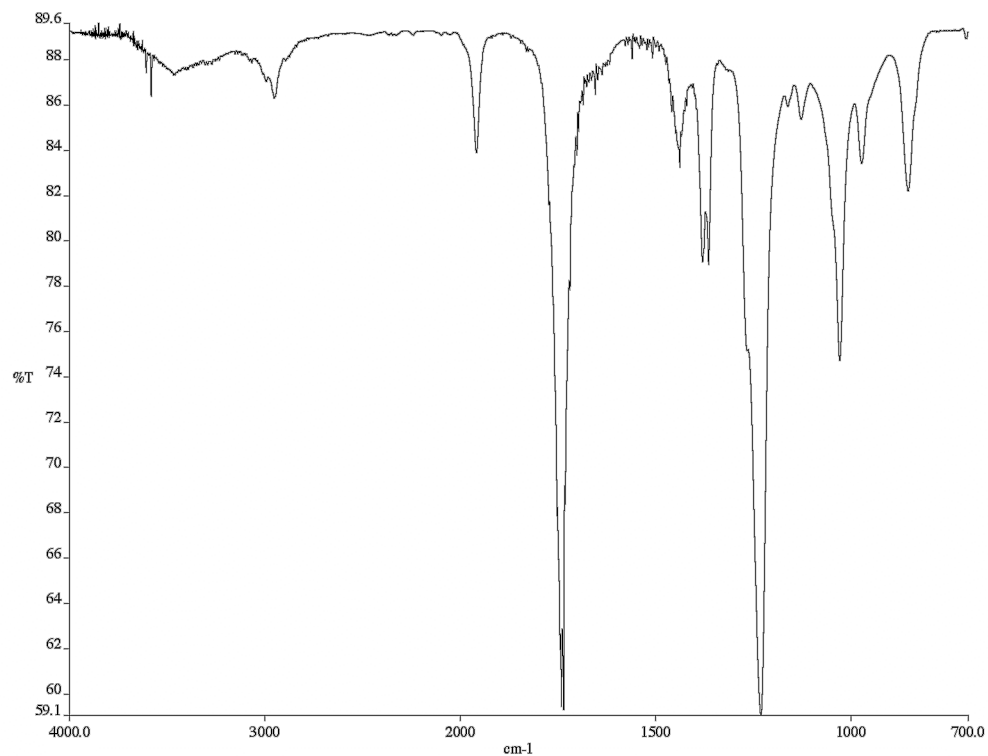


Figure A6.14 Infrared spectrum (thin film/NaCl) of compound **215**

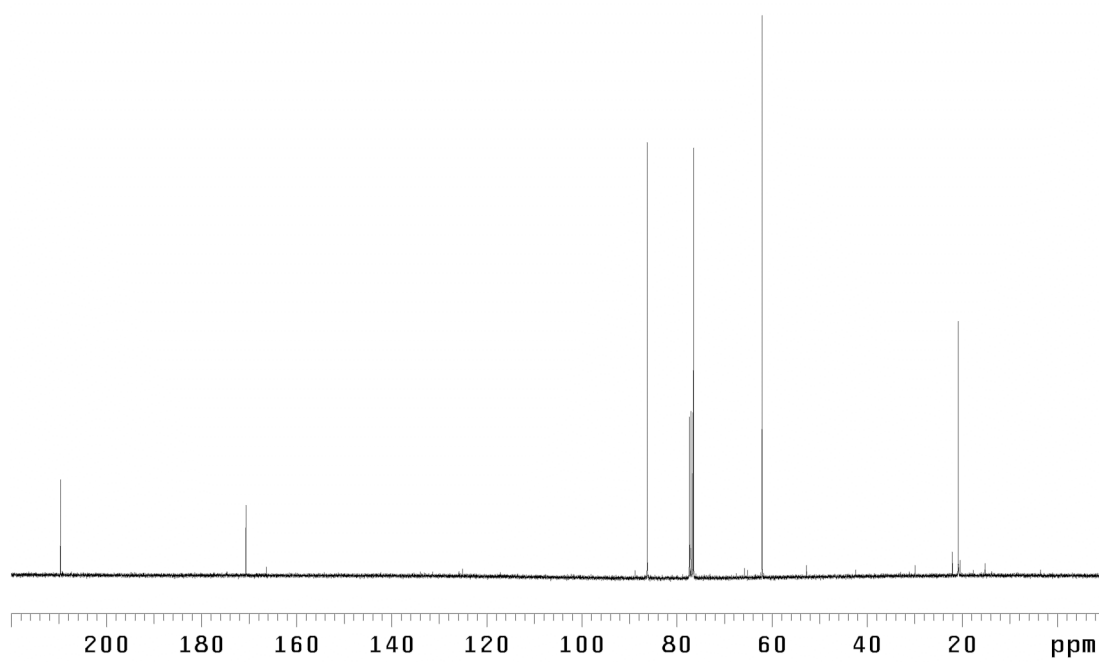


Figure A6.15 ¹³C NMR (100 MHz, CDCl₃) of compound **215**

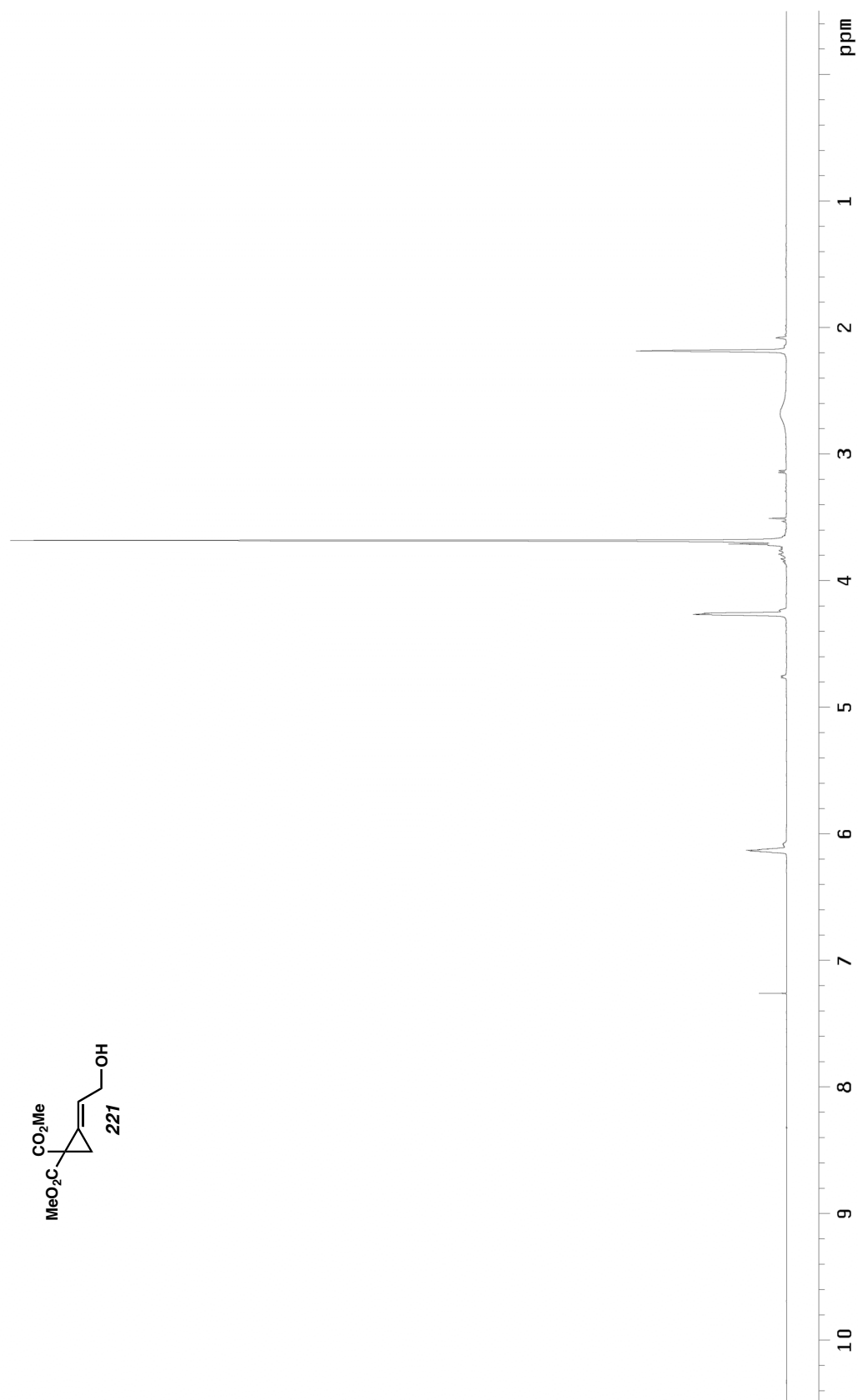


Figure A6.16 ¹H NMR (500 MHz, CDCl₃) of compound **221**

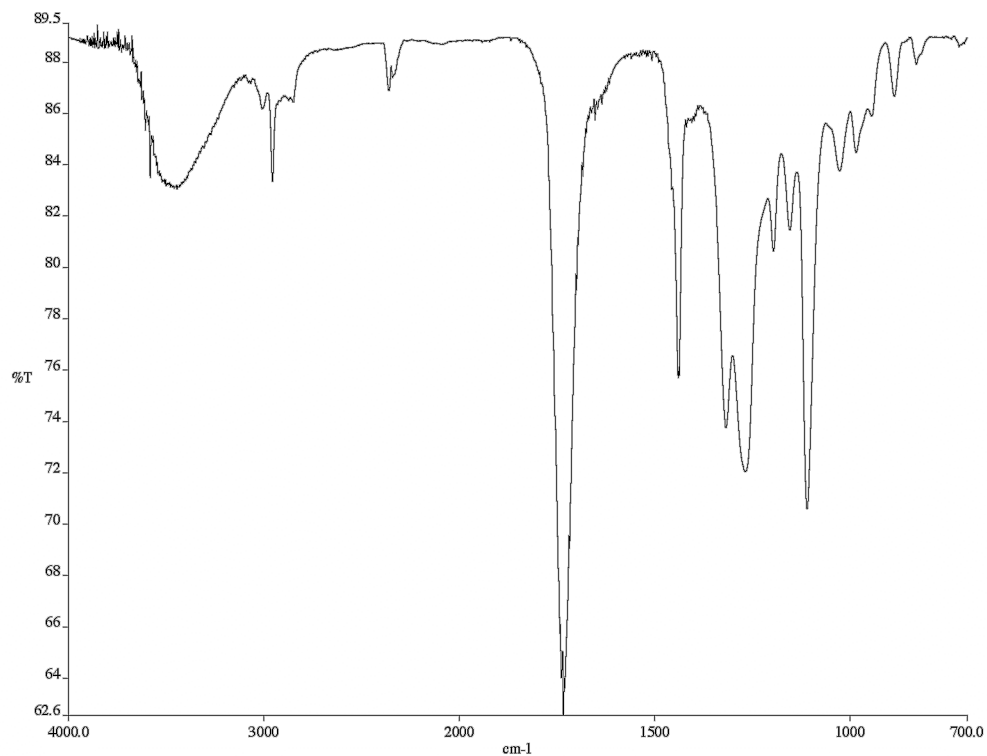


Figure A6.17 Infrared spectrum (thin film/NaCl) of compound **221**

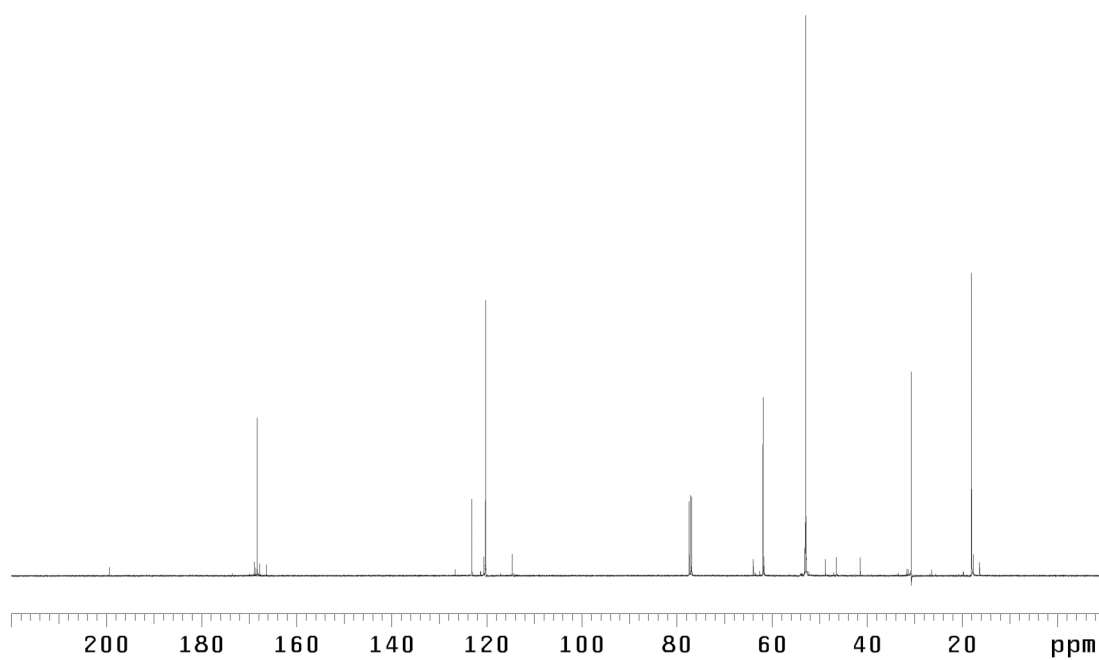


Figure A6.18 ¹³C NMR (126 MHz, CDCl₃) of compound **221**

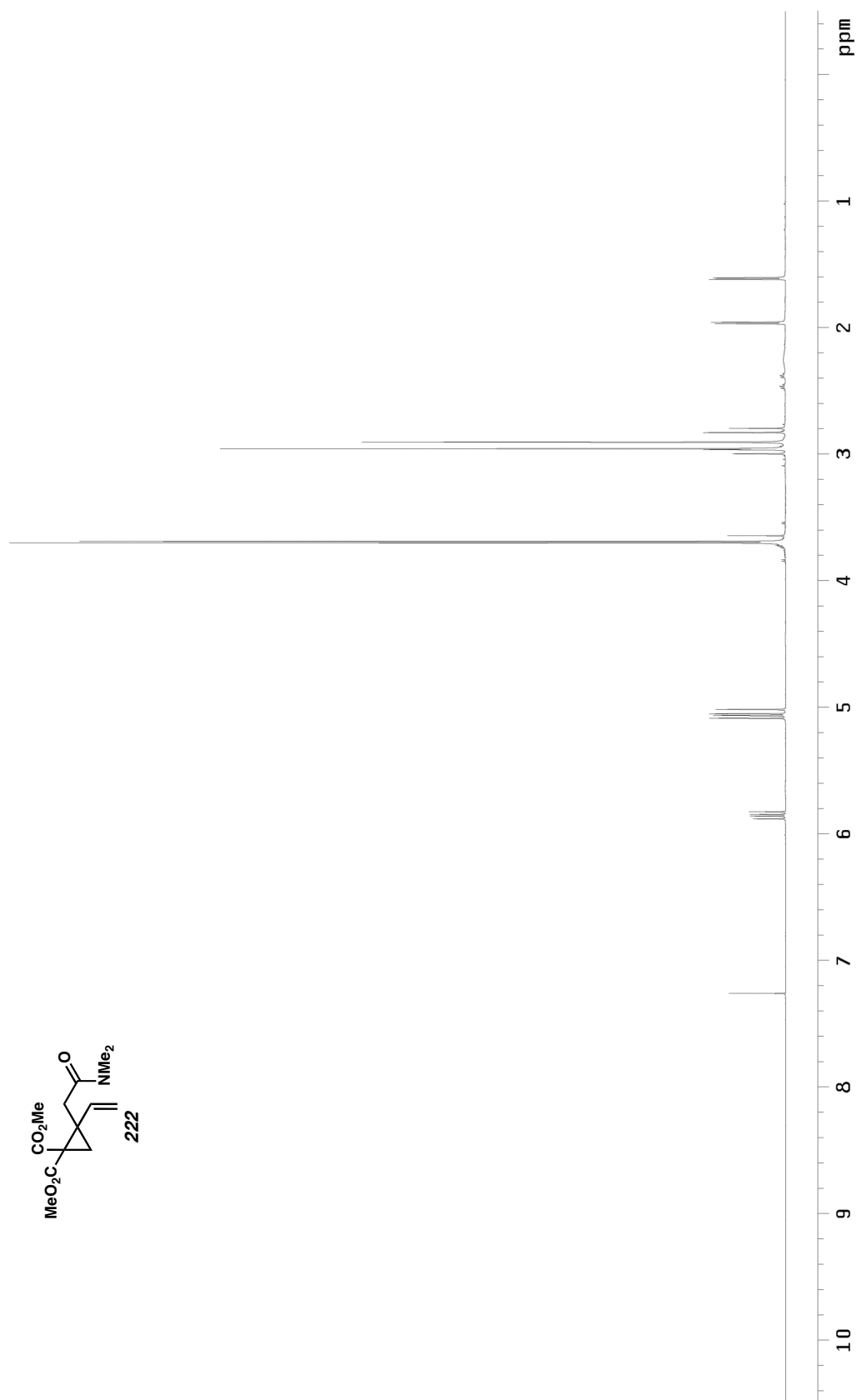


Figure A6.19 ^1H NMR (500 MHz, CDCl_3) of compound **222**.

