Progress Toward the Total Syntheses of the Polycyclic Terpenes Providencin and Bacchopetiolone.
&
Study of Pyrrolysine.

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Abstract

Progress Toward the Total Syntheses of the Polycyclic Terpenes Providencin and Bacchopetiolone.
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The progress toward the total syntheses of two polycyclic terpenes, providencin and bacchopetiolone, are presented. Providencin (**1**) is a highly oxygenated polycyclic diterpene recently isolated from the Caribbean gorgonian ortocoral *Pseudopterogorgia kallos*. This natural product was found to possess modest anticancer activity against human breast, lung and CNS cancer cell lines. The most intriguing structural feature of **1** is a unique bicyclo[12.2.0]hexadecane ring adorned with a variety of potentially labile functional groups (*i.e.*, epoxides, 3-carboxyfuran, cyclobutane).

Bacchopetiolone (**169**) is an unusual dimeric sesquiterpene isolated by Niemeyer *et al.* in 1991 from the Chilean *Baccharis petiolata* species. A tandem phenolic oxidation / Diels-Alder reaction is described for the stereoselective assembly of the polycyclic skeleton of **169**.

Pyrrolysine (**242**), a new naturally occurring amino acid in certain methanogenic archaea, is found in a number of methyl transferases. This amino acid is inserted in response to an in-frame UAG (amber) codon, in the corresponding mRNAs. The proposed structure of pyrrolysine was deduced from the crystal structure of the *Methanosarcina barkeri* monomethylamine methyltransferase.

To Louis-David,

my family and friends.

Acknowledgments

I first I want to thank is my thesis advisor, Professor John Wood, he gave me the opportunity to join his group and provided a stimulating environment to learn from. He was always patient, generous and encouraged independent thinking, which improved my problem solving skills and chemical intuition. I feel privileged to have had the chance to work for John. Thank you!

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Before coming to Yale, I had the chance to obtain a Masters in the laboratory of Professor Frank B. Mallory at Bryn Mawr College. Professor Mallory and his wife Dr. Sally Mallory, were great mentors and I will always be grateful for their continuous guidance and encouragements. While at Bryn Mawr College I met Kelly Butler, Eddie Luzik, Emily and Kevin Minbiole, and I want to thank them for their friendship and support.

My formal training in chemistry actuality began so many years ago... Summer 1997. I joined Professor Stephen Hanessian's laboratories when I was a first year undergraduate at the University of Montréal. This was my first practical research experience, and Professor Hanessian assigned me to a project that showed me the important work that an organic chemist could do and how I could contribute to Science. In the Hanessian group, I worked with Dr. Pratick Devasthale, a post-doctoral fellow who patiently taught me all the basics, from setting up a reaction to interpreting NMRs. By granting me this opportunity to work side-by-side with talented chemists, Professor Hanessian provided me with a decisive first scientific experience for which I will always be greatful.

On a more personal note, I would like to thank my parents Mona and Jean for their love, for always encouraging me to go further and for stressing the value of education. I like to thank my sister Marie-Hélène for being supportive, always understanding and delightful. I would like to thank my best friends, my second family, Annie, Élisabeth, Sandra and Stéphanie for being role models, a source of inspiration, and for their encouragements. I would like to thank M^{me} Pilon and my mother-in-law Nicole Nadeau for their support. Finally, I thank Louis-David, for being the best supportive husband, for making the difficult times sweeter and for never letting me quit. Merci!

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List of Abbreviations

AcOH	acetic acid
aq	aqueous
BF_3•OEt_2	boron trifluoride diethyl etherate
Bn	benzyl
Boc	di-*tert*-butyl dicarbonate
BOP	benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate
br	broad
Bu	butyl
°C	degrees Celsius
CCl_4	carbon tetrachloride
$CDCl_3$	chloroform-*d*
CD_3OD	methanol-*d*
$CHCl_3$	chloroform
CH_3CN	acetonitrile
CNS	central nervous system
conc	concentrated
CSA	Camphorsulfonic acid
δ	chemical shift in ppm downfield from Me_4Si
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublets of doublets
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
ddt	doublet of doublets of triplets
DIBAL	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	dimethyl formamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dt	doublet of triplets
eq	equivalent(s)
Et	ethyl
Et_2O	ethyl ether
EtOAc	ethyl acetate
ESI	electrospray ionization
NEt_3	triethylamine
FTIR	Fourier transform infrared
g	gram(s)
h	hour(s)

H	hydrogen
Hz	hertz
HCl	hydrochloric acid
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrum
IBDA	iodobenzene diacetate
J	coupling constant
KH	potassium hydride
L	liter(s)
LiOH	lithium hydroxide
LRMS	low-resolution mass spectrum
μ	micro
m	milli, medium (FTIR), multiplet (NMR)
M	moles per liter
Me	methyl
MeOH	methanol
$MgSO_4$	magnesium sulfate
MHz	megahertz
min	minute(s)
mol	mole(s)
m.p.	melting point
m/z	mass to charge ratio
NaOMe	sodium methoxide
$NaHCO_3$	sodium bicarbonate
$NaHSO_3$	sodium bisulfite
NaCl	sodium chloride
NaOH	sodium hydroxide
Na_2SO_4	sodium sulfate
Na_2SO_3	sodium sulfite
$Na_2S_2O_3$	sodium thiosulfate
NH_4Cl	ammonium chloride
NMO	4-methylmorpholine N-oxide
NMR	nuclear magnetic resonance
O	oxygen
OAc	acetoxy
p	para
pH	hydrogen ion concentration
PhSH	thiophenol
PMB	*p*-methoxybenzyl
PPh_3	triphenylphosphine
ppm	parts per million
ppt	precipitate
q	quartet
$RhCl_3$	rhodium(III) chloride
s	singlet (NMR), strong (FTIR)
soln	solution

t	triplet
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBSOTf	*tert*-butyldimethylsilyl trifluoromethylsulfonate
TES	triethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
TsOH	toluenesulfonic acid
w	weak

Chapter 1

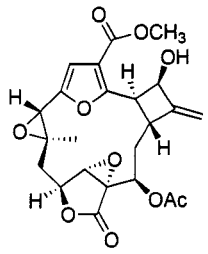
Providencin Initial Studies.

1.1 Background and Introduction.

1.1.1 Providencin: Isolation and Structural Characterization.

Providencin (**1**), a highly oxygenated polycyclic diterpene, was recently isolated from the Caribbean gorgonian ortocoral *Pseudopterogorgia kallos* (Figure 1.1.1).[1] The soft corals of the genus *Pseudopterogorgia* were found to be rich in novel secondary metabolites including architecturally diverse acetogenins, sesquiterpenenoids, diterpenoids and steroids. The gorgonians included over 195 species of sea whips, sea fans and sea plumes, and were found in the warm waters of the Caribbean Sea.[2]

Figure 1.1.1



Providencin (**1**)

Providencin (**1**), a colorless solid, was isolated from 1.07 kg of dry animal specimens to yield only 20 mg of pure **1**, corresponding to an isolation yield of 0.012%. The structure of providencin (**1**) and its relative stereochemistry were elucidated by spectroscopic and X-ray crystallographic analyses.

The molecular formula of providencin (**1**), $C_{23}H_{24}O_{10}$ (HREIMS), indicated 12 degrees of unsaturation. The IR spectrum pointed toward the presence of hydroxyl, ester,

olefin and epoxide functional groups. NMR analyses included ^{1}H, ^{13}C, ^{1}H-^{1}H COSY, NOESY, HMBC, HMQC and DEPT experiments, which helped initially establish the connectivity of the hexacyclic natural diterpene **1**.[1]

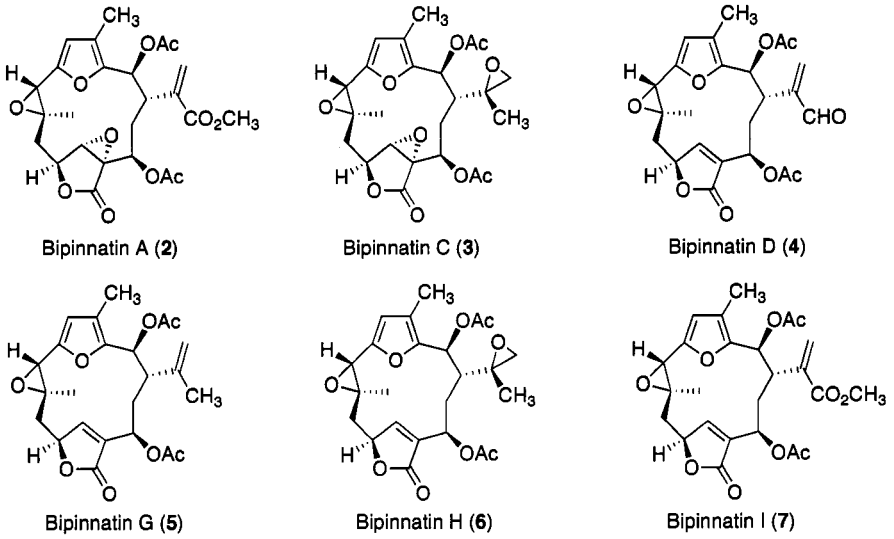
The relative stereochemistry of the nine chiral centers of providencin (**1**) was elucidated using a combination of NMR methods and molecular modeling. Ultimately, recrystallization of providencin (**1**) provided crystals suitable for single-crystal X-ray analysis. The crystallographic data confirmed the proposed connectivity and relative stereochemistry of **1**.

In terms of biological activity, providencin was found to possess modest anticancer activity against human breast (MCF7), lung (NCI-H460) and CNS (SF-268) cancer cell lines. The treated cells had a growth percentage inhibition of approximately 57, 39 and 94% respectively, in comparison to untreated control cells.[1] Based on the bioactivity and structure, providencin (**1**) was seen as an attractive target for total synthesis.[1]

1.1.2 Diterpenes Related to Providencin.

The structure of providencin (**1**) shows a connectivity similar to that of the bipinnatins, a family of highly oxygenated cembrane-based diterpenes isolated from the gorgonian *Pseudopterogorgia bipinnata* (Figure 1.1.2).[3] The common structural features include the 2,3,4-substituted furan, the macrocycle and the butenolide (**4-7**) or epoxidized butenolide (**2** and **3**). The series (**2-7**) displayed inhibition of the nicotinic receptor, as well as anticancer and inflammatory activities.[3]

Figure 1.1.2

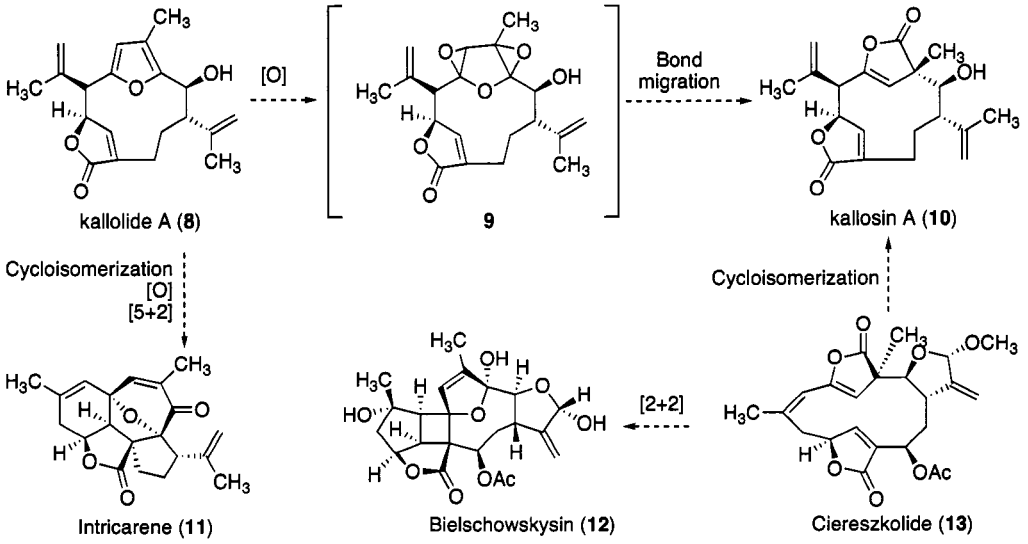


More recently, other structurally diverse natural products besides providencin (**1**) were isolated from the sea plume *Pseudopterogorgia kallos*. For example, kallosin A (**10**)[4] in 2003, ciereszkolide (**13**),[5] bielschowskysin (**12**)[6] in 2004, and intricarene (**11**)[7] in 2005 were all isolated from the same source. Kallolide A (**8**) was the first diterpene to be isolated almost 20 years prior to **1**.[8] Certainly, the gorgonian corals of the genus *Pseudopterogorgia* are a rich source of terpenoid secondary metabolites,[2, 9] these natural products exhibit cytotoxicity (**1**, **8**, **12**) and anti-inflammatory activity (**8**, **12**).

These newly discovered terpenes possessed rearranged carbon skeletons that were previously undescribed. Rodriguez *et al.* proposed that terpenes **8**-**13** were structurally related by simple oxidation, cycloisomerization or cycloaddition (Scheme 1.1.1). For example, the furan moiety of kallolide A (**8**) was oxidized to furnish **9**, a subsequent bond migration delivered kallosin A (**10**).[4] Furthermore, photolysis converted the trisubstituted olefin moiety into the isopropenyl side chain (**13**→**10**),[10] through a [1,3]-sigmatropic rearrangement. Differently, bielschowskysin (**12**) could arise *via* a [2+2]-cycloaddition

from ciereszkolide (**13**). Oxidation and [5+2]-cycloaddition of kallolide A (**8**), or a related terpenoid, could deliver intricarene (**11**).

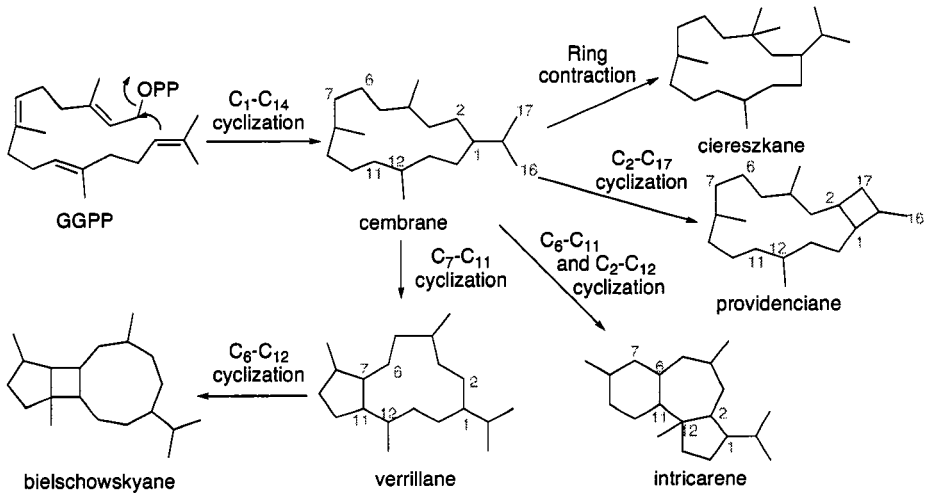
Scheme 1.1.1



These terpenes featured previously undescribed ring systems, forming new classes of natural diterpenes: cembrane, ciereszkane, providenciane, intricarene, and bielschowskyane (Scheme 1.1.2). Providencine (**1**) was identified as the first natural product of the providenciane family, defined by its bicyclo[12.2.0]hexadecane ring system.

Cyclization of GGPP, geranylgeranyl pyrophosphate, was described to be the biogenetic pathway to the cembrane family, and the subsequent ring contraction or cyclization delivered novel classes of marine-derived diterpenes represented in Scheme 1.1.2.[5-7] The various terpenoid subclasses containing a furan and deriving from cembranes are referred to as *furanocembranes*, a more general and inclusive name for this extended family of natural products.

Scheme 1.1.2



1.1.3 Synthetic Studies on Diterpenes Related to Providencin.

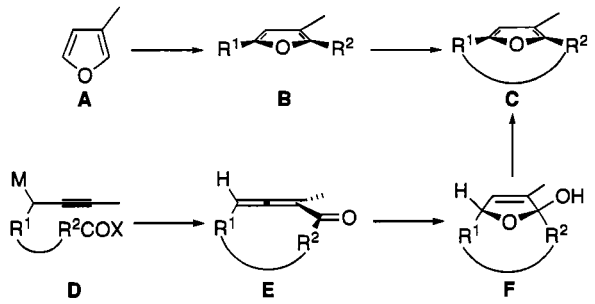
To date there is only one synthetic approach reported regarding providencin (**1**)[11] despite the interest of chemists in several diterpenes related to **1** (*vide supra*). Through their efforts, new methods were developed to construct the furan, butenolide and macrocyclic motifs.

1.1.3.1 Furan Construction.

Upon evaluation of the possible disconnections to make furan containing polycyclic diterpenes, or furanocembranes, Marshall *et al.* suggested two approaches (Scheme 1.1.3).[12] The first approach was to construct a 2,3,5-trisubstituted furan with side chains that could be coupled to form the macrocycle later in the synthesis (**A→B→C**). The disadvantage of this strategy was the need to carry the potentially labile furan through several synthetic steps. Furthermore, the macrocyclization could be entropically and enthalpically challenging. The alternative approach was to construct the

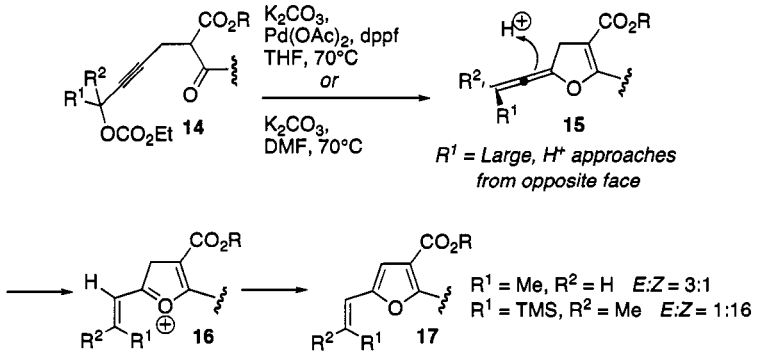
macrocycle first and reserve the furan cyclization for a later stage in the synthesis to minimize the risk of generating unstable intermediates (**D→E→C**). This tactic benefited from a less energetically demanding macrocyclization, the rigidity and conformation of the macrocycle facilitating the furan cyclization.

Scheme 1.1.3[13]



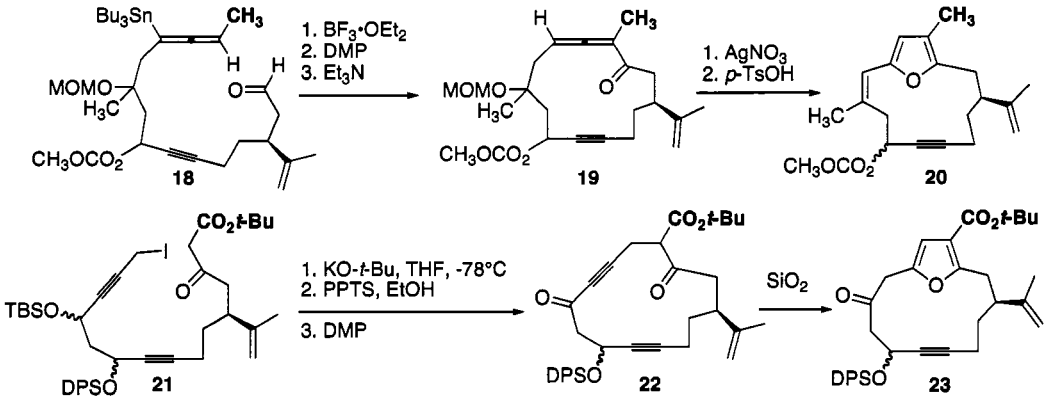
Wipf *et al.* took the former approach to address the synthetic challenges of the furanocembranes; he developed a base or palladium catalyzed cyclization of α-propargyl β-keto esters (**14**) to yield the desired 2-alkenylfurans **17** (Scheme 1.1.4).[14, 15] The *E/Z* selectivity of the alkenyl furan was improved when a large R^1 group (*e.g.* TMS) was introduced, which had a directing effect and favored protonation on the opposite face of R^1 (**15**).

Scheme 1.1.4



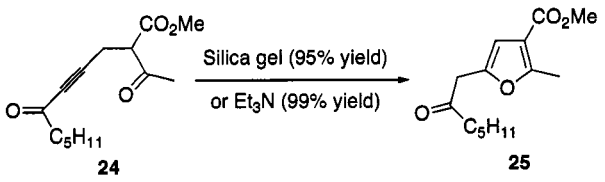
Taking an approach different to that of Wipf, Marshall elected to first cyclize an intermediate in which the furan ring was absent but possessed elements for its formation at a later stage.[12] Marshall built the macrocycle using two different methods (Scheme 1.1.5). Routes toward the synthesis of 3-*methyl*-furanocembrane compounds (**20**) used BF_3•OEt_2 to cyclize an allenylstannane aldehyde (**18**);[13] the resulting alcohol was oxidized with Dess-Martin reagent, then allenone **19** was treated with silver nitrate and acid to affect an intraanular furan formation (**20**).[16]

Scheme 1.1.5



To target 3-*carboxy*-furanocembranes, intramolecular alkylation of β-keto-ester **21** efficiently closed the macrocycle. Deprotection and oxidation of the propargylic alcohol resulted in alkynone **22** which, when treated with silica gel, underwent conjugate addition between the enolizable ketone and the alkynone. Subsequent double bond isomerization provided furan **23**.[17] This novel synthesis of 3-carboxy-2,5-disubstituted furans was performed not only on cyclic systems but also on open intermediate such as **24** (Scheme 1.1.6). The advantages of this cyclization were its mildness and versatility; the reaction could be acid or base catalyzed, allowing for a late stage cyclization in the presence of sensitive functional groups.

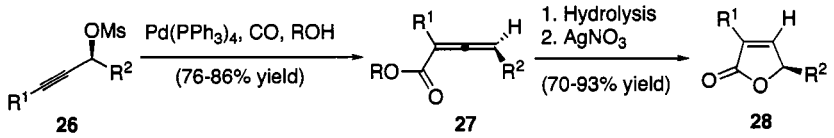
Scheme 1.1.6



1.1.3.2 Butenolide Construction.

While most of the described syntheses toward the furanocembranes used standard conditions to introduce the butenolide moiety, Marshall recognized this substructure as a synthetic opportunity to develop a novel method to access enantiopure butenolides (**28**) from allenic acids and esters (**27**). Nonracemic propargylic mesylates **26** were converted to allenic esters **27** through a palladium catalyzed alkoxycarbonylation with net inversion of configuration (Scheme 1.1.7).[18, 19] Treatment of the corresponding acid **27** with catalytic silver nitrate delivered the desired butenolide (**28**) in good yield and 80% to 95% enantiomeric excess.

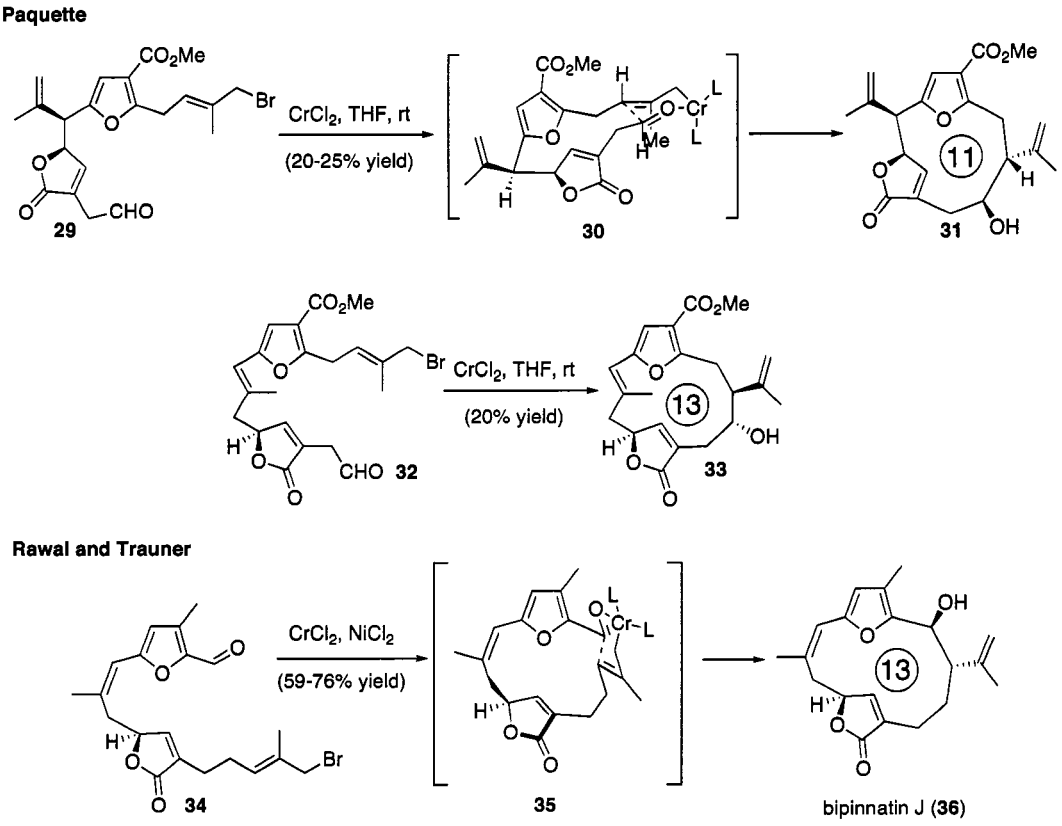
Scheme 1.1.7



1.1.3.3 Macrocycle Construction.

The various groups that worked toward the total syntheses of furanocembranes envisioned the macrocyclization event occurring either with or without the furan moiety. While the latter approach was preferred by Marshall (*vide supra*), late stage macrocyclization of furan containing substrates has also proven successful.

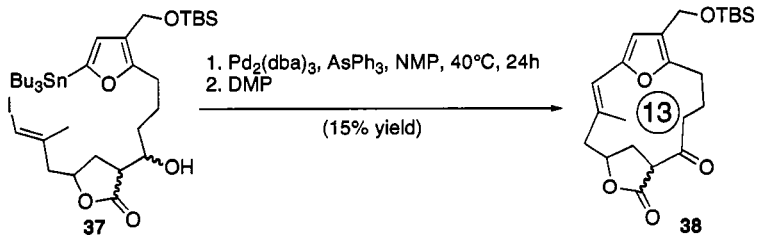
Scheme 1.1.8



Paquette *et al.* relied on the Nozaki-Hiyama-Kishi allylchromium process for the stereoselective closure of medium-to-large rings of furanocembranes. Indeed, Paquette's group successfully formed the 11- and 13-membered-rings (**31** and **33**) following treatment of aldehydes **29** and **32** with $CrCl_2$ at room temperature.[20-22] More recently, the same key reaction was utilized by Trauner *et al.* and Rawal *et al.* in their independent synthesis of bipinnatin J (**36**);[23, 24] the final step of both syntheses was a Nozaki-Hiyama-Kishi cyclization. The key cyclization was performed in presence of the furan and butenolide (**34**), which illustrated the functional group tolerance of these reaction conditions. The diastereoselectivity of the macrocyclization was presumed to arise from a chair-like transition state wherein the remote furanone stereocenter induced the relative

stereochemistry of the two new stereocenters (see **35→36**)[23] and intramolecular π-facial attack at the aldehyde carbonyl by the flanking π-bond such that both large groups are equatorially arranged on the oxachromium six-membered ring (see **30** and **35**).[22]

Scheme 1.1.9



The studies toward the synthesis of furanocembranes led Paterson *et al.* to take advantage of the intramolecular Stille coupling reaction to access the 13-membered ring macrocyclic core **38**.[25, 26]

1.1.3.4 Summary

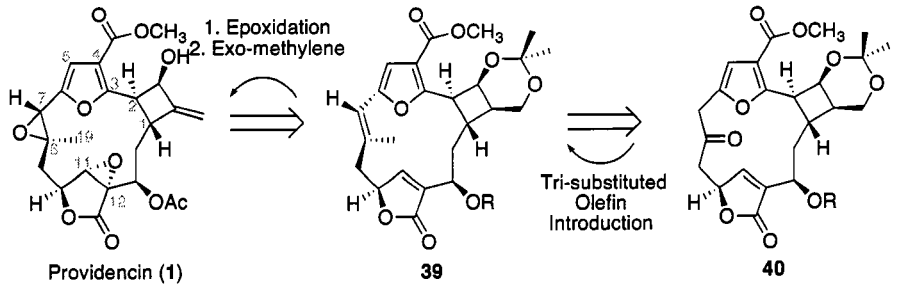
This overview of the different approaches taken to assemble the furan and butenolide substructures, and furanocembranoid macrocycle guided our retrosynthetic approach of providencin (**1**).

1.2 Retrosynthetic Analysis.

Upon considering possible disconnections of providencin (**1**) we took into consideration its most intriguing structural feature, a unique bicyclo[12.2.0]hexadecane ring adorned with a variety of potentially labile functional groups. As illustrated in Scheme 1.2.1, we opted to introduce the epoxides at a late stage to minimize the risk of generating unstable intermediates (**39→1**). This strategy would also allow us to take advantage from *macrocyclic stereocontrol*: we anticipated the rigidity and conformation

of macrocycle **39** would help to direct the epoxidations. The vinylfuran moiety (**39**) would be introduced in turn by methylation of a vinyl triflate generated from β-ketofuran **40**.

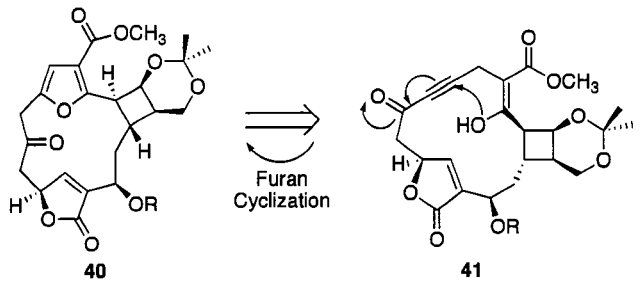
Scheme 1.2.1



Assemblies of the specific substructures are discussed in the following sections (*vide infra*).

1.2.1 Structural Considerations: Furan.

Scheme 1.2.2



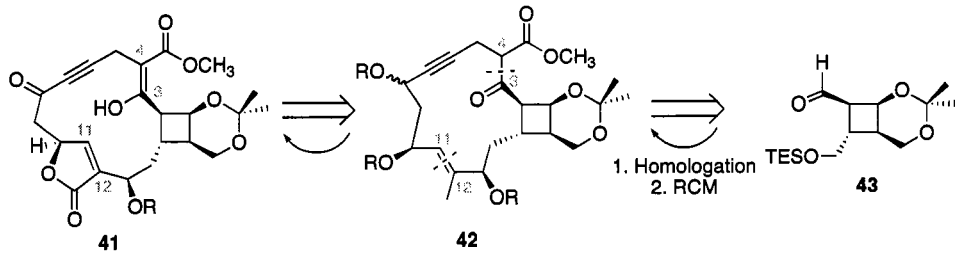
We recognized that the β-ketofuran **40** could be accessed using the method developed by Marshall (Section 1.1.3.1). Enolized β-keto ester **41** would add 1,4 into an alkynone and deliver not only a furan but also a ketone that would serve as a handle to further functionalize the macrocycle. We also selected Marshall's method because of its mildness, which would allow us to reserve the furan formation for a later stage in the

synthesis. Furthermore, there were several methods available to assemble substituted β-ketoesters.

1.2.2 Structural Considerations: Butenolide and Macrocycle.

While considering the retrosynthetic fragmentation of macrocycle **42**, we elected to disconnect the β-ketoester between C3 and C4; homologation of aldehyde **43** would result in the desired furan precursor.

Scheme 1.2.3

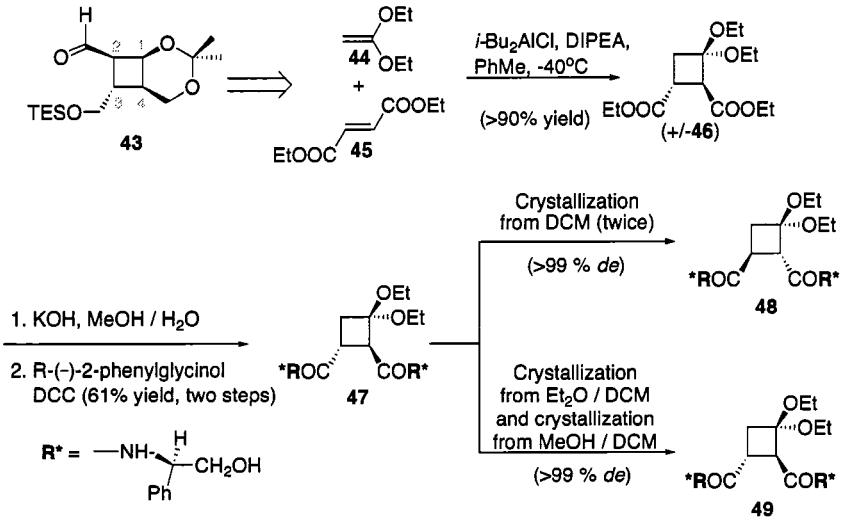


Ring closing metathesis (RCM) was chosen to close the bottom portion of the macrocycle, between C11-C12. This modern cyclization has been successful in many natural product syntheses[27] to make small-to-large rings, including Wood's total synthesis of ingenol.[28] Advantageously, RCM could be performed on advanced substrates; most functionalities and protective groups being compatible with the reaction conditions. Therefore, we planned to take advantage of RCM to access macrocycle **42**, which would allow us to deliver butenolide **41** after oxidation.

1.2.3 Structural Considerations: Cyclobutane.

The cyclobutane embedded within the polycyclic framework of providencin (**1**) was the most attractive feature of the furanocembrane. We envisioned cyclobutyl substructure **43** as a template that would facilitate the formation of the macrocycle. In providencin (**1**), the cyclobutanol subunit is trans-fused to the macrocycle and has an exo-olefin. Substrate **43** is highly oxygenated and strained, therefore susceptible to retro-aldol processes between C1-C2 and C1-C4 if deprotected or in a different oxidation state. The heavily functionalized cyclobutane **43** possesses functionalities poised for further elaboration.

Scheme 1.2.4



Upon looking at different strategies to build highly substituted cyclobutanes we found in the patent literature the report of a [2+2] cycloaddition between a ketene acetal (**44**) and diethyl fumarate (**45**) in the presence of diisobultylaluminium chloride.[29] This procedure was performed on multigram scale in good yield, which is ideal for the first

step of a total synthesis. Furthermore, work by Bisacchi *et al.* showed that the diastereomeric bis-amide derivatives (**47**) of compound **46** could be separated by successive crystallization to give **48** and **49** as enantiopure compounds (> 99% *de*).[30]

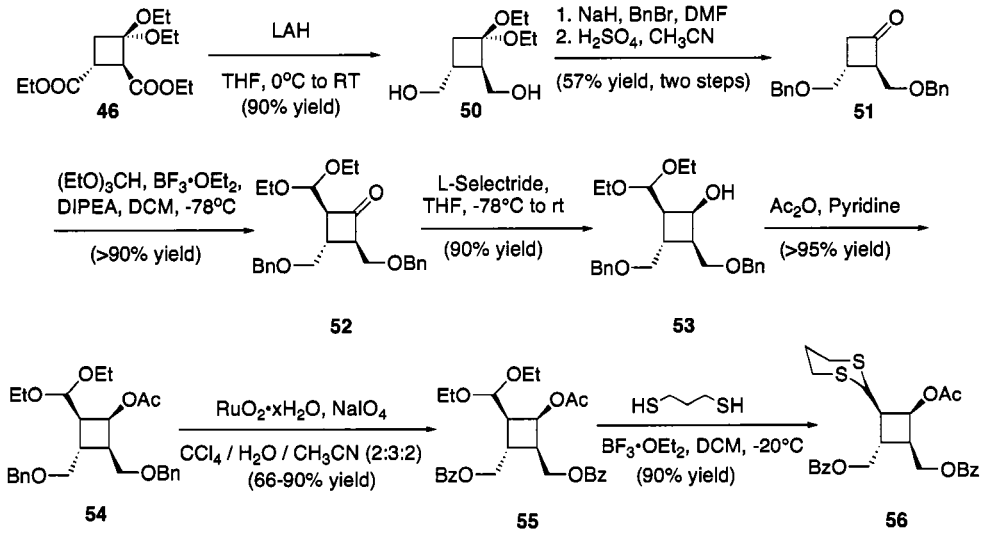
1.2.4 Summary.

In summary, our first task was to assemble a highly substituted cyclobutane fragment. Substrate **43** was designed to bear an aldehyde moiety to be homologated, and with orthogonally protected alcohols. Because fragment **43** is highly oxygenated, careful planning of the protecting group strategies and oxidation states was required to prevent retro-aldol processes between C1 and C2, as well as between C1 and C4.

1.3 Assembly of a Functionalized Cyclobutane (43).

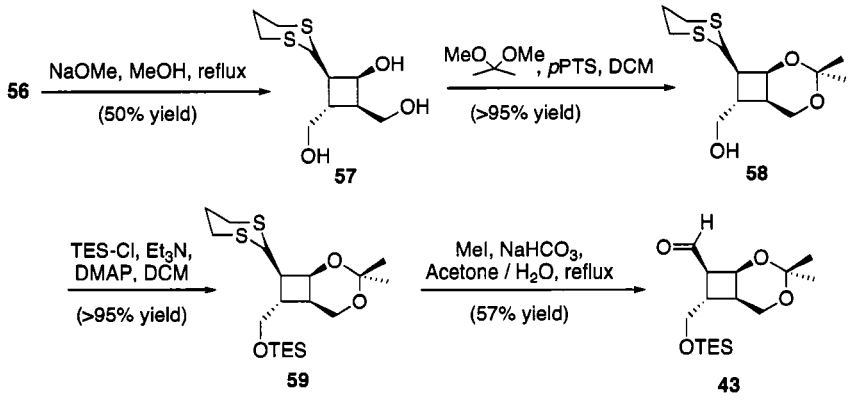
The synthesis of cyclobutane **43** began with the large-scale production of [2+2] cycloadduct **46**; the diester was reduced with LAH, the resulting diol **50** protected as its dibenzyl ether and the ketal removed under acidic conditions to produce ketone **51** (Scheme 1.3.1). Cyclobutanone **51** was formylated at the alpha position using triethyl orthofomate in the presence of Et_3N and $BF_3{\cdot}OEt_2$.[31] The reaction produced a single diastereomer (**52**) where the masked aldehyde was anti to the adjacent bulky substituent. Two *syn*-substituents flanked ketone **52**, which allowed for the diastereoselective reduction of the carbonyl using L-selectride, a bulky reducing agent. The resulting alcohol **53** was obtained in 90% yield and protected as the corresponding acetate **54** in nearly quantitative yield.

Scheme 1.3.1



At this point, some protecting group manipulations were required to prevent retro-aldol fragmentations previously mentioned. We first oxidized the benzyl ethers (**54**) to the benzoic esters (**55**) using ruthenium oxide[32] and replaced the diethylacetal with a dithiane (**56**) using standard conditions. With intermediate **56** in hand, concomitant removal of the three ester protecting groups using NaOMe in refluxing methanol was performed to furnish triol **57** in 50% yield.

Scheme 1.3.2



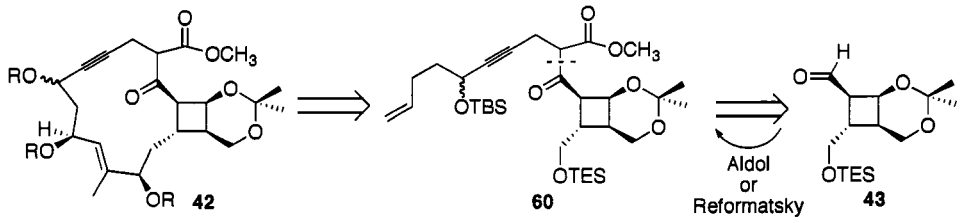
The triol (**57**) was selectively protected as its acetonide in quantitative yield and the remaining primary alcohol (**58**) protected as a silyl ether (**59**). The dithiane was removed using excess methyl iodide in a refluxing acetone/water mixture. Although a number of steps were required to access aldehyde **43**, we were able to prevent retro-aldols and access an orthogonally functionalized cyclobutane ready to be further elaborated.

1.4 Homologation of Aldehyde 43.

1.4.1 Aldol and Reformatsky Reaction.

We had gained access to an orthogonally functionalized cyclobutane (**43**) and were poised to homologate the aldehyde (**43**), thereby initiating the construction of the macrocyclic skeleton of providencin (**1**).

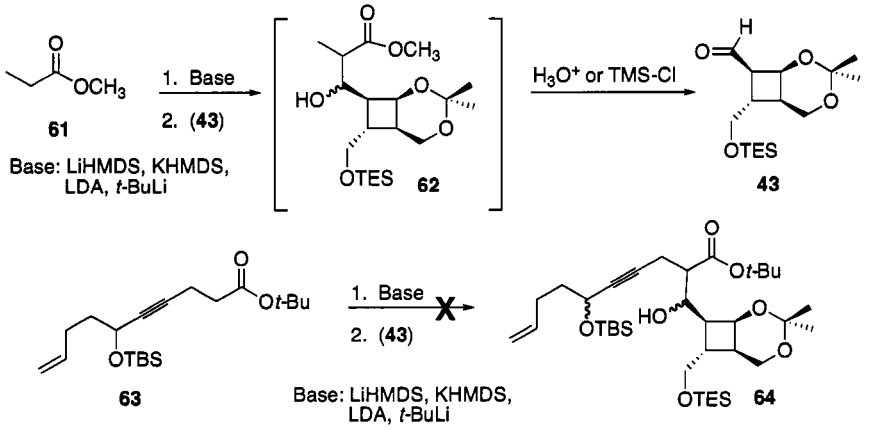
Scheme 1.4.1



We envisioned performing either an aldol or Reformatsky reaction on aldehyde **43** to deliver a β-hydroxyester, which would be only one oxidation state away from the desired β-ketoester **60**. We carried out intermolecular aldol reactions on aldehyde **43** with the enolate of methyl propionate, but the retro-aldol process seemed to predominate as we only recovered the starting aldehyde **43** after the reaction work-up.[1] Similar results were also observed with the more functionalized substrate **63**. We tried lithium, sodium

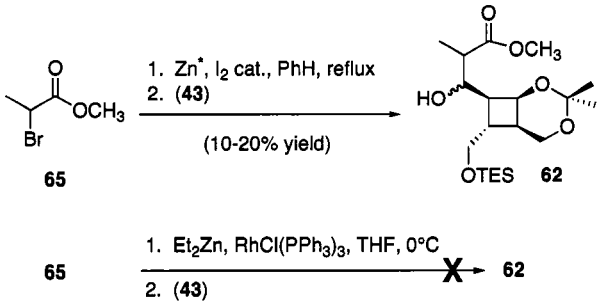
and potassium bases, and also used different quenching methods as an attempt to trap the desired β-hydroxyesters (**62** or **64**), but aldehyde **43** was always the only material recovered from these reactions.

Scheme 1.4.2



In order to avoid retro-aldol reactions, we turned our attention to Reformatsky conditions which are known to proceed under neutral conditions. We first used a model compound to test the feasibility of the Reformatsky reaction on aldehyde **43**. To this end, α-bromo-methylpropionate **65** was treated with activated zinc (Zn*) in refluxing benzene, and aldehyde **43** was added. The desired product (**62**) was isolated in 10 to 20% yield; however, none of aldehyde **43** was recovered, potentially due to decomposition under the reaction conditions. For that reason, we tried milder Reformatsky-type reaction conditions developed by Honda *et al.*[33] This catalytic version called for the use of diethylzinc and Wilkinson's catalyst[34] in THF at 0°C to give β-hydroxyesters, typically within five minutes. However, the zinc enolate did not attack our aldehyde **43** at 0°C or 20°C, only giving back substrate **43**.

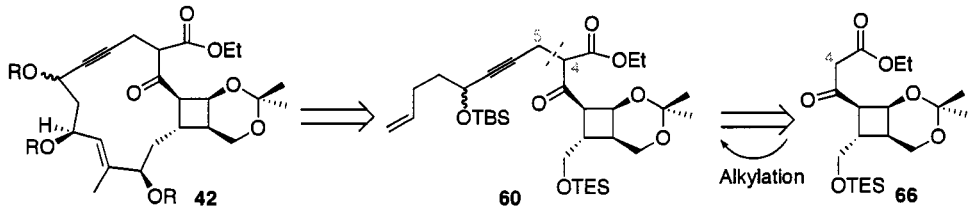
Scheme 1.4.3



1.4.2 β-Keto-Ester Alkylation.

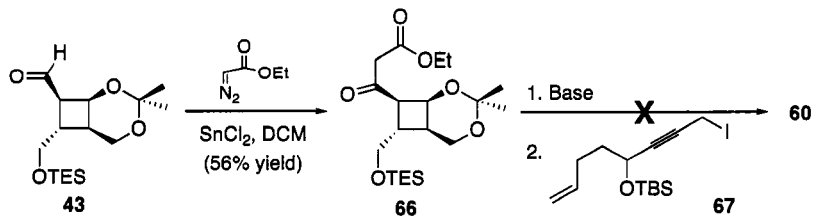
At this junction, we revised our retrosynthetic approach and opted to disconnect between C4 and C5 to allow the alkylation of a preformed β-keto-ester (**66**).

Scheme 1.4.4



Importantly, this revision allowed use of the previously prepared aldehyde **43**. Homologation of **43** to its corresponding β-ketoester (**66**) using ethyl diazoacetate and a catalytic amount of tin chloride was found to proceed in a modest 56% yield.

Scheme 1.4.5



Unfortunately, substrate **66** resisted alkylation attempts with various electrophiles, including propargyl iodide **67**. We also found keto-ester **66** to be highly unstable and sensitive to the range of alkylation conditions tried.

1.5 Conclusion.

In this chapter, we have described the furanocembrane family, discussed the common structural features and illustrated some of the chemistry that has been developed in synthetic efforts toward members of this family. Also described were our initial retrosynthetic analyses of providencin (**1**), which led to the design and successful synthesis of an orthogonally functionalized cyclobutane (**43**).

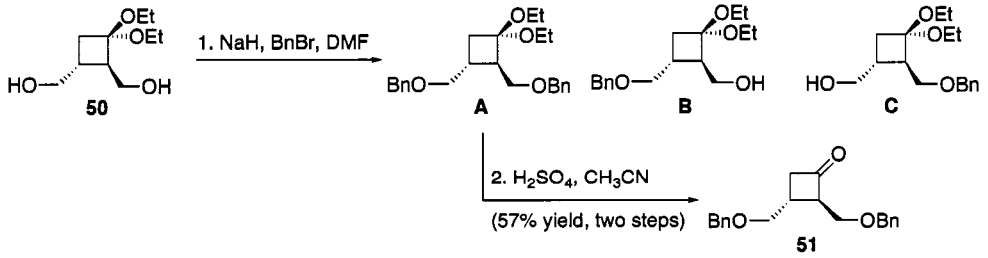
1.6 Experimental Section.

1.6.1. Materials and Methods.

Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). All other commercially obtained reagents were used as received. All reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F254 pre-coated plates (0.25 mm). Column or flash chromatography[35] was performed with the indicated solvents using silica gel (particle size 35 -75 mm) purchased from Silicycle. 1H and 13C NMR spectra were recorded on Bruker Advance DPX-500 or Bruker Advance DPX-400 spectrometers. Chemical shifts are reported relative to internal chloroform (1H ḍ 7.26 ppm, 13C d 77.00 ppm), methanol (1H ḍ 3.31 ppm, 13C d 49.00 ppm). High resolution mass spectra were acquired at The University of Illinois Mass Spectrometry Center.

1.6.2 Preparative Procedures.

Preparation of Cyclobutanone 51:



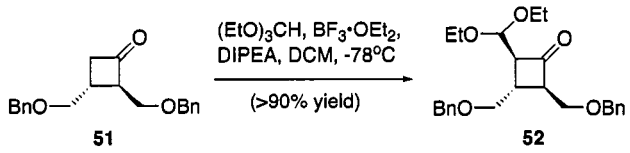
To a solution of diol **50** (4.8 g, 23 mmol) in DMF (100 mL) was added 95% NaH dispersion in mineral oil (1.1 g, 46 mmol) at 0°C. After 30 min, benzyl bromide (5.5 mL,

46 mmol) and NaI (cat amount) were added and the reaction mixture was allowed to warm up to room temperature. After 2 d, the reaction was quenched at 0°C by slow addition of NH_4Cl (saturated in water) and diluted with ether. The biphasic solution was separated, the aqueous phase was extracted five times with ether; the organic phases were combined, backwashed with NaCl (saturated in water), dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (gradient elution, 10→50→100% EtOAc/Hexanes) to yield the bis-protected diol **A** (2.0 g, 23% yield) along with the mono-protected diols **B** and **C** (5.0 g, 74% yield) which were submitted to the same reaction conditions (0.41 g NaH, 2 mL BnBr and cat amount of NaI) to yield additional bis-protected diol **A** (5.0 g, 57% combined yield) as a colorless oil.

To a solution of ketal **A** (4.5 g, 12 mmol) in CH_3CN (120 mL) was added H_2SO_4 (1M in water) at 0°C in a dropwise fashion. The reaction mixture was slowly warmed to room temperature and after 30 min, then diluted with EtOAc. The biphasic solution was separated and the oganic phase washed twice with water, $NaHCO_3$ (saturated in water) and NaCl (saturated in water), dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (10% EtOAc/Hexanes) to yield the title compound **51** (3.7 g, >95% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.24 (m, 10H), 4.55 (s, 2H), 4.50 (s, 2H), 3.72 (dd, J = 10.0, 5.0 Hz, 1H), 3.64 (d, J = 5.9 Hz, 2H), 3.59 (dd, J = 99.9, 4.3 Hz, 1H), 3.37-3.29 (m, 1H), 3.03 (ddd, J = 17.6, 9.0, 2,4 Hz, 1H), 2.87 (ddd, J = 17.6, 6.9, 3.0 Hz, 1H), 2.78-2.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.81, 138.56, 138.50, 130.20, 128.87, 128.80, 128.15, 128.02, 127.92, 73.53, 73.50, 72.64, 67.35, 63.19, 48.55, 28.47; IR (thin layer, NaCl) 2859 (m), 1781 (sh,

s), 1723 (m), 1495 (w), 1453 (m), 1346 (w), 1254 (w), 1112 (m), 1027 (w) cm^{-1}; HRMS (FAB) *m/z* found 327.16, calc'd for $C_{20}H_{25}O_4$ [M+H_3O]: 327.16.

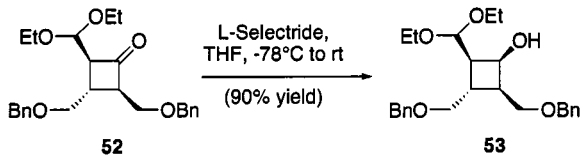
Preparation of Acetal 52:



To a solution of triethyl orthoformate (0.32 mL, 2.0 mmol) in DCM (1 mL) at -30°C was added BF_3•OEt_2 (0.33 mL, 2.6 mmol) in a dropwise fashion. After 15 min the reaction mixture was warmed to 0°C for 15 min and cooled back down to -78°C. To the reaction mixture were added a solution of ketone **51** (0.20 g, 0.65 mmol) in DCM (2mL) and DIPEA (0.57 mL, 3.3 mmol) in a dropwise fashion. After 1 hour at -78°C, the reaction mixture was quenched with $NaHCO_3$ (saturated in water) and diluted with DCM, the biphasic solution was separated, and the aqueous phase was extracted two more times with DCM. The organic phases were combined, backwashed with NaCl (saturated in water), dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (10% EtOAc/Hexanes) to yield the title compound **52** (0.26 g, 97% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.22 (m, 10H), 4.68 (d, J = 5.1 Hz, 1H), 4.54 (d, J = 3.9 Hz, 2H), 4.48 (s, 2H), 3.74-3.54 (m, 6H), 3.51-3.43 (m, 3H), 3.42-3.34 (m, 1H), 2.81-2.76 (m, 1H), 1.18 (t, J = 7.1 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.20, 138.76, 128.96, 128.92, 128.81, 128.78, 128.03, 127.97, 127.96, 100.28, 73.47, 73.42, 71.59, 67.15, 63.29, 63.12, 62.99, 60.49, 31.47, 15.69, 15.64; IR (thin layer, NaCl) 3108 (w), 3092 (w), 3046 (w), 2976 (m), 2915 (w), 2858 (m), 1779 (sh, s), 1722 (w), 1496 (w), 1454 (m), 1362 (m), 1273 (m),

1118 (s), 1059 (s), 1028 (w) cm^{-1}; LRMS (ES) *m/z* found 451.21, calc'd for $C_{25}H_{32}O_5K$ [M+K]: 451.22.

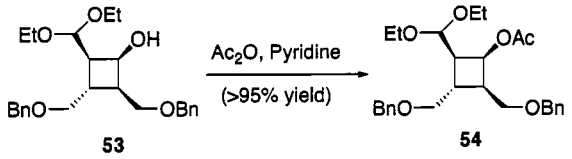
Preparation of Cyclobutanol 53:



52 **53**

To a solution of ketone **52** (0.15 g, 0.36 mmol) in THF (2 mL) was added a 1M solution of L-Selectride in THF (0.44 mL, 0.44 mmol) at -78°C. The reaction mixture was warmed up to room temperature over 30 min and cooled back down to 0°C to be quenched with 0.5 mL of $NaHCO_3$ (saturated in water) and 0.2 mL of H_2O_2 (40% in water). The solution was diluted with water and EtOAc, the biphasic solution was separated and the organic phase was washed three times with water, dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (20% EtOAc/Hexanes) to yield the title compound **53** (0.14 g, 97% yield) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.22 (m, 10H), 4.75 (d, J = 6.9 Hz, 1H), 4.51 (s, 2H), 4.51-4.45 (m, 3H), 3.77-3.43 (m, 8H), 3.20 (brs, 1H), 2.58-2.45 (m, 3H), 1.18 (t, J = 7.0 Hz, 3H), 1.30 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.14, 138.82, 128.94, 128.90, 128.81, 128.76, 128.71, 128.07, 128.00, 127.82, 103.01, 73.58, 73.34, 69.32, 68.15, 42.55, 40.80, 37.72, 15.90, 15.83; IR (thin layer, NaCl) 3448 (br, s), 3330 (w), 2973 (m), 2929 (m), 2862 (m), 1495 (w), 1453 (m), 1366 (m), 1273 (w), 1205 (w), 1118 (s), 1056 (s), 1028 (w) cm^{-1}; HRMS (ES) *m/z* found 437.23, calc'd for $C_{25}H_{34}O_5Na$ [M+Na]: 437.24.

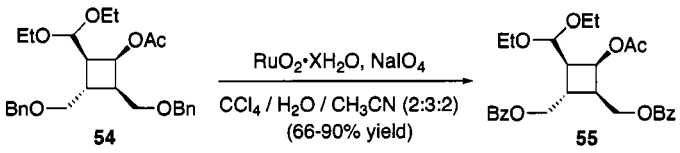
Preparation of Acetate 54:



53 54

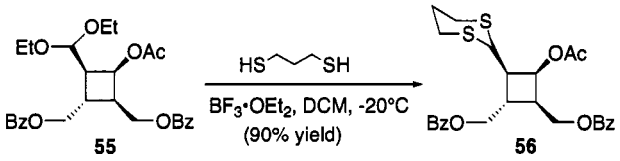
To a solution of alcohol **53** (0.15 g, 0.36 mmol) in Pyr (2 mL) were added acetic anhydride (0.1 mL, 1.1 mmol) and DMAP (cat amount). After 12 h, the reaction mixture was diluted with DCM and HCl (1M solution in water) was added until the aqueous phase reached a pH of 1. The aqueous phase was extracted three times with DCM, the organic phases were combined, backwashed with water, dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (10% EtOAc/Hexanes) to yield the title compound **54** (0.16 g, >95% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.24 (m, 10H), 5.43 (t, J = 6.9 Hz, 1H), 4.68 (d, J = 8.5 Hz, 1H), 4.51 (d, J = 2.1 Hz, 2H), 4.45 (d, J = 5.5 Hz, 2H), 3.63-3.39 (m, 8H), 2.81-2.69 (m, 2H), 2.44-2.36 (m, 1H), 1.99 (s, 3H), 1.14 (t, J = 7.1 Hz, 3H), 1.11 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.53, 139.00, 138.91, 128.72, 128.70, 127.98, 127.87, 127.83, 102.03, 73.40, 73.38, 71.67, 69.24, 68.92, 61.71, 61.33, 40.95, 39.81, 38.94, 21.45, 15.75, 15.69; IR (thin layer, NaCl) 3082 (w), 3045 (w), 3030 (w), 2974 (m), 2933 (w), 2860 (m), 1744 (sh, s), 1495 (w), 1454 (m), 1371 (m), 1238 (s), 1115 (s), 1058 (s), 1017 (m) cm^{-1}; HRMS (ES) *m/z* found 479.24, calc'd for $C_{27}H_{36}O_6Na$ [M+Na]: 479.24.

Preparation of Triester 55:



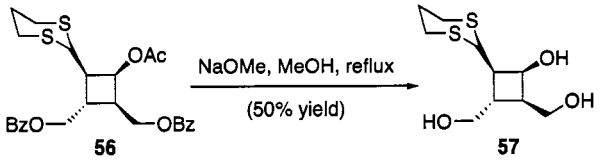
To a solution of dibenzyl ether **54** (0.51 g, 1.1 mmol) in a mixture of water (9 mL) CH_3CN (6 mL) and CCl_4 (6 mL) were added $NaIO_4$ (2.0 g, 9.2 mmol) and $RuO_2 \cdot XH_2O$ (15 mg, 0.11 mmol). The reaction mixture was vigorously stirred and the color changed from black to yellow, indicating completion of the reaction after about 1 h. The reaction mixture was absorbed on silica gel and put directly on the column to be purified by flash chromatography (20% EtOAc/Hexanes) to yield the title compound **55** (0.42 g, 69% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, J = 18.9, 7.1 Hz, 4H), 7.56 (t, J = 7.4 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.43 (d, J = 8.1, 2H), 7.40 (d, J = 7.9 Hz, 2H), 5.58 (t, J = 7.0 Hz, 1H), 4.78 (d, J = 8.0 Hz, 1H), 4.53-4.40 (m, 3H), 4.33 (dd, J = 11.4, 6.0 Hz, 1H), 3.70-3.43 (m, 4H), 2.94 (q, J = 7.3 Hz, 1H), 2.85 (q, J = 8.0 Hz, 1H), 2.80-2.71 (m, 1H), 2.06 (s, 3H), 1.19 (t, J = 7.0 Hz, 3H), 1.17 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.44, 166.88, 133.51, 133.44, 129.98, 128.85, 128.81, 101.84, 68.34, 66.18, 63.05, 62.33, 62.08, 41.60, 39.06, 37.96, 37.56, 21.24, 15.80, 15.72; IR (thin layer, NaCl) 2977 (m), 2940 (w), 2888 (w), 1745 (sh, s), 1721 (sh, s), 1717 (sh, s), 1602 (w), 1585 (w), 1452 (m), 1372 (m), 1315 (m), 1273 (s), 1236 (s), 1177 (w), 1115 (m), 1070 (m), 1026 (m) cm^{-1}; HRMS (ES) *m/z* found 507.20, calc'd for $C_{27}H_{32}O_8Na$ [M+Na]: 507.21.

Preparation of Dithiane 56:



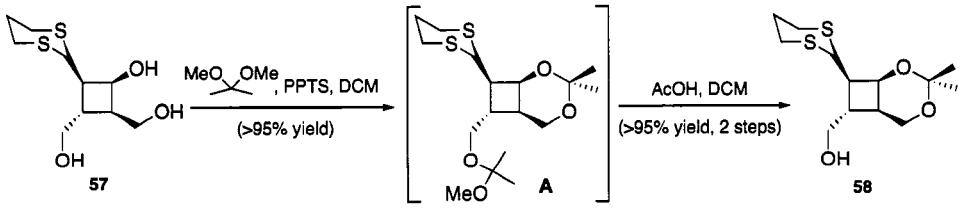
To a solution of acetal **55** (0.27 g, 0.56 mmol) in DCM (6 mL) were added propane dithiol (67 μL, 0.67 mmol) and BF_3•OEt_2 (78 μL, 0.62 mmol) at -20°C. After 10 min, the reaction was diluted with Et_2O and quenched with slow addition of water (1 mL), the reaction mixture was poured over $NaHCO_3$ (saturated in water). The biphasic solution was separated and the aqueous phase extracted two more times with Et_2O. The organic phases were combined, backwashed with water, and NaCl (saturated in water), dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (20% EtOAc/Hexanes) to yield the title compound **56** (0.26 g, 91% yield) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07-7.97 (m, 4H), 7.61-7.50 (m, 2H), 7.49-7.38 (m, 4H), 5.68 (t, J = 6.4, 1H), 4.61-4.42 (m, 2H), 4.42 (d, J = 7.3 Hz, 2H), 4.17 (d, J = 11.4 Hz, 1H), 3.02-2.70 (m, 6H), 2.09 (s, 3H), 2.09-1.83 (m, 1H), 1.24 (t, J = 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.41, 166.79, 133.55, 133.45, 130.28, 130.25, 130.00, 129.00, 128.89, 128.82, 128.73, 68.72, 66.26, 62.72, 44.80, 41.88, 38.28, 28.51, 26.02, 21.32, 14.63; IR (thin layer, NaCl) 3075 (w), 2946 (w), 2903 (w), 1745 (sh,s), 1721 (sh,s), 1716 (sh, s), 1601 (m), 1584 (w), 1451 (m), 1372 (m), 1315 (m), 1273 (s), 1237 (m), 1176 (w), 1114 (m), 1070 (w), 1026 (w) cm^{-1}; HRMS (ES) *m/z* found 501.13, calc'd for $C_{26}H_{29}O_6S_2$ [M+H]: 501.13 .

Preparation of Triol 57:



To a solution of triester **56** (0.26 g, 0.51 mmol) in MeOH (8 mL) was added a 25wt% solution of NaOMe in MeOH (0.11 mL, 0.51 mmol) and was heated to reflux. After 12 h, the reaction mixture was cooled to room temperature, concentrated and the residue purified by flash chromatography (5% MeOH/DCM) to yield the title compound **57** (64 mg, 50% yield) as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 4.32 (t, J = 5.6 Hz, 1H), 4.10 (d, J = 11.5 Hz, 1H), 3.72-3.61 (m, 2H), 3.53 (dd, J = 10.9, 6.2 Hz, 1H), 3.37 (dd, J = 10.7, 6.7 Hz, 1H), 2.80-2.65 (m, 4H), 2.33-2.22 (m, 1H), 2.21-2.09 (m, 2H), 2.07-1.91 (m, 1H), 1.84-1.72 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 68.92, 65.72, 61.61, 46.35, 46.11, 44.21, 43.94, 29.91, 29.70, 27.63; IR (thin layer, NaCl) 3284 (brs), 2970 (w), 2940 (w), 2884 (w), 3828 (w), 1421 (s), 1397 (s), 1352 (m), 1276 (m), 1182 (m), 1142 (w), 1102 (s), 1077 (s), 1020 (s) cm^{-1}; HRMS (ES) *m/z* found 273.06, calc'd for $C_{10}H_{18}O_3S_2Na$ [M+Na]: 273.07.

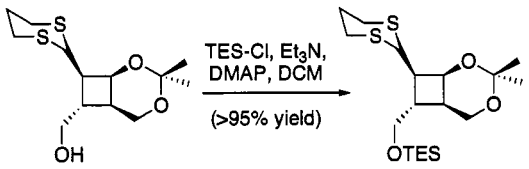
Preparation of Acetonide 58:



To a solution of triol **57** (45 mg, 0.18 mmol) in DCM (5 mL) were added excess 2,2-dimethoxypropane (1.5 mL) and *p*PTS (cat amount). After 12 h, the reaction was

diluted with DCM and poured over $NaHCO_3$ (saturated in water); the biphasic solution was separated and the aqueous phase extracted two more times with DCM. The organic phases were combined, dried over Na_2SO_4, filtered and rotary evaporated. The crude mixed-acetal **A** was dissolved in DCM and a drop of AcOH was added; after 3 hours, the reaction was concentrated and AcOH was removed by azeotropic distillation with heptane. The crude product was purified by flash chromatography (3% MeOH/DCM) to yield the title compound **58** (52 mg, >95% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.49 (t, J = 4.8 Hz, 1H), 4.29 (d, J = 11.5 Hz, 1H), 4.04 (dd, J = 12.4, 4.2 Hz, 1H), 3.73 (ddd, J = 16.3, 11.3, 5.0 Hz, 2H), 3.62 (d, J = 12.4 Hz, 1H), 2.93-2.72 (m, 6H), 2.73 (brs, 1H), 2.48 (ddd, J = 11.0, 4.6, 1.8 Hz, 1H), 2.13-2.02 (m, 1H), 1.99-1.88 (m, 2H), 1.44 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 96.63, 66.02, 64.54, 59.67, 43.83, 43.64, 43.48, 29.87, 29.52, 28.45, 26.17, 19.91; IR (thin layer, NaCl) 33415 (br, s), 2990 (w), 2934 (m), 2903 (m), 2866 (w), 1457 (w), 1422 (w), 1372 (m), 1268 (w), 1221 (w), 1195 (m), 1118 (m) cm^{-1}; HRMS (ES) *m/z* found 291.11, calc'd for $C_{13}H_{23}O_3S_2$ [M+H]: 291.10.

Preparation of Silyl Ether 59:

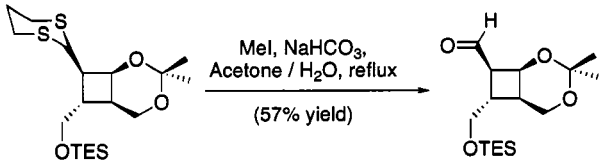


58 **59**

To a solution of alcohol **58** (52 mg, 0.18 mmol) in DCM (5 mL) were added TES-Cl (30 μL, 0.18 mmol), Et_3N (51 μL, 0.36 mmol) and DMAP (cat amount). After 30 min, the reaction was diluted with DCM and poured over NH_4Cl (saturated in water); the

biphasic solution was separated and the aqueous phase extracted two more times with DCM. The organic phases were combined, dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (5% EtOAc/Hexanes) to yield the title compound **59** (0.24 g, >95% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (t, J = 4.8 Hz, 1H), 4.35 (d, J = 11.5 Hz, 1H), 4.02 (dd, J = 12.3, 4.3 Hz, 1H), 3.79 (dd, J = 11.2, 3.0 Hz, 1H), 3.70 (dd, J = 11.1, 5.4 Hz, 1H), 3.61 (d, J = 12.2 Hz, 1H), 2.92-2.70 (m, 5H), 2.54-2.96 (m, 1H), 2.12-1.87 (m, 3H), 1.44 (s, 3H), 1.41 (s, 3H), 0.95 (t, J = 8.0 Hz, 9H), 0.59 (q, J = 7.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 96.45, 66.00, 63.71, 59.84, 44.51, 43.22, 41.59, 29.86, 29.55, 29.05, 28.99, 26.36, 19.93, 7.24, 4.78; IR (thin layer, NaCl) 2990 (w), 2951 (s), 2903 (m), 2875 (w), 1461 (w), 1415 (w), 1379 (m), 1277 (w), 1195 (m), 1117 (s), 1002 (s) cm^{-1}; HRMS (ES) *m/z* found 405.20, calc'd for $C_{19}H_{37}O_3S_2Si$ [M+H]: 405.19.

Preparation of Aldehyde 43:

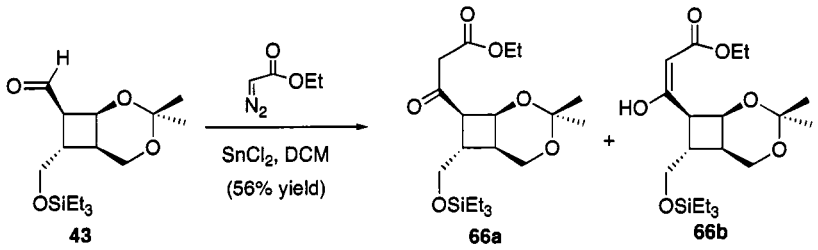


59 **43**

To a solution of dithiane **59** (0.1 g, 0.25 mmol) in a mixture of CH_3CN (6 mL), water (1.5 mL) and acetone (1.5 mL) were added $NaHCO_3$ (0.62 g, 7.4 mmol) and MeI (1.6 mL, 25 mmol) and the reaction mixture was heated to reflux. After 1 h, the reaction mixture was cooled to room temperature, the salts were dissolved with water and the aqueous phase extracted three times with DCM. The organic phases were combined, dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by

flash chromatography (10% EtOAc/Hexanes) to yield the title compound **43** (45 mg, 56% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 4.77 (t, J = 5.1 Hz, 1H), 4.02 (dd, J = 12.4, 4.5 Hz, 1H), 3.71-3.61 (m, 3H), 3.33-3.26 (m, 1H), 2.96 (ddd, J = 9.0, 5.2, 1.3 Hz, 1H), 2.22-2.17 (m, 1H), 1.42 (s, 3H), 1.34 (s, 3H), 0.94 (t, J = 7.9 Hz, 9H), 0.58 (q, J = 7.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.78, 96.69, 67.67, 62.58, 59.85, 49.04, 39.07, 30.23, 29.22, 19.81, 7.17, 4.73; IR (thin layer, NaCl) 2992 (w), 2954 (s), 2910 (m), 2876 (s), 1721 (sh, s), 1372 (m), 1207 (m), 1121 (s), 1004 (m), 970 (w) cm^{-1}; HRMS (ES) *m/z* found 337.10, calc'd for $C_{16}H_{30}O_4SiNa$ [M+Na]: 337.19.

Preparation of Ketoester 66:



To a solution of aldehyde **43** (64 mg, 0.5 mmol) in DCM (0.5 mL) were added a solution of ethyl diazoacetate (25 μL, 0.2 mmol) in DCM (0.2 mL) and $SnCl_2$ (cat amount), effervescence was observed. The yellow reaction became colorless after 30 min, indicating that the diazoacetate was consumed. The solvent was rotary evaporated and the residue purified by flash chromatography (10% EtOAc/Hexanes) to yield the title compound **66** (45 mg, 56% yield) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.69 (t, J = 4.8 Hz, 1H), 4.31-4.10 (m, 1H), 4.18 (q, J = 7.1 Hz, 2H), 4.03-3.96 (m, 1H), 3.83-3.39 (m, 5H), 3.32-3.17 (m, 1H), 2.20-1.98 (m, 1H), 1.40 (s, 3H), 1.39 (s, 3H), 1.27 (t, J = 7.0 Hz, 3H), 0.93 (t, J = 7.9 Hz, 9H), 0.58 (q, J = 8.0 Hz, 6H); ^{13}C NMR (125

MHz, $CDCl_3$) δ 201.09, 167.47, 96.35, 67.26, 62.10, 61.10, 59.33, 48.97, 48.71, 39.29, 29.06, 28.83, 19.65, 14.12, 6.78, 4.40; IR (thin layer, NaCl) 3000 (w), 2954 (s), 2910 (m), 2876 (m), 1747 (sh, s), 1715 (sh, s), 1457 (w), 1414 (w), 1381 (m), 1371 (m), 1324 (w), 1195 (m), 1118 (s), 1003 (m) cm^{-1}; HRMS found no ionization, calc'd for $C_{20}H_{36}O_6Si$ [M]: 400.23.

1.7 Notes and References.

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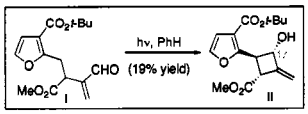

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Appendix A1: Spectra Relevant to Chapter 1.

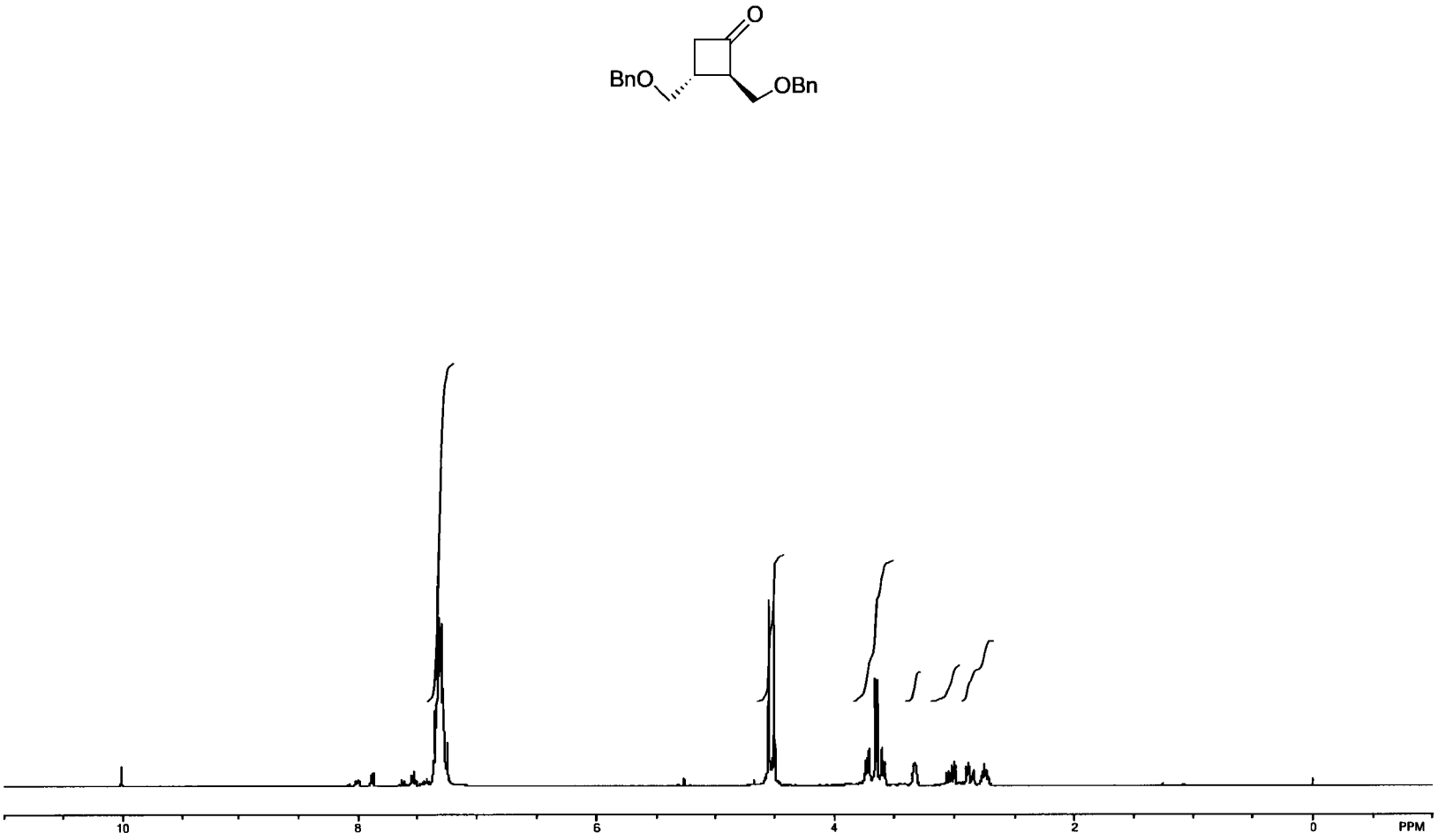


Figure A1.1 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **51**.

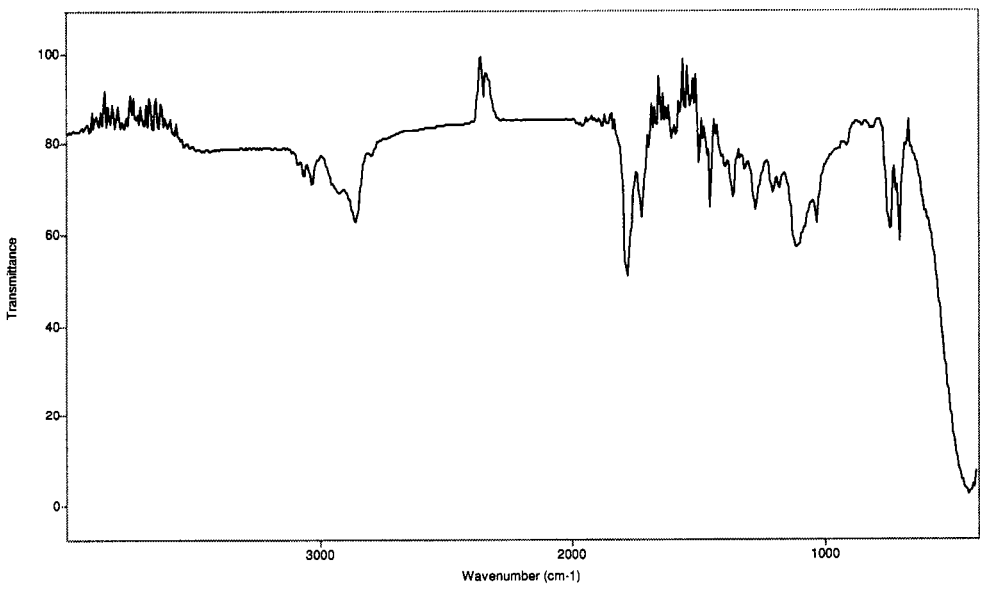


Figure A1.2 IR spectrum (thin film/NaCl) of compound **51**.

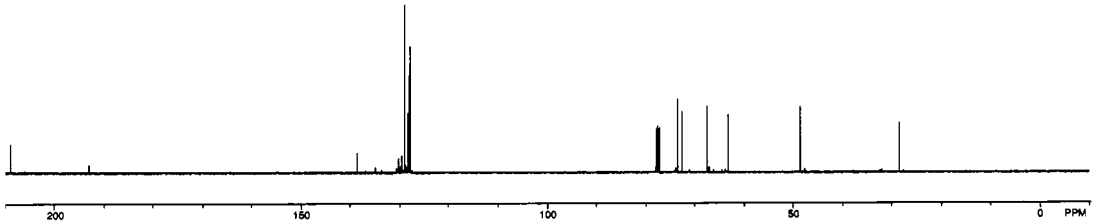


Figure A1.3 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **51**.

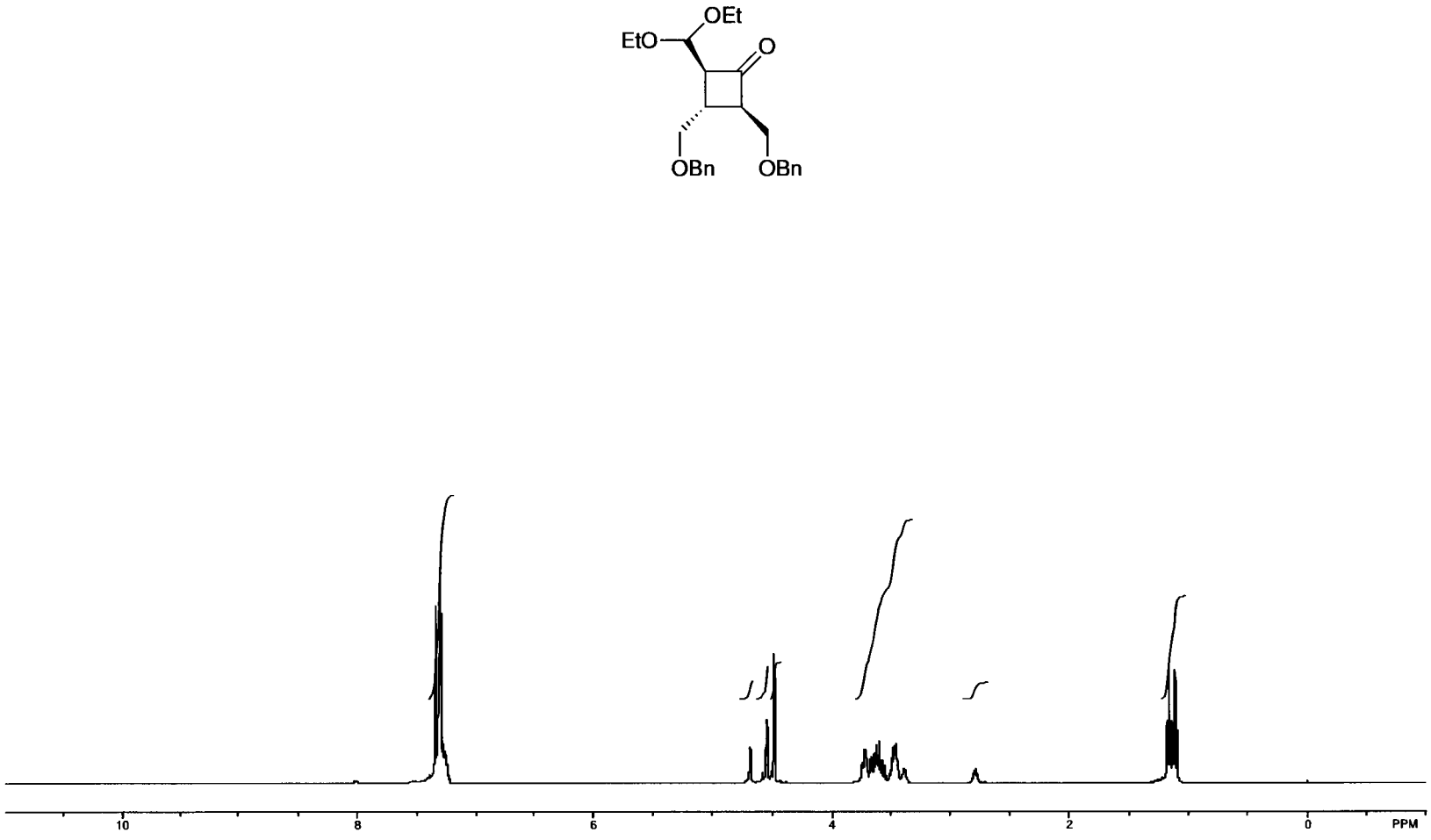


Figure A1.4 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **52**.

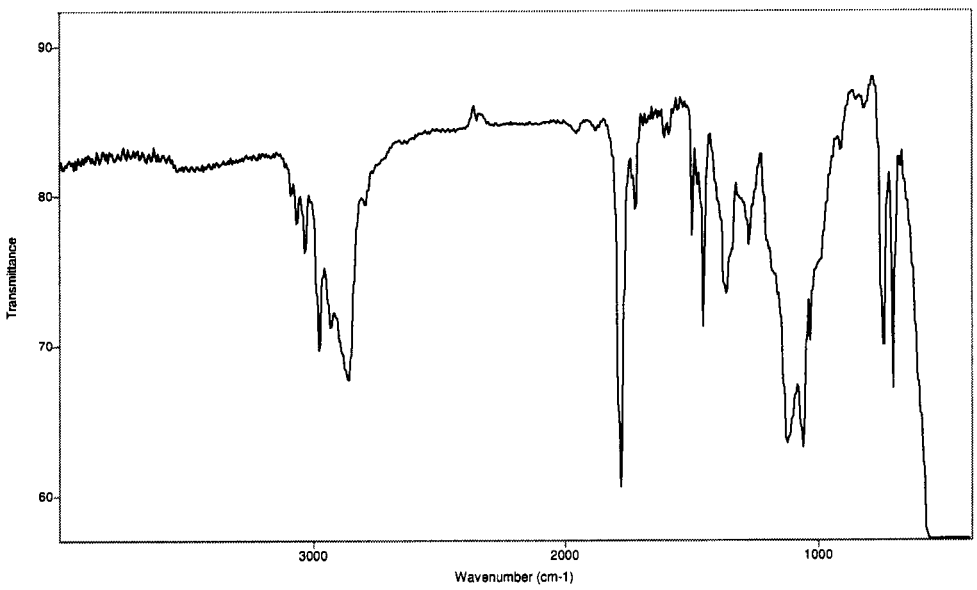


Figure A1.5 IR spectrum (thin film/NaCl) of compound **52**.

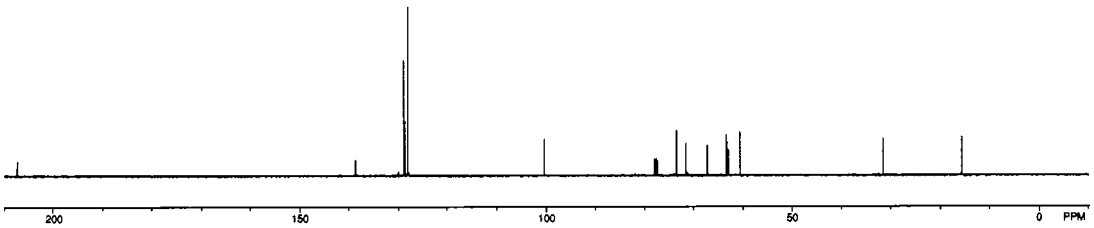


Figure A1.6 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **52**.

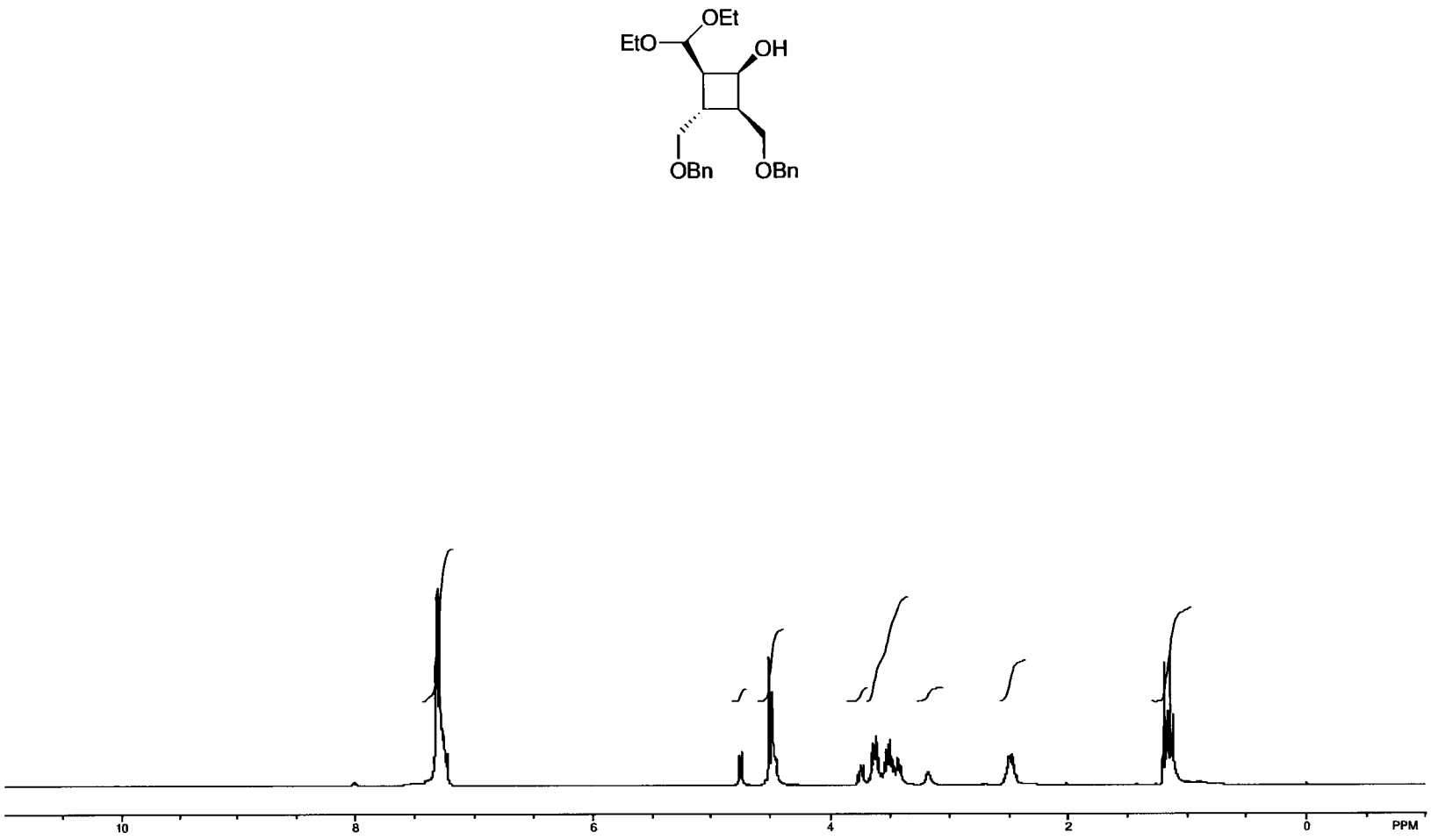


Figure A1.7 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **53**.

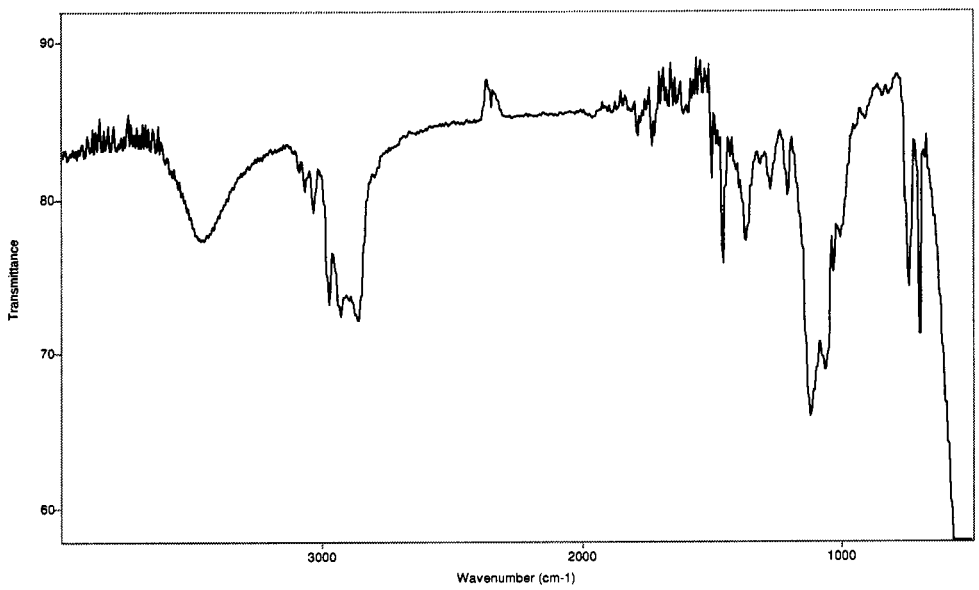


Figure A1.8 IR spectrum (thin film/NaCl) of compound **53**.

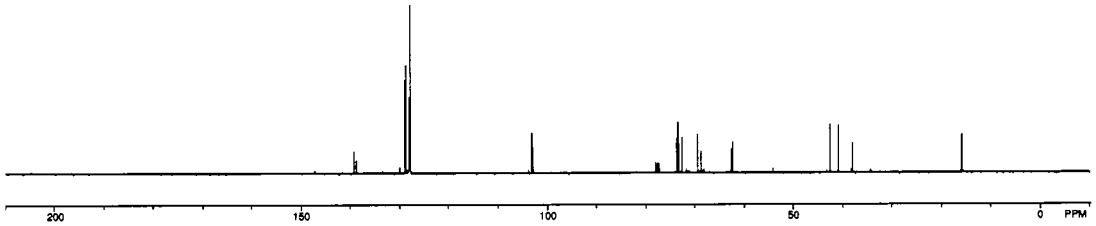


Figure A1.9 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **53**.

