PROGRESS TOWARD THE SYNTHESIS OF (+)-ZOANTHENOL

AND

THE DEVELOPMENT OF AN ASYMMETRIC TSUJI ALLYLATION REACTION

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To my parents

for their constant support

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ABSTRACT

The stereoselective synthesis of all carbon quaternary stereocenters is an important problem in synthetic chemistry due to their common occurrence in bioactive compounds. The zoanthamine class of marine natural products highlights the challenge in constructing such stereocenters. After a summary of the isolation, structure determination, and biological activities of the zoanthamine natural products, published approaches toward their chemical synthesis are reviewed.

Synthetic strategies toward the carbocyclic portion of zoanthenol focus on the synthesis of the three challenging quaternary stereocenters located on the central C ring. An unusual acid-mediated S_N' cyclization of a nucleophilic arene with an allylic alcohol forms the B ring and diastereoselectively constructs the benzylic C(12) quaternary stereocenter. However, difficulties with late-stage installation of the remaining C(9) quaternary stereocenter compelled the use of C ring synthons containing the vicinal C(9) and C(22) stereocenters installed at an early stage in the synthesis. Desymmetrization of a *meso*-anhydride containing vicinal quaternary stereocenters accomplishes this goal in an enantioselective fashion. Several C ring synthons bearing the vicinal quaternary stereocenters are elaborated with A ring fragments, and several methods for the formation of the C(11)-C(12) bond in these systems are explored. Ultimately, a radical conjugate addition strategy provides the carbocyclic core of zoanthenol with the correct relative configuration of all three quaternary stereocenters.

These efforts toward the synthesis of zoanthenol highlight the difficulty in generating enantioenriched α-quaternary cycloalkanones derived from ketones with multiple acidic α-hydrogens. The first direct catalytic enantioselective access to such products is achieved by the application of chiral bidentate phosphinooxazoline (PHOX) ligands to Tsuji's non-enantioselective allylation reactions. Cyclic allyl enol carbonates, silyl enol ethers, and allyl β-ketoesters all provide uniformly excellent yields and high enantioselectivity in the reaction. The limitations on the substrate scope of the reaction are discussed. Preliminary studies into the mechanism of these allylation reactions with prochiral enolate fragments suggest that they occur by a different mechanism than the outer-sphere nucleophilic attack commonly proposed in the alkylation of prochiral allyl fragments.

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List of Abbreviations

$[\alpha]_D$	specific rotation at wavelength of sodium D line
Ac	acetyl
ACN	acetonitrile
Ad	adamantyl
app	apparent
aq	aqueous
Ar	aryl group
atm	atmosphere
BBN	borabicyclo[3.3.1]nonane
BHT	2,6-di-*tert*-butyl-4-methylphenol
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOM	benzyloxymethyl
bp	boiling point
br	broad
BSA	*N*,*O*-bis(trimethylsilyl)acetamide
Bu	butyl
n-Bu	*n*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl
c	concentration for optical rotation measurement

^{13}C	carbon 13, isotope
/C	supported on activated carbon
°C	degrees Celsius
cat.	catalytic
calc'd	calculated
CAM	ceric ammonium molybdate stain
CAN	ammonium cerium (IV) nitrate
Cbz	benzyloxycarbonyl
CCDC	Cambridge Crystallographic Data Centre
comp	complex
CSA	camphorsulfonic acid
conv	conversion
Cy	cyclohexyl
d	doublet
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane or methylene chloride
DEAD	diethyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DIOP	2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DIPA	diisopropyl amine

DMA	N,N’-dimethylacetamide
DMAP	4-dimethylaminopyridine
dmdba	3,5,3’,5’-dimethoxydibenzylideneacetone
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMPU	N,N'-dimethyl propylene urea
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DPPB	1,4-bis(diphenylphosphino)butane
DPPE	1,2-bis(diphenylphosphino)ethane
dr	diastereomeric ratio
ee	enantiomeric excess
E	entgegen olefin geometry
EI	electrospray ionization
equiv	equivalent(s)
Et	ethyl
EtOAc	ethyl acetate
FAB	fast atom bombardment
g	gram
GC	gas chromatography
Grubbs II	Grubbs’ second generation metathesis catalyst

[H]	reduction
h	hour(s)
hν	light
^{1}H	proton
^{3}H	tritium
HMDS	hexamethyldisilazide or hexamethyldisilizane
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
η^n	eta; n = number of atoms coordinated to metal
IC_{50}	concentration required for 50% growth inhibition
imid.	imidazole
IR	infrared spectroscopy
J	coupling constant
k_n	rate constant, n refers to various reactions, negative n indicates reverse reaction
kcal	kilocalories
KHMDS	potassium hexamethyldisilazide
L	liter
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LD_{50}	Lethal Dosage to kill 50% of test population
LiHMDS	lithium hexamethyldisilazide

m	meta
m	multiplet or milli
μ	micro
M	mega, metal, or molar
m/*z*	mass to charge ratio
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
(*R*,*R*)-Me-DUPHOS	(-)-1,2-Bis((2R,5R)-2,5-dimethylphospholano)benzene
MEK	methyl ethyl ketone
MH-60	mouse myelohybridoma cells
MIC	minimal inhibitory concetration
min	minute(s)
mol	mole(s)
mol%	percentage used based on moles
MOM	methoxymethyl
(*R*)-MOP	(R)-(+)-2-(Diphenylphosphino)-2'-methoxy-1,1'-binaphthyl
mp	melting point
Ms	methanesulfonyl
MS	molecular sieves
MTPA	α-methoxy-α-(trifluoromethyl)phenylacetic acid
MVK	methyl vinyl ketone
N	normal

NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
o	ortho
[O]	oxidation
p	para
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PG	prostaglandin
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
Ph-H	benzene
PHOX	phosphinooxazoline
Phth	phthalamidyl
Piv	pivaloyl
PMA	phorbol myristate acetate
PMB	*p*-methoxybenzyl
PMBM	*p*-methoxybenzyloxymethyl
p.o.	administered orally
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
i-Pr	isopropyl

psi	pounds per square inch
Py or Pyr	pyridine
q	quartet
QUINAP	(R)-(+)-1-(2-Diphenylphosphino-1-naphthyl)isoquinoline
R	alkyl group
R	rectus (configurational)
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
R_f	retention factor
RNA	ribonucleic acid
s	singlet
S	sinister (configurational)
SAR	structure-activity relationship
sat.	saturated
stoich.	stoichiometric
t	triplet
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium triphenyldifluorosilicate
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
temp	temperature
TEA	triethylamine
TES	triethylsilyl
Tf	trifluoromethanesulfonyl

TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TOF	turnover frequency
TON	turnover number
TPAP	tetrapropylammonium perruthenate
TROC	trichloroethoxycarbonyl
Ts	*p*-toluenesulfonyl or *p*-toluenesulfonic
UV	ultraviolet
Vis	visual wavelength
v/v	volume per volume
w/v	weight per volume
X	halide or trifluoromethanesulfonate
Z	zusammen olefin geometry

CHAPTER ONE

A Biological and Chemical Introduction to the Zoanthamine Alkaloids

1.1 Isolation of Zoanthamine Alkaloids

1.1.1 *The Order Zoantharia*

The order zoantharia comprises an intriguing group of marine polyps. This order has been morphologically classified into at least a dozen genera, and recent analysis of their respective mitochondrial DNA has elucidated the relationships between them.[1] Species in this order are widely dispersed throughout the temperate and tropical littoral regions of the Indian, Pacific, and Atlantic Oceans. These soft corals are generally aggressive colonizers of reef environments. In the wild, they are known to reproduce both sexually[2] and by asexual budding of new polyps.

Figure 1.1 Representative Zoanthids



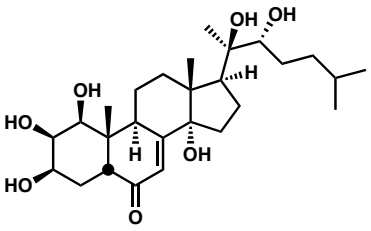
The polyps have a tube-shaped body and are radially symmetric. Atop the body are tentacles that guide food to the central orifice for digestion. Additionally, zoanthids frequently contain symbiotic microalgae, which provide energy via photosynthesis. These dinoflagellate algae also play an important role in the biosynthesis of secondary metabolites originally isolated from the zoanthids.[3] When alarmed, the polyps contract their tentacles inward, and some species also expel from their bodies a stream of water laden with powerful toxins as a means of defense from predators. As a result of their vibrant pigmentation, zoanthids are prized as specimens for marine aquariums and are commonly sold as "sea mats."

1.1.2 *Natural Products Isolated from the Order Zoantharia*

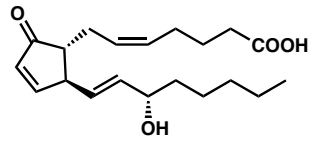
A rich diversity of natural product archetypes has been isolated from species in the order zoantharia (Figure 1.2). Zoanthusterone (**1**) is a representative ecdysteroid isolated from a *Zoanthus sp*.[4] Prostaglandins like PGA_2 (**2**), isolated from *Palythoa kochii*, have been shown to stabilize microtubules in a manner similar to paclitaxel.[5] A family of more than a dozen natural products based on the highly fluorescent zoanthoxanthin (**3**) skeleton has been isolated from *Parazoanthus axinellae*.[6] A related demethylated structure, parazoanthoxanthin A, has shown significant anticholinesterase activity.[7] Both red[8] and yellow[9] fluorescent proteins containing novel chromophores have been isolated and crystallographically studied. Perhaps the best known compound isolated from these marine organisms is palytoxin (**4**). Palytoxin was isolated from *Palythoa sp*. in the Hawaiian islands and remains one of the most toxic compounds

known, with an LD_{59} of 15 μg/kg in mice.[10] The structure of palytoxin was determined and later synthesized by Kishi.[11]

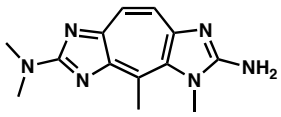
Figure 1.2 Representative Natural Products from Zoanthids



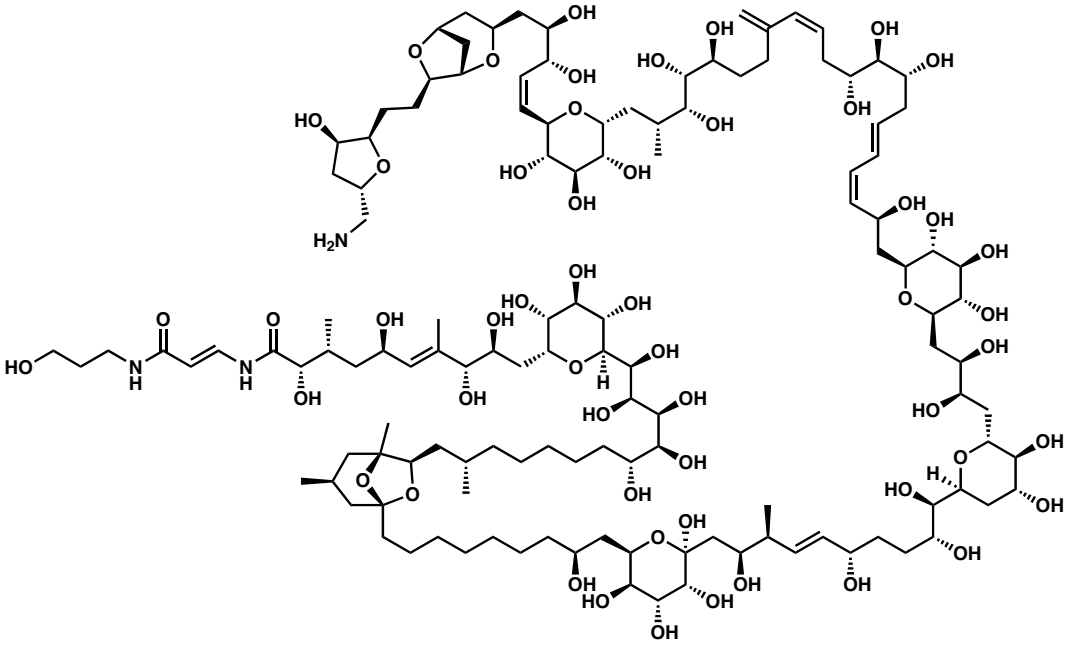
Zoanthusterone ***(1)***



PGA_2 ***(2)***



Zoanthoxanthin ***(3)***



Palytoxin ***(4)***

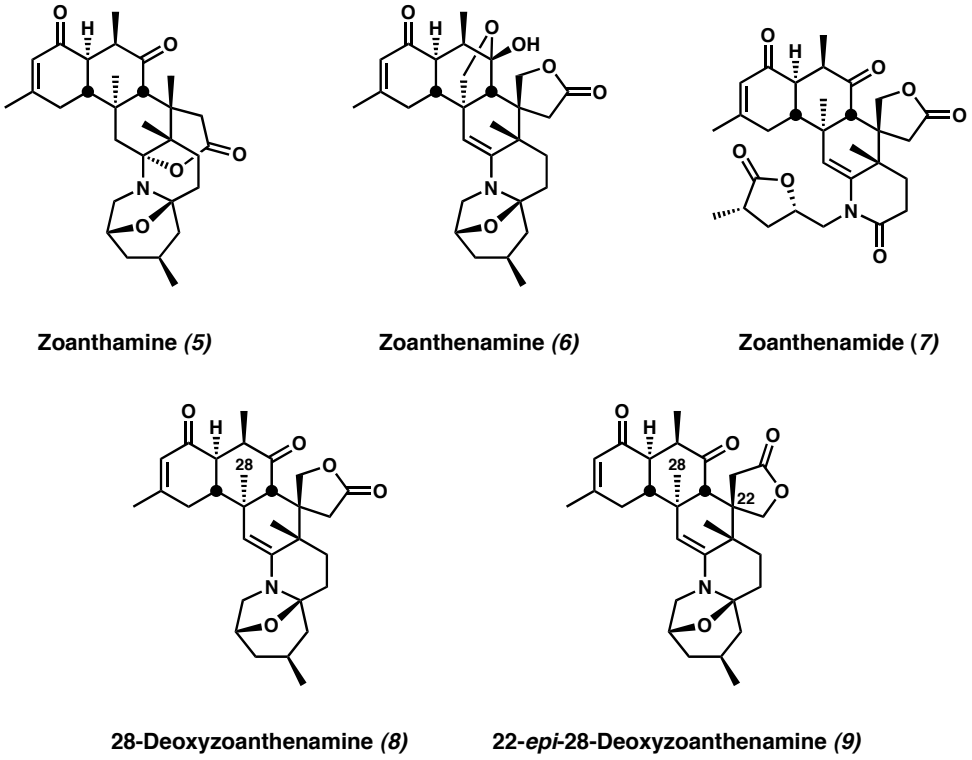
1.2 The Zoanthamine Natural Products

1.2.1 *Isolation and Structural Characterization*

In 1984, the isolation of the natural product zoanthamine (**5**) from a species of the genus Zoanthus off the Visakhapatnam coast of India was disclosed. The connectivity

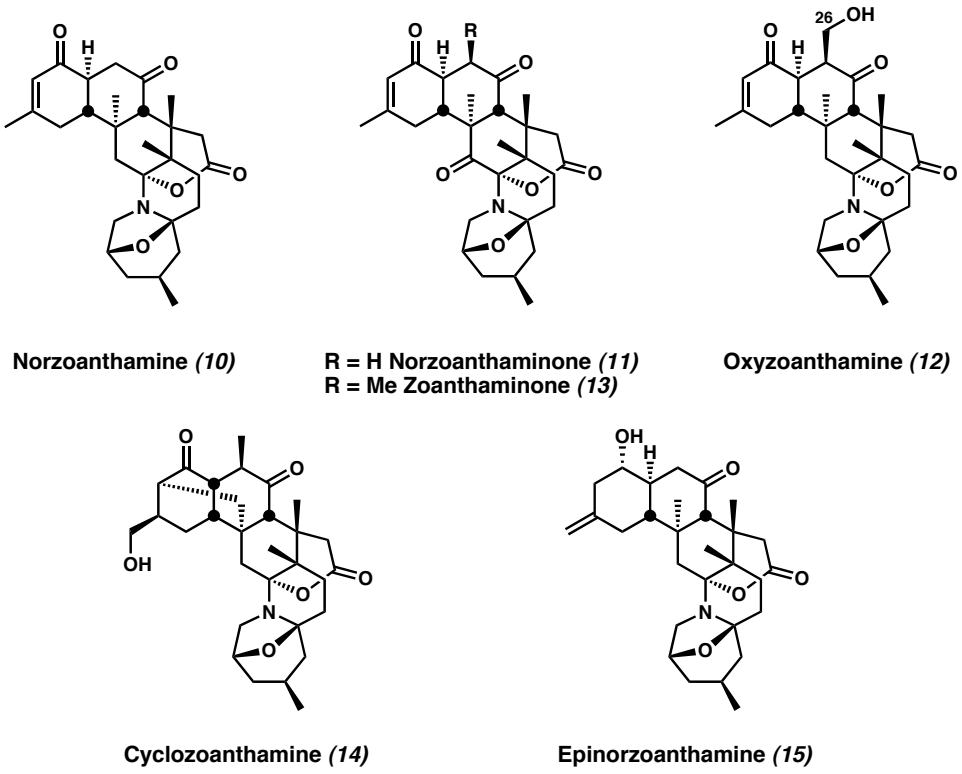
and relative stereochemistry of the previously unknown alkaloid skeleton was unambiguously determined by single crystal X-ray diffraction.[12] This isolation effort also afforded the related natural products zoanthenamine (**6**) and zoanthenamide (**7**).[13] The same group later described 28-deoxyzoanthenamine (**8**) and 22-*epi*-28-deoxyzoanthenamine (**9**) from a Zoanthus species isolated in the Bay of Bengal.[14] The latter four structures were deduced by comparison with zoanthamine's spectroscopic data. Originally, this isolation effort was undertaken in search of a known eye irritant produced by the Zoanthus species. However, all five of the isolated alkaloids showed some inhibition of phorbol myristate acetate (PMA) inflammation in mouse ears. The function of the zoanthamine alkaloids in the producing organisms is unknown.

Figure 1.3 Zoanthamine Natural Products Isolated by Rao



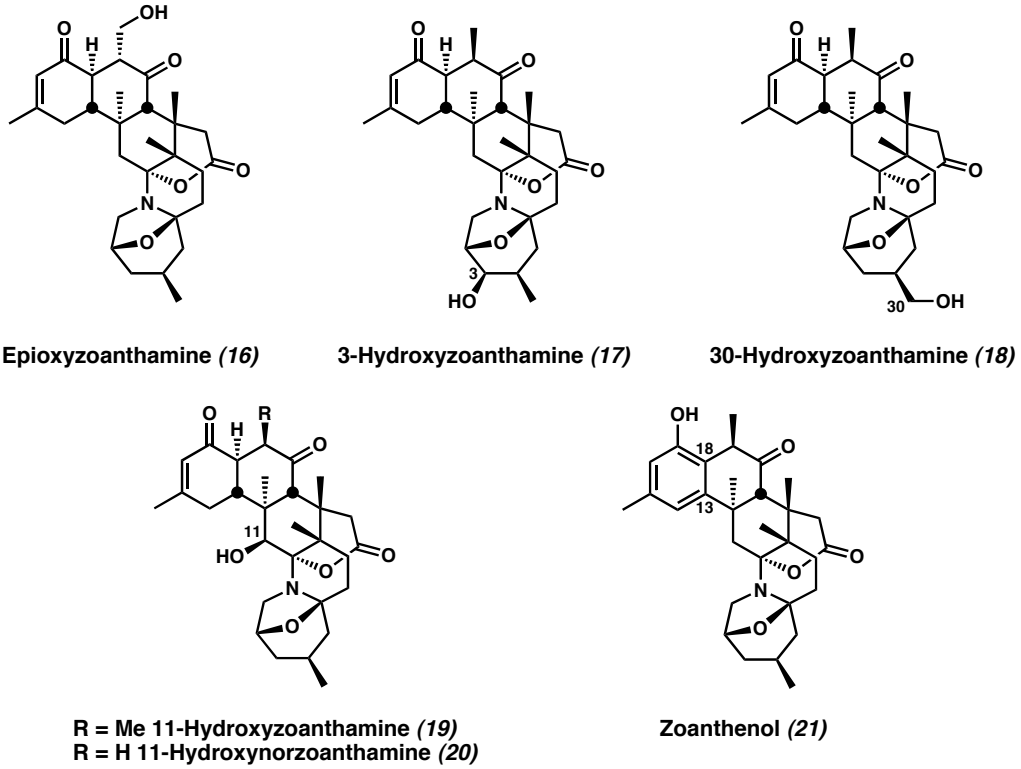
In 1995, Uemura and coworkers identified five new zoanthamine natural products isolated from a Zoanthus species collected off the Ayamaru coast of the Amami Islands south of Japan.[15] Among these, norzoanthamine (**10**) and norzoanthaminone (**11**) lack the C(26) methyl group, while in oxyzoanthamine (**12**) the C(26) methyl group has been oxidized. The relative configuration of norzoanthamine was confirmed by X-ray diffraction.[15] The absolute configuration of norzoanthamine, later determined by NMR analysis of MTPA derivatives, is shown in Figure 1.4.[16] The C_{30} alkaloid related to norzoanthaminone (**11**), zoanthaminone (**13**), was amenable to X-ray crystal structure determination as disclosed by Clardy.[17] Cyclozoanthamine (**14**) and epinorzoanthamine (**15**) represent intriguing modifications to the enone functionality typical of zoanthamines. Both structures were assigned by extensive NOE experiments.[15]

Figure 1.4 Zoanthamine Natural Products Isolated by Uemura and Clardy



Zoanthids isolated from the Canary Islands by Norte and coworkers in 1996 provide zoanthamine natural products with several interesting oxidation patterns (Figure 1.5). Epioxyzoanthamine (**16)** is unique in its C(19) stereochemistry, which was determined by comparison with NMR data for oxyzoanthamine.[18] 3-Hydroxyzoanthamine (**17)** and 30-hydroxyzoanthamine (**18)** show novel sites of oxidation, while 11-hydroxyzoanthamine (**19)** and 11-hydroxynorzoanthamine (**20)** are presumably related to zoanthaminone and norzoanthamineone. Finally, zoanthenol (**21**) has a unique oxidized aromatic A ring, which removes the C(13) and C(18) stereocenters. As a result of the structural change, extensive HMBC and ROESY correlation experiments were performed to confirm its structure and relative stereochemistry.[19]

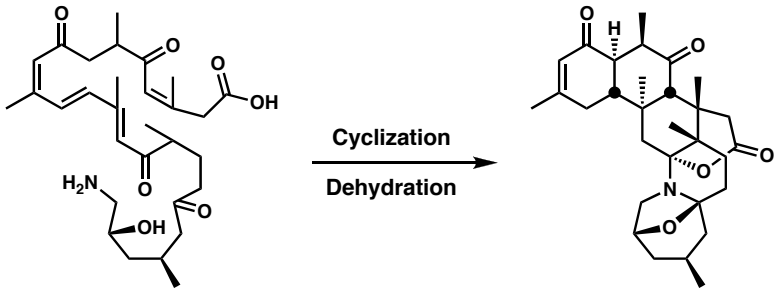
Figure 1.5 Zoanthamine Natural Products Isolated by Norte



1.2.2 *Biosynthesis of the Zoanthamine Natural Products*

The C_{30} skeleton of the zoanthamine natural products led to initial biosynthetic speculation focused on triterpene precursors.[12] However, no normal head-to-tail isoprene connectivity could account for the zoanthamine skeleton. More recently, Uemura has proposed that the zoanthamine natural products may arise via a polyketide construction (Scheme 1.1).[16,20] The proposed intermediate **22** accounts for most of the oxygenation found in the zoanthamines. While no definitive statement can be made about biosynthesis, there appears to be support for the polyketide hypothesis.[18]

Scheme 1.1 Hypothetical Polyketide Precursor

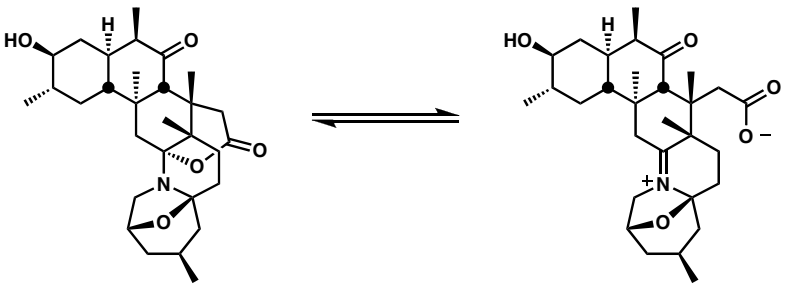


Hypothetical Polyketide Precursor *(22)* **Zoanthamine *(5)***

Another factor complicating the understanding of zoanthamine alkaloid biosynthesis is the role of the symbiotic dinoflagellate algae that are commonly contained in zoanthids. Although such symbiotic strains are difficult to culture in isolation, Nakamura and coworkers have been able to produce quantities of *Symbiodinium sp*. free of zoanthids.[21] Algae of the genus *Symbiodinium* have been isolated from zoanthids of the genus Zoanthus.[22] While the algae produced different distributions of metabolites depending on the media used, Nakamura's group was able to isolate a new C_{30} alkaloid

they named zooxanthellamine (**23)** after significant experimentation with culture conditions. Zooxanthellamine exists as a mixture of imine and lactone forms (Figure 1.6). Its structure and relative configuration were delineated from extensive NMR studies. Zooxanthellamine was shown to have the same sense of absolute configuration as the zoanthamine alkaloids by NMR comparison of its MTPA esters.[21] The remarkable similarity between zooxanthellamine and zoanthamine has called into question the role of the zoanthids in producing the zoanthamine natural products.[23] It may be that the zoanthids play only a small role in adjusting the oxidation state of the completed zoanthamine skeleton. The subtle variations in the alkaloids' structures could be determined by factors in the marine environment or by the host zoanthid species. Alternatively, different algae species may be involved in the production of different zoanthamines.

Figure 1.6 Structure of Zooxanthellamine

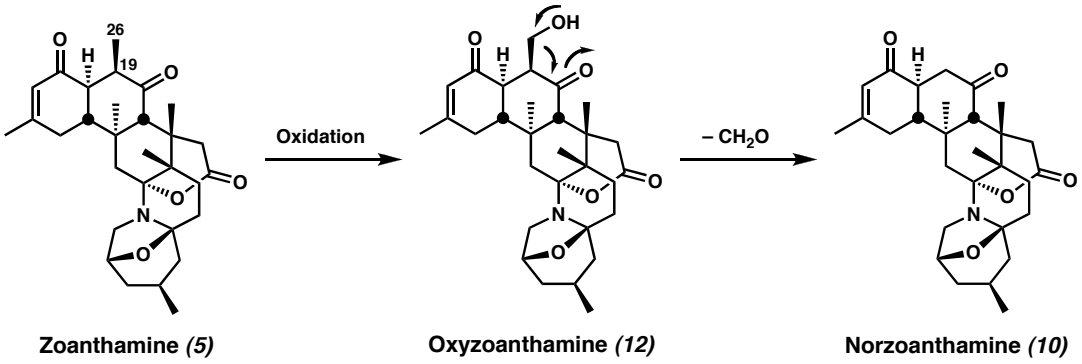


Zooxanthellamine *(23)*

Another intriguing biosynthetic question involving the zoanthamine natural products is the origin of the norzoanthamine-type alkaloids, which lack the C(26) methyl group. The isolation of oxyzoanthamine prompted Uemura and coworkers to propose a

mechanism for the demethylation of zoanthamines (Scheme 1.2). They propose oxidation of the zoanthamine to the intermediate oxyzoanthamine, which then undergoes a retro aldol, formally releasing formaldehyde and the noralkaloid.[15]

Scheme 1.2 Proposed Biosynthesis of the Norzoanthamines

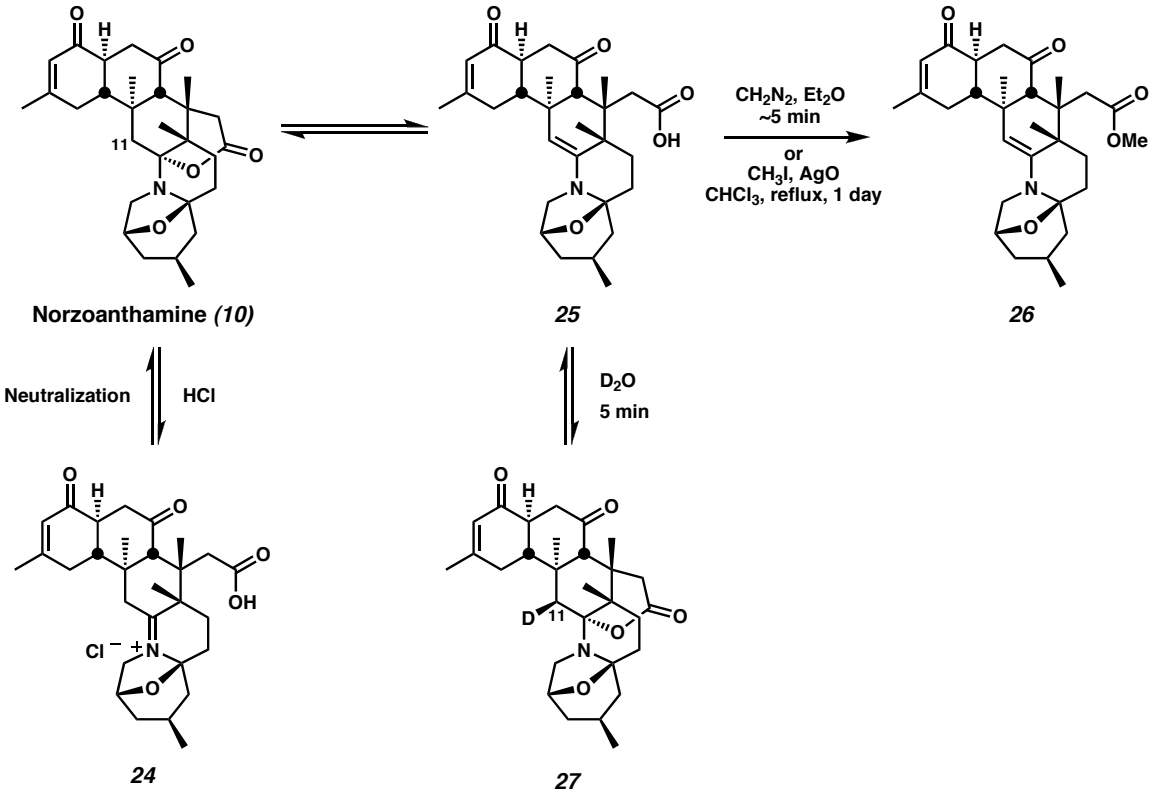


1.2.3 *Chemical Reactivity of the Zoanthamine Natural Products*

Fluxion between lactone and imine isomers, similar to the equilibration observed with zooxanthellamine, has been demonstrated in several zoanthamine natural products (Scheme 1.3). Norzoanthamine forms iminium **24** under acidic conditions and reverts upon neutralization.[20] Under neutral to basic conditions, elimination forms enamine **25**. The equilibrium between norzoanthamine and enamine **25** was demonstrated by the conversion of norzoanthamine to methyl ester **26** in minutes upon exposure to diazomethane.[20] Furthermore, NMR spectra of norzoanthamine in D_2O show specific and complete deuterium incorporation at the 11β position to give deuteride **27** in minutes.[18,19] Similar rates of deuterium incorporation were observed with zoanthenol, 3-hydroxynorzoanthamine, and 30-hydroxnorzoanthamine. In contrast, the 11β-hydroxyzoanthamines did not show significant deuterium incorporation, suggesting that

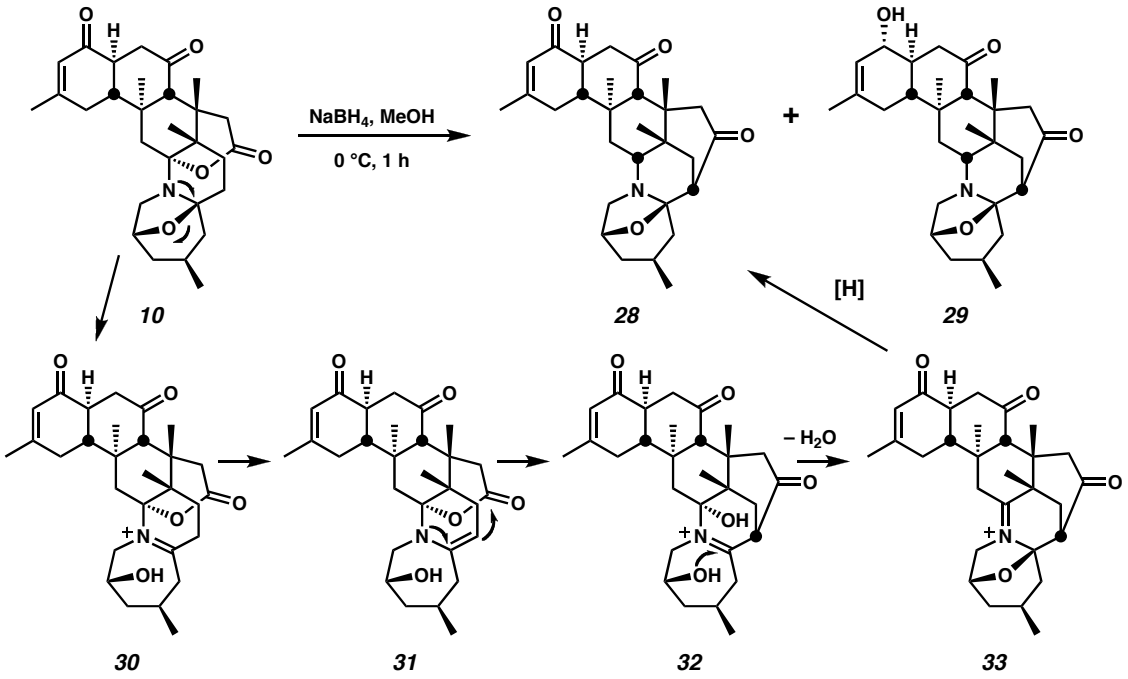
the elimination to an enamine is inaccessible.[19] This fluxional behavior in aqueous media at physiologically relevant pHs may play an important role in determining the bioactivities of these molecules.

Scheme 1.3 Equilibria Between Lactone and Enamine Isomers of Norzoanthamine



The hemiaminal region of the zoanthamine alkaloids also shows intriguing reactivity under reductive conditions. Treatment of norzoanthamine with sodium borohydride generates two anomalous products, enone **28** and allylic alcohol **29** (Scheme 1.4).[20,16] Under the reaction conditions, enamine **31** is believed to attack the lactone in an intramolecular fashion to afford keto-iminium **32**. Dehydration generates iminium **33**, which undergoes reduction to give enone **28**. Further reduction affords allylic alcohol **30**.

Scheme 1.4 Anomalous Reduction of Norzoanthamine



1.3 Biological Activities of Zoanthamine Alkaloids

1.3.1 *Antiosteoporotic Activity*

Perhaps the best studied and most well-known biological activity of the zoanthamine alkaloids is the antiosteoporotic effect first reported by Uemura in 1996.[24] Norzoanthamine and its hydrochloride salt have been shown in vivo to prevent the symptoms of osteoporosis in ovariectomized mice, a pharmaceutical model for postmenopausal osteoporosis. Osteoporosis is a loss of bone mineral density that often results when osteoclasts reabsorb bone tissue at a rate faster than it is regenerated.[25] In the model, ovariectomized mice, lacking in estrogen, quickly lose bone mass and strength. At doses of 0.4 and 2.0 mg/kg/d (five days a week for 4 weeks, *p.o.*) of norzoanthamine hydrochloride, the ovariectomized mice retained femur weight at statistically higher rates than untreated ovariectomized mice.[26] Additionally, with doses

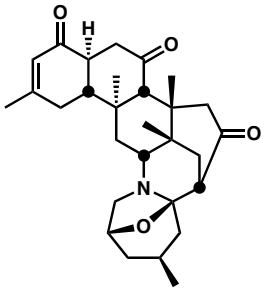
from 0.016-0.4 mg/kg/d of norzoanthamine hydrochloride the femurs of ovariectomized mice maintained strength, as measured by failure load, nearly comparable to unovariectomized control mice.[27] Finally, mice treated with norzoanthamine hydrochloride were observed to possess cortical bone significantly thicker than that found in the control animals.[28]

In analogy to estrogen replacement therapy in postmenopausal women, ovariectomized mice can be rescued from the effects of osteoporosis by treatment with 17β-estradiol. However, treatment with norzoanthamine hydrochloride shows interesting differences from estrogen therapy. Uterine atrophy, a side effect of estrogen deficiency after ovariectomy, is not affected by treatment with norzoanthamine hydrochloride.[28] This ability to restore bone strength without eliciting other side effects associated with steroid hormone receptors is a highly desirable property.

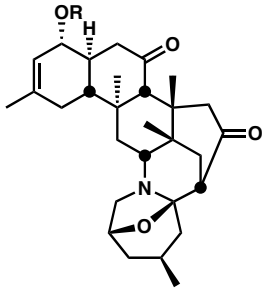
The origin of norzoanthamine's antiosteoporotic effect may lie in its ability to suppress the production of interleukin 6 (IL-6). Norzoanthamine and its hydrochloride salt **24** have been shown to suppress the excretion of IL-6 from preosteoblastic cells at concentrations of 13 and 4.6 μg/ml, respectively, in vitro.[29] IL-6 is in turn involved in stimulating the generation of osteoclasts, which reabsorb bone tissue. Estrogen derives its antiosteoporotic properties from the inhibition of IL-6 production.[30] However, in vitro studies on osteoblasts with norzoanthamine hydrochloride showed no effect on osteoclast formation. Also, the suppression of IL-6 secretion has not yet been demonstrated in vivo.[28] These last two points, along with the lack of uterine weight gain in ovariectomized mice, suggest that the zoanthamine alkaloids may act by a mechanism distinct from estrogen's.[31]

The need to find non-estrogen therapies to prevent the onset of osteoporosis has spurred considerable effort to define a structure activity relationship (SAR) for norzoanthamine's antiosteoporotic effects, despite its unclear molecular target. Via semi-synthesis, Uemura and coworkers produced and tested a number of norzoanthamine derivatives.[20,29] It should be noted that all of the derivatives assayed were significantly less efficacious (higher IC_{50} values) in limiting IL-6 production than norzoanthamine (Figure 1.7).[32] The removal of the olefin (ketone **35** and diol **36**) caused some loss in activity. However, disruption of the lactone/hemiaminal functionality (carboxylic acid **37** and ester **27**) caused the greatest drops in activity.[20]

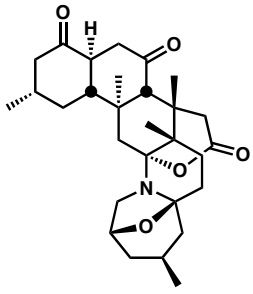
Figure 1.7 SAR Study of Norzoanthamine's Ability to Inhibit IL-6 Production



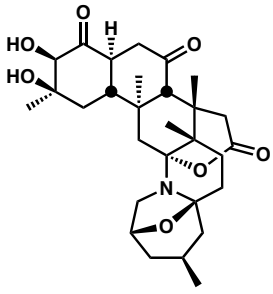
28



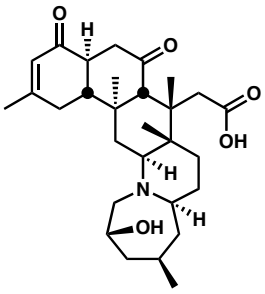
29, R = H
34, R = OAc



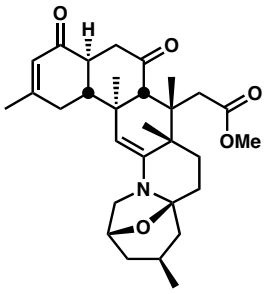
35



36



37

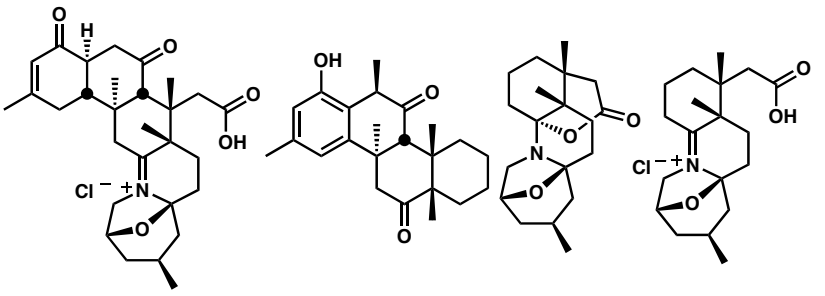


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Compound	IC_{50} (μg/mL) for Suppression of IL-6 Production
Norzoanthamine *(10)*	13
28	25
29	30
34	23
35	45
36	35
37	42
26	>100

More recently, Hirama and coworkers have studied the SAR of zoanthenol-related molecules to inhibit the growth of IL-6 dependent MH-60 cells (Figure 1.8). In their assays, the zoanthamine hydrochloride salts **24** and **38** showed the strongest inhibition of IL-6 production with IC_{50} values of 13 and 26 μM, respectively. A truncated mimic of zoanthenol's "northern" carbocyclic region **39** and a mimic of the zoanthamine "southern" heterocyclic region **40** both showed very poor activity. However, iminium **41**, the hydrochloride salt of heterocycle **40**, demonstrated a significant amount of the activity found in the zoanthamine hydrochlorides.[33] This result provides further support for two trends: (a) the hydrochloride salt form of a zoanthamine molecule is a more active inhibitor of IL-6 production than the natural product, and (b) the heterocyclic portion of the molecule contains a large part of the pharmacophore for IL-6 inhibition.

Figure 1.8 SAR of Zoanthenol Analogues' Inhibition of IL-6 Dependent Cell Growth



Compound	IC_{50} (μM) for IL-6 Dependent Cell Growth
24	13
38	26
39	>100
40	>100
41	~70

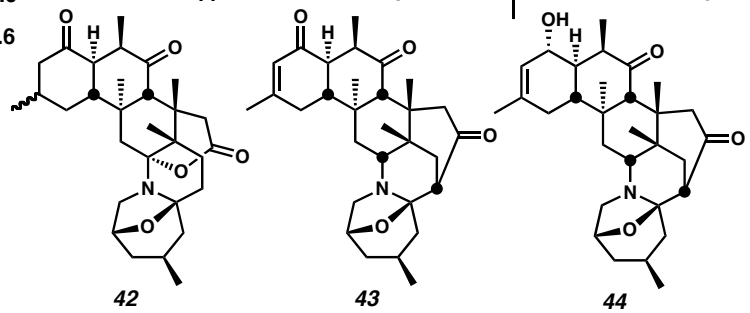
1.3.2 *Miscellaneous Biological Activities*

A multitude of other biological activities have been discovered for molecules in the zoanthamine family. As previously mentioned, zoanthamine, zoanthenamine, and zoanthamide were found to be inhibitors of PMA-induced inflammation in mouse ear.[12,13]

In addition to the isolation of norzoanthamine, norzoanthamineone, oxyzoanthamine, cyclozoanthamine, and epinorzoanthamine, Uemura and coworkers reported that these structures had significant cytotoxicity against P388 murine leukemia cells (Table 1.1).[15] The most potent cytotoxicity was displayed by norzoanthaminone. The antibacterial properties of zoanthamine and several of its reduced derivatives have been investigated.[34] In disk susceptibility experiments, the zoanthamine alkaloids showed broad spectrum activity against both Gram negative and Gram positive bacteria (Table 1.1). More recently the effect of zoanthamine alkaloids on human platelet aggregation has been investigated.[35] These experiments showed that at concentrations of 0.5 mM 11-hydroxyzoanthamine and methyl ester **26** prevent the majority of platelet aggregation caused by collagen, arachidonic acid, and thrombin. In contrast, oxyzoanthamine and zoanthenol were highly effective inhibitors of aggregation in the presence of collagen at 0.5 mM, but showed almost no activity in the presence of arachidonic acid or thrombin.

Table 1.1 Summary of Miscellaneous Biological Activities

Cytotoxicity		**Antibacterial Activity**				
			Inhibition Zone (dia. in mm)			
Compound	**IC_{50} (μg/ml) for Inhibition of P388 Murine Leukemia Cells**	**Compound**	**Gram Negative**		**Gram Positive**	
			S. typhimurium	***E. coli***	***B. sphaericus***	***S. aureus***
Norzoanthamine *(10)*	**24.0**	**Zoanthamine *(5)***	**6**	**6**	**8**	**7**
Norzoanthaminone *(11)*	**1.0**	***42***	**12**	**6**	**8**	**10**
Oxyzoanthamine *(12)*	**7.0**	***43***	**7**	**6**	**8**	**10**
Cyclozoanthamine *(14)*	**24.0**	***44***	**6**	**7**	**7**	**9**
Epinorzoanthamine *(15)*	**2.6**					



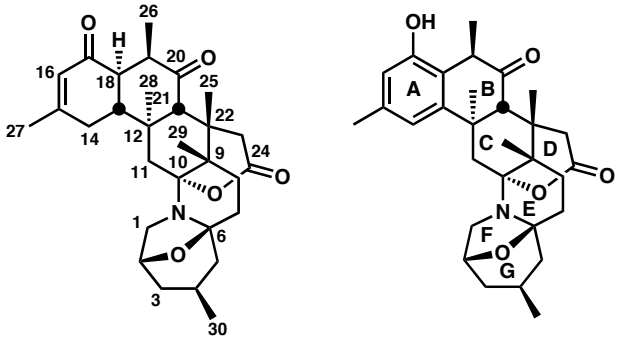
42 ***43*** ***44***

1.4 Approaches Toward the Synthesis of Zoanthamine Natural Products

1.4.1 *General Remarks*

The intriguing diversity of biological activities and the challenging structures of the zoanthamine alkaloids have inspired no fewer than seven synthetic chemistry groups to publish strategies toward the total synthesis of these molecules. Carbon numbering and ring naming will refer to the zoanthamine numbering scheme throughout this thesis (Figure 1.9). Though the focus of the work in our laboratories has been toward the synthesis of zoanthenol, a survey of the synthetic work toward any of the zoanthamines is instructive due to the similar challenges posed by all the molecules in this family. Many researchers have focused their efforts on the synthesis of the ABC rings, which poses a significant synthetic challenge due to its stereochemical density. For example, the C ring contains three quaternary stereocenters in vicinal and non-vicinal relationships. In addition to the difficulty of synthesizing quaternary centers, their steric bulk also renders even routine transformations on nearby functionally recalcitrant. Other researchers have focused on the synthesis of the heterocyclic DEFG rings. DEFG ring synthesis presents the challenge of forming the heterocycles with the correct hemiaminal connectivity.

Figure 1.9 Carbon Numbering and Ring Naming Scheme for the Zoanthamine Alkaloids



Zoanthamine *(5)* **Zoanthenol *(21)***

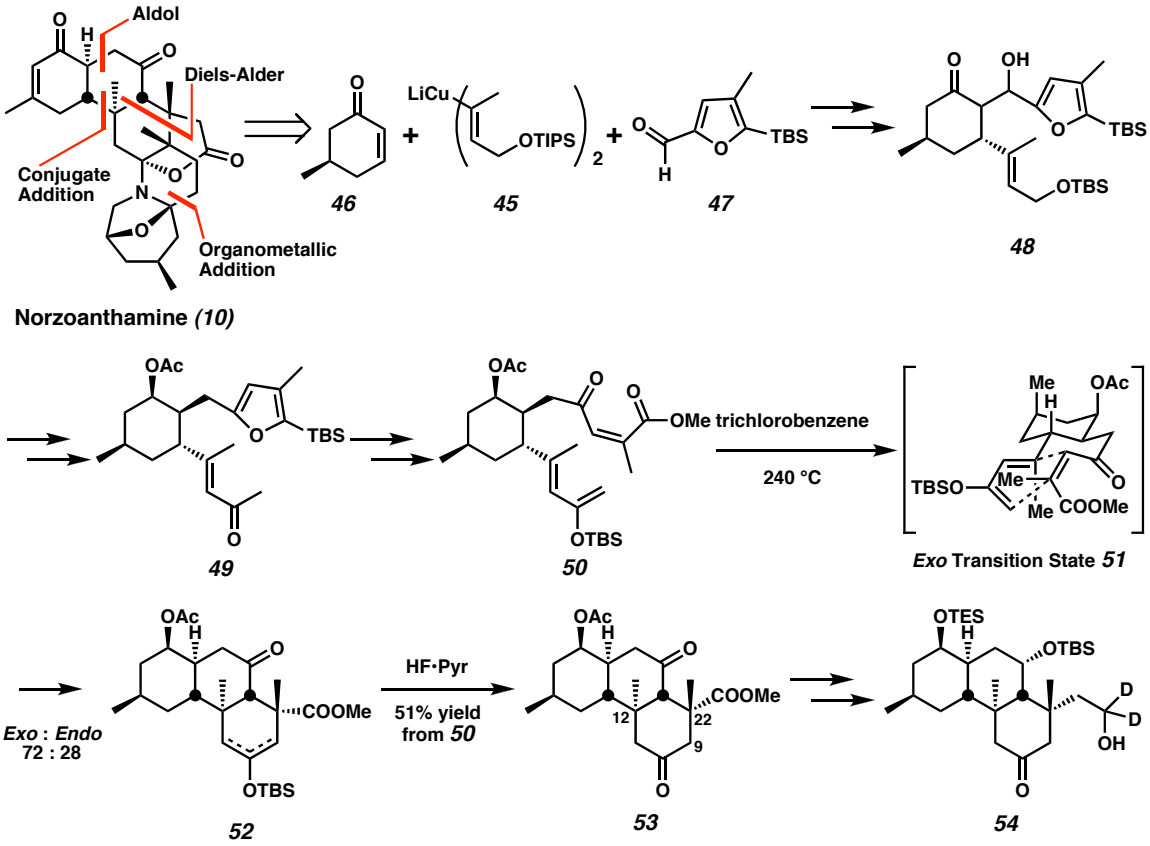
1.4.2 *Miyashita's Synthesis of Norzoanthamine*

Twenty years after the isolation of the first zoanthamine alkaloids, Miyashita and coworkers reported the only completed total synthesis to date of a zoanthamine alkaloid with their synthesis of norzoanthamine.[36] This impressive 41-step effort included several creative solutions to problems that likely arose during the execution of the synthesis. Their Diels-Alder strategy for the construction of the ABC ring system of norzoanthamine was disclosed in 2002 (Scheme 1.5).[37] Addition of cuprate **45** to enantiopure enone **46** followed by aldol reaction with aldehyde **47** provided ketone **48**. This efficient three component coupling sequence established all the carbons of the ABC ring system. After further manipulation, furan **49** was oxidized and its enone silylated to give Diels-Alder substrate **50**. Upon heating to 240 °C, the Diels-Alder reaction proceeded predominantly through the desired *exo* transition state **51** (72:28). After silyl cleavage, diastereomerically pure ketone **53** was isolated in 51% yield. This impressive Diels-Alder reaction sets both the C(12) and C(22) quaternary centers of norzoanthamine with the correct relative stereochemistry. However, this strategy provided little functionality to aid in the construction of the C(9) quaternary stereocenter. After significant functional group manipulation, ketone **53** was converted to ketoalcohol **54**.

Ketoalcohol **54** contains suitable functionality to attempt the formation of the C(9) quaternary center (Scheme 1.6). To that end, acylation of ketoalcohol **54** with dimethyl carbonate and lithium *tert*-butoxide proceeded regioselectively, presumably due to lactone formation, and was followed by quenching with methyl iodide to give *O*-alkylated β-ketolactone **55**. Upon treatment with lithium *tert*-butoxide and methyl iodide in DMPU, the *O*-alkylated β-ketolactone **55** underwent C-alkylation to give quaternized

δ-lactone **56**. Impressively, this difficult transformation was accomplished in 83% yield as a single diastereomer.

Scheme 1.5 Miyashita's Diels-Alder Construction of the ABC Rings of Norzoanthamine

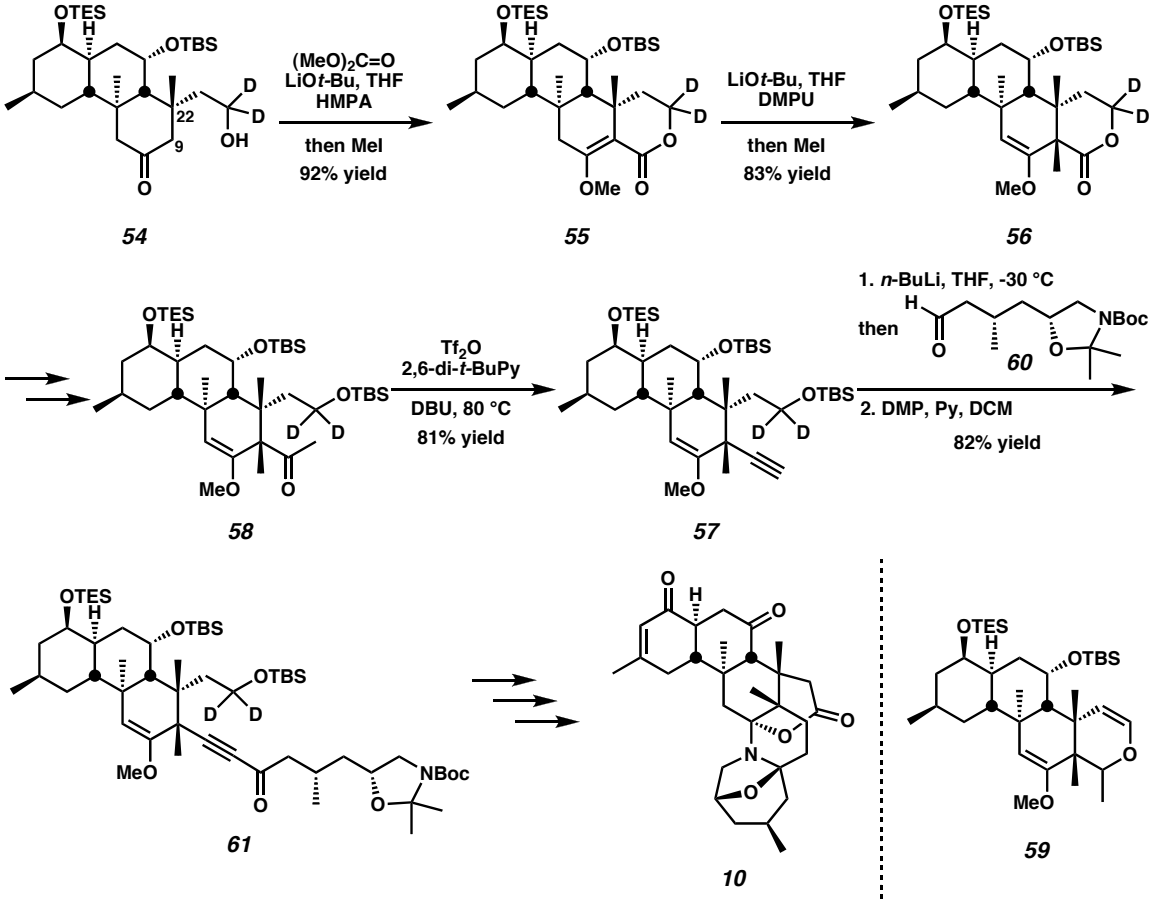


The next challenge lay in converting δ-lactone **56** to acetylene **57** (Scheme 1.6). The addition of methyl lithium with subsequent silylation converted δ-lactone **56** to ketone **58**. While the dehydration of ketone **58** appeared routine, it was at this point that Miyashita's clever incorporation of deuterium proved necessary. When the hydrido equivalent of ketone **58** was treated with triflic anhydride, the intermediate carbocation was predominantly intercepted by intramolecular hydride addition leading to

dihydropyran **59**. However, deuteride transfer proved much slower, and the deutero ketone **58** could be dehydrated to alkyne **57** with only minor amounts of the dihydropyran formed.

The carbon skeleton of norzoanthamine was completed by the addition of aldehyde **60** to the lithium salt of alkyne **57** and oxidation of the resulting alcohol to ynone **61**. Completion of the target required a further twelve steps of deprotection, oxidation state adjustment, and dehydration. In addition to the impressive synthetic accomplishment, this synthesis also served to unambiguously confirm the absolute stereochemistry of norzoanthamine that had been deduced from NMR experiments.

Scheme 1.6 The Completion of Norzoanthamine

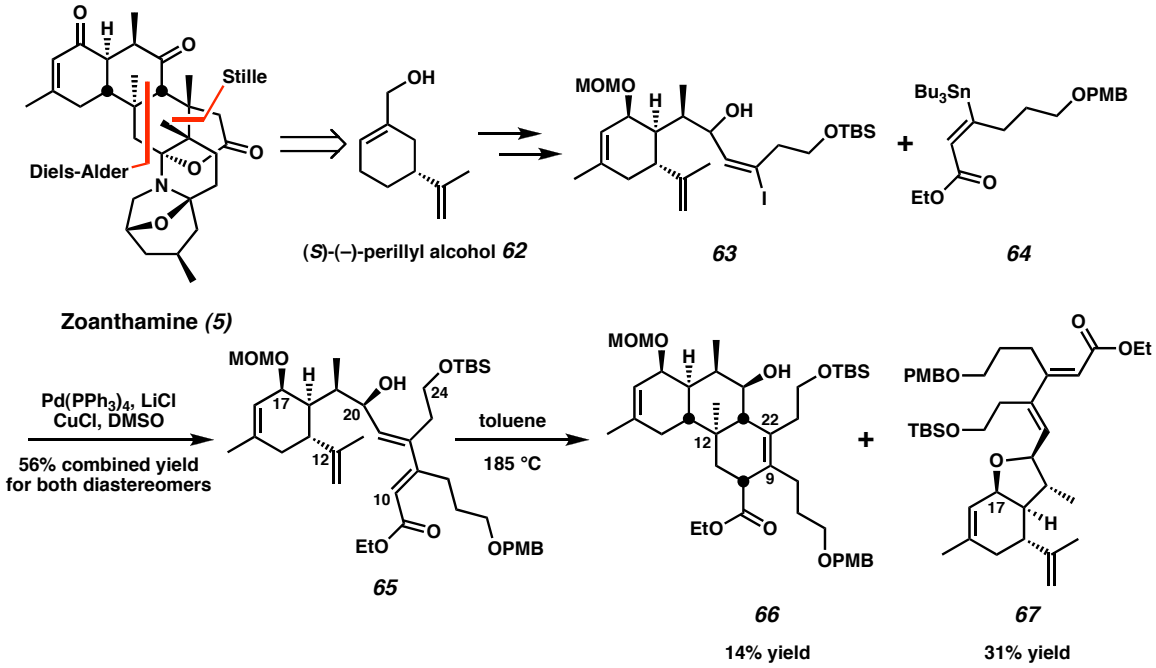


1.4.3 *Tanner's Diels-Alder Approach to the Zoanthamine ABC Ring System*

Tanner and coworkers also chose to assemble the ABC rings via a Diels-Alder approach (Scheme 1.7). Their synthesis began with (*S*)-(–)-perillyl alcohol **62** as a chiral synthon for the A ring.[38] After numerous steps, (*S*)-(–)-perillyl alcohol was transformed into iodide **63**.[39] Stille coupling with stannane **64** proved difficult and required conditions reported by Corey to afford reasonable yields of the Diels-Alder substrate **65**.[40,41] Though not the originally conceived or most direct substrate, diene **65** evolved through significant experimentation.[42] The alcohol oxidation state at C(20) was found to be necessary to prevent elimination of the primary TBS group at C(24), which occurred from the corresponding ketone. However, without the C(20) carbonyl, the diene was no longer electron deficient enough to support the desired inverse demand Diels-Alder reaction. Thus the stannane fragment was redesigned to stannane **64**, incorporating an ester moiety at the C(10) position that would need to be excised later in the synthesis. Of the two C(20) alcohol diastereomers isolated, only diene **65** underwent thermal Diels-Alder reaction. The reaction proceeded with high diastereoselectivity to afford β,γ unsaturated ester **66**, albeit in modest yield. The major product isolated involved displacement of C(17) methoxymethyl ether to give tetrahydrofuran **67**. This problem can likely be circumvented with a more robust protecting group at C(17) or protection of the C(20) alcohol. While this Diels-Alder strategy nicely establishes the quaternary center at C(12), it requires the formation of the difficult vicinal C(9) and C(22) quaternary centers at a late stage. Tanner proposes to carryout this transformation by conjugate addition into the latent C(10) enone, which is to be revealed by oxidative cleavage of the ethyl ester in

Diels-Alder adduct **66**, followed by methyl iodide trapping. No model studies were presented to demonstrate this strategy's ability to form vicinal quaternary stereocenters.[43]

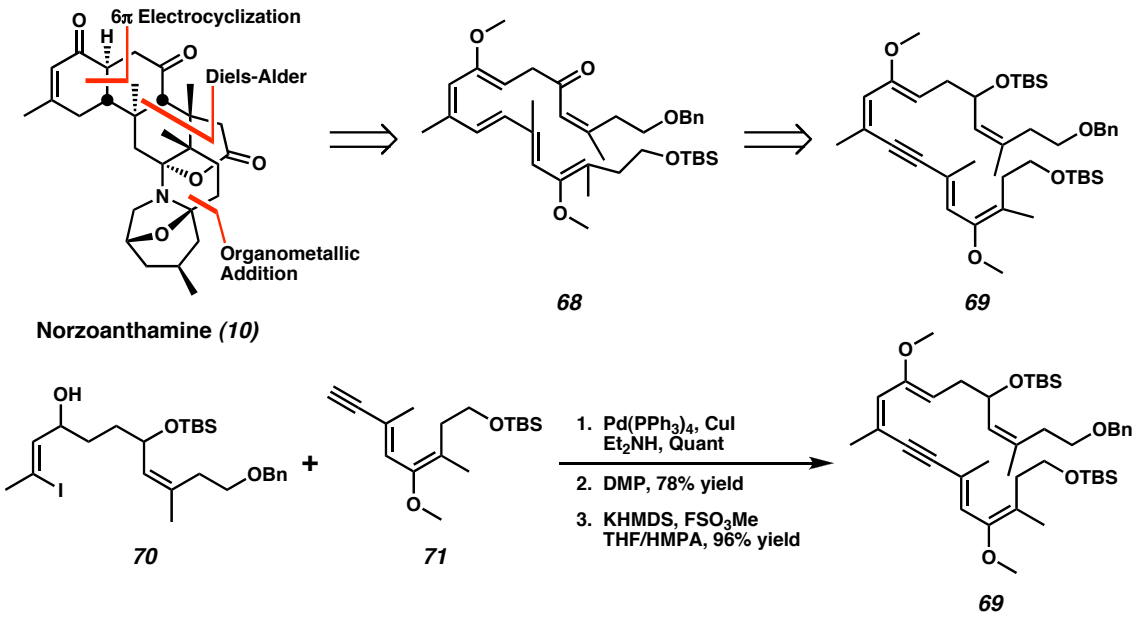
Scheme 1.7 Tanner's Approach to the ABC Ring System



1.4.4 *Uemura's Biomimetic Approach to the Norzoanthamine ABC Ring System*

Recently, Uemura and coworkers have proposed a synthetic strategy based on their biosynthetic hypothesis, which purports that the zoanthamine alkaloids arise from a linear polyketide skeleton, which then undergoes numerous cyclizations.[44] To support this hypothesis, they endeavored to synthesize and cyclize polyene **68**, which would in turn arise from enyne **69** (Scheme 1.8). Vinyl iodide **70** and alkyne **71** were efficiently assembled by Sonogashira coupling[45] and conversion to enyne **69** was completed by oxidation and methylation. No report has appeared on the selective reduction of enyne **69** to the linear polyene **68** or on attempts to cyclize polyene **68**.

Scheme 1.8 Uemura's Biomimetic Cyclization Approach to Norzoanthamine



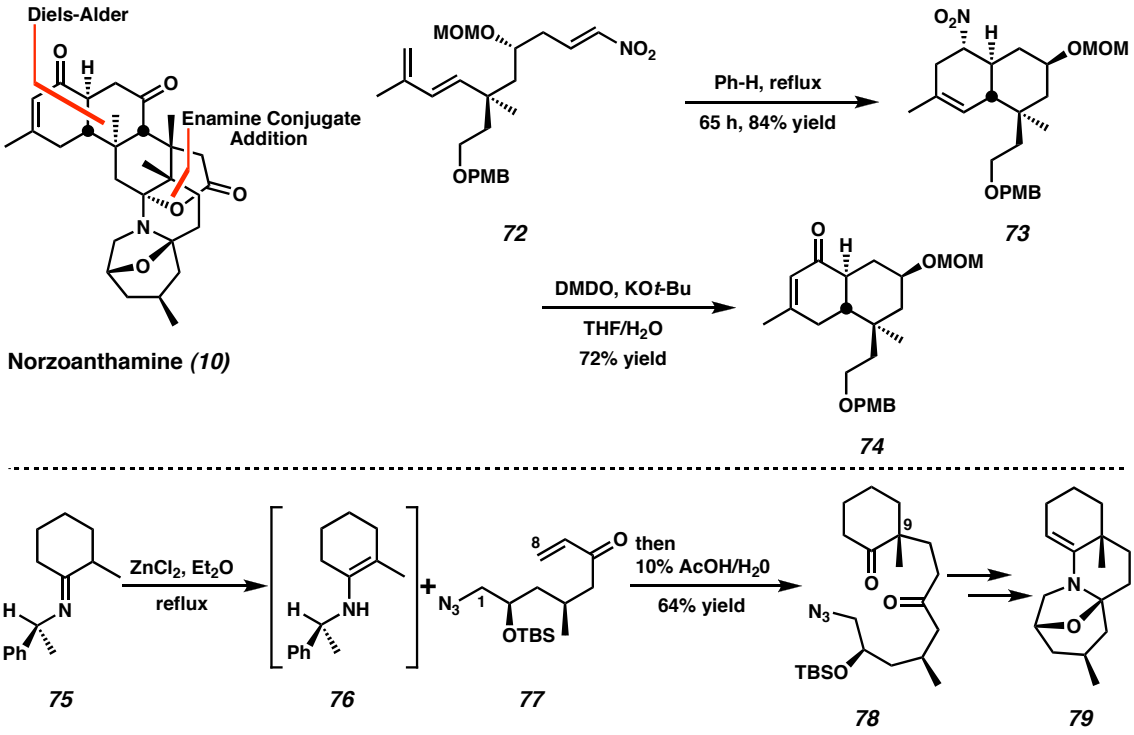
1.4.5 *Williams's Approach to the Norzoanthamine AB and EFG Ring Systems*

Williams and coworkers have contributed approaches to both the synthesis of the carbocyclic AB rings and the heterocyclic EFG rings. Their Diels-Alder strategy constructs the AB rings and subsequently appends the C ring (Scheme 1.9).[46] In the event, nitro alkene **72** underwent reaction in refluxing benzene via an *endo* transition state to afford decalin **73** in good yield and 10:1 dr. A Nef reaction[47] converted the nitro moiety to the desired ketone and facilitated olefin migration. The product enone **74** has the necessary stereochemistry and functionality to begin C ring annulation.

In addition, the Williams group demonstrated an efficient strategy to append the C(1)-C(8) fragment to the ABC ring system and stereospecifically establish the C(9) quaternary center.[48] When heated with zinc (II) chloride, chiral imine **75** generates a significant amount of enamine **76** at equilibrium. The enamine **76** undergoes conjugate addition from the β-face (over the smaller methyl group) of the energy minimized

conformation depicted. Enone **77** was prepared in enantioenriched form using the Evans chiral oxazolidinone.[49] Hydrolysis of the intermediate imine affords diketone **78** with excellent diastereoselectivity (22:1). Upon Staudinger reduction and silyl deprotection of azide **78**, the desired imine formation, ketalization, and dehydration occur without further intervention to give the EFG model enamine **79**.

Scheme 1.9 William's Efforts Toward Norzoanthamine

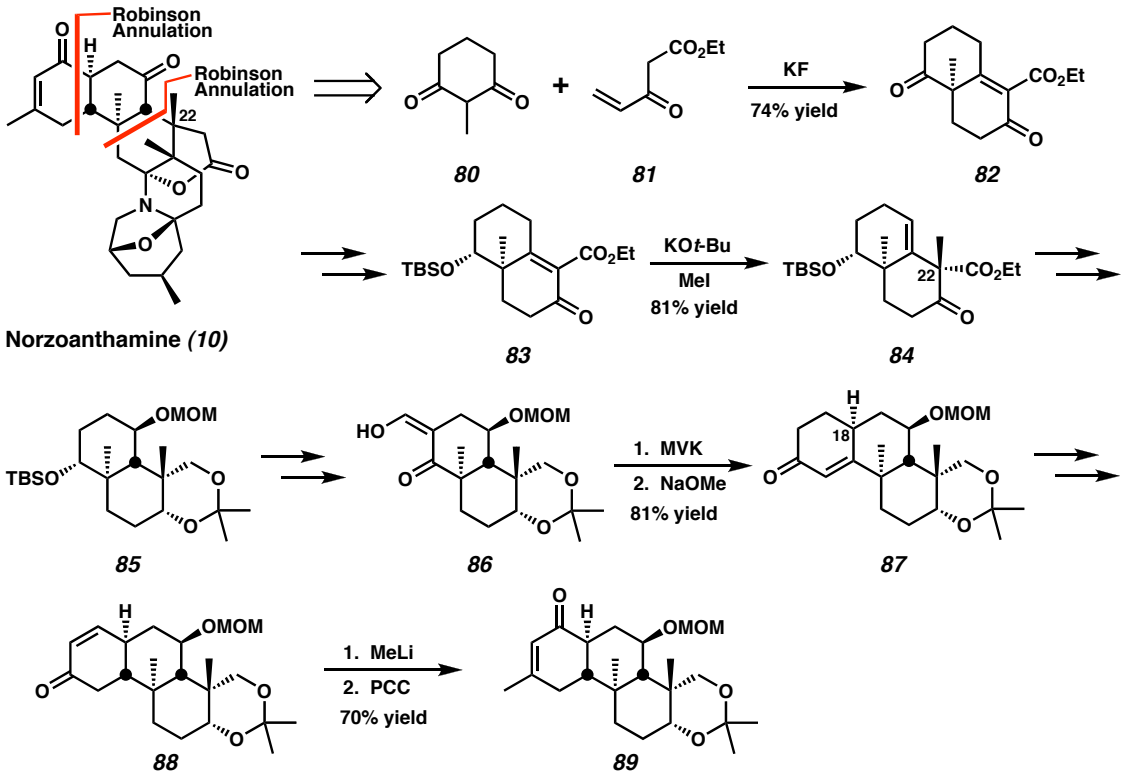


1.4.6 *Theodorakis's Annulation Approach to the Norzoanthamine ABC Ring System*

The annulation strategy proposed by Theodorakis and coworkers is unique in that it starts with the B ring intact and sequentially appends the C and A rings.[50] Condensation of diketone **80** and ketoester **81** with potassium fluoride conditions previously described by their group afforded enone **82** (Scheme 1.10).[51] The formation of

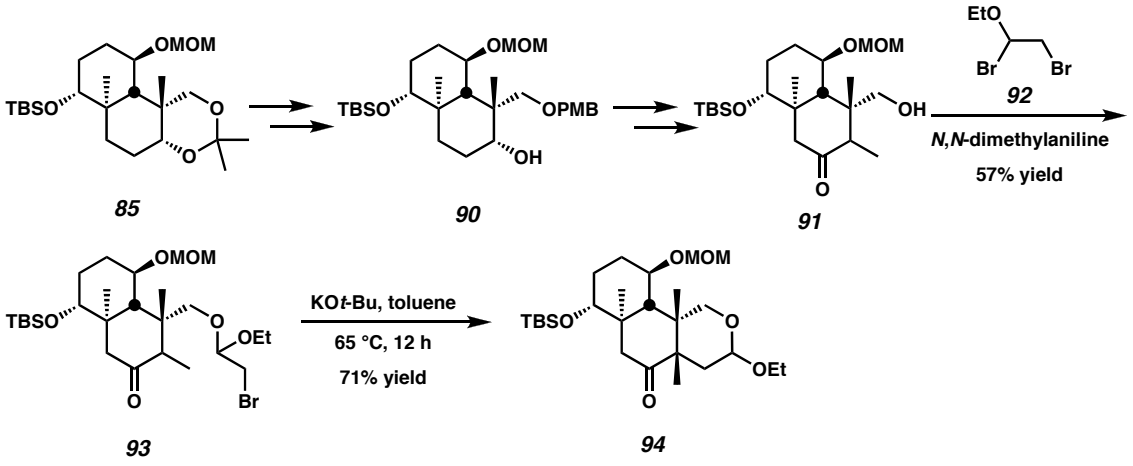
the quaternary stereocenter at C(22) was the next challenge. Treatment of α,β unsaturated ketoester **83** with potassium *tert*-butoxide and methyl iodide produced the quaternized ketoester **84** with complete diastereomeric control. After significant functional group modification, hydroxymethylene-ketone **86** was ready for A ring annulation. A two-step Robinson annulation[52] protocol gave enone **87** as a single isomer at the newly formed C(18) center. After straightforward transformation to enone **88**, methyl lithium addition and PCC oxidation afforded the transposed enone **89**, which contained all the functionality and stereochemistry in the AB rings.

Scheme 1.10 Theodorakis's Annulation Approach to the ABC Ring System



In a related study, Theodorakis demonstrated that the installation of the difficult C(9) quaternary center was possible from intermediate acetonide **85** (Scheme 1.11).[53] Acetonide **85** was advanced by selective protection to give alcohol **90**, which could in turn be converted to methyl ketone **91**. Acetal formation between Stork's dibromo-acetal reagent **92**[54] and the alcohol moiety of methyl ketone **91** produced bromide **93**. Exposure of bromide **93** to base gave a single intramolecular alkylation product **94** in 71% yield. The efficiency of this protocol is impressive given the difficulty of establishing vicinal quaternary centers. Additionally, the alkylation gave complete selectivity for the desired C(9) diastereomer of acetal **94**, as affirmed by X-ray structure determination. Taken in conjunction with Theodorakis's other work, this strategy solved the difficult problem of generating all three of the C ring quaternary centers and produced a norzoanthamine ABC ring system well accoutered for the completion of the total synthesis.

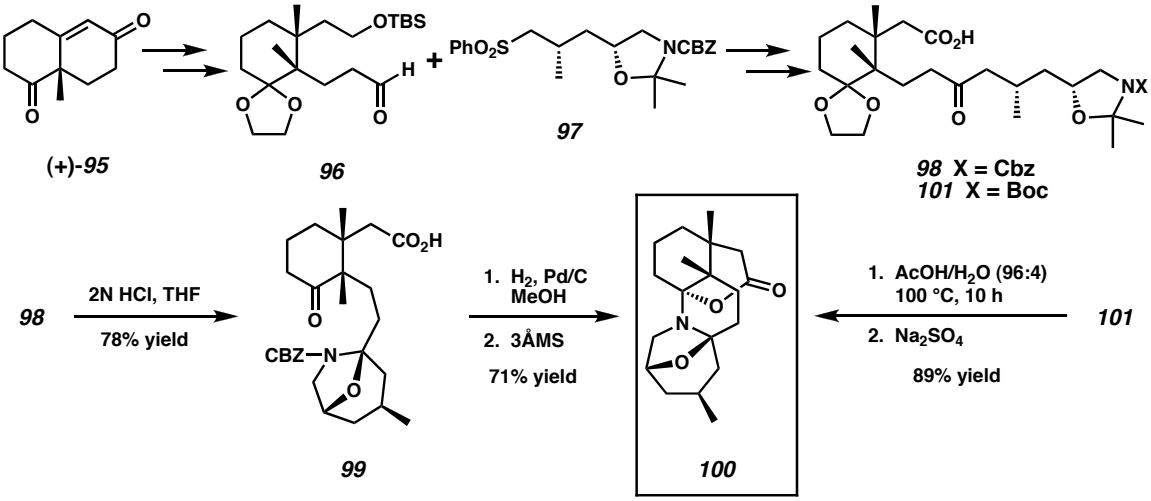
Scheme 1.11 Theodorakis's Installation of the C(9) Quaternary Center



1.4.7 *Kobayashi's Synthesis of the Heterocyclic CDEFG Zoanthamine Ring System*

In 1998 Kobayashi and coworkers disclosed an enantioselective route to the complete CDEFG ring system.[55] The Wieland-Miescher ketone **95**[56] served as the starting material to produce aldehyde **96** (Scheme 1.12). The coupling of sulfone **97**'s lithium salt to aldehyde **96** and oxidation state adjustment completed the Cbz protected cyclization substrate **98**. Treatment with hydrochloric acid removed the acetonide and formed the FG rings. Tricyclic intermediate **99** underwent hydrogenolysis and dehydration to complete the pentacyclic hemiaminal **100**. A one-pot, two-step protocol for cyclization, using Boc protected substrate **101** and acidic conditions, was subsequently investigated and gave an excellent yield of the hemiaminal **100**.[57]

Scheme 1.12 Kobayashi's Sulfone Approach to the Heterocyclic DCEFG Ring System

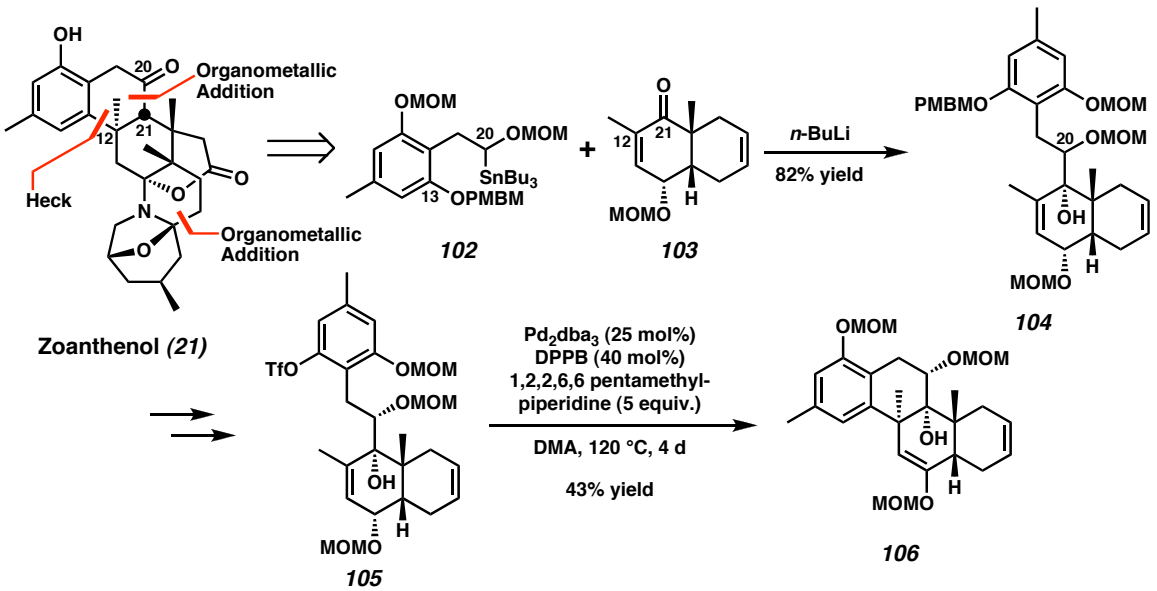


1.4.8 *Hirama's Strategy for the Zoanthenol ABC Ring System*

The strategy proposed by Hirama and coworkers is uniquely geared toward the synthesis of zoanthenol's ABC ring system. The key Heck[58] disconnection of the C(12)-

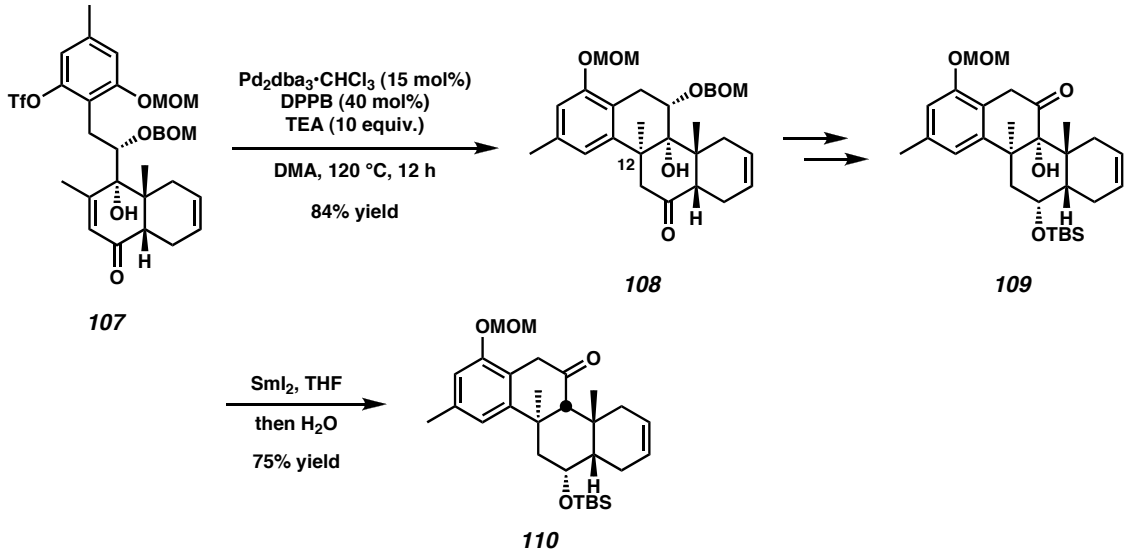
C(13) bond relies on the aromatic A ring unique to zoanthenol (Scheme 1.13). Further disconnection of the B ring at the C(20)-C(21) bond reveals stannane **102** and enone **103** as appropriate fragments. The C ring synthon, enone **103**, was envisioned to arise in enantioenriched form from an asymmetric quinone Diels-Alder reaction also developed in the Hirama group.[59] In practice, transmetallation of stannane **102** and addition into enone **103** afforded tertiary alcohol **104** as a mixture of diastereomers at C(20). Straightforward conversion of tertiary alcohol **104** to triflate **105** allowed for the investigation of the key intramolecular Heck reaction. After significant optimization, conditions were discovered to produce the desired enol ether **106** in modest yield.[60] Though the reaction did proceed with excellent diastereoselectivity, it had several drawbacks, including reduction of the substrate, high palladium loading, and long reaction times.

Scheme 1.13 Hirama's Heck Strategy for the Zoanthenol ABC Ring System



In light of these problems, Heck substrate **105** was altered to increase the electrophilicity of the accepting olefin. As shown in Scheme 1.14, exposure of enone **107** to reductive Heck conditions produced ketone **108** in excellent yield. With the difficult C(12) stereocenter established, their next goal was the reduction of the tertiary alcohol moiety of ketone **109**. Samarium (II) iodide gave the reduced ketone **110** as a single diastereomer and in good yield.[61]

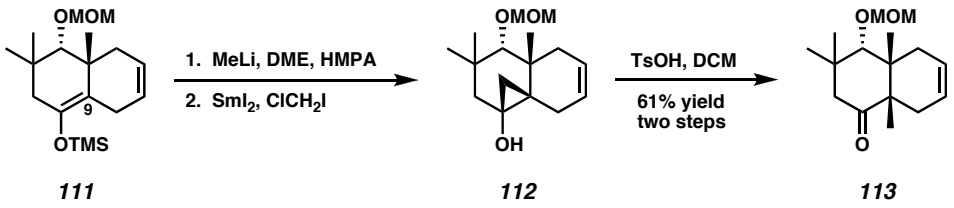
Scheme 1.14 Hirama's Alternate Heck Strategy



107 *108* *109* *110*

The largest challenge that remains in Hirama's synthesis is the establishment of the C(9) quaternary stereocenter. However, his group has already demonstrated a highly diastereoselective methylation of silyl enol ether **111** as a model of methylation at C(9) (Scheme 1.15).[62] The methylation was achieved by samarium (II) iodide promoted cyclopropanation and acid-mediated ring opening to give methyl ketone **113** and its C(9) epimer with a favorable 3:1 dr.

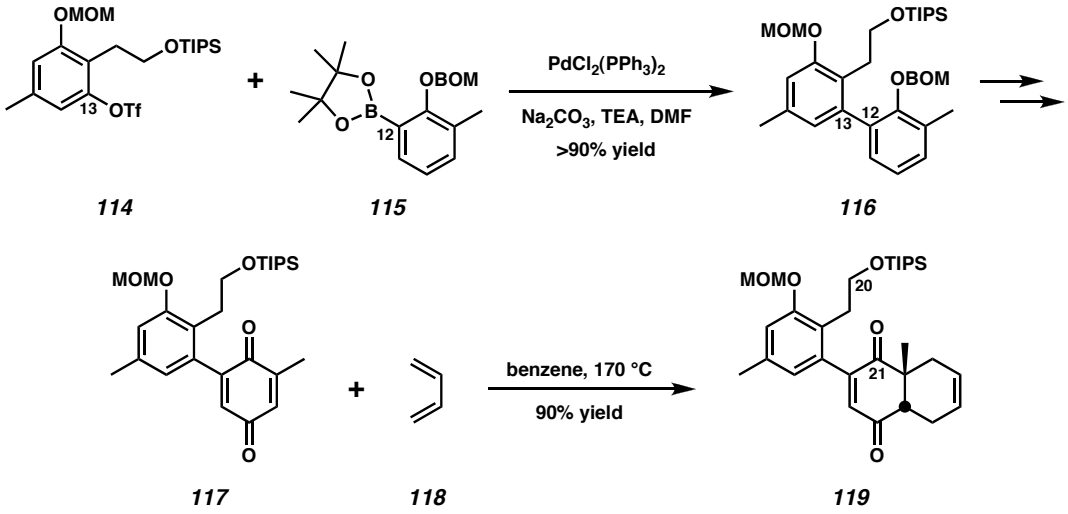
Scheme 1.15 Hirama's Installation of the C(9) Methyl



111 *112* *113*

Recently, Hirama and coworkers have disclosed an alternate strategy for the assembly of zoanthenol's ABC ring system. This strategy reverses the order in which the B ring bonds are formed.[63] As depicted in Scheme 1.16, Suzuki coupling of aryl triflate **114** and borane **115** unite the A and C ring synthons via the C(12)-C(13) bond to yield biaryl **116**. Upon the elaboration of Diels-Alder adduct **119**, the final B ring bond, C(20)-C(21), will likely be constructed by an organometallic addition analogous to the synthesis of tertiary alcohol **104**.

Scheme 1.15 Hirama's Alternate Heck Strategy



114 *115* *116*

117 *118* *119*

1.5 Conclusion

The zoanthamine alkaloids are a structurally unique family of natural products. Though they are isolated from soft coral of the order zoantharia, it may be that symbiotic algae play a large role in the biosynthesis of these secondary metabolites. Their biosynthesis is believed to be polyketide in origin, but no specifics of the pathway are known. The benefit of these complicated natural products to the producing organisms is unknown, but the isolation of various zoanthamine alkaloids in the Indian, Pacific, and Atlantic Oceans suggests that these widespread metabolites may have an important function. Species in the order zoantharia have produced several classes of biologically active natural products. The zoanthamines are no exception. Antiosteoporotic, antibiotic, anti-inflammatory, and cytotoxic biological activities have been discovered in various zoanthamines. As a result, these molecules have garnered increasing attention from synthetic chemists.

As synthetic targets, the zoanthamine alkaloids are a challenge to current synthetic methods and an inspiration for the creation of new reactions. In the contemporary era, it is common for newly isolated natural products of interesting structure or biological significance to succumb to total synthesis in one to two years' time. By comparison, twenty years passed between the isolation of zoanthamine and Miyashita's total synthesis of norzoanthamine in 2004. Any successful synthesis of these alkaloids requires expertise in both carbocyclic and heterocyclic chemistry. Construction of the carbocyclic ABC rings is hindered by the stereochemical density of this tricycle. In particular, the three quaternary centers of the C ring represent a major challenge. This challenge has inspired a number of creative annulation strategies utilizing Diels-Alder,

Heck, and Robinson annulation reactions. The heterocyclic DEFG rings are topographically complex and contain a number of sensitive functional groups. Pioneering syntheses of the heterocyclic region of these molecules determined the feasibility of different cyclization strategies.

1.6 Notes and Citations

(1) Sinniger, F.; Montoya-Burgos, J. I.; Chevaldonné, P.; Pawlowski, J. *Marine Biology* **2005**, *147*, 1121-1128.

(2) Ono, S.; Reimer, J. D.; Tsukahara, J. *Zoological Science* **2005**, *22*, 247-255.

(3) Nakamura, H.; Kawase, Y.; Maruyama, K.; Muria, A. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 781-787.

(4) (a) Suksamrarn, A.; Jankam, A.; Tarnchompoo, B.; Putchakarn, S. *J. Nat. Prod.* **2002**, *65*, 1194-1197. (b) Shigemori, H.; Sato, Y.; Kagata, T.; Kobayashi, J. *J. Nat. Prod.* **1999**, *62*, 372-374.

(5) Han, C.; Qi, J.; Shi, X.; Sakagami, Y.; Shibata, T.; Uchida, K.; Ojika, M. *Biosci. Biotechnol. Biochem.* **2006**, *70*, 706-711.

(6) Fernández, J. J.; Souto, M. L.; Daranas, A. H.; Norte, M. *Current Topics in Phytochemistry* **2000**, *4*, 106-119.

(7) Sepcic, K.; Turk, T.; Macek, P. *Toxicon* **1998**, *36*, 93-940.

(8) Pletneva, N.; Pletnev, S.; Tikhonova, T.; Popov, V.; Martynov, V.; Pletnev, V. *Acta Cryst. Sec. D* **2006**, *62*, 527-532.

(9) Remington, S. J.; Wachtner, R. M.; Yarbrough, D. K.; Branchaud, B.; Anderson, D. C.; Kallio, K.; Lukyanov, K. A. *Biochemistry* **2005**, *44*, 202-212.

(10) Moore, R. E.; Scheuer, P. J. *Science* **1971**, *172*, 495-498.

(11) For structure determination see: Cha, J. K.; Christ, W. J.; Finan, J. M.; Fujioka, H.; Kishi, Y.; Klein, L. L.; Ko, S. S.; Leder, J.; McWhorter, W. W.; Pfaff, K.-P.; Yonaga, M.; Uemura, D.; Hirata, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7369-7371. For

total synthesis see: Suh, E. M.; Kishi, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11205-11206.

(12) Roa, C. B.; Anjaneyula, A. S. R.; Sarma, N. S.; Venkatateswarlu, Y.; Rosser, R. M.; Faulkner, D. J.; Chen, M. H. M.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *106*, 7983-7984.

(13) Roa, C. B.; Anjaneyula, A. S. R.; Sarma, N. S.; Venkatateswarlu, Y. *J. Org. Chem.* **1985**, *50*, 3757-3760.

(14) Roa, C. B.; Roa, D. V.; Raju, V. S. N. *Heterocycles* **1989**, *28*, 103-106.

(15) Fukuzawa, S.; Hayashi, Y.; Uemura, D.; Nagatsu, A.; Yamada, K.; Ijuin, Y. *Heterocyclic Communications* **1995**, *1*, 207-214.

(16) Kuramoto, M.; Hayashi, K.; Fujitani, Y.; Yamaguchi, K.; Tsuji, T.; Yamada, K.; Ijuin, Y.; Uemura, D. *Tetrahedron Lett.* **1997**, *38*, 5683-5686.

(17) Atta-ur-Rahman; Alvi, K. A.; Abbas, S. A.; Choudhary, M. I.; Clardy, J. *Tetrahedron Lett.* **1989**, *30*, 6825-6828.

(18) Daranas, A. H.; Fernández, J. J.; Gavín, J. A.; Norte, M. *Tetrahedron* **1998**, *54*, 7891-7896.

(19) Daranas, A. H.; Fernández, J. J.; Gavín, J. A.; Norte, M. *Tetrahedron* **1999**, *55*, 5539-5546.

(20) Kuramoto, M.; Hayashi, K.; Yamaguchi, K.; Yada, M.; Tsuji, T.; Uemura, D. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 771-779.

(21) Nakamura, H.; Kawase, Y.; Maruyama, K.; Murai, A. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 781-789.

(22) Trench, R. K. *Pure Appl. Chem.* **1981**, *53*, 819-835.

(23) Also in this study, a molecule closely related to palytoxin, zooxanthellatoxin, was isolated. See ref. 21 for details.

(24) Kuramoto, M.; Arimoto, H.; Hayashi, K.; Hayakawa, I.; Uemura, D.; Chou, T.; Yamada, K.; Tsuji, T.; Yamaguchi, K.; Yazawa, K. *Symposium Papers, 38th Symposium on the Chemistry of Natural Products*, **1996**, 79-84.

(25) Chambers, T. J. *J. Cell Sci.* **1982**, *57*, 247-260.

(26) The dose given in the text (0.4 mg/kg/d) for $p < 0.05$ is from ref. 27. However, in ref. 20, when the femur weight is analyzed per body mass (mg/g), a dose of 0.08 mg/kg/d is sufficient to give $p < 0.05$.

(27) The dose range given in the text (0.016-0.4 mg/kg/d) for $p < 0.05$ is from ref. 20. However, in ref. 27 only dosing at 0.4 mg/kg/day gave a significant ($p < 0.05$) increase in failure load. No explanation for this disparity is given.

(28) Yamaguchi, K.; Yada, M.; Tsuji, T.; Kuramoto, M.; Uemura, D. *Biol. Pharm. Bull.* **1999**, *22*, 920-924.

(29) Kuramoto, M.; Yamaguchi, K.; Tsuji, T.; Uemura, D. Zoanthamines, Antiosteoporotic Alkaloids. In *Drugs from the Sea*, Fusetani, N., Ed.; Karger: Basel, 2000, 98-106.

(30) Bodine, P. V. N.; Harris, H. A.; Komm, B. S. *Endocrinology* **1999**, *140*, 2439-2451.

(31) For other descriptions of this activity, see: (a) Kuramoto, M.; Arimoto, H.; Uemura, D. *J. Synth. Org. Chem., Jpn.* **2003**, *61*, 59-65. (b) Kuramoto, M.; Arimoto, H.; Uemura, D. *Mar. Drugs* **2004**, *1*, 39-54. (c) Kita, M.; Uemura, D.

Chem. Lett. **2005**, *34*, 454-459. (d) Yamada, K.; Kuramoto, M.; Uemura, D. *Recent Res. Devel. Pure & Applied Chem.* **1999**, *3*, 245-254.

(32) The IC_{50} values are for inhibition of IL-6 production from preosteoblastic MC3T3-E1 cells stimulated by parathyroid hormone. See ref. 28.

(33) Hirai, G.; Oguri, H.; Hayashi, M.; Koyama, K.; Koizumi, Y.; Moharram, S. M.; Hirama, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2647-2651.

(34) Venkateswarlu, Y.; Reddy, N. S.; Ramesh, P.; Reddy, P. S.; Jamil, K. *Heterocyclic Communications* **1998**, *4*, 575-580.

(35) Villar, R. M.; Gil-Longo, J.; Daranas, A. H.; Souto, M. L.; Fernández, J. J.; Peixinho, S.; Barral, M. A.; Santafé, G.; Rodríguez, J.; Jiménez, C. *Bioorg. Med. Lett.* **2003**, *11*, 2301-2306.

(36) Miyashita, M.; Sasaki, M.; Hattori, I.; Sakai, M.; Tanino, K. *Science* **2004**, *305*, 495-499.

(37) Sakai, M.; Sasaki, M.; Tanino, K.; Miyashita, M. *Tetrahedron Lett.* **2002**, *43*, 1705-1708.

(38) Tanner, D.; Anderson, P. G.; Tedenborg, L.; Somfai, P. *Tetrahedron* **1994**, *50*, 9135-9144.

(39) (a) Tanner, D.; Tedenborg, L.; Somfai, P. *Acta Chem. Scand.* **1997**, *51*, 1217-1223. (b) Nielsen, T. E.; Tanner, D. *J. Org. Chem.* **2002**, *67*, 6366-6371.

(40) Nielsen, T. E.; Le Quement, S.; Juhl, M.; Tanner, D. *Tetrahedron* **2005**, *61*, 8013-8024.

(41) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600-7605.

(42) Juhl, M.; Nielsen, T. E.; Le Quement, S.; Tanner, D. *J. Org. Chem.* **2006**, *71*, 265-280.

(43) Beilstein searches reveal only seven such examples of conjugate additions into tetrasubstituted enones to form quaternary centers, none of which involved addition to a cyclic system.

(44) Irifune, T.; Ohashi, T.; Ichino, T.; Sakia, E.; Suenaga, K.; Uemura, D. *Chem. Lett.* **2005**, *34*, 1058-1059.

(45) Sonogashira, K.; Tohdo, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467-4470.

(46) Williams, D. R.; Brugel, T. A. *Org. Lett.* **2000**, *2*, 1023-1026.

(47) For a review of Nef reactions see: Pinnick, H. W. *Org. React.* **1990**, *38*, 655-792.

(48) Williams, D. R.; Cortez, G. A. *Tetrahedron Lett.* **1998**, *39*, 2675-2678.

(49) For a review of Evans aldol methodology see: Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichimica Acta* **1997**, *30*, 3-12.

(50) Ghosh, S.; Rivas, F.; Fischer, D.; González, M. A.; Theodorakis, E. A. *Org. Lett.* **2004**, *6*, 941-944.

(51) (a) Ling, T.; Chowdhury, C.; Kramer, B. A.; Vong, B. G.; Palladino, M. A.; Theodorakis, E. A. *J. Org. Chem.* **2001**, *66*, 8843-8853. (b) Ling, T.; Kramer, B. A.; Palladino, M. A.; Theodorakis, E. A. *Org. Lett.* **2000**, *2*, 2073-2076.

(52) For a review of Robinson annulations see: Gawley, R. E. *Synthesis* **1976**, 777-794.

(53) Rivas, F.; Ghosh, S.; Theodorakis, E. A. *Tetrahedron Lett.* **2005**, *46*, 5281-5284.

(54) The use of dibromide **92** for radical cyclizations was explored by Stork, see: (a) Stork, G.; Mook, R.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**,

105, 3741-3742. (b) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1983**, *105*, 6765-6766.

(55) (a) Hikage, N.; Furukawa, H.; Takao, K.; Kobayashi, S. *Tetrahedron Lett.* **1998**, *39*, 6237-6240. (b) Hikage, N.; Furukawa, H.; Takao, K.; Kobayashi, S. *Tetrahedron Lett.* **1998**, *39*, 6241-6244.

(56) Weiland, P.; Miescher, K. *Helv. Chim. Acta* **1950**, *33*, 2215-2228. For enantioselective preparation see: Buchschacher, P.; Fürst, A.; Gutzwiller, J. *Org. Synth.* **1985**, *63*, 37-43.

(57) Hikage, N.; Furukawa, H.; Takao, K.; Kobayashi, S. *Chem. Pharm. Bull.* **2000**, *48*, 1370-1372.

(58) (a) Heck, R. F.; Nolley, J. P. *J. Am. Chem. Soc.* **1968**, *90*, 5518-5526. (b) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146-151. (c) Heck, R. F. *Org. React.* **1982**, *27*, 345-390.

(59) Moharram, S. M.; Hirai, G.; Koyama, K.; Oguri, H.; Hirama, M. *Tetrahedron Lett.* **2000**, *41*, 6669-6673.

(60) Hirai, G.; Oguri, H.; Moharram, S. M.; Koyama, K.; Hirama, M. *Tetrahedron Lett.* **2001**, *42*, 5783-5787.

(61) Hirai, G.; Koizumi, Y.; Moharram, S. M.; Oguri, H.; Hirama, M. *Org. Lett.* **2002**, *4*, 1627-1630.

(62) Hirai, G.; Oguri, H.; Hirama, M. *Chem. Lett.* **1999**, *28*, 141-142.

(63) Moharram, S. M.; Oguri, H.; Hirama, M. *Egypt. J. Pharm. Sci.* **2003**, *44*, 177-193.

CHAPTER TWO

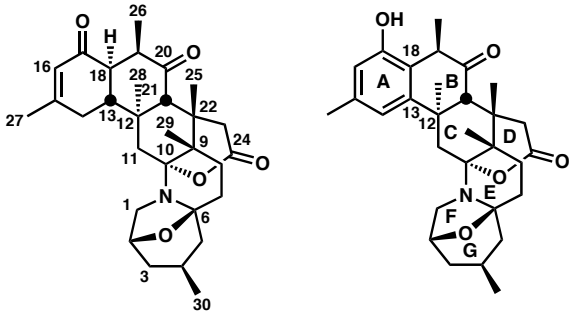
Early Approaches to the Synthesis of Zoanthenol

2.1 Synthetic Planning

2.1.1 *Introduction*

In late 2000, our laboratory became interested in the total synthesis of the zoanthamine alkaloids. At that time, Tanner[1] and Williams[2] had published the most comprehensive strategies toward the total synthesis of these natural products. In 1998, Kobayashi[3] and Williams[4] had described routes for the construction of the heterocyclic portion of these molecules. No work had yet been published toward the total synthesis of zoanthenol. Our interest in zoanthenol was piqued by its unique aromatic A ring. Aromatization of the A ring removes the C(13) and C(18) stereocenters from the zoanthamine skeleton (Figure 2.1). Despite this simplification, we felt that zoanthenol still embodied the core challenges of the zoanthamines. Additionally, the aromatic A ring allowed us to consider a number of disconnections of the C(12)-C(13) bond that were not readily applicable to the non-aromatic zoanthamines.

Figure 2.1 Zoanthamine and Zoanthenol



Zoanthamine *(5)* **Zoanthenol *(21)***

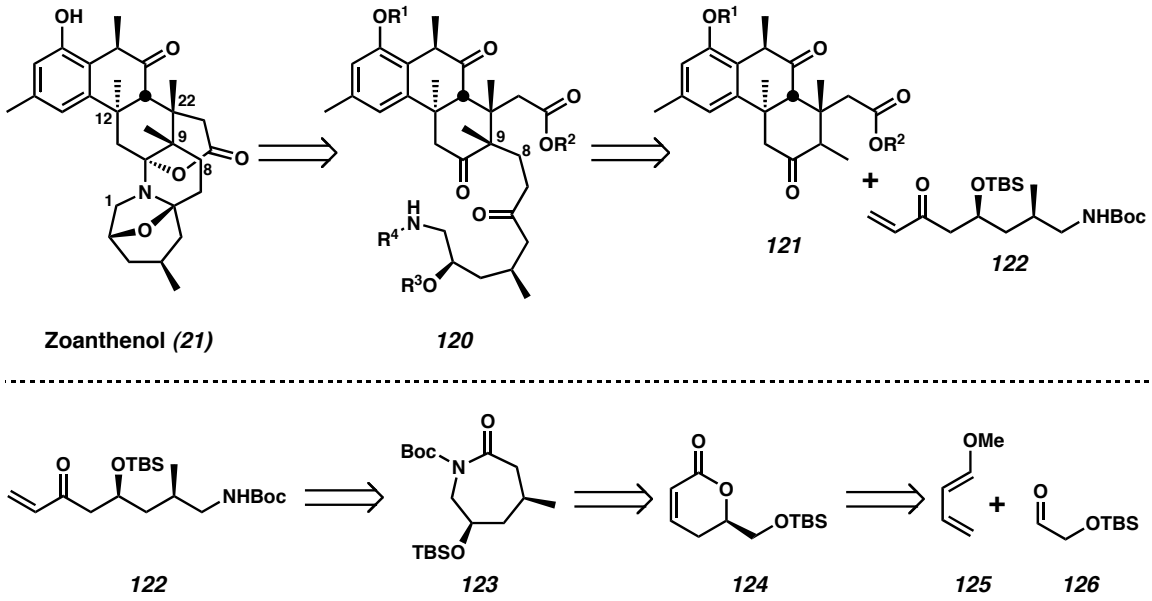
2.1.2 *Retrosynthesis*

Zoanthenol is a densely functionalized, topographically complex target molecule. Though only a C_{30} molecule, it is comprised of seven rings and nine stereocenters. The C ring poses the single greatest stereochemical challenge with three quaternary centers and five contiguous stereocenters (Scheme 2.1). The quaternary stereocenters are disposed in vicinal (C(9) and C(22)) and remote (C(12) and C(22)) relationships. Our overarching strategy in assembling the C ring was to generate one of these quaternary centers in enantioenriched fashion, and then derive the rest of the stereocenters in a highly diastereoselective manner. Another design feature common to all our strategies was to unite A and C ring synthons in a convergent manner by forging the B ring. With respect to the heterocyclic portion of the molecule, our goal was to introduce all the functionality of the C(1) to C(8) fragment in a single operation.

Our disconnections began with the heterocyclic portion of the molecule. Previous work had demonstrated that the complicated hemiaminals forming the DEFG rings were thermodynamically favored.[3,4] Thus, retrosynthetically, the heterocycles could be unraveled to give triketone **120** with a linear C(1) to C(8) side chain (Scheme 2.1). Disconnection of the C(8)-C(9) bond in the sense of a conjugate addition of an enamine affords methyl ketone **121** and enone **122**. Enone **122** may be derived from a vinyl anion addition to the amide carbonyl of caprolactam **123**. Caprolactam **123** may be simplified to lactone **124** by conjugate methyl addition and amination. Ultimately, lactone **124** may arise in enantioenriched form via an asymmetric hetero Diels-Alder reaction pioneered by Jacobsen and coworkers.[5] The synthesis of optically active caprolactam **123** was carried

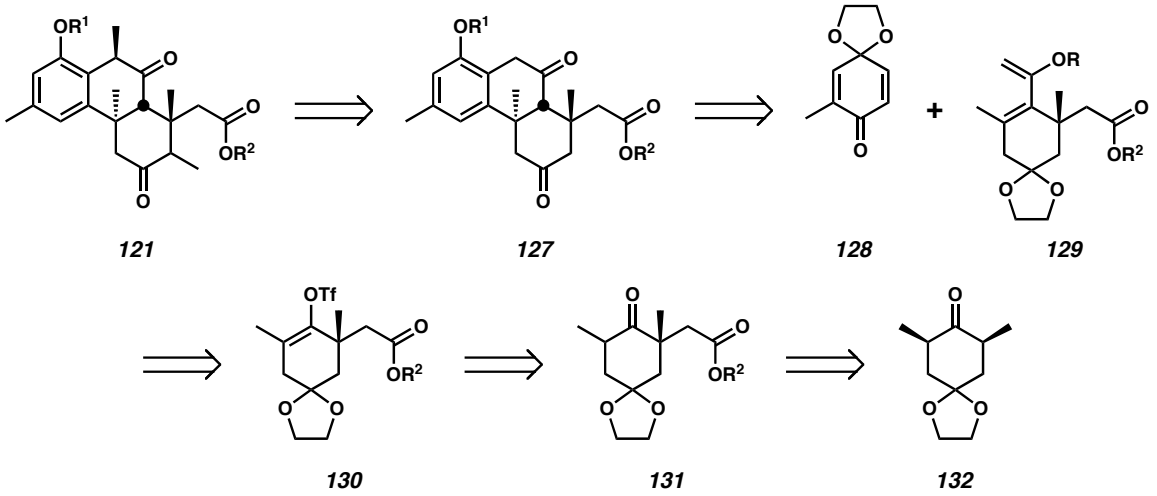
out by Dr. Jeffrey Bagdanoff, a former graduate student in the lab, and has been detailed elsewhere.[6]

Scheme 2.1 Retrosynthetic Analysis of Zoanthenol



Further simplification of methyl ketone **121** commences by removing the methyl group at C(9) to afford tricyclic diketone **127** (Scheme 2.2). Oxidation state adjustment and Diels-Alder disconnection across the B ring of diketone **127** yields the known mono-protected quinone **128**[7] and diene **129** as target fragments. Diene **129** could be assembled by Stille coupling involving enol triflate **130**, which could in turn be derived from ketoester **131**. Finally, asymmetric deprotonation of meso ketone **132** and reaction with an appropriate electrophile could afford ketoester **131** in enantioenriched form.

Scheme 2.2 Retrosynthetic Analysis of Zoanthenol's ABC Ring System

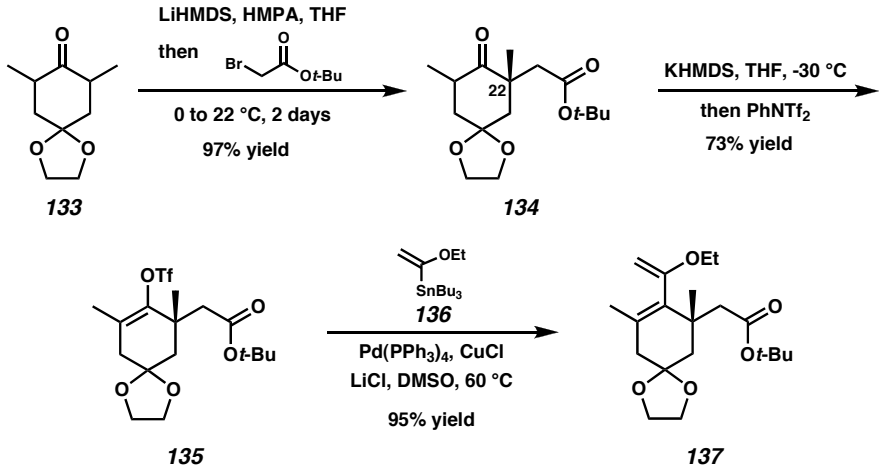


2.2 A Diels-Alder Approach to the Zoanthenol ABC Ring System

2.2.1 *Racemic Synthesis of the Substrate Diene*

In order to determine the feasibility of the quinone Diels-Alder strategy, the target diene was synthesized racemically (Scheme 2.3). Known dimethyl ketone **133**[8,9] was deprotonated with LiHMDS and alkylated with *t*-butyl bromoacetate in the presence of HMPA to give ketoester **134** in excellent yield as a mixture of diastereomers. Low temperature deprotonation of ketoester **134** with KHMDS and quenching with $PhNTf_2$ afforded enol triflate **135**, which underwent Stille coupling with vinyl stannane **136** to produce a diene **137** in excellent yield. The use of copper (I) chloride promoted Stille coupling conditions, reported by Corey, was essential.[10] Numerous other conditions failed to give significant amounts of diene **137**.

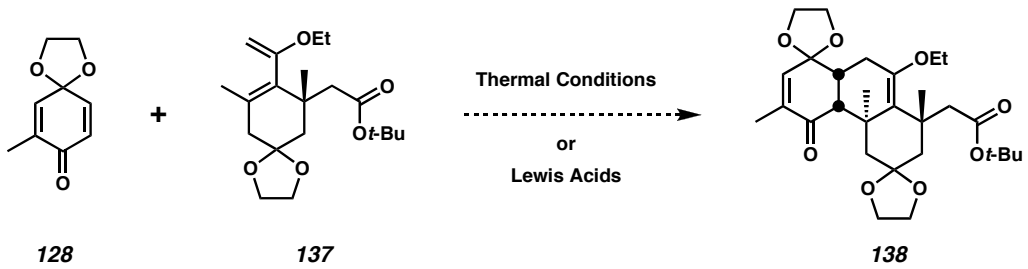
Scheme 2.3 Diene Synthesis



2.2.2 *Diels-Alder Reactions for B Ring Synthesis*

With quantities of both quinone **128** and diene **137** in hand, numerous trials to effect Diels-Alder reaction were performed. Thermal reaction of the two reactants up to 180 °C failed to give any Diels-Alder adducts. Treatment with Lewis acids including tin (IV) chloride, titanium (IV) chloride, ethyl aluminum dichloride, TBSOTf, methyl aluminum dichloride, and $TiCl_2(O\textit{i}\text{-}Pr)_2$ also failed to give a productive reaction.[11] More asynchronous or stepwise versions of the reaction that replaced ethyl enol ether **137** with its enolate equivalent did not produce any of the desired C-C bonds.

Scheme 2.4 Attempted Diels-Alder Reactions

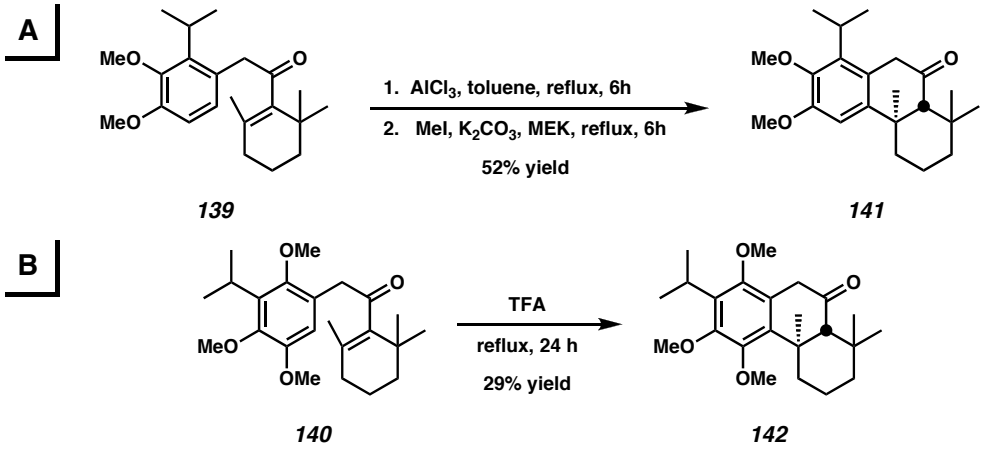


2.3 An Intramolecular Conjugate Addition Approach to the Zoanthenol ABC Rings

2.3.1 *Revised Retrosynthetic Analysis*

As a result of our inability to construct the B ring in a single Diels-Alder reaction, we considered strategies that would construct the B ring in a stepwise manner. One such strategy with good historical precedent was the intramolecular conjugate addition of electron-rich arenes into enones. This reaction has been demonstrated with steric environments as demanding as zoanthenol, as shown with enones **139** and **140** (Scheme 2.5).[12] These cyclizations were commonly employed in syntheses of Abietane natural products.[13] This Friedel-Crafts cyclization has been shown to proceed under either strongly Lewis acidic or Brønsted acidic conditions, but the reaction does require an extremely electron-rich arene for effective cyclization.[14]

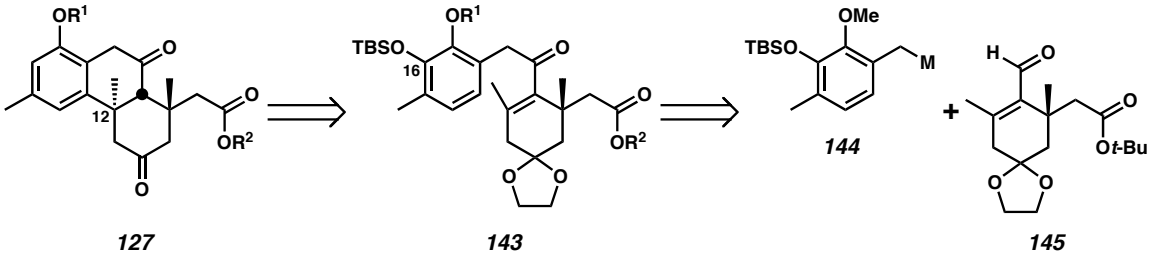
Scheme 2.5 Intramolecular Conjugate Additions in the Synthesis of Abietane Skeleton



Encouraged by the ability of such intramolecular 6-*endo* conjugate additions to form difficult benzylic quaternary centers, analogous to zoanthenol's C(12) stereocenter, we altered our retrosynthesis of diketone **127** to incorporate this disconnection (Scheme

2.6). In order to increase the nucleophilicity of the aromatic ring and facilitate conjugate addition, oxygenation was incorporated at C(16) of enone **143**. In turn, we envisioned enone **143** could arise by 1,2-addition of organometallic reagent **144** into enal **145**.

Scheme 2.6 Intramolecular Conjugate Addition Approach

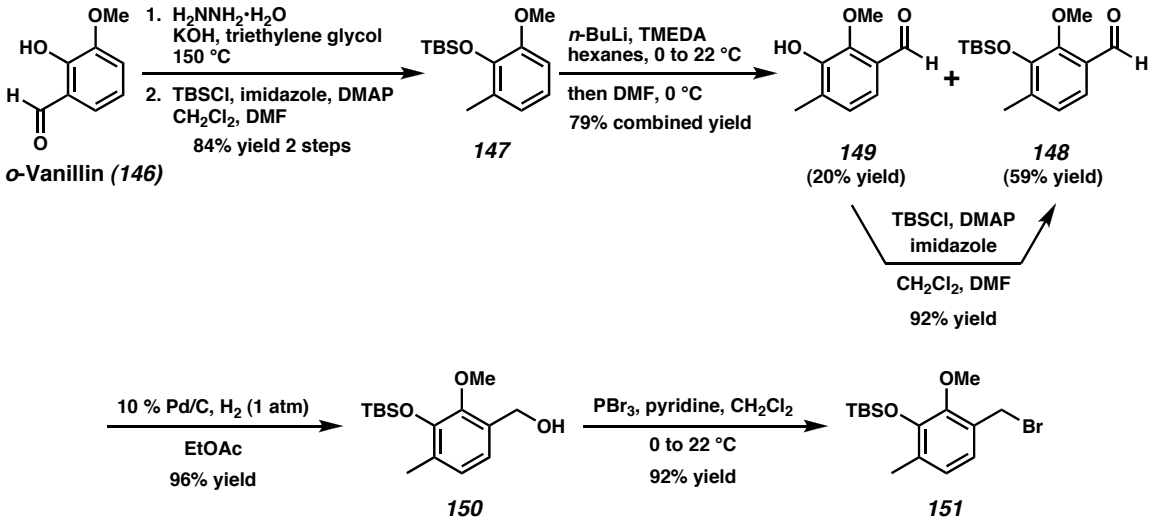


2.3.2 *Synthesis of A Ring Fragment*

The synthesis of the A ring synthon commenced with Wolff-Kishner reduction[15] of *o*-vanillin (**146**) and silyl protection to afford arene **147** in 84% yield over two steps after distillation (Scheme 2.7). Methoxy-directed *ortho*-lithiation of arene **147** and quenching with N,N′-dimethylformamide (DMF) afforded a mixture of the desired benzaldehyde **148** and desilylated benzaldehyde **149**. After chromatographic separation, phenol **149** was readily resilylated under standard conditions to provide additional benzaldehyde **148**. Carefully monitored reduction of benzaldehyde **148** with 10% Pd/C under a balloon of hydrogen afforded an excellent yield of benzylic alcohol **150**. If alcohol **150** was allowed to persist under the reaction conditions for several additional hours after the consumption of benzaldehyde **148**, significant over-reduction was observed. Benzylic alcohol **150** was converted with phosphorus tribromide and pyridine to benzyl bromide **151** in 92% yield after distillation. Benzyl bromide **151** was

anticipated to allow for the synthesis of several potential organometallic nucleophiles. Overall, the synthesis of the A ring synthon was efficient and scalable. We routinely produced 20-25 g of benzyl bromide **151** per batch.

Scheme 2.7 Synthesis of A Ring Benzyl Bromide



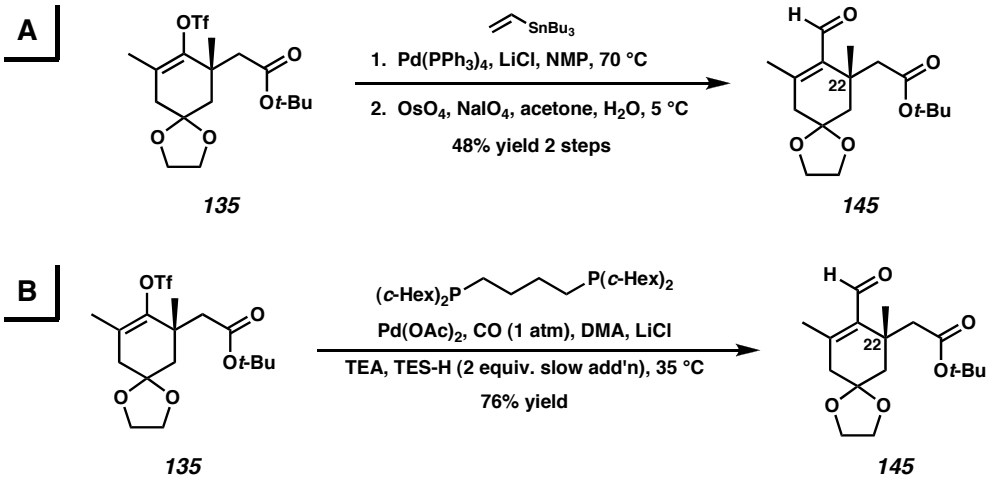
2.3.3 *Synthesis of the C Ring Synthon*

Two syntheses of the desired enal **145** were developed starting from intermediate triflate **135** (Scheme 2.8). A two-step approach involved Stille coupling with vinyl tributyltin to produce an intermediate diene. Oxidative cleavage with osmium (VIII) tetraoxide (OsO_4) and sodium periodate gave enal **145** (Reaction A). This route had several disadvantages. The oxidative cleavage required a minimum of 5 mol% of the expensive and toxic OsO_4 to consume all the hindered diene. In addition, modest yields in the oxidative cleavage resulted from poor olefin selectivity during the dihydroxylation.

As a result of these difficulties, a one-step palladium-catalyzed carbonylation method was developed for the synthesis of enal **145** (Reaction B). Treatment of triflate

135 under an atmosphere of carbon monoxide with palladium (II) acetate, 1,4-bis-(dicyclohexylphosphino)butane as a ligand, and TES-H as a reducing agent afforded the desired enal **145** in good yield. The use of this bulky, electron-rich bisphosphine ligand was essential. For example, the use of 1,4-bis(diphenylphosphino)butane (DPPB) afforded significant amounts of the corresponding reduced olefin. Additionally, the slow addition of the hydride source, TES-H, was necessary to minimize direct reduction of triflate **135**. While operationally demanding, this reaction greatly improved the efficiency and throughput in making enal **145**.[16]

Scheme 2.8 Syntheses of C Ring Enal



2.3.4 *Asymmetric Tsuji Allylation for the Synthesis of C Ring Enal **145***

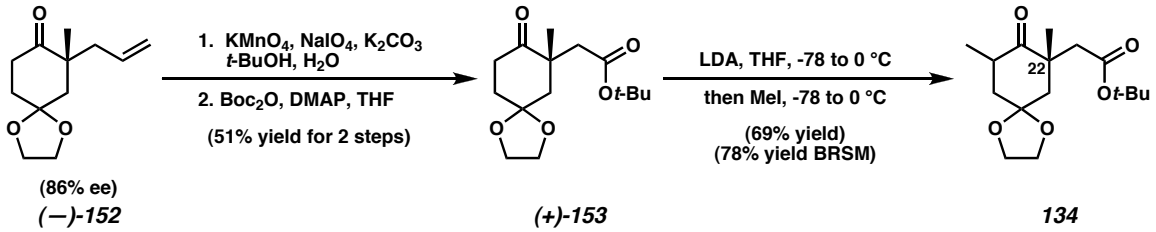
Although racemic material was adequate for exploratory studies, our goal from the outset was the catalytic asymmetric total synthesis of zoanthenol. In accord with our strategy to set a single enantiopure stereocenter and relay that stereochemistry

diastereoselectively throughout the structure, we considered several approaches to set the C(22) quaternary stereocenter in ketoester **134** enantioselectively (Scheme 2.3).

Our first strategy was based on the enantioselective deprotonation of *meso*-ketones. The use of chiral lithium amides for asymmetric deprotonation of ketones was pioneered by Koga[17] and refined by Simpkins.[18] While we had some success in the desymmetrization of *meso*-ketone **132**, the use of stoichiometric amounts of chiral lithium amides seemed impractical on scale.[19]

Ultimately, we found that the asymmetric Tsuji allylation methodology developed in our laboratory was a reliable and efficient method to produce enantioenriched ketoester **134** (Scheme 2.9). Quaternary (*S*)-(–)-ketone **152** could be produced in good ee from several enolate precursors by a palladium (0) phosphinooxazoline catalyst.[20] Oxidative olefin cleavage and esterification gave (+)-*t*-butyl ester **153** in 51% yield over two steps. Methylation of (+)-*t*-butyl ester **153** under standard conditions gave a separable mixture of diastereomeric methyl ketoesters **134**, an intermediate in our racemic C ring synthesis.

Scheme 2.9 Asymmetric Synthesis of Ketoester **134**

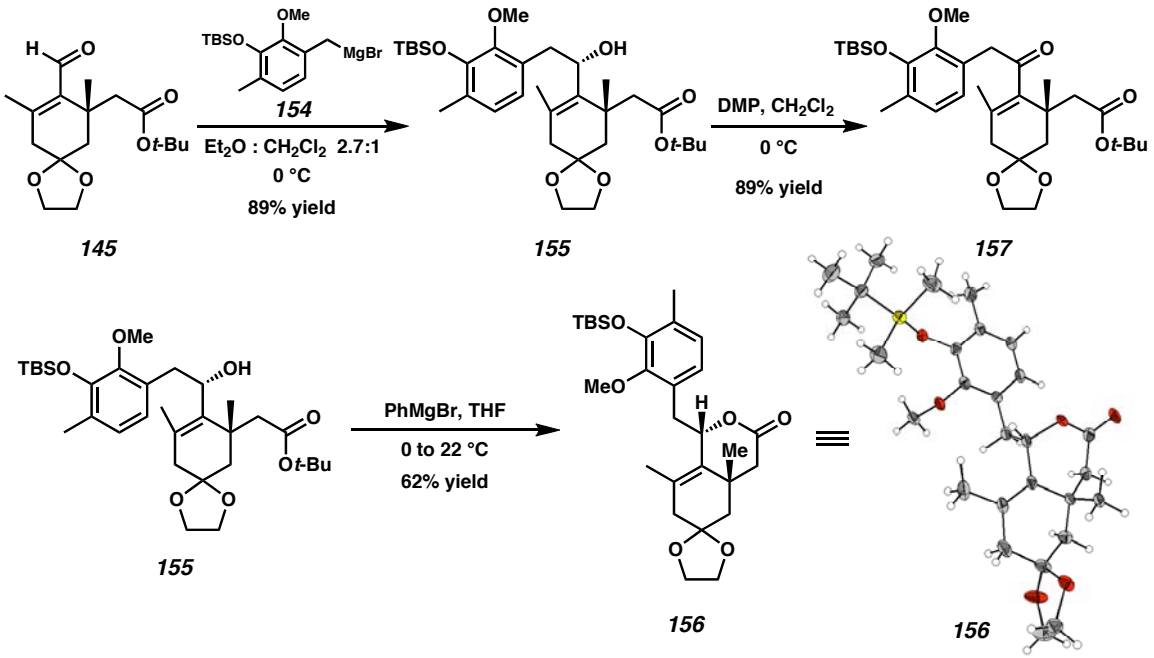


2.3.5 *Fragment Coupling and Cyclization Attempts*

With the new A and C ring fragments available, work to complete an intramolecular conjugate addition substrate began (Scheme 2.10). Treatment of benzyl

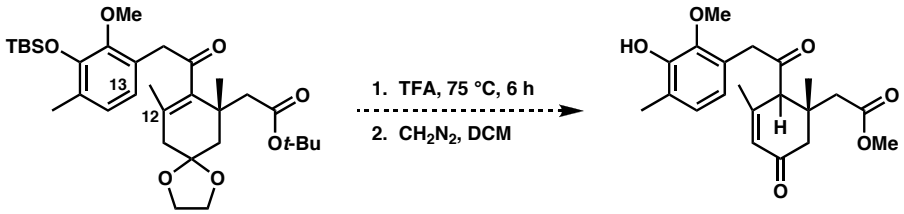
bromide **151** with magnesium turnings in refluxing ethyl ether afforded good conversion to Grignard reagent **154**. While the generation of Grignard reagent **154** was highly reproducible, it should be noted that analogous benzyl bromides with different protecting groups (e.g., methoxy replaced with BOM) afforded very poor yields of organomagnesium and organozinc reagents. Grignard reagent **154** was added immediately upon generation to enal **145** to produce allylic alcohol **155**. We found that the use of methylene chloride as a cosolvent improved the diastereoselectivity of the 1,2-addition and minimized the formation of lactone **156** in situ. Fortuitously, lactone **156**, which could be intentionally formed by deprotonation in ethereal solvents, was amenable to X-ray structure determination and established the relative configuration of the newly formed alcohol stereocenter. Simple Dess-Martin oxidation of allylic alcohol **155** provided the desired enone **157**.

Scheme 2.10 Grignard Addition



Enone **157** was subjected to numerous acidic conditions that were precedented to affect intramolecular cyclization (Scheme 2.11). However, none produced the desired C(12)-C(13) bond.[21] Treatment with trifluoroacetic acid (TFA) followed by methylation afforded a mixture of products resembling enone **158**. This tentative structural assignment piqued our interest in the possibility of a 6-*exo* acid-mediated cyclization.

Scheme 2.11 Attempted Cyclization



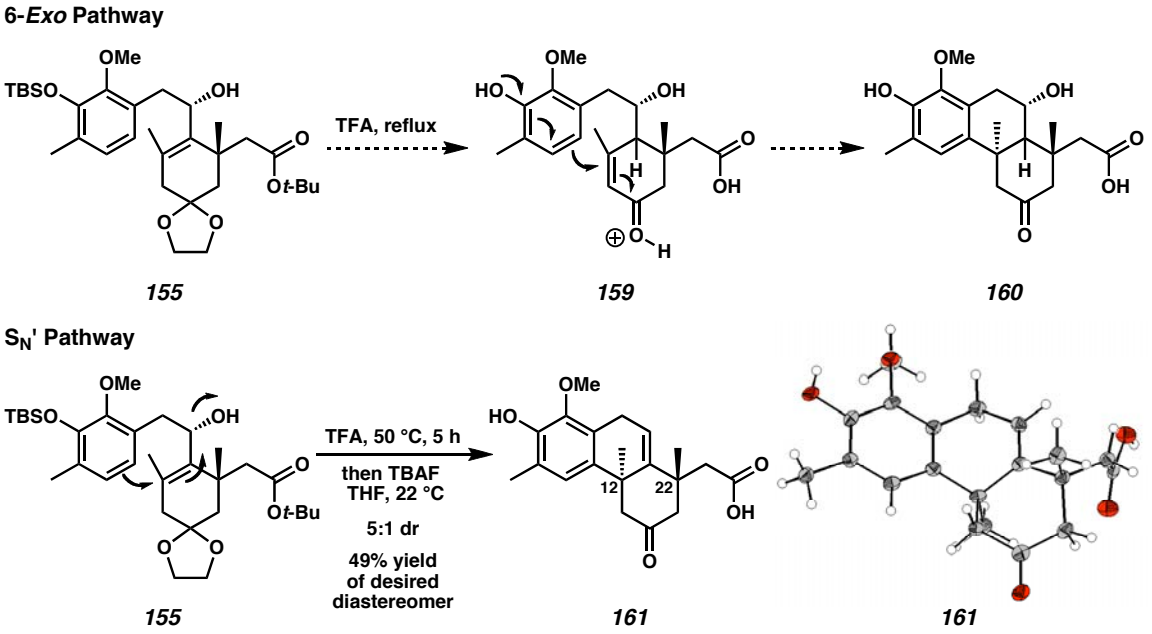
157 *158*

2.4 Development of an S_N' Strategy for the Zoanthenol ABC Ring System

In order to examine the possibility of 6-*exo* cyclization, allylic alcohol **155** was exposed to refluxing TFA (Scheme 2.12). We anticipated the loss of protecting groups and olefin migration would afford enone **159**. Enone **159** could then undergo 6-*exo* conjugate addition giving keto alcohol **160**. The major product isolated from the reaction contained a single aromatic C-H by ^{1}H NMR, suggesting that cyclization had occurred. However, the presence of another olefinic proton in the NMR suggested an elimination had occurred. Proton NMR also showed a roughly 5:1 mixture of diastereomeric acids, which were chromatographically separable. To our delight, upon standing in $CDCl_3$, the major product formed crystals suitable for X-ray diffraction. Cyclization of allylic alcohol **155** had indeed occurred, but not by the anticipated 6-*exo* mechanism. Instead,

an S_N' cyclization had produced acid **161**.[22] The solid state structure confirmed the desired *trans* disposition of the methyl groups at C(12) and C(22). Optimized conditions, including lowering the temperature to 50 °C and desilylation of the crude reaction mixture with TBAF afforded a 49% yield of diastereomerically pure acid **161**.[23]

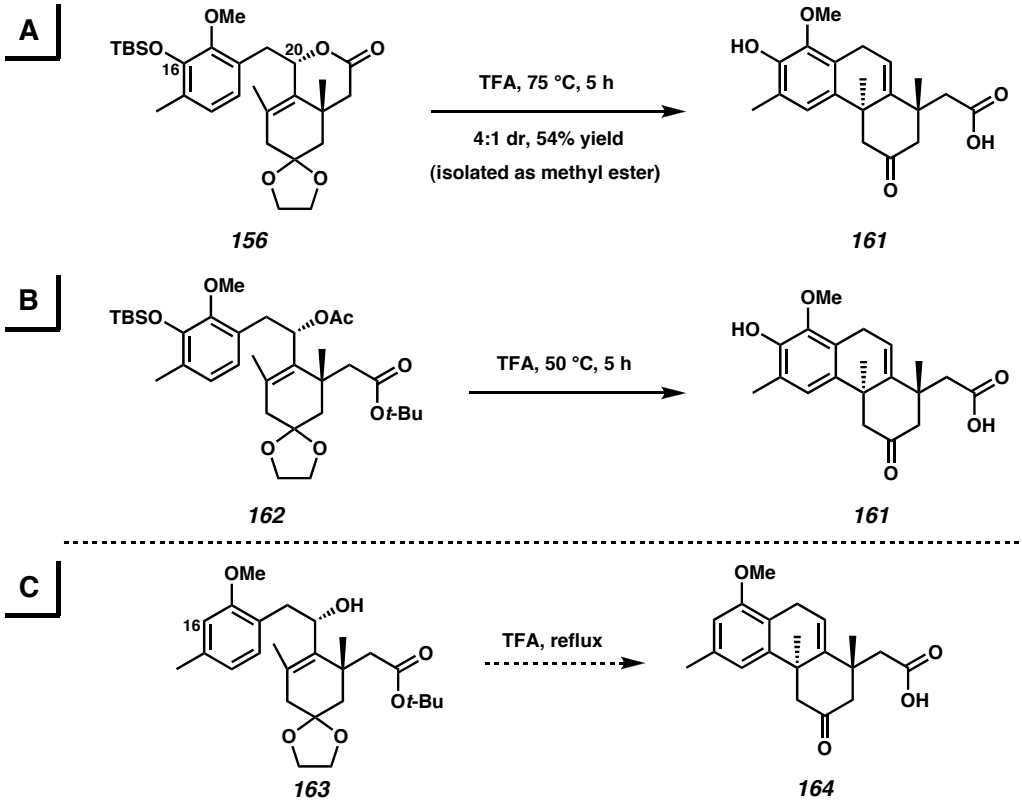
Scheme 2.12 Trifluoroacetic Acid-Mediated Cyclization



The S_N' Friedel-Crafts reaction to produce carboxylic acid **161** achieved the important goal of generating the C(12) quaternary stereocenter with the desired relative configuration. In order to improve the yield and better understand the reaction pathway, a number of modifications were evaluated. The choice of acid in the reaction is crucial. Trifluoroacetic acid was unique in promoting S_N' cyclization. Both stronger acids (e.g., triflic acid) and weaker acids (e.g., acetic acid) failed to produce carboxylic acid **161**. Even the dilution of neat TFA with methylene chloride, benzene, or acetic acid caused

nearly complete inhibition of cyclization. Interestingly, both lactone **156** and allylic acetate **162**[24] underwent cyclization in TFA to give acid **161** with similar yields and diastereoselectivities as allylic alcohol **155** (Scheme 2.13).[25] The des-oxy arene **163** failed to generate any cyclized products, even under forcing conditions. This confirmed the importance of the arene nucleophilicity imparted by C(16) oxygenation. Additionally, compounds analogous to lactone **156** and allylic alcohol **155**, but epimeric at C(20), failed to cyclize when treated under the same conditions.

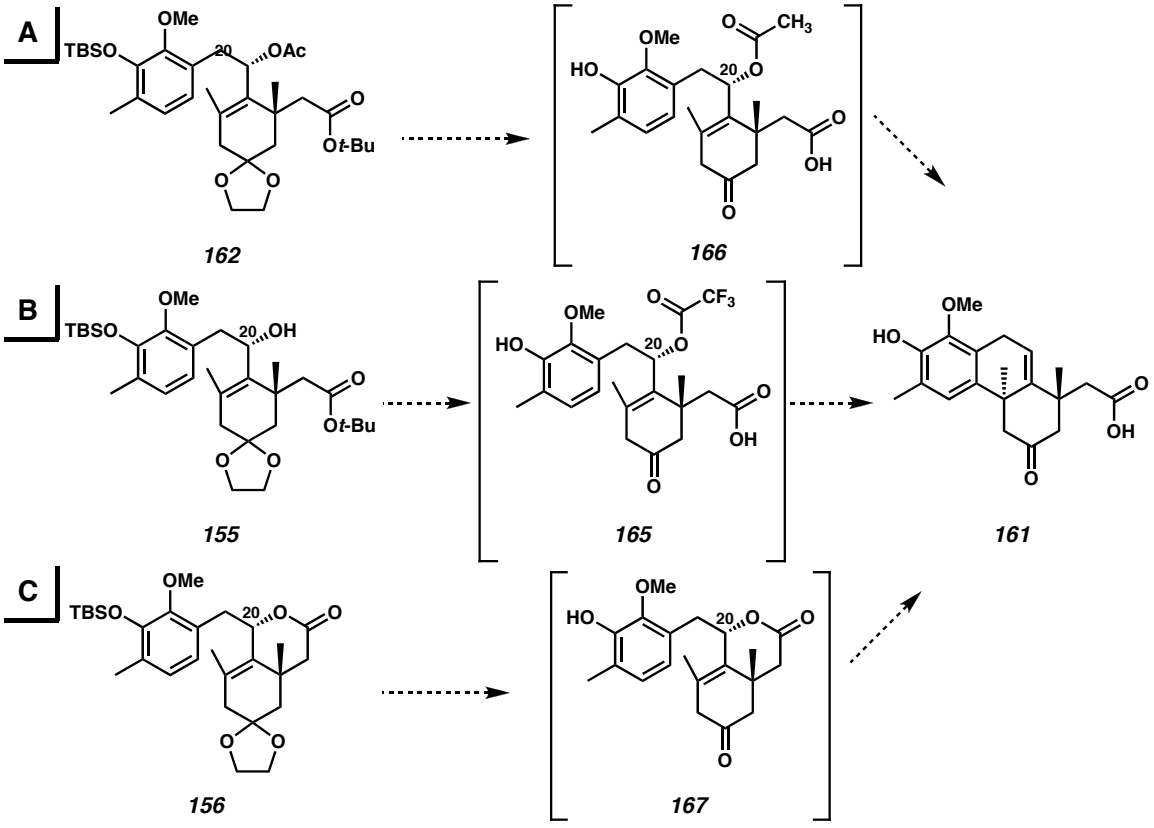
Scheme 2.13 Further Substrates for TFA-Mediated S_N' Cyclization



Taken together, these experiments give some insight into the likely pathways for the S_N' reaction (Scheme 2.14). The unique ability of TFA, among numerous other Lewis and Brønsted acids, to mediate the reaction suggests that its properties as a strong acid, a

dehydrating agent, and a good leaving group (as a trifluoroacetate) are important to the reaction mechanism. It seems likely that all three substrates proceed through an intermediate with a leaving group at C(20). Allylic alcohol **155** may be converted to intermediate trifluoroacetate **165** in situ,[26] while the other substrates already contain good leaving groups. Because the C(20) epimers of the substrates do not readily undergo cyclization, it seems likely that the reactions proceed via a concerted displacement that relies on the trajectory of the leaving group, rather than through a full allyl cation.

Scheme 2.14 Possible Pathways in the S_N' Reaction



2.5 Elaboration Toward the Zoanthenol ABC Ring System

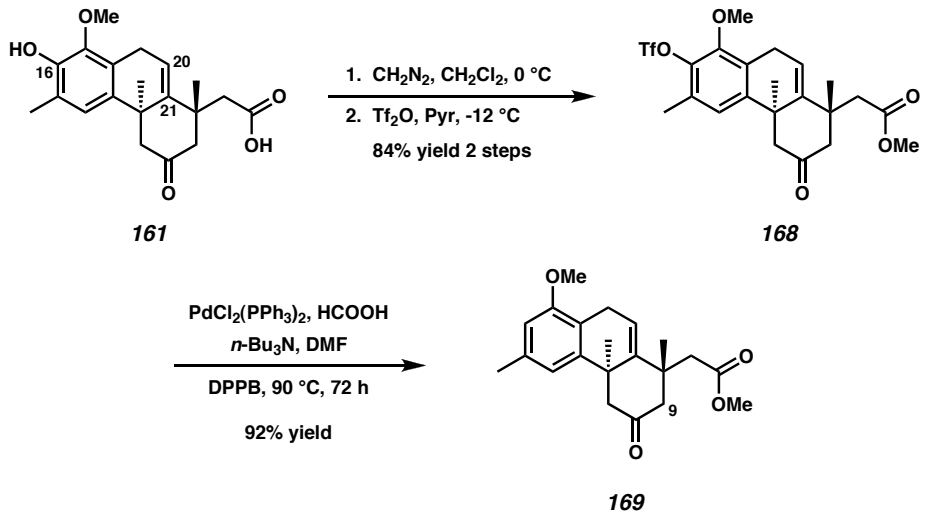
2.5.1 *General Remarks*

With an efficient route in hand to construct the zoanthenol ABC ring system with two of the three quaternary stereocenters, we turned our attention to adjusting the functionality on the rings to complete the synthesis. Our objectives were the removal of the now superfluous phenol and the reoxygenation of the olefin in carboxylic acid **161**.

2.5.2 *Reduction of the Phenol*

The C(16) phenol moiety had served only to increase the nucleophilicity of the arene in the cyclization. With that complete, our next task was its deoxygenation (Scheme 2.15). Esterification of carboxylic acid **161** with diazomethane followed by treatment with triflic anhydride and pyridine afforded aryl triflate **168** in good yield for the two steps. The reduction of congested bis-*ortho* substituted aryl triflates are typically difficult. However, conditions specifically designed for such substrates,[27] involving a number of potential hydride sources, proved highly effective in producing deoxygenated ketoester **169**. Ketoester **169** was an important branch point. It provided a suitable substrate to investigate both the installation of the C(9) substituents and the olefin oxygenation.

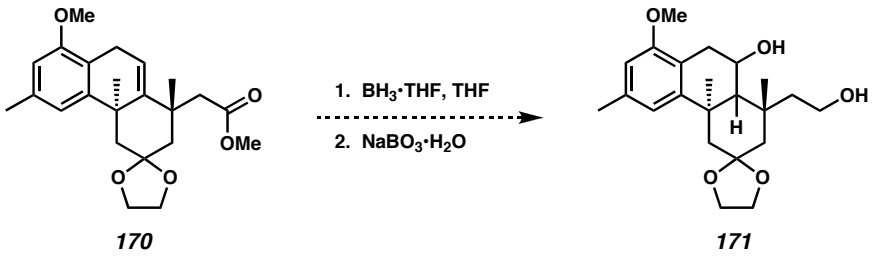
Scheme 2.15 A Ring Deoxygenation



2.5.3 *Olefin Refunctionalization*

Due to our serendipitous discovery of the S_N' reaction, we had not anticipated the reoxygenation of the olefin in our retrosynthetic planning. Significant experimentation was required to find a synthetic strategy to reoxygenate the olefin of ketoester **169**. A number of atom-transfer oxidations were considered. Epoxidation conditions based on *m*CPBA, DMDO, UHP,[28] iron (III) acetylacetate and hydrogen peroxide,[29] hexafluoroacetone and hydrogen peroxide,[30] potassium permanganate and copper (II) sulfate,[31] and methyltrioxorhenium and hydrogen peroxide[32] all failed to give the desired oxidation.[33] Hydroboration of ester **170** with BH_3•THF did appear to affect hydroboration from both faces of the olefin. However, the products also seemed to have undergone reduction of the ester functionality and were inseparable (Scheme 2.16). Milder and more sterically demanding hydroborating reagents either caused ester reduction or failed to react at all.

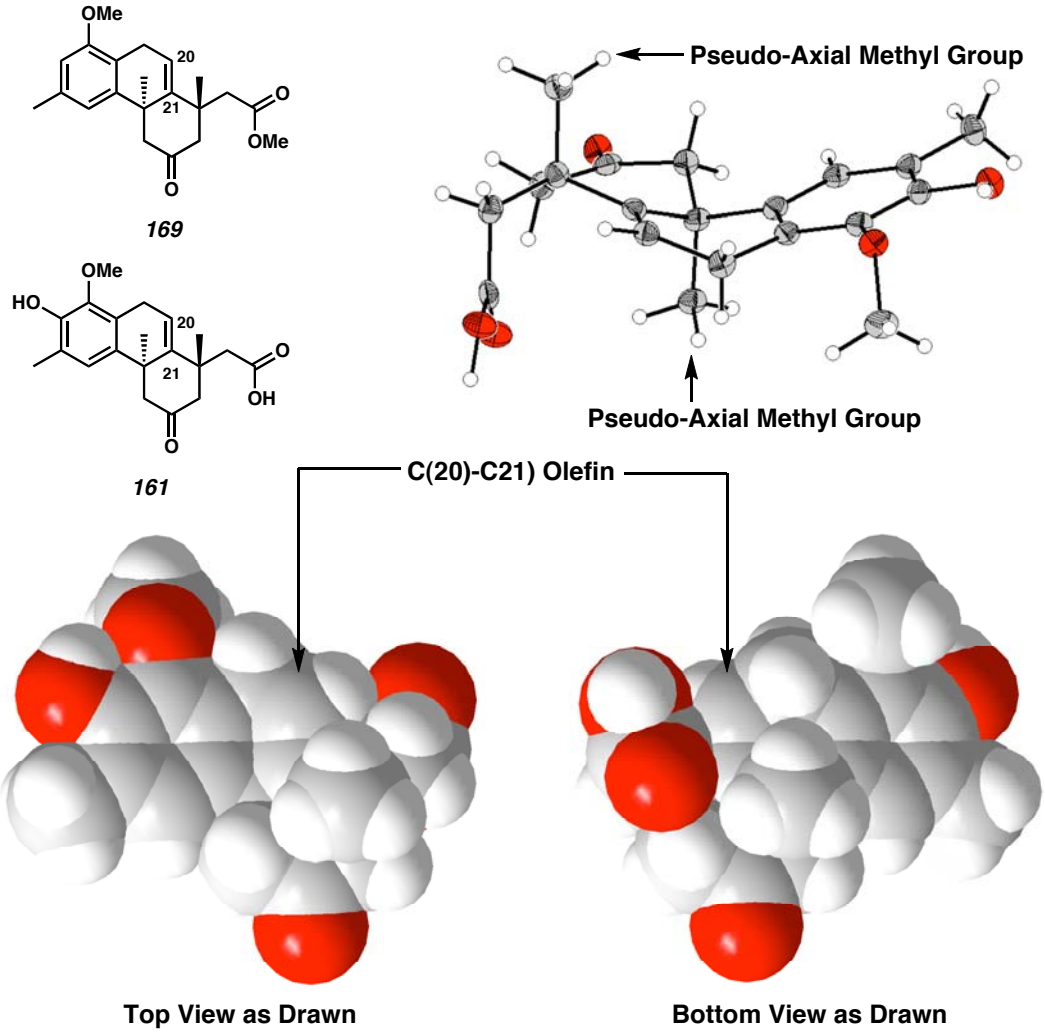
Scheme 2.16 Hydroboration of Ester **170**



170 *171*

These difficulties were largely attributed to steric encumbrance around the C(20)-C(21) olefin. Figure 2.2 shows representations of the solid state structure of carboxylic acid **161**. While it is often problematic to infer solution conformations from solid state structures, the rigid nature of the carbocyclic system found in carboxylic acid **161** and ketoester **169** make it reasonable to assume that they will have conformations similar to one another in solution and in the solid state. The ball and stick model demonstrates that the C ring methyl groups are disposed in a nearly axial manner on either face of the olefin. The space-filling model demonstrates that a significant portion of the olefin is obstructed. In light of this, we chose to pursue a more classical, and importantly intramolecular, method of olefin oxygenation.

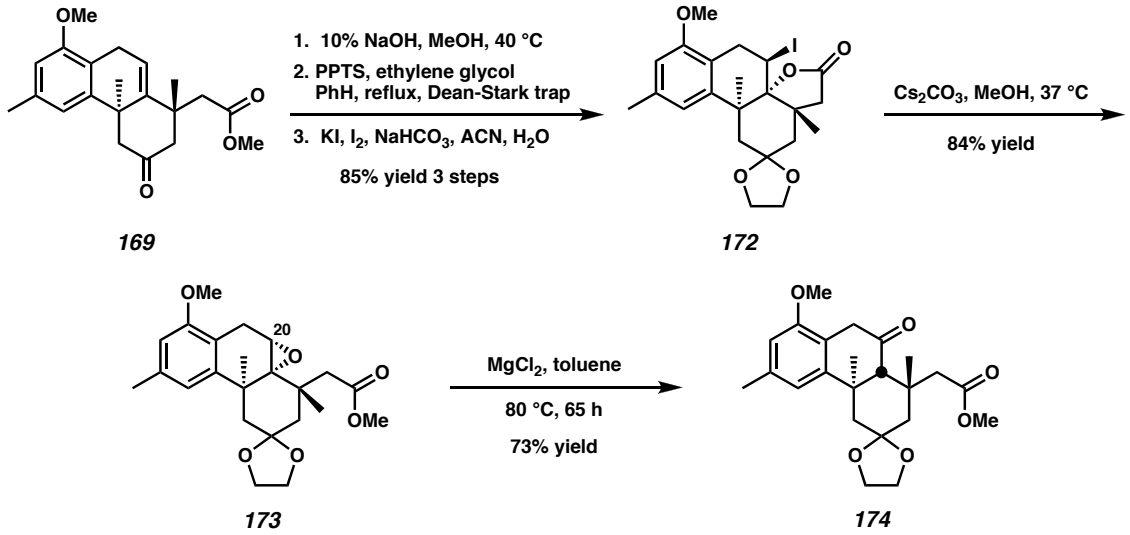
Figure 2.2 Ball and Stick and Space-Filling Representations of Carboxylic Acid **161**'s Solid State Structure



Our intramolecular functionalization began with saponification of ketoester **169** followed by ketalization under Dean-Stark conditions (Scheme 1.17). Although the two operations could be performed in either order, the rate of ketalization was greatly improved when the carboxylic acid was present in the molecule. Treatment of the crude ketalized acid with potassium iodide and iodine under mildly basic conditions gave iodolactone **172** in 85% yield for three steps after recrystallization. Treatment with

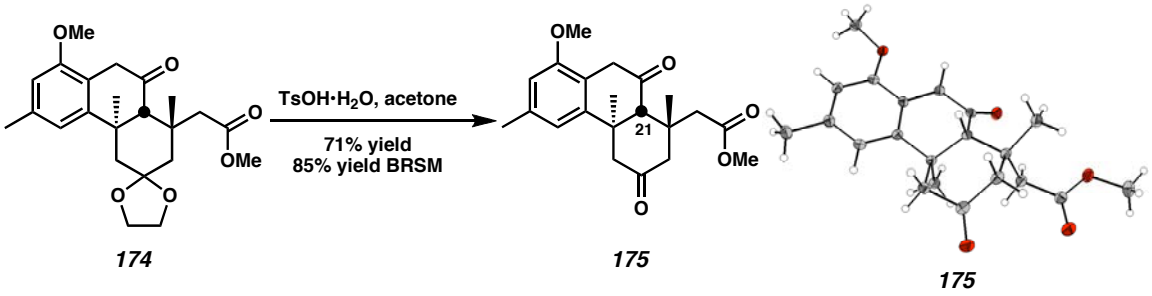
cesium carbonate in methanol afforded smooth conversion to epoxide **173**. Hydride migration from C(20) was affected by heating epoxide **173** in nonpolar solvents with magnesium chloride.[34,35] Though the reaction was somewhat sluggish, it gave clean conversion to rearranged ketoester **174** in 73% yield.

Scheme 2.17 Reoxygenation of the C(20)-C(21) Olefin



Typically, rearrangements of epoxides to carbonyl compounds give products of *syn*-hydride migration due to a concerted hydride shift, but anomalous products are known.[36] As a result, we wished to confirm the stereochemical outcome of the hydride migration (Scheme 2.18). Exposure of ketoester **174** to tosic acid in acetone produced diketone **175**, which gave crystals from acetone/heptane suitable for X-ray structure determination. The structure confirmed the desired C(21) stereochemistry from the hydride shift. With a successful strategy in hand for olefin refunctionalization, our next major objective was the synthesis of the final quaternary stereocenter.

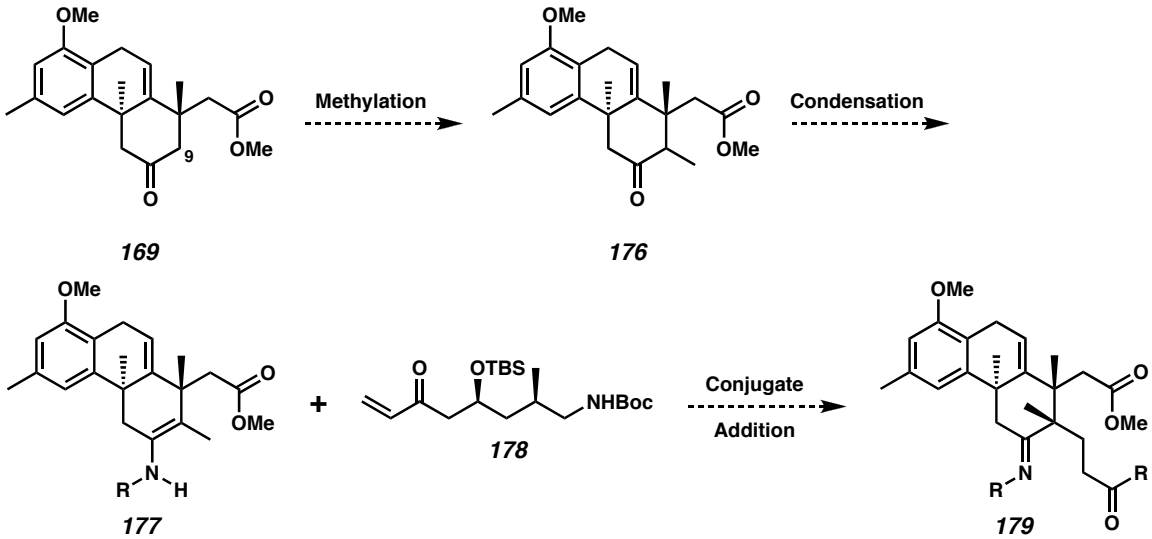
Scheme 2.18 Confirmation of the Hydride Migration Stereochemistry



2.6 Introduction of the C(9) Quaternary Stereocenter

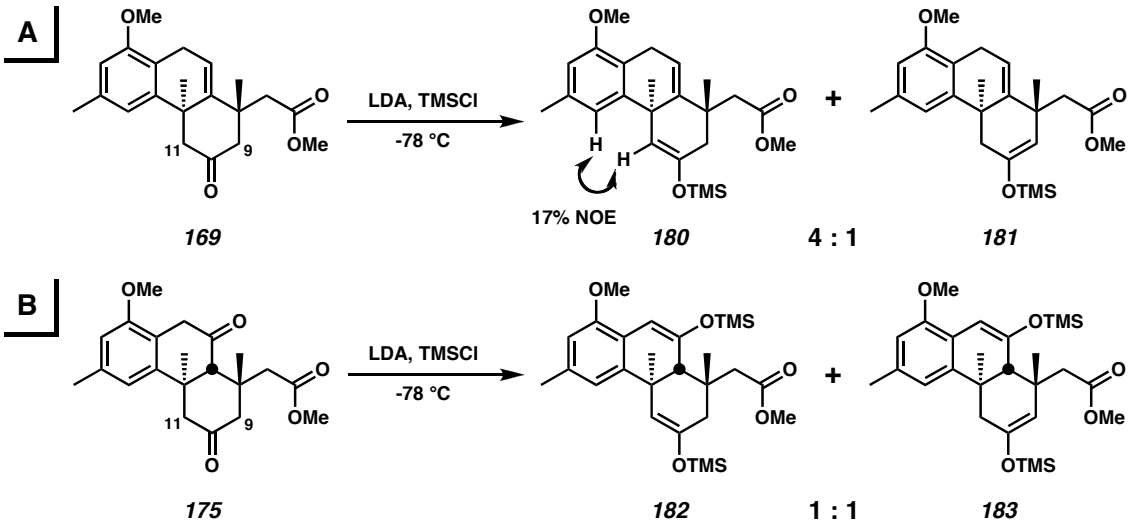
As shown in Scheme 2.19, our initial strategy for constructing the C(9) quaternary center involved three steps: (1) position-selective methylation at C(9), (2) condensation with an amine to give an enamine, and (3) conjugate addition of the enamine **177** or deprotonated metalloenamine into enone **178**. This strategy was closely modeled on the work of Williams.[37]

Scheme 2.19 Initial Strategy for Functionalization at C(9)



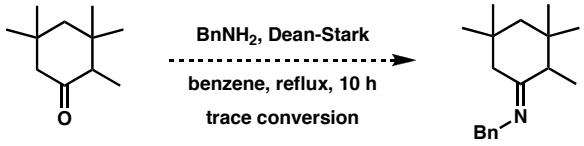
Selective enolization of C(9) over C(11) proved difficult (Scheme 2.20). When treated under kinetic conditions, ketoester **169** showed an unfavorable 4:1 ratio of silyl enol ethers. Though the silyl enol ethers were not separable, the major product was identified as silyl enol ether **180** due to a strong NOE interaction between vinylic enol proton and the arene proton. Analogous silylation with diketone **175** afforded an improved 1:1 mixture of silyl enol ethers **182** and **183**.[38] The bis silyl enol ethers were again inseparable and significant experimentation failed to improve the ratio. Under thermodynamic enolization conditions, nearly exclusive enolization was obtained at C(11) with ketoester **169**.[39]

Scheme 2.20 Positional Selectivity in Kinetic Silyl Enol Ether Formation



Further difficulties were encountered when trying to model the condensation to form the required imine (Scheme 2.21). Known ketone **184**[40] was treated with Dean-Stark dehydration conditions in the presence of benzyl amine, but afforded only trace amounts of what appeared to be the desired imine **185**.

Scheme 2.21 Amine Condensation with a Sterically Demanding Ketone



184 *185*

Our difficulty in modeling the conjugate addition strategy led us to consider other strategies to generate the C(9) quaternary stereocenter. Specifically, we examined a cyclopropanation approach,[41] similar to Hirama's strategy,[42] and a Tsuji allylation-based approach.[43] Ultimately, due to the lack of success with these additional strategies, we made the strategic decision to install the difficult vicinal quaternary stereocenters (i.e., C(9) and C(22)) early in the synthesis.

2.7 Concluding Remarks

A concise method for the construction of the zoanthenol ABC ring system was developed. Common to all our routes was the underlying strategy of combining A and C ring synthons and in the process generating the B ring. The final convergent strategy generated a fully functionalized A ring synthon from *o*-vanillin in six steps. Racemic synthesis of the C ring synthon was completed in just three steps from known materials. Of note is the carbonylation of hindered triflate **135** to enal **145**. Addition of the A ring Grignard **154** to enal **145** proceeded in a highly diastereoselective manner to combine the A and C ring fragments.

In the key step of the synthesis, allylic alcohol **155** underwent a S_N' Friedel-Crafts reaction in TFA. This diastereoselective transformation forms the B ring, sets the

difficult benzylic quaternary stereocenter, and removes three protecting groups in a single step. Only eight linear steps were required to establish the ABC ring system of zoanthenol. To our knowledge, this represents the first use of such an S_N' cyclization in total synthesis. Significant progress was made in advancing the ABC ring system to include all the functionality needed to complete the synthesis. Ultimately, difficulties in forming the final quaternary stereocenter at a late stage forced us to re-evaluate our retrosynthetic path. The route did not allow us to complete the total synthesis, but experience with the advanced ABC carbocycles taught us invaluable lessons about the difficulty of generating quaternary stereocenters and the increased challenge of performing otherwise standard chemistries adjacent to them.

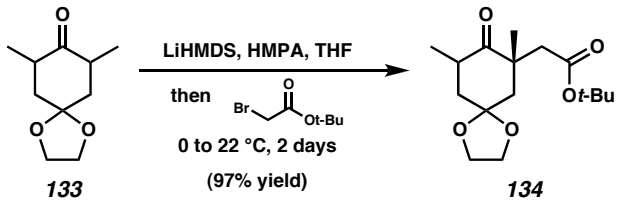
2.8 Experimental Procedures

2.8.1 *Materials and Methods*

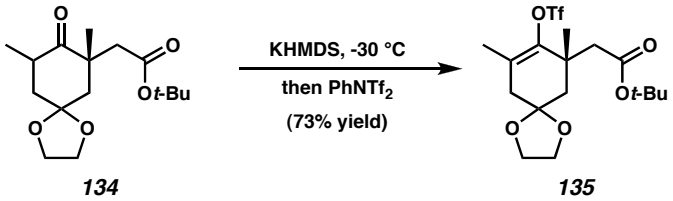
Unless otherwise stated, reactions were performed at ambient temperature (typically 19-24 °C) in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. TMEDA, HMPA, TEA, DIPA and pyridine were freshly distilled from CaH. KHMDS (95%) was purchased from Aldrich and stored in a glovebox until use. Trifluoroacetic acid (99%) was purchased from Aldrich. Tf_2O was freshly distilled from P_2O_5. Magnesium chloride (~325 mesh, <1.5% H_2O) was purchased from Aldrich. All other commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254

precoated plates (0.25 mm) and visualized by UV fluorescence quenching, anisaldehyde, $KMnO_4$, or CAM staining. ICN silica gel (particle size 0.032-0.063 mm) was used for flash chromatography. Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz, respectively), or a Varian Inova 500 (at 500 MHz and 125 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, sept. = septet, m = multiplet, comp. m = complex multiplet, app. = apparent, bs = broad singlet. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility. Crystallographic analyses were performed at the California Institute of Technology Beckman Institute X-Ray Crystallography Laboratory. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, and copies can be obtained on request, free of charge, from the CCDC by quoting the publication citation and the deposition number (see Appendix Three for deposition numbers).

2.8.2 *Preparation of Compounds*

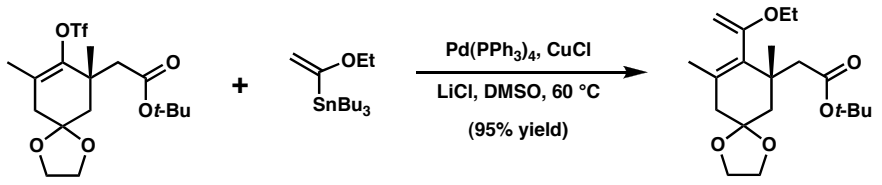


Ketoester 134. To a cooled (0 °C) 1.00 M LiHMDS (52.2 mL, 52.2 mmol, 1.20 equiv) solution in THF was added ketone **133** (8.00 g, 43.5 mmol, 1.00 equiv) in THF (50 mL) in a dropwise manner over 30 min. After an additional 30 min at 0 °C, HMPA (8.31 mL, 47.8 mmol, 1.10 equiv) was added and maintained at 0 °C for 1 h. *t*-butyl bromoacetate (10.6 mL, 69.5 mmol, 1.60 equiv) was added in portions over 1 h and, after a further 2 h at 0 °C, allowed to warm to ambient temperature. After 48 h, the reaction mixture was poured into H_2O (300 mL), extracted with Et_2O (6 x 150 mL), dried ($MgSO_4$), and concentrated to an oil, which was purified by flash chromatography on silica gel (7 to 10% EtOAc in hexanes) to provide ketoester **134** (12.5 g, 97% yield) as a pale yellow oil (as a ~3:1 mixture of diastereomers). See below for full characterization of both methyl diastereomers, synthesized in enantioenriched form via asymmetric allylation.



Triflate 135. To a cooled (-30 °C) solution of KHMDS (4.41 g, 22.1 mmol, 1.20 equiv) in THF (35 mL) was added ketoester **134** (5.50 g, 18.5 mmol, 1.00 equiv) in THF (30 mL) in a dropwise manner over 10 min. After 5 h at -30 °C, $PhNTf_2$ (7.20 g, 20.2

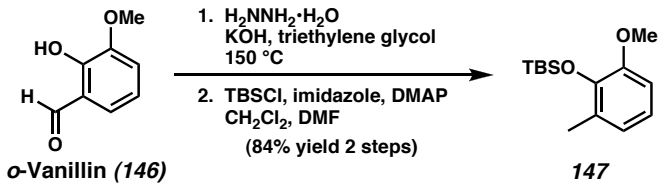
mmol, 1.09 equiv) in THF (30 mL) was added, maintained for an additional 30 min at -30 °C, and warmed to 0 °C for 2 h. The reaction mixture was diluted with Et_2O (200 mL), poured into a mixture of brine (150 mL), H_2O (150 mL), and 1 M NaOH (50 mL), and extracted with Et_2O (3 x 50 mL). The organic layers were washed with 1 M NaOH (6 x 50 mL), H_2O (50 mL), and brine (3 x 50 mL), dried (Na_2SO_4), and concentrated to an oil, which was purified by flash chromatography on silica gel (7 to 10% EtOAc in hexanes and 0.5 % TEA) to provide triflate **135** (5.74 g, 73% yield) as a pale yellow oil: R_f 0.63 (35% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.02-3.92 (comp. m, 4H), 2.71 (d, J = 14.5 Hz, 1H), 2.45 (s, 2H), 2.42 (d, J = 13.5 Hz, 1H), 2.30 (d, J = 14.7 Hz, 1H), 1.78 (s, 3H), 1.70 (d, J = 13.8 Hz, 1H), 1.42 (s, 9H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.2, 146.9, 124.5, 118.7 (q, $J_{C\text{-}F}$ = 319 Hz), 106.2, 80.5, 64.4, 64.3, 43.1, 42.0, 41.9, 39.2, 28.0, 25.0, 17.8; IR (Neat film NaCl) 2980, 2935, 2888, 1726, 1403, 1212, 1142, 1007, 862 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{17}H_{25}SF_3O_7+H]^+$: m/z 431.1351, found 431.1365.



135 *136* *137*

Diene 137. A solution of triflate **135** (azeotroped from PhH, 717 mg, 1.67 mmol, 1.0 equiv) in DMSO (17 mL) was added to an argon-filled, flame-dried Schlenk flask (50 mL) charged with LiCl (flamed-dried under vacuum, 422 mg, 10.0 mmol, 6.0 equiv), $Pd(PPh_3)_4$ (193 mg, 0.167 mmol, 0.10 equiv), and CuCl (825 mg, 8.33 mmol, 5.0 equiv). The flask was purged (5 x) with argon, and vinyl stannane **136** (1.02 g, 2.83 mmol, 1.70

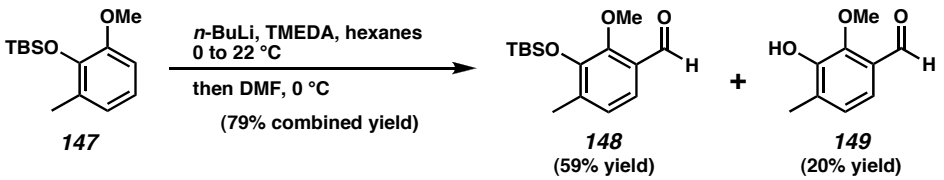
equiv) was added as a neat liquid. The resulting mixture was degassed (3 x) by the freeze/pump-thaw process (-78 to 25 °C, Ar), and stirred at ambient temperature for 1 h, then for a further 12 h at 60 °C. The reaction mixture was quenched with Et_2O (30 mL), brine (120 mL), and 5% aq. NH_4OH (30 mL), and the aqueous layer was further extracted with Et_2O (4 x 30 mL). The combined organic layers were washed with H_2O (4 x 30 mL), then brine (2 x30 mL), dried ($MgSO_4$), and concentrated to give an oil, which was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to give diene **137** (557 mg, 95% yield) as a pale yellow oil: R_f 0.59 (20% EtOAc in hexanes developed twice); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.18 (d, *J* = 1.8 Hz, 1H), 4.08-3.90 (comp. m, 4H), 3.84 (d, *J* = 1.8 Hz, 1H), 3.72 (dq, *J* = 1.5, 6.9 Hz, 2H), 2.62 (d, *J* = 14.4 Hz, 1H), 2.39 (d, *J* = 13.8 Hz, 1H), 2.35 (d, *J* = 17.7 Hz, 1H), 2.28 (dd, *J* = 1.0, 13.7 Hz, 1H), 2.25 (d, *J* = 18.0 Hz, 1H), 1.67 (s, 3H), 1.56 (d, *J* = 13.8 Hz, 1H), 1.43 (s, 9H), 1.29 (t, *J* = 7.0 Hz, 3H), 1.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 158.9, 135.7, 130.3, 107.6, 86.3, 79.7, 64.2, 64.0, 62.5, 44.5, 41.6, 40.3, 38.4, 28.2, 26.6, 21.1, 14.5; IR (Neat film NaCl) 2978, 2930, 2879, 1722, 1606, 1368, 1268, 1142, 1093, 977, 806 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{20}H_{32}O_5+H]^+$: *m/z* 353.2328, found 353.2334.



Arene 147. To a warmed solution (110 °C for 45 min) of *o*-vanillin (60.0 g, 0.394 mol, 1.00 equiv) and NH_2NH_2•H_2O (53.6 mL, 1.10 mol, 2.79 equiv) in triethylene glycol (320 mL) in a 1 L round bottom flask was added KOH (132 g, 2.37 mol, 6.02

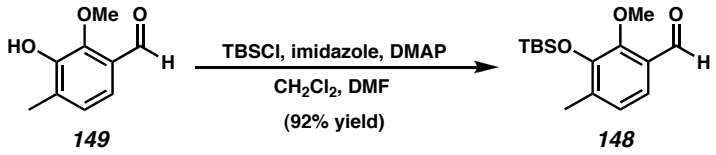
equiv) [*Caution: gas evolution and exotherm*] in portions over 20 min. The reaction mixture was maintained at 150 °C under a reflux condenser for 5 h, cooled to ambient temperature, and poured into H_2O (750 mL), ice (200 g), and 6 M HCl (500 mL). The mixture was further acidified to pH 2 with 6 M HCl, then extracted with $CHCl_3$ (7 x 200 mL), dried ($MgSO_4$), and evaporated to give a green solid (~60 g) that was immediately used in the next step without further purification.

To a solution of this crude solid in DMF (300 mL) and CH_2Cl_2 (300 mL) were added imidazole (53.6 g, 0.788 mol, 2.00 equiv), DMAP (62.5 g, 0.512 mol, 1.30 equiv), and TBSCl (62.1 g, 0.414 mol, 1.05 equiv). After 4 h at ambient temperature, the reaction mixture was poured into H_2O (1.3 L), extracted with CH_2Cl_2 (3 x 150 mL), and the combined organic layers were washed with cold 0.25 M HCl (2 x 250 mL), 1 M NaOH (250 mL), and brine (2 x 200 mL). Evaporation of the organics gave an oil, which was purified by distillation at reduced pressure (~2 mmHg) to give arene **147** (83.6 g, bp 120-127 °C at 2 mmHg, 84% yield over 2 steps) as a colorless oil: R_f 0.74 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83-6.69 (comp. m, 3H), 3.78 (s, 3H), 2.24 (s, 3H), 1.01 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 143.1, 129.6, 122.8, 120.5, 109.1, 54.8, 26.1, 18.9, 17.1, -3.9; IR (Neat film NaCl) 2955, 2930, 1488, 1280, 1251, 1233, 1086, 920, 781 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{14}H_{24}SiO_2+H]^+$: *m/z* 253.1624, found 253.1633.



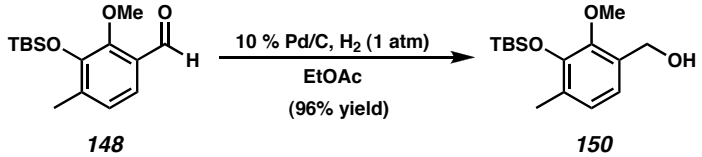
Benzaldehyde 148 from arene **147**. To a cooled (0 °C) solution of arene **147** (30.0 g, 119 mmol, 1.00 equiv), and TMEDA (25.1 mL, 166 mmol, 1.40 equiv) in hexanes (200 mL) was added *n*-BuLi (2.25 M in hexanes, 63.4 mL, 142 mmol, 1.20 equiv) in a dropwise manner over 15 min. After 1 h at 0 °C, the reaction mixture was allowed to warm to ambient temperature for 6 h. The reaction mixture was cooled (0 °C) again and DMF (15.6 mL, 202 mmol, 1.70 equiv) was added dropwise over 10 min. After an additional 1 h at 0 °C, saturated aqueous NH_4Cl (100 mL) was added, and the mixture was allowed to warm to ambient temperature overnight. The mixture was poured into H_2O (200 mL) and Et_2O (200 mL), then extracted with Et_2O (2 x 100 mL). The aqueous layers were then acidified with 2 M HCl to pH 1, and further extracted with Et_2O (5 x 150 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), and evaporated to give an oil that was purified by gradient flash chromatography on silica gel (2 to 20% EtOAc in hexanes) to give benzaldehyde **148** (19.7 g, 59% yield) as a colorless oil: R_f 0.67 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.28 (s, 1H), 7.36 (d, J = 7.5 Hz, 1H), 6.98 (d, J = 8.1 Hz, 1H), 3.81 (s, 3H), 2.28 (s, 3H), 1.03 (s, 9H), 0.20 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.7, 154.2, 147.2, 138.4, 128.1, 126.4, 120.7, 62.5, 26.0, 18.6, 17.9, -4.1; IR (Neat film NaCl) 2957, 2932, 2859, 1691, 1464, 1273, 1255, 838 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{15}H_{24}SiO_3+H]^+$: m/z 281.1573, found 281.1572 and phenol **149** (3.9 g, 20% yield) as a white solid: mp 90.0-91.0 °C; R_f 0.25 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz,

$CDCl_3$) δ 10.18 (s, 1H), 7.27 (d, *J* = 8.1 Hz, 1H), 7.01 (d, *J* = 8.1 Hz, 1H), 6.02 (bs, 1H), 3.95 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.4, 148.4, 147.5, 132.8, 126.7, 126.5, 121.3, 63.8, 16.3; IR (Neat film NaCl) 3410, 2938, 2857, 1686, 1466, 1261, 1061, 782 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_9H_{10}O_3+H]^+$: *m/z* 167.0708, found 167.0708.



149 ***148***

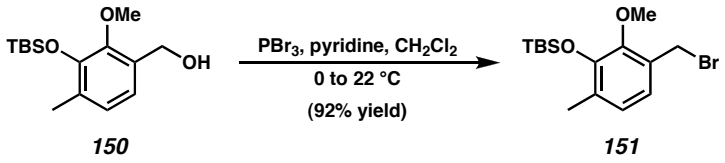
Benzaldehyde 148 from phenol **149**. To a solution of phenol **149** (10.0 g, 60.2 mmol, 1.00 equiv) in DMF (60 mL) and CH_2Cl_2 (60 mL) were added imidazole (8.20 g, 120 mmol, 2.00 equiv), DMAP (9.55 g, 78.3 mmol, 1.30 equiv), and TBSCl (11.7 g, 78.3 mmol, 1.30 equiv). After 36 h, the reaction mixture was quenched with H_2O (200 mL) and CH_2Cl_2 (200 mL), and extracted with CH_2Cl_2 (3 x 50 mL) The combined organics were washed with H_2O (200 mL) and then brine (100 mL), dried ($MgSO_4$), and concentrated to an oil, which was purified by flash chromatography on silica gel (2% EtOAc in hexanes) to provide benzaldehyde **148** (15.5 g, 92% yield).



148 ***150***

Benzyl alcohol 150. A flame-dried 100 mL round-bottom flask was charged with 10% Pd/C (270 mg), EtOAc (55 mL), and benzaldehyde **148** (2.0 g, 7.13 mmol, 1.00 equiv) under an N_2 atmosphere. The reaction mixture and head space were sparged with

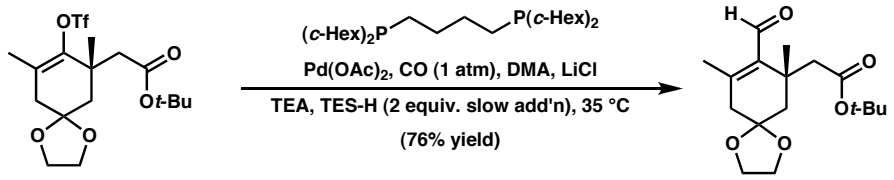
H_2 (5 min) and stirred vigorously under an atmosphere of H_2 (balloon) for 3 h. Immediately following the completion of the reaction, as indicated by TLC, the reaction mixture was sparged with N_2 for 15 min then concentrated to an oil, which was purified by flash chromatography on silica gel (10 to 15% EtOAc in hexanes) to provide benzyl alcohol **150** (1.93 g, 96% yield) as a colorless oil: R_f 0.33 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (d, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 4.65 (d, *J* = 6.3 Hz, 2H), 3.75 (s, 3H), 2.25 (t, *J* = 6.3 Hz, 1H), 2.21 (s, 3H), 1.03 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.4, 147.0, 132.4, 130.6, 126.1, 121.1, 61.7, 60.5, 26.0, 18.6, 17.2, -4.2; IR (Neat film NaCl) 3340, 2956, 2931, 2859, 1464, 1420, 1285, 839, 782 cm^{-1}; HRMS (FAB) $[M+H-H_2]^+$ calc'd for $[C_{15}H_{25}SiO_3]^+$: m/z 281.1573, found 281.1564.



150 ***151***

Benzyl bromide 151. To a cooled (0 °C) solution of benzyl alcohol **150** (16.0 g, 56.7 mmol, 1.00 equiv) and pyridine (4.36 mL, 53.9 mmol, 0.95 equiv) in CH_2Cl_2 (200 mL) was added PBr_3 (4.84 mL, 51.0 mmol, 0.90 equiv) in CH_2Cl_2 (50 mL) over 30 min. After stirring an additional 30 min at 0 °C, the reaction mixture was allowed to come to ambient temperature and stirred for a further 2.5 h. The reaction mixture was diluted with CH_2Cl_2 (300 mL), brine (500 mL), and H_2O (250 mL), then extracted with Et_2O (2 x 150 mL), dried over Na_2SO_4, and concentrated. The resulting oil was passed through a plug of silica gel (10 cm h x 5.5 cm d) (1:1 hexanes:CH_2Cl_2), concentrated, and the resultant oil was purified by distillation at reduced pressure (~2 mmHg) to provide benzyl bromide **151** (27.4 g, bp 146-147 °C at ~2 mmHg, 92% yield) as a colorless oil: R_f 0.50

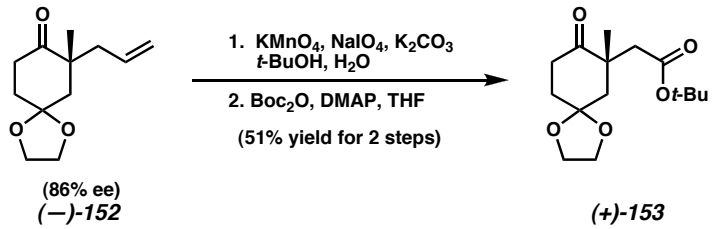
(2.5% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (d, *J* = 8 Hz, 1H), 6.87 (d, *J* = 8 Hz, 1H), 4.56 (s, 2H), 3.83 (s, 3H), 2.23 (s, 3H), 1.04 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.7, 147.2, 131.9, 129.6, 126.2, 123.2, 60.4, 28.8, 26.0, 18.6, 17.3, -4.2; IR (Neat film NaCl) 2957, 2931, 2859, 1464, 1421, 1289, 1259, 1239, 1072, 840, 782 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{15}H_{25}SiBrO_2+H]^+$: *m/z* 345.0885, found 345.0885.



135 ***145***

Enal 145. A solution of flame-dried LiCl (600 mg, 14.2 mmol, 2.69 equiv), $Pd(OAc)_2$ (156 mg, 0.695 mmol, 0.132 equiv), and 1,4-bis-(dicyclohexylphosphino)butane (314 mg, 0.695 mmol, 0.132 equiv) in DMA (16 mL) was sparged with CO and warmed to 90 °C until a color change from red/orange to pale yellow was observed, at which point the reaction mixture was cooled to 35 °C. To the homogenous reaction mixture was added TEA (2.60 mL, 18.6 mmol, 3.53 equiv) and enol triflate **135** (2.27 g, 5.27 mmol, 1.00 equiv) in DMA (16 mL). A solution of Et_3SiH (1.47 mL, 9.28 mmol, 1.76 equiv) in DMA (8.5 mL) was added by syringe pump to the reaction over 10 h. After an additional 14 h at 35 °C, the reaction mixture was cooled to ambient temperature, $KF•2H_2O$ (2.00 g) was added, the mixture was stirred for 45 min, and then poured into ice water (200 mL). This mixture was extracted with 1:1 Et_2O:hexanes (5 x 100 mL). The combined organic layers were washed with brine (2 x 100 mL), dried (Na_2SO_4), and concentrated to give an oil, which was purified by gradient

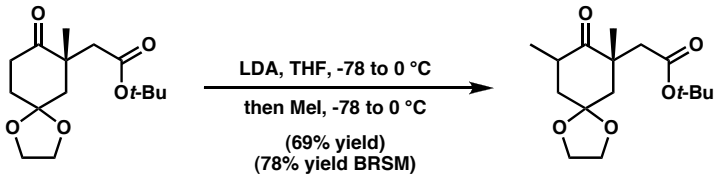
flash chromatography on silica gel (10 to 20% EtOAc in hexanes) to give enal **145** (1.24 g, 76% yield) as a pale yellow oil: R_f 0.42, 0.41 (35% EtOAc in hexanes, 20% EtOAc in hexanes developed twice); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.13 (s, 1H), 4.00-3.90 (comp. m, 4H), 3.04 (d, *J* = 14.4 Hz, 1H), 2.54 (app. dt, *J* = 1.0, 19.2 Hz, 1H), 2.37 (dd, *J* = 1.8, 18.9 Hz, 1H), 2.34 (d, *J* = 14.7 Hz, 1H), 2.15 (d, *J* = 13.6 Hz, 1H), 2.12 (s, 3H), 1.53 (dd, *J* = 2, 13.6 Hz, 1H), 1.35 (s, 9H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 91.0, 171.3, 152.8, 137.4, 106.5, 79.8, 64.3, 64.0, 44.7 (2C), 42.4, 38.3, 28.0, 26.5, 19.3; IR (Neat film NaCl) 2977, 2932, 2884, 1721, 1673, 1368, 1161, 1141, 1079 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{17}H_{26}O_5+H]^+$: *m/z* 311.1858, found 311.1849.



(+)-*t*-Butyl ester 153. A solution of ketone (–)-**152** (1.00 g, 4.76 mmol, 1.00 equiv) and K_2CO_3 (987 mg, 7.14 mmol, 1.5 equiv) in *t*-BuOH (60 mL) was treated (slight exotherm) with a premixed (30 min) solution of $NaIO_4$ (8.14 g, 38.1 mmol, 8.00 equiv) and $KMnO_4$ (113 mg, 0.714 mmol, 0.15 equiv) in H_2O (100 mL) and stirred in a room temperature bath for 3 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and H_2O (100 mL), extracted with CH_2Cl_2 (6 x 50 mL), dried ($MgSO_4$), and concentrated to an oil, which was used immediately in the next step.

A solution of the above crude carboxylic acid in THF (40 mL) was treated with Boc_2O (3.40 g, 15.6 mmol, 3.27 equiv) and DMAP (200 mg, 1.64 mmol, 0.344 equiv). After 12 h, additional Boc_2O (2.00 g, 9.16 mmol, 1.93 equiv) and DMAP (175 mg, 1.43 mmol,

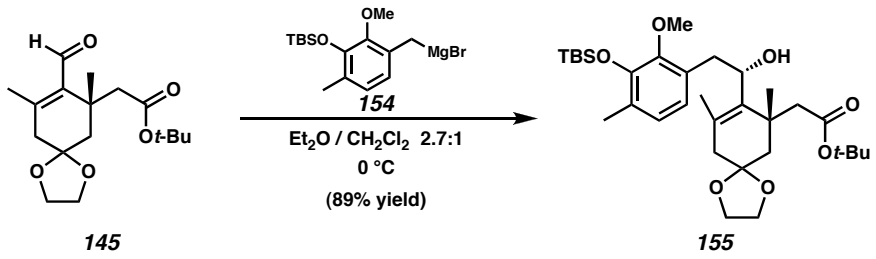
0.30 equiv) were added, and the reaction was stirred for a further 3 h. The reaction mixture was concentrated and purified by gradient flash chromatography on silica gel (5 to 25% Et_2O in hexanes) to give (+)-*t*-butyl ester **153** (688 mg, 51% yield) as a colorless oil: R_f 0.27 (10% EtOAc in hexanes developed 2 times); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.03-3.94 (comp. m, 4H), 2.70 (d, *J* = 15.9 Hz, 1H), 2.63 (d, *J* = 6.6 Hz, 1H), 2.60 (d, *J* = 6.0 Hz, 1H), 2.49 (d, *J* = 15.9 Hz, 1H), 2.22 (dd, *J* = 1.4, 14.0 Hz, 1H), 2.20-2.08 (m, 1H), 2.04-1.92 (m, 1H), 1.78 (dd, *J* = 2.4, 14.1 Hz, 1H), 1.40 (s, 9H), 1.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.7, 170.7, 107.6, 80.7, 64.4, 64.2, 46.0, 44.7, 44.5, 35.6, 33.9, 28.0, 25.1; IR (Neat film NaCl) 2976, 2935, 2885, 1725, 1714, 1368, 1157, 1120, 1074 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{15}H_{24}O_5]^+$: *m/z* 284.1624, found 284.1633; $[\alpha]_D^{26}$ +45.63 (c 1.89, CH_2Cl_2, 86% ee).



(+)-153 *134*

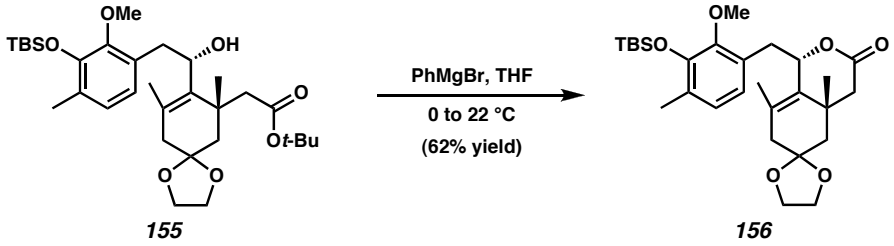
Methyl ketones 134a and 134b. A solution of LDA in THF was prepared by dropwise addition of 2.45 M *n*-BuLi solution in hexanes (787 μL, 1.93 mmol, 1.4 equiv) to diisopropylamine (290 μL, 2.07 mmol, 1.5 equiv) in THF (20.7 mL) at 0 °C, followed by stirring for 1 h. Upon cooling the solution to -78 °C, a solution of (+)-*t*-butyl ester **153** (392 mg, 1.38 mmol, 1.00 equiv) in THF (2.00 mL) was added in a dropwise manner, and the reaction mixture was stirred at -78 °C for 1 h, then 0 °C for 1 h. After cooling again to -78 °C, the reaction mixture was treated with MeI (258 μL, 4.13 mmol, 3.00 equiv), allowed to warm to ambient temperature slowly over 5 h, and stirred for an

additional 12 h at ambient temperature. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 (6 x 30 mL), dried ($MgSO_4$), and concentrated to an oil, which was purified by gradient flash chromatography on silica gel (3 to 10% EtOAc in hexanes) to give diastereomeric methyl ketones **134a** and **134b** (284 mg, 69% combined yield) as colorless oils and recovered *t*-butyl ester **153** (43.2 mg, 11% yield). High R_f diastereomer **134a**: R_f 0.43 (10% EtOAc in hexanes developed 2 times); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10-3.90 (comp. m, 4H), 2.89 (app. d of sept., J = 1.2, 6.6 Hz, 1H), 2.73 (d, J = 16.5 Hz, 1H), 2.36 (d, J = 13.8 Hz, 1H), 2.16 (d, J = 16.2 Hz, 1H), 2.06-1.96 (comp. m, 1H), 1.93 (d, J = 13.5 Hz, 1H), 1.85 (dd, J = 3.3, 13.8 Hz, 1H), 1.42 (s, 9H), 1.29 (s, 3H), 1.07 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.0, 170.9, 107.5, 80.4, 64.6, 64.0, 46.0, 44.5, 44.3, 41.9, 38.0, 28.1, 26.4, 14.7; IR (Neat film NaCl) 2976, 2932, 2880, 1726, 1710, 1367, 1146, 1080 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{16}H_{26}O_5]^+$: m/z 298.1780, found 298.1791; $[\alpha]_D^{26}$ +45.13 (c 1.06, CH_2Cl_2, 86% ee). Low R_f diastereomer **134b**: R_f 0.32 (10% EtOAc in hexanes developed 2 times); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10-3.85 (comp. m, 4H), 3.21 (d, J = 14.7 Hz, 1H), 3.09 (app. d of sept., J = 1.5, 6.6 Hz, 1H), 2.32 (d, J = 14.4 Hz, 1H), 2.14-2.00 (comp. m, 2H), 1.76 (d, J = 14.7 Hz, 1H), 1.68 (app. t, J = 14.0 Hz, 1H), 1.36 (s, 9H), 1.08 (s, 3H), 1.03 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.8, 170.4, 107.2, 80.8, 64.6, 64.0, 46.8, 46.1, 45.2, 43.9, 37.7, 27.9, 23.0, 14.4; IR (Neat film NaCl) 2976, 2933, 2884, 1726, 1717, 1457, 1367, 1232, 1160, 1141, 1084, 979 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{16}H_{26}O_5]^+$: m/z 298.1780, found 298.1775; $[\alpha]_D^{26}$ –25.44 (c 1.17, CH_2Cl_2, 86% ee).



Allylic alcohol 155. A flame-dried two-neck round-bottom flask equipped with a reflux condenser and septum was charged with magnesium turnings (9.00 g, 370 mmol, 34.6 equiv) and Et_2O (120 mL) under an N_2 atmosphere and heated to reflux. To this mixture was added 1,2-dibromoethane (1.53 mL, 17.8 mmol, 1.66 equiv) in a dropwise manner [*Caution: gas evolution!*]. When gas evolution ceased, a solution of benzyl bromide **151** (5.91 g, 17.1 mmol, 1.60 equiv) in Et_2O (50 mL) was added in a dropwise manner over 30 min and heating was continued for an additional 30 min. The Grignard reagent was then cooled (0 °C), and added to a cooled (0 °C) solution of enal **145** (3.32 g, 10.7 mmol, 1.00 equiv) in Et_2O (100 mL) and CH_2Cl_2 (100 mL). After 1 h, the reaction mixture was quenched with H_2O (200 mL) and saturated aqueous NH_4Cl (100 mL), extracted with Et_2O (3 x 200 mL), dried ($MgSO_4$), and concentrated to an oil, which was purified by gradient flash chromatography on silica gel (7.5 to 20% EtOAc in hexanes) to give allylic alcohol **155** (5.51 g, 89% yield) as a thick syrup: R_f 0.59 (20% EtOAc in hexanes developed twice); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (s, 2H), 4.43 (dd, J = 2.1, 9.9 Hz, 1H), 4.04-3.90 (comp. m, 4H), 3.68 (s, 3H), 3.22 (bs, 1H), 3.17 (dd, J = 9.9, 13.8 Hz, 1H), 2.84 (dd, J = 3.3, 13.8 Hz, 1H), 2.64 (d, J = 13.5 Hz, 1H), 2.31 (d, J = 17.4 Hz, 1H), 2.24-2.04 (comp. m, 3H), 2.19 (s, 3H), 2.07 (s, 3H), 1.57 (dd, J = 2.3, 13.8 Hz, 1H), 1.40 (s, 9H), 1.12 (s, 3H), 1.02 (s, 9H), 0.18 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 72.1, 149.6, 147.0, 136.7, 131.3, 130.5, 128.7, 125.7, 123.5, 107.6, 80.9, 70.6,

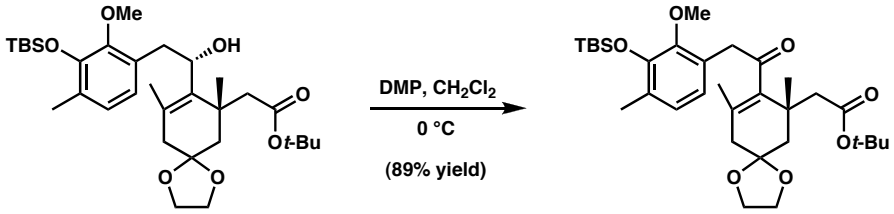
64.2, 63.9, 59.9, 46.4, 43.3, 42.0, 41.3, 36.6, 28.0, 26.8, 26.0, 21.1, 18.6, 17.0, -4.1 (2C); IR (Neat film NaCl) 3499, 2957, 2931, 2896, 2859, 1706, 1462, 1419, 1368, 1286, 1075, 840 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{32}H_{52}SiO_7+H]^+$: *m/z* 577.3561, found 577.3543.



155 *156*

Lactone 156. To a cooled (0 °C) solution of allylic alcohol **155** (108 mg, 0.187 mmol, 1.00 equiv) in THF (12 mL) was added 3.0 M PhMgBr in Et_2O (68.6 μL, 0.206 mmol, 1.10 equiv). Additional 3.0 M PhMgBr in Et_2O (85.0 μL, 0.255 mmol, 1.36 equiv) was added in portions over 4 h. The reaction mixture was quenched into H_2O (30 mL) and EtOAc (30 mL), acidified to pH 2 with 0.1 M HCl, extracted with EtOAc (3 x 20 mL), dried over Na_2SO_4, and concentrated to an oil, which was purified by gradient flash chromatography on silica gel (10 to 20% EtOAc in hexanes) to give lactone **156** (58.5 mg, 62% yield) as white solid. Crystals suitable for X-ray analysis were obtained by crystallization from hexanes at ambient temperature: mp 139-140 °C (hexanes); R_f 0.40 (35% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (d, *J* = 7.8 Hz, 1H), 6.66 (d, *J* = 8.1 Hz, 1H), 5.40 (d, *J* = 9.0 Hz, 1H), 4.08-3.95 (m, 2H), 3.95-3.86 (m, 2H), 3.67 (s, 3H), 3.07 (dd, *J* = 3.5, 14.3 Hz, 1H), 2.75 (dd, *J* = 10.2, 14.4 Hz, 1H), 2.48 (s, 2H), 2.43 (s, 2H), 2.19 (s, 3H), 1.82 (d, *J* = 13.2 Hz, 1H), 1.71 (d, *J* = 13.2 Hz, 1H), 1.71 (s, 3H), 1.22 (s, 3H), 1.03 (s, 9H), 0.18 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 71.4, 149.7, 147.0, 131.2, 129.8, 128.1, 126.0, 125.5, 123.5, 107.8, 80.0, 64.4, 63.6,

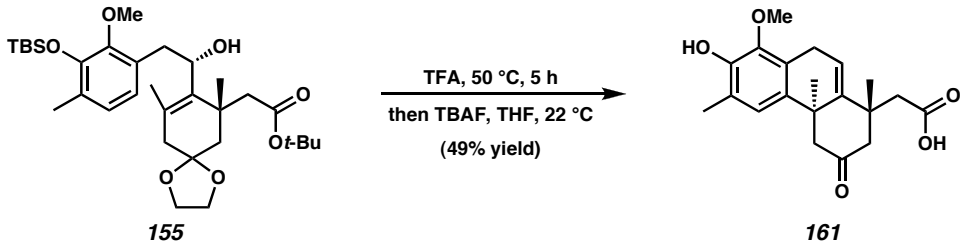
60.0, 45.7, 44.1, 43.4, 38.2, 35.9, 26.0, 25.9, 19.0, 18.5, 17.1, -4.2 (2C); IR (Neat film NaCl) 2957, 2931, 2886, 2859, 1751, 1463, 1419, 1251, 1237, 1078, 841 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{28}H_{42}SiO_6+H]^+$: *m/z* 503.2829, found 503.2809.



155 *157*

Enone 157. To a cooled (0 °C) solution of allylic alcohol **155** (200 mg, 0.347 mmol, 1.00 equiv) in CH_2Cl_2 (22 mL) was added Dess-Martin periodinane (221 mg, 0.521 mmol, 1.50 equiv) and the resulting mixture was stirred for 2 h. The reaction mixture was diluted with Et_2O (75 mL), filtered, and concentrated to an oil, which was purified by gradient flash chromatography on silica gel (7.5 to 20% Et_2O in hexanes) to give enone **157** (177 mg, 89% yield) as a pale yellow oil: R_f 0.37 (25% Et_2O in hexanes developed twice); ^1H NMR (500 MHz, $CDCl_3$) δ 6.85 (d, *J* = 8.0 Hz, 1H), 6.66 (d, *J* = 7.0 Hz, 1H), 4.08-4.02 (m, 1H), 4.02-3.92 (comp. m, 3H), 3.92 (d, *J* = 18.5 Hz, 1H), 3.84 (d, *J* = 18.0 Hz, 1H), 3.65 (s, 3H), 2.76 (d, *J* = 14.5 Hz, 1H), 2.46 (d, *J* = 14.5 Hz, 1H), 2.37 (d, *J* = 18.0 Hz, 1H), 2.35 (dd, *J* = 1.5, 13.5 Hz, 1H), 2.28 (d, *J* = 18.0 Hz, 1H), 2.21 (s, 3H), 1.75 (s, 3H), 1.57 (d, *J* = 13.5 Hz, 1H), 1.43 (s, 9H), 1.30 (s, 3H), 1.03 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.3, 171.3, 150.0, 147.0, 140.9, 129.9, 128.1, 125.8, 125.5, 123.4, 107.4, 80.0, 64.3, 64.0, 59.9, 47.3, 44.1, 41.6, 40.5, 38.4, 28.2, 26.6, 26.1, 20.8, 18.6, 17.1, -4.2; IR (Neat film NaCl) 2959, 2931, 2886, 2860, 1724, 1699,

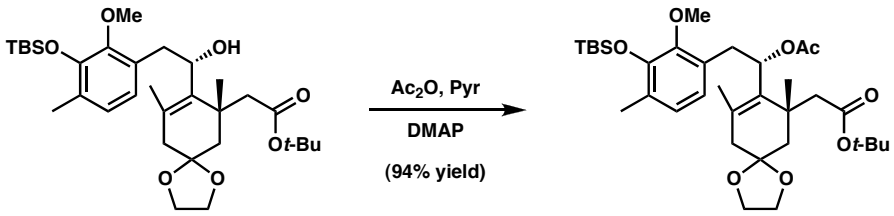
1463, 1421, 1368, 1286, 1253, 1234, 1145, 1075, 1014, 857, 839, 782 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{32}H_{50}SiO_7+H]^+$: *m/z* 575.3404, found 575.3394.



155 *161*

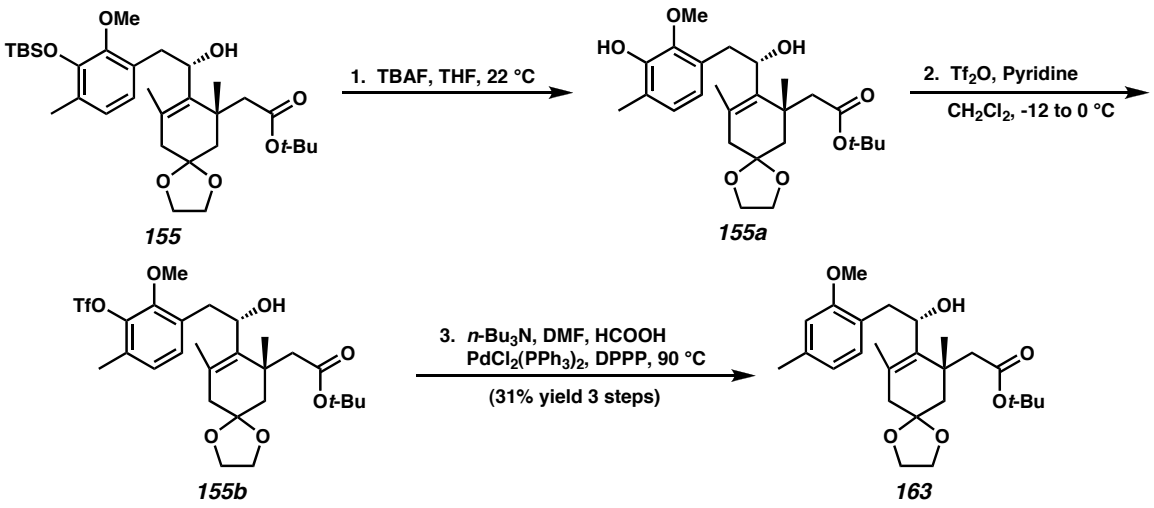
Acid 161. A solution of allylic alcohol **155** (5.50 g, 9.53 mmol, 1.00 equiv) in TFA (240 mL) was warmed to 50 °C for 5 h. The reaction mixture was concentrated and the resulting residue was dissolved in THF (100 mL) and 1.0 M TBAF (12.0 mL, 12.0 mmol, 1.26 equiv) in THF was added. After 1 h, the reaction mixture was concentrated to ~25 mL, quenched with H_2O (100 mL), brine (100 mL), and 3 M HCl (100 mL), and extracted with EtOAc (6 x 100 mL). The organic layers were concentrated to an oil, which was purified by flash chromatography on silica gel (1:1 CH_2Cl_2:$CHCl_3$ + 1% AcOH) to give acid **161** (1.62 g, 49% yield) as a white foam. Crystals suitable for X-ray analysis were obtained by crystallization from $CDCl_3$ at ambient temperature: mp 112-113 °C ($CDCl_3$); R_f 0.32 (1:1 CH_2Cl_2 : $CHCl_3$ + 3% MeOH developed twice); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76 (s, 1H), 6.05 (dd, *J* = 1.8, 6.3 Hz, 1H), 5.63 (bs, 1H), 3.78 (s, 3H), 3.58 (dd, *J* = 6.6, 20.7 Hz, 1H), 3.47 (d, *J* = 17.7 Hz, 1H), 3.17 (d, *J* = 18.3 Hz, 1H), 3.11 (d, *J* = 17.4 Hz, 1H), 2.93 (d, *J* = 15.9 Hz, 1H), 2.76 (d, *J* = 17.4 Hz, 1H), 2.50 (d, *J* = 15.6 Hz, 1H), 2.34 (d, *J* = 17.1 Hz, 1H), 2.24 (s, 3H), 1.24 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 210.8, 176.8, 146.0, 145.4, 143.9, 137.6, 125.3, 123.1, 121.6, 120.6, 61.2, 50.1, 49.2, 46.2, 39.5, 39.0, 33.3, 30.7, 24.9, 16.0; IR (Neat film NaCl) 3500-

2500, 2963, 2926, 1707, 1489, 1461, 1422, 1360, 1295, 1228, 1071, 955, 711 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{20}H_{24}O_5+H]^+$: *m/z* 345.1702, found 345.1709.



155 *162*

Allylic acetate 162. To a solution of allylic alcohol **155** (88.0 mg, 0.153 mmol, 1.00 eq) in pyridine (250 μL) and acetic anhydride (3.00 mL) was added DMAP (28.0 mg, 0.229 mmol, 1.50 equiv). After 2 h, the reaction mixture was concentrated to an oil, which was purified by gradient flash chromatography on silica gel (5 to 10% EtOAc in hexanes) to give allylic acetate **162** (89.3 mg, 94% yield) as a colorless oil: R_f 0.68 (20% EtOAc in hexanes developed twice); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.76 (d, *J* = 7.5 Hz, 1H), 6.69 (d, *J* = 7.5 Hz, 1H), 5.73 (dd, *J* = 2.8, 10.8 Hz, 1H), 4.12-4.04 (m, 1H), 4.00-3.90 (comp. m, 3H), 3.70 (s, 3H), 3.07 (app. t, *J* = 12.5 Hz, 1H), 2.97 (dd, *J* = 3.3, 13.8 Hz, 1H), 2.66 (d, *J* = 15.0 Hz, 1H), 2.57 (d, *J* = 14.5 Hz, 1H), 2.38 (d, *J* = 17.5 Hz, 1H), 2.26 (d, *J* = 13.0 Hz, 1H), 2.24 (d, *J* = 17.5 Hz, 1H), 2.18 (s, 3H), 1.97 (s, 3H), 1.80 (s, 3H), 1.48 (d, *J* = 14.5 Hz, 1H), 1.42 (s, 9H), 1.28 (s, 3H), 1.03 (s, 9H), 0.19 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 169.3, 150.0, 146.9, 135.0, 131.1, 129.3, 129.2, 125.3, 123.4, 107.3, 79.7, 71.5, 64.3, 63.9, 59.9, 43.5, 40.7, 39.9, 35.9, 28.2, 26.2, 26.1, 21.3, 21.0, 18.5, 17.1, -4.2, -4.4; IR (Neat film NaCl) 2958, 2931, 2896, 2860, 1740, 1463, 1419, 1368, 1287, 1235, 1147, 1079, 1014, 854, 841, 783, 734 cm^{-1}; HRMS (FAB) $[M+H-H_2]^+$ calc'd for $[C_{34}H_{53}O_8Si]^+$: *m/z* 617.3510, found 617.3487.

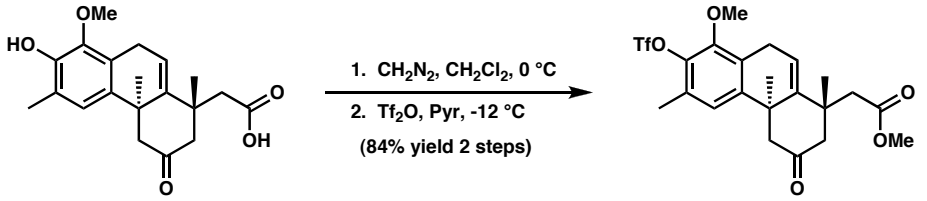


Arene 163. To a solution of allylic alcohol **155** (554 mg, 0.962 mmol, 1.0 equiv) in THF (10 mL) was added 1.00 M TBAF in THF (1.50 mL, 1.50 mmol, 1.56 equiv). After 5 min, the reaction mixture was concentrated to ~5 mL and was purified by gradient flash chromatography on silica gel (20 to 40% EtOAc in hexanes) to give phenol **155a** (223 mg, 52% yield).

To a cooled (-12 °C) solution of phenol **155a** (202 mg, 0.438 mmol, 1.00 equiv) and pyridine (142 μL, 1.75 mmol, 4.0 equiv) in CH_2Cl_2 (5 mL) was added Tf_2O (74.3 μL, 0.526 mmol, 1.2 equiv). After 2 h, additional Tf_2O (10.0 μL, 0.071 mmol, 0.16 equiv) was added. After a further 2 h, the reaction mixture was quenched into a mixture of H_2O (10 mL), brine (10 mL), and CH_2Cl_2 (10 mL), then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), and concentrated to an oil, which was purified by gradient flash chromatography on silica gel (15 to 25% EtOAc in hexanes + 1% TEA) to give triflate **155b** (193 mg, 75% yield).

A flame-dried 25 mL Schlenk flask was charged with triflate **155b** (193 mg, 0.325 mmol, 1.00 equiv), $PdCl_2(PPh_3)_2$ (27.3 mg, 0.0389 mmol, 0.12 equiv), 1,4-bis-(diphenylphosphino)butane (40.2 mg, 0.0974 mmol, 0.30 equiv), DMF (4 mL), *n*-Bu_3N

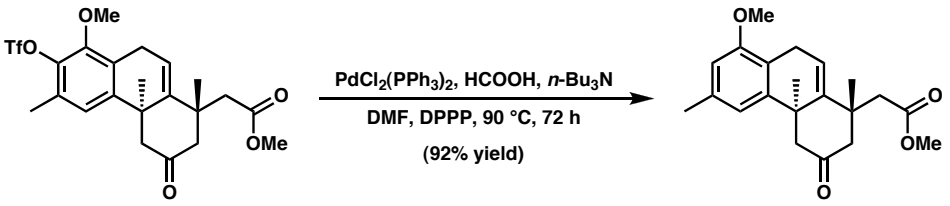
(650 μL, 2.73 mmol, 8.40 equiv), and HCOOH (61.3 μL, 1.62 mmol, 5.00 equiv) under an Ar atmosphere and heated to 90 °C. After 22 h, the reaction mixture was quenched with H_2O (40 mL), extracted with Et_2O (5 x 15 mL), dried ($MgSO_4$), and concentrated to a residue, which was purified by gradient flash chromatography on silica gel (10 to 15% acetone in hexanes) to give arene **163** (117 mg, 80% yield) as a white solid: mp 135-136 °C; R_f 0.50 (35% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, *J* = 7.5 Hz, 1H), 6.73 (d, *J* = 7.5 Hz, 1H), 6.68 (s, 1H), 4.46 (dd, *J* = 2.3, 10.1 Hz, 1H), 4.02-3.90 (comp. m, 4H), 3.80 (s, 3H), 3.08 (dd, *J* = 10.2, 13.8 Hz, 1H), 3.07 (s, 1H), 2.94 (dd, *J* = 3.0, 13.8 Hz, 1H), 2.65 (d, *J* = 13.5 Hz, 1H), 2.33 (s, 3H), 2.30-2.10 (comp. m, 3H), 2.07 (s, 3H), 1.58 (dd, *J* = 2.1, 13.8 Hz, 1H), 1.40 (s, 9H), 1.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 72.1, 157.3, 137.3, 136.8, 131.4, 130.3, 125.1, 121.0, 111.2, 107.6, 80.8, 69.5, 64.2, 63.9, 55.0, 46.4, 43.3, 42.0, 41.3, 36.7, 28.0, 26.7, 21.5, 21.1; IR (Neat film NaCl) 3501, 2974, 2934, 1705, 1368, 1259, 1155, 1126, 1080, 1042 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{26}H_{38}O_6+H]^+$: *m/z* 447.2747, found 447.2749.



161 *168*

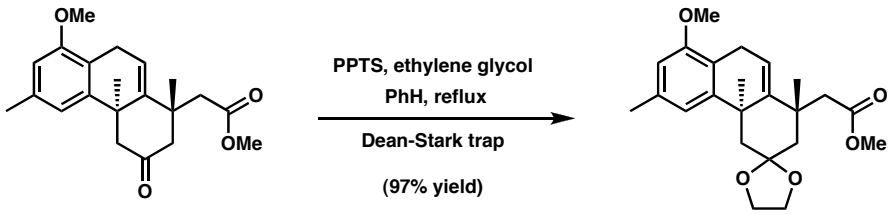
Triflate 168. To a cooled (0 °C) solution of acid **161** (994 mg, 2.88 mmol, 1.00 equiv) in CH_2Cl_2 (30 mL) was added a cooled (0 °C) solution of CH_2N_2 in Et_2O (~0.2 M, 18.7 mL, 1.30 equiv) in a dropwise manner over 10 min. After 20 min, TLC analysis indicated complete consumption of the starting material and the reaction mixture was concentrated *in vacuo*. To a cooled (-12 °C) solution of the crude reaction mixture and

pyridine (2.45 mL, 28.8 mmol, 10.0 equiv) in CH_2Cl_2 (50 mL) was added Tf_2O (1.01 mL, 7.20 mmol, 2.50 equiv) in a dropwise manner over 5 min. After 30 min, additional Tf_2O (1.01 mL, 7.20 mmol, 2.50 equiv) was added. After a further 1 h at -12 °C, the reaction mixture was allowed to warm to 0 °C, stirred for 1 h, and quenched with saturated aqueous $NaHCO_3$ (30 mL). The reaction mixture was poured into half saturated aqueous $NaHCO_3$ (60 mL), extracted with CH_2Cl_2 (5 x 30 mL), dried over K_2CO_3, and concentrated to an oil, which was purified by gradient flash chromatography on silica gel (10 to 25% EtOAc in hexanes) to give triflate **168** (1.18 g, 84% yield) as an off-white solid: mp 123-125 °C (decomp.) (benzene); R_f 0.45 (35% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (s, 1H), 6.03 (dd, J = 2.0, 6.5 Hz, 1H), 3.82 (s, 3H), 3.67 (s, 3H), 3.66 (dd, J = 6.3, 21.0 Hz, 1H), 3.50 (d, J = 17.7 Hz, 1H), 3.17 (app. d, J = 21.9 Hz, 1H), 3.09 (d, J = 17.4 Hz, 1H), 2.91 (d, J = 15.3 Hz, 1H), 2.76 (d, J = 17.4 Hz, 1H), 2.46 (d, J = 15.6 Hz, 1H), 2.34 (s, 3H), 2.33 (d, J = 17.4 Hz, 1H), 1.29 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.1, 171.5, 148.5, 146.0, 144.7, 140.0, 129.4, 127.6, 121.9, 119.7, 118.6 (q, $J_{C\text{-}F}$ = 318 Hz), 61.0, 51.5, 49.3, 48.8, 45.9, 39.4, 38.5, 33.1, 30.3, 24.3, 16.5; IR (Neat film NaCl) 2960, 1735, 1715, 1417, 1210, 1138, 1072, 903, 856 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{22}H_{25}SO_7F_3+H]^+$: m/z 491.1351, found 491.1363.



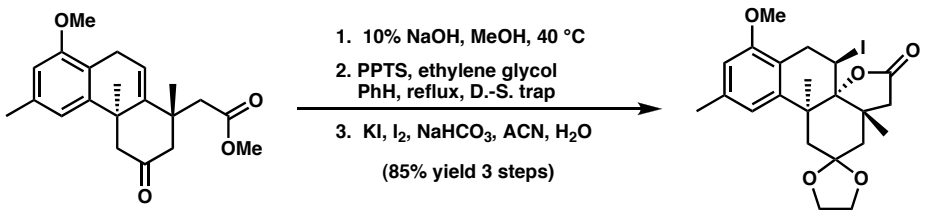
168 *169*

Ketoester 169. A flame-dried 250 mL Schlenk flask was charged with triflate **168** (azeotroped from PhH solution, 1.150 g, 2.34 mmol, 1.00 equiv), $PdCl_2(PPh_3)_2$ (198 mg, 0.282 mmol, 0.12 equiv), 1,4-bis-(diphenylphosphino)butane (290 mg, 0.704 mmol, 0.30 equiv), DMF (20 mL), *n*-Bu_3N (4.70 mL, 19.7 mmol, 8.40 equiv), and HCOOH (443 μL, 11.7 mmol, 5.00 equiv) under an N_2 atmosphere and heated to 90 °C. After 72 h, the reaction mixture was quenched with H_2O (150 mL) and Et_2O (40 mL), extracted with Et_2O (6 x 50 mL), dried ($MgSO_4$), and concentrated to a residue, which was purified by gradient flash chromatography on silica gel (5 to 10% acetone in hexanes) to give ketoester **169** (735 mg, 92% yield) as a colorless oil: R_f 0.53 (35% acetone in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.68 (s, 1H), 6.57 (s, 1H), 6.04 (dd, *J* = 1.8, 6.3 Hz, 1H), 3.83 (s, 3H), 3.66 (s, 3H), 3.64 (dd, *J* = 6.3, 21.8 Hz, 1H), 3.47 (d, *J* = 17.4 Hz, 1H), 3.14 (d, *J* = 17.7 Hz, 1H), 3.02 (app. d, *J* = 21.6 Hz, 1H), 2.89 (d, *J* = 15.6 Hz, 1H), 2.77 (d, *J* = 17.4 Hz, 1H), 2.46 (d, *J* = 15.6 Hz, 1H), 2.35 (s, 3H), 2.32 (d, *J* = 17.4 Hz, 1H), 1.28 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.2, 171.6, 156.1, 146.0, 144.0, 136.9, 120.8, 119.7, 116.3, 108.4, 55.3, 51.4, 49.6, 49.1, 46.2, 39.2, 38.5, 33.2, 30.9, 24.1, 21.9; IR (Neat film NaCl) 2956, 1735, 1711, 1584, 1462, 1314, 1198, 1134, 1064 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{21}H_{26}O_4+H]^+$: *m/z* 343.1909, found 343.1894.



169 ***170***

Ester 170. To a solution of ketoester **169** (200 mg, 0.581 mmol, 1.00 equiv), ethylene glycol (4.00 mL, 71.7 mmol, 124 equiv), and pyridinium *p*-toluenesulfonate (2.00 g, 7.96 mmol, 13.7 equiv) in benzene (70 mL) was fitted with a Dean-Stark apparatus and refluxed at 95 °C for 10 h. The reaction mixture was allowed to cool to ambient temperature, diluted with H_2O (50 mL), and CH_2Cl_2 (50 mL), and extracted with CH_2Cl_2 (5 x 30 mL). The combined organics were washed with a 1:1:1 solution of brine, H_2O, and sat. aq. $NaHCO_3$ (4 x 20 mL), dried (K_2CO_3), and concentrated to a oil, which was purified by gradient flash chromatography on silica gel (30% Et_2O in hexanes) to give ester **170** (217 mg, 97% yield) as a colorless oil: R_f 0.48 (50% Et_2O in hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 6.77 (s, 1H), 6.54 (s, 1H), 6.00 (dd, *J* = 2.3, 6.2 Hz, 1H), 4.18-4.04 (m, 2H), 4.02-3.89 (m, 2H), 3.81 (s, 3H), 3.64 (s, 3H), 3.55 (dd, *J* = 6.2, 21.8 Hz, 1H), 2.96 (d, *J* = 21.8 Hz, 1H), 2.91 (d, *J* = 14.1 Hz, 1H), 2.73 (d, *J* = 14.1 Hz, 1H), 2.52 (dd, *J* = 2.0, 13.7 Hz, 1H), 2.34 (s, 3H), 2.32 (dd, *J* = 2.1, 14.1 Hz, 1H), 2.11 (d, *J* = 13.8 Hz, 1H), 1.56 (d, *J* = 14.1 Hz, 1H), 1.38 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 155.9, 148.3, 144.8, 136.6, 121.2, 119.4, 116.6, 108.6, 107.9, 64.7, 63.2, 55.3, 51.1, 46.5, 45.4, 43.0, 39.3, 38.7, 30.8, 30.2, 24.0, 21.9; IR (Neat film NaCl) 2956, 2883, 1733, 1462, 1348, 1199, 1135, 1067, 1018 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{23}H_{30}O_5+H]^+$: *m/z* 387.2171, found 387.2179.



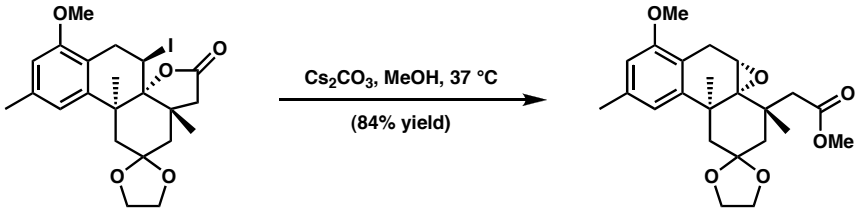
169 *172*

Iodolactone 172. A solution of ketoester **169** (200 mg, 0.581 mmol, 1.00 equiv) in MeOH (13 mL), and 10% w/v aqueous NaOH (13 mL) was heated at 40 °C for 10 h. The reaction mixture was cooled to ambient temperature, poured into brine (50 mL) and H_2O (10 mL), acidified with 3 M HCl to pH 0, extracted with EtOAc (6 x 20 mL), dried (Na_2SO_4), concentrated, and used in the next step without further purification.

A solution of the above crude carboxylic acid, ethylene glycol (500 μL, 8.97 mmol, 15.4 equiv), and pyridinium *p*-toluenesulfonate (500 mg, 1.99 mmol, 3.42 equiv) in benzene (50 mL) was fitted with a Dean-Stark apparatus and refluxed at 100 °C for 2 h. The cooled (0 °C) reaction mixture was diluted with H_2O (25 mL), brine (25 mL), and CH_2Cl_2 (50 mL), and extracted with CH_2Cl_2 (6 x 30 mL). The combined organics were dried (Na_2SO_4), concentrated, and used immediately in the next step without further purification.

To a solution of the crude ketal and $NaHCO_3$ (68.4 mg, 0.814 mmol, 1.4 equiv) in H_2O (5 mL) and acetonitrile (5 mL) was added KI (125 mg, 0.756 mmol, 1.3 equiv) and I_2 (192 mg, 0.756 mmol, 1.3 equiv). The reaction mixture was stirred in the dark for 30 h and quenched with saturated aqueous $Na_2S_2O_3$ (10 mL), H_2O (20 mL), and brine (20 mL). The reaction mixture was extracted with EtOAc (8 x 20 mL), dried (Na_2SO_4), concentrated, and recrystallized (15% acetone in hexanes, ~25 mL, from 80 to –20 °C) to give iodolactone **172** (247 mg, 85% yield) as a white solid: mp 155-160 °C (decomp.)

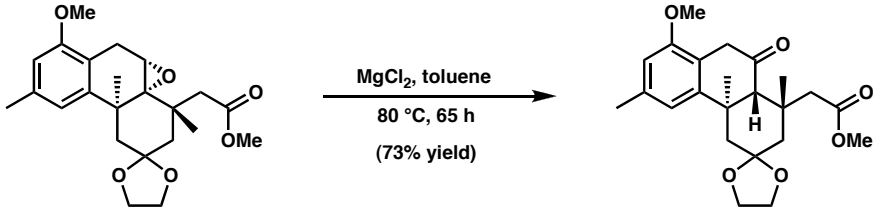
(acetone/hexanes); R_f 0.37 (35% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 6.92 (s, 1H), 6.22 (s, 1H), 5.29 (app. t, *J* = 10.0 Hz, 1H), 3.75 (dd, *J* = 10.0, 19.3 Hz, 1H), 3.52-3.34 (comp. m, 3H), 3.34-3.26 (comp. m, 2H), 3.24 (s, 3H), 3.01 (d, *J* = 18.0 Hz, 1H), 2.76 (d, *J* = 16.0 Hz, 1H), 2.49 (d, *J* = 16.0 Hz, 1H), 2.45 (d, *J* = 18.0 Hz, 1H), 2.12 (s, 3H), 1.54 (d, *J* = 14.5 Hz, 1H), 1.13 (s, 3H), 0.98 (d, *J* = 14.5 Hz, 1H), 0.95 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 173.5, 156.9, 143.6, 138.1, 121.2, 117.6, 109.4, 107.2, 87.2, 64.5, 64.2, 55.1, 46.1, 45.8, 45.4, 43.2, 42.6, 36.5, 30.9, 30.8, 25.2, 22.2; IR (Neat film NaCl) 2964, 2881, 1790, 1461, 1229, 1203, 1071, 1023 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{22}H_{27}IO_5+H]^+$: *m/z* 499.0982, found 499.0986.



172 ***173***

Epoxide 173. To a solution of iodolactone **172** (75.0 mg, 0.151 mmol, 1.00 equiv) in MeOH (15 mL) was added Cs_2CO_3 (981 mg, 3.01 mmol, 20.0 equiv). The reaction mixture was warmed to 37 °C and vigorously stirred for 19 h. The reaction mixture was cooled to ambient temperature, diluted with H_2O (20 mL), brine (20 mL), and CH_2Cl_2 (20 mL), extracted with CH_2Cl_2 (5 x 20 mL) and EtOAc (5 x 25 mL), dried (Na_2SO_4), and concentrated. The resulting residue was purified by flash chromatography on silica gel (15% EtOAc in hexanes + 1% TEA) to give epoxide **173** (51.0 mg, 84% yield) as a colorless oil: R_f 0.54, 0.28 (35% EtOAc in hexanes, 10% EtOAc in hexanes developed 3 times); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (s, 1H), 6.45 (s, 1H), 4.12-4.08

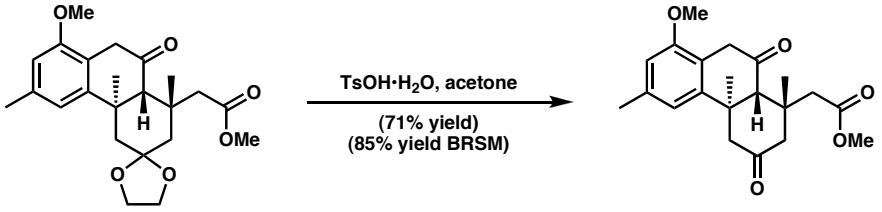
(m, 1H), 4.06-4.01 (m, 1H), 3.94-3.86 (comp. m, 2H), 3.78 (s, 3H), 3.66 (s, 3H), 3.58 (d, J = 2.5 Hz, 1H), 3.24 (d, J = 19.5 Hz, 1H), 2.90 (dd, J = 3.5, 20.0 Hz, 1H), 2.80 (dd, J = 1.0, 14.5 Hz, 1H), 2.79 (d, J = 14.5 Hz, 1H), 2.37 (d, J = 14.0 Hz, 1H), 2.31 (dd, J = 1.0, ~15 Hz, 1H), 2.30 (s, 3H), 2.03 (d, J = 15.0 Hz, 1H), 1.72 (d, J = 15.0 Hz, 1H), 1.63 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 172.8, 157.5, 144.9, 136.6, 120.4, 116.1, 108.9, 108.2, 65.7, 64.8, 63.7, 57.1, 55.2, 51.1, 48.8, 43.4, 41.7, 39.7, 38.3, 27.5, 26.7, 24.4, 22.2; IR (Neat film NaCl) 2950, 1734, 1590, 1462, 1360, 1196, 1135, 1075, 1017 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{23}H_{30}O_6+H]^+$: m/z 403.2121, found 403.2113.



173 *174*

Ketone 174. A solution of epoxide **173** (49.0 mg, 0.122 mmol, 1.00 equiv) in toluene (30 mL) in a flame-dried Schlenk flask under an N_2 atmosphere was treated with magnesium chloride (2.00 g, 21.0 mmol, 172 equiv) and heated to 80 °C for 65 h. After cooling to ambient temperature, the reaction mixture was filtered and the filter cake was washed with toluene (2 x 25 mL). The filter cake was partitioned between EtOAc (20 mL) and ice cold water (20 mL), and further extracted with EtOAc (3 x 20 mL). The combined organics were dried (Na_2SO_4), and concentrated to an oil, which was purified by gradient flash chromatography on silica gel (10 to 20% EtOAc in hexanes) to give ketone **174** (36.0 mg, 73% yield) as a colorless oil: R_f 0.55, 0.33 (35% EtOAc in hexanes, 10% EtOAc in hexanes developed 3 times); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.73

(s, 1H), 6.57 (s, 1H), 4.15-4.05 (m, 2H), 4.00-3.88 (m, 2H), 3.80 (s, 3H), 3.67 (s, 3H), 3.64 (d, *J* = 22.5 Hz, 1H), 3.47 (dd, *J* = 1.5, 14.5 Hz, 1H), 3.34 (d, *J* = 22.0 Hz, 1H), 3.23 (d, *J* = 14.5 Hz, 1H), 2.58 (dd, *J* = 2.5, 14.5 Hz, 1H), 2.56 (s, 1H), 2.45 (dd, *J* = 2.5, 13.5 Hz, 1H), 2.35 (s, 3H), 2.13 (d, *J* = 13.0 Hz, 1H), 1.30 (s, 3H), 1.21 (s, 3H), 1.14 (dd, *J* = 1.5, 14.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.0, 173.9, 156.4, 149.4, 137.6, 117.3, 116.1, 108.7, 108.3, 65.2, 63.0, 62.8, 55.3, 50.9, 46.4, 42.5, 42.3, 40.0, 36.0, 35.6, 28.9, 25.6, 21.9; IR (Neat film NaCl) 2953, 2885, 1731, 1713, 1586, 1462, 1360, 1193, 1065 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{23}H_{30}O_6]^+$: *m/z* 402.2042, found 402.2027.



174 ***175***

Diketone 175. A solution of ketone **174** (29.3 mg, 0.728 mmol, 1.00 equiv) in acetone (10 mL) was treated with TsOH•H_2O (100 mg, 0.526 mmol, 7.22 equiv) and stirred at ambient temperature for 4 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (25 mL), extracted with CH_2Cl_2 (6 x 15 mL), dried (Na_2SO_4), and concentrated to an oil, which was purified by gradient flash chromatography on silica gel (7.5 to 12.5% EtOAc in hexanes) to give starting ketone **164** (4.6 mg, 16% yield) and diketone **175** (18.6 mg, 71% yield) as a white solid. Crystals suitable for X-ray analysis were obtained by crystallization from acetone/heptanes at ambient temperature: mp 184-186 °C (acetone/heptanes); R_f 0.40 (35% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 (s, 1H), 6.59 (s, 1H), 3.82 (s, 3H), 3.71 (d, *J* = 22.0 Hz, 1H), 3.69 (s, 3H),

3.46 (dd, *J* = 1.5, 14.5 Hz, 1H), 3.39 (d, *J* = 22.5 Hz, 1H), 3.08 (s, 1H), 2.99 (dd, *J* = 2.3, 12.8 Hz, 1H), 2.93 (dd, *J* = 2.3, 12.8 Hz, 1H), 2.89 (d, *J* = 12.5 Hz, 1H), 2.36 (s, 3H), 2.33 (d, *J* = 14.5 Hz, 1H), 2.21 (d, *J* = 12.5 Hz, 1H), 1.36 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.7, 207.8, 171.9, 156.6, 147.6, 138.2, 117.1, 115.5, 109.3, 62.7, 55.4, 53.6, 52.2, 51.4, 45.7, 40.1, 39.5, 37.6, 28.0, 26.6, 21.9; IR (Neat film NaCl) 2953, 1732, 1713, 1586, 1462, 1331, 1194, 1063, 731 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{21}H_{26}O_5]^+$: *m/z* 358.1780, found 358.1774.

2.9 Notes and Citations

(1) (a) Tanner, D.; Anderson, P. G.; Tedenborg, L.; Somfai, P. *Tetrahedron* **1994**, *50*, 9135-9144. (b) Tanner, D.; Tedenborg, L.; Somfai, P. *Acta Chem. Scand.* **1997**, *51*, 1217-1223.

(2) Williams, D. R.; Brugel, T. A. *Org. Lett.* **2000**, *2*, 1023-1026.

(3) (a) Hikage, N.; Furukawa, H.; Takao, K.; Kobayashi, S. *Tetrahedron Lett.* **1998**, *39*, 6237-6240. (b) Hikage, N.; Furukawa, H.; Takao, K.; Kobayashi, S. *Tetrahedron Lett.* **1998**, *39*, 6241-6244.

(4) Williams, D. R.; Cortez, G. A. *Tetrahedron Lett.* **1998**, *39*, 2675-2678.

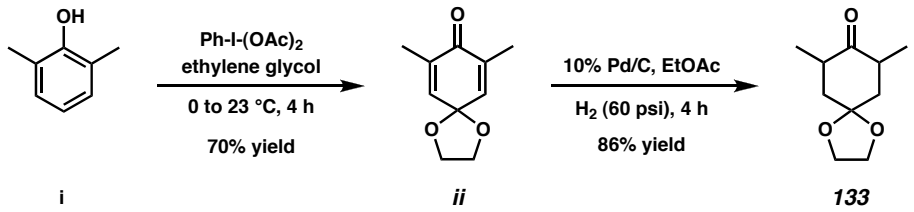
(5) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **1999**, *38*, 2398-2400.

(6) Bagdanoff, J. T. Development of the Enantioselective Oxidation of Secondary Alcohols and Natural Products Total Synthesis. Ph.D., California Institute of Technology, Pasadena, CA, August 2005.

(7) (a) Breuning, M.; Corey, E. J. *Org. Lett.* **2001**, *3*, 1559-1562. (b) Rose, P. A.; Lei, B.; Shaw, A. C.; Abrams, S. R.; Walker-Simmons, M. K.; Napper, S.; Quail, J. W. *Can. J. Chem.* **1996**, *74*, 1836-1843.

(8) Franck-Neumann, M.; Miesch, M.; Barth, F. *Tetrahedron* **1993**, *49*, 1409-1420.

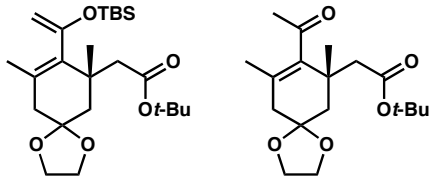
(9) In our experience, the dimethyl ketone **133** was best prepared by iodobenzene diacetate oxidation of 2,6 dimethylphenol **i** to give quinone **ii**. Quinone **ii** was readily reduced to ketone **133** with Pd/C under hydrogen (60 psi).



i *ii* ***133***

(10) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600-7605.

(11) The use of TBS enol ether **iii** analogous to ethyl enol ether **137** in either thermal or Lewis acid-promoted reactions gave none of the desired reaction. Frequently enone **iv** was observed.

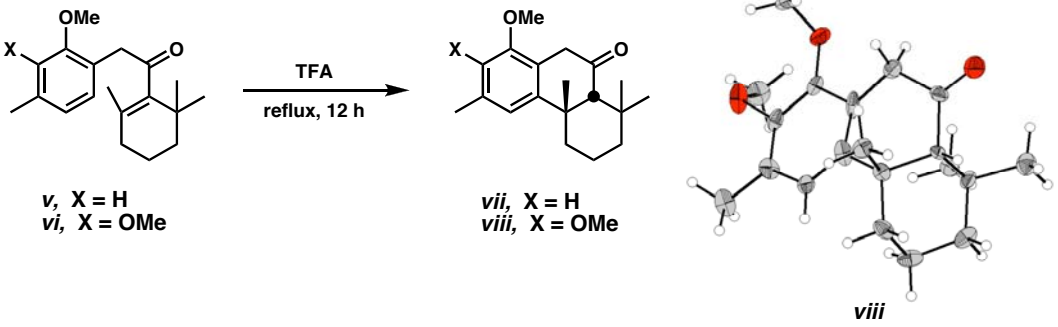


iii ***iv***

(12) (a) Matsumoto, T.; Ohmura, T. *Chem. Lett.* **1977**, 335-338. (b) Liebeskind, L. S.; Chidambaram, R.; Nimkar, S.; Liotta, D. *Tetrahedron Lett.* **1990**, *31*, 3723-3726.

(13) (a) Schmidt, C.; Thazhuthaveetil, J. *Can. J. Chem.* **1973**, *51*, 3620-3624. (b) Matsumoto, T.; Usui, S.; Morimoto, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1575-1579. (c) Matsumoto, T.; Usui, S. *Chem. Lett.* **1978**, 897-900. (d) Stevens, R. V.; Bisacchi, G. S. *J. Org. Chem.* **1982**, *47*, 2396-2399.

(14) This was confirmed by cyclization of enones **v** and **vi**. Ketone **vii** was produced in only ~10% yield, while ketone **viii** was produced in ~40% yield. X-ray structure determination confirmed the relative configuration between the stereocenters in ketone **viii**.



v, X = H
vi, X = OMe

vii, X = H
viii, X = OMe

viii

(15) Stevens, R. V.; Angle, S. R.; Kloc, K.; Mak, K. F.; Trueblood, K. N.; Liu, Y.-X. *J. Org. Chem.* **1986**, *51*, 4347-4353.

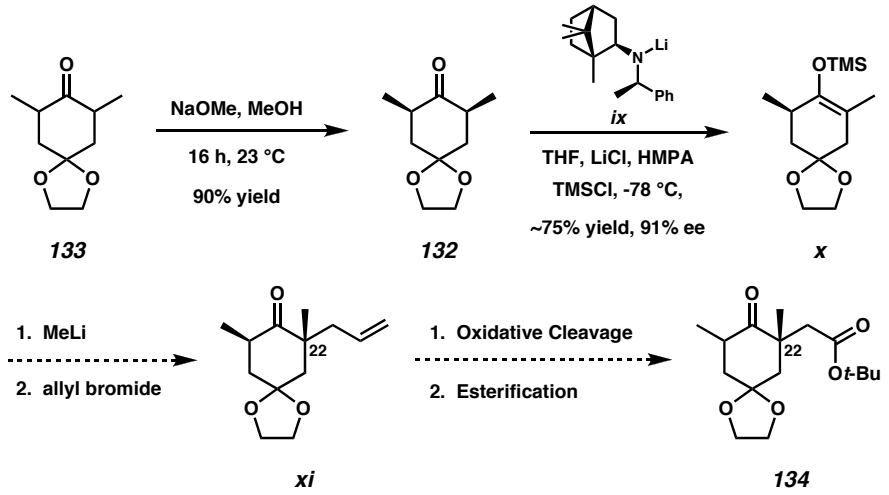
(16) To our knowledge this is the first time that such a hindered enol triflate was carbonylated directly to the enal oxidation state.

(17) (a) Shirai, R.; Tanaka, M.; Koga, K. *J. Am. Chem. Soc.* **1986**, *108*, 543-545. (b) Sato, D.; Kawasaki, H.; Shimada, I,; Arata, Y.; Okamura, K.; Date, T.; Koga, K. *J. Am. Chem. Soc.* **1992**, *114*, 761-763. (c) Aoki, K.; Noguchi, H.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1993**, *34*, 5105-5108.

(18) (a) Cox, P.; Simpkins, N. S. *Tetrahedron Asymmetry* **1991**, *2*, 1-26. (b) Cox, P.; Simpkins, N. S. *Synlett* **1991**, 321-323. (c) Bunn, B. J.; Simpkins, N. S. *J. Org. Chem.* **1993**, *58*, 533-534.

(19) Using chiral lithium amide **ix** we demonstrated that *meso*-ketone **132** could be desymmetrized in up to 91% ee by deprotonation and trapping with TMSCl. We planned to react the silyl enol ether **x** with an allyl electrophile to generate the quaternary center in ketone **xi**. Oxidative cleavage and esterification would complete the asymmetric synthesis of ketoester **134**. However, our experience in alkylating ketone **133** under non-enantioselective conditions suggested that

asymmetric allylation would be slow as well. This would provide ample time for racemization of the intermediate chiral enolate to occur.



(20) See Chapter 4 for details.

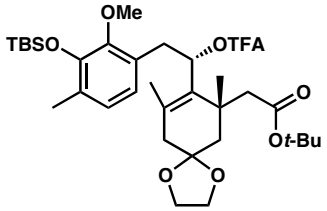
(21) Other acidic conditions included polyphosphoric acid, phosphoric acid/formic acid, and $AlCl_3$.

(22) For an excellent review of S_N' reactions, see: Paquette, L. A.; Stirling, C. J. M.; *Tetrahedron* **1992**, *48*, 7383-7423.

(23) Subsequent to, and independent of, our own studies of the S_N' cyclization of allylic alcohols and arenes under acid conditions, a similar report appeared in the literature, see: Ma, S.; Zhang, J. *Tetrahedron Lett.* **2002**, *43*, 3435-3438.

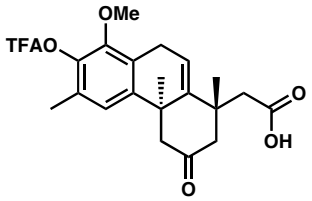
(24) Reaction of allylic acetate **162** in TFA produced more side products than the other substrates. This prevented quantification of dr and yield.

(25) Additionally, the analogous trifluoroacetate **xii** underwent cyclization in TFA to give comparable yields and diastereoselectivities as allylic alcohol **155**.



xii

(26) The formation of trifluoroacetates in situ is supported by the isolation of minor amounts of trifluoroacetylated product **xiii** from S_N' reactions in TFA.



xiii

(27) Saá, J. M.; Dopico, M.; Martorell, G.; García-Raso, A. G. *J. Org. Chem.* **1990**, *55*, 991-995.

(28) Cooper, M. S.; Heaney, H.; Newbold, A. J.; Sanderson, W. R. *Synlett.* **1990**, 533-535.

(29) Tohma, M.; Tomita, T.; Kimura, M. *Tetrahedron Lett.* **1973**, *14*, 4359-4362.

(30) van Vliet, M. C. A.; Arends, I. W. C. E.; Sheldon, R. A. *Synlett.* **2001**, 1305-1307.

(31) (a) Syamala, M. S.; Das, J.; Baskaran, S.; Chandrasekaran, S. *J. Org. Chem.* **1992**, *57*, 1928-1930. (b) Salvador, J. A. R.; Melo, M. L. S.; Neves, A. S. *Tetrahedron Lett.* **1996**, *37*, 687-690.

(32) Rudolph, J.; Reddy, K. L.; Chiang, J. P.; Sharpless, K. B. *J. Am. Chem. Soc.* **1997**, *119*, 6189-6190.

(33) A number of oxidation conditions gave oxidation at the benzylic C(19) position.

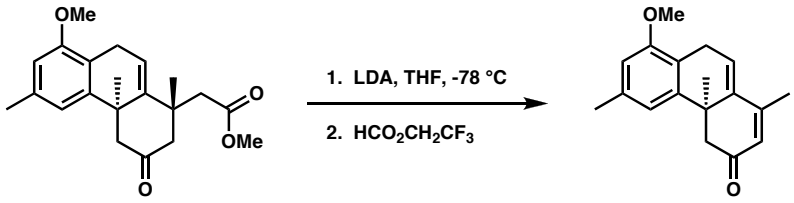
(34) The use of magnesium chloride was critical as use of magnesium bromide afforded the halogen exchange product. Treatment with BF_3•Et_2O gave the desired hydride shift with concomitant deketalization.

(35) Naqvi, S. M.; Horwitz, J. P.; Filler, R. *J. Am. Chem. Soc.* **1957**, *79*, 6283-6286.

(36) (a) House, H. O. *J. Am. Chem. Soc.* **1955**, *77*, 5083-5089. (b) House, H. O. *J. Am. Chem. Soc.* **1955**, *77*, 3070-3075.

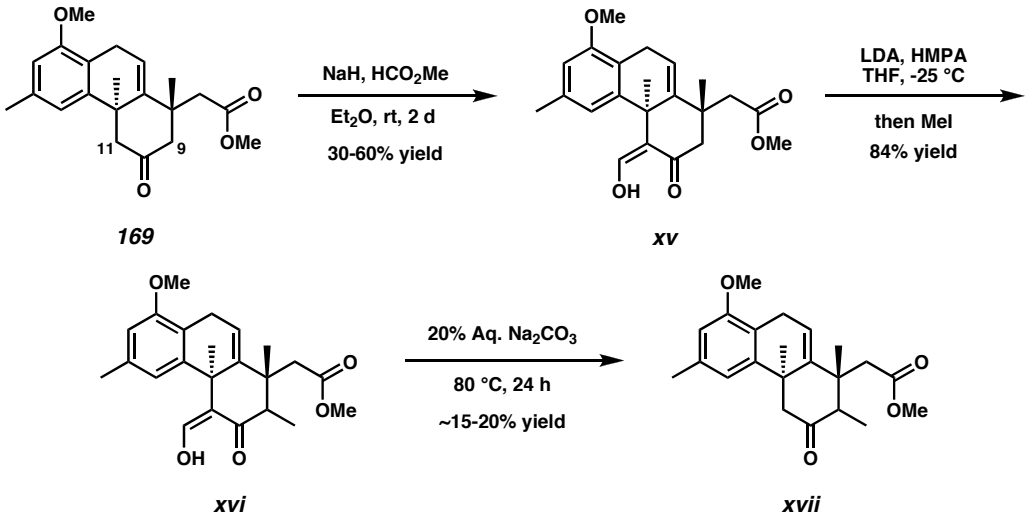
(37) Williams, D. R.; Cortez, G. A. *Tetrahedron Lett.* **1998**, *39*, 2675-2678.

(38) Under other kinetic enolate trapping conditions, fragmentation of ketoester **169** occurred to give the extended enone **xiv**.



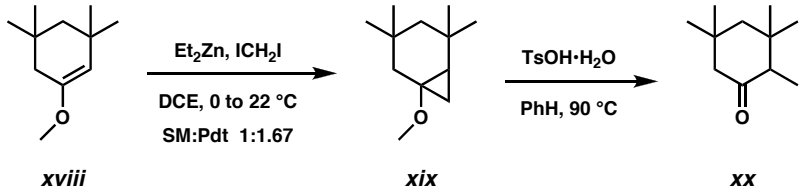
169 ***xiv***

(39) The ability to selectively deprotonate at C(11) led us to pursue a strategy to "protect" C(11). Ketoester **169** was condensed with methyl formate at C(11) and then successfully methylated at C(9). Unfortunately, despite extensive experimentation, no reagents could be found that were capable of removing the hydroxymethylene from methyl ketone **xvi** in greater than ~20% yield.



(40) Bofinger, K. R.; Hanack, M. *Chem. Ber.* **1985**, *118*, 2993-3003.

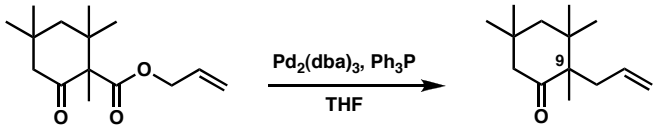
(41) Since selective enolization had proved difficult, we hoped to separate the isomers and cyclopropanate the C(9)-C(10) enol. To that end, cyclopropanation of steric model methyl enol ether **xviii** was attempted with diethyl zinc and methylene iodide. Treatment with tosic acid in benzene opened the cyclopropane **xix** to the desired methyl ketone **xx**. However, in our hands it was difficult to drive the reaction to more than ~60% conversion under optimized conditions.



(42) Hirai, G.; Oguri, H.; Hirama, M. *Chem. Lett.* **1999**, *28*, 141-142.

(43) We were delighted to find that pentamethyl β-ketoester **xxi** underwent allylation selectively at the more substituted α-site with Tsuji's conditions. We envisioned this method as a late-stage means to install the C(9) quaternary stereocenter in the presence of the other C ring quaternary stereocenters. In this case, chiral ligands

may have been used to override the inherent diastereoselectivity of the allylation. These allylation methods have the additional advantage of forming quaternary centers at room temperature in a few hours or less under neutral conditions.

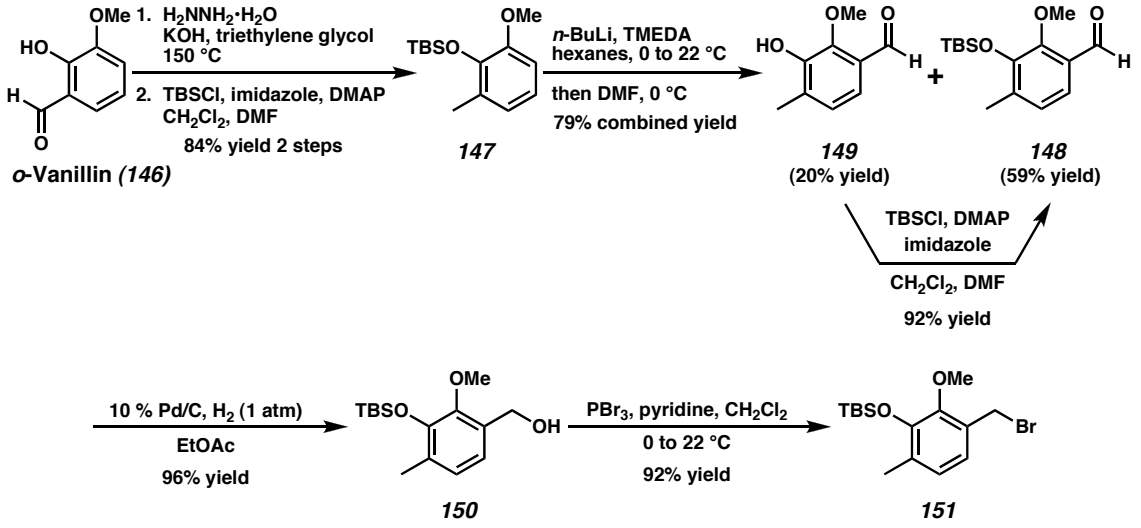


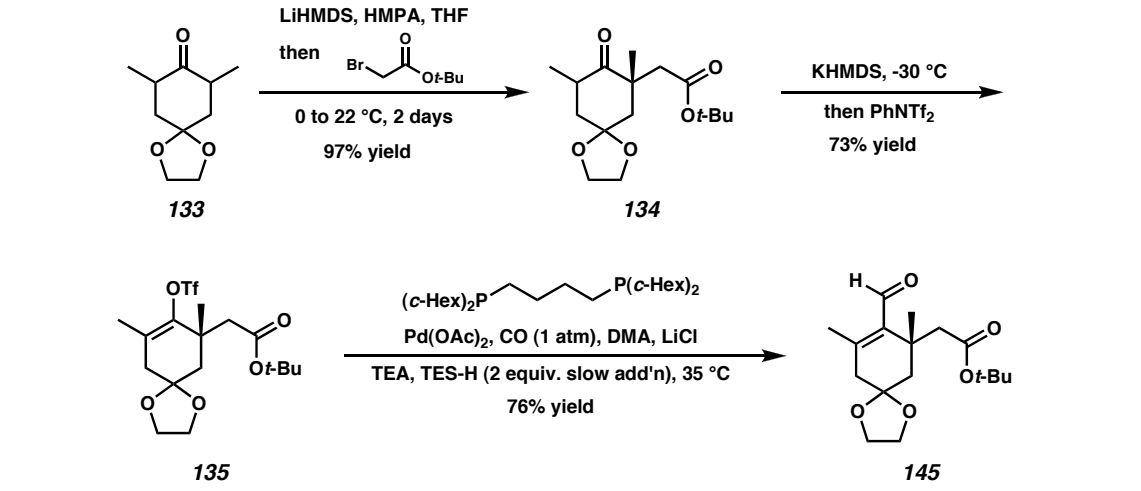
xxi ***xxii***

APPENDIX ONE

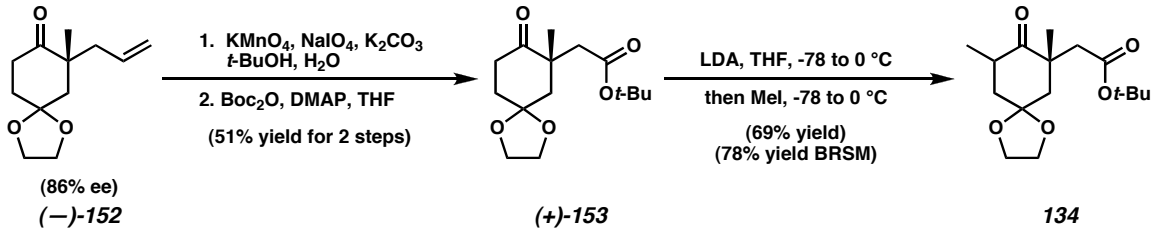
Synthetic Summary of the S_N' Approach to Zoanthenol

Scheme A1.1: Synthesis and Coupling of A and C Ring Synthons

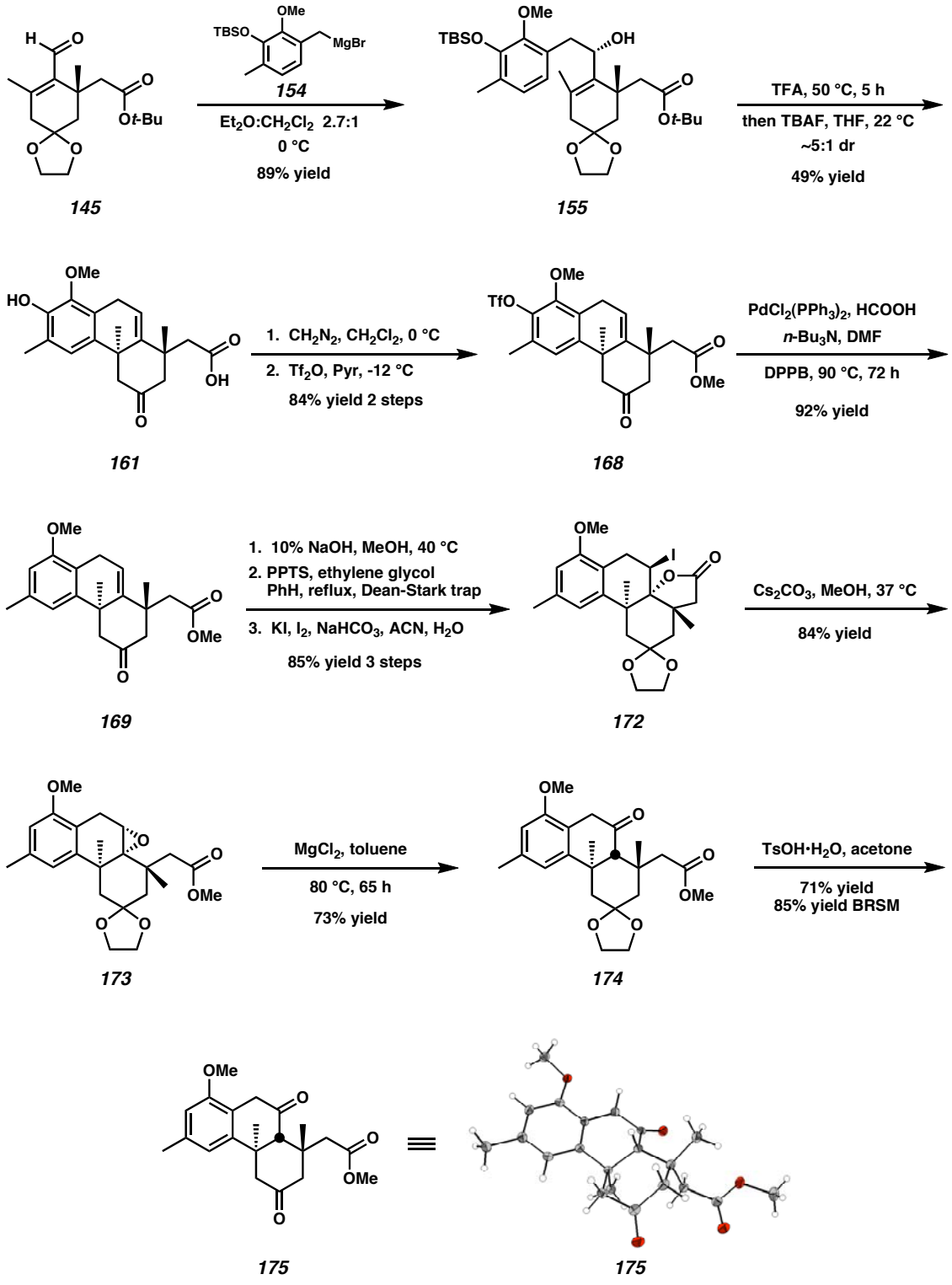




Scheme A1.2 Asymmetric Synthesis of C Ring Intermediate



Scheme A1.3 S_N' Cyclization and Elaboration of the Zoanthenol ABC Rings



APPENDIX TWO

Spectra of Compounds Relevant to Chapter Two

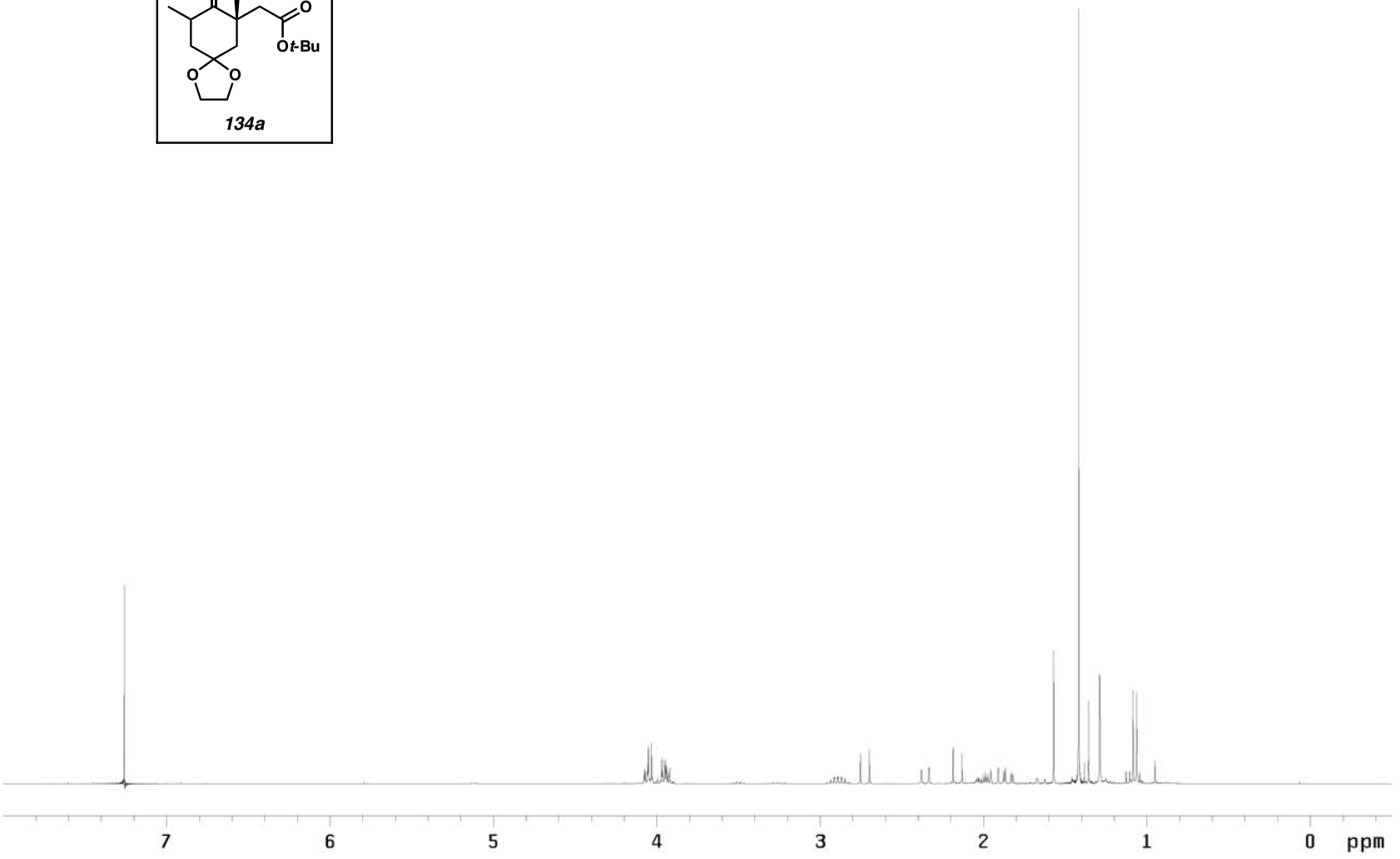


Figure A2.1 ^{1}H NMR of compound **(+)-134a** (300 MHz, $CDCl_3$)

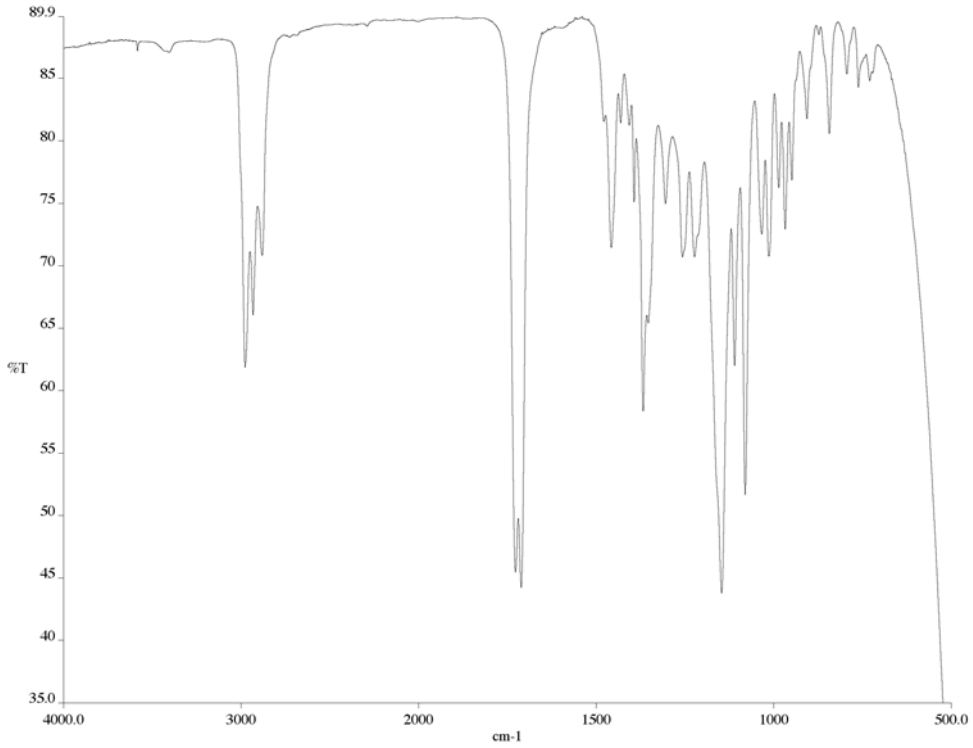


Figure A2.2 IR of compound **(+)-134a** (NaCl/film)

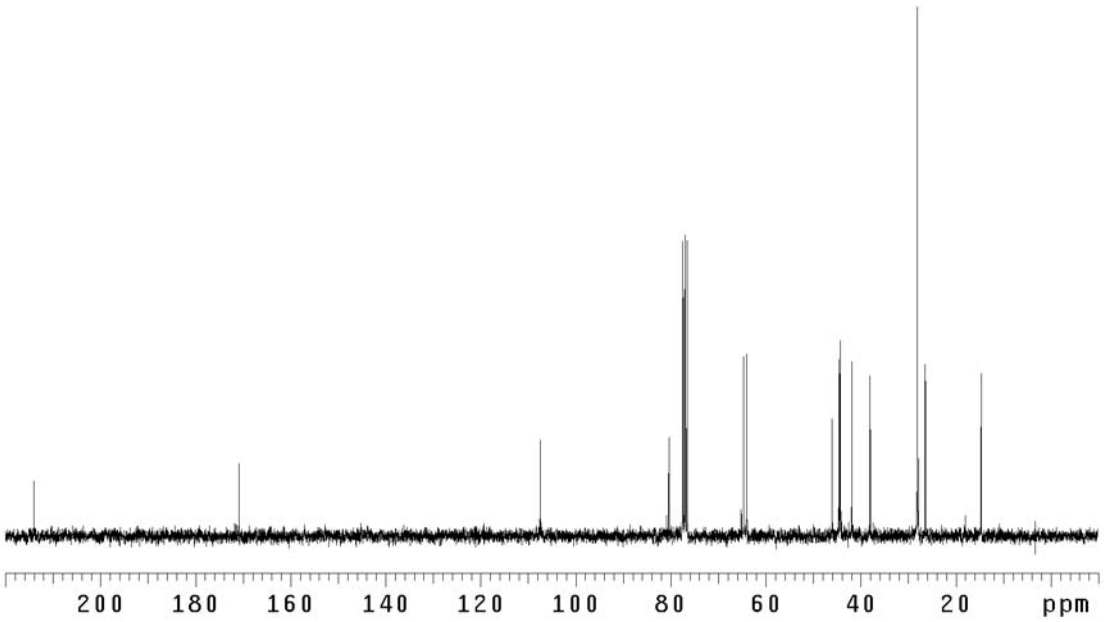


Figure A2.3 ^{13}C NMR of compound **(+)-134a** (75 MHz, $CDCl_3$)

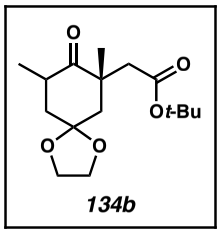


Figure A2.4 ^{1}H NMR of compound **(–)-134b** (300 MHz, $CDCl_3$)

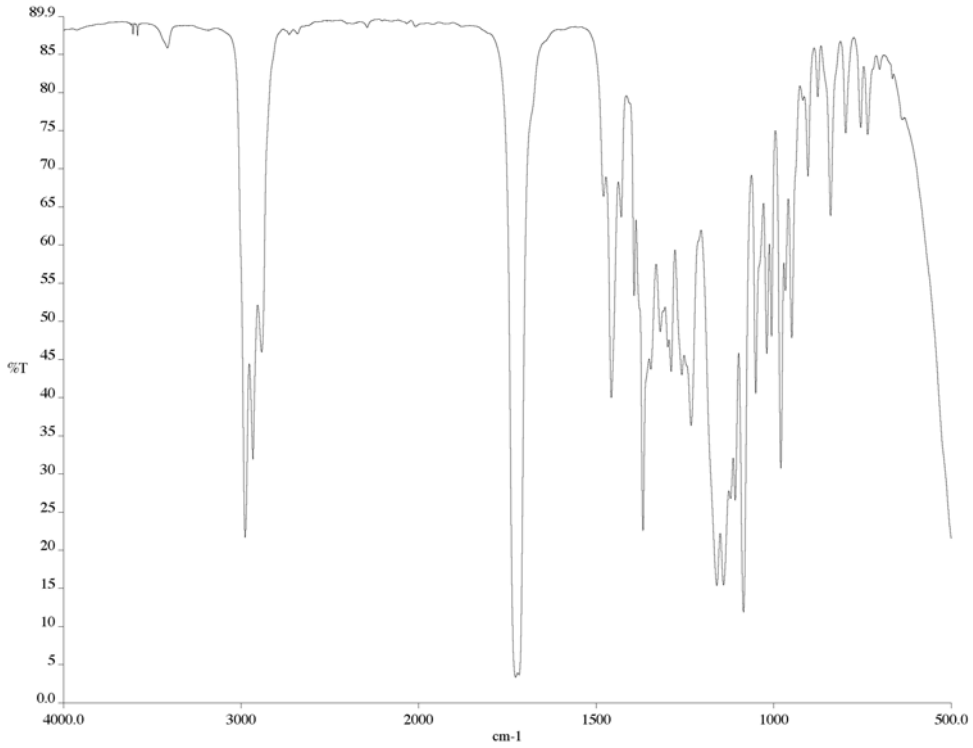


Figure A2.5 IR of compound **(–)-134b** (NaCl/film)

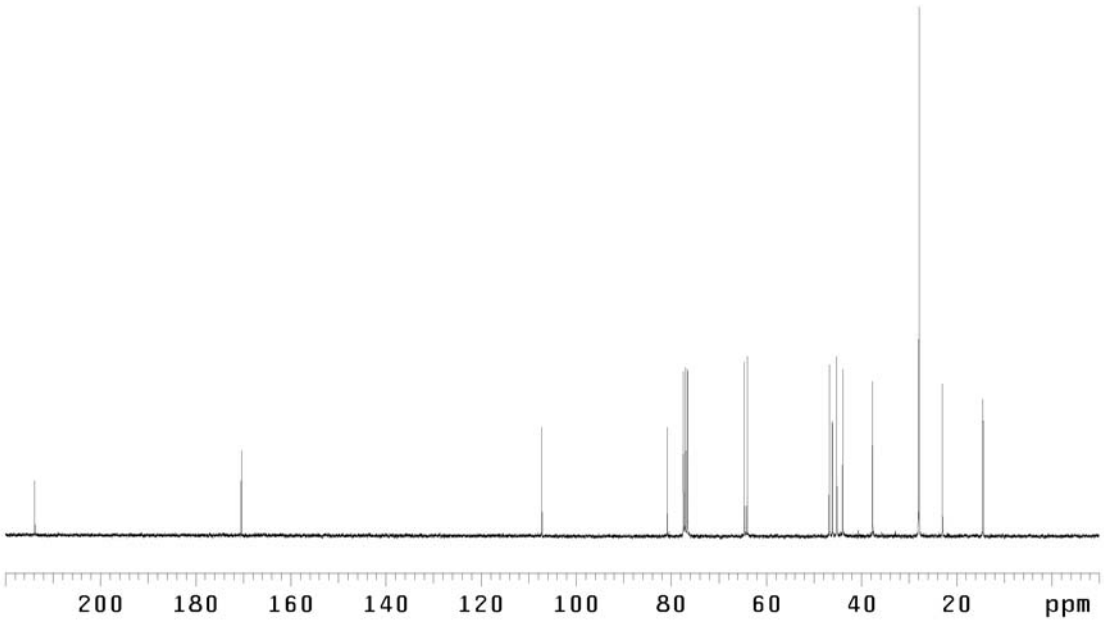


Figure A2.6 ^{13}C NMR of compound **(–)-134b** (75 MHz, $CDCl_3$)

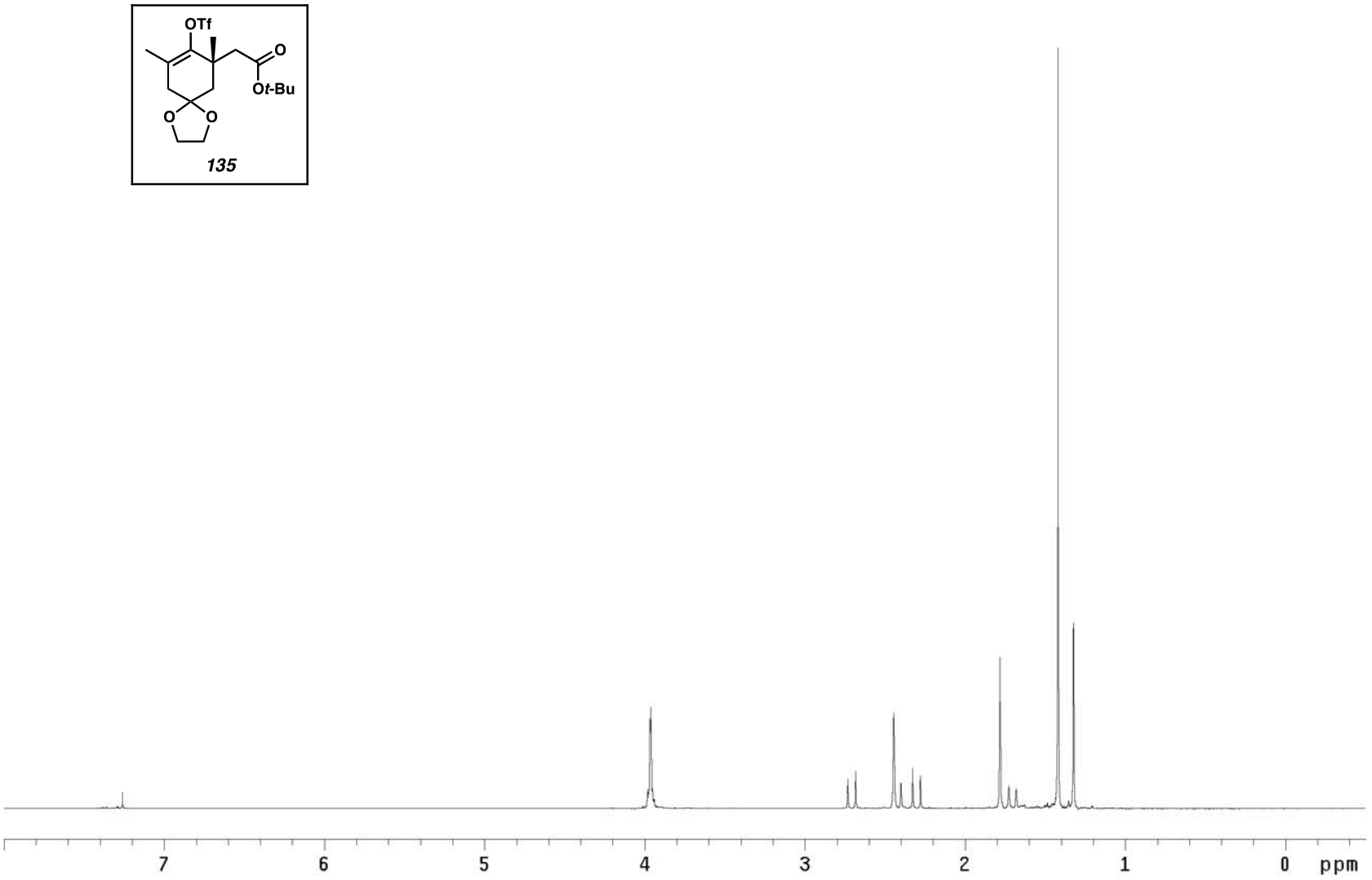


Figure A2.7 ^{1}H NMR of compound **135** (300 MHz, $CDCl_3$)

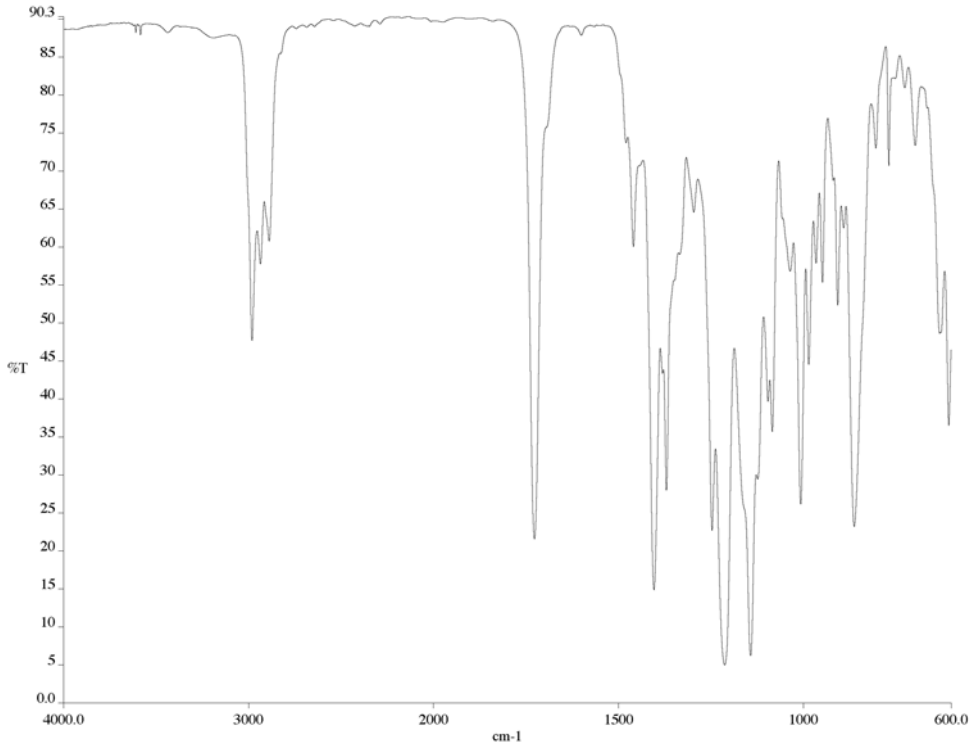


Figure A2.8 IR of compound **135** (NaCl/film)

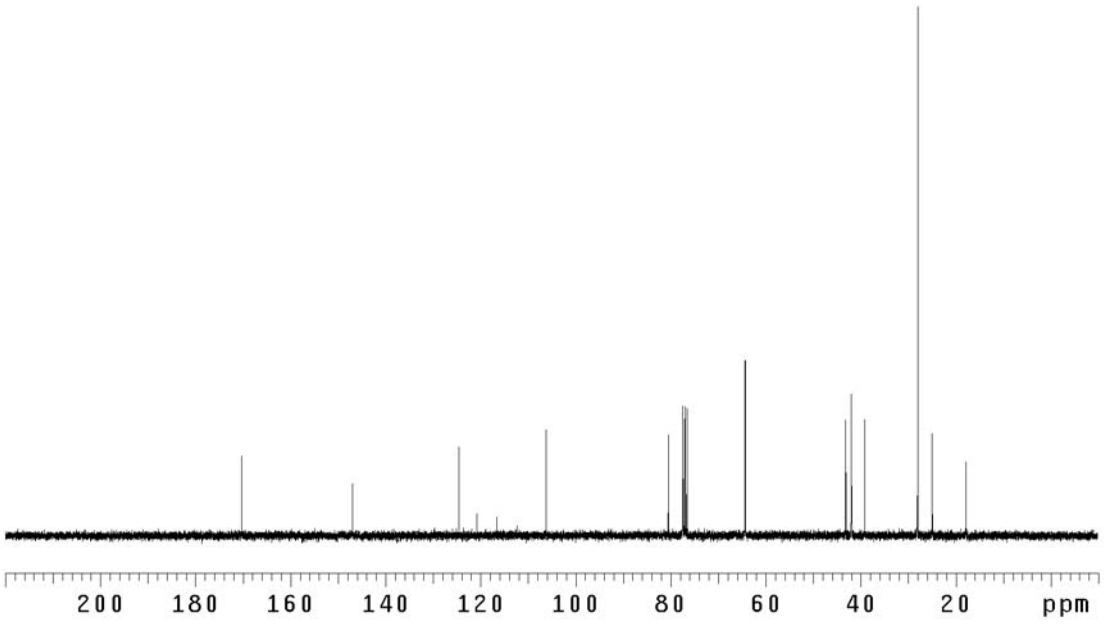
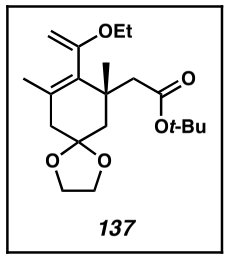


Figure A2.9 ^{13}C NMR of compound **135** (75 MHz, $CDCl_3$)



137

Figure A2.10 ^{1}H NMR of compound **137** (300 MHz, $CDCl_3$)

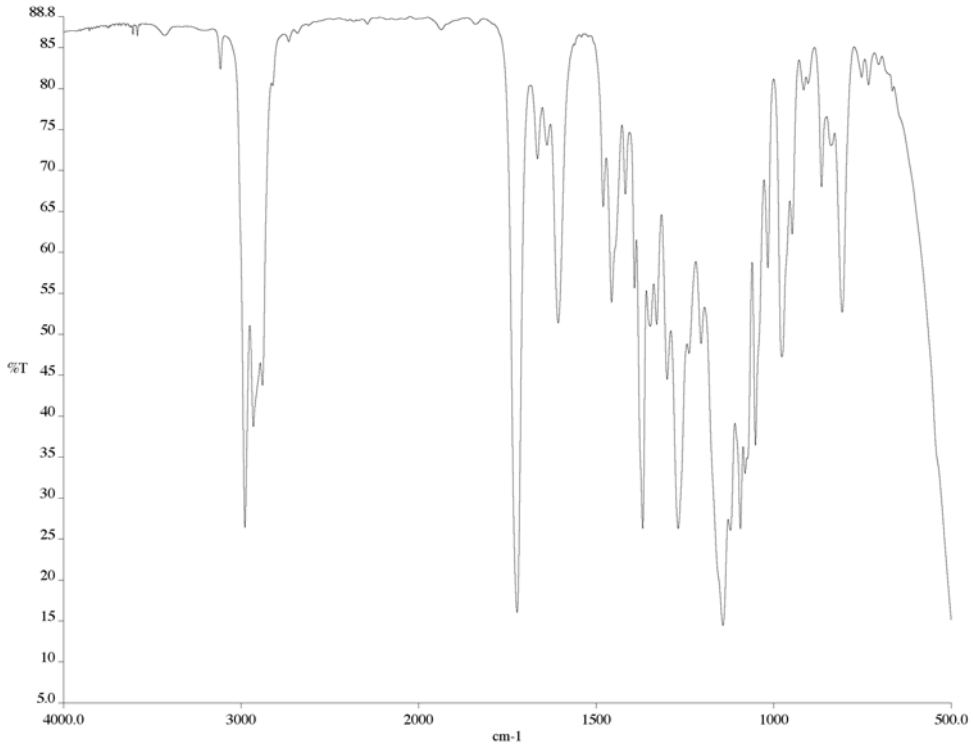


Figure A2.11 IR of compound **137** (NaCl/film)

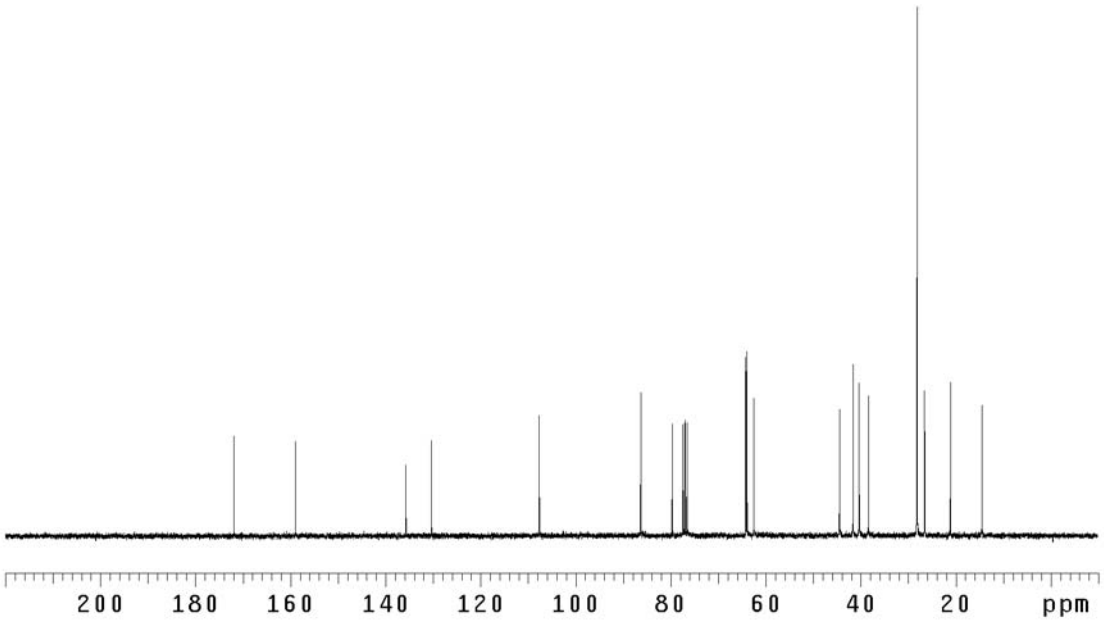


Figure A2.12 ^{13}C NMR of compound **137** (75 MHz, $CDCl_3$)

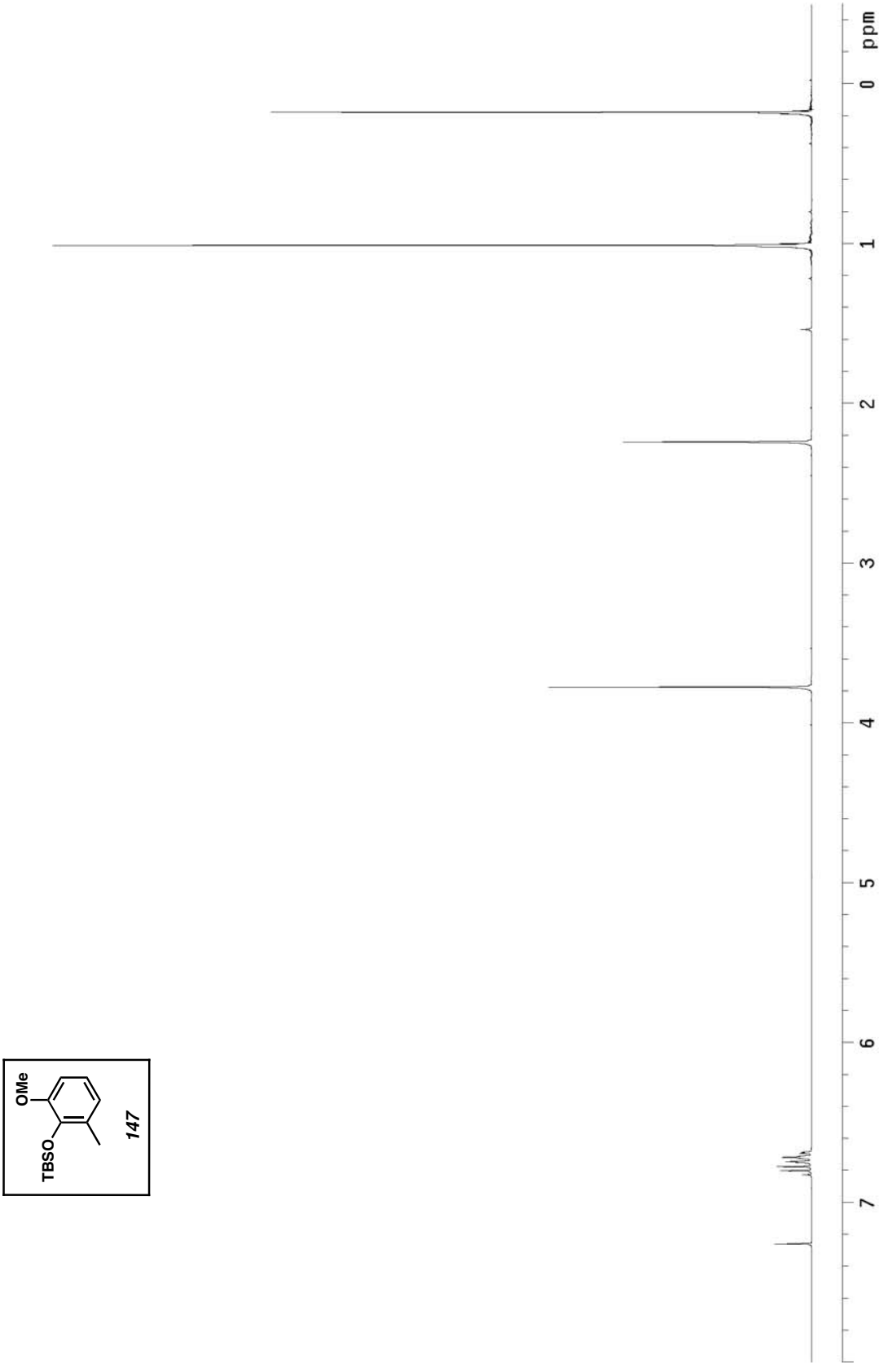


Figure A2.13 ^{1}H NMR of compound **147** (300 MHz, $CDCl_3$)

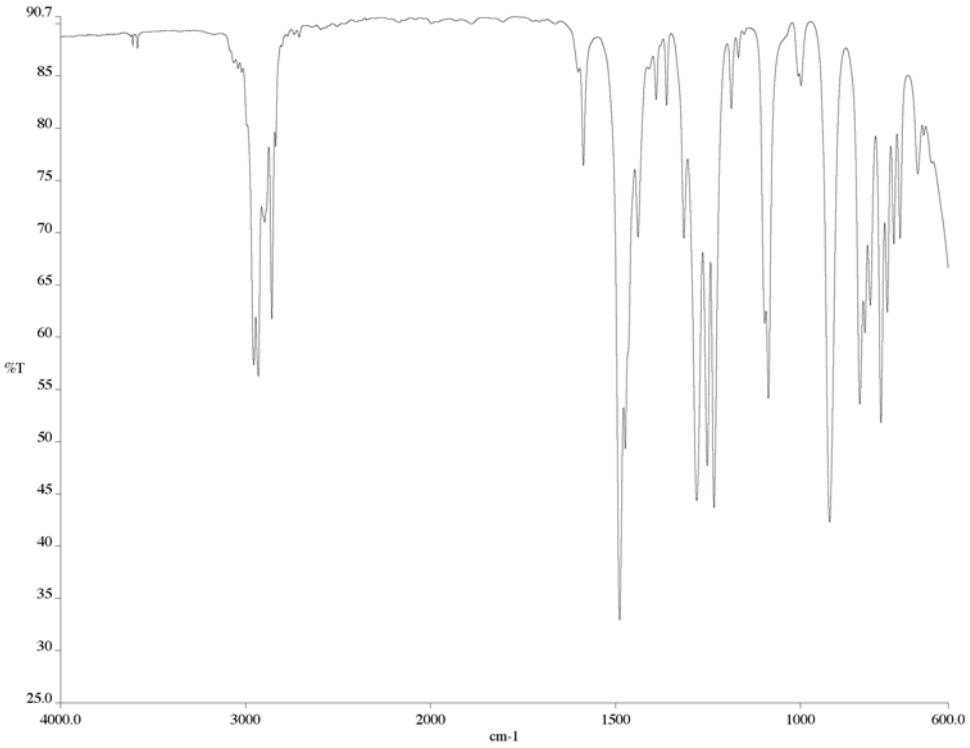


Figure A2.14 IR of compound **147** (NaCl/film)

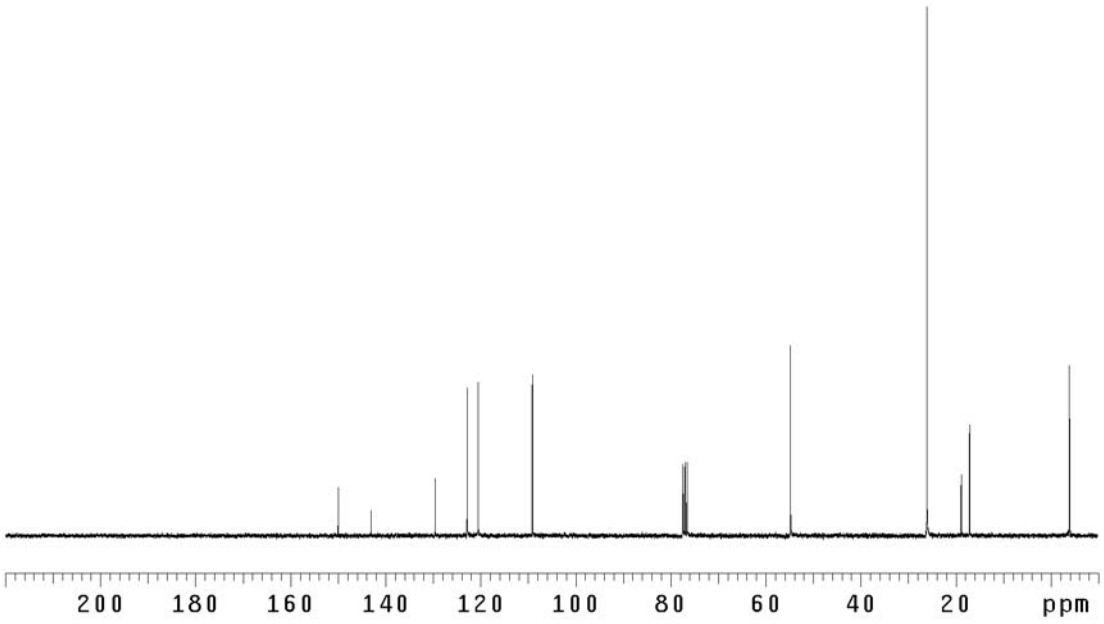


Figure A2.15 ^{13}C NMR of compound **147** (75 MHz, $CDCl_3$)

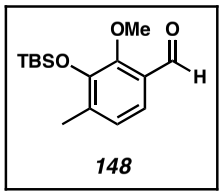


Figure A2.16 ^{1}H NMR of compound **148** (300 MHz, $CDCl_3$)

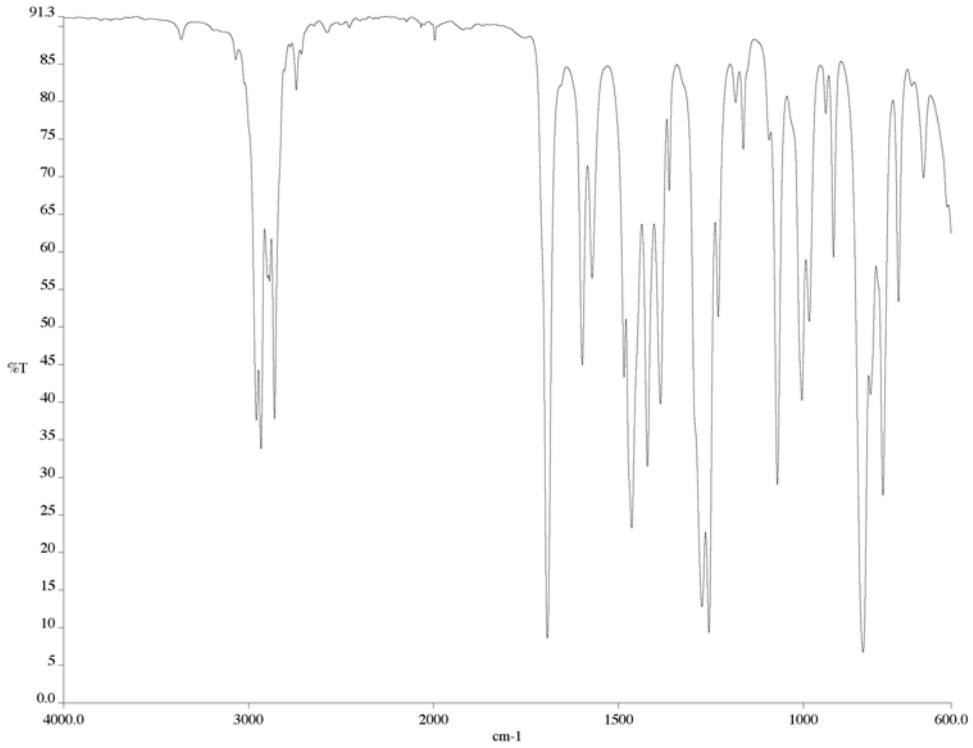


Figure A2.17 IR of compound **148** (NaCl/film)

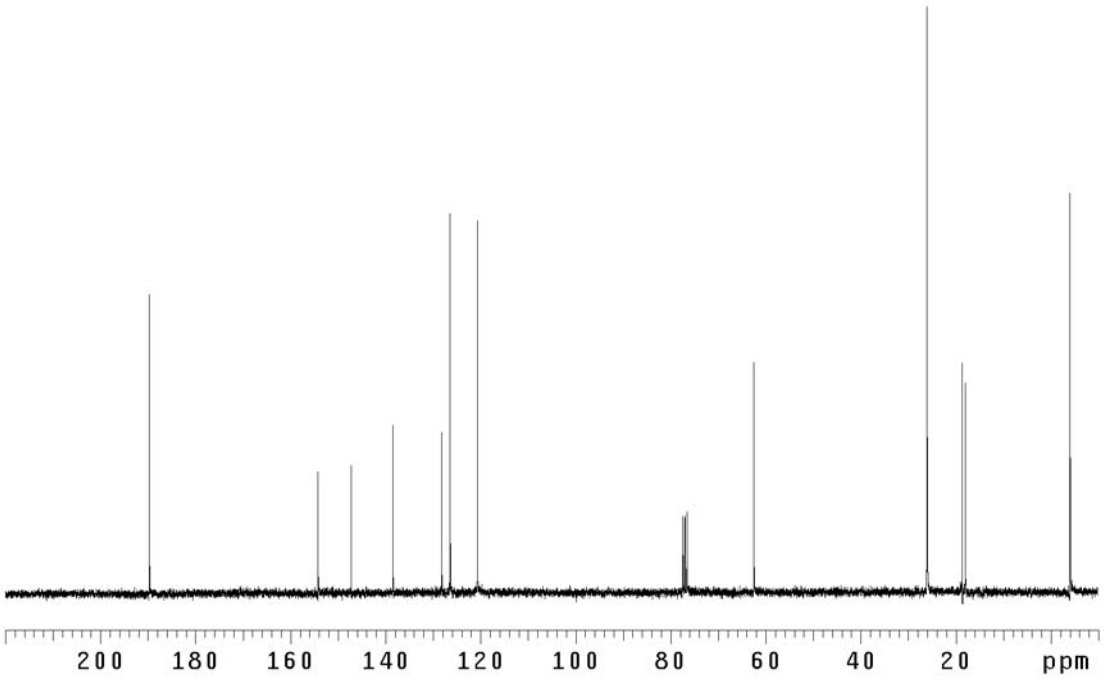


Figure A2.18 ^{13}C NMR of compound **148** (75 MHz, $CDCl_3$)

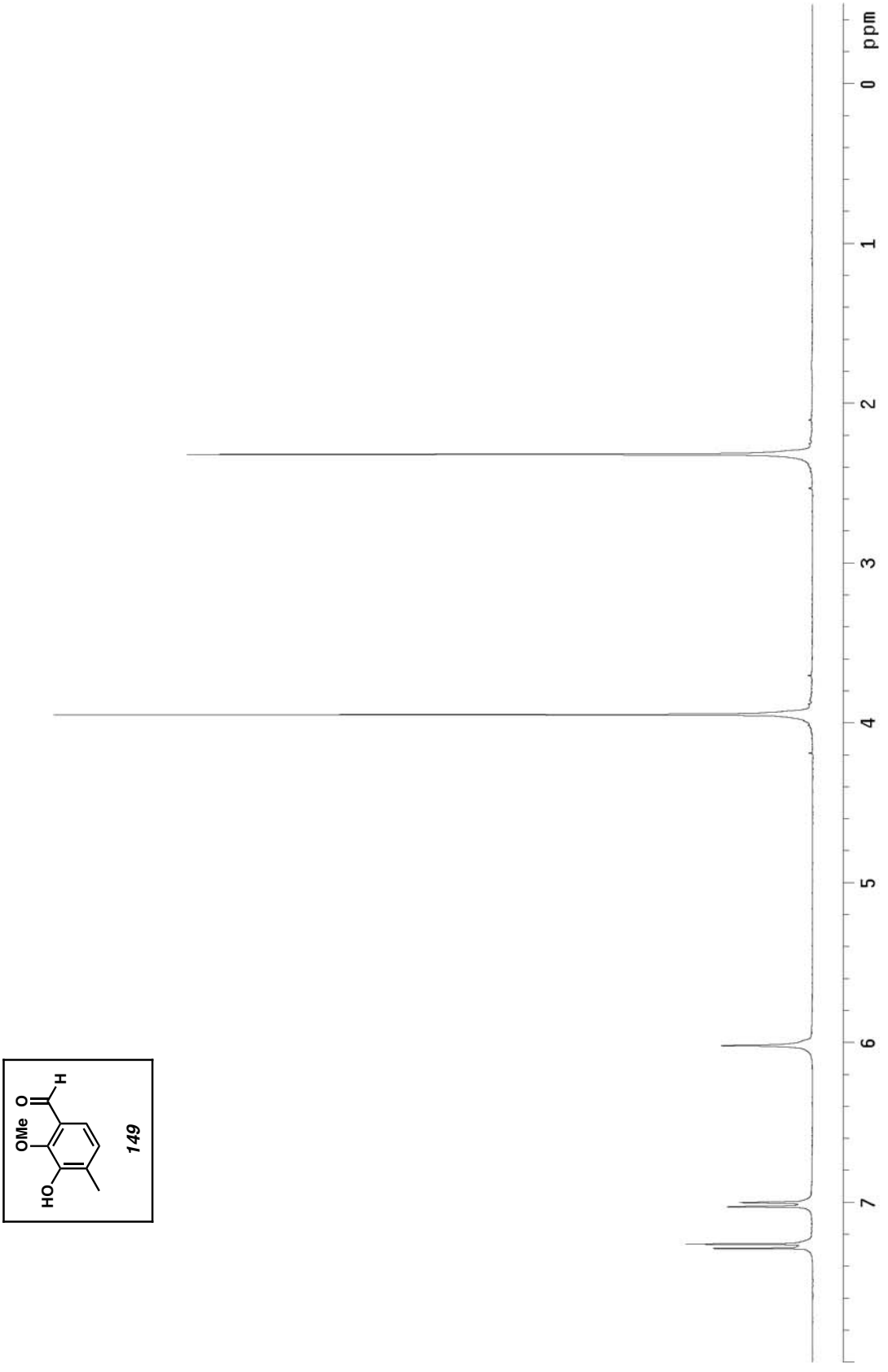


Figure A2.19 ^{1}H NMR of compound **149** (300 MHz, $CDCl_3$)

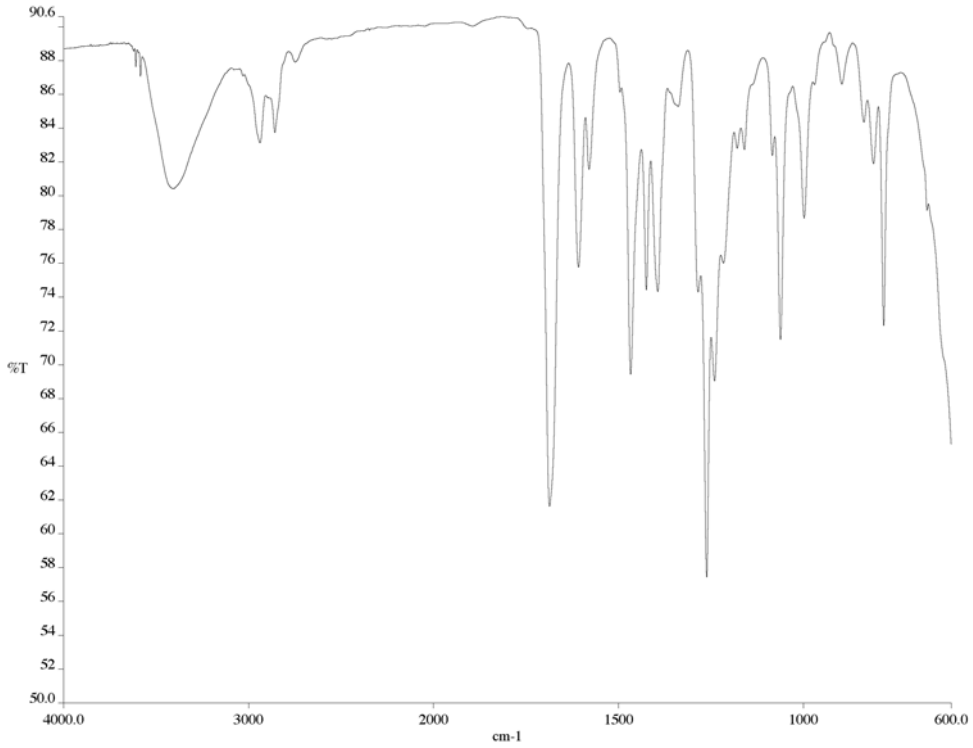


Figure A2.20 IR of compound **149** (NaCl/film)