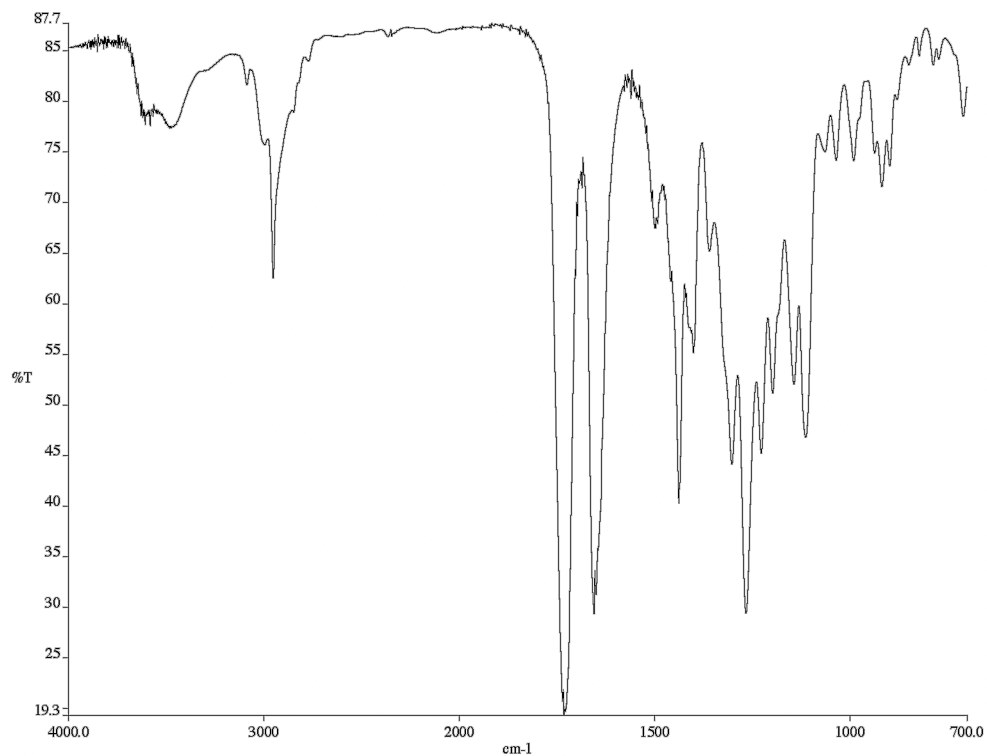


Figure A6.20 Infrared spectrum (thin film/NaCl) of compound **222**

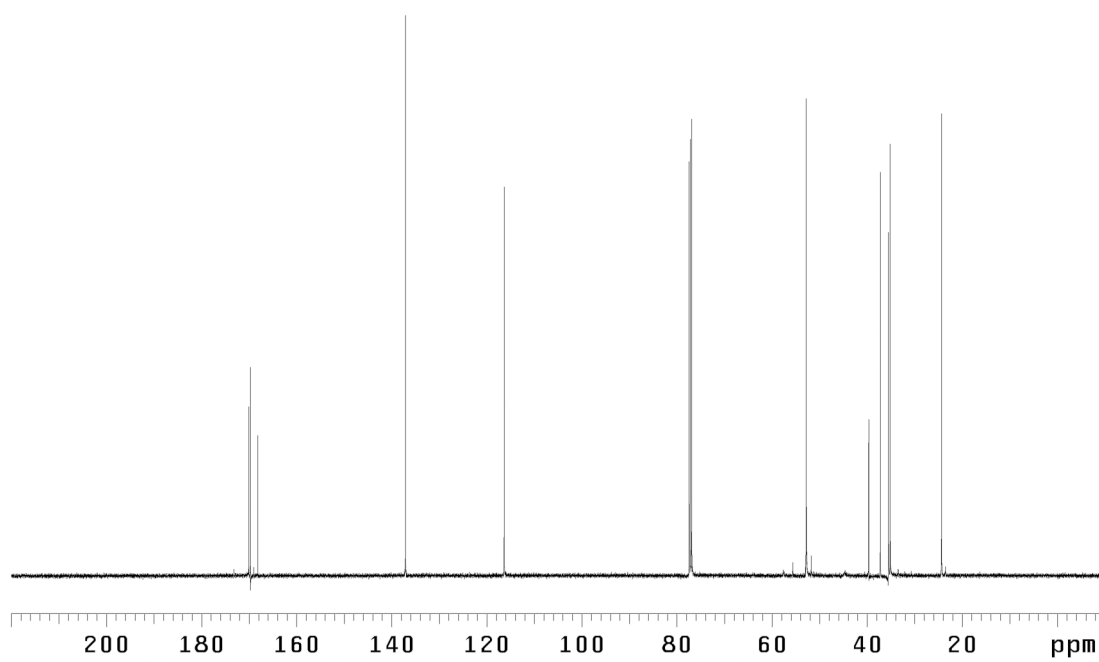


Figure A6.21 ¹³C NMR (126 MHz, CDCl₃) of compound **222**

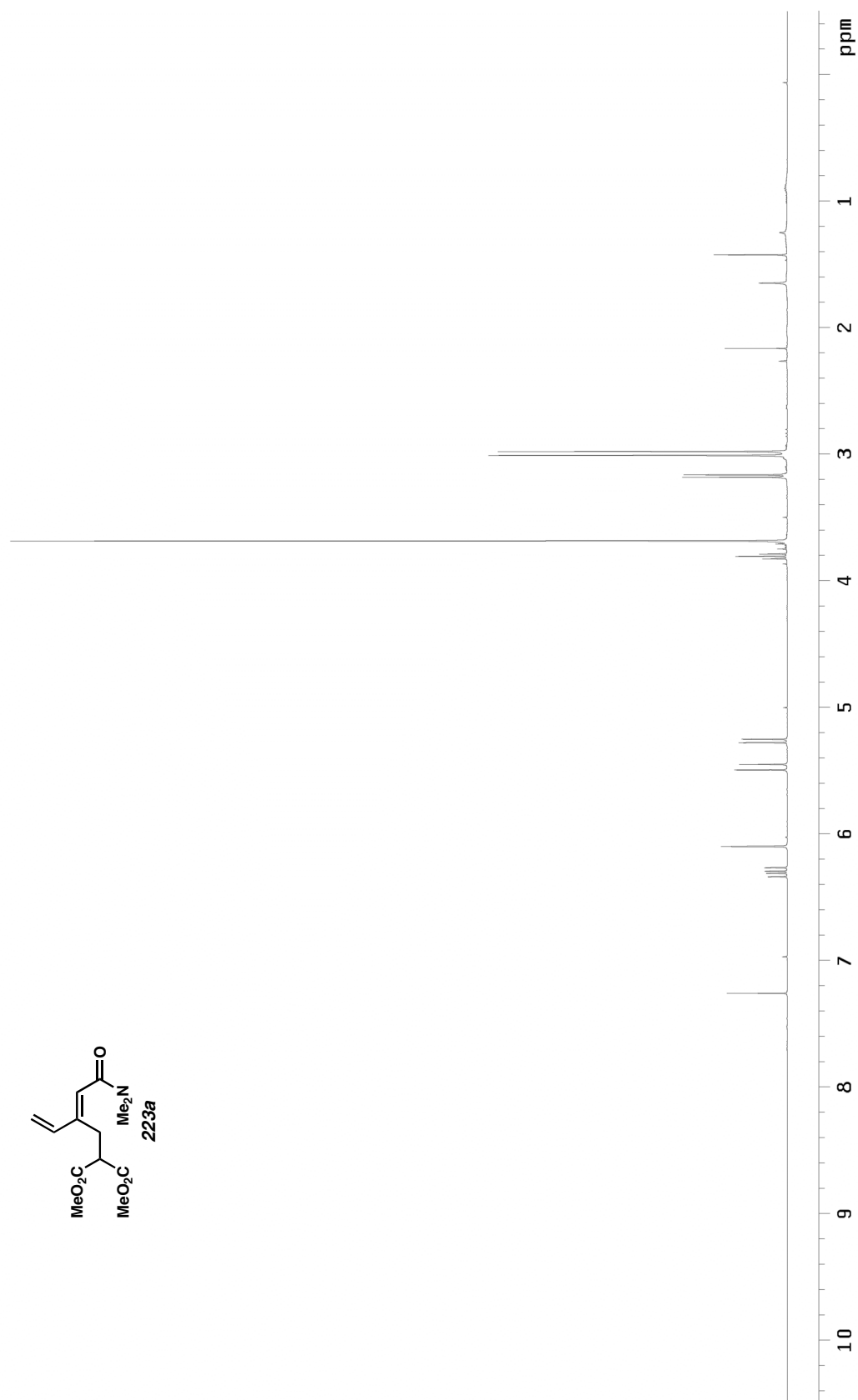


Figure A6.22 ^1H NMR (400 MHz, CDCl_3) of compound **223a**

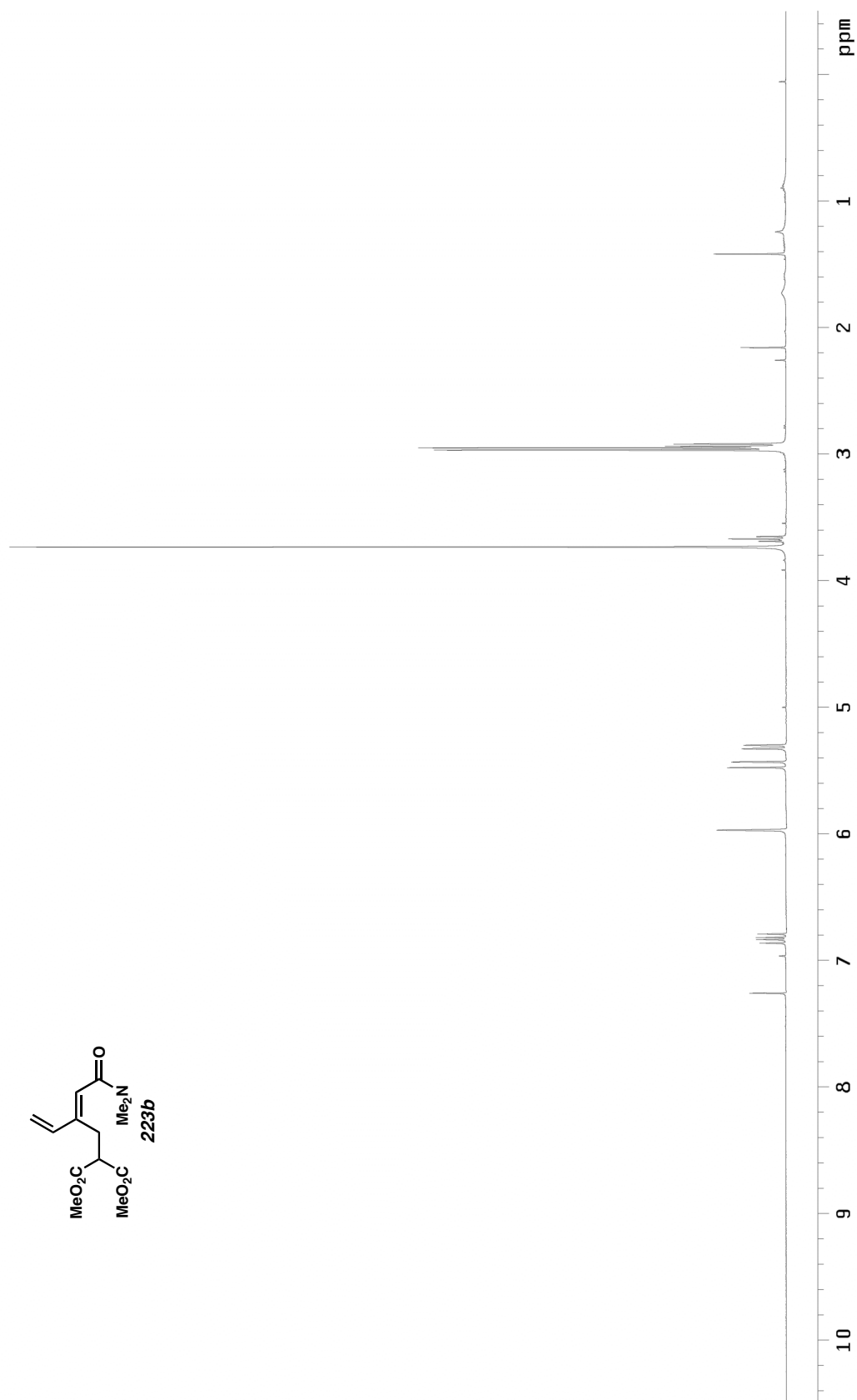


Figure A6.23 ¹H NMR (400 MHz, CDCl₃) of compound **223b**

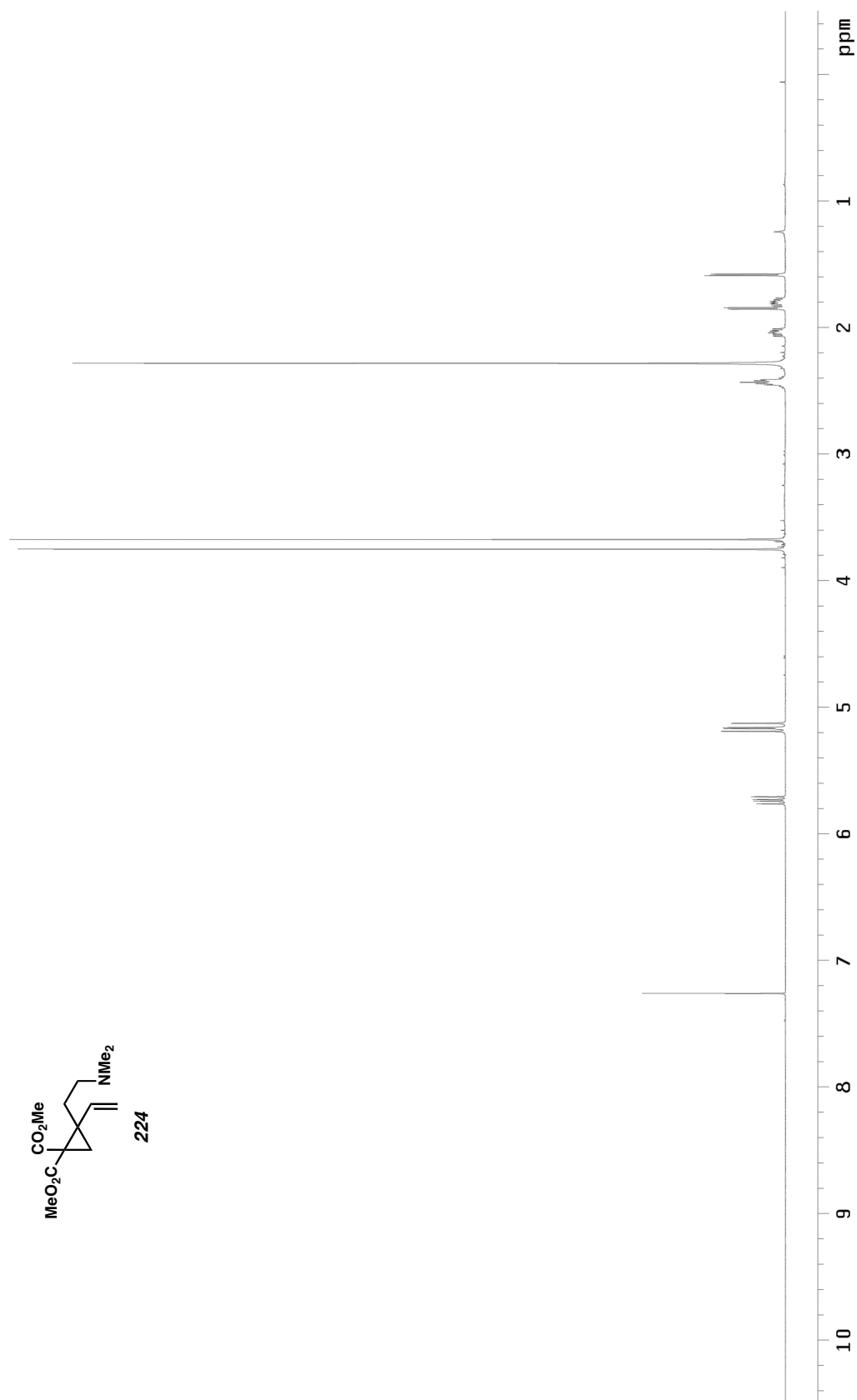


Figure A6.24 ^1H NMR (500 MHz, CDCl_3) of compound **224**

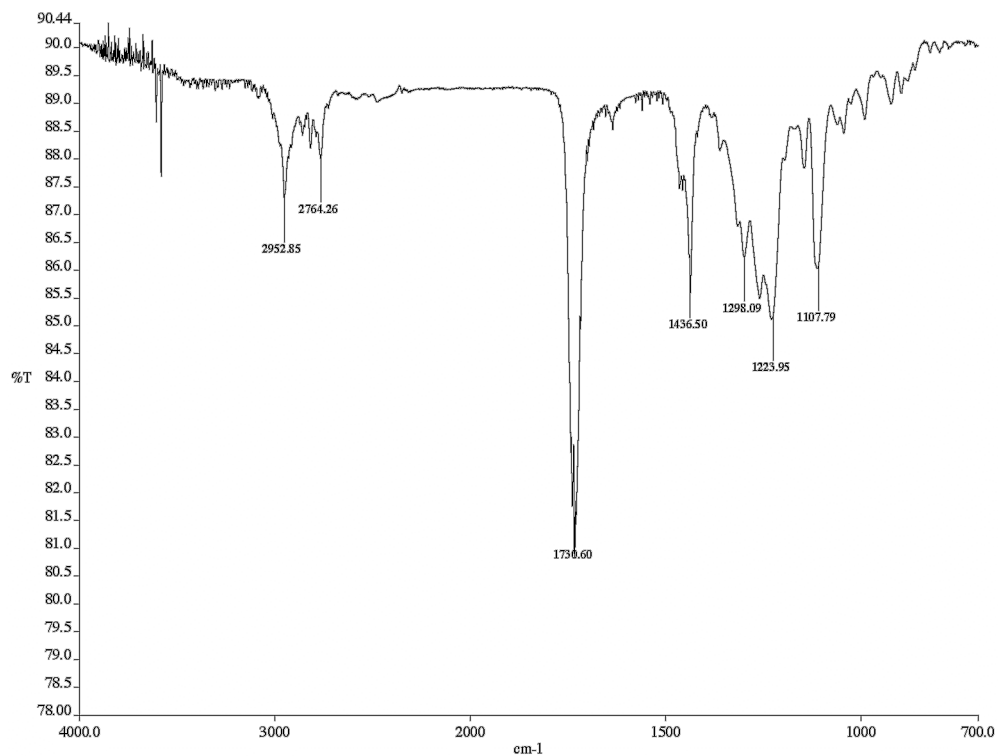


Figure A6.25 Infrared spectrum (thin film/NaCl) of compound **224**

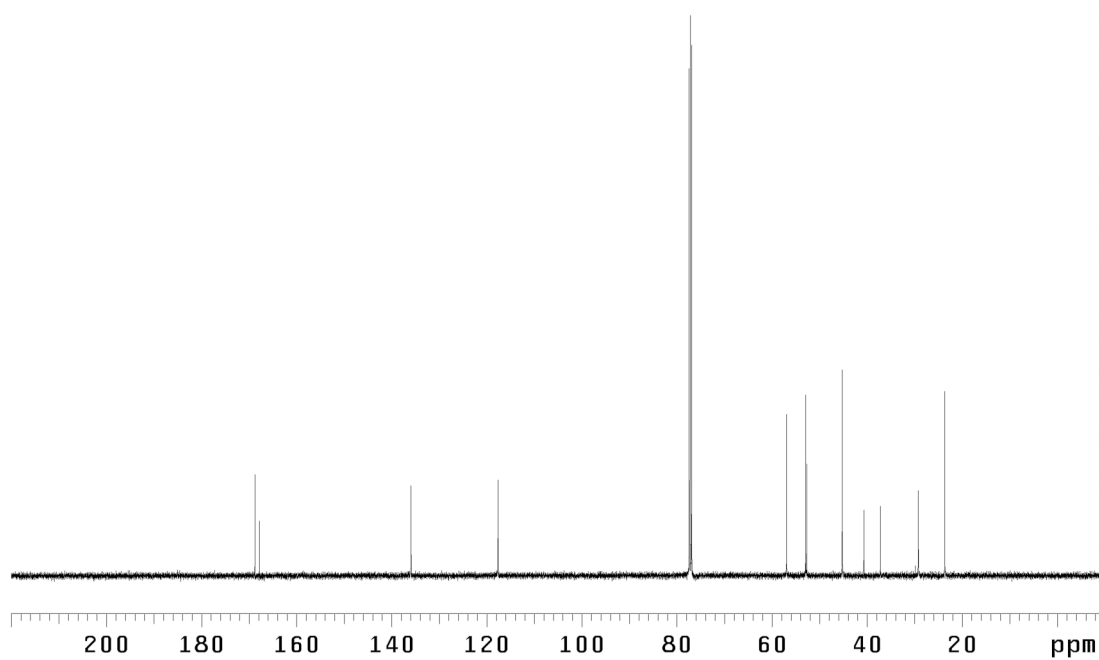


Figure A6.26 ¹³C NMR (126 MHz, CDCl₃) of compound **224**

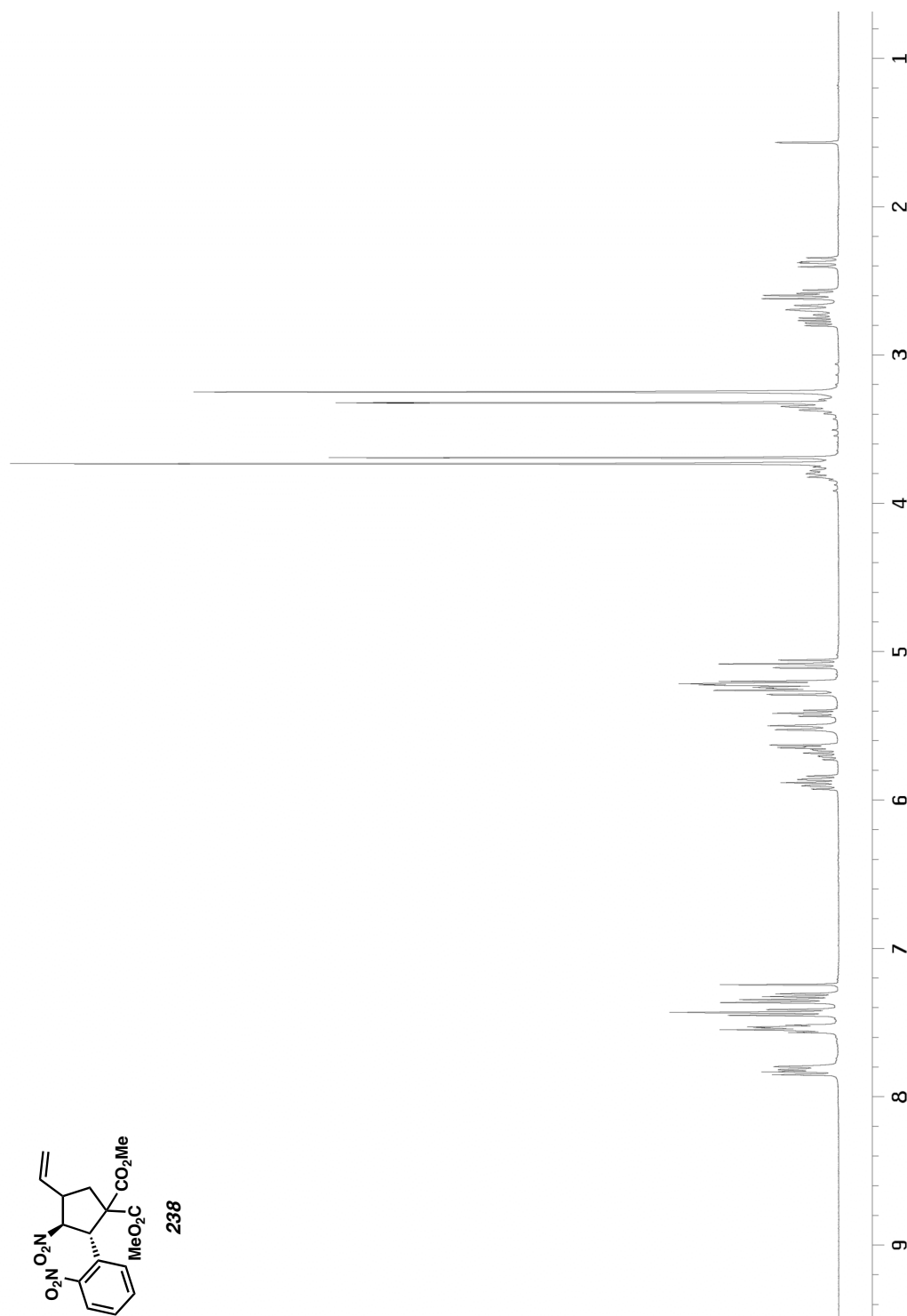


Figure A6.27 ¹H NMR (400 MHz, CDCl₃) of compound **238**

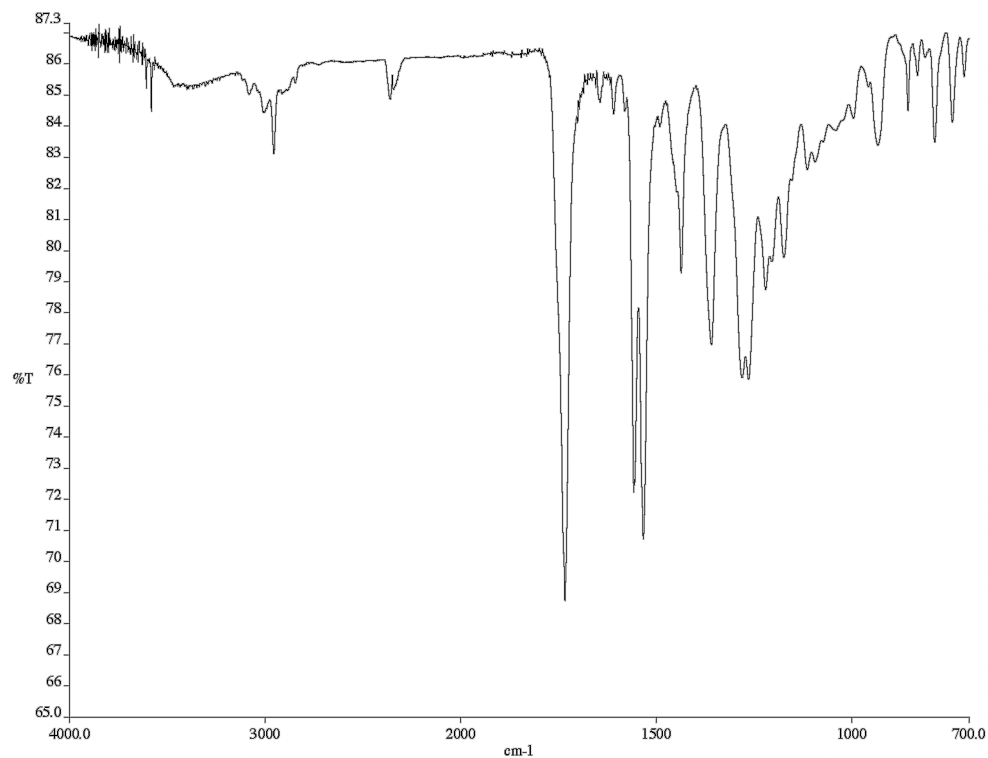


Figure A6.28 Infrared spectrum (thin film/NaCl) of compound **238**

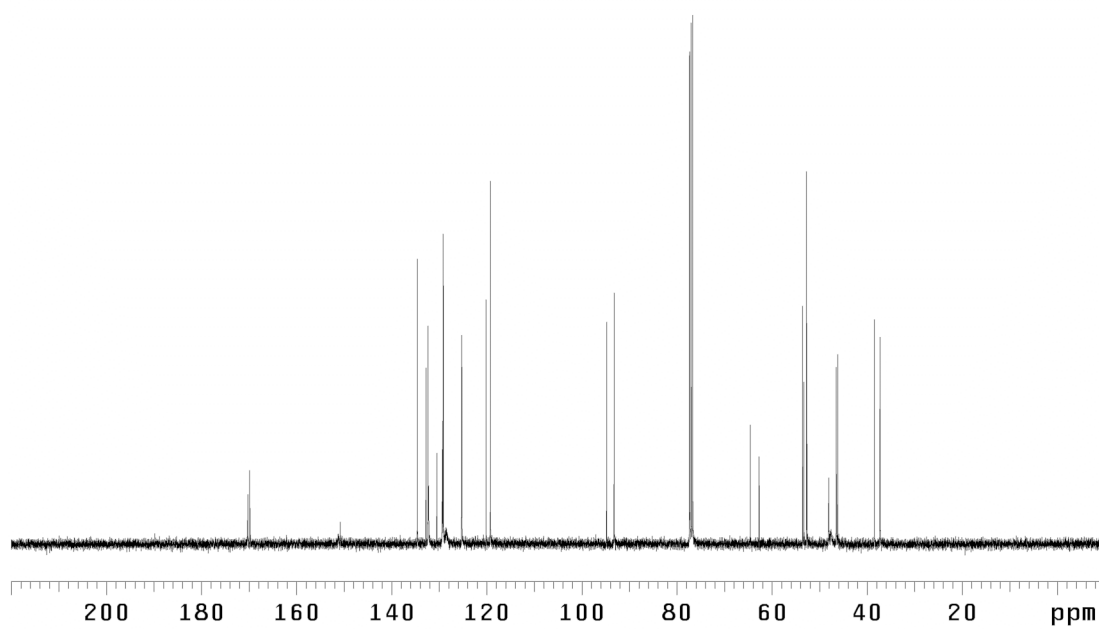


Figure A6.29 ¹³C NMR (100 MHz, CDCl₃) of compound **238**