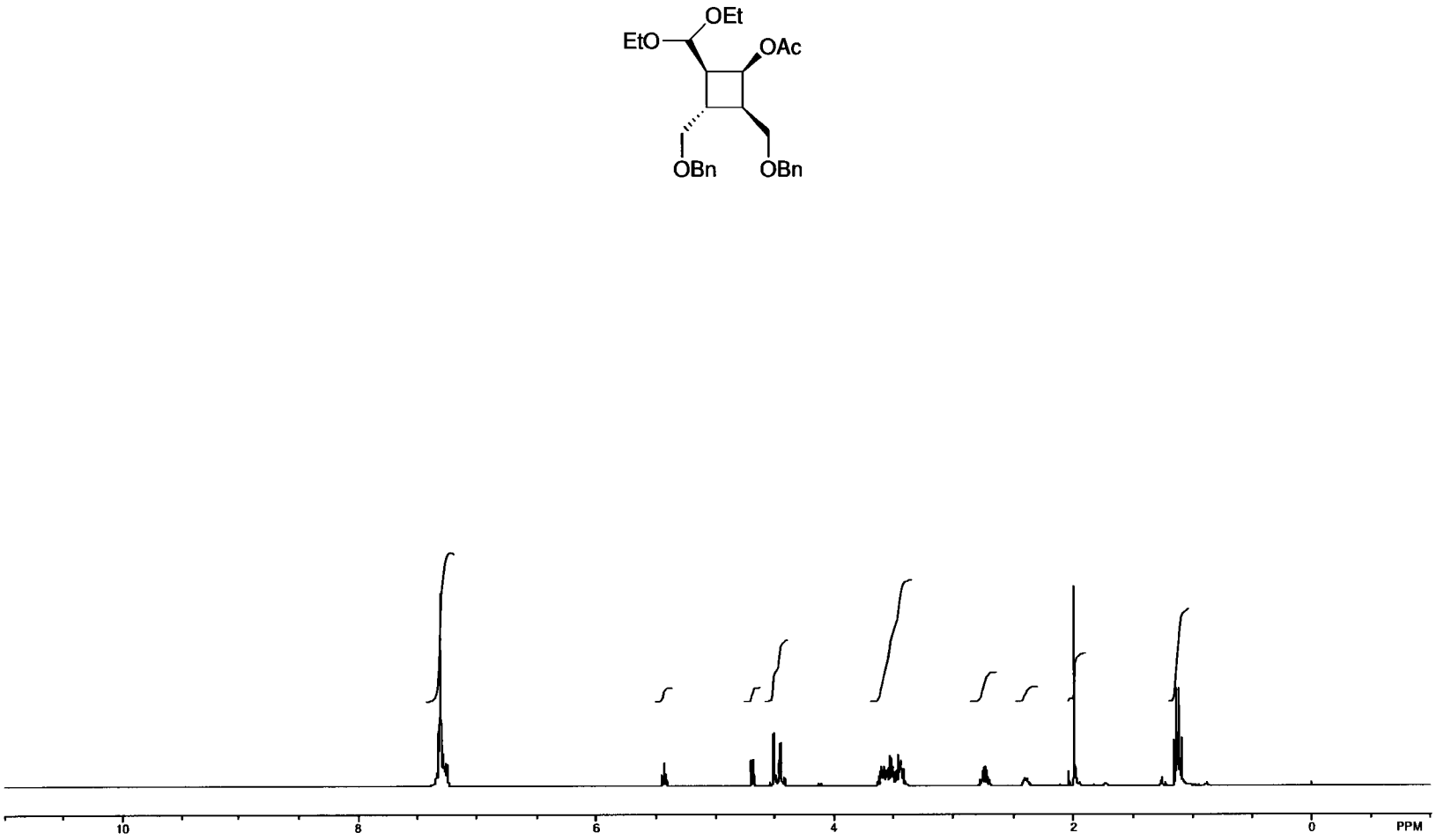


Figure A1.10 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **54**.

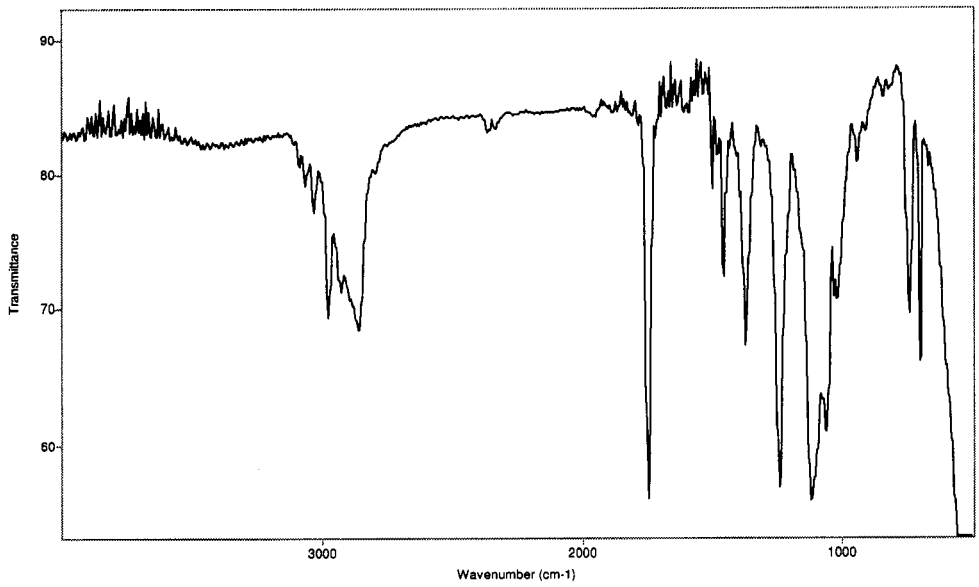


Figure A1.11 IR spectrum (thin film/NaCl) of compound **54**.

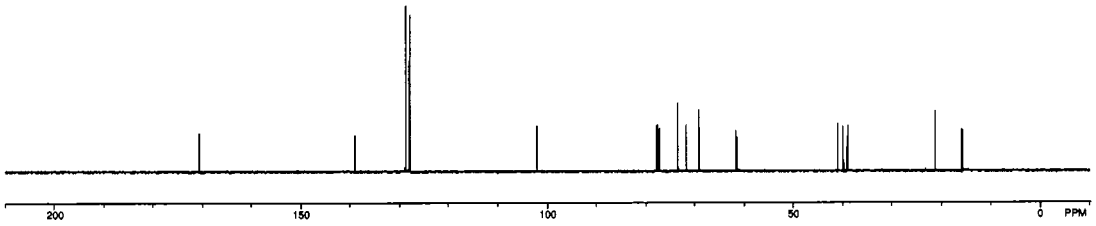


Figure A1.12 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **54**.

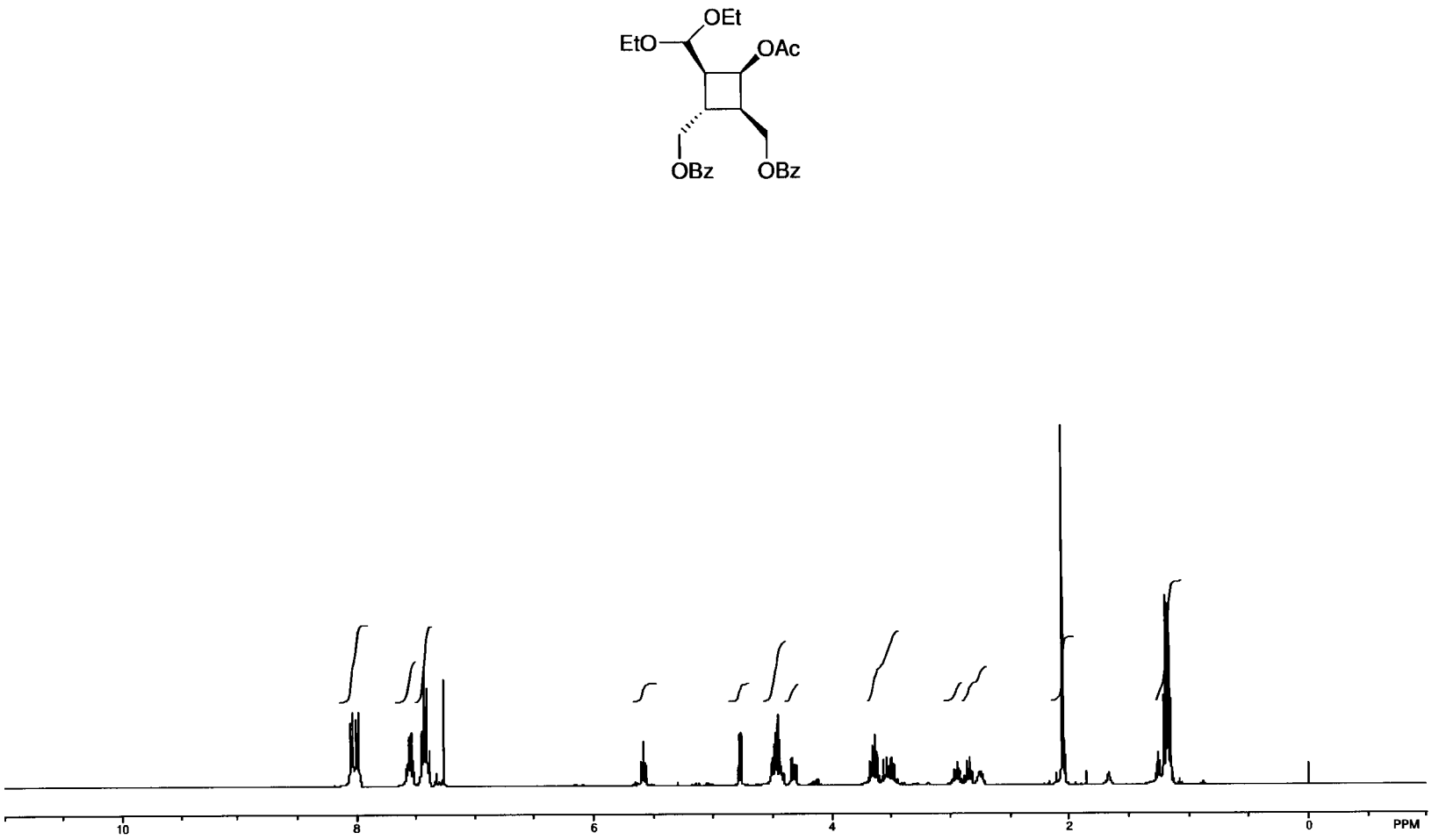


Figure A1.13 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **55**.

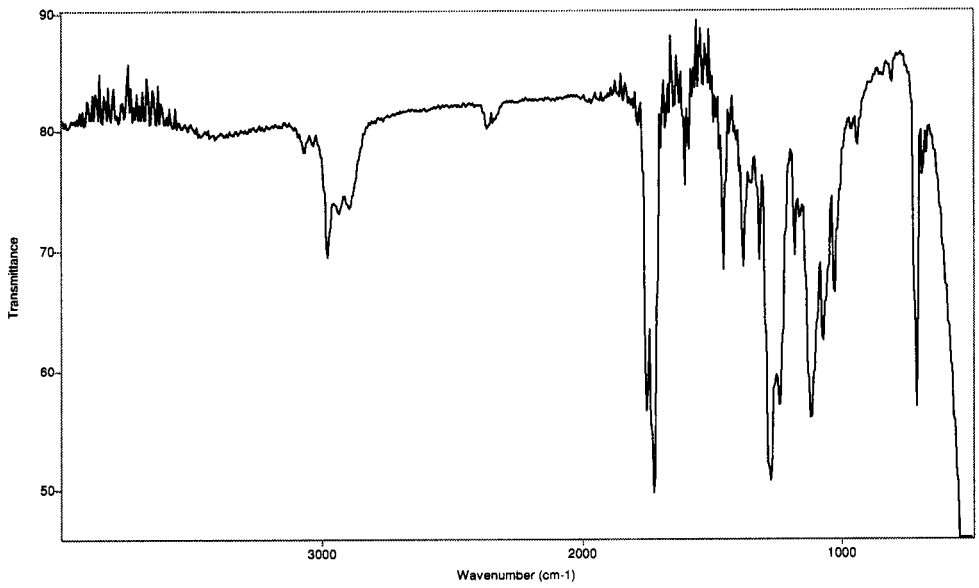


Figure A1.14 IR spectrum (thin film/NaCl) of compound **55**.

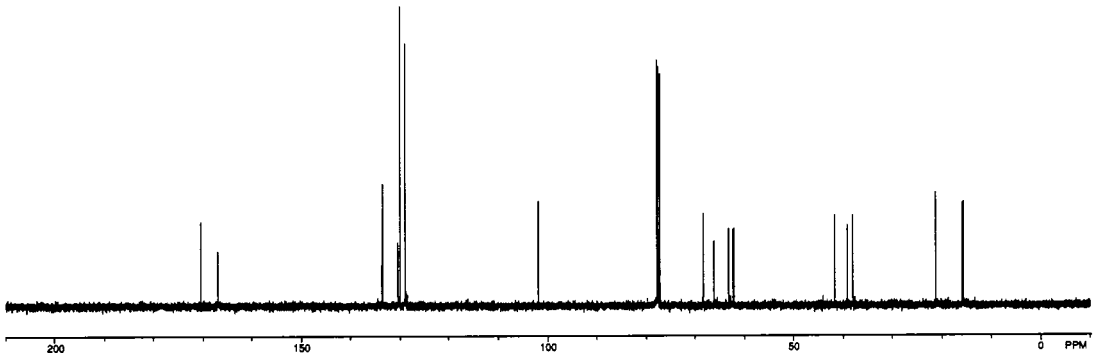


Figure A1.15 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **55**.

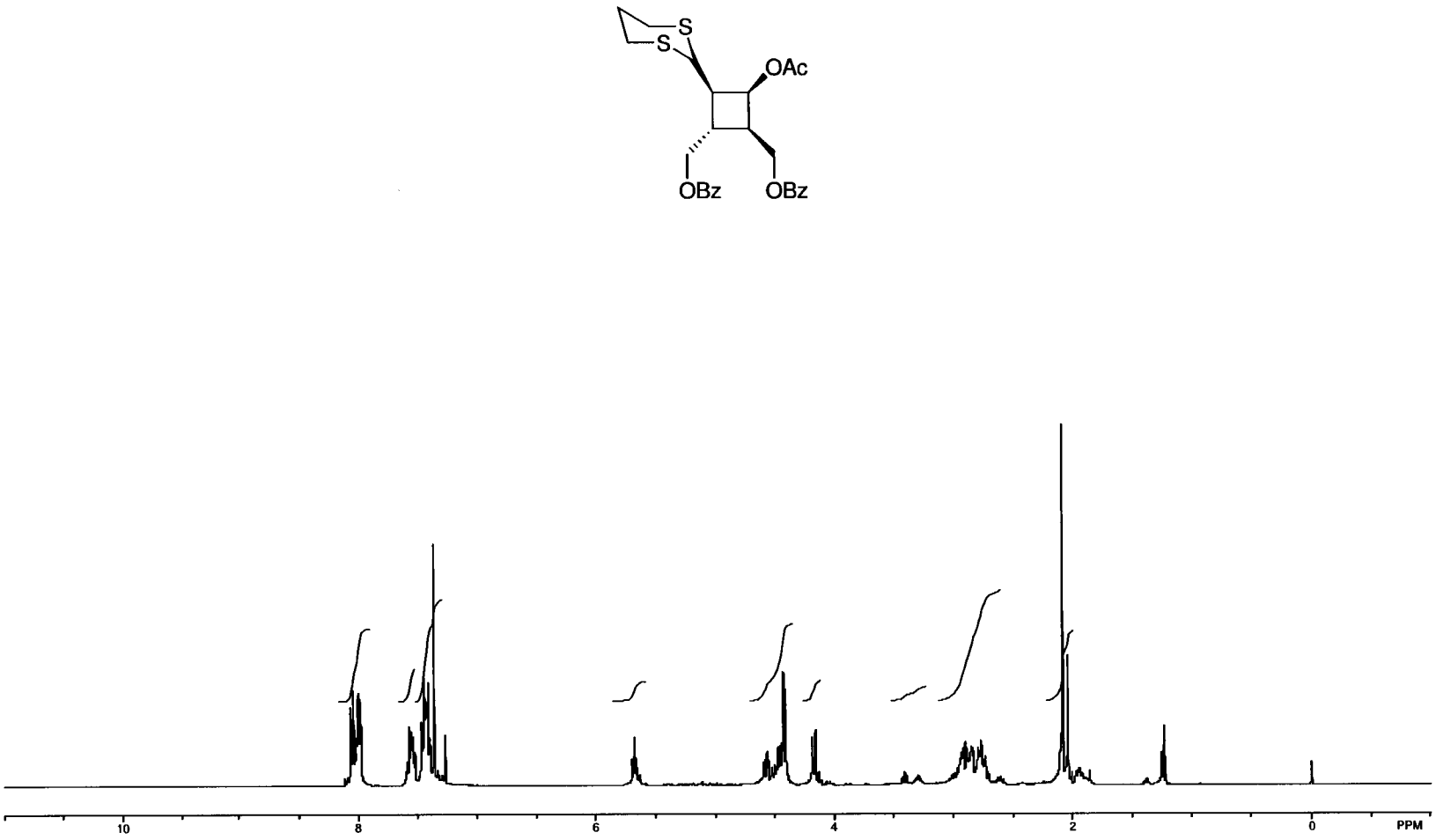


Figure A1.16 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **56**.

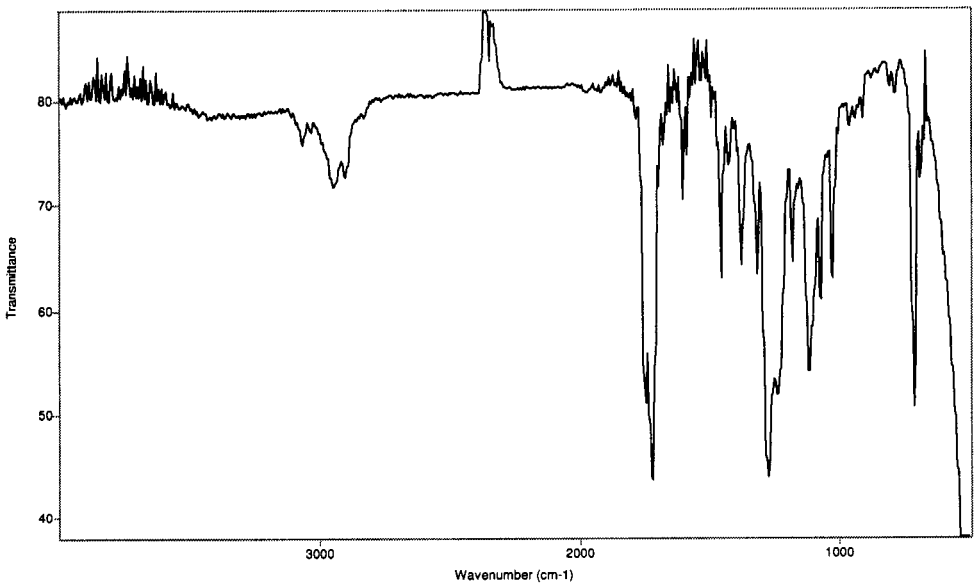


Figure A1.17 IR spectrum (thin film/NaCl) of compound **56**.

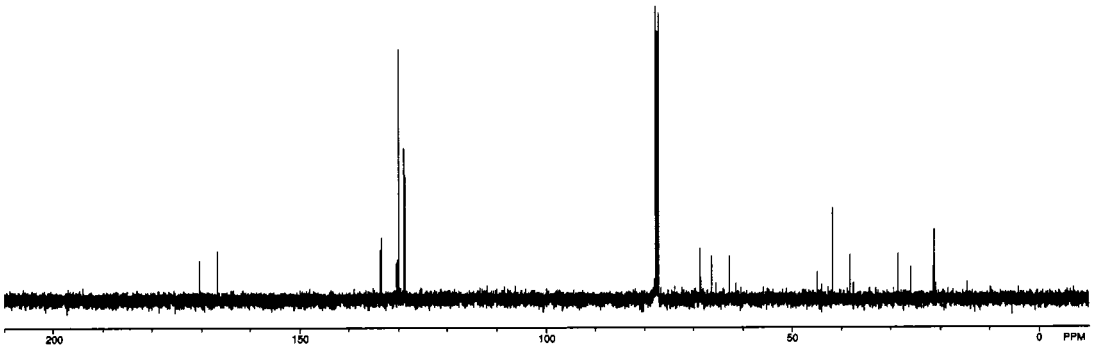


Figure A1.18 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **56**.

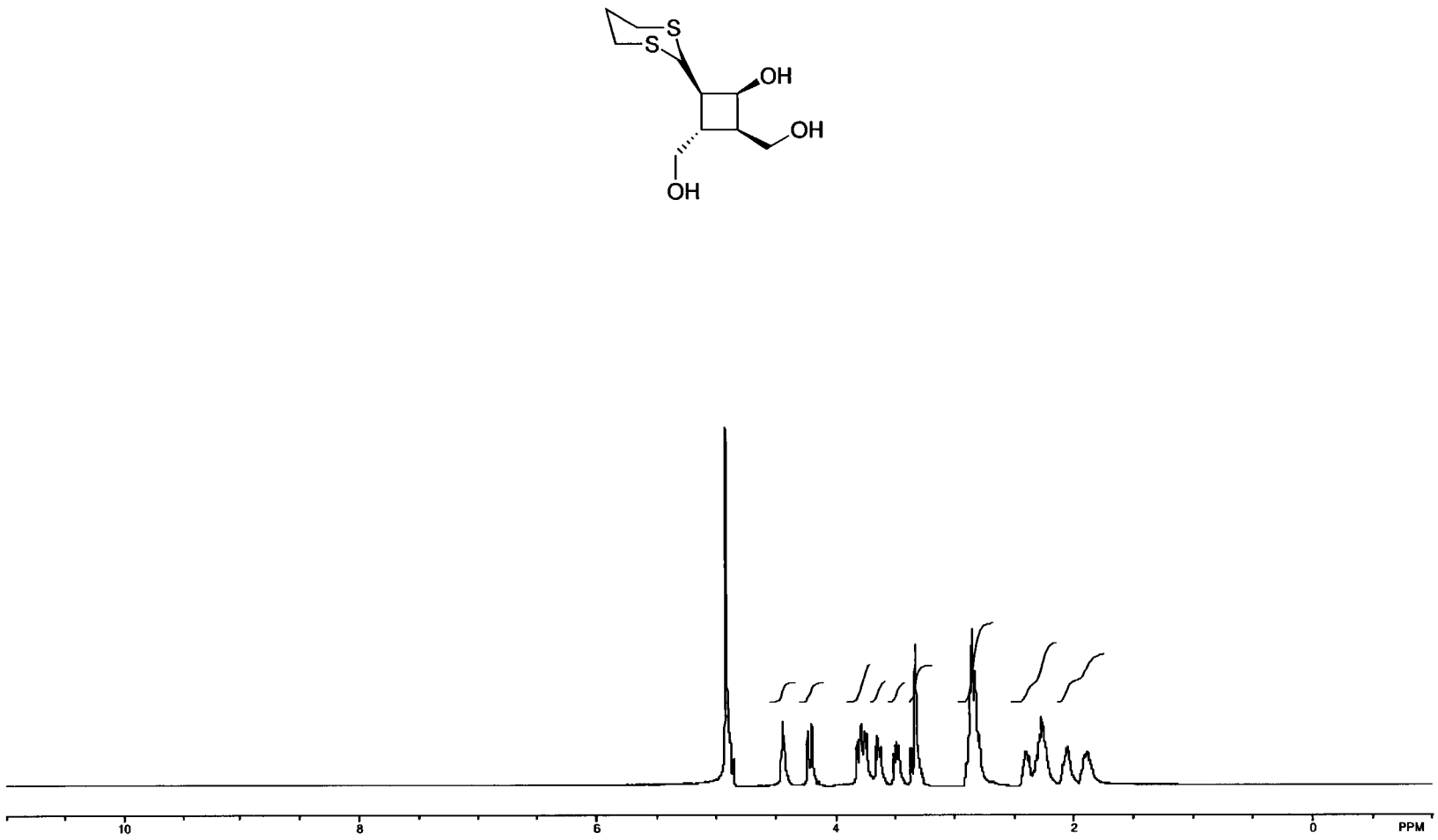


Figure A1.19 ^{1}H NMR spectrum (400 MHz, CD_3OD) of compound **57**.

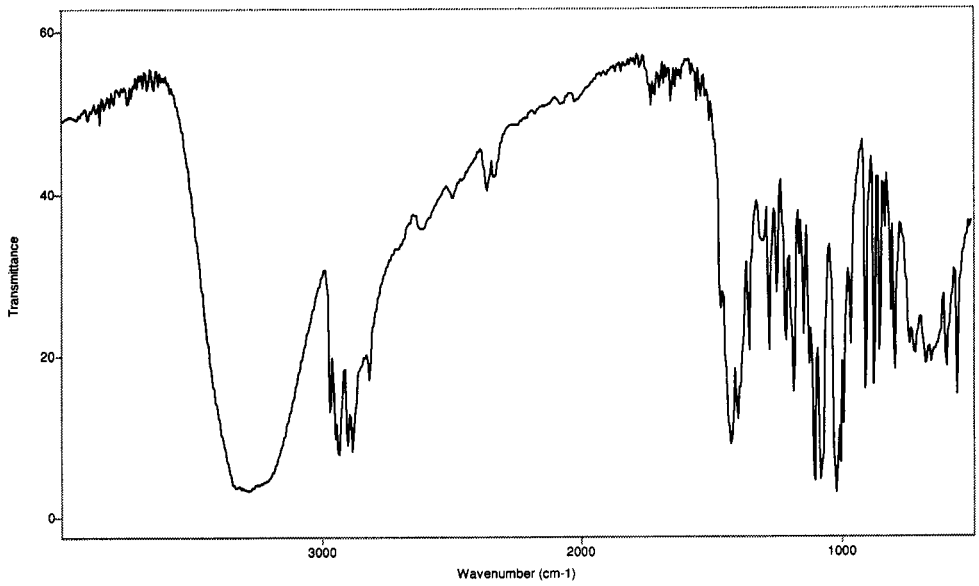


Figure A1.20 IR spectrum (thin film/NaCl) of compound **57**.

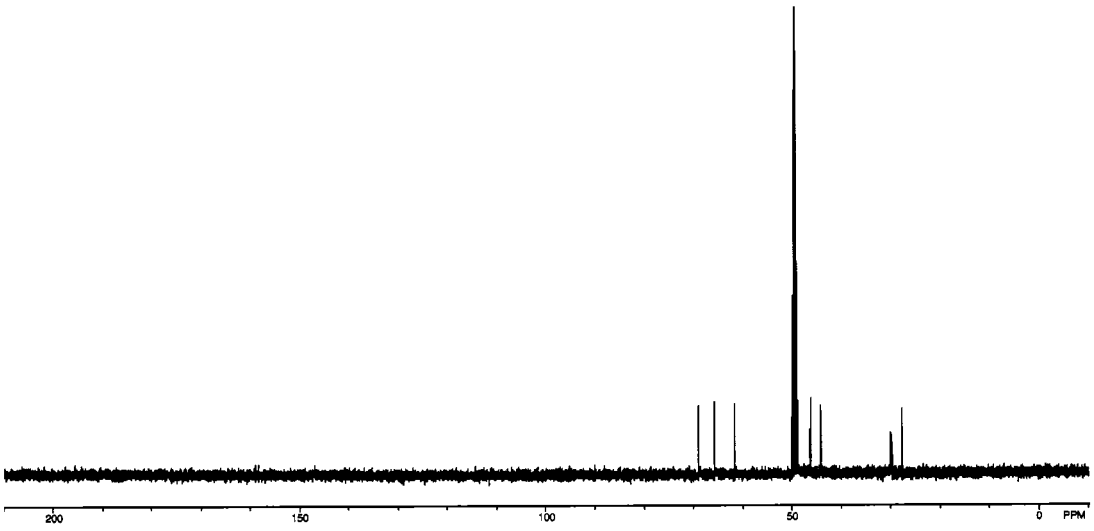


Figure A1.21 ^{13}C NMR spectrum (100 MHz, CD_3OD) of compound **57**.

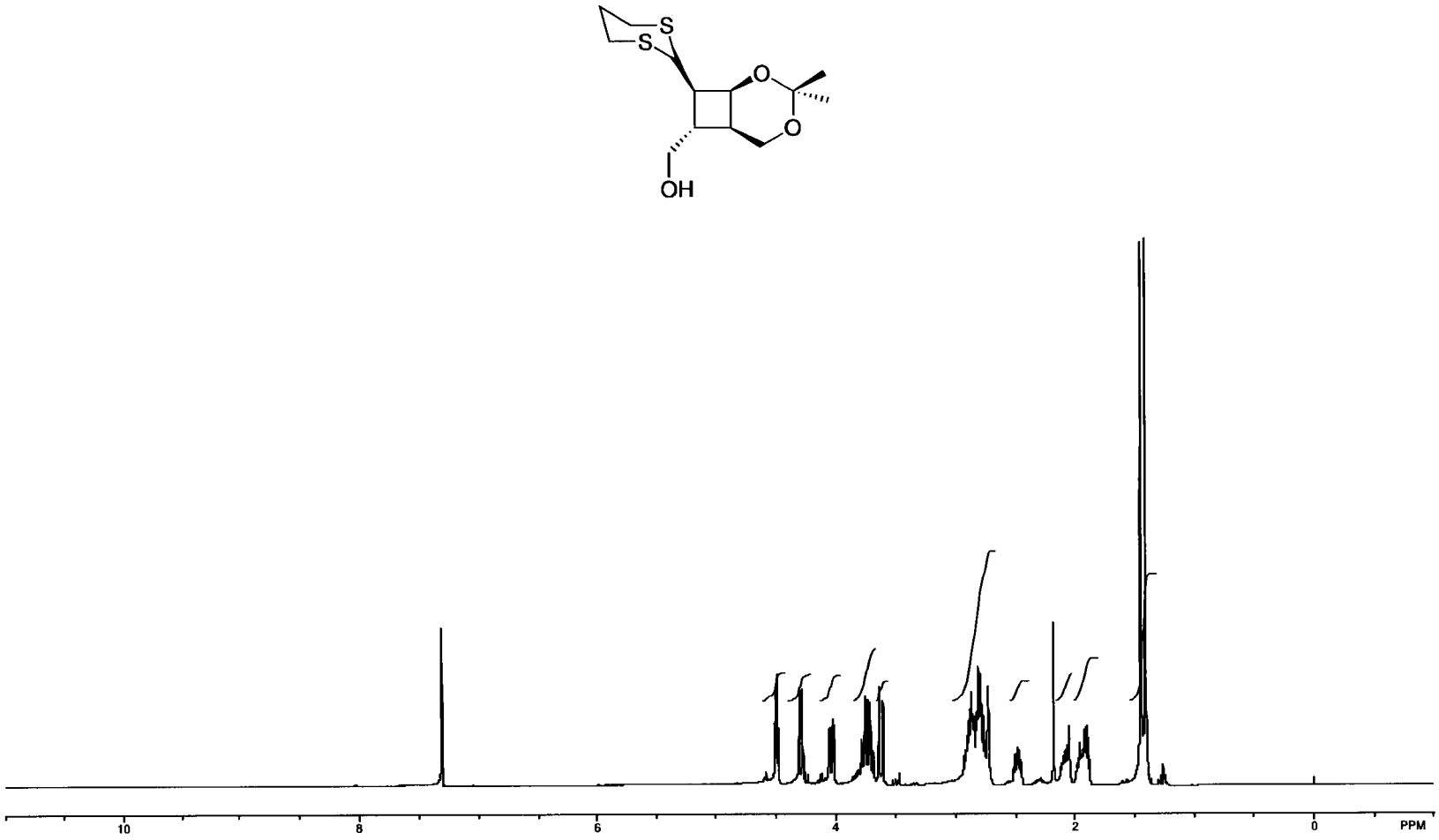


Figure A1.22 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **58**.

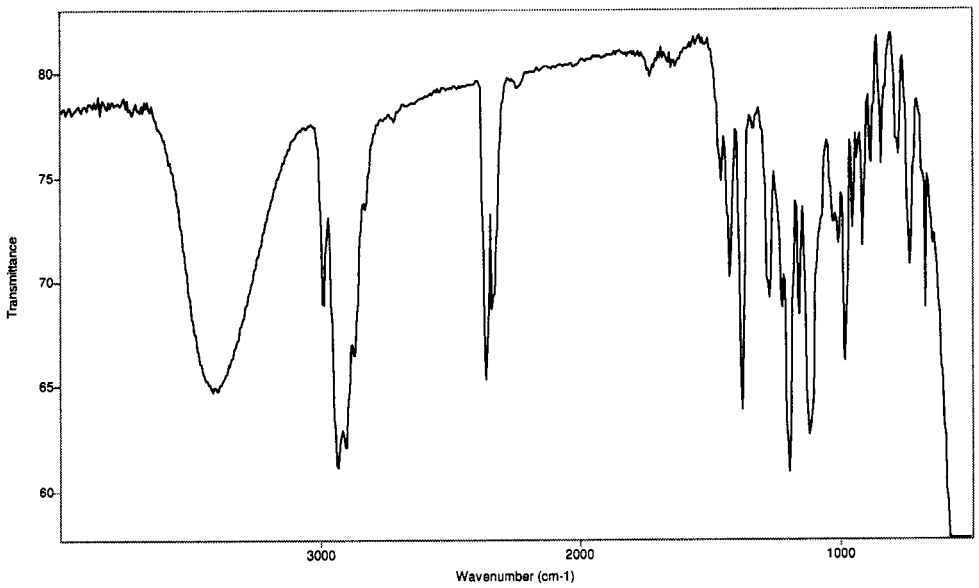


Figure A1.23 IR spectrum (thin film/NaCl) of compound **58**.

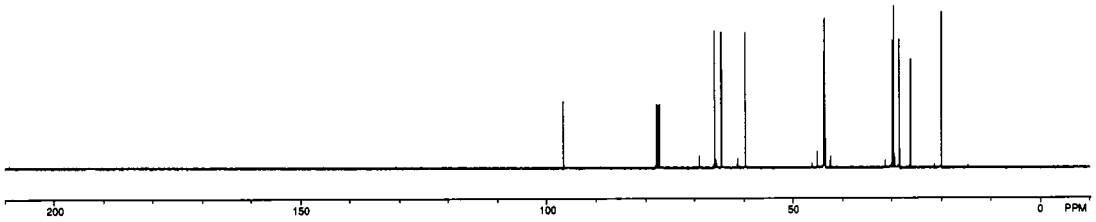


Figure A1.24 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **58**.

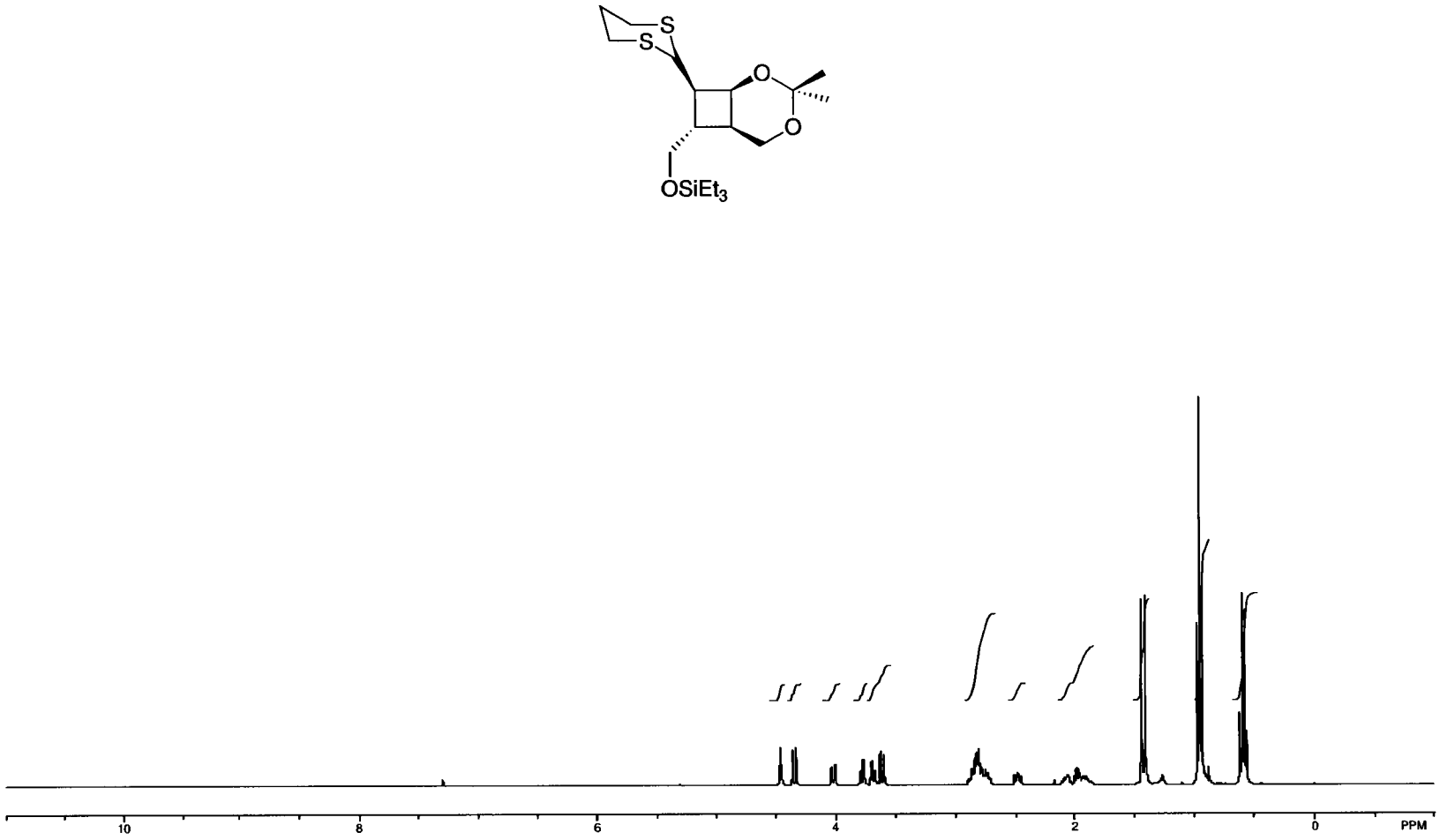


Figure A1.25 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **59**.

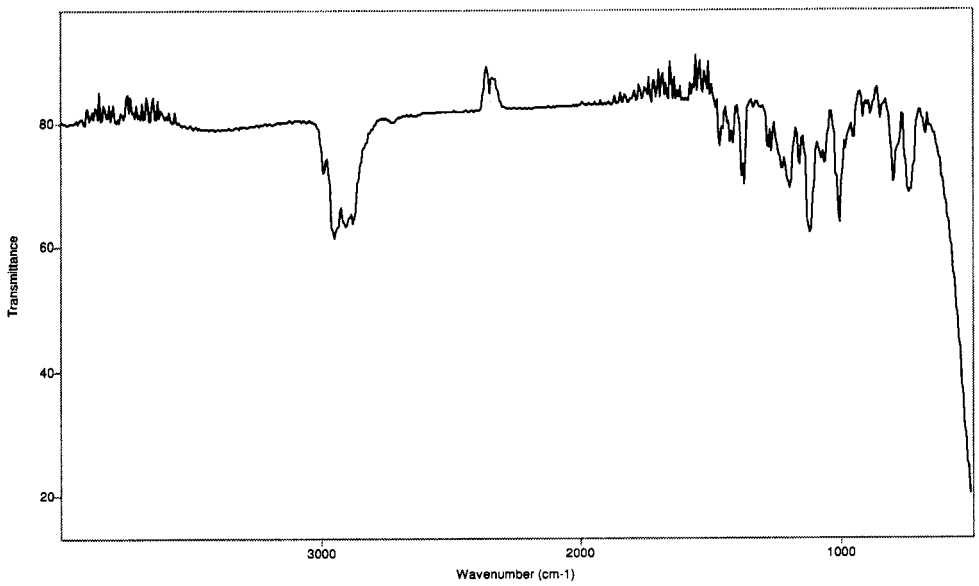


Figure A1.26 IR spectrum (thin film/NaCl) of compound **59**.

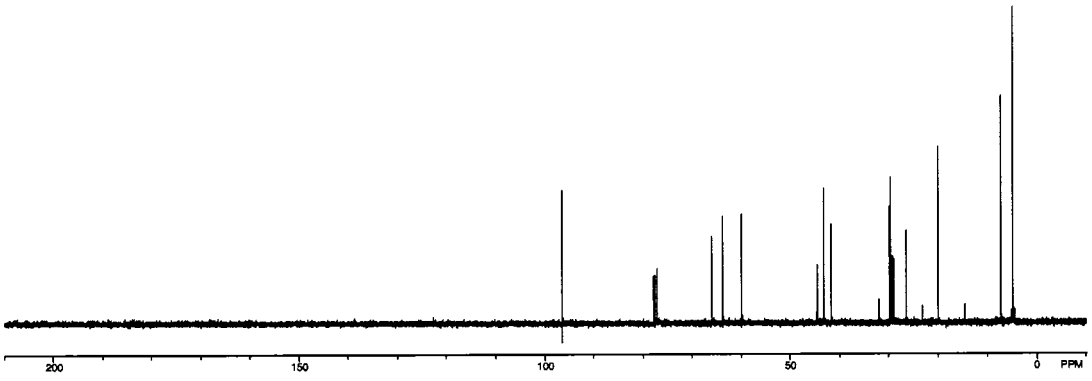


Figure A1.27 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **59**.

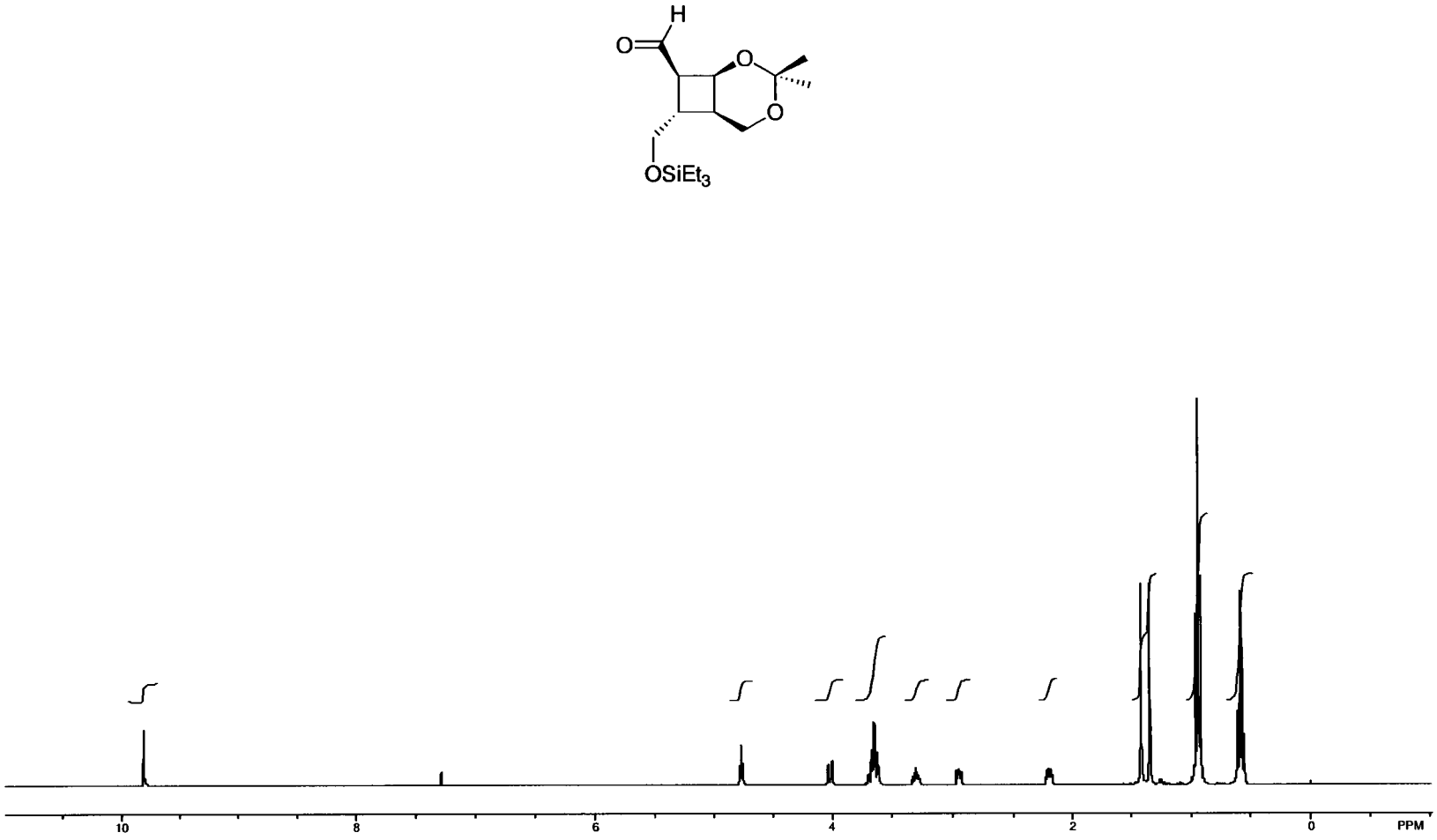


Figure A1.28 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **43**.

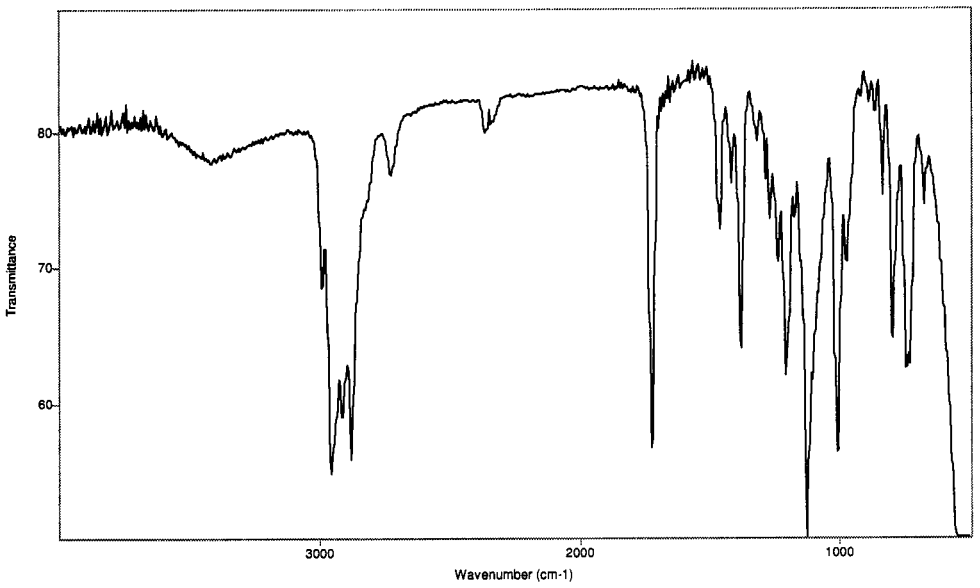


Figure A1.29 IR spectrum (thin film/NaCl) of compound **43**.

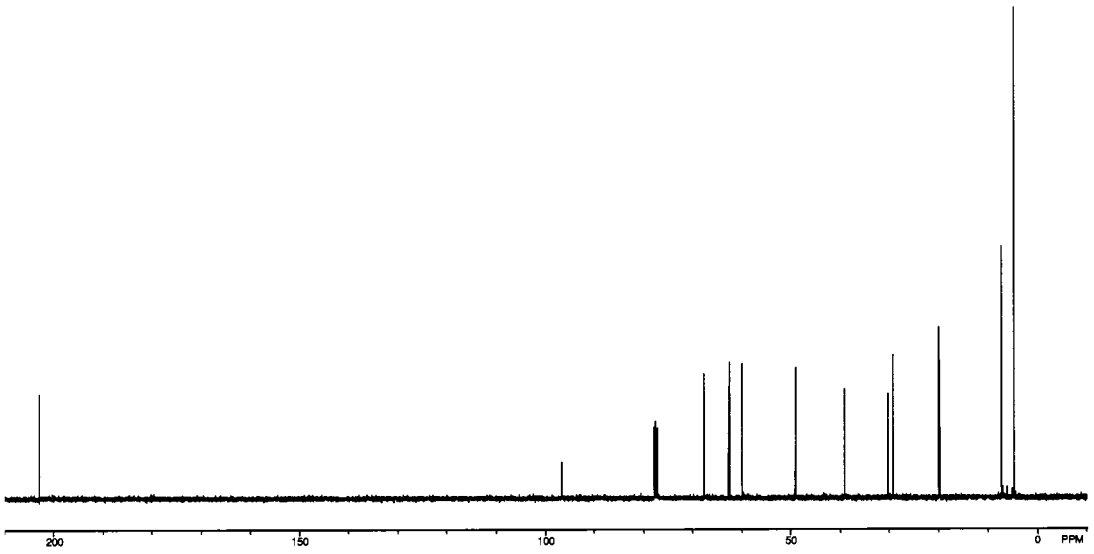


Figure A1.30 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **43**.

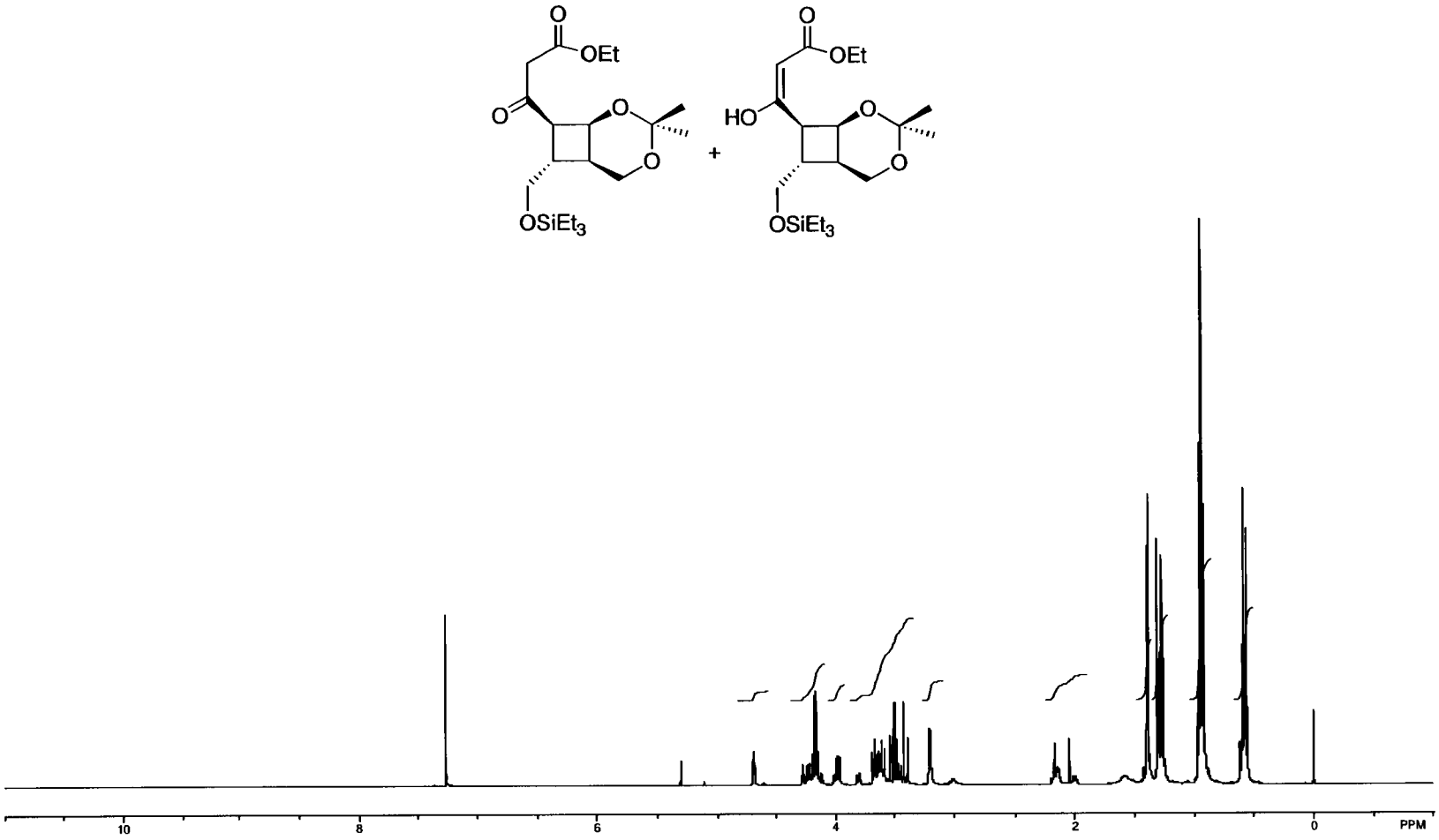


Figure A1.31 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **66**.

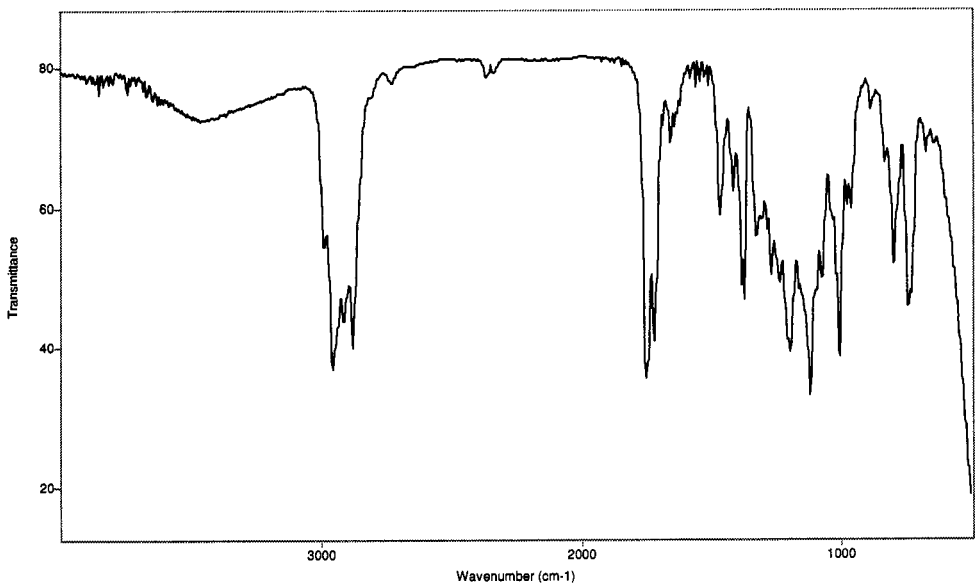


Figure A1.32 IR spectrum (thin film/NaCl) of compound **66**.

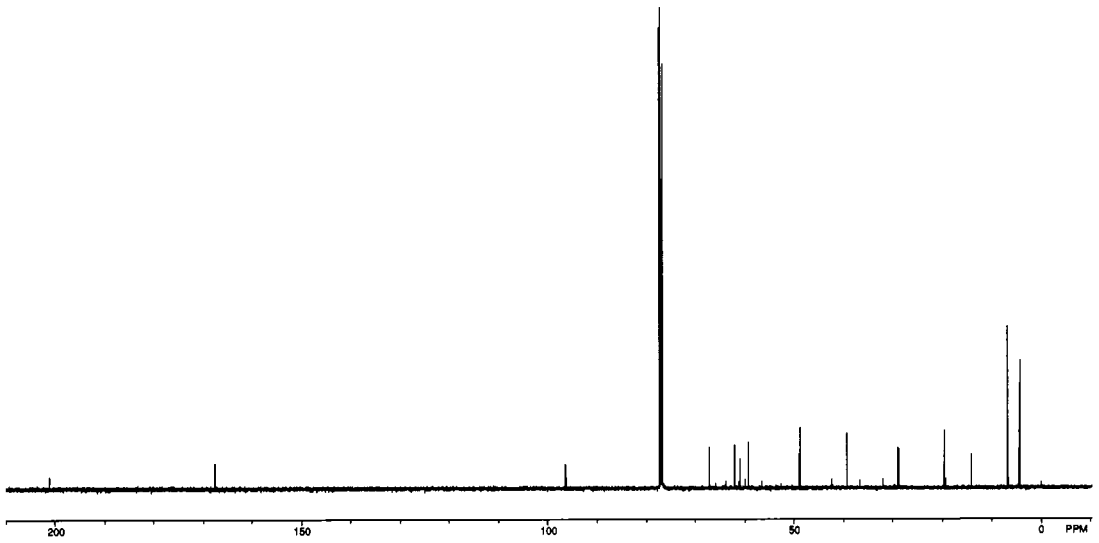


Figure A1.33 ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **66**.

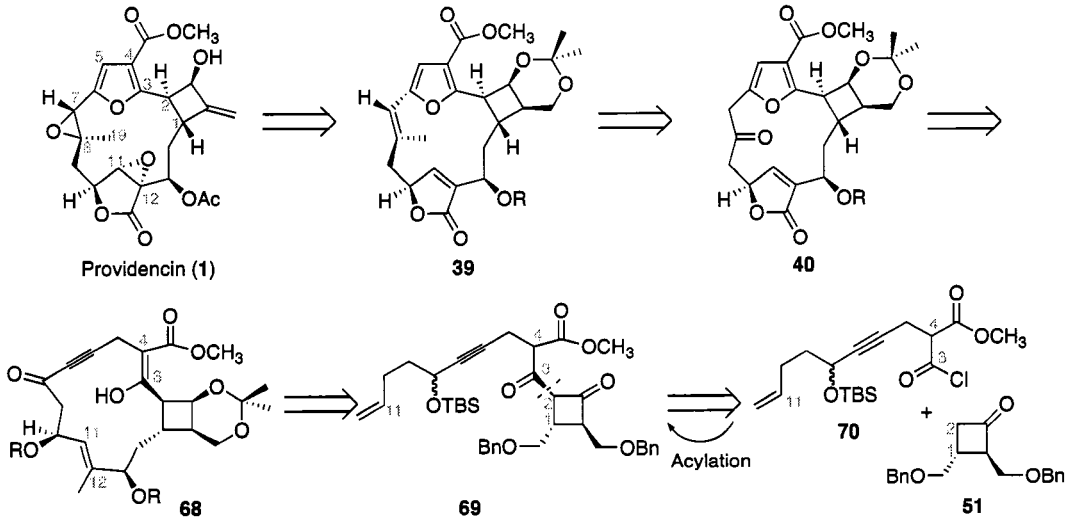
Chapter 2

Assembly of Providencin Framework. Part A.

2.1 Revised Synthetic Plan.

Our initial studies illustrated the difficulties encountered in assembling β-ketoester **60** (Schemes 1.4.1 and 1.4.4). Although this first approach was unsuccessful, the information gained allowed us to revise our synthetic route. Since we had been able to make the C2-C3 bond while assembling a functionalized cyclobutanone (Scheme 1.3.1), we proposed to acylate a cyclobutanone (**51**) with an already alkylated β-ketoester (**70**) providing coupled halves of providencin (**1**).[1-3] Methyl malonyl chloride **70** will serve as an electrophilic β-ketoester.

Scheme 2.1.1



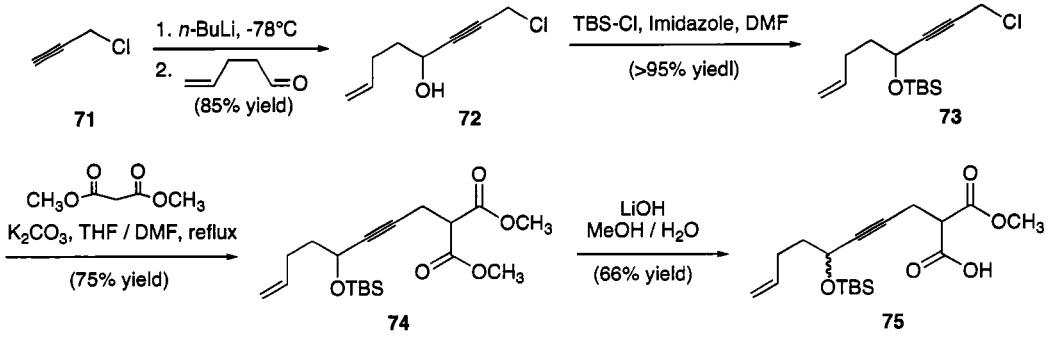
To test this intermolecular acylation, we designed a simple methyl malonyl chloride (**70**) that possessed key functionalities for further advancement, and planned to use cyclobutanone **51** as the nucleophilic coupling partner.

2.2 Acylation of a Model Cyclobutanone.

2.2.1 Synthesis of a Simple Malonate Fragment and Acylation.

Fragment **70** was designed to access the alkynone needed for the furan formation (**68→40**), and to allow macrocyclization *via* RCM with the terminal olefin to introduce the double bond between C11 and C12 of macrocycle **68**. Thus we began the synthesis of fragment **70**; propargyl choride was deprotonated with *n*-BuLi at -78°C and pentenone was added to deliver propargylic alcohol **72**,[4] which was subsequently protected as the corresponding TBS ether (**73**). We then alkylated methyl malonate with propargylic chloride **73**, followed with mono-hydrolysis of the resulting diester **74** using one equivalent of lithium hydroxide, to provide acid **75**.

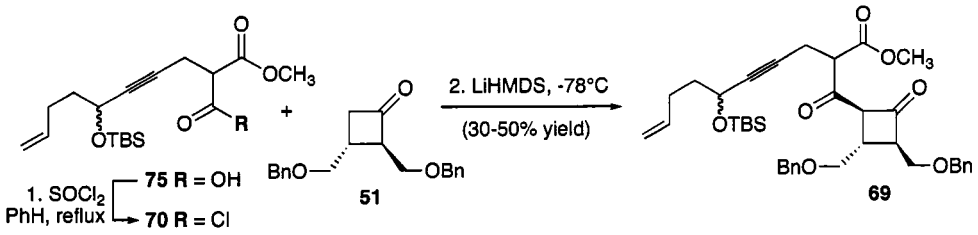
Scheme 2.2.1



Acid **75** was treated with thionyl chloride in refluxing benzene to furnish methyl malonyl chloride **70**. The anion of cyclobutanone **51** was generated using LiHMDS at -78°C before acid chloride **70** was introduced to yield the desired acylated cyclobutanone

in 30% to 50 % yield. The new stereocenter bearing the acyl group is epimerizable suggesting that the thermodynamic product (**69**) was obtained (acyl group *anti* to the adjacent substituent). Despite the modest yield, we were delighted to have successfully coupled the two fragments (**70** and **51**) that represent most of the providencin (**1**) carboskeleton. Furthermore, this new strategy was convergent and allowed advancement to a substrate that allowed us to test the key furan formation.

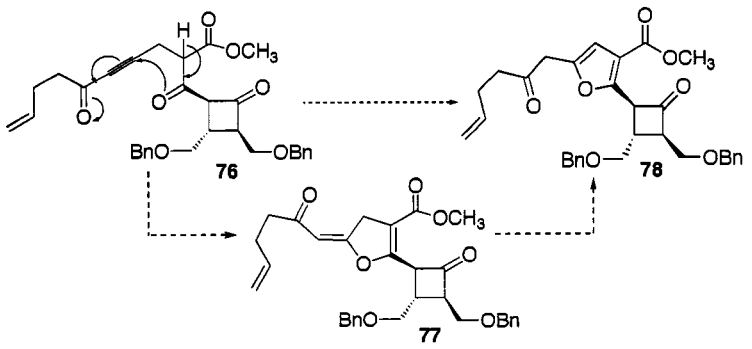
Scheme 2.2.2



2.2.2 3-Carboxy-Furan Cyclization Attempts.

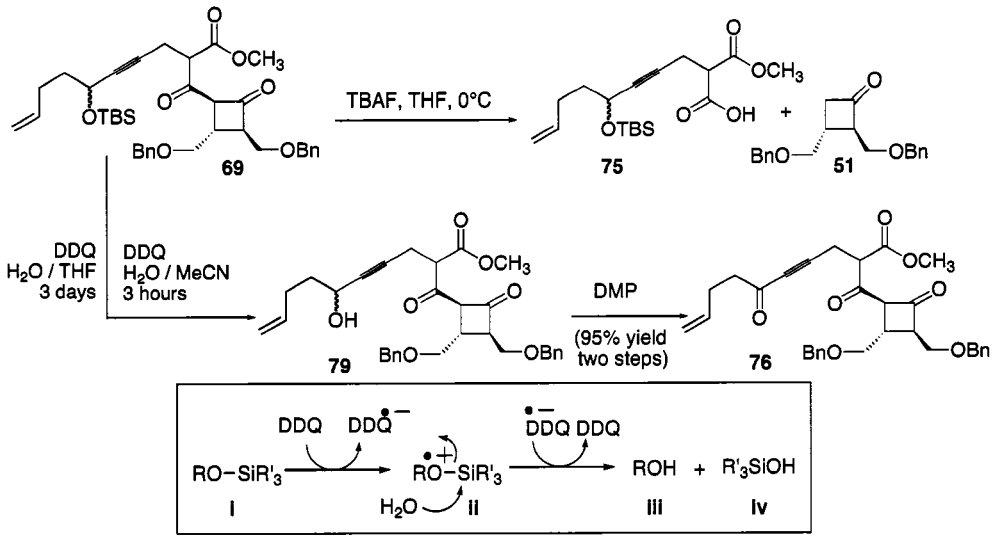
Gaining access to β-ketoester **69** provided us with the opportunity to test the key furan formation. Although this key step was envisioned to occur at a later stage in the synthesis, testing the furan cyclization at this point would hopefully yield valuable information for the end game of our synthesis. Enolization of β-ketoester **76** would occur under acid or base catalysis, taking advantage of mild conditions (*e.i.*, SiO_2 or Et_3N) previously developed by Marshall.[5] Intramolecular 1,4-addition of the enol to the alkynone would deliver vinylic ketone **77**, which after double bond isomerization would yield furan **78** (Scheme 2.2.3).

Scheme 2.2.3



To access propargylic ketone **76**, we first treated silyl ether **69** with TBAF and other fluorine sources typically used for silyl deprotection. Unfortunately, β,δ-diketoester **69** was found to undergo a retro-Claisen-condensation-type fragmentation to give cyclobutanone **51** and acid **75**, this reaction presumably catalyzed by the basic fluorine reagent.

Scheme 2.2.4



We were then intrigued by reports that DDQ can be used to remove TES-ethers in the presence of TBS-ethers; this reaction is mild and neutral because it only used catalytic amount of DDQ. These deprotection conditions involve a single electron transfer (SET)

leading to the displacement of the the silyl group by water accompanied by regeneration of DDQ (**i→iii**, Scheme 2.2.4).[6]

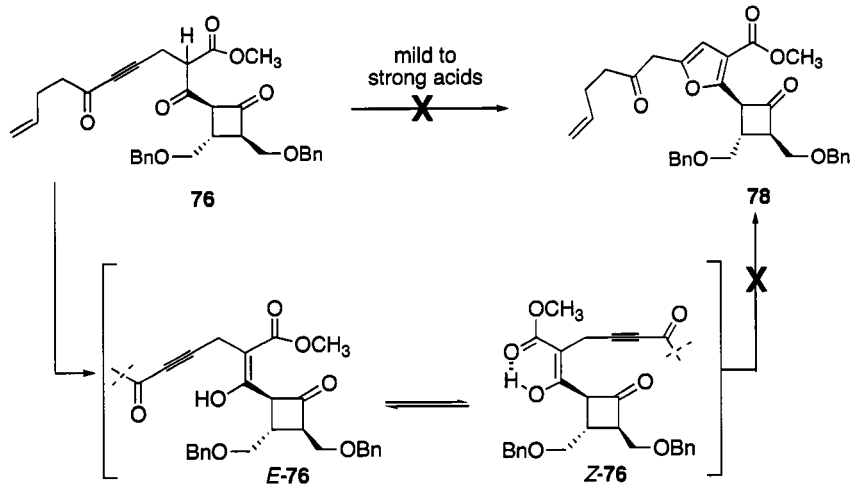
We treated substrate **69** with DDQ and observed cleavage of the TBS-ether without any evidence of fragmentation; propargyl alcohol **79** was isolated in excellent 95% yield. Interestingly, the polarity of the solvent had a significant influence on the rate of reaction. Indeed, we first carried out the deprotection under the reported conditions, using THF as the solvent, but the reaction was very slow, taking 3 days. Upon considering conditions that could accelerate this deprotection, we hypothesized that since this reaction proceeds through SET, a more polar solvent could be beneficial.[7] Indeed, the deprotection performed in acetonitrile was completed in only 3 hours. Next, we carried out a Dess-Martin oxidation on alcohol **79** to access alkynone **76** in nearly quantitative yield.

Subsequently, we screened conditions to effect enolization of β-ketoester **76** and its 1,4-addition into the alkynone moiety. Because we had observed β,δ-diketoester **69** fragmented under basic conditions, we decided to first try different acids (SiO_2, AcOH, H_2SO_4) to generate the desired enol. We were surprised to find that neither mild nor strong acids produced a furan, β-ketoester **76** proving stable to acids.

We rationalized that two enol geometries could result from the acid catalysis, a *E*-**76** enol with the alcohol on the same side as the alkynone, favoring the 1,4-attack and subsequent furan formation, or a *Z*-**76** enol placing the alcohol on the opposite side of the alkynone, thus preventing the 1,4-attack. Acid catalysis may have favored the *Z*-enol, which benefited from H-bonding between the alcohol and the carbonyl of the methyl

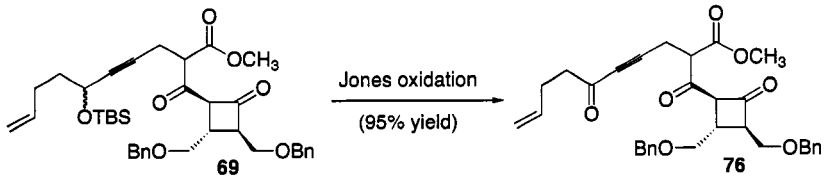
ester, but limited the proximity of the alcohol to the alkyne and prevented the furan formation.

Scheme 2.2.5



Despite being unable to form a furan (**78**), we learned that β-ketoester **76** was stable to strong acids. We could therefore use the Jones oxidation protocol on **69** to concomitantly remove the TBS ether and oxidize the propargylic alcohol, delivering alkynone **76** in near quantitative yield.

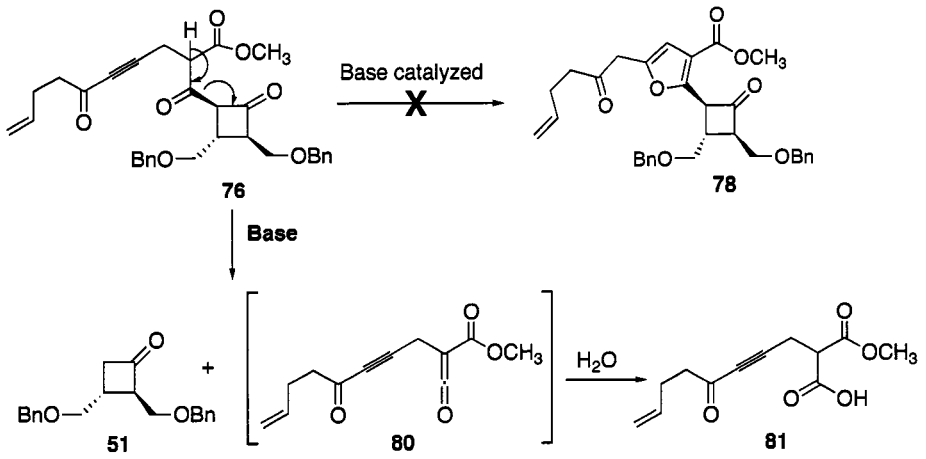
Scheme 2.2.6



We attempted the furan formation under basic conditions even though we were aware of the potential fragmentation of β-δ-diketoester **76**. We were hoping that the furan formation would be faster than the fragmentation. Unfortunately, the fragmentation predominated and cyclobutanone **51** and acid **81** were recovered. The fragmentation was a facile process, with the rate corresponding to the strength of the base used (0.5→10%

Et_3N in Hexane, THF or DCM slower than NaOMe in THF). We also tried Lewis acids to activate the alkyne, however the attempts led to no reaction ($Zn(OTf)_2$, $Hg(OTf)_2$) or decomposition ($PdCl_2$).

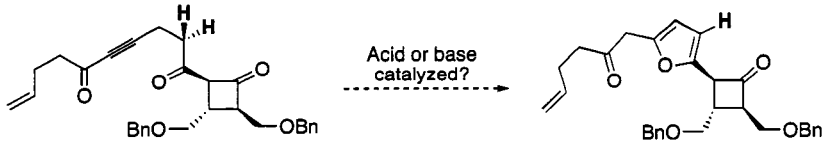
Scheme 2.2.7



76 78 51 80 81

At this point, we had been able to make a furan precursor (**76**), but could not cyclize it to form the desired 3-ketofuran **78**. Indeed, we had tried to generate the furan from β-ketoester **76** under acidic conditions, but only starting material was recovered, and basic conditions led to retro-Claisen-condensation-type fragmentation of β-δ-diketoester **76**. Therefore, we designed a new substrate that could be stable to base, triketone **82**. The triketone might deliver an enolate that would be capable of adding 1,4 into the alkynone moiety and yield furan **83** (Scheme 2.2.8).

Scheme 2.2.8

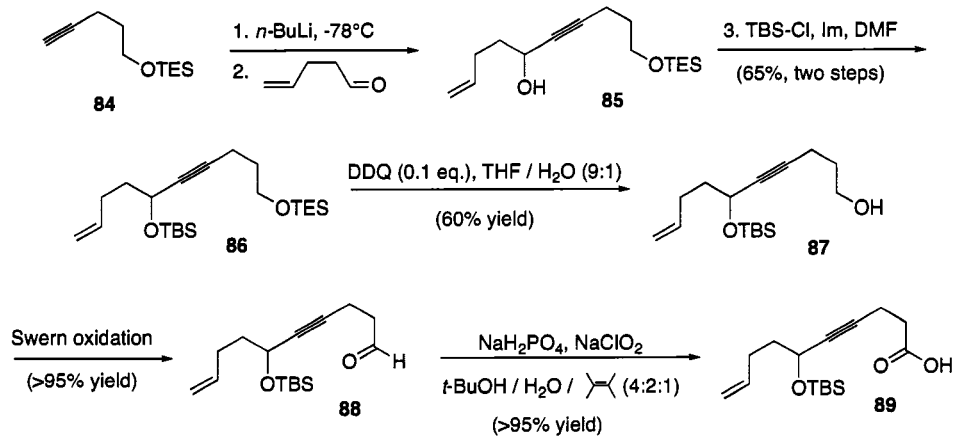


82 83

2.2.3 Synthesis of a Simple Ester and Acylation.

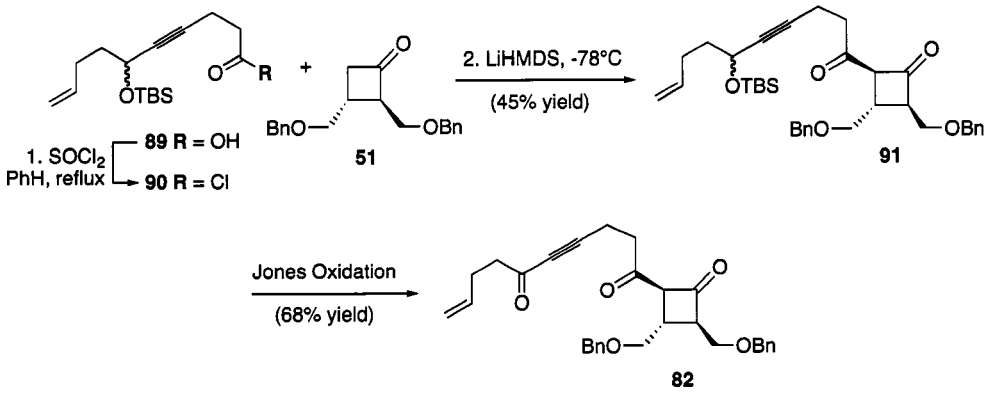
To access triketone **82**, we needed to synthesize a western fragment where the malonyl chloride motif would have been replaced by a simple acid chloride. We began the synthesis of the western piece with the deprotonation of silyl ether **84**, followed by addition into pentenaldehyde, to deliver propargylic alcohol **85**. Propargylic alcohol **85** was protected as the corresponding TBS ether **86** and the TES ether was selectively removed using DDQ in THF to give alcohol **87**. It should be noted that because THF is a less polar solvent than acetonitrile,[7] the TBS remained untouched (*cf.* Scheme 2.2.4). The primary alcohol **87** was oxidized to acid **89** in two steps, a Swern oxidation followed by a sodium chlorite oxidation[8] of aldehyde **88** to acid **89**.

Scheme 2.2.9



Acid chloride **90** was prepared from the corresponding acid **89** using thionyl chloride in refluxing benzene. Cyclobutanone **51** was then deprotonated with LiHMDS and treated with acid chloride **90** to deliver diketone **91** in 45% yield. Jones reagent[9] was used to simultaneously remove the TBS ether and oxidize the propargylic alcohol (**91**), which furnished triketone **82** in 68% yield.

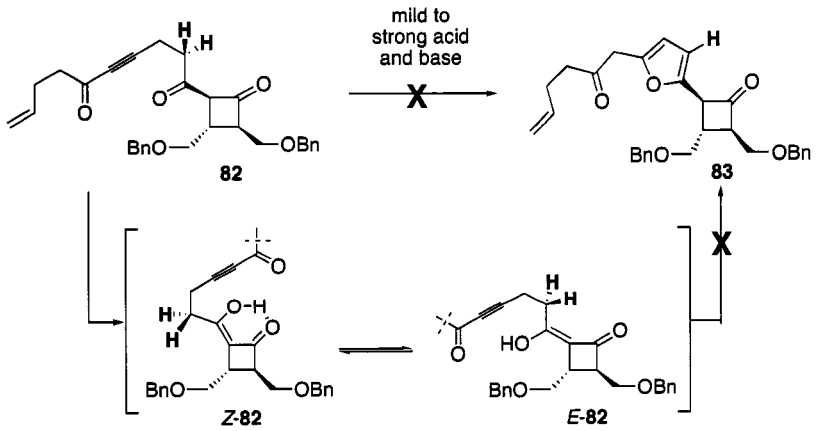
Scheme 2.2.10



2.2.4 Furan Cyclization Attempts.

Access to triketone **82** allowed for the screening of various conditions designed to deliver the desired furan **83**. Furan precursor **82** proved to be stable and unreactive to acidic and basic conditions. Indeed, we exposed triketone **82** to a several bases (Et_3N, LiHMDS, KHMDS) but no furan cyclization resulted, only starting material was recovered.

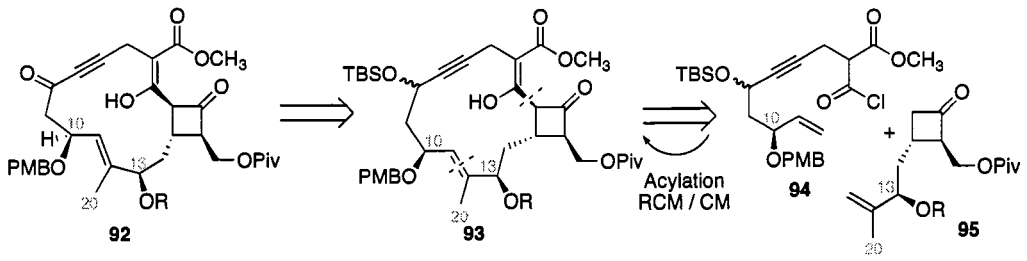
Scheme 2.2.11



At this juncture, it became obvious that we could not form the required furan from acyclic systems. Even though we did not know if we could make a furan using Marshall's method, we moved on toward the synthesis of fragments that would allow the formation of a macrocycle containing the alkynone and β-ketoester motifs required to make a furan. We envisioned that the rigidity of the macrocycle would force and restrain the correct enol geometry, which would allow the proximity of the alcohol to the alkynone moiety therefore facilitating the furan formation.

2.3 Fragment Functionalization.

Scheme 2.3.1

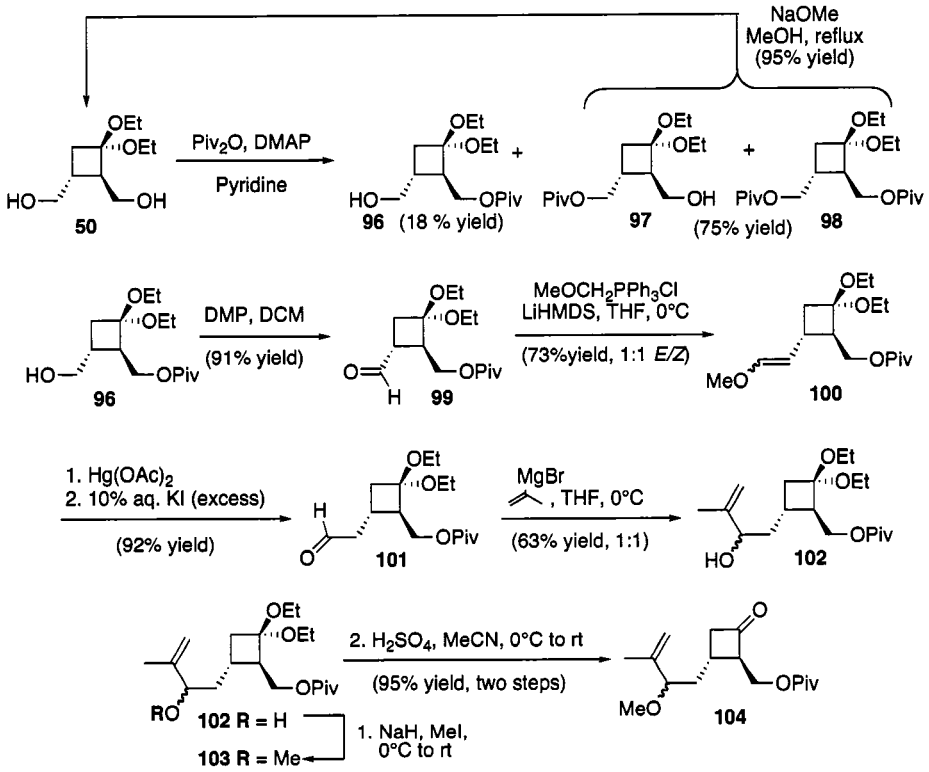


Having been successful with the acylation of the cyclobutanone, we retained this disconnection to access macrocycle **93**, combining it to an olefin metathesis to stitch the bottom section of the macrocycle. We believed that the order of events for the two key steps, the acylation and metathesis, were interchangeable. To perform the metathesis, we needed to append a 1,1 disubstituted olefin to the cyclobutanone (**95**). Substrate **94** needed introduction of the C10 oxidation in a stereocontroled fashion, to set the stage for incorporation of the butenolide moiety.

2.3.1 Synthesis of a Functionalized Cyclobutanone.

The synthesis of the eastern fragment (**95**) began with the differentiation of diol **50**. Although the two alcohols are in different environments, the selective mono-functionalization proved difficult. We eventually found that a bulky pivalate offered some advantages; we could easily separate the two mono-protected diols (**96** and **97**) from each other, and the undesired mono-protected (**97**) and bis-protected diol (**98**) could be deprotected efficiently. Diol **50** was recovered and recycled to the protection. Reiteration of this process provided additional amounts of alcohol **96**.

Scheme 2.3.2



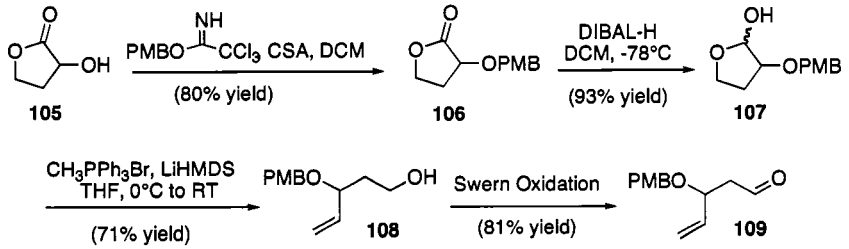
Oxidation of alcohol **96** with Dess-Martin reagent followed by treatment of the aldehyde (**99**) with the phosponium salt of methoxymethylchloride, delivered a 1:1

mixture of *E/Z* methyl enolether **100** in 73% yield. The masked aldehyde (**100**) was selectively deprotected to aldehyde **101** in the presence of the ketal using mercuric acetate and an excess of potassium iodide. Aldehyde **101** was treated with propenyl magnesium bromide to yield a 1:1 diastereomeric mixture of allylic alcohols **102** in 63% yield. The allylic alcohol **102** was protected as the corresponding methyl ether (**103**) and the ketal removed using sulfuric acid in acetonitrile at 0°C. Cyclobutanone **104** was thus obtained in 95% yield over the two steps.

2.3.2 Synthesis of a Functionalized Malonate.

The synthesis of the western portion of providencin (**1**) was initiated from α-hydroxybutyrolactone **105**. This starting material (**105**) is especially attractive since both enantiomers are commercially available, providing us with the opportunity to affect an enantiospecific synthesis. For the purpose of route assessment, we decided to use the less expensive racemic α-hydroxybutyrolactone.

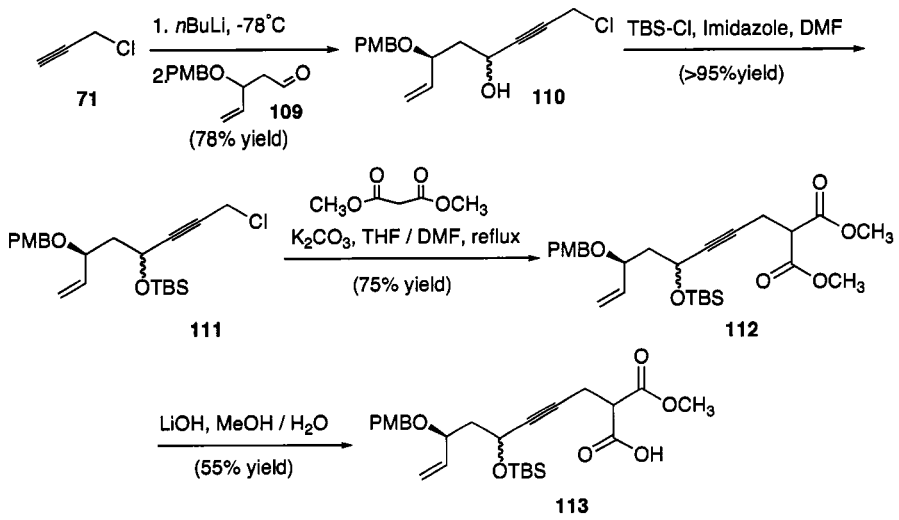
Scheme 2.3.3



The alcohol of **105** was protected using PMB-tricloroacetamidate and catalytic amount of CSA to provide the corresponding PMB-ether **106** in 80% yield. Lactone **106** was then reduced to the corresponding lactol **107** in 93% yield using DIBAl-H at -78°C.

Lactol **107** was treated under Wittig olefination conditions to deliver primary alcohol **108** in 71% yield, and Swern oxidation produced the corresponding aldehyde **109** in 81% yield. Aldehyde **109** was reacted with the anion of propargyl chloride (**71**), providing propargylic alcohol **110** in 78% yield, and **110** was protected as the corresponding TBS ether (**111**) in near quantitative yield. Alkylation of methyl malonate with propargylic chloride **111** was performed in a refluxing mixture of THF and DMF, using potassium carbonate; malonate **112** was obtained in 75% yield. Lithium hydroxide was used to monohydrolyze malonate **112** and furnished acid **113** in 55% yield.

Scheme 2.3.4

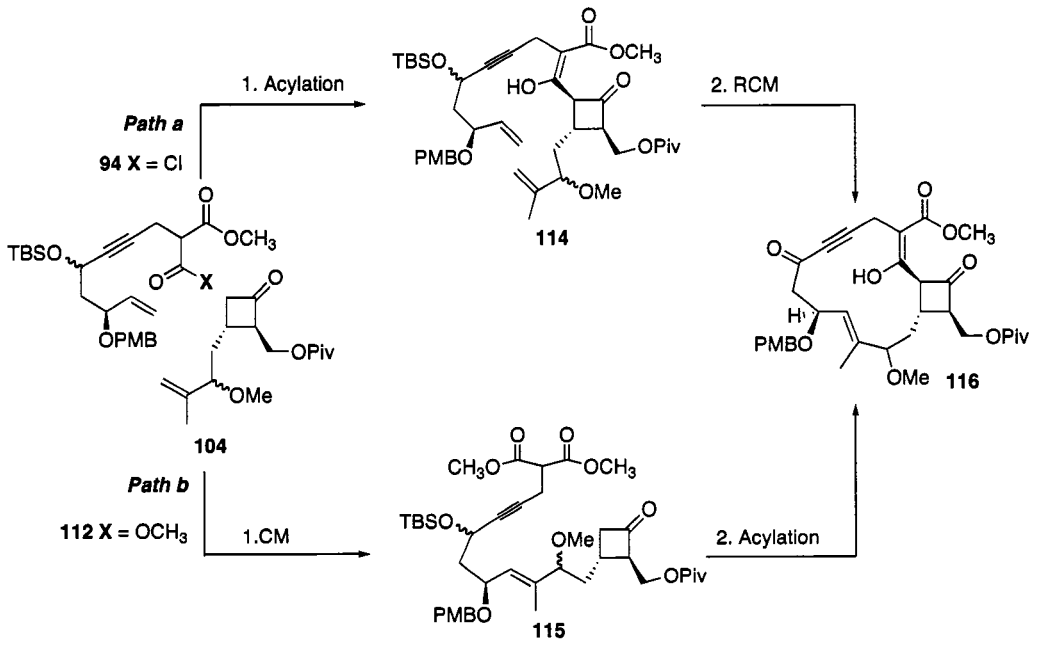


With the two key subunits (**104** and **112/113**) of providencin (**1**) in hand, we could now investigate their coupling and macrocycle formation.

2.3.3 Fragment Assembly.

Having gained access to the two functionalized halves of providencin (**1**), **104** and **112/113**, we were presented with two coupling options. Either acylate cyclobutanone **104** first to yield diene **114**, which after RCM would deliver macrocycle **116** (***Path a***), or perform the cross-olefin-metathesis (CM) between terminal olefin **112** and 1,1-disubstituted olefin **104**, and subsequent intramolecular acylation of cyclobutanone **115**, to provide macrocycle **116** (***Path b***).

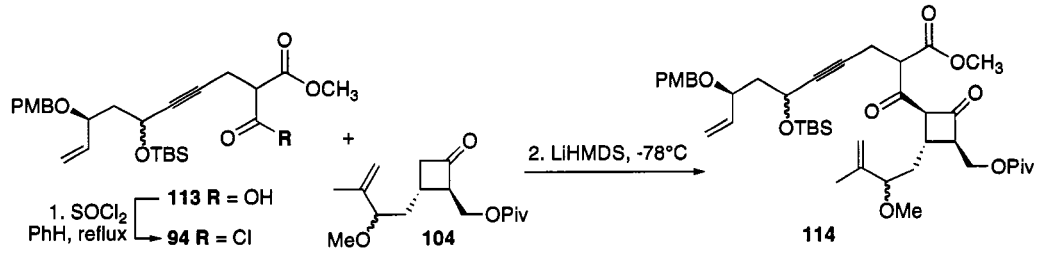
Scheme 2.3.5



2.3.3.1 Acylation.

We initially tried the intermolecular acylation, ***Path a***, because we had been previously successful with this reaction (*cf.* Schemes 2.2.2 and 2.2.10).

Scheme 2.3.6



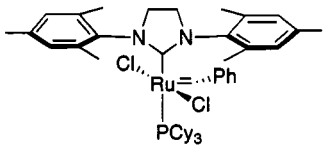
To this end, we treated acid **113** with thionyl chloride in refluxing benzene to generate acid chloride **94**. Cyclobutanone **104** was then treated with LiHMDS and acid chloride **94** at -78°C, but only very small amounts of diene **114** were isolated. We then screened reaction conditions in an attempt to increase the yield. Variation of the stoichiometry, temperature, order of addition, and addition of hexanes to favor nucleophilicity *vs* basicity did not improve the yield. The acylation was not robust on this particular system (**94**+**104**→**114**) and we could not access enough material (**114**) for characterization and to proceed with the subsequent reactions.