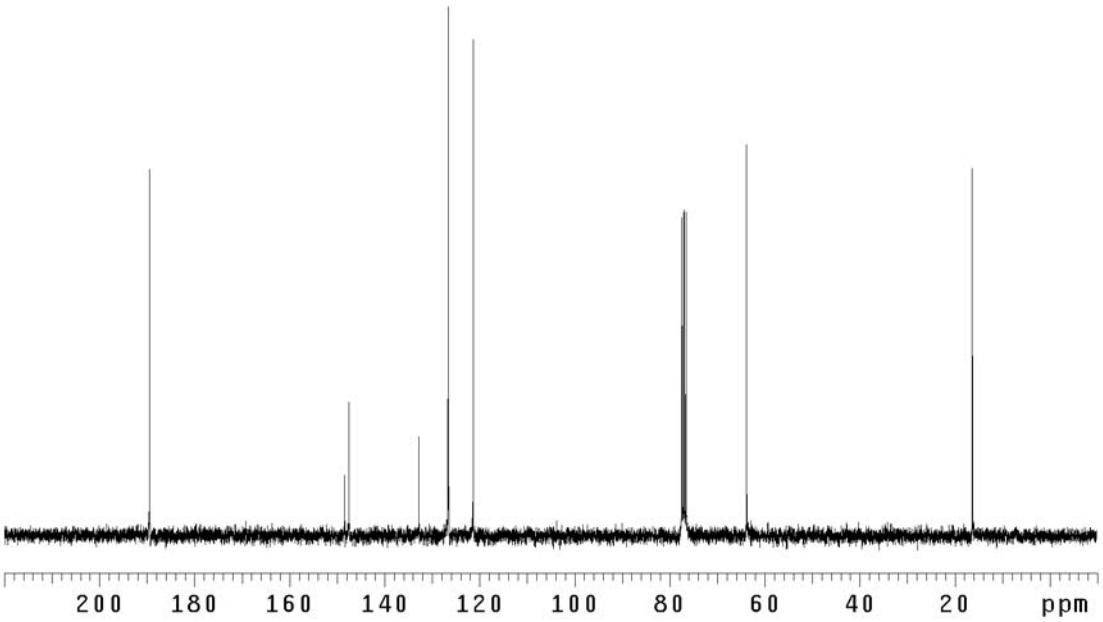


Figure A2.21 ^{13}C NMR of compound **149** (75 MHz, $CDCl_3$)

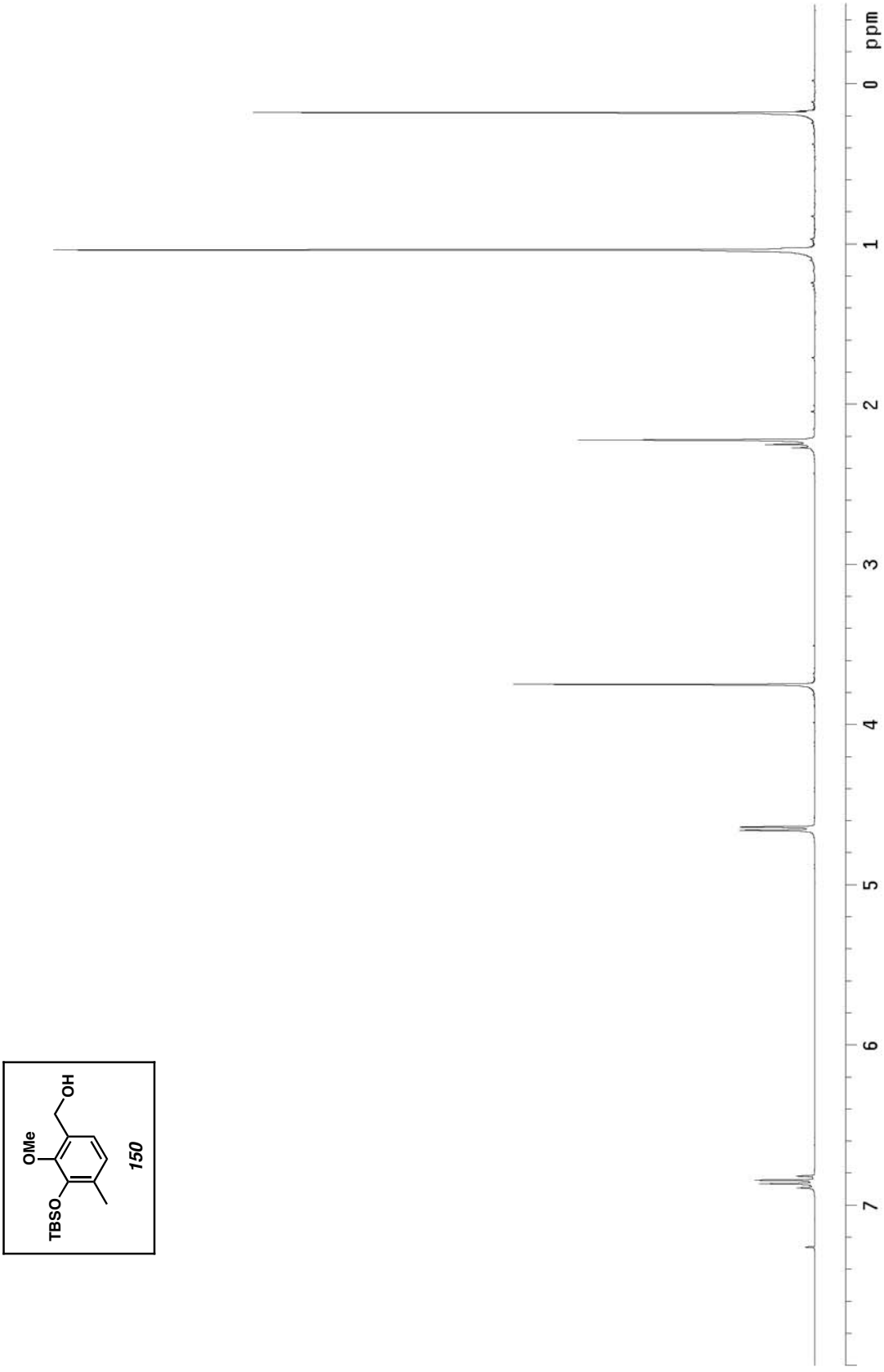


Figure A2.22 ^{1}H NMR of compound **150** (300 MHz, $CDCl_3$)

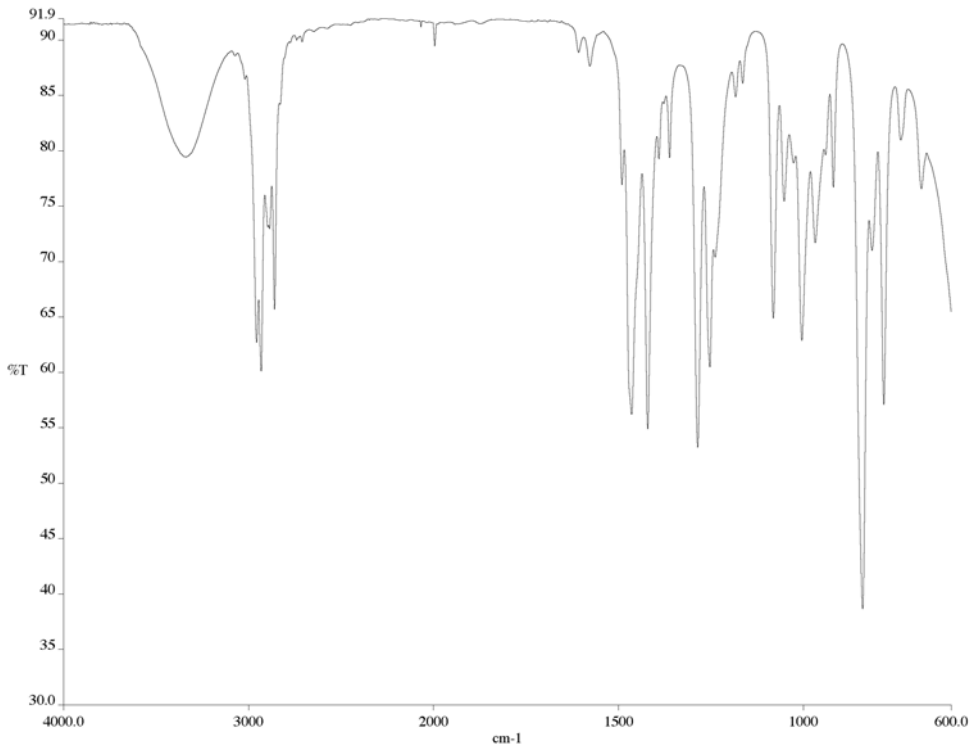


Figure A2.23 IR of compound **150** (NaCl/film)

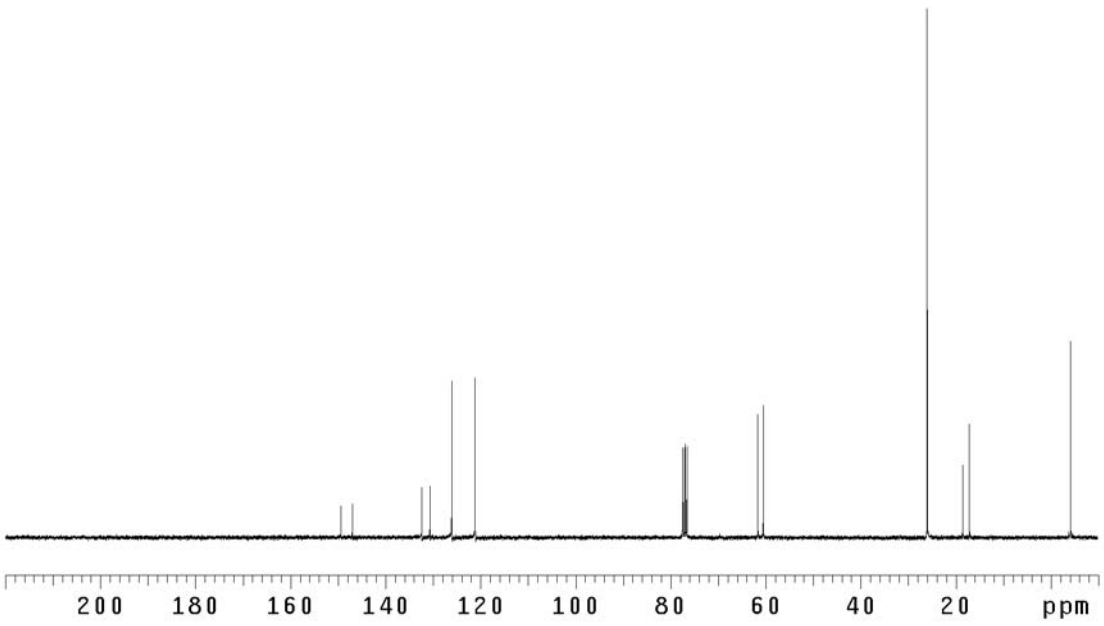


Figure A2.24 ^{13}C NMR of compound **150** (75 MHz, $CDCl_3$)

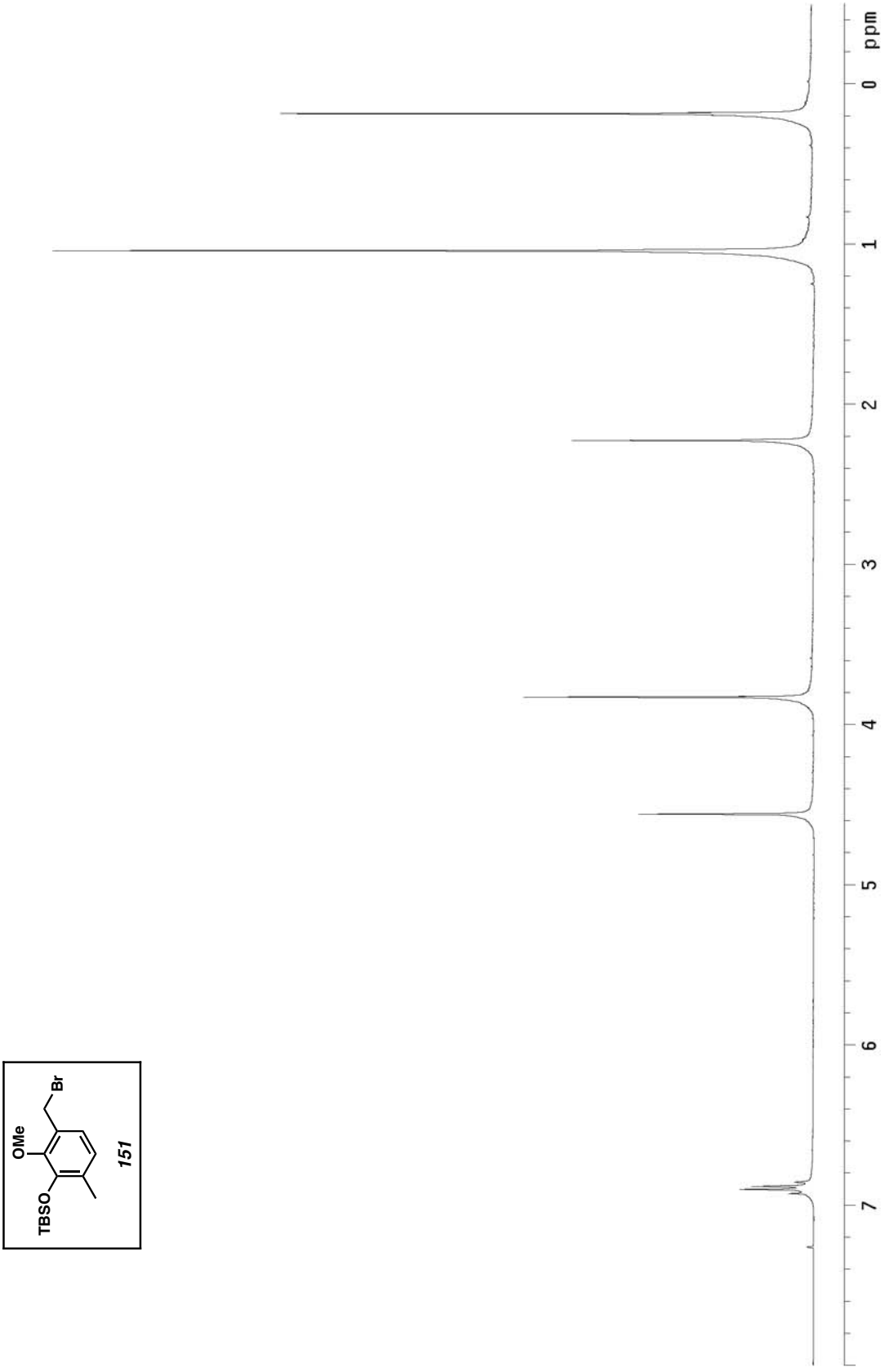


Figure A2.25 ^{1}H NMR of compound **151** (300 MHz, $CDCl_3$)

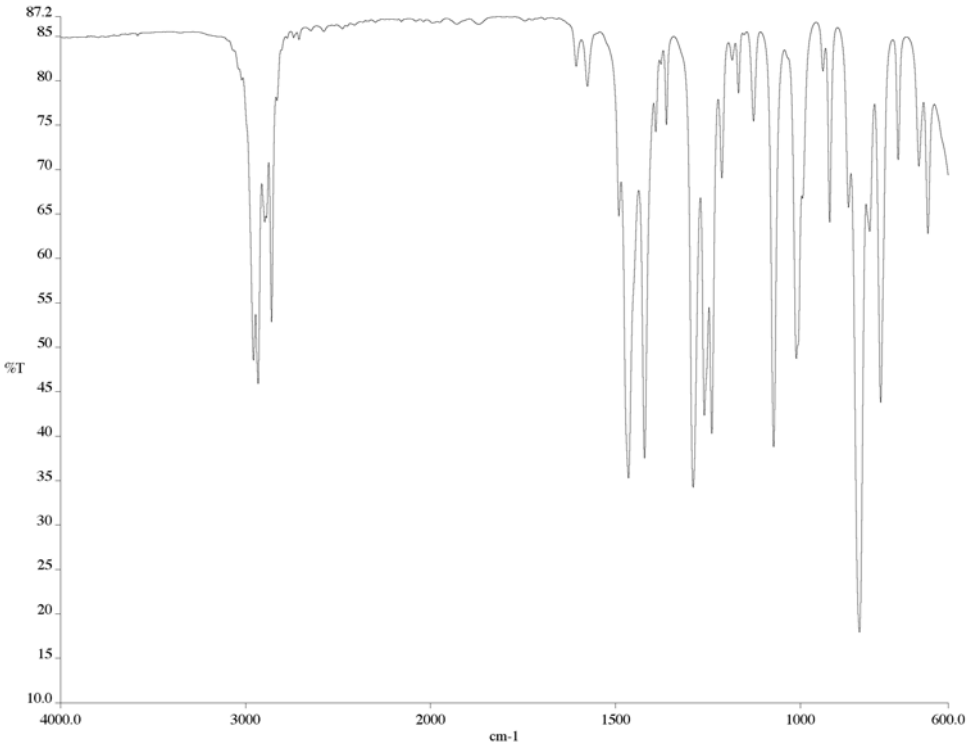


Figure A2.26 IR of compound **151** (NaCl/film)

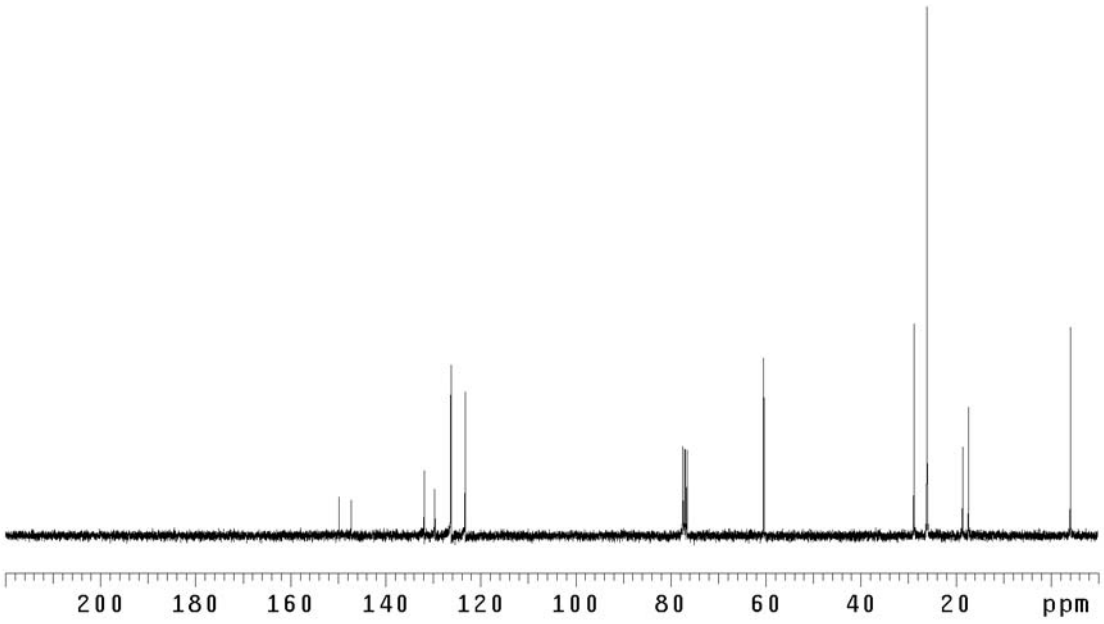


Figure A2.27 ^{13}C NMR of compound **151** (75 MHz, $CDCl_3$)

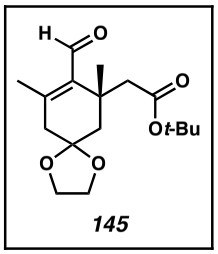


Figure A2.28 ^{1}H NMR of compound **145** (300 MHz, $CDCl_3$)

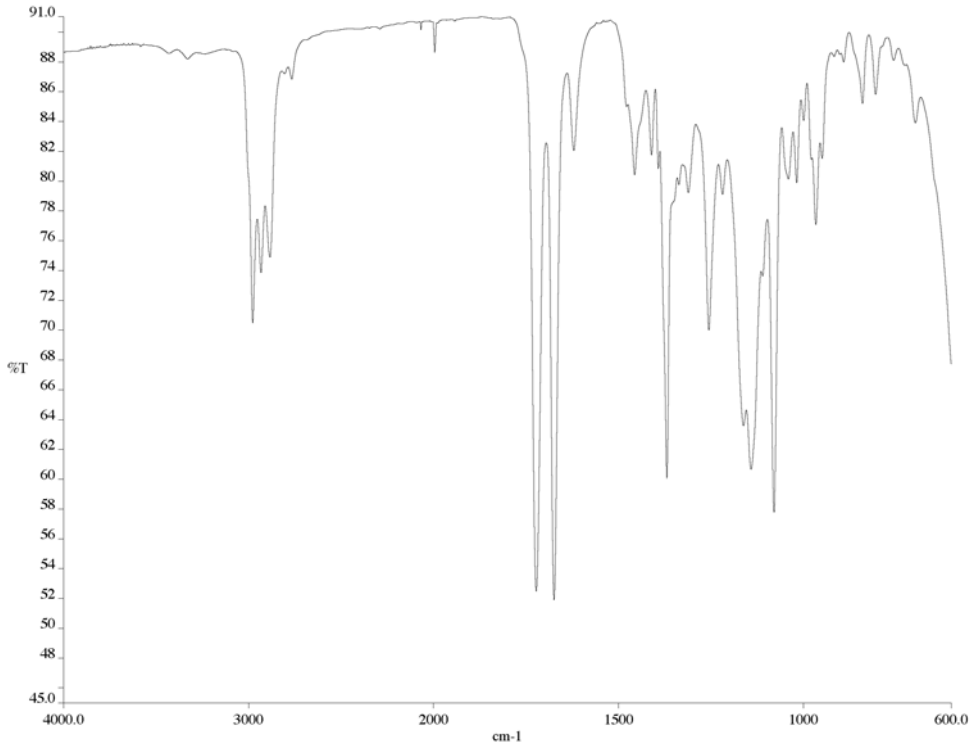


Figure A2.29 IR of compound **145** (NaCl/film)

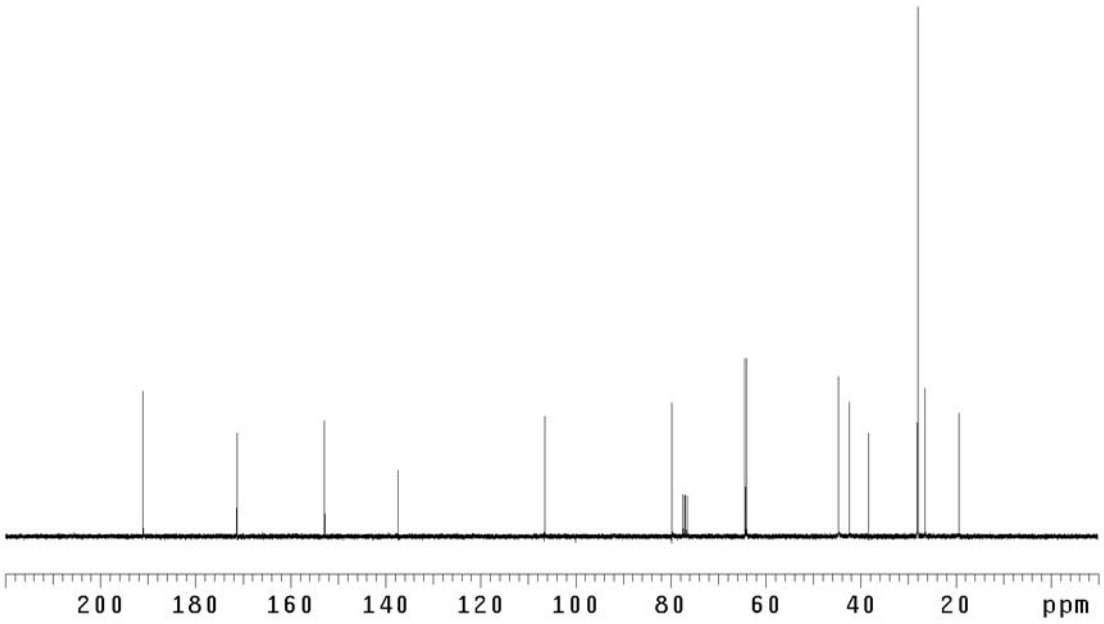


Figure A2.30 ^{13}C NMR of compound **145** (75 MHz, $CDCl_3$)

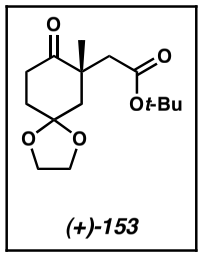


Figure A2.31 ^{1}H NMR of compound **(+)-153** (300 MHz, $CDCl_3$)

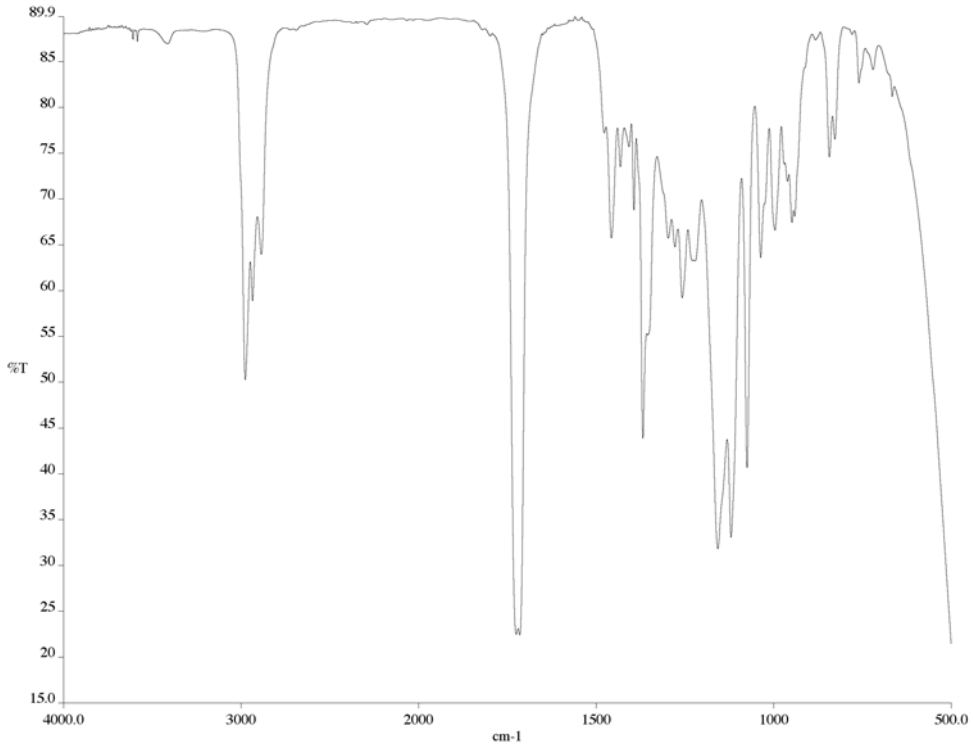


Figure A2.32 IR of compound **(+)-153** (NaCl/film)

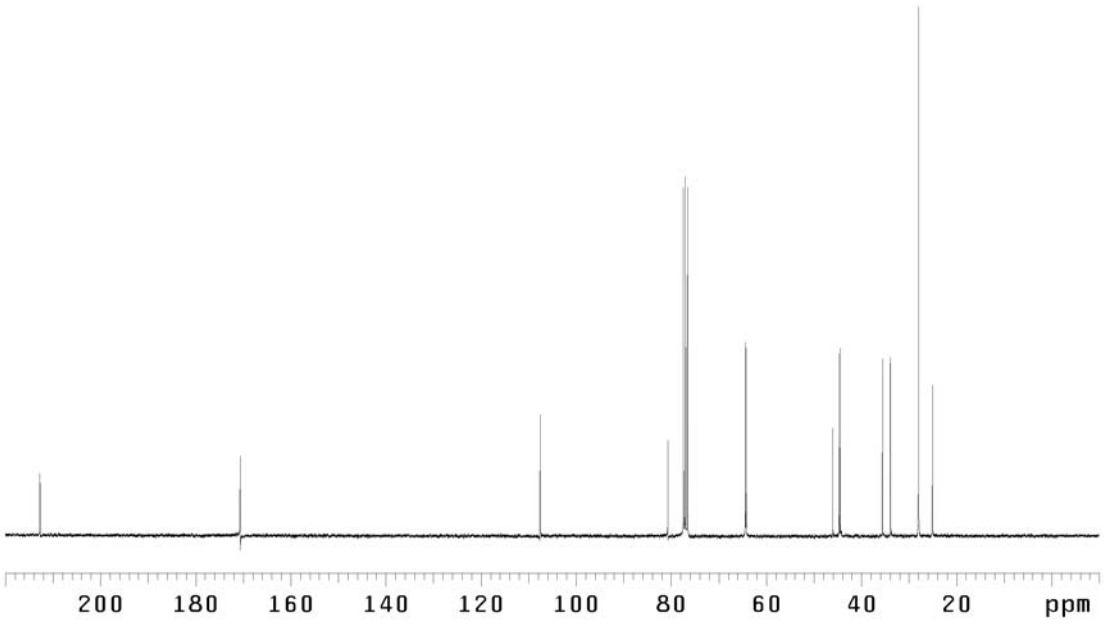
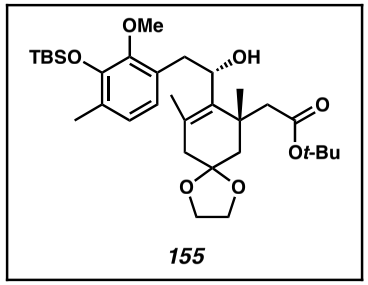


Figure A2.33 ^{13}C NMR of compound **(+)-153** (75 MHz, $CDCl_3$)



155

Figure A2.34 ^{1}H NMR of compound **155** (300 MHz, $CDCl_3$)

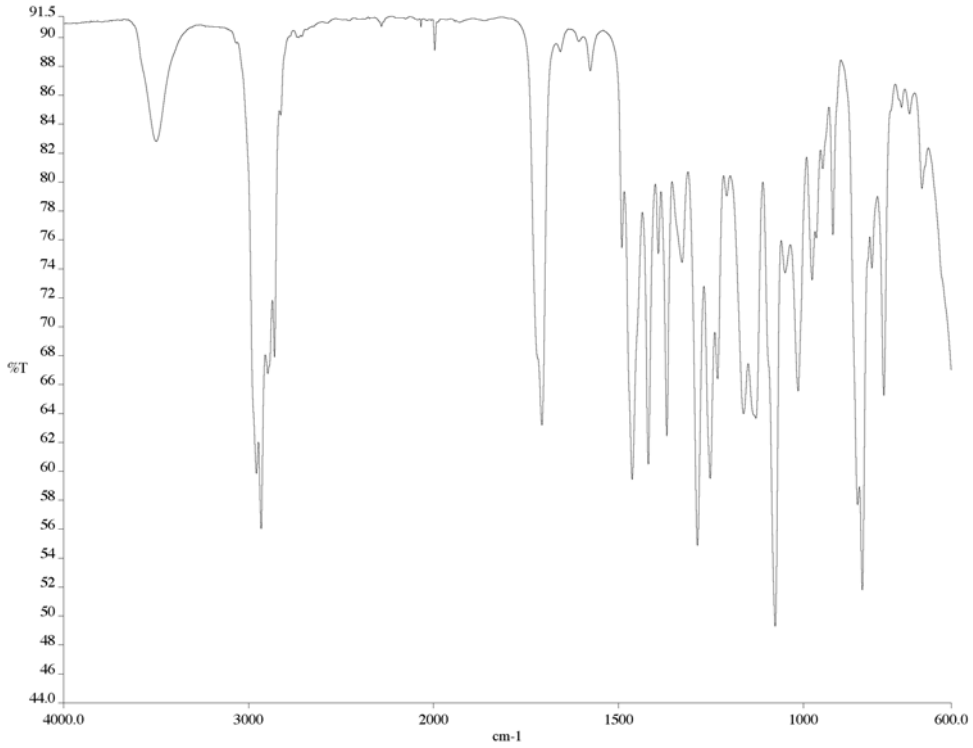


Figure A2.35 IR of compound **155** (NaCl/film)

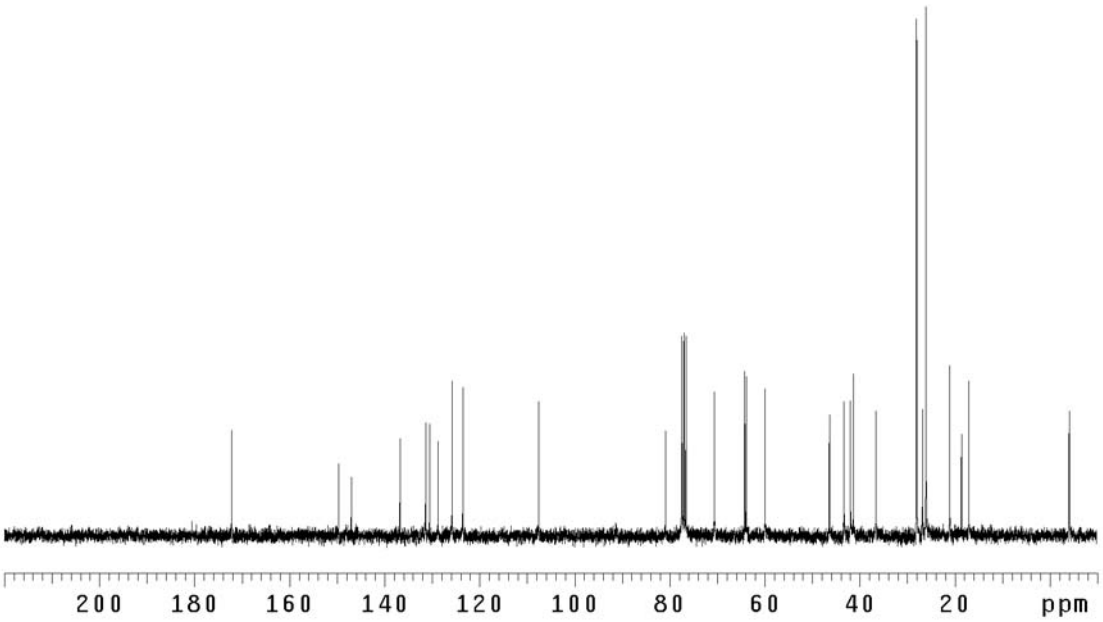


Figure A2.36 ^{13}C NMR of compound **155** (75 MHz, $CDCl_3$)

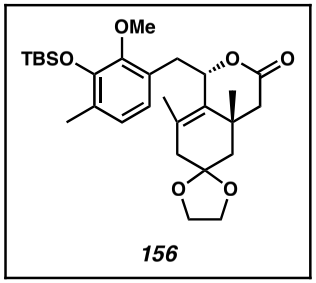


Figure A2.37 ^{1}H NMR of compound **156** (300 MHz, $CDCl_3$)

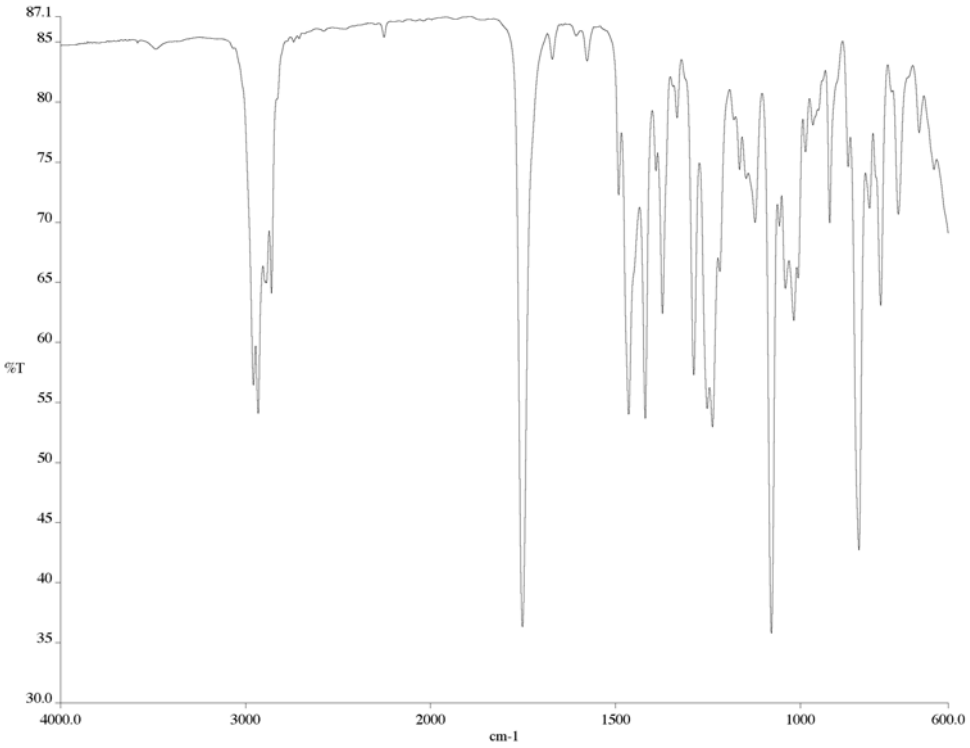


Figure A2.38 IR of compound **156** (NaCl/film)

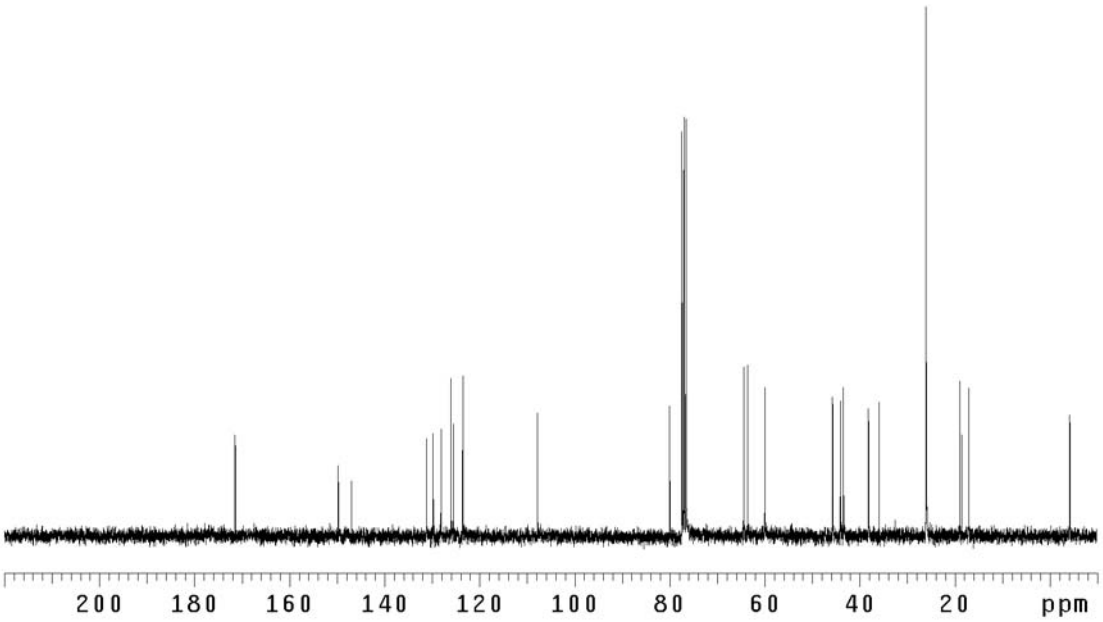


Figure A2.39 ^{13}C NMR of compound **156** (75 MHz, $CDCl_3$)

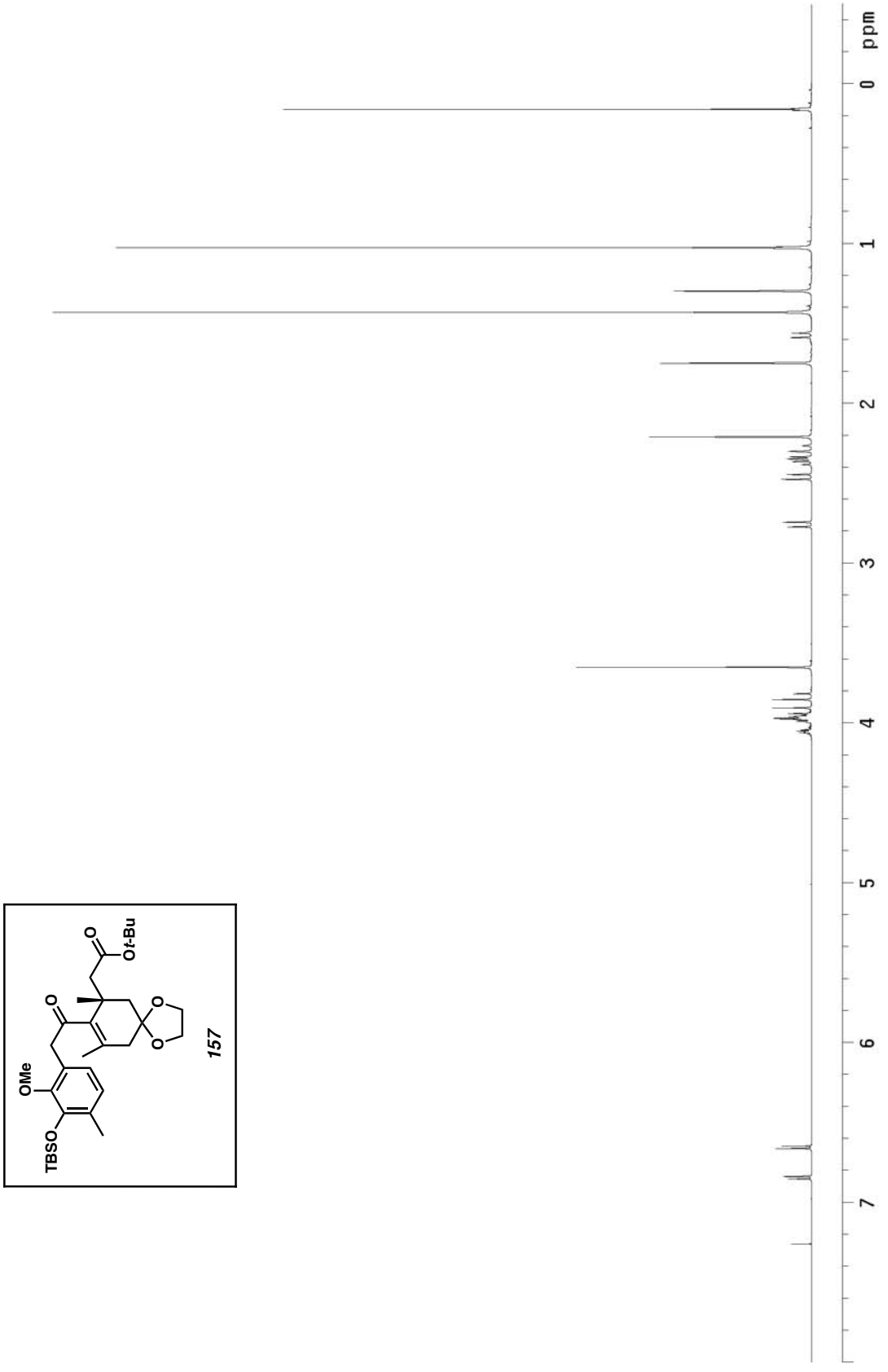


Figure A2.40 ^{1}H NMR of compound **157** (500 MHz, $CDCl_3$)

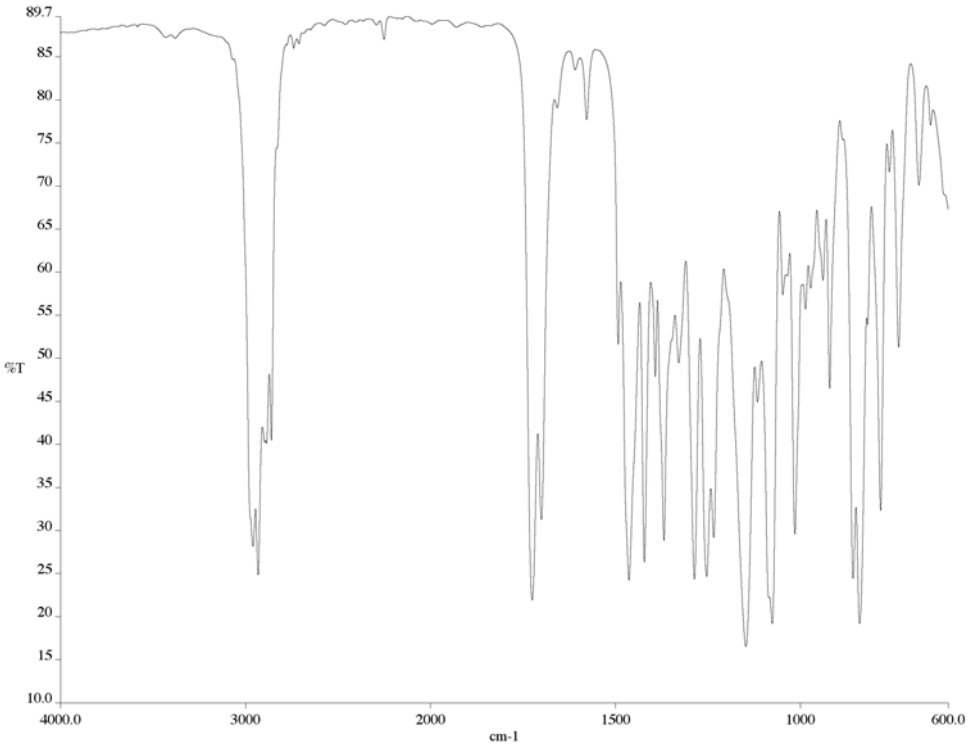


Figure A2.41 IR of compound **157** (NaCl/film)

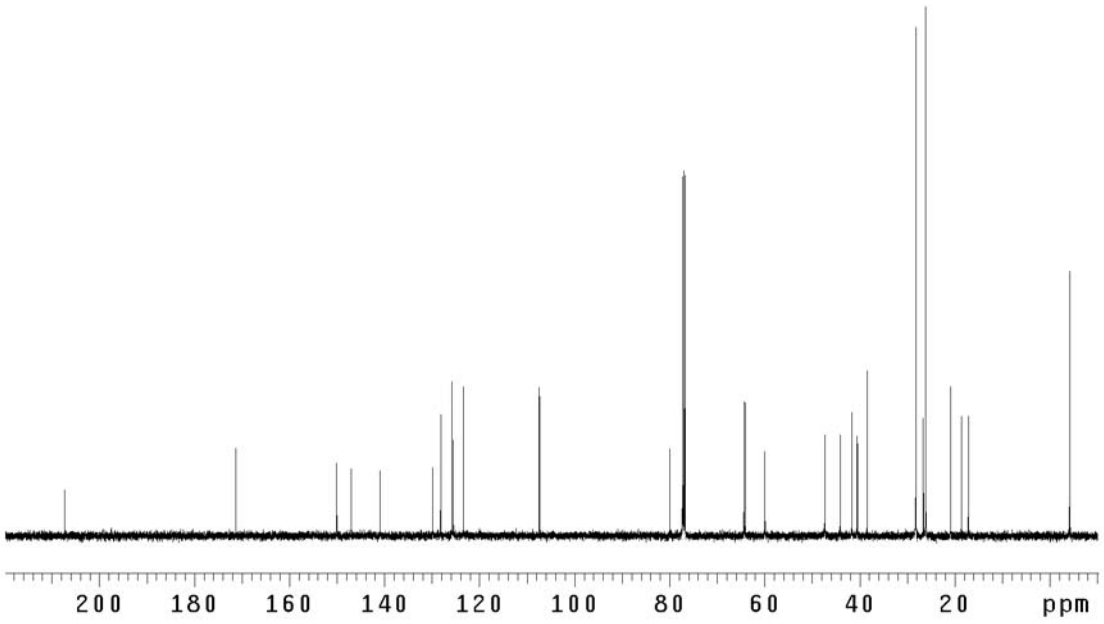


Figure A2.42 ^{13}C NMR of compound **157** (125 MHz, $CDCl_3$)

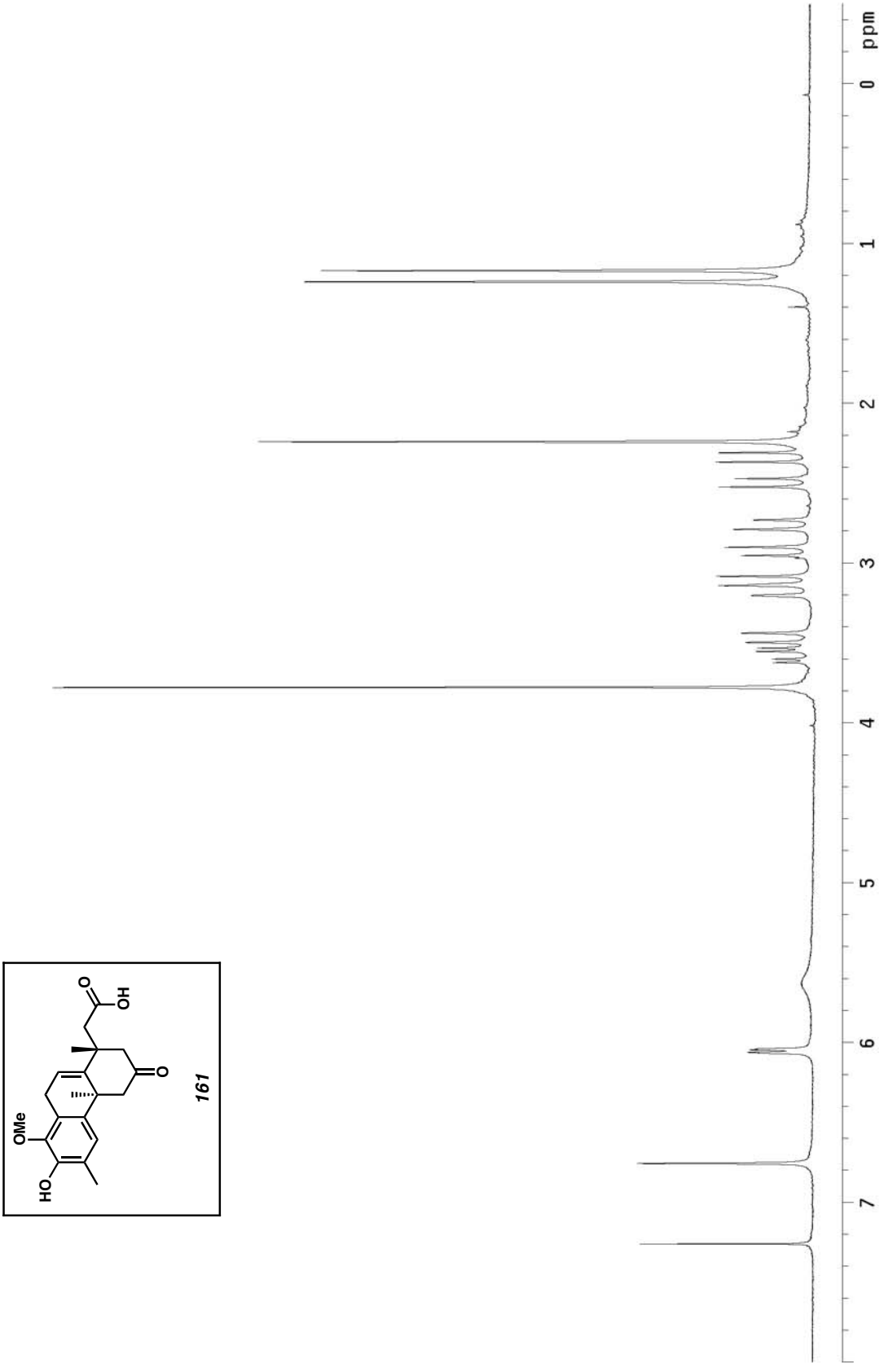


Figure A2.43 ^{1}H NMR of compound **161** (300 MHz, $CDCl_3$)

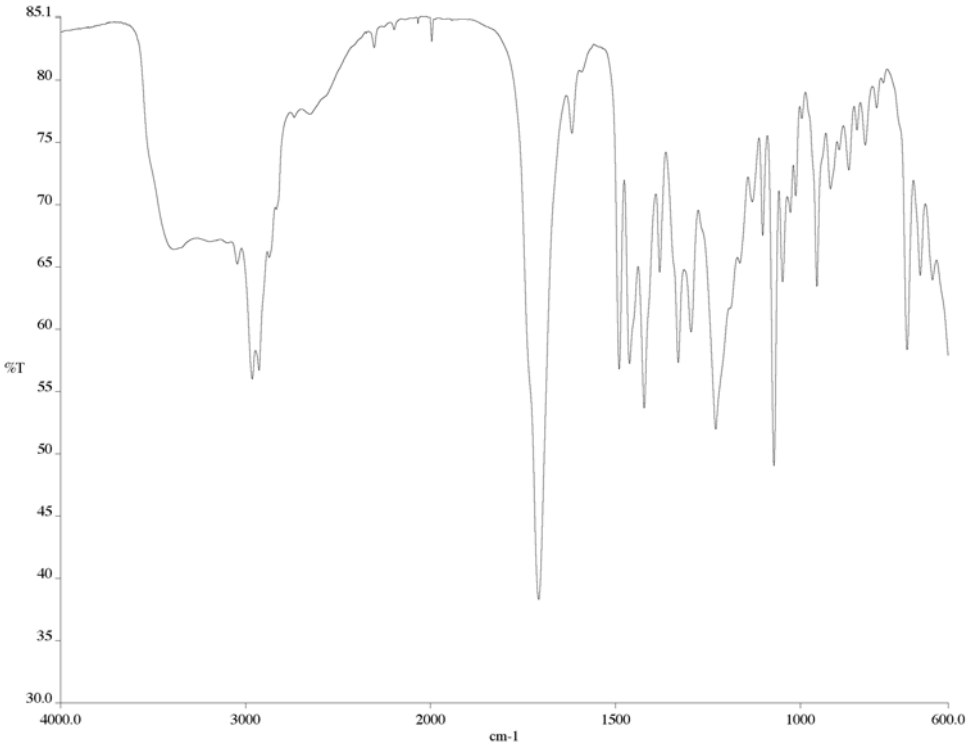


Figure A2.44 IR of compound **161** (NaCl/film)

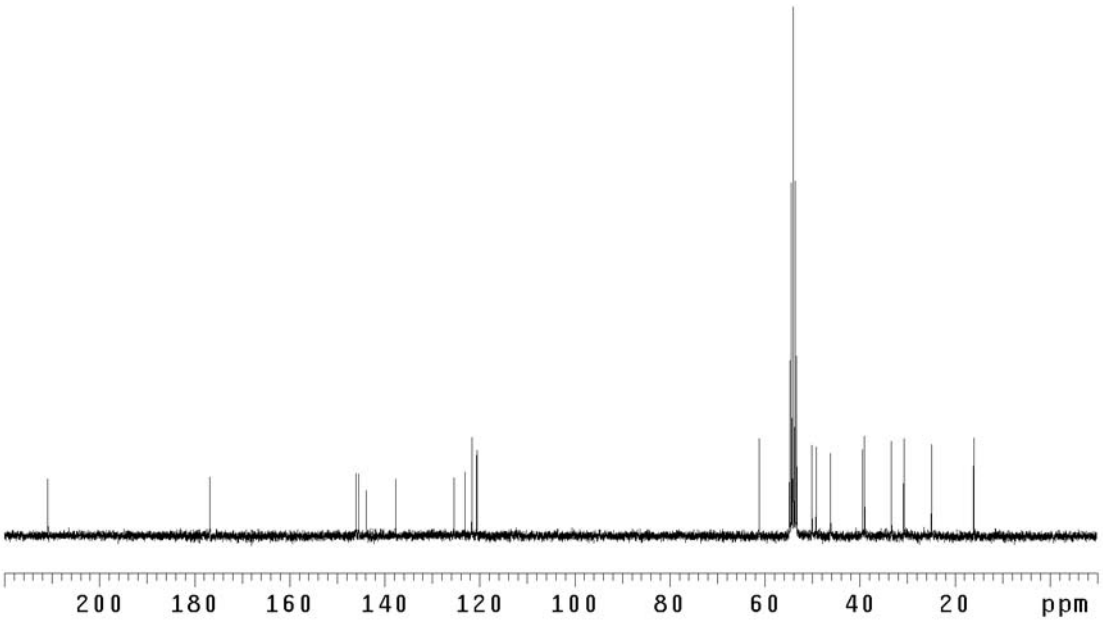
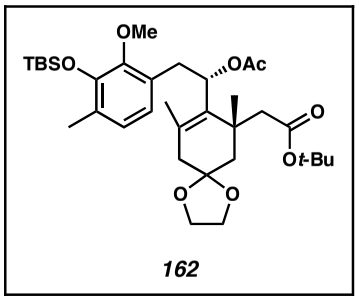


Figure A2.45 ^{13}C NMR of compound **161** (75 MHz, CD_2Cl_2)



162

Figure A2.46 ^{1}H NMR of compound **162** (500 MHz, $CDCl_3$)

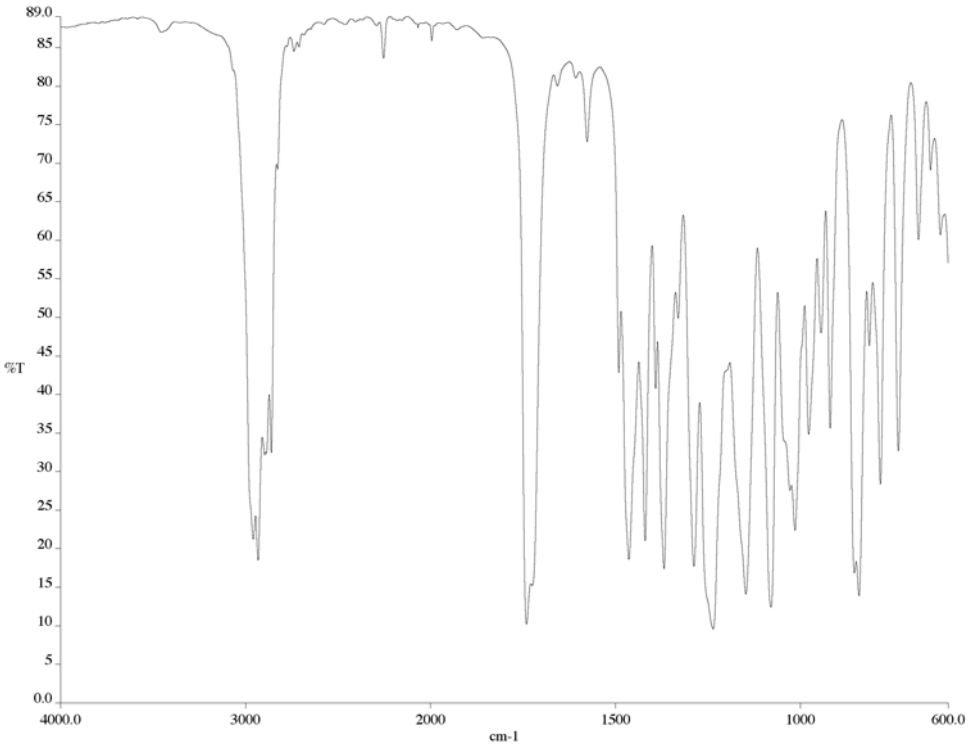


Figure A2.47 IR of compound **162** (NaCl/film)

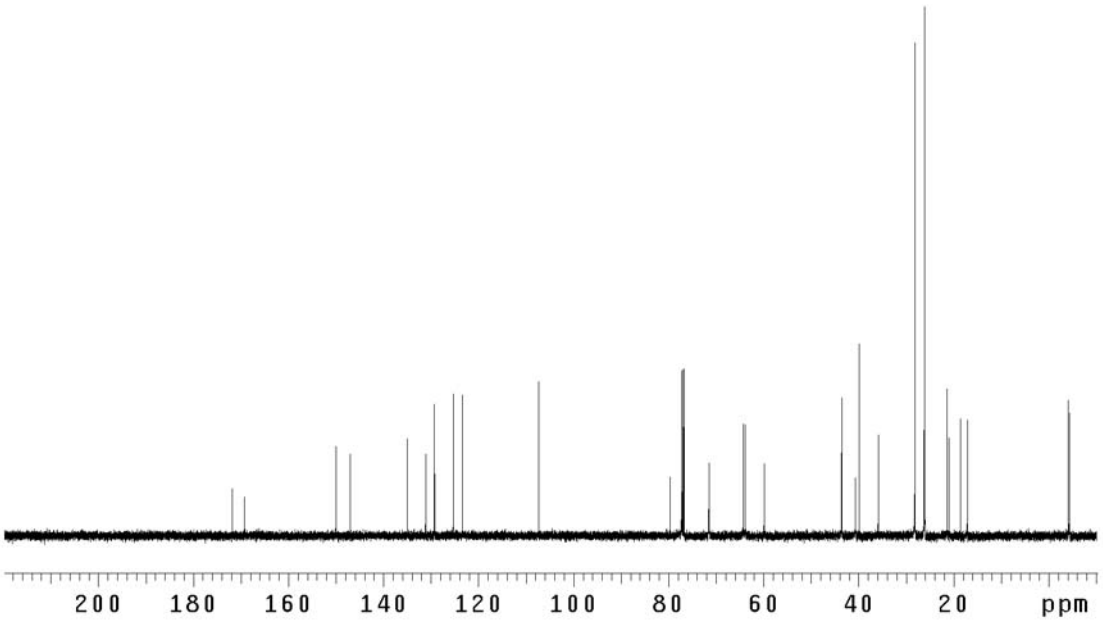
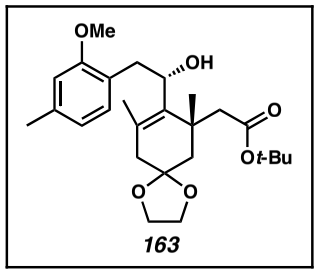


Figure A2.48 ^{13}C NMR of compound **162** (125 MHz, $CDCl_3$)



163

Figure A2.49 ^{1}H NMR of compound **163** (300 MHz, $CDCl_3$)

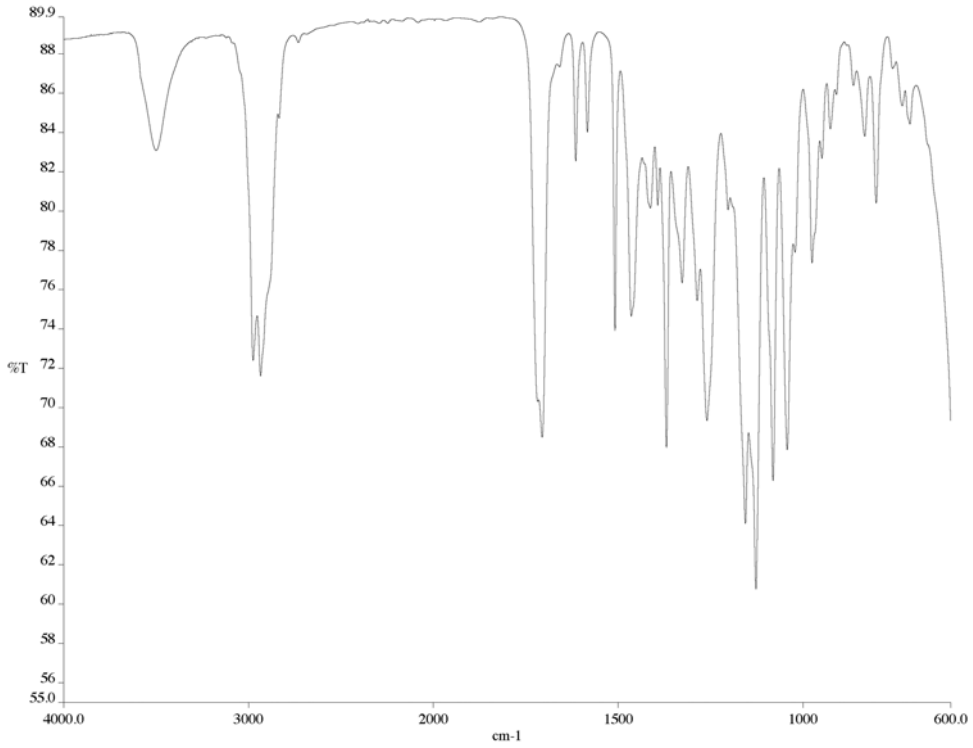


Figure A2.50 IR of compound **163** (NaCl/film)

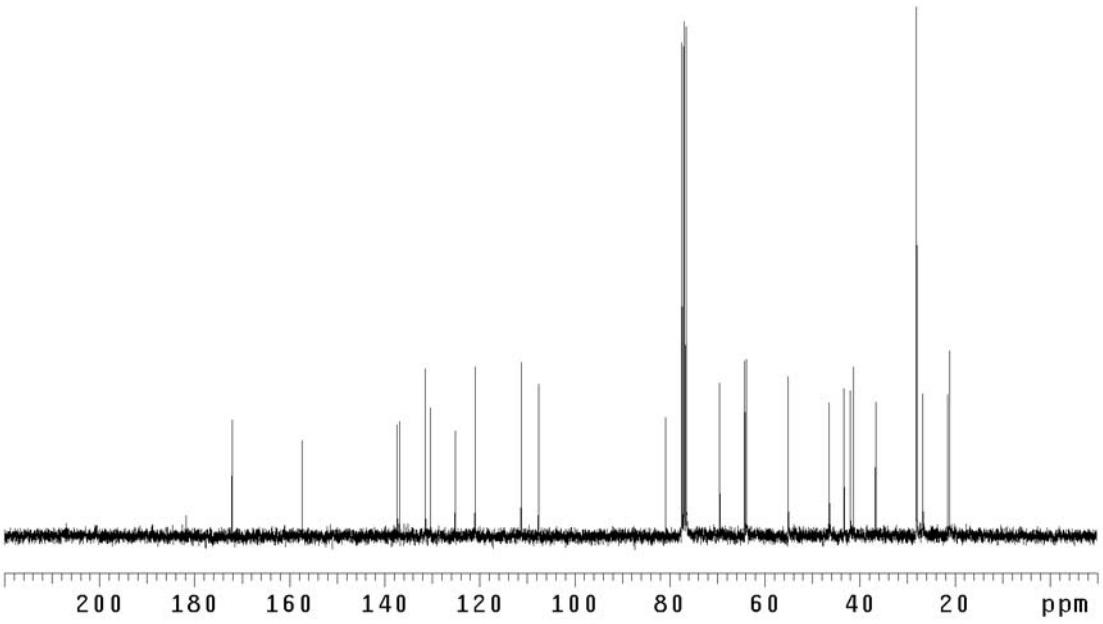


Figure A2.51 ^{13}C NMR of compound **163** (75 MHz, $CDCl_3$)

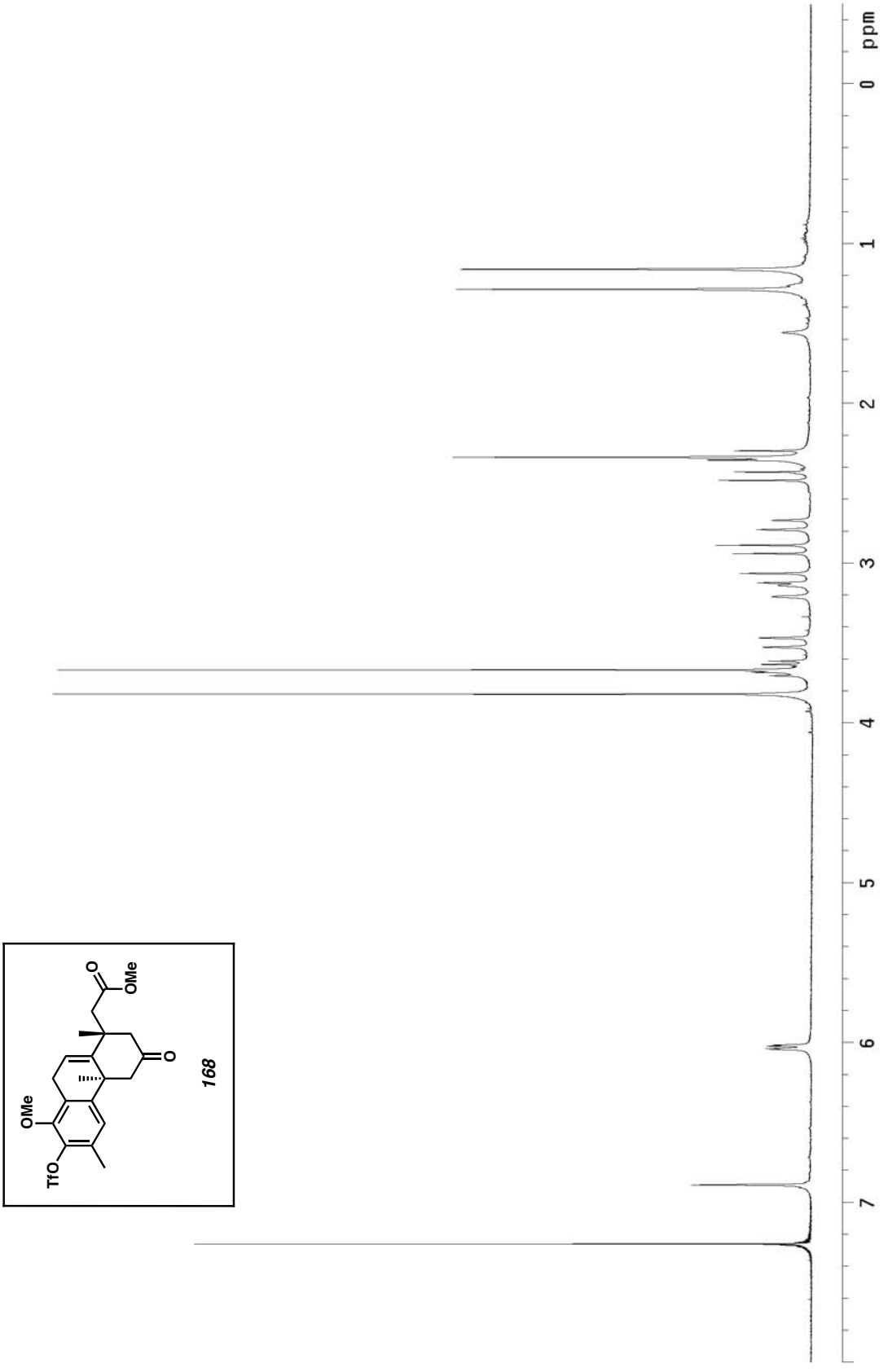


Figure A2.52 ^{1}H NMR of compound **168** (300 MHz, $CDCl_3$)

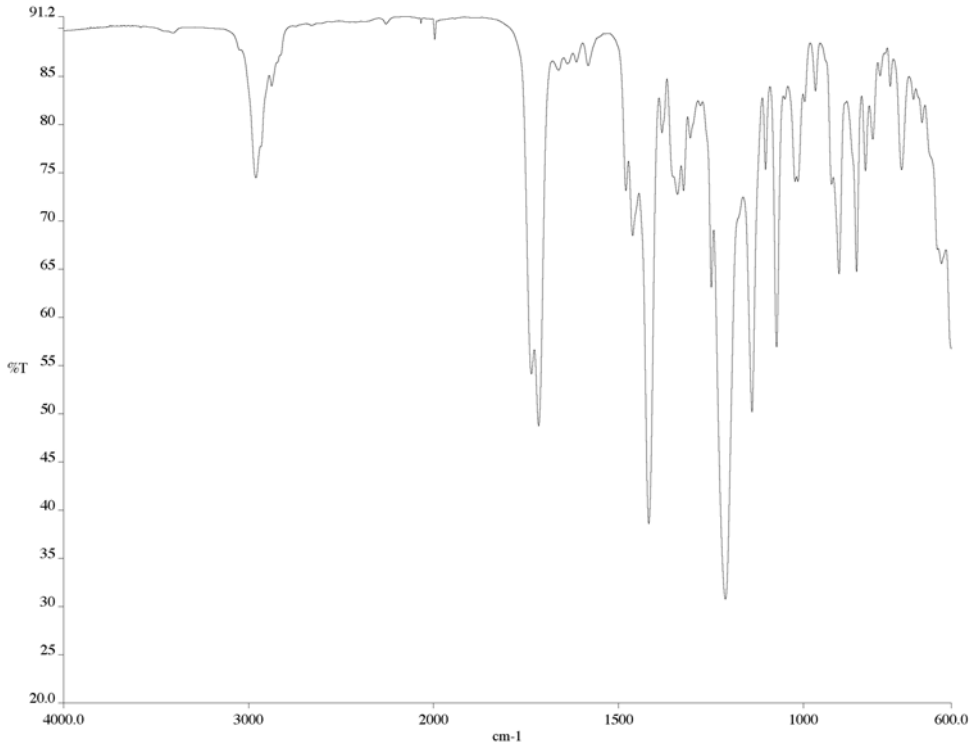


Figure A2.53 IR of compound **168** (NaCl/film)

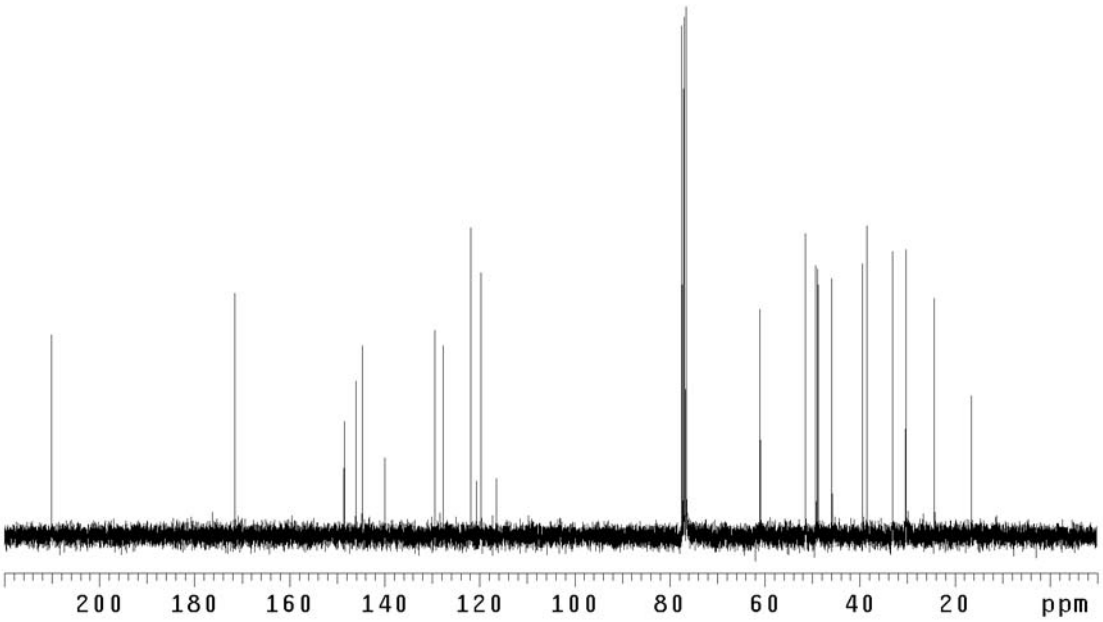


Figure A2.54 ^{13}C NMR of compound **168** (75 MHz, $CDCl_3$)

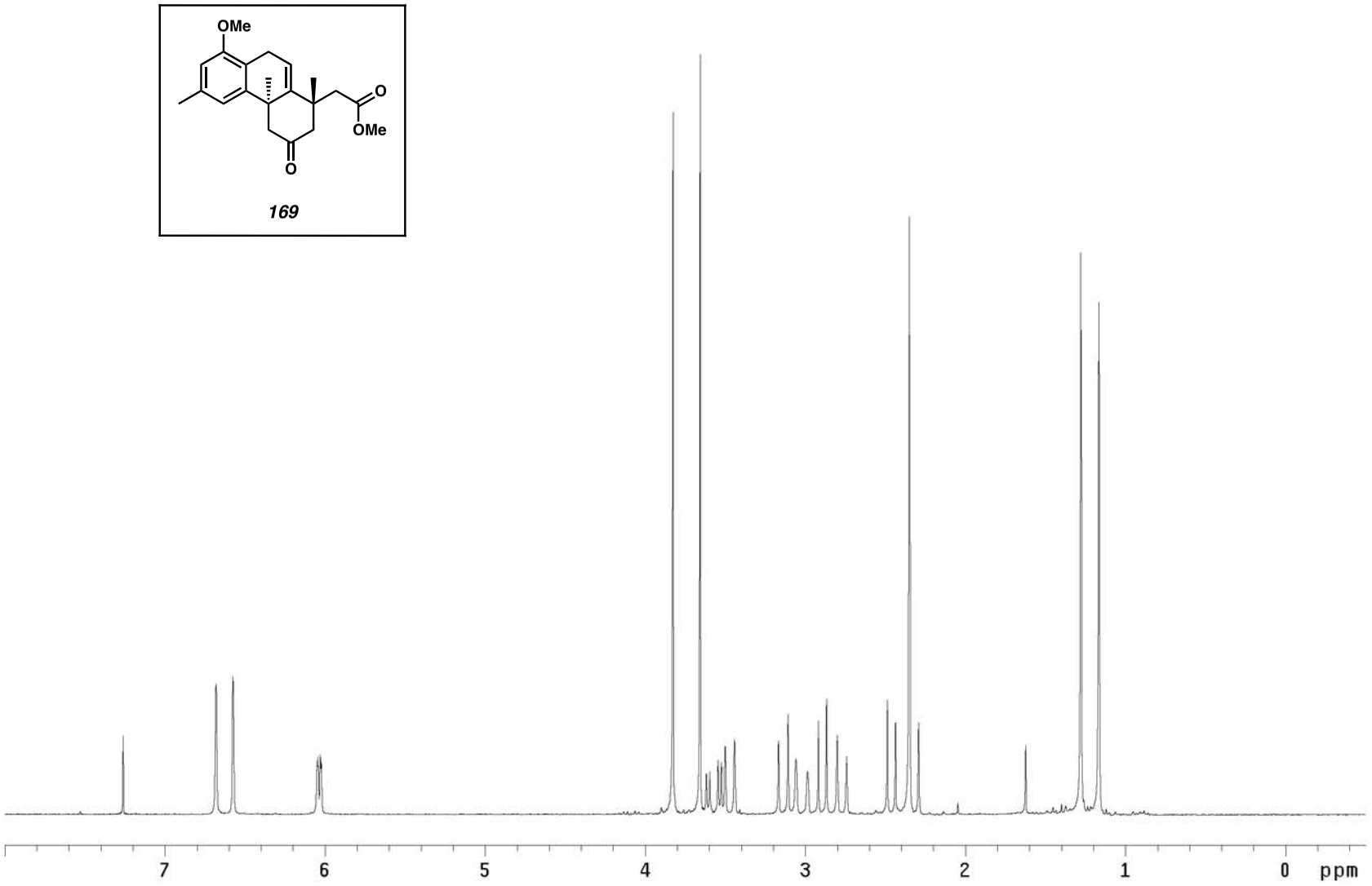


Figure A2.55 ^{1}H NMR of compound **169** (300 MHz, $CDCl_3$)

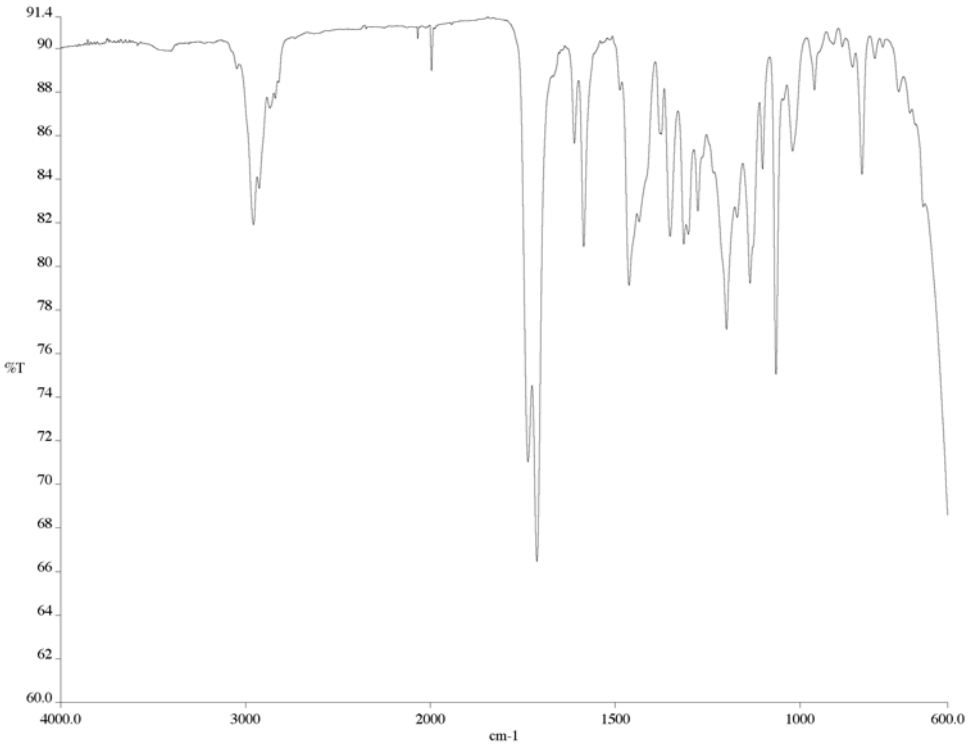


Figure A2.56 IR of compound **169** (NaCl/film)

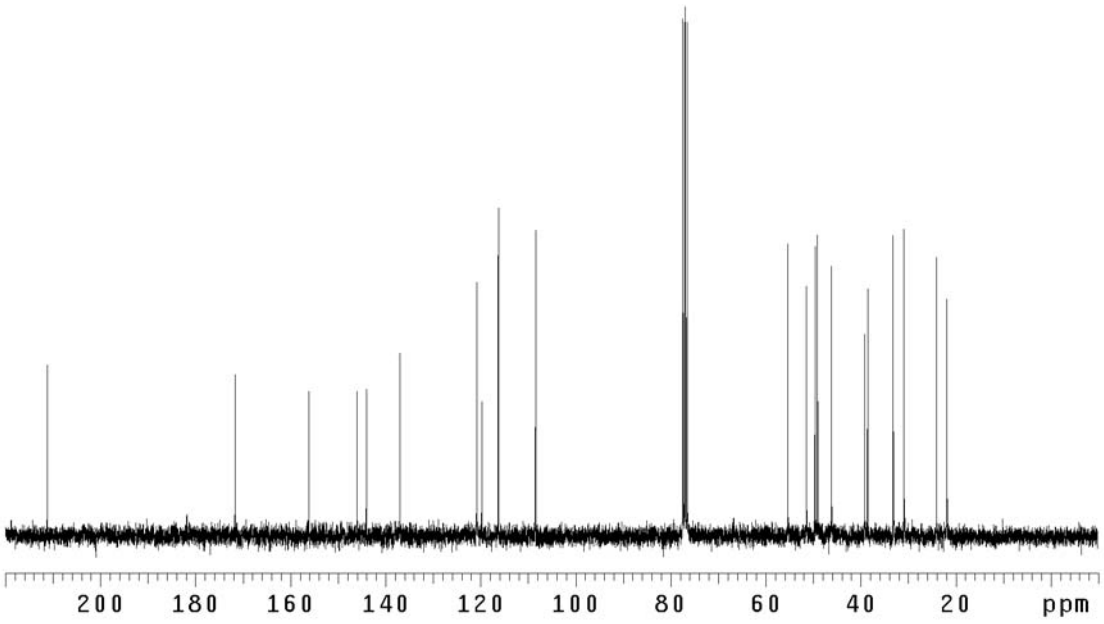
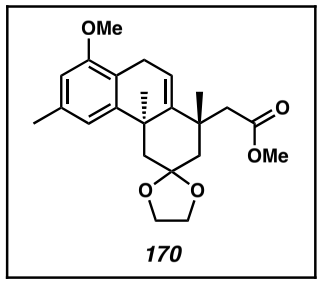


Figure A2.57 ^{13}C NMR of compound **169** (75 MHz, $CDCl_3$)



170

Figure A2.58 ^{1}H NMR of compound **170** (300 MHz, $CDCl_3$)

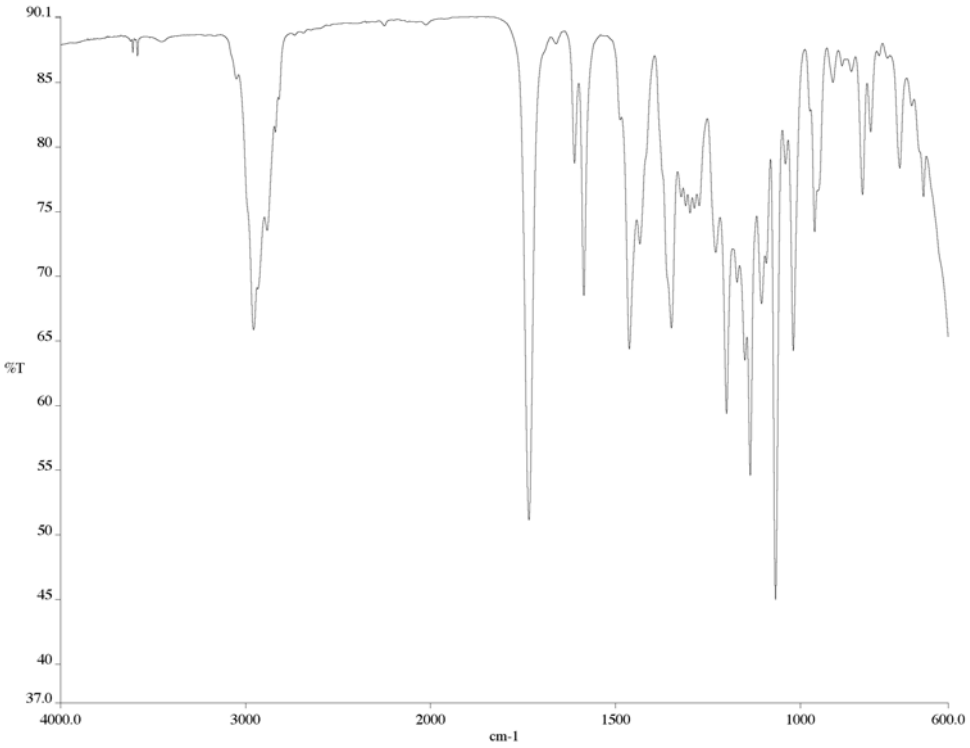


Figure A2.59 IR of compound **170** (NaCl/film)

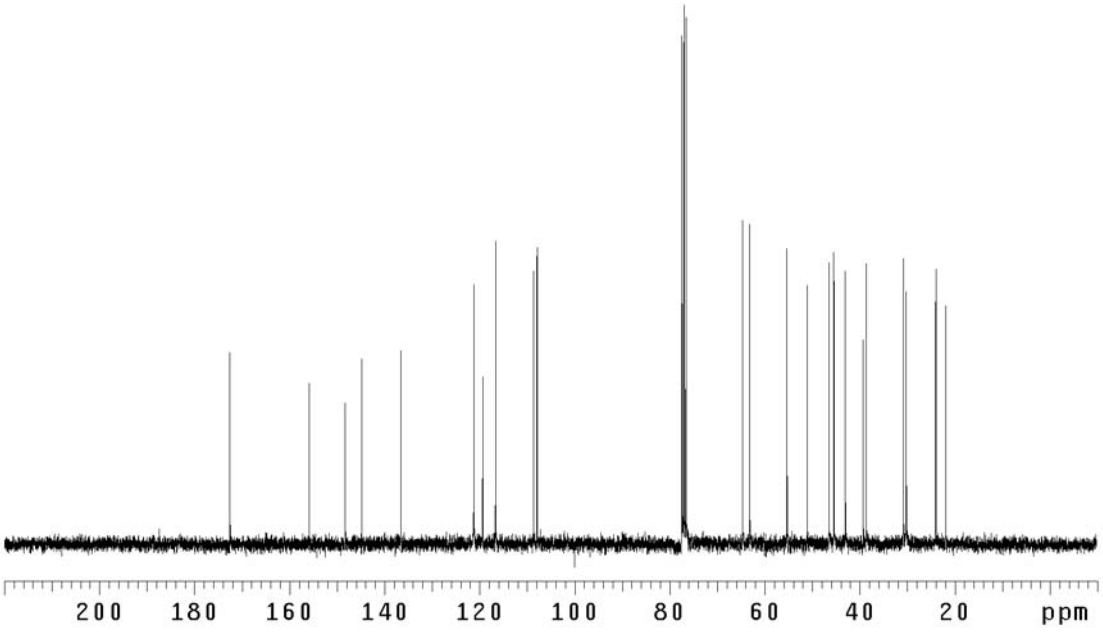


Figure A2.60 ^{13}C NMR of compound **170** (75 MHz, $CDCl_3$)

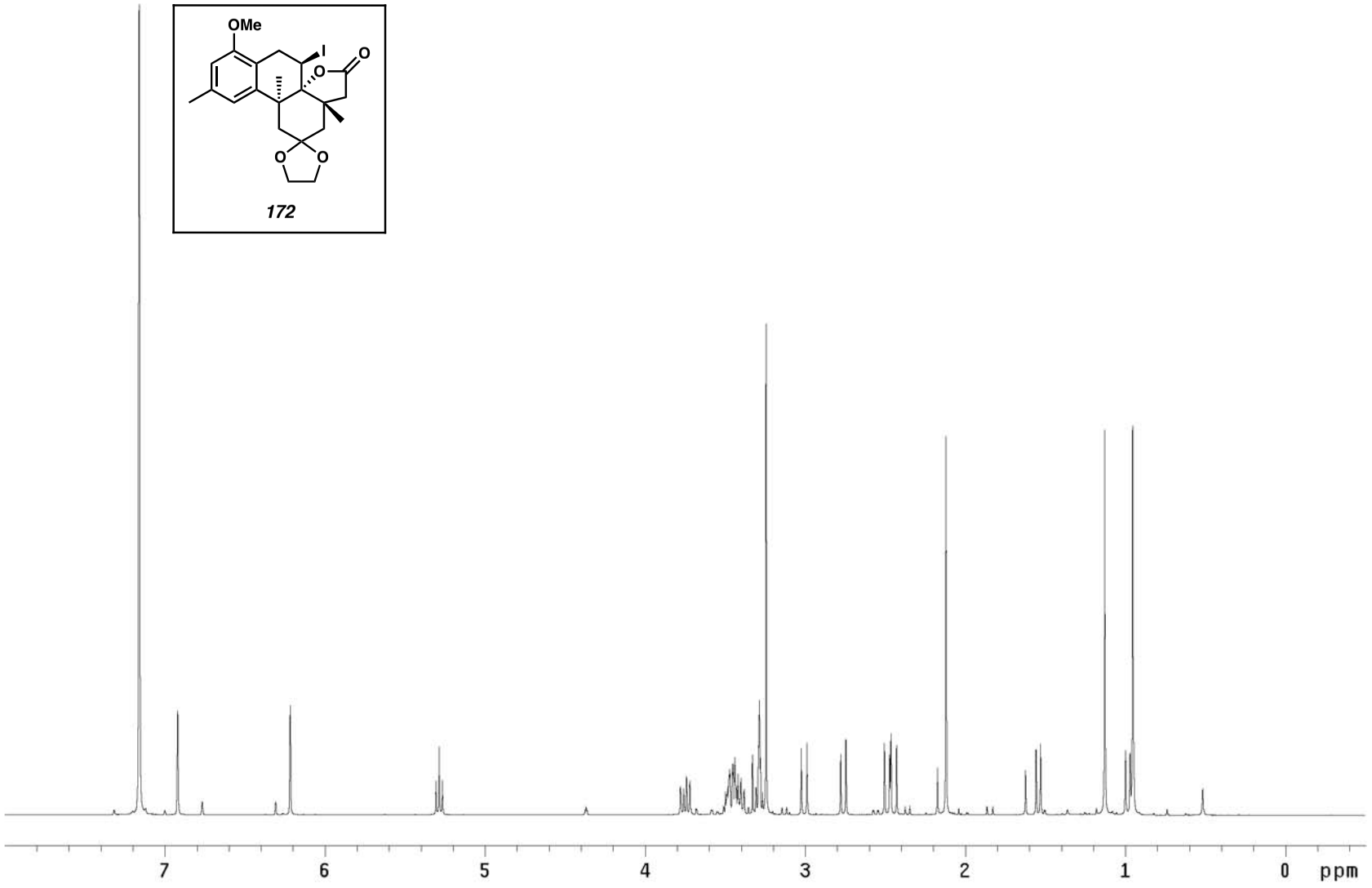


Figure A2.61 ^{1}H NMR of compound **172** (500 MHz, C_6D_6)

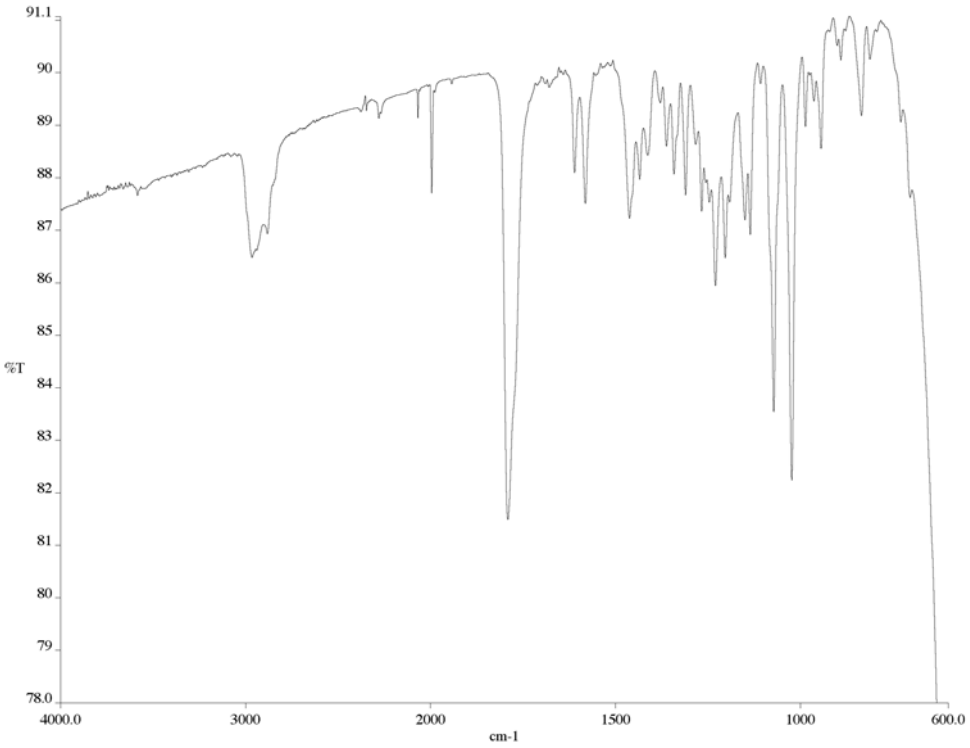


Figure A2.62 IR of compound **172** (NaCl/film)

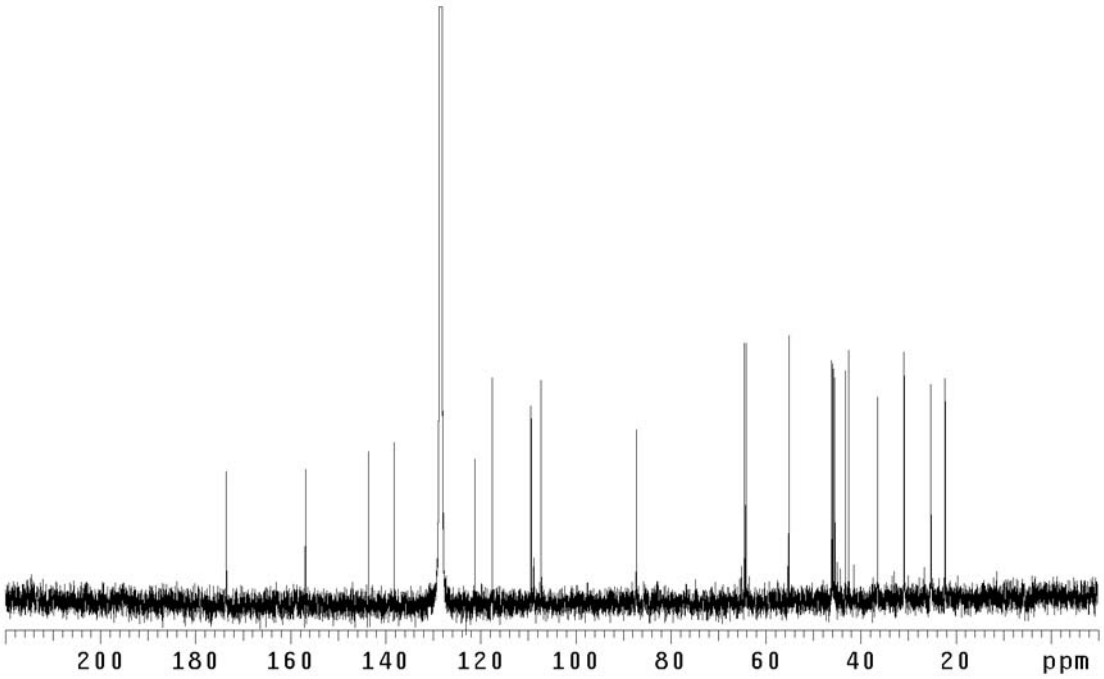


Figure A2.63 ^{13}C NMR of compound **172** (125 MHz, C_6D_6)

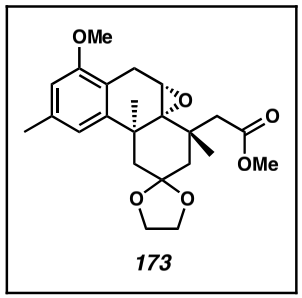


Figure A2.64 ^{1}H NMR of compound **173** (500 MHz, $CDCl_3$)

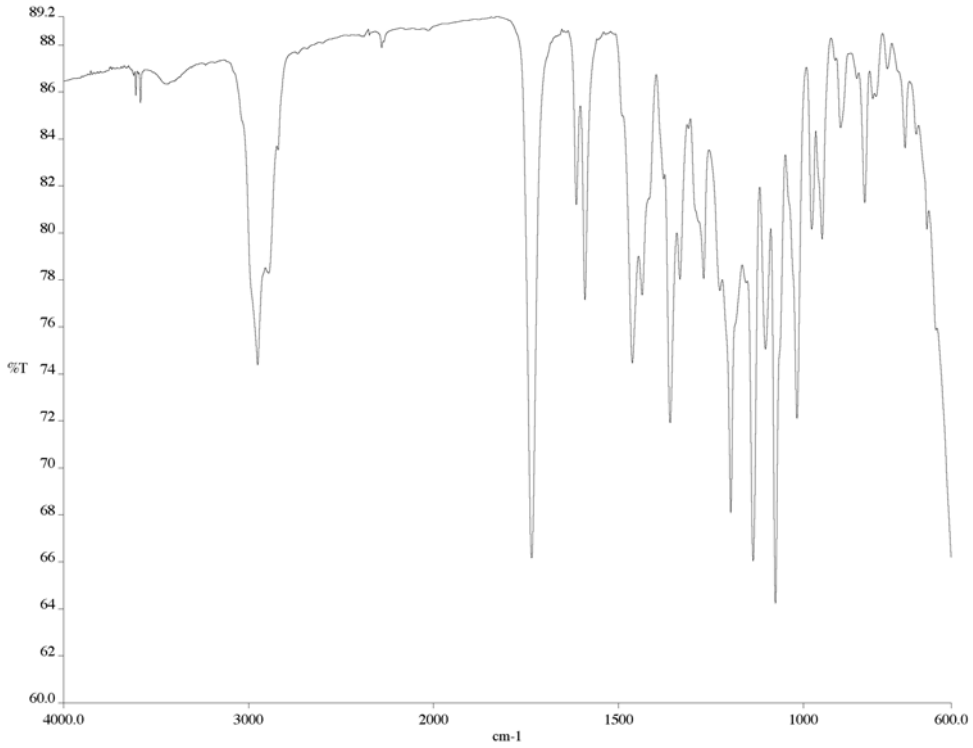


Figure A2.65 IR of compound **173** (NaCl/film)

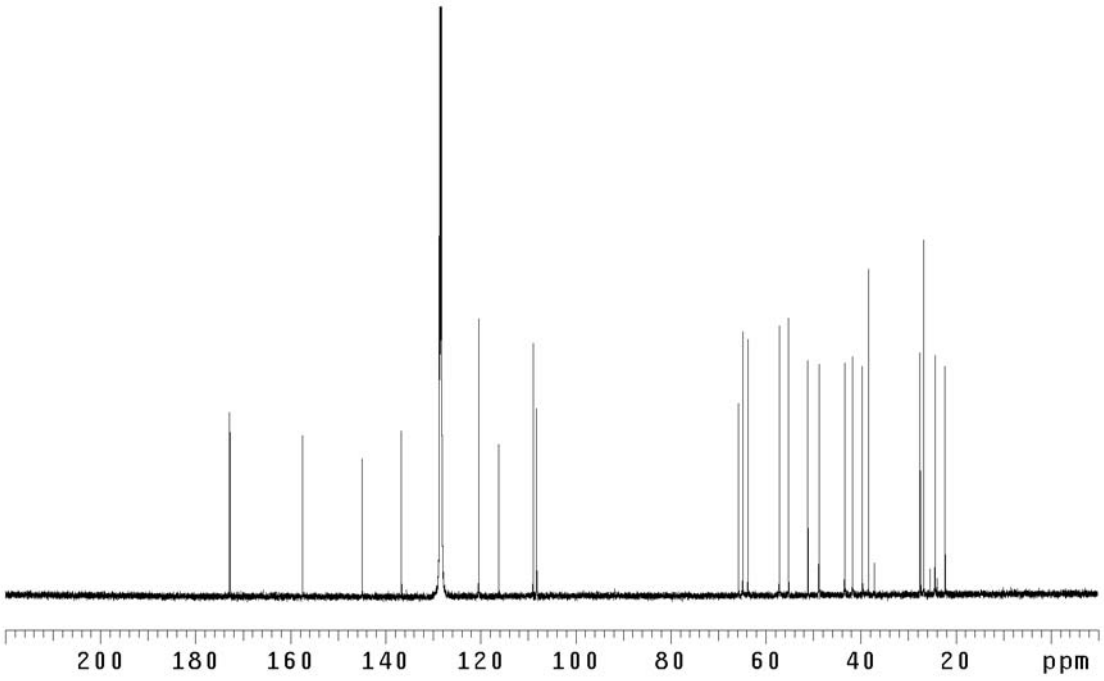


Figure A2.66 ^{13}C NMR of compound **173** (125 MHz, C_6D_6)

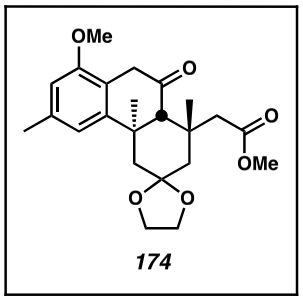


Figure A2.67 ^{1}H NMR of compound **174** (500 MHz, $CDCl_3$)

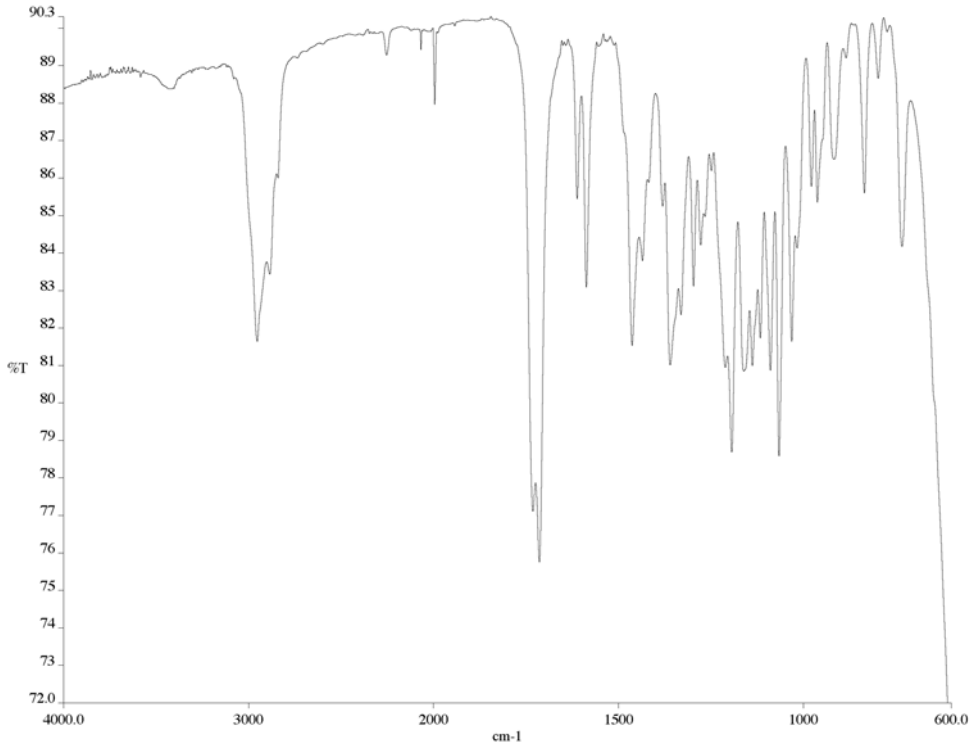


Figure A2.68 IR of compound **174** (NaCl/film)

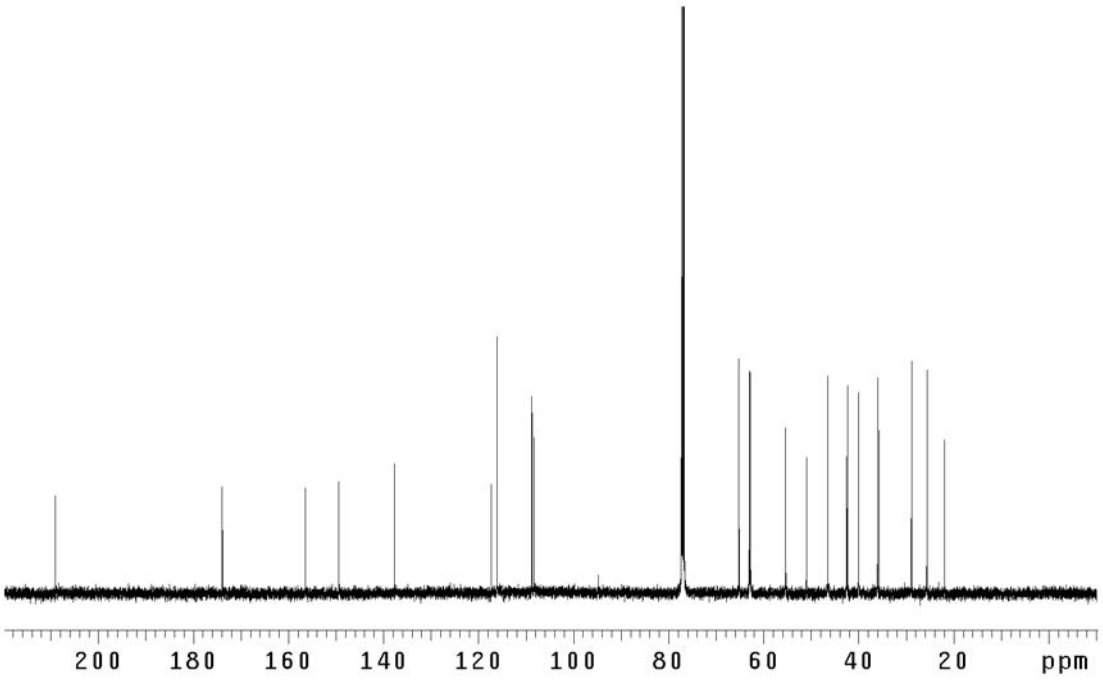
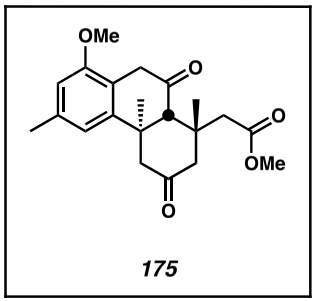


Figure A2.69 ^{13}C NMR of compound **174** (125 MHz, $CDCl_3$)



175

Figure A2.70 ^{1}H NMR of compound **175** (500 MHz, $CDCl_3$)

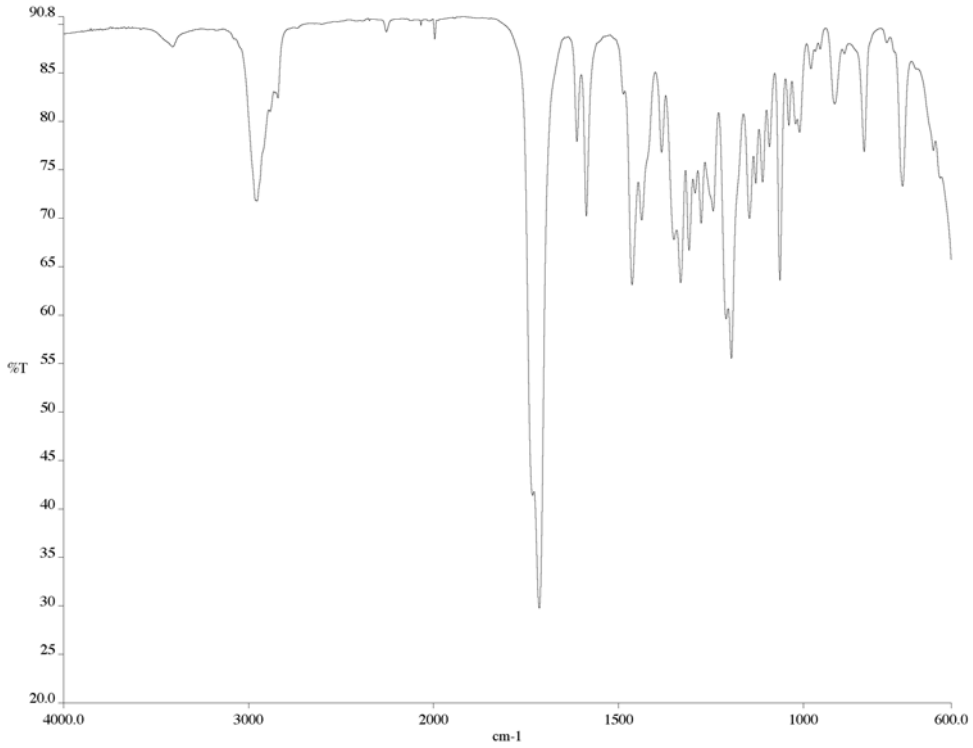


Figure A2.71 IR of compound **175** (NaCl/film)

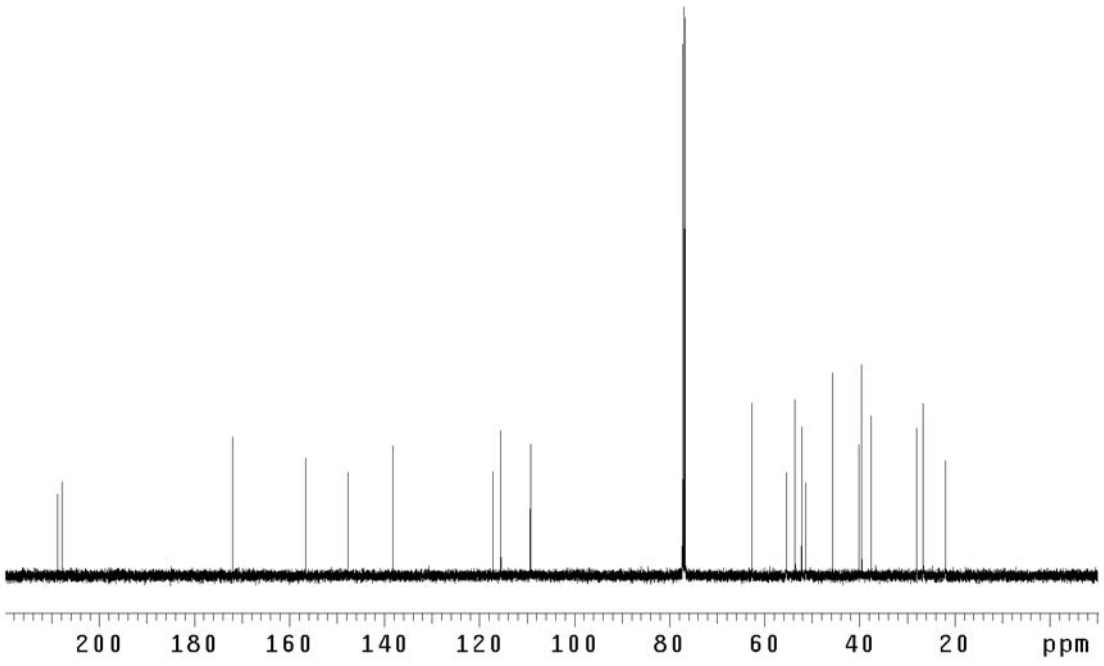


Figure A2.72 ^{13}C NMR of compound **175** (125 MHz, $CDCl_3$)

APPENDIX THREE

X-Ray Crystallographic Data Relevant to Chapter Two

CALIFORNIA INSTITUTE OF TECHNOLOGY

BECKMAN INSTITUTE

X-RAY CRYSTALLOGRAPHY LABORATORY

Crystal Structure Analysis of:

Ketone viii (DCB03)

(CCDC 172324)

Contents

Table 1. Crystal data
Table 2. Atomic coordinates
Table 3. Selected bond distances and angles
Table 4. Anisotropic displacement parameters
Table 5. Hydrogen atomic coordinates

Figure A3.1 Representation of Ketone **viii**

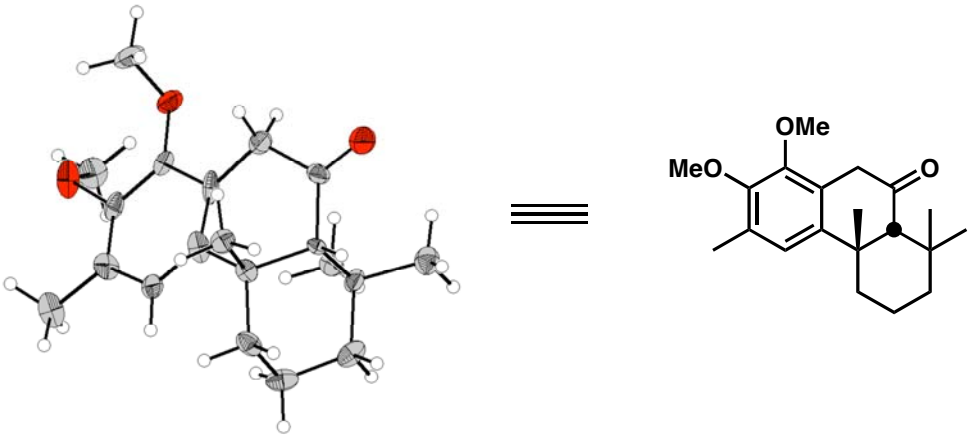


Table 1. Crystal data and structure refinement for DCB03 (CCDC 172324).

Empirical formula	$C_{20}H_{28}O_3$
Formula weight	316.42
Crystallization Solvent	Hexanes
Crystal Habit	Block
Crystal size	0.30 x 0.22 x 0.19 mm^3
Crystal color	Colorless

Data Collection

Preliminary Photos	Rotation
Type of diffractometer	CCD area detector
Wavelength	0.71073 Å MoKα
Data Collection Temperature	98(2) K
θ range for 9714 reflections used in lattice determination	2.60 to 28.29°
Unit cell dimensions	a = 7.900(3) Å b = 8.104(5) Å β= 97.212(6)° c = 13.664(4) Å
Volume	867.8(7) $Å^3$
Z	2
Crystal system	Monoclinic
Space group	$P2_1$
Density (calculated)	1.211 Mg/m^3
F(000)	344
Data collection program	Bruker SMART
θ range for data collection	2.93 to 28.38°
Completeness to θ = 28.38°	29.9 %
Index ranges	$-9 \le h \le 9$, $-10 \le k \le 10$, $-18 \le l \le 17$
Data collection scan type	ω scans at 7 ϕ settings
Data reduction program	Bruker SAINT v6.2
Reflections collected	4065
Independent reflections	4065 [R_{int}= 0.0000]
Absorption coefficient	0.080 mm^{-1}
Absorption correction	None
Max. and min. transmission	0.9854 and 0.9768

Table 1 (cont.)

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 1990)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Geometric positions
Structure refinement program	SHELXL-97 (Sheldrick, 1997)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	4065 / 1 / 215
Treatment of hydrogen atoms	Riding
Goodness-of-fit on F^2	0.983
Final R indices [$I>2\sigma(I)$, 2775 reflections]	R1 = 0.0513, *w*R2 = 0.0823
R indices (all data)	R1 = 0.0790, *w*R2 = 0.0900
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.001
Average shift/error	0.000
Absolute structure parameter	2(3)
Largest diff. peak and hole	0.110 and -0.108 e.Å^{-3}

Special Refinement Details

The crystals are twinned. The twinning is non-merohedral and therefore (since the reciprocal lattices don't overlap exactly) the data required special handling. An orientation matrix was identified for each twin and each matrix was used to integrate the data for each twin component. The two resulting data sets were merged into one set that contained reflections unique to each twin component and reflections exactly overlapping between the two twin components. For component one there were 3057 exact overlaps, 14021 partial overlaps and 538 unique, for component two the corresponding numbers are 3060, 14136 and 505. The data set used for least squares refinement contained only 696 reflections after merging equivalents from both twin components into a single reflection..

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

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

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for DCB03 (CCDC 172324). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
O(1)	5945(12)	3813(7)	2029(5)	33(1)
O(2)	3847(9)	5388(4)	564(3)	34(1)
O(4)	4869(8)	-122(3)	4754(2)	37(1)
C(1)	4219(13)	3657(8)	2004(6)	16(2)
C(2)	3094(15)	4363(9)	1223(8)	24(2)
C(3)	1350(19)	4257(9)	1208(7)	26(2)
C(4)	745(12)	3298(5)	1930(5)	27(1)
C(5)	1789(17)	2637(11)	2680(7)	23(2)
C(6)	1034(11)	1640(7)	3497(5)	20(1)
C(7)	1112(10)	2803(4)	4392(3)	27(1)
C(8)	-797(10)	1109(7)	3252(4)	27(1)
C(9)	-1031(8)	-266(5)	2461(3)	30(1)
C(10)	64(12)	-1751(6)	2817(5)	29(2)
C(11)	1952(10)	-1365(6)	3057(4)	25(1)
C(12)	2789(11)	-2888(3)	3597(3)	31(1)
C(13)	2752(8)	-1097(5)	2147(3)	24(1)
C(14)	2119(9)	111(5)	3821(4)	18(1)
C(15)	3981(10)	547(6)	4091(4)	24(1)
C(16)	4684(10)	1943(5)	3536(5)	28(1)
C(17)	3524(18)	2647(10)	2719(7)	26(3)
C(18)	6548(9)	5292(5)	2521(5)	41(1)
C(19)	4648(11)	4484(7)	-129(3)	35(1)
C(20)	190(13)	5086(7)	378(4)	34(2)

Table 3. Bond lengths [Å] and angles [°] for DCB03 (CCDC 172324).

O(1)-C(1)	1.365(12)	C(20)-H(20A)	0.9800
O(1)-C(18)	1.426(7)	C(20)-H(20B)	0.9800
O(2)-C(2)	1.410(12)	C(20)-H(20C)	0.9800
O(2)-C(19)	1.409(8)		
O(4)-C(15)	1.203(7)	C(1)-O(1)-C(18)	111.3(7)
C(1)-C(2)	1.421(16)	C(2)-O(2)-C(19)	112.6(5)
C(1)-C(17)	1.435(14)	O(1)-C(1)-C(2)	120.7(9)
C(2)-C(3)	1.378(17)	O(1)-C(1)-C(17)	120.1(10)
C(3)-C(4)	1.387(13)	C(2)-C(1)-C(17)	119.0(10)
C(3)-C(20)	1.522(15)	C(3)-C(2)-O(2)	121.9(12)
C(4)-C(5)	1.343(15)	C(3)-C(2)-C(1)	121.1(11)
C(4)-H(4)	0.9500	O(2)-C(2)-C(1)	116.3(10)
C(5)-C(17)	1.365(19)	C(2)-C(3)-C(4)	117.2(12)
C(5)-C(6)	1.557(11)	C(2)-C(3)-C(20)	119.4(11)
C(6)-C(8)	1.506(11)	C(4)-C(3)-C(20)	123.3(12)
C(6)-C(7)	1.539(6)	C(5)-C(4)-C(3)	122.2(11)
C(6)-C(14)	1.539(9)	C(5)-C(4)-H(4)	118.9
C(7)-H(7A)	0.9800	C(3)-C(4)-H(4)	118.9
C(7)-H(7B)	0.9800	C(4)-C(5)-C(17)	123.0(11)
C(7)-H(7C)	0.9800	C(4)-C(5)-C(6)	120.0(10)
C(8)-C(9)	1.547(6)	C(17)-C(5)-C(6)	116.7(12)
C(8)-H(8A)	0.9900	C(8)-C(6)-C(7)	107.1(6)
C(8)-H(8B)	0.9900	C(8)-C(6)-C(14)	108.6(5)
C(9)-C(10)	1.525(9)	C(7)-C(6)-C(14)	107.4(5)
C(9)-H(9A)	0.9900	C(8)-C(6)-C(5)	115.6(8)
C(9)-H(9B)	0.9900	C(7)-C(6)-C(5)	105.7(5)
C(10)-C(11)	1.520(10)	C(14)-C(6)-C(5)	111.9(7)
C(10)-H(10A)	0.9900	C(6)-C(7)-H(7A)	109.5
C(10)-H(10B)	0.9900	C(6)-C(7)-H(7B)	109.5
C(11)-C(13)	1.479(8)	H(7A)-C(7)-H(7B)	109.5
C(11)-C(12)	1.544(7)	C(6)-C(7)-H(7C)	109.5
C(11)-C(14)	1.582(6)	H(7A)-C(7)-H(7C)	109.5
C(12)-H(12A)	0.9800	H(7B)-C(7)-H(7C)	109.5
C(12)-H(12B)	0.9800	C(6)-C(8)-C(9)	112.9(6)
C(12)-H(12C)	0.9800	C(6)-C(8)-H(8A)	109.0
C(13)-H(13A)	0.9800	C(9)-C(8)-H(8A)	109.0
C(13)-H(13B)	0.9800	C(6)-C(8)-H(8B)	109.0
C(13)-H(13C)	0.9800	C(9)-C(8)-H(8B)	109.0
C(14)-C(15)	1.513(9)	H(8A)-C(8)-H(8B)	107.8
C(14)-H(14)	1.0000	C(10)-C(9)-C(8)	109.4(5)
C(15)-C(16)	1.506(8)	C(10)-C(9)-H(9A)	109.8
C(16)-C(17)	1.468(14)	C(8)-C(9)-H(9A)	109.8
C(16)-H(16A)	0.9900	C(10)-C(9)-H(9B)	109.8
C(16)-H(16B)	0.9900	C(8)-C(9)-H(9B)	109.8
C(18)-H(18A)	0.9800	H(9A)-C(9)-H(9B)	108.2
C(18)-H(18B)	0.9800	C(11)-C(10)-C(9)	114.1(5)
C(18)-H(18C)	0.9800	C(11)-C(10)-H(10A)	108.7
C(19)-H(19A)	0.9800	C(9)-C(10)-H(10A)	108.7
C(19)-H(19B)	0.9800	C(11)-C(10)-H(10B)	108.7
C(19)-H(19C)	0.9800	C(9)-C(10)-H(10B)	108.7

H(10A)-C(10)-H(10B)	107.6	H(20B)-C(20)-H(20C)	109.5
C(13)-C(11)-C(10)	111.1(6)		
C(13)-C(11)-C(12)	108.5(5)		
C(10)-C(11)-C(12)	106.8(6)		
C(13)-C(11)-C(14)	115.8(5)		
C(10)-C(11)-C(14)	107.2(6)		
C(12)-C(11)-C(14)	107.1(4)		
C(11)-C(12)-H(12A)	109.5		
C(11)-C(12)-H(12B)	109.5		
H(12A)-C(12)-H(12B)	109.5		
C(11)-C(12)-H(12C)	109.5		
H(12A)-C(12)-H(12C)	109.5		
H(12B)-C(12)-H(12C)	109.5		
C(11)-C(13)-H(13A)	109.5		
C(11)-C(13)-H(13B)	109.5		
H(13A)-C(13)-H(13B)	109.5		
C(11)-C(13)-H(13C)	109.5		
H(13A)-C(13)-H(13C)	109.5		
H(13B)-C(13)-H(13C)	109.5		
C(15)-C(14)-C(6)	111.8(5)		
C(15)-C(14)-C(11)	109.6(5)		
C(6)-C(14)-C(11)	115.0(5)		
C(15)-C(14)-H(14)	106.7		
C(6)-C(14)-H(14)	106.7		
C(11)-C(14)-H(14)	106.7		
O(4)-C(15)-C(16)	120.0(7)		
O(4)-C(15)-C(14)	122.4(7)		
C(16)-C(15)-C(14)	117.5(6)		
C(17)-C(16)-C(15)	116.2(8)		
C(17)-C(16)-H(16A)	108.2		
C(15)-C(16)-H(16A)	108.2		
C(17)-C(16)-H(16B)	108.2		
C(15)-C(16)-H(16B)	108.2		
H(16A)-C(16)-H(16B)	107.4		
C(5)-C(17)-C(1)	116.4(13)		
C(5)-C(17)-C(16)	123.7(11)		
C(1)-C(17)-C(16)	118.9(11)		
O(1)-C(18)-H(18A)	109.5		
O(1)-C(18)-H(18B)	109.5		
H(18A)-C(18)-H(18B)	109.5		
O(1)-C(18)-H(18C)	109.5		
H(18A)-C(18)-H(18C)	109.5		
H(18B)-C(18)-H(18C)	109.5		
O(2)-C(19)-H(19A)	109.5		
O(2)-C(19)-H(19B)	109.5		
H(19A)-C(19)-H(19B)	109.5		
O(2)-C(19)-H(19C)	109.5		
H(19A)-C(19)-H(19C)	109.5		
H(19B)-C(19)-H(19C)	109.5		
C(3)-C(20)-H(20A)	109.5		
C(3)-C(20)-H(20B)	109.5		
H(20A)-C(20)-H(20B)	109.5		
C(3)-C(20)-H(20C)	109.5		
H(20A)-C(20)-H(20C)	109.5		

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^4$) for DCB03 (CCDC 172324). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	230(30)	240(20)	520(30)	-2(18)	90(30)	-50(30)
O(2)	500(40)	275(16)	307(19)	80(13)	280(40)	130(30)
O(4)	370(30)	356(13)	372(15)	109(13)	-10(30)	-60(30)
C(1)	220(40)	150(20)	150(30)	-4(19)	170(30)	-20(30)
C(2)	310(50)	120(20)	330(40)	-10(20)	180(40)	20(30)
C(3)	350(50)	330(30)	70(30)	20(20)	-10(40)	10(40)
C(4)	230(30)	147(19)	420(30)	-56(19)	40(40)	40(30)
C(5)	350(50)	260(20)	130(40)	20(20)	170(40)	130(40)
C(6)	190(30)	220(30)	180(30)	-20(20)	70(40)	50(30)
C(7)	330(30)	224(18)	240(20)	-92(16)	-10(30)	-10(30)
C(8)	180(30)	360(30)	270(30)	60(20)	60(30)	60(30)
C(9)	240(30)	430(20)	250(20)	-58(18)	60(30)	-90(30)
C(10)	300(40)	320(30)	280(30)	40(20)	170(40)	-120(40)
C(11)	220(40)	130(20)	410(30)	-11(18)	60(40)	-10(30)
C(12)	380(40)	252(19)	300(20)	-23(15)	30(40)	10(30)
C(13)	240(30)	228(19)	236(18)	-72(15)	10(30)	30(30)
C(14)	150(30)	180(20)	190(30)	17(17)	-60(30)	0(30)
C(15)	200(30)	210(20)	280(30)	-62(19)	-60(40)	30(30)
C(16)	170(30)	190(20)	490(30)	-20(20)	100(40)	20(30)
C(17)	430(60)	110(20)	280(50)	0(20)	160(50)	110(40)
C(18)	240(30)	266(19)	720(30)	-120(20)	100(40)	-90(30)
C(19)	380(40)	400(20)	290(20)	24(16)	110(40)	0(40)
C(20)	440(50)	370(30)	220(30)	40(20)	140(40)	150(40)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for DCB03 (CCDC 172324).

	x	y	z	U_{iso}
H(4)	-447	3103	1893	32
H(7A)	796	2194	4961	40
H(7B)	316	3722	4237	40
H(7C)	2274	3235	4547	40
H(8A)	-1494	2076	3011	32
H(8B)	-1224	706	3860	32
H(9A)	-2246	-596	2340	36
H(9B)	-688	149	1833	36
H(10A)	-357	-2206	3414	35
H(10B)	-80	-2615	2301	35
H(12A)	2521	-3874	3193	46
H(12B)	2350	-3021	4232	46
H(12C)	4029	-2734	3710	46
H(13A)	2606	-2088	1734	36
H(13B)	3971	-872	2322	36
H(13C)	2207	-156	1784	36
H(14)	1703	-311	4436	21
H(16A)	5041	2838	4011	33
H(16B)	5719	1545	3270	33
H(18A)	6205	5309	3186	61
H(18B)	6058	6248	2149	61
H(18C)	7795	5335	2566	61
H(19A)	3814	3748	-498	53
H(19B)	5580	3827	216	53
H(19C)	5106	5247	-586	53
H(20A)	624	6194	264	51
H(20B)	-967	5170	562	51
H(20C)	167	4430	-226	51

CALIFORNIA INSTITUTE OF TECHNOLOGY

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X-RAY CRYSTALLOGRAPHY LABORATORY

Crystal Structure Analysis of:

Lactone 156 (DCB06)

(CCDC 175859)

Contents:

Table 1. Crystal data
Table 2. Atomic coordinates
Table 3. Full bond distances and angles (for deposit)
Table 4. Anisotropic displacement parameters
Table 5. Hydrogen atomic coordinates

Figure A3.2 Representation of Lactone **156**

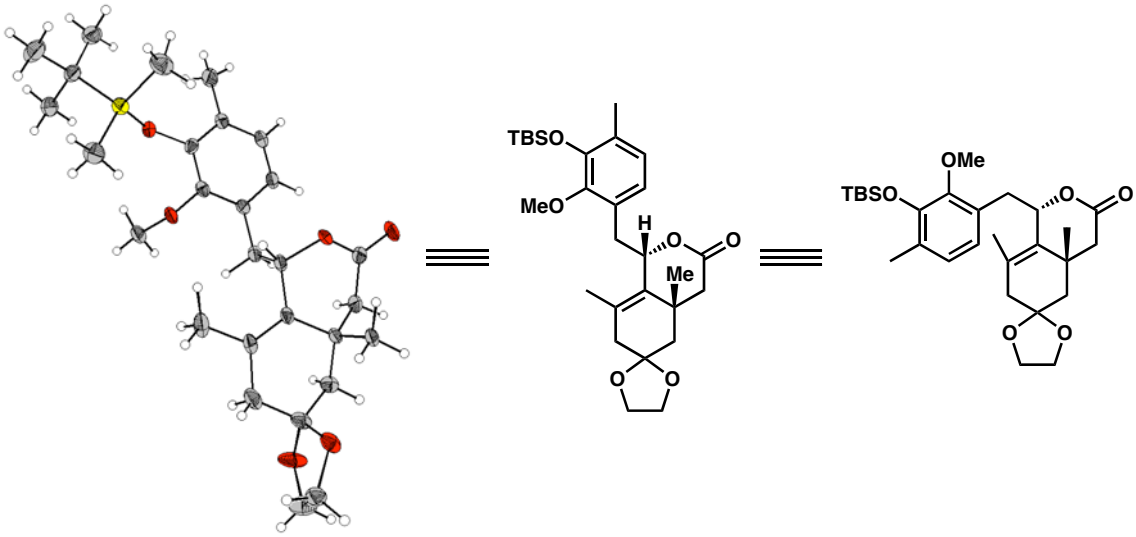


Table 1. Crystal data and structure refinement for DCB06_(CCDC_175859).

Empirical formula	$C_{28}H_{42}O_6Si$
Formula weight	502.71
Crystallization Solvent	Hexanes
Crystal Habit	Block
Crystal size	0.33 x 0.17 x 0.14 mm^3
Crystal color	Colorless

Data Collection

Type of diffractometer	Bruker P4
Wavelength	0.71073 Å MoKα
Data Collection Temperature	96(2) K
θ range for 8201 reflections used in lattice determination	2.79 to 26.49°
Unit cell dimensions	a = 29.220(3) Å b = 6.7215(8) Å β= 90.035(2)° c = 14.4249(17) Å
Volume	2833.0(6) $Å^3$
Z	4
Crystal system	Monoclinic
Space group	$P2_1/c$
Density (calculated)	1.179 Mg/m^3
F(000)	1088
Data collection program	Bruker SMART v5.054
θ range for data collection	1.39 to 28.38°
Completeness to θ = 28.38°	93.9 %
Index ranges	$-37 \le h \le 38, -8 \le k \le 8, -19 \le l \le 19$
Data collection scan type	ω scans at 5 ϕ settings
Data reduction program	Bruker SAINT v6.22
Reflections collected	38935
Independent reflections	6656 [R_{int}= 0.0985]
Absorption coefficient	0.120 mm^{-1}
Absorption correction	None
Max. and min. transmission	0.9829 and 0.9610

Table 1 (cont.)

Structure solution and Refinement

Structure solution program	Bruker SHELXTL
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Difference Fourier map
Structure refinement program	Bruker SHELXTL
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	6656 / 0 / 484
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F^2	1.403
Final R indices [I>2σ(I), 3988 reflections]	R1 = 0.0584, *w*R2 = 0.0804
R indices (all data)	R1 = 0.1062, *w*R2 = 0.0844
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.001
Average shift/error	0.000
Largest diff. peak and hole	0.333 and -0.349 e.Å^{-3}

Special Refinement Details

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

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

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for DCB06_(CCDC_175859). U(eq) the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
Si(1)	6142(1)	3545(1)	4087(1)	25(1)
O(1)	6571(1)	5169(2)	4135(1)	23(1)
O(2)	7293(1)	2606(2)	3725(1)	23(1)
O(3)	8211(1)	1108(2)	6169(1)	28(1)
O(4)	8640(1)	2202(2)	7317(1)	44(1)
O(5)	9414(1)	-4435(2)	4438(1)	30(1)
O(6)	9725(1)	-2363(2)	3364(1)	45(1)
C(1)	5665(1)	5006(3)	3527(1)	27(1)
C(2)	5841(1)	5905(4)	2608(2)	35(1)
C(3)	5260(1)	3633(5)	3329(2)	43(1)
C(4)	5503(1)	6694(4)	4154(2)	36(1)
C(5)	6282(1)	1358(4)	3362(2)	34(1)
C(6)	5995(1)	2734(5)	5291(2)	39(1)
C(7)	6962(1)	5171(3)	4672(1)	21(1)
C(8)	6990(1)	6481(3)	5429(1)	24(1)
C(9)	6595(1)	7823(4)	5660(2)	37(1)
C(10)	7397(1)	6526(4)	5928(1)	27(1)
C(11)	7762(1)	5352(3)	5700(1)	26(1)
C(12)	7740(1)	4049(3)	4942(1)	22(1)
C(13)	7334(1)	3973(3)	4446(1)	20(1)
C(14)	7349(1)	3475(4)	2815(1)	32(1)
C(15)	8145(1)	2785(3)	4670(1)	22(1)
C(16)	8169(1)	761(3)	5164(1)	22(1)
C(17)	8623(1)	1598(3)	6522(1)	28(1)
C(18)	9030(1)	1238(4)	5922(2)	26(1)
C(19)	8979(1)	-684(3)	5354(1)	19(1)
C(20)	8948(1)	-2437(4)	6036(1)	24(1)
C(21)	9394(1)	-899(3)	4715(1)	24(1)
C(22)	9349(1)	-2544(3)	4006(1)	28(1)
C(23)	9638(1)	-5668(3)	3767(2)	29(1)
C(24)	9927(1)	-4215(4)	3241(2)	39(1)
C(25)	8901(1)	-2427(4)	3480(2)	33(1)
C(26)	8502(1)	-1441(3)	3960(1)	24(1)
C(27)	8074(1)	-1401(5)	3388(2)	35(1)
C(28)	8545(1)	-548(3)	4787(1)	19(1)

Table 3. Bond lengths [Å] and angles [°] for DCB06_(CCDC_175859).

Si(1)-O(1)	1.6629(15)	C(16)-C(28)	1.510(3)
Si(1)-C(5)	1.849(3)	C(16)-H(16)	0.995(16)
Si(1)-C(6)	1.872(2)	C(17)-C(18)	1.490(3)
Si(1)-C(1)	1.887(2)	C(18)-C(19)	1.538(3)
O(1)-C(7)	1.379(2)	C(18)-H(18A)	0.96(2)
O(2)-C(13)	1.392(2)	C(18)-H(18B)	0.96(2)
O(2)-C(14)	1.446(2)	C(19)-C(28)	1.512(3)
O(3)-C(17)	1.350(2)	C(19)-C(21)	1.531(3)
O(3)-C(16)	1.473(2)	C(19)-C(20)	1.538(3)
O(4)-C(17)	1.218(2)	C(20)-H(20A)	0.987(19)
O(5)-C(22)	1.428(2)	C(20)-H(20B)	1.016(18)
O(5)-C(23)	1.433(2)	C(20)-H(20C)	1.003(19)
O(6)-C(24)	1.389(3)	C(21)-C(22)	1.512(3)
O(6)-C(22)	1.443(2)	C(21)-H(21A)	0.99(2)
C(1)-C(4)	1.527(3)	C(21)-H(21B)	0.99(2)
C(1)-C(3)	1.528(3)	C(22)-C(25)	1.516(3)
C(1)-C(2)	1.545(3)	C(23)-C(24)	1.498(3)
C(2)-H(2A)	1.05(2)	C(23)-H(23A)	0.98(2)
C(2)-H(2B)	0.99(2)	C(23)-H(23B)	0.940(19)
C(2)-H(2C)	1.00(2)	C(24)-H(24A)	0.86(3)
C(3)-H(3A)	0.98(2)	C(24)-H(24B)	0.97(3)
C(3)-H(3B)	0.95(2)	C(25)-C(26)	1.509(3)
C(3)-H(3C)	1.04(2)	C(25)-H(25A)	0.99(2)
C(4)-H(4A)	0.99(2)	C(25)-H(25B)	0.98(2)
C(4)-H(4B)	0.99(2)	C(26)-C(28)	1.340(2)
C(4)-H(4C)	0.99(2)	C(26)-C(27)	1.498(3)
C(5)-H(5A)	0.97(2)	C(27)-H(27A)	0.95(2)
C(5)-H(5B)	1.01(2)	C(27)-H(27B)	0.97(2)
C(5)-H(5C)	0.98(2)	C(27)-H(27C)	1.06(2)
C(6)-H(6A)	1.03(3)		
C(6)-H(6B)	0.98(3)	O(1)-Si(1)-C(5)	112.26(10)
C(6)-H(6C)	0.98(2)	O(1)-Si(1)-C(6)	109.05(11)
C(7)-C(13)	1.392(3)	C(5)-Si(1)-C(6)	110.16(13)
C(7)-C(8)	1.405(3)	O(1)-Si(1)-C(1)	103.44(9)
C(8)-C(10)	1.389(3)	C(5)-Si(1)-C(1)	109.60(11)
C(8)-C(9)	1.503(3)	C(6)-Si(1)-C(1)	112.21(11)
C(9)-H(9A)	1.02(2)	C(7)-O(1)-Si(1)	130.34(12)
C(9)-H(9B)	0.92(2)	C(13)-O(2)-C(14)	113.73(17)
C(9)-H(9C)	0.95(2)	C(17)-O(3)-C(16)	118.89(15)
C(10)-C(11)	1.369(3)	C(22)-O(5)-C(23)	106.28(14)
C(10)-H(10)	0.98(2)	C(24)-O(6)-C(22)	109.25(17)
C(11)-C(12)	1.403(3)	C(4)-C(1)-C(3)	108.6(2)
C(11)-H(11)	0.965(19)	C(4)-C(1)-C(2)	108.7(2)
C(12)-C(13)	1.388(3)	C(3)-C(1)-C(2)	109.5(2)
C(12)-C(15)	1.508(3)	C(4)-C(1)-Si(1)	111.25(15)
C(14)-H(14A)	0.99(2)	C(3)-C(1)-Si(1)	109.77(18)
C(14)-H(14B)	1.00(2)	C(2)-C(1)-Si(1)	108.96(15)
C(14)-H(14C)	1.05(2)	C(1)-C(2)-H(2A)	113.2(11)
C(15)-C(16)	1.538(3)	C(1)-C(2)-H(2B)	109.5(13)
C(15)-H(15A)	1.047(18)	H(2A)-C(2)-H(2B)	106.4(17)
C(15)-H(15B)	0.950(18)	C(1)-C(2)-H(2C)	108.6(12)

H(2A)-C(2)-H(2C)	108.2(18)	H(14A)-C(14)-H(14C)	108.8(17)
H(2B)-C(2)-H(2C)	110.9(18)	H(14B)-C(14)-H(14C)	114.6(17)
C(1)-C(3)-H(3A)	110.1(14)	C(12)-C(15)-C(16)	114.35(16)
C(1)-C(3)-H(3B)	110.8(14)	C(12)-C(15)-H(15A)	112.3(10)
H(3A)-C(3)-H(3B)	108.4(19)	C(16)-C(15)-H(15A)	104.7(10)
C(1)-C(3)-H(3C)	113.7(12)	C(12)-C(15)-H(15B)	109.6(11)
H(3A)-C(3)-H(3C)	108.5(18)	C(16)-C(15)-H(15B)	108.4(11)
H(3B)-C(3)-H(3C)	105.0(19)	H(15A)-C(15)-H(15B)	107.1(14)
C(1)-C(4)-H(4A)	109.9(14)	O(3)-C(16)-C(28)	112.77(15)
C(1)-C(4)-H(4B)	112.8(12)	O(3)-C(16)-C(15)	108.69(16)
H(4A)-C(4)-H(4B)	110.7(17)	C(28)-C(16)-C(15)	112.34(16)
C(1)-C(4)-H(4C)	115.2(12)	O(3)-C(16)-H(16)	101.4(9)
H(4A)-C(4)-H(4C)	104.1(17)	C(28)-C(16)-H(16)	113.5(10)
H(4B)-C(4)-H(4C)	103.8(18)	C(15)-C(16)-H(16)	107.4(10)
Si(1)-C(5)-H(5A)	113.1(14)	O(4)-C(17)-O(3)	118.11(19)
Si(1)-C(5)-H(5B)	112.4(13)	O(4)-C(17)-C(18)	124.7(2)
H(5A)-C(5)-H(5B)	108(2)	O(3)-C(17)-C(18)	117.06(17)
Si(1)-C(5)-H(5C)	110.5(14)	C(17)-C(18)-C(19)	111.65(18)
H(5A)-C(5)-H(5C)	106.6(19)	C(17)-C(18)-H(18A)	109.4(12)
H(5B)-C(5)-H(5C)	106.0(18)	C(19)-C(18)-H(18A)	112.2(12)
Si(1)-C(6)-H(6A)	110.3(13)	C(17)-C(18)-H(18B)	111.5(11)
Si(1)-C(6)-H(6B)	114.0(13)	C(19)-C(18)-H(18B)	111.1(12)
H(6A)-C(6)-H(6B)	107(2)	H(18A)-C(18)-H(18B)	100.5(16)
Si(1)-C(6)-H(6C)	107.1(13)	C(28)-C(19)-C(21)	110.20(15)
H(6A)-C(6)-H(6C)	111.0(19)	C(28)-C(19)-C(18)	108.56(17)
H(6B)-C(6)-H(6C)	108(2)	C(21)-C(19)-C(18)	108.89(16)
O(1)-C(7)-C(13)	120.97(17)	C(28)-C(19)-C(20)	110.06(16)
O(1)-C(7)-C(8)	119.01(17)	C(21)-C(19)-C(20)	111.11(17)
C(13)-C(7)-C(8)	119.93(18)	C(18)-C(19)-C(20)	107.94(16)
C(10)-C(8)-C(7)	117.79(19)	C(19)-C(20)-H(20A)	111.0(10)
C(10)-C(8)-C(9)	121.9(2)	C(19)-C(20)-H(20B)	108.3(10)
C(7)-C(8)-C(9)	120.24(19)	H(20A)-C(20)-H(20B)	107.8(14)
C(8)-C(9)-H(9A)	109.2(13)	C(19)-C(20)-H(20C)	110.5(11)
C(8)-C(9)-H(9B)	112.5(13)	H(20A)-C(20)-H(20C)	104.4(15)
H(9A)-C(9)-H(9B)	111.6(18)	H(20B)-C(20)-H(20C)	114.8(14)
C(8)-C(9)-H(9C)	112.0(13)	C(22)-C(21)-C(19)	113.99(17)
H(9A)-C(9)-H(9C)	106.5(18)	C(22)-C(21)-H(21A)	107.4(12)
H(9B)-C(9)-H(9C)	104.8(19)	C(19)-C(21)-H(21A)	112.5(11)
C(11)-C(10)-C(8)	122.0(2)	C(22)-C(21)-H(21B)	107.6(10)
C(11)-C(10)-H(10)	120.2(12)	C(19)-C(21)-H(21B)	110.2(10)
C(8)-C(10)-H(10)	117.8(12)	H(21A)-C(21)-H(21B)	104.7(16)
C(10)-C(11)-C(12)	120.8(2)	O(5)-C(22)-O(6)	104.75(15)
C(10)-C(11)-H(11)	120.4(11)	O(5)-C(22)-C(21)	110.15(16)
C(12)-C(11)-H(11)	118.8(11)	O(6)-C(22)-C(21)	107.79(17)
C(13)-C(12)-C(11)	117.63(19)	O(5)-C(22)-C(25)	112.29(19)
C(13)-C(12)-C(15)	121.07(18)	O(6)-C(22)-C(25)	109.41(17)
C(11)-C(12)-C(15)	121.30(19)	C(21)-C(22)-C(25)	112.09(19)
C(12)-C(13)-C(7)	121.79(18)	O(5)-C(23)-C(24)	102.91(18)
C(12)-C(13)-O(2)	118.78(17)	O(5)-C(23)-H(23A)	110.8(11)
C(7)-C(13)-O(2)	119.39(17)	C(24)-C(23)-H(23A)	113.5(12)
O(2)-C(14)-H(14A)	107.7(11)	O(5)-C(23)-H(23B)	109.3(12)
O(2)-C(14)-H(14B)	103.7(13)	C(24)-C(23)-H(23B)	112.7(12)
H(14A)-C(14)-H(14B)	111.7(17)	H(23A)-C(23)-H(23B)	107.6(17)
O(2)-C(14)-H(14C)	109.9(11)	O(6)-C(24)-C(23)	106.3(2)

O(6)-C(24)-H(24A)	111(2)
C(23)-C(24)-H(24A)	121(2)
O(6)-C(24)-H(24B)	107.4(15)
C(23)-C(24)-H(24B)	109.6(15)
H(24A)-C(24)-H(24B)	101(2)
C(26)-C(25)-C(22)	117.35(18)
C(26)-C(25)-H(25A)	105.2(13)
C(22)-C(25)-H(25A)	103.6(13)
C(26)-C(25)-H(25B)	109.0(12)
C(22)-C(25)-H(25B)	108.3(12)
H(25A)-C(25)-H(25B)	113.4(18)
C(28)-C(26)-C(27)	124.0(2)
C(28)-C(26)-C(25)	122.27(19)
C(27)-C(26)-C(25)	113.50(18)
C(26)-C(27)-H(27A)	111.8(14)
C(26)-C(27)-H(27B)	110.0(13)
H(27A)-C(27)-H(27B)	108.2(19)
C(26)-C(27)-H(27C)	118.2(11)
H(27A)-C(27)-H(27C)	102.5(18)
H(27B)-C(27)-H(27C)	105.5(18)
C(26)-C(28)-C(16)	120.96(18)
C(26)-C(28)-C(19)	122.09(18)
C(16)-C(28)-C(19)	116.83(16)

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Table 4. Anisotropic displacement parameters ($Å^2 x 10^4$) for DCB06_(CCDC_175859). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si(1)	252(3)	279(4)	224(3)	4(3)	10(3)	-5(3)
O(1)	223(8)	280(9)	195(7)	-17(6)	-35(6)	7(6)
O(2)	277(8)	286(9)	134(7)	-31(6)	-19(6)	-16(7)
O(3)	292(9)	444(10)	110(7)	15(7)	31(6)	67(7)
O(4)	623(12)	535(12)	148(8)	-121(7)	-86(7)	211(9)
O(5)	483(10)	221(9)	186(7)	34(7)	67(7)	24(7)
O(6)	607(11)	324(10)	426(9)	130(8)	373(8)	165(8)
C(1)	206(12)	327(14)	273(12)	19(10)	-8(10)	-14(10)
C(2)	339(16)	452(18)	257(13)	51(12)	-44(12)	55(14)
C(3)	243(15)	500(19)	547(18)	-31(17)	-58(13)	-29(14)
C(4)	287(15)	436(17)	370(15)	43(13)	11(12)	69(14)
C(5)	344(16)	311(15)	366(15)	-48(12)	17(12)	-74(14)
C(6)	465(18)	396(17)	313(14)	73(13)	77(13)	51(15)
C(7)	190(12)	250(13)	199(11)	50(9)	-14(9)	-7(10)
C(8)	254(12)	283(13)	190(10)	6(10)	-4(9)	29(10)
C(9)	400(17)	389(17)	309(15)	-133(14)	-63(12)	122(14)
C(10)	315(14)	336(14)	170(11)	-59(11)	-37(10)	-4(11)
C(11)	274(14)	329(14)	165(11)	3(10)	-41(10)	-10(11)
C(12)	225(12)	279(13)	143(10)	36(9)	23(9)	1(9)
C(13)	237(12)	217(13)	151(10)	13(9)	9(9)	-59(10)
C(14)	336(16)	453(16)	160(11)	-4(12)	-1(10)	-19(14)
C(15)	208(13)	273(13)	170(11)	13(10)	-15(9)	-33(10)
C(16)	202(12)	323(14)	128(10)	10(9)	-18(9)	-19(10)
C(17)	328(14)	308(14)	207(11)	3(10)	-45(10)	114(11)
C(18)	266(14)	297(15)	202(11)	-55(11)	-68(10)	5(11)
C(19)	191(11)	245(12)	126(10)	-11(9)	3(8)	-18(9)
C(20)	228(14)	356(15)	125(11)	21(11)	-11(10)	15(11)
C(21)	253(13)	218(14)	240(12)	33(10)	54(10)	-15(10)
C(22)	378(14)	250(13)	209(11)	52(10)	128(10)	45(11)
C(23)	364(15)	201(13)	292(13)	-18(11)	14(12)	51(12)
C(24)	351(17)	247(15)	576(18)	-68(13)	127(15)	-24(12)
C(25)	501(16)	330(16)	164(12)	6(12)	1(11)	53(13)
C(26)	318(13)	239(12)	150(10)	21(10)	-44(9)	-16(10)
C(27)	458(17)	310(16)	269(13)	-22(13)	-157(12)	-2(13)
C(28)	208(12)	244(13)	125(10)	42(9)	2(9)	-23(9)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for DCB06_(CCDC_175859).

	x	y	z	U_{iso}
H(2A)	6133(7)	6800(30)	2693(13)	38(6)
H(2B)	5928(7)	4820(40)	2180(15)	49(7)
H(2C)	5594(8)	6750(40)	2334(15)	49(7)
H(3A)	5005(8)	4400(40)	3059(15)	54(8)
H(3B)	5343(7)	2620(40)	2906(15)	47(8)
H(3C)	5141(7)	2890(30)	3909(15)	48(7)
H(4A)	5371(7)	6140(40)	4734(15)	53(7)
H(4B)	5749(7)	7660(30)	4298(13)	29(6)
H(4C)	5256(7)	7520(30)	3897(14)	38(6)
H(5A)	6544(8)	620(40)	3588(15)	55(8)
H(5B)	6018(8)	410(40)	3306(15)	53(7)
H(5C)	6356(8)	1770(40)	2728(16)	53(7)
H(6A)	5864(8)	3910(40)	5662(16)	68(8)
H(6B)	5767(8)	1660(40)	5317(15)	60(8)
H(6C)	6278(8)	2230(30)	5577(15)	50(7)
H(9A)	6319(8)	6970(30)	5851(14)	47(7)
H(9B)	6667(7)	8740(30)	6106(14)	36(7)
H(9C)	6499(7)	8590(30)	5140(16)	48(7)
H(10)	7416(7)	7440(30)	6454(14)	36(6)
H(11)	8045(6)	5450(30)	6044(12)	27(6)
H(14A)	7663(7)	4000(30)	2774(12)	28(6)
H(14B)	7302(7)	2330(40)	2385(15)	49(7)
H(14C)	7118(7)	4650(30)	2727(13)	39(6)
H(15A)	8144(6)	2430(30)	3962(13)	27(5)
H(15B)	8421(6)	3490(30)	4792(11)	16(5)
H(16)	7859(6)	150(20)	5125(10)	8(4)
H(18A)	9081(6)	2380(30)	5535(13)	31(6)
H(18B)	9308(7)	1230(30)	6276(13)	31(6)
H(20A)	8897(6)	-3700(30)	5704(12)	18(5)
H(20B)	9252(6)	-2550(30)	6377(12)	21(5)
H(20C)	8673(7)	-2290(30)	6446(12)	26(5)
H(21A)	9683(7)	-1130(30)	5063(13)	34(6)
H(21B)	9448(6)	360(30)	4373(12)	24(5)
H(23A)	9815(7)	-6710(30)	4072(13)	34(6)
H(23B)	9417(6)	-6290(30)	3393(13)	24(6)
H(24A)	9995(11)	-4420(50)	2670(20)	112(14)
H(24B)	10229(9)	-4160(40)	3514(16)	64(9)
H(25A)	8972(7)	-1560(30)	2948(15)	51(7)
H(25B)	8812(7)	-3770(30)	3298(14)	39(7)
H(27A)	8088(8)	-420(40)	2917(16)	56(8)
H(27B)	8027(7)	-2690(40)	3096(15)	48(7)
H(27C)	7762(7)	-1060(30)	3722(13)	43(7)

CALIFORNIA INSTITUTE OF TECHNOLOGY

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X-RAY CRYSTALLOGRAPHY LABORATORY

Crystal Structure Analysis of:

Acid 161•$CHCl_3$ (DCB05)

(CCDC 175588)

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Table 3. Full bond distances and angles (for deposit)
Table 4. Anisotropic displacement parameters
Table 5. Hydrogen atomic coordinates
Table 6. Hydrogen bonds

Figure A3.3 Representation of Acid **161•$CHCl_3$**

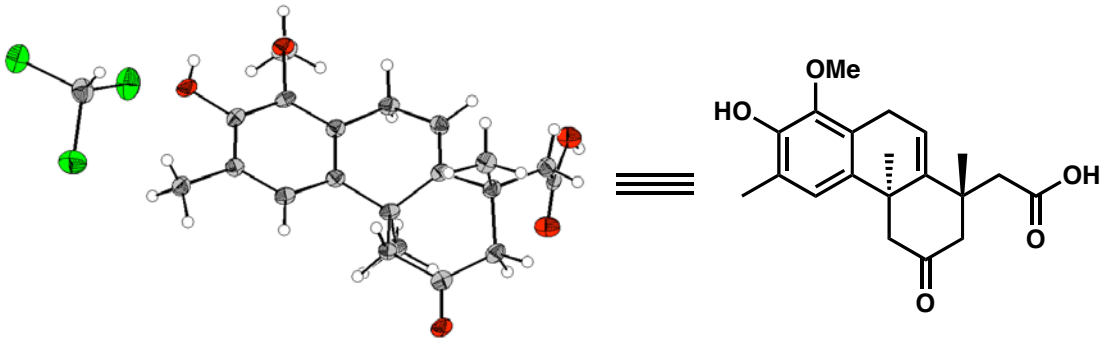


Table 1. Crystal data and structure refinement for DCB05 (CCDC 175588).

Empirical formula	$C_{20}H_{24}O_5 \cdot CHCl_3$
Formula weight	463.76
Crystallization Solvent	Chloroform
Crystal Habit	Fragment
Crystal size	0.22 x 0.15 x 0.15 mm^3
Crystal color	Colorless

Data Collection

Preliminary Photos	Rotation
Type of diffractometer	Bruker SMART 1000
Wavelength	0.71073 Å MoKα
Data Collection Temperature	98(2) K
θ range for 4336 reflections used in lattice determination	2.47 to 25.80°
Unit cell dimensions	a = 11.137(3) Å b = 13.282(3) Å β= 98.762(4)° c = 15.008(4) Å
Volume	2194.3(10) $Å^3$
Z	4
Crystal system	Monoclinic
Space group	$P2_1/n$
Density (calculated)	1.404 Mg/m^3
F(000)	968
Data collection program	Bruker SMART v5.054
θ range for data collection	2.06 to 28.36°
Completeness to θ = 28.36°	93.7 %
Index ranges	$-14 \le h \le 14$, $-17 \le k \le 17$, $-19 \le l \le 19$
Data collection scan type	ω scans at 5 ϕ settings
Data reduction program	Bruker SAINT v6.22
Reflections collected	32070
Independent reflections	5144 [R_{int}= 0.1503]
Absorption coefficient	0.447 mm^{-1}
Absorption correction	None
Max. and min. transmission	0.9368 and 0.9072

Table 1 (cont.)

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 1990)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Difference Fourier map
Structure refinement program	SHELXL-97 (Sheldrick, 1997)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	5144 / 0 / 362
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F^2	1.064
Final R indices [$I>2\sigma(I)$, 2718 reflections]	R1 = 0.0468, *w*R2 = 0.0744
R indices (all data)	R1 = 0.1218, *w*R2 = 0.0862
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.000
Average shift/error	0.000
Largest diff. peak and hole	0.402 and -0.348 e.Å^{-3}

Special Refinement Details

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

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

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for DCB05 (CCDC 175588). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
O(1)	2996(2)	1246(2)	424(1)	23(1)
O(2)	3667(2)	289(1)	2011(1)	23(1)
O(3)	10816(2)	767(1)	809(1)	24(1)
O(4)	10340(2)	21(1)	3988(1)	28(1)
O(5)	9289(2)	-1153(1)	4583(1)	27(1)
C(1)	4196(2)	1102(2)	735(2)	20(1)
C(2)	4579(2)	649(2)	1547(2)	19(1)
C(3)	5789(2)	489(2)	1874(2)	19(1)
C(4)	6178(2)	-65(2)	2727(2)	22(1)
C(5)	7352(2)	-608(2)	2734(2)	20(1)
C(6)	8184(2)	-314(2)	2243(2)	18(1)
C(7)	9343(2)	-929(2)	2231(2)	20(1)
C(8)	9093(3)	-1750(2)	1504(2)	25(1)
C(9)	9748(3)	-1452(2)	3131(2)	22(1)
C(10)	9824(2)	-789(2)	3926(2)	21(1)
C(11)	10377(2)	-254(2)	2003(2)	23(1)
C(12)	10036(2)	410(2)	1214(2)	21(1)
C(13)	8738(2)	652(2)	926(2)	19(1)
C(14)	7993(2)	658(2)	1710(2)	18(1)
C(15)	8424(3)	1530(2)	2337(2)	22(1)
C(16)	6654(2)	805(2)	1345(2)	18(1)
C(17)	6244(2)	1260(2)	531(2)	19(1)
C(18)	5037(2)	1421(2)	199(2)	19(1)
C(19)	4615(3)	1892(3)	-688(2)	24(1)
C(20)	3502(3)	888(3)	2774(2)	28(1)
C(21)	1118(3)	3109(2)	603(2)	31(1)
Cl(1)	1475(1)	3147(1)	1778(1)	41(1)
Cl(2)	2089(1)	3910(1)	117(1)	45(1)
Cl(3)	-397(1)	3458(1)	263(1)	39(1)

Table 3. Bond lengths [Å] and angles [°] for DCB05 (CCDC 175588).

O(1)-C(1)	1.361(3)	C(21)-Cl(3)	1.749(3)
O(1)-H(1)	0.72(3)	C(21)-Cl(1)	1.749(3)
O(2)-C(2)	1.401(3)	C(21)-Cl(2)	1.753(3)
O(2)-C(20)	1.428(3)	C(21)-H(21)	0.91(3)
O(3)-C(12)	1.230(3)		
O(4)-C(10)	1.216(3)	C(1)-O(1)-H(1)	107(3)
O(5)-C(10)	1.319(3)	C(2)-O(2)-C(20)	113.6(2)
O(5)-H(5A)	0.97(4)	C(10)-O(5)-H(5A)	111.0(18)
C(1)-C(2)	1.368(4)	O(1)-C(1)-C(2)	121.6(2)
C(1)-C(18)	1.390(3)	O(1)-C(1)-C(18)	118.2(2)
C(2)-C(3)	1.378(3)	C(2)-C(1)-C(18)	120.3(2)
C(3)-C(16)	1.403(3)	C(1)-C(2)-C(3)	122.7(2)
C(3)-C(4)	1.483(4)	C(1)-C(2)-O(2)	116.2(2)
C(4)-C(5)	1.492(4)	C(3)-C(2)-O(2)	120.9(2)
C(4)-H(4A)	0.94(3)	C(2)-C(3)-C(16)	118.1(2)
C(4)-H(4B)	0.96(3)	C(2)-C(3)-C(4)	121.7(2)
C(5)-C(6)	1.328(3)	C(16)-C(3)-C(4)	120.1(2)
C(5)-H(5)	0.97(3)	C(3)-C(4)-C(5)	112.8(2)
C(6)-C(14)	1.516(4)	C(3)-C(4)-H(4A)	108.3(16)
C(6)-C(7)	1.529(3)	C(5)-C(4)-H(4A)	109.2(15)
C(7)-C(9)	1.525(4)	C(3)-C(4)-H(4B)	108.8(16)
C(7)-C(8)	1.538(4)	C(5)-C(4)-H(4B)	107.1(16)
C(7)-C(11)	1.539(3)	H(4A)-C(4)-H(4B)	111(2)
C(8)-H(8A)	0.95(3)	C(6)-C(5)-C(4)	122.6(3)
C(8)-H(8B)	1.02(3)	C(6)-C(5)-H(5)	119.0(14)
C(8)-H(8C)	1.03(3)	C(4)-C(5)-H(5)	118.4(14)
C(9)-C(10)	1.475(4)	C(5)-C(6)-C(14)	119.3(2)
C(9)-H(9A)	0.92(3)	C(5)-C(6)-C(7)	120.7(2)
C(9)-H(9B)	0.93(2)	C(14)-C(6)-C(7)	119.97(19)
C(11)-C(12)	1.478(4)	C(9)-C(7)-C(6)	111.69(19)
C(11)-H(11A)	0.99(3)	C(9)-C(7)-C(8)	107.6(2)
C(11)-H(11B)	1.00(3)	C(6)-C(7)-C(8)	109.0(2)
C(12)-C(13)	1.480(4)	C(9)-C(7)-C(11)	109.4(2)
C(13)-C(14)	1.541(3)	C(6)-C(7)-C(11)	110.7(2)
C(13)-H(13A)	0.94(2)	C(8)-C(7)-C(11)	108.4(2)
C(13)-H(13B)	1.00(2)	C(7)-C(8)-H(8A)	108.3(15)
C(14)-C(16)	1.520(4)	C(7)-C(8)-H(8B)	107.9(16)
C(14)-C(15)	1.523(4)	H(8A)-C(8)-H(8B)	109(2)
C(15)-H(15A)	1.00(2)	C(7)-C(8)-H(8C)	113.1(14)
C(15)-H(15B)	1.00(2)	H(8A)-C(8)-H(8C)	106(2)
C(15)-H(15C)	1.01(3)	H(8B)-C(8)-H(8C)	113(2)
C(16)-C(17)	1.378(4)	C(10)-C(9)-C(7)	114.7(2)
C(17)-C(18)	1.377(4)	C(10)-C(9)-H(9A)	111.5(15)
C(17)-H(17)	0.97(2)	C(7)-C(9)-H(9A)	114.9(16)
C(18)-C(19)	1.481(4)	C(10)-C(9)-H(9B)	105.6(15)
C(19)-H(19A)	0.94(3)	C(7)-C(9)-H(9B)	111.0(15)
C(19)-H(19B)	0.92(3)	H(9A)-C(9)-H(9B)	97(2)
C(19)-H(19C)	1.03(2)	O(4)-C(10)-O(5)	122.0(2)
C(20)-H(20A)	1.00(3)	O(4)-C(10)-C(9)	123.9(2)
C(20)-H(20B)	0.95(2)	O(5)-C(10)-C(9)	114.2(2)
C(20)-H(20C)	0.99(3)	C(12)-C(11)-C(7)	114.6(2)

C(12)-C(11)-H(11A)	106.0(16)
C(7)-C(11)-H(11A)	112.5(15)
C(12)-C(11)-H(11B)	113.7(14)
C(7)-C(11)-H(11B)	108.6(15)
H(11A)-C(11)-H(11B)	101(2)
O(3)-C(12)-C(11)	120.7(2)
O(3)-C(12)-C(13)	120.3(2)
C(11)-C(12)-C(13)	119.0(2)
C(12)-C(13)-C(14)	113.2(2)
C(12)-C(13)-H(13A)	109.8(13)
C(14)-C(13)-H(13A)	108.8(12)
C(12)-C(13)-H(13B)	110.1(13)
C(14)-C(13)-H(13B)	109.3(12)
H(13A)-C(13)-H(13B)	105.3(19)
C(6)-C(14)-C(16)	110.5(2)
C(6)-C(14)-C(15)	108.5(2)
C(16)-C(14)-C(15)	108.9(2)
C(6)-C(14)-C(13)	110.5(2)
C(16)-C(14)-C(13)	109.8(2)
C(15)-C(14)-C(13)	108.6(2)
C(14)-C(15)-H(15A)	109.5(14)
C(14)-C(15)-H(15B)	111.6(14)
H(15A)-C(15)-H(15B)	107.9(18)
C(14)-C(15)-H(15C)	116.1(16)
H(15A)-C(15)-H(15C)	111(2)
H(15B)-C(15)-H(15C)	100(2)
C(17)-C(16)-C(3)	118.0(2)
C(17)-C(16)-C(14)	123.4(2)
C(3)-C(16)-C(14)	118.6(2)
C(18)-C(17)-C(16)	124.3(2)
C(18)-C(17)-H(17)	117.2(15)
C(16)-C(17)-H(17)	118.6(15)
C(17)-C(18)-C(1)	116.7(2)
C(17)-C(18)-C(19)	123.3(2)
C(1)-C(18)-C(19)	120.0(2)
C(18)-C(19)-H(19A)	114.1(17)
C(18)-C(19)-H(19B)	111.4(17)
H(19A)-C(19)-H(19B)	109(2)
C(18)-C(19)-H(19C)	109.9(15)
H(19A)-C(19)-H(19C)	104(2)
H(19B)-C(19)-H(19C)	107(2)
O(2)-C(20)-H(20A)	111.9(14)
O(2)-C(20)-H(20B)	104.7(14)
H(20A)-C(20)-H(20B)	108(2)
O(2)-C(20)-H(20C)	112.1(16)
H(20A)-C(20)-H(20C)	108(2)
H(20B)-C(20)-H(20C)	111(2)
Cl(3)-C(21)-Cl(1)	110.32(16)
Cl(3)-C(21)-Cl(2)	110.32(17)
Cl(1)-C(21)-Cl(2)	109.98(17)
Cl(3)-C(21)-H(21)	109.2(19)
Cl(1)-C(21)-H(21)	105.5(19)
Cl(2)-C(21)-H(21)	111.4(16)

Table 4. Anisotropic displacement parameters ($Å^2 x 10^4$) for DCB05 (CCDC 175588). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	149(10)	334(13)	235(11)	33(9)	80(9)	-25(9)
O(2)	182(10)	311(11)	210(10)	7(9)	113(8)	-10(8)
O(3)	154(10)	348(11)	253(11)	24(9)	102(8)	-2(8)
O(4)	324(11)	318(12)	214(10)	-30(9)	98(9)	-60(9)
O(5)	325(11)	325(12)	182(11)	-13(10)	95(9)	-42(9)
C(1)	142(14)	230(15)	221(15)	-30(12)	23(11)	8(12)
C(2)	142(14)	248(15)	205(15)	-29(12)	82(11)	-27(11)
C(3)	174(15)	228(15)	167(14)	-8(12)	58(11)	4(11)
C(4)	183(15)	279(17)	222(16)	16(14)	92(12)	-9(13)
C(5)	223(15)	228(16)	165(15)	17(13)	41(12)	4(12)
C(6)	155(14)	222(15)	159(14)	-23(11)	31(11)	-4(11)
C(7)	164(14)	230(15)	198(15)	8(12)	36(11)	1(11)
C(8)	240(17)	298(18)	208(16)	-20(14)	47(13)	18(14)
C(9)	190(16)	242(16)	242(16)	20(13)	49(12)	24(14)
C(10)	148(14)	267(17)	208(15)	27(13)	-21(12)	41(12)
C(11)	150(15)	294(17)	243(16)	-13(14)	53(12)	15(13)
C(12)	216(15)	196(15)	230(16)	-72(12)	56(12)	-7(12)
C(13)	175(15)	235(16)	172(15)	24(13)	71(12)	9(12)
C(14)	158(14)	222(15)	186(14)	-19(12)	92(11)	-10(11)
C(15)	192(15)	254(16)	217(16)	-18(13)	85(12)	-7(13)
C(16)	169(14)	203(14)	180(14)	-3(11)	79(11)	13(11)
C(17)	176(14)	229(15)	194(15)	-22(12)	92(12)	-2(12)
C(18)	184(14)	216(15)	191(14)	-5(12)	67(11)	22(11)
C(19)	181(16)	298(18)	228(16)	44(15)	29(13)	-2(14)
C(20)	237(18)	400(20)	250(17)	-48(15)	140(15)	-19(15)
C(21)	345(18)	274(18)	296(17)	-15(15)	10(14)	23(15)
Cl(1)	443(5)	519(5)	245(4)	-55(4)	17(3)	122(4)
Cl(2)	415(5)	447(5)	491(5)	63(4)	117(4)	-38(4)
Cl(3)	331(4)	475(5)	339(4)	-10(4)	21(3)	69(4)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for DCB05 (CCDC 175588).

	x	y	z	U_{iso}
H(1)	2670(30)	960(20)	710(20)	37(11)
H(4A)	6260(20)	400(20)	3203(17)	23(7)
H(4B)	5570(20)	-560(20)	2799(17)	29(7)
H(5)	7500(20)	-1210(20)	3098(17)	29(8)
H(5A)	9470(30)	-750(30)	5120(20)	60(10)
H(8A)	8480(20)	-2180(20)	1656(18)	30(8)
H(8B)	9870(30)	-2160(20)	1514(18)	40(8)
H(8C)	8770(20)	-1467(19)	875(19)	30(7)
H(9A)	9340(20)	-2040(20)	3214(16)	19(7)
H(9B)	10520(20)	-1729(19)	3152(16)	22(7)
H(11A)	10710(20)	190(20)	2508(19)	39(8)
H(11B)	11100(20)	-680(20)	1959(16)	29(7)
H(13A)	8666(18)	1287(17)	642(14)	3(6)
H(13B)	8370(20)	165(18)	456(16)	16(7)
H(15A)	8294(19)	2176(18)	1999(15)	11(6)
H(15B)	7970(20)	1565(18)	2856(17)	22(7)
H(15C)	9280(30)	1480(20)	2670(19)	39(8)
H(17)	6830(20)	1466(18)	154(16)	23(7)
H(19A)	4240(20)	2520(20)	-652(18)	31(8)
H(19B)	4110(20)	1470(20)	-1056(19)	33(8)
H(19C)	5350(20)	2042(19)	-1011(17)	32(7)
H(20A)	4260(30)	910(20)	3234(18)	29(8)
H(20B)	2880(20)	553(17)	3031(15)	14(6)
H(20C)	3270(20)	1590(20)	2602(19)	38(9)
H(21)	1220(20)	2450(20)	447(19)	39(9)

Table 6. Hydrogen bonds for DCB05 (CCDC 175588) [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1)...O(3)#1	0.72(3)	2.10(3)	2.656(2)	135(3)
O(1)-H(1)...O(2)	0.72(3)	2.28(3)	2.703(3)	119(3)
O(5)-H(5A)...O(4)#2	0.97(4)	1.64(4)	2.600(3)	175(3)

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

CALIFORNIA INSTITUTE OF TECHNOLOGY

BECKMAN INSTITUTE

X-RAY CRYSTALLOGRAPHY LABORATORY

Crystal Structure Analysis of:

Diketone 175 (DCB11)

(CCDC 201187)

Contents:

Table 1. Crystal data
Table 2. Atomic coordinates
Table 3. Full bond distances and angles (for deposit)
Table 4. Anisotropic displacement parameters
Table 5. Hydrogen atomic coordinates

Figure A3.4 Representation of Diketone **175**.

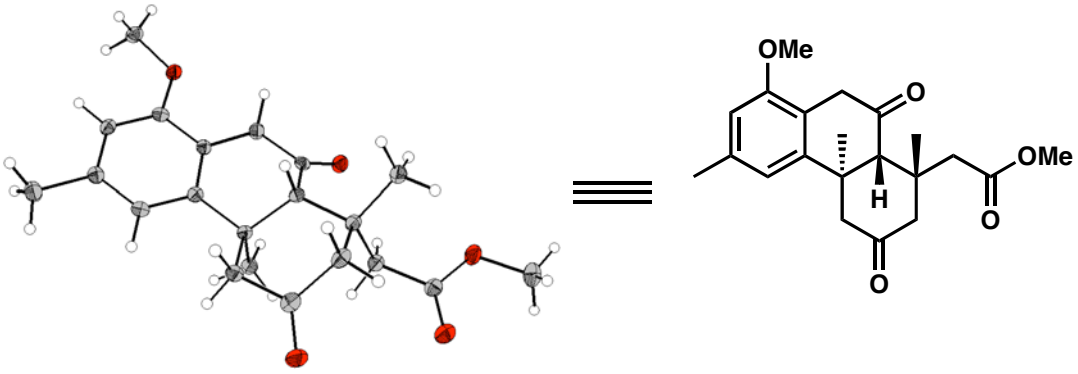


Table 1. Crystal data and structure refinement for DCB11 (CCDC 201187).

Empirical formula	$C_{21}H_{26}O_5$
Formula weight	358.42
Crystallization Solvent	Acetone/heptane
Crystal Habit	Fragment
Crystal size	0.26 x 0.22 x 0.17 mm^3
Crystal color	Colorless

Data Collection

Preliminary Photos	Rotation
Type of diffractometer	Bruker SMART 1000
Wavelength	0.71073 Å MoKα
Data Collection Temperature	98(2) K
θ range for 11980 reflections used in lattice determination	2.28 to 28.32°
Unit cell dimensions	a = 9.0211(6) Å b = 11.3617(7) Å β= 97.5510(10)° c = 17.9596(12) Å
Volume	1824.8(2) $Å^3$
Z	4
Crystal system	Monoclinic
Space group	$P2_1/n$
Density (calculated)	1.305 Mg/m^3
F(000)	768
Data collection program	Bruker SMART v5.054
θ range for data collection	2.13 to 28.32°
Completeness to θ = 28.32°	93.0 %
Index ranges	$-11 \le h \le 11$, $-14 \le k \le 14$, $-23 \le l \le 23$
Data collection scan type	ω scans at 5 ϕ settings
Data reduction program	Bruker SAINT v6.022
Reflections collected	25862
Independent reflections	4226 [R_{int}= 0.0517]
Absorption coefficient	0.092 mm^{-1}
Absorption correction	None
Max. and min. transmission	0.9845 and 0.9764

Table 1 (cont.)

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 1990)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Difference Fourier map
Structure refinement program	SHELXL-97 (Sheldrick, 1997)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	4226 / 0 / 339
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F^2	2.153
Final R indices [$I>2\sigma(I)$, 3426 reflections]	R1 = 0.0404, *w*R2 = 0.0704
R indices (all data)	R1 = 0.0511, *w*R2 = 0.0715
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.001
Average shift/error	0.000
Largest diff. peak and hole	0.326 and -0.254 e.Å^{-3}

Special Refinement Details

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

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

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for DCB11 (CCDC 201187). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
O(1)	7731(1)	4507(1)	529(1)	19(1)
O(2)	4749(1)	8200(1)	472(1)	21(1)
O(3)	9216(1)	11345(1)	2166(1)	25(1)
O(4)	3377(1)	11397(1)	1288(1)	24(1)
O(5)	5418(1)	12446(1)	1710(1)	29(1)
C(1)	10631(1)	7158(1)	1330(1)	16(1)
C(2)	11220(1)	6047(1)	1256(1)	16(1)
C(3)	12869(2)	5814(1)	1455(1)	23(1)
C(4)	10262(1)	5133(1)	986(1)	16(1)
C(5)	8757(1)	5346(1)	789(1)	15(1)
C(6)	8217(2)	3305(1)	562(1)	20(1)
C(7)	8162(1)	6478(1)	851(1)	14(1)
C(8)	6510(1)	6650(1)	623(1)	18(1)
C(9)	5914(1)	7834(1)	811(1)	15(1)
C(10)	6851(1)	8484(1)	1442(1)	14(1)
C(11)	6098(1)	9579(1)	1751(1)	15(1)
C(12)	4682(1)	9175(1)	2071(1)	19(1)
C(13)	5708(1)	10548(1)	1148(1)	17(1)
C(14)	4865(1)	11569(1)	1417(1)	18(1)
C(15)	2478(2)	12330(1)	1540(1)	31(1)
C(16)	7204(1)	10084(1)	2400(1)	18(1)
C(17)	8678(1)	10359(1)	2139(1)	18(1)
C(18)	9450(1)	9319(1)	1844(1)	18(1)
C(19)	8466(1)	8626(1)	1220(1)	14(1)
C(20)	8500(2)	9259(1)	463(1)	19(1)
C(21)	9104(1)	7387(1)	1138(1)	14(1)

Table 3. Bond lengths [Å] and angles [°] for DCB11 (CCDC 201187).

O(1)-C(5)	1.3673(13)	C(20)-H(20A)	0.996(14)
O(1)-C(6)	1.4332(14)	C(20)-H(20B)	0.987(13)
O(2)-C(9)	1.2162(13)	C(20)-H(20C)	0.985(13)
O(3)-C(17)	1.2186(13)		
O(4)-C(14)	1.3457(14)	C(5)-O(1)-C(6)	117.41(9)
O(4)-C(15)	1.4438(16)	C(14)-O(4)-C(15)	115.32(10)
O(5)-C(14)	1.2036(14)	C(2)-C(1)-C(21)	121.54(11)
C(1)-C(2)	1.3828(16)	C(2)-C(1)-H(1)	118.7(7)
C(1)-C(21)	1.3997(16)	C(21)-C(1)-H(1)	119.8(7)
C(1)-H(1)	1.006(12)	C(1)-C(2)-C(4)	118.97(11)
C(2)-C(4)	1.3963(16)	C(1)-C(2)-C(3)	121.17(11)
C(2)-C(3)	1.5069(17)	C(4)-C(2)-C(3)	119.86(11)
C(3)-H(3A)	0.967(14)	C(2)-C(3)-H(3A)	109.9(8)
C(3)-H(3B)	0.963(16)	C(2)-C(3)-H(3B)	111.4(9)
C(3)-H(3C)	0.980(15)	H(3A)-C(3)-H(3B)	109.7(12)
C(4)-C(5)	1.3783(16)	C(2)-C(3)-H(3C)	111.9(9)
C(4)-H(4)	0.958(11)	H(3A)-C(3)-H(3C)	108.7(12)
C(5)-C(7)	1.4037(15)	H(3B)-C(3)-H(3C)	105.1(12)
C(6)-H(6A)	0.978(12)	C(5)-C(4)-C(2)	120.19(11)
C(6)-H(6B)	0.973(12)	C(5)-C(4)-H(4)	119.0(7)
C(6)-H(6C)	0.999(13)	C(2)-C(4)-H(4)	120.8(7)
C(7)-C(21)	1.3926(16)	O(1)-C(5)-C(4)	124.44(10)
C(7)-C(8)	1.5051(16)	O(1)-C(5)-C(7)	114.64(10)
C(8)-C(9)	1.5034(16)	C(4)-C(5)-C(7)	120.92(11)
C(8)-H(8A)	0.993(13)	O(1)-C(6)-H(6A)	105.1(7)
C(8)-H(8B)	0.996(13)	O(1)-C(6)-H(6B)	110.4(7)
C(9)-C(10)	1.5144(16)	H(6A)-C(6)-H(6B)	110.7(10)
C(10)-C(11)	1.5546(16)	O(1)-C(6)-H(6C)	111.8(7)
C(10)-C(19)	1.5679(16)	H(6A)-C(6)-H(6C)	110.0(10)
C(10)-H(10)	0.982(11)	H(6B)-C(6)-H(6C)	108.8(10)
C(11)-C(12)	1.5377(16)	C(5)-C(7)-C(21)	119.20(11)
C(11)-C(13)	1.5525(16)	C(5)-C(7)-C(8)	118.20(10)
C(11)-C(16)	1.5420(16)	C(21)-C(7)-C(8)	122.58(10)
C(12)-H(12A)	0.986(12)	C(7)-C(8)-C(9)	115.21(10)
C(12)-H(12B)	1.025(12)	C(7)-C(8)-H(8A)	112.9(8)
C(12)-H(12C)	0.993(12)	C(9)-C(8)-H(8A)	106.4(7)
C(13)-C(14)	1.5018(16)	C(7)-C(8)-H(8B)	109.6(8)
C(13)-H(13A)	0.986(12)	C(9)-C(8)-H(8B)	105.9(8)
C(13)-H(13B)	0.957(11)	H(8A)-C(8)-H(8B)	106.3(11)
C(15)-H(15A)	0.969(14)	O(2)-C(9)-C(10)	124.61(11)
C(15)-H(15B)	0.980(15)	O(2)-C(9)-C(8)	120.35(11)
C(15)-H(15C)	0.989(15)	C(10)-C(9)-C(8)	115.03(10)
C(16)-C(17)	1.4999(17)	C(9)-C(10)-C(11)	115.52(10)
C(16)-H(16A)	0.980(12)	C(9)-C(10)-C(19)	107.82(9)
C(16)-H(16B)	0.982(12)	C(11)-C(10)-C(19)	118.21(9)
C(17)-C(18)	1.5039(17)	C(9)-C(10)-H(10)	104.1(6)
C(18)-C(19)	1.5492(16)	C(11)-C(10)-H(10)	105.7(6)
C(18)-H(18A)	0.966(12)	C(19)-C(10)-H(10)	103.8(6)
C(18)-H(18B)	0.996(12)	C(12)-C(11)-C(10)	108.53(9)
C(19)-C(21)	1.5357(15)	C(12)-C(11)-C(13)	110.46(10)
C(19)-C(20)	1.5424(16)	C(10)-C(11)-C(13)	112.81(9)

C(12)-C(11)-C(16)	108.40(10)
C(10)-C(11)-C(16)	107.36(9)
C(13)-C(11)-C(16)	109.15(10)
C(11)-C(12)-H(12A)	109.5(7)
C(11)-C(12)-H(12B)	110.2(7)
H(12A)-C(12)-H(12B)	109.2(9)
C(11)-C(12)-H(12C)	109.5(7)
H(12A)-C(12)-H(12C)	108.7(10)
H(12B)-C(12)-H(12C)	109.7(9)
C(14)-C(13)-C(11)	113.64(10)
C(14)-C(13)-H(13A)	104.7(7)
C(11)-C(13)-H(13A)	110.9(7)
C(14)-C(13)-H(13B)	108.1(7)
C(11)-C(13)-H(13B)	109.4(7)
H(13A)-C(13)-H(13B)	110.0(10)
O(5)-C(14)-O(4)	122.87(11)
O(5)-C(14)-C(13)	125.55(12)
O(4)-C(14)-C(13)	111.58(10)
O(4)-C(15)-H(15A)	107.3(8)
O(4)-C(15)-H(15B)	109.3(9)
H(15A)-C(15)-H(15B)	110.0(12)
O(4)-C(15)-H(15C)	110.6(8)
H(15A)-C(15)-H(15C)	111.5(12)
H(15B)-C(15)-H(15C)	108.1(12)
C(17)-C(16)-C(11)	110.67(10)
C(17)-C(16)-H(16A)	108.5(7)
C(11)-C(16)-H(16A)	111.5(7)
C(17)-C(16)-H(16B)	108.4(7)
C(11)-C(16)-H(16B)	107.5(7)
H(16A)-C(16)-H(16B)	110.2(9)
O(3)-C(17)-C(18)	122.40(11)
O(3)-C(17)-C(16)	122.92(11)
C(18)-C(17)-C(16)	114.67(11)
C(17)-C(18)-C(19)	113.93(10)
C(17)-C(18)-H(18A)	109.0(7)
C(19)-C(18)-H(18A)	110.2(7)
C(17)-C(18)-H(18B)	105.8(7)
C(19)-C(18)-H(18B)	109.9(7)
H(18A)-C(18)-H(18B)	107.8(9)
C(21)-C(19)-C(20)	106.90(9)
C(21)-C(19)-C(18)	110.43(9)
C(20)-C(19)-C(18)	108.92(10)
C(21)-C(19)-C(10)	107.65(9)
C(20)-C(19)-C(10)	113.48(10)
C(18)-C(19)-C(10)	109.42(9)
C(19)-C(20)-H(20A)	108.7(7)
C(19)-C(20)-H(20B)	111.1(7)
H(20A)-C(20)-H(20B)	107.8(10)
C(19)-C(20)-H(20C)	112.4(7)
H(20A)-C(20)-H(20C)	107.0(10)
H(20B)-C(20)-H(20C)	109.7(10)
C(1)-C(21)-C(7)	119.14(11)
C(1)-C(21)-C(19)	121.02(10)
C(7)-C(21)-C(19)	119.82(10)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^4$) for DCB11 (CCDC 201187). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	179(5)	129(4)	246(5)	-34(4)	5(4)	-8(3)
O(2)	175(5)	198(5)	252(5)	-10(4)	-23(4)	19(4)
O(3)	239(5)	164(5)	340(5)	-50(4)	-12(4)	-28(4)
O(4)	181(5)	202(5)	316(5)	-22(4)	1(4)	57(4)
O(5)	270(5)	197(5)	396(6)	-85(4)	44(4)	-6(4)
C(1)	170(6)	162(6)	152(6)	-5(5)	26(5)	-28(5)
C(2)	160(6)	188(7)	140(6)	12(5)	29(5)	5(5)
C(3)	165(7)	220(8)	302(8)	-28(7)	7(6)	13(6)
C(4)	189(7)	140(6)	158(6)	10(5)	43(5)	31(5)
C(5)	176(6)	159(6)	118(6)	-7(5)	29(5)	-31(5)
C(6)	223(8)	142(7)	237(7)	-9(6)	13(6)	-2(6)
C(7)	145(6)	157(6)	123(6)	7(5)	31(5)	4(5)
C(8)	162(7)	168(7)	209(7)	-33(6)	8(5)	0(5)
C(9)	142(6)	161(6)	161(6)	30(5)	48(5)	-18(5)
C(10)	151(6)	128(6)	143(6)	26(5)	21(5)	7(5)
C(11)	173(6)	128(6)	153(6)	1(5)	32(5)	14(5)
C(12)	202(7)	167(7)	216(7)	13(6)	73(6)	27(6)
C(13)	185(7)	159(7)	171(7)	4(5)	29(5)	13(5)
C(14)	209(7)	164(7)	163(6)	30(5)	19(5)	19(5)
C(15)	218(8)	287(9)	419(10)	-13(7)	64(7)	94(7)
C(16)	241(7)	145(7)	153(7)	-7(5)	26(5)	29(5)
C(17)	203(7)	172(7)	130(6)	-11(5)	-53(5)	9(5)
C(18)	158(7)	159(7)	206(7)	-1(5)	4(5)	-17(5)
C(19)	139(6)	125(6)	166(6)	0(5)	15(5)	-6(5)
C(20)	196(7)	182(7)	201(7)	18(5)	58(6)	0(6)
C(21)	162(6)	150(6)	114(6)	8(5)	37(5)	3(5)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for DCB11 (CCDC 201187).

	x	y	z	U_{iso}
H(1)	11324(13)	7813(10)	1530(6)	16(3)
H(3A)	13385(15)	6538(12)	1604(7)	35(4)
H(3B)	13289(17)	5469(13)	1039(9)	50(5)
H(3C)	13068(16)	5243(13)	1865(9)	48(5)
H(4)	10635(12)	4351(10)	941(6)	13(3)
H(6A)	7338(14)	2849(10)	357(7)	21(3)
H(6B)	8556(13)	3077(10)	1078(7)	18(3)
H(6C)	9048(14)	3171(10)	254(7)	19(3)
H(8A)	6202(14)	6529(11)	77(8)	29(4)
H(8B)	5944(15)	6062(11)	886(7)	33(4)
H(10)	6980(11)	7914(9)	1856(6)	9(3)
H(12A)	4310(12)	9821(10)	2363(6)	17(3)
H(12B)	3867(14)	8942(10)	1643(7)	22(3)
H(12C)	4927(13)	8491(11)	2410(7)	20(3)
H(13A)	6623(14)	10898(10)	997(6)	18(3)
H(13B)	5112(12)	10214(10)	719(6)	12(3)
H(15A)	1440(17)	12099(12)	1419(8)	38(4)
H(15B)	2664(16)	13060(13)	1277(8)	43(4)
H(15C)	2744(16)	12466(12)	2086(9)	44(4)
H(16A)	6816(13)	10804(10)	2604(6)	16(3)
H(16B)	7366(13)	9478(10)	2792(7)	18(3)
H(18A)	10357(14)	9583(10)	1663(6)	16(3)
H(18B)	9741(13)	8799(10)	2285(7)	22(3)
H(20A)	9509(15)	9153(10)	304(7)	26(3)
H(20B)	7759(14)	8917(10)	69(7)	22(3)
H(20C)	8331(13)	10112(11)	498(6)	21(3)

CHAPTER THREE

Current Approaches to the Synthesis of Zoanthenol: Synthesis of the ABC Ring System Containing All of the Quaternary Stereocenters[†]

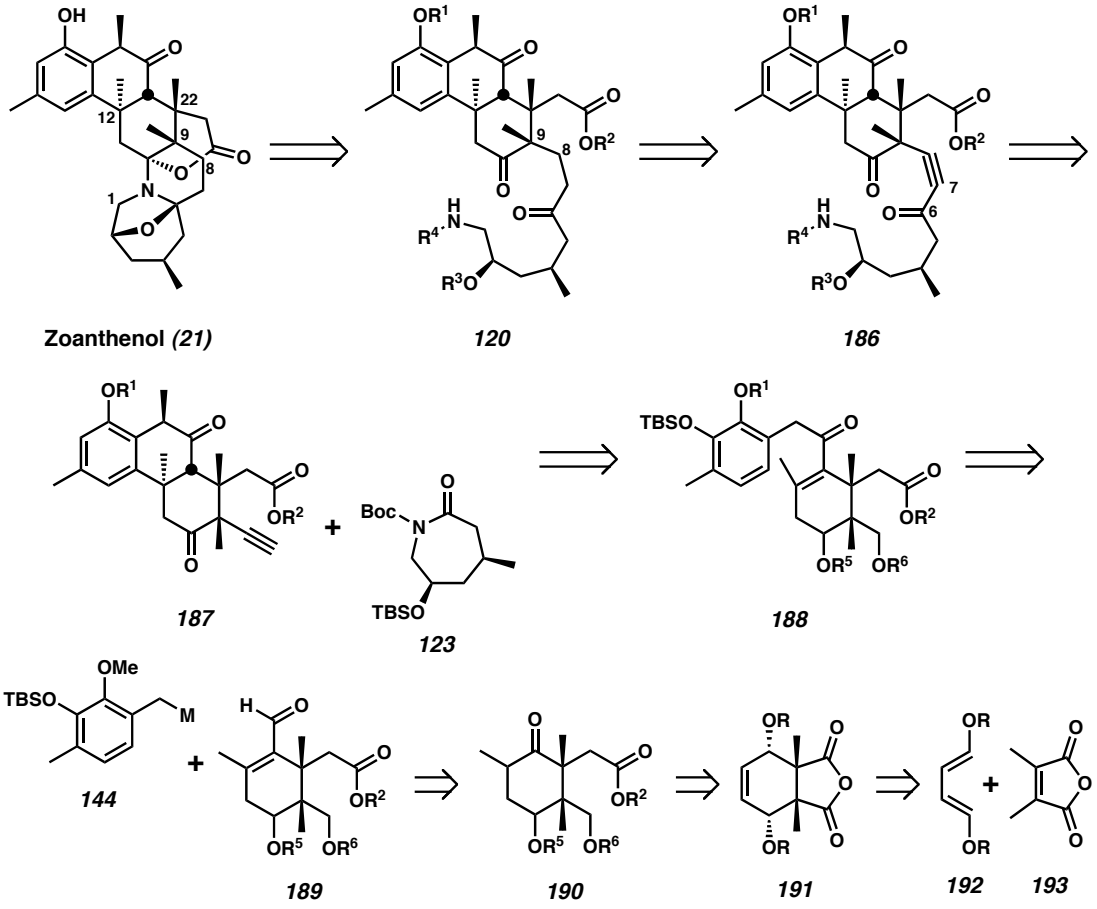
3.1 Revised Retrosynthetic Plan

Our early efforts outlined an expeditious synthesis of the ABC rings of zoanthenol. However, selective late-stage alkylation to form the final quaternary stereocenter proved difficult by a number of strategies. As a result, we decided to alter our retrosynthetic analysis to incorporate the formation of the C(9) quaternary stereocenter early in the synthesis (Scheme 3.1). We envisioned that with the vicinal C(9) and C(22) stereocenters established, we would be able to apply our previously developed methods for cyclization, either S_N' cyclization or Friedel-Crafts type conjugate addition, to directly generate a zoanthenol ABC ring system with all three quaternary centers. In accordance with this plan, we targeted alkyne **186** as an intermediate. Retrosynthetic disconnection of the C(1)-C(6) fragment of alkyne **186** was envisioned to occur by addition of the anion of alkyne **187** into caprolactam **123**. Caprolactam **123** was a previously projected intermediate and had been already synthesized in our laboratories.[1] ABC ring fragment **187** would be simplified to enone **188** via one of our cyclization methods. Using methods analogous to those demonstrated in Chapter Two, enone **188** would be reduced in complexity to ketone **190**. Oxidation state adjustment and a one-carbon homologation of *meso*-anhydride **191** could afford ketone **190**. We targeted *meso*-anhydride **191** as an opportunity to generate enantioenriched intermediates by desymmetrization. Finally, *meso*-anhydride **191** could arise via a Diels-Alder reaction of

[†] This work was performed in collaboration with Ms. Jennifer Stockdill, a graduate student in the Stoltz group.

1,4-oxygenated diene **192** and 2,3-dimethylmaleic anhydride (DMMA, **193**). Although challenging, such a Diels-Alder reaction would generate both the C(9) and C(22) quaternary stereocenters in a single step with reliable relative stereochemistry.

Scheme 3.1 Revised Retrosynthetic Plan for Zoanthenol



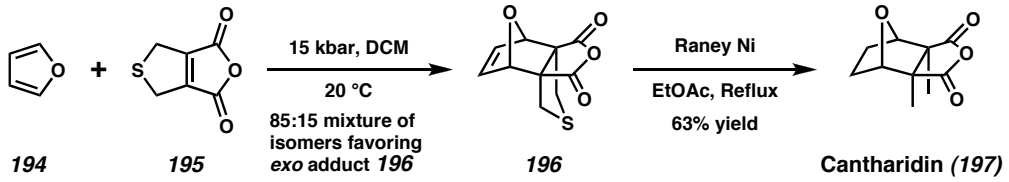
3.2 Synthesis of a C Ring Synthon Containing Vicinal Quaternary Stereocenters

3.2.1 *Diels-Alder Reactions of DMMA*

The preceding plan relies on a Diels-Alder reaction of DMMA. Such reactions are rare and difficult to accomplish.[2] However, the difficulty of generating compounds containing vicinal quaternary stereocenters with predictable relative stereochemistry has

stimulated significant work on the problem of DMMA Diels-Alder reactions. In particular, sulfur heterocycle **195** has been developed as a surrogate for DMMA (Scheme 3.2).[3] The sulfur atom is believed to constrain what would be the methyl groups in DMMA, making them both sterically smaller and less electron donating to the olefin. Dihydrothiophene **195** has been successfully applied in an elegant Diels-Alder strategy to synthesize cantharidin, where DMMA failed to react.[4] It's noteworthy that diydrothiophene **195** still required extremely high pressure (15 kbar) to successfully react with furan.

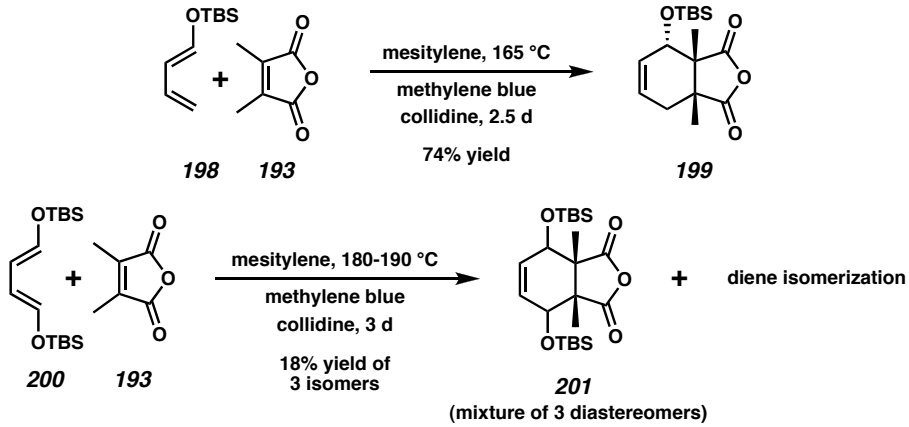
Scheme 3.2 Dauben's Synthesis of Cantharidin



Despite these difficulties, we were encouraged by Danishefsky and Birman's use of a DMMA Diels-Alder reaction in their recent synthesis of merrilactone A (Scheme 3.3).[5] The first step of their synthesis combines oxygenated diene **198** and DMMA in good yield. We hoped to react an even more electron rich 1,4-dioxygenated diene **200**[6] in a similar manner to give the *meso*-Diels-Alder adduct **201**. However, despite the similarity of the reactions, less than 20% yield of Diels-Alder adducts were produced under thermal conditions. This yield of Diels-Alder adducts consisted of similar amounts of three diastereomers. Furthermore, NMR studies with 1,4-dioxygenated diene **200**

showed that isomerization of olefin geometry was favorable and occurred faster than the Diels-Alder reaction. As a result, the use of diene **200** seemed impractical.

Scheme 3.3 Diels-Alder Reactions of DMMA

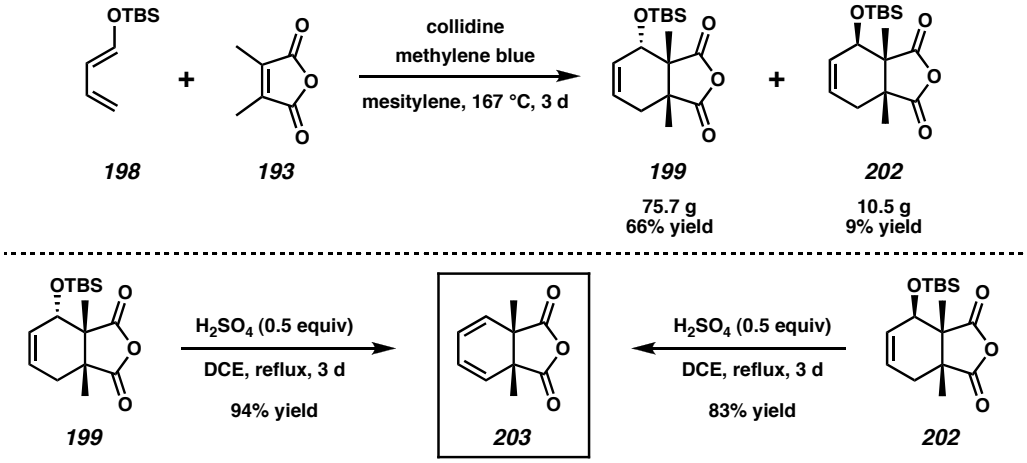


3.2.2 *Advancing Danishefsky's DMMA Diels-Alder Adduct*

Alternatively, we decided to advance Danishefsky's Diels-Alder adduct **199**. Rather than desymmetrize a bisoxygenated Diels-Alder adduct (i.e., **201**), our strategy was to deprotect silyl ether **199** and eliminate it to a *meso*-diene (i.e., **203**) anhydride suitable for desymmetrization. We were encouraged to find the reaction that Danishefsky reported between silyloxy diene **198**[7] and DMMA[8] to be highly reproducible and amenable to scale (Scheme 3.4). Typically, we carried out the reaction on a 0.350 mol scale to give an isolated yield of more than 70 g of *endo*-Diels-Alder product **199**. Treatment of the Diels-Alder adduct with sulfuric acid in refluxing dichloroethane caused TBS deprotection and elimination to *meso*-diene **203** in excellent yield. Additionally, significant amounts of *exo*-Diels-Alder adduct **202** were isolated in the Diels-Alder reaction and underwent elimination to *meso*-diene **203** under identical conditions. Unlike

Danishefsky's synthesis, our route eliminates the allylic stereocenter, thus the *exo*-Diels-Alder adduct **202** improved the overall throughput of the route. With diene **203** in hand, our next goal was to effectively desymmetrize it.

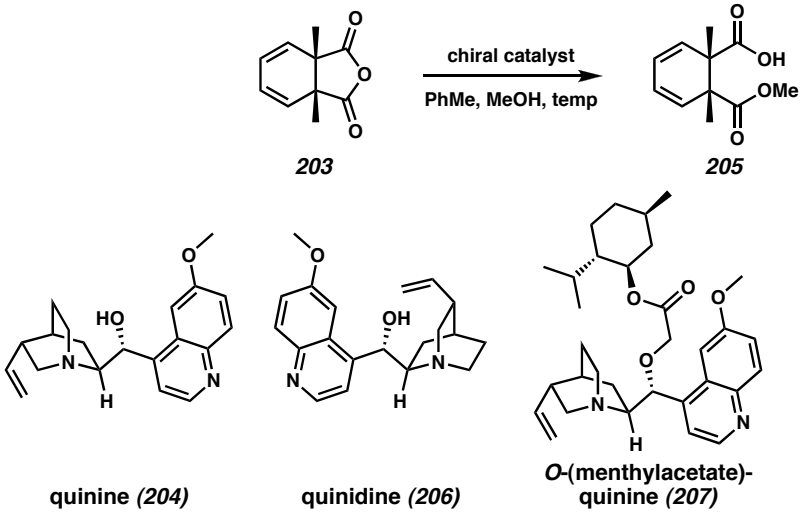
Scheme 3.4 Diels-Alder Route to *meso*-Diene **203**



The desymmetrization of cyclic *meso*-anhydrides to chiral monoesters has been studied by Fujisawa,[9] Bolm,[10] and Deng.[11] Such asymmetric alcoholysis of cyclic anhydrides with cinchona alkaloids has been reviewed.[12] However, prior to our work this strategy had never been applied to set multiple quaternary stereocenters. To our delight, we found that with slight modifications to Bolm's conditions excellent chemical yields and good enantioselectivities could be achieved (Scheme 3.5). Typically, for material throughput purposes, we performed the reaction with catalytic quinine (**204**) and stoichiometric DBU, which gave quick conversion but racemic product. However, with judicious choice of the stoichiometric achiral base, pempidine, the reaction could be completed catalytically with good enantioselectivity (Entry 2). In general, lowering the reaction temperature did cause a significant increase in ee, but also drastically increased

reaction time. Because some of the potential routes we considered to complete zoanthenol reorient monoester **205**, it is noteworthy that the use of quinidine (**206**) provides access to the opposite enantiomer obtained from quinine with similar ee (Entry 3). Additionally, we have found that menthol derivatives **207** and **208** give superior chiral induction.[13] To date, our best results are from quinine derivative **208**, which gave monoester **205** in 85% ee (Entry 5). Likely we will be able to increase the ee of this material by recrystallization. To our knowledge, this is the first desymmetrization of an anhydride to set the absolute configuration of vicinal quaternary stereocenters and is one of only a handful methods available to do so.

Scheme 3.5 Desymmetrization of *meso*-Anhydride **203**

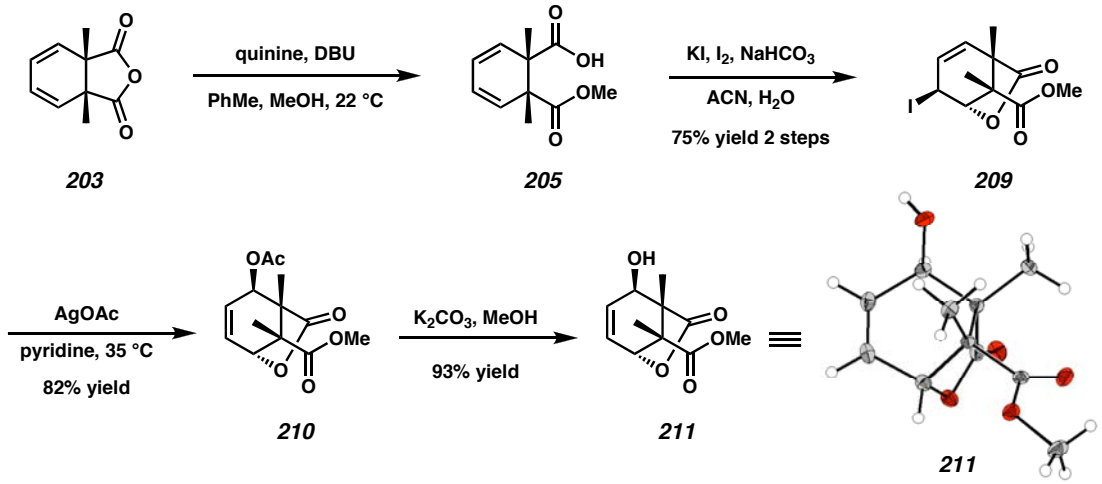


Entry	Chiral Controller (mol%)	Other Conditions	Temperature (°C)	Time (d)	Sign of Rotation	%ee (% yield)
1	*204* (105)	MeOH (5 equiv)	22	0.3	–	50
2	*204* (10)	MeOH (3 equiv) pempidine (1 equiv) 50% CCl_4 v/v	-50	18	–	70 (88)
3	*206* (100)	MeOH (3 equiv)	-50	6	+	70
4	*207* (105)	MeOH (10 equiv)	-25	3	–	72
5	*208* (101)	MeOH (3 equiv)	-50	10	+	85

3.2.3 *C Ring Synthon Reoxygenation*

Due to the difficulty of performing the DMMA Diels-Alder reaction with a 1,4-dioxygenated diene and our desire to desymmetrize a *meso*-diene, we were faced with the problem of reoxygenating the C ring (Scheme 3.6). Selenolactonization and halolactonization were both explored. Classical iodolactonization conditions proved most advantageous, giving predominantly a single iodolactone isomer by the end of the reaction.[14] Typically, the reaction was performed as a two-step sequence without purification of the intermediate monoester **205**. The bridged bicyclic nature of iodolactone **209** hinders S_N2 displacement of the iodide from the concave face, but is well disposed for S_N2' displacement. Treatment of iodolactone **209** with silver (I) acetate in pyridine at 35 °C afforded selectively S_N2' displacement to give allylic acetate **210** with the desired 1,4 oxygenation pattern. Selective acetate cleavage from bicyclic lactone **211** was accomplished by brief treatment with potassium carbonate in methanol. The stereochemical course of this sequence was confirmed by X-ray structure determination of allylic alcohol **211**. This efficient three-step sequence achieves stereospecific 1,4-reoxygenation of the C ring synthon and has proved robust and amenable to scale. Allylic alcohol **211** represents an important branch point in our synthetic efforts. Several increasingly functionalized C ring equivalents were derived from allylic alcohol **211**.

Scheme 3.6 Installation of 1,4-Oxygenation on Diene **203**



203 ***205*** ***209*** ***210*** ***211*** ***211***

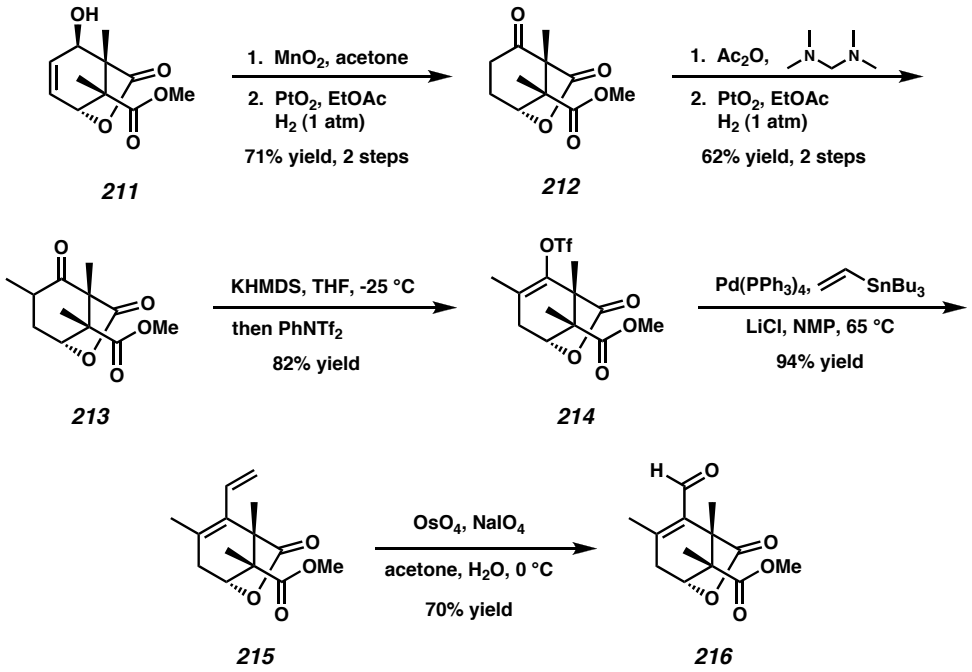
3.3 The Lactone C Ring Synthon Approach

3.3.1 *Completion of the Lactone C Ring Synthon*

The most straightforward elaboration of allylic alcohol **211**, namely leaving its ester and lactone functionality unmodified, gave us speedy access to molecules containing coupled A and C ring synthons. In turn, we could quickly begin experimentation with key B ring cyclization reactions. The sequence began with the conversion of allylic alcohol **211** to ketone **212** (Scheme 3.7). In theory, this transformation could be achieved by transition metal-catalyzed olefin isomerization. Isomerizations were attempted with a large number of catalysts, but all showed insufficient reactivity.[15] In practice, a two-step procedure consisting of manganese (IV) oxide oxidation and olefin reduction to give ketone **212** was superior. Direct methylation of ketone **212** with LDA and methyl iodide in THF consistently gave a surprising mixture of bismethylation and the starting ketone **212**. As a result, a two-step protocol of methylene installation with *N*,*N*,*N*',*N*'-tetramethyldiaminomethane and hydrogenation

with Adams catalyst gave good yields of separable methyl ketones **213**. Triflate formation from both methyl ketone diastereomers occurred under standard conditions. Unfortunately, enol triflate **214** failed to undergo carbonylation when submitted to the one-step palladium-catalyzed carbonylation conditions we developed for hindered enol triflates.[16] However, Stille coupling of enol triflate **214** with vinyl tributyltin followed by oxidative cleavage by osmium (VIII) tetroxide and sodium periodate did afford acceptable yields of enal **216**.

Scheme 3.7 Elaboration to the Complete Lactone C Ring Synthon.

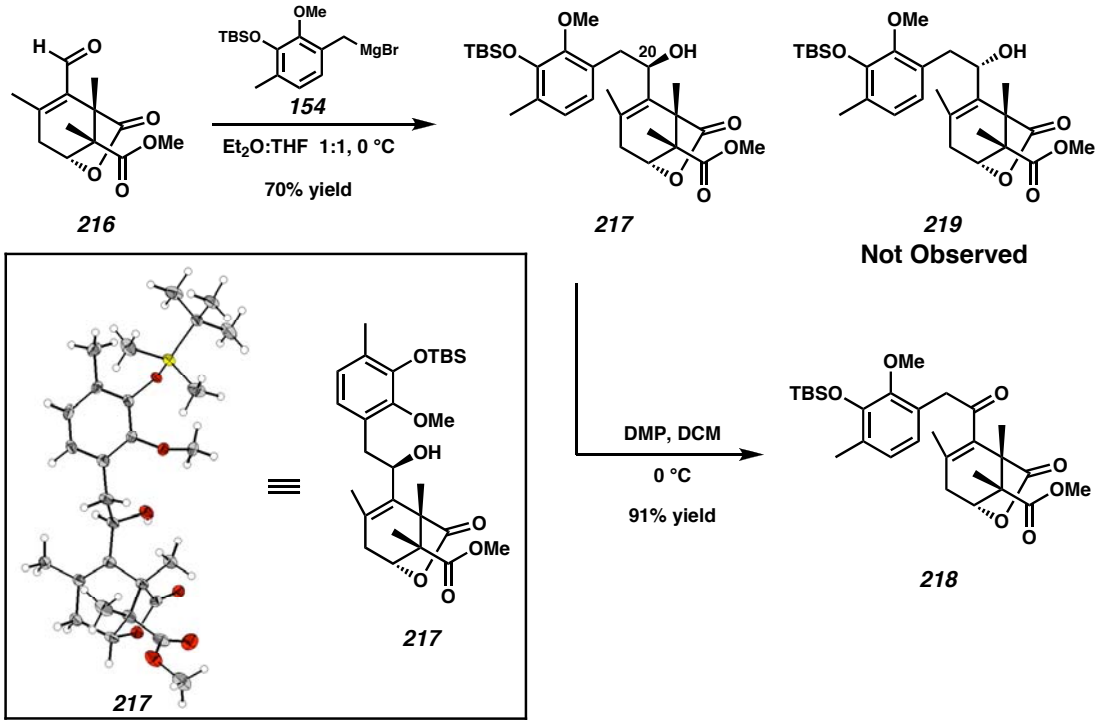


3.3.2 *A and C Ring Fragment Coupling*

Coupling of enal **216** with the A ring Grignard reagent **154** proved more difficult than anticipated (Scheme 3.8). Enal **216** was insoluble in the methylene chloride/ethyl ether mixtures that were found to give good diastereoselectivity for allylic alcohol **155** in

Chapter Two. Enal **216** did not undergo 1,2-addition when not dissolved. A large amount of tetrahydrofuran was required to dissolve enal **216** and, under those conditions, addition strongly favored the formation of allylic alcohol **217**, corresponding to the diastereomeric series at C(20), which did not undergo S_N' cyclization when exposed to TFA.[16] The assignment of allylic alcohol **217**'s C(20) stereocenter was made initially by comparison to ^{1}H NMR splitting patterns in allylic alcohol **155** and later confirmed by X-ray structure determination. Allylic alcohol **217** underwent smooth oxidation with Dess-Martin periodinane to give enone **218**. Attempts to generate allylic alcohol **219** for S_N' cyclization by either Mitsunobu inversion or reduction of enone **218** were unsuccessful.[17] As a result, S_N' cyclization strategy was not accessible with the lactone C ring synthon.

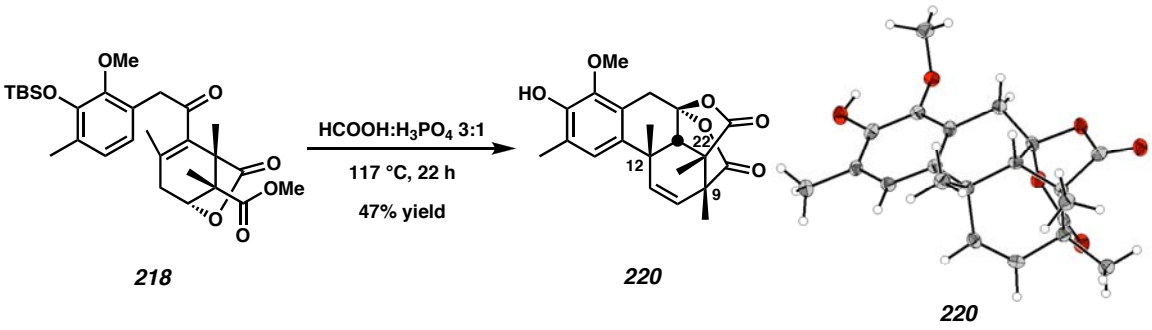
Scheme 3.8 Grignard Addition



3.3.3 *Cyclization By Friedel-Crafts Conjugate Addition*

A number of Lewis and Brønsted acidic conditions are known to promote intramolecular conjugate addition of electron rich arenes into enones.[18] Enone **218** underwent only loss of the TBS group and decomposition when treated with TFA at 110 °C, $AlCl_3$ in toluene at 100 °C, or polyphosphoric acid at 100 °C. However, when treated with a mixture of formic acid and 85% phosphoric acid, enone **218** underwent an interesting cyclization reaction to afford the unusual caged bisacetoxyacetal **220** in 47% yield. Unfortunately, bisacetoxyacetal **220** exhibited the undesired relative stereochemistry between the newly formed C(12) stereocenter and the other quaternary stereocenters (C(9) and C(22)) as determined by X-ray structure analysis.

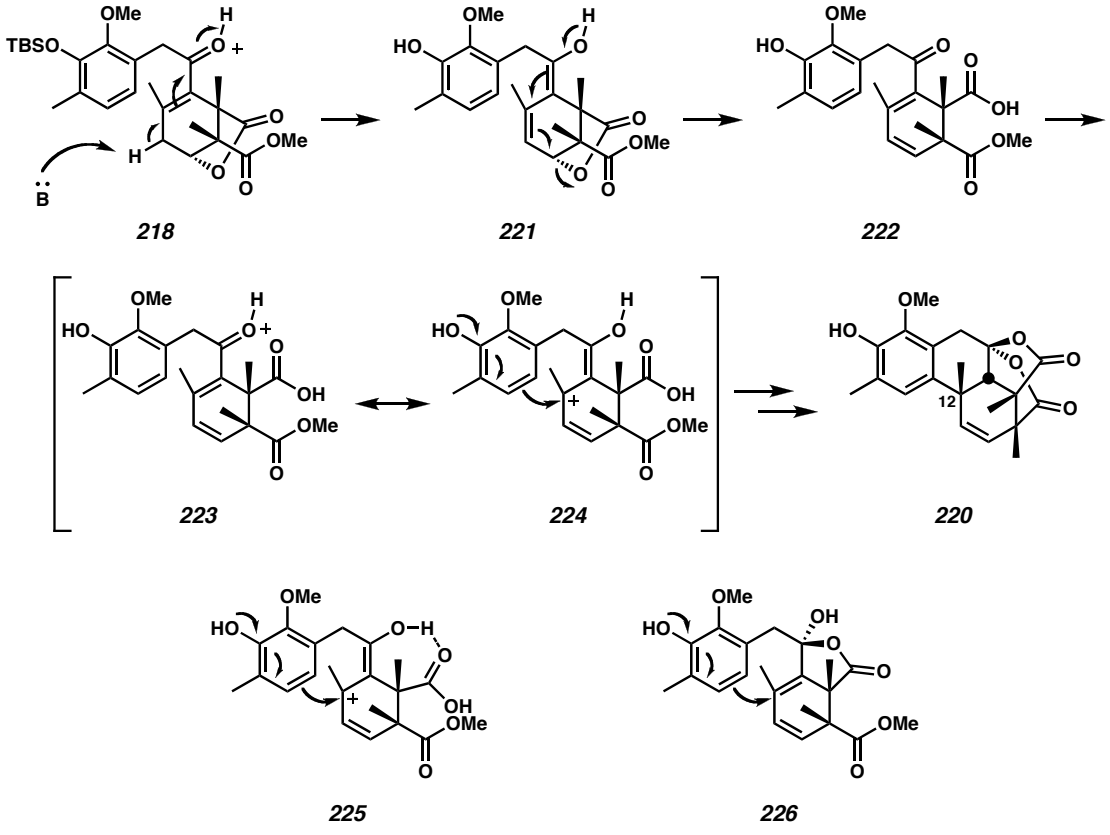
Scheme 3.9 Acid-Mediated Cyclization



Unique to the formic acid/phosphoric acid conditions was an elimination to give the C(11)-C(12) olefin. This was likely crucial to the mechanism of the successful conjugate addition (Scheme 3.10). The formation of extended enol **221** may trigger the elimination of the carboxylic acid to give extended enone **222**. Protonation of enone **222** leads to resonance form **224**, which stabilizes the positive charge as a tertiary allylic

carbocation. The increased contribution of this resonance form encourages conjugate addition and explains the lack of cyclization in cases where no elimination took place. The complete selectivity for bisacetoxyacetal **220**, with the undesired C(12) stereochemistry, suggests that some preorganization involving the ketone moiety guides the outcome of the cyclization. Possibilities for preorganization include intramolecular hydrogen bonding (structure **225**) or hemiacetal formation (structure **226**). Encouraged by the bond-forming reactivity, we hoped to design a substrate that was disposed to generate the desired C(12) stereochemistry.

Scheme 3.10 Possible Mechanism for Enone Cyclization

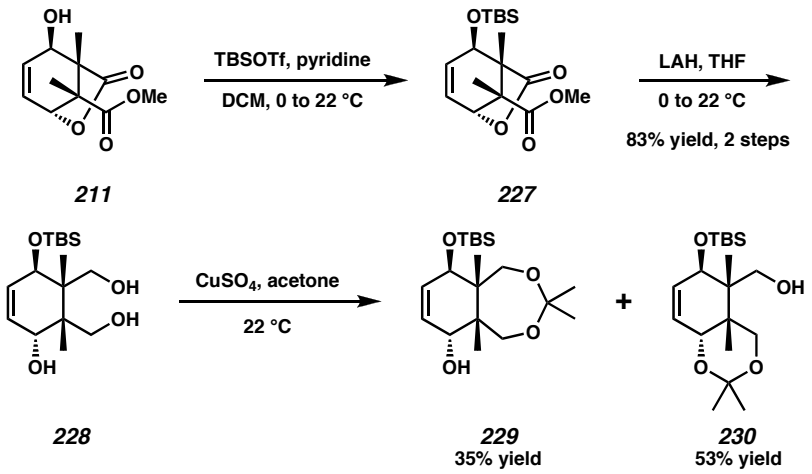


3.4 Studies Toward Elaborated C Ring Synthons

3.4.1 *Elaboration of Intermediate Allylic Alcohol **211***

Our attempts to synthesize more advanced substrates for cyclization had two goals: first, to better differentiate the lactone and methyl ester functionality in allylic alcohol **211** before cyclization, and second, to bias the cyclization toward the desired stereochemistry of the benzylic quaternary center. We began with intermediate allylic alcohol **211**, which was readily protected with TBSOTf to give silyl ether **227** (Scheme 3.11). Less reactive silylating agents (e.g., TBSCl) failed to give complete conversion to silyl ether **227** and demonstrated the challenges of performing even simple manipulations at neopentyl sites. Reduction of silyl ether **227** with LAH in THF afforded triol **228** in 83% yield over two steps. Differential protection of the triol presented a number of challenges. Strongly acidic conditions for acetonide formation removed the silyl protecting group. Anhydrous copper (II) sulfate in acetone showed good reactivity but gave a surprising mixture of 1,3-dioxepane **229** and acetonide **230**.[19,20] Although 1,3-dioxolane **230** is shown as the major product of the reaction, the ratio of the two products varied significantly.[21] While this mixture of products might seem undesirable on first consideration, both modes of protection proved useful in further elaboration.

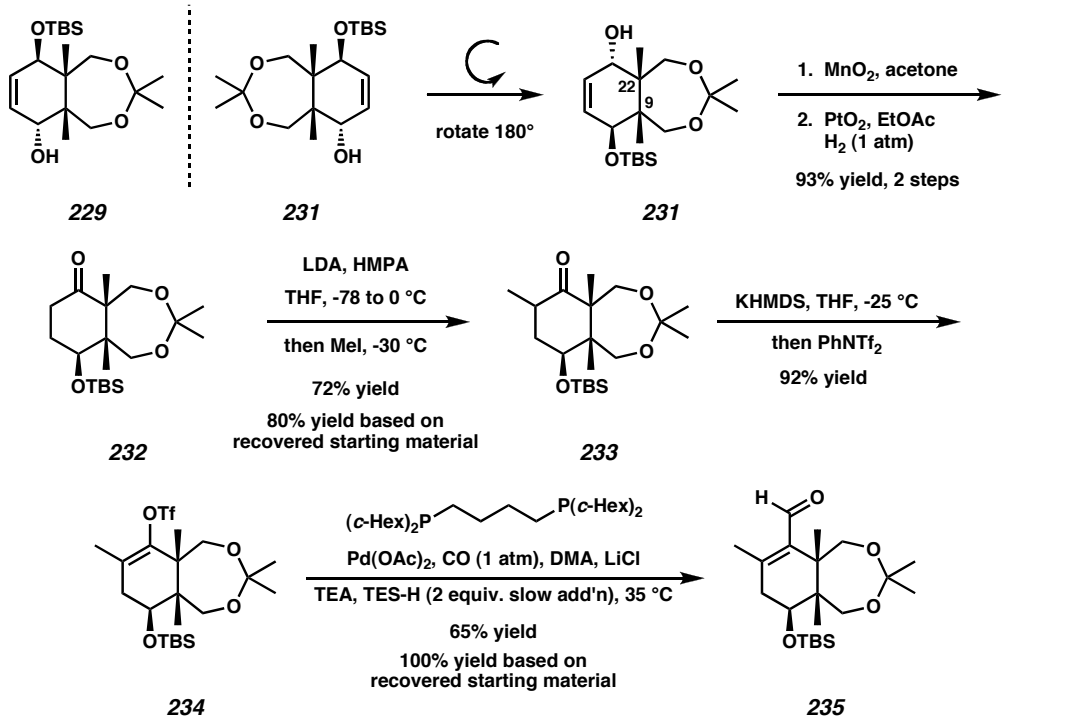
Scheme 3.11 C Ring Elaboration



3.4.2 *Development of the 1,3-Dioxepane Containing C Ring Synthon*

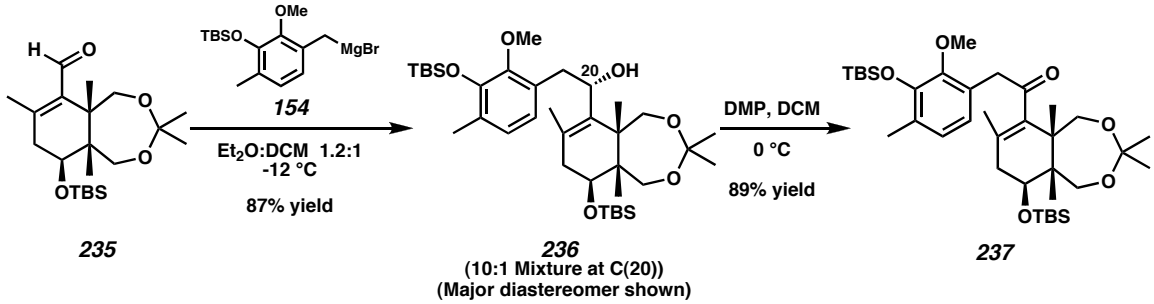
1,3-Dioxepane **229** offered a serendipitous opportunity to construct a C ring fragment capable of elaboration to zoanthenol. Although we typically depict 1,3-dioxepane as enantiomer **229**, we have equally ready access to enantiomer **231** from our desymmetrization process (Scheme 3.12). When rotated by 180°, enantiomer **231** suggests the orientation of the C(9) and C(22) quaternary stereocenters shown. This perspective allowed us to construct a 1,3-dioxepane-containing C ring synthon in a manner analogous to our previous efforts with enal **145** and enal **216**. Conversion of allylic alcohol **231** to ketone **232** was accomplished in excellent yield by a two-step oxidation and hydrogenation sequence. Conventional methylation with LDA and methyl iodide afforded a combined 72% yield of separable methyl ketones **233**. Both ketone diastereomers were readily converted to triflate **234**. Pleasantly, triflate **234** was a good substrate for our palladium-catalyzed carbonylation and afforded a 65% yield of enal **235**, with the remaining material recovered as unreacted triflate.

Scheme 3.12 Completion of the 1,3-Dioxepane-Based C Ring Synthon



Addition of our A ring Grignard synthon gave a good yield of allylic alcohol **236** as a 10:1 mixture of diastereomers. The relative stereochemistry at C(20) of the major diastereomer was assigned by comparison of ^{1}H NMR splitting patterns. Oxidation of allylic alcohol **236** occurred without incident to give enone **237**.

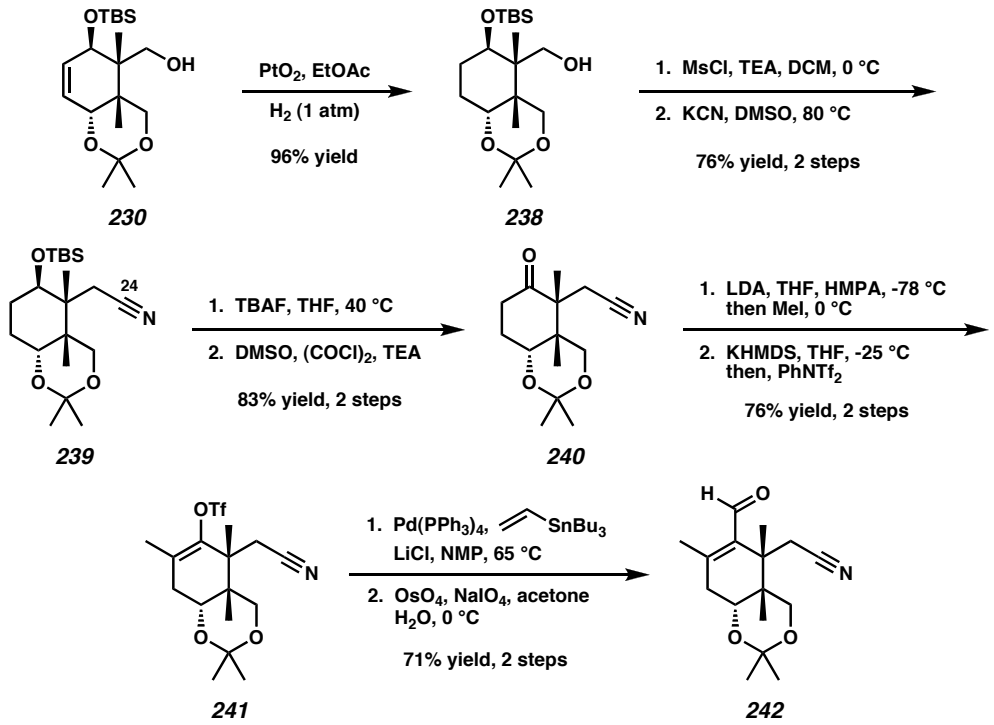
Scheme 3.13 Completion of the 1,3-Dioxepane-Containing Cyclization Substrate



3.4.3 *Development of the 1,3-Dioxane-Containing C Ring Synthon*

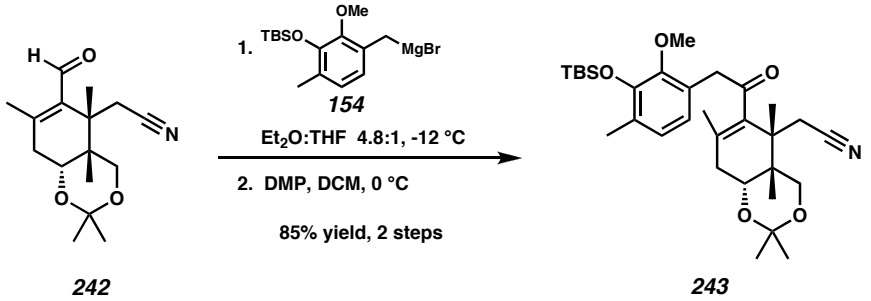
Acetonide **230** was used as a starting material to develop an alternative C ring synthon (Scheme 3.14). The major advantage of this strategy was that it allowed us to consider several methods of homologation to install C(24). Hydrogenation of acetonide **230** with Adams catalyst gave clean conversion to primary alcohol **238**. This molecule had appropriately protected functionality to investigate strategies for homologation. One strategy involved oxidation of alcohol **238** to the corresponding aldehyde and reaction with various Wittig reagents. However, these reactions proved sluggish, and even with a large excess of reagents poor conversion occurred.[22] Another strategy for homologation was cyanide displacement of a leaving group. Although S_N2 displacements at neopentyl positions are difficult to achieve,[23] the opportunity to introduce C(24) in the correct oxidation state as a nitrile encouraged us to pursue the strategy. In the event, mesylation of alcohol **238** with mesyl chloride and TEA, followed immediately by treatment of the crude mesylate with potassium cyanide in DMSO at 80 °C, afforded a 76% yield of nitrile **239**.[24] This material was converted to ketone **240** by silyl ether cleavage and Swern oxidation. Intermediate ketone **240** was converted by standard means to enol triflate **241**. Unfortunately, enol triflate **241** failed to undergo palladium-catalyzed carbonylation, but was instead converted to enal **242** by Stille coupling with tributylvinyltin followed by oxidative cleavage.

Scheme 3.14 Completion of the Nitrile Homologated C Ring Synthon



Fragment coupling with the A ring synthon and completion of enone **243** occurred as anticipated (Scheme 3.15). 1,2-Addition of Grignard reagent **154** afforded a good yield of a 3:1 mixture of diastereomeric allylic alcohols. This mixture was readily oxidized with Dess-Martin periodinane to give enone **243** in 85% yield for two steps.

Scheme 3.15 Completion of the Nitrile-Containing Cyclization Substrate

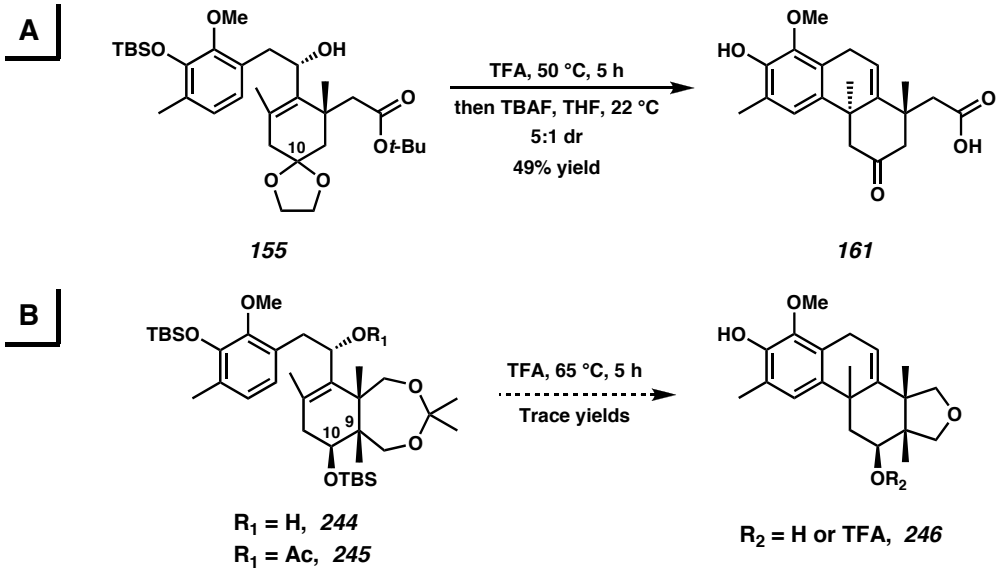


3.5 B Ring Formation Strategies for Advanced C Ring Synthons

3.5.1 *Cyclization Strategies for Substrates in the Alcohol Oxidation State at C(20)*

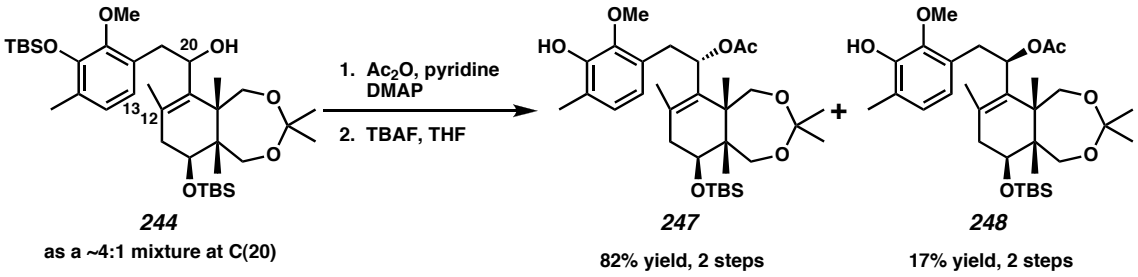
With ready access to several iterations of AC ring adducts, we turned our attention to finding reactions that would efficiently complete the B ring by forming the C(12)-C(13) bond. Directly inspired by our TFA-mediated cyclization of allylic alcohol **155**,[16] we attempted the same transformation with our advanced AC ring adducts (Scheme 3.16). We anticipated that the addition of the remote quaternary stereocenter at C(9) would have little impact on the reaction and that the additional alcohols deprotected during the reaction would be no more burdensome than the phenol present in the original reaction. We were disappointed to find that when either allylic alcohol **244** or acetate **245** were treated with trifluoroacetic acid at 65 °C, only a very small portion of the material exhibited an ^{1}H NMR spectra consistent with cyclization. The cyclized material represented only one of seven isolated products from the reaction, and was tentatively assigned as tetrahydrofuran **246** of the structures shown in Scheme 3.16. The low yield and likely formation of a tetrahydrofuran in structure **246** precluded the use of this strategy with 1,3-dioxepane substrates. Cyclizations of the analogous nitrile-containing AC ring adduct also failed.[25] We hypothesized that the difference in reactivity between allylic alcohols **155** and **244** might be caused by the different C(10) oxidation states. However, the C(10) ketone derived from allylic acetate **245** also failed to undergo significant S_N' cyclization.[26]

Scheme 3.16 Trifluoroacetic Acid-Mediated Cyclization



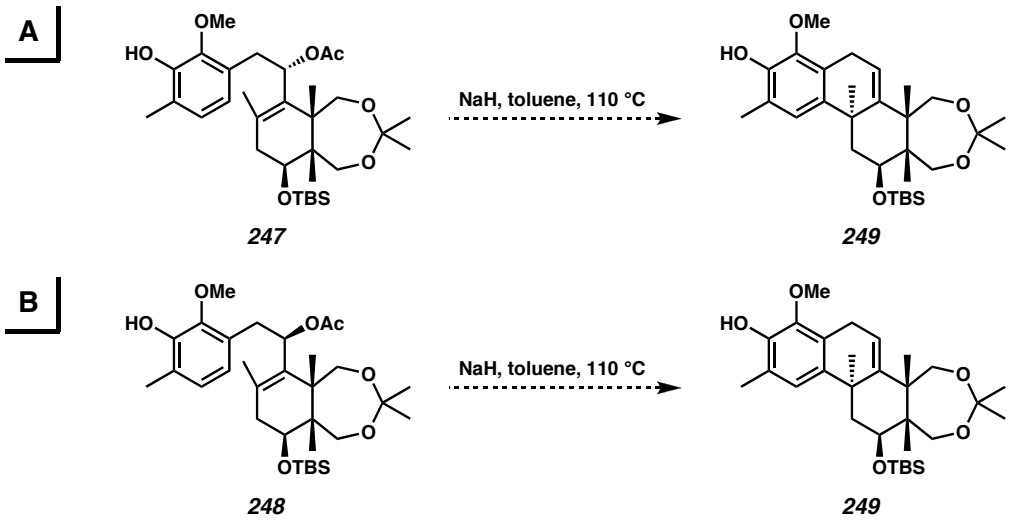
As an alternative, we explored reactions utilizing allylic leaving groups. Allylic alcohol **244** was converted to phenol acetates **247** and **248** by acylation and deprotection of the phenolic silyl group (Scheme 3.17). Fortuitously, the diastereomeric phenols were separable by column chromatography, and their relative stereochemistry was assigned by comparison to ^{1}H NMR spectra of analogous compounds.

Scheme 3.17 Derivatization and Separation of Allylic Alcohol **244**



A straightforward strategy for cyclization relied on treatment of phenol acetates **247** and **248** with sodium hydride to generate phenoxides in situ (Scheme 3.18). We anticipated that these phenoxides might act as carbon nucleophiles in an S_N' process. In the event, treatment with sodium hydride in most solvents simply led to acetate cleavage near ambient temperature. However, in toluene the phenoxides did not show significant deacetylation until much higher temperatures. In the case of phenol **247**, which we anticipated would be more likely to undergo S_N' cyclization,[16] an interesting oxidative cleavage occurred to give enal **235**. No cyclization was observed for either phenoxide.

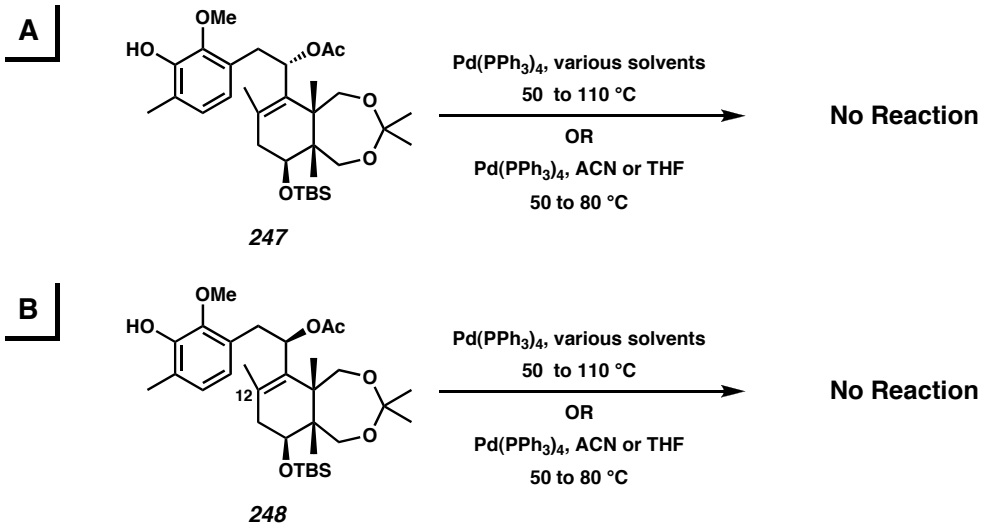
Scheme 3.18 Base-Promoted Cyclization Strategy



Another approach involved the use of palladium π-allyl complexes generated from the phenol acetates **247** and **248** as electrophiles (Scheme 3.19). In keeping with the double inversion mechanism of classical π-allyl chemistry, we anticipated isomer **248** would produce the desired stereochemistry at C(12).[27] Unfortunately, no evidence of oxidative addition into the allylic acetate was ever observed under any conditions. This

lack of reactivity was likely due to the number of sterically demanding substituents on the allyl portion of the molecule.

Scheme 3.19 Palladium π-Allyl Cyclization Strategy

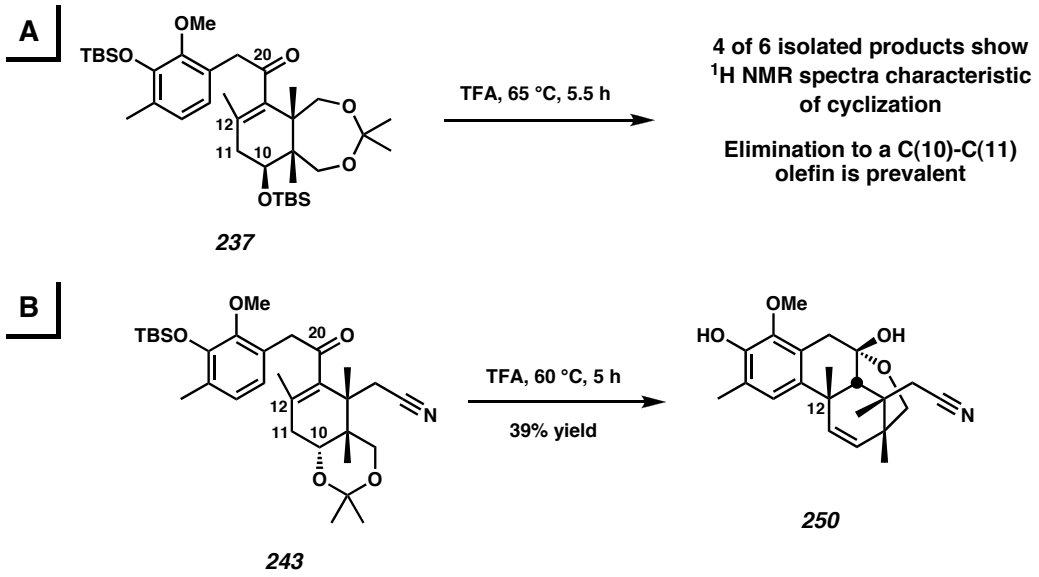


3.5.2 *Cyclization Strategies for Enone Substrates*

Another group of strategies for B ring formation used the AC ring adducts in the ketone oxidation state at C(20) as starting materials (Scheme 3.20). Upon exposure of enones **237** and **243** to trifluoroacetic acid, we anticipated elimination to form a C(10)-C(11) olefin in a manner similar to the formation of bisacetoxy acetal **220**. However, we anticipated that the different functionality of enones **237** and **243** would disrupt the preorganization of the substrate that led to the undesired stereochemistry at C(12) in bisacetoxy acetal **220**. Attempted trifluoroacetic acid cyclization of enone **237** led to a complex mixture of products. Although the majority of isolated products had ^{1}H NMR spectra consistent with cyclization, diastereoselectivity at C(12) appeared low and tetrahydrofuran formation seemed likely. Treatment of enone **243** with trifluoroacetic

acid at 60 °C led predominantly to a cyclized product, which was assigned as hemiacetal **250** by comparison to bisacetoxy acetal **220**. Unfortunately, selectivity was again obtained for the undesired C(12) stereochemistry.[28] Finally, cyclization of enone **243** with $AlCl_3$ in various solvents did not produce any cyclized products.

Scheme 3.20 Trifluoroacetic Acid-Mediated Enone Cyclizations

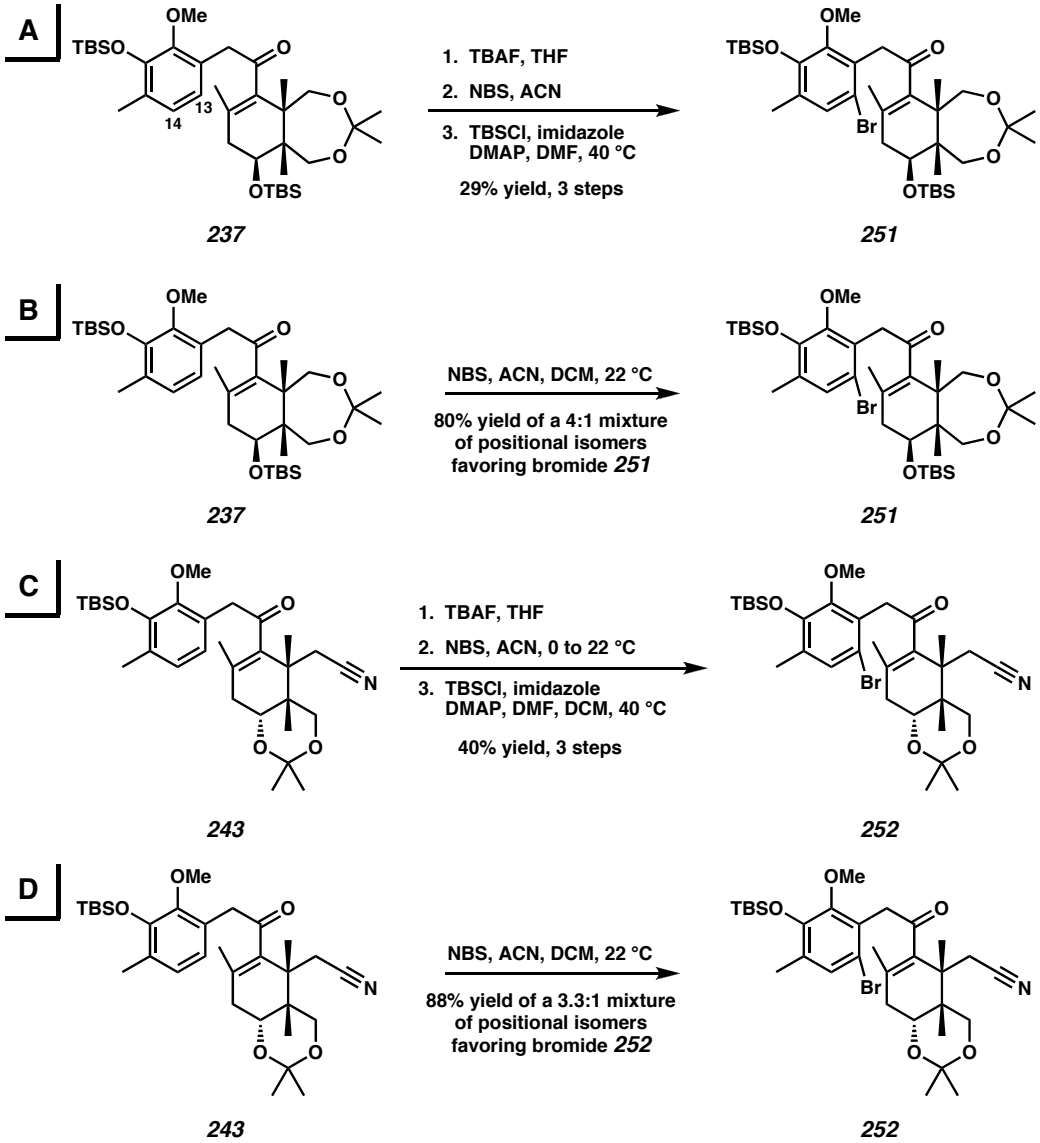


3.5.3 *Cyclization Strategies for Aryl Bromides*

In addition to cyclization strategies of our AC ring enones discussed above, we also considered cyclization strategies based on bromination of the arene nucleus at C(13) (Scheme 3.21). *N*-Bromosuccinimide (NBS) was well known to brominate *para* to electron releasing groups.[29] While there was little precedent for the superiority of silyl ethers over methoxy ethers as the directing group in this reaction, there was significant evidence that phenols were superior to methoxy ethers.[30] As a result, we carried out a three-step protocol to regioselectively produce aryl bromide **251**. Subsequently, we

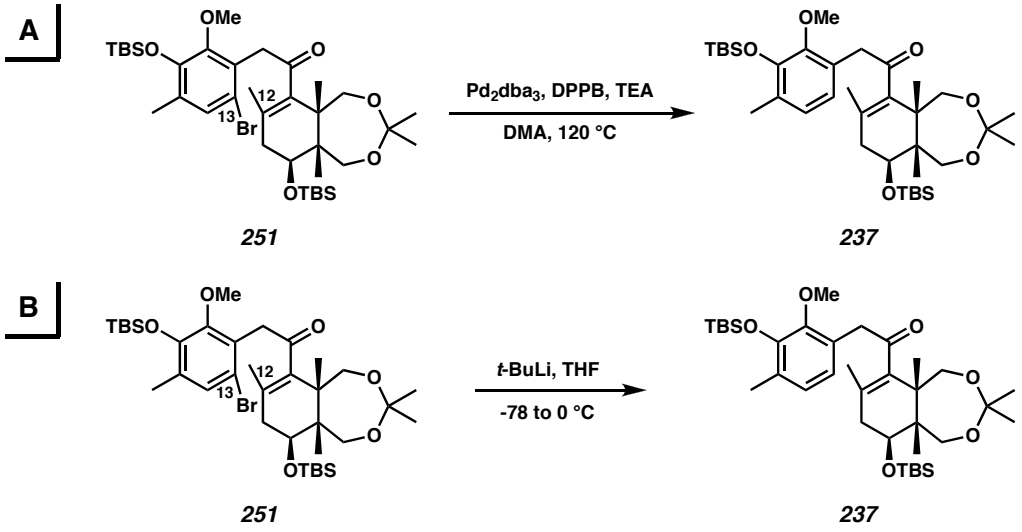
found that direct bromination of enone **237** gave a favorable 4:1 mixture of bromide positional isomers in high yield. This mixture of bromide isomers was adequate for our investigations of cyclization reactions. Homologated enone **243** underwent both the regioselective three-step bromination and direct bromination with similar results to enone **237**.

Scheme 3.21 Bromination Methods for Enone **237** and **243**



The synthesis of aryl bromides allowed us to investigate several metal-based strategies for the formation the B ring. Palladium-catalyzed 6-*exo* Heck cyclizations have been demonstrated to be efficient in forming the final bond (C(12)-C(13)) of the zoanthenol B ring.[31] In general, *exo*-Heck reactions are more favorable and much more common, but in certain cases 6-*endo* Heck cyclizations have been accomplished.[32] The intramolecular Heck reaction has been extensively reviewed.[33] We attempted 6-*endo* Heck cyclizations of bromoarene **251**, but recovered only debrominated material (Scheme 3.22).[34] Analogously, metal-halogen exchange with *tert*-butyl lithium at -78 °C was successful as judged by debromination, but the resulting anion failed to undergo conjugate addition, and led to the isolation of enone **237**.

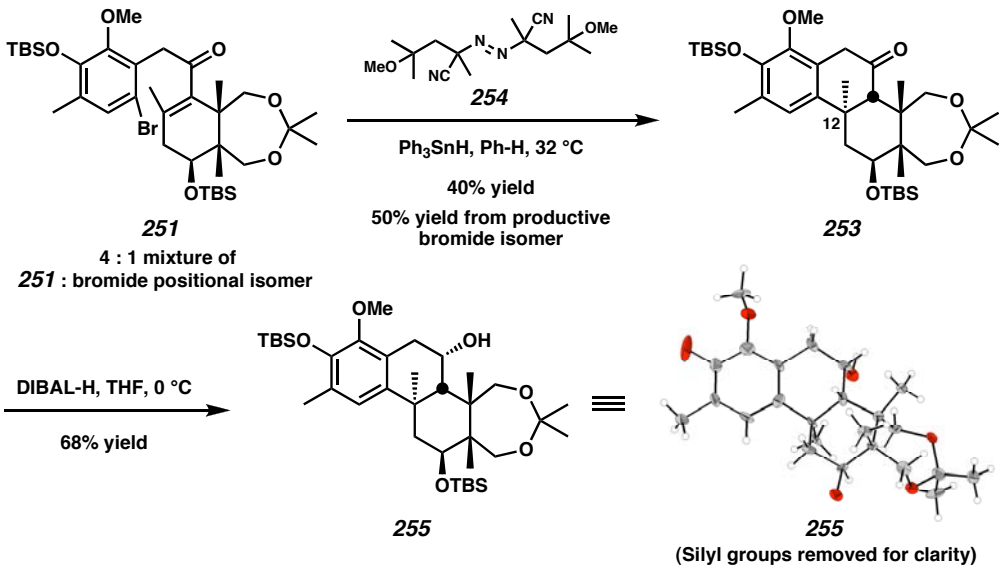
Scheme 3.22 Heck and Metal-Halogen Exchange Strategies for Cyclization



Another strategy that we investigated based on our bromoarenes was radical conjugate addition. As with Heck reactions, *endo* radical conjugate addition cyclization reactions are much less common than *exo* reactions.[35] However, a good precedent for

arene radical conjugate addition to make a quaternary center and a six-membered ring had been demonstrated.[36] To our delight, we found that in the presence of an azo radical initiator (e.g., AIBN) and a hydrogen atom donor (e.g., Bu_3SnH), aryl bromide **251** did form significant amounts of ketone **253** (Scheme 3.23). To date, our best conditions involve azo compound **254** (V-70) and slow addition of Ph_3SnH at 32 °C. In addition to the desired product, significant amounts of the debrominated enone **237** are obtained. The use of V-70 (**254**), which decomposes more readily ($t_{1/2}$ = ~10 h at 30 °C) than AIBN ($t_{1/2}$ = ~10 h at 80 °C), allows us to initiate the radical reaction at lower temperatures and reduces the amount of debrominated enone recovered. The stereochemical outcome of the radical-based cyclization was unambiguously confirmed by X-ray structure analysis of alcohol **255**, which was obtained from DIBAL-H reduction of ketone **255**.[37] While the yield of ketone **253** is still modest, our initial experiments in switching from AIBN to V-70 suggest that many reaction parameters will need to be further optimized (e.g., amounts of reagents, temperature, and rate of addition). We also plan to explore other avenues of optimization, such as the use of Lewis acids.[38]

Scheme 3.23 Radical Cyclization Methods for B Ring Formation



Currently, our efforts are directed at the optimization of the radical conjugate addition reaction conditions and employing the C(24) homologated series of compounds (e.g., aryl bromide **252**) as substrates for radical cyclization.[39] We believe that this radical cyclization strategy provides a novel, efficient, and functional group tolerant method to form the key C(12) quaternary stereocenter and close the B ring. The synthesis of the ABC ring fragments containing all three of zoanthenol's quaternary stereocenters represents an important milestone toward the total synthesis of this interesting alkaloid.

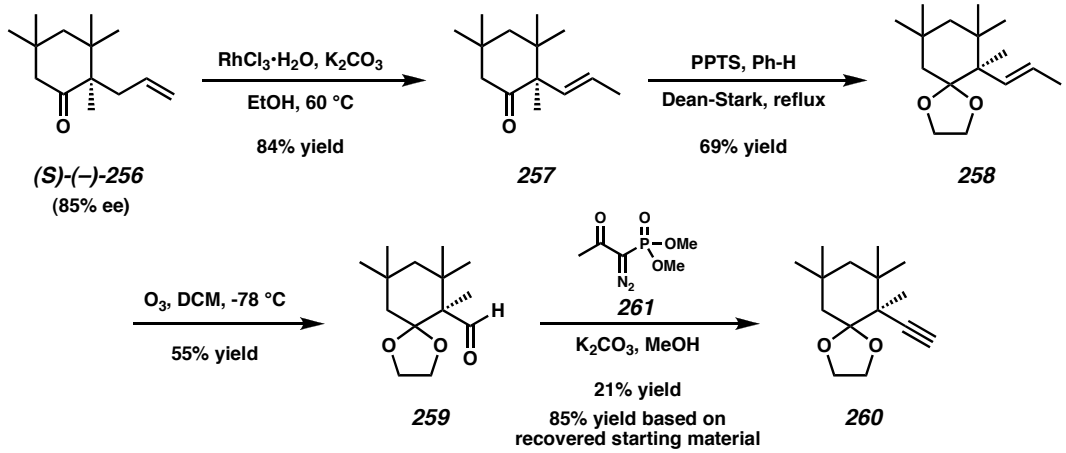
3.6 Model Studies for the Incorporation of the C(1)-C(6) Fragment

A final goal in validating our revised retrosynthetic plan was to model the fragment coupling between caprolactam **123** and the ABC ring fragment containing an alkyne. While alkynes are generally excellent nucleophiles, we judged it prudent to

model this reaction due the extremely crowded steric environment around the C ring and multiple sites of possible addition into caprolactam **123**. A similar alkyne addition strategy was employed in Miyashita's recent synthesis of norzoanthamine.[40]

The model alkyne we designed was intended to represent the worst case steric environment about the C ring (Scheme 3.24). Allyl ketone **256** was prepared in enantioenriched form by our asymmetric Tsuji allylation.[41] Isomerization of the allyl group was achieved with rhodium (III) chloride hydrate to give a 10:1 mixture favoring vinyl ketone **257**. Ketalization of vinyl ketone **258** under standard conditions followed by ozonolysis afforded aldehyde **259**. Conversion to the target alkyne **260** was accomplished using diazo compound **261** according to the Ohira-Bestmann modification of the Gilbert-Seyferth protocol.[42,43]

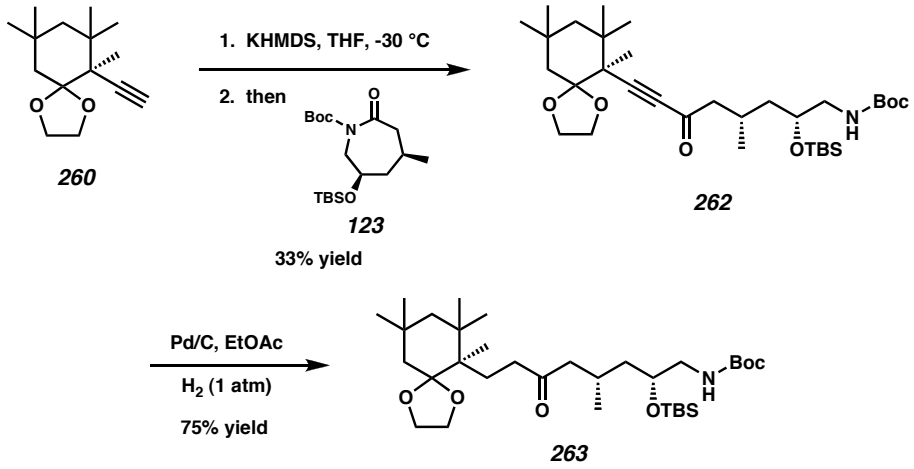
Scheme 3.24 Synthesis of C Ring Model Alkyne



With alkyne **260** in hand we began coupling studies with caprolactam **123** (Scheme 3.25). KHMDS proved to be optimal as the base for the deprotonation of alkyne **260**.[44] While achieving high conversion to ynone **262** proved difficult, the alkyne

anion did cleanly add to the lactam carbonyl of caprolactam **123**.[45] This consistently low conversion is puzzling, as deuterium quenching experiments with the lithium salt of alkyne **260** showed >90% deuterium incorporation. However, the exclusive formation of ynone **262** validates the retrosynthetic disconnection as feasible. Hydrogenation of ynone **262** with Pd/C afforded ketone **263** as expected.

Scheme 3.25 Alkyne Fragment Coupling



3.7 Concluding Remarks

We have demonstrated effective methods for the synthesis of a number of C ring synthons containing vicinal quaternary stereocenters. Our desymmetrization of *meso*-anhydride **203** affords access to either enantiomeric series of these synthons. Oxidation of our C ring intermediates was efficiently achieved by iodolactonization and S_N2' displacement. The resulting allylic alcohol **211** served as a branch point for the synthesis of three progressively more functionalized C ring synthons, the most elaborate of which includes homologation by cyanide displacement to install C(24).

Methods developed in Chapter Two allowed us to append each of these C ring synthons with an appropriately functionalized arene and explore methods to construct the challenging C(12) quaternary center by forming the C(12)-C(13) bond. Unfortunately, our previous S_N' and acid-mediated conjugate addition strategies proved unworkable when the cyclization substrates contained the additional quaternary center. The S_N' reactions gave only trace amounts of cyclized products, while the cyclized products generated by conjugate addition consistently had the undesired configuration at the formed quaternary stereocenter. However, a radical conjugate addition strategy was developed and demonstrated to form the benzylic C(12) quaternary stereocenter with high selectivity for the desired configuration. This radical cyclization approach has the significant advantage of using mild reaction conditions and being highly functional group tolerant. Products from the radical cyclization reactions are well poised to complete the synthesis. Finally, we showed our alkyne addition strategy for fragment coupling of the C(1)-C(6) portion of zoanthenol to be feasible even with extremely hindered alkynes.

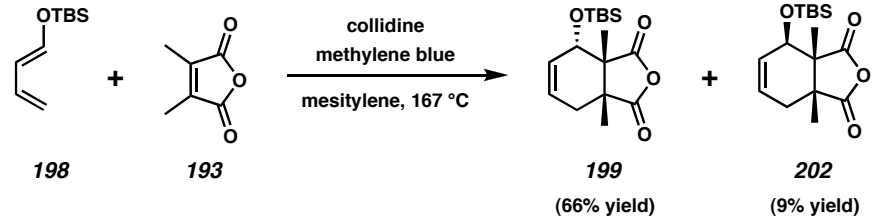
3.8 Experimental Procedures

3.8.1 *Materials and Methods*

Unless otherwise stated, reactions were performed at ambient temperature (typically 19-24 °C) in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. HMPA, TEA, DIPA, and pyridine were freshly distilled from CaH. KHMDS (95%) was purchased from Aldrich and stored in a glovebox until use. Trifluoroacetic acid (99%) was purchased from Aldrich. LiCl was flame-dried

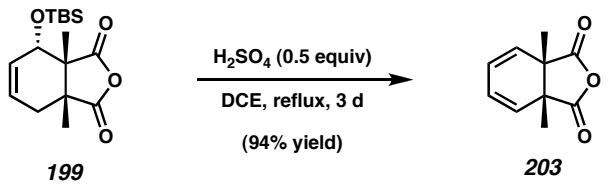
under vacuum prior to use. Magnesium turnings were of 99.98% purity and purchased from Aldrich. TBSCl was purchased from Gelest. TBSOTf was freshly prepared by the method of Corey.[46] V-70 was purchased from Waco Chemicals. All other commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, anisaldehyde, $KMnO_4$, or CAM staining. ICN silica gel (particle size 0.032-0.063 mm) was used for flash chromatography. Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz, respectively), or a Varian Inova 500 (at 500 MHz and 125 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, sept. = septet, m = multiplet, comp. m = complex multiplet, app. = apparent, bs = broad singlet. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the Caltech Mass Spectral Facility. Crystallographic analyses were performed at the California Institute of Technology Beckman Institute X-Ray Crystallography Laboratory. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, and copies can be obtained on request, free of charge, from the CCDC by quoting the publication citation and the deposition number (see individual structures for deposition numbers).

3.8.2 *Preparation of Compounds*

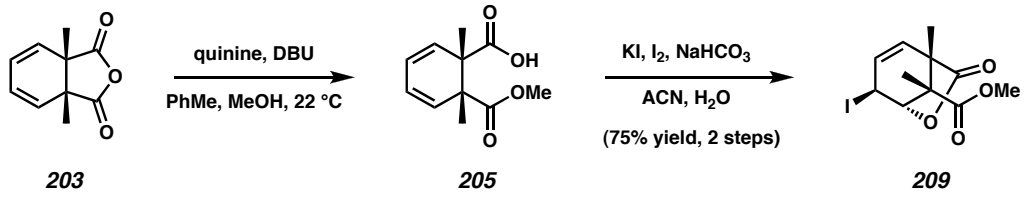


198 *193* *199* (66% yield) *202* (9% yield)

***Endo*-Diels-Alder adduct 199 and *Exo*-Diels-Alder adduct 202.** A mixture of diene **198** (67.3 g, 367.2 mmol, 1.00 equiv), 2,3-dimethylmaleic anhydride (46.3 g, 367.2 mmol, 1.00 equiv), collidine (2.91 mL, 22.0 mmol, 0.06 equiv), methylene blue (68.0 mg, 0.213 mmol, 0.000579 equiv), and mesitylene (80 mL) in a flamed-dried Ar filled Schlenk was sparged with Ar for 10 min, sealed, and heated to 167 °C for 3 d. Upon cooling, the reaction mixture was concentrated at 80 °C to give an oil, which was purified by flash chromatography on silica gel (1 to 10% EtOAc in hexanes) to give known *endo*-Diels-Alder adduct **199** (75.7 g, 66% yield), which solidified on standing: R_f 0.42 (15% EtOAc in hexanes) and *exo*-Diels-Alder adduct **202** (10.5 g, 9.2% yield) as an amorphous solid: : R_f 0.58 (15% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.11 (m, 1H), 5.99 (m, 1H), 4.35 (d, J = 5.5 Hz, 1H), 2.61 (dd, J = 6.3, 16.3 Hz, 1H), 2.42 (app. dt, J = 3.3, 16.5 Hz, 1H), 1.42 (s, 3H), 1.39 (s, 3H), 0.88 (s, 9H), 0.10 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 77.4, 175.1, 132.2, 129.8, 69.1, 53.8, 46.5, 34.2, 25.6, 21.6, 18.0, 17.6, -4.4, -5.2; IR (Neat film NaCl) 2952, 2930, 1774, 1250, 986, 1091, 986, 958, 914, 838, 778 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{16}H_{26}SiO_4+H]^+$: m/z 311.1679, found 311.1671.



Diene 203. To a solution of *endo*-Diels-Alder adduct **199** (19.0 g, 61.4 mmol, 1.0 equiv) in DCE (614 mL) was added H_2SO_4 (1.71 mL, 30.7 mmol, 0.50 equiv), and the resulting solution was refluxed for 3 d. Upon cooling the reaction mixture was washed with sat. aq. $NaHCO_3$ (2 x 300 mL) [*Caution: gas evolution!*] and extracted with CH_2Cl_2 (2 x 120 mL). The combined organics from two such reactions were concentrated to give an oil and purified by flash chromatography on silica gel (1 to 10% EtOAc in hexanes) to give diene **203** (20.7 g, 94% yield) as a white solid: mp 61.5-62.5 °C; R_f 0.33 (15% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.18-6.13 (m, 2H), 5.66-5.61 (m, 2H), 1.37 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 75.1, 126.3, 124.5, 49.9, 18.6; IR (Neat film NaCl) 2984, 2940, 2848, 1856, 1785, 1233, 1196, 962, 912 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{16}H_{26}SiO_4+H]^+$: *m/z* 311.1679, found 311.1671.

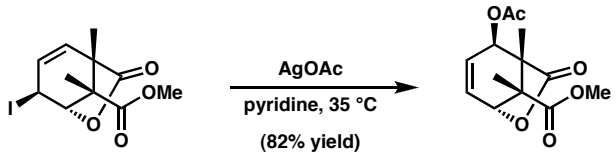


Iodolactone 209. To a solution of diene **203** (17.2 g, 96.6 mmol, 1.00 equiv), quinine (3.48 g, 9.66 mmol, 0.10 equiv), and DBU (15.9 mL, 106 mmol, 1.1 equiv) in toluene (483 mL) was added MeOH (39.1 mL, 966 mmol, 10.0 equiv). After 5 h, the reaction mixture was concentrated and the residue was diluted with EtOAc (1.00 L), washed with 2 M HCl (3 x 200 mL) and brine (1 x 200 mL), dried ($MgSO_4$), and

concentrated. Upon standing under vacuum, carboxylic acid **205** solidified and was typically used immediately in the next step without purification: R_f 0.19 (30% acetone in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80-5.45 (m, 4H), 3.66 (s, 3H), 1.46 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 80.5, 175.1, 131.6, 131.5, 121.9, 121.8, 52.1, 48.4, 48.1, 20.2 (2C); IR (Neat film NaCl) 2985, 2954, 1731, 1700, 1258, 1240, 1132, 1102, 702 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{11}H_{14}O_4]^+$: *m/z* 210.0892, found 210.0898; $[\alpha]_D^{26}$ –10.94 (c 1.03, $CHCl_3$, 50% ee) from reaction with stoichiometric quinine. HPLC analysis (Chirapak AD 4.6 x 25 mm, 5.0% IPA in 95% hexane with 0.1% TFA, 1.0 mL/min, λ = 254 nm) of the asymmetric reaction performed with a catalytic amount of menthol derivative **208** showed carboxylic acid **205** to be of 85% ee (t_{fast} = 10.11 min, major; t_{slow} = 12.13 min, minor).

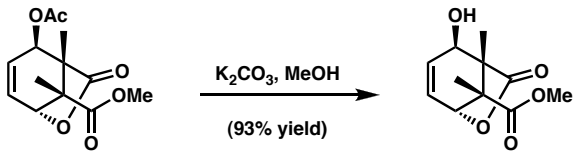
The above residue containing carboxylic acid **205** (theoretical yield: 96.6 mmol, 1.00 equiv) was dissolved in ACN (380 mL) and H_2O (380 mL) and treated with $NaHCO_3$ (24.3 g, 290 mmol, 3.00 equiv), KI (43.3 g, 261 mmol, 2.70 equiv), and I_2 (66.2 g, 261 mmol, 2.70 equiv) and the flask was wrapped in foil to exclude light. After 10 h, the reaction mixture was quenched in the dark with sat. aq. $Na_2S_2O_3$ until colorless, diluted with EtOAc (650 mL), extracted with EtOAc (2 x 300 mL), washed with brine (200 mL), dried ($MgSO_4$), and concentrated to an oil, which was purified by flash chromatography on silica gel (10 to 20% EtOAc in hexanes) to provide iodolactone **209** (24.4 g, 75% yield, 2 steps) as an unstable solid (typically used immediately in the next step): R_f 0.35 (50% EtOAc in hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 5.33 (ddd, *J* = 1.5, 3.0, 9.3 Hz, 1H), 4.86 (dd, *J* = 1.5, 9.3 Hz, 1H), 4.63 (app. t, *J* = 2.1 Hz, 1H), 4.29 (m, 1H), 3.13 (s, 3H), 1.34 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 175.3, 173.0,

133.0, 130.1, 80.4, 53.6, 52.5, 47.0, 16.9, 16.0, 15.0; IR (Neat film NaCl) 2953, 1795, 1732, 1450, 1293, 1247, 1141, 1107, 1062, 969 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{11}H_{14}O_4I]^+$: m/z 336.9937, found 336.9930.



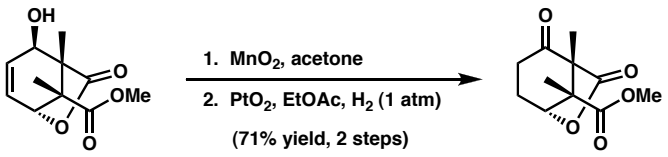
209 *210*

Allylic acetate 210. To a solution of iodolactone **209** (23.0 g, 68.5 mmol, 1.00 equiv) in pyridine (140 mL) was added AgOAc (34.3 g, 206 mmol, 3.00 equiv). The reaction mixture was wrapped in foil to exclude light and heated to 35 °C. After 3.5 d, the reaction mixture was concentrated (~5 torr at 50 °C), diluted with H_2O (500 mL) and CH_2Cl_2 (300 mL), and extracted with CH_2Cl_2 (7 x 150 mL). The combined organics were dried ($MgSO_4$), filtered, concentrated, and purified by flash chromatography on silica gel (15 to 35% EtOAc in hexanes) to provide allylic acetate **210** (15.2 g, 82% yield) as an oil: R_f 0.57 (50% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 6.33 (ddd, J = 1.0, 5.6, 9.1 Hz, 1H), 5.98 (ddd, J = 1.0, 3.5, 9.0 Hz, 1H), 5.35 (dd, J = 1.5, 3.5 Hz, 1H), 4.85 (dd, J = 1.0, 6.0 Hz, 1H), 3.75 (s, 3H), 2.11 (s, 3H), 1.46 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 173.0, 169.6, 131.1, 129.5, 76.8, 69.9, 54.7, 52.7, 50.0, 20.7, 15.6, 13.6; IR (Neat film NaCl) 2986, 2953, 1788, 1735, 1373, 1257, 1219, 1024, 962 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{13}H_{16}O_6+H]^+$: m/z 269.1025, found 269.1014.



210 ***211***

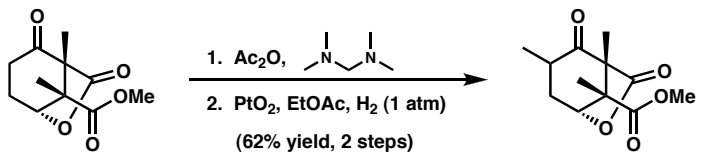
Allylic alcohol 211. To a solution of allylic acetate **210** (15.2 g, 56.2, 1.00 equiv) in MeOH (275 mL) was added K_2CO_3 (1.55 g, 11.3 mmol, 0.20 equiv) and the reaction was vigorously stirred. After 10 min, TLC analysis indicated consumption of the starting material, and the reaction mixture was quenched with H_2O (200 mL), brine (300 mL), and CH_2Cl_2 (200 mL). The pH of the aqueous layer was adjusted to pH 7 with 3 M HCl (~8 mL) [*Caution: gas evolution!*] and extracted with CH_2Cl_2 (10 x 50 mL). The combined organics were washed with brine (100 mL), concentrated, and purified by flash chromatography on silica gel (25 to 35% EtOAc in hexanes) to provide allylic alcohol **211** (11.9 g, 93% yield) as a white solid. Crystals suitable for X-ray analysis were obtained by crystallization from Et_2O/heptanes at ambient temperature: mp 94.5-95.5 °C (Et_2O/heptane); R_f 0.38 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.22 (ddd, J = 1.5, 5.8, 9.3 Hz, 1H), 6.04 (ddd, J = 1.0, 3.3, 9.3 Hz, 1H), 4.79 (dd, J = 1.0, 5.5 Hz, 1H), 4.15 (dd, J = 1.0, 3.5 Hz, 1H), 3.72 (s, 3H), 1.43 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.3, 173.6, 134.8, 127.3, 77.4, 69.8, 54.7, 52.6, 50.8, 15.5, 13.7; IR (Neat film NaCl) 3484, 2954, 1773, 1731, 1454, 1259, 1137, 1110, 1049, 1031, 983, 955 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{11}H_{14}O_5+H]^+$: m/z 227.0919, found 227.0924.



211 *212*

Ketone 212. To a solution of allylic alcohol **211** (2.23 g, 9.86 mmol, 1.00 equiv) in acetone (100 mL) was added activated MnO_2 (17.1 g, 197 mmol, 20.0 equiv) and the reaction mixture was stirred at ambient temperature for 1.25 h. The reaction mixture was filtered, washed with acetone, and concentrated to an oil.

To a solution of this crude material in EtOAc (60 mL) was added PtO_2 (67.1 mg, 0.296 mmol, 0.03 equiv), and the reaction mixture was sparged with H_2 (5 min) and stirred vigorously under an atmosphere of H_2 (balloon) for 1.5 h. The reaction mixture was flushed with N_2 and concentrated to an oil, which was purified by flash chromatography on silica gel (30 to 50% EtOAc in hexanes) to provide ketone **212** (1.59 g, 71% yield) as an amorphous solid: R_f 0.38 (50% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.89 (dd, J = 1.2, 3.9 Hz, 1H), 3.75 (s, 3H), 2.62-2.56 (m, 2H), 2.47-2.37 (m, 1H), 2.15-2.01 (m, 1H), 1.23 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.0, 173.4, 171.3, 79.4, 62.4, 56.5, 53.0, 33.9, 24.9, 14.3, 9.3; IR (Neat film NaCl) 2989, 2955, 1790, 1732, 1343, 1267, 1227, 1152, 1089, 1018, 966 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{11}H_{14}O_5]^+$: m/z 226.0841, found 226.0847.

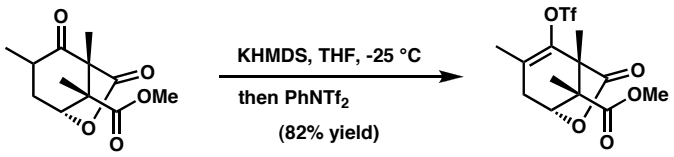


212 *213*

Methyl ketone 213. To a cooled (15 °C) solution of ketone **212** (1.31 g, 5.77 mmol, 1.00 equiv) and Ac_2O (6.55 mL, 69.3 mmol, 12.0 equiv) was added *N*,*N*,*N'*,*N'*-tetramethyldiaminomethane (4.73 mL, 34.6 mmol, 6.00 equiv) in a dropwise manner over 30 min. At the end of the addition, the reaction was allowed to come to ambient temperature. After 4 h, additional Ac_2O (6.00 mL, 63.5 mmol, 11.0 equiv) and *N*,*N*,*N'*,*N'*-tetramethyldiaminomethane (7.00 mL, 51.3 mmol, 8.89 equiv) were added and the reaction was warmed to 32 °C for 12 h. The reaction mixture was then cooled, concentrated in vacuo, quenched into water (40 mL), sat. aq. $NaHCO_3$ (20 mL), and ice (40 g), and extracted with CH_2Cl_2 (4 x 40 mL). The combined organics were dried (Na_2SO_4) and concentrated to give a crude solid that was used immediately in the next step.

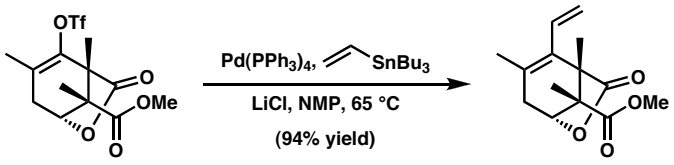
To a solution of the crude material in EtOAc (100 mL) was added PtO_2 (131 mg, 0.577 mmol, 0.10 equiv), and the reaction mixture was sparged with H_2 (5 min) and stirred vigorously under an atmosphere of H_2 (balloon) for 5.5 h. The reaction mixture was flushed with N_2 and concentrated to an oil, which was purified by flash chromatography on silica gel (20 to 40% EtOAc in hexanes) to provide a single diastereomer of methyl ketone **213** (854 mg, 62% yield) as an amorphous solid: R_f 0.57, 0.29 (50% EtOAc in hexanes, 50% Et_2O in hexanes developed twice); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.87 (m, 1H), 3.75 (s, 3H), 2.75-2.56 (m, 2H), 1.82-1.66 (m, 1H), 1.27 (s, 3H), 1.14 (d, J = 6.3 Hz, 3H), 1.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 174.1,

171.3, 79.4, 62.0, 57.3, 53.0, 38.9, 34.0, 14.7, 13.9, 9.6; IR (Neat film NaCl) 2987, 2954, 1788, 1726, 1259, 1154, 1077, 1038 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{12}H_{16}O_5]^+$: m/z 240.0998, found 240.0996.



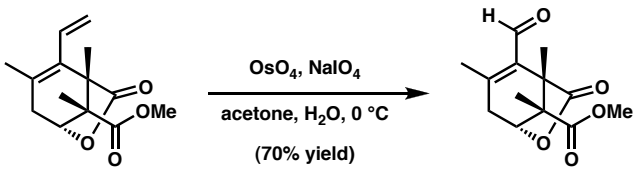
213 ***214***

Triflate 214. To a cooled (-25 °C) solution of KHMDS (339 mg, 1.70 mmol, 1.20 equiv) in THF (12 mL) was added methyl ketone **213** (340 mg, 1.42 mmol, 1.00 equiv) in THF (10 mL) in a dropwise manner over 10 min. After 1.5 h at -25 °C, $PhNTf_2$ (708 mg, 1.98 mmol, 1.40 equiv) in THF (5 mL) was added, and the reaction was maintained for an additional 30 min at -25°C. The reaction mixture was quenched into half-saturated brine (40 mL) and EtOAc (40 mL), and extracted with EtOAc (4 x 15 mL). The combined organics were washed with brine (2 x 20 mL), dried ($MgSO_4$), and concentrated to an oil, which was purified by flash chromatography on silica gel (15 to 40% EtOAc in hexanes) to provide triflate **214** (435 mg, 82% yield) as an oil: R_f 0.20 (50% Et_2O in hexanes developed twice); ^1H NMR (300 MHz, $CDCl_3$) δ 4.59 (app. t, J = 2.7 Hz, 1H), 3.75 (s, 3H), 2.63-2.47 (m, 2H), 1.86 (s, 3H), 1.42 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 172.1, 138.2, 128.2, 118.4 (app. d, $J_{C\text{-}F}$ = 319 Hz), 77.2, 54.6, 53.0, 50.4, 35.0, 17.2, 12.6, 10.0; IR (Neat film NaCl) 2956, 1790, 1727, 1408, 1208, 1138, 824 cm^{-1}; HRMS (EI) $[M+H]^+$ calc'd for $[C_{13}H_{15}O_7F_3S+H]^+$: m/z 373.0569, found 373.0550.



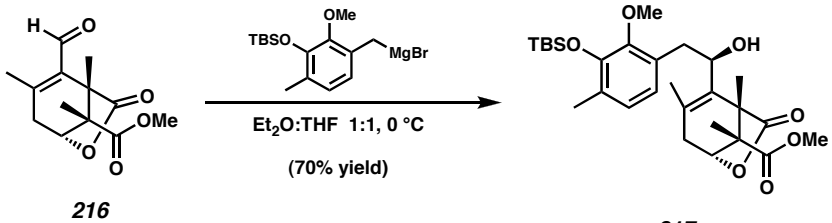
214 *215*

Diene 215. To a solution of triflate **214** (865 mg, 2.32 mmol, 1.00 equiv), $Pd(PPh_3)_4$ (134.2 mg, 0.116 mmol, 0.05 equiv), and LiCl (295 mg, 6.97 mmol, 3.00 equiv) in NMP (18 mL) was added tributyl(vinyl)tin (1.02 mL, 3.48 equiv, 1.50 equiv), and the mixture was heated to 65 °C for 9.5 h. The reaction mixture was cooled to ambient temperature, quenched with H_2O (50 mL) and Et_2O (50 mL), and extracted with Et_2O (5 x 30 mL). The combined organics were washed with brine (2 x 20 mL), dried ($MgSO_4$), and concentrated to an oil, which was purified by flash chromatography on silica gel (5 to 25% EtOAc in hexanes) to provide diene **215** (545 mg, 94% yield) as an oil: R_f 0.63, 0.80 (50% Et_2O in hexanes developed thrice, 50% EtOAc in hexanes developed twice); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.01 (ddd, J = 1.2, 11.3, 17.6 Hz, 1H), 5.34 (dd, J = 2.0, 11.3 Hz, 1H), 5.02 (dd, J = 2.3, 17.6 Hz, 1H), 4.53 (app. t, J = 2.7 Hz, 1H), 3.70 (s, 3H), 2.37 (s, 2H), 1.72 (s, 3H), 1.23 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 173.7, 132.3, 131.5, 130.2, 120.6, 77.7, 53.6, 52.5, 49.3, 35.3, 20.0, 12.9, 12.5; IR (Neat film NaCl) 2985, 2951, 2911, 1782, 1730, 1267, 1198, 1144, 1089, 1035, 972 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{14}H_{18}O_4]^+$: m/z 250.1205, found 250.1204.



215 *216*

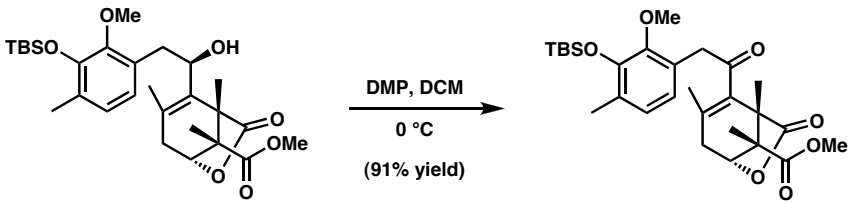
Enal 216. To a cooled (0 °C) solution of diene **215** (271 mg, 1.08 mmol, 1.00 equiv) in acetone (8.00 mL) and H_2O (8.00 mL) was added OsO_4 (27.5 mg, 0.108 mmol, 0.10 equiv) and $NaIO_4$ (511 mg, 2.38 mmol, 2.20 equiv). After 8.5 h at 0 °C, the reaction mixture was quenched with brine (30 mL) and EtOAc (30 mL), and extracted with EtOAc (5 x 30 mL). The combined organics were dried (Na_2SO_4) and concentrated to an oil, which was purified by flash chromatography on silica gel (25 to 50% EtOAc in hexanes) to provide enal **216** (191 mg, 70% yield) as a solid: R_f 0.48 (50% EtOAc in hexanes developed twice); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.88 (s, 1H), 4.54 (app. t, J = 2.4 Hz, 1H), 3.72 (s, 3H), 2.57 (d, J = 1.8 Hz, 2H), 2.07 (s, 3H), 1.49 (s, 2H), 1.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.9, 176.0, 172.8, 151.0, 131.6, 76.7, 53.9, 52.7, 48.2, 37.5, 19.2, 12.5, 12.3; IR (Neat film NaCl) 2952, 1786, 1729, 1681, 1333, 1273, 1250, 1201, 1136, 1082, 1034, 969 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{13}H_{16}O_5]^+$: m/z 252.0998, found 252.0984.



216 *217*

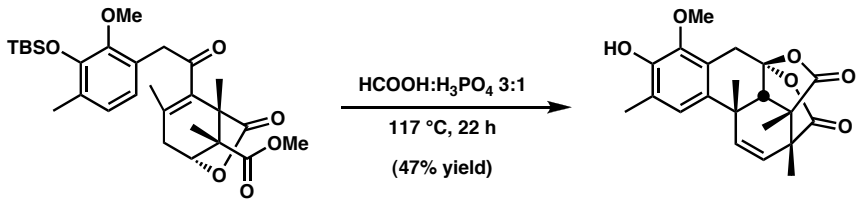
Allylic alcohol 217. A flame-dried two-neck round-bottom flask equipped with a reflux condenser and septum was charged with magnesium turnings (1.03 g, 42.4 mmol,

32.4 equiv) and Et_2O (12 mL) under an N_2 atmosphere and heated to reflux. To this mixture was added 1,2-dibromoethane (150 μL, 1.74 mmol, 1.33 equiv) in a dropwise manner [*Caution: gas evolution!*]. When gas evolution ceased, a solution of benzyl bromide **151** (677 mg, 1.96 mmol, 1.50 equiv) in Et_2O (7.0 mL) was added in a dropwise manner over 30 min and heating was continued for an additional 30 min. The Grignard reagent was then cooled (0 °C) and added to a cooled (0 °C) solution of enal **216** (330 mg, 1.31 mmol, 1.00 equiv) in Et_2O (10 mL) and THF (30 mL). After 1 h at 0 °C, the reaction mixture was allowed to come to ambient temperature, and after an additional 30 min, the reaction was quenched with ice cold H_2O (50 mL), 2 M HCl (2.0 mL), and Et_2O (20 mL), and extracted with Et_2O (4 x 40 mL). The combined organics were washed with brine (2 x 30 mL), dried ($MgSO_4$), and concentrated to an oil, which was purified by flash chromatography on silica gel (15 to 50% EtOAc in hexanes) to give allylic alcohol **217** (477 mg, 70% yield) as a white solid. Crystals suitable for X-ray analysis were obtained by crystallization from EtOAc/heptanes at ambient temperature: mp 154-155 °C (EtOAc/heptane); R_f 0.50 (35% EtOAc in hexanes developed twice); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (d, J = 7.7 Hz, 1H), 6.71 (d, J = 7.5 Hz, 1H), 4.75 (bs, 1H), 4.52 (app. t, J = 2.6 Hz, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.00-2.80 (m, 2H), 2.76-2.54 (bs, 1H), 2.36 (m, 2H), 2.20 (s, 3H), 1.78 (s, 3H), 1.50 (s, 3H), 1.29 (s, 3H), 1.02 (s, 9H), 0.15 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 77.7, 173.8, 149.4, 147.1, 132.5, 131.8, 129.8, 129.6, 126.3, 123.5, 123.3, 72.0, 60.1, 54.4, 52.6, 50.0, 37.4, 37.0, 26.0, 19.4, 18.6, 17.1, 13.1, 12.9, -4.1; IR (Neat film NaCl) 3519, 2953, 2930, 2858, 1777, 1731, 1462, 1419, 1259, 1073, 840 cm^{-1}; HRMS (FAB) $[M+Na]^+$ calc'd for $[C_{28}H_{42}SiO_7+Na]^+$: m/z 541.2598, found 541.2571.



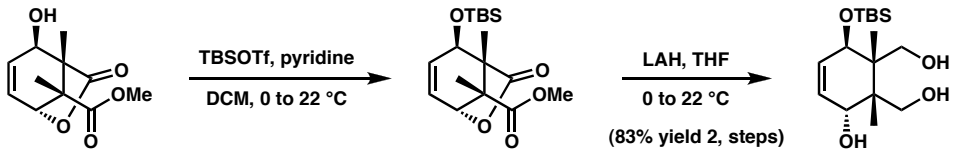
217 *218*

Enone 218. To a cooled (0 °C) solution of allylic alcohol **217** (129 mg, 0.248 mmol, 1.00 equiv) in CH_2Cl_2 (20 mL) was added Dess-Martin periodinane (210 mg, 0.496 mmol, 2.00 equiv) and the resulting mixture was stirred for 1 h. The reaction mixture was diluted with Et_2O (75 mL), filtered, and concentrated to an oil, which was purified by gradient flash chromatography on silica gel (15 to 40% EtOAc in hexanes) to give enone **218** (117 mg, 91% yield) as a foam: R_f 0.57 (35% EtOAc in hexanes developed twice); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (d, J = 7.8 Hz, 1H), 6.64 (d, J = 8.1 Hz, 1H), 4.61 (app. t, J = 2.4 Hz, 1H), 3.94 (d, J = 17.7 Hz, 1H), 3.76 (d, J = 17.7 Hz, 1H), 3.75 (s, 3H), 3.65 (s, 3H), 2.46 (dd, J = 2.7, 18.9 Hz, 1H), 2.35 (dd, J = 1.5, 18.9 Hz, 1H), 2.20 (s, 3H), 1.66 (s, 3H), 1.29 (s, 3H), 1.28 (s, 3H), 1.02 (s, 9H), 0.15 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.3, 176.2, 173.1, 150.0, 146.9, 135.4, 130.6, 130.0, 125.7, 124.4, 123.3, 77.8, 59.8, 53.5, 52.7, 47.8, 46.2, 34.3, 26.0, 18.8, 18.4, 17.0, 12.5, 11.7, -4.3; IR (Neat film NaCl) 2953, 2930, 2858, 1785, 1732, 1463, 1421, 1286, 1252, 1236, 840 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{28}H_{40}SiO_7+H]^+$: m/z 517.2622, found 517.2631.



218 *220*

Bisacetoxyacetal 220. A solution of enone 218 (58.5 mg, 0.113 mmol, 1.00 equiv) in formic acid (2.40 mL) and 85% H_3PO_4 (800 μL) was fitted with a reflux condenser and heated at 117 °C for 22 h. The reaction mixture was cooled to ambient temperature, diluted with ice cold H_2O (60 mL) and extracted with Et_2O (5 x 15 mL). The combined organics were dried ($MgSO_4$) and concentrated to an oil, which was purified by flash chromatography on silica gel (10 to 40% EtOAc in hexanes) to give bisacetoxyacetal **220** (19.6 mg, 47% yield) as a white solid. Crystals suitable for X-ray analysis were obtained by crystallization from Et_2O/hexanes at ambient temperature: mp 185-190 °C decomp. (Et_2O/hexanes); R_f 0.32 (35% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.14 (dd, J = 0.9, 9.3 Hz, 1H), 5.62 (bs, 1H), 5.42 (d, J = 9.3 Hz, 1H), 3.77 (s, 3H), 3.61 (d, J = 15.9 Hz, 1H), 3.02 (dd, J = 0.9, 15.9 Hz, 1H), 2.48 (s, 1H), 2.52 (s, 3H), 1.47 (s, 3H), 1.43 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 169.5, 145.9, 144.4, 137.4, 130.8, 126.0, 124.9, 124.7, 121.8, 105.7, 60.9, 53.0, 45.9, 38.0, 32.2, 31.5, 16.3, 16.2, 15.8; IR (Neat film NaCl) 3468, 2978, 2942, 1801, 1757, 1360, 1213, 1057, 937, 914, 732 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{21}H_{22}O_6]^+$: *m/z* 370.1416, found 370.1410.

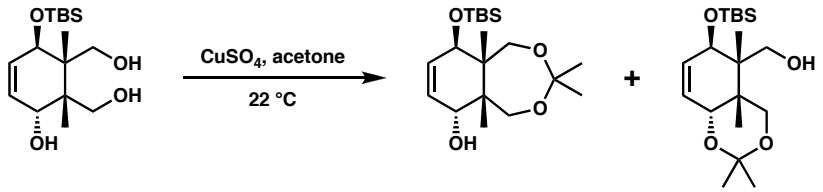


211 ***227*** ***228***

Triol 228. To cooled (0 °C) solution of allylic alcohol **211** (4.37 g, 19.3 mmol, 1.00 equiv) and pyridine (3.12 mL, 38.7 mmol, 2.00 equiv) in CH_2Cl_2 (19 mL) was added TBSOTf (6.66 mL, 29.0 mmol, 1.50 equiv) in a dropwise manner. At the end of the addition, the reaction was allowed to warm to ambient temperature and stirred for 15 h. The reaction mixture was diluted with CH_2Cl_2 (200 mL), quenched with sat. aq. NH_4Cl (75 mL), and extracted with CH_2Cl_2 (4 x 50 mL). The combined organics were dried ($MgSO_4$) and concentrated to give crude silyl ether **227**, which was typically used without purification in the next step: R_f 0.69 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.19 (ddd, J = 1.0, 6.0, 9.0 Hz, 1H), 5.89 (ddd, J = 1.0, 3.5, 9.0 Hz, 1H), 4.78 (d, J = 5.5 Hz, 1H), 4.08 (dd, J = 1.0, 3.5 Hz, 1H), 3.72 (s, 3H), 1.44 (s, 3H), 1.35 (s, 3H), 0.88 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 173.7, 134.8, 126.9, 77.3, 70.5, 54.9, 52.5, 51.3, 25.6, 17.9, 15.7, 14.7, -4.5, -5.1; IR (Neat film NaCl) 2952, 2933, 2857, 1779, 1737, 1725, 1454, 1374, 1254, 1095, 1065, 957, 841, 780 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{17}H_{28}SiO_5+H]^+$: m/z 341.1784, found 341.1781.

The above residue containing silyl ether **227** (theoretical yield: 19.3 mmol, 1.00 equiv) was dissolved in THF (193 mL), cooled (0 °C), and treated with LAH (2.20 g, 58.0 mmol, 3.00 equiv) in portions. At the end of the addition, the reaction was allowed to come to ambient temperature and stirred for 18 h. The cooled (0 °C) reaction mixture was quenched by the careful dropwise addition of EtOAc (66 mL) until out gassing

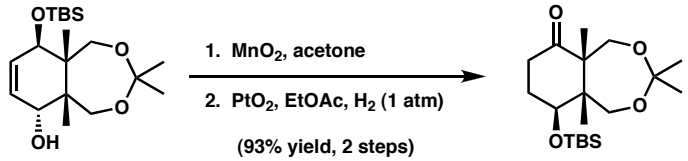
ceased, addition of Celite (7.0 g), and, finally, careful addition of sat. aq. Na_2SO_4 (33 mL). The resulting slurry was filtered, dried (Na_2SO_4), and concentrated to give triol **228** (5.05 g, 83% yield, 2 steps) as a white solid of ~95% purity. Analytically pure material could be obtained by recrystallization from 1% EtOAc in benzene: mp 130.5-132.0 °C (EtOAc/benzene); R_f 0.22 (30% acetone in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68-5.62 (m, 2H), 4.45 (s, 1H), 4.20 (s, 1H), 3.91 (d, *J* = 11.5 Hz, 1H), 3.76 (d, *J* = 11.5 Hz, 1H), 3.69 (d, *J* = 11.5 Hz, 1H), 3.50 (d, *J* = 12.0 Hz, 1H), 1.15 (s, 3H), 0.89 (s, 9H), 0.84 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.3, 129.1, 73.6, 69.3, 65.6, 63.7, 46.1, 45.2, 25.8, 18.0, 16.2, 13.6, -4.0, -5.0; IR (Neat film NaCl) 3255, 2955, 2929, 2886, 2857, 1472, 1253, 1076, 1049, 1026, 880, 835 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{16}H_{32}SiO_4+H]^+$: *m/z* 317.2148, found 317.2162.



228 ***229*** (35% yield) ***230*** (53% yield)

1,3-Dioxepane 229 and Acetonide 230. To a solution of triol **228** (3.75 g, 11.9 mmol, 1.00 equiv) in acetone (120 mL) was added anhydrous $CuSO_4$ (9.46 g, 59.3 mmol, 5.00 equiv), and the reaction mixture was stirred for 40 min. An additional portion of $CuSO_4$ (1.89 g, 11.9 mmol, 1.00 equiv) was added to the reaction mixture, and after an additional 3 h of stirring, a final portion of $CuSO_4$ (1.00 g, 6.27 mmol, 0.53 equiv) was added. After 30 min, the reaction mixture was filtered, concentrated, and purified by flash chromatography on silica gel (5 to 15% EtOAc in hexanes) to give 1,3-dioxepane

229 (1.48 g, 35% yield) as a waxy solid: R_f 0.66 (35% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.57 (dt, *J* = 2.1, 10.2 Hz, 1H), 5.49 (dt, *J* = 2.1, 10.2 Hz, 1H), 4.99 (s, 1H), 4.23 (app. q, *J* = 2.4 Hz, 1H), 3.73 (d, *J* = 12.3 Hz, 1H), 3.58 (d, *J* = 12.6 Hz, 1H), 3.56 (d, *J* = 12.6 Hz, 1H), 3.19 (d, *J* = 12.6 Hz, 1H), 1.33 (s, 3H), 1.30 (s, 3H), 0.90 (s, 9H), 0.71 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 131.7, 129.2, 101.8, 73.5, 68.1, 63.8, 63.0, 46.9, 46.3, 26.5, 25.7, 25.4, 18.8, 18.7, 11.7, -3.7, -4.5; IR (Neat film NaCl) 3446, 2983, 2954, 2858, 1472, 1372, 1253, 1221, 1085, 1070, 1044, 835, 775 cm^{-1}; HRMS (FAB) [M-H_2+H]$^+$ calc'd for [$C_{19}H_{35}SiO_4$]$^+$: *m/z* 355.2305, found 355.2317 and acetonide **230** (2.25 g, 53% yield) as an oil: R_f 0.76 (35% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (dd, *J* = 4.4, 9.6 Hz, 1H), 5.69 (dd, *J* = 4.8, 9.9 Hz, 1H), 4.12 (d, *J* = 4.5 Hz, 1H), 4.01 (d, *J* = 12.9 Hz, 1H), 3.91 (s, 1H), 3.76 (d, *J* = 10.2 Hz, 1H), 3.64 (d, *J* = 10.2 Hz, 1H), 3.56 (d, *J* = 12.9 Hz, 1H), 1.49 (s, 3H), 1.43 (s, 3H), 1.04 (s, 3H), 0.98 (s, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.5, 124.4, 98.6, 71.7, 70.9, 68.9, 65.2, 43.8, 35.1, 28.4, 25.7, 20.9, 20.0 (bs), 17.9, 15.3, -4.1, -5.1; IR (Neat film NaCl) 3451, 2955, 2931, 2886, 2858, 1379, 1256, 1104, 1056, 836, 775 cm^{-1}; HRMS (FAB) [M+H]$^+$ calc'd for [$C_{19}H_{36}SiO_4$+H]$^+$: *m/z* 357.2461, found 357.2478.