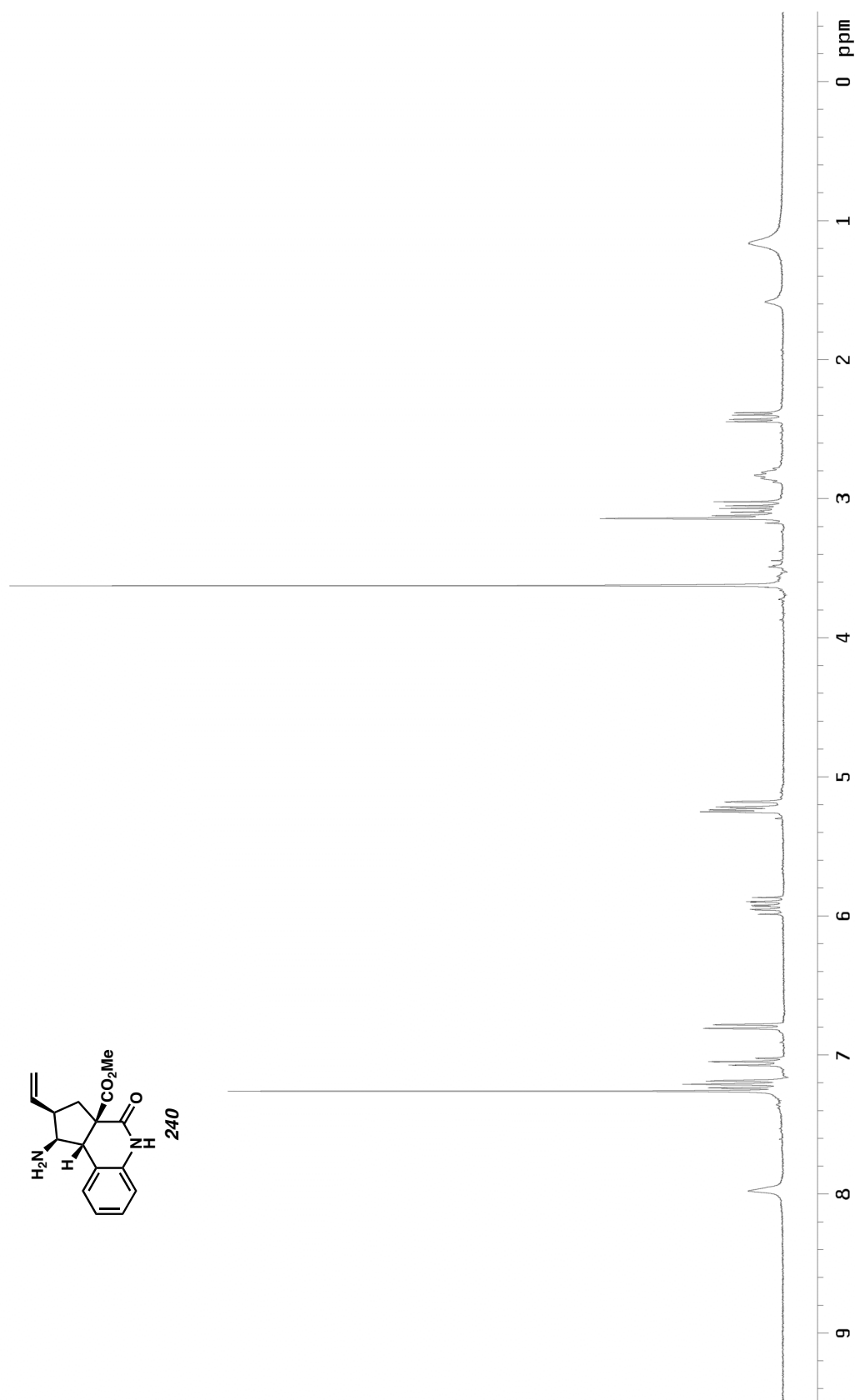


Figure A6.30 ¹H NMR (400 MHz, CDCl₃) of compound **240**

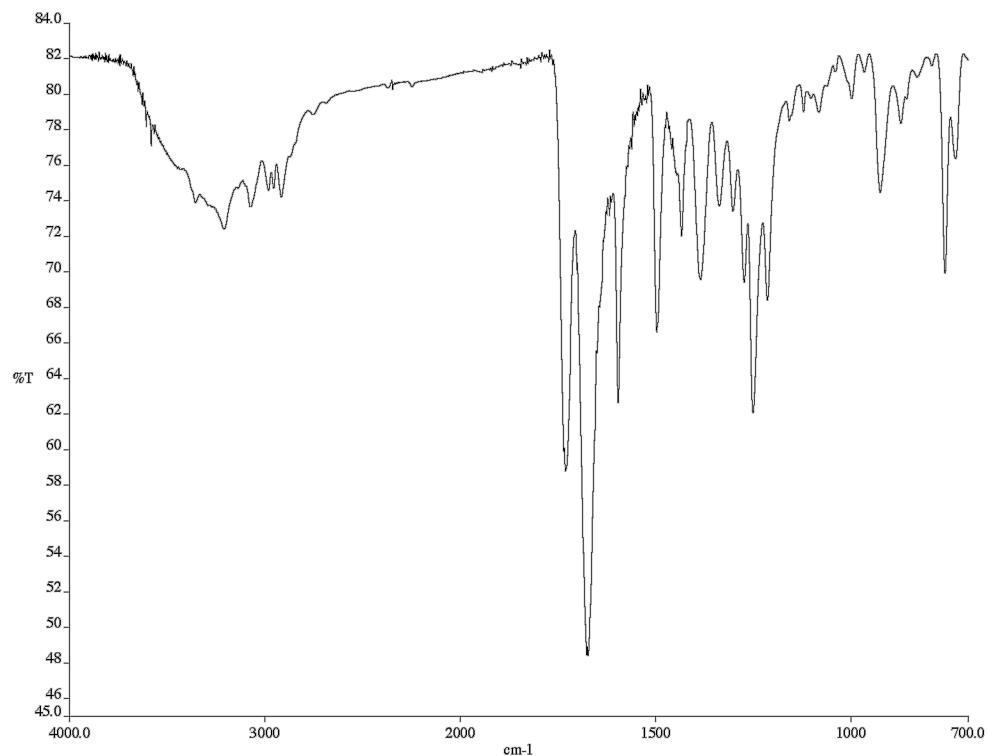


Figure A6.31 Infrared spectrum (thin film/NaCl) of compound **240**

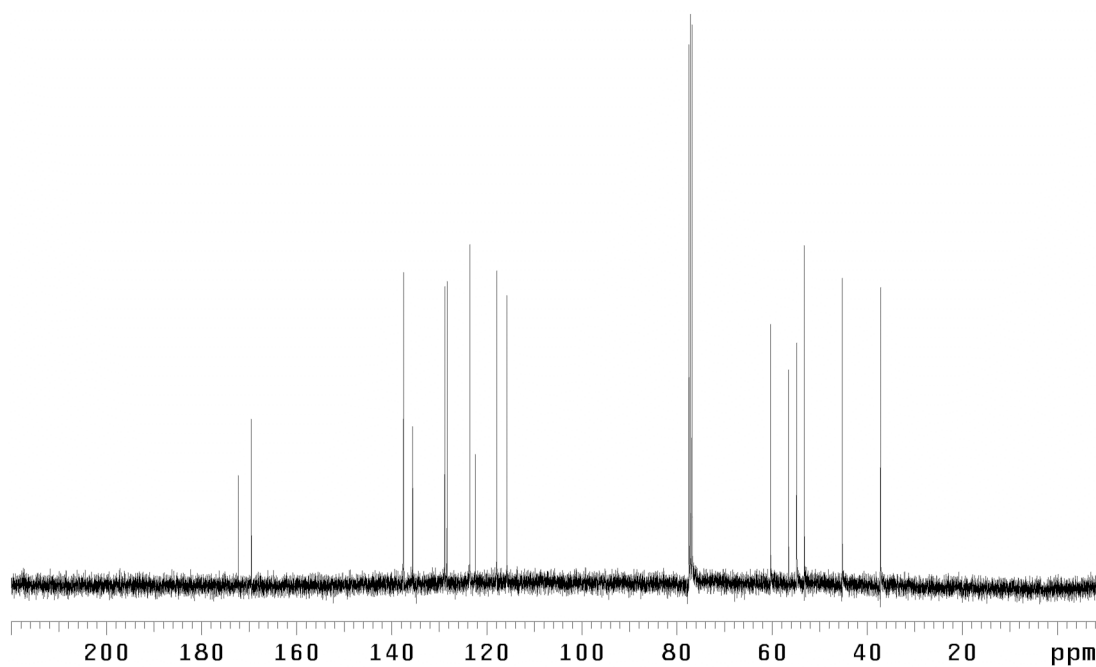


Figure A6.32 ¹³C NMR (100 MHz, CDCl₃) of compound **240**

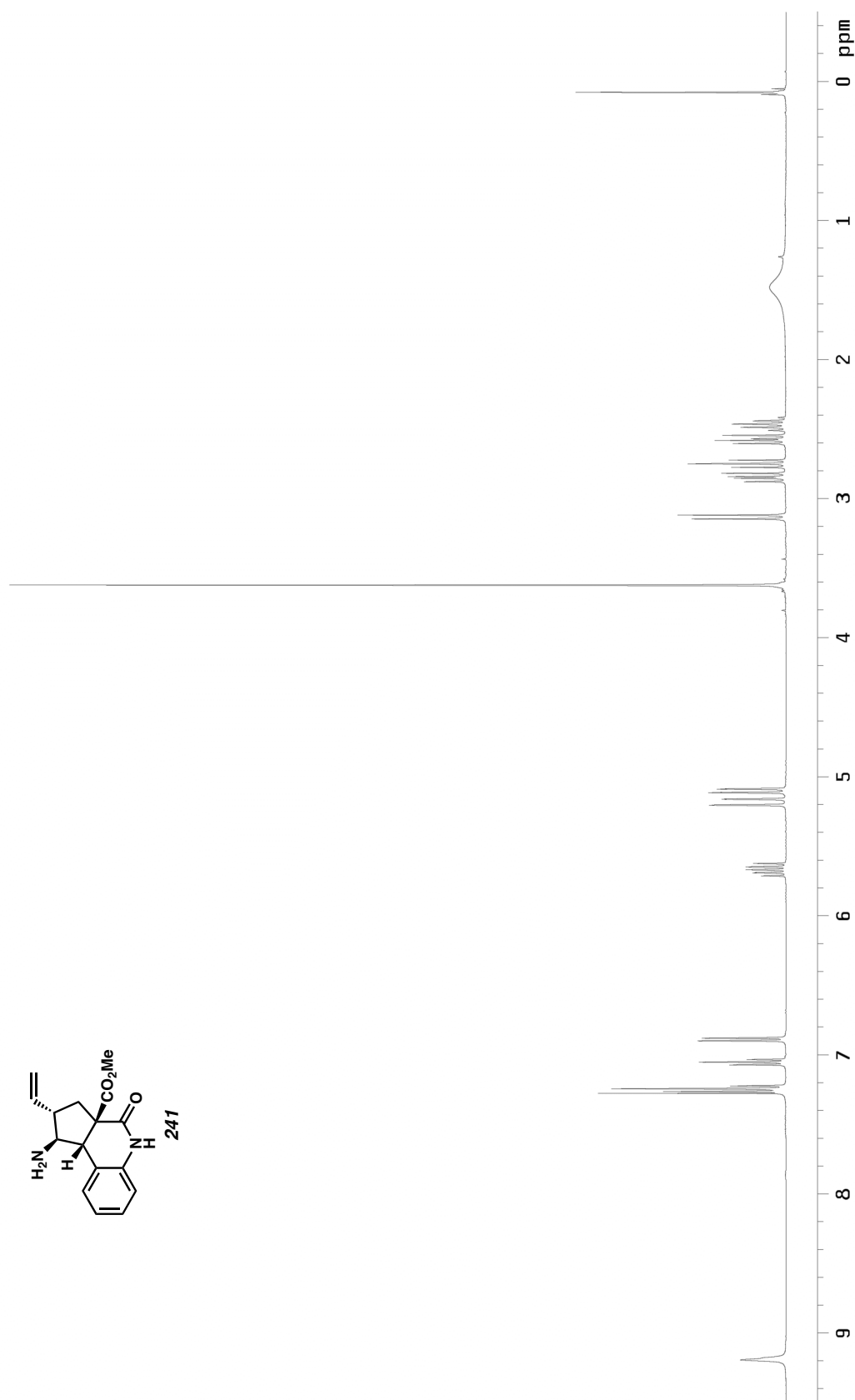


Figure A6.33 ¹H NMR (400 MHz, CDCl₃) of compound **241**

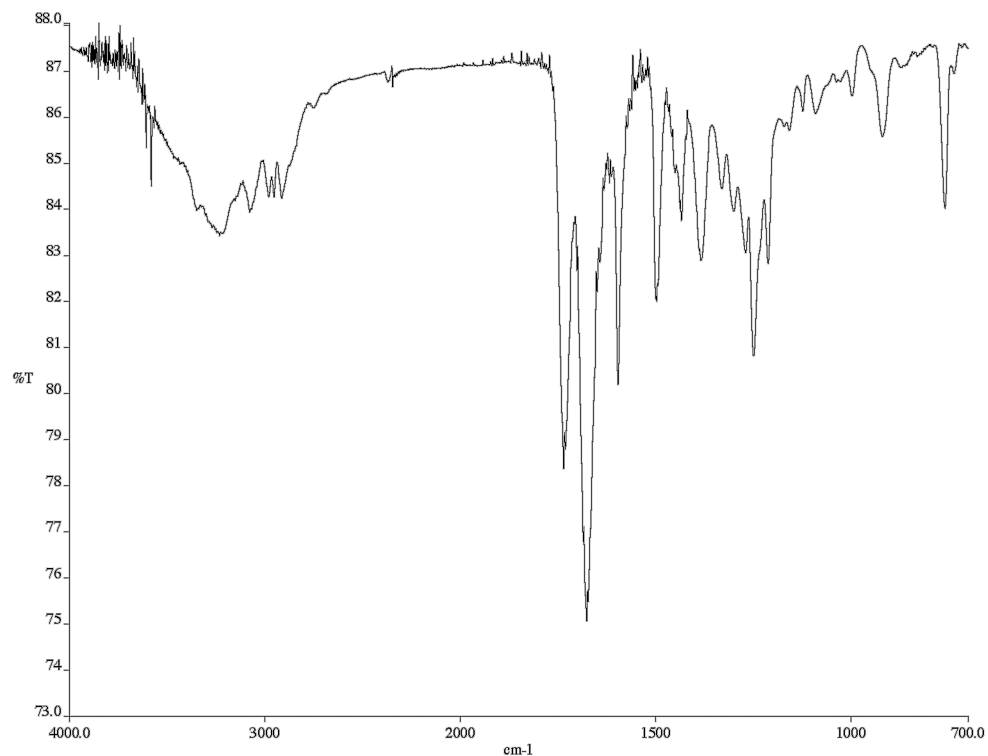


Figure A6.34 Infrared spectrum (thin film/NaCl) of compound **241**

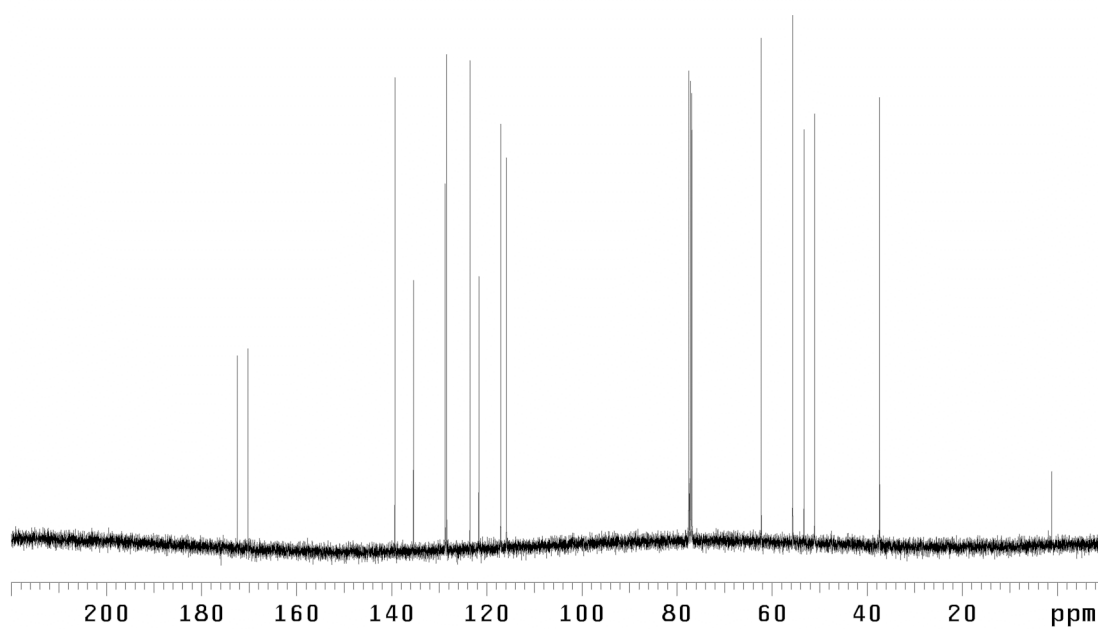


Figure A6.35 ¹³C NMR (100 MHz, CDCl₃) of compound **241**

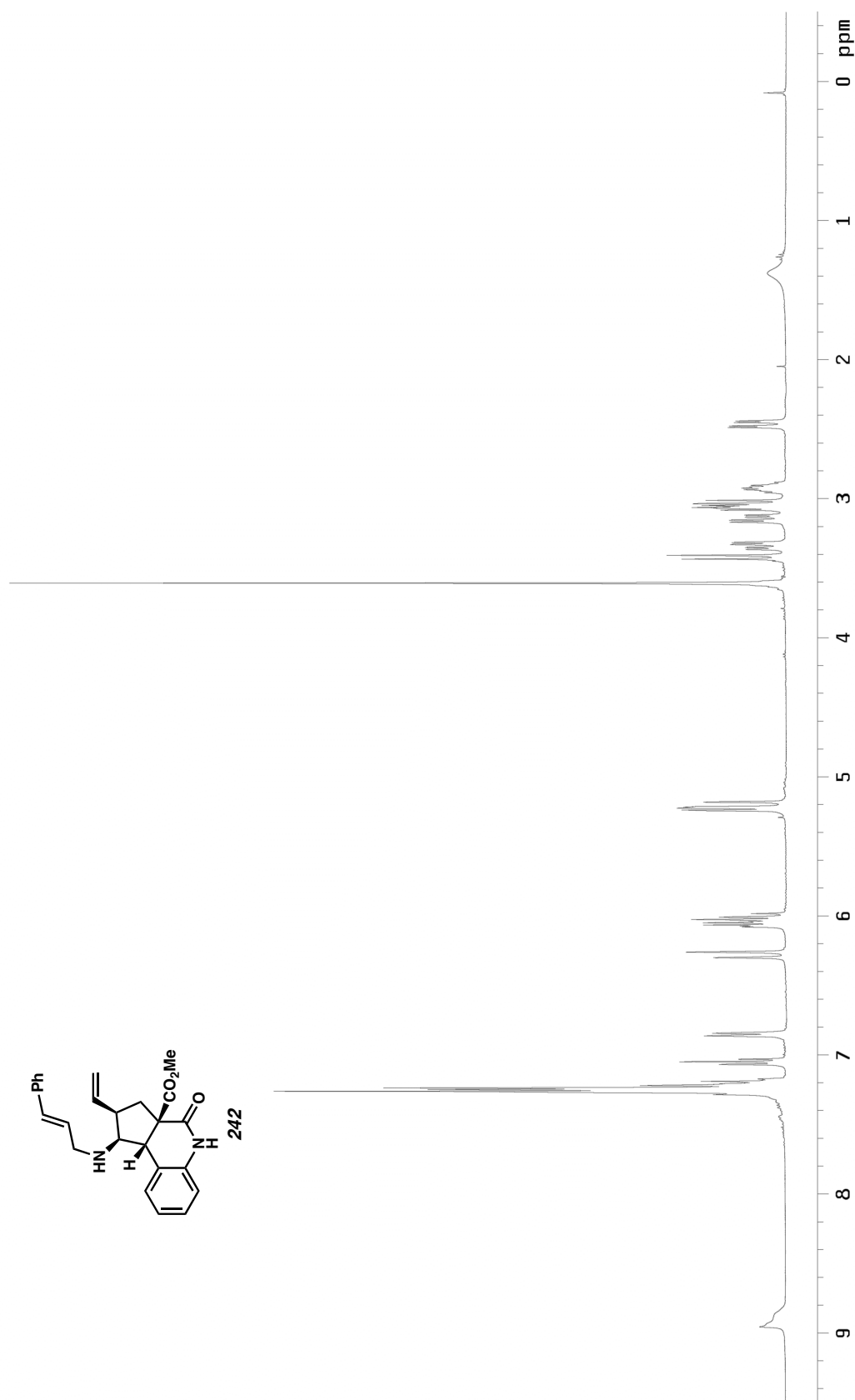


Figure A6.36 ¹H NMR (400 MHz, CDCl₃) of compound **242**

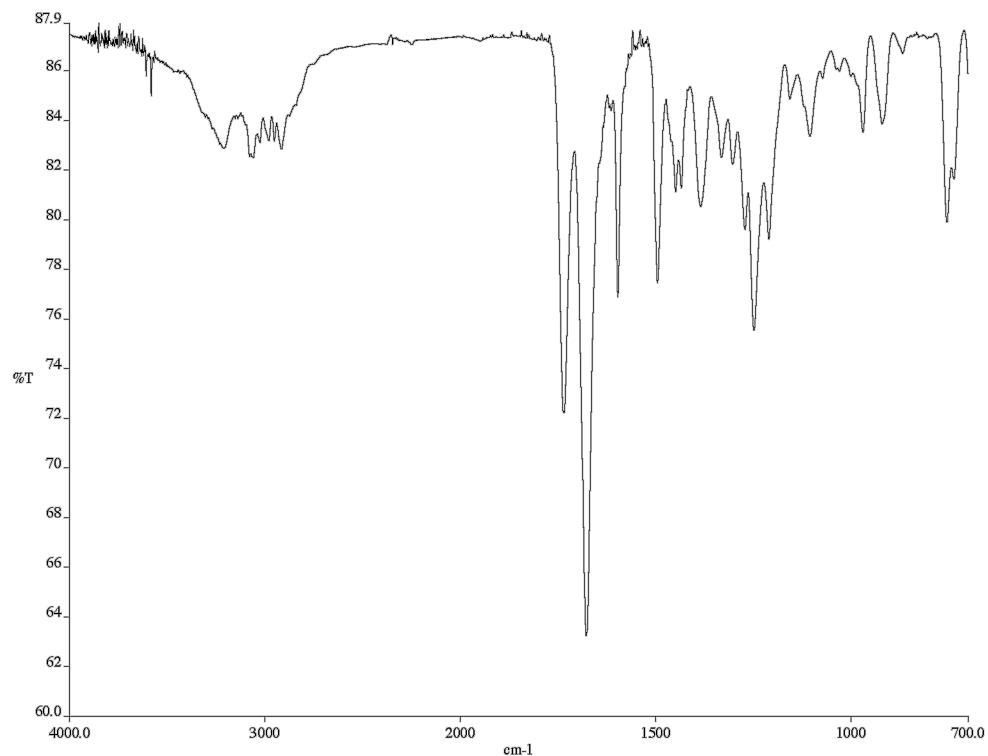


Figure A6.37 Infrared spectrum (thin film/NaCl) of compound **242**

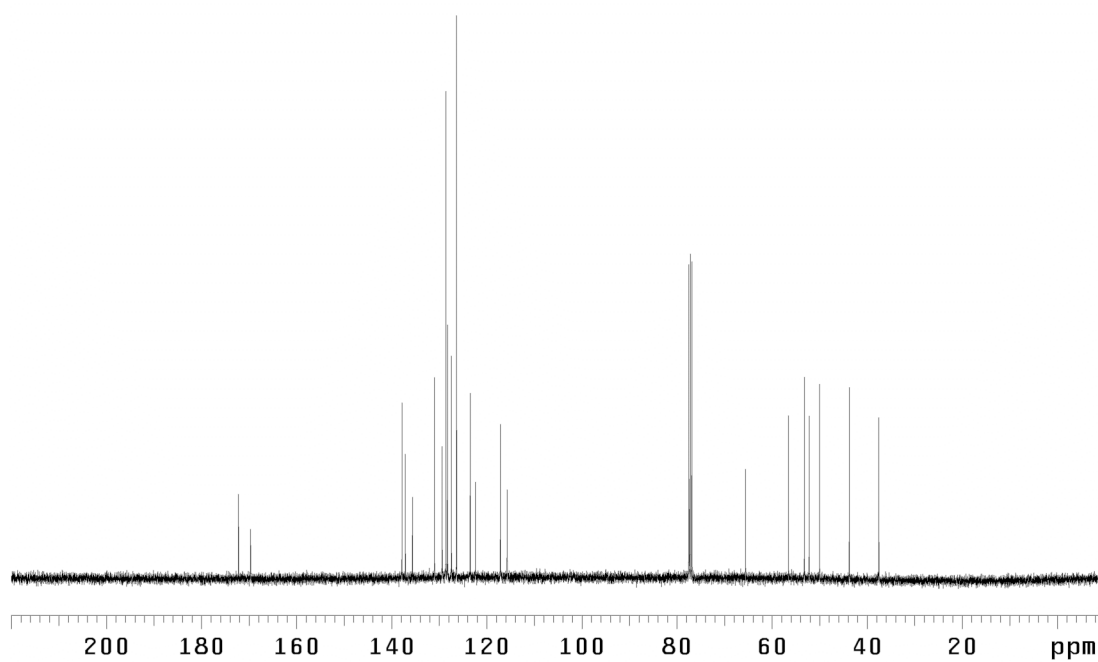


Figure A6.38 ¹³C NMR (100 MHz, CDCl₃) of compound **242**

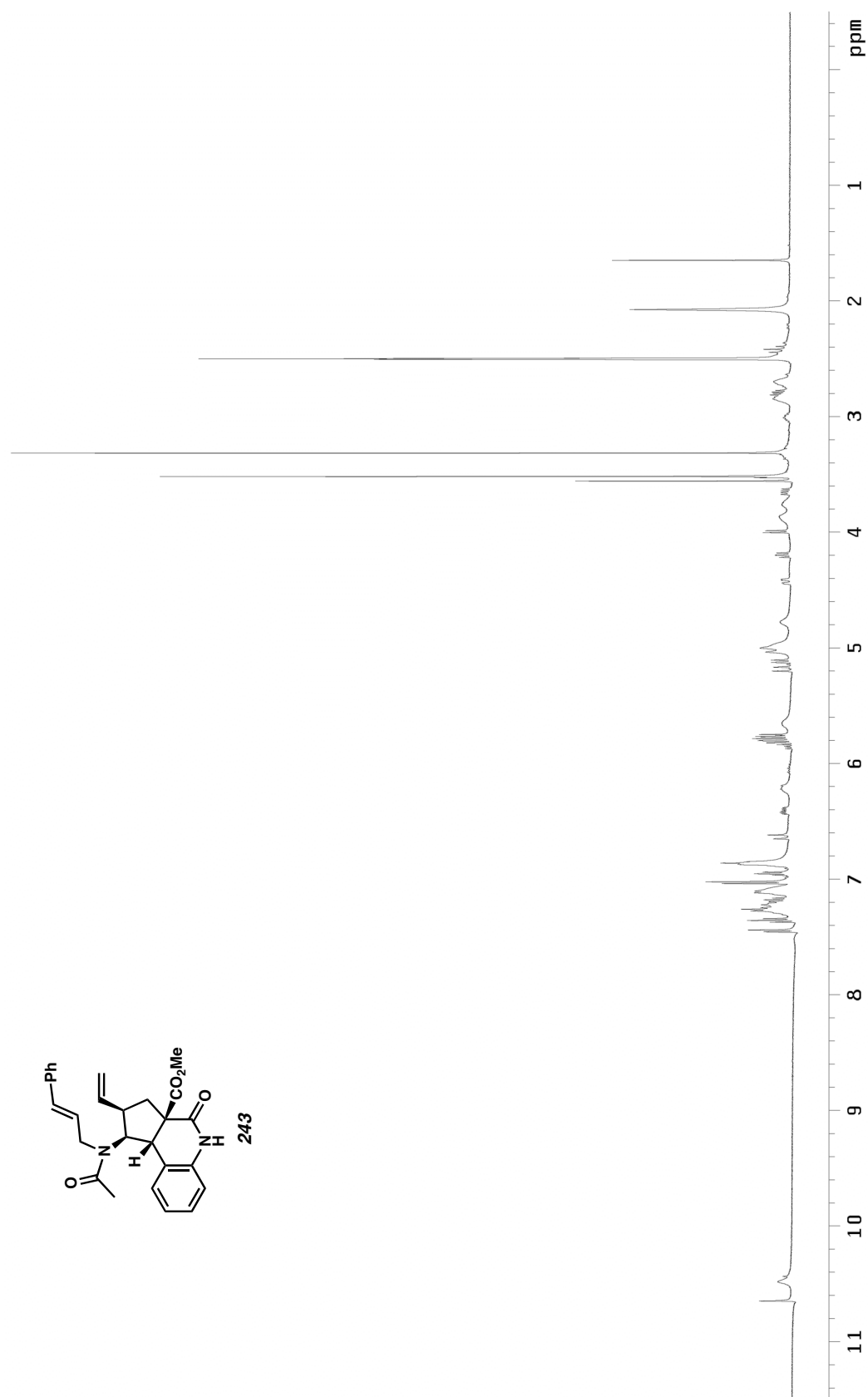


Figure A6.39 ^1H NMR (500 MHz, $\text{d}_6\text{-DMSO}$) of crude compound **243**