2.3.3.2 Cross-Metathesis.

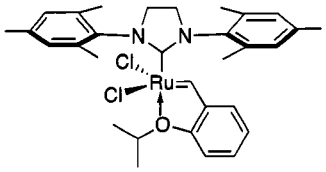
The alternative to the acylation was the coupling of the two fragments *via* cross-metathesis, ***Path B***. Ring-closing metathesis has been widely used in total synthesis[10] but cross-metathesis was just beginning to emerge.[11] Grubbs *et al.* have categorized olefins by their relative ability to undergo homodimerization *via* cross metathesis and susceptibility of their homodimer to undergo a second metathesis. It was found that olefins of two different types (different reactivity) lead to selective metathesis, as opposed to giving a statistical mixture.[12] The olefin reactivity was evaluated according to the steric bulk (substituents) and electronic properties, and the appropriate catalyst was

selected. Our two fragments had been designed to be different types; the terminal olefin **112** was type I (fast homodimerization), and the 1,1-disubstituted olefin **104** was type III (no homodimerization). Before exposing substrate **112** to the metathesis catalysts **I** and **II**, we protected the alkyne moiety as a dicobalt hexacarbonyl cluster to prevent enyne metathesis; thus alkyne **112** was treated with dicobalt octacarbonyl in toluene to provide a red complex (**117**) in 74% yield.

Figure 2.3.1



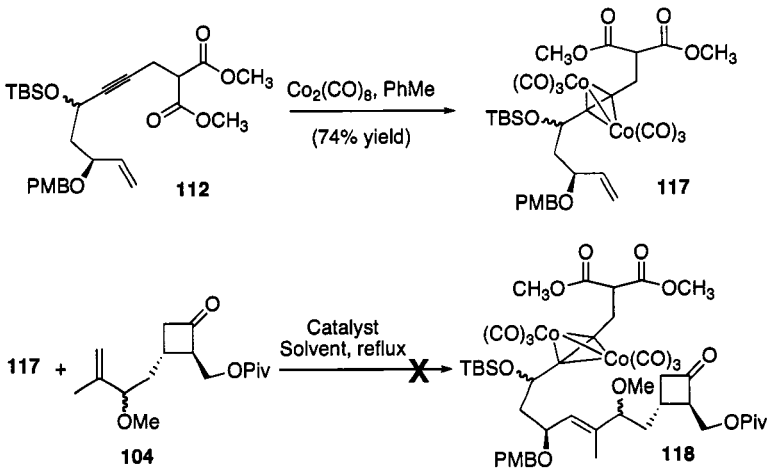
(I) Grubbs Catalyst 2nd Gen.



(II) Hoveyda-Grubbs Catalyst 2nd Gen.

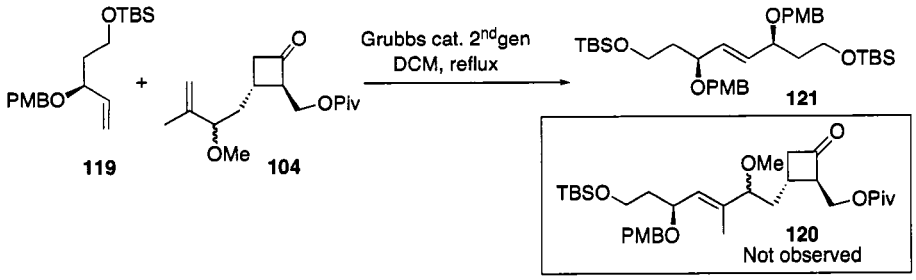
The terminal and 1,1-disubstituted olefins (**117** + **104**) were mixed and refluxed in DCM in the presence of the second generation of Grubbs' catalyst (**I**). After several hours there was no new material formed so the catalyst loading was increased. The solvent was also replaced with dichloroethane to allow for increased reaction temperatures. Still, after several days, no product was observed, cyclobutanone **104** was recovered but **117** had begun to decompose.

Scheme 2.3.7



Although it was well precedented that metatheses could be performed in the presence of a cobalt-protected alkyne,[13, 14] we wondered if it could be interfering with our metathesis. We therefore decided to remove the alkyne moiety by using a simpler terminal olefin (**119**) to test the cross metathesis.

Scheme 2.3.8



Once again, no cross metathesis product (**120**) was isolated, but this time homodimerization product **121** was isolated. This result, homodimerization of **119**, indicated that terminal olefin **119** was reactive but did not readily undergo secondary metathesis with the 1,1-disubstituted olefin **104**. A range of reaction conditions were tried and we observed more homodimer **121** being formed when the reaction was performed in dichloroethane and catalyst **II** was used.

It became apparent that the cross metathesis and potentially the ring closing metathesis were challenging for the substrates in hand. Therefore the retrosynthesis was revised to facilitate this metathesis between C11-C12, which will be discussed in chapter 3.

2.4 Conclusion.

In this chapter, the explored disconnection involved the α-acylation of a cyclobutanone (**51** and **104**) with a substituted methyl malonyl chloride (**70** and **94**). This strategy allowed rapid assembly of the western and eastern fragments of providencin (**1**). On less functionalized substrates (**76** and **82**) we attempted to make the furan moiety (**78** and **83**) from the addition of an enol into an alkynone moiety, but this cyclization was unsuccessful. Under acidic condition, it is possible that the enol geometry was locked, potentially placing the alcohol on the opposite side of the alkynone and therefore preventing the cyclization (Scheme 2.2.5). Under basic conditions we observed retro-Claisen condensation type fragmentation of the β,δ-diketoester (Scheme 2.2.7). We then began to further functionalize the western (**92** and **112**) and eastern fragments (**104**) to allow their coupling not only at the top but also at the bottom to give rise to a macrocycle (**116**). Preparation of the macrocycle prior to furan formation was expected to enforce a favorable enol geometry and thus facilitate addition to the alkynone moiety. Unfortunately, we were unable to couple the more functionalized substrates *via* acylation or cross metathesis; no macrocycle was obtained. At this juncture, we revised our retrosynthetic approach to better assemble the two functionalized halves.

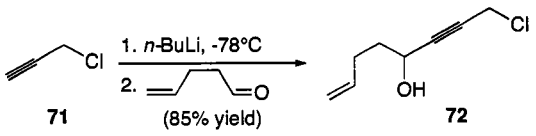
2.5 Experimental Section.

2.5.1 Materials and Methods.

Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). All other commercially obtained reagents were used as received. All reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F254 pre-coated plates (0.25 mm). Column or flash chromatography[15] was performed with the indicated solvents using silica gel (particle size 35 -75 mm) purchased from Silicycle. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Advance DPX-500 or Bruker Advance DPX-400 spectrometers. Chemical shifts are reported relative to internal chloroform (^{1}H δ 7.26 ppm, ^{13}C δ 77.00 ppm), methanol (^{1}H δ 3.31 ppm, ^{13}C δ 49.00 ppm). High resolution mass spectra were acquired at The University of Illinois Mass Spectrometry Center.

2.5.2 Preparative Procedure.

Preparation of Propargylic Alcohol 72:

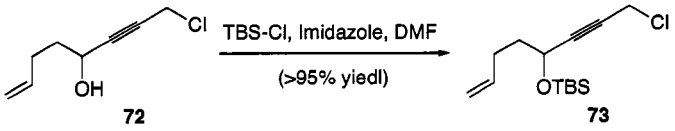


71 (85% yield) 72

To a solution of propargyl chloride **71** (0.44 g, 6 mmol) in Et_2O (12 mL) at -78°C was added a 1.6 M solution of *n*-BuLi in hexane (3.8 mL, 6 mmol) dropwise. After 1h, pentenaldehyde (0.5 g, 6 mmol) was added dropwise and the temperature was kept at -78°C for 2 more h. The reaction was quenched with NH_4Cl (saturated in water), diluted

with EtOAc, the biphasic solution was separated, and the aqueous phase was extracted two more times with EtOAc. The organic phases were combined, backwashed with NaCl (saturated in water), dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (20% EtOAc/Hexanes) to yield the title compound **72** (0.76 g, 80 % yield) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (ddt, J = 17.0, 10.3, 6.6 Hz, 1H), 5.09 (ddd, J = 18.7, 3.2, 1.7 Hz, 1H), 5.01 (dd, J = 10.4, 1.1 Hz, 1H), 4.46 (tt, J = 6.5, 1.7 Hz, 1H), 4.18 (d, J = 1.8 Hz, 2H), 2.24 (q, J = 7.6 Hz, 2H), 1.97 (brs, 1H), 1.87-1.75 (m, 2H); ^{13}C NMR (125MHz, $CDCl_3$) δ 137.82, 115.90, 87.60, 80.33, 62.30, 36.89, 30.72, 29.67; IR (thin layer, NaCl) 3342, (brs), 3077(w), 2978 (w), 2946 (m), 2860 (w), 1641 (m), 1439 (m), 1431 (m), 1263 (sh, s), 1060 (m), 1020 (m) cm^{-1}; HRMS (CI) *m/z* found 157.04, calc'd for $C_8H_{10}ClO$ [M-H]: 157.05.

Preparation of Silyl Ether 73:

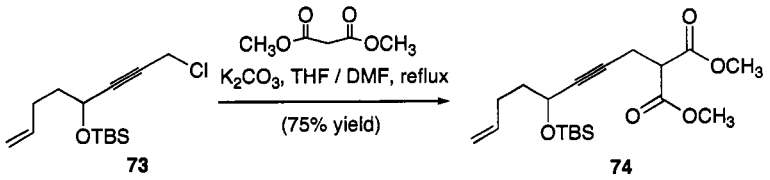


72 **73**

To a solution of propargyl alcohol **72** (0.76 g, 4.8 mmol) in DMF (10 mL) were added TBS-Cl (0.72 g, 4.8 mmol) and imidazole (0.65 g, 9.6 mmol). After 12 h at room temperature, the reaction was quenched at 0°C by slow addition of NH_4Cl (saturated in water) and diluted with ether. The biphasic solution was separated, the aqueous phase was extracted five times with ether; the organic phases were combined, backwashed with NaCl (saturated in water), dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (5% EtOAc/Hexanes) to yield the title

compound **73** (1.2 g, >95% yield) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H), 5.00 (ddd, *J* = 17.2, 3.2, 1.7 Hz, 1H), 4.98 (ddd, *J* = 10.1, 1.7, 1.2 Hz, 1H), 4.40 (tt, *J* = 6.2, 1.8 Hz, 1H), 4.16 (d, *J* = 1.8 Hz, 2H), 2.22-2.15 (m, 2H), 2.82-2.71 (m, 2H), 0.93 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.16, 115.43, 88.58, 79.28, 62.63, 37.89, 30.93, 29.68, 26.18, 18.59, -4.07, -4.63; IR (thin layer, NaCl) 3079 (w), 2953 (s), 2930 (s), 2886 (m), 2857 (s), 1641 (w), 1422 (m), 1262 (s), 1153 (m), 1090 (s) cm^{-1}; HRMS (CI) *m/z* found 273.14, calc'd for $C_{14}H_{26}ClOSi$ [M+H]: 273.14.

Preparation of Malonate 74:

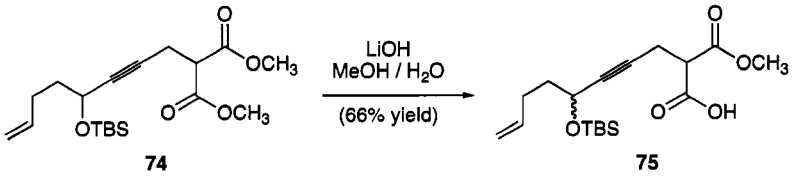


73 **74**

To a solution of propargyl chloride **73** (0.14 g, 0.51 mmol) in a mixture of THF (3 mL) and DMF (3 mL) were added dimethyl malonate (0.29 mL, 2.6 mmol) and K_2CO_3 (0.56 g, 4.1 mmol). The reaction mixture was heated to reflux for 3 h, cooled to room temperature, quenched with NH_4Cl (saturated in water) and diluted with ether. The biphasic solution was separated, the aqueous phase was extracted five times with ether; the organic phases were combined, backwashed with NaCl (saturated in water), dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (5% EtOAc/Hexanes) to yield the title compound **74** (0.14 g, 75% yield) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H), 4.99 (dd, *J* = 15.7, 1.6 Hz, 1H), 4.95 (dd, *J* = 10.2, 1.0 Hz, 1H), 4.30 (tt, *J* = 6.4, 1.7 Hz,

1H), 3.75 (s, 6H), 3.57 (t, J = 7.8 Hz, 1H), 2.80 (dd, J = 7.7, 1.9 Hz, 2H), 2.20-2.07 (m, 2H), 1.76-1.62 (m, 2H), 0.88 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.76, 138.39, 115.21, 84.27, 80.27, 62.71, 53.14, 51.53, 38.29, 29.73, 26.19, 19.23, 18.58, -4.12, -4.68; IR (thin layer, NaCl) 2955 (m), 2930 (m), 2857 (m), 1759 (sh, s), 1743 (sh, s), 1436 (m), 1342 (m), 1251 (m), 1154 (m), 1087 (m) cm^{-1}; HRMS (ES) *m/z* found 391.19, calc'd for $C_{19}H_{32}O_5NaSi$ [M+Na]: 391.20.

Preparation of Acid 75:

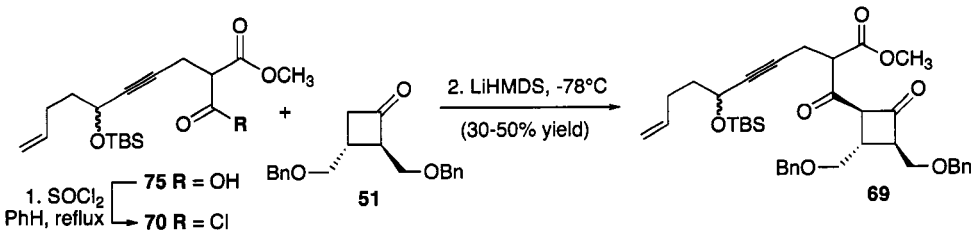


74 **75**

To a solution of the malonate **74** (1.1 g, 2.9 mmol) in a mixture of MeOH (20 mL) and water (10 mL) was added lithium hydroxide (69 mg, 2.9 mmol) and the mixture was heated to reflux for 12 h. The reaction was allowed to cool at room temperature and the MeOH was rotary evaporated. The residue was partitioned between ether and NH_4Cl (saturated in water), the aqueous phase was extracted with ether three more times. The combined organic phases were dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (20% EtOAc/Hexanes with 0.1% AcOH) to yield the title compound **75** (0.68 g, 66% yield) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddt, J = 17.0, 10.3, 6.6 Hz, 1H), 5.03 (dd, J = 17.1, 1.7 Hz, 1H), 4.96 (dd, J = 10.3, 1.7 Hz, 1H), 4.32 (tt, J = 6.4, 1.7 Hz, 1H), 3.79 (s, 6H), 3.61 (t, J = 7.5 Hz, 1H), 2.92 (dt, J = 7.5, 1.8 Hz, 2H), 2.15 (q, J = 7.1 Hz, 2H), 1.76-1.65 (m, 2H), 0.89 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.41, 168.36,

137.97, 114.87, 84.23, 79.44, 62.32, 52.99, 50.77, 37.87, 29.35, 25.79, 18.86, 18.20, -4.54, -5.07; IR (thin layer, NaCl) 3149 (br, m), 3079 (w), 2954 (s), 2929 (s), 2857 (s), 1753 (sh, s), 1720 (sh, s), 1641 (w), 1438 (m), 1342 (m), 1252 (s), 1087 (s) cm^{-1}; HRMS (ES) *m/z* found 355.19, calc'd for $C_{18}H_{31}O_5Si$ [M+H]: 355.19.

Preparation of β,δ-Diketoester 69:

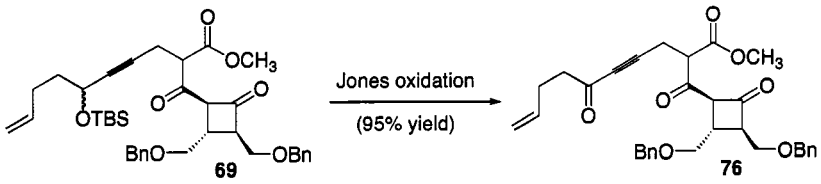


To a solution of acid **75** (74 mg, 0.21 mmol) in benzene (1 mL) was added $SOCl_2$ (15 μL, 0.21 mmol) and the reaction mixture was heated to reflux. After 4 h the reaction was cooled to room temperature, concentrated and put under mechanical vacuum for 2 h. The acid chloride **70** was used immediately and without purification.

To a solution of ketone **51** (48 mg, 0.16 mmol) in THF (1 mL) was added a 1M solution of LiHMDS in THF (0.19 mL, 0.19 mmol) at -78°C dropwise. After 20 min a solution of the acid chloride **70** (*vide supra*, 0.21 mmol) in THF (0.5 mL) was added dropwise and the reaction was kept at the same temperature for 30 min. The reaction was quenched with NH_4Cl (saturated in water), diluted with EtOAc, the biphasic mixture was separated and the aqueous phase extracted two more times with EtOAc. The organic phases were combined, dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (5% EtOAc/Hexanes) to yield the title compound **69** (67 mg, 67% yield) as a pale yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.18 (m, 10H), 5.71 (ddt, J = 17.0, 10.3, 6.6 Hz, 1H), 5.40 (s, 0.3H), 4.94 (d, J =

17.2 Hz, 1H), 4.88 (d, J = 10.0 Hz, 1H), 4.48-4.39 (m, 4H), 4.23 (t, J = 6.4 Hz, 1H), 3.94 (q, J = 13.3 Hz, 1H), 3.68-3.39 (m, 7H), 3.00-2.48 (m, 5H), 2.06 (q, J = 6.9 Hz, 2H), 1.65-1.55 (m, 2H), 0.81 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.18, 165.18, 164.88, 139.88, 138.79, 138.53, 138.36, 128.77, 128.09, 128.01, 127.97, 127.89, 115.32, 84.57, 79.89, 73.60, 73.49, 73.24, 72.77, 63.85, 62.69, 53.32, 51.65, 38.27, 36.75, 36.58, 29.77, 26.22, 19.16, 18.61, -4.06, -4.64; IR (thin layer, NaCl) 3418 (w), 2953(m), 2927 (m), 2855 (m), 1771 (m), 1743 (m), 1734 (m), 1456 (m), 1260 (s), 1198 (m), 1092 (s) cm^{-1}; LRMS (ES) *m/z* found 669.4, calc'd for $C_{38}H_{50}O_7NaSi$ [M+Na]: 669.33.

Preparation of Triketone 76:

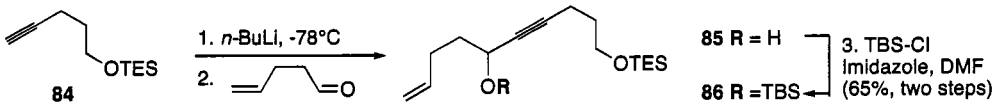


To a solution of TBS ether **69** (15 mg, 0.023 mmol) in acetone (1 mL) was added excess Jones reagent (70 μL). The color of the reaction changed from red to green after 4 h. The reaction was diluted with water and DCM and poured over $NaHCO_3$ (saturated in water). The biphasic mixture was separated, the aqueous phase extracted two more times with DCM, the organic phases were combined, dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (10% EtOAc/Hexanes) to yield the title compound **76** (12 mg, >95% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.28 (m, 10H), 5.77 (ddt, J = 17.0, 10.3, 6.6 Hz, 1H), 5.49 (s, 0.4H), 5.04 (d, J = 17.2 Hz, 1H), 5.00 (d, J = 10.4 Hz, 1H), 4.53-4.47 (m, 4H),

4.02 (q, J = 13.6 Hz, 1H), 3.79-3.50 (m, 7H), 3.08-2.88 (m, 4H), 2.71-2.54 (m, 1H), 2.60 (t, J = 7.3 Hz, 2H), 2.39 (q, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.76, 167.30, 164.05, 139.06, 138.38, 138.12, 136.17, 129.62, 128.54, 128.38, 128.34, 127.67, 127.60, 127.58, 127.50, 115.76, 88.28, 81.90, 73.21, 73.11, 73.00, 72.70, 72.59, 72.47, 63.55, 53.19, 50.00, 44.47, 36.32, 36.03, 27.78, 18.79; IR (thin layer, NaCl) 3403 (br, w), 3015 (w), 2955 (w), 2922 (m), 2853 (m), 2221 (sh, m), 1766 (s), 1745 (s), 1716 (m), 1667 (s), 1453 (w), 1348 (m), 1273 (m) cm^{-1}; HRMS (ES) *m/z* found 553.22, calc'd for $C_{32}H_{34}O_7Na$ [M+Na]: 553.23.

Preparation of Jones reagent (1.4M): To a solution of CrO_3 (13.5 g, 0.14 mol) in water (87.5 mL) was added conc H_2SO_4 (12.5 mL). Shelf life is over 1 year.[9]

Preparation of Silyl Ether 86:

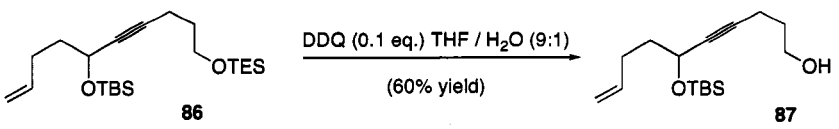


To a solution of propargyl alcohol **84** (5.3 g, 27 mmol) in Et_2O (90 mL) at -78°C was added a 1.6 M solution of *n*-BuLi in hexane (20 mL, 32 mmol) dropwise. After 1h, pentenaldehyde (2.3 g, 27 mmol) was added dropwise, the temperature was kept at -78°C for 2 h. The reaction was quenched with NH_4Cl (saturated in water) and diluted with EtOAc. The biphasic solution was separated, and the aqueous phase was extracted two more times with EtOAc. The organic phases were combined, backwashed with NaCl (saturated in water), dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (gradient elution, 5→10%

EtOAc/Hexanes) to recover alkyne **84** (1.5 g) and yield propargyl alcohol **85** (4.6 g, 60% yield) as a colorless oil.

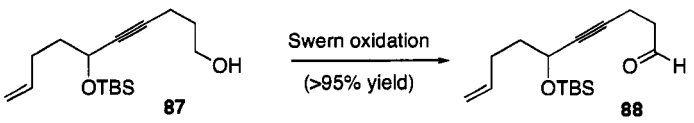
To a solution of propargyl alcohol **85** (4.5 g, 16 mmol) in DMF (80 mL) were added TBS-Cl (2.4 g, 16 mmol) and imidazole (2.2 g, 36 mmol). After 12 h at room temperature, the reaction was quenched at 0°C by slow addition of NH_4Cl (saturated in water) and diluted with ether. The biphasic solution was separated, the aqueous phase was extracted five times with ether; the organic phases were combined, backwashed with NaCl (saturated in water), dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (5% EtOAc/Hexanes) to yield the title compound **86** (5.4 g, >95% yield) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70 (ddt, J = 17.0, 10.3, 6.6 Hz, 1H), 4.90 (d, J = 17.2 Hz, 1H), 4.84 (d, J = 10.2 Hz, 1H), 4.23 (t, J = 6.4 Hz, 1H), 3.57 (t, J = 12.5 Hz, 2H), 2.16 (td, J = 7.1, 1.9 Hz, 2H), 2.13-2.03 (m, 2H), 1.68-1.55 (m, 4H), 0.84 (t, J = 8.0 Hz, 9H), 0.78 (s, 9H), 0.50 (q, J = 8.0 Hz, 6H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.58, 115.04, 84.53, 82.22, 62.94, 61.79, 38.56, 32.20, 29.91, 26.23, 15.54, 7.14, 5.25, 4.80, -4.03, -4.59; IR (thin layer, NaCl) 2954 (s), 2933 (m), 2877 (m), 2851(m), 1641 (w), 1472 (m), 1250 (m), 1104 (s), 1005 (m) cm^{-1}; HRMS (CI) *m/z* found 395.28, calc'd for $C_{22}H_{43}O_2Si_2$ [M-H]: 395.28.

Preparation of Alcohol 87:



To a solution of protected diol **86** (0.1 g, 0.25 mmol) in a mixture of THF (1.8 mL) and water (0.2 mL) was added DDQ (6.0 mg, 0.025 mmol). The reaction was completed after 15 min and was then absorbed onto silica gel to be purified by flash chromatography (gradient elution, 5→20→50% EtOAc/Hexanes) to yield the title compound **87** (42 mg, 60% yield) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H), 4.91 (d, *J* = 17.2 Hz, 1H), 4.84 (d, *J* = 10.2 Hz, 1H), 4.22 (t, *J* = 6.4 Hz, 1H), 3.63 (td, *J* = 6.2, 1.0 Hz, 2H), 2.20 (td, *J* = 7.0, 1.8 Hz, 2H), 2.09-2.01 (m, 2H), 1.66-1.58 (m, 4H), 1.36 (brs, 1H), 0.78 (s, 9H), 0.0 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.50, 128.27, 115.14, 84.10, 82.79, 62.90, 62.23, 38.52, 31.73, 29.90, 26.22, 18.63, 15.70, -4.05, -4.58; IR (thin layer, NaCl) 3336 (br, s), 2951 (m), 2857 (m), 1255 (m), 1087 (m) cm^{-1}; HRMS (ES) *m/z* found 283.21, calc'd for $C_{16}H_{31}O_2Si$ [M+H]: 283.20.

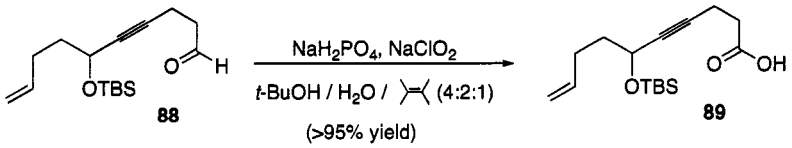
Preparation of Aldehyde 88:



To a solution of oxalyl chloride (0.19 mL, 2.1 mmol) in DCM (2 mL) cooled to -78°C was added dropwise a solution of DMSO (0.5 mL, 2.8 mmol) in DCM (1.5 mL). The mixture was stirred 15 min further and a solution of alcohol **87** (0.4 g, 1.4 mmol) in DCM (2 mL) was then added slowly. After an additional 15 min, triethylamine (0.80 mL, 5.7 mmol) was introduced dropwise and the reaction mixture was warmed to 0°C. After 15 min, the reaction mixture was partitioned between ether and water, and the organic phase was washed with water, NaCl (saturated in water), dried over Na_2SO_4,

filtered and rotary evaporated. The crude product was purified by flash chromatography (gradient elution, 5→20% EtOAc/Hexanes) to yield the title compound **88** (0.38 g, >95% yield) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.67 (s, 1H), 5.69 (ddt, J = 17.0, 10.3, 6.6 Hz, 1H), 4.91 (dd, J = 17.1, 1.6 Hz, 1H), 4.85 (d, J = 10.2 Hz, 1H), 4.22 (t, J = 6.2 Hz, 1H), 2.52 (t, J = 7.0 Hz, 2H), 2.41 (t, J = 7.4 Hz, 2H), 2.01-2.11 (m, 2H), 1.68-1.55 (m, 2H), 0.79 (s, 9H), 0.0 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.70, 138.39, 128.70, 115.90, 83.25, 82.60, 62.78, 42.94, 38.37, 29.83, 26.20, 18.60, 12.42, -4.06, -4.60; IR (thin layer, NaCl) 2955 (s), 2929 (s), 2857 (s), 1731 (sh, s), 1472 (m), 1252 (m), 1087 (m) cm^{-1}; HRMS (CI) *m/z* found 279.19, calc'd for $C_{16}H_{27}O_2Si$ [M-H]: 279.19.

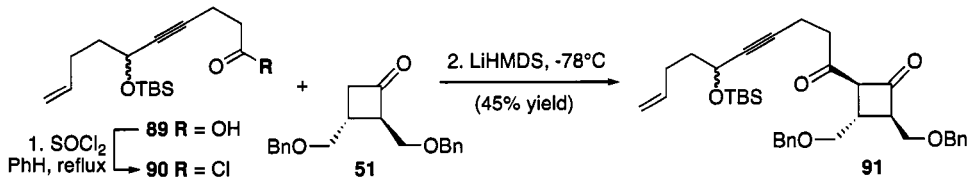
Preparation of Acid 89:



To a solution of aldehyde **88** (0.37 g, 1.3 mmol) in mixture of *t*-BuOH (17 mL) and 2,3-dimethyl-2-butene (4 mL) at room temperature was added a solution of NaH_2PO_4 (0.62 g, 5.2 mmol) and $NaClO_4$ (0.76 g, 8.5 mmol) in water (7 mL). After 1h, the reaction mixture was partitioned between EtOAc and HCl (0.5 M in water), the aqueous phase was extracted with EtOAc two more times. The combined organic phases were dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (20% EtOAc/Hexanes and 0.1% AcOH) to yield the title compound **89** (0.37g, >95% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (ddt, J = 17.0, 10.3, 6.6 Hz, 1H), 4.94 (dd, J = 17.2, 1.5 Hz, 1H), 4.87 (dd, J = 10.2, 1.1

Hz, 1H), 4.24 (t, J = 6.4 Hz, 1H), 2.51-2.40 (m, 4H), 2.12-2.02 (m, 2H), 1.68-1.59 (m, 2H), 0.81 (s, 9H), 0.02 (s, 3H), 0.0 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.39, 138.46, 115.21, 83.13, 82.49, 62.81, 38.34, 33.75, 29.87, 26.30, 18.64, 14.8, -4.07, -4.59; IR (thin layer, NaCl) 3052 (br, m), 2955 (m), 2929 (m), 2857 (m), 1713 (sh, s), 1472 (m), 1463 (m), 1439 (m), 1414 (m), 1256 (m), 1090 (m) cm^{-1}; HRMS (ES) *m/z* found 319.17, calc'd for $C_{16}H_{28}O_3SiNa$[M+Na]: 319.19.

Preparation of Diketone 91:

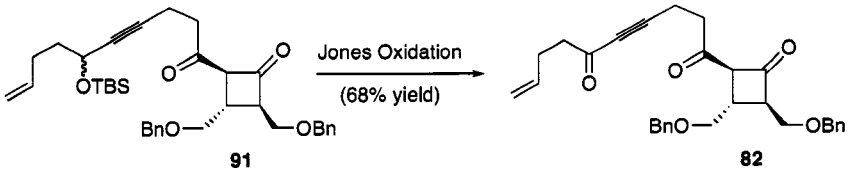


To a solution of acid **89** (0.11 g, 0.37 mmol) in benzene (1 mL) was added $SOCl_2$ (27 μL, 0.37 mmol) and the reaction mixture was heated to reflux. After 4 h the reaction was cooled to room temperature, concentrated and put under mechanical vacuum for 2 h. The acid chloride **90** was used immediately and without purification.

To a solution of ketone **51** (74 mg, 0.24 mmol) in THF (1 mL) was added a 1M solution of LiHMDS in THF (0.29 mL, 0.29 mmol) at -78°C dropwise. After 20 min a solution of the acid chloride **90** (*vide supra*, 0.37 mmol) in THF (0.5 mL) was added dropwise and the reaction was kept at the same temperature for 1h. The reaction was quenched with NH_4Cl (saturated in water), diluted with EtOAc, the biphasic mixture was separated and the aqueous phase extracted two more times with EtOAc. The organic phases were combined, dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (5% EtOAc/Hexanes) to yield the title

compound **91** (64 mg, 56% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.16 (m, 10 H), 5.71 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H), 5.34 (s, 0.7H), 4.94 (dd, *J* = 17.2, 1.5 Hz, 1H), 4.87 (d, *J* = 10.2 Hz, 1H), 4.44 (s, 4H), 4.23 (t, *J* = 6.2 Hz, 1H), 3.64-3.38 (m, 4H), 2.93 (t, *J* = 6.2 Hz, 1H), 2.48 (d, *J* = 4.8 Hz, 2H), 2.43 (d, *J* = 6.5 Hz, 2H), 2.07 (dd, *J* = 13.4, 6.7, 2H), 1.70-1.54 (m, 2H), 0.81 (s, 9H), 0.02 (s, 3H), 0.0 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.26, 168.88, 145.34, 138.87, 138.45, 128.78, 128.76, 128.09, 128.01, 127.94, 115.27, 113.73, 83.18, 82.41, 73.59, 73.47, 73.38, 73.35, 70.67, 62.79, 49.80, 40.50, 38.34, 33.93, 29.88, 26.26, 18.66, 14.76, -3.99, -4.55; IR (thin layer, NaCl) 2940 (m), 2928 (s), 2856 (s), 1766 (sh, s), 1722 (w), 1641 (w), 1620 (w), 1453 (m), 1361 (m), 1093 (s) cm^{-1}; LRMS (ES) *m/z* found 597.57, calc'd for $C_{36}H_{48}O_5SiLi$ [M+Li]: 597.33.

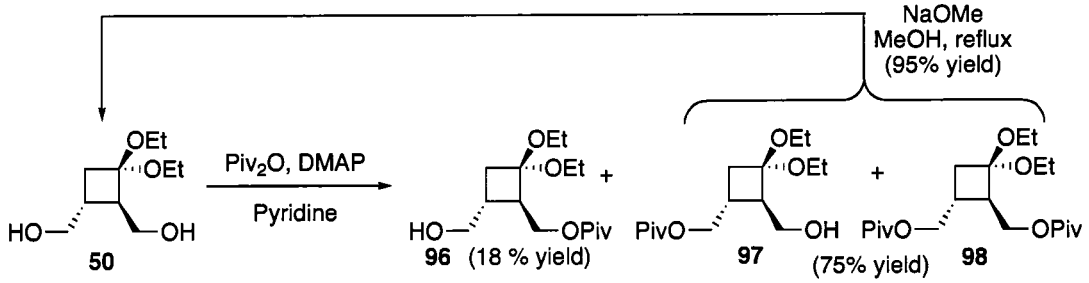
Preparation of Triketone 82:



To a solution of TBS ether **91** (22 mg, 0.023 mmol) in acetone (1 mL) was added excess Jones reagent (0.1 mL). The color of the reaction changed from red to green after 2 h. The reaction was diluted with water and DCM and poured over $NaHCO_3$ (saturated in water). The biphasic mixture was separated, the aqueous phase extracted 2 more times with DCM, the organic phases were combined, dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (10% EtOAc/Hexanes) to yield the title compound **82** (12 mg, 68% yield) as a colorless oil: ^{1}H

NMR (500 MHz, $CDCl_3$) δ 7.36-7.25 (m, 10 H), 5.79 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H), 5.44 (s, 0.8H), 5.05 (dd, *J* = 17.1, 1.4 Hz, 1H), 5.00 (dd, *J* = 10.2, 1.0 Hz, 1H), 4.53 (s, 4H), 3.65 (d, *J* = 6.2 Hz, 2H), 3.56 (d, *J* = 6.4 Hz, 2H), 3.04 (t, *J* = 6.0 Hz, 1H), 2.69-2.60 (m, 5H), 2.60 (t, *J* = 16.2 Hz, 2H), 2.39 (q, *J* = 7.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.35, 168.57, 145.25, 138.85, 136.67, 130.02, 128.76, 128.74, 128.05, 127.98, 127.92, 116.08, 114.01, 91.49, 81.43, 73.59, 73.48, 73.40, 73.28, 73.19, 72.80, 70.61, 64.03, 49.78, 44.86, 40.41, 36.74, 36.54, 32.73, 32.59, 28.24, 14.88; IR (thin layer, NaCl) 2922 (s), 2852 (s), 2217 (m), 1764 (sh, s), 1673 (sh, s), 1453 (m), 1365 (m), 1136 (m) cm^{-1}; HRMS (ES) *m/z* found 495.21, calc'd for $C_{30}H_{32}O_5Na$ [M+Na]: 495.23.

Preparation of Alcohol 96:



To a solution of diol **50** (0.93 g, 4.6 mmol) in pyridine (10 mL) were added trimethyl acetic anhydride (0.92 mL, 4.6 mmol) and DMAP (55 mg, 0.46 mmol). After 12 h, the reaction mixture was diluted with DCM and HCl (1M solution in water) was added until the aqueous phase reached a pH of 1. The aqueous phase was extracted three times with DCM, the organic phases were combined, backwashed with water, dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (gradient elution, 10→20→50% EtOAc/Hexanes) to yield **97** and **98** (1.0g) and the title compound **96** (0.20 g, 18% yield) as a colorless oil: ^1H NMR (400

MHz, $CDCl_3$) δ 4.32 (dd, J = 11.4, 7.0 Hz, 1H), 4.09 (dd, J = 11.4, 7.0 Hz, 1H), 3.73-3.60 (m, 2H), 3.51-3.36 (m, 4H), 2.42 (q, J = 7.2 Hz, 1H), 2.35 (dd, J = 12.2, 9.2 Hz, 1H), 2.08-1.96 (m, 1H), 1.77 (ddd, J = 12.2, 7.9, 0.9 Hz, 1H), 1.23-1.15 (m, 6H), 1.19 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179, 10, 100.08, 66.59, 63.97, 57.16, 56.82, 47.42, 39.11, 32.94, 32.71, 27.60, 15.65, 15.56; IR (thin layer, NaCl) 3437 (br, s), 2974 (m), 2934 (m), 2881 (m), 1725 (sh, s), 1477 (m), 1393 (m), 1284 (m), 1163 (s), 1052 (s) cm^{-1}; HRMS (ES) *m/z* found 288.19, calc'd for $C_{15}H_{28}O_5Na$ [M+Na]: 311.18. Distinguished from **97** by COSY (2D) NMR experiments.

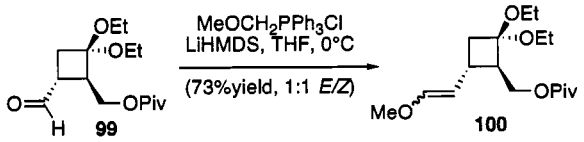
The mixture of undesired protected materials, **97** and **98**, were dissolved in MeOH (30 mL) and NaOMe was added (1 mL), the reaction mixture was heated to reflux temperature. After 12 h, the reaction was cooled at room temperature, quenched with NH_4Cl (saturated in water), and diluted with DCM; the biphasic solution was separated, and the aqueous phase was extracted two more times with DCM. The organic phases were combined, dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (50% EtOAc/Hexanes) to yield diol **50** (0.48g, >95% yield) as a colorless oil to be resubmitted to the protection conditions (*vide supra*).

Preparation of Aldehyde 99:

To a solution of alcohol **96** (0.19 g, 0.66 mmol) in wet DCM (10 mL) was added DMP (0.42 g, 1.0 mmol). After 12 h, the reaction was quenched with $Na_2S_2O_3$ (0.26M solution in saturated $NaHCO_3$ in water), and diluted with DCM; the biphasic solution was

separated, and the aqueous phase was extracted two more times with DCM. The organic phases were combined, dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (gradient elution, 10→20% EtOAc/Hexanes) to yield the title compound **99** (0.17 g, 91% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H), 4.33 (dd, *J* = 11.4, 6.6 Hz, 1H), 4.15 (dd, *J* = 11.4, 8.1 Hz, 1H), 3.52-3.40 (m, 4H), 2.92 (q, *J* = 7.2 Hz, 1H), 2.70 (ddd, *J* = 12.2, 9.5, 1.8 Hz, 1H), 2.44 (dd, *J* = 12.4, 9.5 Hz, 1H), 2.25 (dd, *J* = 12.4, 8.2 Hz, 1H), 1.29-1.04 (m, 6H), 1.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.34, 178.77, 128.69, 99.52, 63.13, 57.42, 57.07, 45.79, 41.44, 39.09, 31.52, 27.53, 15.56, 15.44; IR (thin layer, NaCl) 2974 (s), 2933 (m), 2873 (w), 2817 (w), 2718 (w), 1726 (s), 1478 (w), 1452 (w), 1392 (w), 1278 (m), 1157 (s), 1053 (s) cm^{-1}; LRMS (ES) *m/z* found 325.2, calc'd for $C_{15}H_{26}KO_5$ [M+K]: 325.18.

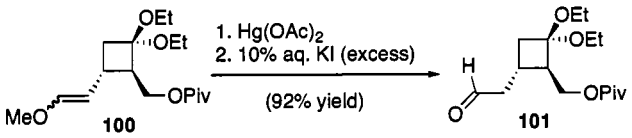
Preparation of Methyl Enol Ether 100:



To a solution of phosphonium salt (1.0 g, 3.0 mmol) in THF (10 mL) was added a 1M solution of LiHMDS (3 mL, 3.0 mmol) in THF at 0°C, the solution turned bright yellow. After 5 min, a solution of aldehyde **99** (0.17 g, 0.6 mmol) in THF (1 mL) was added and the reaction was warmed up to room temperature. After 1 h, the reaction was quenched with NH_4Cl (saturated in water), and diluted with Et_2O; the biphasic solution was separated, and the aqueous phase was extracted two more times with Et_2O. The organic phases were combined, backwashed with NaCl (saturated in water), dried over

Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (gradient elution, 2→10% EtOAc/Hexanes) to yield the title compound **100** as a 1.2/1.0 mixture of E/Z isomers (0.14 g, 73% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.31 (d, J = 12.6 Hz, 0.45H), 5.83 (0.45, J = 6.2 Hz, 0.55H), 4.78 (dd, J = 12.6, 8.6 Hz, 0.45H), 4.39 (dd, J = 9.0, 6.2 Hz, 0.55H), 4.31-4.22 (m, 0.9H), 4.10-4.02 (m, 1.1H), 3.55 (s, 3H), 3.50-3.40 (m, 4H), 3.79-3.69 (m, 0.55H), 3.51-3.33 (m, 1.8H), 3.30-3.20 (m, 0.45H), 1.81-1.69 (m, 1.2H), 1.24-1.12 (m, 6H), 1.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.95, 147.69, 146.71, 110.28, 106.43, 100.22, 100.14, 63.38, 59.97, 57.43, 57.37, 56.89, 56.83, 56.29, 51.90, 51.82, 39.08, 37.59, 37.38, 29.69, 27.59, 27.56, 25.35, 15.62, 15.60; IR (thin layer, NaCl) 2974 (m), 2937 (w), 1728 (sh, s), 1657 (m), 1459 (w), 1394 (w), 1277 (m), 1161 (s), 1109 (w), 1057 (m) cm^{-1}; LRMS (ES) *m/z* found 337.2, calc'd for $C_{17}H_{30}NaO_5$ [M+Na]: 337.21.

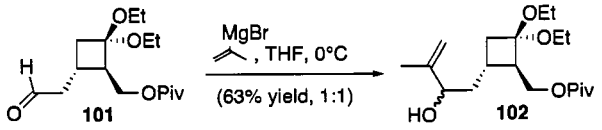
Preparation of Aldehyde 101:



To a solution of vinyl ether **100** (62 mg, 0.2 mmol) in a mixture of THF (6 mL) and water (0.6 mL) was added $Hg(OAc)_2$ (70 mg, 0.6 mmol) at 0°C and the reaction mixture was slowly warmed up to room temperature. After 30 min, the yellow reaction mixture was cooled to 0°C and 20 mL of KI (10% in water) was added until the mixture became colorless. The reaction mixture was diluted with Et_2O; the biphasic solution was separated, and the aqueous phase was extracted two more times with Et_2O. The organic phases were combined, backwashed with KI (10% in water), dried over Na_2SO_4, filtered

and rotary evaporated. The crude product was purified by flash chromatography (5% EtOAc/Hexanes) to yield the title compound **101** (0.55 g, 92% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H), 4.30 (dd, *J* = 11.4, 7.2 Hz, 1H), 4.09 (dd, *J* = 11.4, 6.9 Hz, 1H), 3.47-3.39 (m, 4H), 2.74 (ddd, *J* = 17.4, 6.2, 1.4 Hz, 1H), 2.62 (ddd, *J* = 17.4, 8.3, 1.4 Hz, 1H), 2.53 (dd, *J* = 12.3, 9.1 Hz, 1H), 2.36 (q, *J* = 7.2 Hz, 1H), 2.28-2.18 (m, 1H), 1.70 (dd, *J* = 12.2, 7.8 Hz, 1H), 1.21-1.13 (m, 6H), 1.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.56, 178.87, 100.36, 63.70, 57.18, 56.82, 50.22, 49.99, 39.07, 36.50, 27.59, 24.72, 15.60, 15.58; IR (thin layer, NaCl) 2975 (s), 2936 (s), 2886 (s), 2886 (m), 2722 (m), 1726 (sh, s), 1478 (m), 1453 (m), 1392 (m), 1279 (s), 1159 (s) 1055 (s) cm^{-1}; LRMS (ES) *m/z* found 339.2, calc'd for $C_{16}H_{28}KO_5$ [M+K]: 339.19.

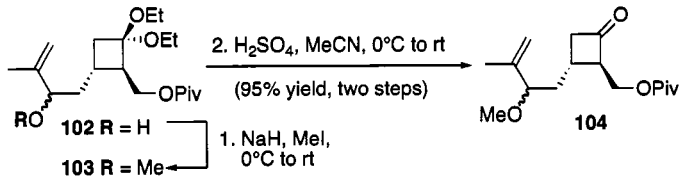
Preparation of Allylic Alcohol 102:



To a solution of aldehyde **101** (55 mg, 0.18 mmol) in THF (1 mL) was added a 0.5M solution of isopropenyl magnesium bromide (1.1 mL, 0.55 mmol) in THF dropwise at 0°C. The reaction was warmed to room temperature and quenched after 30 min with NH_4Cl (saturated in water), and diluted with EtOAc. The biphasic solution was separated, and the aqueous phase extracted two more times with EtOAc. The organic phases were combined, backwashed with NaCl (saturated in water), dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (10% EtOAc/Hexanes) to yield a diastereomeric mixture of the title compound **102** (39 mg, 63% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.93 (d, *J* = 6.7 Hz, 1H),

4.87-4.81 (m, 1H), 4.32-4.23 (m, 1H), 4.14-4.00 (m, 2H), 3.50-3.36 (m, 4H), 2.48-2.28 (m, 2H), 1.94-1.62 (m, 5H), 1.72 (s, 3H), 1.26-1.12 (m, 6H), 1.19 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.06, 179.02, 148.14, 147.73, 128.72, 111.59, 111.30, 100.40, 100.27, 74.89, 74.84, 64.03, 63.78, 57.16, 57.12, 56.70, 56.66, 50.31, 50.08, 41.79, 41.44, 39.08, 36.57, 36.22, 27.61, 27.33, 27.29, 18.07, 17.79, 15.69, 15.62; IR (thin layer, NaCl) 3474 (br, m), 2974 (s), 2932 (m), 1725 (sh, s), 1478 (w), 1448 (w), 1392 (w), 1284 (m), 1251 (w), 1164 (s), 1056 (s) cm^{-1}; HRMS (ES) *m/z* found 365.23, calc'd for $C_{19}H_{34}O_5Na$ [M+Na]: 365.24.

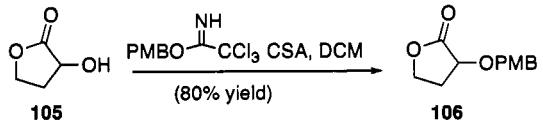
Preparation of Ketone 104:



To a solution of allylic alcohol **102** (16 mg, 61 μmol) in DMF (0.5 mL) was added 60% NaH dispersion in mineral oil (10 mg, 0.24 mmol) at 0°C. After 30 min, excess MeI (0.1 mL) was added and the reaction mixture was allowed to warm up to room temperature. After 1 h, the reaction was quenched at 0°C by slow addition of NH_4Cl (saturated in water) and diluted with ether. The biphasic solution was separated, and the aqueous phase was extracted five times with ether; the organic phases were combined, backwashed with NaCl (saturated in water), dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (5% EtOAc/Hexanes) to yield ketal **103** (16 mg, >95% yield) as a colorless oil.

To a solution of Ketal **103** (16 mg, 61 μmol) in CH_3CN was added a 1M solution of H_2SO_4 (50 μL) in water. After 10 min, the reaction was quenched with $NaHCO_3$ (saturated in water), and diluted with DCM; the biphasic solution was separated, and the aqueous phase extracted two more times with DCM. The organic phases were combined, dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (gradient elution, 5→10% EtOAc/Hexanes) to yield the title compound **104** (11 mg, 95% yield) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 4.98-4.90 (m, 2H), 4.30-4.18 (m, 2H), 3.60-3.52 (m, 1H), 3.31-3.19 (m, 1H), 3.20 (s, 3H), 3.13-3.02 (m, 1H), 2.82-2.67 (m, 1H), 2.46-2.34 (m, 1H), 2.05-1.74 (m, 2H), 1.67 (s, 3H), 1.19 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.36, 207.03, 178.59, 144.46, 144.17, 114.53, 114.42, 85.24, 84.89, 64.92, 64.52, 61.41, 61.33, 56.42, 51.35, 51.27, 40.46, 39.99, 39.21, 27.54, 26.20, 25.93, 16.82, 16.69; IR (thin layer, NaCl) 2973 (m), 2934 (m), 1784 (sh, s), 1733 (sh, s), 1481 (w), 1457 (w), 1397 (w), 1365 (w), 1283 (m), 1157 (s), 1098 (m) cm^{-1}; HRMS (CI) *m/z* found 282.19, calc'd for $C_{16}H_{27}O_4$ [M+H]: 282.18.

Preparation of PMB Ether 106:

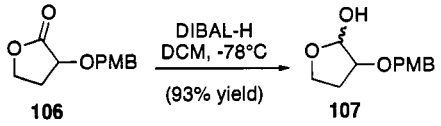


105 **106**

To a solution of alcohol **105** (0.15 g, 1.7 mmol) in DCM (5 mL) were added PMB trichloroacetamidate (1.2 g, 3.4 mmol) and CSA (40 mg, 0.17 mmol). After 12 h, the reaction was quenched with $NaHCO_3$ (saturated in water), the biphasic solution was separated, and the aqueous phase was extracted two more times with DCM. The organic

phases were combined, dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (gradient elution, 10→20% EtOAc/Hexanes) to yield the title compound **106** (0.28 g, 80% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 14.1 Hz, 2H), 4.86 (dd, J = 11.4 Hz, 1H), 4.67 (dd, J = 11.4 Hz, 1H), 4.40 (td, J = 8.8, 4.4 Hz, 1H), 4.24-4.11 (m, 2H), 3.81 (s, 3H), 2.47-2.39 (m, 1H), 2.31-2.21 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.53, 159.99, 130.31, 129.40, 114.35, 72.43, 72.19, 65.89, 55.69, 30.28; IR (thin layer, NaCl) 3003 (w), 2933 (w), 2903 (w), 2813 (w), 1782 (s), 1612 (s), 1514 (s), 1303 (w), 1249 (s), 1220 (m), 1175 (s), 1032 (s) cm^{-1}; HRMS (ES) *m/z* found 245.08, calc'd for $C_{12}H_{14}O_4Na$[M+Na]: 245.22.

Preparation of Lactol 107:

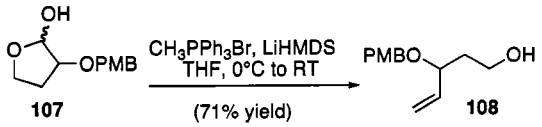


106 107

To a solution of butyrolactone **106** (0.11 g, 0.53 mmol) in DCM (5 mL) was added dropwise a 1M solution of DIBAl-H (0.69 mL, 0.69 mmol) in toluene at -78°C. After 1h, a 2:1 mixture of Na_2SO_4•xH_2O / celite was added until the mixture became difficult to stir, after which the cold bath was removed; DCM was added and the mixture stirred vigorously for 3 h. The mixture was filtered and the filtrate rotary evaporated. The crude product was purified by flash chromatography (20% EtOAc/Hexanes) to yield a diastereomeric mixture of the title compound **107** (0.10 g, 93% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.23 (m, 2H), 6.92-6.86 (m, 2H), 5.42 (s, 0.6H), 5.31 (d, J = 3.5 Hz, 0.4H), 4.60-4.43 (m, 2H), 4.15-3.98 (m, 3H), 3.80 (s, 3H), 2.28-1.94 (m,

2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.37, 130.03, 129.65, 129.42, 129.35, 114.05, 113.93, 100.79, 96.33, 83.11, 72.23, 71.18, 67.09, 64.81, 55.36, 29.93; IR (thin layer, NaCl) 3388 (br, s), 2950 (m), 2903 (m), 2836 (w), 1612 (s), 1586 (m), 1514 (s), 1465 (m), 1302 (m), 1249 (s), 1070 (s), 1032 (s) cm^{-1}; HRMS (ES) *m/z* found 247.09, calc'd for $C_{12}H_{16}O_4Na$ [M+Na]: 247.10.

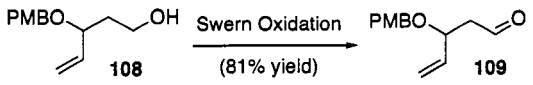
Preparation of Alcohol 108:



To a solution of methyltriphenyl phosphinebromide (0.26 g, 0.71 mmol) in THF (7 mL) was added a 1M solution of LiHMDS (0.7 mL, 0.71 mmol) in THF at 0°C, the reaction turned bright yellow. After 5 min, a solution of lactol **107** (50 mg, 0.24 mmol) in THF (1 mL) was added and the reaction was warmed to room temperature. After 1 h, the reaction was quenched with NH_4Cl (saturated in water) and diluted with Et_2O; the biphasic solution was separated, and the aqueous phase was extracted two more times with Et_2O. The organic phases were combined, backwashed with NaCl (saturated in water), dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (gradient elution, 10→20% EtOAc/Hexanes) to yield the title compound **108** (36 mg, 71% yield) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 7.6 Hz, 2H), 6.88 (d, J = 9.4 Hz, 2H), 5.84-5.73 (m, 1H), 5.28 (d, J = 4.1 Hz, 1H), 5.24 (s, 1H), 4.56 (d, J = 11.4 Hz, 1H), 4.30 (d, J = 11.4 Hz, 1H), 4.05-3.96 (m, 1H), 3.80 (s, 3H), 1.84-1.69 (m, 2H), 1.91-1.72 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.26, 138.24, 130.28, 129.44, 117.40, 113.91, 79.64, 69.95, 60.71, 55.29,

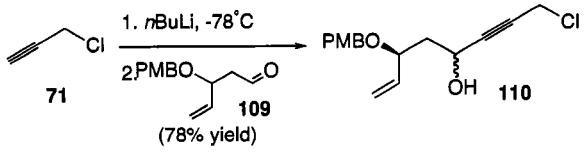
37.77; IR (thin layer, NaCl) 3418 (br, m), 2933 (m), 2858 (m), 2828 (m), 1612 (m), 1514 (s), 1248 (s), 1174 (m), 1035 (s) cm^{-1}; HRMS (ES) *m/z* found 245.12, calc'd for $C_{13}H_{18}O_3Na$ [M+Na]: 245.13.

Preparation of Aldehyde 109:



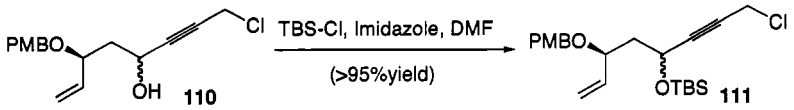
To a solution of oxalyl chloride (0.29 mL, 3.3 mmol) in DCM (3 mL) cooled to -78°C was added dropwise a solution of DMSO (0.76 mL, 4.3 mmol) in DCM (2 mL). The mixture was stirred 15 min further and a solution of alcohol **108** (0.45 g, 2.2 mmol) in DCM (2 mL) was then added slowly. After an additional 15 min, triethylamine (1.2 mL, 8.8 mmol) was introduced dropwise and the reaction mixture was warmed to 0°C. After 15 min, the reaction mixture was partitioned between ether and water, and the organic phase was washed with water, NaCl (saturated in water), dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (10% EtOAc/Hexanes) to yield the title compound **109** (0.37 g, 81% yield) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 9.73 (t, J = 2.0 Hz, 1H), 7.23 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 5.80 (ddd, J = 17.4, 10.2, 7.6 Hz, 1H), 5.35-5.29 (m, 2H), 4.55 (d, J = 11.3 Hz, 1H), 4.33-4.27 (m, 1H), 4.33 (d, J = 11.2 Hz, 1H), 3.80 (s, 3H), 2.72 (ddd, J = 16.3, 8.3, 2.5 Hz, 1H), 2.53 (ddd, J = 16.4, 4.7, 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.23, 159.66, 137.49, 130.39, 129.89, 118.63, 114.24, 75.38, 70.43, 55.69, 49.51; IR (thin layer, NaCl) 2993 (w), 2938 (w), 2818 (w), 2890 (w), 2837 (w), 2712 (w), 1725 (sh, s), 1613 (m), 1514 (s), 1248 (s), 1075 (m), 1034 (m) cm^{-1}; HRMS (ES) *m/z* found 219.10, calc'd for $C_{13}H_{15}O_3$ [M-H]: 219.11.

Preparation of Propargyl Alcohol 110:



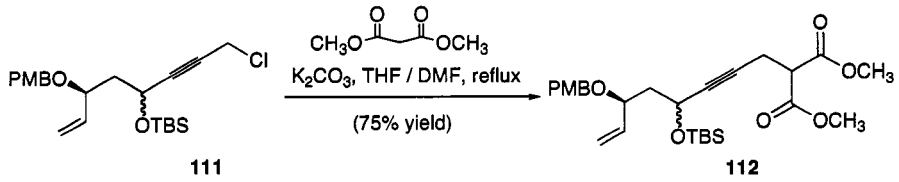
To a solution of propargyl chloride **71** (0.16 mL, 2.2 mmol) in Et_2O (3 mL) at -78°C was added a 1.6 M solution of *n*-BuLi in hexane (1.4 mL, 2.2 mmol) dropwise. After 1h, a solution of aldehyde **109** (0.23 g, 1.1 mmol) in Et_2O (1 mL) was added dropwise and the temperature was kept at -78°C for 2 more h. The reaction was quenched with NH_4Cl (saturated in water) and diluted with EtOAc; the biphasic solution was separated, and the aqueous phase was extracted two more times with EtOAc. The organic phases were combined, backwashed with NaCl (saturated in water), dried over Na_2SO_4, filtered and rotary evaporated. The crude mixture of diastereomers (0.24 g, 78% yield) was purified and separated by flash chromatography (5% EtOAc/Hexanes) to yield the major diastereomer of **110** (0.18 g, 58% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 5.76 (ddd, J = 17.6, 9.9, 7.9 Hz, 1H), 5.30 (d, J = 3.1 Hz, 1H), 5.27 (s, 1H), 4.61 (dd, J = 7.1, 5.4 Hz, 1H), 4.55 (d, J = 11.3 Hz, 1H), 4.28 (d, J = 11.3 Hz, 1H), 4.12 (s, 2H), 4.01 (td, J = 9.1, 3.9 Hz, 1H), 3.80 (s, 3H), 3.22 (brs, 1H), 2.14-2.04 (m, 1H), 1.85 (dt, J = 14.2, 4.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.67, 138.00, 130.24, 130.03, 118.61, 114.29, 87.28, 79.90, 79.21. 70.31, 61.51, 55.69, 43.28, 30.80; IR (thin layer, NaCl) 3418 (br, m), 3000 (w), 2953 (m), 2837 (m), 1613 (s), 1586 (m), 1514 (s), 1248 (s), 1174 (m), 1066 (s), 1033 (s) cm^{-1}; HRMS (ES) *m/z* found 317.09, calc'd for $C_{16}H_{19}ClO_3Na$ [M+Na]: 317.10.

Preparation of Propargyl Chloride 111:



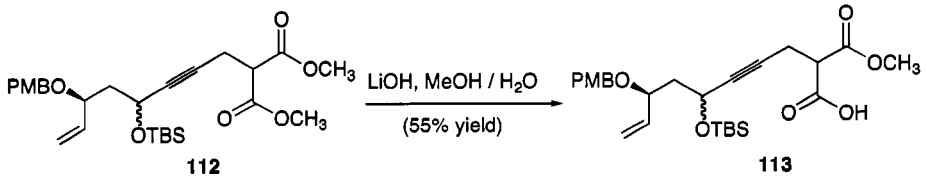
To a solution of propargyl alcohol **110** (0.18 g, 0.64 mmol) in DMF (3 mL) were added TBS-Cl (97 mg, 0.64 mmol) and imidazole (87 mg, 1.3 mmol). After 12 h at room temperature, the reaction was quenched at 0°C by slow addition of NH_4Cl (saturated in water) and diluted with ether. The biphasic solution was separated, the aqueous phase was extracted five times with ether; the organic phases were combined, backwashed with NaCl (saturated in water), dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (5% EtOAc/Hexanes) to yield the title compound **111** (0.25 g, >95% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.5 Hz, 2H), 5.71 (ddd, J = 17.6, 9.7, 7.7 Hz, 1H), 5.24 (s, 1H), 5.21 (d, J = 2.7 Hz, 1H), 4.54 (t, J = 7.4 Hz, 1H), 4.49 (d, J = 11.3 Hz, 1H), 4.25 (d, J = 11.3 Hz, 1H), 4.07 (s, 2H), 3.96-3.85 (m, 1H), 3.78 (s, 3H), 2.08-1.97 (m, 1H), 1.71-1.70 (m, 1H), 0.85 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.48, 138.53, 130.95, 129.88, 118.02, 114.10, 88.22, 79.68, 70.31, 60.69, 55.68, 44.52, 30.93, 26.18, 18.53, -3.98, -4.58; IR (thin layer, NaCl) 3076 (w), 2999 (w), 2955 (s), 2929 (s), 2857 (s), 1613 (m), 1513 (s), 1361 (m), 1302 (m), 1249 (s), 1079 (s) cm^{-1}; HRMS (ES) *m/z* found 409.20, calc'd for $C_{22}H_{34}ClO_3Si$ [M+H]: 409.19.

Preparation of Malonate 112:



To a solution of propargyl chloride **111** (0.16 g, 0.41 mmol) in a mixture of THF (3 mL) and DMF (3 mL) were added dimethyl malonate (0.23 mL, 2.0 mmol) and K_2CO_3 (0.45 g, 3.3 mmol). The reaction mixture was heated to reflux for 3 h, cooled to room temperature, quenched with NH_4Cl (saturated in water) and diluted with ether. The biphasic solution was separated, the aqueous phase was extracted five times with ether; the organic phases were combined, backwashed with NaCl (saturated in water), dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (5% EtOAc/Hexanes) to yield the title compound **112** (1.2 g, >95% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 5.69 (ddd, J = 17.9, 10.3, 7.7 Hz, 1H), 5.23 (d, J = 8.4 Hz, 1H), 5.20 (s, 1H), 4.47 (d, J = 11.3 Hz, 1H), 4.44 (t, J = 5.0 Hz, 1H), 4.23 (d, J = 11.4 Hz, 1H), 3.94-3.83 (m, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 3.48 (t, J = 7.7 Hz, 1H), 3.37 (s, 3H), 2.74 (dd, J = 7.8, 1.7 Hz, 2H), 2.01-1.92 (m, 1H), 1.74-1.63 (m, 1H), 0.82 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.69, 167.32, 159.41, 138.68, 131.02, 129.73, 117.82, 114.03, 83.87, 80.71, 70.27, 60.69, 55.58, 53.13, 52.92, 51.41, 44.98, 41.47, 26.15, 19.15, 18.48, -4.06, -4.67; IR (thin layer, NaCl) 2955 (m), 2930 (m), 2857 (m), 1755 (s), 1742 (s), 1613 (w), 1514 (m), 1438 (m), 1342 (m), 1249 (s), 1155 (m) cm^{-1}; HRMS (ES) *m/z* found 505.26, calc'd for $C_{27}H_{41}O_7Si$ [M+H]: 505.25.

Preparation of Acid 113:



112 **113**

To a solution of the malonate **112** (36 mg, 0.073 mmol) in a mixture of MeOH (2 mL) and water (1 mL) was added lithium hydroxide (2 mg, 0.073 mmol) and the mixture was heated to reflux for 12 h. The reaction was allowed to cool at room temperature and the MeOH was rotary evaporated. The residue was partitioned between DCM and HCl (1N in water), the aqueous phase was extracted with DCM three times. The combined organic phases were dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (20% EtOAc/Hexanes and 0.1% AcOH) to yield the title compound **113** (19 mg, 55% yield) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 5.72 (ddd, J = 17.4, 10.4, 7.8 Hz, 1H), 5.25 (d, J = 7.2 Hz, 1H), 5.23 (s, 1H), 4.51 (d, J = 11.4 Hz, 1H), 4.49-4.45 (m, 1H), 4.26 (d, J = 11.4 Hz, 1H), 3.95-3.89 (m, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.54-3.49 (m, 1H), 2.92-2.74 (m, 2H), 2.04-1.97 (m, 1H), 1.77-1.69 (m, 1H), 1.32-1.29 (m, 1H), 0.86 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.62, 168.63, 159.44, 138.65, 131.07, 131,04, 129.80, 117.81, 114.12, 84.25, 80.36, 70.28, 60.73, 55.65, 53.30, 51.19, 44.99, 31.97, 26.17, 19.17, 18.50, -4.06, -4.64; IR (thin layer, NaCl) 3164 (br, m), 2995 (m), 2929 (m), 2857 (m), 1742 (s), 1721 (s), 1613 (m), 1514 (s), 1249 (s), 1075 (s), 1036 (s) cm^{-1}; HRMS (ES) *m/z* found 513.23, calc'd for $C_{26}H_{38}O_7SiNa$ [M+Na]: 513.24.

2.6 Notes and References.

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7. Polarity Indexes: acetonitrile=5.8, tetrahydrofuran (THF)=4.0, dichloromethane (DCM)=3.1 and hexane=0.0. Values are taken from the Phenomenex catalog, www.phenomenex.com.

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Appendix A2: Spectra Relevant to Chapter 2.

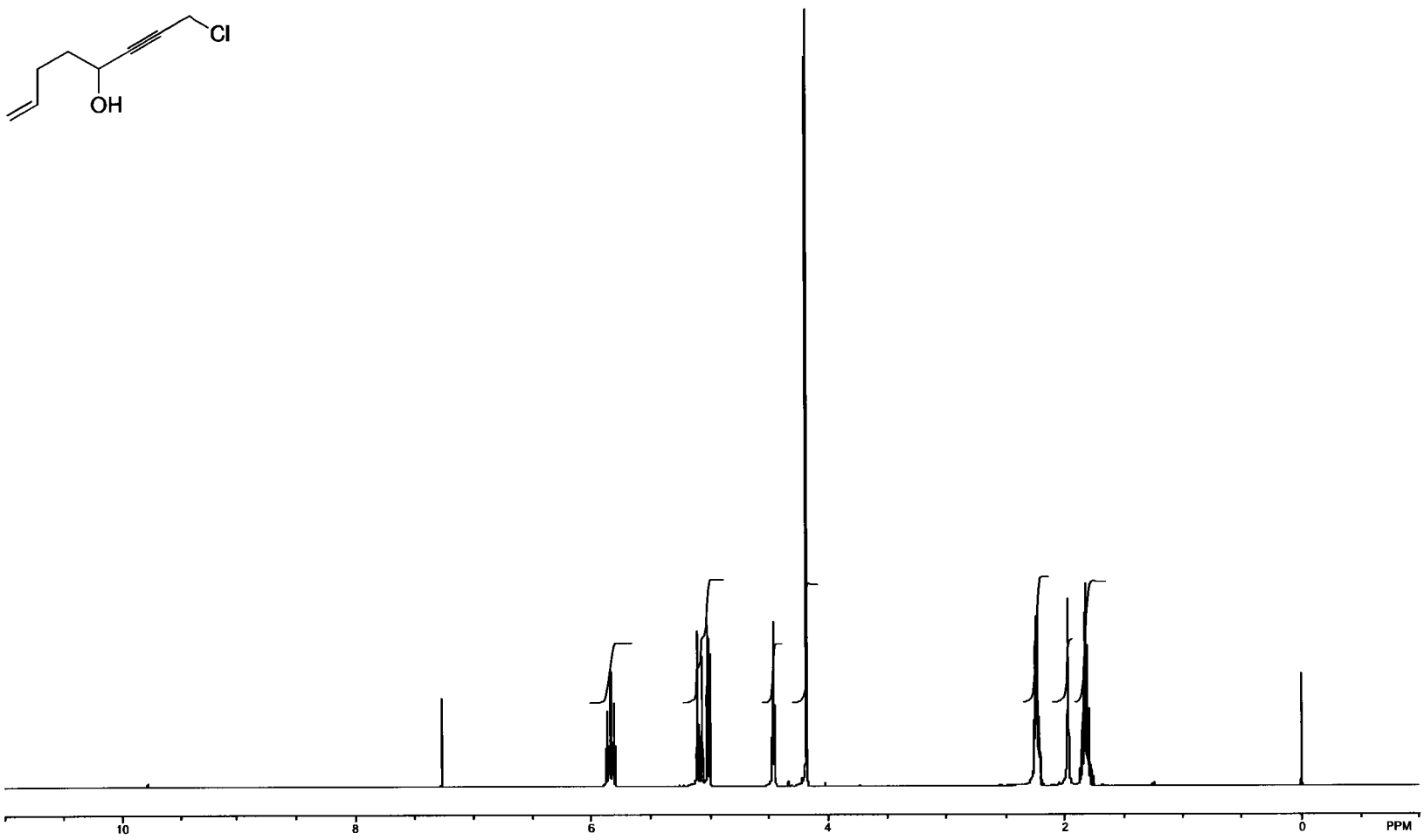


Figure A2.1 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **72**.

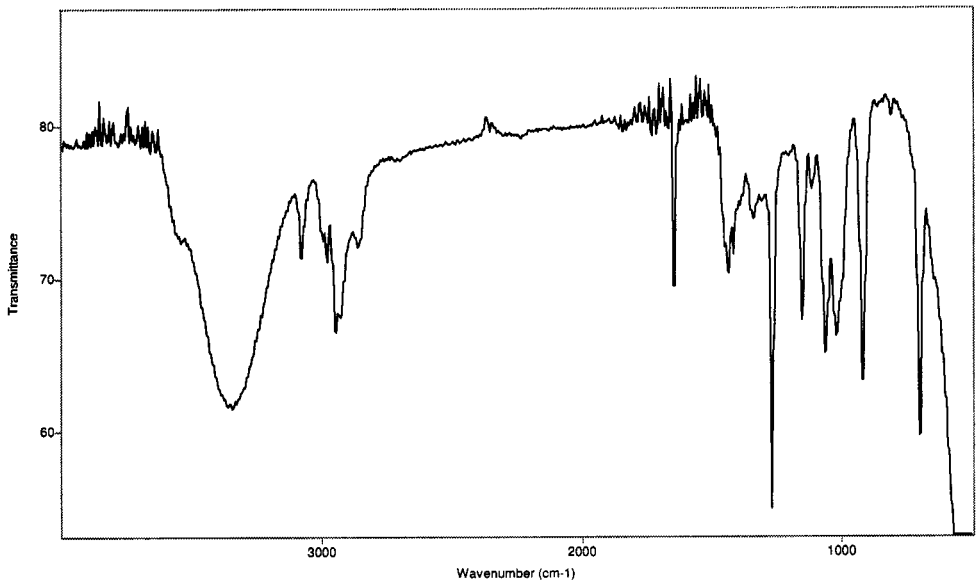


Figure A2.2 IR spectrum (thin film/NaCl) of compound **72**.

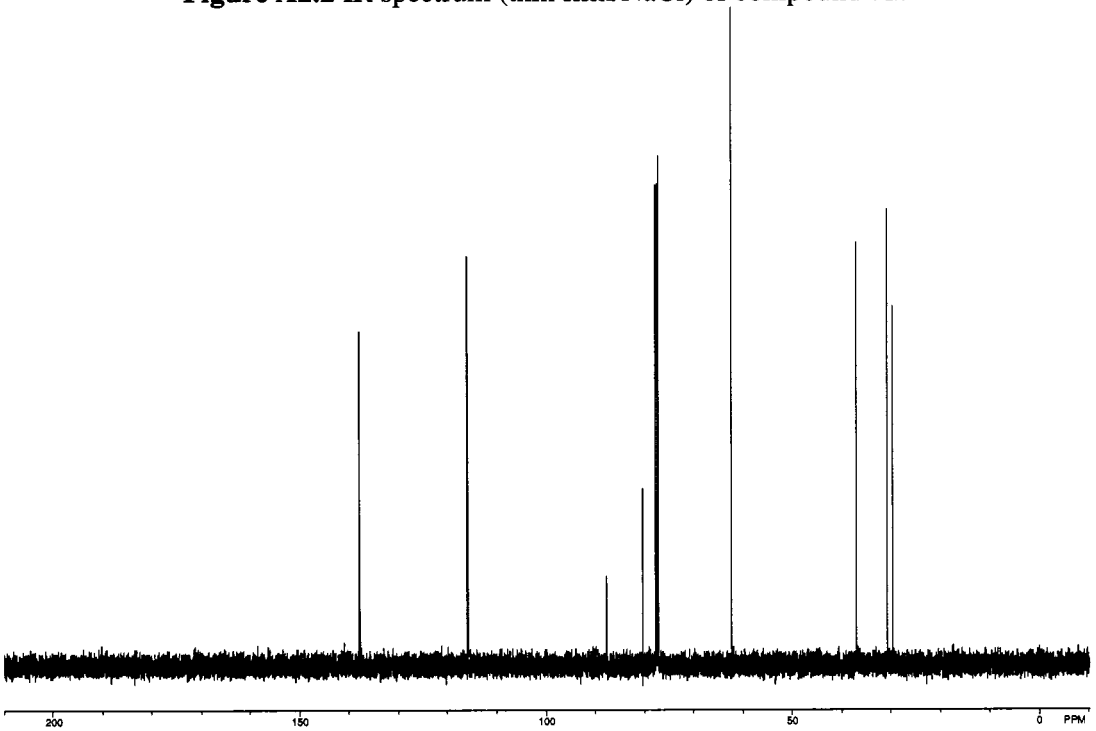


Figure A2.3 ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **72**.

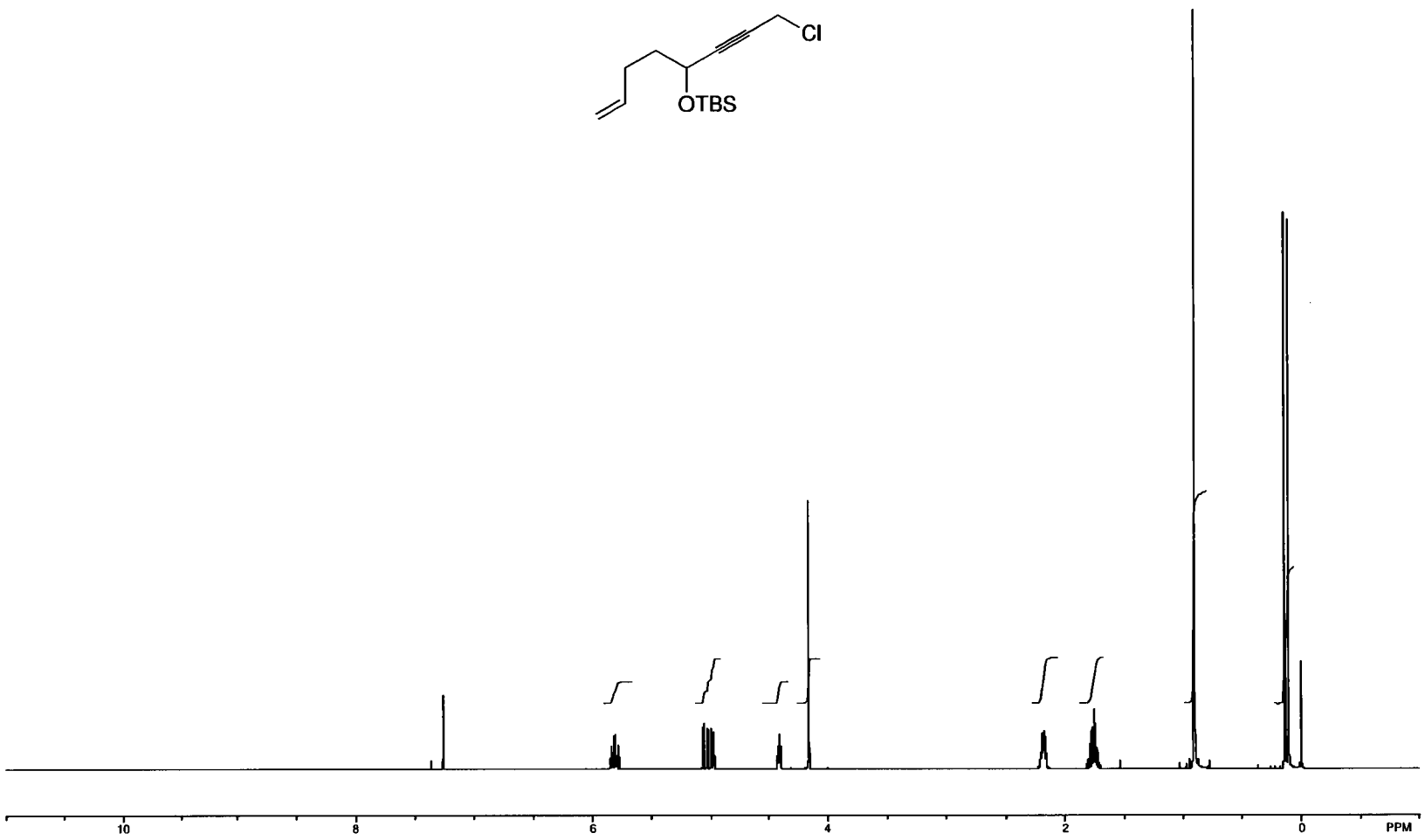


Figure A2.4 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **73**.

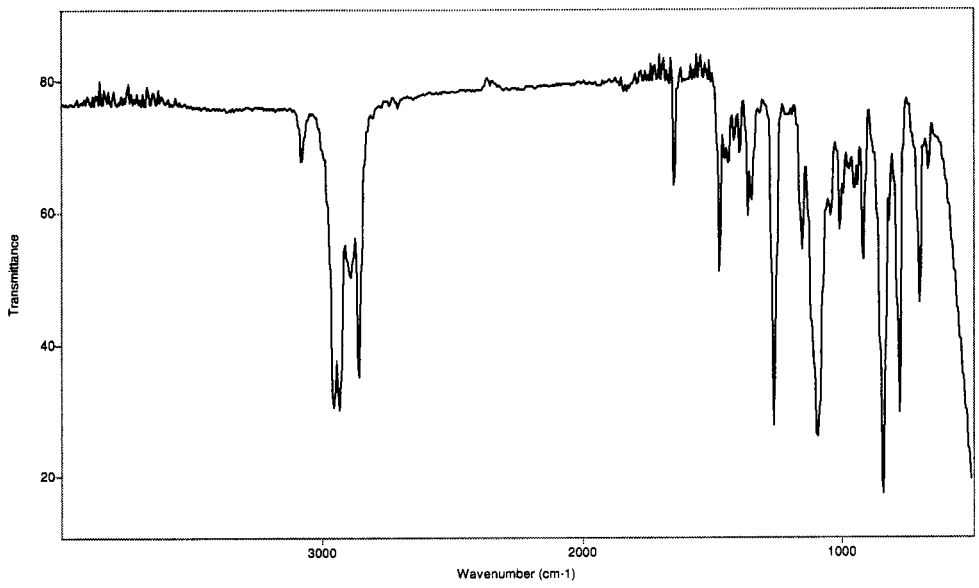


Figure A2.5 IR spectrum (thin film/NaCl) of compound **73**.

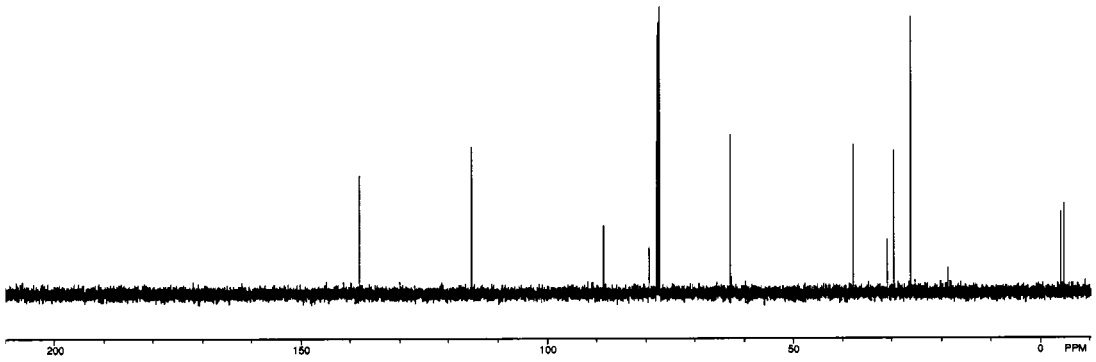


Figure A2.6 ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **73**.

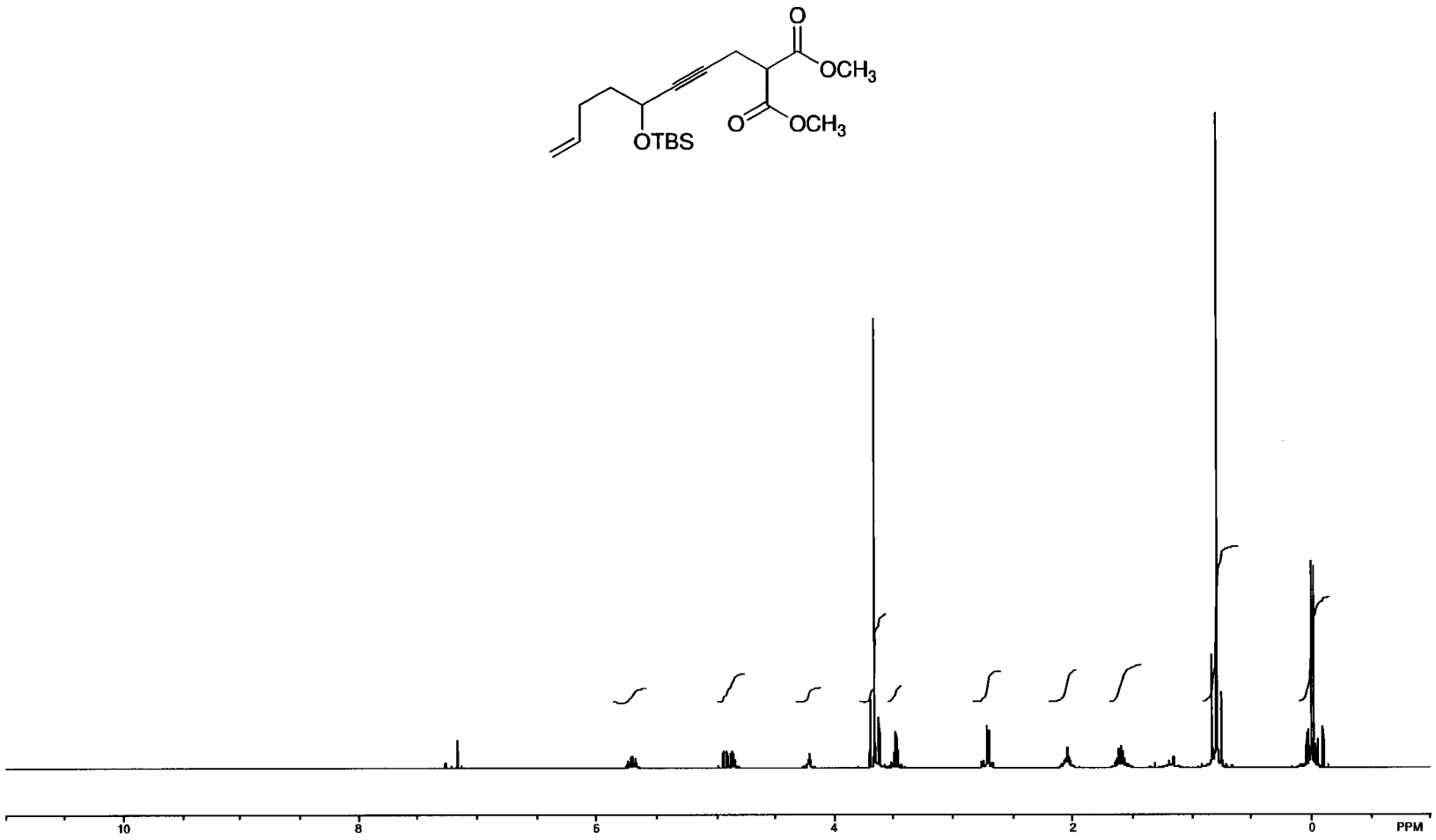


Figure A2.7 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **74**.

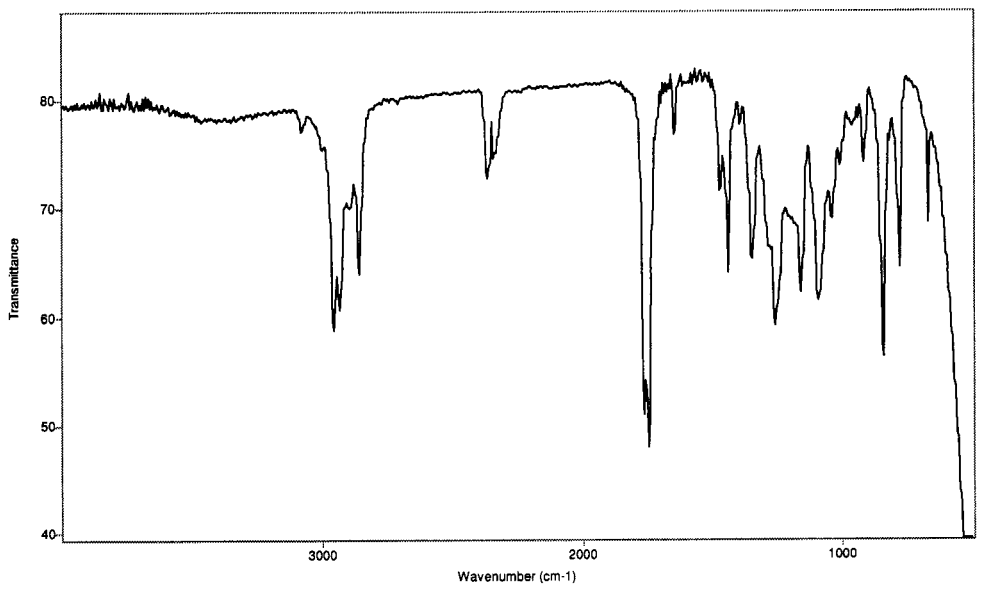


Figure A2.8 IR spectrum (thin film/NaCl) of compound **74**.

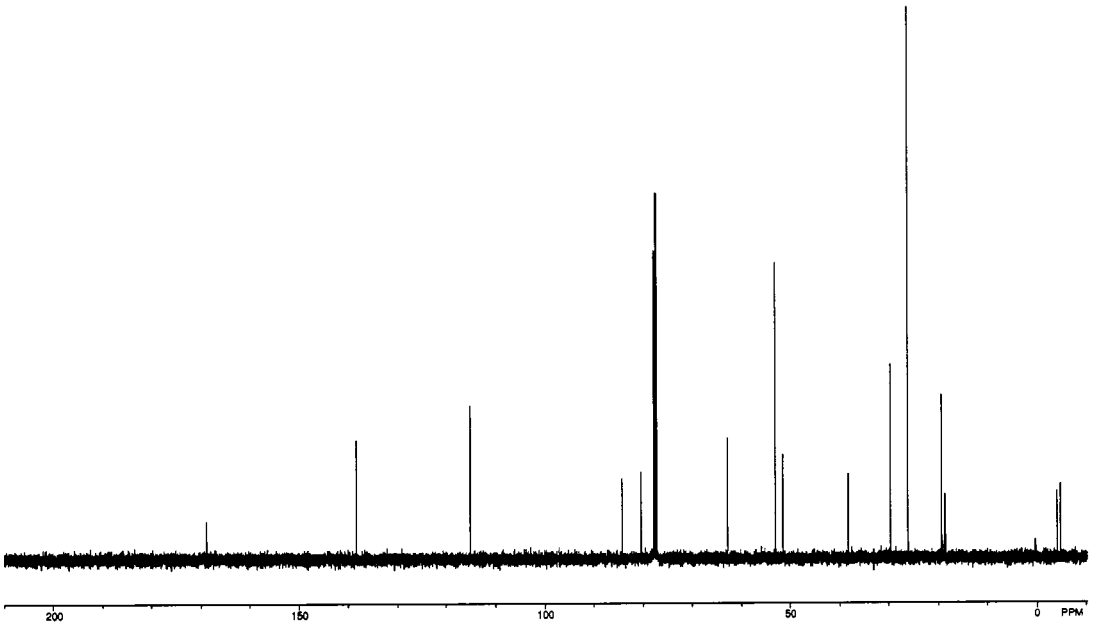


Figure A2.9 ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **74**.

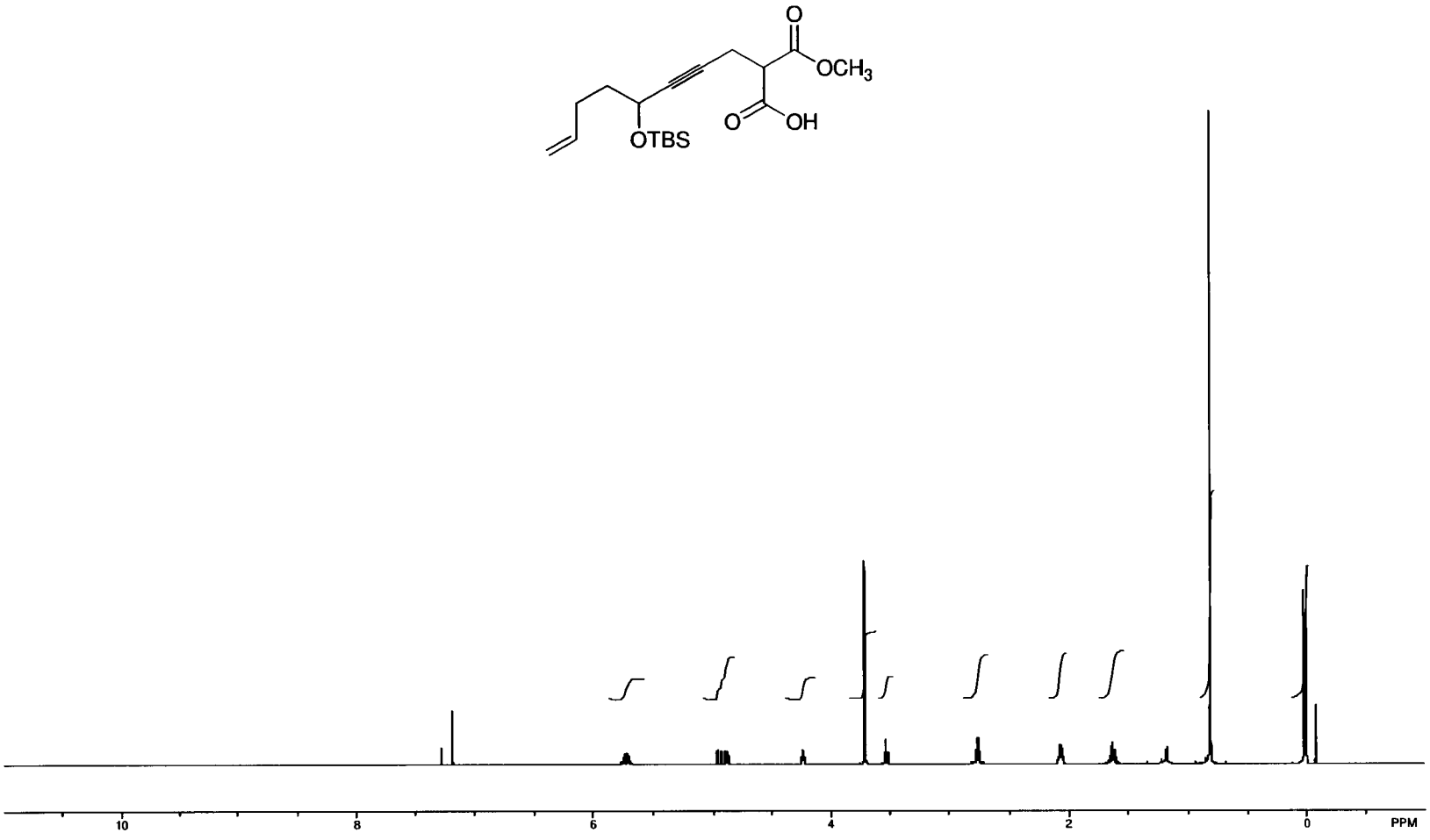


Figure A2.10 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **75**.