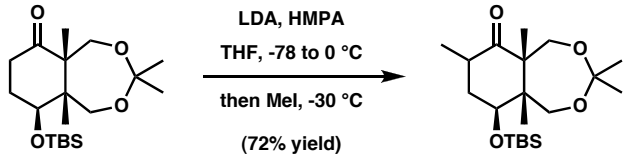


229 ***232***

Ketone 232. To a solution of 1,3-dioxepane **229** (798 mg, 2.24 mmol, 1.00 equiv) in acetone (23 mL) was added activated MnO_2 (3.89 g, 44.7 mmol, 20.0 equiv),

and the reaction mixture was stirred at ambient temperature for 1.5 h. The reaction mixture was filtered, washed with acetone, and concentrated to an oil.

To a solution of this crude material in EtOAc (28 mL) was added PtO_2 (16.0 mg, 67.2 μmol, 0.03 equiv), and the reaction mixture was sparged with H_2 (5 min) and stirred vigorously under an atmosphere of H_2 (balloon) for 1.5 h. The reaction mixture was flushed with N_2 and concentrated to an oil, which was purified by flash chromatography on silica gel (2.5 to 10% EtOAc in hexanes) to provide ketone **232** (744 mg, 93% yield, 2 steps) as an amorphous solid: R_f 0.52 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.59 (bs, 1H), 4.15 (bs, 1H), 3.40 (bs, 2H), 2.99 (bs, 1H), 2.31 (m, 2H), 2.10-1.70 (m, 2H), 1.33 (s, 3H), 1.32 (s, 3H), 1.09 (s, 3H), 0.89 (s, 9H), 0.64 (bs, 3H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.7, 101.8, 67.3, 65.1, 64.0, 57.1, 47.2, 37.9, 29.4, 25.8, 24.8, 24.4, 18.0, 15.8, 11.5, -4.4, -5.1; IR (Neat film NaCl) 2954, 2857, 1709, 1220, 1096, 1073, 884, 836 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{19}H_{36}O_4Si+H]^+$: m/z 357.2461, found 357.2473.

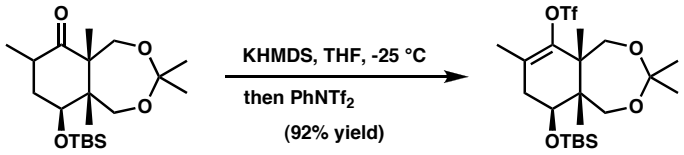


232 *233*

Methyl Ketones 233. A solution of LDA in THF was prepared by dropwise addition of 2.45 M *n*-BuLi solution in hexanes (1.21 mL, 2.96 mmol, 1.20 equiv) to diisopropylamine (519 μL, 3.70 mmol, 1.50 equiv) in THF (30.0 mL) at 0 °C, followed by stirring for 1 h. Upon cooling the solution to -78 °C, a solution of ketone **232** (879 mg, 2.47 mmol, 1.00 equiv) in THF (30.0 mL) was added in a dropwise manner, and the

reaction mixture was stirred at -78 °C for 30 min. HMPA (1.07 mL, 6.17 mmol, 2.50 equiv) was added and the reaction mixture brought to 0 °C for 1 h. After cooling again to -78 °C, the reaction mixture was treated with MeI (200 μL, 3.21 mmol, 1.30 equiv), and after 15 min allowed to warm to -30 °C. The reaction was allowed to warm to 0 °C slowly over 10 h, quenched with H_2O (150 mL) and EtOAc (75 mL), and extracted with EtOAc (4 x 50 mL). The combined organics were washed with brine (50 mL), dried (Na_2SO_4), and concentrated to an oil, which was purified by flash chromatography on silica gel (2.5 to 10% EtOAc in hexanes) to give recovered ketone **232** (90.9 mg, 10% yield), the high R_f diastereomer methyl ketone **233a** (219 mg, 24% yield) as an oil: R_f 0.65 (10% EtOAc in hexanes developed 2 times); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.70 (dd, J = 4.7, 12.2 Hz, 1H), 4.22 (d, J = 12.0 Hz, 1H), 3.49 (d, J = 12.6 Hz, 1H), 3.34 (d, J = 12.3 Hz, 1H), 2.93 (d, J = 11.7 Hz, 1H), 2.41 (dq, J = 6.3, 19.8 Hz, 1H), 1.98 (dt, J = 5.1, 12.9 Hz, 1H), 1.53 (d, J = 13.2 Hz, 1H), 1.34 (s, 3H), 1.10 (s, 3H), 1.01 (d, J = 6.6 Hz, 3H), 0.89 (s, 9H), 0.55 (s, 3H), 0.12 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.4, 101.9, 67.0, 65.5, 63.9, 56.8, 48.1, 41.0, 38.6, 25.8, 24.8, 24.5, 18.0, 15.7, 14.7, 11.3, -4.3, -5.1; IR (Neat film NaCl) 2984, 2955, 2935, 2858, 1709, 1220, 1095, 1072, 1044, 868, 837, 776 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{20}H_{38}O_4Si+H]^+$: m/z 371.2618, found 371.2607, and the low R_f diastereomer methyl ketone **233b** (436 mg, 48% yield) as an oil: R_f 0.36 (10% EtOAc in hexanes developed 2 times); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.80 (d, J = 12.6 Hz, 1H), 3.60 (d, J = 12.0 Hz, 1H), 3.58 (bs, 1H), 3.41 (d, J = 12.6 Hz, 1H), 3.02-2.80 (m, 2H), 1.91 (ddd, J = 4.2, 5.6, 14.0 Hz, 1H), 1.58 (m, 1H), 1.30 (s, 3H), 1.24 (s, 3H), 1.08 (s, 3H), 1.07 (s, 3H), 1.05 (s, 3H), 0.92 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.6, 101.2, 73.0, 67.8, 64.3, 54.4, 47.0, 37.7, 35.3,

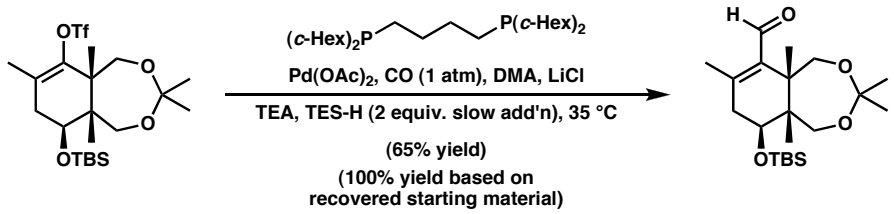
25.8, 25.0, 23.9, 19.4, 18.1, 16.9, 14.7, -4.6, -5.0; IR (Neat film NaCl) 2933, 2858, 1709, 1255, 1222, 1078, 1046, 838, 775 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{20}H_{38}O_4Si+H]^+$: *m/z* 371.2618, found 371.2625.



233 ***234***

Triflate 234. To a cooled (-25 °C) solution of KHMDS (668 mg, 3.35 mmol, 1.20 equiv) in THF (40 mL) was added the low R_f diastereomer methyl ketone **233b** (1.04 g, 2.79 mmol, 1.00 equiv) in THF (20 mL) in a dropwise manner over 10 min. After 2.0 h at -25 °C, $PhNTf_2$ (1.30 g, 3.63 mmol, 1.30 equiv) in THF (20 mL) was added, and the reaction was maintained for an additional 30 min at -25°C. The reaction mixture was quenched into half-saturated $NaHCO_3$ (50 mL) and EtOAc (50 mL), and extracted with EtOAc (5 x 50 mL). The combined organics were washed with brine (1 x 50 mL), dried (Na_2SO_4), and concentrated to an oil, which was purified by flash chromatography on silica gel (0 to 10% EtOAc in hexanes) to provide triflate **234** (1.30 g, 92% yield) as an oil: R_f 0.69 (10% Et_2O in hexanes); ^1H NMR (300 MHz, C_6D_6) δ 4.18 (dd, *J* = 6.3, 9.9 Hz, 1H), 3.79 (d, *J* = 12.3 Hz, 1H), 3.65 (d, *J* = 12.9 Hz, 1H), 3.41 (d, *J* = 12.3 Hz, 1H), 3.33 (d, *J* = 12.6 Hz, 1H), 2.08 (dd, *J* = 6.5, 17.6 Hz, 1H), 1.91 (ddd, *J* = 1.1, 9.9, 17.6 Hz, 1H), 1.61 (s, 3H), 1.20 (s, 3H), 1.17 (s, 3H), 1.16 (s, 3H), 0.98 (s, 9H), 0.49 (s, 3H), 0.15 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 145.9, 127.1, 119.7 (q, $J_{C\text{-}F}$ = 318 Hz), 102.0, 65.4, 65.2, 62.7, 47.4, 45.9, 38.2, 26.5, 25.0, 24.9, 18.6, 18.3, 17.0, 11.0, -3.8,

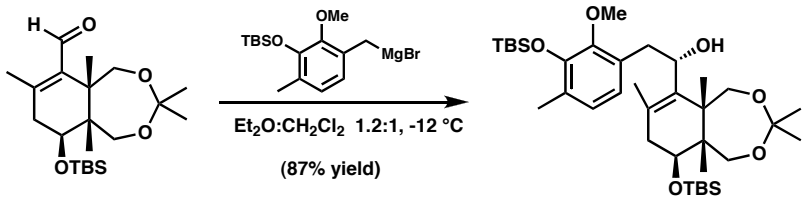
-4.6; IR (Neat film NaCl) 2988, 2954, 2858, 1405, 1213, 1141, 1078, 879 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{21}H_{37}SSiO_6F_3+H]^+$: m/z 503.2110, found 503.2094.



234 ***235***

Enal 235. A solution of flame-dried LiCl (433 mg, 10.2 mmol, 3.0 equiv), $Pd(OAc)_2$ (153 mg, 0.680 mmol, 0.20 equiv), and 1,4-bis-(dicyclohexylphosphino)butane (306 mg, 0.680 mmol, 0.20 equiv) in DMA (16 mL) was sparged with CO and warmed to 85 °C until a color change from red/orange to pale yellow was observed, at which point the reaction mixture was cooled to 40 °C. To the homogenous reaction mixture was added TEA (1.89 mL, 13.6 mmol, 4.00 equiv) and enol triflate **234** (1.71 g, 3.40 mmol, 1.00 equiv) in DMA (20 mL). A solution of Et_3SiH (1.09 mL, 6.80 mmol, 2.0 equiv) in DMA (10.0 mL) was added by syringe pump to the reaction over 10 h. After an additional 14 h at 40 °C, the reaction mixture was cooled to ambient temperature, poured into H_2O (100 mL) and Et_2O (100 mL), and extracted with Et_2O (5 x 50 mL). The combined organic layers were washed with H_2O (20 mL), brine (2 x 20 mL), dried (Na_2SO_4), and concentrated to give an oil, which was purified by flash chromatography on silica gel (2 to 10% EtOAc in hexanes) to give recovered triflate **234** (606 mg, 35% yield) and enal **235** (841 mg, 65% yield) as a pale yellow oil: R_f 0.50, 0.55 (10% EtOAc in hexanes developed twice, 25% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 10.06 (s, 1H), 4.19 (dd, *J* = 7.1, 9.2 Hz, 1H), 3.73 (d, *J* = 12.3 Hz, 1H), 3.60 (d, *J* = 12.0 Hz, 1H), 3.57 (d, *J* = 12.3 Hz, 1H), 3.34 (d, *J* = 12.3 Hz, 1H), 2.32-2.22 (m, 2H), 2.09 (s, 3H),

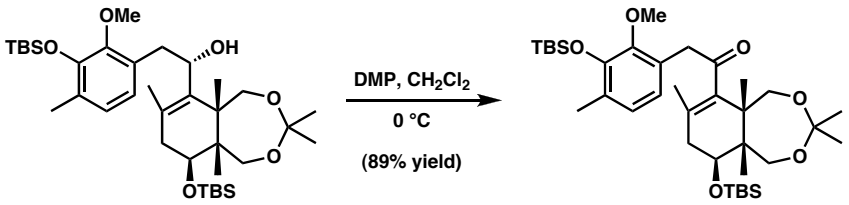
1.31 (s, 3H), 1.24 (s, 6H), 0.89 (s, 9H), 0.53 (s, 3H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 92.7, 154.2, 135.2, 101.0, 65.2, 65.0, 61.4, 45.2, 43.7, 41.3, 25.8, 24.6, 19.6, 18.0, 17.5, 10.7, -4.4, -5.1; IR (Neat film NaCl) 2986, 2953, 2888, 2857, 1677, 1371, 1221, 1101, 1073, 870, 837, 780 cm^{-1}; HRMS (FAB) $[M-H_2+H]^+$ calc'd for $[C_{20}H_{37}O_5]^+$: *m/z* 385.2410, found 385.2412.



235 ***236***

Allylic alcohol 236. A flame-dried two-neck round-bottom flask equipped with a reflux condenser and septum was charged with magnesium turnings (3.00 g, 123 mmol, 56.1 equiv) and Et_2O (45 mL) under an N_2 atmosphere and heated to reflux. To this mixture was added 1,2-dibromoethane (75.0 μL, 0.870 mmol, 0.40 equiv) in a dropwise manner [*Caution: gas evolution!*]. When gas evolution ceased, a solution of benzyl bromide **151** (1.37 g, 3.96 mmol, 1.80 equiv) in Et_2O (18.0 mL) was added in a dropwise manner over 30 min and heating was continued for an additional 30 min. The Grignard reagent was then cooled (0 °C), and added to a cooled (-12 °C) solution of enal **235** (841 mg, 2.20 mmol, 1.00 equiv) in Et_2O (45 mL) and CH_2Cl_2 (90 mL). After 1 h at -12 °C, the reaction was quenched with H_2O (150 mL), 2 M citric acid (20 mL), brine (20 mL), and EtOAc (50 mL), and extracted with EtOAc (4 x 50 mL). The combined organics were washed with brine (2 x 50 mL), dried (Na_2SO_4), and concentrated to an oil, which was purified by flash chromatography on silica gel (2.5 to 12.5% Et_2O in hexanes) to give allylic alcohol **236** (1.24 g, 87% yield) as a foam consisting of a 10:1 mixture of

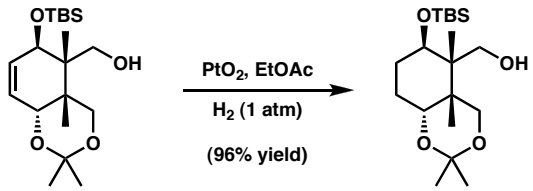
diastereomers. Only the major component (stereochemistry shown above) could be isolated in pure form: R_f 0.41, 0.29 (25% Et_2O in hexanes, 10% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 6.84 (d, *J* = 7.5 Hz, 1H), 6.70 (d, *J* = 7.5 Hz, 1H), 4.46 (d, *J* = 10.2 Hz, 1H), 4.16 (dd, *J* = 7.1, 9.5 Hz, 1H), 3.71 (s, 3H), 3.62 (d, *J* = 12.6 Hz, 1H), 3.53 (d, *J* = 12.3 Hz, 1H), 3.39 (d, *J* = 12.3 Hz, 1H), 3.32 (bs, 1H), 3.27 (dd, *J* = 10.7, 14.0 Hz, 1H), 2.59 (dd, *J* = 3.0, 14.1 Hz, 1H), 2.46 (s, 1H), 2.20 (s, 3H), 2.10-2.00 (m, 2H), 1.98 (s, 3H), 1.31 (s, 3H), 1.26 (s, 3H), 1.21 (s, 3H), 1.03 (s, 9H), 0.90 (s, 9H), 0.56 (s, 3H), 0.19 (s, 3H), 0.16 (s, 3H), 0.10 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.5, 147.2, 134.6, 132.2, 130.8, 129.4, 126.4, 123.1, 100.8, 72.6, 66.1, 65.7, 62.2, 60.0, 47.1, 43.6, 40.0, 38.4, 26.0, 25.9, 24.7(2C), 20.9, 18.6, 18.1, 17.8, 17.0, 10.9, -4.0, -4.2, -4.3, -5.1; IR (Neat film NaCl) 3479, 2955, 2931, 2858, 1463, 1253, 1221, 1074, 838, 780 cm^{-1}; HRMS (FAB) $[M\text{-}H_2+H]^+$ calc'd for $[C_{36}H_{63}Si_2O_6]^+$: *m/z* 647.4163, found 647.4156.



236 ***237***

Enone 237. To a cooled (0 °C) solution of allylic alcohol **236** (1.24 g, 1.91 mmol, 1.00 equiv) in CH_2Cl_2 (120 mL) was added Dess-Martin periodinane (1.21 g, 2.86 mmol, 1.50 equiv) and the resulting mixture was stirred for 2 h. The reaction mixture was concentrated to ~40 mL, diluted with Et_2O (250 mL), filtered, and concentrated to an oil, which was purified by gradient flash chromatography on silica gel (2.5 to 5% EtOAc in hexanes) to give enone **237** (1.10 g, 89% yield) as a foam: R_f 0.43, 0.69 (10% EtOAc in hexanes, 10% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 6.83 (d, *J* = 7.5 Hz, 1H),

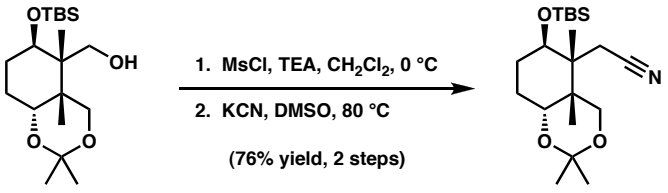
6.63 (d, *J* = 7.8 Hz, 1H), 4.28 (dd, *J* = 7.1, 9.5 Hz, 1H), 3.92 (d, *J* = 18.3 Hz, 1H), 3.80 (d, *J* = 18.0 Hz, 1H), 3.75 (d, *J* = 11.4 Hz, 1H), 3.64 (s, 3H), 3.52 (d, *J* = 12.6 Hz, 1H), 3.39 (d, *J* = 12.3 Hz, 1H), 2.20 (s, 3H), 2.12-1.98 (m, 2H), 1.72 (s, 3H), 1.31 (s, 3H), 1.27 (s, 3H), 1.13 (s, 3H), 1.02 (s, 9H), 0.90 (s, 9H), 0.66 (s, 3H), 0.15 (s, 6H), 0.09 (s, 3H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.1, 150.1, 147.0, 138.2, 129.9 (2C), 125.8, 125.3, 123.2, 101.1, 65.9, 65.5, 61.5, 60.0, 47.1, 45.3, 42.9, 37.9, 26.1, 25.9, 24.7 (2C), 20.7, 18.6, 18.1, 17.1, 11.1, -4.2 (2C), -4.4, -5.1; IR (Neat film NaCl) 2954, 2930, 2858, 1699, 1463, 1252, 1221, 1099, 1073, 864, 836, 780 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{36}H_{63}Si_2O_6+H]^+$: *m/z* 647.4163, found 647.4140.



230 ***238***

Alcohol 238. To a solution of acetonide **230** (5.64 g, 15.8 mmol, 1.00 equiv) in EtOAc (198 mL) was added PtO_2 (108 mg, 0.475 mmol, 0.03 equiv), and the reaction mixture was sparged with a stream of H_2 gas for 4 h. The reaction mixture was concentrated (~10 mL), filtered through a plug of silica gel, and concentrated to give hydrogenated alcohol **238** (5.47 g, 96% yield) as an oil: R_f 0.76 (35% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.43 (dd, *J* = 5.5, 12.0 Hz, 1H), 3.98 (dd, *J* = 5.0, 10.3 Hz, 1H), 3.88 (d, *J* = 13.0 Hz, 1H), 3.79 (app. t, *J* = 3.0 Hz, 1H), 3.45 (s, 1H), 3.32 (d, *J* = 12.0 Hz, 1H), 3.04 (app. t, *J* = 11.0 Hz, 1H), 2.12 (app. tt, *J* = 3.8, 14.3 Hz, 1H), 1.86 (app. tt, *J* = 3.0, 14.0 Hz, 1H), 1.48 (s, 3H), 1.47-1.37 (m, 1H), 1.42 (s, 3H), 0.97 (s, 3H), 0.93 (s, 3H), 0.90 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 98.5, 75.0, 74.4, 69.5, 66.8, 43.5, 35.0, 29.5, 25.9, 25.1, 21.9, 20.2, 18.8, 18.0, 17.2, -4.6, -5.0; IR (Neat film NaCl) 3497, 2953, 2936, 2883, 2858, 1472, 1379, 1257, 1196, 1083, 1060, 1034, 1005, 866, 834, 774 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{19}H_{38}SiO_4+H]^+$: *m/z* 359.2618, found 359.2632.

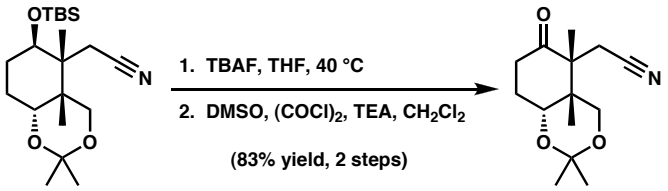


238 ***239***

Nitrile 239. To a cooled (0 °C) solution of alcohol **238** (880 mg, 2.45 mmol, 1.00) and TEA (1.02 mL, 7.36 mmol, 3.00 equiv) in CH_2Cl_2 (25 mL) was added methanesulfonyl chloride (228 μL, 2.95 mmol, 1.20 equiv) in a dropwise manner. After 30 min at 0 °C, the reaction mixture was diluted with CH_2Cl_2 (40 mL), ice cold H_2O (50 mL), and brine (25 mL), and extracted with CH_2Cl_2 (3 x 35 mL). The combined organics were washed with brine (30 mL), dried (Na_2SO_4), and concentrated to a waxy solid that was used in the next step immediately.

The above residue was dissolved in DMSO (25 mL) and treated with KCN (400 mg, 6.14 mmol, 2.50 equiv) at 80 °C for 4 h. The reaction mixture was cooled to ambient temperature, diluted with EtOAc (50 mL) and H_2O (150 mL), and extracted with EtOAc (7 x 40 mL). The combined organics were washed with brine (30 mL), dried (Na_2SO_4), concentrated, and purified by flash chromatography on silica gel (2.5 to 10% EtOAc in hexanes) to provide nitrile **239** (682 mg, 76% yield) as a solid : R_f 0.42 (20% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 4.07 (d, *J* = 8.7 Hz, 1H), 3.83 (d, *J* = 8.4 Hz, 1H), 3.70-3.60 (m, 2H), 3.49 (d, *J* = 8.1 Hz, 1H), 3.46 (d, *J* = 8.7 Hz, 1H), 2.18-2.04 (m,

1H), 1.74-1.45 (m, 3H), 1.55 (s, 6H), 1.14 (s, 3H), 0.90 (s, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 121.7, 78.8, 76.1, 74.8, 71.0, 70.1, 50.8, 48.8, 28.8 (2C), 27.6 (2C), 25.8, 22.6, 18.0, 9.5, -3.9, -5.0; IR (Neat film NaCl) 2956, 2934, 2882, 2860, 1460, 1254, 1183, 1080, 1047, 916, 868, 835, 772 cm^{-1}; HRMS (FAB) [M-H_2+H]$^+$ calc'd for $[C_{20}H_{36}NO_3Si]^+$: *m/z* 366.2464, found 366.2459.

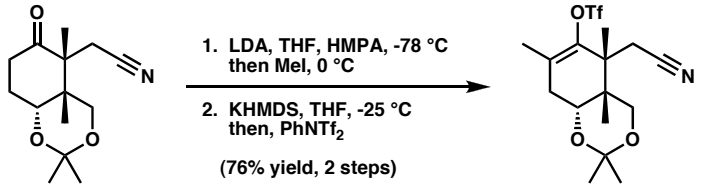


239 ***240***

Ketone 240. To a solution of nitrile **239** (1.13 g, 3.08 mmol, 1.00 equiv) in THF (18.5 mL) was added a 1.0 M solution of TBAF (9.23 mL, 9.23 mmol, 3.00 equiv) in THF, and the reaction mixture was heated to 40 °C for 7.5 h. An additional portion of a 1.0 M solution of TBAF (2.00 mL, 2.00 mmol, 0.65 equiv) in THF was added. After a further 1 h, the reaction mixture was cooled to ambient temperature, diluted with EtOAc (100 mL) and brine (75 mL), and extracted with EtOAc (5 x 75 mL). The combined organics were washed with brine (50 mL), dried (Na_2SO_4), and concentrated to an oil, which was used without further purification.

A solution of DMSO (1.75 mL, 24.6 mmol, 8.0 equiv) in CH_2Cl_2 (100 mL) was cooled (-78 °C) and oxalyl chloride (1.88 mL, 21.5 mmol, 7.00 equiv) was added in a dropwise manner. After 40 min at -78 °C, a solution of the crude alcohol generated above in CH_2Cl_2 (20 mL) was added in a dropwise manner down the wall of the flask over 13 min. After an additional 2.5 h at -78 °C, TEA (8.58 mL, 61.6 mmol, 20.0 equiv) was added and the reaction mixture was allowed to warm to ambient temperature over 3

h, diluted with half-saturated NH_4Cl (75 mL), and extracted with CH_2Cl_2 (4 x 50 mL). The combined organics were washed with saturated $NaHCO_3$ (30 mL), dried ($MgSO_4$), concentrated to an oil, and purified by flash chromatography on silica gel (2.5 to 35% EtOAc in hexanes) to provide ketone **240** (683 mg, 83% yield) as an oil: R_f 0.49 (50% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.53 (d, J = 8.7 Hz, 1H), 4.01 (dd, J = 4.4, 10.7 Hz, 1H), 3.95 (d, J = 9.3 Hz, 1H), 3.50 (d, J = 9.3 Hz, 1H), 3.41 (d, J = 8.1 Hz, 1H), 2.68-2.41 (m, 2H), 2.41-2.24 (m, 1H), 2.10-1.90 (m, 1H), 1.61 (s, 6H), 1.23 (s, 3H), 1.14 (s, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.6, 121.3, 77.5, 75.0, 74.1, 70.7, 58.0, 50.4, 35.6, 28.6, 27.7, 27.5, 21.4, 16.7; IR (Neat film NaCl) 2983, 2881, 2254, 1714, 1387, 1373, 1171, 1052, 907, 729, 651 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{14}H_{21}NO_3]^+$: m/z 251.1521, found 251.1518.

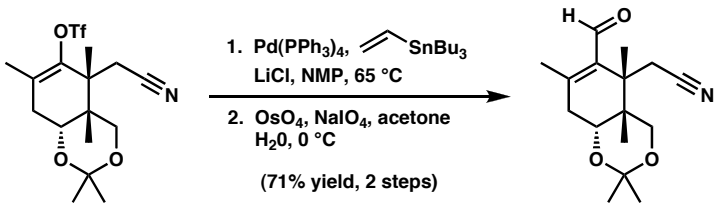


240 *241*

Triflate 241. A solution of LDA in THF was prepared by dropwise addition of 2.50 M *n*-BuLi solution in hexanes (580 μL, 1.45 mmol, 1.05 equiv) to diisopropylamine (252 μL, 1.79 mmol, 1.30 equiv) in THF (15.0 mL) at 0 °C, followed by stirring for 30 min. Upon cooling the solution to -78 °C, a solution of ketone **240** (347 mg, 1.38 mmol, 1.00 equiv) in THF (15.0 mL) was added in a dropwise manner, and the reaction mixture was stirred at -78 °C for 2 h. HMPA (552 μL, 3.18 mmol, 2.30 equiv) was added and the reaction mixture was brought to 0 °C for 1 h. After cooling again to -78 °C, the solution containing the enolate was added to a solution of MeI (258 μL, 4.14 mmol, 3.00 equiv) in

THF (4.00 mL) at -30 °C in a dropwise manner over 25 min. After 6 h at -25 °C, the reaction mixture was quenched with H_2O (30 mL) and CH_2Cl_2 (30 mL), and extracted with CH_2Cl_2 (5 x 30 mL). The combined organics were washed, dried ($MgSO_4$), and concentrated to an oil, which was purified by flash chromatography on silica gel (10 to 25% EtOAc in hexanes) to give to an inseparable mixture of diastereomeric methyl ketones (286 mg, 78% yield).

To a cooled (-25 °C) solution of KHMDS (300 mg, 1.50 mmol, 1.40 equiv) in THF (17 mL) was added the above mixture of methyl ketones (286 mg, 1.07 mmol, 1.00 equiv) in THF (15 mL) in a dropwise manner over 10 min. After 2.5 h at -25 °C, $PhNTf_2$ (614 mg, 1.72 mmol, 1.60 equiv) in THF (10.7 mL) was added, and the reaction maintained for an additional 30 min at -25°C. The reaction mixture was quenched into half-saturated $NaHCO_3$ (100 mL) and extracted with EtOAc (4 x 70 mL). The combined organics were dried (Na_2SO_4) and concentrated to an oil, which was purified by flash chromatography on silica gel (15 to 25% Et_2O in hexanes) to provide triflate **241** (420 mg, 98% yield, 76% yield for 2 steps) as an oil: R_f 0.41 (50% Et_2O in hexanes); ^1H NMR (300 MHz, C_6D_6) δ 4.16 (d, J = 8.7 Hz, 1H), 3.95 (d, J = 9.3 Hz, 1H), 3.52 (dd, J = 6.2, 8.6 Hz, 1H), 3.46 (d, J = 9.0 Hz, 1H), 3.36 (d, J = 9.0 Hz, 1H), 2.17 (dd, J = 6.0, 18.0 Hz, 1H), 1.95 (dd, J = 8.1, 18.0 Hz, 1H), 1.50 (s, 3H), 1.01 (s, 3H), 0.97 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 145.7, 125.1, 121.5, 119.5 (app. d, $J_{C\text{-}F}$ = 296 Hz), 75.2, 74.7, 74.3, 71.0, 51.2, 50.4, 36.1, 28.2, 27.4, 21.6, 18.1, 16.4; IR (Neat film NaCl) 2988, 2942, 2884, 1403, 1211, 1141, 1053, 990, 874 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{16}H_{22}NO_5F_3S]^+$: m/z 397.1171, found 397.1179.

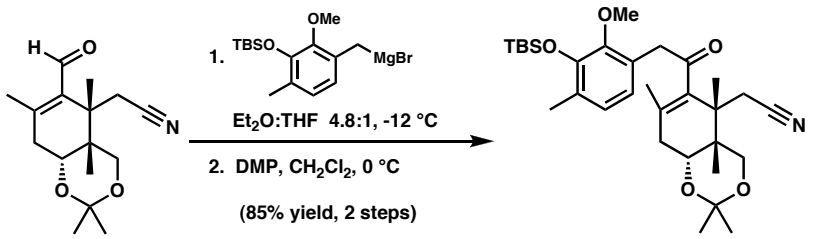


241 *242*

Enal 242. To a solution of triflate **241** (1.41 g, 3.54 mmol, 1.00 equiv), $Pd(PPh_3)_4$ (307 mg, 0.266 mmol, 0.075 equiv), and LiCl (450 mg, 10.6 mmol, 3.00 equiv) in NMP (59 mL) was added tributyl(vinyl)tin (1.55 mL, 5.31 equiv, 1.50 equiv), and the mixture was heated to 65 °C for 0.5 h. The reaction mixture was cooled to ambient temperature, quenched with H_2O (300 mL) and Et_2O (200 mL), and extracted with Et_2O (4 x 125 mL). The combined organics were washed with brine (170 mL), dried ($MgSO_4$), and concentrated to an oil, which was purified by flash chromatography on silica gel (2.5 to 10% EtOAc in hexanes) to provide the intermediate diene (1.04 g, quantitative yield) as a viscous oil containing a small amount of solvent.

To a cooled (0 °C) solution of the intermediate diene (116.7 mg, 0.42 mmol, 1.00 equiv) in acetone (5.30 mL) and H_2O (5.30 mL) was added OsO_4 (10.8 mg, 42.3 μmol, 0.10 equiv) and $NaIO_4$ (227 mg, 1.06 mmol, 2.50 equiv). After 3.5 h at 0 °C, the reaction mixture was diluted with H_2O (35 mL) and EtOAc (35 mL), and extracted with EtOAc (5 x 15 mL). The combined organics from four such reactions were washed with brine (200 mL), dried ($MgSO_4$), and concentrated to an oil, which was purified by flash chromatography on silica gel (20 to 35% EtOAc in hexanes) to provide enal **242** (332 mg, 71% yield, 2 steps) as an oil: R_f 0.28 (35% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.10 (s, 1H), 4.21 (d, J = 9.0 Hz, 1H), 3.87 (d, J = 9.3 Hz, 1H), 3.85 (d, J = 8.4 Hz, 1H), 3.70 (d, J = 9.0 Hz, 1H), 3.51 (d, J = 8.7 Hz, 1H), 2.78 (dd, J = 6.0, 19.8 Hz, 1H), 2.49 (dd, J = 9.0, 19.8 Hz, 1H), 2.16 (s, 3H), 1.60 (s, 3H), 1.59 (s, 3H), 1.20 (s, 3H),

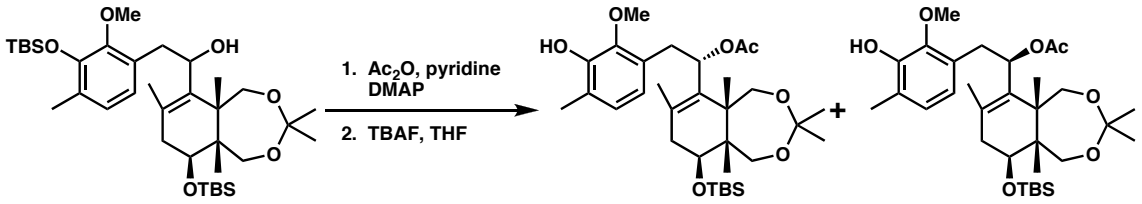
1.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.0, 153.2, 136.8, 121.5, 76.0, 74.2, 74.1, 70.4, 48.7, 48.0, 38.7, 28.7, 27.3, 20.7, 19.0, 18.0; IR (Neat film NaCl) 2982, 2938, 2880, 1671, 1628, 1386, 1177, 1050 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{16}H_{23}NO_3]^+$: m/z 277.1678, found 277.1677.



242 ***243***

Enone 243. A flame-dried two-neck round-bottom flask equipped with a reflux condenser and septum was charged with magnesium turnings (1.66 g, 68.4 mmol, 57.0 equiv) and Et_2O (27 mL) under an N_2 atmosphere and heated to reflux. To this mixture was added 1,2-dibromoethane (120 μL, 1.39 mmol, 1.16 equiv) in a dropwise manner [*Caution: gas evolution!*]. When gas evolution ceased, a solution of benzyl bromide **151** (1.24 g, 3.60 mmol, 3.00 equiv) in Et_2O (8.0 mL) was added in a dropwise manner over 30 min, and heating was continued for an additional 20 min. The Grignard reagent was then cooled (0 °C) and added to a cooled (0 °C) solution of enal **242** (332 mg, 1.20 mmol, 1.00 equiv) in THF (12 mL). After 1 h at 0 °C, the reaction was quenched with 0.5 M citric acid (40 mL) and EtOAc (40 mL), and extracted with EtOAc (5 x 25 mL). The combined organics were dried (Na_2SO_4) and concentrated to an oil, which was purified by flash chromatography on silica gel (10 to 25% EtOAc in hexanes) to give a separable 3:1 mixture of diastereomeric allylic alcohols (533.3 mg, 85% yield).

To a cooled (0 °C) solution of the above allylic alcohol (76.0 mg, 0.140 mmol, 1.00 equiv) in CH_2Cl_2 (5.0 mL) was added Dess-Martin periodinane (89.1 mg, 0.211 mmol, 1.50 equiv) and the resulting mixture was stirred for 2 h. The reaction mixture was diluted with Et_2O (35 mL), filtered, concentrated to an oil, and purified by flash chromatography on silica gel (5 to 20% EtOAc in hexanes) to give enone **243** (75.7 mg, 100% yield, 85% yield 2 steps) as an oil: R_f 0.47 (25% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (d, *J* = 7.8 Hz, 1H), 6.64 (d, *J* = 7.8 Hz, 1H), 4.16 (d, *J* = 8.7 Hz, 1H), 4.08 (d, *J* = 9.0 Hz, 1H), 3.87 (dd, *J* = 6.0, 8.4 Hz, 1H), 3.86 (s, 2H), 3.64 (s, 3H), 3.53 (d, *J* = 8.7 Hz, 1H), 3.52 (d, *J* = 9.0 Hz, 1H), 2.54 (dd, *J* = 6.0, 17.7 Hz, 1H), 2.30 (dd, *J* = 8.3, 18.2 Hz, 1H), 2.21 (s, 3H), 1.79 (s, 3H), 1.62 (s, 3H), 1.61 (s, 3H), 1.17 (s, 3H), 1.15 (s, 3H), 1.02 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.4, 150.0, 147.0, 138.7, 130.0, 128.2, 125.8, 125.2, 123.3, 121.6, 75.5 (2C), 75.2, 70.5, 59.9, 49.7, 47.2, 47.1, 35.5, 28.7, 27.6, 26.0, 21.1, 20.8, 18.5, 18.2, 17.1, -4.2; IR (Neat film NaCl) 2932, 2859, 1699, 1464, 1422, 1286, 1073, 1047, 856, 841 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{31}H_{47}NSiO_5+H]^+$: *m/z* 542.3302, found 542.3296.



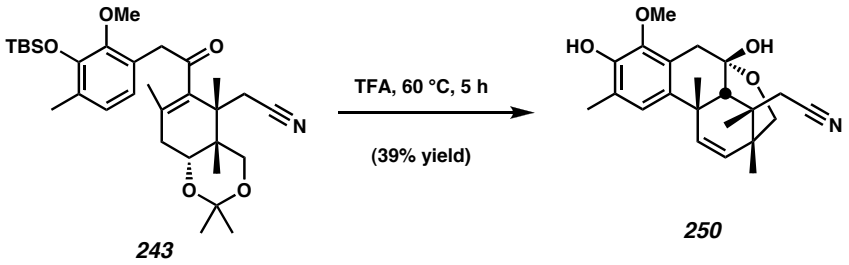
244 **as a ~4:1 mixture at C(20)** ***247*** **(82% yield 2 steps)** ***248*** **(17% yield 2 steps)**

Allylic acetates 247 and 248. To a solution of allylic alcohol **244** (120 mg, 0.185 mmol, 1.00 equiv) in Ac_2O (4.00 mL) and pyridine (1.00 mL) was added DMAP (11.3 mg, 92.4 μmol, 0.50 equiv). After 3 h, the reaction mixture was concentrated and

purified by flash chromatography on silica gel (2.5 to 10% Et_2O in hexanes) to give an inseparable mixture of intermediate acetates (122.1 mg).

To a solution of the above acetates in THF (4.00 mL) was added a 1.0 M solution of TBAF (1.06 mL, 1.06 mmol, 6.00 equiv). After a further 30 min, the reaction mixture was diluted with H_2O (30 mL) and CH_2Cl_2 (30 mL), and extracted with CH_2Cl_2 (6 x 30 mL). The combined organics were dried (Na_2SO_4), concentrated, and purified by flash chromatography on silica gel (5 to 20% EtOAc in hexanes) to give isomerically pure allylic acetate **248** (17.5 mg, 17% yield, two steps) as a white foam: R_f 0.34 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (d, *J* = 7.5 Hz, 1H), 6.61 (d, *J* = 7.5 Hz, 1H), 5.64 (dd, *J* = 3.6, 10.8 Hz, 1H), 5.53 (s, 1H), 4.17 (dd, *J* = 7.1, 9.5 Hz, 1H), 3.79 (s, 3H), 3.55 (s, 2H), 3.52 (d, *J* = 12.6 Hz, 1H), 3.37 (d, *J* = 12.3 Hz, 1H), 3.13 (dd, *J* = 10.8, 14.4 Hz, 1H), 2.93 (dd, *J* = 3.6, 14.4 Hz, 1H), 2.21 (s, 3H), 2.12-2.00 (m, 2H), 1.96 (s, 3H), 1.82 (s, 3H), 1.31 (s, 3H), 1.24 (s, 3H), 1.17 (s, 3H), 0.89 (s, 9H), 0.55 (s, 3H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 69.5, 147.0, 145.4, 133.8, 131.5, 128.0, 126.0, 123.4, 121.4, 101.0, 72.1, 65.5, 65.3, 61.9, 61.1, 46.7, 43.1, 40.0, 35.1, 25.9, 24.8, 24.6, 21.5, 20.9, 18.1, 16.9, 15.5, 11.1, -4.3, -5.1; IR (Neat film NaCl) 3448, 2950, 2856, 1739, 1463, 1373, 1248, 1220, 1067, 1039, 836 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{32}H_{52}SiO_7+H]^+$: *m/z* 577.3561, found 577.3547, and allylic acetate **247** (83 mg, 82% yield, two steps) as a white foam: R_f 0.33 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (d, *J* = 7.8 Hz, 1H), 6.58 (d, *J* = 7.8 Hz, 1H), 5.77 (bs, 1H), 5.59 (s, 3H), 4.09 (m, 1H), 3.81 (s, 3H), 3.50 (d, *J* = 12.3 Hz, 1H), 3.44-3.30 (m, 2H), 3.14 (dd, *J* = 9.6, 13.8 Hz, 1H), 2.99 (d, *J* = 12.0 Hz, 1H), 2.84 (dd, *J* = 5.1, 13.8 Hz, 1H), 2.20 (s, 3H), 2.12-2.00 (m, 2H), 1.98 (s, 3H), 1.89 (s, 3H), 1.28 (s, 3H), 1.19 (s, 3H), 1.14 (s, 3H), 0.89

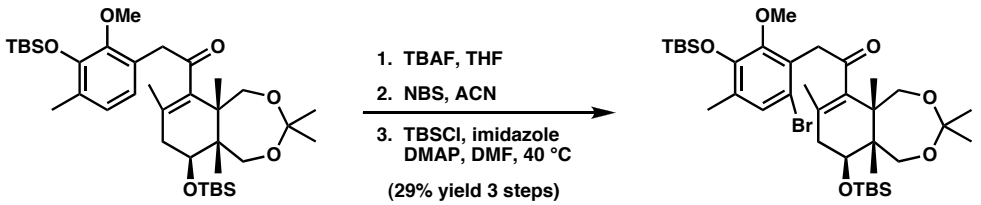
(s, 9H), 0.51 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 69.6, 147.1, 145.5, 134.8, 131.2, 128.0, 126.0, 123.6, 121.7, 100.8, 72.4, 65.8, 65.6, 62.0, 61.1, 47.0, 43.6, 40.0, 36.6, 35.4, 25.9, 24.6, 24.4, 21.3, 21.2, 18.1, 15.4, 10.9, -4.4, -5.1; IR (Neat film NaCl) 3418, 2985, 2952, 2857, 1741, 1464, 1371, 1248, 1221, 1067, 1040, 836, 777 cm^{-1}; HRMS (FAB) $[M\text{-}H_2\text{+}H]^+$ calc'd for $[C_{32}H_{51}SiO_7]^+$: *m/z* 575.3404, found 575.3405.



243 ***250***

Hemiacetal 250. A solution of enone **243** (29.9 mg, 55.2 μmol, 1.00 equiv) in trifluoroacetic acid (4.00 mL) was heated to 60 °C for 5 h. The reaction mixture was then cooled to ambient temperature, concentrated to an oil, and purified by flash chromatography on silica gel (5 to 50% EtOAc in hexanes) to give hemiacetal **250** (7.9 mg, 39% yield) as an off-white solid: R_f 0.30 (35% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (s, 1H), 5.97 (dd, *J* = 1.0, 9.5 Hz, 1H), 5.55 (s, 1H), 5.33 (d, *J* = 9.5 Hz, 1H), 4.18 (d, *J* = 8.5, 1H), 3.74 (s, 3H), 3.60 (d, *J* = 8.5 Hz, 1H), 3.55 (d, *J* = 11.5 Hz, 1H), 3.25 (d, *J* = 16.0, 1H), 3.09 (d, *J* = 11.5, 1H), 2.76 (d, *J* = 15.5, 1H), 2.23 (s, 3H), 1.76 (s, 1H), 1.42 (s, 3H), 1.15 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 144.1, 135.4, 135.1, 130.0, 124.7 (2C), 124.2, 123.1, 105.1, 75.1, 70.1, 60.5, 53.9, 41.7, 39.2, 35.3, 33.8, 31.6, 18.8, 17.7, 15.7; IR (Neat film NaCl) 3402, 2969, 2931, 2876, 2242, 1485, 1419, 1358, 1209, 1102, 1063, 981, 912, 732 cm^{-1}; MS (FAB) [M-

HCN]$^+$ calc'd for $[C_{21}H_{26}O_4]^+$: *m/z* 342.1831, found 342.2 (Hi-Res data not possible due to substrate fragmentation).



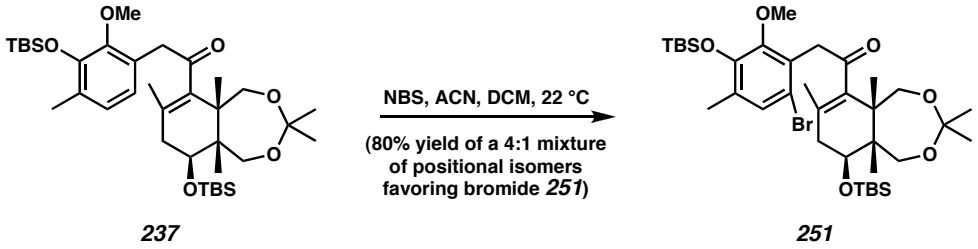
237 ***251***

Aryl bromide 251. To a solution of enone **237** (114 mg, 0.176 mmol, 1.00 equiv) in THF (8.0 mL) was added a 1.0 M solution of TBAF (176 μL, 0.176 mmol, 1.00 equiv) in THF. After 5 min, the reaction mixture was diluted with H_2O (50 mL) and CH_2Cl_2 (50 mL), and extracted with CH_2Cl_2 (4 x 25 mL). The combined organics were dried (Na_2SO_4), concentrated, and purified by flash chromatography on silica gel (5 to 25% EtOAc in hexanes) to give the intermediate phenol (91 mg, 97% yield).

To a solution of intermediate phenol (36.0 mg, 67.6 μmol, 1.00 equiv) in ACN (2.0 mL) was added NBS (18.0 mg, 101 μmol, 1.50 equiv). After 2.5 h, the reaction was diluted with H_2O (8 mL) and EtOAc (8 mL), and extracted with EtOAc (4 x 5 mL). The combined organics were dried (Na_2SO_4), concentrated, and purified by flash chromatography on silica gel (2.5 to 15% EtOAc in hexanes) to give the intermediate bromide (14.4 mg, 35% yield).

To a solution of intermediate bromide (14.4 mg, 23.5 μmol, 1.00 equiv), imidazole (36.0 mg, 0.530 mmol, 22.5 equiv), and TBSCl (26.6 mg, 0.177 mmol, 7.50 equiv) in DMF (2.5 mL) was added DMAP (21.5 mg, 0.176 mmol, 7.50 equiv) and the reaction was warmed to 40 °C. After 36 h, the reaction was diluted with H_2O (8 mL) and EtOAc (8 mL), and extracted with EtOAc (4 x 5 mL). The combined organics were dried

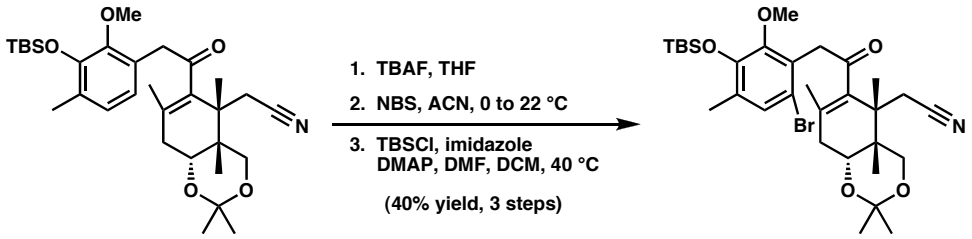
(Na_2SO_4), concentrated, and purified by flash chromatography on silica gel (1 to 5% Et_2O in hexanes) to give isomerically pure bromide **251** (14.5 mg, 85% yield, 29% yield for three steps) as a white foam: R_f 0.76, 0.79 (10% Et_2O in hexanes, 25% Et_2O in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (s, 1H), 4.29 (dd, *J* = 7.1, 9.5 Hz, 1H), 4.11 (d, *J* = 18.6 Hz, 1H), 4.00 (d, *J* = 18.6 Hz, 1H), 3.77 (d, *J* = 12.3 Hz, 1H), 3.62 (s, 3H), 3.55 (d, *J* = 12.9 Hz, 1H), 3.54 (d, *J* = 12.6 Hz, 1H), 3.39 (d, *J* = 12.3 Hz, 1H), 2.19 (s, 3H), 2.14-2.04 (m, 2H), 1.82 (s, 3H), 1.31 (s, 3H), 1.28 (s, 3H), 1.23 (s, 3H), 1.01 (s, 9H), 0.90 (s, 9H), 0.67 (s, 3H), 0.15 (s, 6H), 0.14 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 151.0, 146.4, 137.8, 131.4, 130.9, 129.4, 126.0, 116.4, 101.1, 66.0, 65.5, 61.5, 60.0, 48.0, 45.5, 43.0, 38.1, 26.0, 25.9, 24.7 (2C), 20.7, 18.5, 18.2, 18.1, 16.9, 11.1, -4.2, -4.3, -4.4, -5.1; IR (Neat film NaCl) 2954, 2930, 2858, 1700, 1471, 1404, 1233, 1220, 1099, 1075, 855, 837, 779 cm^{-1}; HRMS (FAB) $[M\text{-}H_2+H]^+$ calc'd for $[C_{36}H_{60}Si_2O_6Br]^+$: *m/z* 723.3112, found 723.3128.



237 *251*

Aryl bromide 251 directly from enone **237**. To a solution of enone **237** (200 mg, 0.309 mmol, 1.00 equiv) in ACN (8.0 mL) and CH_2Cl_2 (1.2 mL) was added NBS (66.0 mg, 0.371 mmol, 1.20 equiv). After 2.5 h, the reaction was diluted with H_2O (30 mL) and EtOAc (15 mL), and extracted with EtOAc (5 x 15 mL). The combined organics were washed with brine (10 mL), dried (Na_2SO_4), concentrated, and purified by flash chromatography on silica gel (1 to 5% Et_2O in hexanes) to give aryl bromide **241** (179

mg, 80% yield) as a 4:1 mixture of bromide isomers favoring the desired aryl bromide **251**.



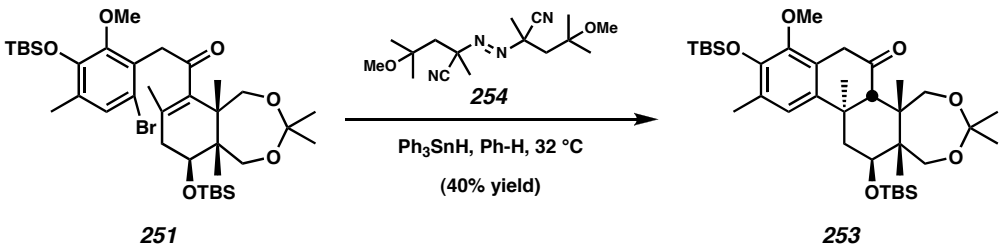
243 ***252***

Aryl bromide 252. To a solution of enone **243** (60.0 mg, 0.111 mmol, 1.00 equiv) in THF (3.7 mL) was added a 1.0 M solution of TBAF (166 μL, 0.166 mmol, 1.50 equiv) in THF. After 15 min, the reaction mixture was diluted with EtOAc (15 mL), H_2O (5 mL), and saturated aqueous NH_4Cl (5 mL), and extracted with EtOAc (5 x 20 mL). The combined organics were dried ($MgSO_4$), concentrated, and purified by flash chromatography on silica gel (20 to 30% EtOAc in hexanes) to give the intermediate phenol (40.0 mg, 85% yield).

To a cooled (0 °C) solution of intermediate phenol (33.7 mg, 78.8 μmol, 1.00 equiv) in ACN (1.6 mL) was added NBS (15.4 mg, 86.7 μmol, 1.10 equiv), and the reaction mixture was allowed to come to ambient temperature. After 5 h, the reaction was diluted with H_2O (10 mL) and EtOAc (20 mL), and extracted with EtOAc (5 x 10 mL). The combined organics were dried ($MgSO_4$), concentrated, and used without further purification in the next step.

To a solution of the above crude material (theory: 78.8 μmol, 1.00 equiv), imidazole (16.1 mg, 0.236 mmol, 3.00 equiv), TBSCl (17.8 mg, 0.118 mmol, 1.50 equiv) in DMF (200 μL) and CH_2Cl_2 (200 μL) was added DMAP (9.6 mg, 78.8 μmol, 1.00

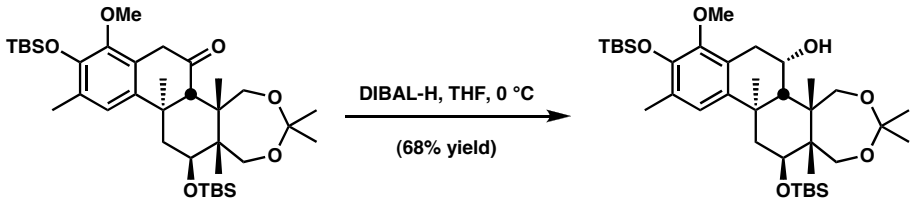
equiv) and the reaction was stirred at ambient temperature for 24 h and then at 30 °C for 18 h. An additional portion of DMAP (10.0 mg, 81.9 μmol, 1.04 equiv) and TBSCl (20.0 mg, 132.7 μmol, 1.69 equiv) were added and the reaction mixture was heated at 40 °C for 4 h. The reaction was diluted with EtOAc (10 mL), washed with saturated aqueous NH_4Cl (3 x 5 mL), and extracted with EtOAc (3 x 10 mL). The combined organics were concentrated and purified by flash chromatography on silica gel (5 to 15% Et_2O in hexanes) to give isomerically pure bromide **252** (23.0 mg, 47% yield, 40% yield for three steps) as an amorphous white solid: R_f 043 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (s, 1H), 4.29 (d, *J* = 8.5 Hz, 1H), 4.10 (d, *J* = 7.0 Hz, 1H), 4.07 (d, *J* = 7.0 Hz, 1H), 4.06 (d, *J* = 4.0 Hz, 1H), 3.88 (dd, *J* = 6.3, 8.8 Hz, 1H), 3.62 (s, 3H), 3.54 (app. t, *J* = 9.3 Hz, 1H), 2.55 (dd, *J* = 6.3, 17.8 Hz, 1H), 2.32 (dd, *J* = 8.5, 18.0 Hz, 1H), 2.18 (s, 3H), 1.87 (s, 3H), 1.62 (s, 3H), 1.61 (s, 3H), 1.21 (s, 3H), 1.17 (s, 3H), 1.01 (s, 9H), 0.14 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.4, 150.9, 146.4, 138.3, 131.4, 129.3, 128.7, 126.0, 121.5, 116.3, 75.5, 75.3, 75.2, 70.5, 60.0, 49.7, 47.7, 47.2, 35.7, 28.7, 27.6, 26.0, 21.0, 20.8, 18.1, 16.8, -4.3; IR (Neat film NaCl) 2932, 2860, 2252, 1699, 1470, 1404, 1234, 1171, 1083, 1047, 853, 842, 734 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{31}H_{46}NSiBrO_5+H]^+$: *m/z* 620.2407, found 620.2394.



251 *253*

Cyclized ketone 253. To a solution of aryl bromide **251** (25.0 mg, 34.4 μmol, 1.00 equiv of a 4:1 mixture of isomers) and initiator V-70 (**254**) (15.9 mg, 51.7 μmol,

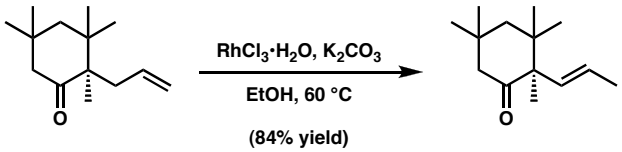
1.50 equiv) in benzene (2.0 mL) at 32 °C was added a solution of Ph_3SnH (24.2 mg, 68.8 μmol, 2.00 equiv) in benzene (0.5 mL) by syringe pump over 5 h. At the end of the addition, the reaction was cooled to ambient temperature, concentrated, and purified by flash chromatography on silica gel (2 to 7.5% Et_2O in hexanes) to give ketone **253** (8.9 mg, 40% yield, 50% yield based on the correct isomer of the starting material) as an oil: R_f 0.52 (25% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 6.77 (s, 1H), 4.53 (d, J = 12.0 Hz, 1H), 4.43 (dd, J = 4.5, 12.5 Hz, 1H), 3.97 (d, J = 12.5 Hz, 1H), 3.66 (d, J = 22.0 Hz, 1H), 3.64 (s, 3H), 3.55 (d, J = 12.5 Hz, 1H), 3.39 (d, J = 22.0 Hz, 1H), 3.33 (d, J = 12.5 Hz, 1H), 2.84 (s, 1H), 2.22 (s, 3H), 2.18 (dd, J = 4.5, 12.5 Hz, 1H), 1.92 (app. t, J = 12.5 1H), 1.33 (s, 3H), 1.31 (s, 3H), 1.16 (s, 3H), 1.14 (s, 3H), 1.03 (s, 9H), 0.94 (s, 9H), 0.57 (s, 3H), 0.19 (s, 6H), 0.18 (s, 3H), 0.15 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.3, 147.8, 145.1, 141.5, 129.0, 123.8, 120.8, 100.9, 65.8, 62.2, 62.1, 59.3, 58.8, 44.7, 43.5, 42.5, 41.2, 41.0, 27.4, 26.0 (2C), 24.8, 24.6, 20.0, 18.6, 18.2, 17.6, 10.1, -4.0, -4.2 (2C), -4.9; IR (Neat film NaCl) 2954, 2929, 2857, 1715, 1472, 1462, 1254, 1221, 1088, 1071, 838 cm^{-1}; HRMS (FAB) $[M-H_2+H]^+$ calc'd for $[C_{36}H_{61}Si_2O_6]^+$: m/z 645.4007, found 645.4007.



253 *255*

Alcohol 255. To a cooled (0 °C) solution of ketone **253** (19.9 mg, 30.8 μmol, 1.00 equiv) in THF (5.0 mL) was added a 1.0 M solution of DIBAL-H (250 μL, 0.250 mmol, 8.12 equiv) in toluene. After 4 h, an additional portion of DIBAL-H (100 μL,

0.100 mmol, 3.25 equiv) in toluene was added. After an additional 1 h at 0 °C, the reaction mixture was quenched with Na_2SO_4•$10H_2O$ (300 mg) in a portionwise manner, filtered, washed (CH_2Cl_2), concentrated, and purified by flash chromatography on silica gel (10 to 40% Et_2O in hexanes) to give alcohol **255** (13.6 mg, 68% yield) as a white solid. Crystals suitable for X-ray analysis were obtained by crystallization from CH_2Cl_2 at ambient temperature: mp 185-190 °C decomp. (CH_2Cl_2); R_f 0.21 (25% Et_2O in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78 (s, 1H), 4.68 (s, 1H), 4.47 (dd, *J* = 3.8, 12.3 Hz, 1H), 4.28 (d, *J* = 12.5 Hz, 1H), 3.93 (d, *J* = 13.0 Hz, 1H), 3.65 (s, 3H), 3.53 (d, *J* = 12.0 Hz, 1H), 3.37 (d, *J* = 12.5 Hz, 1H), 2.95 (s, 1H), 2.94 (s, 1H), 2.20 (s, 3H), 2.07 (dd, *J* = 4.0, 12.5 Hz, 1H), 1.66 (s, 1H), 1.62 (d, *J* = 12.0 Hz, 1H), 1.58 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H), 1.20 (bs, 1H), 1.11 (s, 3H), 1.03 (s, 9H), 0.92 (s, 9H), 0.57 (s, 3H), 0.19 (s, 3H), 0.17 (s, 6H), 0.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.6, 144.4, 141.8, 128.3, 122.8, 122.1, 100.9, 66.4, 65.4, 65.3, 63.0, 59.2, 48.6, 45.7, 45.4, 44.6, 37.5, 36.7, 29.6, 26.1, 26.0, 25.0, 24.6, 22.2, 18.6, 18.1, 17.5, 10.4, -4.0 (2C), -4.1, -4.9; IR (Neat film NaCl) 3454, 2954, 2930, 2858, 1473, 1252, 1220, 1089, 1061, 836 cm^{-1}; HRMS (FAB) [M-H_2+H]$^+$ calc'd for $[C_{36}H_{63}Si_2O_6]^+$: *m/z* 647.4163, found 647.4162.

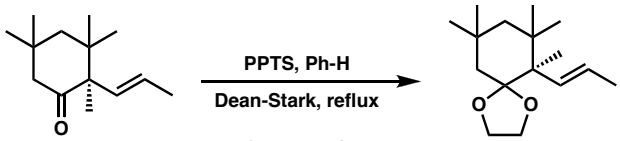


256
(85% ee)

257

Vinyl ketone 257. To a solution of allyl ketone **256** (905 mg, 4.35 mmol, 1.00 equiv) in EtOH (45 mL) in a sealable Schlenk flask (100 mL) was added K_2CO_3 (601 mg, 4.35 mmol, 1.00 equiv) and $RhCl_3$•H_2O (49.4 mg, 0.218 mmol, 0.05 equiv). The reaction

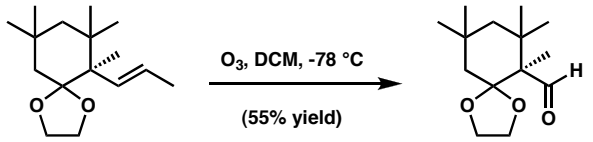
mixture was sparged with Ar for 10 min, sealed and heated to 60 °C for 12 h. After cooling to ambient temperature, the reaction mixture was filtered, washed with EtOH, concentrated, and purified by flash chromatography on silica gel (7.5 to 10% Et_2O in pentane) to give vinyl ketone **257** (759 mg, 84% yield of a 10:1 mixture containing allyl ketone **256** as the minor component) as an amorphous solid: R_f 0.67, 0.46 (25% Et_2O in hexanes, 5% Et_2O in hexanes developed twice); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (dq, J = 1.8, 15.5 Hz, 1H), 5.42 (dq, J = 6.3, 15.3 Hz, 1H), 2.53 (d, J = 13.2 Hz, 1H), 2.11 (dd, J = 1.8, 13.5 Hz, 1H), 1.85 (d, J = 14.4 Hz, 1H), 1.71 (dd, J = 1.7, 6.5 Hz, 3H), 1.42 (dd, J = 1.8, 14.4 Hz, 1H), 1.09 (s, 3H), 1.04 (s, 3H), 1.01 (s, 3H), 0.90 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.1, 132.5, 126.2, 56.4, 50.7, 49.6, 40.6, 35.4, 33.7, 30.2, 26.9, 26.8, 18.6, 15.6; IR (Neat film NaCl) 2957, 1707, 1458, 1391, 1370, 1283, 977 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{14}H_{24}O]^+$: m/z 208.1827, found 208.1820; $[\alpha]_D^{25}$ –59.07 (c 1.04, $CHCl_3$, 85% ee).



257 ***258***

Ketal 258. A solution of the vinyl ketone **257** (700 mg, 3.36 mmol, 1.00 equiv), ethylene glycol (1.30 mL, 23.5 mmol, 7.00 equiv), and pyridinium *p*-toluenesulfonate (211 mg, 0.84 mmol, 0.25 equiv) in benzene (70 mL) was fitted with a Dean-Stark apparatus and refluxed at 100 °C for 30 h. The reaction mixture was cooled to ambient temperature, diluted with saturated aqueous $NaHCO_3$ (40 mL), and extracted with Ph-H (3 x 30 mL). The combined organics were washed with brine (20 mL), dried (Na_2SO_4),

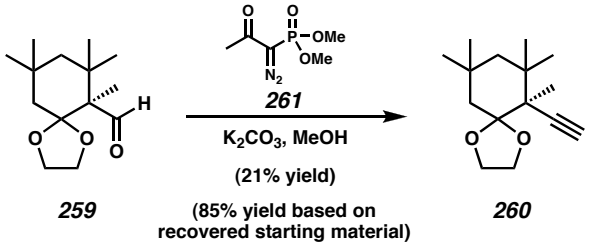
concentrated, and purified by flash chromatography on silica gel (1 to 2% Et_2O in hexane) to give acetal **258** (585 mg, 70% yield) as an oil: R_f 0.61, 0.67 (5% Et_2O in hexanes developed twice, 25% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.74 (dq, *J* = 1.5, 15.8 Hz, 1H), 5.44 (dq, *J* = 6.3, 15.8 Hz, 1H), 3.92-3.78 (m, 4H), 1.72 (dd, *J* = 1.7, 6.5 Hz, 3H), 1.52 (s, 2H), 1.37 (d, *J* = 14.1 Hz, 1H), 1.30 (d, *J* = 14.1 Hz, 1H), 1.03 (s, 6H), 1.02 (s, 3H), 0.96 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.7, 124.3, 113.8, 64.6, 64.4, 49.8, 48.6, 42.2, 38.0, 32.3, 32.0, 31.5, 28.3, 27.7, 18.7, 14.2; IR (Neat film NaCl) 2952, 1455, 1388, 1225, 1146, 1124, 1078, 981 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{16}H_{28}O]^+$: m/z 252.2089, found 252.2090; $[\alpha]_D^{24}$ +1.51 (c 1.11, $CHCl_3$, 85% ee).



258 ***259***

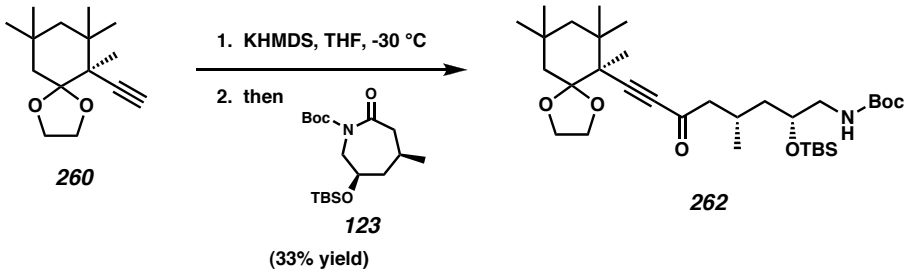
Aldehyde 259. Through a cooled (-78 °C) solution of acetal **258** (252 mg, 1.00 mmol, 1.00 equiv) in CH_2Cl_2 (25 mL) was bubbled a stream of ozone until the reaction mixture turned blue. The reaction mixture was quenched with dimethyl sulfide (0.20 mL), allowed to warm to ambient temperature, concentrated to an oil, and purified by flash chromatography on silica gel (2.5 to 10% Et_2O in hexane) to give aldehyde **259** (132 mg, 55% yield) as an oil: R_f 0.41, 0.29 (25% Et_2O in hexanes, 5% Et_2O in hexanes developed twice); ^1H NMR (300 MHz, $CDCl_3$) δ 9.93 (s, 1H), 3.98-3.85 (m, 4H), 1.69 (d, *J* = 14.4 Hz, 3H), 1.57 (dd, *J* = 1.2, 14.4 Hz, 1H), 1.50 (d, *J* = 14.4 Hz, 1H), 1.37 (dd, *J* = 1.2, 14.4 Hz, 1H), 1.08 (s, 3H), 1.07 (s, 3H), 1.06 (s, 3H), 1.04 (s, 3H), 1.03 (s, 3H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 206.2, 112.1, 64.5, 64.3, 58.0, 50.3, 43.0, 38.1, 32.9, 31.6, 30.6, 27.8, 27.7, 11.1; IR (Neat film NaCl) 2954, 2899, 1722, 1241, 1110, 1075, 964 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{14}H_{24}O_3]^+$: m/z 240.1726, found 240.1720; $[\alpha]_D^{24}$ –39.53 (c 0.385, $CHCl_3$, 85% ee).



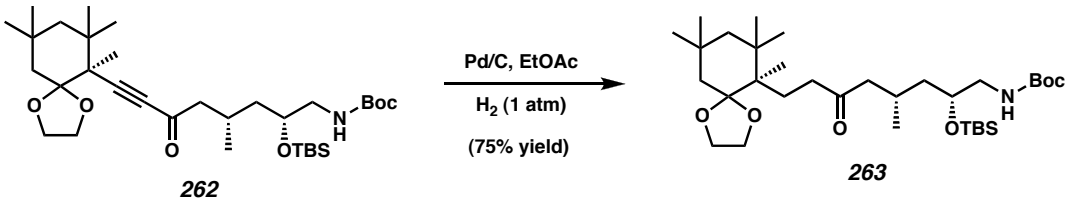
Alkyne 260. To a solution of aldehyde **259** (75.0 mg, 0.312 mmol, 1.00 equiv), and K_2CO_3 (108 mg, 0.780 mmol, 2.50 equiv) in MeOH (3.10 mL) was added diazoketone **261** (89.9 mg, 0.468 mmol, 1.5 equiv). After 1 h, an additional portion of K_2CO_3 (214 mg, 1.56 mmol, 5.00 equiv) and of diazoketone **261** (150 mg, 0.780 mmol, 2.5 equiv) were added. After a further 4 h, a final portion of K_2CO_3 (200 mg, 1.45 mmol, 4.65 equiv) and of diazoketone **261** (200 mg, 1.05 mmol, 3.37 equiv) were added. After stirring for 20 h, the reaction mixture was diluted with H_2O (10 mL), extracted with CH_2Cl_2 (8 x 5 mL), dried ($MgSO_4$), concentrated, and purified by flash chromatography on silica gel (1 to 7% Et_2O in hexanes) to give recovered aldehyde **259** (55.6 mg, 74% yeld) and alkyne **260** (15.5 mg, 21% yield, 85% yield based on recovered aldehyde **259**) as an oil: R_f 0.40 (5% Et_2O in hexanes developed twice); ^1H NMR (300 MHz, C_6D_6) δ 3.62-3.40 (m, 4H), 2.01 (d, J = 14.1 Hz, 1H), 1.93 (s, 1H), 1.72 (d, J = 14.1 Hz, 1H), 1.47 (dd, J = 1.8, 13.8 Hz, 1H), 1.36 (s, 3H), 1.34 (s, 3H), 1.22 (s, 3H), 1.17 (dd, J = 1.7, 14.3 Hz, 1H), 1.10 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 112.5, 89.1, 76.6, 70.7,

65.5, 64.2, 49.8, 47.3, 42.5, 38.0, 34.6, 31.4, 29.8, 28.8, 24.9, 16.2; IR (Neat film NaCl) 3309, 2954, 2911, 2111, 1454, 1390, 1367, 1235, 1148, 1088, 1073, 984 cm^{-1}; HRMS (EI) $[M]^+$ calc'd for $[C_{15}H_{24}O_2]^+$: m/z 236.1776, found 236.1786; $[\alpha]_D^{26}$ –20.35 (c 1.25, CH_2Cl_2, 85% ee).



Ynone 262. To a cooled (-30 °C) solution of KHMDS (24.1 mg, 0.121 mmol, 2.20 equiv) in THF (1.00 mL) was added alkyne **260** (13.0 mg, 0.055 mmol, 1.00 equiv) in THF (1.00 mL). The solution was maintained for 30 min each at -30 °C, 0 °C, and 22 °C. The alkyne anion was cooled to -78 °C, and caprolactam **123** (23.6 mg, 0.066 mmol, 1.2 equiv) in THF (1.00 mL) was added. After 1 h, additional KHMDS (12.0 mg, 0.061 mmol, 1.10 equiv) in THF (0.50 mL) was added. After a further 5 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (0.50 mL), diluted with H_2O (2 mL), brine (4 mL), and Et_2O (4 mL), and extracted with Et_2O (6 x 4 mL) and CH_2Cl_2 (2 x 2 mL). The combined organics were dried (Na_2SO_4) and concentrated to an oil, which was purified by flash chromatography on silica gel (2.5 to 15% EtOAc in hexanes) to give ynone **262** (10.9 mg, 33% yield) as a oil: R_f 0.24, 0.50 (10% EtOAc in hexanes developed twice, 20% EtOAc in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 4.78 (s, 1H), 4.07-4.02 (m, 1H), 4.00-3.94 (m, 3H), 3.84 (bs, 1H), 3.38-3.30 (m, 1H), 2.97 (dt, J = 6.0, 14.5 Hz, 1H), 2.58 (dd, J = 5.5, 15.5 Hz, 1H), 2.38 (dd, J = 8.0, 15.5 Hz, 1H), 2.26-2.16

(m, 1H), 1.76 (d, J = 14.0 Hz, 1H), 1.62-1.44 (comp. m, 4H), 1.46 (s, 9H), 1.40-1.30 (m, 1H), 1.26 (s, 3H), 1.17 (s, 3H), 1.14 (s, 3H), 1.07 (s, 3H), 1.01 (s, 3H), 1.00 (s, 3H), 0.91 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 87.2, 155.9, 112.1, 98.7, 83.7, 79.1, 69.4, 65.5, 64.6, 53.2, 49.8, 48.1, 45.9, 43.0, 42.2, 38.7, 33.8, 31.4, 29.7, 29.6, 28.4, 28.0, 26.3, 25.9, 25.6, 20.2, 18.0, -4.5, -4.6; IR (Neat film NaCl) 3383, 2955, 2930, 2208, 1716, 1673, 1504, 1391, 1366, 1252, 1171, 1090, 836 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{33}H_{59}NO_6Si+H]^+$: m/z 594.4190, found 594.4208; $[\alpha]_D^{26}$ –36.12 (c 0.545, EtOAc).



Ketone 263. To a solution of ynone **262** (10.9 mg, 18.3 μmol, 1.00 equiv) in EtOAc (6 mL) was added 10% Pd/C (4.0 mg), and the reaction mixture was sparged with H_2 (5 min). After 18 h of vigorous stirring under an atmosphere of H_2 (balloon), the reaction mixture was concentrated and purified by flash chromatography on silica gel (5 to 10% EtOAc in hexanes). NMR analysis of the chromatographed product indicated the presence of some partially hydrogenated material. A solution of this material in EtOAc (5 mL) was treated again with 10% Pd/C (5.0 mg) under an atmosphere of H_2 (balloon) for 4 h. The reaction mixture was concentrated to an oil and purified by flash chromatography on silica gel (5 to 10% EtOAc in hexanes) to give ketone **263** (8.2 mg, 75% yield) as a oil: R_f 0.53 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.79 (s, 1H), 3.96 (app. t, J = 6.8 Hz, 1H), 3.83 (app. q, J = 7.0 Hz, 1H), 3.79 (bs, 1H),

3.74 (app. q, *J* = 7.0 Hz, 1H), 3.34-3.26 (m, 1H), 2.98 (dt, *J* = 6.5, 13.5 Hz, 1H), 2.60-2.50 (m, 1H), 2.48-2.36 (m 2H), 2.20 (dd, *J* = 7.8, 16.3 Hz, 1H), 2.12-2.02 (m, 1H), 2.00-1.92 (m, 1H), 1.56-1.24 (comp. m, 9H), 1.44 (s, 9H), 1.15 (d, *J* = 14.0 Hz, 1H), 1.11 (s, 3H), 1.05 (s, 3H), 0.96 (s, 3H), 0.92-0.89 (m, 6H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.9, 156.2, 115.2, 79.3, 69.8, 64.9, 62.6, 50.6, 50.5, 46.2, 44.2, 42.7, 41.4, 40.9, 39.1, 34.7, 31.5, 30.0, 29.4, 28.7, 28.3, 26.8, 26.1, 26.0, 24.4, 20.6, 18.3, 16.8, -4.3; IR (Neat film NaCl) 3391, 2953, 2930, 1714, 1503, 1366, 1253, 1173, 1076, 836, 776 cm^{-1}; HRMS (FAB) $[M+H]^+$ calc'd for $[C_{33}H_{63}NO_6Si+H]^+$: *m/z* 598.4503, found 598.4489; $[\alpha]_D^{26}$ 9.33 (c 0.105, CH_2Cl_2).

3.9 Notes and Citations

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(1) Bagdanoff, J. T. Development of the Enantioselective Oxidation of Secondary Alcohols and Natural Products Total Synthesis. Ph.D., California Institute of Technology, Pasadena, CA, August 2005.

(2) For limitations of DMMA Diels-Alder reactions, see: (a) Rae, I. D.; Serelis, A. K. *Aust. J. Chem.* **1990**, *43*, 1941-1948. (b) Ziegler, K.; Flaig, W.; Velling, G. *Justus Liebig Ann. Chem.* **1950**, *567*, 204-214.

(3) For synthesis of dihydrothiophene **195**, see: (a) Baker, B. R.; Querry, M. V.; Kadish, A. F. *J. Am. Chem. Soc.* **1980**, *102*, 6893-6894. (b) Dauben, W. G.; Gerdes, J. M.; Smith, D. B. *J. Org. Chem.* **1985**, *50*, 2576-2578.

(4) (a) Dauben, W. G.; Kessel, C. R.; Takemura, K. H. *J. Am. Chem. Soc.* **1980**, *102*, 6894-6896.

(5) Birman, V. B.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2080-2081.

(6) For the synthesis of known diene **200,** see: Duke, R. K.; Rickards, R. W. *J. Org. Chem.* **1984**, *49*, 1898-1904.

(7) Diene **198** is readily available in one step from crotonaldehyde and TBSOTf, see: Trost, B. M.; Chupak, L. S.; Lübbers, T. *J. Org. Chem.* **1997**, *62*, 736-737.

(8) DMMA is commercially available, but on scale is readily and more economically made from maleic anhydride, see: Baumann, M. E.; Bosshard, H.; Breitenstein, W.; Rihs, G.; Winkler, T. *Helv. Chim. Acta* **1984**, *67*, 1897-1905.

(9) Shimizu, M.; Matsukawa, K.; Fujisawa, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2128-2130.

(10) Bolm, C.; Schiffers, I.; Dinter, C. L.; Gerlach, A. *J. Org. Chem.* **2000**, *65*, 6984-6991.

(11) (a) Chen, Y.; Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2000**, *122*, 9542-9543. (b) Chen, Y.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 11302-11303.

(12) (a) Chen, Y.; McDaid, P.; Deng, L. *Chem. Rev.* **2003**, *103*, 2965-2983. (b) Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621-631.

(13) We acknowledge Thomas C. Scotton for the synthesis and testing of **207**. Menthol derivative **208** was a generous gift from Prof. Deng.

(14) Analysis of samples taken early during the reaction suggest that iodolactone **209** is a thermodynamic sink as other isomers appear to be initially formed.

(15) The most isomerization to ketone **212** (~30%) was observed with $RhI_3 \bullet H_2O$ in EtOH at 80 °C.

(16) See Chapter Two for details.

(17) Standard Mitsunobu conditions do not give reactivity, likely due to steric difficulties caused by nearby quaternary centers. For Mitsunobu protocol, see: Majetich, G.; Defauw, J.; Ringold, C. *J. Org. Chem.* **1988**, *53*, 50-68.

Reduction of enone **218** with $NaBH_4$ gave selective reduction of the methyl ester. Reduction under Luche conditions afforded only the undesired diastereomer **217**.

(18) See Chapter Two for more examples and discussion.

(19) The purity of triol **228** drastically modulates the efficacy of $CuSO_4$ in the acetonide forming reaction. Chromatography or recrystallization is required to remove what

are likely hydrated aluminum salts. Without purification of triol **228**, the reaction often fails to progress to more than 20% conversion.

(20) For other examples of favorable 1,3-dioxepane formation in synthesis, see: (a) Ritter, T.; Zarotti, P.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 4371-4374. (b) Brewster, A. G.; Leach, A. *Tetrahedron Lett.* **1986**, *27*, 2539-2542.

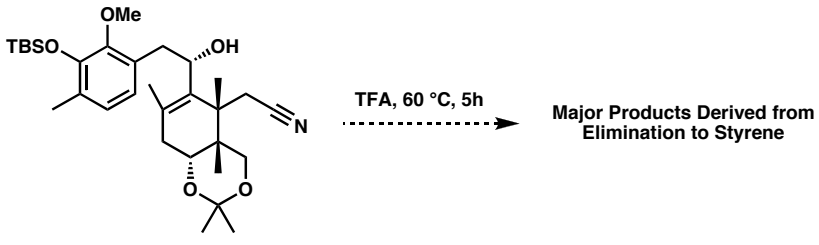
(21) The ratio of products seemed to depend most on the duration of the reaction, suggesting that some equilibration was possible between the products. On a number of occasions 1,3-dioxepane **229** was the major product (e.g., 44% yield of 1,3-dioxepane **229**, and 41% yield of 1,3-dioxolane **230**).

(22) Reaction with the methoxy methylene Wittig reagent gave ~25-40% yields.

(23) For recent examples, see: (a) Sano, S.; Kenji, M. *Eur. J. Org. Chem.* **1999**, *7*, 1679-1686. (b) Hamilton, J. G. C.; Hooper, A. M.; Mori, K.; Pickett, J. A.; Sano, S. *Chem. Commun.* **1999**, 355-356. (c) Hoffman, H. M. R.; Eggert, U.; Gibbels, U.; Giesel, K.; Koch, O.; Lies, R.; Rabe, J. *Tetrahedron* **1988**, *44*, 3899-3918.

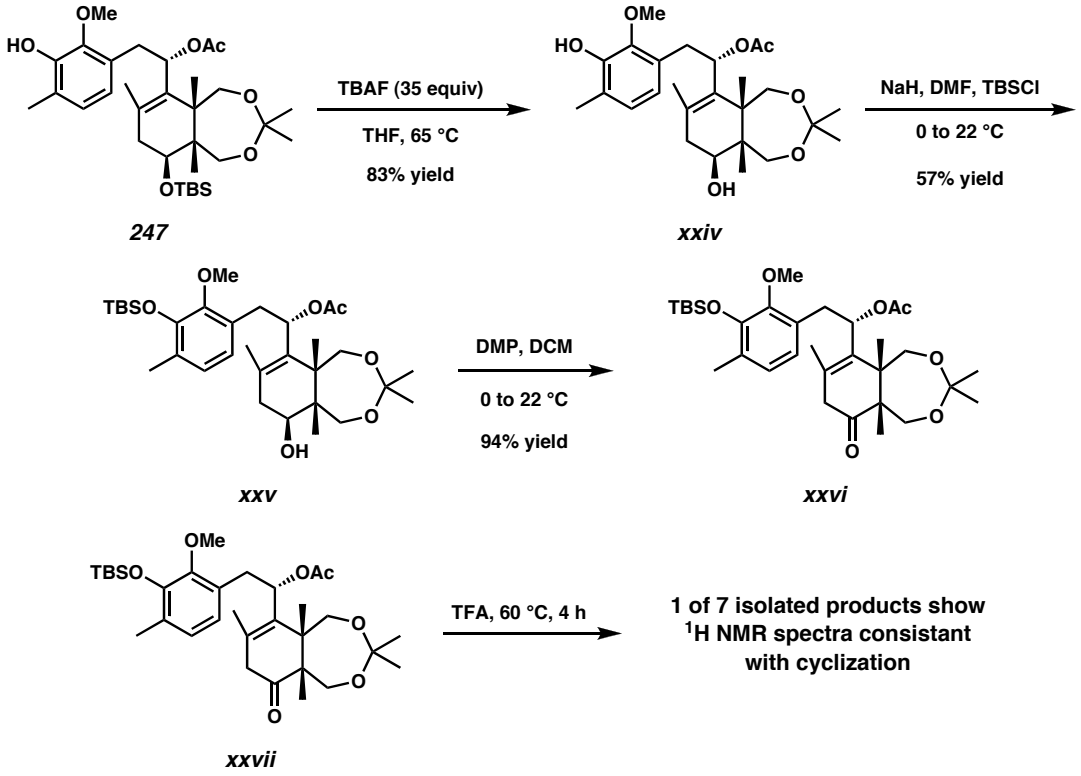
(24) DMSO was uniquely effective among polar solvents used in optimization trials of the KCN displacement reactions. ACN, DMF, NMP, and HMPA all proved to be grossly inferior. The addition of 18-C-6 did not improve the yield of the reaction.

(25) Attempts to carry out S_N' cyclization of allylic alcohol **xxiii** gave mostly styrene elimination products.



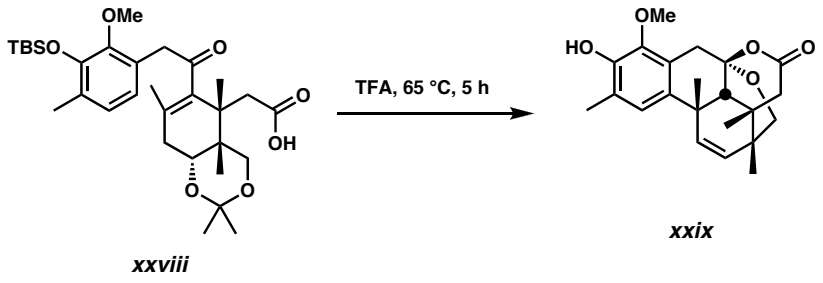
xxiii

(26) Synthesis of keto allylic acetate **247** was completed in several steps as shown below. The attempted S_N' cyclization of keto allylic acetate **xxvii** qualitatively gave less cyclized material and many more byproducts than either allylic alcohol **244** or allylic acetate **255**.



(27) Both C(20) stereoisomers were tried in parallel because the identity of each isomer had not been rigorously proven.

(28) Trifluoroacetic acid cyclization of the related enone **xxviii** afforded the related mixed acetal **xxix**.



(29) (a) Carreno, M. C.; Ruano, J. L. G.; Sanz, G.; Toledo, M. A.; Urbano, A. *J. Org. Chem.* **1995**, *60*, 5328-5331. (b) Berthelot, J.; Guette, C.; Desbène, P.-J.; Basselier, J.-J. *Can. J. Chem.* **1989**, *67*, 2061-2066.

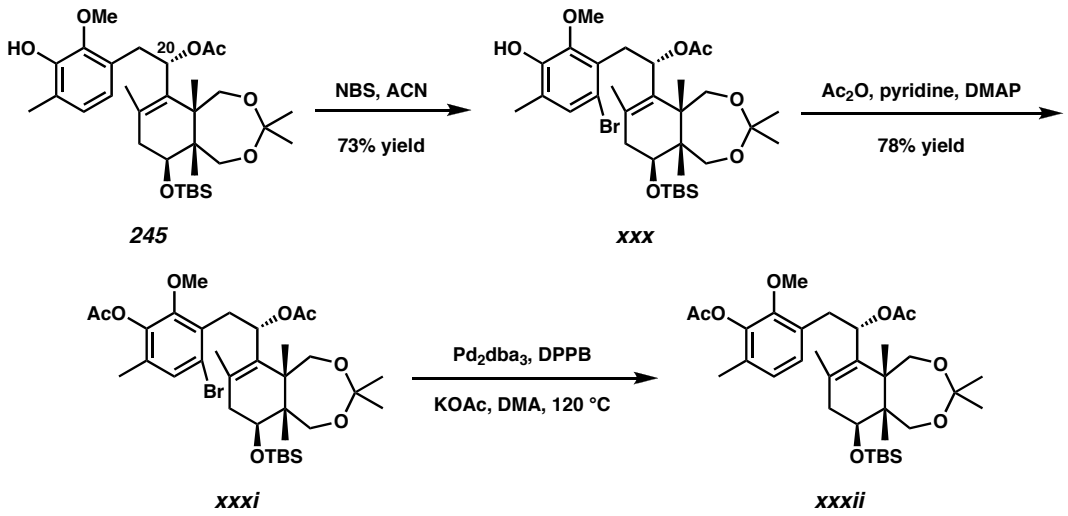
(30) Carreno, M. C.; Ruano, J. L. G.; Sanz, G.; Toledo, M. A.; Urbano, A. *Synlett.* **1997**, 1241-1242.

(31) (a) Hirai, G.; Koizumi, Y.; Moharram, S. M.; Oguri, H.; Hirama, M. *Org. Lett.* **2002**, *4*, 1627-1630. (b) Hirai, G.; Oguri, H.; Moharram, S. M.; Koyama, K.; Hirama, M. *Tetrahedron Lett.* **2001**, *42*, 5783-5787.

(32) (a) Rigby, J. H.; Hughes, R. C.; Heeg, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 7834-7835. (b) Dankwardt, J. W.; Flippin, L. A. *J. Org. Chem.* **1995**, *60*, 2312-2313. (c) Gibson, S.E.; Middleton, R. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1743-1744. (d) Gibson, S.E.; Guillo, N.; Tozer, M. J. *Chem. Commun.* **1997**, 637-638.

(33) (a) Link, J. T. The Intramolecular Heck Reaction. In *Organic Reactions*; Overman, L. E., Ed.; John Wiley & Sons: New York, 2002, 60, pp 157-325. (b) Bräse, S.; De Meijee A. Intramolecular Heck Reaction. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002, pp 1223-1254.

(34) Attempted Heck reactions from substrates with the C(20) alcohol oxidation also resulted in debrominated material.



(35) For an excellent review of intramolecular radical conjugate addition, see: Zhang, W. *Tetrahedron* **2001**, *57*, 7237-7262.

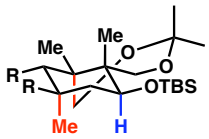
(36) Rajamannar, T.; Balasubramanian, K. K. *J. Chem. Soc., Chem. Commun.* **1994**, 25-26.

(37) TBS groups removed from the figure for clarity.

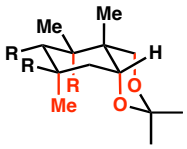
(38) Lewis acids have been used numerous times to promote radical conjugate additions, see: (a) Sibi, M. P.; Ji, J.; Sausker, J. B.; Jasperse, C. P. *J. Am. Chem. Soc*. **1999**, *121*, 7517-7526. (b) Iserloh, U.; Curran, D. P.; Kanemasa, S. *Tetrahedron: Asymmetry* **1999**, *10*, 2417-2428. (c) Murakata, M.; Tsutsui, H.; Hoshino, O, *Org. Lett*. **2001**, *3*, 299-302. (d) Sibi, M. P.; Manyem, S. *Org. Lett*. **2002**, *4*, 2929-2932.

(39) Preliminary studies with aryl bromide **252** suggest that cyclized products with both C(12) relative stereochemistries are formed. Our conjecture at this time is that the C(10) stereocenter may play a crucial role in determining the stereochemical

outcome of the radical conjugate addition reaction due to the additional 1,3-diaxial interactions that occur formed in the products.



Cyclization product from aryl bromide *251* experiences only 1 new 1,3-diaxial interaction



Cyclization product from aryl bromide *252* experiences several new 1,3-diaxial interactions

(40) Miyashita, M.; Sasaki, M.; Hattori, I.; Sakai, M.; Tanino, K. *Science* **2004**, *305*, 495-499.

(41) See Chapter Four for details.

(42) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561-564. (b) Müller, S.; Liepold, B.; Ruth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521-522.

(43) Complete consumption of aldehyde **259** is observed by TLC during the reaction. However, it reappears again upon workup, suggesting that the collapse of the intermediate addition adduct to the olefin is slow. Attempts to drive the reaction to completion with heat or additional equivalents of phosphate **261** were unsuccessful. Reaction of aldehyde **259** with lithiated TMS diazomethane gave a slightly higher yield (~35%), but no aldehyde could be recovered.

(44) KHMDS caused significantly less degradation of caprolactam **123** than potassium *t*-butoxide, or LDA.

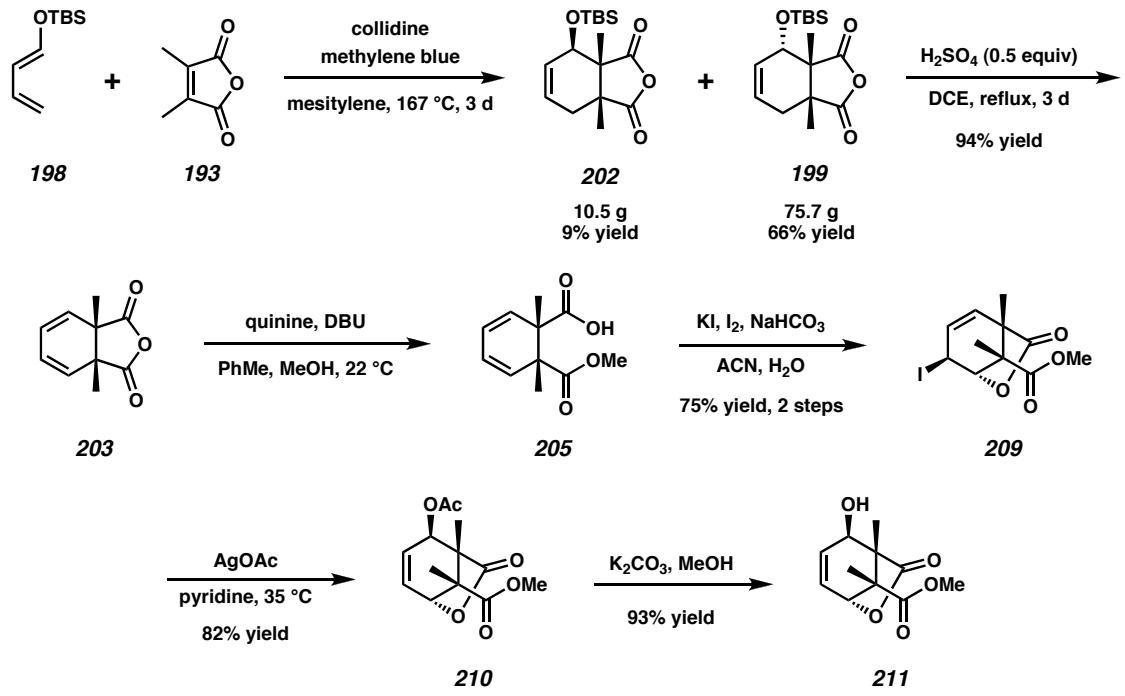
(45) It should be noted that ynone **262** is diastereomeric to an exact zoanthenol model. (*R*)-Alkyne **260** would be required to model the correct absolute stereochemistry of the natural product. Caprolactam **123** is of the correct enantiomeric series for completion of the natural product.

(46) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455-3458.

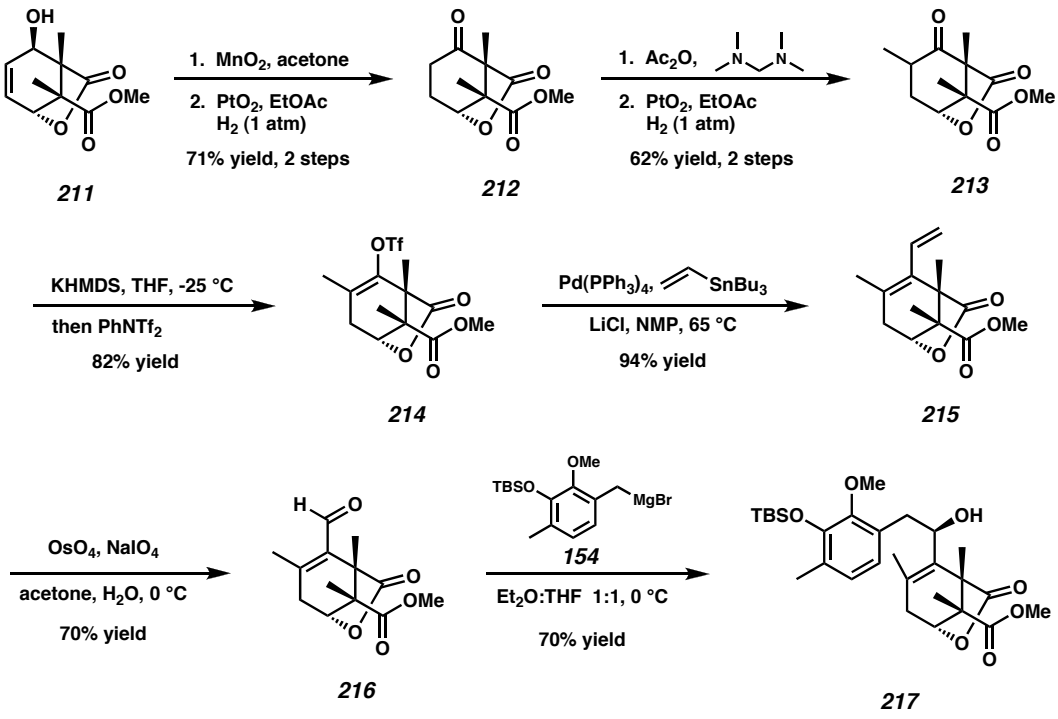
APPENDIX FOUR

Synthetic Summary of Approaches Toward Advanced Zoanthenol ABC Ring Systems Containing Three Quaternary Stereocenters

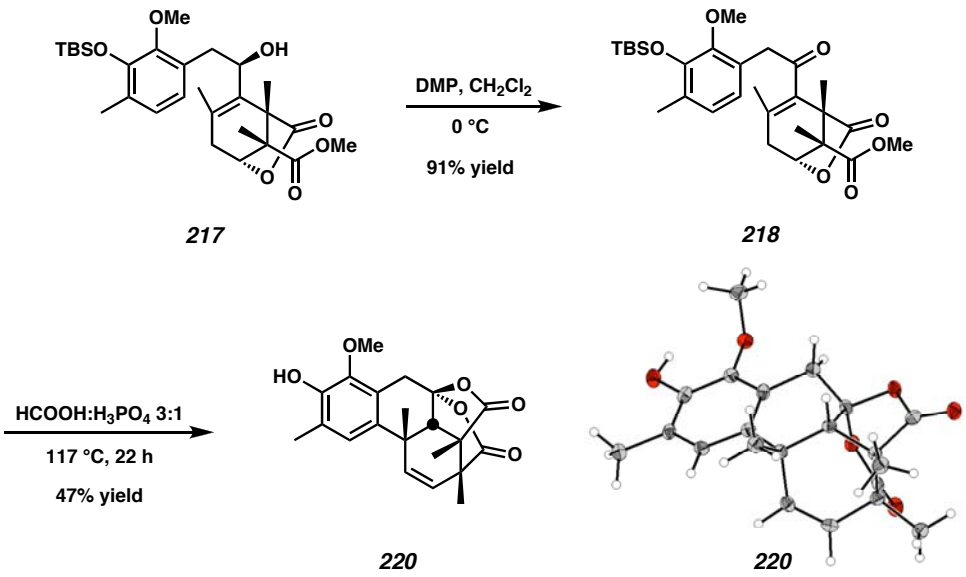
Scheme A4.1: Synthesis of C Ring Precursor with Vicinal Quaternary Centers



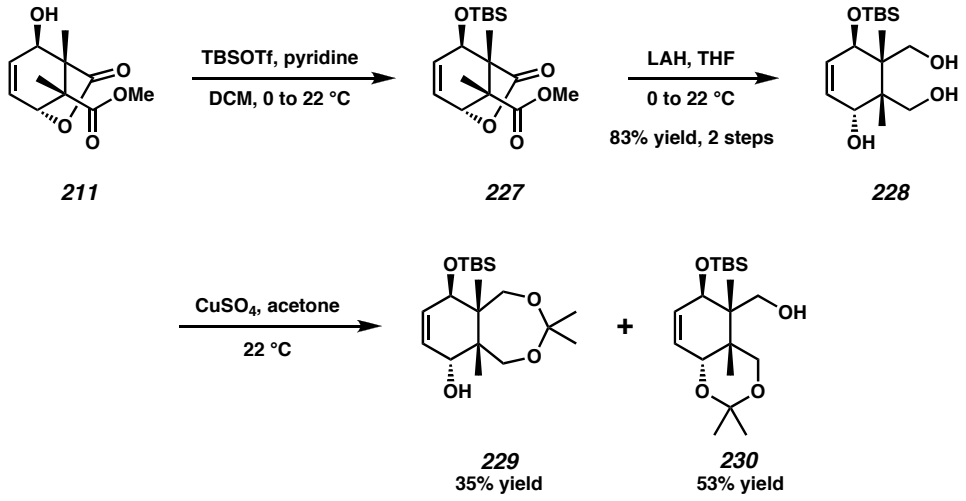
Scheme A4.2 Elaboration of the Lactone C Ring Synthon



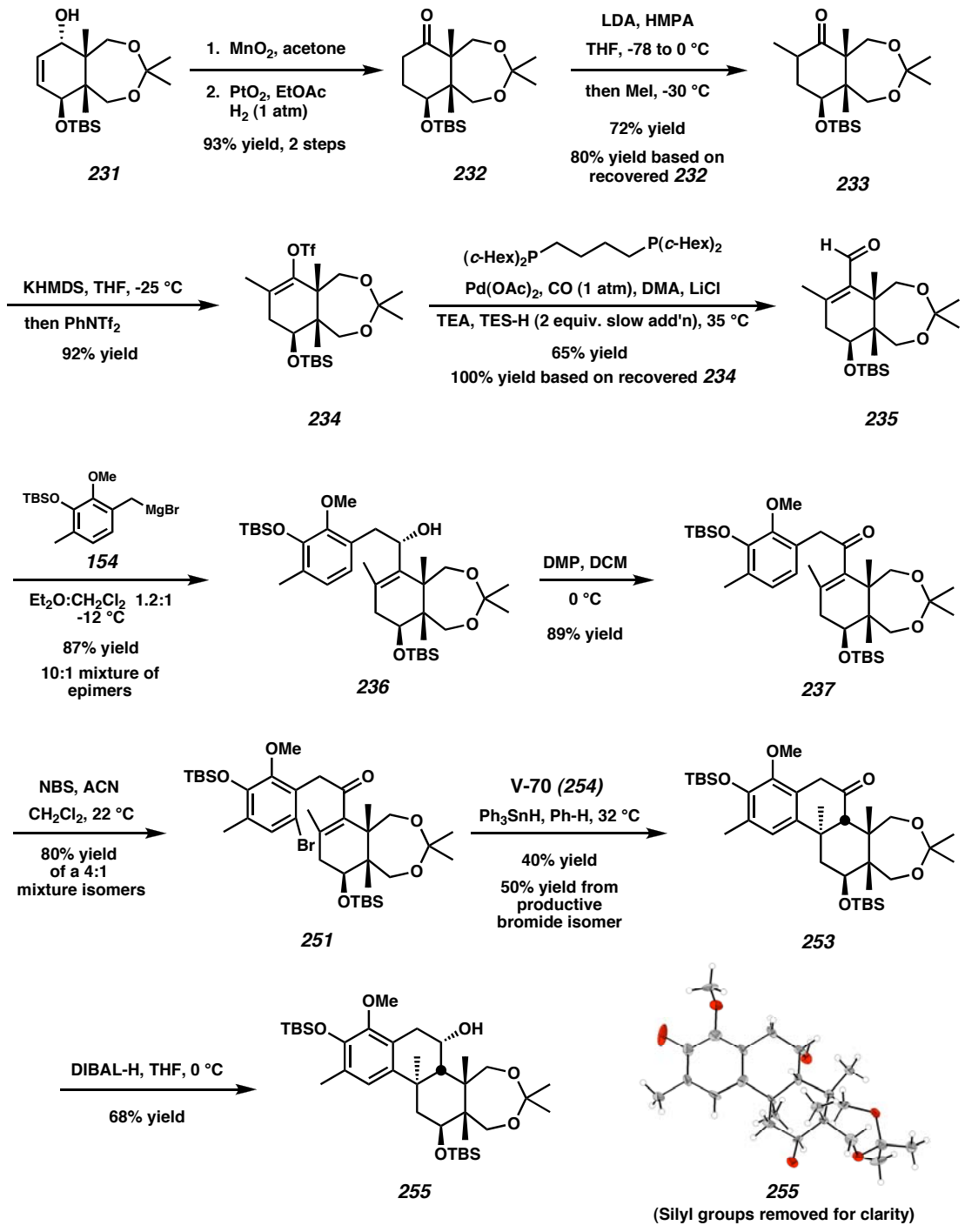
Scheme A4.3 Completion and Cyclization of the Lactone C Ring Synthon



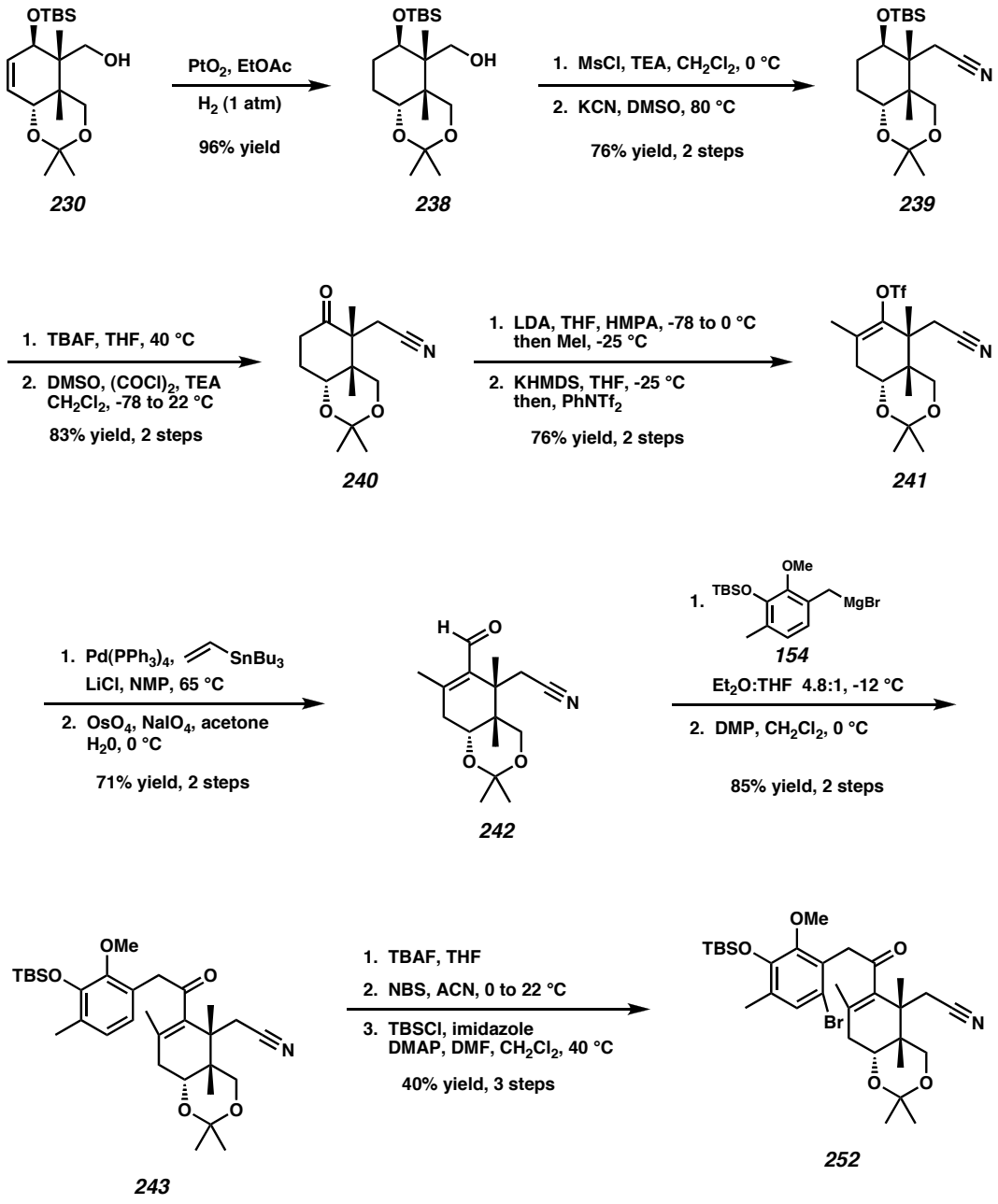
Scheme A4.4 Common Steps of the 1,3-Dioxepane and Acetonide C Ring Synthon Syntheses



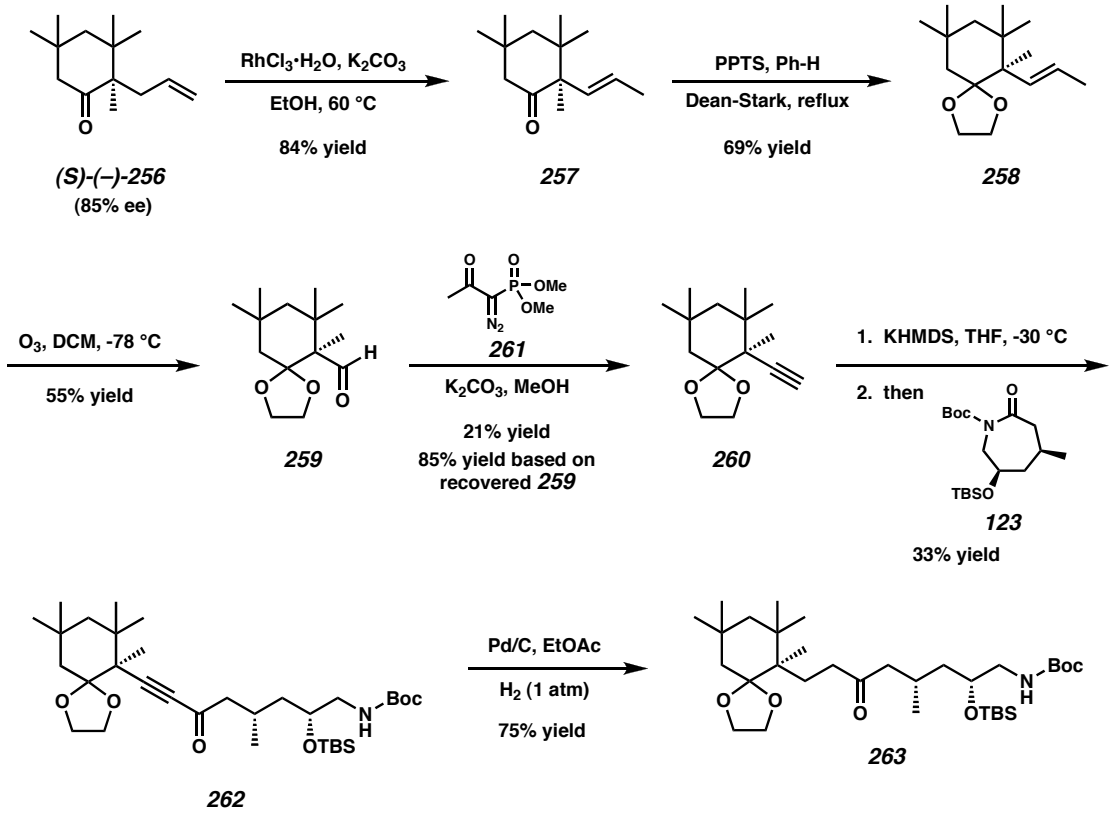
Scheme A4.5 Synthesis and Cyclization of the 1,3-Dioxepane C Ring Synthon



Scheme A4.6 Synthesis of the Nitrile Acetonide C Ring Synthon



Scheme A4.7 Model C(1)-C(6) Fragment Coupling



APPENDIX FIVE

Spectra of Compounds Relevant to Chapter Three

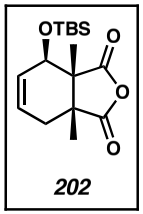


Figure A5.1 ^{1}H NMR of compound **202** (500 MHz, $CDCl_3$)

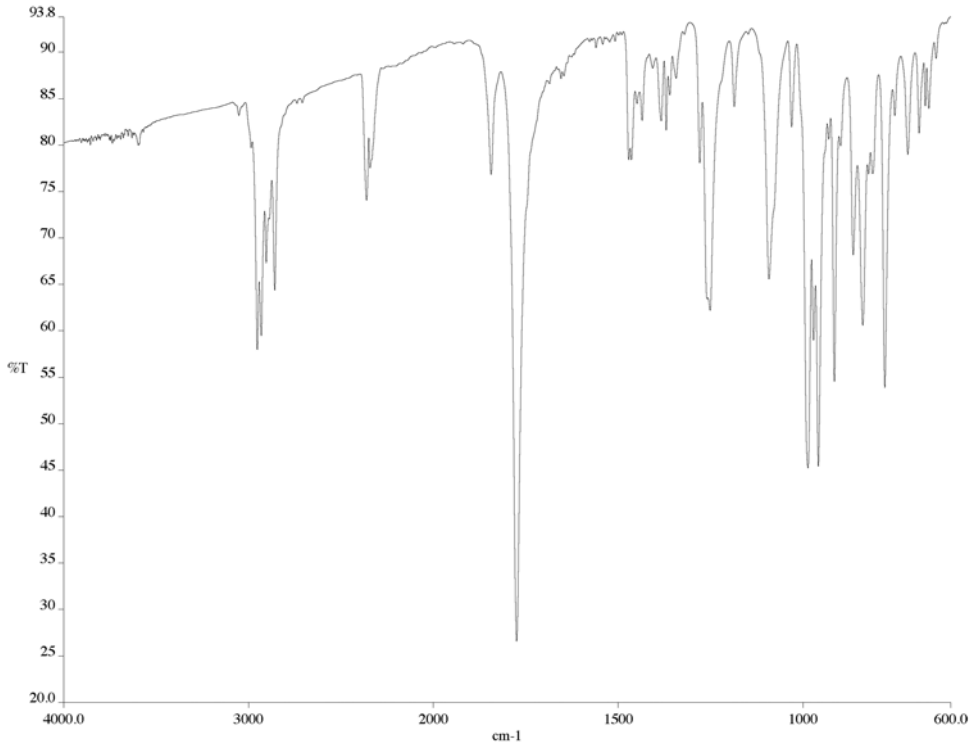


Figure A5.2 IR of compound **202** (NaCl/film)

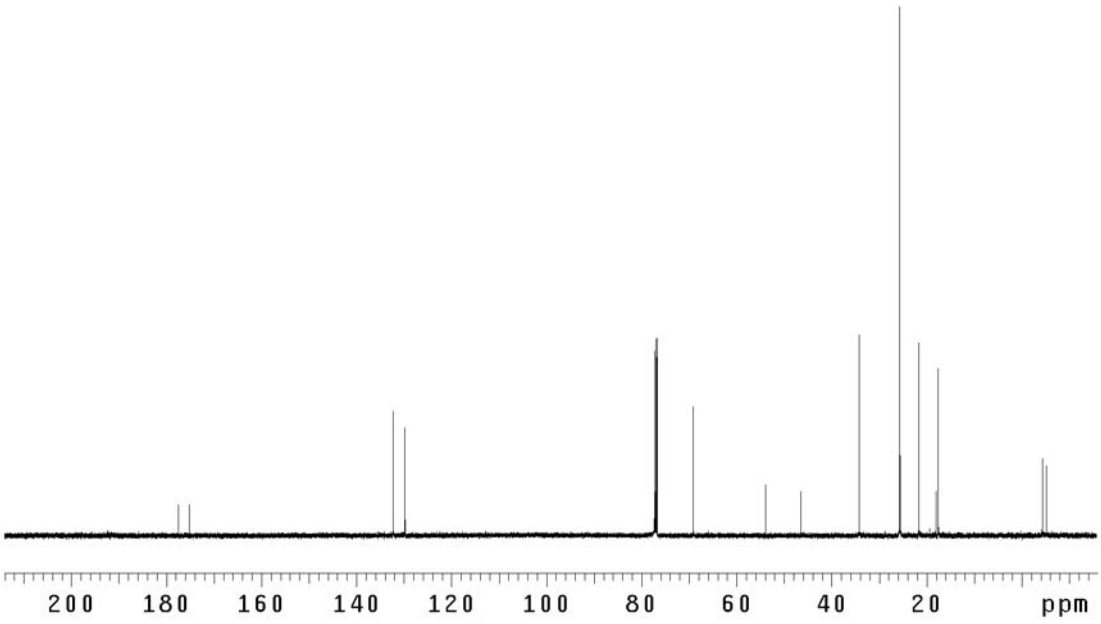


Figure A5.3 ^{13}C NMR of compound **202** (125 MHz, $CDCl_3$)

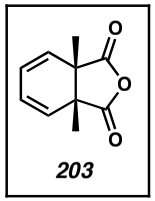


Figure A5.4 ^{1}H NMR of compound **203** (500 MHz, $CDCl_3$)

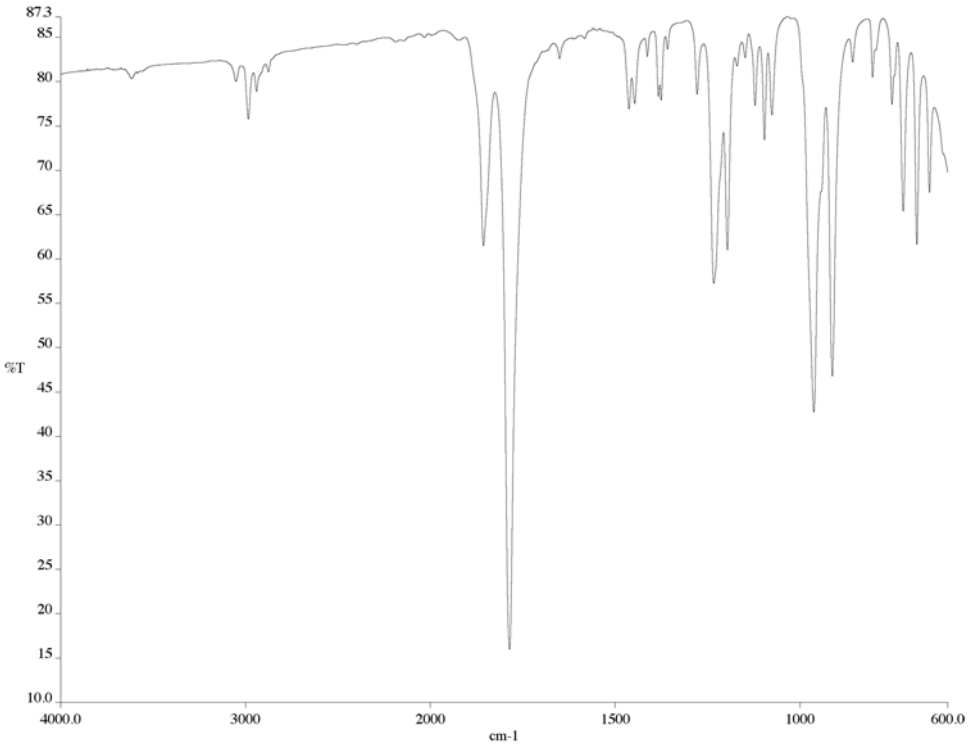


Figure A5.5 IR of compound **203** (NaCl/film)

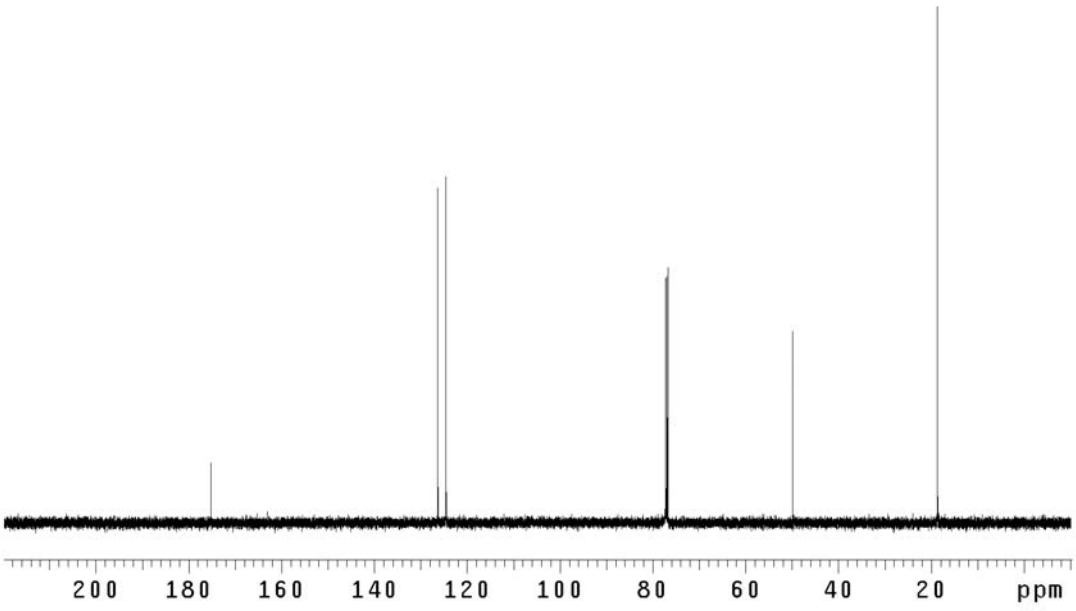
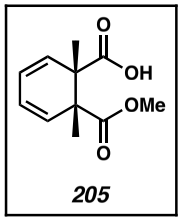


Figure A5.6 ^{13}C NMR of compound **203** (125 MHz, $CDCl_3$)



205

Figure A5.7 ^{1}H NMR of compound **205** (500 MHz, $CDCl_3$)

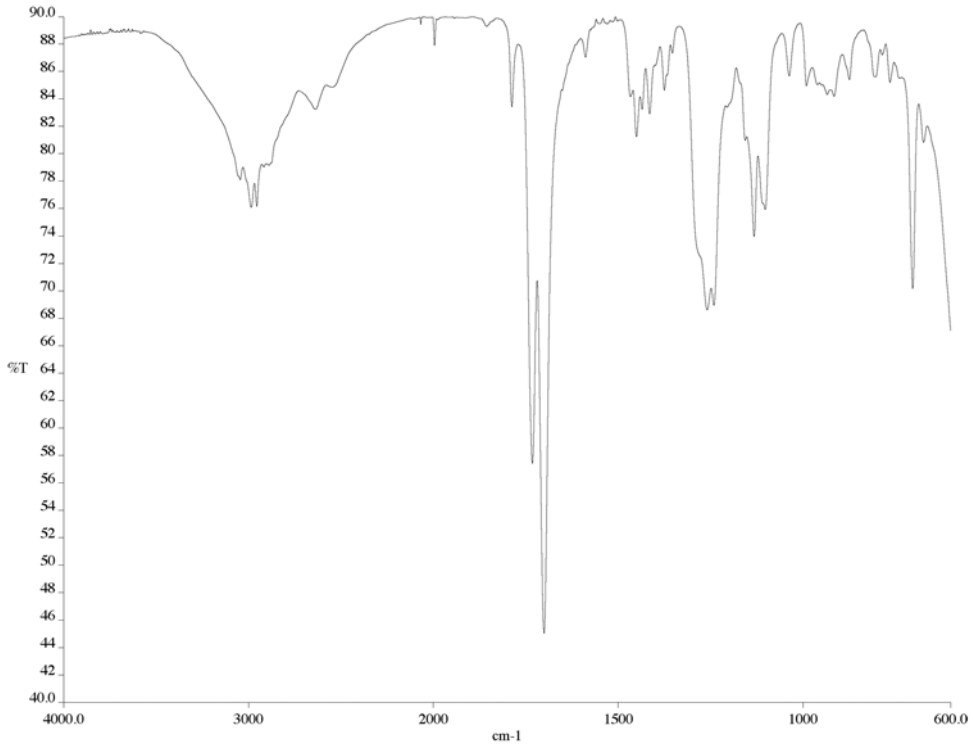


Figure A5.8 IR of compound **205** (NaCl/film)

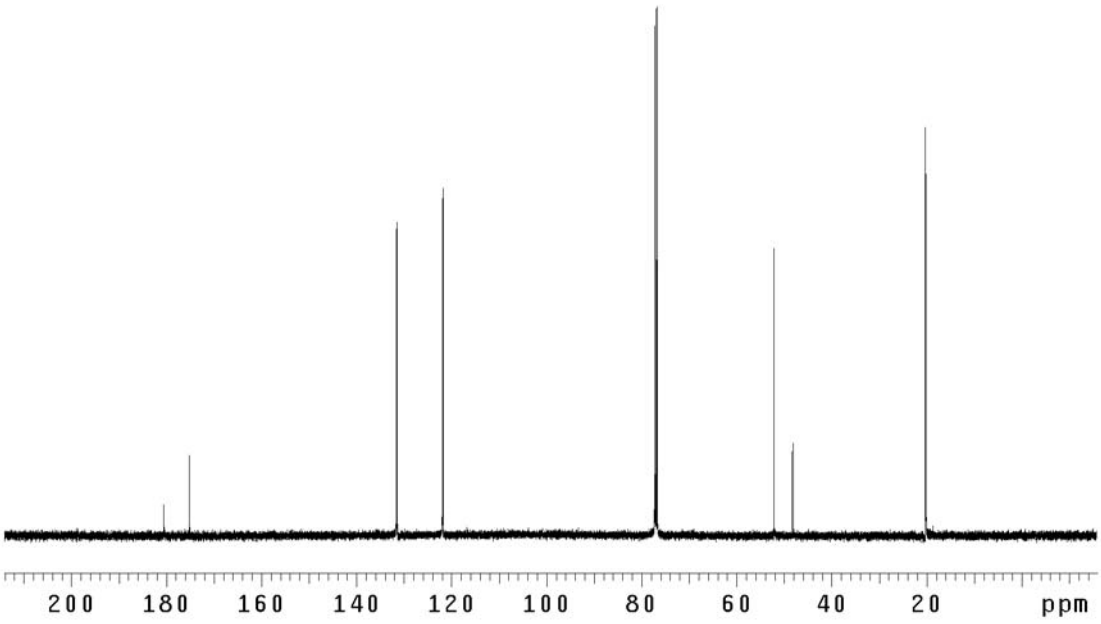


Figure A5.9 ^{13}C NMR of compound **205** (125 MHz, $CDCl_3$)

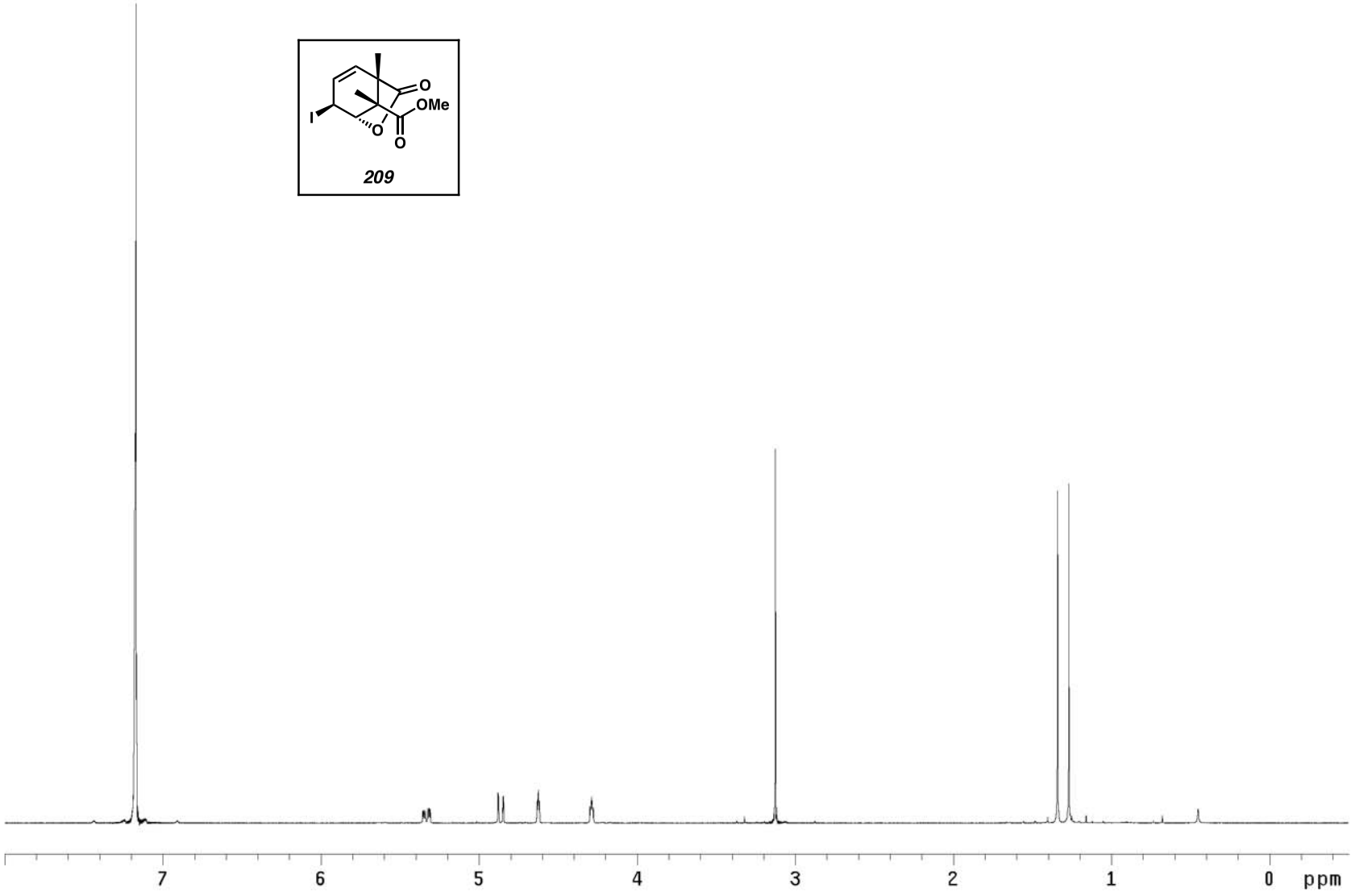


Figure A5.10 ^{1}H NMR of compound **209** (300 MHz, C_6D_6)

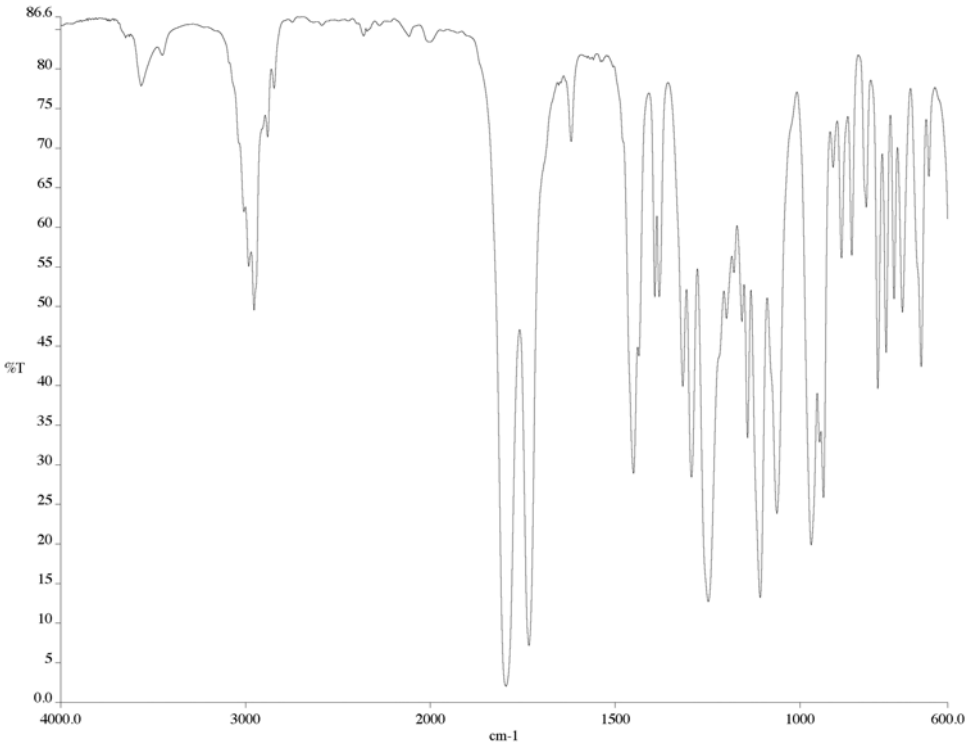


Figure A5.11 IR of compound **209** (NaCl/film)

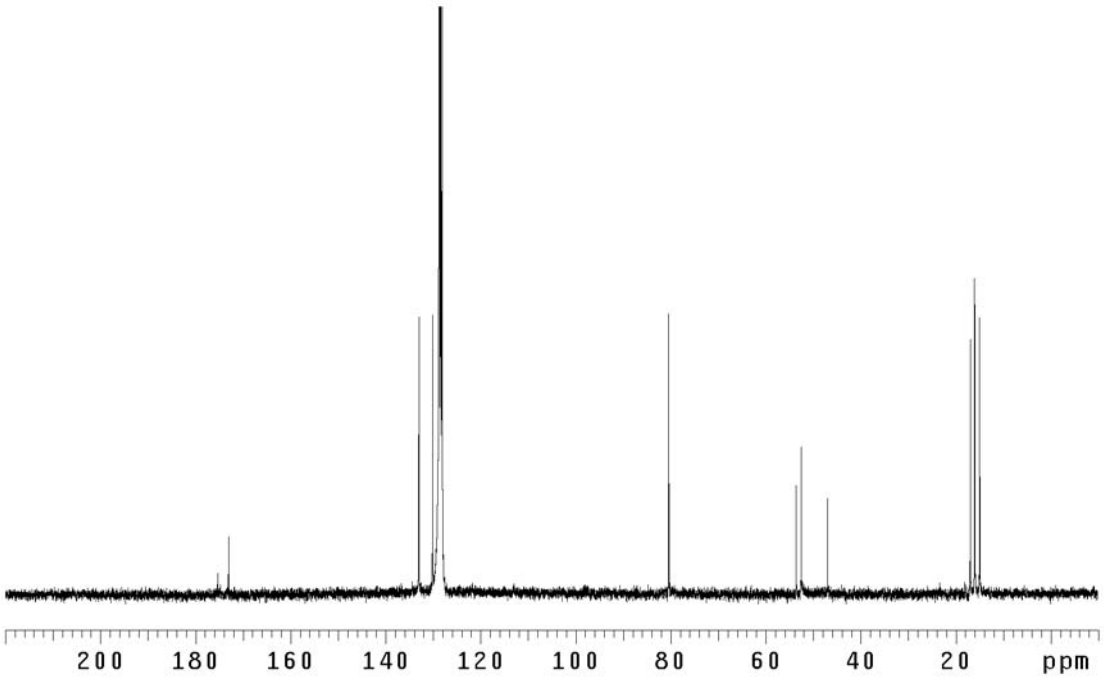


Figure A5.12 ^{13}C NMR of compound **209** (75 MHz, C_6D_6)

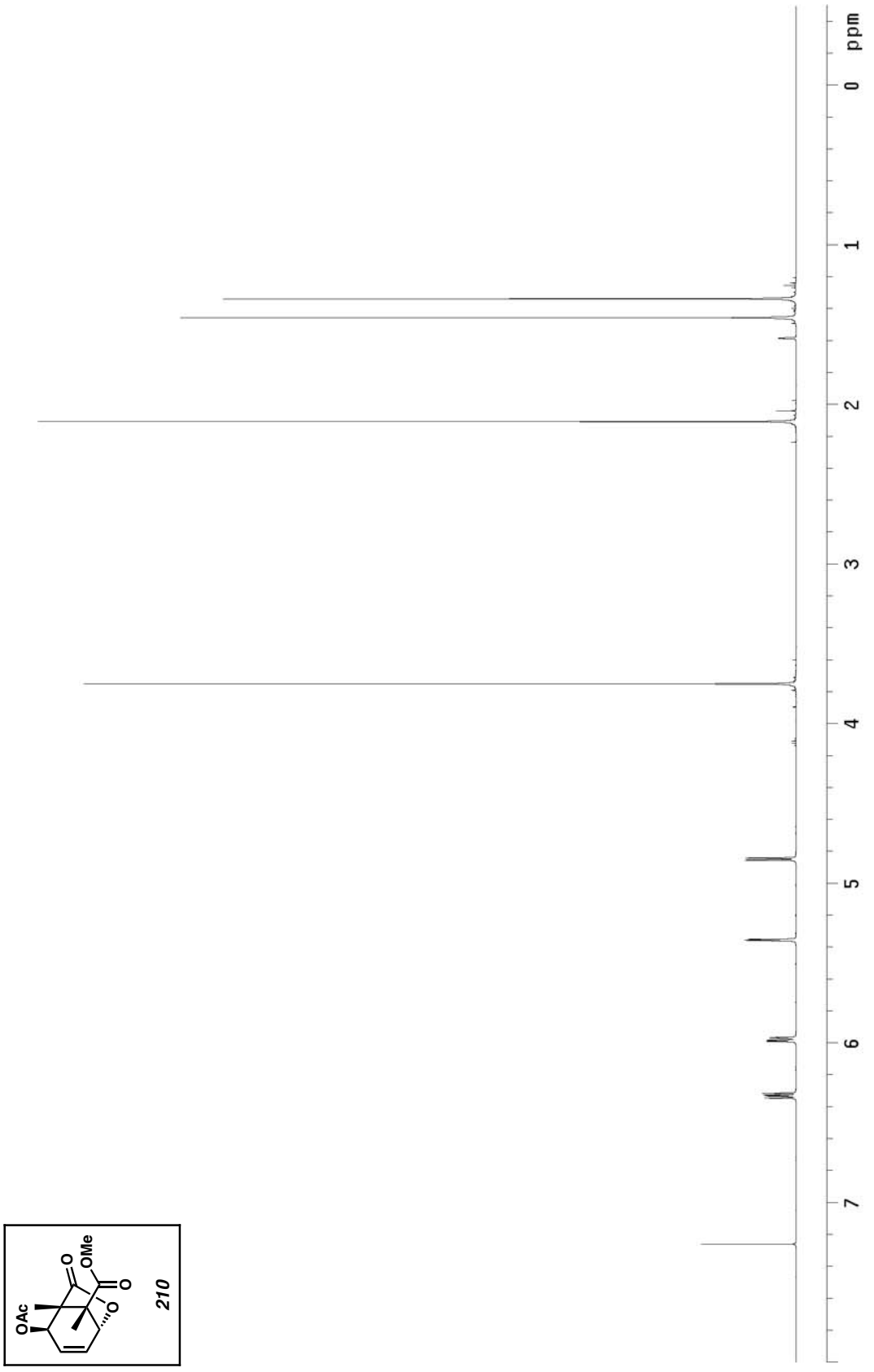


Figure A5.13 ^{1}H NMR of compound **210** (500 MHz, $CDCl_3$)

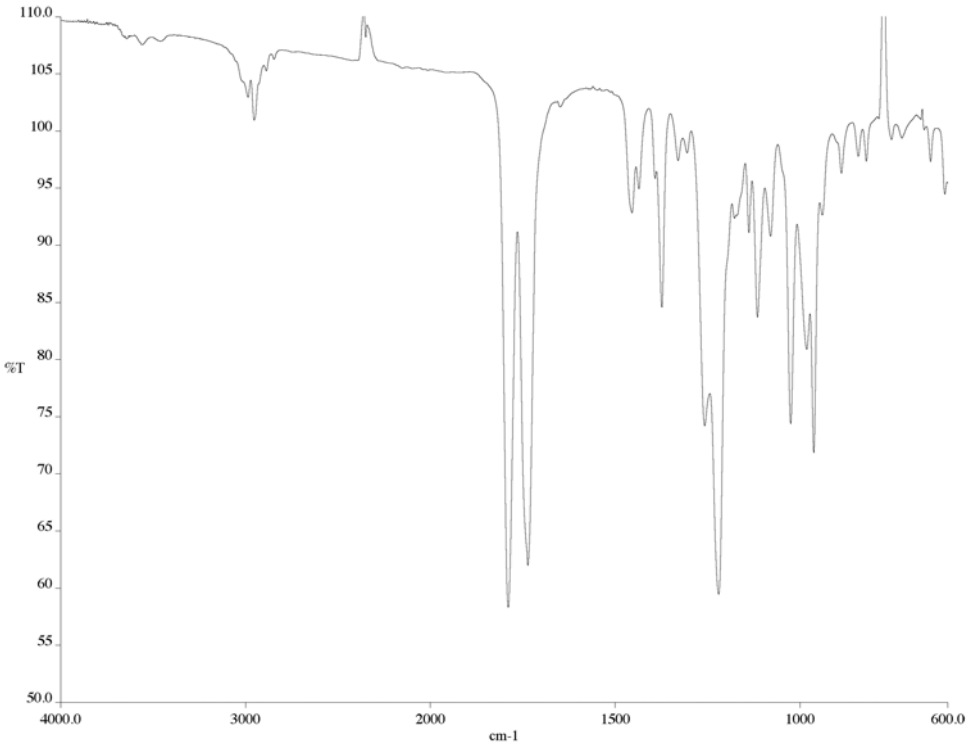


Figure A5.14 IR of compound **210** (NaCl/film)

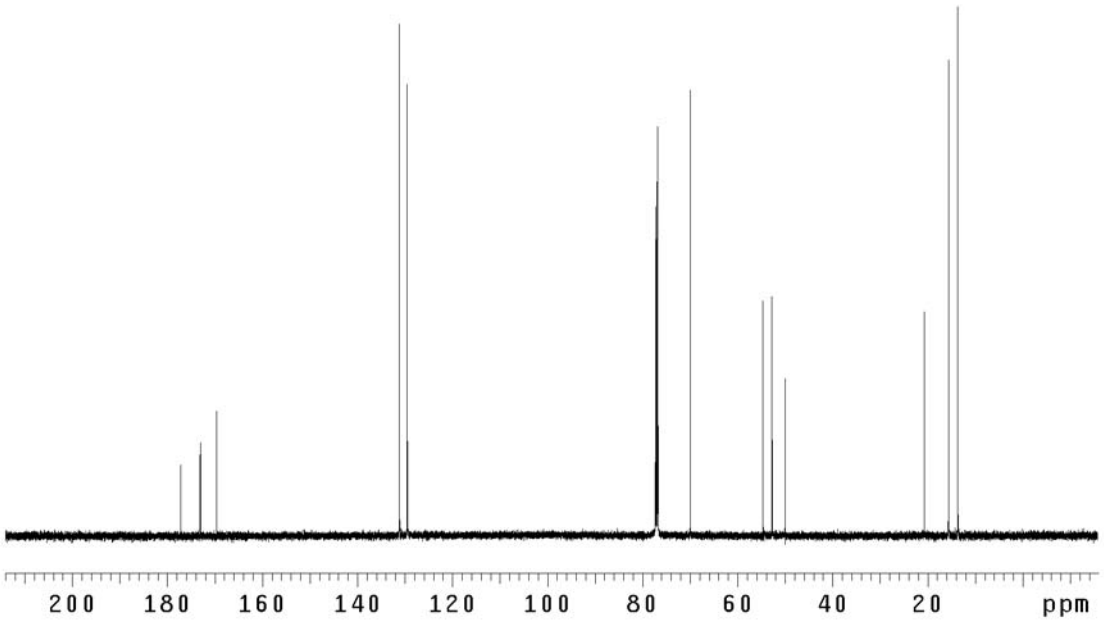


Figure A5.15 ^{13}C NMR of compound **210** (125 MHz, $CDCl_3$)

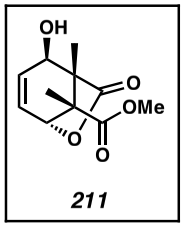


Figure A5.16 ^{1}H NMR of compound **211** (500 MHz, $CDCl_3$)

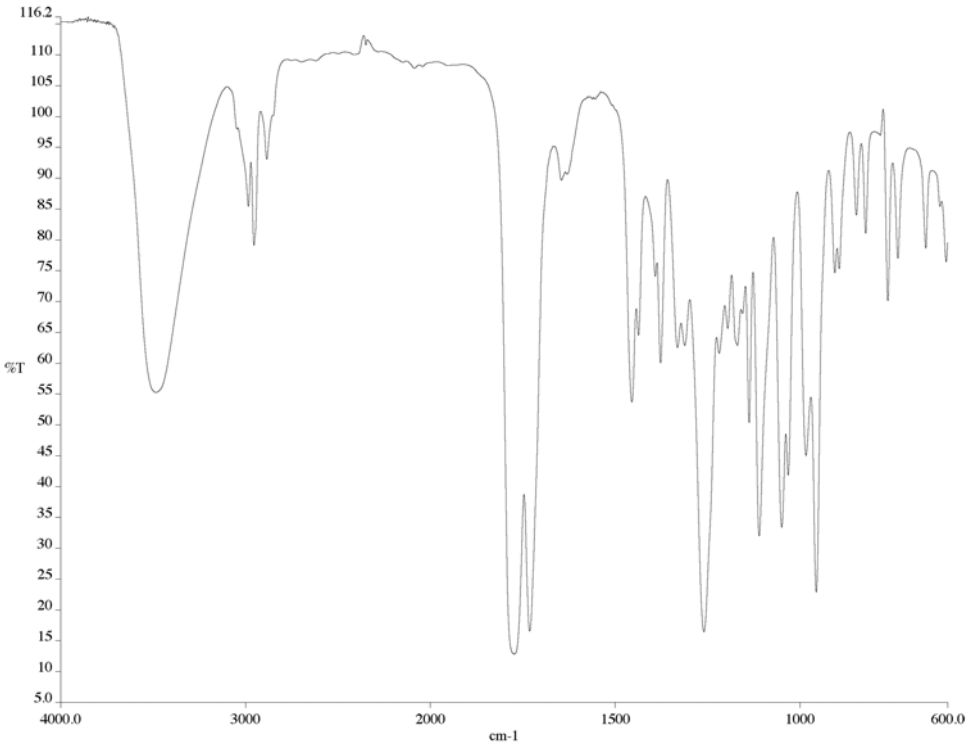


Figure A5.17 IR of compound **211** (NaCl/film)

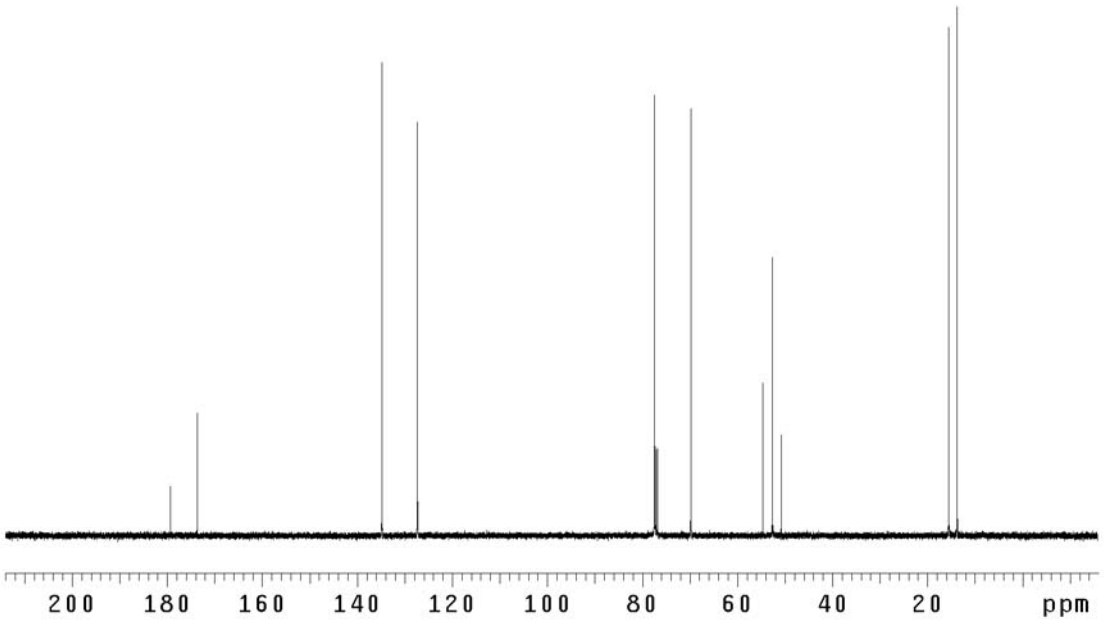


Figure A5.18 ^{13}C NMR of compound **211** (125 MHz, $CDCl_3$)

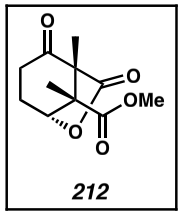


Figure A5.19 ^{1}H NMR of compound **212** (300 MHz, $CDCl_3$)

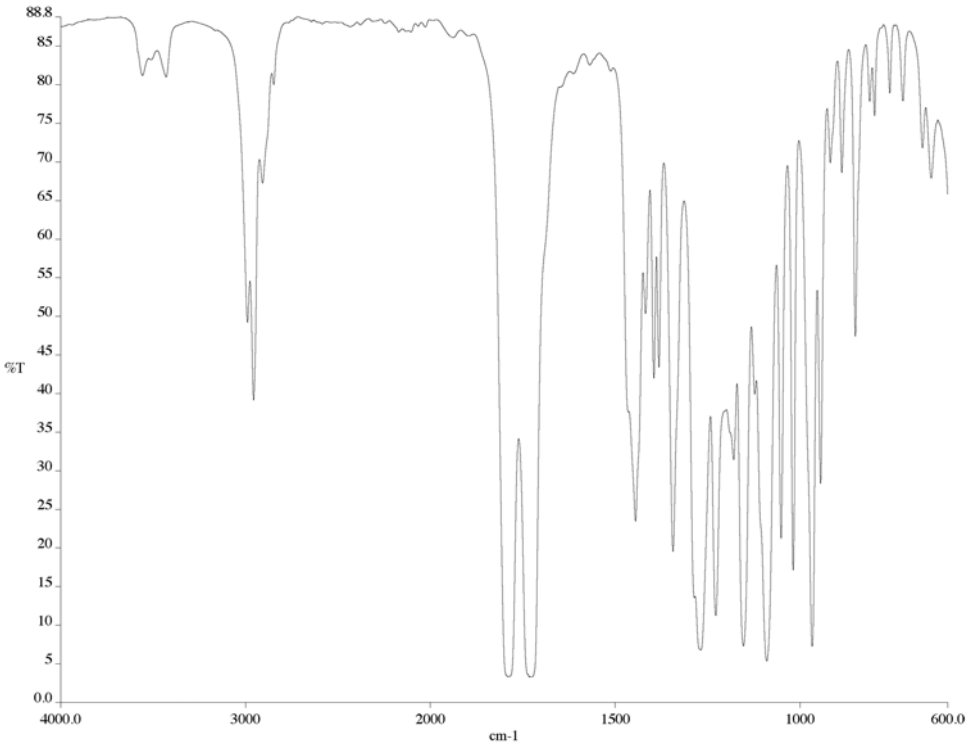


Figure A5.20 IR of compound **212** (NaCl/film)

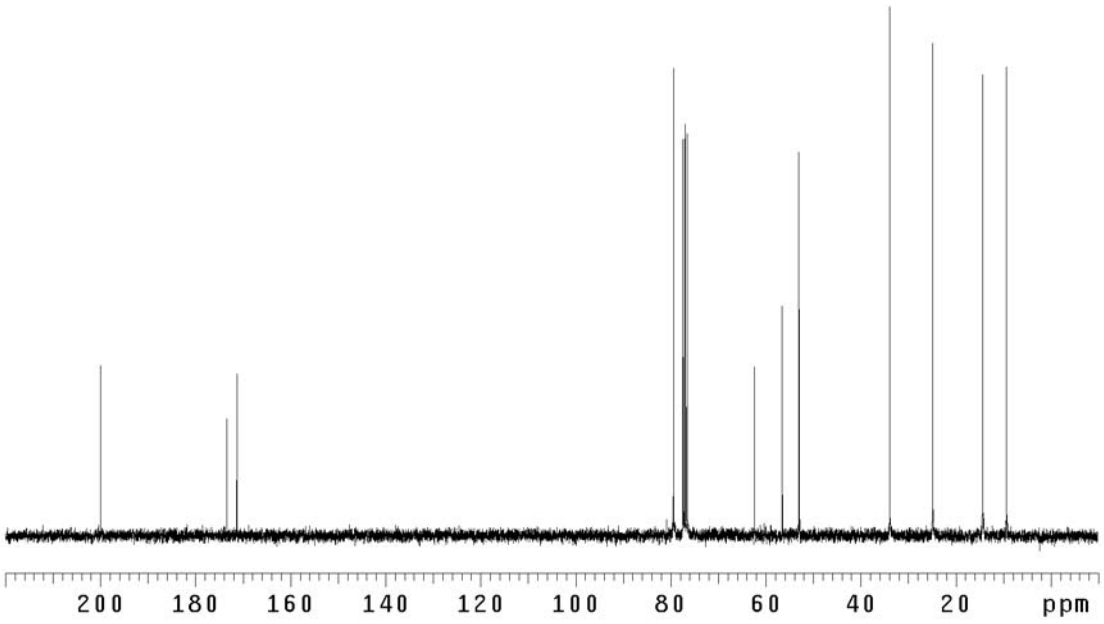


Figure A5.21 ^{13}C NMR of compound **212** (75 MHz, $CDCl_3$)

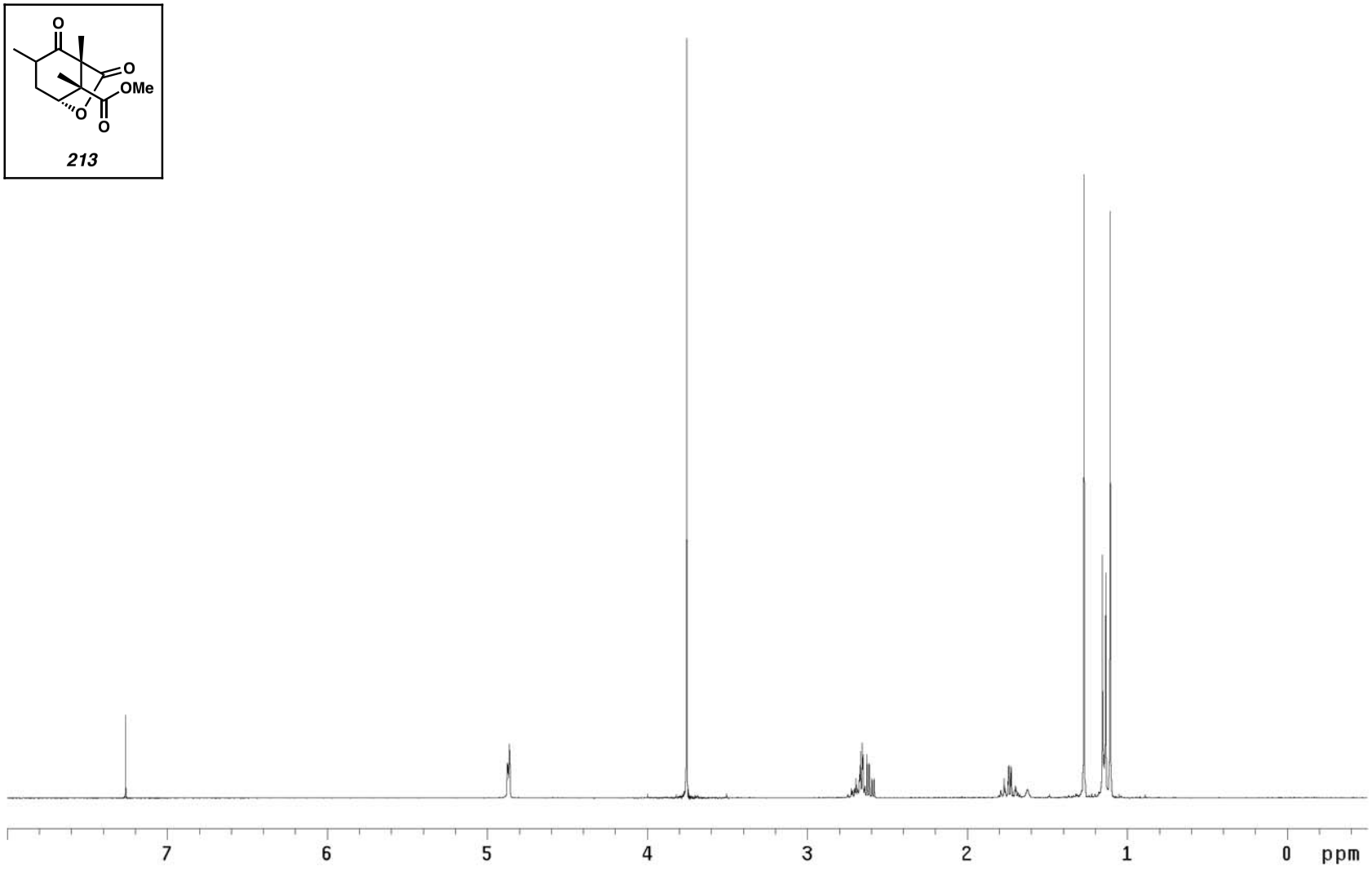


Figure A5.22 ^{1}H NMR of compound **213** (300 MHz, $CDCl_3$)

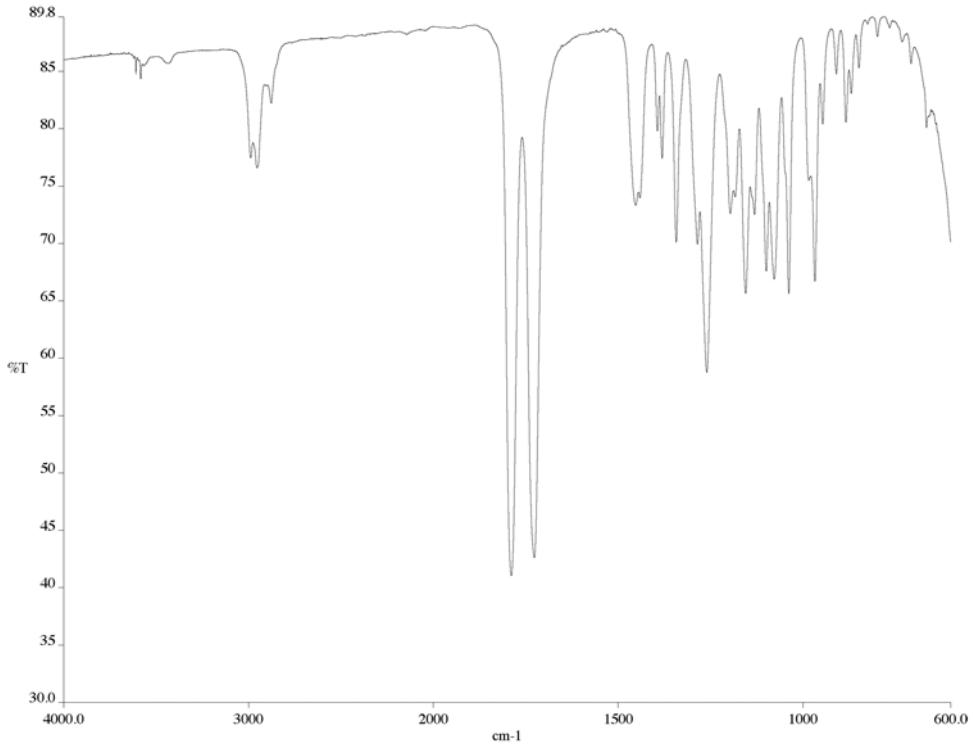


Figure A5.23 IR of compound **213** (NaCl/film)

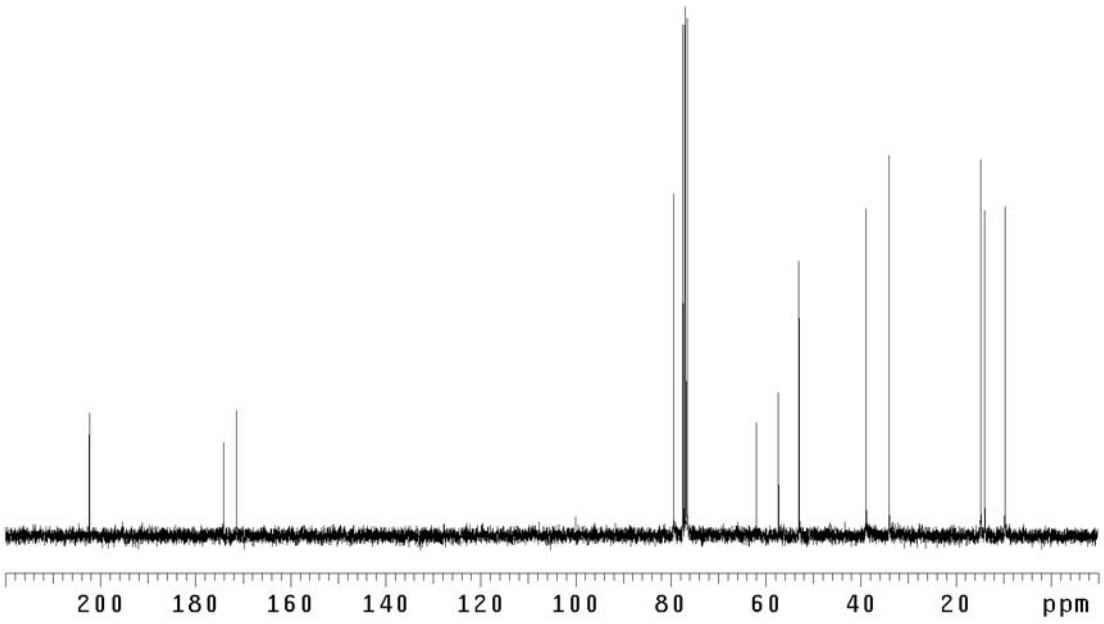


Figure A5.24 ^{13}C NMR of compound **213** (75 MHz, $CDCl_3$)

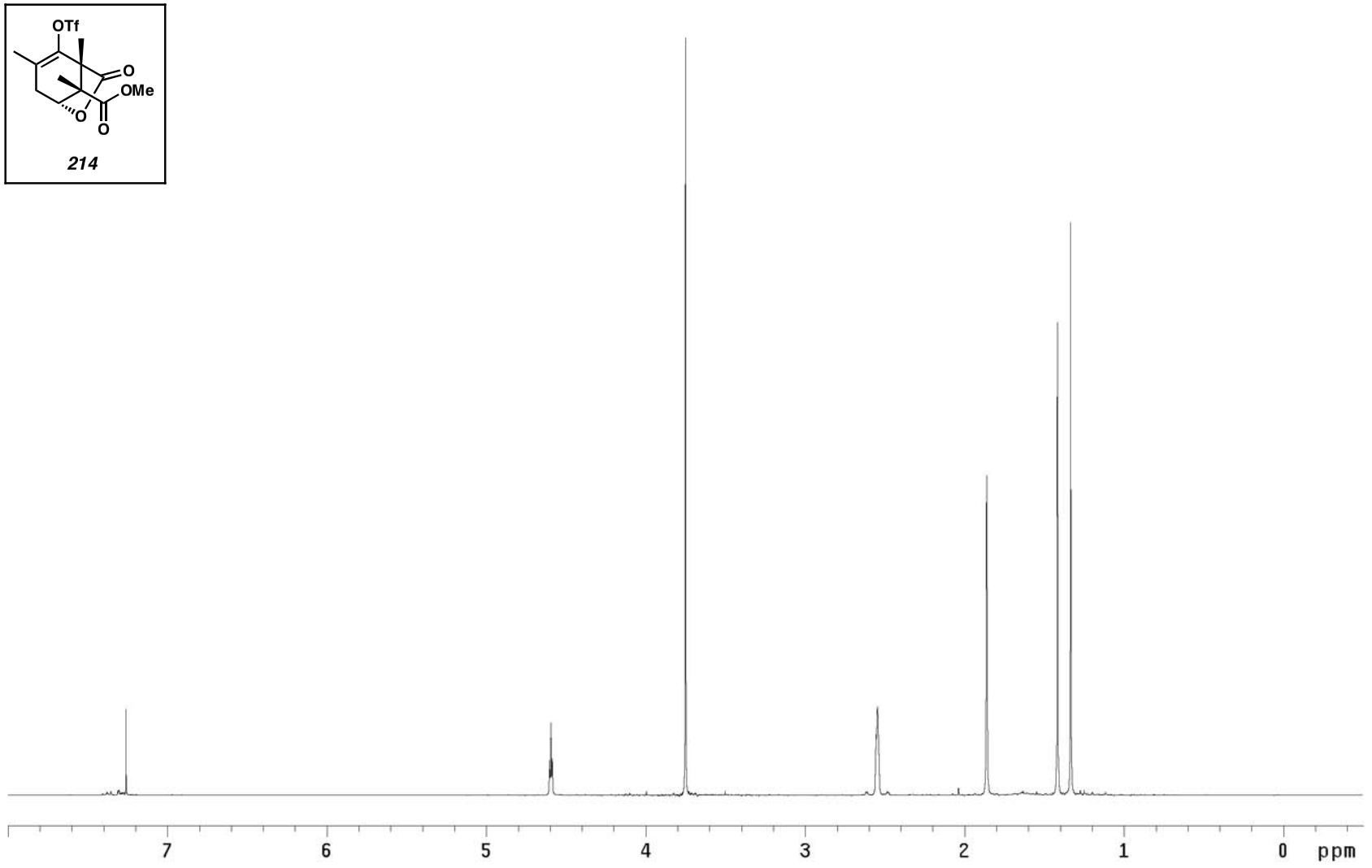


Figure A5.25 ^{1}H NMR of compound **214** (300 MHz, $CDCl_3$)

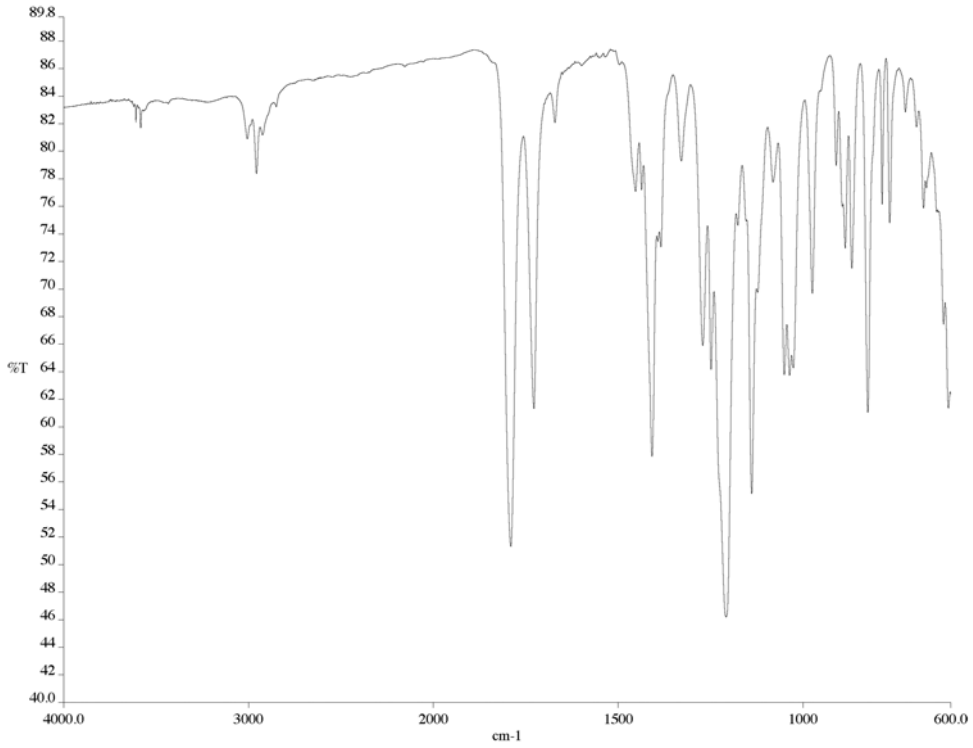


Figure A5.26 IR of compound **214** (NaCl/film)

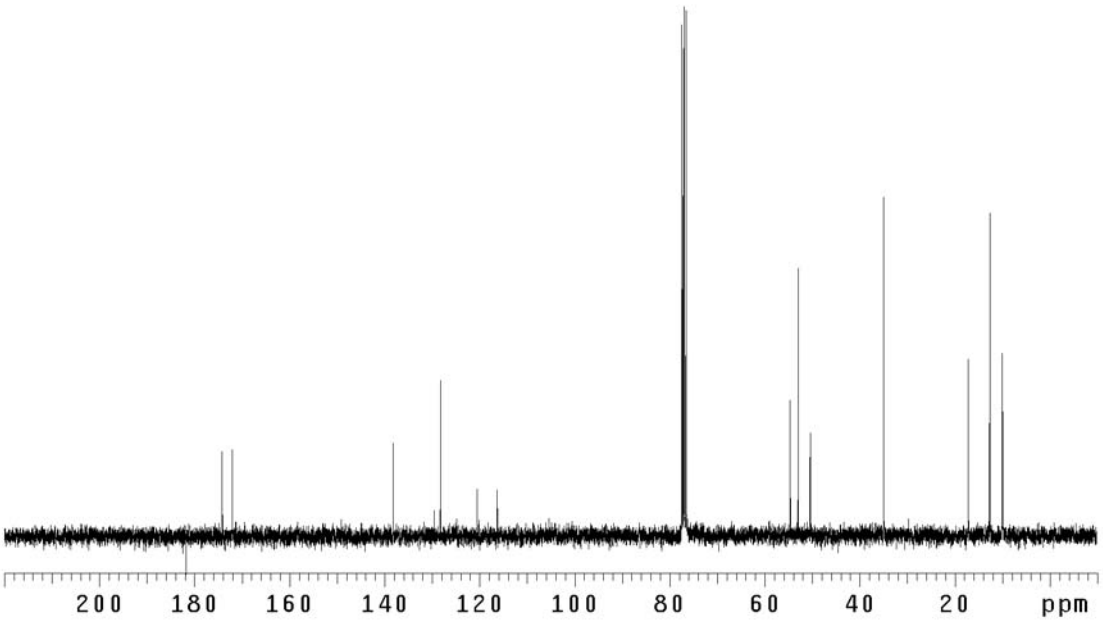
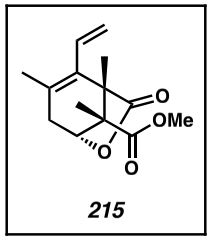


Figure A5.27 ^{13}C NMR of compound **214** (75 MHz, $CDCl_3$)



215

Figure A5.28 ^{1}H NMR of compound **215** (300 MHz, $CDCl_3$)

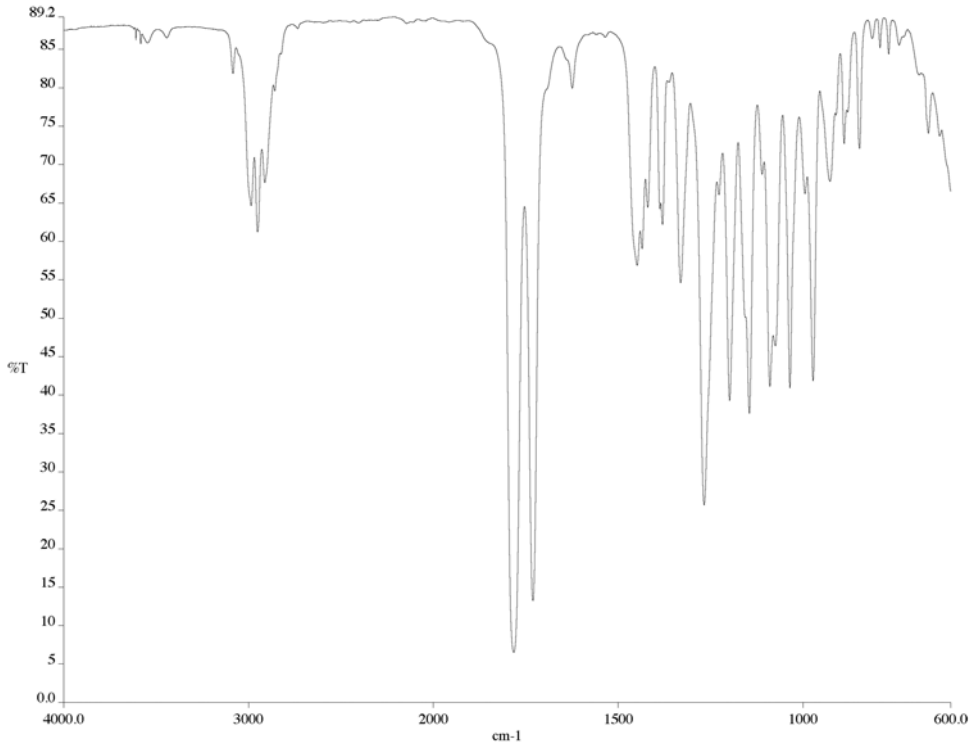


Figure A5.29 IR of compound **215** (NaCl/film)

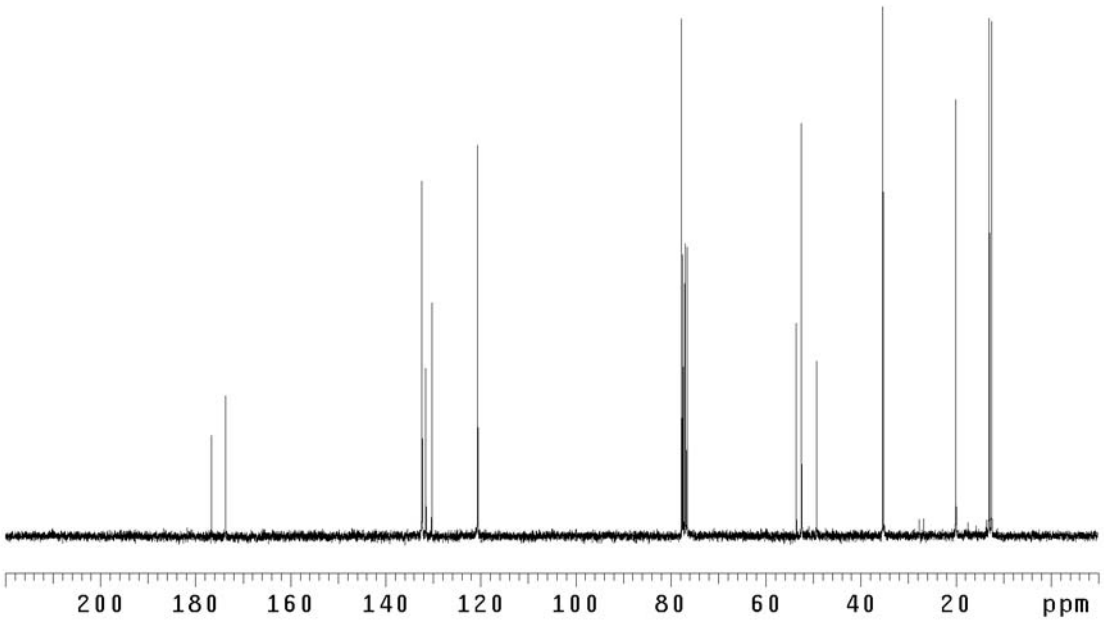


Figure A5.30 ^{13}C NMR of compound **215** (75 MHz, $CDCl_3$)

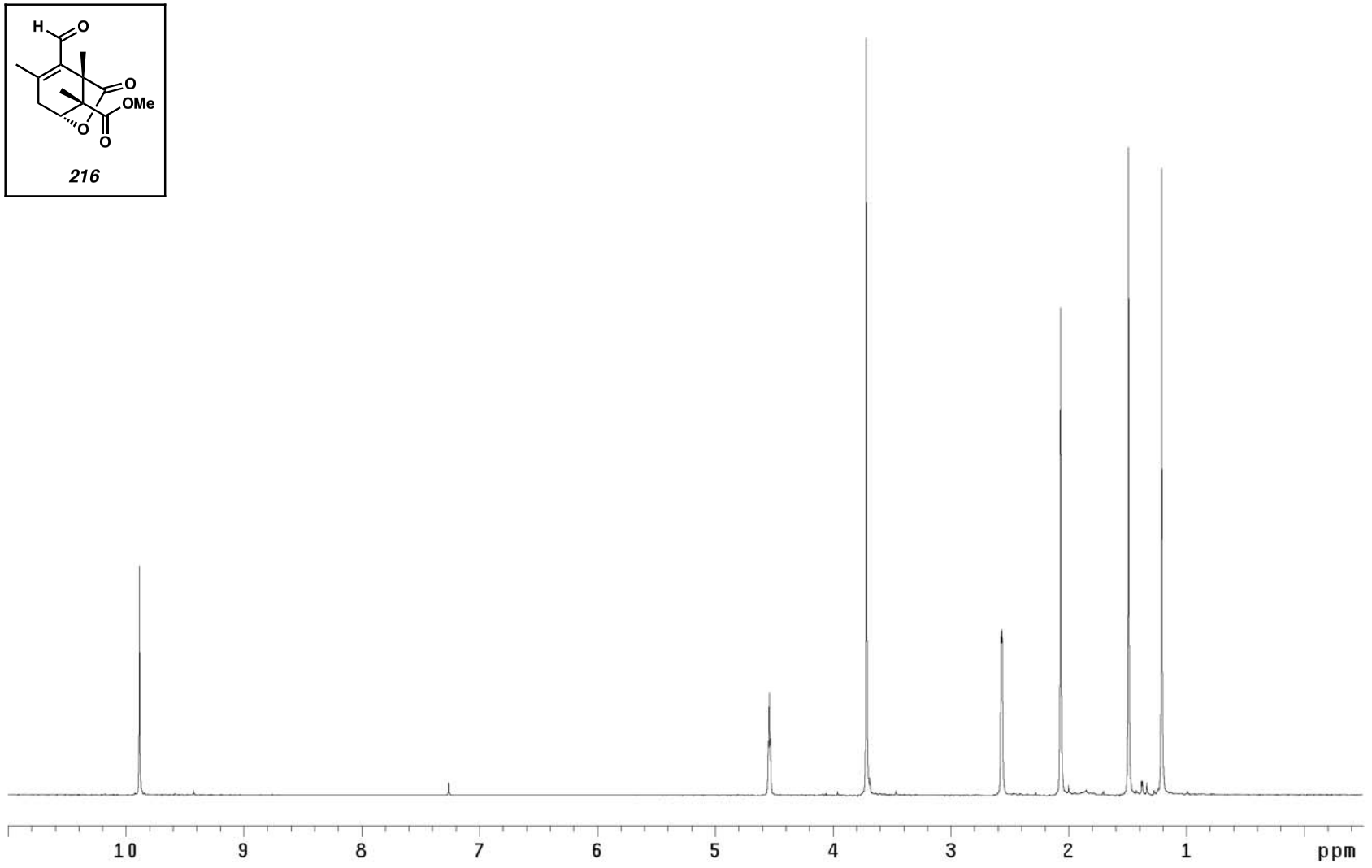


Figure A5.31 ^{1}H NMR of compound **216** (300 MHz, $CDCl_3$)

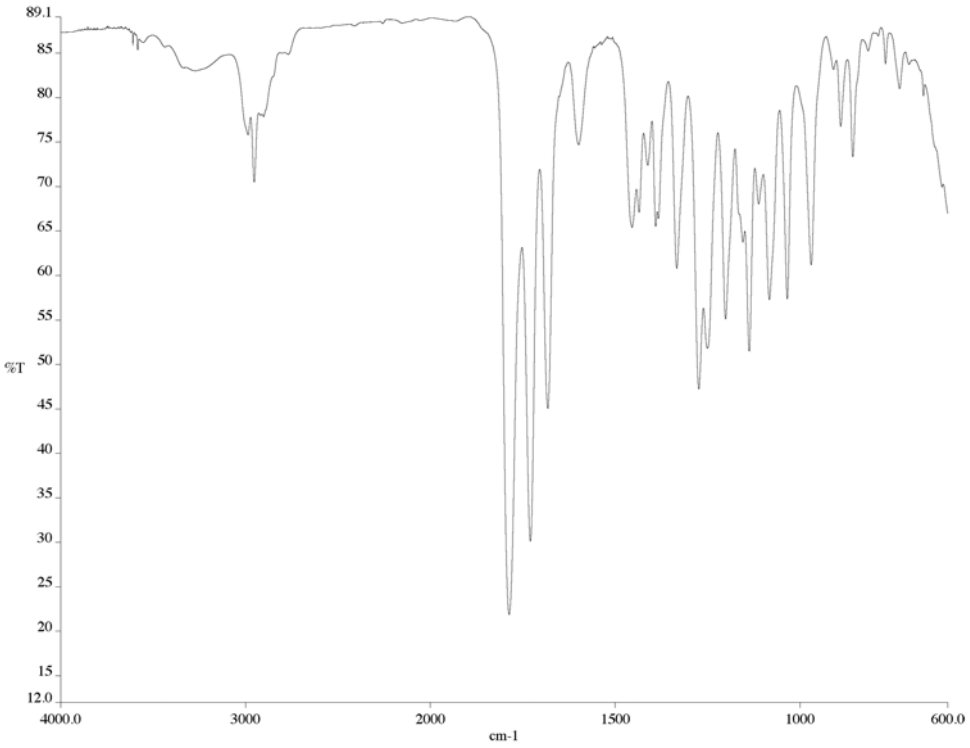


Figure A5.32 IR of compound **216** (NaCl/film)

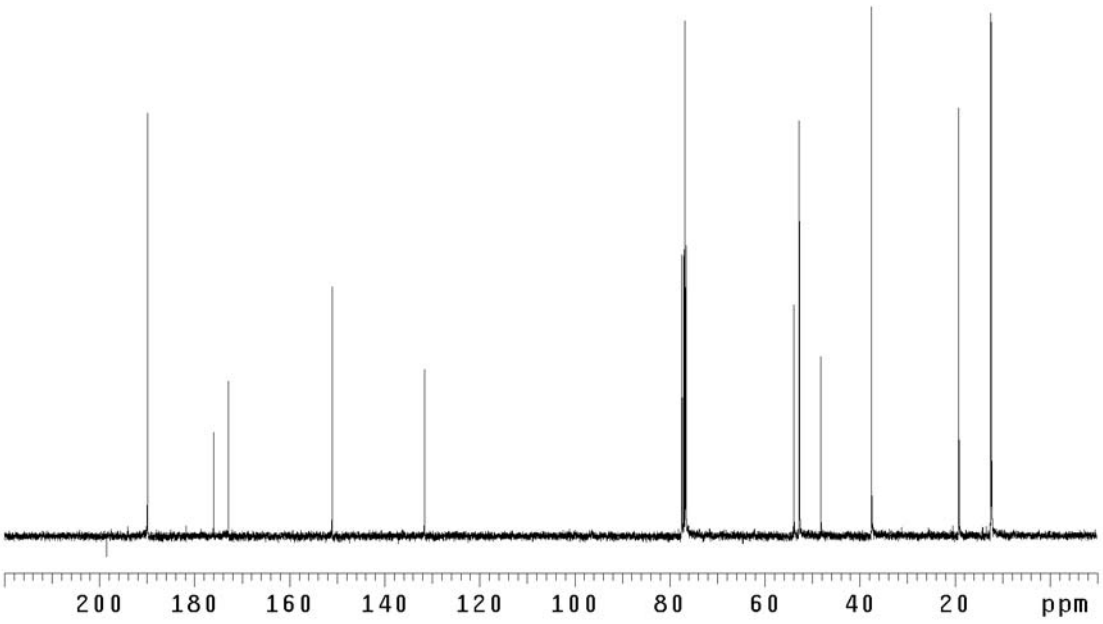


Figure A5.33 ^{13}C NMR of compound **216** (75 MHz, $CDCl_3$)

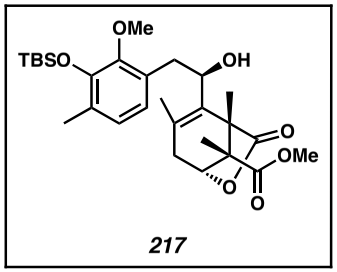


Figure A5.34 ^{1}H NMR of compound **217** (300 MHz, $CDCl_3$)

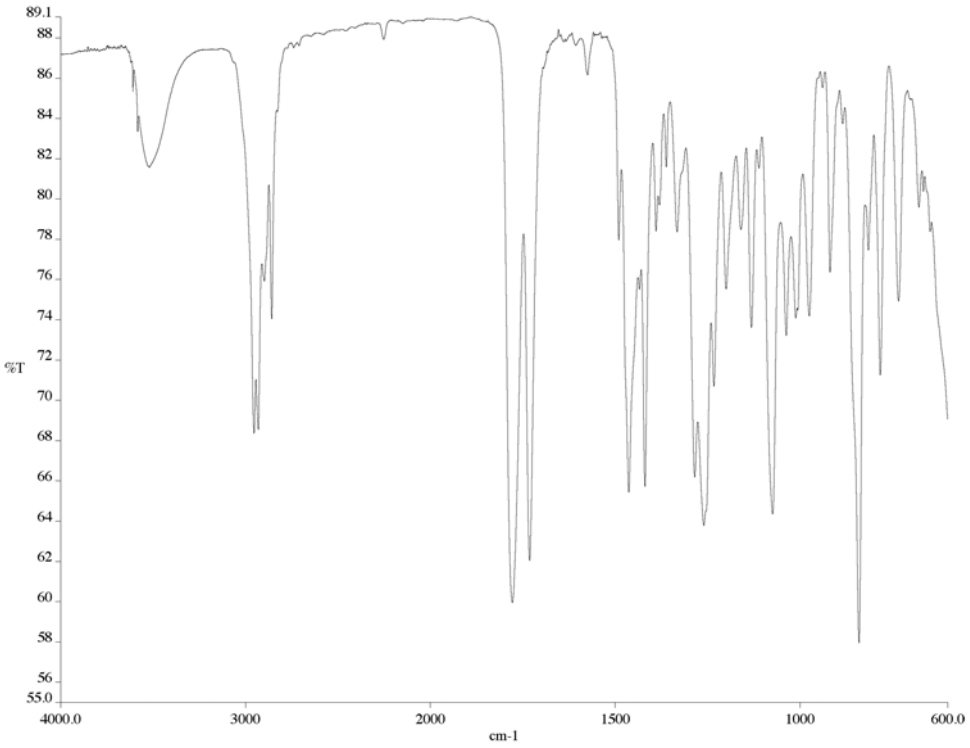


Figure A5.35 IR of compound **217** (NaCl/film)

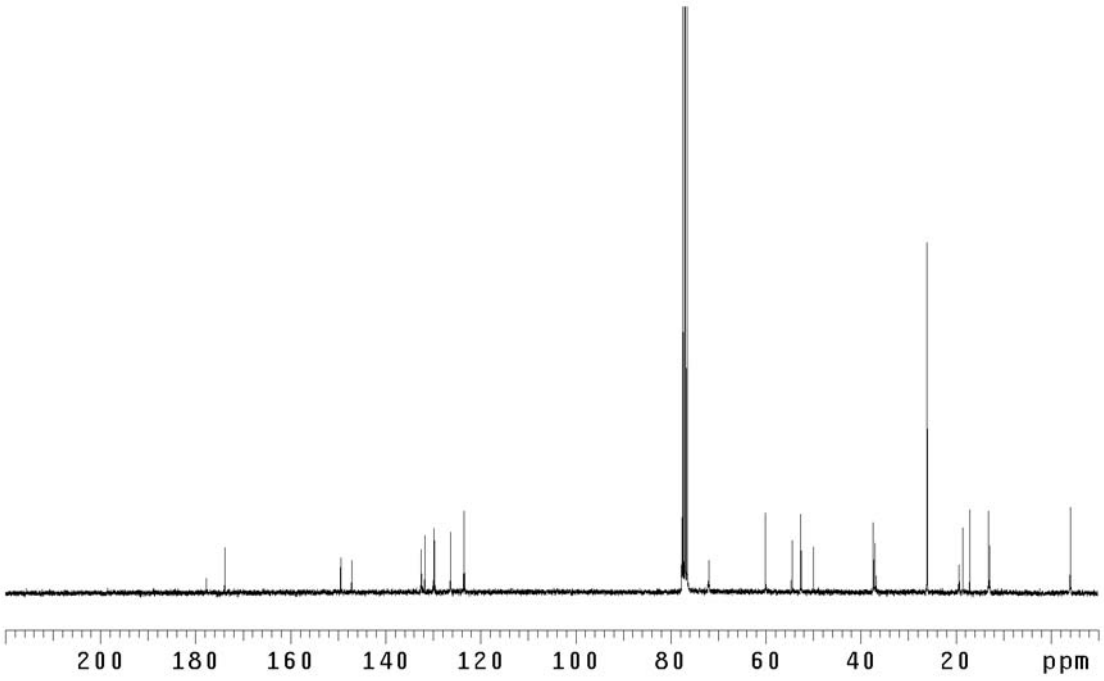
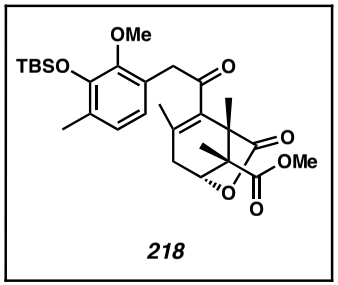


Figure A5.36 ^{13}C NMR of compound **217** (75 MHz, $CDCl_3$)



218

Figure A5.37 ^{1}H NMR of compound **218** (300 MHz, $CDCl_3$)

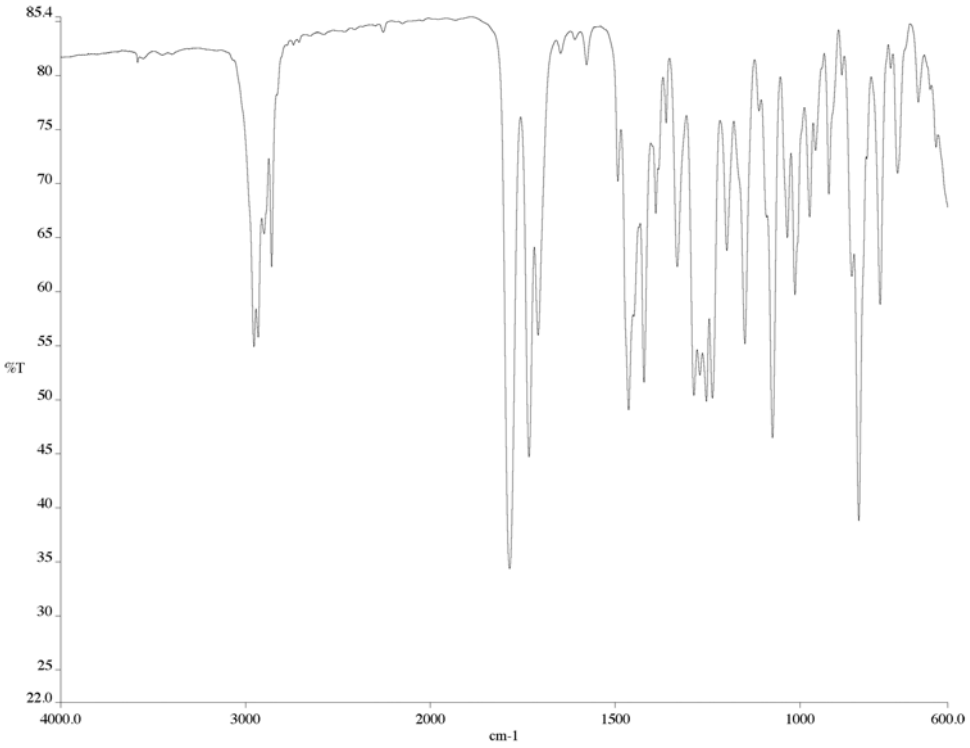


Figure A5.38 IR of compound **218** (NaCl/film)

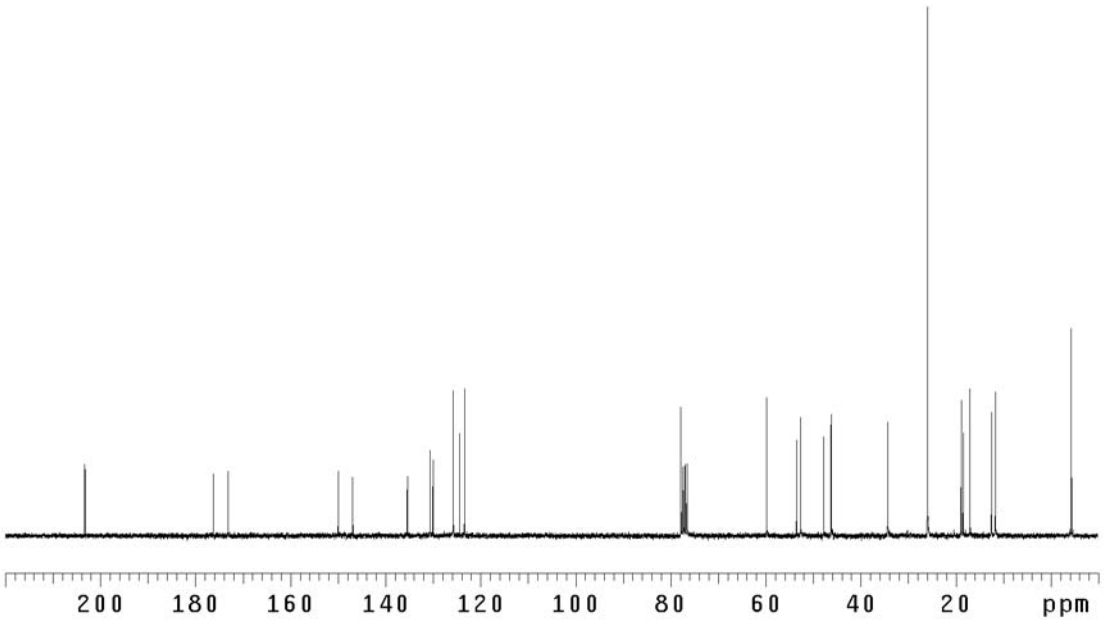
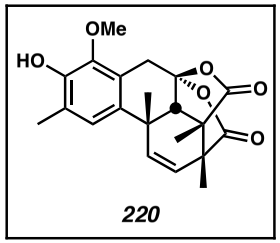


Figure A5.39 ^{13}C NMR of compound **218** (75 MHz, $CDCl_3$)



220

Figure A5.40 ^{1}H NMR of compound **220** (300 MHz, $CDCl_3$)

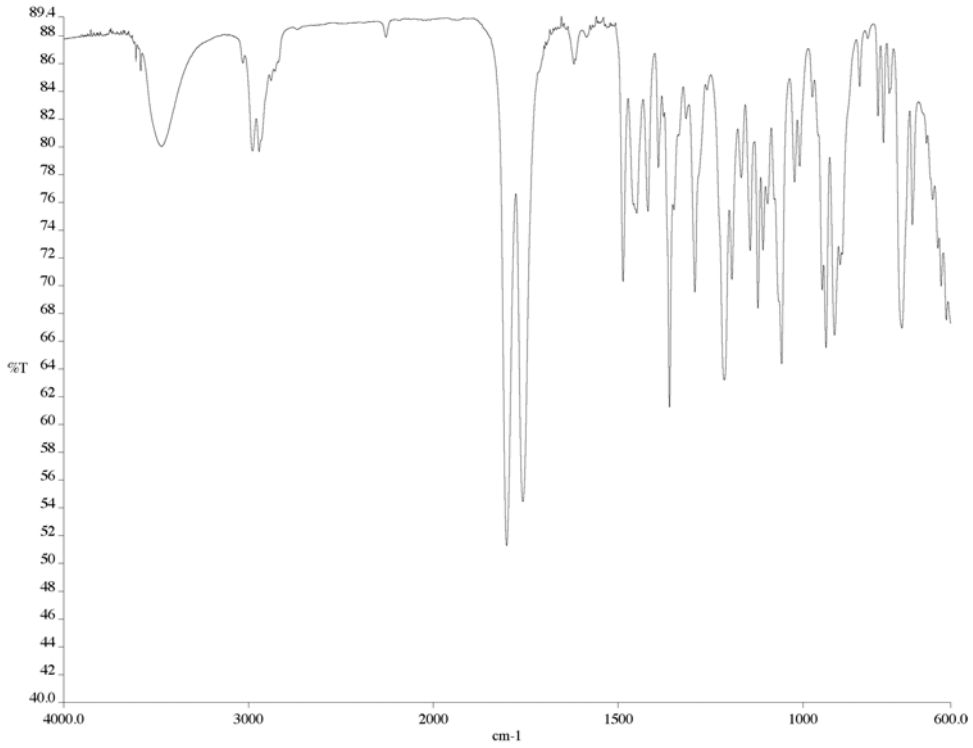


Figure A5.41 IR of compound **220** (NaCl/film)

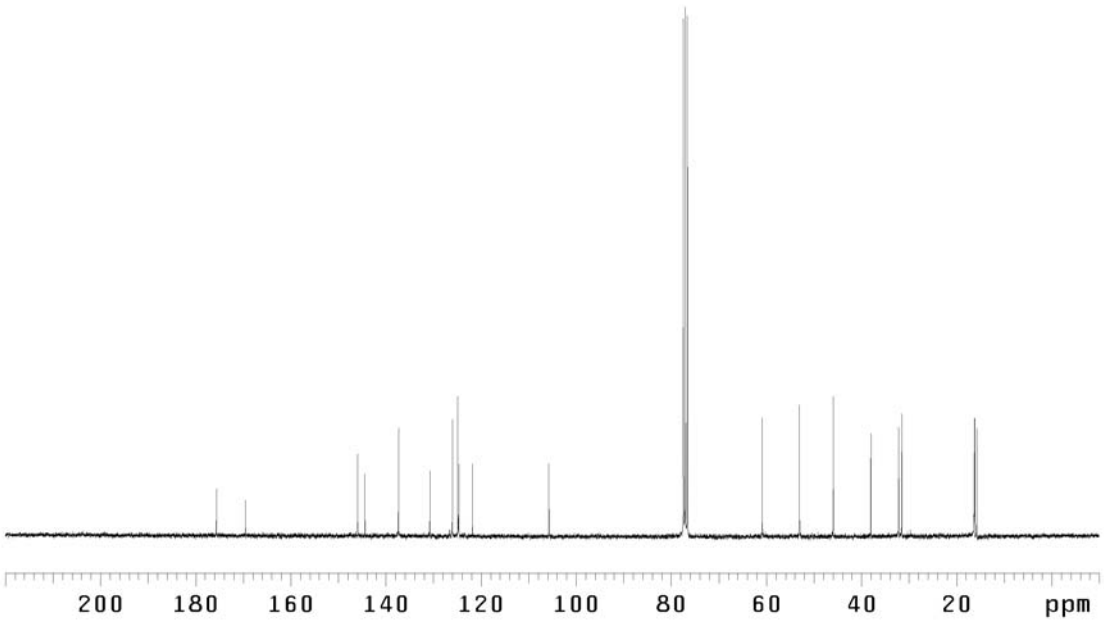
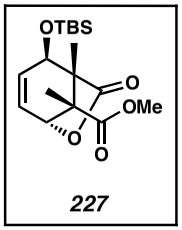


Figure A5.42 ^{13}C NMR of compound **220** (75 MHz, $CDCl_3$)



227

Figure A5.43 ^{1}H NMR of compound **227** (500 MHz, $CDCl_3$)

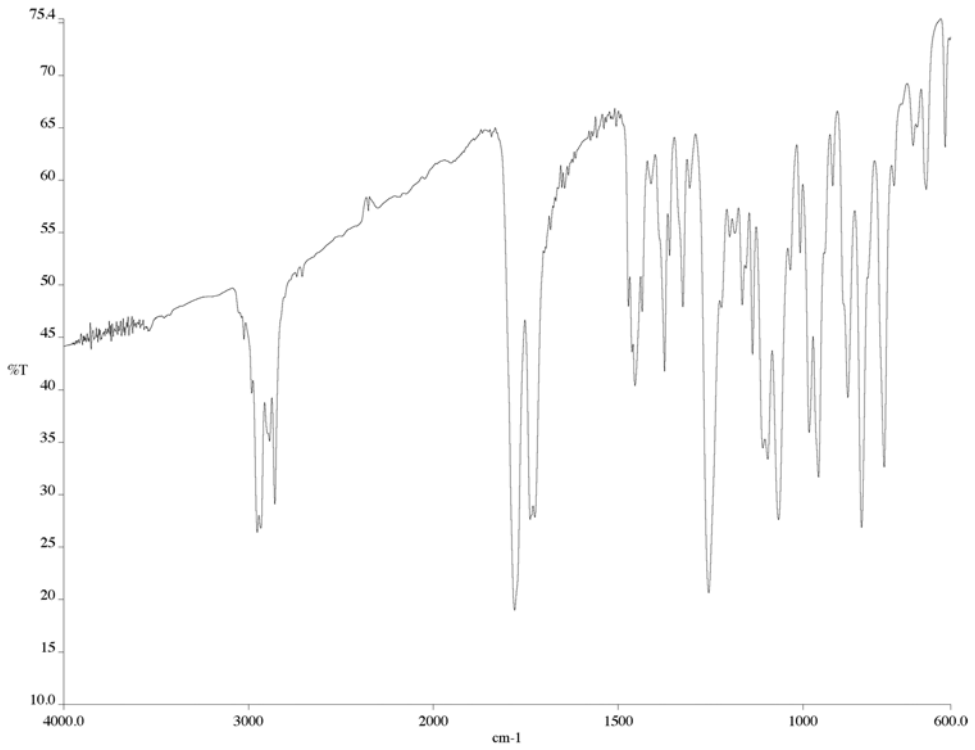


Figure A5.44 IR of compound **227** (NaCl/film)

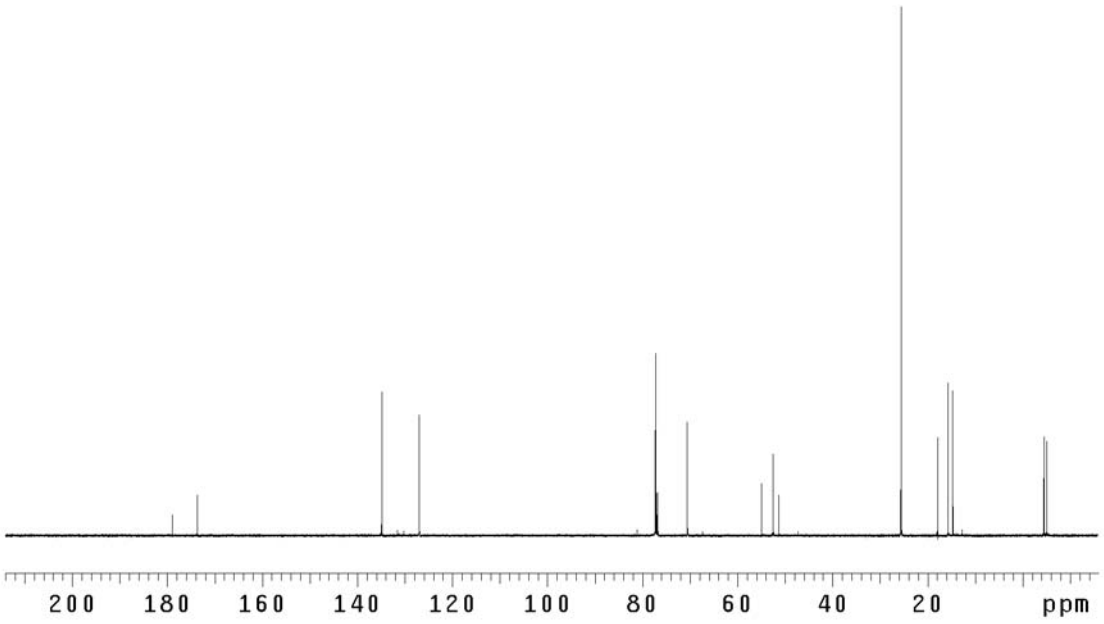


Figure A5.45 ^{13}C NMR of compound **227** (125 MHz, $CDCl_3$)

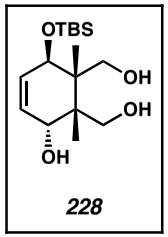


Figure A5.46 ^{1}H NMR of compound **228** (500 MHz, $CDCl_3$)

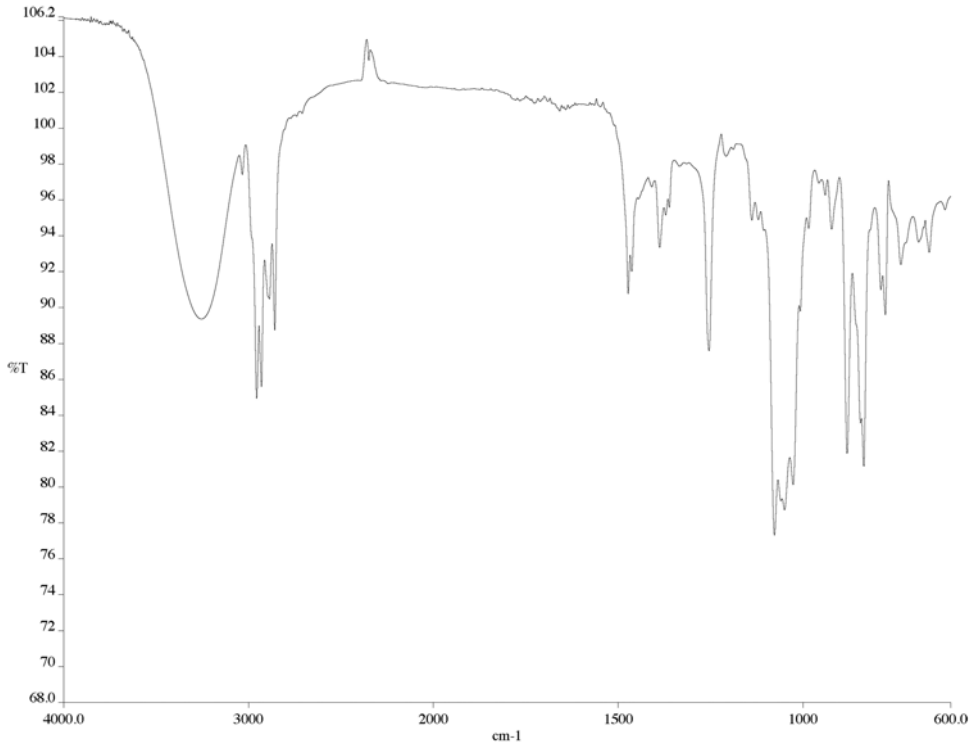


Figure A5.47 IR of compound **228** (NaCl/film)

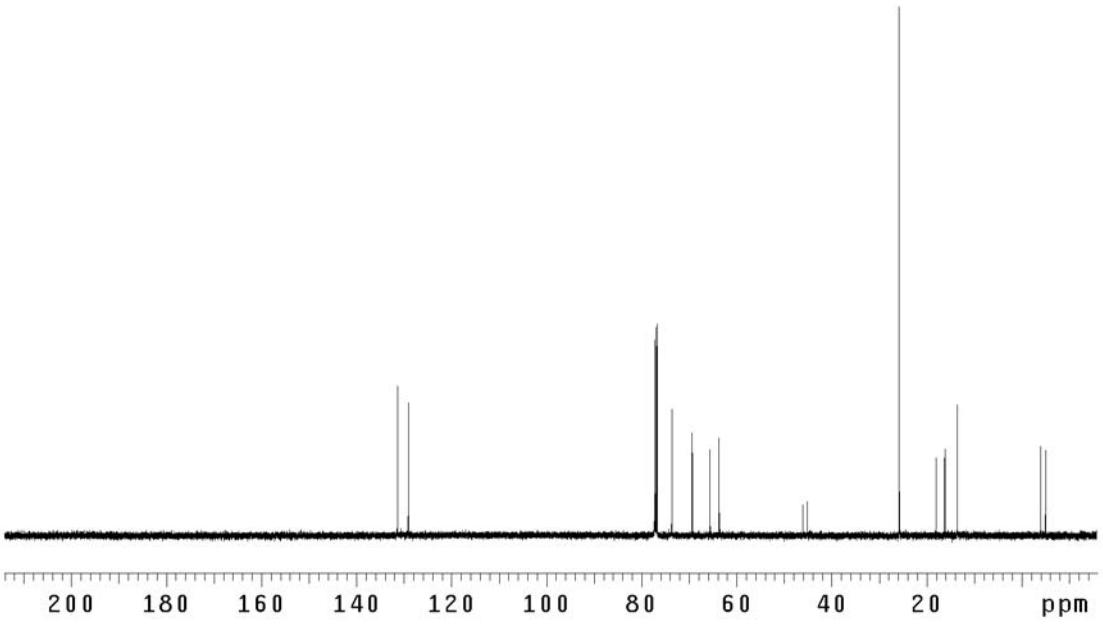


Figure A5.48 ^{13}C NMR of compound **228** (125 MHz, $CDCl_3$)

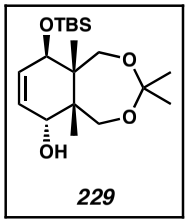


Figure A5.49 ^{1}H NMR of compound **229** (300 MHz, $CDCl_3$)

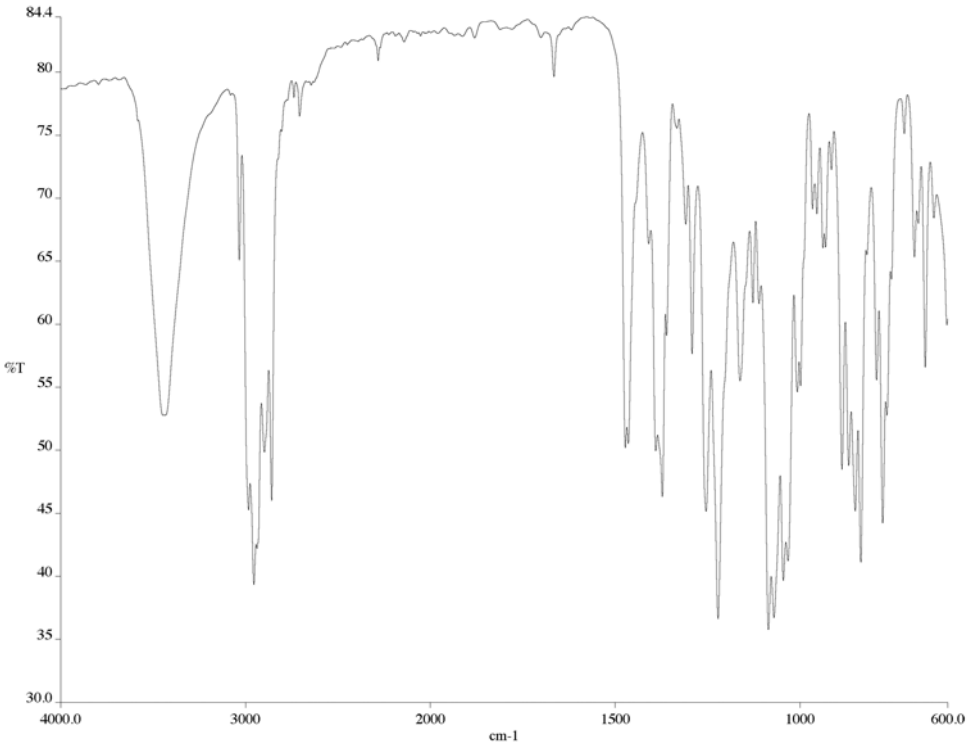


Figure A5.50 IR of compound **229** (NaCl/film)

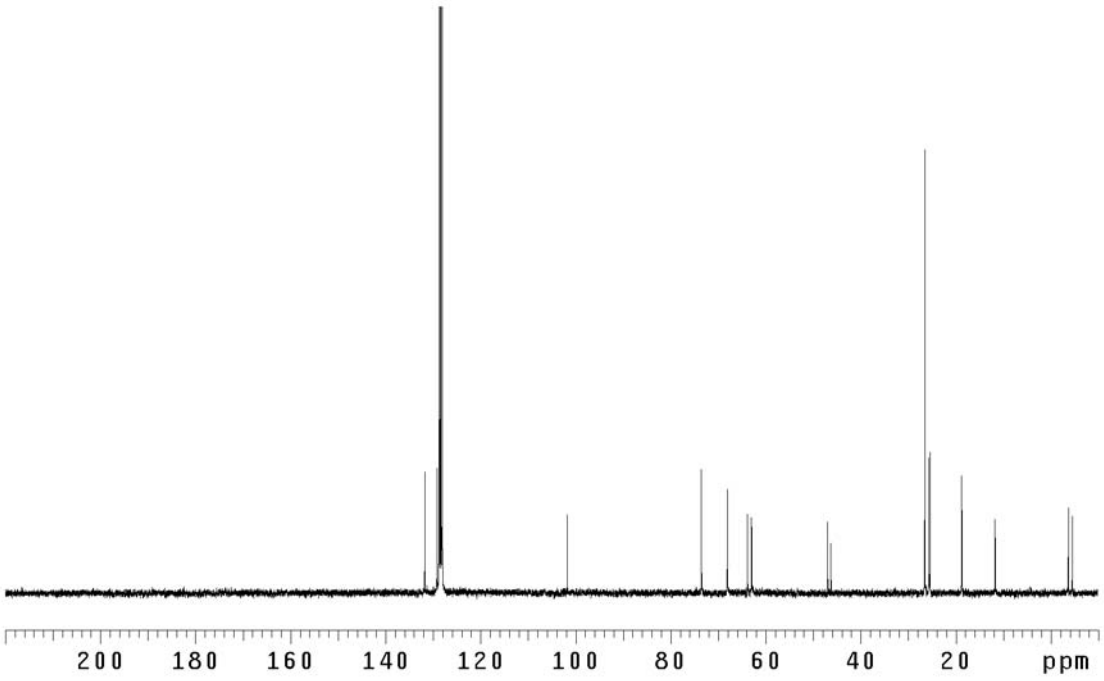


Figure A5.51 ^{13}C NMR of compound **229** (75 MHz, C_6D_6)

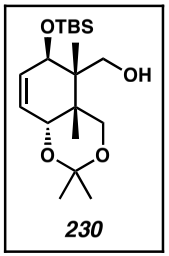


Figure A5.52 ^{1}H NMR of compound **230** (300 MHz, $CDCl_3$)

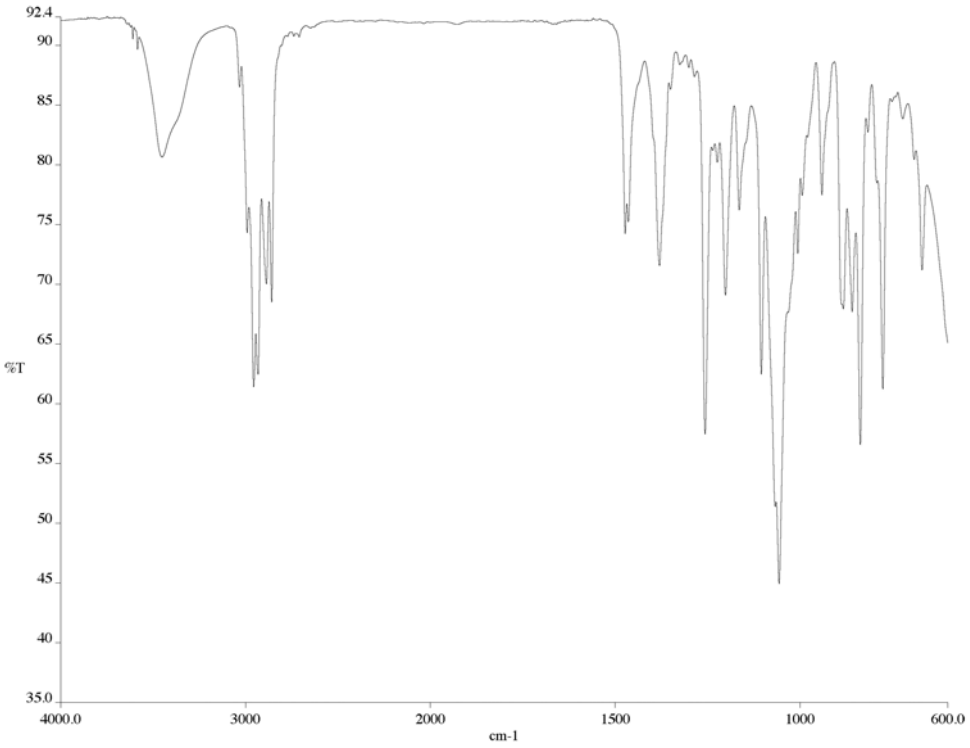


Figure A5.53 IR of compound **230** (NaCl/film)

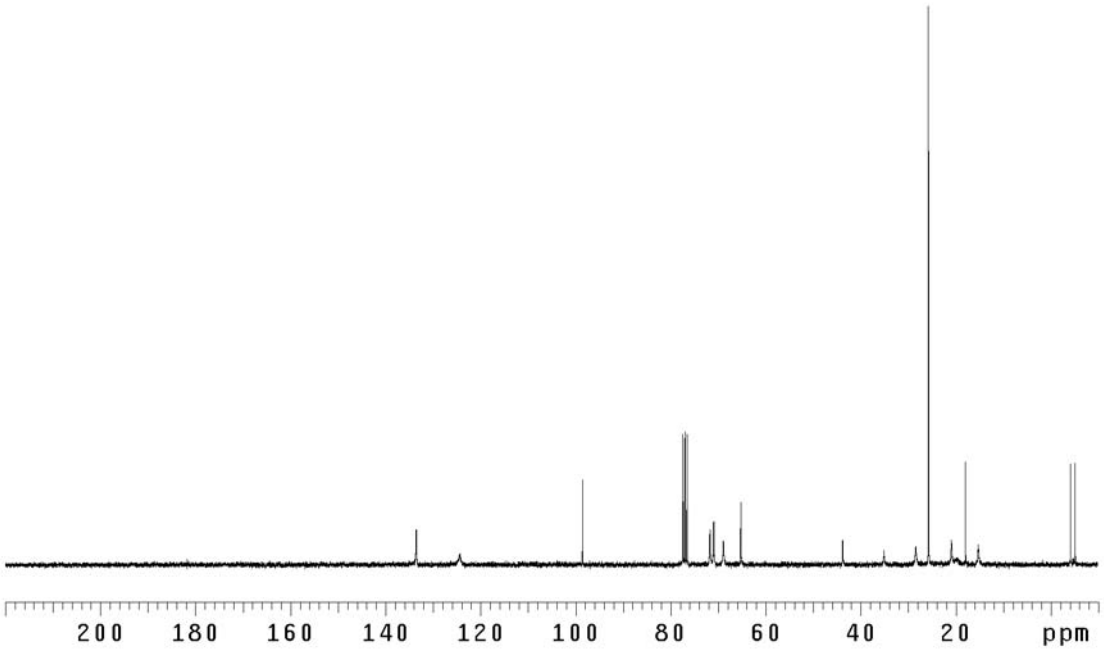
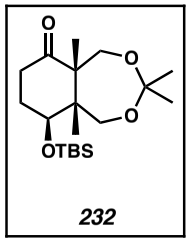


Figure A5.54 ^{13}C NMR of compound **230** (75 MHz, $CDCl_3$)



232

Figure A5.55 ^{1}H NMR of compound **232** (300 MHz, $CDCl_3$)

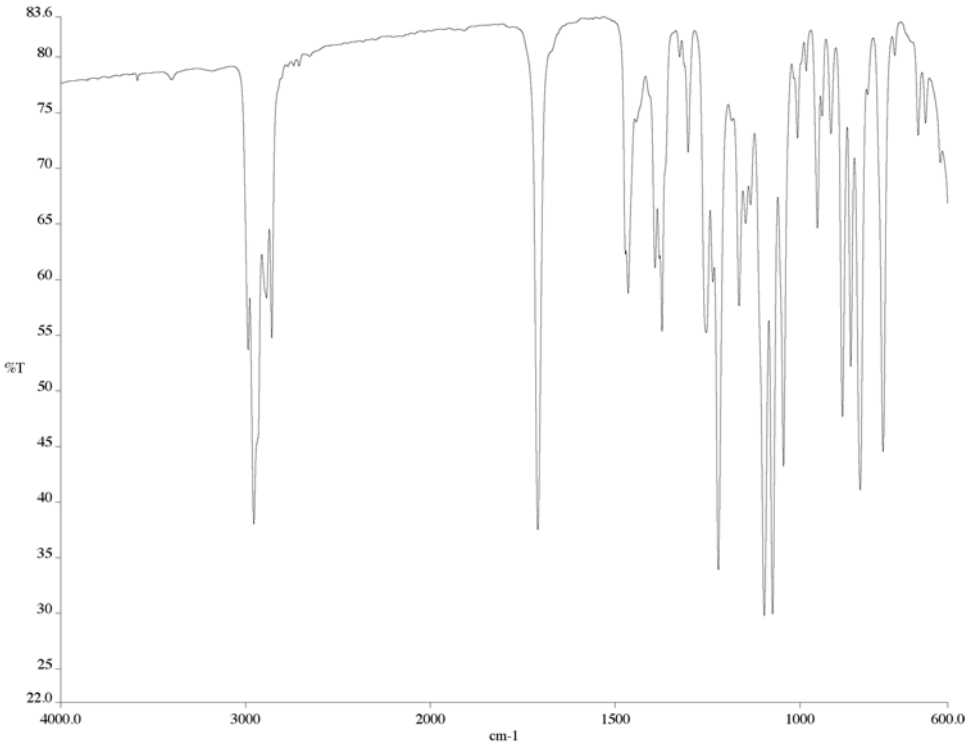


Figure A5.56 IR of compound **232** (NaCl/film)

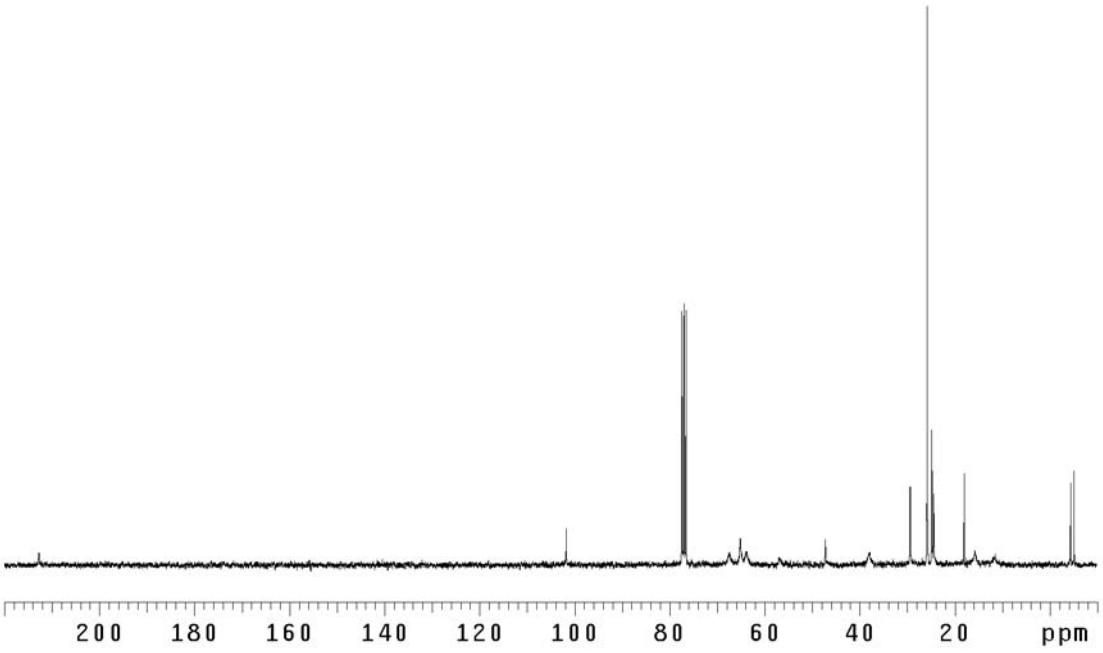
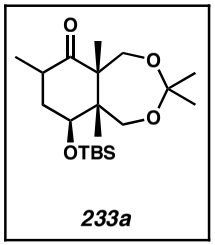


Figure A5.57 ^{13}C NMR of compound **232** (75 MHz, $CDCl_3$)



233a

Figure A5.58 ^{1}H NMR of compound **233a** (300 MHz, $CDCl_3$)

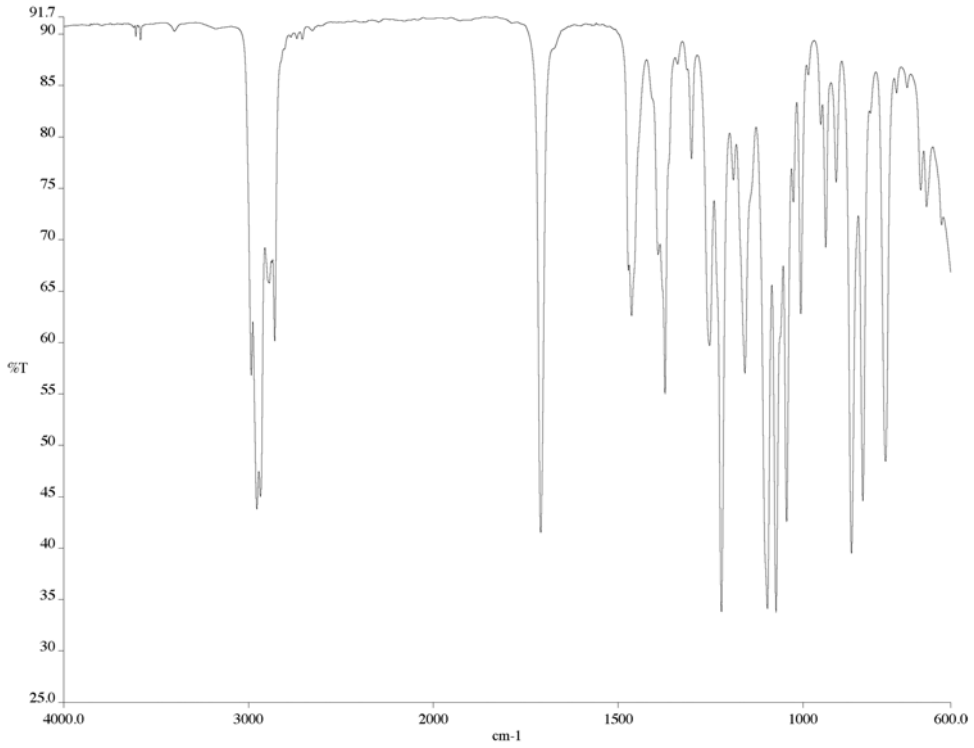


Figure A5.59 IR of compound **233a** (NaCl/film)

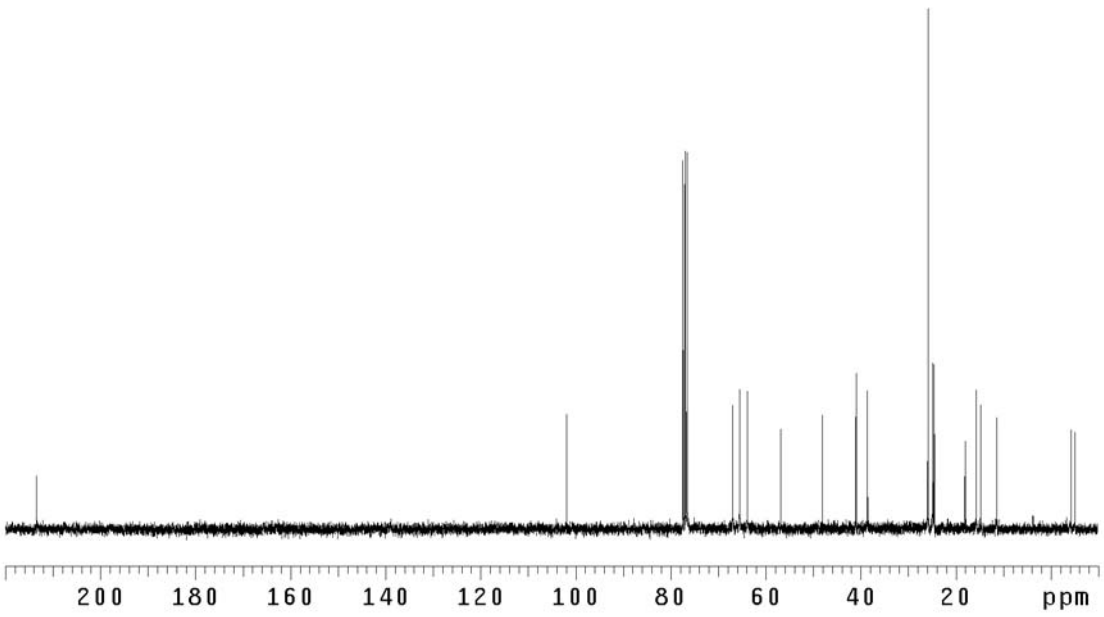
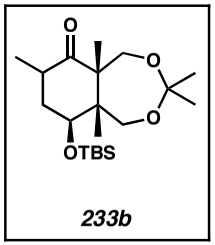


Figure A5.60 ^{13}C NMR of compound **233a** (75 MHz, $CDCl_3$)



233b

Figure A5.61 ^{1}H NMR of compound **233b** (300 MHz, $CDCl_3$)

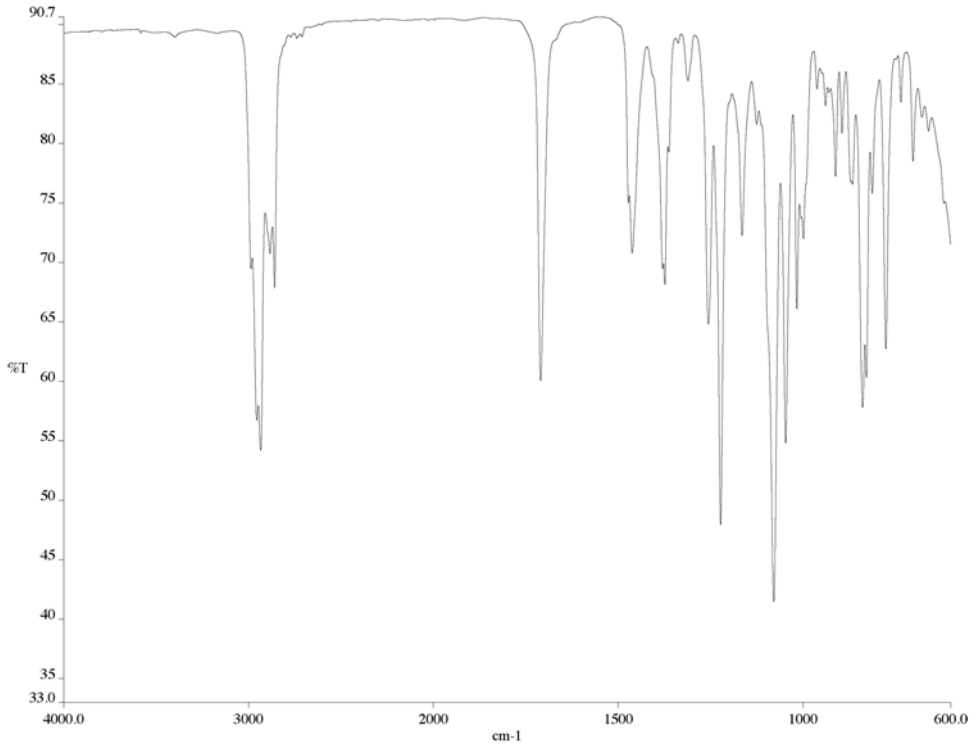


Figure A5.62 IR of compound **233b** (NaCl/film)

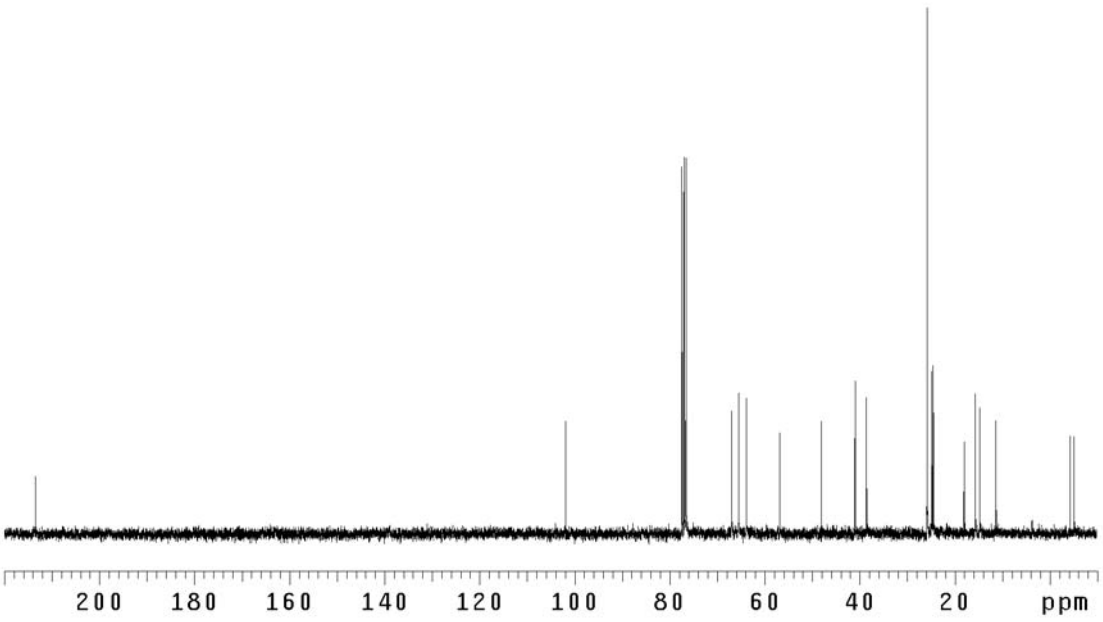
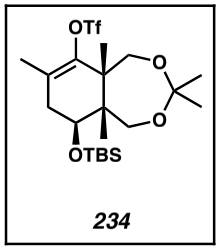


Figure A5.63 ^{13}C NMR of compound **233b** (75 MHz, $CDCl_3$)



234

Figure A5.64 ^{1}H NMR of compound **234** (300 MHz, C_6D_6)

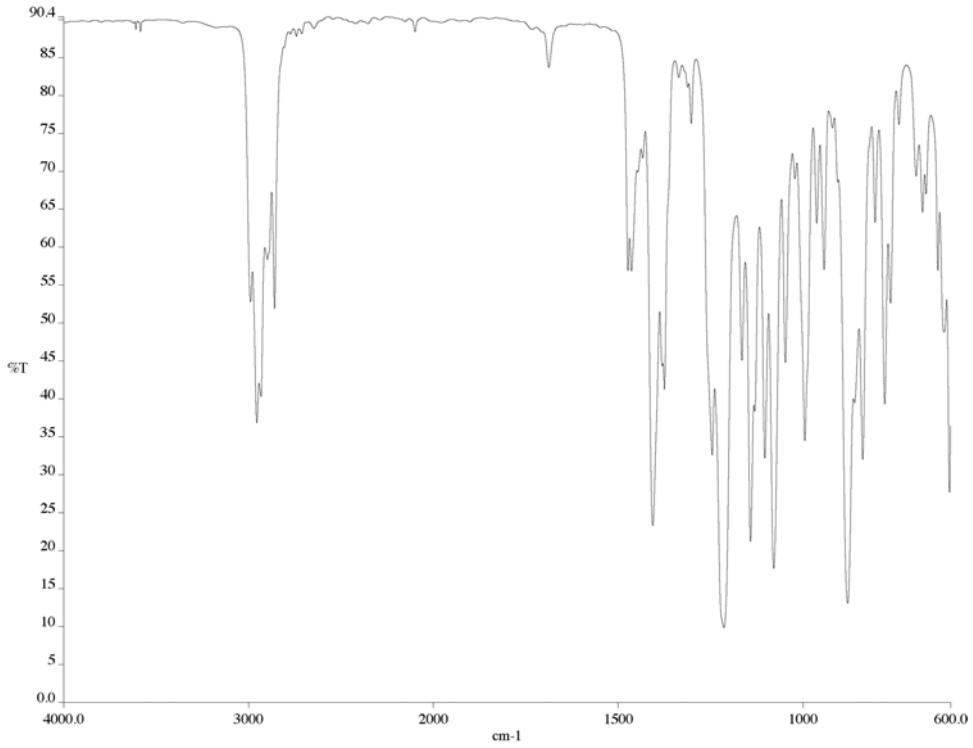


Figure A5.65 IR of compound **234** (NaCl/film)

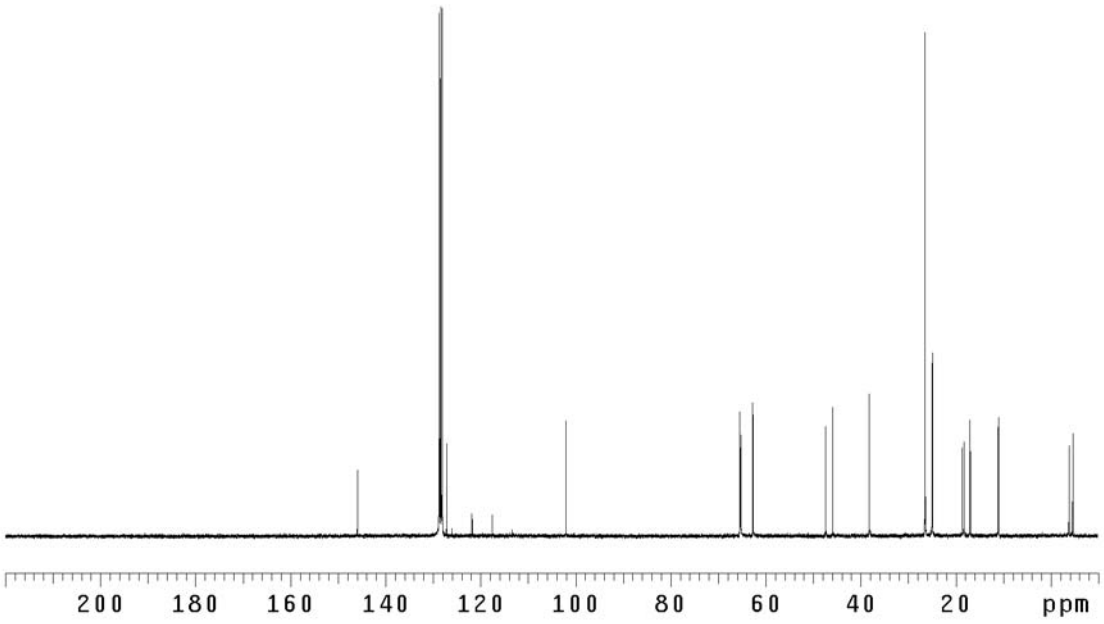
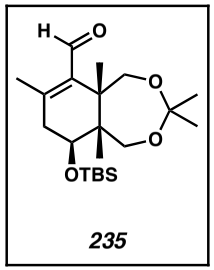


Figure A5.66 ^{13}C NMR of compound **234** (75 MHz, C_6D_6)



235

Figure A5.67 ^{1}H NMR of compound **235** (300 MHz, $CDCl_3$)

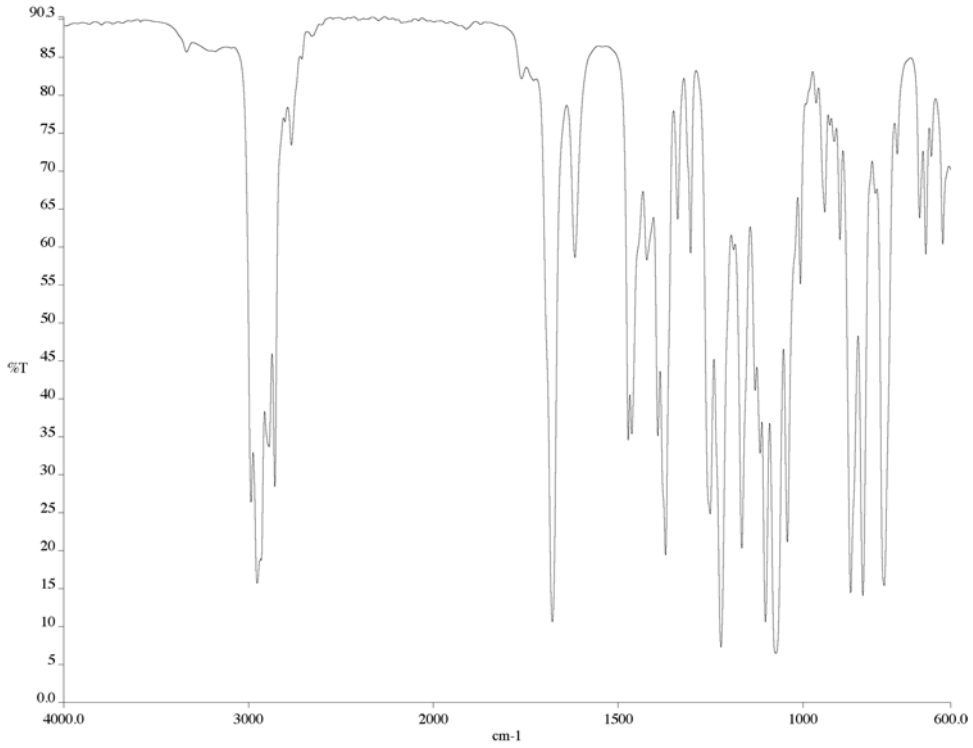


Figure A5.68 IR of compound **235** (NaCl/film)

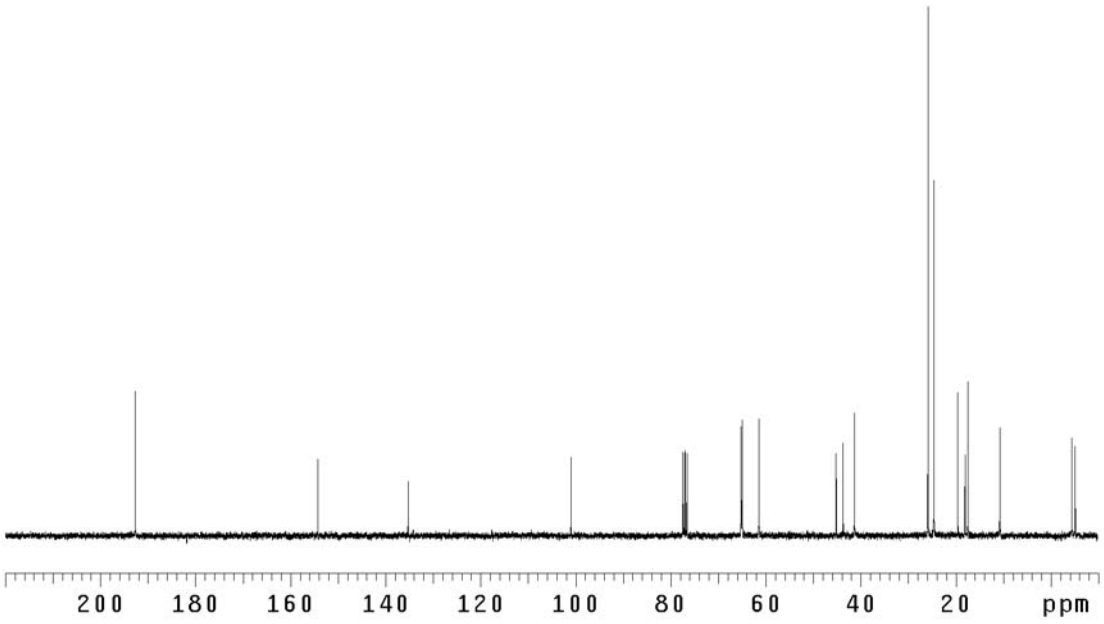
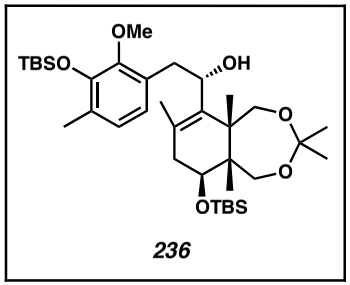


Figure A5.69 ^{13}C NMR of compound **235** (75 MHz, $CDCl_3$)



236

Figure A5.70 ^{1}H NMR of compound **236** (300 MHz, $CDCl_3$)

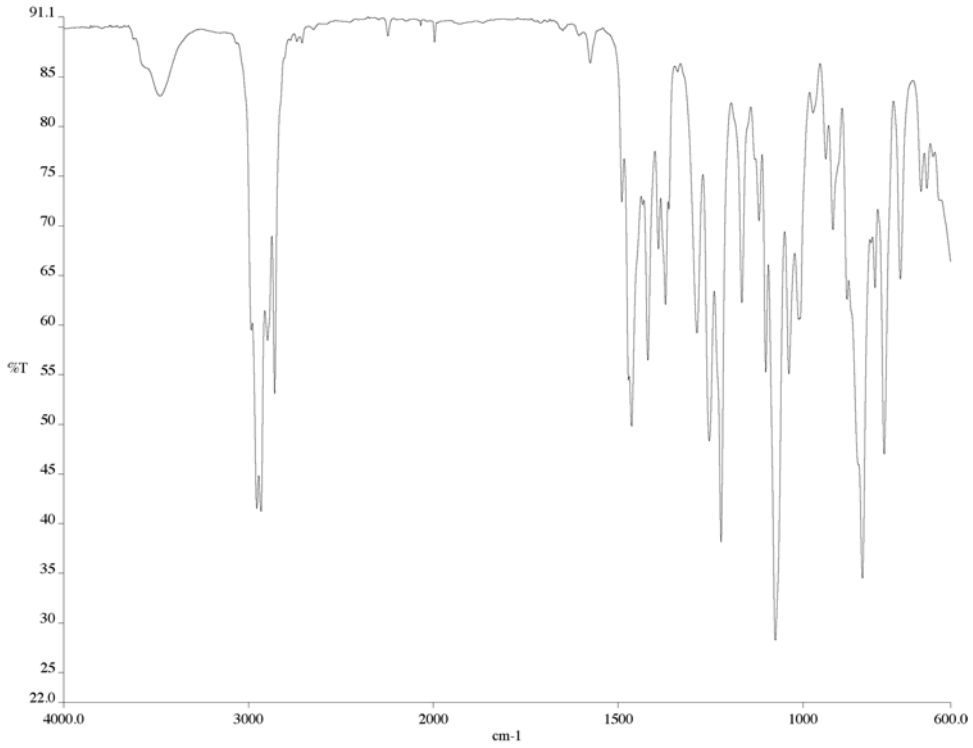


Figure A5.71 IR of compound **236** (NaCl/film)

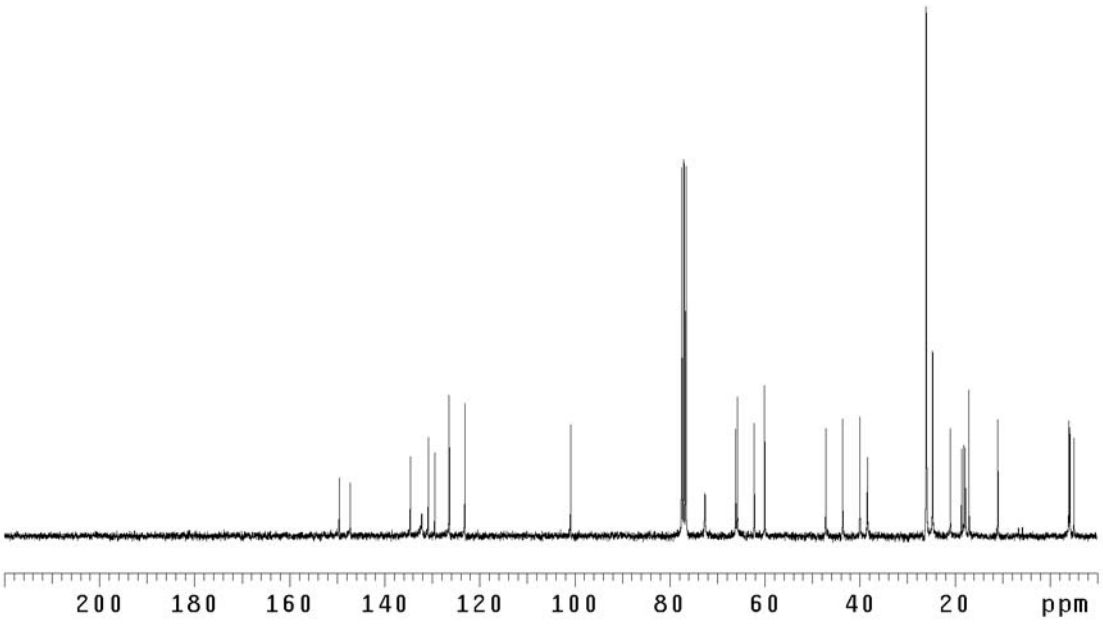
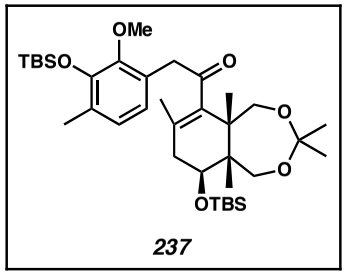


Figure A5.72 ^{13}C NMR of compound **236** (75 MHz, $CDCl_3$)



237

Figure A5.73 ^{1}H NMR of compound **237** (300 MHz, $CDCl_3$)

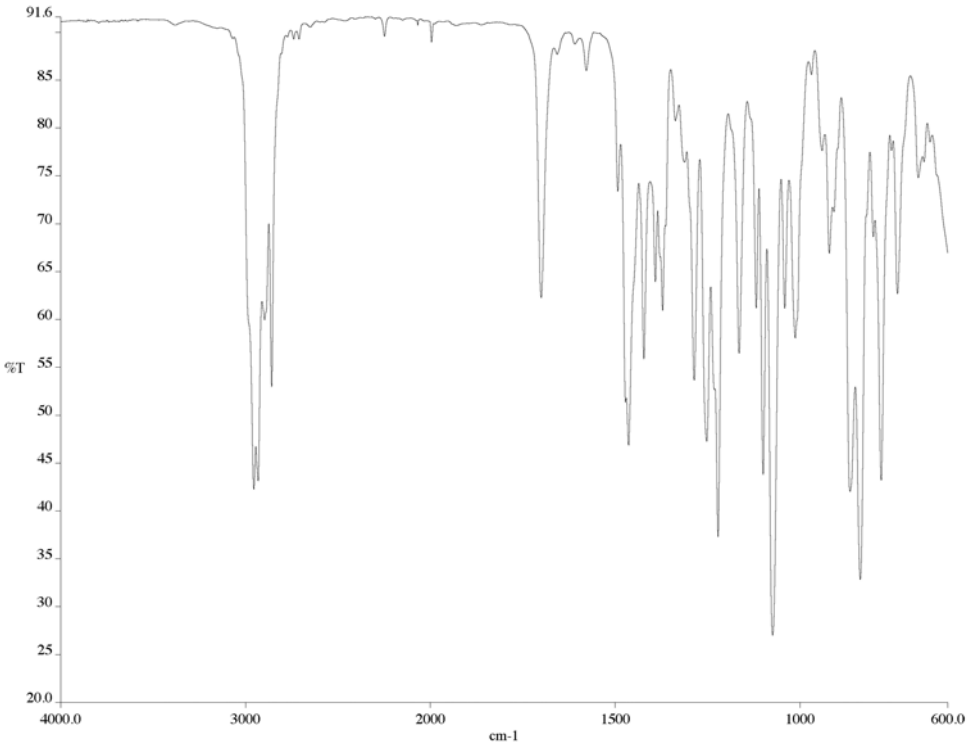


Figure A5.74 IR of compound **237** (NaCl/film)

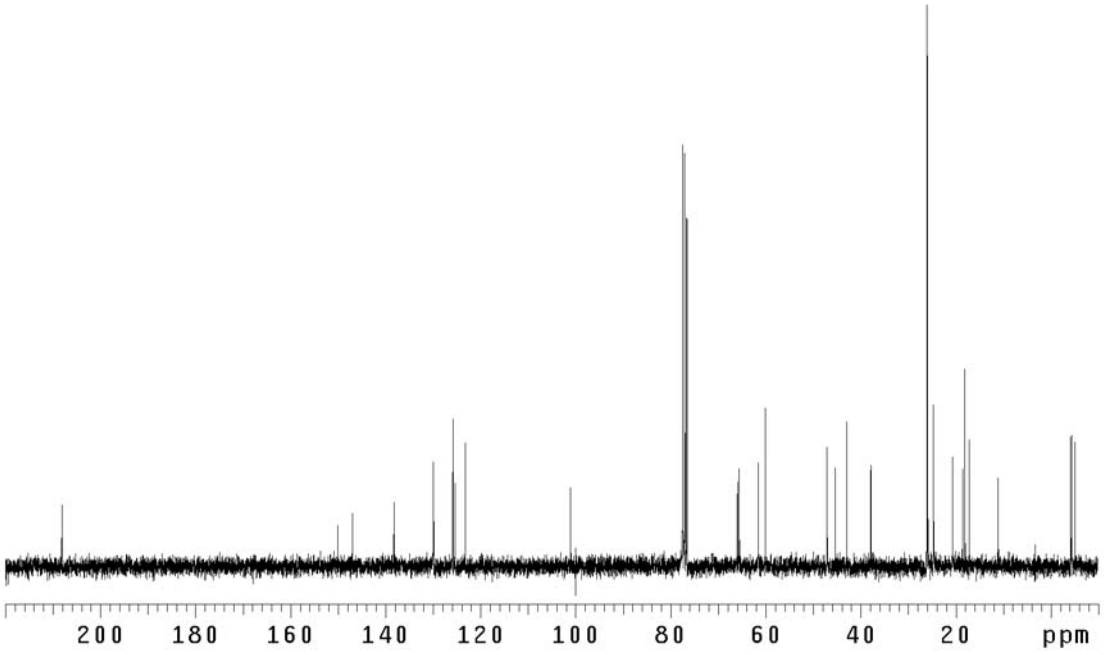


Figure A5.75 ^{13}C NMR of compound **237** (75 MHz, $CDCl_3$)

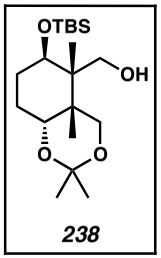


Figure A5.76 ^{1}H NMR of compound **238** (500 MHz, $CDCl_3$)

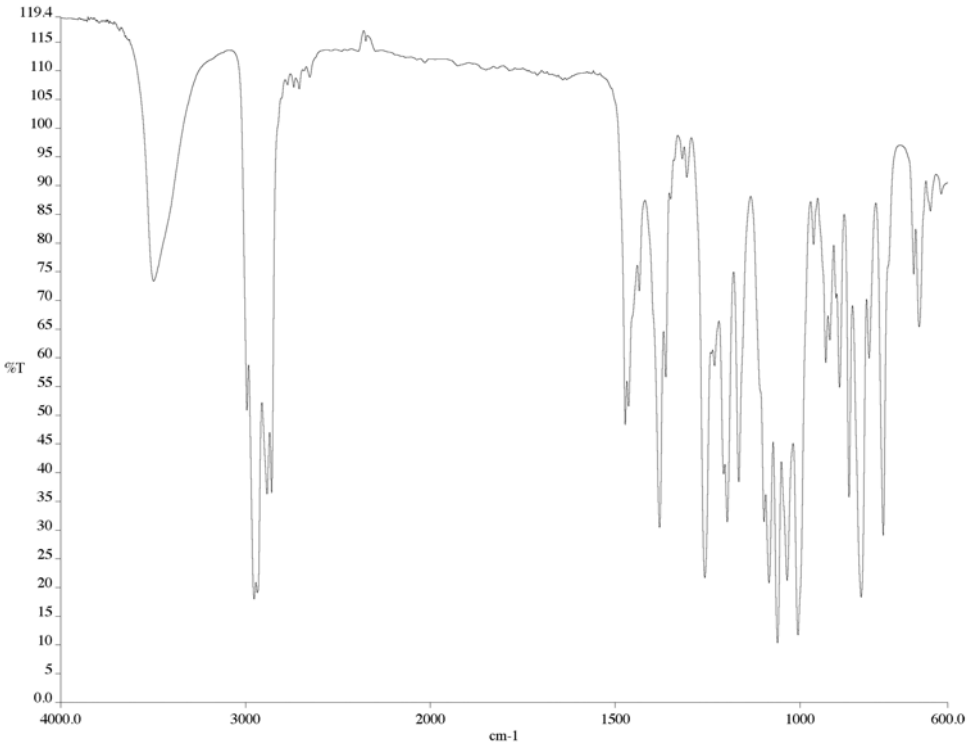


Figure A5.77 IR of compound **238** (NaCl/film)

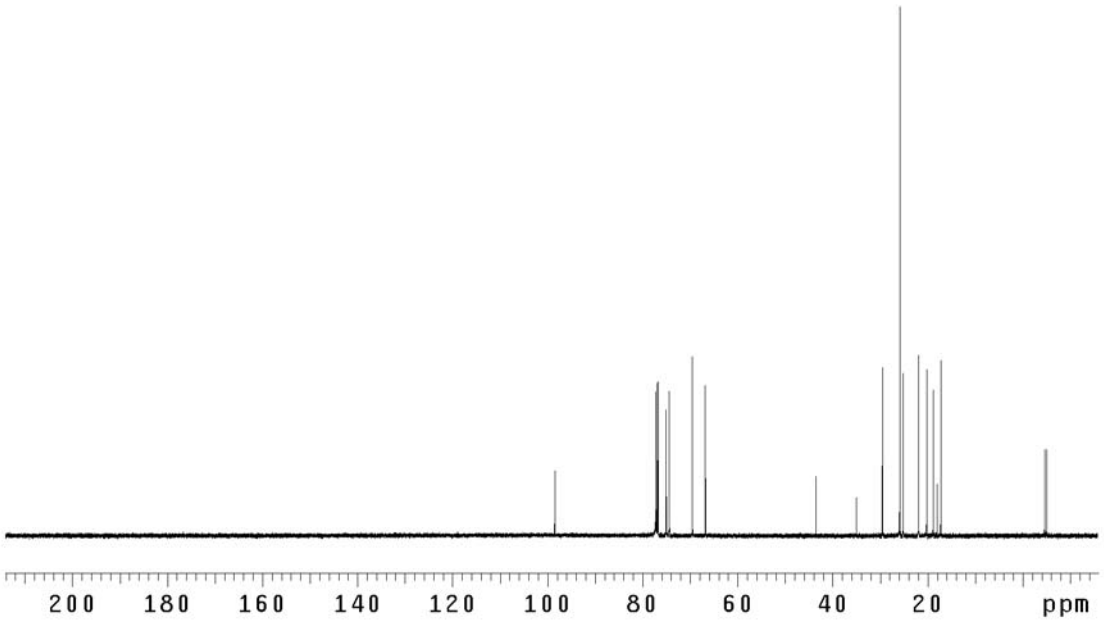


Figure A5.78 ^{13}C NMR of compound **238** (125 MHz, $CDCl_3$)

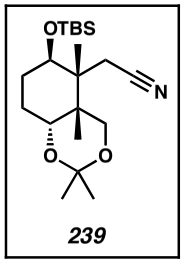


Figure A5.79 ^{1}H NMR of compound **239** (300 MHz, $CDCl_3$)

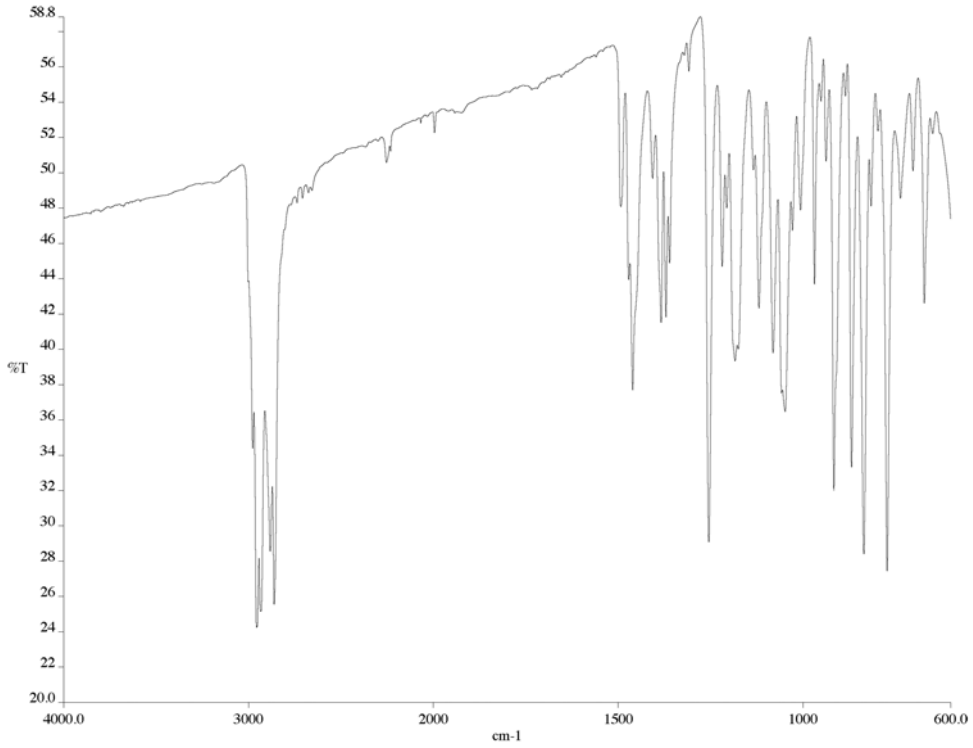


Figure A5.80 IR of compound **239** (NaCl/film)

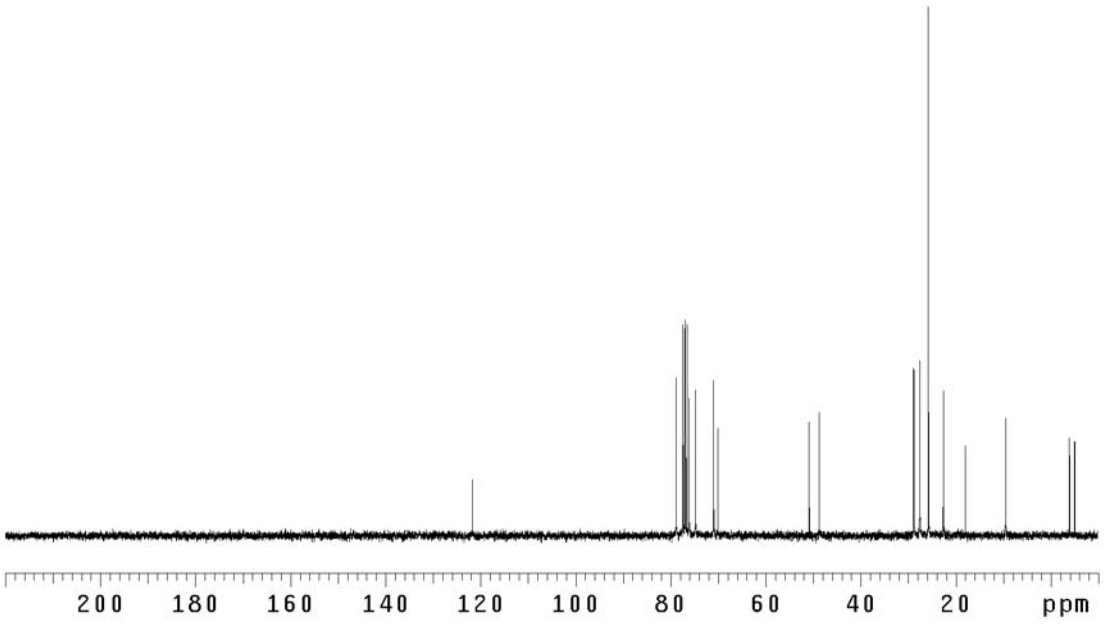


Figure A5.81 ^{13}C NMR of compound **239** (75 MHz, $CDCl_3$)

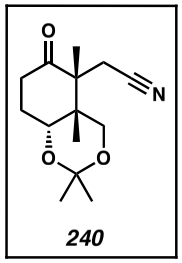


Figure A5.82 ^{1}H NMR of compound **240** (300 MHz, $CDCl_3$)

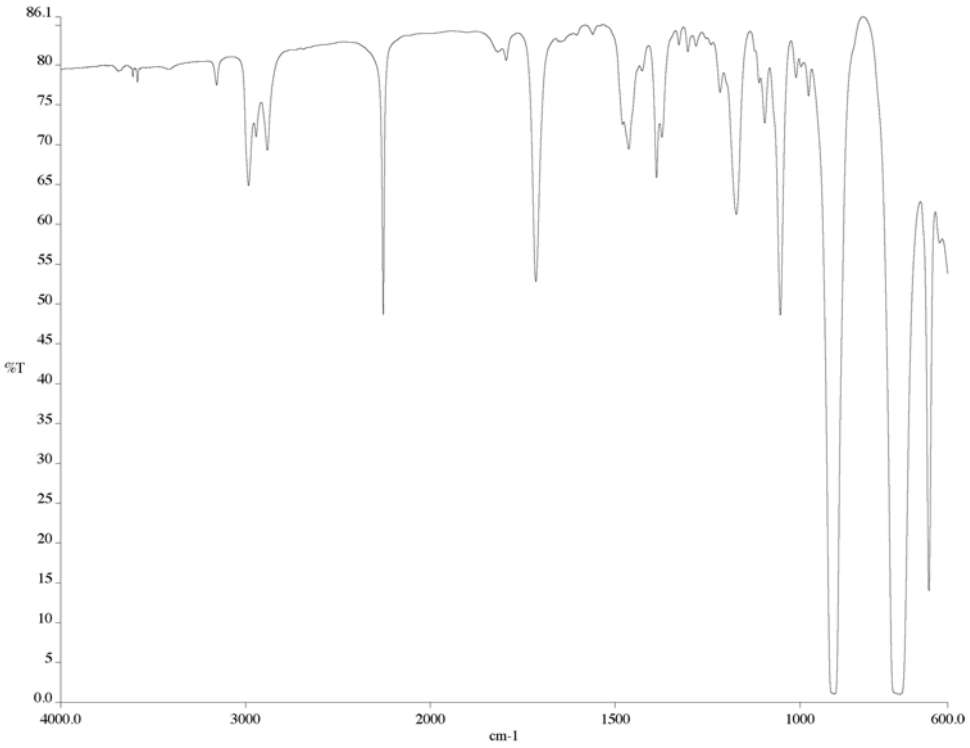


Figure A5.83 IR of compound **240** (NaCl/film)

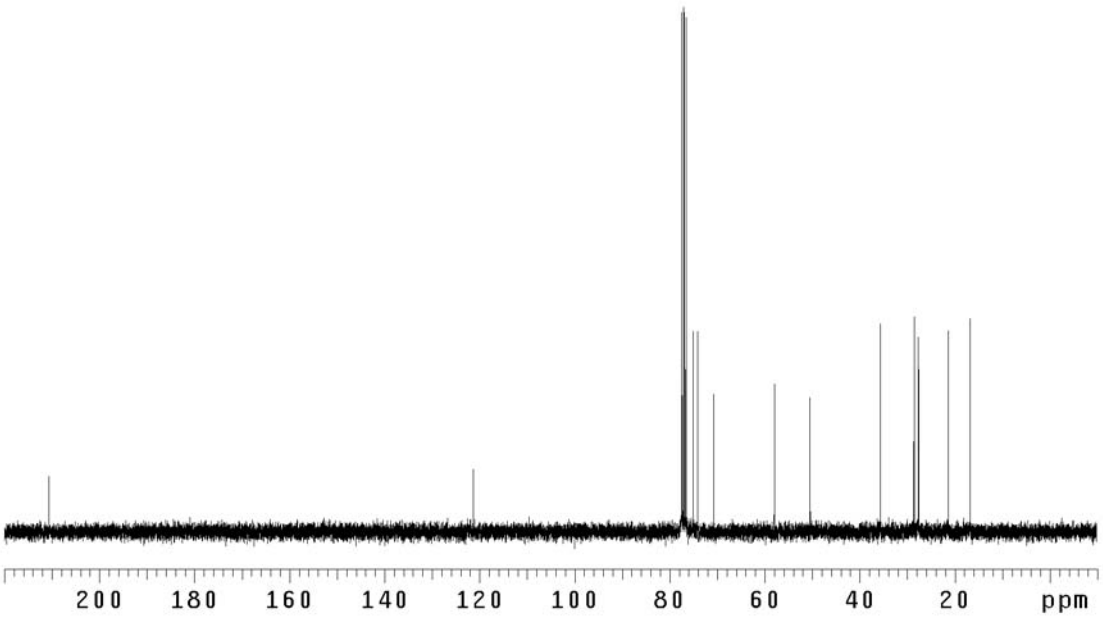


Figure A5.84 ^{13}C NMR of compound **240** (75 MHz, $CDCl_3$)

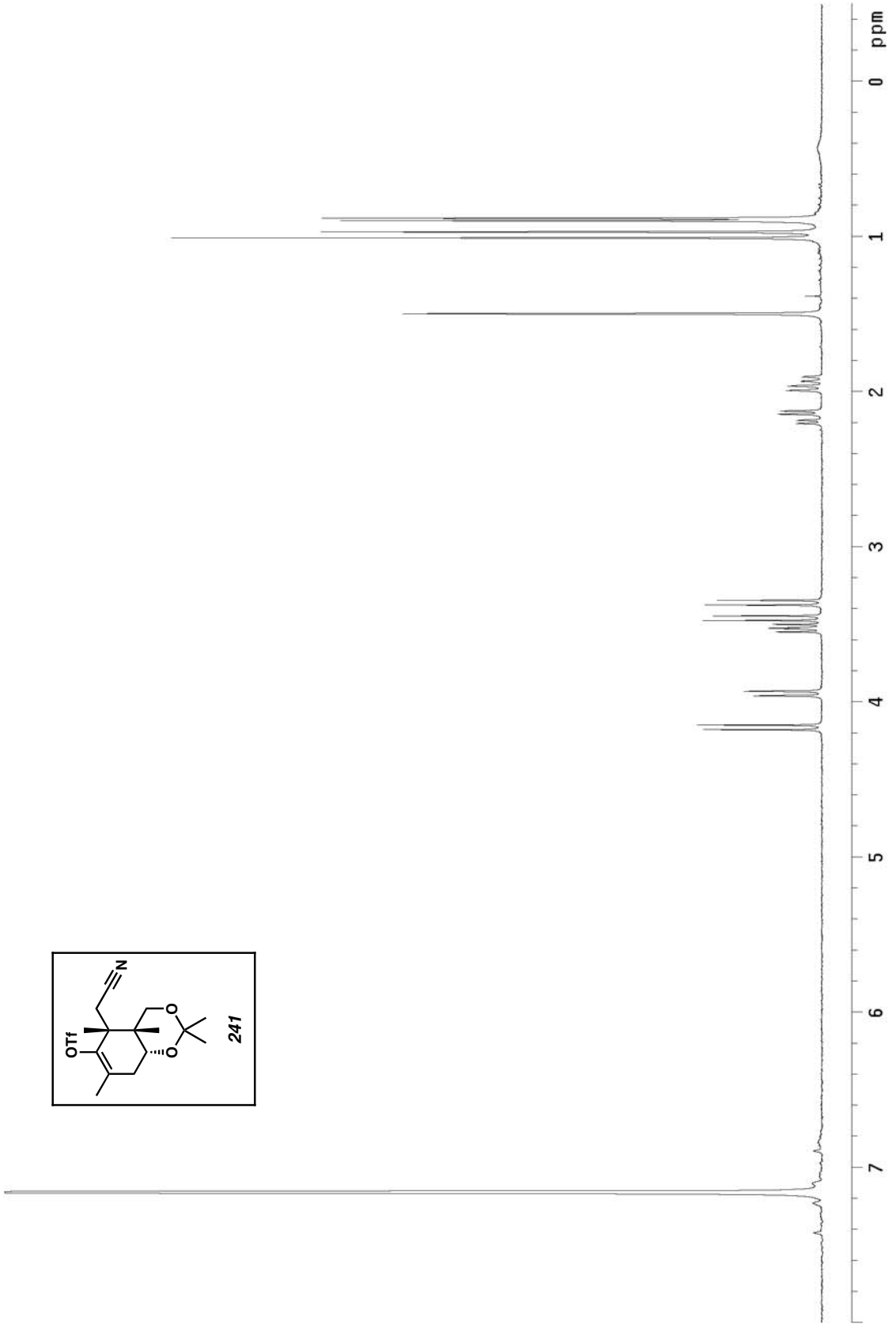


Figure A5.85 ^{1}H NMR of compound **241** (300 MHz, C_6D_6)

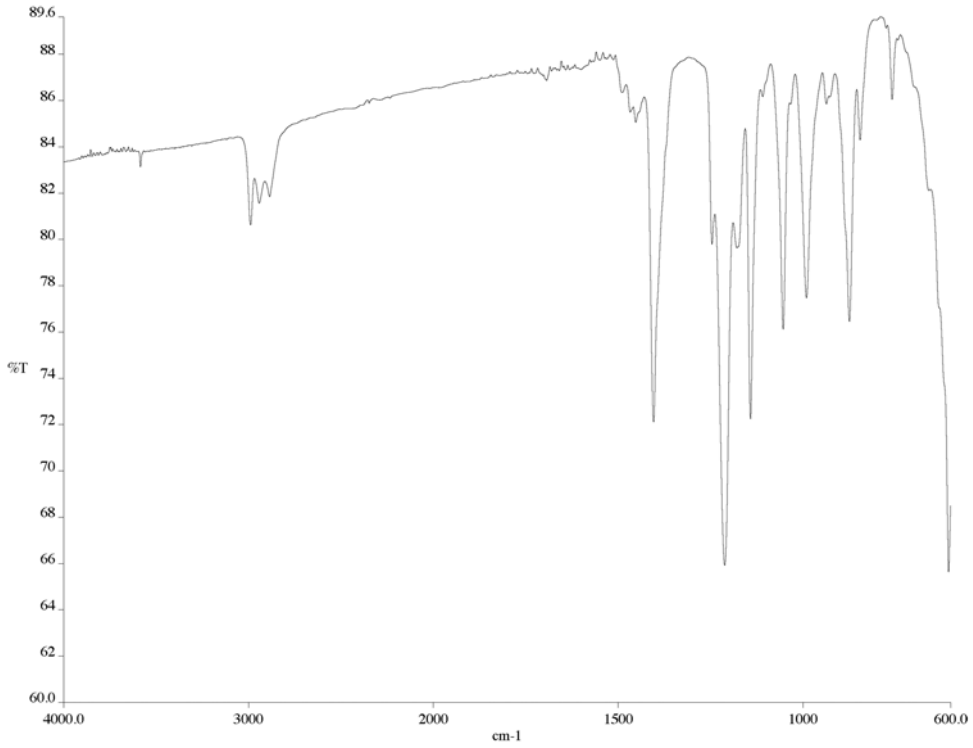


Figure A5.86 IR of compound **241** (NaCl/film)

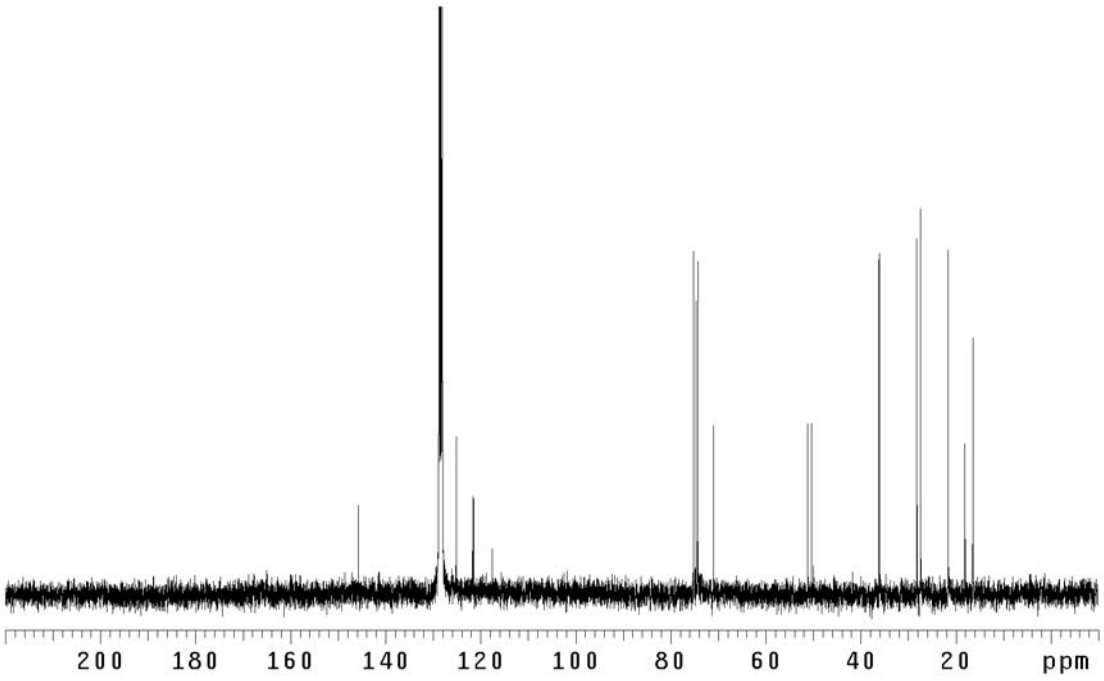


Figure A5.87 ^{13}C NMR of compound **241** (75 MHz, C_6D_6)

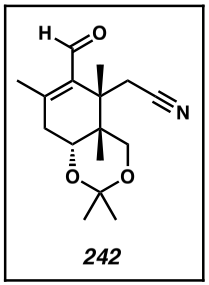


Figure A5.88 ^{1}H NMR of compound **242** (300 MHz, $CDCl_3$)

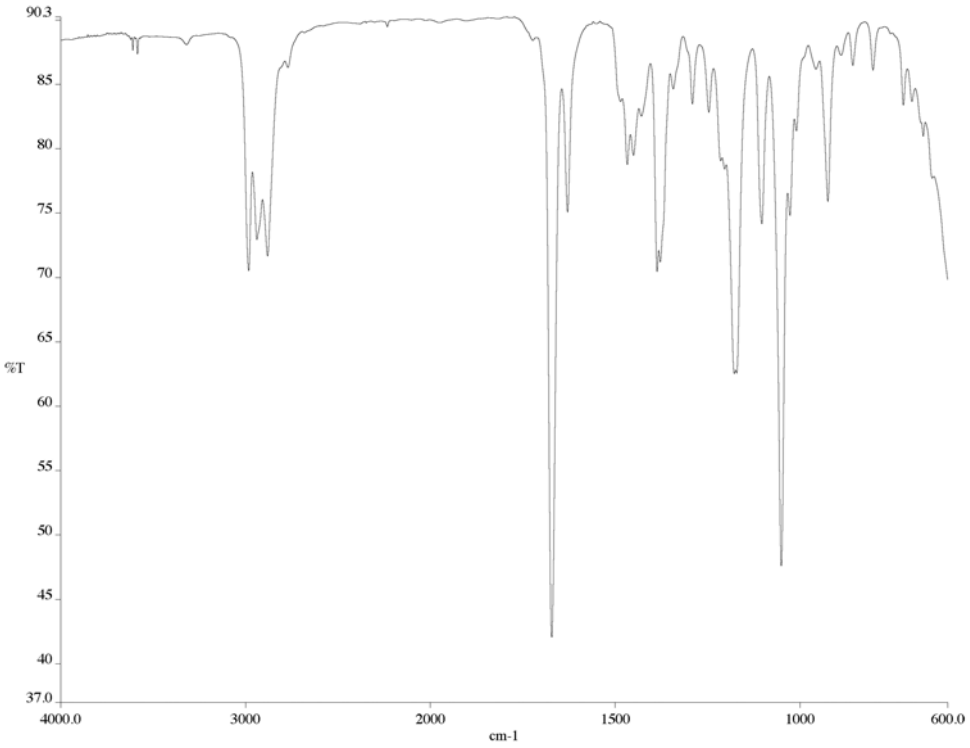


Figure A5.89 IR of compound **242** (NaCl/film)

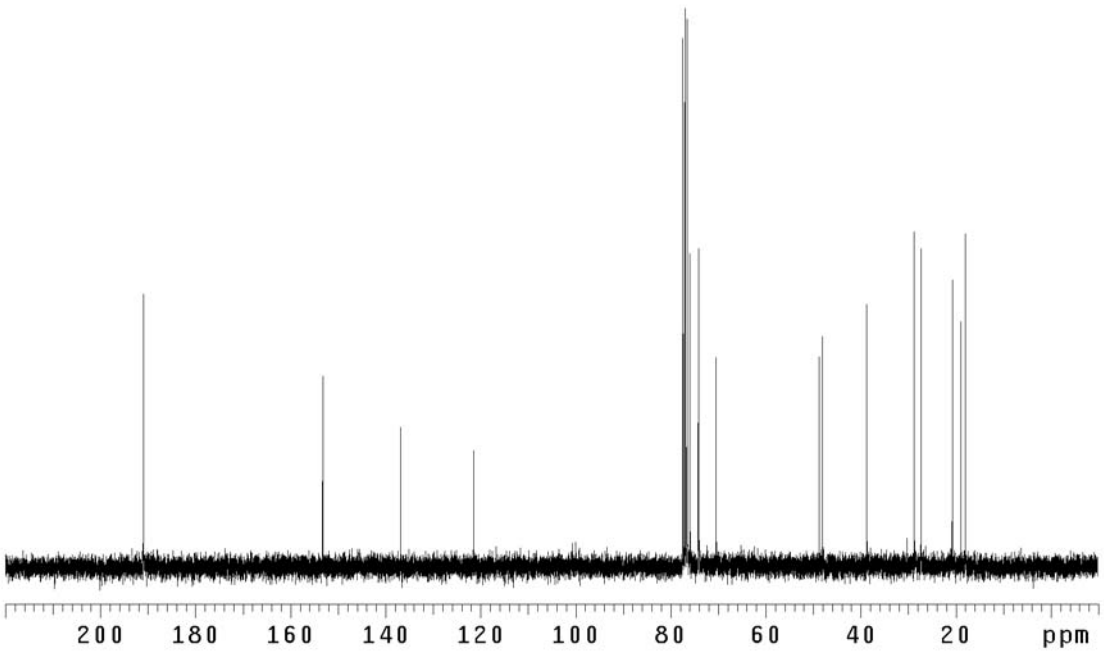


Figure A5.90 ^{13}C NMR of compound **242** (75 MHz, $CDCl_3$)

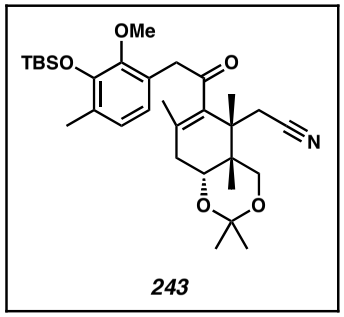


Figure A5.91 ^{1}H NMR of compound **243** (300 MHz, $CDCl_3$)

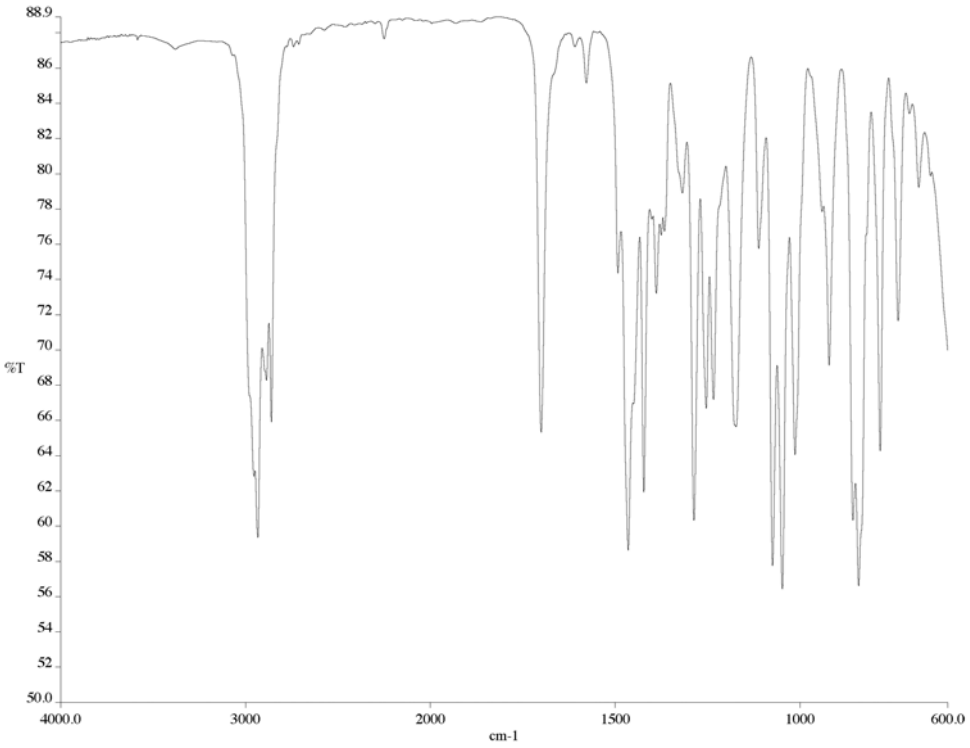


Figure A5.92 IR of compound **243** (NaCl/film)

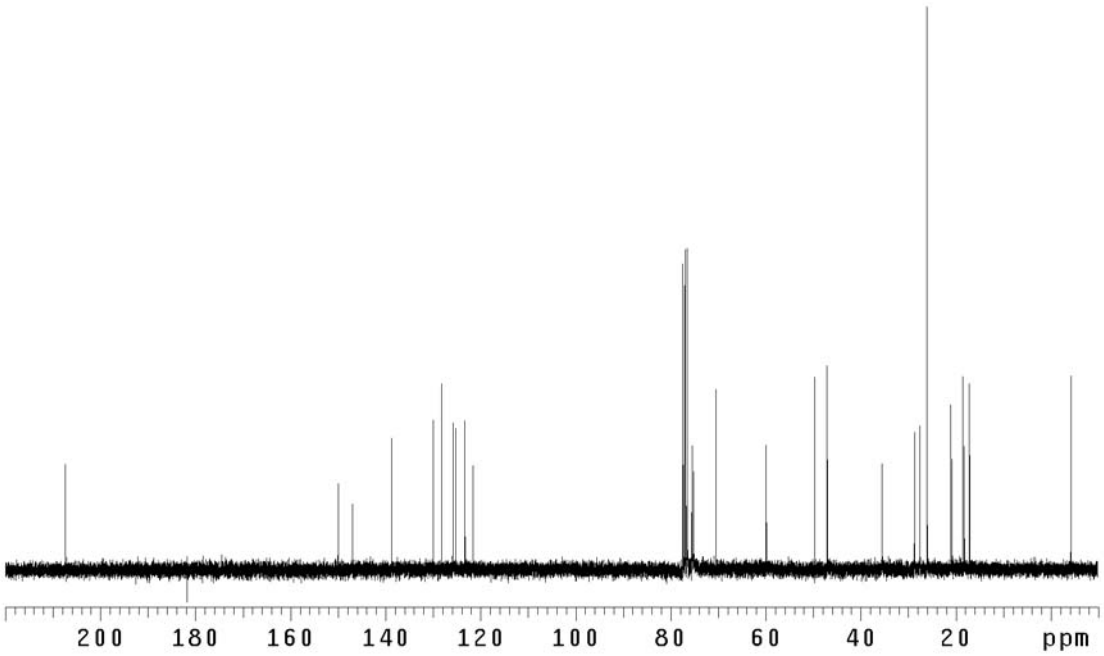


Figure A5.93 ^{13}C NMR of compound **243** (75 MHz, $CDCl_3$)

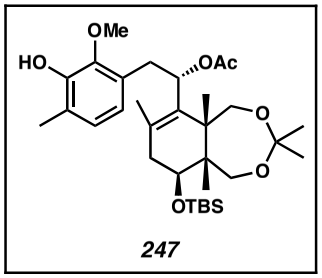


Figure A5.94 ^{1}H NMR of compound **247** (300 MHz, $CDCl_3$)

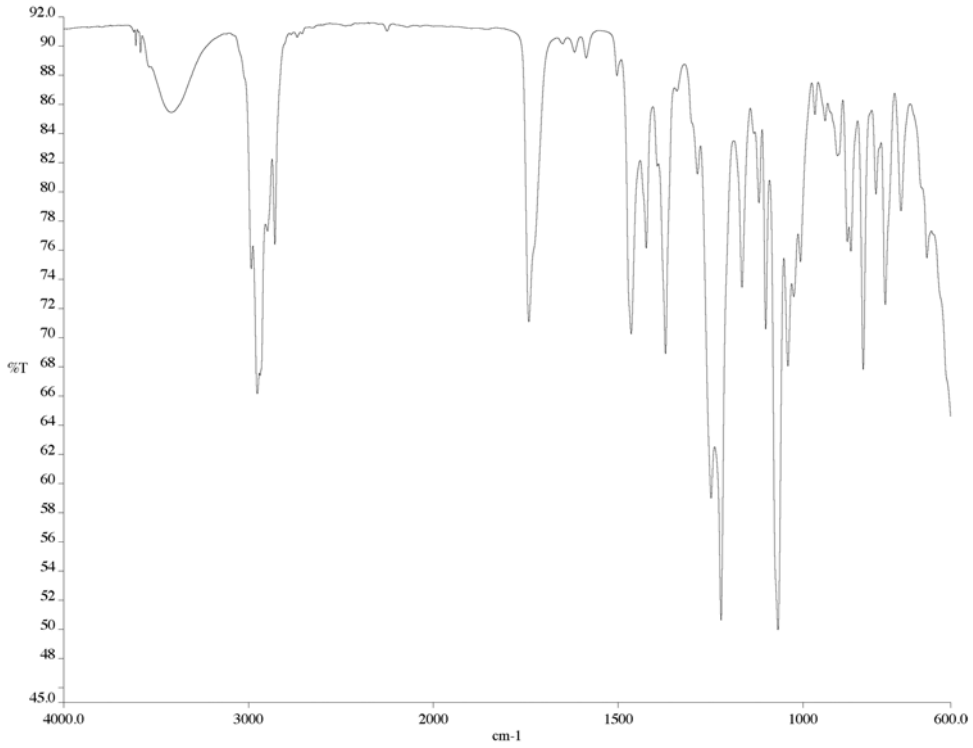


Figure A5.95 IR of compound **247** (NaCl/film)

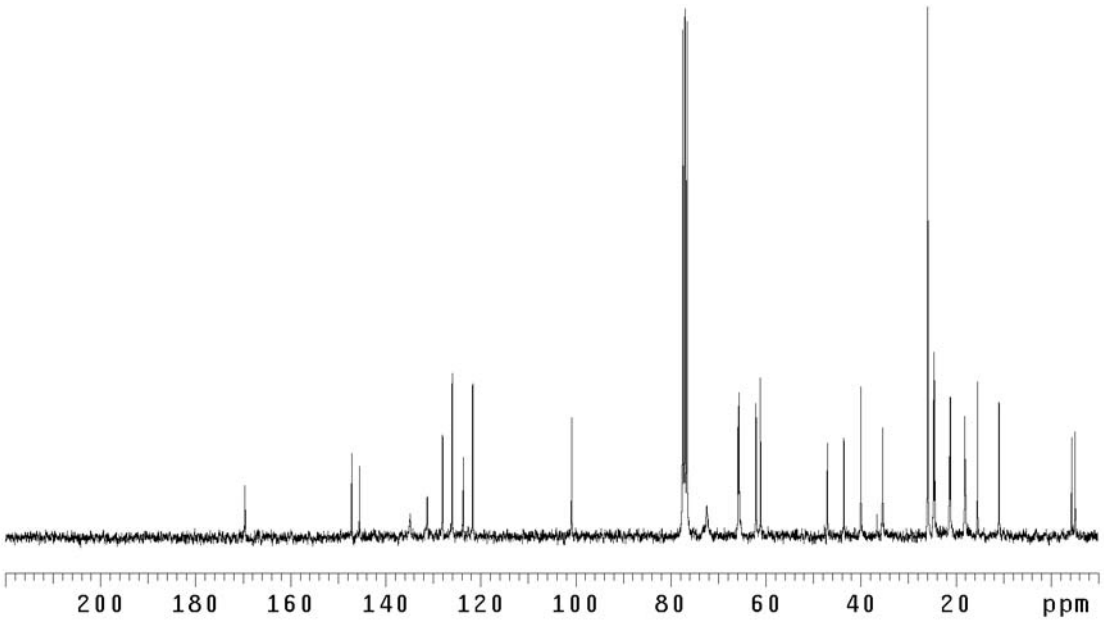


Figure A5.96 ^{13}C NMR of compound **247** (75 MHz, $CDCl_3$)

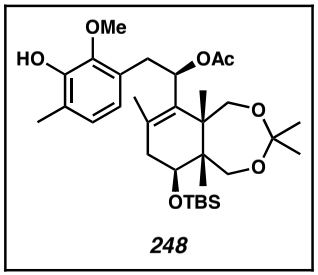


Figure A5.97 ^{1}H NMR of compound **248** (300 MHz, $CDCl_3$)

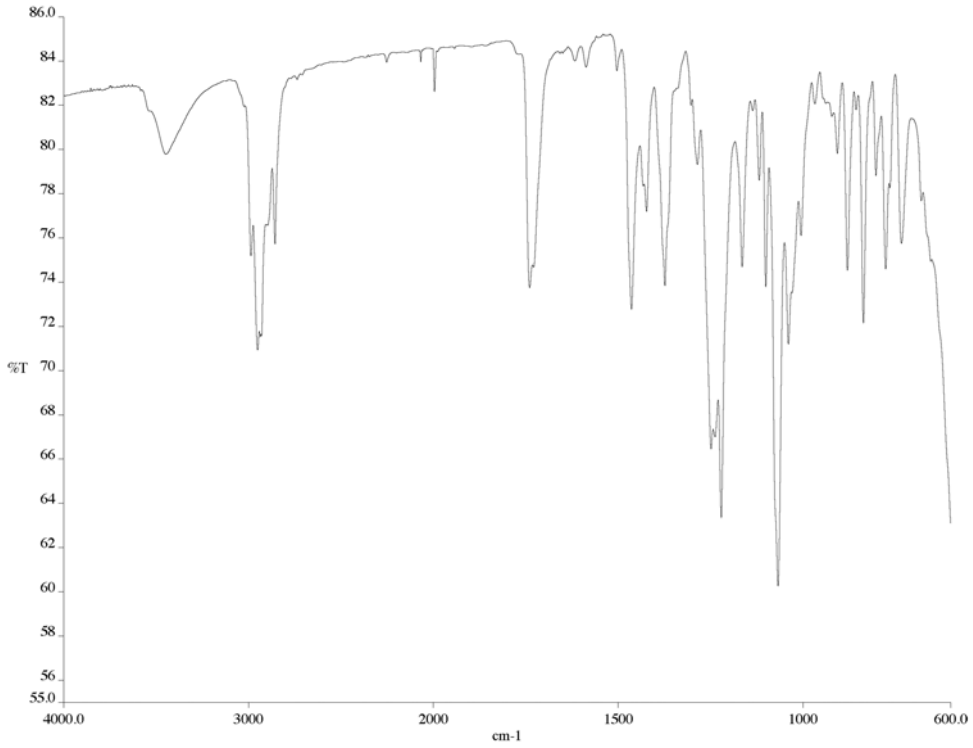


Figure A5.98 IR of compound **248** (NaCl/film)

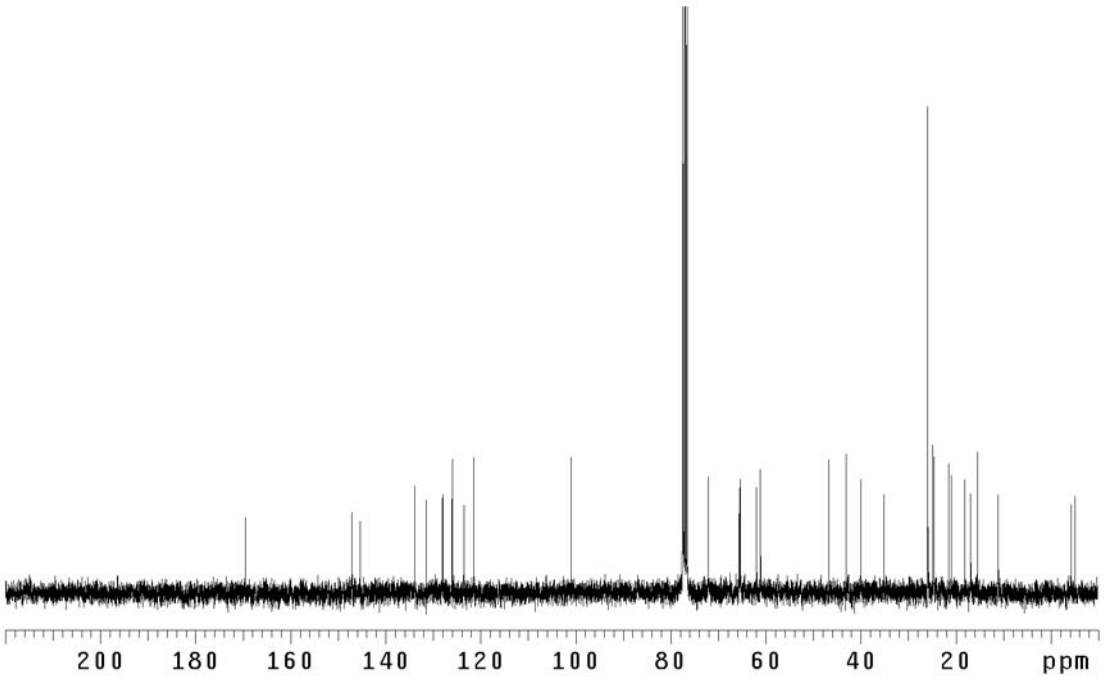


Figure A5.99 ^{13}C NMR of compound **248** (75 MHz, $CDCl_3$)

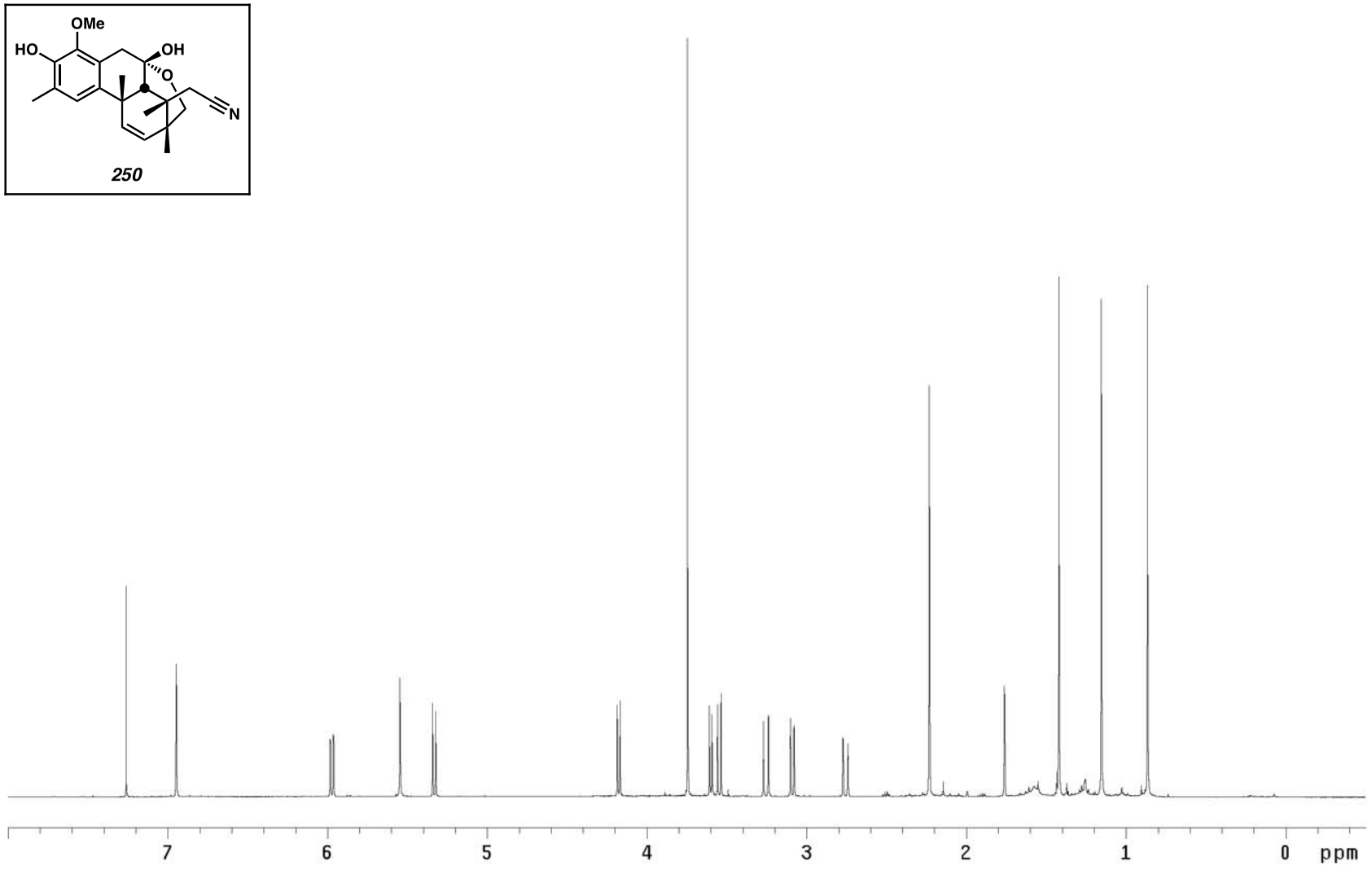


Figure A5.100 ^{1}H NMR of compound **250** (500 MHz, $CDCl_3$)