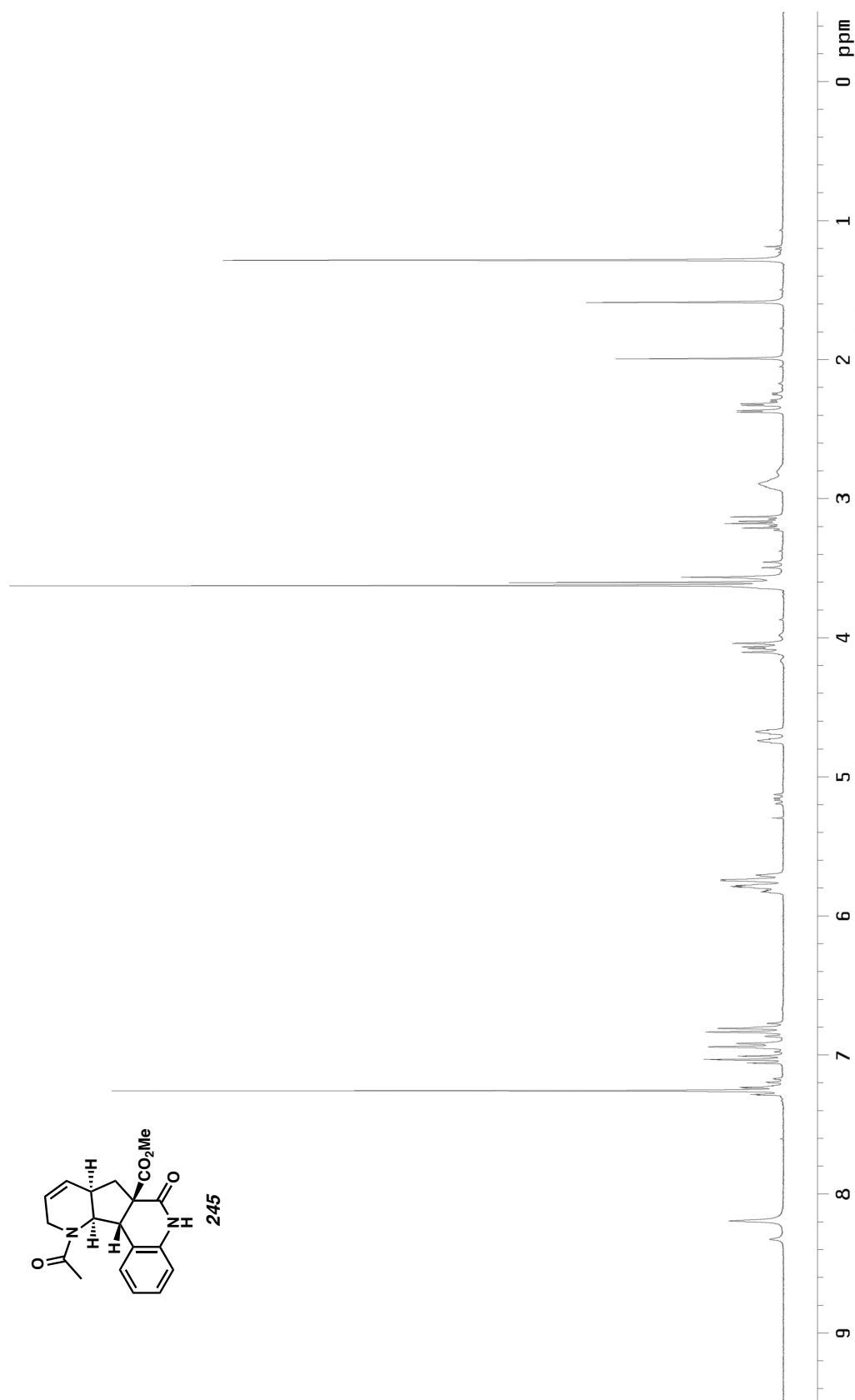


Figure A6.40 ^1H NMR (300 MHz, CDCl_3) of compound **245**

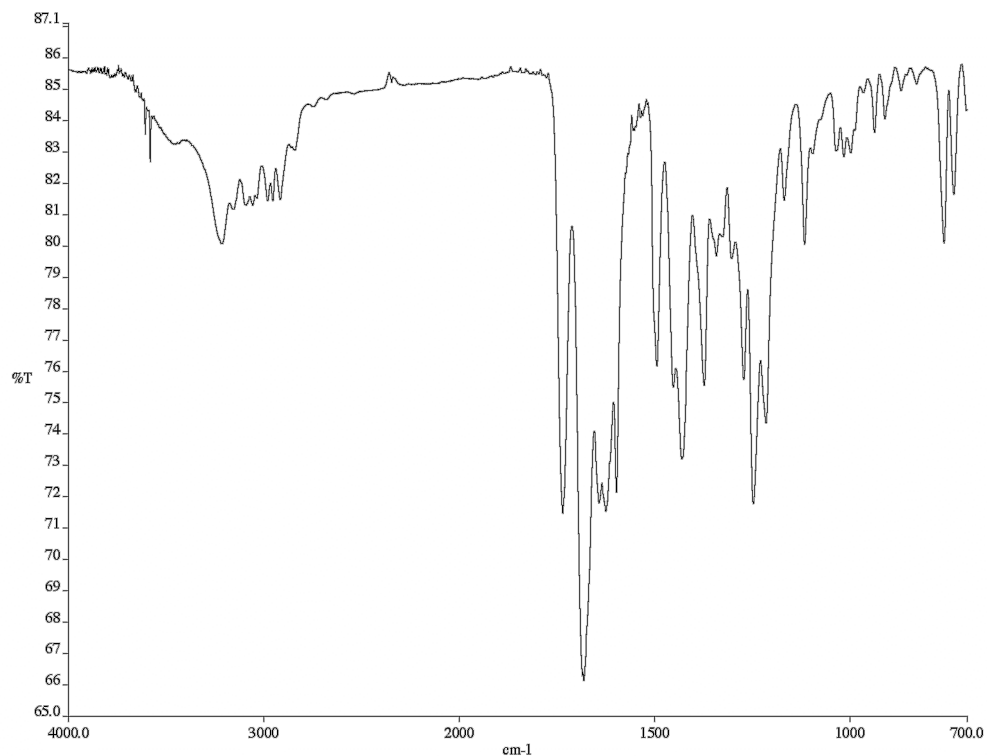


Figure A6.41 Infrared spectrum (thin film/NaCl) of compound **245**

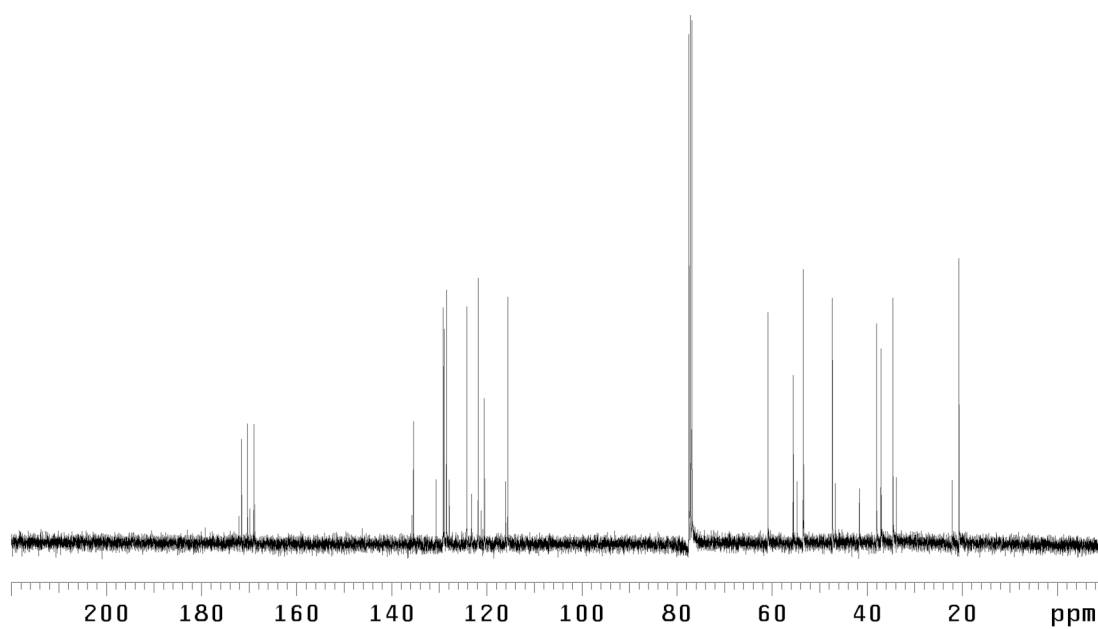


Figure A6.42 ¹³C NMR (100 MHz, CDCl₃) of compound **245**

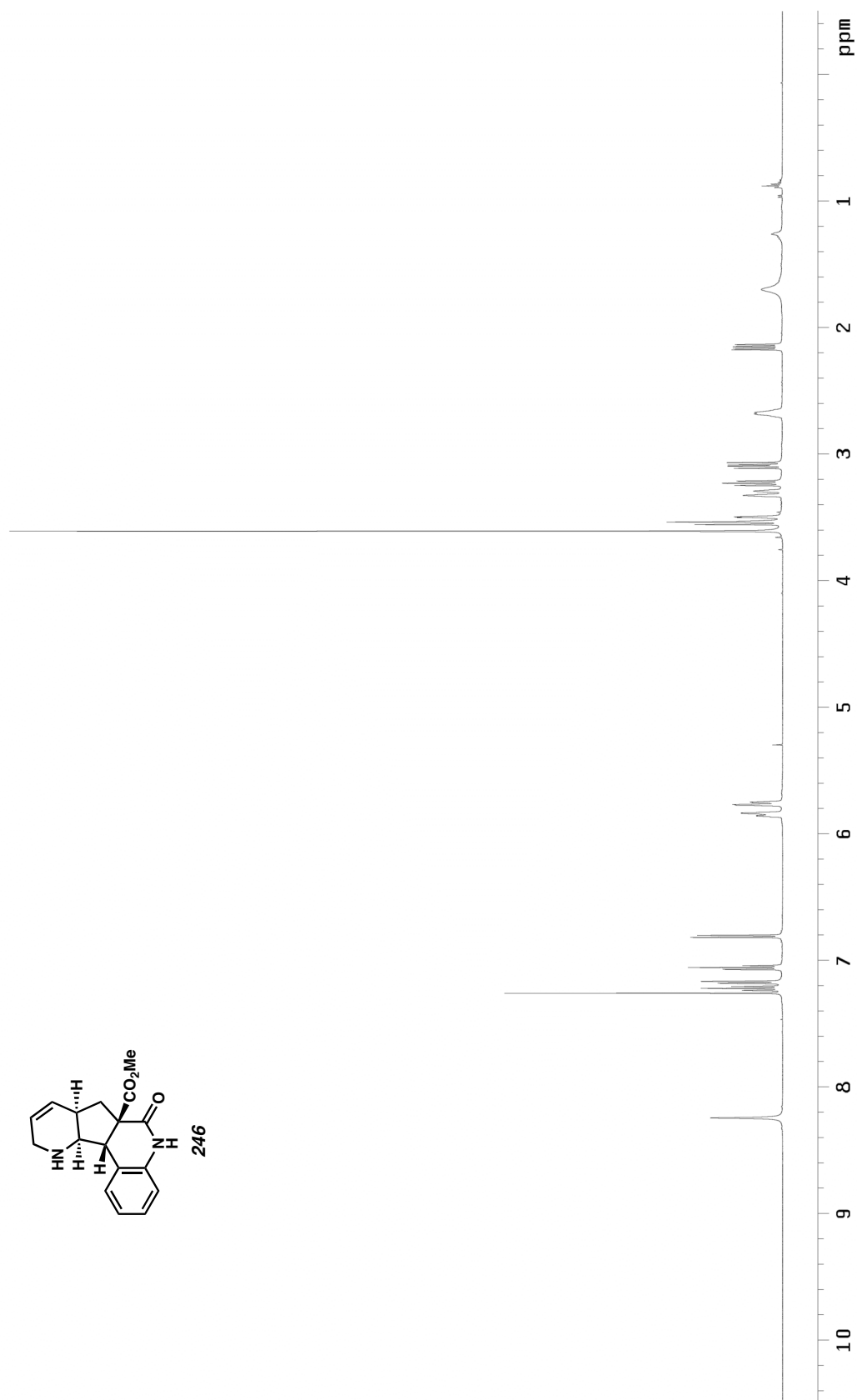


Figure A6.43 ^1H NMR (500 MHz, CDCl_3) of compound **246**

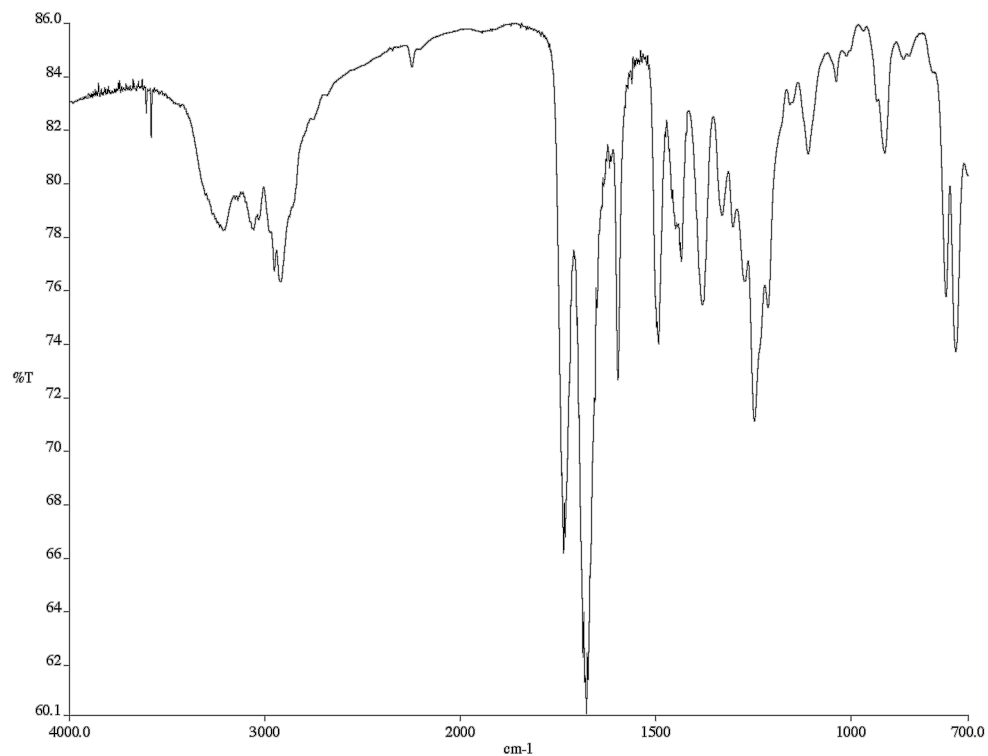


Figure A6.44 Infrared spectrum (thin film/NaCl) of compound **246**

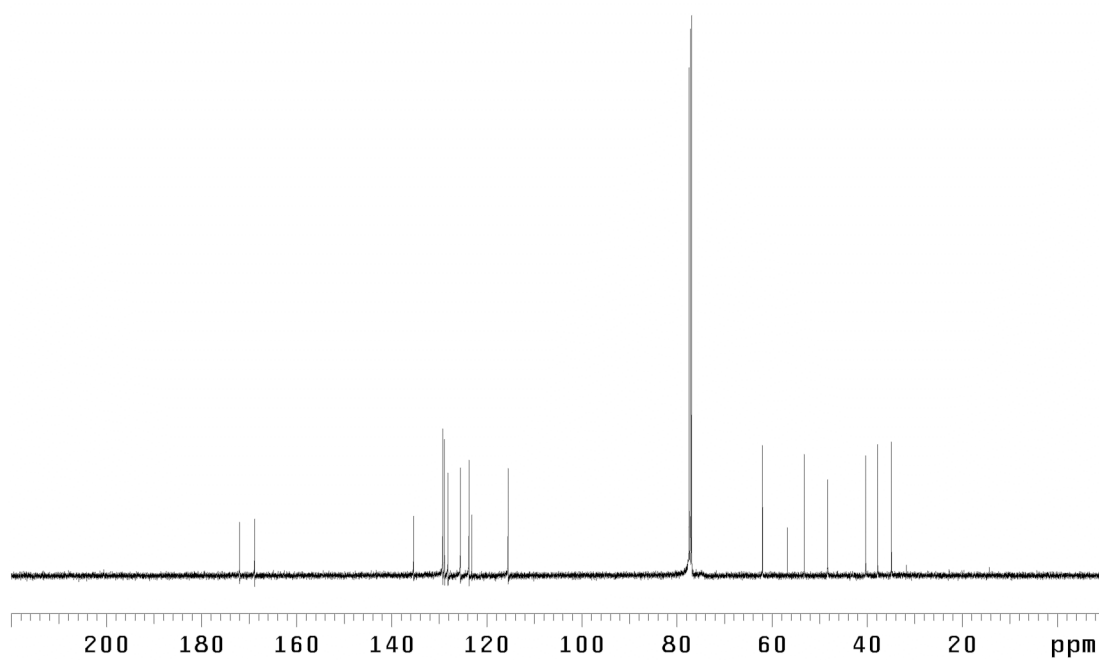


Figure A6.45 ¹³C NMR (126 MHz, CDCl₃) of compound **246**

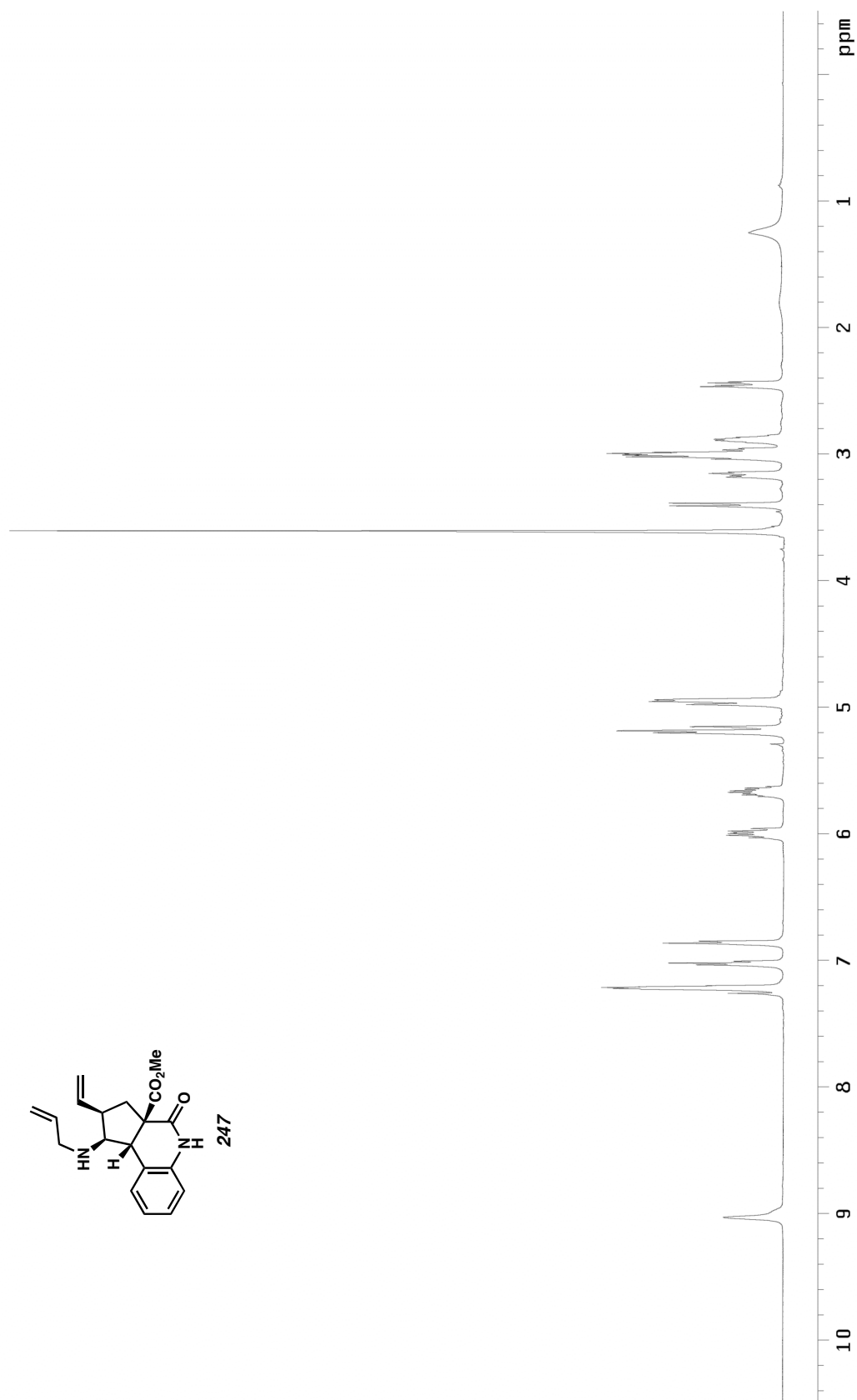


Figure A6.46 ^1H NMR (500 MHz, CDCl_3) of compound **247**

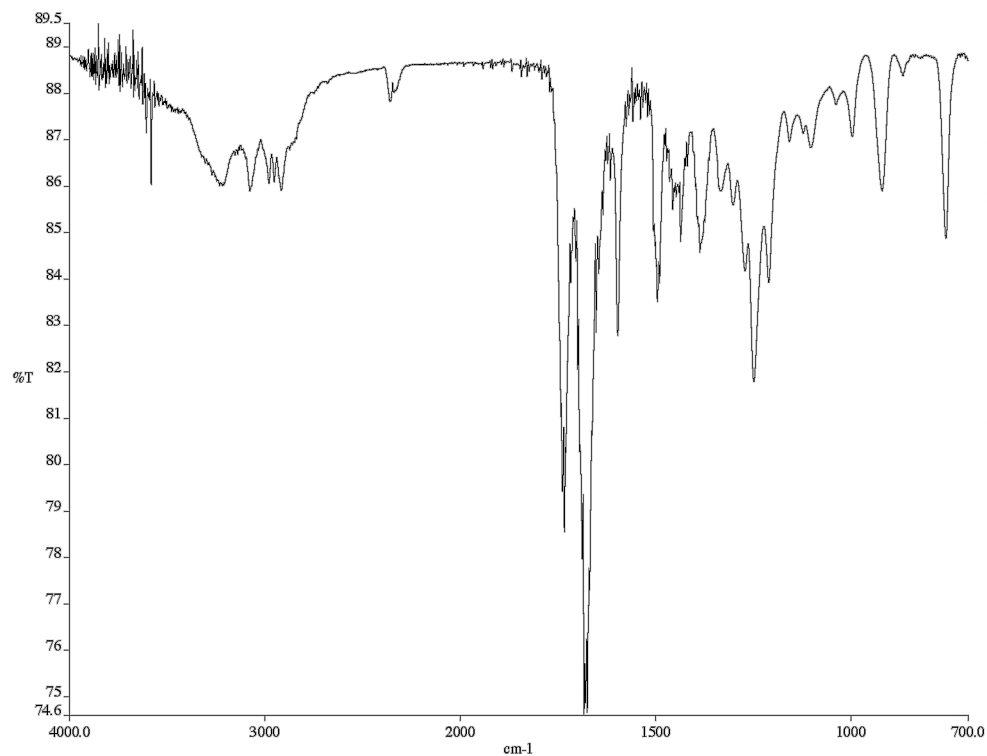


Figure A6.47 Infrared spectrum (thin film/NaCl) of compound **247**

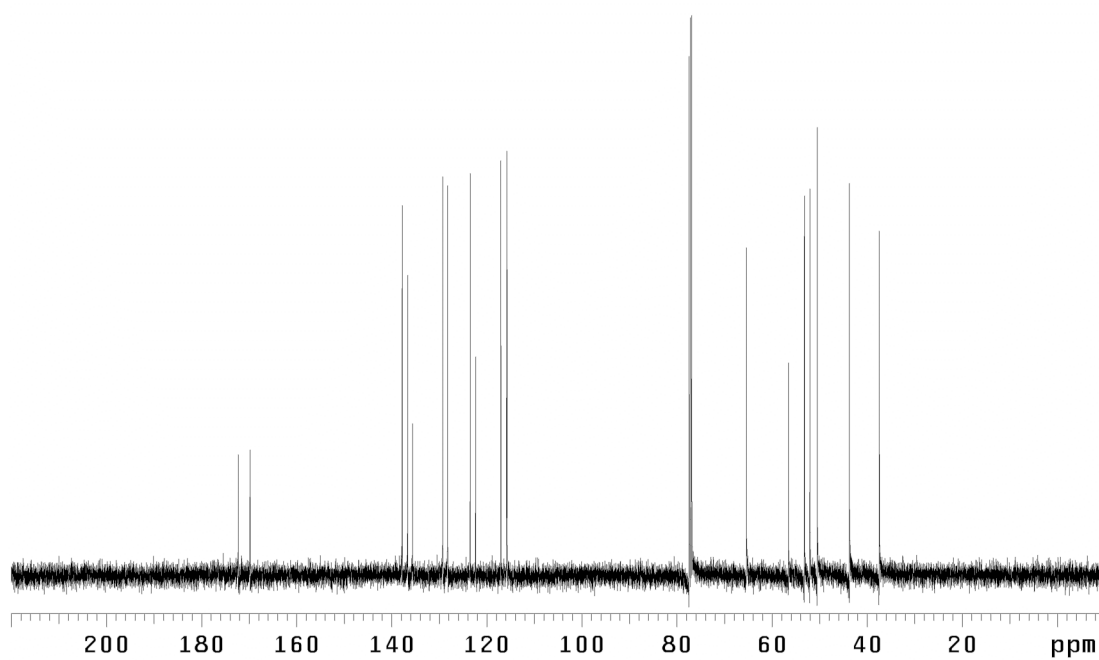


Figure A6.48 ¹³C NMR (126 MHz, CDCl₃) of compound **247**

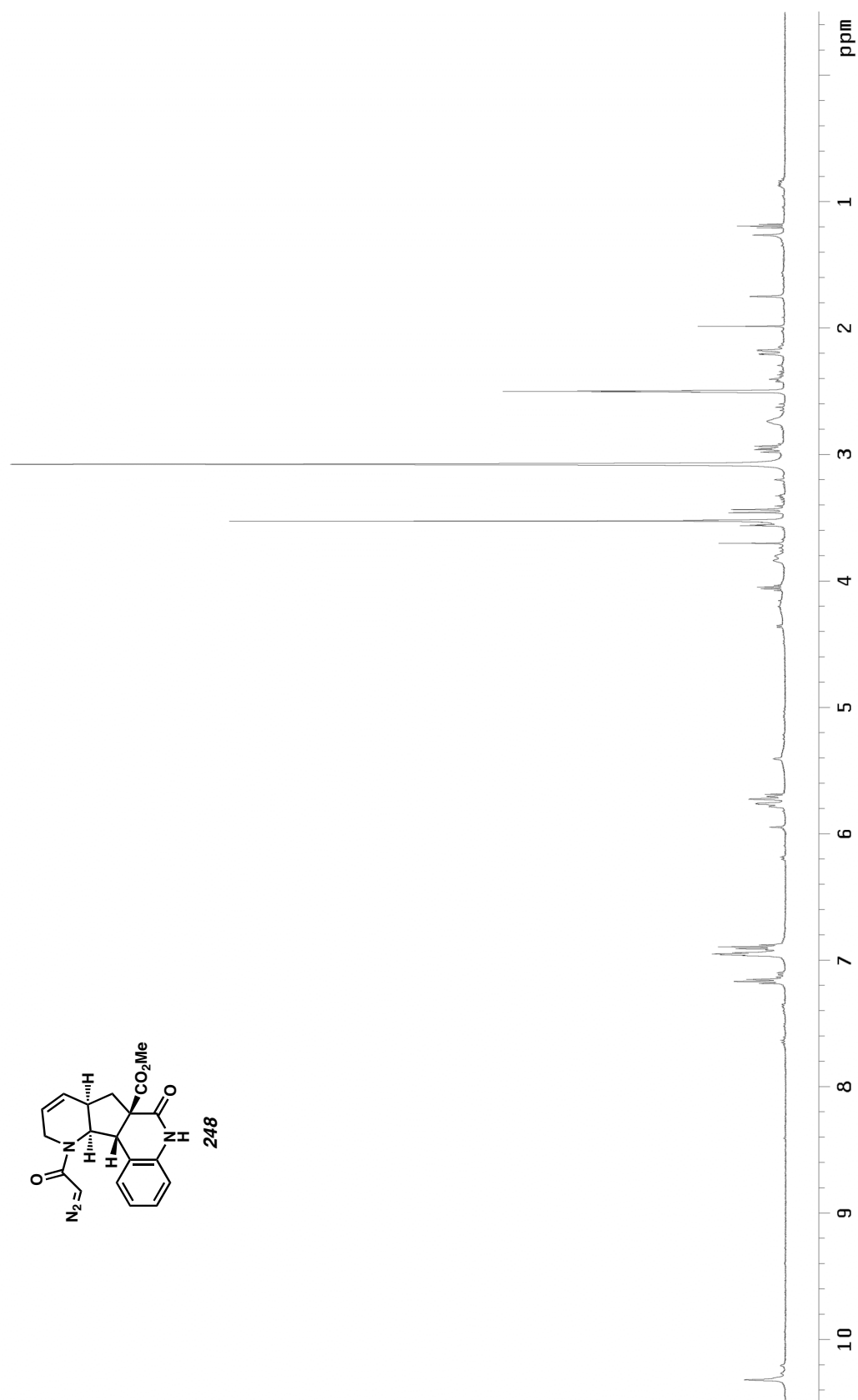


Figure 6.49 ^1H NMR (500 MHz, $\text{d}_6\text{-DMSO}$, 80°C) of compound **248**

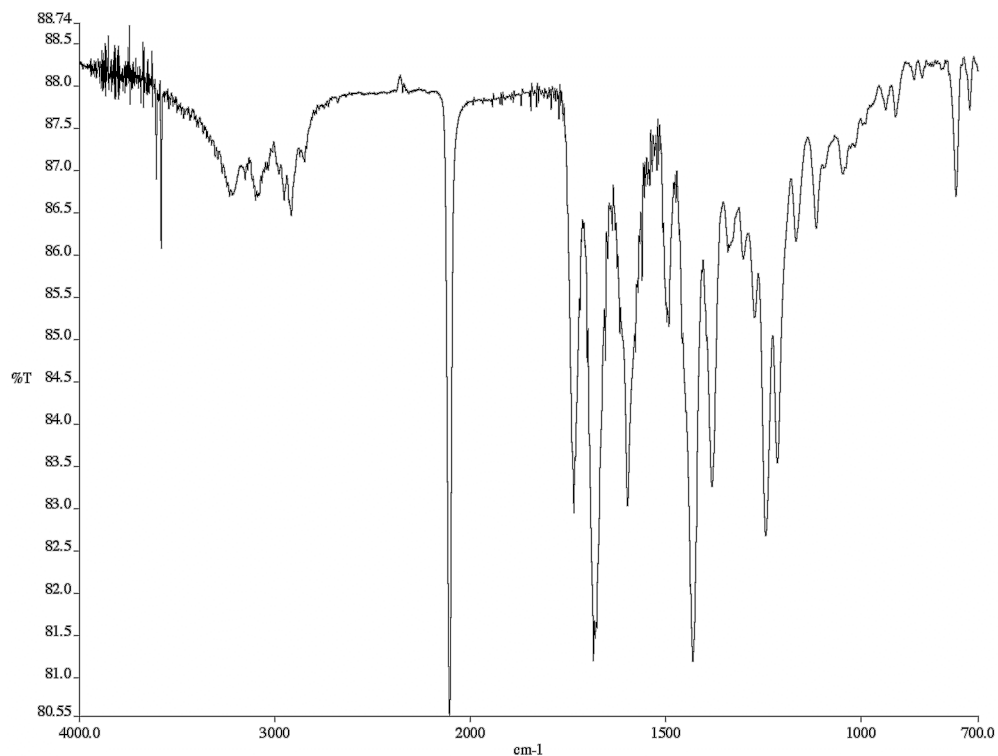


Figure 6.50 Infrared spectrum (thin film/NaCl) of compound **248**

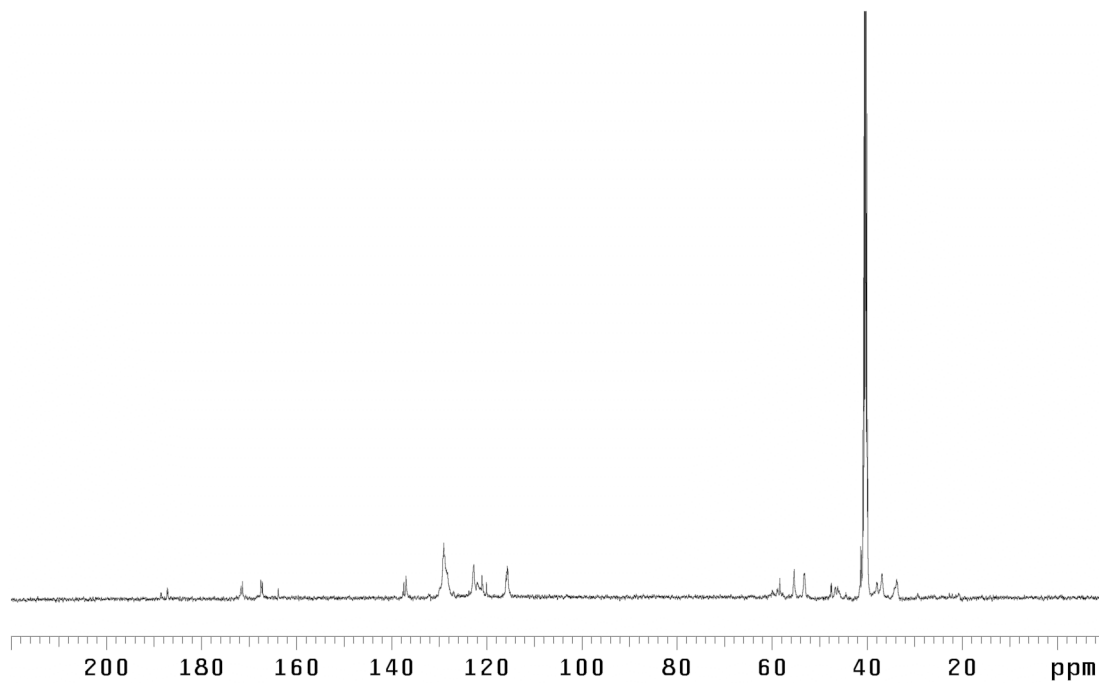


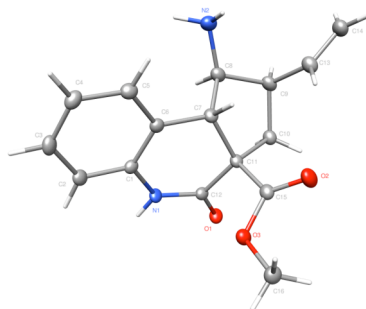
Figure 6.51 ¹³C NMR (126 MHz, d₆-DMSO, 80 °C) of compound **248**

APPENDIX 7

X-ray Crystallography Reports

Relevant to Chapter 2

A7.1 CRYSTAL STRUCTURE ANALYSIS OF 240



240

Note: The crystallographic data have been deposited in the Cambridge Database (CCDC). The deposition number is 820779.