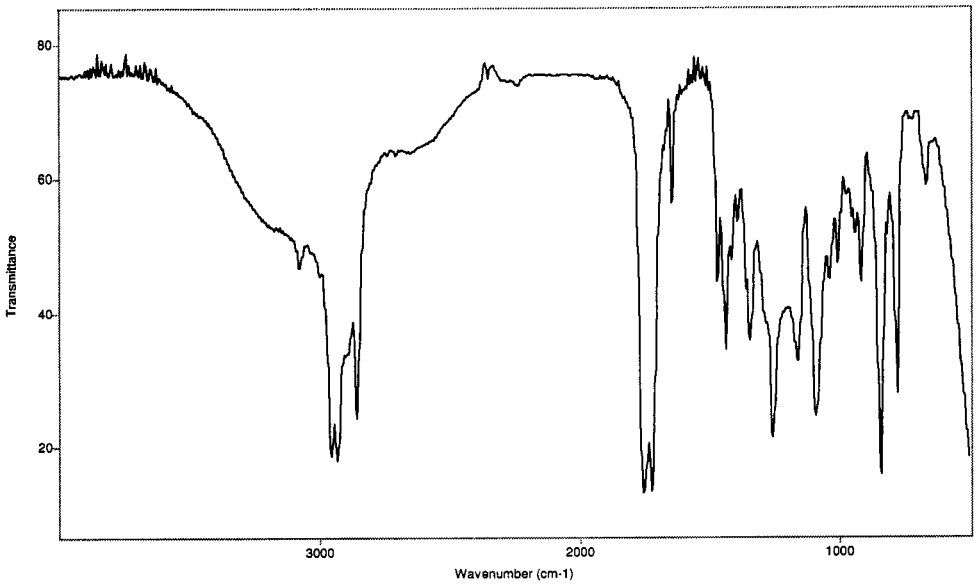


Figure A2.11 IR spectrum (thin film/NaCl) of compound **75**.

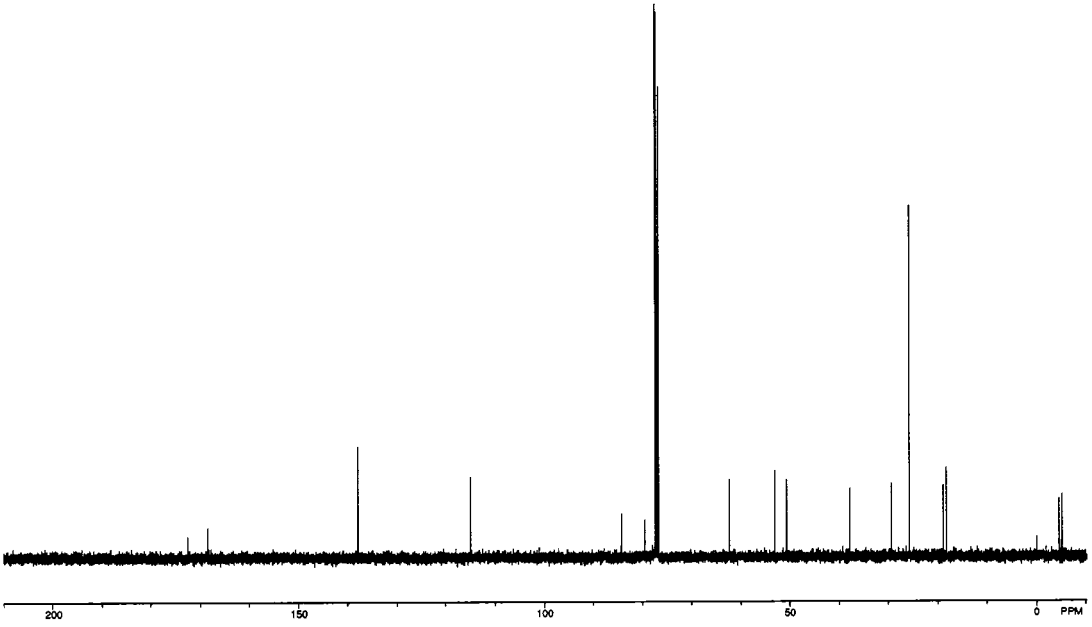


Figure A2.12 ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **75**.

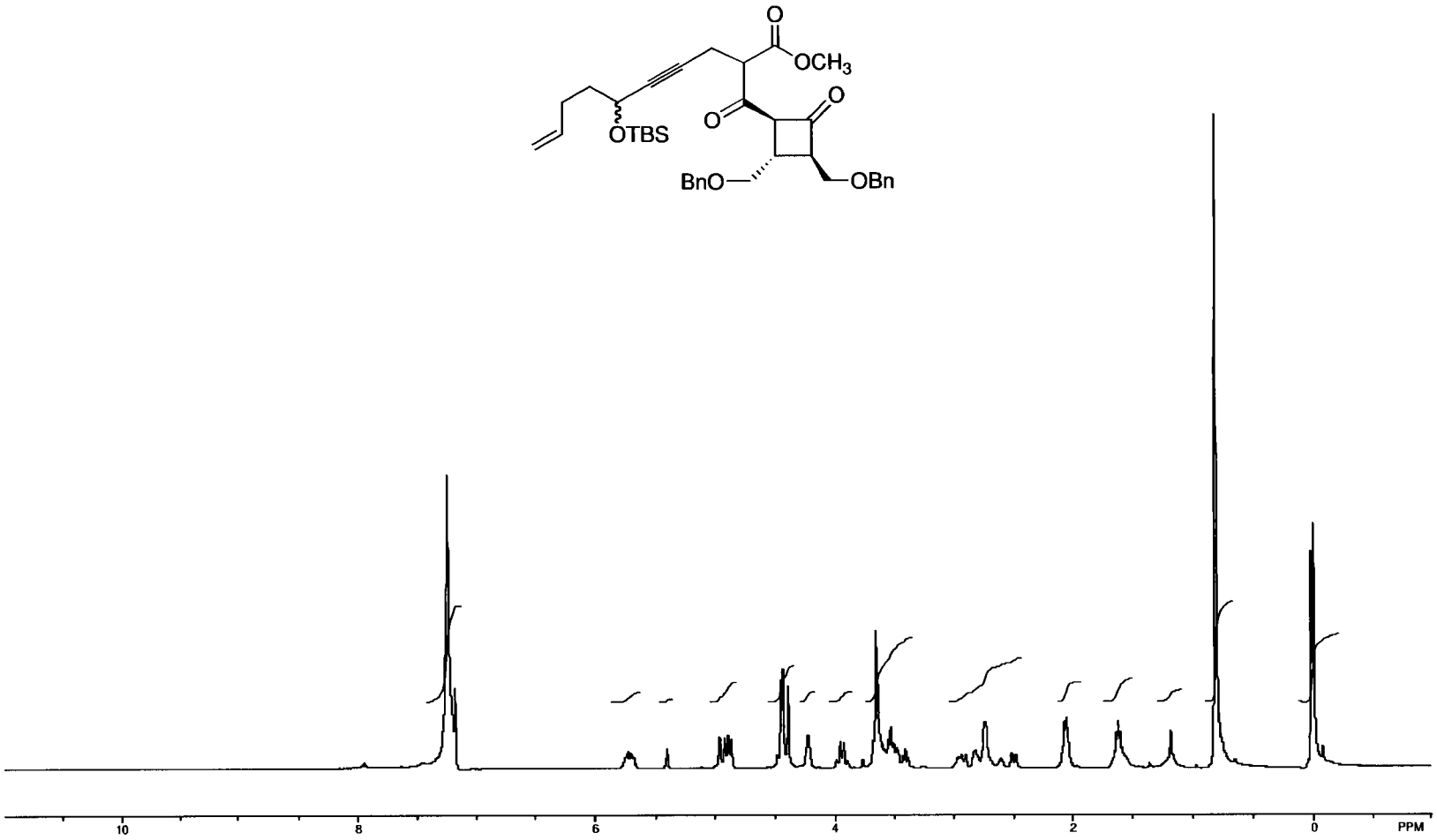


Figure A2.13 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **69**.

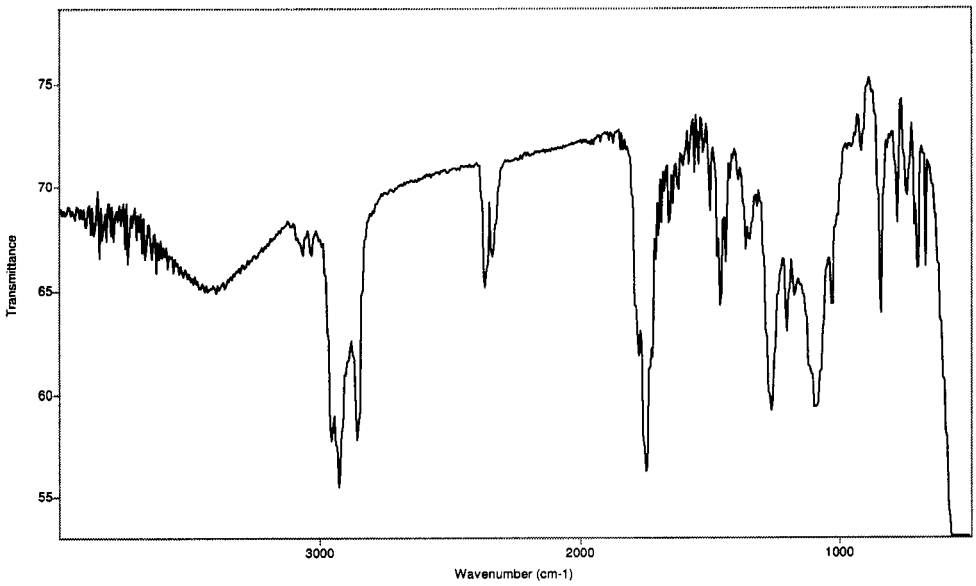


Figure A2.14 IR spectrum (thin film/NaCl) of compound **69**.

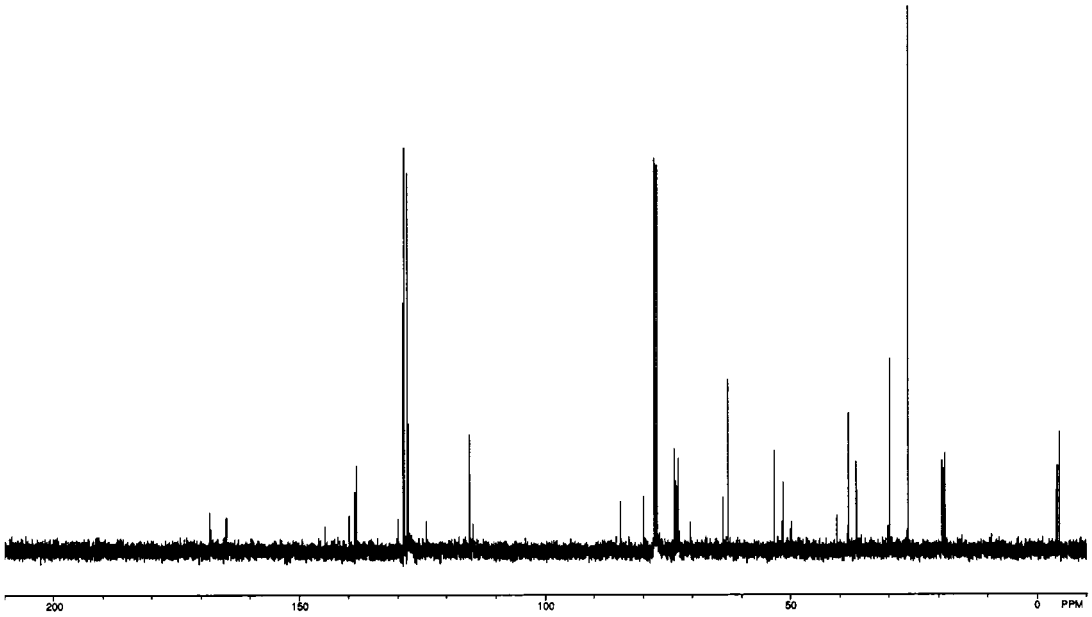


Figure A2.15 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **69**.

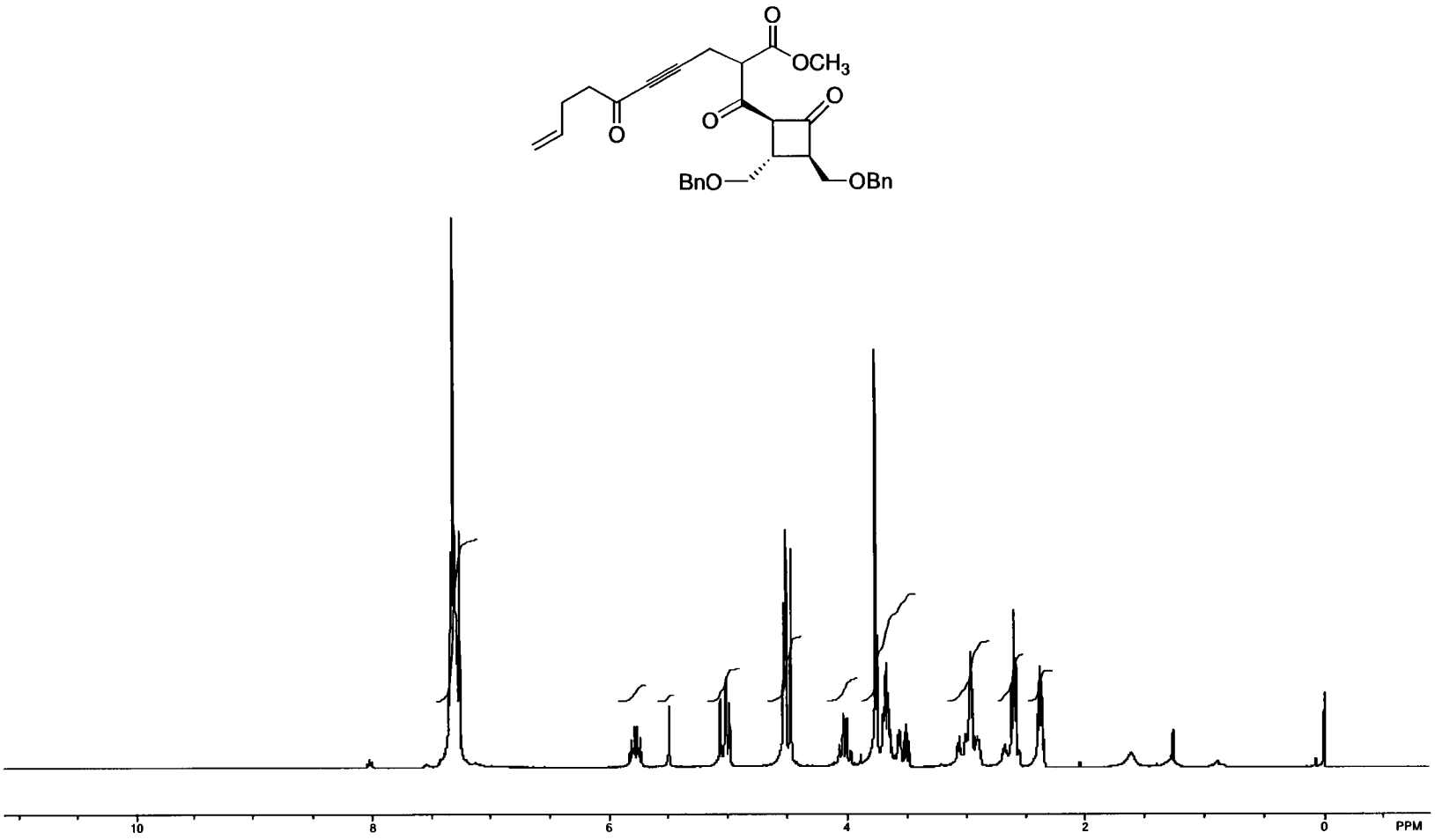


Figure A2.16 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **76**.

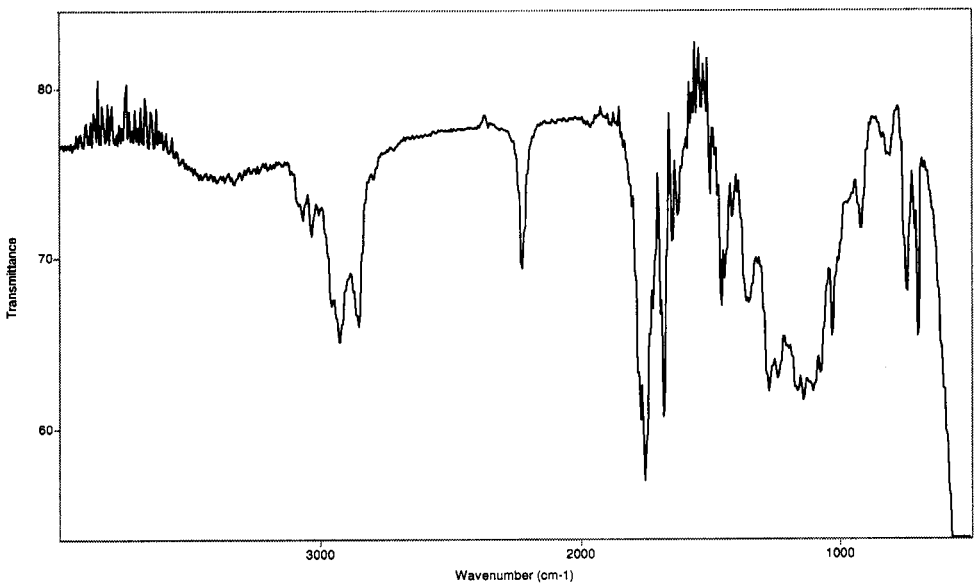


Figure A2.17 IR spectrum (thin film/NaCl) of compound **76**.

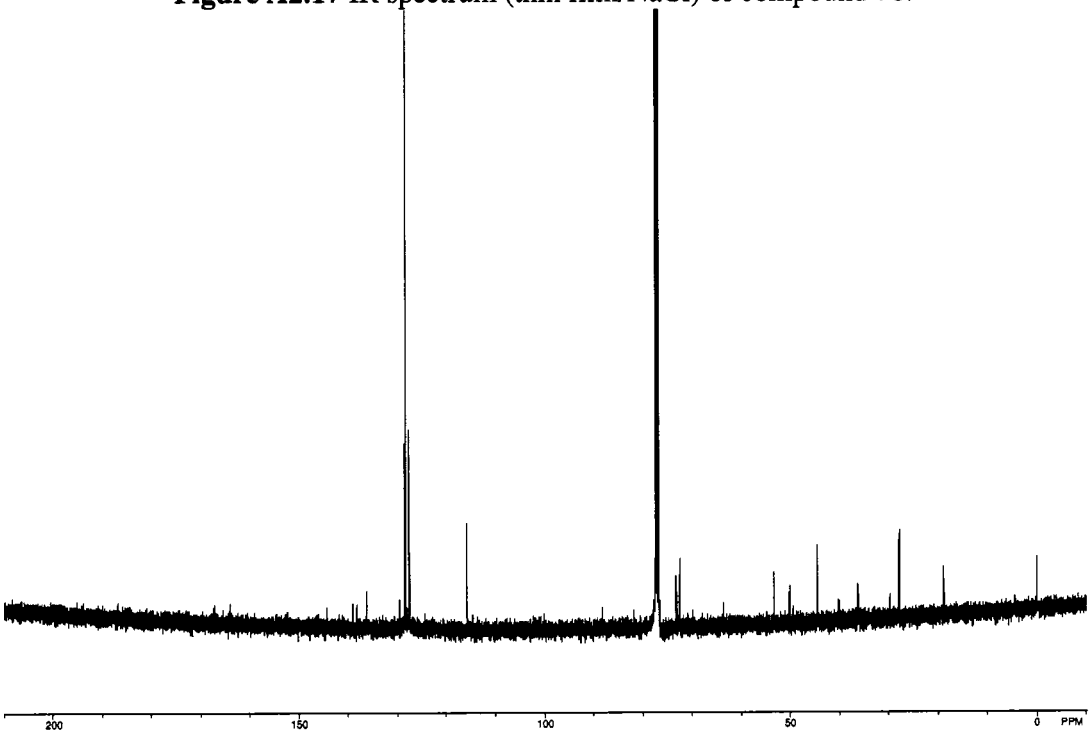


Figure A2.18 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **76**.

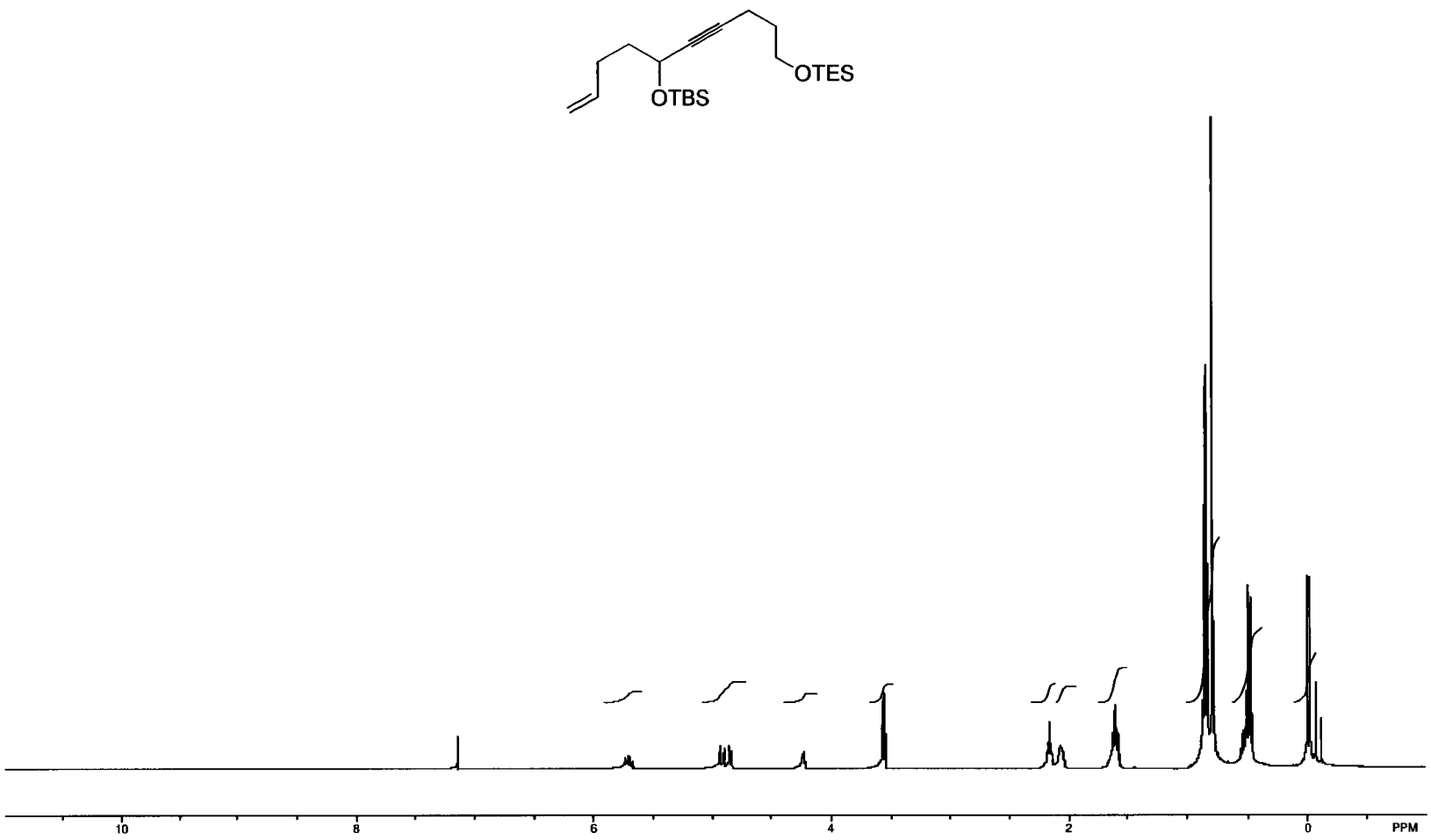


Figure A2.19 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **86**.

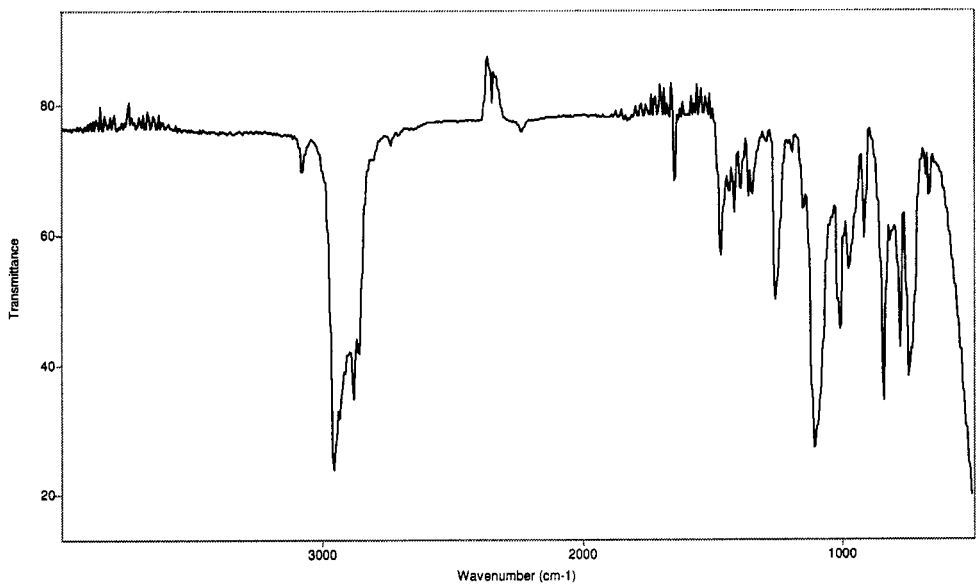


Figure A2.20 IR spectrum (thin film/NaCl) of compound **86**.

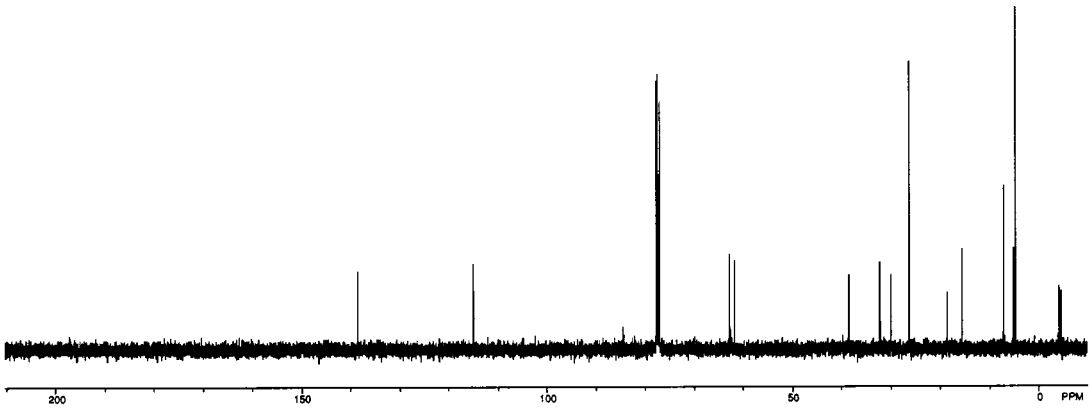


Figure A2.21 ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **86**.

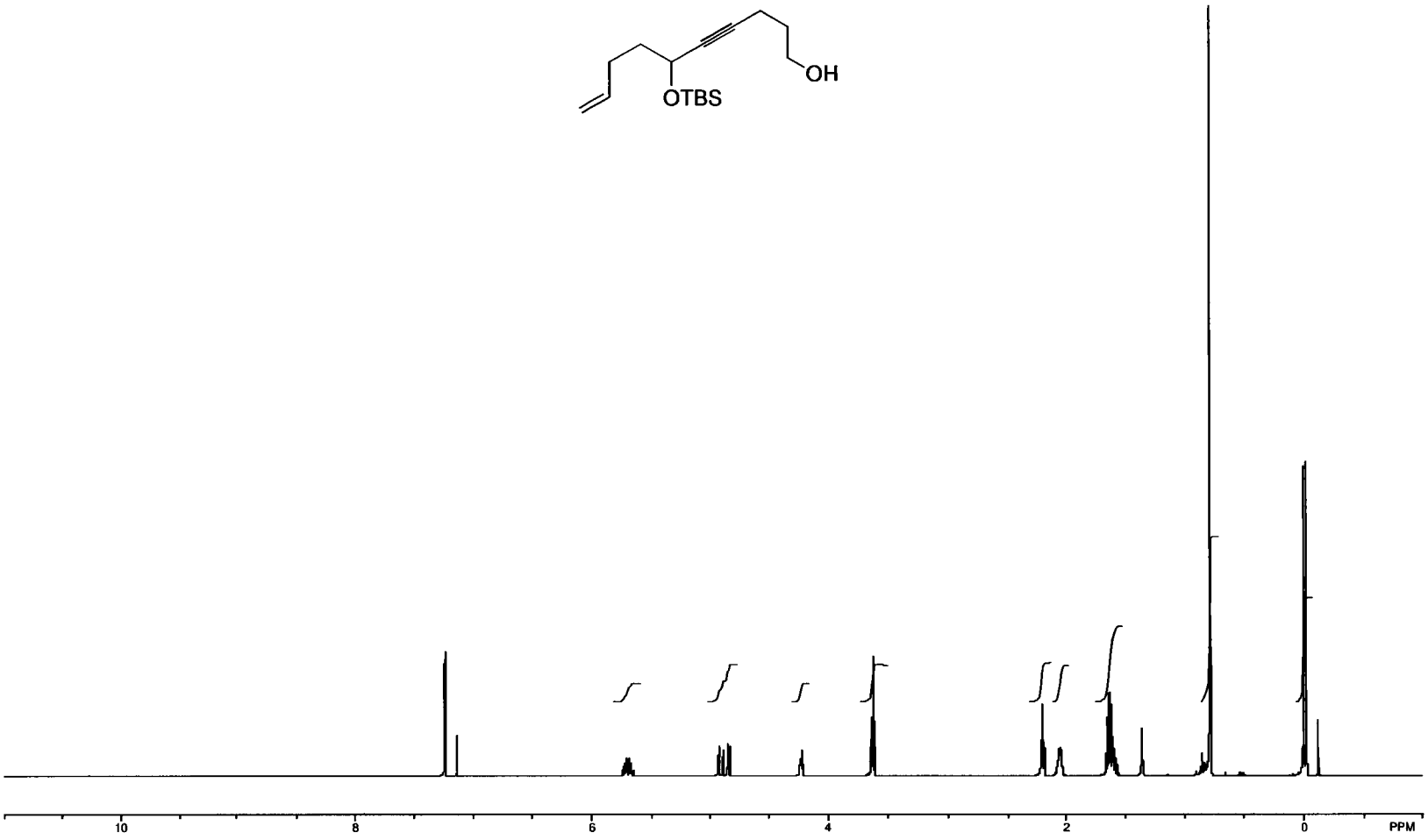


Figure A2.22 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **87**.

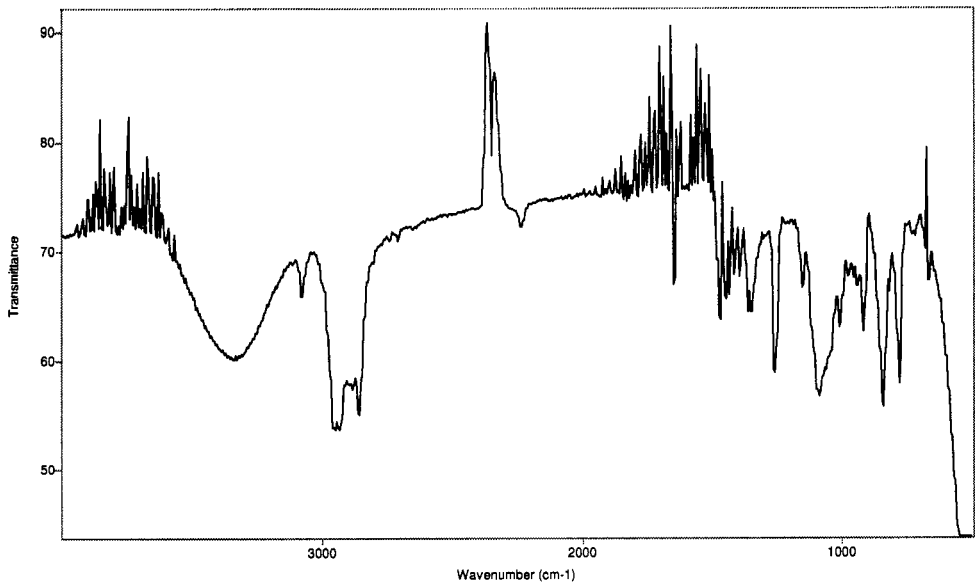


Figure A2.23 IR spectrum (thin film/NaCl) of compound **87**.

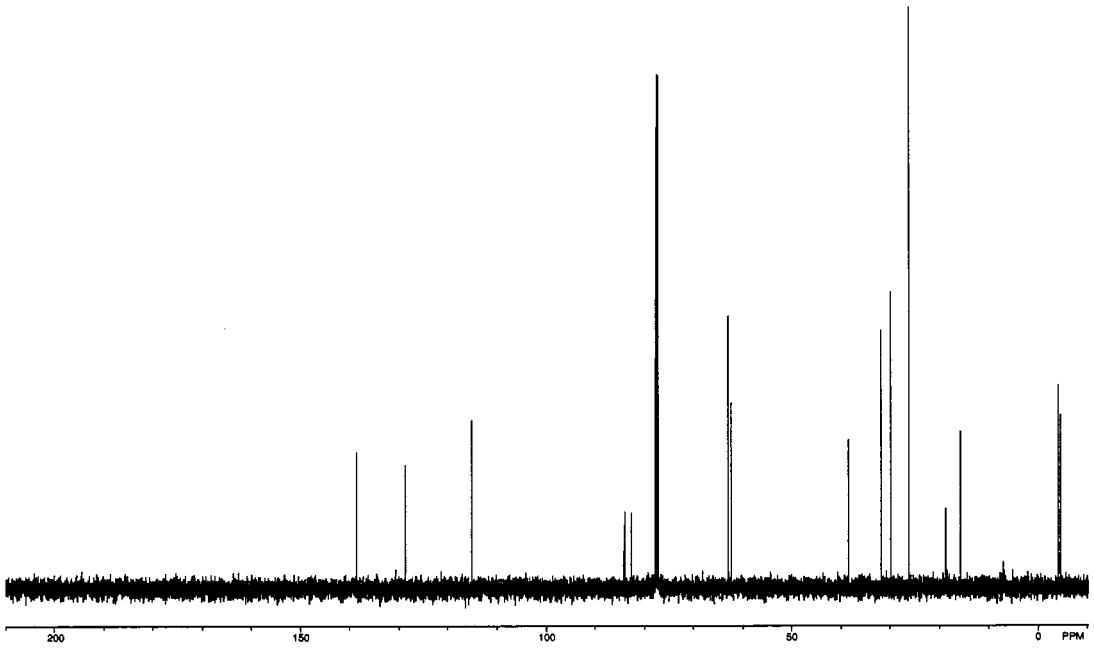


Figure A2.24 ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **87**.

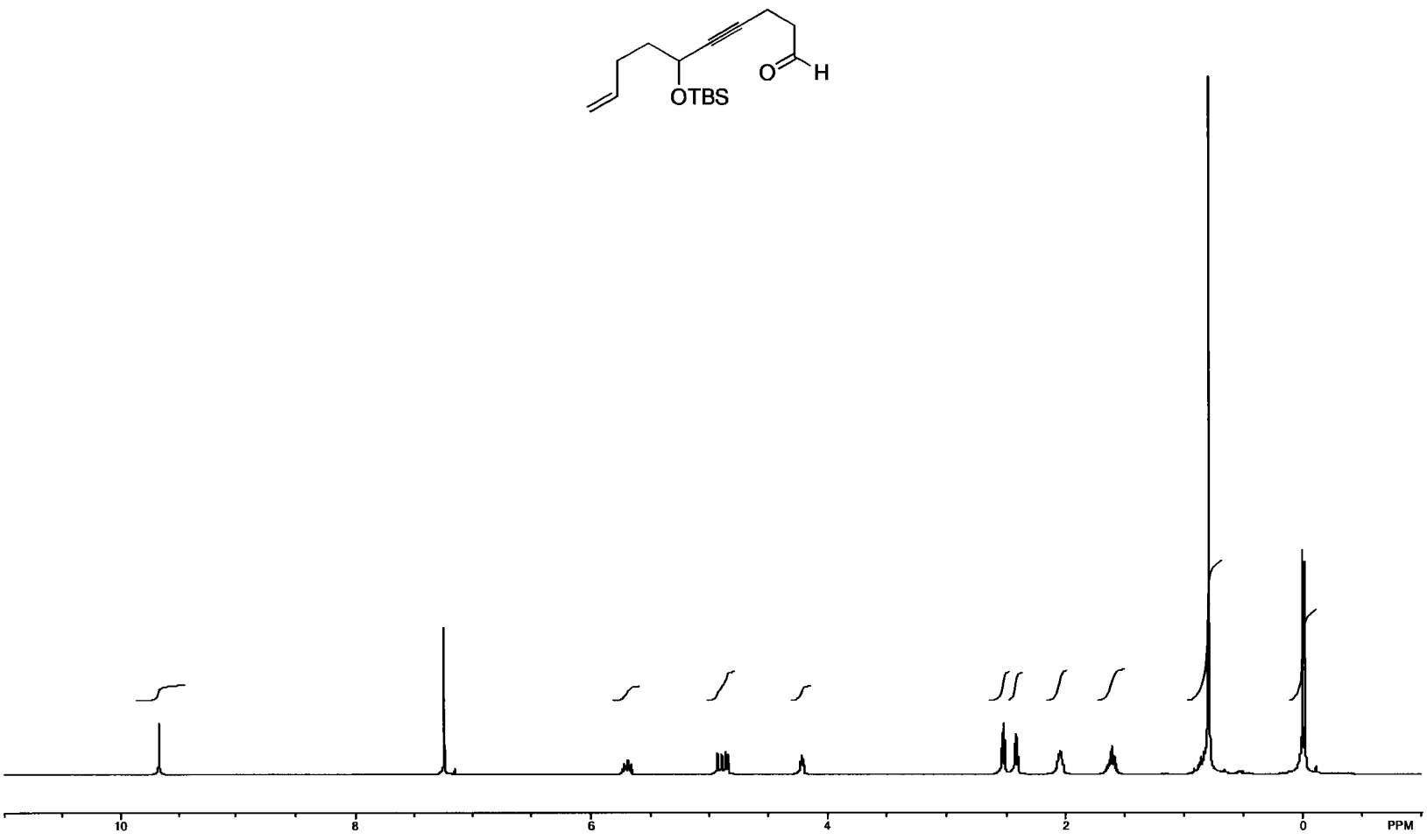


Figure A2.25 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **88**.

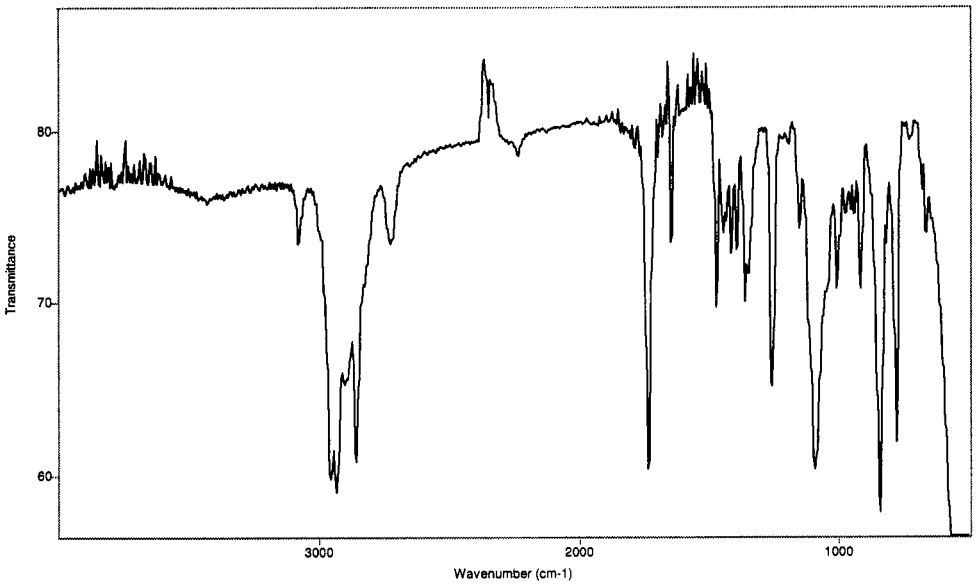


Figure A2.26 IR spectrum (thin film/NaCl) of compound **88**.

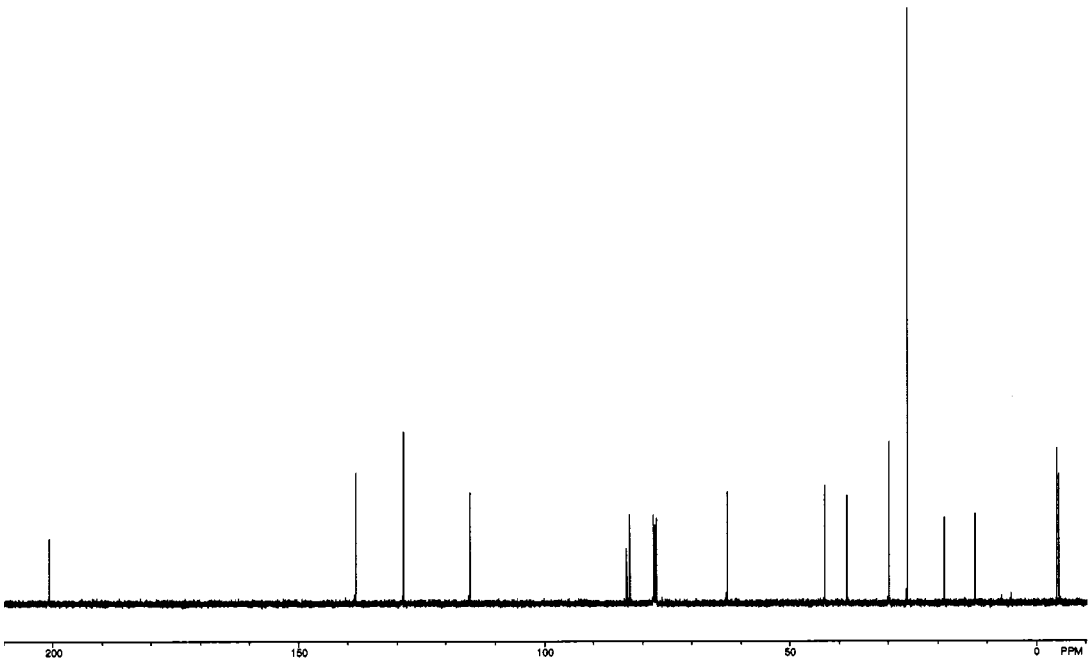


Figure A2.27 ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **88**.

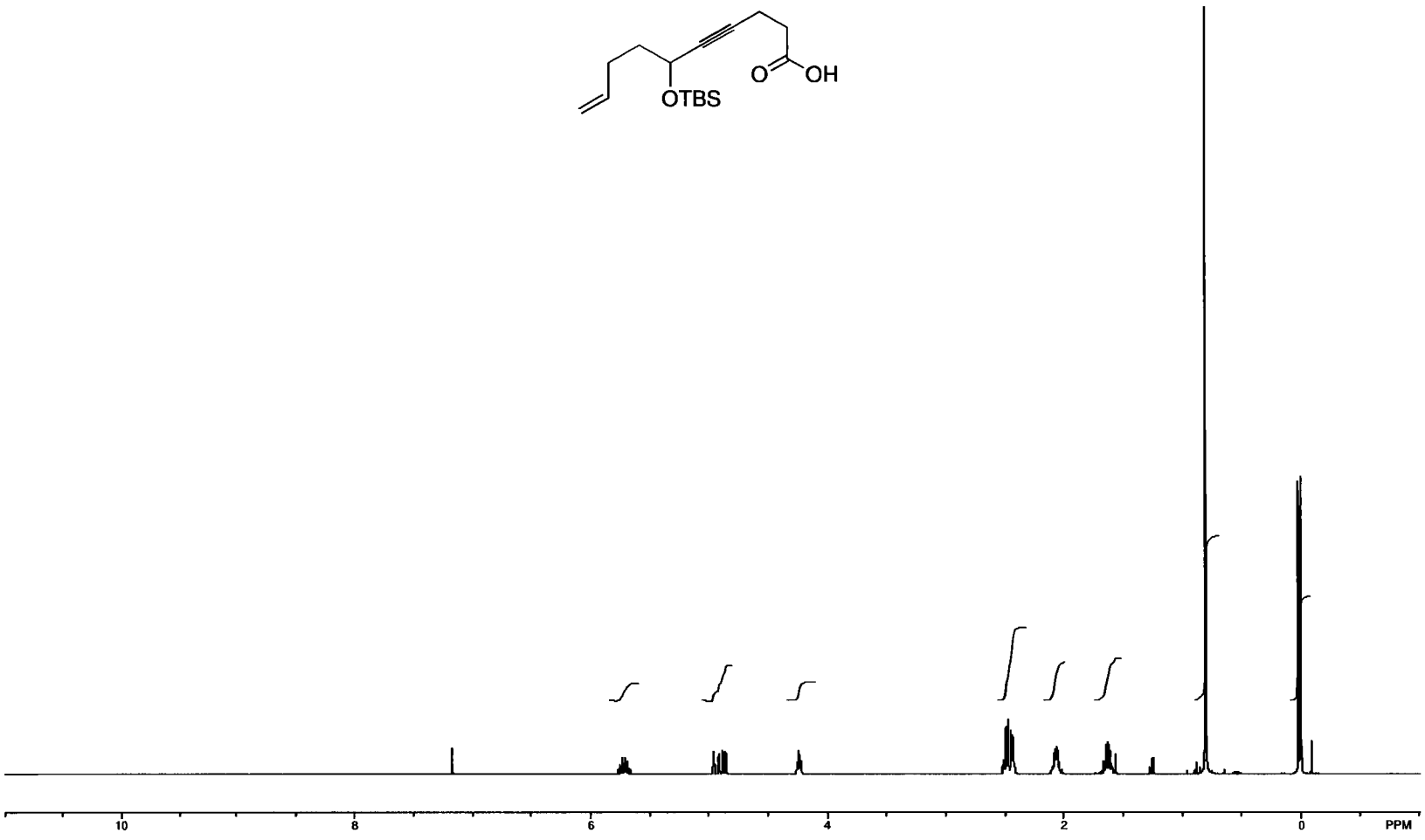


Figure A2.28 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **89**.

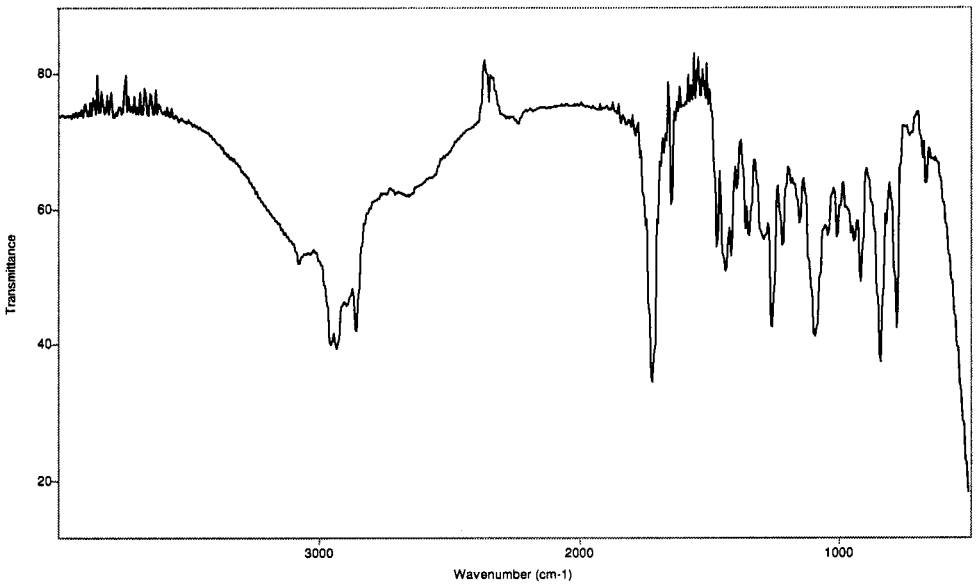


Figure A2.29 IR spectrum (thin film/NaCl) of compound **89**.

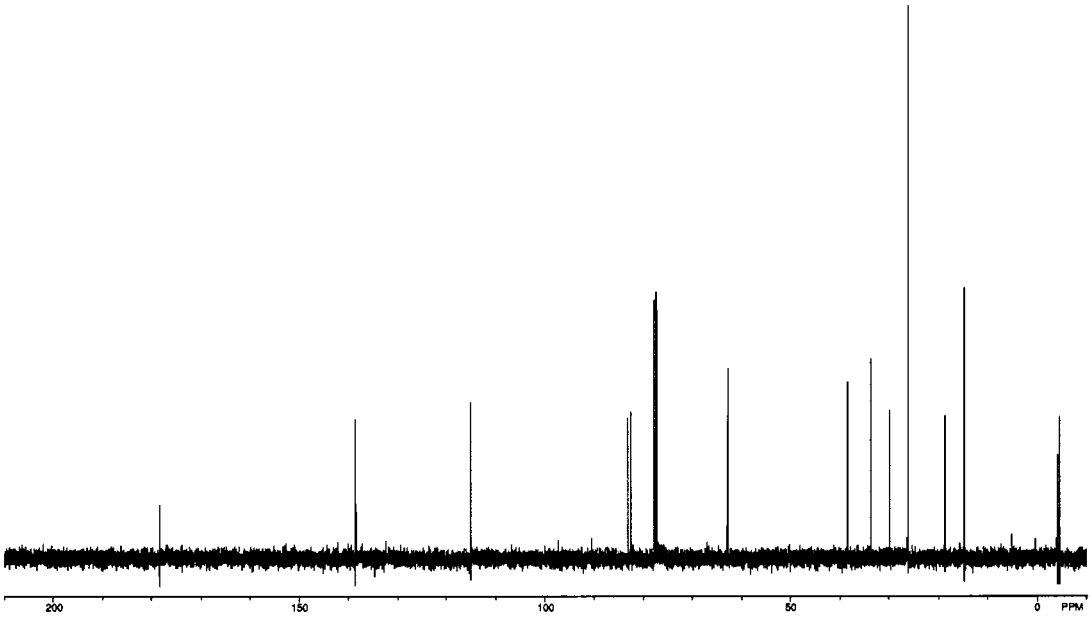


Figure A2.30 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **89**.

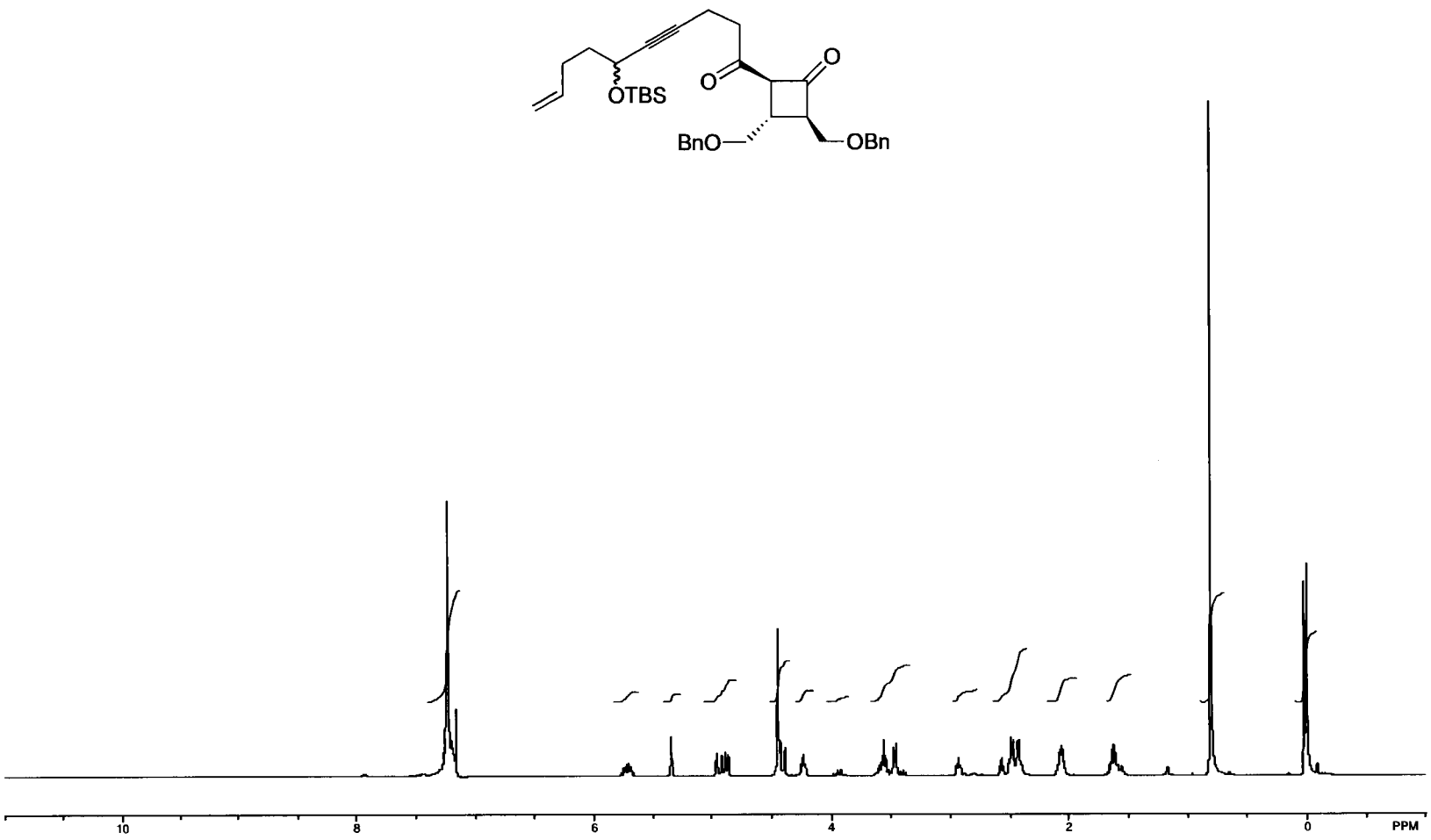


Figure A2.31 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **91**.

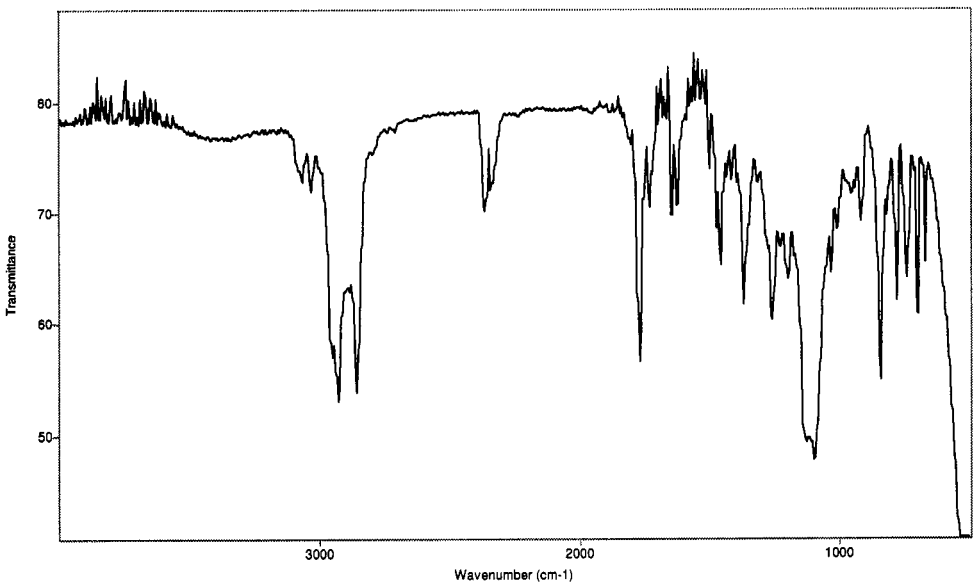


Figure A2.32 IR spectrum (thin film/NaCl) of compound **91**.

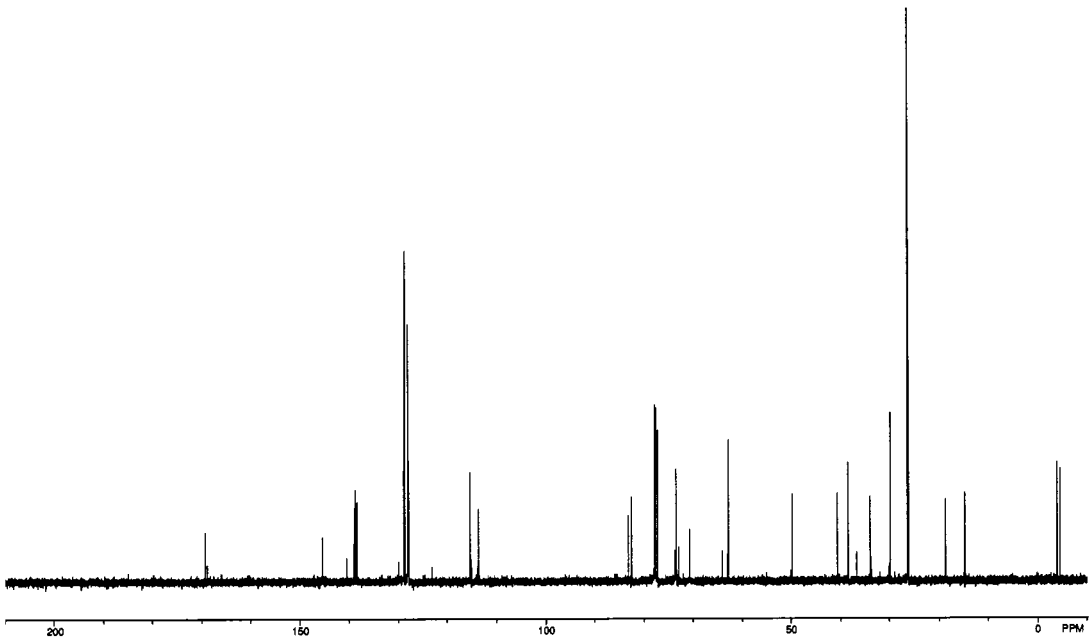


Figure A2.33 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **91**.

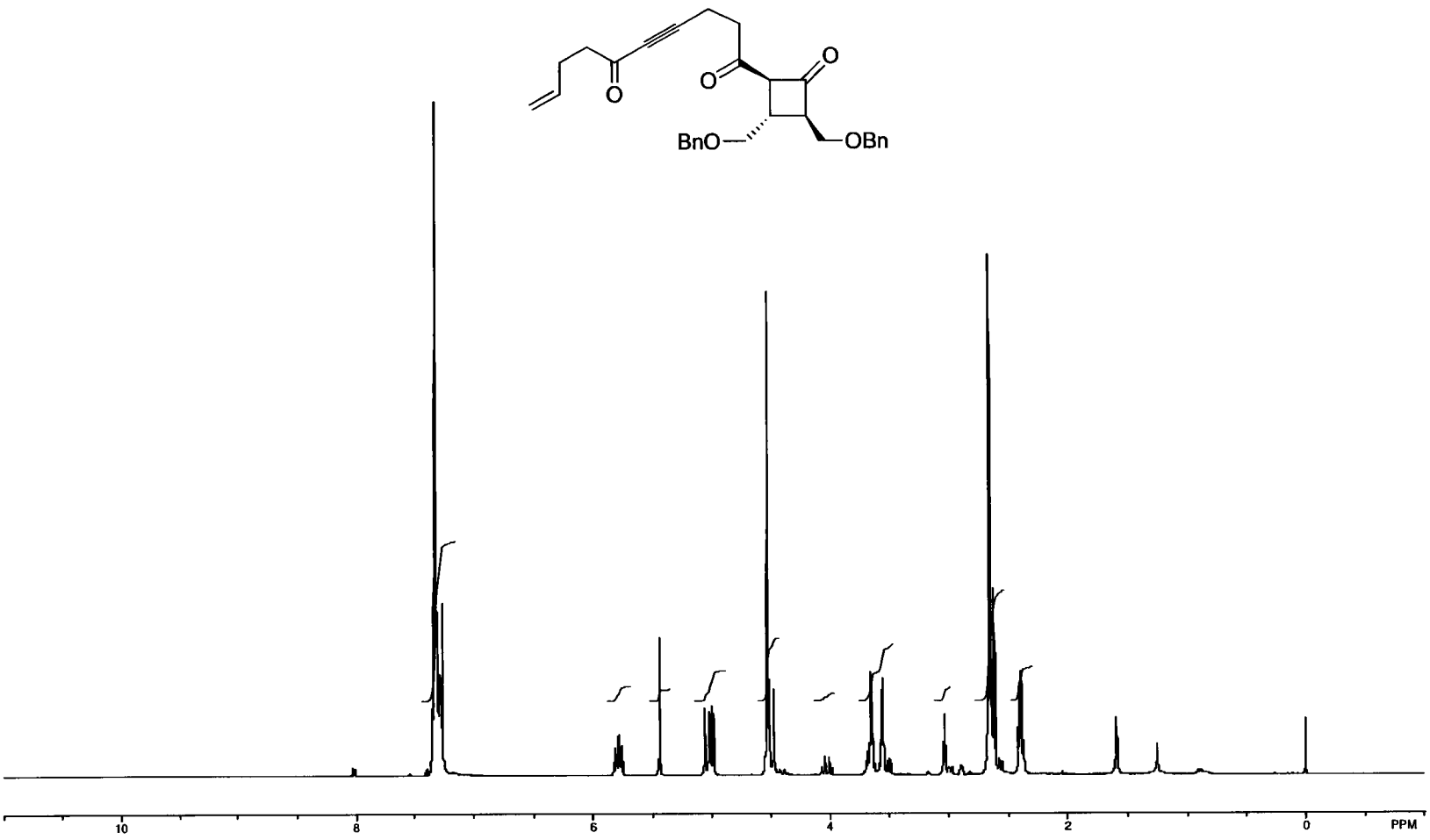


Figure A2.34 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **82**.

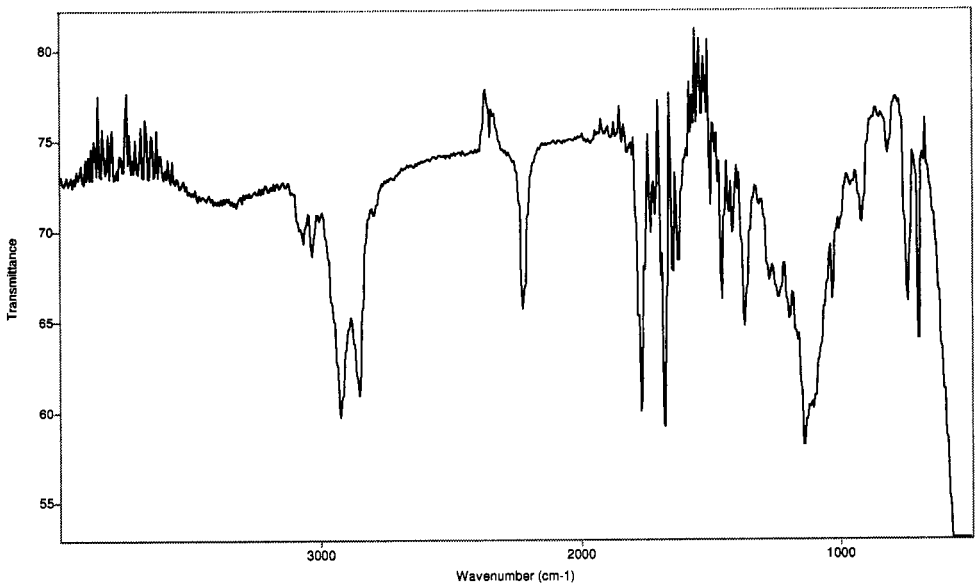


Figure A2.35 IR spectrum (thin film/NaCl) of compound **82**.

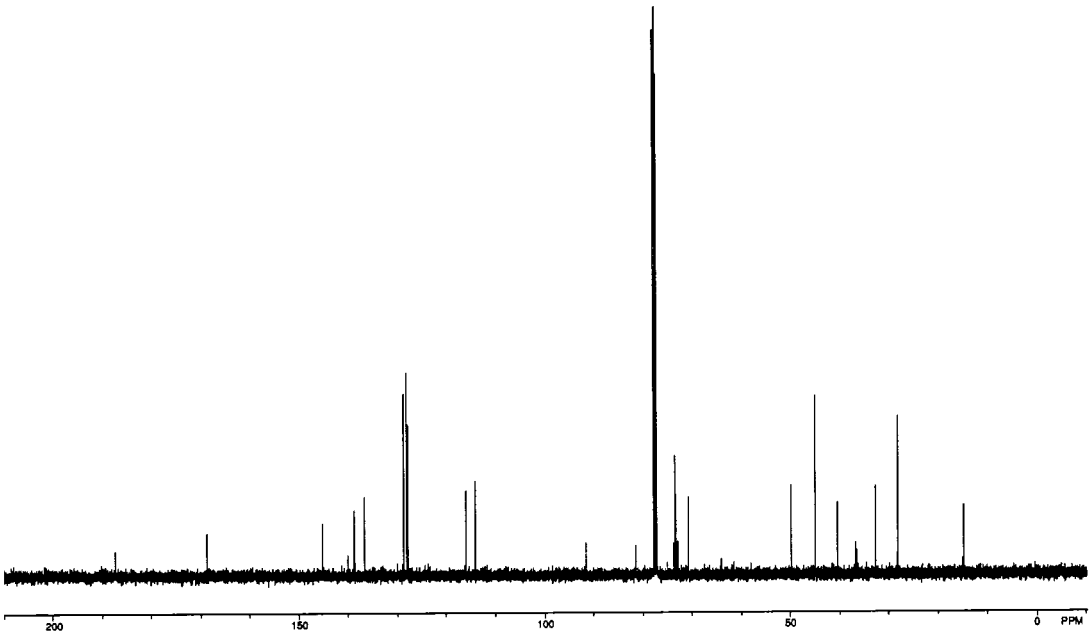


Figure A2.36 ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **82**.

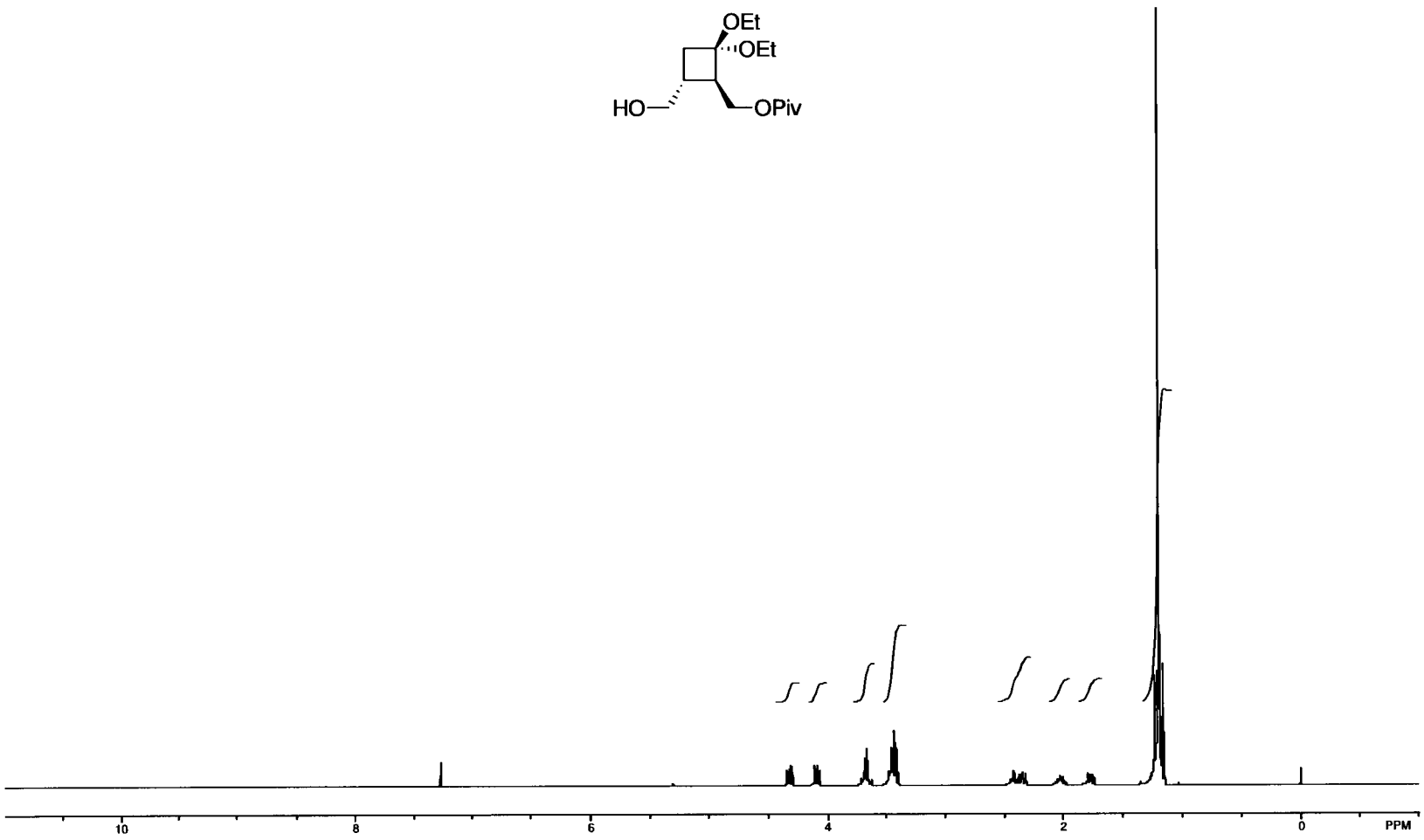


Figure A2.37 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **96**.

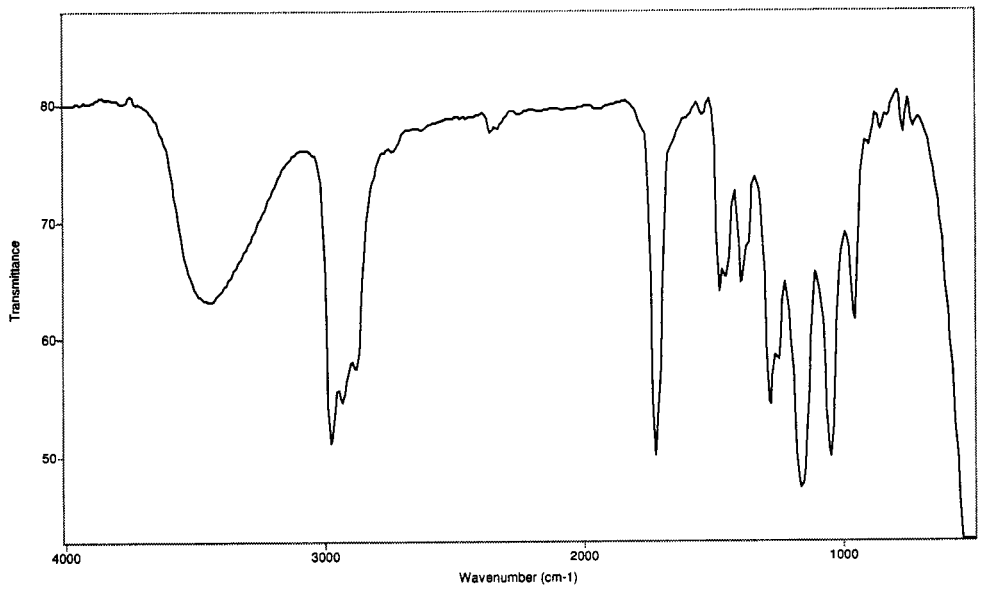


Figure A2.38 IR spectrum (thin film/NaCl) of compound **96**.

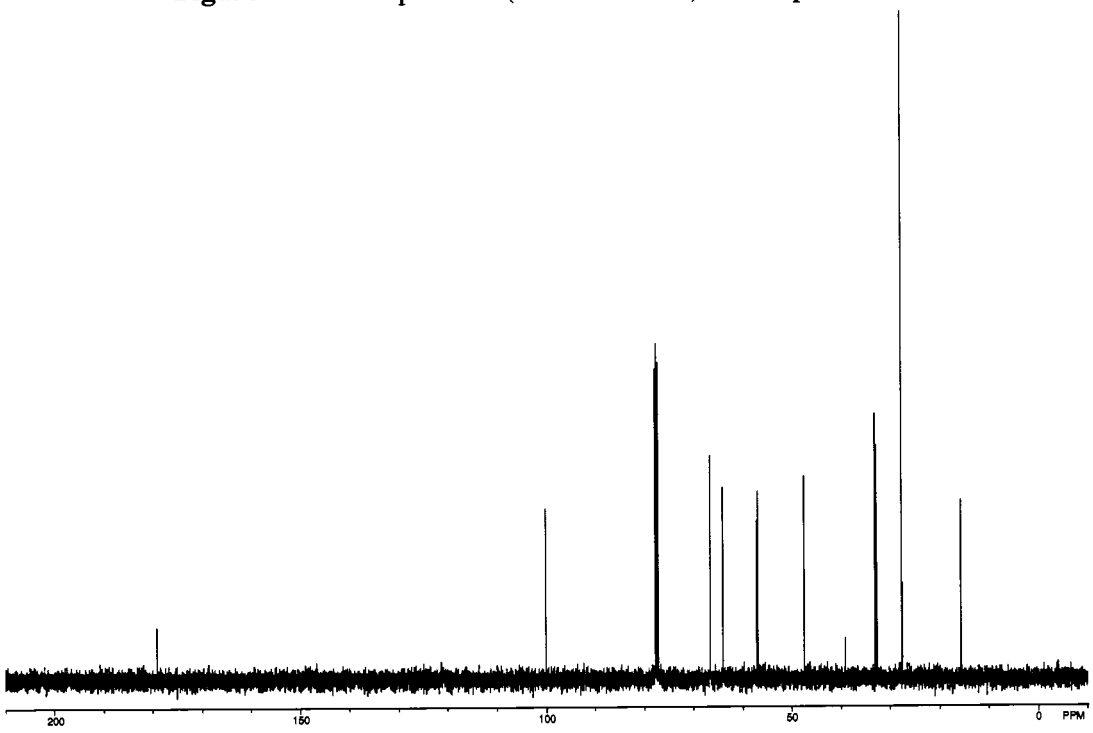


Figure A2.39 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **96**.

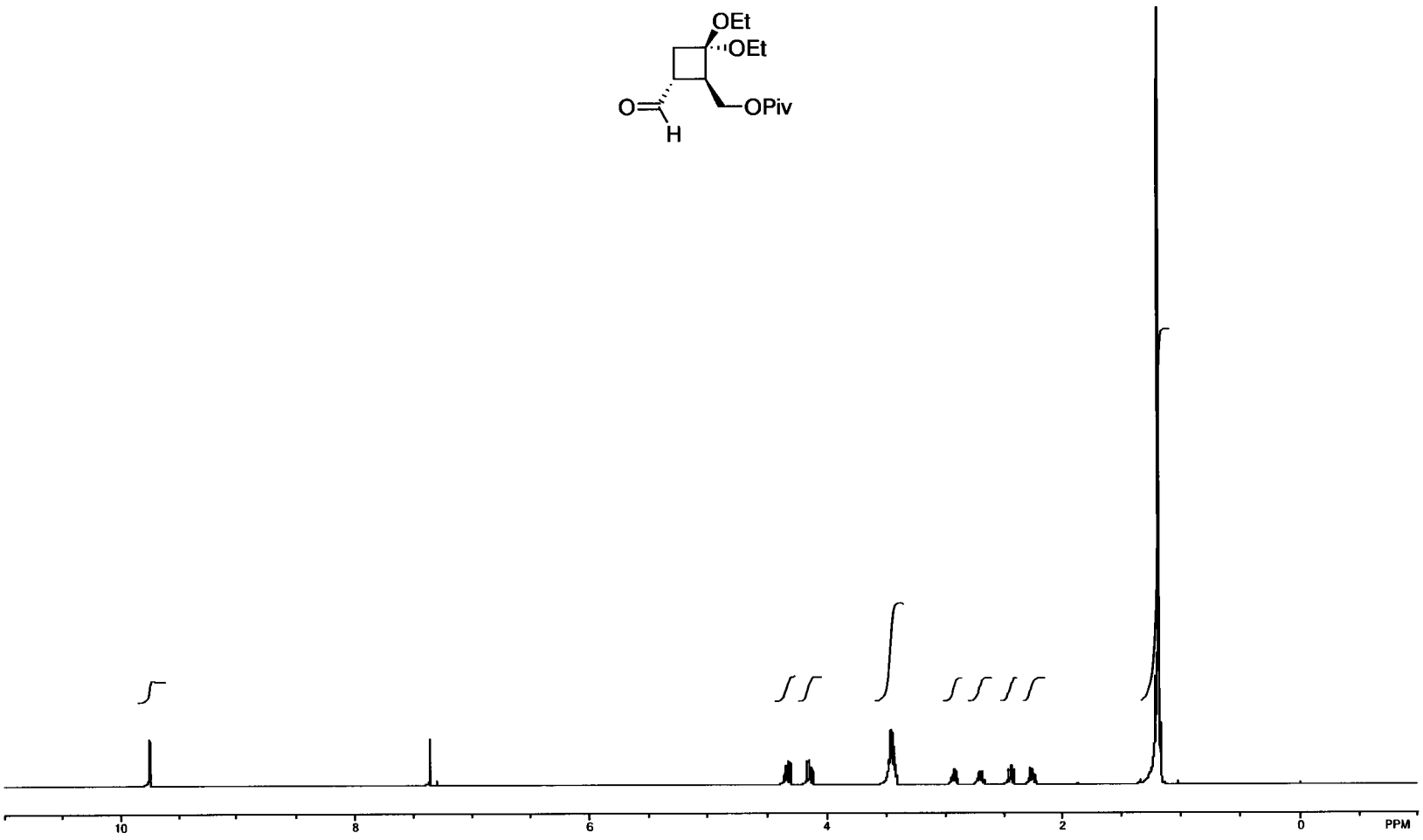


Figure A2.40 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **99**.

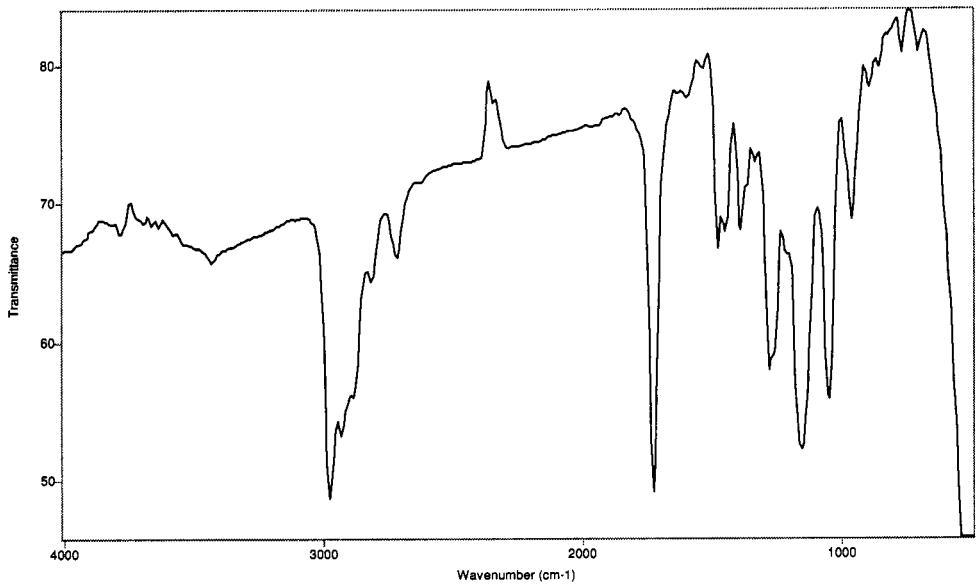


Figure A2.41 IR spectrum (thin film/NaCl) of compound **99**.

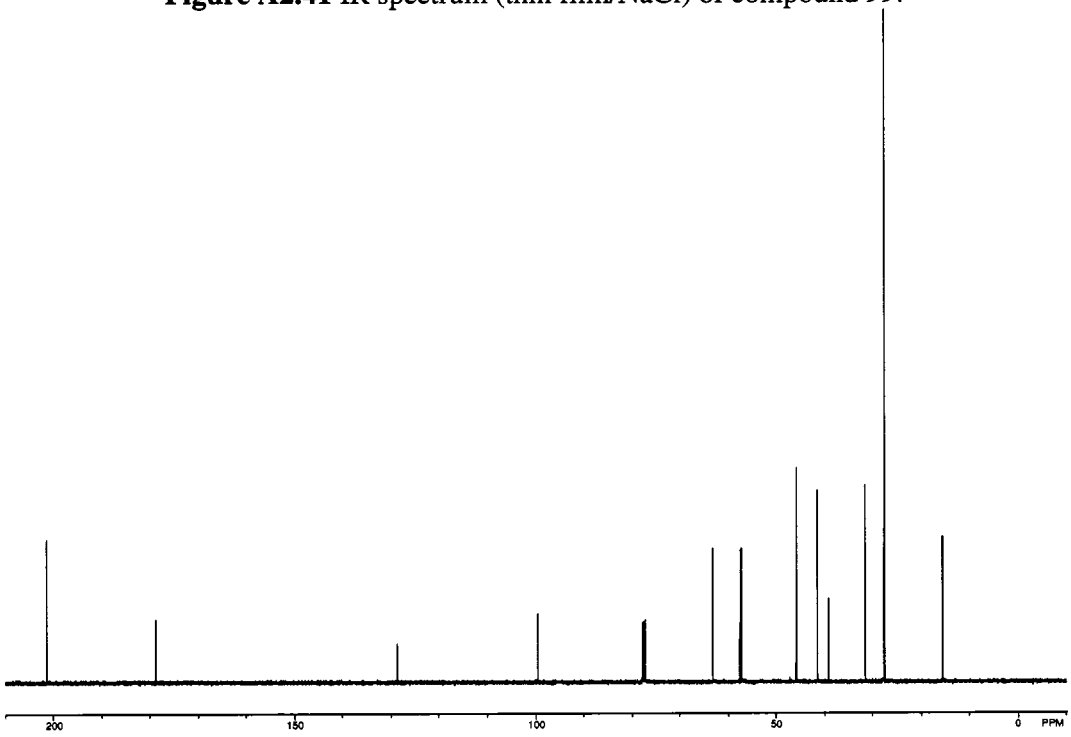


Figure A2.42 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **99**.

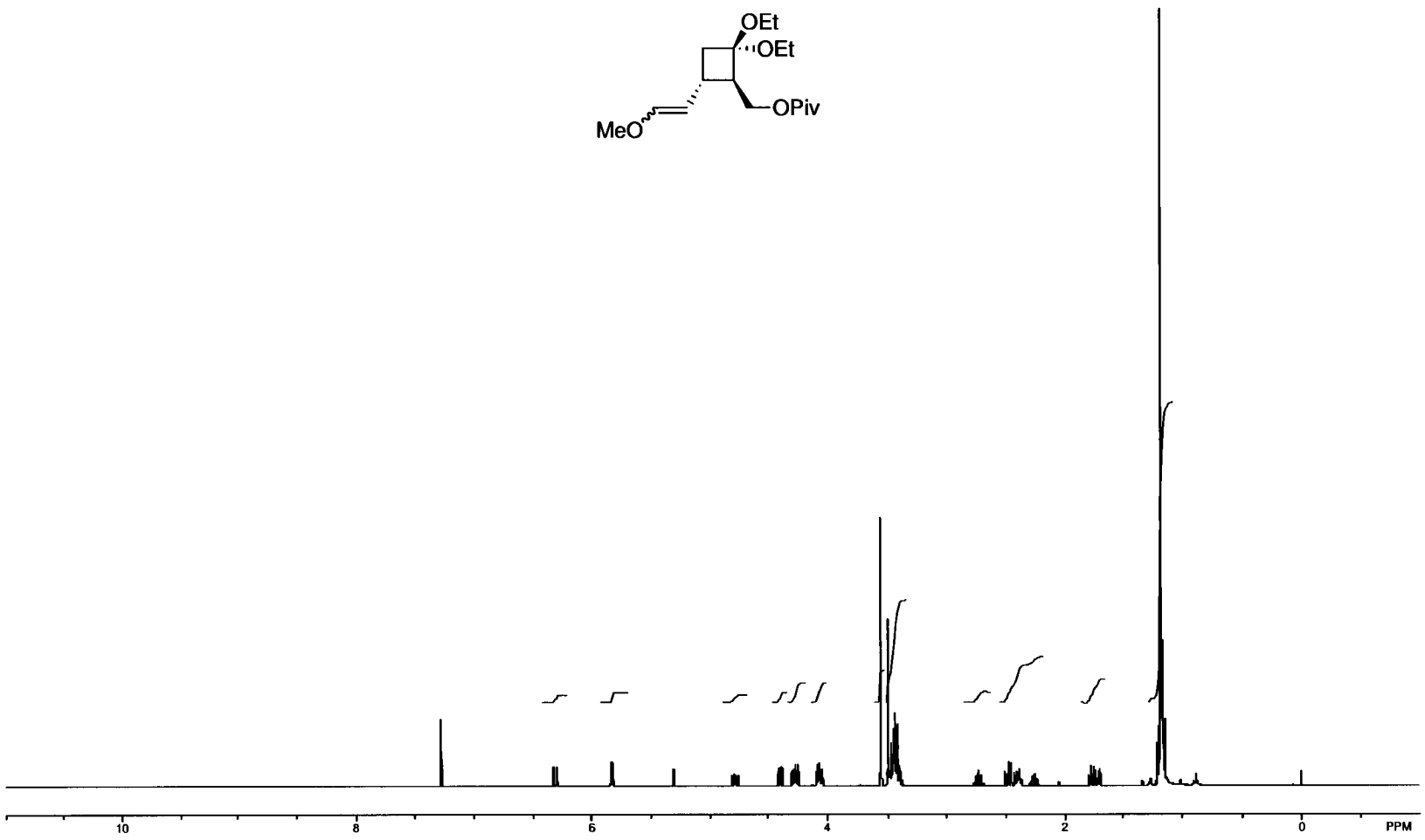


Figure A2.43 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **100**.

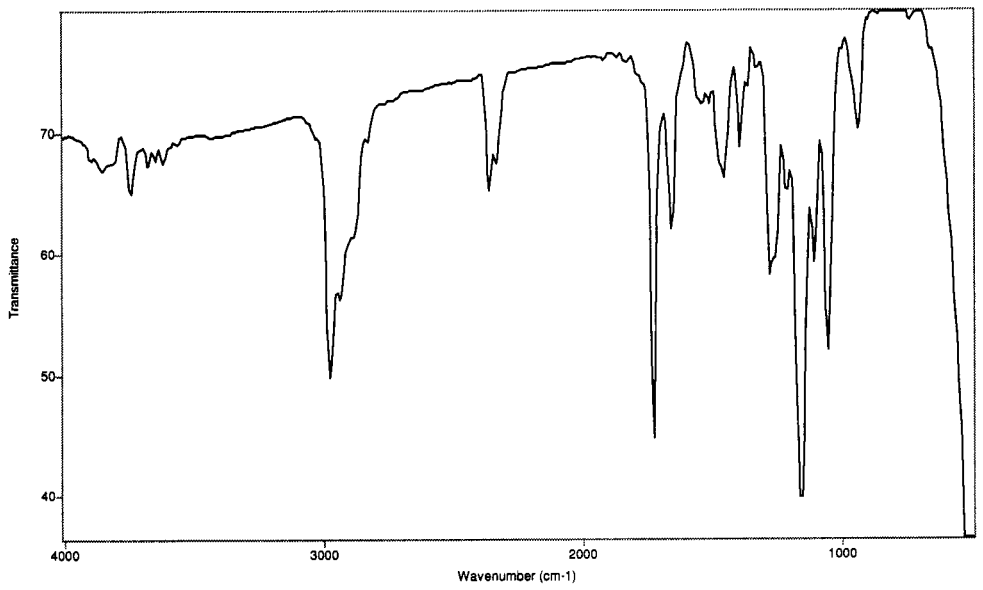


Figure A2.44 IR spectrum (thin film/NaCl) of compound **100**.

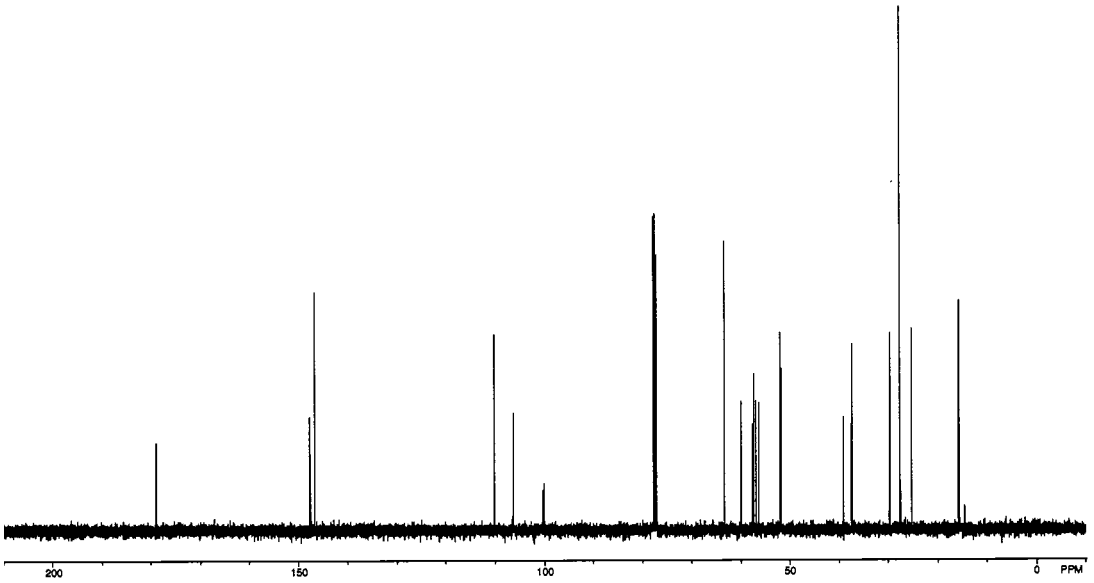


Figure A2.45 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **100**.