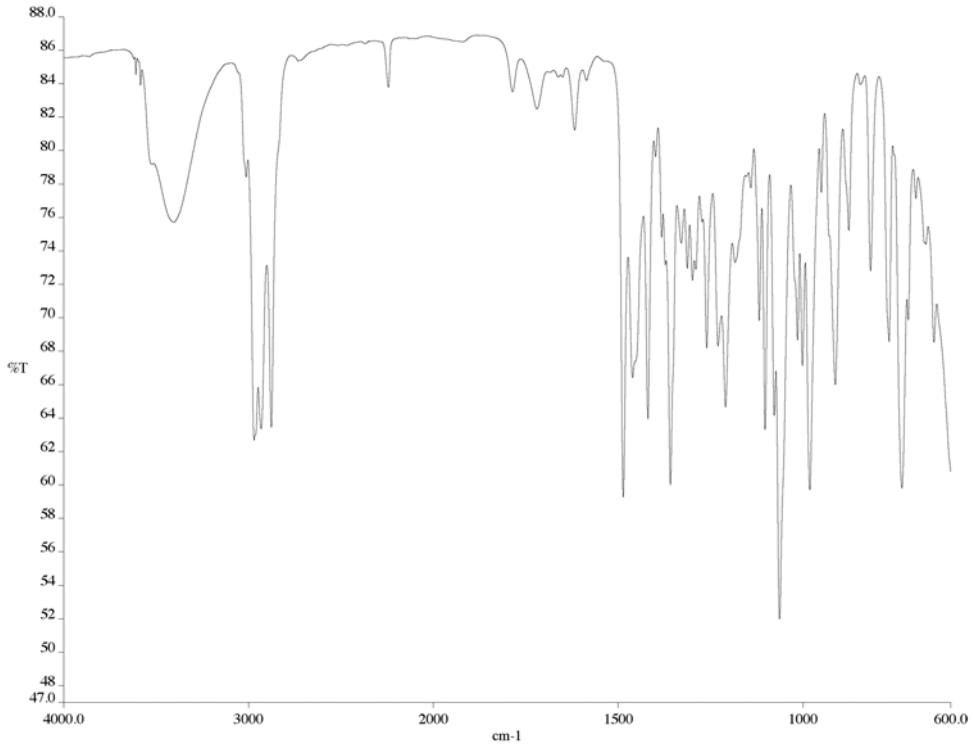


Figure A5.101 IR of compound **250** (NaCl/film)

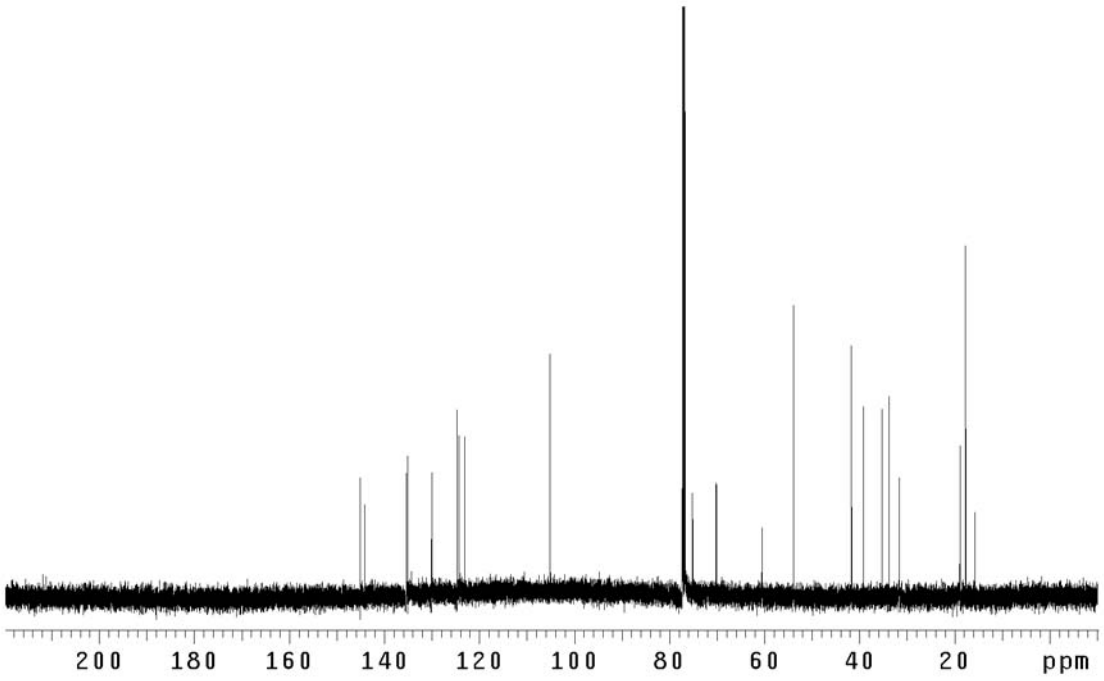


Figure A5.102 ^{13}C NMR of compound **250** (125 MHz, $CDCl_3$)

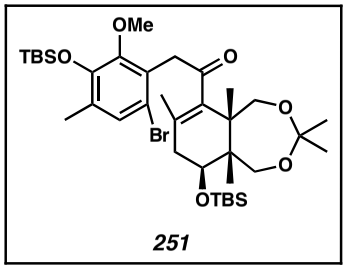


Figure A5.103 ^{1}H NMR of compound **251** (300 MHz, $CDCl_3$)

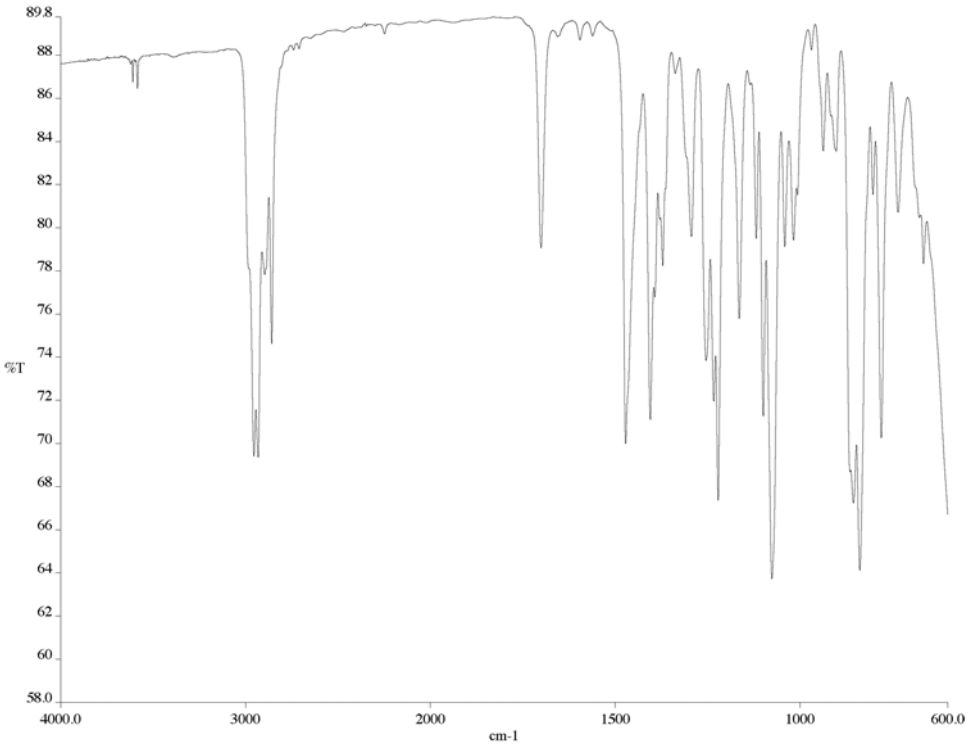


Figure A5.104 IR of compound **251** (NaCl/film)

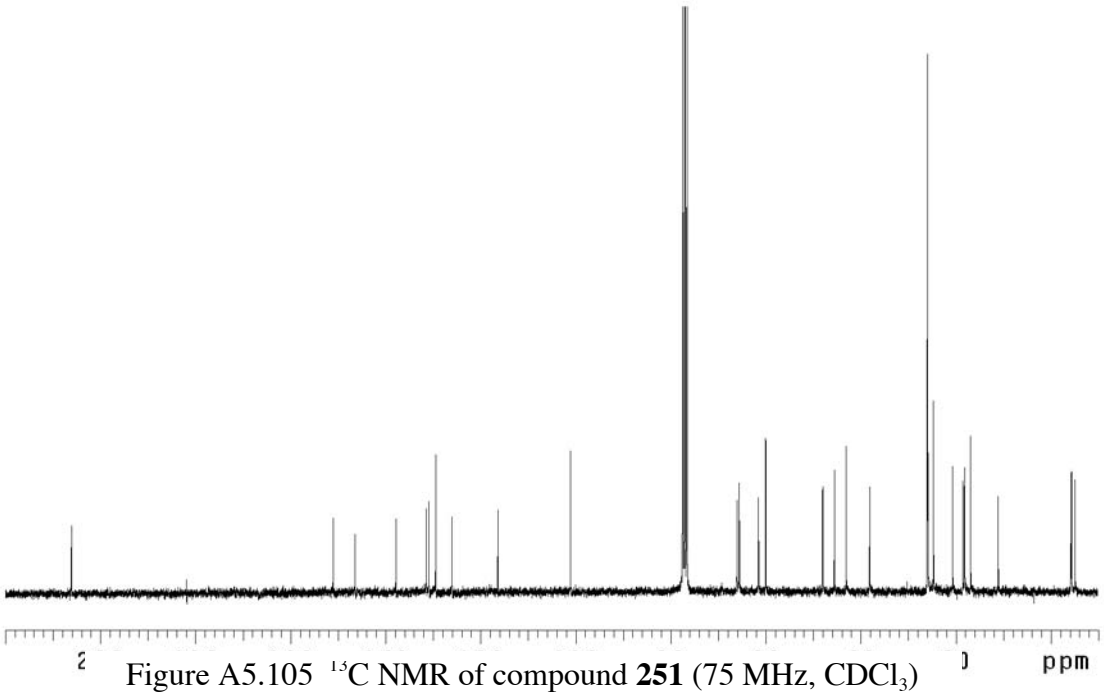


Figure A5.105 ^{13}C NMR of compound **251** (75 MHz, $CDCl_3$)

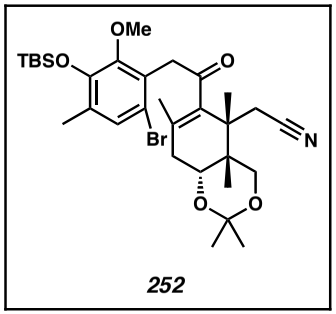


Figure A5.106 ^{1}H NMR of compound **252** (500 MHz, $CDCl_3$)

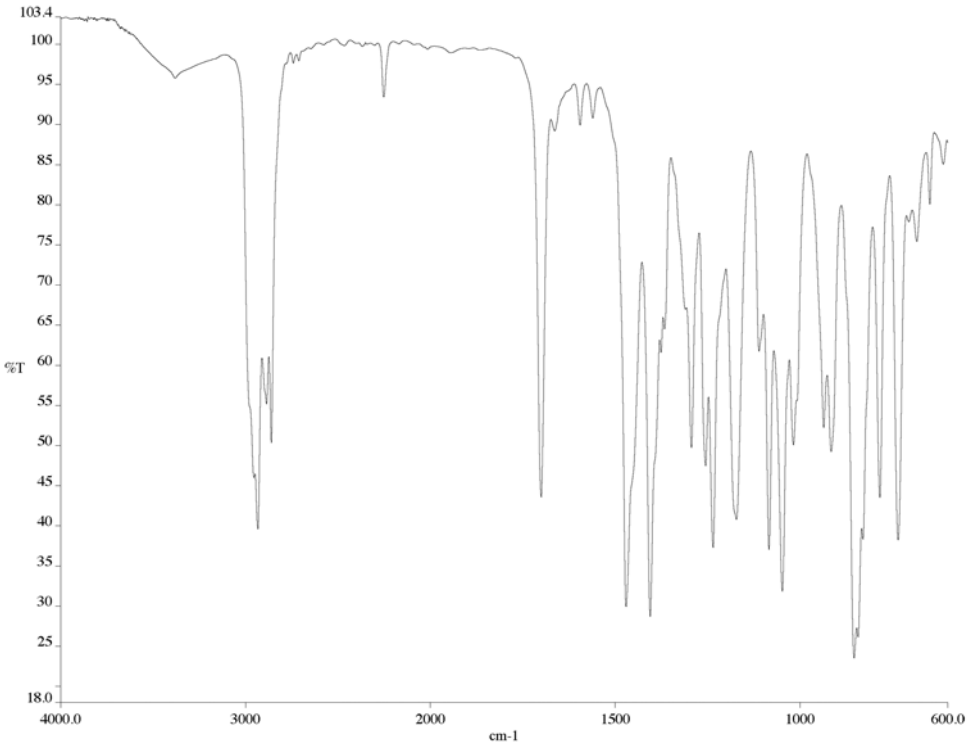


Figure A5.107 IR of compound **252** (NaCl/film)

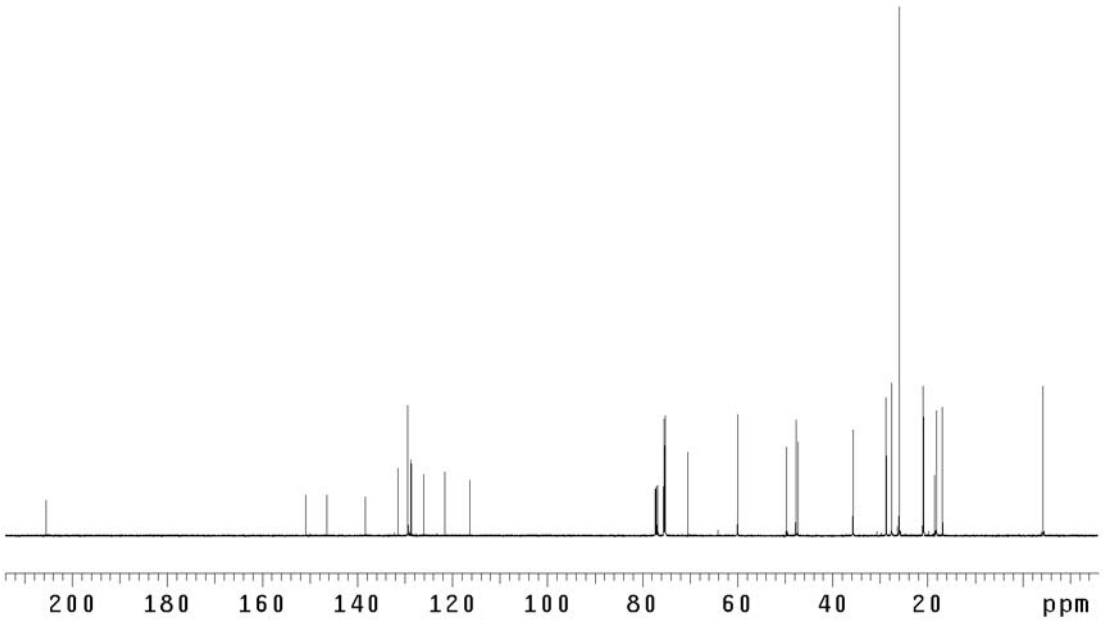
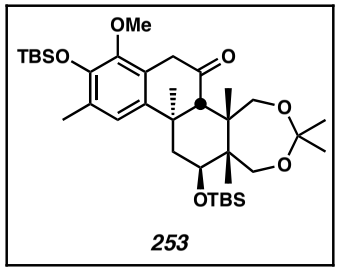


Figure A5.108 ^{13}C NMR of compound **252** (125 MHz, $CDCl_3$)



253

Figure A5.109 ^{1}H NMR of compound **253** (500 MHz, $CDCl_3$)

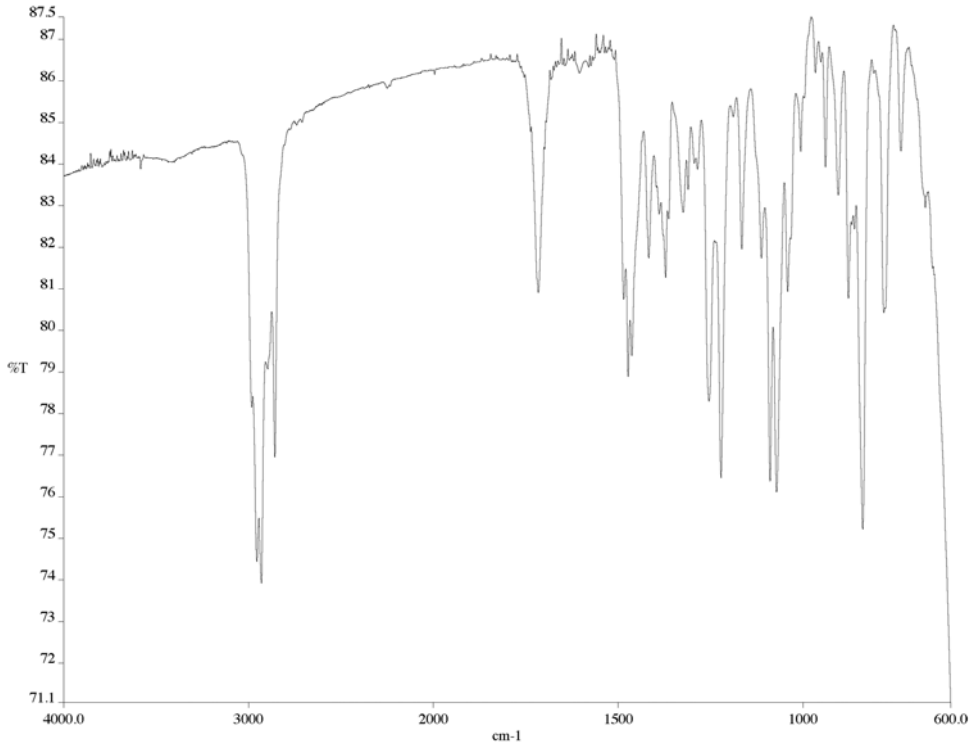


Figure A5.110 IR of compound **253** (NaCl/film)

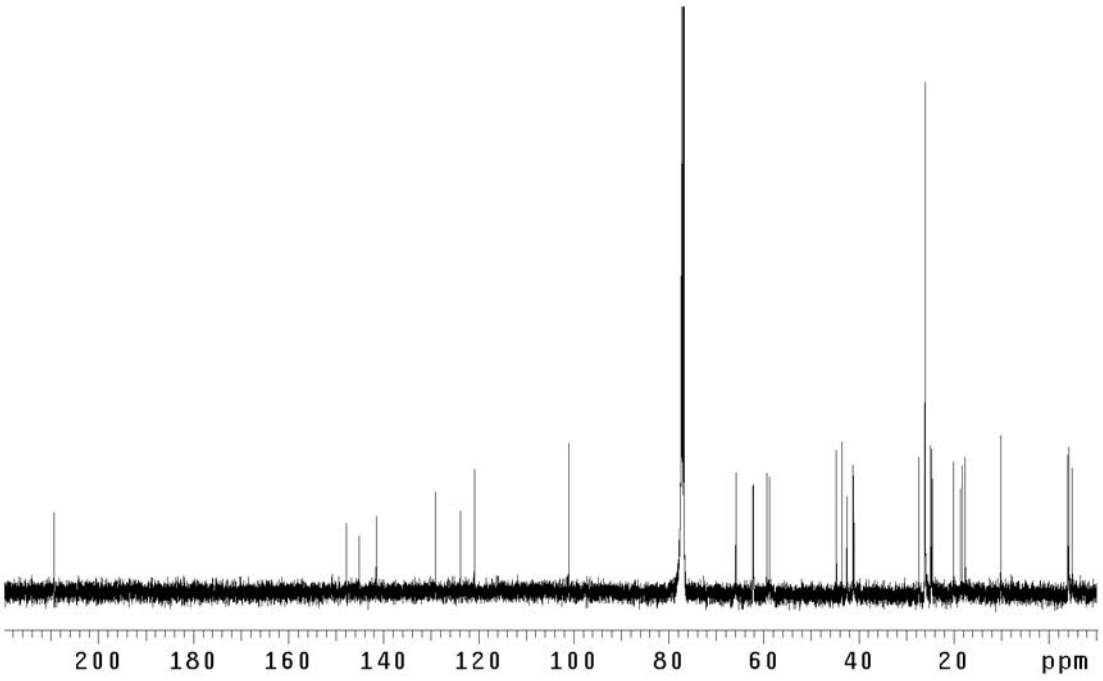


Figure A5.111 ^{13}C NMR of compound **253** (125 MHz, $CDCl_3$)

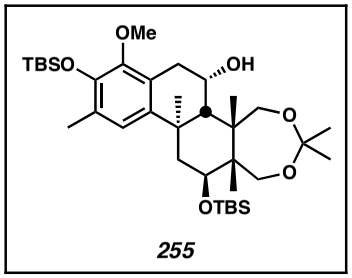


Figure A5.112 ^{1}H NMR of compound **255** (500 MHz, $CDCl_3$)

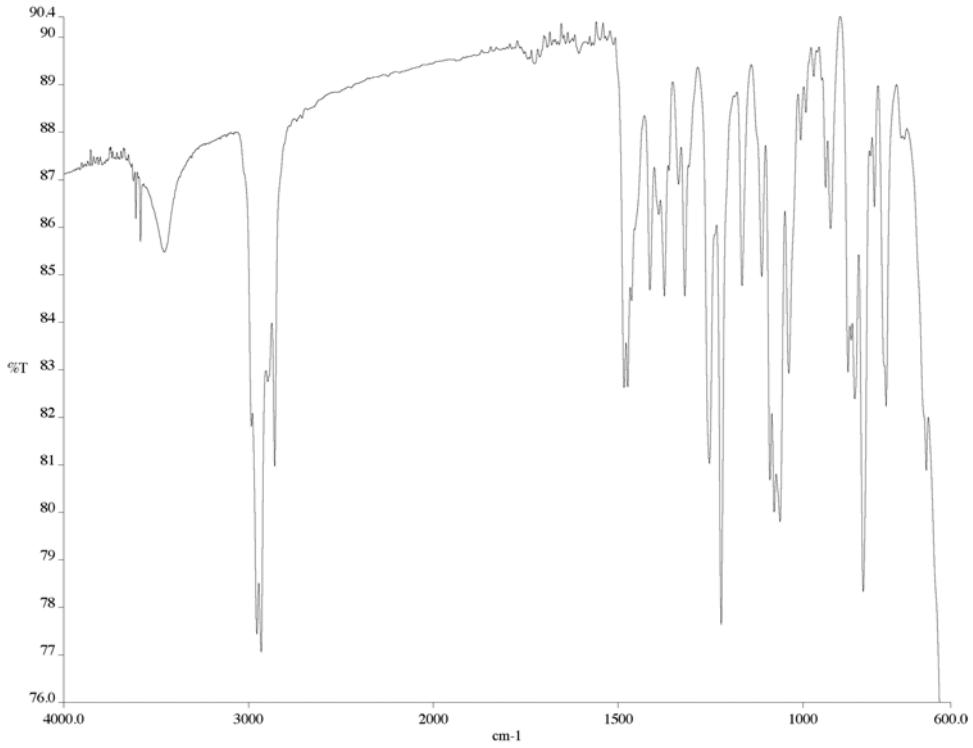


Figure A5.113 IR of compound **255** (NaCl/film)

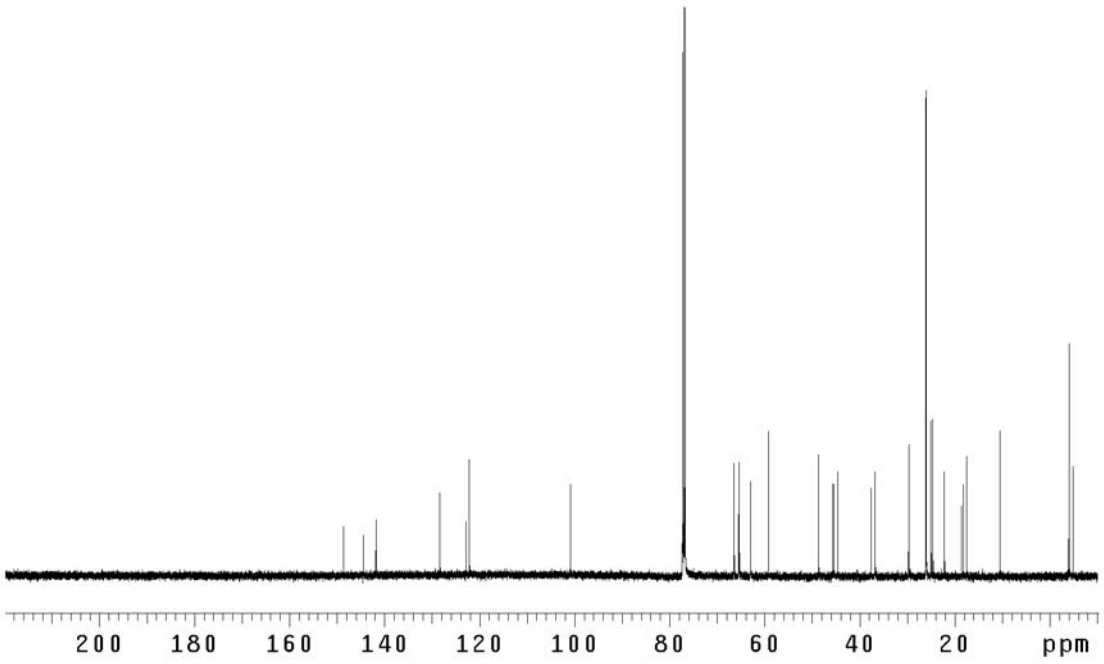


Figure A5.114 ^{13}C NMR of compound **255** (125 MHz, $CDCl_3$)

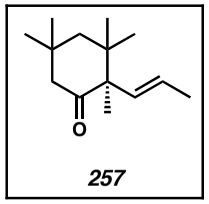


Figure A5.115 ^{1}H NMR of compound **257** (300 MHz, $CDCl_3$)

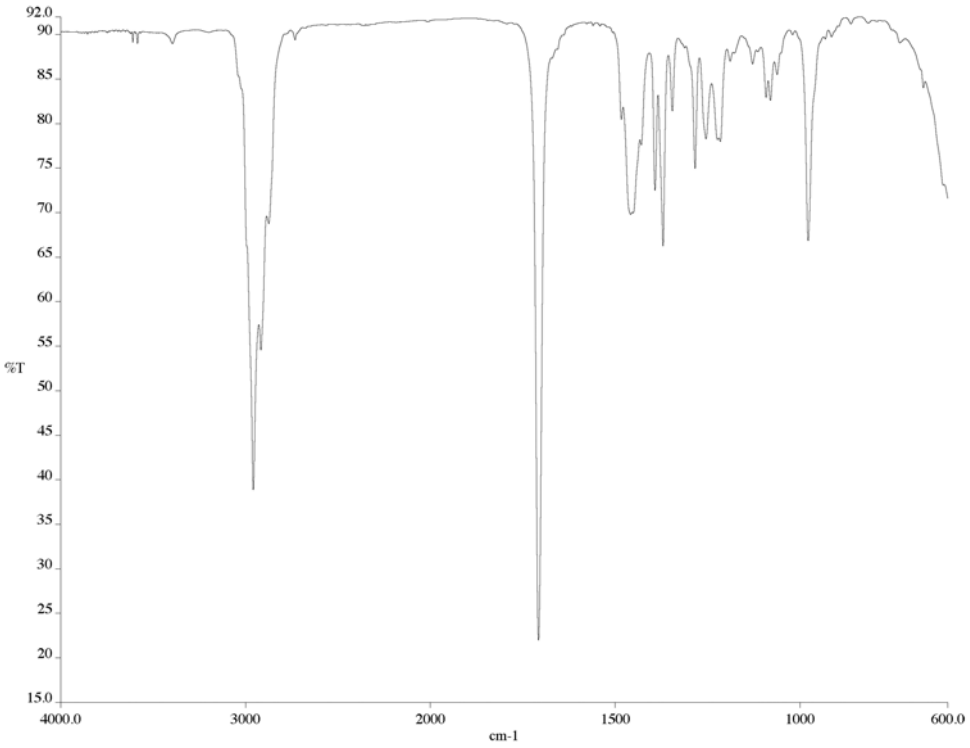


Figure A5.116 IR of compound ***257*** (NaCl/film)

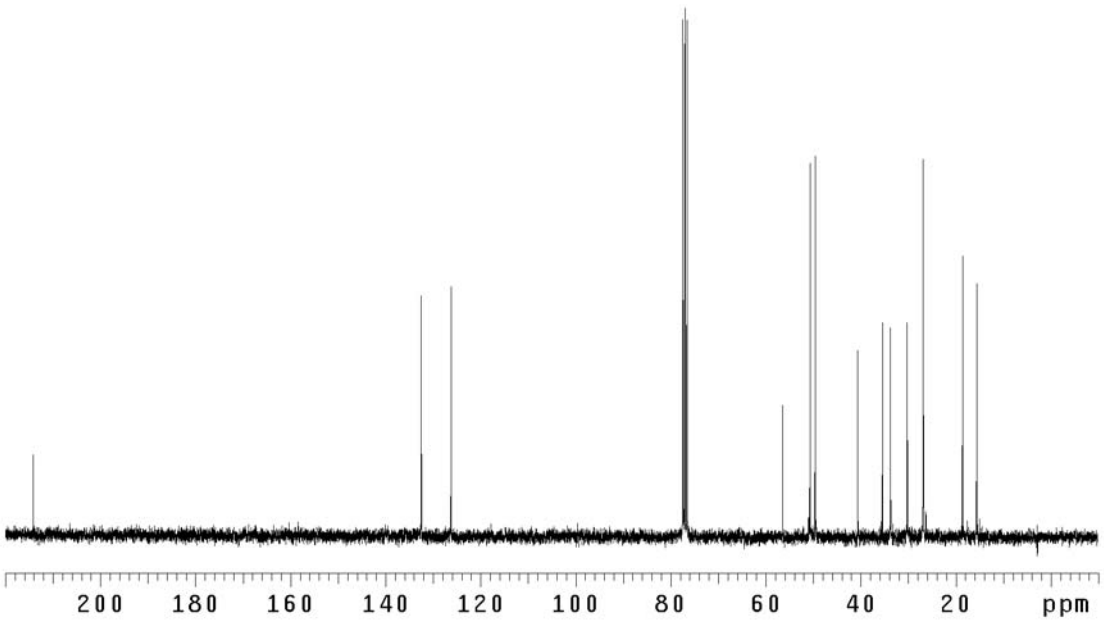


Figure A5.117 ^{13}C NMR of compound ***257*** (75 MHz, $CDCl_3$)

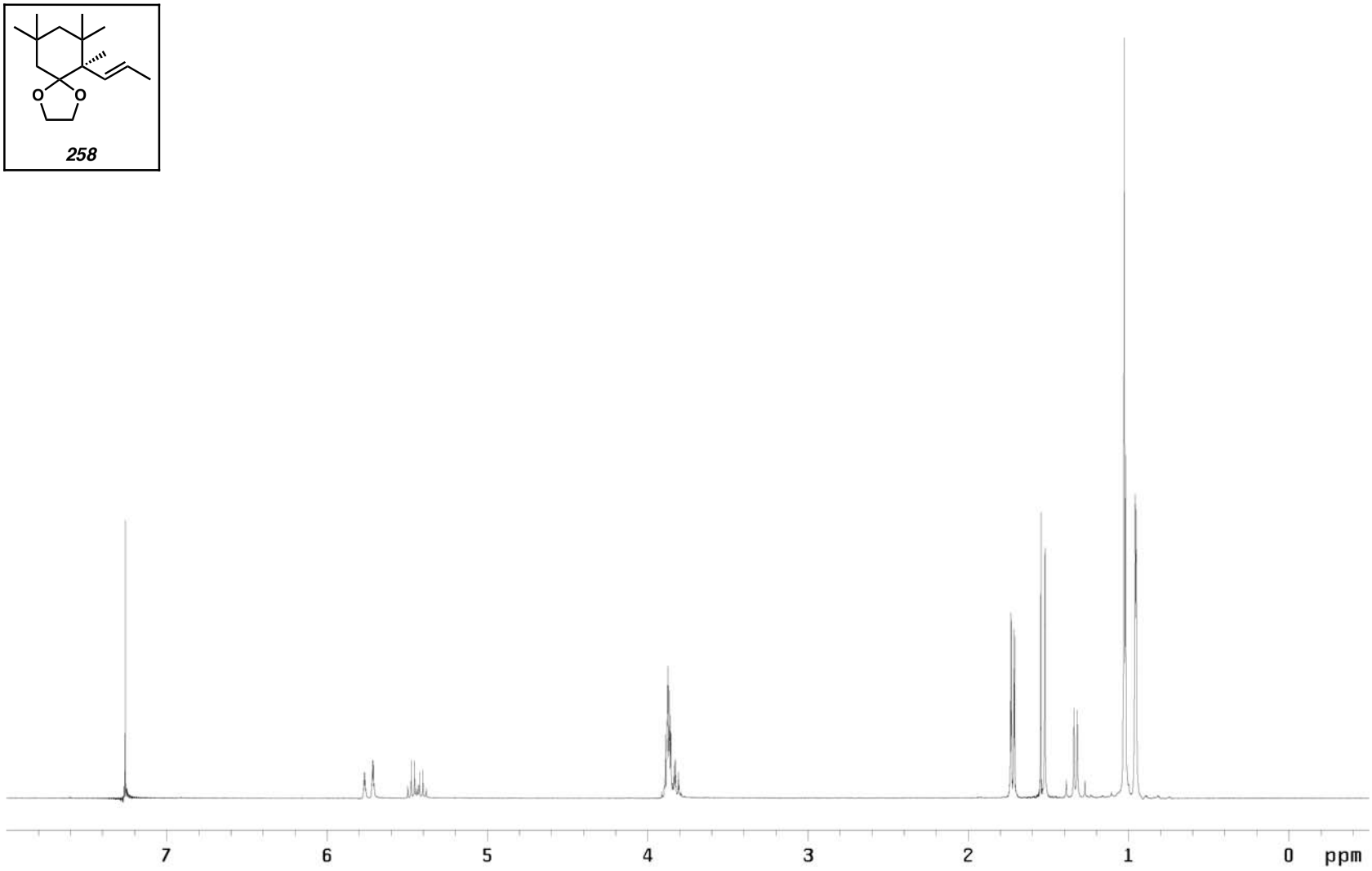


Figure A5.118 ^{1}H NMR of compound **258** (300 MHz, $CDCl_3$)

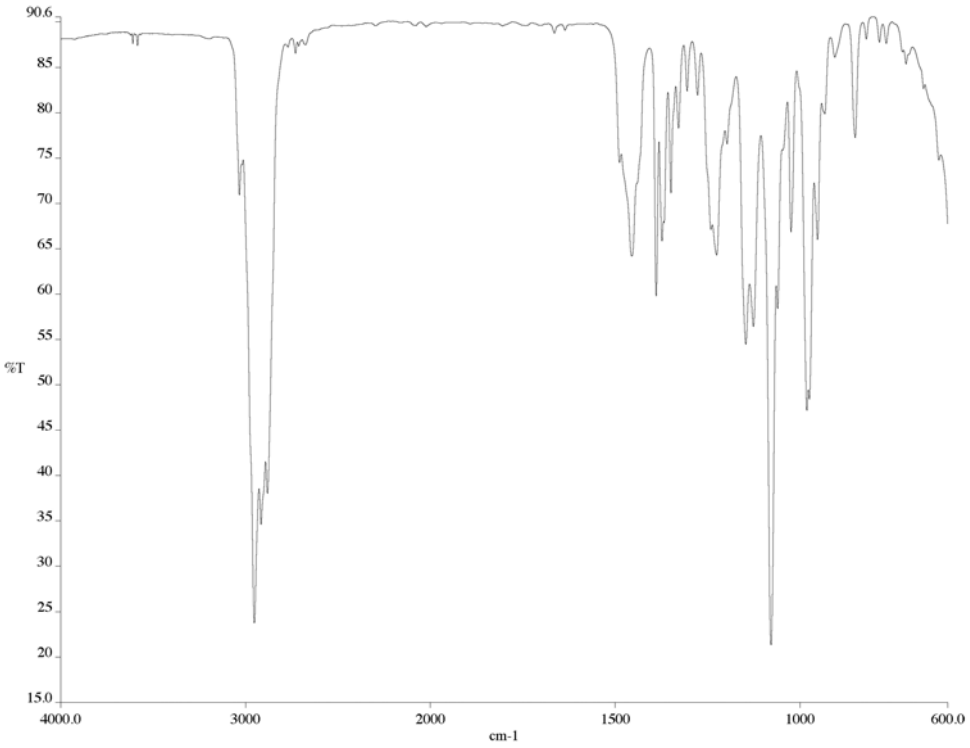


Figure A5.119 IR of compound **258** (NaCl/film)

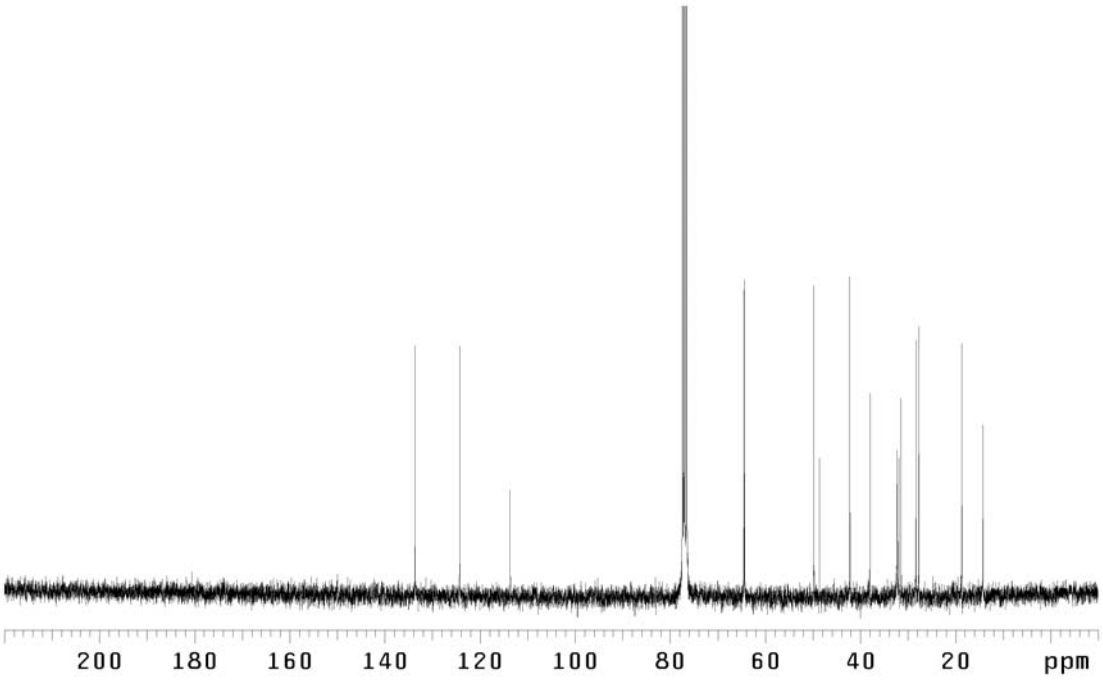
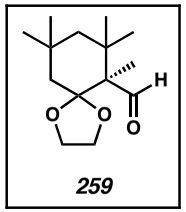


Figure A5.120 ^{13}C NMR of compound **258** (75 MHz, $CDCl_3$)



259

Figure A5.121 ^{1}H NMR of compound **259** (300 MHz, $CDCl_3$)

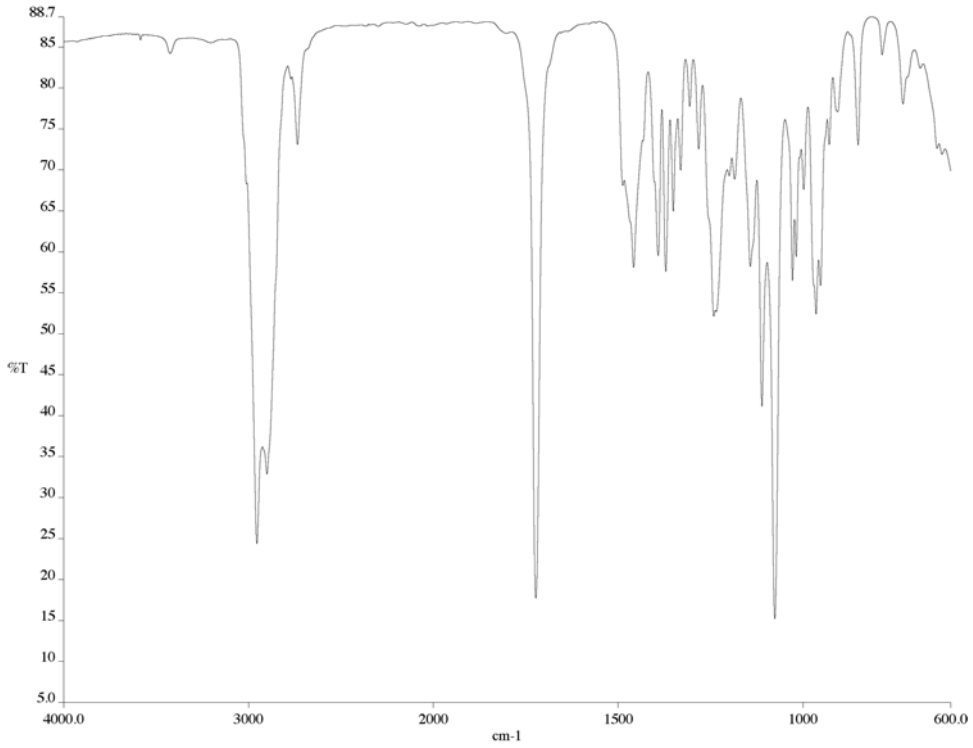


Figure A5.122 IR of compound **259** (NaCl/film)

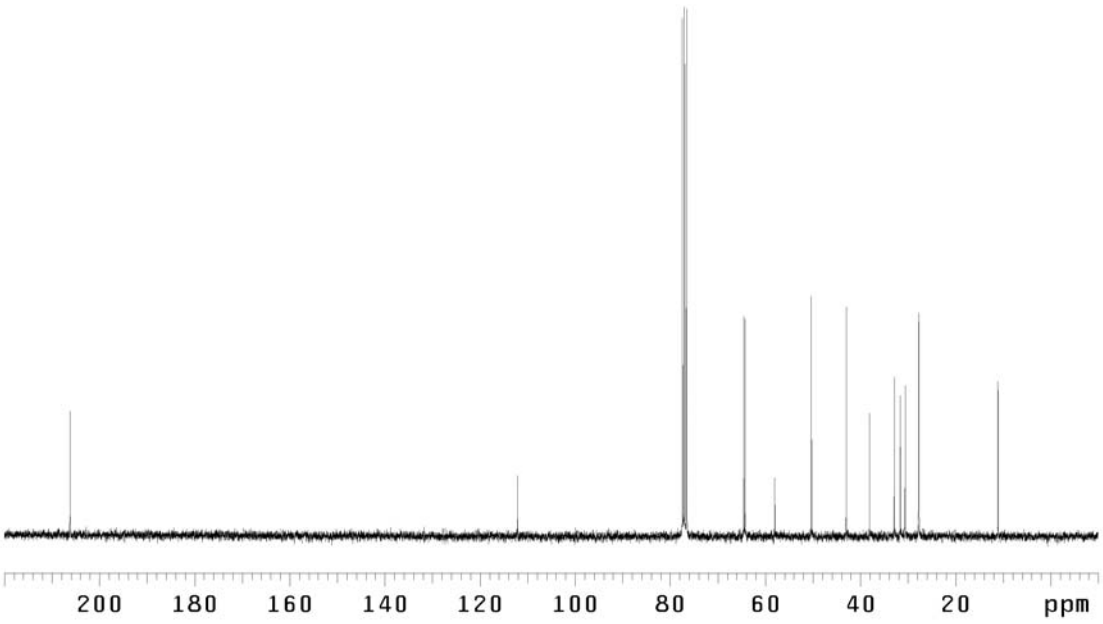


Figure A5.123 ^{13}C NMR of compound **259** (75 MHz, $CDCl_3$)

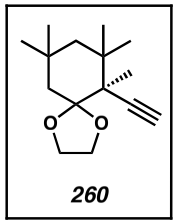


Figure A5.124 ^{1}H NMR of compound **260** (300 MHz, $CDCl_3$)

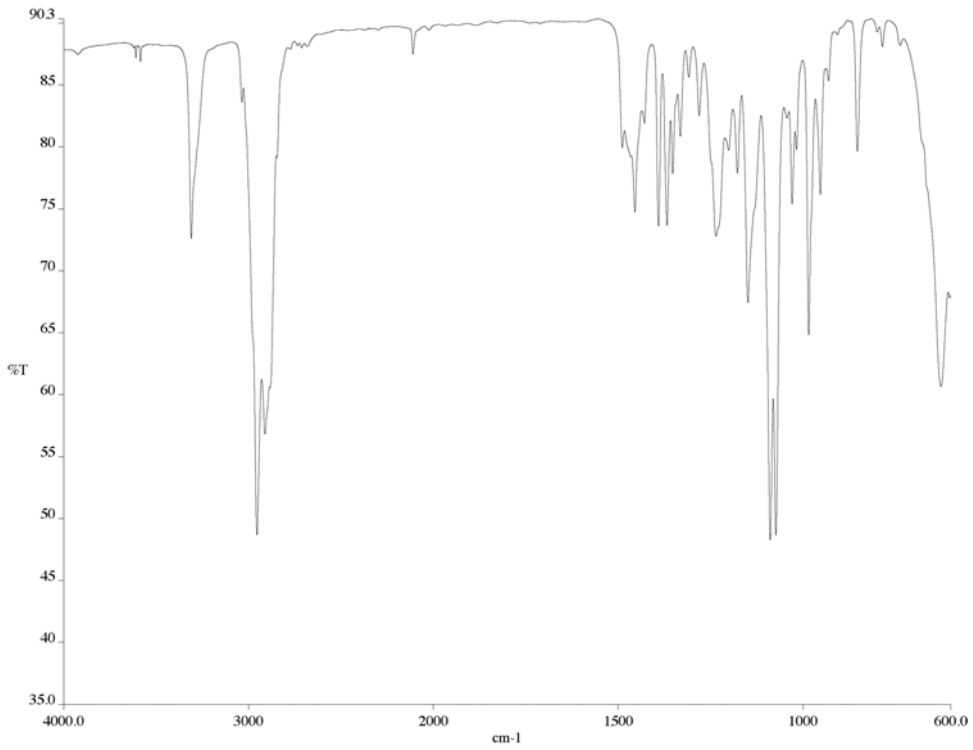


Figure A5.125 IR of compound **260** (NaCl/film)

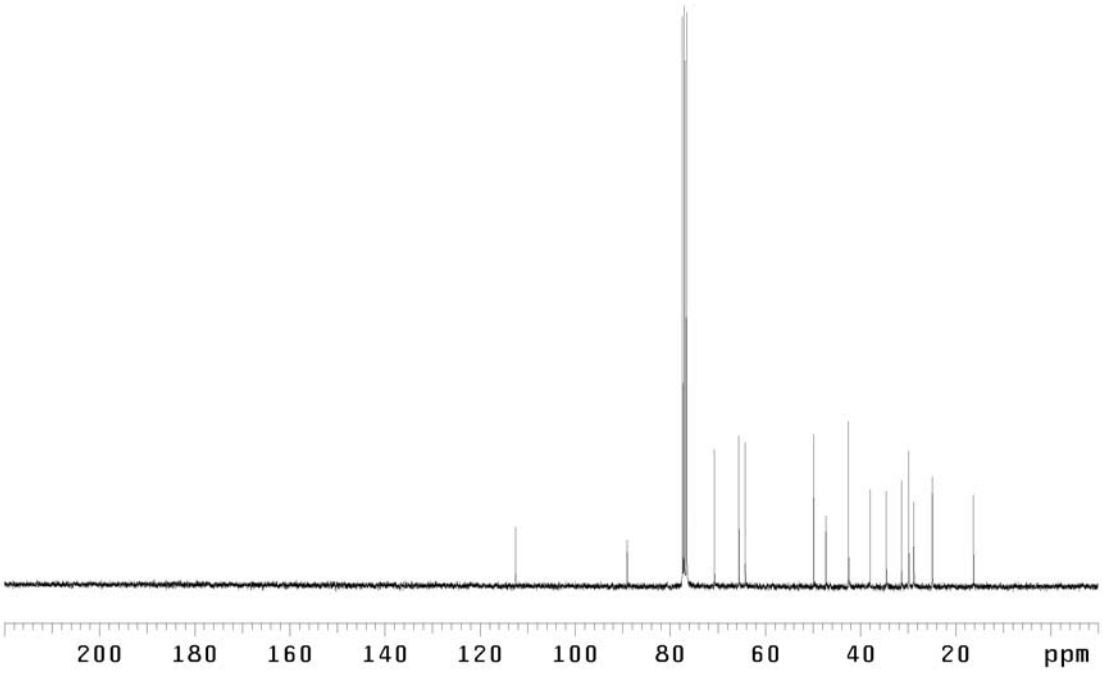
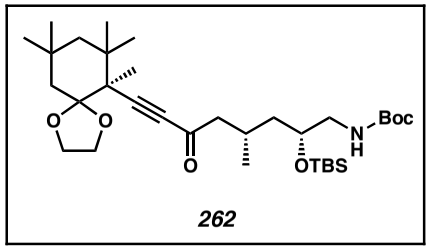


Figure A5.126 ^{13}C NMR of compound **260** (75 MHz, $CDCl_3$)



262

Figure A5.127 ^{1}H NMR of compound **262** (500 MHz, $CDCl_3$)

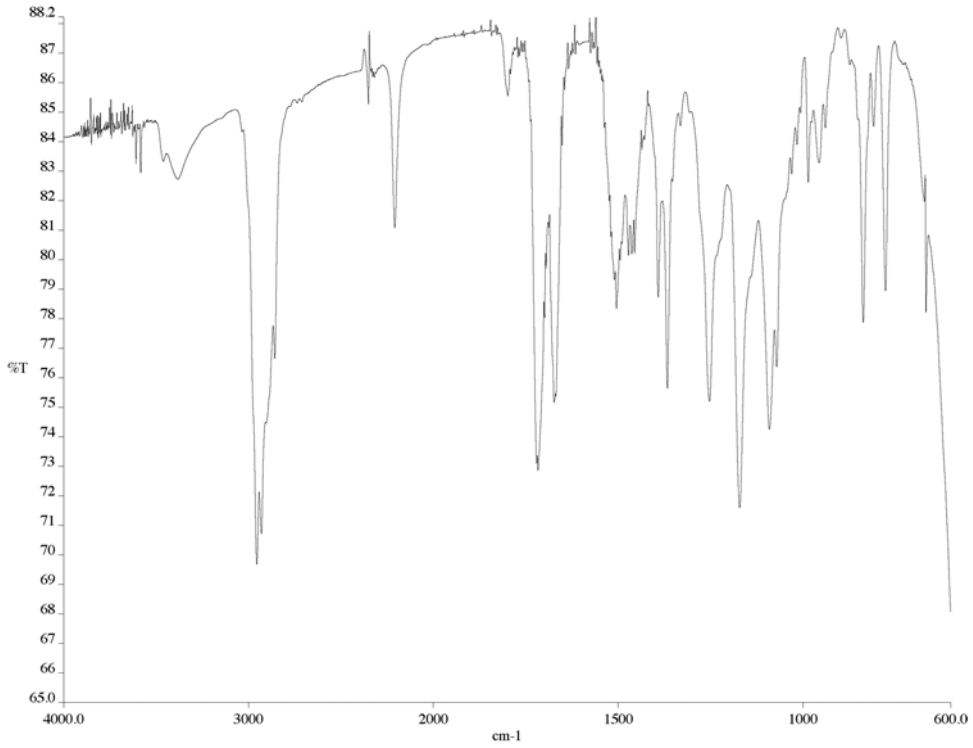


Figure A5.128 IR of compound **262** (NaCl/film)

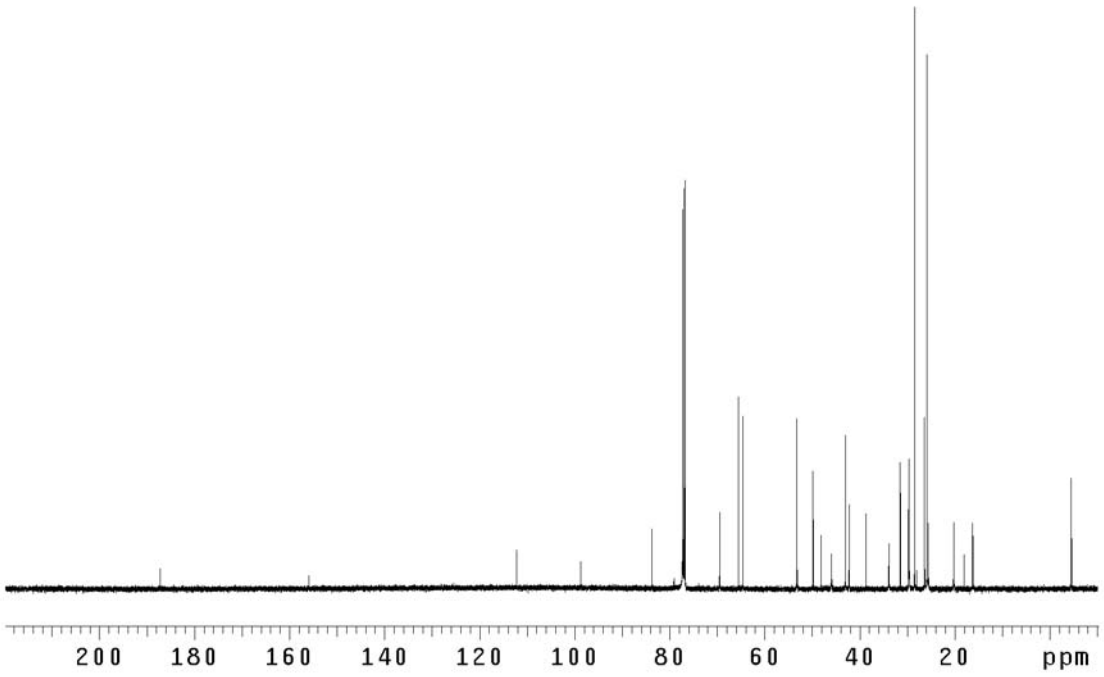
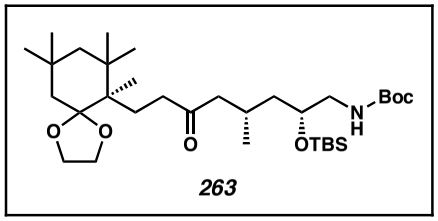


Figure A5.129 ^{13}C NMR of compound **262** (125 MHz, $CDCl_3$)



263

Figure A5.130 ^{1}H NMR of compound **263** (500 MHz, $CDCl_3$)

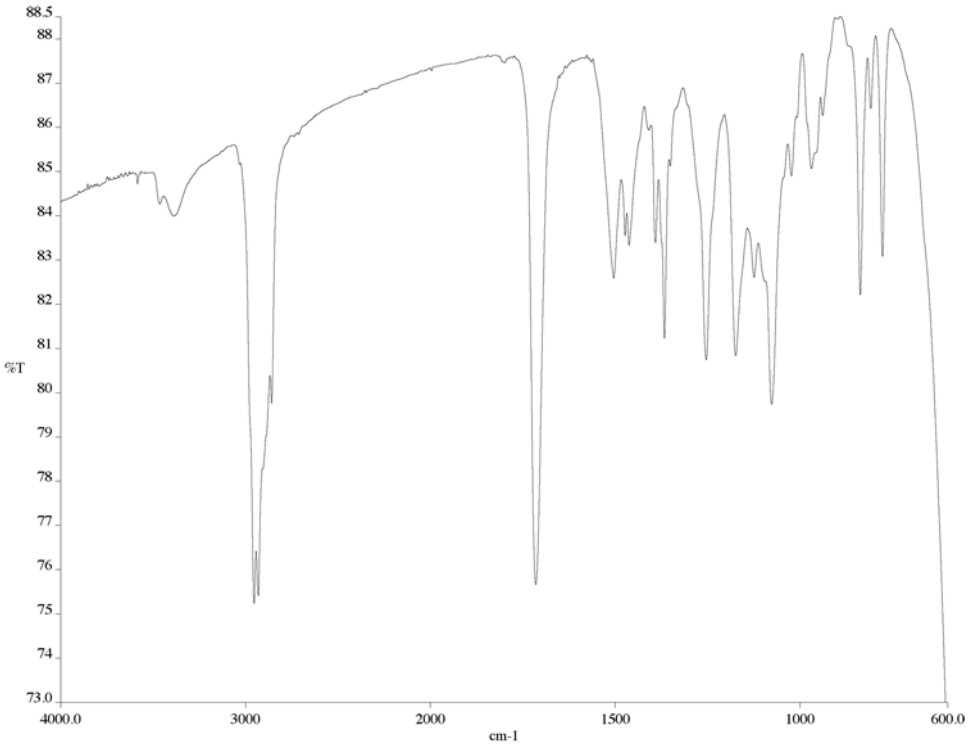


Figure A5.131 IR of compound **263** (NaCl/film)

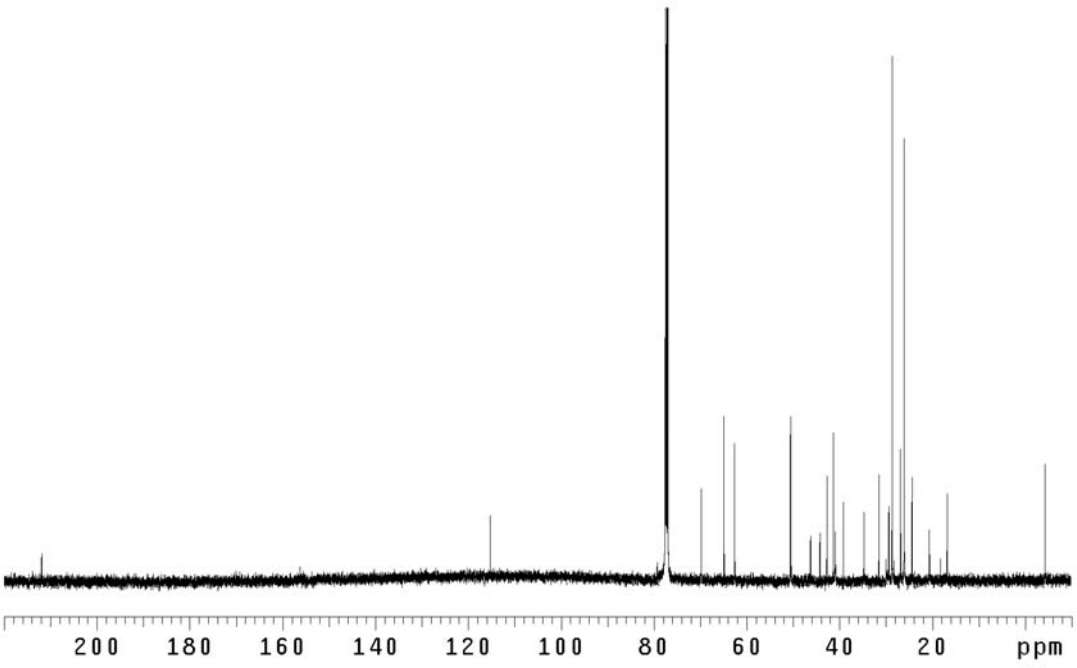


Figure A5.132 ^{13}C NMR of compound **263** (125 MHz, $CDCl_3$)

APPENDIX SIX

X-Ray Crystallographic Data Relevant to Chapter Three

CALIFORNIA INSTITUTE OF TECHNOLOGY

BECKMAN INSTITUTE

X-RAY CRYSTALLOGRAPHY LABORATORY

Crystal Structure Analysis of:

Allylic Alcohol 211 (DCB30)

(CCDC 277462)

Contents:

Table 1. Crystal data
Table 2. Atomic coordinates
Table 3. Full bond distances and angles
Table 4. Anisotropic displacement parameters
Table 5. Hydrogen atomic coordinates
Table 6. Hydrogen bond distances and angles

Figure A6.1 Representation of Allylic Alcohol **211**

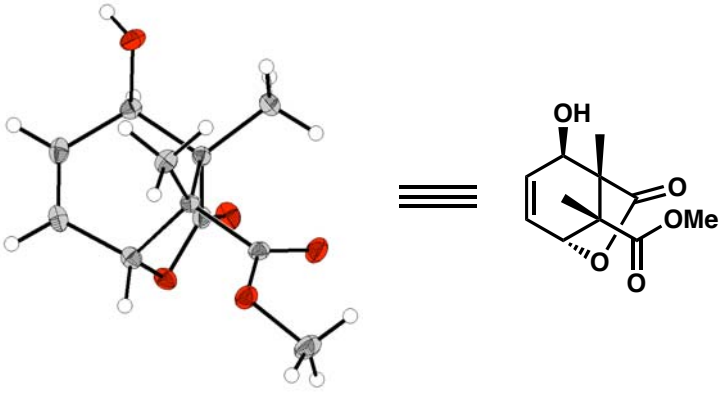


Table 1. Crystal data and structure refinement for DCB30 (CCDC 277462).

Empirical formula	$C_{11}H_{14}O_5$
Formula weight	226.22
Crystallization Solvent	Heptane/diethylether
Crystal Habit	Fragment
Crystal size	0.41 x 0.24 x 0.16 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 8068 reflections used in lattice determination	2.74 to 39.14°
Unit cell dimensions	a = 8.5469(4) Å b = 8.7203(4) Å c = 14.1988(6) Å
Volume	1058.26(8) $Å^3$
Z	4
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Density (calculated)	1.420 Mg/m^3
F(000)	480
Data collection program	Bruker SMART v5.630
θ range for data collection	2.74 to 40.70°
Completeness to θ = 40.70°	92.3 %
Index ranges	$-15 \le h \le 13$, $-15 \le k \le 15$, $-25 \le l \le 23$
Data collection scan type	ω scans at 5 ϕ settings
Data reduction program	Bruker SAINT v6.45A
Reflections collected	19516
Independent reflections	6114 [R_{int}= 0.0607]
Absorption coefficient	0.113 mm^{-1}
Absorption correction	None
Max. and min. transmission	0.9822 and 0.9553

Table 1 (cont.)

Structure solution and Refinement

Structure solution program	Bruker XS v6.12
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Difference Fourier map
Structure refinement program	Bruker XL v6.12
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	6114 / 0 / 201
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F^2	1.304
Final R indices [I>2σ(I), 4485 reflections]	R1 = 0.0415, *w*R2 = 0.0690
R indices (all data)	R1 = 0.0621, *w*R2 = 0.0715
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.001
Average shift/error	0.000
Absolute structure determination	Not possible to reliably determine absolute configuration
Absolute structure parameter	-0.2(6)
Largest diff. peak and hole	0.427 and -0.273 e.Å^{-3}

Special Refinement Details

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

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

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for DCB30 (CCDC 277462). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
O(1)	1165(1)	11191(1)	7918(1)	16(1)
O(2)	1872(1)	13004(1)	8946(1)	21(1)
O(3)	4173(1)	9617(1)	8803(1)	21(1)
O(4)	3237(1)	7678(1)	7931(1)	18(1)
O(5)	-878(1)	9680(1)	10618(1)	19(1)
C(1)	-1241(1)	9774(1)	8195(1)	17(1)
C(2)	492(1)	9626(1)	8002(1)	15(1)
C(3)	1380(1)	8989(1)	8868(1)	12(1)
C(4)	1180(1)	10414(1)	9520(1)	12(1)
C(5)	-565(1)	10628(1)	9813(1)	14(1)
C(6)	-1706(1)	10259(1)	9031(1)	17(1)
C(7)	1471(1)	11701(1)	8802(1)	14(1)
C(8)	2214(1)	10544(1)	10395(1)	16(1)
C(9)	763(1)	7465(1)	9253(1)	16(1)
C(10)	3095(1)	8815(1)	8558(1)	14(1)
C(11)	4809(1)	7460(1)	7566(1)	23(1)

Table 3. Bond lengths [Å] and angles [°] for DCB30 (CCDC 277462).

O(1)-C(7)	1.3559(11)	C(8)-C(4)-C(7)	113.05(7)
O(1)-C(2)	1.4855(11)	C(8)-C(4)-C(3)	118.58(7)
O(2)-C(7)	1.2050(11)	C(7)-C(4)-C(3)	99.84(6)
O(3)-C(10)	1.2082(11)	C(8)-C(4)-C(5)	109.06(7)
O(4)-C(10)	1.3387(11)	C(7)-C(4)-C(5)	104.16(7)
O(4)-C(11)	1.4519(12)	C(3)-C(4)-C(5)	111.03(7)
O(5)-C(5)	1.4350(11)	O(5)-C(5)-C(6)	110.00(7)
O(5)-H(5A)	0.783(13)	O(5)-C(5)-C(4)	108.75(7)
C(1)-C(6)	1.3223(13)	C(6)-C(5)-C(4)	113.26(7)
C(1)-C(2)	1.5115(13)	O(5)-C(5)-H(5)	109.9(6)
C(1)-H(1)	0.973(11)	C(6)-C(5)-H(5)	108.8(6)
C(2)-C(3)	1.5486(12)	C(4)-C(5)-H(5)	106.0(6)
C(2)-H(2)	0.989(9)	C(1)-C(6)-C(5)	122.26(8)
C(3)-C(9)	1.5301(12)	C(1)-C(6)-H(6)	120.8(6)
C(3)-C(10)	1.5380(13)	C(5)-C(6)-H(6)	116.9(6)
C(3)-C(4)	1.5586(12)	O(2)-C(7)-O(1)	121.44(8)
C(4)-C(8)	1.5294(12)	O(2)-C(7)-C(4)	128.47(8)
C(4)-C(7)	1.5365(12)	O(1)-C(7)-C(4)	110.07(7)
C(4)-C(5)	1.5600(12)	C(4)-C(8)-H(8A)	108.8(6)
C(5)-C(6)	1.5120(13)	C(4)-C(8)-H(8B)	108.5(7)
C(5)-H(5)	0.994(11)	H(8A)-C(8)-H(8B)	109.1(9)
C(6)-H(6)	0.951(10)	C(4)-C(8)-H(8C)	112.1(7)
C(8)-H(8A)	1.025(12)	H(8A)-C(8)-H(8C)	105.7(10)
C(8)-H(8B)	0.977(11)	H(8B)-C(8)-H(8C)	112.6(10)
C(8)-H(8C)	0.976(12)	C(3)-C(9)-H(9A)	110.7(6)
C(9)-H(9A)	0.987(11)	C(3)-C(9)-H(9B)	111.9(7)
C(9)-H(9B)	0.952(11)	H(9A)-C(9)-H(9B)	104.0(9)
C(9)-H(9C)	0.952(12)	C(3)-C(9)-H(9C)	110.2(7)
C(11)-H(11A)	0.967(12)	H(9A)-C(9)-H(9C)	108.6(9)
C(11)-H(11B)	0.940(13)	H(9B)-C(9)-H(9C)	111.2(10)
C(11)-H(11C)	0.962(12)	O(3)-C(10)-O(4)	123.45(8)
		O(3)-C(10)-C(3)	125.99(8)
C(7)-O(1)-C(2)	107.57(7)	O(4)-C(10)-C(3)	110.48(7)
C(10)-O(4)-C(11)	114.73(8)	O(4)-C(11)-H(11A)	107.9(7)
C(5)-O(5)-H(5A)	104.1(10)	O(4)-C(11)-H(11B)	106.0(8)
C(6)-C(1)-C(2)	119.00(8)	H(11A)-C(11)-H(11B)	111.7(10)
C(6)-C(1)-H(1)	122.2(6)	O(4)-C(11)-H(11C)	108.7(7)
C(2)-C(1)-H(1)	118.8(6)	H(11A)-C(11)-H(11C)	111.6(9)
O(1)-C(2)-C(1)	108.39(7)	H(11B)-C(11)-H(11C)	110.6(10)
O(1)-C(2)-C(3)	101.75(7)		
C(1)-C(2)-C(3)	111.51(7)		
O(1)-C(2)-H(2)	105.7(6)		
C(1)-C(2)-H(2)	112.9(6)		
C(3)-C(2)-H(2)	115.6(5)		
C(9)-C(3)-C(10)	110.19(7)		
C(9)-C(3)-C(2)	115.23(8)		
C(10)-C(3)-C(2)	105.96(7)		
C(9)-C(3)-C(4)	116.29(7)		
C(10)-C(3)-C(4)	110.65(7)		
C(2)-C(3)-C(4)	97.55(7)		

Table 4. Anisotropic displacement parameters ($Å^2 x 10^4$) for DCB30 (CCDC 277462). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	203(3)	149(3)	142(3)	30(2)	-26(3)	-27(3)
O(2)	239(4)	146(3)	239(3)	28(3)	-42(3)	-47(3)
O(3)	154(3)	239(4)	236(3)	-25(3)	30(3)	-54(3)
O(4)	154(3)	204(3)	196(3)	-37(3)	29(3)	16(3)
O(5)	178(3)	213(3)	185(3)	47(3)	60(3)	34(3)
C(1)	159(4)	156(4)	203(4)	11(3)	-58(3)	-11(4)
C(2)	167(4)	130(4)	149(4)	-4(3)	-18(3)	-17(4)
C(3)	129(4)	116(4)	122(3)	8(3)	3(3)	-2(3)
C(4)	120(4)	119(4)	124(3)	11(3)	-4(3)	0(3)
C(5)	147(4)	127(4)	144(4)	9(3)	21(3)	14(3)
C(6)	129(4)	162(4)	230(4)	24(3)	-19(3)	10(4)
C(7)	118(4)	149(4)	157(4)	18(3)	-10(3)	3(3)
C(8)	163(4)	190(5)	138(4)	6(3)	-24(3)	-5(4)
C(9)	154(4)	117(4)	201(4)	11(3)	21(4)	-5(4)
C(10)	148(4)	151(4)	120(4)	32(3)	18(3)	10(4)
C(11)	191(5)	259(6)	230(5)	-5(4)	75(4)	52(4)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for DCB30 (CCDC 277462).

	x	y	z	U_{iso}
H(5A)	-1603(15)	10067(15)	10856(9)	35(4)
H(1)	-1977(13)	9484(13)	7703(7)	18(3)
H(2)	719(11)	9112(11)	7397(7)	6(2)
H(5)	-680(12)	11727(13)	9986(7)	15(3)
H(6)	-2786(12)	10404(12)	9164(7)	14(3)
H(8A)	1942(13)	11540(14)	10742(8)	23(3)
H(8B)	1993(13)	9673(14)	10807(7)	23(3)
H(8C)	3321(14)	10627(15)	10235(8)	29(3)
H(9A)	1386(12)	7128(12)	9800(8)	17(3)
H(9B)	-271(13)	7561(12)	9496(8)	17(3)
H(9C)	815(14)	6693(14)	8779(8)	27(3)
H(11A)	5491(14)	7243(13)	8093(8)	20(3)
H(11B)	4748(14)	6625(15)	7148(9)	29(3)
H(11C)	5121(13)	8376(14)	7239(8)	20(3)

Table 6. Hydrogen bonds for DCB30 (CCDC 277462) [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(5)-H(5A)...O(2)#1	0.783(13)	2.147(13)	2.8567(10)	151.0(13)

Symmetry transformations used to generate equivalent atoms:
#1 x-1/2,-y+5/2,-z+2

CALIFORNIA INSTITUTE OF TECHNOLOGY

BECKMAN INSTITUTE

X-RAY CRYSTALLOGRAPHY LABORATORY

Crystal Structure Analysis of:

Allylic Alcohol 217 (DCB31)

(CCDC 283708)

Contents:

Table 1. Crystal data
Table 2. Atomic coordinates
Table 3. Full bond distances and angles
Table 4. Anisotropic displacement parameters
Table 5. Hydrogen atomic coordinates
Table 6. Hydrogen-bond distances and angles

Figure A6.2 Representation of Allylic Alcohol **217**

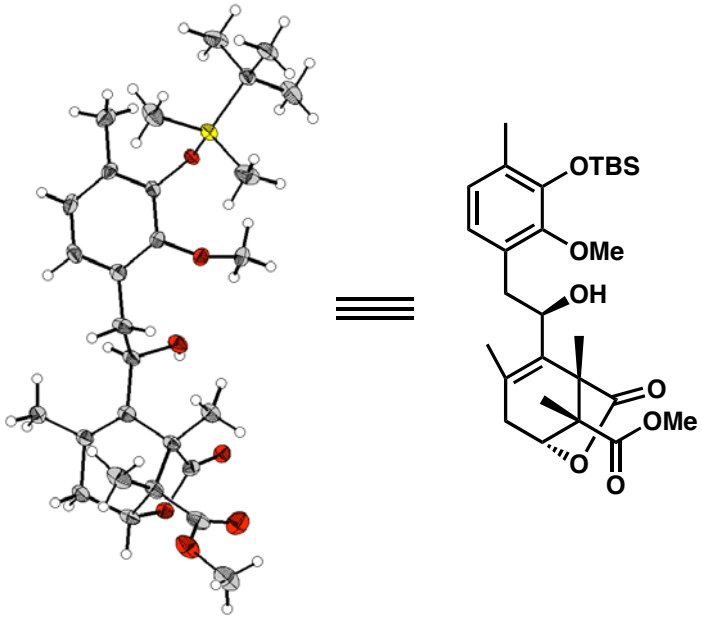


Table 1. Crystal data and structure refinement for DCB31 (CCDC 283708).

Empirical formula	$C_{28}H_{42}O_7$ Si	
Formula weight	518.71	
Crystallization Solvent	EtOAc/heptane	
Crystal Habit	Block	
Crystal size	0.32 x 0.31 x 0.22 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 15772 reflections used in lattice determination	2.32 to 28.21°	
Unit cell dimensions	a = 12.6604(8) Å b = 15.4100(10) Å c = 15.7147(10) Å	α= 81.0750(10)° β= 66.6280(10)° γ = 87.6100(10)°
Volume	2779.6(3) $Å^3$	
Z	4	
Crystal system	Triclinic	
Space group	P-1	
Density (calculated)	1.240 Mg/m^3	
F(000)	1120	
Data collection program	Bruker SMART v5.630	
θ range for data collection	1.75 to 28.27°	
Completeness to θ = 28.27°	92.1 %	
Index ranges	$-16 \le h \le 16, -20 \le k \le 19, -20 \le l \le 20$	
Data collection scan type	ω scans at 7 ϕ settings	
Data reduction program	Bruker SAINT v6.45A	
Reflections collected	56601	
Independent reflections	12691 [R_{int}= 0.0626]	
Absorption coefficient	0.127 mm^{-1}	
Absorption correction	None	
Max. and min. transmission	0.9725 and 0.9604	

Table 1 (cont.)

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 1990)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Difference Fourier map
Structure refinement program	SHELXL-97 (Sheldrick, 1997)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	12691 / 0 / 985
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F^2	1.502
Final R indices [$I>2\sigma(I)$, 7901 reflections]	R1 = 0.0455, *w*R2 = 0.0721
R indices (all data)	R1 = 0.0839, *w*R2 = 0.0763
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.003
Average shift/error	0.000
Largest diff. peak and hole	0.492 and -0.382 e.Å^{-3}

Special Refinement Details

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

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

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for DCB31 (CCDC 283708). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
Si(1)	-42(1)	510(1)	2060(1)	21(1)
O(1A)	816(1)	1084(1)	2346(1)	19(1)
O(2A)	1297(1)	2515(1)	937(1)	23(1)
O(3A)	3033(1)	4131(1)	770(1)	26(1)
O(4A)	3980(1)	6315(1)	-2542(1)	37(1)
O(5A)	2422(1)	7069(1)	-2515(1)	38(1)
O(6A)	4208(1)	6810(1)	-903(1)	21(1)
O(7A)	4924(1)	5456(1)	-917(1)	22(1)
C(1A)	646(1)	1925(1)	2572(1)	18(1)
C(2A)	899(1)	2648(1)	1864(1)	18(1)
C(3A)	719(1)	3501(1)	2073(1)	21(1)
C(4A)	306(2)	3607(1)	3011(1)	27(1)
C(5A)	107(2)	2895(1)	3709(1)	26(1)
C(6A)	276(1)	2039(1)	3508(1)	20(1)
C(7A)	81(2)	1260(1)	4263(1)	29(1)
C(8A)	2448(2)	2186(2)	597(2)	28(1)
C(9A)	166(2)	811(2)	810(2)	38(1)
C(10A)	-1553(2)	709(2)	2806(2)	35(1)
C(11A)	375(1)	-659(1)	2268(1)	22(1)
C(12A)	-338(2)	-1258(1)	1990(2)	30(1)
C(13A)	1656(2)	-771(2)	1691(2)	37(1)
C(14A)	138(2)	-938(1)	3311(1)	34(1)
C(15A)	999(2)	4291(1)	1317(1)	25(1)
C(16A)	2140(1)	4736(1)	1130(1)	21(1)
C(17A)	2349(1)	5629(1)	503(1)	20(1)
C(18A)	2866(1)	5673(1)	-583(1)	20(1)
C(19A)	2473(1)	6519(1)	-1042(1)	24(1)
C(20A)	3079(2)	7190(1)	-749(1)	24(1)
C(21A)	2454(2)	7262(1)	276(1)	24(1)
C(22A)	2158(1)	6374(1)	879(1)	22(1)
C(23A)	1640(2)	6435(1)	1910(1)	29(1)
C(24A)	2706(2)	4851(1)	-947(1)	25(1)
C(25A)	4114(2)	5923(1)	-833(1)	20(1)
C(26A)	1171(2)	6613(2)	-701(2)	35(1)
C(27A)	3055(2)	6601(1)	-2107(1)	28(1)
C(28A)	2900(3)	7207(2)	-3527(2)	44(1)
Si(2)	5149(1)	9590(1)	2638(1)	21(1)
O(1B)	4218(1)	9004(1)	2444(1)	20(1)
O(2B)	3743(1)	7599(1)	3860(1)	24(1)
O(3B)	1918(1)	5944(1)	4116(1)	26(1)
O(4B)	1344(1)	3774(1)	7408(1)	34(1)
O(5B)	2918(1)	2985(1)	7232(1)	32(1)
O(6B)	863(1)	3261(1)	5877(1)	21(1)
O(7B)	126(1)	4607(1)	5934(1)	23(1)
C(1B)	4350(1)	8159(1)	2224(1)	17(1)
C(2B)	4097(1)	7444(1)	2943(1)	18(1)

C(3B)	4225(1)	6587(1)	2749(1)	21(1)
C(4B)	4584(1)	6466(1)	1817(1)	24(1)
C(5B)	4779(1)	7171(1)	1112(1)	24(1)
C(6B)	4666(1)	8032(1)	1295(1)	19(1)
C(7B)	4854(2)	8801(1)	525(1)	26(1)
C(8B)	2574(2)	7893(1)	4228(1)	29(1)
C(9B)	5680(2)	8968(1)	3484(2)	29(1)
C(10B)	6404(2)	9919(2)	1510(2)	33(1)
C(11B)	4327(2)	10573(1)	3092(1)	25(1)
C(12B)	5122(2)	11175(1)	3282(2)	32(1)
C(13B)	3289(2)	10289(2)	4020(2)	46(1)
C(14B)	3894(2)	11088(2)	2385(2)	46(1)
C(15B)	3966(2)	5805(1)	3514(1)	25(1)
C(16B)	2821(1)	5350(1)	3733(1)	19(1)
C(17B)	2636(1)	4457(1)	4354(1)	19(1)
C(18B)	2219(1)	4416(1)	5438(1)	19(1)
C(19B)	2690(1)	3582(1)	5839(1)	22(1)
C(20B)	2018(2)	2897(1)	5624(1)	22(1)
C(21B)	2507(2)	2827(1)	4603(1)	22(1)
C(22B)	2764(1)	3713(1)	3988(1)	20(1)
C(23B)	3189(2)	3634(1)	2963(1)	26(1)
C(24B)	2419(2)	5244(1)	5771(1)	23(1)
C(25B)	955(2)	4150(1)	5785(1)	19(1)
C(26B)	3999(2)	3506(2)	5394(2)	29(1)
C(27B)	2231(2)	3484(1)	6908(1)	25(1)
C(28B)	2541(2)	2794(2)	8236(1)	35(1)

Table 3. Bond lengths [Å] and angles [°] for DCB31 (CCDC 283708).

Si(1)-O(1A)	1.6602(11)	C(15A)-H(15B)	1.012(16)
Si(1)-C(10A)	1.847(2)	C(16A)-C(17A)	1.529(2)
Si(1)-C(9A)	1.860(2)	C(16A)-H(16A)	1.032(13)
Si(1)-C(11A)	1.8719(17)	C(17A)-C(22A)	1.342(2)
O(1A)-C(1A)	1.3834(18)	C(17A)-C(18A)	1.559(2)
O(2A)-C(2A)	1.3854(18)	C(18A)-C(25A)	1.520(2)
O(2A)-C(8A)	1.440(2)	C(18A)-C(24A)	1.519(2)
O(3A)-C(16A)	1.4266(19)	C(18A)-C(19A)	1.552(2)
O(3A)-H(3A)	0.92(2)	C(19A)-C(26A)	1.525(2)
O(4A)-C(27A)	1.203(2)	C(19A)-C(27A)	1.525(2)
O(5A)-C(27A)	1.337(2)	C(19A)-C(20A)	1.538(2)
O(5A)-C(28A)	1.442(2)	C(20A)-C(21A)	1.506(2)
O(6A)-C(25A)	1.3611(19)	C(20A)-H(20A)	1.015(16)
O(6A)-C(20A)	1.4637(19)	C(21A)-C(22A)	1.505(2)
O(7A)-C(25A)	1.2020(18)	C(21A)-H(21A)	0.976(15)
C(1A)-C(2A)	1.394(2)	C(21A)-H(21B)	1.002(16)
C(1A)-C(6A)	1.393(2)	C(22A)-C(23A)	1.505(2)
C(2A)-C(3A)	1.392(2)	C(23A)-H(23A)	0.95(2)
C(3A)-C(4A)	1.389(2)	C(23A)-H(23B)	0.963(19)
C(3A)-C(15A)	1.508(2)	C(23A)-H(23C)	0.98(2)
C(4A)-C(5A)	1.378(2)	C(24A)-H(24A)	0.973(16)
C(4A)-H(4A)	0.933(16)	C(24A)-H(24B)	1.022(16)
C(5A)-C(6A)	1.392(2)	C(24A)-H(24C)	0.984(16)
C(5A)-H(5A)	0.918(15)	C(26A)-H(26A)	1.042(16)
C(6A)-C(7A)	1.504(2)	C(26A)-H(26B)	0.994(18)
C(7A)-H(7A1)	0.978(19)	C(26A)-H(26C)	0.944(18)
C(7A)-H(7A2)	0.991(17)	C(28A)-H(28A)	0.96(2)
C(7A)-H(7A3)	0.977(17)	C(28A)-H(28B)	1.00(2)
C(8A)-H(8A1)	0.96(2)	C(28A)-H(28C)	0.95(2)
C(8A)-H(8A2)	0.96(2)	Si(2)-O(1B)	1.6614(12)
C(8A)-H(8A3)	0.980(18)	Si(2)-C(9B)	1.844(2)
C(9A)-H(9A1)	0.96(2)	Si(2)-C(10B)	1.864(2)
C(9A)-H(9A2)	0.99(2)	Si(2)-C(11B)	1.8712(17)
C(9A)-H(9A3)	1.04(2)	O(1B)-C(1B)	1.3842(18)
C(10A)-H(10A)	1.032(18)	O(2B)-C(2B)	1.3868(18)
C(10A)-H(10B)	0.95(2)	O(2B)-C(8B)	1.441(2)
C(10A)-H(10C)	0.91(2)	O(3B)-C(16B)	1.4298(19)
C(11A)-C(13A)	1.530(2)	O(3B)-H(3B)	0.98(3)
C(11A)-C(14A)	1.537(2)	O(4B)-C(27B)	1.2025(19)
C(11A)-C(12A)	1.539(2)	O(5B)-C(27B)	1.3347(19)
C(12A)-H(12A)	0.995(16)	O(5B)-C(28B)	1.441(2)
C(12A)-H(12B)	1.002(16)	O(6B)-C(25B)	1.3590(19)
C(12A)-H(12C)	0.939(17)	O(6B)-C(20B)	1.4668(19)
C(13A)-H(13A)	0.986(18)	O(7B)-C(25B)	1.2030(18)
C(13A)-H(13B)	0.990(17)	C(1B)-C(6B)	1.396(2)
C(13A)-H(13C)	1.072(16)	C(1B)-C(2B)	1.396(2)
C(14A)-H(14A)	1.043(18)	C(2B)-C(3B)	1.389(2)
C(14A)-H(14B)	1.016(17)	C(3B)-C(4B)	1.391(2)
C(14A)-H(14C)	0.982(18)	C(3B)-C(15B)	1.509(2)
C(15A)-C(16A)	1.525(2)	C(4B)-C(5B)	1.378(2)
C(15A)-H(15A)	0.967(16)	C(4B)-H(4B)	0.941(15)

C(5B)-C(6B)	1.391(2)	C(26B)-H(26F)	0.902(18)
C(5B)-H(5B)	0.956(15)	C(28B)-H(28D)	0.973(19)
C(6B)-C(7B)	1.508(2)	C(28B)-H(28E)	1.01(2)
C(7B)-H(7B1)	0.984(18)	C(28B)-H(28F)	1.005(18)
C(7B)-H(7B2)	0.973(18)		
C(7B)-H(7B3)	0.959(18)	O(1A)-Si(1)-C(10A)	108.83(9)
C(8B)-H(8B1)	0.994(16)	O(1A)-Si(1)-C(9A)	112.73(9)
C(8B)-H(8B2)	0.949(17)	C(10A)-Si(1)-C(9A)	108.59(12)
C(8B)-H(8B3)	0.976(19)	O(1A)-Si(1)-C(11A)	104.53(7)
C(9B)-H(9B1)	1.021(19)	C(10A)-Si(1)-C(11A)	112.83(9)
C(9B)-H(9B2)	0.968(18)	C(9A)-Si(1)-C(11A)	109.35(9)
C(9B)-H(9B3)	0.910(18)	C(1A)-O(1A)-Si(1)	126.87(10)
C(10B)-H(10D)	0.929(19)	C(2A)-O(2A)-C(8A)	112.94(13)
C(10B)-H(10E)	0.972(19)	C(16A)-O(3A)-H(3A)	109.0(14)
C(10B)-H(10F)	1.041(19)	C(27A)-O(5A)-C(28A)	116.14(17)
C(11B)-C(14B)	1.529(3)	C(25A)-O(6A)-C(20A)	108.79(12)
C(11B)-C(12B)	1.537(3)	O(1A)-C(1A)-C(2A)	119.97(14)
C(11B)-C(13B)	1.541(3)	O(1A)-C(1A)-C(6A)	119.17(14)
C(12B)-H(12D)	0.961(18)	C(2A)-C(1A)-C(6A)	120.77(16)
C(12B)-H(12E)	0.976(16)	O(2A)-C(2A)-C(3A)	119.27(15)
C(12B)-H(12F)	1.036(18)	O(2A)-C(2A)-C(1A)	119.52(15)
C(13B)-H(13D)	0.99(2)	C(3A)-C(2A)-C(1A)	121.17(15)
C(13B)-H(13E)	0.97(2)	C(4A)-C(3A)-C(2A)	117.57(16)
C(13B)-H(13F)	0.988(19)	C(4A)-C(3A)-C(15A)	120.43(17)
C(14B)-H(14D)	1.009(19)	C(2A)-C(3A)-C(15A)	121.96(16)
C(14B)-H(14E)	0.99(2)	C(5A)-C(4A)-C(3A)	121.26(18)
C(14B)-H(14F)	1.010(19)	C(5A)-C(4A)-H(4A)	120.0(10)
C(15B)-C(16B)	1.526(2)	C(3A)-C(4A)-H(4A)	118.7(10)
C(15B)-H(15C)	0.983(16)	C(4A)-C(5A)-C(6A)	121.60(17)
C(15B)-H(15D)	0.969(15)	C(4A)-C(5A)-H(5A)	120.6(10)
C(16B)-C(17B)	1.527(2)	C(6A)-C(5A)-H(5A)	117.8(10)
C(16B)-H(16B)	1.061(14)	C(5A)-C(6A)-C(1A)	117.47(16)
C(17B)-C(22B)	1.336(2)	C(5A)-C(6A)-C(7A)	121.95(16)
C(17B)-C(18B)	1.562(2)	C(1A)-C(6A)-C(7A)	120.58(16)
C(18B)-C(24B)	1.519(2)	C(6A)-C(7A)-H(7A1)	113.2(11)
C(18B)-C(25B)	1.524(2)	C(6A)-C(7A)-H(7A2)	110.5(10)
C(18B)-C(19B)	1.545(2)	H(7A1)-C(7A)-H(7A2)	109.8(14)
C(19B)-C(27B)	1.528(2)	C(6A)-C(7A)-H(7A3)	111.4(10)
C(19B)-C(26B)	1.530(2)	H(7A1)-C(7A)-H(7A3)	105.1(15)
C(19B)-C(20B)	1.538(2)	H(7A2)-C(7A)-H(7A3)	106.4(13)
C(20B)-C(21B)	1.494(2)	O(2A)-C(8A)-H(8A1)	109.8(11)
C(20B)-H(20B)	0.966(15)	O(2A)-C(8A)-H(8A2)	107.6(11)
C(21B)-C(22B)	1.511(2)	H(8A1)-C(8A)-H(8A2)	113.2(16)
C(21B)-H(21C)	1.005(15)	O(2A)-C(8A)-H(8A3)	111.8(10)
C(21B)-H(21D)	0.945(15)	H(8A1)-C(8A)-H(8A3)	106.8(15)
C(22B)-C(23B)	1.505(2)	H(8A2)-C(8A)-H(8A3)	107.7(15)
C(23B)-H(23D)	1.002(18)	Si(1)-C(9A)-H(9A1)	110.4(11)
C(23B)-H(23E)	0.977(19)	Si(1)-C(9A)-H(9A2)	110.6(11)
C(23B)-H(23F)	0.991(17)	H(9A1)-C(9A)-H(9A2)	107.4(16)
C(24B)-H(24D)	0.991(16)	Si(1)-C(9A)-H(9A3)	112.4(11)
C(24B)-H(24E)	0.985(17)	H(9A1)-C(9A)-H(9A3)	108.1(16)
C(24B)-H(24F)	0.994(16)	H(9A2)-C(9A)-H(9A3)	107.9(16)
C(26B)-H(26D)	1.02(2)	Si(1)-C(10A)-H(10A)	108.2(10)
C(26B)-H(26E)	1.022(17)	Si(1)-C(10A)-H(10B)	108.1(11)

H(10A)-C(10A)-H(10B)	104.5(15)	C(20A)-C(19A)-C(18A)	97.74(13)
Si(1)-C(10A)-H(10C)	108.5(13)	O(6A)-C(20A)-C(21A)	109.08(14)
H(10A)-C(10A)-H(10C)	115.9(16)	O(6A)-C(20A)-C(19A)	103.63(13)
H(10B)-C(10A)-H(10C)	111.3(17)	C(21A)-C(20A)-C(19A)	110.94(15)
C(13A)-C(11A)-C(14A)	108.50(17)	O(6A)-C(20A)-H(20A)	107.1(9)
C(13A)-C(11A)-C(12A)	109.27(16)	C(21A)-C(20A)-H(20A)	112.5(9)
C(14A)-C(11A)-C(12A)	108.78(16)	C(19A)-C(20A)-H(20A)	113.0(9)
C(13A)-C(11A)-Si(1)	110.65(13)	C(22A)-C(21A)-C(20A)	112.11(15)
C(14A)-C(11A)-Si(1)	110.17(12)	C(22A)-C(21A)-H(21A)	108.0(9)
C(12A)-C(11A)-Si(1)	109.44(13)	C(20A)-C(21A)-H(21A)	111.1(9)
C(11A)-C(12A)-H(12A)	110.6(9)	C(22A)-C(21A)-H(21B)	111.3(9)
C(11A)-C(12A)-H(12B)	110.9(9)	C(20A)-C(21A)-H(21B)	107.9(9)
H(12A)-C(12A)-H(12B)	109.3(13)	H(21A)-C(21A)-H(21B)	106.3(13)
C(11A)-C(12A)-H(12C)	109.0(11)	C(17A)-C(22A)-C(21A)	121.63(16)
H(12A)-C(12A)-H(12C)	110.9(14)	C(17A)-C(22A)-C(23A)	125.70(16)
H(12B)-C(12A)-H(12C)	106.0(14)	C(21A)-C(22A)-C(23A)	112.67(16)
C(11A)-C(13A)-H(13A)	109.7(10)	C(22A)-C(23A)-H(23A)	115.5(12)
C(11A)-C(13A)-H(13B)	111.0(9)	C(22A)-C(23A)-H(23B)	108.7(11)
H(13A)-C(13A)-H(13B)	106.6(14)	H(23A)-C(23A)-H(23B)	102.7(15)
C(11A)-C(13A)-H(13C)	107.1(9)	C(22A)-C(23A)-H(23C)	113.8(11)
H(13A)-C(13A)-H(13C)	113.9(14)	H(23A)-C(23A)-H(23C)	108.7(17)
H(13B)-C(13A)-H(13C)	108.6(13)	H(23B)-C(23A)-H(23C)	106.5(16)
C(11A)-C(14A)-H(14A)	111.0(10)	C(18A)-C(24A)-H(24A)	112.1(10)
C(11A)-C(14A)-H(14B)	108.8(9)	C(18A)-C(24A)-H(24B)	110.3(9)
H(14A)-C(14A)-H(14B)	107.3(14)	H(24A)-C(24A)-H(24B)	107.2(13)
C(11A)-C(14A)-H(14C)	110.1(10)	C(18A)-C(24A)-H(24C)	111.6(9)
H(14A)-C(14A)-H(14C)	111.2(14)	H(24A)-C(24A)-H(24C)	107.9(13)
H(14B)-C(14A)-H(14C)	108.3(14)	H(24B)-C(24A)-H(24C)	107.4(13)
C(3A)-C(15A)-C(16A)	112.34(15)	O(7A)-C(25A)-O(6A)	121.67(15)
C(3A)-C(15A)-H(15A)	110.7(9)	O(7A)-C(25A)-C(18A)	129.29(16)
C(16A)-C(15A)-H(15A)	105.5(9)	O(6A)-C(25A)-C(18A)	108.93(14)
C(3A)-C(15A)-H(15B)	110.2(9)	C(19A)-C(26A)-H(26A)	110.5(9)
C(16A)-C(15A)-H(15B)	110.8(9)	C(19A)-C(26A)-H(26B)	107.7(10)
H(15A)-C(15A)-H(15B)	107.2(13)	H(26A)-C(26A)-H(26B)	107.1(13)
O(3A)-C(16A)-C(15A)	107.75(15)	C(19A)-C(26A)-H(26C)	109.7(11)
O(3A)-C(16A)-C(17A)	112.97(13)	H(26A)-C(26A)-H(26C)	109.4(14)
C(15A)-C(16A)-C(17A)	113.83(14)	H(26B)-C(26A)-H(26C)	112.4(15)
O(3A)-C(16A)-H(16A)	99.6(7)	O(4A)-C(27A)-O(5A)	123.21(17)
C(15A)-C(16A)-H(16A)	112.7(7)	O(4A)-C(27A)-C(19A)	125.58(16)
C(17A)-C(16A)-H(16A)	109.1(7)	O(5A)-C(27A)-C(19A)	111.16(16)
C(22A)-C(17A)-C(16A)	120.51(15)	O(5A)-C(28A)-H(28A)	110.6(12)
C(22A)-C(17A)-C(18A)	119.78(15)	O(5A)-C(28A)-H(28B)	103.5(13)
C(16A)-C(17A)-C(18A)	119.58(15)	H(28A)-C(28A)-H(28B)	109.6(18)
C(25A)-C(18A)-C(24A)	114.37(15)	O(5A)-C(28A)-H(28C)	110.8(11)
C(25A)-C(18A)-C(19A)	100.28(13)	H(28A)-C(28A)-H(28C)	112.4(17)
C(24A)-C(18A)-C(19A)	113.17(14)	H(28B)-C(28A)-H(28C)	109.6(17)
C(25A)-C(18A)-C(17A)	101.39(12)	O(1B)-Si(2)-C(9B)	112.15(8)
C(24A)-C(18A)-C(17A)	116.05(14)	O(1B)-Si(2)-C(10B)	109.07(9)
C(19A)-C(18A)-C(17A)	109.92(14)	C(9B)-Si(2)-C(10B)	108.51(10)
C(26A)-C(19A)-C(27A)	112.09(16)	O(1B)-Si(2)-C(11B)	104.44(7)
C(26A)-C(19A)-C(20A)	114.62(16)	C(9B)-Si(2)-C(11B)	111.62(9)
C(27A)-C(19A)-C(20A)	106.69(14)	C(10B)-Si(2)-C(11B)	111.00(9)
C(26A)-C(19A)-C(18A)	114.66(15)	C(1B)-O(1B)-Si(2)	127.35(10)
C(27A)-C(19A)-C(18A)	109.97(14)	C(2B)-O(2B)-C(8B)	112.18(13)

C(16B)-O(3B)-H(3B)	107.7(14)	C(11B)-C(12B)-H(12F)	112.8(10)
C(27B)-O(5B)-C(28B)	116.43(15)	H(12D)-C(12B)-H(12F)	105.8(14)
C(25B)-O(6B)-C(20B)	108.58(13)	H(12E)-C(12B)-H(12F)	110.6(14)
O(1B)-C(1B)-C(6B)	119.68(14)	C(11B)-C(13B)-H(13D)	109.3(12)
O(1B)-C(1B)-C(2B)	119.45(14)	C(11B)-C(13B)-H(13E)	110.6(12)
C(6B)-C(1B)-C(2B)	120.76(16)	H(13D)-C(13B)-H(13E)	108.2(17)
O(2B)-C(2B)-C(3B)	119.92(14)	C(11B)-C(13B)-H(13F)	108.0(10)
O(2B)-C(2B)-C(1B)	118.93(15)	H(13D)-C(13B)-H(13F)	110.4(16)
C(3B)-C(2B)-C(1B)	121.12(15)	H(13E)-C(13B)-H(13F)	110.3(16)
C(2B)-C(3B)-C(4B)	117.72(16)	C(11B)-C(14B)-H(14D)	109.6(10)
C(2B)-C(3B)-C(15B)	121.99(16)	C(11B)-C(14B)-H(14E)	110.8(12)
C(4B)-C(3B)-C(15B)	120.27(17)	H(14D)-C(14B)-H(14E)	105.5(15)
C(5B)-C(4B)-C(3B)	121.15(17)	C(11B)-C(14B)-H(14F)	108.6(12)
C(5B)-C(4B)-H(4B)	119.8(9)	H(14D)-C(14B)-H(14F)	115.0(16)
C(3B)-C(4B)-H(4B)	119.0(9)	H(14E)-C(14B)-H(14F)	107.3(17)
C(4B)-C(5B)-C(6B)	121.71(17)	C(3B)-C(15B)-C(16B)	112.59(15)
C(4B)-C(5B)-H(5B)	120.8(10)	C(3B)-C(15B)-H(15C)	108.3(10)
C(6B)-C(5B)-H(5B)	117.5(10)	C(16B)-C(15B)-H(15C)	110.0(9)
C(5B)-C(6B)-C(1B)	117.39(16)	C(3B)-C(15B)-H(15D)	110.1(9)
C(5B)-C(6B)-C(7B)	121.52(16)	C(16B)-C(15B)-H(15D)	107.5(9)
C(1B)-C(6B)-C(7B)	121.08(16)	H(15C)-C(15B)-H(15D)	108.3(13)
C(6B)-C(7B)-H(7B1)	113.2(10)	O(3B)-C(16B)-C(17B)	112.54(13)
C(6B)-C(7B)-H(7B2)	112.6(10)	O(3B)-C(16B)-C(15B)	108.21(14)
H(7B1)-C(7B)-H(7B2)	104.5(15)	C(17B)-C(16B)-C(15B)	114.24(14)
C(6B)-C(7B)-H(7B3)	111.5(11)	O(3B)-C(16B)-H(16B)	98.2(7)
H(7B1)-C(7B)-H(7B3)	109.7(14)	C(17B)-C(16B)-H(16B)	110.5(8)
H(7B2)-C(7B)-H(7B3)	104.8(14)	C(15B)-C(16B)-H(16B)	112.1(7)
O(2B)-C(8B)-H(8B1)	110.8(9)	C(22B)-C(17B)-C(16B)	120.84(15)
O(2B)-C(8B)-H(8B2)	107.1(10)	C(22B)-C(17B)-C(18B)	119.74(14)
H(8B1)-C(8B)-H(8B2)	110.8(14)	C(16B)-C(17B)-C(18B)	119.31(14)
O(2B)-C(8B)-H(8B3)	109.1(11)	C(24B)-C(18B)-C(25B)	113.84(15)
H(8B1)-C(8B)-H(8B3)	107.0(14)	C(24B)-C(18B)-C(19B)	113.46(14)
H(8B2)-C(8B)-H(8B3)	112.0(14)	C(25B)-C(18B)-C(19B)	100.43(13)
Si(2)-C(9B)-H(9B1)	110.4(11)	C(24B)-C(18B)-C(17B)	116.12(14)
Si(2)-C(9B)-H(9B2)	109.6(10)	C(25B)-C(18B)-C(17B)	102.22(12)
H(9B1)-C(9B)-H(9B2)	106.8(15)	C(19B)-C(18B)-C(17B)	109.14(13)
Si(2)-C(9B)-H(9B3)	109.9(11)	C(27B)-C(19B)-C(26B)	112.00(15)
H(9B1)-C(9B)-H(9B3)	110.6(15)	C(27B)-C(19B)-C(20B)	105.71(14)
H(9B2)-C(9B)-H(9B3)	109.6(15)	C(26B)-C(19B)-C(20B)	114.79(16)
Si(2)-C(10B)-H(10D)	109.2(11)	C(27B)-C(19B)-C(18B)	110.73(14)
Si(2)-C(10B)-H(10E)	110.5(10)	C(26B)-C(19B)-C(18B)	114.56(14)
H(10D)-C(10B)-H(10E)	107.8(15)	C(20B)-C(19B)-C(18B)	97.96(13)
Si(2)-C(10B)-H(10F)	113.3(10)	O(6B)-C(20B)-C(21B)	108.63(14)
H(10D)-C(10B)-H(10F)	108.2(15)	O(6B)-C(20B)-C(19B)	103.56(13)
H(10E)-C(10B)-H(10F)	107.7(14)	C(21B)-C(20B)-C(19B)	111.22(14)
C(14B)-C(11B)-C(12B)	109.06(17)	O(6B)-C(20B)-H(20B)	107.2(9)
C(14B)-C(11B)-C(13B)	108.9(2)	C(21B)-C(20B)-H(20B)	112.0(9)
C(12B)-C(11B)-C(13B)	108.43(17)	C(19B)-C(20B)-H(20B)	113.7(9)
C(14B)-C(11B)-Si(2)	111.31(14)	C(20B)-C(21B)-C(22B)	112.67(15)
C(12B)-C(11B)-Si(2)	108.80(13)	C(20B)-C(21B)-H(21C)	110.0(8)
C(13B)-C(11B)-Si(2)	110.29(13)	C(22B)-C(21B)-H(21C)	110.7(8)
C(11B)-C(12B)-H(12D)	110.8(11)	C(20B)-C(21B)-H(21D)	108.8(9)
C(11B)-C(12B)-H(12E)	111.3(10)	C(22B)-C(21B)-H(21D)	110.2(9)
H(12D)-C(12B)-H(12E)	105.1(14)	H(21C)-C(21B)-H(21D)	104.2(12)

C(17B)-C(22B)-C(23B)	126.52(16)
C(17B)-C(22B)-C(21B)	121.36(15)
C(23B)-C(22B)-C(21B)	112.11(15)
C(22B)-C(23B)-H(23D)	115.8(10)
C(22B)-C(23B)-H(23E)	113.2(10)
H(23D)-C(23B)-H(23E)	108.1(14)
C(22B)-C(23B)-H(23F)	108.3(9)
H(23D)-C(23B)-H(23F)	104.7(13)
H(23E)-C(23B)-H(23F)	105.9(14)
C(18B)-C(24B)-H(24D)	113.2(9)
C(18B)-C(24B)-H(24E)	110.4(10)
H(24D)-C(24B)-H(24E)	108.6(13)
C(18B)-C(24B)-H(24F)	110.5(9)
H(24D)-C(24B)-H(24F)	108.5(13)
H(24E)-C(24B)-H(24F)	105.3(13)
O(7B)-C(25B)-O(6B)	121.65(16)
O(7B)-C(25B)-C(18B)	129.16(16)
O(6B)-C(25B)-C(18B)	109.13(14)
C(19B)-C(26B)-H(26D)	109.0(11)
C(19B)-C(26B)-H(26E)	109.2(9)
H(26D)-C(26B)-H(26E)	111.8(14)
C(19B)-C(26B)-H(26F)	110.8(11)
H(26D)-C(26B)-H(26F)	105.9(15)
H(26E)-C(26B)-H(26F)	110.2(15)
O(4B)-C(27B)-O(5B)	123.36(17)
O(4B)-C(27B)-C(19B)	125.61(16)
O(5B)-C(27B)-C(19B)	110.94(15)
O(5B)-C(28B)-H(28D)	112.0(11)
O(5B)-C(28B)-H(28E)	107.3(11)
H(28D)-C(28B)-H(28E)	117.1(16)
O(5B)-C(28B)-H(28F)	112.6(10)
H(28D)-C(28B)-H(28F)	96.4(14)
H(28E)-C(28B)-H(28F)	111.3(15)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^4$) for DCB31 (CCDC 283708). The anisotropic displacement factor exponent takes the form: $-2\pi^2$ [$h^2 a^{*2} U^{11}$ + ... + 2 h k a* b* U^{12}]

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si(1)	246(3)	166(3)	247(3)	-46(2)	-122(2)	20(2)
O(1A)	218(7)	140(6)	209(6)	-42(5)	-89(5)	25(5)
O(2A)	235(7)	253(7)	173(6)	-30(5)	-67(5)	39(6)
O(3A)	198(7)	203(7)	373(8)	-42(6)	-118(6)	22(6)
O(4A)	350(8)	465(9)	301(8)	4(7)	-165(6)	64(7)
O(5A)	562(9)	293(8)	437(9)	-82(7)	-372(7)	140(7)
O(6A)	189(7)	196(7)	260(7)	-20(5)	-99(5)	-15(5)
O(7A)	170(7)	244(7)	230(7)	-32(5)	-82(5)	31(6)
C(1A)	140(9)	163(10)	236(10)	-59(8)	-64(8)	2(8)
C(2A)	125(9)	219(10)	200(10)	-34(8)	-58(7)	3(8)
C(3A)	99(9)	196(10)	304(11)	-37(8)	-44(8)	0(8)
C(4A)	175(10)	184(11)	378(12)	-115(10)	-14(9)	-18(8)
C(5A)	205(10)	327(12)	211(11)	-121(9)	0(8)	-51(9)
C(6A)	156(9)	238(11)	176(10)	-32(8)	-27(8)	-46(8)
C(7A)	308(13)	319(13)	205(11)	-27(9)	-78(9)	-47(11)
C(8A)	227(12)	296(13)	235(12)	-65(10)	4(9)	37(10)
C(9A)	642(18)	241(13)	365(13)	-23(10)	-322(13)	-22(12)
C(10A)	281(12)	289(13)	538(16)	-137(12)	-195(11)	40(10)
C(11A)	254(10)	188(10)	231(10)	-56(8)	-103(8)	11(8)
C(12A)	390(14)	169(12)	358(13)	-41(10)	-182(11)	1(10)
C(13A)	351(13)	250(13)	550(16)	-136(11)	-187(12)	57(10)
C(14A)	506(15)	206(12)	379(13)	22(10)	-264(12)	-19(11)
C(15A)	157(10)	174(11)	395(13)	2(9)	-100(9)	-11(8)
C(16A)	163(10)	150(10)	287(11)	-20(8)	-78(8)	13(8)
C(17A)	116(9)	190(10)	297(10)	-27(8)	-78(8)	-11(8)
C(18A)	178(10)	160(10)	270(10)	-26(8)	-103(8)	10(8)
C(19A)	222(10)	189(10)	341(11)	-43(8)	-145(9)	34(8)
C(20A)	242(11)	139(10)	339(11)	8(9)	-143(9)	4(8)
C(21A)	213(11)	162(10)	324(11)	-52(9)	-93(9)	17(9)
C(22A)	140(9)	178(10)	300(11)	-25(8)	-48(8)	10(8)
C(23A)	272(12)	208(12)	307(12)	-50(10)	-27(10)	10(10)
C(24A)	238(12)	217(11)	321(12)	-52(9)	-141(10)	12(9)
C(25A)	220(10)	213(11)	163(9)	-8(8)	-94(8)	-19(8)
C(26A)	263(12)	263(13)	599(16)	-47(12)	-252(12)	52(10)
C(27A)	365(12)	184(11)	394(12)	-14(9)	-269(10)	-28(9)
C(28A)	750(20)	329(15)	444(15)	-103(12)	-428(14)	111(14)
Si(2)	224(3)	166(3)	247(3)	-30(2)	-96(2)	14(2)
O(1B)	223(7)	140(7)	237(7)	-21(5)	-98(5)	13(5)
O(2B)	255(7)	269(7)	176(7)	0(6)	-64(5)	-3(6)
O(3B)	237(8)	179(7)	385(8)	-45(6)	-133(6)	34(6)
O(4B)	300(8)	425(9)	267(7)	-10(6)	-100(6)	72(7)
O(5B)	431(8)	303(8)	273(7)	-35(6)	-207(6)	95(6)
O(6B)	175(7)	173(7)	257(7)	-21(5)	-58(5)	-15(5)
O(7B)	179(7)	243(7)	246(7)	-58(6)	-74(5)	33(6)
C(1B)	149(9)	135(9)	218(10)	-21(8)	-63(8)	1(7)
C(2B)	141(9)	212(10)	167(9)	1(8)	-48(7)	7(8)

C(3B)	121(9)	188(10)	273(10)	15(8)	-54(8)	-24(8)
C(4B)	182(10)	150(11)	346(12)	-63(9)	-58(9)	-11(8)
C(5B)	171(10)	289(12)	213(11)	-96(9)	-15(8)	-23(8)
C(6B)	149(9)	212(10)	178(9)	-1(8)	-37(7)	-24(8)
C(7B)	294(12)	270(12)	189(11)	31(9)	-89(9)	-29(10)
C(8B)	303(13)	269(13)	222(12)	-62(10)	-26(9)	15(10)
C(9B)	321(13)	249(12)	356(13)	-55(10)	-177(11)	25(10)
C(10B)	290(12)	329(13)	334(13)	-78(11)	-82(10)	-43(11)
C(11B)	242(10)	183(10)	341(11)	-73(8)	-111(9)	19(8)
C(12B)	332(13)	219(12)	412(14)	-126(10)	-134(11)	19(10)
C(13B)	329(14)	304(14)	624(18)	-215(13)	7(12)	17(12)
C(14B)	586(17)	253(13)	755(19)	-156(13)	-461(16)	154(13)
C(15B)	181(11)	171(11)	348(12)	48(9)	-92(9)	-14(9)
C(16B)	171(10)	135(10)	264(10)	2(8)	-92(8)	-13(8)
C(17B)	128(9)	179(10)	227(10)	0(8)	-58(8)	-16(8)
C(18B)	186(10)	141(10)	236(10)	-8(8)	-88(8)	-2(8)
C(19B)	231(10)	186(10)	232(10)	-4(8)	-93(8)	9(8)
C(20B)	213(10)	139(10)	267(11)	27(8)	-74(8)	0(8)
C(21B)	215(11)	154(10)	265(11)	-55(8)	-66(9)	22(9)
C(22B)	169(10)	174(10)	218(10)	-17(8)	-50(8)	-14(8)
C(23B)	279(12)	219(12)	218(11)	-32(9)	-31(9)	14(10)
C(24B)	243(12)	193(11)	284(12)	-45(9)	-124(9)	-5(9)
C(25B)	231(10)	207(10)	142(9)	-28(8)	-79(8)	-4(9)
C(26B)	214(11)	284(13)	350(13)	20(10)	-119(10)	53(10)
C(27B)	272(11)	193(10)	312(11)	-10(9)	-156(9)	-17(9)
C(28B)	468(15)	337(13)	264(12)	-40(10)	-188(11)	62(12)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for DCB31 (CCDC 283708).

	x	y	z	U_{iso}
H(3A)	3688(19)	4314(14)	814(14)	78(8)
H(4A)	201(13)	4175(11)	3162(11)	30(5)
H(5A)	-132(13)	2974(10)	4325(11)	25(5)
H(7A1)	-544(16)	867(12)	4330(12)	46(6)
H(7A2)	-69(13)	1455(11)	4872(12)	32(5)
H(7A3)	760(15)	894(11)	4127(11)	40(6)
H(8A1)	2967(16)	2594(13)	644(12)	53(7)
H(8A2)	2642(16)	2081(13)	-37(14)	60(7)
H(8A3)	2505(14)	1627(12)	968(12)	41(6)
H(9A1)	45(16)	1427(14)	673(13)	59(7)
H(9A2)	-397(16)	488(13)	676(13)	58(7)
H(9A3)	985(18)	670(14)	351(14)	71(8)
H(10A)	-1676(14)	505(12)	3497(13)	46(6)
H(10B)	-2032(17)	324(13)	2692(13)	55(7)
H(10C)	-1708(17)	1284(14)	2659(14)	66(8)
H(12A)	-171(13)	-1113(10)	1309(12)	28(5)
H(12B)	-1181(15)	-1199(10)	2360(11)	29(5)
H(12C)	-170(14)	-1847(12)	2143(11)	33(5)
H(13A)	1874(15)	-1379(12)	1840(12)	45(6)
H(13B)	2135(14)	-385(11)	1849(11)	29(5)
H(13C)	1796(13)	-581(11)	968(12)	34(5)
H(14A)	-721(16)	-845(12)	3734(12)	49(6)
H(14B)	627(14)	-554(11)	3490(11)	31(5)
H(14C)	355(14)	-1552(12)	3421(12)	43(6)
H(15A)	425(13)	4736(10)	1503(10)	25(5)
H(15B)	998(13)	4120(11)	721(11)	30(5)
H(16A)	2236(11)	4803(8)	1738(9)	3(4)
H(20A)	3219(13)	7783(11)	-1165(11)	34(5)
H(21A)	2915(13)	7589(10)	494(10)	21(5)
H(21B)	1745(13)	7611(10)	350(10)	26(5)
H(23A)	1387(17)	5894(14)	2315(14)	64(7)
H(23B)	941(17)	6760(13)	2048(12)	54(7)
H(23C)	2132(17)	6743(13)	2117(13)	60(7)
H(24A)	3128(14)	4891(11)	-1621(12)	33(5)
H(24B)	1857(15)	4754(10)	-810(11)	32(5)
H(24C)	2960(13)	4324(11)	-645(11)	28(5)
H(26A)	782(14)	6455(11)	27(12)	33(5)
H(26B)	880(14)	6179(12)	-967(11)	39(6)
H(26C)	997(14)	7196(12)	-883(12)	40(6)
H(28A)	3459(16)	7683(14)	-3771(13)	55(7)
H(28B)	2220(20)	7377(15)	-3685(15)	87(9)
H(28C)	3208(16)	6680(13)	-3761(13)	53(7)
H(3B)	1220(20)	5723(16)	4087(17)	114(10)
H(4B)	4665(12)	5890(10)	1672(10)	19(5)
H(5B)	5010(13)	7083(10)	475(11)	26(5)
H(7B1)	5590(16)	9117(12)	338(12)	44(6)
H(7B2)	4273(15)	9247(12)	709(12)	45(6)

H(7B3)	4798(14)	8624(11)	-15(12)	39(6)
H(8B1)	2458(13)	8392(11)	3792(11)	29(5)
H(8B2)	2434(13)	8067(11)	4816(12)	32(5)
H(8B3)	2056(16)	7416(13)	4285(12)	51(6)
H(9B1)	5015(17)	8795(12)	4117(14)	58(7)
H(9B2)	6204(15)	9337(12)	3590(11)	43(6)
H(9B3)	6052(15)	8483(12)	3257(12)	41(6)
H(10D)	6756(15)	9418(13)	1273(12)	47(6)
H(10E)	6969(15)	10252(12)	1610(12)	45(6)
H(10F)	6179(15)	10302(12)	1002(13)	52(6)
H(12D)	4742(15)	11708(12)	3470(12)	43(6)
H(12E)	5801(14)	11364(11)	2713(12)	30(5)
H(12F)	5359(15)	10891(12)	3820(13)	47(6)
H(13D)	3564(17)	9949(14)	4480(14)	66(8)
H(13E)	2761(17)	9917(13)	3923(13)	60(7)
H(13F)	2901(15)	10825(12)	4254(12)	44(6)
H(14D)	3408(15)	11588(12)	2666(12)	48(6)
H(14E)	3379(17)	10716(13)	2251(13)	62(7)
H(14F)	4577(18)	11267(13)	1777(14)	62(8)
H(15C)	3961(13)	6006(11)	4080(11)	29(5)
H(15D)	4563(13)	5374(10)	3328(10)	20(5)
H(16B)	2690(11)	5298(9)	3116(10)	13(4)
H(20B)	1938(12)	2330(10)	6009(10)	21(5)
H(21C)	1972(13)	2468(10)	4457(10)	21(5)
H(21D)	3183(13)	2494(10)	4462(10)	19(5)
H(23D)	3419(14)	4199(12)	2518(12)	43(6)
H(23E)	2648(16)	3318(12)	2812(12)	47(6)
H(23F)	3899(15)	3285(11)	2794(11)	34(5)
H(24D)	2117(13)	5778(11)	5512(10)	26(5)
H(24E)	3246(15)	5340(11)	5603(11)	34(5)
H(24F)	2058(13)	5180(10)	6467(12)	29(5)
H(26D)	4364(16)	3949(13)	5623(12)	55(7)
H(26E)	4271(14)	3613(11)	4680(12)	42(6)
H(26F)	4218(15)	2973(12)	5585(12)	39(6)
H(28D)	2178(16)	3296(13)	8539(13)	51(6)
H(28E)	3210(17)	2533(13)	8372(13)	60(7)
H(28F)	1846(15)	2391(12)	8536(12)	41(6)

Table 6. Hydrogen bonds for DCB31 (CCDC 283708) [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(3A)-H(3A)...O(7A)#1	0.92(2)	1.88(2)	2.7946(17)	173(2)
O(3B)-H(3B)...O(7B)#2	0.98(3)	1.81(3)	2.7910(17)	176(2)

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

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Crystal Structure Analysis of:

Bisacetoxyacetal 220 (DCB32)

(CCDC 289914)

Contents:

Table 1. Crystal data
Table 2. Atomic coordinates
Table 3. Full bond distances and angles
Table 4. Anisotropic displacement parameters
Table 5. Hydrogen atomic coordinates
Table 6. Hydrogen bond distances and angles

Figure A6.3 Representation of Bisacetoxyacetal **220**

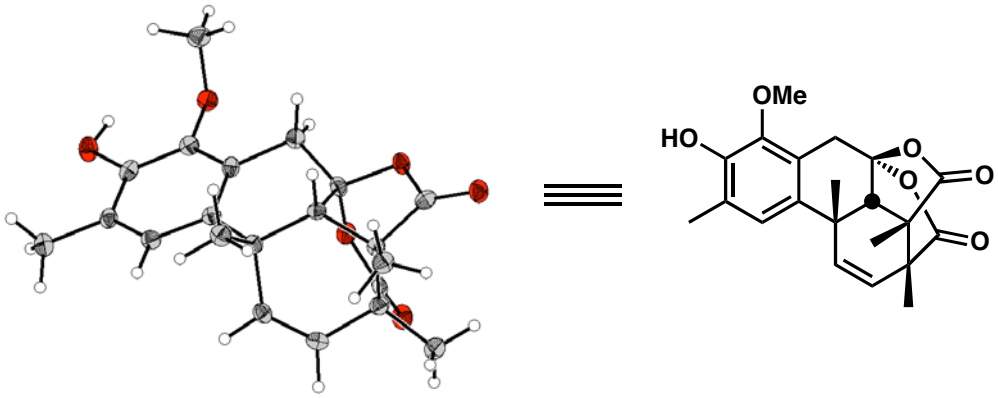


Table 1. Crystal data and structure refinement for DCB32 (CCDC 289914).

Empirical formula	$C_{21}H_{22}O_6$
Formula weight	370.39
Crystallization Solvent	Et_2O/hexanes
Crystal Habit	Needle
Crystal size	0.39 x 0.22 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 13215 reflections used in lattice determination	2.27 to 28.03°
Unit cell dimensions	a = 21.9617(16) Å b = 8.5236(6) Å c = 19.6358(14) Å
Volume	3675.7(5) $Å^3$
Z	8
Crystal system	Orthorhombic
Space group	Pbcn
Density (calculated)	1.339 Mg/m^3
F(000)	1568
Data collection program	Bruker SMART v5.630
θ range for data collection	1.85 to 28.38°
Completeness to θ = 28.38°	94.2 %
Index ranges	$-28 \le h \le 28$, $-11 \le k \le 11$, $-24 \le l \le 26$
Data collection scan type	ω scans at 5 ϕ settings
Data reduction program	Bruker SAINT v6.45A
Reflections collected	50823
Independent reflections	4344 [R_{int}= 0.0809]
Absorption coefficient	0.098 mm^{-1}
Absorption correction	None
Max. and min. transmission	0.9816 and 0.9628

Table 1 (cont.)

Structure solution and Refinement

Structure solution program	Bruker XS v6.12
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Difference Fourier map
Structure refinement program	Bruker XL v6.12
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	4344 / 0 / 332
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F^2	1.880
Final R indices [I>2σ(I), 3001 reflections]	R1 = 0.0466, *w*R2 = 0.0611
R indices (all data)	R1 = 0.0778, *w*R2 = 0.0633
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.001
Average shift/error	0.000
Largest diff. peak and hole	0.331 and -0.276 e.Å^{-3}

Special Refinement Details

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

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

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for DCB32 (CCDC 289914). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
O(1)	2750(1)	8498(1)	11657(1)	20(1)
O(2)	3463(1)	6194(1)	12216(1)	22(1)
O(3)	4347(1)	12923(1)	9814(1)	24(1)
O(4)	3652(1)	11114(1)	10020(1)	19(1)
O(5)	2849(1)	12317(1)	8276(1)	22(1)
O(6)	2812(1)	11335(1)	9329(1)	18(1)
C(1)	3243(1)	8168(2)	10565(1)	16(1)
C(2)	3171(1)	7737(2)	11243(1)	16(1)
C(3)	3539(1)	6609(2)	11548(1)	17(1)
C(4)	3993(1)	5863(2)	11174(1)	17(1)
C(5)	4067(1)	6316(2)	10500(1)	17(1)
C(6)	3705(1)	7443(2)	10182(1)	16(1)
C(7)	3834(1)	7839(2)	9427(1)	15(1)
C(8)	3386(1)	9079(2)	9173(1)	15(1)
C(9)	3172(1)	10217(2)	9710(1)	17(1)
C(10)	2832(1)	9437(2)	10272(1)	18(1)
C(11)	2149(1)	7822(2)	11619(1)	25(1)
C(12)	4388(1)	4633(2)	11498(1)	24(1)
C(13)	3759(1)	6327(2)	8998(1)	20(1)
C(14)	4480(1)	8405(2)	9339(1)	18(1)
C(15)	4634(1)	9789(2)	9089(1)	19(1)
C(16)	4175(1)	11058(2)	8904(1)	18(1)
C(17)	3586(1)	10261(2)	8630(1)	15(1)
C(18)	4452(1)	12247(2)	8416(1)	23(1)
C(19)	3652(1)	9638(2)	7907(1)	21(1)
C(20)	4062(1)	11828(2)	9598(1)	19(1)
C(21)	3057(1)	11422(2)	8689(1)	17(1)

Table 3. Bond lengths [Å] and angles [°] for DCB32 (CCDC 289914).

O(1)-C(2)	1.3917(16)	C(19)-H(19B)	1.006(15)
O(1)-C(11)	1.4405(18)	C(19)-H(19C)	0.974(17)
O(2)-C(3)	1.3695(17)		
O(2)-H(2)	0.887(19)	C(2)-O(1)-C(11)	113.13(12)
O(3)-C(20)	1.2002(16)	C(3)-O(2)-H(2)	108.0(13)
O(4)-C(20)	1.3677(17)	C(20)-O(4)-C(9)	117.64(11)
O(4)-C(9)	1.4373(16)	C(21)-O(6)-C(9)	107.19(11)
O(5)-C(21)	1.2031(16)	C(2)-C(1)-C(6)	118.61(13)
O(6)-C(21)	1.3697(16)	C(2)-C(1)-C(10)	118.79(13)
O(6)-C(9)	1.4462(16)	C(6)-C(1)-C(10)	122.58(13)
C(1)-C(2)	1.3899(19)	C(1)-C(2)-C(3)	121.92(13)
C(1)-C(6)	1.4059(19)	C(1)-C(2)-O(1)	120.79(13)
C(1)-C(10)	1.521(2)	C(3)-C(2)-O(1)	117.17(13)
C(2)-C(3)	1.3915(19)	O(2)-C(3)-C(2)	121.36(13)
C(3)-C(4)	1.3917(19)	O(2)-C(3)-C(4)	118.33(13)
C(4)-C(5)	1.388(2)	C(2)-C(3)-C(4)	120.30(13)
C(4)-C(12)	1.503(2)	C(5)-C(4)-C(3)	117.36(14)
C(5)-C(6)	1.3954(19)	C(5)-C(4)-C(12)	122.04(14)
C(5)-H(5)	0.960(12)	C(3)-C(4)-C(12)	120.60(14)
C(6)-C(7)	1.546(2)	C(4)-C(5)-C(6)	123.54(14)
C(7)-C(14)	1.5080(19)	C(4)-C(5)-H(5)	118.2(7)
C(7)-C(8)	1.5268(19)	C(6)-C(5)-H(5)	118.2(7)
C(7)-C(13)	1.548(2)	C(5)-C(6)-C(1)	118.25(14)
C(8)-C(9)	1.5086(19)	C(5)-C(6)-C(7)	118.43(13)
C(8)-C(17)	1.5300(19)	C(1)-C(6)-C(7)	123.32(13)
C(8)-H(8)	0.966(13)	C(14)-C(7)-C(8)	110.30(12)
C(9)-C(10)	1.490(2)	C(14)-C(7)-C(6)	110.57(12)
C(10)-H(10A)	1.027(14)	C(8)-C(7)-C(6)	110.27(12)
C(10)-H(10B)	0.976(14)	C(14)-C(7)-C(13)	107.68(12)
C(11)-H(11A)	1.018(15)	C(8)-C(7)-C(13)	109.33(12)
C(11)-H(11B)	0.941(14)	C(6)-C(7)-C(13)	108.64(12)
C(11)-H(11C)	1.017(15)	C(9)-C(8)-C(7)	114.69(12)
C(12)-H(12A)	0.965(18)	C(9)-C(8)-C(17)	98.80(11)
C(12)-H(12B)	0.994(18)	C(7)-C(8)-C(17)	119.94(12)
C(12)-H(12C)	0.989(17)	C(9)-C(8)-H(8)	106.2(8)
C(13)-H(13A)	1.003(14)	C(7)-C(8)-H(8)	107.8(8)
C(13)-H(13B)	0.988(15)	C(17)-C(8)-H(8)	108.4(8)
C(13)-H(13C)	0.996(14)	O(4)-C(9)-O(6)	105.61(11)
C(14)-C(15)	1.323(2)	O(4)-C(9)-C(10)	106.90(12)
C(14)-H(14)	0.975(13)	O(6)-C(9)-C(10)	113.83(12)
C(15)-C(16)	1.523(2)	O(4)-C(9)-C(8)	114.14(12)
C(15)-H(15)	0.987(11)	O(6)-C(9)-C(8)	103.46(11)
C(16)-C(18)	1.520(2)	C(10)-C(9)-C(8)	112.83(13)
C(16)-C(20)	1.533(2)	C(9)-C(10)-C(1)	107.47(13)
C(16)-C(17)	1.5582(19)	C(9)-C(10)-H(10A)	107.7(7)
C(17)-C(19)	1.523(2)	C(1)-C(10)-H(10A)	113.2(8)
C(17)-C(21)	1.530(2)	C(9)-C(10)-H(10B)	111.0(8)
C(18)-H(18A)	0.989(14)	C(1)-C(10)-H(10B)	110.6(8)
C(18)-H(18B)	0.977(15)	H(10A)-C(10)-H(10B)	106.9(11)
C(18)-H(18C)	1.001(16)	O(1)-C(11)-H(11A)	111.2(8)
C(19)-H(19A)	0.956(14)	O(1)-C(11)-H(11B)	104.9(8)

H(11A)-C(11)-H(11B)	109.5(11)
O(1)-C(11)-H(11C)	111.2(8)
H(11A)-C(11)-H(11C)	110.5(12)
H(11B)-C(11)-H(11C)	109.4(12)
C(4)-C(12)-H(12A)	112.6(11)
C(4)-C(12)-H(12B)	111.6(10)
H(12A)-C(12)-H(12B)	104.8(14)
C(4)-C(12)-H(12C)	112.2(10)
H(12A)-C(12)-H(12C)	108.5(14)
H(12B)-C(12)-H(12C)	106.7(14)
C(7)-C(13)-H(13A)	109.3(8)
C(7)-C(13)-H(13B)	111.2(8)
H(13A)-C(13)-H(13B)	109.6(11)
C(7)-C(13)-H(13C)	108.8(8)
H(13A)-C(13)-H(13C)	110.4(11)
H(13B)-C(13)-H(13C)	107.5(11)
C(15)-C(14)-C(7)	124.68(14)
C(15)-C(14)-H(14)	118.8(8)
C(7)-C(14)-H(14)	116.5(7)
C(14)-C(15)-C(16)	123.55(14)
C(14)-C(15)-H(15)	119.1(7)
C(16)-C(15)-H(15)	117.2(7)
C(18)-C(16)-C(15)	111.10(13)
C(18)-C(16)-C(20)	109.81(13)
C(15)-C(16)-C(20)	101.49(11)
C(18)-C(16)-C(17)	113.92(13)
C(15)-C(16)-C(17)	108.83(12)
C(20)-C(16)-C(17)	111.00(12)
C(19)-C(17)-C(21)	111.62(12)
C(19)-C(17)-C(8)	116.54(13)
C(21)-C(17)-C(8)	99.01(11)
C(19)-C(17)-C(16)	113.21(12)
C(21)-C(17)-C(16)	108.81(12)
C(8)-C(17)-C(16)	106.55(11)
C(16)-C(18)-H(18A)	107.5(8)
C(16)-C(18)-H(18B)	111.6(8)
H(18A)-C(18)-H(18B)	110.3(12)
C(16)-C(18)-H(18C)	108.8(9)
H(18A)-C(18)-H(18C)	111.5(12)
H(18B)-C(18)-H(18C)	107.2(12)
C(17)-C(19)-H(19A)	107.7(8)
C(17)-C(19)-H(19B)	110.6(8)
H(19A)-C(19)-H(19B)	111.7(12)
C(17)-C(19)-H(19C)	113.5(9)
H(19A)-C(19)-H(19C)	104.7(12)
H(19B)-C(19)-H(19C)	108.6(12)
O(3)-C(20)-O(4)	118.39(14)
O(3)-C(20)-C(16)	124.22(14)
O(4)-C(20)-C(16)	117.06(13)
O(5)-C(21)-O(6)	120.27(13)
O(5)-C(21)-C(17)	130.33(14)
O(6)-C(21)-C(17)	109.40(12)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^4$) for DCB32 (CCDC 289914). The anisotropic displacement factor exponent takes the form: $-2\pi^2$ [$h^2 a^{*2} U^{11}$ + ... + 2 h k a* b* U^{12}]

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	219(6)	189(6)	191(6)	-17(5)	52(5)	31(5)
O(2)	300(7)	204(6)	154(6)	14(5)	13(5)	46(5)
O(3)	273(6)	157(6)	288(7)	-25(5)	-80(5)	-20(5)
O(4)	233(6)	155(6)	172(6)	-15(5)	-14(5)	-8(5)
O(5)	248(6)	236(6)	179(6)	56(5)	-2(5)	32(5)
O(6)	215(6)	187(6)	141(6)	24(5)	18(5)	52(5)
C(1)	198(9)	125(8)	164(8)	-5(7)	-11(7)	-4(7)
C(2)	186(8)	133(8)	168(9)	-39(7)	23(7)	0(7)
C(3)	227(9)	148(9)	130(9)	-8(7)	-8(7)	-46(7)
C(4)	201(9)	112(8)	200(9)	-4(7)	-20(7)	-16(7)
C(5)	172(9)	147(8)	204(9)	-35(7)	31(7)	20(7)
C(6)	172(8)	139(8)	166(8)	-26(7)	1(7)	-13(7)
C(7)	156(8)	139(8)	161(8)	-18(7)	3(7)	18(7)
C(8)	136(8)	152(8)	162(9)	-18(7)	-2(7)	-18(7)
C(9)	166(8)	156(8)	183(8)	15(7)	-40(7)	20(7)
C(10)	211(9)	175(9)	157(9)	1(7)	36(8)	24(7)
C(11)	232(10)	239(10)	269(11)	-6(9)	92(9)	14(8)
C(12)	245(10)	208(10)	272(11)	45(8)	2(8)	35(8)
C(13)	221(10)	182(9)	205(10)	-34(8)	4(8)	11(8)
C(14)	179(9)	198(9)	159(9)	-11(7)	3(7)	40(7)
C(15)	141(8)	234(9)	180(9)	-23(7)	3(7)	0(7)
C(16)	168(8)	170(8)	188(9)	-1(7)	3(7)	-14(7)
C(17)	167(8)	146(8)	148(8)	-11(7)	10(7)	7(7)
C(18)	228(10)	218(10)	249(10)	30(8)	2(8)	-26(8)
C(19)	239(10)	241(10)	159(9)	7(8)	3(8)	-8(9)
C(20)	178(9)	154(9)	228(9)	32(7)	-44(7)	41(7)
C(21)	188(9)	169(8)	159(9)	-30(7)	-2(7)	-52(7)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for DCB32 (CCDC 289914).

	x	y	z	U_{iso}
H(2)	3183(9)	6820(20)	12395(10)	66(7)
H(5)	4383(6)	5822(14)	10239(6)	7(3)
H(8)	3027(6)	8542(15)	9011(6)	11(4)
H(10A)	2434(6)	9003(15)	10073(7)	16(4)
H(10B)	2719(6)	10191(17)	10624(7)	21(4)
H(11A)	1959(6)	8003(17)	11152(8)	27(4)
H(11B)	1921(6)	8358(16)	11952(7)	15(4)
H(11C)	2158(6)	6658(19)	11731(7)	26(4)
H(12A)	4187(8)	3630(20)	11532(9)	59(6)
H(12B)	4495(7)	4910(20)	11975(9)	56(6)
H(12C)	4777(8)	4488(19)	11252(8)	49(5)
H(13A)	4066(6)	5529(17)	9151(7)	26(4)
H(13B)	3815(6)	6542(16)	8508(8)	22(4)
H(13C)	3338(7)	5917(15)	9061(7)	22(4)
H(14)	4801(6)	7679(15)	9475(6)	12(4)
H(15)	5070(5)	10055(15)	9044(6)	9(4)
H(18A)	4804(6)	12732(16)	8649(7)	23(4)
H(18B)	4157(7)	13051(17)	8286(7)	29(4)
H(18C)	4578(6)	11692(17)	7990(8)	32(5)
H(19A)	3300(6)	9017(16)	7809(7)	20(4)
H(19B)	4038(7)	9014(17)	7859(7)	30(5)
H(19C)	3650(6)	10458(19)	7561(8)	36(5)

Table 6. Hydrogen bonds for DCB32 (CCDC 289914) [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2)...O(5)#1	0.887(19)	2.02(2)	2.7848(15)	144.2(17)
O(2)-H(2)...O(1)	0.887(19)	2.248(19)	2.7418(14)	114.8(15)

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

CALIFORNIA INSTITUTE OF TECHNOLOGY

BECKMAN INSTITUTE

X-RAY CRYSTALLOGRAPHY LABORATORY

Crystal Structure Analysis of:

Alcohol 255 (DCB34)

Contents:

Table 1. Crystal data
Table 2. Atomic coordinates
Table 3. Full bond distances and angles

Figure A6.4 Representation of Alcohol **255**

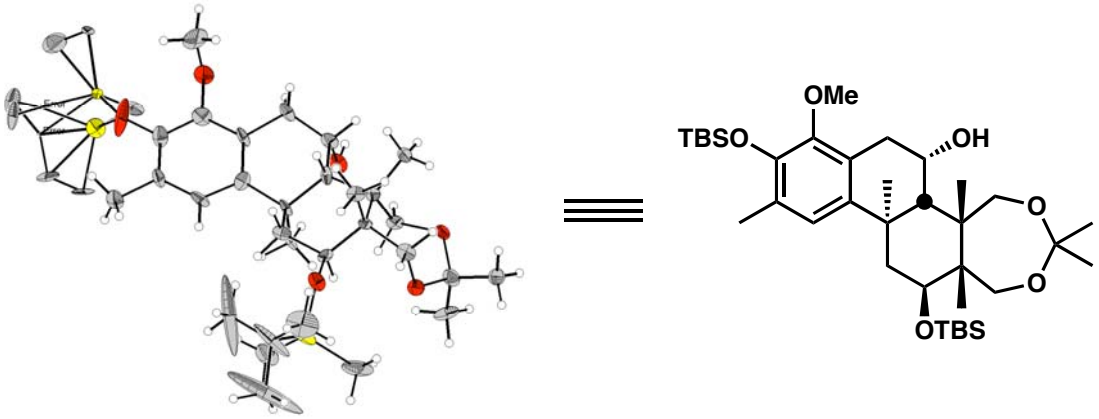


Table 1. Crystal data and structure refinement for dcb34.

Empirical formula	C36 H49 O6 Si2
Formula weight	633.93
Crystallization Solvent	Methylene Chloride
Crystal Habit	Fragment
Crystal size	0.45 x 0.20 x 0.19 mm^3
Crystal color	Colorless

Data Collection

Preliminary Photos		
Type of diffractometer	Bruker SMART 1000	
Wavelength	0.71073 Å MoKα	
Data Collection Temperature	100(2) K	
θ range for 2391 reflections used in lattice determination	2.25 to 25.75°	
Unit cell dimensions	a = 8.012(3) Å b = 12.103(5) Å c = 21.064(8) Å	α= 104.652(5)° β= 92.405(7)° γ = 98.610(6)°
Volume	1947.0(12) $Å^3$	
Z	2	
Crystal system	Triclinic	
Space group	P-1	
Density (calculated)	1.081 Mg/m^3	
F(000)	682	
θ range for data collection	1.76 to 27.12°	
Completeness to θ = 27.12°	78.9 %	
Index ranges	-10<=h<=8, -15<=k<=15, -26<=l<=12	
Data collection scan type	scans at 3 settings	
Reflections collected	8155	
Independent reflections	6807 [R_{int}= 0.0961; GOF_{merge}=]	
Absorption coefficient	0.129 mm^{-1}	
Absorption correction	None	

Table 1 (cont.)

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 1990)
Primary solution method	direct
Secondary solution method	difmap
Hydrogen placement	geom
Structure refinement program	SHELXL-97 (Sheldrick, 1997)
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6807 / 0 / 456
Treatment of hydrogen atoms	mixed
Goodness-of-fit on F^2	2.722
Final R indices [I>2σ(I), 4077 reflections]	R1 = 0.1484, wR2 = 0.1836
R indices (all data)	R1 = 0.2120, wR2 = 0.1890
Type of weighting scheme used	calc
Weighting scheme used	calc w=1/[^2^(Fo^2^)+(0.0000P)^2^+0.0000P] where P=(Fo^2^+2Fc^2^)/3
Max shift/error	1.254
Average shift/error	0.004
Largest diff. peak and hole	0.655 and -0.594 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for dcb34. U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}	Occ
Si(2A)	11898(6)	1267(5)	4132(2)	15(2)	0.480(9)
Si(2B)	12395(6)	2036(5)	4004(2)	32(2)	0.520(9)
O(6)	2561(6)	4434(4)	2066(2)	26(1)	1
O(4)	3040(6)	1577(4)	-102(2)	21(1)	1
O(3)	7053(6)	620(4)	947(2)	27(1)	1
O(5)	2281(6)	3355(4)	432(2)	24(1)	1
O(1A)	10070(40)	1775(16)	4115(16)	23(7)	0.480(9)
C(1)	2380(8)	2466(5)	1362(3)	16(2)	1
O(2)	8803(7)	-67(4)	2989(3)	41(2)	1
C(2)	4738(9)	3387(6)	2278(3)	23(2)	1
C(3)	4299(8)	1754(6)	459(3)	21(2)	1
C(4)	4798(8)	1409(6)	1584(3)	20(2)	1
C(5)	5795(9)	384(6)	1376(3)	23(2)	1
C(6)	5952(8)	2528(5)	1996(3)	19(2)	1
C(7)	7591(9)	3162(6)	3129(4)	25(2)	1
C(8)	7268(8)	3098(6)	1588(3)	21(2)	1
C(9)	3425(8)	1492(6)	1051(3)	16(2)	1
C(10)	3552(8)	3555(5)	1752(3)	19(2)	1
C(11)	8602(9)	3023(6)	3647(3)	24(2)	1
C(12)	6986(9)	2280(7)	2562(3)	24(2)	1
C(13)	7315(8)	1161(6)	2542(3)	22(2)	1
C(14)	1097(8)	2053(6)	1829(3)	20(2)	1
C(15)	1296(8)	2793(6)	853(3)	22(2)	1
C(16)	8395(9)	1028(6)	3049(4)	30(2)	1
C(17)	9097(10)	1930(7)	3580(4)	30(2)	1
C(18)	976(8)	2272(6)	-653(3)	25(2)	1
C(19)	2236(8)	320(5)	817(3)	23(2)	1
C(20)	6564(9)	111(6)	1978(3)	24(2)	1
C(21)	9165(10)	4017(6)	4246(3)	38(2)	1
C(22)	2536(10)	2627(6)	-208(4)	28(2)	1
C(23)	5312(9)	6404(7)	2242(4)	45(2)	1
C(24)	3956(9)	3325(6)	-466(4)	34(2)	1
C(25)	2088(11)	6074(7)	1347(5)	71(3)	1
C(26)	26(11)	6041(8)	2774(4)	64(3)	1
C(27)	2062(17)	7851(9)	2892(9)	241(12)	1
C(28)	1911(11)	6533(7)	2886(6)	80(4)	1
C(29)	2709(15)	6347(16)	3472(5)	225(13)	1
C(30)	7871(15)	-666(8)	3383(5)	95(5)	1
C(34)	15112(10)	2027(7)	4889(4)	39(2)	1
C(33)	12570(10)	2764(7)	5392(3)	43(2)	1
C(32)	13620(60)	2710(70)	4690(20)	330(60)	0.480(9)
O(1B)	10270(40)	1780(20)	4019(18)	67(10)	0.520(9)
C(37)	13940(30)	3570(18)	4427(13)	49(8)	0.480(9)
C(38)	12530(30)	502(17)	4794(9)	62(7)	0.520(9)
C(39)	13340(30)	2090(30)	4776(15)	42(7)	0.520(9)
C(42)	12884(10)	1006(6)	3290(3)	33(2)	1
C(40)	11720(20)	-94(12)	4414(8)	21(4)	0.480(9)

C(41)	13220(20)	3598(12)	3960(8)	30(4)	0.520(9)
Si(1)	2960(3)	5826(2)	2116(1)	36(1)	1

Table 3. Bond lengths [Å] and angles [°] for dcb34.

Si(2A)-O(1A)	1.68(3)	C(14)-H(14A)	0.9800
Si(2A)-C(40)	1.876(15)	C(14)-H(14B)	0.9800
Si(2A)-C(42)	1.943(8)	C(14)-H(14C)	0.9800
Si(2A)-C(32)	2.11(7)	C(15)-H(15A)	0.9900
Si(2B)-O(1B)	1.69(3)	C(15)-H(15B)	0.9900
Si(2B)-C(39)	1.75(3)	C(16)-C(17)	1.381(10)
Si(2B)-C(42)	1.793(8)	C(17)-O(1B)	1.35(3)
Si(2B)-C(41)	1.934(15)	C(18)-C(22)	1.470(9)
O(6)-C(10)	1.464(7)	C(18)-H(18A)	0.9800
O(6)-Si(1)	1.643(5)	C(18)-H(18B)	0.9800
O(4)-C(22)	1.456(8)	C(18)-H(18C)	0.9800
O(4)-C(3)	1.471(7)	C(19)-H(19A)	0.9800
O(3)-C(5)	1.426(8)	C(19)-H(19B)	0.9800
O(3)-H(3)	0.8400	C(19)-H(19C)	0.9800
O(5)-C(15)	1.441(7)	C(20)-H(20A)	0.9900
O(5)-C(22)	1.454(8)	C(20)-H(20B)	0.9900
O(1A)-C(17)	1.41(3)	C(21)-H(21A)	0.9800
C(1)-C(15)	1.516(9)	C(21)-H(21B)	0.9800
C(1)-C(10)	1.520(9)	C(21)-H(21C)	0.9800
C(1)-C(14)	1.567(9)	C(22)-C(24)	1.516(9)
C(1)-C(9)	1.572(8)	C(23)-Si(1)	1.892(8)
O(2)-C(16)	1.388(8)	C(23)-H(23A)	0.9800
O(2)-C(30)	1.403(11)	C(23)-H(23B)	0.9800
C(2)-C(10)	1.502(8)	C(23)-H(23C)	0.9800
C(2)-C(6)	1.554(8)	C(24)-H(24A)	0.9800
C(2)-H(2A)	0.9900	C(24)-H(24B)	0.9800
C(2)-H(2B)	0.9900	C(24)-H(24C)	0.9800
C(3)-C(9)	1.535(9)	C(25)-Si(1)	1.847(8)
C(3)-H(3A)	0.9900	C(25)-H(25A)	0.9800
C(3)-H(3B)	0.9900	C(25)-H(25B)	0.9800
C(4)-C(6)	1.551(9)	C(25)-H(25C)	0.9800
C(4)-C(5)	1.556(8)	C(26)-C(28)	1.523(11)
C(4)-C(9)	1.570(9)	C(26)-H(26A)	0.9800
C(4)-H(4)	1.0000	C(26)-H(26B)	0.9800
C(5)-C(20)	1.519(9)	C(26)-H(26C)	0.9800
C(5)-H(5)	1.0000	C(27)-C(28)	1.578(15)
C(6)-C(12)	1.540(9)	C(27)-H(27A)	0.9800
C(6)-C(8)	1.576(9)	C(27)-H(27B)	0.9800
C(7)-C(11)	1.391(9)	C(27)-H(27C)	0.9800
C(7)-C(12)	1.397(9)	C(28)-C(29)	1.449(17)
C(7)-H(7)	0.9500	C(28)-Si(1)	1.923(9)
C(8)-H(8A)	0.9800	C(29)-H(29A)	0.9800
C(8)-H(8B)	0.9800	C(29)-H(29B)	0.9800
C(8)-H(8C)	0.9800	C(29)-H(29C)	0.9800
C(9)-C(19)	1.537(9)	C(30)-H(30A)	0.9800
C(10)-H(10)	1.0000	C(30)-H(30B)	0.9800
C(11)-C(17)	1.412(10)	C(30)-H(30C)	0.9800
C(11)-C(21)	1.505(9)	C(34)-C(39)	1.45(3)
C(12)-C(13)	1.410(9)	C(34)-C(32)	1.65(5)
C(13)-C(16)	1.402(9)	C(33)-C(39)	1.55(3)
C(13)-C(20)	1.528(8)	C(33)-C(32)	1.73(5)

C(32)-C(37)	1.29(9)
C(38)-C(39)	1.94(4)
O(1A)-Si(2A)-C(40)	113.4(11)
O(1A)-Si(2A)-C(42)	112.9(13)
C(40)-Si(2A)-C(42)	108.8(5)
O(1A)-Si(2A)-C(32)	103.6(15)
C(40)-Si(2A)-C(32)	117(2)
C(42)-Si(2A)-C(32)	100.4(15)
O(1B)-Si(2B)-C(39)	109.1(16)
O(1B)-Si(2B)-C(42)	106.2(11)
C(39)-Si(2B)-C(42)	119.3(11)
O(1B)-Si(2B)-C(41)	112.0(12)
C(39)-Si(2B)-C(41)	99.8(12)
C(42)-Si(2B)-C(41)	110.5(6)
C(10)-O(6)-Si(1)	126.8(4)
C(22)-O(4)-C(3)	115.3(5)
C(5)-O(3)-H(3)	109.5
C(15)-O(5)-C(22)	116.3(5)
C(17)-O(1A)-Si(2A)	130(2)
C(15)-C(1)-C(10)	107.9(5)
C(15)-C(1)-C(14)	104.9(5)
C(10)-C(1)-C(14)	108.9(5)
C(15)-C(1)-C(9)	113.1(6)
C(10)-C(1)-C(9)	110.7(5)
C(14)-C(1)-C(9)	111.1(5)
C(16)-O(2)-C(30)	112.3(6)
C(10)-C(2)-C(6)	112.6(5)
C(10)-C(2)-H(2A)	109.1
C(6)-C(2)-H(2A)	109.1
C(10)-C(2)-H(2B)	109.1
C(6)-C(2)-H(2B)	109.1
H(2A)-C(2)-H(2B)	107.8
O(4)-C(3)-C(9)	110.2(5)
O(4)-C(3)-H(3A)	109.6
C(9)-C(3)-H(3A)	109.6
O(4)-C(3)-H(3B)	109.6
C(9)-C(3)-H(3B)	109.6
H(3A)-C(3)-H(3B)	108.1
C(6)-C(4)-C(5)	112.0(5)
C(6)-C(4)-C(9)	119.5(6)
C(5)-C(4)-C(9)	115.5(5)
C(6)-C(4)-H(4)	102.2
C(5)-C(4)-H(4)	102.2
C(9)-C(4)-H(4)	102.2
O(3)-C(5)-C(20)	111.5(6)
O(3)-C(5)-C(4)	111.1(6)
C(20)-C(5)-C(4)	110.5(6)
O(3)-C(5)-H(5)	107.9
C(20)-C(5)-H(5)	107.9
C(4)-C(5)-H(5)	107.9
C(12)-C(6)-C(4)	110.9(6)
C(12)-C(6)-C(2)	110.1(5)
C(4)-C(6)-C(2)	105.8(5)
C(12)-C(6)-C(8)	106.6(6)
C(4)-C(6)-C(8)	113.9(5)
C(2)-C(6)-C(8)	109.6(5)
C(11)-C(7)-C(12)	124.2(7)
C(11)-C(7)-H(7)	117.9
C(12)-C(7)-H(7)	117.9
C(6)-C(8)-H(8A)	109.5
C(6)-C(8)-H(8B)	109.5
H(8A)-C(8)-H(8B)	109.5
C(6)-C(8)-H(8C)	109.5
H(8A)-C(8)-H(8C)	109.5
H(8B)-C(8)-H(8C)	109.5
C(3)-C(9)-C(19)	108.6(5)
C(3)-C(9)-C(4)	109.4(5)
C(19)-C(9)-C(4)	108.9(5)
C(3)-C(9)-C(1)	110.8(5)
C(19)-C(9)-C(1)	109.7(5)
C(4)-C(9)-C(1)	109.4(5)
O(6)-C(10)-C(2)	107.6(5)
O(6)-C(10)-C(1)	110.2(5)
C(2)-C(10)-C(1)	115.2(6)
O(6)-C(10)-H(10)	107.9
C(2)-C(10)-H(10)	107.9
C(1)-C(10)-H(10)	107.9
C(7)-C(11)-C(17)	117.5(7)
C(7)-C(11)-C(21)	120.5(6)
C(17)-C(11)-C(21)	122.0(7)
C(7)-C(12)-C(13)	117.3(6)
C(7)-C(12)-C(6)	120.7(6)
C(13)-C(12)-C(6)	121.9(6)
C(16)-C(13)-C(12)	118.3(6)
C(16)-C(13)-C(20)	120.0(6)
C(12)-C(13)-C(20)	121.7(6)
C(1)-C(14)-H(14A)	109.5
C(1)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	109.5
C(1)-C(14)-H(14C)	109.5
H(14A)-C(14)-H(14C)	109.5
H(14B)-C(14)-H(14C)	109.5
O(5)-C(15)-C(1)	113.0(6)
O(5)-C(15)-H(15A)	109.0
C(1)-C(15)-H(15A)	109.0
O(5)-C(15)-H(15B)	109.0
C(1)-C(15)-H(15B)	109.0
H(15A)-C(15)-H(15B)	107.8
C(17)-C(16)-O(2)	119.7(7)
C(17)-C(16)-C(13)	123.3(7)
O(2)-C(16)-C(13)	117.0(7)
O(1B)-C(17)-C(16)	120.7(14)
O(1B)-C(17)-O(1A)	11(3)
C(16)-C(17)-O(1A)	123.0(10)
O(1B)-C(17)-C(11)	120.6(14)
C(16)-C(17)-C(11)	118.6(7)
O(1A)-C(17)-C(11)	117.5(11)

C(22)-C(18)-H(18A)	109.5	H(26A)-C(26)-H(26B)	109.5
C(22)-C(18)-H(18B)	109.5	C(28)-C(26)-H(26C)	109.5
H(18A)-C(18)-H(18B)	109.5	H(26A)-C(26)-H(26C)	109.5
C(22)-C(18)-H(18C)	109.5	H(26B)-C(26)-H(26C)	109.5
H(18A)-C(18)-H(18C)	109.5	C(28)-C(27)-H(27A)	109.5
H(18B)-C(18)-H(18C)	109.5	C(28)-C(27)-H(27B)	109.5
C(9)-C(19)-H(19A)	109.5	H(27A)-C(27)-H(27B)	109.5
C(9)-C(19)-H(19B)	109.5	C(28)-C(27)-H(27C)	109.5
H(19A)-C(19)-H(19B)	109.5	H(27A)-C(27)-H(27C)	109.5
C(9)-C(19)-H(19C)	109.5	H(27B)-C(27)-H(27C)	109.5
H(19A)-C(19)-H(19C)	109.5	C(29)-C(28)-C(26)	112.9(11)
H(19B)-C(19)-H(19C)	109.5	C(29)-C(28)-C(27)	113.7(11)
C(5)-C(20)-C(13)	115.6(6)	C(26)-C(28)-C(27)	106.1(9)
C(5)-C(20)-H(20A)	108.4	C(29)-C(28)-Si(1)	110.7(7)
C(13)-C(20)-H(20A)	108.4	C(26)-C(28)-Si(1)	107.6(6)
C(5)-C(20)-H(20B)	108.4	C(27)-C(28)-Si(1)	105.4(8)
C(13)-C(20)-H(20B)	108.4	C(28)-C(29)-H(29A)	109.5
H(20A)-C(20)-H(20B)	107.5	C(28)-C(29)-H(29B)	109.5
C(11)-C(21)-H(21A)	109.5	H(29A)-C(29)-H(29B)	109.5
C(11)-C(21)-H(21B)	109.5	C(28)-C(29)-H(29C)	109.5
H(21A)-C(21)-H(21B)	109.5	H(29A)-C(29)-H(29C)	109.5
C(11)-C(21)-H(21C)	109.5	H(29B)-C(29)-H(29C)	109.5
H(21A)-C(21)-H(21C)	109.5	O(2)-C(30)-H(30A)	109.5
H(21B)-C(21)-H(21C)	109.5	O(2)-C(30)-H(30B)	109.5
O(5)-C(22)-O(4)	107.4(5)	H(30A)-C(30)-H(30B)	109.5
O(5)-C(22)-C(18)	112.5(6)	O(2)-C(30)-H(30C)	109.5
O(4)-C(22)-C(18)	107.1(6)	H(30A)-C(30)-H(30C)	109.5
O(5)-C(22)-C(24)	105.3(6)	H(30B)-C(30)-H(30C)	109.5
O(4)-C(22)-C(24)	111.1(6)	C(39)-C(34)-C(32)	30(4)
C(18)-C(22)-C(24)	113.4(7)	C(39)-C(33)-C(32)	28(3)
Si(1)-C(23)-H(23A)	109.5	C(37)-C(32)-C(34)	123(4)
Si(1)-C(23)-H(23B)	109.5	C(37)-C(32)-C(33)	124(4)
H(23A)-C(23)-H(23B)	109.5	C(34)-C(32)-C(33)	96(4)
Si(1)-C(23)-H(23C)	109.5	C(37)-C(32)-Si(2A)	116(3)
H(23A)-C(23)-H(23C)	109.5	C(34)-C(32)-Si(2A)	99(4)
H(23B)-C(23)-H(23C)	109.5	C(33)-C(32)-Si(2A)	93(3)
C(22)-C(24)-H(24A)	109.5	C(17)-O(1B)-Si(2B)	127(3)
C(22)-C(24)-H(24B)	109.5	C(34)-C(39)-C(33)	113.8(18)
H(24A)-C(24)-H(24B)	109.5	C(34)-C(39)-Si(2B)	123(2)
C(22)-C(24)-H(24C)	109.5	C(33)-C(39)-Si(2B)	117(2)
H(24A)-C(24)-H(24C)	109.5	C(34)-C(39)-C(38)	95.0(19)
H(24B)-C(24)-H(24C)	109.5	C(33)-C(39)-C(38)	100.8(16)
Si(1)-C(25)-H(25A)	109.5	Si(2B)-C(39)-C(38)	98.6(14)
Si(1)-C(25)-H(25B)	109.5	Si(2B)-C(42)-Si(2A)	32.6(2)
H(25A)-C(25)-H(25B)	109.5	O(6)-Si(1)-C(25)	108.9(3)
Si(1)-C(25)-H(25C)	109.5	O(6)-Si(1)-C(23)	111.8(3)
H(25A)-C(25)-H(25C)	109.5	C(25)-Si(1)-C(23)	109.2(4)
H(25B)-C(25)-H(25C)	109.5	O(6)-Si(1)-C(28)	104.3(4)
C(28)-C(26)-H(26A)	109.5	C(25)-Si(1)-C(28)	113.9(5)
C(28)-C(26)-H(26B)	109.5	C(23)-Si(1)-C(28)	108.8(4)

CHAPTER FOUR

The Development of an Asymmetric Tsuji Allylation Reaction[†]

4.1 Introduction

The catalytic asymmetric synthesis of all-carbon quaternary stereocenters stands as a significant challenge in synthetic chemistry.[1] Despite the demanding sterics, a number of useful catalytic transformations, including Diels-Alder,[2] Heck,[3] cyclopropanation,[4] alkylation,[5] acylation,[6] and desymmetrization[7] reactions, have been demonstrated to form quaternary stereocenters with good levels of enantioinduction. Although palladium-catalyzed enantioselective allylation chemistry has long been an important asymmetric catalytic tool,[8] only recently has palladium (II) π-allyl chemistry been used for the formation of quaternary stereocenters. The vast majority of palladium (II) allylic alkylations studied by Trost, Helmchen, Pfaltz, and others form tertiary stereocenters by the attack of malonate anions on prochiral 1,3-disubstituted allyl fragments. Helmchen has shown that such reactions with palladium phosphinooxazoline (PHOX) complexes typically occur via an outer sphere malonate attack at the allyl termini.[9] The tendency of palladium to give the less branched products in allylic alkylations with differentially substituted allyl termini makes the formation of quaternary stereocenters on the allyl fragment problematic.[10]

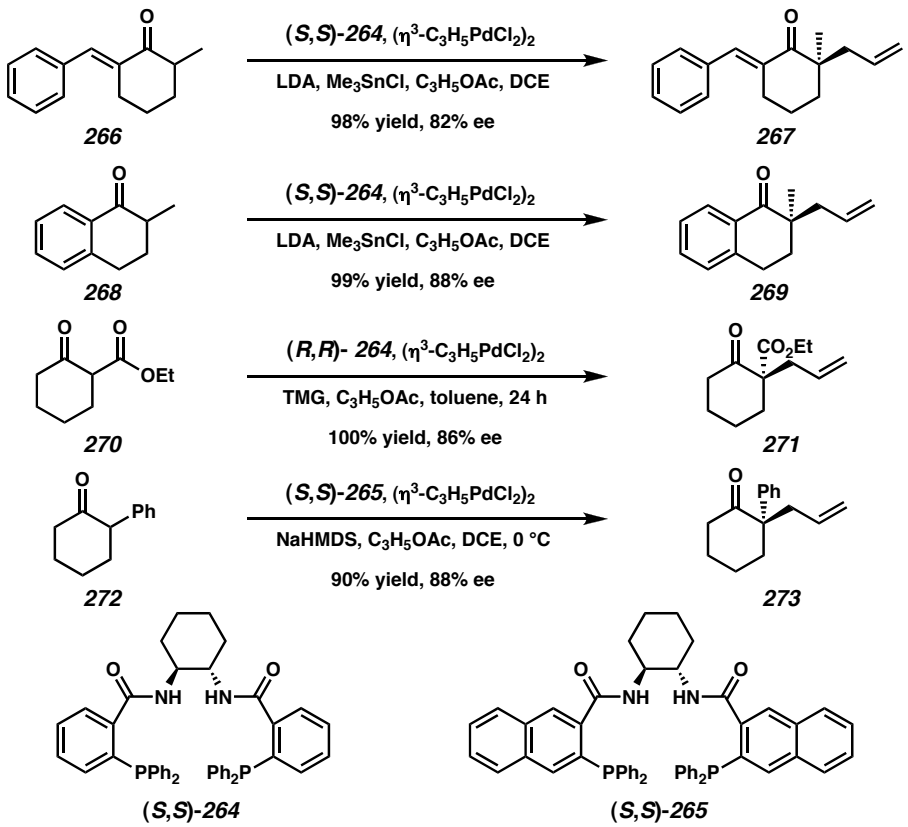
An alternative, less common strategy in allylic alkylation is the use of prochiral nucleophiles. A quaternary stereocenter may formed on the prochiral nucleophile when it possesses three distinct carbon substituents. A priori, such reactions requiring the remote

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[†] This work was performed in collaboration with Justin Mohr, Dr. Andrew Harned, Dr. Kousuke Tani, Dr. Zoltán Novák, Sandy Ma, Nathaniel Sherden, Mike Krout, and Ryan McFadden.

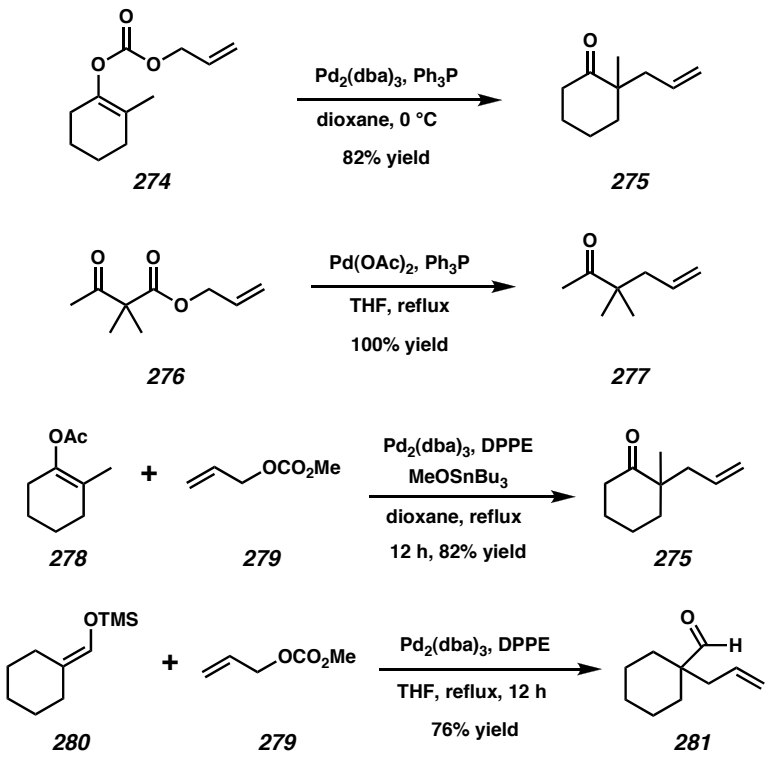
chiral ligand to discriminate between the prochiral faces of the incoming nucleophile seem improbable. However, Hayashi[11] and Ito[12] have demonstrated the asymmetric allylation of prochiral enolates derived from 1,3-dicarbonyl compounds. Trost and coworkers demonstrated that diamine-derived ligands **264** and **265**, which were designed to project bulk forward of the allyl fragment due to their large bite angle, are able to favor one face of the in situ generated ketone enolate (Scheme 4.1).[13] These reactions represent a significant advance in asymmetric allylation technology by forming quaternary stereocenters with excellent yield and good ee. However, the substrate scope of these reactions was limited by the restriction that the ketone contain either a single acidic site (e.g., ketone **266** and tetralone **268**) or two α sites that have a large difference in acidity (e.g., β-ketoester **270** and phenyl ketone **272**).[1a] These limitations prevented direct access to simple α-quaternary ketones, such as 2-methyl-2-allylcyclohexanone **275**. Indeed, this simple cyclohexanone derivative was not known as a single enantiomer prior to our work.

Scheme 4.1 Trost's Allylic Alkylations with Prochiral Nucleophiles



We were confronted by these limitations during studies toward the synthesis of several natural products. A survey of the literature revealed that the non-enantioselective allylation reactions developed by Tsuji in the early 1980s had the proper reactivity and selectivity to form quaternary stereocenters in the presence of similarly acidic and less substituted ketone α sites (Scheme 4.2). Allyl enol carbonate **274** and allyl β-ketoester **276** contain both the latent enolate and allyl fragment.[14] Alternatively, enol acetate **278** and silyl enol ether **280** may serve as enolate precursors in intermolecular reactions with allyl carbonates.[15] These allylations have the advantage that reaction occurs under nearly neutral conditions and at mild temperatures. Despite these advantages, these allylation reactions have been utilized rarely during the interceding twenty years.[16]

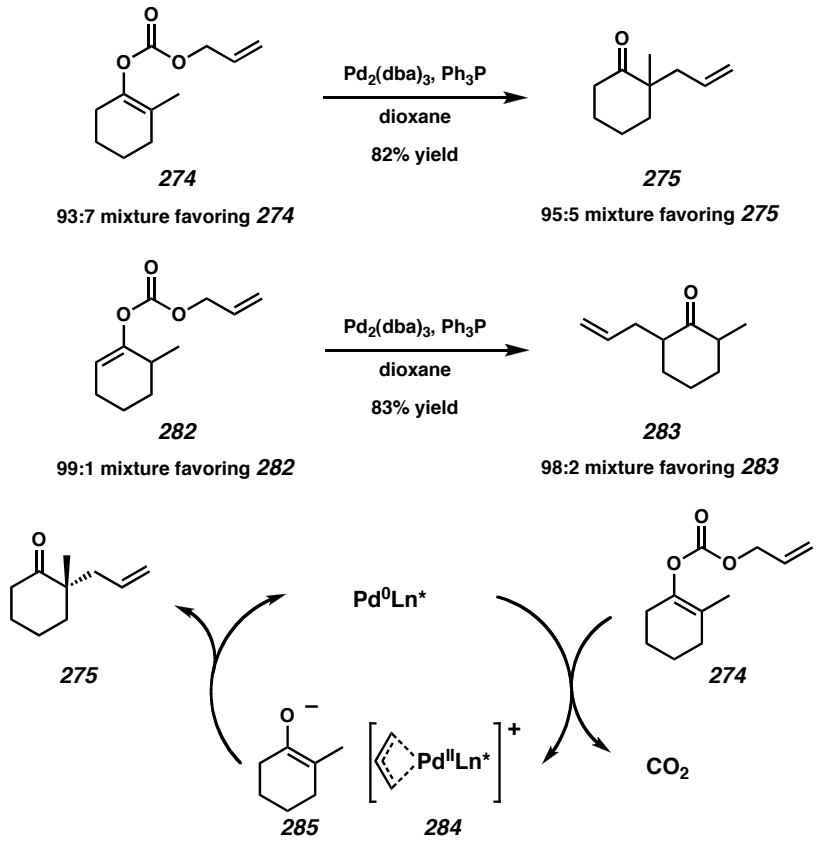
Scheme 4.2 Tsuji's Allylation Methods



Our analysis of Tsuji's allylation reaction showed it to be an ideal candidate for asymmetric catalysis. These high yielding allylation reactions are a clear case of ligand-accelerated catalysis, occurring only in the presence of phosphine ligands.[17] Of additional interest was the regiochemical fidelity observed in the allylation reactions (Scheme 4.3). Tsuji demonstrated that both the tetrasubstituted allyl enol carbonate isomer **274** and the trisubstituted allyl enol carbonate isomer **281** undergo reaction to give allylated ketones **275** and **283** in ratios essentially unchanged from that of the substrates.[14a] These reactions are believed to proceed via oxidative addition to the allyl fragment and loss of CO_2 to give Pd(II)(allyl) complex **284** and enolate **285**. However, the details involving the recombination of the ion pair to give cyclohexanone **275** and Pd(0) were unclear at the time of Tsuji's original reports. Coupled with the ability to

purify the stable enolate precursors, we believed that the regiochemical fidelity afforded in the palladium-catalyzed reaction would provide direct access to enantioenriched α-quaternary ketones if a suitable chiral ligand could be found.

Scheme 4.3 Regiochemical Fidelity in Tsuji's Palladium-Catalyzed Allylation



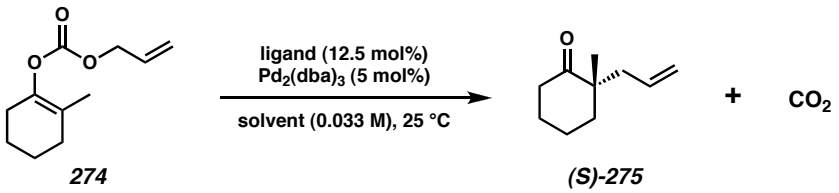
4.2 Results and Discussion

4.2.1 *Initial Screening of Chiral Ligands*

Our initial goal was to show that a chiral ligand could transmit useful levels of asymmetric induction in the reaction while maintaining the important property of enolate regiochemical fidelity found in the non-enantioselective system. We chose allyl enol carbonate **274** as a simple test substrate to evaluate the effect of various ligands (Table

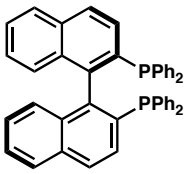
4.1). Although allyl enol carbonates are less common than the other enolate precursors explored by Tsuji, they allowed us to add a single reagent to our catalyst system without extraneous initiators or counter ions that might affect enantioselectivity. In accord with Tsuji's reports, we performed our initial trials in 1,4-dioxane solvent. Due to the prevalence of bisphosphine ligands in asymmetric catalysis, we began with several privileged bisphosphine ligands, but found that only Trost's ligand **264** gave significant ee. However, commercially available (*R*)-QUINAP (**290**), a chelating N/P-type ligand, gave more uniform ee. It is noteworthy that despite our change from monodentate ligands (i.e., PPh_3) to N/P chelates, high levels of conversion are still observed. Encouraged, we quickly found that the phosphinooxazoline (PHOX) class of N/P-type ligands also provides excellent reactivity and promising levels of enantioselectivity. The ready availability of numerous amino acid-derived PHOX ligands[18] allowed us to rapidly identify that bulkier aliphatic R groups provided higher levels of enantioinduction, with (*S*)-*t*-Bu-PHOX providing α-quaternary ketone **275** in 86% ee when 1,4-dioxane was used as solvent. Additionally, we found that the use of THF typically gave slightly higher ee in reactions with (*R*)-*i*-Pr-PHOX and (*S*)-*t*-Bu-PHOX.[19] Having attained satisfying levels of enantioselectivity and selectivity in forming ketone **275**, we began a more thorough investigation of reaction conditions.

Table 4.1 Initial Ligand Screen

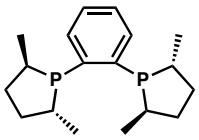


274 *(S)-275*

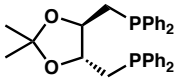
		1,4-dioxane			THF		
entry	ligand	time (h)	% yield[a]	% ee[b]	time (h)	% yield[a]	% ee[b]
1	*(R)-BINAP (286)*	5	92	5[c]	5	76	2[c]
2	*(R,R)-Me-DUPHOS (287)*	5	61	0	5	66	0
3	*(R,R)-DIOP (288)*	2	91	2[c]	2	59	2[c]
4	*(R)-MOP (289)*	3	93	18	3	47	13
5	*(R,R)-Trost ligand (264)*	2	97	46[c]	5	92	64[c]
6	*(R)-QUINAP (290)*	2	98	61	2	97	61
7	*(R)-Ph-PHOX (291)*	2	95	62[c]	2	95	65[c]
8	*(S)-Bn-PHOX (292)*	3	96	65	5	94	63
9	*(R)-i-Pr-PHOX (293)*	3	96	82[c]	2	95	83[c]
10	*(S)-t-Bu-PHOX (294)*	2	95	86	2	96	88



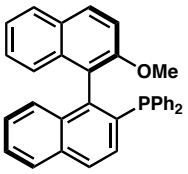
(R)-BINAP (286)



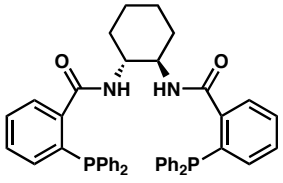
(R,R)-Me-DUPHOS (287)



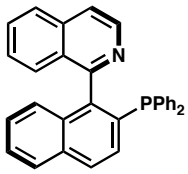
(R,R)-DIOP (288)



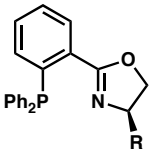
(R)-MOP (289)



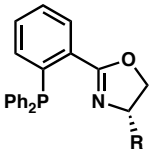
(R,R)-Trost ligand (264)



(R)-QUINAP (290)



R = Ph
(R)-Ph-PHOX (291)
R = i-Pr
(R)-i-Pr-PHOX (293)



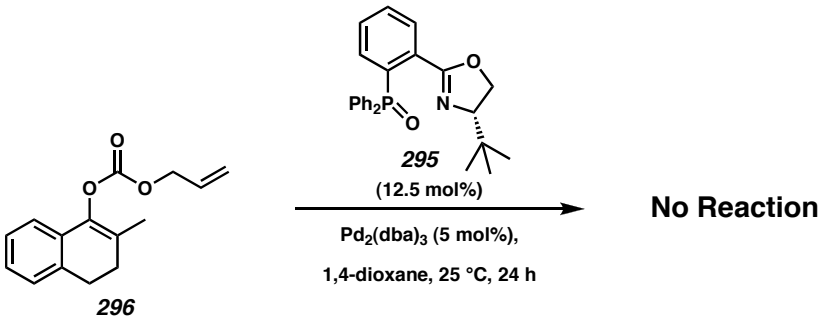
R = Bn
(S)-Bn-PHOX (292)
R = t-Bu
(S)-t-Bu-PHOX (294)

[a] GC yield relative to internal standard (tridecane). [b] Enantiomeric excess measured by chiral GC. [c] (*R*)-***275*** produced as the major product.

4.2.2 *Optimization of Reaction Parameters*

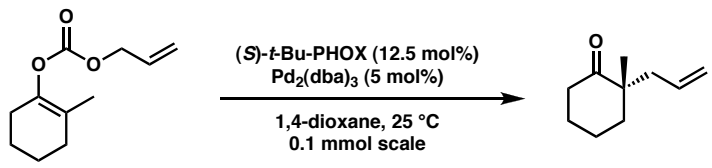
Tsuji's straightforward experimental procedure for allylation provided several opportunities to optimize the asymmetric reaction. One important experimental parameter is complexation time for the (*S*)-*t*-Bu-PHOX and $Pd_2(dba)_3$. Our optimal 30 minutes complexation time represents a balance between short complexation times (e.g., 5 minutes) in which lower yields but complete conversion were observed, and longer complexation times (e.g., 1-3 hours) in which poor conversion was observed. Long complexation times seem to be complicated by adventitious amounts of O_2 that readily oxidize the ligated PHOX molecule at phosphorus and prevent significant consumption of the starting material. We have independently synthesized (*S*)-*t*-Bu-PHOX oxide (**295**) and shown that it does not catalyze the allylation of tetralone-derived allyl enol carbonate **296** (Scheme 4.4).[20]

Scheme 4.4 Catalytic Inactivity of (*S*)-*t*-Bu-PHOX Oxide



In adapting Tsuji's non-enantioselective conditions, we also investigated the effect of concentration on the reaction (Table 4.2). At higher concentrations, significantly lower yields were observed, as well as slightly decreased ee. No further increase in enantioselectivity was observed below 0.03 M.

Table 4.2 Effect of Concentration on Asymmetric Allylation



274 *275*

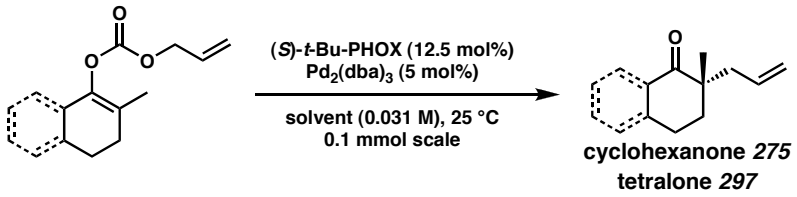
entry[a]	concentration (M)	time (h)	% yield[b]	% ee[c]
1	0.500	3	81	82
2	0.250	2	90	84
3	0.125	2	94	84
4[d]	0.063	2	99	85
5	0.031	2	95	86

[a] Data reported is the average of three trials. [b] GC yield relative to internal standard (tridecane). [c] Enantiomeric excess measured by chiral GC. [d] Data reported is the average of two trials.

Encouraged by our initial discovery that THF gave better levels of enantioinduction than 1,4-dioxane, we undertook a more thorough study of solvent effects on the reaction (Table 4.3). Many of the ethereal solvents investigated gave good results. Ethyl ether, *t*-butyl methyl ether (TBME), and diisopropyl ether all gave good yields and slightly higher ee than THF with allyl enol carbonate **274** (Entries 3 to 5). However, the methyl tetralone-derived allyl enol carbonate **296** gives substantially lower enantioselectivity in ethyl ether and TBME. The catalyst system's poor solubility in these solvents occasionally led to incomplete conversion, a disadvantage that outweighed the slight increase in ee. Interestingly, several non-ethereal solvents also perform well in the reaction. Benzene and toluene gave similar yields and enantioselectivity as THF (Entries 8 and 9). Carbonyl containing solvents are tolerated in the reaction (Entries 10 and 13). Ethyl acetate gives good yields and enantioselectivity in the asymmetric allylation, while acetone gives inferior yield and enantioinduction. Interestingly, triethyl amine produces a level of enantioselectivity equal to the best ethereal solvents, albeit

with lower yields. Halogenated solvents fair poorly in the reaction, producing small amounts of product (Entries 14 and 15). Overall, we were surprised that a variety of solvents with vastly different lone pair donating abilities and polarities perform equally well.

Table 4.3 Effect of Solvent on Asymmetric Allylation



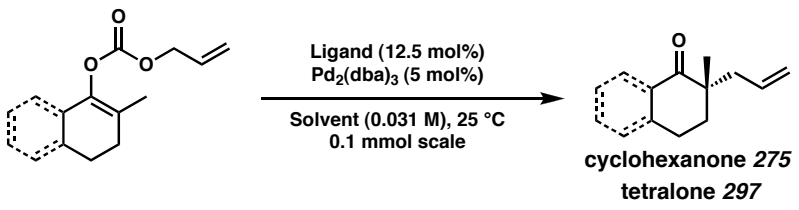
		275[a]			297[a,b]	
entry	solvent	time (h)	% yield[c]	% ee[d]	time (h)	% ee[e]
1	1,4-dioxane	2	95	86	1	87
2	tetrahydrofuran	2	96	88	1	88
3	ethyl ether	2	98	89	1	80
4	*t*-butyl methyl ether	2	98	89	1	78
5	diisopropyl ether	2	95	89		
6	anisole	3	82	81		
7	dimethoxy ethane	2	72	56		
8	benzene	2	99	88	1	89
9	toluene	2	99	88	1	87
10	ethyl acetate	2	97	86		
11	triethyl amine	2	72	89		
12	fluorobenzene	3	58	51		
13	acetone	3	26	60		
14	methylene chloride	3	42	13		
15	chloroform	6	0	NA		

[a] Data reported is the average of three trials. [b] All reactions went to complete conversion. [c] GC yield relative to internal standard (tridecane). [d] Enantiomeric excess measured by chiral GC. [e] Enantiomeric excess measured by chiral HPLC.

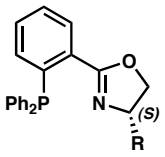
4.2.3 *Fine Tuning of Phosphinooxazoline Ligands*

A substantial effort was undertaken to improve the enantioselectivity of the reaction by modifying the PHOX ligand structure (Table 4.4).[21] Hoping to continue the trend of increasing enantioselectivity initially noted in moving from *i*-Pr to *t*-Bu-PHOX, we undertook the synthesis of numerous PHOX ligands with varied sterics and evaluated them in the reaction of allyl enol carbonates **274** and **296**. (Entries 1 to 9). In general, ligands bearing saturated substituents seem to perform better than those with aryl groups with respect to enantioselectivity. Moving the steric bulk away from the oxazoline framework by inserting a methylene group (i.e., ligand **299**) substantially lowers enantioselectivity. Of particular note are the L-serine-derived ligands **303** and **304**,[22] which allow access to the enantiomeric *R* product series with nearly the same level of enantioselectivity as *t*-Bu-PHOX, but without the need for prohibitively expensive (*R*)-*t*-Bu-glycine. The known 1-amino indanol-derived ligand **305** and bornyl-derived ligand **306**, both with uniquely shaped substituents, give slightly less enantioselectivity than *t*-Bu-PHOX.[23] It is noteworthy that regardless of the shape or type of the substituent on the PHOX ligand, they produced ketones with quaternary stereocenters with a consistent sense of configuration (e.g., (*S*)-PHOX ligands provide (*S*)-**275**). With *t*-Bu-PHOX established as the optimal steric frame work, we next considered the electronics of the ligand.

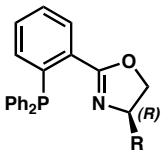
Table 4.4 Effect of Phosphinooxazoline Sterics on Asymmetric Allylation



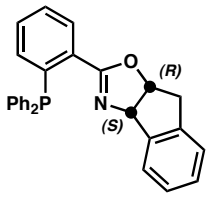
entry	ligand	product[a]	solvent	% ee[b]	major enantiomer
1	*294*	*275*	THF	88	*S*
2[c]	*298*	*297*	1,4-dioxane	78	*S*
3	*292*	*275*	THF	63	*S*
4	*299*	*297*	THF	59	*S*
5	*300*	*275*	THF	41	*S*
6	*293*	*275*	THF	83	*R*
7	*301*	*275*	THF	83	*R*
8	*291*	*275*	THF	85	*R*
9	*302*	*275*	THF	69	*R*
10	*303*	*297*	THF	85	*R*
11	*304*	*297*	THF	85	*R*
12	*305*	*297*	THF	79	*S*
13	*306*	*297*	THF	81	*S*



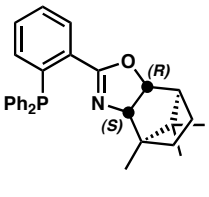
294, R = ***t*-Bu**
298, R = **1-Ad**
292, R = **Bn**
299, R = **CH_2-*t*-Bu**
300, R = **CH_2-1-Naphthyl**



293, R = ***i*-Pr**
301, R = **Cy**
291, R = **Ph**
302, R = **$CHPh_2$**
303, R = **$C(Me)_2OBn$**
304, R = **$C(Me)_2OTBS$**



305



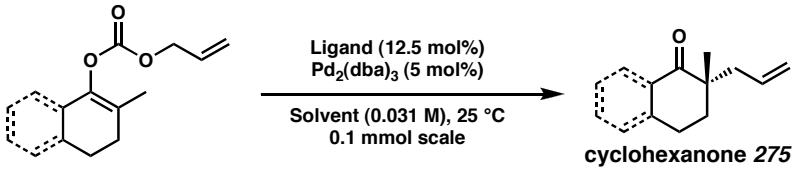
306

[a] All reactions went to complete conversion. [b] Enantiomeric excess measured by chiral HPLC or GC. [c] Reaction run at 0.2 M in 1,4-dioxane; result would likely be 3-5% ee higher under dilute concentrations in THF.

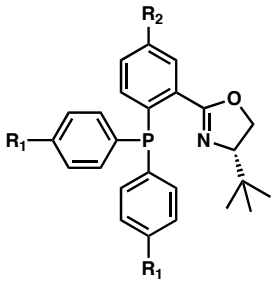
A number of *t*-Bu-PHOX derivatives were synthesized to probe the importance of phosphine electronics (Table 4.5). We investigated ligands ranging from electron rich to electron poor phosphines with allyl enol carbonates **296** and **274** (Entries 1 to 7 and 8 to

14, respectively). The electronic perturbation has no significant effect on reaction yield. However, electron releasing *para* substituents on the phenyl rings tend to lower the ee of the product relative to that observed with (*S*)-*t*-Bu-PHOX (Entries 1 and 8). When allyl enol carbonate **296** was used as the substrate, a slight increase in enantioselectivity is observed with electron withdrawing substitution at the *p*-phenyl positions (Entries 3 to 5). However, enantioselectivity decreases significantly with extremely electron poor PHOX ligands (Entries 6 and 7). This trend is not apparent in the enantioselectivities of cyclohexyl-derived allyl enol carbonate **274** (Entries 9 to 14).

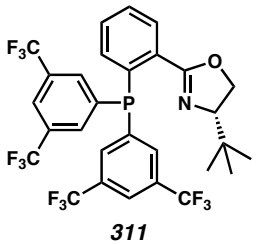
Table 4.5 Effect of Phosphine Electronics on Asymmetric Allylation



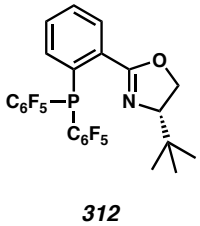
entry	ligand	product[a]	solvent	% ee[b]	entry	ligand	product	solvent	% yield[c]	% ee[d]
1	*307*	*297*	1,4-dioxane	81	8	*313*	*275*	THF	99	86
2	*294*	*297*	1,4-dioxane	87	9	*294*	*275*	THF	96	88
3	*308*	*297*	1,4-dioxane	88	10	*314*	*275*	THF	99	89
4	*309*	*297*	1,4-dioxane	89	11	*308*	*275*	THF	95	88
5	*310*	*297*	1,4-dioxane	90	12[e]	*309*	*275*	THF	97	87
6	*311*	*297*	1,4-dioxane	83	13[e]	*310*	*275*	THF	89	88
7	*312*	*297*	1,4-dioxane	81	14	*315*	*275*	THF	99	87



307, R_1 = Me, R_2 = H
294, R_1 = H, R_2 = H
308, R_1 = F, R_2 = H
309, R_1 = CF_3, R_2 = H
310, R_1 = H, R_2 = NO_2
313, R_1 = H, R_2 = OMe
314, R_1 = H, R_2 = CF_3
315, R_1 = CF_3, R_2 = CF_3



311

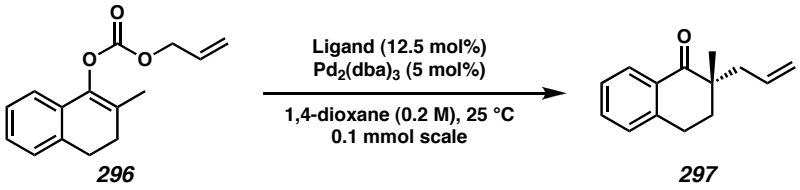


312

[a] All reactions went to complete conversion. [b] Enantiomeric excess measured by chiral HPLC. [c] GC yield relative to internal standard (tridecane). [d] Enantiomeric excess measured by chiral GC. [e] Data reported is the average of two trials.

As a final investigation into the PHOX ligand structure, we prepared a number of non-N/P mixed chelates based on the phenyl oxazoline skeleton of the PHOX ligands (Table 4.6). As mentioned above, the phosphine oxide of *t*-Bu-PHOX is inactive as a catalyst (Entry 2). Sulfur analogue **316** also fails to catalyze the reaction (Entry 3).[24] Moving down the periodic table from phosphorus, arsenic oxazoline analogue **317** has excellent activity as a catalyst, but gave tetralone **297** in only moderate ee (Entry 4). The nitrogen analogue **318** shows little activity as a catalyst, and the small amount of product produced is nearly racemic (Entry 5). As a final derivative that maintains the six-membered chelation, but changes the hybridization of the backbone atoms involved, known ligand **319** was found to give only moderate ee (Entry 6).[25]

Table 4.6 Effect of Varied Heteroatom Chelates on Asymmetric Allylation



296 ***297***

entry	ligand	% conversion[a]	% ee[b]
1	***294***, R = PPh_2	100	82
2	***295***, R = $P(O)Ph_2$	0	ND
3	***316***, R = SPh	0	ND
4	***317***, R = $AsPh_2$	100	52
5	***318***	<5	7
6[c]	***319***	87	56

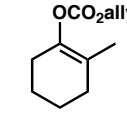
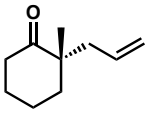
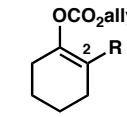
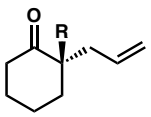
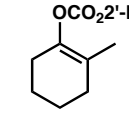
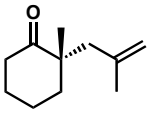
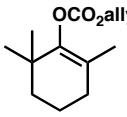
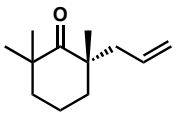
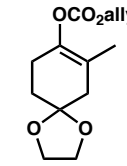
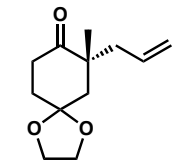
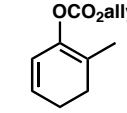
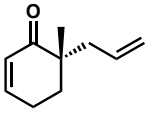
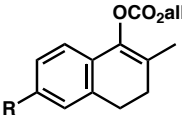
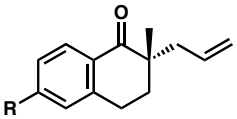
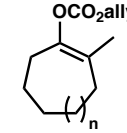
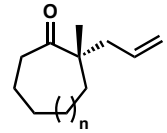
[a] Conversion based on TLC analysis. [b] Enantiomeric excess measured by chiral HPLC. [c] Trial performed with allyl enol carbonate ***274***. Conversion measured by GC relative to internal standard (tridecane). Enantiomeric excess measured by chiral GC.

Although some electron deficient derivatives of *t*-Bu-PHOX did provide slightly better enantioselectivities than those observed with *t*-Bu-PHOX on certain substrates, ultimately this slight improvement did not balance the added difficulty in synthesizing substituted PHOX ligands. Our studies clearly show that N/P chelates are particularly effective at inducing high levels of asymmetry in allylation. As a result, we retained the use of (*S*)-*t*-Bu-PHOX in our optimized conditions for exploring scope of the reaction.

4.2.4 *Asymmetric Allylation of Allyl Enol Carbonates*

A variety of allyl enol carbonates was demonstrated successfully in our asymmetric Tsuji allylation (Table 4.7).[26] Alkyl substitution at the 2-position of the allyl enol carbonates is well tolerated (Entries 4 to 7). *t*-Butyl substituted carbonate **322** is of note, as it forms a quaternary stereocenter vicinal to a quaternary carbon atom in the allylation. The allyl fragment may also be substituted at the internal position (Entry 8). Substitution at the 4 and 6 positions of the cyclohexyl ring do not greatly affect the rate or enantioselectivity of the process (Entries 9 and 10). Interestingly, unsaturation of the substrate still affords the desired α-quaternary ketone in excellent yield and good enantioselectivity (Entries 11 to 13). The isolation of enone **334** in excellent yield without the observation of any Michael products highlights the mild and nearly neutral reaction conditions. Performing the allylation reaction at 10-12 °C typically increases the enantioselectivity by 1-2%, but significantly lengthens the reaction time (Entries 3, 12, and 13). Reactions at 0 °C or lower appear to have difficulty undergoing oxidative addition and are only reliably performed with highly activated substrates.[27] In addition to six-membered ring substrates, seven- and eight-membered ring substrates also provide good yields.

Table 4.7 Substrate Scope for Asymmetric Allylation of Allyl Enol Carbonates

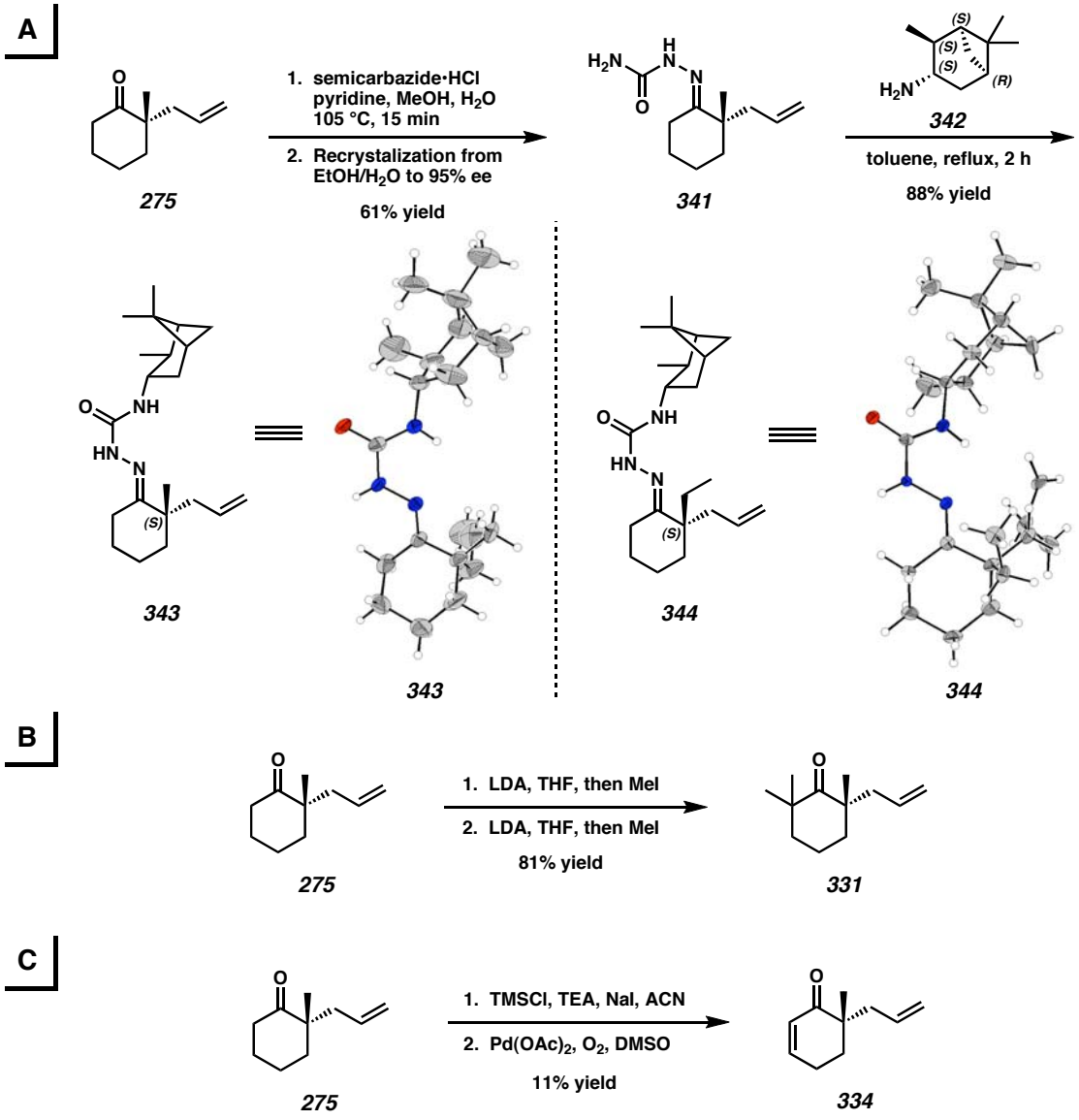
entry	substrate[a]	product	time (h)	% yield[b]	% ee[c]
1			2	85	87
2[d]	***274***	***275***	5	85	88 (96)[e]
3[f]			9	90	89
4	 ***320***, R = CH_2CH_3	 ***321***, R = CH_2CH_3	2	96	92
5[g]	***322***, R = *t*-Bu	***323***, R = *t*-Bu	10	55[h]	82
6	***324***, R = CH_2Ph	***325***, R = CH_2Ph	2	96	85
7	***326***, R = $(CH_2)_3OBn$	***327***, R = $(CH_2)_3OBn$	2	87	88
8[g]	 ***328***	 ***329***	8	89	91
9	 ***330***	 ***331***	1	94	92
10	 ***332***	 ***152***	1	87	86
11	 ***333***	 ***334***	1	91	89
12[i]	 ***296***, R = H	 ***297***, R = H	2	87	91
13[i]	***335***, R = OCH_3	***336***, R = OCH_3	8	94	91
14	 ***337***, n = 1	 ***338***, n = 1	6	81	87
15	***339***, n = 2	***340***, n = 2	2	90	79

[a] Reactions were performed using 1.0 mmol of substrate in THF (0.033 M in substrate) at 25 °C with $Pd_2(dba)_3$ (2.5 mol%), *(S)-t*-Bu-PHOX (6.25 mol%), unless stated otherwise. [b] Isolated yields. [c] Measured by chiral GC or HPLC. [d] Performed on 5.1 mmol scale. [e] In parentheses is the % ee after one recrystallization of the corresponding semicarbazone. [f] Reaction performed at 12 °C (GC yield). [g] Performed with 5 mol% $Pd_2(dba)_3$ and 12.5 mol% *(S)-t*-Bu-PHOX. [h] Isolated yield after conversion to the corresponding diketone via Wacker oxidation. [i] Performed at 10 °C.

At the time of our investigations, 2-methyl-2-allyl cyclohexanone was not known in enantioenriched form. Consequently, we wished to determine the absolute stereochemistry for several of our substrates (Scheme 4.5). To definitively assign the

absolute stereochemistry of the newly formed quaternary stereocenter, we derivatized ketone **275** as its semicarbazone **341**. Semicarbazone **341** is highly crystalline and recrystallization from EtOH/H_2O produced material of near enantiopurity (98% ee after two recrystallizations).[28] Treatment of the semicarbazone with amine **342** of known absolute stereochemistry in refluxing toluene gave the substituted semicarbazone **343**. Amino-substituted semicarbazone **343** also proved to be crystalline and amenable to X-ray structure determination when recrystallized from acetone. As the absolute stereochemistry of the isopinocampheylamine portion of semicarbazone **343** was known, the quaternary stereocenter set during the allylation could be assigned *S* configuration. This sequence was performed on ethyl quaternary ketone **321**, which confirmed that it too is of *S* configuration.[29] Additionally, quaternary ketone (*S*)-**275** could be transformed in a straightforward manner to trimethyl ketone **331** and enone **334** (Reactions B and C). These transformations confirmed that the allylation reaction forms ketone **331** and enone **334** with the same sense of absolute configuration. Finally, tetralone **297** was confirmed to be produced in our allylation with *S* stereochemistry by comparison with literature data.[13b]

Scheme 4.5 Determination of Absolute Stereochemistry



Our use of allyl enol carbonates enabled direct access to α-quaternary ketones with multiple acidic sites. However, allyl enol carbonates are rarely encountered in the literature, and the synthesis of isomerically pure enol carbonates often requires the synthesis of silyl enol ethers.[30] Since Tsuji had used silyl enol ethers in his racemic

allylation, we hoped to adapt our conditions such that silyl enol ethers could be employed as well.

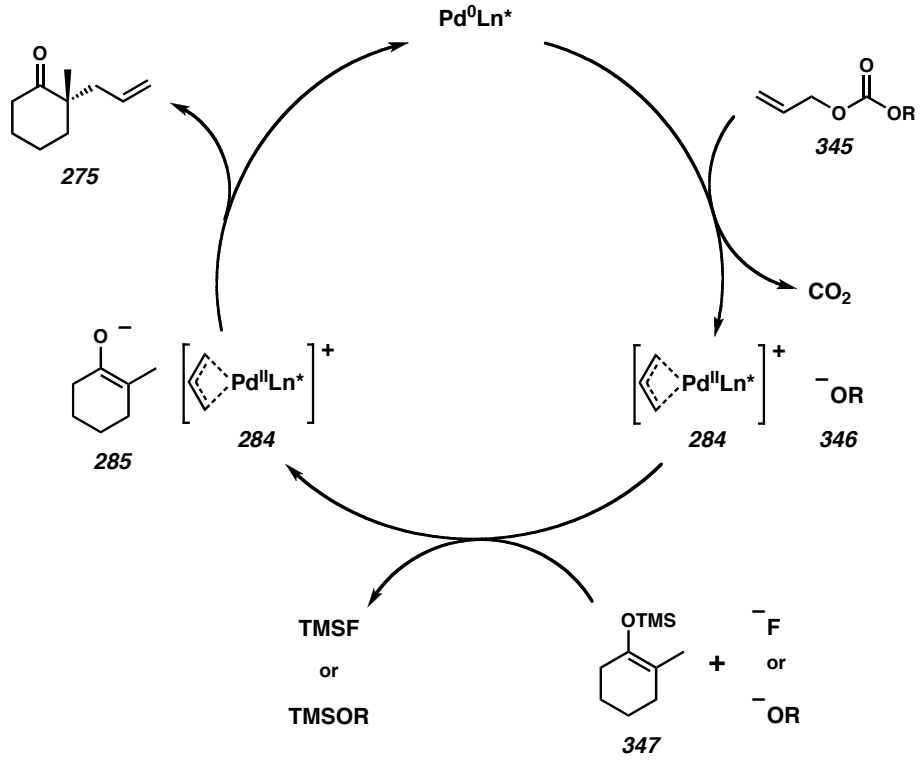
4.2.5 *Asymmetric Allylation of Silyl Enol Ethers*

The use of silyl enol ethers offered several advantages over allyl enol carbonates. Silyl enol ethers are commonly encountered enolate equivalents in organic chemistry. Unlike allyl enol carbonates, employing silyl enol ethers renders the reaction intermolecular, with the enolate precursor and allyl fragment introduced separately. We discovered in our initial studies that silyl enol ethers are not sufficiently nucleophilic to react with the Pd(II) allyl fragment under our reaction conditions at 25 °C. However, we found that the reaction could be initiated in the presence of $Bu_4NPh_3SiF_2$ (TBAT), a dry fluoride source.

The use of TBAT as an initiator complicates the proposed catalytic cycle (Scheme 4.6). In the case of allyl enol carbonates, the oxidative addition to allyl carbonate **274** leads immediately to the enolate and Pd(II) allyl ion pair, which can collapse directly to the product (Scheme 4.3). For the intermolecular reaction, we primarily use diallyl carbonates as an allyl precursor, but mixed carbonates are also effective. Oxidative addition of diallyl carbonate occurs readily at 25 °C to give Pd(II) allyl species **284** and alkoxide **346**. The addition of TBAT immediately generates the enolate. We hoped the enolate would react with the palladium complex **284** by the same enantioselective mechanism observed with the allyl enol carbonates. A substoichiometric amount of TBAT is sufficient, as the alkoxide generated in the reaction is also capable of generating the enolate in situ.[31] In principle, it should be possible for the small amount of allyl

alkoxide generated from oxidative addition to initiate the reaction. In practice, we found that 35 mol% TBAT was usually sufficient to ensure complete conversion of the silyl enol ether. Having developed an effective means of silyl enol ether activation, we attempted asymmetric allylation with a range of tetrasubstituted silyl enol ethers.

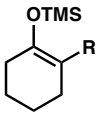
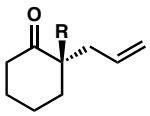
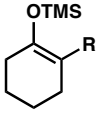
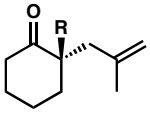
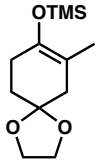
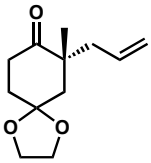
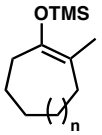
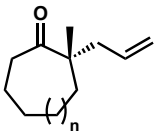
Scheme 4.6 General Mechanism for Silyl Enol Ether Allylation



Gratifyingly, allylation of the silyl enol ether substrates occurs with levels of enantioinduction similar to those observed for the allyl enol carbonate substrates and over a similar diversity of substrates (Table 4.8). Specifically, quaternary ketones **275** and **321** are produced with the same ee observed in the allyl enol carbonate reactions (Entries 1 and 2). α-Oxygenated silyl enol ether **349** undergoes allylation to give ketone **350** with a tertiary ether stereocenter, albeit with moderate enantioselectivity (Entry 3). In addition

to diallyl carbonate, dimethallyl carbonate serves as a suitable allyl fragment precursor (Entries 4 and 5). Impressively, allyl methallyl ketone **352**, bearing only a remote methyl group to engender chirality, is formed in 91% ee. As with the reactions of allyl enol carbonates, substitution about the ring and larger ring size are tolerated (Entries 6 to 8).

Table 4.8 Substrate Scope for Asymmetric Allylation of Silyl Enol Ethers

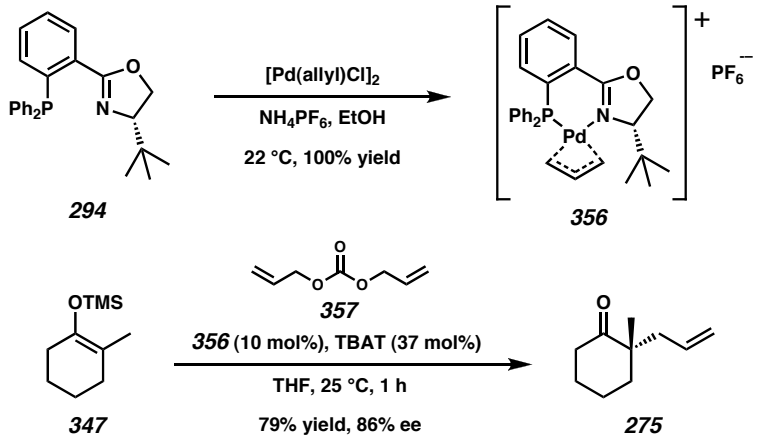
entry	substrate[a]		product		time (h)	% yield[b]	% ee[c]
1		***347*, R = CH_3**		***275*, R = CH_3**	2	95	87
2		***348*, R = CH_2CH_3**		***321*, R = CH_2CH_3**	3	96	92
3		***349*, R = OBn**		***350*, R = OBn**	3	83	59
4[d]		***347*, R = CH_3**		***329*, R = CH_3**	4	79	91
5[d]		**351, R = allyl**		**352, R = allyl**	5	82	91
6		***353***		***152***	2	99	81
7		***354*, n = 1**		***338*, n = 1**	2	94	86
8		***355*, n = 2**		***340*, n = 2**	3	96	79

[a] Reactions were performed using 1.0 mmol of substrate in THF (0.033 M in substrate) at 25 °C with $Pd_2(dba)_3$ (2.5 mol%), *(S)-t*-Bu-PHOX (6.25 mol%), diallyl carbonate (1.05 equiv), TBAT (35 mol%) unless stated otherwise. [b] Isolated yields. [c] Measured by chiral GC or HPLC. [d] Reaction performed with dimethallyl carbonate (1.05 equiv).

In addition to the flexibility afforded by the intermolecular reaction of silyl enol ethers and diallyl carbonates, the use of silyl enol ethers as a means to generate enolates independent of the allyl fragment allows the catalytic cycle to commence at the stage of a Pd(II) allyl salt **356** (Scheme 4.7). The Pd(II)(allyl)PHOX•PF_6 salt **356** readily precipitates upon mixing (*S*)-*t*-Bu-PHOX, $[Pd(allyl)Cl]_2$, and NH_4PF_6 in ethanol.[32] The

salt serves as an active catalyst in the asymmetric Tsuji allylation reaction, giving good yields and nearly identical enantioselectivity to the in situ generated catalyst. The Pd(II)PF_6 salt **356** has several practical advantages. It is a stable non-hygroscopic solid, which may be stored indefinitely. Moreover, using the preformed Pd(allyl)PHOX catalyst prevents the introduction of dba, which often complicates the purification of the α-quaternary ketone products.

Scheme 4.7 Allylation with Pd(II)•PF_6 Salt **356**

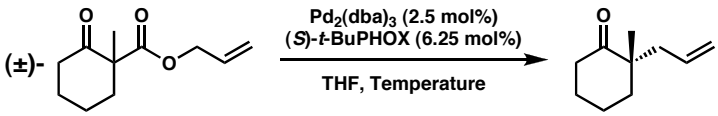


Our work with silyl enol ethers demonstrated that our enantioselective process is robust enough to overcome the intermolecular introduction of the enolate and allyl fragments and to tolerate the presence of other ions in solution. Silyl enol ethers are a more familiar substrate class and greatly increase the practicality of the reaction. However, we rely on thermodynamically driven silyl enol ether syntheses, which typically produce a 10:1 ratio of isomers that require tedious purification to obtain isomerically pure substrates.[33] A direct method for the synthesis of isomerically pure substrates would further increase the practicality of the catalyst system.

4.2.6 *Asymmetric Allylation with Racemic Allyl β-Ketoesters*

β-Ketoesters represent a classical solution to the problem of regioselective ketone alkylation. However, as stereogenic racemic substrates for a catalytic asymmetric reaction, the allyl β-ketoesters required could in principle undergo kinetic resolution or experience diastereomeric transition states. In the event, no significant kinetic resolution of the allyl β-ketoesters was observed.[34] The similar levels of enantioselectivity observed between the allyl β-ketoester substrates and the other classes of substrate suggest that the enantiodetermining transition state of the reaction remains unchanged. The only modification to our standard conditions required for the use of β-ketoester substrates is slight warming (Table 4.9). While the extent to which decarboxylation slowed at ambient temperature varied from substrate to substrate, β-ketoesters are uniformly more sluggish in decarboxylation than allyl enol carbonates.[35] However, this difficulty could typically be overcome by performing the reaction 5 °C warmer, which had a negligible effect on enantioselectivity.

Table 4.9 Temperature Effects on Decarboxylative Allylation of Allyl β-Ketoesters



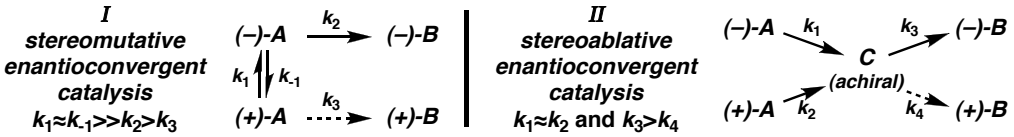
358 *275*

entry	temp (°C)	time (h)	% yield[a]	% ee[b]
1	18	48	0	ND
2	25	7.5	85	88
3	30	2.25	82	87
4	35	1.25	85	86
5	40	0.67	86	85
6	60	0.15	82	83

[a] Isolated yield from reaction of 1.0 mmol substrate at 0.033 M. [b] Determined by chiral GC.

The use of quaternary β-ketoesters renders this deracemization reaction unusual (Scheme 4.8). Typical deracemizations involve a pre-equilibrium epimerization of the starting material, A, followed by enantioselective conversion to product B (Pathway I).[36] However, quaternary stereocenters are not typically epimerizable, and we believe that both enantiomers of the starting material, A, are converted to a prochiral intermediate, C,[37] which preferentially forms one enantiomer of the product B under the influence of the chiral catalyst (Pathway II). We have termed such transformations stereoablative enantioconvergent catalysis.[38] As a result of this interesting mechanism and the facile synthesis of quaternary β-ketoesters, we have been able to expand our substrate scope greatly.

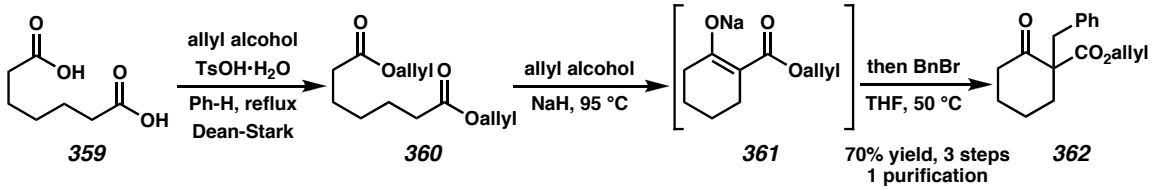
Scheme 4.8 Stereoablative Enantioconvergent Catalysis



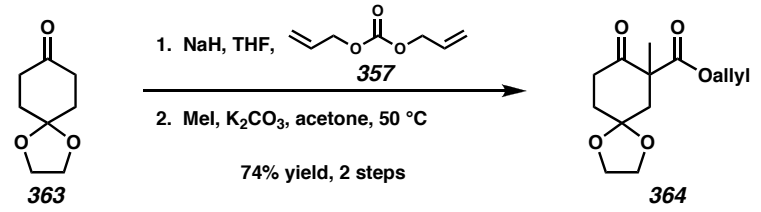
During the course of our studies, several practical methods for the synthesis of quaternary β-ketoesters have been frequently used (Scheme 4.9). The Dieckmann cyclization of pimelic acid diallyl ester (**360**) gives an intermediate cyclized sodium salt **361**, which can be alkylated to give quaternary β-ketoesters, such as benzylated compound **362**.[39] Alternatively, sodium salt **361** can be protonated to give the 2-carboxyallylcyclohexanone, and alkylated in a separate step. Cyclic ketones, such as 1,4-cyclohexandione *mono*-ethylene ketal (**363**), may be treated with base and diallyl carbonate to effect acylation. Mild alkylation conditions (MeI and K_2CO_3 in acetone) allow the C-methylated β-ketoester to be isolated in 74% yield over two steps with only one chromatographic purification. Both of these methods are inexpensive and can be readily carried out on large scale. In cases where O-acylation or multiple sites of C-acylation are problematic, such as enone **365**, treatment with LDA under kinetic conditions and then allyl Mander's reagent **366** frequently gives selective acylation.[40]

Scheme 4.9 Methods for the Synthesis of Racemic Quaternary β-Ketoesters

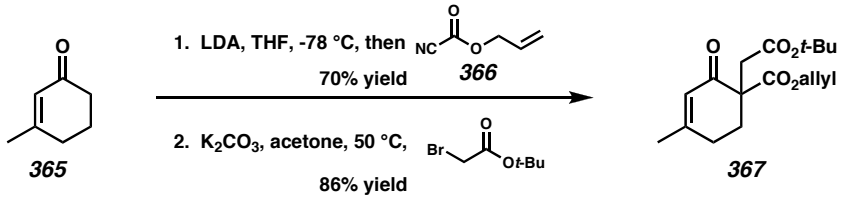
Dieckmann Cyclization Method



Diallyl Carbonate Method



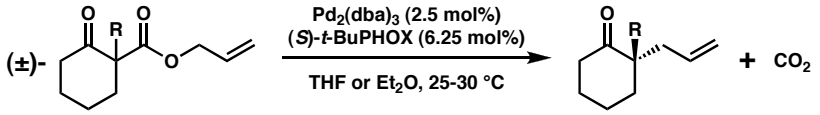
Mander's Reagent Method



A number of α-substituted 2-carboxyallylcyclohexanones are readily prepared by the above methods and were successfully subjected to enantioconvergent decarboxylative allylation (Table 4.10). Acrylonitrile and ethyl acrylate-derived substrates **370** and **372** undergo smooth reaction, to give the α-quaternary ketone products in excellent yield (Entries 4 and 5). Interestingly, these products are equivalent to the products of an asymmetric conjugate addition with the enolate of 2-allyl cyclohexanone. Silylated formaldehyde adduct **378** demonstrates the allylation of a substrate with a heteroatom positioned for β-elimination from the intermediate enolate (Entry 9).[41] Another noteworthy substrate is α-fluorinated β-ketoester **380**. Decarboxylative allylation of **380** afforded tertiary fluoride **381** in 80% yield and 91% ee.[42] Such α-fluorinated carbonyl

compounds with well defined absolute stereochemistry may find use as NMR probes in biological systems or as non-epimerizable isosteres for stereocenters α to carbonyls.[43]

Table 4.10 Enantioconvergent Decarboxylative Allylation of α-Substituted 2-Carboxyallylcyclohexanones



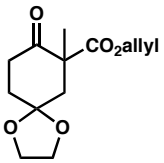
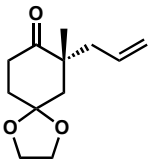
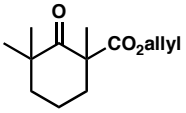
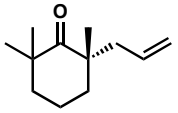
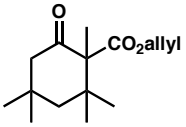
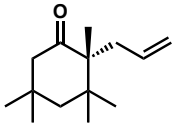
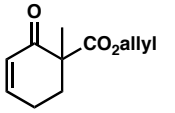
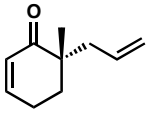
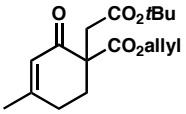
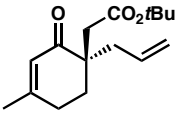
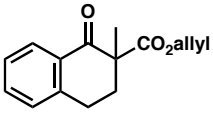
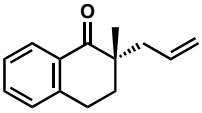
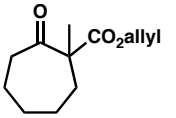
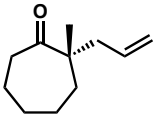
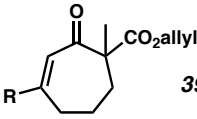
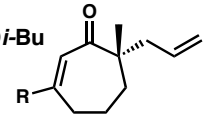
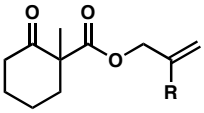
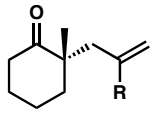
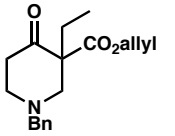
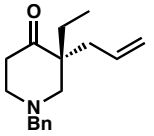
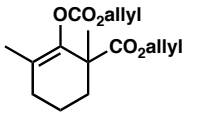
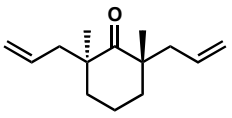
entry	R	substrate	product	solvent	temp (°C)	time (h)	% yield[a]	% ee[b]
1	CH_3	*358*	*275*	THF	25	7.5	85	88
2	CH_3	*358*	*275*	Et_2O	25	4.75	89	88
3	prenyl	*368*	*369*	Et_2O	30	6	97	91
4	CH_2CH_2CN	*370*	*371*	Et_2O	25	6.5	97	88
5[c]	$CH_2CH_2CO_2Et$	*372*	*373*	Et_2O	25	6	96	90
6	$CH_2C_6H_5$	*362*	*325*	THF	25	0.5	99	85
7	$CH_2(4\text{-}CH_3OC_6H_4)$	*374*	*375*	THF	25	10	80	86
8	$CH_2(4\text{-}CF_3C_6H_4)$	*376*	*377*	THF	25	0.5	99	82
9[c]	$CH_2OTBDPS$	*378*	*379*	THF	25	5	86	81
10	F	*380*	*381*	Et_2O	30	3.5	80	91

[a] Isolated yield from reaction of 1.0 mmol substrate at 0.033 M in solvent, unless otherwise noted. [b] Determined by chiral GC or HPLC. [c] 4 mol% $Pd_2(dba)_3$, 10 mol% (*S*)-*t*-Bu-PHOX, 0.021 M.

In addition to modifications at the α-position of the substrate, the decarboxylative asymmetric allylation tolerates a wide variety of modification to the carbocycle and allyl fragment of the substrate (Table 4.11). In particular, the reaction is exceptionally tolerant to the steric demands of substitution at the 3, 4, 5, and 6 positions of the cyclohexane ring. Each position can be fully substituted without significantly affecting yield or enantioselection (Entries 1 to 4). Unsaturated substrates (Entries 5 to 7) as well as seven-membered ring containing substrates (Entries 8 to 10) perform well in the reaction. Of note are vinylogous ester **388** and vinylogous thioester **390**. Interestingly, thioester

390 provides significantly higher enantioselectivity in the allylation than ester **388** (89 vs. 85% ee).[44] As with the previous substrate classes, substitution at the central position of the allyl fragment has a slightly beneficial effect on the enantioselectivity of the reaction (Entries 11 and 12). The incorporation of a chlorine atom on the allyl fragment provides another functional group handle for further manipulation and higher oxidation state. Piperidinone **395** demonstrates the use of a nitrogen heterocycle in the allylation (Entry 13). In an effort to construct more than one quaternary stereocenter in a single transformation, we prepared allyl enol carbonate **397**. This substrate contains a latent allyl β-ketoester moiety, which would be revealed by the reaction of the allyl enol carbonate portion of the molecule. To our delight, tandem allylation occurred to afford C_2 symmetric ketone **398** as the predominant product in 92% ee.

Table 4.11 Enantioconvergent Decarboxylative Allylation of β-Ketoesters with Substituted Carbocycles and Allyl Fragments

entry	substrate		product		temp (°C)	time (h)	% yield[a]	% ee[b]
1		*364*		*152*	25	1.5	94	85
2[c]		*364*		*152*	25	24	94	86
3		*382*		*331*	30	9	89	90
4		*383*		*256*	25	5	90	85
5[d,e]		*384*		*334*	30	4	77	90
6[d]		*367*		*385*	30	9	73	86
7[d]		*386*		*297*	25	10	97	92
8		*387*		*338*	25	9.5	83	87
9[d,e]		*388*, R = O*i*-Bu		*389*, R = O*i*-Bu	30	6	92	85
10[d,f]		*390*, R = SPh		*391*, R = SPh	30	5	86	89
11[d]		*392*, R = CH_3		*329*, R = CH_3	35	6.5	87	92
12[d,g]		*393*, R = Cl		*394*, R = Cl	35	2.5	87	91
13		*395*		*396*	25	2.5	91	92
14[h]		*397*		*398*	40	6	76[i]	92

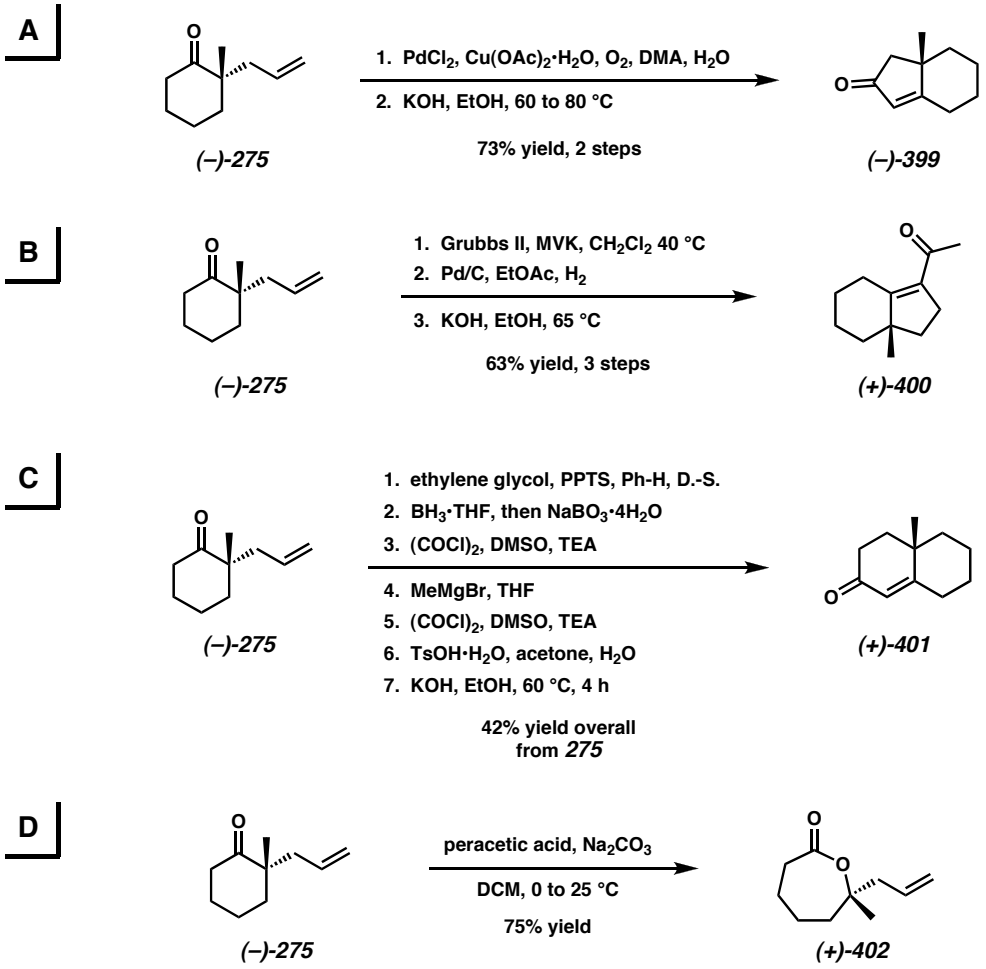
[a] Isolated yield from reaction of 1.0 mmol substrate, 2.5 mol% $Pd_2(dba)_3$ and 6.25 mol% (*S*)-*t*-Bu-PHOX at 0.033 M in THF, unless otherwise noted. [b] Determined by chiral GC or HPLC. [c] 25 mmol substrate, 1.5 mol% $Pd_2(dba)_3$, and 3.75 mol% (*S*)-*t*-Bu-PHOX. [d] Performed in Et_2O. [e] Reaction performed on 0.16 mmol scale, 5 mol% $Pd(dmdba)_2$, and 6.25 mol% (*S*)-*t*-Bu-PHOX at 0.100 M. [f] Reaction performed on 0.29 mmol scale, 5 mol% $Pd(dmdba)_2$, and 6.25 mol% (*S*)-*t*-Bu-PHOX at 0.100 M. [g] 4 mol% $Pd_2(dba)_3$, and 10 mol% (*S*)-*t*-Bu-PHOX at 0.021 M. [h] 4 mol% $Pd_2(dba)_3$ and 10 mol% (*S*)-*t*-Bu-PHOX. [i] 4:1 mixture of C_2:meso diastereomers.

4.3 Synthetic Applications

The α-quaternary allyl cycloalkanones produced in the asymmetric Tsuji allylation are highly useful chiral building blocks. Each substrate contains at least two functional groups, a ketone and an olefin, for further manipulation. Moreover, the preceding section has demonstrated these allylation reactions to be highly functional group tolerant. The application of this suite of allylation reactions to the catalytic asymmetric synthesis of natural products is an ongoing topic of research in our laboratories.[28b]

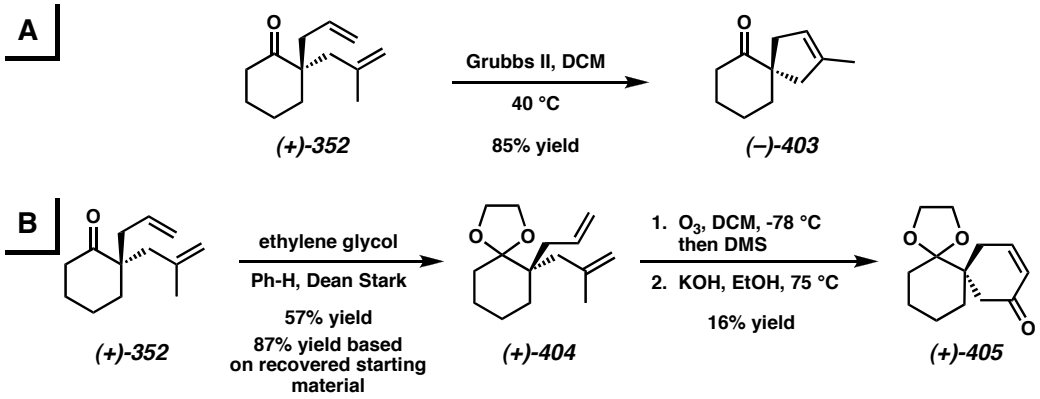
To demonstrate further the utility of these products, we transformed ketone (–)-(*S*)-**275** into several familiar cyclic frameworks (Scheme 4.10). Wacker oxidation of (–)-(*S*)-**275** followed by aldol condensation gave enone **399** in good yield (Reaction A). An alternative [6-5] skeleton was formed in a three-step sequence by olefin cross metathesis with methyl vinyl ketone, olefin hydrogenation, and aldol condensation under basic conditions to afford exocyclic enone **400** (Reaction B). Carbocyclic [6-6] ring systems are accessible as well. Multi-step elaboration of the allyl group afforded an intermediate diketone, which underwent aldol condensation to enone **401** in 43% overall yield (Reaction C). Enone **401**, which has been classically produced by Robinson annulation, has been extensively used in synthesis.[45] As a final transformation of (–)-(*S*)-**275**, we executed a Baeyer-Villiger oxidation with peracetic acid to give caprolactone **402**. This transformation demonstrates the conversion of our enantioenriched quaternary stereocenter into a latent tertiary alcohol with defined absolute stereochemistry (Reaction D).

Scheme 4.10 Useful Derivatives of *(–)-(S)-***275**



Spiro quaternary stereocenters represent a particularly challenging subclass of quaternary stereocenters. In addition to the fused cyclic skeletons above, allyl methallyl ketone **32** was used as an entry into the synthesis of ring systems containing spiro quaternary stereocenters (Scheme 4.11). Ketone **352** can be treated with Grubbs' second generation catalyst in methylene chloride to give a good yield of the spiro[4.5]ketone **403**. Spiro[5.5]enone **405** is produced in a modest yield by treatment of ketone **352** with standard ketal protection conditions, followed by ozonolysis, and base.

Scheme 4.11 Synthesis of Derivatives with Spiro Quaternary Stereocenters



4.4 Reaction Scope and Limitations

4.4.1 *Introductory Remarks*

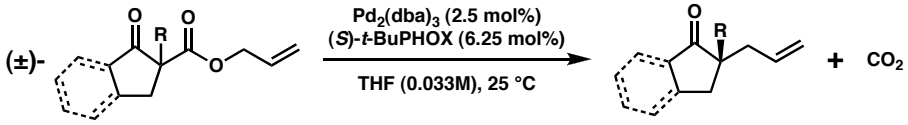
We have demonstrated that our allylation catalyst is capable of producing a great variety of highly enantioenriched quaternary stereocenters α to ketones, which were previously difficult to access, from several classes of pro-nucleophiles. However, in our studies we have encountered several substrate classes that provided substantially lower than expected levels of enantioselectivity. Interestingly, these substrates still give generally excellent chemical yield. We consider these substrates as an impetus for the development of more effective catalysts and as useful probes of the reaction's mechanism.

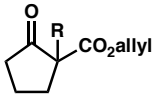
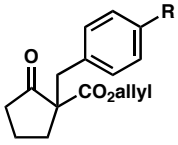
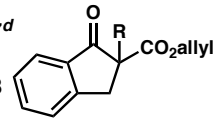
4.4.2 *Substrates Containing Five-Membered Rings*

While enolate precursors contained in six-membered rings comprise the bulk of our substrates, we have demonstrated that seven- and eight-membered rings are tolerated with only slight loss in enantioselectivity. Allyl β-ketoesters constructed on five-

membered rings also give useful levels of enantioselectivity (Table 4.12). These substrates generally give good yields of α-quaternary ketones with enantiomeric excesses about 10% lower than the cyclohexanone analogue. Ethyl substituted ketone **407** is formed in 86% ee, only 6% lower than the corresponding cyclohexanone (Entry 1). Benzyl appended cyclopentenone substrates give consistent yields, but electron deficient aromatic rings decrease enantioselectivity more significantly than in the reactions of six-membered β-ketoesters (Entries 4 to 6). Indanones are produced good yield and useful ee (Entries 7 and 8).

Table 4.12 Enantioconvergent Decarboxylative Allylation of β-Ketoesters Containing Five-Membered Rings.



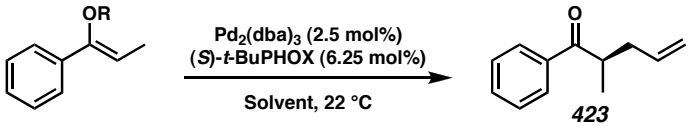
entry	substrate[a]	product	time (h)	% yield[b]	% ee[c]
1		***406***, R = CH_2CH_3	***407***, R = CH_2CH_3	3	82	86
2		***408***, R = $CH(CH_3)_2$	***409***, R = $CH(CH_3)_2$	3	77	84
3		***410***, R = CH_2NPhth	***411***, R = CH_2NPhth	2	67	48
4		***412***, R = OMe	***413***, R = OMe	2	84	73
5		414, R = Me	***415***, R = Me	2	84	73
6		***416***, R = CF_3	***417***, R = CF_3	2	83	60
7[d]		***418***, R = Me	***419***, R = Me	1	82	80
8		***420***, R = Bn	***421***, R = Bn	1	93	71

[a] Reactions were performed using 1.0 mmol of substrate in THF (0.033 M in substrate) with $Pd_2(dba)_3$ (2.5 mol%), *(S)-t*-Bu-PHOX (6.25 mol%) unless stated otherwise.
[b] Isolated yields. [c] Measured by chiral GC or HPLC. [d] Performed on 0.1 mmol scale with $Pd_2(dba)_3$ (5 mol%), *(S)-t*-Bu-PHOX (12.5 mol%).

4.4.3 *The Synthesis of Tertiary Stereocenters from Acyclic Enolate Precursors*

While we have principally employed our asymmetric allylation for the synthesis of quaternary stereocenters, the mild and nearly neutral conditions of the reaction are well suited for the synthesis of tertiary stereocenters α to carbonyls (Table 4.13).[46] Such stereocenters are prone to epimerization and over-alkylation under the strongly basic conditions traditionally used for enolate generation.[47] We found that allyl enol carbonate **422** underwent allylation to phenyl ketone **423** in 67% ee (Entry 1). In analogy to the results of Hou and coworkers, we found that the addition of silver (I) bromide gave a significant increase in the ee of the product (Entry 2).[48] Both TMS[49] and TBS[50] silyl enol ethers were competent enolate precursors when TBAT was used as an initiator (Entries 3 and 4). Unlike the tetrasubstituted silyl enol ethers, cesium fluoride proved to be the optimal fluoride source for the less substituted silyl enol ethers, engendering noticeably higher ee (Entry 5). Unfortunately, the use of silver(I) bromide in the presence of cesium fluoride greatly reduced reactivity and only slightly increased enantioselectivity (Entry 6). Similarly, the use of ethyl ether as a solvent increased enantioselectivity at the cost of lowered yield (Entry 7). Although our allylation methods have provided tertiary stereocenters in only moderate ee, we have recently disclosed a decarboxylative protonation of quaternary allyl β-ketoesters based on a similar catalyst system, which provides access to tertiary stereocenters α to ketones in excellent ee.[51]

Table 4.13 Asymmetric Allylation of Allyl Enol Carbonates and Silyl Enol Ethers Not Contained in Ring



423

entry	substrate[a]	solvent	additive	% yield[b]	% ee[c]
1	*422*, R = CO_2allyl	THF		79	67
2	*422*, R = CO_2allyl	THF	AgBr (40 mol%)	75	79
3[d]	*424*, R = TMS	THF	TBAT (35 mol%)	60	62
4[d]	*425*, R = TBS	THF	TBAT (35 mol%)	82	73
5[d]	424, R = TMS	THF	CsF (48 mol%)	79	77
6[d]	424, R = TMS	THF	CsF (48 mol%), AgBr (40 mol%)	20	79
7[d]	*424*, R = TMS	Ether	CsF (48 mol%)	38	82

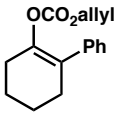
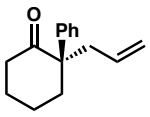
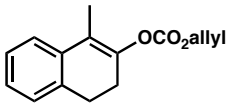
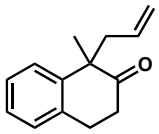
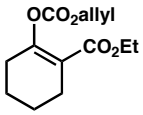
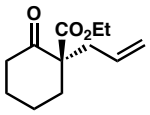
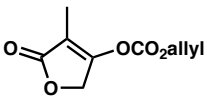
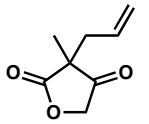
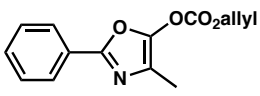
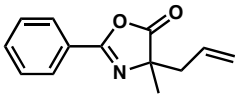
[a] Reactions were performed using 0.092 mmol of substrate (0.092 M in substrate). [b] Isolated yields. [c] Measured by chiral HPLC. [d] Reaction performed with diallyl carbonate (1.05 equiv).

4.4.4 *Substrates Proceeding via Weakly Basic Enolates*

The allylation of substrates derived from ketones of unusually low pK_a (i.e., stabilized enolates) as a group give by far the lowest levels of enantioselectivity we have observed with the PHOX catalyst system (Table 4.14). Despite this, these substrates give consistently excellent chemical yields of the allylated products. It is noteworthy that the phenyl ketone (Entries 1 and 2) and β-ketoester (Entries 3 and 4) derived enolates that gave excellent enantioselectivities in Trost's earlier asymmetric allylation reactions[13] fail to give useful levels of enantioselectivity under our conditions. Oxazole **431**, designed with the hope of executing an enantioselective synthesis of α,α-disubstituted amino acids, also underwent allylation with little enantioselectivity, presumably due to the stability of the intermediate aromatic enolate (Entry 5). The orthogonality of the

substrate scope, in terms of asymmetric induction, between our method and Trost's early reports may be indicative of fundamentally different mechanisms underlying the two allylation reactions.

Table 4.14 Asymmetric Allylation via Stabilized Allyl Enol Carbonates

entry	substrate[a]		product[b]		time (h)	% yield[c]	% ee[d]
1		*425*		*273*	2	99	11
2		*426*		*427*	2	93	0
3		*428*		*271*	2	89	24
4		*429*		*430*	2	87	2
5		*431*		*432*	2	89	2

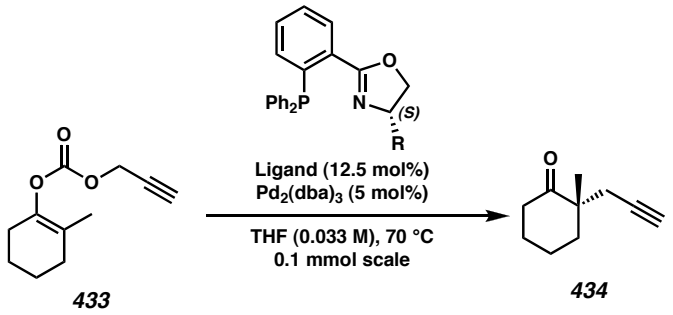
[a] Reactions were performed using 1.0 mmol of substrate in THF (0.033 M in substrate) at 25 °C with $Pd_2(dba)_3$ (2.5 mol%), *(S)-t*-Bu-PHOX (6.25 mol%). [b] Absolute stereochemistry of products assigned by analogy. [c] Isolated yields. [d] Measured by chiral GC or HPLC.

4.4.6 *Application of the Palladium PHOX Catalyst System to Propargylation*

In addition to allylation, we also explored propargylation of enol carbonates with the palladium/PHOX catalyst system (Table 4.15).[52] Our preliminary studies found that propargylation of ketone enolates required significantly higher temperatures than are required for allylation.[53] Additionally, the optimal structure of the PHOX ligand is significantly different for propargylation than for allylation. Moving the bulk of the *t*-Bu

group away from the oxazoline by insertion of a methylene group gave higher ee (Entry 2 vs. 1). Unlike allylation, PHOX ligands derived from amino acids containing aromatic side chains gave higher enantioselectivity than aliphatic side chains, with anthracenyl derivative **437** giving the highest level of enantioselectivity. While still preliminary, these studies suggest that the palladium/PHOX catalyst system may find use outside allylation reactions.[51]

Table 4.15 Asymmetric Propargylation



433 ***434***

entry	ligand	% yield[a]	% ee[b]	major enantiomer
1	***294,*** R = *t*-Bu	84	12	***S***
2	***299***, R = CH_2-*t*-Bu	83	32	***S***
3	***292***, R = CH_2Ph	54	26	***S***
4	***300***, R = CH_2-1-Naphthyl	57	37	***S***
5	***435***, R = CH_2-2-Naphthyl	71	26	***S***
6	***436***, R = CH_2-(3,5-di-*t*-Bu-Ph)	94	25	***S***
7	***437***, R = CH_2-9-Anthracenyl	80	44	***S***

[a] GC yield relative to internal standard (tridecane). [b] Enantiomeric excess measured by chiral GC.

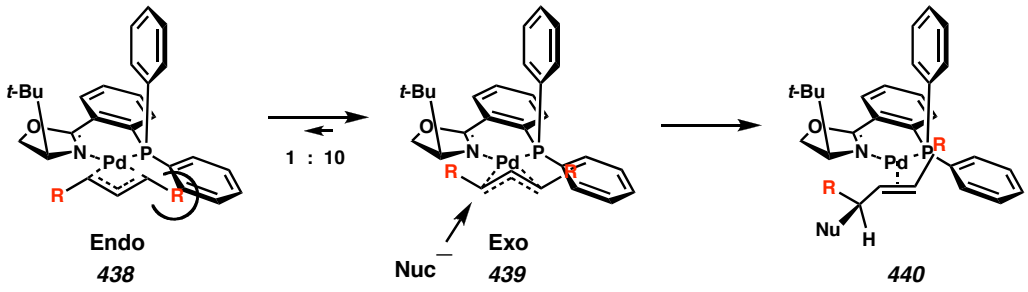
4.5 Mechanistic Insights

While it is premature at this time to make definitive statements about the fine mechanistic details of our palladium/PHOX-based allylation, an intriguing picture of the reaction's general mechanism has emerged from our experimental studies.[54] A number of

experimental observations suggest that our allylation of prochiral nucleophiles differs substantially in mechanism from palladium/PHOX-catalyzed malonate alkylation of prochiral allyl fragments, which has been studied in detail by Helmchen.[9]

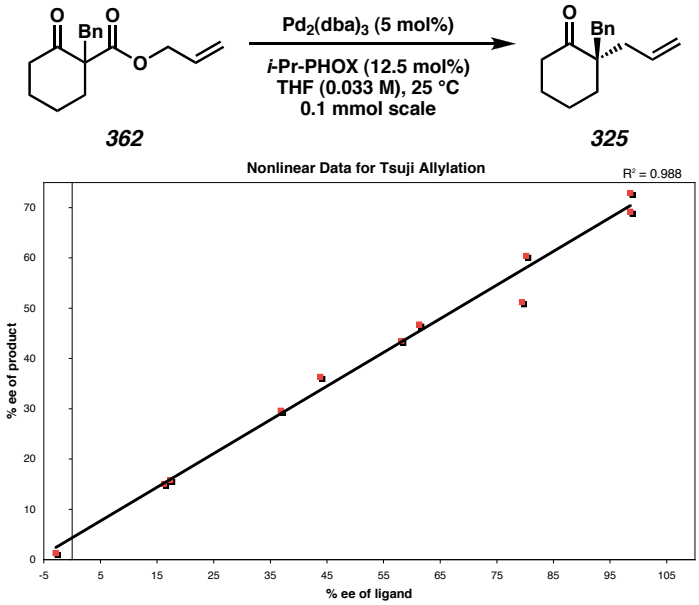
Helmchen's model for the asymmetric allylic alkylation of prochiral allyl electrophiles with palladium/PHOX catalysts involves attack at the allyl terminus by an outer sphere malonate anion (Scheme 4.12). The allyl group isomers **438** and **439** are in rapid equilibrium such that the nucleophile's preferred attack (**439**), from the open quadrant at the allyl terminus trans to phosphorus, is the nearly exclusive reaction pathway. The resulting palladium(0) olefin complex **440** has been observed at low temperature.[9] It is difficult to rationalize the high levels of stereoinduction observed in our allylation by this mechanism. In our case, the chiral palladium complex would be required to differentiate the prochiral faces of the unassociated enolate, when steric and electronic interactions should be minimal. Alternatively, an inner-sphere mechanism would allow for close contact of the enolate to the chiral environment and facilitate the discrimination between the prochiral enolates faces.[55]

Scheme 4.12 Helmchen's Mechanism for Asymmetric Allylation of Prochiral Allyl Electrophiles



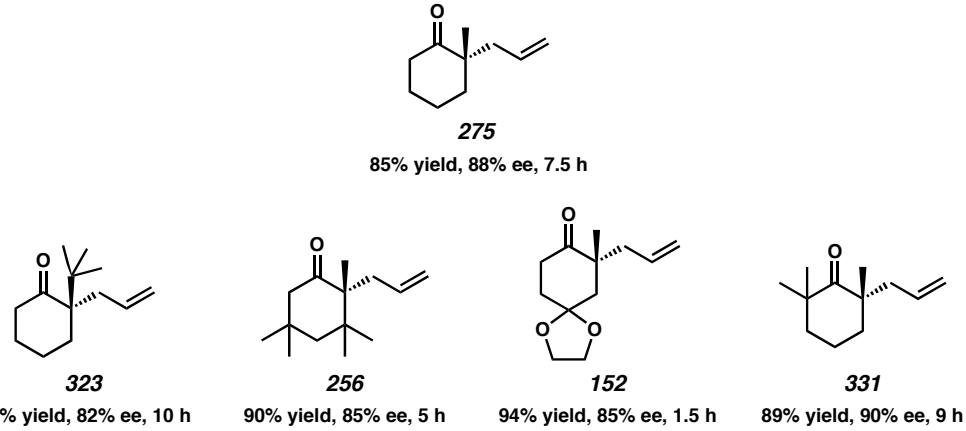
Allylation of a palladium bound enolate is consistent with many experimental trends we have observed, which do not correlate well to an outer-sphere enolate attack mechanism. The high enantioselectivity under our conditions appears to correspond with conditions that would keep ion pairs tightly associated. The range of effective solvents for our reaction demonstrates this trend. Ethereal solvents (e.g., THF), aromatic solvents (e.g., benzene), ethyl acetate, and triethylamine share few properties other than having low dielectric constants in the range of 2 to 8 (Table 4.3). In such low dielectric media, dissociative solvation of ion pairs is difficult. In conjunction with the lack of other counter ions in the reaction, the dielectric would tend to enforce an inner-sphere mechanism. While it is conceivable that multiple ion pairs could be involved in the transition state (e.g., an enolate bound to one Pd(allyl)PHOX fragment attacks the allyl fragment associated with another enolate), simple kinetics experiments[56] and the lack of a nonlinear effect suggest that a single Pd•PHOX is operative in the reaction mechanism (Figure 4.1). Furthermore, less basic enolates, whose charge is delocalized and should therefore tend to ion pair only weakly, give extremely low levels of enantioselectivity (Table 4.14).[57] This suggests that in such cases allylation proceeds via the more conventional outer-sphere attack.

Figure 4.1 Plot of *i*-Pr-PHOX ee vs. Product ee



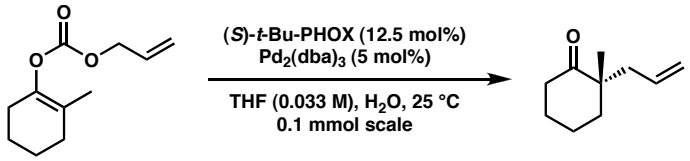
The reactivity of sterically demanding substrates is also inconsistent with an intermolecular nucleophilic enolate attack. In a nucleophilic bimolecular reaction, such as the Helmchen allylation mechanism, steric bulk near the site of bond formation typically impedes the rate of the reaction. However, there is very little difference in the reaction time, yield, or enantioselectivity when comparing the formation of ketone **275** with more sterically demanding ketones (Figure 4.2). This observation is more consistent with an intramolecular reaction mechanism.

Figure 4.2 Comparison of Sterically Varied Products Formed at 25 °C in THF



Another observation at odds with an external attack mechanism is the allylation's unusual tolerance of water (Table 4.16). Multiple equivalents of water introduced into the reaction have only a moderate effect on the yield of the reaction. This contrasts typical enolates, which are quickly quenched by water even at low temperatures, and suggests that the intermediate enolate formed in the reaction is tightly associated with its counterion for most of its lifetime.

Table 4.16 Effect of Water on Asymmetric Allylation



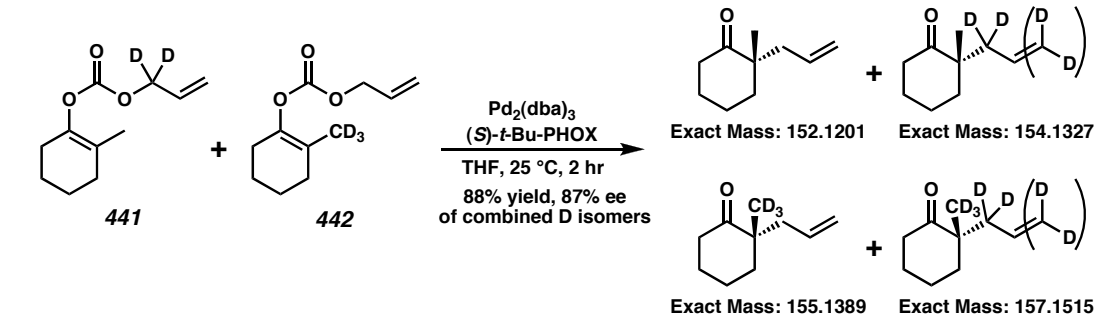
274 275

entry[a]	H_2O added (equiv)[b]	% yield[c]	% ee[d]
1	0	95	86
2	0.55	99	87
3	1.64	88	84
4	8.25	70	61
5	16.5	67	49
6	33.3	63	40

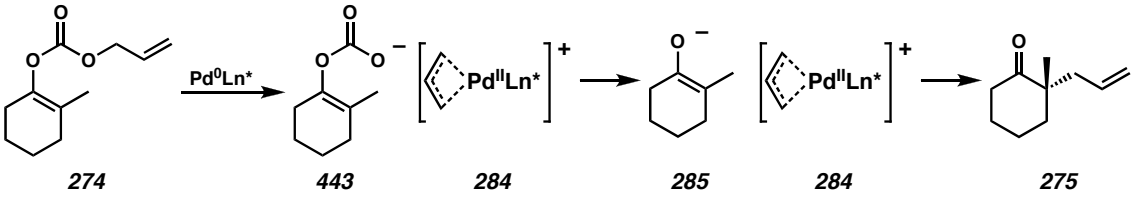
[a] Data reported is the average of three trials. [b] H_2O added after Pd/PHOX complexation, but before substrate. [c] GC yield relative to internal standard (tridecane). [d] Enantiomeric excess measured by chiral GC.

In an effort to trace the fate of the allyl and enolate fragments in the course of the reaction, we performed a crossover experiment with deuterated allyl enol carbonates **441** and **442** in THF, 1,4-dioxane, and benzene (Scheme 4.13).[58] Analysis of the products by high resolution mass spectrometry showed all four possible product masses in nearly equal amounts.[59] In conjunction with the water addition experiments, this observation suggests that a palladium enol carbonate species (**443**) may be a long-lived intermediate. Such an intermediate would not be readily protonated by water, and as a delocalized anion may facilitate crossover by dissociation from the metal center. In the case of β-ketoester substrates, a β-ketocarboxylate intermediate may play an analogous role.

Scheme 4.13 Crossover Experiments with Deuterated Allyl Enol Carbonates

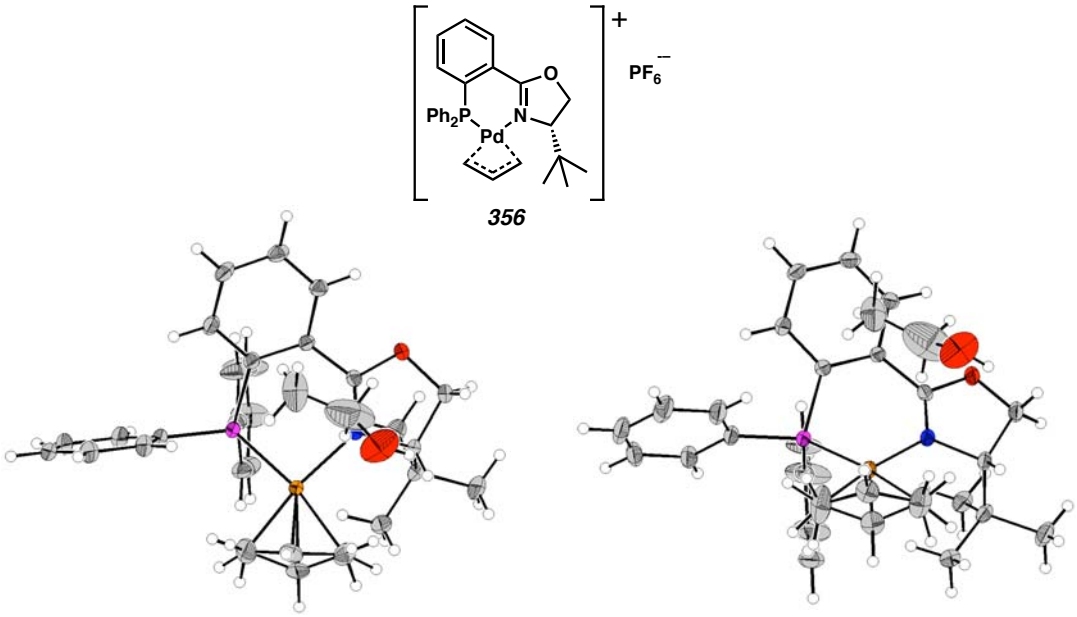


Mass	Integral	% Abundance
152	459336	21.23 %
154	478480	22.12 %
155	720536	33.31 %
157	504864	23.34 %
Total	2163216	100 %



Finally, the solid-state structure of Pd(II)(allyl)PHOX•PF_6 salt **356** lends credence to the possibility of a palladium bound enolate. As shown in Figure 4.3, the complex co-crystallizes with a molecule of ethanol in its unoccupied quadrant.[60] We envision this as the likely site of enolate coordination. Experiments and computational studies[54] to better characterize the reaction mechanism are under way with the hope of improving the enantioselectivity and scope of the asymmetric allylation.

Figure 4.3 Solid-State Structure of Pd(II)(allyl)PHOX•PF_6 Salt **356**



4.6 Concluding Remarks

Although palladium-catalyzed allylic alkylation is one of the most widely used asymmetric C-C bond forming reactions, at the outset of this work a significant limitation existed: the in situ generated enolate nucleophiles utilized were required to have a single acidic α-hydrogen or a large difference in acidity between sites to prevent multiple reactions. As a strategy to overcome this deficiency, we chose to adapt Tsuji's non-enantioselective allylation reactions. Critical to our success was the use of enolate precursors, which could be converted to enolates under mild conditions, and the use of a chiral catalyst that exhibited the enolate isomeric fidelity found in Tsuji's racemic system. We quickly discovered that N/P type ligands, and in particular *t*-Bu-PHOX, were capable of imparting enantioselectivity in the allylation of allyl enol carbonates, silyl enol ethers, and β-ketoesters. The reactivity and enantioselectivity of the allylation have

proven to be quite general with respect to substrate steric bulk, ring size, unsaturation, and diverse functional groups. The in situ enolate generation with TBAT enabled the use of silyl enol ethers, perhaps the most commonly used isolable enolate surrogate in organic chemistry, for intermolecular asymmetric allylation with varied allyl carbonates. The use of racemic allyl β-ketoesters was enabled by the enantioconvergent mechanism of the reaction, whereby both enantiomers of the starting material are converted to a common achiral intermediate and then proceed to an enantioenriched product. The utility of the reaction was greatly increased by the facile synthesis of a wide variety of α-alkylated allyl β-ketoesters. Additionally, we have demonstrated the relevance of the α-quaternary ketones produced in the reaction by their conversion to a number of carbocyclic chiral building blocks, including several spiro quaternary motifs.

A body of evidence has developed suggesting that our asymmetric Tsuji allylation proceeds by a mechanism distinct from that typically invoked in the asymmetric alkylation of prochiral allyl fragments with PHOX ligands. Indeed the coordination of the enolate to the palladium atom is likely essential to our use of prochiral enolates. Substrate classes with less than exemplary levels of enantioselectivity provide both insights about reaction mechanism and challenges for future catalyst development.

In summary, this work provides the first direct access to enantioenriched α-quaternary ketones with multiple similarly acidic α-hydrogens. This advance significantly increases the scope of one of more widely used catalytic asymmetric C-C bond forming reactions. Further development of the catalyst system to new applications is currently being pursued.[51] Our work highlights the broad applicability of this new allylation methodology. Indeed, studies directed toward the application of the

asymmetric Tsuji allylation as a key enantiodetermining step in natural products synthesis will be reported in due course.[28b]

4.7 Experimental Procedures

4.7.1 *Materials and Methods*

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Tetrabutylammonium triphenyldifluorosilicate (TBAT) was purchased from Sigma-Aldrich Chemical Company and azeotropically dried five times from acetonitrile prior to use. Bis(3,5,3',5'-dimethoxydibenzylideneacetone)-palladium(0) ($Pd(dmdba)_2$), alkyl halides, diallyl carbonate, Select-fluor, and pimelic acid were purchased from Sigma-Aldrich Chemical Company and used as received. 3-Methylcyclohex-2-en-1-one and cyclohex-2-en-1-one were purchased from Acros and used as received. Dimethyallyl carbonate was purchased from Alfa Aesar and used as received. Trimethylsilyl chloride (TMSCl) and triethyl amine (TEA) were distilled from sodium hydride immediately prior to use. Sodium iodide was dried by heating at 90 °C (2 torr) for 12 h. (*R,R*)-Trost Ligand, (*R*)-BINAP, (*R,R*)-Me-DUPHOS, (*R,R*)-DIOP, (*R*)-MOP, (*R*)-QUINAP, (*R*)-*i*-Pr-PHOX, and Tris(dibenzylideneacetone)-dipalladium(0) ($Pd_2(dba)_3$) were purchased from Strem and stored in a glovebox until immediately before use. (*R*)-Ph-PHOX and (*S*)-Bn-PHOX were prepared by the method of Helmchen.[18c] Allyl cyanoformate was prepared by known methods.[39b] Methallyl chloroformate was prepared by the method of Kirby.[2] Reaction temperatures were controlled by an IKAmag temperature modulator.

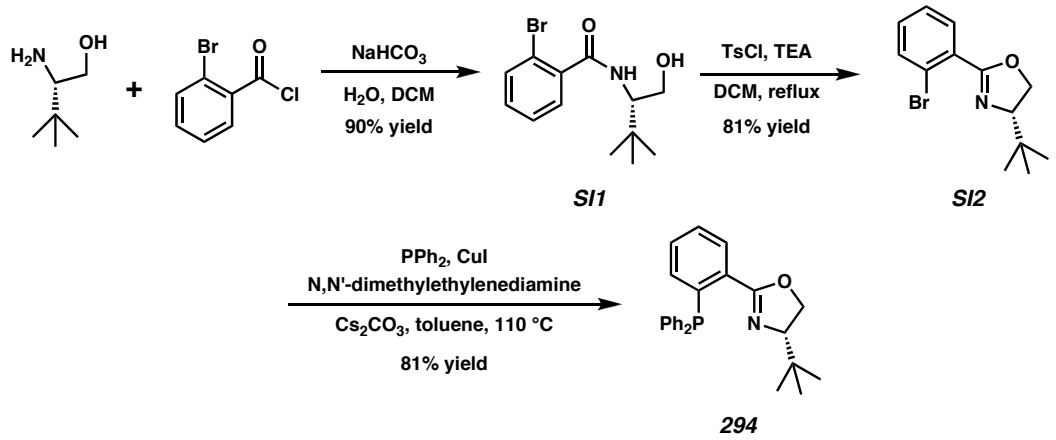
Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, anisaldehyde, or CAM staining. ICN Silica gel (particle size 0.032-0.063 mm) was used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing chiralcel AD, OD-H, or OJ columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd., with visualization at 254 nm. Analytical chiral GC was performed with an Agilent 6850 GC utilizing a G-TA (30 m x 0.25cm) column (1.0 mL/min carrier gas flow). Analytical achiral GC was performed with an Agilent 6850 GC utilizing a DB-WAX (30m x 0.25 mm) column (1.0 mL/min carrier gas flow). Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz, respectively) or a Varian Inova 500 (at 500 MHz and 125 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, sept. = septet, m = multiplet, comp. m = complex multiplet, app. = apparent, bs = broad singlet. Data for ^{13}C NMR spectra are reported in terms of chemical shift relative to Me_4Si (δ 0.0). ^{19}F NMR spectra were recorded on a Varian Mercury 300 spectrometer at 282 MHz, and are reported relative to the external standard F_3CCO_2H (δ -76.53 ppm) or $CFCl_3$ (δ 0.0 ppm). ^{31}P NMR spectra were recorded on a Varian Mercury 300 spectrometer at 121 MHz, and are reported relative to the external standard H_3PO_4 (δ 0.0 ppm). IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the Caltech Mass

Spectral Facility. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number.

4.7.2 *Preparation of Compounds*

4.7.2.1 *Synthesis of PHOX ligands*

General Procedure 1: Synthesis of PHOX Ligands



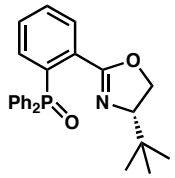
Amide SI1. To a solution of *(S)-t*-leucinol[61] (3.57 g, 30.5 mmol, 1.0 equiv) in DCM (100 mL) was added a solution of Na_2CO_3 (9.70 g, 91.5 mmol, 3.0 equiv) in water (75.0 mL). To the vigorously stirred biphasic mixture was added 2-bromobenzoyl chloride (4.58 mL, 35.1 mmol, 1.15 equiv) in a dropwise manner. After 12 h ambient temperature, the layers were separated, and aqueous layer extracted with DCM (2 x 50 mL). The combined organics were treated with KOH (15 mL of a 1 M methanolic solution) for 15 min, neutralized with 3 M HCl, and water (50 mL) was added. The layers were separated, and the aqueous layer extracted with DCM (2 x 50 mL). The combined organics were dried (Na_2SO_4), evaporated, and the residue chromatographed (25→35% Acetone in Hexanes on SiO_2) to give amide **SI1** (8.19 g, 89.5 % yield): m.p. 50.0-51.0 °C from acetone / hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (dd, J = 7.8, 0.9 Hz, 1H), 7.54 (dd, J = 7.5, 1.8 Hz, 1H), 7.34 (app. dt, J = 7.4, 1.1 Hz, 1H), 7.26 (app. dt, J = 7.7, 1.8 Hz, 1H), 6.24 (bd, J = 8.1 Hz, 1H), 4.05 (m, 1H), 3.93 (dd, J = 11.4, 3.6 Hz, 1H), 3.66 (dd, J = 11.4, 7.5 Hz, 1H), 2.68 (bs, 1H), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$)

δ 168.7, 137.9, 133.3, 131.2, 129.7, 127.6, 119.0, 62.9, 60.2, 33.8, 27.1; IR (Neat Film NaCl) 3245, 3070, 2963, 1640, 1557 cm^{-1}; HRMS *m/z* calc'd for $C_{13}H_{19}NO_2Br$ $[M+H]^+$: 300.0599, found 300.0590; $[\alpha]_D^{29}$ +20.19° (*c* = 2.38, methanol, 100% ee).

Phenyloxazoline SI2.[18c] A solution of amide **SI1** (8.10 g, 27.0 mmol, 1.0 equiv), tosyl chloride (6.69 g, 35.1 mmol, 1.3 equiv), triethylamine (18.7 mL, 135.0 mmol, 5.0 equiv) in DCM (200 mL) in a rb flask equipped with a reflux condenser was heated at 55 °C for 22 h. At which time, water (28 mL) was added and heating continued at 75 °C for 2 h. The reaction mixture was cooled, the layers separated, and the aqueous layer extracted with DCM (2 x 25 mL). The combined organics were dried (Na_2SO_4), evaporated, and the residue chromatographed (5% EtOAc in Hexanes on SiO_2) to give phenyloxazoline **SI2** (6.19 g, 81.2% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (app. dt, *J* = 8.7, 1.7 Hz, 2H), 7.33 (app. dt, *J* = 7.7, 1.5 Hz, 1H), 7.26 (m, 1H), 4.38 (dd, *J* = 10.5, 8.9 Hz, 1H), 4.25 (app. t, *J* = 8.3 Hz, 1H), 4.10 (dd, *J* = 10.2, 8.1 Hz, 1H), 1.00 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8, 133.6, 131.4, 131.2, 130.2, 127.0, 121.8, 76.6, 69.0, 34.0, 25.9; IR (Neat Film NaCl) 2956, 1661, 1478, 1354, 1099, 1022, 963 cm^{-1}; HRMS *m/z* calc'd for $C_{13}H_{17}NOBr$ $[M+H]^+$: 282.0493, found 282.0488; $[\alpha]_D^{29}$ -48.32° (*c* = 3.77, hexane, 100% ee).

***(S)-t*-Bu-PHOX (294).**[21] A mixture of copper(I) iodide (338.3 mg, 1.77 mmol, 0.125 equiv), diphenylphosphine (4.64 mL, 26.7 mmol, 1.88 equiv), N,N'-dimethylethylenediamine (1.32 mL, 12.4 mmol, 0.875 equiv) in toluene (60 mL) was stirred for 20 min at ambient temperature. At which point, phenyloxazoline **SI2** (4.00 g, 14.2 mmol, 1.0 equiv), cesium carbonate (17.4 g, 53.3 mmol, 3.75 equiv), and toluene

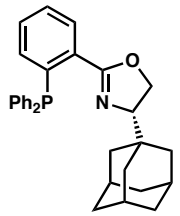
(60 mL) were added, the flask sealed and heated to 110 °C with stirring. The reaction mixture became deep red after ~15 min of heating. After 6 h, the reaction mixture was allowed to cool to ambient temperature, filtered, and washed with DCM (2 x 50 mL). Evaporation of the solvent and chromatography (3→7% EtO_2 in Hexanes on SiO_2) afforded the known[18c] *(S)-t*-Bu-PHOX (4.48 g, 81.4% yield).



295

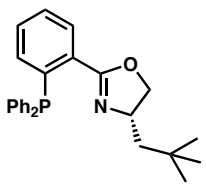
***(S)-t*-Bu-PHOX oxide (295).** To a solution of *(S)-t*-Bu-PHOX (150 mg, 0.387 mmol, 1.00 equiv) in THF (2.5 mL) was added a 5% aqueous H_2O_2 solution (1.94 mL). After 15 min the reaction mixture was diluted with EtOAc (5 mL) and brine (5 mL), washed with 10% aqueous Na_2CO_3 (5 mL) and brine (5 mL), dried ($MgSO_4$), and purified by flash chromatography on silica gel (5% MeOH in DCM) to give *(S)-t*-Bu-PHOX oxide **295** (149.3 mg, 96% yield) as a white foam: R_f 0.47 (10% MeOH in DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (ddd, *J* = 7.5, 3.9, 1.2 Hz, 1H), 7.81-7.33 (comp. m, 7H), 7.52-7.31 (comp. m, 7H), 3.84 (dd, *J* = 8.1, 8.1 Hz, 1H), 3.57 (dd, *J* = 9.9, 9.9 Hz, 1H), 3.41 (dd, *J* = 9.9, 8.4 Hz, 1H), 0.77 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 135.0 (d, *J* = 10.1 Hz), 133.7 (d, *J* = 107.1 Hz), 133.3 (d, *J* = 107.1 Hz), 132.6, 132.4-131.0 (7 lines), 130.8 (d, *J* = 8.6 Hz), 130.3 (d, *J* = 11.7 Hz), 138.2 (app. dd, *J* = 12.3, 1.4 Hz), 75.9, 68.8, 33.6, 25.8; ^{31}P NMR (121 MHz, $CDCl_3$) δ 30.3; IR (Neat Film NaCl) 3057, 2957, 2903, 2868, 2217, 1664, 1589, 1565, 1477, 1438, 1356, 1337, 1307, 1248, 1201, 1119, 1108,

1067, 1028, 963, 930, 905 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{25}H_{27}O_2NP$ $[M]^+$: 404.1779, found 404.1799; $[\alpha]_D^{27.6}$ –69.3 (*c* 1.96, CH_2Cl_2).



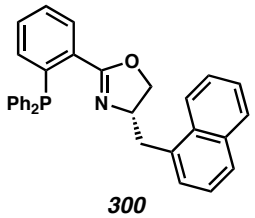
298

***(S)*-1-Ad-PHOX (298).** Prepared by general procedure 1 in 71% yield as a white solid; mp 163-164 ºC; R_f = 0.59 (Hexanes/AcOEt, 5/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (m, 1H), 7.40-7.20 (m, 12H), 6.85 (m, 1H), 4.11 (t, *J* = 9.0 Hz, 1H), 4.03 (t, *J* = 9.0 Hz, 1H), 3.73 (t, *J* = 9.0 Hz, 1H), 1.85 (m, 3H), 1.68-1.46 (m, 6H), 1.44-1.34 (m, 3H), 1.24-1.14 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4 (d, J_{CP} = 3 Hz), 138.8-138.3 (6 lines), 134.4 (d, J_{CP} = 21 Hz), 134.1, 133.4 (d, J_{CP} = 20 Hz), 132.0 (d, J_{CP} = 20 Hz), 130.3, 129.7 (d, J_{CP} = 3 Hz), 128.5-128.0 (7 lines), 76.8, 66.8, 38.2, 37.0, 35.3, 28.1; ^{31}P NMR (121 MHz, $CDCl_3$) δ -5.67; FTIR (Neat Film NaCl) 3053, 2902, 2848, 1651, 1586, 1477, 1434, 1346, 1248, 1089, 1044, 1026, 963, 744, 696 cm^{-1}; HRMS (FAB, Pos.) *m/z* calc'd for $C_{31}H_{33}NOP$ $[M+H]^+$: 466.2300, found 466.2309; $[\alpha]^{27}_D$ = -31.8 (*c* 0.48, $CHCl_3$).



299

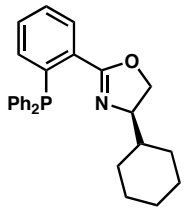
(*S*)-2-(2-(Diphenylphosphino)phenyl)-4-neopentyl-4,5-dihydrooxazole (299). Prepared by general procedure 1 in 73% yield as a white solid; mp 83-86 ºC; R_f = 0.52 (Hexanes/AcOEt, 5/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (ddd, *J* = 7.8, 3.6, 1.5 Hz, 1H), 7.38-7.23 (m, 12H), 6.84 (ddd, *J* = 7.8, 4.5, 1.5 Hz, 1H), 4.25 (dd, *J* = 9.3, 8.1 Hz, 1H), 4.03 (m, 1H), 3.58 (t, *J* = 8.1 Hz, 1H), 1.52 (dd, *J* = 14.1, 4.5 Hz, 1H), 0.93 (dd, *J* = 14.1, 8.1 Hz, 1H), 0.84 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0 (d, J_{CP} = 3 Hz), 138.7 (d, J_{CP} = 25 Hz), 137.9 (d, J_{CP} = 12 Hz), 137.8 (d, J_{CP} = 10 Hz), 134.3 (d, J_{CP} = 21 Hz), 133.9 (d, J_{CP} = 21 Hz), 133.5 (d, J_{CP} = 2 Hz), 131.8 (d, J_{CP} = 18 Hz), 130.3, 129.8 (d, J_{CP} = 3 Hz), 128.6-128.3 (6 lines), 127.9, 73.9, 64.0, 49.7, 30.0, 29.8; ^{31}P NMR (121 MHz, $CDCl_3$) δ -3.95; FTIR (Neat Film NaCl) 3054, 2955, 1652, 1586, 1476, 1434, 1355, 1248, 1089, 1035, 968, 742, 697 cm^{-1}; HRMS (FAB, Pos.) *m/z* calc'd for $C_{26}H_{29}NOP$ $[M+H]^+$: 402.1987, found 402.2002; $[\alpha]^{26}_D$ = -6.9 (*c* 1.03, $CHCl_3$).



300

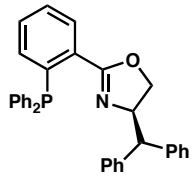
(*S*)-2-(2-(Diphenylphosphino)phenyl)-4-(naphthalen-1-ylmethyl)-4,5-dihydrooxazole (300). Prepared by general procedure 1 in 54% yield as a white amorphous solid; R_f = 0.29 (Hexanes/Et_2O, 3/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (m, 1H), 7.91 (m, 1H), 7.85 (m, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.56-7.45 (m, 2H), 7.42-7.28 (m, 13H), 7.16 (m, 1H), 6.87 (m, 1H), 4.55 (m, 1H), 3.97 (t, *J* = 8.4 Hz, 1H), 3.86 (dd, *J* = 8.4, 7.2 Hz, 1H), 3.44 (dd, *J* = 14.4, 4.2 Hz, 1H), 2.39 (dd, *J* = 14.4, 10.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1 (d, J_{CP} = 3 Hz), 138.9 (d, J_{CP} = 25 Hz), 137.84 (d, J_{CP} =

10 Hz), 137.79 (d, J_{CP} = 12 Hz), 134.5 (d, J_{CP} = 21 Hz), 134.0, 133.82 (d, J_{CP} = 21 Hz), 133.80, 133.5 (d, J_{CP} = 3 Hz), 131.9, 131.3 (d, J_{CP} =17 Hz), 130.6, 130.0 (d, J_{CP} =3 Hz), 128.8-128.4 (6 lines), 127.9, 127.2, 126.6, 126.0, 125.6, 125.4, 123.8, 71.7, 66.7, 38.2; ^{31}P NMR (121 MHz, $CDCl_3$) δ -3.59; FTIR (Neat Film NaCl) 3052, 2962, 1651, 1585, 1511, 1476, 1434, 1354, 1216, 1089, 1037, 963, 745, 697 cm^{-1}; HRMS (FAB, Pos.) *m/z* calc'd for $C_{32}H_{27}NOP$ $[M+H]^+$: 472.1830, found 472.1835; $[\alpha]^{24}_D$ = +29.7 (*c* 0.50, $CHCl_3$).



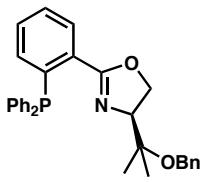
301

***(S)*-1-Cy-PHOX (301).** Prepared by general procedure 1 in 68% yield as a white solid; mp 122-124 ºC; R_f = 0.57 (Hexanes/AcOEt, 4/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (ddd, *J* = 7.7, 4.1, 1.7 Hz, 1H), 7.27 (m, 13H), 6.82 (ddd, *J* = 7.7, 4.1, 1.1 Hz, 1H), 4.12 (ddd, *J* = 14.6, 9.1, 1.4 Hz, 1H), 3.85 (t, *J* = 8.3 Hz, 1H), 3.81 (t, *J* = 8.5 Hz, 1H), 1.60 (m, 4H), 1.28 (d, *J* = 13.5 Hz, 1H), 1.05 (m, 4H), 0.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7 (d, J_{CP} = 3 Hz), 138.0-139.0 (6 lines), 134.5 (d, J_{CP} = 21 Hz), 133.8, 133.7 (d, J_{CP} = 20 Hz), 131.8 (d, J_{CP} = 19 Hz), 130.4, 129.8 (d, J_{CP} = 3 Hz), 128.6-128.0 (7 lines), 71.2, 70.1, 42.7, 29.4, 29.0, 26.4, 26.1, 26.0; ^{31}P NMR (121 MHz, $CDCl_3$) δ -4.21; FTIR (Neat Film NaCl) 3053, 2923, 2852, 1651, 1478, 1434, 1356, 1089, 1044, 964, 908 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{27}H_{28}NOP$ $[M^+]$: 413.1909, found 413.1923; $[\alpha]^{25}_D$ = +47.9 (*c* 0.175, $CHCl_3$).



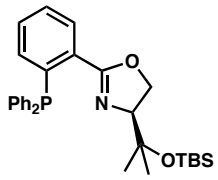
302

(*R*)-4-Benzhydryl-2-(2-(diphenylphosphino)phenyl)-4,5-dihydrooxazole (302). Prepared by general procedure 1 in 89% yield as a white amorphous solid; R_f = 0.45 (Hexanes/AcOEt, 5/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (m, 1H), 7.38-7.13 (m, 22H), 6.88 (m, 1H), 4.92 (q, *J* = 9.0 Hz, 1H), 4.13 (dd, *J* = 9.3, 9.0 Hz, 1H), 3.79 (t, *J* = 9.0 Hz, 1H), 3.72 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 142.2, 142.1, 138.8 (d, J_{CP} = 25 Hz), 138.0-137.7 (3 lines), 134.1 (d, J_{CP} = 21 Hz), 133.9 (d, J_{CP} = 21 Hz), 133.7 (d, J_{CP} = 2 Hz), 131.7 (d, J_{CP} = 19 Hz), 130.5, 130.0 (d, J_{CP} = 3 Hz), 128.7-128.2 (9 lines), 128.0, 126.5, 126.2, 71.1, 70.1, 56.1; ^{31}P NMR (121 MHz, $CDCl_3$) δ -5.22; FTIR (Neat Film NaCl) 3056, 3026, 2895, 1649, 1598, 1584, 1494, 1477, 1451, 1434, 1356, 1091, 1029, 909, 741 cm^{-1}; HRMS (FAB, Pos.) *m/z* calc'd for $C_{34}H_{29}NOP$ $[M+H]^+$: 498.1987, found 498.1963; $[\alpha]^{24}_D$ = +10.4 (*c* 1.00, $CHCl_3$).



303

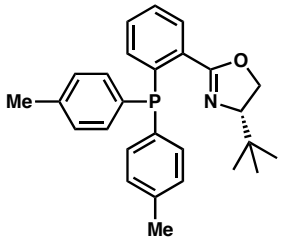
(*S*)-4-(2-(Benzyloxy)propan-2-yl)-2-(2-(diphenylphosphino)phenyl)-4,5-dihydrooxazole (303). Prepared by general procedure 1 in 75% yield as a colorless viscous oil; R_f = 0.45 (Hexanes/AcOEt, 5/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (ddd, *J* = 7.5, 3.6, 1.2 Hz, 1H), 7.41-7.19 (m, 17H), 6.88 (ddd, *J* = 7.5, 4.2, 0.9 Hz, 1H), 4.43-4.23 (m, 4H), 4.15 (dd, *J* = 9.6, 7.8 Hz, 1H), 1.21 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8 (d, J_{CP} = 3 Hz), 139.5, 139.1-138.3 (5 lines), 134.4 (d, J_{CP} = 21 Hz), 134.2, 133.5 (d, J_{CP} = 20 Hz), 131.6 (d, J_{CP} = 19 Hz), 130.5, 129.9 (d, J_{CP} = 3 Hz), 128.6-128.1 (6 lines), 127.14, 127.12, 76.9, 74.9, 68.5, 63.9, 23.9, 19.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ -5.51; FTIR (Neat Film NaCl) 3067, 2973, 2905, 1649, 1586, 1478, 1434, 1352, 1248, 1155, 1091, 1065, 1027, 964, 743, 697 cm^{-1}; HRMS (FAB, Pos.) *m/z* calc'd for $C_{31}H_{31}NO_2P$ $[M+H]_+$: 480.2092, found 480.2078; $[\alpha]^{26}_D$ = -2.0 (*c* 1.03, $CHCl_3$).



304

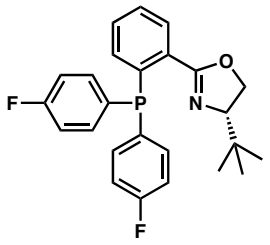
(*S*)-4-(2-(*tert*-Butyldimethylsilyloxy)propan-2-yl)-2-(2-(diphenylphosphino)phenyl)-4,5-dihydrooxazole (304). Prepared by general procedure 1 in 84% yield as a white solid; mp 104-106 ºC; R_f = 0.62 (Hexanes/AcOEt, 5/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (ddd, *J* = 7.5, 3.6, 1.2 Hz, 1H), 7.40-7.20 (m, 12H), 6.88 (ddd, *J* = 7.5, 3.9, 0.9 Hz, 1H), 4.32 (dd, *J* = 7.5, 6.6 Hz, 1H), 4.09 (dd, *J* = 10.2, 7.5 Hz, 1H), 4.02 (dd, *J* = 10.2, 6.6 Hz, 1H), 1.15 (s, 3H), 0.86 (s, 3H), 0.78 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 139.0-138.3 (6 lines), 134.3 (d, J_{CP} = 21 Hz), 134.2, 133.5 (d, J_{CP} = 20 Hz), 131.9 (d, J_{CP} = 19 Hz), 130.4, 129.8 (d, J_{CP} = 3 Hz),

128.5-128.0 (5 lines), 76.8, 74.9, 68.7, 28.7, 25.7, 23.9, 17.9, -2.2, -2.3; ^{31}P NMR (121 MHz, $CDCl_3$) δ -5.99; FTIR (Neat Film NaCl) 3054, 2955, 2929, 2856, 1652, 1586, 1472, 1434, 1353, 1251, 1162, 1091, 1058, 835, 774, 743, 696 cm^{-1}; HRMS (FAB, Pos.) *m/z* calc'd for $C_{30}H_{39}NO_2PSi$ $[M+H]^+$: 504.2488, found 504.2469; $[\alpha]^{26}_D$ = +19.8 (*c* 1.16, $CHCl_3$).



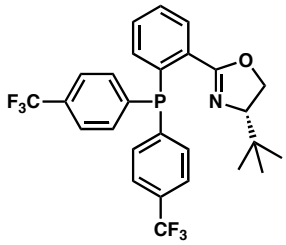
307

(*S*)-4-*tert*-Butyl-2-(2-(di-*p*-tolylphosphino)phenyl)-4,5-dihydrooxazole (307). Prepared by general procedure 1 using (*p*-Tol)$_2$PH in 73% yield as a colorless viscous oil; R_f = 0.39 (Hexanes/AcOEt, 9/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (ddd, *J* = 7.5, 3.6, 1.5 Hz, 1H), 7.33 (m, 1H), 7.26 (m, 1H), 7.23-7.05 (m, 8H), 6.89 (ddd, *J* = 7.5, 4.2, 1.5 Hz, 1H), 4.06 (dd, *J* = 10.2, 8.4 Hz, 1H), 3.98 (t, *J* = 8.3 Hz, 1H), 3.85 (dd, *J* = 10.2, 7.8 Hz, 1H), 2.33 (s, 3H), 2.32 (s, 3H), 0.75 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0 (d, J_{CP} = 3 Hz), 139.3 (d, J_{CP} = 25 Hz), 138.4, 138.1, 135.0-134.7 (4 lines), 134.3 (d, J_{CP} = 21 Hz), 133.9, 133.6 (d, J_{CP} = 20 Hz), 131.9 (d, J_{CP} = 20 Hz), 130.2, 129.9 (d, J_{CP} = 3 Hz), 129.2 (d, J_{CP} = 7 Hz), 129.0 (d, J_{CP} = 7 Hz), 127.8, 76.5, 68.3, 33.6, 25.7, 21.3, 21.2; ^{31}P NMR (121 MHz, $CDCl_3$) δ -6.98; FTIR (Neat Film NaCl) 2953, 1653, 1496, 1476, 1394, 1353, 1306, 1248, 1185, 1134, 1089, 1024, 967, 805, 743 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{27}H_{30}NOP$ $[M^+]$: 415.2065, found 415.2065; $[\alpha]^{25}_D$ = -58.8 (*c* 2.23, $CHCl_3$).



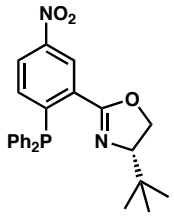
308

(*S*)-2-(2-(bis(4-fluorophenyl)phosphino)phenyl)-4-*tert*-butyl-4,5-dihydrooxazole (308). Prepared by Helmchen's Grignard method[18c] in 14% yield as a colorless oil; R_f = 0.50 (5% Et_2O in hexanes developed twice); ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (ddd, *J* = 7.0, 3.0, 1.0 Hz, 1H), 7.39 (ddd, *J* = 8.0, 8.0, 1.5 Hz, 1H), 7.31 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 7.26-7.14 (comp. m, 4H), 7.01 (app. dt, *J* = 13.0, 8.5 Hz, 4H), 6.83 (ddd, *J* = 7.5, 4.0, 1.0 Hz, 1H), 4.12 (dd, *J* = 10.0, 8.5 Hz, 1H), 4.03 (dd, *J* = 8.0, 8.0 Hz, 1H), 3.90 (dd, *J* = 10.0, 8.0 Hz, 1H), 0.74 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3 (d, $J_{C\text{-}F}$ = 247.5 Hz), 163.1 (d, $J_{C\text{-}F}$ = 246.5 Hz), 162.3, 138.6 (d, $J_{C\text{-}P}$ = 25.3 Hz), 136.1 (dd, $J_{C\text{-}P}$ = 22.5 Hz, $J_{C\text{-}F}$ = 8.1 Hz), 135.3 (dd, $J_{C\text{-}P}$ = 21.9 Hz, $J_{C\text{-}F}$ = 8.1 Hz), 134.1 (dd, $J_{C\text{-}P}$ = 12.5, $J_{C\text{-}F}$ = 4.1 Hz), 134.0 (dd, $J_{C\text{-}P}$ = 10.4 Hz, $J_{C\text{-}F}$ = 4.0 Hz), 133.9, 131.7 (d, $J_{C\text{-}P}$ = 20.0 Hz), 130.5, 130.0 (d, $J_{C\text{-}P}$ = 2.9 Hz), 128.3, 115.6 (dd, $J_{C\text{-}F}$ = 18.6 Hz, $J_{C\text{-}P}$ = 7.6 Hz), 115.5 (dd, $J_{C\text{-}F}$ = 18.6 Hz, $J_{C\text{-}P}$ = 7.6 Hz) 76.8, 68.3, 33.6, 25.7; ^{31}P NMR (121 MHz, $CDCl_3$) δ –8.2 (app. t, *J* = 3.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ –113.6, –114.1; IR (Neat Film NaCl) 2955, 2904, 2868, 1653, 1587, 1494, 1392, 1354, 1336, 1225, 1159, 1091, 1039, 1025, 966, 827, 744 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{25}H_{25}ONPF_2$ $[M + H]^+$: 424.1642, found 424.1622; $[\alpha]_D^{26.4}$ -17.7 (*c* 0.53, CH_2Cl_2).



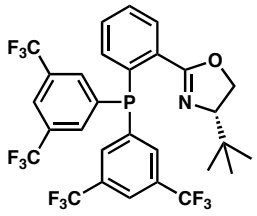
309

(*S*)-2-(2-(Bis(4-(trifluoromethyl)phenyl)phosphino)phenyl)-4-*tert*-butyl-4,5-dihydrooxazole (309). Prepared by general procedure 1 using (p-$CF_3Ph)_2PH$ in 75% yield as a white amorphous powder; R_f = 0.44 (Hexanes/AcOEt, 9/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (ddd, J = 7.5, 3.9, 1.2 Hz, 1H), 7.62-7.50 (m, 4H), 7.44 (m, 1H), 7.40-7.28 (m, 5H), 6.82 (ddd, J = 7.5, 3.9, 0.9 Hz, 1H), 4.20 (dd, J = 10.2, 8.4 Hz, 1H), 4.06 (t, J = 8.4 Hz, 1H), 3.93 (dd, J = 10.2, 8.4 Hz, 1H), 0.69 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8 (d, J_{CP} = 3 Hz), 143.4-143.2 (m), 136.7 (d, J_{CP} = 24 Hz), 134.4 (d, J_{CP} = 21 Hz), 134.2, 133.7 (d, J_{CP} = 20 Hz), 132.0 (d, J_{CP} = 20 Hz), 130.74, 130.65 (q, J_{CF} = 32 Hz), 130.5 (q, J_{CF} = 32 Hz), 129.9 (d, J_{CP} = 3 Hz), 128.9, 125.3-124.9 (m), 124.1 (q, J_{CF} = 271 Hz,), 77.0, 68.4, 33.6, 25.6; ^{31}P NMR (121 MHz, $CDCl_3$) δ -7.29; ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.23, -63.28; FTIR (Neat Film NaCl) 2958, 1653, 1606, 1480, 1396, 1324, 1166, 1128, 1106, 1061, 1017, 831, 700 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{27}H_{24}NOPF_6$ [M^+]: 523.1500, found 523.1494; $[\alpha]^{25}_D$ = -21.1 (*c* 2.26, $CHCl_3$).



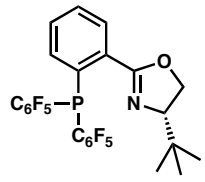
310

(*S*)-4-*tert*-Butyl-2-(2-(diphenylphosphino)-5-nitrophenyl)-4,5-dihydrooxazole (310). Prepared by a modification of Andreas' method[62] in 8% yield as a red oil; R_f = 0.57 (25% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.77 (dd, *J* = 3.0, 3.0 Hz, 1H), 8.07 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.40-7.29 (comp. m, 6H), 7.29-7.18 (comp. m, 4H), 7.04 (dd, *J* = 8.5, 3.0 Hz, 1H), 4.15 (dd, *J* = 10.0, 8.5 Hz, 1H), 4.04 (dd, *J* = 9.0, 8.0 Hz, 1H), 3.90 (dd, *J* = 9.5, 8.0 Hz, 1H), 0.72 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7 (d, *J* = 3.8 Hz), 148.6 (d, *J* = 33.0 Hz), 147.4, 137.2 (d, *J* = 12.0 Hz), 136.9 (d, *J* = 8.5 Hz), 135.1 (d, *J* = 1.4 Hz), 134.3 (d, *J* = 21.5 Hz), 133.6 (d, *J* = 20.5 Hz), 132.7 (d, *J* = 18.6 Hz), 129.2-128.6 (6 lines), 124.4 (d, *J* = 1.9 Hz), 124.1, 77.2, 68.6, 33.6, 25.7; ^{31}P NMR (121 MHz, $CDCl_3$) δ –3.4; IR (Neat Film NaCl) 3071, 2956, 2904, 2868, 1656, 1522, 1478, 1434, 1346, 1118, 1086, 1026, 970, 913, 742, 696 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{25}H_{26}O_3N_2P$ $[M + H]^+$: 433.1681, found 433.1702; $[\alpha]_D^{26.4}$ -16.2 (*c* 0.87, $CHCl_3$).



311

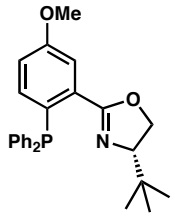
(*S*)-2-(2-(Bis(3,5-bis(trifluoromethyl)phenyl)phosphino)phenyl)-4-*tert*-butyl-4,5-dihydrooxazole (311). Prepared by Helmchen's Grignard method[18c] in 6% yield as a colorless oil; R_f = 0.29 (5% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (ddd, *J* = 7.5, 4.0, 1.5 Hz, 1H), 7.86 (app. d, *J* = 11.0 Hz, 2H), 7.64 (app. dd, *J* = 21.0, 6.0 Hz, 4H), 7.53 (ddd, *J* = 7.0, 7.0, 1.0, 1H), 7.42 (ddd, *J* = 7.5, 7.5 1.0 Hz, 1H), 6.77 (ddd, *J* = 7.5, 3.5, 1.0 Hz, 1H), 4.28 (dd, *J* = 10.0, 8.5 Hz, 1H), 4.12 (dd, *J* = 9.0, 9.0 Hz, 1H), 3.91 (dd, *J* = 10.5, 9.0 Hz, 1H), 0.68 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.4 (d, *J* = 3.4 Hz), 141.9 (d, *J* = 13.9 Hz), 141.8 (d, *J* = 11.9 Hz), 134.8 (d, *J* = 23.9 Hz), 134.0, 133.7 (d, *J* = 19.1 Hz), 133.2 (d, *J* = 21.5 Hz), 131.8 (app. dq, *J* = 31.5, 4.8 Hz), 131.3, 130.0 (d, *J* = 2.9 Hz), 129.8, 123.1 (q, *J* = 271.8 Hz), 122.7 (app. d of septets, *J* = 25.3, 3.3 Hz), 77.1, 68.7, 33.4, 25.5;^{31}P NMR (121 MHz, $CDCl_3$) δ –6.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.9 (2 peaks); HRMS (FAB+) *m/z* calc'd for $C_{29}H_{23}ONPF_{12}$ $[M + H]^+$: 660.1325, found 660.1328; $[\alpha]_D^{26.2}$ -5.0 (*c* 0.35, $CHCl_3$).



312

(*S*)-4-*tert*-Butyl-2-(2-(diperfluorophenylphosphino)phenyl)-4,5-dihydrooxazole (312). Prepared by Helmchen's Grignard method[18c] in 13% yield as a

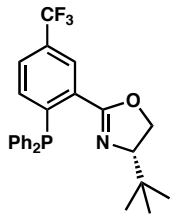
colorless oil; R_f = 0.39 (2.5% Et_2O in hexanes developed twice); ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (ddd, *J* = 7.4, 4.8, 1.3 Hz, 1H), 7.51 (app. tt, *J* = 7.5, 1.3 Hz, 1H), 7.41 (app. tt, *J* = 7.7, 1.3 Hz, 1H), 7.16 (dd, *J* = 7.7, 3.5 Hz, 1H), 4.35 (dd, *J* = 10.1, 8.8 Hz, 1H), 4.18 (dd, *J* = 8.8, 8.8 Hz, 1H), 3.93 (dd, *J* = 10.1, 8.8 Hz, 1H), 0.75 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3 (d, *J* = 5.0 Hz), 132.5, 130.9, 129.7 (2 peaks), 129.6, 77.3, 69.1, 33.6, 25.7; ^{31}P NMR (121 MHz, $CDCl_3$) δ -54.7 (app. quintet, *J* = 38.1 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -130.6 (app. t, *J* = 27.5 Hz), -131.1 (app. t, *J* = 27.5 Hz), -151.9 (app. t, *J* = 18.6 Hz), -152.4 (app. t, *J* = 21.2 Hz), –161.8 (app. t, *J* = 18.0 Hz), -162.0 (app. t, *J* = 15.0 Hz); IR (Neat Film NaCl) 2962, 2908, 2872, 1654, 1516, 1476, 1382, 1360, 1287, 1139, 1087, 1052, 978, 908, 834, 740 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{25}H_{17}ONPF_{10}$ $[M + H]^+$: 568.0888, found 568.0868; $[\alpha]_D^{26.2}$ -6.3 (*c* 0.56, CH_2Cl_2).



313

(*S*)-4-*tert*-Butyl-2-(2-(diphenylphosphino)-5-methoxyphenyl)-4,5-dihydrooxazole (313). Prepared by general procedure 1 in 72% yield as a white amorphous powder; R_f = 0.61 (Hexanes/AcOEt, 3/1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (t, *J* = 2.9 Hz, 1H), 7.34-7.18 (m, 10H), 6.84 (ddd, *J* = 8.7, 2.4, 0.6 Hz, 1H), 6.78 (ddd, *J* = 8.7, 3.3, 0.6 Hz, 1H), 4.13 (dd, *J* = 10.2, 8.4 Hz, 1H), 4.03 (t, *J* = 8.1 Hz, 1H), 3.92 (dd, *J* = 10.2, 8.1 Hz, 1H), 3.82 (s, 3H), 0.73 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5 (d, J_{CP} = 3 Hz), 159.4, 139.0 (d, J_{CP} = 13 Hz), 138.7 (d, J_{CP} = 10 Hz), 135.8, 134.1 (d, J_{CP} =

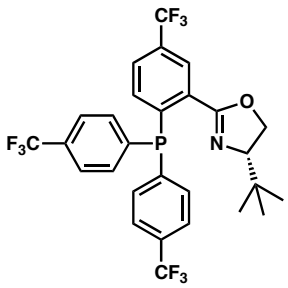
20 Hz), 133.41 (d, J_{CP} = 33 Hz), 133.36 (d, J_{CP} = 20 Hz), 129.3 (d, J_{CP} = 22 Hz), 128.3-128.0 (6 lines), 116.5, 114.9 (d, J_{CP} = 4 Hz), 76.7, 68.3, 55.3, 33.6, 25.7; ^{31}P NMR (121 MHz, $CDCl_3$) δ -10.12; FTIR (Neat Film NaCl) 3069, 2956, 2903, 1654, 1594, 1561, 1479, 1434, 1354, 1336, 1297, 1224, 1181, 1093, 1050, 1022, 973, 744, 697 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{26}H_{28}NO_2P$ [M$^+$]: 417.1858, found 417.1844; $[\alpha]^{25}_D$ = -48.8 (*c* 2.11, $CHCl_3$).



314

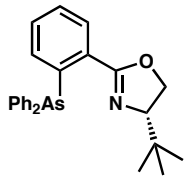
(*S*)-4-*tert*-Butyl-2-(2-(diphenylphosphino)-5-(trifluoromethyl)phenyl)-4,5-dihydrooxazole (314). Prepared by general procedure 1 in 77% yield as a white powder; mp 98-100 ºC; R_f = 0.45 (Hexanes/AcOEt, 9/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (m, 1H), 7.51 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.38-7.18 (m, 10H), 6.99 (dd, *J* = 8.1, 3.3 Hz, 1H), 4.12 (dd, *J* = 10.2, 8.4 Hz, 1H), 4.03 (t, *J* = 8.4 Hz, 1H), 3.90 (dd, *J* = 10.2, 8.4 Hz, 1H), 0.72 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4 (d, J_{CP} = 3 Hz), 144.2 (d, J_{CP} = 30 Hz), 137.7 (d, J_{CP} = 12 Hz), 137.3 (d, J_{CP} = 9 Hz), 134.6, 134.3 (d, J_{CP} = 21 Hz), 133.6 (d, J_{CP} = 20 Hz), 132.2 (d, J_{CP} = 19 Hz), 130.1 (q, J_{CF} = 33 Hz), 128.9-128.4 (6 lines), 126.6-126.3 (m), 123.7 (q, J_{CF} = 271 Hz), 77.0 (d, J_{CP} = 1 Hz), 68.4, 33.6, 25.7; ^{31}P NMR (121 MHz, $CDCl_3$) δ -6.55 (J_{PF} = 2 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.36; FTIR (Neat Film NaCl) 3071, 2957, 1655, 1478, 1434, 1407, 1357, 1343, 1326, 1302, 1262, 1244, 1174,

1131, 1080, 969, 744, 696 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{26}H_{25}NOPF_3$ [M^+]: 455.1626, found 455.1646; $[\alpha]^{25}_D$ = -36.3 (*c* 2.39, $CHCl_3$).



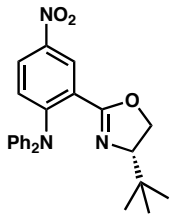
315

(*S*)-2-(2-(Bis(4-(trifluoromethyl)phenyl)phosphino)-5-(trifluoromethyl)phenyl)-4-*tert*-butyl-4,5-dihydrooxazole (315). Prepared by general procedure 1 using (*p*-$CF_3Ph)_2PH$ in 74% yield as a white amorphous powder; R_f = 0.63 (Hexanes/AcOEt, 9/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (m, 1H), 7.64-7.54 (m, 5H), 7.39-7.27 (m, 4H), 6.95 (dd, *J* = 7.8, 3.0 Hz, 1H), 4.25 (dd, *J* = 10.2, 8.7 Hz, 1H), 4.09 (t, *J* = 8.7 Hz, 1H), 3.95 (dd, *J* = 10.2, 8.7 Hz, 1H), 0.69 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7 (d, J_{CP} = 4 Hz), 142.6-141.7 (6 lines), 134.7-133.6 (5 lines), 132.4 (d, J_{CP} = 20 Hz), 131.1 (q, J_{CF} = 32 Hz), 130.9 (q, J_{CF} = 32 Hz), 127.0 (q, J_{CF} = 3 Hz), 126.7-126.4 (6 lines), 125.6-125.1 (8 lines), 123.9 (q, J_{CF} = 271 Hz), 123.5 (q, J_{CF} = 271 Hz), 77.3 (d, J_{CP} = 1 Hz), 68.6, 33.5, 25.6; ^{31}P NMR (121 MHz, $CDCl_3$) δ -6.57; ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.33, -63.39, -63.53; FTIR (Neat Film NaCl) 2960, 1657, 1606, 1479, 1397, 1324, 1169, 1129, 1107, 1082, 1061, 1017, 832, 700 cm^{-1}; HRMS (FAB, Pos) *m/z* calc'd for $C_{28}H_{24}F_9NOP$ $[M+H]^+$: 592.1452, found 592.1480; $[\alpha]^{24}_D$ = -16.0 (*c* 2.56, $CHCl_3$).



317

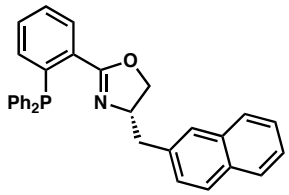
(*S*)-4-*tert*-Butyl-2-(2-(diphenylarsino)phenyl)-4,5-dihydrooxazole (317). Prepared by Helmchen's S_NAr method[18c] in 40% yield using lithium diphenylarsine generated by lithium reduction of triphenylarsine as a colorless oil; R_f = 0.42 (5% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.37 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 7.34-7.23 (comp. m, 10H), 7.01 (dd, *J* = 8.0, 1.0, 1H), 4.15 (dd, *J* = 9.5, 8.0 Hz, 1H), 4.04 (dd, *J* = 8.5, 8.5 Hz, 1H), 3.88 (dd, *J* = 10.5, 9.0 Hz, 1H), 0.75 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.7, 141.9 (2 peaks), 141.5, 134.6, 134.0, 133.7, 131.8, 130.6, 129.5, 128.4 (2 peaks), 128.0, 127.9, 76.7, 68.3, 33.6, 25.7; IR (Neat Film NaCl) 3066, 3052, 2955, 2903, 2867, 1652, 1480, 1433, 1354, 1336, 1306, 1253, 1132, 1088, 1024, 967, 903, 736, 696 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{25}H_{27}ONAs$ [M + H]$^+$: 432.1309, found 432.1290; $[\alpha]_D^{25.6}$ -33.8 (*c* 1.47, $CHCl_3$).