Table A7.1.1. Crystal data and structure refinement for **240** (CCDC 820779).

Empirical formula	C ₁₆ H ₁₈ N ₂ O ₃		
Formula weight	286.32		
Crystallization Solvent	Dichloromethane/hexane		
Crystal Habit	Column		
Crystal size	0.36 x 0.19 x 0.19 mm ³		
Crystal color	Colorless		
Data Collection			
Type of diffractometer	Bruker SMART 1000		
Wavelength	0.71073 Å MoKα		
Data Collection Temperature	100(2) K		
θ range for 8222 reflections used in lattice determination	2.71 to 36.32°		
Unit cell dimensions	a = 7.6777(3) Å b = 9.1864(3) Å c = 10.8584(4) Å	α = 71.309(2)° β = 69.829(2)° γ = 75.7590(10)°	
Volume	673.01(4) Å ³		
Z	2		
Crystal system	Triclinic		
Space group	P-1		
Density (calculated)	1.413 Mg/m ³		
F(000)	304		
Data collection program	Bruker SMART v5.630		
θ range for data collection	2.07 to 36.35°		
Completeness to θ = 36.35°	98.4 %		
Index ranges	-12 ≤ h ≤ 12, -15 ≤ k ≤ 15, -18 ≤ l ≤ 18		
Data collection scan type	ω scans at 10 settings		
Data reduction program	Bruker SAINT-Plus v7.66A		
Reflections collected	24459		
Independent reflections	6449 [R _{int} = 0.0431]		
Absorption coefficient	0.099 mm ⁻¹		
Absorption correction	None		
Max. and min. transmission	0.9815	and	0.9654

Table A7.1.1 (cont.)

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 2008)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Difference Fourier map
Structure refinement program	SHELXL-97 (Sheldrick, 2008)
Refinement method	Full matrix least-squares on F ²
Data / restraints / parameters	6449 / 0 / 262
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F ²	2.646
Final R indices [I>2σ(I), 4636 reflections]	R1 = 0.0623, wR2 = 0.0933
R indices (all data)	R1 = 0.0829, wR2 = 0.0954
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(F_o^2)$
Max shift/error	0.001
Average shift/error	0.000
Largest diff. peak and hole	0.666 and -0.395 e.Å ⁻³

Special Refinement Details

Crystals were mounted on a glass fiber using Paratone oil then placed on the diffractometer under a nitrogen stream at 100K.

Refinement of F² against ALL reflections. The weighted R-factor (wR) and goodness of fit (S) are based on F², conventional R-factors (R) are based on F, with F set to zero for negative F². 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 F² are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

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

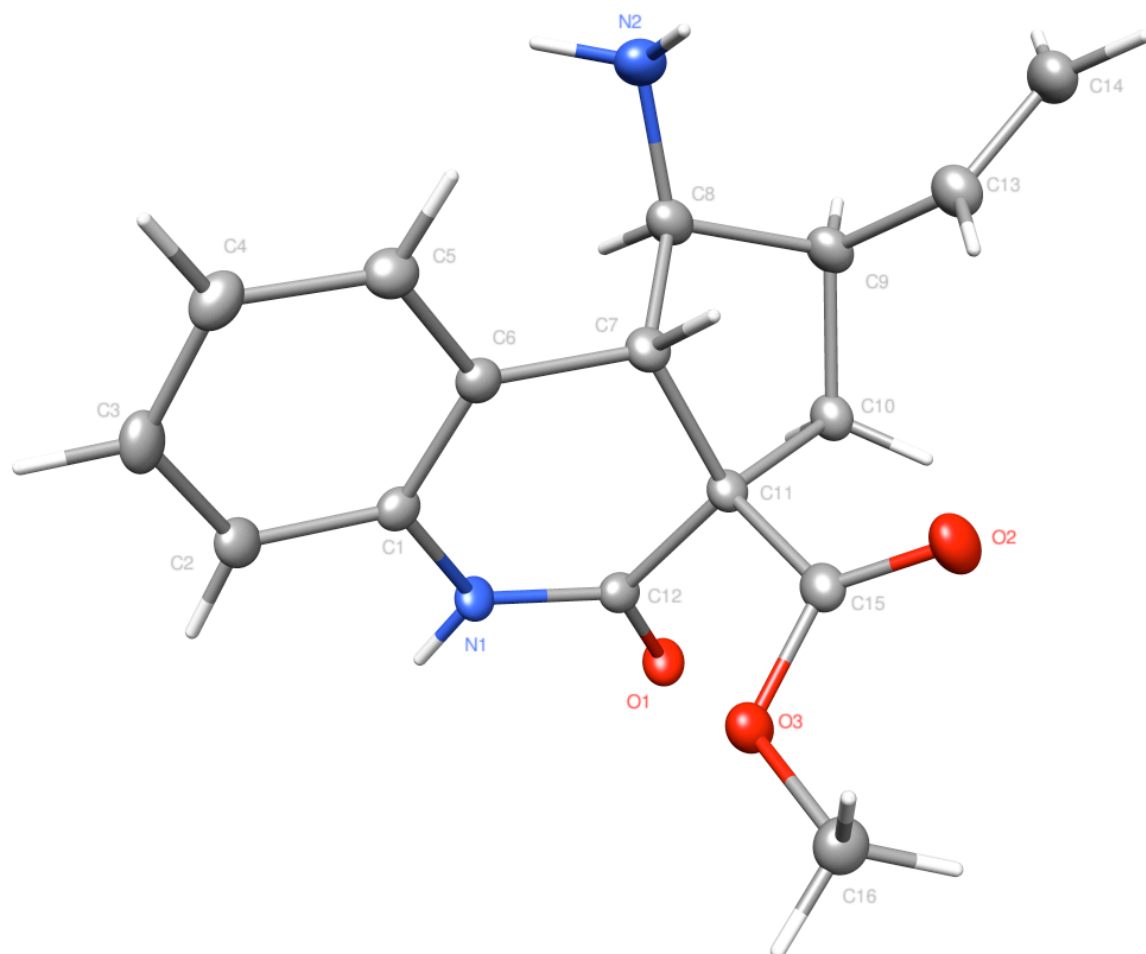


Table A7.1.2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for XXa (CCDC 820779). $U(\text{eq})$ is defined as the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U_{eq}
O(1)	4408(1)	7089(1)	4178(1)	19(1)
O(2)	7024(1)	9577(1)	237(1)	26(1)
O(3)	6615(1)	7073(1)	1117(1)	19(1)
N(1)	7276(1)	5626(1)	3956(1)	16(1)
N(2)	10859(2)	9851(1)	3092(1)	24(1)
C(1)	9253(1)	5399(1)	3465(1)	15(1)
C(2)	10235(2)	3896(1)	3734(1)	18(1)
C(3)	12183(2)	3662(1)	3300(1)	20(1)
C(4)	13148(2)	4913(1)	2592(1)	20(1)
C(5)	12157(2)	6406(1)	2289(1)	19(1)
C(6)	10199(2)	6674(1)	2726(1)	15(1)
C(7)	9129(2)	8291(1)	2420(1)	16(1)
C(8)	9097(2)	9371(1)	3279(1)	20(1)
C(9)	7562(2)	10747(1)	2922(1)	19(1)
C(10)	6011(2)	9897(1)	2999(1)	18(1)
C(11)	7013(1)	8352(1)	2576(1)	14(1)
C(12)	6129(2)	6970(1)	3640(1)	15(1)
C(13)	8229(2)	11823(1)	1535(1)	22(1)
C(14)	8438(2)	13284(2)	1290(1)	26(1)
C(15)	6863(2)	8427(1)	1186(1)	16(1)
C(16)	6494(2)	7061(2)	-190(1)	21(1)

Table A7.1.3. Bond lengths [$\text{\AA}$] and angles [$^\circ$] for **240** (CCDC 820779).

O(1)-C(12)	1.2396(13)
O(2)-C(15)	1.2129(13)
O(3)-C(15)	1.3331(13)
O(3)-C(16)	1.4571(14)
N(1)-C(12)	1.3493(14)
N(1)-C(1)	1.4101(14)
N(1)-H(1)	0.894(14)
N(2)-C(8)	1.4532(15)
N(2)-H(2A)	0.874(16)
N(2)-H(2B)	0.923(16)
C(1)-C(2)	1.3935(15)
C(1)-C(6)	1.3990(14)
C(2)-C(3)	1.3881(16)
C(2)-H(2)	0.958(12)
C(3)-C(4)	1.3862(17)
C(3)-H(3)	0.963(12)
C(4)-C(5)	1.3918(16)
C(4)-H(4)	0.941(14)
C(5)-C(6)	1.3954(15)
C(5)-H(5)	0.949(13)
C(6)-C(7)	1.5046(15)
C(7)-C(8)	1.5555(16)
C(7)-C(11)	1.5630(14)
C(7)-H(7)	1.000(13)
C(8)-C(9)	1.5509(16)
C(8)-H(8)	1.005(12)
C(9)-C(13)	1.5060(16)
C(9)-C(10)	1.5433(16)
C(9)-H(9)	0.980(13)
C(10)-C(11)	1.5665(15)
C(10)-H(10A)	0.948(12)
C(10)-H(10B)	0.995(12)
C(11)-C(15)	1.5308(15)
C(11)-C(12)	1.5333(14)
C(13)-C(14)	1.3213(17)
C(13)-H(13)	1.001(14)
C(14)-H(14A)	0.955(14)
C(14)-H(14B)	0.968(14)
C(16)-H(16A)	0.990(13)
C(16)-H(16B)	0.938(13)
C(16)-H(16C)	0.944(14)
C(15)-O(3)-C(16)	115.23(9)
C(12)-N(1)-C(1)	125.72(9)
C(12)-N(1)-H(1)	116.1(9)
C(1)-N(1)-H(1)	118.1(9)
C(8)-N(2)-H(2A)	111.6(10)
C(8)-N(2)-H(2B)	111.6(9)
H(2A)-N(2)-H(2B)	106.0(14)
C(2)-C(1)-C(6)	121.00(10)

C(2)-C(1)-N(1)	118.99(10)
C(6)-C(1)-N(1)	120.01(10)
C(3)-C(2)-C(1)	119.60(10)
C(3)-C(2)-H(2)	121.6(8)
C(1)-C(2)-H(2)	118.7(8)
C(2)-C(3)-C(4)	120.27(11)
C(2)-C(3)-H(3)	118.2(7)
C(4)-C(3)-H(3)	121.5(7)
C(3)-C(4)-C(5)	119.80(11)
C(3)-C(4)-H(4)	119.3(8)
C(5)-C(4)-H(4)	120.8(8)
C(4)-C(5)-C(6)	121.02(11)
C(4)-C(5)-H(5)	121.5(8)
C(6)-C(5)-H(5)	117.5(8)
C(5)-C(6)-C(1)	118.25(10)
C(5)-C(6)-C(7)	121.02(10)
C(1)-C(6)-C(7)	120.72(9)
C(6)-C(7)-C(8)	116.70(9)
C(6)-C(7)-C(11)	114.37(9)
C(8)-C(7)-C(11)	104.20(9)
C(6)-C(7)-H(7)	107.1(8)
C(8)-C(7)-H(7)	105.8(7)
C(11)-C(7)-H(7)	108.1(7)
N(2)-C(8)-C(9)	113.55(10)
N(2)-C(8)-C(7)	117.56(10)
C(9)-C(8)-C(7)	102.10(9)
N(2)-C(8)-H(8)	108.3(7)
C(9)-C(8)-H(8)	107.3(7)
C(7)-C(8)-H(8)	107.4(7)
C(13)-C(9)-C(10)	111.69(10)
C(13)-C(9)-C(8)	113.01(10)
C(10)-C(9)-C(8)	101.94(9)
C(13)-C(9)-H(9)	109.3(7)
C(10)-C(9)-H(9)	112.2(7)
C(8)-C(9)-H(9)	108.5(7)
C(9)-C(10)-C(11)	107.07(9)
C(9)-C(10)-H(10A)	113.9(7)
C(11)-C(10)-H(10A)	109.5(7)
C(9)-C(10)-H(10B)	109.0(7)
C(11)-C(10)-H(10B)	108.6(7)
H(10A)-C(10)-H(10B)	108.6(10)
C(15)-C(11)-C(12)	109.43(9)
C(15)-C(11)-C(7)	107.53(8)
C(12)-C(11)-C(7)	114.40(9)
C(15)-C(11)-C(10)	110.87(9)
C(12)-C(11)-C(10)	110.03(9)
C(7)-C(11)-C(10)	104.48(8)
O(1)-C(12)-N(1)	121.40(10)
O(1)-C(12)-C(11)	120.58(9)
N(1)-C(12)-C(11)	118.01(9)
C(14)-C(13)-C(9)	125.48(12)
C(14)-C(13)-H(13)	120.0(8)
C(9)-C(13)-H(13)	114.5(8)
C(13)-C(14)-H(14A)	119.3(8)

C(13)-C(14)-H(14B)	122.8(8)
H(14A)-C(14)-H(14B)	117.8(11)
O(2)-C(15)-O(3)	123.70(10)
O(2)-C(15)-C(11)	123.68(10)
O(3)-C(15)-C(11)	112.57(9)
O(3)-C(16)-H(16A)	110.0(8)
O(3)-C(16)-H(16B)	107.2(8)
H(16A)-C(16)-H(16B)	108.9(11)
O(3)-C(16)-H(16C)	109.2(8)
H(16A)-C(16)-H(16C)	112.1(11)
H(16B)-C(16)-H(16C)	109.3(1)

Table A7.1.4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^4$) for **240** (CCDC 820779). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
O(1)	135(4)	188(4)	200(4)	-10(3)	-24(3)	-30(3)
O(2)	364(5)	196(4)	198(4)	13(3)	-101(4)	-86(4)
O(3)	230(4)	166(4)	166(4)	-23(3)	-69(3)	-42(3)
N(1)	132(4)	148(4)	154(4)	6(3)	-27(3)	-38(3)
N(2)	243(5)	230(5)	277(6)	-18(4)	-111(5)	-80(4)
C(1)	131(5)	176(5)	124(5)	-31(4)	-36(4)	-24(4)
C(2)	186(5)	172(5)	156(5)	-16(4)	-55(4)	-29(4)
C(3)	204(6)	191(6)	178(5)	-36(4)	-66(4)	26(4)
C(4)	130(5)	257(6)	193(6)	-63(4)	-35(4)	2(4)
C(5)	155(5)	209(6)	189(5)	-37(4)	-28(4)	-49(4)
C(6)	143(5)	168(5)	152(5)	-38(4)	-45(4)	-25(4)
C(7)	135(5)	160(5)	165(5)	-13(4)	-22(4)	-42(4)
C(8)	215(6)	178(5)	193(6)	-28(4)	-59(4)	-51(4)
C(9)	219(6)	163(5)	193(5)	-50(4)	-38(4)	-41(4)
C(10)	157(5)	161(5)	187(5)	-38(4)	-28(4)	-15(4)
C(11)	120(5)	142(5)	146(5)	-18(4)	-19(4)	-31(4)
C(12)	152(5)	160(5)	126(5)	-20(4)	-39(4)	-40(4)
C(13)	202(6)	185(6)	227(6)	-39(4)	-35(4)	-34(4)
C(14)	269(7)	199(6)	314(7)	-16(5)	-124(5)	-49(5)
C(15)	128(5)	158(5)	183(5)	-35(4)	-29(4)	-15(4)
C(16)	244(6)	218(6)	173(6)	-46(4)	-72(5)	-37(5)

Table A7.1.5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **240** (CCDC 820779).

	x	y	z	U _{iso}
H(1)	6719(19)	4828(16)	4556(14)	29(4)
H(2)	9539(17)	3045(15)	4204(13)	21(3)
H(2A)	11470(20)	10154(18)	2232(16)	40(4)
H(2B)	11660(20)	9042(19)	3473(16)	43(4)
H(3)	12833(17)	2615(15)	3504(12)	18(3)
H(4)	14470(20)	4737(15)	2302(14)	29(4)
H(5)	12784(18)	7277(15)	1776(13)	26(4)
H(7)	9747(18)	8815(15)	1456(13)	24(3)
H(8)	8599(16)	8819(14)	4261(12)	14(3)
H(9)	7155(17)	11335(14)	3609(13)	19(3)
H(10A)	5241(16)	10483(14)	2433(12)	15(3)
H(10B)	5202(16)	9630(13)	3954(12)	14(3)
H(13)	8473(18)	11360(15)	762(14)	28(4)
H(14A)	8124(19)	13735(16)	2033(14)	32(4)
H(14B)	8860(19)	13939(16)	381(14)	28(4)
H(16A)	5459(19)	7866(15)	-436(13)	24(3)
H(16B)	6227(18)	6081(16)	-92(13)	22(3)
H(16C)	7662(19)	7209(15)	-849(14)	25(4)

Table A7.1.6. Hydrogen bonds for **240** (CCDC 820779) [$\text{\AA}$ and $^\circ$].

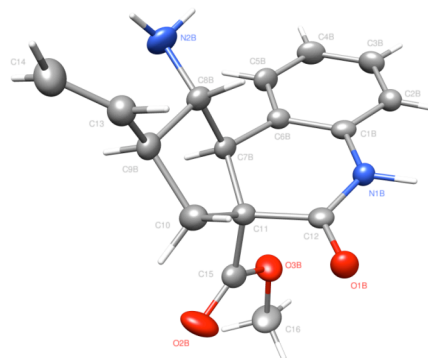
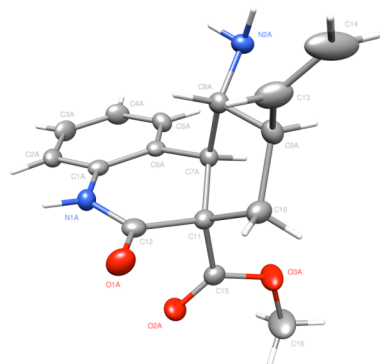
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1)...O(1)#1	0.894(14)	2.029(14)	2.9217(12)	175.5(13)
N(2)-H(2A)...O(2)#2	0.874(16)	2.483(16)	3.3366(15)	165.7(13)
N(2)-H(2B)...O(1)#3	0.923(16)	2.576(16)	3.4855(13)	168.5(13)

Symmetry transformations used to generate equivalent atoms:

#1 $-x+1, -y+1, -z+1$

#2 $-x+2, -y+2, -z$

#3 $x+1, y, z$

A7.2 CRYSTAL STRUCTURE ANALYSIS OF 241**241**

Note: The crystallographic data have been deposited in the Cambridge Database (CCDC). The deposition number is 820778."

Table A7.2.1. Crystal data and structure refinement for **241** (CCDC 820778).

Empirical formula	C ₁₆ H ₁₈ N ₂ O ₃		
Formula weight	286.32		
Crystallization Solvent	Dichloromethane/hexane		
Crystal Habit	Plate		
Crystal size	0.43 x 0.40 x 0.08 mm ³		
Crystal color	Colorless		
Data Collection			
Type of diffractometer	Bruker SMART 1000		
Wavelength	0.71073 Å MoKα		
Data Collection Temperature	100(2) K		
θ range for 9885 reflections used in lattice determination	2.42 to 28.07°		
Unit cell dimensions	a = 19.947(2) Å b = 13.3646(15) Å c = 11.2796(13) Å	α= 90° β= 105.507(2)° γ = 90°	
Volume	2897.5(6) Å ³		
Z	8		
Crystal system	Monoclinic		
Space group	P2(1)/c		
Density (calculated)	1.313 Mg/m ³		
F(000)	1216		
Data collection program	Bruker SMART v5.630		
θ range for data collection	1.06 to 29.00°		
Completeness to θ = 29.00°	92.1 %		
Index ranges	-26 ≤ h ≤ 26, -17 ≤ k ≤ 17, -15 ≤ l ≤ 15		
Data collection scan type	ω scans at 5 settings		
Data reduction program	Bruker SAINT-Plus v7.66A		
Reflections collected	44322		
Independent reflections	7100 [R _{int} = 0.0500]		
Absorption coefficient	0.092 mm ⁻¹		
Absorption correction	None		
Max. and min. transmission	0.9927	and	0.9617

Table A7.2.1. (cont.)

Structure solution and Refinement

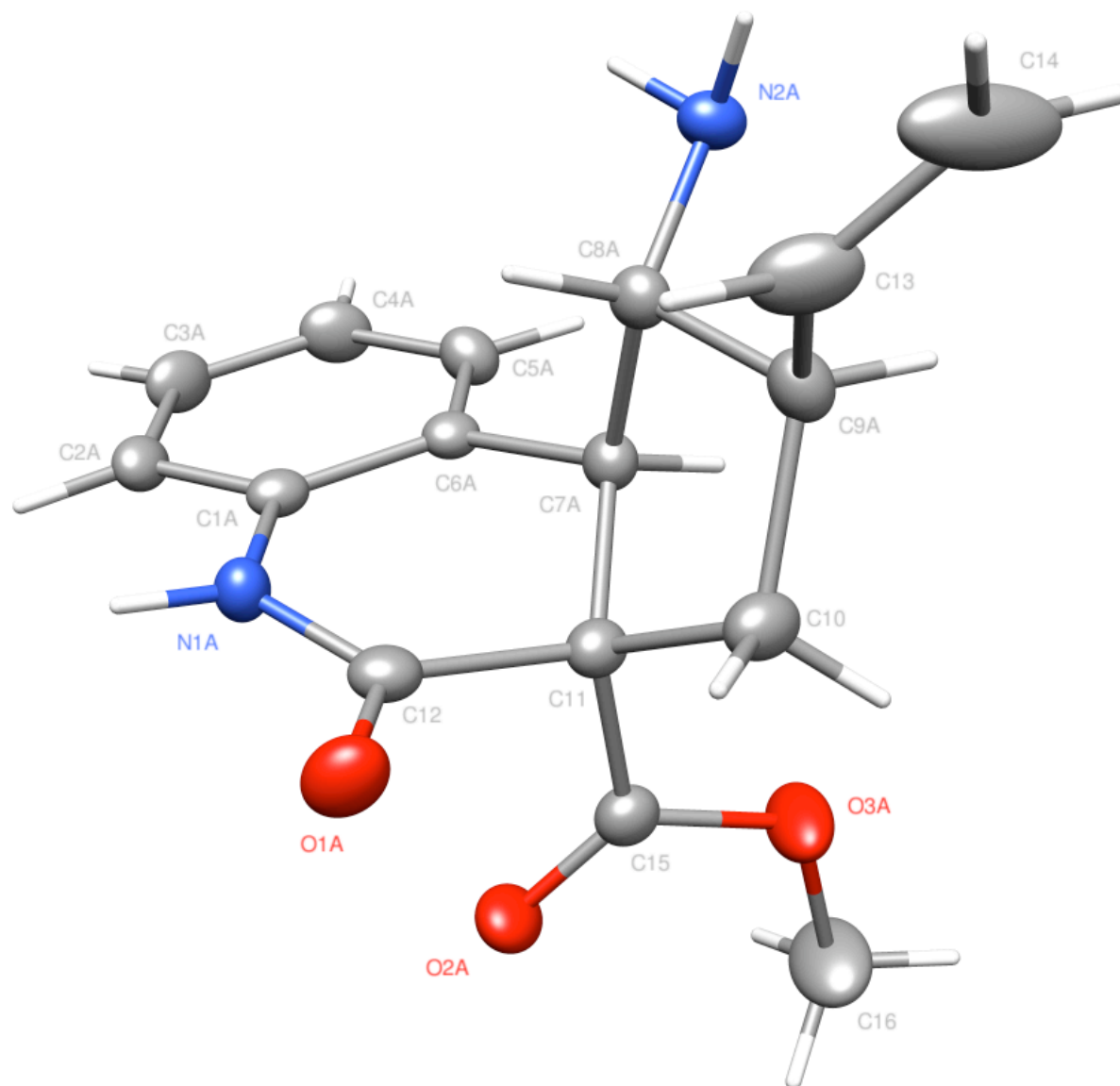
Structure solution program	SHELXS-97 (Sheldrick, 2008)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Difference Fourier map
Structure refinement program	SHELXL-97 (Sheldrick, 2008)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	7100 / 0 / 523
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F^2	2.160
Final R indices [$I > 2\sigma(I)$, 5019 reflections]	$R1 = 0.0507$, $wR2 = 0.0645$
R indices (all data)	$R1 = 0.0748$, $wR2 = 0.0664$
Type of weighting scheme used	Sigma
Weighting scheme used	$w = 1/\sigma^2(F_o^2)$
Max shift/error	0.001
Average shift/error	0.000
Largest diff. peak and hole	0.362 and -0.287 e. $\text{\AA}^{-3}$

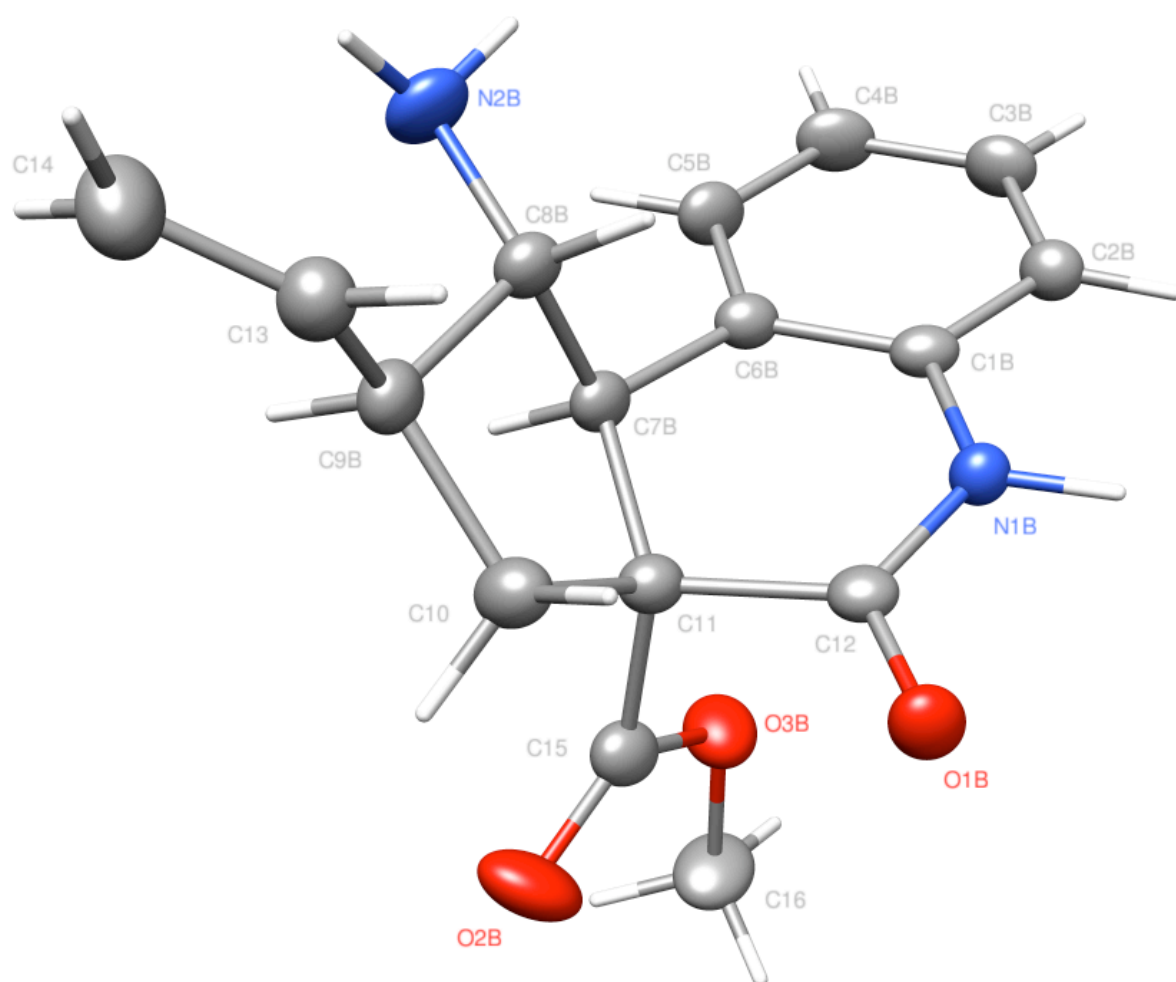
Special Refinement Details

Crystals were mounted on a glass fiber using Paratone oil then placed on the diffractometer under a nitrogen stream at 100K.