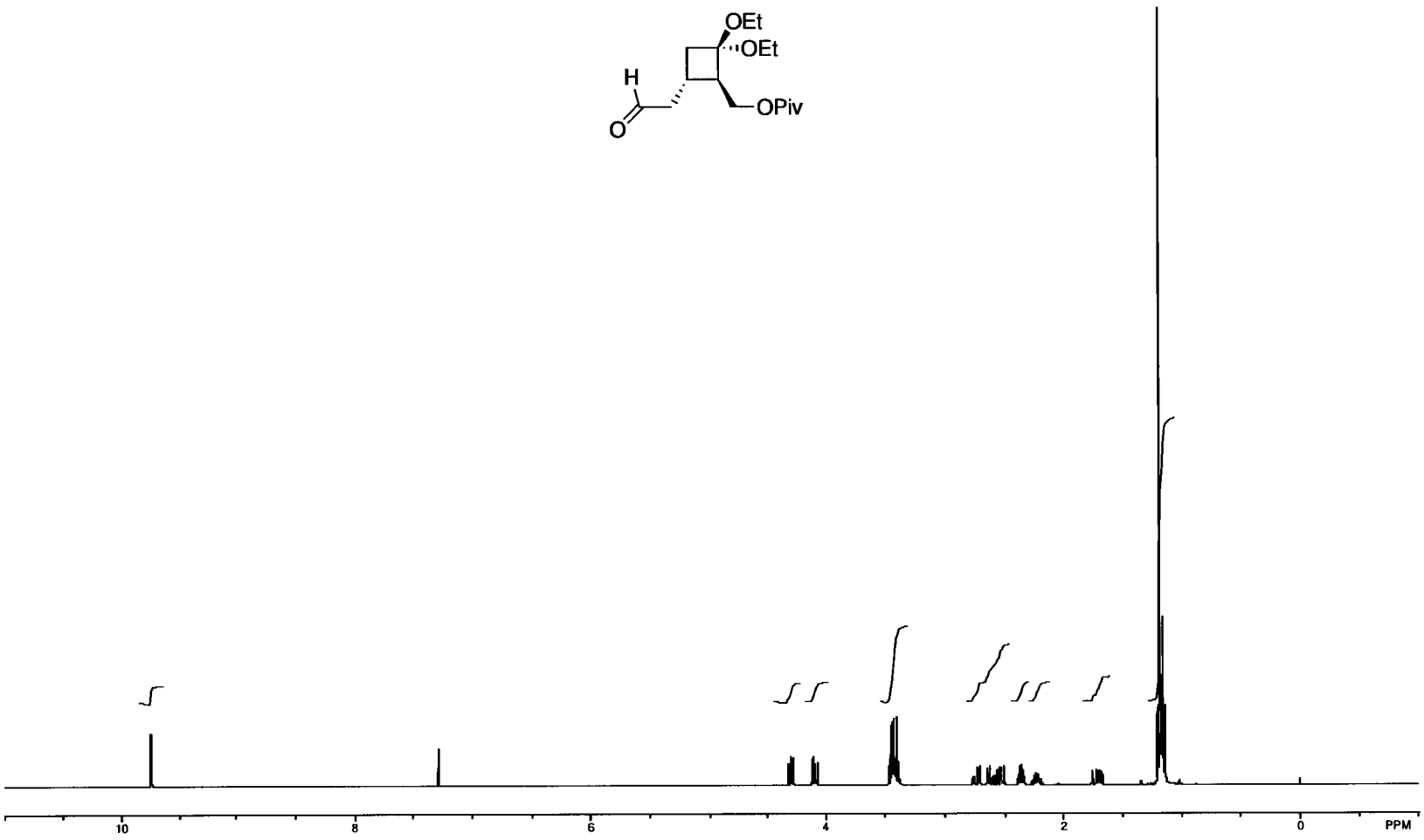


Figure A2.46 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **101**.

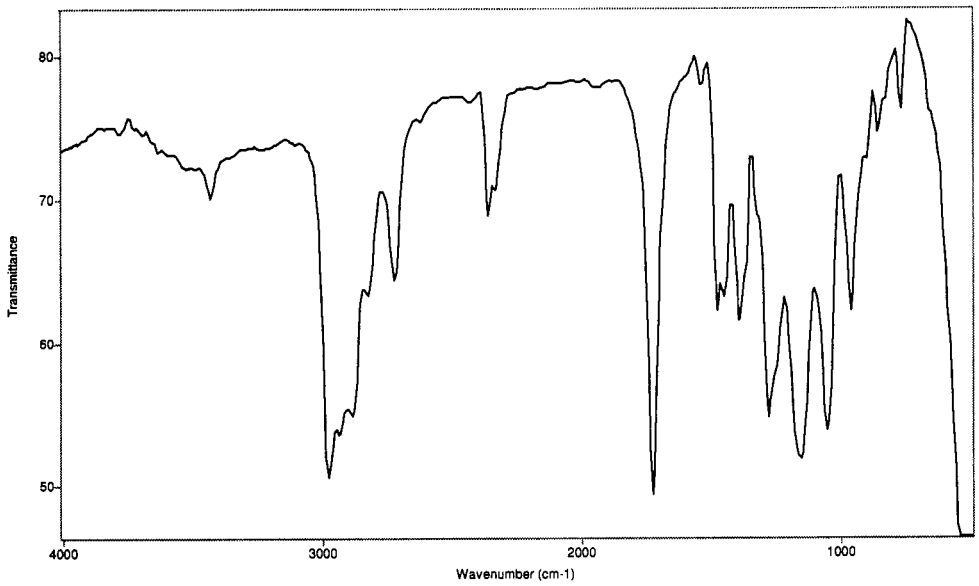


Figure A2.47 IR spectrum (thin film/NaCl) of compound **101**.

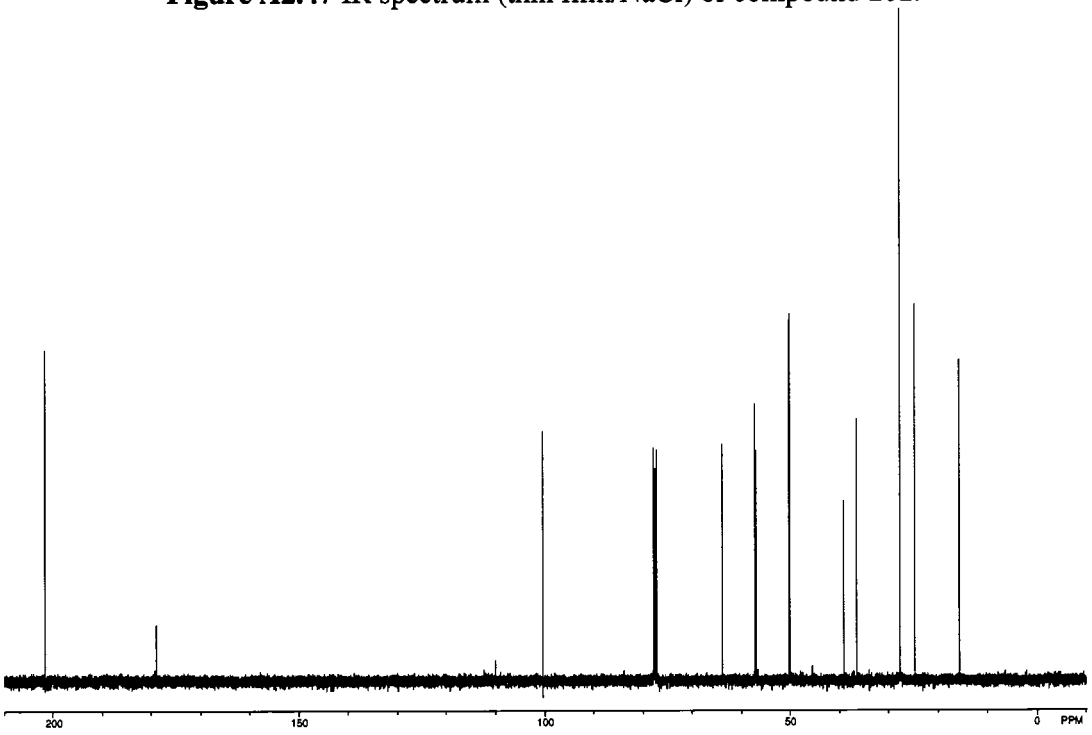


Figure A2.48 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **101**.

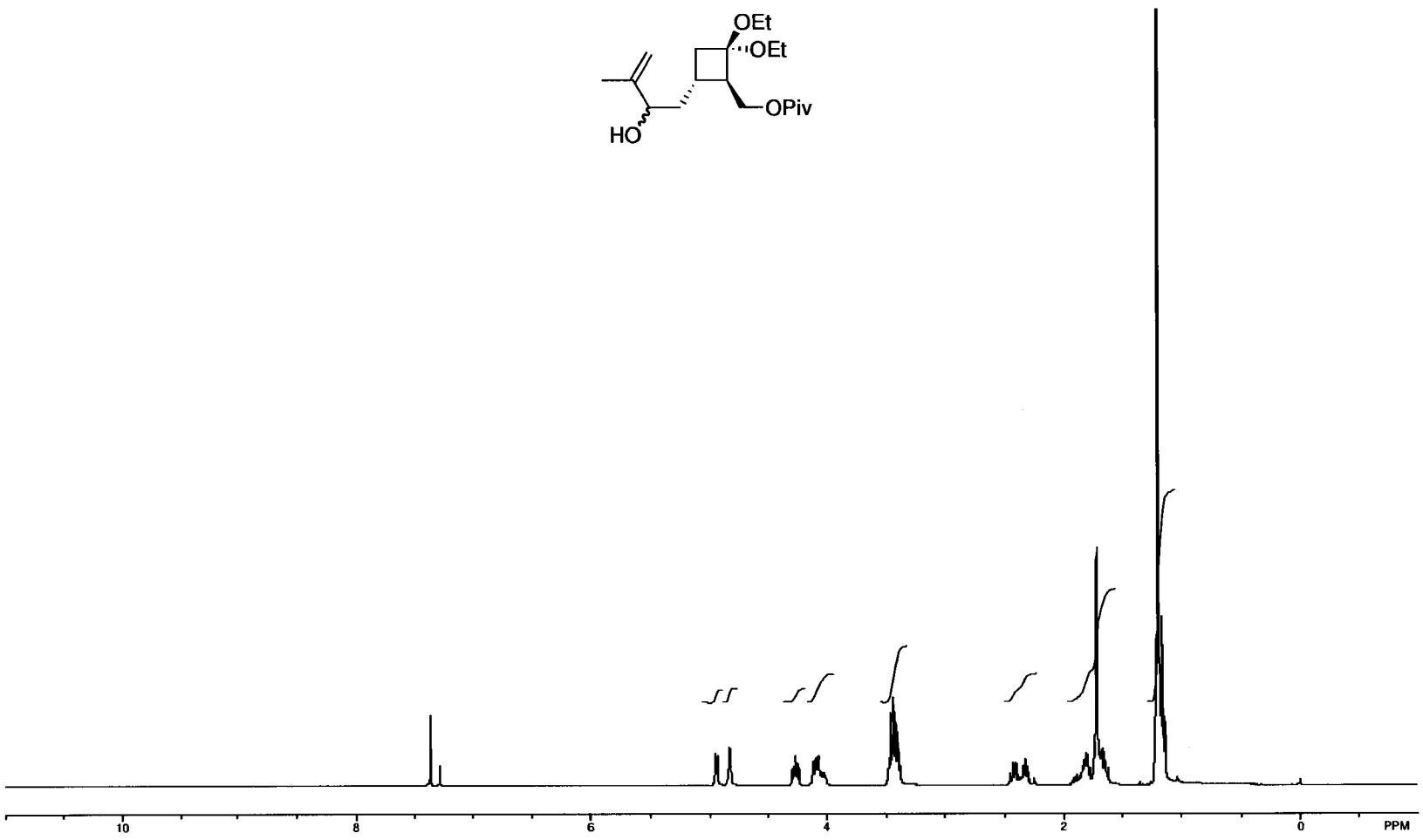


Figure A2.49 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **102**.

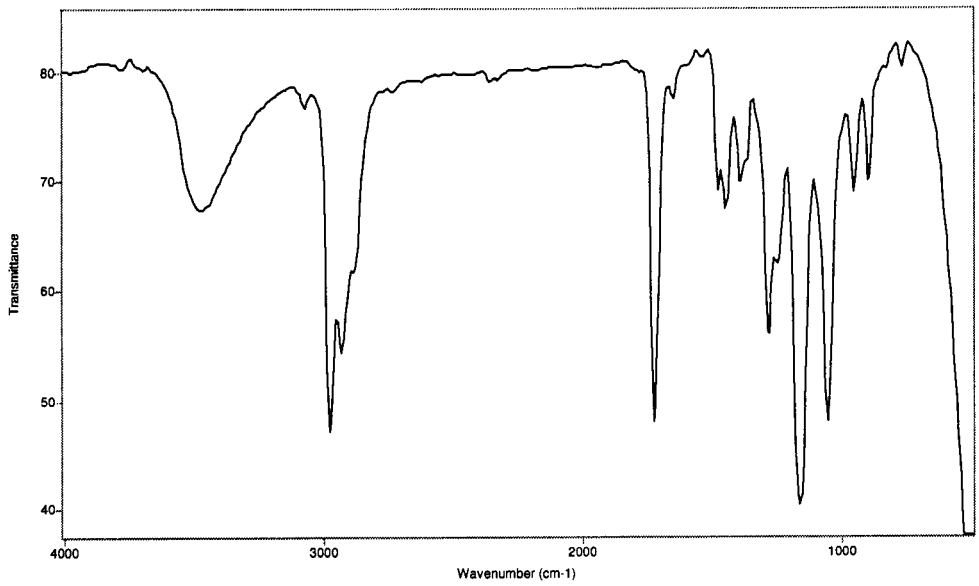


Figure A2.50 IR spectrum (thin film/NaCl) of compound **102**.

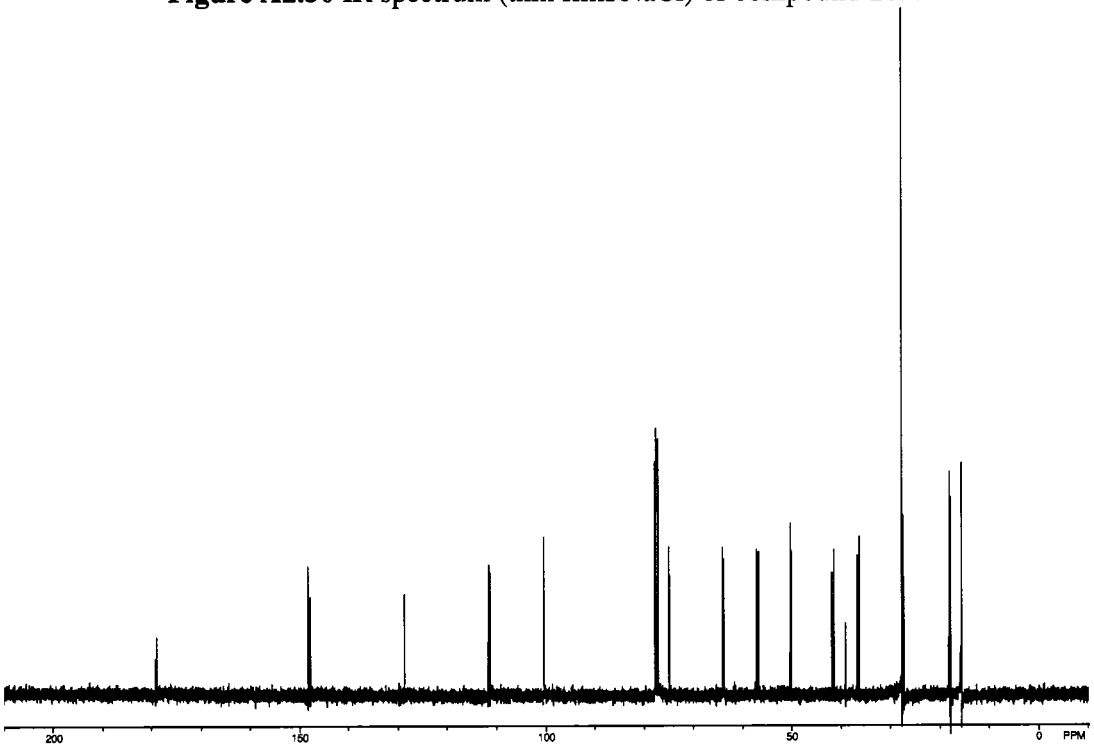


Figure A2.51 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **102**.

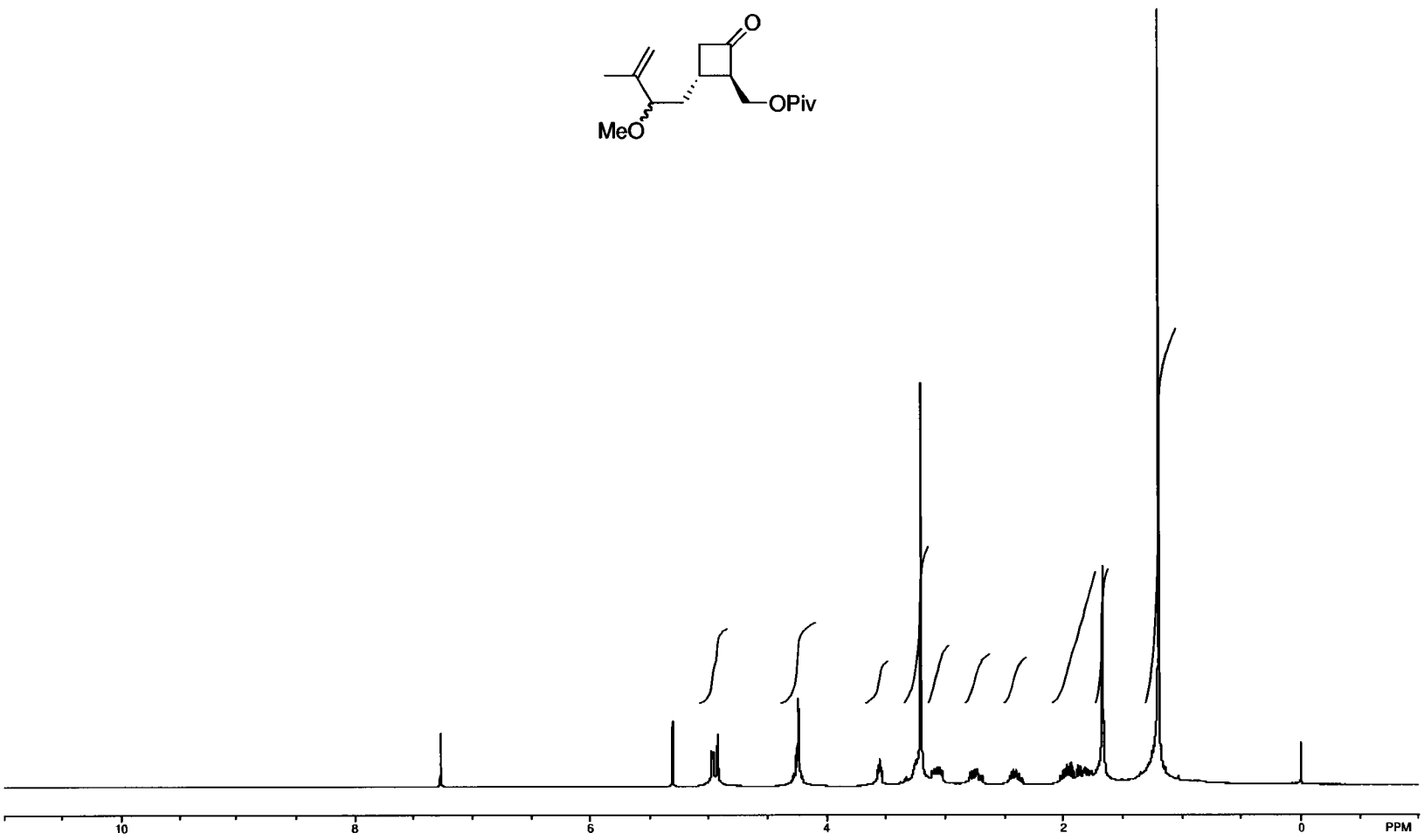


Figure A2.52 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **104**.

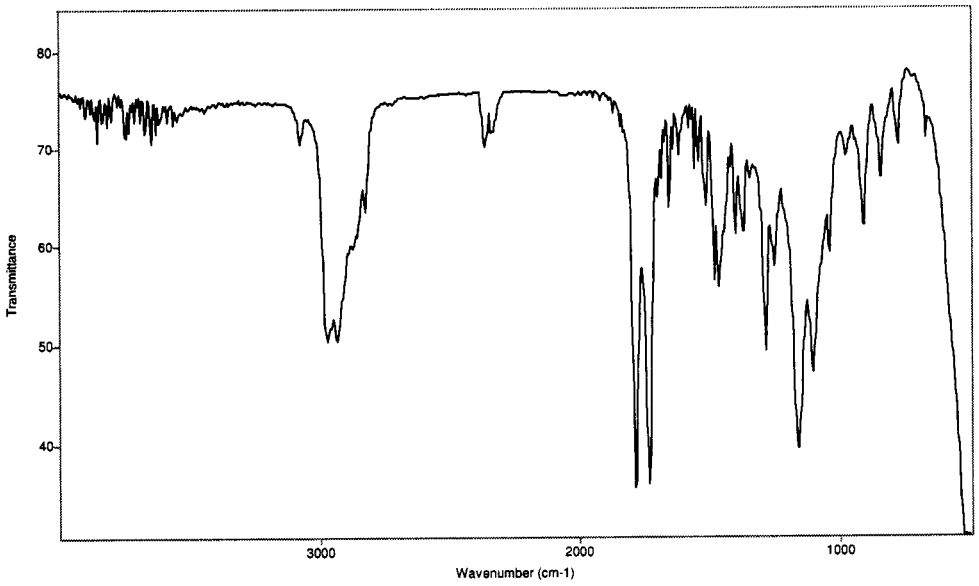


Figure A2.53 IR spectrum (thin film/NaCl) of compound **104**.

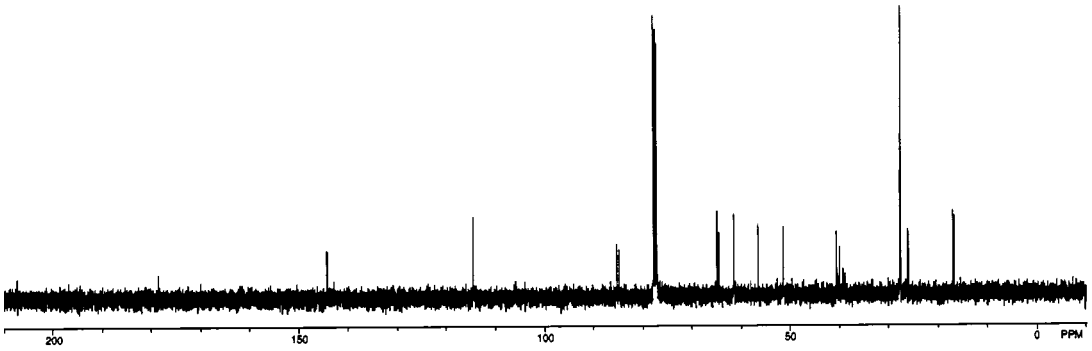


Figure A2.54 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **104**.

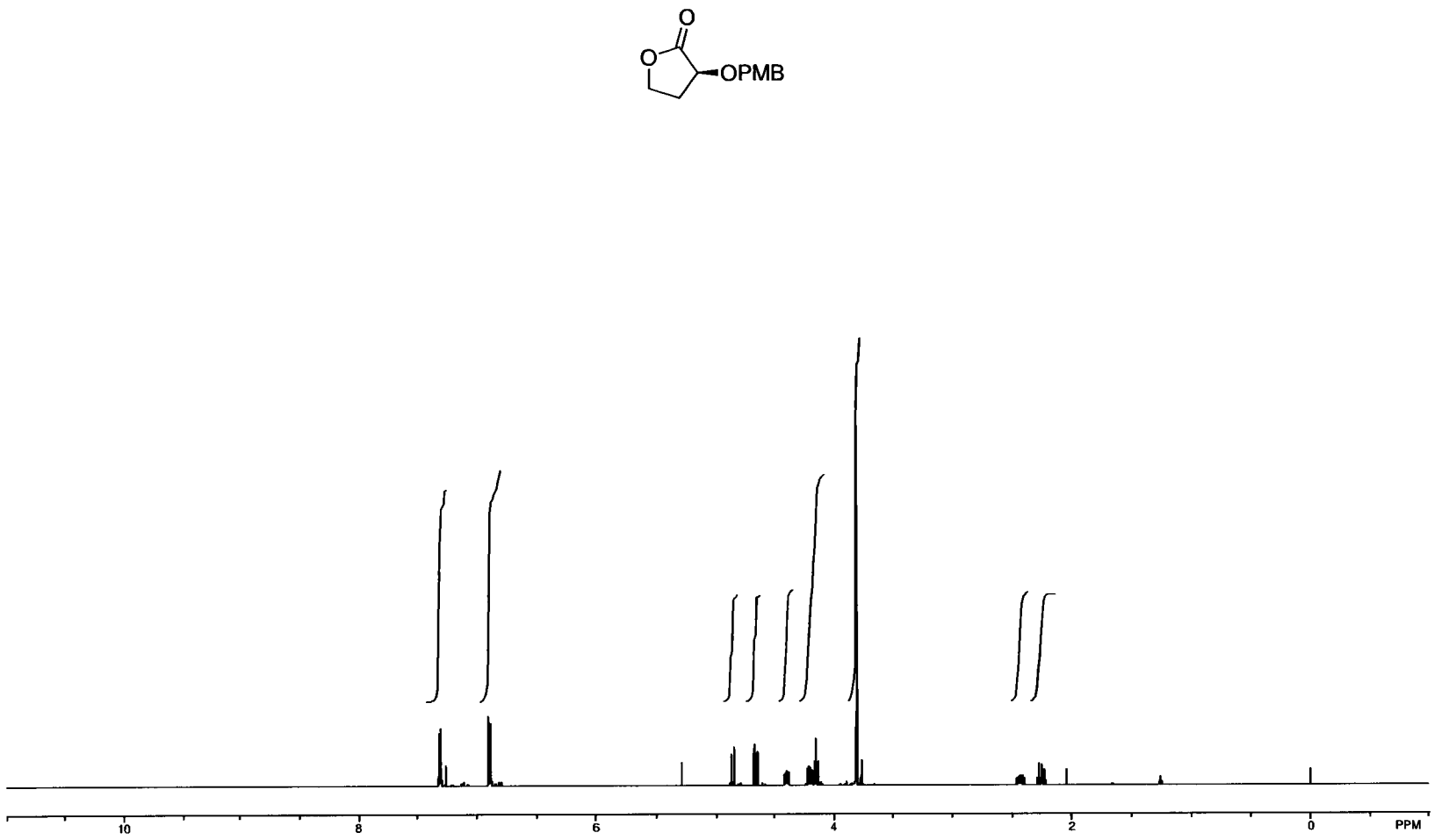


Figure A2.55 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **106**.

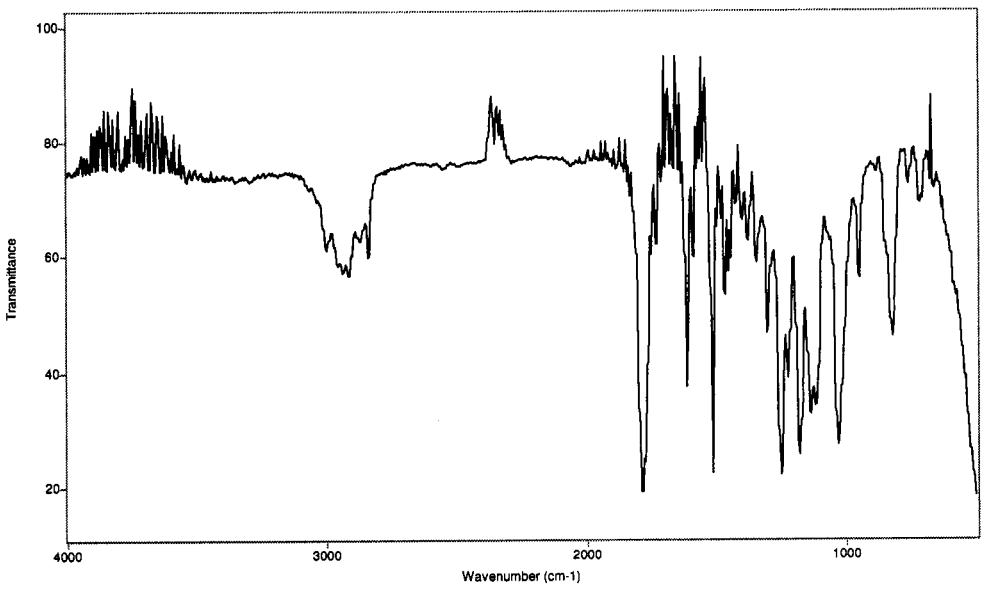


Figure A2.56 IR spectrum (thin film/NaCl) of compound **106**.

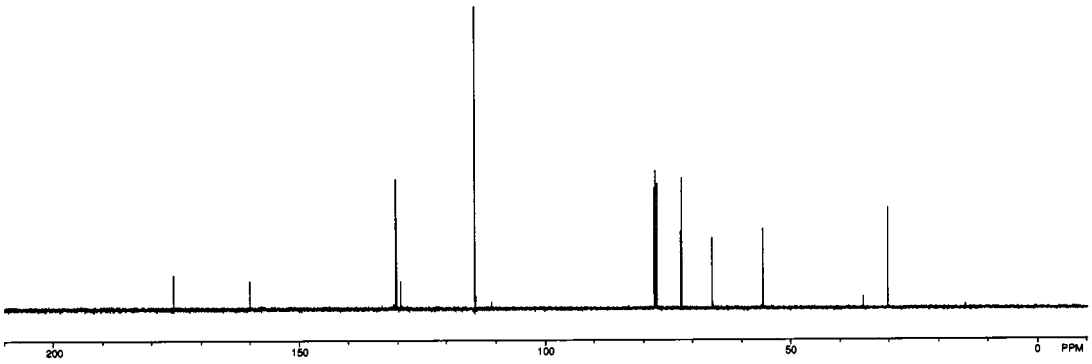


Figure A2.57 ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **106**.

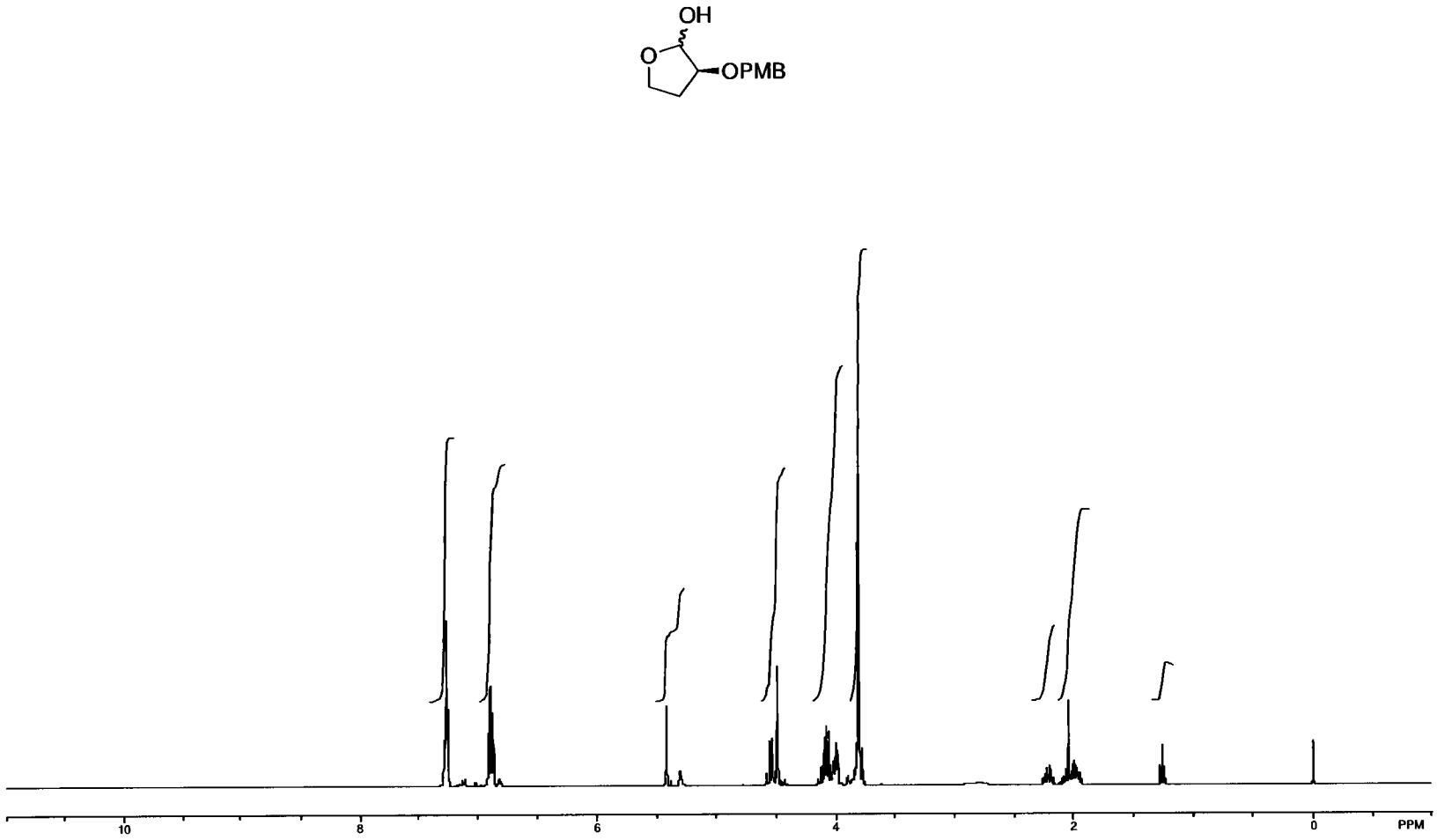


Figure A2.58 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **107**.

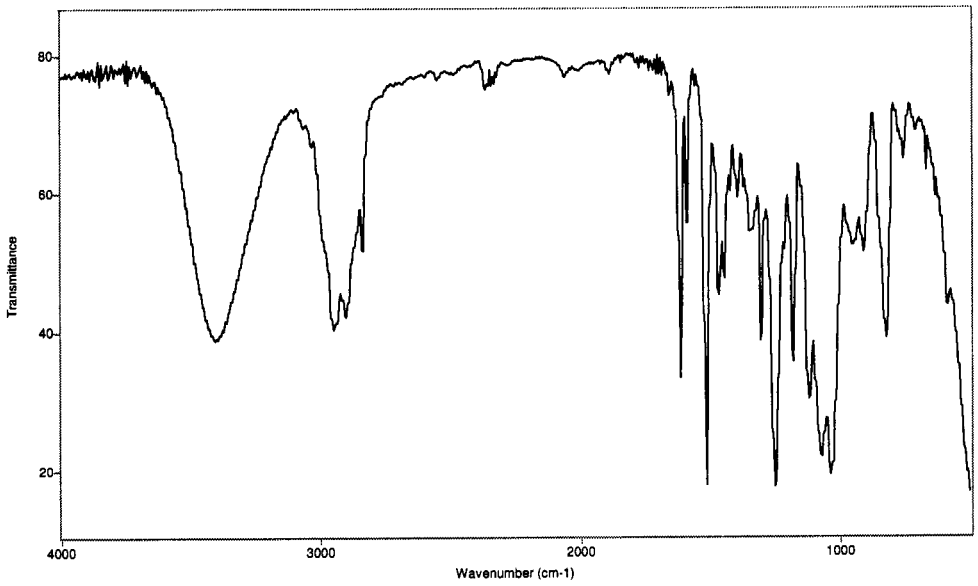


Figure A2.59 IR spectrum (thin film/NaCl) of compound **107**.

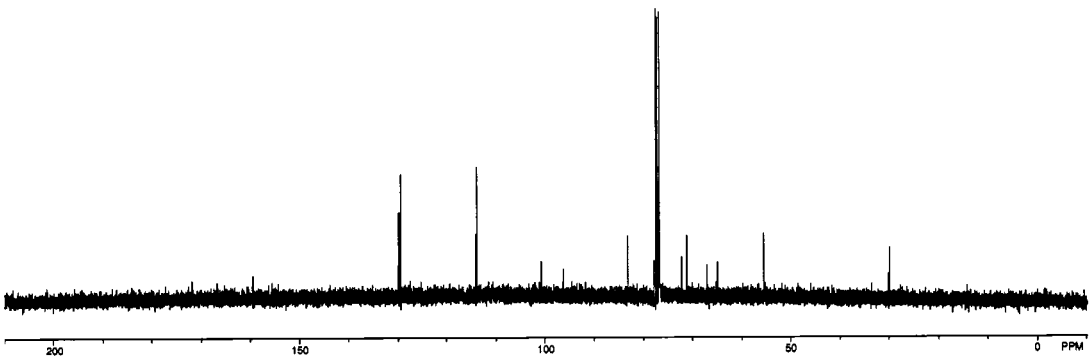


Figure A2.60 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **107**.

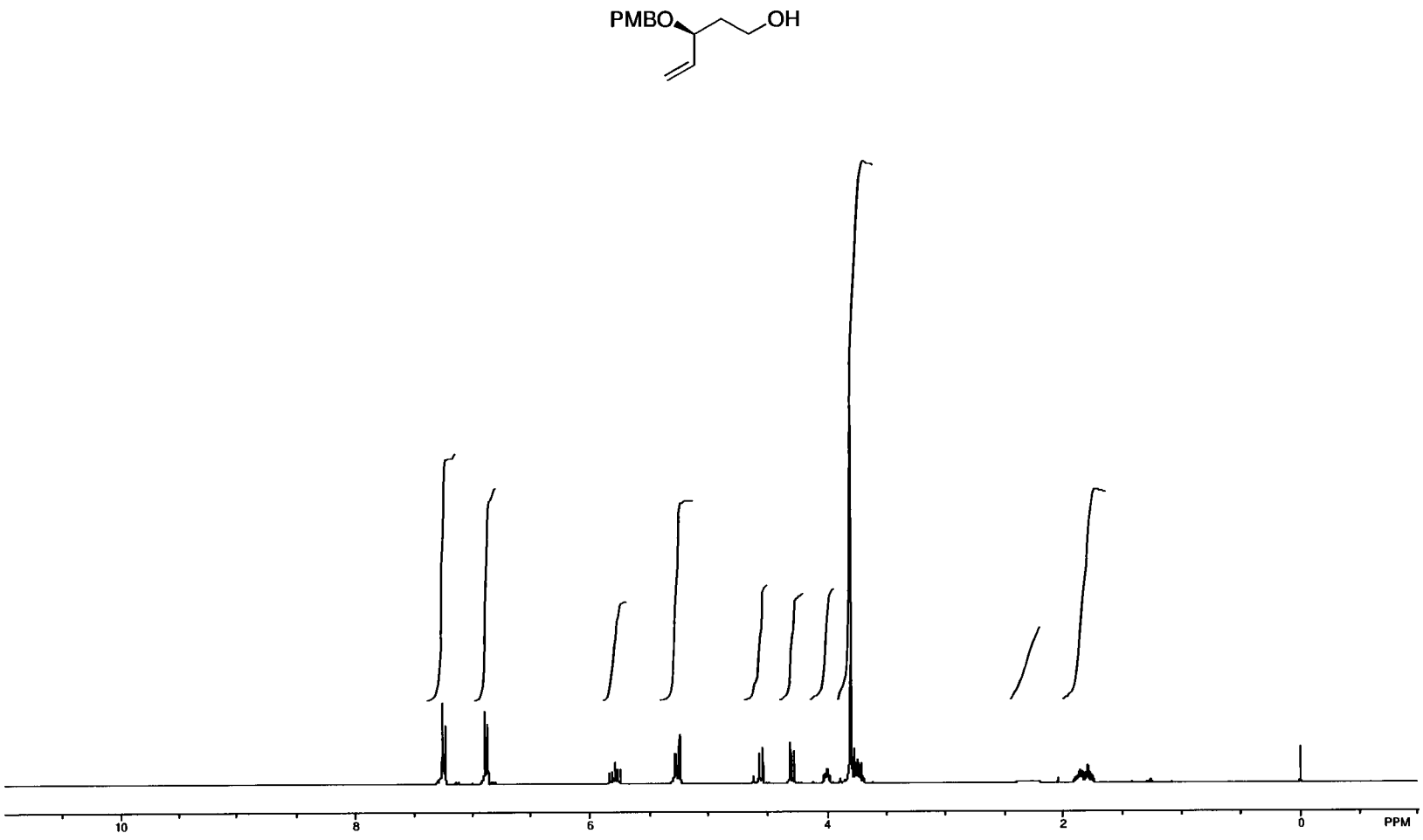


Figure A2.61 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **108**.

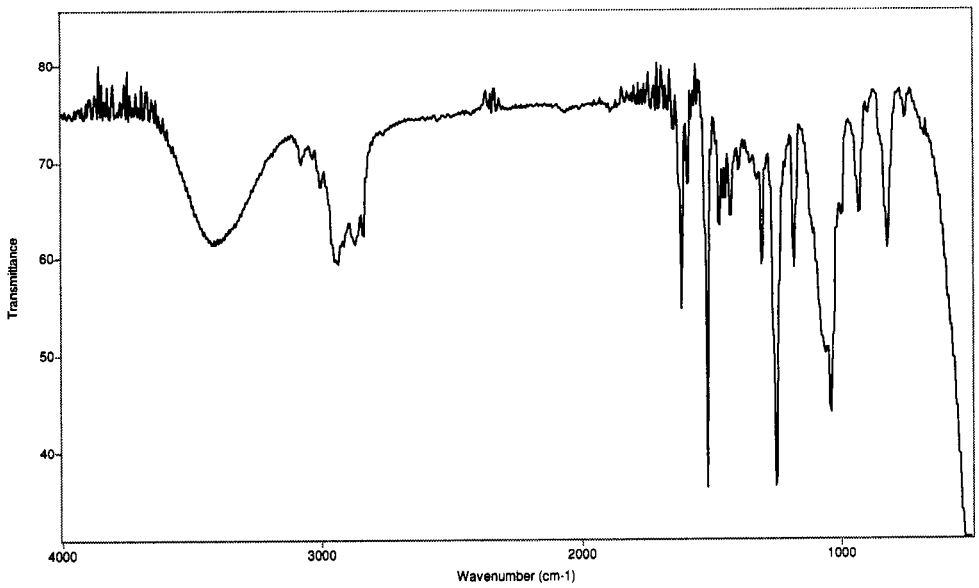


Figure A2.62 IR spectrum (thin film/NaCl) of compound **108**.

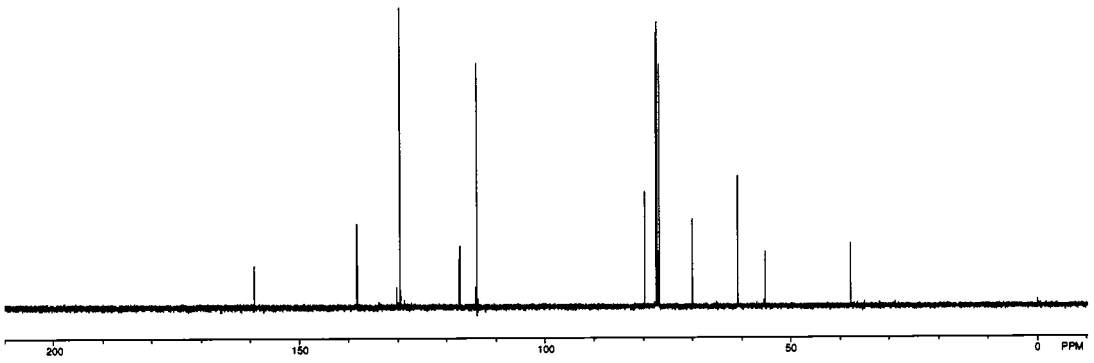


Figure A2.63 ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **108**.

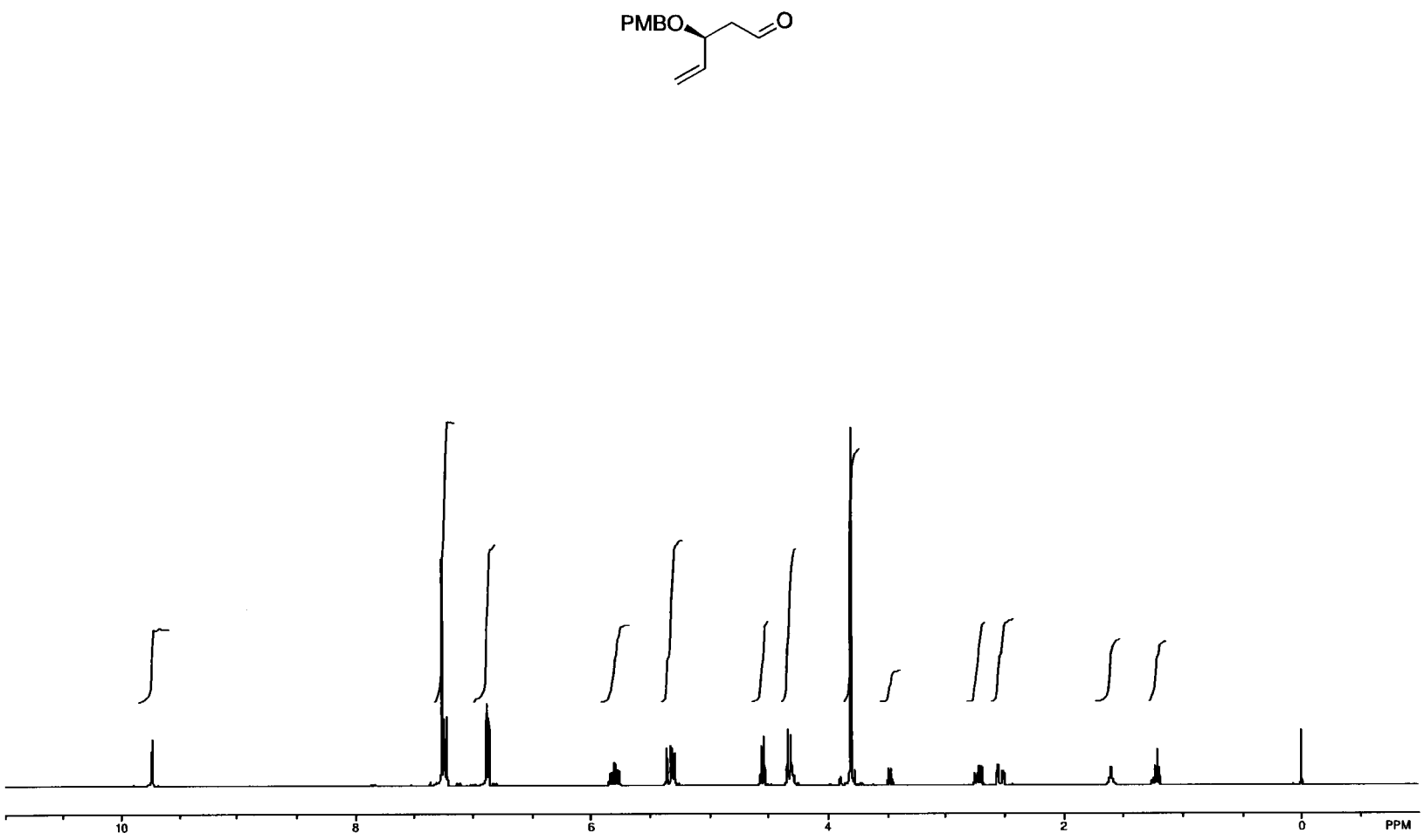


Figure A2.64 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **109**.

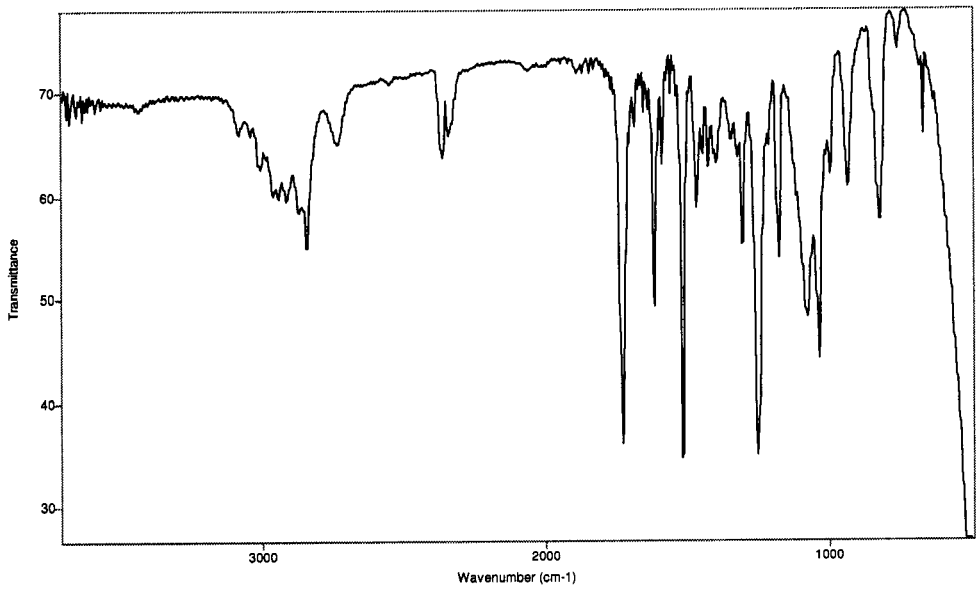


Figure A2.65 IR spectrum (thin film/NaCl) of compound **109**.

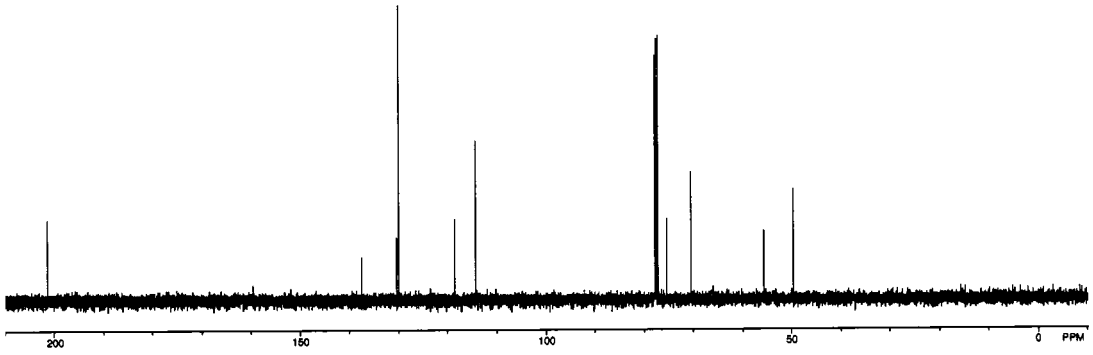


Figure A2.66 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **109**.

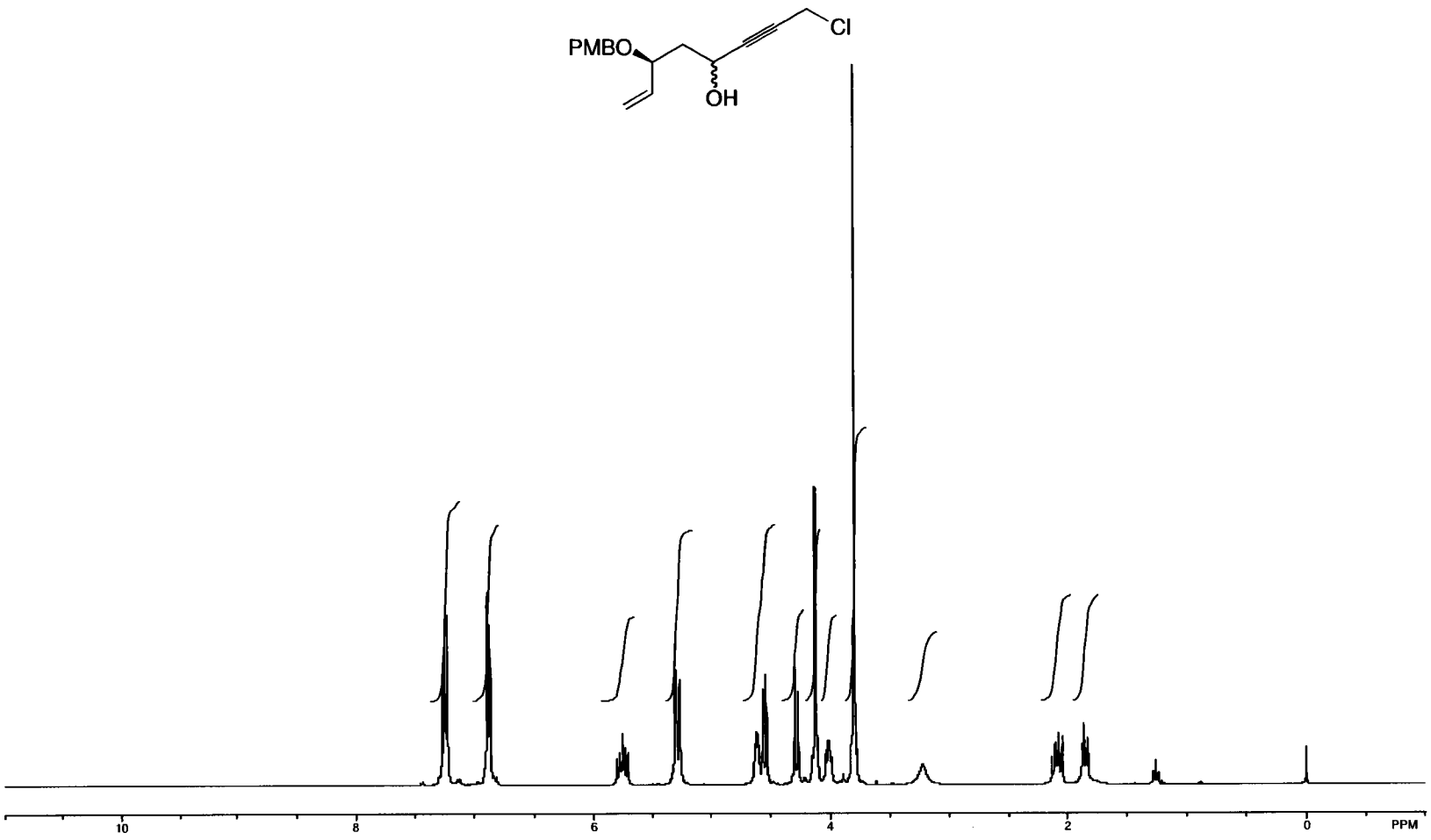


Figure A2.67 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **110**.

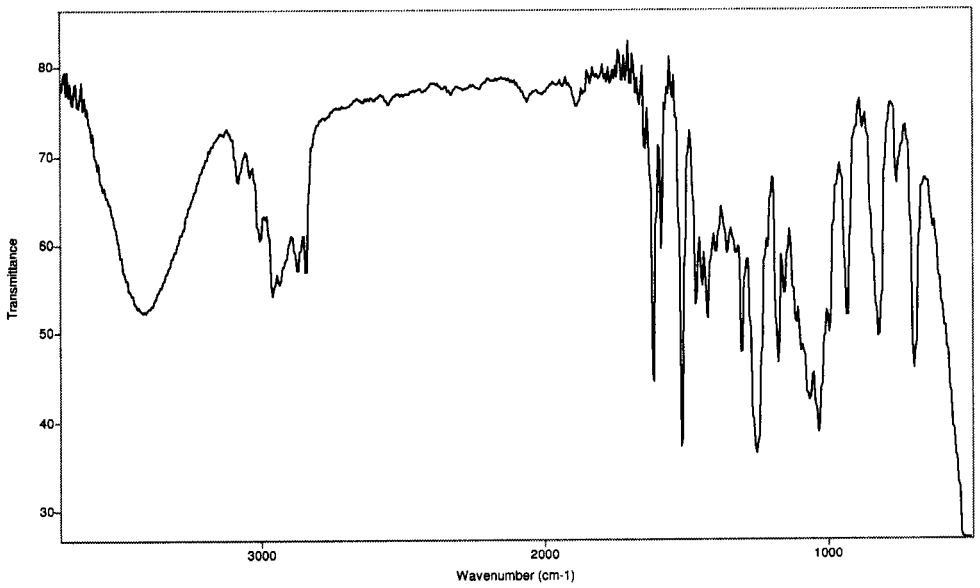


Figure A2.68 IR spectrum (thin film/NaCl) of compound **110**.

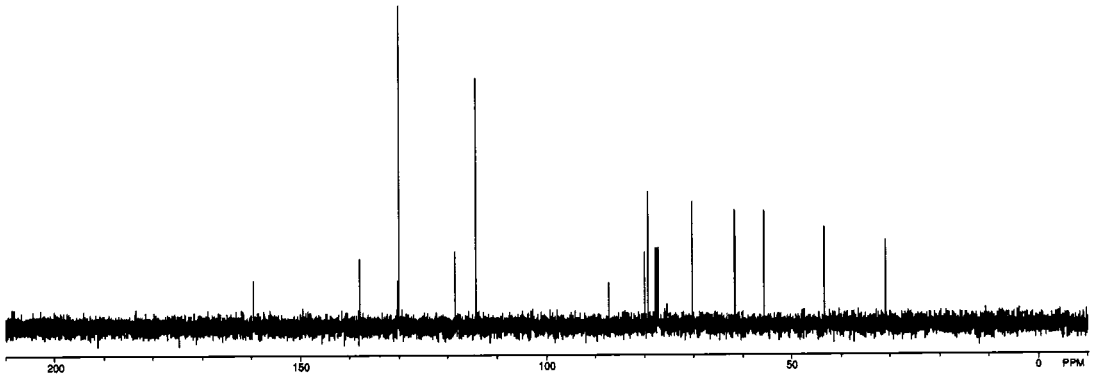


Figure A2.69 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **110**.

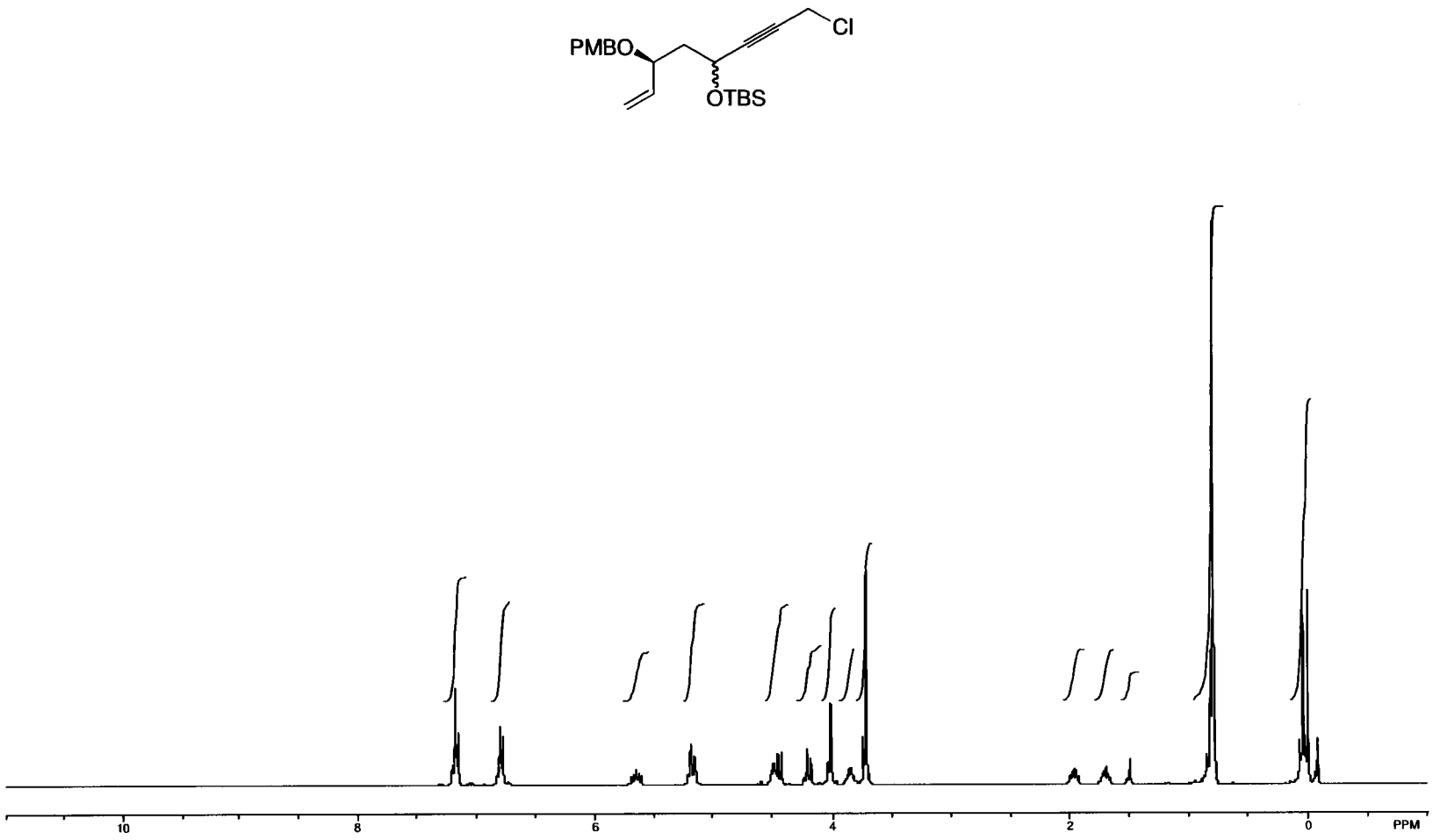


Figure A2.70 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **111**.

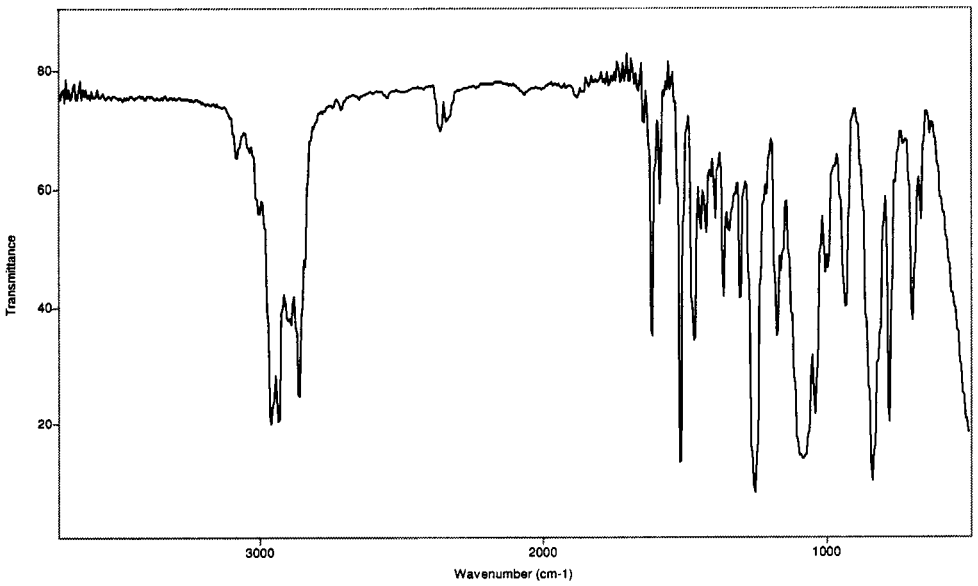


Figure A2.71 IR spectrum (thin film/NaCl) of compound **111**.

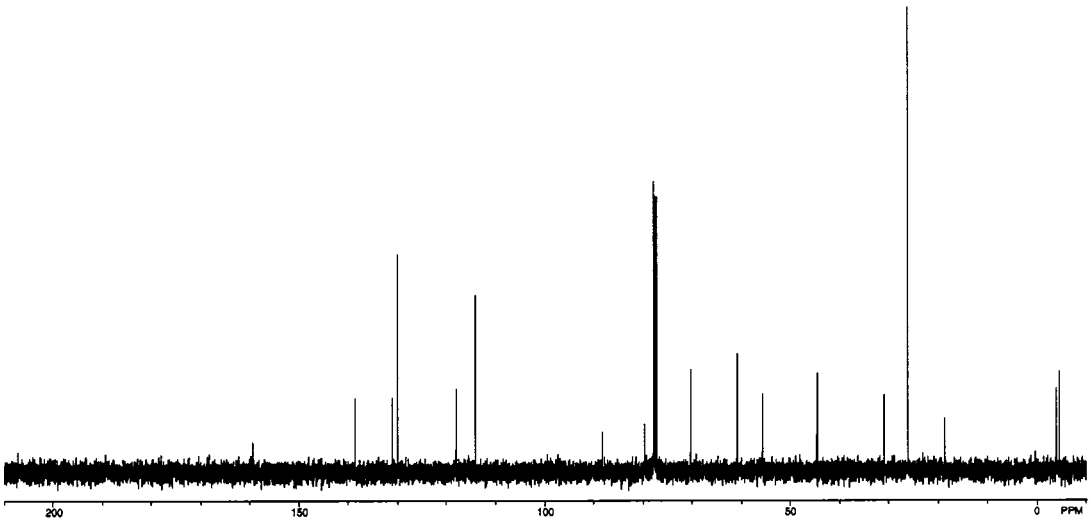


Figure A2.72 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **111**.

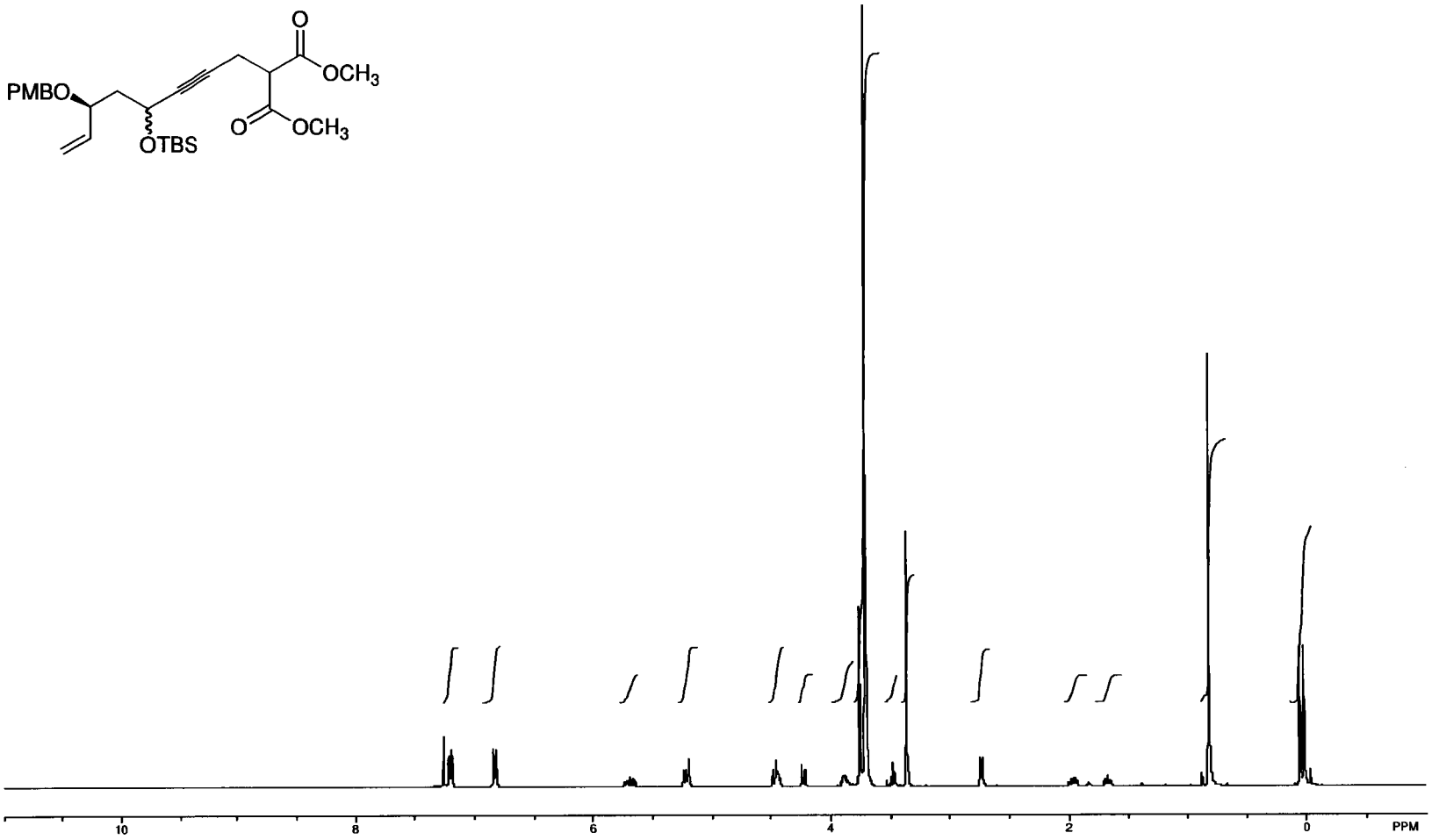


Figure A2.73 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **112**.

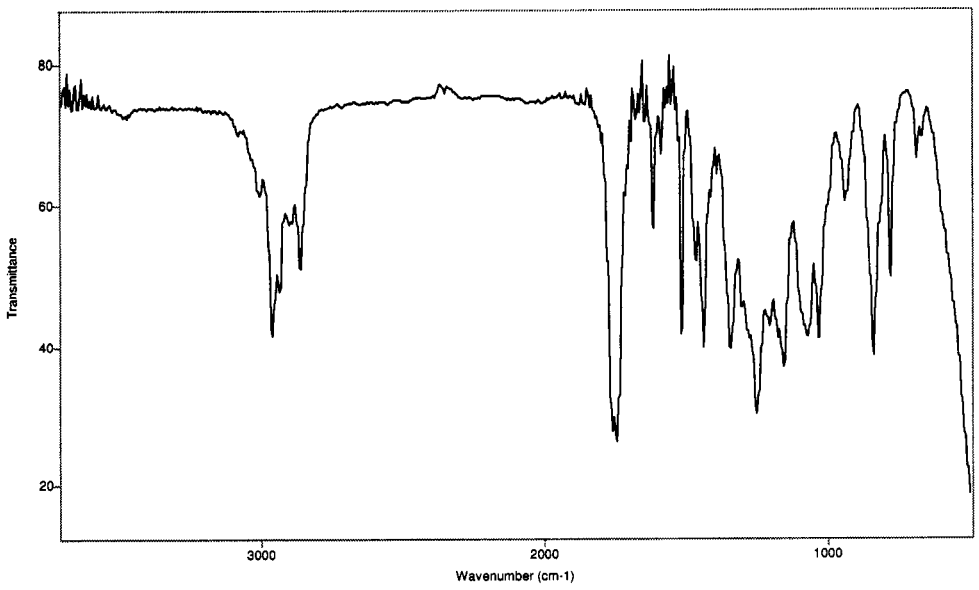


Figure A2.74 IR spectrum (thin film/NaCl) of compound **112**.

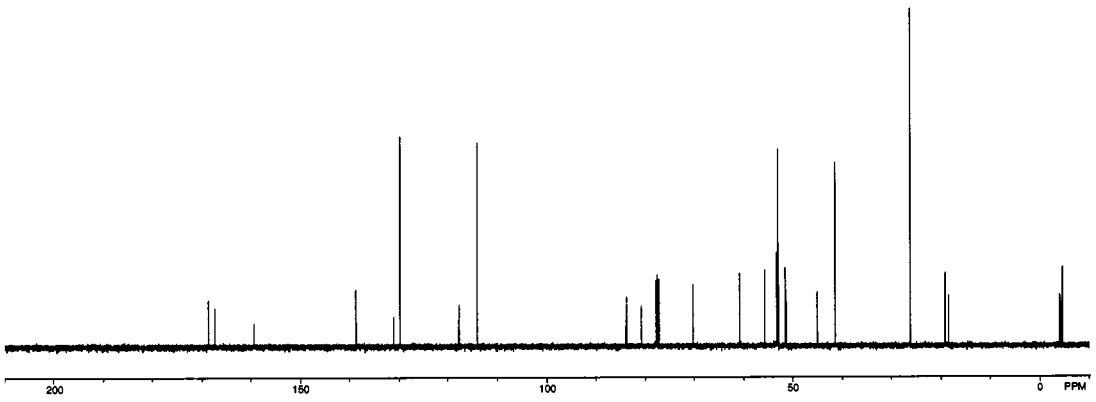


Figure A2.75 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **112**.

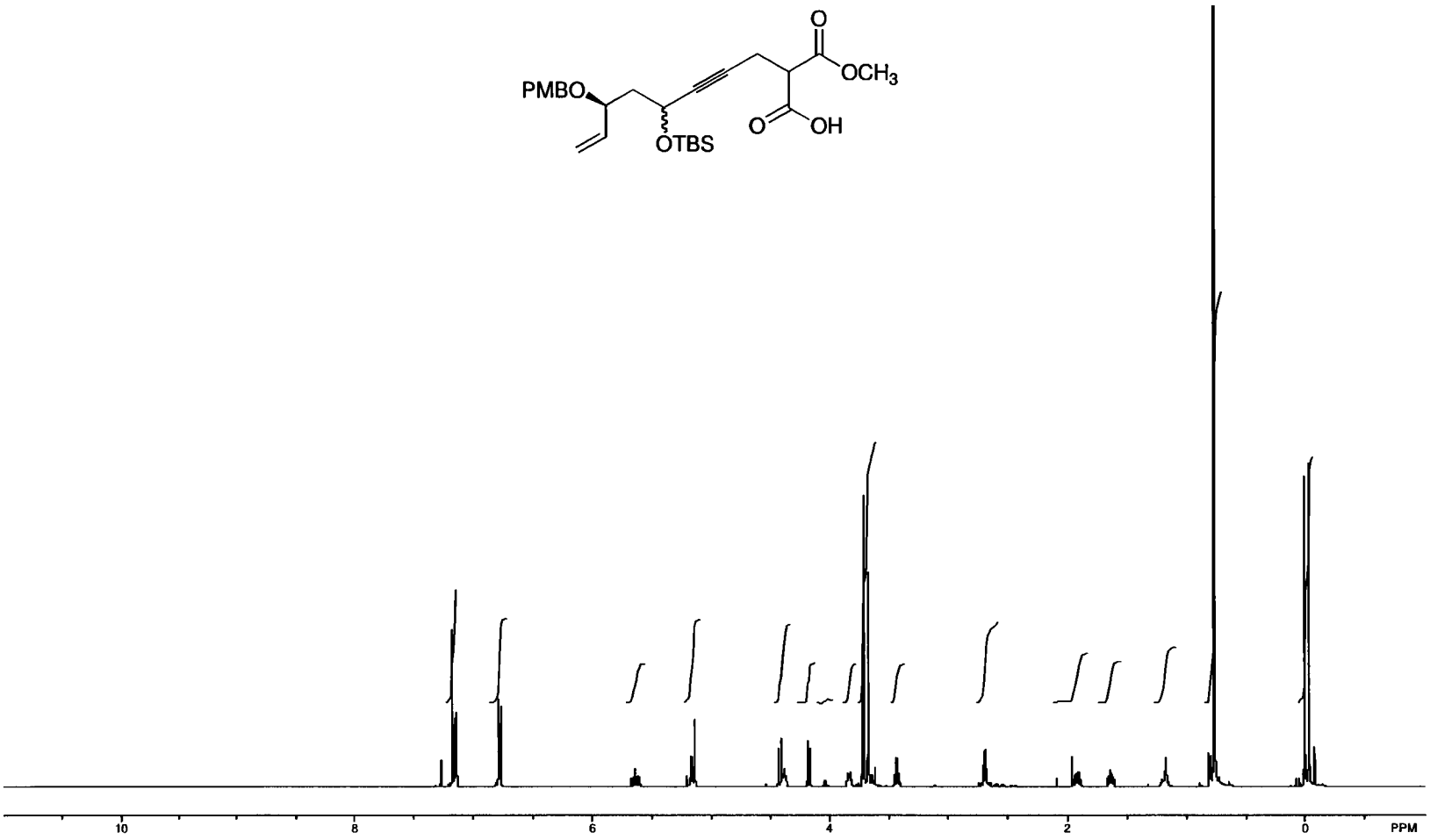


Figure A2.76 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **113**.

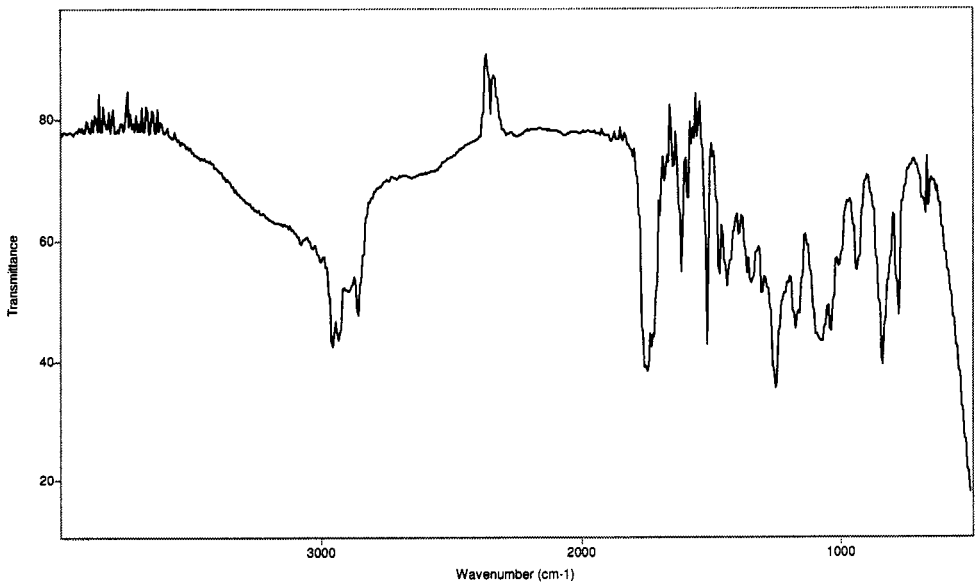


Figure A2.77 IR spectrum (thin film/NaCl) of compound **113**.

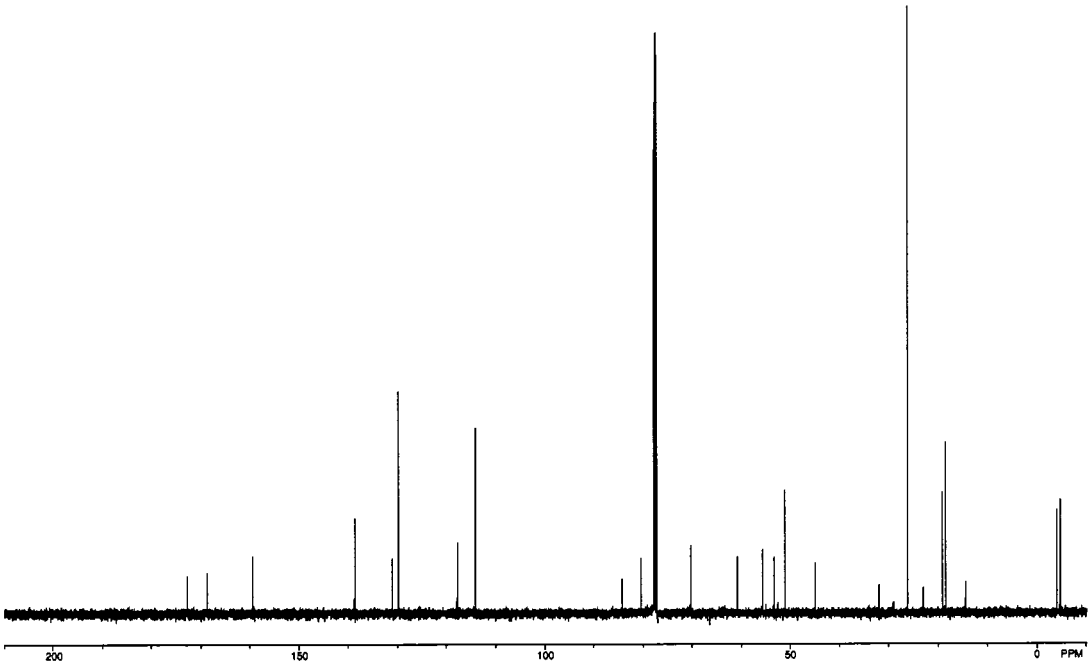


Figure A2.78 ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **113**.

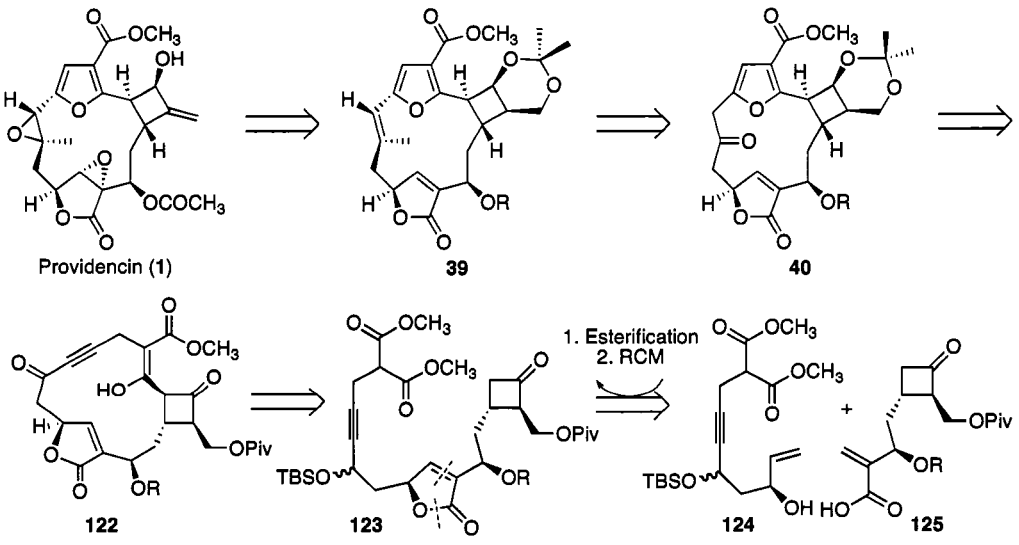
Chapter 3

Assembly of Providencin Framework. Part B. Future Elaboration.

3.1 Retrosynthetic Analysis.

In chapter 2, we synthesized two fragments (**104** and **112**) which once coupled, would have resulted in a substrate possessing most of the providencin (**1**) carbon skeleton along with handles necessary to install the remaining functionalities or oxidation states (*e.i.*, furan, butenolide, etc.). Unfortunately, we were unable to couple the two halves to assemble the macrocyclic skeleton of providencin (**1**). The two key coupling reactions attempted were an intermolecular acylation of a cyclobutanone (Scheme 2.3.6) and a cross metathesis (Scheme 2.3.8 and 2.3.9).

Scheme 3.1.1

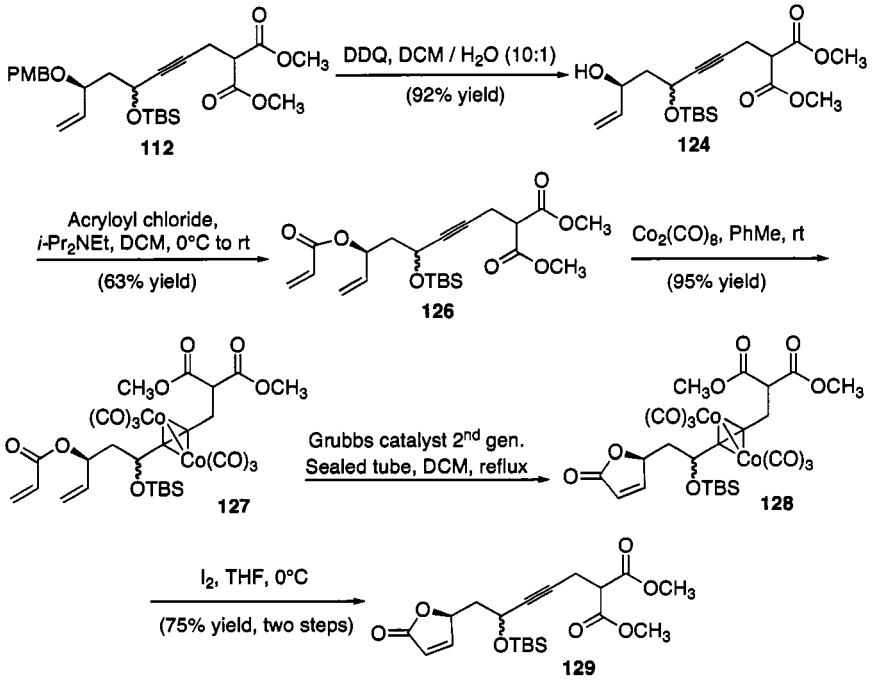


Because of the difficulties encountered with the coupling reactions, we sought a more robust approach to assemble macrocycle **122**. We envisioned the esterification of a "western" allylic alcohol (**124**) with an "eastern" acrylic acid (**125**). This strategy would allow for the intramolecular RCM and efficient delivery of butenolide **123**. The synthesis of butenolides *via* intramolecular olefin metathesis is well precedented in natural product synthesis, therefore we were confident of its success.[1, 2]

3.2 Model Study.

In order to screen the esterification and RCM reaction conditions, we first used acrylic acid as a model. To access the western fragment, we selectively removed the PMB ether using DDQ in a mixture of water and DCM to access allylic alcohol **124**.

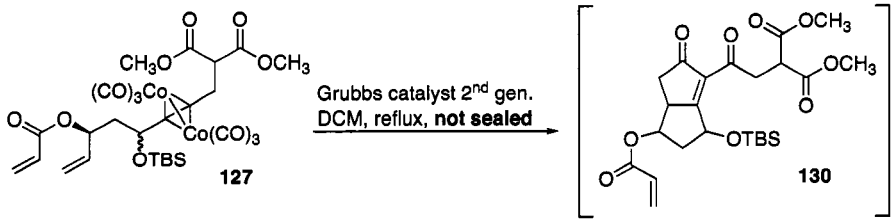
Scheme 3.2.1



We found that alcohol **124** could not be effectively esterified with acrylic acid in the presence of DCC coupling reagent. Instead, we used acryloyl chloride with Hünig's base in DCM at 0°C to obtain acrylate **126** in 63% yield. To prevent enyne metathesis, we protected alkyne **126** as the corresponding dicobalt hexacarbonyl cluster **127**, before carrying out the RCM in DCM utilizing Grubbs second generation catalyst (**I**, Scheme 2.3.7) in a sealed vessel. Butenolide **129** was obtained, after alkyne deprotection using iodine in THF at 0°C, in 75% overall yield from diene **126**.

During our optimization work of the RCM, we observed a side reaction. When exposing diene **127** with Grubbs catalyst in refluxing DCM at atmospheric pressure, an unusual product was isolated. This side-product was no longer complexed to cobalt and appeared to result from a Pauson-Khand-type reaction. Indeed, when the reaction was performed at atmospheric pressure, the dicobalt hexacarbonyl cluster **127** could release a molecule of CO, the initial step in a Pauson-Khand reaction. The loss of a carbonyl allowed the rearrangement into a polycycle. In depth NMR experiments (COSY, HMBC, HMQC, DEPT 90 and 135) allowed us to tentatively propose the structure to be bicycle **130**. We could not obtain a crystal structure to fully support this hypothesis and mechanism.

Scheme 3.2.2

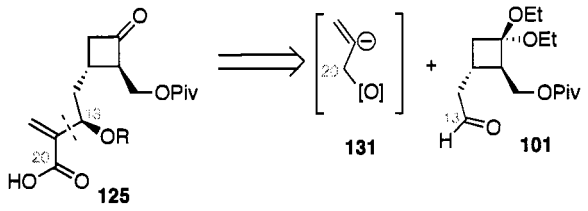


Luckily, this unexpected rearrangement could be avoided when the RCM was performed in a sealed tube, precluding the CO release.

3.3 Progress Toward Cyclobutane 125.

Having gained a better understanding of the reactions leading to the butenolide construction, we were poised to make a more functionalized eastern substrate, which possessed the cyclobutanone appended to the acrylic moiety (**125**). The strategies undertaken to access the desired substituted acrylic acid **125** are discussed below. The disconnection envisioned involved the addition of vinylic anion synthon **131** into aldehyde **101**.

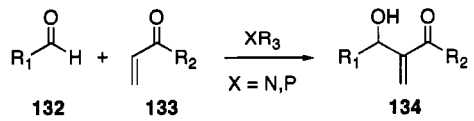
Scheme 3.3.1



3.3.1 Baylis-Hillman Coupling Reaction.

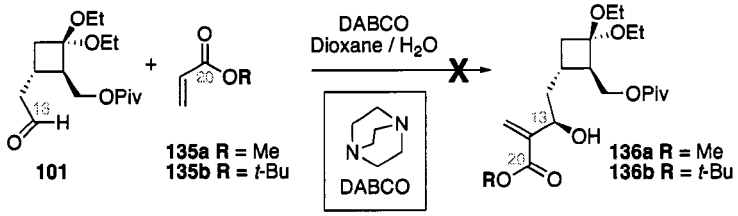
We recognized that the Baylis-Hillman reaction would deliver the highly functionalized acrylate (**134**) needed. The Baylis-Hillman reaction is catalyzed by a tertiary amine, coupling of an aldehyde (**132**) with an α,β-unsaturated carbonyl compound (**133**).[3]

Scheme 3.3.2



In recent years, the reaction conditions have been optimized to accelerate the coupling, improve conversion, and suppress aldehyde polymerization.[4-6] Also, the Baylis-Hillman coupling reaction can be performed enantioselectively,[7-9] which would potentially allow us to set the C13-stereocenter.

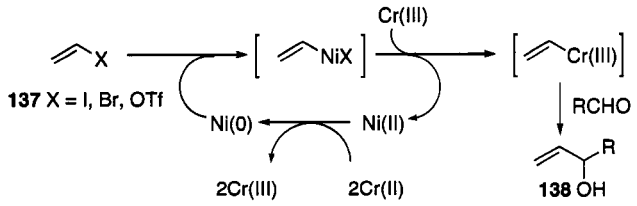
Scheme 3.3.3



We performed the Baylis-Hillman on aldehyde **101**, however no coupling was observed after several days, only aldehyde **101** was recovered. After careful review of the literature, we explored various conditions to modulate this reaction, such as temperature, additives, and solvent mixtures. Despite these variations, only aldehyde **101** was recovered.

3.3.2 Nozaki-Kishi Coupling Reaction.

Scheme 3.3.4

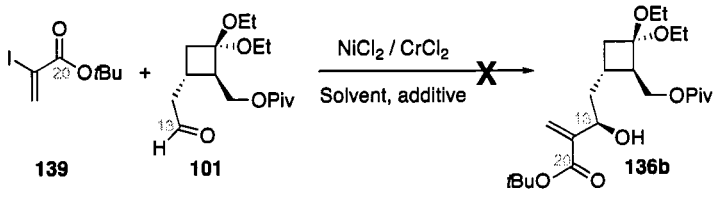


Independently developed by Nozaki[10] and Kishi[11], the nickel-catalyzed one-pot Barbier-type reaction allowed for the coupling of vinyl halides (or triflates) **137** and

aldehydes under mild condition. Recent reports have also shown that the reaction can be performed enantioselectively.[12-15]

The Ni(II)/Cr(II)-mediated coupling was attempted between vinyl iodide **139**[16] and aldehyde **101**. After screening reaction conditions,[17] we believe that we may have oxidatively added Cr(II) to alkenyliodide **139**, as we observed the disappearance of the alkenyl iodide by TLC. We used deoxygenated DMF to solubilize the Cr(II) salts, which increased the reducing ability; a dark green mixture was obtained. Amine additives, such as bispyridinyl and 4-*t*-butylpyridine, were utilized to help solubilize Cr(II) and suppress homocoupling of the alkenyliodide.[18] We also varied the number of equivalents of $NiCl_2$ and $CrCl_2$ but never observed addition of the alkenylchromium reagent to aldehyde **101**. This lack of success and the frequent decomposition of aldehyde **101**, prompted us to abandon this route.