318

(*S*)-4-*tert*-Butyl-2-(2-(diphenylamino)-5-nitrophenyl)-4,5-dihydrooxazole (318). Prepared by a modification of Zhu's method[63] in 18% yield as a red oil; R_f = 0.45 (10% Et_2O in hexanes developed thrice); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (d, *J* = 3.0

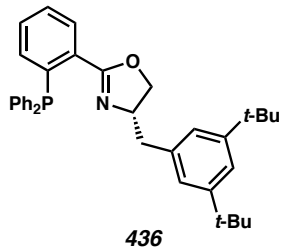
Hz, 1H), 8.13 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.28 (app. t, *J* = 7.5 Hz, 4H), 7.09 (app. t, *J* = 7.5, 2H), 7.09 (d, *J* = 9.0 Hz, 1H), 7.03 (app. d, *J* = 7.5 Hz, 4H), 3.77 (dd, *J* = 8.5, 8.5 Hz, 1H), 3.59 (dd, *J* = 10.0, 8.5 Hz, 1H), 3.24 (dd, *J* = 10.0, 8.0 Hz, 1H), 0.80 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.3, 151.8, 146.6, 141.8, 129.4, 128.6, 126.6, 126.5, 124.6, 124.3, 123.3, 75.0, 68.7, 33.6, 25.9; IR (Neat Film NaCl) 2958, 2904, 2868, 1647, 1588, 1574, 1518, 1490, 1333, 1299, 1278, 1116, 968, 912, 860, 751, 695 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{25}H_{26}O_3N_3$ $[M + H]^+$: 416.1974, found 416.1969; $[\alpha]_D^{25.6}$ +203.9 (*c* 0.55, $CHCl_3$).



435

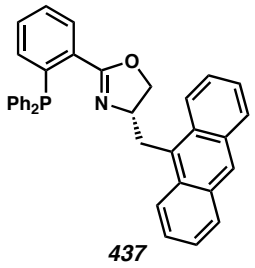
(*S*)-2-(2-(Diphenylphosphino)phenyl)-4-(naphthalen-2-ylmethyl)-4,5-dihydrooxazole (435). Prepared by general procedure 1 in 71% yield as a white amorphous solid; R_f = 0.24 (Hexanes/Et_2O, 3/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (m, 1H), 7.82-7.72 (m, 3H), 7.53 (br s, 1H), 7.49-7.27 (m, 14H), 7.23 (m, 1H), 6.88 (m, 1H), 4.46 (m, 1H), 4.05 (dd, *J* = 9.0, 8.7 Hz, 1H), 3.83 (dd, *J* = 9.0, 7.5 Hz, 1H), 3.08 (dd, *J* = 14.1, 5.1 Hz, 1H), 2.30 (dd, *J* = 14.1, 9.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0 (d, J_{CP} = 3 Hz), 138.9 (d, J_{CP} = 25 Hz), 137.0-137.7 (3 lines), 135.6, 134.4 (d, J_{CP} = 21 Hz), 133.8 (d, J_{CP} = 21 Hz), 133.5 (d, J_{CP} = 2 Hz), 133.4, 132.1, 131.4 (d, J_{CP} = 18 Hz), 130.5, 129.9 (d, J_{CP} = 3 Hz), 128.7-127.4 (12 lines), 125.9, 125.4, 71.4, 67.7, 41.2; ^{31}P NMR (121 MHz, $CDCl_3$) δ -4.05; FTIR (Neat Film NaCl) 3052, 1651, 1508, 1476, 1434,

1354, 1217, 1090, 1027, 964, 817, 743, 697 cm^{-1}; HRMS (FAB, Pos.) *m/z* calc'd for $C_{32}H_{27}NOP$ $[M+H]^+$: 472.1830, found 472.1845; $[\alpha]^{25}_D$ = +42.7 (*c* 0.50, $CHCl_3$).



436

(*R*)-4-(3,5-Di-*tert*-butylbenzyl)-2-(2-(diphenylphosphino)phenyl)-4,5-dihydrooxazole (436). Prepared by general procedure 1 in 55% yield as a colorless viscous oil; R_f = 0.52 (Hexanes/EtOAc, 5/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (m, 1H), 7.40-7.28 (m, 13H), 6.92 (d, *J* = 1.8 Hz, 2H), 6.86 (m, 1H), 4.33 (m, 1H), 4.00 (t, *J* = 8.7 Hz, 1H), 3.78 (dd, *J* = 8.7, 7.5 Hz, 1H), 2.95 (dd, *J* = 13.8, 4.2 Hz, 1H), 2.01 (dd, *J* = 13.8, 10.2 Hz, 1H), 1.30 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9 (d, J_{CP} = 3 Hz), 150.8, 138.9 (d, J_{CP} = 25 Hz), 137.9 (d, J_{CP} = 12 Hz), 137.8 (d, J_{CP} = 10 Hz), 137.2, 134.4 (d, J_{CP} = 21 Hz), 134.0 (d, J_{CP} = 21 Hz), 133.4 (d, J_{CP} = 3 Hz), 131.5 (d, J_{CP} = 17 Hz), 130.5, 130.0 (d, J_{CP} = 3 Hz), 128.8-128.4 (6 lines), 127.9, 123.3, 120.3, 71.6, 68.1, 41.6, 34.7, 31.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ -3.60; FTIR (Neat Film NaCl) 2963, 1649, 1598, 1477, 1434, 1361, 1248, 1090, 1027, 965, 742, 696 cm^{-1}; HRMS (FAB, Pos.) *m/z* calc'd for $C_{36}H_{41}NOP$ $[M+H]^+$: 534.2926, found 534.2905; $[\alpha]^{25}_D$ = -49.3 (*c* 0.36, $CHCl_3$).



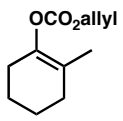
437

(*S*)-4-(Anthracen-9-ylmethyl)-2-(2-(diphenylphosphino)phenyl)-4,5-dihydrooxazole (437). Prepared by general procedure 1 in 42% yield as a yellow powder; Mp 165-169 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.16 (m, 2H), 7.99 (m, 2H), 7.94 (m, 1H), 7.55-7.29 (m, 16H), 6.88 (m, 1H), 4.63 (m, 1H), 3.92 (dd, *J* = 9.0, 6.3 Hz, 1H), 3.77 (dd, *J* = 14.7, 4.5 Hz, 1H), 3.68 (t, *J* = 9.0 Hz, 1H), 3.17 (dd, *J* = 14.7, 10.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) d 164.3 (d, J_{CP} = 3 Hz, *C*=N), 138.9 (d, J_{CP} = 25 Hz), 138.1 (d, J_{CP} = 10 Hz), 137.8 (d, J_{CP} = 13 Hz), 134.6 (d, J_{CP} = 21 Hz), 133.8 (d, J_{CP} = 21 Hz), 133.5 (d, J_{CP} = 3 Hz), 131.5, 130.7, 130.2, 130.0, 129.2, 128.9-128.5 (6 lines), 128.0, 126.5, 125.8, 124.9, 124.5, 71.2 (CH*C*H_2O), 67.8 (CH_2*C*HN), 32.1 (Ar*C*H_2); ^{31}P NMR (120 MHz, $CDCl_3$) δ -3.57; IR (Neat Film NaCl) cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{36}H_{29}NOP$ [M^+]: 521.1909, found 521.1905; $[\alpha]^{26}_{D}$ = -5.1 (*c* 0.20, $CHCl_3$); TLC R_f = 0.38 (Hexanes/AcOEt, 5/1).

4.7.2.2 *Synthesis of Allyl Enol Carbonates*

General Procedures for the Synthesis of Allyl Enol Carbonates.

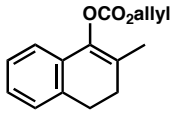
General Procedure 2:



274

Table 4.7 Entry 1. 274:[14a] To a solution of potassium *t*-butoxide (5.88 g, 52.5 mmol, 1.05 equiv) in DMF (100 mL) was added 2-methylcyclohexanone (6.13 mL, 50 mmol, 1.0 equiv). After 12 h, the reaction mixture was cooled in an ice bath and allyl chloroformate (6.4 mL, 60 mmol, 1.2 equiv) was added in a dropwise fashion. After an additional 30 min in the ice bath and 15 min at 25 °C, the reaction mixture was quenched into water (250 mL), extracted with DCM/hexanes 2/1 (4 x 125 mL), dried ($MgSO_4$), and evaporated. Chromatography (2.5 to 4 % Et_2O in Hexanes on SiO_2) afforded the allyl enol carbonate **274** (4.49 g, 46% yield) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 5.94 (ddt, *J* = 17.4, 10.5, 5.6 Hz, 1H), 5.36 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.26 (dq, *J* = 10.2, 1.2 Hz, 1H), 4.63 (dt, *J* = 5.7, 1.4 Hz, 2H), 2.13 (m, 2H), 2.02 (m, 2H), 1.70 (m, 2H), 1.59 (m, 2H), 1.55 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 142.2, 131.5, 120.8, 118.8, 68.5, 30.0, 26.6, 23.1, 22.3, 15.7; IR (Neat Film NaCl) 3936, 1755, 1275, 1239, 1037 cm^{-1}; HRMS *m/z* calc'd for $C_{11}H_{16}O_3$ $[M]^+$: 196.1100, found 196.1092.

General Procedure 3:

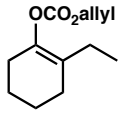


296

Table 4.7 Entry 12 (296).[64] To a cooled (0 °C) solution of LiHMDS (17.16 mmol, 1.1 equiv) in THF (37 mL) was added 2-methyl-1-tetralone (2.37 mL, 15.6 mmol, 1.0 equiv) in a dropwise manner over 15 min. After an additional 1.5 h at 0 °C, the enolate solution was added dropwise over 15 min to a -78 °C solution of allyl chloroformate (2.0 mL, 18.7 mmol, 1.2 equiv) in THF (80 mL). The reaction mixture

was allowed to warm to 25 °C in a Dewar vessel over 8 h. At which time, the reaction was quenched into DCM (100 mL) and half-saturated aqueous NH_4Cl (100 mL). The layers were separated and the aqueous layer extracted with DCM (2 x 50 mL). The organic fractions were washed with brine (100 mL), and dried (Na_2SO_4). Evaporation of the solvents under reduced pressure, and chromatography (2 to 5% Et_2O in Hexanes on SiO_2) afforded the allyl enol carbonate **296** (3.34 g, 88% yield) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20-7.08 (m, 4H), 6.01 (ddt, *J* = 17.7, 10.4, 5.6 Hz 1H), 5.41 (dq, *J* = 17.3, 1.5 Hz, 1H), 5.32 (dd, *J* = 10.2, 1.0 Hz, 1H), 4.72 (dt, *J* = 6.3, 1.4 Hz, 2H), 2.87 (t, *J* = 8.0 Hz, 2H), 2.40 (t, *J* = 8.0 Hz, 2H), 1.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 140.6, 135.2, 131.3, 130.8, 127.3, 127.0, 126.4, 124.4, 119.9, 119.1, 68.9, 28.8, 27.4, 16.5; IR (Neat Film NaCl) 2935, 2833, 1760, 1239 cm^{-1}; HRMS *m/z* calc'd for $C_{15}H_{16}O_3$ $[M]^+$: 244.1100, found 244.1098.

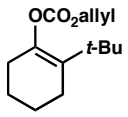
General Procedure 4:



320

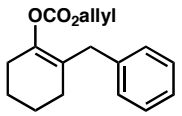
Table 4.7 Entry 4. (320):[65] To a solution of (2-ethylcyclohex-1-enyloxy)trimethylsilane (**348**) (1.50 g, 7.56 mmol, 1.0 equiv) in THF (14 mL) cooled to -78 °C was added a solution of potassium *t*-butoxide (0.933 g, 8.32 mmol, 1.1 equiv) in THF (8 mL) in a dropwise fashion over 2 min. The reaction mixture was maintained at -60 °C for 2.5 h, at which time allyl chloroformate (847 μL, 7.93 mmol, 1.05 equiv) in THF (3 mL) was added. After 1 h at -50 °C, the reaction mixture was poured into a

mixture of DCM (20 mL) and half-saturated aqueous NH_4Cl (20 mL). The layers were separated and the aqueous layer extracted with DCM (3 x 10 mL). The organic fractions were washed with water (50 mL), brine (50 mL), and dried (Na_2SO_4). Evaporation of the solvents under reduced pressure followed by chromatography on (2% Et_2O in Hexanes on SiO_2) and heating (rt to 105 °C) at 2 torr in a kugelrohr distillation apparatus afforded the allyl enol carbonate **320** (0.944 g, 59% yield) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (ddt, *J* = 17.4, 10.5, 5.6 Hz, 1H), 5.37 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.27 (dq, *J* = 10.5, 1.2 Hz, 1H), 4.64 (dt, *J* = 5.7, 1.5 Hz, 2H), 2.16 (m, 2H), 2.05 (m, 2H), 1.99 (q, *J* = 7.8, 2H), 1.70 (m, 2H), 1.61 (m, 2H), 0.4 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 141.7, 131.5, 126.3, 118.8, 68.5, 27.2, 26.6, 23.0, 22.9, 22.3, 11.9; IR (Neat Film NaCl) 2936, 1754, 1239 cm^{-1}; HRMS *m/z* calc'd for $C_{12}H_{18}O_3$ $[M]^+$: 210.1256, found 210.1255.



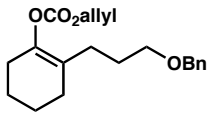
322

Table 4.7 Entry 5. (322): Prepared by general procedure 4 in 18% yield as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (ddt, *J* = 17.3, 10.4, 5.7 Hz, 1H), 5.38 (d, *J* = 17.4 Hz, 1H), 5.27 (d, *J* = 10.5 Hz, 1H), 5.65 (app. dt, *J* = 5.7, 1.2 Hz, 2H), 2.19 (m, 2H), 2.10 (m, 2H), 1.63 (m, 4H), 1.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 142.1, 131.6, 130.7, 118.9, 68.4, 34.8, 29.4, 28.1, 26.4, 23.1, 22.7; IR (Neat Film NaCl) 2926, 1754, 1241 cm^{-1}; HRMS *m/z* calc'd for $C_{14}H_{22}O_3$ $[M]^+$: 238.1569, found 238.1566.



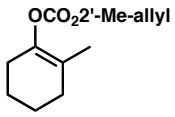
324

Table 4.7 Entry 6. (324): Prepared by general procedure 2 in 52% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.16 (m, 5H), 5.95 (ddt, *J* = 17.3, 10.4, 5.7 Hz, 1H), 5.38 (dq, *J* = 17.3, 1.5 Hz, 1H), 5.28 (dq, *J* = 10.2,1.2 Hz, 1H), 4.66 (app. dt, *J* = 5.7, 1.2 Hz, 2H), 3.35 (s, 2H), 2.27 (app. t, *J* = 6.3 Hz, 2H), 1.95 (m, 2H), 1.73 (m, 2H), 1.58 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 143.1, 139.3, 131.4, 128.8, 128.3, 126.0, 123.9, 119.0, 68.6, 36.0, 27.5, 26.7, 23.0, 22.2; IR (Neat Film NaCl) 2937, 1754, 1702, 1648, 1600, 1239 cm^{-1}; HRMS *m/z* calc'd for $C_{17}H_{20}O_3$ $[M]^+$: 272.1413, found 272.1416.



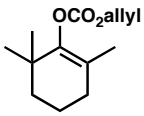
326

Table 4.7 Entry 7. (326): Prepared by general procedure 2 in 48% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.26 (m, 5H), 5.92 (ddt, *J* = 17.1, 10.5, 5.7 Hz, 1H), 5.35 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.25 (dq, *J* = 10.5, 1.1 Hz, 1H), 4.60 (app. dt, *J* = 5.7, 0.9 Hz, 2H), 4.49 (s, 2H), 3.44 (t, *J* = 6.6 Hz, 2H), 2.11 (m, 6H), 1.64 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 142.6, 138.7, 131.5, 128.3, 127.6, 127.4, 124.3, 118.8, 72.7, 70.0, 68.5, 27.7, 27.3, 26.6, 26.5, 23.0, 22.3; IR (Neat Film NaCl) 2924, 1754, 1240 cm^{-1}; HRMS *m/z* calc'd for $C_{20}H_{27}O_4$ $[M+H]^+$: 331.1909, found 331.1907.



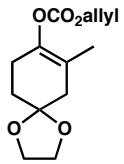
328

Table 4.7 Entry 8. (328): Prepared by general procedure 4 in 16% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.03 (s, 1H), 4.96 (s, 1H), 4.57 (s, 2H), 2.16 (m, 2H), 2.034 (bs, 2H), 1.79 (s, 3H), 1.77-1.58 (m, 4H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 142.2, 139.4, 120.9, 113.4, 71.1, 30.1, 26.6, 23.1, 22.3, 19.3, 15.8; IR (Neat Film NaCl) 2926, 1755, 1236 cm^{-1}; HRMS *m/z* calc'd for $C_{12}H_{18}O_3$ $[M]^+$: 210.1256, found 210.1259.



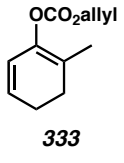
330

Table 4.7 Entry 9. (330): Prepared by general procedure 3 in 59% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 (m, 1H), 5.38 (d, *J* = 17.4 Hz, 1H), 5.28 (d, *J* = 10.5 Hz, 1H), 4.65 (d, *J* = 6.9 Hz, 2H), 2.05 (t, *J* = 5.4 Hz, 2H), 1.56 (m, 4H), 1.49 (s, 3H), 1.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 147.9, 131.6, 120.7, 118.8, 68.5, 39.2, 34.9, 31.1, 26.7, 19.1, 16.5; IR (Neat Film NaCl) 2935, 1759, 1238 cm^{-1}; HRMS *m/z* calc'd for $C_{13}H_{20}O_3$ $[M]^+$: 224.1413, found 224.1418.



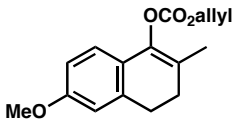
332

Table 4.7 Entry 10. (332): Prepared by general procedure 4 in 31% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (ddt, *J* = 17.1, 10.5, 5.7 Hz, 1H), 5.41 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.28 (dq, *J* = 10.5, 1.2 Hz, 1H), 4.65 (app. dt, *J* = 5.7, 1.5 Hz, 2H), 3.97 (m, 4H), 2.37 (m, 2H), 2.30 (bs, 2H), 1.87 (app. t, *J* = 6.6 Hz, 2H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 141.3, 131.4, 119.0, 118.5, 107.3, 68.6, 64.5, 39.9, 31.3, 25.3, 15.8; IR (Neat Film NaCl) 2919, 1756, 1250 cm^{-1}; HRMS *m/z* calc'd for $C_{13}H_{19}O_5$ $[M+H]^+$: 255.1232, found 255.1227.



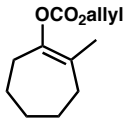
333

Table 4.7 Entry 11. (333): Prepared by general procedure 3 in 45% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (ddt, *J* = 17.1, 10.5, 5.7 Hz, 1H), 5.75 (m, 2H), 5.39 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.29 (d, *J* = 10.5, 1.2 Hz, 1H), 4.67 (app. dt, *J* = 5.7, 1.5 Hz, 2H), 2.42 (bs, 4H), 1.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 140.4, 131.3, 126.1, 122.7, 120.0, 119.1, 68.8, 28.2, 22.4, 15.7; IR (Neat Film NaCl) 2933, 1760, 1260 cm^{-1}; HRMS *m/z* calc'd for $C_{11}H_{14}O_3$ $[M]^+$: 194.0943, found 194.0938.



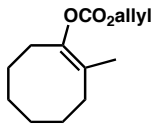
335

Table 4.7 Entry 13. (335): Prepared by general procedure 3 in 88% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (m, 1H), 6.70 (m, 2H), 5.98 (ddt, *J* = 17.1, 10.4, 5.7 Hz 1H), 5.42 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.32 (dq, *J* = 10.5, 1.2 Hz, 1H), 4.71 (dt, *J* = 5.7, 1.2 Hz, 2H), 3.78 (s, 3H), 2.84 (t, *J* = 7.8 Hz, 2H), 2.38 (t, *J* = 8.1 Hz, 2H), 1.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 153.1, 140.4, 137.2, 131.3, 123.9, 121.4, 121.1, 119.1, 113.7, 110.9, 68.9, 55.2, 28.8, 27.8, 16.3; IR (Neat Film NaCl) 2933, 1758, 1237 cm^{-1}; HRMS *m/z* calc'd for $C_{16}H_{18}O_4$ $[M]^+$: 274.1205, found 274.1213.



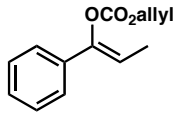
337

Table 4.7 Entry 14. (337): Prepared by general procedure 4 in 36% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (ddt, *J* = 17.1, 10.5, 5.7 Hz 1H), 5.37 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.28 (dq, *J* = 10.5, 1.2 Hz, 1H), 4.65 (app. dt, *J* = 6.0, 1.5 Hz, 2H), 2.33 (m, 2H), 2.10 (m, 2H), 1.70-1.54 (m, 6H), 1.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4, 146.2, 131.5, 125.5, 118.8, 68.5, 32.8, 32.5, 31.0, 25.7, 25.3, 18.3; IR (Neat Film NaCl) 2925, 1753, 1255, 1226 cm^{-1}; HRMS *m/z* calc'd for $C_{12}H_{18}O_3$ $[M]^+$: 210.1256, found 210.1253.



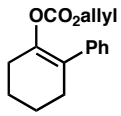
339

Table 4.7 Entry 15. (339): Prepared by general procedure 4 in 28% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (m, 1H), 5.39 (d, J = 16.5 Hz, 1H), 5.29 (d, J = 10.5 Hz, 1H), 4.66 (d, J = 5.4 Hz, 2H), 2.34 (app. t, J = 5.7 Hz, 2H), 2.15 (app. t, J = 5.4 Hz, 2H), 1.59 (s, 3H), 1.64-1.48 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4, 143.7, 131.5, 123.0, 118.8, 68.5, 31.4, 29.7, 28.7, 28.4, 26.6, 25.6, 15.5; IR (Neat Film NaCl) 2927, 1754, 1227 cm^{-1}; HRMS *m/z* calc'd for $C_{13}H_{20}O_3$ $[M]^+$: 224.1413, found 224.1419.



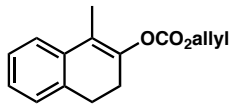
422

Table 4.13 Entry 1. (422): Prepared by general procedure 3 in 69% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46-7.43 (m, 2H), 7.37-7.26 (m, 3H), 6.04-5.85 (m, 2H), 5.44-5.28 (m, 2H), 4.71 (td, J_1 = 5.7 Hz, J_2 = 1.5 Hz, 2H), 1.80 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ =152.6, 150.7, 147.2, 134.6, 131.1, 128.4, 128.1, 119.0, 68.9, 11.2; IR (Neat Film NaCl) 3061, 2920, 1760, 1673, 1496, 1446, 1366, 1227, 1186, 966, 765, 693 cm^{-1}; HRMS *m/z* calc'd for $C_{13}H_{14}O_3$ $[M]^+$: 218.0943, found 218.0938.



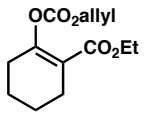
425

Table 4.14 Entry 1. (425): Prepared by general procedure 2 in 43% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.18 (comp. m, 5H), 5.80 (ddt, *J* = 17.4, 10.5, 5.4 Hz, 1H), 5.20 (ddt, *J* = 17.4, 1.8, 1.2 Hz, 1H), 5.18 (ddt, *J* = 10.5, 1.5, 1.2 Hz, 1H), 5.02 (ddd, *J* = 5.7, 1.5, 1.5 Hz, 2H), 2.46-2.38 (m, 2H), 2.37-2.30 (m, 2H), 1.90-1.72 (comp. m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 143.4, 138.8, 131.3, 128.1, 127.6, 126.8, 125.9, 118.4, 68.4, 30.1, 27.1, 22.8, 22.5; IR (Neat Film NaCl) 3081, 3057, 3024, 2938, 2862, 1753, 1687, 1601, 1492, 1444, 1367, 1238, 1178, 1091, 1036, 941, 784, 760, 700 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{16}H_{18}O_3$ $[M]^+$: 258.1256, found 258.1256.



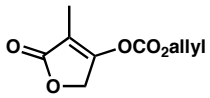
426

Table 4.14 Entry 2. (426): Prepared by general procedure 2 in 59% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.11 (comp. m, 4H), 6.00 (ddt, *J* = 17.1, 10.2, 6.0 Hz, 1H), 5.43 (ddt, *J* = 17.1, 1.8, 1.2 Hz, 1H), 5.33 (ddt, *J* = 10.2, 1.5, 1.2 Hz, 1H), 4.72 (ddd, *J* = 6.0, 1.5, 1.2 Hz, 2H), 2.97 (t, *J* = 7.8 Hz, 2H), 2.55 (tq, *J* = 8.1, 1.5 Hz, 2H), 2.00 (t, *J* = 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 145.9, 135.0, 134.1, 131.2, 127.1, 126.6, 126.5, 123.4, 119.7, 119.2, 68.9, 28.7, 26.0, 10.9; IR (Neat Film NaCl) 3021, 2993, 2944, 2891, 2836, 1757, 1674, 1488, 1451, 1365, 1304, 1279, 1246, 1217, 1181, 1157, 1031, 1018, 986, 943, 782, 760 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{15}H_{16}O_3$ $[M]^+$: 244.1100, found 244.1095.



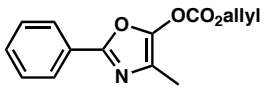
428

Table 4.14 Entry 3. (428): Prepared by general procedure 2 in 78% yield as a light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 (ddt, *J* = 17.1, 10.5, 5.7 Hz, 1H), 5.39 (ddt, *J* = 17.1, 1.5, 1.5 Hz, 1H), 5.28 (ddt, *J* = 10.5, 1.5, 1.2 Hz, 1H), 4.67 (ddd, *J* = 5.7, 1.2, 1.2 Hz, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 2.44-2.34 (m, 2H), 2.32-2.24 (m, 2H), 1.80-1.58 (comp. m, 4H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 154.8, 152.2, 131.2, 119.2, 118.3, 69.0, 60.5, 28.6, 25.1, 21.9, 21.5, 14.0; IR (Neat Film NaCl) 3087, 1983, 2942, 2866, 1760, 1715, 1666, 1449, 1368, 1233, 1189, 1081, 1056, 1035, 994, 946, 767 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{18}O_5$ $[M]^+$: 254.1154, found 254.1153.



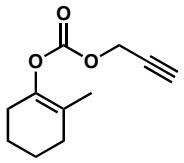
429

Table 4.14 Entry 4. (429): Prepared by a modification of general procedure 2 using TEA as the base and THF as solvent in 79% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (ddt, *J* = 17.1, 10.2, 6.0 Hz, 1H), 4.93 (ddt, *J* = 17.1, 2.7, 1.2 Hz, 1H), 5.37 (ddt, *J* = 10.2, 2.1, 0.9 Hz, 1H), 5.07 (q, *J* = 1.8 Hz, 2H), 4.74 (ddd, *J* = 6.0, 1.2, 0.9 Hz, 2H), 1.81 (t, *J* = 1.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 163.4, 150.2, 130.0, 120.8, 109.4, 70.3, 67.5, 6.9; IR (Neat Film NaCl) 3089, 2958, 2931, 1774, 1702, 1446, 1392, 1360, 1330, 1240, 1132, 1079, 1025, 945, 889, 775, 754 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_9H_{11}O_5$ $[M + H]^+$: 199.0606, found 199.0600.



431

Table 4.14 Entry 5. (431): Prepared by a modification of Leplawy's procedure[66] in 96% yield as a colorless oil that solidifies on standing; Mp 37.5-39 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97-7.90 (m, 2H), 7.45-7.38 (comp. m, 3H), 5.99 (ddt, *J* = 17.4, 10.5, 5.7 Hz, 1H), 5.45 (ddt, *J* = 17.4, 1.5, 1.2 Hz, 1H), 5.36 (ddt, *J* = 10.5, 1.2, 1.2 Hz, 1H), 4.78 (ddd, *J* = 6.0, 1.2, 1.2 Hz, 2H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 155.0, 151.6, 146.2, 130.5 (2C), 128.9, 127.3, 126.1, 120.6, 70.7, 10.5; IR (Neat Film NaCl) 3066, 2930, 1786, 1669, 1554, 1490, 1450, 1367, 1213, 1082, 1069, 1026, 992, 939, 774, 711, 692 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{14}H_{13}O_4N$ $[M]^+$: 259.0845, found 259.0855.

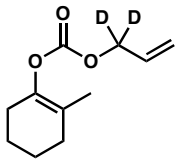


433

Propargyl enol carbonate 433: A 50 mL flask equipped with a septum was flame-dried under vacuum and cooled under dry nitrogen. To this was added methyllithium in ether (1.6 M, 7.5 mL, 12.0 mmol, 1.10 equiv) followed by dry ether (10 mL). To this solution was added ether (5 mL) solution of trimethyl(2-methylcyclohex-1-enyloxy)silane **(347)** (2.003 g, 10.9 mmol, 1.00 equiv) at 0 ºC and the resulting colorless solution was stirred for 1.5 h at ambient temperature to afford an ether solution of lithium enolate.

To a solution of propargyl chloroformate (1.18 mL, 12.0 mmol, 1.10 eq.) in ether (10 mL) was added the above lithium enolate solution at 0 ºC. The resulting mixture was

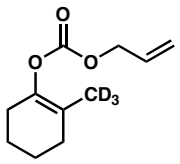
stirred and warmed to 10 ºC over 1 h. The resulting mixture was poured into saturated aqueous NH_4Cl and extracted with ether twice. The combined organic layers were washed with water, brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a crude oil. The crude residue was purified residue by SiO_2 chromatographed (2 to 10% Et_2O in hexanes) to give propargyl enol carbonate **443** (733 mg, 35% yield) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.75 (d, J = 2.4 Hz, 2H), 2.53 (t, J = 2.4 Hz, 1H), 2.20-2.11 (m, 2H), 2.07-2.00 (m, 2H), 1.76-1.66 (m, 2H), 1.66-1.56 (m, 2H), 1.57 (m, 3H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 142.3, 121.1, 76.9, 75.7, 55.4, 30.0, 26.5, 23.1, 22.3, 15.8; IR (Neat Film NaCl) 3295, 2937, 2862, 2130, 1756, 1709, 1439, 1376, 1275, 1250, 1220, 1045 cm^{-1}; HRMS *m/z* calc'd for $C_{11}H_{14}O_3$ $[M]^+$: 194.0943, found 194.0939.



441

Dideuterio allyl enol carbonate 441. Prepared by general procedure 1 with dideuterioallyl chroroformate, which was synthesized from 1-dideuterioallyl alcohol[67] and 20% phosgene in toluene. Flash chromatography (SiO_2, 1 to 2.5% Et_2O in hexanes) gave dideuterio allyl enol carbonate **441** (6% yield) as a colorless oil; R_f = 0.82 (25% Et_2O in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (dd, *J* = 17.0, 10.4 Hz, 1H), 5.38 (d, *J* = 17.1 Hz, 1H), 5.28 (d, *J* = 10.5 Hz, 1H), 2.21-2.09 (comp. m, 2H), 2.08-1.98 (comp. m, 2H), 1.77-1.66 (comp. m, 2H), 1.65-1.53 (comp. m, 2H), 1.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 142.2, 131.4, 120.9, 119.0, 30.3, 26.6, 23.1, 22.3, 21.7,

15.8; IR (Neat Film NaCl) 2935, 2862, 1753, 1710, 1280, 1262, 1078 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{14}D_2O_3$ $[M]^+$: 198.1225, found 198.1217.



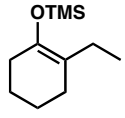
442

Trideuterio allyl enol carbonate 442. Prepared by general procedure 1 with 2-trideuteriomethylcyclohexanone.[68.] Flash chromatography (SiO_2, 2 to 2.5% Et_2O in hexanes) gave trideuterio allyl enol carbonate **442** (22% yield) as a colorless oil; $R_f = 0.82$ (25% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.96 (ddt, *J* = 17.1, 10.8, 6.0 Hz, 1H), 5.38 (d, *J* = 17.3 Hz, 1H), 5.28 (d, *J* = 10.5 Hz, 1H), 4.65 (d, *J* = 5.7 Hz, 2H), 2.21-2.09 (comp. m, 2H), 2.08-1.98 (comp. m, 2H), 1.77-1.66 (comp. m, 2H), 1.66-1.53 (comp. m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 142.2, 131.5, 120.8, 118.8, 68.5, 30.0, 26.6, 23.1, 22.3; IR (Neat Film NaCl) 2936, 1755, 1705, 1367, 1276, 1247, 1216, 1034, 786 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{13}D_3O_3$ $[M]^+$: 199.1288, found 199.1280.

4.7.2.3 *Synthesis of Silyl Enol Ethers*

General Procedures for the Synthesis of Silyl Enol Ethers.

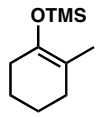
General Procedure 5:



348

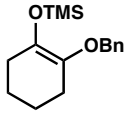
Table 4.8 Entry 2 (348).[69] To a solution of sodium iodide (15.0 g, 100 mmol, 1.25 equiv) in ACN (125 mL) were added 2-ethylcyclohexanone (10.1 g, 80 mmol, 1.0

equiv), TEA (14.0 mL, 100 mmol, 1.25 equiv), and finally TMSCl (11.6 mL, 91.2 mmol, 1.14 equiv) in a dropwise fashion. After 1 h, pentane (75 mL) was added, the biphasic mixture was stirred for 2 min, and the pentane decanted. After additional pentane extractions (5 x 75 mL), the combined pentane fractions were washed with water (2 x 50 mL) and brine (1 x 50 mL), and dried (Na_2SO_4). Evaporation under reduced pressure gave the crude silyl enol ether (12.0 g) as an 80:20 mixture (NMR) of isomers favoring the tetrasubstituted silyl enol ether. An oxygen balloon was affixed to a flask containing a solution of the crude silyl enol ether (6.0 g) and palladium (II) acetate (338.9 mg, 1.51 mmol) in DMSO (250 mL). The reaction mixture darkened and became heterogeneous. After 48 h, ^{1}H NMR analysis of an aliquot indicated less than 2% of the undesired isomer, and the reaction mixture was poured into a separatory funnel containing pentane (300 mL), water (300 mL), and ice (200 g). The layers were separated and the aqueous layer extracted with pentane (3 x 200 mL). The pentane fractions were washed with water (2 x 100 mL) and brine (100 mL), and dried (Na_2SO_4). Evaporation and chromatography (2% Et_2O in Hexanes on SiO_2) afforded the pure silyl enol ether **348** (3.21 g, 41% yield) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.08-1.90 (m, 6H), 1.62 (m, 2H), 1.54 (m, 2H), 0.92 (t, J = 7.8 Hz, 3H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.2, 117.4, 30.4, 27.0, 23.7, 23.1, 22.9, 12.2, 0.7; IR (Neat Film NaCl) 2961, 2933, 1680, 1252, 922, 843 cm^{-1}; HRMS *m/z* calc'd for $C_{11}H_{22}OSi$ $[M]^+$: 198.1440, found 198.1436.



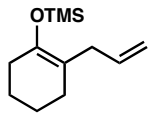
347

Table 4.8 Entry 1 (347). Prepared by general procedure 5, the initial 10:1 mixture favoring the tetrasubstituted isomer was purified by fractional distillation with a spinning band column[68] to give silyl enol ether **347** (84% yield) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00 (m, 2H), 1.94 (m, 2H), 1.64 (m, 2H), 1.58-1.49 (m, 5H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9, 111.8, 30.3, 30.1, 23.8, 23.0, 16.3, 0.7; IR (Neat Film NaCl) 2930, 1688, 1252, 1185, 843 cm^{-1}; HRMS *m/z* calc'd for $C_{10}H_{20}OSi$ $[M]^+$: 184.1284, found 184.1275.



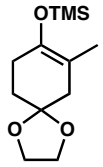
349

Table 4.8 Entry 3 (349). Prepared by general procedure 5 in 11% yield as a colorless oil; ^{1}H NMR (300 MHz, C_6D_6) δ 7.40 (d, *J* = 7.2 Hz, 2H), 7.19 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.09 (t, *J* = 7.5 Hz, 1H), 4.77 (s, 2H), 2.12-1.98 (comp. m, 4H), 1.39 (app. quintet, *J* = 3.3 Hz, 4H), 0.25 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6) δ 139.9, 136.9, 135.5, 128.8, 128.2, 128.0, 71.3, 30.8, 27.1, 23.9, 23.7, 1.2; IR (Neat Film NaCl) 3065, 3032, 2934, 2860, 2841, 1694, 1497, 1454, 1343, 1250, 1245, 1195, 1122, 1017, 930, 860, 844, 750, 698 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{16}H_{24}O_2Si$ $[M]^+$: 276.1546, found 276.1545.



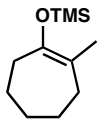
351

Table 4.8 Entry 5 (351). Prepared by general procedure 5 in 59% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (ddt, *J* = 16.8, 9.9, 6.9 Hz, 1H), 4.99 (ddt, *J* = 16.5, 2.1, 1.8 Hz, 1H), 4.95 (ddt, *J* = 9.6, 2.1, 1.5 Hz, 1H), 2.77 (app. d, *J* = 6.6 Hz, 2H), 2.14-1.88 (comp. m, 4H), 1.75-1.42 (comp. m, 4H), 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 136.9, 114.6, 113.5, 34.8, 30.4, 27.5, 23.7, 23.0, 0.7; IR (Neat Film NaCl) 3077, 2931, 2838, 1682, 1638, 1448, 1433, 1355, 1252, 1204, 1168, 948, 905, 888, 844, 753 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{12}H_{22}OSi$ $[M]^+$: 210.1440, found 210.1449.



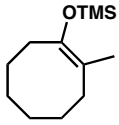
353

Table 4.8 Entry 6 (353). Prepared by general procedure 5 in 51% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.96 (m, 4H), 2.21 (m, 4H), 1.79 (app. t, *J* = 6.9 Hz, 2H), 1.54 (s, 3H), 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.2, 108.9, 108.0, 64.4, 39.9, 31.7, 28.7, 16.2, 0.69; IR (Neat Film NaCl) 2956, 1691, 1252 cm^{-1}; HRMS *m/z* calc'd for $C_{12}H_{22}O_3Si$ $[M]^+$: 242.1338, found 242.1334.



354

Table 4.8 Entry 7 (354). Prepared by general procedure 5 in 39% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.23 (app. t, J = 5.4 Hz, 2H), 2.01 (app. t, J = 5.1 Hz, 2H), 1.66 (m, 2H), 1.59 (s, 3H), 1.56-1.45 (m, 4H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 116.9, 35.1, 32.7, 31.6, 26.5, 25.5, 18.7, 0.6; IR (Neat Film NaCl) 2921, 1678, 1251, 1171, 892, 842 cm^{-1}; HRMS *m/z* calc'd for $C_{11}H_{22}OSi$ [M]+: 198.1440, found 198.1439.



355

Table 4.8 Entry 8 (355). Prepared by general procedure 5 (pyridine substituted for TEA) in 29% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21 (m, 2H), 2.05 (m, 2H), 1.61-1.44 (m, 8H), 1.57 (s, 3H), 0.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 113.5, 31.7, 28.9, 28.8, 26.7, 26.3, 15.8, 0.8; IR (Neat Film NaCl) 2924, 1678, 1251 cm^{-1}; HRMS *m/z* calc'd for $C_{12}H_{24}OSi$ [M]+: 212.1597, found 212.1590.

4.7.2.4 *Synthesis of Allyl β-Ketoesters*

General Procedures for the Synthesis of Allyl *b*-Ketoesters.

General Procedure 6: Dieckmann Cyclization Method

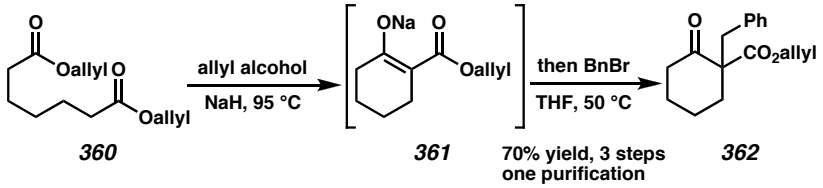


Table 4.10 Entry 6 (362). To a suspension of NaH (166.4 mg, 4.16 mmol, 1.0 equiv) in toluene (2 mL) was added allyl alcohol (79.2 μL, 1.17 mmol, 0.28 equiv). Once gas evolution ceased, pimelic acid diallyl ester (1.00 g, 4.16 mmol, 1.0 equiv) was added slowly and the resulting mixture heated to 95 °C for 1 h. Additional toluene (~2 mL) was added during this time to maintain a fluid reaction mixture. The reaction mixture was cooled to rt and the solvent removed by rotary evaporation *in vacuo*. The resulting solid salt was placed under dry N_2 and dissolved in THF (9 mL) at rt. Benzyl bromide (643.2 μL, 5.4 mmol, 1.3 equiv) was then added dropwise. The resulting mixture was warmed to 50 °C for 2.5 h, cooled to rt, quenched with saturated aqueous NH_4Cl solution (5 mL) followed by H_2O (5 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (1 x 10 mL), then dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting oil was purified by flash chromatography (5 x 18 cm SiO_2, 10% Et_2O in pentane) to afford the quaternary compound **362** as a colorless oil (781.4 mg, 70% yield). R_f = 0.30 (10% Et_2O in pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.23 (comp. m, 3H), 7.20-7.13 (comp. m, 2H), 5.86 (dddd, J = 17.2, 10.3, 5.9, 5.9 Hz, 1H), 5.29 (m, 2H), 4.57 (m, 2H), 3.38 (d, 1H, J = 13.8 Hz), 2.94 (d, J = 13.8 Hz, 1H), 2.60-

2.39 (comp. m, 3H), 2.14-1.97 (m, 1H), 1.83-1.60 (comp. m, 3H), 1.59-1.45 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.8, 170.5, 136.3, 131.2, 130.2, 127.9, 126.5, 119.0, 65.6, 62.1, 41.1, 40.3, 35.7, 27.4, 22.3; IR (Neat Film NaCl) 3029, 2942, 1713, 1452, 1179, 1085 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{17}H_{20}O_3$ $[M]^+$: 272.1412, found 272.1425.

General Procedure 7: Mander's Reagent Method

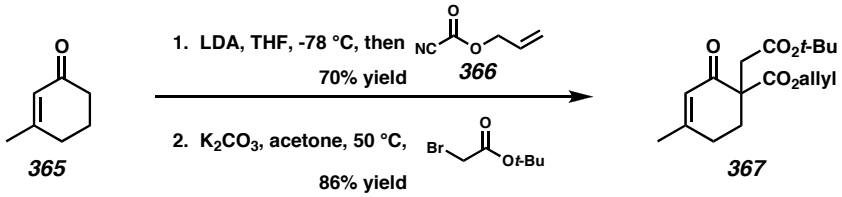
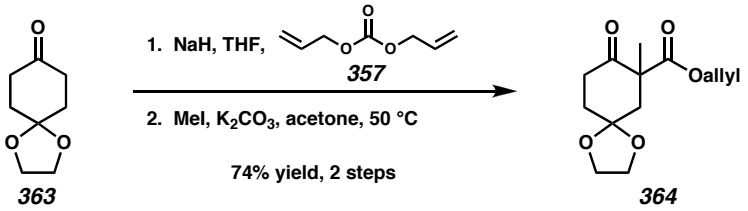


Table 4.11 Entry 6 (367). To a cooled (-78 °C) solution of LDA (18.70 mmol, 1.05 equiv) in THF (90 mL) was added 3-methylcyclohex-2-enone (2.02 mL, 17.81 mmol, 1.0 equiv) in a dropwise fashion. The resulting solution was stirred at -78 °C for 30 min and then allyl cyanoformate (2.00 g, 18.17 mmol, 1.02 equiv) was added dropwise. The dry ice bath was removed and the reaction mixture slowly warmed to rt and stirred for 8 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (15 mL) followed by H_2O (15 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine (1 x 30 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (5 x 24 cm SiO_2, 50% EtOAc in hexanes) to afford the intermediate β-keto ester as a yellow oil (2.4152 g, 70% yield).

A portion of this β-keto ester (500.0 mg, 2.57 mmol, 1.0 equiv) was added to a suspension of anhydrous K_2CO_3 (711.8 mg, 5.15 mmol, 2.0 equiv) in acetone (2.5 mL). To the reaction mixture was added *t*-butyl bromoacetate (760.5 μL, 5.15 mmol, 2.0

equiv). The reaction mixture was then warmed to 50 °C and stirred for 48 h. The reaction mixture was then cooled, filtered, and the solids washed with acetone. The filtrate was concentrated and purified by flash chromatography (3 x 20 cm SiO_2, 10→30% EtOAc in hexanes) to afford the desired quaternary β-ketoester **367** as a colorless oil (684.7 mg, 86% yield; 60% overall yield for 2 steps). R_f = 0.28 (30% Et_2O in pentane). ^1H NMR (300 MHz, $CDCl_3$) δ 5.93 (s, 1H), 5.87 (dddd, J = 17.3, 10.5, 5.4, 5.4 Hz, 1H), 5.23 (m, 2H), 4.61 (m, 2H), 2.83 (d, J = 16.4 Hz, 1H), 2.73 (d, J = 16.4 Hz, 1H), 2.58-2.36 (comp. m, 2H), 2.31-2.16 (comp. m, 2H), 1.94 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.2, 169.8, 161.9, 131.7, 125.6, 118.2, 81.1, 65.8, 54.2, 39.8, 30.5, 28.7, 28.0, 24.2; IR (Neat Film NaCl) 2979, 1733, 1677, 1368, 1153 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{17}H_{24}O_5$ $[M]^+$: 308.1624, found 308.1609.

General Procedure 8: Diallyl Carbonate Method



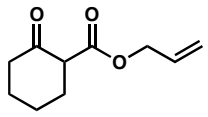
Part 1, Acylation:

To a cooled (0 °C) suspension of NaH (9.22 g, 240.1 mmol, 2.5 equiv) in THF (125 mL) was added a solution of 1,4-cyclohexanedione *mono*-ethylene ketal (15.0 g, 96 mmol, 1.0 equiv) in THF (30 mL) dropwise over 15 min. The reaction mixture was warmed to rt and diallyl carbonate (20.65 mL, 144.0 mmol, 1.5 equiv) was added and the reaction mixture stirred for 16 h. The reaction was quenched with saturated aqueous NH_4Cl and 1 N HCl until a pH of 4 was reached. The phases were separated and the

aqueous phase was extracted with EtOAc (7 x 150 mL). The combined organic extracts were dried (Na_2SO_4), filtered, concentrated, redissolved in DCM, dried ($MgSO_4$), filtered, and concentrated.

Part 2, Alkylation:

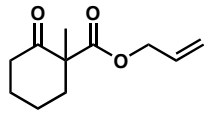
The resulting oil was added to a suspension of anhydrous K_2CO_3 (26.5 g, 192.0 mmol, 2.0 equiv) in acetone (128 mL). To the reaction mixture was added iodomethane (12.0 mL, 192.0 mmol, 2.0 equiv) and the reaction mixture was then heated to 50 °C for 14 h. The mixture was then cooled to rt, filtered, and the solids washed with acetone. The filtrate was concentrated and the resulting oil purified by flash chromatography (SiO_2, 5→40% Et_2O in hexanes) to afford the desired quaternary quaternary β-ketoester **364** as a colorless oil (18.0 g, 74% yield). R_f = 0.28 (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 5.90 (dddd, *J* = 17.4, 10.5, 5.7, 5.7 Hz, 1H), 5.26 (m, 2H), 4.60 (m, 2H), 3.97 (comp. m, 4H), 3.02 (dt, *J* = 14.8, 10.2 Hz, 1H), 2.68 (dt, *J* = 14.0, 2.0 Hz, 1H), 2.49 (dt, *J* = 14.8, 4.4 Hz, 1H), 2.00 (comp. m, 2H), 1.72 (d, *J* = 14.1 Hz, 1H), 1.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.0, 172.9, 131.6, 118.5, 106.5, 65.9, 64.8, 64.3, 54.6, 43.6, 37.4, 35.2, 21.7; IR (Neat Film NaCl) 2939, 2891, 1733, 1717, 1304, 1141 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{13}H_{18}O_5$ $[M]^+$: 254.1154, found 254.1153.



SI3

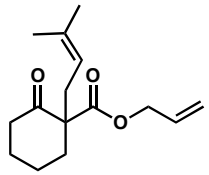
SI3: Prepared by method 1. The reaction was quenched with 10% HCl. The product was isolated by bulb-to-bulb distillation once at 150-155 °C (bath temp, 2 torr),

then at 136 °C (bath temp, 2 torr). 75% yield. R_f = 0.53 (10:1 Hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of enol tautomers) δ 12.14 (s, 0.7H), 5.99 (dddd, *J* = 5.7, 5.7, 10.8, 17.1 Hz, 0.7H), 5.96 (dddd, *J* = 5.7, 5.7, 10.2, 17.1 Hz, 0.3H), 5.38 (dddd, *J* = 1.5, 1.5, 1.5, 17.1 Hz, 0.3H), 5.37 (dddd, *J* = 1.5, 1.5, 1.5, 17.1 Hz, 0.7H), 5.24 (dddd, *J* = 1.5, 1.5, 1.5, 10.5 Hz, 1H), 4.72-4.55 (m, 2H), 3.41 (ddd, *J* = 1.5, 6.6, 9.6 Hz, 0.3H), 2.52 (dddd, *J* = 1.5, 5.4, 5.4, 14.1 Hz, 0.3H), 2.37 (m, 0.3H), 2.26 (m, 2.7H), 2.22-2.10 (m, 0.6H), 2.04-1.78 (m, 0.9H), 1.75-1.55 (m, 3.3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.9, 172.4, 172.2, 169.6, 132.3, 131.8, 118.4, 117.7, 97.5, 65.6, 64.6, 57.2, 41.5, 29.9, 29.1, 27.0, 23.3, 22.3, 22.3, 21.9; IR (Neat Film NaCl) 3086, 2941, 1746, 1716, 1659, 1617, 1299, 1259, 1217, 1176, 831 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{10}H_{14}O_3$ $[M]^+$: 182.0943, found 182.0941.



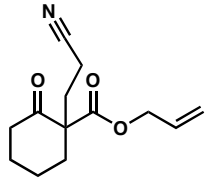
358

Table 4.10, Entry 1 (358). Prepared by general procedure 6. 62% yield. R_f = 0.38 (10:1 Hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (dddd, *J* = 17.1, 10.2, 5.9, 5.9 Hz, 1H), 5.24 (m, 2H), 4.59 (d, *J* = 5.7 Hz, 2H), 2.58-2.34 (comp. m, 3H), 2.08-1.88 (m, 1H), 1.80-1.54 (comp. m, 3H), 1.52-1.37 (m, 1H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.9, 172.6, 131.4, 118.7, 65.6, 57.1, 40.5, 38.1, 27.4, 22.5, 21.1; IR (Neat Film NaCl) 3086, 2939, 2867, 1715, 1452, 1259, 1211, 1159, 1084, 976 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{15}H_{16}O_3$ $[M]^+$: 196.1099, found 196.1096.



368

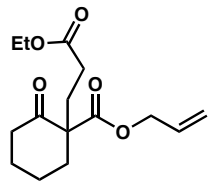
Table 4.10, Entry 3 (368). Prepared by general procedure 8 part B from **SI3** and prenyl bromide. Flash chromatography (SiO_2, 2→12% Et_2O in pentane). 20% yield. R_f = 0.24 (10% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 5.87 (dddd, J = 17.1, 10.4, 5.8, 5.8 Hz, 1H), 5.31 (d, J = 17.1 Hz, 1H), 5.24 (d, J = 10.1 Hz, 1H), 5.06 (t, J = 7.7 Hz, 1H), 4.59 (d, J = 5.7 Hz, 2H), 2.65-2.27 (comp. m, 5H), 2.07-1.93 (m, 1H), 1.79-1.69 (m, 1H), 1.68 (s, 3H), 1.66-1.59 (m, 1H), 1.58 (s, 3H), 1.54-1.39 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.7, 171.4, 134.8, 131.6, 118.8, 118.5, 65.7, 61.3, 41.2, 35.5, 33.2, 27.5, 26.0, 22.5, 17.8; IR (Neat Film NaCl) 2938, 2863, 1714, 1451, 1438, 1210, 1178, 989 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{15}H_{22}O_3$ $[M]^+$: 250.1569, found 250.1574.



370

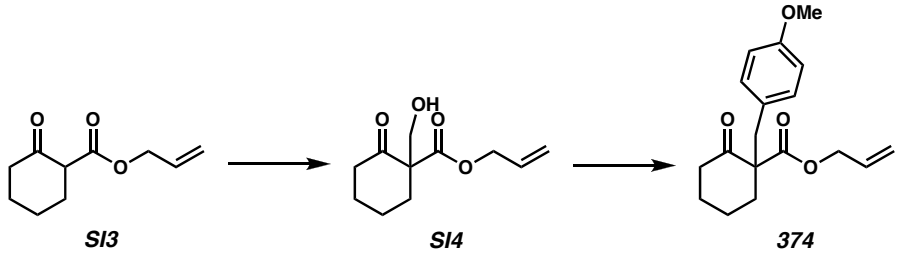
Table 4.10, Entry 4 (370). Prepared by general procedure 8 part B from **SI3** and acrylonitrile. Flash chromatography (SiO_2, 10% Et_2O in pentane). 55% yield. R_f = 0.27 (CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 5.91 (dddd, J = 17.6, 10.2, 6.0, 6.0 Hz, 1H), 5.41-5.25 (m, 2H), 4.68 (d, J = 6.0 Hz, 2H), 2.64-2.38 (comp. m, 4H), 2.37-2.13 (comp. m, 2H), 2.13-1.86 (comp. m, 2H), 1.85-1.40 (comp. m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.0, 170.6, 130.9, 120.0, 119.3, 66.4, 59.7, 40.9, 36.7, 30.8, 27.4, 22.4, 13.0; IR (Neat

Film NaCl) 2945, 2868, 2248, 1713, 1450, 1192, 1136, 941 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{13}H_{17}NO_3$ $[M]^+$: 235.1208, found 235.1218.



372

Table 4.10, Entry 5 (372). Prepared by general procedure 8 part B from **SI3** and ethyl acrylate. Flash chromatography (SiO_2, 10% Et_2O in pentane). 81% yield. $R_f = 0.37$ (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 5.89 (dddd, *J* = 17.3, 10.3, 5.9, 5.9 Hz, 1H), 5.33 (dd, *J* = 17.3, 1.1 Hz, 1H), 5.26 (dd, *J* = 10.4, 1.3 Hz, 1H), 4.63 (app. t, *J* = 14.9 Hz, 2H), 4.11 (q, *J* = 7.2 Hz, 2H), 2.51-2.31 (comp. m, 4H), 2.31-2.11 (comp. m, 2H), 2.08-1.85 (comp. m, 2H), 1.84-1.57 (comp. m, 3H), 1.55-1.40 (m, 1H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.4, 173.0, 171.4, 131.3, 119.3, 65.9, 60.4, 60.1, 41.0, 36.2, 29.6, 29.5, 27.5, 22.5, 14.2; IR (Neat Film NaCl) 2943, 2868, 1734, 1715, 1456, 1181 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{15}H_{22}O_5$ $[M]^+$: 282.1467, found 282.1474.

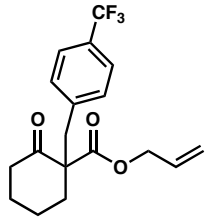


SI3 ***SI4*** ***374***

Table 4.10, Entry 7 (374). To a cooled (0 °C) solution of **SI3** (4.00 g, 22.0 mmol, 1.0 equiv) in THF (40 ml) was added 35% aqueous formaldehyde (11.3 mL) and

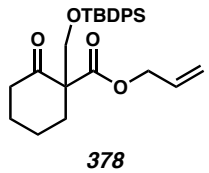
$KHCO_3$ (5.93 g, 65.9 mmol, 3.0 equiv). After 30 min at 0 °C the reaction mixture was allowed to warm to ambient temperature. After an additional 90 min, the reaction was quenched with water (100 mL) and DCM (100mL). After the layers were separated, the aqueous layer was extracted with DCM (4 x 50 mL), the combined organics dried (Na_2SO_4) and evaporated. The oil obtained was treated with THF (40 mL) and 3M HCl (4 drops) for 60 min, concentrated, and purified by flash chromatography (SiO_2, 10→45% EtOAc in hexanes) to give **SI4** (3.75g, 81% yield).

To a cooled (0 °C) suspension of 60% NaH (251 mg, 6.28 mmol, 1.1 equiv) in DMF (20 mL) was added **SI4** (1.20g, 5.71 mmol, 1.0 equiv) in a dropwise manner over 2 min. Once gas evolution had ceased (10 min), Bu_4NI (527 mg, 1.43 mmol. 0.25 equiv) and PMB-Cl (930 μL, 6.85 mmol, 1.2 equiv) were added, and the reaction mixture slowly allowed to warm to ambient temperature. After 12 h, the reaction mixture was quenched with water (50 mL) and 2/1 DCM/hexanes (50 mL), the aqueous layer extracted with 2/1 DCM/hexanes (3 x 50 mL), dried (Na_2SO_4), evaporated, and purified by flash chromatography (SiO_2, 10→20% Et_2O in hexanes) to give the desired compound **374** (485 mg, 28% yield). R_f = 0.30 (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.03 (d, J = 8.7 Hz, 2H), 6.77 (d, J = 8.7 Hz, 2H), 5.89-5.76 (m, 1H) 5.31-5.21 (m, 2H), 4.59-4.47 (m, 2H), 3.76 (s, 3H), 3.25 (d, J = 14.1 Hz, 1H), 2.84 (d, J = 14.1 Hz, 1H), 2.51-2.35 (m, 3H), 2.04-1.96 (m, 1H), 1.76-1.54 (m, 3H), 1.50-1.40 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.2, 170.8, 158.4, 131.4, 131.3, 128.4, 119.1, 113.4, 65.8, 62.3, 55.1, 41.3, 39.5, 35.8, 27.5, 22.5; IR (Neat Film NaCl) 2943, 1713, 1612, 1513, 1247, 1179 cm^{-1}; HRMS (EI) m/z calc'd for $C_{18}H_{22}O_4$ $[M]^+$: 302.1518, found 302.1514.



376

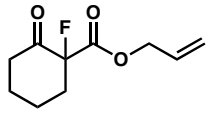
Table 4.10, Entry 8 (376). Prepared by general procedure 6 with 4-(trifluoroumethyl)benzyl bromide. Flash chromatography (SiO_2, 2→12% Et_2O in pentane). 56% yield. Mp 40-41 ºC; R_f = 0.63 (30% Et_2O in pentane); ^{1}H NMR (300 MHz, C_6D_6) δ 7.29 (d, J = 8.1 Hz, 2H), 7.02 (d, J = 8.1 Hz, 2H), 5.45 (dddd, J = 17.3, 10.4, 6.0, 6.0 Hz, 1H), 4.91 (m, 2H), 4.18 (m, 2H), 3.34 (d, J = 13.7 Hz, 1H), 2.78 (d, J = 13.7 Hz, 1H), 2.37-2.15 (comp. m, 3H), 1.57-1.38 (comp. m, 2H), 1.32-1.11 (comp. m, 2H), 1.09-0.94 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.7, 170.4, 140.8 (q, J_{CF} = 1.2 Hz), 131.0, 130.7, 129.0 (q, J_{CF} = 32.3 Hz), 124.9 (q, J_{CF} = 3.9 Hz), 124.2 (q, J_{CF} = 271.7 Hz), 119.4, 65.9, 62.2, 41.2, 40.2, 36.2, 27.5, 22.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.0; IR (Neat Film NaCl) 2945, 1715, 1326, 1164, 1123, 1068 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{18}H_{19}F_3O_3$ $[M]^+$: 340.1286, found 340.1277.



378

Table 4.10, Entry 9 (378). To a solution of **SI4** (1.20 g, 5.71 mmol. 1.0 equiv), imidazole (583 mg, 8.57 mmol, 1.5 equiv), and DMAP (1.04 g, 8.57 mmol, 1.5 equiv) in DMF (20 mL) was added TBDPS-Cl (1.75 mL, 6.85 mmol, 1.2 equiv). After 24 h at ambient temperature, the reaction mixture was poured into water (75 mL) and 2/1

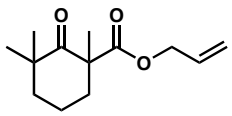
DCM/hexanes (150 mL), extracted with 2/1 DCM/hexanes (4 x 30 mL), dried (Na_2SO_4), and evaporated. Flash chromatography (SiO_2, 2.5→12% EtOAc in hexanes) gave the desired compound (1.85 g, 72% yield). Mp 59-60 °C; R_f = 0.24 (10% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.72-7.68 (m, 4H), 7.48-7.37 (m, 6H), 6.00-5.86 (m, 1H), 5.38-5.31 (m, 1H), 5.28-5.23 (m, 1H), 4.74-4.59 (m, 2H), 4.24 (d, *J* = 9.9 Hz, 1H), 3.82 (d, *J* = 9.9 Hz, 1H), 2.78 (dq, *J* = 13.4, 3.3 Hz, 1H), 2.53-2.38 (m, 2H), 2.10-1.99 (m, 1H), 1.88-1.54 (m, 4H) 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.4, 169.8, 135.6, 135.5, 133.1, 132.9, 131.5, 129.6, 127.6(2C), 118.8, 66.4, 65.8, 62.9, 41.2, 33.6, 27.3, 26.6, 22.1, 19.2; IR (Neat Film NaCl) 3072, 2933, 2858, 1715, 1428, 1200, 1112, 703 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{27}H_{33}O_4Si$ $[M-H]^+$: 449.2148, found 449.2165.



380

Table 4.10, Entry 10 (380). To a solution of **SI3** (946.4 mg, 5.19 mmol, 1 equiv) in 50 mL CH_3CN, was added $TiCl_4$ (50 mL, 0.456 mmol, 0.09 equiv). Select-fluor (2.2224 g, 6.27 mmol, 1.2 equiv) was added after 10 min and the mixture stirred at rt for 2 h and 40 min, over which time the orange color disappeared. The mixture was partitioned between H_2O (200 mL) and Et_2O (50 mL). The aqueous layer was separated and washed with Et_2O (30 mL). The combined organic layers were dried ($MgSO_4$), concentrated to about 30 mL, passed through a pad of silica that was washed with Et_2O (5 x 10 mL), and evaporated *in vacuo*. The residue was the bulb-to-bulb distilled at 180-190 °C (bath temp, 2 torr) to afford the title compound as a colorless oil (947.6 mg, 91% yield). R_f = 0.19 (10:1 Hexane:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 5.93 (dddd, *J* =

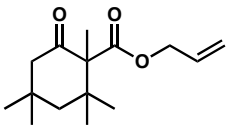
5.7, 5.7, 10.5, 17.1 Hz, 1H), 5.37 (dddd, J = 1.5, 1.5, 1.5, 17.4 Hz, 1H), 5.29 (dddd, J = 1.5, 1.5, 1.5, 10.5 Hz, 1H), 4.73 (bd, J = 5.7 Hz, 2H), 2.80-2.67 (m, 1H), 2.66-2.38 (m, 2H), 2.24-2.10 (m, 1H), 1.98-1.80 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5 (d, $J_{C\text{-}F}$ = 19.8 Hz), 166.4 (d, $J_{C\text{-}F}$ = 24.8 Hz), 130.8, 119.2, 96.2 (d, $J_{C\text{-}F}$ = 196.9 Hz), 66.5, 39.4, 35.8 (d, $J_{C\text{-}F}$ = 21.8 Hz), 26.4, 20.7 (d, $J_{C\text{-}F}$ = 6.0 Hz); IR (Neat Film NaCl) 3087, 2952, 1759, 1735, 1650, 1452, 1281, 1223, 1150, 1097, 990 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{10}H_{13}O_3F$ $[M]^+$: 200.0849, found 200.0858.



382

Table 4.11, Entry 3 (382). To a cooled (-78 °C) solution of LDA (13.5 mmol, 1.12 equiv) in THF (30 mL) was added 2,2,6-trimethylcyclohexanone (1.6938 g, 12.08 mmol, 1.0 equiv) dropwise. The resulting solution was warmed to 0 °C for 1 hour, cooled to -78 °C and HMPA (2.2 mL, 12.6 mmol, 1.04 equiv) was added. After 5 min, allyl cyanoformate (1.5014g, 13.5 mmol, 1.12 equiv) was added dropwise. The reaction was warmed to rt and allowed to stir overnight. The reaction was then quenched with 50% saturated NH_4Cl (40 mL). The aqueous layer was separated and washed with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (SiO_2, 3% Et_2O in hexanes) to afford the β-keto ester as a colorless oil (585.6 mg, 22%), along with the known enol carbonate (R_f = 0.53, 10:1 Hexane:EtOAc) as a colorless oil (1.3117 g, 48%). R_f = 0.50 (10:1 Hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (dddd, J = 5.7, 5.7, 10.2, 16.8 Hz, 1H), 5.30 (dddd, J = 1.2, 1.2, 1.2, 17.1

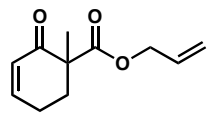
Hz, 1H), 5.22 (dddd, *J* = 0.9, 0.9, 0.9, 10.2 Hz, 1H), 4.62 (dddd, *J* = 1.2, 1.2, 5.7, 13.2 Hz, 1H), 4.51 (dddd, *J* = 1.2, 1.2, 5.7, 13.2 Hz, 1H), 2.54 (dddd, *J* = 2.4, 3.9, 3.9, 13.8 Hz, 1H), 1.98 (ddddd, *J* = 3, 4.2, 12, 14.1, 15.6 Hz, 1H), 1.77-1.68 (m, 1H), 1.66-1.52 (m, 2H), 1.42 (ddd, *J* = 4.2, 12.3, 13.8, 1H), 1.32 (s, 3H), 1.09 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.4, 172.4, 131.5, 118.8, 65.7, 55.1, 46.1, 40.6, 36.8, 26.8, 25.5, 23.6, 18.5; IR (Neat Film NaCl) 3089, 2938, 1736, 1707, 1649, 1456, 1377, 1243, 1209, 1174, 1150, 972 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{13}H_{20}O_3$ $[M]^+$: 224.1413, found 224.1413.



383

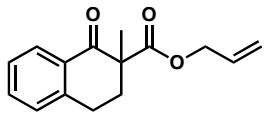
Table 4.11, Entry 4 (383). Prepared by a modification of general procedure 8. Part 1: Reaction of 3,3,5,5-tetramethylcyclohexanone in benzene (1 M) at 80 °C for 40 h using NaH (2 equiv) and diallylcarbonate (3 equiv) gave an ~1:1 mixture of mono and bisacylated material after flash chromatography (SiO_2, 1→8% Et_2O in hexanes). Part 2: Reaction in acetone (0.42 M) at 75 °C in a sealed flask for 24 h using Cs_2CO_3 (3 equiv) and MeI (4 equiv). Flash chromatography (SiO_2, 1→4% Et_2O in hexanes) gave the desired compound. 25% overall yield. R_f = 0.60 (25% Et_2O in pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (dddd, *J* = 17.4, 10.5, 6.0, 6.0 Hz, 1H), 5.29 (d, *J* = 17.1 Hz, 1H), 5.22 (d, *J* = 10.5 Hz, 1H), 4.55 (d, *J* = 6.0 Hz, 2H), 2.78 (d, *J* = 13.5 Hz, 1H), 2.23-2.12 (comp. m, 2H), 1.33 (d, *J* = 14.4 Hz, 1H), 1.26 (s, 3H), 1.11 (s, 3H), 1.04 (s, 3H), 1.01 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.9, 171.5, 131.5, 118.8, 65.5, 62.6,

51.7, 49.4, 40.9, 34.8, 34.5, 29.6, 27.7, 26.9, 14.7; IR (Neat Film NaCl) 3087, 2959, 1715, 1456, 1371, 1216, 1101, 979 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{15}H_{24}O_3$ $[M]^+$: 252.1725, found 252.1719.



384

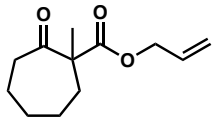
Table 4.11, Entry 5 (384). Prepared by general procedure 8 from cyclohex-2-en-1-one. Flash chromatography (SiO_2, CH_2Cl_2). 23% yield. R_f = 0.38 (30% Et_2O in pentane). ^1H NMR (300 MHz, $CDCl_3$) δ 6.92 (m, 1H), 6.06 (dt, *J* = 10.1, 2.1 Hz, 1H), 5.86 (dddd, *J* = 17.3, 10.4, 5.6, 5.6 Hz, 1H), 5.24 (m, 2H), 4.61 (m, 2H), 2.57-2.41 (m, 2H), 2.41-2.27 (m, 1H), 1.97-1.82 (m, 1H), 1.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.8, 172.3, 149.4, 131.6, 128.9, 118.3, 65.7, 53.4, 33.3, 23.6, 20.3; IR (Neat Film NaCl) 2936, 1733, 1678, 1249, 1192, 1110 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{14}O_3$ $[M]^+$: 194.0943, found 194.0941.



386

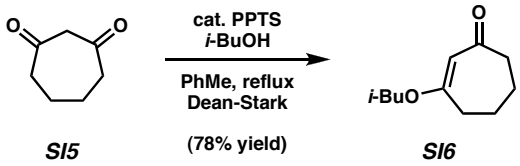
Table 4.11, Entry 7 (386). Prepared by general procedure 8 from 1-tetralone. Flash chromatography (SiO_2, 10% Et_2O in pentane). 60% yield. R_f = 0.61 (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.8 Hz, 1H), 7.47 (app. t, *J* = 7.5 Hz, 1H), 7.31 (app. t, *J* = 8.1 Hz, 1H), 7.22 (d, *J* = 7.8 Hz, 1H), 5.79 (dddd, *J* = 17.1, 10.7, 5.4, 5.4 Hz, 1H), 5.19-5.09 (m, 2H), 4.58 (m, 2H), 3.12-2.87 (m, 2H), 2.68-2.57 (m,

1H), 2.13-2.01 (m, 1H), 1.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.9, 172.5, 143.1, 133.4, 131.7, 131.5, 128.7, 128.0, 126.8, 118.0, 65.6, 53.9, 33.9, 26.0, 20.6; IR (Neat Film NaCl) 3071, 2982, 2938, 1736, 1690, 1602, 1456, 1377, 1308, 1228, 1189, 1112, 979, 743 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{15}H_{16}O_3$ [M]$^+$: 244.1099, found 244.1094.



387

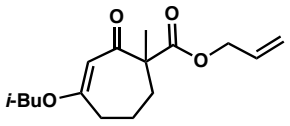
Table 4.11, Entry 8 (387). Prepared by general procedure 8 from cycloheptanone. Flash chromatography (SiO_2, 25→100% CH_2Cl_2 in pentane). 30% yield. R_f = 0.60 (30% Et_2O in pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (dddd, *J* = 17.3, 10.4, 5.6, 5.6 Hz, 1H), 5.26 (m, 2H), 4.61 (m, 2H), 2.81-2.67 (m, 1H), 2.57-2.45 (m, 1H), 2.25-2.11 (m, 1H), 1.91-1.70 (comp. m, 3H), 1.69-1.49 (comp. m, 4H), 1.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 131.6, 118.5, 65.6, 58.8, 42.0, 35.4, 30.1, 25.8, 24.7, 21.5; IR (Neat Film NaCl) 2936, 1740, 1710, 1229, 1151, 1105 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{12}H_{18}O_3$ [M]$^+$: 210.1256, found 210.1249.



SI5 ***SI6***

SI6: To a flask containing a Dean-Stark trap, reflux condensor, and a solution of 1,3-cycloheptanedione (**SI5**) (5.2793 g, 41.85 mmol, 1.0 equiv) in toluene (42 mL, 1.0 M) was added *i*-butanol (30.9 mL, 335 mmol, 8.0 equiv) and PPTS (157.8 mg, 0.63 mmol, 0.015 equiv). The solution was immersed in an oil bath at 130 °C and monitored

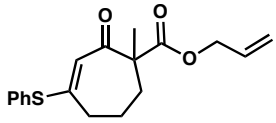
by TLC. When the starting material was consumed, the reaction was cooled to room temperature and concentrated under reduced pressure to a thick oil. The resulting oil was purified by short path distillation (1.0 torr, bp = 100-111 °C) to yield a light yellow oil (5.0073 g, 27.47 mmol). The residue remaining in the distillation pot was purified by flash chromatography (2.5 x 7 cm SiO_2, 2:1 Hex-EtOAc) to yield a maroon oil (0.9680 g, 5.31 mmol). The combined yield of vinylogous ester **SI6** was 5.9753 g (32.78 mmol, 78% yield); R_f = 0.22 (2:1 Hexanes-EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.37 (s, 1H), 3.49 (d, *J* = 6.6 Hz, 2H), 2.60-2.56 (comp. m, 4H), 2.00 (septuplet, *J* = 6.6 Hz, 1H), 1.88-1.77 (comp. m, 4H), 0.96 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 176.6, 106.0, 75.0, 41.9, 33.1, 27.9, 23.7, 21.5, 19.3; IR (Neat Film NaCl) 2958, 2872, 1646, 1607, 1469, 1237, 1190, 1174 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{18}O_2$ $[M]^{+\bullet}$: 182.1307; found 182.1310.



388

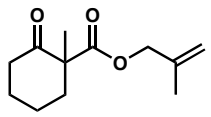
Table 4.11, Entry 9 (388). Prepared by general procedure 7 from **SI6** in 82% yield (1.220 g, 4.35 mmol) over two steps as a light yellow oil; purified by flash chromatography (2.5 x 22 cm SiO_2, 5:1 to 3:1 Hex-Et_2O); R_f = 0.43 (4:1 Hexanes-EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (dddd, *J* = 17.1, 10.7, 5.6, 5.6 Hz, 1H), 5.39 (s, 1H), 5.29 (ddd, *J* = 17.1, 2.9, 1.5 Hz, 1H), 5.20 (app d, *J* = 10.5 Hz, 1H), 4.59 (dddd, *J* = 19.0, 13.2, 5.6, 1.2 Hz, 2H), 3.50 (dd, *J* = 9.3, 6.8 Hz, 1H), 3.47 (dd, *J* = 9.3, 6.6 Hz, 1H), 2.59 (ddd, *J* = 17.8, 9.8, 3.9 Hz, 1H), 2.45-2.38 (comp. m, 2H), 2.02-1.94 (m, 1H),

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



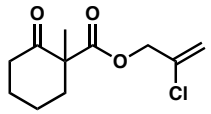
390

Table 4.11, Entry 10 (390). Prepared by general procedure 7 from the corresponding vinylogous thioester[44] in 33% yield (0.3426 g, 1.08 mmol) over two steps as a light yellow oil; purified by flash chromatography (2.5 x 15 cm SiO_2, 6:1 to 3:1 Hex-Et_2O); R_f = 0.25 (3:1 Hex:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46-7.38 (comp. m, 5H), 5.86 (dddd, *J* = 10.5, 5.6, 5.6, 0.7 Hz, 1H), 5.56 (d, *J* = 1.5 Hz, 1H), 5.29 (dddd, *J* = 17.1, 1.5, 1.5, 1.5 Hz, 1H), 5.23 (dddd, *J* = 10.5, 1.2, 1.2, 1.2 Hz, 1H), 4.60 (dddd, *J* = 19.5, 5.9, 1.5, 1.5 Hz, 2H), 2.67 (dddd, *J* = 17.6, 10.3, 3.7, 1.7 Hz, 1H), 2.50-2.43 (comp. m, 2H), 2.08-1.98 (m, 1H), 1.86-1.77 (m, 1H), 1.68 (ddd, *J* = 14.2, 6.4, 5.4 Hz, 1H), 1.38 (s, 3H)); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.6, 173.6, 159.5, 135.6, 131.8, 130.1, 129.9, 123.8, 118.7, 66.0, 58.8, 34.2, 33.7, 23.9, 23.8; IR (Neat Film NaCl) 3060, 2982, 2935, 1735, 1650, 1593, 1440, 1230, 1178, 1113, 980, 750, 692 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{18}H_{20}O_3S$ $[M]^{+\bullet}$: 316.1133; found 316.1119.



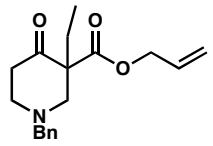
392

Table 4.11, Entry 11 (392). Prepared by general procedure 8 from cyclohexanone with dimethyallyl carbonate in part 1. Flash chromatography (SiO_2, 10% Et_2O in pentane). 46% yield. R_f = 0.24 (10% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 4.94 (m, 2H), 4.54 (s, 2H), 2.58-2.42 (comp. m, 3H), 2.08-1.93 (m, 1H), 1.80-1.57 (comp. m, 6H), 1.55-1.40 (m, 1H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.1, 172.8, 139.4, 113.5, 68.4, 57.2, 40.6, 38.2, 27.5, 22.6, 21.3, 19.5; IR (Neat Film NaCl) 2940, 2867, 1715, 1452, 1260, 1211, 1160, 1086, 907 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{12}H_{18}O_3$ $[M]^+$: 210.1256, found 210.1256.



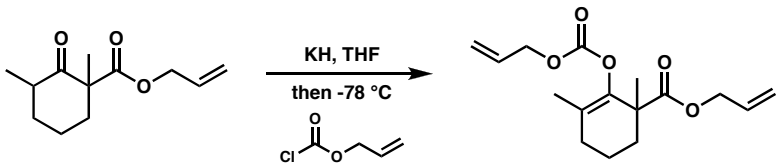
393

Table 4.11, Entry 12 (393). Prepared by method 3 from cyclohexanone with 1.25 equiv of 2-chloroallyl carbonate (*vide infra*) in part 1. Flash chromatography (SiO_2, 10% Et_2O in pentane). 62% yield. R_f = 0.20 (10% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 5.45 (m, 2H), 4.71 (m, 2H), 2.62-2.41 (comp. m, 3H), 2.10-1.93 (m, 1H), 1.81-1.62 (comp. m, 3H), 1.57-1.41 (m, 1H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.8, 172.3, 135.4, 115.8, 66.5, 57.2, 40.6, 38.2, 27.4, 22.5, 21.2; IR (Neat Film NaCl) 2942, 2868, 1716, 1640, 1453, 1248, 1221, 1153, 1084, 903 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{15}O_3Cl$ $[M]^+$: 230.0710, found 230.0711.



395

Table 4.11, Entry 13 (395). Prepared by general procedure 8 from 1-benzylpiperidin-4-one (part 1) and iodoethane (part 2). Flash chromatography (SiO_2, 2.5→20% EtOAc in hexanes). 55% yield. R_f = 0.50 (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33-7.25 (m, 5H), 5.90 (dddd, *J* = 17.4, 10.7, 5.7, 5.7 Hz, 1H), 5.33 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.24 (dq, *J* = 10.4, 1.5 Hz, 1H), 4.70 (ddt, *J* = 13.0, 6.0, 1.4 Hz, 1H), 4.62 (ddt, *J* = 13.0, 6.0, 1.4 Hz, 1H), 3.62 (d, *J* = 13.2 Hz, 1H), 3.56 (d, *J* = 13.2 Hz, 1H), 3.42 (dd, *J* = 11.4, 2.7 Hz, 1H), 3.04-2.80 (m, 2H), 2.45-2.35 (m, 2H), 2.25 (d, *J* = 11.7 Hz, 1H), 1.94-1.82 (m, 1H), 1.65-1.53 (m, 1H), 0.87 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.9, 171.3, 137.9, 131.7, 128.8, 128.2, 127.3, 118.7, 65.6, 61.8, 61.5, 61.0, 53.5, 40.6, 25.2, 9.1; IR (Neat Film NaCl) 2966, 2939, 1719, 1224, 1139, 699 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{18}H_{23}O_3$ $[M]^+$: 301.1678, found 301.1691.



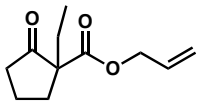
SI7 *397*

Allyl 2,6-dimethyl-2-cyclohexanonecarboxylate (SI7): To a cooled (-78 °C) solution of LDA (8.0 mmol, 1.09 equiv) in THF (24 mL) was added 2,6-dimethylcyclohexanone (1 mL, 7.33 mmol, 1.0 equiv) dropwise. The resulting solution was warmed to 0 °C for 1 hour, cooled to -78 °C and HMPA (1.3 mL, 7.47 mmol, 1.02 equiv) was added. After 15 min, allyl cyanoformate (845.3 mg, 7.61 mmol, 1.04 equiv)

was added dropwise. The reaction was warmed to ambient temperature for 30 min and then quenched with 50% saturated NH_4Cl. The aqueous layer was separated and washed with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (3 x 20 cm, SiO_2, 4% Et_2O in hexanes, then 8% Et_2O in hexanes) to afford β-ketoester **SI7** as a colorless oil (629.1 mg, 41%), along with the corresponding enol carbonate as a colorless oil (187.1 mg, 12%); R_f = 0.43 (10:1 Hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (dddd, *J* = 6.0, 6.0, 10.5, 17.4 Hz, 1H), 5.28 (dddd, *J* = 1.5, 1.5, 1.5, 17.1 Hz, 1H), 5.22 (dddd, *J* = 1.2, 1.2, 1.2, 10.5 Hz, 1H), 4.63 (dddd, *J* = 1.2, 1.2, 5.4, 13.2 Hz, 1H), 4.56 (dddd, *J* = 1.5, 1.5, 5.7, 13.2 Hz, 1H), 2.61-2.46 (m, 2H), 2.01 (dddd, *J* = 3.2, 3.2, 6.3, 16.2 Hz, 1H), 1.85-1.63 (m, 2H), 1.45-1.31 (m, 2H), 1.28 (s, 3H), 1.03 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.1, 172.9, 131.5, 118.7, 65.6, 57.1, 44.3, 38.9, 36.7, 22.8, 21.5, 14.7; IR (Neat Film NaCl) 3087, 2936, 1743, 1715, 1649, 1452, 1377, 1253, 1214, 1161, 976 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{12}H_{18}O_3$ $[M]^+$: 210.1256, found 210.1249.

Table 4.11, Entry 13 (397). To a suspension of KH (155.9 mg, 3.89 mmol, 1.2 equiv, from a ~30% dispersion in mineral oil, oil removed by washing with hexane) in 10 mL THF was added **SI7** (680.9 mg, 3.24 mmol, 1 equiv) dropwise. The mixture was stirred at rt for 2.5 h, at which time it was cooled to -78 °C. Allyl chloroformate (420 μL, 3.95 mmol, 1.2 equiv) was added and the mixture stirred 30 min at -78 °C, then 30 min at rt. The reaction was quenched with 50% saturated NH_4Cl (10 mL). Et_2O (5 mL) was added and the organic layer separated. The aqueous layer was washed with Et_2O (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. Silica

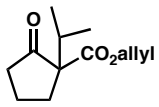
gel chromatography (2 x 16 cm, 20:1 hexane:EtOAc) afforded the title compound **397** as a colorless oil (883 mg, 93% yield). R_f = 0.29 (10:1 Hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 (dddd, *J* = 5.7, 5.7, 10.2, 17.1 Hz, 1H), 5.90 (dddd, *J* = 5.7, 5.7, 10.5, 17.1 Hz, 1H), 5.37 (dddd, *J* = 1.2, 1.2, 1.2, 17.1 Hz, 1H), 5.31 (dddd, *J* = 1.2, 1.2, 1.2, 17.1 Hz, 1H), 5.27 (dddd, *J* = 1.2, 1.2, 1.2, 10.2 Hz, 1H), 5.20 (dddd, *J* = 1.5, 1.5, 1.5, 10.5 Hz, 1H), 4.66-4.58 (m. 3H), 4.55 (dddd, *J* = 1.2, 1.2, 5.4, 13.5 Hz, 1H), 2.25-2.10 (m, 3H), 1.80-1.52 (m, 3H), 1.58 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 152.9, 142.0, 132.2, 131.5, 124.7, 118.9, 117.7, 68.7, 65.5, 46.7, 35.8, 30.6, 22.4, 19.2, 17.0; IR (Neat Film NaCl) 3087, 2942, 1760, 1732, 1649, 1452, 1366, 1235, 1168, 992 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{16}H_{22}O_5$ $[M]^+$: 294.1467, found 294.1464.



406

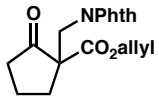
Table 4.12, Entry 1 (406). Prepared by general procedure 8 part B from allyl 2-cyclopentanonecarboxylate and using ethyl iodide as the electrophile. Flash chromatography (3 x 25 cm SiO_2, 10% Et_2O/hexane) afforded the title compound as a colorless oil (1.5335 g, 85% yield). R_F = 0.27 (10:1 Hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (dddd, *J* = 5.7, 5.7, 10.5, 17.4 Hz, 1H), 5.30 (dddd, *J* = 1.6, 1.6, 1.6, 17.1 Hz, 1H), 5.23 (dddd, *J* = 1.4, 1.4, 1.4, 10.5 Hz, 1H), 4.60 (dddd, *J* = 1.4, 1.4, 1.4, 5.7 Hz, 2H), 2.57-2.36 (m, 2H), 2.31-2.19 (m, 1H), 2.08-1.86 (m, 4H), 1.64 (dddd, *J* = 7.5, 7.5, 7.5, 21 Hz, 1H), 0.89 (dd, *J* = 7.2, 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.6, 170.6, 131.5, 118.1, 65.5, 60.7, 37.9, 32.0, 26.6, 19.4, 9.0; IR (Neat Film NaCl) 3085,

2971, 1752, 1726, 1225, 1142 cm^{-1}; HRMS *m/z* calc'd for $C_{11}H_{16}O_3$ $[M]^+$: 196.1100, found 196.1099.



408

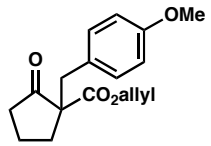
Table 4.12, Entry 2 (408). Prepared by general procedure 8 part B from allyl 2-cyclopentanonecarboxylate and using 2-iodopropane as the electrophile. Flash chromatography (3 x 25 cm SiO_2, 10% → 30% Et_2O/hexane) afforded the title compound as a colorless oil (1.5521 g, 82% yield). R_F = 0.32 (10:1 Hexane:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 5.88 (dddd, *J* = 5.7, 5.7, 10.5, 17.1 Hz, 1H), 5.30 (dddd, *J* = 1.6, 1.6, 1.6, 17.4 Hz, 1H), 5.22 (dddd, *J* = 1.4, 1.4, 1.4, 10.5 Hz, 1H), 4.59 (dddd, *J* = 1.4, 1.4, 1.4, 5.7 Hz, 2H), 2.59 (qq, *J* = 6.9, 6.9 Hz, 1H), 2.51-2.34 (m, 2H), 2.19-2.06 (m, 1H), 1.99-1.83 (m, 3H), 0.87 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.4, 169.8, 131.5, 118.3, 65.6, 65.3, 38.9, 31.9, 27.2, 19.5, 18.3, 17.6; IR (Neat Film NaCl) 3085, 2967, 1752, 1723, 1228, 1130 cm^{-1}; HRMS *m/z* calc'd for $C_{12}H_{18}O_3$ $[M]^+$: 210.1256, found 210.1255.



410

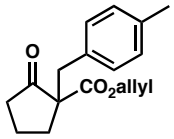
Table 4.12, Entry 3 (410). Prepared by general procedure 8 part B from allyl 2-cyclopentanonecarboxylate and using (*N*-chloromethyl)phthalimide as the electrophile. Purified by flash chromatography (SiO_2, 20 → 30% EtOAc in hexanes). 54% yield. Mp 56-57 °C. R_f = 0.27 (30% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (dd, *J*

= 5.6, 3.2 Hz, 2H), 7.73 (dd, *J* = 5.6, 3.2 Hz, 2H), 5.92 (dddd, *J* = 17.0, 10.6, 5.9, 5.9 Hz, 1H), 5.32 (app. ddd, *J* = 17.0, 2.9, 1.6 Hz, 1H), 5.23 (app. ddd, *J* = 10.6, 2.7, 1.3 Hz, 1H), 4.65 (app. ddt, *J* = 5.9, 4.5, 1.3 Hz, 2H), 4.34 (d, *J* = 14.4 Hz, 1H), 3.99 (d, *J* = 14.4 Hz, 1H), 2.59-2.47 (m, 1H), 2.46-2.25 (comp. m, 2H), 2.11-1.84 (comp. m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.0, 169.0, 168.3, 134.3, 131.9, 131.6, 123.7, 118.8, 66.8, 60.5, 41.0, 37.7, 32.1, 19.5; IR (Neat Film NaCl) 2953, 1774, 1752, 1718, 1467, 1457, 1428, 1395, 1359, 1256, 1231, 1170, 991, 722 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{18}H_{17}O_5N$ $[M]^+$: 327.1107, found 327.1106.



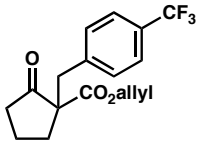
412

Table 4.12, Entry 4 (412). Prepared by general procedure 8 part B from allyl 2-cyclopentanonecarboxylate and using 4-methoxybenzyl chloride as the electrophile. Flash chromatography (3 x 25 cm SiO_2, 10:1 hexane/EtOAc) afforded the title compound as a colorless oil (2.5584 g, 95% yield). R_F = 0.17 (10:1 Hexane:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 5.87 (dddd, *J* = 5.7, 5.7, 10.8, 17.1 Hz, 1H), 5.31 (dddd, *J* = 1.5, 1.5, 1.5, 17.1 Hz, 1H), 5.24 (dddd, *J* = 1.2, 1.2, 1.2, 10.5 Hz, 1H), 4.61 (dddd, *J* = 1.4, 1.4, 1.4, 5.7 Hz, 2H), 3.77 (s, 3H), 3.15 (d, *J* = 13.8 Hz, 1H), 3.09 (d, *J* = 13.8 Hz, 1H), 2.45-2.31 (m, 2H), 2.08-1.81 (m, 3H), 1.67-1.53 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.7, 170.5, 158.3, 131.5, 131.0, 128.2, 118.3, 113.6, 65.8, 61.4, 55.0, 38.3, 38.0, 31.5, 19.3; IR (Neat Film NaCl) 2958, 1751, 1726, 1611, 1513, 1249 cm^{-1}; HRMS *m/z* calc'd for $C_{17}H_{20}O_4$ $[M]^+$: 288.1362, found 288.1369.



414

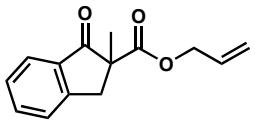
Table 4.12, Entry 5 (414). Prepared by general procedure 8 part B from allyl 2-cyclopentanonecarboxylate and using *p*-methyl benzyl bromide as the electrophile. Purified by flash chromatography (SiO_2, 10% Et_2O in pentane). 89% yield. R_f = 0.20 (10% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 8.3 Hz, 2H), 5.89 (dddd, *J* = 17.3, 10.5, 5.5, 5.5 Hz, 1H), 5.31 (app. ddd, *J* = 17.3, 3.0, 1.7 Hz, 1H), 5.24 (app. ddd, *J* = 10.5, 2.4, 1.1 Hz, 1H), 4.61 (app. ddd, *J* = 6.9, 2.8, 1.4 Hz, 1H), 4.61 (app. ddd, *J* = 6.9, 2.8, 1.4 Hz, 1H), 3.17 (d, *J* = 13.8 Hz, 1H), 3.10 (d, *J* = 13.8 Hz, 1H), 2.52-2.32 (m, 2H), 2.30 (s, 3H), 2.12-1.81 (comp. m, 3H), 1.68-1.52 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.1, 170.9, 136.6, 133.5, 131.7, 130.2, 129.2, 118.7, 66.1, 61.6, 38.7, 38.6, 31.8, 21.2, 19.6; IR (Neat Film NaCl) 2963, 2925, 1752, 1724, 1652, 1515, 1456, 1404, 1264, 1220, 1184, 1158, 1141, 1116, 992, 924, 813 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{20}O_3$ $[M]^+$: 272.1412, found 272.1412.



416

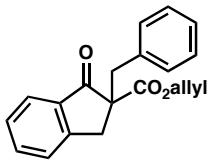
Table 4.12, Entry 6 (416). Prepared by general procedure 8 part B from allyl 2-cyclopentanonecarboxylate and using 4-(trifluoromethyl)benzyl bromide as the electrophile. ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 7.8 Hz, 2H), 5.87 (dddd, *J* = 6.0, 6.0, 10.5, 17.4 Hz, 1H), 5.30 (dddd, *J* = 1.7, 1.7, 1.7, 17.4 Hz,

1H), 5.25 (dddd, J = 1.1, 1.1, 1.1, 10.5 Hz, 1H), 4.61 (bd, J = 6 Hz, 2H), 3.29 (d, J = 13.5 Hz, 1H), 3.15 (d, J = 13.5 Hz, 1H), 2.50-2.33 (m, 2H), 2.13-1.86 (m, 3H), 1.73-1.62 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.1, 170.3, 140.7, 131.3, 130.6, 142.0, 133.1, 130.6, 129.2 (q, $J_{C\text{-}F}$ = 32.2 Hz), 125.3 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.1 (q, $J_{C\text{-}F}$ = 271.5 Hz), 118.8, 66.2, 61.3, 38.6, 38.1, 31,8, 19.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.54; IR (Neat Film NaCl) 3080, 2966, 1754, 1728, 1619, 1326, 1164, 1116, 1068 cm^{-1}; HRMS m/z calc'd for $C_{17}H_{17}O_3F_3$ $[M]^+$: 326.1130, found 326.1129.



418

Table 4.12, Entry 7 (418). Prepared by general procedure 8 from 1-indanone and using methyl iodide as the electrophile. Purified by flash chromatography (SiO_2, 10% Et_2O in pentane). 30% yield. R_f = 0.55 (30% Et_2O in pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 7.7 Hz, 1H), 7.63 (dd, J = 7.6, 7.3 Hz, 1H), 7.48 (d, J = 7.7 Hz, 1H), 7.41 (dd, J = 7.6, 7.3 Hz, 1H), 5.83 (dddd, J = 17.2, 10.6, 5.6, 5.6 Hz, 1H), 5.21 (dddd, J = 17.2, 2.7, 1.6, 1.1 Hz, 1H), 5.16 (dddd, J = 10.5, 2.4, 1.3, 1.3 Hz, 1H), 4.58 (ddd, J = 5.6, 2.7, 1.1 Hz, 1H), 4.58 (ddd, J = 5.6, 2.7, 1.1 Hz, 1H), 3.73 (d, J = 17.1 Hz, 1H), 3.01 (d, J = 17.1 Hz, 1H), 1.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.5, 171.8, 152.7, 135.5, 134.9, 131.7, 128.0, 126.6, 125.2, 118.3, 66.0, 56.2, 40.2, 21.2; IR (Neat Film NaCl) 3080, 2982, 2935, 1745, 1715, 1608, 1495, 1282, 1184, 967, 747 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{14}H_{14}O_3$ $[M]^+$: 230.0943, found 230.0936.



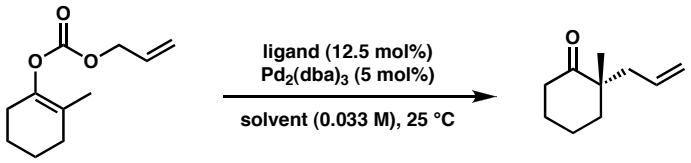
420

Table 4.12, Entry 8 (420). Prepared by general procedure 8 from 1-indanone and using benzyl bromide as the electrophile. Purified by flash chromatography (SiO_2, 20% Et_2O in pentane). 78% yield. Mp 49-50 °C. R_f = 0.18 (10% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.1 Hz, 1H), 7.53 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.33 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.23-7.06 (comp. m, 5H), 5.84 (dddd, *J* = 17.3, 10.4, 5.6, 5.3 Hz, 1H), 5.22 (app. ddd, *J* = 17.3,, 2.9, 1.6 Hz, 1H), 5.18 (dddd, *J* = 10.4, 2.4, 1.3, 1.1 Hz, 1H), 4.65-4.57 (m, 2H), 3.63 (d, *J* = 17.6 Hz, 1H), 3.50 (d, *J* = 13.8 Hz, 1H), 3.31 (d, *J* = 14.1 Hz, 1H), 3.18 (d, *J* = 17.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.2, 170.6, 153.3, 136.4, 135.5, 135.3, 131.6, 130.2, 128.4, 127.8, 127.0, 126.4, 124.8, 118.5, 66.3, 61.9, 39.8, 35.5; IR (Neat Film NaCl) 3031, 2929, 1744, 1711, 1606, 1589, 1496, 1464, 1454, 1432, 1277, 1244, 1210, 1178, 1051, 1028, 930, 752, 703 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{20}H_{18}O_3$ $[M]^+$: 306.1256, found 306.1259.

4.7.2.5 *Asymmetric Allylation Methods*

General Procedures for Asymmetric Tsuji Allylation.

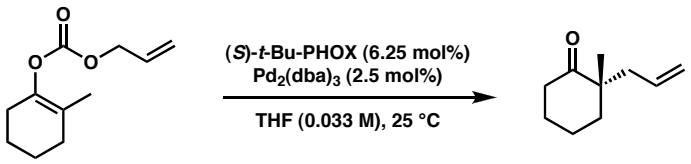
General Procedure 9: 0.1 mmol Optimization Reactions of Allyl Enol Carbonates



274 *(S)-275*

A 1 dram vial equipped with a magnetic stir bar was flame dried under vacuum. After cooling under dry argon, $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol, 0.05 equiv) and ligand (0.0125 mmol, 0.125 equiv) were added. After the flask was flushed with argon, THF (3.0 mL) was added, and the contents were stirred at 25 °C for 30 min, at which time tridecane (12.25 μL) and allyl enol carbonate **274** (19.6 mg, 0.1 mmol, 1.0 equiv) were added by syringe. When the reaction was complete by TLC, the reaction mixture was diluted with hexanes (5 mL), filtered through a small plug of silica gel and analyzed by GC. GC yield determined on DB-WAX column (70 °C initial temp, 5 °C/min ramp to 180 °C), tridecane ret. time = 7.000 min, ketone **275** Ret. Time = 12.309 min.

General Procedure 10: 1.0 mmol Preparative Reactions of Allyl Enol Carbonates

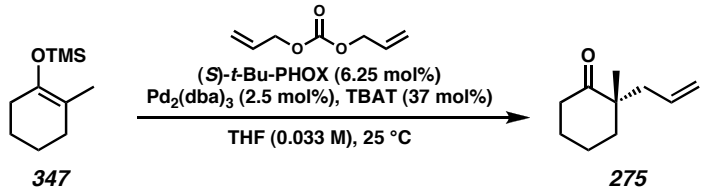


274 *(S)-275*

A 50 mL rb flask equipped with a magnetic stir bar was flame dried under vacuum. After cooling under dry argon, $Pd_2(dba)_3$ (22.9 mg, 0.025 mmol, 0.025 equiv) and *(S)-t*-Bu-PHOX (24.2 mg, 0.0625 mmol, 0.0625 equiv) were added. After the flask

was flushed with argon, THF (30 mL) was added and the contents were stirred at 25 °C for 30 min, at which time allyl enol carbonate **274** (196.2 mg, 1.0 mmol, 1.0 equiv) was added by syringe in one portion. When the reaction was complete by TLC, the reaction mixture was evaporated under reduced pressure and the residue chromatographed (2 to 3 % Et_2O in pentane on SiO_2) to afford (*S*)-2-allyl-2-methylcyclohexanone (**275**) (129.6 mg, 85.1% yield) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 5.75-5.61 (m, 1H), 5.05 (s, 1H), 5.01 (m, 1H), 2.40-2.31 (m, 3H), 2.21 (dd, *J* = 13.8, 7.5 Hz, 1H), 1.78 (m, 5H), 1.56 (m, 1H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.4, 133.7, 117.9, 48.4, 41.9, 38.8, 38.5, 27.4, 22.6, 21.0; IR (Neat Film NaCl) 2934, 2865, 1707, 1451, 912 cm^{-1}; HRMS *m/z* calc'd for $C_{10}H_{16}O$ $[M]^+$: 152.1201, found 152.1204; $[\alpha]_D^{28}$ -22.90° (*c* 2.09, hexane, 98% ee).

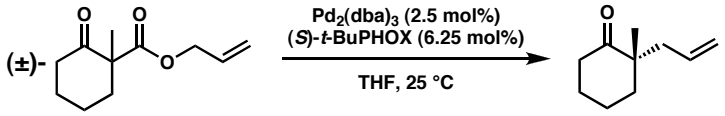
General Procedure 11: 1.0 mmol Preparative Reactions of Silyl Enol Ethers



A 50 mL rb flask equipped with a magnetic stir bar was flame dried under vacuum. After cooling under dry argon, $Pd_2(dba)_3$ (22.9 mg, 0.025 mmol, 0.025 equiv), *(S)-t*-Bu-PHOX (24.2 mg, 0.0625 mmol, 0.0625 equiv), and TBAT (189 mg, 0.35 mmol, 0.35 equiv) were added. After the flask was flushed with argon, THF (30 mL) was added, and the contents were stirred at 25 °C for 30 min, at which time diallyl carbonate (150.6 μL, 1.05 mmol, 1.05 equiv) and then (2-methylcyclohex-1-enyloxy)trimethylsilane **347** (184.35 mg, 1.0 mmol, 1.0 equiv) were added by syringe in

one portion. When the reaction was complete by TLC, the reaction mixture was evaporated under reduced pressure and the residue chromatographed (2 to 3 % Et_2O in pentane on SiO_2) to afford ketone **275** (144.3 mg, 94.8% yield).

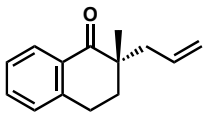
General Procedure 12: 1.0 mmol Preparative Reactions of Allyl β-Ketoesters



358 *275*

A 100 mL rb flask was equipped with a magnetic stir bar and flame dried under vacuum. After cooling under dry nitrogen, $Pd_2(dba)_3$ (22.9 mg, 0.025 mmol, 0.025 equiv) and (*S*)-*t*-Bu-PHOX (24.2 mg, 0.0625 mmol, 0.0625 equiv) were added. The flask containing the solids was evacuated for 15 min and then refilled with dry nitrogen. Dry THF (30 mL) was then added and the resulting solution stirred at 25 ºC for 30 min. At this point, allyl 1-methyl-2-oxocyclohexanecarboxylate (**358**) was added via syringe in one portion. When the reaction was complete by TLC, the reaction mixture was evaporated under reduced pressure and the residue purified by column chromatography (SiO_2, 1.5 to 2.5% Et_2O in pentane) to afford ketone **275** (129.6 mg, 85% yield, 88% ee).

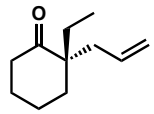
4.7.2.5 *Ketones Prepared by Asymmetric Tsuji Allylation*



297

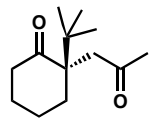
Ketone 297. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.45 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.29 (app. t, *J* = 7.2 Hz, 1H), 7.21 (app. d, *J* = 7.5 Hz, 1H),

5.85-5.71 (m, 1H), 5.10 (s, 1H), 5.05 (s, 1H), 2.97 (t, *J* = 6.3 Hz, 2H), 2.46 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.27 (ddt, *J* = 14.0, 7.5, 1.2 Hz, 1H), 2.07 (ddd, *J* = 13.4, 7.2, 6.0 Hz 1H), 1.89 (ddd, *J* = 14.0, 6.9, 5.7 1H), 1.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 143.2, 133.9, 133.0, 131.5, 128.6, 127.9, 126.5, 118.1, 44.5, 41.0, 33.2, 25.3, 21.8; IR (Neat Film NaCl) 3073, 2930, 1682, 1455, 1220, 916, 742 cm^{-1}; HRMS *m/z* calc'd for $C_{14}H_{16}O$ [M]$^+$: 200.1201, found 200.1194; $[\alpha]_D^{27}$ -18.59° (*c* 2.08, hexane, 88% ee).



321

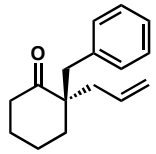
Ketone 321. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.66 (m, 1H), 5.02 (m, 2H), 2.47-2.18 (m, 4H), 1.90-1.60 (m, 7H), 1.46 (ddd, *J* = 21.6, 15.0, 7.2 Hz, 1H), 0.75 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.0, 134.2, 117.6, 51.6, 39.2, 38.5, 36.0, 27.2, 27.1, 20.7, 7.8; IR (Neat Film NaCl) 2937, 1703 cm^{-1}; HRMS *m/z* calc'd for $C_{11}H_{18}O$ [M]$^+$: 166.1358, found 166.1362; $[\alpha]_D^{28}$ +28.58° (*c* 1.51, hexane, 92% ee).



SI8

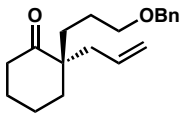
Diketone SI8. Prepared by Wacker odixation of ketone **322**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.29 (d, *J* = 18.0 Hz, 1H), 2.58 (app. dt, *J* = 16.2, 4.8 Hz, 1H), 2.34 (d, *J* = 17.7 Hz, 1H), 2.23 (dd, *J* = 11.1, 6.0 Hz, 1H), 2.18-2.00 (m, 2H), 2.07 (s, 3H), 1.92-1.60 (m, 4H), 0.94 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.5, 207.6, 53.0, 51.3, 43.2, 36.6, 31.6, 30.5, 27.7, 24.0, 23.9; IR (Neat Film NaCl) 2955, 1716, 1692, 1372, 1171 cm$^-$

[1]; HRMS *m/z* calc'd for $C_{13}H_{22}O_2$ $[M]^+$: 210.1620, found 210.1615; $[\alpha]_D^{28}$ +132.01° (*c* 1.38, hexane, 81% ee).



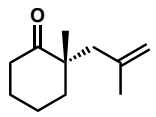
325

Ketone 325. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (m, 3H), 7.12 (m, 2H), 5.74 (ddt, *J* = 17.2, 10.1, 7.2 Hz, 1H), 5.12-5.03 (m, 2H), 2.91 (s, 2H), 2.46 (m, 2H), 2.28 (d, *J* = 7.2 Hz, 2H), 1.86-1.65 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.1, 137.5, 133.7, 130.6, 127.9, 126.3, 118.2, 52.5, 40.8, 39.6, 39.2, 35.5, 26.8, 20.8; IR (Neat Film NaCl) 2937, 1704, 1638, 1602 cm^{-1}; HRMS *m/z* calc'd for $C_{16}H_{20}O$ $[M]^+$: 228.1514, found 228.1514; $[\alpha]_D^{28}$ -12.34° (*c* 2.07, hexane, 85% ee).



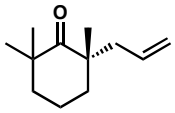
327

Ketone 327. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.26 (m, 5H), 5.68 (m, 1H), 5.06 (s, 1H), 5.01 (m, 1H), 4.84 (s, 2H), 3.44 (app. t, *J* = 6.3 Hz, 2H), 2.32 (m, 4H), 1.88-1.24 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.8, 138.5, 133.9, 128.3, 127.5, 127.5, 117.8, 72.8, 70.5, 51.2, 39.2, 39.0, 36.4, 31.2, 27.1, 23.8, 20.7; IR (Neat Film NaCl) 2926, 1703, 1102 cm^{-1}; HRMS *m/z* calc'd for $C_{19}H_{27}O_2$ $[M+H]^+$: 287.2011, found 287.2001; $[\alpha]_D^{27}$ +24.19° (*c* 2.73, hexane, 88% ee).



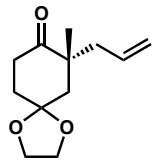
329

Ketone 329. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.81 (s, 1H), 4.64 (s, 1H), 2.52 (m, 1H), 2.48 (d, *J* = 13.5 Hz, 1H), 2.36 (app. dt, *J* = 14.7, 6.0 Hz, 1H), 2.25 (d, *J* = 13.8 Hz, 1H), 1.94-1.53 (m, 6H), 1.65 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.8, 142.2, 114.7, 48.7, 45.4, 40.0, 38.9, 27.6, 24.3, 23.3, 21.1; IR (neat) 2927, 1707 cm^{-1}; HRMS *m/z* calc'd for $C_{11}H_{18}O$ $[M]^+$: 166.1358, found 166.1358; $[\alpha]_D^{27}$ -26.42° (*c* 1.85, hexane, 90% ee).



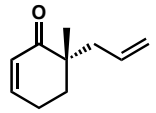
331

Ketone 331. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63 (m, 1H), 5.01 (m, 2H), 2.33 (dd, *J* = 13.8, 6.9 Hz, 1H), 2.18 (dd, *J* = 13.8, 7.8 Hz, 1H), 1.82-1.53 (m, 6H), 1.11 (s, 3H), 1.09 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.8, 134.6, 117.9, 47.6, 44.4, 43.9, 39.7, 36.8, 27.8, 27.2, 25.5, 17.7; IR (Neat Film NaCl) 2933, 1697, 1463 cm^{-1}; HRMS *m/z* calc'd for $C_{12}H_{20}O$ $[M]^+$: 180.1514, found 180.1521; $[\alpha]_D^{27}$ -35.69° (*c* 2.15, hexane, 92% ee).



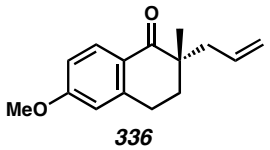
152

Ketone 152. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.67 (ddt, *J* = 17.1, 10.5, 7.2 Hz, 1H), 5.07 (bs, 1H), 5.02 (app. d, *J* = 9.3 Hz, 1H), 3.99 (app. d, *J* = 1.5 Hz, 4H), 2.57 (app. t, *J* = 6.3 Hz, 1H), 2.42 (m, 2H), 2.00 (d, *J* = 13.8 Hz, 1H), 1.98 (app. t, *J* = 7.2 Hz, 1H), 1.75 (d, *J* = 14.1 Hz, 1H), 1.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.9, 133.7, 118.4, 107.6, 64.4, 64.3, 47.5, 44.3, 42.7, 35.7, 34.5, 23.9; IR (Neat Film NaCl) 2964, 1710, 1116 cm^{-1}; HRMS *m/z* calc'd for $C_{12}H_{18}O_3$ $[M]^+$: 210.1256, found 210.1255; $[\alpha]_D^{29}$ -7.99° (*c* 2.41, hexane, 86% ee).



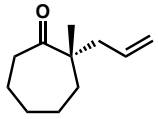
334

Ketone 334. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (app. dt, *J* = 10.2, 4.2 Hz, 1H), 5.91 (app. dt, *J* = 10.2, 2.1 Hz, 1H), 5.72 (m, 1H), 5.07 (m, 1H), 5.02 (d, *J* = 9.3 Hz, 1H), 2.35 (m, 3H), 2.16 (dd, *J* = 13.8, 7.5, Hz, 1H), 1.91 (dt, *J* = 13.8, 6.0 Hz, 1H), 1.74 (dt, *J* = 13.8, 6.0 Hz, 1H), 1.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.7, 148.8, 134.0, 128.4, 118.0, 44.4, 40.9, 32.9, 23.1, 21.6; IR (Neat Film NaCl) 2927, 1673 cm^{-1}; HRMS *m/z* calc'd for $C_{10}H_{14}O$ $[M]^+$: 150.1045, found 150.1039; $[\alpha]_D^{26}$ +14.62° (*c* 1.56, hexane, 89% ee).



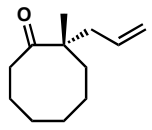
336

Ketone 336. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.7 Hz, 1H), 6.82 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.66 (d, *J* = 2.4 Hz, 1H), 5.78 (m, 1H), 5.09 (s, 1H), 5.04 (m, 1H), 3.84 (s, 3H), 3.93 (app. t, *J* = 6 Hz, 2H), 2.45 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.25 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.05 (m, 1H), 1.87 (m, 1H), 1.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9, 163.3, 145.7, 134.1, 130.4, 125.1, 118.0, 113.2, 112.2, 55.4, 44.3, 41.3, 33.4, 25.7, 22.0; IR (Neat Film NaCl) 2931, 1672, 1601, 1256 cm^{-1}; HRMS *m/z* calc'd for $C_{15}H_{18}O_2$ $[M]^+$: 230.1307, found 230.1313; $[\alpha]_D^{26}$ -13.71° (*c* 1.5, hexane, 89% ee).



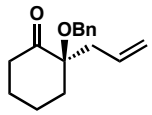
338

Ketone 338. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (ddt, *J* = 16.8, 10.2, 7.5, 1H), 5.02 (m, 2H), 2.59 (app. td, *J* = 11.1, 2.7 Hz, 1H), 2.42 (app. t, *J* = 9.0 Hz, 1H), 2.24 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.16 (dd, *J* = 13.8, 7.8 Hz, 1H), 1.78-1.30 (m, 8H), 1.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.4, 133.8, 117.9, 50.8, 43.6, 40.6, 36.6, 30.6, 26.4, 24.4, 22.3; IR (Neat Film NaCl) 2930, 1702, 1458 cm^{-1}; HRMS *m/z* calc'd for $C_{11}H_{18}O$ $[M]^+$: 166.1358, found 166.1360; $[\alpha]_D^{28}$ -34.70° (*c* 1.52, hexane, 87% ee).



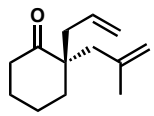
340

Ketone 340. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.67 (m, 1H), 5.04 (app. d, *J* = 1.2 Hz, 1H), 5.00 (app. d, *J* = 8.1 Hz, 1H), 2.59 (m, 1H), 2.29 (m, 2H), 2.12 (dd, *J* = 14.1, 7.7 Hz, 1H), 2.01 (m, 1H), 1.83-1.70 (m, 3H), 1.61-1.32 (m, 5H), 1.18 (m, 1H), 1.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.3, 133.9, 117.8, 50.1, 42.0, 36.8, 33.5, 30.4, 25.9, 24.8, 24.3, 19.8; IR (Neat Film NaCl) 2929, 1699 cm^{-1}; HRMS *m/z* calc'd for $C_{12}H_{20}O$ $[M]^+$: 180.1514, found 180.1508; $[\alpha]_D^{26}$ -21.22° (*c* 1.56, hexane, 79% ee).



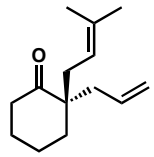
350

Ketone 350. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.25 (comp. m, 5H), 5.83 (dddd, *J* = 16.5, 10.8, 6.9, 6.9 Hz, 1H), 5.15 (app. ddd, *J* = 16.5, 3.0, 1.5 Hz, 1H), 5.13 (app. d, *J* = 10.8 Hz, 1H), 4.54 (d, *J* = 11.1 Hz, 1H), 4.16 (d, *J* = 11.1 Hz, 1H), 2.85-2.68 (m, 2H), 2.42-2.24 (comp. m, 3H), 2.13-1.95 (comp. m, 2H), 1.76-1.44 (comp. m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.5, 138.2, 132.8, 128.4, 127.5, 127.3, 118.3, 82.1, 65.3, 39.5, 37.8, 36.0, 27.9, 20.6; IR (Neat Film NaCl) 3068, 3032, 2942, 2864, 1715, 1640, 1498, 1454, 1433, 1384, 1311, 1254, 1157, 1121, 1085, 1060, 1028, 997, 970, 915, 735, 696 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{16}H_{20}O_2$ $[M]^+$: 244.1463, found 244.1455; $[\alpha]_D^{28.3}$ +47.3 (*c* 2.38, hexanes, 59% ee).



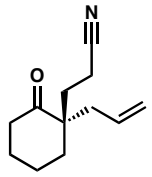
352

Ketone 352. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69 (dddd, *J* = 16.5, 10.8, 7.5, 7.2 Hz, 1H), 5.00 (dddd, *J* = 16.5, 2.1, 1.2, 1.2 Hz, 1H), 5.01 (dddd, *J* = 10.2, 2.1, 1.5, 1.5 Hz, 1H), 4.82 (app. ddd, *J* = 2.7, 1.2, 1.2 Hz, 1H), 4.66 (app. ddd, *J* = 3.0, 0.9, 0.9 Hz, 1H), 2.56-2.28 (comp. m, 6H), 1.91-1.66 (comp. m, 6H), 1.64 (app. ddd, *J* = 0.9, 0.9, 0.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.5, 142.1, 134.1, 118.0, 115.0, 51.5, 43.0, 39.9, 39.5, 36.5, 27.1, 24.3, 20.9; IR (Neat Film NaCl) 3075, 2938, 2865, 1704, 1640, 1453, 1376, 1312, 1206, 1124, 1062, 997, 913, 894 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{20}O$ $[M]^+$: 192.1514, found 192.1514; $[\alpha]_D^{29.3}$ +3.9 (*c* 3.52, hexanes, 91% ee).



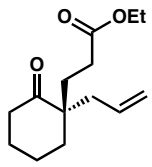
369

Ketone 369. Reaction performed in Et_2O at 30 ºC. Flash chromatography (SiO_2, 1.5→2.5% Et_2O in pentane). 97% yield. R_f = 0.38 (10% Et_2O in pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.67 (dddd, *J* = 16.5, 10.6, 7.2, 7.2 Hz, 1H), 5.07-4.93 (comp. m, 3H), 2.44-2.24 (comp. m, 5H), 2.16 (dd, *J* = 14.6, 7.2 Hz, 1H), 1.89-1.64 (comp. m, 9H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.7, 134.2, 134.1, 119.0, 117.7, 52.1, 39.4, 39.3, 35.9, 33.3, 27.1, 26.0, 20.9, 18.0; IR (Neat Film NaCl) 3075, 2934, 2863, 1706, 1446, 1124, 914 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{14}H_{23}O$ $[M+H]^+$: 207.1749, found 207.1744; $[\alpha]_D^{26.0}$ +1.95° (*c* 1.29, CH_2Cl_2, 91% ee).



371

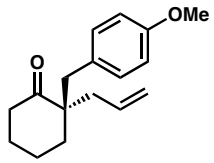
Ketone 371. Reaction performed in Et_2O. Flash chromatography (SiO_2, 25% Et_2O in pentane). 97% yield. R_f = 0.32 (CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 5.60 (dddd, J = 16.7, 10.4, 7.4, 7.4 Hz, 1H), 5.17-5.07 (m, 2H), 2.53-2.16 (comp. m, 6H), 2.03-1.62 (comp. m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.2, 131.9, 120.0, 119.3, 50.8, 39.0, 38.9, 35.4, 30.6, 26.9, 20.5, 12.1; IR (Neat Film NaCl) 3081, 2939, 2863, 2246, 1702, 1453, 1126, 921 cm^{-1}; HRMS (EI) m/z calc'd for $C_{12}H_{17}NO$ $[M]^+$: 191.1310, found 191.1307; $[\alpha]_D^{25.6}$ -27.00° (c 1.56, CH_2Cl_2, 88% ee).



373

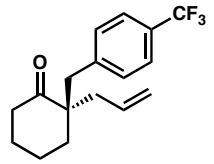
Ketone 373. Reaction performed in Et_2O. Flash chromatography (SiO_2, 5→14% Et_2O in pentane). 96% yield. R_f = 0.44 (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 5.66 (dddd, J = 16.2, 10.9, 7.7, 7.2 Hz, 1H), 5.11-5.07 (m, 1H), 5.07-5.02 (m, 1H), 4.11 (app. q, J = 7.1 Hz, 2H), 2.48-2.18 (comp. m, 5H), 2.16-1.94 (comp. m, 2H), 1.90-1.65 (comp. m, 7H), 1.24 (app. t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.2, 173.5, 133.3, 118.3, 60.4, 50.8, 39.1, 39.0, 36.2, 29.7, 28.8, 27.0, 20.7, 14.2; IR (Neat Film NaCl) 3076, 2937, 2866, 1735, 1704, 1454, 1377, 1309, 1181, 917 cm^{-1};

HRMS (EI) *m/z* calc'd for $C_{14}H_{22}O_3$ $[M]^+$: 238.1569, found 238.1574; $[\alpha]_D^{25.8}$ +9.60° (*c* 1.13, CH_2Cl_2, 90% ee).



375

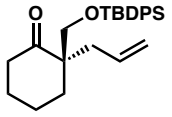
Ketone 375. Flash chromatography (SiO_2, 3% Et_2O in pentane). 80% yield. R_f = 0.54 (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.02 (d, *J* = 9.0 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 2H), 5.72 (dddd, *J* = 17.1, 9.8, 7.0, 7.0 Hz, 1H), 5.12-4.98 (m, 2H), 3.78 (s, 3H), 2.84 (s, 2H), 2.53-2.34 (m, 2H), 2.33-2.17 (m, 2H), 1.91-1.70 (comp. m, 4H), 1.70-1.61 (comp. m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.3, 158.1, 133.9, 131.5, 129.5, 118.1, 113.4, 55.2, 52.6, 40.1, 39.6, 39.3, 35.4, 26.8, 20.8; IR (Neat Film NaCl) 3076, 2935, 2863, 2361, 1702, 1611, 1513, 1456, 1249, 1179, 1036, 834 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{17}H_{22}O_2$ $[M]^+$: 258.1620, found 258.1627; $[\alpha]_D^{25.9}$ +3.60° (*c* 1.05, CH_2Cl_2, 86% ee).



377

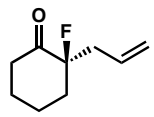
Ketone 377. Flash chromatography (SiO_2, 8→14% Et_2O in pentane). 99% yield. R_f = 0.85 (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.7 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 5.71 (dddd, *J* = 17.0, 10.1, 7.4, 6.9 Hz, 1H), 5.17-5.04 (m, 2H), 3.01 (d, *J* = 13.8 Hz, 1H), 2.88 (d, *J* = 13.8 Hz, 1H), 2.50-2.31 (comp. m, 3H), 2.29-2.17

(m, 1H), 1.97-1.82 (m, 1H), 1.82-1.69 (comp. m, 3H), 1.70-1.59 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.3, 142.0 (q, J_{CF} = 1.2 Hz), 133.0, 130.9, 128.4 (q, J_{CF} = 32.3 Hz), 124.7 (q, J_{CF} = 3.9 Hz), 124.2 (q, J_{CF} = 271.7 Hz), 118.5, 52.5, 40.4, 39.3, 39.3, 35.5, 26.6, 20.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.9; IR (Neat Film NaCl) 3076, 2940, 2867, 1705, 1618, 1418, 1326, 1164, 1123, 1068, 852 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{17}H_{19}F_3O$ $[M]^+$: 296.1388, found 296.1402; $[\alpha]_D^{26.6}$ –16.31° (*c* 1.17, CH_2Cl_2, 82% ee).



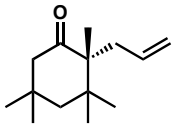
379

Ketone 379. Flash chromatography (SiO_2, 1→2.5% EtOAc in hexanes). 92% yield. R_f = 0.32 (5% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68-7.64 (m, 4H), 7.46-7.36 (m, 6H), 5.69-5.55 (m, 1H), 5.38-5.31 (m, 1H), 5.08-4.99 (m, 2H), 3.84 (d, *J* = 10.2 Hz, 1H), 3.66 (d, *J* = 10.2 Hz, 1H), 2.48 (d, *J* = 7.5 Hz, 2H), 2.40-2.20 (m, 2H), 1.90-1.60 (m, 6H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.4, 135.7, 133.8, 133.3(2C), 129.7, 129.6, 127.6(2C), 117.9, 66.4, 53.8, 39.7, 37.3, 34.0, 26.9(2C), 21.0, 19.3; IR (Neat Film NaCl) 3072, 2933, 2858, 1708, 1428, 1113, 703 cm^{-1}; HRMS (FAB) *m/z* calc'd for $C_{26}H_{35}O_2Si$ $[M+H]^+$: 407.2406, found 407.2398; $[\alpha]_D^{25}$ –3.96° (*c* 5.00, $CHCl_3$, 81% ee).



381

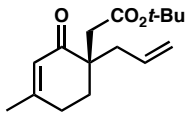
Ketone 381. Reaction performed in Et_2O at 30 ºC. Flash chromatography (SiO_2, 2% Et_2O/pentane). 80% yield. R_f = 0.36 (10:1 Hexane:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 5.88-5.71 (m, 1H), 5.20-5.10 (m, 2H), 2.76-2.31 (m, 4H), 2.16-2.02 (m, 1H), 1.99-1.78 (m, 4H), 1.75-1.60 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.2 (d, $J_{C\text{-}F}$ = 20.0 Hz), 130.7 (d, $J_{C\text{-}F}$ = 3.8 Hz), 119.2, 97.7 (d, $J_{C\text{-}F}$ = 184.3 Hz), 39.4, 38.7 (d, $J_{C\text{-}F}$ = 22.7 Hz), 37.3 (d, $J_{C\text{-}F}$ = 22.2 Hz), 27.2, 21.4 (d, $J_{C\text{-}F}$ = 6.6 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -158.15; IR (Neat Film NaCl) 3080, 2946, 1729, 1642, 1453, 1433, 1126, 923 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_9H_{13}OF$ $[M]^+$: 156.0950, found 156.0946; $[\alpha]_D^{24.4}$ -74.65° (*c* 1.05, CH_2Cl_2, 91% ee).



256

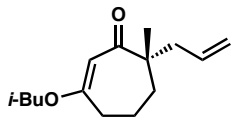
Ketone 256. Flash chromatography (SiO_2, 1→4% Et_2O in hexanes). 90% yield. R_f = 0.48 (10% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.63-5.46 (m, 1H), 5.10-4.94 (m, 2H), 2.61 (d, *J* = 13.5 Hz, 1H), 2.34 (d, *J* = 12.9 Hz, 1H), 2.11 (d, *J* = 12.9 Hz, 1H), 2.02 (d, *J* = 13.8 Hz, 1H), 1.83 (d, *J* = 14.6 Hz, 1H), 1.40 (d, *J* = 14.5 Hz, 1H), 1.02 (s, 3H), 0.99 (s, 3H), 0.95 (s, 3H), 0.92 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.5, 134.2, 117.9, 53.8, 51.0, 49.5, 40.5, 39.1, 35.7, 33.7, 29.8, 26.9, 26.3, 15.4; IR (Neat Film NaCl) 3077, 2957, 1708, 1639, 1460, 1392, 1370, 913 cm^{-1}; HRMS (EI) *m/z*

calc'd for $C_{14}H_{24}O$ $[M]^+$: 208.1827, found 208.1837; $[\alpha]_D^{22.5}$ -4.14° (*c* 2.705, hexane, 85% ee).



385

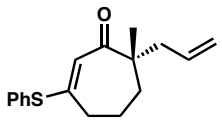
Ketone 385. Reaction performed in Et_2O at 30 ºC . Flash chromatography (SiO_2, 3% Et_2O in pentane). 73% yield. R_f = 0.45 (30% Et_2O in pentane). ^1H NMR (300 MHz, $CDCl_3$) δ 5.84 (s, 1H), 5.70 (dddd, *J* = 16.8, 10.2, 7.3, 7.3 Hz, 1H), 5.12-5.11 (m, 2H), 2.71 (d, *J* = 15.6 Hz, 1H), 2.48-2.13 (comp. m, 6H), 1.93 (s, 3H), 1.91-1.81 (m, 1H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 170.8, 160.3, 133.3, 125.4, 118.7, 80.5, 45.4, 40.5, 39.0, 29.8, 28.1, 27.8, 24.1; IR (Neat Film NaCl) 2978, 1728, 1670, 1367, 1213, 1152 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{16}H_{25}O_3$ $[M+H]^+$: 265.1804, found 265.1803; $[\alpha]_D^{25.4}$ -39.22° (*c* 1.05, CH_2Cl_2, 86% ee).



389

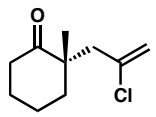
Ketone 389. Reaction run on 0.16 mmol at 30 °C in Et_2O (0.1 M) for 6 h using (*S*)-*t*-BuPHOX and $Pd(dmdba)_2$. The product was purified by flash chromatography (2 x 15 cm SiO_2, 12:1 → 9:1 Hex-Et_2O) and isolated in 91.7% yield (0.147 mmol) as a light yellow oil; R_f = 0.31 (3:1 Hexanes-Et_2O); ^1H NMR (500 MHz, $CDCl_3$) δ 5.72 (dddd, *J* = 16.6, 10.5, 7.3, 7.3 Hz, 1H), 5.31 (s, 1H), 5.05-5.00 (m, 2H), 3.50 (dd, *J* = 9.3, 6.6 Hz, 1H), 3.47 (dd, *J* = 9.3, 6.6 Hz, 1H), 2.53-2.42 (m, 2H), 2.38 (dd, *J* = 13.7, 7.1 Hz, 1H),

2.20 (dd, *J* = 13.7, 7.8 Hz, 1H), 1.98 (app septuplet, J = 6.6 Hz, 1H), 1.86-1.70 (comp. m, 3H), 1.62-1.56 (m, 1H), 1.14 (s, 3H), 0.95 (app d, *J* = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.7, 171.3, 134.6, 117.9, 105.0, 74.5, 51.5, 45.4, 36.1, 35.2, 28.0, 25.2, 19.9, 19.3, 19.3; IR (Neat Film NaCl) 2960, 2933, 2873, 1614, 1470, 1387, 1192, 1171, 998, 912 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{15}H_{24}O_2$ $[M]^{+\bullet}$: 36.1776; found 36.1767; $[\alpha]_D^{25.5}$ – 50.84 ° (*c* 0.73, CH_2Cl_2, 85.0% ee).



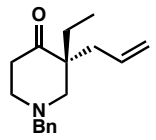
391

Ketone 391. Reaction run on 0.287 mmol at 30 °C in Et_2O (0.1 M) for 5 h using (*S*)-*t*-BuPHOX and $Pd(dmdba)_2$. The product was purified by flash chromatography (1.5 x 18 cm SiO_2, 15:1 → 9:1 Hex-Et_2O, PhMe load) and isolated in 86% yield (0.246 mmol) as a light yellow oil; R_f = 0.46 (3:1 Hex:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49-7.46 (comp. m, 2H), 7.42-7.38 (comp. m, 3H), 5.66 (dddd, *J* = 16.8, 10.1, 7.3, 7.3 Hz, 1H), 5.54 (s, 1H), 5.04-4.98 (comp. m, 2H), 2.59-2.48 (m, 2H), 2.29 (dd, *J* = 13.7 7.3 Hz, 1H), 2.20 (dd, *J* = 13.7, 7.6 Hz, 1H), 1.93-1.77 (comp. m, 2H), 1.64-1.58 (m, 1H), 1.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.0, 155.7, 135.5, 134.2, 130.4, 129.8, 129.8, 124.0, 118.1, 51.3, 44.6, 36.3, 35.2, 24.3, 22.5; IR (Neat Film NaCl) 3074, 2931, 2865, 1650, 1597, 1474, 1440, 1197, 916, 749, 691 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{17}H_{20}SO$ $[M]^{+\bullet}$: 272.1235; found 272.1243; $[\alpha]_D^{24.8}$ –86.35 ° (*c* 0.905, CH_2Cl_2, 89.1% ee).



394

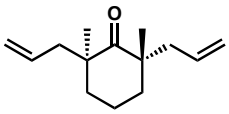
Ketone 394. Reaction performed in Et_2O at 35 ºC with 4 mol% $Pd_2(dba)_3$ (45.8 mg, 0.040 mmol), and 10 mol% (*S*)-*t*-BuPHOX (48.4 mg, 0.10 mmol). Flash chromatography (SiO_2, 1→2.5% Et_2O in pentane). 87% yield. R_f = 0.63 (30% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 5.27 (app. d, *J* = 1.2 Hz, 1H), 5.15-5.09 (m, 1H), 2.80 (d, *J* = 14.4 Hz, 1H), 2.61 (d, *J* = 14.4 Hz, 1H), 2.56-2.37 (m, 2H), 1.94-1.61 (comp. m, 6H), 1.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.4, 138.7, 116.3, 48.4, 46.5, 39.2, 38.8, 27.4, 22.7, 21.1; IR (Neat Film NaCl) 2936, 2868, 1708, 1630, 1456, 1126, 887 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{10}H_{16}ClO$ $[M+H]^+$: 187.0890, found 187.0884; $[\alpha]_D^{26.6}$ -5.40° (*c* 3.21, CH_2Cl_2, 91% ee).



396

Ketone 396. Flash chromatography (SiO_2, 5 → 7% Et_2O in pentane). 91% yield. R_f = 0.29 (10% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.23 (comp. m, 5H), 5.62 (dddd, *J* = 12.3, 9.6, 7.2, 7.2 Hz, 1H), 5.03 (m, 1H), 4.99 (m, 1H), 3.56 (s, 2H), 2.83-2.69 (m, 1H), 2.65-2.33 (comp. m, 6H), 2.33-2.20 (m, 1H) 1.95 (dq, *J* = 15.3, 7.5 Hz, 1H), 1.51 (dq, *J* = 15.0, 7.5 Hz, 1H), 0.75 (dd, *J* = 7.5, 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.6, 138.6, 133.8, 128.7, 128.3, 127.2, 117.8, 62.2, 61.8, 53.4, 52.2, 39.3, 37.3, 26.7, 7.8; IR (Neat Film NaCl) 3065, 3028, 2965, 2801, 1709, 1454, 1352,

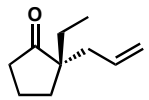
1200, 915, 699 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{17}H_{23}NO$ $[M]^+$: 257.1780, found 257.1772; $[\alpha]_D^{26.6}$ +31.21° (*c* 1.51, CH_2Cl_2, 92% ee).



398

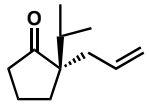
(2*S*,6*S*)-2,6-Diallyl-2,6-dimethylcyclohexanone (398). A 50 mL rb flask equipped with a magnetic stir bar was flame dried under vacuum. After cooling under nitrogen, $Pd_2(dba)_3$ (31.4 mg, 0.0343 mmol, 0.034 equiv) and *(S)-t*-Bu-PHOX (31.3 mg, 0.0808 mmol, 0.080 equiv) were added. After the flask was evacuated and filled with nitrogen three times, THF (32 mL) was added and the contents were stirred at 25 °C for 30 min, at which time allyl 2-(allyloxycarbonyloxy)-1,3-dimethylcycohex-2-enecarboxylate (298 mg, 1.012 mmol, 1.0 equiv) was added by syringe in one portion. The reaction was stirred at 40 °C for 6 hours at which time TLC indicated complete reaction. The reaction mixture was allowed to cool and then concentrated to ~1 mL under reduced pressure and the residue chromatographed (100 mL pentane, then 1 to 2% Et_2O in pentane on 2 x 14 cm SiO_2) to afford the title compound **398** and a colorless, volatile oil (157.9 mg, 76% yield). GC analysis indicated the isolated compound was an 80:20 mixture (R_f = 0.51, 10:1 Hexane:EtOAc) of C_2-symmetric:*meso* diastereomers. The C_2-symmetric isomer was isolated in pure form after ring closing metathesis of the *meso* isomer. C_2-symmetric ketone **398**: R_f = 0.17 (2% Et_2O in hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 5.65 (m, 2H), 5.10-4.95 (m, 4H), 2.33 (dd, *J* = 6.9, 13.8 Hz, 2H), 2.18 (dd, *J* = 7.8, 13.8 Hz, 2H), 1.87-1.68 (m, 4H), 1.59-1.48 (m, 2H), 1.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.6, 134.4, 118.0, 47.6, 43.9, 36.4, 25.0, 17.3; IR (Neat Film NaCl)

3076, 2930, 1694, 1639, 1461, 1374, 992, 914 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{14}H_{22}O$ $[M]^+$: 206.1671, found 206.1675; $[\alpha]_D^{23.6}$ -54.04° (*c* 0.95, hexane, 92% ee).



407

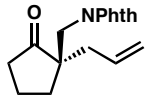
Ketone 407. Flash chromatography (2 x 12 cm SiO_2, 3% → 4% Et_2O/pentane) afforded the title compound as a colorless oil (125.9 mg, 82% yield). R_f = 0.44 (10:1 Hexane:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 5.68 (dddd, *J* = 7.2, 7.2, 9.3, 12.3 Hz, 1H), 5.09-5.00 (m, 2H), 2.24-2.14 (m, 4H), 1.90-1.80 (m, 4H), 1.46 (q, *J* = 7.2 Hz, 1H), 1.46 (q, *J* = 7.2 Hz, 1H), 0.83 (dd, *J* = 7.2, 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.4, 169.8, 131.5, 118.3, 65.6, 38.9, 31.9, 27.2, 19.5, 18.3, 17.6; IR (Neat Film NaCl) 3077, 2965, 1735, 1640, 1460, 1406, 1162, 915 cm^{-1}; HRMS *m/z* calc'd for $C_{10}H_{16}O$ $[M]^+$: 152.1201, found 152.1195; $[\alpha]_D^{25.2}$ -18.55 (*c* 1.050, CH_2Cl_2, 86% ee).



409

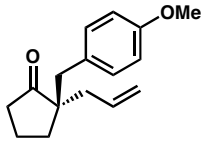
Ketone 409. Flash chromatography (2 x 13 cm SiO_2, 3% Et_2O/pentane) afforded the title compound as a colorless oil (130.4 mg, 77% yield). R_f = 0.44 (10:1 Hexane:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 5.70 (dddd, *J* = 7.5, 7.5, 9.3, 13.2 Hz, 1H), 5.07-5.00 (m, 2H), 2.30-2.07 (m, 4H), 2.01-1.69 (m, 5H), 0.87 (d, *J* = 7.2 Hz, 3H), 0.80 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 223.6, 134.2, 117.8, 55.1, 39.7, 39.6, 31.8, 29.0, 18.9, 18.2, 17.1; IR (Neat Film NaCl) 3077, 2963, 1734, 1640, 1471,

1406, 1388, 1370, 1190, 914 cm^{-1}; HRMS *m/z* calc'd for $C_{11}H_{18}O$ $[M]^+$: 166.1358, found 166.1359; $[\alpha]_D^{24.9}$ +43.05 (*c* 1.085, CH_2Cl_2, 84% ee).



411

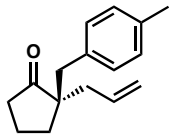
Ketone 411. Flash chromatography (SiO_2, 10 → 15% EtOAc in hexanes). 67% yield, 48% ee. R_f = 0.34 (30% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 5.9, 3.2 Hz, 2H), 7.72 (dd, *J* = 5.9, 3.2 Hz, 2H), 5.73 (dddd, *J* = 16.8, 9.8, 7.7, 6.4 Hz, 1H), 5.18-5.06 (m, 2H), 3.80 (d, *J* = 14.1 Hz, 1H), 3.74 (d, *J* = 14.1 Hz, 1H), 2.56-2.41 (m, 1H), 2.38-2.10 (comp. m, 3H), 2.10-1.86 (comp. m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.1, 168.8, 134.2, 133.3, 132.0, 123.6, 119.4, 53.0, 41.8, 38.7, 38.3, 31.9, 18.9; IR (Neat Film NaCl) 2966, 1773, 1734, 1713, 1429, 1395, 1354, 715, 666 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{17}O_3N$ $[M]^+$: 283.1208, found 283.1209; $[\alpha]_D^{26.5}$ 14.1 (*c* 1.49, CH_2Cl_2, 48% ee).



413

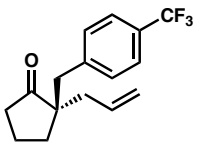
Ketone 413. Flash chromatography (2 x 14 cm SiO_2, 3% Et_2O/pentane) afforded the title compound as a colorless oil (207.6 mg, 84% yield). R_F = 0.32 (10:1 Hexane:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.01 (d, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 5.71 (dddd, *J* = 7.5, 7.5, 10.2, 14.7 Hz, 1H), 5.14-5.01 (m, 2H), 3.78 (s, 3H), 2.86 (d, *J* = 13.8 Hz, 1H), 2.53 (d, *J* = 13.8 Hz, 1H), 2.26 (dd, *J* = 7.2, 13.5 Hz, 1H),

2.20-2.09 (m, 2H), 1.99 (dd, *J* = 6.6, 8.7 Hz, 1H), 1.95-1.66 (m, 2H), 1.86 (app dd, *J* = 7.5, 7.5 Hz, 1H), 1.55-1.41 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 223.0, 158.2, 133.7, 131.1, 129.6, 118.5, 113.5, 55.1, 53.2, 40.8, 40.8, 38.9, 30.9, 18.6; IR (Neat Film NaCl) 3075, 2958, 1733, 1611, 1512, 1248, 1178, 1036 cm^{-1}; HRMS *m/z* calc'd for $C_{16}H_{20}O_2$ $[M]^+$: 244.1463, found 156244.1465; $[\alpha]_D^{25.1}$ +7.34 (*c* 1.065, CH_2Cl_2, 73% ee).



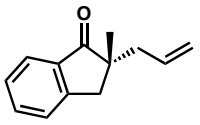
415

Ketone 415. Flash chromatography (SiO_2, 5% Et_2O in pentane). 84% yield, 73% ee. R_f = 0.39 (10% Et_2O in pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (d, *J* = 7.7 Hz, 2H), 6.98 (d, *J* = 8.0 Hz, 2H), 5.72 (dddd, *J* = 17.0, 10.4, 8.0, 6.9 Hz, 1H), 5.10 (app. ddd, *J* = 10.1, 2.1, 1.1 Hz, 1H), 5.06 (app. ddd, *J* = 16.7, 2.1, 1.3 Hz, 1H), 2.87 (d, *J* = 13.3 Hz, 1H), 2.55 (d, *J* = 13.3 Hz, 1H), 2.31 (s, 3H), 2.29-2.22 (m, 1H), 2.21-2.07 (comp. m, 2H), 2.05-1.82 (comp. m, 3H), 1.82-1.65 (m, 1H), 1.56-1.41 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 223.2, 136.1, 134.7, 133.9, 130.3, 129.0, 118.8, 53.4, 41.4, 41.0, 39.1, 31.1, 21.2, 18.8; IR (Neat Film NaCl) 3080, 2961, 2915, 1737, 1515, 1441, 1157, 921, 810, 666 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{16}H_{20}O$ $[M]^+$: 228.1514, found 228.1505; $[\alpha]_D^{26.2}$ +9.1 (*c* 2.68, CH_2Cl_2, 73% ee).



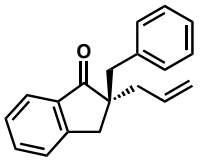
417

Ketone 417. Flash chromatography (2 x 14 cm SiO_2, 2% → 3% Et_2O/pentane) afforded the title compound as a colorless oil (239.3 mg, 83% yield). R_F = 0.39 (10:1 Hexane:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 5.73 (dddd, *J* = 7.5, 7.5, 10.2, 17.4 Hz, 1H), 5.17-5.05 (m, 2H), 2.97 (d, *J* = 13.2 Hz, 1H), 2.66 (d, *J* = 13.2 Hz, 1H), 2.26 (dd, *J* = 7.2, 13.5 Hz, 1H), 2.24-2.19 (m, 1H), 2.16 (dd, *J* = 7.2, 13.5 Hz, 1H), 2.01-1.70 (m, 3H), 1.59-1.43 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 222.1, 142.0, 133.1, 130.6, 128.7 (q, $J_{C\text{-}F}$ = 32.2 Hz), 125.1 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.2 (q, $J_{C\text{-}F}$ = 269.2 Hz), 119.0, 53.1, 41.0, 40.7, 38.6, 31.0, 18.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.29; IR (Neat Film NaCl) 3078, 2964, 1736, 1618, 1326, 1163, 1123, 1068 cm^{-1}; HRMS *m/z* calc'd for $C_{16}H_{17}OF_3$ $[M]^+$: 282.1232, found 282.1237; $[\alpha]_D^{24.8}$ +5.65 (*c* 1.085, CH_2Cl_2, 60% ee).



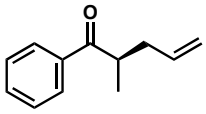
419

Ketone 419. Purified by flash chromatography (SiO_2, 10% Et_2O in pentane). 82% yield, 80% ee. R_f = 0.37 (10% Et_2O in pentane); $[\alpha]_D^{26.4}$ -38.5 (*c* 0.47, CH_2Cl_2, 80% ee). Spectral data matched that reported in the literature.[26]



421

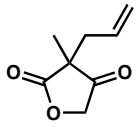
Ketone 421. Purified by flash chromatography (SiO_2, 2 → 4% Et_2O in pentane). 93% yield, 71% ee. R_f = 0.37 (10% Et_2O in pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.7 Hz, 1H), 7.63 (ddd, *J* = 7.7, 7.7, 1.1 Hz, 1H), 7.49 (comp. m, 2H), 7.36-7.20 (comp. m, 5H), 5.74 (dddd, *J* = 16.7, 10.1, 8.0, 6.6 Hz, 1H), 5.21 (app. d, *J* = 16.8 Hz, 1H), 5.12 (app. d, *J* = 10.1 Hz, 1H), 3.26 (d, *J* = 17.3 Hz, 1H), 3.25 (d, *J* = 13.3 Hz, 1H), 3.10 (d, *J* = 17.3 Hz, 1H), 2.96 (d, *J* = 13.6 Hz, 1H), 2.70 (dd, *J* = 13.6, 6.4 Hz, 1H), 2.46 (dd, *J* = 13.6, 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.3, 153.0, 137.3, 136.8, 134.8, 133.4, 130.2, 128.0, 127.2, 126.4, 126.3, 123.8, 118.7, 53.7, 42.7, 42.5, 35.3; IR (Neat Film NaCl) 3076, 3029, 2917, 1708, 1608, 1496, 1465, 1436, 1296, 1210, 1030, 995, 922, 756, 703 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{19}H_{18}O$ $[M]^+$: 262.1358, found 262.1365; $[\alpha]_D^{26.1}$ +28.4 (*c* 1.42, CH_2Cl_2, 71% ee).



423

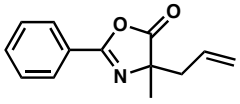
Ketone 423. Purified by preparative TLC. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 7.2 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 5.77 (m, 1H), 5.00 (m, 2H), 3.52 (sextet, *J* = 6.9 Hz, 1H), 2.54 (m, 1H), 2.19 (m, 1H), 1.21 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.6, 136.4, 135.9, 133.0, 128.5, 116.7, 40.5, 37.7, 17.1; IR (Neat Film NaCl) 3078, 2976, 2933, 1682, 1642, 1448, 1209, 976, 917,

704 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{12}H_{14}O$ $[M]^+$: 174.1045, found 174.1048; $[\alpha]_D^{27.0}$ –38.1 (*c* 1.73, hexanes, 70% ee).



430

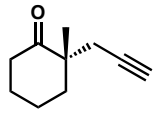
Ketone 430. Purified by flash chromatography (SiO_2, 2 →12% EtOAc in hexanes). 87% yield, 2% ee. R_f = 0.20 (10% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.62 (dddd, *J* = 17.7, 9.6, 7.5, 7.2 Hz, 1H), 5.13 (app. ddd, *J* = 9.6, 1.8, 0.9 Hz, 1H), 5.12 (app. ddd, *J* = 17.1, 1.5, 0.9 Hz, 1H), 4.59 (d, *J* = 17.1 Hz, 1H), 4.44 (d, *J* = 17.4 Hz, 1H), 2.53-2.37 (m, 2H), 1.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.9, 176.6, 130.1, 121.1, 72.5, 45.6, 40.2, 19.0; IR (Neat Film NaCl) 3543, 3083, 2983, 2939, 2877, 1803, 1758, 1642, 1454, 1436, 1378, 1341, 1231, 1122, 1065, 1043, 998, 912, 664 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_8H_{10}O_3$ $[M]^+$: 154.0630, found 154.0626.



432

Ketone 432. Purified by flash chromatography (SiO_2, 4 →7% Et_2O in hexanes). 89% yield, 2% ee. R_f = 0.39 (25% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.99 (ddd, *J* = 7.2, 1.5, 1.2 Hz, 2H), 7.57 (tt, *J* = 7.8, 1.2 Hz, 1H), 7.48 (ddd, *J* = 7.8, 6.9, 1.5 Hz, 2H), 5.67 (dddd, *J* = 17.1, 9.9, 7.5, 6.9 Hz, 1H), 5.18 (dddd, *J* = 17.1, 1.5, 1.5, 1.5 Hz, 1H), 5.11 (dddd, *J* = 10.2, 1.5, 0.9, 0.9 Hz, 1H), 2.64 (dddd, *J* = 13.8, 6.9, 0.9, 0.9 Hz, 1H), 2.57 (dddd, *J* = 13.8, 7.5, 1.2, 1.2 Hz, 1H), 1.53 (s, 3H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 180.2, 159.8, 132.7, 130.8, 128.7, 127.9, 125.9, 120.4, 69.7, 42.3, 23.2; IR (Neat Film NaCl) 3078, 2982, 2934, 1819, 1655, 1581, 1493, 1451, 1321, 1293, 1177, 1094, 1071, 1005, 930, 889, 780, 700 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{13}O_2N$ $[M]^+$: 215.0946, found 215.0938.



434

Propargyl ketone 434. A flame dried, 50 mL two-neck round-bottom flask containing a stirbar was equipped with a three-way stopcock, evacuated, and cooled under dry nitrogen. To this was added $Pd_2(dba)_3$ (11.4 mg, 0.0125 mmol, 0.05 equiv.) and (*S*)-*t*-Bu-PHOX (12.5 mg, 0.0313 equiv.). The flask was evacuated and backfilled with dry nitrogen twice. THF (15 mL) was then added and the mixture was stirred for 30 minutes at 25ºC. To the resulting yellow solution was added propargyl enol carbonate **433** (97.1 mg, 0.50 mmol) and then this mixture was stirred at 70 ºC. After the reaction was completed, the resulting mixture was concentrated in vacuo. The residue was purified by flash column chromatography to give propargyl ketone (*S*)-**434** (64.3 mg, 86% yield) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 2.55-2.29 (m, 4H), 1.99 (t, J = 2.7 Hz, 1H), 1.98-1.65 (m, 6H), 1.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.9, 81.1, 70.7, 47.8, 38.5, 37.8, 27.6, 27.3, 22.3, 21.1; IR (Neat Film NaCl) 3292, 2936, 2865, 2117, 1709, 1451, 1425, 1377, 1314, 1128, 1075 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{10}H_{14}O$ $[M]^+$: 150.1045, found 150.1044; $[\alpha]^{25}_D$ = +0.74 (*c* 1.50, $CHCl_3$, 31% ee).

Table 4.17 Methods Utilized for the Determination of Enantiomeric Excess

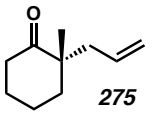
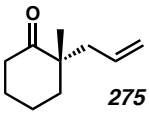
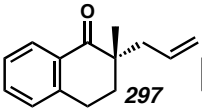
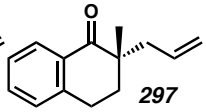
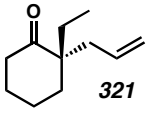
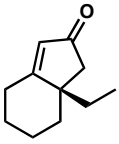
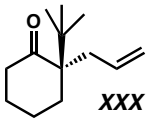
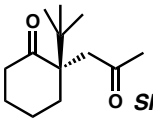
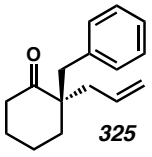
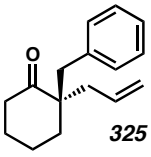
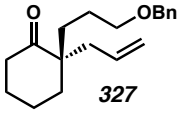
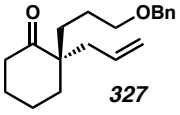
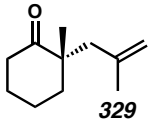
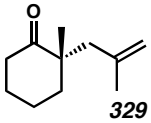
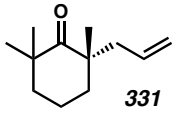
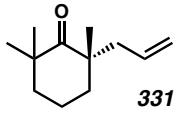
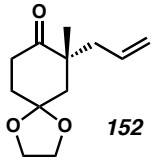
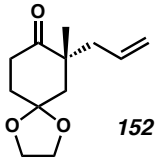
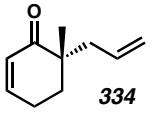
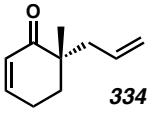
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2	 *297*	 *297*	HPLC Chiracel OD-H 0.1% IPA in heptane isocratic, 0.7 mL/min	19.97	21.48	92
3	 *321*		GC, G-TA 100 °C isotherm	14.52	13.35	92
4	 *XXX*	 *SI8*	GC, G-TA 110 °C isotherm	63.65	62.01	82
5	 *325*	 *325*	HPLC Chiracel OJ 2% EtOH in hexane isocratic, 1.0 mL/min	19.81	13.82	85
6	 *327*	 *327*	HPLC Chiralpak AD 0.75% IPA in hexane isocratic, 1.0 mL/min	11.95	13.80	88
7	 *329*	 *329*	GC, G-TA 100 °C isotherm	15.76	17.65	92
8	 *331*	 *331*	GC, G-TA 80 °C isotherm	25.48	27.90	92
9	 *152*	 *152*	GC, G-TA 120 °C isotherm	26.90	28.64	86
10	 *334*	 *334*	GC, G-TA 100 °C isotherm	15.31	18.04	90

Table 4.17 (continued)

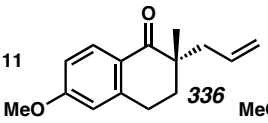
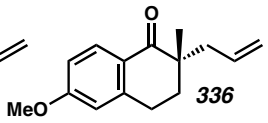
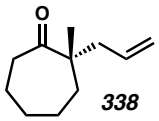
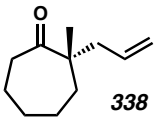
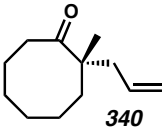
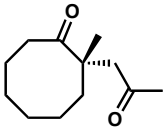
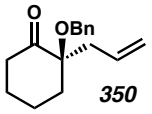
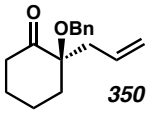
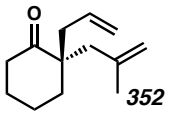
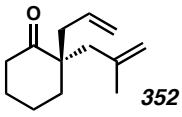
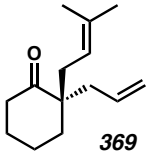
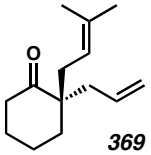
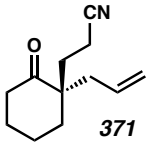
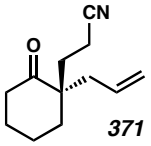
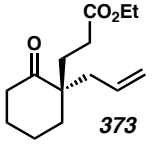
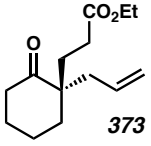
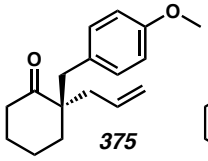
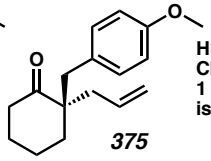
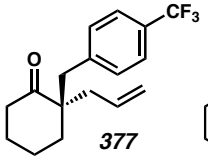
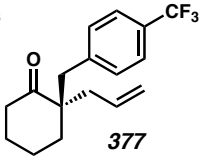
entry	product	compound assayed	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
11	 336	 336	HPLC Chiracel OJ 1% EtOH in hexane isocratic 1.0 mL/min	11.38	10.16	91
12	 338	 338	GC, G-TA 110 °C isotherm	9.88	10.68	87
13	 340		GC, G-TA 110 °C isotherm	63.25	61.94	79
14	 350	 350	HPLC Chiracel OB-H 0.2% EtOH in hexane isocratic, 1.0 mL/min	13.56	16.96	59
15	 352	 352	GC, G-TA 95 °C isotherm	49.77	47.98	91
16	 369	 369	GC, G-TA 100 °C isotherm	55.511	52.56	91
17	 371	 371	GC, G-TA 150 °C isotherm	18.75	21.06	88
18	 373	 373	GC, G-TA 120 °C isotherm	90.98	94.22	90
19	 375	 375	HPLC Chiracel AD 1 % EtOH in hexane isocratic, 1.0 mL/min	12.87	15.36	86
20	 377	 377	GC, G-TA 120 °C isotherm for 120 mins, then ramp 3 °C/min	127.74	126.43	82

Table 4.17 (continued)

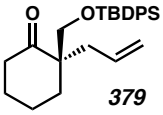
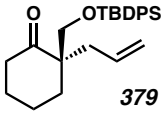
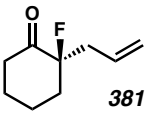
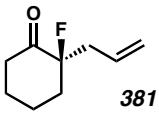
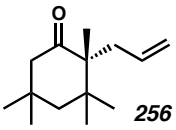
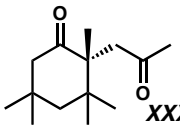
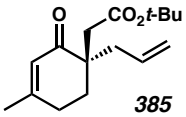
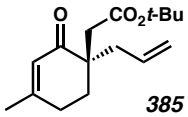
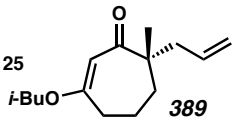
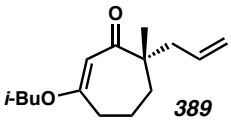
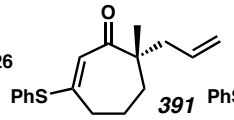
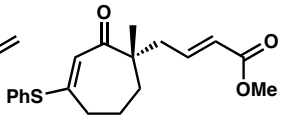
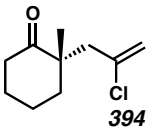
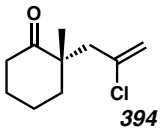
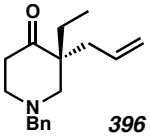
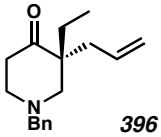
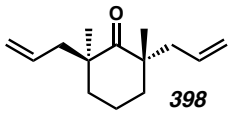
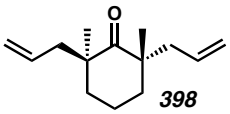
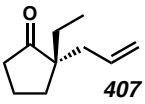
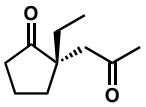
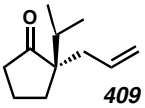
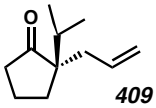
entry	product	compound assayed	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
21	 *379*	 *379*	HPLC Chiracel OD-H 100% hexane isocratic, 1.0 mL/min	16.75	23.91	81
22	 *381*	 *381*	GC, G-TA 110 °C isotherm	6.27	8.02	91
23	 *256*	 *XXX*	GC, G-TA 120 °C isotherm	49.12	50.57	85
24	 *385*	 *385*	GC, G-TA 130 °C isotherm	59.36	61.19	86
25	 *389*	 *389*	HPLC Chiracel OD-H 1% IPA in hexane isocratic, 1.0 mL/min	6.30	7.26	85
26	 *391*		HPLC Chiralpak AD 3% EtOH in hexane isocratic 1.0 mL/min	18.66	22.33	89
27	 *394*	 *394*	GC, G-TA 100 °C isotherm	44.91	50.06	91
28	 *396*	 *396*	HPLC Chiracel OJ 1 % EtOH in hexane isocratic, 1.0 mL/min	7.95	8.82	92
29	 *398*	 *398*	GC, G-TA 75 °C isotherm	118.51	127.37	92
30	 *407*		GC, G-TA 110 °C isotherm	45.22	38.91	86
31	 *409*	 *409*	GC, G-TA 80 °C isotherm	43.95	49.93	84

Table 4.17 (continued)

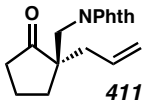
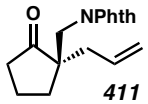
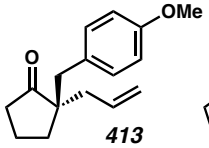
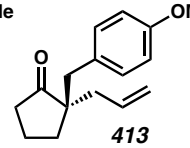
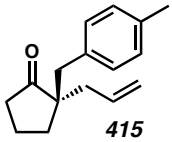
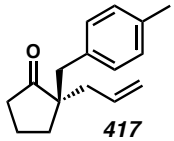
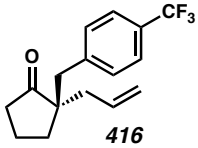
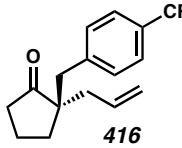
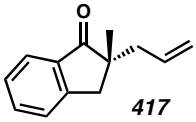
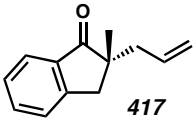
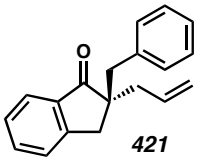
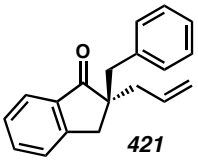
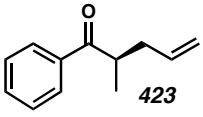
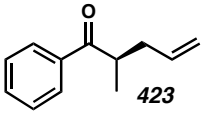
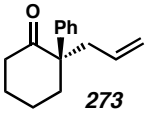
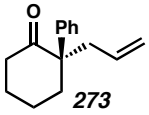
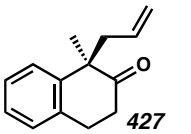
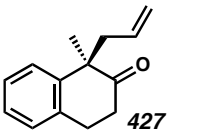
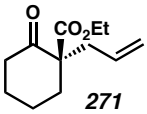
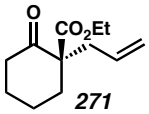
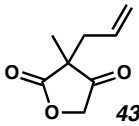
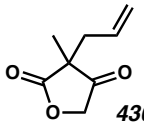
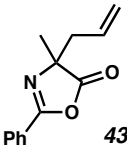
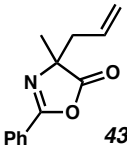
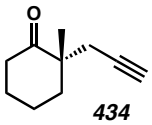
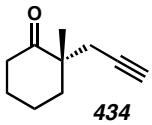
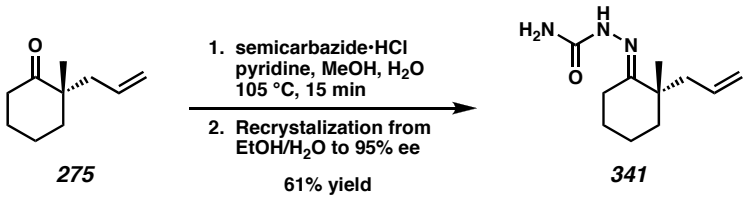
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32	 411	 411	HPLC Chiracel OD-H 4% IPA in hexane isocratic, 1.0 mL/min	24.13	18.26	48
33	 413	 413	HPLC Chiralpak AD 1% IPA in hexane isocratic, 1.0 mL/min	10.07	11.84	73
34	 415	 417	HPLC Chiracel OJ 0.3% EtOH in hexane isocratic, 1.0 mL/min	14.88	12.80	73
35	 416	 416	HPLC Chiralpak AD 1% EtOH in hexane isocratic, 1.0 mL/min	6.42	7.47	60
36	 417	 417	HPLC Chiracel OD-H 0.1% IPA in hexane isocratic, 0.7 mL/min	21.78	23.74	80
37	 421	 421	HPLC Chiracel OJ 1% EtOH in hexane isocratic, 1.0 mL/min	28.93	22.38	71
38	 423	 423	HPLC Chiracel OD-H 0.1% IPA in heptane isocratic, 0.7 mL/min	21.63	25.04	70
39	 273	 273	HPLC Chiracel OJ 0.1% IPA in hexane isocratic, 1.0 mL/min	7.76	8.59	11
40	 427	 427	HPLC Chiracel OJ 3% IPA in hexane isocratic, 1.0 mL/min	9.03	7.38	0
41	 271	 271	GC, G-TA 120 °C isotherm	15.55	16.66	24

Table 4.17 (continued)

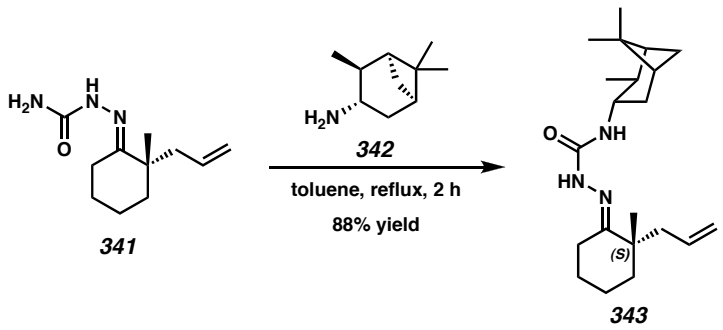
entry	product	compound assayed	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
42	 *430*	 *430*	GC, G-TA 100 °C isotherm	19.67	21.64	2
43	 *432*	 *432*	HPLC Chiracel OD-H 2% IPA in hexane isocratic, 1.0 mL/min	6.61	5.40	2
44	 *434*	 *434*	GC, B-DM 90 °C isotherm	21.8	23.0	31

4.7.2.6 *Preparation of α-Quaternary Ketone Derivatives*

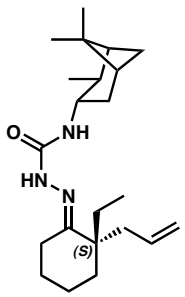


275 *341*

Semicarbazone 341. To a solution of ketone **275** (661.4 mg, 4.34 mmol, 1.0 equiv) of 88% ee in pyridine (1.22 mL), water (3.0 mL), and MeOH (8.0 mL) was added semicarbazide•HCl (848.1 mg, 7.60 mmol, 1.75 equiv). The reaction mixture was heated at 105 °C for 15 min, cooled, diluted with water (10 mL), filtered, and dried to give the semicarbazone (763 mg, 84% yield). The semicarbazone (3.10 g, 14.8 mmol, 87% ee) was suspended in EtOH/water (35/65 v/v 355 mL) and warmed to 90 °C. When all the material had dissolved, heating was discontinued, and the flask allowed to cool in the heating bath. After 8 h, crystals were filtered and dried giving the enantioenriched semicarbazone (1.894 g, 61% yield, 95% ee). Recrystalization of this material in EtOH/water (30/70 v/v 175 mL) by the same procedure gave semicarbazone (1.692 g, 89% yield, 98% ee) as white crystals; m.p. 188-189 °C (EtOH/water); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (bs, 1H), 5.73 (m, 1H), 5.05 (s, 1H), 5.00 (app. d, J = 3.3 Hz, 1H), 2.40-2.11 (m, 4H), 1.71-1.44 (m, 6H), 1.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 156.8, 134.6, 117.2, 42.9, 41.5, 38.6, 25.9, 24.5, 22.5, 21.0; IR (Neat Film NaCl) 3465, 3195, 1693, 1567, 1478 cm^{-1}; HRMS m/z calc'd for $C_{11}H_{20}N_3O$ $[M+H]^+$: 210.1606, found 210.1599; $[\alpha]_D^{28}$ -50.35° (c = 2.60, methanol).

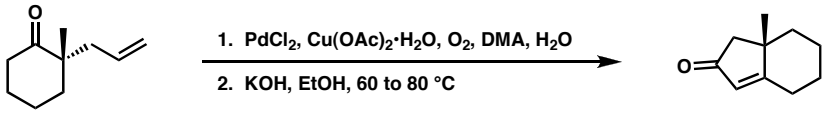


(isopinocampheylamine)-Semicarbazone (343): To a solution of the semicarbazone (100 mg, 0.43 mmol, 1.0 equiv) in xylenes (1.0 mL) was added (1*S*,2*S*,3*S*,5*R*)-(+)-isopinocampheylamine (76.2 μL, 0.45 mmol, 1.05 equiv). The reaction mixture was refluxed for 2 h, cooled, and concentrated. Chromatography (10→50 % EtOAc in Hexanes on SiO_2) afforded the (isopinocampheylamine)-semicarbazone **343** (130.5 mg, 87.8 % yield): m.p. 131-133° from acetone; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (bs, 1H), 6.08 (bd, *J* = 8.7 Hz, 1H), 5.77 (m, 1H), 5.06 (s, 1H), 5.01 (s, 1H), 4.18 (m, 1H), 2.63 (app. tdd, *J* = 9.9, 3.6, 2.4 Hz, 1H), 2.45-2.13 (m, 4H), 1.96 (m, 1H), 1.82 (m, 2H), 1.74-1.41 (m, 8H), 1.23 (s, 3H), 1.15 (d, *J* = 7.2 Hz, 3H), 1.11 (s, 3H), 1.10 (s, 3H), 0.89 (d, *J* = 9.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 155.5, 134.9, 117.0, 48.0, 47.8, 46.8, 43.0, 41.6, 41.5, 38.5, 38.3, 37.8, 35.3, 28.0, 25.9, 24.5, 23.4, 22.4, 21.0, 20.8; IR (Neat Film NaCl) 3400, 3189, 3074, 2929, 1672, 1526 cm^{-1}; HRMS *m/z* calc'd for $C_{21}H_{36}N_3O$ $[M+H]^+$: 346.2858, found 346.2874; $[\alpha]_D^{27}$ -18.92° (*c* = 0.53, hexane). The semicarbazone was recrystallized from EtOH/H_2O to provide suitable crystals for X-ray analysis.



344

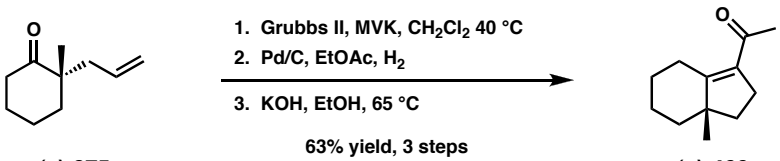
(isopinocampheylamine)-Semicarbazone (344). Prepared in an analogous manner to **343**: m.p. 145-146° from acetone; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 21.3 Hz, 1H), 6.07 (d, *J* = 4.4 Hz, 1H), 5.86-5.72 (m, 1H), 5.08-5.04 (m, 1H), 5.00 (s, 1H), 4.23-4.12 (m, 1H), 2.68-2.55 (m, 1H), 2.46-2.34 (m, 2H), 2.30 (d, *J* = 7.5 Hz, 2H), 2.12-2.00 (m, 1H), 1.98-1.90 (m, 1H), 1.88-1.40 (m, 11H), 1.22 (s, 3H), 1.15 (d, *J* = 7.2 Hz, 3H), 1.05 (s, 3H), 0.88 (d, *J* = 9.6 Hz, 1H), 0.77 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 154.4, 135.3, 116.7, 48.0, 47.9, 46.8, 44.2, 41.7, 39.9, 38.3, 37.9, 35.6, 35.3, 28.1, 28.0, 25.6, 23.4, 22.6, 20.8, 20.7, 7.8; IR (Neat Film NaCl) 3402, 3194, 3074, 2930, 1672, 1526 cm^{-1}; HRMS *m/z* calc'd for $C_{22}H_{37}N_3O$ $[M]^+$: 359.2937, found 359.2940; $[\alpha]_D^{29}$ -4.43° (*c* = 0.38, hexane). The semicarbazone was recrystallized from acetone to provide suitable crystals for X-ray analysis.



(–)-275 *(–)-399*

Enone 399.[70] To a solution of ketone **275** (304.4 mg, 2.0 mmol, 2.0 equiv) in dimethylacetamide (2.8 mL) and water (0.4 mL) was added palladium (II) chloride (53.1 mg, 1.2 mmol, 0.15 equiv), copper (II) acetate hydrate (217.9 mg, 1.20 mmol, 0.60

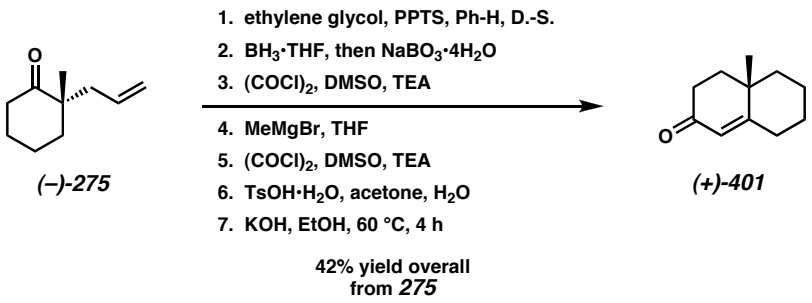
equiv), and an oxygen balloon. After 24 h of vigorous stirring at 25 °C the reaction mixture was chromatographed (5→25 % EtOAc in Hexanes on SiO_2). To a solution of the resulting diketone in EtOH (30 mL) was added KOH (3.4 mL of a 50 mg/mL ethanolic solution), and the reaction mixture was heated at 60 °C for 6 h. The temperature was increased to 80 °C and additional KOH (200 mg) was added. After 4 h the reaction was cooled and concentrated. The resulting residue was partitioned between EtOAc (30 mL) and water (20 mL) and acidified to pH = 2 with HCl (3 M). The layers were separated, and the aqueous layer extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine (30 mL), dried (Na_2SO_4), and concentrated. Chromatography (10→30% Et_2O in pentane on SiO_2) afforded enone **399** (219.1 mg, 72.9% overall yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74 (s, 1H), 2.62 (bd, *J* = 12.0 Hz, 1H), 2.35 (td, *J* = 13.5, 5.4 Hz, 1H), 2.27 (dd, *J* = 18.3, 0.9 Hz, 1H), 2.17 (d, *J* = 18.6 Hz, 1H), 2.26-1.88 (m, 2H), 1.64 (m, 2H), 1.36 (m, 2H), 1.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.2, 188.6, 126.0, 52.1, 43.1, 40.6, 27.9, 27.8, 24.0, 21.8; IR (Neat Film NaCl) 2934, 1713, 1622, 1221 cm^{-1}; HRMS *m/z* calc'd for $C_{10}H_{14}O$ [M]$^+$: 150.1045, found 150.1041; $[\alpha]_D^{27}$ -44.86° (*c* = 3.55, hexane, 98 % ee).



(–)-275 *(+)-400*

Enone 400.[71] To a solution of ketone **275** (152.2 mg, 1.0 mmol, 1.0 equiv) and methyl vinyl ketone (208.1 μL, 2.5 mmol, 2.5 equiv) in DCM (5 mL) was added Grubbs' 2nd generation catalyst (42.4 mg, 0.05 mmol, 0.05 equiv). The reaction mixture was

heated at 40 °C for 18 h, cooled to 25 °C, and concentrated. Chromatography (20% EtOAc in hexanes on SiO_2) gave the enone (152.1 mg 78.3% yield), which was dissolved in EtOAc (12 mL) and treated with 10% Pd/C (30 mg) under an atmosphere of hydrogen gas for 12 h. The system was purged with argon, filtered through a small pad of silica gel, and concentrated. To a solution of the crude diketone in EtOH (12 mL) was added KOH (2.0 mL of a 50 mg/mL ethanolic solution). The reaction mixture was heated to 65 °C for 8 h, cooled to 25 °C, concentrated, and the residue partitioned between EtOAc (10 mL) and 1 M HCl (10 mL) The layers were separated, the aqueous layer extracted with Et_2O (3 x 25 mL), and the combined organics were washed with saturated $NaHCO_3$ (25 mL) then brine (25 mL), dried ($MgSO_4$) and concentrated. Chromatography (10→15 % Et_2O in hexanes on SiO_2) gave enone **400** (112.4 mg, 81% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.32 (d, *J* = 14.7 Hz, 1H), 2.59 (m, 2H), 2.23 (s, 3H), 2.01 (app. t, *J* = 13.5 Hz, 1H), 1.82 (m, 3H), 1.59 (m, 3H), 1.43-1.23 (m, 2H), 1.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.2, 162.2, 131.9, 48.6, 41.5, 39.0, 30.9, 30.5, 27.1, 25.2, 22.9, 22.0; IR (Neat Film NaCl) 2931, 1678, 1654, 1614, 1357 cm^{-1}; HRMS *m/z* calc'd for $C_{10}H_{18}O$ $[M]^+$: 178.1358, found 178.1355; $[\alpha]_D^{27}$ +82.91° (*c* = 3.26 , hexane, 98% ee).

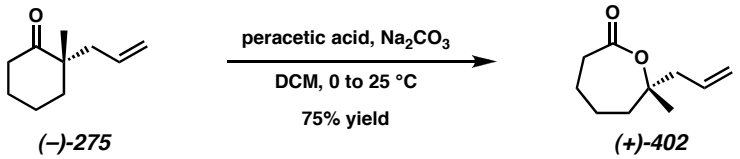


Enone 401. A solution of ketone **275** (1.23 g, 8.11 mmol, 1.0 equiv), ethylene glycol (1.8 mL), pyridinium tosylate (0.6 g),and benzene (45 mL) was refluxed for 22 h in a Dean-Stark apparatus. The reaction mixture was cooled, poured into saturated $NaHCO_3$ (50 mL), the aqueous layer extracted with hexanes/Et_2O (1/1) (2 x 20 mL), and washed with brine (2 x 15 mL). The combined organics were dried ($MgSO_4$), concentrated, and chromatographed to give the ketal (1.59 g). The ketal in THF (15 mL) was added dropwise to a cooled (-25 °C) solution of BH_3•THF (20.3 mmol, 2.5 equiv) in THF (100 mL), and after 4 h was allowed to warm to 25 °C overnight. The reaction mixture was then cooled to -10 °C, water (25 mL) was slowly added, followed by $NaBO_3$•$4H_2O$ (4.99 g, 32.4 mmol, 4.0 equiv), and the reaction mixture was allowed to warm to 25 °C. After 48 h, the reaction mixture was partitioned between water (100 mL) and EtOAc (100 mL), the layers separated, the aqueous layer extracted with EtOAc (5 x 75 mL), and the organic fractions were dried (Na_2SO_4). Evaporation of the solvents under reduced pressure, and chromatography (20→40% EtOAc in hexanes on SiO_2) gave the primary alcohol (1.50 g, 87% yield).

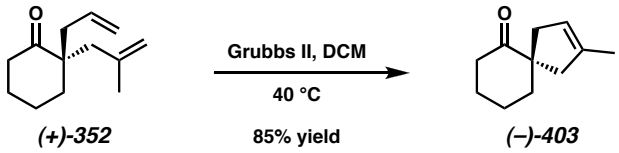
To a cooled (-78 °C) solution of DMSO (479.0 μL, 6.72 mmol, 1.6 equiv) in DCM (45 mL) was added oxalyl chloride (475.2 μL, 5.45mmol, 1.3 equiv). After 45 min, the primary alcohol (900 mg, 4.19 mmol, 1.0 equiv) in DCM (5 mL) was added in a dropwise manner. After an additional 30 min, TEA (2.32 mL, 16.8 mmol, 4.0 equiv) was

added, the reaction mixture warmed to 25 °C, and quenched with half-saturated aq. $NaHCO_3$. The aqueous layer was extracted with DCM (3 x 30 mL), the combined organics dried ($MgSO_4$), and solvents evaporated. This crude aldehyde in THF (45 mL) was cooled to -10 °C, treated with methyl magnesium bromide 3 M in Et_2O (8.40 mmol, 2.0 equiv), quenched with water (20 mL) and saturated aq. NH_4Cl (20 mL), extracted DCM (4 x 20 mL), dried ($MgSO_4$), and solvents evaporated. The resulting crude secondary alcohol was resubmitted to the Swern oxidation conditions described above to give a crude methyl ketone. A solution of the methyl ketone in acetone (45 mL) and water (0.7 mL) was treated with $TsOH•H_2O$ (60 mg), and heated at 50 °C for 4 h. The reaction mixture was then concentrated and chromatographed (7.5→20% EtOAc in hexanes on SiO_2) to give the diketone (515.8 mg, 68% yield for 4 steps).

To a solution of KOH (300mg 5.36 mmol, 1.91 equiv) in EtOH (40 mL) was added the diketone (510.0 mg, 2.80 mmol, 1.0 eq) dissolved in EtOH (15 mL), and the reaction mixture heated at 60 °C for 4 h. The reaction was quenched with acetic acid (306 μL, 5.36 mmol, 1.91 equiv), concentrated and chromatographed (5→20% Et_2O in hexanes on SiO_2) to give enone **401** (334.2 mg, 73% yield, 42% overall yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (s, 1H), 2.56-2.22 (m, 4H), 1.92-1.64 (m, 6H), 1.44-1.30 (m, 2H), 1.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.6, 170.5, 124.1, 41.5, 38.0, 35.9, 34.0, 32.7, 27.1, 22.0, 21.7; IR (Neat Film NaCl) 2930, 1678 cm^{-1}; HRMS *m/z* calc'd for $C_{11}H_{16}O$ $[M]^+$: 164.1201, found 164.1196; $[\alpha]_D^{28}$ +216.15° (*c* = 1.05, ethanol, 98% ee).

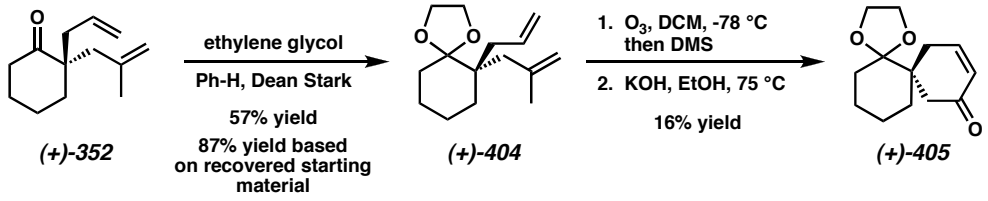


Lactone 402.[72] To a cooled (0 °C) solution of ketone **275** (152.2 mg, 1.0 mmol, 1.0 equiv) in DCM (20 mL) was added Na_2CO_3 (593.6 mg, 5.6 mmol, 5.6 equiv) and peracetic acid (800 μL of 32% solution in dilute acetic acid). The reaction mixture was maintained at 0 °C for 9 h, then allowed to warm to 25 °C for an additional 12 h, diluted with saturated $NaHCO_3$, and the organic layer dried (Na_2SO_4). Chromatography (5→20% EtOAc in hexanes on SiO_2) afforded lactone **402** (125.6 mg, 75% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (m, 1H), 5.15 (m, 1H), 5.11 (app. d, J = 8.4 Hz, 1H), 2.78-2.61 (m, 2H), 2.51 (dd, J = 13.8, 7.2 Hz, 1H), 2.42 (dd, J = 14.1, 7.5 Hz, 1H), 1.86-1.62 (m, 6H), 1.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 132.8, 119.0, 82.7, 46.7, 38.4, 37.3, 24.8, 23.8, 23.3; IR (Neat Film NaCl) 2936, 1717, 1172 cm^{-1}; HRMS *m/z* calc'd for $C_{10}H_{16}O_2$ $[M]^+$: 168.1150, found 168.1154; $[\alpha]_D^{27}$ +20.58° (*c* = 3.46, hexane, 98% ee).



Spiro[4.5]ketone 403. To a sparged (Ar, 5 min) solution of ketone **352** (526 mg, 2.73 mmol, 1.00 equiv) in DCM (56 mL) was added the second generation Grubbs catalyst (69.6 mg, 0.082 mmol, 0.03 equiv) and the reaction was heated at 40 °C for 10 h. The reaction mixture was cooled to ambient temperature, concentrated, and the residue purified by flash chromatography (1→2% Et_2O in hexanes on SiO_2) to give

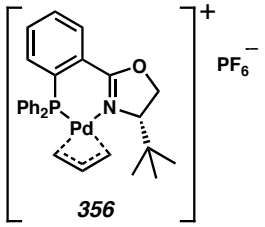
spiro[4.5]ketone **403** (381 mg, 85% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.14 (m, 1H), 2.86-2.71 (m, 2H), 2.44-2.35 (m, 2H), 2.17 (dddd, *J* = 16.2, 5.4, 4.2, 2.1 Hz, 1H), 2.02 (ddd, *J* = 16.5, 3.0, 1.2 Hz, 1H), 1.88-1.68 (comp. m, 6H), 1.67-1.64 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.3, 137.5, 121.1, 56.3, 45.7, 41.9, 40.3, 39.4, 27.2, 22.2, 16.4; IR (Neat Film NaCl) 3042, 2930, 2860, 1710, 1666, 1438, 1338, 1312, 1207, 1129, 1056, 1019, 899, 853, 838, 807 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{11}H_{16}O$ $[M]^+$: 164.1201, found 164.1201; $[\alpha]_D^{27.1}$ –21.7 (*c* 2.65, CH_2Cl_2, 91% ee).



Ketal 404. A solution of ketone **352** (1.27 g, 6.60 mmol, 1.0 equiv), ethylene glycol (1.8 mL), pyridinium tosylate (0.600 g), and benzene (80 mL) was refluxed for 15 h in a Dean-Stark apparatus. The reaction mixture was cooled, poured into saturated $NaHCO_3$ (20 mL), and diluted with H_2O (30 mL) and DCM (30 mL). The aqueous layer extracted with DCM (3 x 30 mL). The combined organics were dried (Na_2SO_4), concentrated, and purified by flash chromatography (1→2% Et_2O in hexanes on SiO_2) to give ketal **404** (889 mg, 57% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.02 (dddd, *J* = 16.2, 11.1, 7.2, 7.2 Hz, 1H), 4.95 (app. ddd, *J* = 15.9, 1.8, 1.8 Hz, 1H), 4.95 (app. ddd, *J* = 11.1, 1.2, 1.2 Hz, 1H), 4.85 (app. ddd, *J* = 4.2, 2.4, 1.5 Hz, 1H), 4.78-4.71 (m, 1H), 3.98-3.84 (comp. m, 4H), 2.43-2.17 (comp. m, 4H), 1.82 (s, 3H), 1.67-1.40 (comp. m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 136.9, 114.9, 114.8, 112.9, 64.4, 64.1, 45.0, 39.4, 38.1, 33.1, 30.5, 25.6, 23.4, 20.7; IR (Neat Film NaCl) 3073, 2936, 2882, 1638, 1452,

11374, 1275, 1215, 1173, 1089, 1060, 1026, 957, 892 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{15}H_{24}O_2$ $[M]^+$: 236.1776, found 236.1779; $[\alpha]_D^{26.7}$ +5.0 (*c* 2.71, CH_2Cl_2, 91% ee).

Spiro[5.5]ketone 405. Through a cooled (-78 °C) solution of ketal **404** (441 mg, 1.86 mmol, 1.00 equiv) in CH_2Cl_2 (40 mL) was bubbled a stream of ozone until the reaction mixture turned blue. The reaction mixture was quenched with dimethyl sulfide (0.50 mL), allowed to warm to ambient temperature, and concentrated to an oil. This residue was dissolved in EtOH (35 mL), treated with an ethanolic KOH solution (3.0 mL of 50 mg/mL), and heated to 75 °C for 3 h. The reaction mixture was cooled to ambient temperature, neutralized with acetic acid, concentrated, and purified by flash chromatography (5→25% EtOAc in hexanes on SiO_2) to give spiro[5.5]ketone **305** (65.7 mg, 16% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 6.84 (ddd, *J* = 10.2, 5.7, 2.7 Hz, 1H), 5.98 (app. dd, *J* = 9.9, 3.0 Hz, 1H), 4.02-3.87 (comp. m, 4H), 2.66 (ddd, *J* = 19.2, 2.7, 2.7 Hz, 1H), 2.64 (d, *J* = 16.2 Hz, 1H), 2.46 (d, *J* = 15.9 Hz, 1H), 2.33 (ddd, 19.2, 6.0, 1.5 Hz, 1H) 1.68-1.50 (comp. m, 6H), 1.48-1.34 (comp. m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.9, 148.1, 128.5, 111.1, 65.0 (2C), 44.7, 43.3, 31.5, 31.1, 30.1, 23.1, 20.4; IR (Neat Film NaCl) 2935, 2865, 1677, 1448, 1389, 1346, 1253, 1179, 1142, 1101, 1063, 1022, 961, 909, 885, 736 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{13}H_{17}O_3$ $[(M + H) - H_2]^+$: 221.1178, found 221.1185; $[\alpha]_D^{28.1}$ +27.9 (*c* 1.13, CH_2Cl_2, 91% ee).



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Pd(II)(allyl)PHOX•PF_6 salt 356. Prepared using Zehnder's method[32] with (*S*)-*t*-Bu-PHOX, as a mixture of *endo* and *exo* isomers (ca. 60:40 ratio) quantitative yield as a light yellow powder; Mp (EtOH) 152-154 °C (decomp.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (app. ddd, *J* = 7.7, 4.1, 1.1 Hz, 0.6H), 8.24 (app. ddd, *J* = 7.7, 4.4, 1.1 Hz, 0.4H), 7.74-7.42 (comp. m, 8H), 7.39-7.11 (comp. m, 4H), 7.04-6.87 (comp m, 1H), 5.96-5.82 (m, 0.4H), 5.82-5.67 (m, 0.6H), 4.96-4.86 (comp. m, 1H), 4.68 (app. q, *J* = 9.9 Hz, 1H), 4.49 (app. dt, *J* = 11.3, 3.9 Hz, 1H), 4.19 (app. dt, *J* = 10.2, 4.4 Hz, 1H), 4.03 (app. dd, *J* = 14.3, 9.4 Hz, 0.6H), 3.63-3.48 (comp. m, 1H), 3.32 (app. d, *J* = 6.6 Hz, 0.4H), 3.16 (app. d, *J* = 12.7 Hz, 0.4H), 2.77 (app. d, *J* = 12.1 Hz, 0.6H), 0.64 (s, 3.5H), 0.56 (s, 5.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9-164.8 (3 peaks), 134.9, 134.8, 134.0-133.3 (7 peaks), 132.9-132.6 (4 peaks), 132.2-132.1 (3 peaks), 131.8 (app. d, *J* = 2.3 Hz), 130.2-128.8 (13 peaks), 128.5-127.8 (5 peaks), 127.3, 122.4 (app. d, *J* = 6.0 Hz), 122.4, 83.3-79.4 (6 peaks), 69.8, 69.7, 58.6, 54.1, 54.0, 34.3, 25.2; ^{31}P NMR (121 MHz, $CDCl_3$) δ 22.7 (d, *J* = 118.1 Hz), -143.8 (septet, 711.0 Hz); IR (Neat Film from $CDCl_3$, NaCl) 3062, 2964, 2872, 2271, 1971, 1899, 1826, 1621, 1584, 1568, 1482, 1437, 1372, 1315, 1249, 1211, 1145, 1121, 1100, 1060, 1028, 958, 913, 836, 778, 732, 697, 678 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{28}H_{31}ONPPd$ $[M]^+$: 534.1178, found 534.1182; $[\alpha]_D^{27.1}$ +256.6 (*c* 3.72, CH_2Cl_2).

4.8 Notes and Citations

(1) For excellent general reviews on the catalytic enantioselective generation of quaternary stereocenters, see: (a) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363-5367. (b) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591-4597. (c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388-401.

(2) For examples, see: (a) Maruoka, K. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 467-491. (b) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650-1667. (c) Hayashi, U. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S.; Jorgensen, K. A., Eds.; Wiley-VCH: New York, 2002; pp 5-56. (d) Evans, D. A.; Johnson, J. S. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 3, pp 1177-1235. (e) Ryu, D. U.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388-6390. (f) Evans, D. A.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10162-10163.

(3) For examples, see: (a) Donde, Y.; Overman, L. E. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 675-697. (b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945-2963. (c) Sato, Y.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 4738-4739. (d) Carpenter, N. E.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5845-5848.

(4) For examples, see: (a) Pfaltz, A. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 2, pp 513-538. (b) Lydon, K. M.; McKervey, M. A. In *Comprehensive Asymmetric*

Catalysis; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 2, pp 539-580. (c) Charette, A. B.; Lebel, H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 2, pp 581-603. (d) Doyle, M. P. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 191-228. (e) Denmark, S. E.; O'Connor, S. P. *J. Org. Chem.* **1997**, *62*, 584-594.

(5) For examples, see: (a) Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 62-63. (b) Bhattacharya, A.; Dolling, U.-H.; Grabowski, E. J. J.; Karady, S.; Ryan, K. M.; Weinstock, L. *Angew. Chem., Int. Ed.* **1986**, *25*, 476-477. (c) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187-2209.

(6) For examples, see: (a) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985-3012. (b) Mermerian, A. H.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 4050-4051. (c) Hills, I. D.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3921-3924. (d) Shaw, S. A.; Aleman, P.; Vedejs, E. *J. Am. Chem. Soc.* **2003**, *125*, 13368-13369. (e) Buono, G.; Chiodi, O.; Wills, M. *Synlett* **1999**, 377-388.

(7) For examples, see: (a) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861-2903. (b) Wu, M. H.; Hansen, K. B.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2012-2014. (c) Watanabe, N.; Ogawa, T.; Ohtake, Y.; Ikegami, S.; Hashimoto, S. *Synlett* **1996**, 85-86. (d) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615-1621.

(8) (a) Trost, B. M.; Lee, C. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; 593-649. (b) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H.,

Eds.; Springer: New York, 1999; Vol. 2, 833-884. (c) Helmchen, G. *J. Organomet. Chem.* **1999**, *576*, 203-214. (d) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1-14. (e) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395-422. (f) Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355-364. (g) Trost, B. M. *J. Org Chem.* **2004**, *69*, 5813-5837.

(9) (a) Steinhagen, H.; Regglin, M.; Helmchen, G. *Angew. Chem., Int. Ed.* **1997**, *36*, 2108-2110. (b) Helmchen, G.; Steinhagen, H.; Reggelin, M.; Kudis, S. In *Selective Reactions of Metal-Activated Molecules*; Werner, H., Schreier, P., Eds.; Vieweg Verlag: Wiesbaden, 1998; 205-215.

(10) While palladium often produces the linear product, other transition metals tend to produce the more branched products in allylic allylation, see: (a) Graening, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 17192-17193. (b) Trost, B. M.; Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104-1105. (c) Glorius, F.; Pfaltz, A. *Org. Lett.* **1999**, *1*, 141-144. (d) Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581-5582. (e) Lloyd-Jones, G. C.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1995**, *34*, 462-464.

(11) Hayashi, T.; Kanehira, K.; Hagihara, T.; Kumada, M. *J. Org. Chem.* **1988**, *53*, 113-120.

(12) (a) Sawamura, M.; Nagata, H.; Sakamoto, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2586-2592. (b) Kuwano, R.; Ito, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3236-3237. (c) Kuwano, R.; Uchida, K.; Ito, Y. *Org. Lett.* **2003**, *5*, 2177-2179.

(13) (a) Trost, B. M.; Schroeder, G .M.; Kristensen, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3492-3495. (b) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*,

6759-6760. (c) Trost, B. M.; Radinov, R.; Grenzer, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 7879-7880.

(14) (a) Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 1793-1796. (b) Shimizu, I.; Yamada, T.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 3199-3202.

(15) (a) Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 4713-4714. (b) Tsuji, J.; Minami, I.; Shimizu, I. *Chem. Lett.* **1983**, 1325-1326.

(16) For examples of Tsuji enol-carbonate allylations in synthesis, see: (a) Ohmori, N. *J. Chem. Soc., Perkin Trans. 1* **2002**, 755-767. (b) Nicolaou, K. C.; Vassilikogiannakis, G.; Mägerlein, W.; Kranich, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2482-2486. (c) Herrinton, P. M.; Klotz, K. L.; Hartley, W. M. *J. Org. Chem.* **1993**, *58*, 678-682.

(17) Treatment of allyl enol carbonate **274** with $Pd_2(dba)_3$ in 1,4-dioxane gave no reaction after 24 h.

(18) (a) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000,** *33*, 336-345. (b) Williams, J. M. J. *Synlett* **1996**, 705-710, and references therein. (c) Peer, M.; de Jong, J. C.; Kiefer, M.; Langer, T.; Rieck, H.; Schell, H.; Sennhenn, P.; Sprinz, J.; Steinhagen, H.; Wiesse, B.; Helmchen, G. *Tetrahedron* **1996**, *52*, 7547-7583.

(19) THF also offered practical advantages of being easier to obtain pure and dry than 1,4-dioxane. THF also simplified the isolation of volatile ketones like **275**.

(20) ^{31}P NMR of (*S*)-*t*-Bu-PHOX oxide **295** shows a peak at 27.2 ppm in THF very similar to the peak seen at 27.7 ppm in THF for reactions when air has been introduced. Non-ligated (*S*)-*t*-Bu-PHOX has a ^{31}P resonance at -5.8 ppm in THF

while what we believe to be the active Pd complex is observed at 31.1 ppm during the reaction.

(21) As a result of our desire to generate a large variety of PHOX ligands, we adapted a procedure for C-P bond formation disclosed by Buchwald and coworkers for the synthesis of PHOX ligands. See experimental section for details. Gelman, D.; Jiang, L.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2315-2318.

(22) Synthesized in analogy to PHOX ligands prepared by Helmchen, see reference 18c.

(23) Wiese, B.; Helmchen, G. *Tetrahedron Lett.* **1998**, *39*, 5727-5730.

(24) Dawson, G.J.; Frost, C. G.; Martin C. J.; Williams, J. M.; Coote, S. J. *Tetrahedron Lett.* **1993**, *34*, 7793-7796.

(25) Smidt, S. P.; Menges, F.; Pfaltz, A. *Org. Lett.* **2004**, *6*, 2023-2026.

(26) Subsequent to our report on the use of allyl enol carbonates in asymmetric allylation, a similar report appeared using a different catalyst system, see: Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846-2847.

(27) Goodwin, N. T. Application of iminium activation technologies to natural product synthesis: Total syntheses of the spiculisporic acids, progress towards the total synthesis of cylindrocyclophane F, and a formal synthesis of cylindrocyclophane A. Ph.D., California Institute of Technology, Pasadena, CA, July 2006.

(28) (a) The recrystallization of semicarbazone derivatives as a means to increase the ee of our products has proved to be of general use with the α-quaternary ketones and their derivatives. For an example, see: (b) McFadden, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 7738-7739.

(29) Allyl fragment is disordered over two conformations in the solid state structure.

(30) While isomerically pure enol carbonates and silyl enol ethers were desired for substrate characterization and to maximize the yield of α-quaternary ketone, it should be noted that this is not required for the allylation reaction. The less substituted enolate precursors are cleanly transformed to 2,6-substituted ketones, which are typically readily removed by chromatography, and has no effect on the ee of the desired product.

(31) Sodium and potassium methoxide (1 equiv) could be used directly as silyl enol ether activators. However, lower yields (14% and 36%, respectively) and slightly lower ee (81% and 80%, respectively) were observed.

(32) For procedure, see: Liu, S.; Müller, J. F. K.; Neuburger, M.; Schaffner, S.; Zehnder, M. *J. Organomet. Chem.* **1997**, *549*, 283-293.

(33) Isomerically pure substrates are required only to achieve the highest yield possible of the desired α-quaternary compounds. The presence of the trisubstituted silyl enol ethers or allyl enol carbonates does not effect the ee of the α-quaternary product. The 2,6-substituted ketones generated from the trisubstituted impurity are typically easily removed by chromatography.

(34) Aliquots taken during the reaction of β-ketoester **358** at 30 °C in THF show the starting material reaches a maximum of 5% ee at 83% conversion for a K_{rel} of 1.1.

(35) Presumably this is the result of the cleavage of a C-C bond during decarboxylation, rather than C-O bond found in carbonates.

(36) For reviews, see: (a) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36-56. (b) Stecher, H.; Faber, K. *Synthesis* **1997**, 1-16. (c) Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J.-E. *Chem. Soc. Rev.* **2001**, *30*, 321-331. (d)

Pellissier, H. *Tetrahedron* **2003**, *59*, 8291-8327. For representative stereomutative examples, see: (d) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 2, pp. 833-884. (e) Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968-5976.

(37) This hypothesis has been experimentally supported for non-enantioselective systems, see: (a) Tsuji, J.; Yamada, T.; Minami, I.; Yuhara, M.; Nisar, M.; Shimizu, I. *J. Org. Chem.* **1987**, *52*, 2988-2995. (b) Detalle, J.-F.; Riahi, A.; Steinmetz, V.; Hénin, F.; Muzart, J. *J. Org. Chem.* **2004**, *69*, 6528-6532.

(38) For representative stereoablative examples, see: (a) Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261-1268. (b) Mase, N.; Tanaka, F.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2004**, *43*, 2420-2423. (c) Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594-4595.

(39) This is an adaptation of a procedure by Tsuji and coworkers, see: (a) Tsuji, J.; Nisar, M.; Shimizu, I,; Minami, I. *Synthesis* **1984**, *12*, 1009. (b) Donnelly, D. M. X.; Finet, J.-P.; Rattigan, B. A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1729-1735.

(40) This procedure is a modification of the acylation procedure reported in: Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425-5428.

(41) While only trace β-elimination was observed with this substrate, substrates with better leaving groups (e.g., OAc) predominantly underwent β-elimination to the α,β unsaturated compounds.

(42) Subsequent to our studies, others have used our method for the synthesis of other fluorinated substrates in related allylation reactions, see: (a) Nakamura, M.; Hajra,

A.; Endo, K.; Nakamura, E. *Angew. Chem., Int. Ed.* **2005**, *44*, 7248-7251. (b) Burger, E. C.; Barron, B. R.; Tunge, J. A. *Synlett* **2006**, 2824-2826.

(43) Fluorinated compounds have gained frequent use in medicinal chemistry, see: (a) Zoute, L.; Audouard, C.; Plaquevent, J.-C.; Cahard, D. *Org. Biomol. Chem.* **2003**, *1*, 1833-1834. (b) Nagai, K.; Davies, T. A.; Dewasse, B. E.; Jacobs, M. R.; Appelbaum, P. C. *J. Antimicrob. Chemother.* **2001**, *48*, 365-374.

(44) Recently thioesters substrates have been demonstrated in similar allylation reactions, see: Trost, B. M.; Bream, R. N.; Xu, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3109-3112.

(45) Boger, D. L. Key Ring Forming Reactions. *Modern Organic Synthesis: Lecture Notes*, TSRI Press: La Jolla, CA, 1999; pp 273-281.

(46) Recently a report of allylic alkylation for the synthesis of acyclic tertiary stereocenters using a different catalyst system has appeared, see: Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 17180-17181.

(47) Under our conditions we found that negligible racemization of phenyl ketone **423** was observed when allowed to remain under the reaction conditions for an additional 12 h.

(48) Yan, X.-X.; Liang, C.-G.; Zhang, Y.; Hong, W.; Cao, B.-X.; Dai, L.-X.; Hou, X.-L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6544-6546.

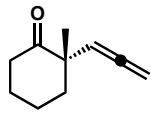
(49) Munoz-Muniz, O.; Quintanar-Audelo, M.; Juaristi, E. *J. Org. Chem.* **2003**, *68*, 1622-1625.

(50) Trimitsis, G.; Beers, S.; Ridella, J.; Carlon, M.; Cullin, D.; High, J.; Brutts, D. J. *Chem. Soc., Chem. Commun.* **1984**, 1088-1089.

(51) Mohr, J. T.; Nishimata, T.; Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 11348-11349.

(52) For examples of propargylation of similar enolates, see: (a) Matsuda, I.; Komori, K.; Itoh, K. *J. Am. Chem. Soc.* **2002**, *124*, 9072-9073. (b) Bienaymé, H. *Tetrahedron Lett.* **1994**, *35*, 7383-7386. (c) Bienaymé, H. *Tetrahedron Lett.* **1994**, *35*, 7387-7390.

(53) In addition to α-propargylated ketone **434**, small amounts of (*S*)-allene **xxxiii** are produced in 56% ee.



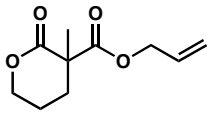
xxxiii

(54) The fine details of the reaction mechanism involving the origin of enantioselectivity are being studied computationally in collaboration with John Keith of the Goddard research group and will be reported in due course.

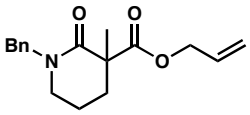
(55) Unusual patterns in enantioselectivity in a different asymmetric allylation system have led other researchers to consider enolate associated allylation mechanisms as well, see: (a) Reference 25. (b) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590-4591.

(56) Varying the concentration of Pd•PHOX gives a proportional decrease in reaction rate, suggesting the reaction is 1st order in Pd•PHOX. This supports the hypothesis that a single metal center is involved in the mechanism.

(57) Substrates which would possess highly basic enolate intermediates, such as lactone **xxxiv** and lactam **xxxv**, have been problematic as decarboxylation has proved difficult.

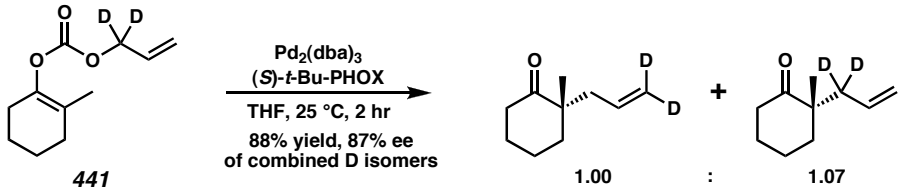


xxxiv



xxxv

(58) A separate reaction with dideuterio allyl enol carbonate **441** confirms that the allyl termini are scrambled during the course of the reaction.



441

(59) While the total ion counts are not rigorously quantitative, they clearly suggest that all four masses are present in nearly equal proportions. The slight excess of the 155 m/z ion is likely due to the natural abundance of ^{13}C present in the dideuterio product.

(60) PF_6^- counterions removed for clarity. Two out of four of the crystallographically unique Pd(allyl)PHOX complexes in the unit cell crystallized with a molecule of ethanol. The endo and exo allyl isomers were present in equal electron density and are modeled as a superposition of the two isomers.

(61) McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M. . *J. Org. Chem.* **1993**, *58*, 3568-3571.

(62) Laue, S.; Greiner, L.; Woelfinger, J.; Andreas, L. *Adv. Syn. Catal.* **2001**, *343*, 711-720.

(63) Neuville, L.; Chastanet, J.; Zhu, J. *Tetrahedron Lett.* **1999**, *40*, 7087-7090.

(64) Aboulhoda, S. J.; Henin, F.; Muzart, J.; Thorey, C. *Tetrahedron Lett.* **1995**, *36*, 4795-4796.

(65) (a) Yu, W.; Jin, Z. *Tetrahedron Lett.* **2001**, *42*, 369-372. (b) Duhamel, P.; Cahard, D.; Quesnel, Y.; Poirier, J.-M. *J. Org. Chem.* **1996**, *61*, 2232-2235. (c) Duhamel, P.; Cahard, D.; Poirier, J.-M. *Chem. Soc., Perkin Trans. 1* **1993**, 2509-2511.

(66) Slomczynska, U.; Kaminski, Z. J.; Leplawy, M. T. *Bull. Pol. Acad. Sci. Chem.* **1991**, *39*, 85-88.

(67) Dua, S.; Taylor, M. S.; Buntine, M. A.; Bowie, J. H.; *J. Chem. Soc. Perkin Trans. 2* **1997**, 1991-1997.

(68) House, H. O.; Roelofs, W. L.; Trost, B. M. *J. Org. Chem.* **1966**, *31*, 646-655.

(69) (a) Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dungogues, J. *Tetrahedron* **1987**, *43*, 2075-2088. (b) Larock, R. C.; Hightower, T. R.; Kraus, G. A.; Hahn, P.; Zheng, D. *Tetrahedron Lett.* **1995**, *36*, 2423-2426.

(70) Smith, A. B.; Cho, Y. S.; Friestad, G. K. *Tetrahedron Lett.* **1998**, *39*, 8765-8768.

(71) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783-3784.

(72) Buono, F.; Tenaglia, A. *J. Org. Chem.* **2000**, *65*, 3869-3874.

APPENDIX SEVEN

Spectra of Compounds Relevant to Chapter Four

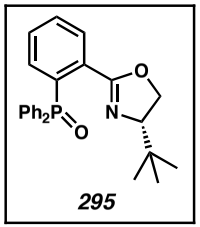


Figure A7.1 ^{1}H NMR of compound **295** (300 MHz, $CDCl_3$)

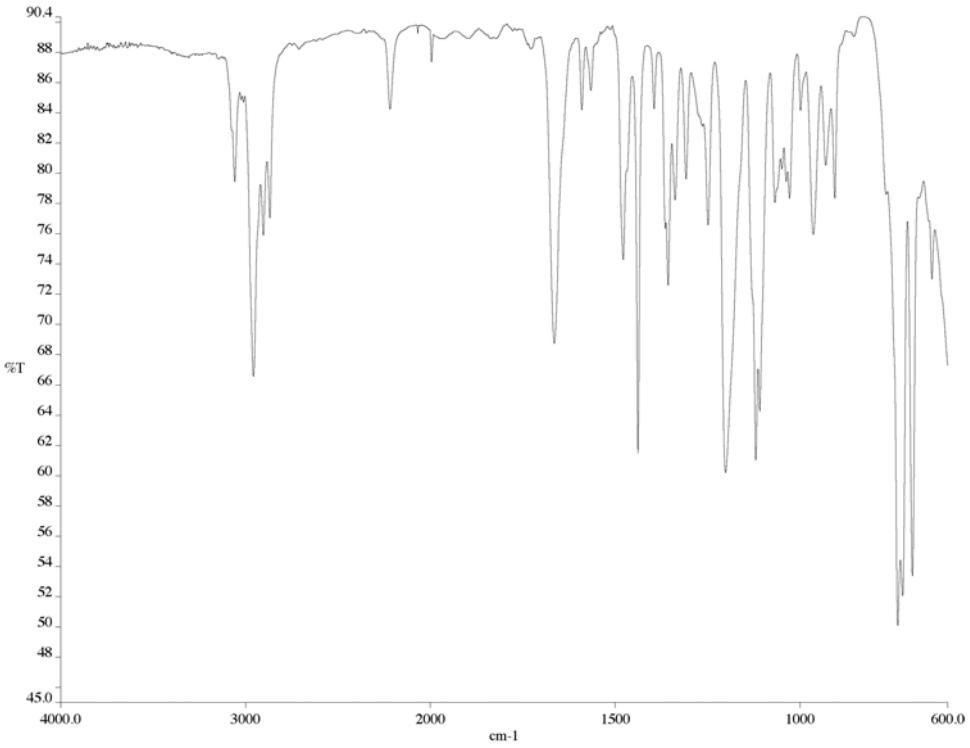


Figure A7.2 IR of compound **295** (NaCl/film)

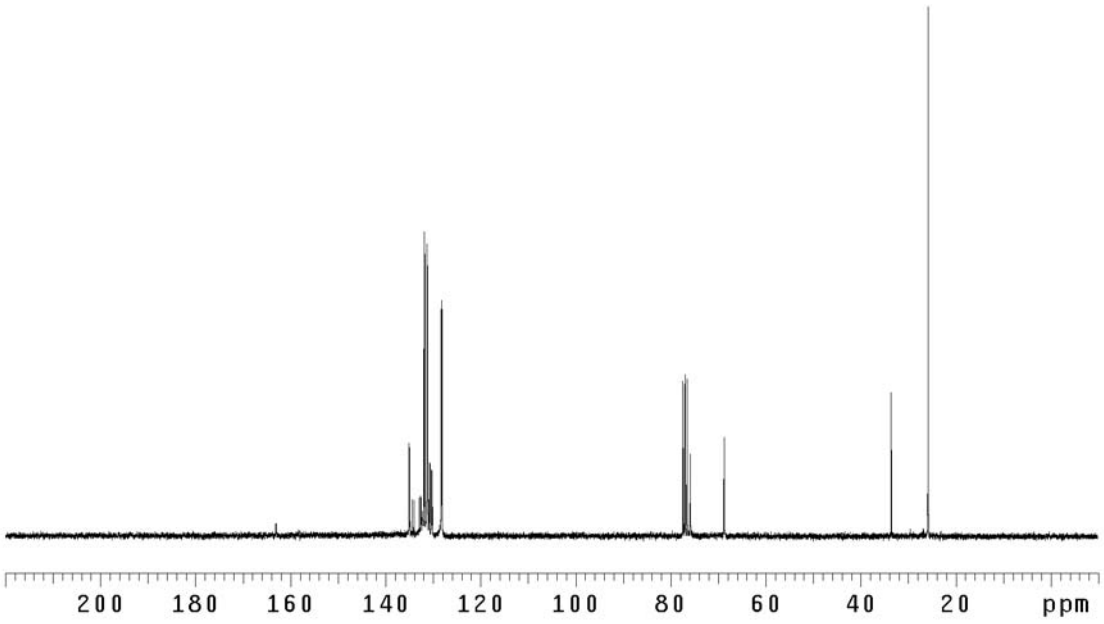


Figure A7.3 ^{13}C NMR of compound **295** (75 MHz, $CDCl_3$)

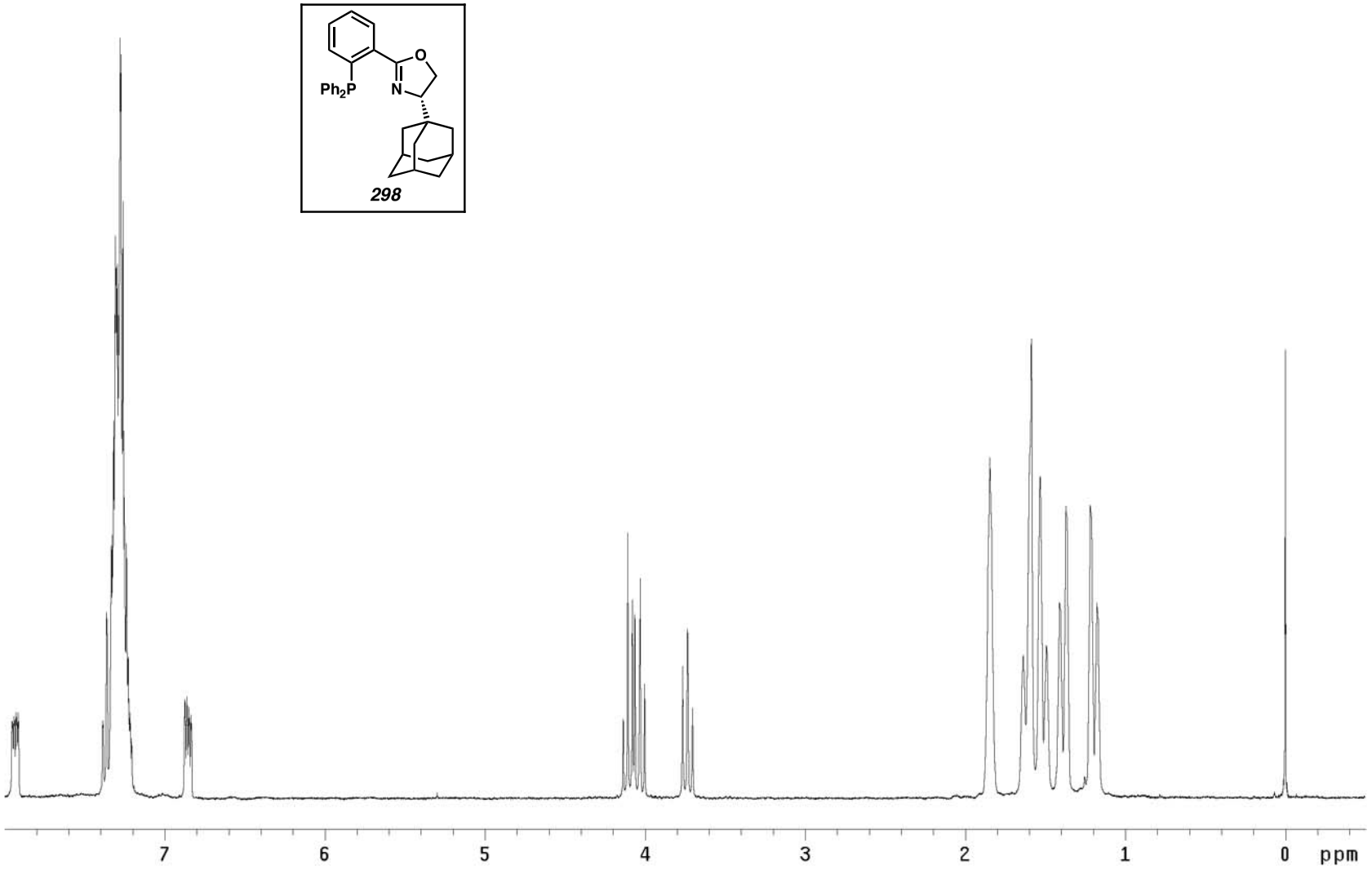


Figure A7.4 ^{1}H NMR of compound **298** (300 MHz, $CDCl_3$)

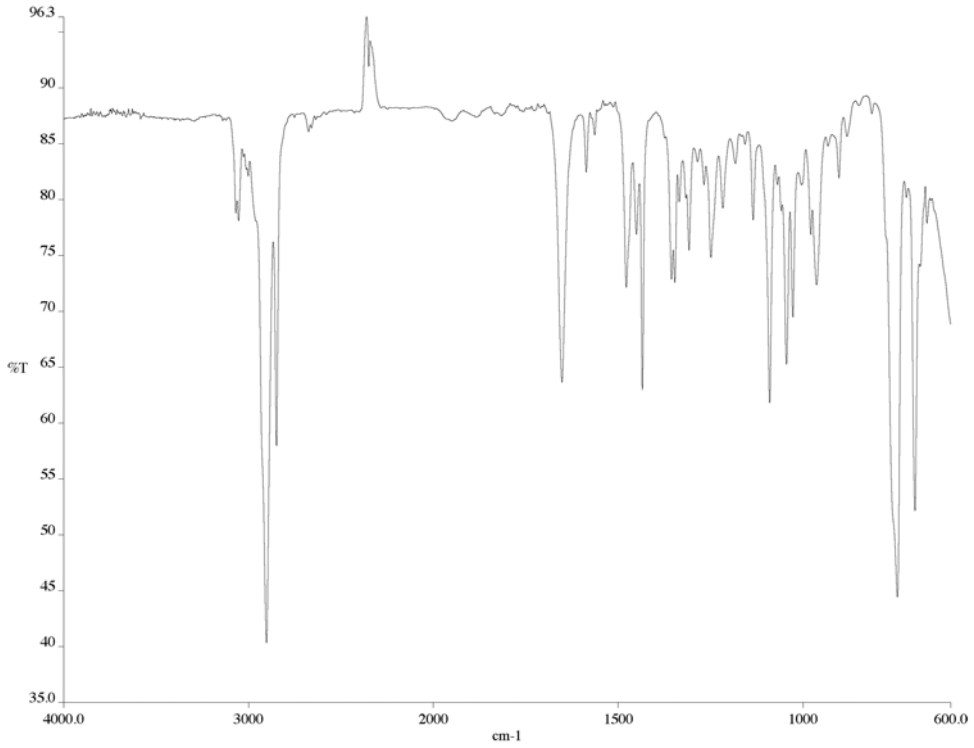


Figure A7.5 IR of compound **298** (NaCl/film)

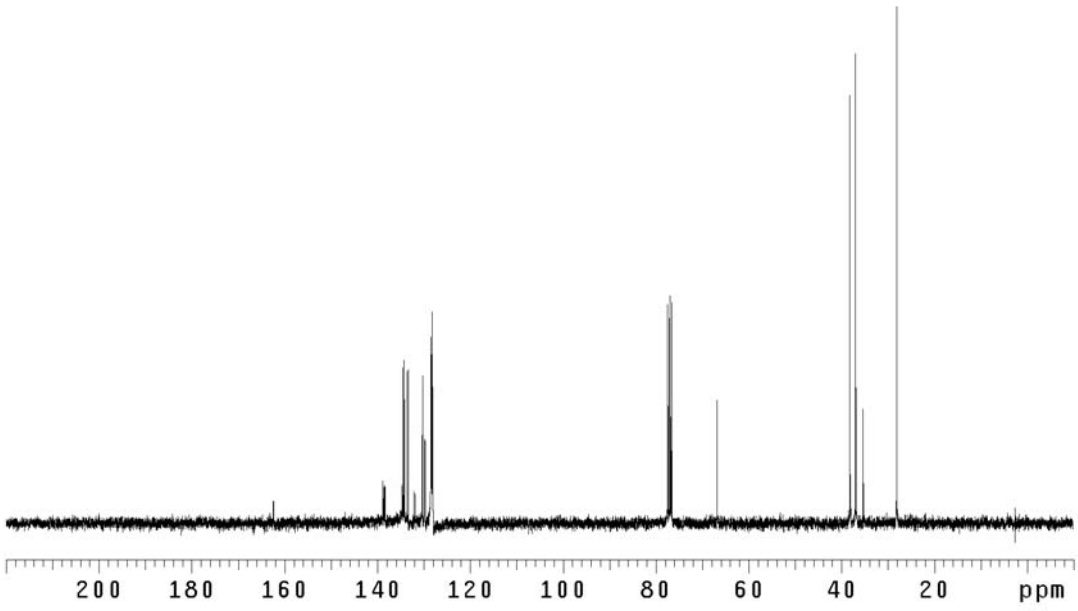


Figure A7.6 ^{13}C NMR of compound **298** (75 MHz, $CDCl_3$)

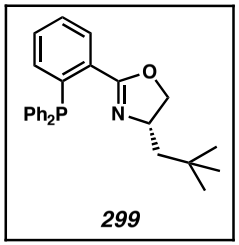


Figure A7.7 ^{1}H NMR of compound **299** (300 MHz, $CDCl_3$)

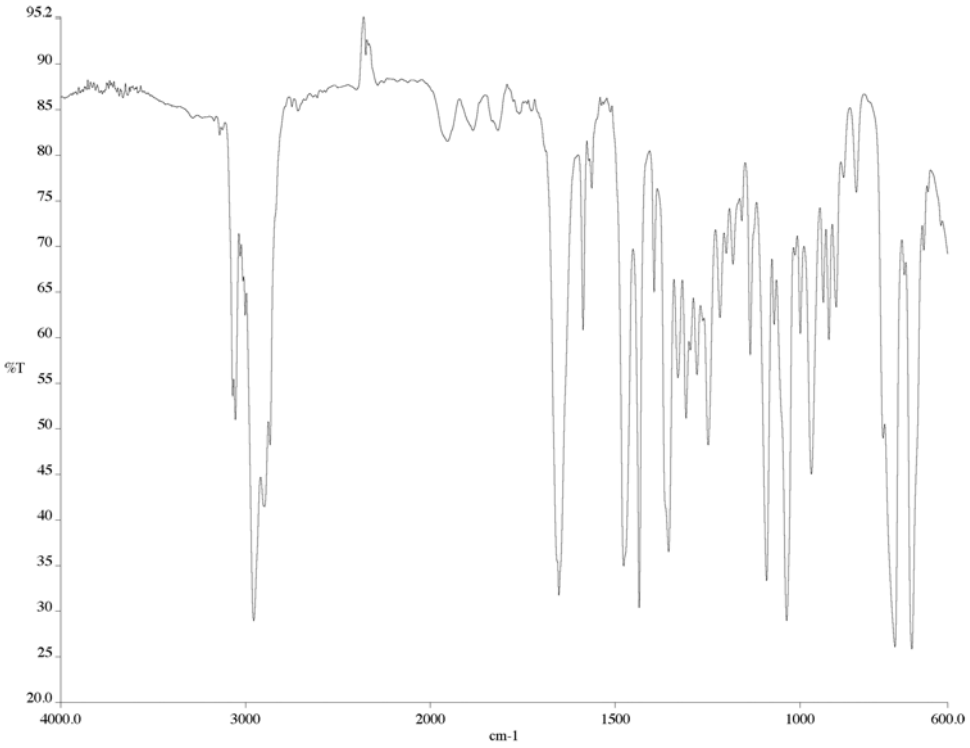


Figure A7.8 IR of compound **299** (NaCl/film)

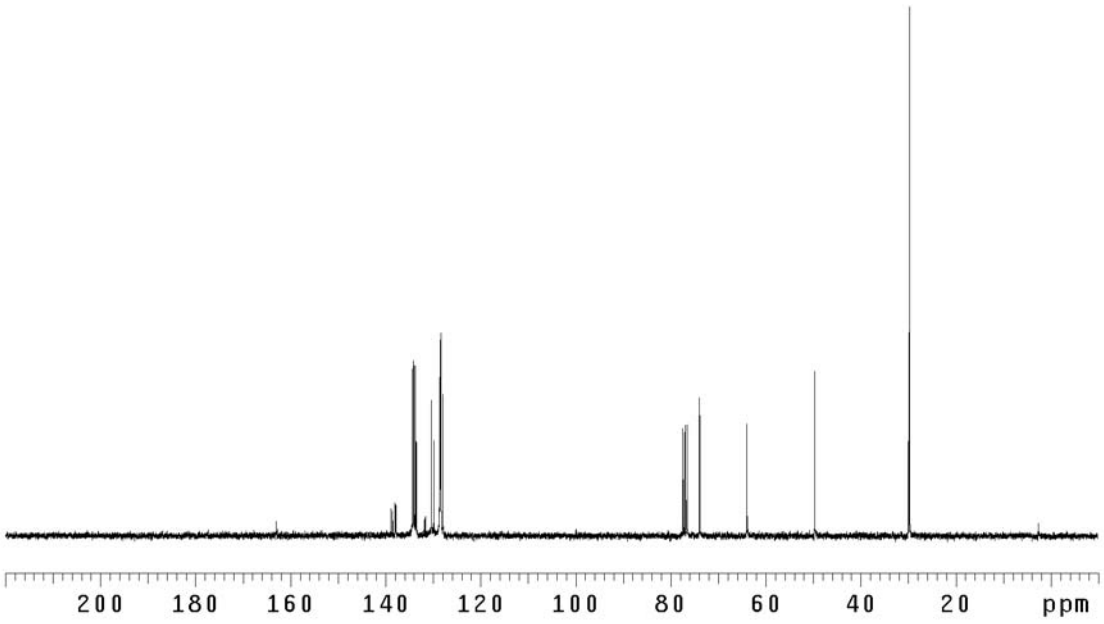


Figure A7.9 ^{13}C NMR of compound **299** (75 MHz, $CDCl_3$)

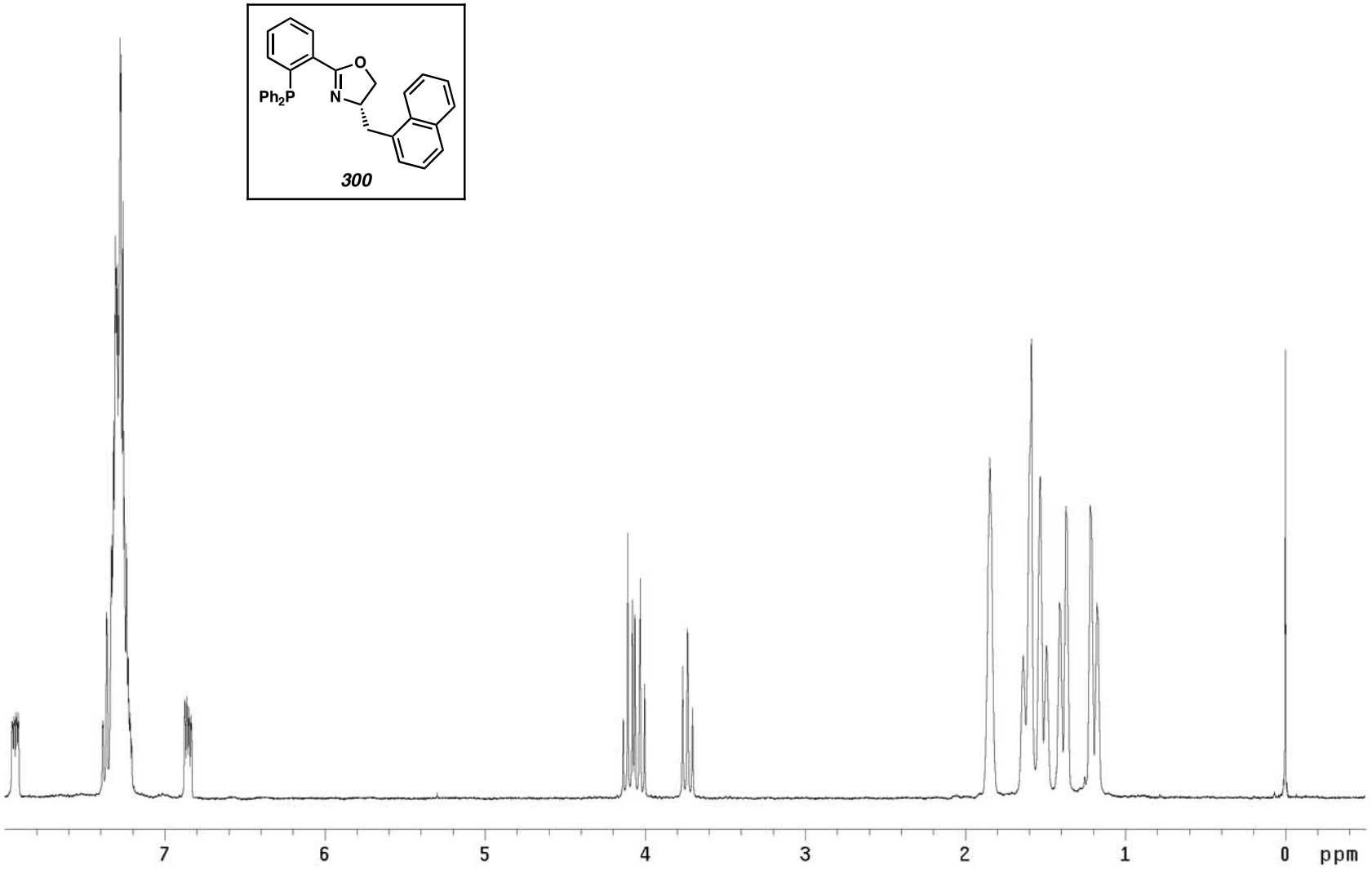


Figure A7.10 ^{1}H NMR of compound **300** (300 MHz, $CDCl_3$)

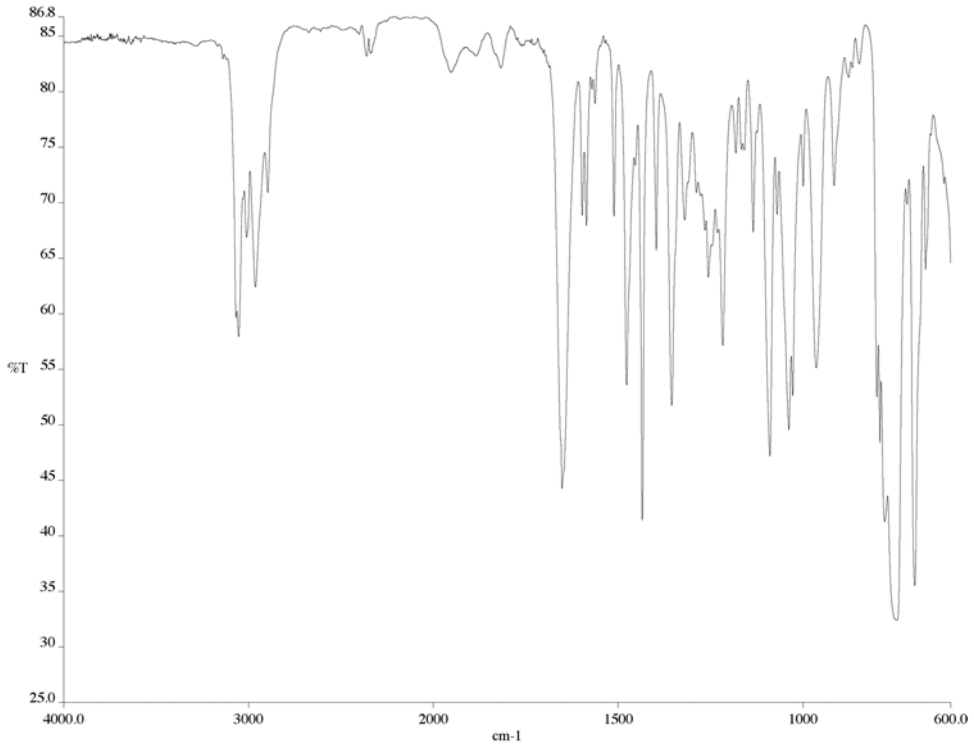


Figure A7.11 IR of compound **300** (NaCl/film)

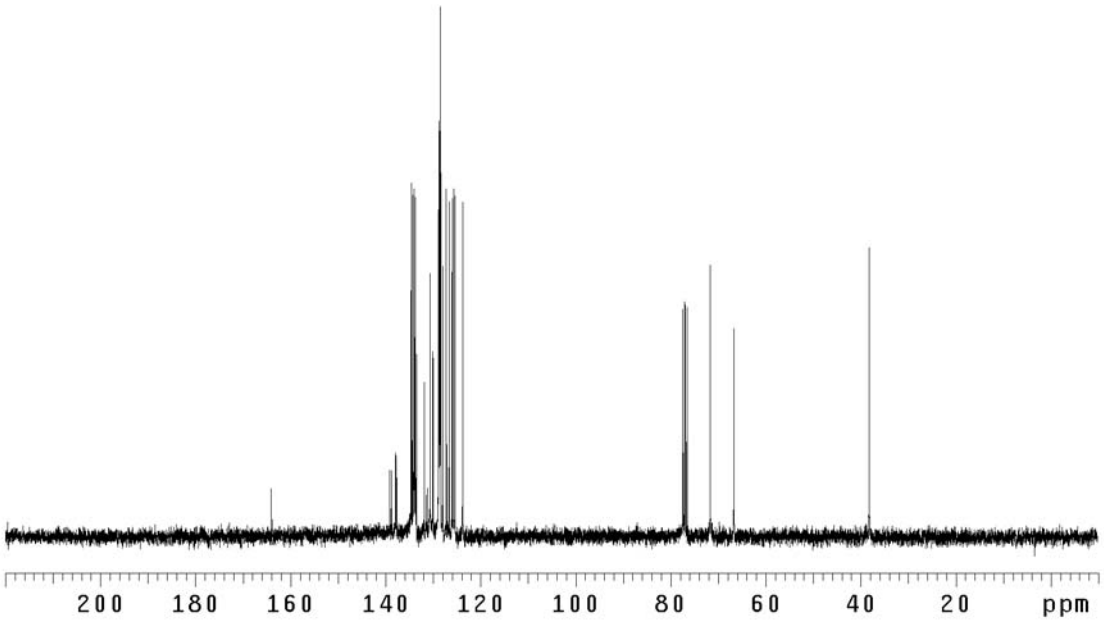


Figure A7.12 ^{13}C NMR of compound **300** (75 MHz, $CDCl_3$)

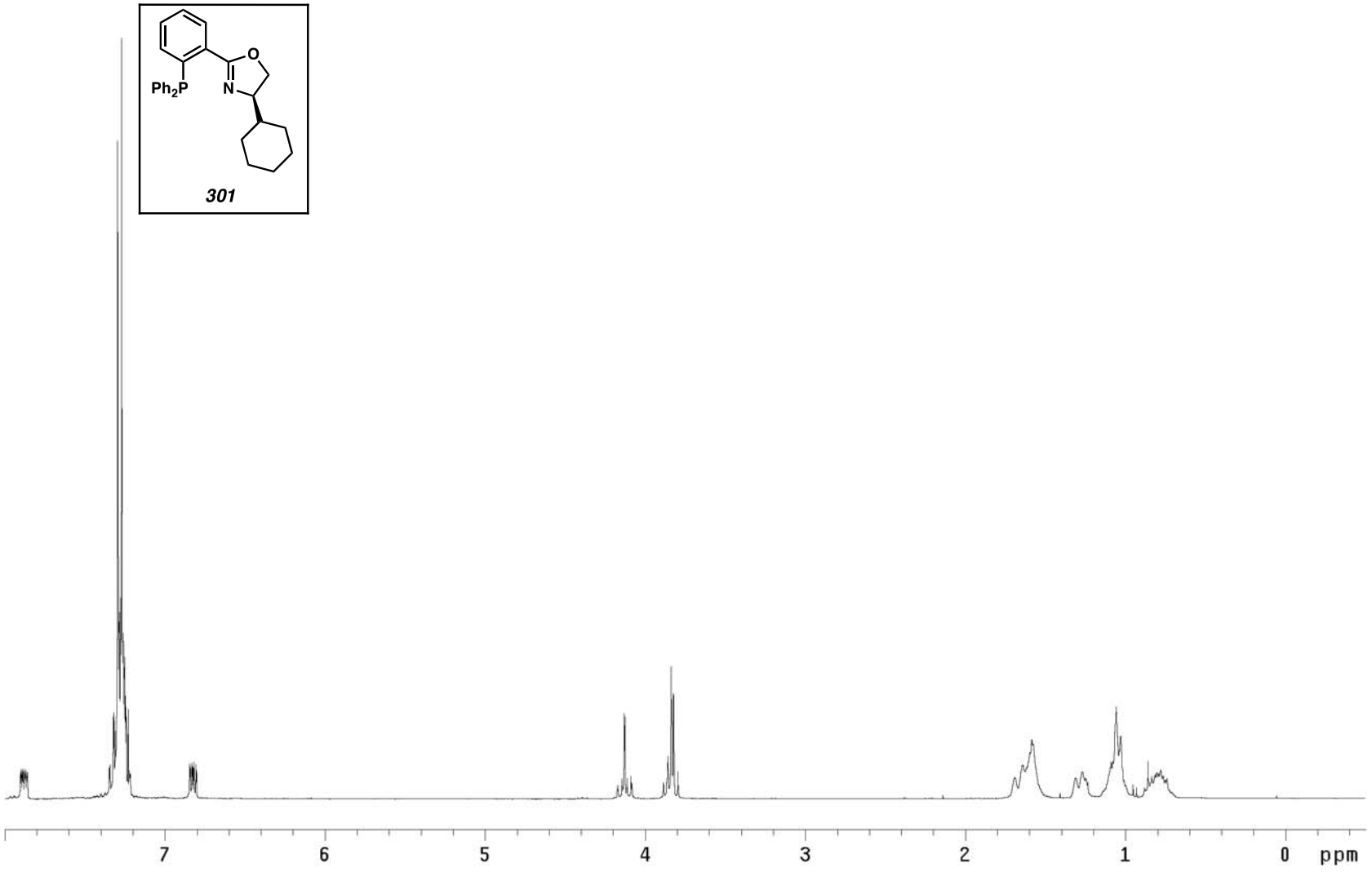


Figure A7.13 ^{1}H NMR of compound **301** (300 MHz, $CDCl_3$)

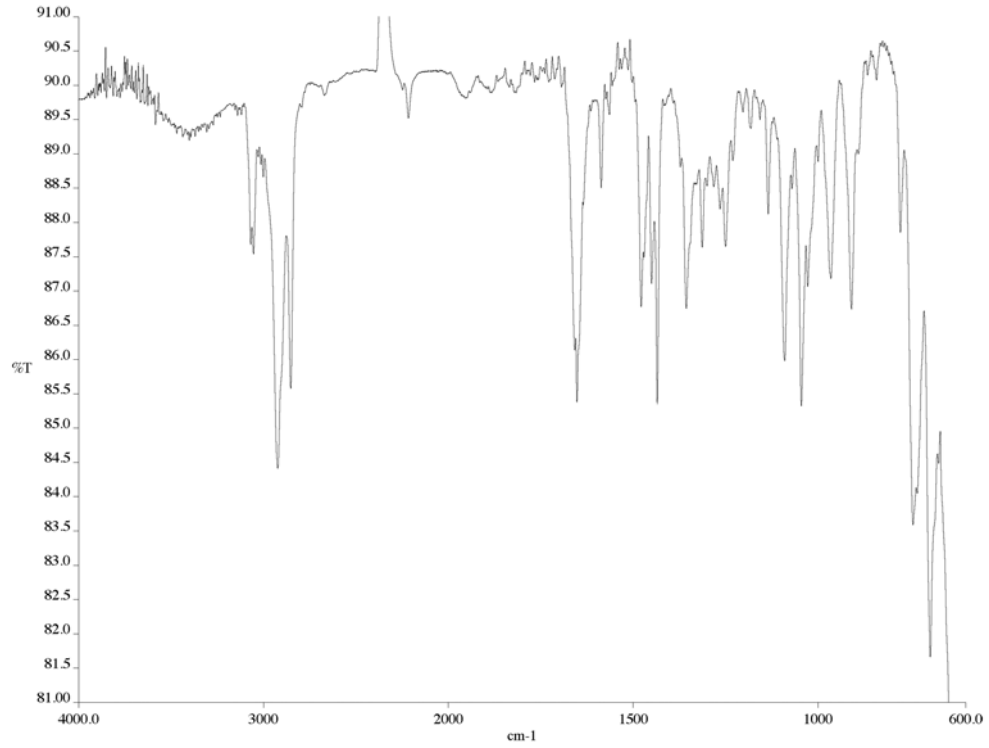


Figure A7.14 IR of compound **301** (NaCl/film)

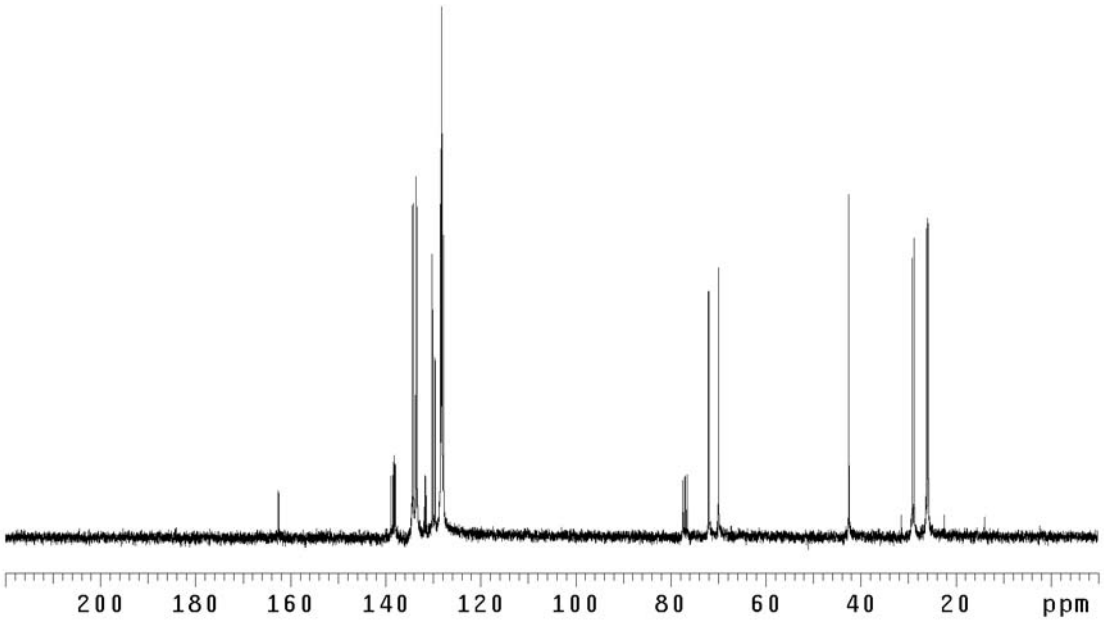


Figure A7.15 ^{13}C NMR of compound **301** (75 MHz, $CDCl_3$)

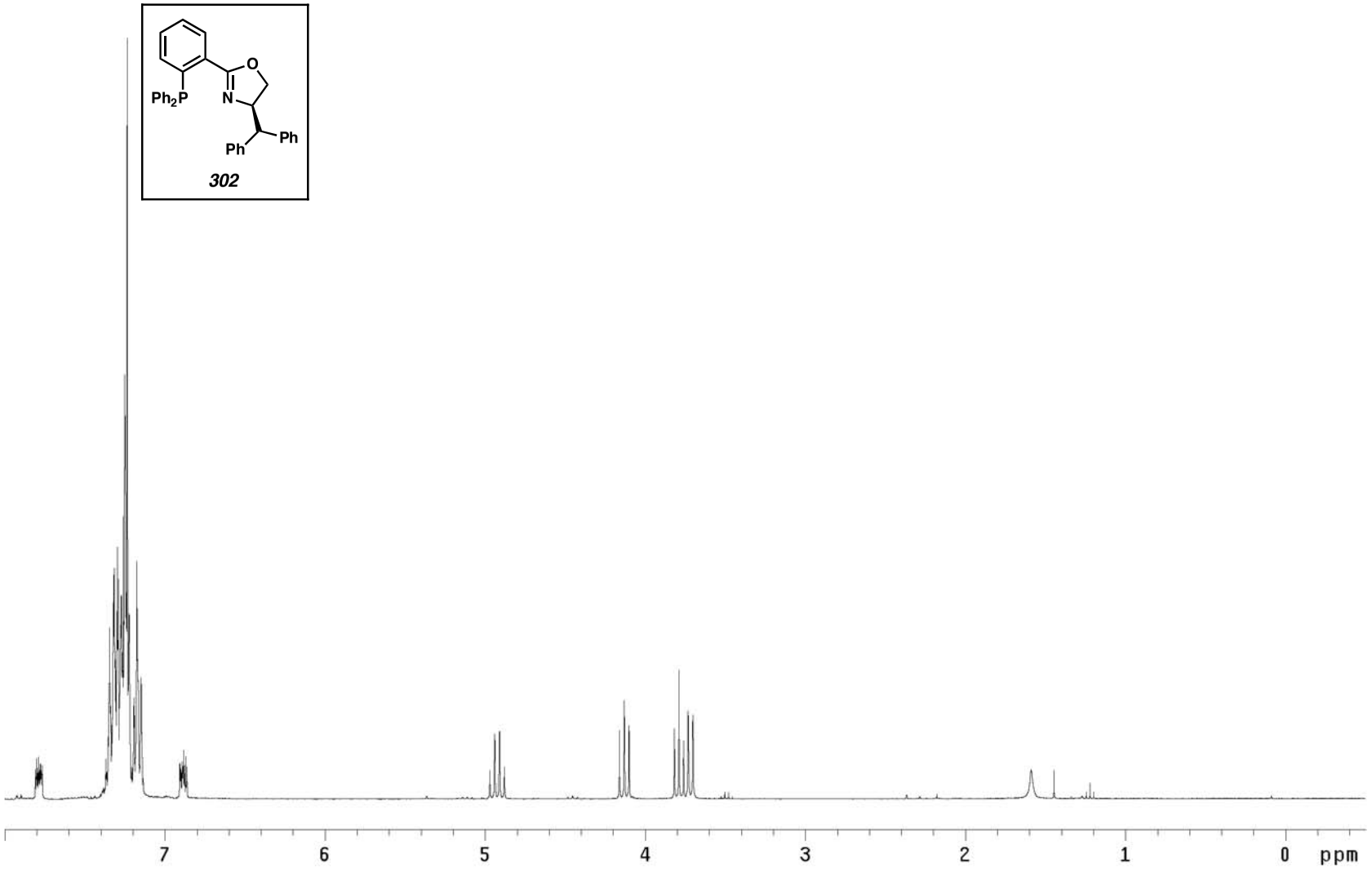


Figure A7.16 ^{1}H NMR of compound **302** (300 MHz, $CDCl_3$)

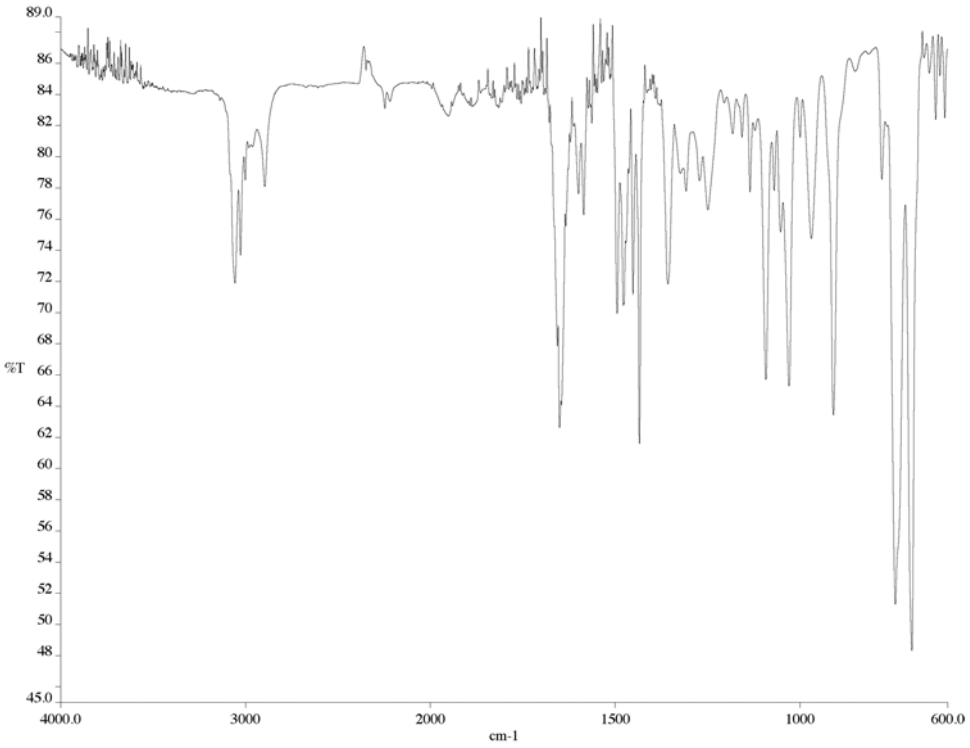


Figure A7.17 IR of compound **302** (NaCl/film)

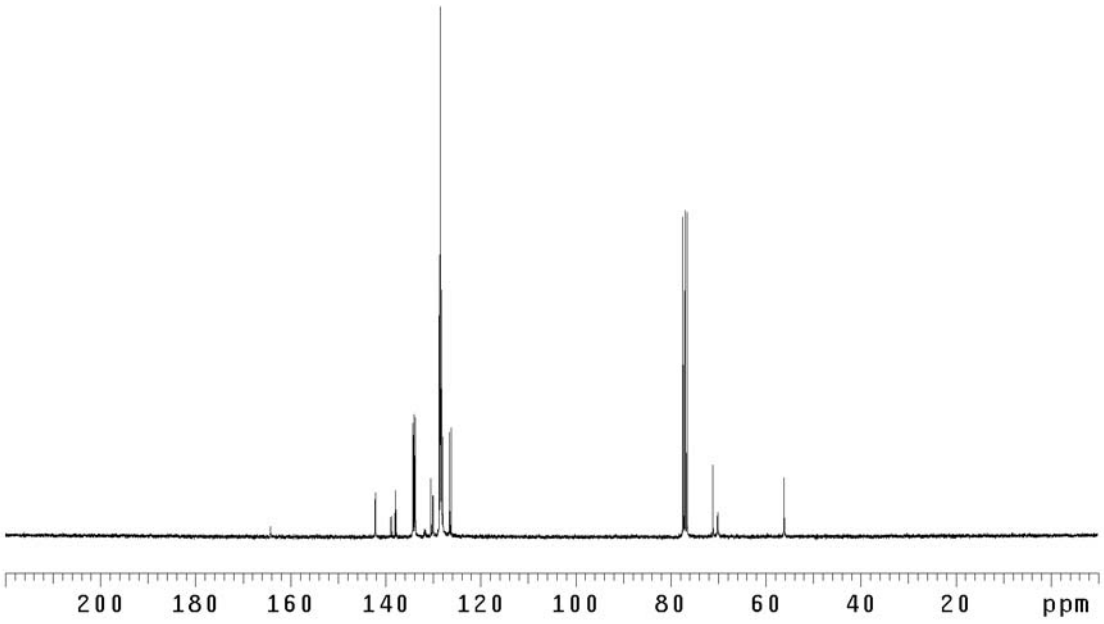


Figure A7.18 ^{13}C NMR of compound **302** (75 MHz, $CDCl_3$)

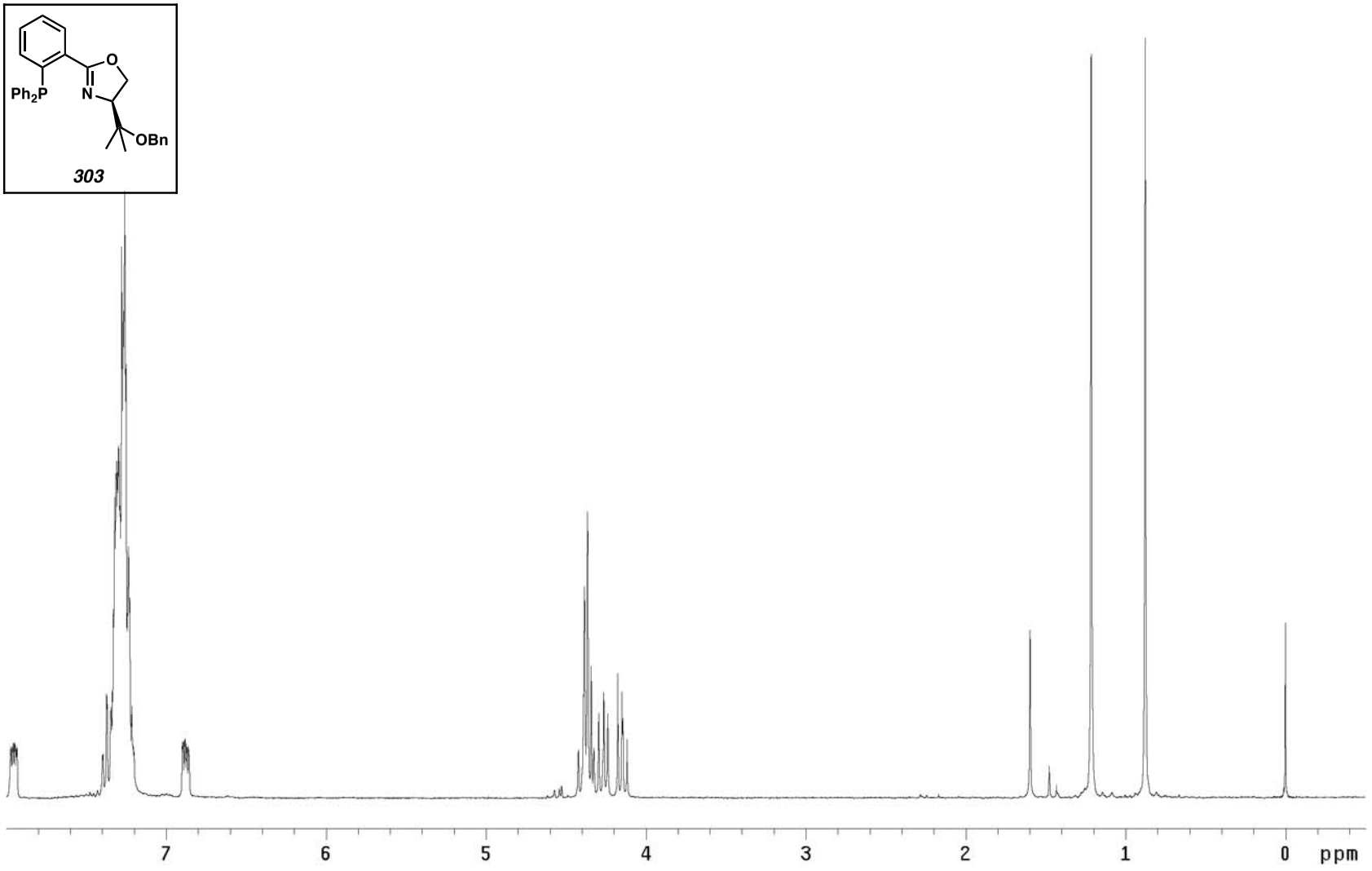


Figure A7.19 ^{1}H NMR of compound **303** (300 MHz, $CDCl_3$)

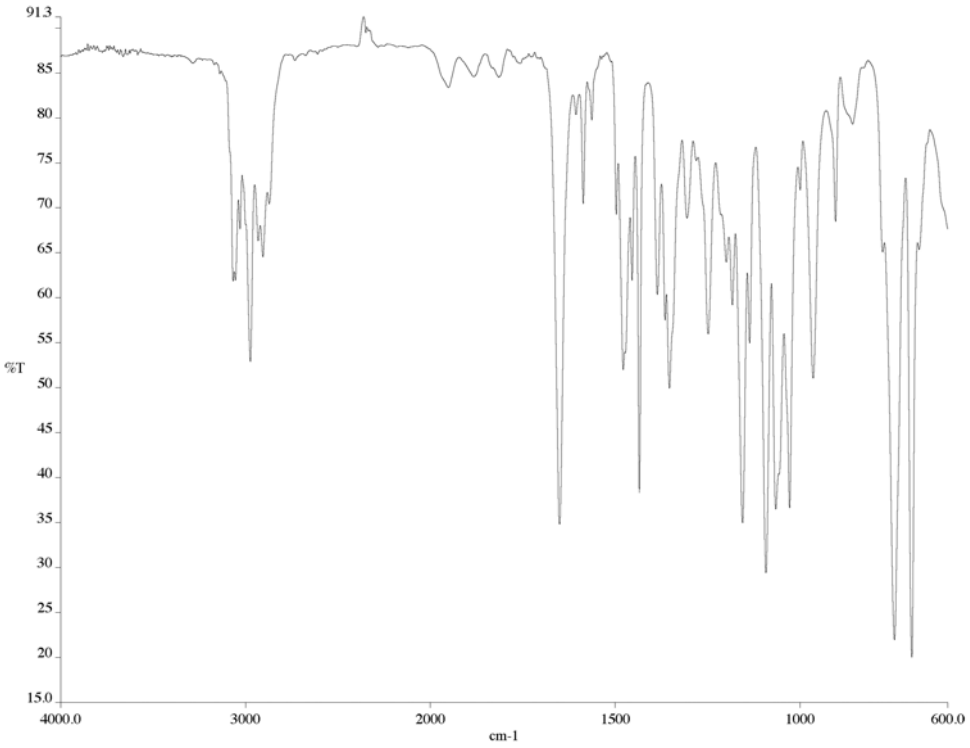


Figure A7.20 IR of compound **303** (NaCl/film)

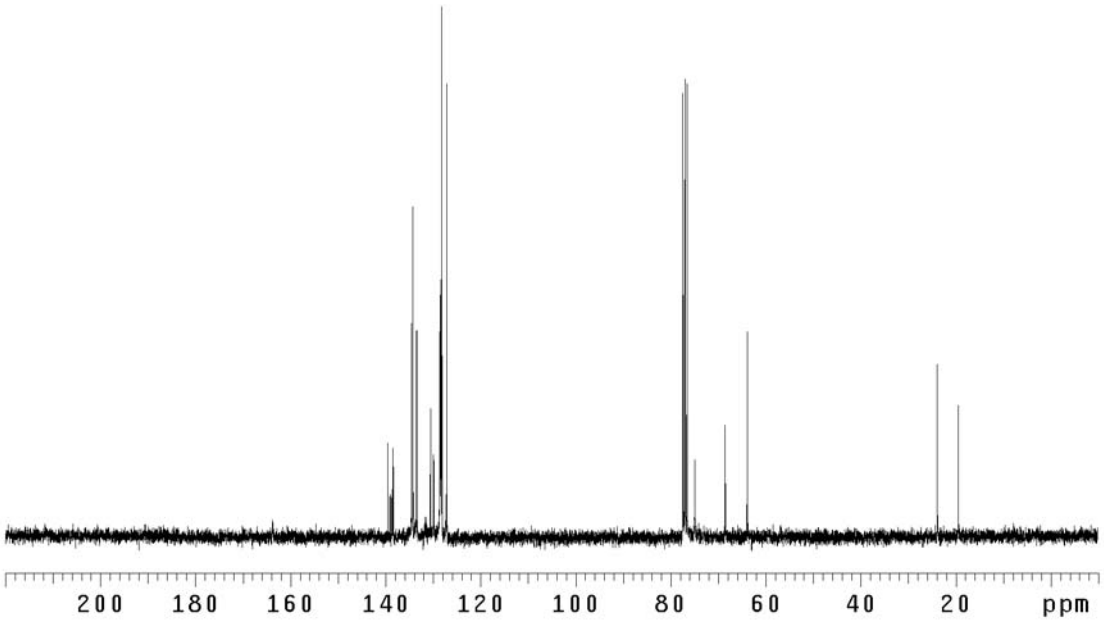
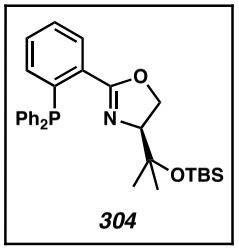


Figure A7.21 ^{13}C NMR of compound **303** (75 MHz, $CDCl_3$)



304

Figure A7.22 ^{1}H NMR of compound **304** (300 MHz, $CDCl_3$)

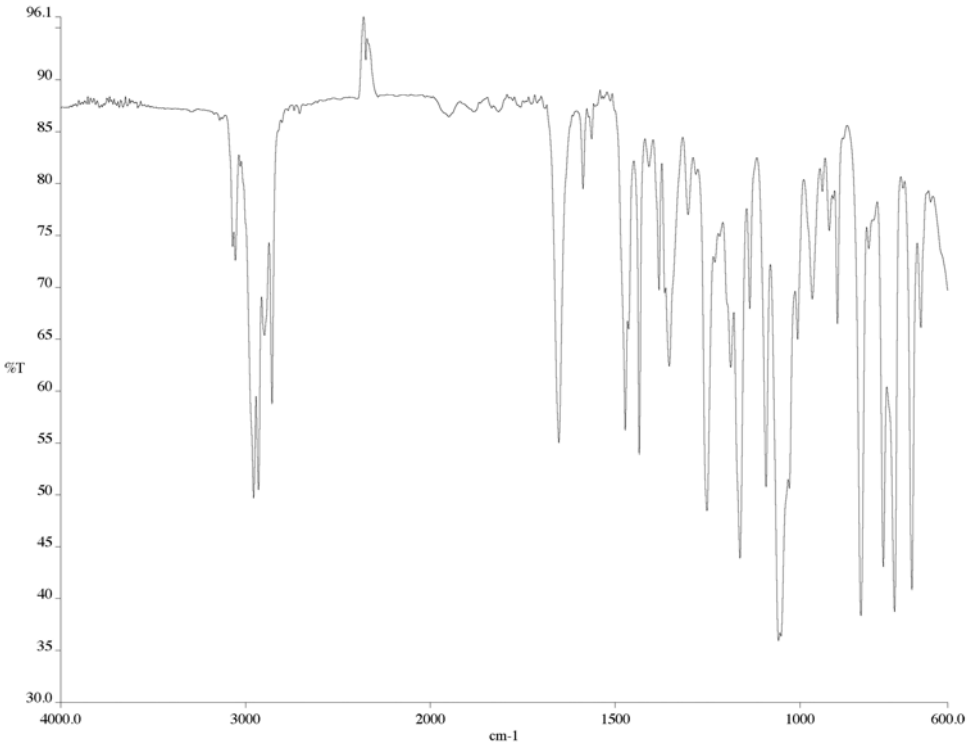


Figure A7.23 IR of compound **304** (NaCl/film)

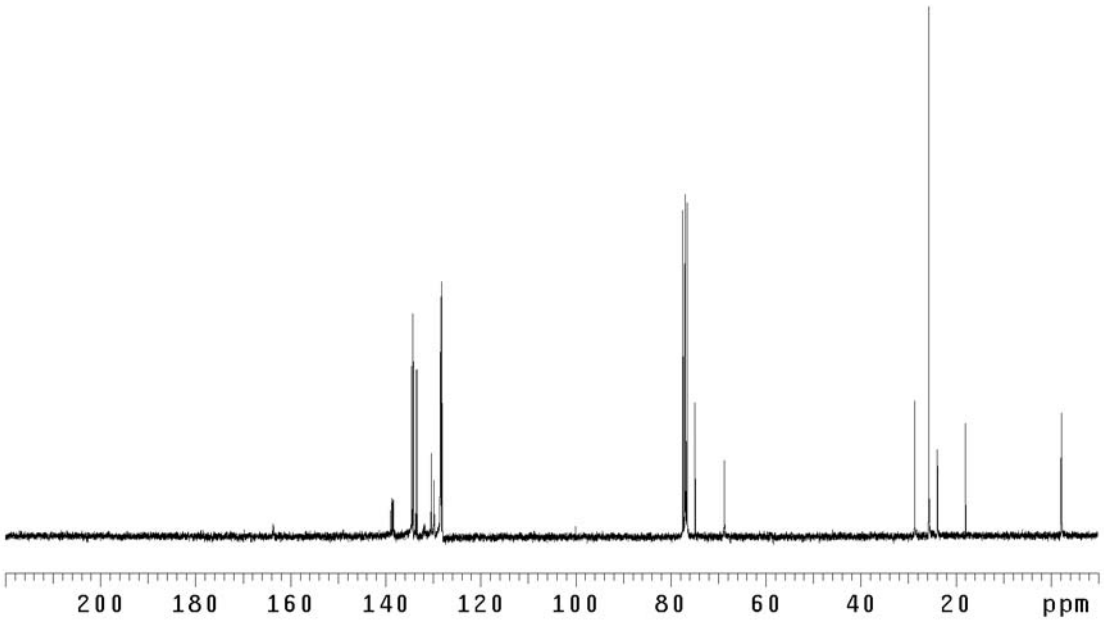


Figure A7.24 ^{13}C NMR of compound **304** (75 MHz, $CDCl_3$)

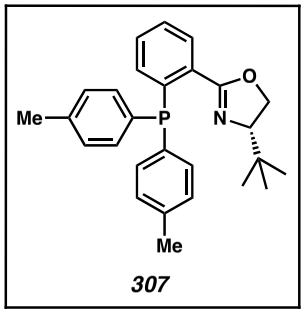


Figure A7.25 ^{1}H NMR of compound **307** (300 MHz, $CDCl_3$)

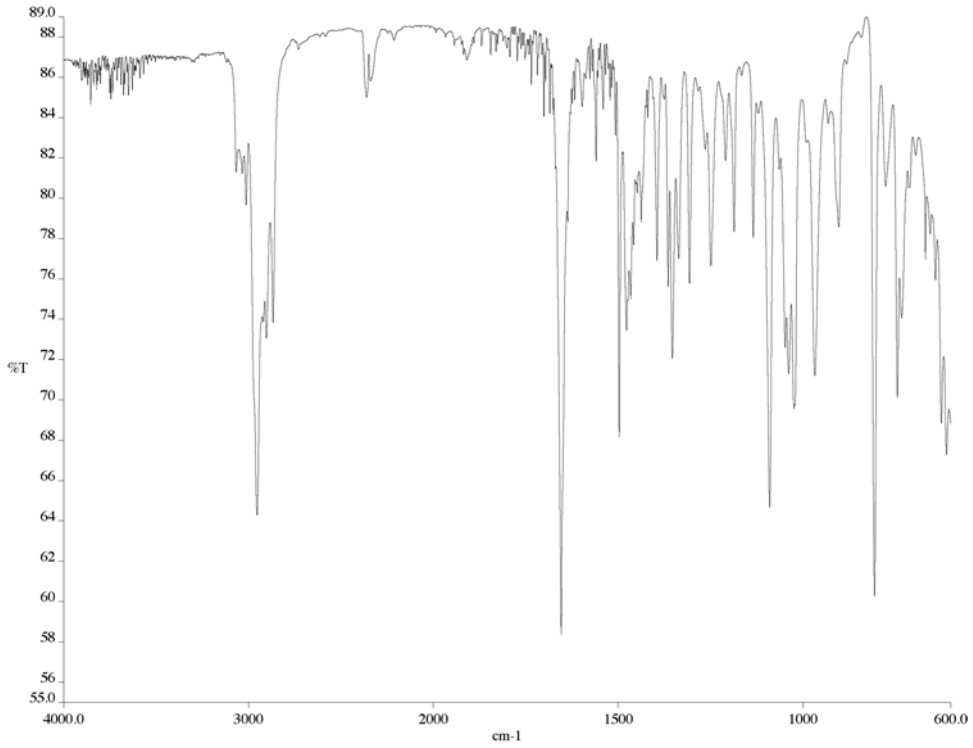


Figure A7.26 IR of compound **307** (NaCl/film)

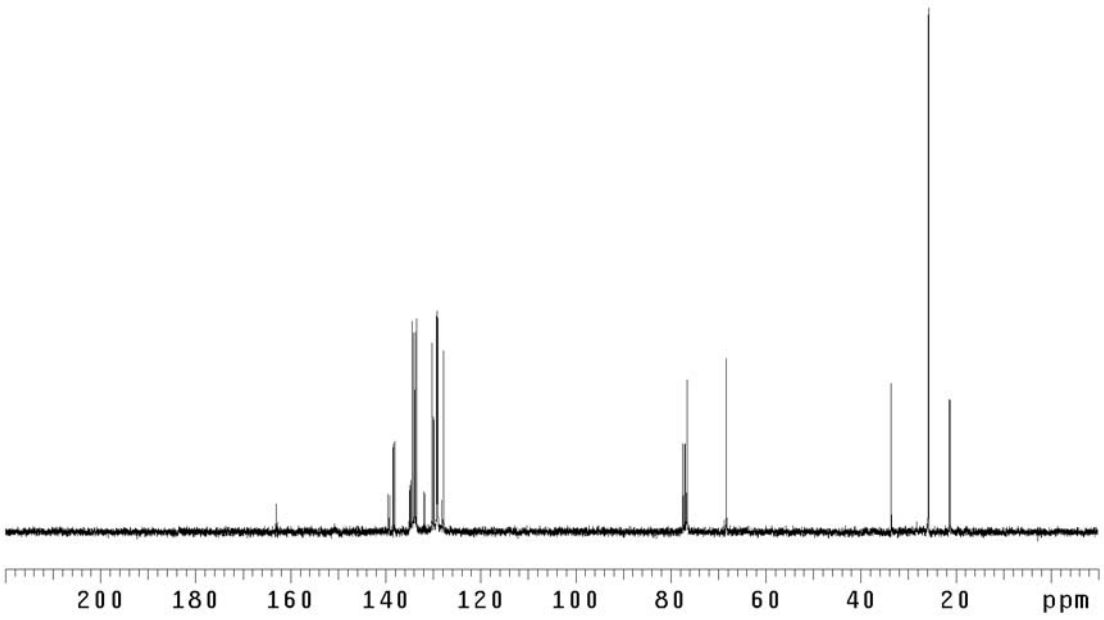


Figure A7.27 ^{13}C NMR of compound **307** (75 MHz, $CDCl_3$)

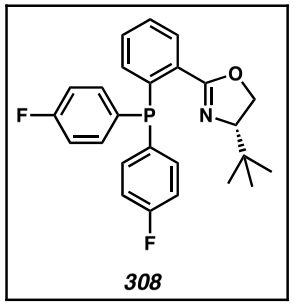


Figure A7.28 ^{1}H NMR of compound **308** (500 MHz, $CDCl_3$)

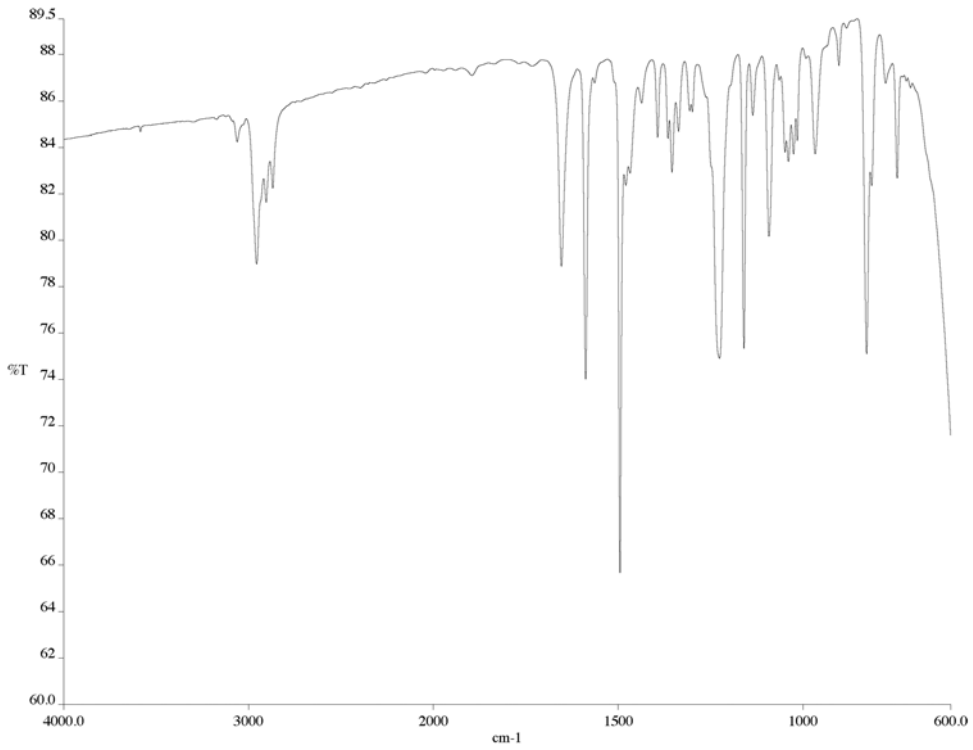


Figure A7.29 IR of compound **308** (NaCl/film)

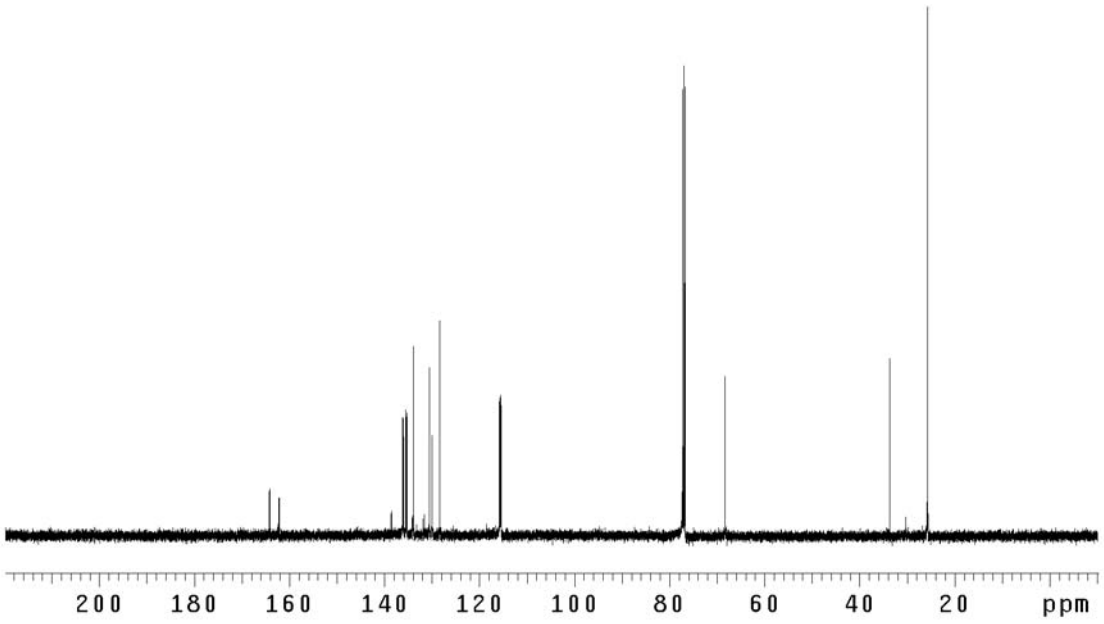


Figure A7.30 ^{13}C NMR of compound **308** (125 MHz, $CDCl_3$)

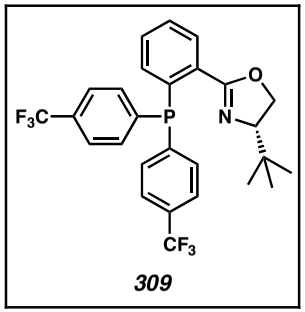


Figure A7.31 ^{1}H NMR of compound **309** (300 MHz, $CDCl_3$)

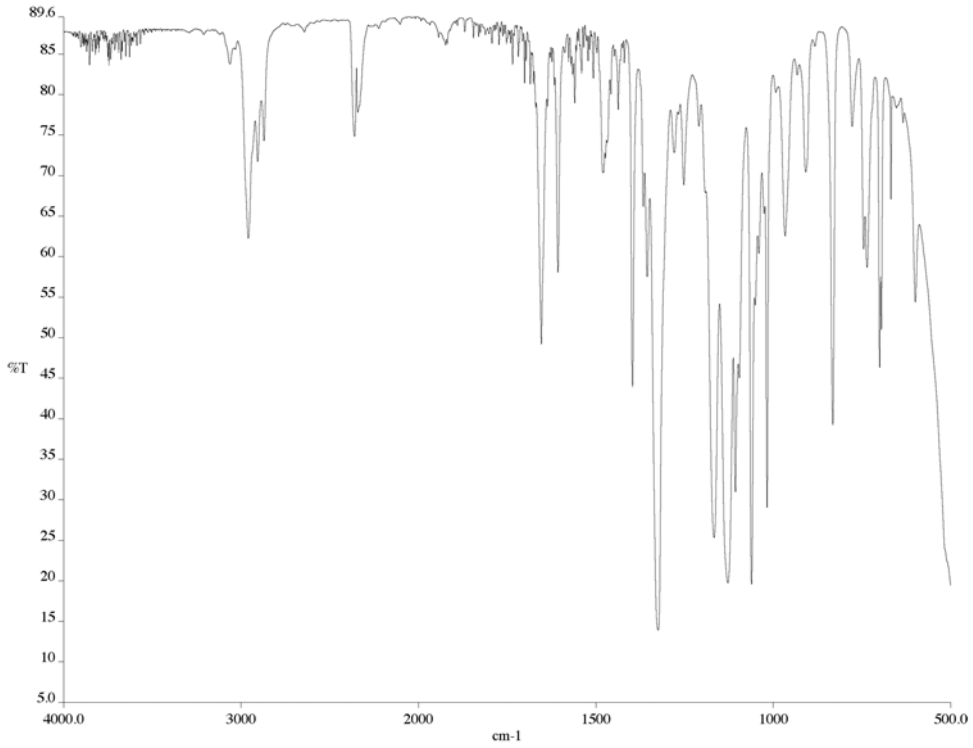


Figure A7.32 IR of compound **309** (NaCl/film)

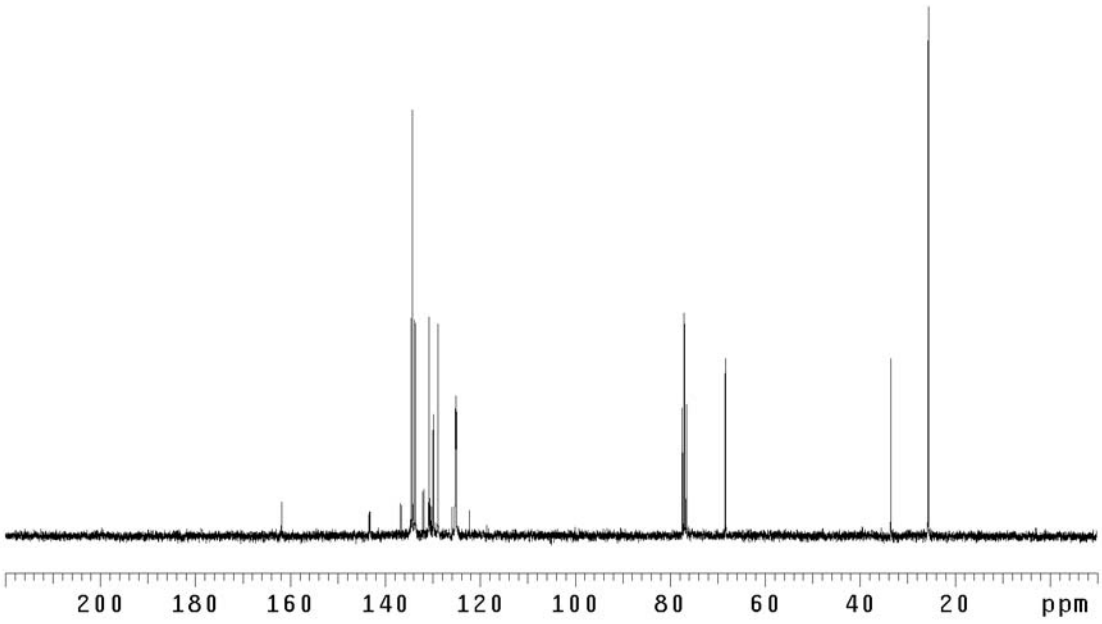


Figure A7.33 ^{13}C NMR of compound **309** (75 MHz, $CDCl_3$)

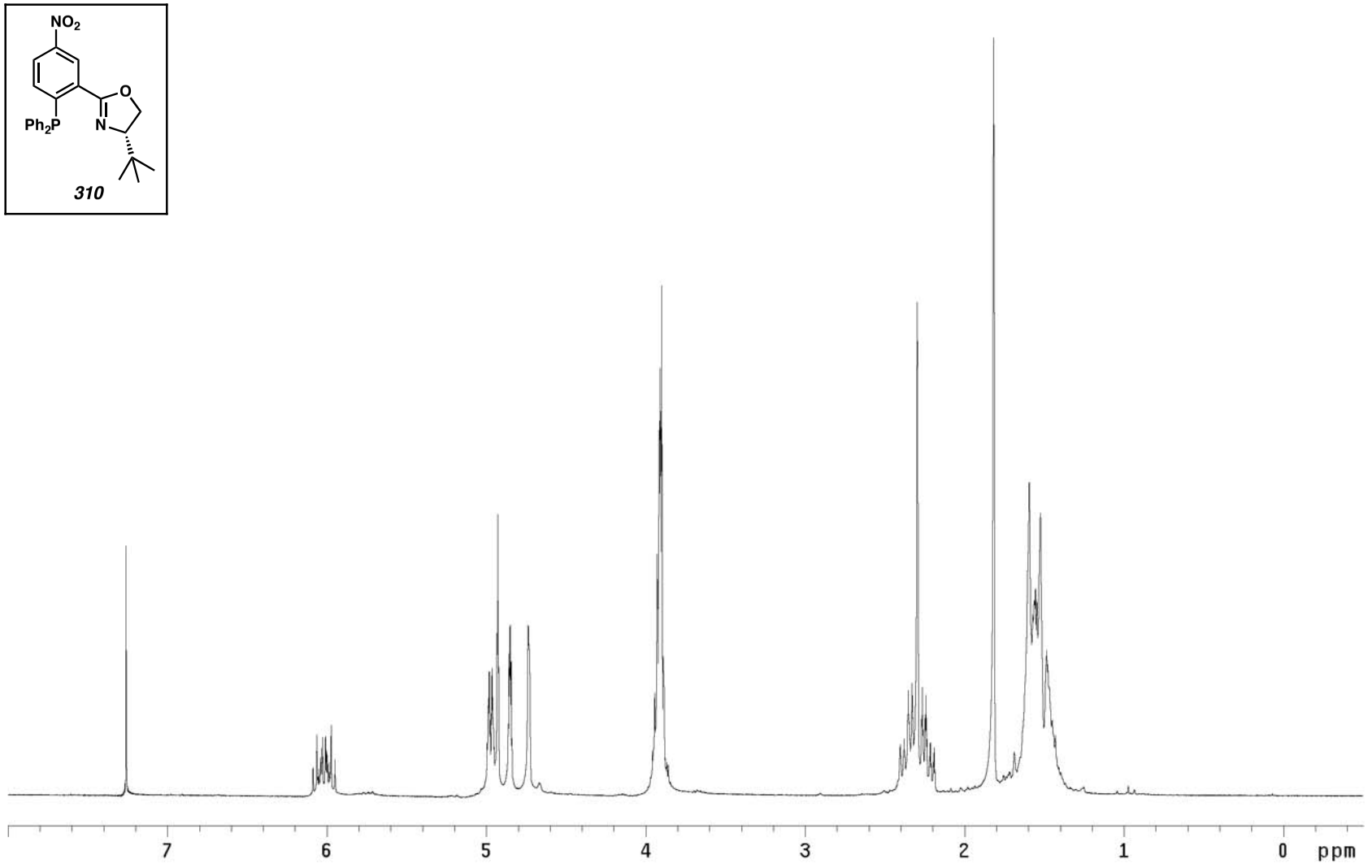


Figure A7.34 ^{1}H NMR of compound **310** (500 MHz, $CDCl_3$)

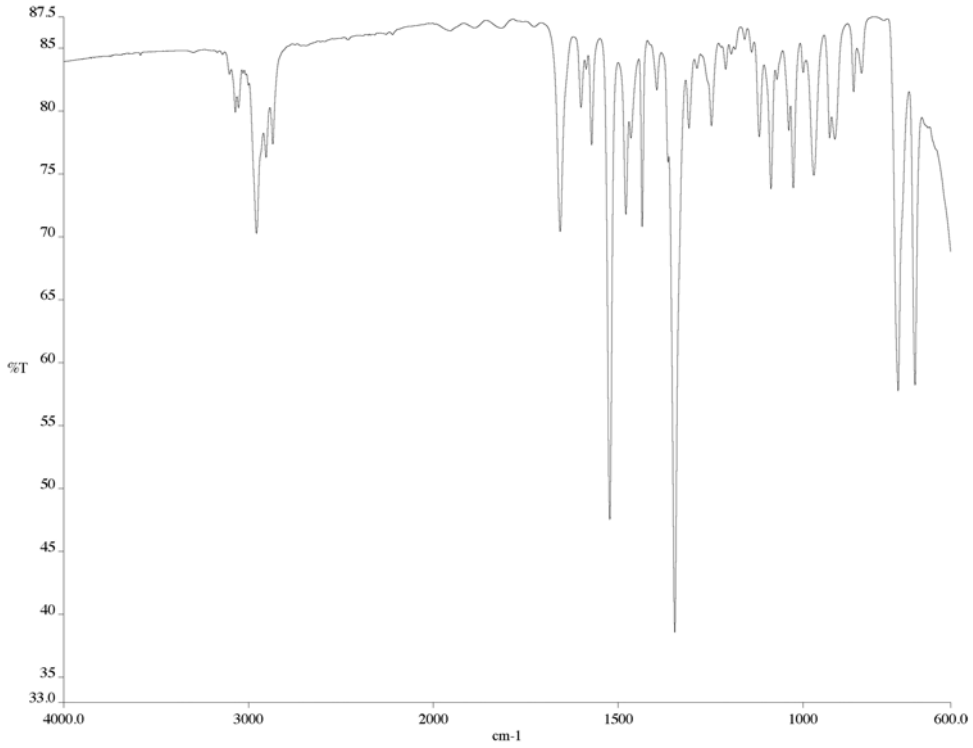


Figure A7.35 IR of compound **310** (NaCl/film)

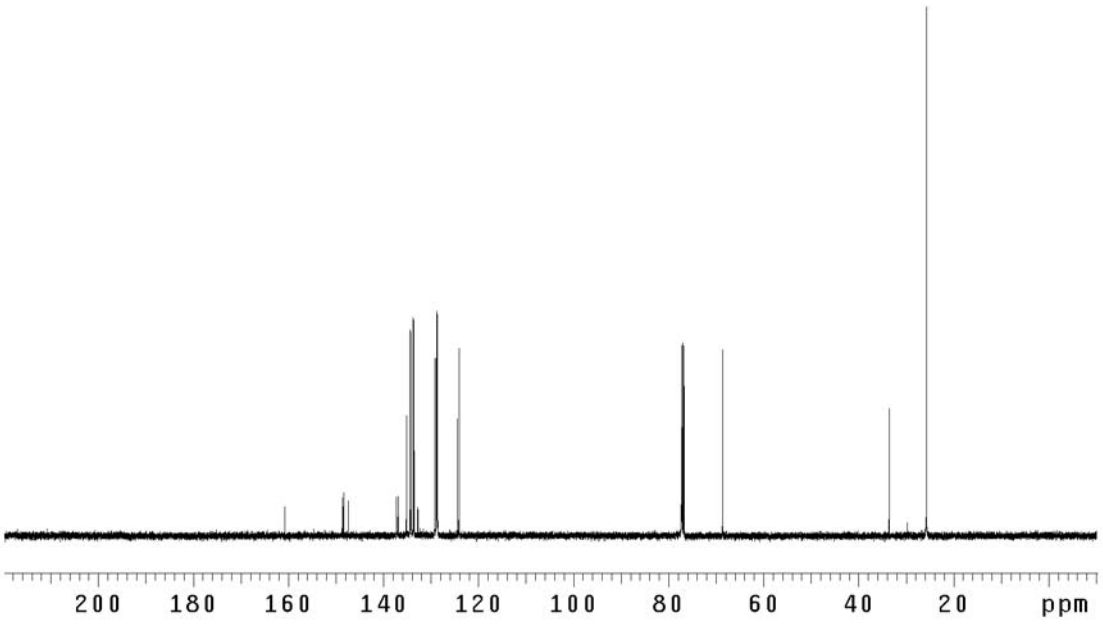


Figure A7.36 ^{13}C NMR of compound **310** (125 MHz, $CDCl_3$)

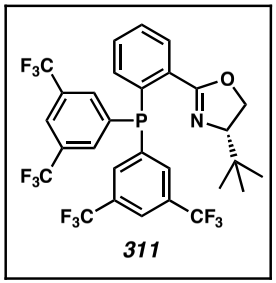


Figure A7.37 ^{1}H NMR of compound **311** (500 MHz, $CDCl_3$)

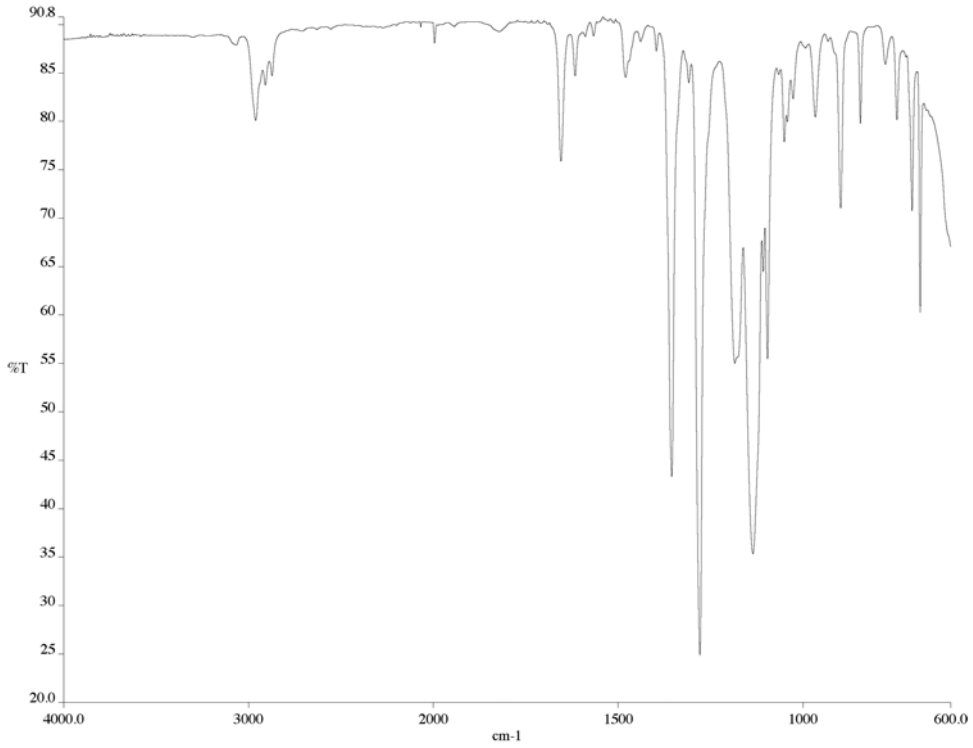


Figure A7.38 IR of compound **311** (NaCl/film)

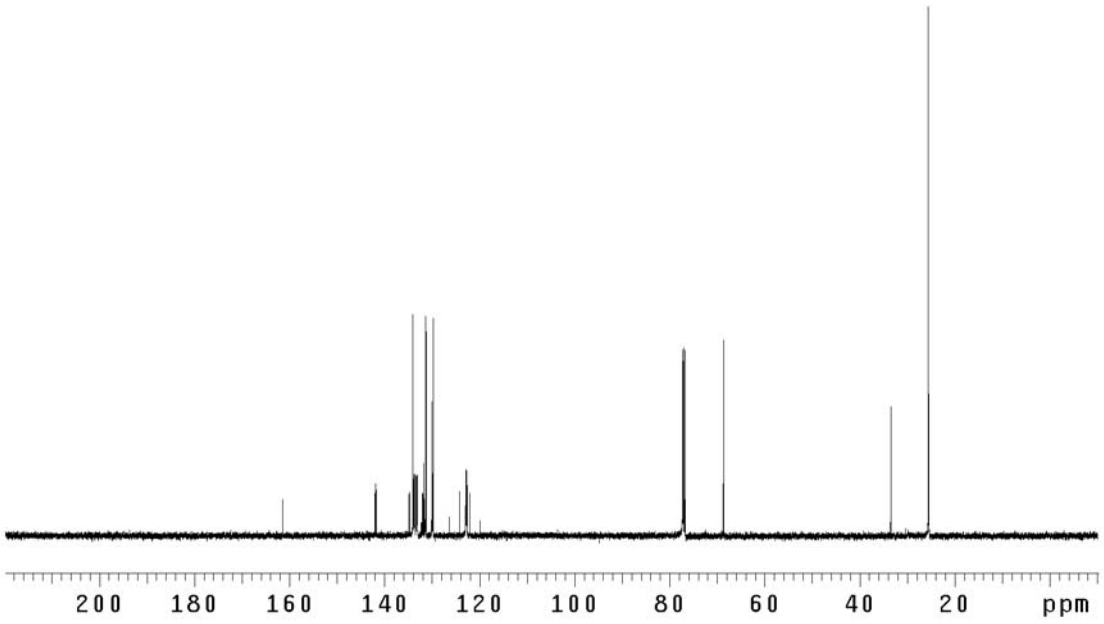


Figure A7.39 ^{13}C NMR of compound **311** (125 MHz, $CDCl_3$)

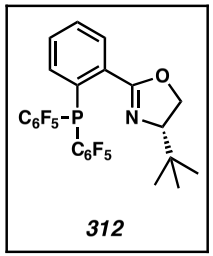


Figure A7.40 ^{1}H NMR of compound **312** (300 MHz, $CDCl_3$)

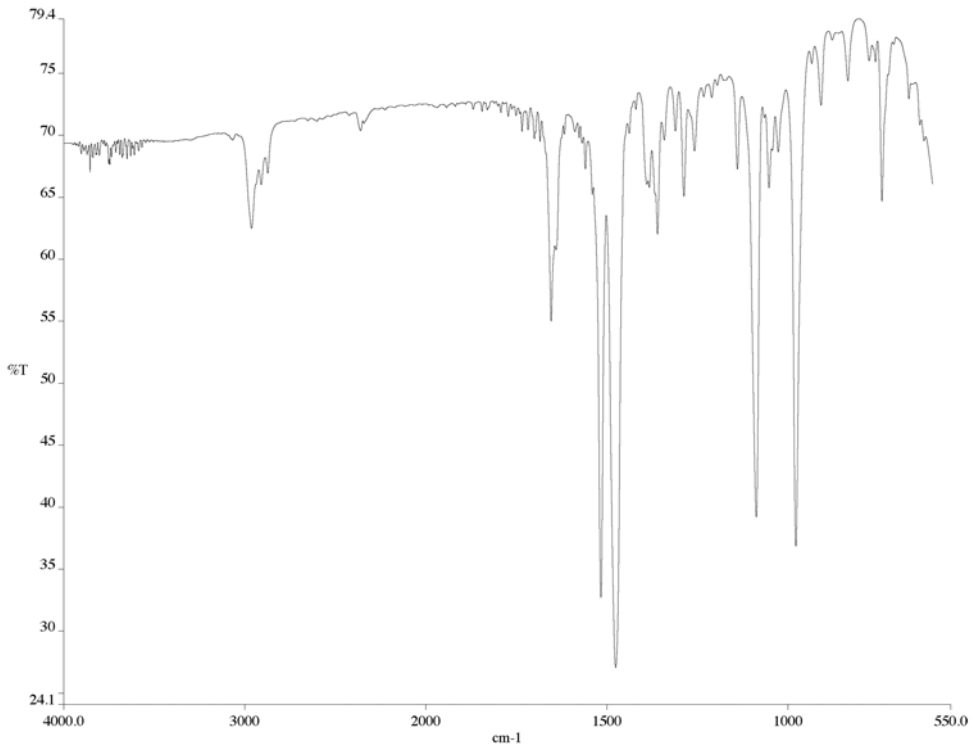


Figure A7.41 IR of compound **312** (NaCl/film)

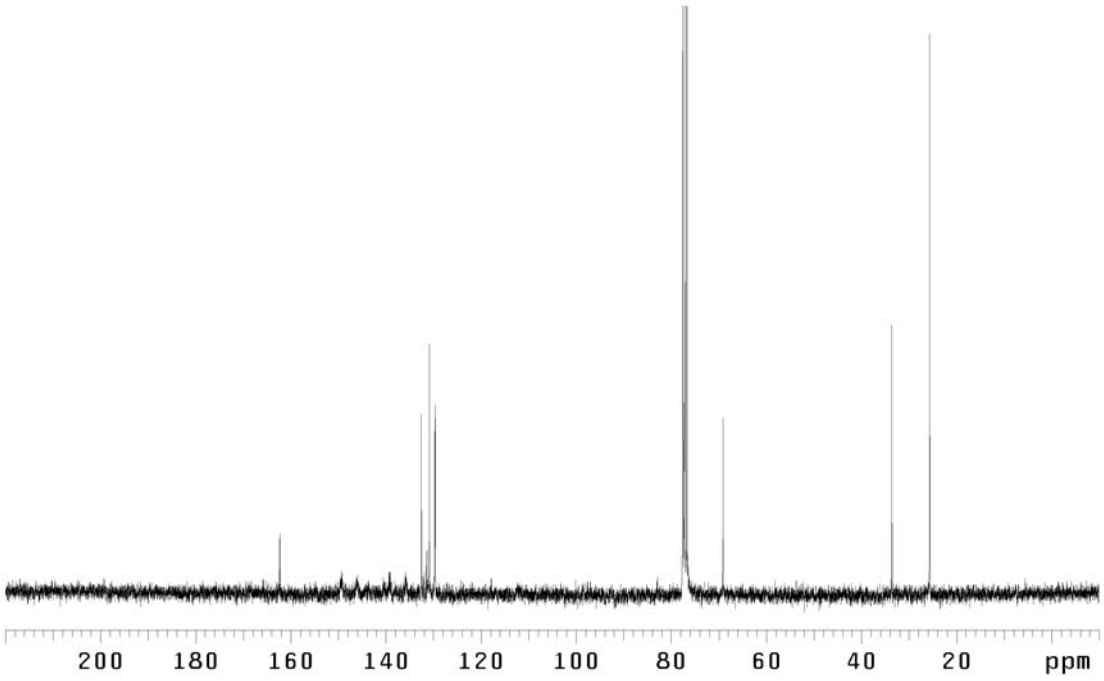


Figure A7.42 ^{13}C NMR of compound **312** (75 MHz, $CDCl_3$)

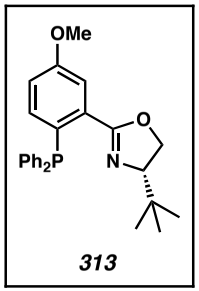


Figure A7.43 ^{1}H NMR of compound **313** (300 MHz, $CDCl_3$)

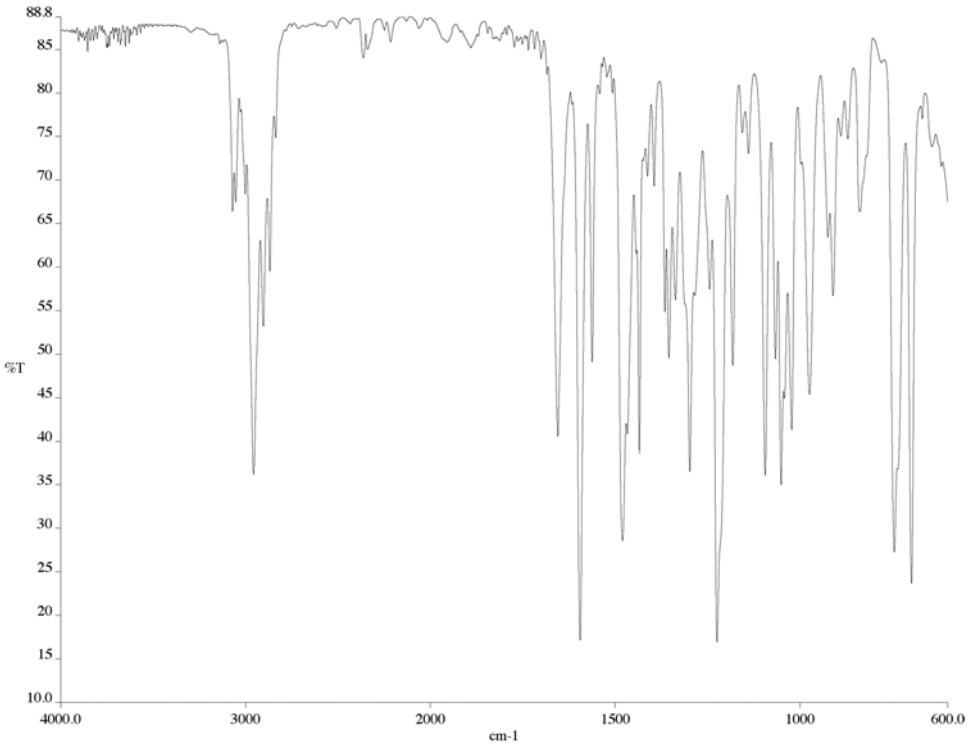


Figure A7.44 IR of compound **313** (NaCl/film)

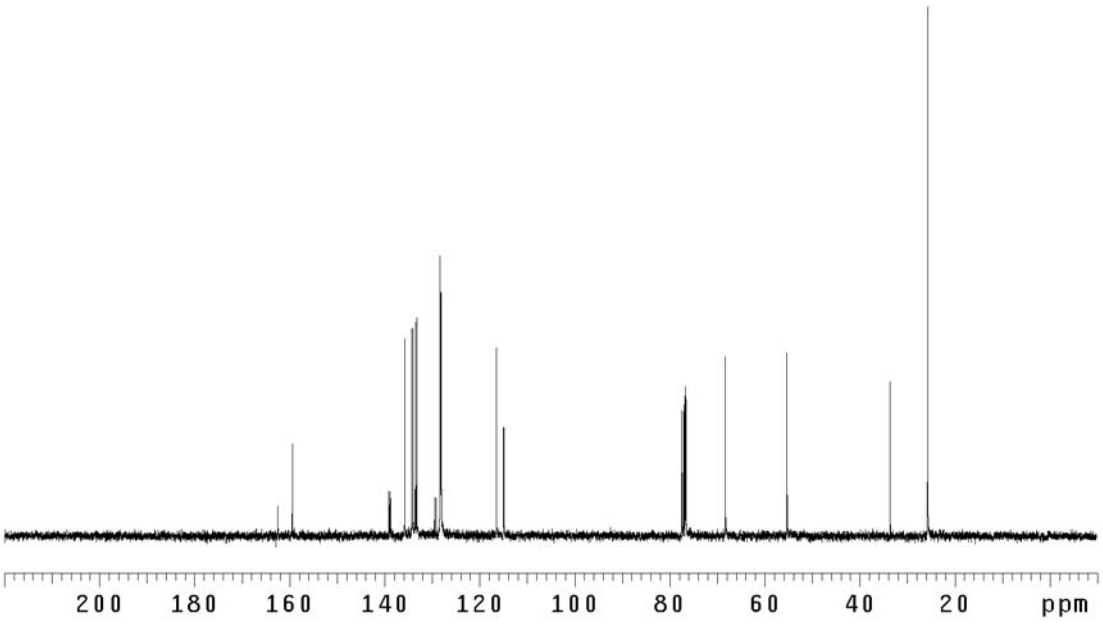


Figure A7.45 ^{13}C NMR of compound **313** (75 MHz, $CDCl_3$)