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

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





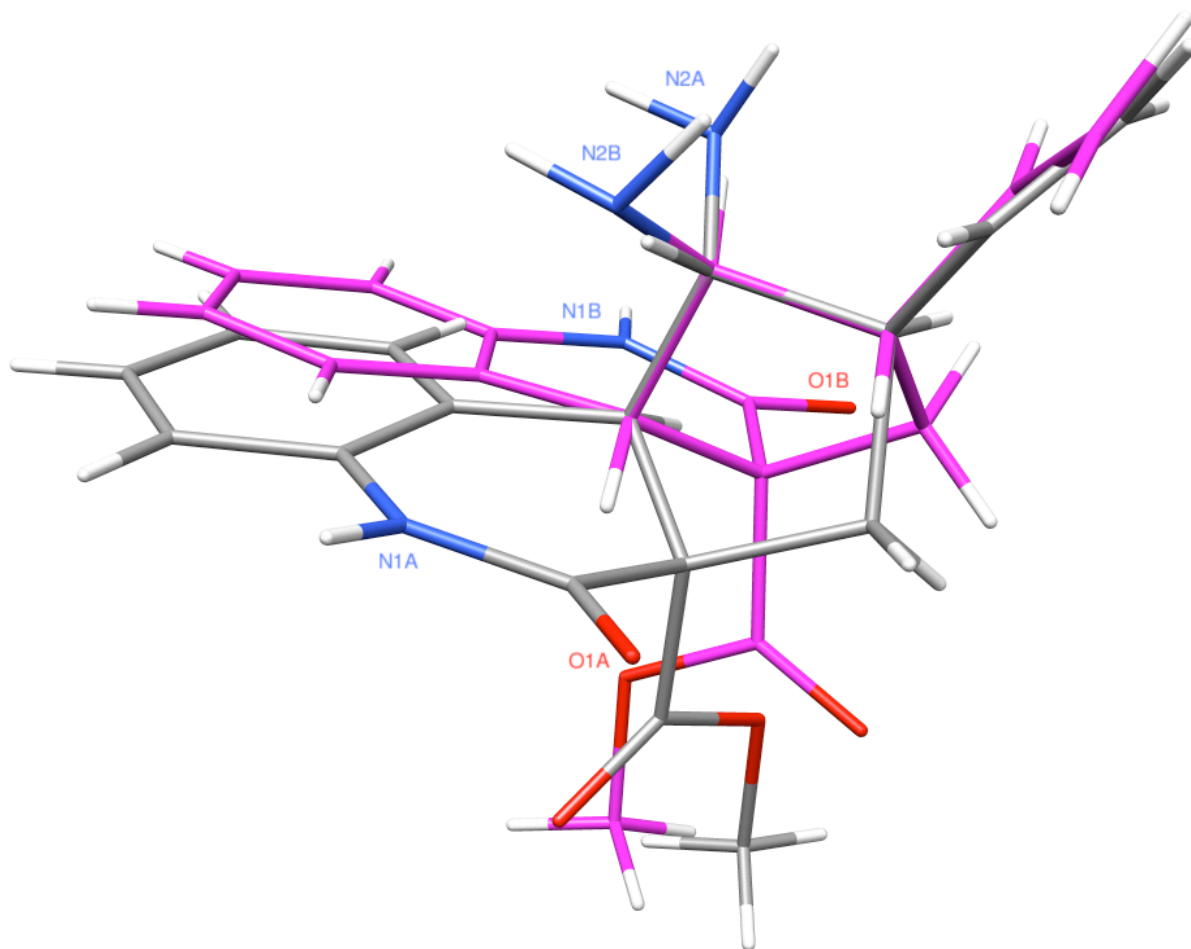


Table A7.2.2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **241** (CCDC 820778). $U(\text{eq})$ is defined as the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U_{eq}
O(1A)	6702(1)	965(1)	10260(1)	30(1)
O(2A)	5913(1)	-380(1)	7880(1)	29(1)
O(3A)	6207(1)	438(1)	6371(1)	40(1)
N(1A)	5544(1)	1226(1)	9712(1)	21(1)
N(2A)	5566(1)	3969(1)	7309(1)	22(1)
C(1A)	4910(1)	1456(1)	8853(1)	18(1)
C(2A)	4287(1)	1269(1)	9137(1)	22(1)
C(3A)	3667(1)	1512(1)	8294(1)	27(1)
C(4A)	3665(1)	1922(1)	7172(2)	28(1)
C(5A)	4288(1)	2101(1)	6890(1)	23(1)
C(6A)	4918(1)	1880(1)	7728(1)	18(1)
C(7A)	5609(1)	2116(1)	7503(1)	19(1)
C(8A)	5924(1)	3121(1)	8029(1)	20(1)
C(9A)	6683(1)	3049(1)	7979(1)	22(1)
C(10A)	6869(1)	1925(1)	8123(2)	26(1)
C(11A)	6188(1)	1377(1)	8134(1)	20(1)
C(12A)	6171(1)	1172(1)	9462(1)	22(1)
C(13A)	7153(1)	3721(1)	8882(2)	32(1)
C(14A)	7450(1)	4528(1)	8569(3)	54(1)
C(15A)	6091(1)	375(1)	7477(1)	23(1)
C(16A)	6124(1)	-490(2)	5675(2)	50(1)
O(1B)	9130(1)	9861(1)	5062(1)	29(1)
O(2B)	8139(1)	9887(1)	7206(1)	45(1)
O(3B)	9269(1)	9904(1)	8214(1)	36(1)
N(1B)	10085(1)	9132(1)	6282(1)	22(1)
N(2B)	9194(1)	5996(1)	7029(1)	38(1)
C(1B)	10439(1)	8525(1)	7274(1)	22(1)
C(2B)	11161(1)	8550(1)	7645(1)	26(1)
C(3B)	11516(1)	7954(1)	8606(1)	29(1)
C(4B)	11153(1)	7340(1)	9203(2)	33(1)
C(5B)	10430(1)	7324(1)	8825(1)	30(1)
C(6B)	10065(1)	7911(1)	7857(1)	23(1)
C(7B)	9289(1)	7838(1)	7351(1)	24(1)
C(8B)	9075(1)	6972(1)	6433(1)	27(1)
C(9B)	8305(1)	7173(1)	5848(2)	28(1)
C(10B)	8283(1)	8303(1)	5632(2)	31(1)
C(11B)	8929(1)	8747(1)	6584(1)	24(1)
C(12B)	9393(1)	9284(1)	5913(1)	22(1)
C(13B)	8014(1)	6569(1)	4712(2)	33(1)
C(14B)	7622(1)	5776(1)	4621(2)	47(1)
C(15B)	8714(1)	9570(1)	7353(1)	29(1)

C(16B)	9139(1)	10740(1)	8951(2)	42(1)
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Table A7.2.3. Bond lengths [$\text{\AA}$] and angles [$^\circ$] for **241** (CCDC 820778).

O(1A)-C(12A)	1.2239(15)
O(2A)-C(15A)	1.1996(15)
O(3A)-C(15A)	1.3307(16)
O(3A)-C(16A)	1.4539(19)
N(1A)-C(12A)	1.3544(16)
N(1A)-C(1A)	1.4057(16)
N(1A)-H(1A)	0.877(14)
N(2A)-C(8A)	1.4642(17)
N(2A)-H(2A2)	0.878(14)
N(2A)-H(2A3)	0.950(14)
C(1A)-C(2A)	1.3868(18)
C(1A)-C(6A)	1.3936(17)
C(2A)-C(3A)	1.3823(19)
C(2A)-H(2A)	0.968(12)
C(3A)-C(4A)	1.378(2)
C(3A)-H(3A)	0.953(11)
C(4A)-C(5A)	1.3832(19)
C(4A)-H(4A)	0.945(13)
C(5A)-C(6A)	1.3878(18)
C(5A)-H(5A)	0.941(11)
C(6A)-C(7A)	1.4997(18)
C(7A)-C(8A)	1.5328(18)
C(7A)-C(11A)	1.5427(18)
C(7A)-H(7A)	0.938(11)
C(8A)-C(9A)	1.5334(18)
C(8A)-H(8A)	0.975(11)
C(9A)-C(13A)	1.487(2)
C(9A)-C(10A)	1.5448(19)
C(9A)-H(9A)	0.929(12)
C(10A)-C(11A)	1.5453(19)
C(10A)-H(10A)	0.949(13)
C(10A)-H(10B)	0.966(13)
C(11A)-C(15A)	1.5177(18)
C(11A)-C(12A)	1.5333(18)
C(13A)-C(14A)	1.323(2)
C(13A)-H(13A)	0.972(13)
C(14A)-H(14A)	0.99(2)
C(14A)-H(14B)	0.958(17)
C(16A)-H(16A)	0.984(16)
C(16A)-H(16B)	0.945(18)
C(16A)-H(16C)	0.977(16)
O(1B)-C(12B)	1.2332(15)
O(2B)-C(15B)	1.1911(16)
O(3B)-C(15B)	1.3395(17)
O(3B)-C(16B)	1.4563(18)
N(1B)-C(12B)	1.3454(17)
N(1B)-C(1B)	1.4098(17)
N(1B)-H(1B)	0.984(15)
N(2B)-C(8B)	1.4569(18)
N(2B)-H(2B2)	0.944(17)
N(2B)-H(2B3)	1.006(19)
C(1B)-C(2B)	1.3877(18)
C(1B)-C(6B)	1.3878(18)
C(2B)-C(3B)	1.378(2)

C(2B)-H(2B)	0.963(12)
C(3B)-C(4B)	1.384(2)
C(3B)-H(3B)	0.924(12)
C(4B)-C(5B)	1.390(2)
C(4B)-H(4B)	0.996(13)
C(5B)-C(6B)	1.3835(19)
C(5B)-H(5B)	0.958(13)
C(6B)-C(7B)	1.5015(19)
C(7B)-C(8B)	1.5351(19)
C(7B)-C(11B)	1.5521(19)
C(7B)-H(7B)	1.020(12)
C(8B)-C(9B)	1.5252(19)
C(8B)-H(8B)	1.039(12)
C(9B)-C(13B)	1.494(2)
C(9B)-C(10B)	1.529(2)
C(9B)-H(9B)	1.001(13)
C(10B)-C(11B)	1.558(2)
C(10B)-H(10C)	0.992(14)
C(10B)-H(10D)	1.061(15)
C(11B)-C(12B)	1.5233(18)
C(11B)-C(15B)	1.5307(19)
C(13B)-C(14B)	1.304(2)
C(13B)-H(13B)	1.017(15)
C(14B)-H(14C)	1.009(16)
C(14B)-H(14D)	1.028(18)
C(16B)-H(16D)	1.006(15)
C(16B)-H(16E)	1.000(16)
C(16B)-H(16F)	1.011(15)

C(15A)-O(3A)-C(16A)	115.42(13)
C(12A)-N(1A)-C(1A)	125.33(13)
C(12A)-N(1A)-H(1A)	116.4(9)
C(1A)-N(1A)-H(1A)	118.3(9)
C(8A)-N(2A)-H(2A2)	110.6(9)
C(8A)-N(2A)-H(2A3)	112.2(8)
H(2A2)-N(2A)-H(2A3)	102.5(12)
C(2A)-C(1A)-C(6A)	120.81(13)
C(2A)-C(1A)-N(1A)	119.86(13)
C(6A)-C(1A)-N(1A)	119.33(12)
C(3A)-C(2A)-C(1A)	119.39(14)
C(3A)-C(2A)-H(2A)	121.8(7)
C(1A)-C(2A)-H(2A)	118.8(7)
C(4A)-C(3A)-C(2A)	120.60(15)
C(4A)-C(3A)-H(3A)	119.6(7)
C(2A)-C(3A)-H(3A)	119.7(7)
C(3A)-C(4A)-C(5A)	119.74(15)
C(3A)-C(4A)-H(4A)	118.2(8)
C(5A)-C(4A)-H(4A)	122.1(8)
C(4A)-C(5A)-C(6A)	120.88(14)
C(4A)-C(5A)-H(5A)	121.6(7)
C(6A)-C(5A)-H(5A)	117.5(7)
C(5A)-C(6A)-C(1A)	118.56(13)
C(5A)-C(6A)-C(7A)	123.09(13)
C(1A)-C(6A)-C(7A)	118.29(12)

C(6A)-C(7A)-C(8A)	114.80(11)
C(6A)-C(7A)-C(11A)	113.34(11)
C(8A)-C(7A)-C(11A)	101.70(11)
C(6A)-C(7A)-H(7A)	109.6(7)
C(8A)-C(7A)-H(7A)	107.1(7)
C(11A)-C(7A)-H(7A)	109.9(7)
N(2A)-C(8A)-C(7A)	112.03(11)
N(2A)-C(8A)-C(9A)	111.57(12)
C(7A)-C(8A)-C(9A)	103.79(11)
N(2A)-C(8A)-H(8A)	111.9(7)
C(7A)-C(8A)-H(8A)	107.7(7)
C(9A)-C(8A)-H(8A)	109.5(7)
C(13A)-C(9A)-C(8A)	112.64(12)
C(13A)-C(9A)-C(10A)	115.17(13)
C(8A)-C(9A)-C(10A)	105.56(11)
C(13A)-C(9A)-H(9A)	108.2(8)
C(8A)-C(9A)-H(9A)	106.8(7)
C(10A)-C(9A)-H(9A)	108.1(7)
C(9A)-C(10A)-C(11A)	105.98(11)
C(9A)-C(10A)-H(10A)	112.4(8)
C(11A)-C(10A)-H(10A)	109.9(8)
C(9A)-C(10A)-H(10B)	111.1(8)
C(11A)-C(10A)-H(10B)	111.2(8)
H(10A)-C(10A)-H(10B)	106.4(11)
C(15A)-C(11A)-C(12A)	106.60(11)
C(15A)-C(11A)-C(7A)	110.96(11)
C(12A)-C(11A)-C(7A)	110.81(11)
C(15A)-C(11A)-C(10A)	114.37(11)
C(12A)-C(11A)-C(10A)	110.02(12)
C(7A)-C(11A)-C(10A)	104.15(11)
O(1A)-C(12A)-N(1A)	121.61(13)
O(1A)-C(12A)-C(11A)	121.19(13)
N(1A)-C(12A)-C(11A)	117.20(12)
C(14A)-C(13A)-C(9A)	123.67(19)
C(14A)-C(13A)-H(13A)	119.8(8)
C(9A)-C(13A)-H(13A)	116.6(8)
C(13A)-C(14A)-H(14A)	124.0(13)
C(13A)-C(14A)-H(14B)	116.5(11)
H(14A)-C(14A)-H(14B)	119.5(16)
O(2A)-C(15A)-O(3A)	123.49(13)
O(2A)-C(15A)-C(11A)	124.74(13)
O(3A)-C(15A)-C(11A)	111.73(12)
O(3A)-C(16A)-H(16A)	109.5(10)
O(3A)-C(16A)-H(16B)	104.6(11)
H(16A)-C(16A)-H(16B)	112.8(15)
O(3A)-C(16A)-H(16C)	109.5(10)
H(16A)-C(16A)-H(16C)	106.8(14)
H(16B)-C(16A)-H(16C)	113.6(15)
C(15B)-O(3B)-C(16B)	115.53(13)
C(12B)-N(1B)-C(1B)	126.00(13)
C(12B)-N(1B)-H(1B)	115.0(9)
C(1B)-N(1B)-H(1B)	118.7(9)
C(8B)-N(2B)-H(2B2)	111.7(11)
C(8B)-N(2B)-H(2B3)	104.7(10)

H(2B2)-N(2B)-H(2B3)	112.9(14)
C(2B)-C(1B)-C(6B)	121.21(13)
C(2B)-C(1B)-N(1B)	119.00(13)
C(6B)-C(1B)-N(1B)	119.78(13)
C(3B)-C(2B)-C(1B)	119.80(15)
C(3B)-C(2B)-H(2B)	121.2(7)
C(1B)-C(2B)-H(2B)	119.0(7)
C(2B)-C(3B)-C(4B)	119.97(15)
C(2B)-C(3B)-H(3B)	120.0(8)
C(4B)-C(3B)-H(3B)	120.0(8)
C(3B)-C(4B)-C(5B)	119.63(15)
C(3B)-C(4B)-H(4B)	120.6(8)
C(5B)-C(4B)-H(4B)	119.7(8)
C(6B)-C(5B)-C(4B)	121.26(15)
C(6B)-C(5B)-H(5B)	118.1(8)
C(4B)-C(5B)-H(5B)	120.6(8)
C(5B)-C(6B)-C(1B)	118.13(14)
C(5B)-C(6B)-C(7B)	122.38(13)
C(1B)-C(6B)-C(7B)	119.26(13)
C(6B)-C(7B)-C(8B)	112.21(12)
C(6B)-C(7B)-C(11B)	115.94(12)
C(8B)-C(7B)-C(11B)	102.14(11)
C(6B)-C(7B)-H(7B)	109.4(7)
C(8B)-C(7B)-H(7B)	107.4(7)
C(11B)-C(7B)-H(7B)	109.2(7)
N(2B)-C(8B)-C(9B)	112.24(13)
N(2B)-C(8B)-C(7B)	112.46(13)
C(9B)-C(8B)-C(7B)	103.05(12)
N(2B)-C(8B)-H(8B)	112.5(6)
C(9B)-C(8B)-H(8B)	107.8(7)
C(7B)-C(8B)-H(8B)	108.2(7)
C(13B)-C(9B)-C(8B)	113.00(13)
C(13B)-C(9B)-C(10B)	114.15(13)
C(8B)-C(9B)-C(10B)	103.03(12)
C(13B)-C(9B)-H(9B)	109.4(7)
C(8B)-C(9B)-H(9B)	104.5(7)
C(10B)-C(9B)-H(9B)	112.3(7)
C(9B)-C(10B)-C(11B)	106.44(12)
C(9B)-C(10B)-H(10C)	111.1(8)
C(11B)-C(10B)-H(10C)	109.8(8)
C(9B)-C(10B)-H(10D)	109.6(8)
C(11B)-C(10B)-H(10D)	107.0(8)
H(10C)-C(10B)-H(10D)	112.8(12)
C(12B)-C(11B)-C(15B)	104.11(11)
C(12B)-C(11B)-C(7B)	113.14(11)
C(15B)-C(11B)-C(7B)	113.85(12)
C(12B)-C(11B)-C(10B)	109.70(12)
C(15B)-C(11B)-C(10B)	111.03(12)
C(7B)-C(11B)-C(10B)	105.12(11)
O(1B)-C(12B)-N(1B)	121.49(13)
O(1B)-C(12B)-C(11B)	119.52(13)
N(1B)-C(12B)-C(11B)	118.97(13)
C(14B)-C(13B)-C(9B)	126.38(18)
C(14B)-C(13B)-H(13B)	120.7(9)

C(9B)-C(13B)-H(13B)	112.9(8)
C(13B)-C(14B)-H(14C)	117.8(10)
C(13B)-C(14B)-H(14D)	119.9(10)
H(14C)-C(14B)-H(14D)	122.0(14)
O(2B)-C(15B)-O(3B)	124.10(14)
O(2B)-C(15B)-C(11B)	125.52(15)
O(3B)-C(15B)-C(11B)	110.37(13)
O(3B)-C(16B)-H(16D)	108.7(9)
O(3B)-C(16B)-H(16E)	102.4(9)
H(16D)-C(16B)-H(16E)	117.4(13)
O(3B)-C(16B)-H(16F)	111.0(9)
H(16D)-C(16B)-H(16F)	104.4(12)
H(16E)-C(16B)-H(16F)	113.0(13)

Table A7.2.4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^4$) for **241** (CCDC 820778). The anisotropic displacement factor exponent takes the form: $-2\pi^2[$

$$h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}$$

	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
O(1A)	253(6)	371(7)	237(6)	-16(5)	14(5)	87(5)
O(2A)	349(6)	203(6)	340(6)	-11(5)	151(5)	-42(5)
O(3A)	730(8)	230(6)	323(7)	-81(5)	306(6)	-52(6)
N(1A)	236(7)	231(7)	176(7)	22(6)	75(6)	28(6)
N(2A)	235(8)	169(7)	260(7)	-7(6)	66(6)	-6(6)
C(1A)	191(8)	137(7)	206(8)	-36(6)	40(6)	1(6)
C(2A)	278(9)	173(8)	245(9)	-15(7)	112(7)	-24(7)
C(3A)	211(9)	257(9)	359(10)	-34(8)	112(8)	-40(7)
C(4A)	198(9)	274(9)	334(10)	-11(8)	10(8)	-2(7)
C(5A)	279(9)	203(8)	207(9)	7(7)	44(7)	-25(7)
C(6A)	205(8)	129(7)	202(8)	-32(6)	59(6)	-10(6)
C(7A)	228(8)	188(8)	161(8)	-3(6)	63(7)	1(6)
C(8A)	233(8)	194(8)	163(8)	2(7)	55(7)	4(7)
C(9A)	226(8)	222(9)	206(8)	27(7)	55(7)	-15(7)
C(10A)	232(9)	221(9)	338(10)	-20(8)	112(8)	8(7)
C(11A)	205(8)	176(8)	213(8)	-15(6)	73(6)	0(6)
C(12A)	253(9)	158(8)	237(9)	-19(7)	51(7)	22(7)
C(13A)	235(9)	288(10)	381(11)	-83(8)	-17(8)	55(8)
C(14A)	224(10)	263(11)	1040(20)	-139(13)	28(12)	-15(8)
C(15A)	214(8)	235(9)	241(9)	-3(7)	69(7)	31(7)
C(16A)	862(19)	309(12)	416(13)	-147(10)	319(13)	-61(12)
O(1B)	262(6)	314(6)	272(6)	94(5)	53(5)	48(5)
O(2B)	376(7)	523(8)	461(7)	-28(6)	106(6)	209(6)
O(3B)	371(7)	321(7)	408(7)	-122(5)	149(6)	-33(5)
N(1B)	212(7)	210(7)	226(7)	33(6)	54(6)	5(6)
N(2B)	411(10)	219(8)	492(10)	91(7)	91(8)	14(7)
C(1B)	263(9)	184(8)	203(8)	-19(6)	46(7)	39(7)
C(2B)	248(9)	242(9)	273(9)	-7(7)	66(7)	4(7)
C(3B)	228(9)	308(10)	290(9)	-1(8)	8(8)	46(8)
C(4B)	355(10)	328(10)	257(9)	54(8)	18(8)	98(8)
C(5B)	362(10)	266(9)	280(9)	74(7)	124(8)	38(8)
C(6B)	258(9)	206(8)	231(8)	4(7)	72(7)	26(7)
C(7B)	268(9)	203(8)	275(9)	48(7)	110(7)	10(7)
C(8B)	278(9)	202(9)	337(10)	32(7)	101(8)	2(7)
C(9B)	271(9)	234(9)	365(10)	11(8)	120(8)	-32(7)
C(10B)	248(9)	237(10)	431(11)	0(8)	47(8)	5(7)
C(11B)	242(8)	201(8)	277(9)	15(7)	79(7)	22(7)
C(12B)	244(9)	174(8)	238(9)	-29(7)	55(7)	21(7)
C(13B)	266(10)	279(10)	449(11)	-18(8)	99(8)	-21(8)
C(14B)	375(11)	426(12)	656(15)	-141(11)	227(11)	-88(9)

C(15B)	316(10)	266(9)	298(9)	61(7)	118(8)	29(8)
C(16B)	580(14)	312(11)	432(12)	-127(9)	232(12)	-18(10)

Table A7.2.5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **241** (CCDC 820778).

	x	y	z	U _{iso}
H(1A)	5539(7)	1098(10)	10472(13)	34(5)
H(2A2)	5783(7)	4531(10)	7573(13)	34(5)
H(2A3)	5119(7)	4079(10)	7431(12)	38(5)
H(2A)	4299(6)	966(9)	9922(11)	16(4)
H(3A)	3237(6)	1368(9)	8474(11)	15(4)
H(4A)	3231(7)	2080(9)	6620(12)	31(4)
H(5A)	4301(6)	2378(9)	6130(11)	16(4)
H(7A)	5564(5)	2131(8)	6654(11)	9(3)
H(8A)	5908(6)	3154(8)	8884(11)	11(3)
H(9A)	6693(6)	3246(9)	7194(11)	15(4)
H(10A)	7040(6)	1680(9)	7471(12)	29(4)
H(10B)	7229(7)	1801(9)	8872(12)	27(4)
H(13A)	7228(7)	3553(10)	9747(13)	36(5)
H(14A)	7393(10)	4747(16)	7705(19)	113(10)
H(14B)	7747(9)	4902(13)	9228(15)	66(6)
H(16A)	6398(8)	-1022(13)	6186(15)	61(6)
H(16B)	6281(9)	-339(12)	4975(17)	70(6)
H(16C)	5637(9)	-701(12)	5475(15)	59(6)
H(1B)	10359(8)	9538(11)	5853(14)	56(5)
H(2B2)	9672(9)	5832(13)	7271(16)	73(7)
H(2B3)	8911(9)	5518(14)	6404(17)	88(7)
H(2B)	11404(6)	8983(9)	7218(11)	18(4)
H(3B)	11996(7)	7978(9)	8865(12)	25(4)
H(4B)	11405(7)	6906(9)	9899(12)	31(4)
H(5B)	10172(7)	6897(10)	9223(12)	33(4)
H(7B)	9067(6)	7713(9)	8053(11)	19(4)
H(8B)	9335(6)	7055(8)	5755(11)	18(4)
H(9B)	8070(6)	6974(9)	6494(12)	29(4)
H(10C)	7851(7)	8599(10)	5759(13)	43(5)
H(10D)	8346(7)	8456(11)	4745(14)	52(5)
H(13B)	8177(7)	6812(11)	3980(14)	52(5)
H(14C)	7503(8)	5535(12)	5387(16)	67(6)
H(14D)	7481(9)	5385(13)	3807(17)	86(7)
H(16D)	8958(8)	11320(12)	8388(14)	52(5)
H(16E)	9600(8)	10826(12)	9569(15)	60(6)
H(16F)	8750(8)	10579(11)	9338(14)	51(5)

Table A7.2.6. Hydrogen bonds for **241** (CCDC 820778) [$\text{\AA}$ and $^\circ$].