Scheme 3.3.5



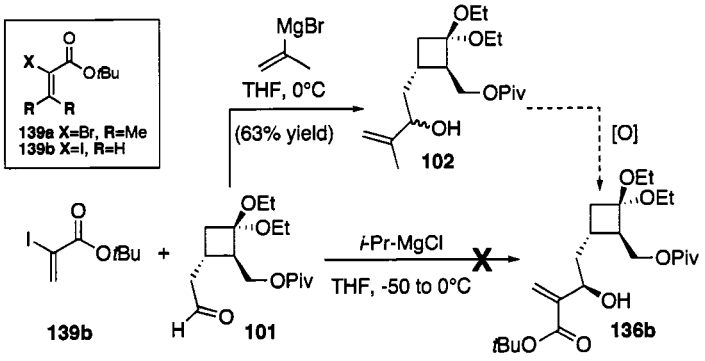
139 **101** **136b**

3.3.3 Other Strategies.

With aldehyde **101** in hand, we explored other strategies to use this advanced intermediate. We had successfully added a vinyl Grignard to aldehyde **101** to obtain alcohol **102** (Chapter 2, Section 2.3.1), however we were unable to cleanly oxidize the allylic position of **102** to access an acrylate (mixture of enones and ketal deprotection). However, to take advantage of the reactivity of aldehyde **101** with Grignard reagents

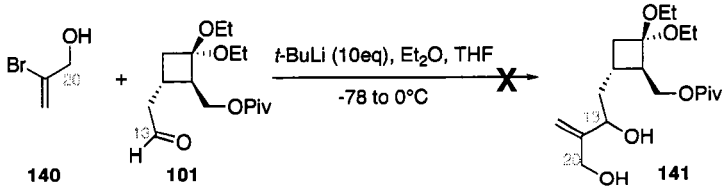
while introducing the C-20 oxidation, we turned to Knochel's preparation of highly functionalized organomagnesium reagents: a sequence that can be performed in the presence of carbonyls. Indeed, Knochel's method uses isopropylmagnesium bromide (or chloride) to generate acrylic Grignards from corresponding halides (*e.g.*, **139a**), the resulting magnesium compound can react with a range of electrophiles such as benzaldehyde, benzoyl chloride and crotonaldehyde.[19, 20]

Scheme 3.3.6



When vinyl iodide **139b** was treated with isopropylmagnesium chloride, the reaction produced a mixture of unidentified products. The main difference between Knochel's substrate (**139a**) and **139b** is the β-substitution of the acrylate (R = H *vs* Me). Acrylate **139b** may be susceptible to polymerization.

Scheme 3.3.7

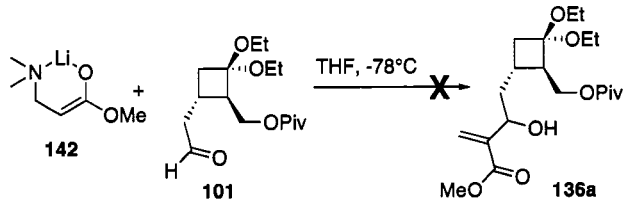


We continued exploring this strategy by attempting the addition of a vinyl nucleophile bearing an allylic methyl (C-20) already oxidized (**131**, Scheme 3.3.1). Corey's *O*,2-dilithio derivative of allyl alcohol **140**, $H_2C{=}C(Li)CH_2O^-Li^{+}$[21] was

generated, however a mixture of unidentified products was produced after addition of aldehyde **101** (Scheme 3.3.6).

Still focusing on synthon **131**, we planned to use reagent **142** (Scheme 3.3.7), which, in the progress toward the total synthesis of phomoidride B, Wood *et al.* could add to a hindered ketone, then eliminate the amine and deliver an acrylate.[22] Applying these conditions to our aldehyde **101** did not provide us with **136a**, and starting material was recovered.

Scheme 3.3.8

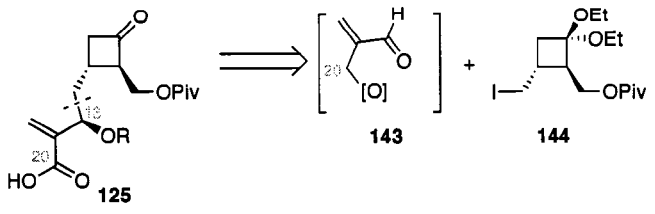


3.4 Future Elaboration.

This section will describe other strategies that could be considered to assemble the polycyclic framework of providencin (**1**). Some exploratory work has already been performed on a few approaches and is indicated when appropriate.

3.4.1 Reversal of the Coupling Partners.

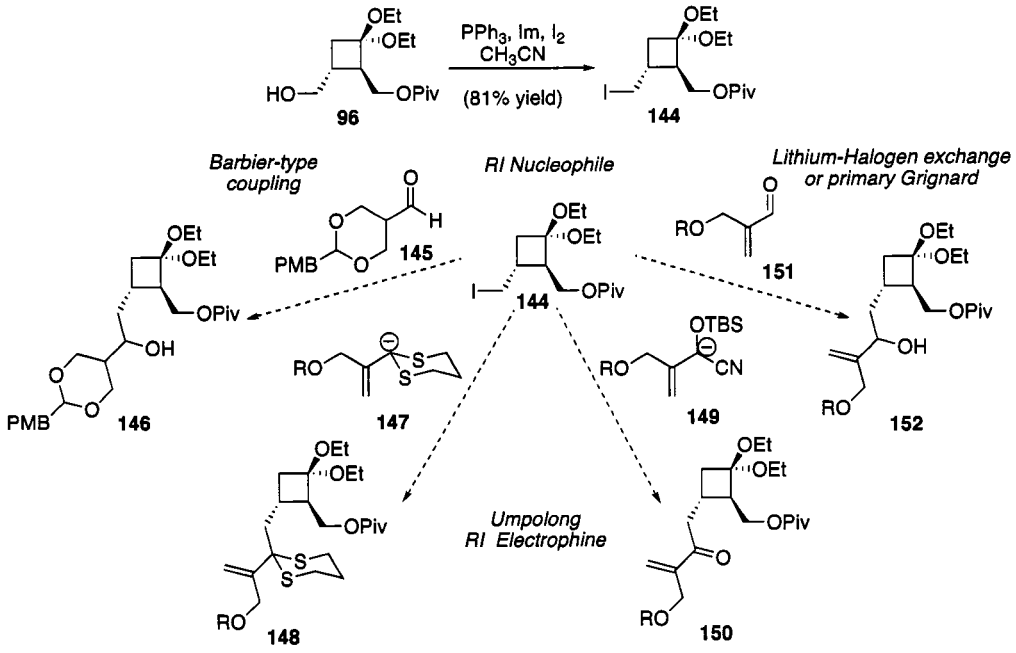
Scheme 3.4.1



Having no success with the assembly of acrylate **125**, we considered reversing the roles by using alkyl halide **144** and aldehyde synthon **143**, disconnecting between C12 and C13 (Scheme 3.4.1).

Pursuing this approach, we proceeded to generate alkyl iodide **144** from alcohol **96** by exposure to iodine, imidazole, and triphenylphosphine in acetonitrile (Scheme 3.4.2). With alkyl iodide **144** in hand, we had the option of either performing a Barbier type coupling between iodide **144** and aldehyde **145**,[23] or carrying out a lithium halogen exchange of primary halide **144** to add into aldehyde **151**.[24]

Scheme 3.4.2

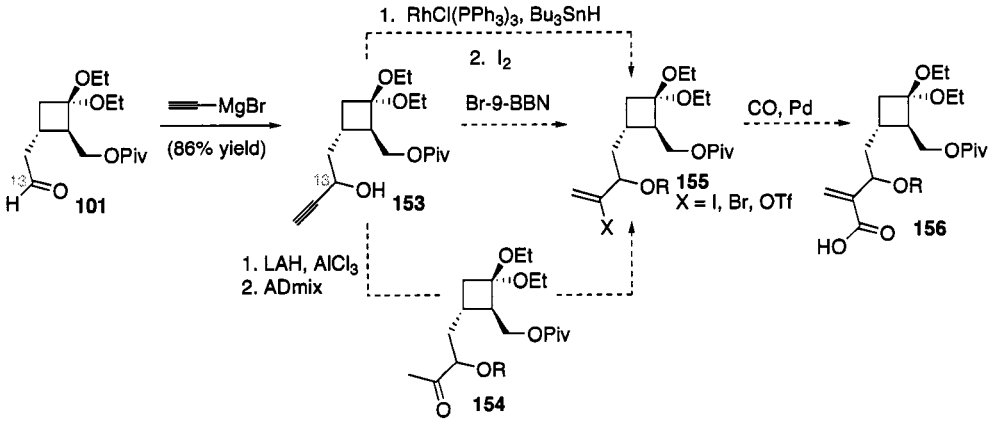


Alternatively, we could attempt a nucleophilic displacement of iodide **144** with a masked acyl anion generated from dithiane **147** or cyanohydrin **149**. Preliminary studies of these reactions have begun and will be pursued beyond the work described in this thesis.

3.4.2 Utilizing a Propargyl Precursor to 125.

We were able to access propargylic alcohol **153** in 86% yield, which offered diverse options to prepare acrylate **156**. From **153**, we envisioned accessing a vinyl halide or triflate (**155**) that would allow a palladium-mediated carbonylation and provide acrylate **156** (Scheme 3.4.3). Hydrobromination of alkyne **153** did not generate a vinyl bromide (**155**, X = Br) and the starting material was recovered. An alternative approach could be to synthesize a vinyl stannane from which the corresponding vinyl iodide (**155**, X = I) could be obtained.[25] Alternatively, a vinyl triflate (**155**, X = OTf) could be obtained from α-hydroxyketone **154**, which in turn would come from the dihydroxylation of an allene generated from propargylic alcohol **153**.[26]

Scheme 3.4.3

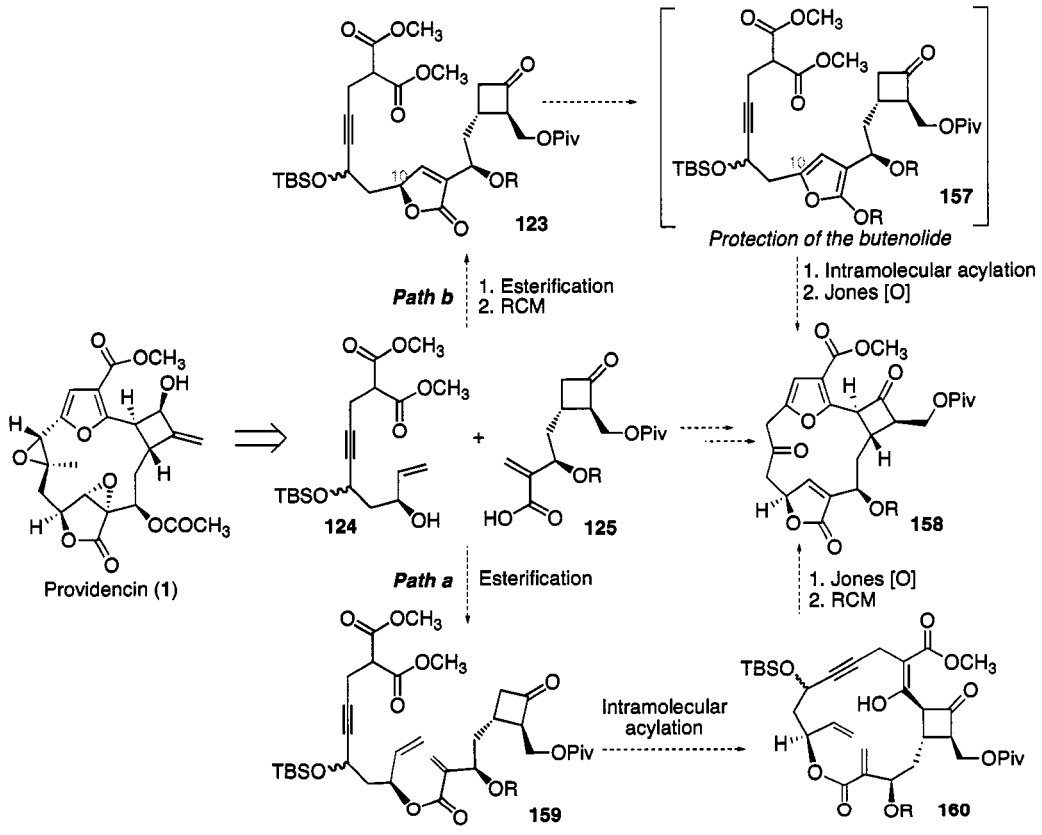


Methods to access substituted acrylic acid **156** have not been exhausted, and we believe that gaining access to this substructure (**156**) will allow for the coupling with the western fragment, and further advancement to the macrocyclic skeleton of providencin.

3.4.3 Strategies to Couple the Two Halves of Providencin.

Once the two fully functionalized fragments (**124** and **125**) are obtained, they could be coupled *via* esterification followed by macrocyclization. The preferred path (***Path a***) would be to make the macrocycle and furan prior to the butenolide moiety (Scheme 3.4.4). Malonate **159** could be monohydrolyzed, the resulting acid treated with thionyl chloride and base to form macrocycle **160**. The furan and butenolide moieties comprised in skeleton **158** would be obtained after Jones oxidation and RCM.

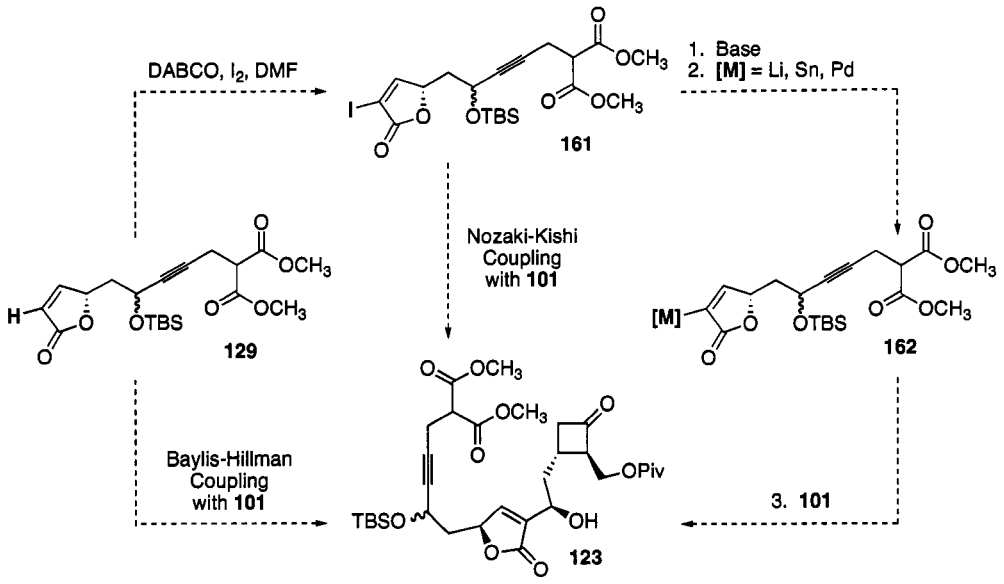
Scheme 3.4.4



The alternative path (***Path b***) to macrocycle **158**, would be to perform the RCM following the esterification to obtain butenolide **123**. This approach would have the

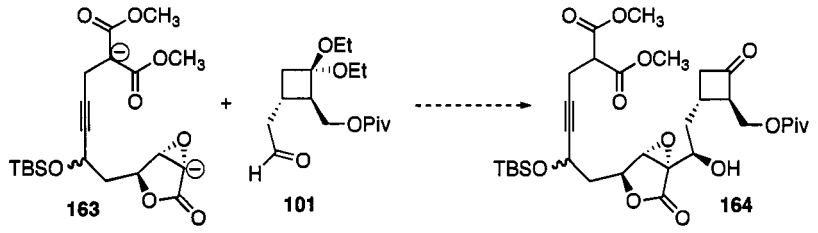
advantage of rigidifying the long carbon chain. Butenolide **123** would require to be protected; making the corresponding extended enol ether **157** would unfortunately destroy the C10 stereochemistry. Next, monohydrolysis of malonate **157**, followed by treatment with thionyl chloride and base would allow intramolecular acylation of the cyclobutanone. Treatment with Jones reagent would remove the extended enol ether, TBS group and oxidize the propargylic alcohol to the alkynone to deliver furan **158**. The disconnection of **123** could also be envisioned as the result of the nucleophilic addition of a butenolide (**129**, **161**, or **162**) to aldehyde **101** (Scheme 3.4.5).

Scheme 3.4.5



Alternatively, deprotonation of epoxide **163**, prepared from butenolide **129** (Scheme 3.4.6), could allow its addition to aldehyde **101**. Anions of epoxylactones have been shown to add to a variety of aldehydes such as benzaldehyde, propionaldehyde and 2-methylcrotonyldehyde.[27] The disadvantage of making an epoxide so early on in the synthesis, would be the need to carry labile intermediates over several steps.

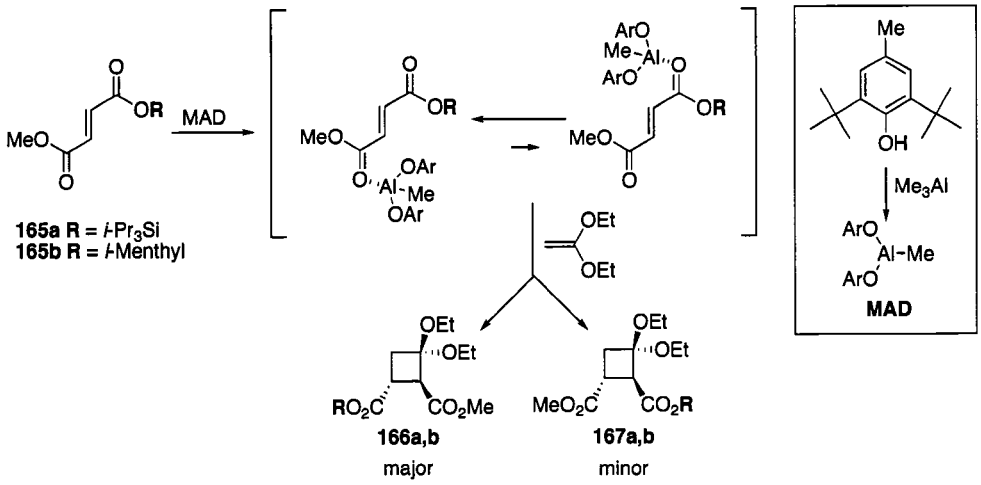
Scheme 3.4.6



3.4.4 Improvements to the Existing Sequence.

One of the areas that would warrant further optimization would be the cyclobutane preparation. Specifically, the differentiation of diol **50** has proven difficult, forcing us to rely on a protection / deprotection-recycling sequence of the undesired products (Scheme 2.3.2). Because of the need to access large quantities of a monoprotected diol, a regiocontrolled [2+2] cycloaddition of unsymmetrical fumarate could be useful. Yamamoto *et al.* have shown that high regiocontrol can be achieved by selective complexation with exceptionally bulky methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide), MAD (Scheme 3.4.5),[28, 29] these conditions may prove useful in this case. Gaining access to the major regioisomer **166**, would allow selective manipulation of the mixed diester. This cycloaddition can also be performed with enantiopure *l*-menthyl methyl fumarate (**165b**), which could provide enantiopure material.

Scheme 3.4.7

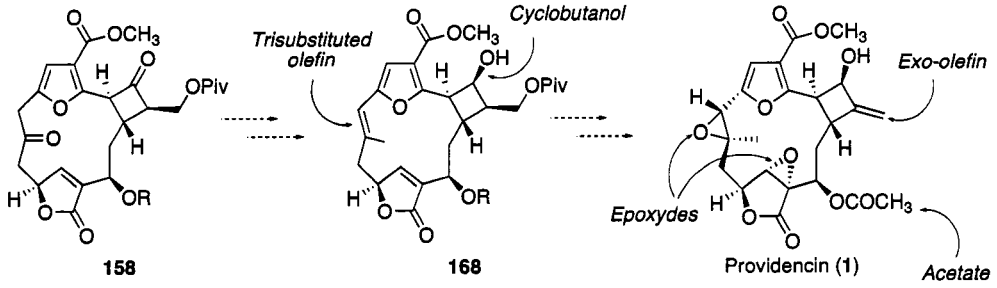


Gaining access to the major regioisomer **166**, would allow selective manipulation of the mixed diester. This cycloaddition can also be performed with enantiopure *l*-menthyl methyl fumarate (**165b**), which could provide enantiopure material.

3.4.5 Remaining Challenges.

Once the polycyclic core of providencin (**1**) is obtained (*e.i.,* **158**), the remaining challenges will be to install the tri-substituted and exo-olefins, reduce the cyclobutanone, acylate the C13-alcohol and epoxidize the butenolide and tri-substituted olefins. The order of steps will need to be carefully planned to avoid over oxidation or reduction of the different intermediates. Marshall has shown that enol triflates could be generated from the corresponding β-ketofuran, which could subsequently be methylated.[30] The exo-olefin should be installed after the epoxidation of the butenolide and tri-substituted olefins. We have already demonstrated that the cyclobutanone could be diastereoselectively reduced with L-selectride (Scheme 1.3.1).

Scheme 3.4.8



3.5 Conclusion.

Although there still are several remaining challenges to complete the total synthesis of providencin (**1**), we learned how to functionalized the cyclobutane moiety and were able to access acyclic systems (Chapter 2, **76** and **82**) containing most of the carbons and oxidation states in providencin (**1**).

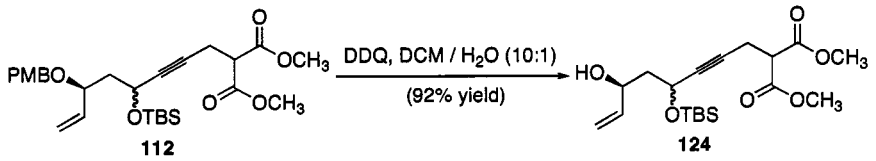
3.6 Experimental Section.

3.6.1 Materials and Methods.

Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). All other commercially obtained reagents were used as received. All reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F254 pre-coated plates (0.25 mm). Column or flash Chromatography[31] was performed with the indicated solvents using silica gel (particle size 35 -75 mm) purchased from Silicycle. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Advance DPX-500 or Bruker Advance DPX-400 spectrometers. Chemical shifts are reported relative to internal chloroform (^{1}H δ 7.26 ppm, ^{13}C δ 77.00 ppm), methanol (^{1}H δ 3.31 ppm, ^{13}C δ 49.00 ppm). High resolution mass spectra were acquired at The University of Illinois Mass Spectrometry Center.

3.6.2 Preparative Procedures.

Preparation of Allylic Alcohol 124:

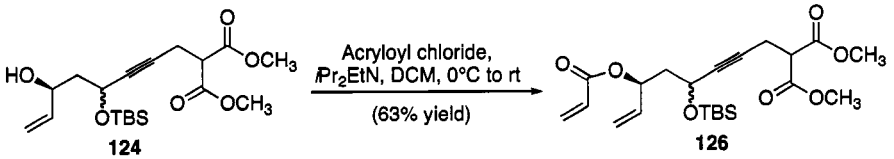


112 **124**

To a solution of protected PMB ether **112** (0.11 g, 0.22 mmol) in a mixture of DCM (9 mL) and water (0.5 mL) was added DDQ (9.0 mg, 0.40 mmol). The reaction was completed after 30 min and was then absorbed onto silica gel to be purified by flash

chromatography (gradient elution, 10→20% EtOAc/Hexanes) to yield the title compound **124** (81 mg, 86% yield) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77-5.69 (m, 1H), 5.15 (dt, *J* = 17.2, 1.5 Hz, 1H), 4.97 (dt, *J* = 10.5, 1.4 Hz, 1H), 4.45-4.42 (m, 1H), 4.23-4.18 (m, 1H), 3.63 (s, 6H), 3.44 (t, *J* = 7.7 Hz, 1H), 2.69 (dd, *J* = 7.8, 1.9 Hz, 2H), 1.80-1.63 (m, 2H), 0.77 (s, 9H), 0.02 (s, 3H), 0.0 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.66, 140.68, 114.81, 83.65, 81.49, 71.51, 62.59, 53.18, 51.34, 45.65, 26.13, 19.19, 18.42, -3.96, -4.72; IR (thin layer, NaCl) 3477 (br, w), 2956 (m), 2930 (m), 2587 (m), 1742 (s), 1472 (m), 1436 (m), 1342 (m), 1253 (s), 1084 (s) cm^{-1}; HRMS (ES) *m/z* found 385.21, calc'd for $C_{19}H_{33}O_6Si$ [M+H]: 385.21.

Preparation of Acrylate 126:

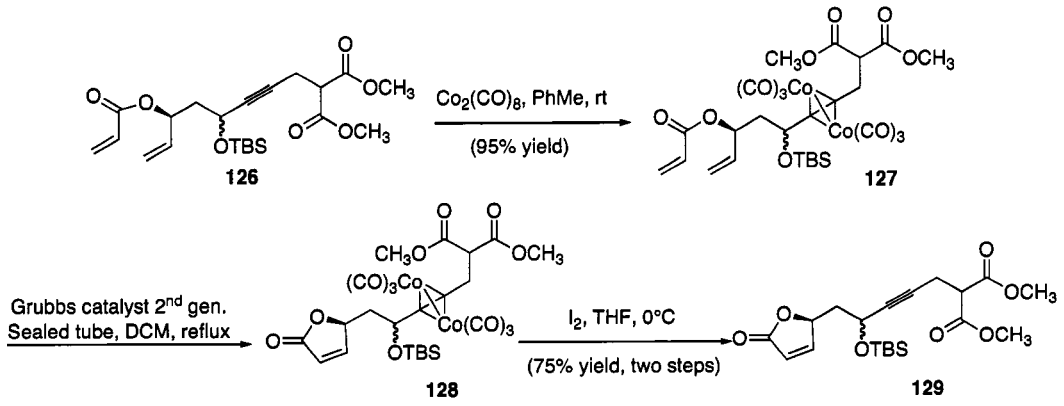


124 **126**

To a solution of allylic alcohol **124** (60 mg, 0.19 mmol) in DCM (5 mL) were added *i*Pr_2EtN (0.16 mL, 0.9 mmol) and acryloyl chloride (36 μL, 0.45 mmol) at 0°C. The reaction mixture was slowly warmed up to room temperature, quenched after 1h with NH_4Cl (saturated in water) and diluted with DCM; the biphasic solution was separated, and the aqueous phase was extracted two more times with DCM. The organic phases were combined, dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (gradient elution, 5→10% EtOAc/Hexanes) to yield the title compound **126** (44 mg, 64% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (dt, *J* = 17.4, 0.7 Hz, 1H), 6.04 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.79-5.69 (m,

1H), 5.75 (d, J = 11.2 Hz, 1H), 5.37 (q, J = 6.21 Hz, 1H), 5.20 (d, J = 17.2, 1H), 5.12 (d, J = 10.5 Hz, 1H), 4.30 (t, J = 6.8 Hz, 1H), 3.68 (s, 6H), 3.49 (t, J = 7.7 Hz, 1H), 2.72 (dd, J = 7.7, 1.8 Hz, 2H), 2.07-1.97 (m, 2H), 1.88-1.80 (m, 1H), 0.81 (s, 9H), 0.03 (s, 3H), 0.0 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.71, 165.48, 136.25, 131.12, 129.03, 128.74, 117.64, 83.31, 81.27, 72.53, 60.36, 53.21, 51.39, 43.62, 26.17, 19.20, 18.54, -4.04, -4.67; IR (thin layer, NaCl) 2956 (m), 2930 (m), 2857 (m), 1758 (s), 1742 (s), 1675 (w), 1473 (w), 1462 (w), 1437 (m), 1406 (m), 1343 (w), 1268 (m), 1189 (s), 1094 (m), 1043 (w) cm^{-1}; HRMS (ES) *m/z* found 461.20, calc'd for $C_{22}H_{34}O_7SiNa$ [M+Na]: 461.21.

Preparation of Butenolide 129:



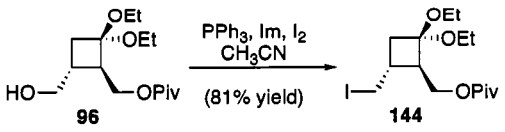
To a solution of diene **126** (55 mg, 0.13 mmol) in toluene (5 mL) was added Co_2CO_8 (58 mg, 0.17 mmol), the reaction turned brick red. After 1 h, the reaction mixture was absorbed onto silica gel to be purified by flash chromatography (gradient elution, 5→10% EtOAc/Hexanes) to yield the cobalt complex **127** as a red solid (86 mg, 95% yield).

To a solution of the complex **127** (12 mg, 17 μmol) in DCM (2 mL) was added Grubbs's 2nd generation cat (8.5 mg, 10 μmol) and the reaction mixture was heated to

reflux temperature in a sealed tube for 2 h. The reaction mixture was absorbed onto silica gel to be purified by flash chromatography (gradient elution, 5→10→20% EtOAc/Hexanes) to yield the butenolide **128** (12 mg, >95% yield) as a red solid.

To a solution of butenolide **128** (12 mg, 17 μmol) in THF (1 mL) was added a solution of I_2 (65 mg, 0.26 mmol) in THF (4 mL) at 0°C. After 30 min, the reaction mixture was diluted with Et_2O and quenched with $NaHSO_4$ (saturated in water); the biphasic solution was separated, and the organic phase was washed with $NaHCO_3$ (saturated in water), NH_4Cl (saturated in water), dried over Na_2SO_4, filtered and rotary evaporated. The crude product was purified by flash chromatography (gradient elution, 10→20% EtOAc/Hexanes) to yield the title compound **129** (4 mg, 59% yield) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (dd, J = 5.7, 1.3 Hz, 1H), 6.08 (dd, J = 5.7, 1.9 Hz, 1H), 5.26 (t, J = 6.7 Hz, 1H), 4.60 (dd, J = 6.7, 5.0 Hz, 1H), 3.75 (s, 6H), 3.58 (t, J = 7.7 Hz, 1H), 2.83 (dd, J = 7.6, 1.8 Hz, 2H), 2.11-2.02 (m, 1H), 1.97-1.88 (m, 1H), 0.88 (s, 9H), 0.12 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.98, 167.20, 156.06, 119.69, 81.00, 79.84, 59.16, 51.83, 49.88, 41.02, 24.69, 17.75, 17.05, -5.62, -6.21; IR (thin layer, NaCl) 2955 (m), 2930 (m), 2857 (m), 1754 (s), 1733 (s), 1436 (m), 1160 (m), 1074 (m) cm^{-1}; HRMS (ES) *m/z* found 411.18, calc'd for $C_{20}H_{31}O_7Si$ [M+H]: 411.18.

Preparation of Alkyl Iodide 144:



To a solution of alcohol **96** (36 mg, 0.12 mmol) in acetonitrile (4 mL) were added PPh_3 (65 mg, 0.25 mmol), imidazole (25 mg, 0.37 mmol) and iodine (63 mg, 0.25 mmol). The reaction was completed after 2 h and was then absorbed onto silica gel to be purified by flash chromatography (10% EtOAc/Hexanes) to yield the title compound **144** (41 mg, 81% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28 (dd, J = 11.3, 7.3 Hz, 1H), 4.11 (dd, J = 11.3, 7.2 Hz, 1H), 3.46-3.39 (m, 5H), 3.22 (t, J = 9.1 Hz, 1H), 2.43 (dd, J = 12.3, 9.0 Hz, 1H), 2.34 (q, J = 7.1 Hz, 1H), 2.20-2.12 (m, 1H), 1.69 (ddd, J = 12.3, 7.6, 0.9 Hz, 1H), 1.21-1.13 (m, 6H), 1.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.44, 97.88, 62.87, 56.89, 56.55, 50.27, 38.71, 37.54, 33.45, 29.70, 27.25, 15.21, 11.67; IR (thin layer, NaCl) 2974 (s), 2928 (s), 1730 (sh, s), 1481 (m), 1457 (m), 1283 (m), 1263 (s), 1158 (s) cm^{-1}; HRMS (ES) *m/z* found 321.09, calc'd for $C_{15}H_{27}O_4INa$ [M+Na]: 421.10.

3.7 Notes and references.

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Appendix A3: Spectra Relevant to Chapter 3.

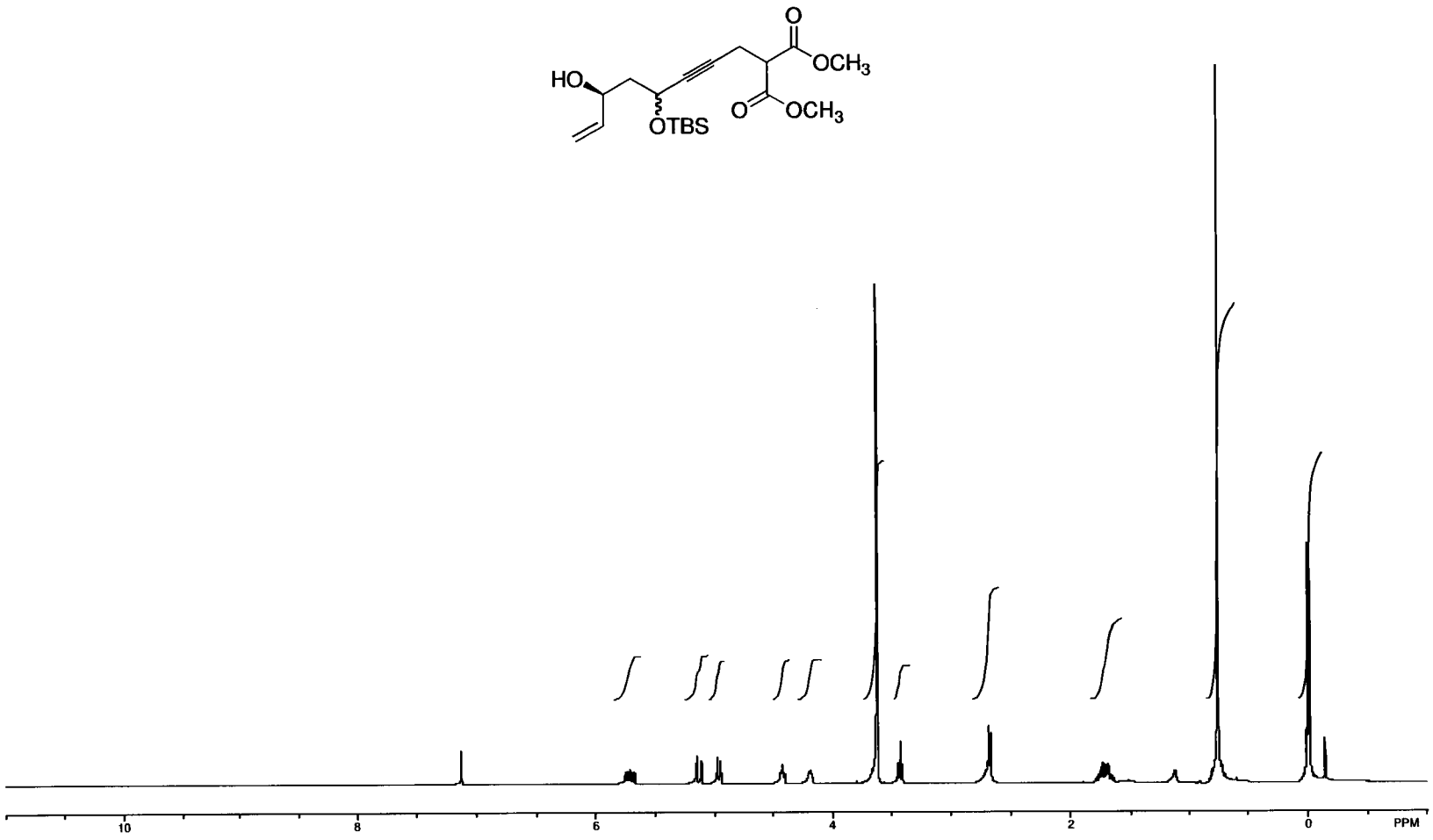


Figure A3.1 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **124**.

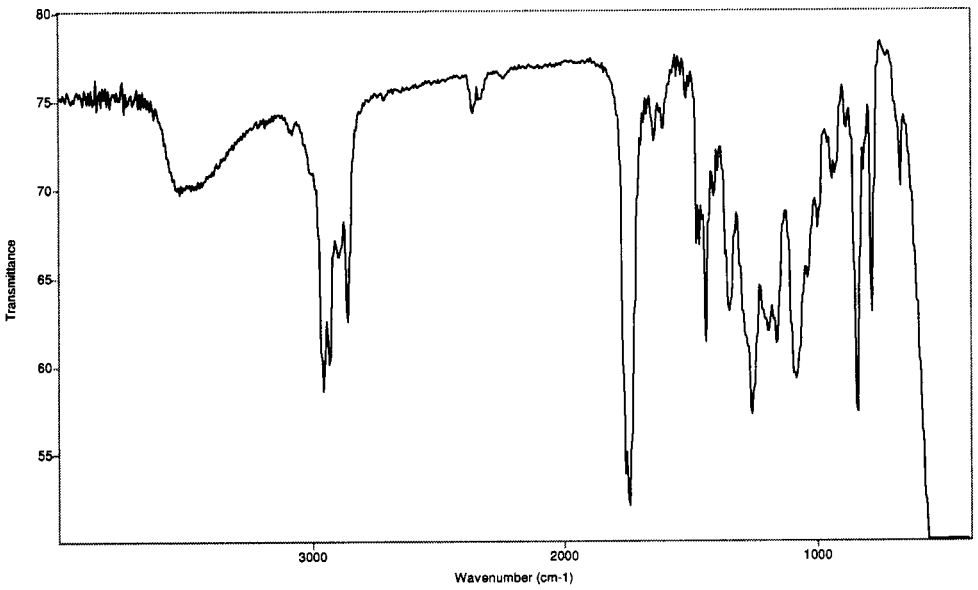


Figure A3.2 IR spectrum (thin film/NaCl) of compound **124**.

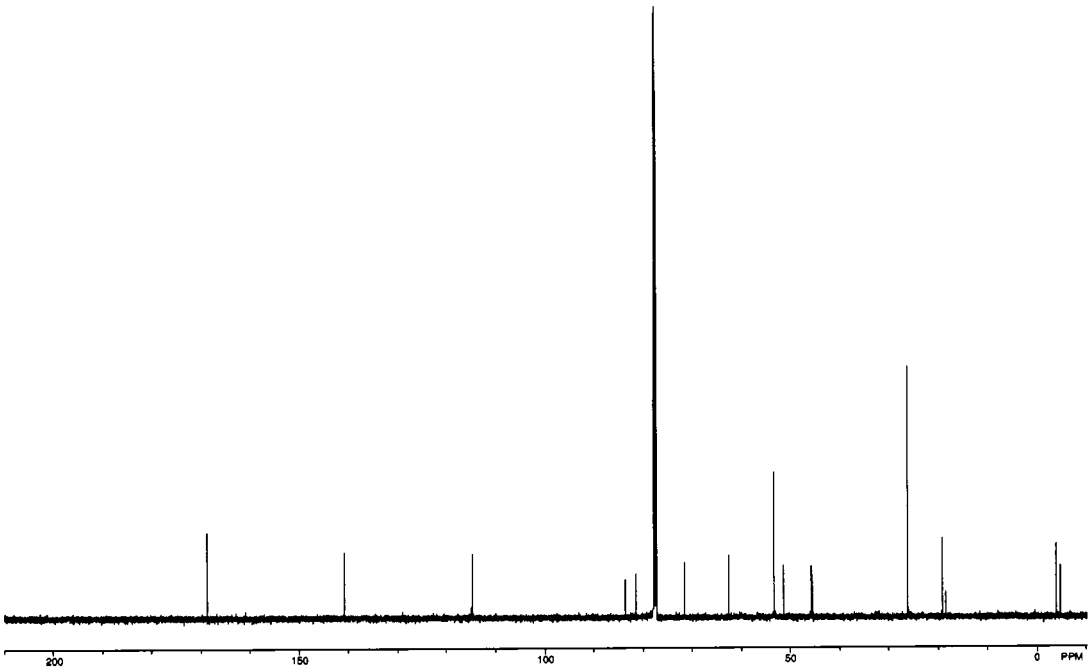


Figure A3.3 ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **124**.

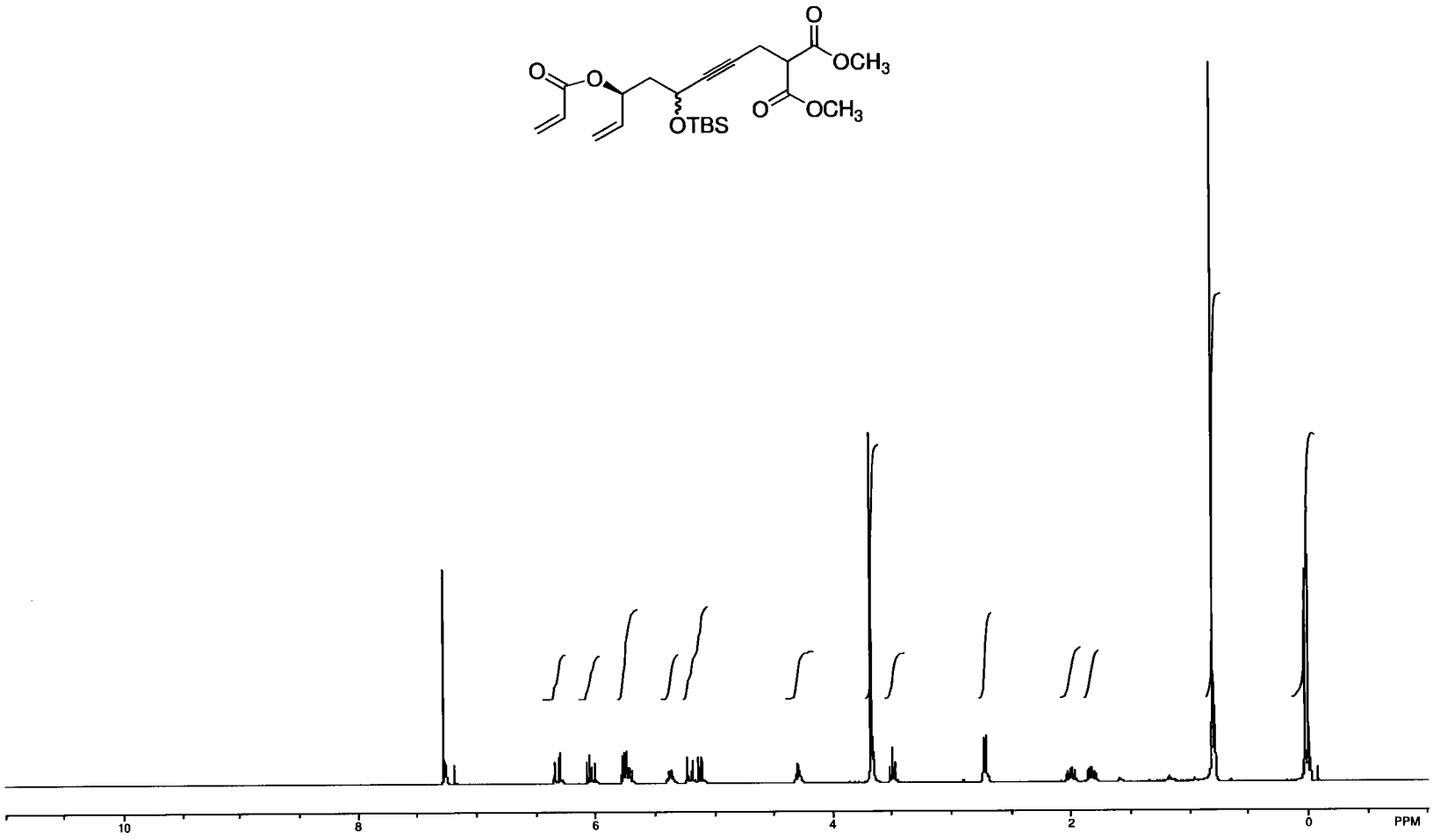


Figure A3.4 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **126**.

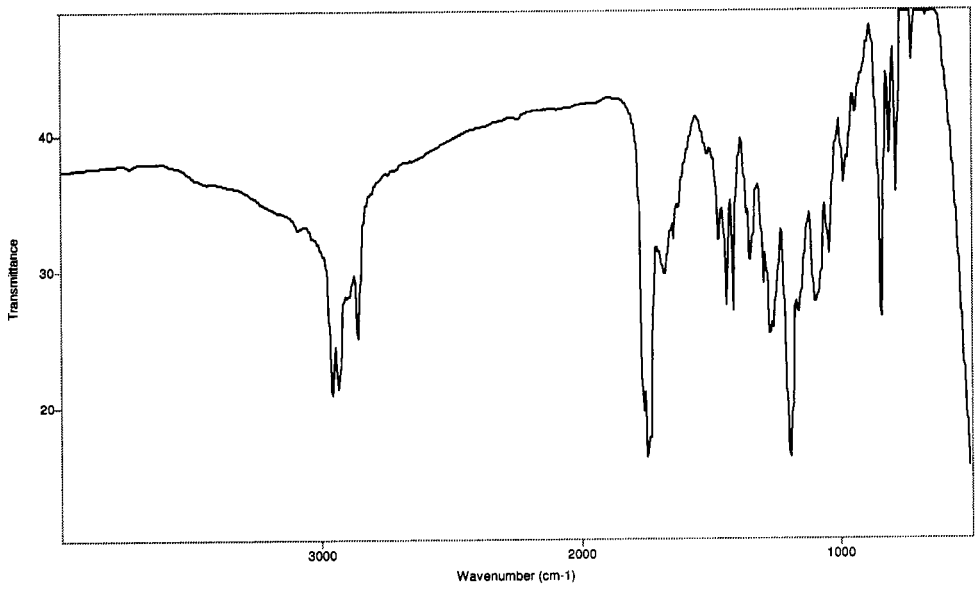


Figure A3.5 IR spectrum (thin film/NaCl) of compound **126**.

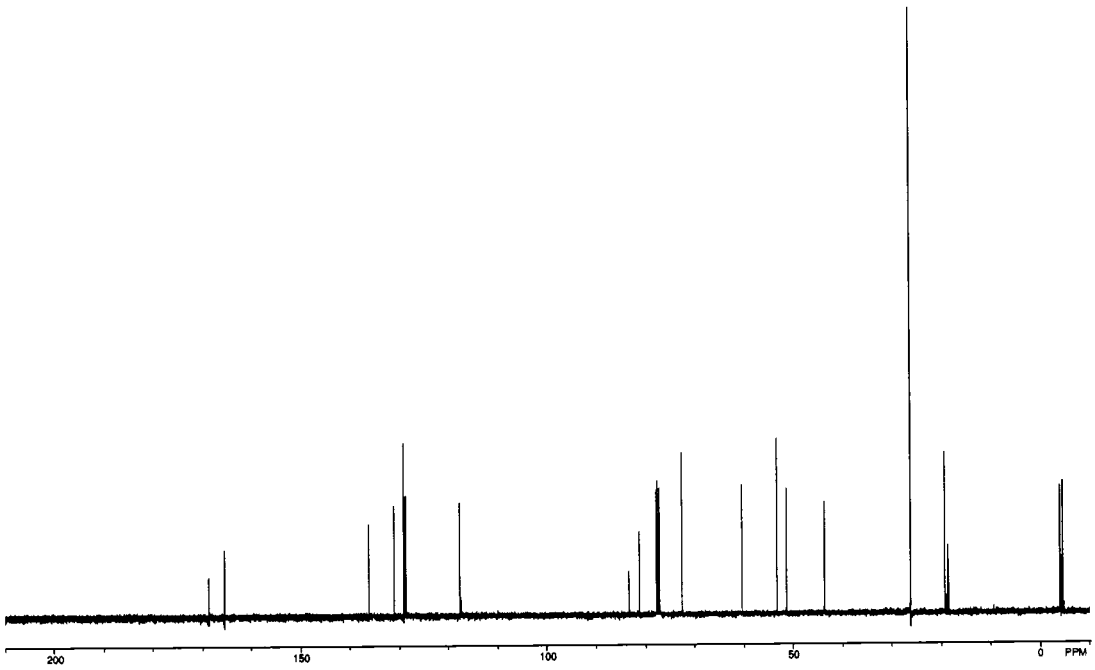


Figure A3.6 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **126**.

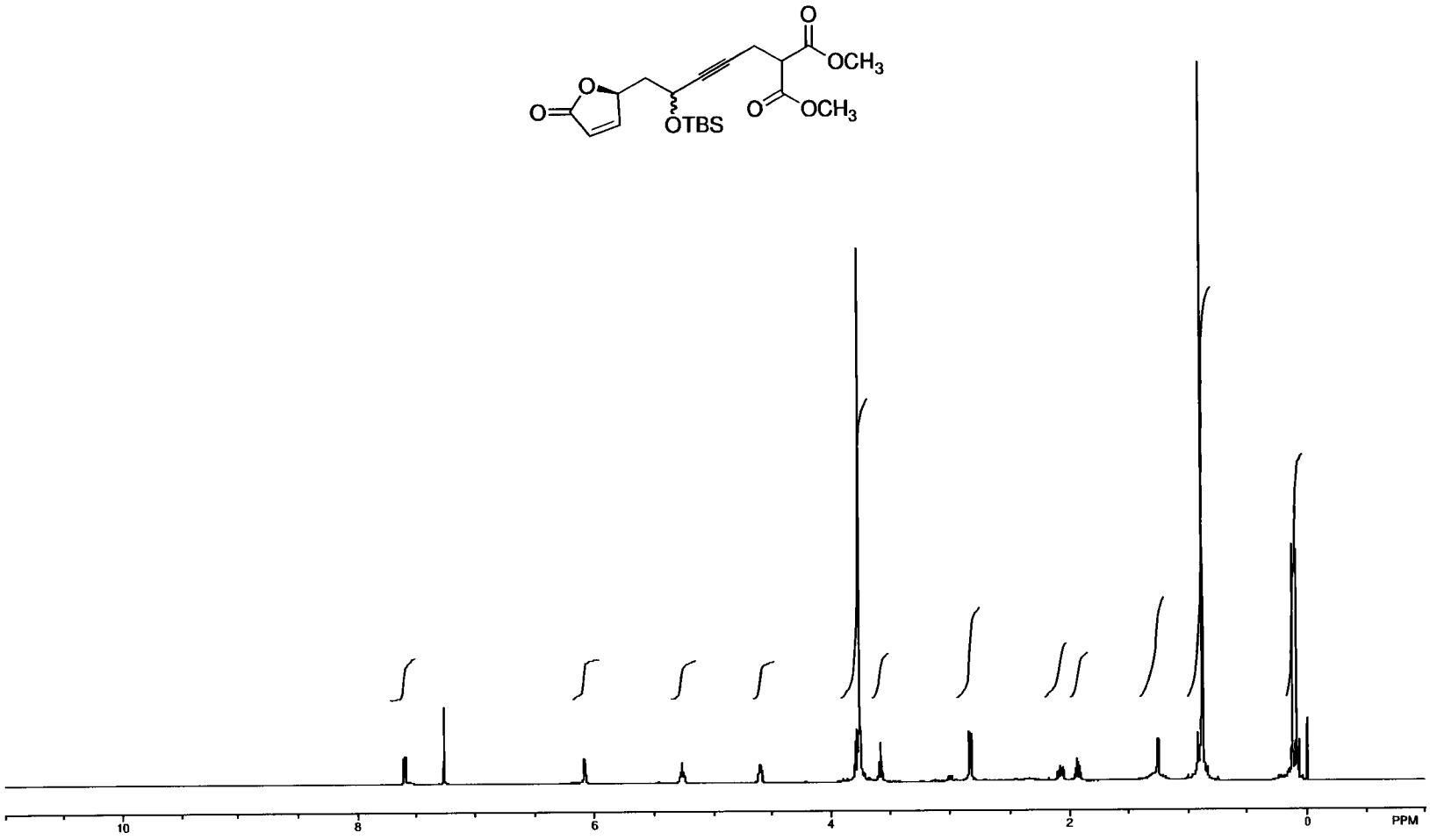


Figure A3.7 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **129**.

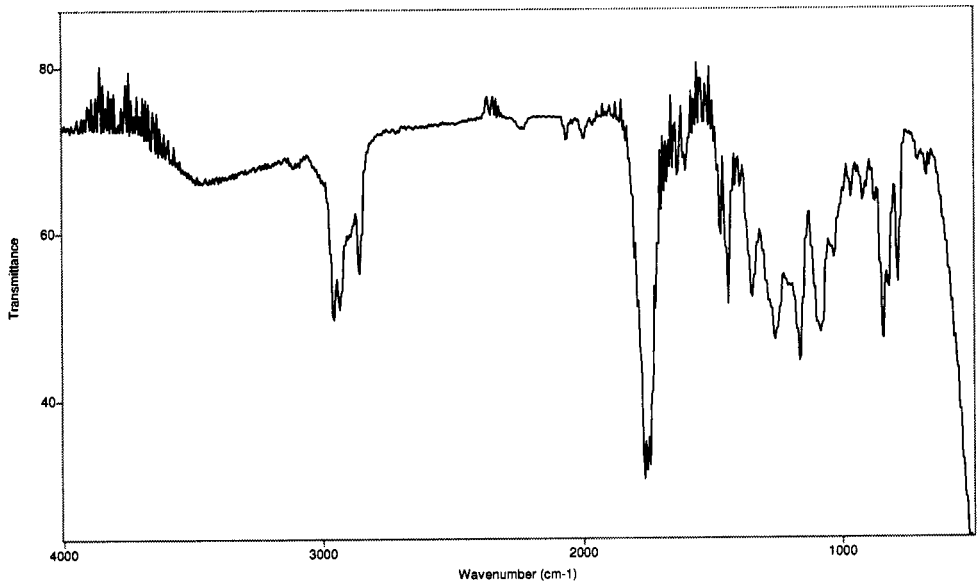


Figure A3.8 IR spectrum (thin film/NaCl) of compound **129**.

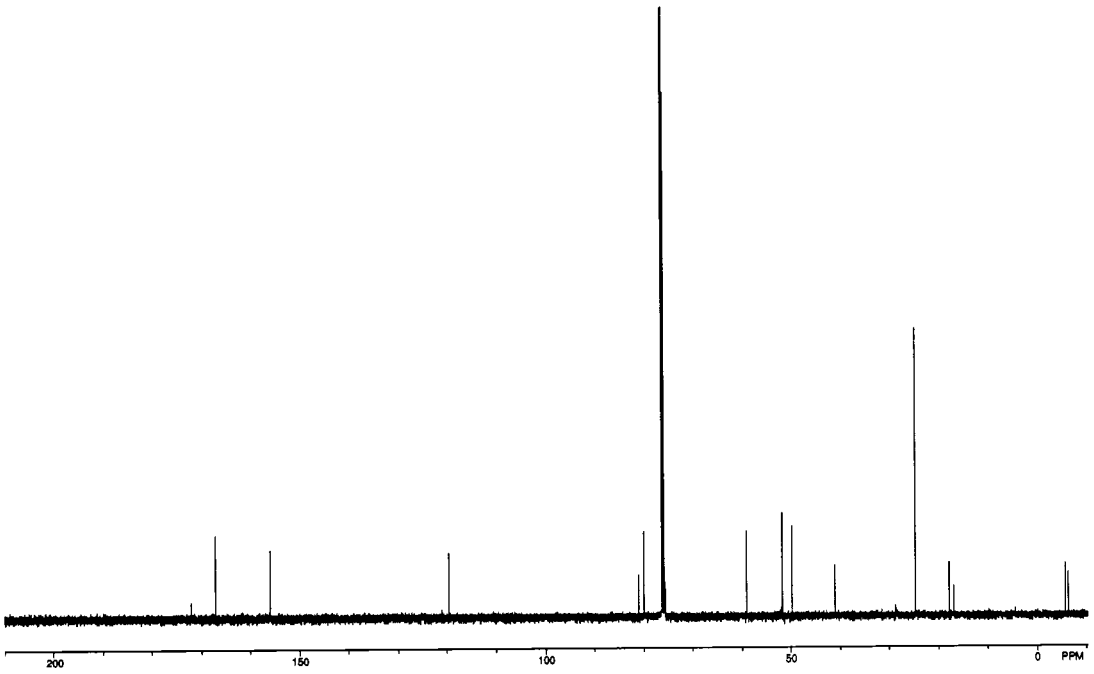


Figure A3.9 ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **129**.

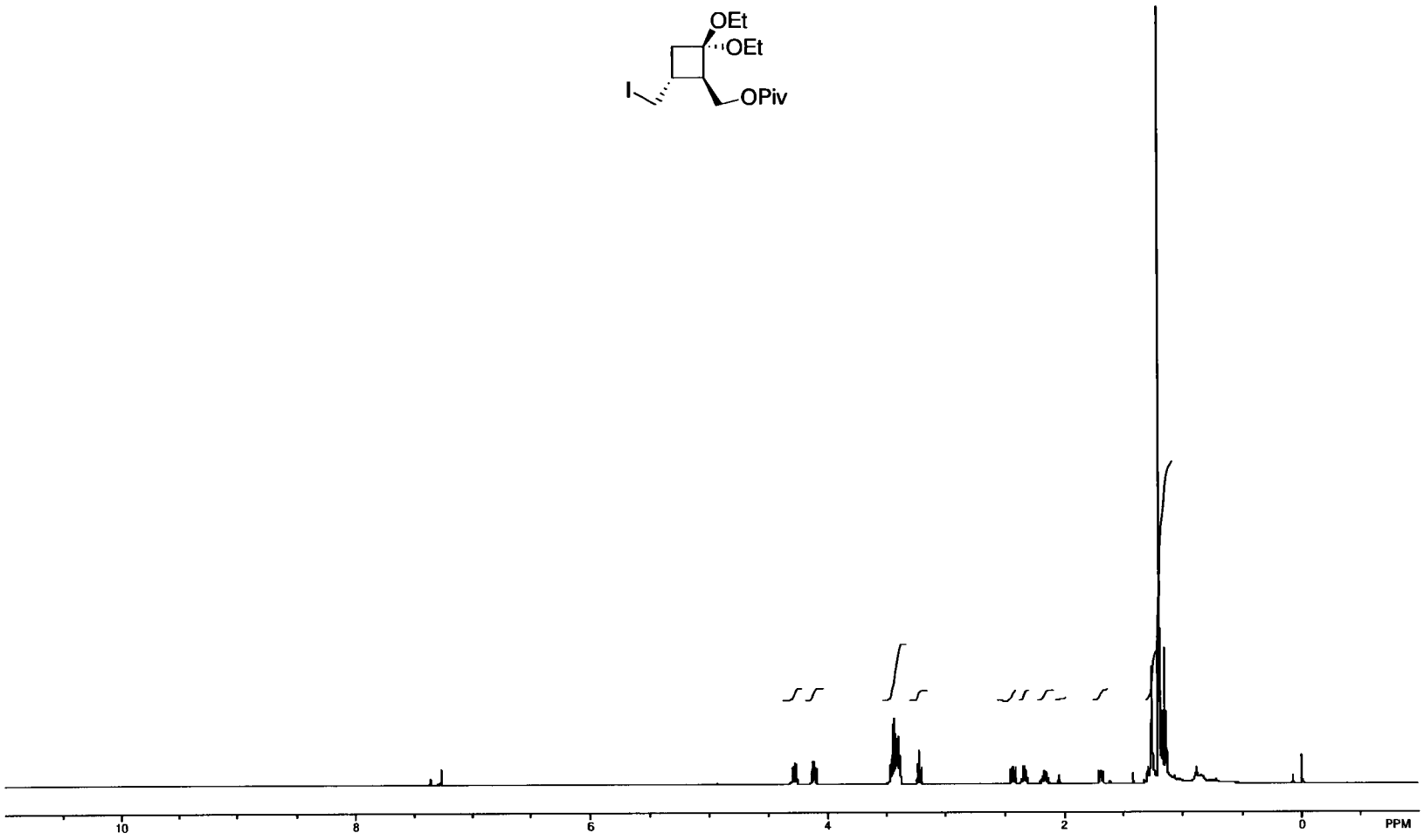


Figure A3.10 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **144**.

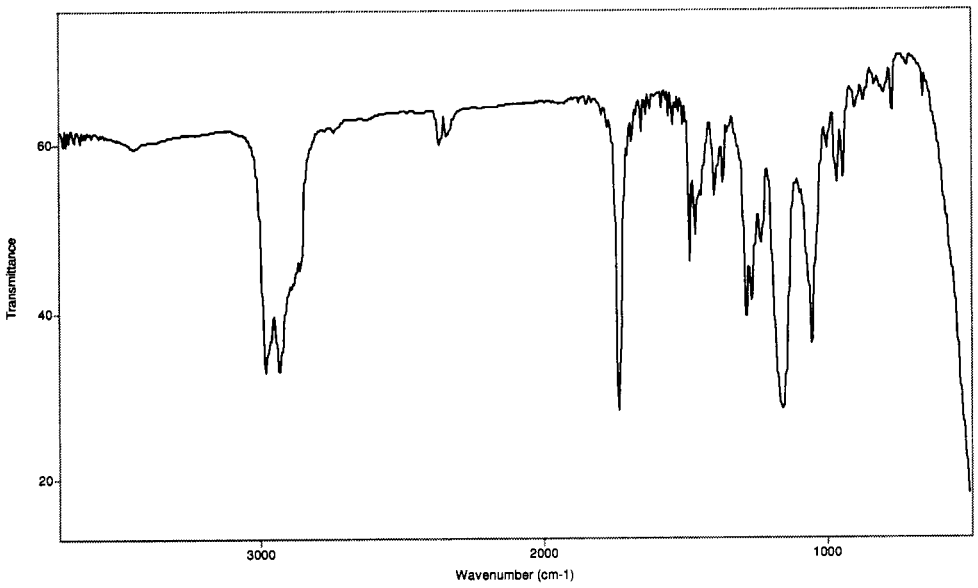


Figure A3.11 IR spectrum (thin film/NaCl) of compound **144**.

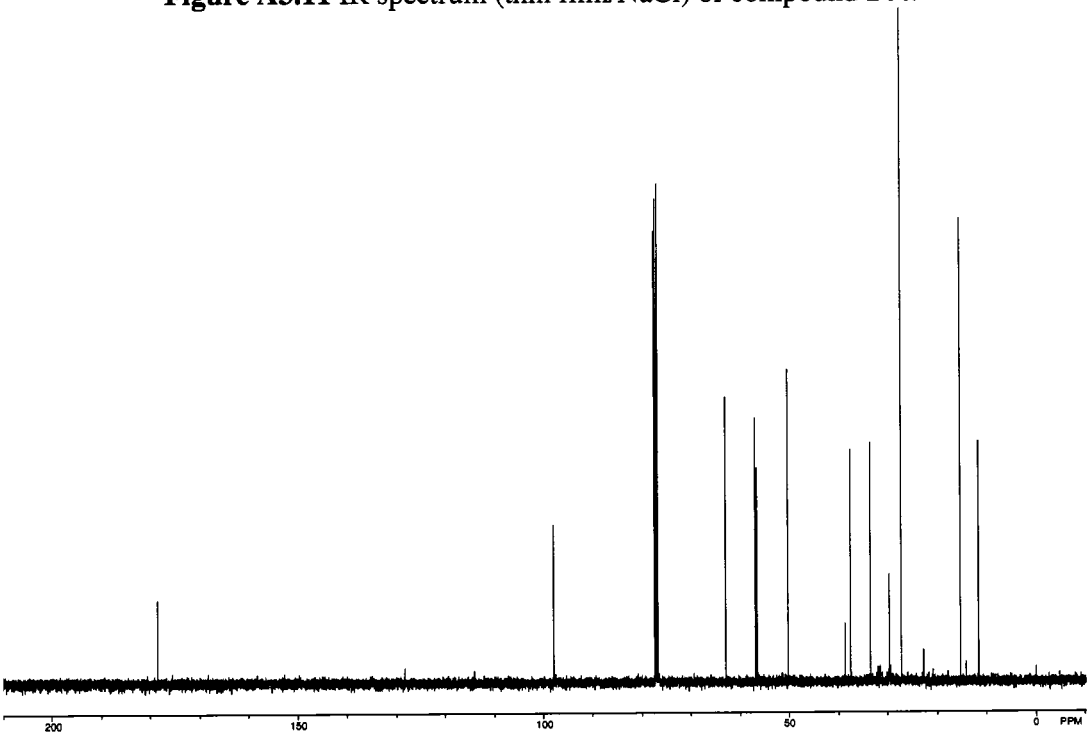


Figure A3.12 ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **144**.

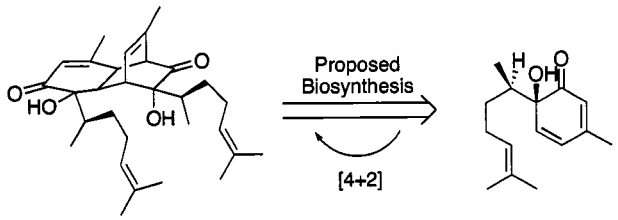
Chapter 4

Progress Toward the Total Synthesis of Bacchopetiolone.

4.1 Bacchopetiolone: Isolation and Structural Characterization.

Bacchopetiolone (**169**) is a dimeric sesquiterpene that was isolated from a Chilean shrub, *Baccaris petiolata,* and reported by Niemeyer and co-workers in 1991.[1]

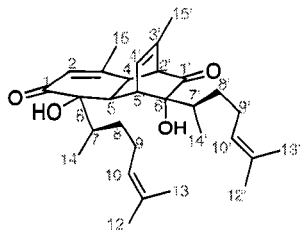
Scheme 4.1.1



Bacchopetiolone (169) **170**

Although no total synthesis has been reported, the biogenesis of **169** has been proposed to proceed through a [4+2] cycloaddition of the bisabolene derivative **170** (Scheme 4.1.1). There are 64 possible stereo- and regioisomers that could result from a [4+2] *endo-* or *exo*-cycloaddition of bisabolene **170** with itself.

Table 4.1.1



Bacchopetiolone (169)

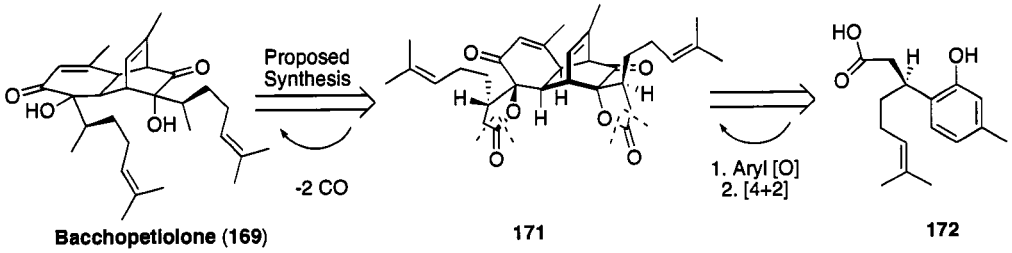
H irradiated	NOE (%)
14	H-2 (3), 9 (3), 5 (2), 4 (1), 7 (3)
14'	H-5' (3), 9' (4)
15	H-4 (5), 2 (10), 9 (3)
15'	H-2' (10), 4' (6), 2 (4)
4	H-15 (6), 2' (6)
2'	H-15 (6), 15' (4), 4 (6)
5	H-7 (3), 9 (3), 5' (3)
5'	H-14' (3), 8' (4), 5 (4)
6-OH	H-5' (4), 4' (2), 14 (3)
6'-OH	H-5' (4), 5 (3), 14' (10)
4'	H-5' (5), 15' (4), 7 (4)
2	H-15 (10), 7 (2), 14 (2), 15' (3)

The structure of **169** was elucidated after extensive NMR studies, and NOEs allowed identification of the stereoisomer (Table 4.1.1).

4.2 Retrosynthetic Analysis.

In considering a synthesis of dimer **169** we recognized the potential of a biomimmetic strategy wherein a tandem phenolic oxidation / Diels-Alder reaction of propionic acid derivative **172** would give rise to **171**, an advanced intermediate which is only two CO units removed from the natural product (Scheme 4.2.1).

Scheme 4.2.1



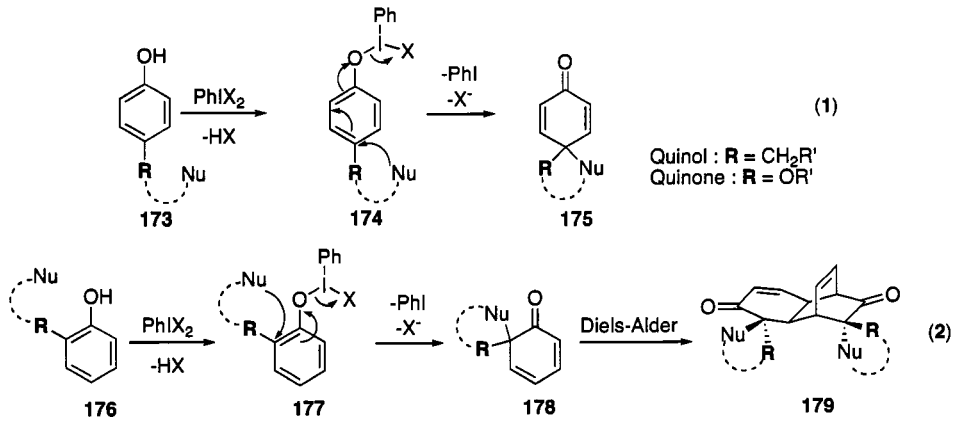
4.3 Tandem Aromatic Oxidation / Diels-Alder.

4.3.1 Phenolic Oxidation Background.

Phenolic oxidations have been widely used as a means to access structurally diverse compounds (**175**, **178**, **179**, Scheme 4.3.1). Following the oxidation of phenols **173** and **176**, the attack of a nucleophile de-aromatizes and de-symmetrizes the aromatic ring (**175** and **178**). The nucleophile can either add para (eq. 1, Scheme 4.3.1) or ortho (eq. 2, Scheme 4.3.1) to the phenol in an intra- or intermolecular fashion. When the

attack occurs at an already substituted position of the aromatic ring, synthetically useful quinol and quinone equivalents are generated (*e.g.*, **175** and **178** where Nu = O).[2]

Scheme 4.3.1



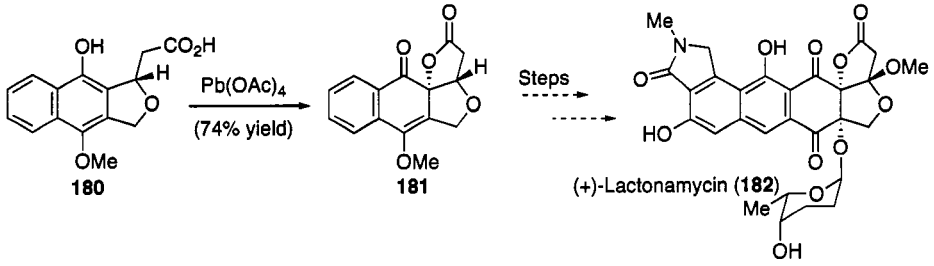
The mildness of these reaction conditions and compatibility with diverse functional groups have favored the phenolic oxidation as a key step for several natural product syntheses.[2] Another advantage is the diverse array of nucleophiles (alcohols, acids, thiols, oximes, and amines) that can be used, allowing for flexibility in the elaboration of a particular substitution pattern. Furthermore, conjugated cyclohexadienones that arise from the phenolic oxidation can undergo a Diels-Alder cycloaddition with either itself (**178→179**, Scheme 4.3.1) or with an external dienophile (*e.g.* methyl vinyl ketone, Scheme 4.3.4), giving rise to highly functionalized polycycles with high regio- and stereocontrol.

4.3.2 Precedents.

The formation of lactones *via* nucleophilic attack of carboxylic acids on oxidized phenols was well precedented by Danishefsky *et al.* Indeed the authors have

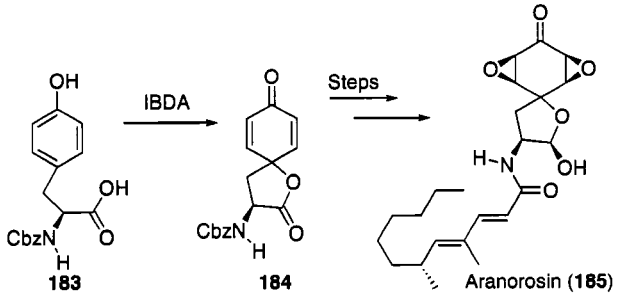
demonstrated that carboxylic acid **180** could intramolecularly attack the ortho position of the corresponding oxidized phenol and delivered lactone **181**, where lead tetracetate (LTA) served as the oxidant. This strategy enabled the authors to construct the right hand portion of (+)-lactonamycin (**182**), a synthetically challenging natural product.[3]

Scheme 4.3.2



Prior to that, Wipf *et al.* reported a very elegant and efficient synthesis of aranorosin (**185**), which showcased a phenolic oxidation as their key step. Intermediate **184** was accessed *via* a de-aromatization and de-symmetrization of protected tyrosine **183**. Indeed, the authors showed that a 1,4-cyclohexadienone-spiro-lactone (**184**) could be generated from the addition of the carboxylic acid moiety at the para position of corresponding phenol **183**.[4, 5]

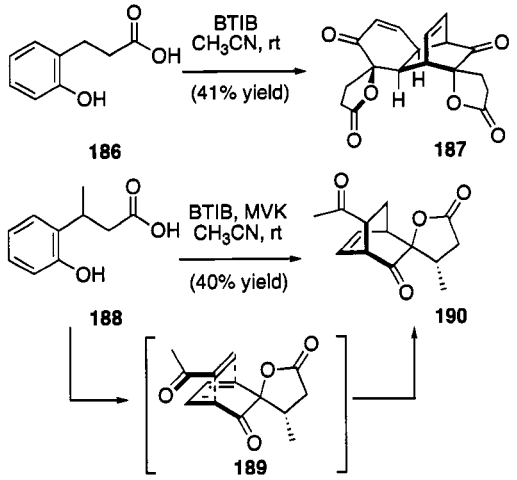
Scheme 4.3.3



Finally, the feasibility of the proposed retrosynthetic strategy (Scheme 4.2.1) was supported by recent studies in the Wood laboratories on the tandem phenolic oxidation /

Diels-Alder reactions of aryl propionic acids. Of particular relevance was the reactivity observed for 3-(2-hydroxyphenyl) propionic acid **186** (Scheme 4.3.4) which, upon exposure to bis(trifluoroacetoxy)-iodobenzene (BTIB), produced a polycycle (**187**) that possesses the same relative stereochemistry as found in bacchopetiolone (**169**).[6] This stereochemical outcome indicated that the initially formed spirolactone underwent dimerization *via* approach of the two oxygen-bearing faces[7] in an endo transition state.[8]

Scheme 4.3.4

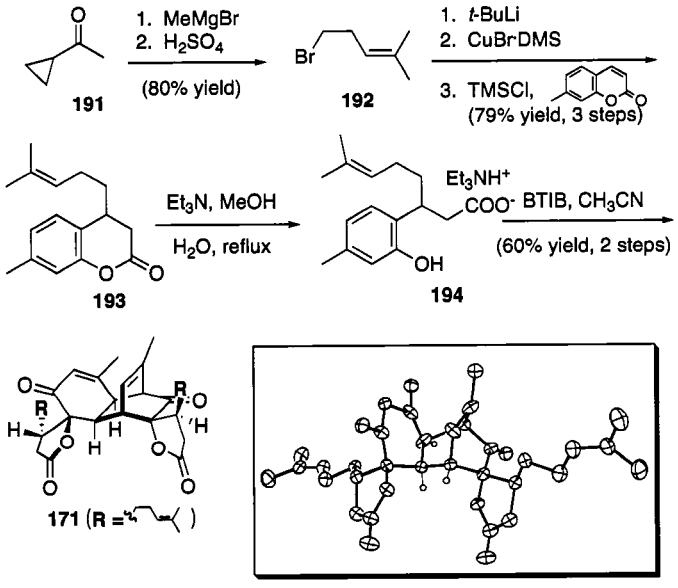


In addition to **186**, the reactivity of 3-(2-hydroxyphenyl) butyric acid (**188**) was explored, wherein stereogenicity resided at the benzylic position. Importantly, this substrate underwent diastereoselective spirolactonization to furnish spirolactone **189** which, in the presence of MVK, engaged in a stereoelectronically controlled [4+2] reaction (*c.f.*, **186** to **187**) to furnish polycycle **190** as a single diastereomer. Based on the previously observed reactivity of acids **186** and **188**, we speculated that exposure of an appropriately substituted 3-(2-hydroxyphenyl)-propionic acid (*e.g.*, **172**) to BTIB would result in the strereoselective formation of dimer **171** (Scheme 4.2.1).

4.4 Synthesis of Dimer 171.

To explore the application of the phenolic oxidation / Diels-Alder sequence we initiated a synthetic effort that began with large scale production of bromide **192** from cyclopropylmethyl ketone (**191**).[9] Exposure of **192** to lithium-halogen exchange followed by copper-mediated conjugate addition to 7-methylcoumarin provided the alkylated dihydrocoumarin (**193**, Scheme 4.4.1) in 79% isolated yield. Hydrolysis of the lactone **193** and *in-situ* conversion to the triethylamine salt (**194**) set the stage for the key phenolic oxidation. To our delight, we found that treatment of **194** with BTIB resulted in smooth aromatic oxidation followed by Diels-Alder cycloaddition to provide dimer **171** as a single diastereomer in 60% yield.[10] This short reaction sequence allowed access to several grams of dimer **171** and single X-ray analysis provided structural proof that **171** possessed the relative stereochemistry found in bacchopetiolone (Scheme 4.4.1, Inset).

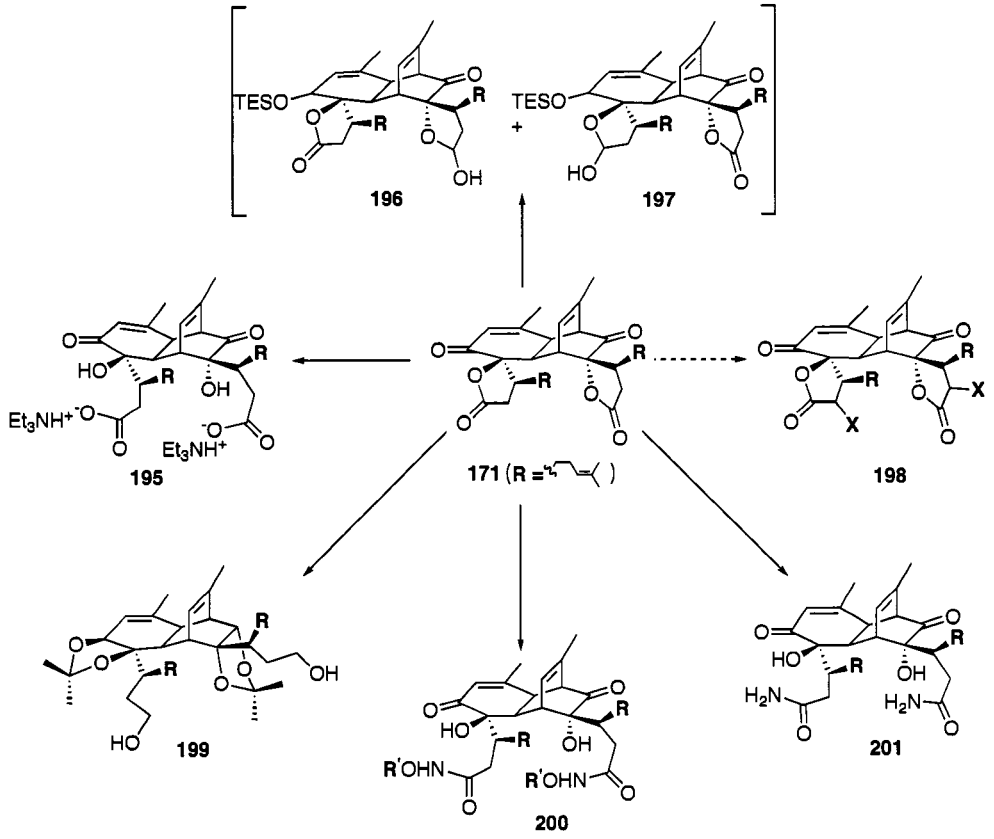
Scheme 4.4.1



4.5 Decarbonylation and Decarboxylation.

Having assembled the polycyclic skeleton of bacchopetiolone (**169**), we turned our attention to the bis-decarbonylation required for converting **171** to **169**. In order to successfully cleave the carbonyl-methylene bond of the bis-lactone **171** we have resorted to several strategies and synthesized a number of substrates possessing handles to help effect this key carbon-carbon bond cleavage (Scheme 4.5.1).

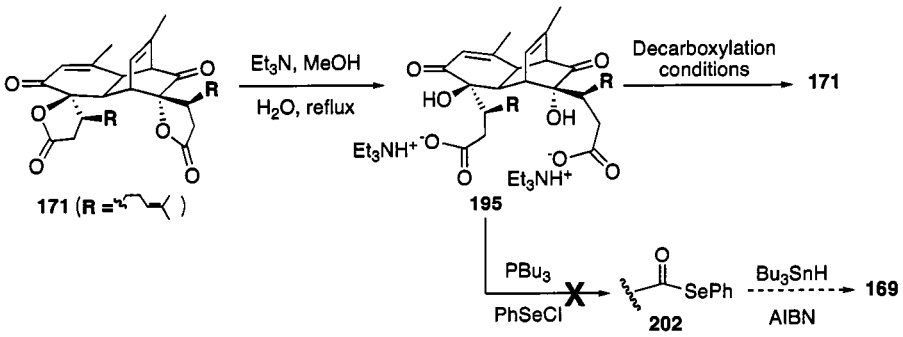
Scheme 4.5.1



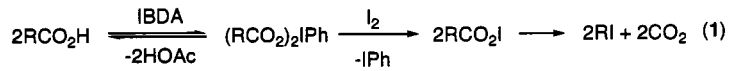
4.5.1 Decarboxylation and Decarbonylation Substrates.

Our first strategy was to install a handle on dimer **171** that would allow the carbon-carbon bond cleavage, minimize the use of protecting group and oxidation state manipulation. We initially tried to install a halogen or hydroxyl alpha to the lactone carbonyl, but our efforts were unsuccessful (**171**→**198**, X = Br, Cl or OH). Another idea explored was the opening of both lactones and initiation of an anionic or radical decarboxylation. Thus, dimer **171** was refluxed in a mixture of methanol, triethylamine and water to open the lactones and produce the corresponding triethylamine salt **195** quantitatively.

Scheme 4.5.2



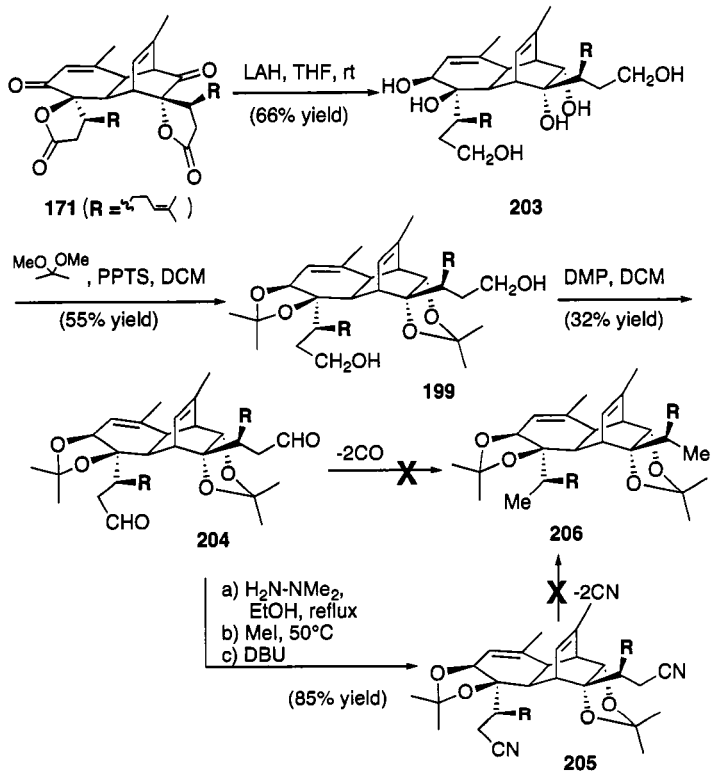
There have been several reports regarding the generation of carbon-centered radicals through the decarboxylation of acids[11-13] or the corresponding salts[14, 15] using hypervalent organoiodine reagents (Equation 1). Carbon dioxide formation from acetoxy radical (RCH_2CO_2•) should drive this reaction, however salt **195** relactonized readily and the decarboxylation did not proceed.



The decarboxylation of **195** would have minimized the number of transformations to access bacchopetiolone, but of course, the acids closure was to be expected. In order to keep the lactones opened, we attempted to form the corresponding *Se*-phenyl selenoester (**202**),[16] from which we would attempt to generate an acyl radical.[17, 18] Unfortunately, the lactones closed and no selenoesters were isolated. Similarly, Barton's acyl derivatives could not be isolated from either salt **195** or lactone **171**.[19]

Following our initial attempts, it soon became apparent that the lactones would need to be in a different oxidation state or the tertiary alcohols protected to generate a suitable substrate for the carbon-carbon bond cleavage.

Scheme 4.5.3



To this end, we found that dimer **171** could be reduced to the corresponding hexol **203**, which allowed for the selective protection of the 1,2-diols as their acetonides.[10] The

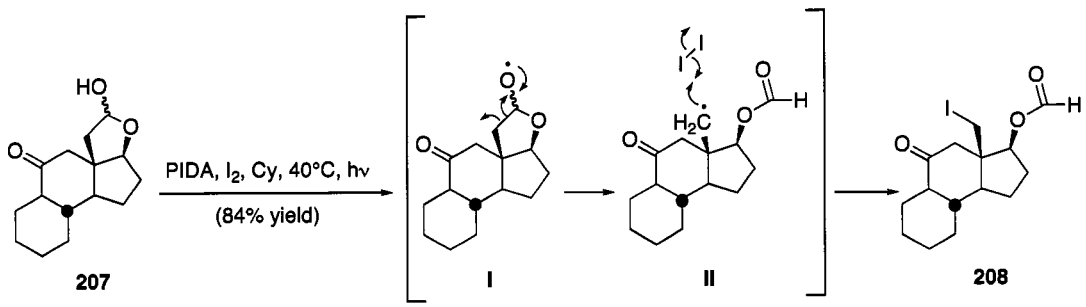
primary alcohols were then both oxidized to furnish bis-aldehyde **204** using Dess-Martin[20] oxidation in a modest 32% yield. We submitted the latter substrate to thermal, photochemical[21-23] and transition metal catalyzed decarbonylations.[24] Thermal decarbonylations were carried out in the presence of peroxide to initiate the deformylation, but bis-aldehyde **204** was unstable to heat and to light, and several unidentified compounds were generated. We subsequently tried rhodium catalyzed decarbonylation using Wilkinson's catalyst[25, 26] in several solvents (toluene, DCM, benzonitrile, THF), the aldehyde decomposed over time and none of the reduced product (**206**) was isolated. We then tried to oxidize bis-aldehyde **204** to the corresponding bis-carboxylic acid, but none of the isolated compounds possessed the characteristics of an acid moiety. Unlike the bis-acid, bis-nitrile **205** could be efficiently accessed and reductive decyanation was attempted under dissolving metal conditions.[27-33] Two different procedures were used, the first called for $Fe(acac)_3$ and sodium metal, and the second for potassium metal and 18-crown-6. The former conditions led to no reduction with recovery of starting material (**205**); the latter produced a very small amount of a potentially reduced compound. Despite repeating the reduction several times, we could not improve the conversion and never isolated sufficient amounts of material for its identification.

4.5.2 Suárez Reaction.

Suárez *et al.* have reported several fragmentation reactions of alkoxy radicals generated from phenyliodosodiacetate (PIDA). Among them, the photolysis of lactol moieties to generate alkoxy-radicals, could potentially be useful to us.[34] An alkoxy-

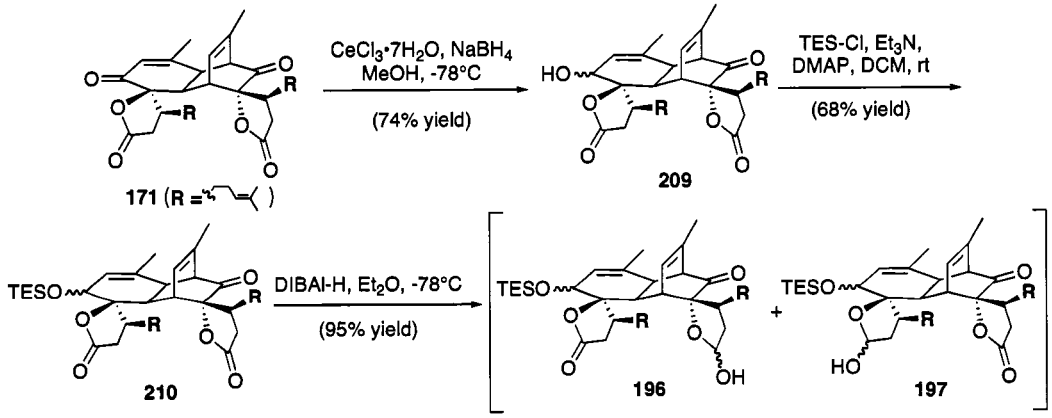
radical (**I**) can undergo a β-fragmentation that gives rise to a carbon-radical (**II**), leading to an alkyl iodide when the fragmentation is performed in the presence of iodine. Stork *et al.* have shown the application of this photochemically-initiated transformation, where hemiacetal **207** was irradiated in the presence of PIDA and iodine to generate the iodomethyl formate **208**.[35]

Scheme 4.5.4



In order to attempt this fragmentation, we needed to synthesize a lactol-containing substrate, starting from dimer **171**. A Luche[36] reduction was first performed on enone **171** and the resulting allylic alcohol protected as the corresponding silyl ether (**210**). The bis-lactone was treated with DIBAl-H to cleanly deliver a mono-lactol, either **196** or **197**.

Scheme 4.5.5

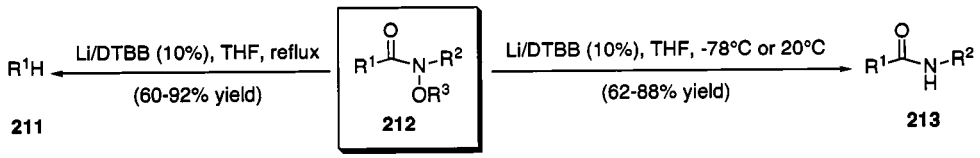


Although the reduction only delivered one lactol, we followed the procedures reported by Suárez and Stork only to discover that the lactol readily decomposes upon exposure to light. Given this unproductive result, we did not think necessary to develop conditions to cleanly produce a bis-lactol.

4.5.3 Yus Reaction.

Further literature searches identified the work of Yus *et al.*, where *N*-alkoxyamides and *N*-methoxy-*N*-methylamides (Weinreb amides) were dealkoxylated by reductive cleavage of the N-O bond with lithium powder and catalytic amount of 4,4'-di-*t*-butylbiphenyl (DTBB, 10 mol%) at room or reflux temperatures to yield the corresponding amides **213** and alkanes **211** respectively (Scheme 4.5.6).[37] The latter case was the result of a formal deaminocarbonylation process.