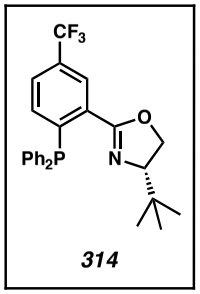


Figure A7.46 ^{1}H NMR of compound **314** (300 MHz, $CDCl_3$)

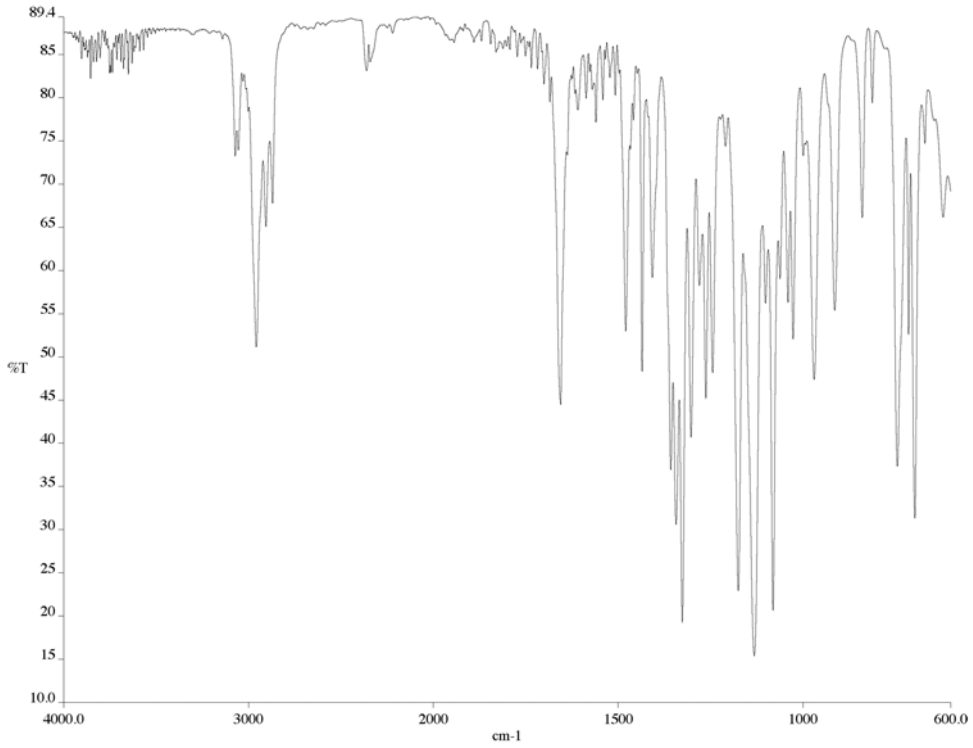


Figure A7.47 IR of compound **314** (NaCl/film)

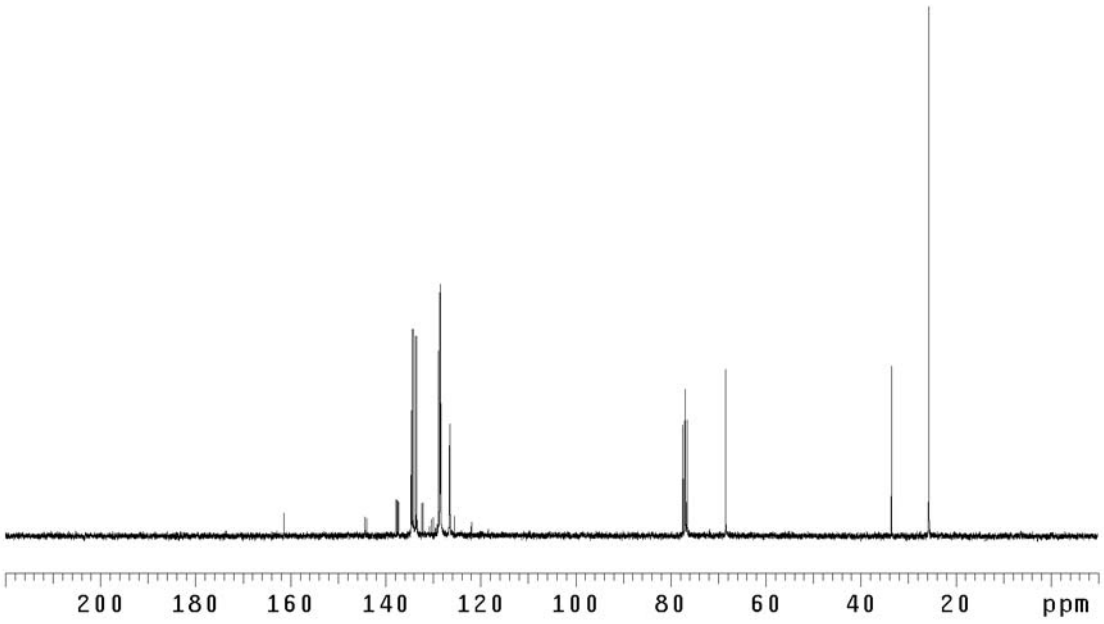


Figure A7.48 ^{13}C NMR of compound **314** (75 MHz, $CDCl_3$)

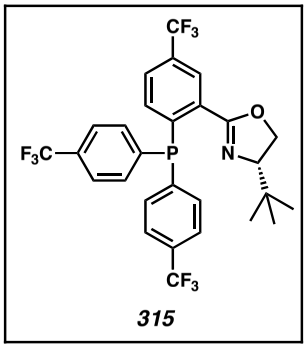


Figure A7.49 ^{1}H NMR of compound **315** (300 MHz, $CDCl_3$)

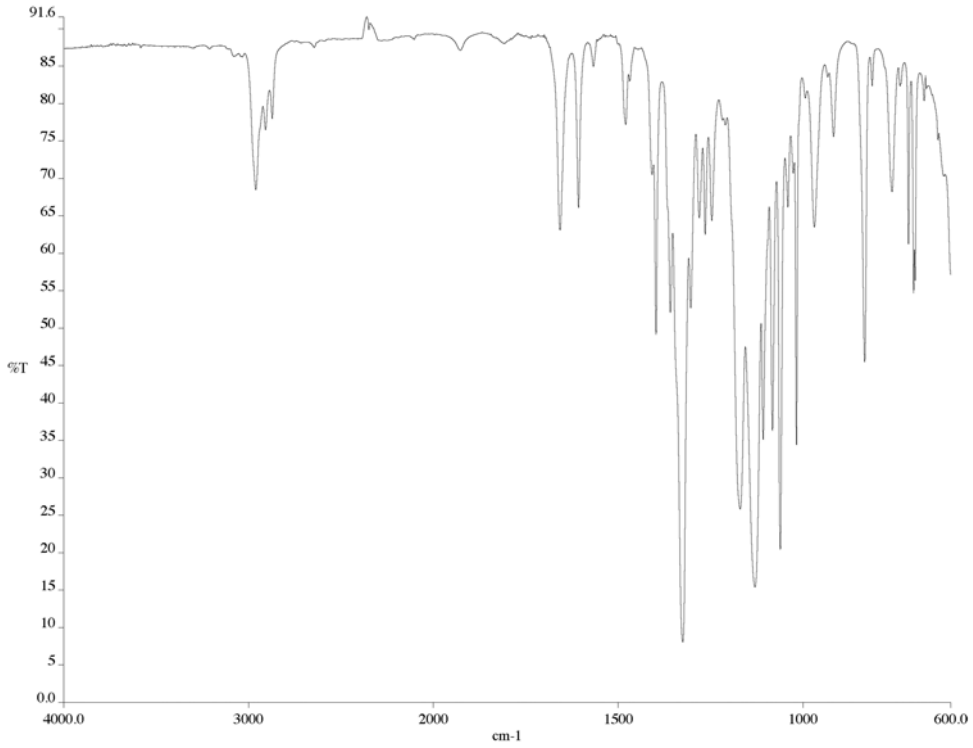


Figure A7.50 IR of compound **315** (NaCl/film)

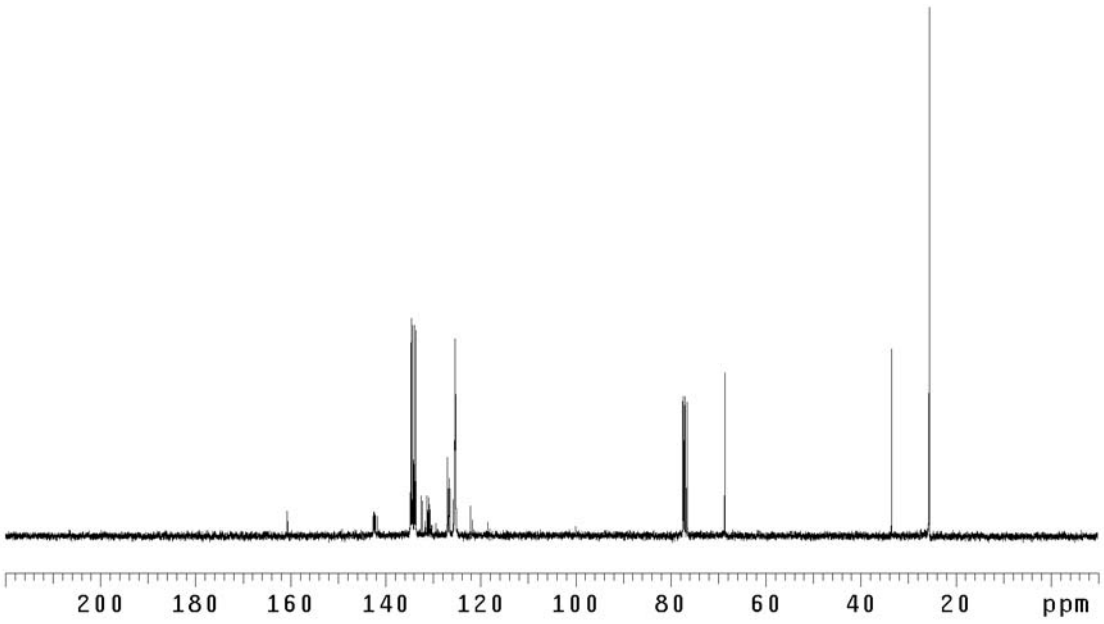


Figure A7.51 ^{13}C NMR of compound **315** (75 MHz, $CDCl_3$)

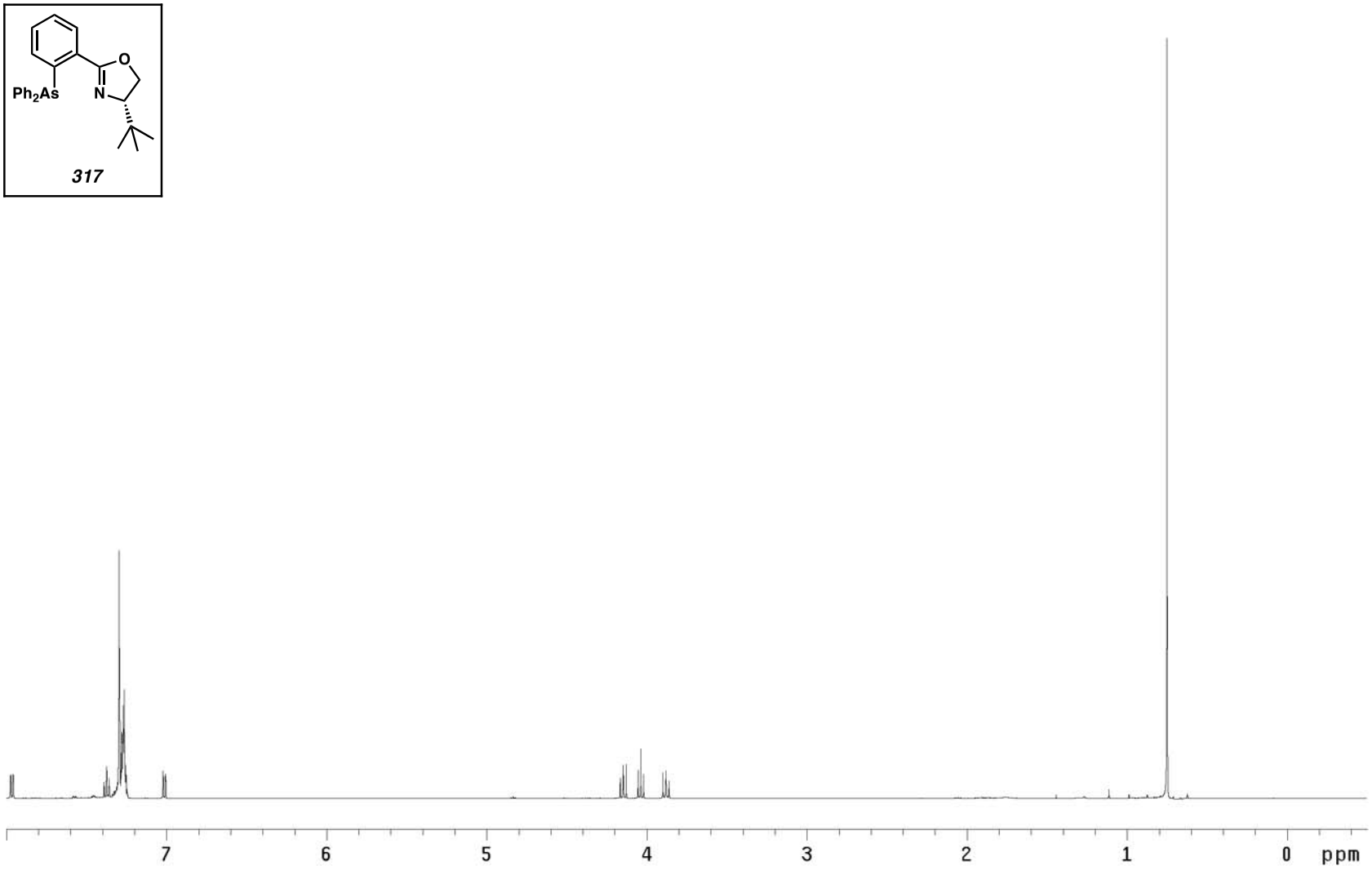


Figure A7.52 ^{1}H NMR of compound **317** (500 MHz, $CDCl_3$)

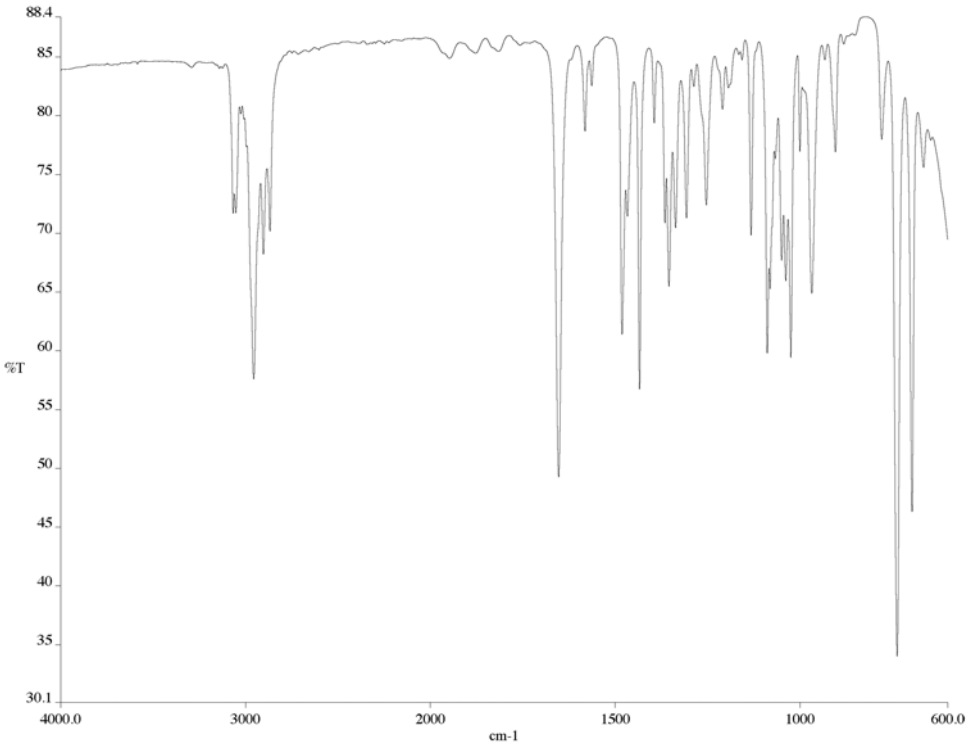


Figure A7.53 IR of compound **317** (NaCl/film)

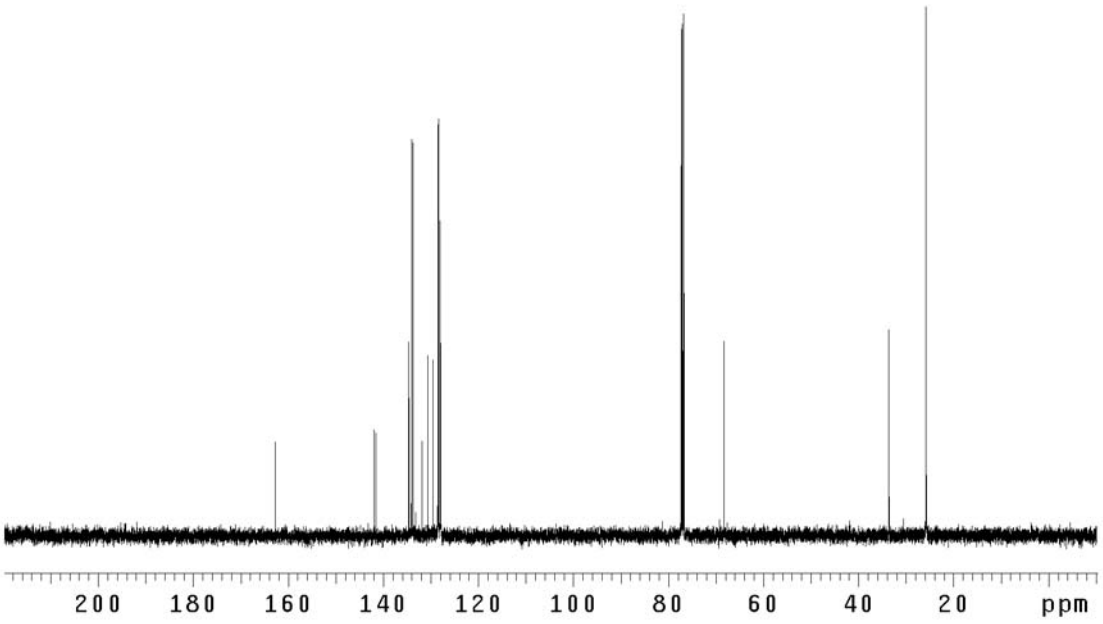


Figure A7.54 ^{13}C NMR of compound **317** (125 MHz, $CDCl_3$)

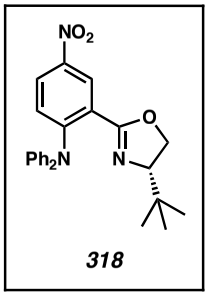


Figure A7.55 ^{1}H NMR of compound **318** (500 MHz, $CDCl_3$)

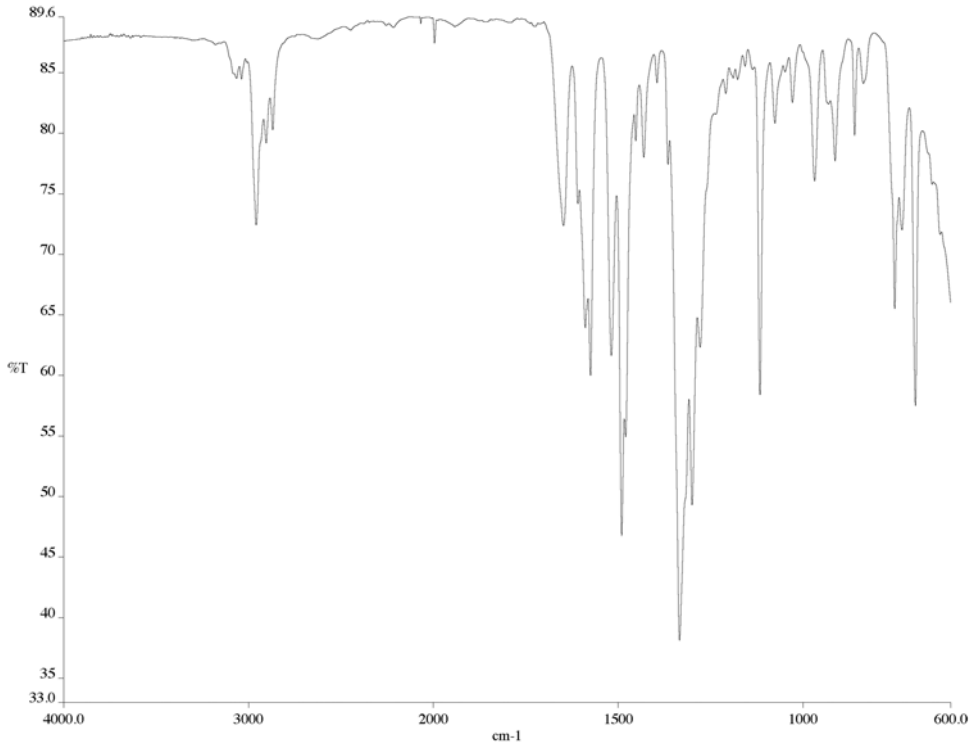


Figure A7.56 IR of compound **318** (NaCl/film)

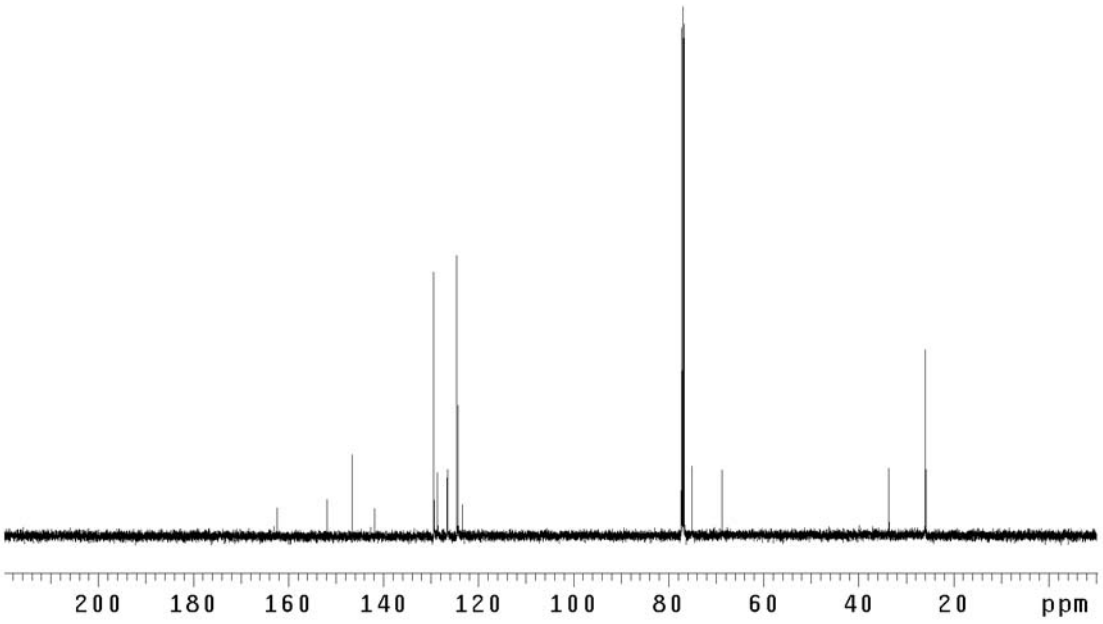


Figure A7.57 ^{13}C NMR of compound **318** (125 MHz, $CDCl_3$)

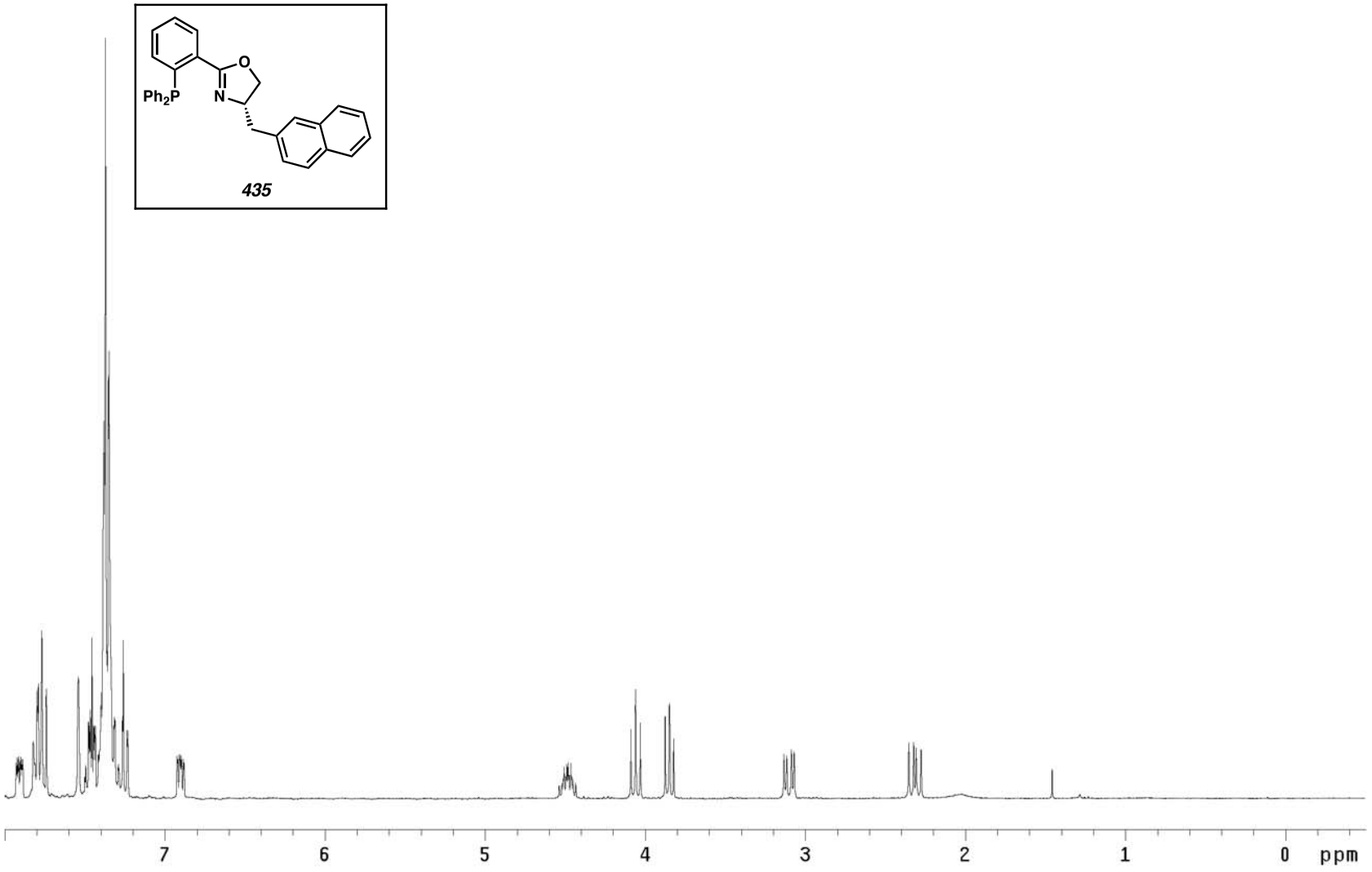


Figure A7.58 ^{1}H NMR of compound **435** (300 MHz, $CDCl_3$)

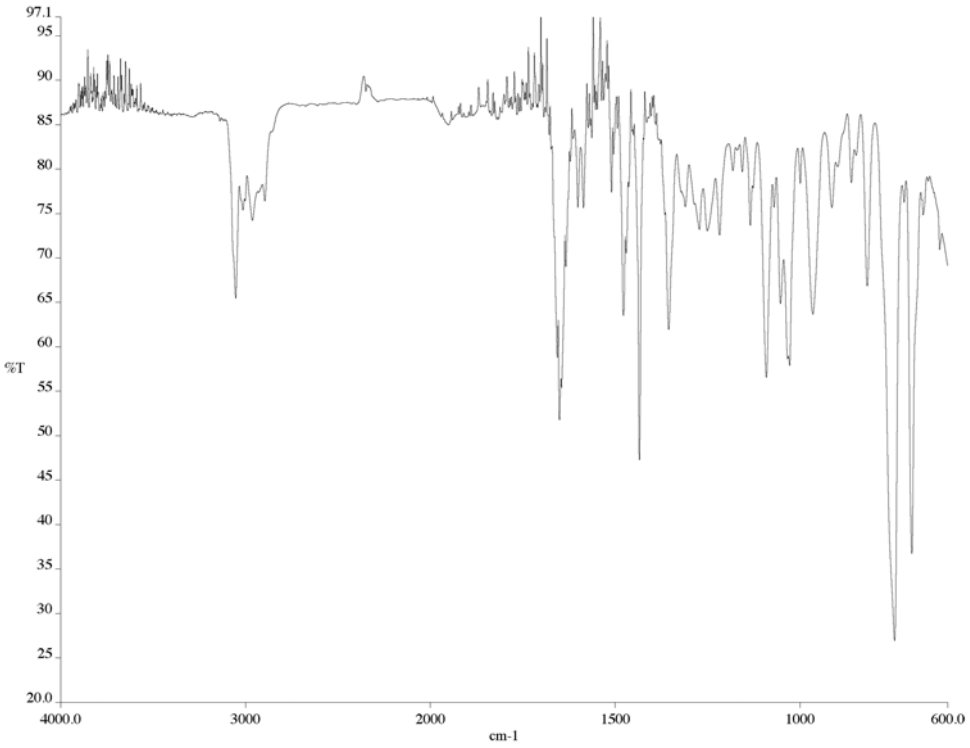


Figure A7.59 IR of compound **435** (NaCl/film)

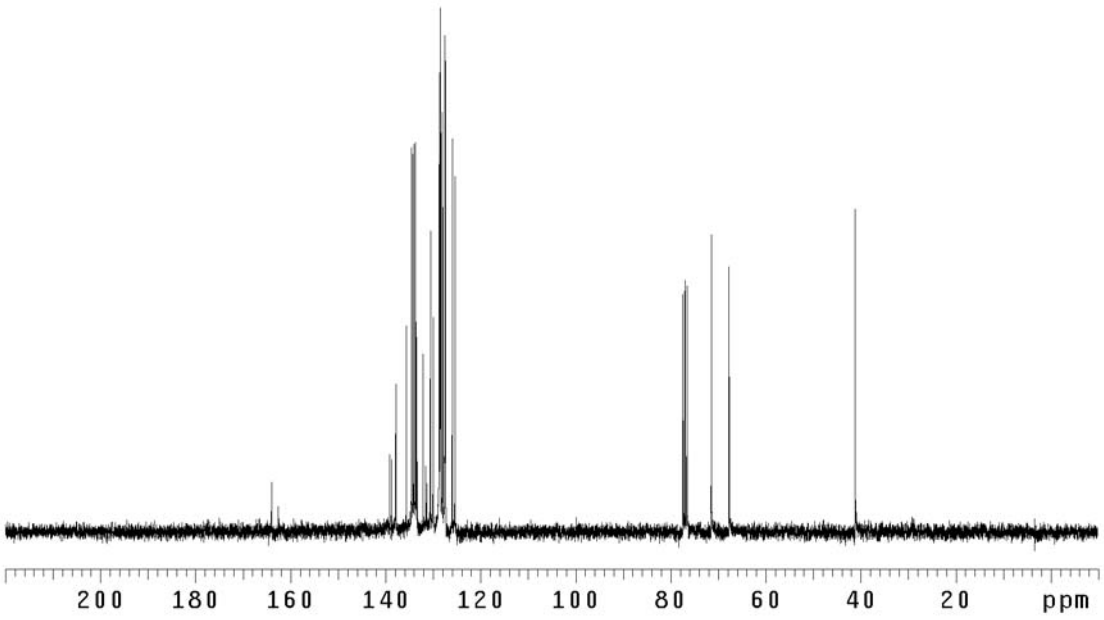


Figure A7.60 ^{13}C NMR of compound **435** (75 MHz, $CDCl_3$)

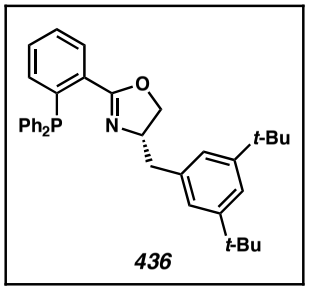


Figure A7.61 ^{1}H NMR of compound **436** (300 MHz, $CDCl_3$)

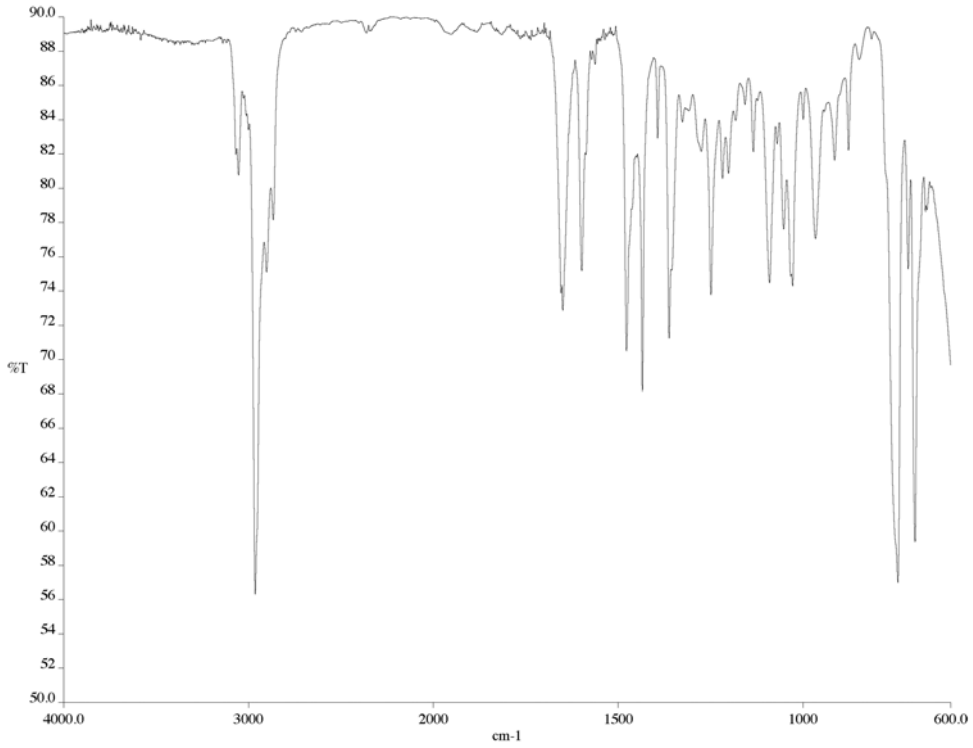


Figure A7.62 IR of compound **436** (NaCl/film)

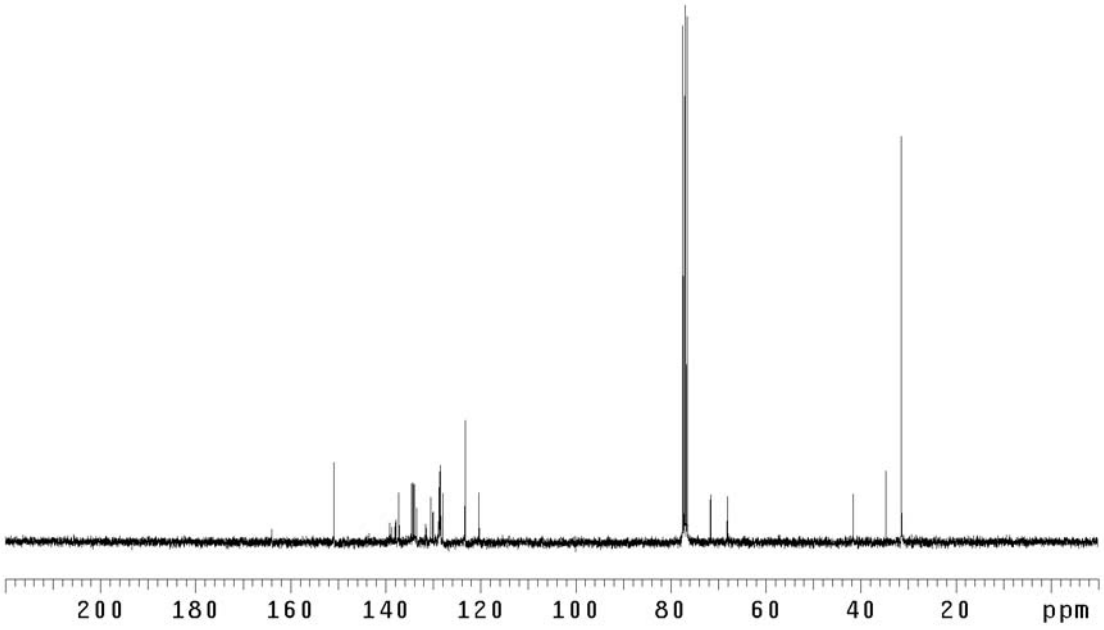


Figure A7.63 ^{13}C NMR of compound **436** (75 MHz, $CDCl_3$)

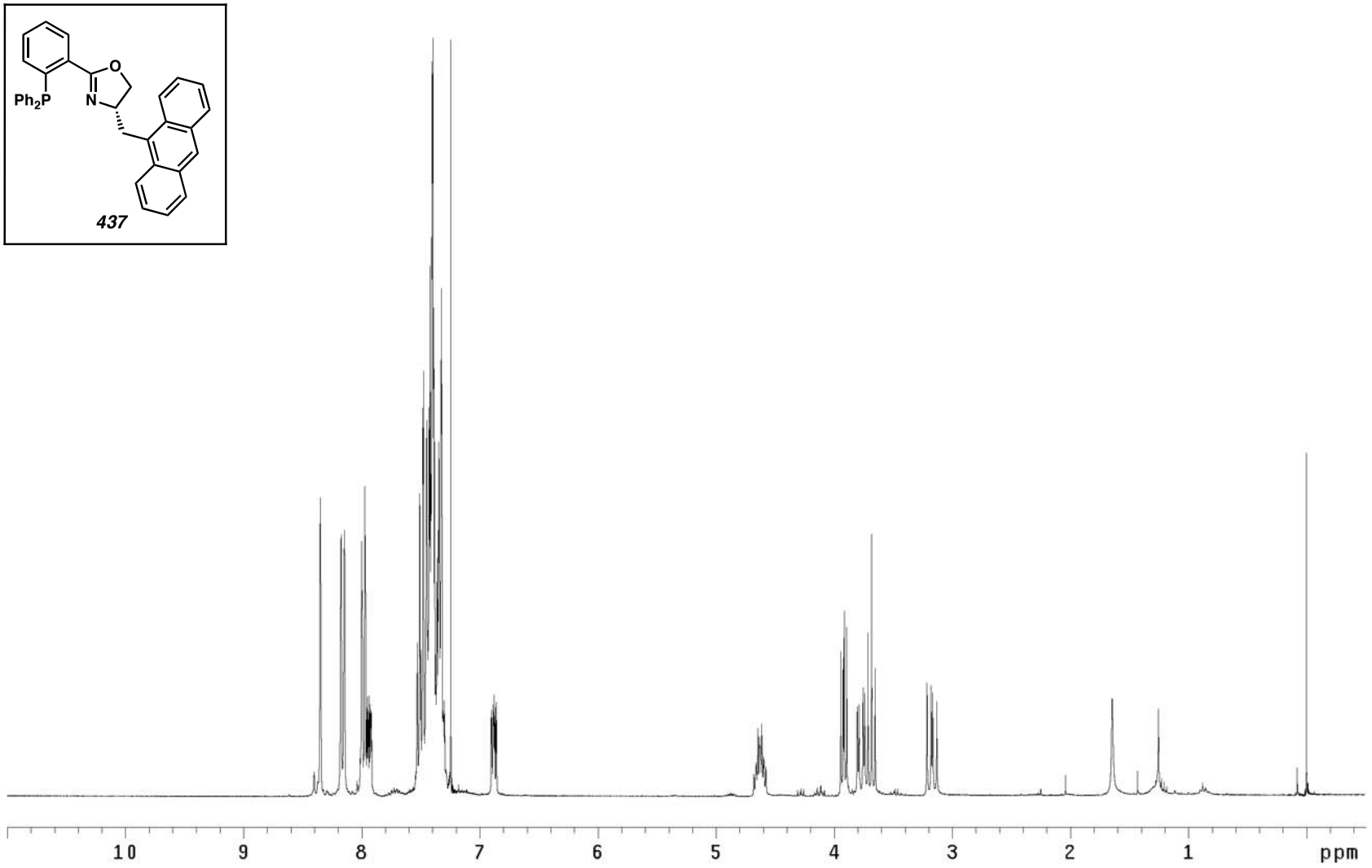


Figure A7.64 ^{1}H NMR of compound **437** (300 MHz, $CDCl_3$)

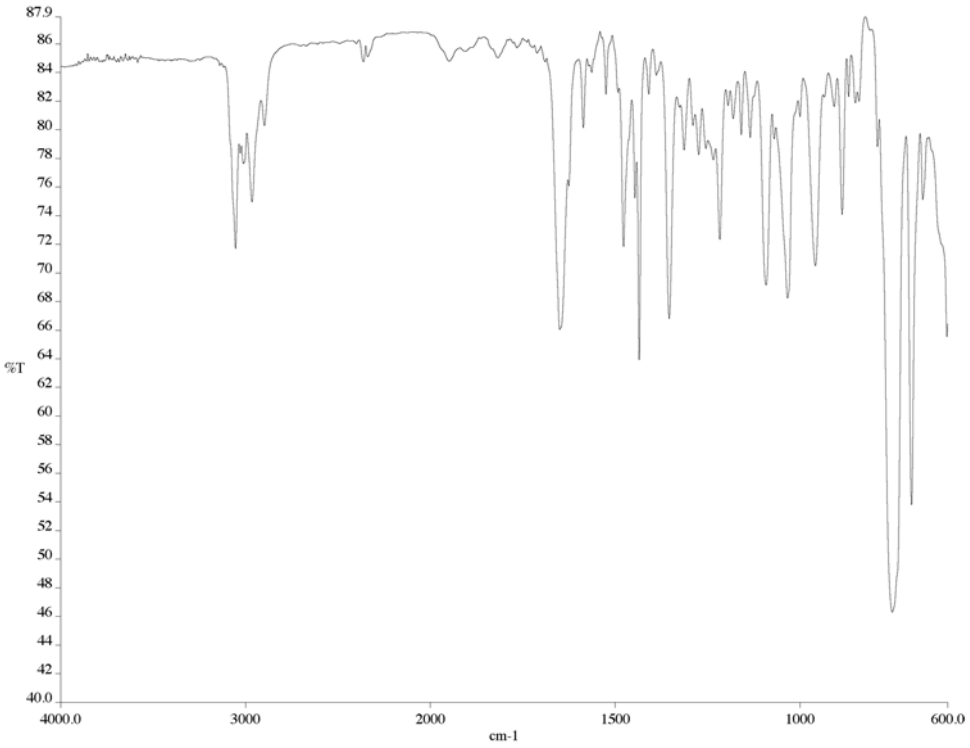


Figure A7.65 IR of compound **437** (NaCl/film)

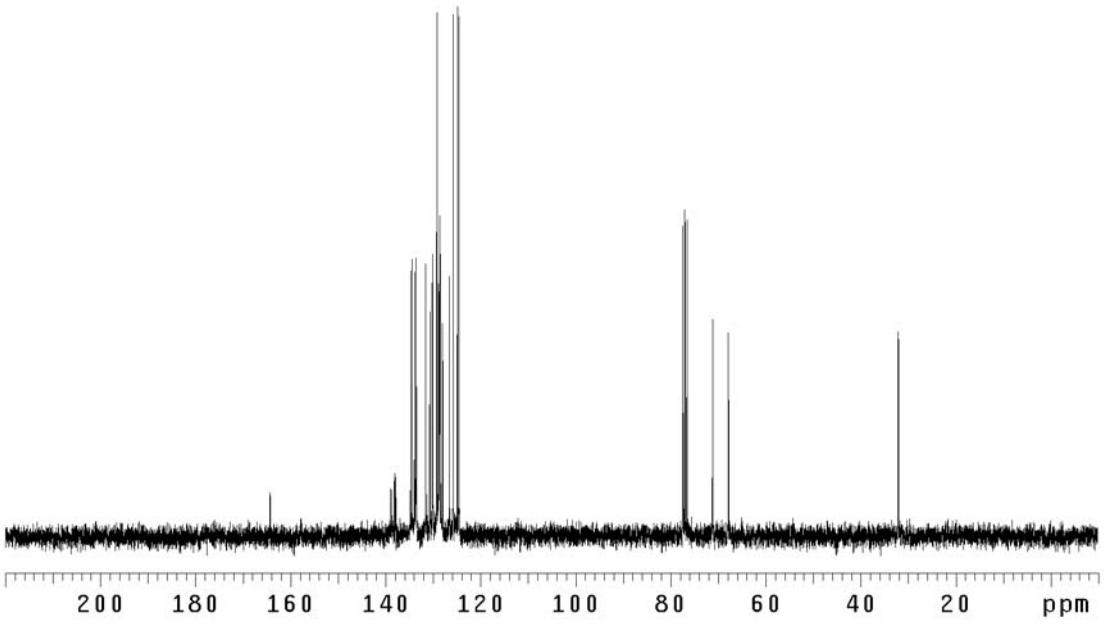


Figure A7.66 ^{13}C NMR of compound **437** (75 MHz, $CDCl_3$)

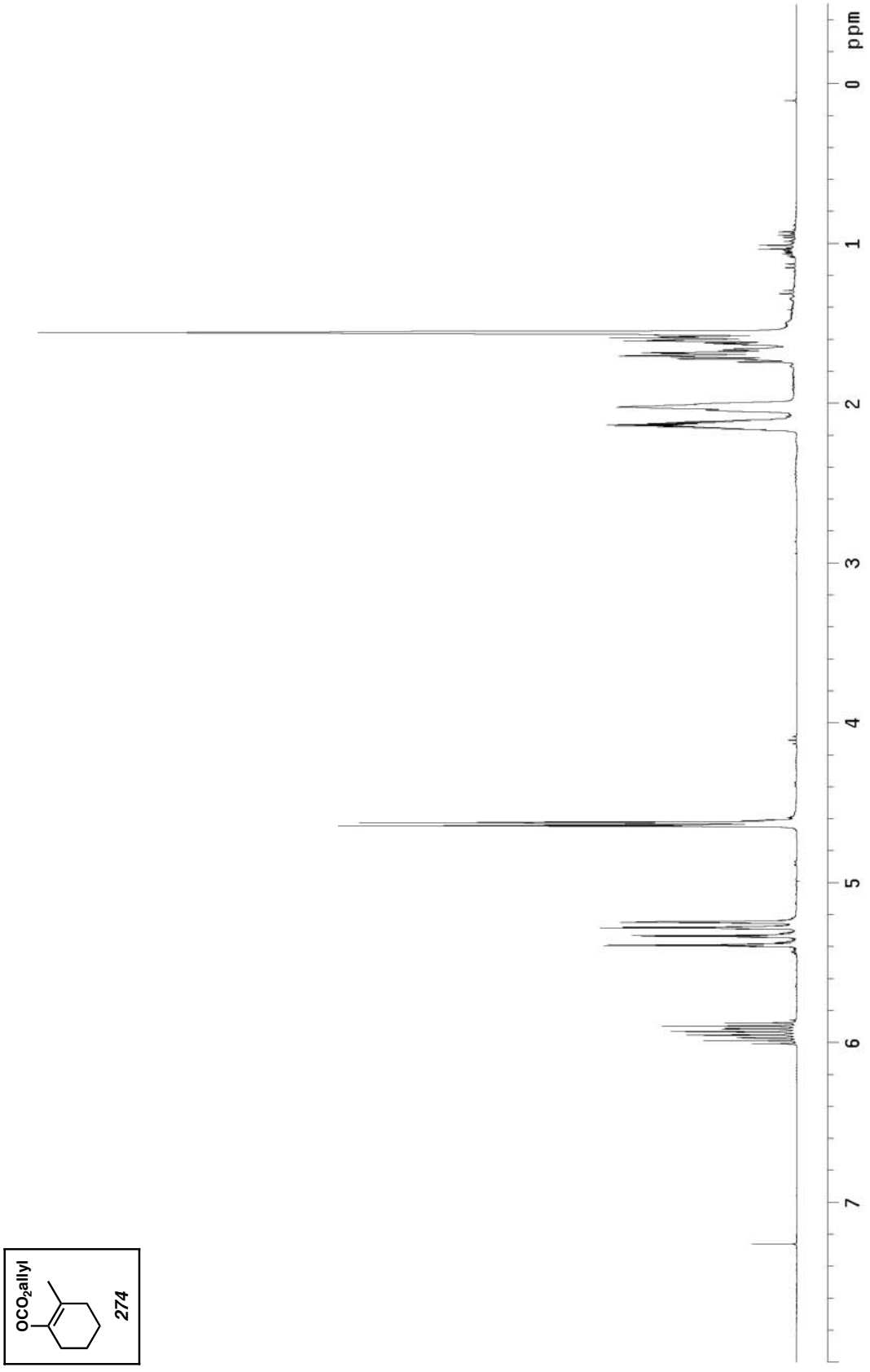


Figure A7.67 ^{1}H NMR of compound **274** (300 MHz, $CDCl_3$)

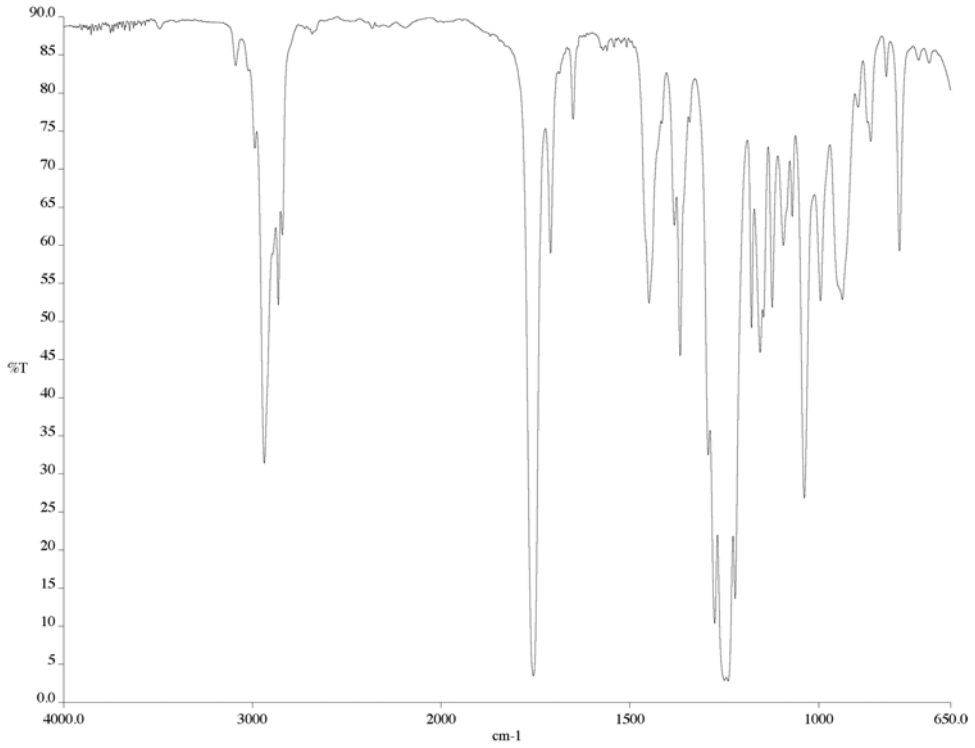


Figure A7.68 IR of compound **274** (NaCl/film)

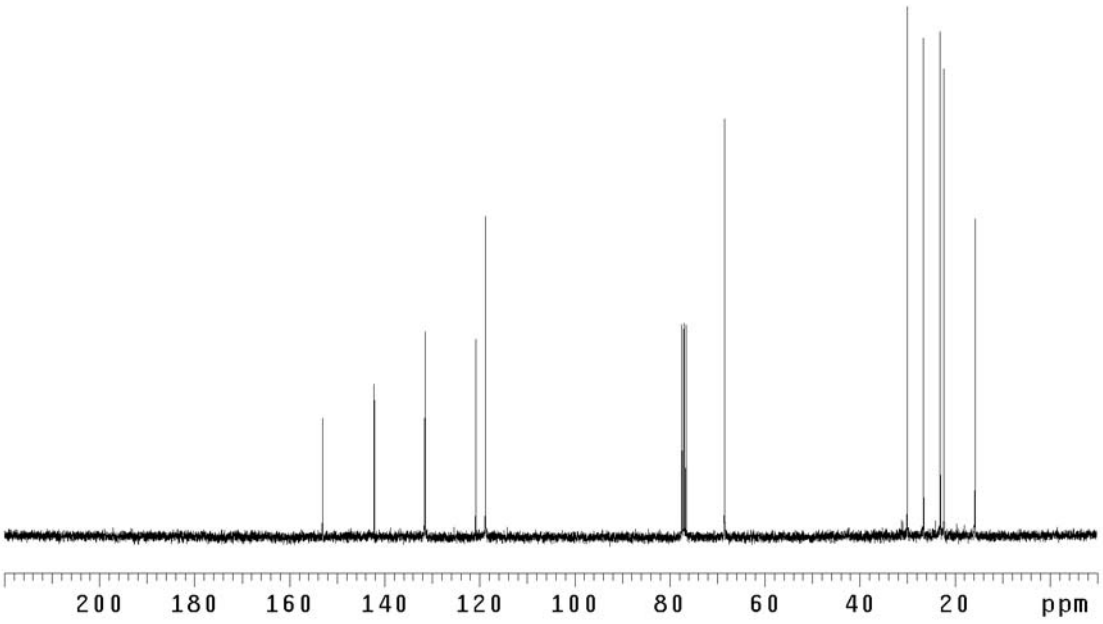


Figure A7.69 ^{13}C NMR of compound **274** (75 MHz, $CDCl_3$)

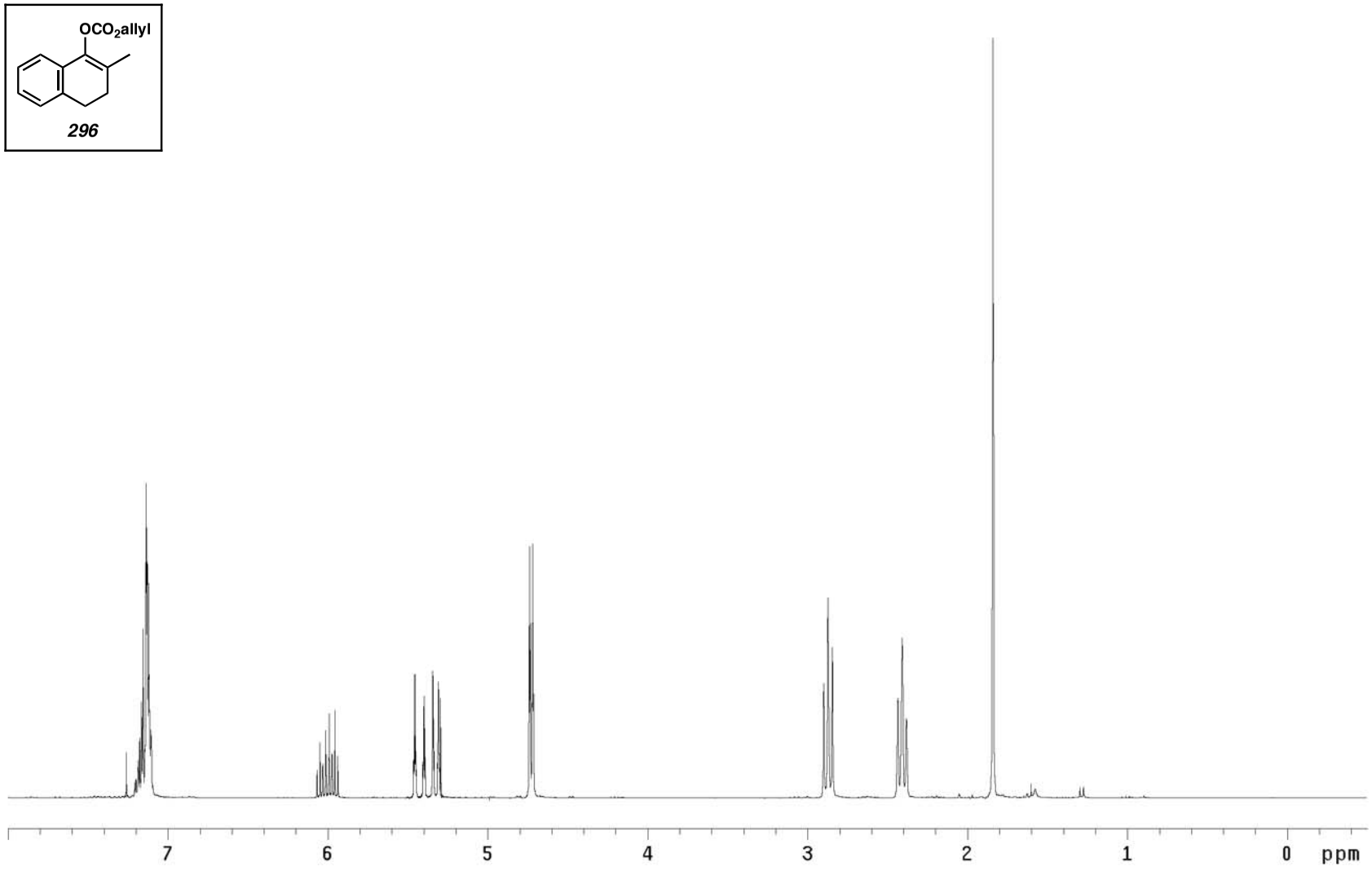


Figure A7.70 ^{1}H NMR of compound **296** (300 MHz, $CDCl_3$)

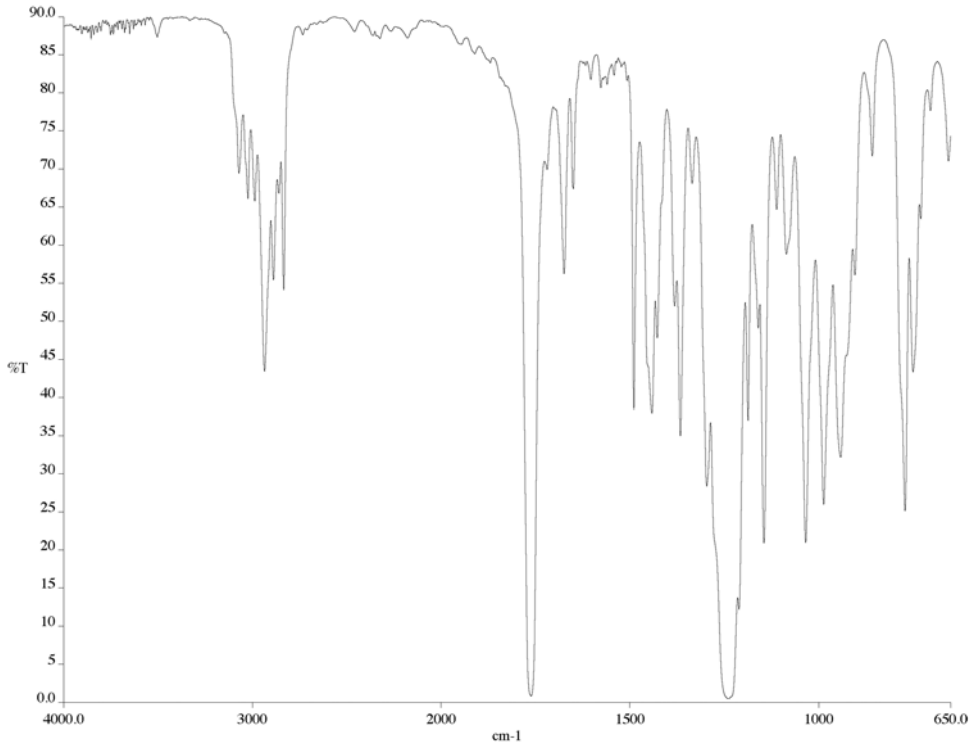


Figure A7.71 IR of compound **296** (NaCl/film)

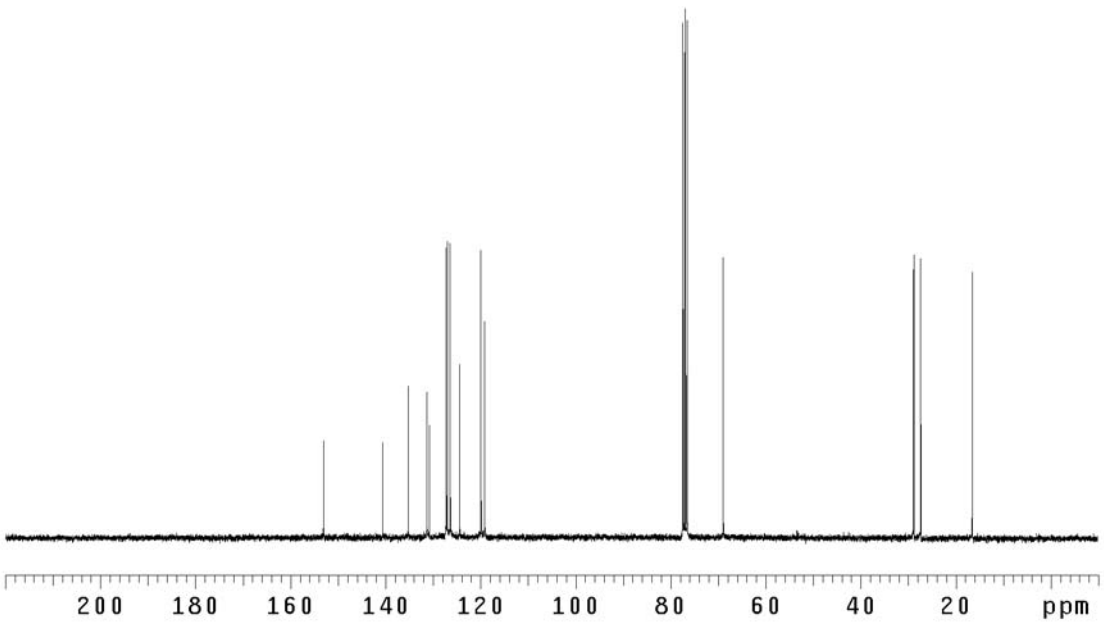


Figure A7.72 ^{13}C NMR of compound **296** (75 MHz, $CDCl_3$)

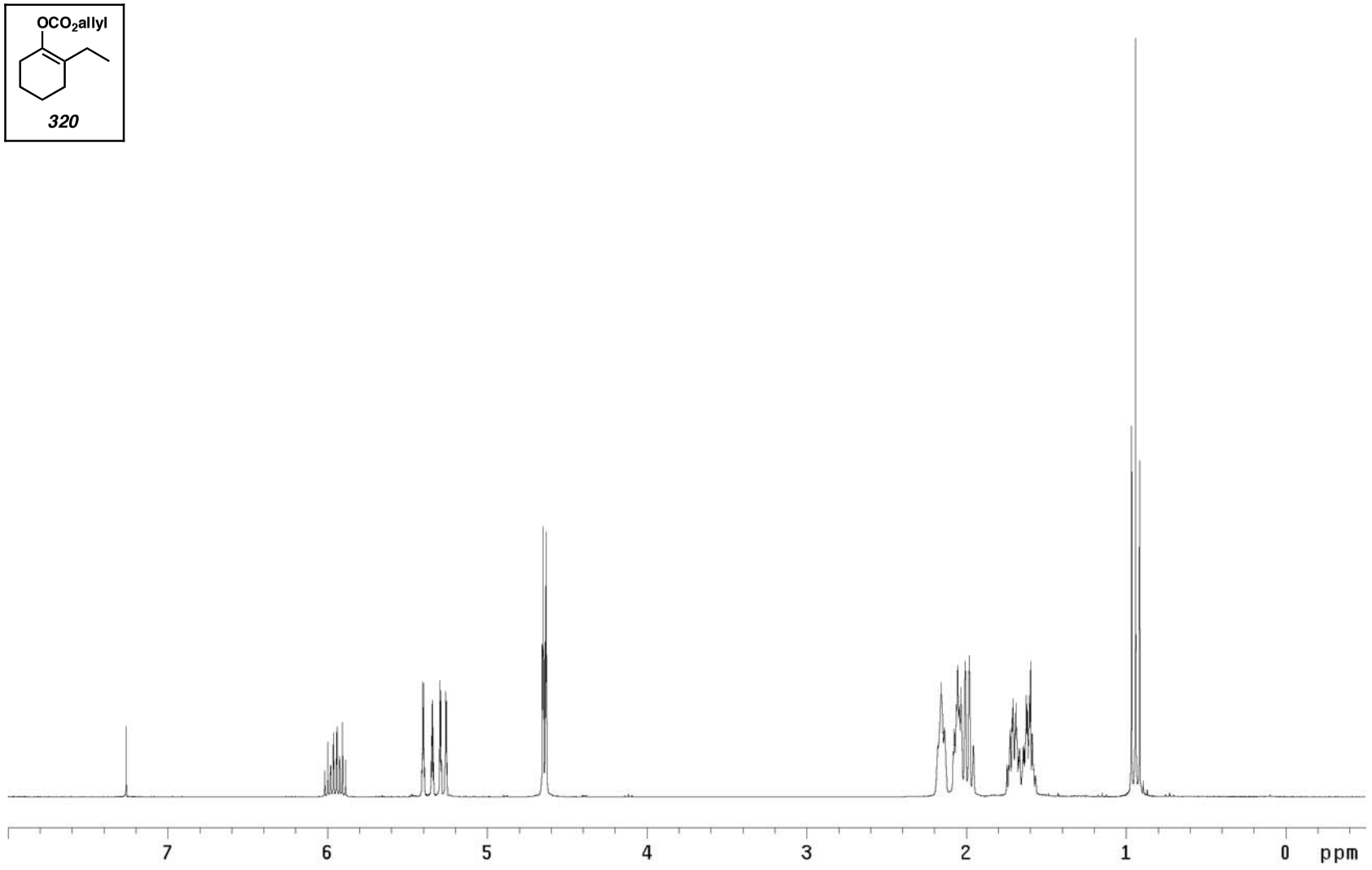


Figure A7.73 ^{1}H NMR of compound **320** (300 MHz, $CDCl_3$)

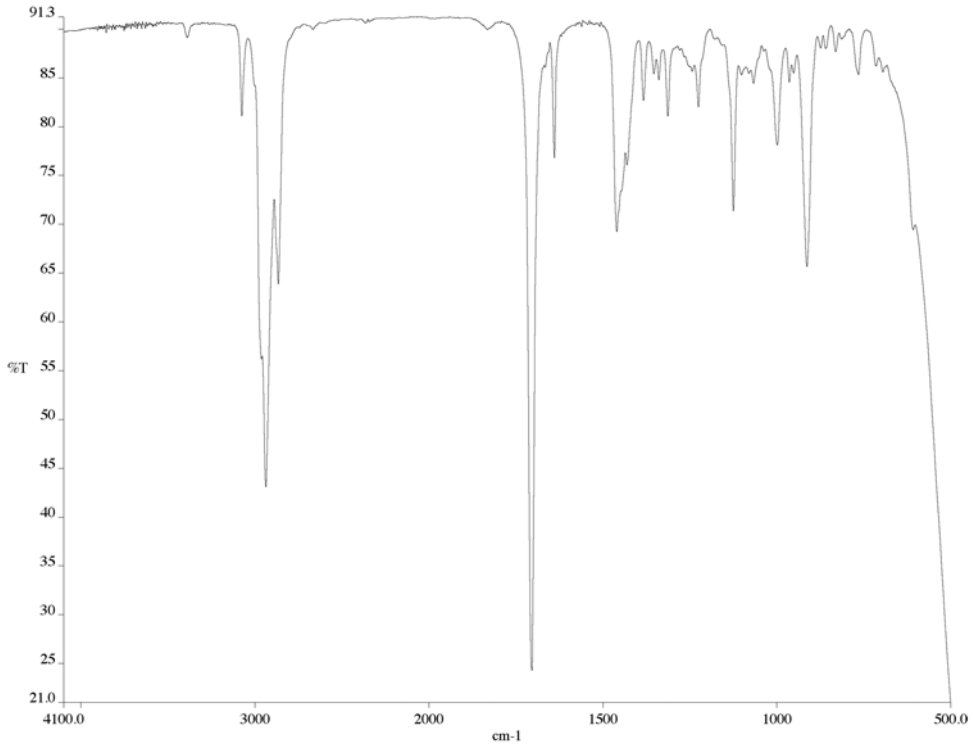


Figure A7.74 IR of compound **320** (NaCl/film)

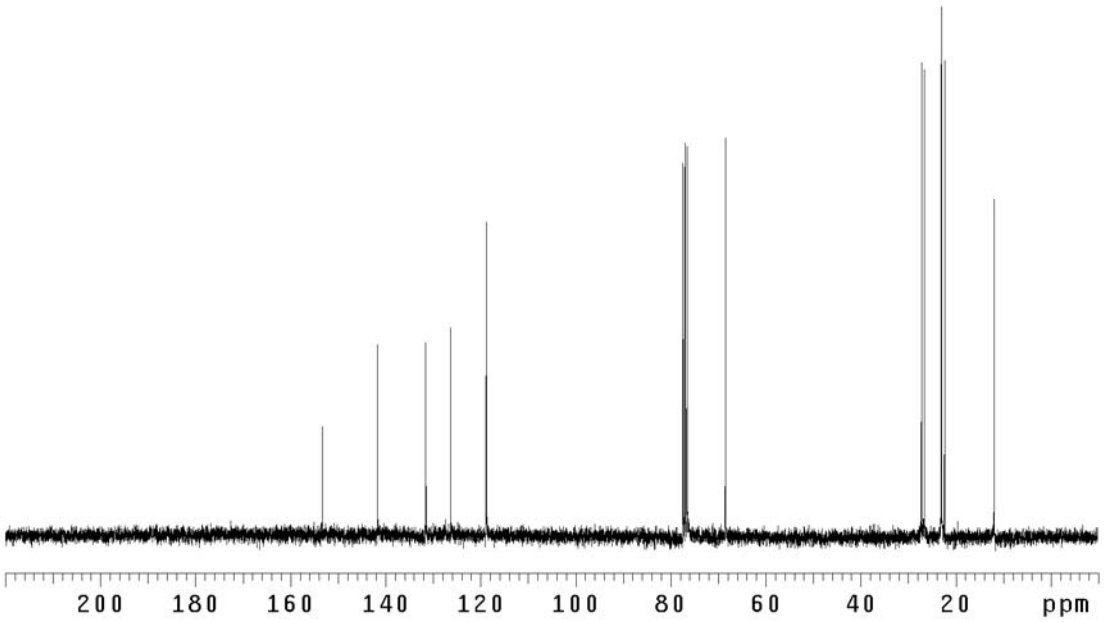


Figure A7.75 ^{13}C NMR of compound **320** (75 MHz, $CDCl_3$)

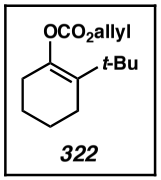


Figure A7.76 ^{1}H NMR of compound **322** (300 MHz, $CDCl_3$)

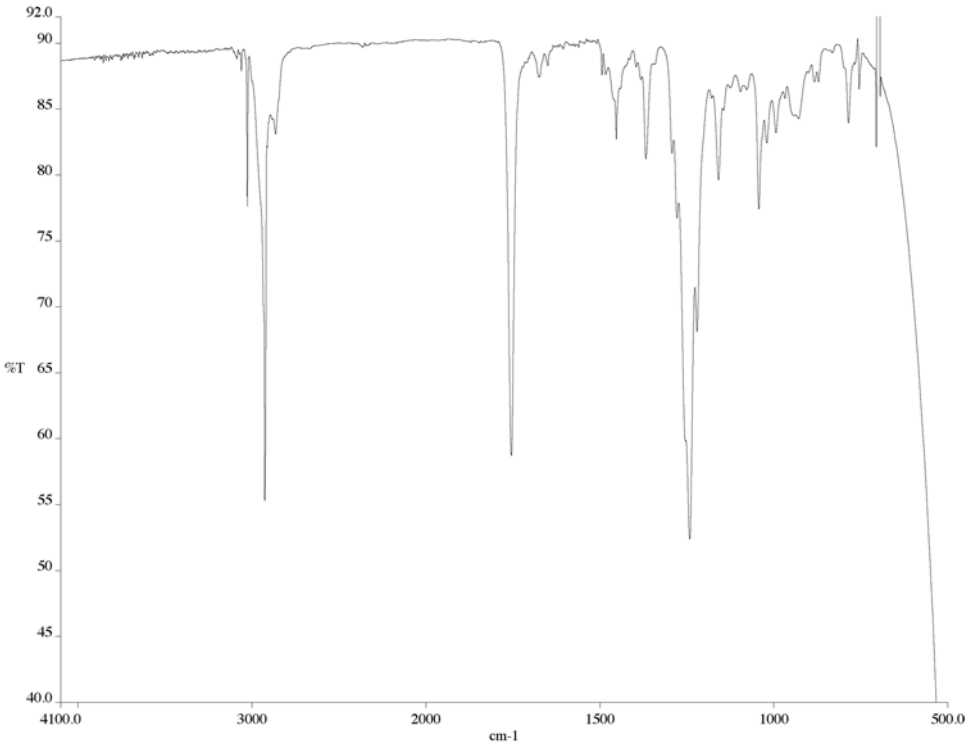


Figure A7.77 IR of compound **322** (NaCl/film)

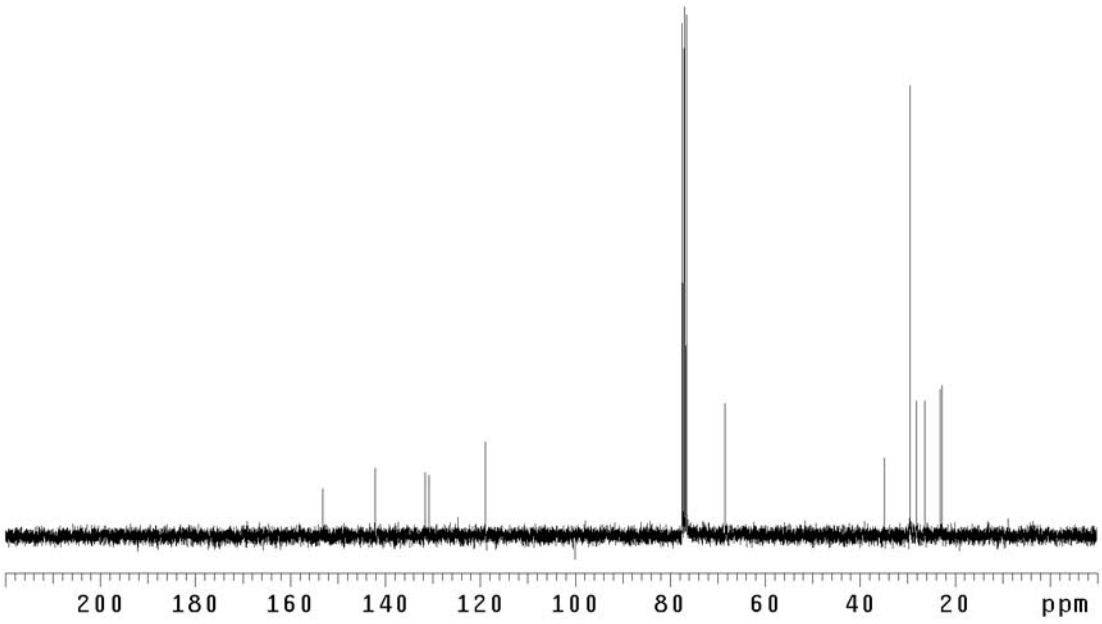


Figure A7.78 ^{13}C NMR of compound **322** (75 MHz, $CDCl_3$)

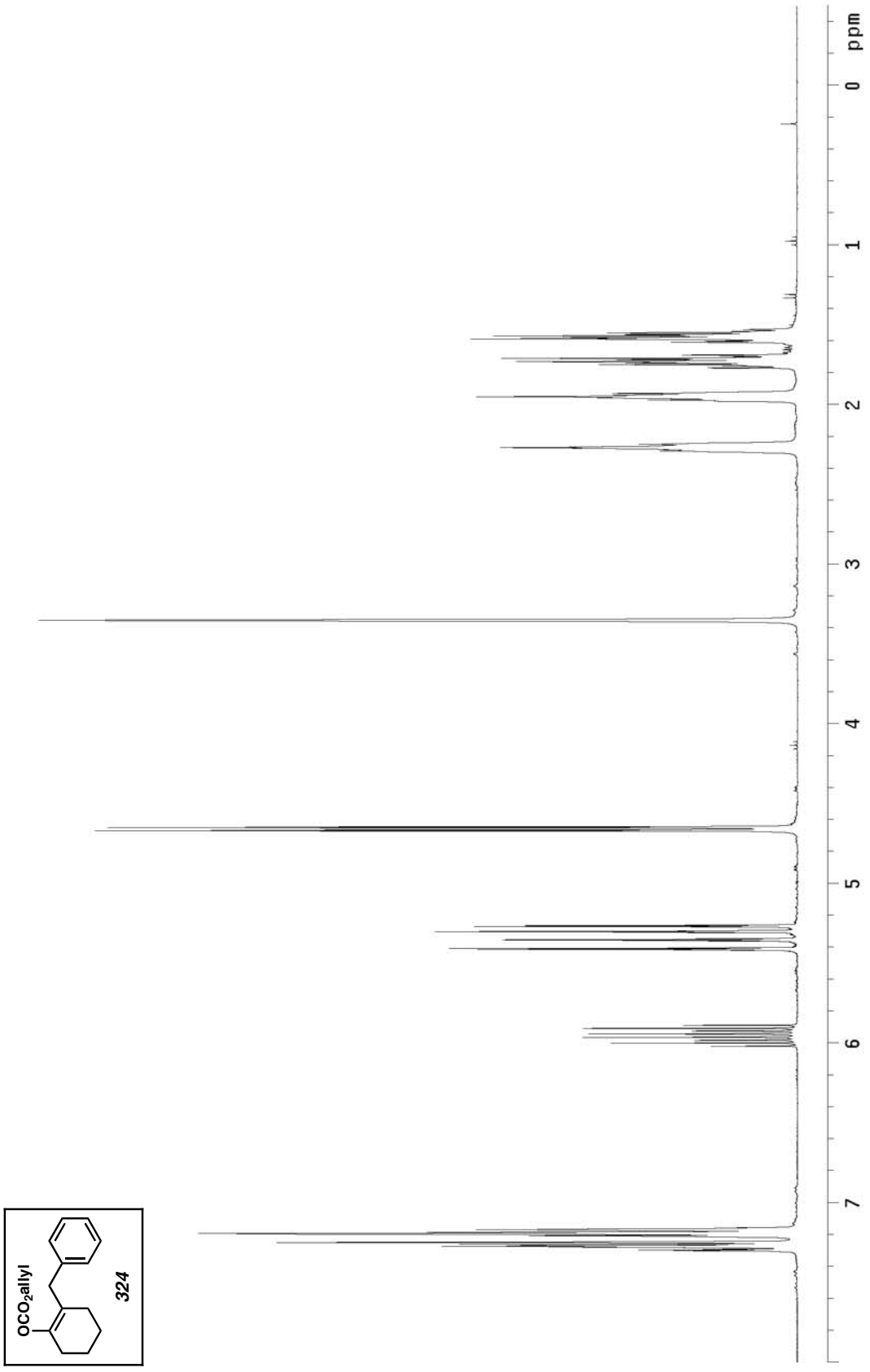


Figure A7.79 ^{1}H NMR of compound **324** (300 MHz, $CDCl_3$)

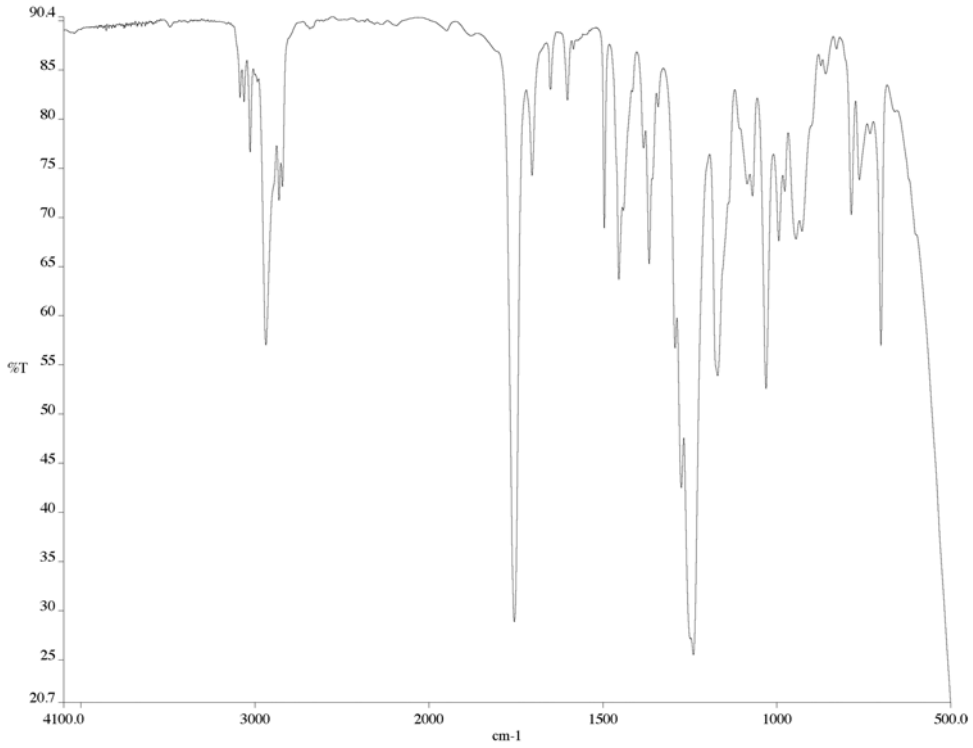


Figure A7.80 IR of compound **324** (NaCl/film)

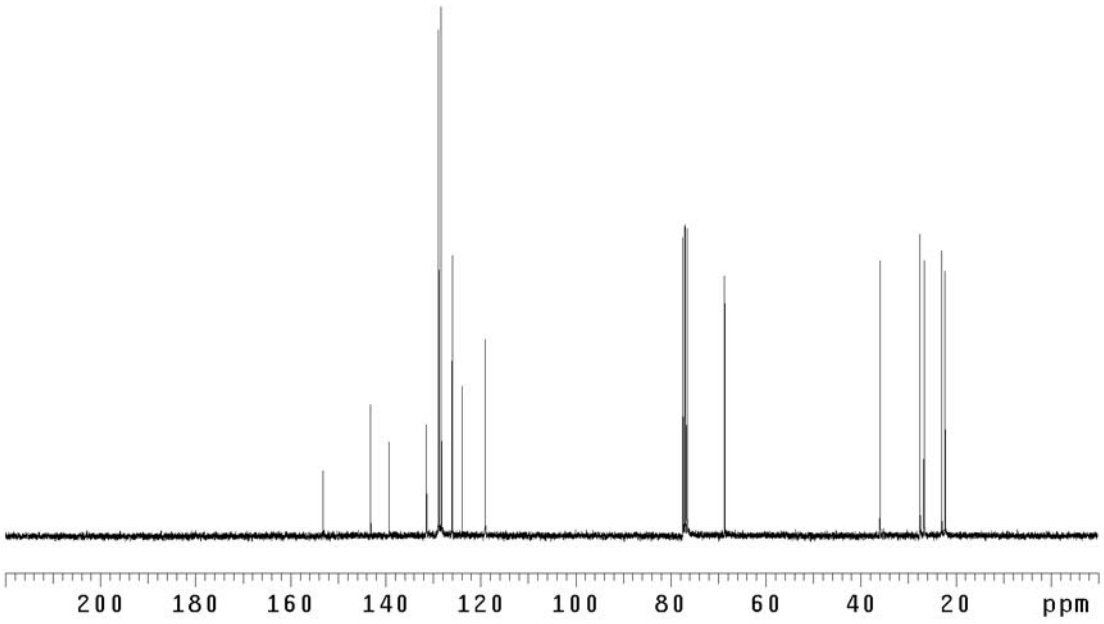


Figure A7.81 ^{13}C NMR of compound **324** (75 MHz, $CDCl_3$)

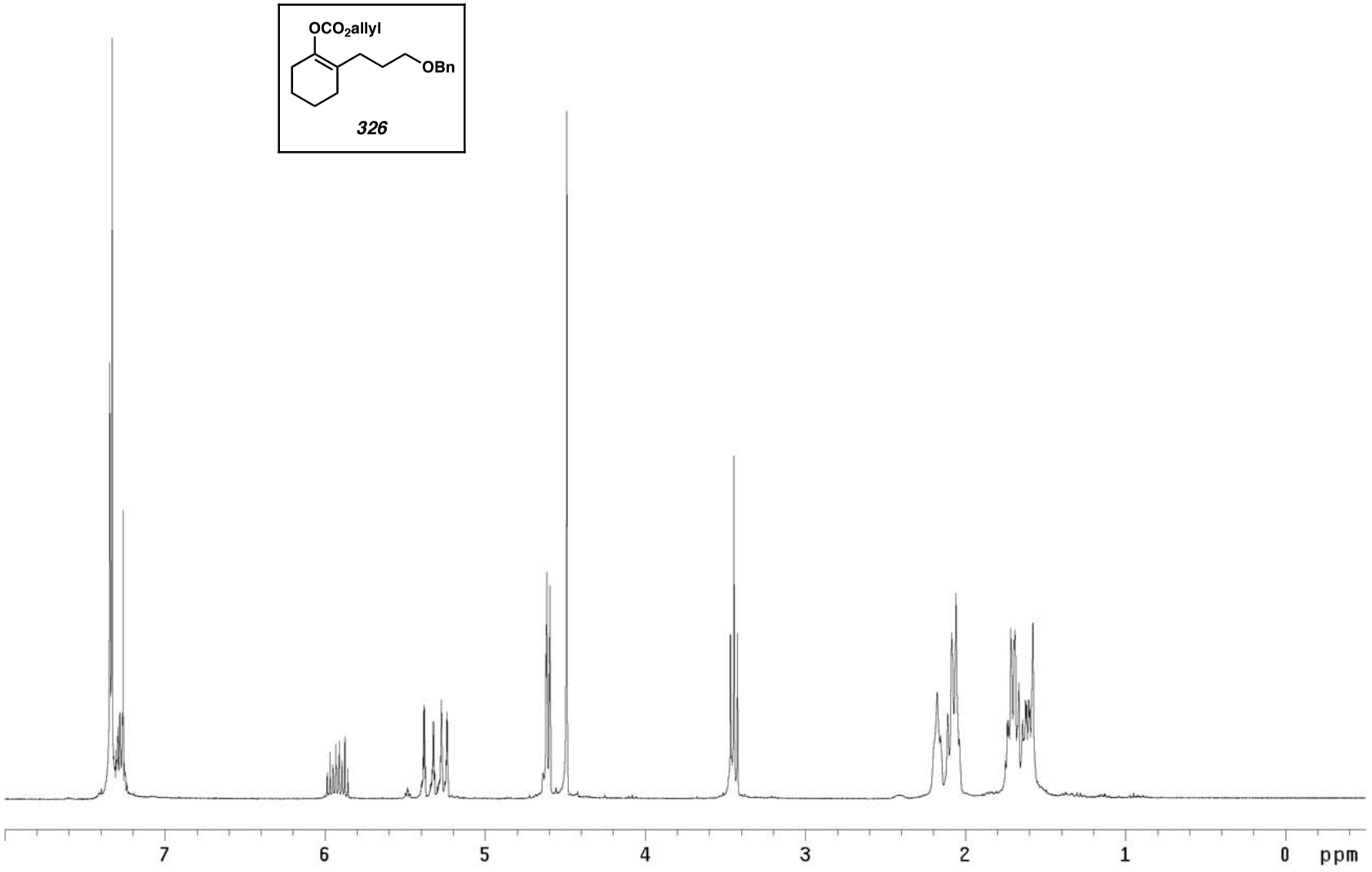


Figure A7.82 ^{1}H NMR of compound **326** (300 MHz, $CDCl_3$)

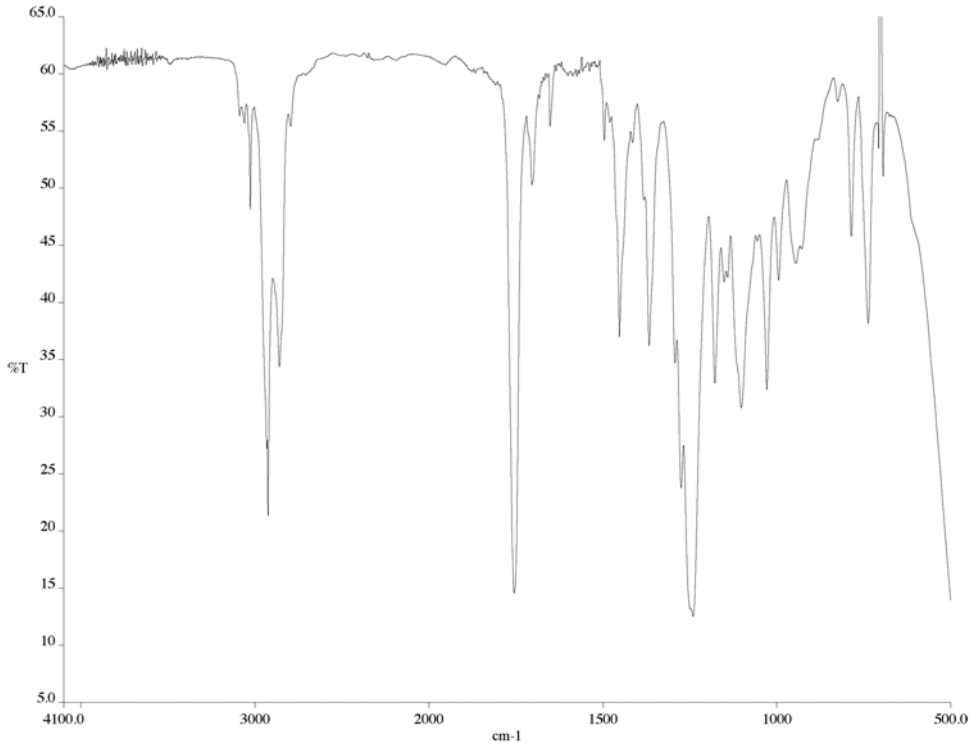


Figure A7.83 IR of compound **326** (NaCl/film)

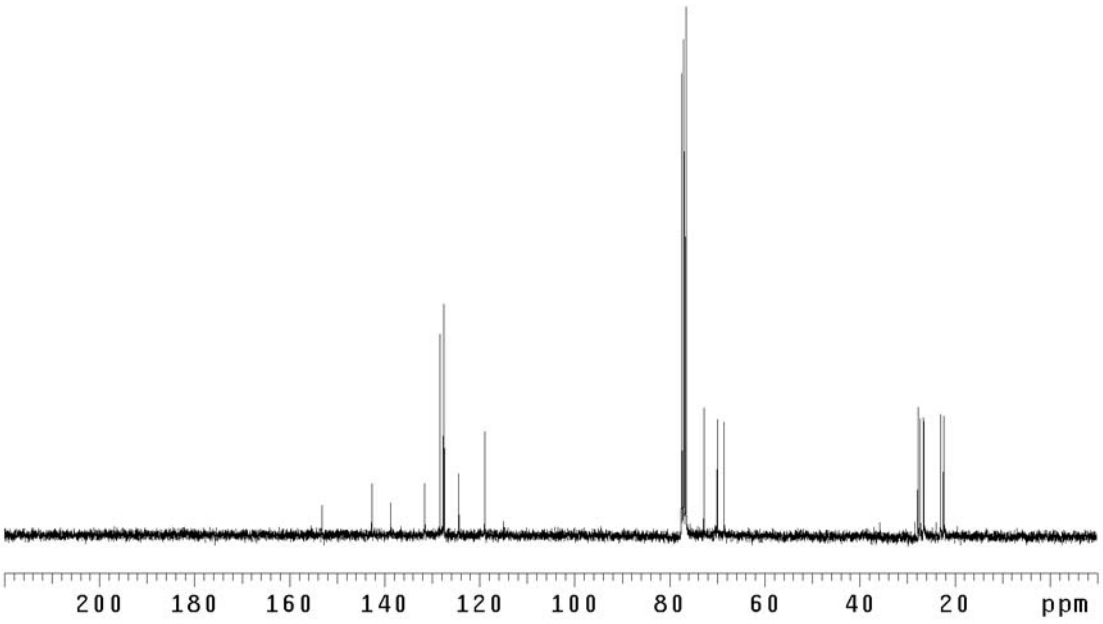


Figure A7.84 ^{13}C NMR of compound **326** (75 MHz, $CDCl_3$)

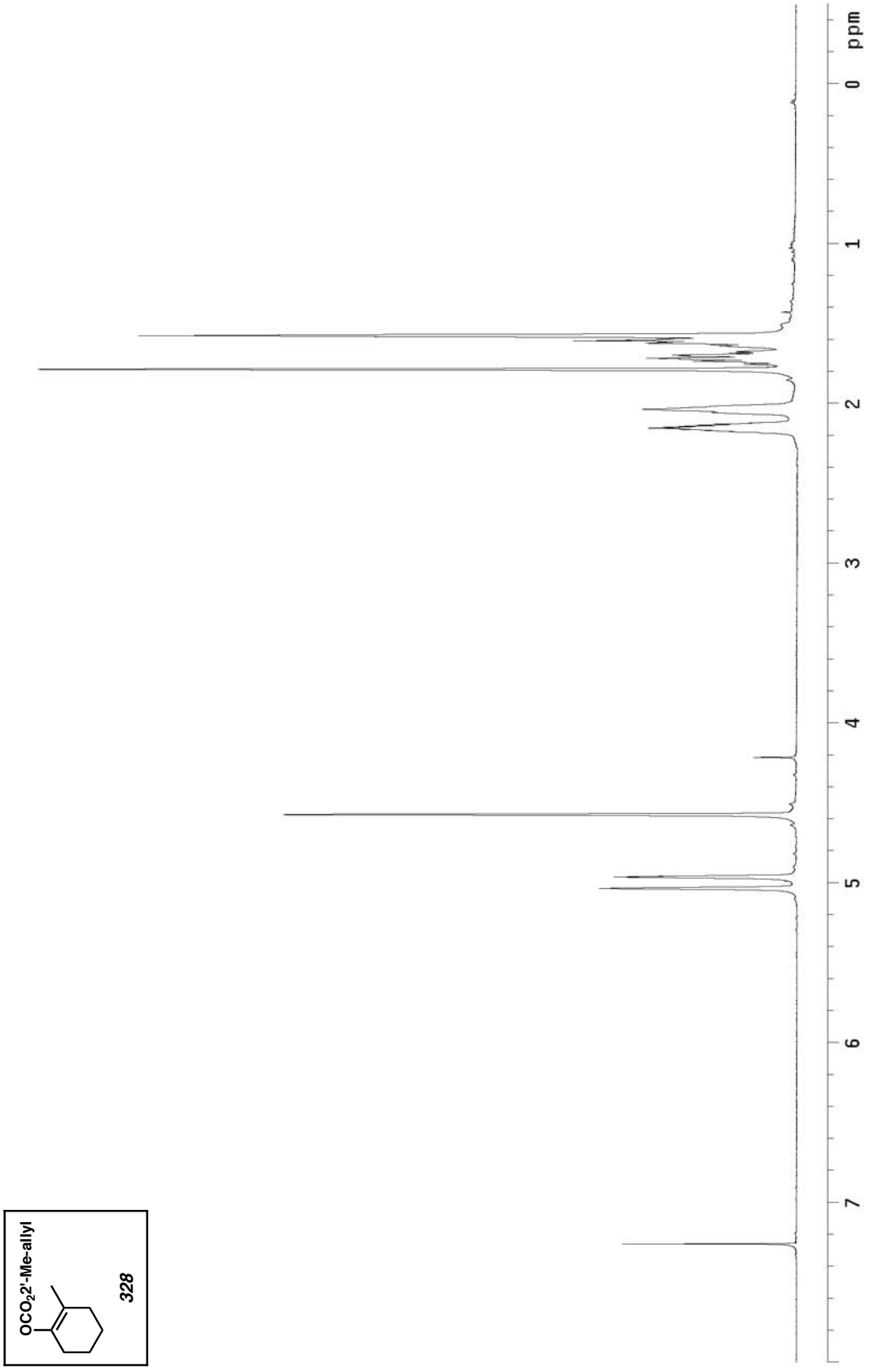


Figure A7.85 ^{1}H NMR of compound **328** (300 MHz, $CDCl_3$)

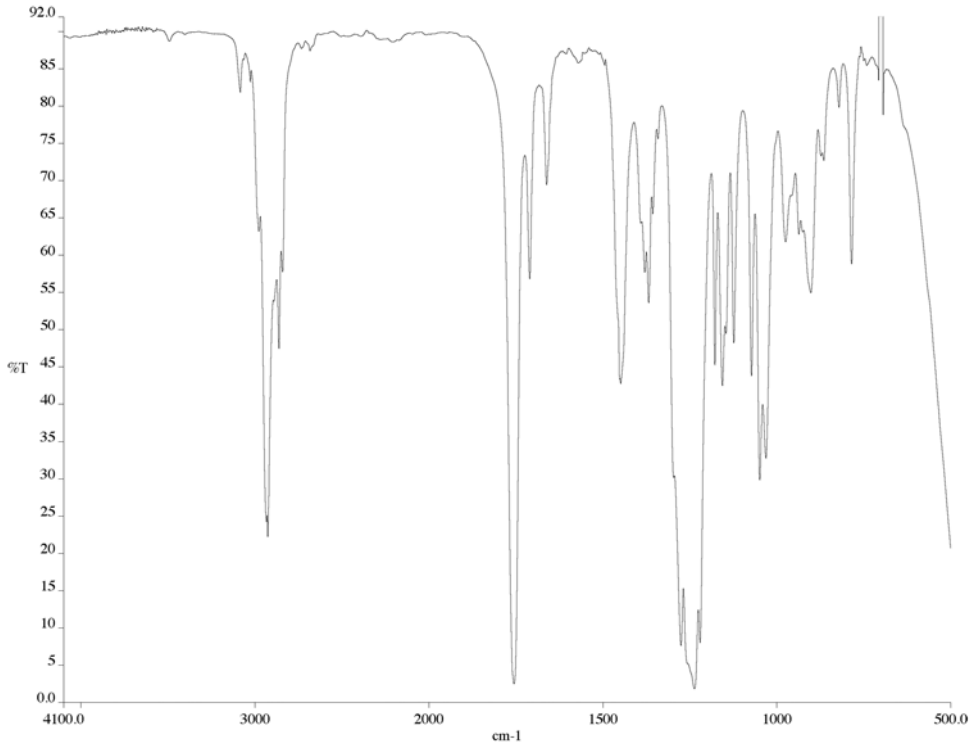


Figure A7.86 IR of compound **328** (NaCl/film)

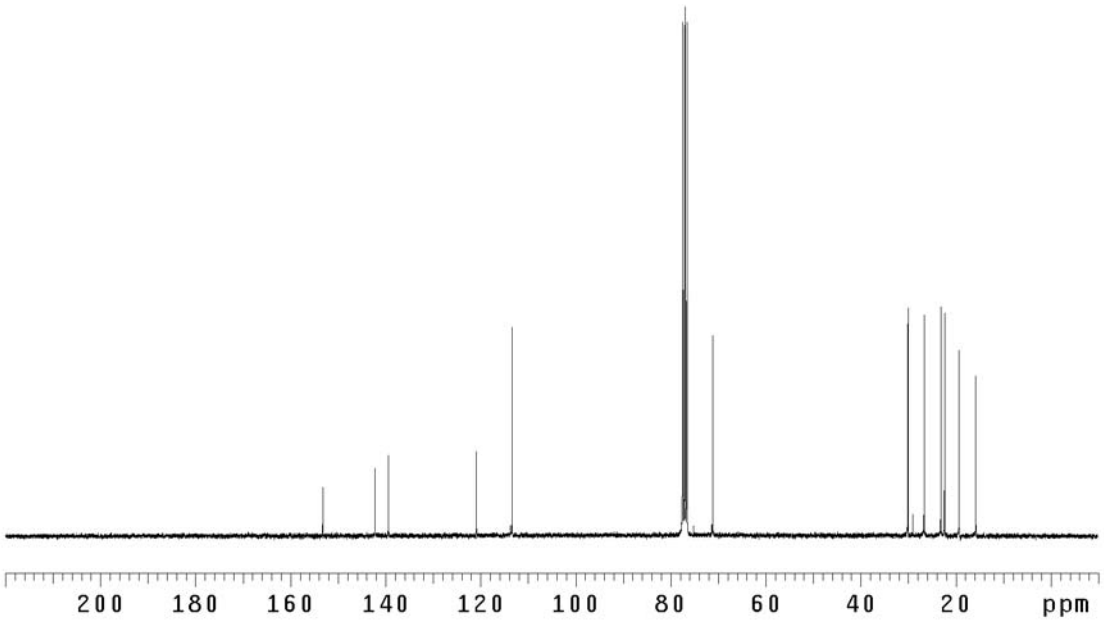


Figure A7.87 ^{13}C NMR of compound **328** (75 MHz, $CDCl_3$)

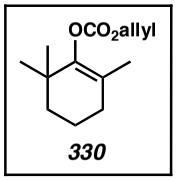


Figure A7.88 ^{1}H NMR of compound **330** (300 MHz, $CDCl_3$)

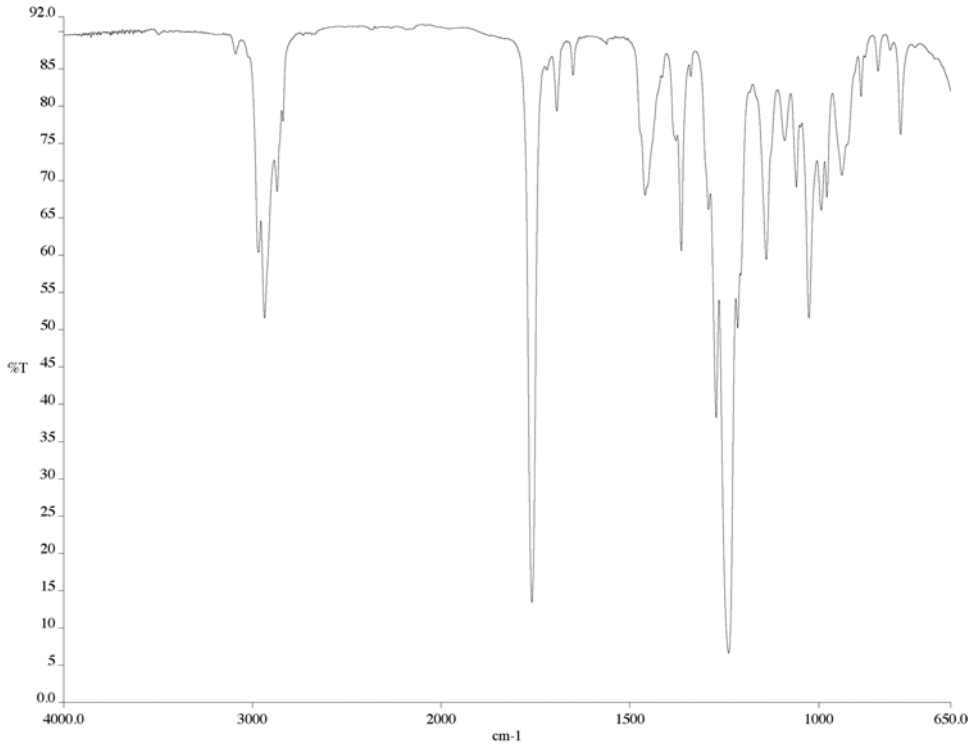


Figure A7.89 IR of compound **330** (NaCl/film)

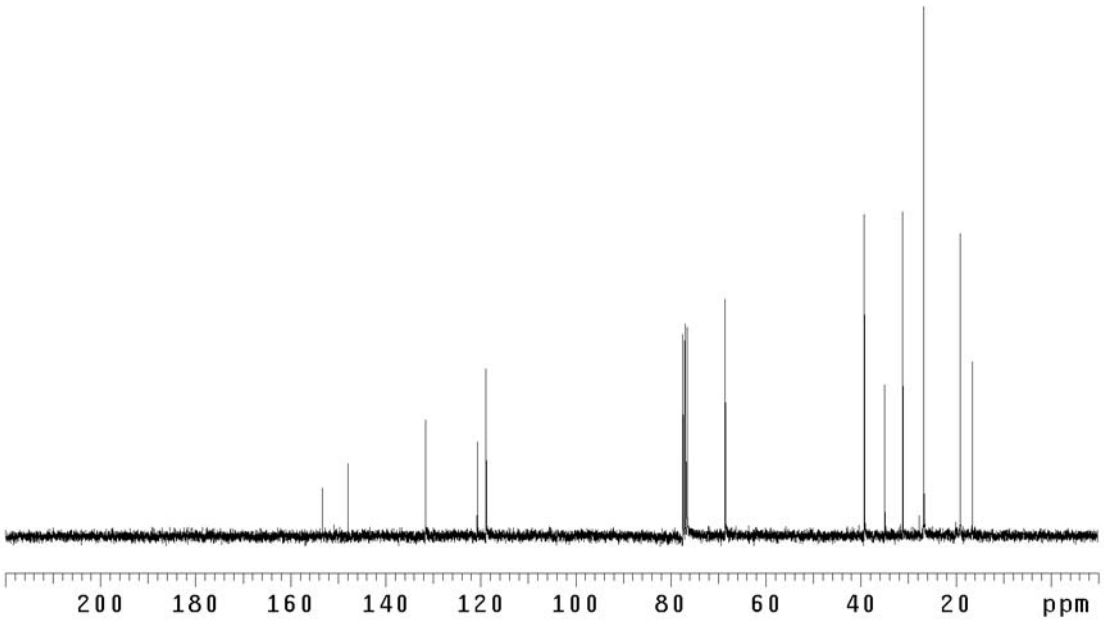


Figure A7.90 ^{13}C NMR of compound **330** (75 MHz, $CDCl_3$)

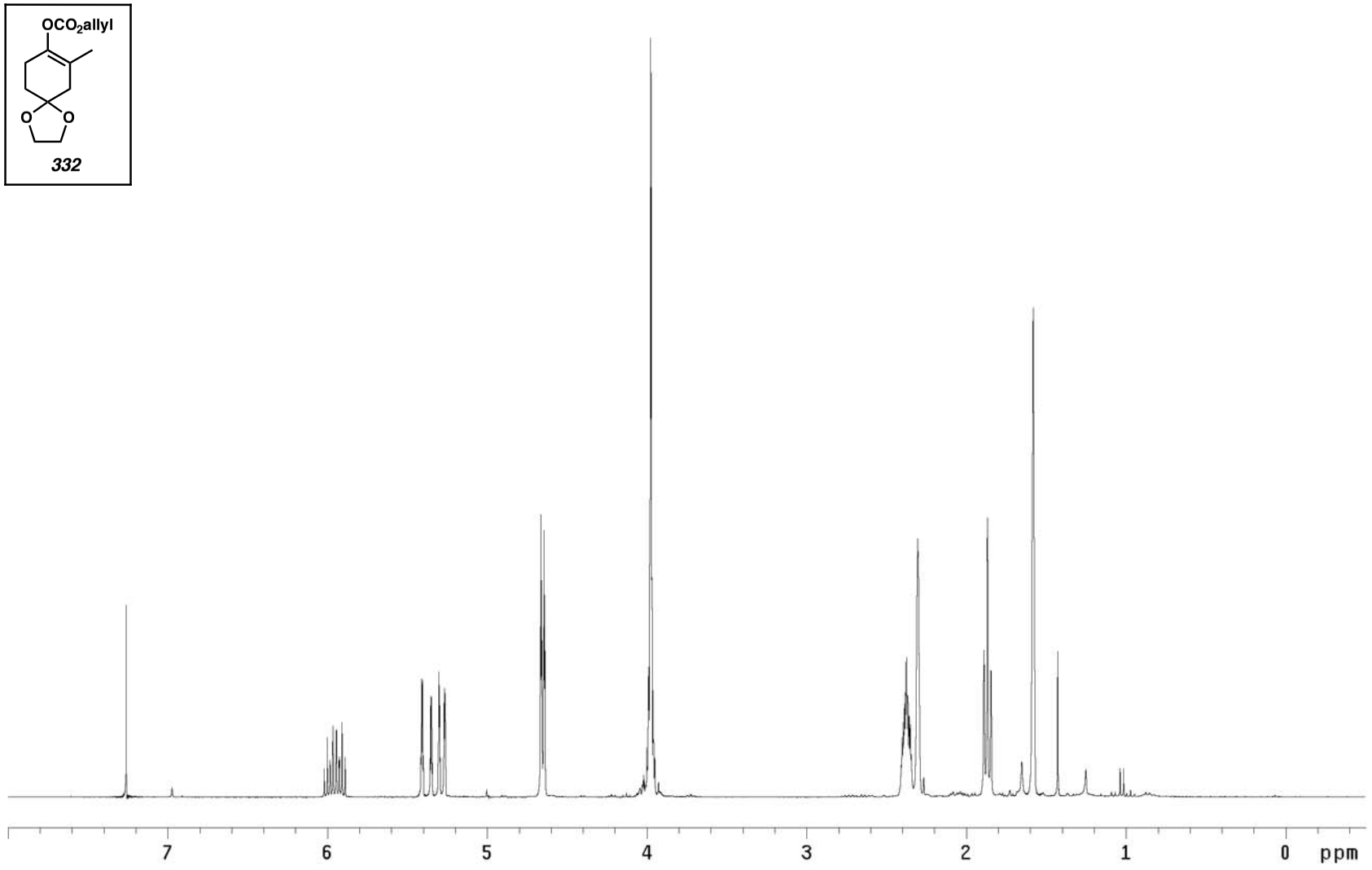


Figure A7.91 ^{1}H NMR of compound **332** (300 MHz, $CDCl_3$)

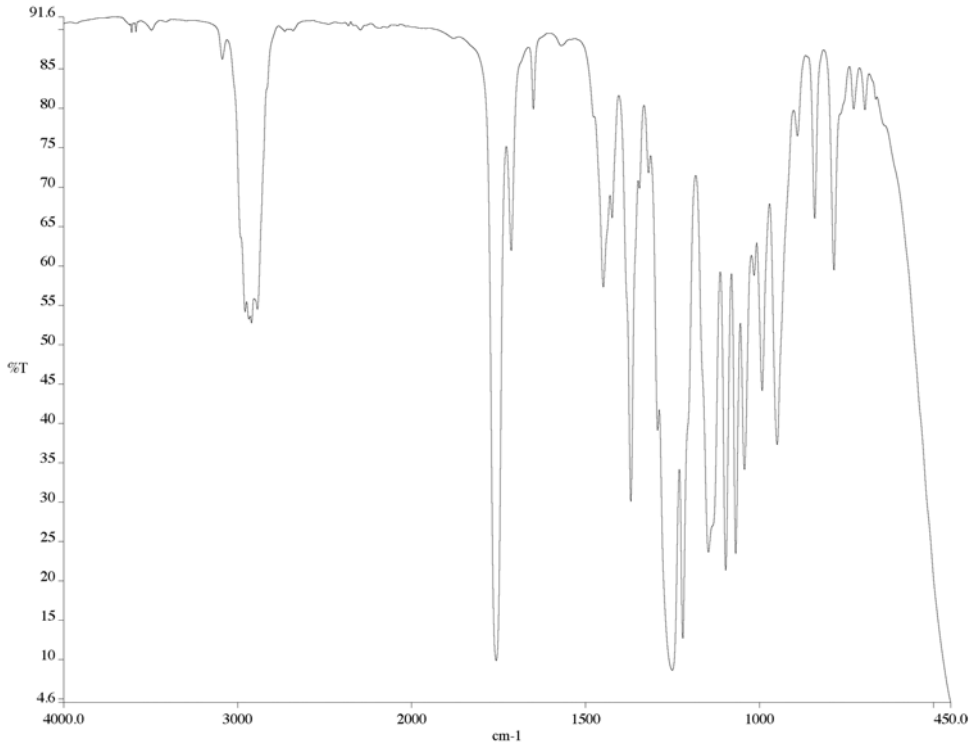


Figure A7.92 IR of compound **332** (NaCl/film)

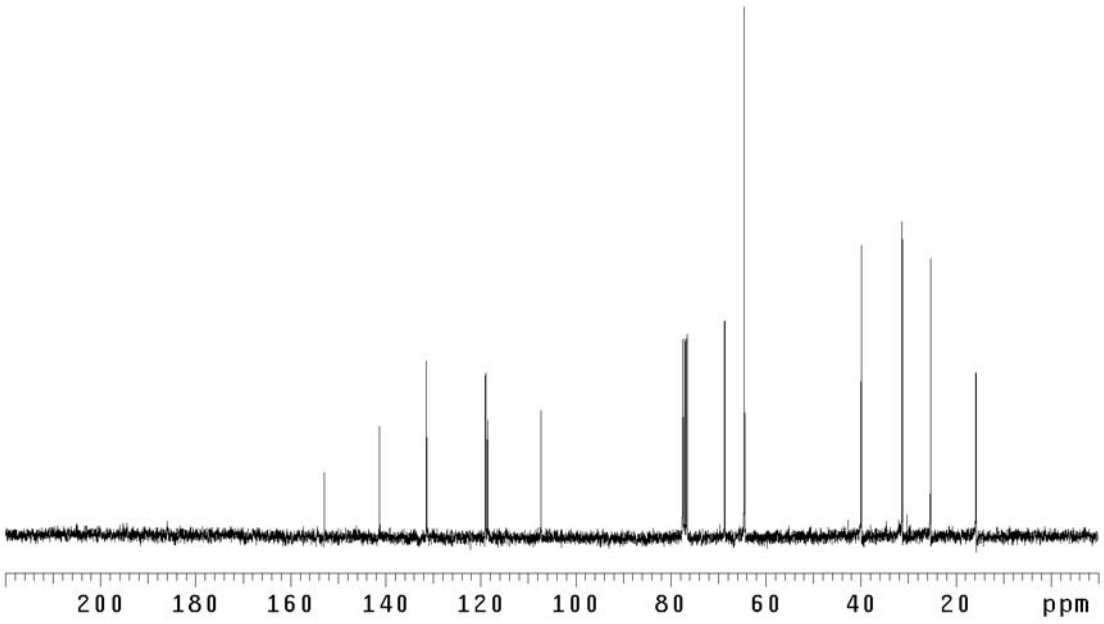


Figure A7.93 ^{13}C NMR of compound **332** (75 MHz, $CDCl_3$)

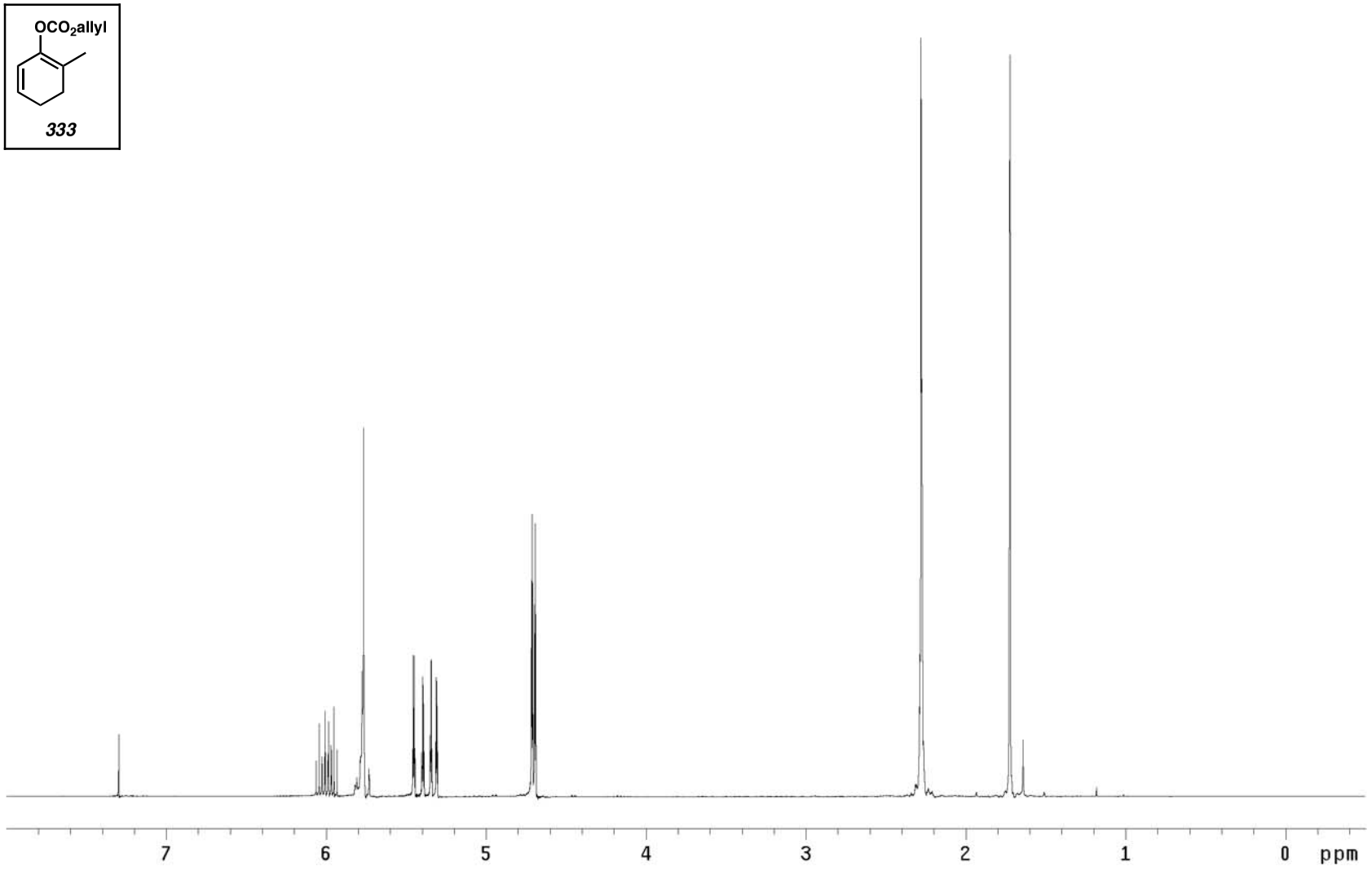


Figure A7.94 ^{1}H NMR of compound **333** (300 MHz, $CDCl_3$)

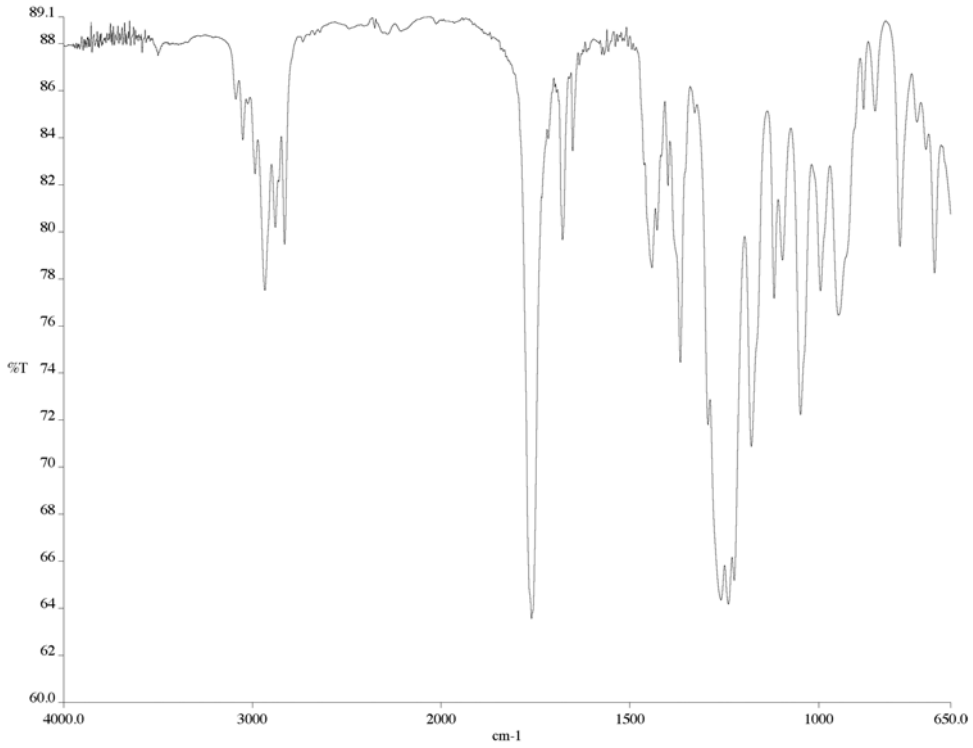


Figure A7.95 IR of compound **333** (NaCl/film)

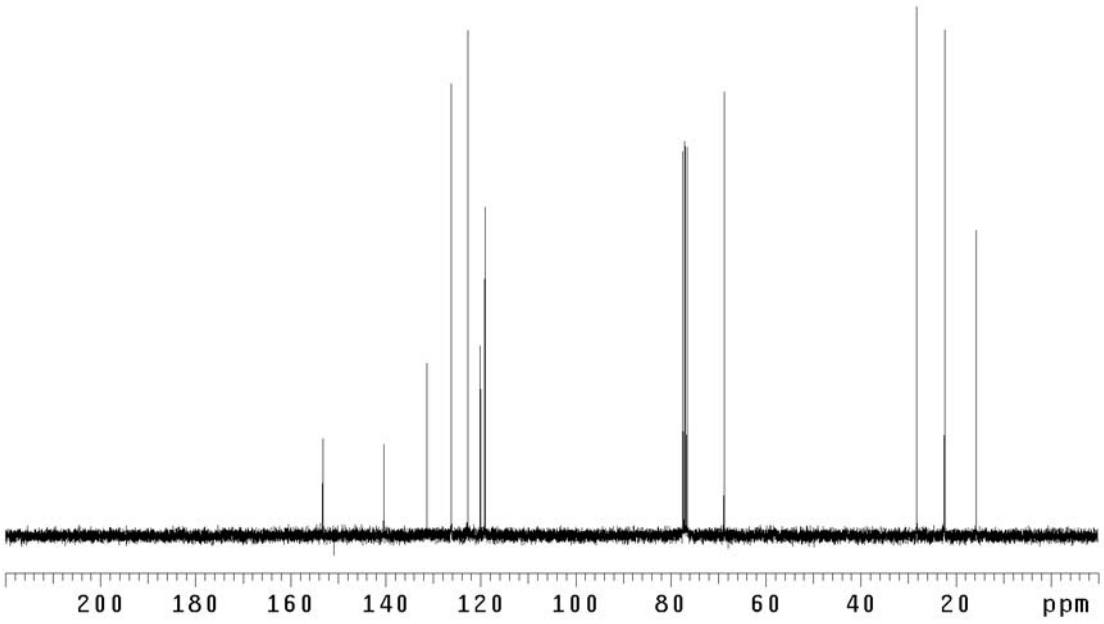


Figure A7.96 ^{13}C NMR of compound **333** (75 MHz, $CDCl_3$)

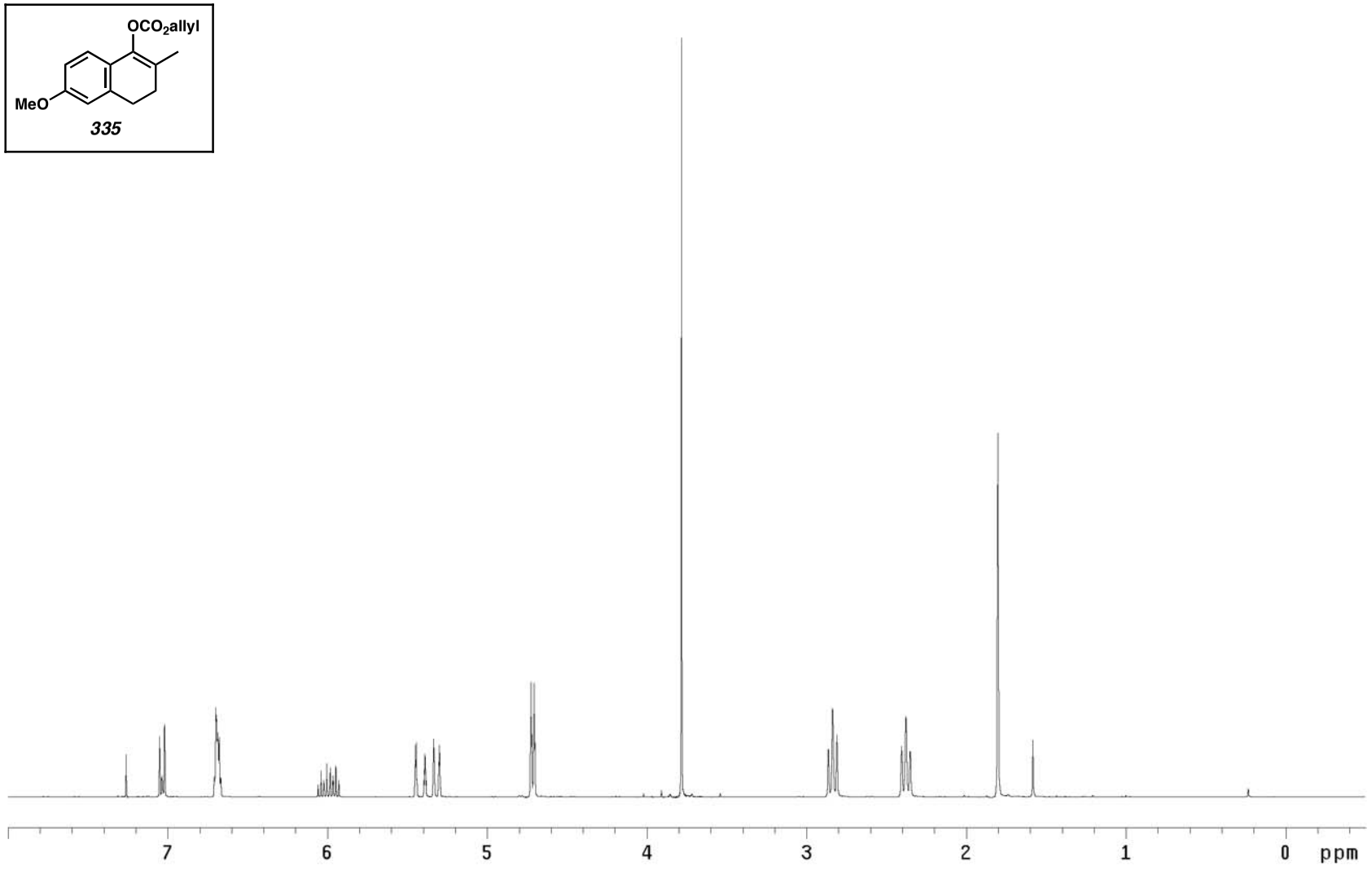


Figure A7.97 ^{1}H NMR of compound **335** (300 MHz, $CDCl_3$)

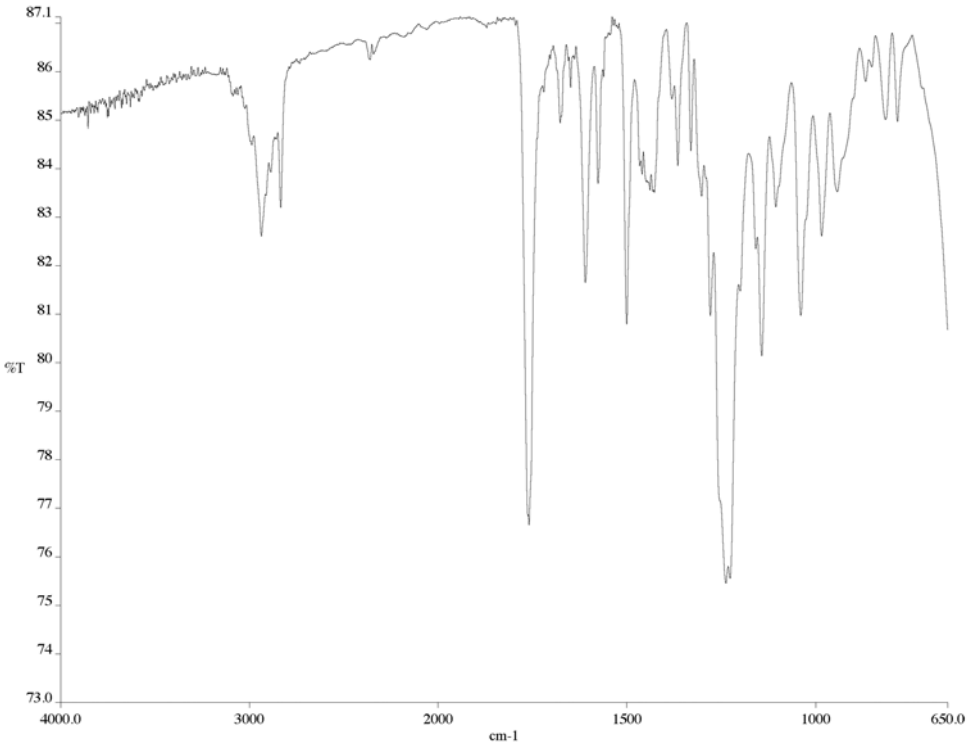


Figure A7.98 IR of compound **335** (NaCl/film)

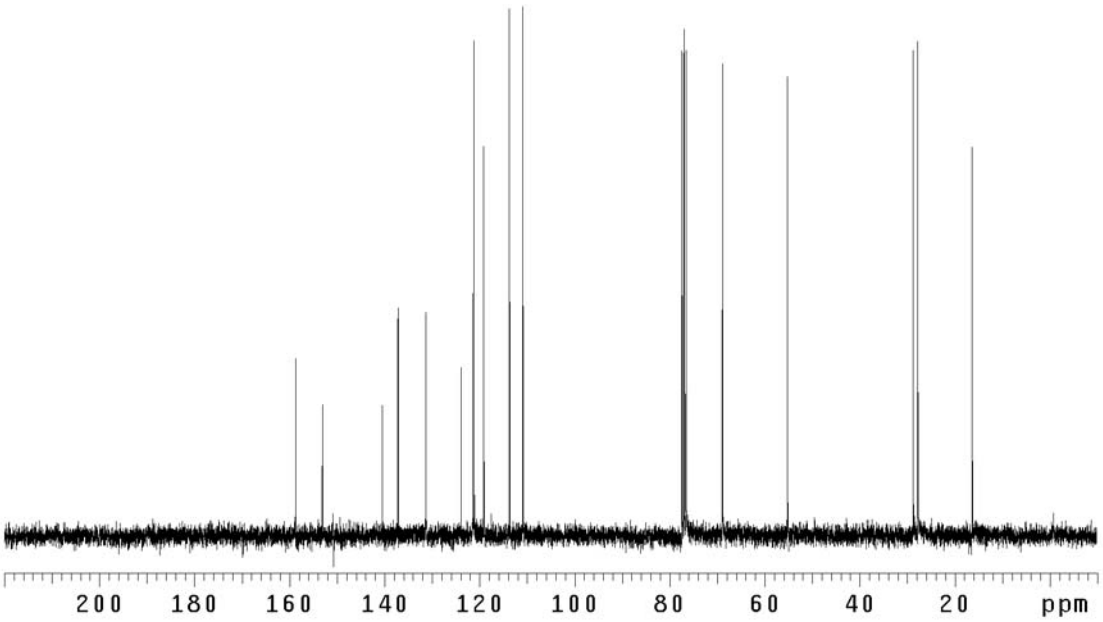


Figure A7.99 ^{13}C NMR of compound **335** (75 MHz, $CDCl_3$)

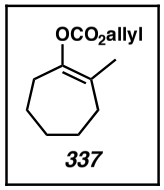


Figure A7.100 ^{1}H NMR of compound **337** (300 MHz, $CDCl_3$)

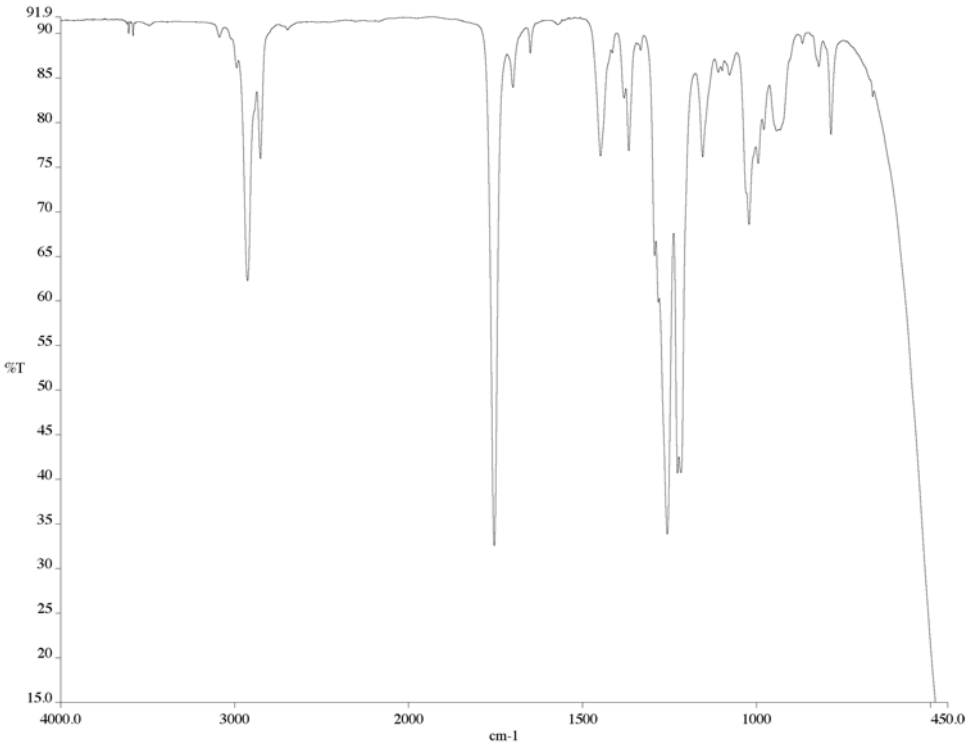


Figure A7.101 IR of compound **337** (NaCl/film)

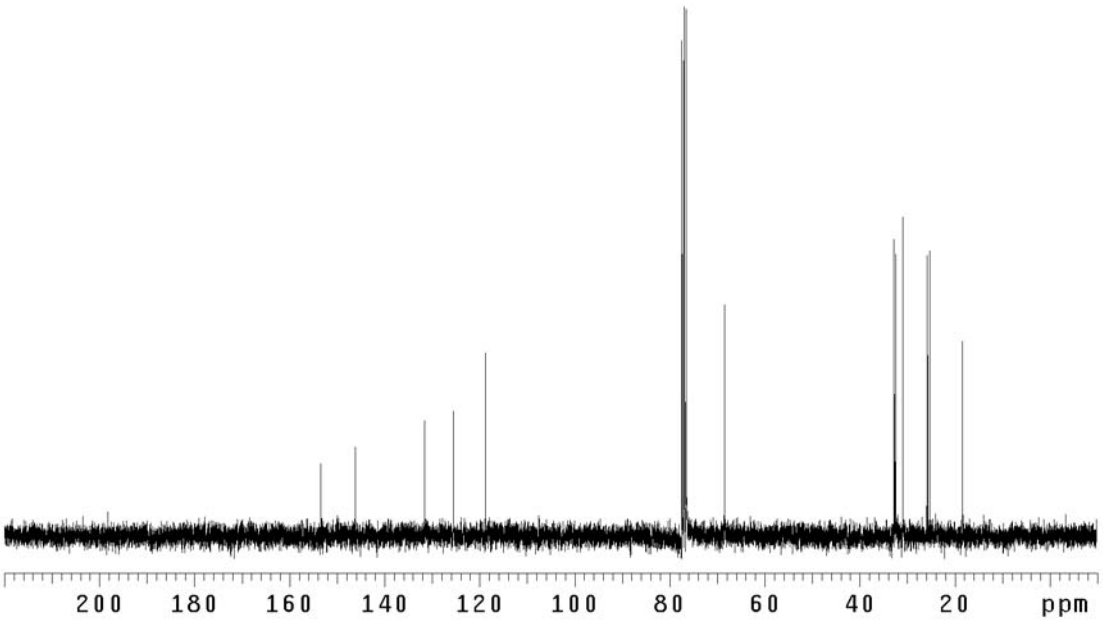


Figure A7.102 ^{13}C NMR of compound **337** (75 MHz, $CDCl_3$)

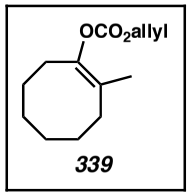


Figure A7.103 ^{1}H NMR of compound **339** (300 MHz, $CDCl_3$)

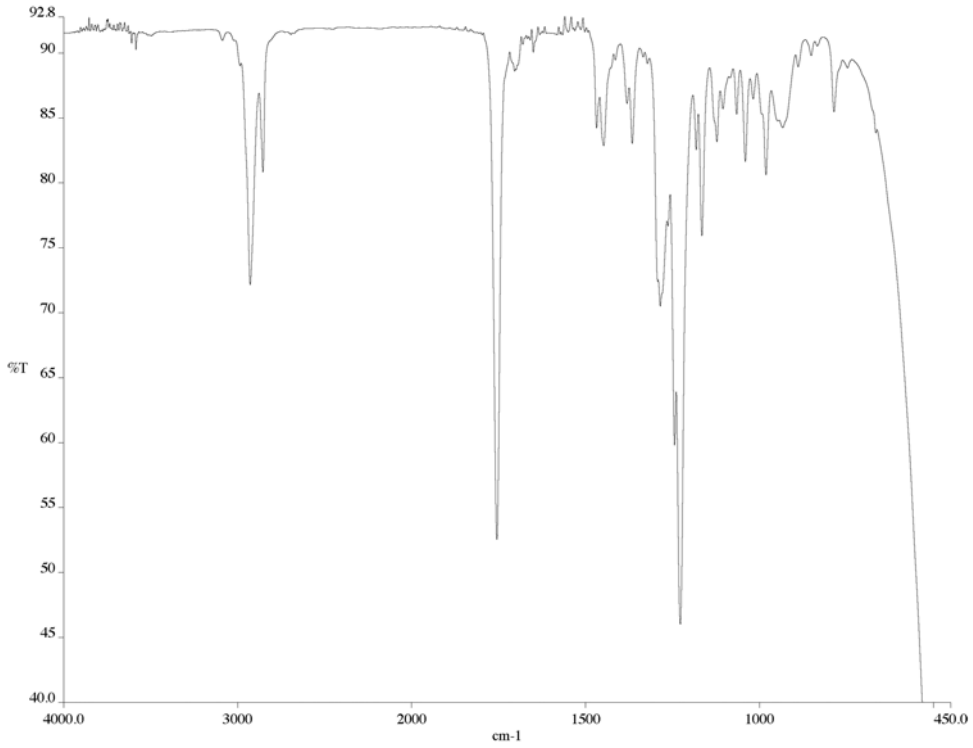


Figure A7.104 IR of compound **339** (NaCl/film)

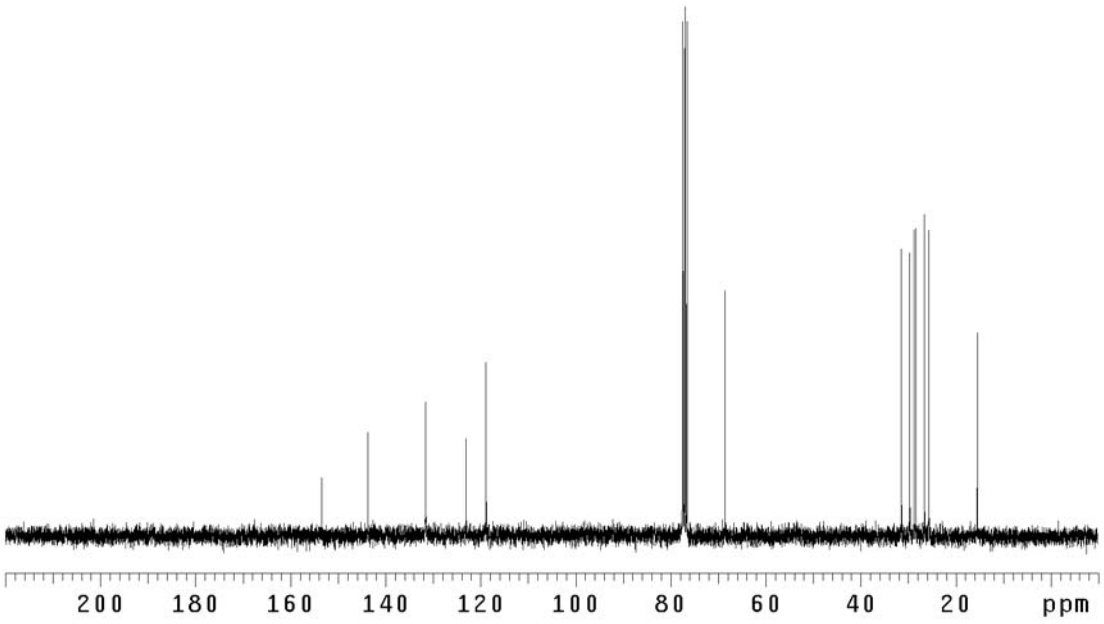


Figure A7.105 ^{13}C NMR of compound **339** (75 MHz, $CDCl_3$)

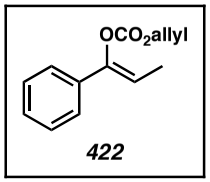


Figure A7.106 ^{1}H NMR of compound **422** (300 MHz, $CDCl_3$)

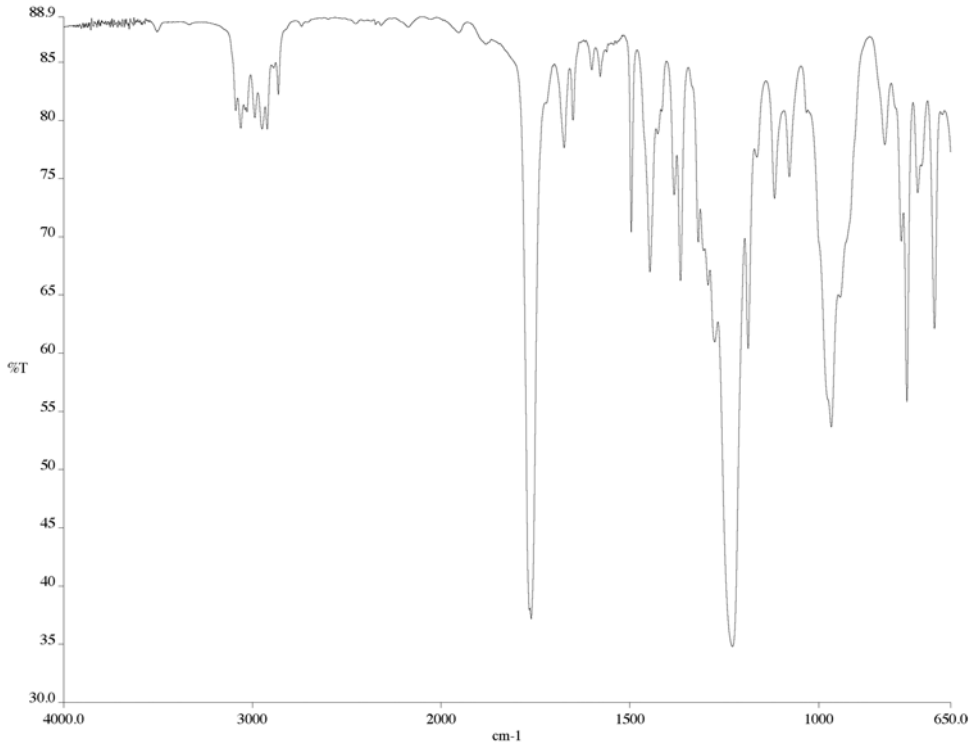


Figure A7.107 IR of compound **422** (NaCl/film)

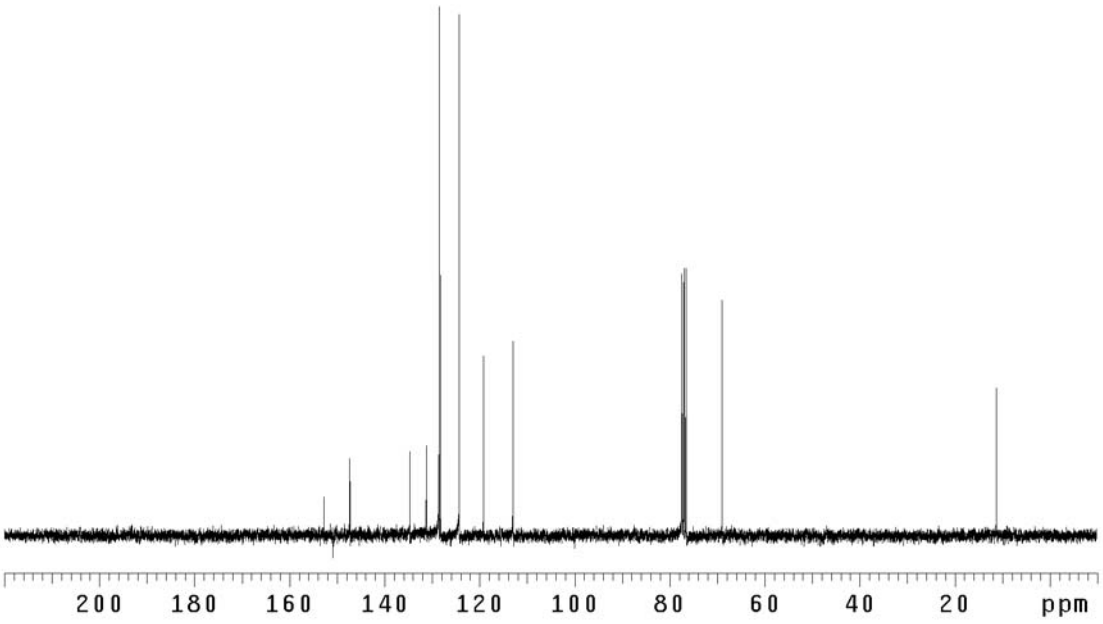


Figure A7.108 ^{13}C NMR of compound **422** (75 MHz, $CDCl_3$)

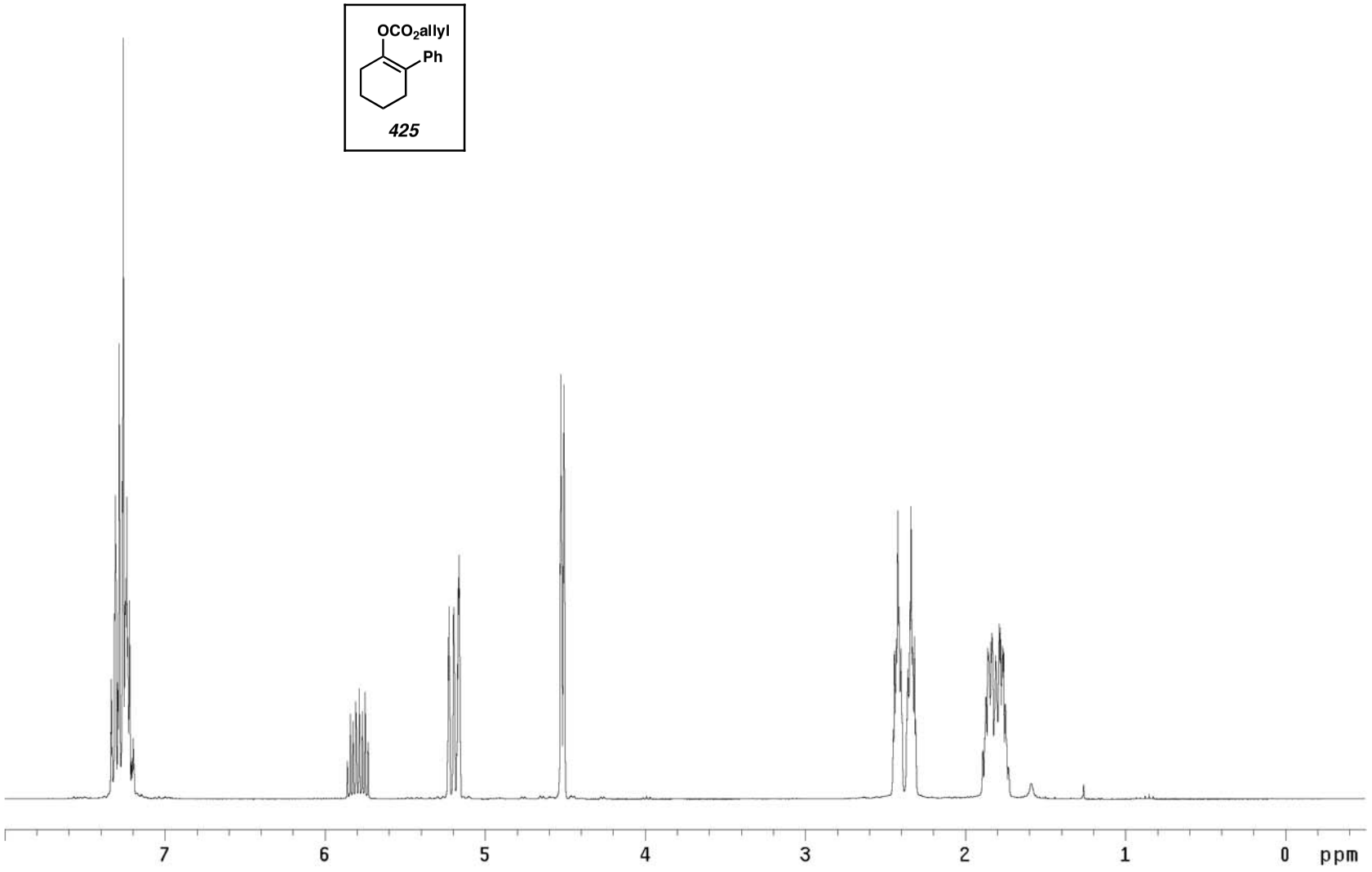


Figure A7.109 ^{1}H NMR of compound **425** (300 MHz, $CDCl_3$)

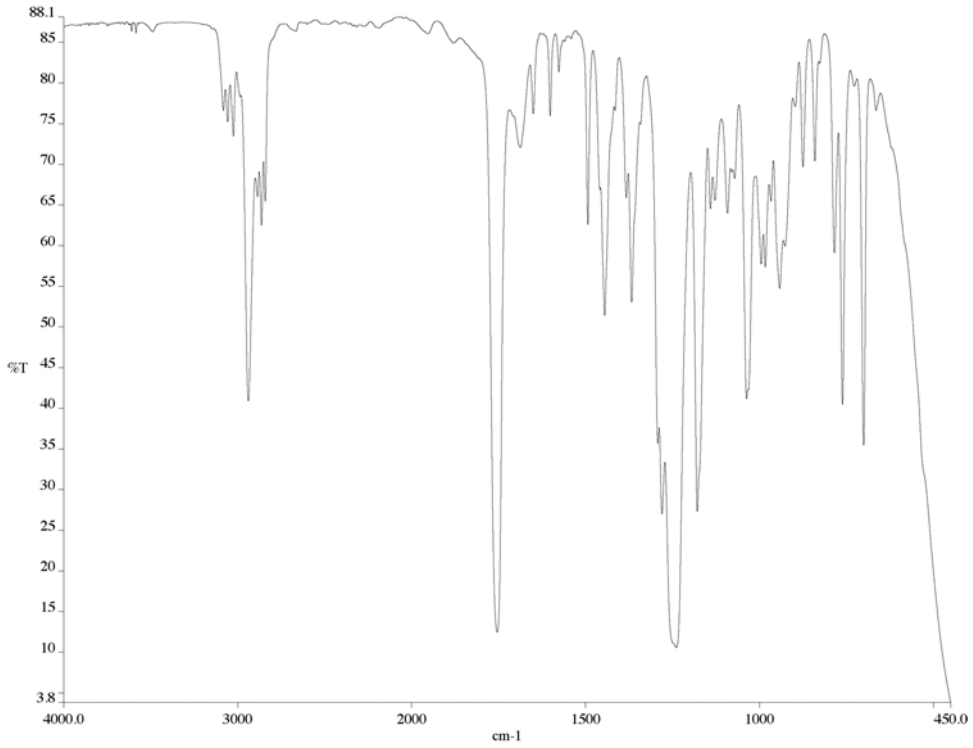


Figure A7.110 IR of compound **425** (NaCl/film)

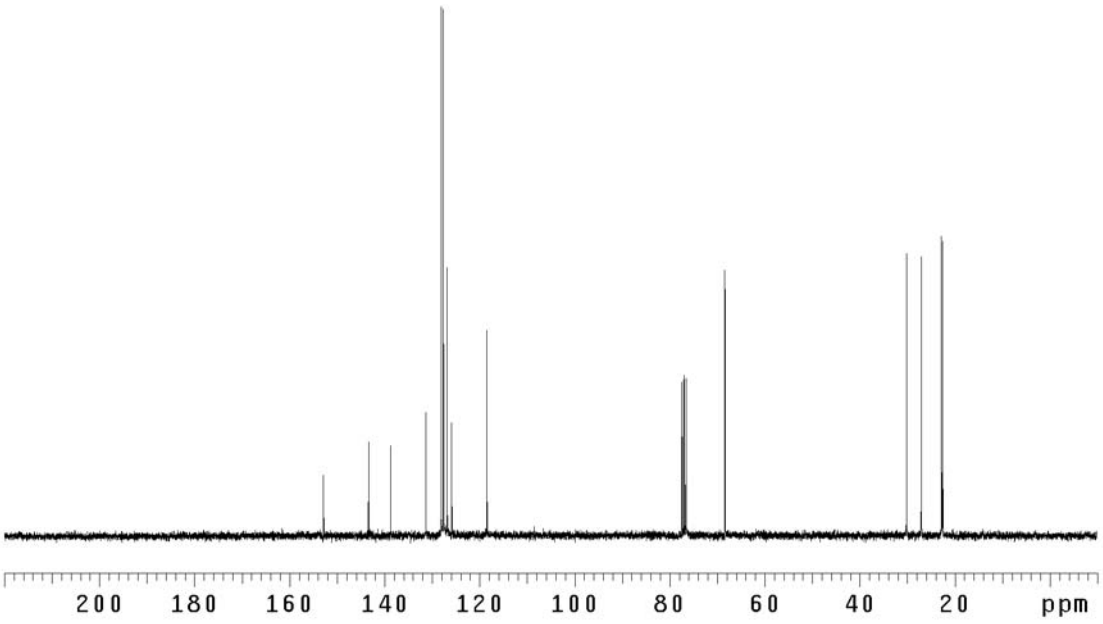


Figure A7.111 ^{13}C NMR of compound **425** (75 MHz, $CDCl_3$)

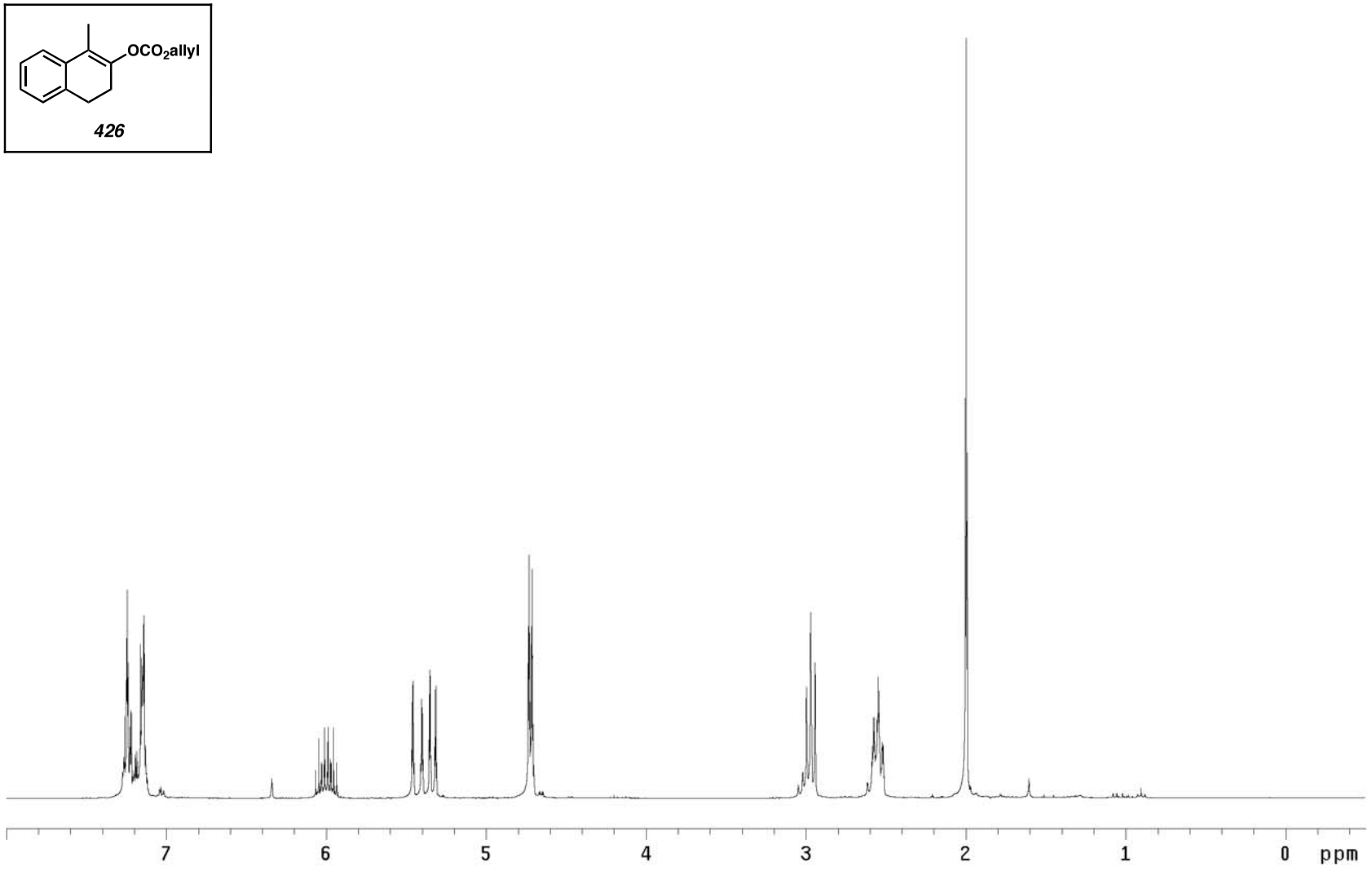


Figure A7.112 ^{1}H NMR of compound **426** (300 MHz, $CDCl_3$)

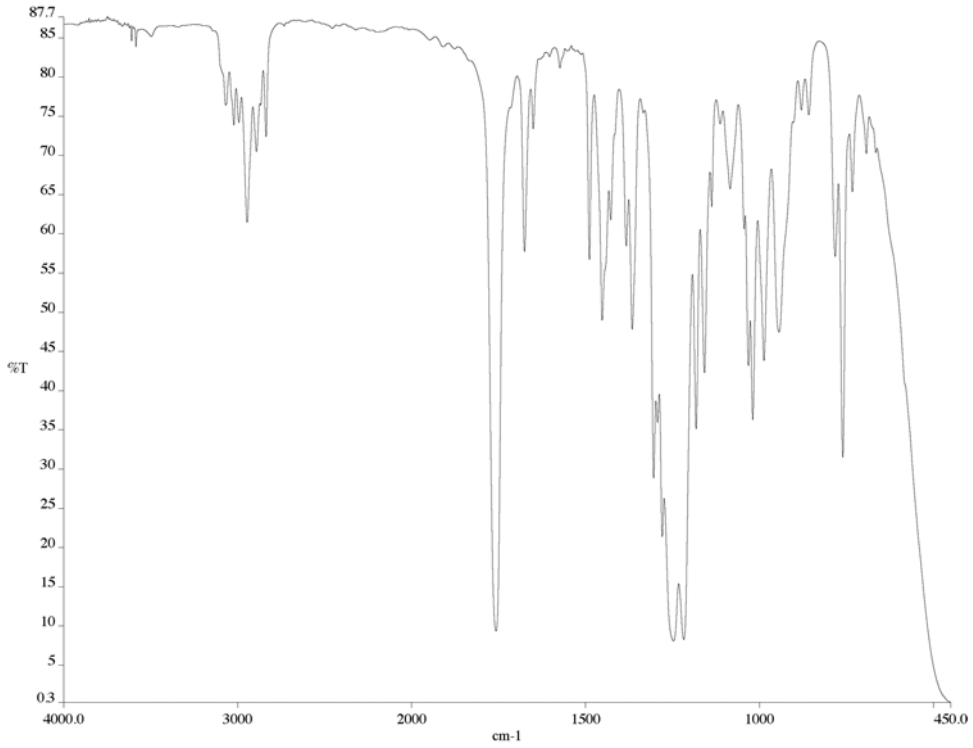


Figure A7.113 IR of compound **426** (NaCl/film)

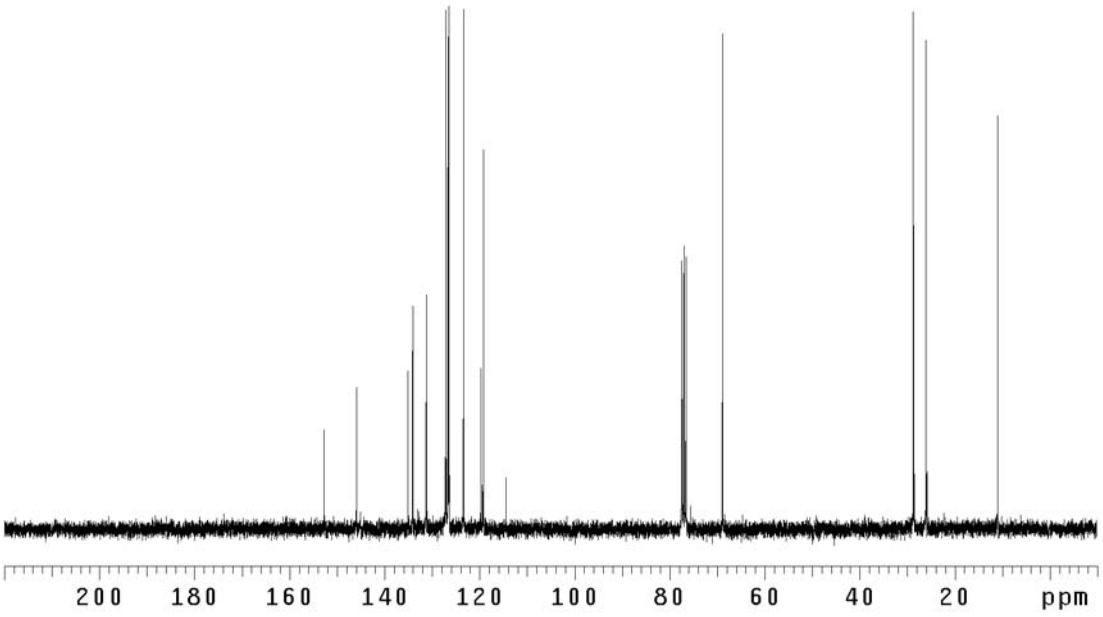


Figure A7.114 ^{13}C NMR of compound **426** (75 MHz, $CDCl_3$)

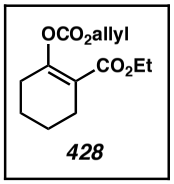


Figure A7.115 ^{1}H NMR of compound **428** (300 MHz, $CDCl_3$)

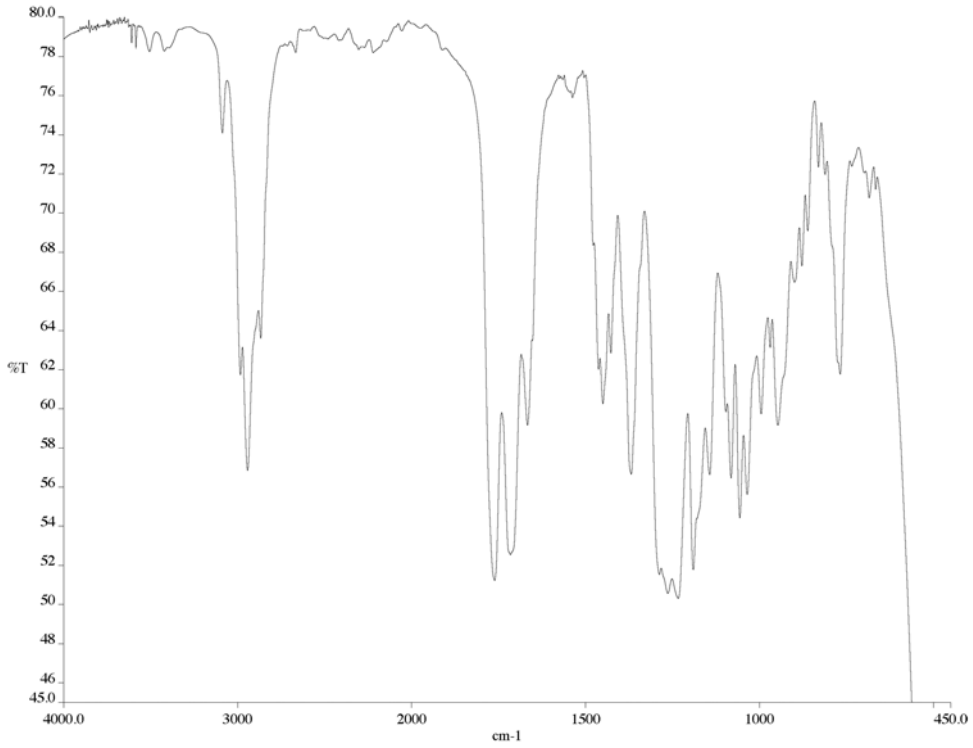


Figure A7.116 IR of compound **428** (NaCl/film)

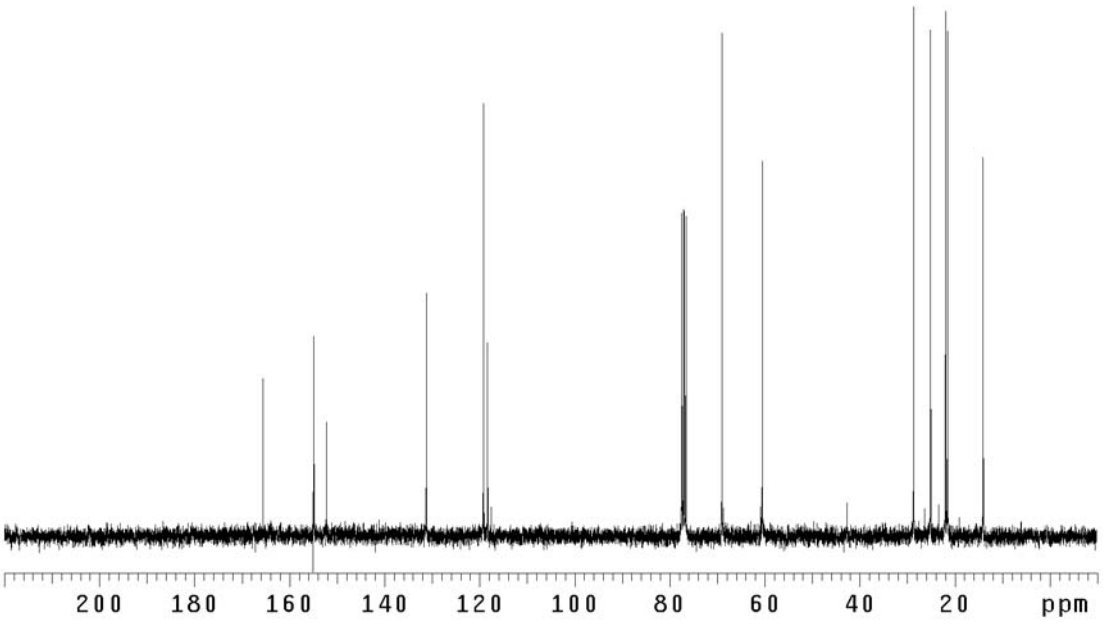


Figure A7.117 ^{13}C NMR of compound **428** (75 MHz, $CDCl_3$)

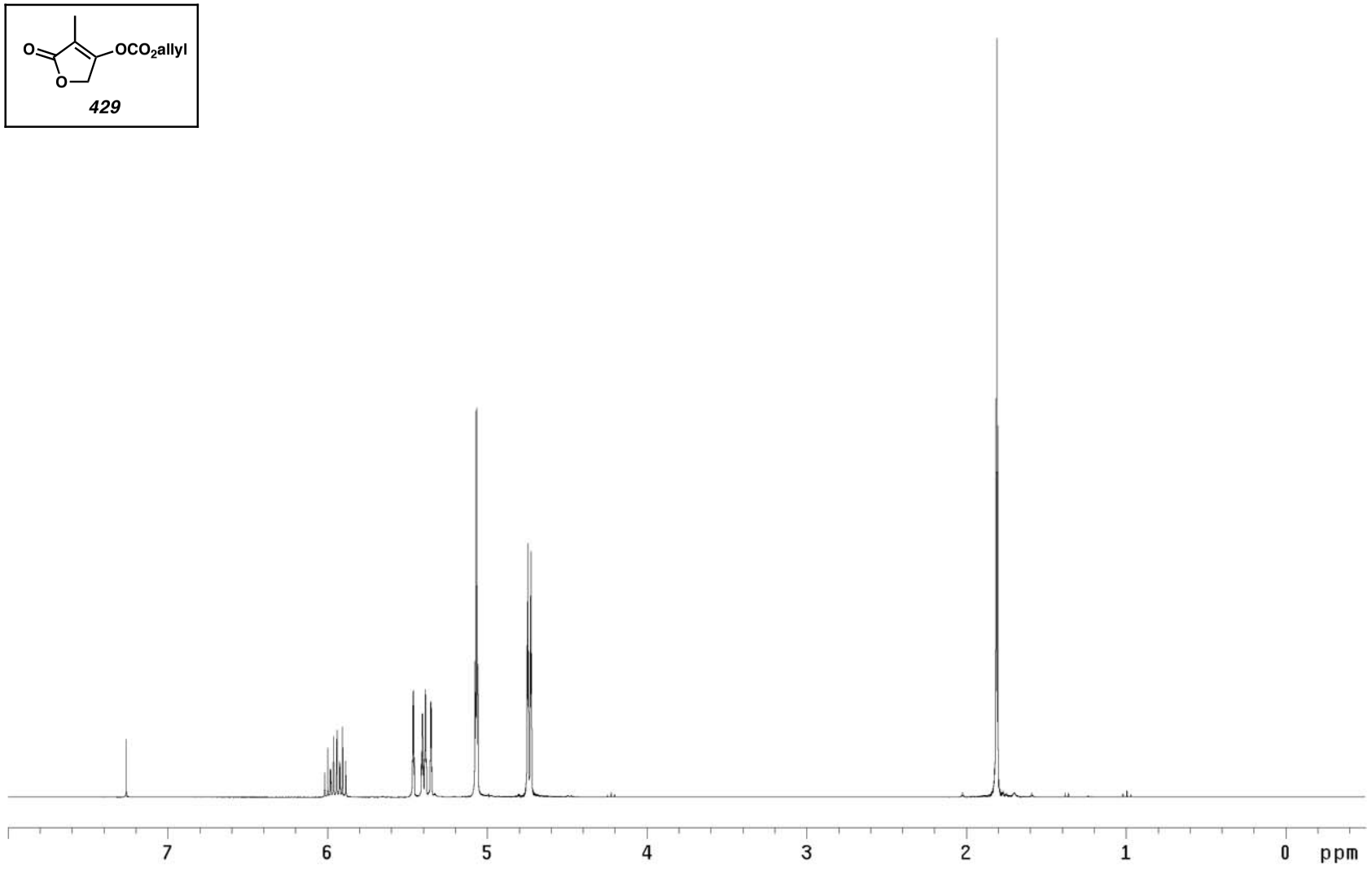


Figure A7.118 ^{1}H NMR of compound **429** (300 MHz, $CDCl_3$)

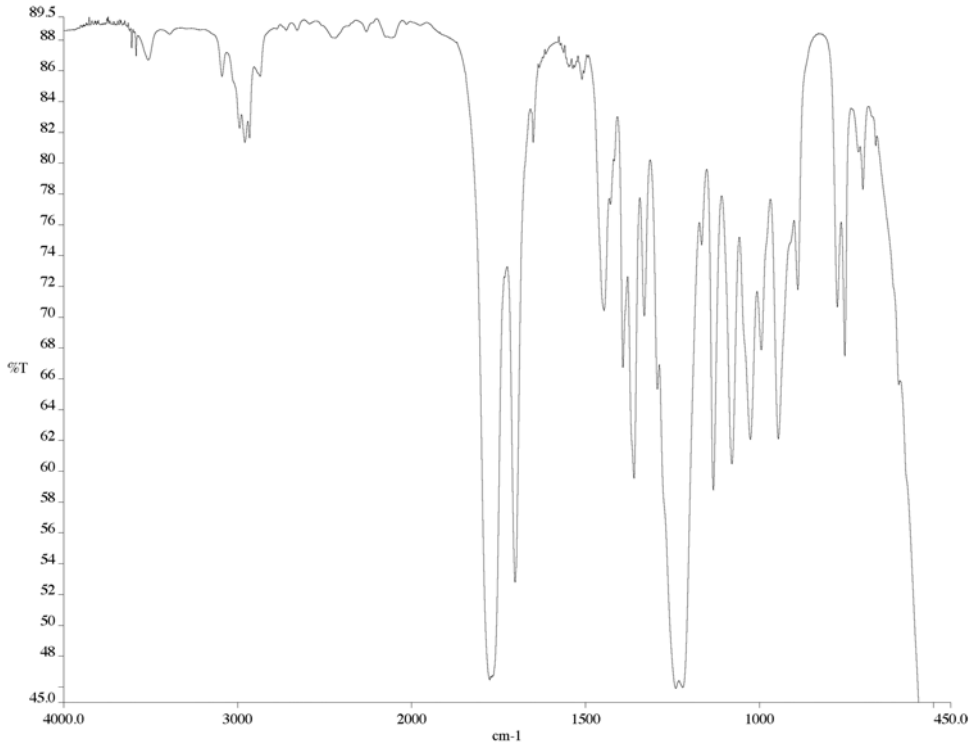


Figure A7.119 IR of compound **429** (NaCl/film)

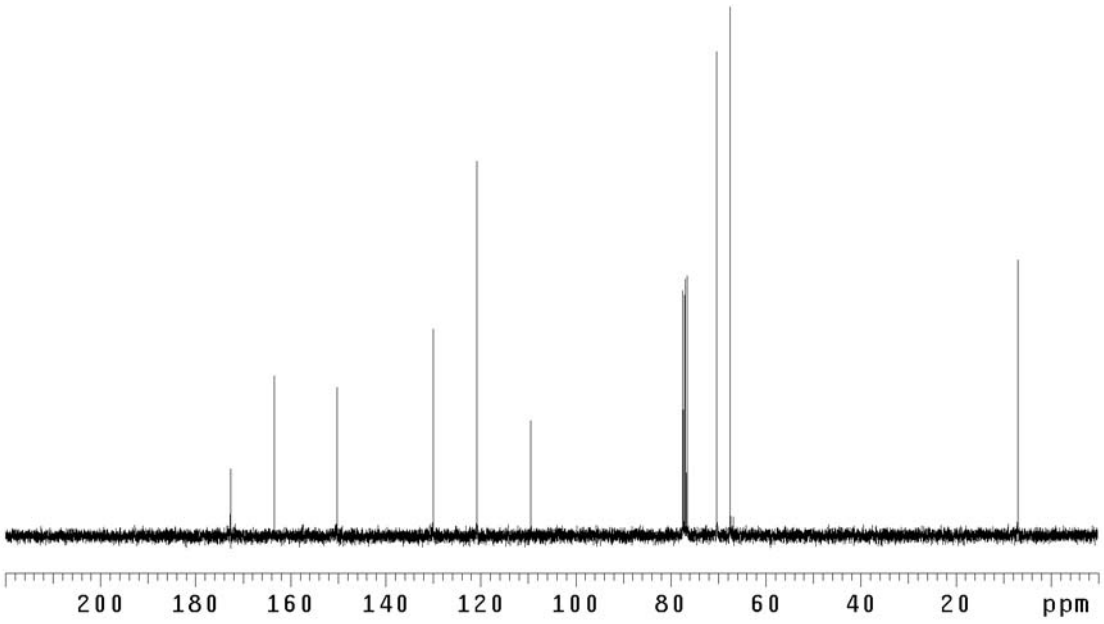


Figure A7.120 ^{13}C NMR of compound **429** (75 MHz, $CDCl_3$)

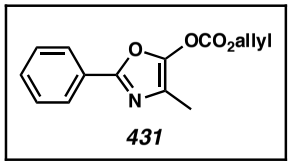


Figure A7.121 ^{1}H NMR of compound **431** (300 MHz, $CDCl_3$)

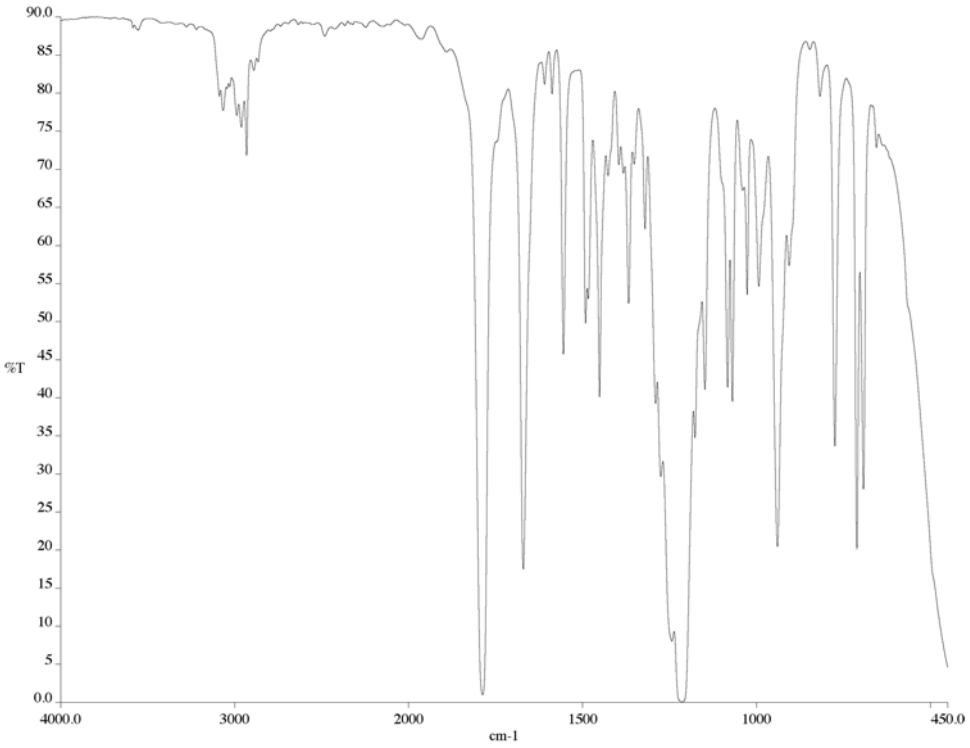


Figure A7.122 IR of compound **431** (NaCl/film)

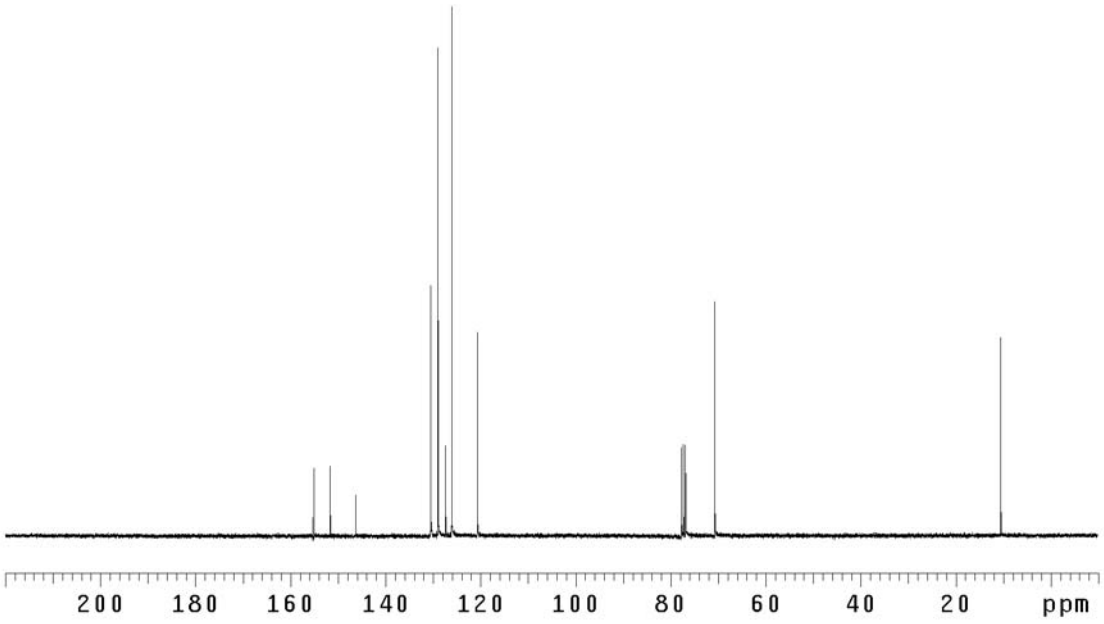


Figure A7.123 ^{13}C NMR of compound **431** (75 MHz, $CDCl_3$)

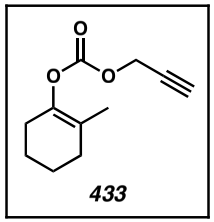


Figure A7.124 ^{1}H NMR of compound **433** (300 MHz, $CDCl_3$)

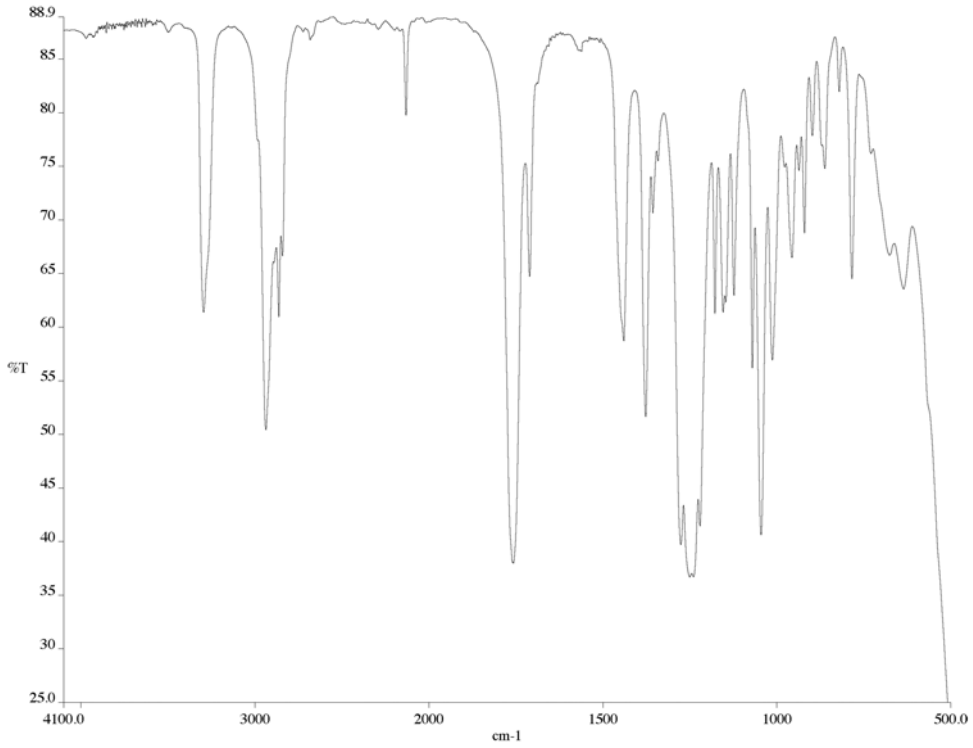


Figure A7.125 IR of compound **433** (NaCl/film)

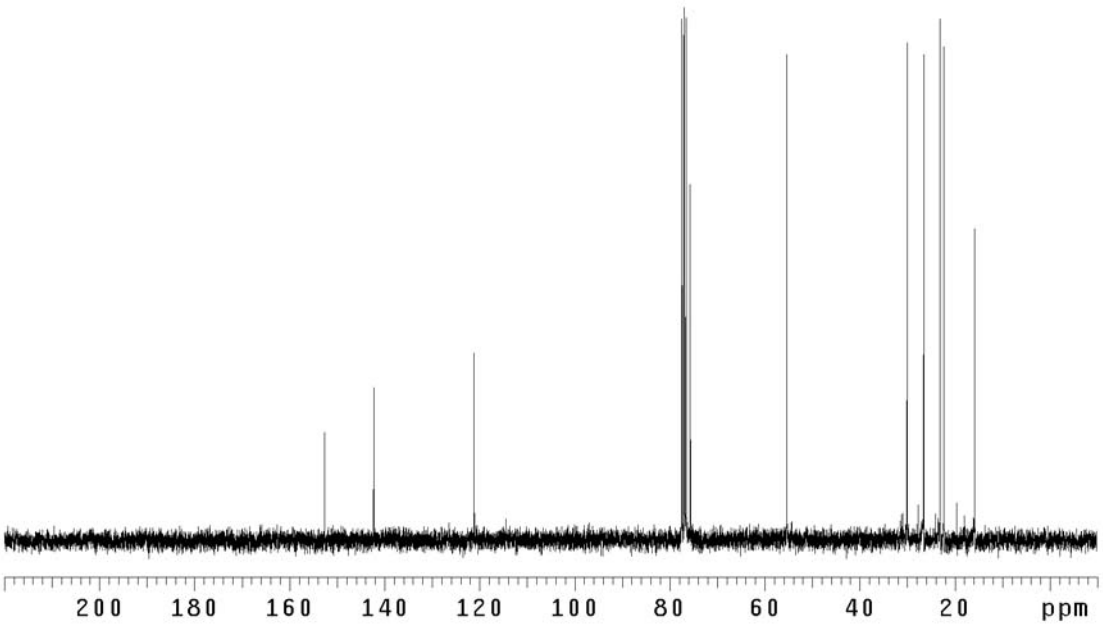


Figure A7.126 ^{13}C NMR of compound **433** (75 MHz, $CDCl_3$)

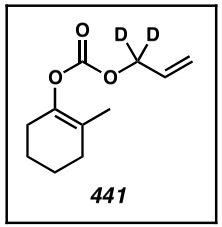


Figure A7.127 ^{1}H NMR of compound **441** (300 MHz, $CDCl_3$)

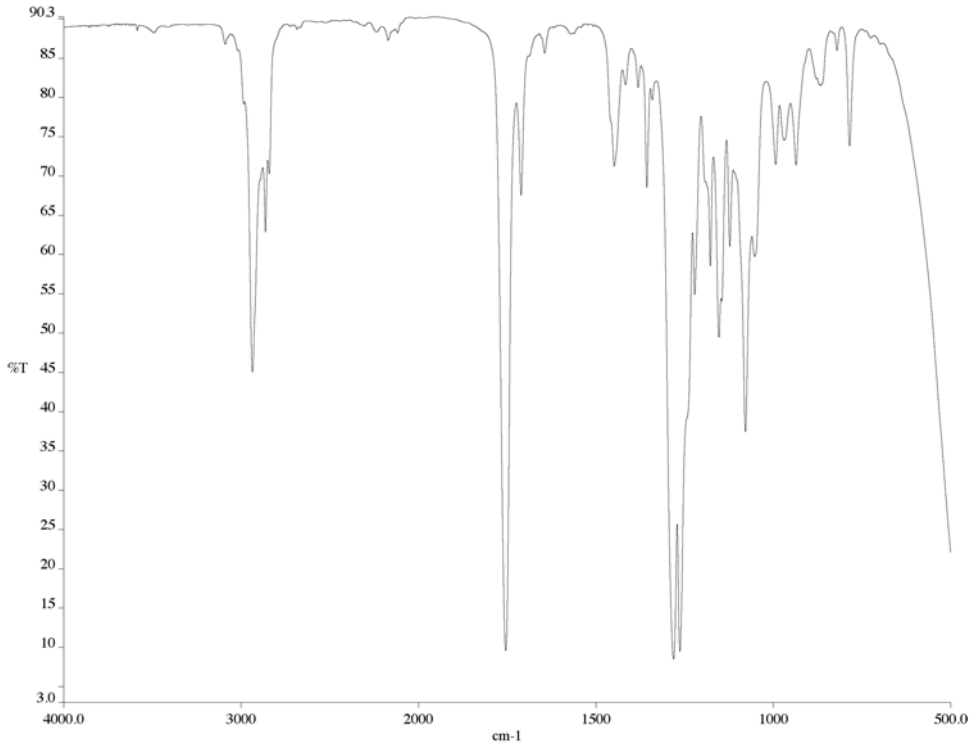


Figure A7.128 IR of compound **441** (NaCl/film)

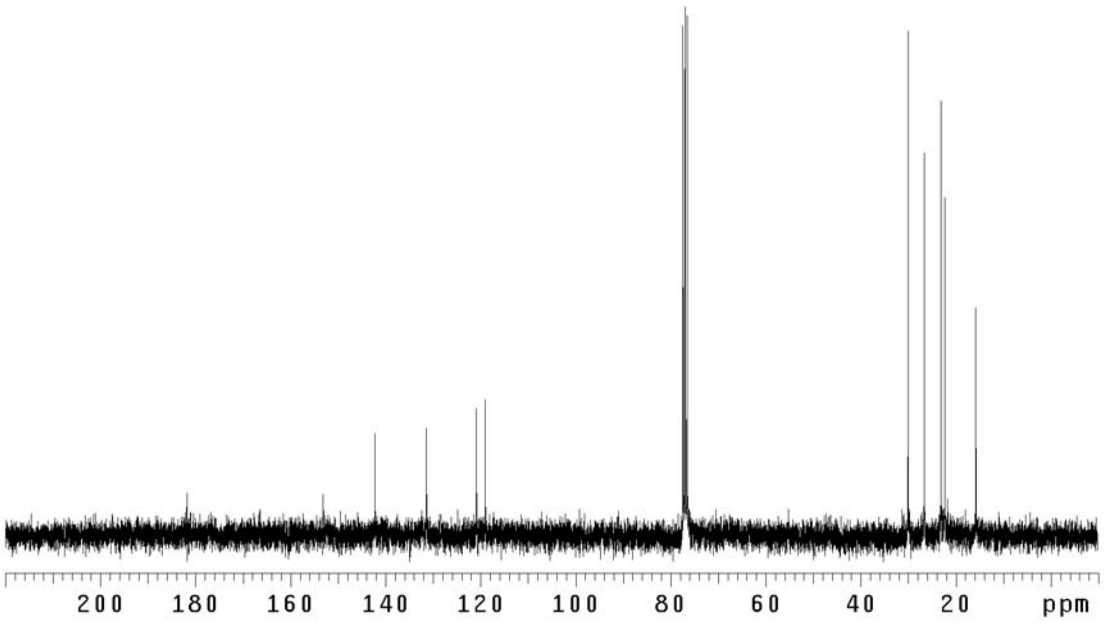
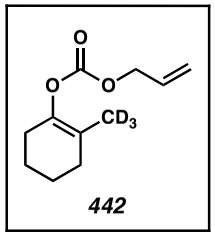


Figure A7.129 ^{13}C NMR of compound **441** (75 MHz, $CDCl_3$)



442

Figure A7.130 ^{1}H NMR of compound **442** (300 MHz, $CDCl_3$)

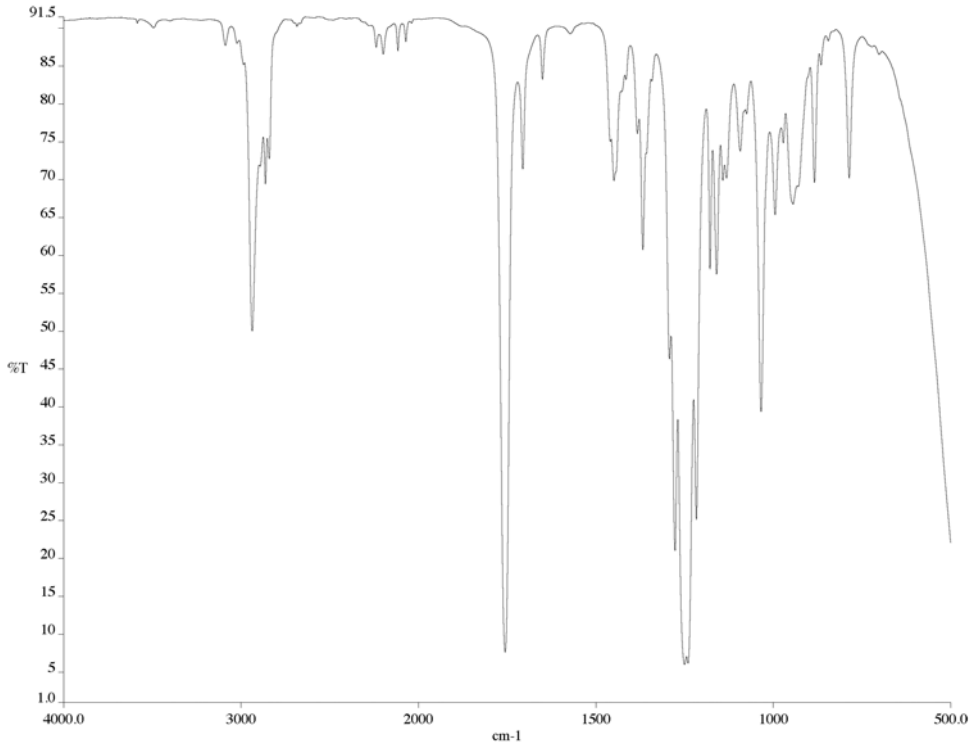


Figure A7.131 IR of compound **442** (NaCl/film)

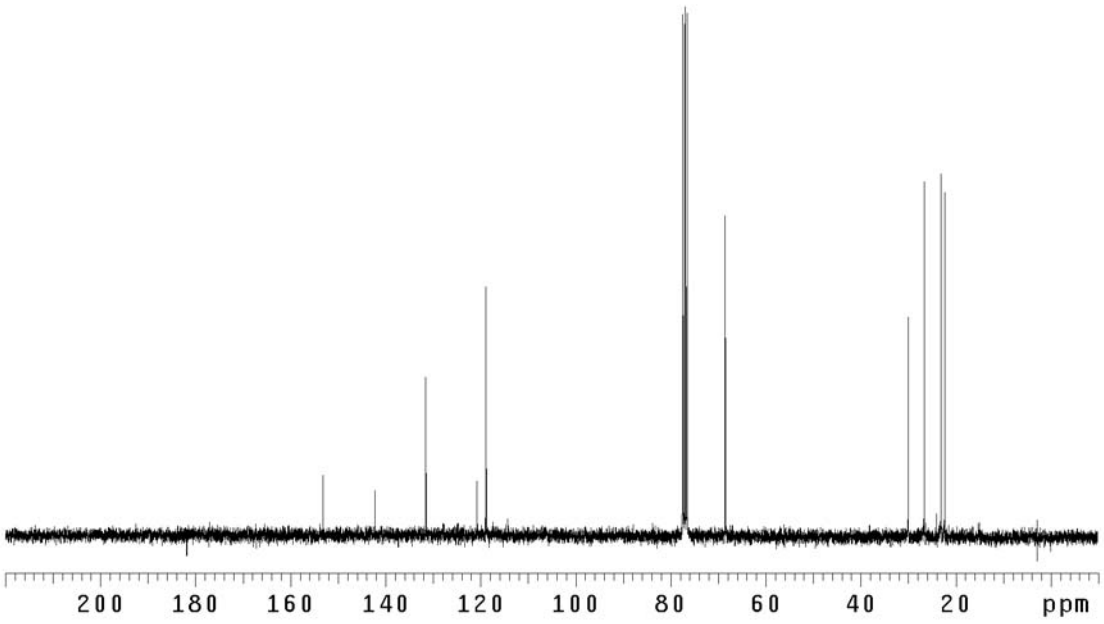


Figure A7.132 ^{13}C NMR of compound **442** (75 MHz, $CDCl_3$)

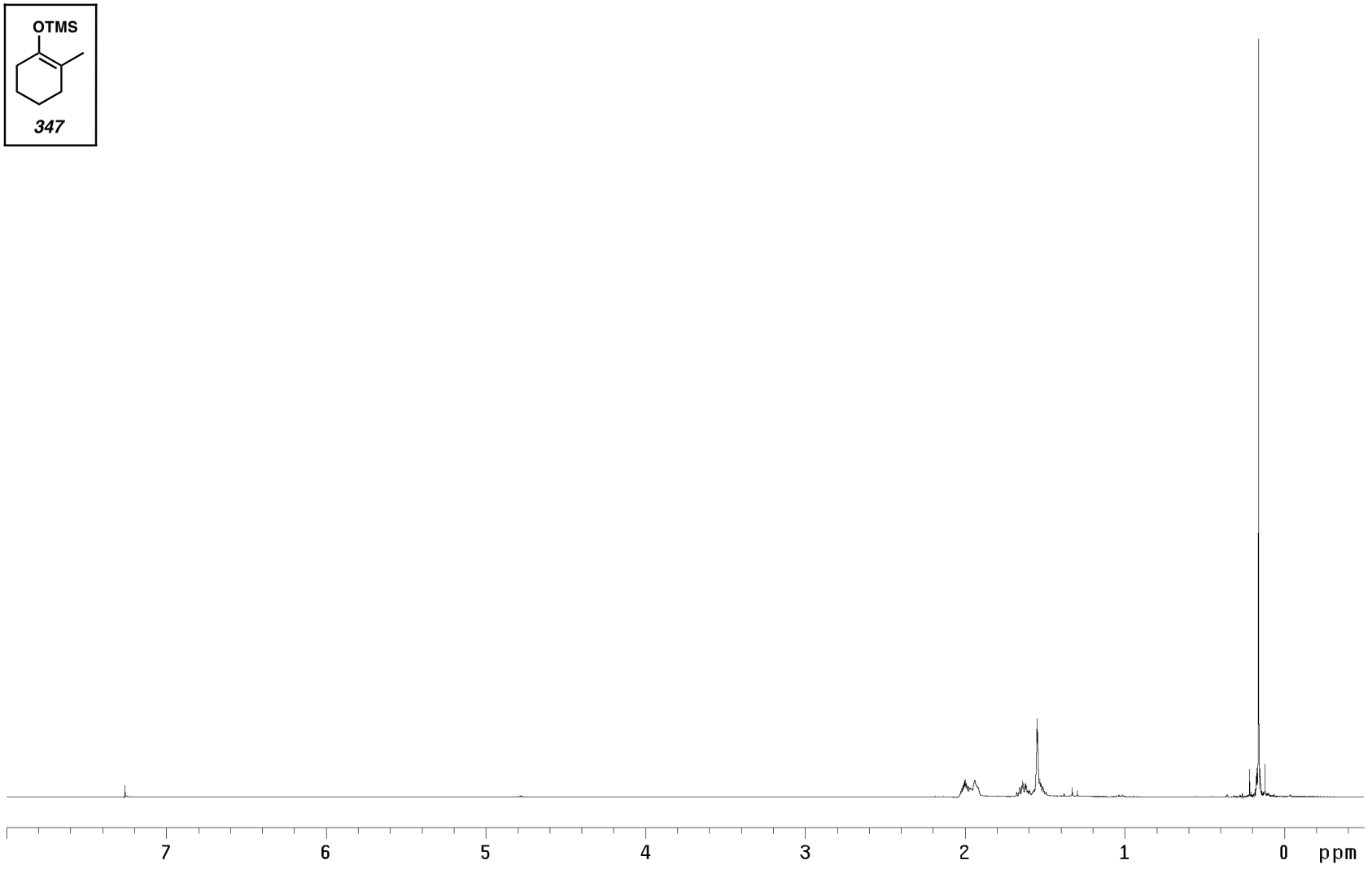


Figure A7.133 ^{1}H NMR of compound **347** (300 MHz, $CDCl_3$)

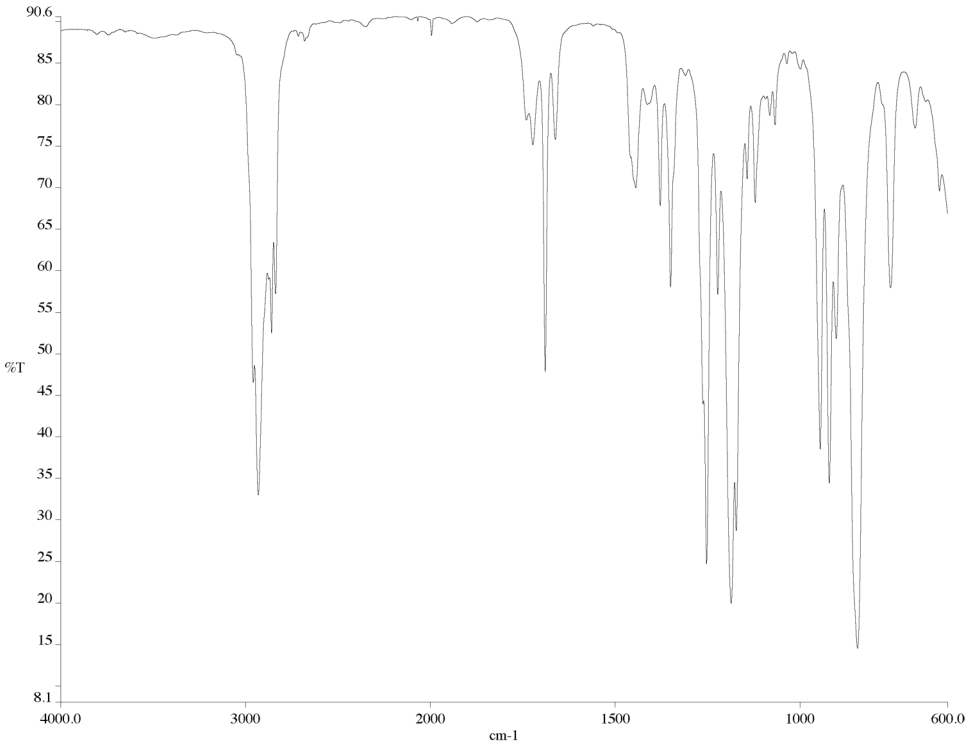


Figure A7.134 IR of compound **347** (NaCl/film)

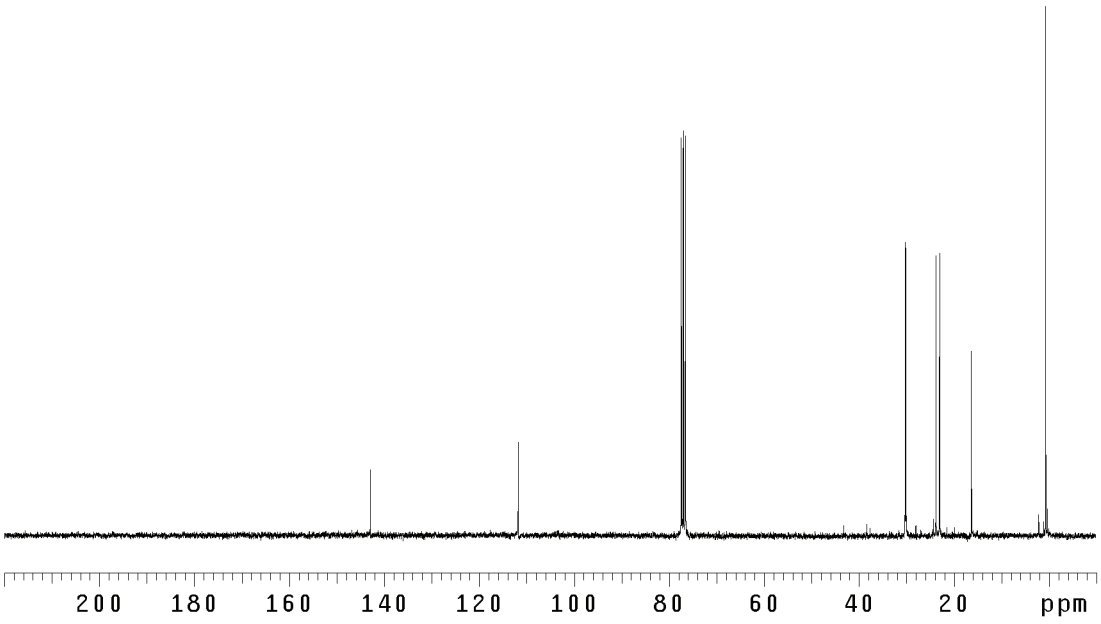


Figure A7.135 ^{13}C NMR of compound **347** (75 MHz, $CDCl_3$)

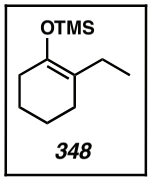


Figure A7.136 ^{1}H NMR of compound **348** (300 MHz, $CDCl_3$)

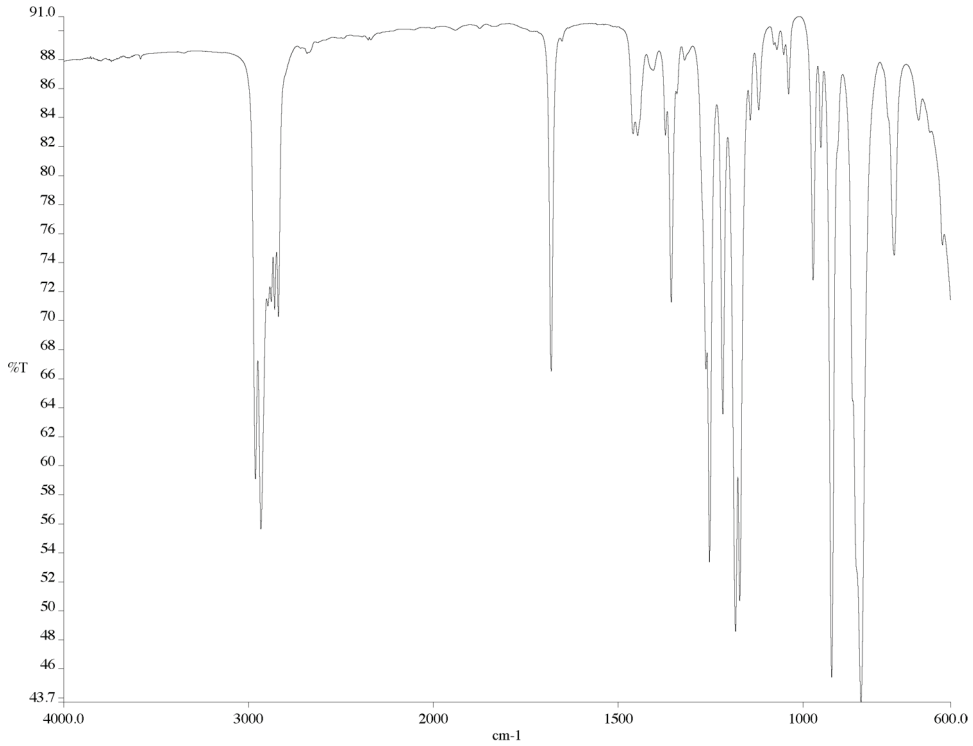


Figure A7.137 IR of compound **348** (NaCl/film)

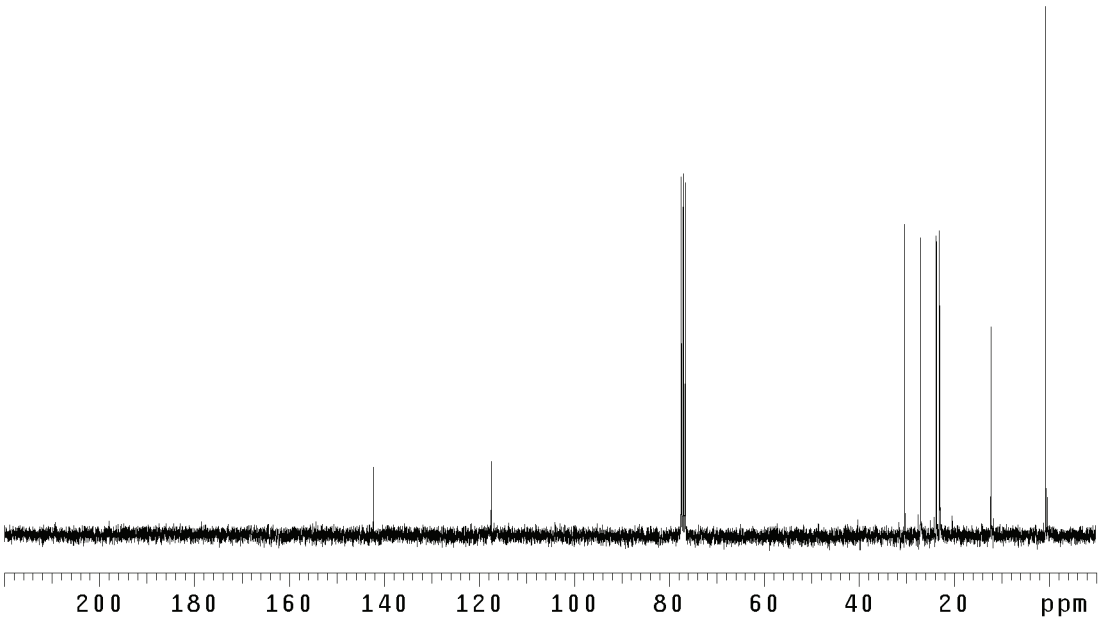


Figure A7.138 ^{13}C NMR of compound **348** (75 MHz, $CDCl_3$)

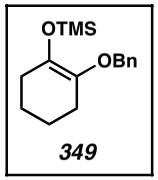


Figure A7.139 ^{1}H NMR of compound **349** (300 MHz, C_6D_6)

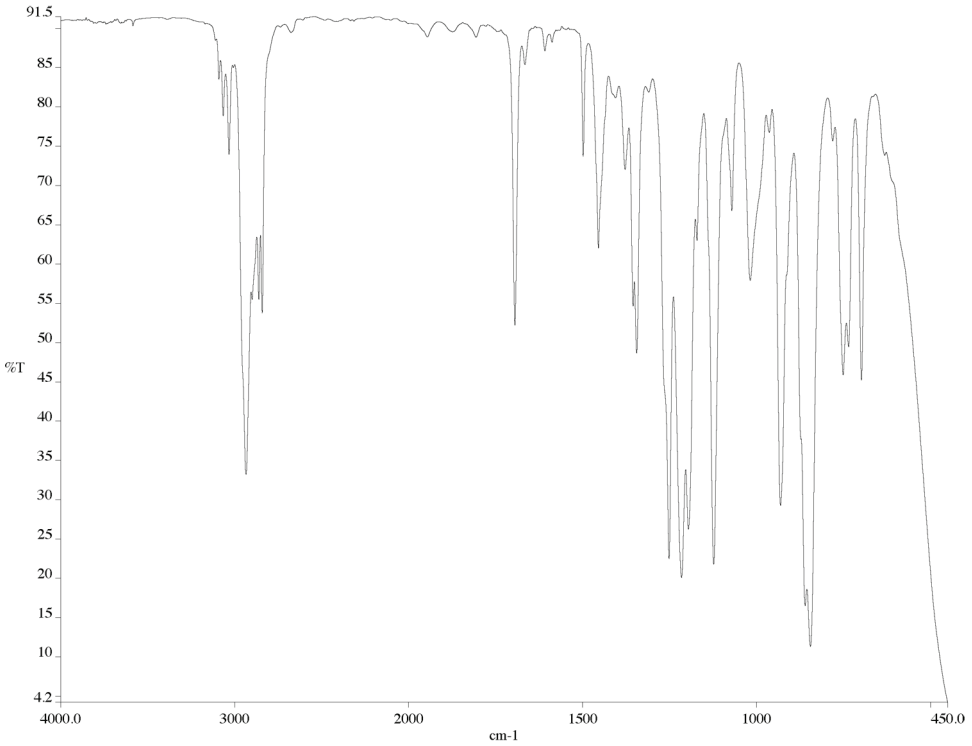


Figure A7.140 IR of compound **349** (NaCl/film)

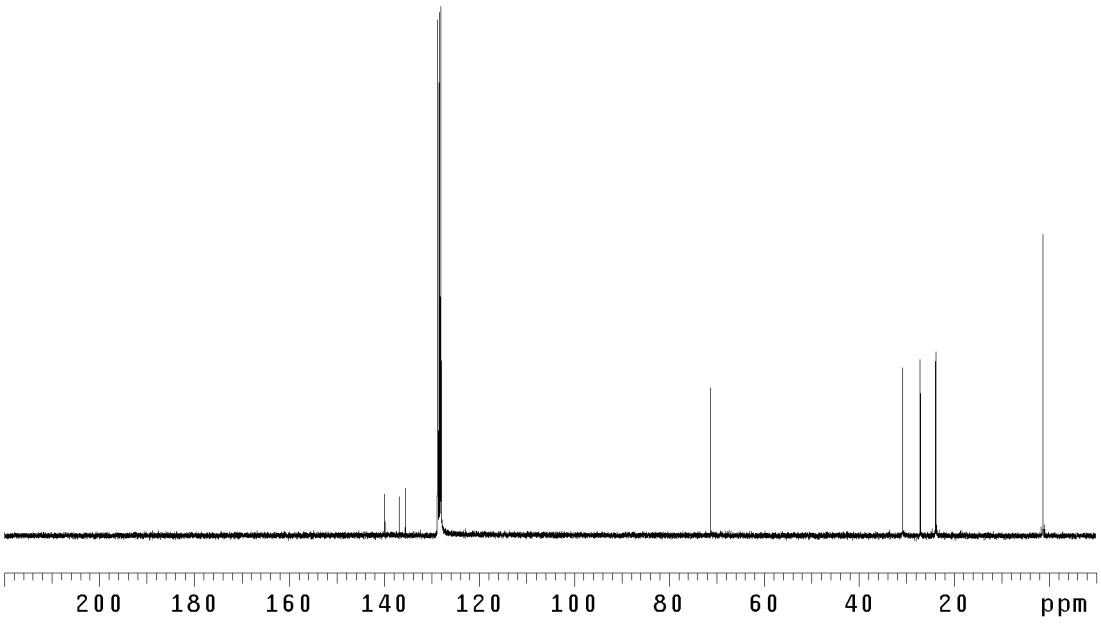


Figure A7.141 ^{13}C NMR of compound **349** (75 MHz, C_6D_6)

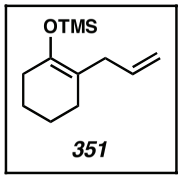


Figure A7.142 ^{1}H NMR of compound **351** (300 MHz, $CDCl_3$)

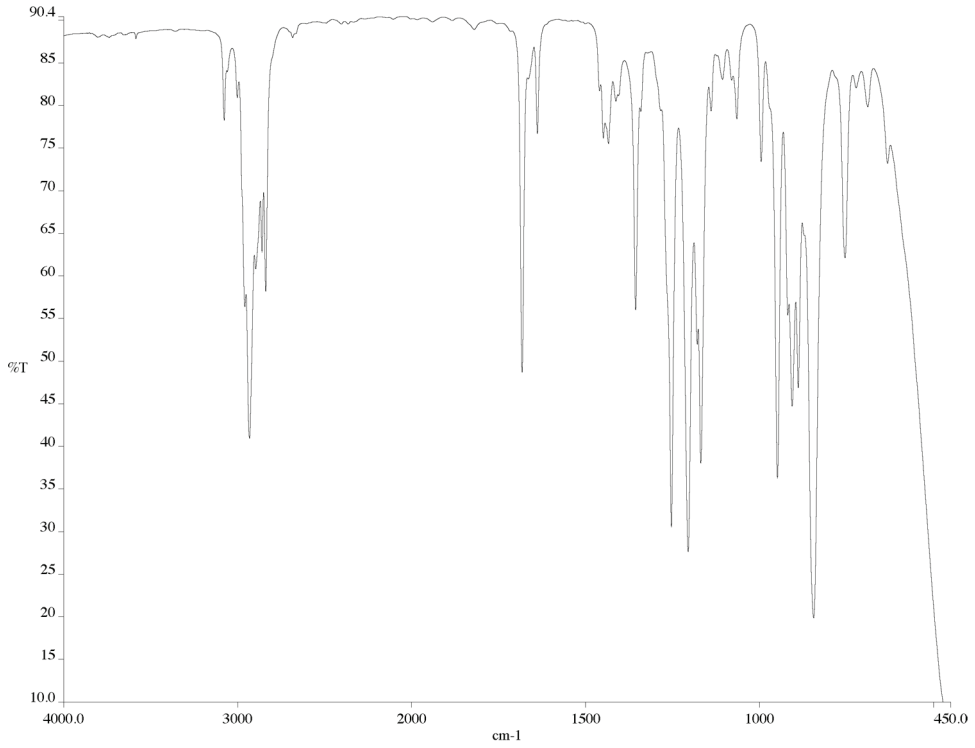


Figure A7.143 IR of compound **351** (NaCl/film)

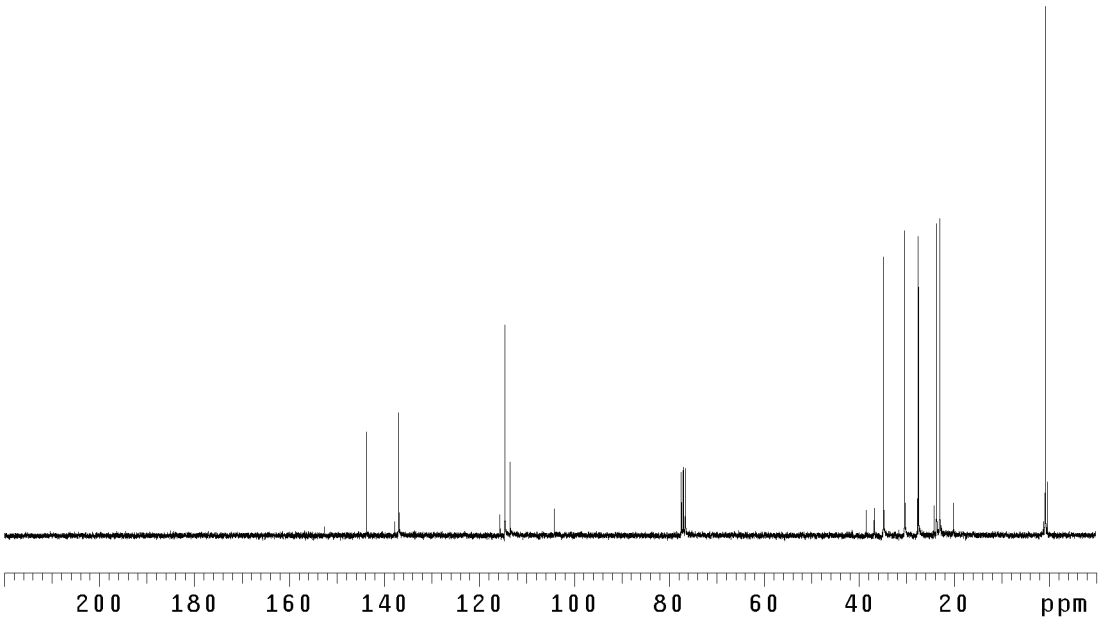


Figure A7.144 ^{13}C NMR of compound **351** (75 MHz, $CDCl_3$)

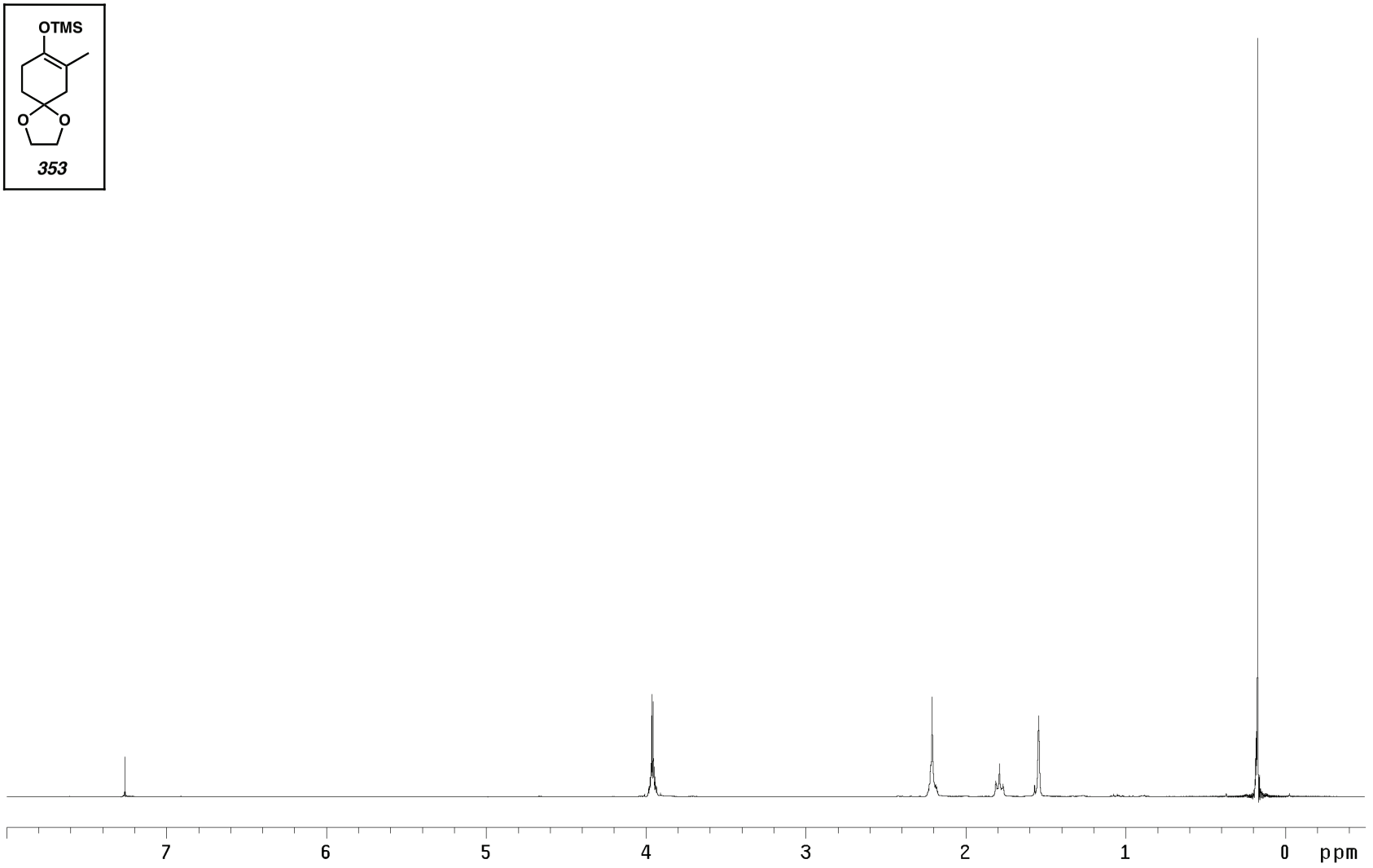


Figure A7.145 ^{1}H NMR of compound **353** (300 MHz, $CDCl_3$)

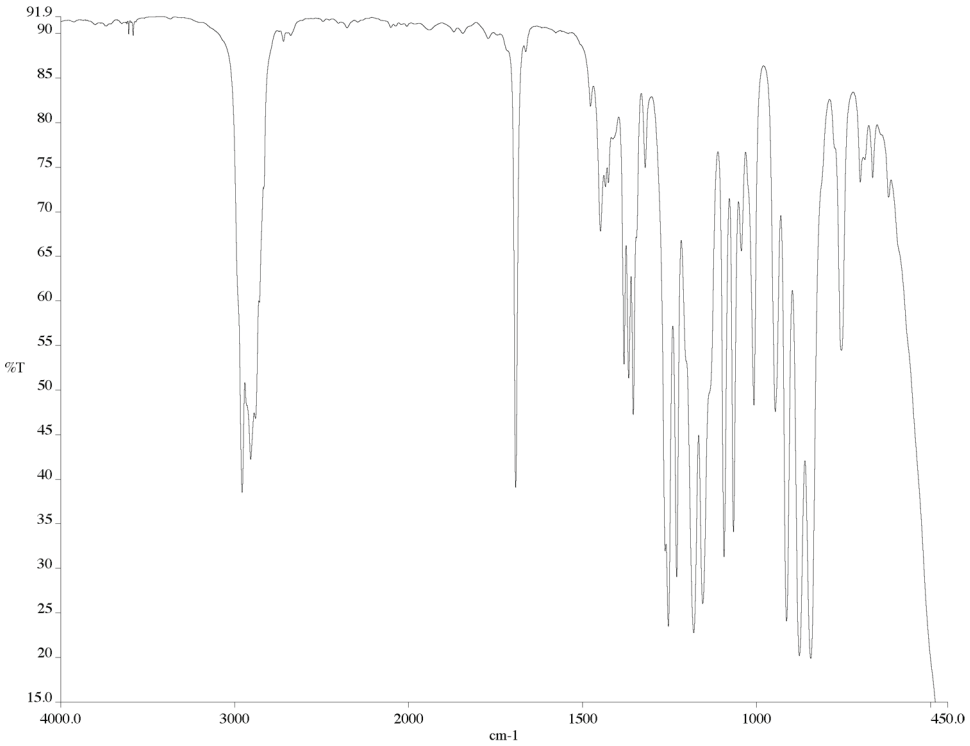


Figure A7.146 IR of compound **353** (NaCl/film)

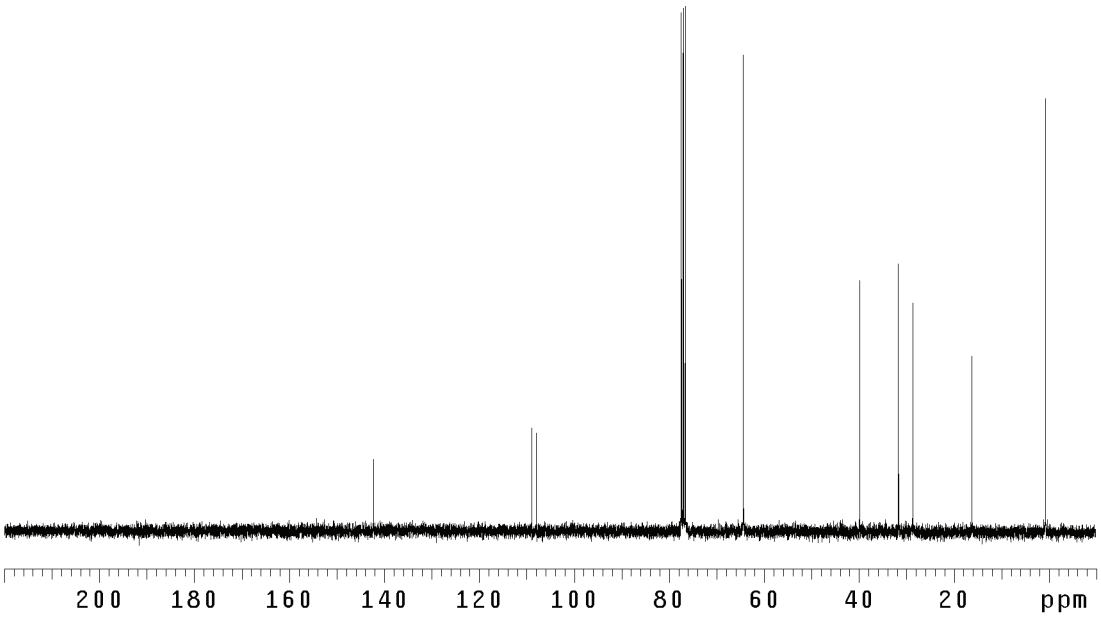


Figure A7.147 ^{13}C NMR of compound **353** (75 MHz, $CDCl_3$)

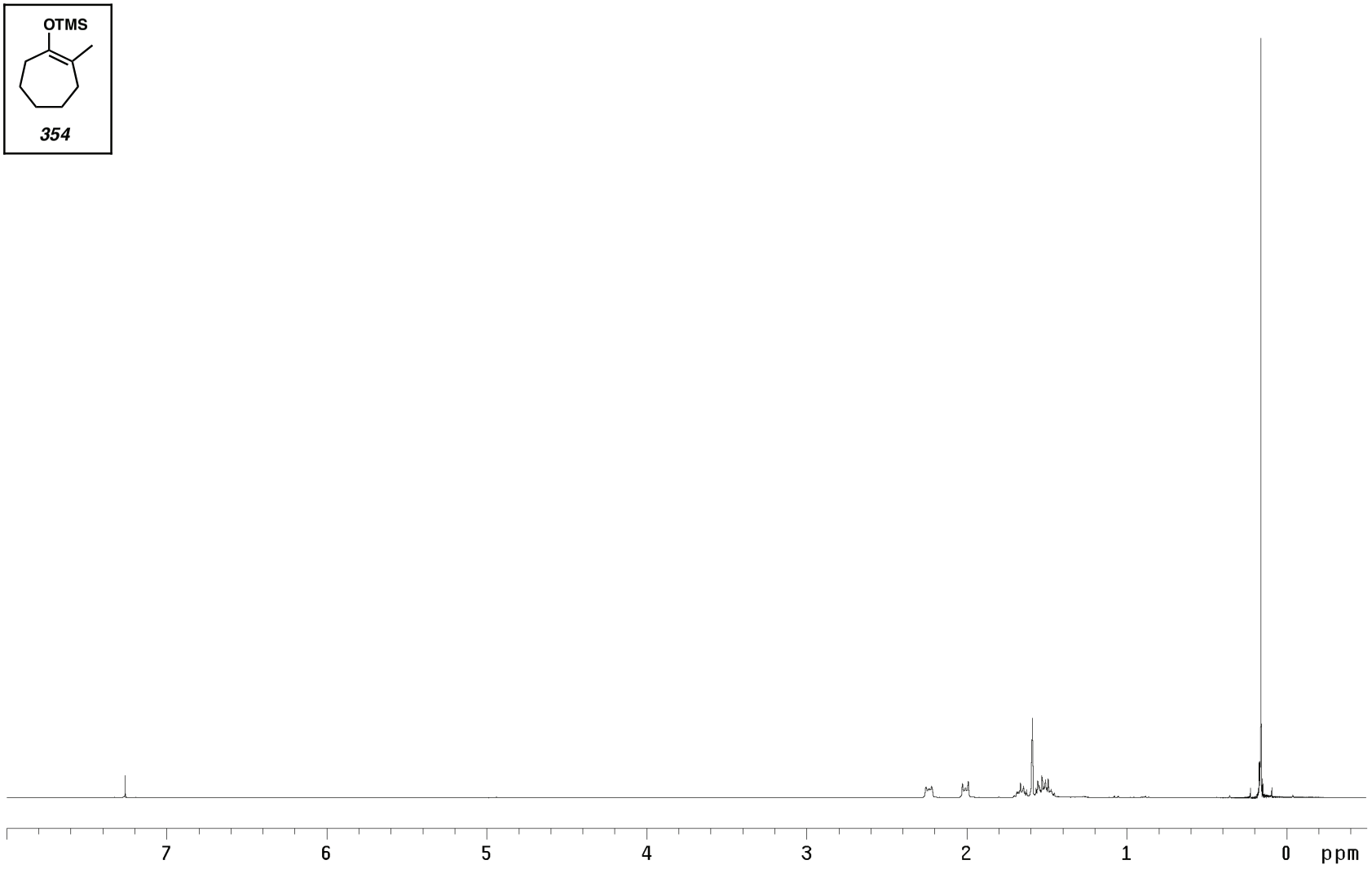


Figure A7.148 ^{1}H NMR of compound **354** (300 MHz, $CDCl_3$)

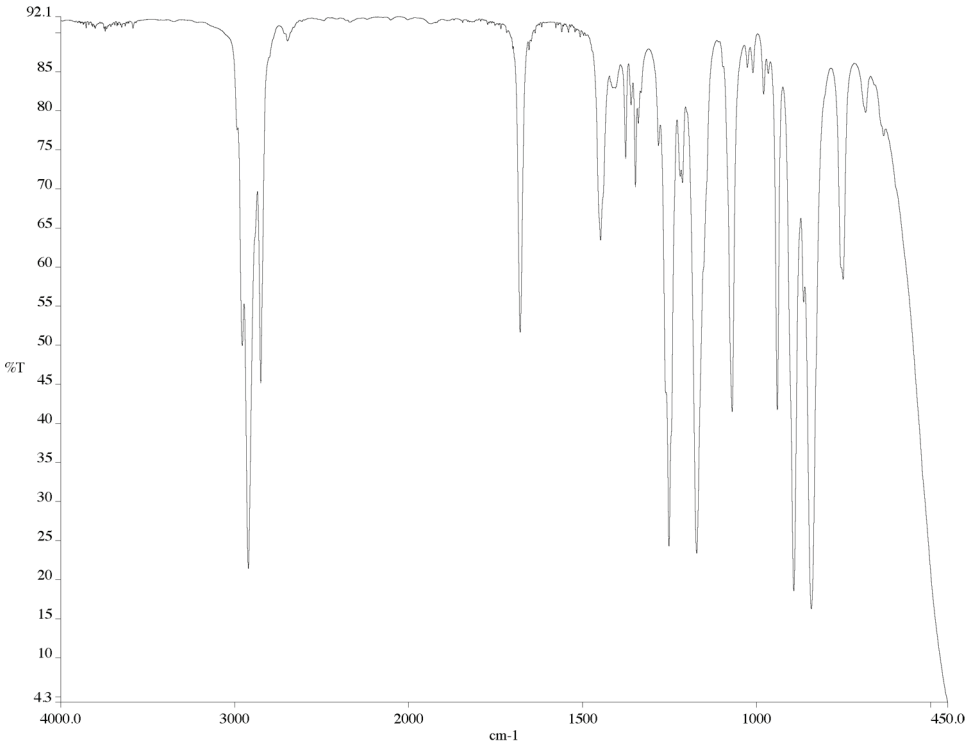


Figure A7.149 IR of compound **354** (NaCl/film)

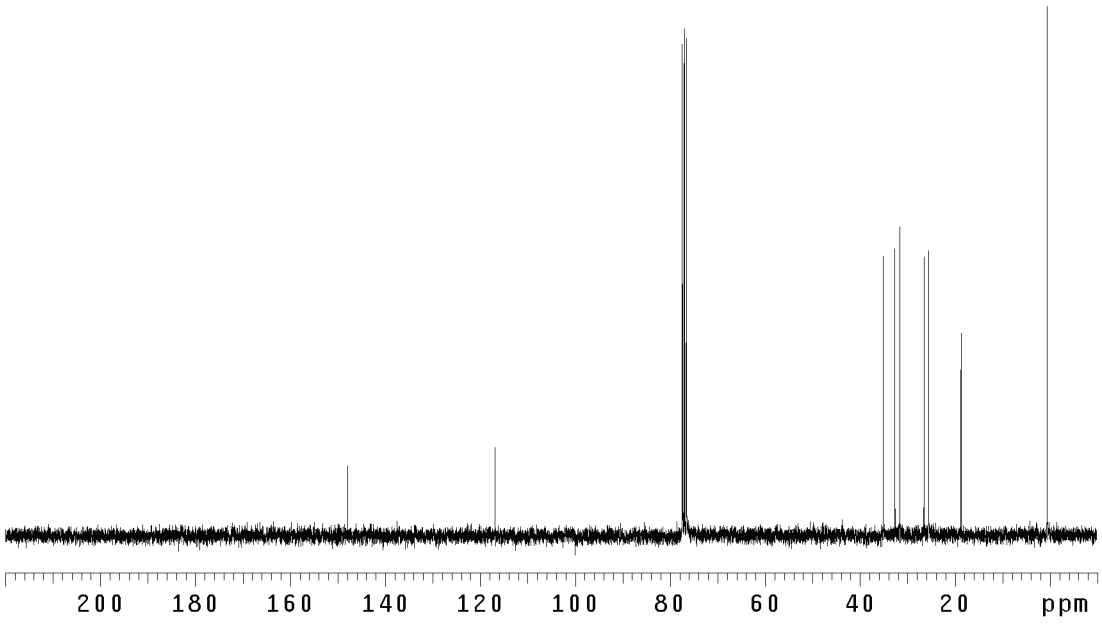


Figure A7.150 ^{13}C NMR of compound **354** (75 MHz, $CDCl_3$)

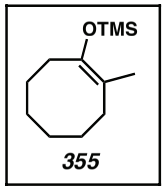


Figure A7.151 ^{1}H NMR of compound **355** (300 MHz, $CDCl_3$)

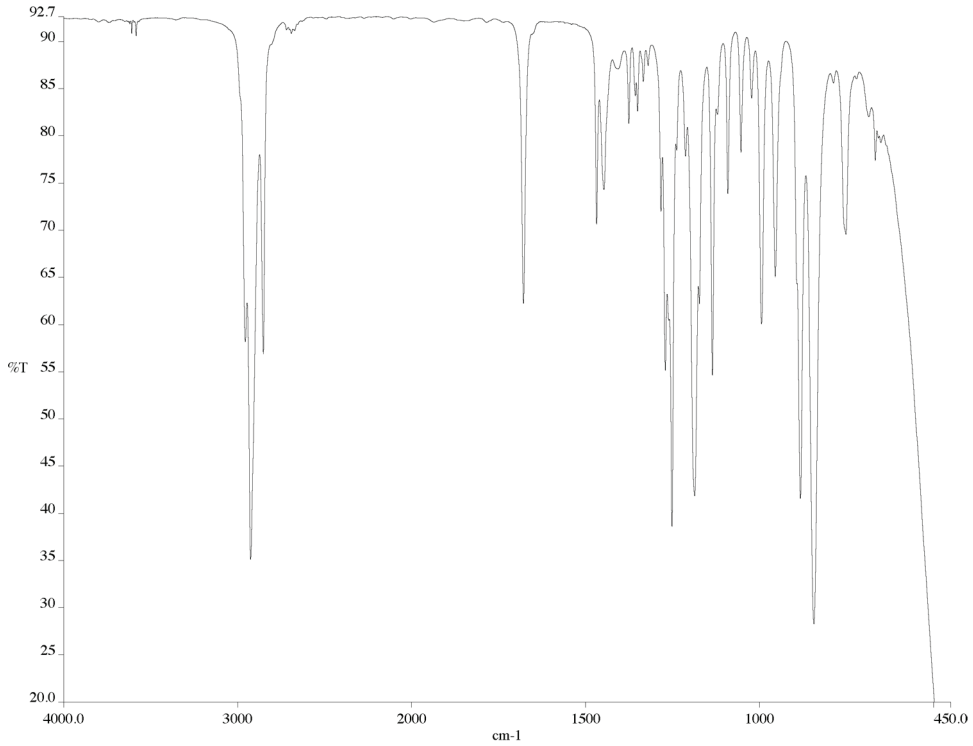


Figure A7.152 IR of compound **355** (NaCl/film)

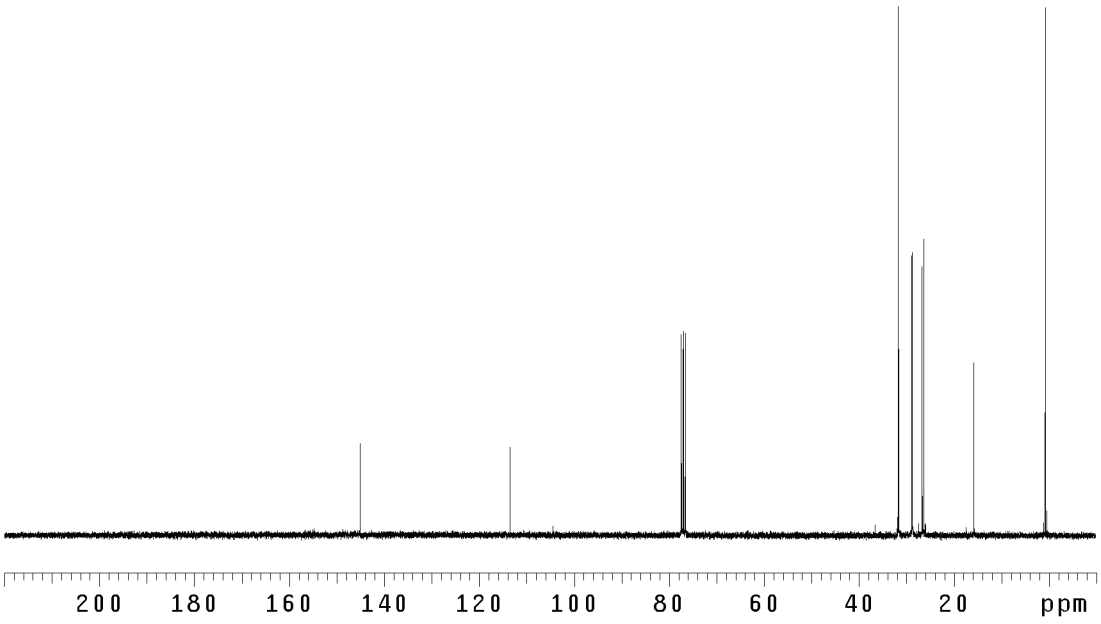


Figure A7.153 ^{13}C NMR of compound **355** (75 MHz, $CDCl_3$)

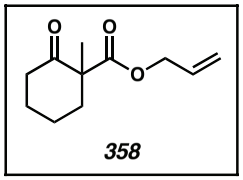


Figure A7.154 ^{1}H NMR of compound **358** (300 MHz, $CDCl_3$)

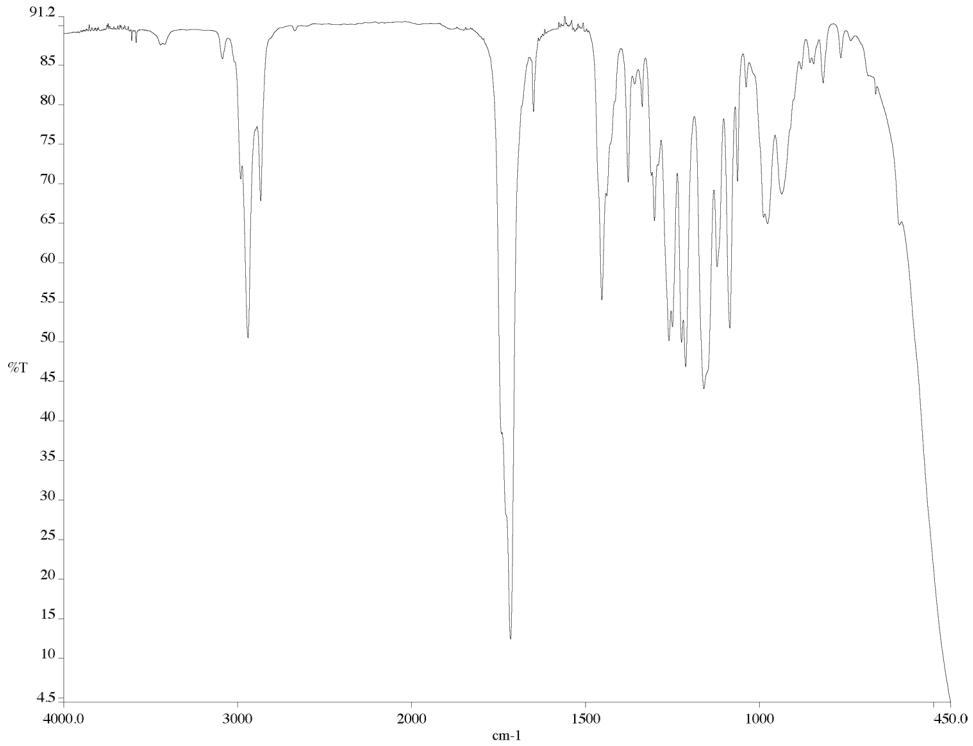


Figure A7.155 IR of compound **358** (NaCl/film)

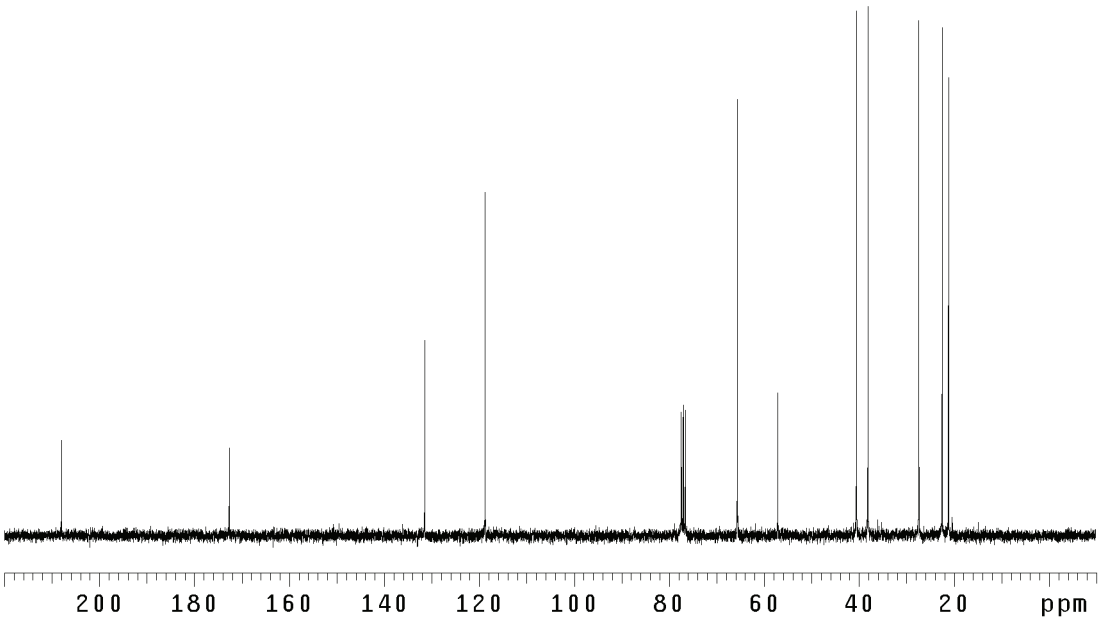


Figure A7.156 ^{13}C NMR of compound **358** (75 MHz, $CDCl_3$)

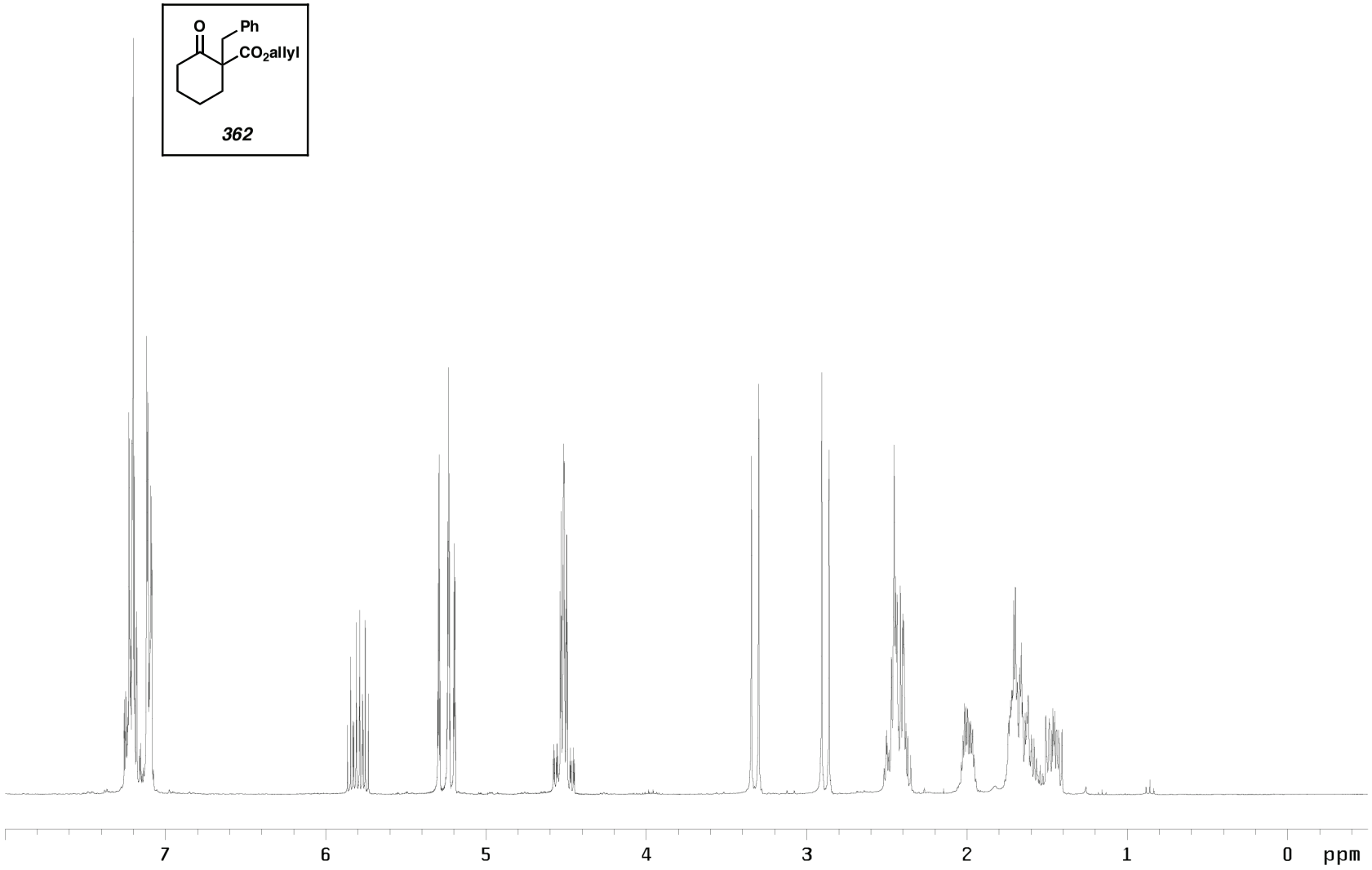


Figure A7.157 ^{1}H NMR of compound **362** (300 MHz, $CDCl_3$)

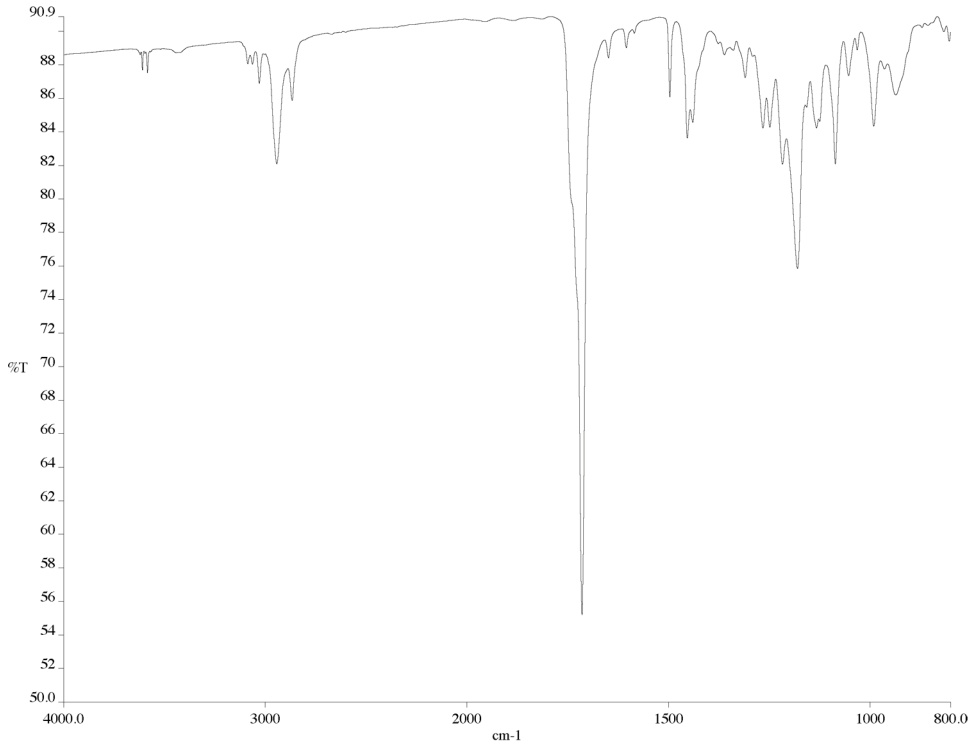


Figure A7.158 IR of compound **362** (NaCl/film)

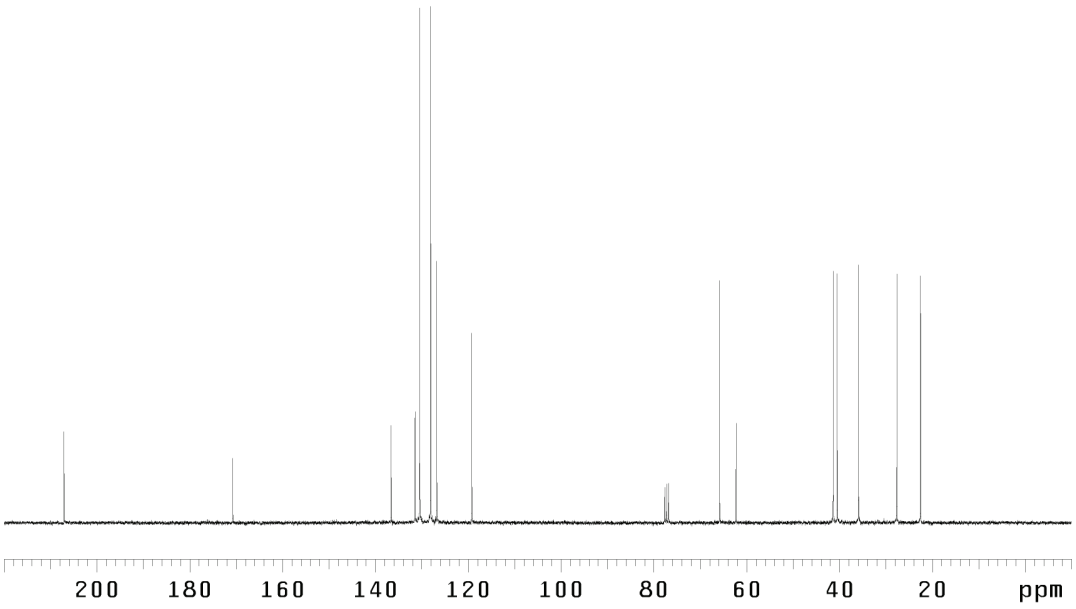


Figure A7.159 ^{13}C NMR of compound **362** (75 MHz, $CDCl_3$)

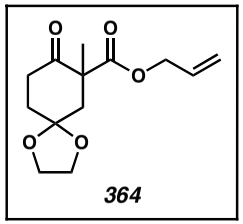


Figure A7.160 ^{1}H NMR of compound **364** (300 MHz, $CDCl_3$)

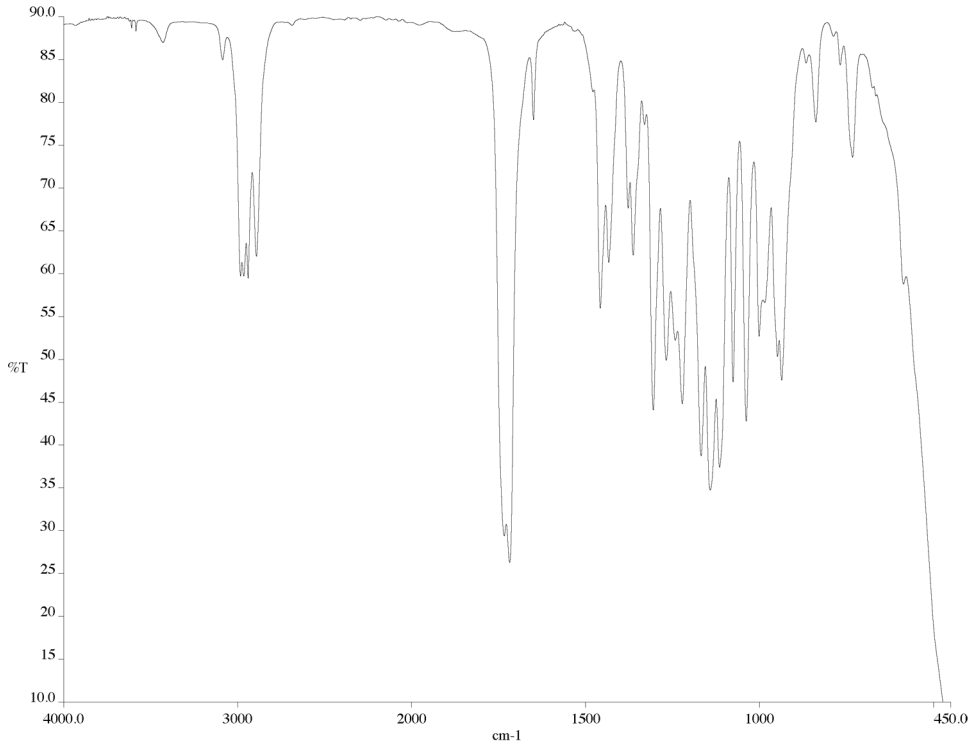


Figure A7.161 IR of compound **364** (NaCl/film)

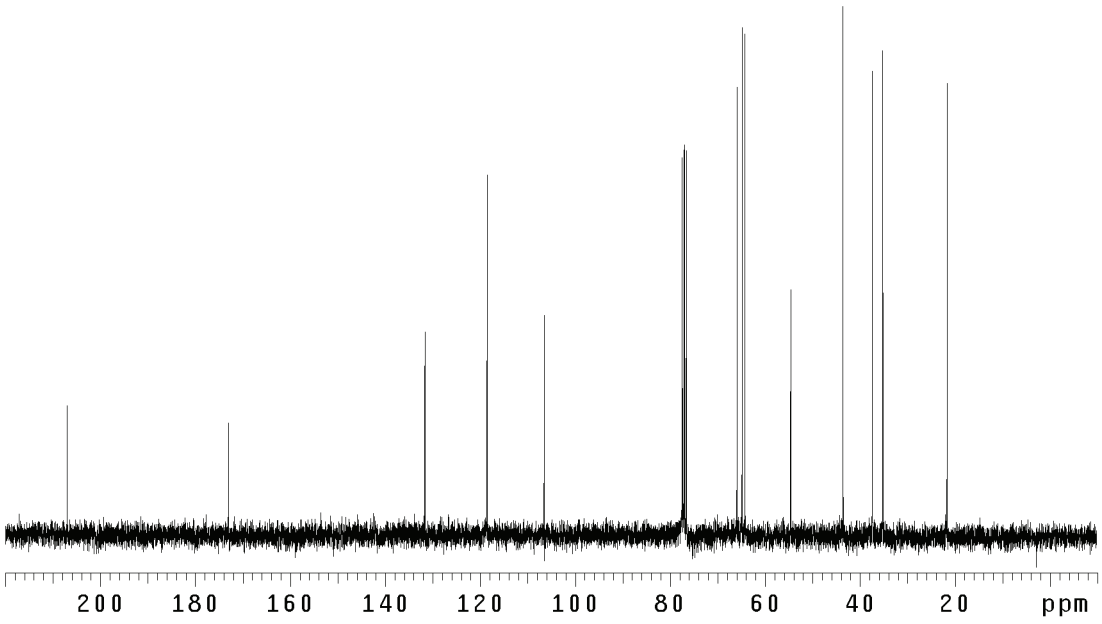


Figure A7.162 ^{13}C NMR of compound **364** (75 MHz, $CDCl_3$)

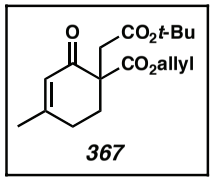


Figure A7.163 ^{1}H NMR of compound **367** (300 MHz, $CDCl_3$)

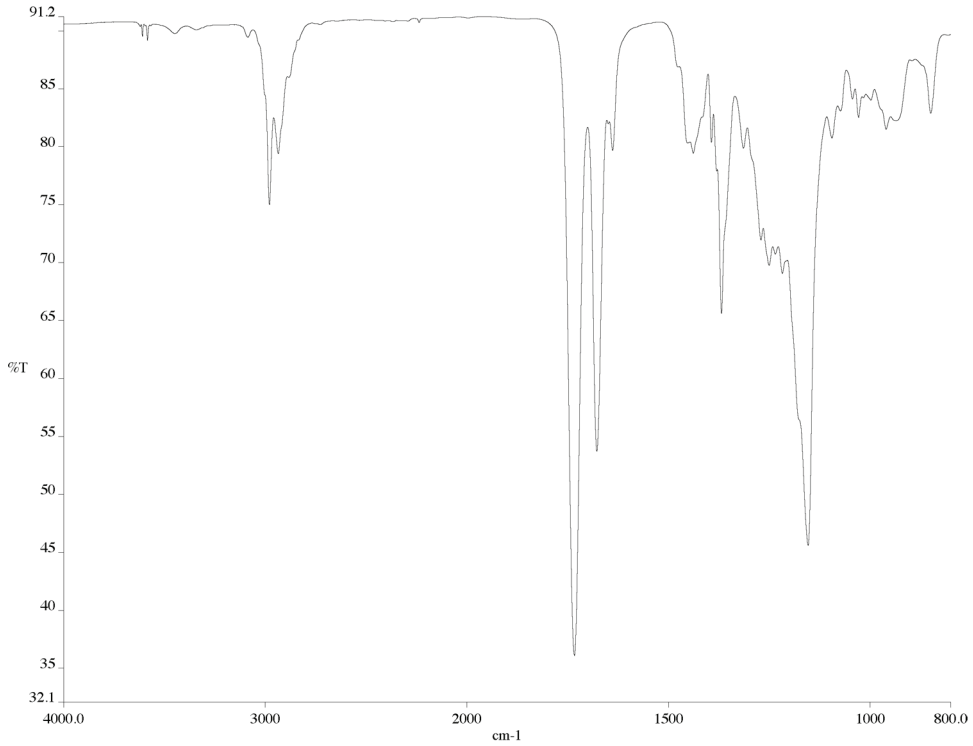


Figure A7.164 IR of compound **367** (NaCl/film)

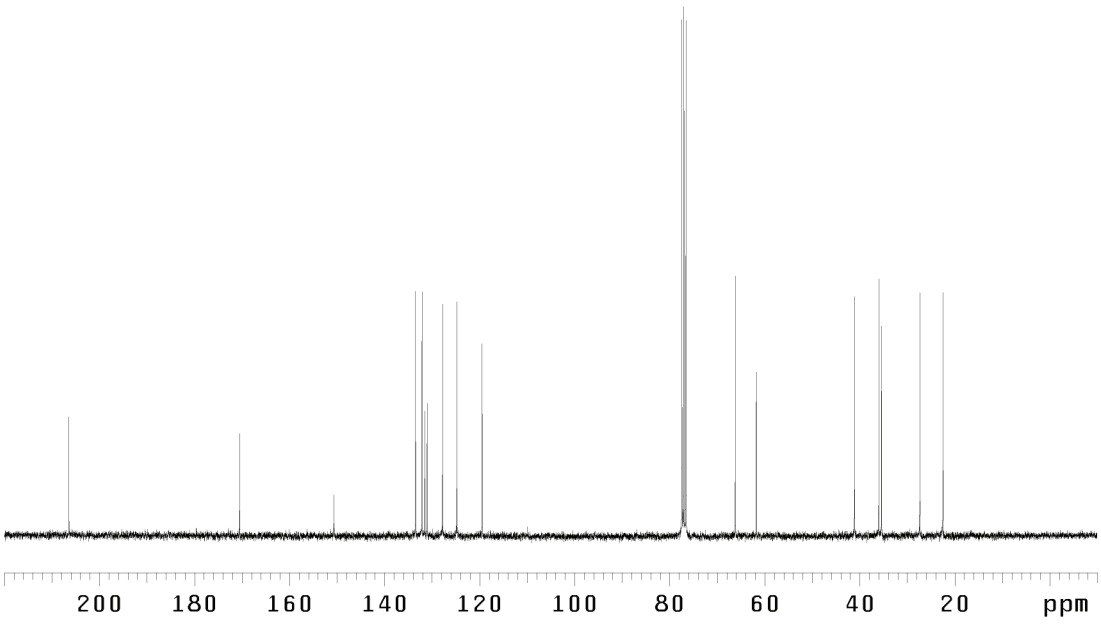


Figure A7.165 ^{13}C NMR of compound **367** (75 MHz, $CDCl_3$)

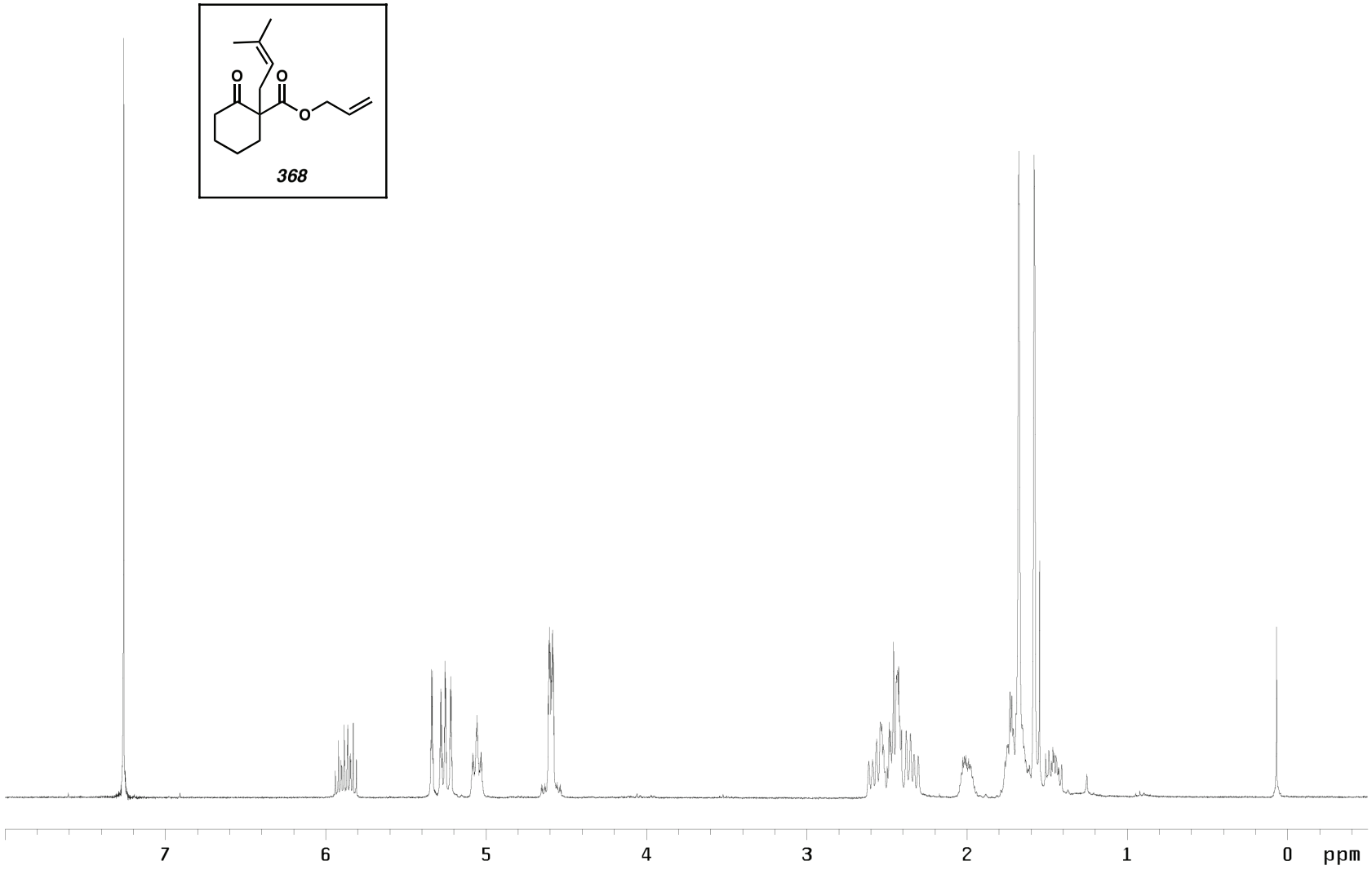


Figure A7.166 ^{1}H NMR of compound **368** (300 MHz, $CDCl_3$)

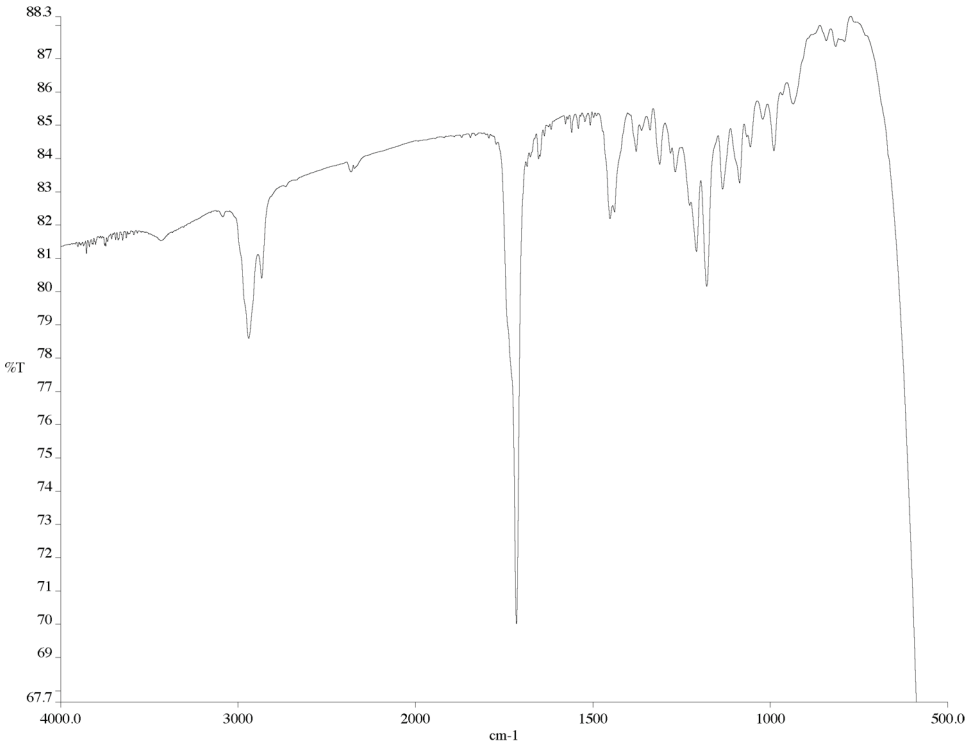


Figure A7.167 IR of compound **368** (NaCl/film)

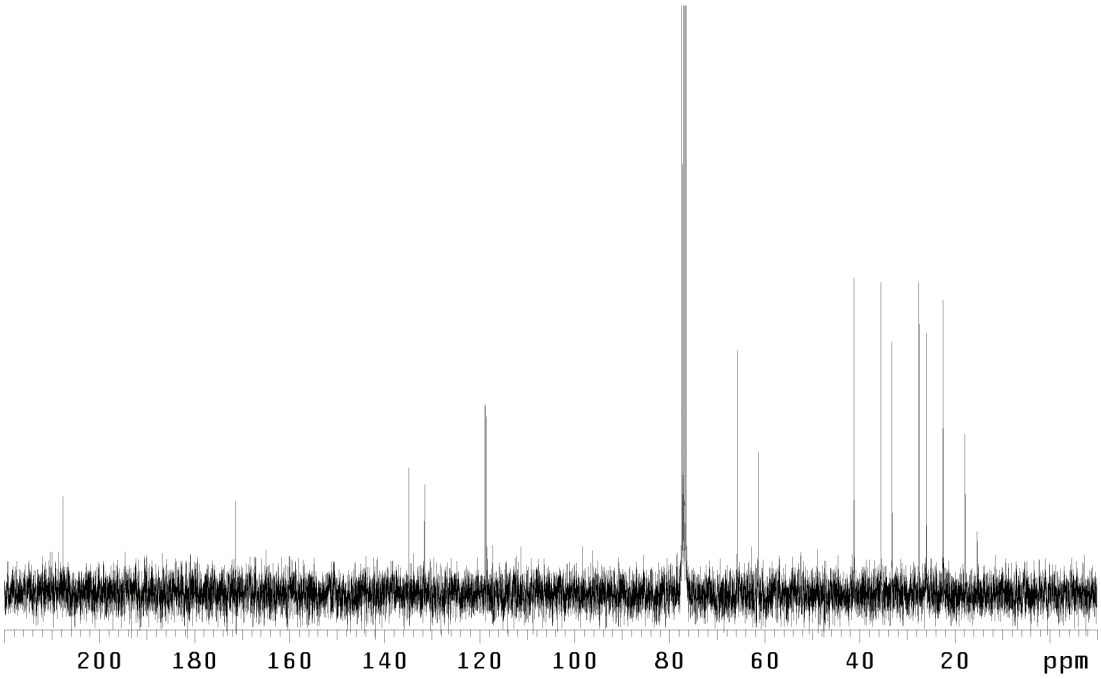


Figure A7.168 ^{13}C NMR of compound **368** (75 MHz, $CDCl_3$)

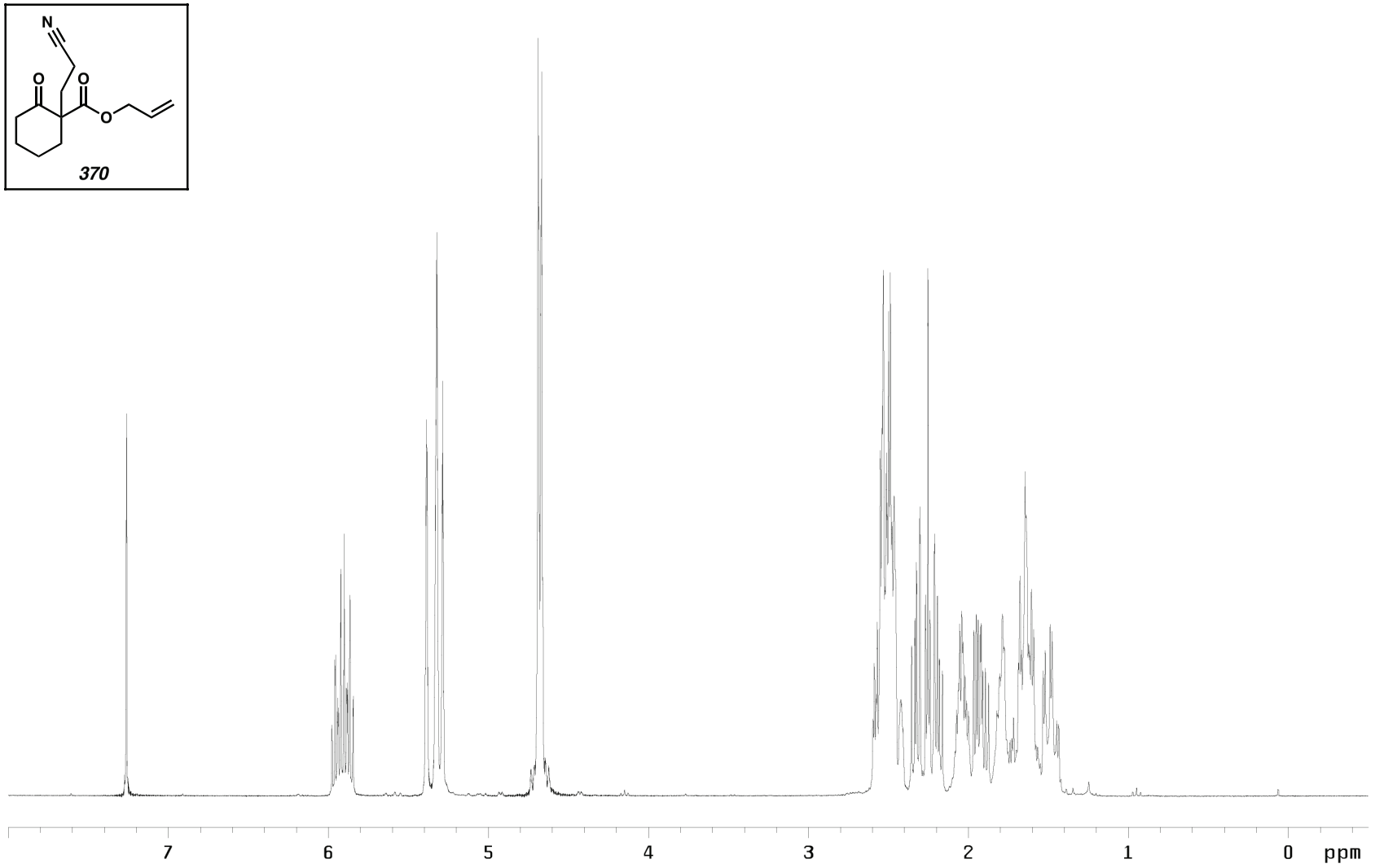


Figure A7.169 ^{1}H NMR of compound **370** (300 MHz, $CDCl_3$)

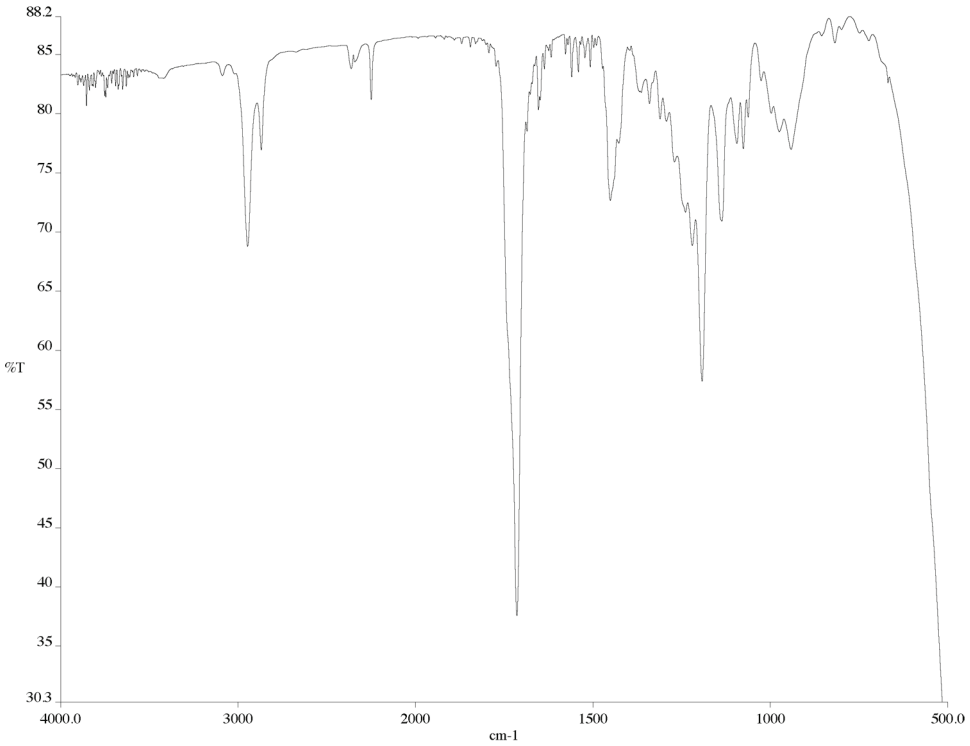


Figure A7.170 IR of compound **370** (NaCl/film)

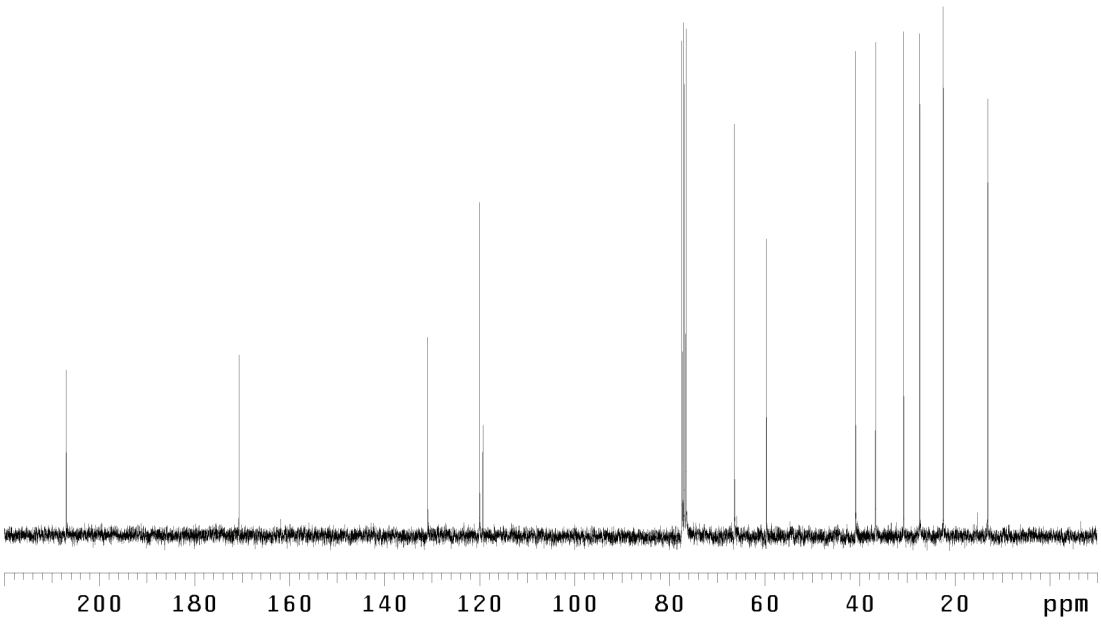


Figure A7.171 ^{13}C NMR of compound **370** (75 MHz, $CDCl_3$)

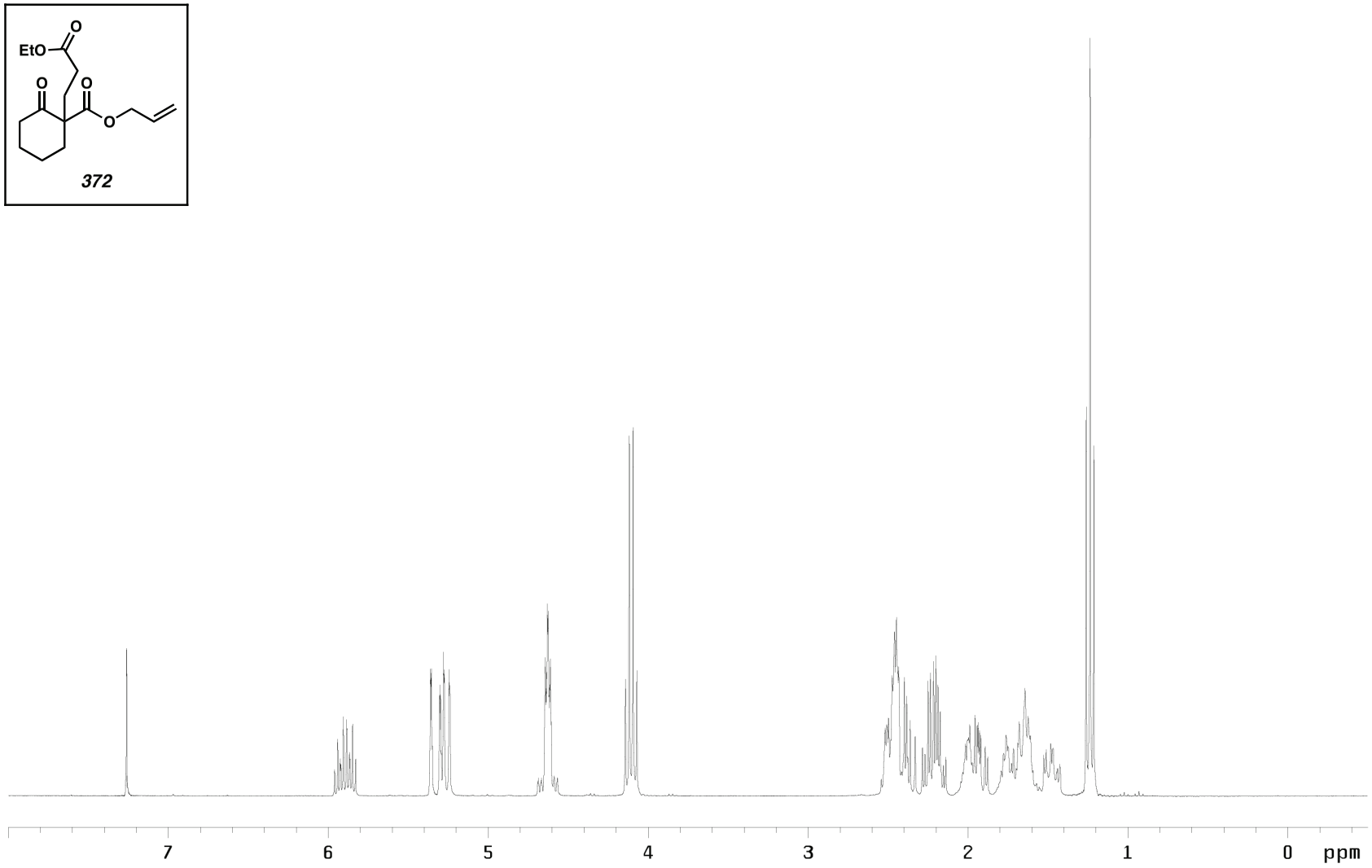


Figure A7.172 ^{1}H NMR of compound **372** (300 MHz, $CDCl_3$)

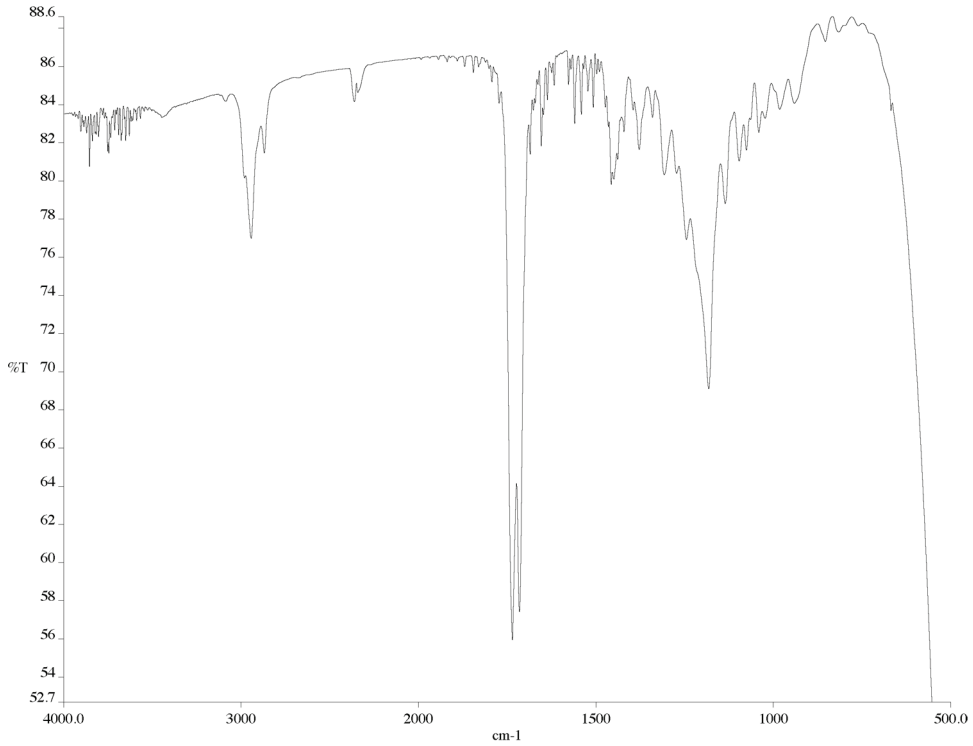


Figure A7.173 IR of compound **372** (NaCl/film)

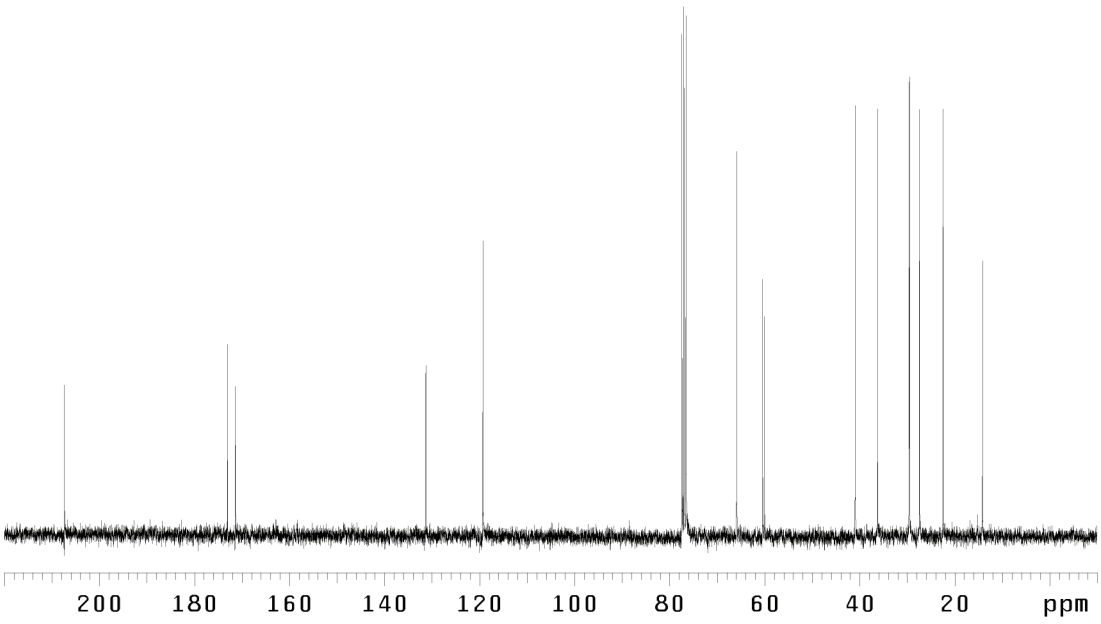


Figure A7.174 ^{13}C NMR of compound **372** (75 MHz, $CDCl_3$)

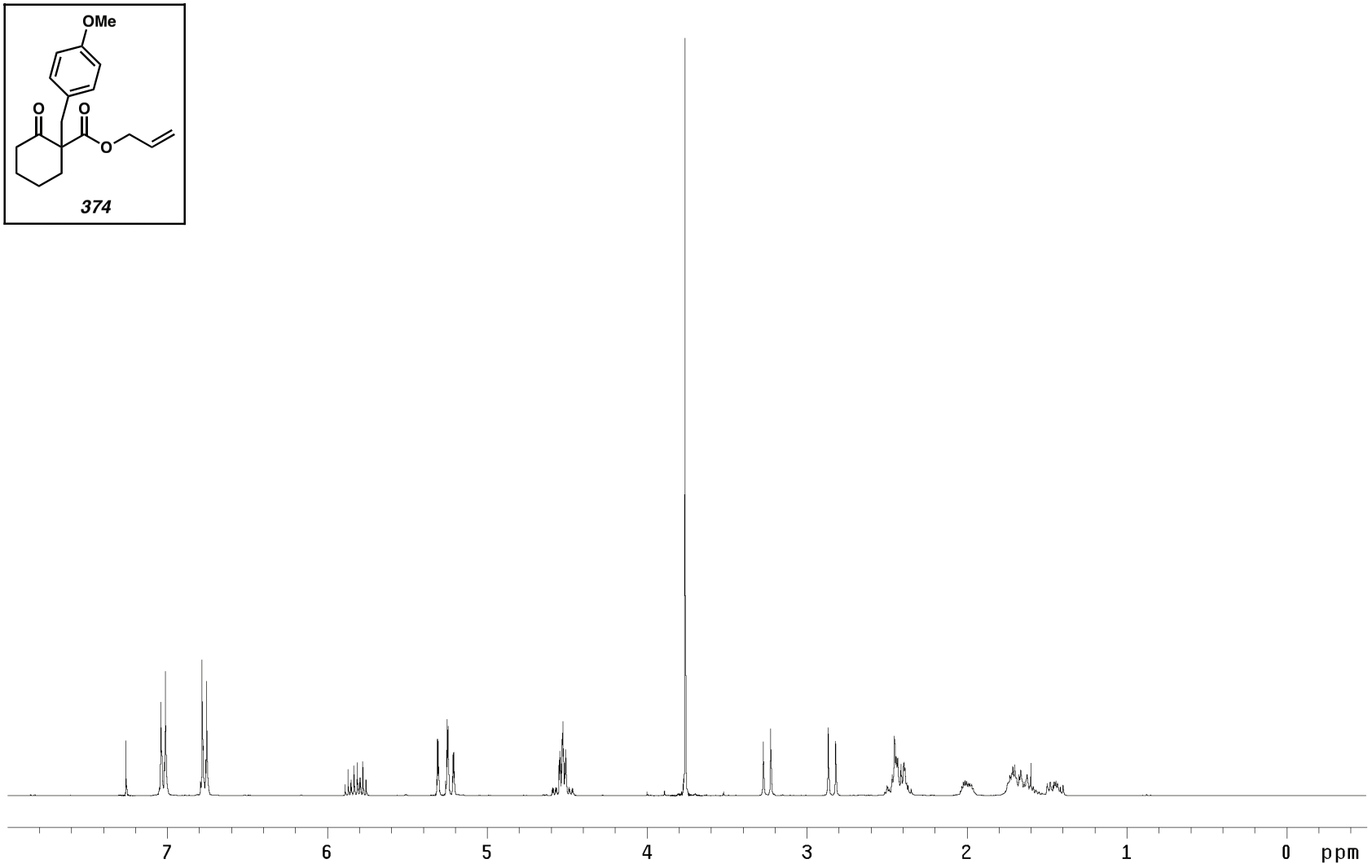


Figure A7.175 ^{1}H NMR of compound **374** (300 MHz, $CDCl_3$)

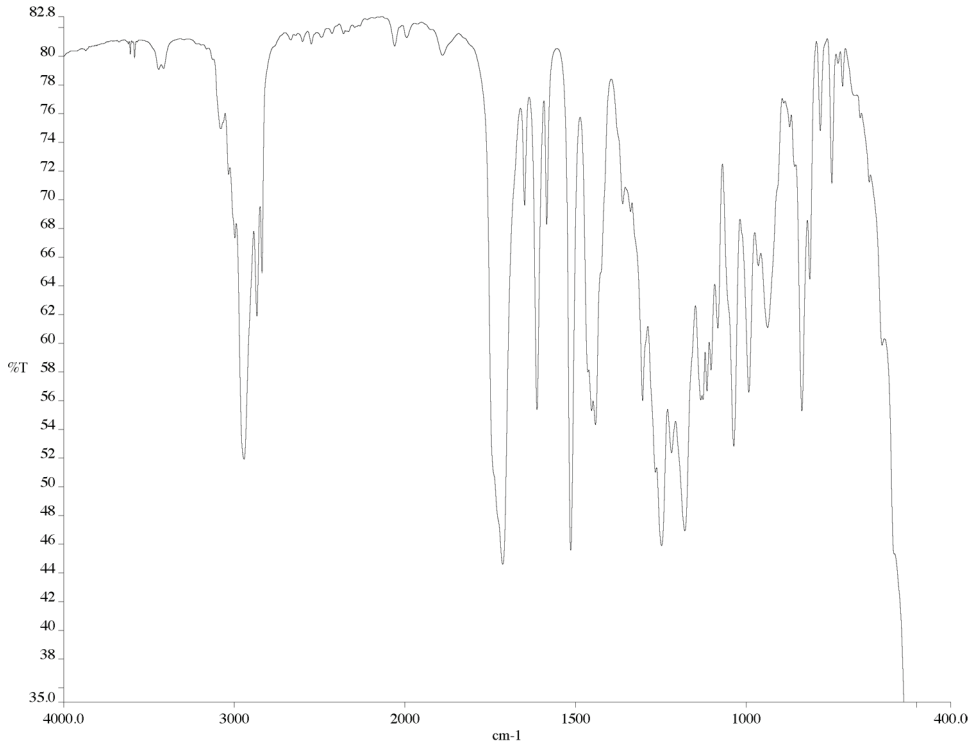


Figure A7.176 IR of compound **374** (NaCl/film)

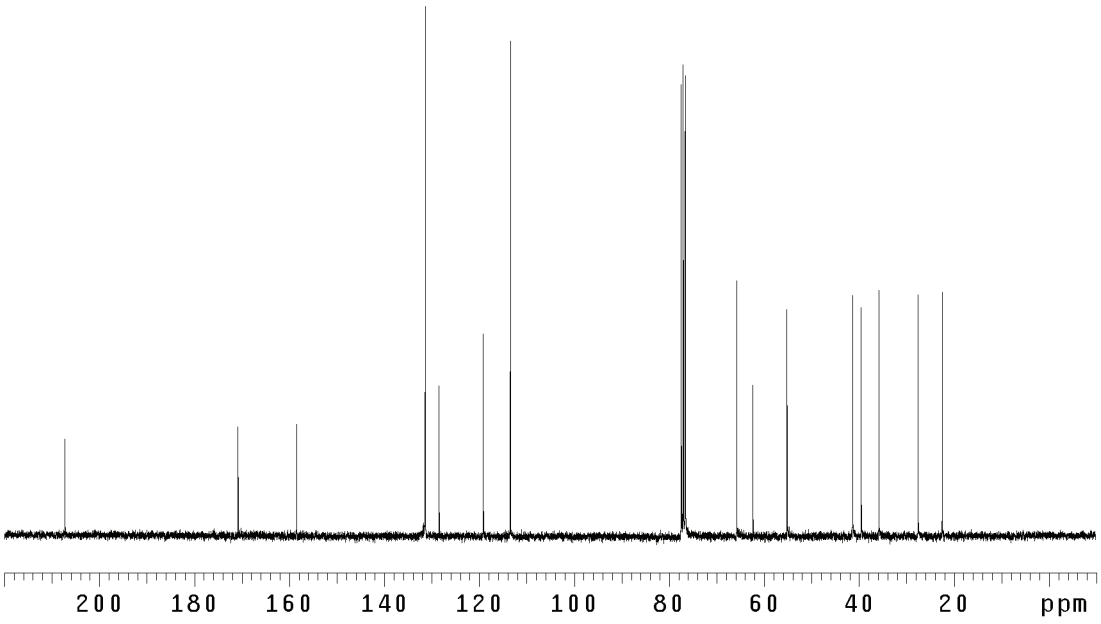


Figure A7.177 ^{13}C NMR of compound **374** (75 MHz, $CDCl_3$)

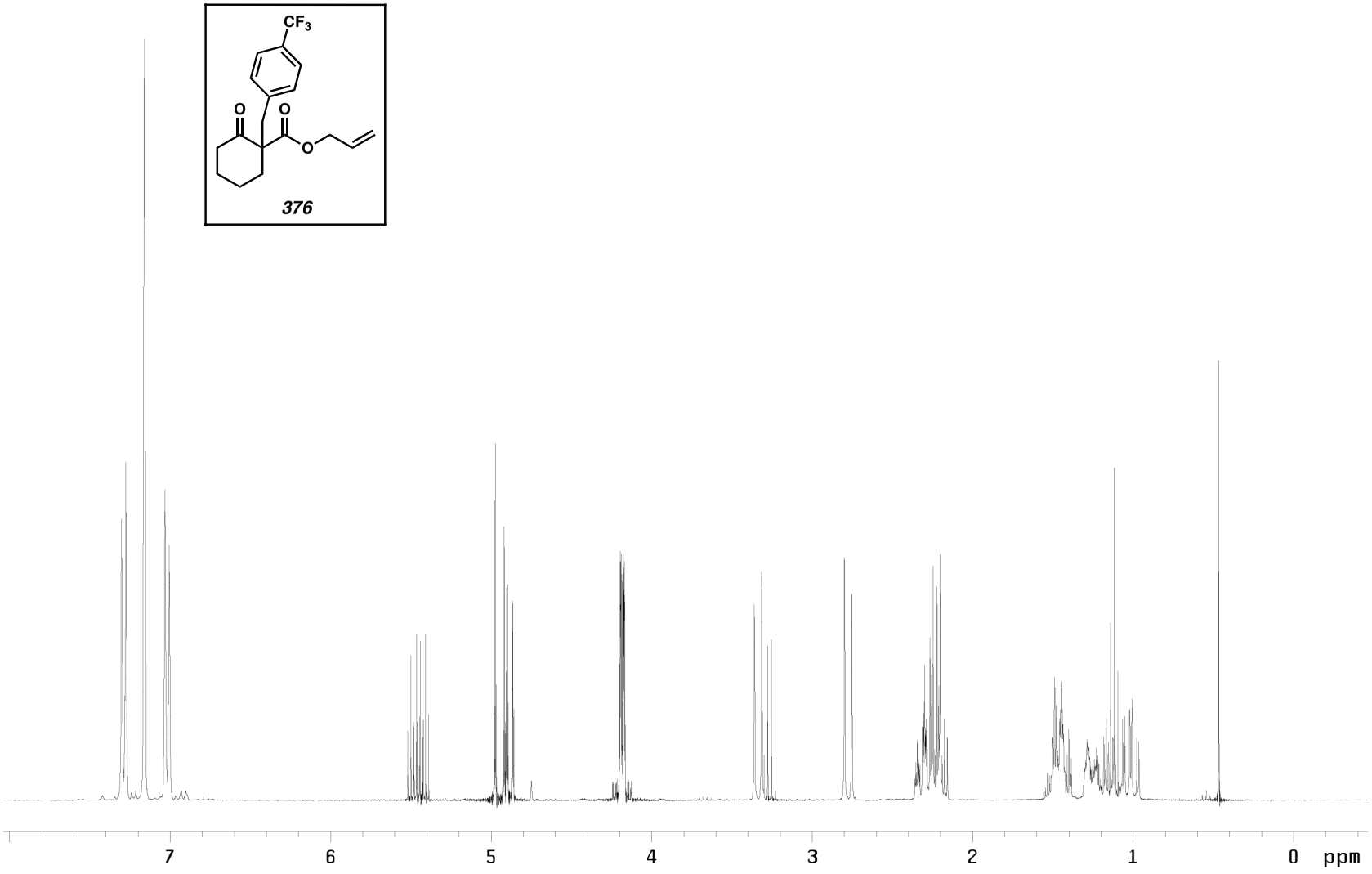


Figure A7.178 ^{1}H NMR of compound **376** (300 MHz, $CDCl_3$)