D-H...A	d(D-H)	d(H...A)	d(D...A)	$\angle(\text{DHA})$
N(1A)-H(1A)...N(2A)#1	0.877(14)	2.060(14)	2.9300(18)	171.0(13)
N(2A)-H(2A3)...O(2A)#2	0.950(14)	2.120(14)	3.0283(17)	159.6(12)
N(1B)-H(1B)...O(1B)#3	0.984(15)	1.820(16)	2.7986(15)	172.3(13)
N(2B)-H(2B2)...O(3B)#4	0.944(17)	2.630(17)	3.4707(18)	148.6(14)

Symmetry transformations used to generate equivalent atoms:

#1 $x, -y+1/2, z+1/2$

#2 $-x+1, y+1/2, -z+3/2$

#3 $-x+2, -y+2, -z+1$

#4 $-x+2, y-1/2, -z+3/2$

APPENDIX 8

Catalytic Asymmetric Alkylations of

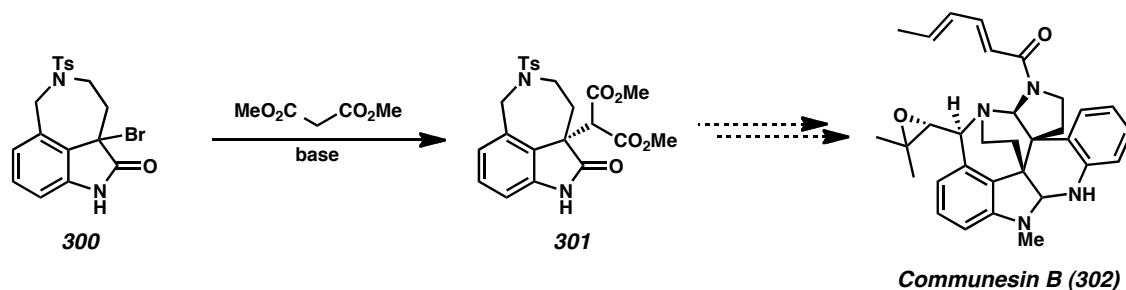
Ortho-Quinone Methides[†]

A8.1 INTRODUCTION

A8.1.1 ASYMMETRIC ALKYLATIONS OF HALO-OXINDOLES

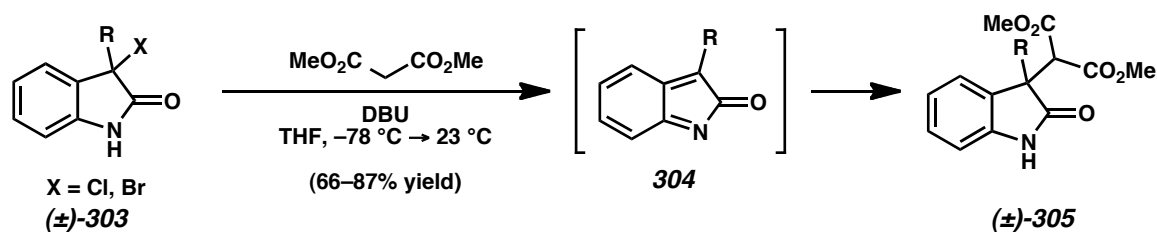
The enantioselective synthesis of chiral α -quaternary oxindoles and their application to total synthesis has been a long-standing goal in our research group. This project was initially inspired by our efforts toward natural product synthesis, wherein the asymmetric alkylation of a 3-halooxindole (**300**) was conceived as a method for installing one of the two vicinal quaternary centers in communesin B (**302**, Scheme A8.1.1). While a variety of other catalytic enantioselective methods for installing this motif have been developed, this transformation represented the first case in which the oxindole unit served as an electrophilic reaction partner in an enantioselective transformation.¹

[†] This appendix was adapted from a research report produced for the author's candidacy examination. Aspects of this work are currently being investigated in collaboration with Christopher Tonge, an undergraduate researcher in the Stoltz group.

Scheme A8.1.1. Proposed key step toward the synthesis of communesin B (**302**)

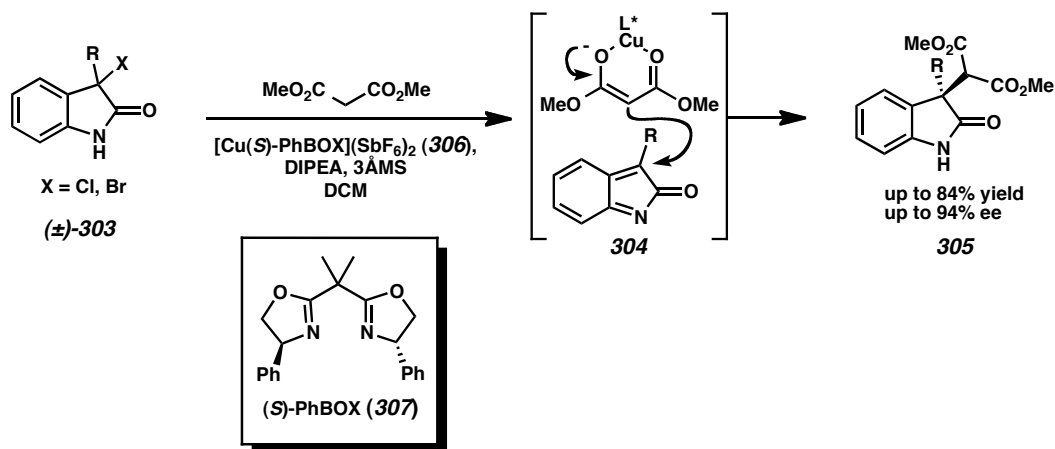
Our group reported conditions in 2007 for a non-stereoselective alkylation reaction of 3-haloindoles, which tolerated a variety of aryl and alkyl functionality at the 3-position, proceeding via a putative *ortho*-azaxylylene intermediate (**304**, Scheme A8.1.2).² The model compound for communesin B (**300**, *c.f.* Scheme A8.1.2) was alkylated in 87% yield.

Scheme A8.1.2. Discovery of the alkylation of 3-haloindoles to form racemic products

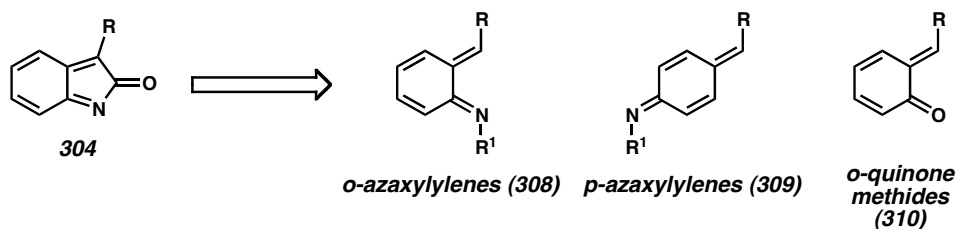


Soon afterward, the Stoltz group established conditions for an enantioselective variant of this reaction using a cationic copper (II) bisoxazoline complex (**306**).¹ With this catalytic system, quaternary stereocenters were installed in high yields and enantiomeric excesses (Scheme A8.1.3). Our group proposed that the copper catalyst binds to the malonate nucleophile, generating a chiral environment for reaction with prochiral *o*-azaxylylene **304**. This hypothesis suggests the potential for enantioselective nucleophilic additions to other prochiral, activated electrophiles.

Scheme A8.1.3. Catalytic enantioselective stereoablative alkylation of 3-haloindoles



We therefore considered acyclic analogues of the original system including acyclic *ortho*-azaxylylenes (**307**),³ *para*-azaxylylenes (**308**) and analogous *ortho*-quinone methides (**309**) (Scheme A8.1.4).

Scheme A8.1.4. Reactive intermediates analogous to cyclic *ortho*-azaxylylenes **304**

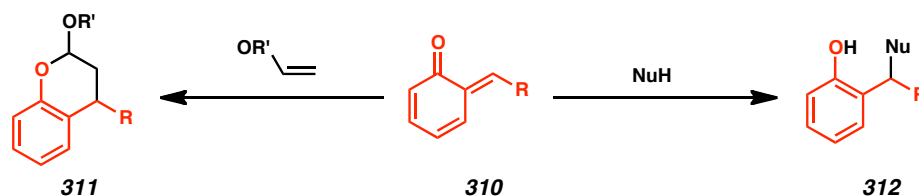
Some progress has been made toward investigating each of these compound classes within our research group.⁴ Described in this report are efforts to develop a method for asymmetric alkylations of *ortho*-quinone methides (OQMs).

A8.1.2 ORTHO-QUINONE METHIDES

Ortho-quinone methides (OQMs, **310**) are reactive intermediates observed in both natural and synthetic systems.⁵ Under ordinary circumstances, OQMs are transient species, formed in situ from a stable precursor, often by breaking aromaticity. Products

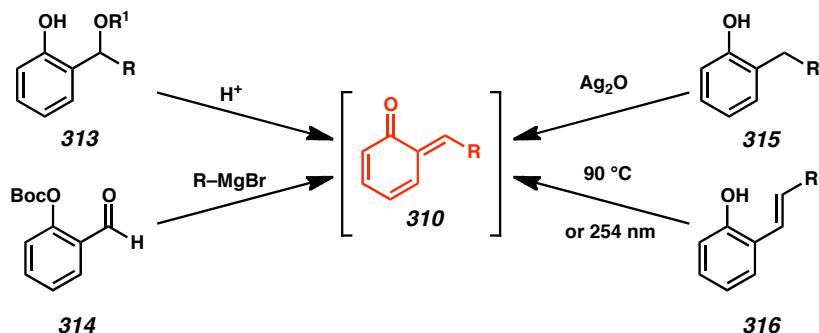
of OQMs primarily include [4+2] cycloaddition adducts (**311**) and 1,4-conjugate addition products (**312**), and their high reactivity is attributed to the rearomatization afforded through product formation (Scheme A8.1.5).

Scheme A8.1.5. Common reactions of ortho-quinone methides



OQMs can be generated from a number of precursors and under a variety of conditions. These include thermal,⁶ photochemical,⁷ oxidative,⁸ reductive,⁹ acidic¹⁰ and basic conditions (Scheme A8.1.6). Each of these methods carries certain advantages and drawbacks related to the stability and reactivity of the precursor, susceptibility to side reactions, and compatibility with the desired reaction mode.⁵ For the purposes of applying OQMs as electrophilic partners under conditions closely related to those optimized for 3-halooxindoles, a suitable precursor would be activated in the presence of base and a Lewis acid.

Scheme A8.1.6. Common ortho-quinone methide (**310**) precursors

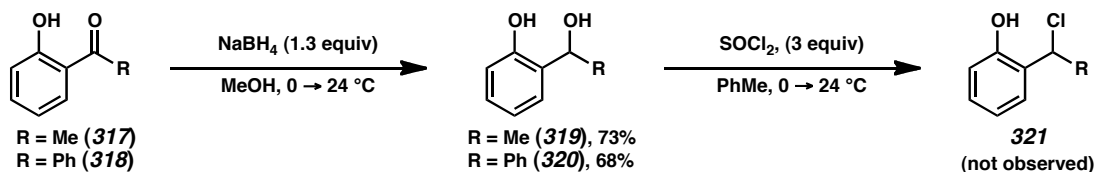


A8.2 DEVELOPMENT OF A BASE-ACTIVATED OQM PRECURSOR

A8.2.1 INITIAL EFFORTS

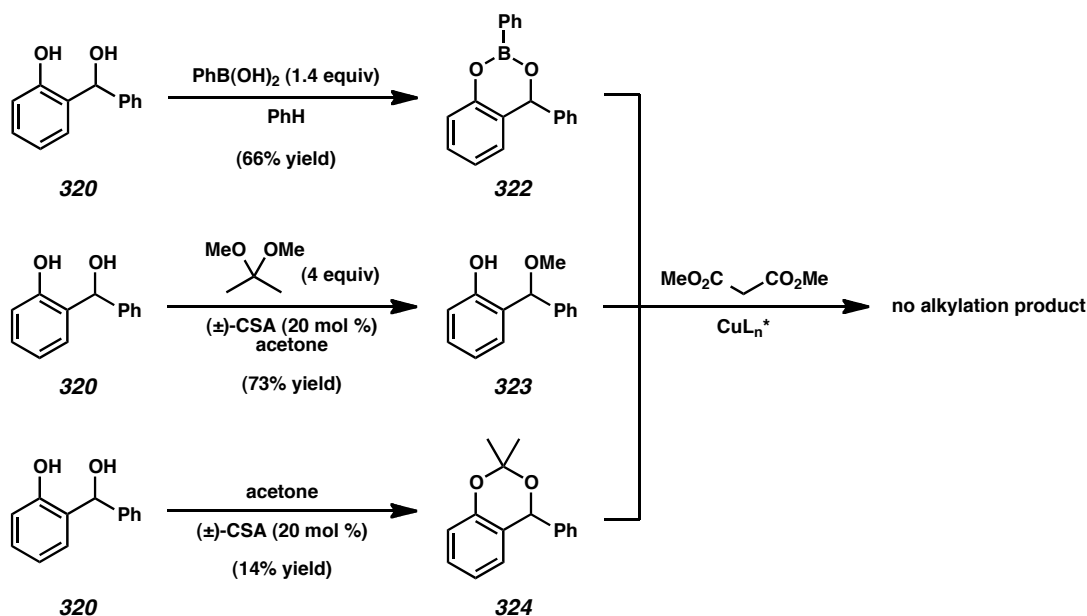
We sought to prepare *o*-hydroxybenzyl chlorides—a direct analogue of the 3-halooxindole starting materials—capable of undergoing base-promoted elimination to generate the OQM under the previously optimized alkylation conditions. Treatment of 2'-hydroxyacetophenone (**317**) and 2-hydroxybenzophenone (**318**) with sodium borohydride produced their corresponding benzyl alcohols (Scheme A8.2.1). Unfortunately, upon treatment with thionyl chloride we found that the desired materials were too unstable to be isolated.

Scheme A8.2.1. Attempts to prepare substituted *o*-hydroxybenzyl chlorides (**321**)



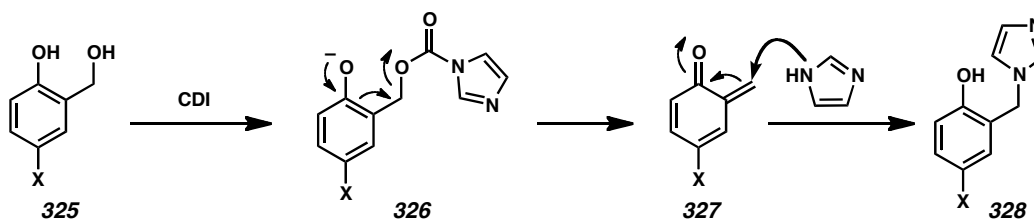
We turned instead to other known OQM precursors, dioxaborin **322**, acetonide **324**, and methoxide **323**, considering the possibility that the chiral Lewis acid used in the halooxindole alkylation system may serve to activate the precursors. Dioxaborin **322** was prepared by condensation of phenylboronic acid with diol **320** (Scheme A8.2.2). In an attempt to prepare an acetonide with the use of 2,2-dimethoxypropane, methoxide **323** was obtained as the major product instead. We were able to isolate the desired acetonide (**324**) in low yield with the use of distilled acetone in the presence of an organic Brønsted acid. Unfortunately, none of these substrates, nor diol **320**, produced any alkylation products under the optimized conditions for halooxindole alkylation.

Scheme A8.2.2. Synthesis and examination of several OQM precursors



Based on these experiments and our hypothesis about the mechanism of the oxindole system, we recognized the need for a base-sensitive precursor, preferably one that would be stable to isolation and long-term storage. However, these types of substrates are not well-precedented in the literature. This is best explained by the fact that a base used to prepare the precursor may proceed to trigger formation of the OQM itself. This is exemplified by Ogata and coworkers' attempt to react diol **325** with *N,N'*-carbonyldiimidazole (CDI).¹¹ Instead of an acylated product, imidazole adduct **328** is isolated, which is likely formed via an OQM mechanism (Scheme A8.2.3).⁵

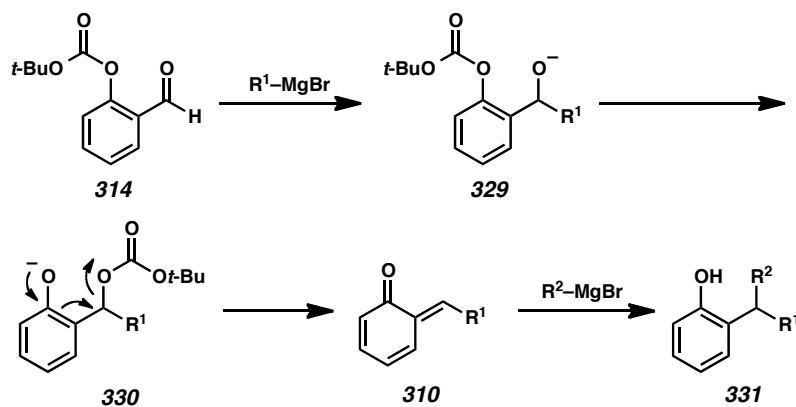
Scheme A8.2.3. Reaction of o-hydroxybenzyl alcohol with carbonyldiimidazole (CDI)



A8.2.2 NUCLEOPHILIC OQM GENERATION

The Pettus group has developed a system which elegantly exploits a similar acylation-elimination sequence (Scheme A8.2.4).¹² Upon reaction with Grignard reagents, Boc-protected salicylaldehydes (**314**) undergo nucleophilic attack followed by acyl transfer and elimination to form an OQM (**310**). A second nucleophile may be added sequentially to give mixed substitution at the benzylic position. This method bears certain disadvantages when considering the development of an asymmetric system. Firstly, the presence of additional metal salts in may lead to undesired complexity in the reaction mixture. The other limitation is that the OQM appears to be generated quantitatively prior to reaction with the second nucleophile, which could result in a significant unselective background reaction under asymmetric alkylation conditions. Conditions affording a low, steady-state concentration of reactive OQM would be preferable in asymmetric alkylation efforts.

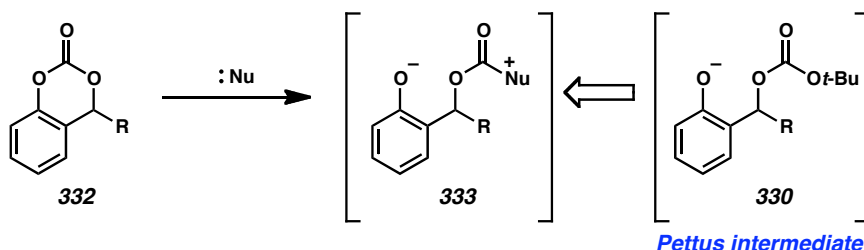
Scheme A8.2.4. Grignard-promoted OQM generation via acyl-transfer/elimination



We considered the cyclic carbonate **332** to be a potential candidate as a substrate for an enantioselective alkylation. Nucleophilic opening of the carbonate would afford an

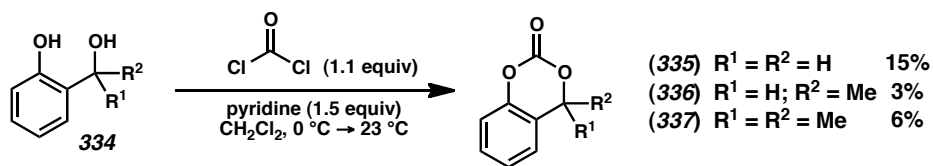
acyl benzyl alcohol derivative (**333**) which would serve as an analogue to Pettus's intermediate (**330**, Scheme A8.2.5).

Scheme A8.2.5. Cyclic carbonates as OQM precursors



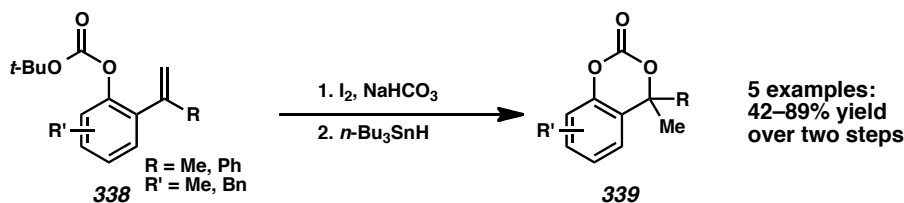
At the outset of this work, there were only two reports in the literature describing the synthesis of cyclic carbonates of this type, neither of which is in the context of *ortho*-quinone methide generation.¹³ The first involves cyclization of *o*-hydroxybenzyl alcohols (**334**) with phosgene using pyridine as a base; however, the yields for this transformation were quite low, likely due to OQM generation under the reaction conditions (Scheme A8.2.6).¹⁴

Scheme A8.2.6. Podraza synthesis of cyclic carbonates with phosgene



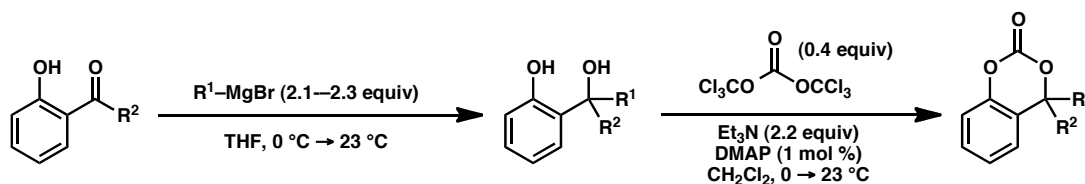
The other known method for the synthesis of these substrates involves an iodocyclization of Boc-protected *o*-hydroxystyrenes (**338**) followed by a tributyltin hydride reduction of the resulting alkyl iodide.¹⁵ While the yields are good, this route is limited in that the *o*-hydroxystyrenes are not broadly commercially available. In addition, the reaction sequence results in the installation of a methyl group at the benzylic position which may not always be desired (Scheme A8.2.7).

Scheme A8.2.7. Synthesis of cyclic carbonates by iodination/cyclization sequence



Based on its potential amenability to a broad substrate scope, we chose to employ Podraza's strategy for carbonate synthesis with several modifications. First, we used triphosgene as a safe, more easily handled surrogate for phosgene. In addition, we substituted the pyridine with the less nucleophilic base triethylamine, accompanied by catalytic DMAP. Also, the base was added slowly to the rest of the reaction mixture in order to limit the quantity of free base in solution. Overall, these modifications resulted in a marked improvement in yield in comparison to the original conditions, and a variety of substrates could be prepared in a two-step sequence from inexpensive, commercially available starting materials (Table A8.2.1). Future investigations may examine broader use of these carbonates as thermally or base initiated OQM precursors.

Table A8.2.1. Two-step synthesis of carbonate OQM precursors

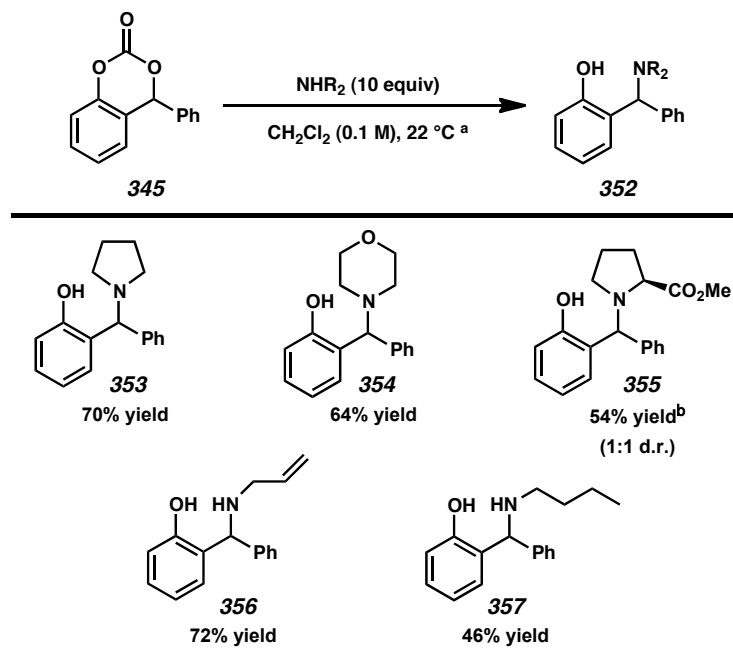


entry	R^1	R^2	Diol Product	Yield ^a	Carbonate	Yield ^a
1	Ph	H	320	94%	345	79%
2	Ph	Me	340	81%	346	82%
3		H	341	65% ^b	347	40%
4		H	342	92%	348	69%
5		H	343	52% ^b	349	43%
6		H	344	70% ^c	350	89%
7	Me	H	319	— ^d	351	77%

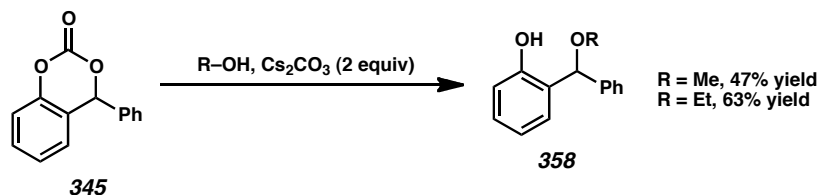
^a Isolated yields ^b Reaction performed in Et₂O ^c This product was prepared by deprotonation of 1-hexyne with *n*-BuLi ^d This product was prepared by NaBH₄ reduction of 2'-hydroxyacetophenone

A8.3 REACTIVITY WITH *N*- AND *O*-BASED NUCLEOPHILES

With a general and operationally simple route in hand to cyclic carbonates (e.g. **345**), we studied their reactivity under mild conditions, with amine and alcohol nucleophiles. We found that benzylic secondary and tertiary amines could be prepared in moderate yields by treatment of carbonate **345** with an excess of amine (Table A8.3.1). Alternatively, benzylic ethers were formed with similar efficiency by reaction of the same carbonate (**345**) in an alcoholic solvent in the presence of base (Scheme A8.3.1).

Table A8.3.1 Reaction of carbonate **345** with amine nucleophiles

^a Isolated yields. ^b Proline methyl ester $\cdot$ HCl and exogenous base were used.

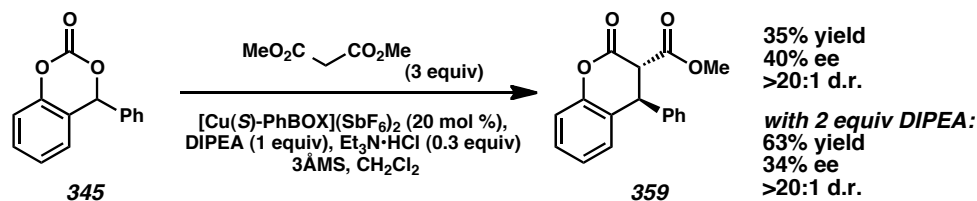
Scheme A8.3.1. Reaction of carbonate **345** with alcohols

A8.4 ASYMMETRIC ALKYLATION WITH MALONATES

A8.4.1 INITIAL DISCOVERY

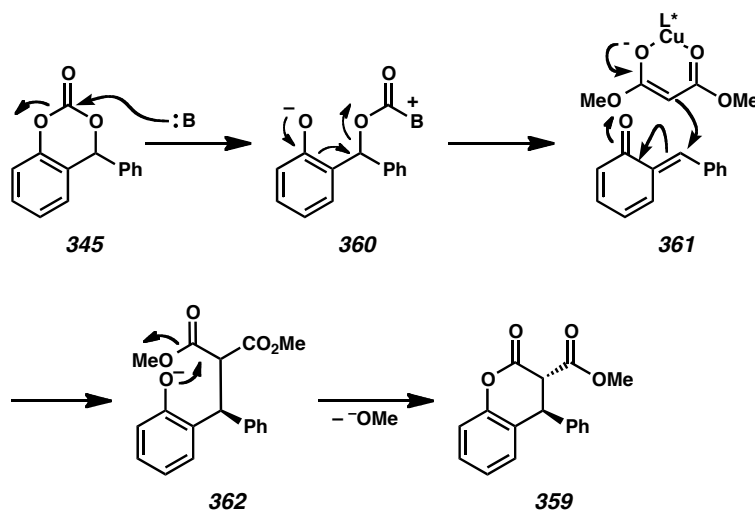
We turned our attention to the development of an enantioselective, stereoablative alkylation reaction. On our first attempt, using the halooxindole alkylation conditions,¹⁶ we were delighted to observe conversion of cyclic carbonate **345** to dihydrocoumarin **359** with modest enantioselectivity (Scheme A8.4.1).

Scheme A8.4.1. Initial observation of asymmetric alkylation with dimethylmalonate



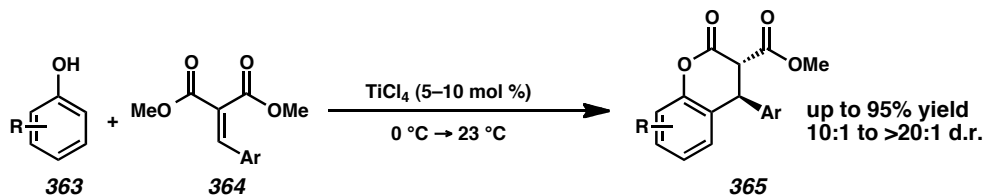
Under these conditions, a base-promoted decarboxylation of carbonate **345** occurs, forming the OQM (**361**, Scheme A8.4.2).¹⁷ An enantioselective alkylation and lactonization ensue to form dihydrocoumarin **359**.

Scheme A8.4.2. Proposed mechanism for OQM alkylation reaction



The diastereoselectivity observed in our initial result is similar to that seen in racemic syntheses of similar dihydrocoumarins. For instance, Tunge and co-workers reported a racemic Lewis acid coupling of phenols (**363**) with benzylidene malonate esters (**364**) to produce similar products (**365**) with high diastereoselectivities (Scheme A8.4.3).¹⁸ Although thermodynamic equilibration of the product is possible, it remained unclear at this point whether the high diastereomeric ratio in our system is a result of equilibration or an irreversible diastereoselective cyclization.