Scheme 4.5.6

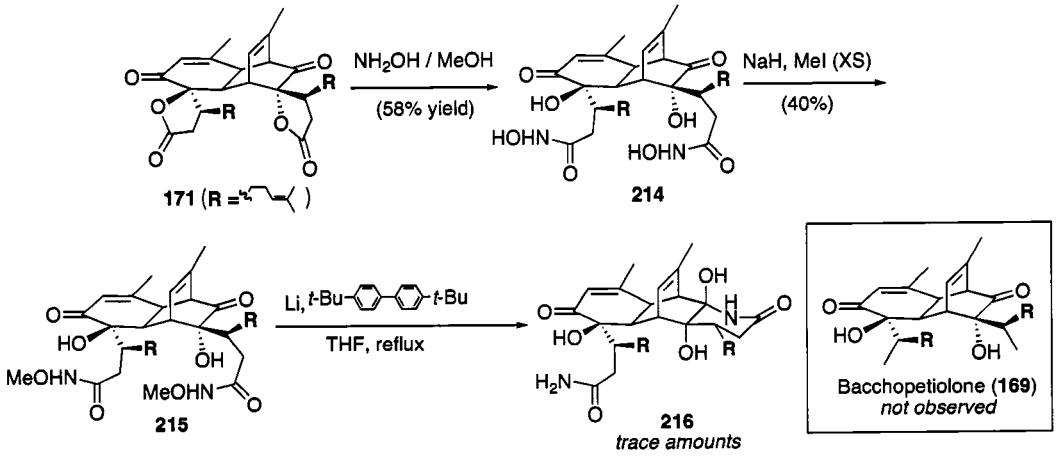


R^1 = alkyl, cycloalkyl, aryl; R^2 = H, Me; R^3 = Me, Ph, Bn

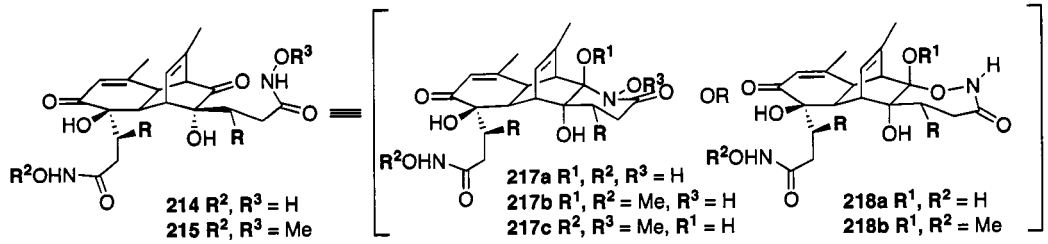
We envisioned this reaction as potentially useful for the removal of the two extra CO units contained in dimer **171**. We were therefore delighted to find that the two lactones could be opened with hydroxylamine to furnish a bis-hydroxamic acid (**214**). Further spectroscopic analysis of **214** indicated that the nitrogen or hydroxyl of the hydroxamic acid moiety on the right side of the molecule had added into the nearby ketone (**217a** or **218a**, Scheme 4.5.8). Next, we methylated the hydroxamic acids to yield an isomer of hydroxymate **215** (for simplicity we represent the hydroxymate as **215**, but

in fact, it can correspond to **217b**, **217c** or **218b**, which are three possible bis-methylated products, Scheme 4.5.8). Using excess of lithium powder and 4,4'-di-*t*-butylbiphenyl (DTBB) generated a dianion species, with a high reductive potential. Then, hydroxymate **215** was added to the green solution and the reaction mixture refluxed in THF. Under these conditions, most of the starting material decomposed, but we were able to identify and characterize one reduction product as amide **216**, which was the result of N-O bond cleavage.

Scheme 4.5.7



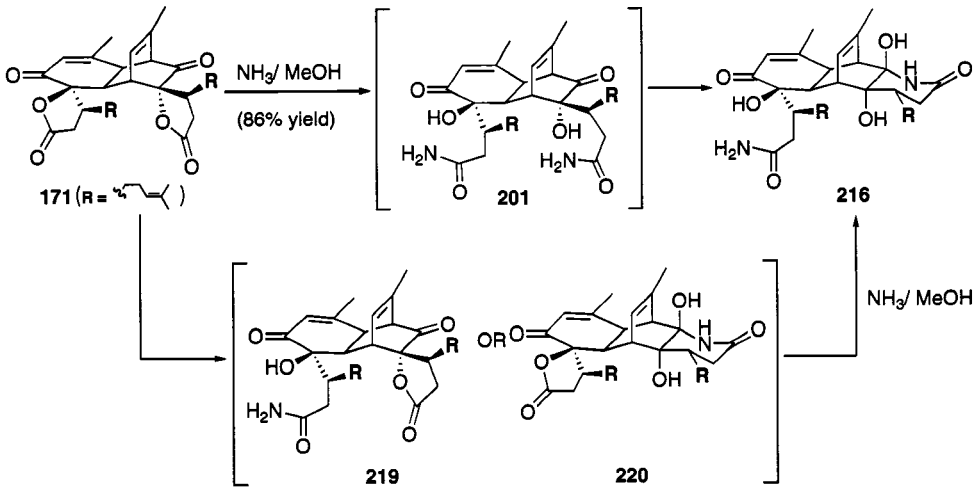
Scheme 4.5.8



4.5.4 Hofmann Rearrangement and an Interesting Ring Expansion.

Unable to access bacchopetiolone (**169**) directly, we turned our attention to bis-amide **201** (Scheme 4.5.9) in hope of employing a Hofmann-type rearrangement. The bis-amide was readily available from dimer **171** *via* treatment with ammonia; subsequent addition of one amide moiety into the nearby ketone delivered cyclic carbinolamide **216**. Still, we were hoping that the cyclic hemiaminal formation would be reversible, allowing for potential Hofmann-type rearrangement on both amide functional groups of **201**.

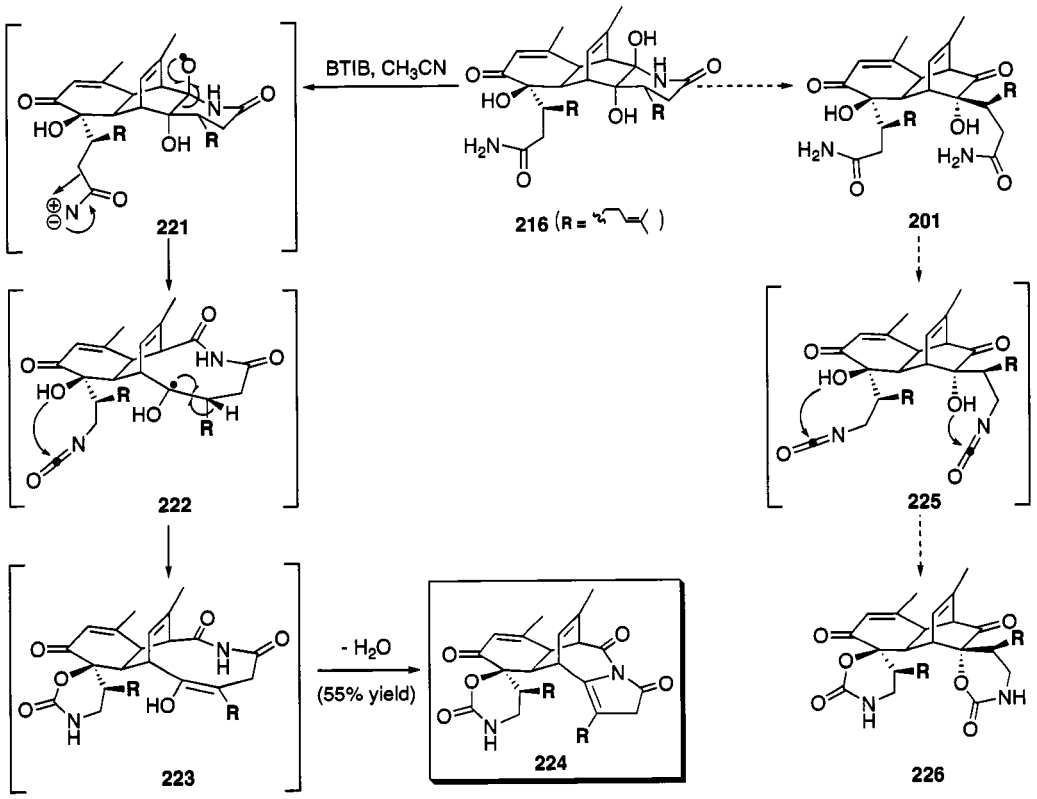
Scheme 4.5.9



To this end we explored the use of BTIB in anhydrous acetonitrile as a means of generating the nitrene species[38, 39] and rearranging them to bis-isocyanate **225**, we had anticipated **226** to arise upon intramolecular trapping by the tertiary alcohols. Although exposure of **216** to BTIB efficiently produced nitrene **221**, it also generated an alkoxy radical (**221**). The subsequent reactivity was bifurcated and furnished the undesired polycycle **224**, confirmed by single X-ray analysis (Figure 4.5.1).[40] As illustrated in Scheme 4.5.10, this ring expansion product (**224**) is believed to arise from **221** *via* the

desired rearrangement and intramolecular trapping to the cyclic urethane on the left side; concomitantly and in contrast, the right portion of **221** undergoes ring expansion to a [2.2.3]bicycle, presumably via radical β-fragmentation.

Scheme 4.5.10

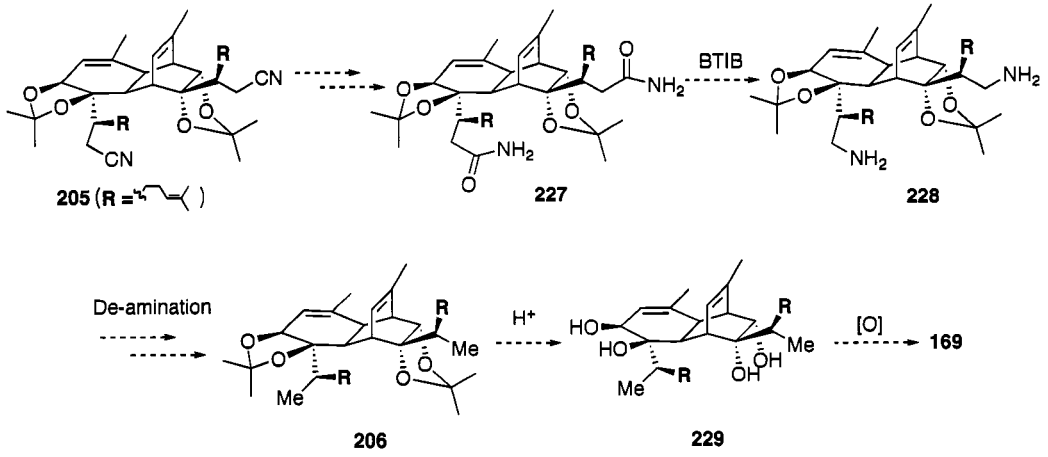


Suárez *et al.* have reported similar β-fragmentation of bicyclo[3.3.0]-carbinolamidyl radicals generated by irradiation with visible light in the presence of hypervalent organoiodine.[41, 42] In contrast to Suárez's substrates, the fragmentation of **221** delivered a tertiary C-radical (**222**) that can presumably lose a hydrogen and generate enol **223**, which can tautomerize to the corresponding ketone and condense with the imide nitrogen to furnish enamine **224**. Although we did not achieve a double

decarbonylation, we observed a novel fragmentation that transforms α-hydroxy-carbinolamides to bicyclic imides.

Evidently, this rearrangement could only be prevented by supressing the formation of the cyclic carbinolamide **216**; protection of the ketone would be ideal prior the opening of the lactones (**171**). Therefore, on dimer **171**, we tried to protect the ketones as their corresponding ketals, dithianes or cyanohydrins. However, these attempts were unsuccessful, most likely due to steric hindrance. One alternative, would be to reduce the ketones (*vide supra*). Earlier, we had prepared a bis-nitrile (**205**), in which the ketones were reduced and alcohols protected. This substrate could be hydrolysed to the corresponding bis-amide **228**, and a Hofmann rearrangement attempted again.

Scheme 4.5.11



A Hofmann rearrangement on bis-amide **227** would deliver bis-amine **228**; reduction of the amines, and subsequent deprotection and oxidation of the secondary alcohols (**229**) would possibly provide bacchopetiolone (**169**). Although this stategy

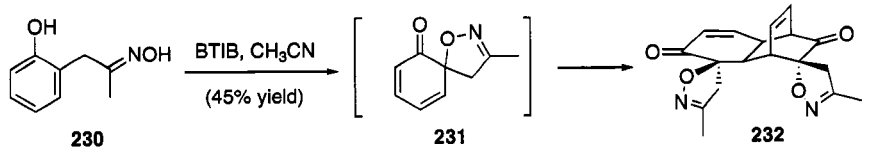
implies several oxidation state manipulations and utilizes protecting groups, it might allow completion of the total synthesis.

4.6 Future Elaboration.

We demonstrated the efficient assembly of dimer **171**, requiring only four steps and using a powerful phenolic oxidation / Diels-Alder sequence to set the relative stereochemistry at all eight stereocenters. Although our goal was to showcase the method developed in the Wood group for the total synthesis of bacchopetiolone, we did not expect the removal of the two CO units to be so challenging. A different strategy might be necessary to complete the total synthesis of **169**; the use of a monomer with the correct number of carbons may be an unavoidable solution to the encountered difficulties.

McKillop had reported an intramolecular oxidative cyclization of phenols possessing an oxime containing side chain (**230**).[43] The resulting cyclohexadienone (**231**) underwent a dimerization with itself (**232**) with the same regio and stereoselectivity as our previously described sequence.

Scheme 4.6.1

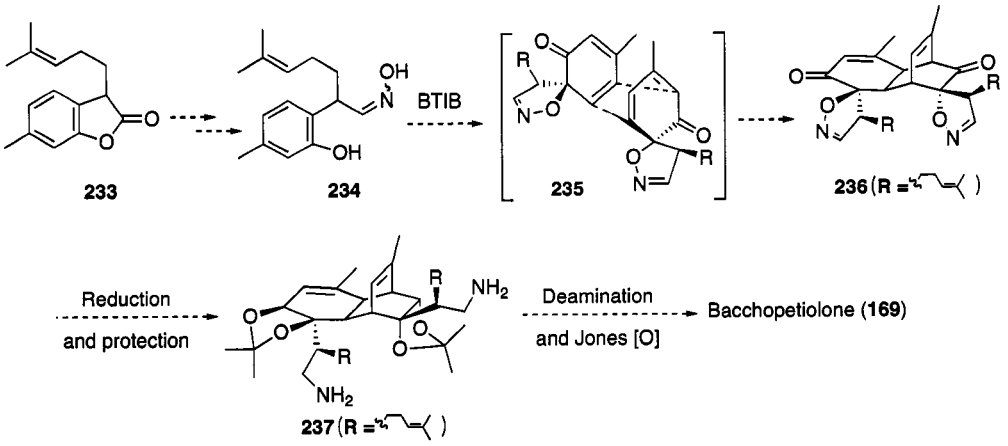


230 **231** **232**

To make this method applicable to the synthesis of bacchopetiolone (**169**) we would need to synthesize oxime **234**. In contrast to McKillop's oxime, **234** would not arise from a ketone but from an aldehyde. This subtlety may have further implications on

the isomeric ratio of the corresponding oxime (*E/Z*-**234**), which might be unfavorable to the cyclization.

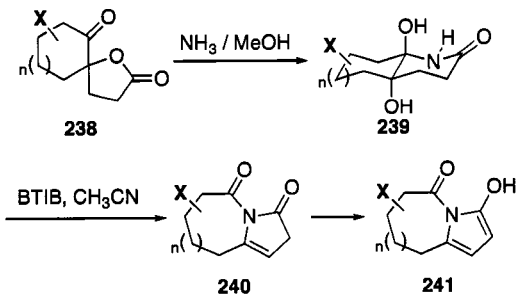
Scheme 4.6.2



While this strategy offers the possibility to make a substrate with the correct number of carbons, it also suffers setbacks, such as oxidation state manipulation, a N-O bond cleavage, de-amination and use of protecting groups.

A new aspect of this project was the discovery of the fragmentation of α-hydroxycarbinolamides into condensed imides (**221**→**224**, Scheme 4.5.10), which was not explored further. The reaction could constitute a new method to assemble pyrroles (**241**) and the scope and limitations would need to be studied to make it synthetically useful.

Scheme 4.6.3



4.7 Conclusion.

In conclusion, we have developed a highly efficient phenolic oxidation / Diels-Alder sequence that furnishes the desired tricyclic skeleton of bacchopetiolone with complete control of the relative stereochemistry. Although as yet unsuccessful in delivering **169**, decarbonylation attempts have illustrated the potential utility of BTIB mediated oxidations in delivering ring expansion products (e.g., **224** in Scheme 4.5.10). Efforts should be directed both on alternatives for completing the synthesis and on Suárez fragmentation modifications (Scheme 4.6.3).

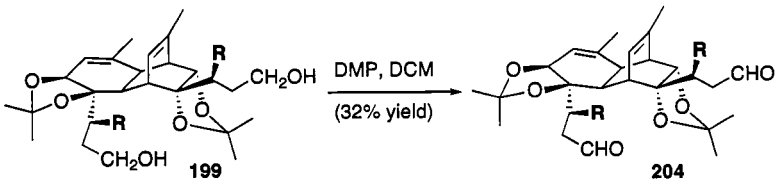
4.8 Experimental Section.

4.8.1 Materials and Methods.

Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). All other commercially obtained reagents were used as received. All reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F254 pre-coated plates (0.25 mm). Column or flash chromatography[44] was performed with the indicated solvents using silica gel (particle size 35 -75 mm) purchased from Silicycle. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Advance DPX-500 or Bruker Advance DPX-400 spectrometers. Chemical shifts are reported relative to internal chloroform (^{1}H δ 7.26 ppm, ^{13}C δ 77.00 ppm), methanol (^{1}H δ 3.31 ppm, ^{13}C δ 49.00 ppm). High resolution mass spectra were acquired at The University of Illinois Mass Spectrometry Center.

4.8.2 Preparative Procedures.

Preparation of bis-aldehyde 204:

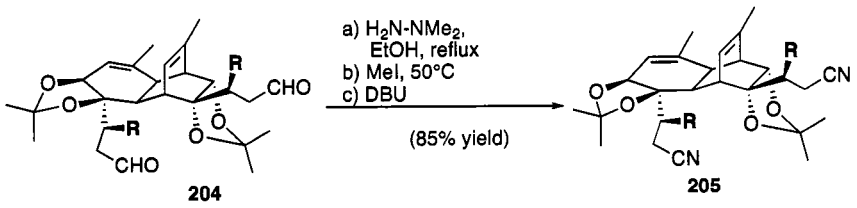


199 204

To a solution of diol **199** (64 mg, 0.1 mmol) in DCM (25 mL) were added Dess-Martin periodinane (0.5 g, 1.26 mmol) in 5 portions, over 1 hour. The reaction was monitored by TLC until complete consumption of starting material was observed. The reaction is diluted with DCM, washed twice with $NaHCO_3$ (saturated in water), dried over Na_2SO_4, filtered and rotary evaporated. The residue was purified by flash

chromatography (10% EtOAc/Hexanes) to yield the title compound **204** (20 mg, 32% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (br s, 2H), 5.60 (d, *J*=6.8 Hz, 1H), 5.56 (d, *J*=3.8 Hz, 1H), 5.02 (t, *J*=6.3 Hz, 2H), 4.23 (s, 1H), 4.08 (d, *J*=4.5 Hz, 1H), 3.06 (d, *J*=6.3 Hz, 1H), 2.95 (d, *J*=4.5 Hz, 1H), 2.86 (ddd, *J*=15.4, 7.1, 3 Hz, 1H), 2.80 (s, 1H), 2.69-2.79 (m, 2H), 2.49 (m, 1H), 2.42 (ddd, *J*=15.4, 4.8, 1.5 Hz, 1H), 2.27-2,36 (m, 2H), 1.88-2.06 (m, 3H), 0.93-1.86 (m, 5H), 1.77 (s, 3H), 1.68 (s, 9H), 1.58 (s, 6H), 1.47 (s, 3H), 1.42 (s, 3H), 1.36 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.05, 135.94, 131.89, 130.34, 130.26, 125.24, 121.46, 121.08, 120.65, 109.14, 106.23, 87.30, 87.10, 80.43, 80.27, 76.75, 74.26, 44.85, 43.64, 42.84, 42.70, 42.07, 40.34, 37.71, 37.52, 37.34, 32.51, 31.30, 31.22, 29.07, 27.36, 26.99, 26.84, 25.62, 25.52, 25.30, 24.61, 24.27, 23.38, 23.35, 19.85, 18.40, 15.56, 15.46; IR (thin layer, NaCl) 2925 (m), 2855 (m), 1724 (sh, s), 1456 (w), 1378 (w), 1243 (w) cm^{-1}; LRMS (CI) *m/z* found 609.4, calc'd for $C_{38}H_{57}O_8$ [M+H]: 609.41.

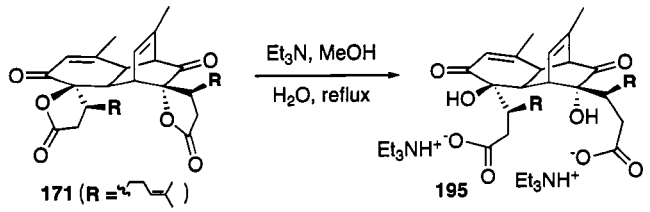
Preparation of bis-nitrile 205:



To a solution of bis-aldehyde **204** (10 mg, 0.016 mmol) in EtOH (1 mL) was added 1,1-dimethyl hydrazine (3 μL, 0.036 mmol) and heated to reflux. After 1 h, the reaction mixture was allowed to cool at room temperature and the EtOH was rotary evaporated. The residue was dissolved in MeI (0.4 mL) and heated to 50 °C. After 4 h, the reaction mixture was allowed to cool at room temperature and the MeI was rotary

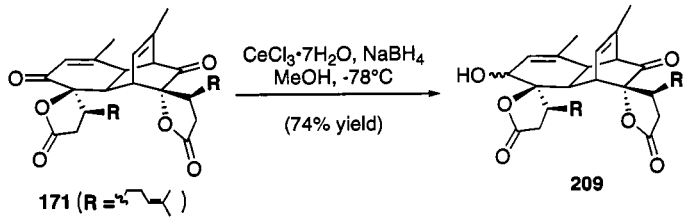
evaporated. The residue was dissolved in DBU and stir for 12 h at room temperature. The reaction mixture was partitioned between DCM and HCl (1N in water), the aqueous phase was extracted with DCM two more times. The combined organic phases were dried over Na_2SO_4, filtered and rotary evaporated. The residue was purified by flash chromatography (10% EtOAc/Hexanes) to yield the title compound **205** (8.5 mg, 85% yield) as a white foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.69 (d, J = 6.6 Hz, 1H), 5.56 (br s, 1H), 5.02 (dd, J = 14.3, 7.6 Hz, 2H), 4.18 (br s, 1H), 4.04 (d, J = 4.4 Hz, 1H), 3.05 (d, J = 6.6 Hz, 1H), 2.95 (br s, 1H), 2.88 (dd, J = 16.8, 4.8 Hz, 1H), 2.73-2.86 (m, 3H), 2.59 (dd, J = 17.3, 6.0 Hz, 1H), 2.34 (q, J = 8.4 Hz, 1H), 1.82-2.29 (m, 6H), 1.77 (s, 3H), 1.69 (s, 9H), 1.62 (s, 3H), 1.61 (s, 3H), 1.50 (s, 3H), 1.38 (s, 6H), 1.34 (s, 3H), 1.31-1.43 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.36, 134.86, 133.62, 127.80, 123.51, 123.44, 123.41, 119.61, 111.93, 109.18, 89.07, 81.96, 79.34, 48.33, 45.25, 45.01, 40.44, 39.95, 34.00, 31.99, 28.31, 28.18, 27.93, 27.54, 26.93, 26.09, 26.08, 22.48, 21.13, 18.68, 18.27, 18.23, 18.11; IR (thin layer, NaCl) 2977 (m), 2946 (m), 2930 (s), 2246 (w), 1452 (m), 1379 (m), 1242 (m), 1205 (m), 1173 (w), 1059 (m), 1036 (m) cm^{-1}; HRMS (FAB) *m/z* Found 625.40, calc'd for $C_{38}H_{61}O_6Na$ [M+Na]: 625.41.

Preparation of triethylamine salts 195:



To a suspension of **171** (11.22 g, 46 mmol) in H_2O (250mL) was added Et_3N (50mL) in MeOH (50mL) and the reaction was heated to reflux for 4 h. The solvent was evaporated under reduced pressure, and the residue was dried by azeotropic distillation with benzene. The residue (**195**) was used immediately without further purification, no characterization data was collected for this compound.

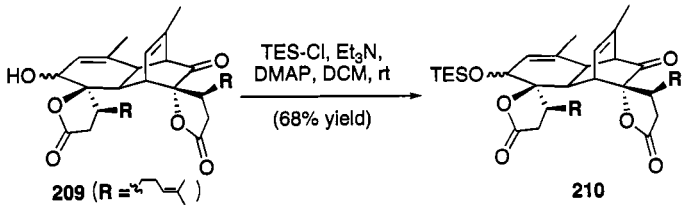
Preparation of allylic alcohol 209:



To a solution of dimer **171** (100 mg, 0.19 mmol) and $CeCl_3{\cdot}7H_2O$ (160 mg, 0.42 mmol) in a mixture of MeOH (5 mL) and DCM (2 mL) at -78°C was added $NaBH_4$ (20 mg, 0.53 mmol). After 1 h, the reaction was poured over $NaHCO_3$ (saturated in water), the aqueous phase was extracted three times with DCM, the combined organic layers were dried over Na_2SO_4, filtered and rotary evaporated. The residue was purified by flash chromatography (gradient elution, 20→50% EtOAc/Hexanes) to yield an unseparable mixture of diastereomers (4:1) of the title compound **209** (73 mg, 74% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (s, 0.8H), 5.96 (s, 0.2H), 5.76 (d, J = 6.5 Hz, 0.2H), 5.67 (d, J = 5.1 Hz, 0.8H), 4.96-5.06 (m, 2H), 4.11 (dd, J = 2.2, 6.2 Hz, 0.2H), 3.58 (d, J = 3.4 Hz, 0.8H), 3.02-3.11 (m, 3H), 2.73-2.80 (m, 2H), 2.55-2.69 (m, 2H), 2.38 (dd, J = 17.5, 7.4 Hz, 1H), 2.29 (dd, J = 17.7, 6.2 Hz, 1H), 2.06-2.22 (m, 2H), 2.05 (s, 3H), 1.95-2.06 (m, 2H), 1.75-1.92 (m, 2H), 1.68 (s, 3H), 1.62 (s, 3H), 1.58 (s, 3H), 1.57 (s, 3H), 1.40–1.56 (m, 3H), 1.14–1.31 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 193.84, 176.47, 175.03, 159.90, 158.23, 141.72, 140.96, 133.42, 133.05, 132.61, 125.89, 123.12, 123.04, 122.66, 122.39, 92.63, 87.74, 87.66, 85.76, 71.85, 49.80, 48.97, 45.73, 44.51, 44.42, 43.34, 39.11, 38.27, 38.03, 37.85, 35.10, 34.95, 34.54, 33.23, 33.04, 32.96, 30.29, 30.13, 29.28, 29.06, 26.14, 25.95, 25.85, 25.74, 23.19, 22.56, 21.82; IR (thin layer, NaCl) 3458 (br, s), 2929 (s), 1782 (sh, s), 1689 (sh, s), 1440 (w), 1198 (br, m) cm^{-1}; HRMS (FAB) *m/z* found 523.31, calc'd for $C_{32}H_{43}O_6$ [M+H]: 523.30.

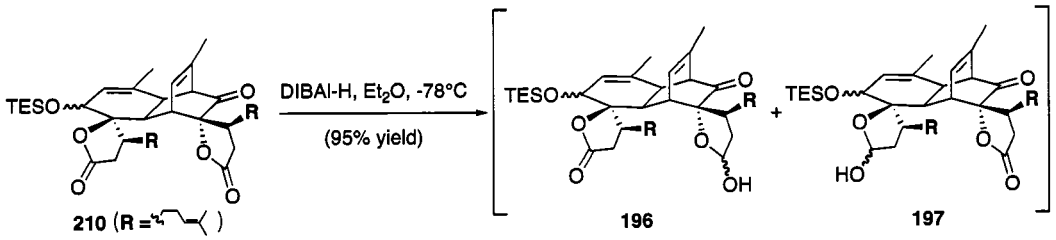
Preparation of TES ether 210:



To a solution of the allylic alcohol **209** (55 mg, 0.10 mmol) in DCM (5 mL) were added Et_3N (60 μL, 0.42 mmol), TES-Cl (40 μL, 0.23 mmol) and a catalytic amount of DMAP (5 mg) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 1d. The reaction was diluted with DCM, washed with $NaHCO_3$ (saturated in water), dried over Na_2SO_4, filtered and rotary evaporated. The residue was purified by flash chromatography (20% EtOAc/Hexanes) to yield the title compound **210** (46 mg, 68% yield) as a white foam: ^1H NMR (500 MHz, $CDCl_3$) δ 5.97 (br s, 1H), 5.68(d, J = 6.3 Hz, 1H), 4.99 (d, J = 6.6 Hz, 1H), 3.59 (d, J = 3.2 Hz, 1H), 3.2 (d, J = 8.0 Hz, 1H), 3.12 (d, J = 7.2 Hz, 1H), 2.99 (d, J = 6.4 Hz, 1H), 2.61 (br s, 1H), 2.60-2.51 (m, 2H), 2.34-2.27 (m, 2H), 2.20-2.15 (m, 1H), 2.04-1.95 (m, 2H), 2.00 (s, 3H), 1.95-1.90 (m, 1H), 1.90-1.77 (m, 2H), 1.68 (s, 6H), 1.61 (s, 3H), 1.58 (s, 3H), 1.57 (s, 3H), 1.57-1.45 (m, 3H), 1.27-1.15 (m, 2H), 1.00 (t, J = 7.9 Hz, 9H), (q, J = 7.9 Hz, 6H); ^{13}C NMR (125

MHz, $CDCl_3$) δ 194.40,178.85, 175.29, 160.25, 141.35, 133.58, 133.30, 128.71, 126.40, 123.72, 123.26, 122.89, 88.23, 85.83, 73.27, 50.53, 46.18, 44.97, 38.92, 38.71, 35.51, 33.84, 33.48, 30.45, 29.66, 29.32, 26.22, 26.05, 22.78, 22.20, 18.13, 7.26, 5.42; IR (thin layer, NaCl) 3956 (br, m), 2897 (br, m), 1785 (sh, m), 1691 (sh, m), 1636 (sh, m), 1441 (m), 1381 (m) cm^{-1}; HRMS (ES) *m/z* found 659.39, calc'd for $C_{38}H_{56}O_6Na$ [M+Na]: 659.38.

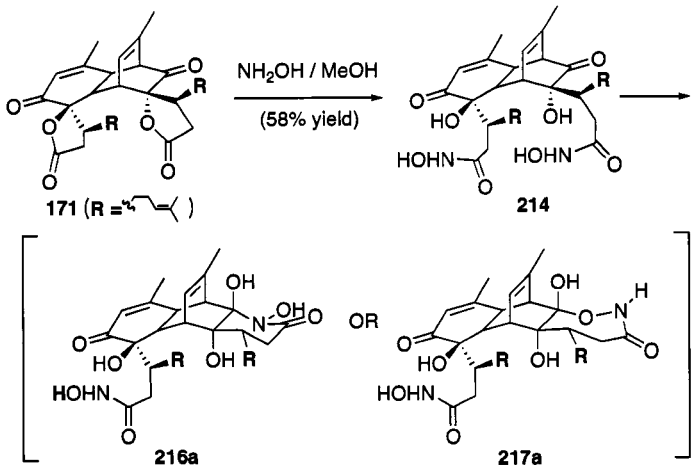
Preparation of lactols 196 and 197:



To a solution of bis-lactone **210** (75 mg, 0.12 mmol) in Et_2O (3 mL) was added a 1M solution of DiBAl-H in PhMe (0.24 mL, 0.24 mmol) dropwise at -78°C. The reaction was monitored by TLC until complete consumption of starting material was observed. After about 5 min, cold water (1 mL) was added to quench the reaction, was then warmed up to 0°C, and HCl (1M in water) was added dropwise until the white suspension went in solution. The aqueous and ether phases were partitioned and the aqueous phase was extracted two more times with ether. The organic phases were combined, dried over Na_2SO_4, filtered and rotary evaporated. The residue was purified by flash chromatography (50% EtOAc/Hexanes) to yield an unseparable mixture of the title compounds **196** and **197** (79 mg, 95% yield) as a white foam: ^1H NMR (500 MHz, $CDCl_3$) δ 5.99 (s, 1H), 5.97-5.92 (m, 1H), 5.66 (d, J = 5.7 Hz, 2H), 5.50 (br s, 2H), 5.05-

4.94 (m, 4H), 4.14 (br s, 1H), 3.57 (d, J = 5.1 Hz, 1H), 3.43-3.22 (m, 2H), 3.16 (dd, J = 9.1, 2.4 Hz, 1H), 3.11 (dd, J = 8.1, 2.8 Hz, 1H), 3.06-2.99 (m, 1H), 2.86 (dd, J = 8.3, 2.5 Hz, 1H), 2.57 (br s, 1H), 2.53 (t, J = 6.1 Hz, 1H), 2.49-2.36 (m, 1H), 2.31 (dd, J = 18.0, 6.1 Hz, 1H), 2.00 (s, 3H), 1.95-1.88 (m, 1H), 1.87-1.77 (m, 1H), 1.68 (s, 6H), 1.59 (s, 3H), 1.58 (s, 3H), 1.57 (s, 3H), 1.53-1.35 (m, 2H), 1.00 (t, J = 7.9 Hz, 9H), 0.66 (q, J = 8.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.70, 175.94, 160.67, 140.70, 132.83, 132.44, 126.52, 124.03, 123.95, 123.84, 123.57, 123.39, 123.04, 98.20, 88.70, 85.88, 73.08, 50.11, 47.16, 45.97, 40.47, 38.93, 38.10, 36.15, 33.65, 30.59, 29.05, 26.94, 25.67, 22.40, 21.80, 17.74, 17.71, 6.89, 6.82, 5.10; IR (thin layer, NaCl) 3426 (br, m), 2955 (m), 28.76 (m), 1779 (sh,m), 1680 (sh, m), 1441 (m), 1380 (m) cm^{-1}; HRMS (FAB) *m/z* found 661.50, calc'd for $C_{38}H_{58}O_6NaSi$ [M+Na]: 661.39.

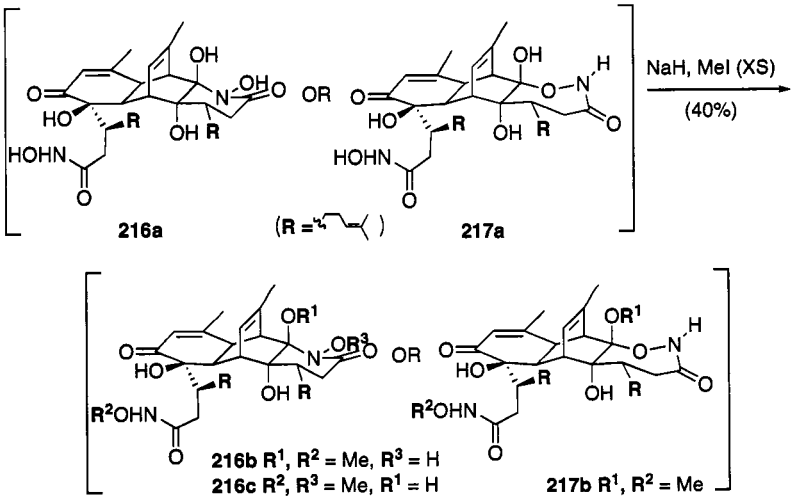
Preparation of hydroxamic acid 216a or 217a:



To a solution of dimer **171** (240 mg, 0.46 mmol) in MeOH (10 mL) was added a 1M solution of NH_2OH in MeOH (3.6 mL, 3.6 mmol). The reaction was monitored by TLC until complete consumption of starting material was observed. After 2 d, the

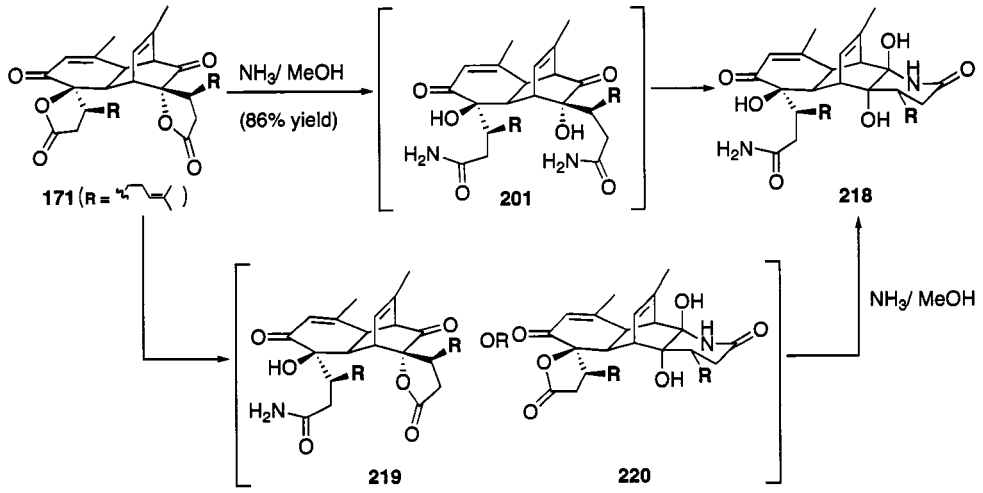
reaction was rotary evaporated and the residue purified by flash chromatography (gradient elution, 1→3% MeOH/DCM) to yield the title compound **216a** or **217a** (163 mg, 58% yield) as a yellow foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (br s, 1H), 5.99 (s, 1H), 5.67 (d, J = 5.9 Hz, 1H), 5.32 (br s, 1H), 4.99 (d, J = 5.2 Hz, 1H), 4.32 (s, 1H), 3.61 (s, 1H), 3.26 (d, J = 6.7 Hz, 1H), 3.17 (d, J = 4.6 Hz, 2H), 2.59 (dd, J = 17.6, 8.5 Hz, 1H), 2.47 (d, J = 16.2 Hz, 1H), 2.38-2.30 (m, 2H), 2.28-2.18 (m, 1H), 2.10-1.97 (m, 2H), 2.06 (s, 3H), 1.93-1.83 (m, 2H), 1.78 (t, J = 10.4 Hz, 1H), 1.73-1.53 (m, 2H), 1.68 (s, 3H), 1.66 (s, 3H), 1.65 (s, 3H), 1.58 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.76, 176.47, 171.65, 160.02, 140.76, 133.50, 132.76, 128.34, 126.61, 123.54, 123.38, 122.35, 88.77, 88.03, 48.27, 44.46, 41.16, 41.07, 38.57, 33.41, 31.45, 30.10, 27.84, 27.79, 25.86, 25.71, 25.67, 25.19, 21.58, 17.88, 17.80; IR (thin layer, NaCl) 3324 (br, s), 2963 (w), 2928 (m), 2858 (w), 1790 (sh, s), 1772 (sh, s), 1686 (sh, s), 1663 (sh, s), 1653 (sh, s), 1437 (m), 1382 (m) cm^{-1}; HRMS (FAB) *m/z* found 554.30, calc'd for $C_{32}H_{46}N_2O_6$ [M-NH_2O]: 554.33.

Preparation of hydroxymate 216b or 216c or 217b:



To a solution of hydroxamic acid **216a** or **217a** (150 mg, 0.26 mmol) in DMF (8 mL) was added a 60% oil suspension of NaH (26 mg, 0.64 mmol) at 0°C. After 30 min, excess MeI (0.3 mL) was added dropwise and the reaction was allowed to warm up to room temperature. After 2 d, the reaction was diluted with ether and washed with NH_4Cl (saturated in water), aqueous phase was extracted four more times with ether. The organic phases were combined, dried over Na_2SO_4, filtered and rotary evaporated. The residue was purified by flash chromatography (gradient elution, 1→3% MeOH/DCM) to yield the title compound **216b** or **216c** or **217b** (63 mg, 40% yield) as a yellow oil along with the starting material **216a** or **217a** (77 mg, 50% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (s, 1H), 5.81 (d, J = 7.8 Hz, 1H), 5.02 (dt, J = 15.4, 7.7 Hz, 2H), 3.84 (s, 3H), 3.53 (s, 3H), 3.17 (dd, J = 13.0, 6.8 Hz, 2H), 2.97 (d, J = 7.5 Hz, 1H), 2.60 (dd, J = 17.8, 8.9 Hz, 1H), 2.49 (dd, J = 17.2, 3.4 Hz, 1H), 2.38-2.32 (m, 2H), 2.24-2.15 (m, 1H), 2.10-1.97 (m, 2H), 2.08 (s, 3H), 1.93-1.83 (m, 2H), 1.73-1.53 (m, 3H), 1.71 (s, 3H), 1.69 (s, 3H), 1.68 (s, 3H), 1.58 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.14, 174.88, 172.78, 158.47, 138.25, 133.46, 132.24, 128.34, 126.59, 126.53, 123.75, 123.39, 122.46, 91.61, 87.83, 63.67, 53.85, 45.74, 44.30, 41.95, 40.68, 39.96, 34.05, 33.42, 33.20, 30.25, 28.01, 25.77, 25.72, 25.67, 25.53, 22.45, 17.80; IR (thin layer, NaCl) 3467 (br, m), 2924 (sh, s), 2854 (sh, m), 1786 (sh, s), 1691 (sh, s), 1457 (m), 1378 (m), 1332 (w), 1269 (w) cm^{-1}; HRMS (FAB) *m/z* found 637.32, calc'd for $C_{34}H_{50}N_2O_8Na$ [M+Na]: 637.36.

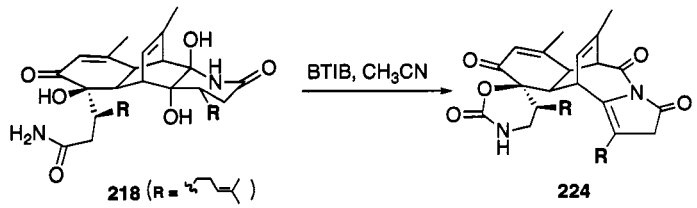
Preparation of amide 218:



To dimer **171** (1.8 g, 3.5 mmol) was added a saturated solution of NH_3 in MeOH (200 mL). The reaction was monitored by TLC until complete consumption of starting material was observed. After 2 d, the reaction was rotary evaporated and the residue purified by flash chromatography (gradient elution, 3→7% MeOH/DCM) to yield the title compound **218** (1.16 g, 60% yield) as a beige solid, along with mixture of mono-amides **219** and **220** (0.75 g, 40 % yield) that were treated again with NH_3 to access more amide **218**: ^{1}H NMR (500 MHz, CD_3OD) δ 5.77 (s, 1H), 5.35 (d, J = 6.6 Hz, 1H), 5.06 (t, J = 6.6 Hz, 1H), 4.97 (t, J = 6.5 Hz, 1H), 3.13 (d, J = 6.4 Hz, 1H), 3.08 (d, J = 6.5 Hz, 1H), 2.99 (d, J = 6.7 Hz, 1H), 2.77 (t, J = 1.8 Hz, 1H), 2.15 (dd, J = 15.9, 12.8 Hz, 1H), 2.00 (dd, J = 15.9, 2.9 Hz, 2H), 1.9 (s, 6H), 1.85-1.72 (m, 3H), 1.62-1.45 (m, 8H), 1.62 (s, 3H), 1.58 (s, 3H), 1.53 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 204.73, 178.00, 177.86, 161.80, 141.30, 133.51, 127.51, 126.76, 126.13, 125.97, 125.72, 84.84, 80.48, 75.89, 54.66, 45.14, 43.05, 42.96, 41.51, 41.37, 37.96, 37.51, 33.57, 30.30, 31.17, 28.72, 26.89, 26.49, 26.32, 22.82, 22.68, 18.36, 18.25; IR (thin layer, KBr) 3404 (br, s), 3217 (br, s), 2968 (br, s), 2916 (br, s), 1659 (sh, s), 1441 (s), 1410 (s), 1374 (s), 1234 (m),

1213 (m) cm^{-1}; HRMS (FAB) *m/z* found 577.32, calc'd for $C_{32}H_{46}N_2O_6Na$ [M+Na]: 577.34 .

Preparation of carbamate 224:



218 (R =) **224**

To a solution of amide **218** (13 mg, 0.023mmol) in CH_3CN (2 mL) was added BTIB (20 mg, 0.047 mmol). The reaction was monitored by TLC until complete consumption of starting material was observed (about 3 h). The CH_3CN was rotary evaporated and the residue dissolved in DCM. The oganic phase was washed with $NaHCO_3$ (saturated in water), and the aqueous phase extracted twice with DCM. The organic phases were combined, backwashed with NaCl (saturated in water), dried over Na_2SO_4, filtered and rotary evaporated. The residue was purified by flash chromatography (gradient elution, 1→3% MeOH/DCM) to yield the title compound **224** (6.7 mg, 55% yield) as a white solid: ^1H NMR (500 MHz, $CDCl_3$) δ 6.00 (s, 1H), 5.70 (d, J = 9.3 Hz, 1H), 5.38 (d, J = 3.1 Hz, 1H), 5.06 (dd, J = 14.5, 7.5 Hz, 2H), 4.09 (d, J = 7.4 Hz, 1H), 3.60 (s, 1H), 3.44 (d, J = 7.1 Hz, 1H), 3.13 (d, J = 12.0 Hz, 1H), 3.04-2.90 (m, 4H), 2.33-2.29 (m, 3H), 2.16-2.06 (m, 3H), 2.02-1.83 (m, 3H), 1.97 (s, 3H), 1.75 (s, 3H), 1.71 (s, 3H), 1.65 (s, 3H), 1.58 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.04, 175.45, 166.58, 156.60, 152.30, 136.27, 135.27, 133.73, 132.81, 128.35, 126.95, 123.40, 123.09, 122.64, 112.46, 84.67, 55.64, 44.32, 41.10, 39.97, 38.76, 35.62, 28.04, 26.95, 26.05, 25.72, 25.45, 22.46, 21.69, 17.87, 17.83; IR (thin layer, NaCl) 3366 (br, s),

2924 (m), 2854(w), 1773 (sh, s), 1721 (sh, s), 1695 (sh, s), 1661 (sh, s), 1489 (w), 1446 (w), 1377 (w), 1310 (m), 1243 (m), 1110 (w), 1086 (w) cm^{-1}; HRMS (FAB) *m/z* found 533.30, calc'd for $C_{32}H_{41}N_2O_5$ [M+H]: 533.29.

4.9 Notes and References.

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Appendix A4: Spectra Relevant to Chapter 4.

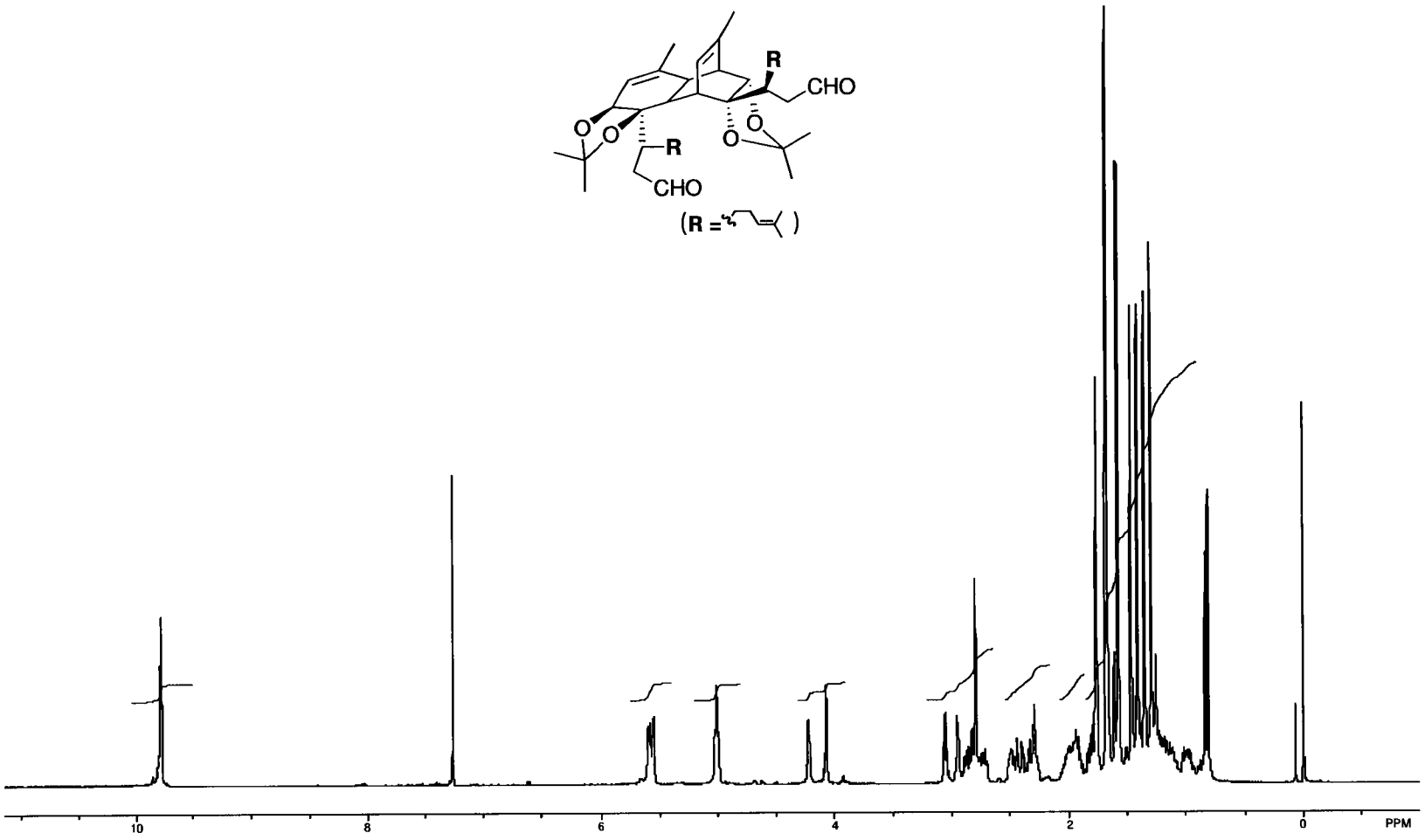


Figure A4.1 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **204**.

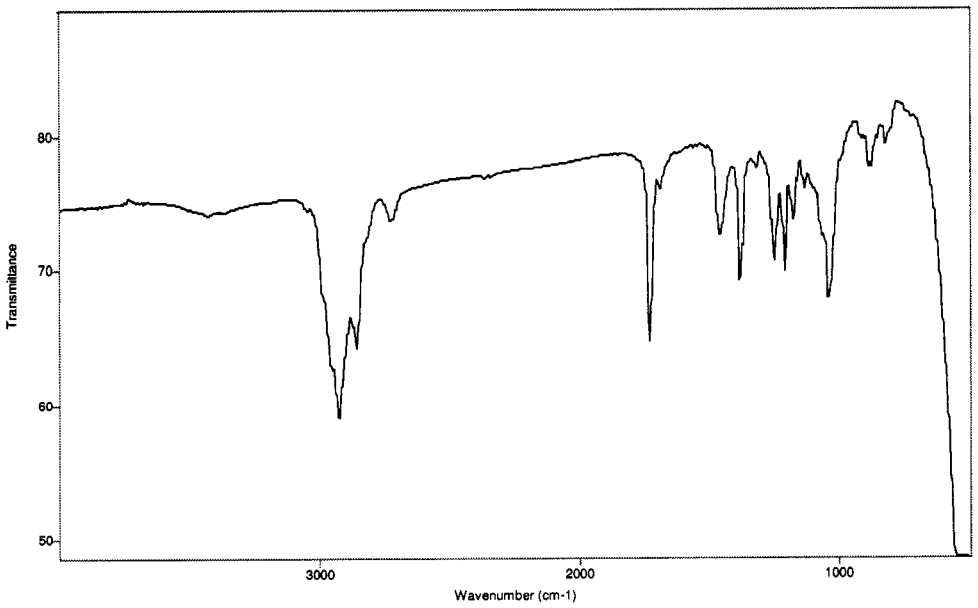


Figure A4.2 IR spectrum (thin film/NaCl) of compound **204**.

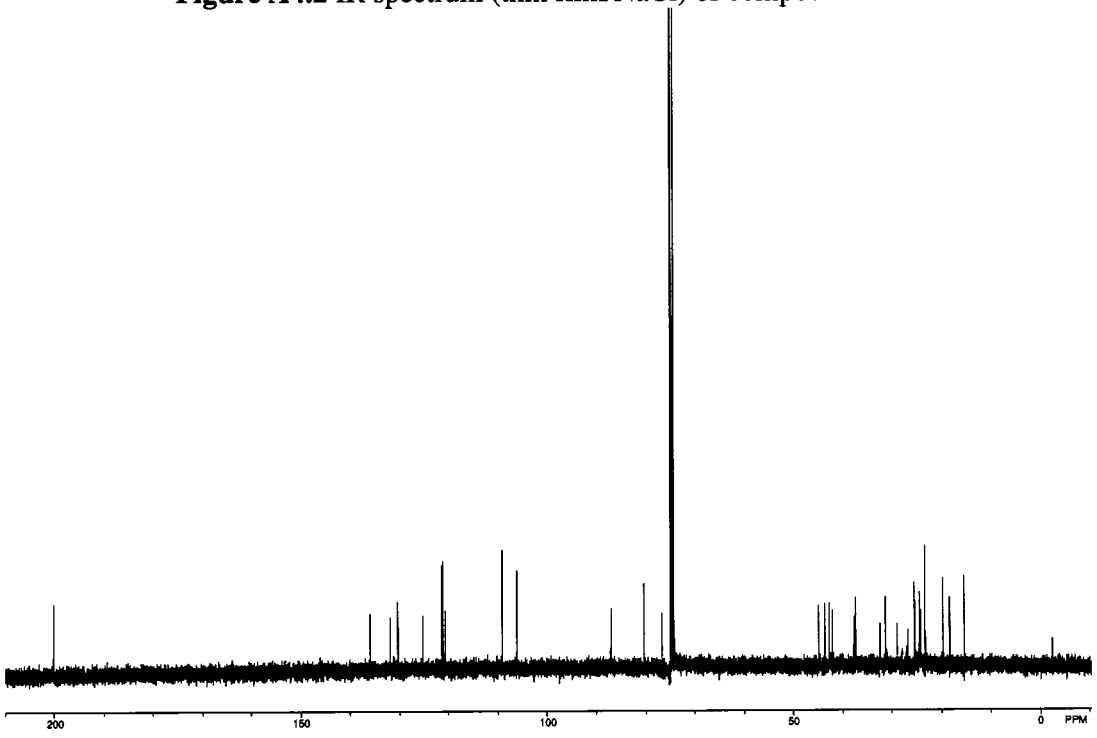


Figure A4.3 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **204**.

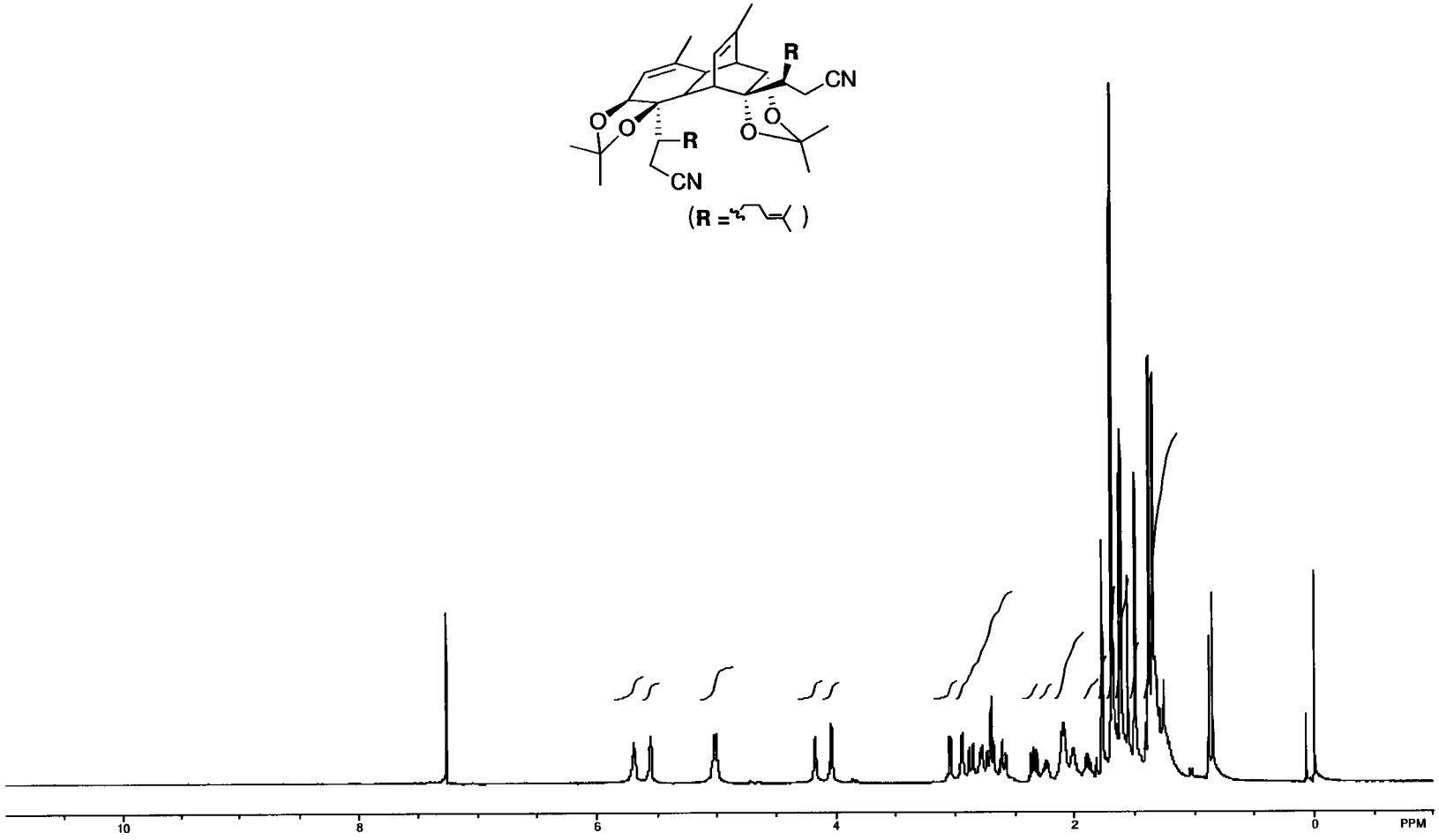


Figure A4.4 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **205**.

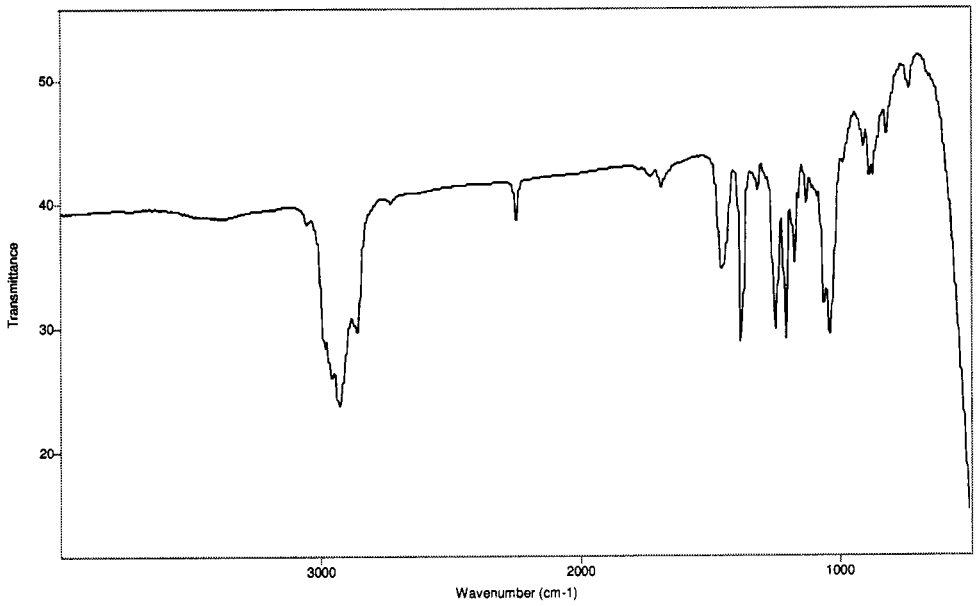


Figure A4.5 IR spectrum (thin film/NaCl) of compound **205**.

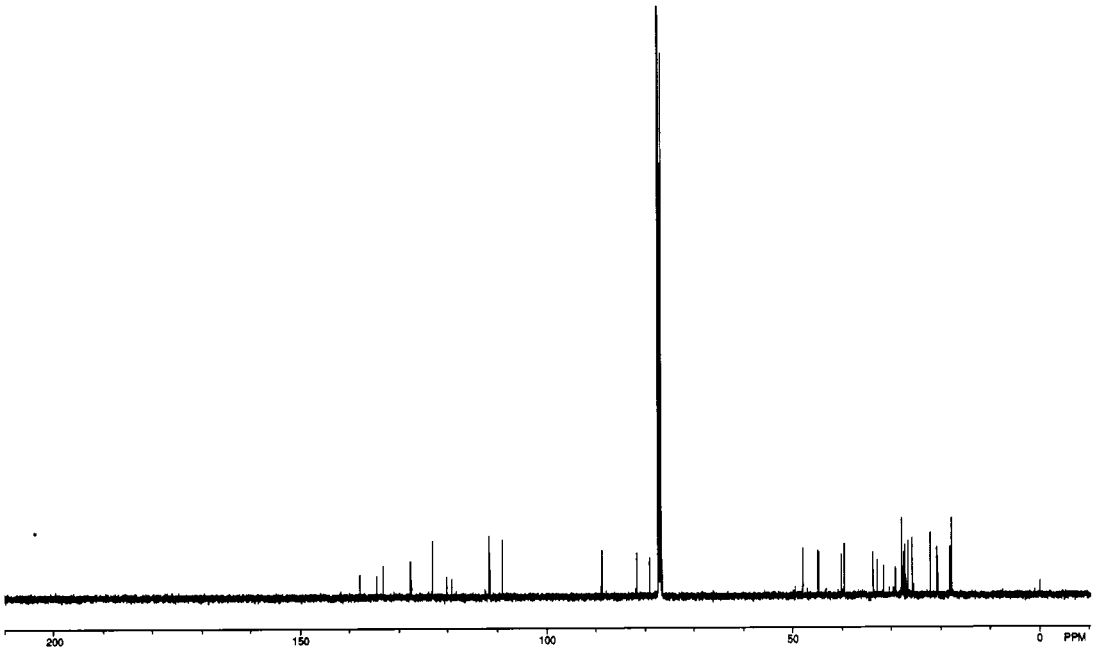


Figure A4.6 ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **205**.

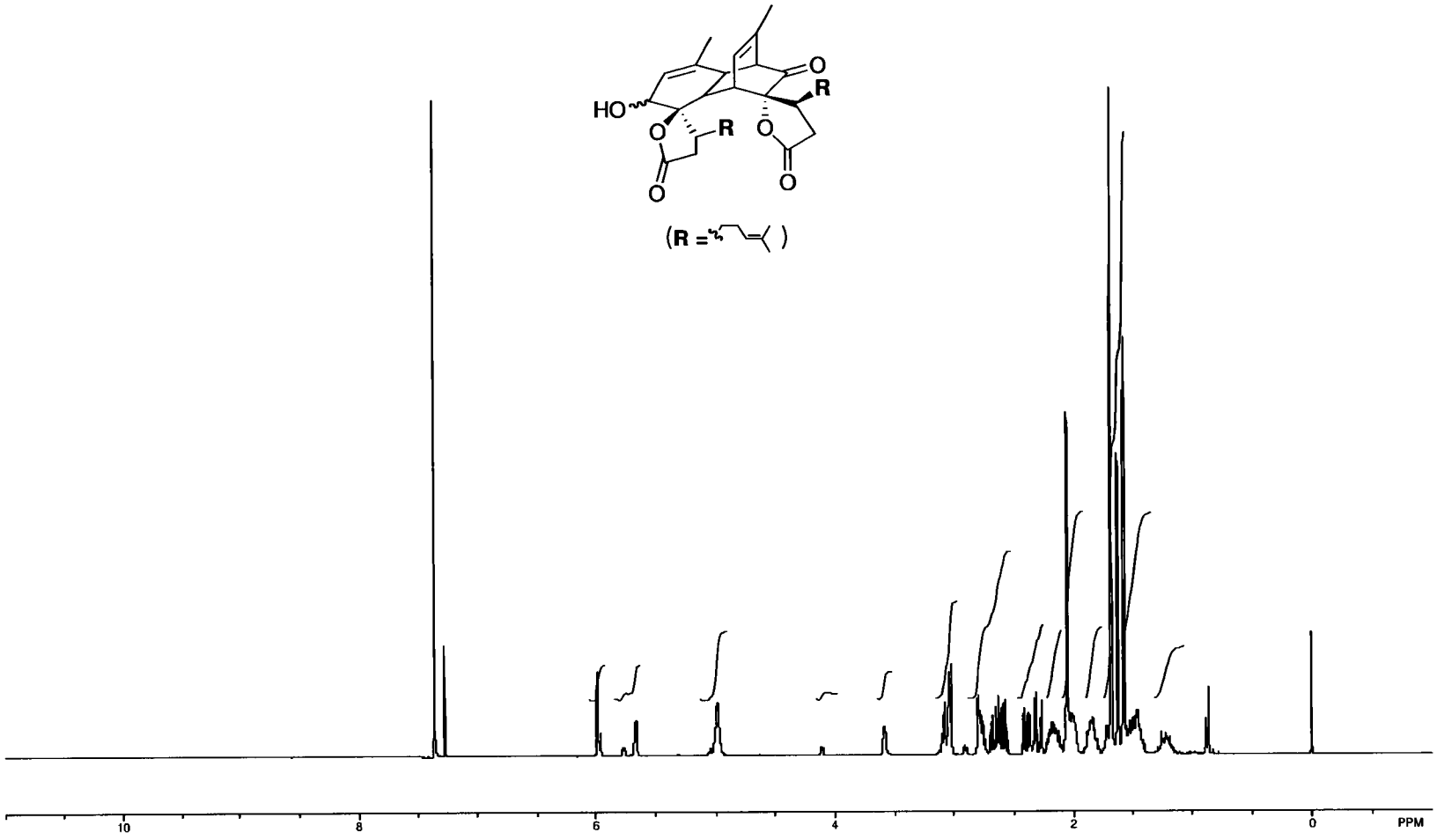


Figure A4.7 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **209**.

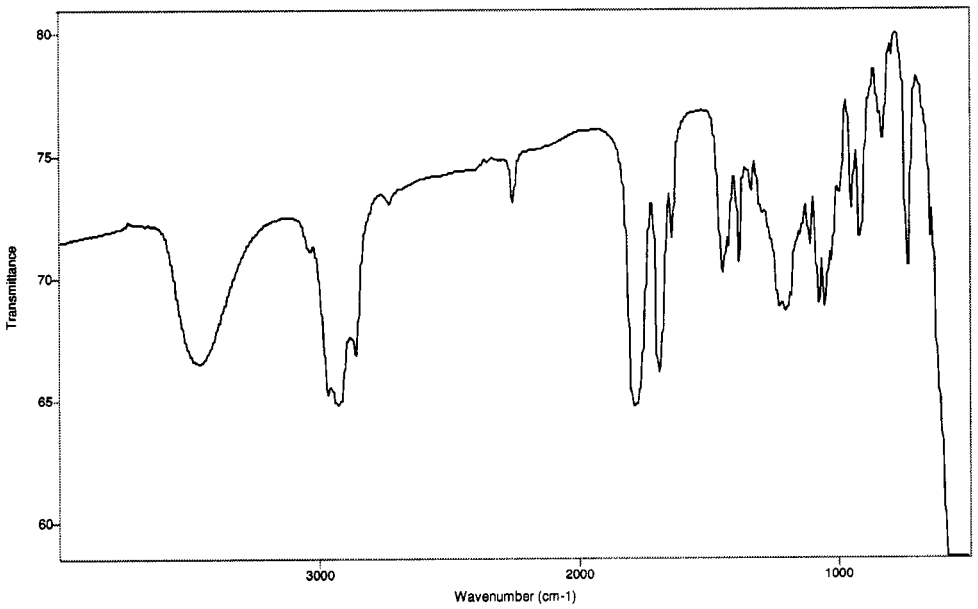


Figure A4.8 IR spectrum (thin film/NaCl) of compound **209**.

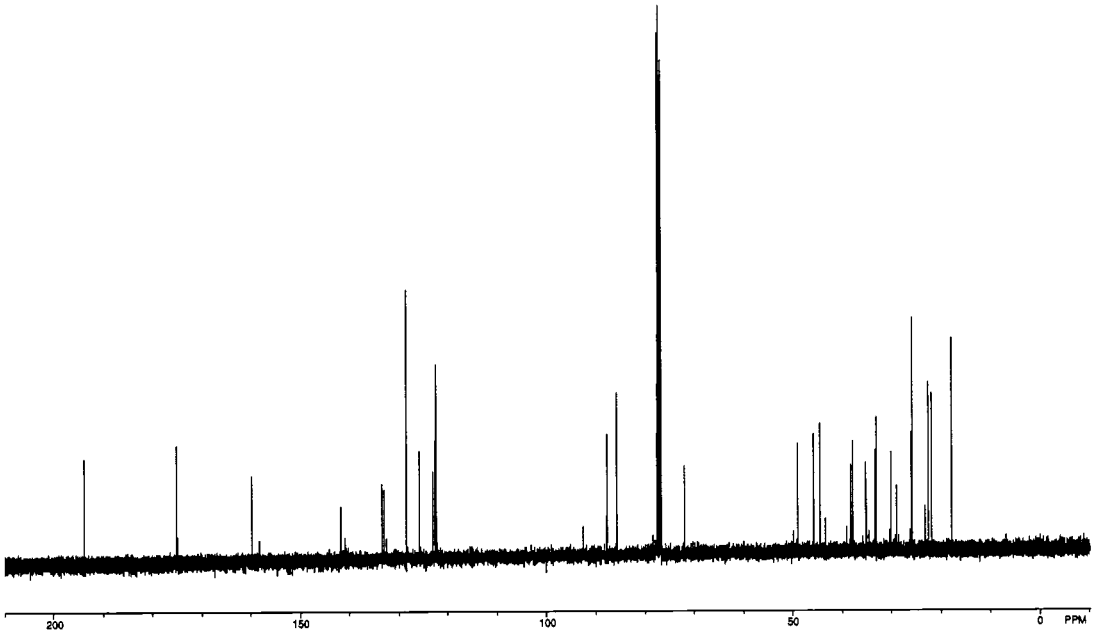


Figure A4.9 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **209**.

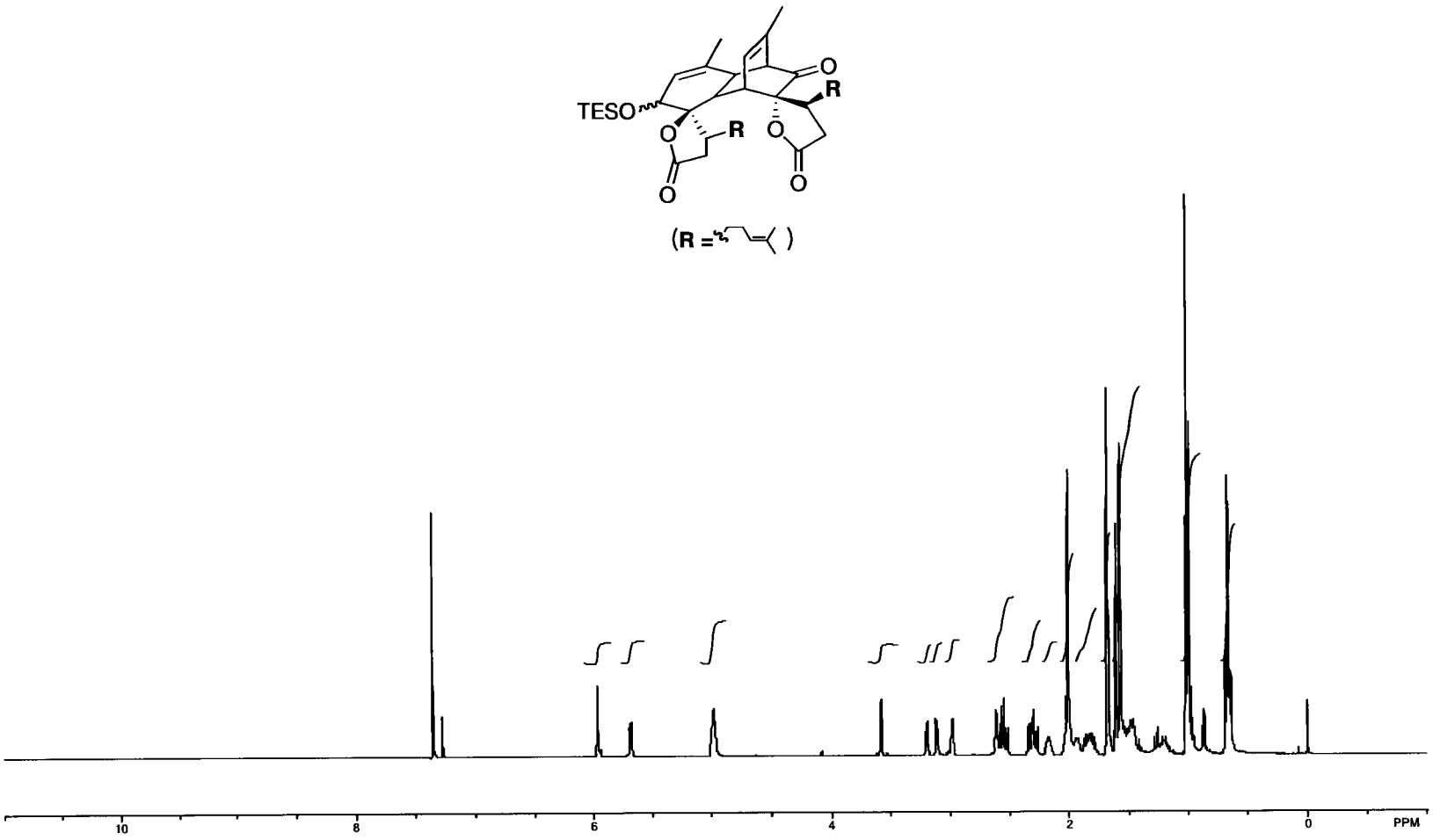


Figure A4.10 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **210**.

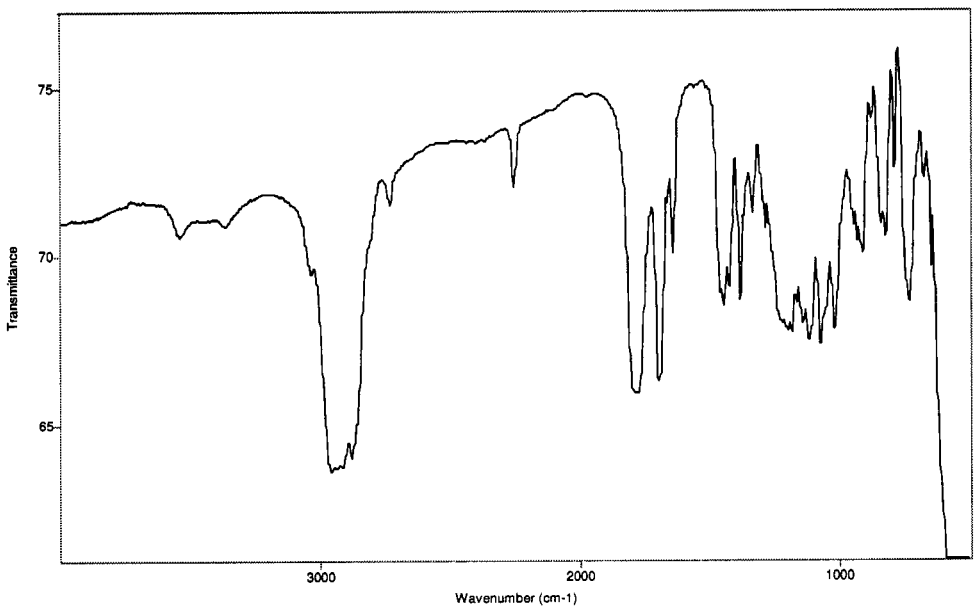


Figure A4.11 IR spectrum (thin film/NaCl) of compound **210**.

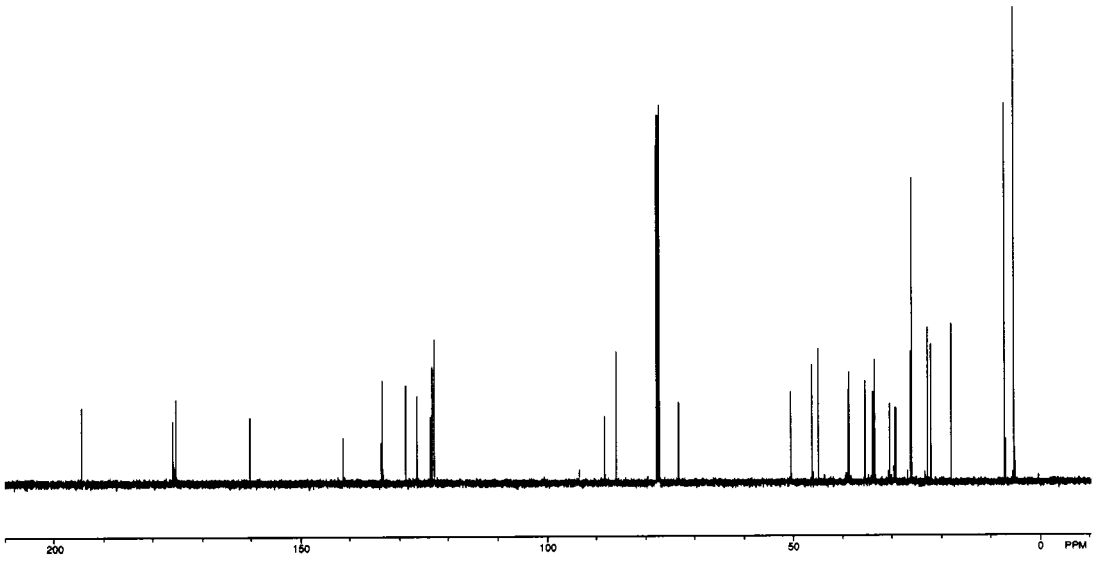


Figure A4.12 ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **210**.

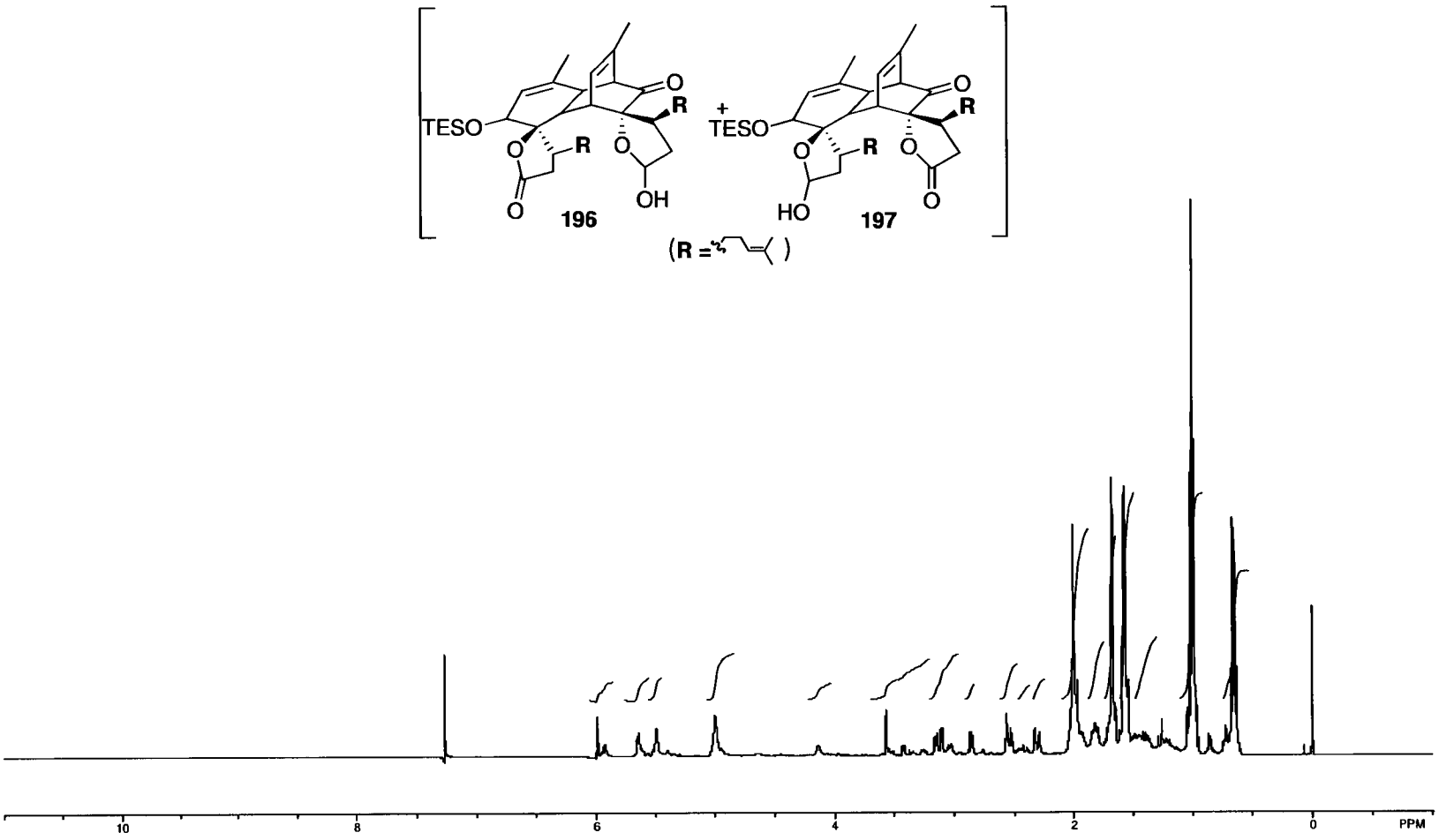


Figure A4.13 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **196** and **197**.

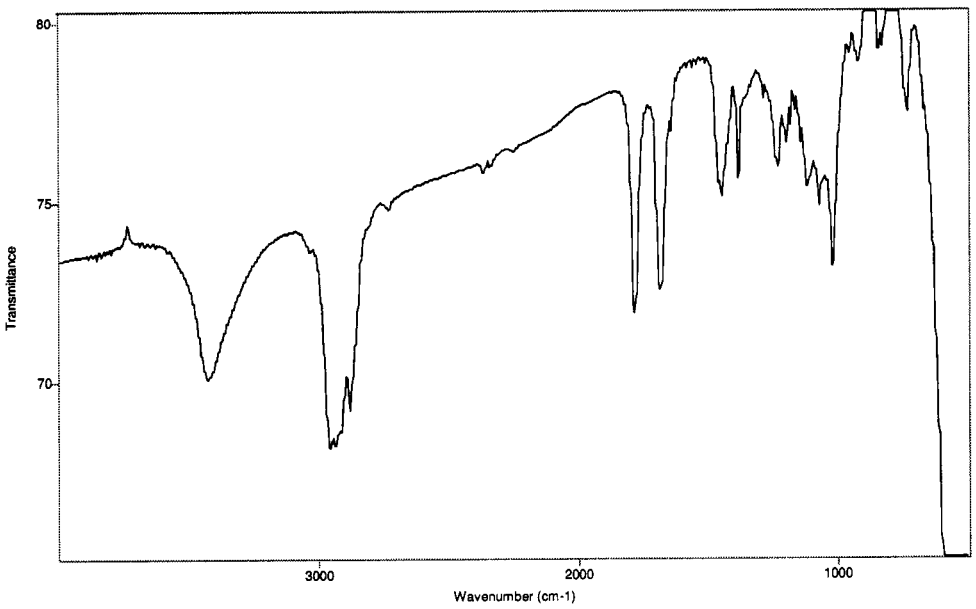


Figure A4.14 IR spectrum (thin film/NaCl) of compound **196** and **197**.

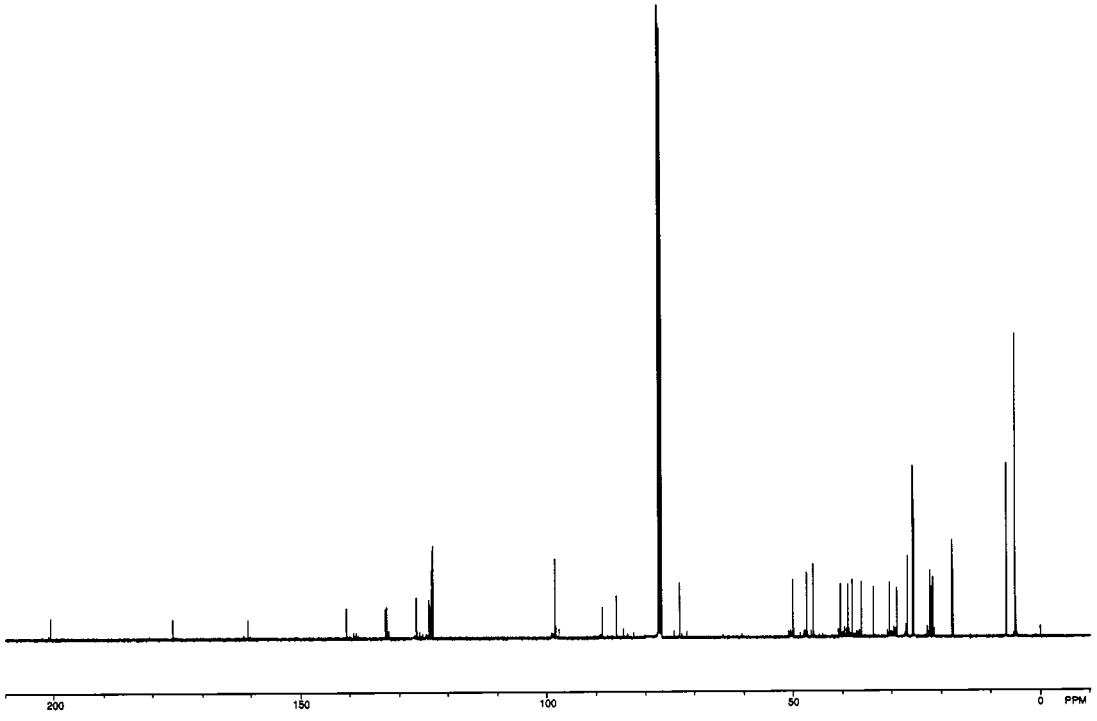


Figure A4.15 ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **196** and **197**.

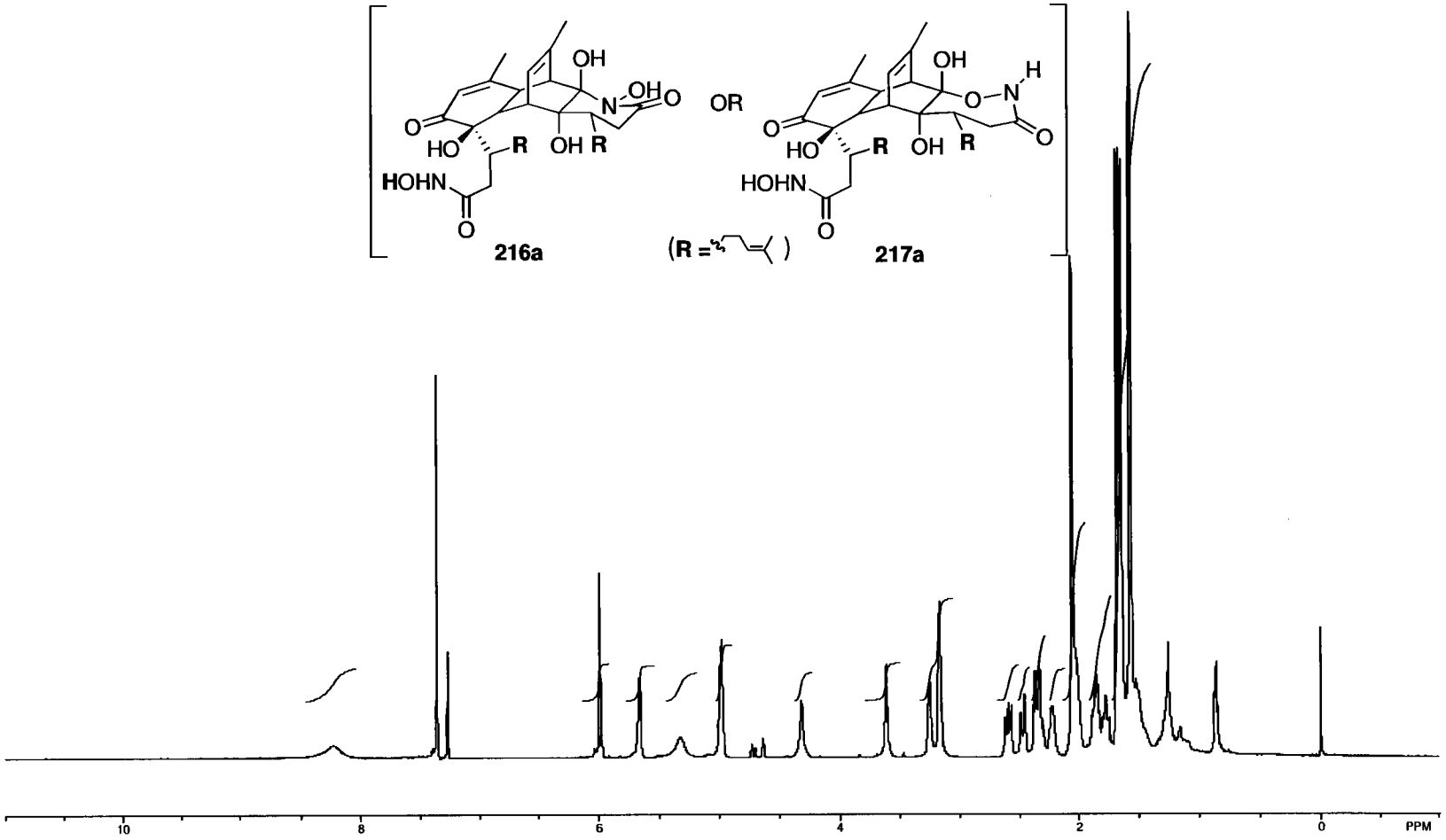


Figure A4.16 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **216a** or **217a**.

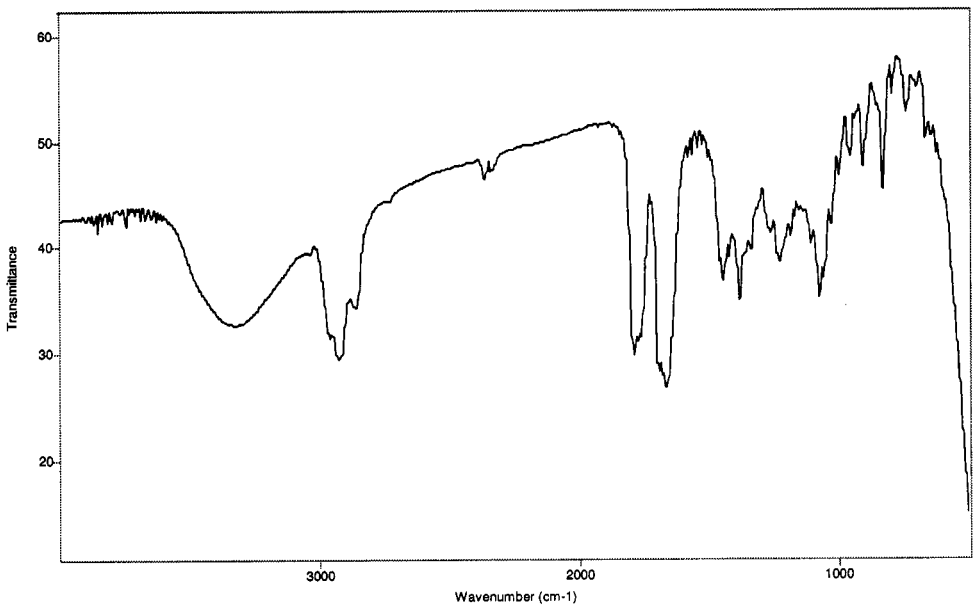


Figure A4.17 IR spectrum (thin film/NaCl) of compound **216a** or **217a**.