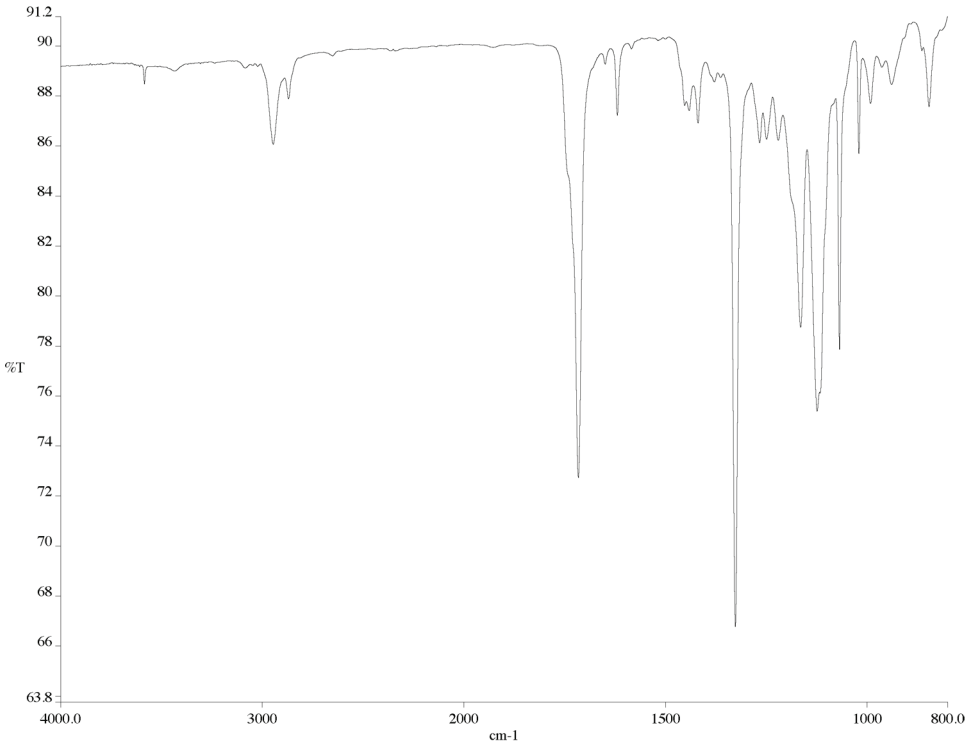


Figure A7.179 IR of compound **376** (NaCl/film)

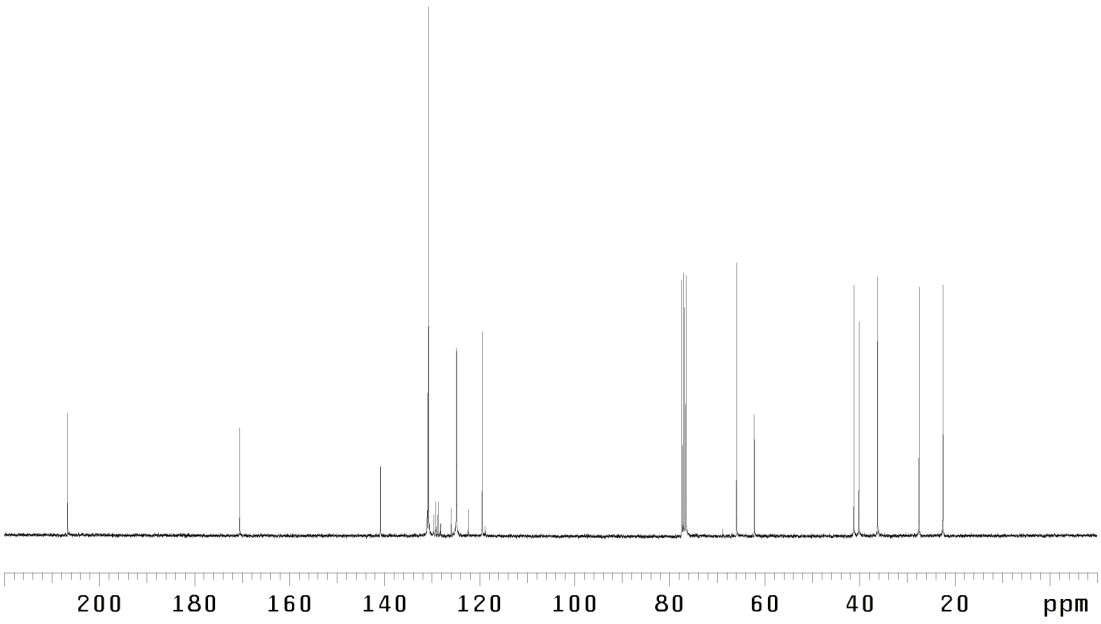


Figure A7.180 ^{13}C NMR of compound **376** (75 MHz, $CDCl_3$)

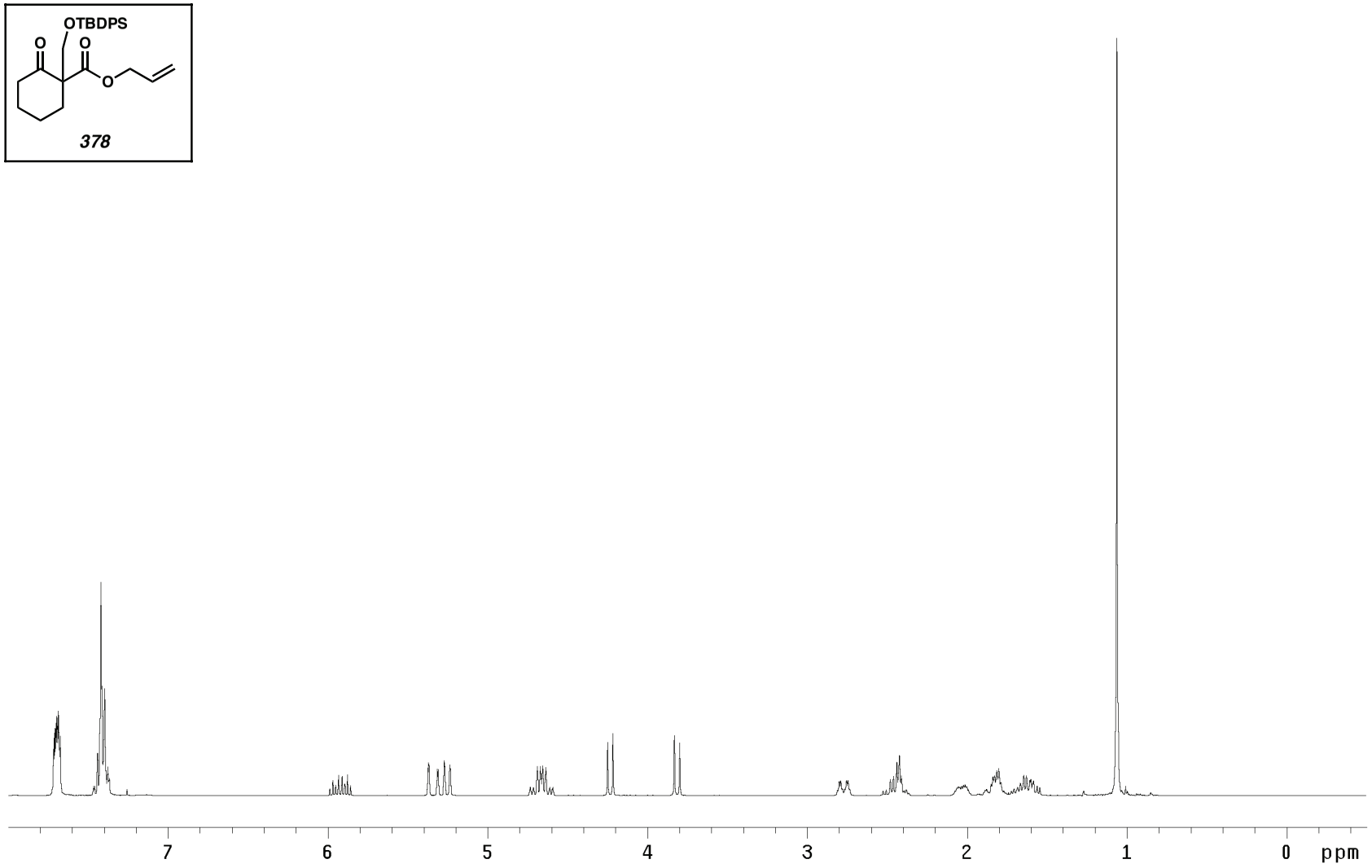


Figure A7.181 ^{1}H NMR of compound **378** (300 MHz, $CDCl_3$)

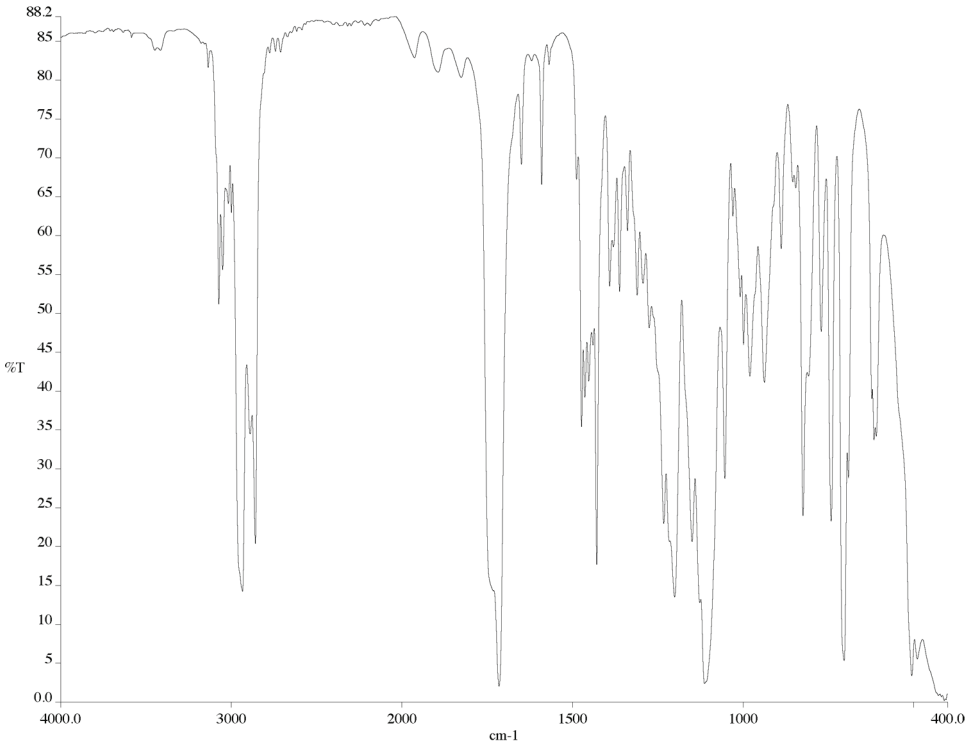


Figure A7.182 IR of compound **378** (NaCl/film)

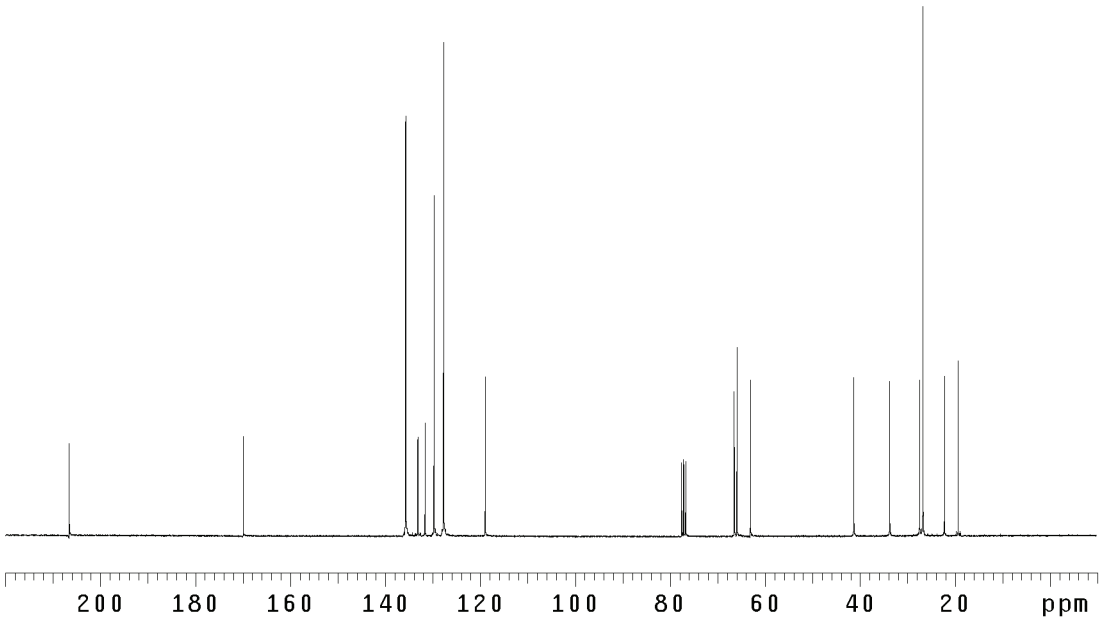


Figure A7.183 ^{13}C NMR of compound **378** (75 MHz, $CDCl_3$)

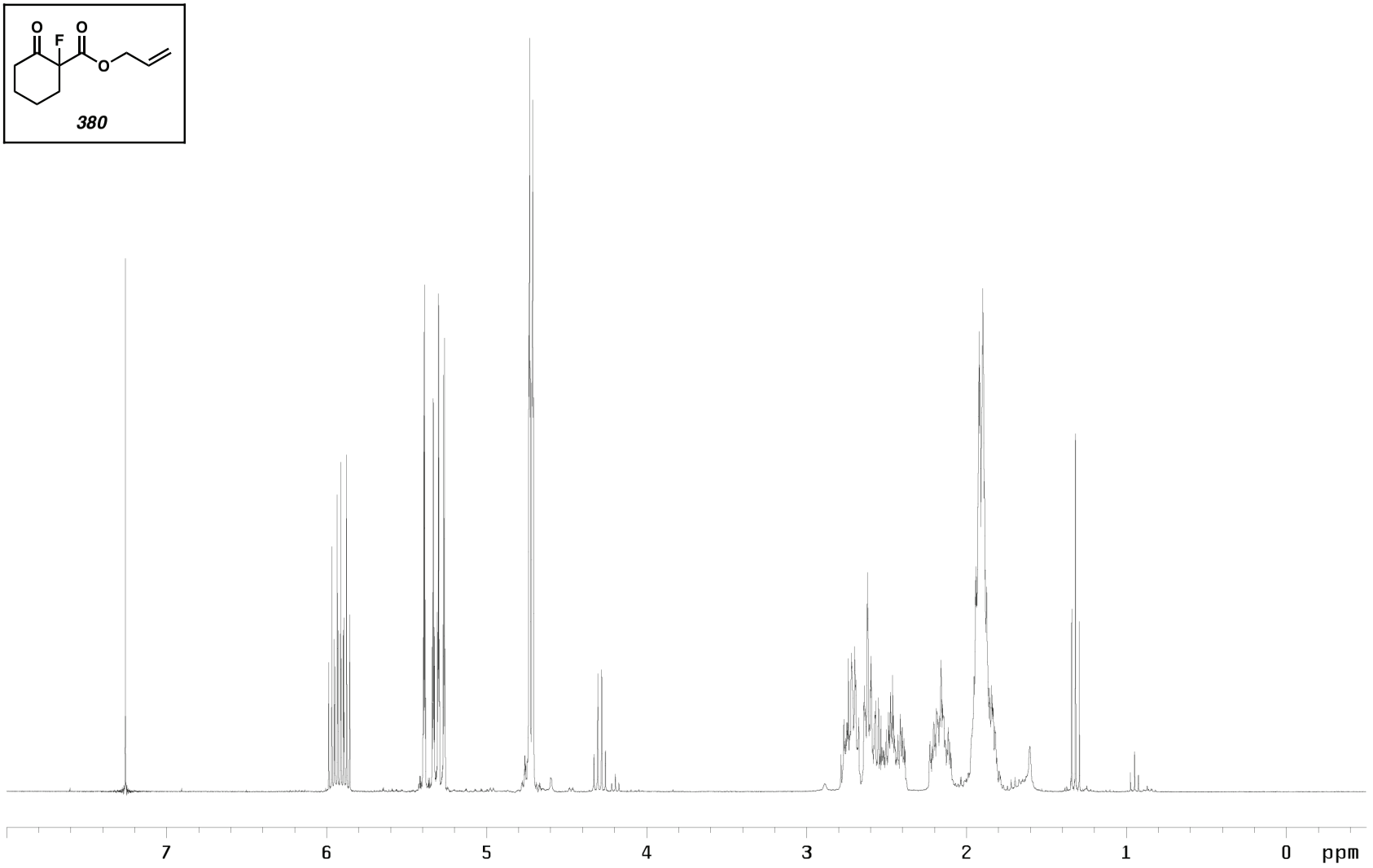


Figure A7.184 ^{1}H NMR of compound **380** (300 MHz, $CDCl_3$)

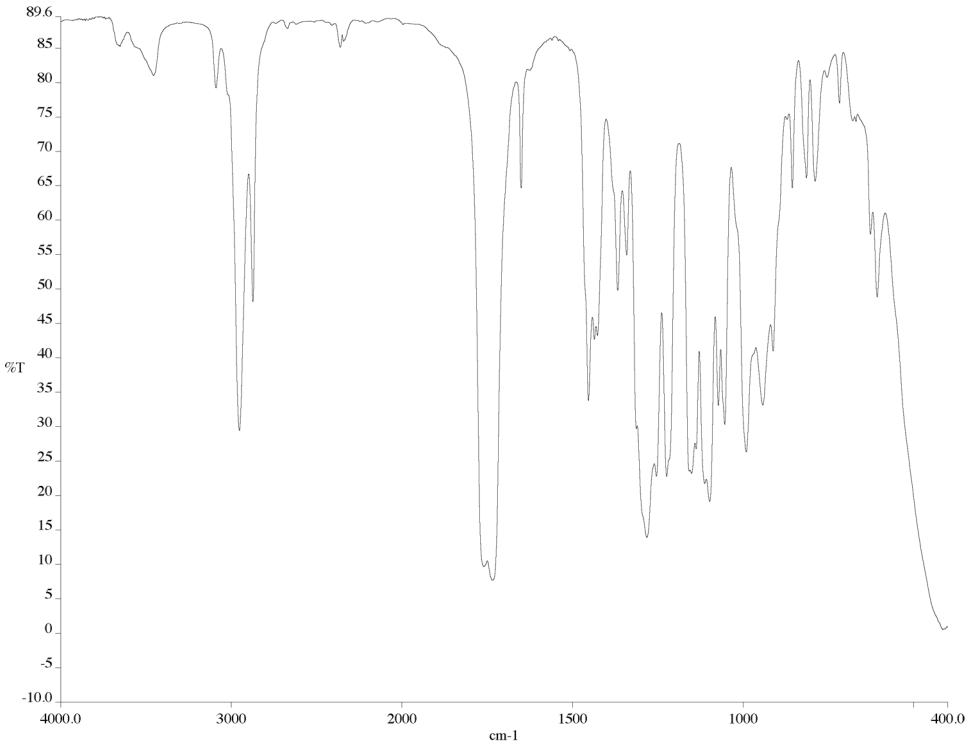


Figure A7.185 IR of compound **380** (NaCl/film)

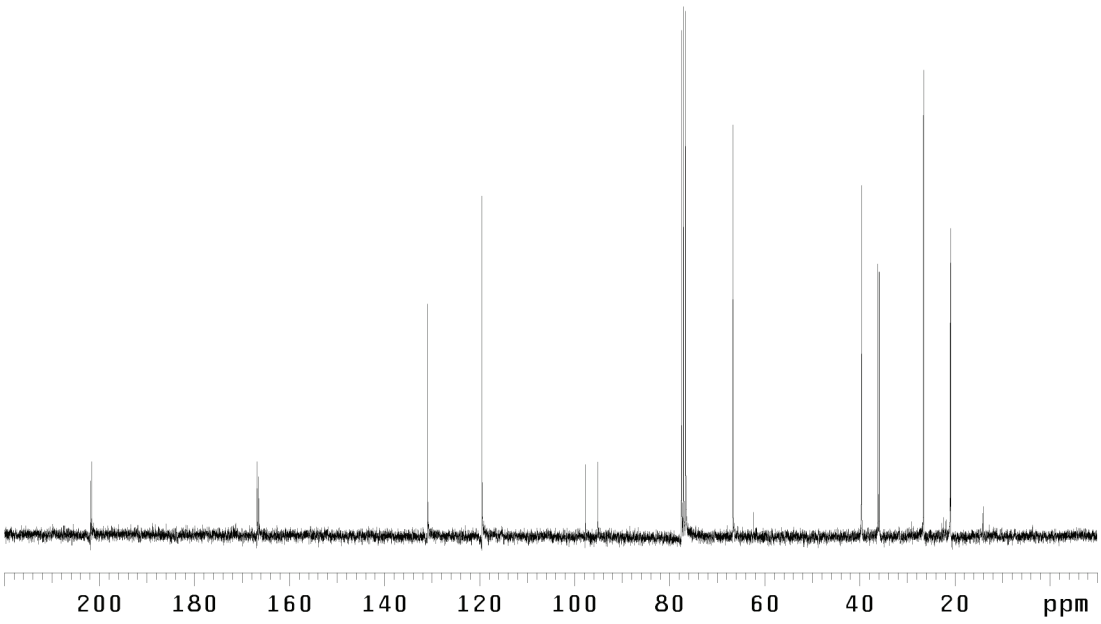


Figure A7.186 ^{13}C NMR of compound **380** (75 MHz, $CDCl_3$)

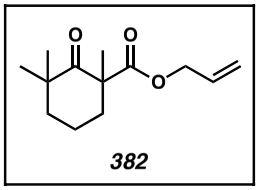


Figure A7.187 ^{1}H NMR of compound **382** (300 MHz, $CDCl_3$)

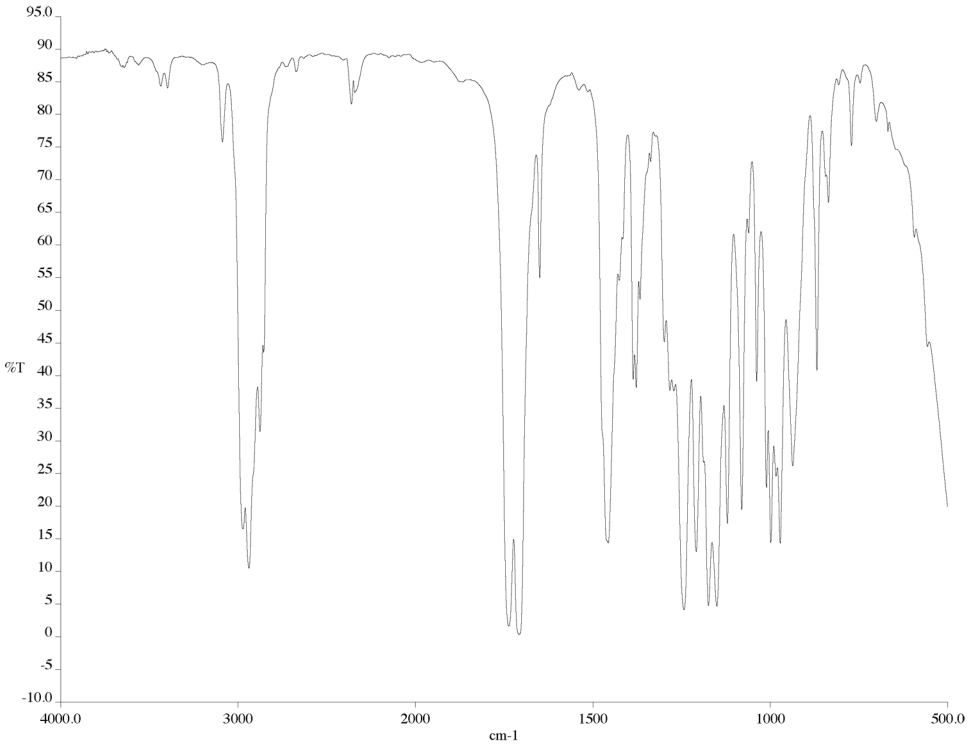


Figure A7.188 IR of compound **282** (NaCl/film)

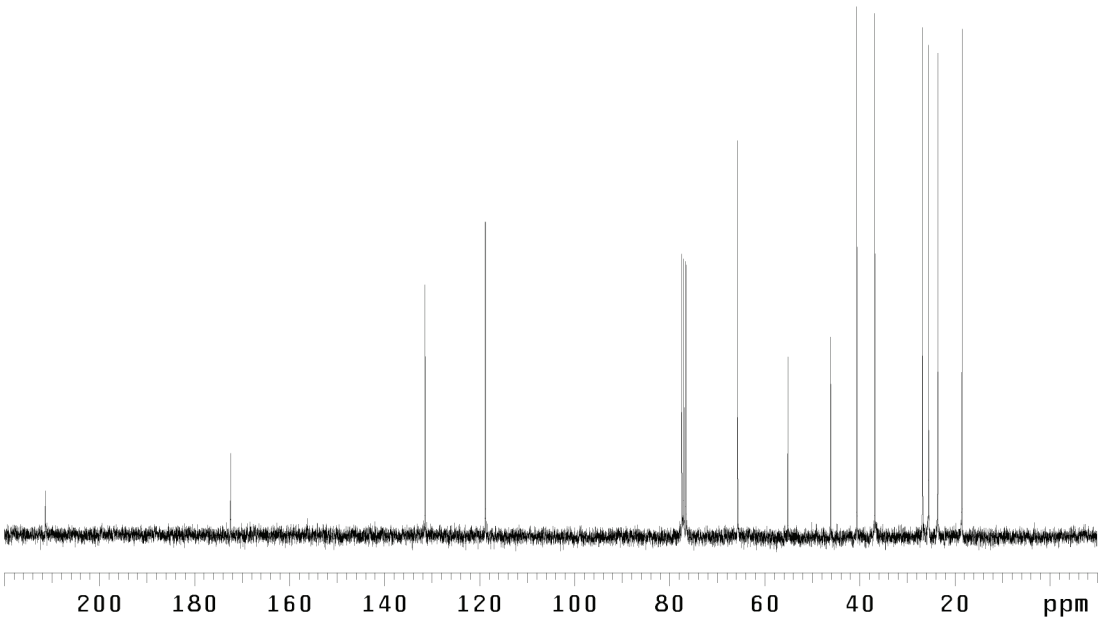


Figure A7.189 ^{13}C NMR of compound **282** (75 MHz, $CDCl_3$)

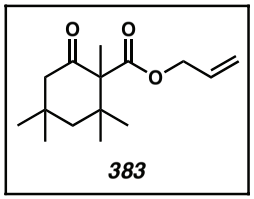


Figure A7.190 ^{1}H NMR of compound **383** (300 MHz, $CDCl_3$)

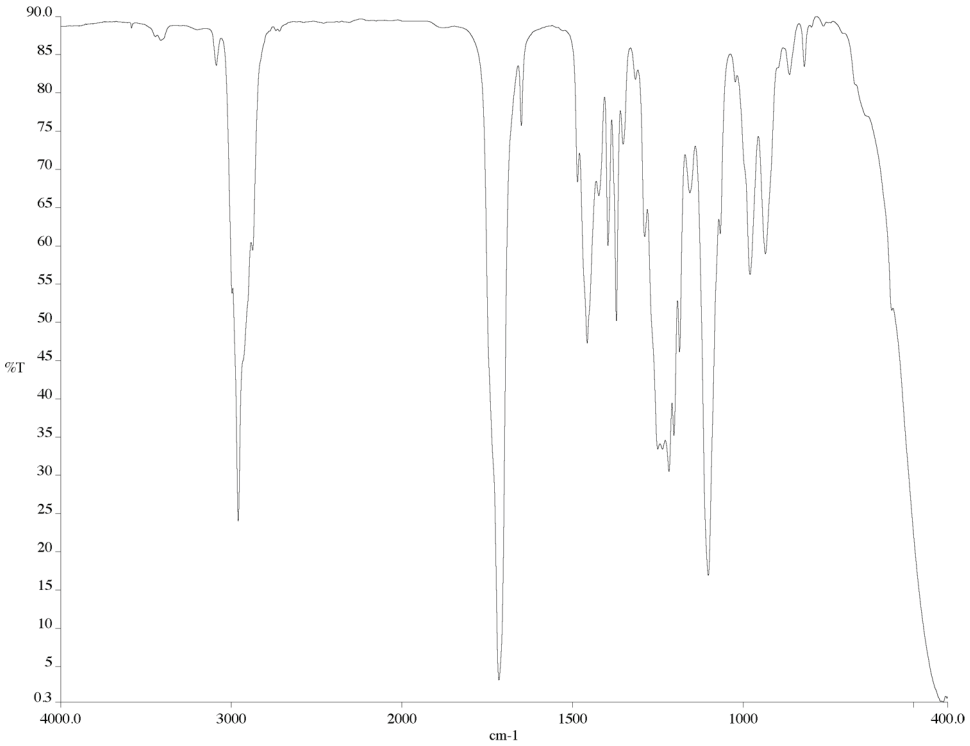


Figure A7.191 IR of compound **383** (NaCl/film)

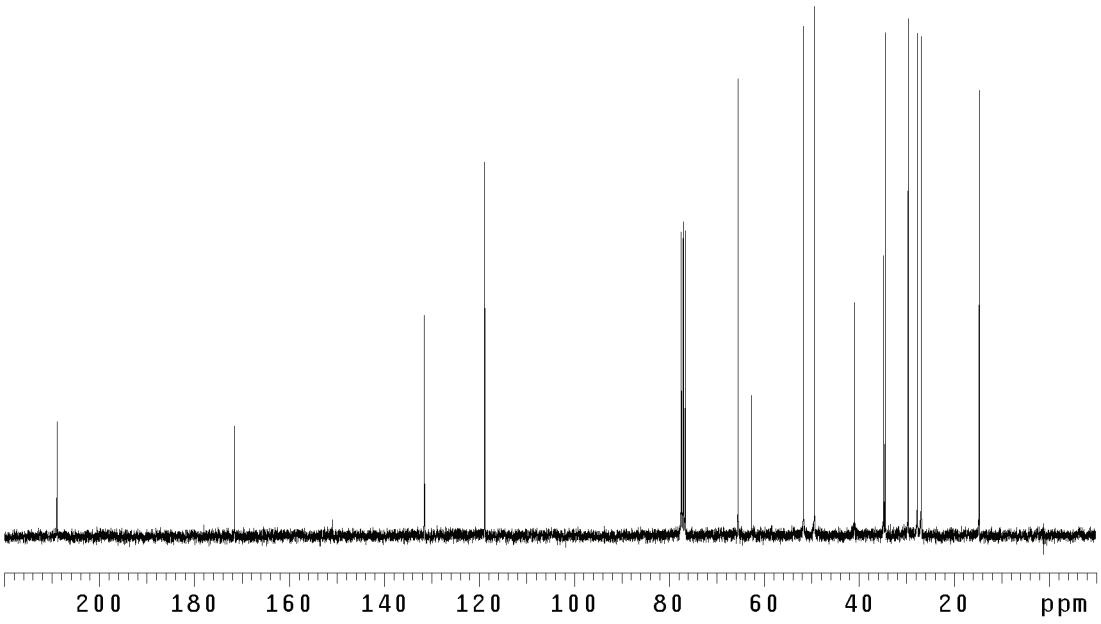


Figure A7.192 ^{13}C NMR of compound **383** (75 MHz, $CDCl_3$)

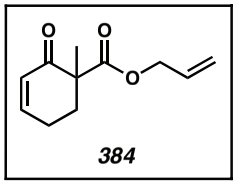


Figure A7.193 ^{1}H NMR of compound **384** (300 MHz, $CDCl_3$)

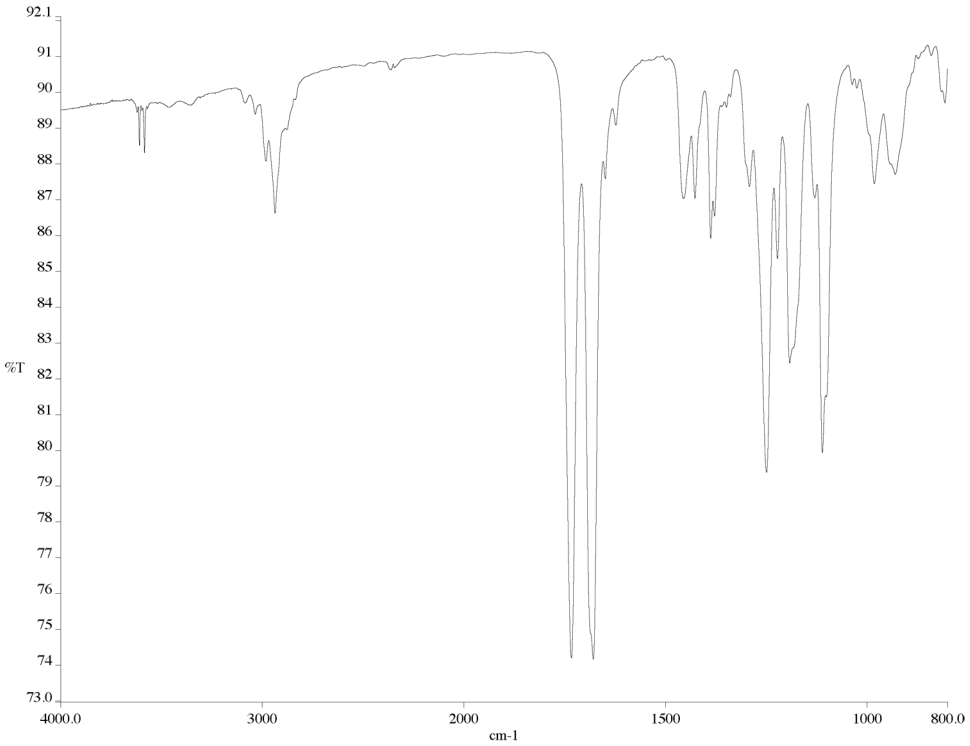


Figure A7.194 IR of compound **384** (NaCl/film)

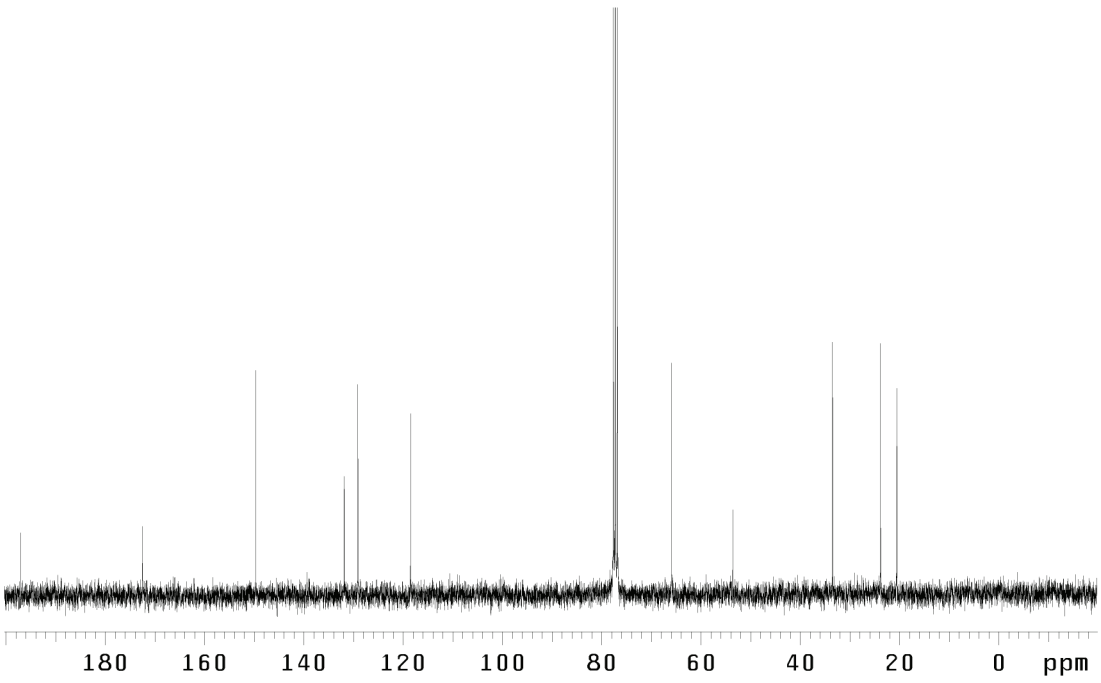


Figure A7.195 ^{13}C NMR of compound **384** (75 MHz, $CDCl_3$)

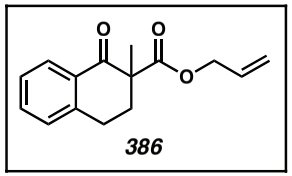


Figure A7.196 ^{1}H NMR of compound **386** (300 MHz, $CDCl_3$)

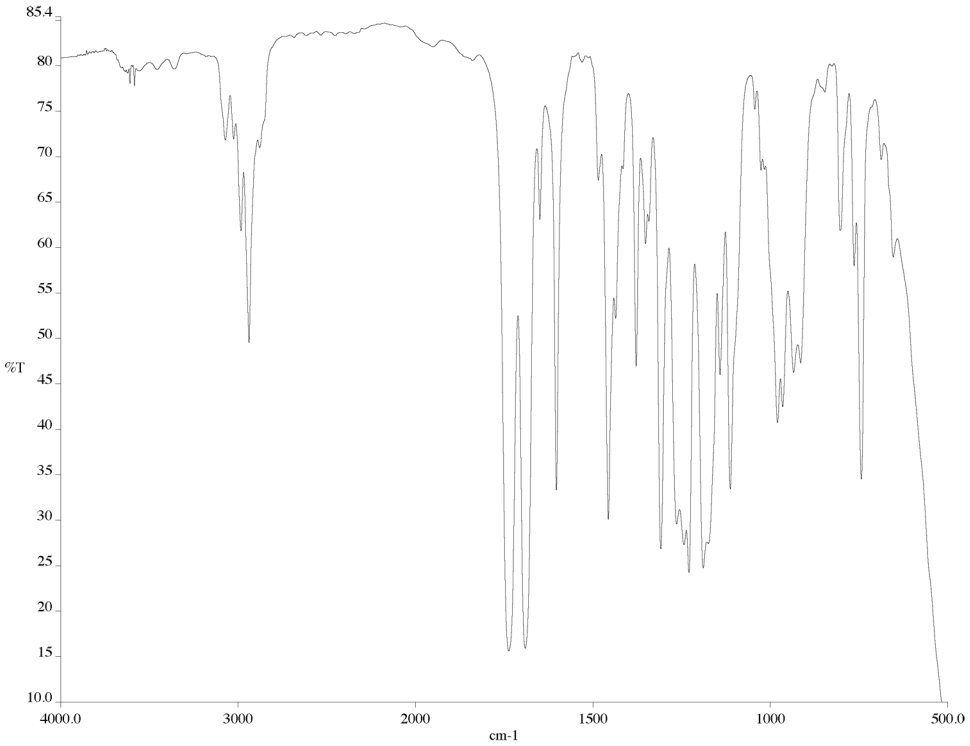


Figure A7.197 IR of compound **386** (NaCl/film)

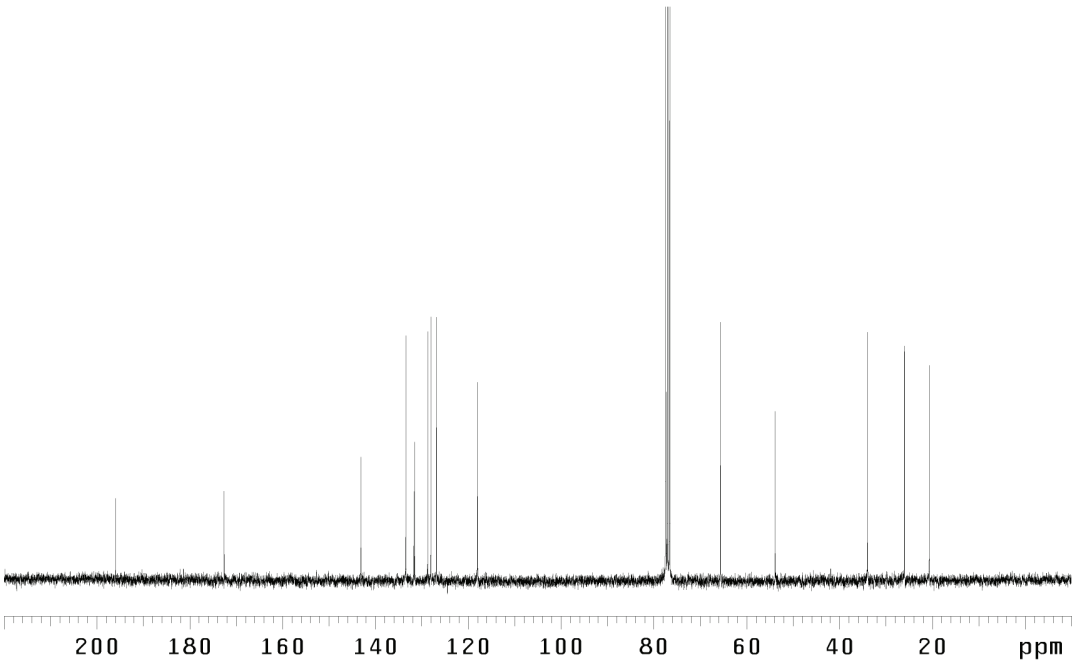


Figure A7.198 ^{13}C NMR of compound **386** (75 MHz, $CDCl_3$)

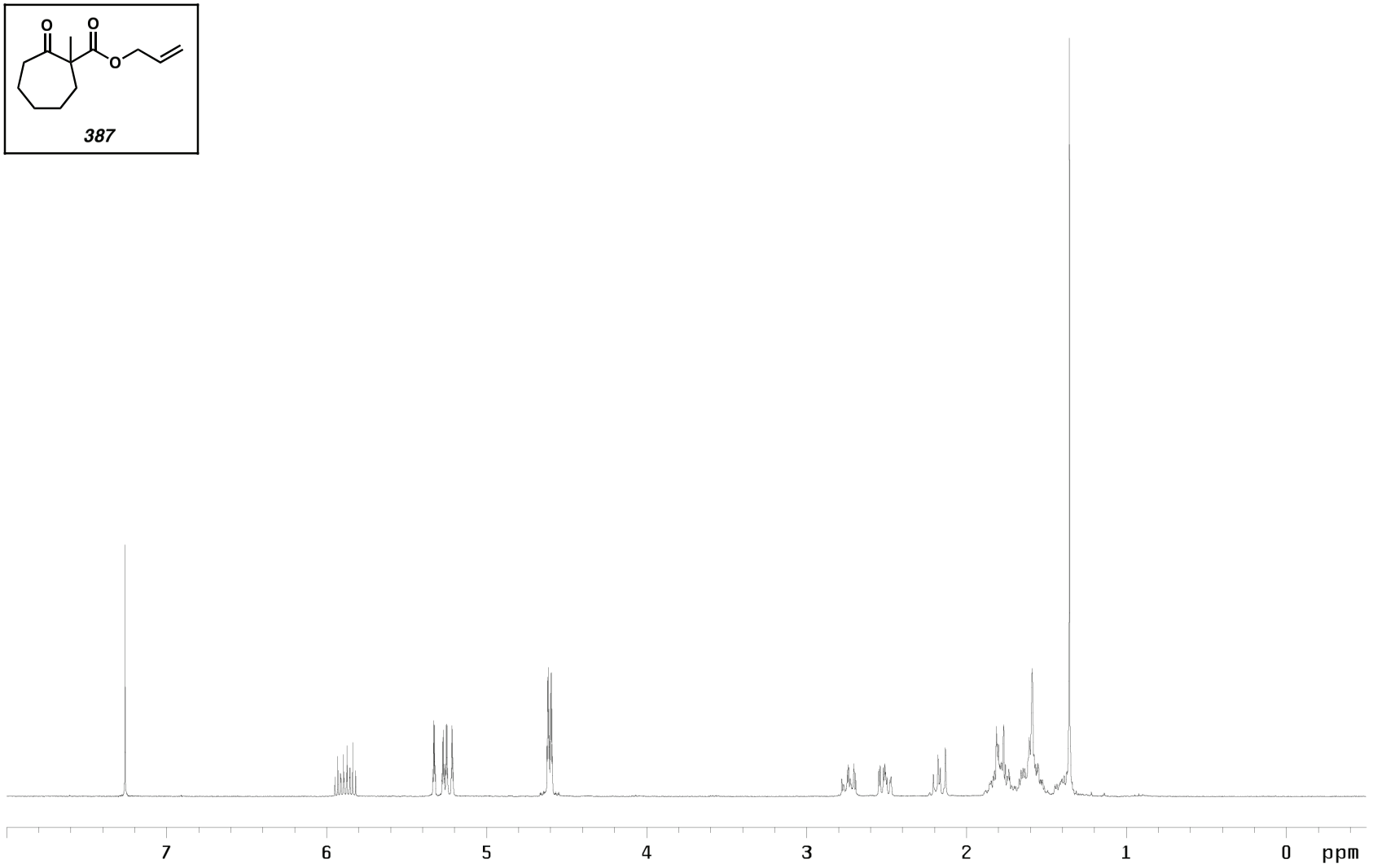


Figure A7.199 ^{1}H NMR of compound **387** (300 MHz, $CDCl_3$)

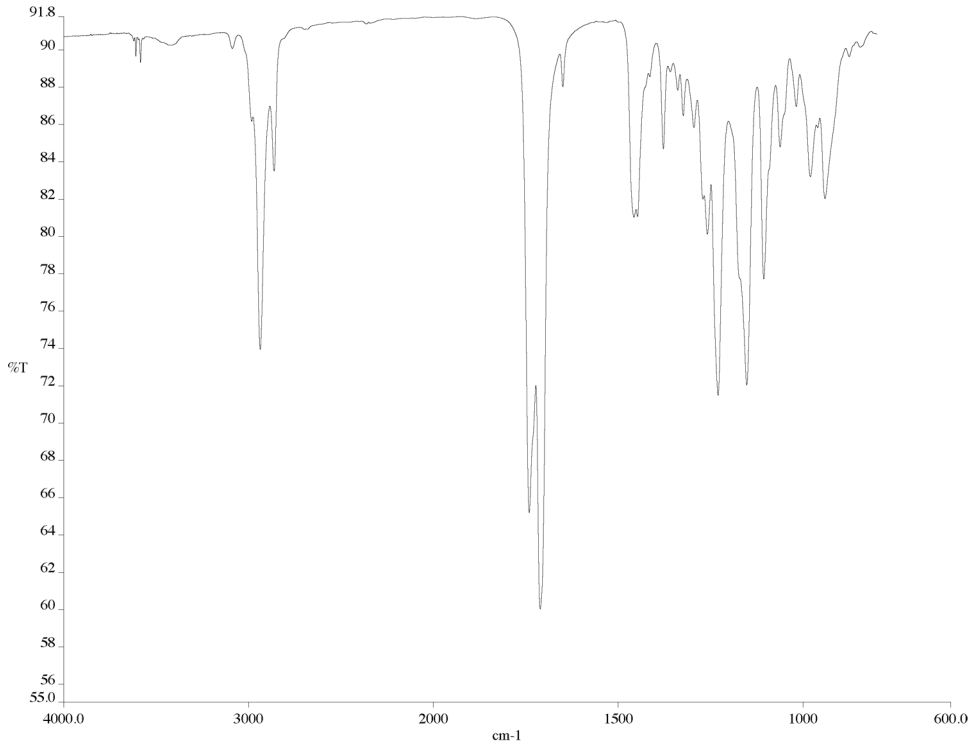


Figure A7.200 IR of compound **387** (NaCl/film)

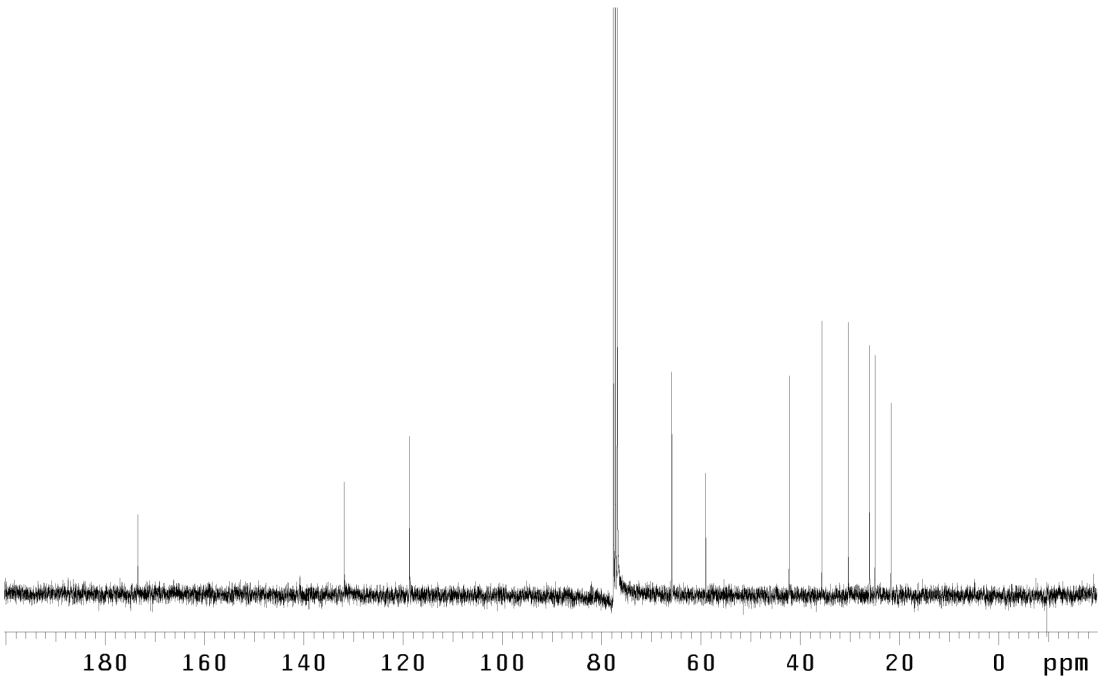


Figure A7.201 ^{13}C NMR of compound **387** (75 MHz, $CDCl_3$)

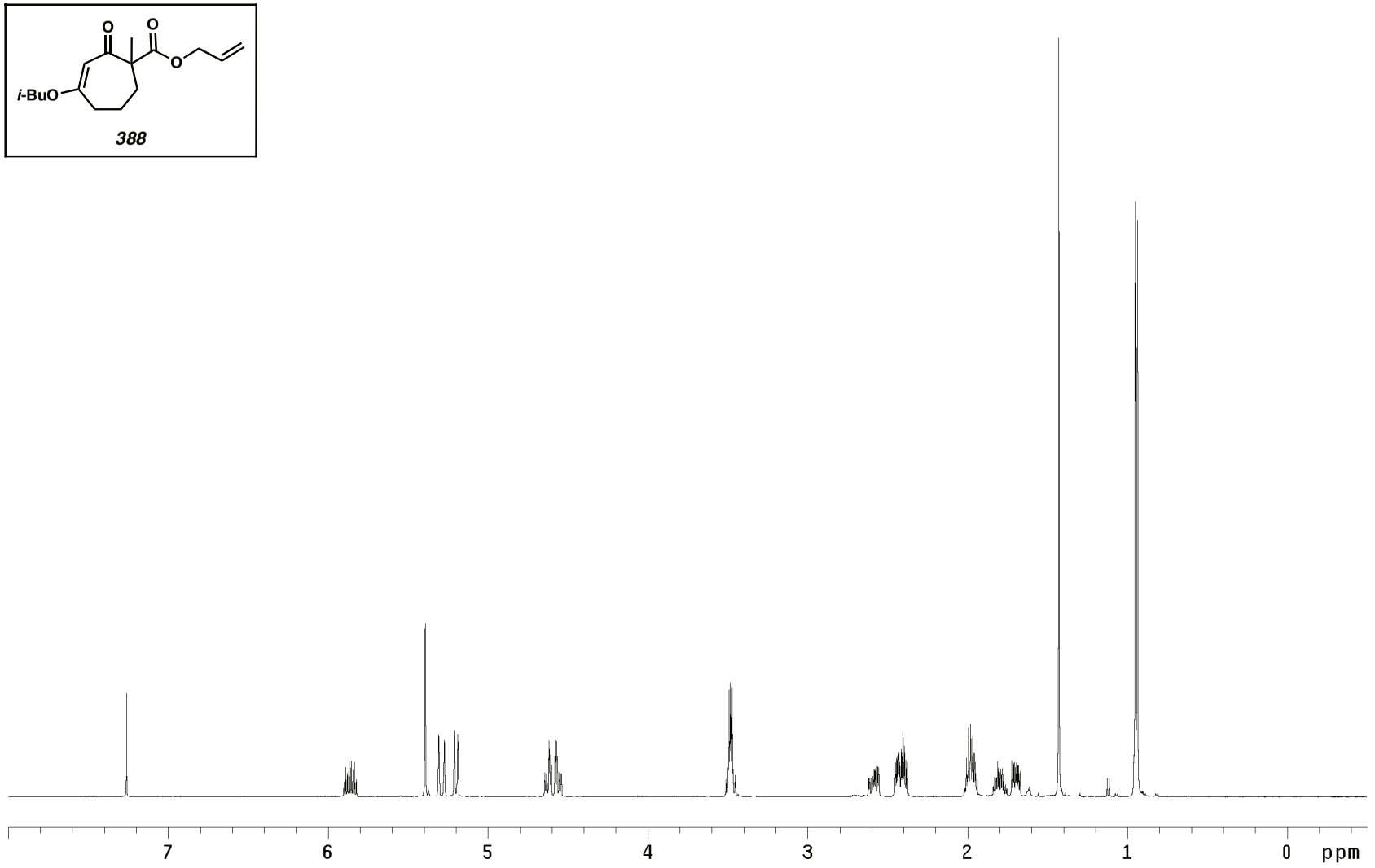


Figure A7.202 ^{1}H NMR of compound **388** (500 MHz, $CDCl_3$)

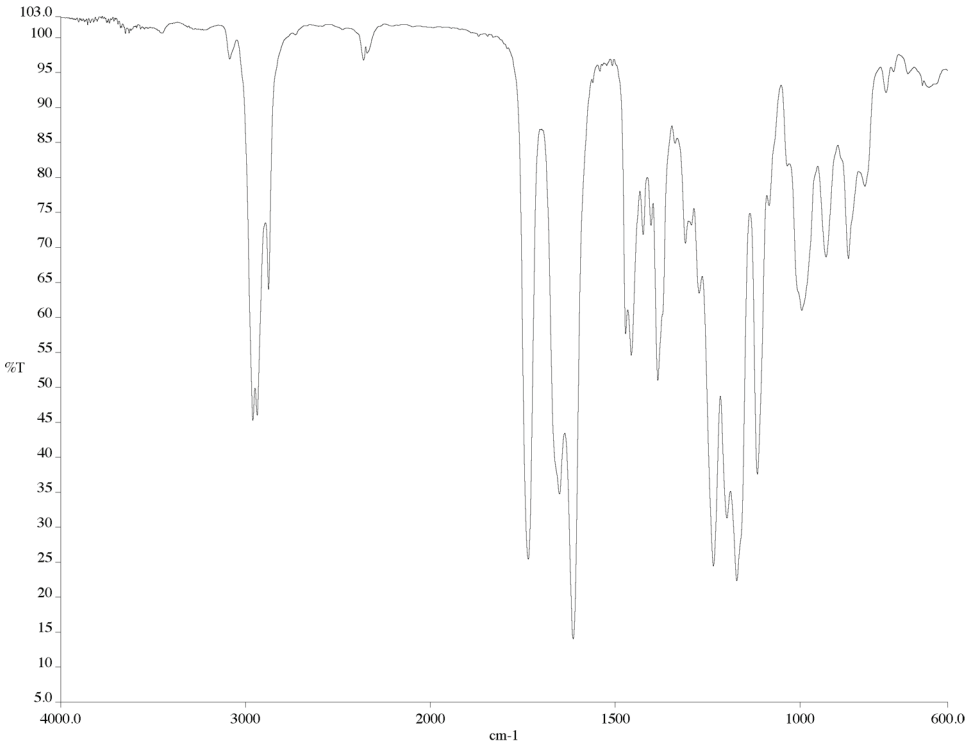


Figure A7.203 IR of compound **388** (NaCl/film)

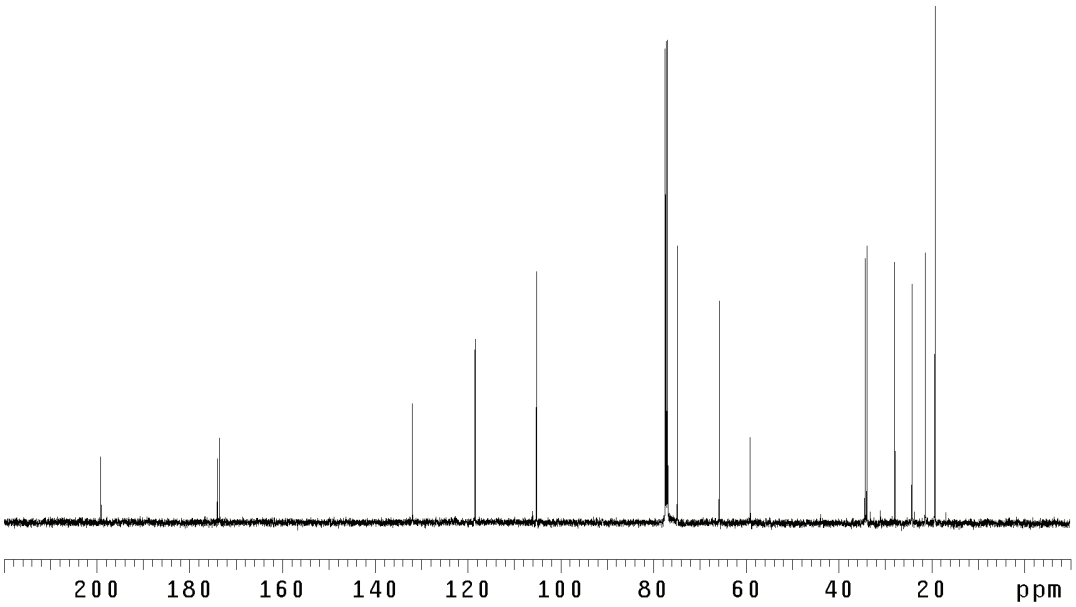


Figure A7.204 ^{13}C NMR of compound **388** (125 MHz, $CDCl_3$)

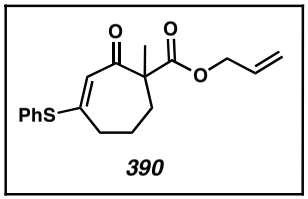


Figure A7.205 ^{1}H NMR of compound **390** (500 MHz, $CDCl_3$)

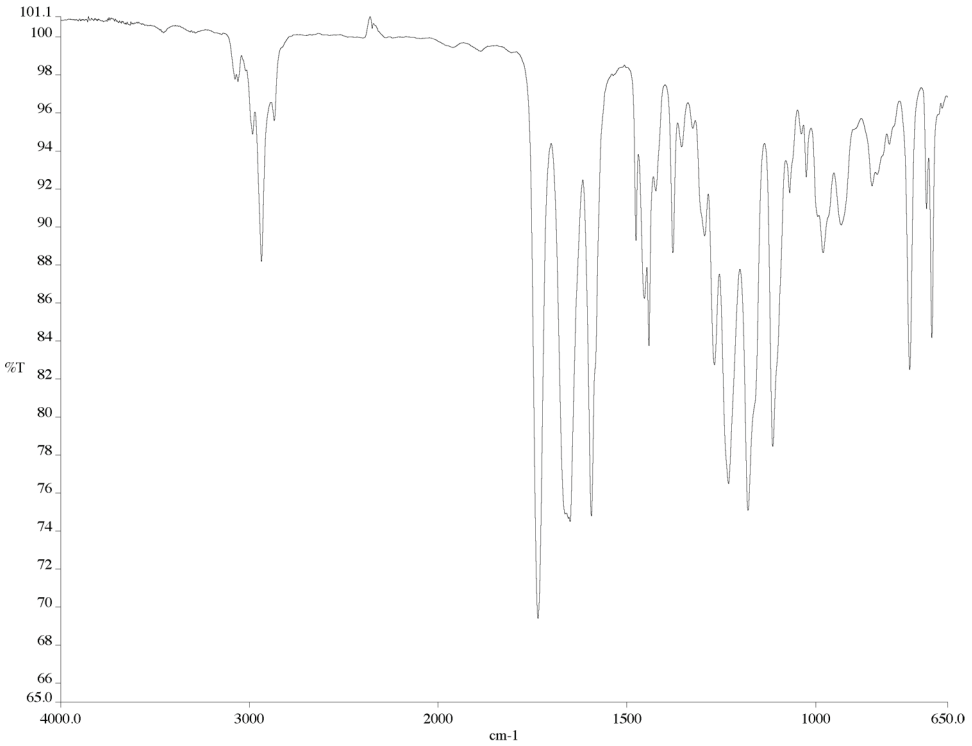


Figure A7.206 IR of compound **390** (NaCl/film)

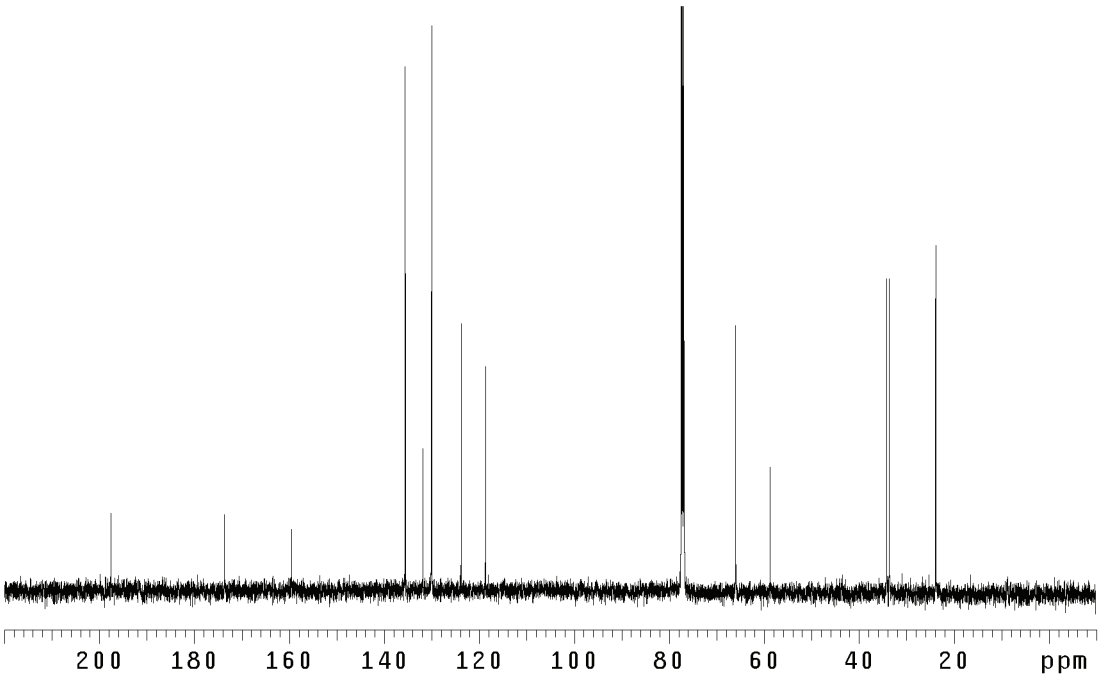


Figure A7.207 ^{13}C NMR of compound **390** (125 MHz, $CDCl_3$)

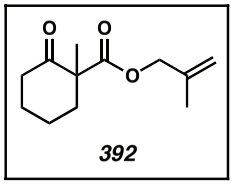


Figure A7.208 ^{1}H NMR of compound **392** (300 MHz, $CDCl_3$)

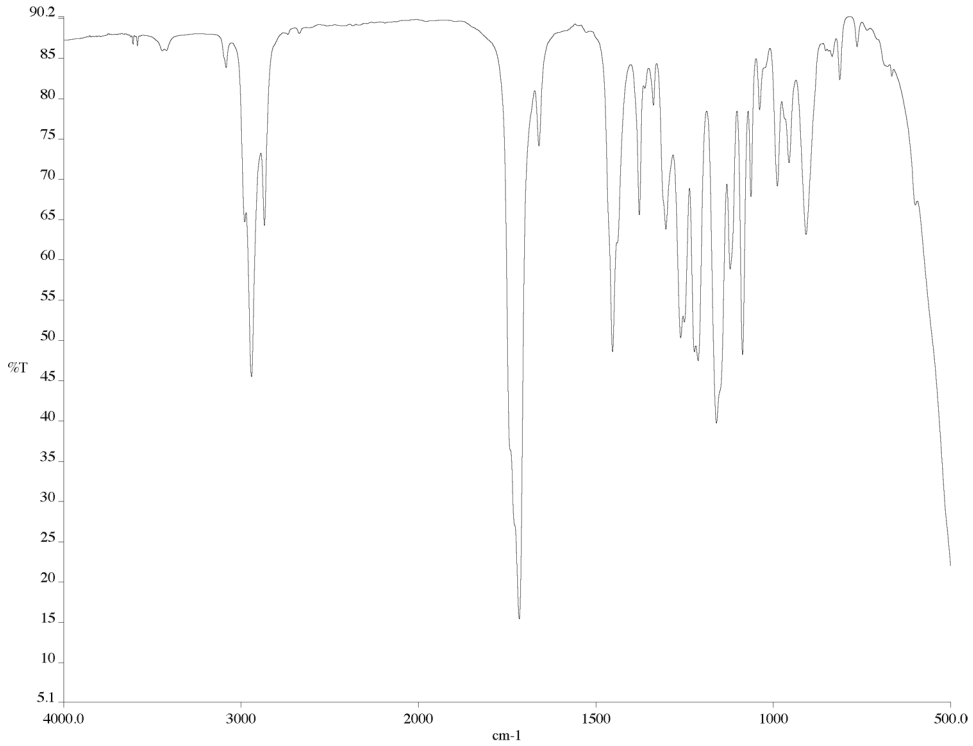


Figure A7.209 IR of compound **392** (NaCl/film)

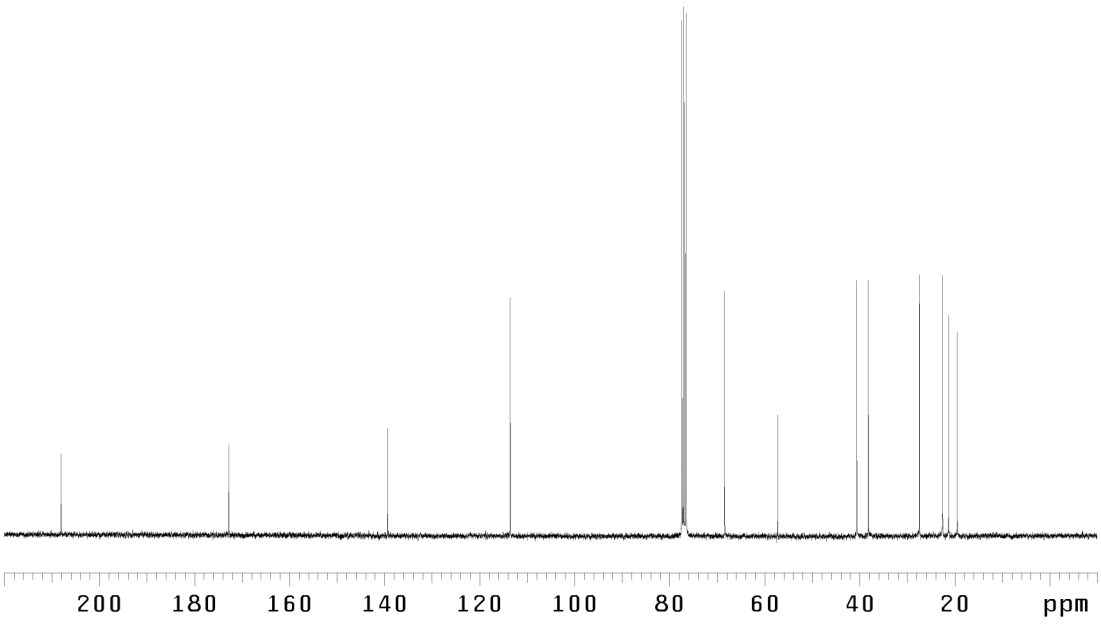
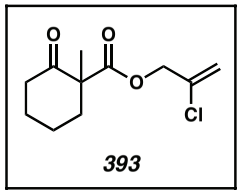


Figure A7.210 ^{13}C NMR of compound **392** (75 MHz, $CDCl_3$)



393

Figure A7.211 ^{1}H NMR of compound **393** (300 MHz, $CDCl_3$)

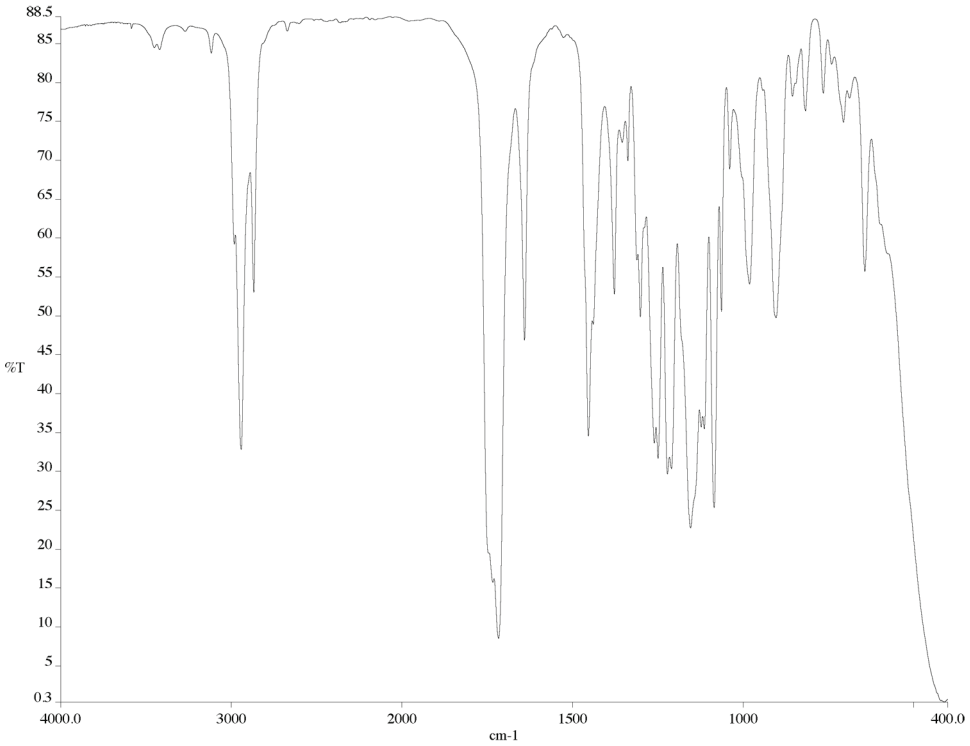


Figure A7.212 IR of compound **393** (NaCl/film)

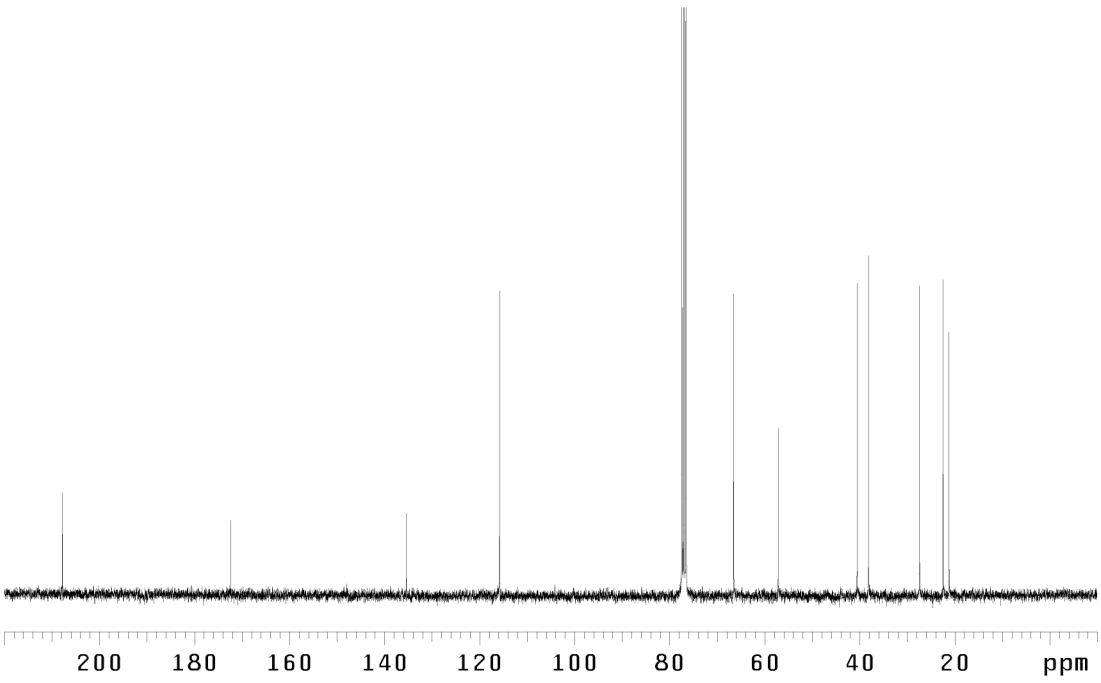


Figure A7.213 ^{13}C NMR of compound **393** (75 MHz, $CDCl_3$)

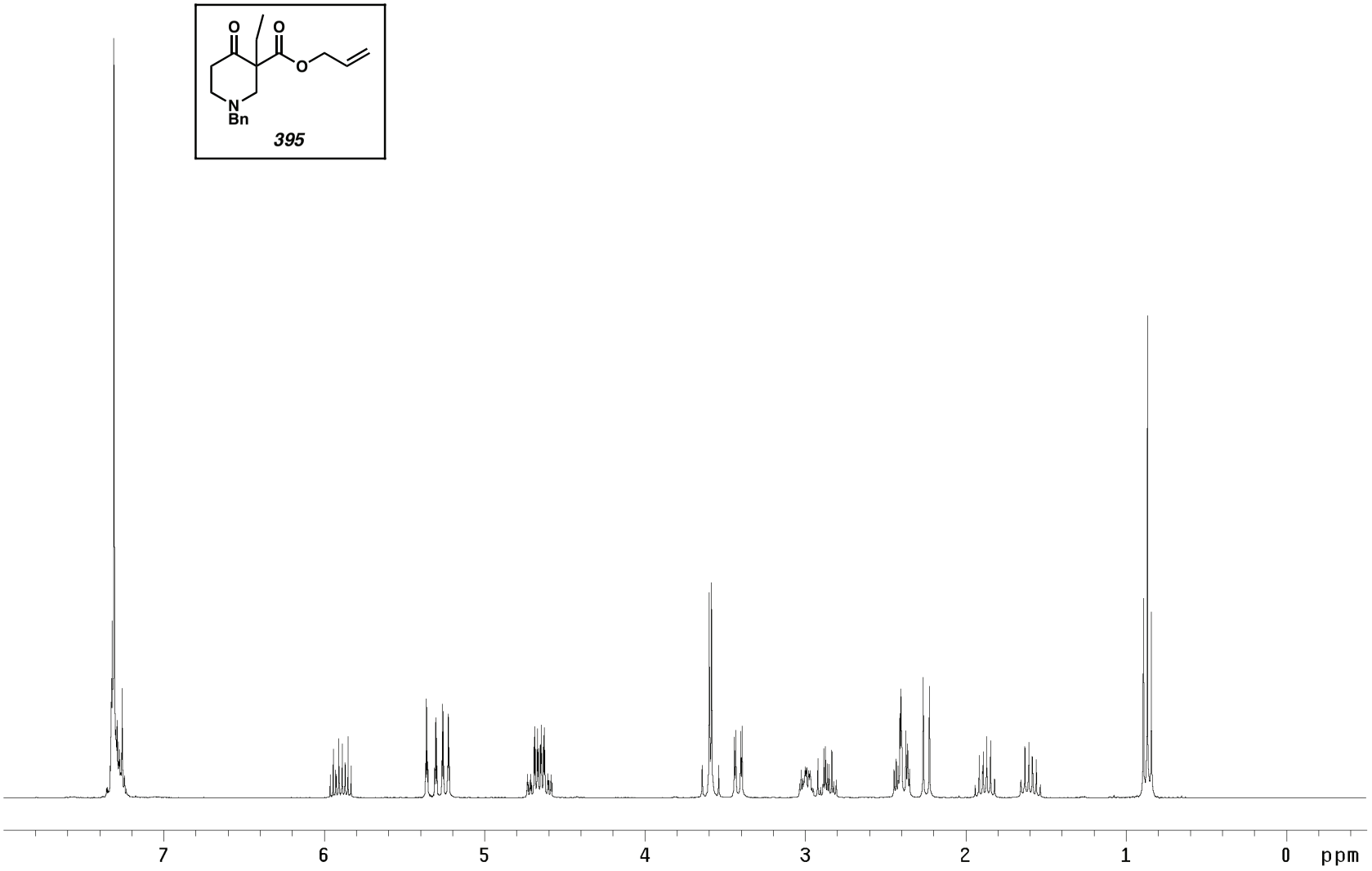


Figure A7.214 ^{1}H NMR of compound **395** (300 MHz, $CDCl_3$)

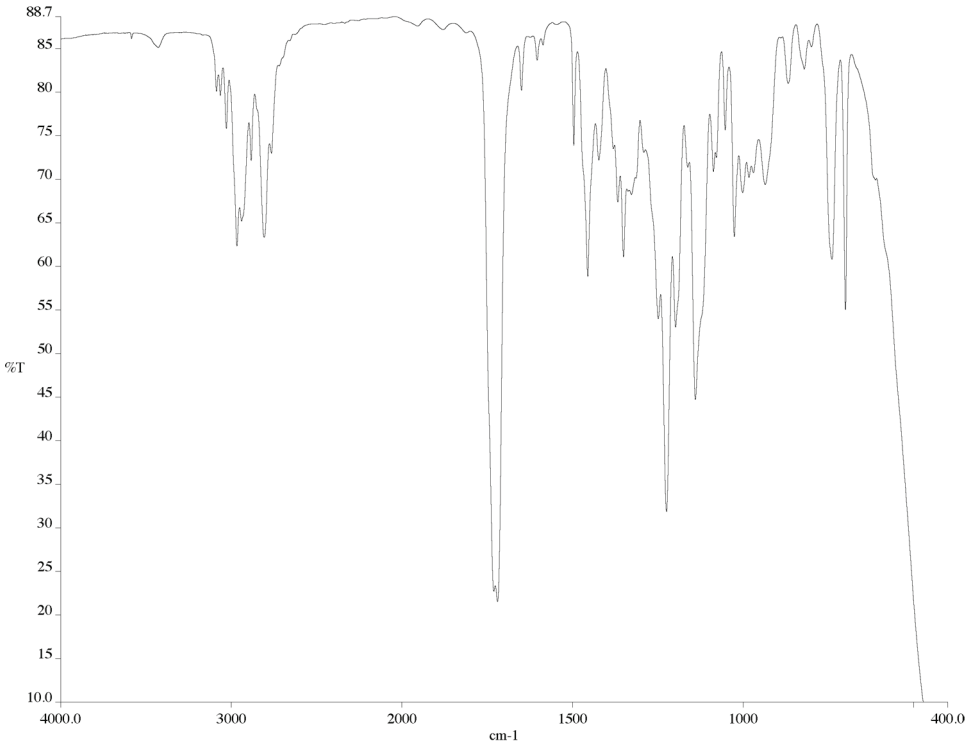


Figure A7.215 IR of compound **395** (NaCl/film)

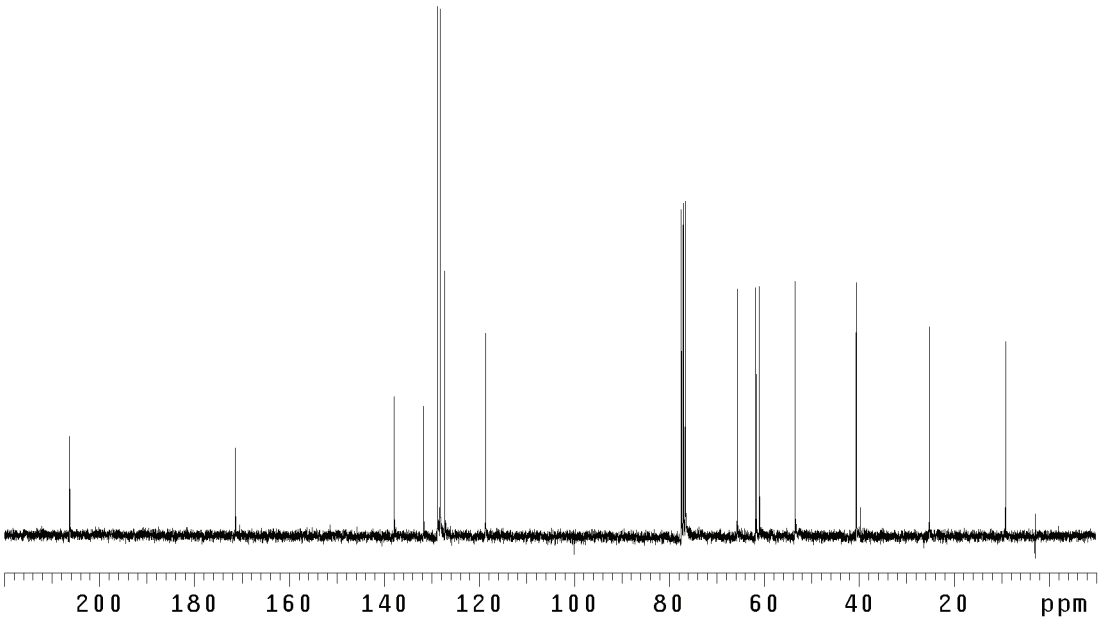


Figure A7.216 ^{13}C NMR of compound **395** (75 MHz, $CDCl_3$)

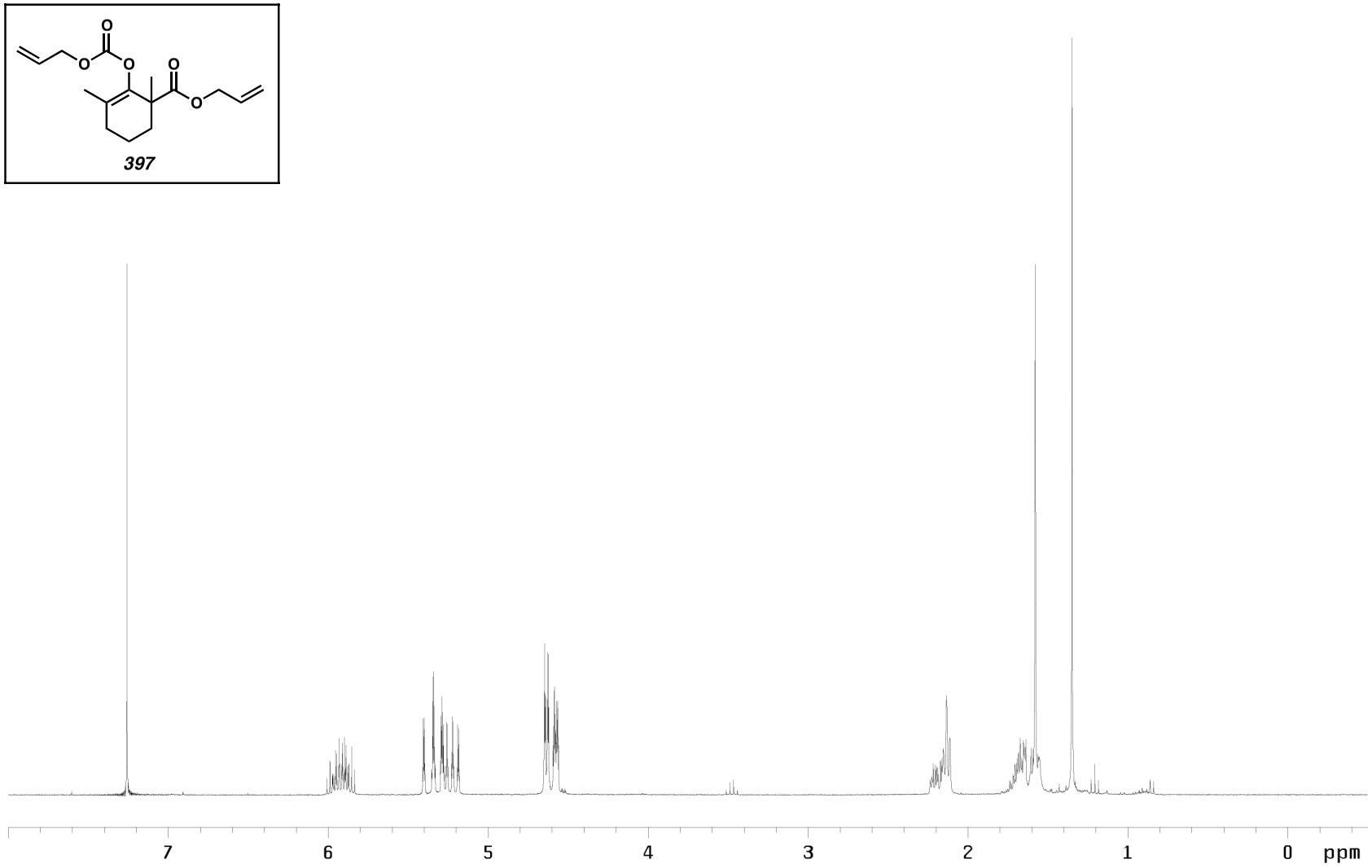


Figure A7.217 ^{1}H NMR of compound **397** (300 MHz, $CDCl_3$)

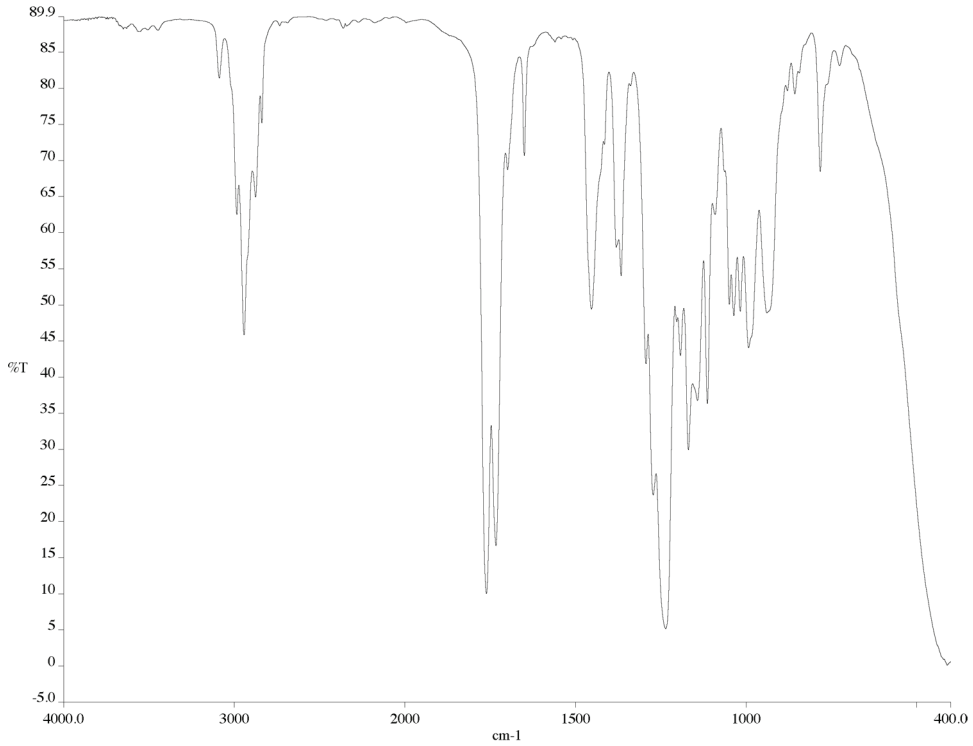


Figure A7.218 IR of compound **397** (NaCl/film)

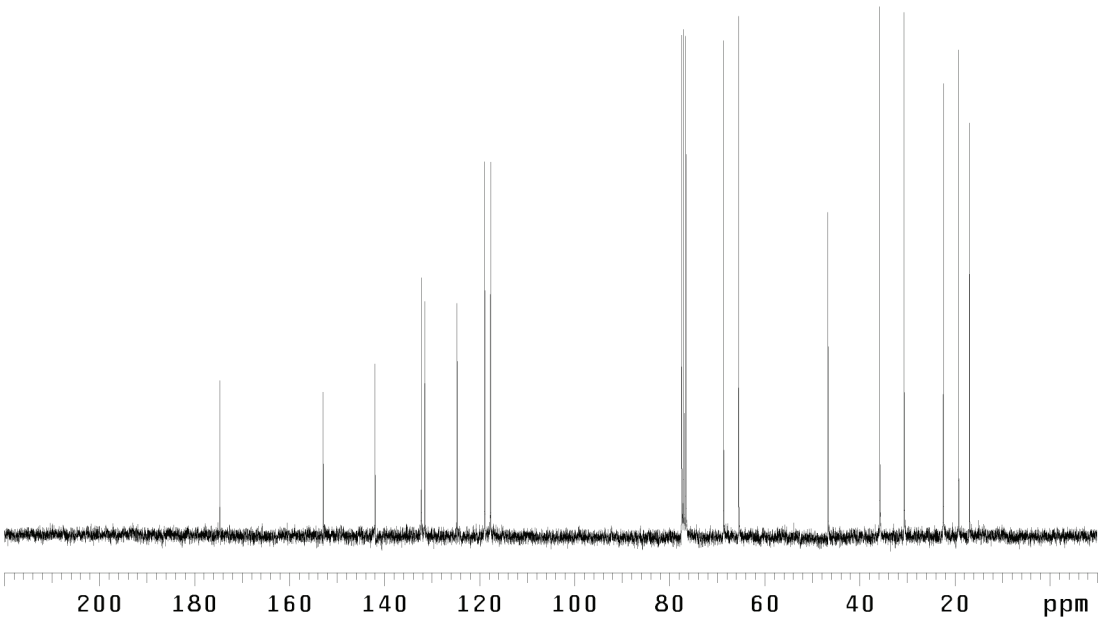


Figure A7.219 ^{13}C NMR of compound **397** (75 MHz, $CDCl_3$)

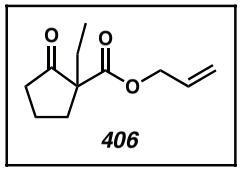


Figure A7.220 ^{1}H NMR of compound **406** (300 MHz, $CDCl_3$)

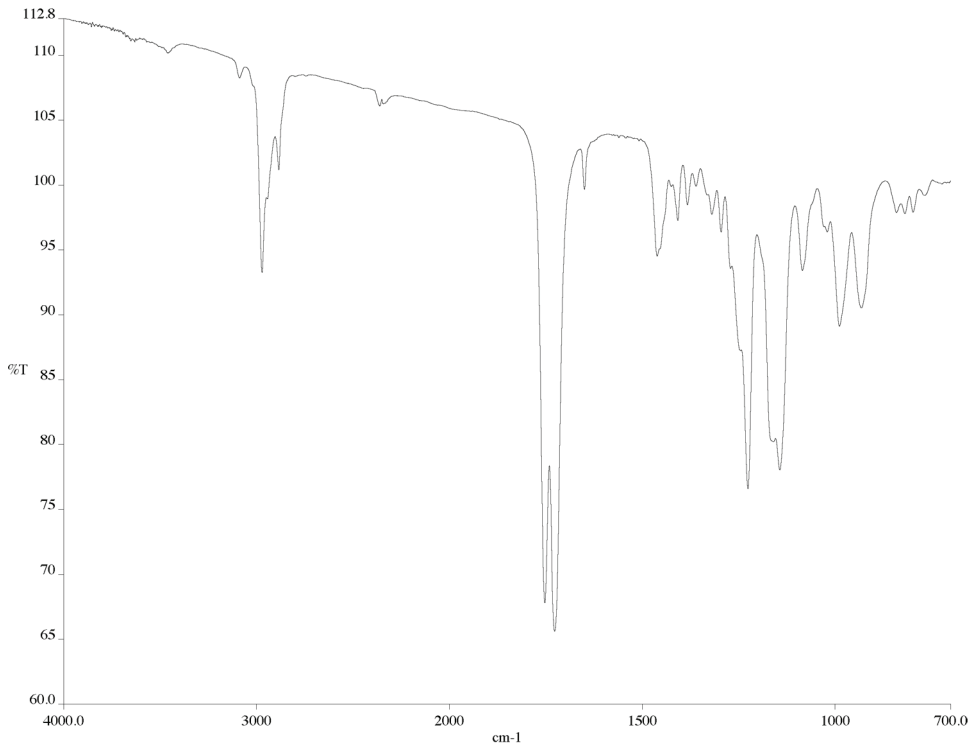


Figure A7.221 IR of compound **406** (NaCl/film)

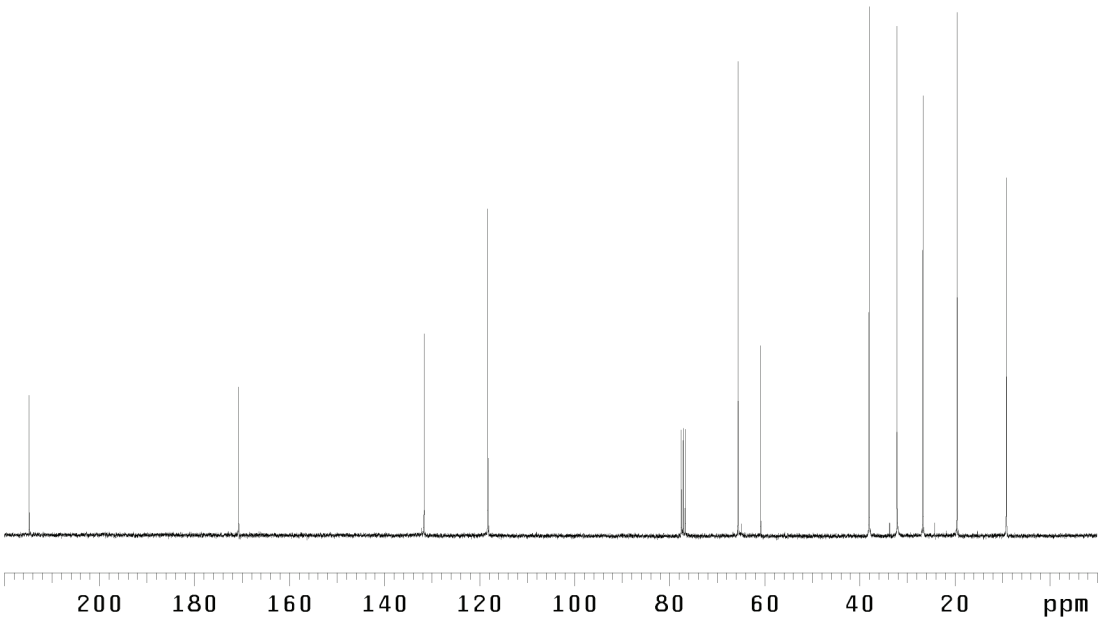


Figure A7.222 ^{13}C NMR of compound **406** (75 MHz, $CDCl_3$)

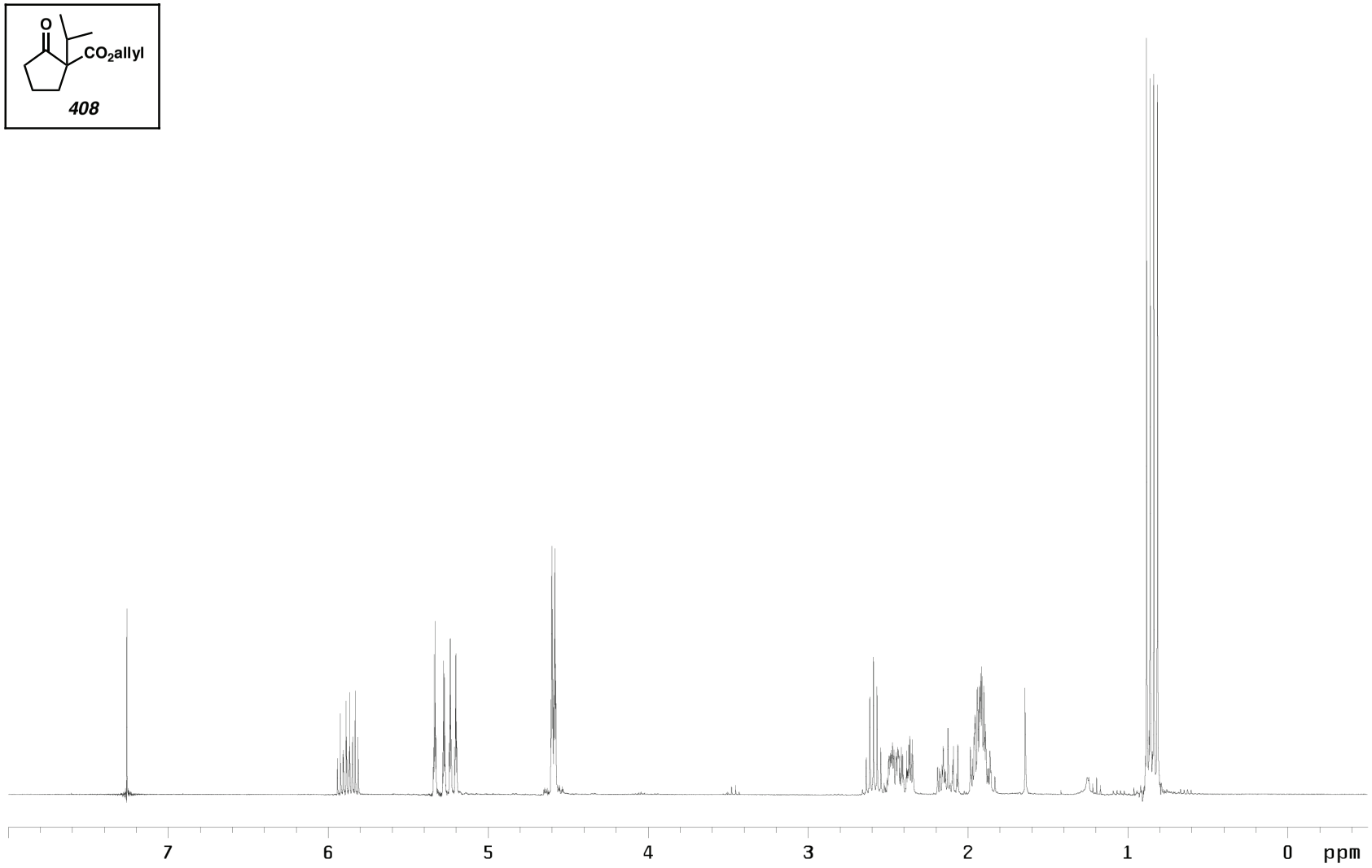


Figure A7.223 ^{1}H NMR of compound **408** (300 MHz, $CDCl_3$)

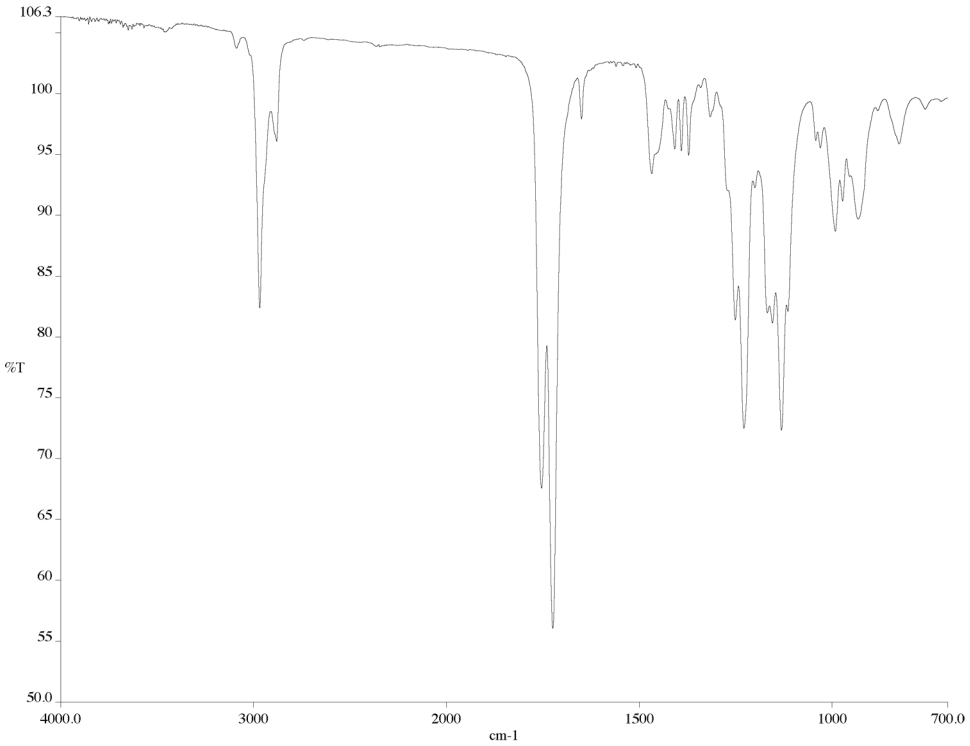


Figure A7.224 IR of compound **408** (NaCl/film)

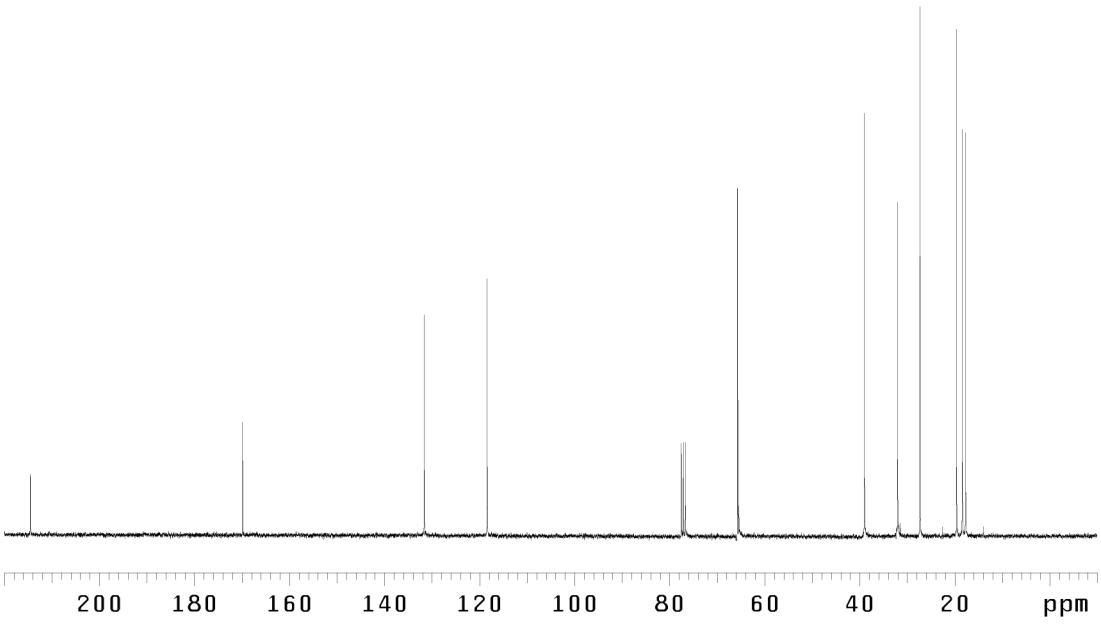


Figure A7.225 ^{13}C NMR of compound **408** (75 MHz, $CDCl_3$)

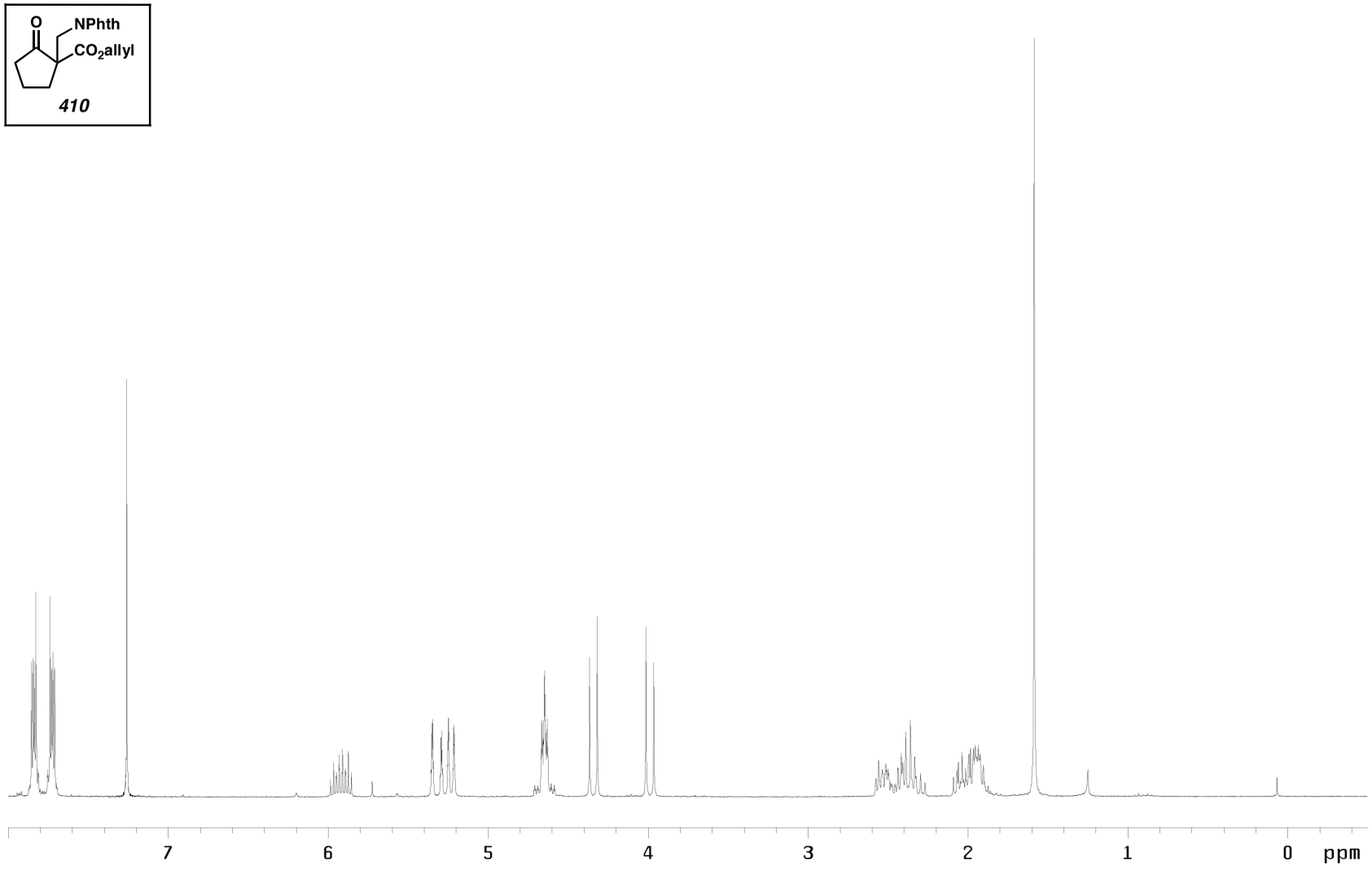


Figure A7.226 ^{1}H NMR of compound **410** (300 MHz, $CDCl_3$)

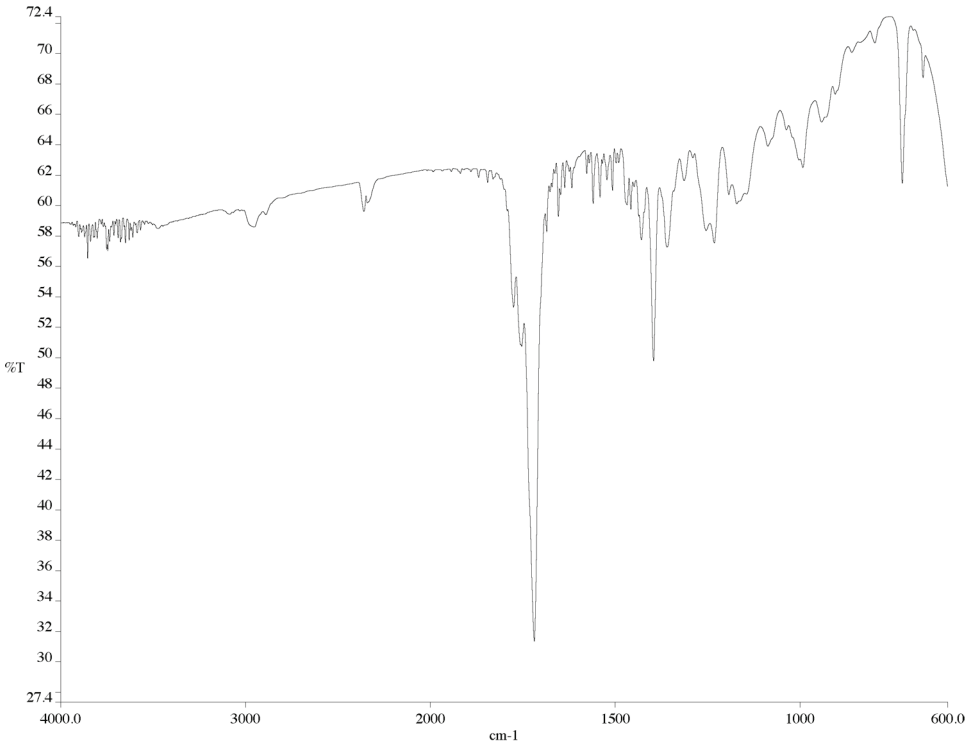


Figure A7.227 IR of compound **410** (NaCl/film)

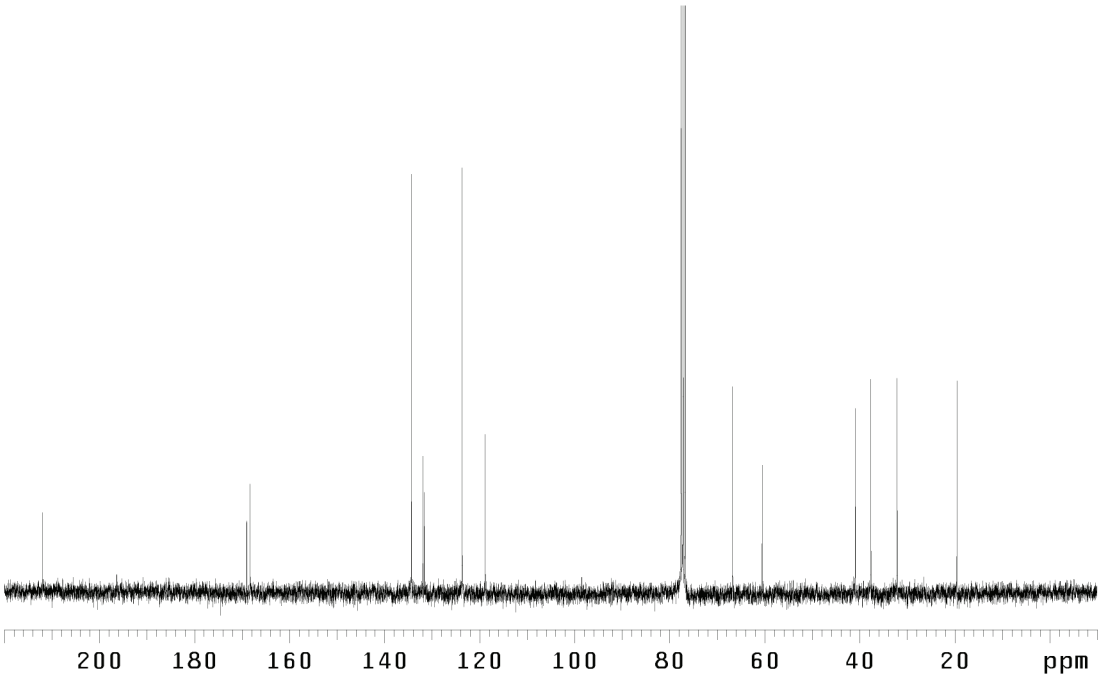


Figure A7.228 ^{13}C NMR of compound **410** (75 MHz, $CDCl_3$)

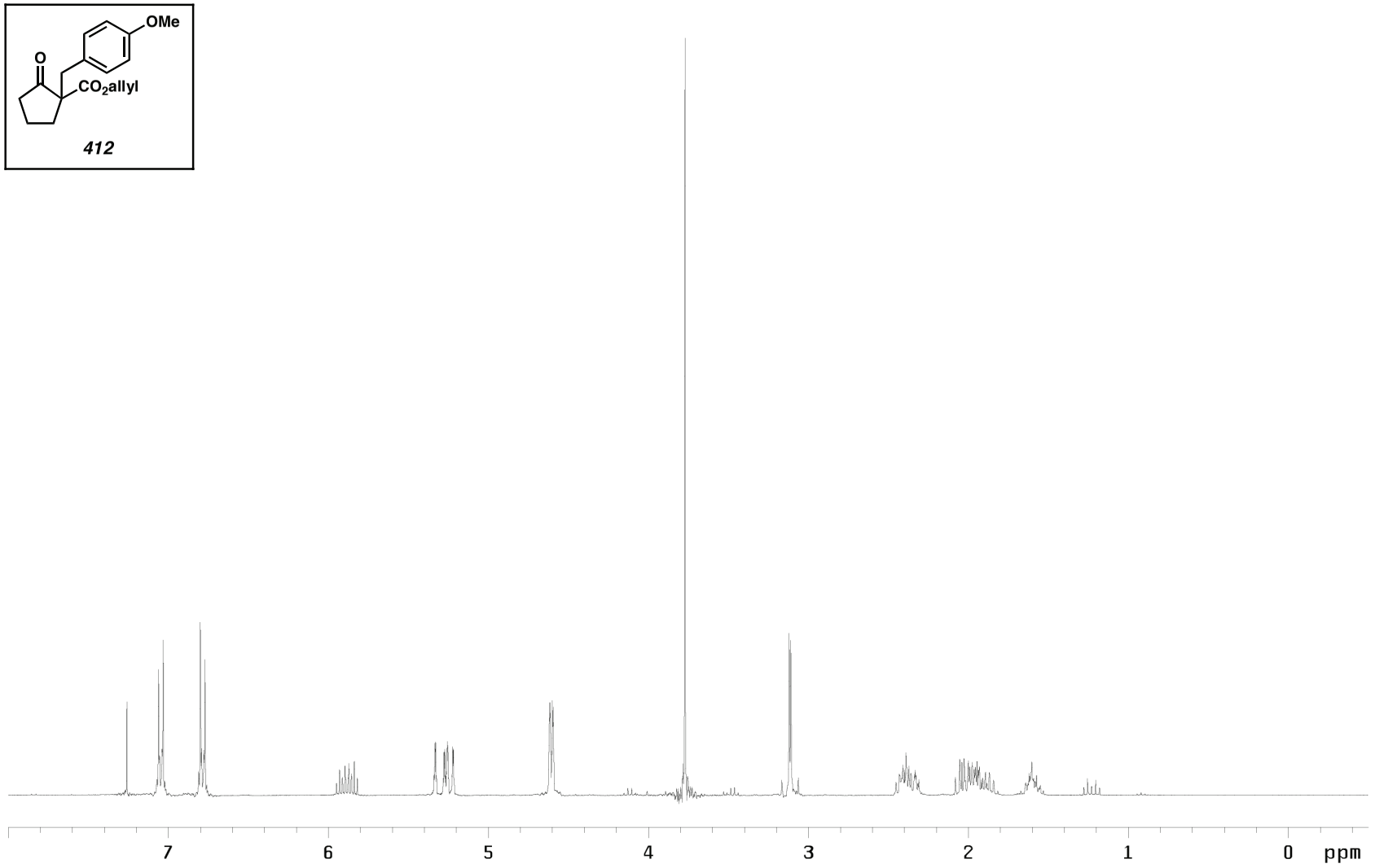


Figure A7.229 ^{1}H NMR of compound **412** (300 MHz, $CDCl_3$)

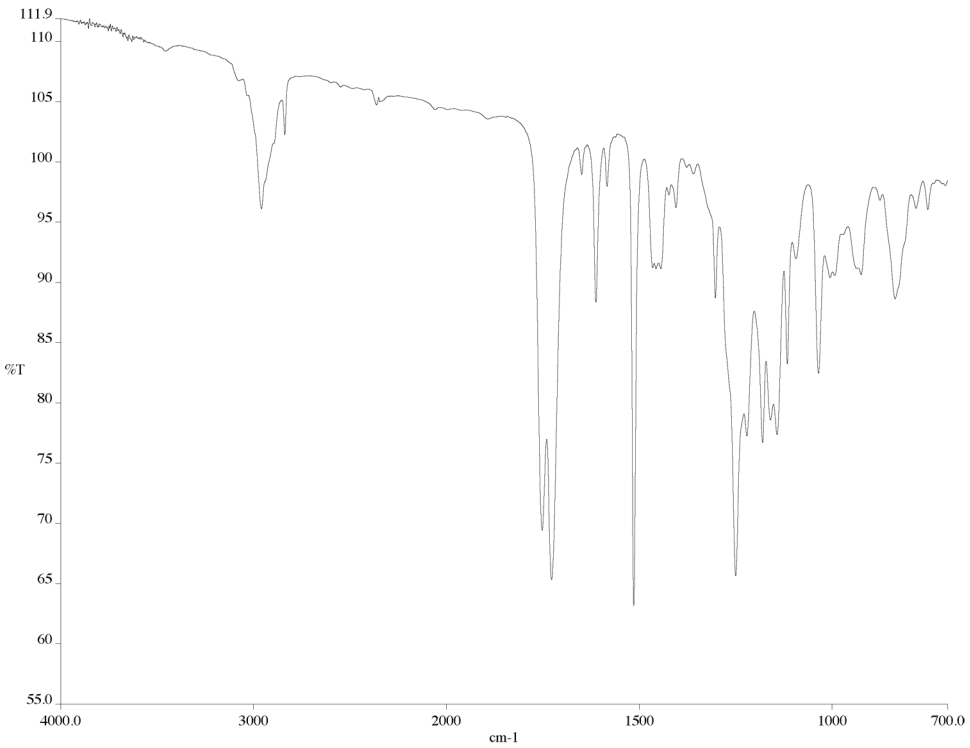


Figure A7.230 IR of compound **412** (NaCl/film)

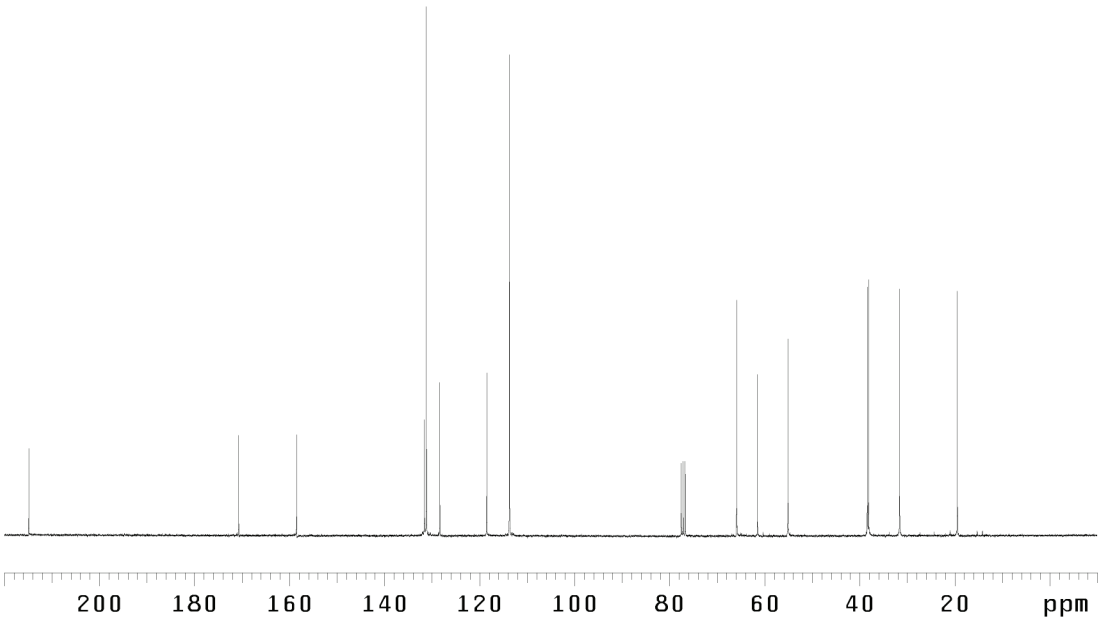


Figure A7.231 ^{13}C NMR of compound **412** (75 MHz, $CDCl_3$)

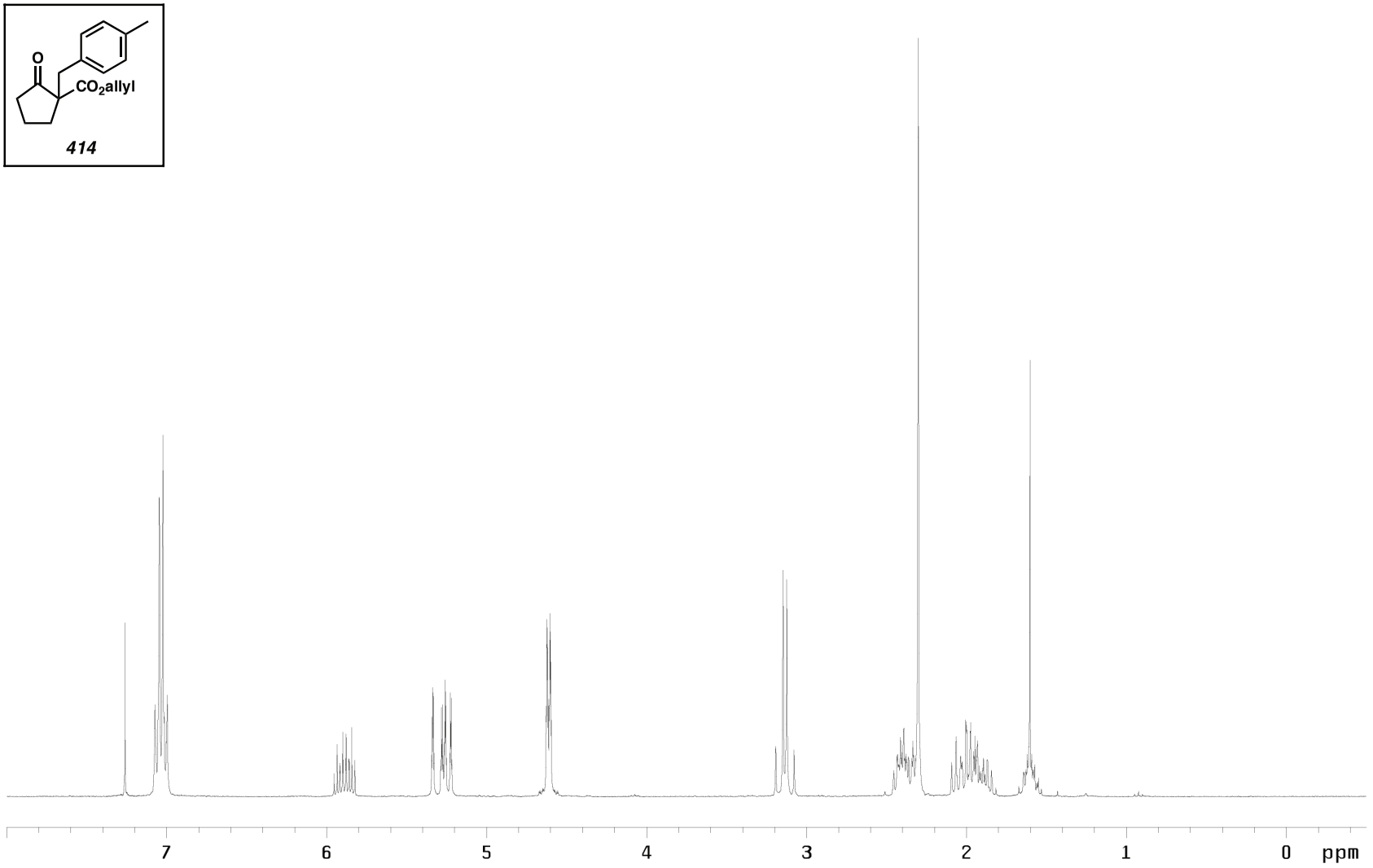


Figure A7.232 ^{1}H NMR of compound **414** (300 MHz, $CDCl_3$)

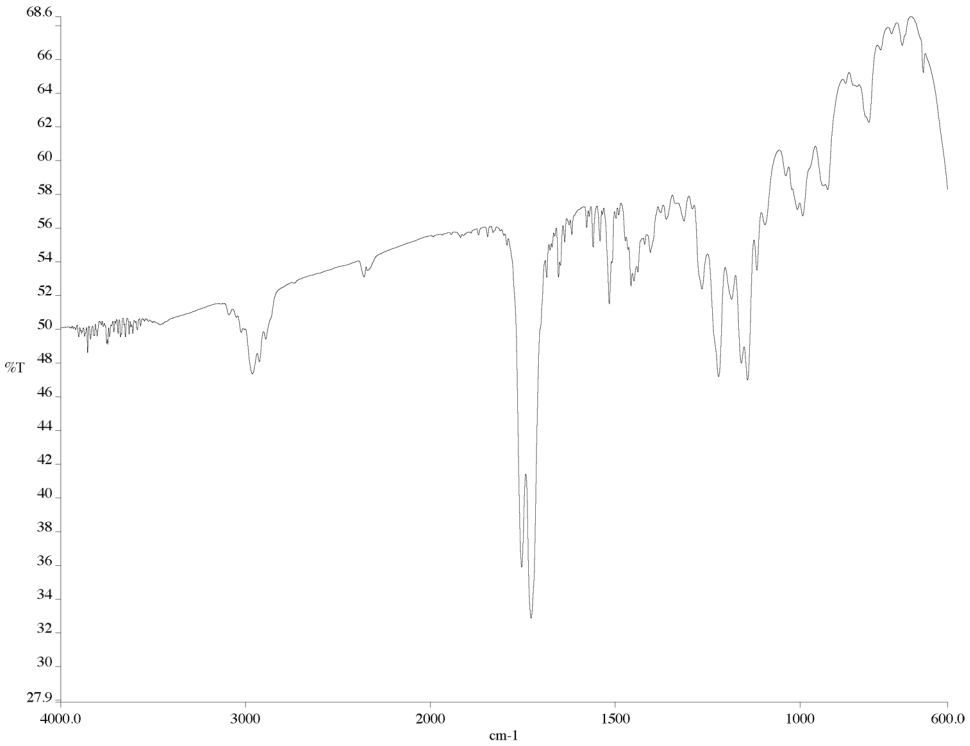


Figure A7.233 IR of compound **414** (NaCl/film)

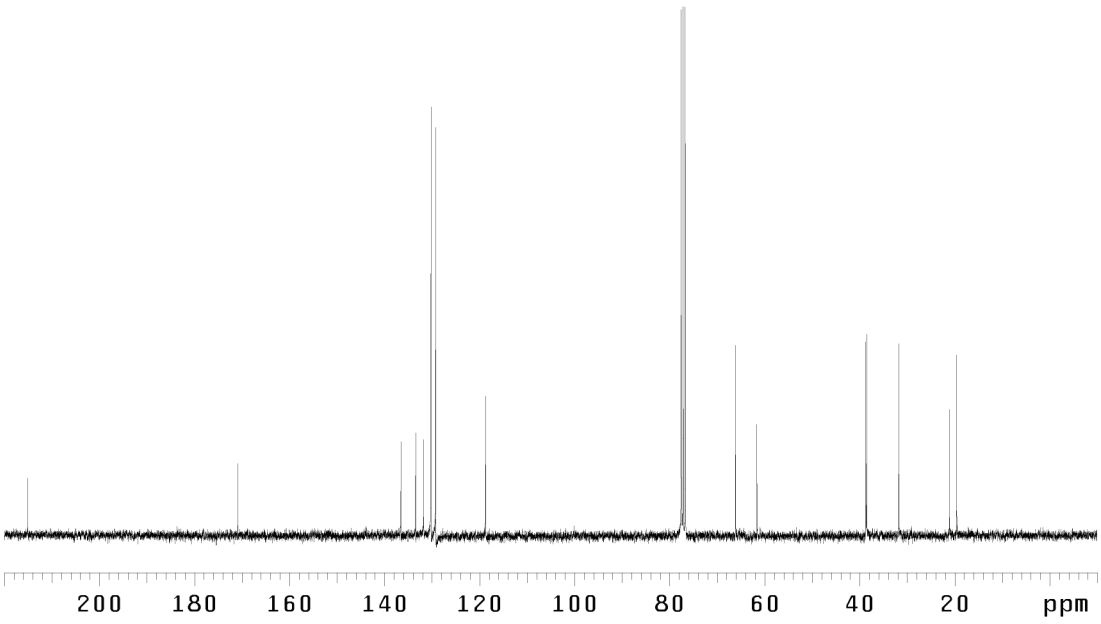


Figure A7.234 ^{13}C NMR of compound **414** (75 MHz, $CDCl_3$)

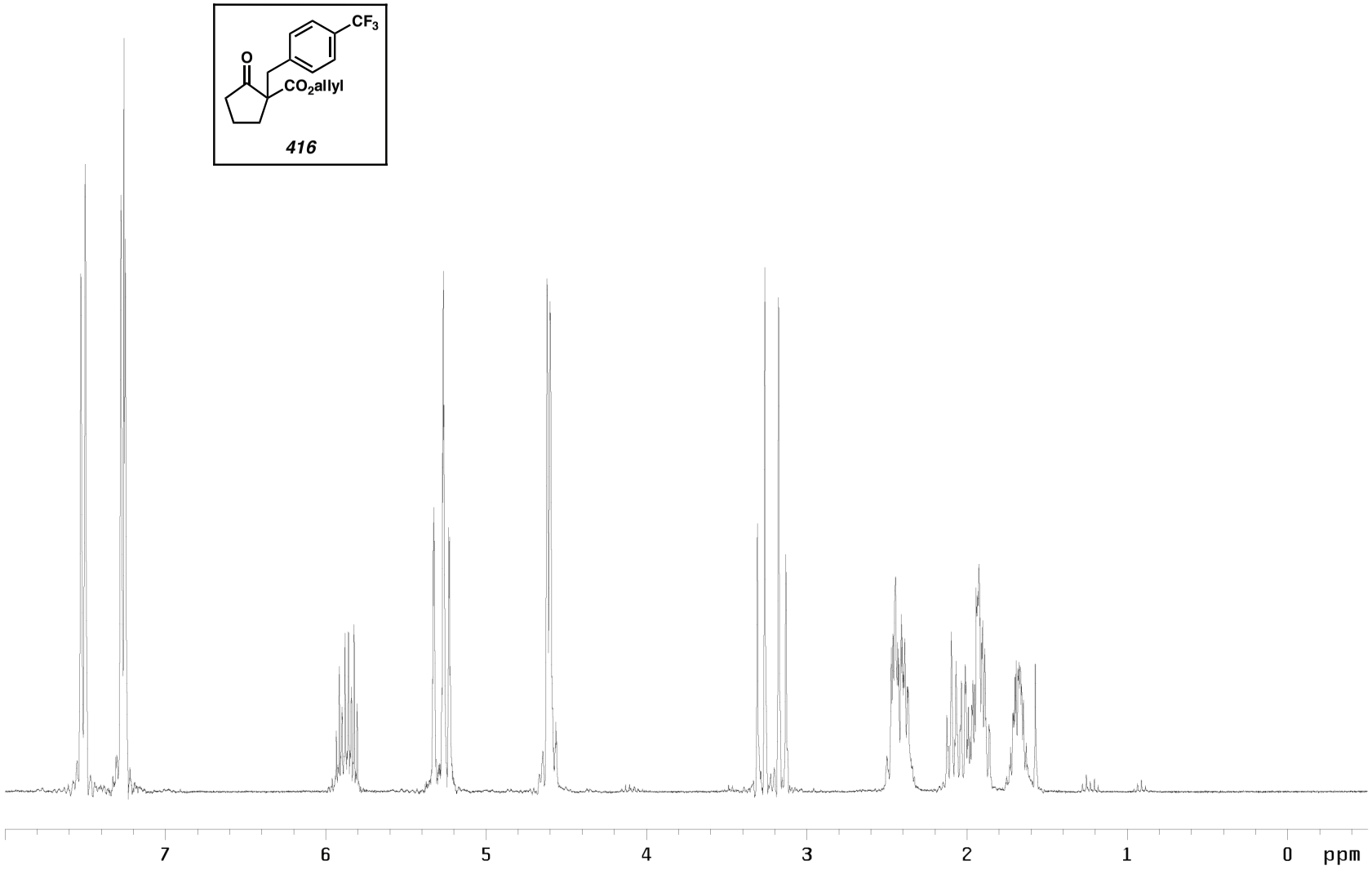


Figure A7.235 ^{1}H NMR of compound **416** (300 MHz, $CDCl_3$)

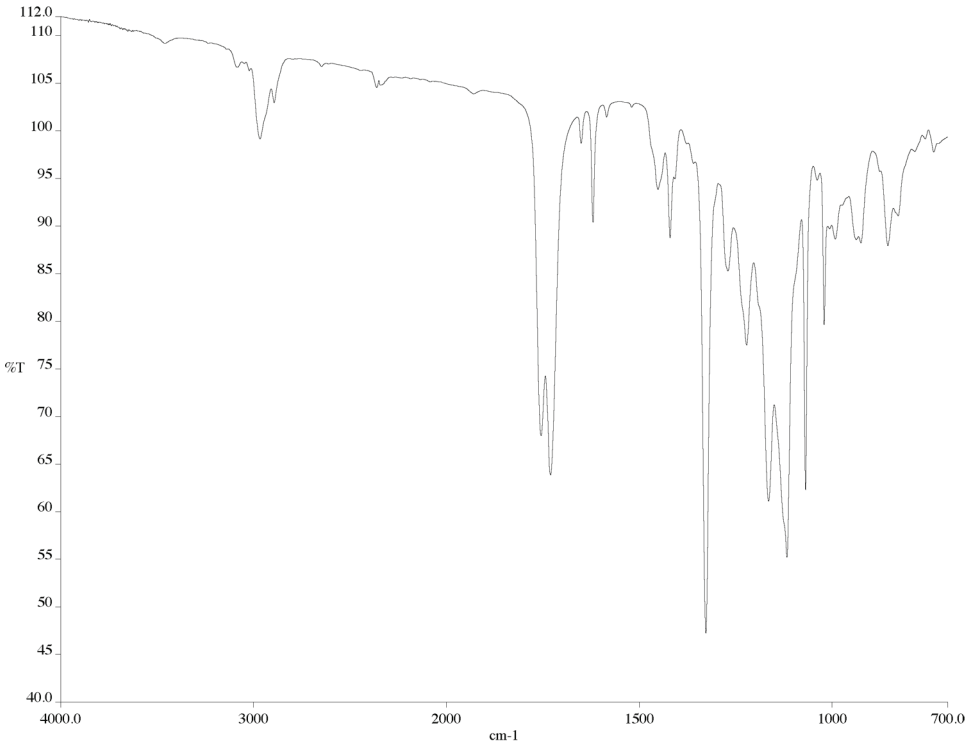


Figure A7.236 IR of compound **416** (NaCl/film)

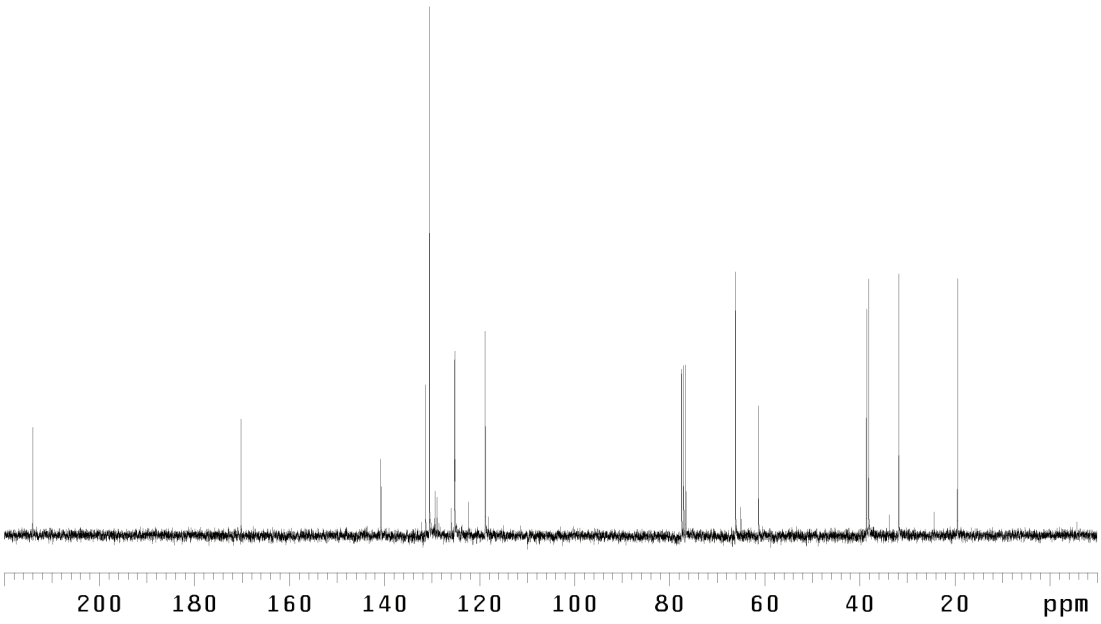


Figure A7.237 ^{13}C NMR of compound **416** (75 MHz, $CDCl_3$)

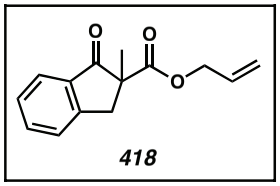


Figure A7.238 ^{1}H NMR of compound **418** (300 MHz, $CDCl_3$)

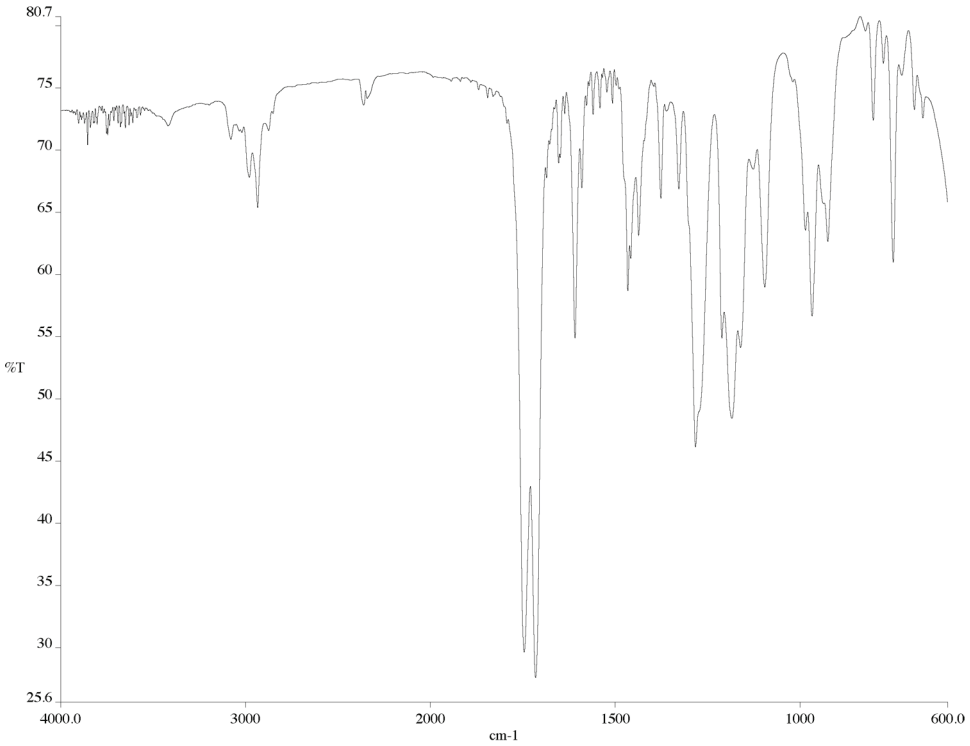


Figure A7.239 IR of compound **418** (NaCl/film)

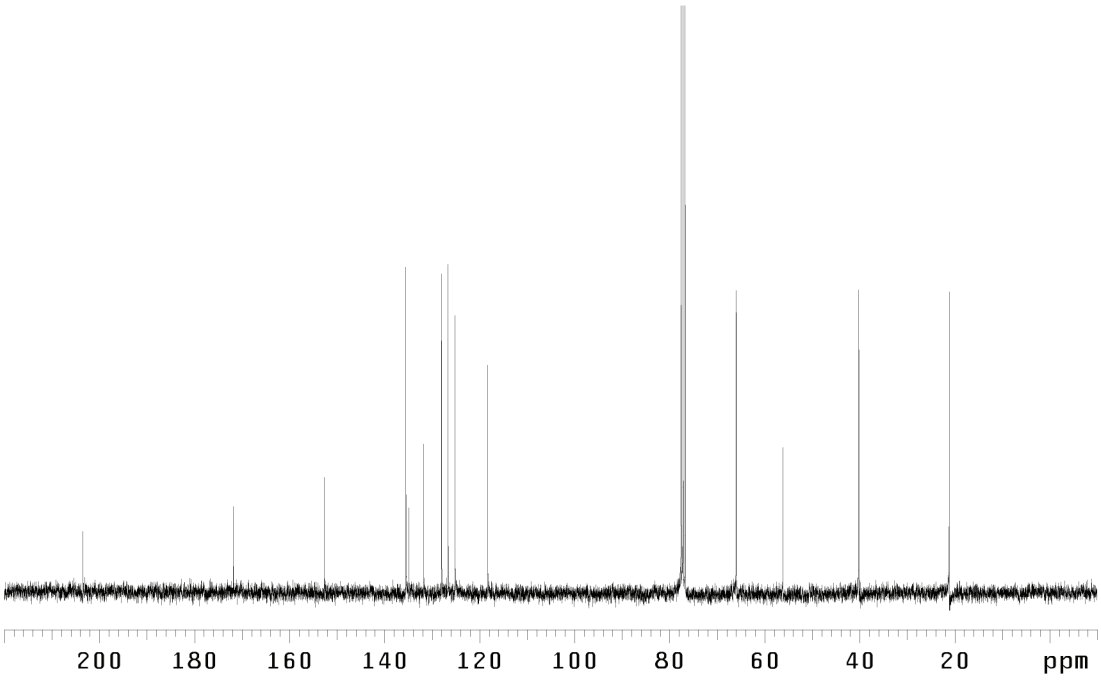


Figure A7.240 ^{13}C NMR of compound **418** (75 MHz, $CDCl_3$)

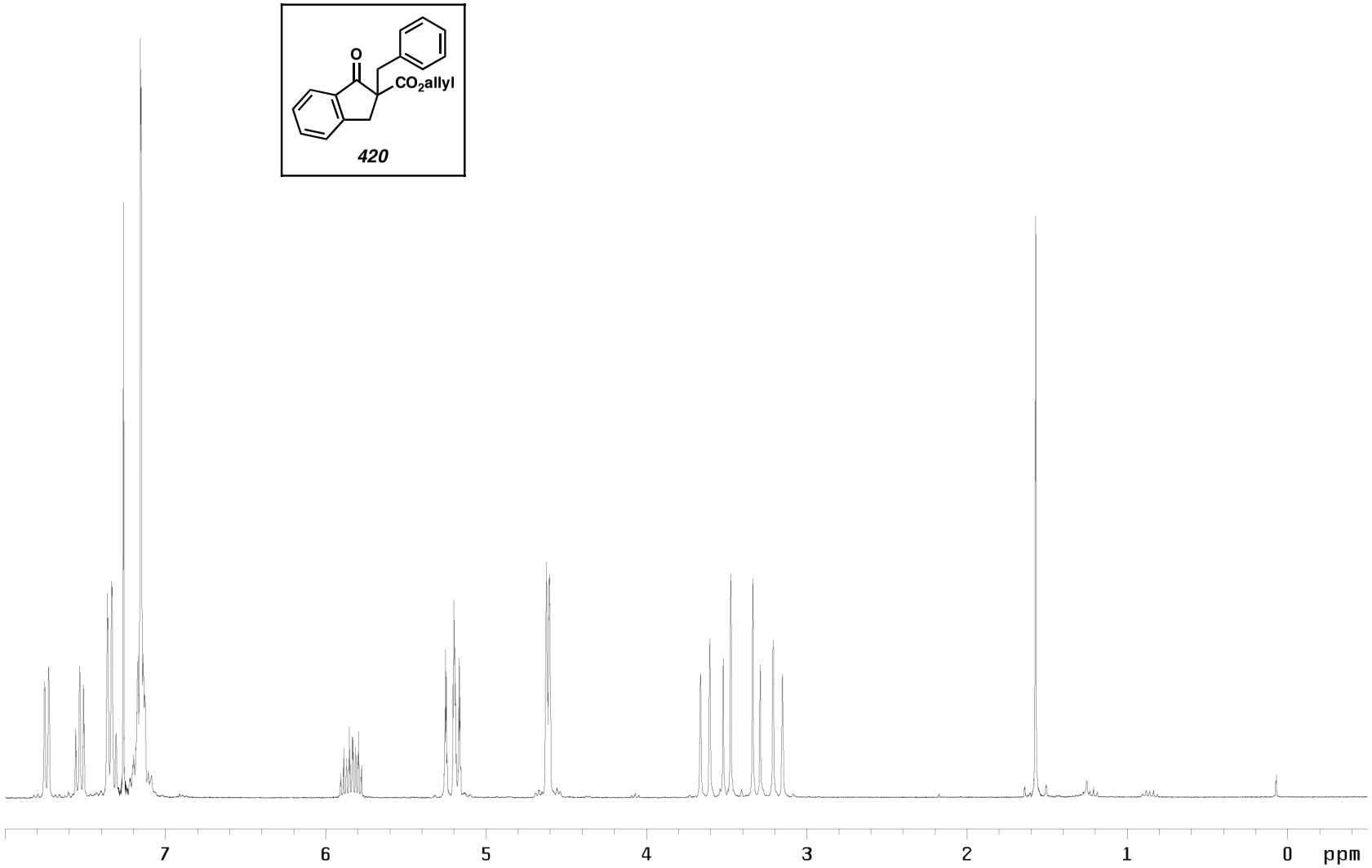


Figure A7.241 ^{1}H NMR of compound **420** (300 MHz, $CDCl_3$)

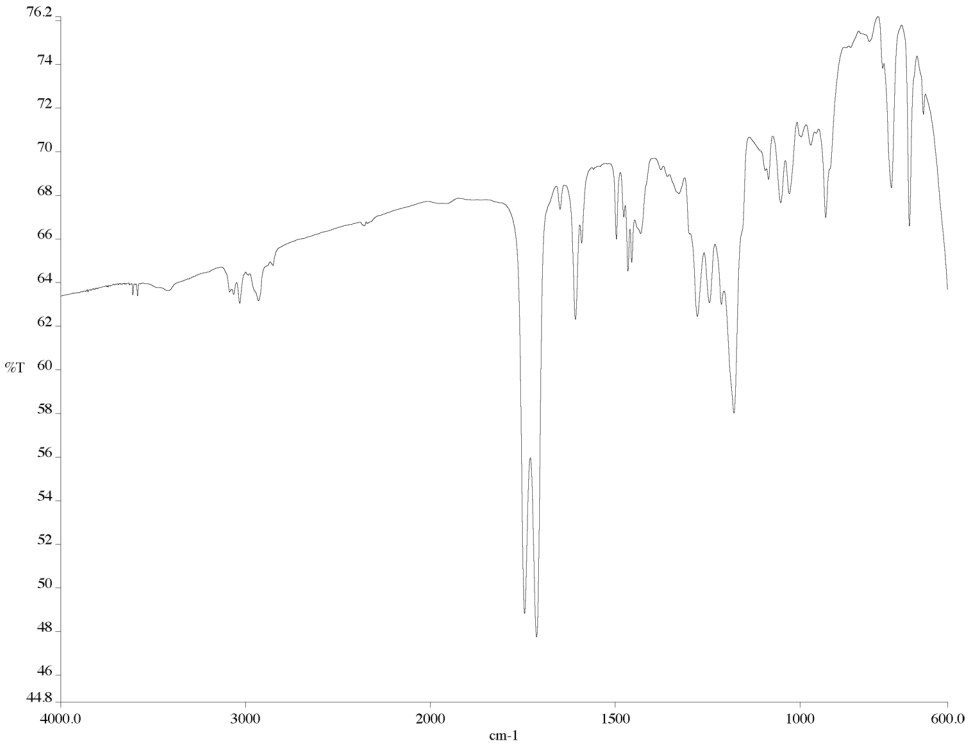


Figure A7.242 IR of compound **420** (NaCl/film)

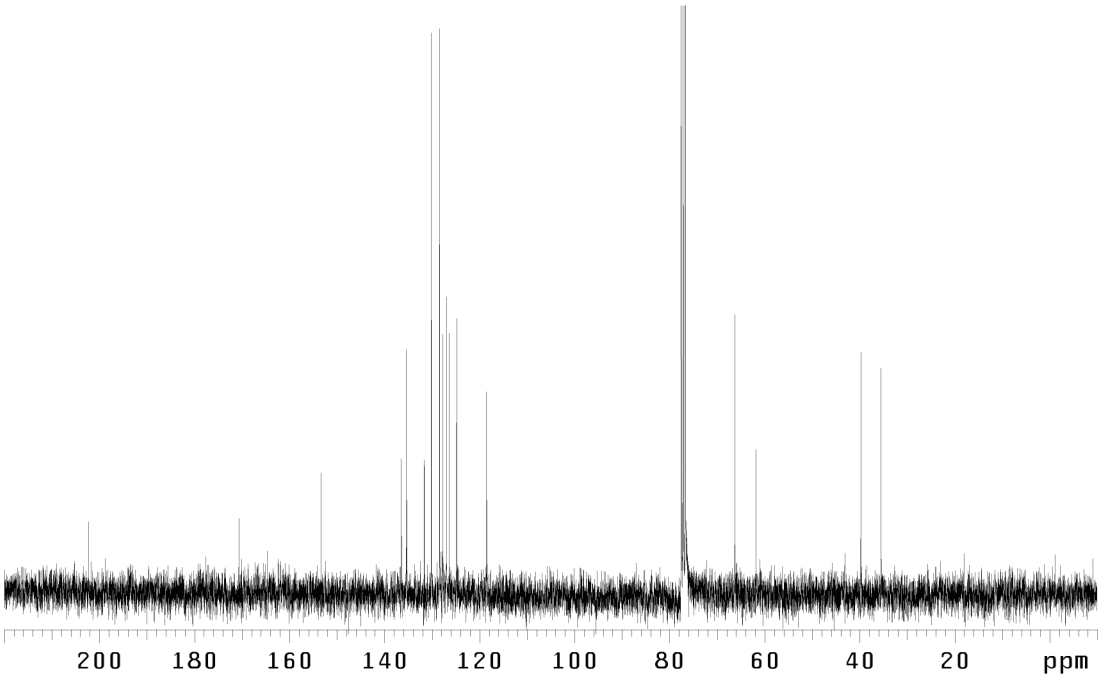


Figure A7.243 ^{13}C NMR of compound **420** (75 MHz, $CDCl_3$)

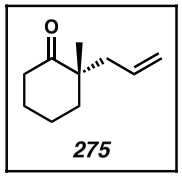


Figure A7.244 ^{1}H NMR of compound **275** (300 MHz, $CDCl_3$)

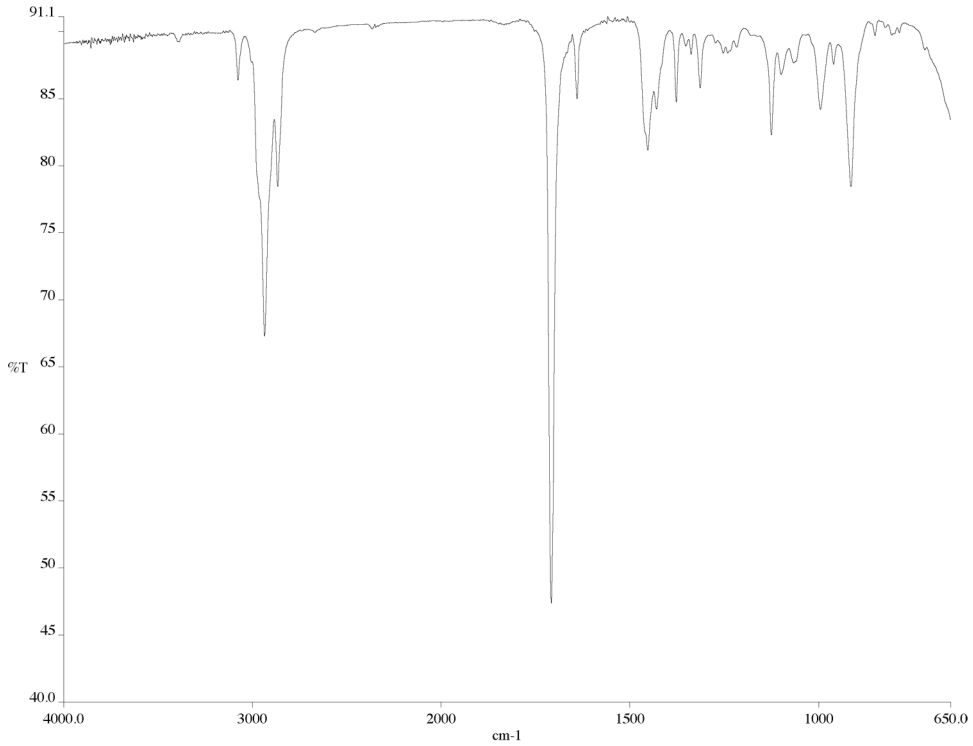


Figure A7.245 IR of compound **275** (NaCl/film)

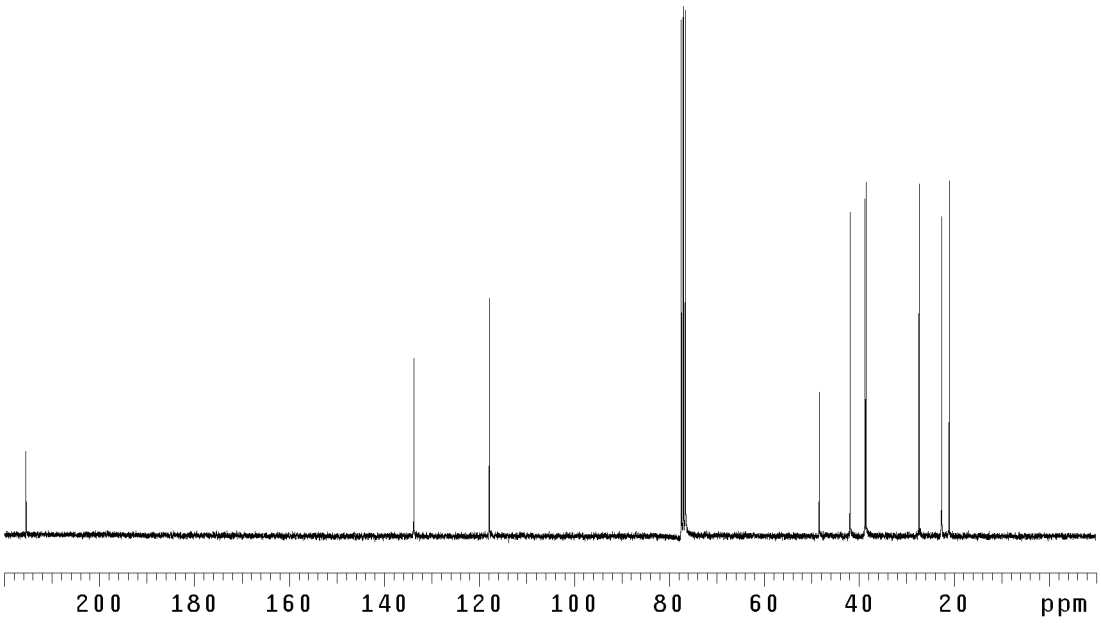


Figure A7.246 ^{13}C NMR of compound **275** (75 MHz, $CDCl_3$)

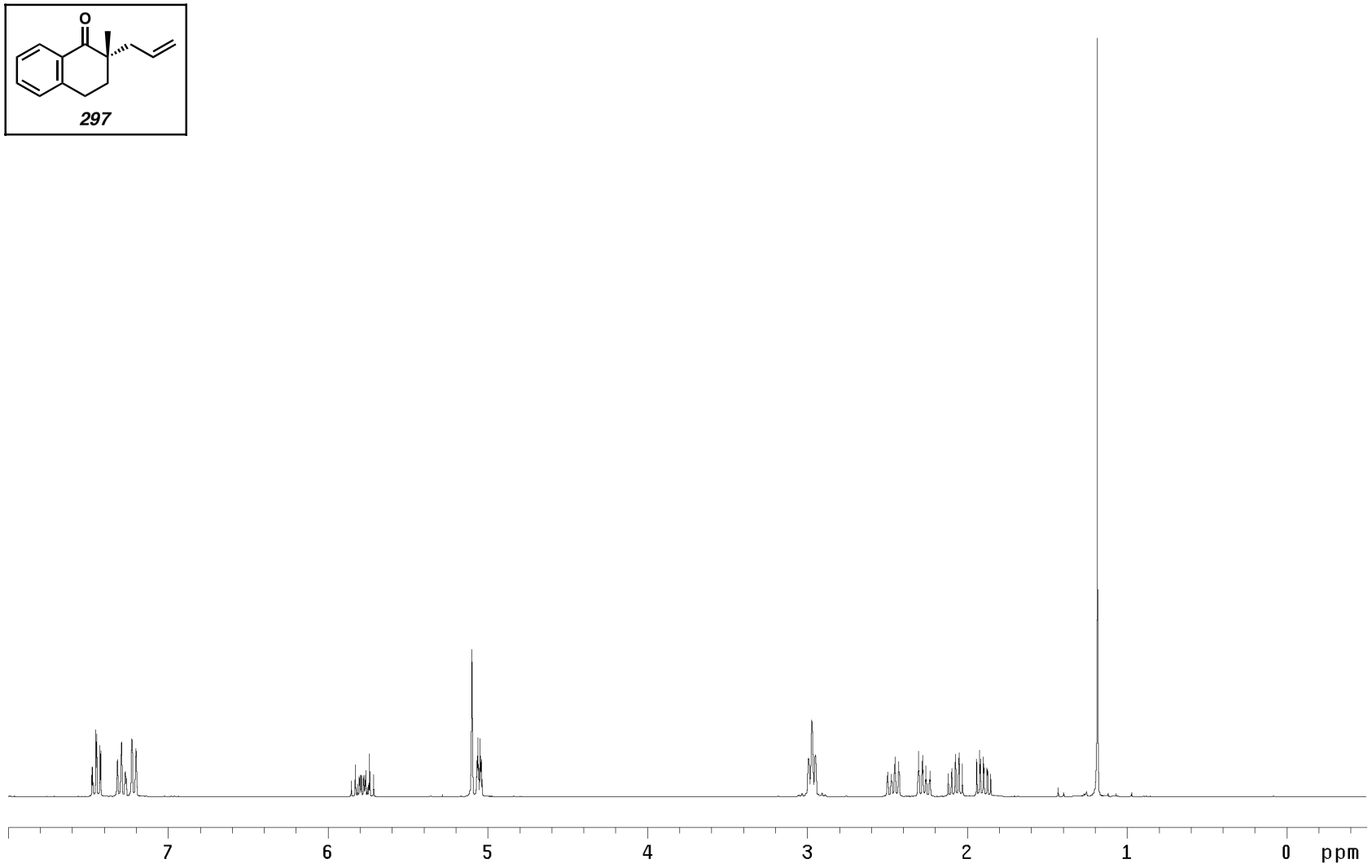


Figure A7.247 ^{1}H NMR of compound **297** (300 MHz, $CDCl_3$)

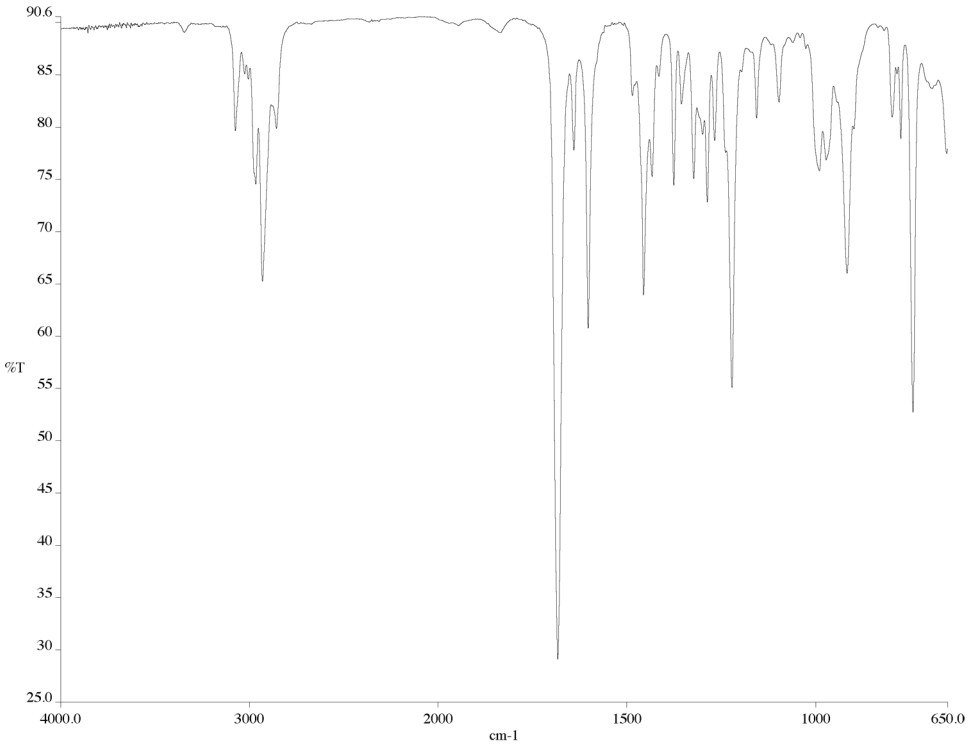


Figure A7.248 IR of compound **297** (NaCl/film)

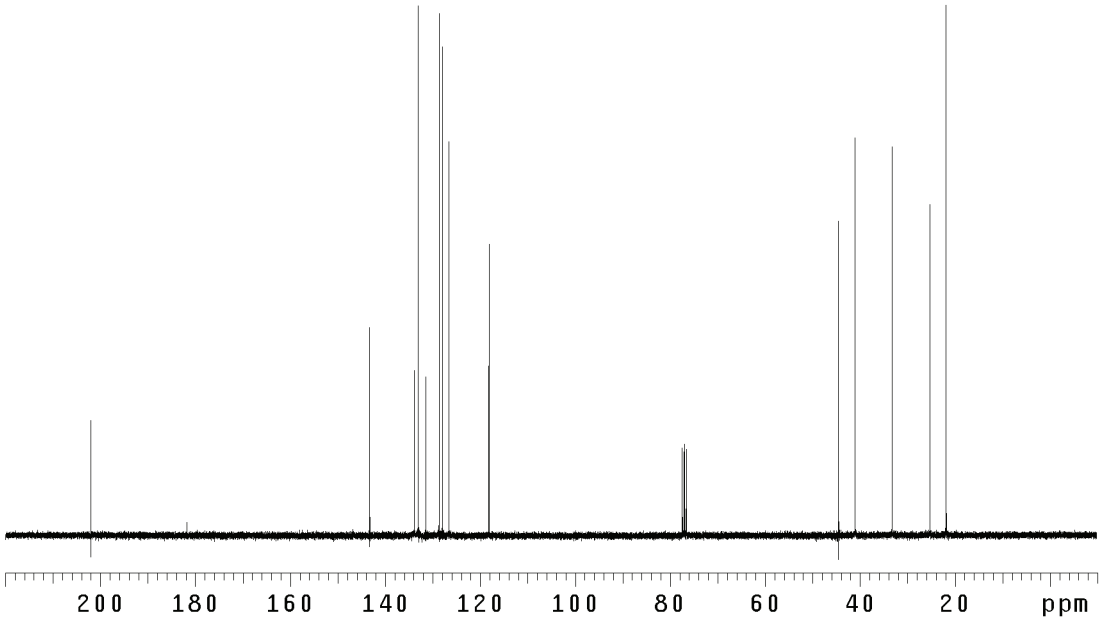


Figure A7.249 ^{13}C NMR of compound **297** (75 MHz, $CDCl_3$)

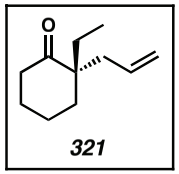


Figure A7.250 ^{1}H NMR of compound **321** (300 MHz, $CDCl_3$)

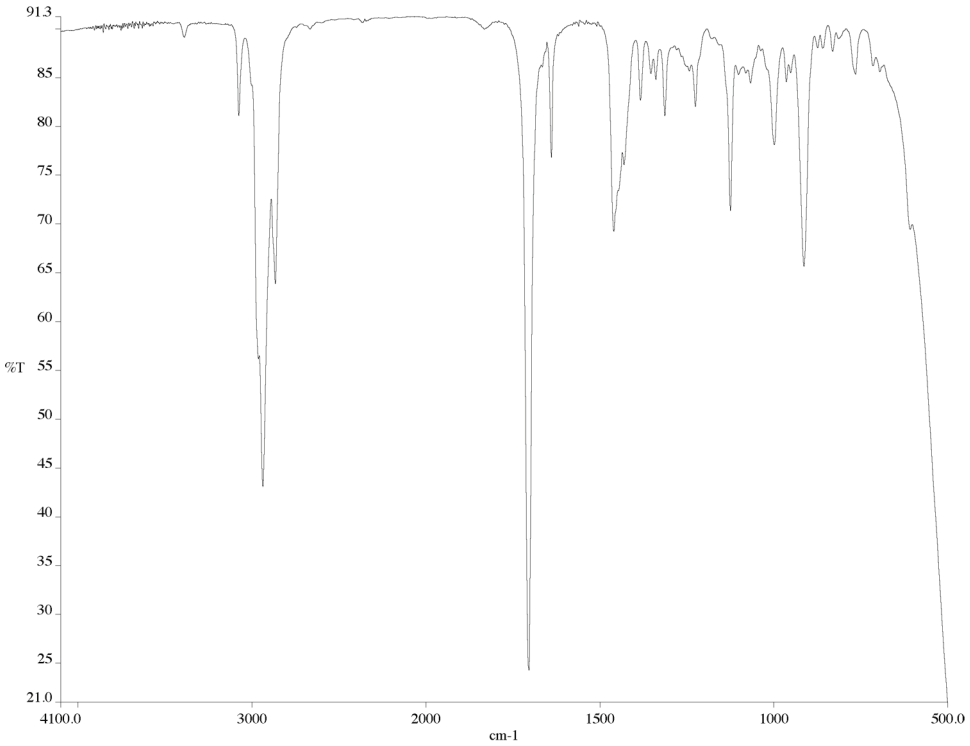


Figure A7.251 IR of compound **321** (NaCl/film)

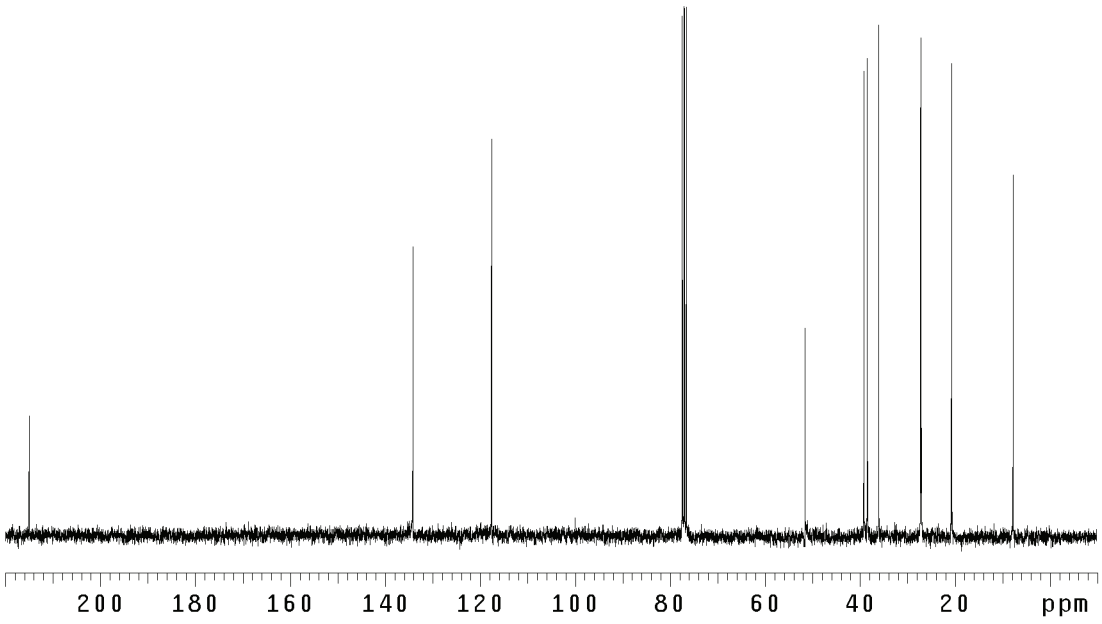


Figure A7.252 ^{13}C NMR of compound **321** (75 MHz, $CDCl_3$)

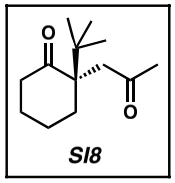


Figure A7.253 ^{1}H NMR of compound **SI8** (300 MHz, $CDCl_3$)

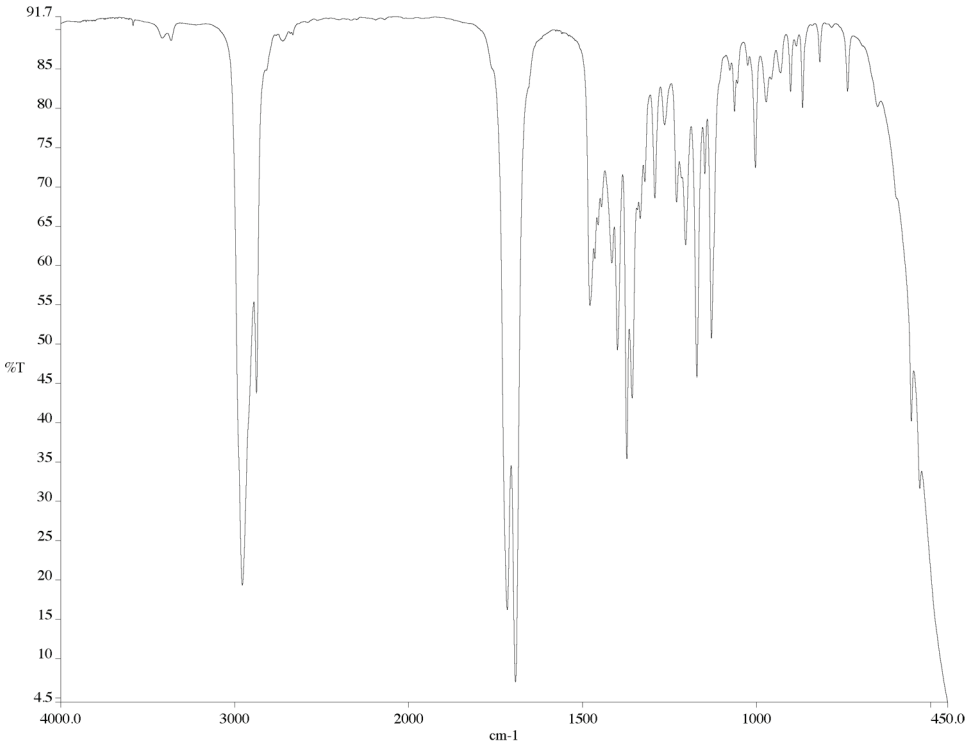


Figure A7.254 IR of compound **SI8** (NaCl/film)

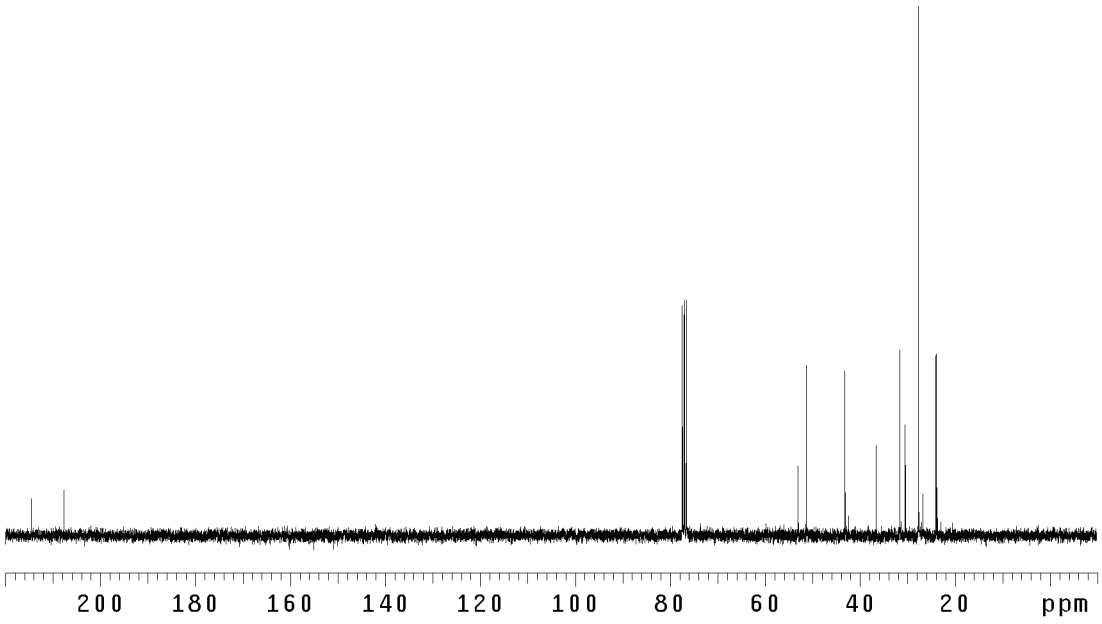


Figure A7.255 ^{13}C NMR of compound **SI8** (75 MHz, $CDCl_3$)

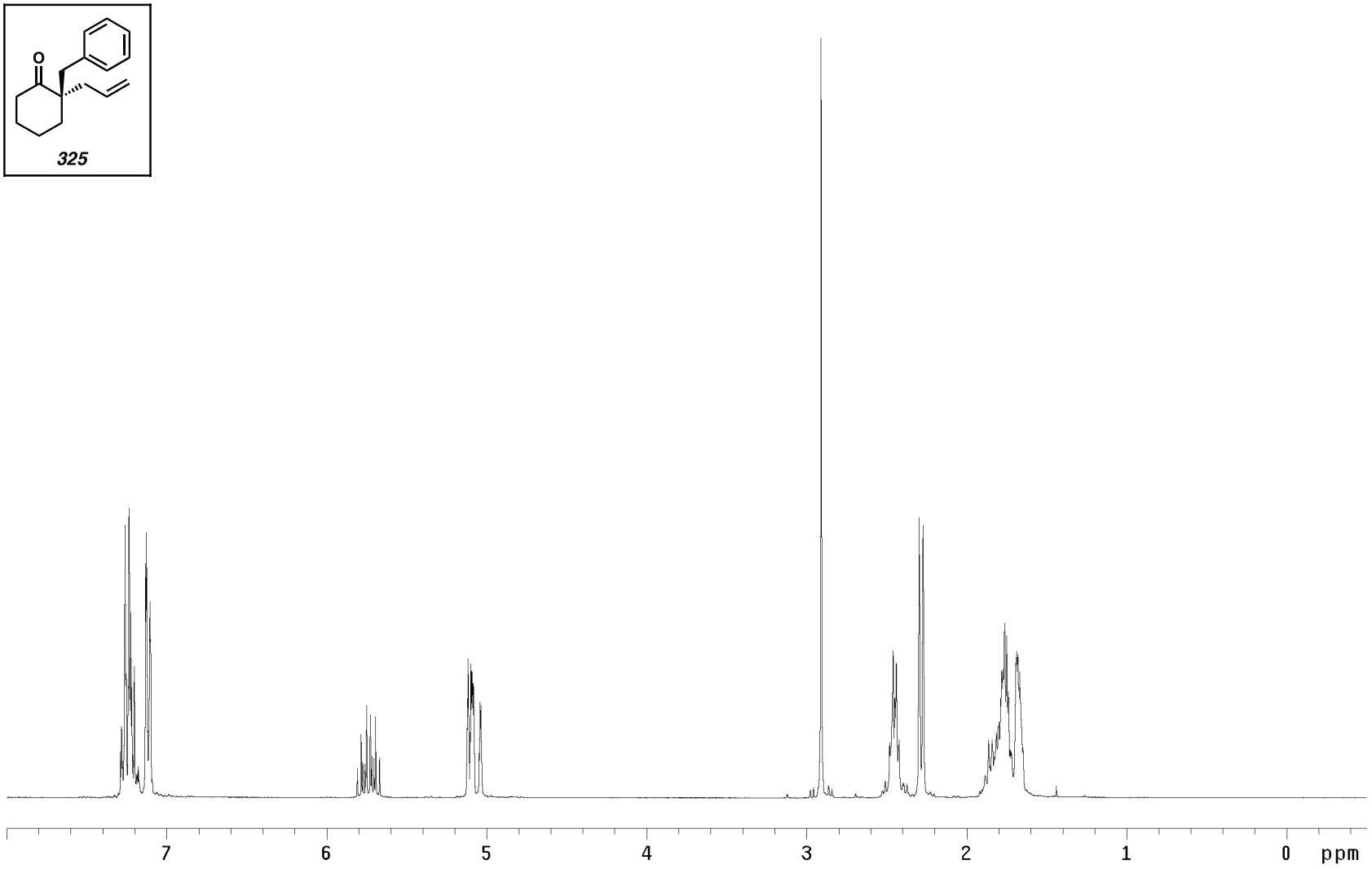


Figure A7.256 ^{1}H NMR of compound **325** (300 MHz, $CDCl_3$)

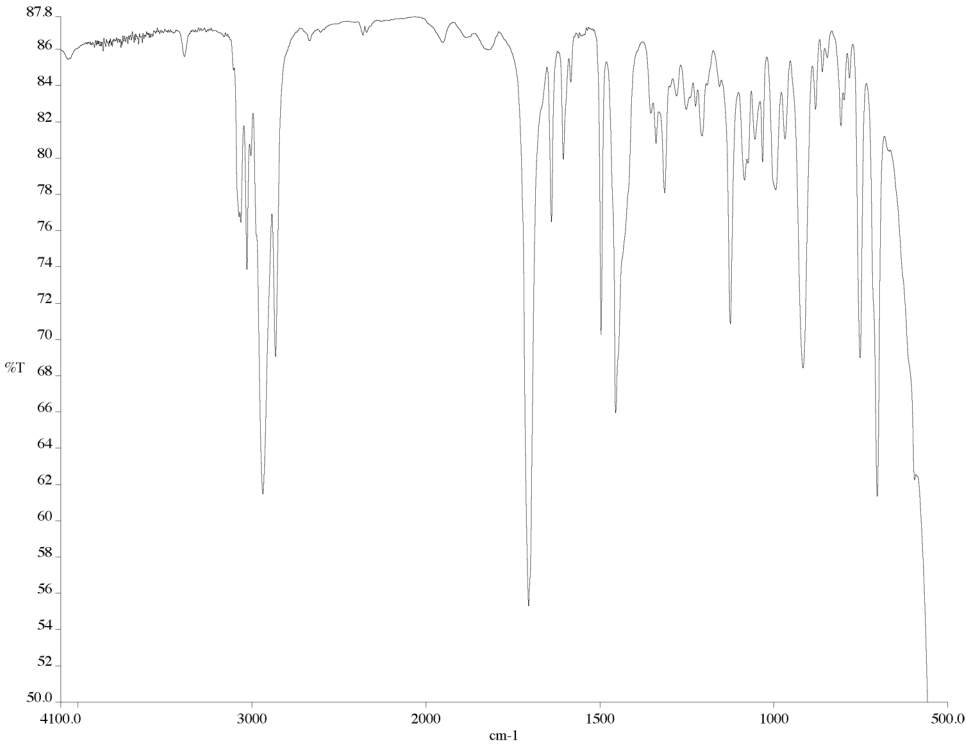


Figure A7.257 IR of compound **325** (NaCl/film)

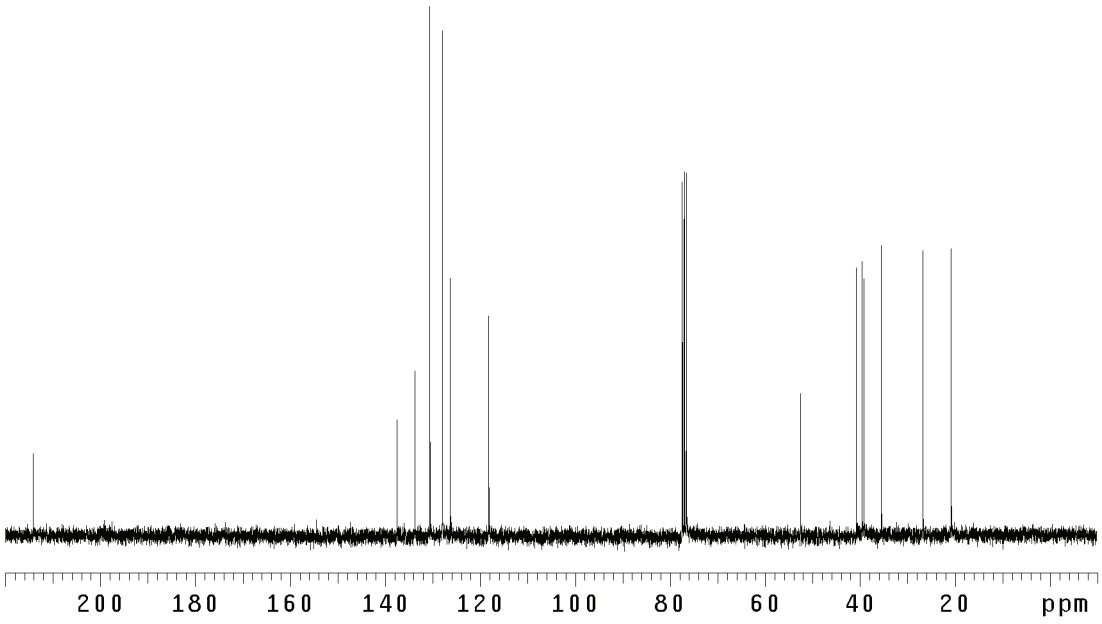


Figure A7.158 ^{13}C NMR of compound **325** (75 MHz, $CDCl_3$)

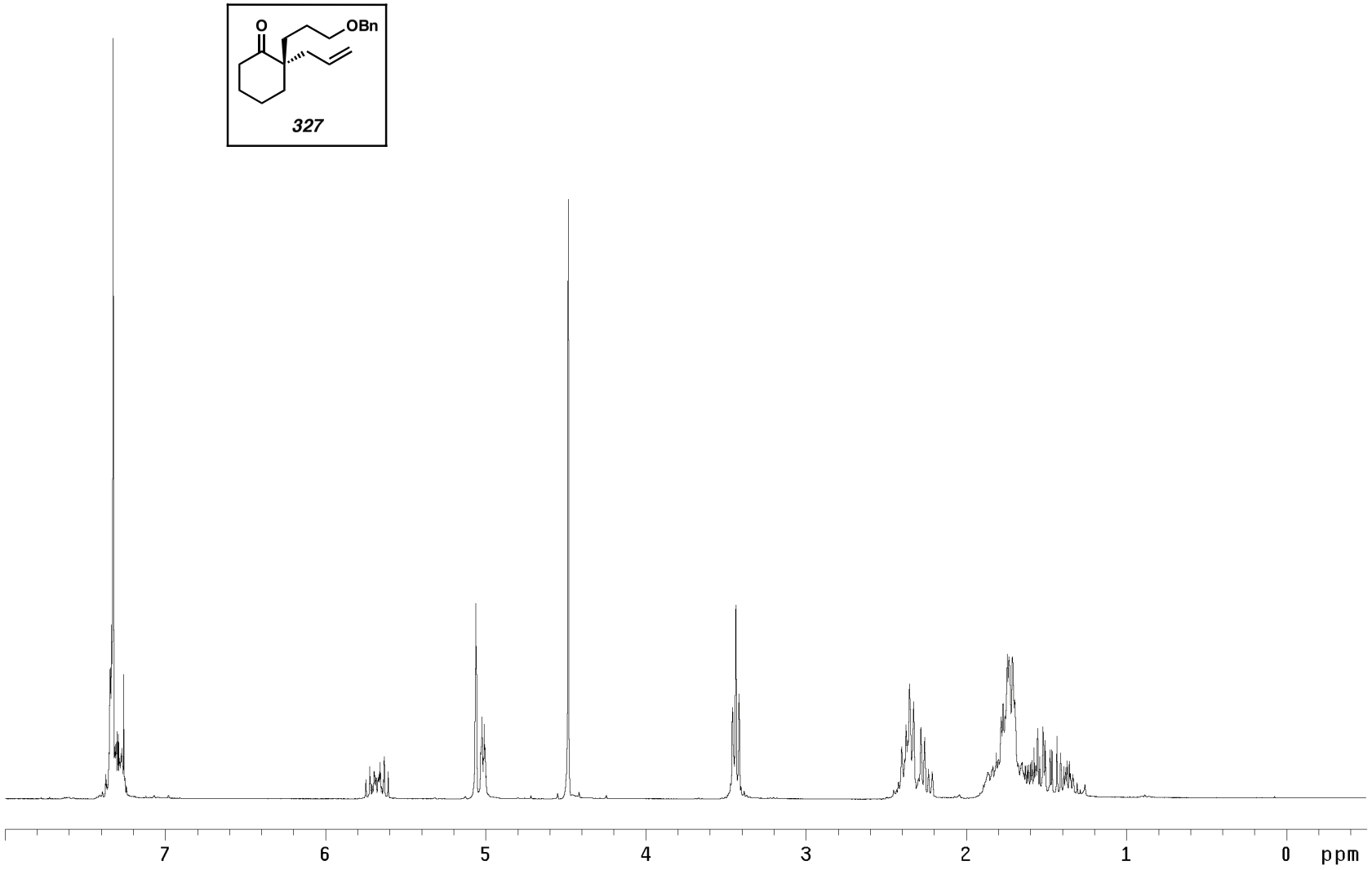


Figure A7.259 ^{1}H NMR of compound **327** (300 MHz, $CDCl_3$)

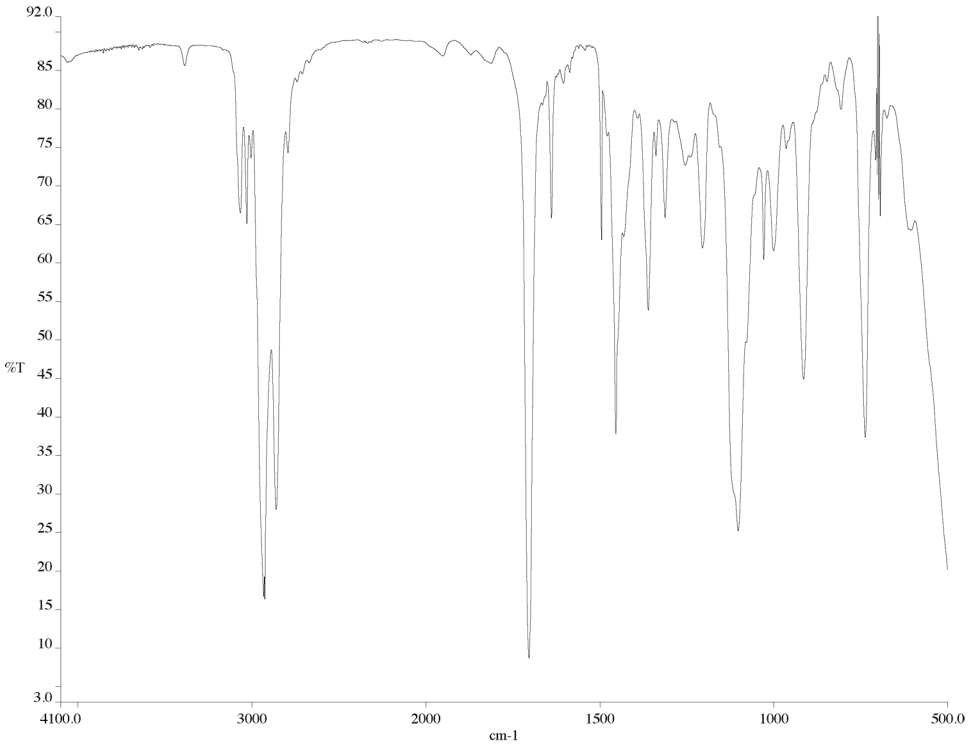


Figure A7.260 IR of compound **327** (NaCl/film)

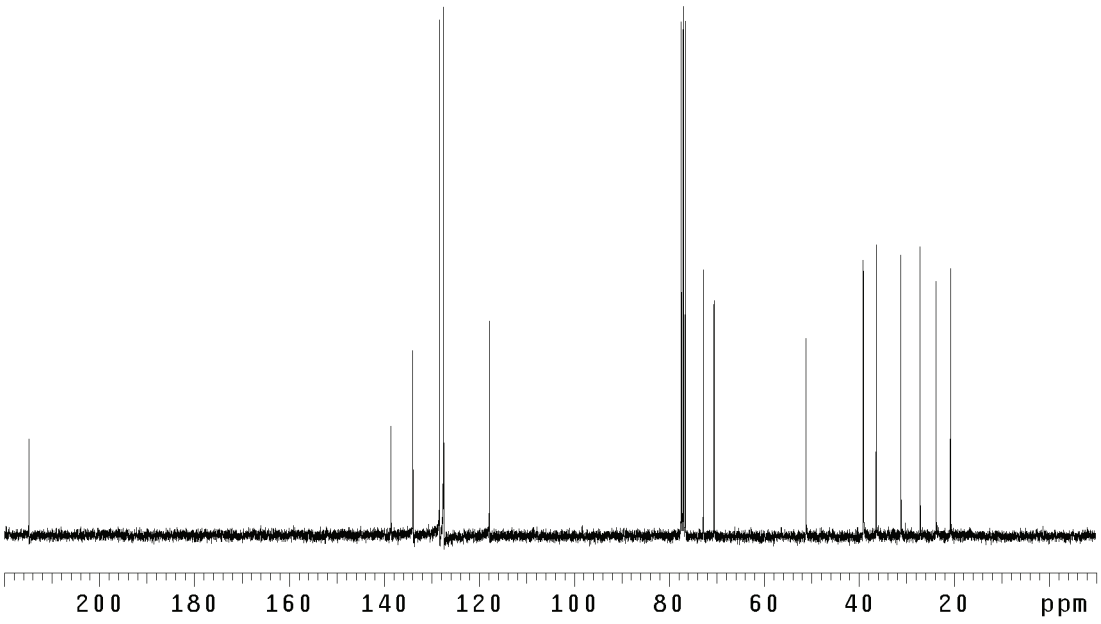


Figure A7.261 ^{13}C NMR of compound **327** (75 MHz, $CDCl_3$)

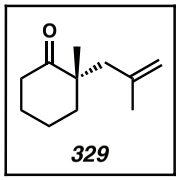


Figure A7.262 ^{1}H NMR of compound **329** (300 MHz, $CDCl_3$)

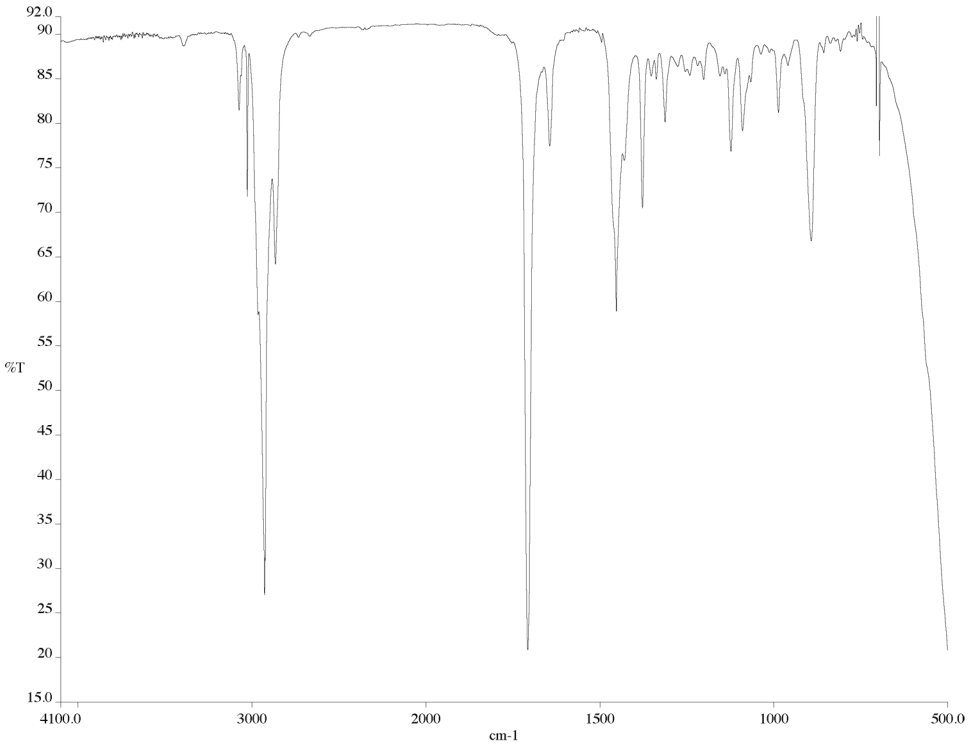


Figure A7.263 IR of compound **329** (NaCl/film)

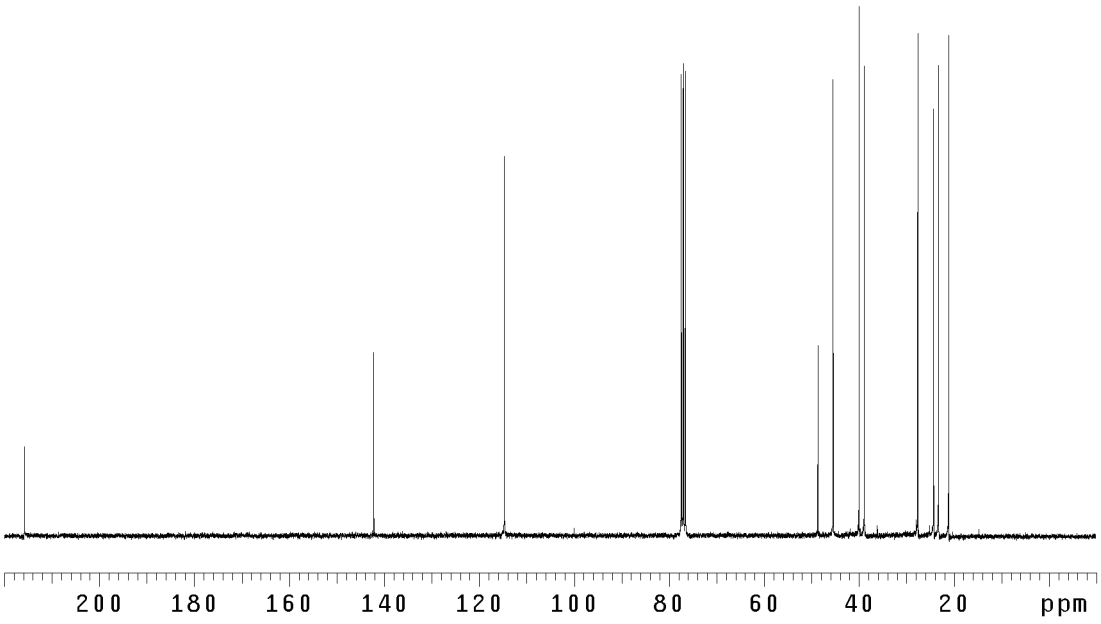


Figure A7.264 ^{13}C NMR of compound **329** (75 MHz, $CDCl_3$)

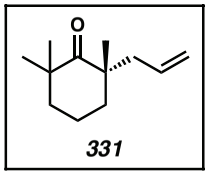


Figure A7.265 ^{1}H NMR of compound **331** (300 MHz, $CDCl_3$)

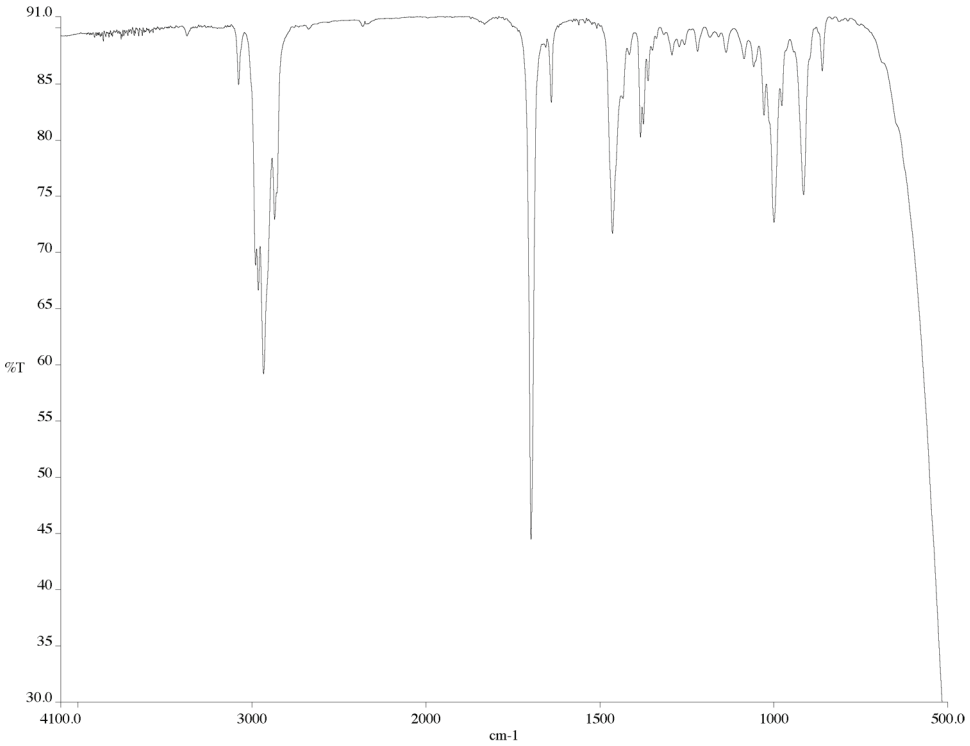


Figure A7.266 IR of compound **331** (NaCl/film)

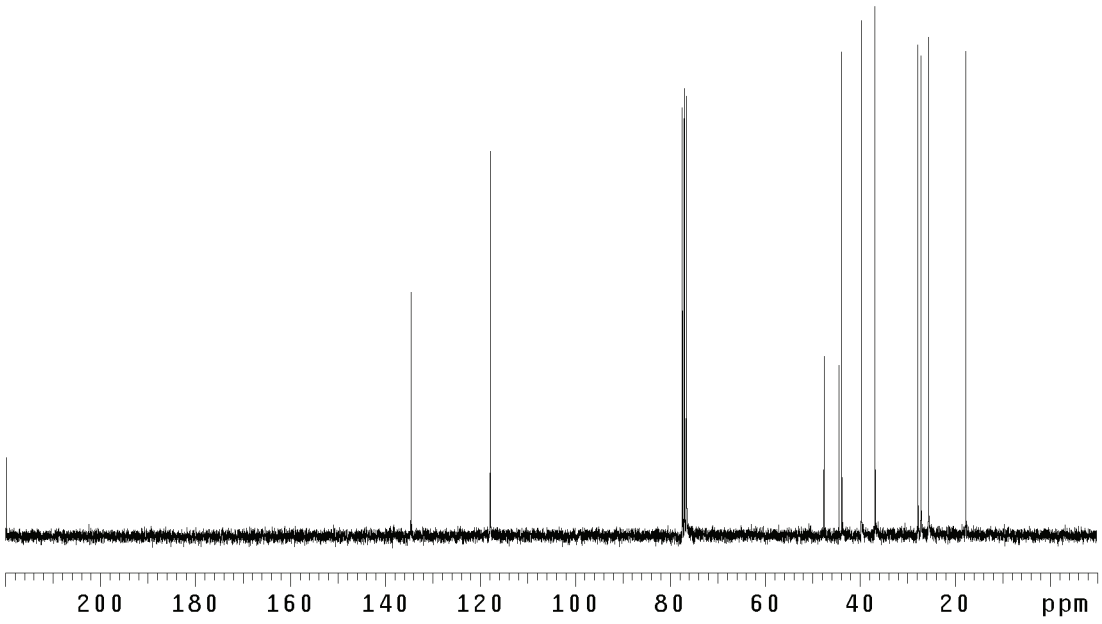


Figure A7.267 ^{13}C NMR of compound **331** (75 MHz, $CDCl_3$)

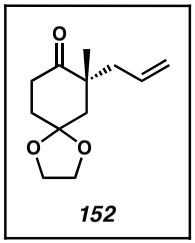


Figure A7.268 ^{1}H NMR of compound **152** (300 MHz, $CDCl_3$)

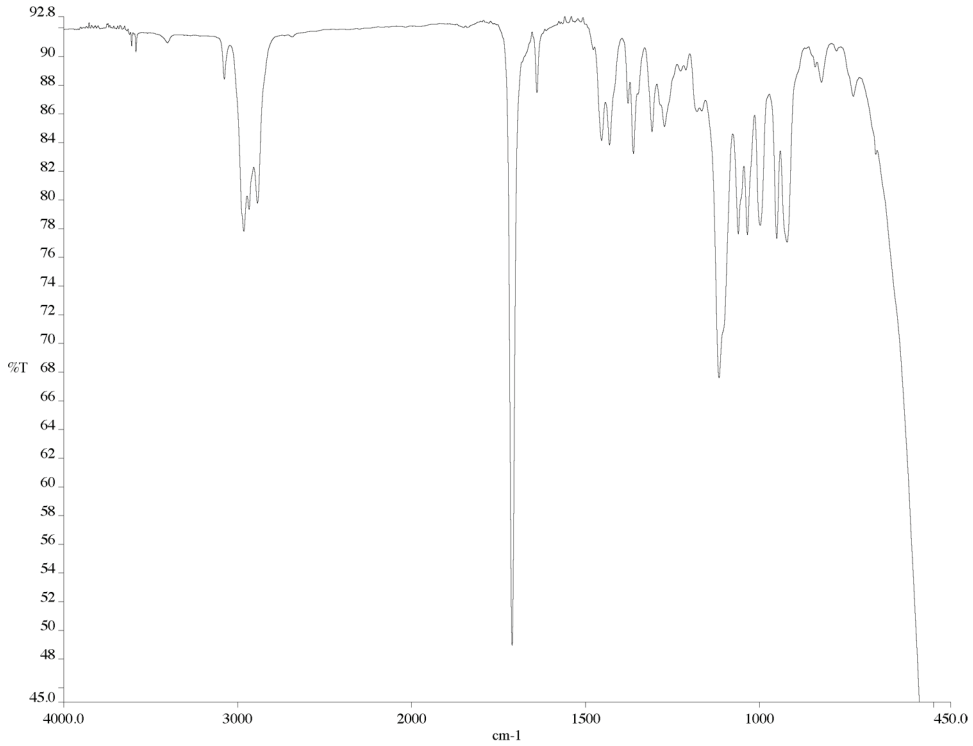


Figure A7.269 IR of compound **152** (NaCl/film)

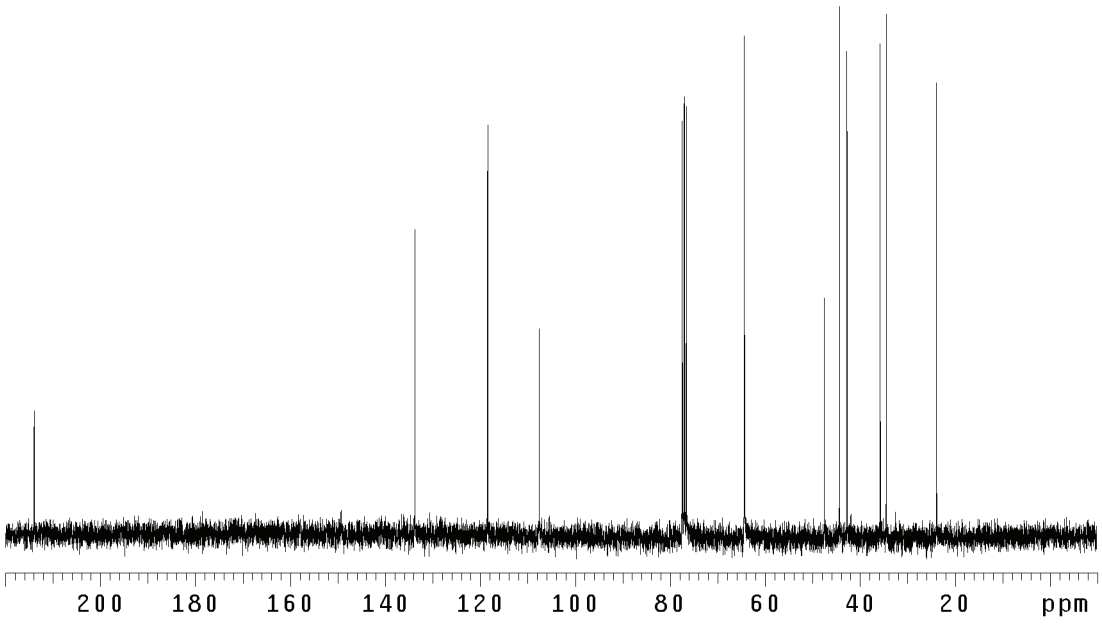


Figure A7.270 ^{13}C NMR of compound **152** (75 MHz, $CDCl_3$)

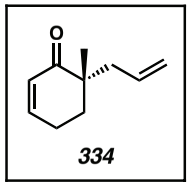


Figure A7.271 ^{1}H NMR of compound **334** (300 MHz, $CDCl_3$)

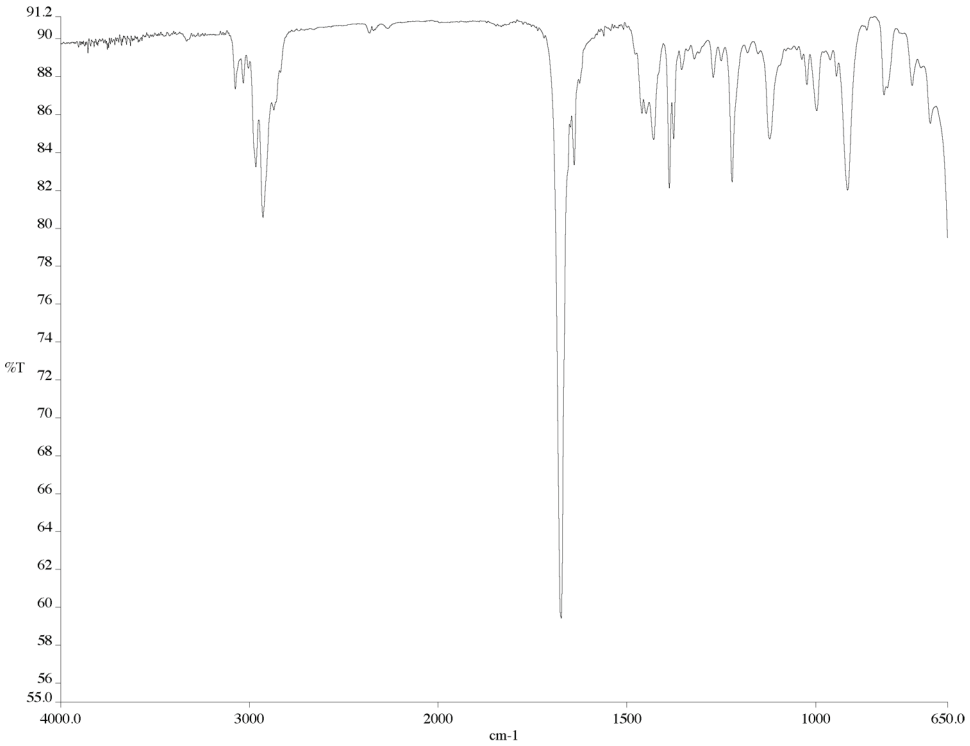


Figure A7.272 IR of compound **334** (NaCl/film)

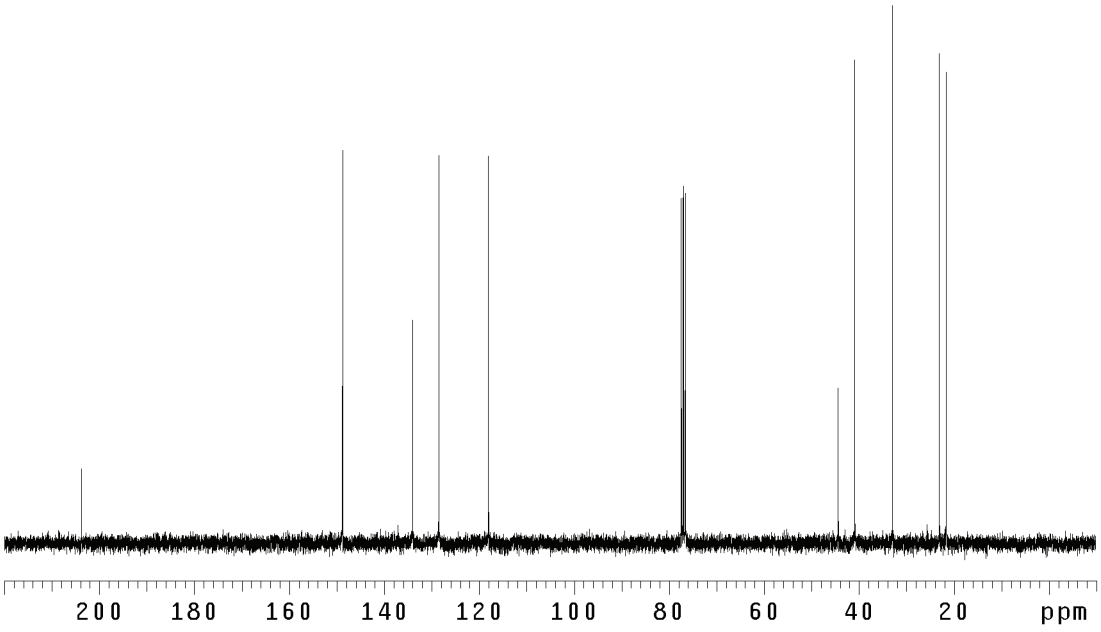


Figure A7.273 ^{13}C NMR of compound **334** (75 MHz, $CDCl_3$)

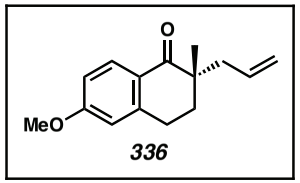


Figure A7.274 ^{1}H NMR of compound **336** (300 MHz, $CDCl_3$)

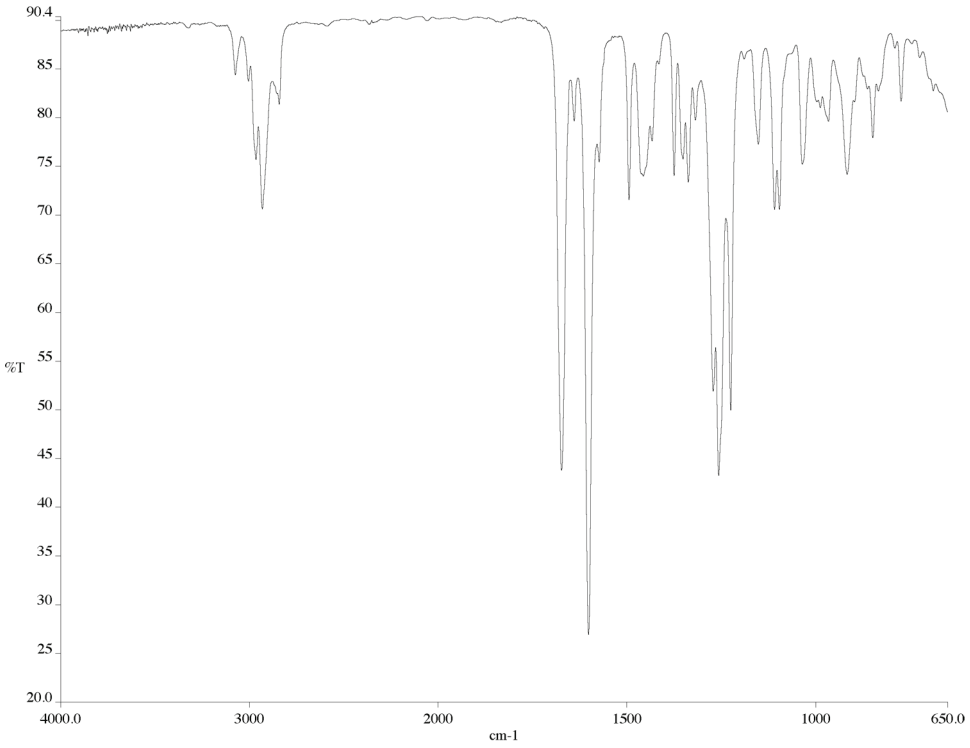


Figure A7.275 IR of compound **336** (NaCl/film)

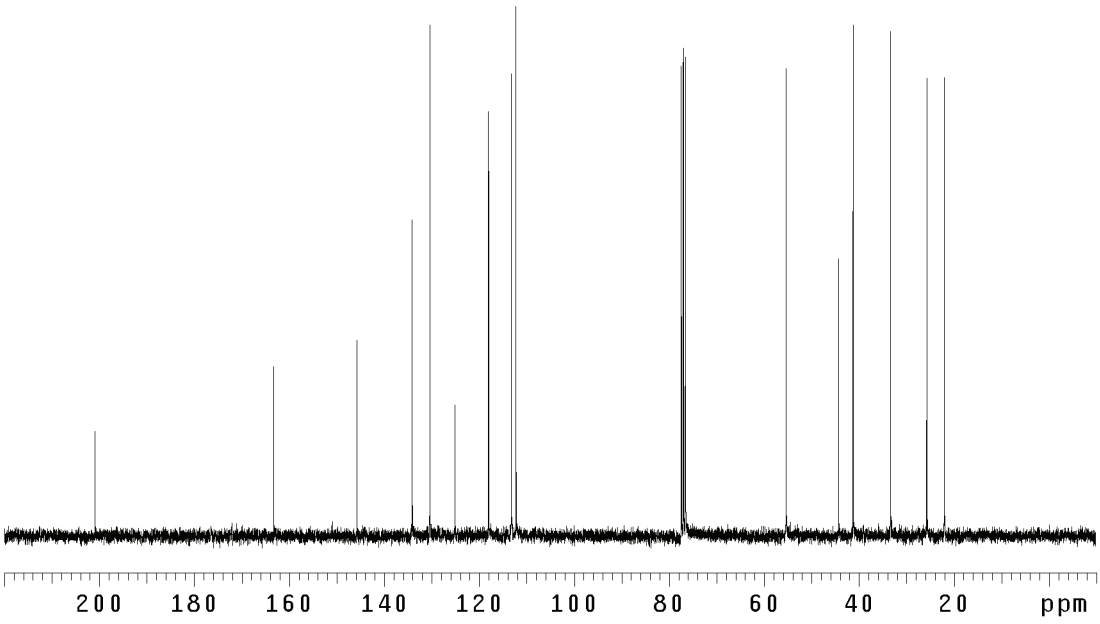


Figure A7.276 ^{13}C NMR of compound **336** (75 MHz, $CDCl_3$)

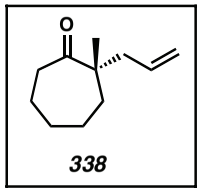


Figure A7.277 ^{1}H NMR of compound **338** (300 MHz, $CDCl_3$)

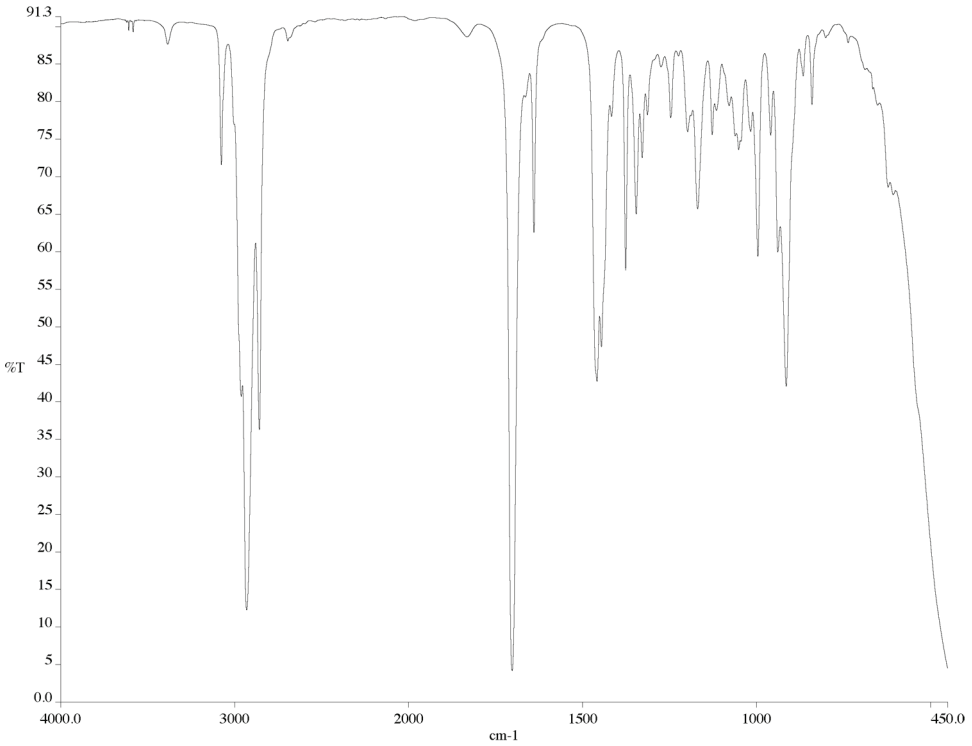


Figure A7.278 IR of compound **338** (NaCl/film)

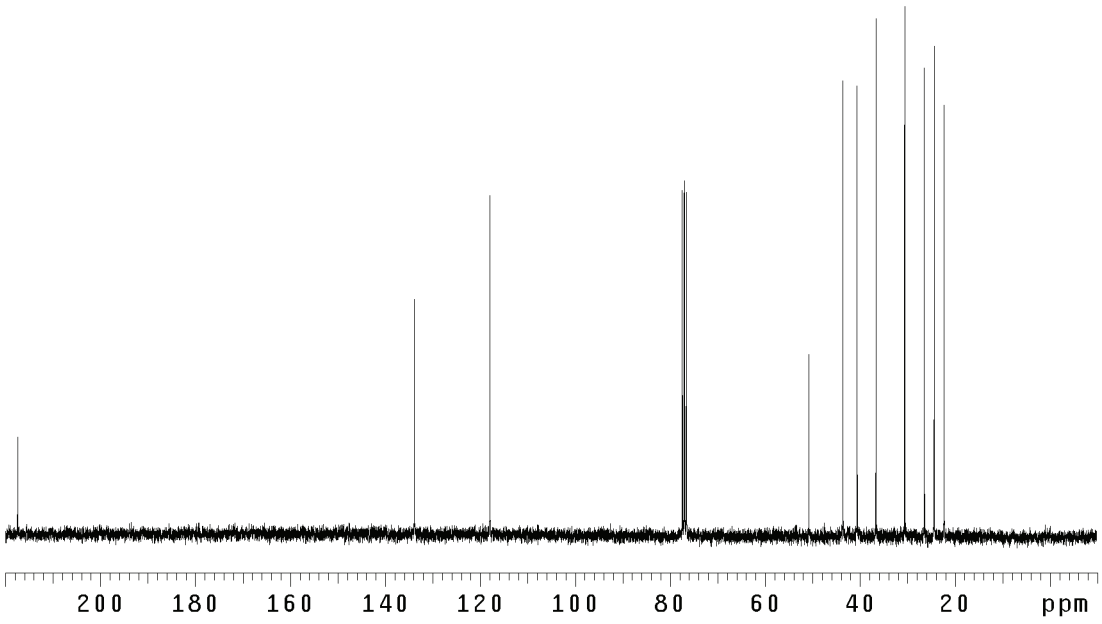


Figure A7.279 ^{13}C NMR of compound **338** (75 MHz, $CDCl_3$)

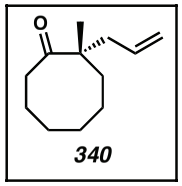


Figure A7.280 ^{1}H NMR of compound **340** (300 MHz, $CDCl_3$)

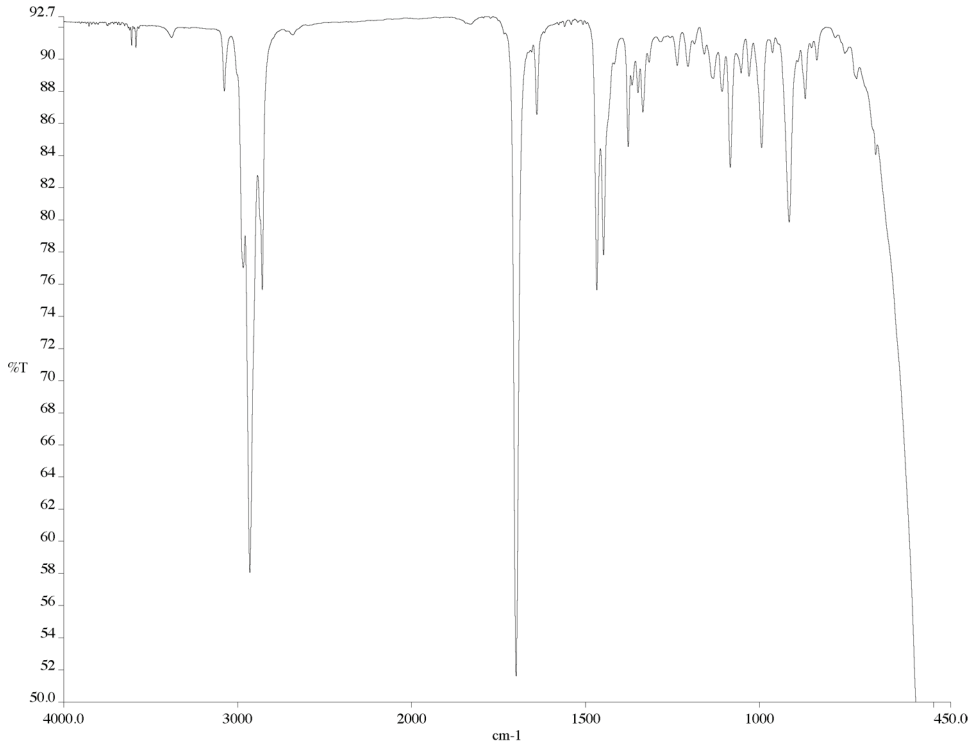


Figure A7.281 IR of compound **340** (NaCl/film)

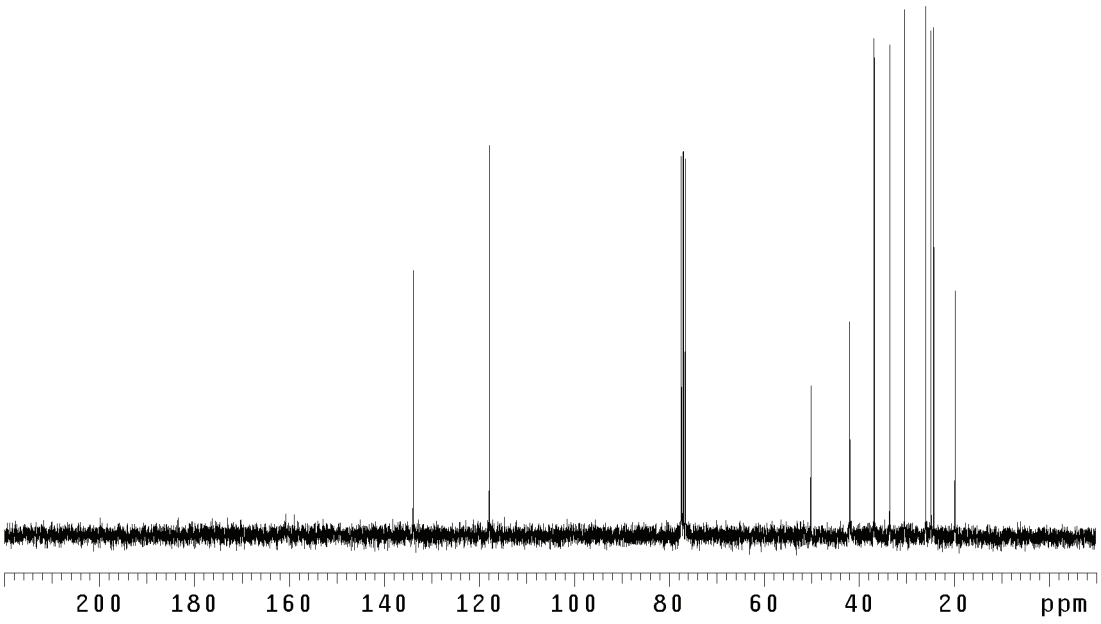


Figure A7.282 ^{13}C NMR of compound **340** (75 MHz, $CDCl_3$)

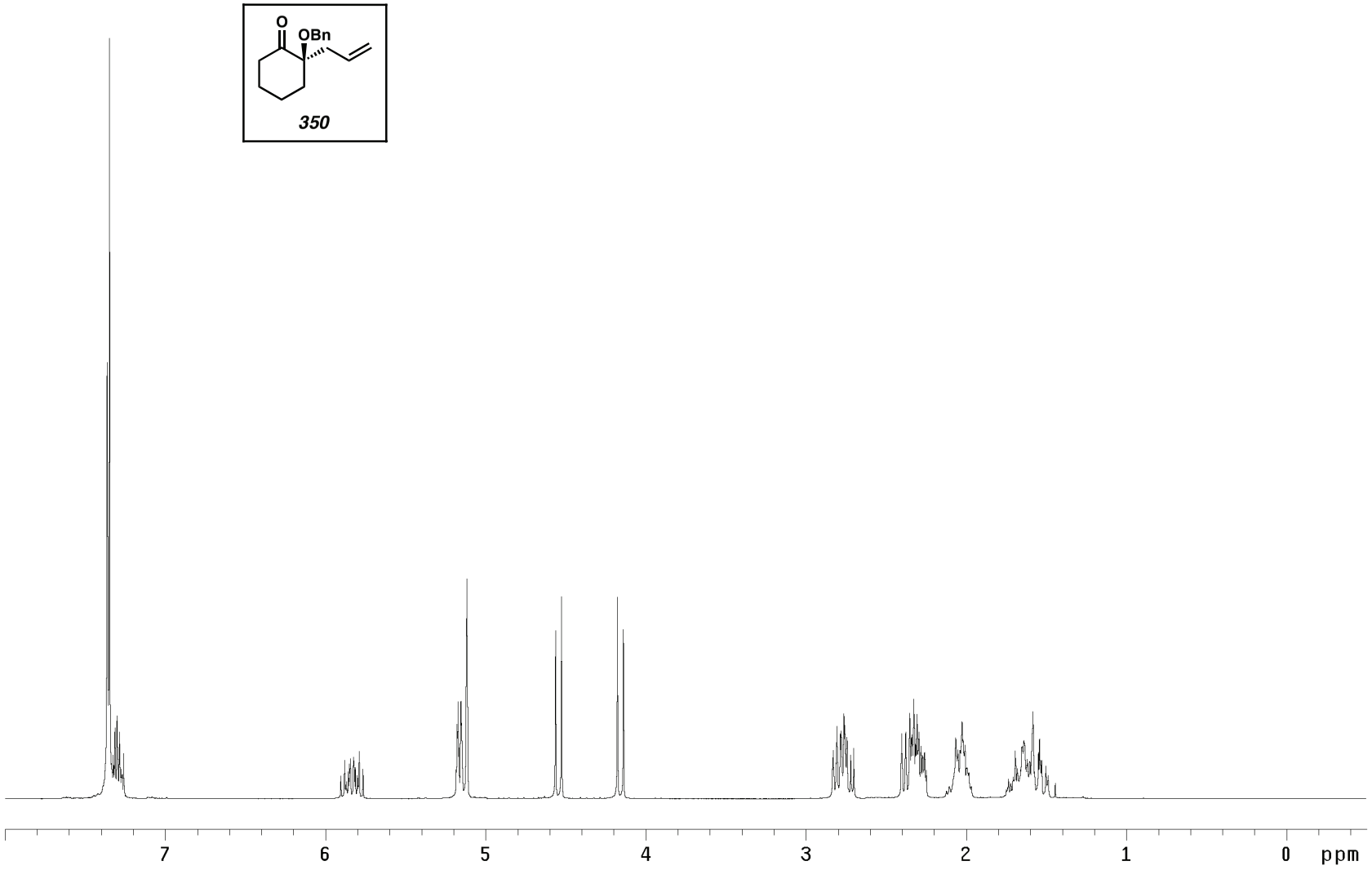


Figure A7.283 ^{1}H NMR of compound **350** (300 MHz, $CDCl_3$)

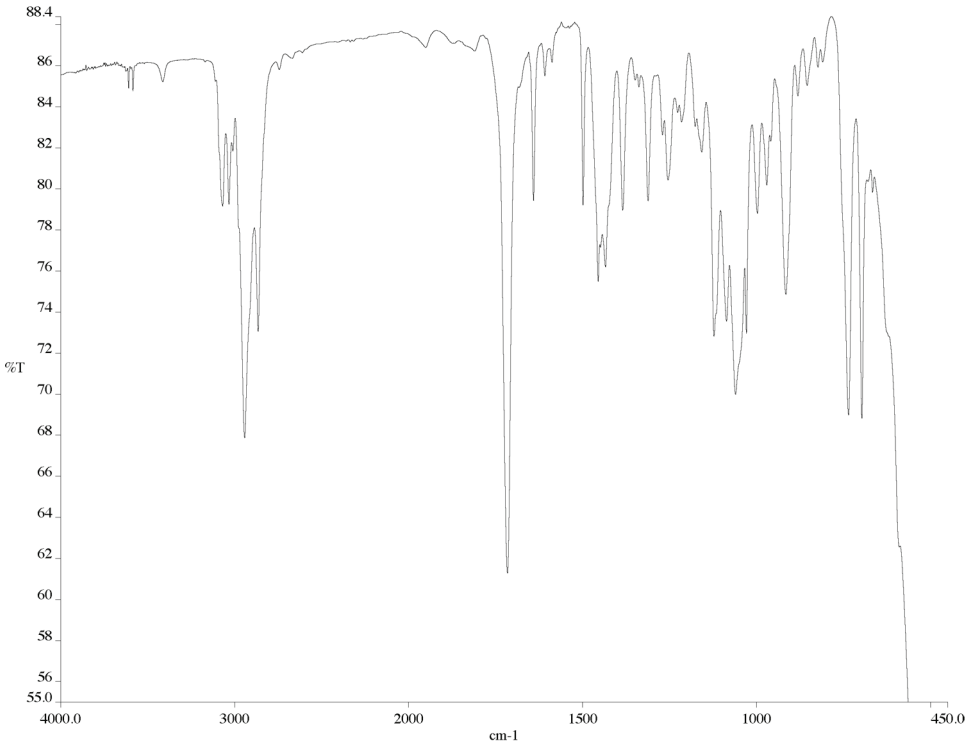


Figure A7.284 IR of compound **350** (NaCl/film)

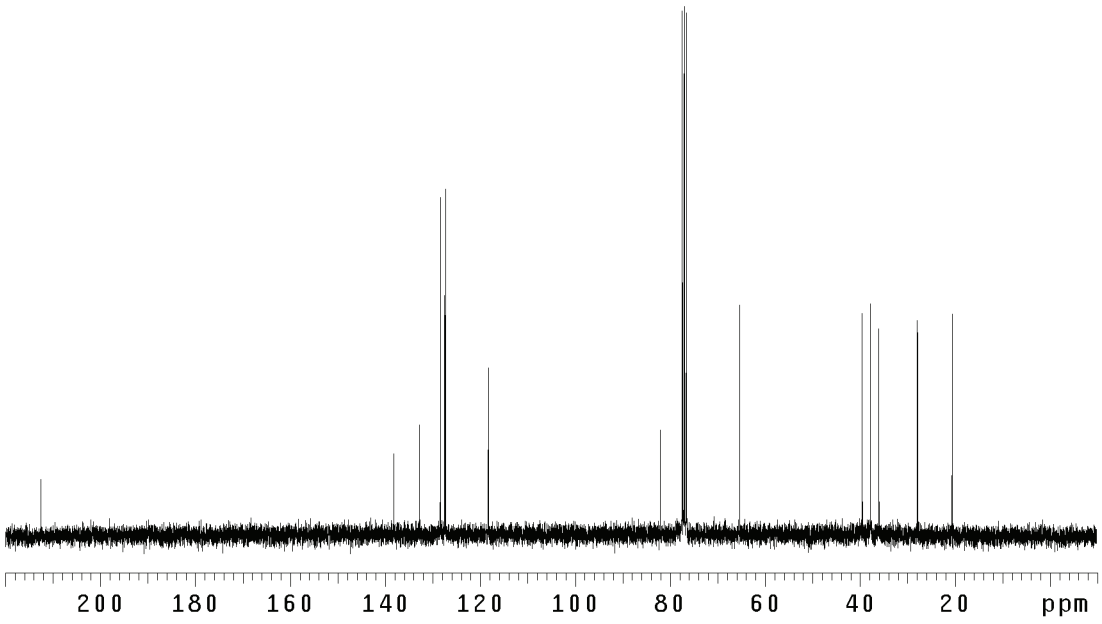


Figure A7.285 ^{13}C NMR of compound **350** (75 MHz, $CDCl_3$)

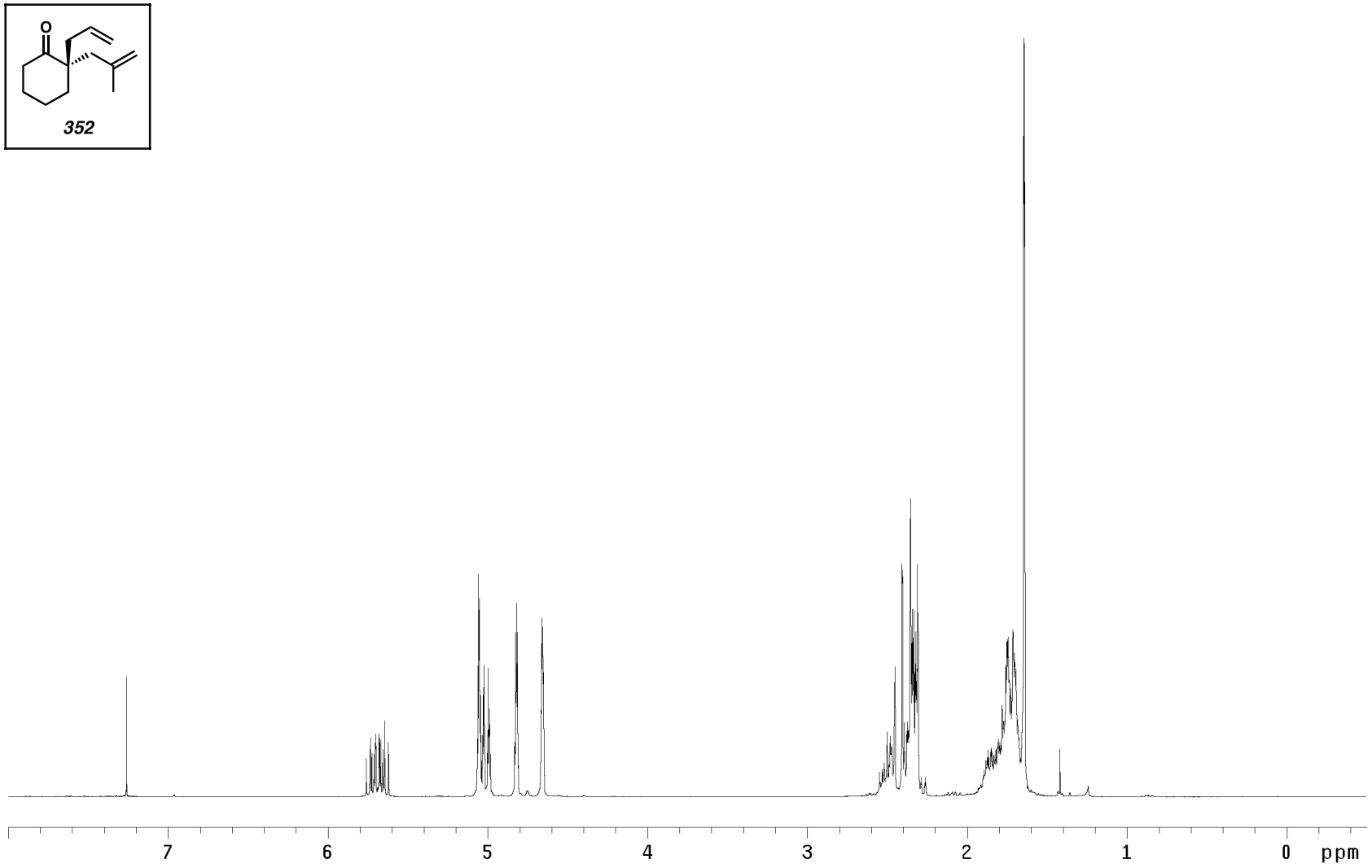


Figure A7.286 ^{1}H NMR of compound **352** (300 MHz, $CDCl_3$)

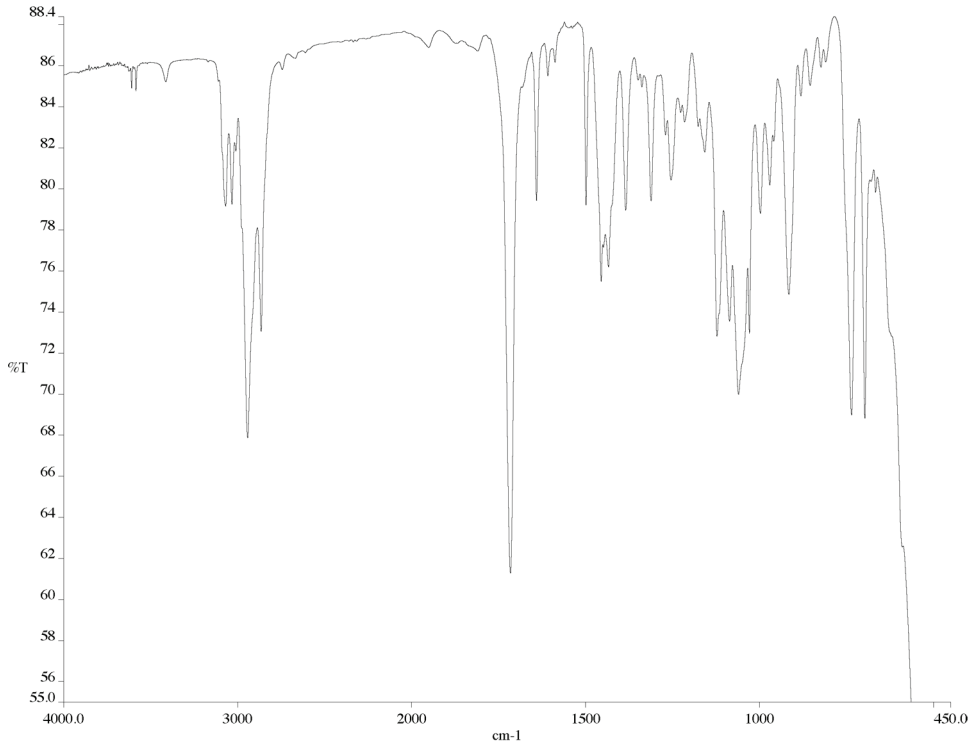


Figure A7.287 IR of compound **352** (NaCl/film)

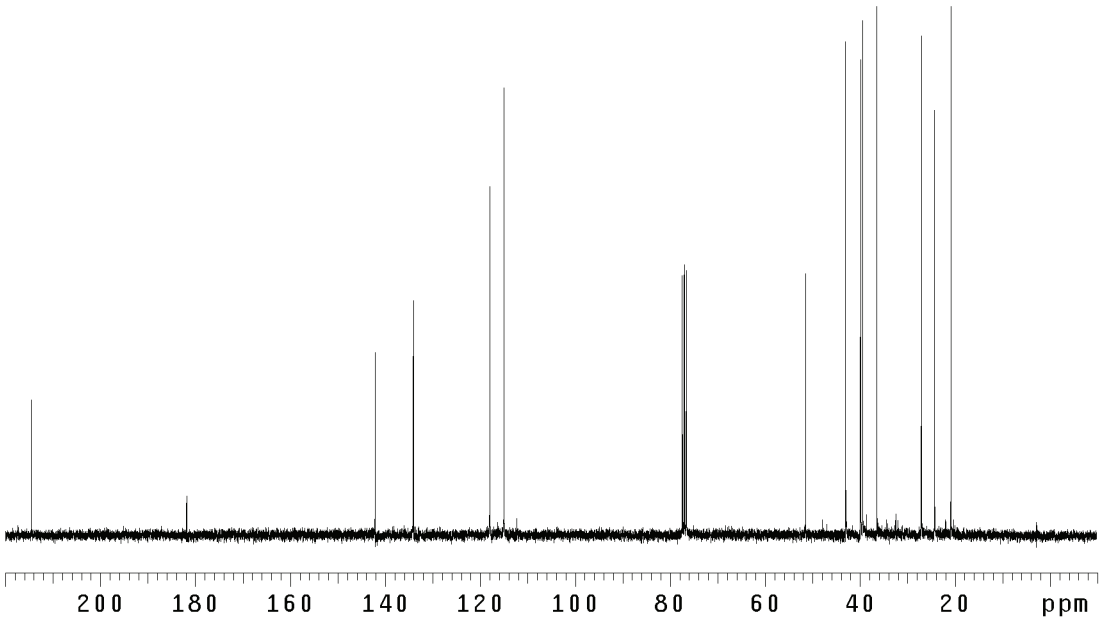


Figure A7.288 ^{13}C NMR of compound **352** (75 MHz, $CDCl_3$)

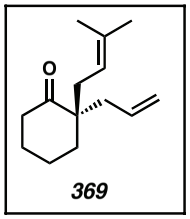


Figure A7.289 ^{1}H NMR of compound **369** (300 MHz, $CDCl_3$)

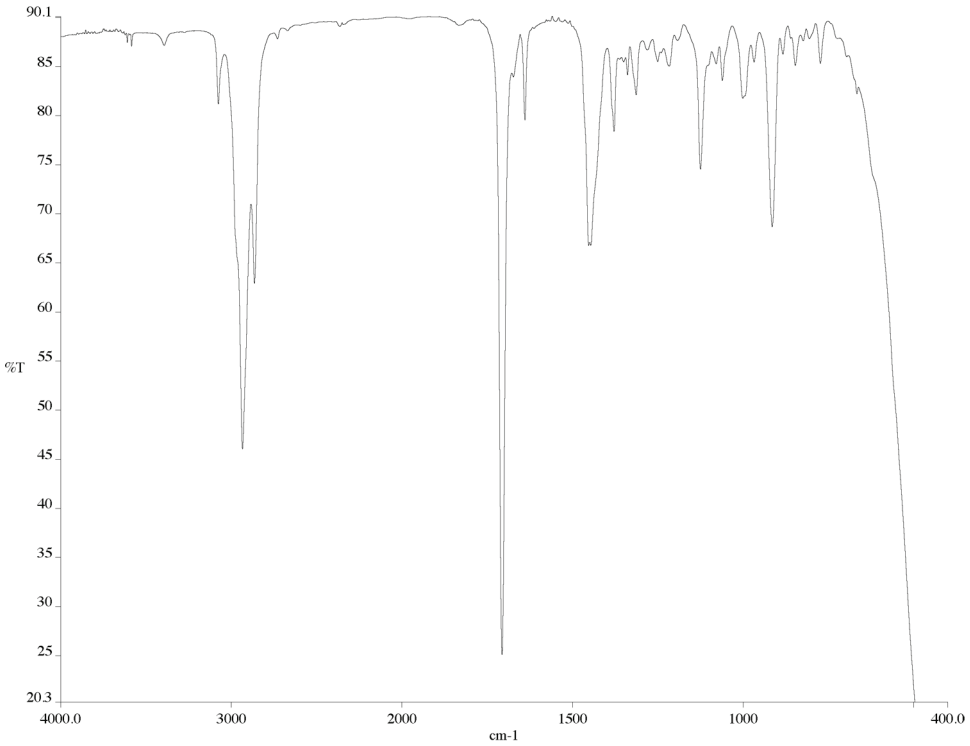


Figure A7.290 IR of compound **369** (NaCl/film)

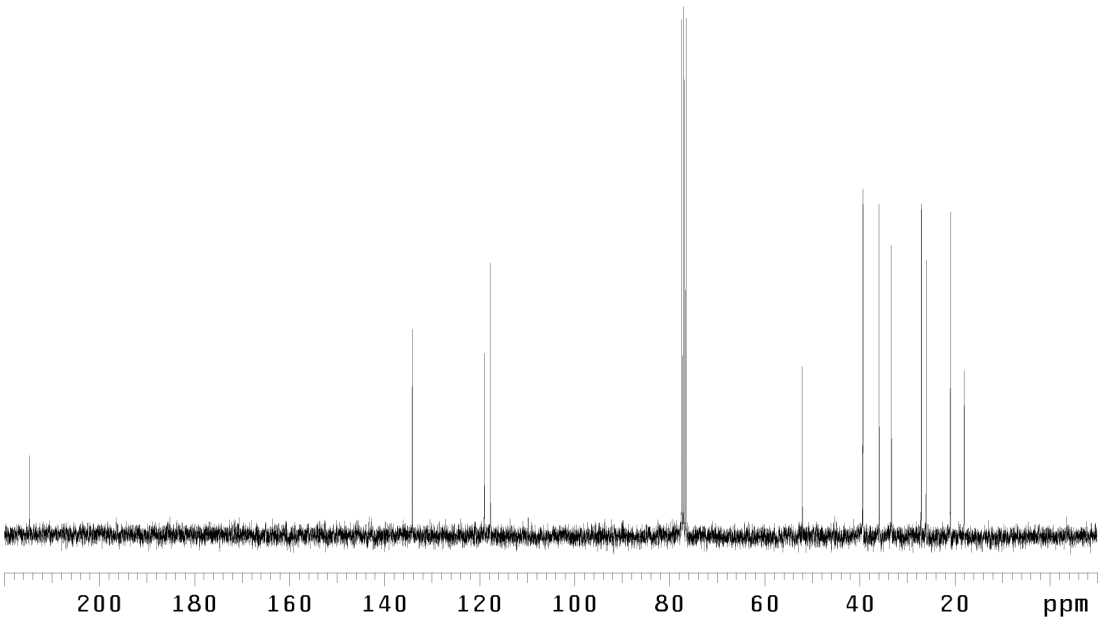


Figure A7.291 ^{13}C NMR of compound **369** (75 MHz, $CDCl_3$)

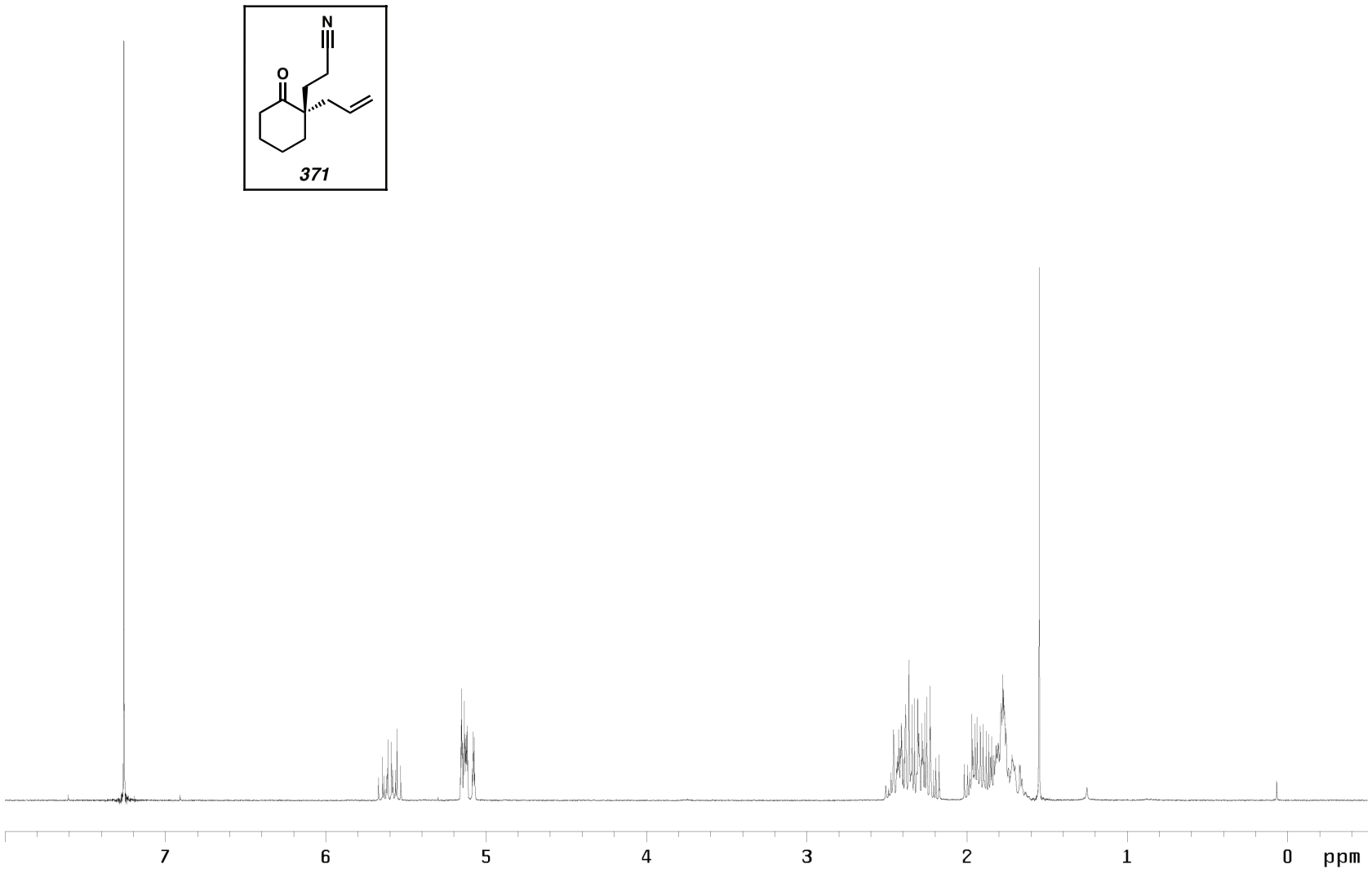


Figure A7.292 ^{1}H NMR of compound **371** (300 MHz, $CDCl_3$)

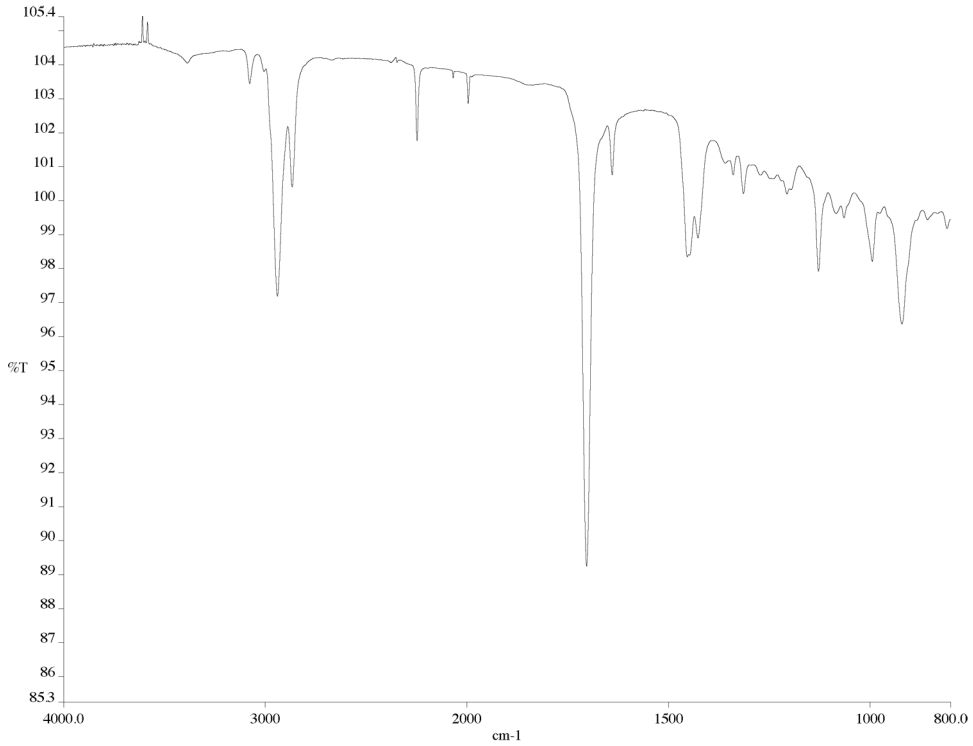


Figure A7.293 IR of compound **371** (NaCl/film)

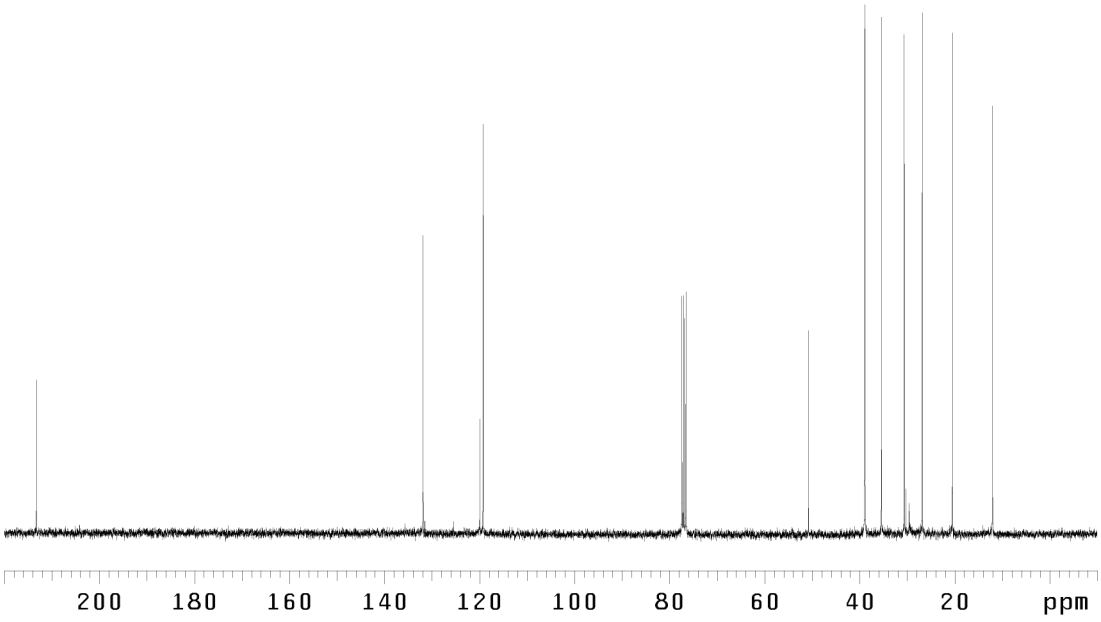


Figure A7.294 ^{13}C NMR of compound **371** (75 MHz, $CDCl_3$)

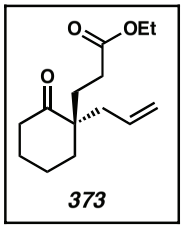


Figure A7.295 ^{1}H NMR of compound **373** (300 MHz, $CDCl_3$)

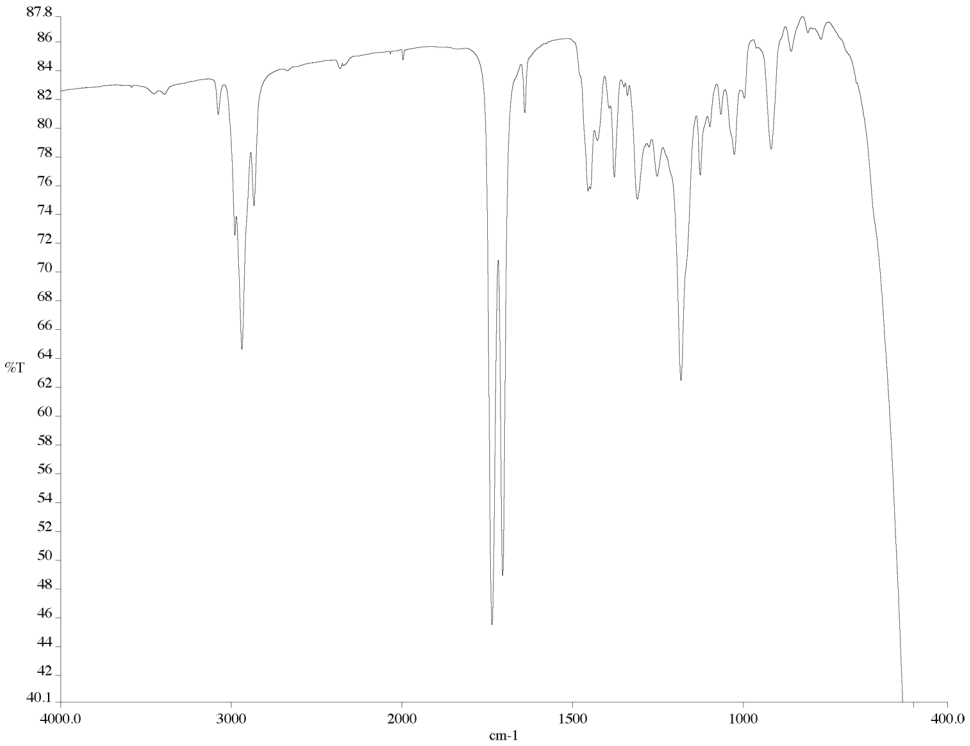


Figure A7.296 IR of compound **373** (NaCl/film)

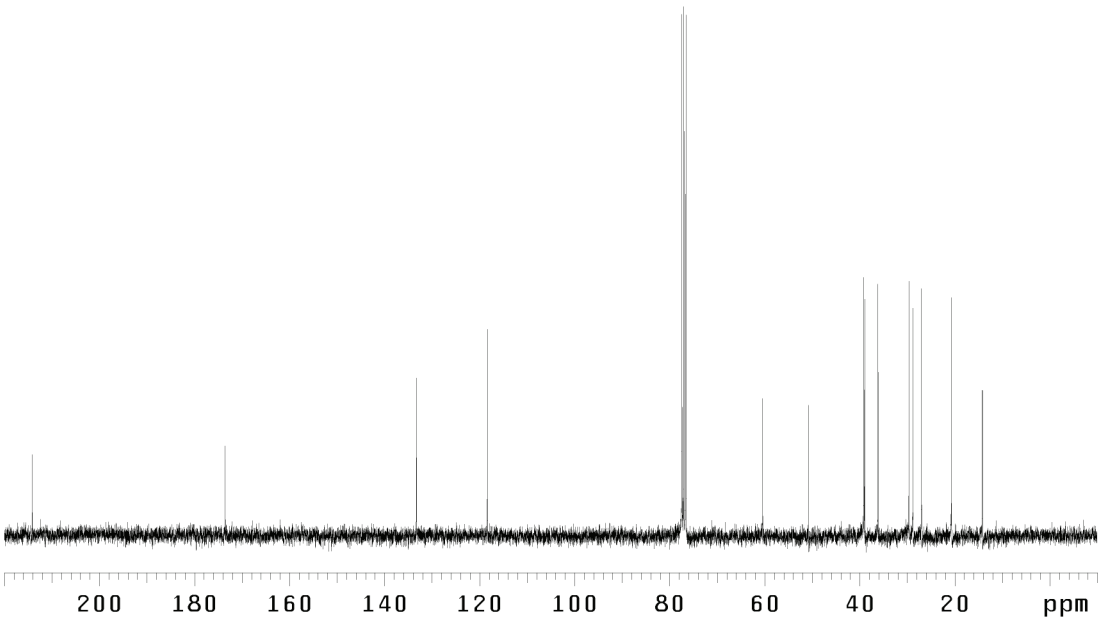


Figure A7.297 ^{13}C NMR of compound **373** (75 MHz, $CDCl_3$)

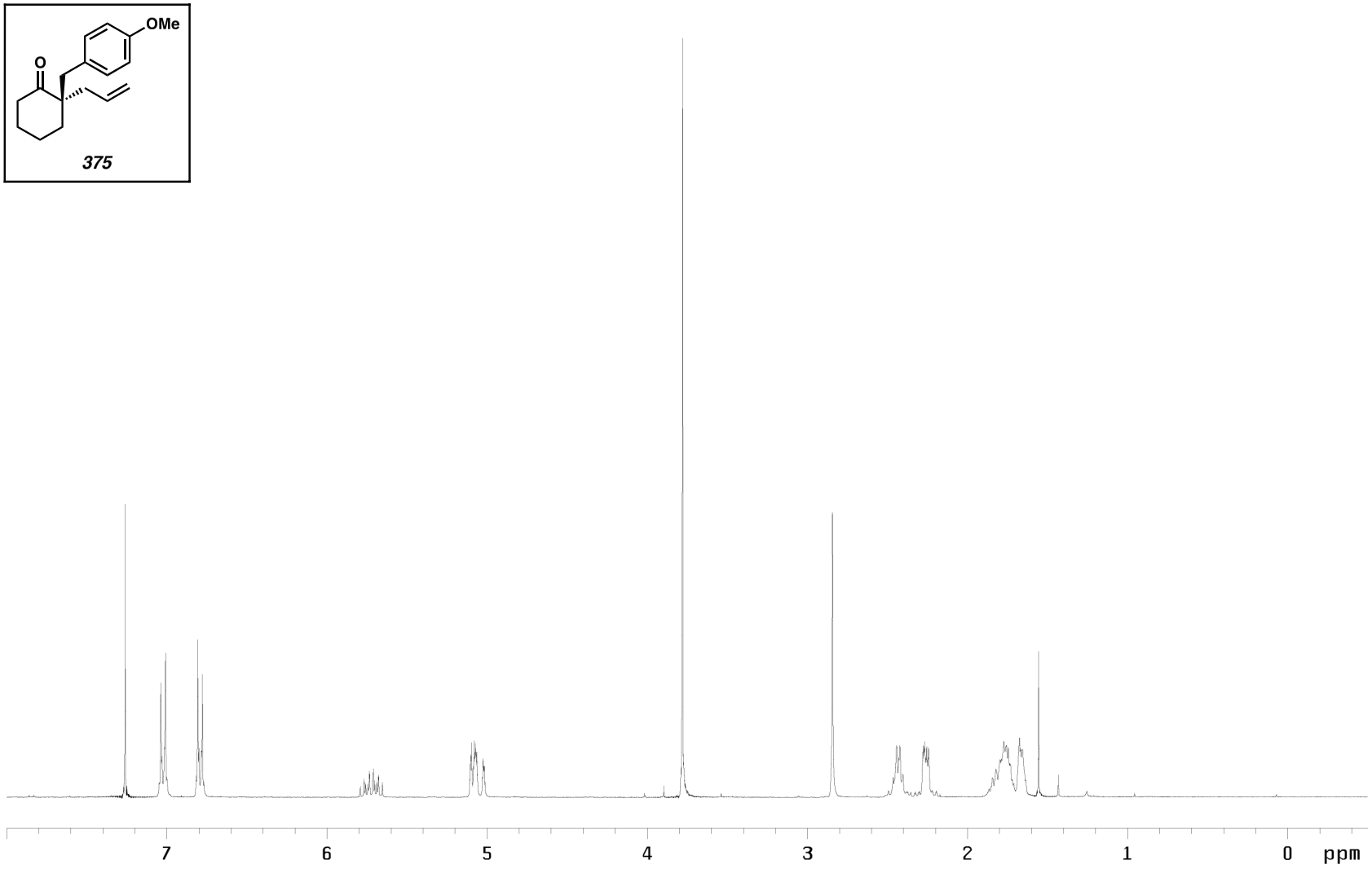


Figure A7.298 ^{1}H NMR of compound **375** (300 MHz, $CDCl_3$)

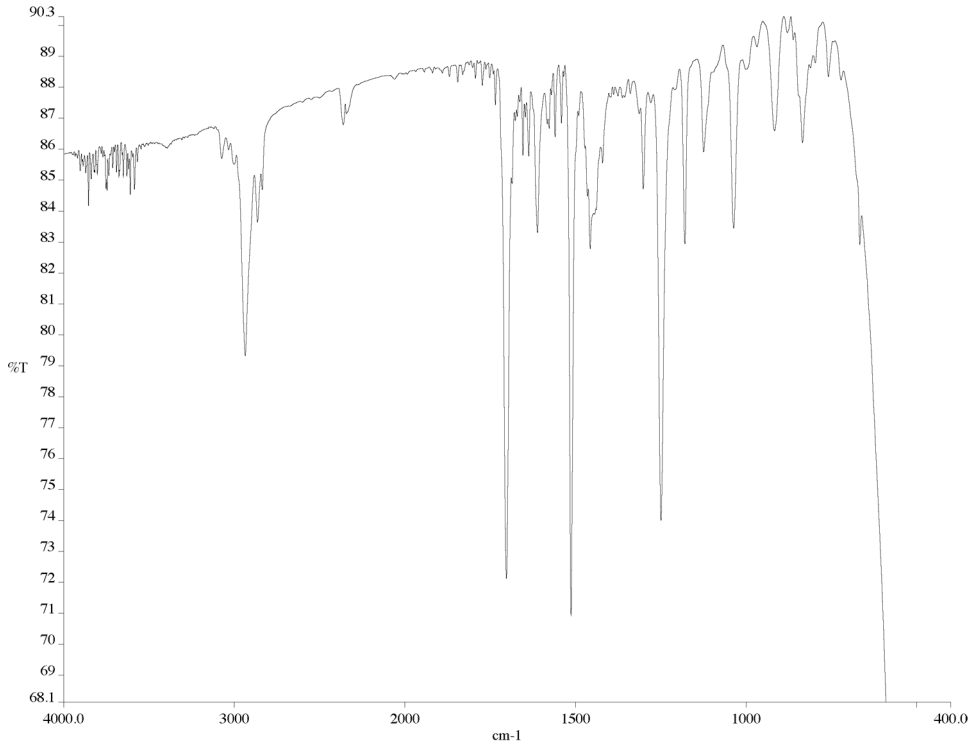


Figure A7.299 IR of compound **375** (NaCl/film)

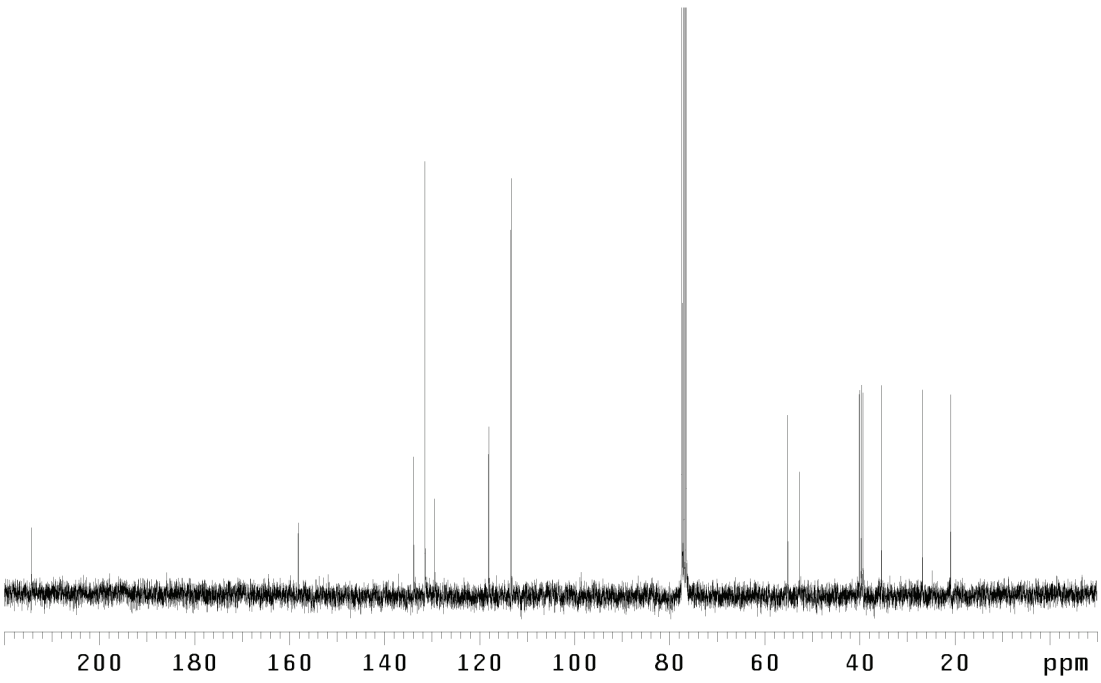


Figure A7.300 ^{13}C NMR of compound **375** (75 MHz, $CDCl_3$)

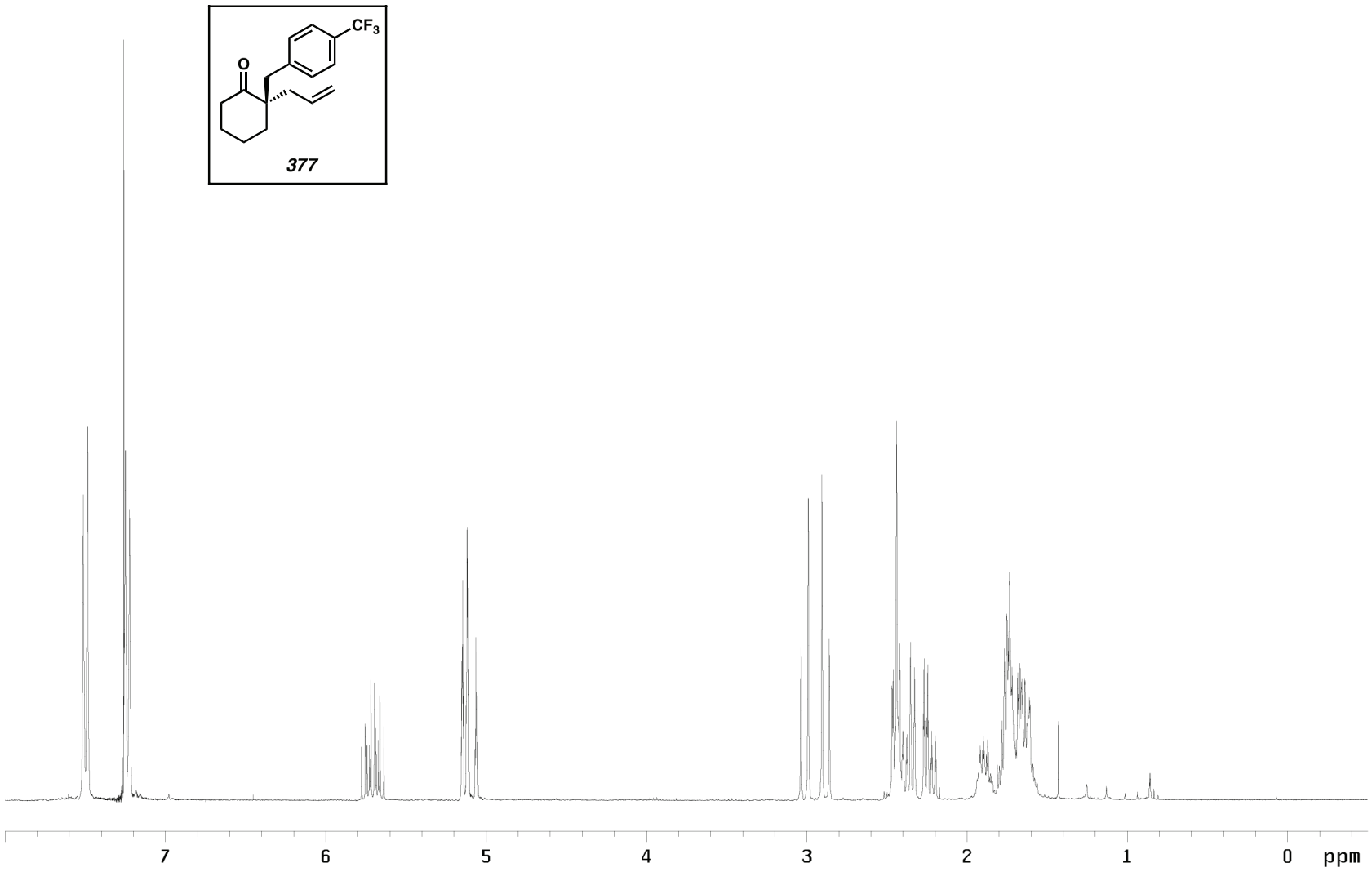


Figure A7.301 ^{1}H NMR of compound **377** (300 MHz, $CDCl_3$)

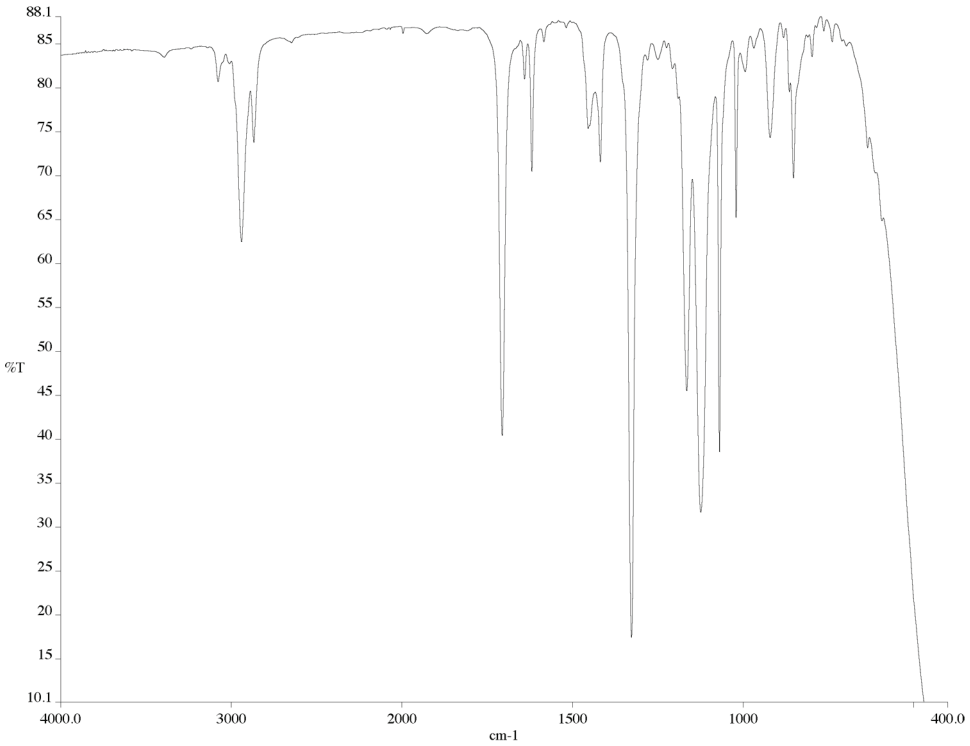


Figure A7.302 IR of compound **377** (NaCl/film)

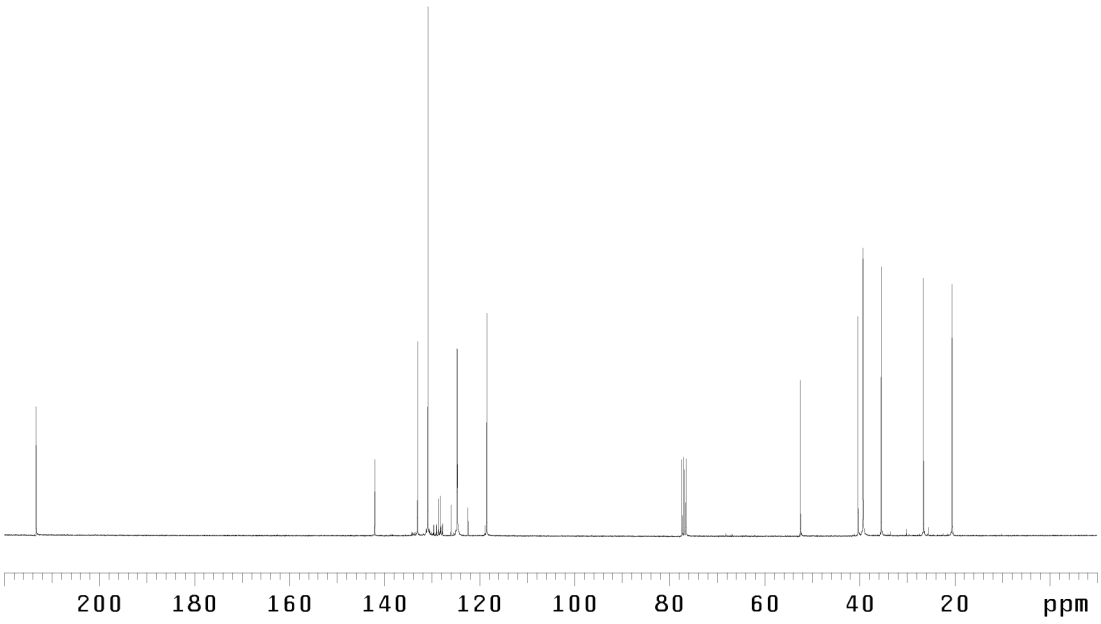


Figure A7.303 ^{13}C NMR of compound **377** (75 MHz, $CDCl_3$)

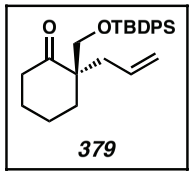


Figure A7.304 ^{1}H NMR of compound **379** (300 MHz, $CDCl_3$)

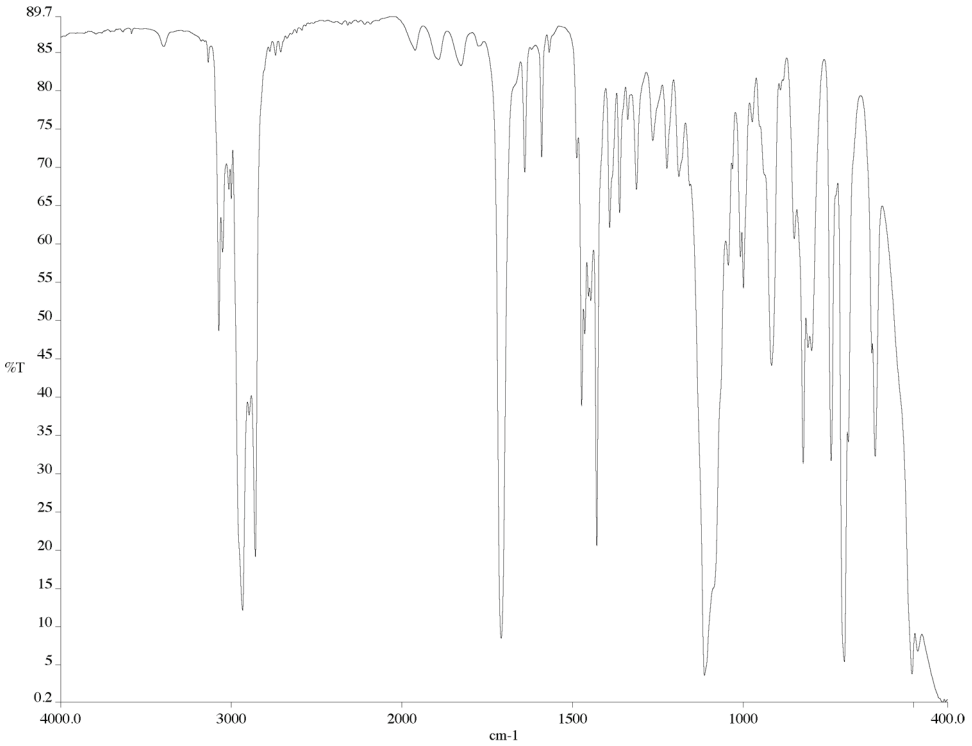


Figure A7.305 IR of compound **379** (NaCl/film)

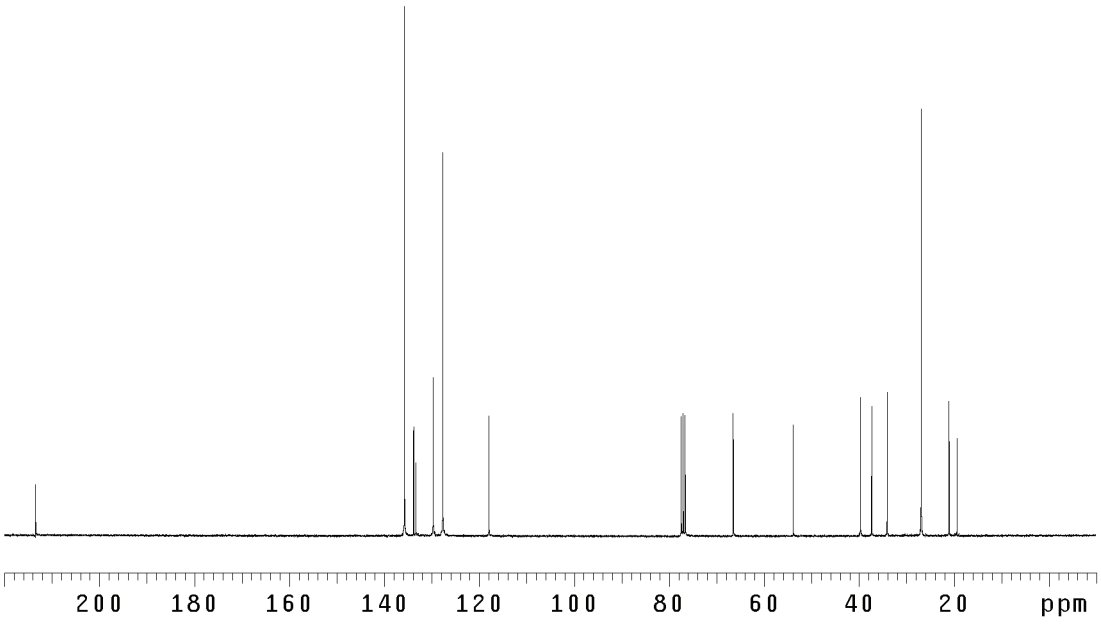


Figure A7.306 ^{13}C NMR of compound **379** (75 MHz, $CDCl_3$)

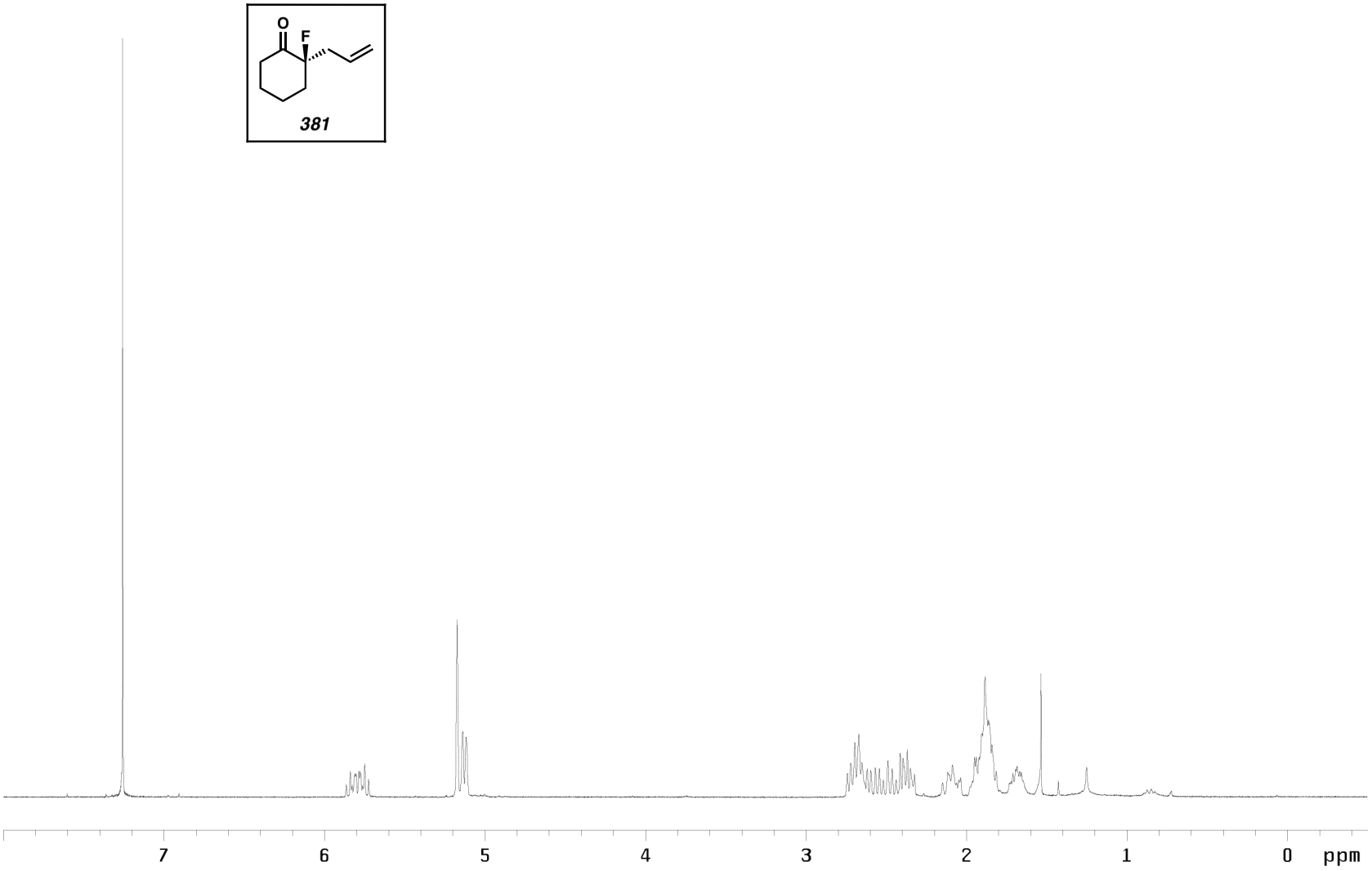


Figure A7.307 ^{1}H NMR of compound **381** (300 MHz, $CDCl_3$)

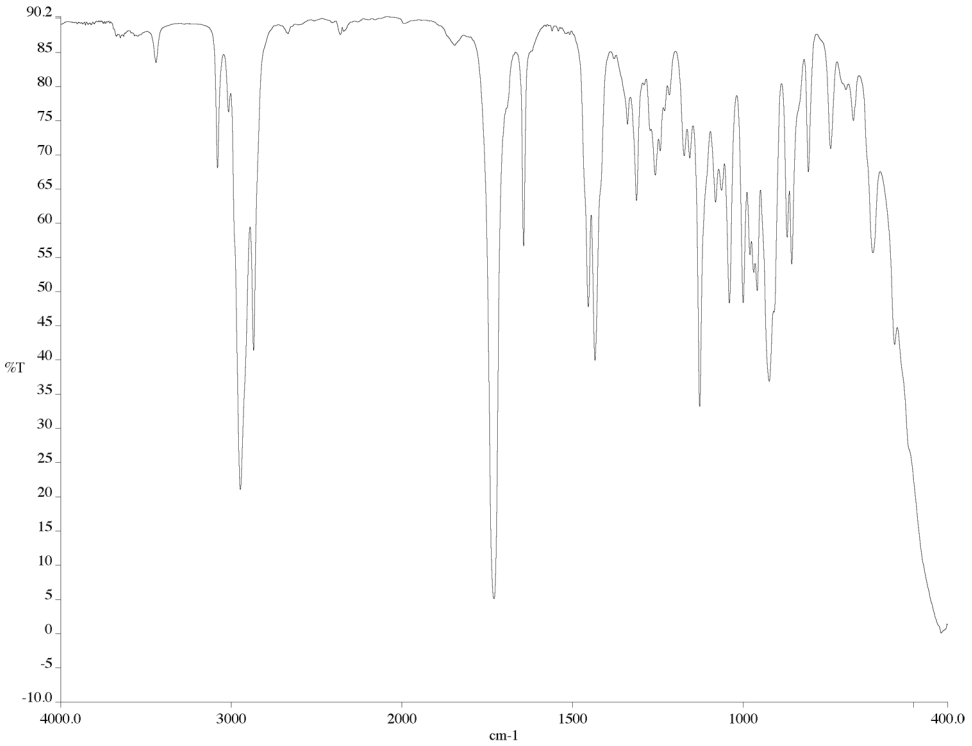


Figure A7.308 IR of compound **381** (NaCl/film)

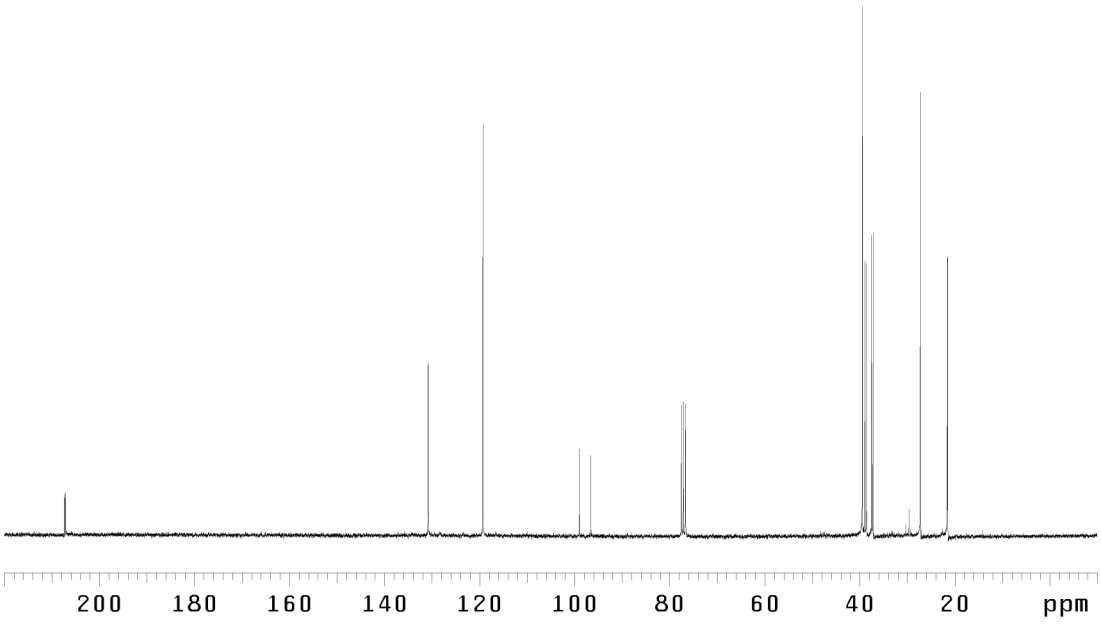


Figure A7.309 ^{13}C NMR of compound **381** (75 MHz, $CDCl_3$)

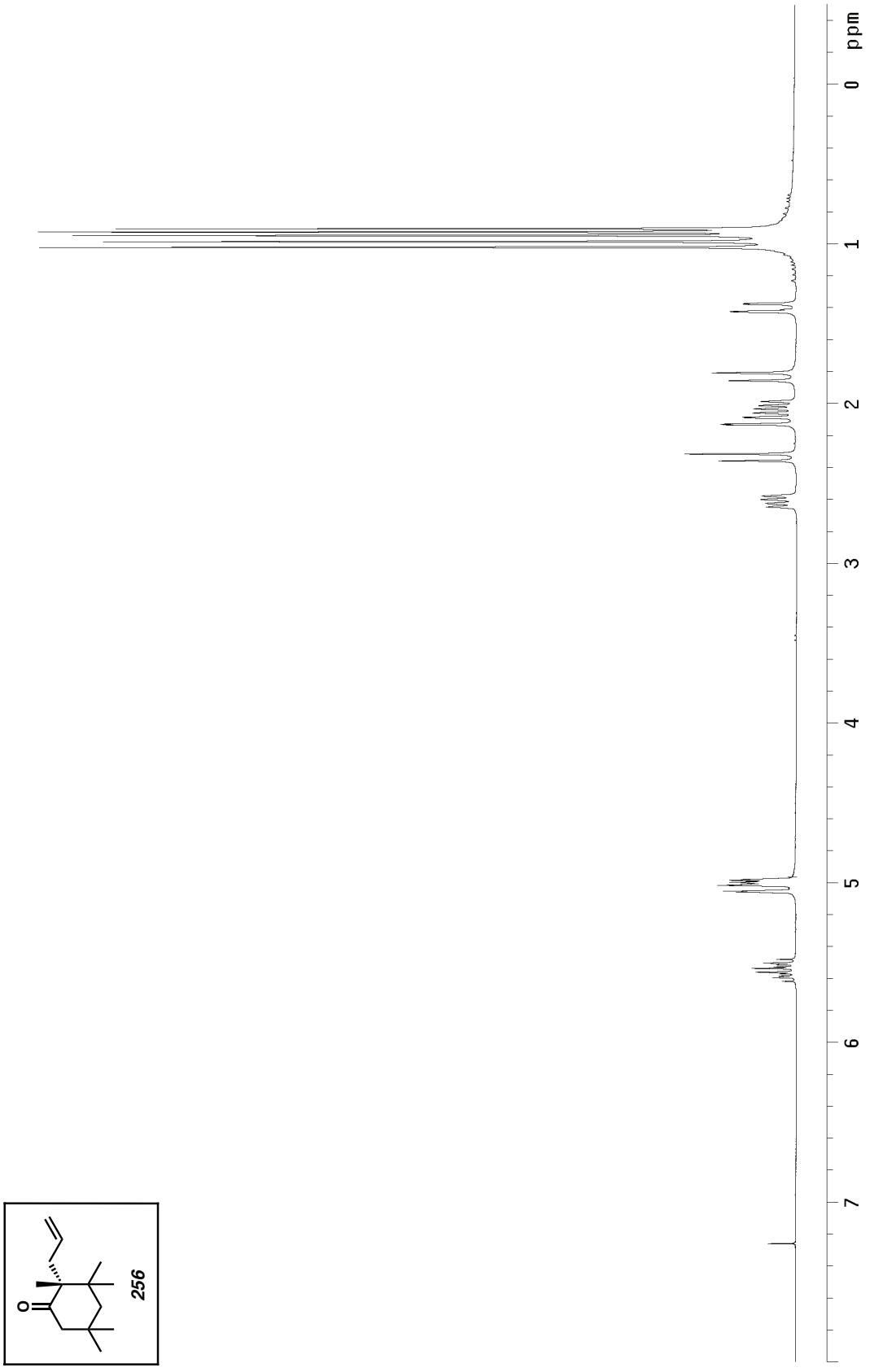


Figure A7.310 ^{1}H NMR of compound **256** (300 MHz, $CDCl_3$)

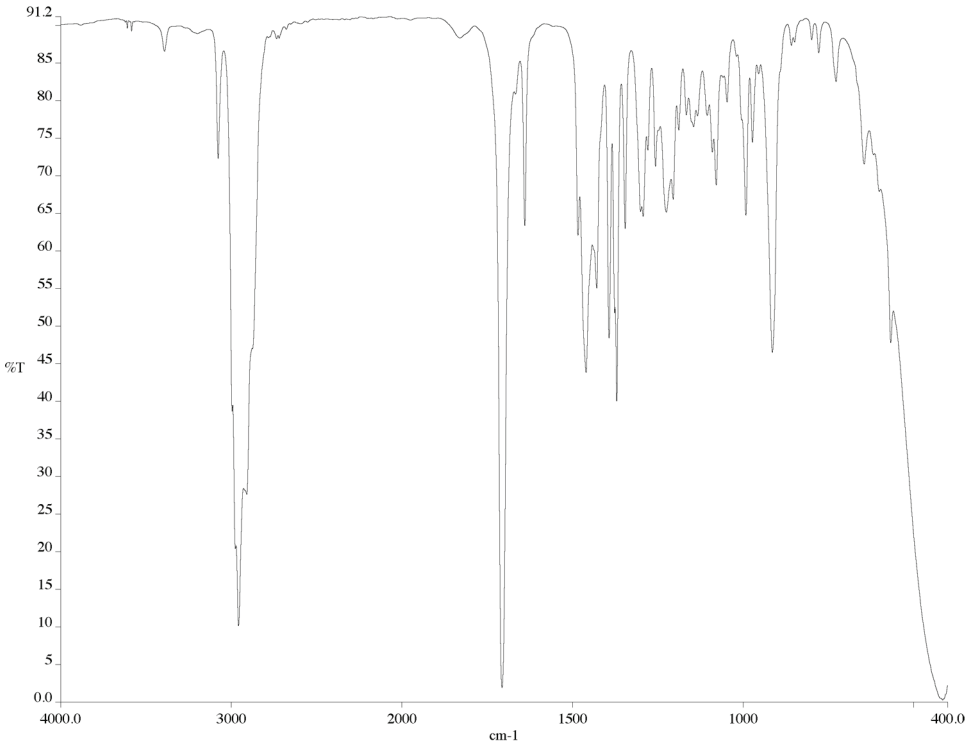


Figure A7.311 IR of compound **256** (NaCl/film)

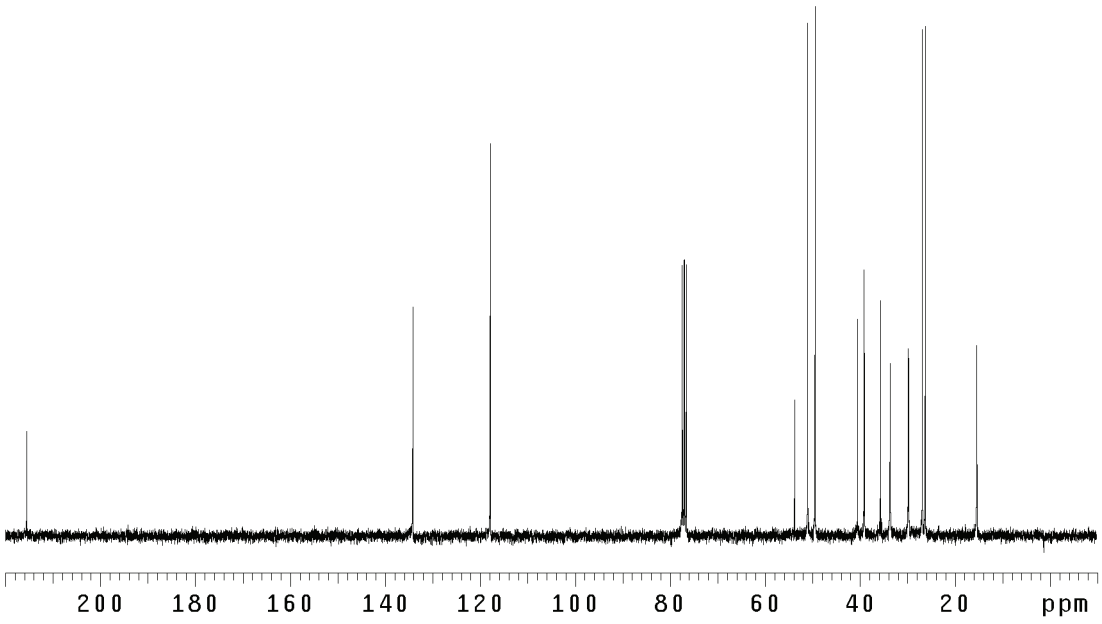


Figure A7.312 ^{13}C NMR of compound **256** (75 MHz, $CDCl_3$)

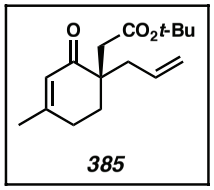


Figure A7.313 ^{1}H NMR of compound **385** (300 MHz, $CDCl_3$)