Scheme A8.4.3. Tunge's Lewis acid catalyzed coupling of phenols and benzylidene malonates



A8.4.2 REACTION OPTIMIZATION

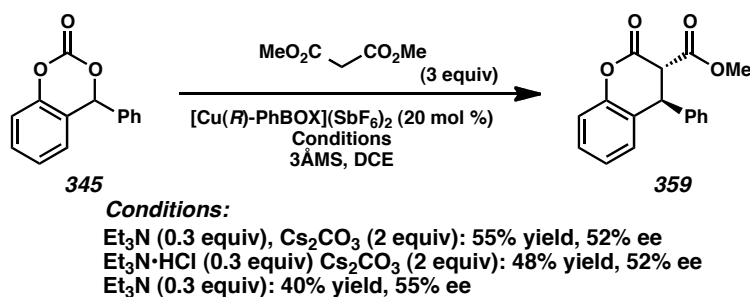
Following our initial enantioselective alkylation result, we sought to optimize the reaction for ee and yield. We initially examined eight solvent systems as well as four different bases with the assistance of a Symyx robot module (Table A8.4.1). We found that triethylamine and diisopropylethylamine generally gave comparable ee's, while DBU gave little product formation and negligible enantioselectivity. With cesium carbonate, the enantioselectivity was improved considerably; in the best case, with the use of 1,2-dichloroethane (DCE) as a solvent, 78% ee was achieved. In this case, the use of a heterogeneous base potentially limits the amount of base (and by extension, OQM intermediate) in solution as the reaction progresses.

Table A8.4.1. Solvent and base screen for OQM alkylation reaction

(% ee)	CH ₂ Cl ₂	DCE	CH ₂ Cl ₂ /PhMe (1:1)	PhMe	CH ₂ Cl ₂ /Et ₂ O (1:1)	CH ₂ Cl ₂ /THF (1:1)	THF	<i>t</i> -BuOH
Et ₃ N	37	51	35	40	35	44	27	53
DIPEA	36	54	33	27	33	37	29	54
DBU	0	0	0	9	—	0	0	—
Cs ₂ CO ₃	63	78	61	57	69	36	48	15

However, when attempts were made to replicate the best result by hand, we were unable to reproduce the 78% e.e. obtained with the Symyx robot. Indeed, after several attempts were made, the enantiomeric excesses were approximately 52% and the dihydrocoumarin product (**359**) was obtained in 55% yield at most (Scheme A8.4.4).

Scheme A8.4.4. Reproduction attempts for Symyx optimized conditions



Undeterred, we continued to screen conditions and examined the use of other metal salts and ligands in this reaction (Figure 8.4.1). For the purpose of higher throughput screening, catalyst complexes were formed in situ from copper (II) triflate and ligand, which gave comparable results to the preformed hexafluoroantimonate complex (Table A8.4.2). We examined other aryl (entries 4–6) and alkyl (entries 7–9) bisoxazoline ligands as well as other ligand classes (entries 10–12), and obtained our best result with perfluorinated phenyl bisoxazoline ligand (**368**) (entry 6).¹⁹ Once again however, we were unable to reproduce this result, obtaining the dihydrocoumarin product (**359**) in lower ee's in replicate reactions (entries 13 & 14).

Figure 8.4.1. Ligands examined in the o-QM asymmetric alkylation screen

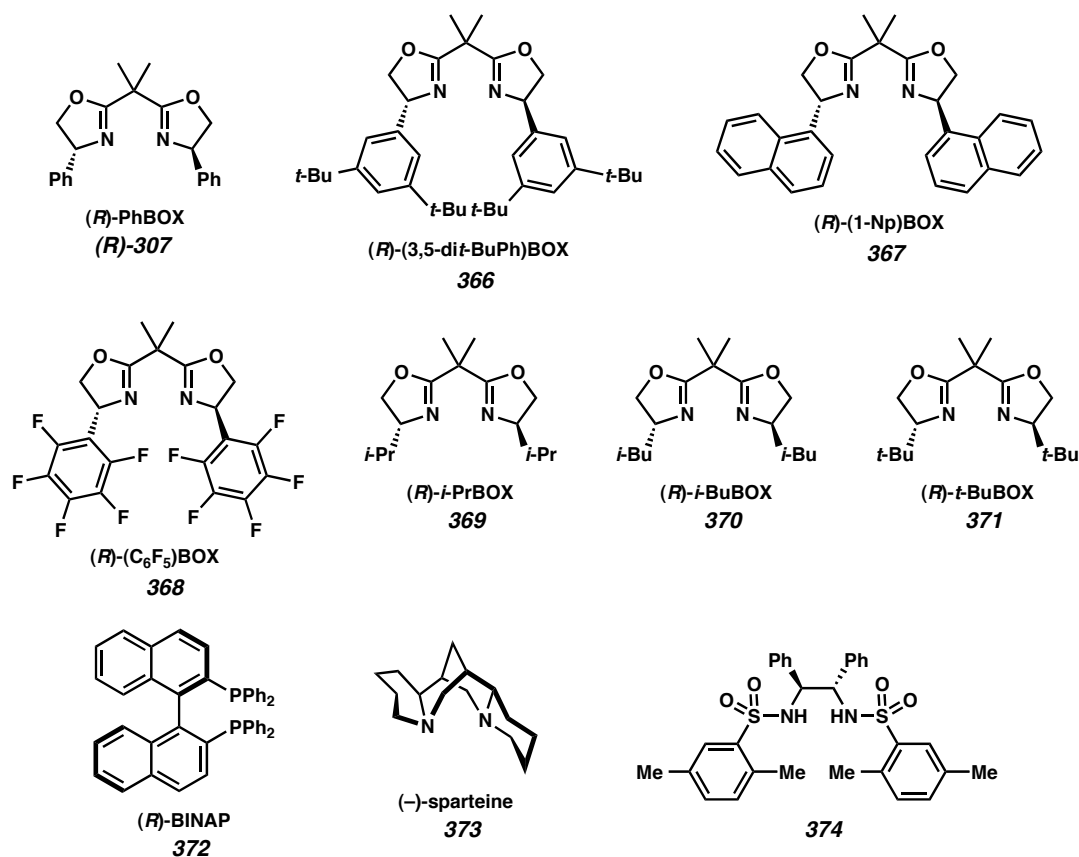


Table A8.4.2. Catalyst screening for OQM alkylation reaction

Entry	Metal	Ligand	ee (%)	Entry	Metal	Ligand	ee (%) ^a
1	Cu(OTf) ₂	(<i>R</i>)-PhBOX (307)	52	8	Cu(OTf) ₂	(<i>R</i>)- <i>i</i> -BuBOX (370)	49
2	Zn(OTf) ₂	(<i>R</i>)-PhBOX (307)	58	9	Cu(OTf) ₂	(<i>R</i>)- <i>t</i> -BuBOX (371)	61
3	Ln(OTf) ₃	(<i>R</i>)-PhBOX (307)	57	10	Cu(OTf) ₂	(<i>R</i>)-BINAP (372)	17 (40%)
4	Cu(OTf) ₂	(<i>R</i>)-(3,5-di- <i>t</i> -BuPh)BOX (366)	–28	11	Cu(OTf) ₂	(-)-sparteine (373)	–30 (5%)
5	Cu(OTf) ₂	(<i>R</i>)-(1-Np)BOX (367)	60	12	Cu(OTf) ₂	374	0 (33%)
6	Cu(OTf) ₂	(<i>R</i>)-(C ₆ F ₅)BOX (368)	–74	13	Cu(OTf) ₂	(<i>R</i>)-(C ₆ F ₅)BOX (368)	56 (44%)
7	Cu(OTf) ₂	(<i>R</i>)- <i>i</i> -PrBOX (369)	61	14	Cu(OTf) ₂	(<i>R</i>)-(C ₆ F ₅)BOX (369)	53 (48%) ^b

^a Isolated yields (%) in parentheses. ^b Reaction run with 10 mol% catalyst loading.

We were interested in learning more about the reaction in order to gain insight into the irreproducibility of the process. Accordingly, we altered various components of the reaction mixture, using *i*-PrBOX (**369**) due to the limited availability of the (C₆F₅)BOX ligand (**368**, Table A8.4.3). While changing the quantity of triethylamine had little effect, lowering the amount of cesium carbonate improved the yield (entry 4). Adjusting the equivalents of malonate dropped the yield slightly (entries 6, 7), and lowering the reaction concentration slightly improved the yield at the expense of enantiomeric excess (entry 8).

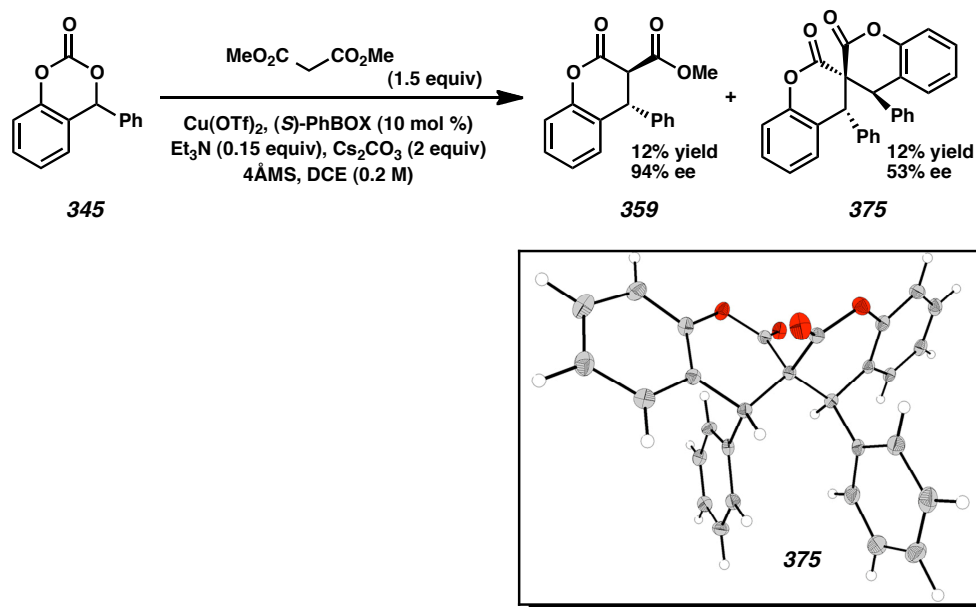
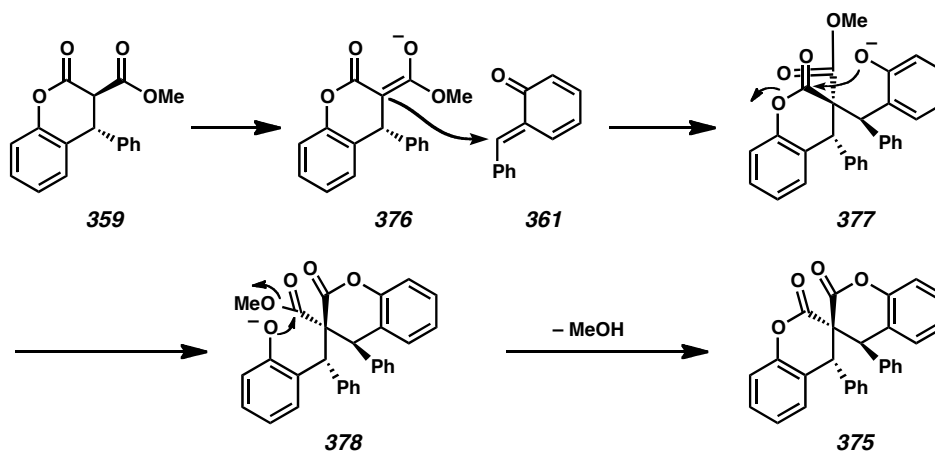
We considered the possibility that the methoxide produced from the product cyclization may be lowering the enantioselectivity by binding to the catalyst; substituting either the triethylamine or cesium carbonate for sodium methoxide had a deleterious effect on the yield and enantiomeric excess (entries 9, 10). Furthermore, the substitution of 3Å molecular sieves for 4Å sieves improved the enantioselectivity albeit at the expense of yield.

Table A8.4.3. Modifications to OQM alkylation conditions

Entry	Modifications	yield (%)	ee (%)
1	none	48	62
2	Et ₃ N (0.15 equiv), Cs ₂ CO ₃ (2 equiv)	41	58
3	Et ₃ N (0.6 equiv), Cs ₂ CO ₃ (2 equiv)	50	60
4	Et ₃ N (0.3 equiv), Cs ₂ CO ₃ (1 equiv)	66	61
5	DIPEA (0.3 equiv), Cs ₂ CO ₃ (2 equiv)	42	58
6	MeO ₂ C-CH ₂ -CO ₂ Me (2 equiv)	38	58
7	MeO ₂ C-CH ₂ -CO ₂ Me (4 equiv)	40	57
8	DCE (0.1 M)	54	55
9	NaOMe (0.3 equiv), Cs ₂ CO ₃ (2 equiv)	42	51
10	Et ₃ N (0.3 equiv), NaOMe (2 equiv)	38	12
11	MS 4Å	41	75

In an experiment where the quantities of starting material and cesium carbonate were doubled, we were surprised to obtain the dihydrocoumarin product (**359**) in a remarkably high enantiomeric excess and unusually low yield (Scheme A8.4.5). Concurrently, we were able to identify the major side product of these reactions as spirocycle **375**, which is formed from an addition of the product into a second equivalent of OQM **361**. The relative stereochemistry, confirmed by x-ray crystallography, appears counter-intuitive. Based on the orientation of the quaternary stereocenter, it appears to suggest an alkylation of enolate **376** on its more hindered face (Scheme A8.4.6). However, one may consider a mechanism which involving enolate alkylation on the less hindered face followed by inversion of the quaternary center by translactonization.

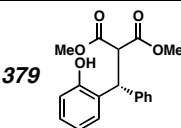
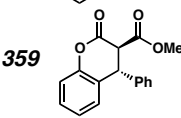
Scheme A8.4.5. Isolation of spirocyclic bis-OQM adduct

Scheme A8.4.6. Proposed mechanism for formation of spirocycle **375**

With this dimerization pathway in mind, we considered the possibility that the product may be undergoing a kinetic resolution, which could account for the irreproducibility of ee in some experiments. Indeed, we found that the enantiomeric excess of the dihydrocoumarin product **359** increased over the course of the reaction (Table A8.4.4). In addition, the initial malonate adduct **379** was formed in approximately 30% ee, which effectively represents the enantioselectivity of the desired alkylation

reaction. Accordingly, spirocycle **375** (cf. Scheme A8.4.5) is enantioenriched with respect to the first alkylation ee, consistent with the bisalkylation playing a role in a kinetic resolution. For a full picture, it will be necessary to monitor enantioenrichment of spirocycle **375** over the course of the reaction.

Table A8.4.4. Change in enantiomeric excess of intermediate **379** and product **359** over time.

time (min):	70	130	195	270	390
379 	ee: 30%	28%	–	–	–
359 	ee: 26%	30%	51%	62%	68%

In order to prevent a second alkylation event from occurring, we continued our optimization with dimethyl methylmalonate (**380**), (Table A8.4.5). An additional challenge of diastereoselectivity was introduced since the diastereomers can no longer be interconverted simply by enolization. Indeed this was reflected in our first result when we subjected malonate **380** to our best conditions. Under these conditions, it was found that the diastereomeric ratio was reduced to 2:1, and curiously, the diastereoselectivity was improved to > 20:1 when no ligand was used. When zinc triflate was substituted for copper in the presence of PhBOX, the diastereomeric ratio remained at 20:1 with comparable enantioselectivity. Notably, the diastereoselectivity was inverted with the use of metal chlorides such as zinc and cobalt (II) chloride. In addition, the use of cobalt salts reversed the enantioselectivity, perhaps a result of a tetrahedral geometry at the metal center.

Table A8.4.5. Metal screen with dimethyl methylmalonate (**380**)

Reaction scheme: **345** + **380** (3 equiv) → **381 / 382**
 Reagents: Metal Salt, (S)-PhBOX (20 mol %), Et₃N (0.3 equiv), Cs₂CO₃ (2 equiv), 4ÅMS, DCE (0.2 M)

Entry	Metal	d.r. (381:382)	ee (381)	ee (382)
1	Cu(OTf) ₂	2:1	35%	72%
2	Cu(OTf) ₂ ^a	> 20:1	—	—
3	Zn(OTf) ₂	> 20:1	30%	n.d.
4	ZnCl ₂	1:4	64%	52%
5	CoCl ₂	1:2.1	4%	-31%
6	CoCl ₂ ^b	1:1.9	-13%	-43%
7	CoBr ₂	1:1.4	-2%	-28%

^a no ligand used. ^b 2 equiv ligand used.

Having discovered that zinc triflate provides excellent diastereoselectivity without compromising enantioselectivity to a large degree, we continued to optimize the reaction conditions, examining a range of amine bases and temperatures (Table A8.4.6). We have found that reducing the temperature to 10 °C boosts enantioselectivity at the expense of diastereoselectivity (entry 7). However, diastereoselectivity can be restored with judicious choice of base; for example, the use of 2,6-di-*t*-butyl pyridine gave the highest diastereomeric ratio at 10 °C, in addition to a high yield (entry 13). The highest enantioselectivity in this system to date was achieved with dimethylcyclohexyl amine (entry 8), and the best yield with triisobutylamine (entry 10).

Table A8.4.6. Base and temperature optimization for OQM alkylation with malonate **380**

Entry	Base	Yield ^a	d.r.	ee (381) (%)	ee (382) (%)
1	Et ₃ N	44%	> 20:1	30	—
2	DIPEA	54%	> 20:1	19	—
3	DBU	20%	> 20:1	5	—
4		45%	> 20:1	24	—
5	DABCO	60%	> 20:1	49	—
6	DABCO	4% ^b	1:1.2	70	—
7	DABCO	77% ^c	1:1.5	66	54
8	Me ₂ CyN	60% ^c	1:1.9	71	55
9	MeCy ₂ N	57% ^c	1:2.1	69	56
10	(<i>i</i> -Bu) ₃ N	94% ^c	2.5:1	61	57
11		75% ^c	1:1.3	70	52
12	pyridine	48% ^c	1.4:1	15	-19
13		85% ^c	10:1	60	—

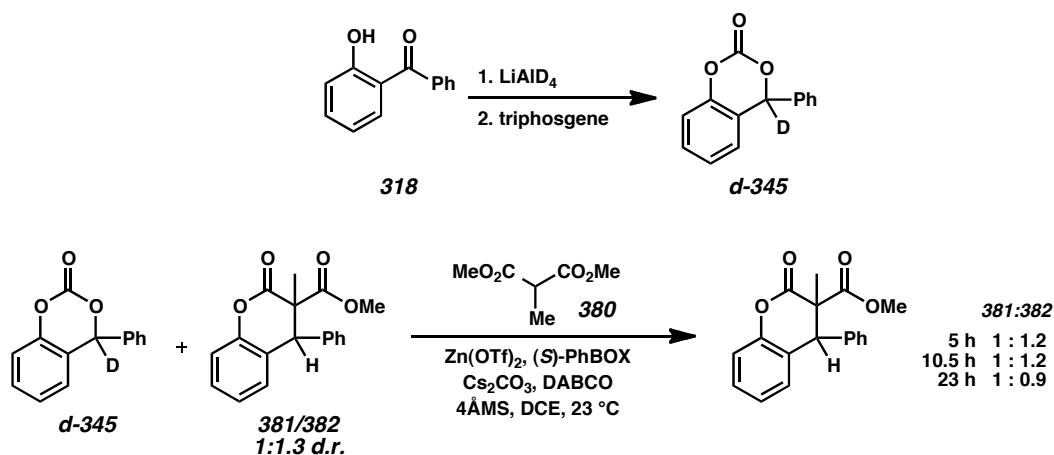
^a Isolated yields. ^b Reaction run at 0 °C. ^c Reaction run at 10 °C

A8.4.3 DISCUSSION OF MECHANISM

The relative stereochemistry of each of the diastereomers (**381** and **382**) has not been conclusively determined to date.²⁰ Nevertheless, the observed trends in diastereoselectivity present a mechanistic challenge for which several scenarios are possible. First, reversibility of lactonization may be considered. In such a case, the diastereoselectivity may be an issue of kinetic versus thermodynamic product formation. To test for reversible lactonization, we prepared a deuterated starting material (**d-345**), and subjected it to alkylation conditions (similar to entry 5, Table A8.4.6), spiking the

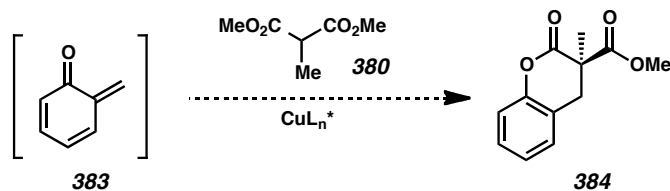
reaction with a non-deuterated mixture of diastereomeric products (Scheme A8.4.7). Since the diastereomeric ratio of the product mixture is determined based on the integration of ^1H NMR resonances for the benzylic proton of **381/382**, products (**d-381/d-382**) formed from the deuterated starting material will not affect the observed diastereomeric ratio of the nondeuterated product (**359**). In this experiment, NMR would reveal if the diastereomers of the product are interconverting under the reaction conditions. In the event, it was found that the diastereomeric ratio did not change substantially over the course of the reaction. This result suggested that the diastereomeric products (**381** and **382**) do not interconvert on the time scale of this reaction.²¹

Scheme A8.4.7. Deuterium labeling study: test for reversible lactonization.



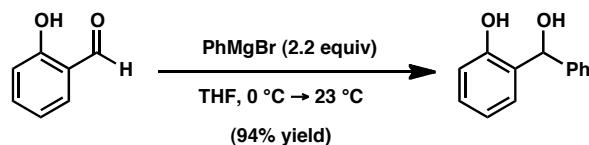
Another potential mechanistic explanation for the observed diastereoselectivity would involve a catalyst-controlled ring-closure, which could be substantiated by observing enantioselectivity in the reaction of malonate **380** with an unsubstituted OQM (**383**, Scheme A8.4.8).

Scheme A8.4.8. Proposed test for catalyst-controlled lactonization

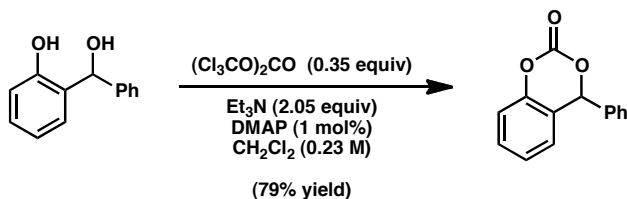


A8.5 CONCLUSION

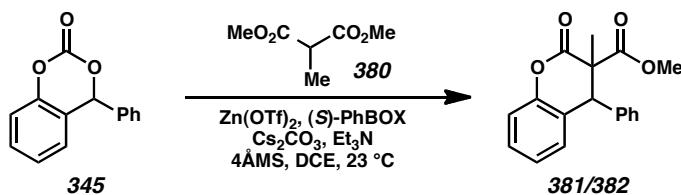
Future work will be directed toward optimizing the alkylation reaction and examining the substrate scope of the reaction. Reaction components including ligands, solvent, reagent concentration, and malonates (or β -ketoesters) must be further evaluated. In addition, further mechanistic studies will be conducted to determine factors contributing to diastereoselectivity. The scope of this reaction will be explored with the use of a variety of substituted OQMs. Finally, the cyclic carbonate precursors will be examined for their utility in other known OQM reactions.

A8.6 EXPERIMENTAL SECTION**A8.6.1 PREPARATIVE PROCEDURES**

Diol 320. Representative procedure. A round-bottom flask was equipped with a magnetic stir bar, sealed with a rubber septum, flame-dried under vacuum and cooled under an inert atmosphere. To the flask was added salicylaldehyde (1.0 mL, 9.4 mmol, 1 equiv) by syringe, followed by tetrahydrofuran (50 mL). Stirring was initiated and the flask was cooled in an ice-water bath. Phenylmagnesium bromide (3.0 M in diethyl ether, 6.6 mL, 20 mmol) was added dropwise. Through the addition, the reaction mixture became dark green then grey. After 45 min, the reaction was quenched by addition of saturated ammonium chloride, and diluted with water. The bulk of the THF was removed in vacuo, and the resulting mixture was extracted with ethyl acetate (3 x 65 mL). The combined organics were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO₂ (10:1 hexanes:EtOAc) to afford diol **320** (1.76 g, 94% yield): ¹H NMR (300 MHz, CDCl₃) δ 7.84 (s, 1H), 7.46–7.30 (m, 5H), 7.24–7.15 (m, 1H), 6.95–6.77 (m, 3H), 6.04 (d, J = 3.2 Hz, 1H), 2.82 (d, J = 3.3 Hz, 1H).



Carbonate 345. To a flame-dried round-bottom flask was added diol (731.3 mg, 3.65 mmol, 1 equiv), 4-(*N,N*-dimethylamino)pyridine (3.2 mg, 0.026 mmol, 0.01 equiv), and triphosgene (387.7 mg, 1.28 mmol, 0.35 equiv). The flask was sealed with a rubber septum under an inert atmosphere, dichloromethane (16 mL, 0.23M) was added, stirring was initiated, and upon dissolution of the solids, the flask was lowered into an ice-water bath. To the cooled solution was added dropwise freshly distilled triethylamine (1.04 mL, 7.49 mmol, 2.05 equiv). Upon consumption of starting material, the reaction mixture was quenched with saturated aqueous ammonium chloride and diluted with water. The phases were separated, and the aqueous phase was extracted with dichloromethane. The combined organics were dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on SiO₂ (9:9:2 toluene:hexanes:EtOAc) to afford carbonate **345** (650 mg, 79% yield): ¹H NMR (300 MHz, CDCl₃) δ 7.46–7.39 (m, 4H), 7.37–7.31 (m, 2H), 7.21–7.14 (m, 2H), 6.96–6.90 (m, 1H), 6.46 (s, 1H).



Dihydrocoumarins 381/382. Representative procedure: In a nitrogen filled glovebox, an oven-dried 1 dram vial was charged with zinc triflate (7.0 mg, 0.02 mmol, 0.2 equiv), and 4Å molecular sieves (36.8 mg). The vial was sealed with a cap lined with a teflon septum, removed from the glovebox, and placed under an inert atmosphere. To this vial was added (*S*)-PhBOX (8.3 mg, 0.025 mmol, 0.2 equiv) via syringe in freshly-

distilled 1,2-dichloroethane (DCE, 0.25 mL). Methyl dimethylmalonate (0.031 mL, 0.3 mmol, 3 equiv) was added neat via syringe, followed by carbonate **345** (22.4 mg, 0.1 mmol, 1 equiv) in DCE (0.25 mL). The reaction mixture was cooled in a 10 °C bath (dioxane) and neat triisobutylamine (0.007 mL, 0.03 mmol, 0.3 equiv) was added. Finally, under a stream of argon, solid cesium carbonate (63.9 mg, 0.2 mmol, 2 equiv) was added quickly and the vial was resealed. Upon completion, the mixture was filtered through a short plug of silica gel, then purified by column chromatography on SiO₂ (15:1 hexanes:EtOAc) to afford dihydrocoumarin (27.7 mg, 94% yield) as a 5:2 mixture of diastereomers **381** (61% ee) and **382** (57% ee): ¹H NMR (300 MHz, CDCl₃) δ 7.38 – 7.04 (m, 9H), 4.54 (s, 1H, **381**), 4.22 (s, 1H, **382**), 3.61 (s, 3H, **381**), 3.42 (s, 3H, **382**), 1.58 (s, 3H, **381**), 1.36 (s, 3H, **382**).

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- (21) An alternative explanation is the diastereomeric mixture used in this experiment constituted the thermodynamic product mixture. Subjection of a single diastereomer of the product to the same experiment would test this hypothesis.

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His undergraduate studies began in 2004 at Queen's University in Kingston, ON, where he was informed by his freshman Chemistry professor that “the golden age of Chemistry is over.” Undeterred, he completed a four-year program with Chemistry as his Subject of Specialization, working in the laboratories of Profs. Cathleen Crudden at Queen's, and Mark Lautens at University of Toronto as an NSERC USRA.

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