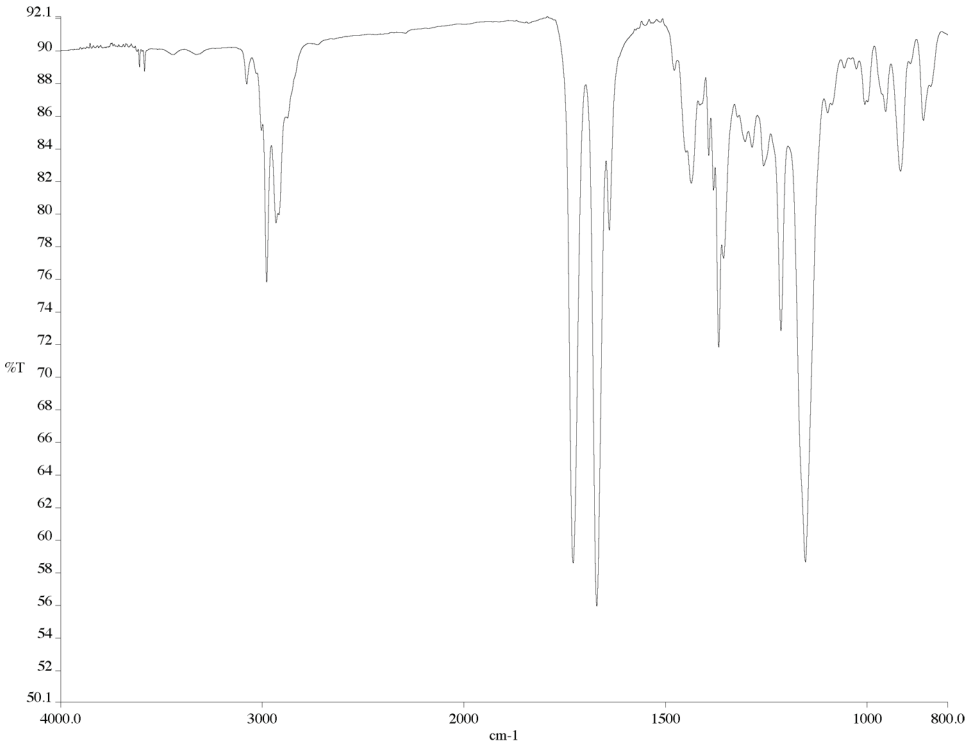


Figure A7.314 IR of compound **385** (NaCl/film)

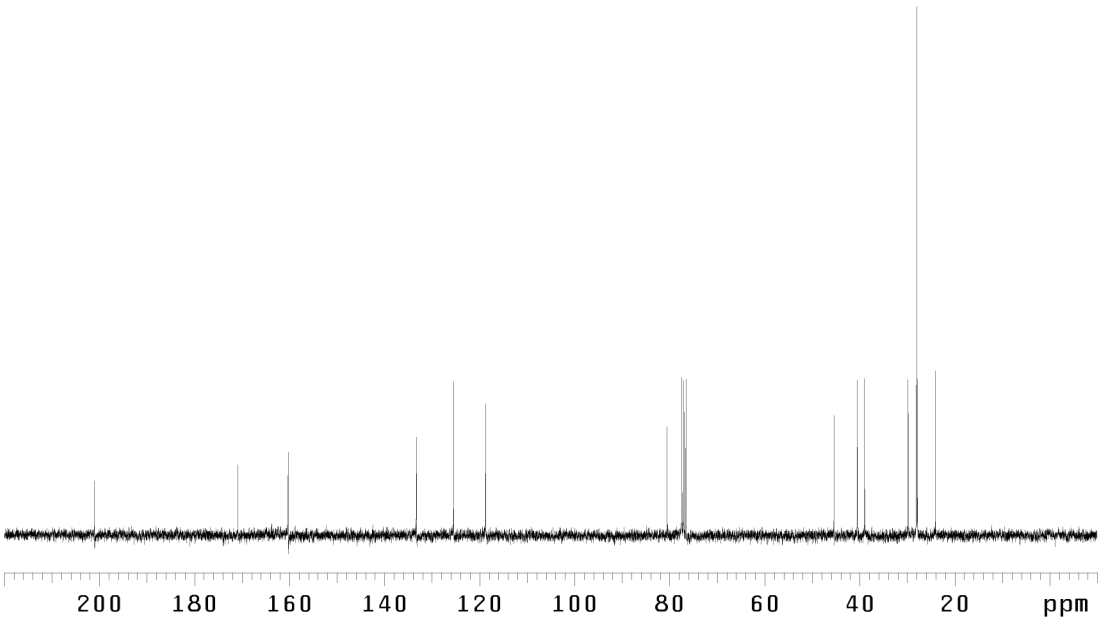
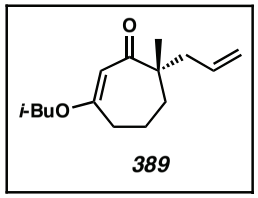


Figure A7.315 ^{13}C NMR of compound **385** (75 MHz, $CDCl_3$)



389

Figure A7.316 ^{1}H NMR of compound **389** (500 MHz, $CDCl_3$)

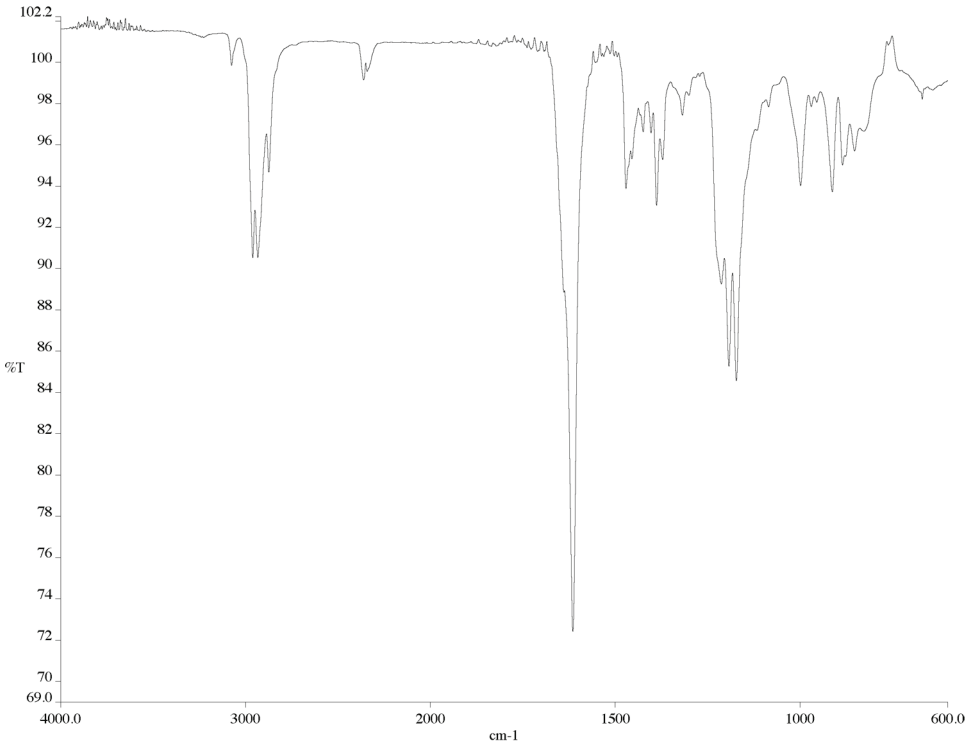


Figure A7.317 IR of compound **389** (NaCl/film)

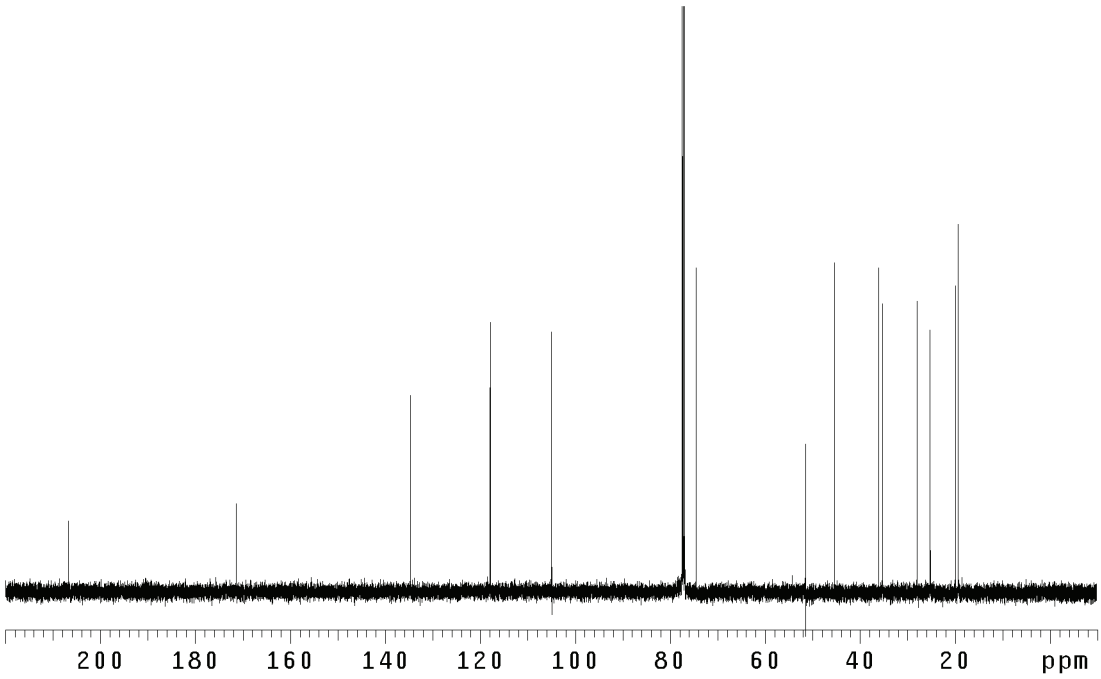


Figure A7.318 ^{13}C NMR of compound **389** (125 MHz, $CDCl_3$)

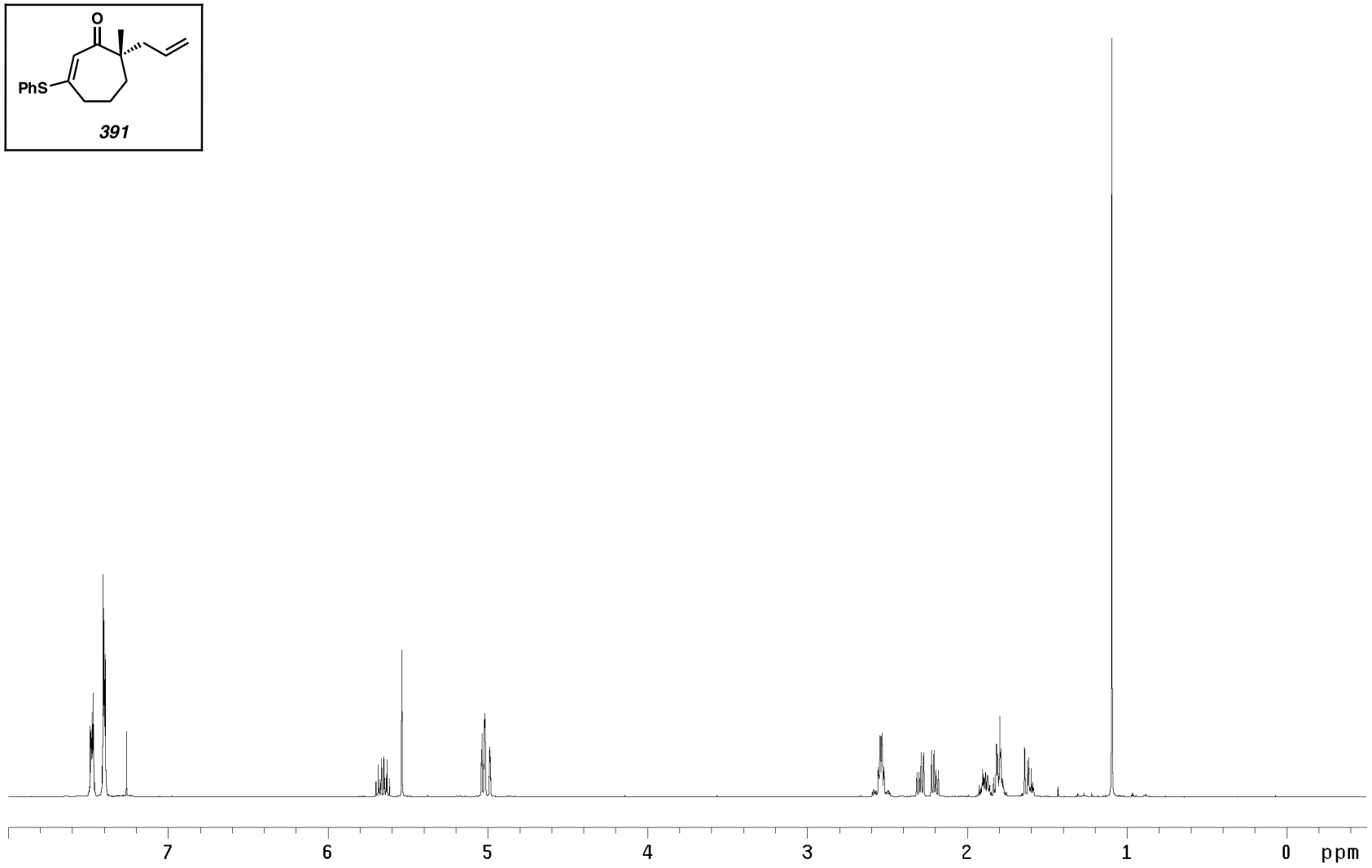


Figure A7.319 ^{1}H NMR of compound **391** (300 MHz, $CDCl_3$)

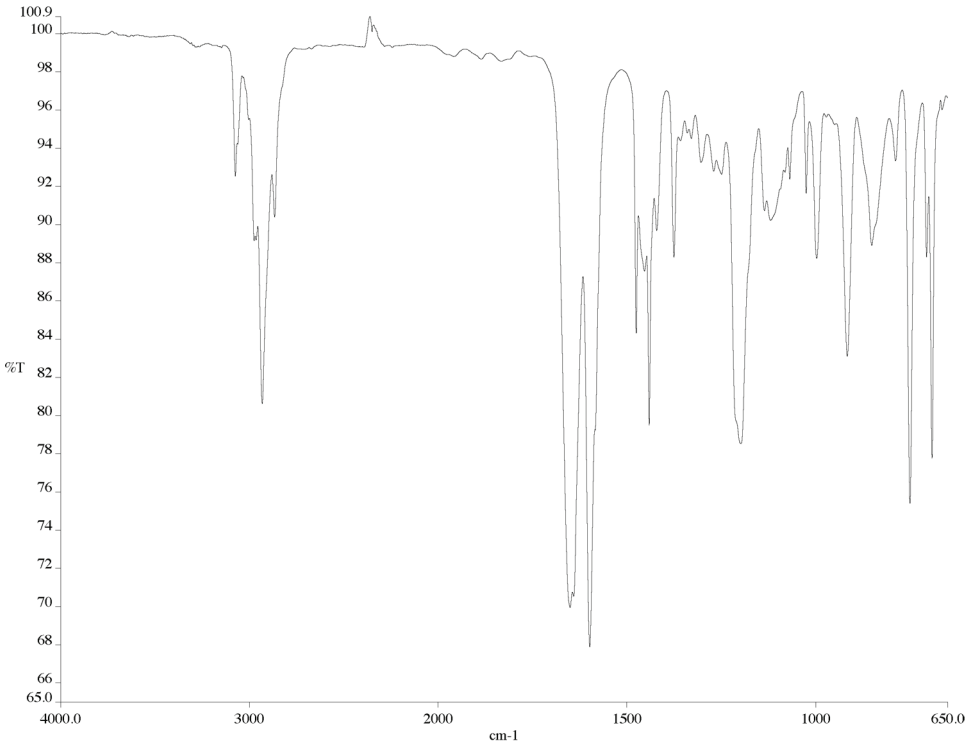


Figure A7.320 IR of compound **391** (NaCl/film)

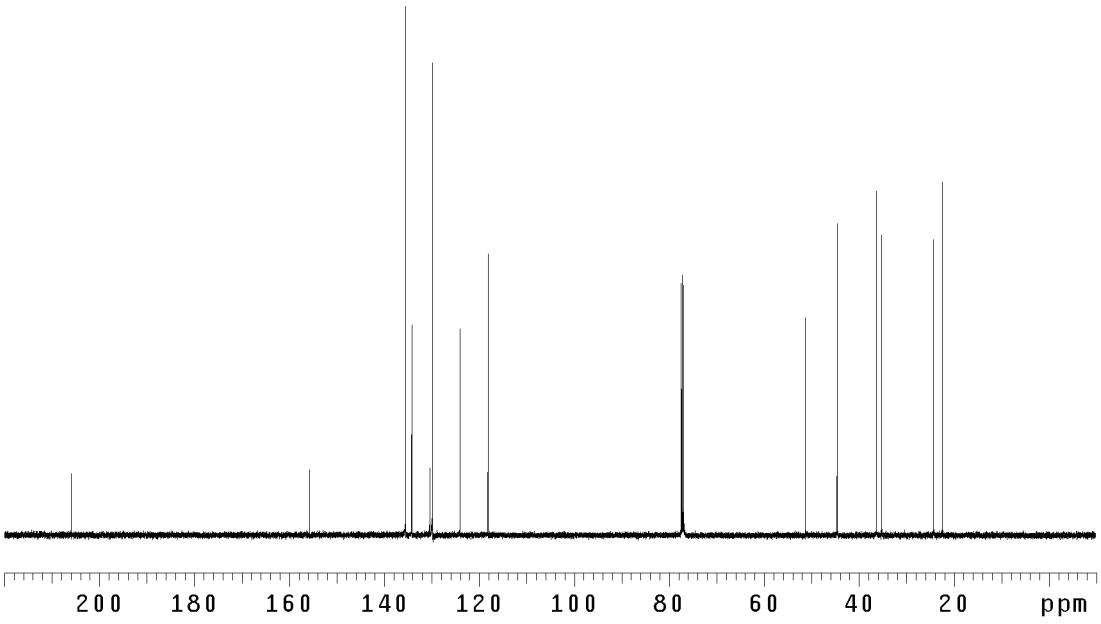


Figure A7.321 ^{13}C NMR of compound **391** (125 MHz, $CDCl_3$)

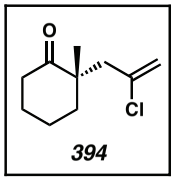


Figure A7.322 ^{1}H NMR of compound **394** (300 MHz, $CDCl_3$)

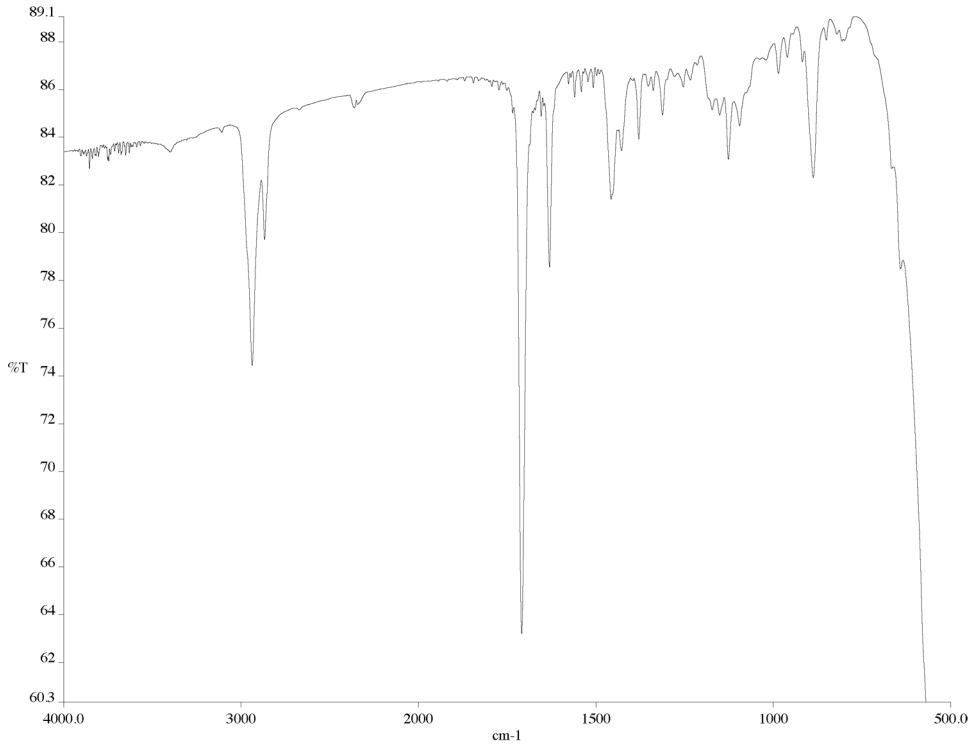


Figure A7.323 IR of compound **394** (NaCl/film)

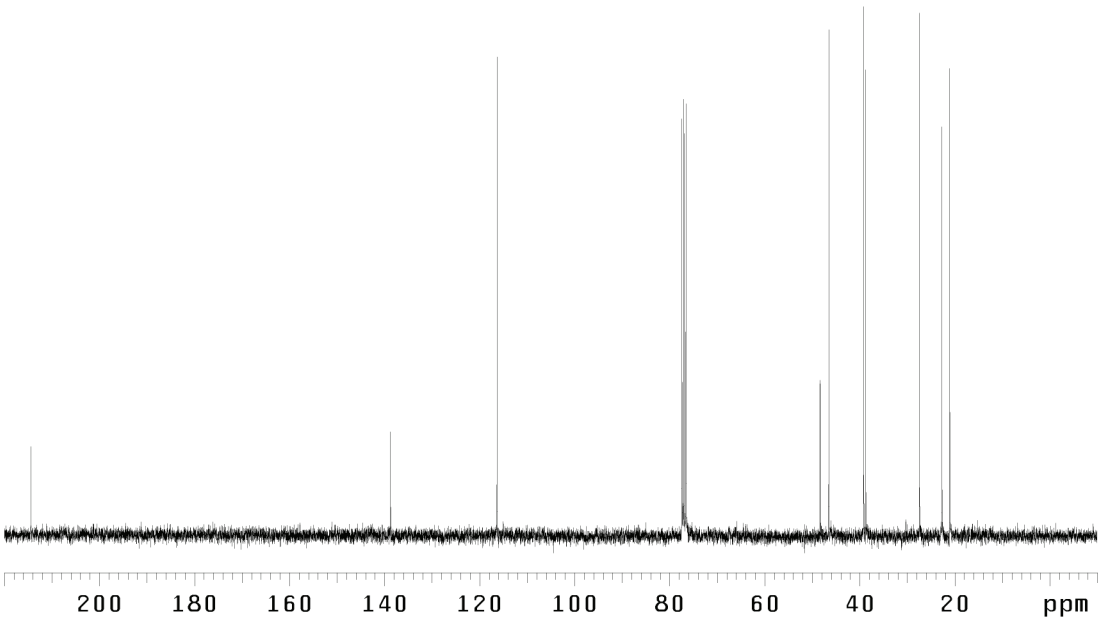


Figure A7.324 ^{13}C NMR of compound **394** (75 MHz, $CDCl_3$)

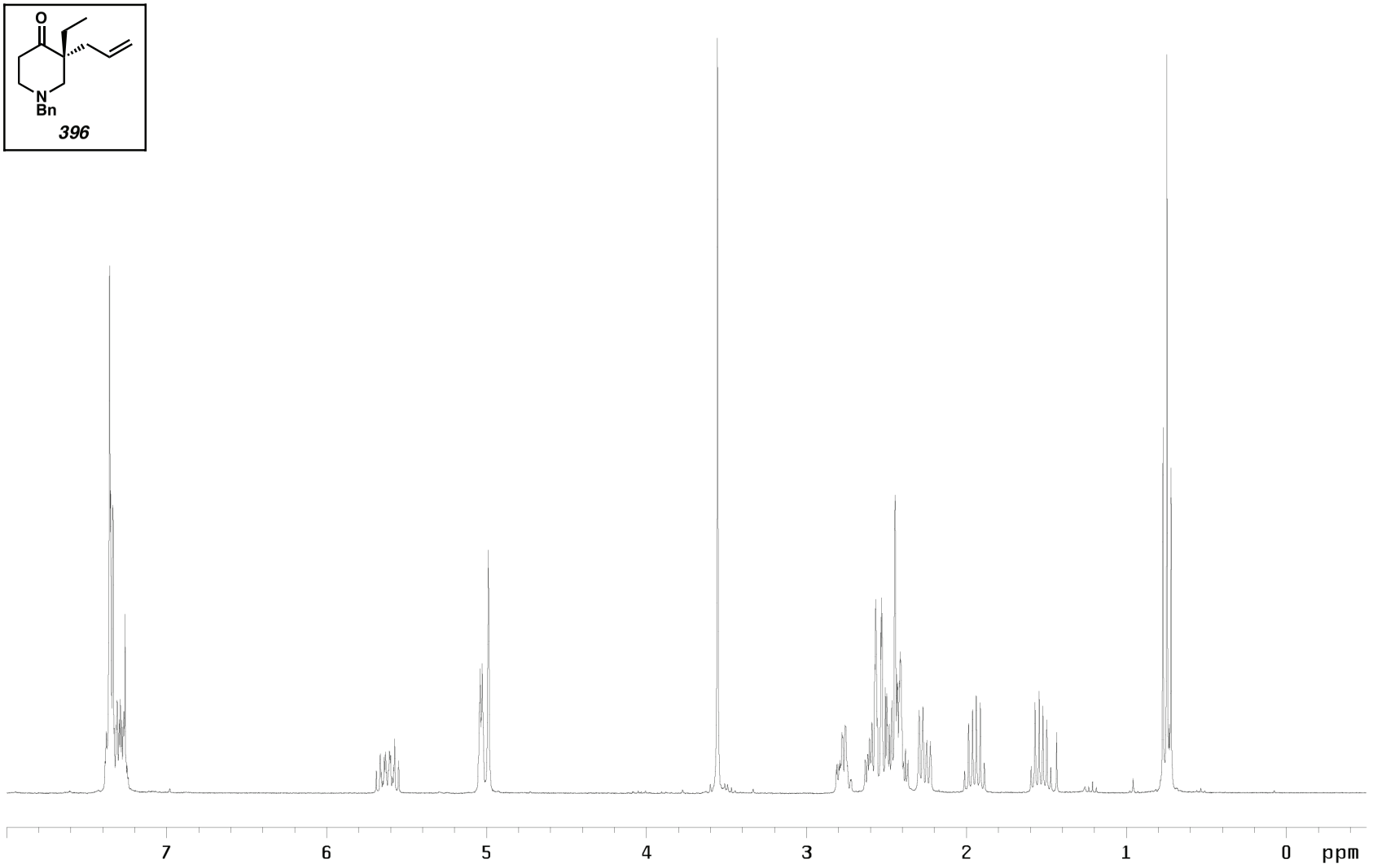


Figure A7.325 ^{1}H NMR of compound **396** (300 MHz, $CDCl_3$)

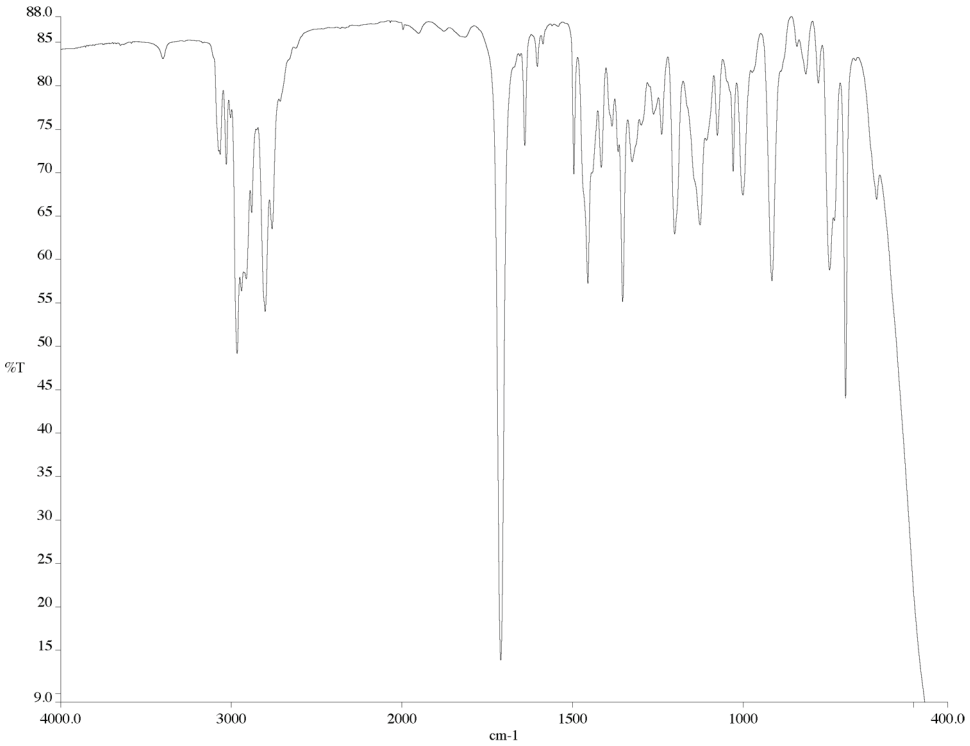


Figure A7.326 IR of compound **396** (NaCl/film)

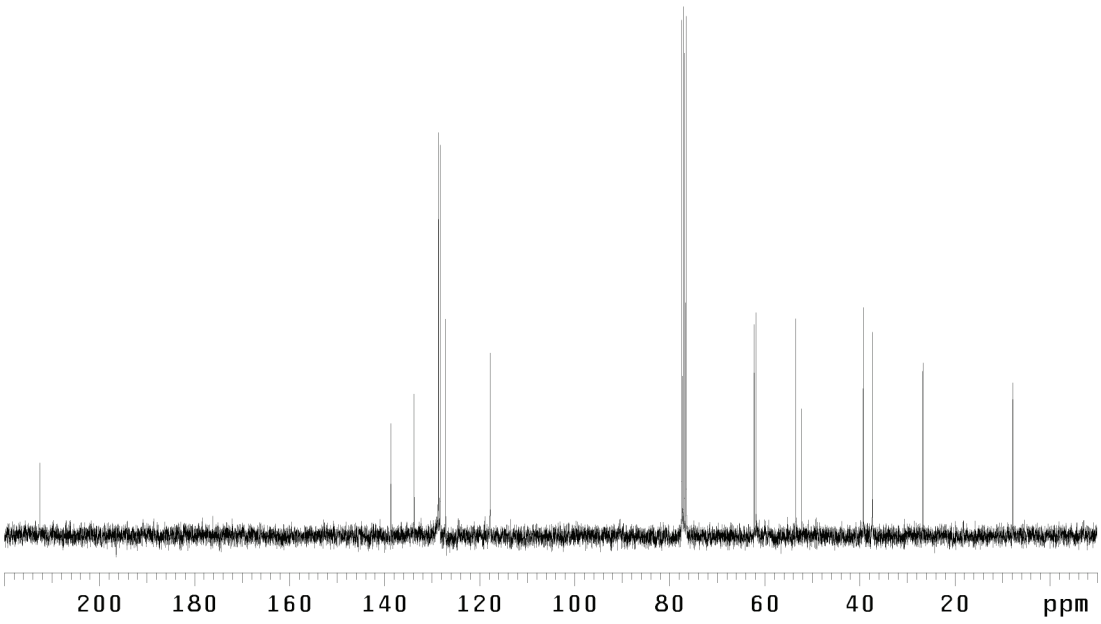


Figure A7.327 ^{13}C NMR of compound **396** (75 MHz, $CDCl_3$)

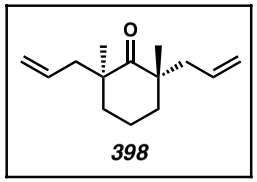


Figure A7.328 ^{1}H NMR of compound **398** (300 MHz, $CDCl_3$)

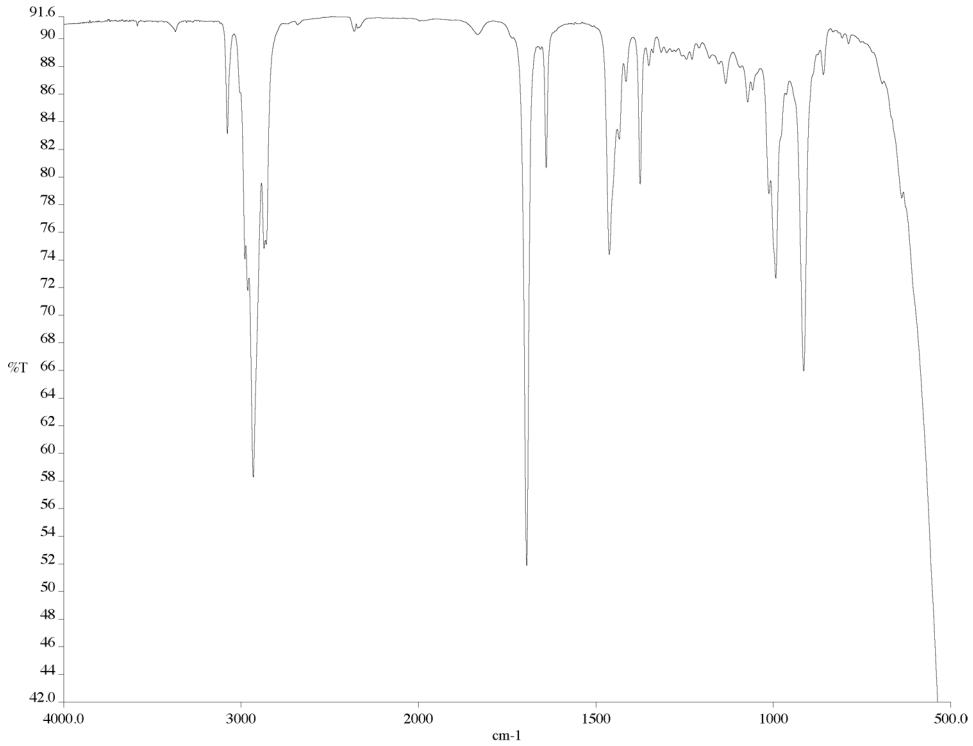


Figure A7.329 IR of compound **398** (NaCl/film)

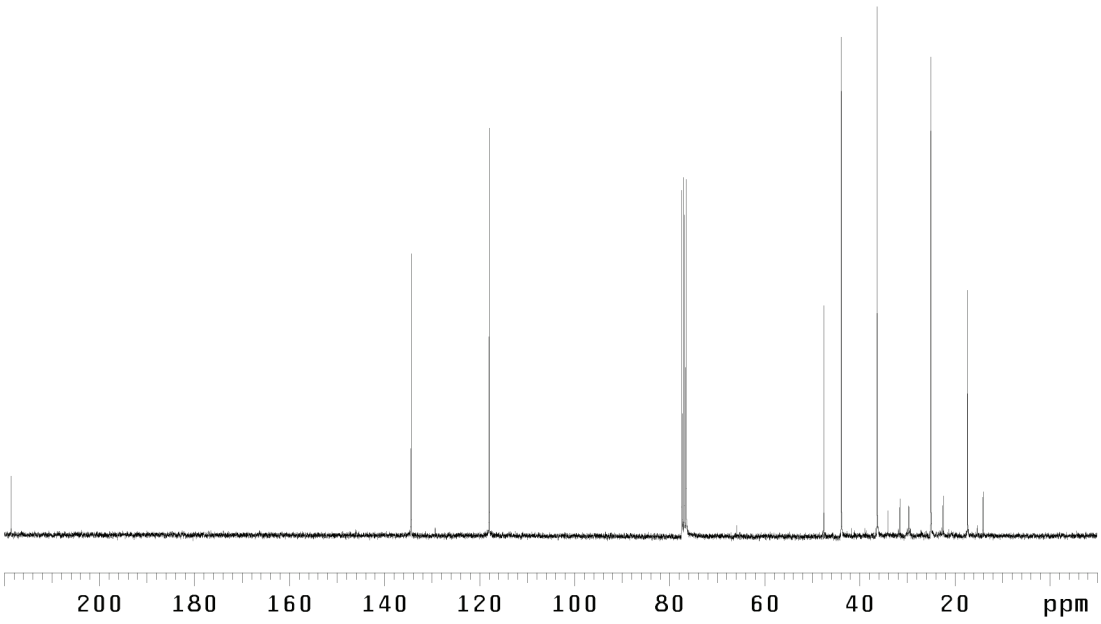


Figure A7.330 ^{13}C NMR of compound **398** (75 MHz, $CDCl_3$)

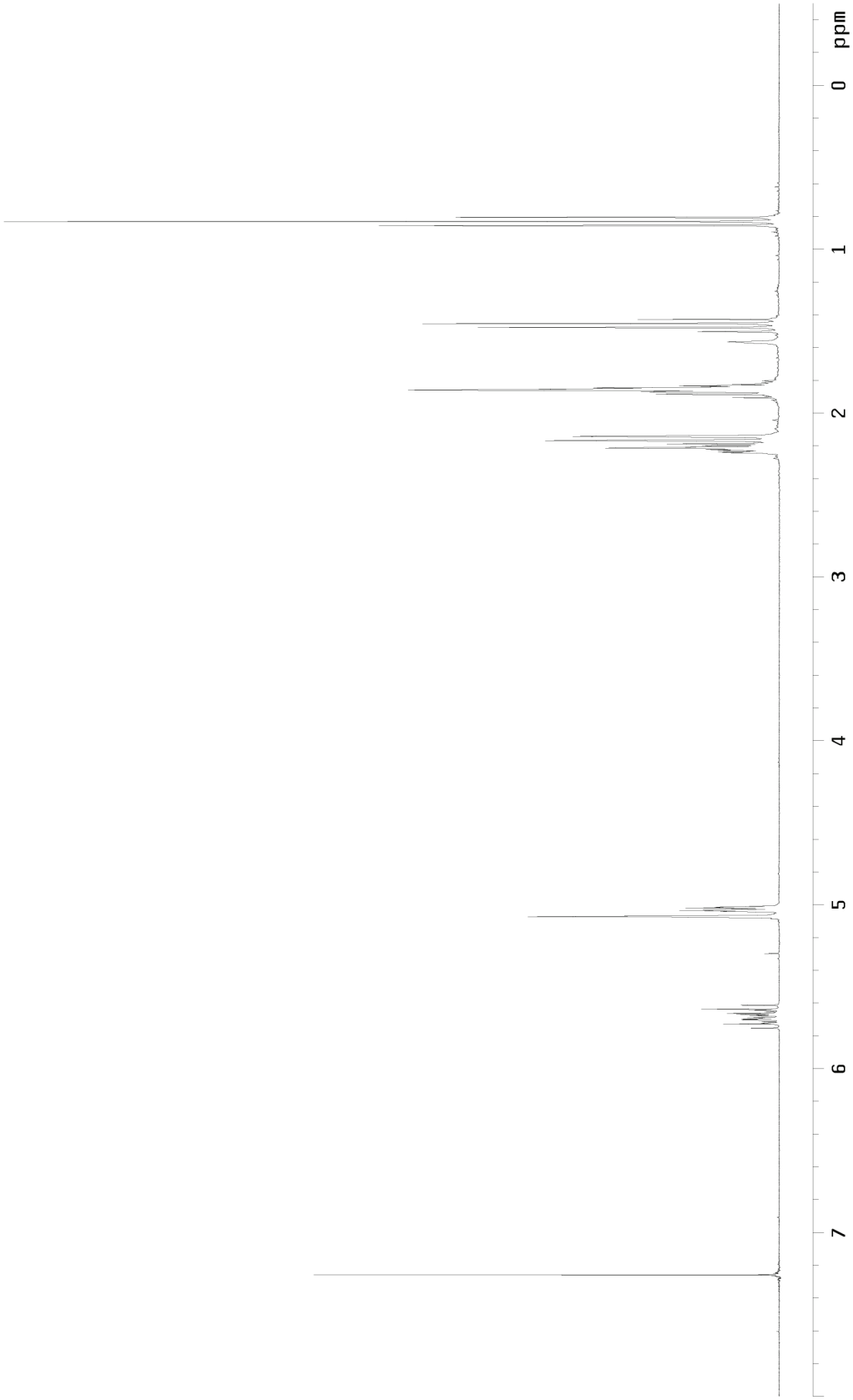


Figure A7.331 ^{1}H NMR of compound **407** (300 MHz, $CDCl_3$)

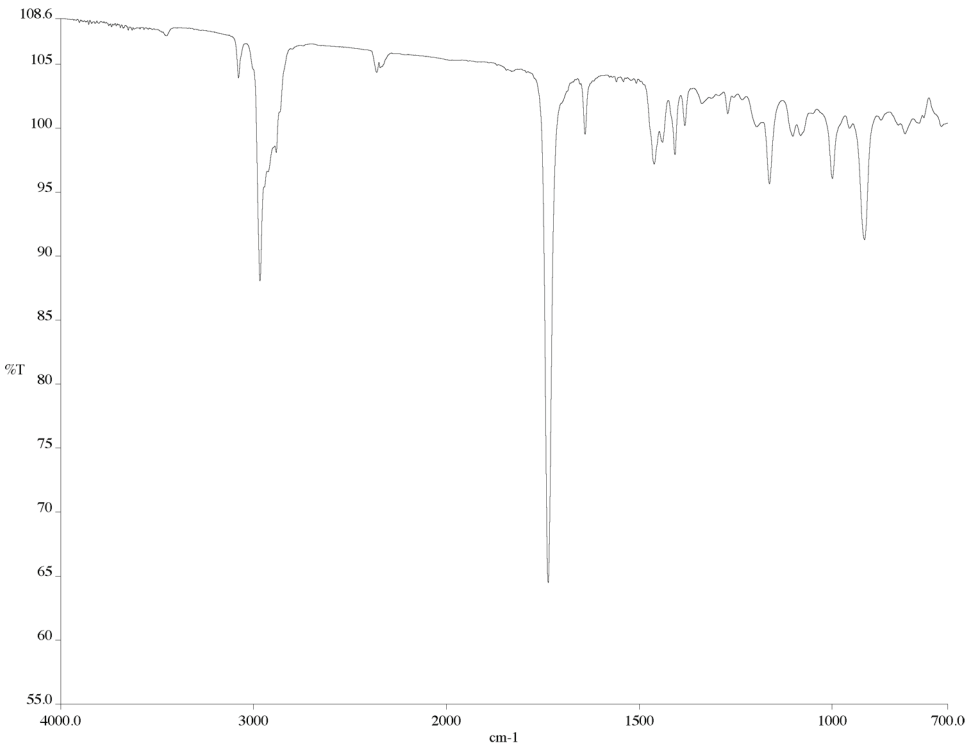


Figure A7.332 IR of compound **407** (NaCl/film)

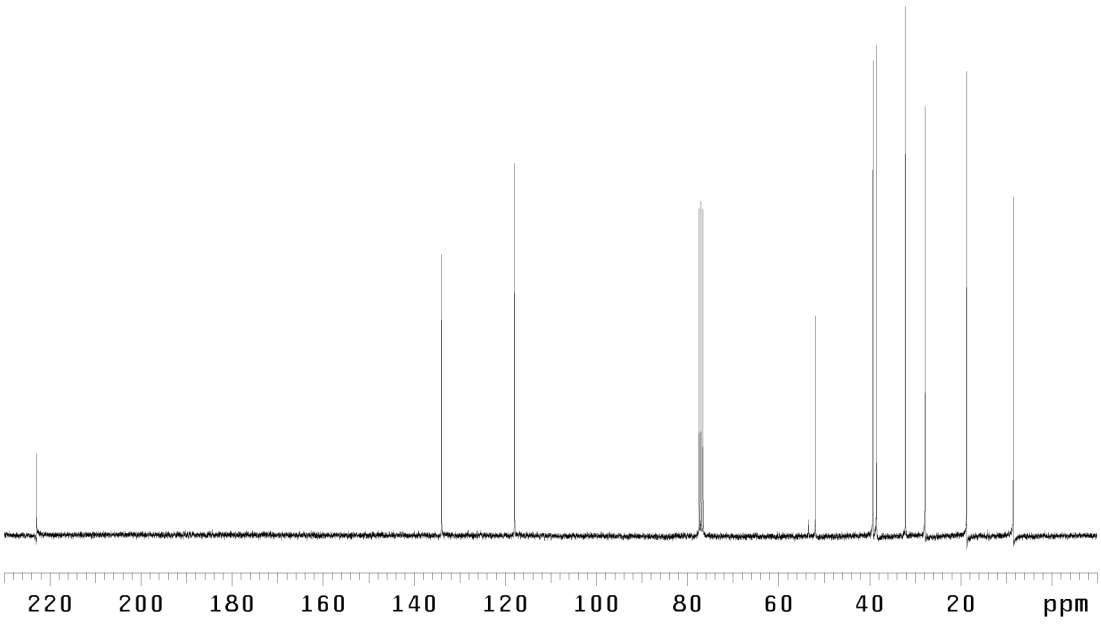


Figure A7.333 ^{13}C NMR of compound **407** (75 MHz, $CDCl_3$)

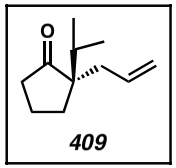


Figure A7.334 ^{1}H NMR of compound **409** (300 MHz, $CDCl_3$)

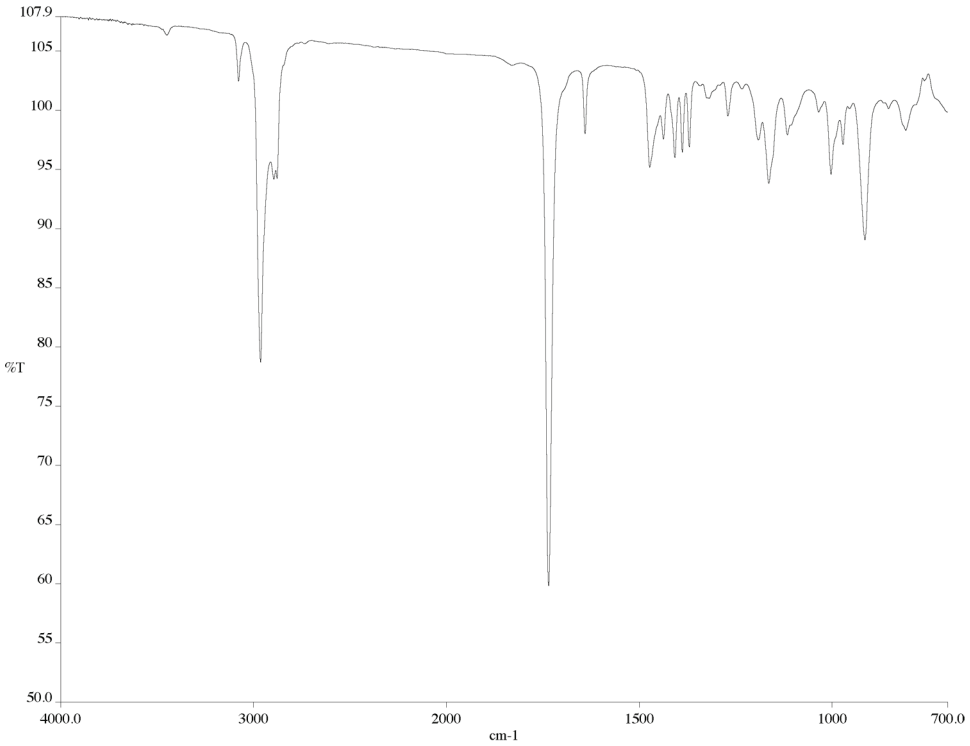


Figure A7.335 IR of compound **409** (NaCl/film)

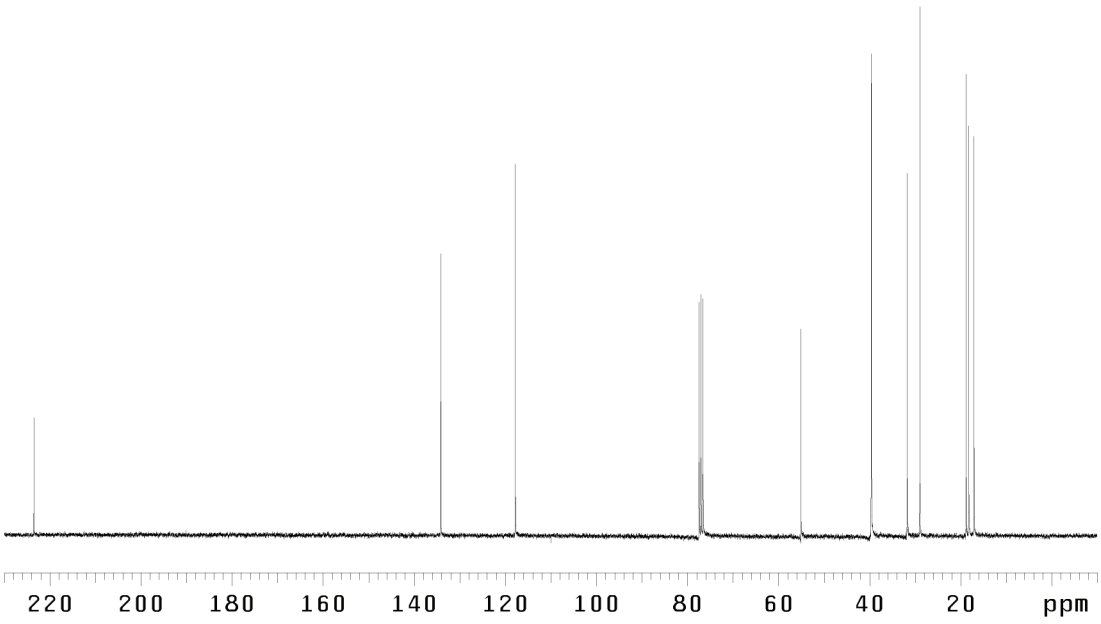


Figure A7.336 ^{13}C NMR of compound **409** (75 MHz, $CDCl_3$)

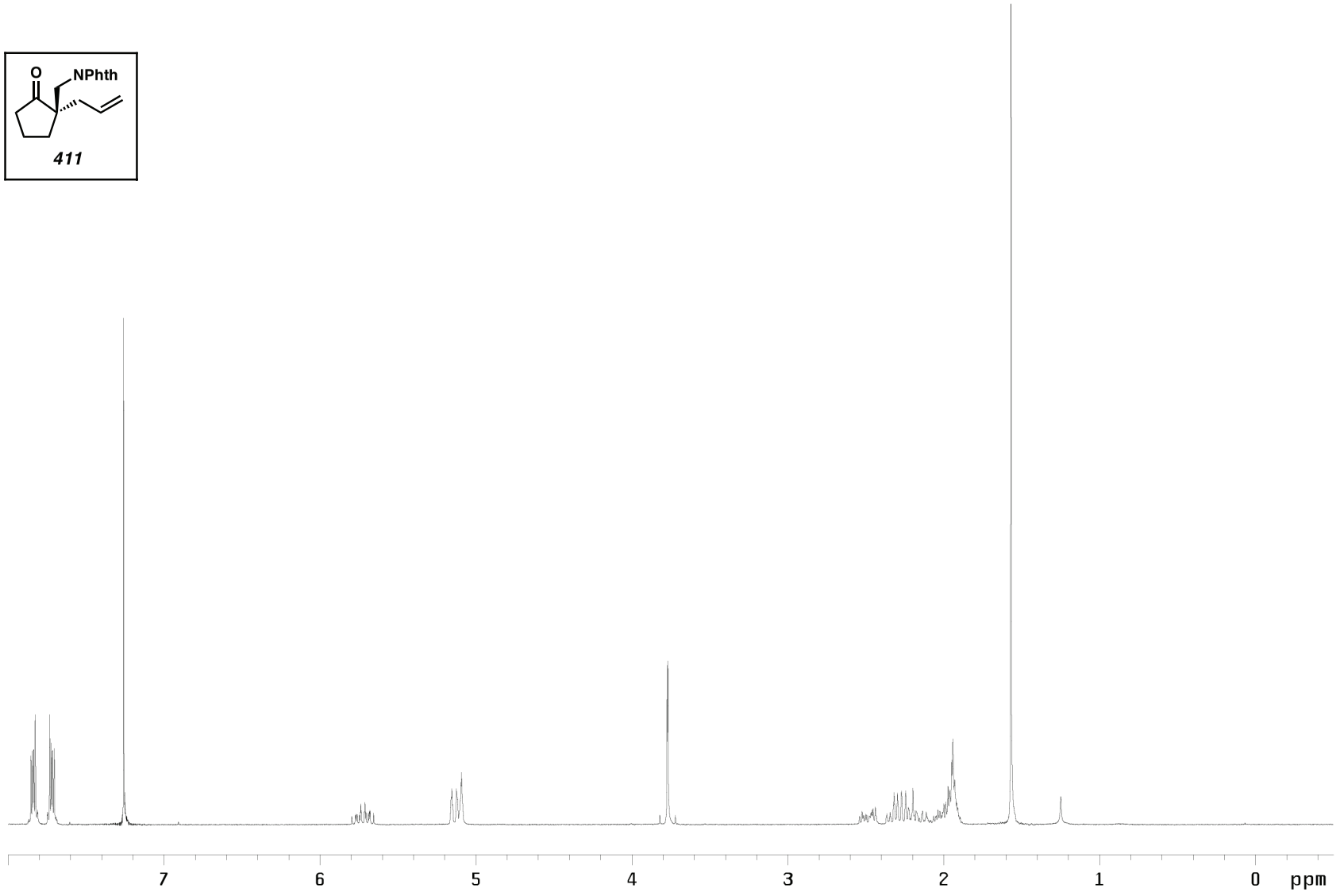


Figure A7.337 ^{1}H NMR of compound **411** (300 MHz, $CDCl_3$)

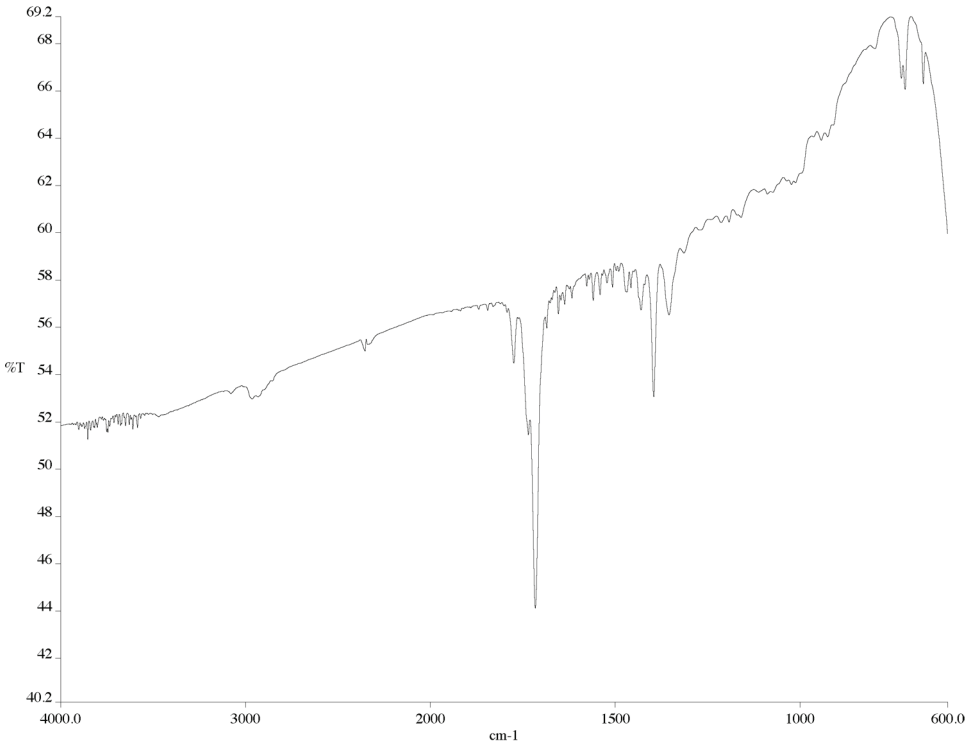


Figure A7.338 IR of compound **411** (NaCl/film)

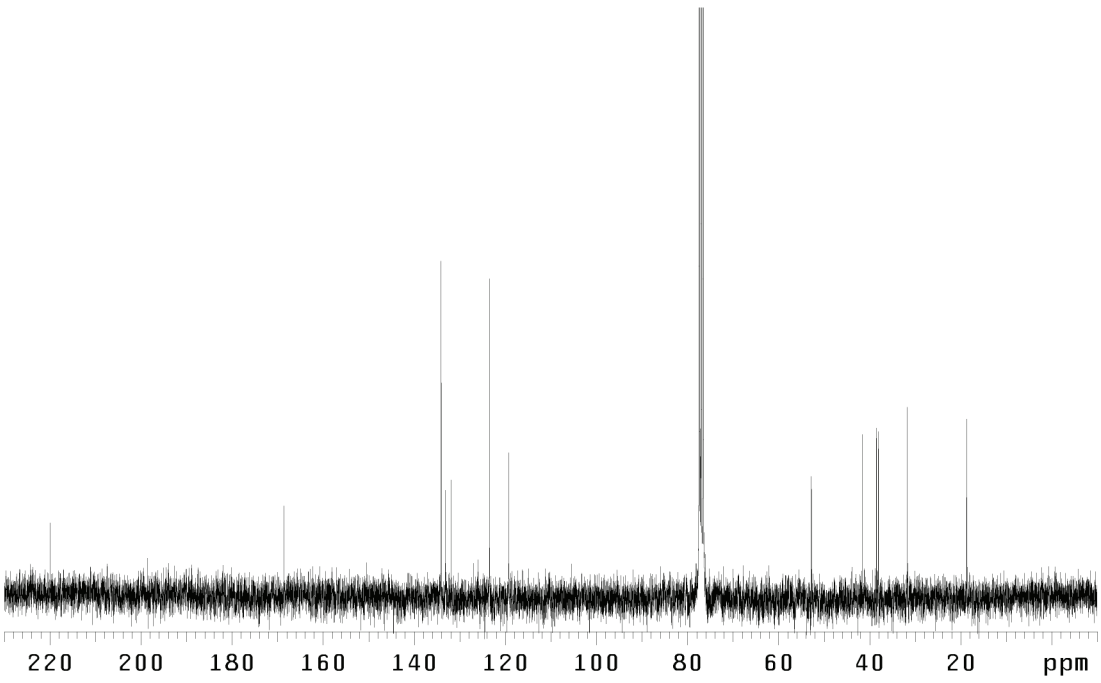


Figure A7.339 ^{13}C NMR of compound **411** (75 MHz, $CDCl_3$)

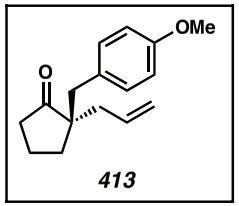


Figure A7.340 ^{1}H NMR of compound **413** (300 MHz, $CDCl_3$)

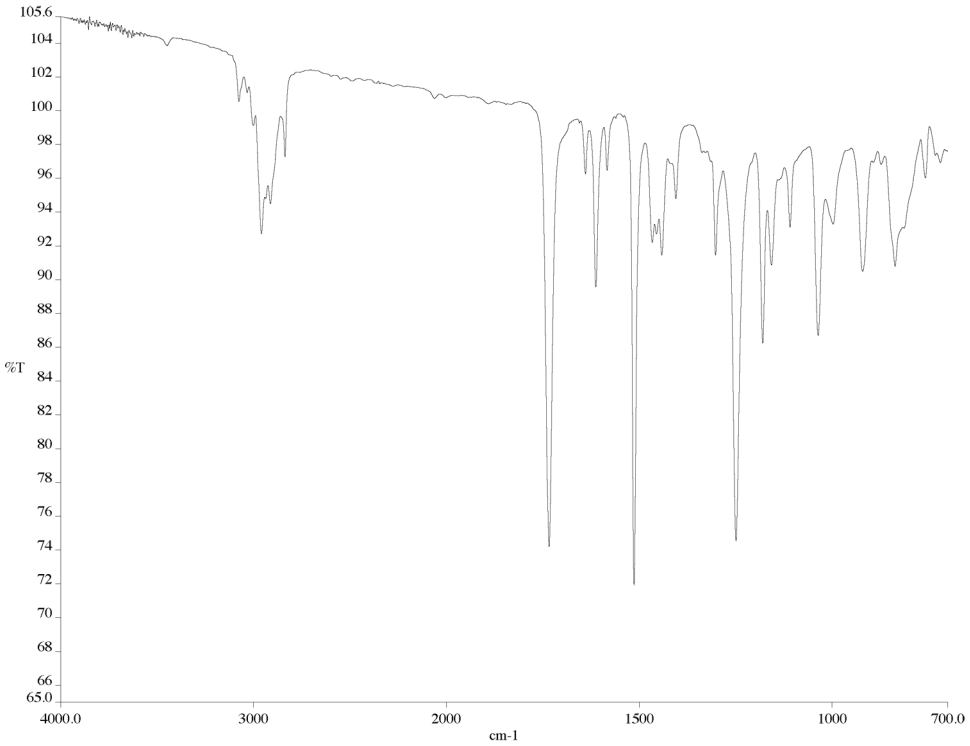


Figure A7.341 IR of compound **413** (NaCl/film)

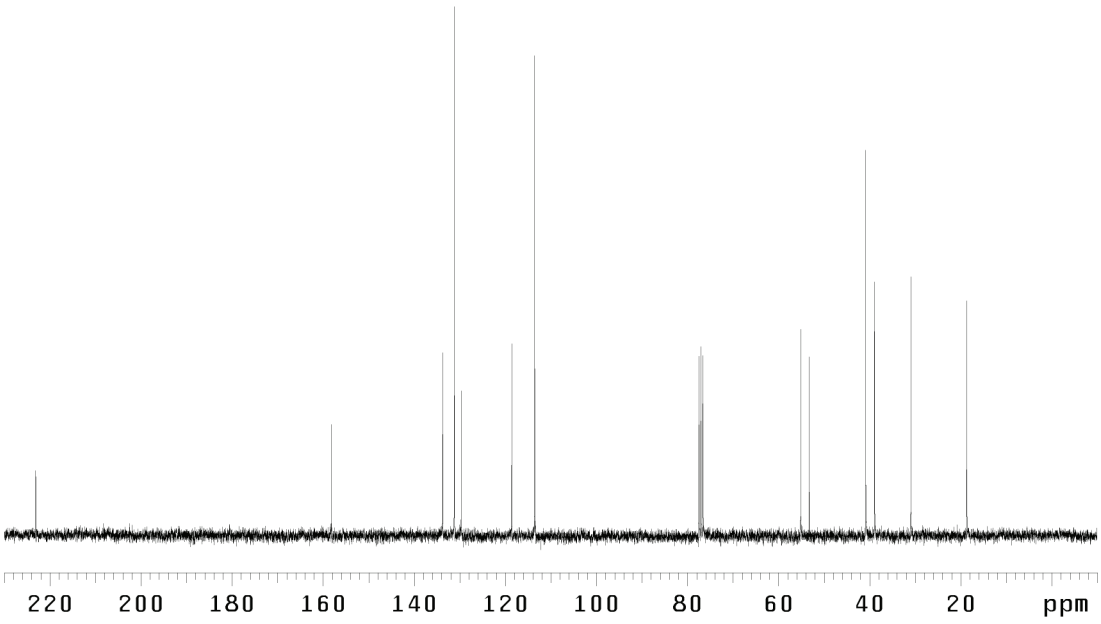


Figure A7.342 ^{13}C NMR of compound **413** (75 MHz, $CDCl_3$)

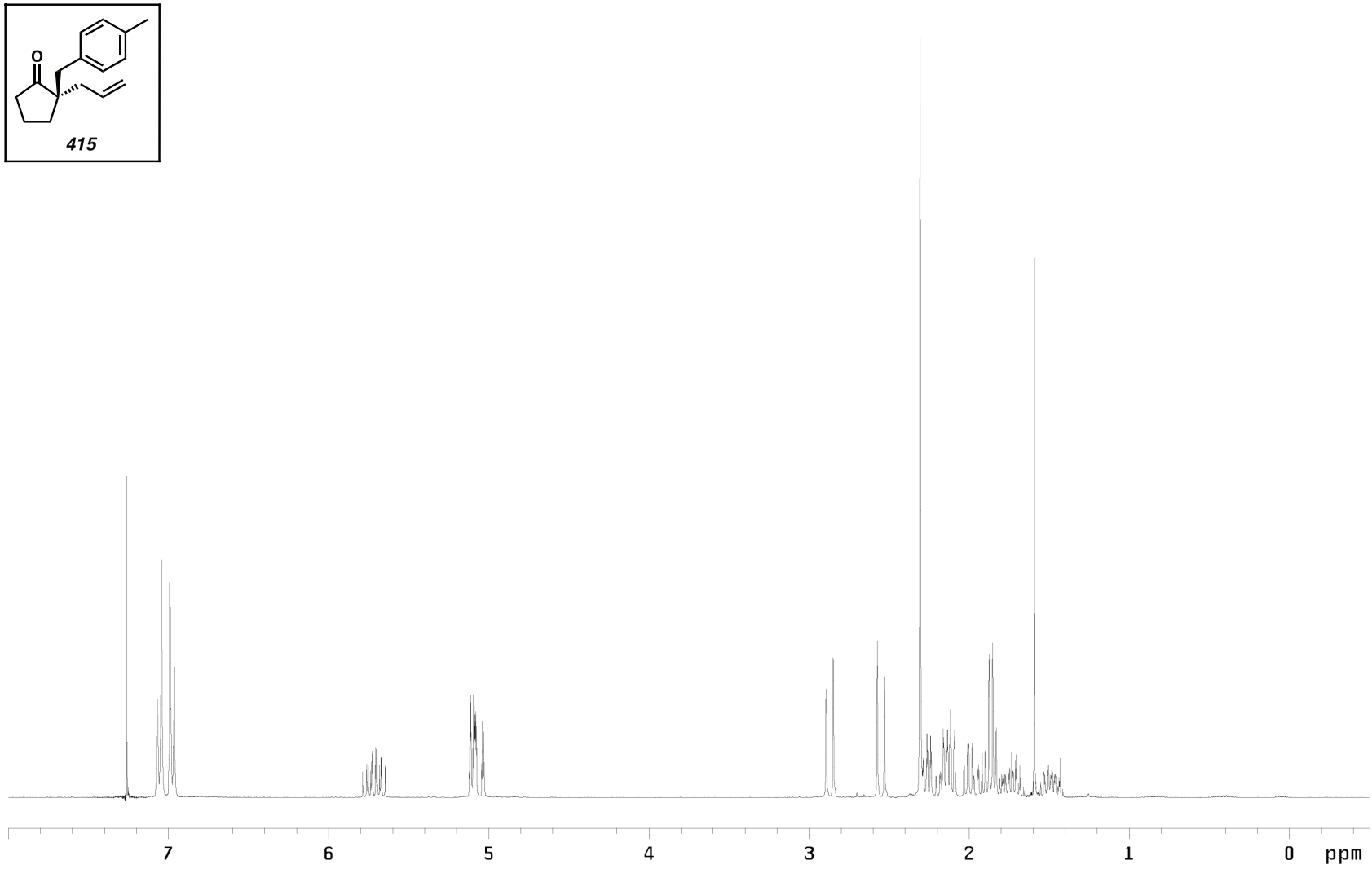


Figure A7.343 ^{1}H NMR of compound **415** (300 MHz, $CDCl_3$)

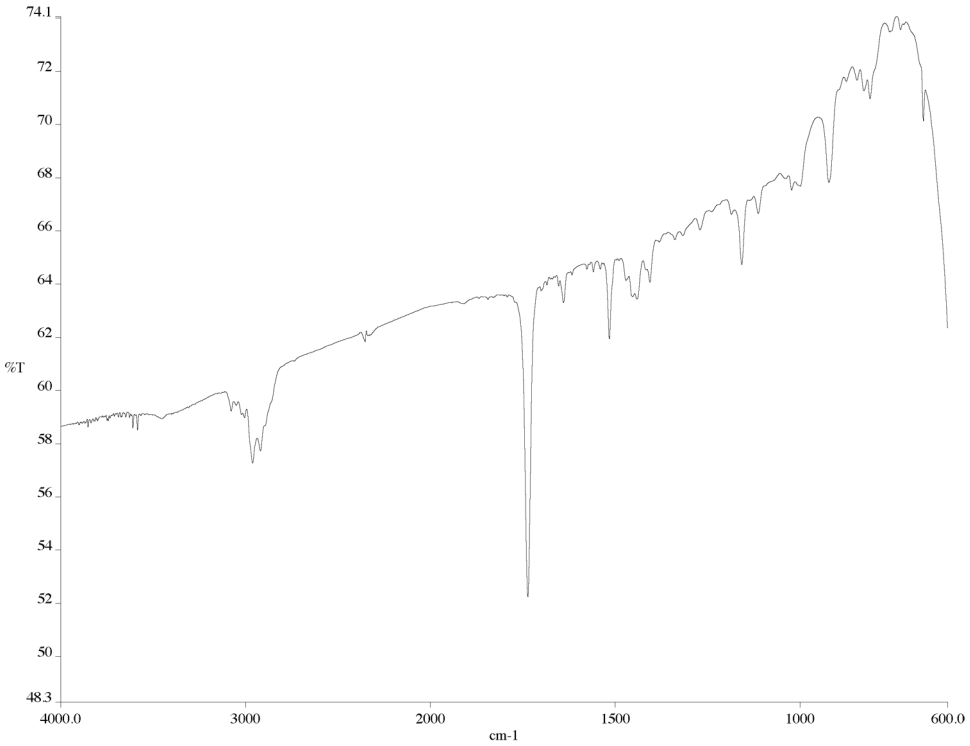


Figure A7.344 IR of compound **415** (NaCl/film)

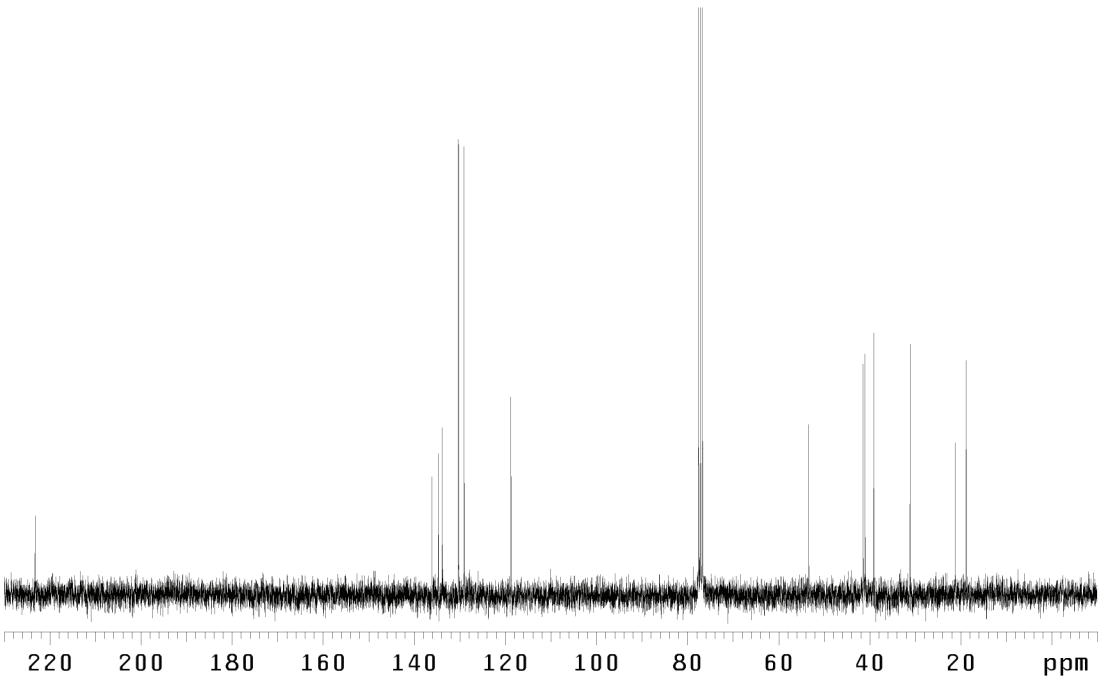


Figure A7.345 ^{13}C NMR of compound **415** (75 MHz, $CDCl_3$)

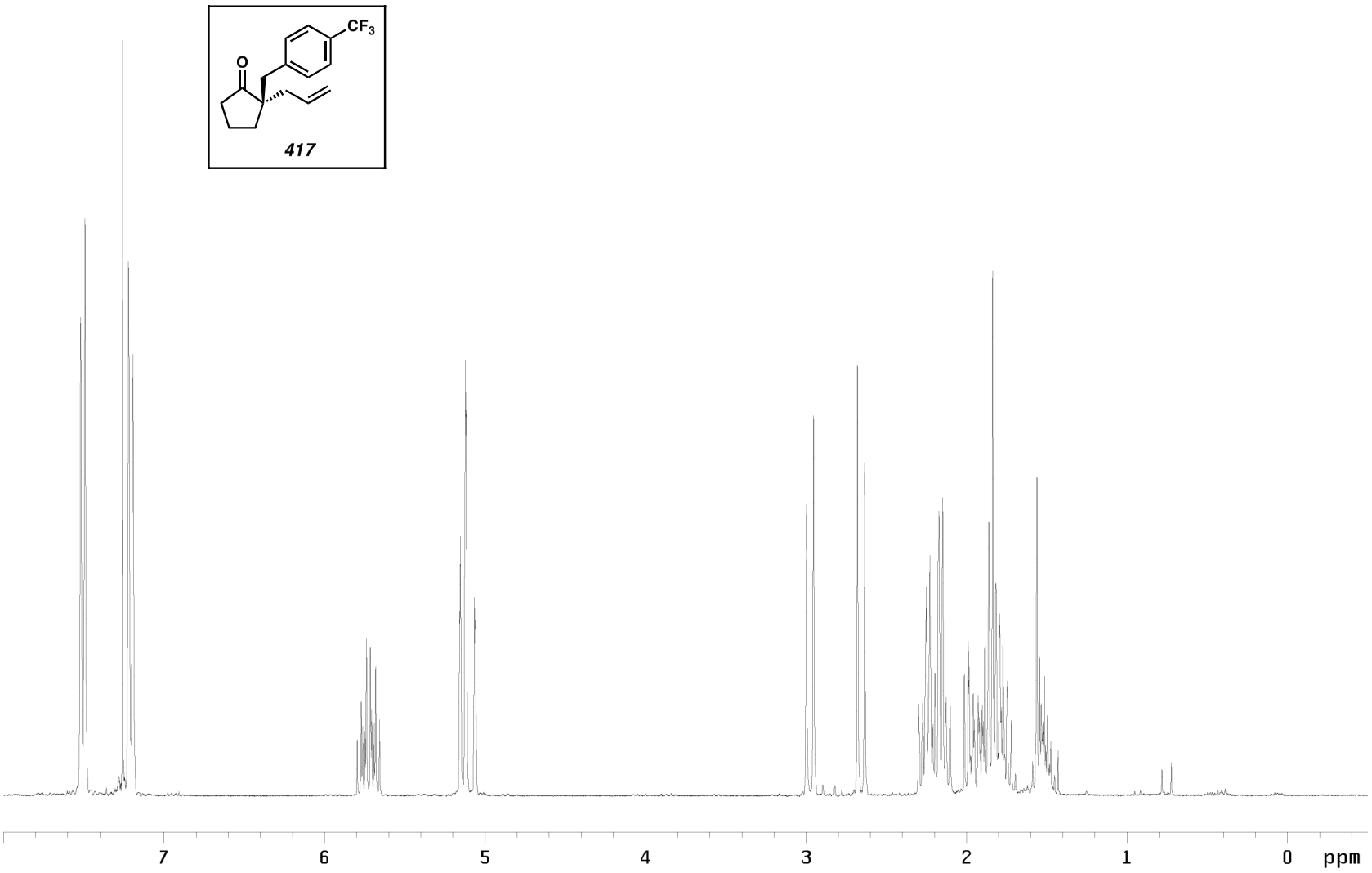


Figure A7.346 ^{1}H NMR of compound **417** (300 MHz, $CDCl_3$)

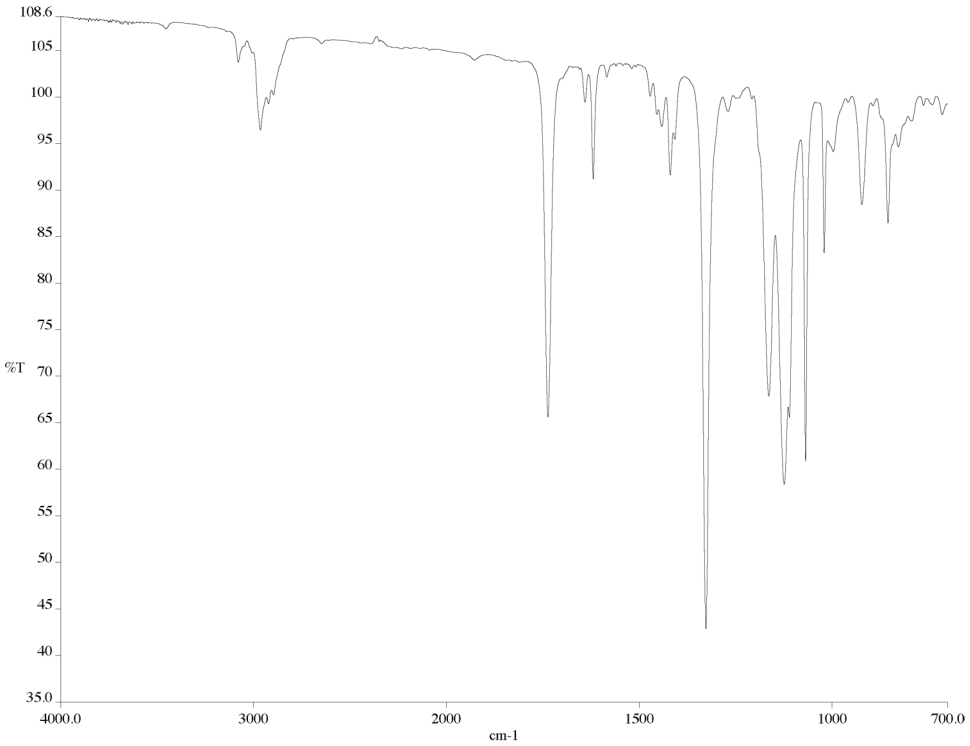


Figure A7.347 IR of compound **417** (NaCl/film)

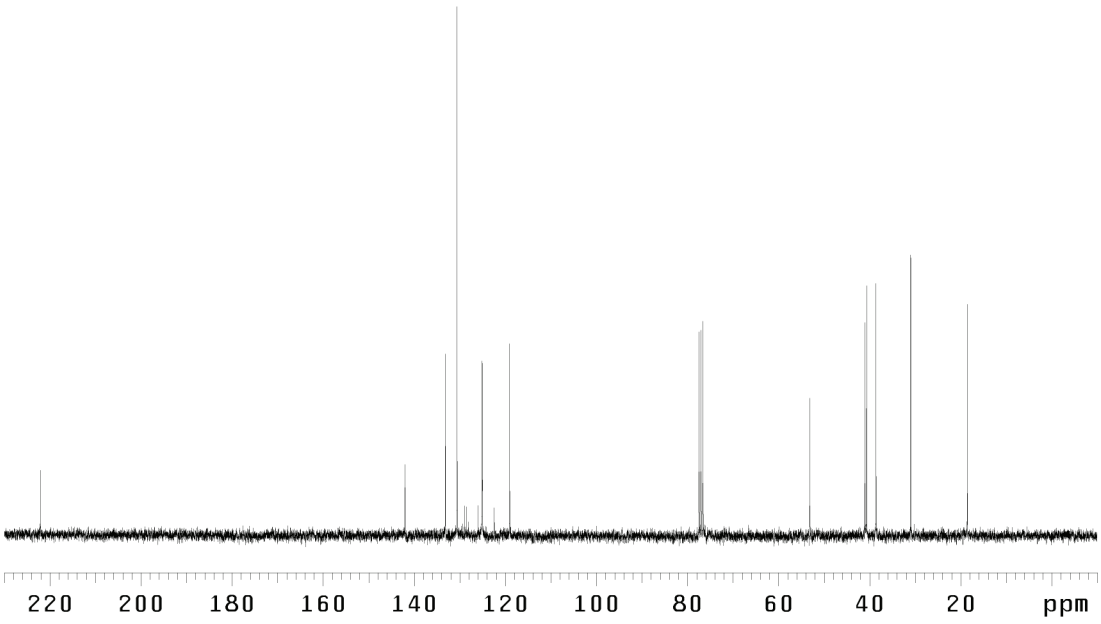


Figure A7.348 ^{13}C NMR of compound **417** (75 MHz, $CDCl_3$)

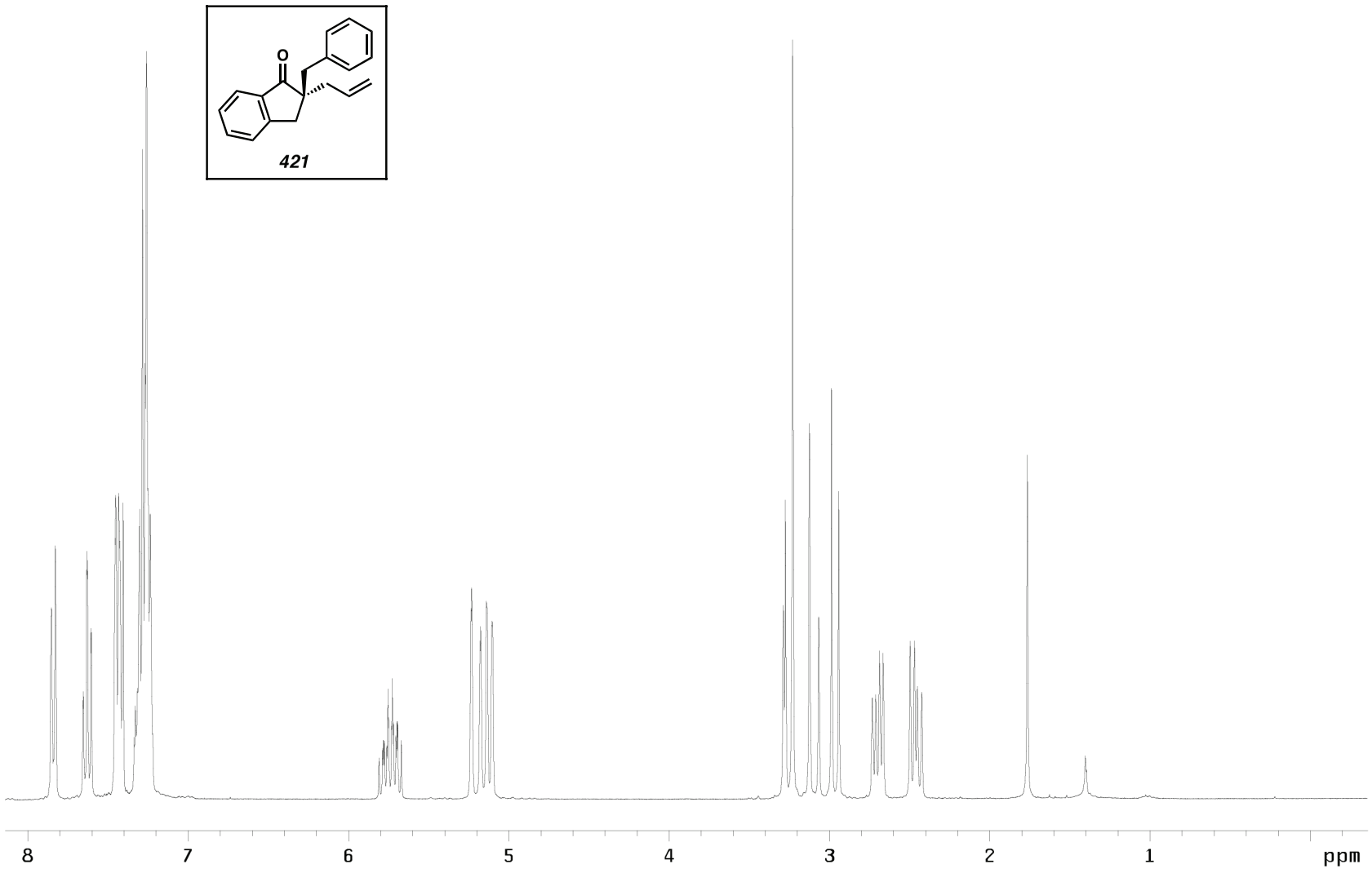


Figure A7.349 ^{1}H NMR of compound **421** (300 MHz, $CDCl_3$)

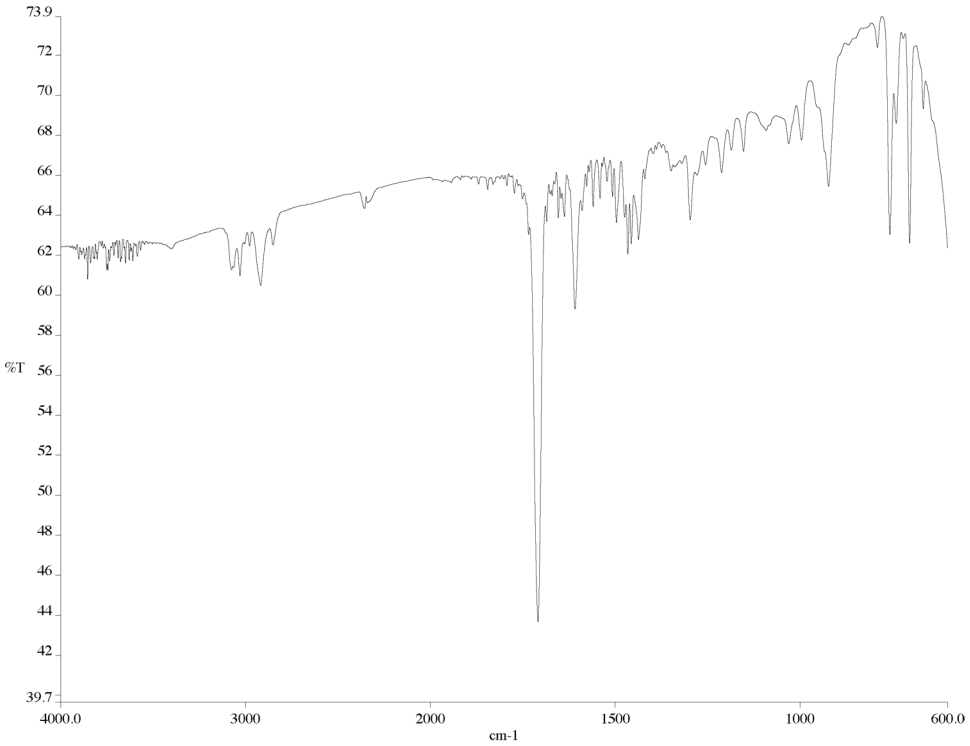


Figure A7.350 IR of compound **421** (NaCl/film)

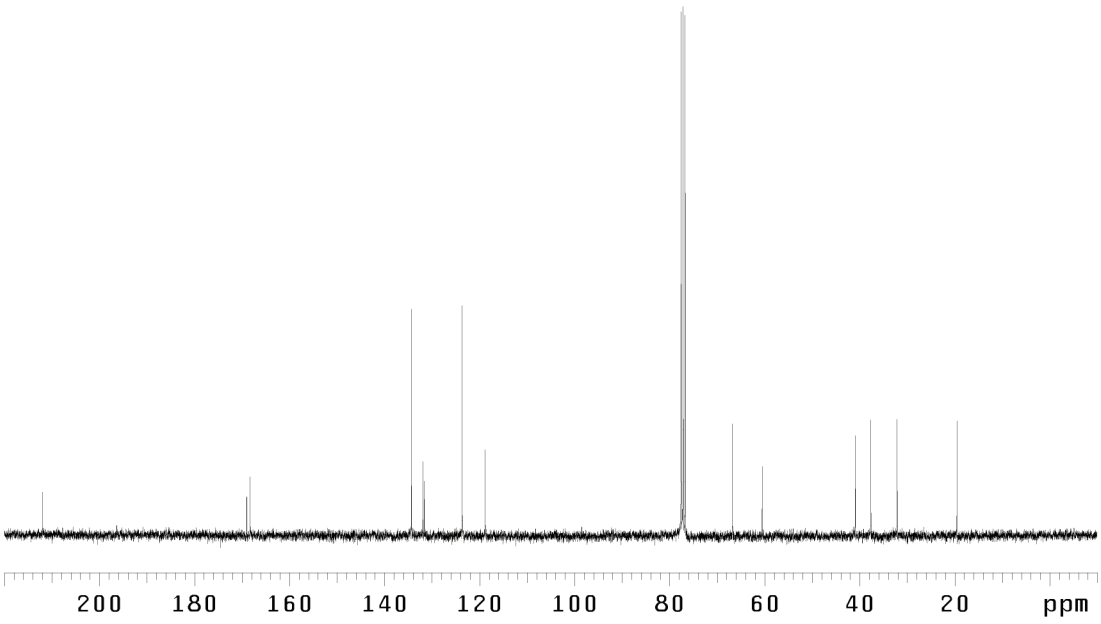


Figure A7.351 ^{13}C NMR of compound **421** (75 MHz, $CDCl_3$)

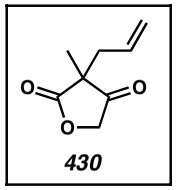


Figure A7.352 ^{1}H NMR of compound **430** (300 MHz, $CDCl_3$)

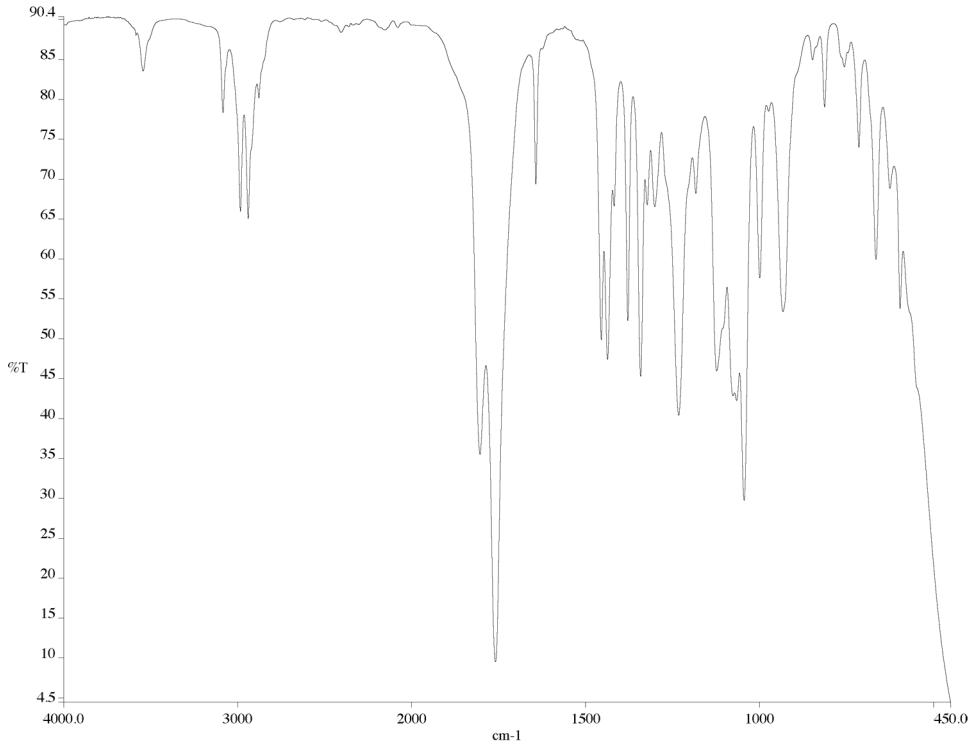


Figure A7.353 IR of compound **430** (NaCl/film)

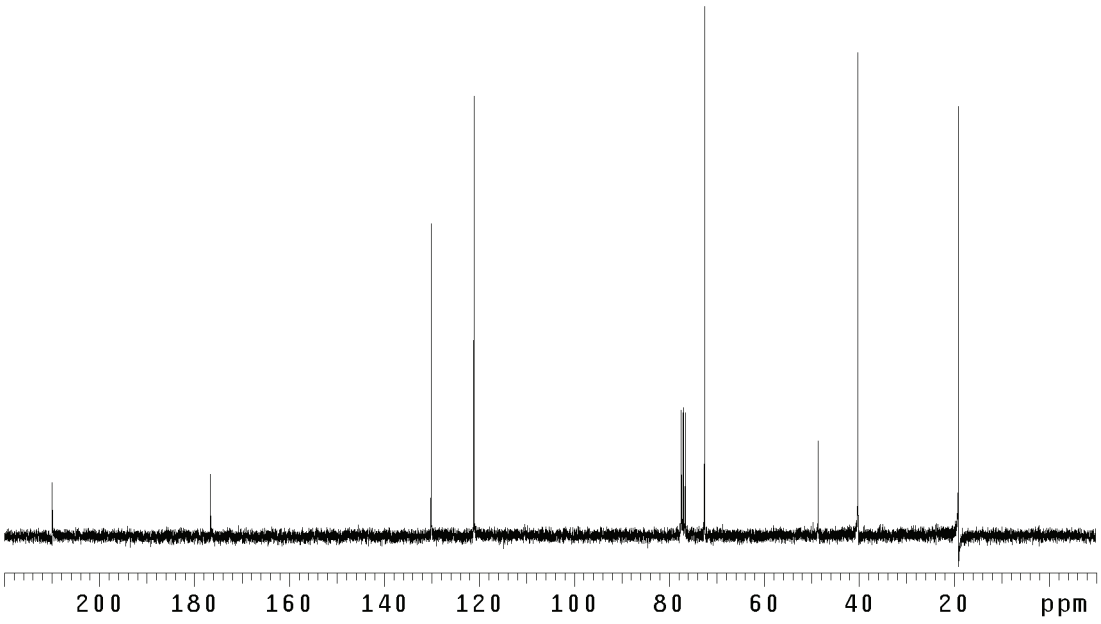


Figure A7.354 ^{13}C NMR of compound **430** (75 MHz, $CDCl_3$)

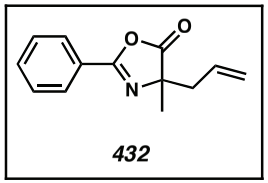


Figure A7.355 ^{1}H NMR of compound **432** (300 MHz, $CDCl_3$)

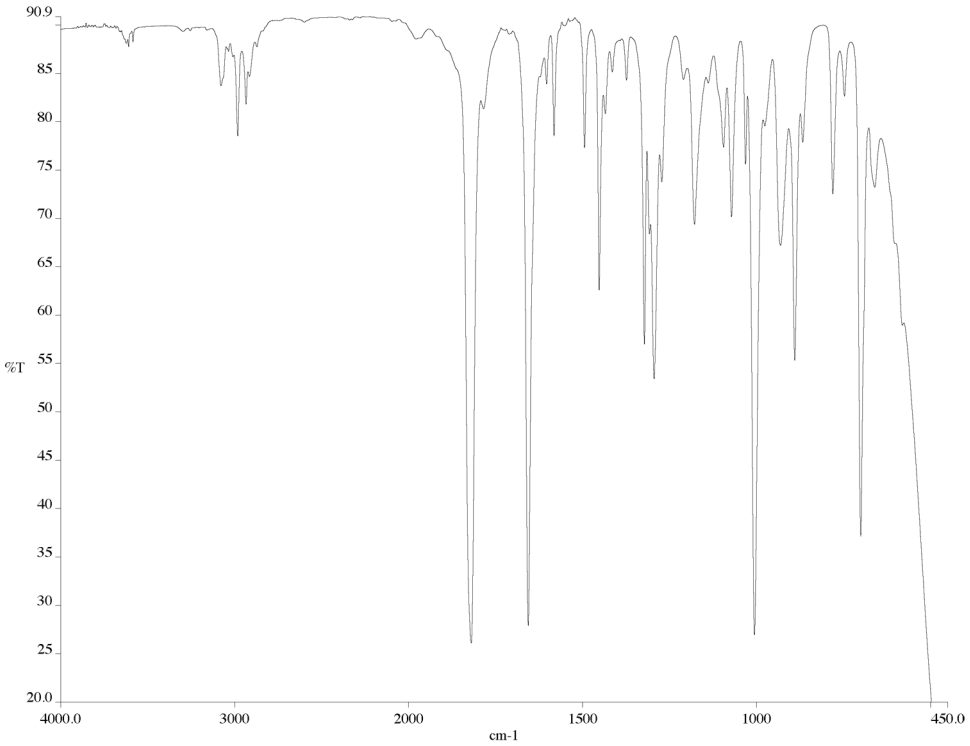


Figure A7.356 IR of compound **432** (NaCl/film)

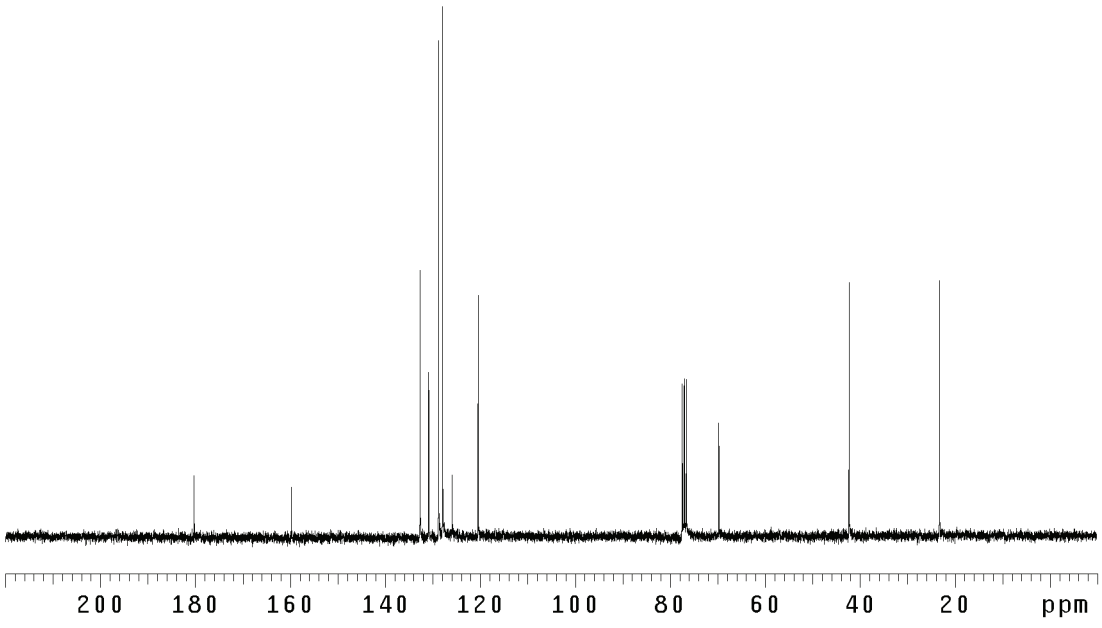


Figure A7.357 ^{13}C NMR of compound **432** (75 MHz, $CDCl_3$)

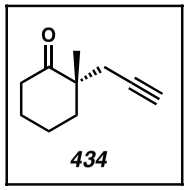


Figure A7.358 ^{1}H NMR of compound **434** (300 MHz, $CDCl_3$)

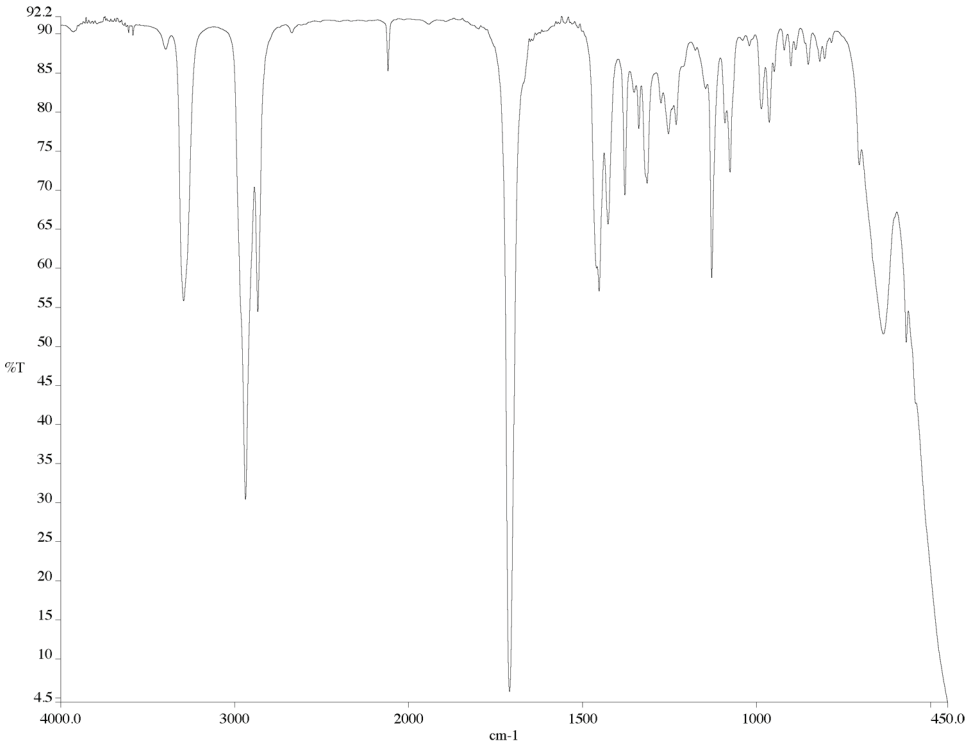


Figure A7.359 IR of compound **434** (NaCl/film)

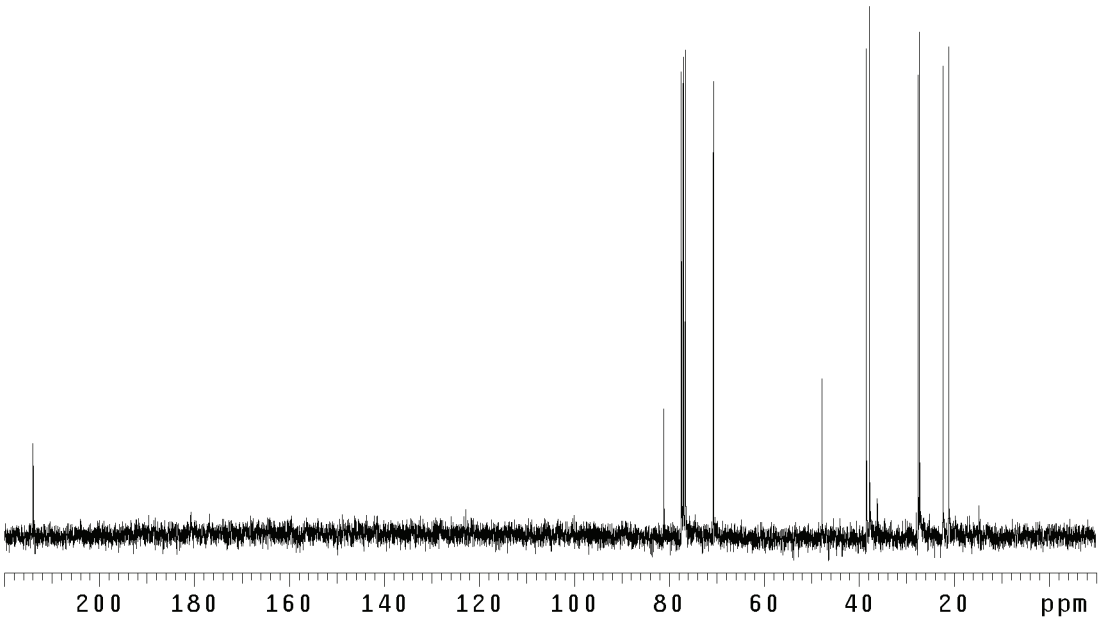


Figure A7.360 ^{13}C NMR of compound **434** (75 MHz, $CDCl_3$)

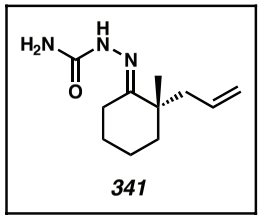


Figure A7.361 ^{1}H NMR of compound **341** (300 MHz, $CDCl_3$)

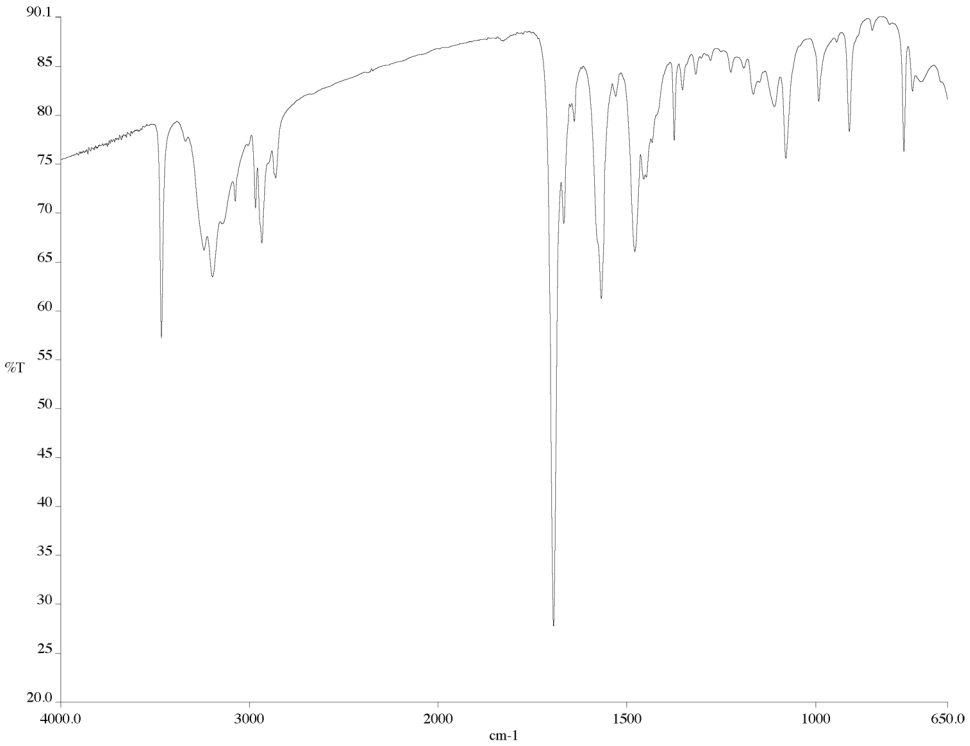


Figure A7.362 IR of compound **341** (NaCl/film)

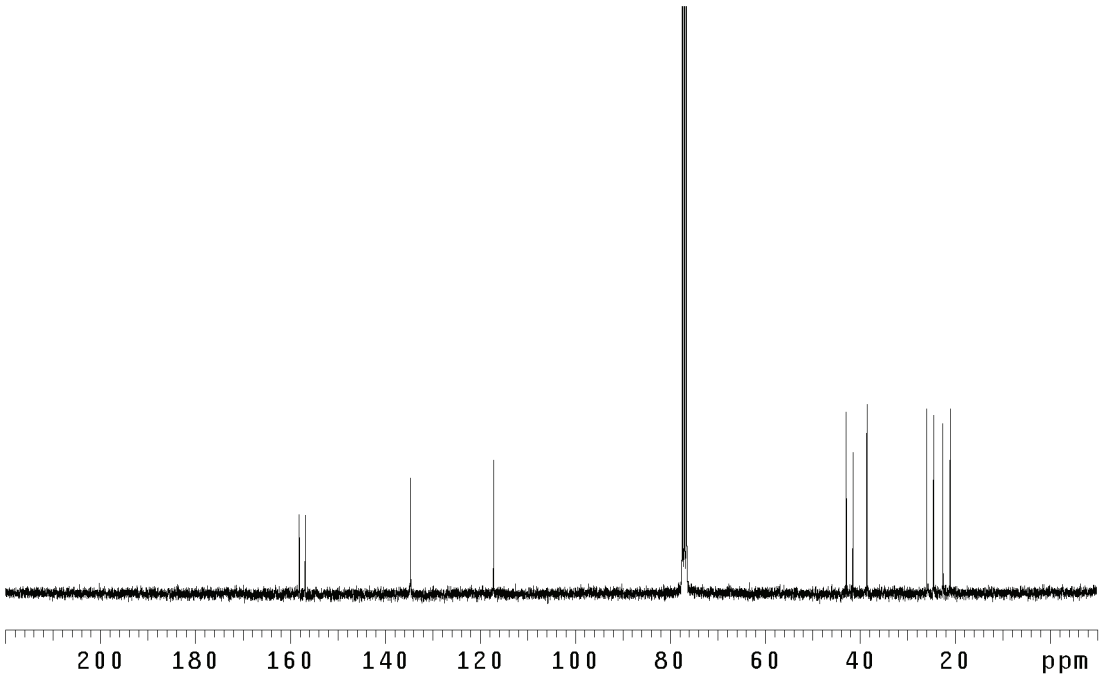


Figure A7.363 ^{13}C NMR of compound **341** (75 MHz, $CDCl_3$)

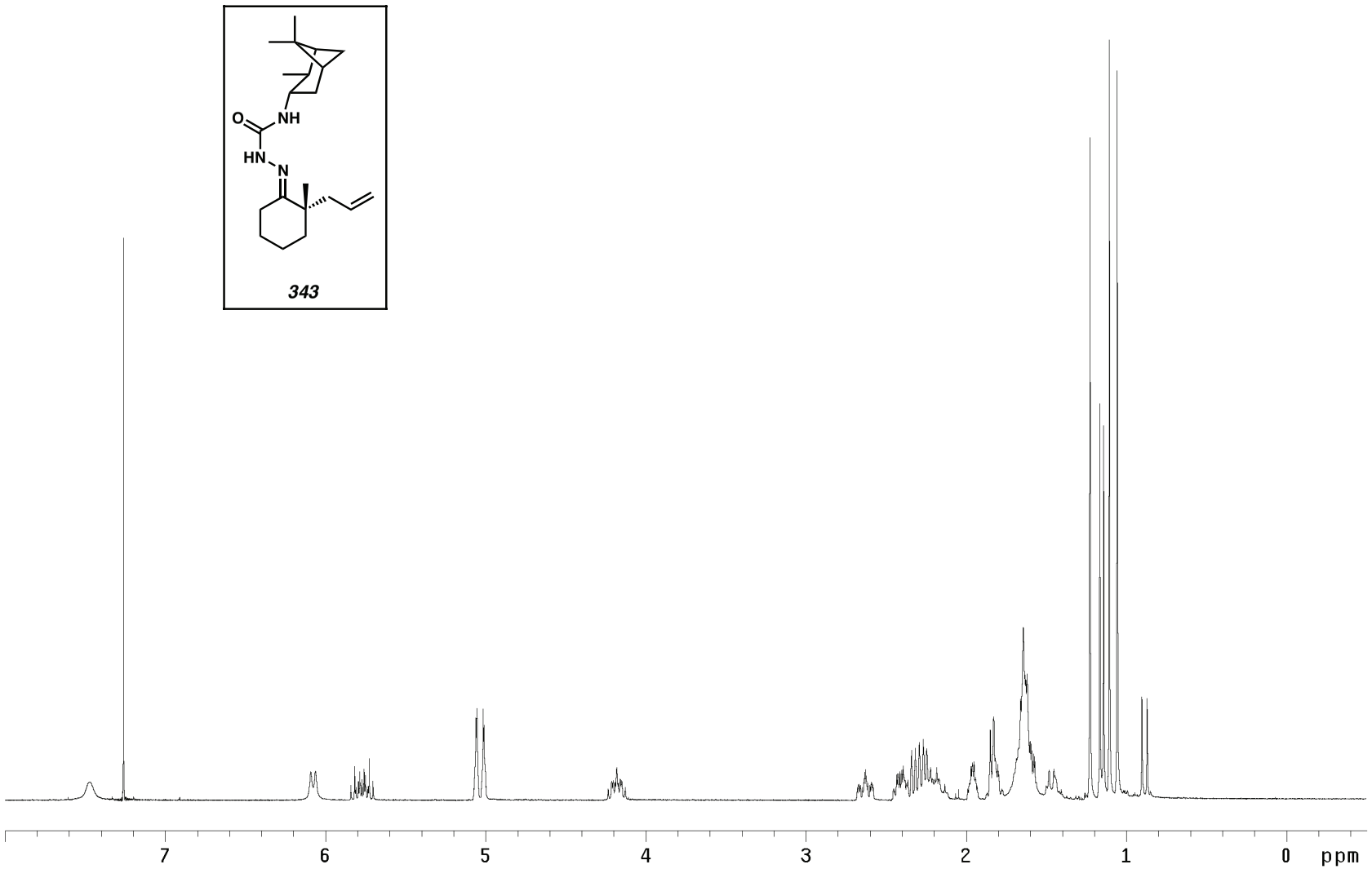


Figure A7.364 ^{1}H NMR of compound **343** (300 MHz, $CDCl_3$)

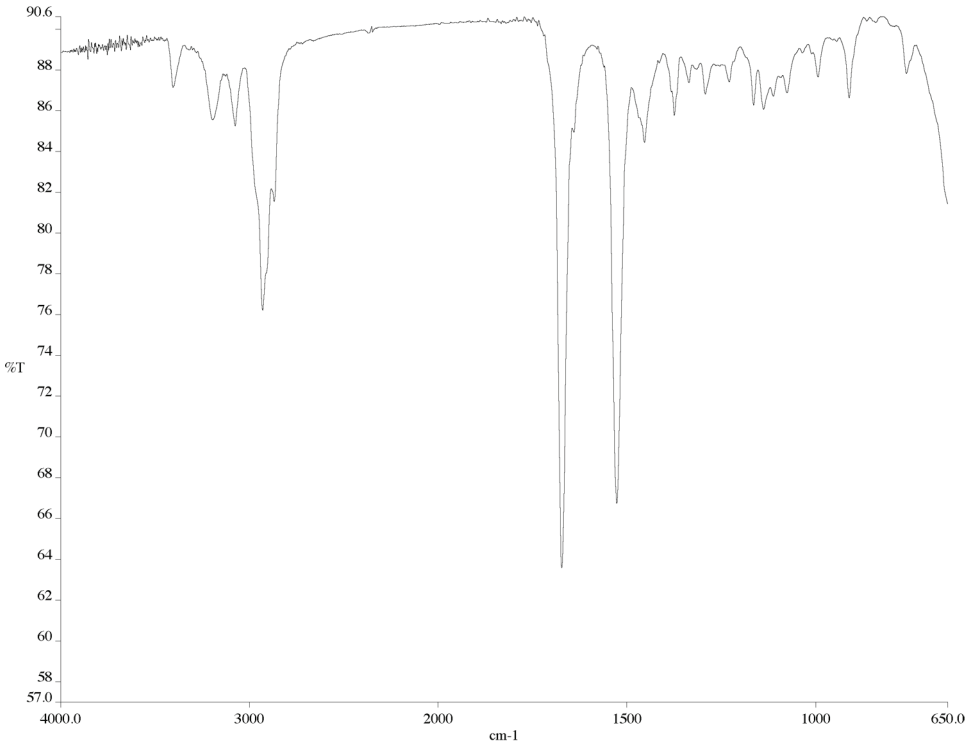


Figure A7.365 IR of compound **343** (NaCl/film)

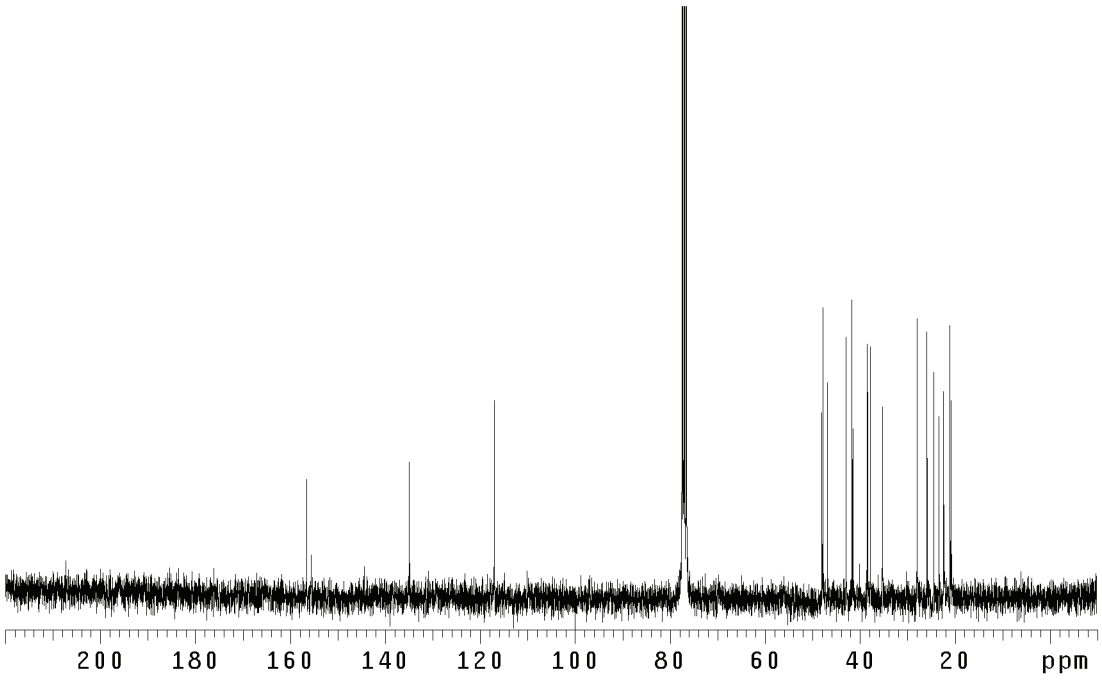


Figure A7.366 ^{13}C NMR of compound **343** (75 MHz, $CDCl_3$)

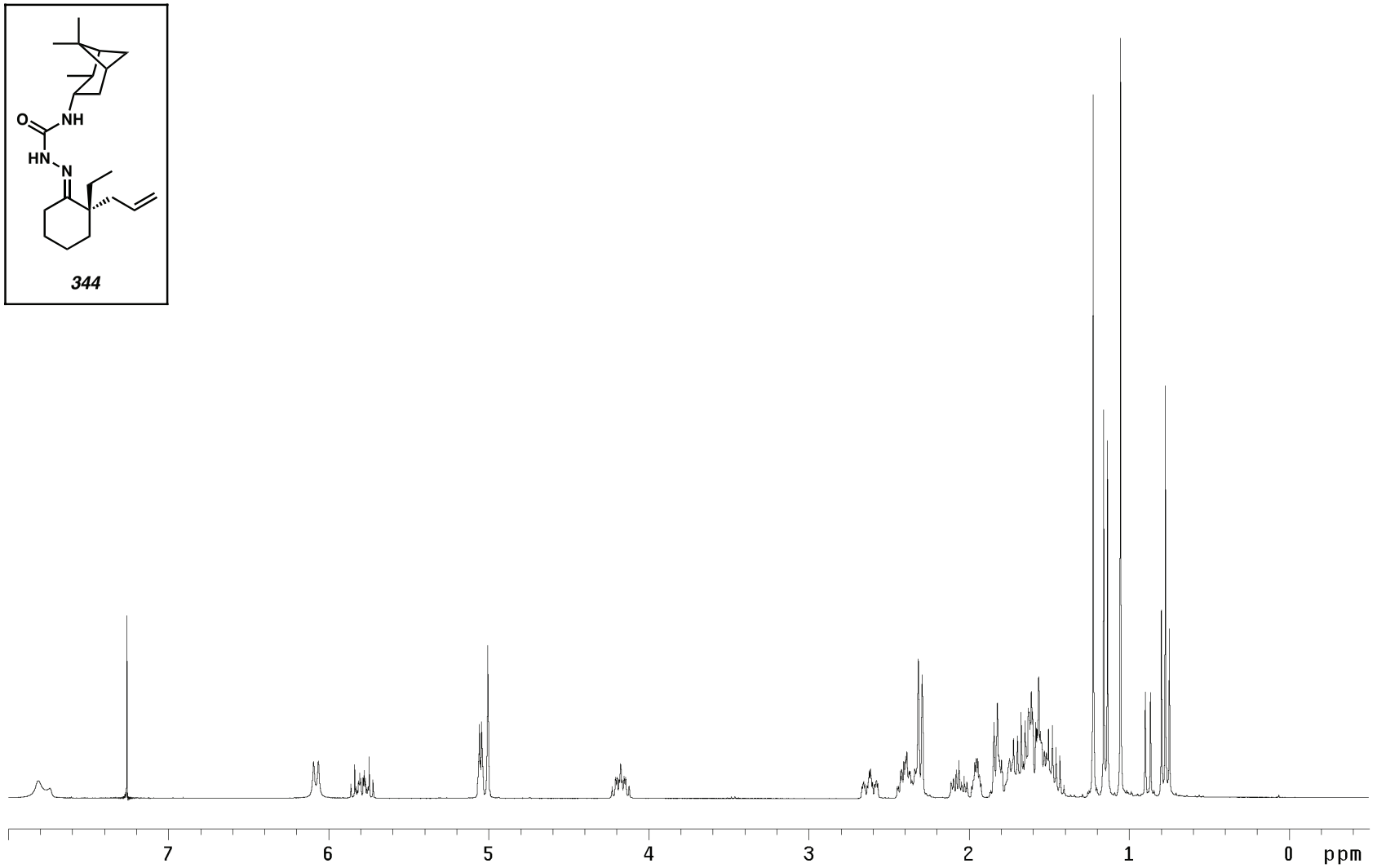


Figure A7.367 ^{1}H NMR of compound **344** (300 MHz, $CDCl_3$)

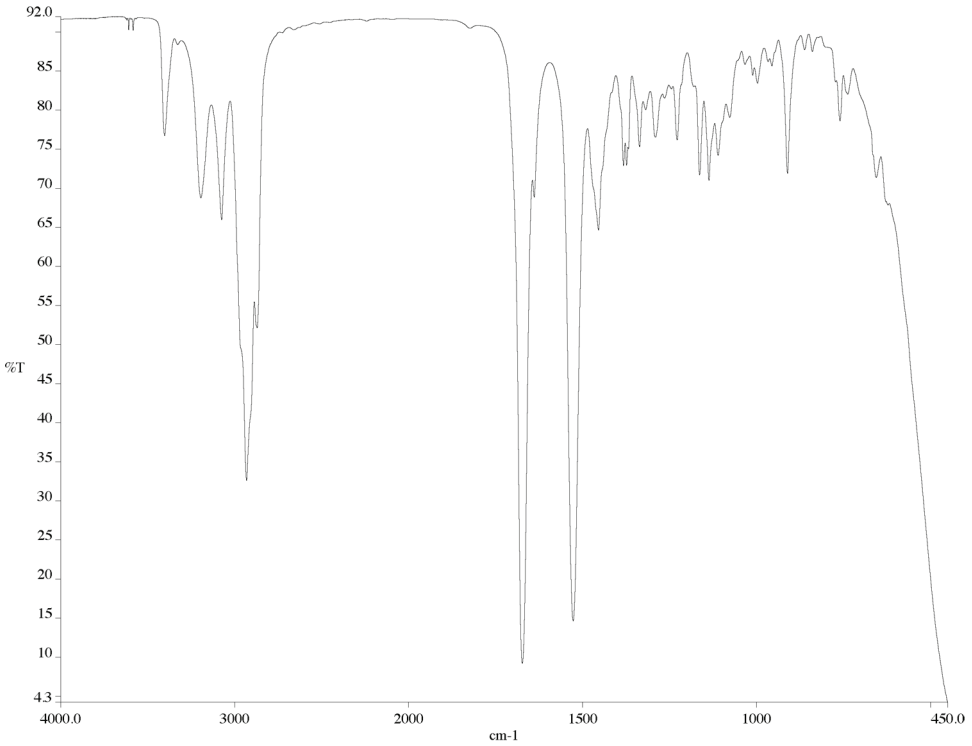


Figure A7.368 IR of compound **344** (NaCl/film)

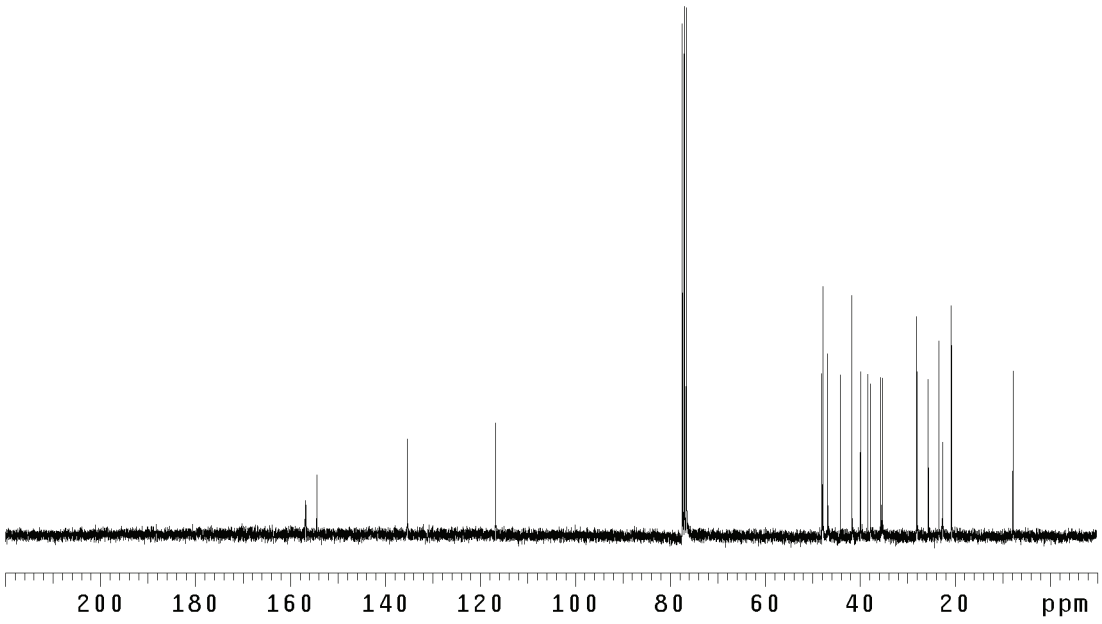


Figure A7.369 ^{13}C NMR of compound **344** (75 MHz, $CDCl_3$)

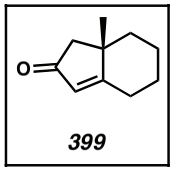


Figure A7.370 ^{1}H NMR of compound **399** (300 MHz, $CDCl_3$)

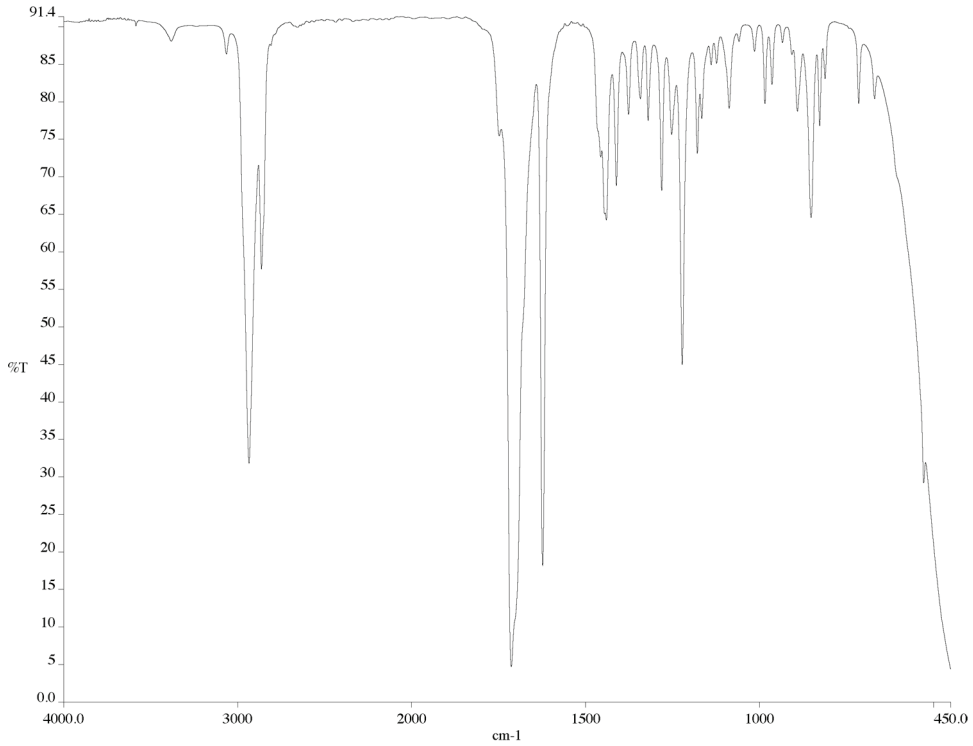


Figure A7.371 IR of compound **399** (NaCl/film)

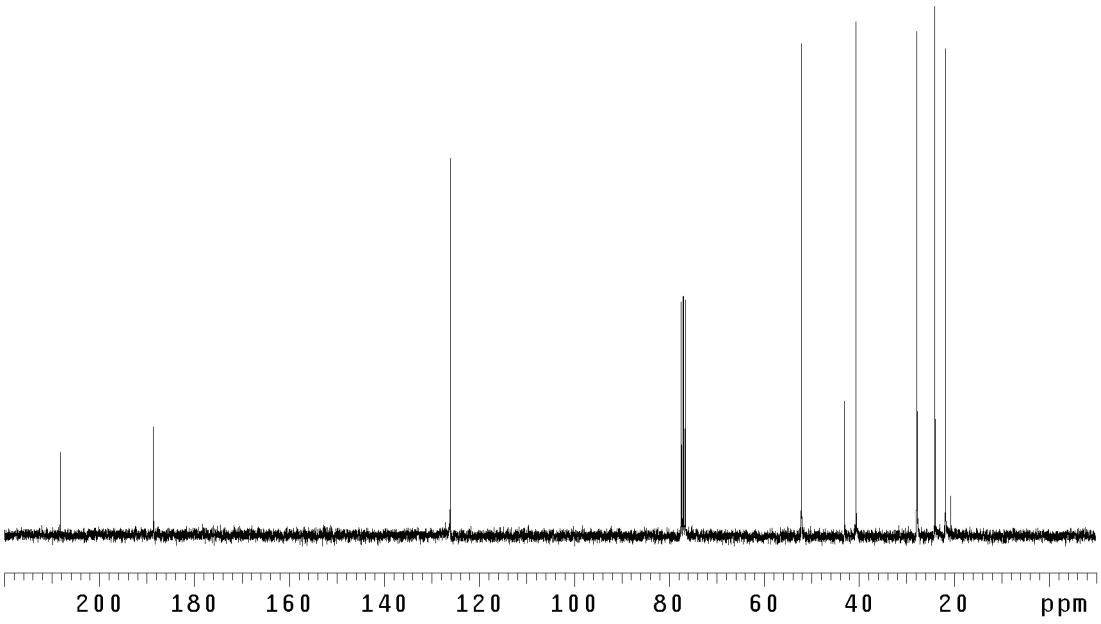


Figure A7.372 ^{13}C NMR of compound **399** (75 MHz, $CDCl_3$)

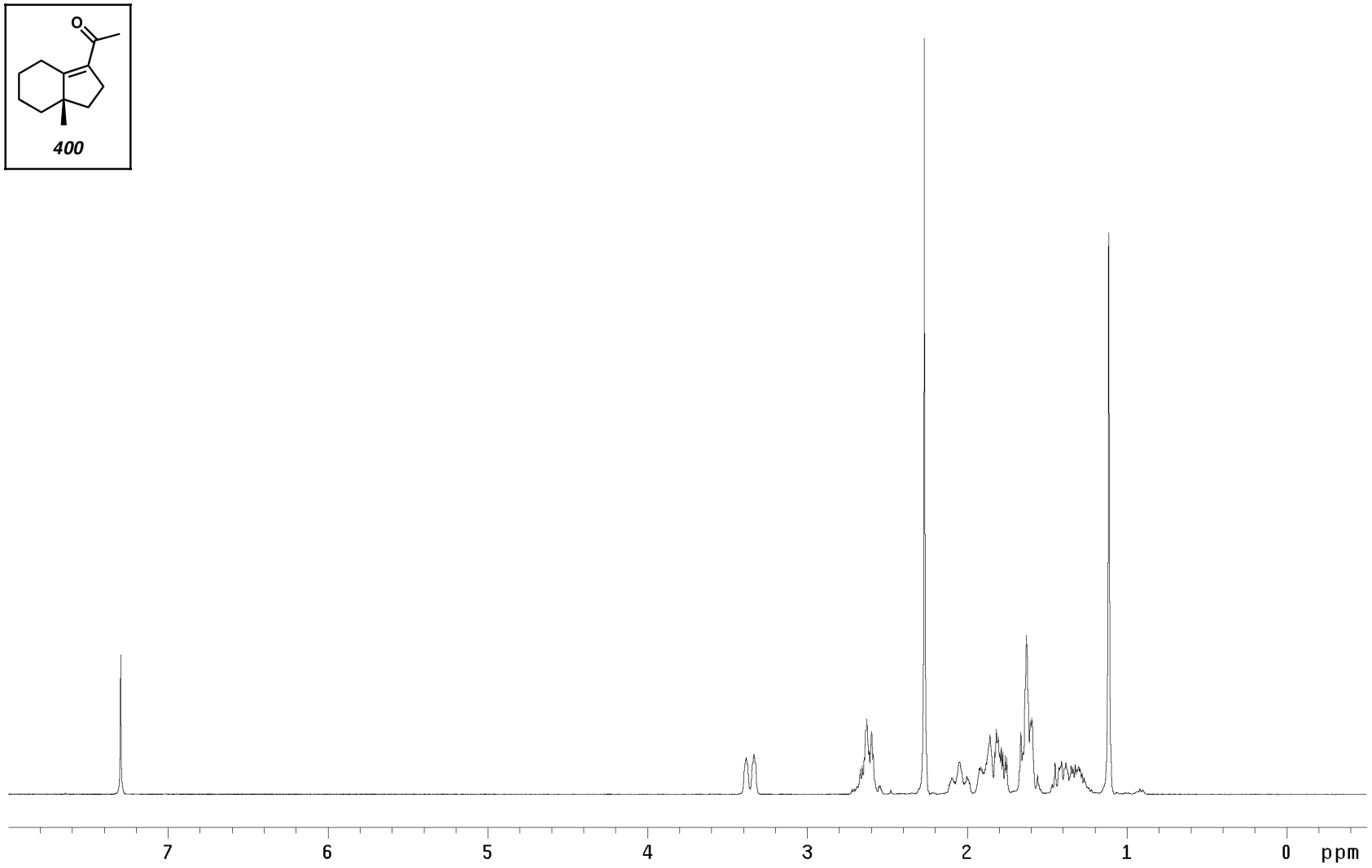


Figure A7.373 ^{1}H NMR of compound **400** (300 MHz, $CDCl_3$)

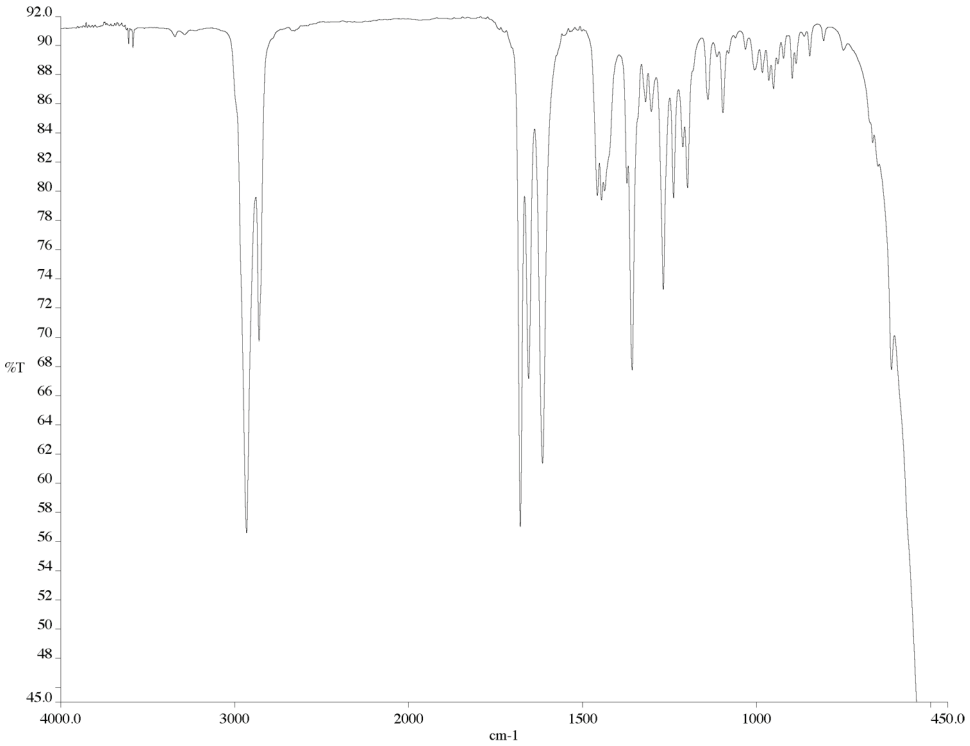


Figure A7.374 IR of compound **400** (NaCl/film)

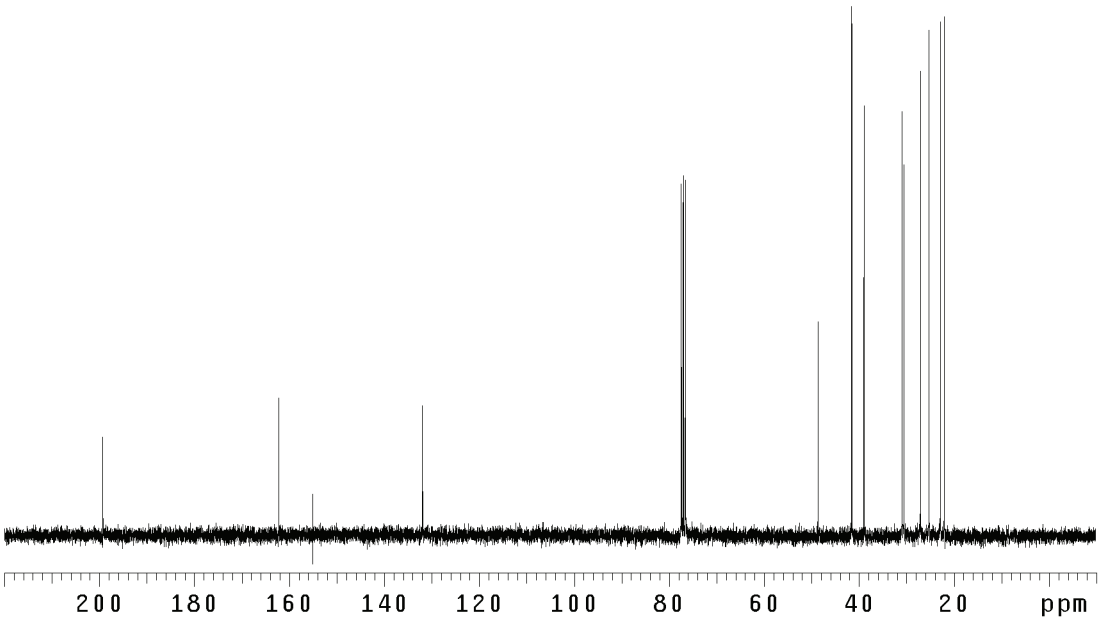


Figure A7.475 ^{13}C NMR of compound **400** (75 MHz, $CDCl_3$)

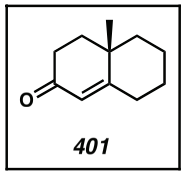


Figure A7.376 ^{1}H NMR of compound **401** (300 MHz, $CDCl_3$)

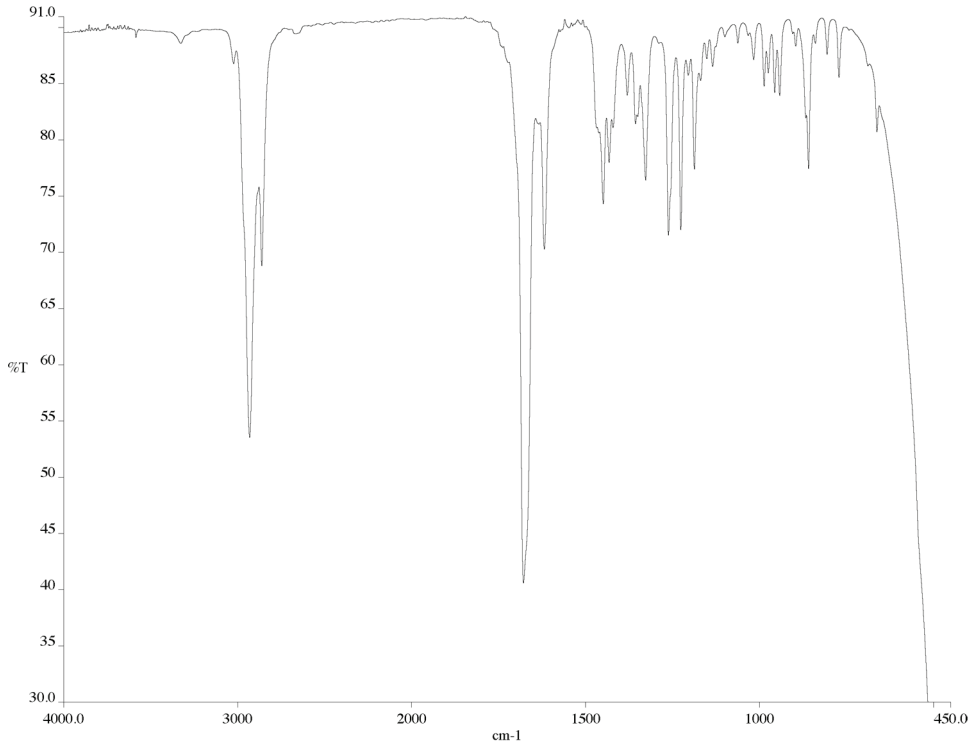


Figure A7.377 IR of compound **401** (NaCl/film)

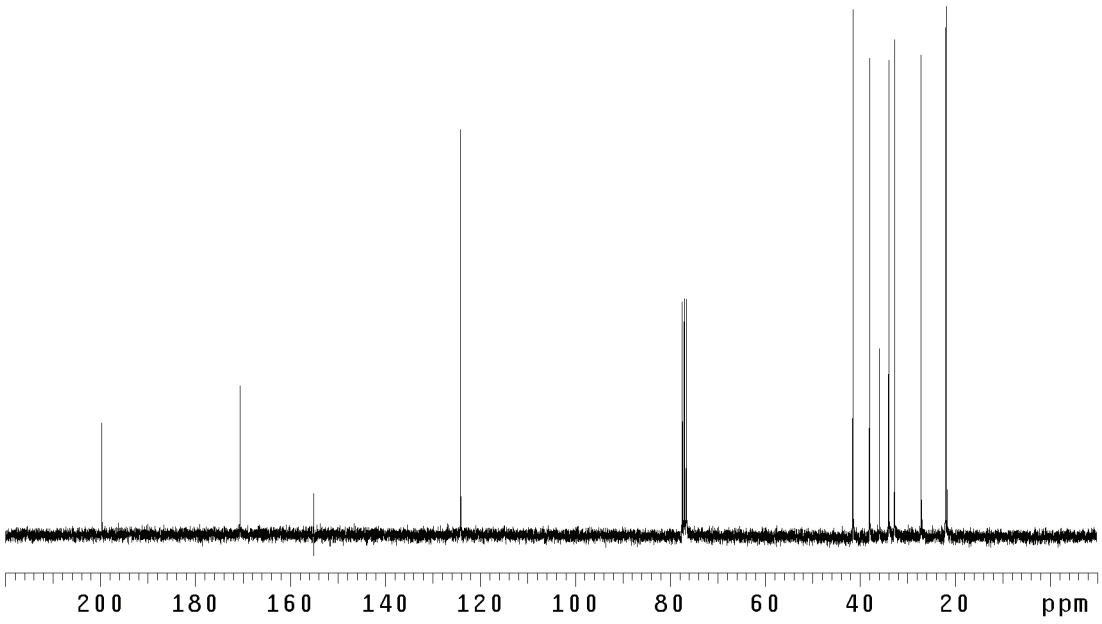


Figure A7.378 ^{13}C NMR of compound **401** (75 MHz, $CDCl_3$)

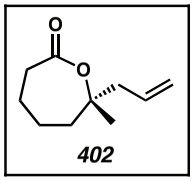


Figure A7.379 ^{1}H NMR of compound **403** (300 MHz, $CDCl_3$)

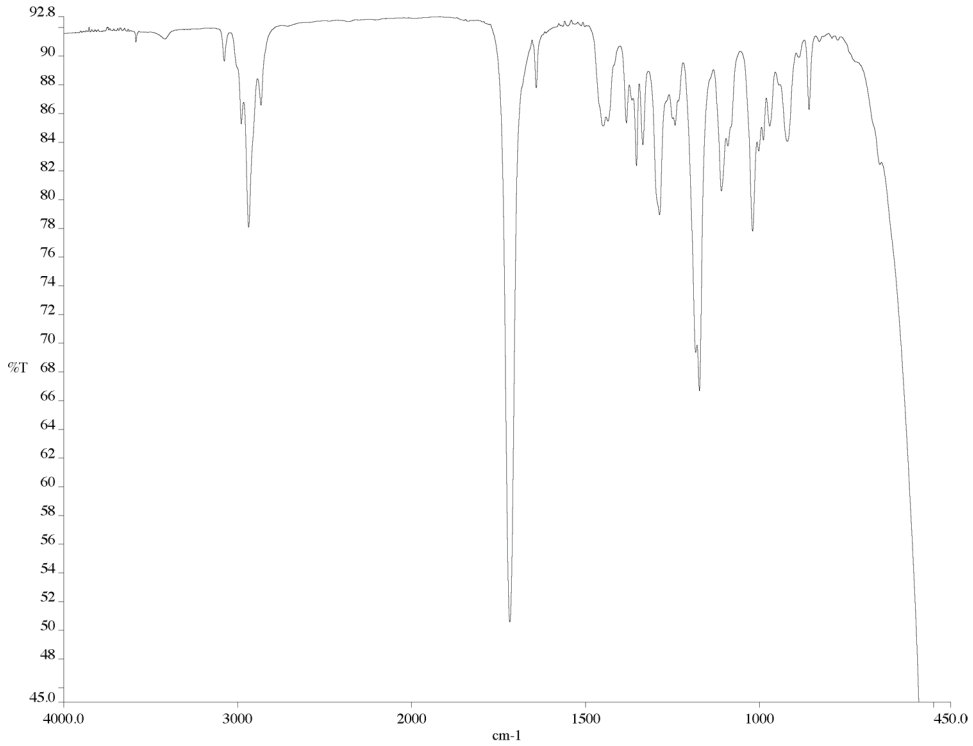


Figure A7.380 IR of compound **402** (NaCl/film)

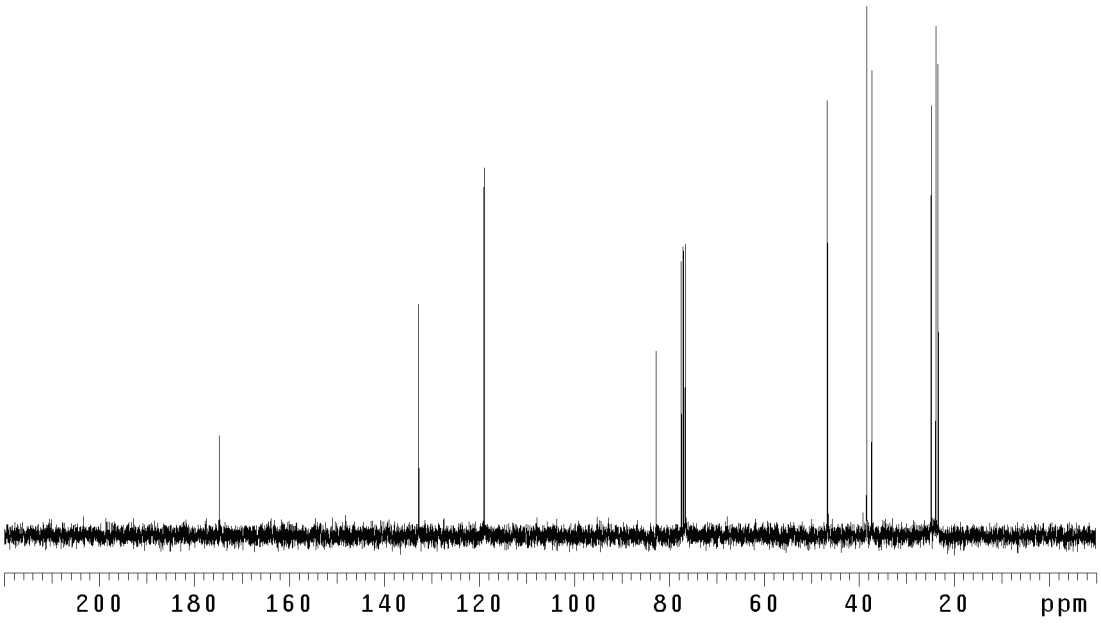


Figure A7.381 ^{13}C NMR of compound **402** (75 MHz, $CDCl_3$)

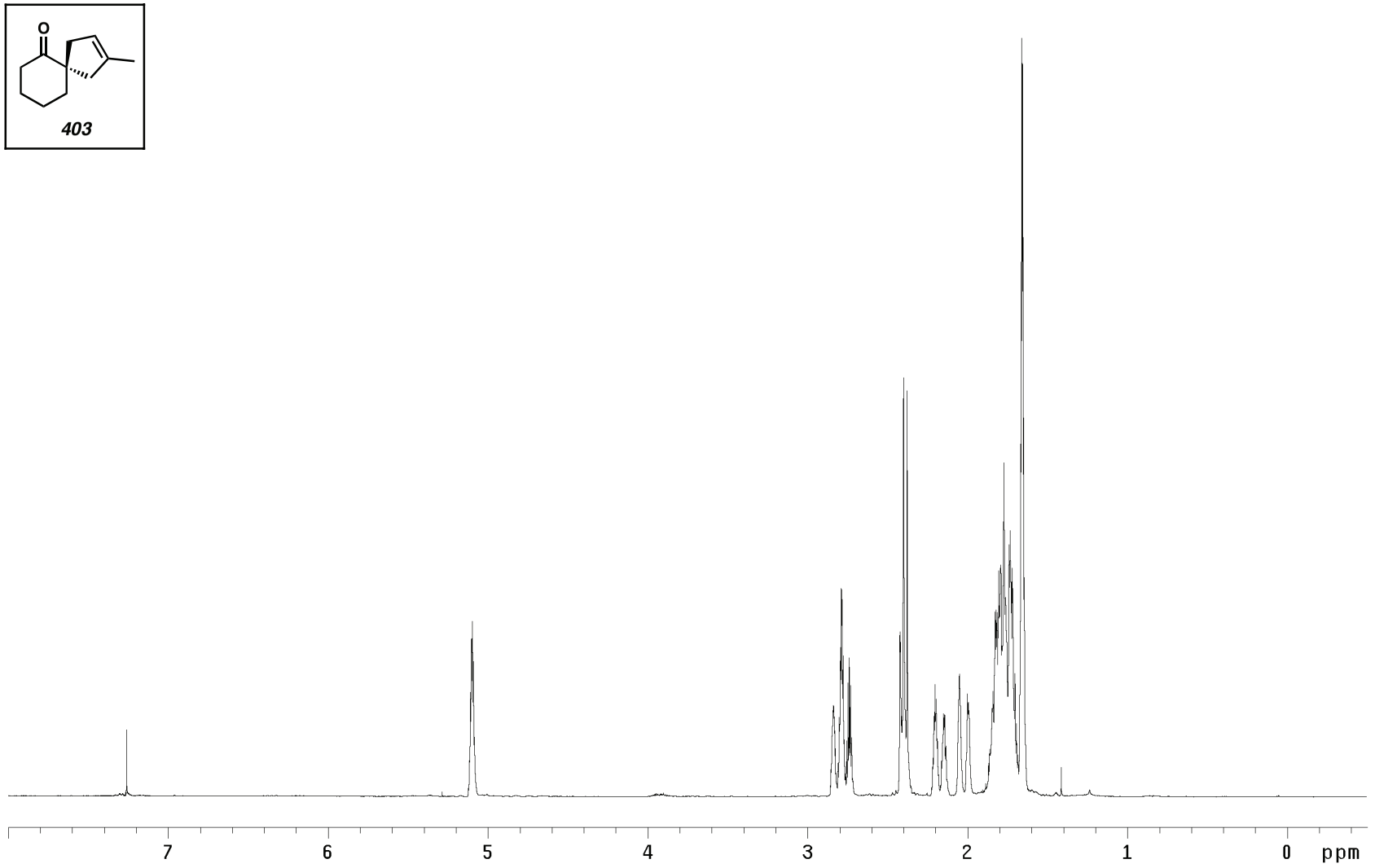


Figure A7.382 ^{1}H NMR of compound **403** (300 MHz, $CDCl_3$)

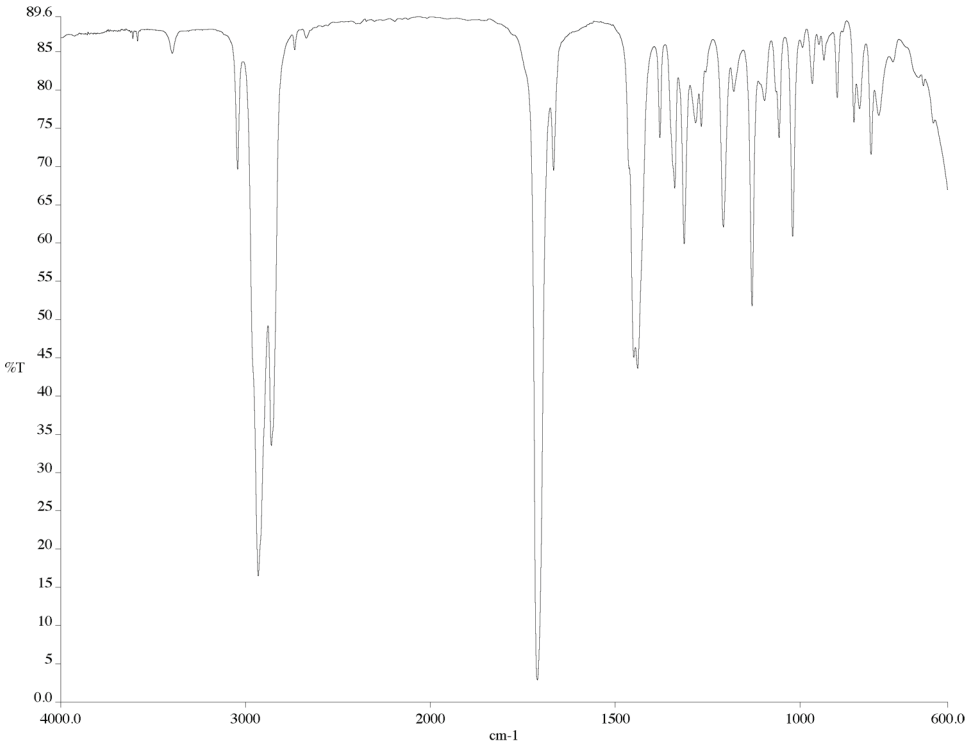


Figure A7.383 IR of compound **403** (NaCl/film)

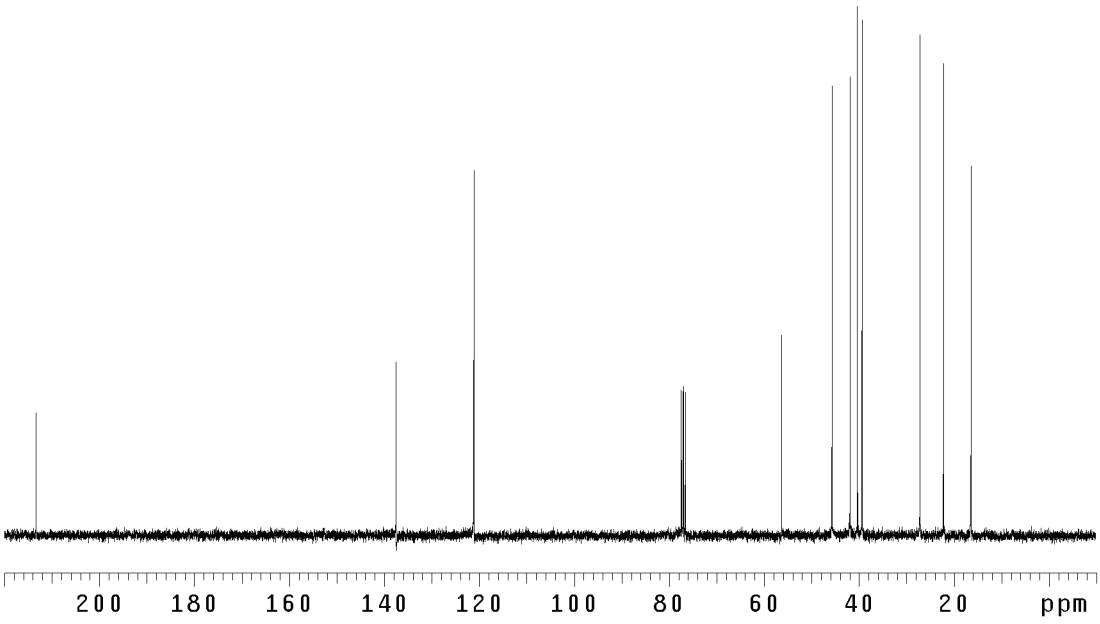


Figure A7.384 ^{13}C NMR of compound **403** (75 MHz, $CDCl_3$)

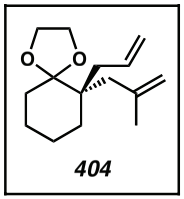


Figure A7.385 ^{1}H NMR of compound **404** (300 MHz, $CDCl_3$)

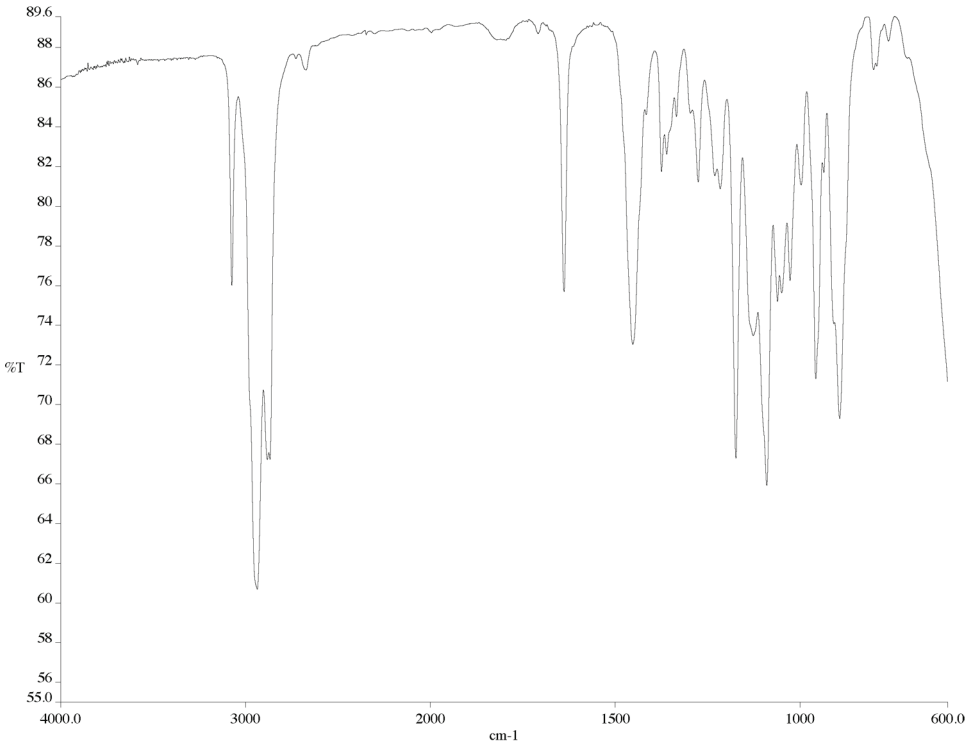


Figure A7.386 IR of compound **404** (NaCl/film)

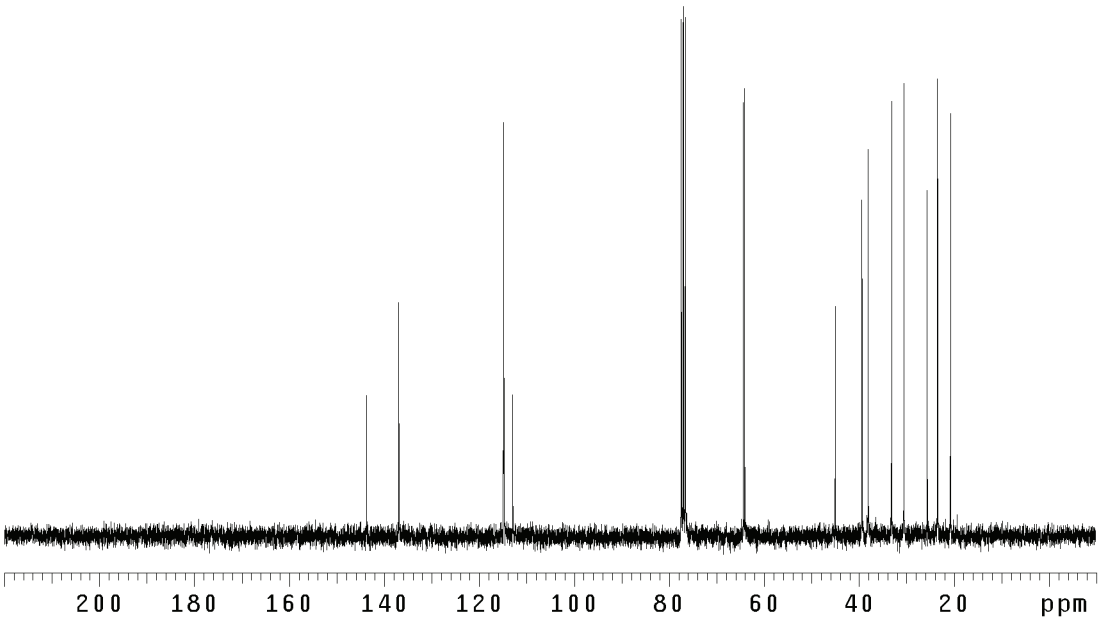


Figure A7.387 ^{13}C NMR of compound **404** (75 MHz, $CDCl_3$)

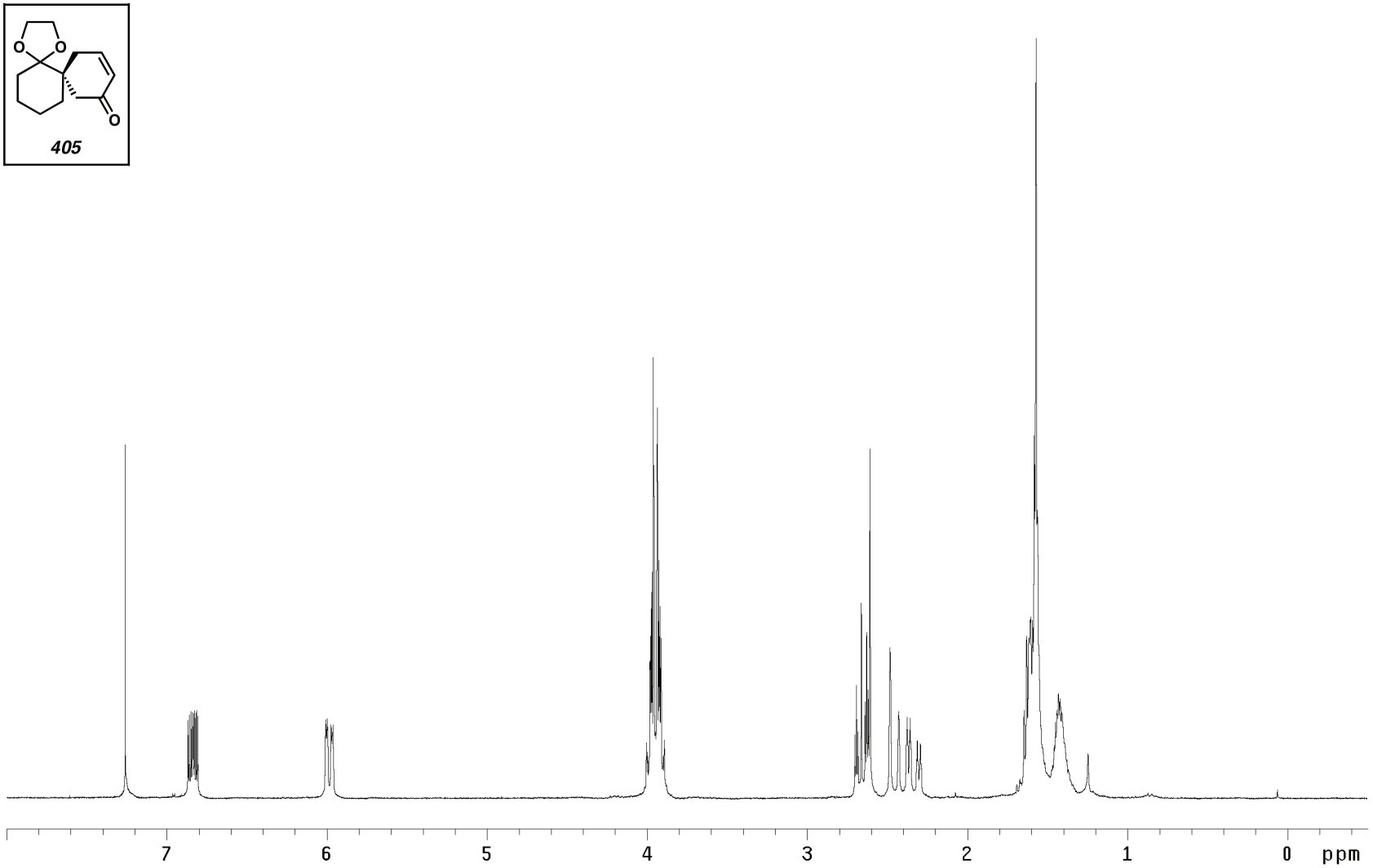


Figure A7.388 ^{1}H NMR of compound **405** (300 MHz, $CDCl_3$)

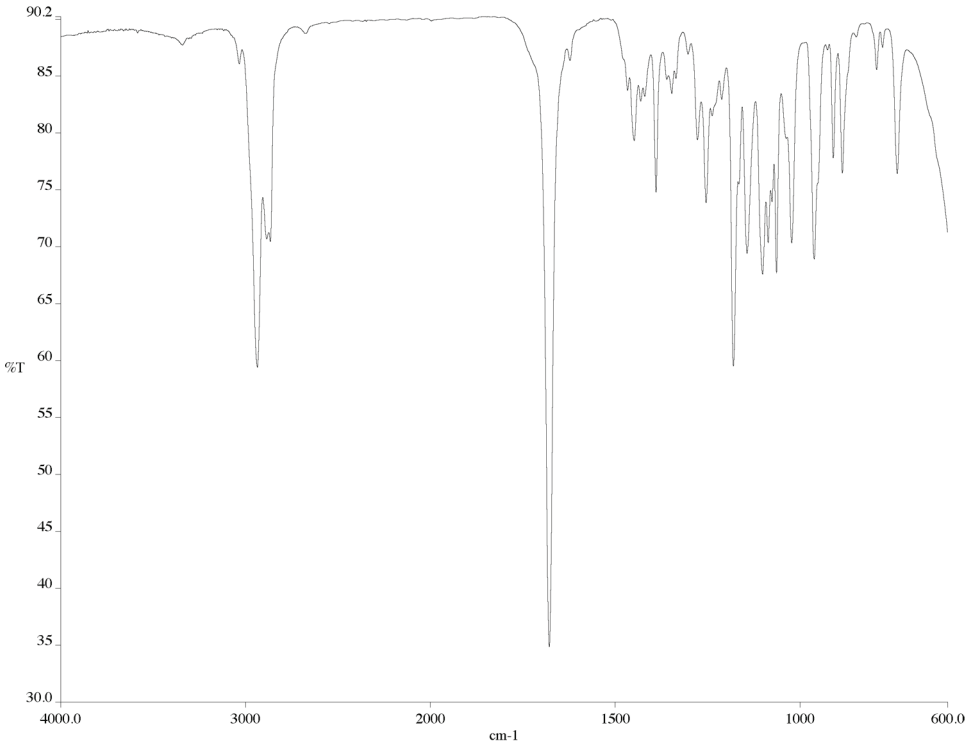


Figure A7.389 IR of compound **405** (NaCl/film)

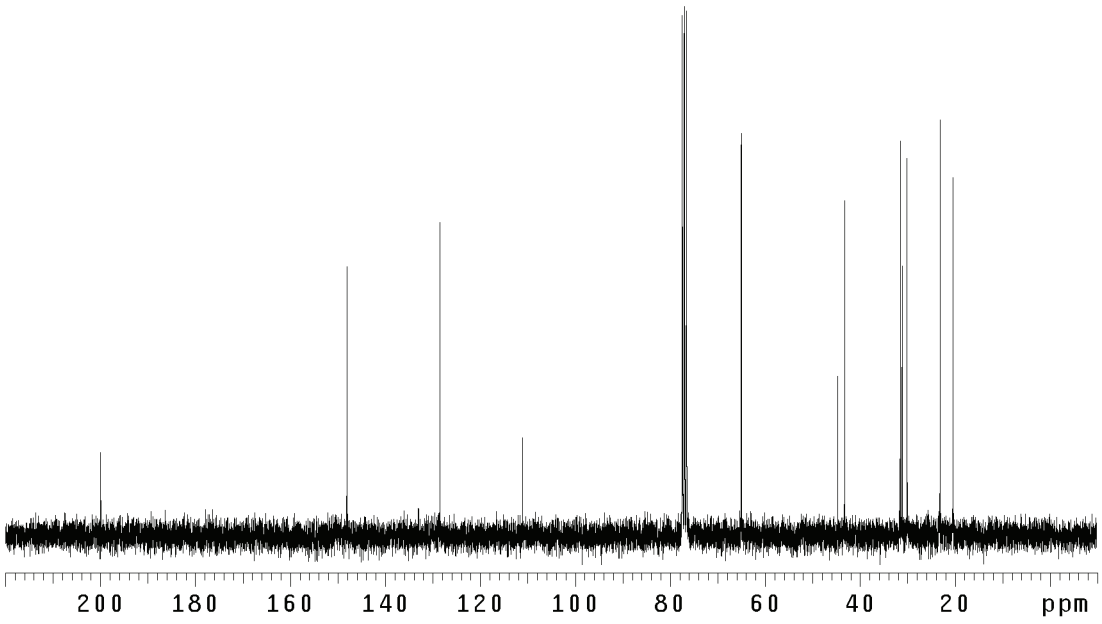


Figure A7.390 ^{13}C NMR of compound **405** (75 MHz, $CDCl_3$)

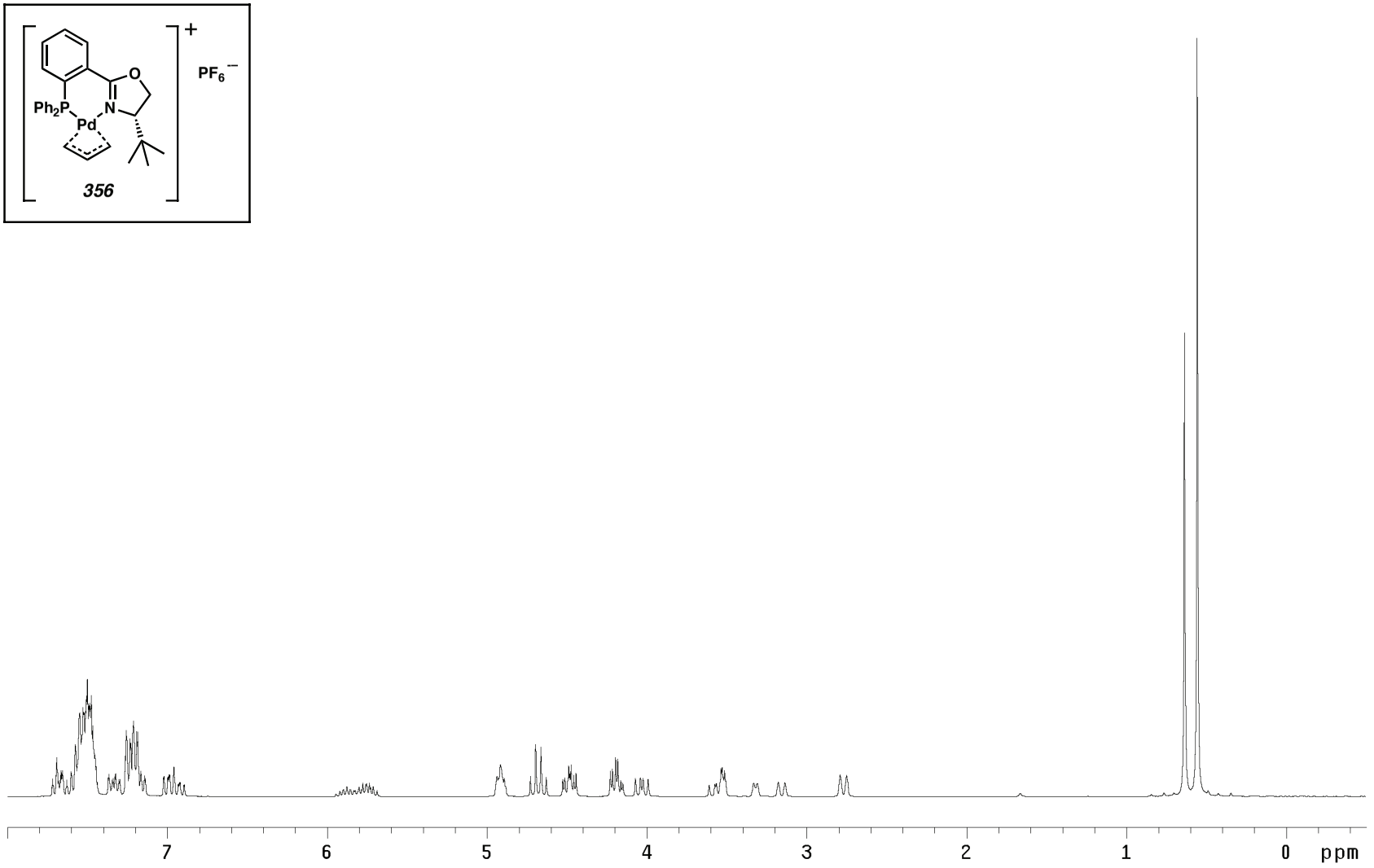


Figure A7.391 ^{1}H NMR of compound **356** (300 MHz, $CDCl_3$)

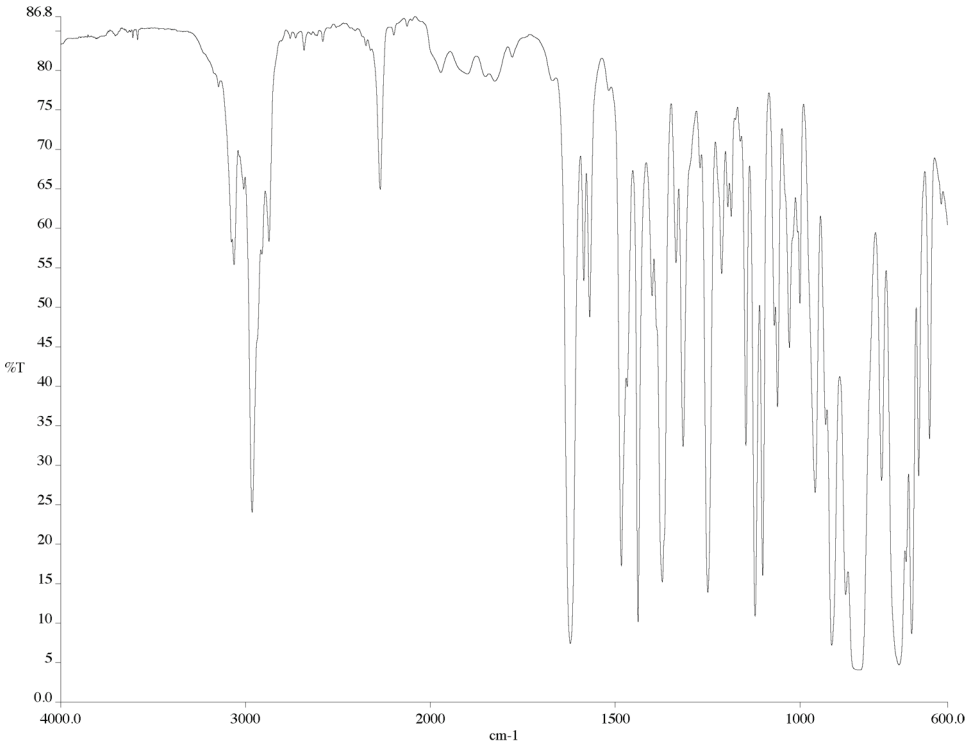


Figure A7.392 IR of compound **356** (NaCl/film)

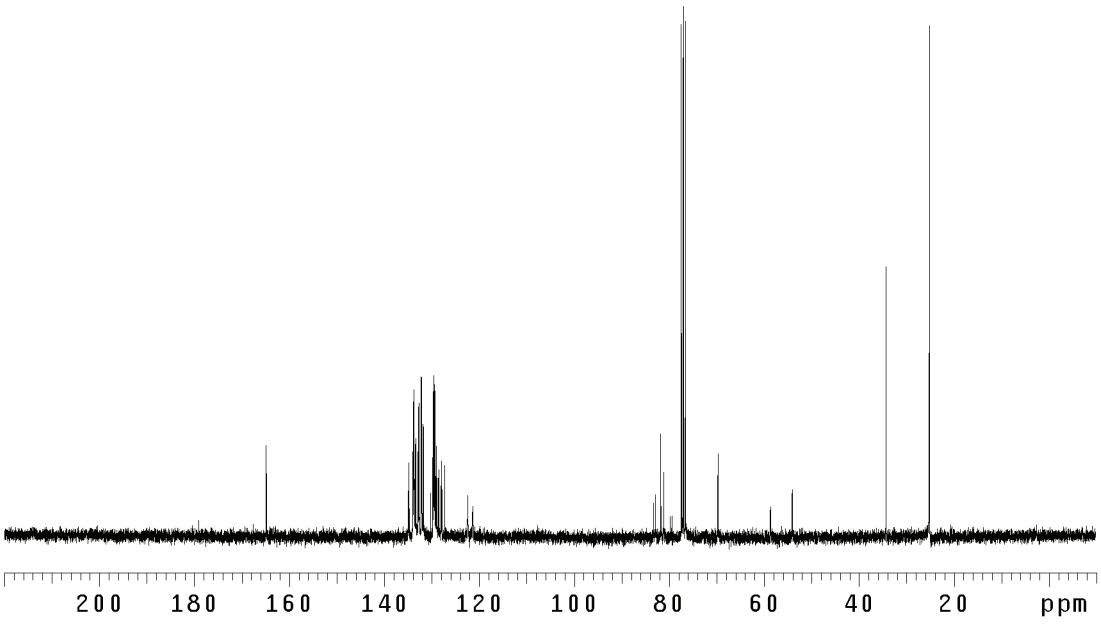


Figure A7.393 ^{13}C NMR of compound **356** (75 MHz, $CDCl_3$)

APPENDIX EIGHT

X-Ray Crystallographic Data Relevant to Chapter Four

CALIFORNIA INSTITUTE OF TECHNOLOGY

BECKMAN INSTITUTE

X-RAY CRYSTALLOGRAPHY LABORATORY

Crystal Structure Analysis of:

Semicarbazone 343 (DCB26)

(CCDC 246585)

Contents:

Table 1. Crystal data
Table 2. Atomic coordinates
Table 3. Full bond distances and angles
Table 4. Anisotropic displacement parameters
Table 5. Hydrogen bond distances and angles

Figure A8.1 Representation of Semicarbazone **343**

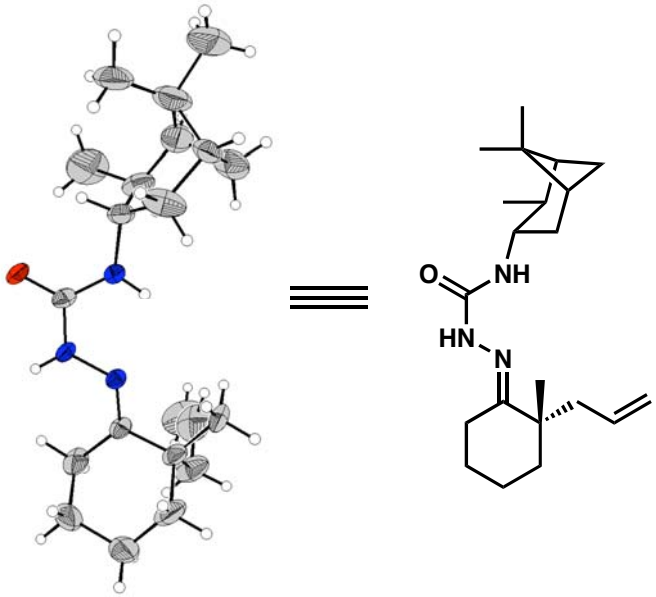


Table 1. Crystal data and structure refinement for DCB26 (CCDC 246585).

Empirical formula	$C_{21}H_{35}N_3O$
Formula weight	345.52
Crystallization Solvent	Ethanol/water
Crystal Habit	Fragment
Crystal size	0.41 x 0.37 x 0.24 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 7110 reflections used in lattice determination	2.31 to 24.12°
Unit cell dimensions	a = 23.1170(16) Å b = 13.6467(9) Å β= 90.396(2)° c = 13.2060(9) Å
Volume	4166.0(5) $Å^3$
Z	8
Crystal system	Monoclinic
Space group	C2
Density (calculated)	1.102 Mg/m^3
F(000)	1520
θ range for data collection	1.73 to 33.55°
Completeness to θ = 33.55°	81.9 %
Index ranges	$-29 \le h \le 34$, $-20 \le k \le 20$, $-18 \le l \le 17$
Data collection scan type	ω scans at 4 ϕ settings
Reflections collected	30377
Independent reflections	12571 [R_{int}= 0.0616]
Absorption coefficient	0.068 mm^{-1}
Absorption correction	None
Max. and min. transmission	0.9838 and 0.9726

Table 1 (cont.)

Structure Solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 1990)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Geometric positions
Structure refinement program	SHELXL-97 (Sheldrick, 1997)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	12571 / 64 / 486
Treatment of hydrogen atoms	Riding
Goodness-of-fit on F^2	1.972
Final R indices [I>2σ(I), 5761 reflections]	R1 = 0.0873, *w*R2 = 0.1490
R indices (all data)	R1 = 0.1657, *w*R2 = 0.1573
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.002
Average shift/error	0.000
Absolute structure parameter	0.4(16)
Largest diff. peak and hole	0.630 and -0.361 e.Å^{-3}

Special Refinement Details

The data are weak and the structure is disordered, in the allyl of molecule B. These two factors combine to produce a final structure that falls short of the desired quality. Nevertheless, the quality is sufficient to determine the relative stereochemistry around C1 and, given the known stereochemistry of another chiral center, the absolute conformation can be deduced. Care should be taken when including these results in a publication. The allylic fragments were restrained to have similar geometry and the anisotropic displacement factors of the B molecule allyl fragment (only) were restrained to tend towards isotropic behavior.

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

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

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for DCB26 (CCDC 246585). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}	Occ
O(1A)	1866(1)	5514(2)	7391(2)	63(1)	1
N(1A)	1997(1)	3514(2)	9031(2)	41(1)	1
N(2A)	2165(1)	4328(2)	8469(2)	42(1)	1
N(3A)	1189(1)	4560(2)	8180(2)	55(1)	1
C(1A)	2171(2)	2117(3)	10056(2)	62(1)	1
C(2A)	2532(2)	1239(3)	9644(4)	94(2)	1
C(3A)	3184(2)	1396(4)	9725(4)	115(2)	1
C(4A)	3351(2)	2343(4)	9182(4)	118(2)	1
C(5A)	3008(2)	3211(4)	9569(3)	83(1)	1
C(6A)	2373(2)	3018(3)	9517(2)	47(1)	1
C(7A)	1528(2)	1903(3)	9804(3)	83(1)	1
C(8A)	2283(2)	2153(3)	11192(3)	104(2)	1
C(9A)	1979(3)	2990(4)	11616(3)	135(2)	1
C(10A)	2111(3)	3520(4)	12331(5)	177(3)	1
C(11A)	1739(2)	4842(3)	7984(2)	50(1)	1
C(12A)	687(2)	5024(3)	7720(3)	62(1)	1
C(13A)	282(2)	4213(4)	7270(3)	96(2)	1
C(14A)	-358(2)	4407(4)	7437(3)	73(1)	1
C(15A)	-446(2)	4624(4)	8568(4)	104(2)	1
C(16A)	-251(2)	5685(4)	8322(5)	117(2)	1
C(17A)	383(2)	5701(3)	8439(4)	92(2)	1
C(18A)	636(3)	6736(4)	8286(6)	179(3)	1
C(19A)	-497(2)	5511(5)	7207(5)	122(2)	1
C(20A)	-236(2)	6069(6)	6377(4)	192(4)	1
C(21A)	-1153(2)	5720(5)	7159(5)	168(3)	1
O(1B)	3303(1)	4867(2)	7779(2)	48(1)	1
N(1B)	3109(1)	6461(2)	5747(2)	60(1)	1
N(2B)	2975(1)	5799(2)	6490(2)	48(1)	1
N(3B)	3956(1)	5670(2)	6811(2)	56(1)	1
C(1B)	2867(2)	7524(3)	4351(4)	90(1)	1
C(2B)	2506(2)	8484(4)	4476(4)	105(2)	1
C(3B)	1857(2)	8263(3)	4489(4)	92(2)	1
C(4B)	1723(2)	7549(4)	5348(3)	100(2)	1
C(5B)	2062(2)	6614(3)	5281(3)	81(1)	1
C(6B)	2705(2)	6838(3)	5208(3)	55(1)	1
C(7B)	2755(3)	7037(5)	3331(4)	141(2)	1
C(8B)	3511(2)	7659(4)	4178(4)	31(2)	0.455(5)
C(9B)	3746(2)	8286(3)	4973(4)	35(2)	0.455(5)
C(10B)	3835(3)	9173(3)	4968(6)	76(3)	0.455(5)
C(8C)	3380(2)	8093(5)	4778(8)	121(4)	0.545(5)
C(9C)	3906(2)	7537(7)	4605(7)	137(4)	0.545(5)
C(10C)	4395(3)	7656(6)	4955(6)	106(3)	0.545(5)
C(11B)	3420(2)	5421(3)	7066(3)	43(1)	1
C(12B)	4459(1)	5290(3)	7340(3)	52(1)	1
C(13B)	4691(1)	4327(3)	6851(3)	61(1)	1
C(14B)	5348(2)	4274(3)	6798(3)	55(1)	1

C(15B)	5567(2)	5213(3)	6268(3)	58(1)	1
C(16B)	5535(1)	5710(3)	7323(2)	47(1)	1
C(17B)	4926(2)	6093(3)	7461(3)	53(1)	1
C(18B)	4835(2)	6662(3)	8438(3)	84(1)	1
C(19B)	5639(2)	4677(3)	7786(3)	56(1)	1
C(20B)	5383(2)	4423(3)	8834(3)	75(1)	1
C(21B)	6293(2)	4428(3)	7801(3)	73(1)	1

Table 3. Bond lengths [Å] and angles [°] for DCB26 (CCDC 246585).

O(1A)-C(11A)	1.242(4)	C(15B)-C(16B)	1.552(4)
N(1A)-C(6A)	1.272(4)	C(16B)-C(17B)	1.515(4)
N(1A)-N(2A)	1.392(3)	C(16B)-C(19B)	1.555(4)
N(2A)-C(11A)	1.365(4)	C(17B)-C(18B)	1.522(5)
N(3A)-C(11A)	1.355(4)	C(19B)-C(20B)	1.548(5)
N(3A)-C(12A)	1.452(4)	C(19B)-C(21B)	1.548(5)
C(1A)-C(6A)	1.497(5)		
C(1A)-C(8A)	1.521(4)	C(6A)-N(1A)-N(2A)	120.1(3)
C(1A)-C(7A)	1.549(5)	C(11A)-N(2A)-N(1A)	117.3(3)
C(1A)-C(2A)	1.560(5)	C(11A)-N(3A)-C(12A)	123.0(3)
C(2A)-C(3A)	1.525(6)	C(6A)-C(1A)-C(8A)	113.0(3)
C(3A)-C(4A)	1.528(6)	C(6A)-C(1A)-C(7A)	110.8(3)
C(4A)-C(5A)	1.516(7)	C(8A)-C(1A)-C(7A)	111.9(3)
C(5A)-C(6A)	1.492(5)	C(6A)-C(1A)-C(2A)	107.2(3)
C(8A)-C(9A)	1.455(5)	C(8A)-C(1A)-C(2A)	106.3(3)
C(9A)-C(10A)	1.226(5)	C(7A)-C(1A)-C(2A)	107.2(3)
C(12A)-C(17A)	1.503(6)	C(3A)-C(2A)-C(1A)	113.5(4)
C(12A)-C(13A)	1.564(5)	C(2A)-C(3A)-C(4A)	109.8(3)
C(13A)-C(14A)	1.521(6)	C(5A)-C(4A)-C(3A)	111.6(4)
C(14A)-C(15A)	1.536(6)	C(6A)-C(5A)-C(4A)	111.4(4)
C(14A)-C(19A)	1.569(7)	N(1A)-C(6A)-C(5A)	126.7(3)
C(15A)-C(16A)	1.551(7)	N(1A)-C(6A)-C(1A)	117.6(3)
C(16A)-C(17A)	1.473(7)	C(5A)-C(6A)-C(1A)	115.6(3)
C(16A)-C(19A)	1.592(8)	C(9A)-C(8A)-C(1A)	109.1(3)
C(17A)-C(18A)	1.542(7)	C(10A)-C(9A)-C(8A)	129.9(5)
C(19A)-C(20A)	1.467(7)	O(1A)-C(11A)-N(3A)	123.8(3)
C(19A)-C(21A)	1.544(7)	O(1A)-C(11A)-N(2A)	120.2(3)
O(1B)-C(11B)	1.238(3)	N(3A)-C(11A)-N(2A)	116.0(3)
N(1B)-C(6B)	1.279(4)	N(3A)-C(12A)-C(17A)	112.3(3)
N(1B)-N(2B)	1.370(3)	N(3A)-C(12A)-C(13A)	109.0(3)
N(2B)-C(11B)	1.376(4)	C(17A)-C(12A)-C(13A)	113.1(4)
N(3B)-C(11B)	1.331(4)	C(14A)-C(13A)-C(12A)	113.7(4)
N(3B)-C(12B)	1.448(4)	C(13A)-C(14A)-C(15A)	108.0(3)
C(1B)-C(7B)	1.523(6)	C(13A)-C(14A)-C(19A)	109.7(4)
C(1B)-C(8B)	1.521(4)	C(15A)-C(14A)-C(19A)	88.6(4)
C(1B)-C(8C)	1.522(4)	C(14A)-C(15A)-C(16A)	86.3(4)
C(1B)-C(6B)	1.517(5)	C(17A)-C(16A)-C(15A)	106.3(4)
C(1B)-C(2B)	1.562(6)	C(17A)-C(16A)-C(19A)	116.6(5)
C(2B)-C(3B)	1.530(6)	C(15A)-C(16A)-C(19A)	87.3(5)
C(3B)-C(4B)	1.529(6)	C(16A)-C(17A)-C(12A)	113.2(4)
C(4B)-C(5B)	1.500(6)	C(16A)-C(17A)-C(18A)	112.2(4)
C(5B)-C(6B)	1.521(5)	C(12A)-C(17A)-C(18A)	107.5(5)
C(8B)-C(9B)	1.456(5)	C(20A)-C(19A)-C(21A)	106.4(5)
C(9B)-C(10B)	1.228(5)	C(20A)-C(19A)-C(14A)	124.0(5)
C(8C)-C(9C)	1.454(5)	C(21A)-C(19A)-C(14A)	112.5(5)
C(9C)-C(10C)	1.228(5)	C(20A)-C(19A)-C(16A)	117.9(5)
C(12B)-C(17B)	1.545(4)	C(21A)-C(19A)-C(16A)	110.7(5)
C(12B)-C(13B)	1.562(5)	C(14A)-C(19A)-C(16A)	83.8(4)
C(13B)-C(14B)	1.524(5)	C(6B)-N(1B)-N(2B)	119.7(3)
C(14B)-C(15B)	1.547(5)	N(1B)-N(2B)-C(11B)	118.1(3)
C(14B)-C(19B)	1.564(5)	C(11B)-N(3B)-C(12B)	122.2(3)

C(7B)-C(1B)-C(8B)	94.6(4)
C(7B)-C(1B)-C(8C)	132.6(5)
C(8B)-C(1B)-C(8C)	39.8(4)
C(7B)-C(1B)-C(6B)	110.4(4)
C(8B)-C(1B)-C(6B)	115.7(4)
C(8C)-C(1B)-C(6B)	103.6(5)
C(7B)-C(1B)-C(2B)	111.8(4)
C(8B)-C(1B)-C(2B)	116.1(4)
C(8C)-C(1B)-C(2B)	87.1(4)
C(6B)-C(1B)-C(2B)	107.7(4)
C(3B)-C(2B)-C(1B)	111.2(4)
C(4B)-C(3B)-C(2B)	109.6(4)
C(5B)-C(4B)-C(3B)	113.0(4)
C(4B)-C(5B)-C(6B)	110.1(4)
N(1B)-C(6B)-C(5B)	126.5(3)
N(1B)-C(6B)-C(1B)	118.7(3)
C(5B)-C(6B)-C(1B)	114.7(3)
C(9B)-C(8B)-C(1B)	108.8(3)
C(10B)-C(9B)-C(8B)	129.6(5)
C(9C)-C(8C)-C(1B)	109.1(3)
C(10C)-C(9C)-C(8C)	129.9(5)
O(1B)-C(11B)-N(3B)	123.8(3)
O(1B)-C(11B)-N(2B)	118.9(3)
N(3B)-C(11B)-N(2B)	117.3(3)
N(3B)-C(12B)-C(17B)	110.7(2)
N(3B)-C(12B)-C(13B)	112.2(3)
C(17B)-C(12B)-C(13B)	113.5(3)
C(14B)-C(13B)-C(12B)	113.8(3)
C(13B)-C(14B)-C(15B)	108.1(3)
C(13B)-C(14B)-C(19B)	111.6(3)
C(15B)-C(14B)-C(19B)	86.9(2)
C(14B)-C(15B)-C(16B)	86.5(2)
C(17B)-C(16B)-C(15B)	108.0(3)
C(17B)-C(16B)-C(19B)	114.0(3)
C(15B)-C(16B)-C(19B)	87.0(2)
C(18B)-C(17B)-C(16B)	114.3(3)
C(18B)-C(17B)-C(12B)	110.5(3)
C(16B)-C(17B)-C(12B)	113.1(3)
C(20B)-C(19B)-C(21B)	108.6(3)
C(20B)-C(19B)-C(16B)	119.7(3)
C(21B)-C(19B)-C(16B)	110.6(3)
C(20B)-C(19B)-C(14B)	120.1(3)
C(21B)-C(19B)-C(14B)	110.3(3)
C(16B)-C(19B)-C(14B)	85.8(2)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^4$) for DCB26 (CCDC 246585). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1A)	638(16)	458(13)	802(18)	329(13)	-72(14)	-23(11)
N(1A)	548(18)	313(13)	371(16)	24(12)	-86(14)	9(12)
N(2A)	486(16)	322(13)	450(16)	90(13)	-135(13)	-71(12)
N(3A)	467(19)	535(17)	650(20)	230(15)	-54(15)	9(14)
C(1A)	790(30)	570(20)	510(30)	211(18)	110(20)	190(20)
C(2A)	1350(50)	610(30)	860(30)	320(20)	230(30)	320(30)
C(3A)	850(40)	1450(50)	1140(40)	790(40)	170(30)	490(30)
C(4A)	570(30)	1630(50)	1350(50)	820(40)	160(30)	390(30)
C(5A)	680(30)	1020(30)	790(30)	480(30)	-340(20)	-120(30)
C(6A)	580(20)	512(19)	318(19)	86(16)	-87(17)	-35(17)
C(7A)	880(30)	550(20)	1050(40)	340(20)	220(30)	-120(20)
C(8A)	1590(50)	910(30)	630(30)	230(30)	170(30)	360(30)
C(9A)	1730(60)	1700(60)	630(40)	280(40)	-120(40)	50(50)
C(10A)	2220(80)	1770(60)	1300(60)	-300(50)	-820(60)	170(60)
C(11A)	570(20)	451(19)	460(20)	26(18)	-130(18)	3(18)
C(12A)	580(20)	680(20)	610(30)	110(20)	-40(20)	210(20)
C(13A)	840(30)	1190(40)	860(30)	-370(30)	-240(30)	350(30)
C(14A)	420(20)	1180(30)	570(30)	180(30)	-38(19)	150(20)
C(15A)	790(30)	1360(50)	980(40)	-90(30)	200(30)	370(30)
C(16A)	920(40)	860(40)	1740(60)	270(40)	420(40)	450(30)
C(17A)	1090(40)	630(30)	1040(40)	80(30)	-40(30)	360(30)
C(18A)	1730(60)	580(30)	3050(90)	-50(40)	-240(60)	100(40)
C(19A)	710(40)	1620(60)	1320(50)	170(50)	-90(40)	520(30)
C(20A)	790(40)	3690(110)	1280(50)	1540(70)	210(40)	790(50)
C(21A)	930(40)	2030(70)	2070(70)	510(60)	-40(40)	670(40)
O(1B)	552(14)	414(12)	461(14)	115(11)	-81(11)	-33(10)
N(1B)	630(20)	529(17)	650(20)	303(16)	115(17)	143(15)
N(2B)	542(18)	382(14)	504(17)	139(13)	-6(14)	20(13)
N(3B)	499(19)	519(16)	670(20)	330(15)	89(16)	96(14)
C(1B)	830(30)	880(30)	980(30)	410(30)	-10(20)	200(20)
C(2B)	660(30)	950(30)	1540(50)	620(30)	80(30)	330(30)
C(3B)	850(40)	820(30)	1080(40)	320(30)	70(30)	320(30)
C(4B)	940(40)	1270(40)	800(30)	310(30)	40(30)	280(30)
C(5B)	760(30)	1010(30)	670(30)	220(20)	-180(20)	80(30)
C(6B)	630(30)	580(20)	460(20)	131(18)	60(20)	120(20)
C(7B)	1700(40)	1730(40)	790(30)	430(30)	160(30)	410(40)
C(8B)	160(30)	420(30)	360(30)	130(30)	80(30)	160(20)
C(9B)	350(30)	250(30)	430(40)	120(30)	30(30)	20(30)
C(10B)	690(40)	780(40)	820(50)	-100(40)	-180(40)	80(40)
C(8C)	1470(60)	980(50)	1190(60)	330(40)	340(40)	170(40)
C(9C)	1460(60)	1350(60)	1310(60)	280(40)	-30(40)	-410(50)
C(10C)	1520(50)	730(40)	960(50)	170(40)	460(40)	110(40)
C(11B)	590(20)	312(16)	400(20)	67(15)	-18(18)	53(16)
C(12B)	540(20)	353(17)	670(30)	127(17)	20(19)	-4(16)
C(13B)	500(20)	490(20)	830(30)	0(20)	-170(20)	-76(18)
C(14B)	530(20)	487(19)	630(20)	-87(18)	-98(19)	39(17)

C(15B)	540(20)	830(30)	370(20)	-18(18)	-73(17)	40(20)
C(16B)	560(20)	444(18)	400(20)	38(16)	30(17)	-76(17)
C(17B)	560(20)	323(17)	700(30)	186(17)	117(19)	26(16)
C(18B)	1080(40)	430(20)	1020(30)	-60(20)	420(30)	-150(20)
C(19B)	650(20)	418(19)	620(20)	136(17)	-92(19)	-23(17)
C(20B)	1090(30)	600(20)	570(30)	230(20)	-180(20)	-190(20)
C(21B)	560(20)	670(20)	960(30)	60(20)	-310(20)	20(20)

Table 5. Hydrogen bonds for DCB26 (CCDC 246585) [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(2A)-H(2A)...O(1B)	0.88	2.05	2.886(3)	158.8
N(2B)-H(2B)...O(1A)	0.88	2.04	2.860(4)	155.6

CALIFORNIA INSTITUTE OF TECHNOLOGY

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Crystal Structure Analysis of:

Semicarbazone 344 (DCB27)

(CCDC 248956)

Contents:

Table 1. Crystal data
Table 2. Atomic coordinates
Table 3. Full bond distances and angles
Table 4. Anisotropic displacement parameters
Table 5. Hydrogen bond distances and angles

Figure A8.2 Representation of Semicarbazone **344**

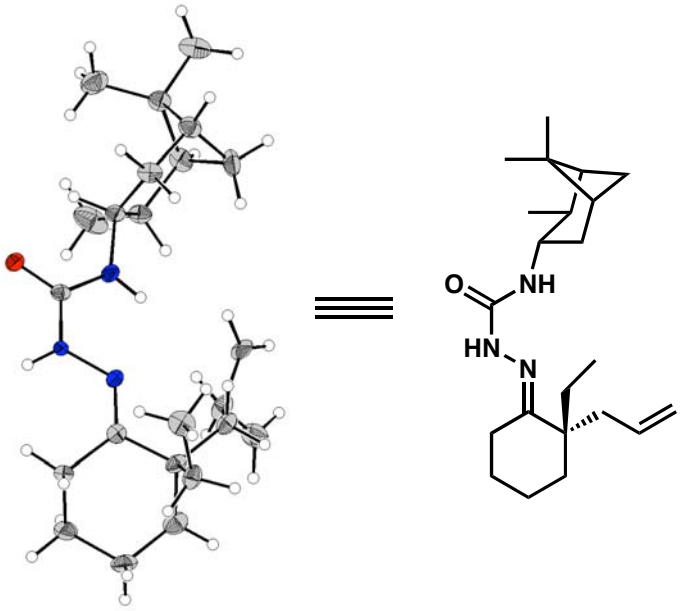


Table 1. Crystal data and structure refinement for DCB27 (CCDC 248956).

Empirical formula	$C_{22}H_{37}N_3O$
Formula weight	359.55
Crystallization Solvent	Acetone
Crystal Habit	Fragment
Crystal size	0.39 x 0.37 x 0.24 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 13615 reflections used in lattice determination	2.25 to 21.58°
Unit cell dimensions	a = 13.4105(11) Å b = 13.4433(11) Å c = 24.353(2) Å
Volume	4390.4(6) $Å^3$
Z	8
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Density (calculated)	1.088 Mg/m^3
F(000)	1584
θ range for data collection	1.67 to 28.34°
Completeness to θ = 28.34°	94.5 %
Index ranges	$-17 \le h \le 17$, $-17 \le k \le 17$, $-32 \le l \le 30$
Data collection scan type	ω scans at 5 ϕ settings
Reflections collected	63444
Independent reflections	10086 [R_{int}= 0.0909]
Absorption coefficient	0.067 mm^{-1}
Absorption correction	None
Max. and min. transmission	0.9841 and 0.9744

Table 1 (cont.)

Structure Solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 1990)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Geometric positions
Structure refinement program	SHELXL-97 (Sheldrick, 1997)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	10086 / 447 / 570
Treatment of hydrogen atoms	Riding
Goodness-of-fit on F^2	2.208
Final R indices [$I>2\sigma(I)$, 6214 reflections]	R1 = 0.0842, *w*R2 = 0.1195
R indices (all data)	R1 = 0.1330, *w*R2 = 0.1224
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.000
Average shift/error	0.000
Absolute structure parameter	0.6(17)
Largest diff. peak and hole	0.271 and -0.287 e.Å^{-3}

Special Refinement Details

The diffraction intensities fall off sharply past $2\theta=40^\circ$, presumably because the structure is disordered. The asymmetric unit contains two molecules (hydrogen bonded to each other and of the same configuration) disordered in different ways. Molecule A is disordered about the terminal carbon (C11) of the allyl ligand (see figures 1 and 2). Both orientations were modeled, including riding hydrogen atoms, with the only restraint being a total occupancy of 1.0 for C11A and C11C. Molecule B is disordered in the camphene moiety, C13B-C22B. The disorder manifests as a rotation of the camphene around the N3B-C13B bond (see figures 3 and 4). Both orientations were restrained to have geometry similar to the corresponding part of the A molecule, using the SAME command. Additional restraints were imposed in this portion of molecule B as follows; 1) SIMU – to restrained bonded atoms to have similar displacement parameters and 2) ISOR – to restrain the anisotropic displacement parameters, U_{ij}, to approximate isotropic behavior without placing restraint on the refined value of the isotropic U.

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

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

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for DCB27 (CCDC 248956). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}	Occ
O(1A)	2809(2)	2335(2)	1779(1)	32(1)	1
N(1A)	817(2)	3903(2)	2093(1)	27(1)	1
N(2A)	1655(2)	3309(2)	2175(1)	24(1)	1
N(3A)	1824(2)	3282(2)	1236(1)	34(1)	1
C(1A)	-518(2)	4936(2)	2388(1)	33(1)	1
C(2A)	-437(3)	5977(2)	2642(2)	47(1)	1
C(3A)	-112(3)	5977(2)	3235(2)	49(1)	1
C(4A)	882(3)	5438(3)	3291(2)	57(1)	1
C(5A)	795(3)	4365(2)	3076(1)	42(1)	1
C(6A)	420(2)	4360(2)	2493(1)	28(1)	1
C(7A)	-1419(2)	4400(2)	2646(1)	39(1)	1
C(8A)	-1470(3)	3264(2)	2527(1)	49(1)	1
C(9A)	-735(2)	5058(2)	1763(1)	39(1)	1
C(10A)	12(3)	5597(3)	1434(2)	48(1)	1
C(11A)	185(5)	5261(5)	885(3)	54(3)	0.511(7)
C(11C)	-125(6)	6553(7)	1281(3)	66(3)	0.489(7)
C(12A)	2114(2)	2934(2)	1725(1)	27(1)	1
C(13A)	2259(2)	2928(2)	725(1)	34(1)	1
C(14A)	1576(2)	2156(2)	446(1)	38(1)	1
C(15A)	1565(2)	2226(3)	-177(1)	42(1)	1
C(16A)	1262(3)	3289(3)	-322(2)	54(1)	1
C(17A)	2374(3)	3537(2)	-258(1)	39(1)	1
C(18A)	2554(2)	3800(2)	349(1)	36(1)	1
C(19A)	3603(3)	4144(3)	469(2)	77(1)	1
C(20A)	2622(2)	2441(2)	-411(1)	38(1)	1
C(21A)	3522(3)	1891(3)	-180(2)	59(1)	1
C(22A)	2637(3)	2320(3)	-1038(1)	61(1)	1
O(1B)	2342(2)	2440(2)	3187(1)	34(1)	1
N(1B)	4099(2)	678(2)	2784(1)	37(1)	1
N(2B)	3295(2)	1310(2)	2738(1)	37(1)	1
N(3B)	3367(2)	1432(2)	3679(1)	60(1)	1
C(1B)	5294(3)	-479(3)	2425(2)	48(1)	1
C(2B)	6017(3)	-264(3)	1958(2)	88(2)	1
C(3B)	5500(4)	-304(3)	1385(2)	81(2)	1
C(4B)	4622(3)	410(3)	1357(2)	63(1)	1
C(5B)	3895(3)	189(3)	1803(2)	54(1)	1
C(6B)	4383(3)	205(3)	2358(2)	46(1)	1
C(7B)	4962(3)	-1591(3)	2413(2)	72(1)	1
C(8B)	4290(3)	-1903(3)	2885(2)	72(1)	1
C(9B)	5798(3)	-326(3)	2981(2)	72(1)	1
C(10B)	6309(3)	682(4)	3049(2)	81(2)	1
C(11B)	7251(3)	828(3)	3119(2)	103(2)	1
C(12B)	2981(2)	1775(3)	3210(1)	35(1)	1
C(13B)	3160(7)	2001(7)	4235(3)	34(3)	0.515(3)
C(14B)	2103(6)	1773(7)	4394(3)	71(3)	0.515(3)
C(15B)	1912(8)	1565(8)	5018(3)	97(4)	0.515(3)

C(16B)	2704(8)	702(6)	5131(3)	82(3)	0.515(3)
C(17B)	3526(10)	1499(10)	5209(4)	72(4)	0.515(3)
C(18B)	3936(6)	1742(9)	4670(4)	80(3)	0.515(3)
C(19B)	4820(8)	2450(9)	4663(4)	117(4)	0.515(3)
C(20B)	2622(8)	2162(6)	5387(3)	54(3)	0.515(3)
C(21B)	2403(7)	1991(7)	5992(3)	92(4)	0.515(3)
C(22B)	2701(5)	3269(5)	5261(3)	60(2)	0.515(3)
C(13C)	2948(10)	1526(7)	4183(4)	45(3)	0.485(3)
C(14C)	3136(8)	604(5)	4553(3)	88(3)	0.485(3)
C(15C)	3848(9)	798(7)	5059(3)	77(3)	0.485(3)
C(16C)	4712(8)	1489(8)	4870(5)	108(4)	0.485(3)
C(17C)	3935(8)	2363(7)	4946(4)	80(3)	0.485(3)
C(18C)	3386(6)	2503(5)	4419(3)	35(2)	0.485(3)
C(19C)	2648(6)	3361(5)	4450(3)	65(3)	0.485(3)
C(20C)	3451(10)	1701(11)	5380(4)	68(4)	0.485(3)
C(21C)	3921(10)	1826(10)	5948(3)	160(6)	0.485(3)
C(22C)	2319(9)	1719(9)	5426(6)	99(6)	0.485(3)

Table 3. Bond lengths [Å] and angles [°] for DCB27 (CCDC 248956).

O(1A)-C(12A)	1.238(3)	C(15B)-C(16B)	1.597(11)
N(1A)-C(6A)	1.268(4)	C(16B)-C(17B)	1.549(12)
N(1A)-N(2A)	1.394(3)	C(17B)-C(18B)	1.460(12)
N(2A)-C(12A)	1.354(4)	C(17B)-C(20B)	1.565(12)
N(3A)-C(12A)	1.337(4)	C(18B)-C(19B)	1.521(11)
N(3A)-C(13A)	1.455(4)	C(20B)-C(21B)	1.521(10)
C(1A)-C(6A)	1.499(4)	C(20B)-C(22B)	1.523(10)
C(1A)-C(2A)	1.534(4)	C(13C)-C(18C)	1.549(9)
C(1A)-C(7A)	1.541(4)	C(13C)-C(14C)	1.554(11)
C(1A)-C(9A)	1.557(4)	C(14C)-C(15C)	1.580(11)
C(2A)-C(3A)	1.510(4)	C(15C)-C(20C)	1.539(13)
C(3A)-C(4A)	1.523(5)	C(15C)-C(16C)	1.554(12)
C(4A)-C(5A)	1.540(4)	C(16C)-C(17C)	1.582(11)
C(5A)-C(6A)	1.507(4)	C(17C)-C(18C)	1.490(10)
C(7A)-C(8A)	1.556(4)	C(17C)-C(20C)	1.527(13)
C(9A)-C(10A)	1.474(4)	C(18C)-C(19C)	1.521(9)
C(10A)-C(11C)	1.350(9)	C(20C)-C(22C)	1.523(13)
C(10A)-C(11A)	1.431(7)	C(20C)-C(21C)	1.527(12)
C(13A)-C(18A)	1.540(4)		
C(13A)-C(14A)	1.542(4)	C(6A)-N(1A)-N(2A)	120.4(3)
C(14A)-C(15A)	1.521(4)	C(12A)-N(2A)-N(1A)	117.7(3)
C(15A)-C(16A)	1.526(4)	C(12A)-N(3A)-C(13A)	122.0(3)
C(15A)-C(20A)	1.555(4)	C(6A)-C(1A)-C(2A)	110.1(3)
C(16A)-C(17A)	1.537(4)	C(6A)-C(1A)-C(7A)	110.3(2)
C(17A)-C(18A)	1.538(4)	C(2A)-C(1A)-C(7A)	108.5(3)
C(17A)-C(20A)	1.556(4)	C(6A)-C(1A)-C(9A)	112.2(3)
C(18A)-C(19A)	1.509(4)	C(2A)-C(1A)-C(9A)	108.1(3)
C(20A)-C(21A)	1.523(4)	C(7A)-C(1A)-C(9A)	107.5(3)
C(20A)-C(22A)	1.535(4)	C(3A)-C(2A)-C(1A)	113.9(3)
O(1B)-C(12B)	1.240(3)	C(2A)-C(3A)-C(4A)	109.8(3)
N(1B)-C(6B)	1.275(4)	C(3A)-C(4A)-C(5A)	110.4(3)
N(1B)-N(2B)	1.377(3)	C(6A)-C(5A)-C(4A)	110.5(3)
N(2B)-C(12B)	1.373(4)	N(1A)-C(6A)-C(1A)	118.1(3)
N(3B)-C(12B)	1.337(4)	N(1A)-C(6A)-C(5A)	125.9(3)
N(3B)-C(13C)	1.355(12)	C(1A)-C(6A)-C(5A)	116.0(3)
N(3B)-C(13B)	1.579(9)	C(1A)-C(7A)-C(8A)	114.7(3)
C(1B)-C(2B)	1.521(5)	C(10A)-C(9A)-C(1A)	117.1(3)
C(1B)-C(9B)	1.528(5)	C(11C)-C(10A)-C(11A)	93.6(5)
C(1B)-C(6B)	1.538(4)	C(11C)-C(10A)-C(9A)	121.7(5)
C(1B)-C(7B)	1.561(5)	C(11A)-C(10A)-C(9A)	117.5(4)
C(2B)-C(3B)	1.559(6)	O(1A)-C(12A)-N(3A)	122.8(3)
C(3B)-C(4B)	1.521(5)	O(1A)-C(12A)-N(2A)	119.9(3)
C(4B)-C(5B)	1.488(4)	N(3A)-C(12A)-N(2A)	117.2(3)
C(5B)-C(6B)	1.503(5)	N(3A)-C(13A)-C(18A)	111.3(3)
C(7B)-C(8B)	1.520(5)	N(3A)-C(13A)-C(14A)	111.0(3)
C(9B)-C(10B)	1.526(5)	C(18A)-C(13A)-C(14A)	113.8(2)
C(10B)-C(11B)	1.290(5)	C(15A)-C(14A)-C(13A)	113.8(3)
C(13B)-C(14B)	1.501(10)	C(14A)-C(15A)-C(16A)	107.0(3)
C(13B)-C(18B)	1.526(10)	C(14A)-C(15A)-C(20A)	111.6(3)
C(14B)-C(15B)	1.566(9)	C(16A)-C(15A)-C(20A)	89.1(3)
C(15B)-C(20B)	1.535(11)	C(15A)-C(16A)-C(17A)	85.5(2)

C(16A)-C(17A)-C(18A)	107.5(3)
C(16A)-C(17A)-C(20A)	88.7(3)
C(18A)-C(17A)-C(20A)	114.5(3)
C(19A)-C(18A)-C(17A)	113.8(3)
C(19A)-C(18A)-C(13A)	110.9(3)
C(17A)-C(18A)-C(13A)	110.8(3)
C(21A)-C(20A)-C(22A)	107.8(3)
C(21A)-C(20A)-C(15A)	119.8(3)
C(22A)-C(20A)-C(15A)	110.9(3)
C(21A)-C(20A)-C(17A)	122.7(3)
C(22A)-C(20A)-C(17A)	110.0(3)
C(15A)-C(20A)-C(17A)	83.9(2)
C(6B)-N(1B)-N(2B)	118.4(3)
C(12B)-N(2B)-N(1B)	116.9(3)
C(12B)-N(3B)-C(13C)	125.5(6)
C(12B)-N(3B)-C(13B)	119.8(4)
C(2B)-C(1B)-C(9B)	110.8(4)
C(2B)-C(1B)-C(6B)	108.2(3)
C(9B)-C(1B)-C(6B)	111.4(3)
C(2B)-C(1B)-C(7B)	110.5(3)
C(9B)-C(1B)-C(7B)	105.8(3)
C(6B)-C(1B)-C(7B)	110.1(3)
C(1B)-C(2B)-C(3B)	112.3(4)
C(4B)-C(3B)-C(2B)	111.2(4)
C(5B)-C(4B)-C(3B)	110.4(3)
C(4B)-C(5B)-C(6B)	111.6(3)
N(1B)-C(6B)-C(5B)	127.6(3)
N(1B)-C(6B)-C(1B)	116.7(3)
C(5B)-C(6B)-C(1B)	115.7(3)
C(8B)-C(7B)-C(1B)	114.8(3)
C(10B)-C(9B)-C(1B)	114.4(3)
C(11B)-C(10B)-C(9B)	126.1(4)
O(1B)-C(12B)-N(3B)	123.7(3)
O(1B)-C(12B)-N(2B)	120.2(3)
N(3B)-C(12B)-N(2B)	116.1(3)
C(14B)-C(13B)-C(18B)	114.7(7)
C(14B)-C(13B)-N(3B)	106.8(7)
C(18B)-C(13B)-N(3B)	111.4(7)
C(13B)-C(14B)-C(15B)	116.2(7)
C(20B)-C(15B)-C(14B)	111.9(7)
C(20B)-C(15B)-C(16B)	82.3(6)
C(14B)-C(15B)-C(16B)	100.8(8)
C(17B)-C(16B)-C(15B)	89.5(7)
C(18B)-C(17B)-C(16B)	108.2(8)
C(18B)-C(17B)-C(20B)	114.4(10)
C(16B)-C(17B)-C(20B)	82.9(7)
C(17B)-C(18B)-C(19B)	116.4(9)
C(17B)-C(18B)-C(13B)	114.7(8)
C(19B)-C(18B)-C(13B)	112.4(9)
C(21B)-C(20B)-C(22B)	110.8(7)
C(21B)-C(20B)-C(15B)	111.6(8)
C(22B)-C(20B)-C(15B)	115.9(7)
C(21B)-C(20B)-C(17B)	109.4(8)
C(22B)-C(20B)-C(17B)	116.5(9)
C(15B)-C(20B)-C(17B)	91.2(7)
N(3B)-C(13C)-C(18C)	105.0(9)
N(3B)-C(13C)-C(14C)	112.6(8)
C(18C)-C(13C)-C(14C)	113.5(8)
C(13C)-C(14C)-C(15C)	114.7(6)
C(20C)-C(15C)-C(16C)	86.4(8)
C(20C)-C(15C)-C(14C)	108.6(8)
C(16C)-C(15C)-C(14C)	108.6(7)
C(15C)-C(16C)-C(17C)	85.3(8)
C(18C)-C(17C)-C(20C)	117.4(8)
C(18C)-C(17C)-C(16C)	108.5(8)
C(20C)-C(17C)-C(16C)	85.8(8)
C(17C)-C(18C)-C(19C)	112.0(7)
C(17C)-C(18C)-C(13C)	113.6(7)
C(19C)-C(18C)-C(13C)	114.5(8)
C(22C)-C(20C)-C(17C)	117.7(10)
C(22C)-C(20C)-C(21C)	110.1(11)
C(17C)-C(20C)-C(21C)	112.8(10)
C(22C)-C(20C)-C(15C)	113.2(11)
C(17C)-C(20C)-C(15C)	87.8(8)
C(21C)-C(20C)-C(15C)	113.8(10)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^4$) for DCB27 (CCDC 248956). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1A)	329(13)	309(13)	330(13)	-1(11)	10(11)	59(11)
N(1A)	235(16)	241(15)	326(17)	-5(13)	4(13)	24(13)
N(2A)	267(15)	245(15)	201(15)	-20(12)	-28(13)	47(13)
N(3A)	423(17)	357(17)	248(17)	44(14)	32(14)	173(14)
C(1A)	320(20)	218(19)	450(20)	-51(17)	42(18)	11(16)
C(2A)	460(20)	330(20)	610(30)	-30(20)	40(20)	-18(18)
C(3A)	510(20)	370(20)	580(30)	-210(20)	60(20)	35(18)
C(4A)	480(20)	620(30)	600(30)	-350(20)	-130(20)	80(20)
C(5A)	440(20)	450(20)	360(20)	-177(18)	-78(18)	138(19)
C(6A)	248(19)	238(19)	370(20)	6(17)	16(17)	-84(16)
C(7A)	260(20)	460(20)	450(20)	105(19)	38(17)	26(17)
C(8A)	560(30)	340(20)	560(20)	58(19)	40(20)	-201(19)
C(9A)	261(19)	410(20)	510(20)	10(20)	50(20)	45(17)
C(10A)	460(30)	430(30)	550(30)	150(20)	50(20)	150(20)
C(11A)	800(60)	420(50)	390(50)	90(40)	0(40)	410(40)
C(11C)	640(60)	940(80)	410(50)	-110(50)	50(50)	70(60)
C(12A)	268(19)	252(18)	300(20)	-59(17)	26(17)	-49(15)
C(13A)	390(20)	410(20)	229(18)	-16(17)	54(17)	86(18)
C(14A)	450(20)	320(20)	380(20)	-4(17)	100(19)	-82(18)
C(15A)	380(20)	480(20)	400(20)	-55(19)	10(19)	-66(19)
C(16A)	500(30)	750(30)	380(20)	60(20)	-150(20)	150(20)
C(17A)	560(30)	340(20)	280(20)	129(17)	30(20)	-97(18)
C(18A)	450(20)	318(19)	300(20)	2(17)	77(18)	-30(17)
C(19A)	670(30)	990(40)	660(30)	-280(30)	60(30)	-430(30)
C(20A)	370(20)	430(20)	330(20)	4(18)	87(18)	-30(18)
C(21A)	460(30)	650(30)	670(30)	-100(20)	130(20)	70(20)
C(22A)	790(30)	560(30)	490(20)	-140(20)	160(20)	-110(20)
O(1B)	331(13)	372(14)	312(13)	-13(11)	50(11)	46(11)
N(1B)	301(17)	392(18)	430(20)	56(15)	58(15)	132(15)
N(2B)	281(16)	544(19)	283(17)	-60(14)	-40(14)	184(16)
N(3B)	600(20)	950(30)	246(19)	125(18)	18(18)	350(20)
C(1B)	330(20)	410(20)	700(30)	180(20)	130(20)	206(19)
C(2B)	530(30)	830(40)	1270(50)	220(30)	380(30)	350(30)
C(3B)	960(40)	610(30)	850(40)	60(30)	500(30)	240(30)
C(4B)	620(30)	720(30)	560(30)	210(20)	250(20)	130(20)
C(5B)	520(30)	480(30)	620(30)	80(20)	120(20)	74(19)
C(6B)	390(20)	430(20)	550(30)	80(20)	80(20)	185(19)
C(7B)	620(30)	480(30)	1070(40)	150(30)	280(30)	170(20)
C(8B)	640(30)	760(30)	760(30)	370(30)	90(30)	-130(20)
C(9B)	470(30)	520(30)	1170(40)	280(30)	-120(30)	210(20)
C(10B)	400(30)	750(40)	1290(40)	260(30)	-230(30)	10(20)
C(11B)	550(30)	680(30)	1850(60)	500(30)	-40(40)	-50(30)
C(12B)	290(20)	390(20)	360(20)	43(19)	18(18)	29(17)
C(13B)	530(70)	260(60)	220(50)	-90(50)	-100(40)	130(60)
C(14B)	920(70)	720(60)	490(60)	-200(50)	130(50)	-240(60)
C(15B)	1490(100)	1050(80)	370(50)	170(60)	-200(60)	-640(80)

C(16B)	1720(100)	370(50)	380(50)	60(40)	-20(60)	-340(60)
C(17B)	1300(100)	830(90)	30(60)	40(60)	-110(60)	-60(80)
C(18B)	770(70)	1070(80)	570(60)	-190(60)	-230(60)	200(70)
C(19B)	890(80)	1720(120)	890(80)	240(80)	60(70)	280(90)
C(20B)	690(70)	560(70)	360(60)	-190(50)	-170(50)	-90(60)
C(21B)	1150(80)	1480(90)	120(40)	-130(50)	220(50)	-600(70)
C(22B)	520(50)	520(50)	770(60)	-320(50)	20(50)	80(40)
C(13C)	590(70)	350(60)	410(60)	-90(50)	-170(50)	-100(60)
C(14C)	1880(100)	280(50)	480(50)	0(40)	310(60)	-350(60)
C(15C)	1460(100)	550(70)	300(60)	220(50)	190(60)	370(70)
C(16C)	1400(110)	890(80)	950(90)	-210(70)	-550(80)	440(80)
C(17C)	1100(90)	470(60)	810(80)	-190(60)	-560(70)	-90(60)
C(18C)	460(50)	180(50)	410(60)	90(40)	-50(40)	-140(40)
C(19C)	960(70)	430(50)	550(60)	190(40)	170(50)	280(50)
C(20C)	1100(100)	800(90)	150(70)	120(60)	-160(60)	-80(80)
C(21C)	2130(140)	2230(140)	450(70)	0(80)	-370(80)	880(120)
C(22C)	1330(130)	620(90)	1040(110)	310(80)	270(100)	-550(80)

Table 5. Hydrogen bonds for DCB27 (CCDC 248956) [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(2A)-H(2AA)...O(1B)	0.88	2.03	2.880(3)	161.8
N(2B)-H(2BA)...O(1A)	0.88	2.01	2.789(3)	146.4

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Crystal Structure Analysis of:

Pd(II)(allyl)PHOX•PF_6 salt 356 (DCB24)

(CCDC 245187)

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Table 2. Atomic coordinates
Table 3. Full bond distances and angles
Table 4. Anisotropic displacement parameters
Table 5. Hydrogen bond distances and angles

Figure A8.3 Representation of Pd(II)(allyl)PHOX•PF_6 salt **356**

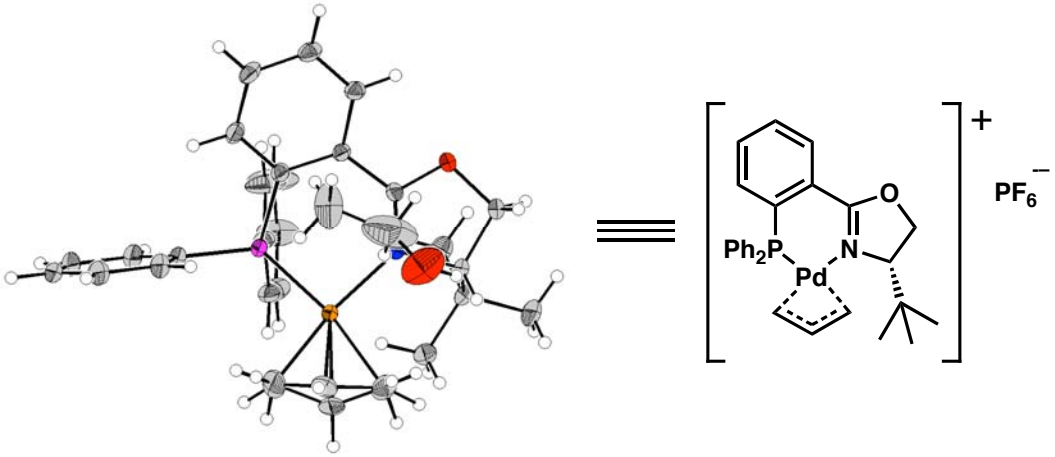


Figure A8.4 Representation of the unit cell of Pd(II)(allyl)PHOX•PF_6 salt **356**

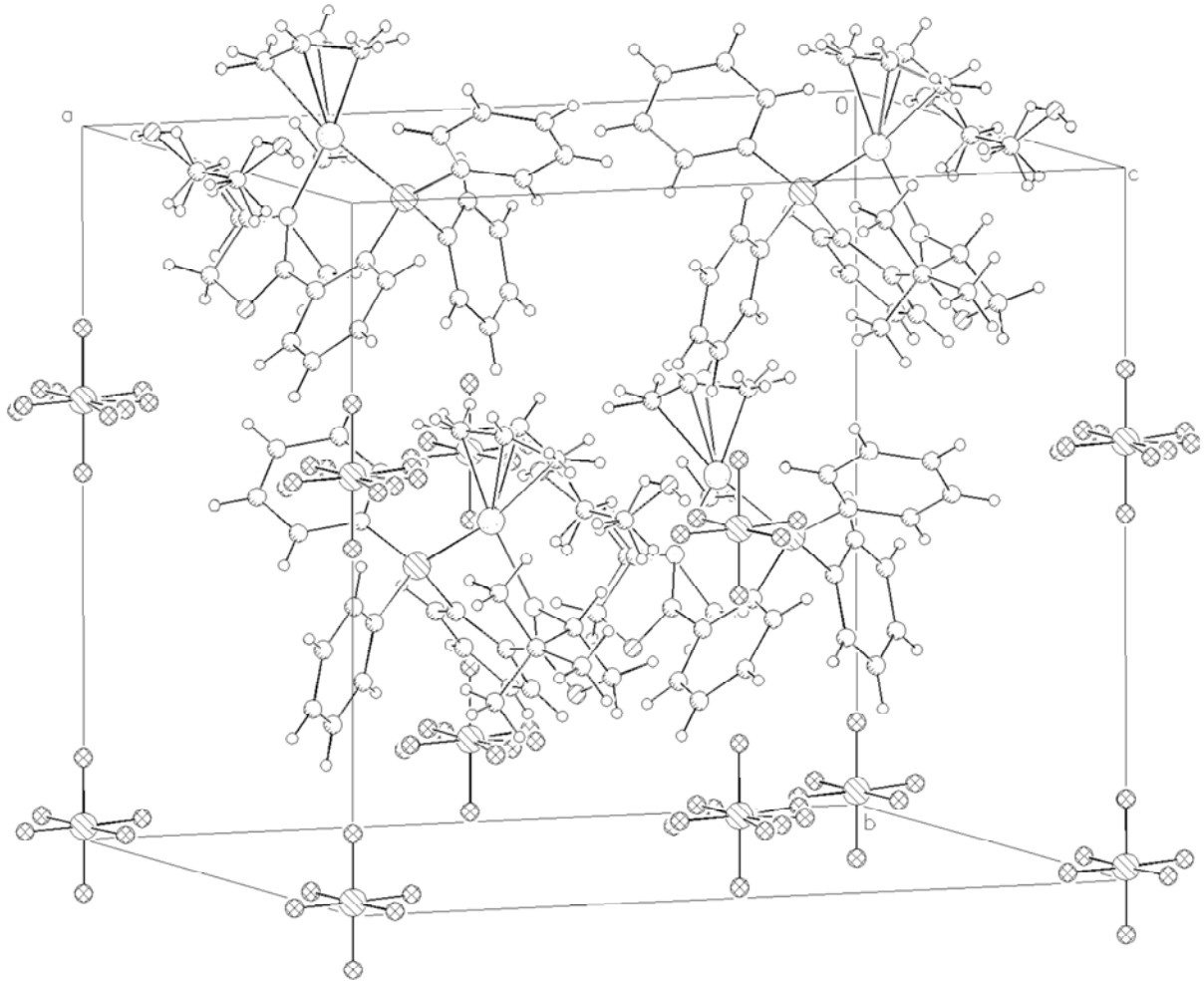


Table 1. Crystal data and structure refinement for DCB24 (CCDC 245187).

Empirical formula	$[C_{28}H_{31}NOPPd]^+ PF_6^- \bullet \frac{1}{2}C_2H_5OH$
Formula weight	702.91
Crystallization Solvent	Ethanol
Crystal Habit	Fragment
Crystal size	0.35 x 0.34 x 0.23 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 15322 reflections used in lattice determination	2.31 to 41.00°
Unit cell dimensions	a = 17.5183(6) Å b = 15.7792(5) Å β= 107.0990(10)° c = 11.3736(4) Å
Volume	3004.98(18) $Å^3$
Z	4
Crystal system	Monoclinic
Space group	C2
Density (calculated)	1.554 Mg/m^3
F(000)	1428
θ range for data collection	1.77 to 42.31°
Completeness to θ = 42.31°	85.0 %
Index ranges	$-32 \le h \le 32$, $-28 \le k \le 29$, $-20 \le l \le 15$
Data collection scan type	ω scans at 3 ϕ settings of 2θ=-28° and 2 at 2θ=-59°
Reflections collected	28501
Independent reflections	15572 [R_{int}= 0.0351]
Absorption coefficient	0.787 mm^{-1}
Absorption correction	SADABS
Max. and min. transmission	0.8397 and 0.7702

Table 1 (cont.)

Structure Solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 1990)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Geometric positions
Structure refinement program	SHELXL-97 (Sheldrick, 1997)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	15572 / 1 / 408
Treatment of hydrogen atoms	Riding
Goodness-of-fit on F^2	1.343
Final R indices [I>2σ(I), 13582 reflections]	R1 = 0.0373, *w*R2 = 0.0725
R indices (all data)	R1 = 0.0459, *w*R2 = 0.0748
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.004
Average shift/error	0.000
Absolute structure parameter	-0.019(13)
Largest diff. peak and hole	1.422 and -0.710 e.Å^{-3}

Special Refinement Details

The propyl ligand, C26-C27-C28, is disordered in two alternate orientations, differing by "up-down" positions for C27. Additional disorder is observed in one PF_6 counterion and an included solvent molecule, modeled as ethanol hydrogen bonded to a fluorine of one counterion.

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

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

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for DCB24 (CCDC 245187). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}	Occ
Pd(1)	2838(1)	4922(1)	2994(1)	18(1)	1
P(1)	2327(1)	5673(1)	4282(1)	19(1)	1
O(1)	3784(1)	7349(1)	2545(1)	22(1)	1
N(1)	3187(1)	6087(1)	2419(2)	17(1)	1
C(1)	3099(1)	6431(1)	5056(2)	18(1)	1
C(2)	3275(1)	6569(1)	6320(2)	23(1)	1
C(3)	3845(1)	7170(1)	6920(2)	24(1)	1
C(4)	4208(1)	7669(1)	6242(2)	25(1)	1
C(5)	4040(1)	7544(1)	4982(2)	21(1)	1
C(6)	3512(1)	6903(1)	4381(2)	17(1)	1
C(7)	3458(1)	6748(1)	3074(2)	17(1)	1
C(8)	3836(1)	6994(1)	1381(2)	25(1)	1
C(9)	3264(1)	6242(1)	1155(2)	20(1)	1
C(10)	2441(1)	6383(1)	190(2)	23(1)	1
C(11)	2594(2)	6514(2)	-1064(2)	33(1)	1
C(12)	1931(1)	5586(2)	100(2)	29(1)	1
C(13)	2015(1)	7156(1)	510(2)	28(1)	1
C(14)	2024(1)	5153(1)	5500(2)	26(1)	1
C(15)	2543(2)	4578(2)	6254(2)	33(1)	1
C(16)	2337(2)	4162(2)	7193(2)	41(1)	1
C(17)	1591(2)	4315(2)	7372(3)	45(1)	1
C(18)	1070(2)	4884(2)	6615(2)	43(1)	1
C(19)	1277(2)	5303(2)	5676(2)	35(1)	1
C(20)	1492(1)	6337(1)	3474(2)	22(1)	1
C(21)	888(1)	5982(1)	2497(2)	24(1)	1
C(22)	256(1)	6481(2)	1823(2)	33(1)	1
C(23)	218(2)	7332(2)	2102(3)	50(1)	1
C(24)	812(2)	7686(2)	3061(4)	63(1)	1
C(25)	1439(1)	7192(2)	3747(3)	44(1)	1
C(26)	3314(2)	3965(2)	1935(3)	41(1)	1
C(27A)	3201(3)	3620(2)	2979(5)	30(1)	0.563(11)
C(27B)	2776(4)	3655(3)	2334(7)	32(2)	0.437(11)
C(28)	2576(3)	3683(2)	3388(3)	56(1)	1
P(2)	0	3840(1)	0	18(1)	1
F(1)	0	2828(1)	0	36(1)	1
F(2)	0	4853(2)	0	32(1)	1
F(3)	955(3)	3812(3)	530(5)	49(1)	0.77(3)
F(4)	-75(4)	3827(4)	1359(6)	51(1)	0.77(3)
F(3B)	900(13)	3927(11)	140(50)	100(9)	0.23(3)
F(4B)	170(30)	3897(16)	1430(20)	94(10)	0.23(3)
P(3)	5000	4813(1)	0	36(1)	1
F(5)	5000	3850(3)	0	210(4)	1
F(6)	5000	5758(3)	0	223(5)	1
F(7)	4919(1)	4802(3)	1329(2)	120(2)	1
F(8)	4076(1)	4798(4)	-481(2)	120(1)	1

C(30)	4962(4)	5145(5)	5617(6)	55(4)	0.50
C(31)	5035(8)	5160(5)	4359(7)	106(8)	0.50
O(30)	5453(3)	4644(3)	3892(5)	68(2)	0.50

Table 3. Selected bond lengths [Å] and angles [°] for DCB24 (CCDC 245187).

Pd(1)-C(28)	2.087(2)	C(28)-Pd(1)-N(1)	171.47(9)
Pd(1)-N(1)	2.1020(15)	C(28)-Pd(1)-C(27B)	37.19(19)
Pd(1)-C(27B)	2.127(4)	N(1)-Pd(1)-C(27B)	134.59(17)
Pd(1)-C(27A)	2.153(4)	C(28)-Pd(1)-C(27A)	36.07(16)
Pd(1)-C(26)	2.239(2)	N(1)-Pd(1)-C(27A)	135.98(13)
Pd(1)-P(1)	2.2639(5)	C(27B)-Pd(1)-C(27A)	23.7(2)
		C(28)-Pd(1)-C(26)	67.92(10)
		N(1)-Pd(1)-C(26)	103.55(9)
		C(27B)-Pd(1)-C(26)	33.40(17)
		C(27A)-Pd(1)-C(26)	36.35(15)
		C(28)-Pd(1)-P(1)	101.37(8)
		N(1)-Pd(1)-P(1)	87.15(5)
		C(27B)-Pd(1)-P(1)	136.98(16)
		C(27A)-Pd(1)-P(1)	132.75(14)
		C(26)-Pd(1)-P(1)	168.99(7)

Table 4. Bond lengths [Å] and angles [°] for DCB24 (CCDC 245187).

Pd(1)-C(28)	2.087(2)	P(3)-F(6)	1.492(5)
Pd(1)-N(1)	2.1020(15)	P(3)-F(5)	1.520(5)
Pd(1)-C(27B)	2.127(4)	P(3)-F(8)	1.549(2)
Pd(1)-C(27A)	2.153(4)	P(3)-F(8)#2	1.549(2)
Pd(1)-C(26)	2.239(2)	P(3)-F(7)#2	1.5592(19)
Pd(1)-P(1)	2.2639(5)	P(3)-F(7)	1.5592(19)
P(1)-C(20)	1.814(2)	C(30)-C(31)	1.4740
P(1)-C(14)	1.8179(19)	C(31)-O(30)	1.3080
P(1)-C(1)	1.8262(18)		
O(1)-C(7)	1.337(2)	C(28)-Pd(1)-N(1)	171.47(9)
O(1)-C(8)	1.465(2)	C(28)-Pd(1)-C(27B)	37.19(19)
N(1)-C(7)	1.287(2)	N(1)-Pd(1)-C(27B)	134.59(17)
N(1)-C(9)	1.502(2)	C(28)-Pd(1)-C(27A)	36.07(16)
C(1)-C(2)	1.397(3)	N(1)-Pd(1)-C(27A)	135.98(13)
C(1)-C(6)	1.412(2)	C(27B)-Pd(1)-C(27A)	23.7(2)
C(2)-C(3)	1.399(3)	C(28)-Pd(1)-C(26)	67.92(10)
C(3)-C(4)	1.382(3)	N(1)-Pd(1)-C(26)	103.55(9)
C(4)-C(5)	1.390(3)	C(27B)-Pd(1)-C(26)	33.40(17)
C(5)-C(6)	1.406(2)	C(27A)-Pd(1)-C(26)	36.35(15)
C(6)-C(7)	1.482(3)	C(28)-Pd(1)-P(1)	101.37(8)
C(8)-C(9)	1.526(3)	N(1)-Pd(1)-P(1)	87.15(5)
C(9)-C(10)	1.549(3)	C(27B)-Pd(1)-P(1)	136.98(16)
C(10)-C(13)	1.529(3)	C(27A)-Pd(1)-P(1)	132.75(14)
C(10)-C(12)	1.529(3)	C(26)-Pd(1)-P(1)	168.99(7)
C(10)-C(11)	1.541(3)	C(20)-P(1)-C(14)	105.92(10)
C(14)-C(15)	1.388(3)	C(20)-P(1)-C(1)	103.80(8)
C(14)-C(19)	1.401(3)	C(14)-P(1)-C(1)	105.63(9)
C(15)-C(16)	1.388(3)	C(20)-P(1)-Pd(1)	112.83(6)
C(16)-C(17)	1.401(4)	C(14)-P(1)-Pd(1)	121.10(7)
C(17)-C(18)	1.386(5)	C(1)-P(1)-Pd(1)	106.03(6)
C(18)-C(19)	1.391(3)	C(7)-O(1)-C(8)	106.45(14)
C(20)-C(25)	1.394(3)	C(7)-N(1)-C(9)	107.51(15)
C(20)-C(21)	1.407(3)	C(7)-N(1)-Pd(1)	128.28(14)
C(21)-C(22)	1.391(3)	C(9)-N(1)-Pd(1)	123.75(12)
C(22)-C(23)	1.386(4)	C(2)-C(1)-C(6)	118.94(16)
C(23)-C(24)	1.385(4)	C(2)-C(1)-P(1)	120.43(14)
C(24)-C(25)	1.385(4)	C(6)-C(1)-P(1)	120.61(14)
C(26)-C(27B)	1.259(6)	C(1)-C(2)-C(3)	121.19(18)
C(26)-C(27A)	1.372(6)	C(4)-C(3)-C(2)	119.57(19)
C(27A)-C(28)	1.314(6)	C(3)-C(4)-C(5)	120.13(18)
C(27B)-C(28)	1.345(7)	C(4)-C(5)-C(6)	120.84(18)
P(2)-F(3B)	1.543(18)	C(5)-C(6)-C(1)	119.03(17)
P(2)-F(3B)#1	1.543(18)	C(5)-C(6)-C(7)	116.43(15)
P(2)-F(4B)	1.57(2)	C(1)-C(6)-C(7)	124.49(15)
P(2)-F(4B)#1	1.57(2)	N(1)-C(7)-O(1)	116.61(16)
P(2)-F(4)	1.590(5)	N(1)-C(7)-C(6)	128.16(16)
P(2)-F(4)#1	1.590(5)	O(1)-C(7)-C(6)	115.06(14)
P(2)-F(2)	1.598(2)	O(1)-C(8)-C(9)	103.71(14)
P(2)-F(1)	1.5982(18)	N(1)-C(9)-C(8)	101.78(15)
P(2)-F(3)	1.603(4)	N(1)-C(9)-C(10)	112.07(15)
P(2)-F(3)#1	1.603(4)	C(8)-C(9)-C(10)	115.76(17)

C(13)-C(10)-C(12)	110.76(17)
C(13)-C(10)-C(11)	110.13(18)
C(12)-C(10)-C(11)	107.80(17)
C(13)-C(10)-C(9)	111.34(16)
C(12)-C(10)-C(9)	109.42(17)
C(11)-C(10)-C(9)	107.27(17)
C(15)-C(14)-C(19)	119.5(2)
C(15)-C(14)-P(1)	118.74(16)
C(19)-C(14)-P(1)	121.78(19)
C(14)-C(15)-C(16)	120.8(2)
C(15)-C(16)-C(17)	119.7(3)
C(18)-C(17)-C(16)	119.5(2)
C(17)-C(18)-C(19)	120.8(2)
C(18)-C(19)-C(14)	119.7(3)
C(25)-C(20)-C(21)	118.5(2)
C(25)-C(20)-P(1)	122.91(16)
C(21)-C(20)-P(1)	118.53(15)
C(22)-C(21)-C(20)	120.12(19)
C(23)-C(22)-C(21)	120.4(2)
C(24)-C(23)-C(22)	119.8(2)
C(25)-C(24)-C(23)	120.2(3)
C(24)-C(25)-C(20)	120.9(2)
C(28)-C(27A)-C(26)	128.5(5)
C(26)-C(27B)-C(28)	136.7(6)
F(3B)-P(2)-F(3B)#1	169.8(13)
F(3B)-P(2)-F(4B)	90.7(14)
F(3B)#1-P(2)-F(4B)	88.7(14)
F(3B)-P(2)-F(4B)#1	88.7(14)
F(3B)#1-P(2)-F(4B)#1	90.7(14)
F(4B)-P(2)-F(4B)#1	173.5(18)
F(3B)-P(2)-F(4)	105.8(18)
F(3B)#1-P(2)-F(4)	74.3(18)
F(4B)#1-P(2)-F(4)	165(2)
F(3B)-P(2)-F(4)#1	74.3(18)
F(3B)#1-P(2)-F(4)#1	105.8(18)
F(4)-P(2)-F(4)#1	178.4(5)
F(3B)-P(2)-F(2)	84.9(7)
F(3B)#1-P(2)-F(2)	84.9(7)
F(4B)-P(2)-F(2)	86.8(9)
F(4B)#1-P(2)-F(2)	86.8(9)
F(4)-P(2)-F(2)	90.8(3)
F(4)#1-P(2)-F(2)	90.8(3)
F(3B)-P(2)-F(1)	95.1(7)
F(3B)#1-P(2)-F(1)	95.1(7)
F(4B)-P(2)-F(1)	93.2(9)
F(4B)#1-P(2)-F(1)	93.2(9)
F(4)-P(2)-F(1)	89.2(3)
F(4)#1-P(2)-F(1)	89.2(3)
F(2)-P(2)-F(1)	180.0
F(3B)#1-P(2)-F(3)	164.4(18)
F(4B)-P(2)-F(3)	75.9(19)
F(4B)#1-P(2)-F(3)	104.3(19)
F(4)-P(2)-F(3)	90.6(3)
F(4)#1-P(2)-F(3)	89.4(3)
F(2)-P(2)-F(3)	91.6(2)
F(1)-P(2)-F(3)	88.4(2)
F(3B)-P(2)-F(3)#1	164.4(18)
F(4B)-P(2)-F(3)#1	104.3(19)
F(4B)#1-P(2)-F(3)#1	75.9(19)
F(4)-P(2)-F(3)#1	89.4(4)
F(4)#1-P(2)-F(3)#1	90.6(3)
F(2)-P(2)-F(3)#1	91.6(2)
F(1)-P(2)-F(3)#1	88.4(2)
F(3)-P(2)-F(3)#1	176.8(4)
F(6)-P(3)-F(5)	180.000(1)
F(6)-P(3)-F(8)	90.9(2)
F(5)-P(3)-F(8)	89.1(2)
F(6)-P(3)-F(8)#2	90.9(2)
F(5)-P(3)-F(8)#2	89.1(2)
F(8)-P(3)-F(8)#2	178.3(4)
F(6)-P(3)-F(7)#2	90.64(19)
F(5)-P(3)-F(7)#2	89.36(19)
F(8)-P(3)-F(7)#2	92.36(12)
F(8)#2-P(3)-F(7)#2	87.63(12)
F(6)-P(3)-F(7)	90.64(19)
F(5)-P(3)-F(7)	89.36(19)
F(8)-P(3)-F(7)	87.63(12)
F(8)#2-P(3)-F(7)	92.36(12)
F(7)#2-P(3)-F(7)	178.7(4)
O(30)-C(31)-C(30)	127.1

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

Table 5. Anisotropic displacement parameters ($Å^2 x\ 10^4$) for DCB24 (CCDC 245187). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Pd(1)	249(1)	152(1)	169(1)	-17(1)	102(1)	-31(1)
P(1)	209(2)	217(2)	157(2)	-38(2)	86(2)	-57(2)
O(1)	270(6)	206(6)	201(7)	-11(5)	116(5)	-71(5)
N(1)	204(7)	184(6)	156(8)	-27(5)	87(6)	-26(5)
C(1)	165(7)	215(7)	168(9)	-20(6)	54(6)	-17(5)
C(2)	219(8)	303(9)	177(9)	-41(7)	90(6)	-23(6)
C(3)	205(8)	354(10)	166(9)	-79(7)	51(7)	-6(7)
C(4)	184(8)	309(9)	235(10)	-102(7)	43(6)	-28(6)
C(5)	183(7)	219(7)	217(9)	-44(6)	61(6)	-25(5)
C(6)	152(6)	186(6)	157(8)	-25(5)	45(5)	-7(5)
C(7)	156(6)	171(6)	187(8)	0(5)	69(5)	-16(5)
C(8)	339(10)	257(9)	205(10)	-22(7)	156(8)	-94(7)
C(9)	261(8)	209(7)	169(9)	-16(6)	122(6)	-43(6)
C(10)	297(9)	266(8)	146(9)	-36(6)	90(7)	-33(7)
C(11)	459(13)	381(12)	182(11)	8(8)	141(9)	-24(9)
C(12)	310(10)	332(10)	208(10)	-58(8)	62(7)	-86(8)
C(13)	301(10)	319(10)	203(10)	15(8)	67(7)	20(7)
C(14)	351(10)	292(9)	196(10)	-70(6)	156(8)	-132(7)
C(15)	479(13)	311(10)	261(12)	-10(8)	201(10)	-86(9)
C(16)	698(18)	313(11)	271(13)	-1(9)	233(12)	-136(11)
C(17)	830(20)	342(12)	308(13)	-148(10)	375(14)	-305(13)
C(18)	540(13)	487(13)	403(12)	-178(16)	351(11)	-278(15)
C(19)	403(12)	419(12)	300(12)	-104(9)	225(10)	-149(9)
C(20)	172(7)	261(8)	228(10)	-94(7)	67(6)	-52(6)
C(21)	232(8)	267(8)	226(10)	-87(7)	70(7)	-72(6)
C(22)	221(9)	419(12)	325(13)	-131(9)	26(8)	-40(8)
C(23)	261(11)	445(14)	680(20)	-170(14)	-48(11)	86(10)
C(24)	311(13)	421(15)	980(30)	-389(17)	-102(15)	122(11)
C(25)	221(10)	410(13)	591(18)	-309(12)	-44(10)	35(8)
C(26)	668(17)	230(10)	422(16)	-52(9)	325(14)	39(10)
C(27A)	400(30)	150(14)	370(30)	4(14)	120(20)	-16(13)
C(27B)	440(40)	154(18)	410(40)	-103(18)	190(30)	-37(18)
C(28)	1130(30)	165(9)	595(19)	10(10)	600(20)	-74(12)
P(2)	208(3)	164(2)	159(3)	0	52(2)	0
F(1)	453(11)	158(7)	586(14)	0	334(10)	0
F(2)	458(9)	159(8)	316(9)	0	61(7)	0
F(3)	201(11)	356(18)	770(30)	35(16)	-63(14)	-7(11)
F(4)	890(30)	440(20)	310(20)	47(14)	357(19)	125(16)
F(3B)	390(70)	340(50)	2400(300)	500(110)	640(110)	170(50)
F(4B)	2200(300)	320(60)	120(60)	130(40)	150(120)	130(130)
P(3)	413(4)	349(6)	402(5)	0	235(3)	0
F(5)	2790(100)	370(20)	3230(110)	0	1010(80)	0
F(6)	4250(130)	290(20)	3080(100)	0	2540(100)	0
F(7)	772(14)	2450(40)	439(11)	130(20)	293(10)	-630(20)
F(8)	562(12)	2360(50)	671(14)	-350(30)	185(11)	-300(20)

C(30)	250(30)	870(110)	530(50)	330(50)	120(30)	250(40)
C(31)	890(100)	540(90)	1800(200)	-350(90)	380(130)	-80(80)
O(30)	770(30)	560(30)	640(30)	-10(20)	130(30)	380(20)

Table 6. Hydrogen bonds for DCB24 (CCDC 245187) [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(30)-H(30)...F(7)	0.85	1.99	2.799(6)	157.8

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

Appendix Nine

Notebook Cross-Reference for New Compounds

NOTEBOOK CROSS-REFERENCE FOR NEW COMPOUNDS

The following notebook cross-reference has been included to facilitate access to the original spectroscopic data obtained for the compounds presented in this thesis. For each compound, both hard copy and electronic characterization folders have been created that contain the original ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, ^{31}P NMR, and IR spectra. All notebooks and spectroscopic data are stored in the Stoltz group archives.

Table A9.1 Compounds in Chapter Two: Early Approaches to the Synthesis of Zoanthenol.

Compound	Procedure	^{1}H NMR	^{13}C NMR	IR
(+)-134a	DCBXXV_103	DCBXXV_103_HighRf_H	DCBXXV_103_HighRf_C	DCBXXV_103_HighRf
(–)-134b	DCBXXV_103	DCBXXV_103_LowRf_H	DCBXXV_103_LowRf_C	DCBXXV_103_LowRf
135	DCBX_175	DCBXXVIII_235_H	DCBXXVIII_235_C	DCBXXVIII_235
137	DCBI_251	DCBXXIX_65_H	DCBXXIX_65_C	DCBXXIX_65
147	DCBX_339	DCBXII_239_H	DCBXII_239_C	DCBXII_239
148	DCBX_299	DCBXI_Benzaldehyde_H	DCBXI_Benzaldehyde_C	DCBXXVI_93_HighRf
149	DCBX_299	DCBXXVI_93_LowRf_H	DCBXXVI_93_LowRf_C	DCBXXVI_93_LowRf
150	DCBXXVIII_225	DCBXXVIII_225_H	DCBXXVIII_225_C	DCBXXVIII_225
151	DCBXII_217	DCBXII_217_H	DCBXII_217_C	DCBXII_217
145	DCBXI_59	DCBXXVIII_237_H	DCBXXVIII_237_C	DCBXXVIII_237
(+)-153	DCBXXV_101	DCBXXV_99_41_H	DCBXXV_99_C	DCBXXV_99
155	DCBXI_67	BBG_Grignard_H	BBG_Grignard_Pdt_C	BBG_Grignard_Pdt
156	DCBXXVIII_227	DCBXXVIII_227_H	DCBXXVIII_227_C	DCBXXVIII_227
157	DCBXXIX_61	DCBXXIX_61_	DCBXXIX_61_	DCBXXIX_61

		H	C	
161	DCBXI_99	DCBXXVIII_241_H	DCBXXVIII_241_CD2CL2_C	DCBXXVIII_241
162	DCBVII_189	DCBVII_189_H	DCBVII_189_C	DCBVII_189
163	DCBX_281-285	DCBX_185_H	DCBX_185_C	DCBX_185
168	DCBXII_93	DCBXXVIII_Tf_H	DCBXXVIII_Tf_C	DCBXXVIII_Tf
169	DCBX_235	DCBVIII_115_H	DCBVIII_115_C	DCBVIII_115
170	DCBVIII_173	DCBVIII_173_H	DCBVIII_173_C	DCBVIII_173
172	DCBVIII_223, 227,231	DCBXXVIII_257_final_H	DCBXXVIII_257_C	DCBXXVIII_257
173	DCBIX_69	DCBXXVIII_259_CDCL3_H	DCBXXVIII_259A_C	DCBXXVIII_259
174	DCBIX_131	DCBXXVIII_261_H	DCBXXVIII_261_C	DCBXXVIII_261
175	DCBXXVIII_269	DCBXXVIII_269_H	DCBXXVIII_269_C	DCBXXVIII_269

Table A9.2 Compounds in Chapter Three: Current Approaches to the Synthesis of Zoanthenol: Synthesis of the ABC Ring System Containing All of the Quaternary Stereocenters.

Compound	Procedure	^{1}H NMR	^{13}C NMR	IR
202	DCBXXVI-77	ThesisChar1_1Hredo	ThesisChar1_13C	ThesisChar1
203	JLSIX_155	Diene_H	Diene_C	JLSX_295
205	JLSXI_25	ThesisChar9_1H	ThesisChar9_13C	JLSVII_73
209	JLSXI_27	JLSV_87_1	IodoLact_C	JLSV_153
210	DCBXXVIII_143	ThesisChar2_1H	ThesisChar2_13C	ThesisChar2
211	DCBXXVIII_151	ThesisChar3_1H	ThesisChar3_13C	ThesisChar3
212	DCBXXVI_163	DCBXXVI_163_H	DCBXXVI_163_C	DCBXXVI_163
213	DCBXXVI_149	DCBXXVI_149_H	DCBXXVI_149_C	DCBXXVI_149

214	DCBXXVI_191	DCBXXVI_191_H	DCBXXVI_191_C	DCBXXVI_191
215	DCBXXVI_137	DCBXXVI_195_H	DCBXXVI_195_C	DCBXXVI_195
216	DCBXXVI_199	DCBXXVI_199_H	DCBXXVI_199_C	DCBXXVI_199
217	DCBXXVI_147	DCBXXVI_101_24_H	DCBXXVI_147_C	DCBXXVI_147
218	DCBXXVI_189	DCBXXVI_189_H	DCBXXVI_189_C	DCBXXVI_189
220	DCBXXVI_193	DCBXXVI_193_H	DCBXXVI_193_C	DCBXXVI_193
227	JLSVIII_299	ThesisChar4_1H	ThesisChar4_13C	ThesisChar4
228	JLSVIII_303	ThesisChar5_1H	ThesisChar5_13C	ThesisChar5
229	JLSX_49	DCBXXVII_157_LS	JLSIX_47_2_C	JLSIX_47_2
230	JLSX_49	DCBXXVII_161TS	JLSIX-47_1_CDCL3_C	JLSIX-47_1
232	DCBXXVII_215	JLSIX_25_1_H	JLSIX_25_1_C	JLSIX_25_1
233a	DCBXXVII_225	DCBXXVII_225 HighRf_H	DCBXXVII_225_HighRf_C	DCBXXVII_225_HighRf
233b	DCBXXVII_225	DCBXXVII_211_39	DCBXXVIII_33_LowRf_C	DCBXXVIII_33_LowRf
234	DCBXXVII_219	DCBXXVII_243_SM_H	DCBXXVII_243_SM_C	DCBXXVII_243_SM
235	DCBXXVIII 239	DCBXXVIII_51_H	DCBXXVIII_51_C	DCBXXVIII_51
236	DCBXXVIII_243	DCBXXVIII_243_H	DCBXXVIII_243_C	DCBXXVIII_243
237	DCBXXVIII_247	DCBXXVIII_95_H	DCBXXVIII_95_C	DCBXXVIII_95
238	JLSIX_213	ThesisChar6_1HRedo	ThesisChar6_13CRedo	ThesisChar6
239	DCBXXVII_217	DCBXXVII_217_H	DCBXXVII_217_C	DCBXXVII_217
240	JLSIX_105	DCBXXVII_145SM_H	DCBXXVII_145SM_C	DCBXXVII_145SM
241	JLS IX_101 JLS IX_107	DCBXXVII_153C6D6_H	DCBXXVII_153C6D6_C	DCBXXVII_153
242	JLSX_21 JLSIX_179	DCBXXVII_163_H	DCBXXVII_163_C	DCBXXVII_163
243	JLSIX_193	DCBXXVIII_9	DCBXXVIII_97	DCBXXVIII_9

	JLSIX_211	7_H	_C	7
247	DCBXXVII_255 and 257	DCBXXVIII_53_LowRf_H	DCBXXVIII_53_LowRf_C	DCBXXVIII_53_LowRf
248	DCBXXVII_255 and 257	DCBXXVIII_53_HighRf_H	DCBXXVIII_53_HighRf_C	DCBXXVIII_53_HighRf
250	DCBXXVIII_99	DCBXXVIII_99_48_H	DCBXXVIII_99_48_C	DCBXXVIII_99_48
251	DCBXXVIII_251	DCBXXVIII_159_H	DCBXXVIII_159_C	DCBXXVIII_159
252	JLSX_31 JLSX_121 JLSX_135	ThesisChar7_1Hb	ThesisChar7_13C	ThesisChar7
253	DCBXXIX_49	DCBXXIX57_H	DCBXXVIII_255_C	DCBXXVIII_163_29B
255	DCBXXIX_59	DCBXXIX_59_H	DCBXXIX_59_C	DCBXXIX_55
257	DCBXXV_31	DCBXXIV_249_19_H	DCBXXIV_249_19_C	DCBXXIV_249_19
258	DCBXXV_39	DCBXXV_39_19_H	DCBXXV_39_19_C	DCBXXV_39
259	DCBXXV_77	DCBXXV_77_37_H	DCBXXV_77_C	DCBXXV_77
260	DCBXXV_79	DCBXXV_83_H	DCBXXV_83_C	DCBXXV_83
262	DCBXXV_113	DCBChar11_H	DCBXXIX_Char11_C	DCBXXV_113
263	DCBXXV_115	DCBthesisChar10_H	DCBthesisChar10_C	DCBXXIX_thesisChar10

Table A9.3 Compounds in Chapter Four: The Development of an Asymmetric Tsuji Allylation Reaction.

Compound	^{1}H NMR	^{13}C NMR	IR
295	DCBXVI_195_H	DCBXVI_195_C	DCBXVI_195
298	KTIII_033_H	KTIII_033_C	KTIII033
299	KTIII_021_H	KTIII_021_C	KTIII_021
300	KTIII_061_H	KTIII_061_C	KTI_261
301	CyPHOX_H	CyPHOX_C	CYPHOX
302	KTII_225_H	KTII_225_C	KTII_225
303	KTIII_023_H	KTIII_023_C	KTIII_023
304	KTIII_025_H	KTIII_025_C	KTIII_025
307	KTIII_223_H	KTIII_223_C	KTIII_223
308	DCBXIV_107_H	DCBXIV_107_C	DCBXIV_107

309	KTIII_221_H	KTIII_221_C	KTIII_221
310	DCBXVIII_299_H	DCBXVIII_299_C	DCBXVIII_299
311	DCBXV_99_H	DCBXV_99_C	DCBXV_99
312	DCBXIV_165_1HChar	DCBXIV_165_13C	DCBXIV_165
313	KTIII_213_H	KTIII_213_C	KTIII_213
314	KTIII_215_H	KTIII_215_C	KTIII_215
315	KTIII_231_H	KTIII_231_C	KTIII_231
317	DCBXIV_233_H	DCBXIV_233_C	DCBXIV_233
318	DCBXV_45_H	DCBXV_45_C	DCBXV_45
435	KTIII_063_H	KTIII_063_C	KTI_265
436	KTII_075_H	KTII_075_C	KTII_075
437	KTIII_191_H	KTIII_191_C	KTIII_191
274	DCBXXI_243_H	DCBXXI_243_C	DCBXXII_51
296	DCBXVI_241_H	DCBXVI_241_C	DCBXVI_241
320	DCBXXI_243_H	DCBXXSI_243_C	DCBXXII_123
322	DCBXXII_199_final_H	DCBXXII_199_final_C	DCBXXII_199
324	DCBXVII_047_20_H1	DCBXVII_047_20_C	DCBXVII_047
326	DCBXVII_075_H	DCBXVII_075_C	DCBXVII_075
328	DCBXXII_193_H	DCBXXII_193_C	DCBXXII_193
330	DCBXV_249_H	DCBXV_249_C 1	DCBXV_249
332	DCBXXIII_93_H	DCBXXIII_93_C	DCBXXIII_93
333	DCBXXII_91_21_H	DCBXXII_91_21_C	DCBXXII_91
335	DCBXXII_89_H	DCBXXII_89_C	DCBXXII_89
337	DCBXXIII_35_H	DCBXXIII_35_C	DCBXXIII_35
339	DCBXXIII_95_H	DCBXXIII_95_C	DCBXXIII_95
422	DCBXV_259_H	DCBXV_259_C	DCBXV_259
425	ECKI_61_H	ECKI_61_C	ECKI_61
426	DCBXXIII_251_H	DCBXXIII_251_C	DCBXXIII_251
428	DCBXV_283_H	DCBXV_283_C	DCBXV_283
429	DCBXVI_153_H	DCBXVI_153_C	DCBXVI_153
431	DCBXV_285_H	DCBXV_285_C	DCBXV_285
433	DCBXXII_183_H	DCBXXII_183_C	DCBXXII_183
441	DCBXV_231_H	DCBXV_231_C	DCBXV_231
442	DCBXV_233_H	DCBXV_233_C	DCBXV_233
347	DCBXXII_MeSilylenolEther_H	DCBXXII_MeSilylenol Ether_C	DCBXXII_MeSi
348	DCBXXII_247_H	DCBXXII_247_C	DCBXXII_247
349	DCBXXIII_273_C6D6_H	DCBXXIII_273_C6D6Hg2_C	DCBXXIII_273
351	DCBXXIII_073_H	DCBXXIII_073_C	DCBXXIII_073
353	DCBXXIII_81_H	DCBXXIII_81_C	DCBXXIII_81
354	DCBXXII_295 _H	DCBXXII_295 _C	DCBXXII_295

355	DCBXXIII_79_H	DCBXXIII_79_C	DCBXXIII_79
358	DCBXXIII_265_H	DCBXXIII_265_C	DCBXXIII_265
262	JTMVI-85C_1H	JTMVI-85C_13C	JTMVI-85C_IR
364	DCBXXIV_101_H	DCBXXIV_101_C	DCBXXIV_101
367	JTMVI-151B_1H	JTMVI-151B_13C	JTMVI-151B_IR
368	JTMVII-35C_1H	JTMVII-35C_13C	JTMVII-35C_IR
370	JTMVII-39E_1H	JTMVII-39E_13C	JTMVII-39E_IR
372	JTMVII-37D_1H	JTMVII-37D_13C	JTMVII-37D
374	DCBXXIV_297_H	DCBXXIV_297_C	DCBXXIV_297
376	JTMVI-121D_1H	JTMVI-121D_13C	JTMVI-121D_IR
378	DCBXXIV_295_H	DCBXXIV_295_C	DCBXXIV_295
380	AMH-I-225	AMH-I-193-13C	AMH-I-225-IR
382	AMH-III-055B	AMH-III-055B-13C	AMH-III-055B-IR
383	DCBXXIV_121_H	DCBXXIV_121_C	DCBXXIV_121
384	JTMVI-105B_1H	JTMVI-105B_13C	JTMVI-105B_IR
386	JTMVI-217B_1H	JTMVI-217B_13C	JTMVI-217B_IR
387	JTMVI-99B_1H	JTMVI-99B_13C	JTMVI-99B_IR
388	MRKVI-227b_1H	MRKVI-227b_13C	MRKVI-227b
390	MRKVIII-61c_1H	MRKVIII-61c_13C	MRKVIII-61c
392	JTMVI-213B_1H	JTMVI-213B_13C	JTMVI-213B_IR
393	JTMVI-215B_1H	JTMVI-215B_13C	JTMVI-215B_IR
395	DCBXXV_37_H	DCBXXV_37_C	DCBXXV_37
397	AMH-II-159	AMH-II-159-13C	AMH-II-159-IR
406	AMH-V-035-H	AMH-II-035-13C	AMH-II-035-IR
408	AMH-V-037B-H	AMH-V-037B-13C	AMH-II-037B-IR
410	JTMVII-273B_1H	JTMVII-273B_13C	JTMVII-273B_IR
412	AMH-V-067-H	AMH-V-067-13C	AMH-V-067-IR
414	JTMVII-275B_1H	JTMVII-275B_13C	JTMVII-275B_IR
416	AMH-V-065A-H	AMH-V-065A-13C	AMH-V-065A-IR
418	JTMVII-189B_1H	JTMVII-189B_13C	JTMVII-189B_IR
420	JTMVII-245B_1H	JTMVII-245B_13C	JTMVII-245B_IR
275	DCBXXII_061_H	DCBXXII_061_C	DCBXXII_061
297	DCBXXII_71_H	DCBXXII_71_C	DCBXXII_71
321	DCBXXII_133_H	DCBXXII_133_C	DCBXXII_133
SI8	DCBXXIII_33_H	DCBXXIII_33_C	DCBXXIII_33
325	DCBXXII_135_H	DCBXXII_135_C	DCBXXII_135
327	DCBXXII_229_H	DCBXXII_229_C	DCBXXII_229
329	DCBXXII_201_H	DCBXXII_201_C	DCBXXII_201
331	DCBXXII_115_H	DCBXXII_115_C	DCBXXII_115
152	DCBXXIII_97_H	DCBXXIII_97_C	DCBXXIII_97
334	DCBXXII_109_H	DCBXXII_109_C	DCBXXII_109
336	DCBXXII_105_H	DCBXXII_105_C	DCBXXII_105
338	DCBXXIII_51_H	DCBXXIII_51_C	DCBXXIII_51
340	DCBXXIII_103_H	DCBXXIII_103_C	DCBXXIII_103
350	DCBXXIII_299_H	DCBXXIII_287_C	DCBXXIII_287

352	DCBXXIII_297_H	DCBXXIII_297_C	DCBXXIII_297
369	JTMVII-63B_1H	JTMVII-63B_13C	JTMVII-63B_IR
371	JTMVII-89B_1H	JTMVII-89B_13C	JTMVII-89B_IR
373	JTMVII-73B_1H	JTMVII-73B_13C	JTMVII-73B_IR
375	JTMVII-57B_1H	JTMVII-57B_13C	JTMVII-57B_IR
377	JTMVI-177B_1H	JTMVI-177B_13C	JTMVI-177B_IR
379	DCBXXV_59_H	DCBXXV_59_C	DCBXXV_59
381	AMH-I-229	AMH-I-229-13C	AMH-I-229-IR
256	DCBXXIV_151_H	DCBXXIV_151_C	DCBXXIV_151
385	JTMVI-161B_1H	JTMVI-161B_13C	JTMVI-161B_IR
389	MRKVII-33b_1H	MRKVII-33b_13C	MRKVII-33b
391	MRKVIII-65_1H	MRKVIII-65_13C	MRKVIII-65
394	JTMVII-31C_1H	JTMVII-31C_13C	JTMVII-31C
396	JTMVII-81B_1H	JTMVII-81B_13C	JTMVII-81B
398	AMH-III-061-C2	AMH-III-061-C2-13C	AMH-III-061-C2 -IR
407	AMH-V-075-H	AMH-V-075-13C	AMH-V-075-IR
409	AMH-V-073-H	AMH-V-073-13C	AMH-V-073-IR
411	JTMVII-283B_1H	JTMVII-283B_13C	JTMVII-283B
413	AMHV-127-H	AMHV-127_-3C	AMHV-127-IR
415	JTMVII-291B_1H	JTMVII-291B_13C	JTMVII-291B
417	AMHV-133-1H	AMHV-133-13C	AMHV-133-IR
421	JTMVII-287B_1H	JTMVII-287B_13C	JTMVII-287B
430	DCBXXIII_301_H	DCBXXIII_301_C	DCBXXIII_301
432	DCBXXIII_259_H	DCBXXIII_259_C	DCBXXIII_259
434	DCBXXIII_263_H	DCBXXIII_263_C	DCBXXIII_263
341	DCBXVI_227_H	DCBXVI_227_C	DCBXVI_227
343	DCBXXII_079_H	DCBXXII_079_C	DCBXXII_079
344	DCBXXIII_49_H	DCBXXIII_49_C	DCBXXIII_49
399	DCBXXIII_223_H	DCBXXIII_223_C	DCBXXIII_223
400	DCBXXIII_209_H	DCBXXIII_209_C	DCBXXIII_209
401	DCBXXIII_219_H	DCBXXIII_219_C	DCBXXIII_219
402	DCBXXIV_041_H	DCBXXIV_041_C	DCBXXIII_159
403	DCBXXVIII_301_H	DCBXXVIII_301_C	DCBXXVIII_301
404	DCBXXVIII_299_H	DCBXXVIII_299_C	DCBXXVIII_299
405	DCBXXVIII_303_H	DCBXXVIII_303_C	DCBXXVIII_303
356	DCBXXVIII_295_H	DCBXXVIII_295_C	DCBXXVIII_295

COMPREHENSIVE BIBLIOGRAPHY

Aboulhoda, S. J.; Henin, F.; Muzart, J.; Thorey, C. *Tetrahedron Lett.* **1995**, *36*, 4795-4796.

Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichimica Acta* **1997**, *30*, 3-12.

Aoki, K.; Noguchi, H.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1993**, *34*, 5105-5108.

Atta-ur-Rahman; Alvi, K. A.; Abbas, S. A.; Choudhary, M. I.; Clardy, J. *Tetrahedron Lett.* **1989**, *30*, 6825-6828.

Bagdanoff, J. T. Development of the Enantioselective Oxidation of Secondary Alcohols and Natural Products Total Synthesis. Ph.D., California Institute of Technology, Pasadena, CA, August 2005.

Baker, B. R.; Querry, M. V.; Kadish, A. F. *J. Am. Chem. Soc.* **1980**, *102*, 6893-6894.

Baumann, M. E.; Bosshard, H.; Breitenstein, W.; Rihs, G.; Winkler, T. *Helv. Chim. Acta* **1984**, *67*, 1897-1905.

Berthelot, J.; Guette, C.; Desbène, P.-J.; Basselier, J.-J. *Can. J. Chem.* **1989**, *67*, 2061-2066.

Bhattacharya, A.; Dolling, U.-H.; Grabowski, E. J. J.; Karady, S.; Ryan, K. M.; Weinstock, L. *Angew. Chem., Int. Ed.* **1986**, *25*, 476-477.

Bienaymé, H. *Tetrahedron Lett.* **1994**, *35*, 7383-7386.

Bienaymé, H. *Tetrahedron Lett.* **1994**, *35*, 7387-7390.

Birman, V. B.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2080-2081.

Bodine, P. V. N.; Harris, H. A.; Komm, B. S. *Endocrinology* **1999**, *140*, 2439-2451.

Bofinger, K. R.; Hanack, M. *Chem. Ber.* **1985**, *118*, 2993-3003.

Boger, D. L. Key Ring Forming Reactions. *Modern Organic Synthesis: Lecture Notes*, TSRI Press: La Jolla, CA, 1999; pp 273-281.

Bolm, C.; Schiffers, I.; Dinter, C. L.; Gerlach, A. *J. Org. Chem.* **2000**, *65*, 6984-6991.

Bräse, S.; De Meijee A. Intramolecular Heck Reaction. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002, pp 1223-1254.

Breuning, M.; Corey, E. J. *Org. Lett.* **2001**, *3*, 1559-1562.

Brewster, A. G.; Leach, A. *Tetrahedron Lett.* **1986**, *27*, 2539-2542.

Buchschacher, P.; Fürst, A.; Gutzwiller, J. *Org. Synth.* **1985**, *63*, 37-43.

Bunn, B. J.; Simpkins, N. S. *J. Org. Chem.* **1993**, *58*, 533-534.

Buono, F.; Tenaglia, A. *J. Org. Chem.* **2000**, *65*, 3869-3874.

Buono, G.; Chiodi, O.; Wills, M. *Synlett* **1999**, 377-388.

Burger, E. C.; Barron, B. R.; Tunge, J. A. *Synlett* **2006**, 2824-2826.

Carpenter, N. E.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5845-5848.

Carreno, M. C.; Ruano, J. L. G.; Sanz, G.; Toledo, M. A.; Urbano, A. *J. Org. Chem.* **1995**, *60*, 5328-5331.

Carreno, M. C.; Ruano, J. L. G.; Sanz, G.; Toledo, M. A.; Urbano, A. *Synlett.* **1997**, 1241-1242.

Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dungogues, J. *Tetrahedron* **1987**, *43*, 2075-2088.

Cha, J. K.; Christ, W. J.; Finan, J. M.; Fujioka, H.; Kishi, Y.; Klein, L. L.; Ko, S. S.; Leder, J.; McWhorter, W. W.; Pfaff, K.-P.; Yonaga, M.; Uemura, D.; Hirata, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7369-7371.

Chambers, T. J. *J. Cell Sci*. **1982**, *57*, 247-260.

Charette, A. B.; Lebel, H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 2, pp 581-603.

Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc*. **2000**, *122*, 3783-3784.

Chen, Y.; Deng, L. *J. Am. Chem. Soc*. **2001**, *123*, 11302-11303.

Chen, Y.; McDaid, P.; Deng, L. *Chem. Rev*. **2003**, *103*, 2965-2983.

Chen, Y.; Tian, S.-K.; Deng, L. *J. Am. Chem. Soc*. **2000**, *122*, 9542-9543.

Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591-4597.

Cooper, M. S.; Heaney, H.; Newbold, A. J.; Sanderson, W. R. *Synlett*. **1990**, 533-535.

Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650-1667.

Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett*. **1981**, *22*, 3455-3458.

Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed*. **1998**, *37*, 388-401.

Cox, P.; Simpkins, N. S. *Synlett* **1991**, 321-323.

Cox, P.; Simpkins, N. S. *Tetrahedron Asymmetry* **1991**, *2*, 1-26.

Dankwardt, J. W.; Flippin, L. A. *J. Org. Chem*. **1995**, *60*, 2312-2313.

Daranas, A. H.; Fernández, J. J.; Gavín, J. A.; Norte, M. *Tetrahedron* **1998**, *54*, 7891-7896.

Daranas, A. H.; Fernández, J. J.; Gavín, J. A.; Norte, M. *Tetrahedron* **1999**, *55*, 5539-5546.

Dauben, W. G.; Gerdes, J. M.; Smith, D. B. *J. Org. Chem*. **1985**, *50*, 2576-2578.

Dauben, W. G.; Kessel, C. R.; Takemura, K. H. *J. Am. Chem. Soc*. **1980**, *102*, 6894-

6896.

Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861-2903.

Dawson, G.J.; Frost, C. G.; Martin C. J.; Williams, J. M.; Coote, S. J. *Tetrahedron Lett.* **1993**, *34*, 7793-7796.

Denmark, S. E.; O'Connor, S. P. *J. Org. Chem.* **1997**, *62*, 584-594.

Detalle, J.-F.; Riahi, A.; Steinmetz, V.; Hénin, F.; Muzart, J. *J. Org. Chem.* **2004**, *69*, 6528-6532.

Donde, Y.; Overman, L. E. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 675-697.

Donnelly, D. M. X.; Finet, J.-P.; Rattigan, B. A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1729-1735.

Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **1999**, *38*, 2398-2400.

Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363-5367.

Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945-2963.

Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 62-63.

Doyle, M. P. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 191-228.

Dua, S.; Taylor, M. S.; Buntine, M. A.; Bowie, J. H.; *J. Chem. Soc. Perkin Trans. 2* **1997**, 1991-1997.

Duhamel, P.; Cahard, D.; Poirier, J.-M. *Chem. Soc., Perkin Trans. 1* **1993**, 2509-2511.

Duhamel, P.; Cahard, D.; Quesnel, Y.; Poirier, J.-M. *J. Org. Chem.* **1996**, *61*, 2232-2235.

Duke, R. K.; Rickards, R. W. *J. Org. Chem.* **1984**, *49*, 1898-1904.

Evans, D. A.; Johnson, J. S. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 3, pp 1177-1235.

Evans, D. A.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10162-10163.

Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581-5582.

Fernández, J. J.; Souto, M. L.; Daranas, A. H.; Norte, M. *Current Topics in Phytochemistry* **2000**, *4*, 106-119.

Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594-4595.

France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985-3012.

Franck-Neumann, M.; Miesch, M.; Barth, F. *Tetrahedron* **1993**, *49*, 1409-1420.

Fukuzawa, S.; Hayashi, Y.; Uemura, D.; Nagatsu, A.; Yamada, K.; Ijuin, Y. *Heterocyclic Communications* **1995**, *1*, 207-214.

Gawley, R. E. *Synthesis* **1976**, 777-794.

Gelman, D.; Jiang, L.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2315-2318.

Ghosh, S.; Rivas, F.; Fischer, D.; González, M. A.; Theodorakis, E. A. *Org. Lett.* **2004**, *6*, 941-944.

Gibson, S.E.; Guillo, N.; Tozer, M. J. *Chem. Commun.* **1997**, 637-638.

Gibson, S.E.; Middleton, R. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1743-1744.

Glorius, F.; Pfaltz, A. *Org. Lett.* **1999**, *1*, 141-144.

Goodwin, N. T. Application of iminium activation technologies to natural product synthesis: Total syntheses of the spiculisporic acids, progress towards the total synthesis of cylindrocyclophane F, and a formal synthesis of

cylindrocyclophane A. Ph.D., California Institute of Technology, Pasadena, CA, July 2006.

Graening, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 17192-17193.

Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615-1621.

Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261-1268.

Hamilton, J. G. C.; Hooper, A. M.; Mori, K.; Pickett, J. A.; Sano, S. *Chem. Commun.* **1999**, 355-356.

Han, C.; Qi, J.; Shi, X.; Sakagami, Y.; Shibata, T.; Uchida, K.; Ojika, M. *Biosci. Biotechnol. Biochem.* **2006**, *70*, 706-711.

Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600-7605.

Hayashi, T.; Kanehira, K.; Hagihara, T.; Kumada, M. *J. Org. Chem.* **1988**, *53*, 113-120.

Hayashi, U. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S.; Jorgensen, K. A., Eds.; Wiley-VCH: New York, 2002; pp 5-56.

Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146-151.

Heck, R. F. *Org. React.* **1982**, *27*, 345-390.

Heck, R. F.; Nolley, J. P. *J. Am. Chem. Soc.* **1968**, *90*, 5518-5526.

Helmchen, G. *J. Organomet. Chem.* **1999**, *576*, 203-214.

Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000,** *33*, 336-345.

Helmchen, G.; Steinhagen, H.; Reggelin, M.; Kudis, S. In *Selective Reactions of Metal-Activated Molecules*; Werner, H., Schreier, P., Eds.; Vieweg Verlag: Wiesbaden, 1998; 205-215.

Herrinton, P. M.; Klotz, K. L.; Hartley, W. M. *J. Org. Chem.* **1993**, *58*, 678-682.

Hikage, N.; Furukawa, H.; Takao, K.; Kobayashi, S. *Chem. Pharm. Bull.* **2000**, *48*, 1370-1372.

Hikage, N.; Furukawa, H.; Takao, K.; Kobayashi, S. *Tetrahedron Lett.* **1998**, *39*, 6237-6240.

Hikage, N.; Furukawa, H.; Takao, K.; Kobayashi, S. *Tetrahedron Lett.* **1998**, *39*, 6241-6244.

Hills, I. D.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3921-3924.

Hirai, G.; Koizumi, Y.; Moharram, S. M.; Oguri, H.; Hirama, M. *Org. Lett.* **2002**, *4*, 1627-1630.

Hirai, G.; Oguri, H.; Hayashi, M.; Koyama, K.; Koizumi, Y.; Moharram, S. M.; Hirama, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2647-2651.

Hirai, G.; Oguri, H.; Hirama, M. *Chem. Lett.* **1999**, *28*, 141-142.

Hirai, G.; Oguri, H.; Moharram, S. M.; Koyama, K.; Hirama, M. *Tetrahedron Lett.* **2001**, *42*, 5783-5787.

Hoffman, H. M. R.; Eggert, U.; Gibbels, U.; Giesel, K.; Koch, O.; Lies, R.; Rabe, J. *Tetrahedron* **1988**, *44*, 3899-3918.

House, H. O. *J. Am. Chem. Soc.* **1955**, *77*, 3070-3075.

House, H. O. *J. Am. Chem. Soc.* **1955**, *77*, 5083-5089.

House, H. O.; Roelofs, W. L.; Trost, B. M. *J. Org. Chem.* **1966**, *31*, 646-655.

Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J.-E. *Chem. Soc. Rev.* **2001**, *30*, 321-331.

Irifune, T.; Ohashi, T.; Ichino, T.; Sakia, E.; Suenaga, K.; Uemura, D. *Chem. Lett.* **2005**, *34*, 1058-1059.

Iserloh, U.; Curran, D. P.; Kanemasa, S. *Tetrahedron: Asymmetry* **1999**, *10*, 2417-2428.

Juhl, M.; Nielsen, T. E.; Le Quement, S.; Tanner, D. *J. Org. Chem.* **2006**, *71*, 265-280.

Kita, M.; Uemura, D. *Chem. Lett.* **2005**, *34*, 454-459.

Kuramoto, M.; Arimoto, H.; Hayashi, K.; Hayakawa, I.; Uemura, D.; Chou, T.; Yamada, K.; Tsuji, T.; Yamaguchi, K.; Yazawa, K. *Symposium Papers, 38th Symposium on the Chemistry of Natural Products*, **1996**, 79-84.

Kuramoto, M.; Arimoto, H.; Uemura, D. *J. Synth. Org. Chem., Jpn.* **2003**, *61*, 59-65.

Kuramoto, M.; Arimoto, H.; Uemura, D. *Mar. Drugs* **2004**, *1*, 39-54.

Kuramoto, M.; Hayashi, K.; Fujitani, Y.; Yamaguchi, K.; Tsuji, T.; Yamada, K.; Ijuin, Y.; Uemura, D. *Tetrahedron Lett.* **1997**, *38*, 5683-5686.

Kuramoto, M.; Hayashi, K.; Yamaguchi, K.; Yada, M.; Tsuji, T.; Uemura, D. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 771-779.

Kuramoto, M.; Yamaguchi, K.; Tsuji, T.; Uemura, D. Zoanthamines, Antiosteoporotic Alkaloids. In *Drugs from the Sea*, Fusetani, N., Ed.; Karger: Basel, 2000, 98-106.

Kuwano, R.; Ito, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3236-3237.

Kuwano, R.; Uchida, K.; Ito, Y. *Org. Lett.* **2003**, *5*, 2177-2179.

Larock, R. C.; Hightower, T. R.; Kraus, G. A.; Hahn, P.; Zheng, D. *Tetrahedron Lett.* **1995**, *36*, 2423-2426.

Laue, S.; Greiner, L.; Woelfinger, J.; Andreas, L. *Adv. Syn. Catal.* **2001**, *343*, 711-720.

Liebeskind, L. S.; Chidambaram, R.; Nimkar, S.; Liotta, D. *Tetrahedron Lett.* **1990**, *31*, 3723-3726.

Ling, T.; Chowdhury, C.; Kramer, B. A.; Vong, B. G.; Palladino, M. A.; Theodorakis, E.

A. *J. Org. Chem.* **2001**, *66*, 8843-8853.

Ling, T.; Kramer, B. A.; Palladino, M. A.; Theodorakis, E. A. *Org. Lett.* **2000**, *2*, 2073-2076.

Link, J. T. The Intramolecular Heck Reaction. In *Organic Reactions*; Overman, L. E., Ed.; John Wiley & Sons: New York, 2002, 60, pp 157-325.

Liu, S.; Müller, J. F. K.; Neuburger, M.; Schaffner, S.; Zehnder, M. *J. Organomet. Chem.* **1997**, *549*, 283-293.

Lloyd-Jones, G. C.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1995**, *34*, 462-464.

Lydon, K. M.; McKervey, M. A. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 2, pp 539-580.

Ma, S.; Zhang, J. *Tetrahedron Lett.* **2002**, *43*, 3435-3438.

Majetich, G.; Defauw, J.; Ringold, C. *J. Org. Chem.* **1988**, *53*, 50-68.

Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425-5428.

Maruoka, K. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 467-491.

Mase, N.; Tanaka, F.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2004**, *43*, 2420-2423.

Matsuda, I.; Komori, K.; Itoh, K. *J. Am. Chem. Soc.* **2002**, *124*, 9072-9073.

Matsumoto, T.; Ohmura, T. *Chem. Lett.* **1977**, 335-338.

Matsumoto, T.; Usui, S. *Chem. Lett.* **1978**, 897-900.

Matsumoto, T.; Usui, S.; Morimoto, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1575-1579.

McFadden, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 7738-7739.

McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M. . *J. Org. Chem.* **1993**, *58*,

3568-3571.

Mermerian, A. H.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 4050-4051.

Miyashita, M.; Sasaki, M.; Hattori, I.; Sakai, M.; Tanino, K. *Science* **2004**, *305*, 495-499.

Moharram, S. M.; Hirai, G.; Koyama, K.; Oguri, H.; Hirama, M. *Tetrahedron Lett.* **2000**, *41*, 6669-6673.

Moharram, S. M.; Oguri, H.; Hirama, M. *Egypt. J. Pharm. Sci.* **2003**, *44*, 177-193.

Mohr, J. T.; Nishimata, T.; Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 11348-11349.

Moore, R. E.; Scheuer, P. J. *Science* **1971**, *172*, 495-498.

Müller, S.; Liepold, B.; Ruth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521-522.

Munoz-Muniz, O.; Quintanar-Audelo, M.; Juaristi, E. *J. Org. Chem.* **2003**, *68*, 1622-1625.

Murakata, M.; Tsutsui, H.; Hoshino, O, *Org. Lett.* **2001**, *3*, 299-302.

Nagai, K.; Davies, T. A.; Dewasse, B. E.; Jacobs, M. R.; Appelbaum, P. C. *J. Antimicrob. Chemother.* **2001**, *48*, 365-374.

Nakamura, H.; Kawase, Y.; Maruyama, K.; Muria, A. *Bull. Chem. Soc. Jpn.* 1998, *71*, 781-787.

Nakamura, M.; Hajra, A.; Endo, K.; Nakamura, E. *Angew. Chem., Int. Ed.* **2005**, *44*, 7248-7251.

Naqvi, S. M.; Horwitz, J. P.; Filler, R. *J. Am. Chem. Soc.* **1957**, *79*, 6283-6286.

Neuville, L.; Chastanet, J.; Zhu, J. *Tetrahedron Lett.* **1999**, *40*, 7087-7090.

Nicolaou, K. C.; Vassilikogiannakis, G.; Mägerlein, W.; Kranich, R. *Angew. Chem., Int.*

Ed. **2001**, *40*, 2482-2486.

Nielsen, T. E.; Le Quement, S.; Juhl, M.; Tanner, D. *Tetrahedron* **2005**, *61*, 8013-8024.

Nielsen, T. E.; Tanner, D. *J. Org. Chem.* **2002**, *67*, 6366-6371.

Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36-56.

Ohira, S. *Synth. Commun.* **1989**, *19*, 561-564.

Ohmori, N. *J. Chem. Soc., Perkin Trans. 1* **2002**, 755-767.

Ono, S.; Reimer, J. D.; Tsukahara, J. *Zoological Science* **2005**, *22*, 247-255.

Paquette, L. A.; Stirling, C. J. M.; *Tetrahedron* **1992**, *48*, 7383-7423.

Peer, M.; de Jong, J. C.; Kiefer, M.; Langer, T.; Rieck, H.; Schell, H.; Sennhenn, P.; Sprinz, J.; Steinhagen, H.; Wiesse, B.; Helmchen, G. *Tetrahedron* **1996**, *52*, 7547-7583.

Pellissier, H. *Tetrahedron* **2003**, *59*, 8291-8327.

Pfaltz, A. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 2, pp 513-538.

Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 2, 833-884.

Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 2, pp. 833-884.

Pinnick, H. W. *Org. React.* **1990**, *38*, 655-792.

Pletneva, N.; Pletnev, S.; Tikhonova, T.; Popov, V.; Martynov, V.; Pletnev, V. *Acta Cryst. Sec. D* **2006**, *62*, 527-532.

Rae, I. D.; Serelis, A. K. *Aust. J. Chem.* **1990**, *43*, 1941-1948.

Rajamannar, T.; Balasubramanian, K. K. *J. Chem. Soc., Chem. Commun.* **1994**, 25-26.

Remington, S. J.; Wachtner, R. M.; Yarbrough, D. K.; Branchaud, B.; Anderson, D. C.; Kallio, K.; Lukyanov, K. A. *Biochemistry* **2005**, *44*, 202-212.

Rigby, J. H.; Hughes, R. C.; Heeg, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 7834-7835.

Ritter, T.; Zarotti, P.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 4371-4374.

Rivas, F.; Ghosh, S.; Theodorakis, E. A. *Tetrahedron Lett.* **2005**, *46*, 5281-5284.

Roa, C. B.; Anjaneyula, A. S. R.; Sarma, N. S.; Venkatateswarlu, Y. *J. Org. Chem.* **1985**, *50*, 3757-3760.

Roa, C. B.; Anjaneyula, A. S. R.; Sarma, N. S.; Venkatateswarlu, Y.; Rosser, R. M.; Faulkner, D. J.; Chen, M. H. M.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *106*, 7983-7984.

Roa, C. B.; Roa, D. V.; Raju, V. S. N. *Heterocycles* **1989**, *28*, 103-106.

Rose, P. A.; Lei, B.; Shaw, A. C.; Abrams, S. R.; Walker-Simmons, M. K.; Napper, S.; Quail, J. W. *Can. J. Chem.* **1996**, *74*, 1836-1843.

Rudolph, J.; Reddy, K. L.; Chiang, J. P.; Sharpless, K. B. *J. Am. Chem. Soc.* **1997**, *119*, 6189-6190.

Ryu, D. U.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388-6390.

Saá, J. M.; Dopico, M.; Martorell, G.; García-Raso, A. G. *J. Org. Chem.* **1990**, *55*, 991-995.

Sakai, M.; Sasaki, M.; Tanino, K.; Miyashita, M. *Tetrahedron Lett.* **2002**, *43*, 1705-1708.

Salvador, J. A. R.; Melo, M. L. S.; Neves, A. S. *Tetrahedron Lett.* **1996**, *37*, 687-690.

Sano, S.; Kenji, M. *Eur. J. Org. Chem.* **1999**, *7*, 1679-1686.

Sato, D.; Kawasaki, H.; Shimada, I,; Arata, Y.; Okamura, K.; Date, T.; Koga, K. *J. Am.*

Chem. Soc. **1992**, *114*, 761-763.

Sato, Y.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 4738-4739.

Sawamura, M.; Nagata, H.; Sakamoto, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2586-2592.

Schmidt, C.; Thazhuthaveetil, J. *Can. J. Chem.* **1973**, *51*, 3620-3624.

Sepcic, K.; Turk, T.; Macek, P. *Toxicon* **1998**, *36*, 93-940.

Shaw, S. A.; Aleman, P.; Vedejs, E. *J. Am. Chem. Soc.* **2003**, *125*, 13368-13369.

Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187-2209.

Shigemori, H.; Sato, Y.; Kagata, T.; Kobayashi, J. *J. Nat. Prod.* **1999**, *62*, 372-374.

Shimizu, I.; Yamada, T.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 3199-3202.

Shimizu, M.; Matsukawa, K.; Fujisawa, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2128-2130.

Shirai, R.; Tanaka, M.; Koga, K. *J. Am. Chem. Soc.* **1986**, *108*, 543-545.

Sibi, M. P.; Ji, J.; Sausker, J. B.; Jasperse, C. P. *J. Am. Chem. Soc.* **1999**, *121*, 7517-7526.

Sibi, M. P.; Manyem, S. *Org. Lett.* **2002**, *4*, 2929-2932.

Sinniger, F.; Montoya-Burgos, J. I.; Chevaldonné, P.; Pawlowski, J. *Marine Biology* **2005**, *147*, 1121-1128.

Slomczynska, U.; Kaminski, Z. J.; Leplawy, M. T. *Bull. Pol. Acad. Sci. Chem.* **1991**, *39*, 85-88.

Smidt, S. P.; Menges, F.; Pfaltz, A. *Org. Lett.* **2004**, *6*, 2023-2026.

Smith, A. B.; Cho, Y. S.; Friestad, G. K. *Tetrahedron Lett.* **1998**, *39*, 8765-8768.

Sonogashira, K.; Tohdo, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467-4470.

Stecher, H.; Faber, K. *Synthesis* **1997**, 1-16.

Steinhagen, H.; Regglin, M.; Helmchen, G. *Angew. Chem., Int. Ed.* **1997**, *36*, 2108-2110.

Stevens, R. V.; Angle, S. R.; Kloc, K.; Mak, K. F.; Trueblood, K. N.; Liu, Y.-X. *J. Org. Chem.* **1986**, *51*, 4347-4353.

Stevens, R. V.; Bisacchi, G. S. *J. Org. Chem.* **1982**, *47*, 2396-2399.

Stork, G.; Mook, R.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741-3742.

Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1983**, *105*, 6765-6766.

Suh, E. M.; Kishi, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11205-11206.

Suksamrarn, A.; Jankam, A.; Tarnchompoo, B.; Putchakarn, S. *J. Nat. Prod.* **2002**, *65*, 1194-1197.

Syamala, M. S.; Das, J.; Baskaran, S.; Chandrasekaran, S. *J. Org. Chem.* **1992**, *57*, 1928-1930.

Tanner, D.; Anderson, P. G.; Tedenborg, L.; Somfai, P. *Tetrahedron* **1994**, *50*, 9135-9144.

Tanner, D.; Tedenborg, L.; Somfai, P. *Acta Chem. Scand.* **1997**, *51*, 1217-1223.

Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Rev.* **2004**, *37*, 621-631.

Tohma, M.; Tomita, T.; Kimura, M. *Tetrahedron Lett.* **1973**, *14*, 4359-4362.

Trench, R. K. *Pure Appl. Chem.* **1981**, *53*, 819-835.

Trimitsis, G.; Beers, S.; Ridella, J.; Carlon, M.; Cullin, D.; High, J.; Brutts, D. J. *Chem. Soc., Chem. Commun.* **1984**, 1088-1089.

Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355-364.

Trost, B. M. *J. Org Chem.* **2004**, *69*, 5813-5837.

Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1-14.

Trost, B. M.; Bream, R. N.; Xu, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3109-3112.

Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968-5976.

Trost, B. M.; Chupak, L. S.; Lübbers, T. *J. Org. Chem.* **1997**, *62*, 736-737.

Trost, B. M.; Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104-1105.

Trost, B. M.; Lee, C. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; 593-649.

Trost, B. M.; Radinov, R.; Grenzer, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 7879-7880.

Trost, B. M.; Schroeder, G .M.; Kristensen, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3492-3495.

Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759-6760.

Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395-422.

Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 17180-17181.

Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846-2847.

Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590-4591.

Tsuji, J.; Minami, I.; Shimizu, I. *Chem. Lett.* **1983**, 1325-1326.

Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 1793-1796.

Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 4713-4714.

Tsuji, J.; Nisar, M.; Shimizu, I,; Minami, I. *Synthesis* **1984**, *12*, 1009.

Tsuji, J.; Yamada, T.; Minami, I.; Yuhara, M.; Nisar, M.; Shimizu, I. *J. Org. Chem.* **1987**, *52*, 2988-2995.

van Vliet, M. C. A.; Arends, I. W. C. E.; Sheldon, R. A. *Synlett.* **2001**, 1305-1307.

Venkateswarlu, Y.; Reddy, N. S.; Ramesh, P.; Reddy, P. S.; Jamil, K. *Heterocyclic Communications* **1998**, *4*, 575-580.

Villar, R. M.; Gil-Longo, J.; Daranas, A. H.; Souto, M. L.; Fernández, J. J.; Peixinho, S.; Barral, M. A.; Santafé, G.; Rodríguez, J.; Jiménez, C. *Bioorg. Med. Lett.* **2003**, *11*, 2301-2306.

Watanabe, N.; Ogawa, T.; Ohtake, Y.; Ikegami, S.; Hashimoto, S. *Synlett* **1996**, 85-86.

Weiland, P.; Miescher, K. *Helv. Chim. Acta* **1950**, *33*, 2215-2228.

Wiese, B.; Helmchen, G. *Tetrahedron Lett.* **1998**, *39*, 5727-5730.

Williams, D. R.; Brugel, T. A. *Org. Lett.* **2000**, *2*, 1023-1026.

Williams, D. R.; Cortez, G. A. *Tetrahedron Lett.* **1998**, *39*, 2675-2678.

Williams, J. M. J. *Synlett* **1996**, 705-710, and references therein.

Wu, M. H.; Hansen, K. B.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2012-2014.

Yamada, K.; Kuramoto, M.; Uemura, D. *Recent Res. Devel. Pure & Applied Chem.* **1999**, *3*, 245-254.

Yamaguchi, K.; Yada, M.; Tsuji, T.; Kuramoto, M.; Uemura, D. *Biol. Pharm. Bull.* **1999**, *22*, 920-924.

Yan, X.-X.; Liang, C.-G.; Zhang, Y.; Hong, W.; Cao, B.-X.; Dai, L.-X.; Hou, X.-L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6544-6546.

Yu, W.; Jin, Z. *Tetrahedron Lett.* **2001**, *42*, 369-372.

Zhang, W. *Tetrahedron* **2001**, *57*, 7237-7262.

Ziegler, K.; Flaig, W.; Velling, G. *Justus Liebig Ann. Chem.* **1950**, *567*, 204-214.

Zoute, L.; Audouard, C.; Plaquevent, J.-C.; Cahard, D. *Org. Biomol. Chem.* **2003**, *1*, 1833-1834.

ABOUT THE AUTHOR

Douglas Carl Behenna was born in Norristown, Pennsylvania, on May 14, 1978. He is the only child of Donald B. and Dorothy R. Behenna. Shortly after his birth the family moved from Norristown to bucolic Warwick township, in northern Chester County, Pennsylvania, which was until recently home to more livestock than people. His formative years were largely spent outside biking, gardening, or fishing. He attended Owen J. Roberts High School, where he pursued tennis, theatre, and alto saxophone as extracurricular activities.

In the fall of 1996, Doug began his studies at the University of Pennsylvania and began acclimating to the very urban environment of west Philadelphia. He quickly realized his interests lay in chemistry, but it wasn't until he had the pleasure of taking Professor Winkler's class that he decided to focus on organic chemistry. After getting a taste of research in the labratory of Dr. Axelsen, Doug got his first chemistry research experience under the guidance of Professor Dewey McCafferty studying the mechanism of action and chemical synthesis of the potent lipoglycodepsipeptide antibiotic ramoplanin. When not in lab, Doug could frequently be found helping with the construction of the Penn Solar Racing Team's car "lightning." Despite his grades in French, Doug graduated Magna cum Laude with a Bachelor of Arts degree in chemistry and a minor in computer science in 2000.

In the fall of 2000, Doug moved to Pasadena, California, where he began doctoral research with Professor Brian Stoltz at the California Institute of Technology. Doug's doctoral research involved efforts to synthesize the natural product zoanthenol and the development of an asymmetric allylation methodology. On Christmas day 2005, he became engaged to Ms. Angela Jenks. He is looking forward to starting their life together in Cambridge. Doug will begin postdoctoral studies with Professor Corey at Harvard University in November 2006.