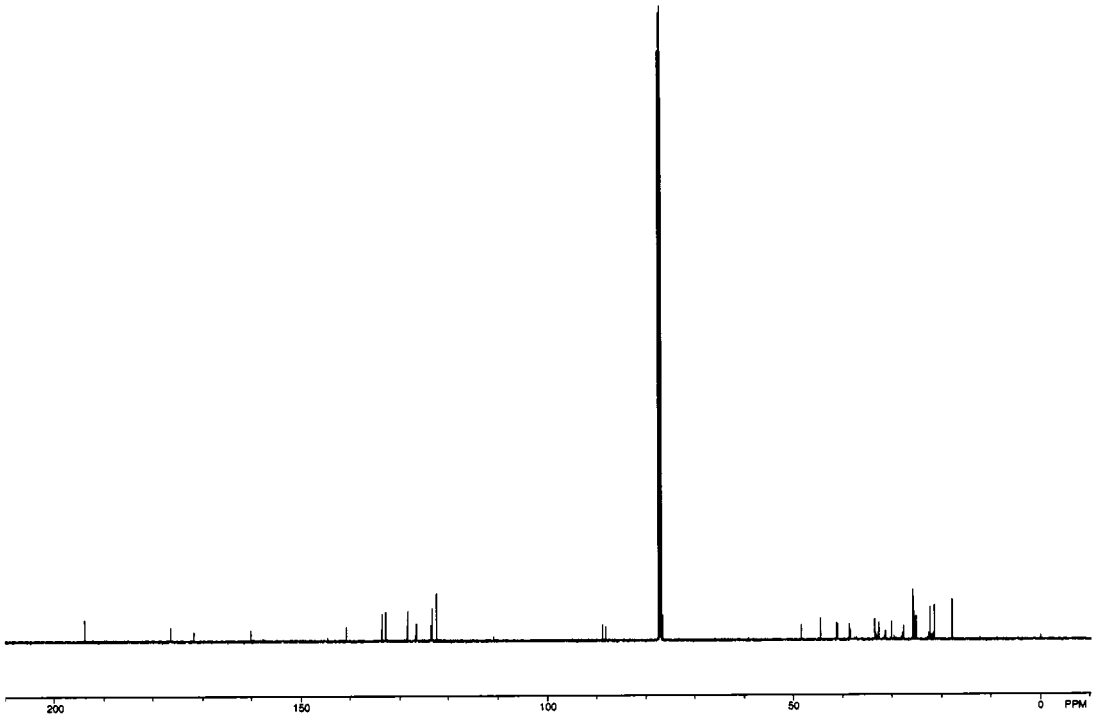


Figure A4.18 ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **216a** or **217a**.

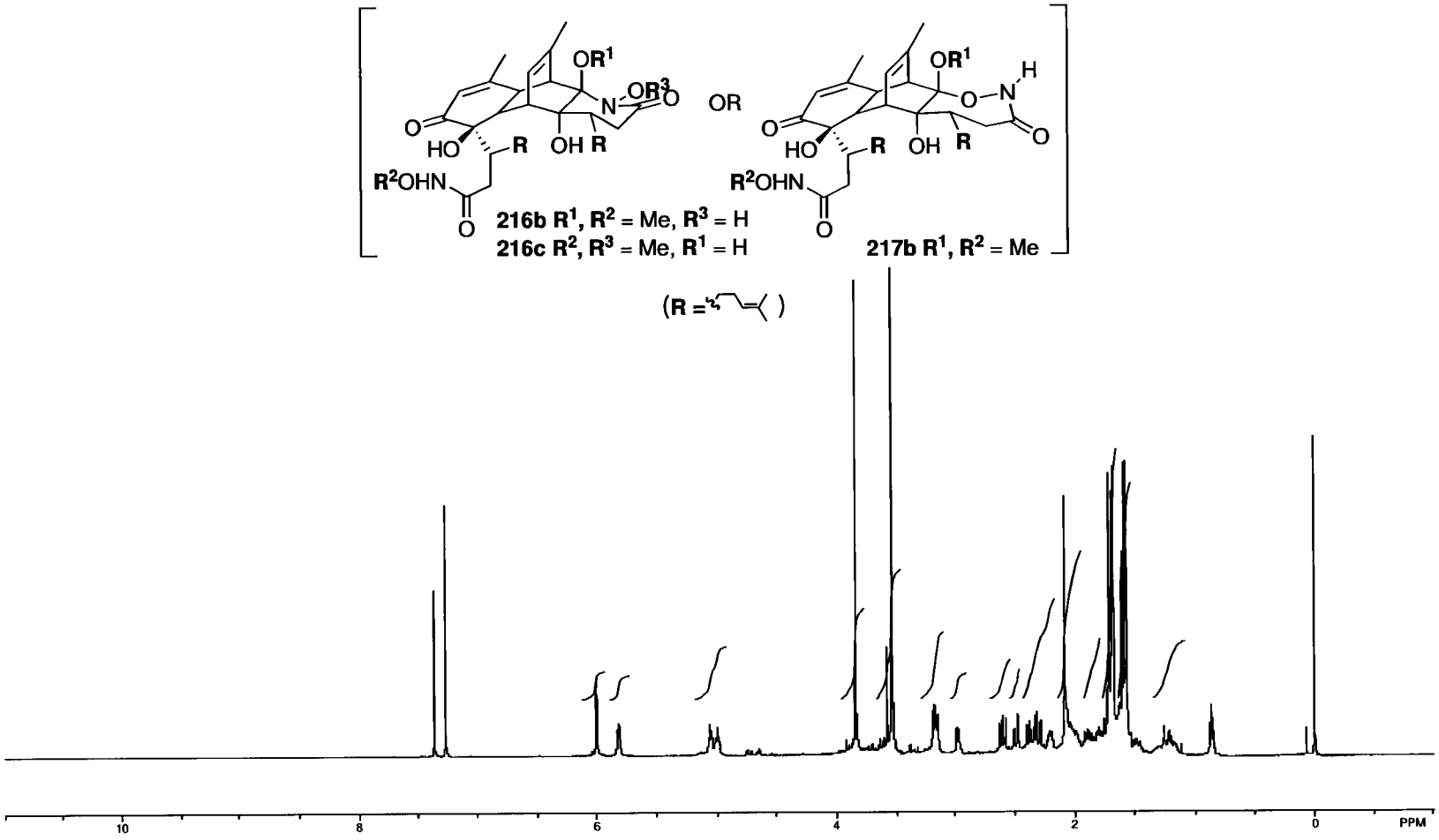


Figure A4.19 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **216b** or **216c** or **217b**.

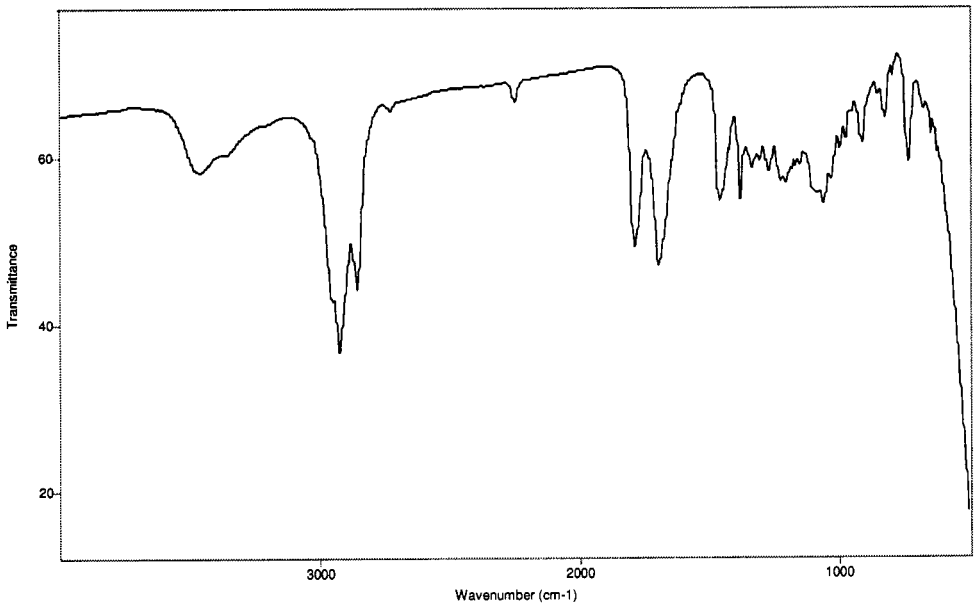


Figure A4.20 IR spectrum (thin film/NaCl) of compound **216b** or **216c** or **217b**.

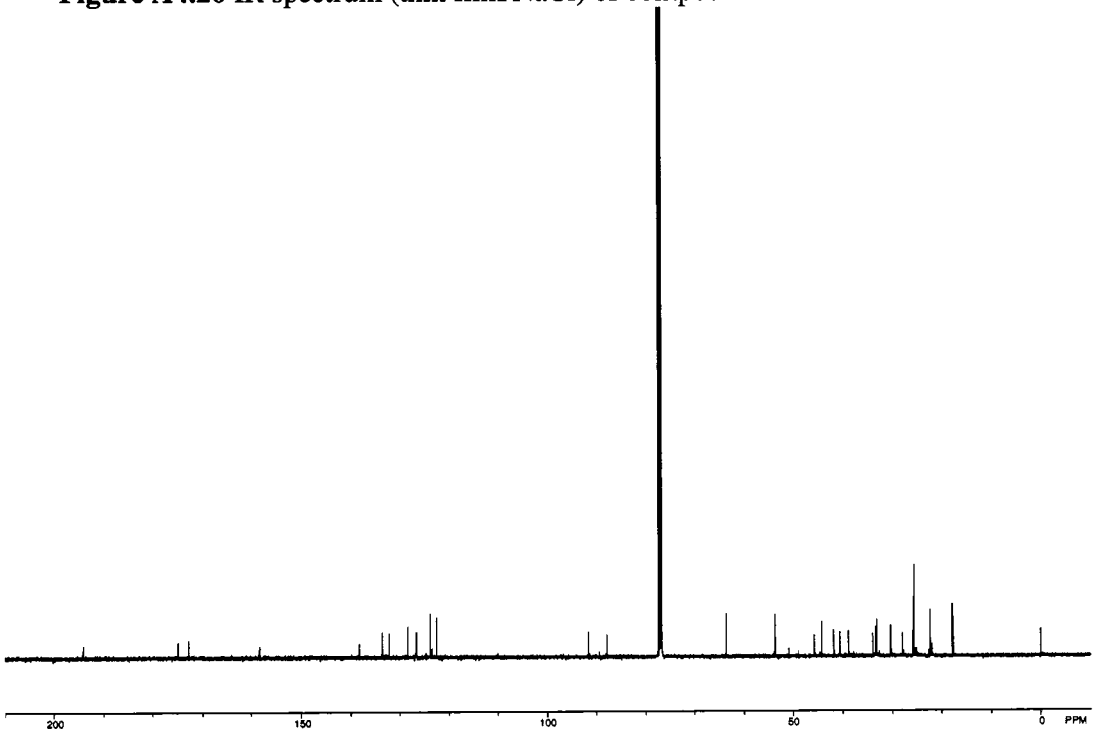


Figure A4.21 ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **216b** or **216c** or **217b**.

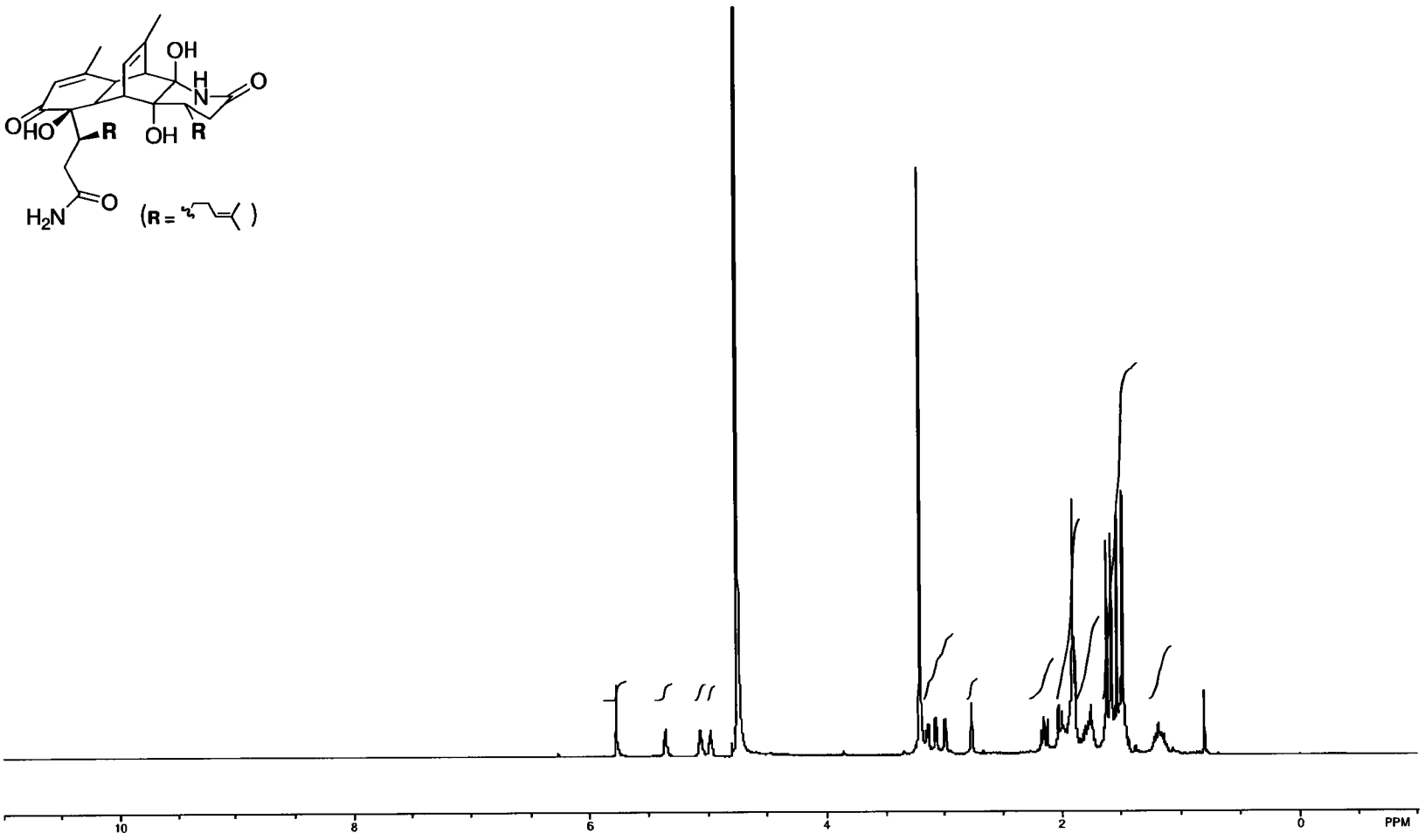


Figure A4.22 ^{1}H NMR spectrum (500 MHz, CD_3OD) of compound **218**.

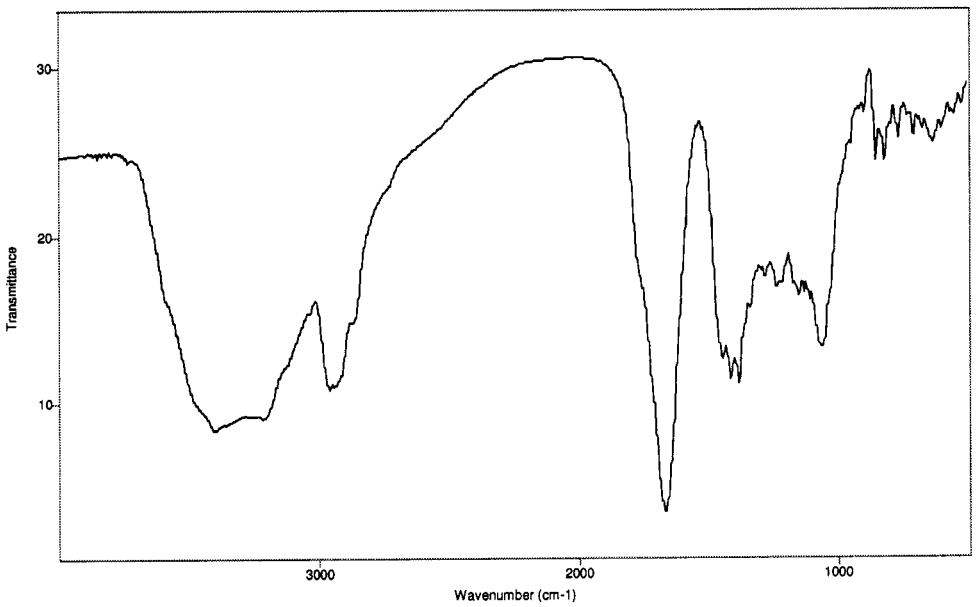


Figure A4.23 IR spectrum (thin film/NaCl) of compound **218**.

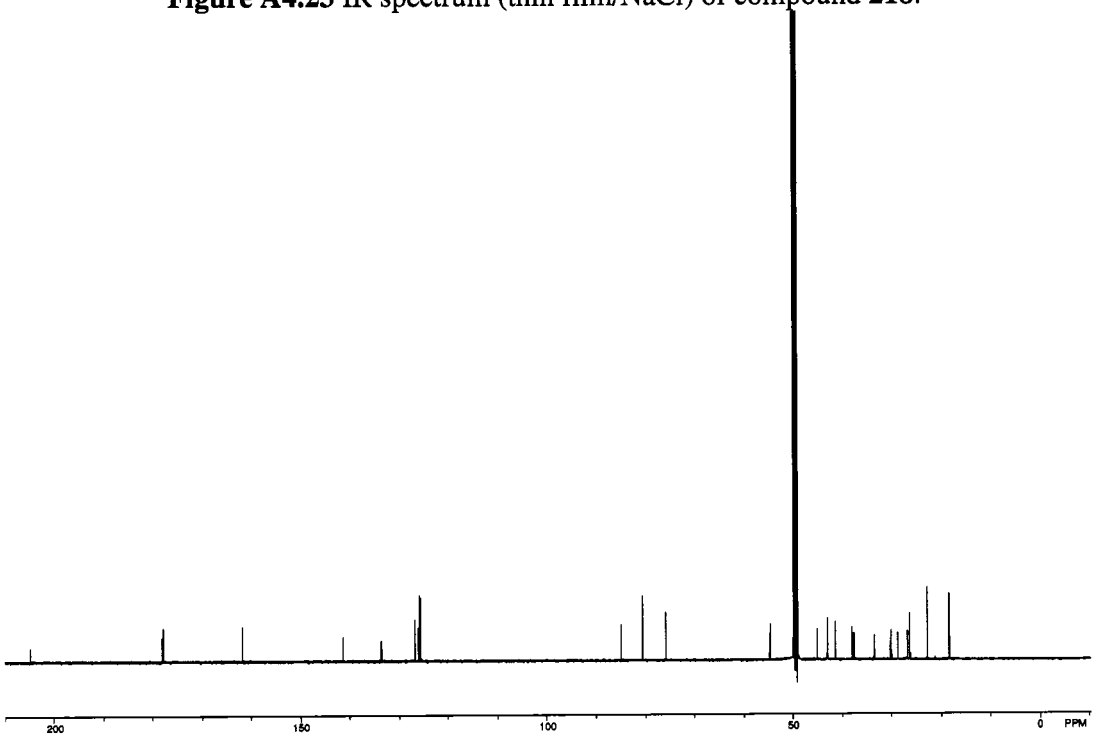


Figure A4.24 ^{13}C NMR spectrum (125 MHz, CD_3OD) of compound **218**.

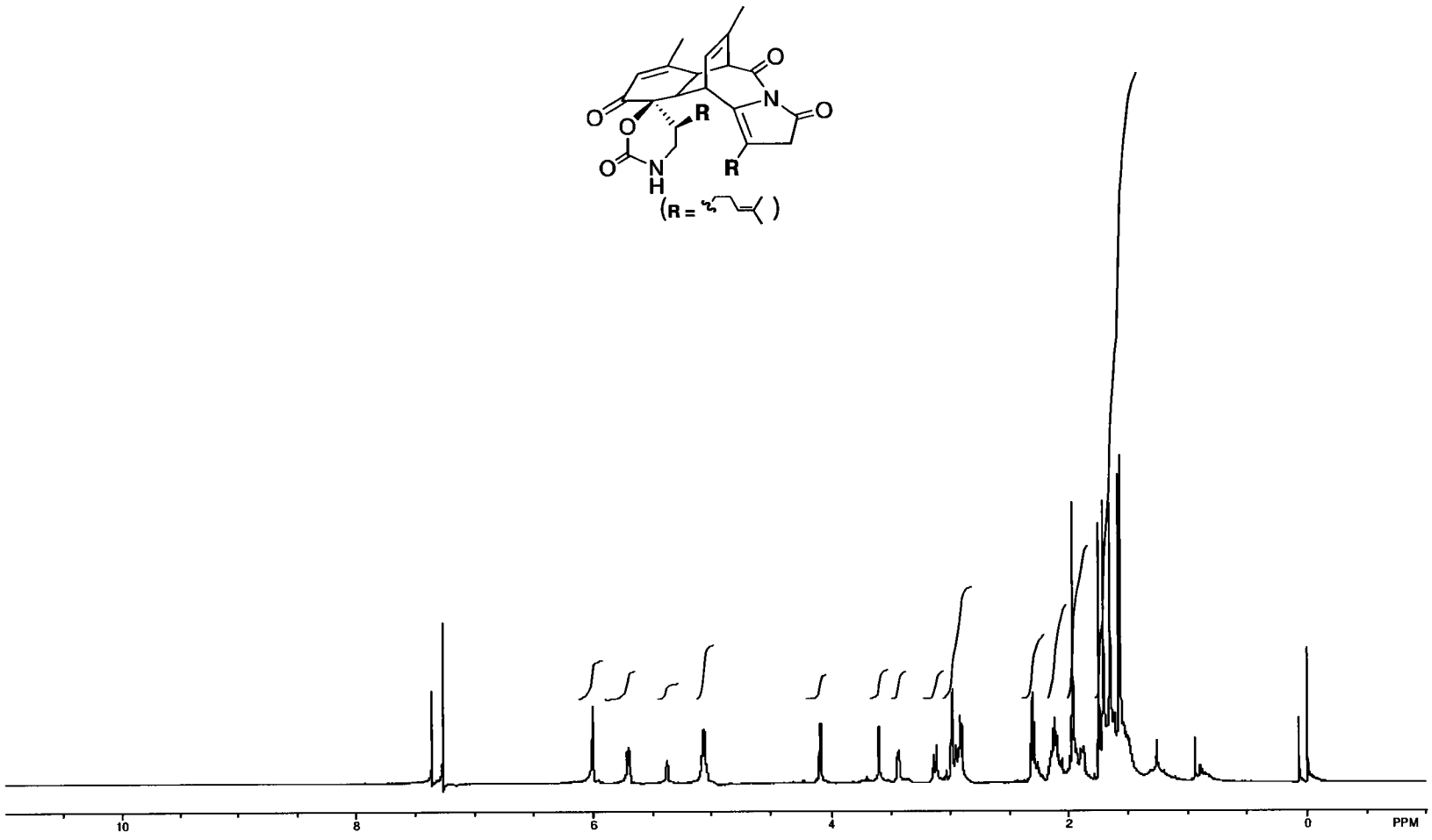


Figure A4.25 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **224**.

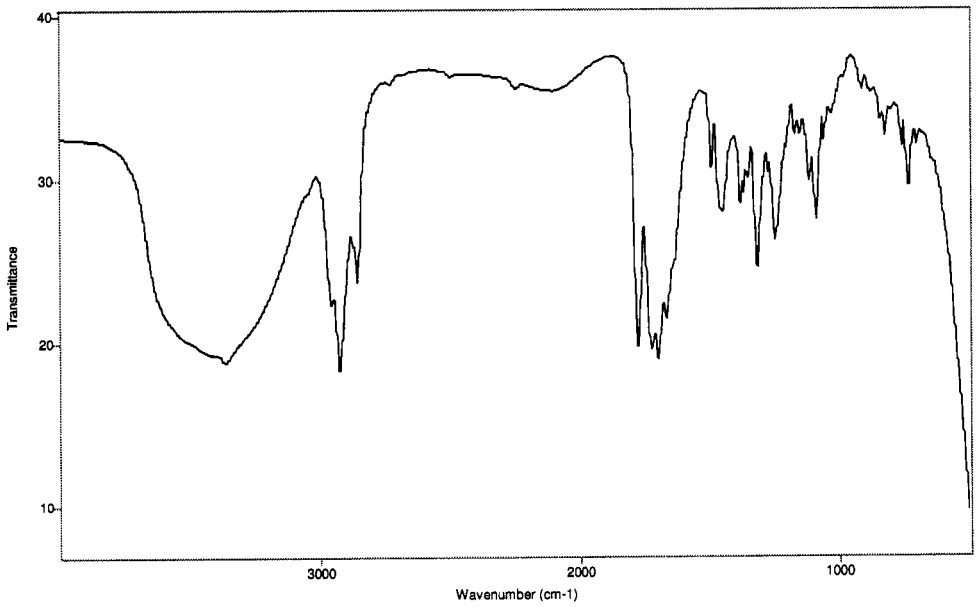


Figure A4.26 IR spectrum (thin film/NaCl) of compound **224**.

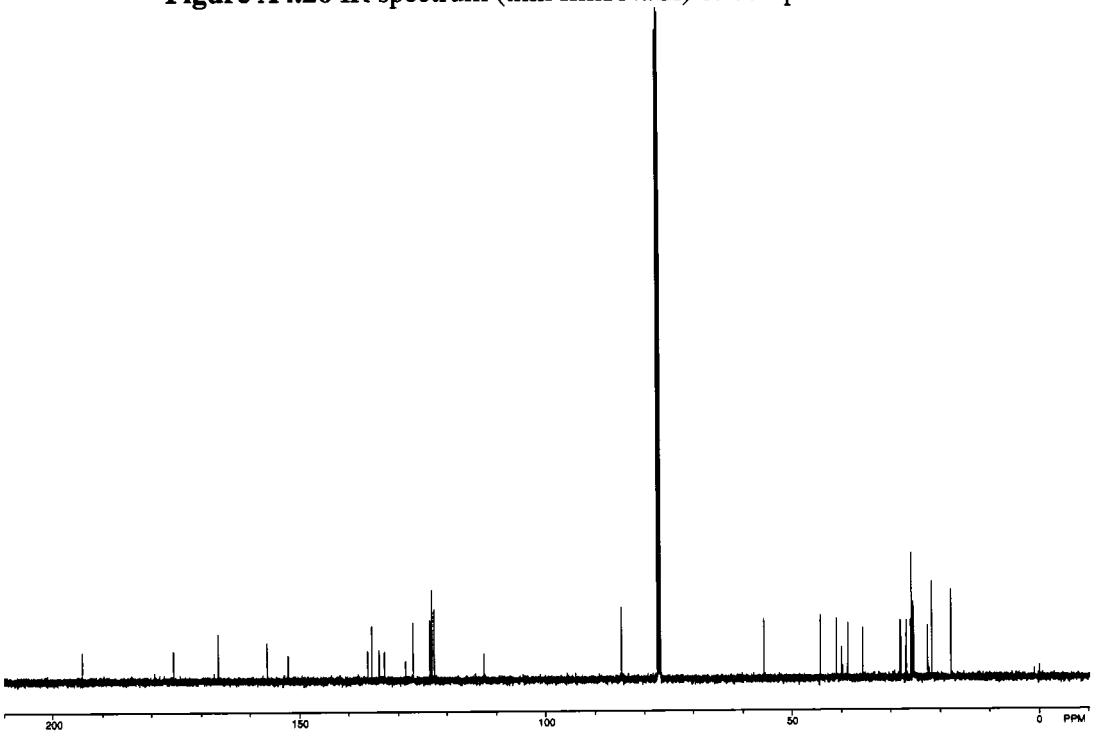


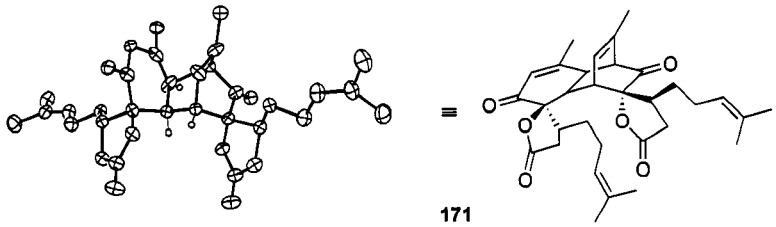
Figure A4.27 ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **224**.

Appendix A5: X-Ray Data Relevant to Chapter 4.

A5.1 X-Ray Crystallographie Report for Dimer 171.

A5.1.1 Structure and ORTEP Plot of Dimer 171.

Figure A5.1.1



171

A5.1.2 Reference Information.

YALE CHEMICAL INSTRUMENTATION CENTER

X-Ray Structure Report

Reference Number: WOOD_AB01

A5.1.3 Data Collection.[1]

A colorless plate crystal of $C_{32}H_{40}O_6$ having approximate dimensions of 0.35 x 0.25 x 0.10 mm^3 was mounted with epoxy cement on the tip of a fine glass fiber. All measurements were made on a Nonius KappaCCD diffractometer with graphite monochromated Mo-Kα radiation.

Cell constants and an orientation matrix for data collection corresponded to a primitive orthorhombic cell with dimensions:

a = 26.120(5) Å α = 90°

b = 9.0920(18) Å β = 90°

c = 11.853(2) Å γ = 90°

V = 2814.8(10) $Å^3$

For Z = 4 and F.W. = 520.64, the calculated density is 1.229 g/cm^3. Based on a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be: *Pbcn* (# 60)

The data were collected at a temperature of 183(2) K to a maximum 2θ value of 52.04°. Three omega scans consisting of 134, 121 and 83 data frames, respectively, were collected with a frame width of 0.8° and a detector-to-crystal distance, Dx, of 35 mm. Each frame was exposed twice (for the purpose of de-zingering) for a total of 120 seconds. The data frames were processed and scaled using the DENZO software package.[1]

A5.1.4 Data Reduction.

A total of 9345 reflections were collected of which 2764 were unique and observed (Rint = 0.0473). The linear absorption coefficient, μ, for Mo-Kα radiation is 0.84 cm^{-1} and no absorption correction was applied. The data were corrected for Lorentz and polarization effects.

A5.1.5 Structure Solution and Refinement.

The structure was solved by direct methods and expanded using Fourier techniques.[2] The non-hydrogen atoms were refined anisotropically and hydrogen atoms were treated as idealized contributions. The final cycle of full-matrix least-squares refinement[3] on F was based on 2764 observed reflections ($I > 2.00\sigma(I)$) and 182 variable parameters and converged with unweighted and weighted agreement factors of:

$$R = \Sigma \, ||Fo| - |Fc|| \, / \, \Sigma \, |Fo| = 0.0764$$

$$Rw = [\Sigma w (|Fo| - |Fc|)^2 / \Sigma w Fo^2]^{1/2} = 0.2128$$

The maximum and minimum peaks on the final difference Fourier map corresponded to 0.264 and -0.197 e-/Å^3, respectively.

A5.1.6 Structural Description.

The compound crystallized in the orthorhombic space group Pbcn with one-half molecule in the asymmetric unit and four molecules in the unit cell. The unique half-molecule resides on a crystallographic two-fold axis of rotation which the whole molecule does not inherently possess giving rise to a unique form of disorder. The lactone rings and alkyl chains are related by a pseudo two-fold axis, as seen in Figure 4, and therefore govern the lattice packing despite the lack of symmetry in the core of the molecule. Positional disorder in the core is imposed by the crystallographic symmetry producing two different, yet equally occupied, orientations of the three-carbon alkenyl bridge. As seen in Figures 1 and 2 the three-carbon bridge can consist of either C(3A), C(4A) and C(7A) or C(3), C(4) and C(7). All atoms except C(2) and C(2') [C(2A) and C(2'A)] are common to both components.

There are no significant intermolecular contacts. ORTEPs, packing diagrams, and full crystallographic tables follow.

A5.1.7 References.

(1) Crystallographic data collected and structure report prepared by C.D. Incarvito, Yale University Chemical Instrumentation Center, March 2003.

(2) Otwinowski, Z. and Minor, W. "Processing of X-Ray Diffraction Data Collected in Oscillation Mode," *Methods in Enzymology*, vol. 276: Macromolecular

Crystallography, part A, 307-326, **1997**, C.W. Carter, Jr. & R.M. Sweet, Eds., Academic Press.

(3) *Acta Cryst.* **1990**, *A46*, 467-473.

(4) Least Squares function minimized:
$\Sigma w(|F_o| - |F_c|)^2$

Figure A5.1.2 **Unit cell:**

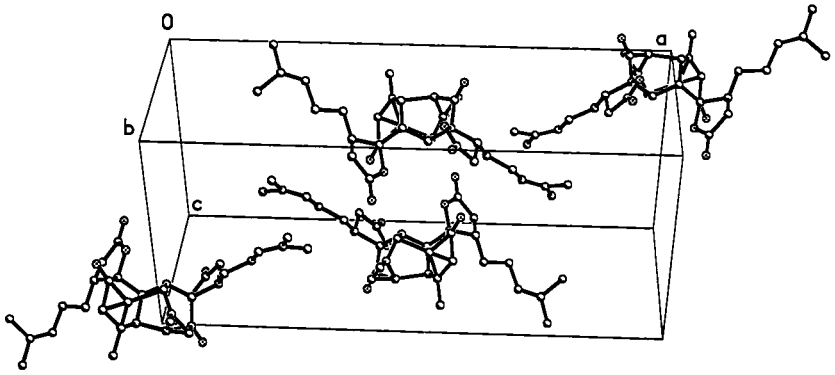


Figure A5.1.3 **Packing diagram:** view down the a-axis.

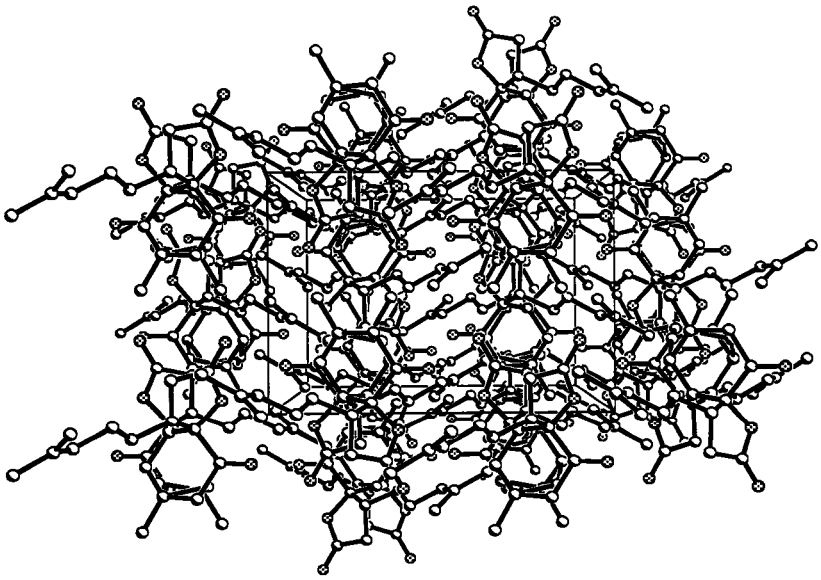


Figure A5.1.4 **Packing diagram:** view down the b-axis.

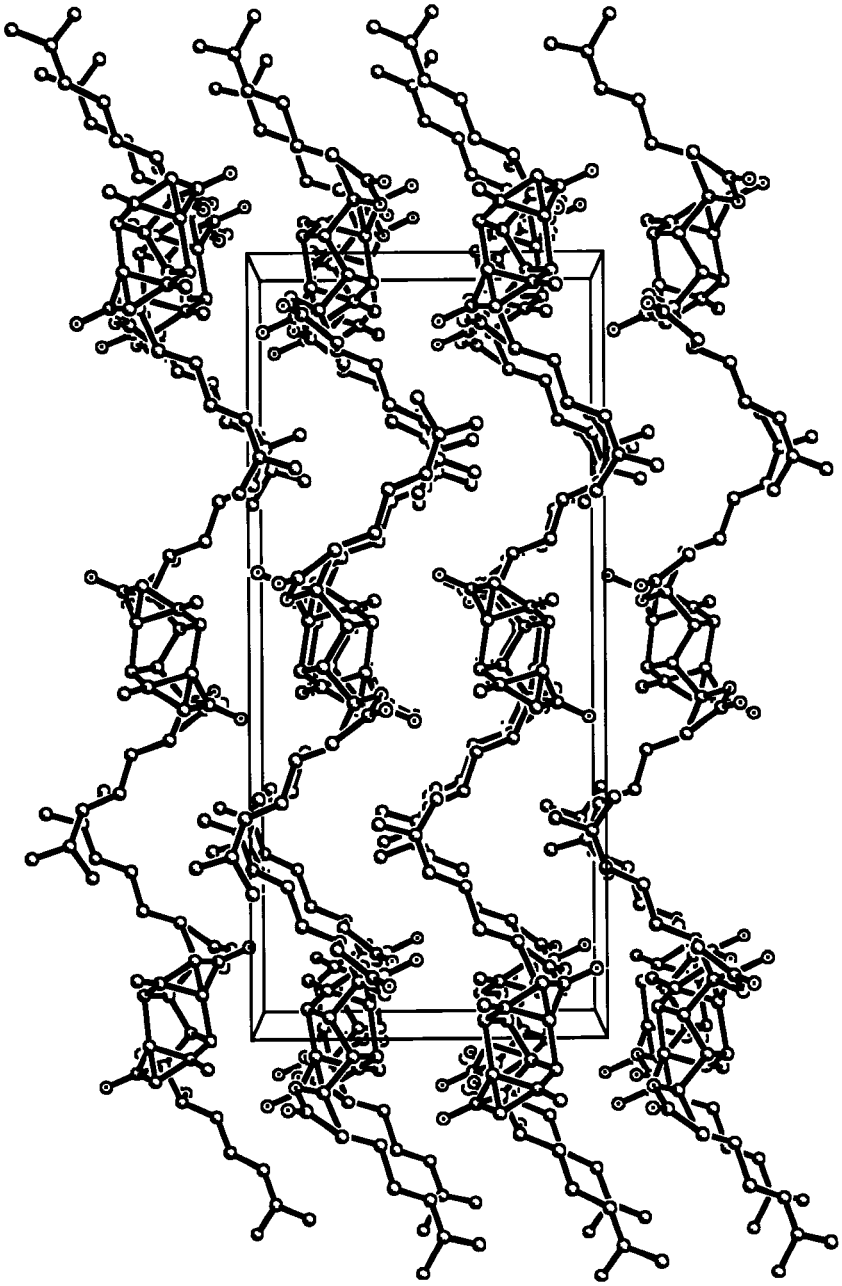


Figure A5.1.5 **Packing diagram:** view down the c-axis.

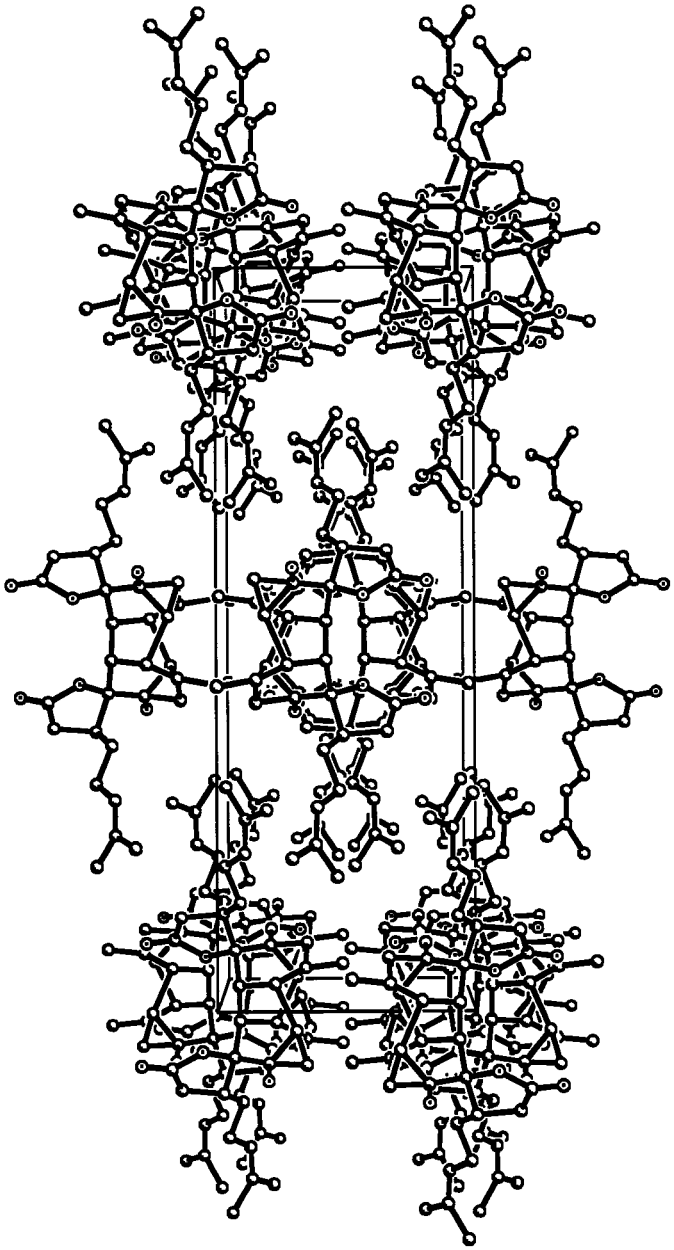


Table A5.1.1 **Crystal Data and Structure Refinement for Dimer 171.**

Identification code	wood_ab01	
Empirical formula	$C_{32} H_{40} O_6$	
Formula weight	520.64	
Temperature	183(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbcn	
Unit cell dimensions	a = 26.120(5) Å	α= 90°.
	b = 9.0920(18) Å	β= 90°.
	c = 11.853(2) Å	γ = 90°.
Volume	2814.8(10) Å	
Z	4	
Density (calculated)	1.229 g/cm^3	
Absorption coefficient	0.84 cm^{-1}	
F(000)	1120	
Crystal size	0.35 x 0.25 x 0.10 mm^3	
Theta range for data collection	3.23 to 26.02°.	
Index ranges	-32<=h<=32, -11<=k<=11, -14<=l<=14	
Reflections collected	9345	
Independent reflections	2764 [R(int) = 0.0473]	
Completeness to theta = 26.02°	99.5 %	
Absorption correction	None	
Max. and min. transmission	0.9917 and 0.9713	
Refinement method	Full-matrix least-squares on F2	
Data / restraints / parameters	2764 / 0 / 182	
Goodness-of-fit on F2	1.534	
Final R indices [I>2sigma(I)]	R1 = 0.0764, wR2 = 0.2128	
R indices (all data)	R1 = 0.1169, wR2 = 0.2252	
Largest diff. peak and hole	0.264 and -0.197 e. Å^{-3}	

Table A5.1.2 **Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters ($Å^2$x 10^3) for Dimer X [U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor].**

	x	y	z	U(eq)
O(1)	939(1)	-1955(2)	4637(2)	69(1)
O(2)	592(1)	661(2)	3758(1)	59(1)
O(3)	772(1)	3047(2)	3899(2)	85(1)
C(1)	751(1)	-1942(3)	3720(2)	61(1)
C(2)	808(2)	-3419(6)	3088(4)	51(1)
C(2')	340(2)	-3001(6)	3273(4)	47(1)
C(3)	506(1)	-3372(4)	2056(2)	69(1)
C(4)	310(1)	-2179(4)	1528(2)	84(1)
C(5)	254(1)	-745(3)	2169(2)	50(1)
C(6)	707(1)	-556(3)	3003(2)	52(1)
C(7)	587(1)	-4823(3)	1483(2)	70(1)
C(8)	839(1)	1891(4)	3431(2)	65(1)
C(9)	1182(1)	1561(3)	2454(2)	67(1)
C(10)	1231(1)	-110(3)	2491(2)	57(1)
C(11)	1410(1)	-833(3)	1409(2)	59(1)
C(12)	1932(1)	-249(4)	1035(3)	80(1)
C(13)	2132(1)	-1050(4)	14(2)	82(1)
C(14)	2604(1)	-1106(4)	-359(3)	78(1)
C(15)	2752(2)	-1957(5)	-1382(3)	103(1)
C(16)	3040(2)	-335(5)	231(4)	120(2)

Table A5.1.3 **Bond Lengths [Å] and Angles [°].**

O(1)-C(1)	1.192(3)	C(1)-C(2')-C(3)	105.2(3)
O(2)-C(8)	1.349(3)	C(1)-C(2')-C(4)#1	109.9(3)
O(2)-C(6)	1.454(3)	C(3)-C(2')-C(4)#1	117.5(3)
O(3)-C(8)	1.201(3)	C(4)-C(3)-C(2)	128.1(3)
C(1)-C(6)	1.524(4)	C(4)-C(3)-C(7)	123.3(2)
C(1)-C(2')	1.538(6)	C(2)-C(3)-C(7)	106.2(3)
C(1)-C(2)	1.545(6)	C(4)-C(3)-C(2')	98.6(3)
C(2)-C(3)	1.456(6)	C(2)-C(3)-C(2')	51.3(3)
C(2')-C(3)	1.543(5)	C(7)-C(3)-C(2')	131.0(3)
C(2')-C(4)#1	1.869(6)	C(3)-C(4)-C(5)	119.6(2)
C(3)-C(4)	1.354(4)	C(3)-C(4)-C(2')#1	88.0(3)
C(3)-C(7)	1.499(4)	C(5)-C(4)-C(2')#1	101.1(2)
C(4)-C(5)	1.516(4)	C(4)-C(5)-C(5)#1	109.8(2)
C(4)-C(2')#1	1.869(6)	C(4)-C(5)-C(6)	109.9(2)
C(5)-C(5)#1	1.540(5)	C(5)#1-C(5)-C(6)	109.4(2)
C(5)-C(6)	1.553(3)	O(2)-C(6)-C(1)	107.55(18)
C(6)-C(10)	1.550(4)	O(2)-C(6)-C(10)	103.01(19)
C(8)-C(9)	1.494(4)	C(1)-C(6)-C(10)	111.6(2)
C(9)-C(10)	1.525(4)	O(2)-C(6)-C(5)	108.5(2)
C(10)-C(11)	1.515(4)	C(1)-C(6)-C(5)	108.8(2)
C(11)-C(12)	1.529(4)	C(10)-C(6)-C(5)	116.89(19)
C(12)-C(13)	1.506(4)	O(3)-C(8)-O(2)	121.5(3)
C(13)-C(14)	1.309(4)	O(3)-C(8)-C(9)	128.4(3)
C(14)-C(15)	1.490(5)	O(2)-C(8)-C(9)	110.1(3)
C(14)-C(16)	1.508(5)	C(8)-C(9)-C(10)	103.2(2)
		C(11)-C(10)-C(9)	115.7(2)
C(8)-O(2)-C(6)	110.8(2)	C(11)-C(10)-C(6)	119.4(2)
O(1)-C(1)-C(6)	123.2(2)	C(9)-C(10)-C(6)	101.4(2)
O(1)-C(1)-C(2')	126.6(3)	C(10)-C(11)-C(12)	111.8(2)
C(6)-C(1)-C(2')	105.8(3)	C(13)-C(12)-C(11)	112.0(3)
O(1)-C(1)-C(2)	113.2(3)	C(14)-C(13)-C(12)	128.1(3)
C(6)-C(1)-C(2)	117.1(2)	C(13)-C(14)-C(15)	122.6(3)

C(2')-C(1)-C(2)	49.9(3)	C(13)-C(14)-C(16)	122.4(3)
C(3)-C(2)-C(1)	109.2(4)	C(15)-C(14)-C(16)	115.0(3)

Table A5.1.4 **Anisotropic Displacement Parameters ($Å^2 x\ 10^3$) for Dimer 171 [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)	84(1)	75(2)	48(1)	5(1)	-22(1)	0(1)
O(2)	77(1)	66(1)	34(1)	-9(1)	2(1)	-11(1)
O(3)	145(2)	67(2)	42(1)	-5(1)	6(1)	-14(1)
C(1)	84(2)	68(2)	31(1)	4(1)	2(1)	-15(2)
C(2)	63(3)	51(3)	38(3)	-1(2)	-3(2)	5(3)
C(2')	56(3)	55(3)	30(2)	5(2)	3(2)	4(2)
C(3)	95(2)	76(2)	36(1)	-10(1)	12(2)	-35(2)
C(4)	110(3)	98(3)	43(2)	-34(2)	-35(2)	48(2)
C(5)	61(2)	56(2)	33(1)	-5(1)	-2(1)	-1(1)
C(6)	62(2)	64(2)	29(1)	-10(1)	-1(1)	-6(1)
C(7)	89(2)	65(2)	55(2)	5(2)	1(2)	-1(2)
C(8)	96(2)	66(2)	32(1)	2(1)	-6(1)	-9(2)
C(9)	85(2)	75(2)	41(1)	3(1)	2(1)	-12(2)
C(10)	63(2)	68(2)	40(1)	4(1)	-3(1)	-4(1)
C(11)	62(2)	72(2)	43(1)	8(1)	5(1)	4(1)
C(12)	76(2)	95(3)	67(2)	6(2)	15(2)	-5(2)
C(13)	71(2)	114(3)	60(2)	9(2)	11(2)	3(2)
C(14)	68(2)	96(3)	69(2)	22(2)	12(2)	12(2)
C(15)	95(3)	146(4)	67(2)	8(2)	17(2)	27(2)

C(16)	81(3)	135(4)	144(4)	-23(3)	27(2)	-5(2)

Table A5.1.5 **Hydrogen Coordinates (x 10^4) and Isotropic Displacement Parameters ($Å^2$x 10^3) for Dimer 171.**

	x	y	z	U(eq)
H(2A)	1008	-4230	3334	61
H(2'A)	357	-3925	3728	57
H(4A)	208	-2239	760	101
H(5A)	253	93	1622	60
H(7A)	698	-4656	704	104
H(7B)	266	-5378	1482	104
H(7C)	850	-5382	1888	104
H(9A)	1519	2040	2546	80
H(9B)	1026	1891	1735	80
H(10A)	1495	-337	3076	68
H(11A)	1156	-650	806	71
H(11B)	1433	-1909	1526	71
H(12A)	1901	812	858	95
H(12B)	2179	-356	1662	95
H(13A)	1886	-1582	-412	98
H(15A)	2447	-2418	-1708	154
H(15B)	2999	-2720	-1173	154
H(15C)	2906	-1293	-1937	154
H(16A)	2908	199	887	180
H(16B)	3202	359	-291	180
H(16C)	3293	-1064	478	180

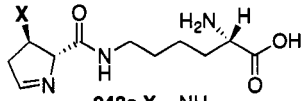
Chapter 5

Pyrrolysine: the 22nd Amino Acid.

5.1 Pyrrolysine: Introduction and Structural Characterization.

A new amino acid, pyrrolysine (**242**),[1] was shown to be present in the mono-, di- and tri-methylamine methyltransferase (MtmB, MtbB and MttB) of the *Methanosarcinaceae*, a family of methanogenic archaea.[2] Pyrrolysine (Pyl) is co-translationaly inserted in response to an in-frame UAG codon located in the corresponding mRNAs; the insertion relies on the presence of a specific suppressor tRNA ($tRNA^{Pyl}$) and of a new type of aminoacyl-tRNA synthetase, pyrrolysyl-tRNA synthetase (PylRS) specific only for $tRNA^{Pyl}$ and Pyl.[3, 4]

Figure 5.1.1



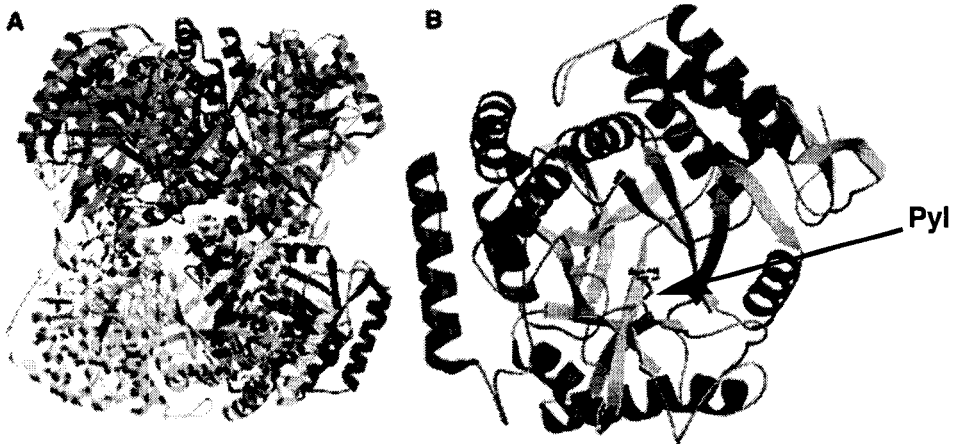
242a X = NH_2
242b X = OH
242c X = Me

5.1.1 Structure Elucidation.

The structure of *Methanosarcina barkeri* monomethylamine methyltransferase (MtmB) consists of a homohexamer arranged into a dimer of trimers (**A**, Ribbon diagram of the MtmB hexamer, Figure 5.1.2). Krzycki and Chan were resolving the structure of MtmB to clarify the identity of the UAG-encoded residue when they serendipitously

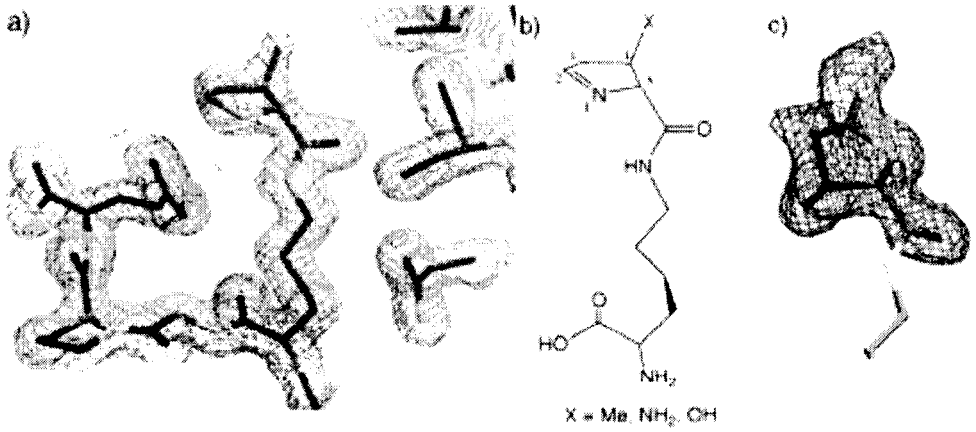
found a residue that was distinct from the 21 known natural amino acids (**B**, Ribbon diagram of one MtmB subunit, Figure 5.1.2).[5]

Figure 5.1.2[5]



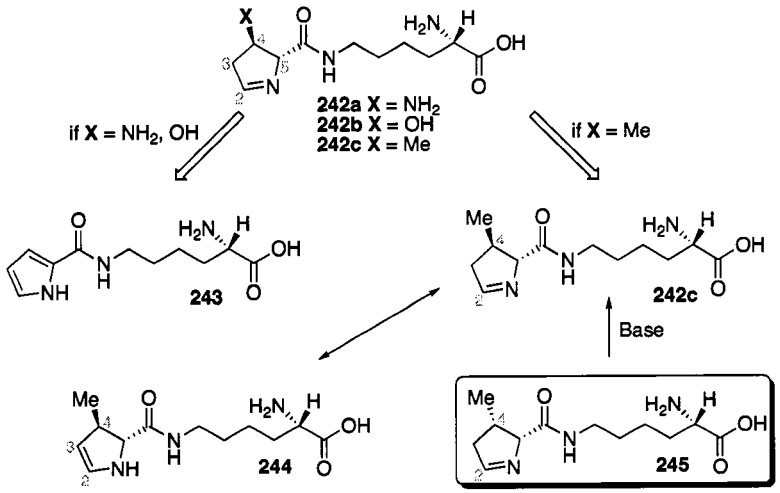
Characterization of the crystal structure of native MtmB allowed for the elucidation of the molecular structure of this new amino acid (**242**, Pyl). Analysis of the electron density showed that pyrrolysine (**242**) is a di-peptide composed of a lysine modified at its ε-*N* with a 4-substituted-pyrroline-5-carboxylate (Figure 5.1.3).[5]

Figure 5.1.3[5]



However, due to a lack of local resolution in the enzyme original structure, the nature of the C4 substituent (**X**) on the pyrroline ring could not be ascertained; it was proposed to be either a methyl (Me), a hydroxyl (OH) or an amino group (NH_2).[5] Therefore we analyzed the three proposed structures of **242** to determine the most probable one. Thus, if the structure was either **242a** or **242b**, the amino or hydroxy groups would likely eliminate to generate pyrrole **243**; however **242c** (**X** = Me) would not aromatize and is therefore a more plausible structure for pyrrolysine. Only later, mass spectroscopy analysis of the native MtbB and MttB suggested the presence of a methyl group at the C4 ring position.[2]

Scheme 5.1.1



The electron density of the Mtmb crystal structure suggested an anti relationship between the unknown C4 substituent and the amide group (Figure 5.1.3). The relationship was not yet established when we initiated this project, but we proposed that epimerization of the syn isomer **245** would allow access to both isomers. Also, it was suggested that the pyrroline double bond was between the nitrogen and C2. Krzycki and Chan's main evidence for the double bond location was the addition of ammonia at C2

when the enzyme was crystallized in the presence of ammonium sulfate ($(NH_4)_2SO_4$). However, after searching the literature, we found few examples of imine-pyrrolines in comparison to numerous enamine-pyrroline substructures, thus the two tautomers were viable possibilities.

5.1.2 Mode of co-Translational Insertion?

This project was done in collaboration with Professor Dieter Söll in the Molecular Biophysics & Biochemistry Department at Yale University. His recent work has concentrated on the diverse roles of transfer RNA in various biological systems. Therefore, when pyrrolysine (**242**) was discovered, the Söll group was interested in determining the route by which pyrrolysine could be introduced into monomethylamine methyl transferase: post-translational modification of lysine in the mature protein or co-translational insertion via pyrrolysyl-tRNA formed by pre-translational modification.[6]

Figure 5.1.4[6]

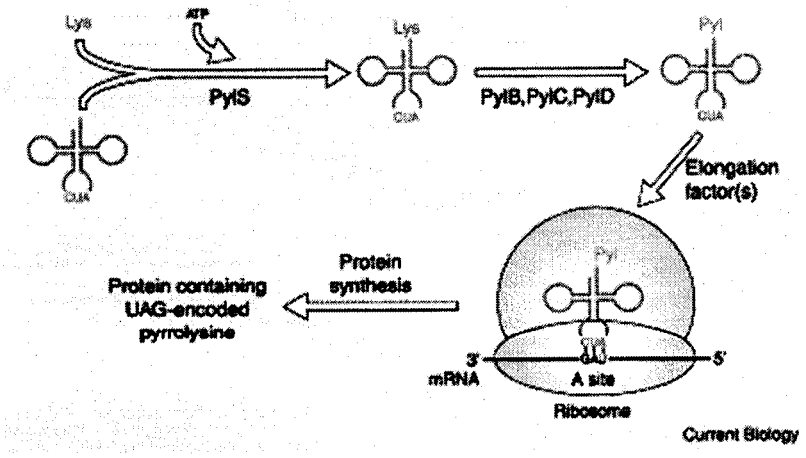
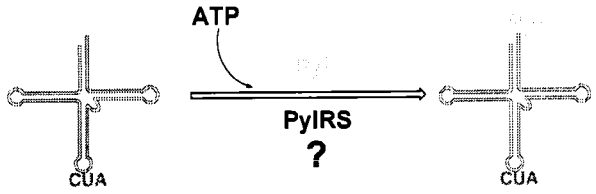


Figure 5.1.4 represents an amber suppressing tRNA ($tRNA_{CUA}$) being first charged with lysine by aminoacyl-tRNA synthetase (PylS) to give Lys-$tRNA_{CUA}$, which then undergoes pre-translational modification to produce Pyl-$tRNA_{CUA}$ which is then used for the translation on in-frame amber codons during ribosomal protein synthesis.[6] However, another pathway could be the direct incorporation of pyrrolysine (Pyl) by pyrrolysyl-tRNA synthetase (PylRS) (Figure 5.1.5). In order to fully investigate whether pyrrolysine was directly attached to $tRNA^{Pyl}$, a synthesis of the amino acid was required.

Figure 5.1.5



5.2 Pyrrolysine: Synthesis.

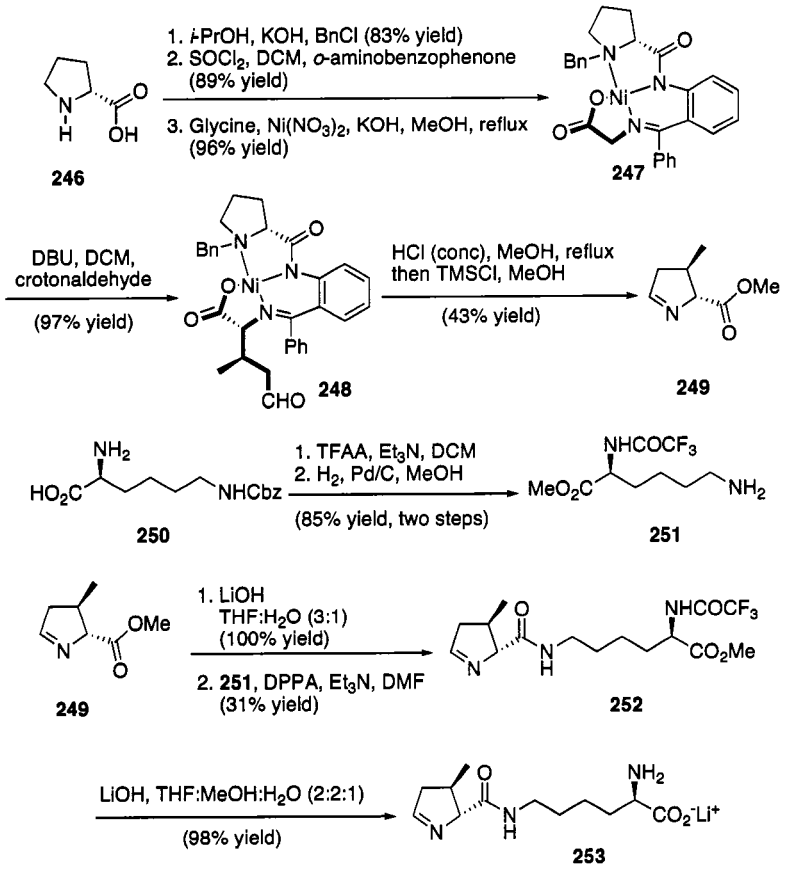
Concomitantly, Chan *et al.* were working toward the synthesis of pyrrolysine, and their synthesis was published in 2004.[7]

5.2.1 Chan's Synthesis.

Chan's strategy utilized Belokon's asymmetric Michael addition[8-11] of (*E*)-2-butenal to a prepared nickel complex, a 4-methyl substituted glutamate γ-semialdehyde (**248**) was produced, and delivered desired pyrroline **249** via cyclization. Hydrolysis of ester **249** and amide coupling with protected lysine **251** delivered L-pyrrolysine after

deprotection of **252** under basic conditions. Although this synthesis is enantioselective, the coupling between **249** and **251** could not be reproduced in our hands. Indeed, not only our group, but also others have tried to use Chan's synthesis to gain access to enantiopure pyrrolysine, however all efforts were unsuccessful.[7]

Scheme 5.2.1[7]

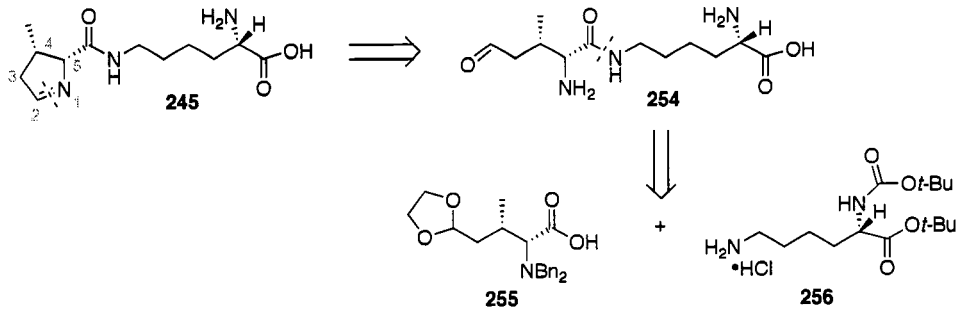


5.2.2 Retrosynthetic Analysis.

As previously mentioned, our target was the pyrrolysine derivative bearing a methyl group at the C4 position with a syn relationship with the amide group (**245**, Scheme 5.1.1). To reveal the imine functionality, we proposed to construct the pyrroline

substructure through the intramolecular condensation of an aldehyde and amine moieties under acidic condition (**254**, Scheme 5.2.2). The ε-NH_2 of protected lysine **256** would be coupled with acid **255** using standard peptidic coupling conditions.

Scheme 5.2.2

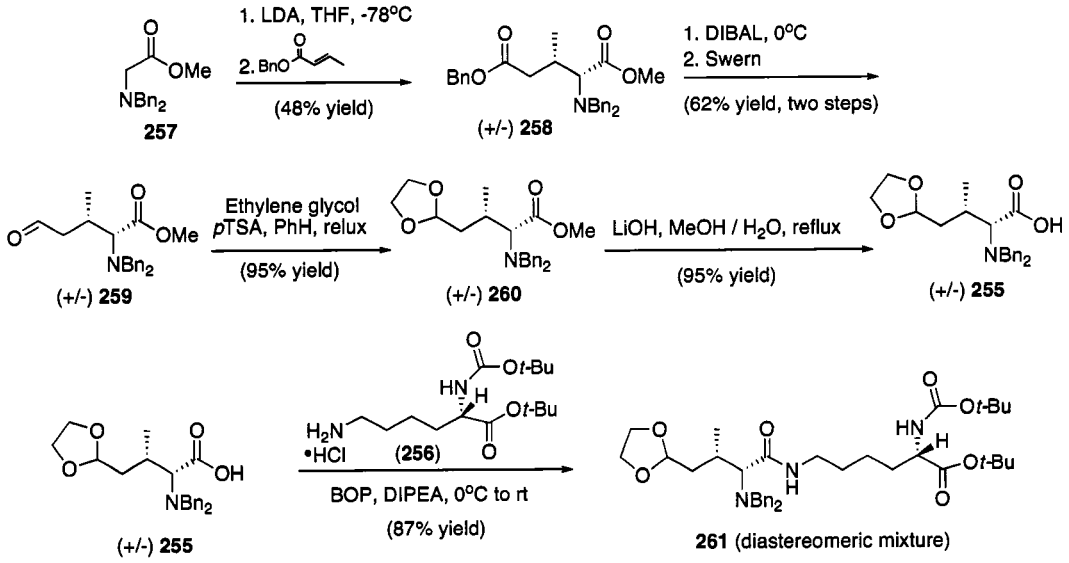


5.2.3 Synthesis.

The synthesis began with the large-scale production of glutamic acid methyl ester **258** from protected glycine **257** and the crotyl benzyl ester *via* Michael addition proceeding with high threo-selectivity.[12] The bis-ester **258** was then treated with diisobutyl aluminum hydride (DIBAl-H) at 0°C to selectively reduce the less hindered benzyl ester and give the corresponding alcohol, which provided aldehyde **259** after Swern oxidation.[13] Acid **255** was obtained after protection of aldehyde **259** as the corresponding acetal **260**, and hydrolysis of the methyl ester with lithium hydroxide. Acid (**255**) was then coupled to the selectively protected lysine **256**[14] using BOP, a coupling reagent, to produce amide **261** as an inseparable mixture of diastereomers in 87 % yield. We continued by deprotecting the dipeptide (**261**); first the benzyl groups were removed under hydrogenation conditions using a catalytic amount of Pearlman's catalyst ($Pd(OH)_2$)[15] to yield amine **262**. This step was followed by removal of the *t*-

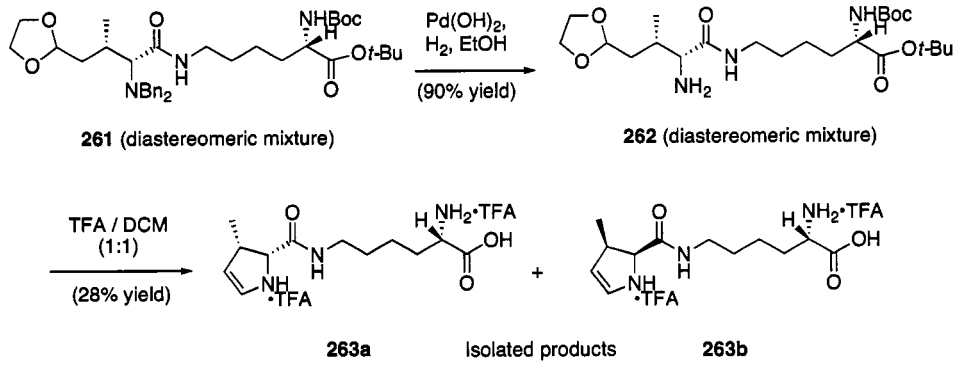
butylcarbamate, *t*-butyl ester and the acetal upon treatment with a 1:1 solution of TFA and dichloromethane, allowing for condensation of the amine portion with the aldehyde (**263a-b**).

Scheme 5.2.3



Surprisingly, rather than obtaining the desired imine **245**, we isolated the corresponding enamines **263a-b**, which could result from the isomerization of the imine under acidic conditions or from the dehydration step. These processes would give rise to the less strained product (the mixture of diastereomers was inseparable).

Scheme 5.2.4



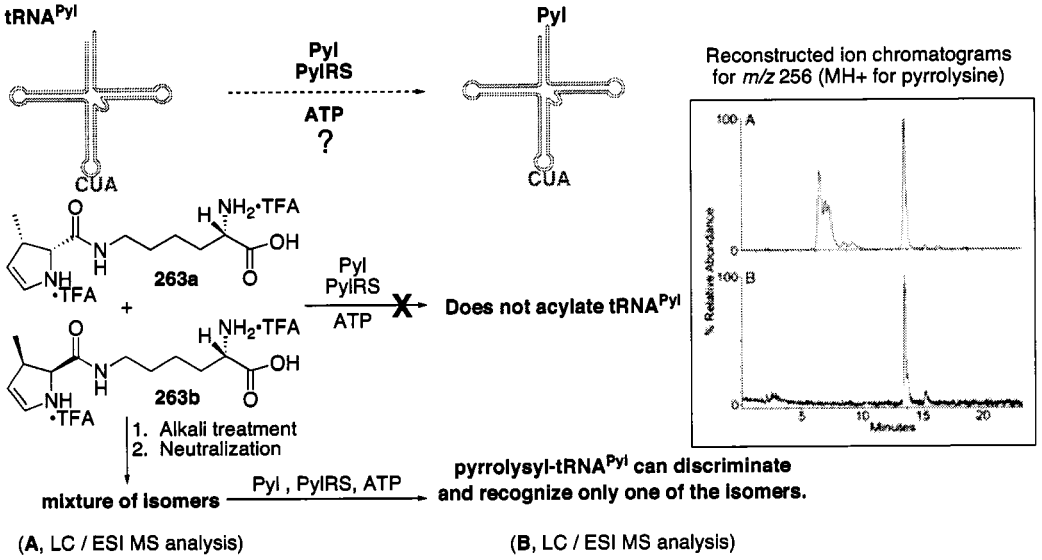
While our synthesis was racemic and the obtained product an isomer of the proposed structure of pyrrolysine (**242c**), it was otherwise reliable and reproducible, which allowed access to at least 100 mg of enamines **263a-b**. The Söll group then began to investigate whether pyrrolysine could be directly attached to $tRNA^{Pyl}$.[3]

5.3 Biological Studies.

5.3.1 Mode of co-Translational Insertion.

The ability of PylRS to activate pyrrolysine enamine **263** was verified by an ATP-^{32}PPi exchange reaction. In order to optimize the reaction conditions, our collaborators in the Söll group used different buffers with pH ranging from 6.5 to 10.0.

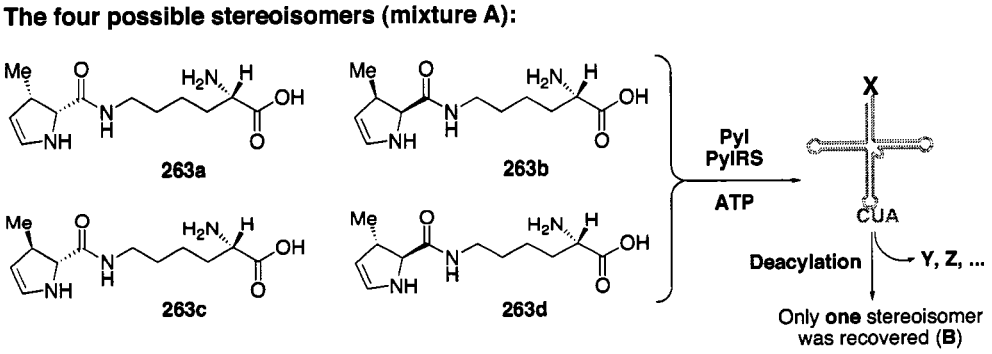
Figure 5.3.1



The Söll group noticed a clear activity enhancement when basic conditions were used (tRNA was charged). In order to determine whether high pH conditions were affecting the efficiency of the enzyme, or modifying the structure of the pyrrolysine substrate they were using, they separated these two factors. The enamines **263a-b** were

treated with a NaOH solution and subsequently neutralized with HCl. The effects of basic treatment on PylRS activity were then measured both at pH 6.5 and pH 8.8, and a significant increase in activity upon basic treatment of the enamine **263a-b** was noticed. Variation of the pH of the buffer had little effect on PylRS activity when using the base-treated enamines **263a-b** as substrate (mixture **A**). From these results, we concluded that basic treatment triggered either isomerisation of the enamine into an imine or, more likely, epimerization of the ring C5 stereocenter to obtain the anti relationship represented in the proposed structure (**242c**). We were unable to ascertain the changes triggered by the NaOH treatment, but could propose the presence of four stereoisomers (**263a-d**, Figure 5.3.2). Indeed, after treatment with base, the LC/MS displayed a mixture of at least four isomers (Chromatogram **A**, Figure 5.3.1). The $tRNA^{Pyl}$ was treated with mixture **A** and the uncharged isomers washed away. After deacylation of $tRNA^{Pyl}$ (Figure 5.3.2), it was found that only one isomer had been charged and recovered (Chromatogram **B**, Scheme 5.3.1). Isomer **B** might be pyrrolysine or a closely related isomer. Importantly, PylS could discriminate among the isomers of pyrrolysine (mixture **A**) and specifically recognize only one of them (**B**).

Figure 5.3.2



Our studies, in collaboration with the Söll group, clearly pointed toward a direct pathway, and of pyrrolysine being a normal metabolite in Methanosarcinaceae. Our collaborators have also shown that PylS is an aminoacyl-tRNA synthetase-like enzyme specific for pyrrolysine (but not lysine) and $tRNA^{Pyl}$ (but not $tRNA^{Lys}$).[3]

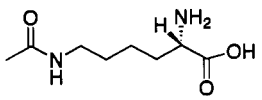
5.3.2 Enzymatic Activity of Pyrrolysyl-tRNA-Synthetase.

We could not measure the degree of difference between the biological product and the "pyrrolysine isomer" selected by PylRS from our synthetic sample (**263a-d**, Figure 5.3.2). Thus, it was certainly possible that the enzymatic activity observed in this work may only be a fraction of what the natural substrate would yield.[3] To help answer this question and for a more complete definition of pyrrolysyl-tRNA synthetase we made analogs of pyrrolysine.

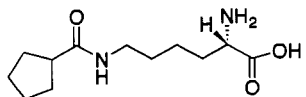
5.3.3 Synthesis of Analogs.

The selected compounds were the commercially available *N*-ε-acetyl-L-lysine (**264**) and *N*-ε-(cyclopentylcarbonyl)-L-lysine (**265**), and D/L-prolyl-L-lysine (**267a-b**).

Figure 5.3.3



264

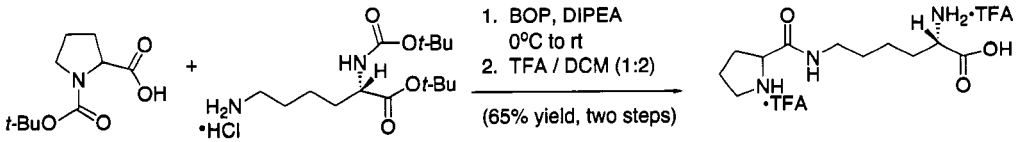


265

Compounds **264** and **265**, and dipeptides **267a-b** were selected to help identify the structural features recognized by PylRS, which allowed the synthetase to discriminate among the isomers of pyrrolysine (mixture **A**, Scheme 5.3.2) and specifically recognize

and charge one of them (**B**, Scheme 5.3.1). We found that acylated lysine (**264**) was not a good dipeptide model, being mildly recognized and charged by the enzyme onto $tRNA^{Pyl}$. On the other hand, cyclopentylcarboxy-lysine (**265**) was better recognized and some was charged on $tRNA^{Pyl}$, meaning that the five-member ring was an important recognition element.

Scheme 5.3.1



266a : Boc-L-Pro-OH
266b : Boc-D-Pro-OH

256

267a: L-Pro-L-Lys-OH
267b: D-Pro-L-Lys-OH

Next, we assembled dipeptides **267a** and **267b** *via* coupling between Boc protected L- or D-proline (**266a-b**) and protected lysine **256**; deprotection of the dipeptide was effected upon acid treatment. These two dipeptides were tested, revealing that D-prolyl-L-lysine (**267b**) was recognized at a much higher degree than its epimer L-prolyl-L-lysine (**267a**). Our conclusion was that the enzyme was selective to a dipeptide having a C5 stereocenter (R), which is in agreement with the proposed structure of pyrrolysine (**242c**).

5.4 Conclusion.

The detailed characterization of the novel synthetase PylRS relied on the production of practical amounts of pyrrolysine. Based on the reported structure of Pyl (**242c**) we devised the synthetic route described above. The products obtained (**263a-b**, Scheme 5.2.4) allowed us to experimentally demonstrate the direct attachment of Pyl to

$tRNA^{Pyl}$ by PylRS.[3] We also synthesized L- and D-prolyl-L-lysine (**267a** and **267b**, Scheme 5.3.1) and purchased **264** and **265**, those analogues were potential substrate for PylRS characterization.

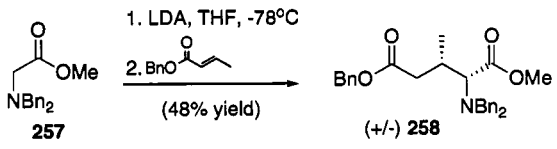
5.5 Experimental Section.

5.5.1 Materials and Methods.

Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). All other commercially obtained reagents were used as received. All reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F254 pre-coated plates (0.25 mm). Column or flash chromatography[16] was performed with the indicated solvents using silica gel (particle size 35 -75 mm) purchased from Silicycle. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Advance DPX-500 or Bruker Advance DPX-400 spectrometers. Chemical shifts are reported relative to internal chloroform (^{1}H, δ 7.26 ppm, ^{13}C δ 77.00 ppm), methanol (^{1}H, δ 3.31 ppm, ^{13}C δ 49.00 ppm). High Resolution Mass Spectra were acquired at The University of Illinois Mass Spectrometry Center. High Performance Liquid Chromatography Purification was done on a Waters 490E HPLC using a Phenomenex Luna C-18(2) HPLC column (250 x 21.20 mm, 5 mm) with a UV detector set at 214 nm, eluted with a gradient 0% to 30 % of acetonitrile in water (containing 0.1% of TFA) in 30 min.

5.5.2 Preparative Procedures.

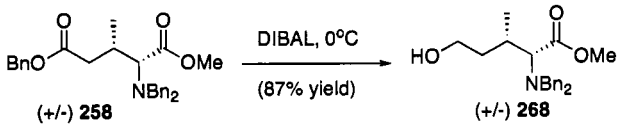
Preparation of Diester 258:



257 (+/-) **258**

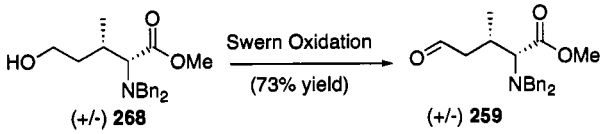
To a solution of diisopropylamine (5.0 mL, 35.5 mmol) in THF (40 mL) cooled to 0°C was added dropwise a 2.5 *M* solution of n-butyllithium in hexane (11.9 mL, 29.9 mmol). The solution was kept at this temperature for 30 min and was then cooled at -78°C. A solution of the protected glycine (7.3 g, 27.1 mmol) in THF (20 mL) was added to the base *via* cannula and the mixture was allowed to stir for 40 min before the crotyl benzyl ester (3.2g, 18.2mmol) in THF (10 mL) was added *via* cannula. After 3 h at -78°C, the reaction was quenched by addition of NH_4Cl (saturated in water) and the aqueous layer was extracted three times with ether. The combined organic layers were washed with NaCl (saturated in water), dried over $MgSO_4$, filtered and rotary evaporated. The residue was purified by flash chromatography (gradient elution, 4→10% EtOAc/Hexanes) to yield the title compound **258** (3.86g, 48% yield) as a white foam and the major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.24 (m, 10H), 5.06 (s, 2H), 4.00 (d, *J* = 13.8 Hz, 2H), 3.79 (s, 3H), 3.35 (d, *J* = 13.8 Hz, 2H), 3.08 (d, *J* = 10.7 Hz, 1H), 2.65-2.55 (m, 1H), 2.31 (dd, *J* = 15.2, 3.7 Hz, 1H), 2.05 (dd, *J* = 15.2, 9.3 Hz, 1H), 1.07 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.43, 172.10, 129.49, 129.09, 128.87, 128.78, 128.71, 127.67, 66.69, 66.61, 66.23, 55.34, 51.41, 39.36, 30.25, 17.46; IR (thin layer, NaCl) 3086 (w), 3062 (w), 3029 (m), 2949 (m), 2840 (w), 1734 (sh, s), 1495 (m), 1454 (m), 1378 (m) cm^{-1}; HRMS (MALDI) *m/z* found 446.23, calc'd for $C_{28}H_{32}NO_4$ [M+H] : 446.23.

Preparation of Alcohol 268:



To a solution of **258** (3.02 g, 6.78 mmol) in THF (100 mL) cooled to 0°C was added dropwise a 1.0 *M* solution of diisobutylaluminium hydride in toluene (6.8 mL, 6.78 mmol). An equivalent of DiBAl-H was added every 45 min until completion of the reaction (usually 4 equivalents were needed). When no starting material was observed by TLC, the mixture was cooled at -78°C and treated with HCl (1N in water, 5 mL) and water (5 mL). The suspension was allowed to warm to room temperature and the salts were removed by filtration and washed with ether. The layers of the filtrate were separated and the aqueous layer was extracted with ether three times. The combined organic layers were washed with $NaHCO_3$ (saturated in water) twice, washed with NaCl (saturated in water) twice, dried over $MgSO_4$, filtered and rotary evaporated. The residue was purified by flash chromatography (gradient elution, 10→30% EtOAc/Hexanes) to yield methyl *N,N*-dibenzyl-5-hydroxyisoleucinate **268** (2.00 g, 87% yield) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55-7.23 (m, 10H), 4.07 (d, J = 13.9 Hz, 2H), 3.84 (s, 3H), 3.69-3.58 (m, 2H), 3.37 (d, J = 13.9 Hz, 2H), 3.09 (d, J = 10.9 Hz, 1H), 2.54 (s, 1H), 2.31-2.26 (m, 1H), 1.53-1.47 (m, 1H), 1.25-1.18 (m, 1H), 1.11 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.83, 140.00, 129.35, 128.74, 127.66, 67.28, 60.86, 55.10, 51.26, 37.31, 29.46, 16.81; IR (thin layer, NaCl) 3408 (br, s), 3061 (w), 3028 (m), 2936 (m), 2840 (m), 1730 (sh, s), 1495 (m), 1453 (m), 1376 (m), 1238 (w), 1164 (m) cm^{-1}; HRMS (MALDI) *m/z* found 342.21, calc'd for $C_{21}H_{28}NO_3$ [M+H]: 342.21.

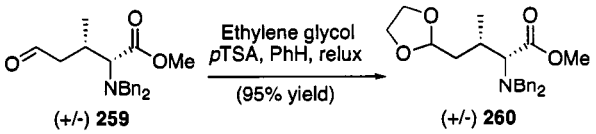
Preparation of Aldehyde 259:



(+/-) **268** (+/-) **259**

To a solution of oxalyl chloride (63 μL, 0.72 mmol) in DCM (0.6 mL) cooled to -78°C was added dropwise a solution of DMSO (0.16 mL, 0.96 mmol) in DCM (0.4 mL). The mixture was stirred 15 min further and a solution of methyl *N,N*-dibenzyl-5-hydroxyisoleucinate **268** (164 mg, 0.48 mmol) in DCM (0.5 mL) was then added slowly. After an additional 15 min, triethylamine (0.27 mL, 1.92 mmol) was introduced dropwise and the reaction mixture was warmed to 0°C. After 15 min, the reaction mixture was partitioned between ether and water, and the organic phase was washed with water, NaCl (saturated in water), dried over Na_2SO_4, filtered and rotary evaporated. The residue was purified by flash chromatography (25% EtOAc/Hexanes) to yield the title compound **259** (118 mg, 73% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 1H), 7.29-7.14 (m, 10 H), 3.90 (d, J = 13.8 Hz, 2H), 3.70 (s, 3H), 3.24 (d, J = 13.8 Hz, 2H), 2.97 (d, J = 10.6 Hz, 1H), 2.62-2.54 (m, 1H), 2.19 (dd, J = 16.6, 3.5 Hz, 1H), 1.98 (ddd, J = 16.6, 8.8, 2.6Hz, 1H), 0.97 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.59, 172.12, 139.44, 129.37, 128.79, 127.61, 66.21, 55.21, 51.47, 48.70, 27.80, 17.65; IR (thin layer, NaCl) 3086 (w), 3029 (m), 2950 (m), 2839 (m), 2723 (w), 1727 (sh, s), 1495 (m), 1453 (m), 1433 (m), 1377 (m), 1191 (w), 1167 (m), 1071 (w) cm^{-1}; HRMS (MALDI) *m/z* found 3340.19, calc'd for $C_{21}H_{26}NO_3$ [M+H]: 340.18.

Preparation of Acetal 260 :

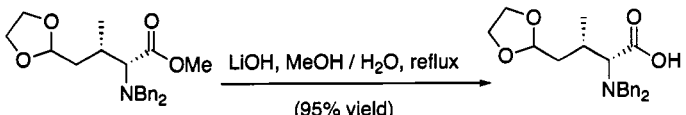


(+/-) **259** (+/-) **260**

To a solution of the aldehyde **259** (118 mg, 0.35 mmol) in benzene (5 mL) were added ethylene glycol (1 mL) and *p*-toluene sulfonic acid (3 mg, 0.018 mmol). The

mixture was heated under reflux with a Dean-Stark trap for 4 h. The reaction was allowed to cool at room temperature and the mixture was partitioned between DCM and $NaHCO_3$ (saturated in water), the aqueous phase was extracted with DCM twice. The combined organic phases were dried over Na_2SO_4, filtered and rotary evaporated. The residue was used without further purification to yield acetal **260** (134 mg, 95% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.11 (m, 10H), 4.74 (t, J = 4.5 Hz, 1H), 3.90 (d, J = 13.9 Hz, 2H), 3.80-3.76 (m, 2H), 3.70-3.64 (m, 2H), 3.68 (s, 3H), 3.21 (d, J = 13.9 Hz, 2H), 2.92 (d, J = 10.8 Hz, 1H), 2.25-2.18 (m, 1H), 1.40 (ddd, J = 3.1, 5.7, 13.7 Hz, 1H), 1.26-1.19 (m, 1H), 1.01 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.31, 139.78, 129.32, 128.71, 127.64, 103.83, 67.15, 65.21, 64.93, 55.07, 51.24, 38.38, 29.37, 17.09; IR (thin layer, NaCl) 3086 (w), 3029 (m), 2949 (m), 2883 (m), 2842 (w), 1730 (sh, s), 1495 (m), 1453 (m), 1433 (m), 1377 (m), 1190 (w), 1139 (m), 1071 (w) cm^{-1}; HRMS (MALDI) *m/z* found 384.22, calc'd for $C_{23}H_{30}NO_4$ [M+H]: 384.21.

Preparation of Acid 255:

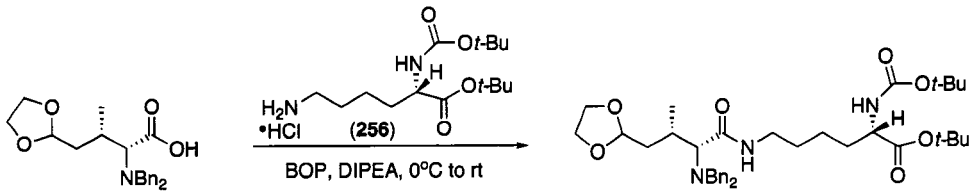


(+/-) **260** (+/-) **255**

To a solution of the methyl ester **260** (160 mg, 0.39 mmol) in a mixture of MeOH (1.6 mL) and water (0.4 mL) was added lithium hydroxide (30 mg, 1.2 mmol) and the mixture was heated to reflux for 2 d. The reaction was allowed to cool at room temperature and the MeOH was rotary evaporated. The residue was partitioned between ether and NH_4Cl (saturated in water), the aqueous phase was extracted with ether three more times. The combined organic phases were dried over Na_2SO_4, filtered and rotary

evaporated. The residue was purified by flash chromatography (2% MeOH/DCM with 0.1 % of acetic acid) to yield the title compound **255** (137 mg, 95% yield) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.09 (m, 10H), 4.74 (t, J = 4.4 Hz, 1H), 3.87 (d, J = 13.7 Hz, 2H), 3.79-3.74 (m, 2H), 3.68-3.63 (m, 2H), 3.33 (d, J = 13.8 Hz, 2H), 2.93 (d, J = 10.5 Hz, 1H), 2.24-2.12 (m, 1H), 1.57-1.52 (m, 1H), 1.33-1.26 (m, 1H), 0.99 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.15, 139.47, 129.47, 128.74, 127.53, 103.83, 66.79, 65.22, 64.92, 54.99, 38.26, 29.08, 17.07; IR (thin layer, NaCl) 3062 (w), 3029 (m), 2963 (m), 2886 (m), 1700 (sh, s), 1495 (m), 1454 (m), 1412 (w), 1378 (w), 1268 (w), 1137 (m), 1029 (m) cm^{-1}; HRMS (MALDI) *m/z* found 370.20, calc'd for $C_{22}H_{28}NO_4$ [M+H]: 370.19.

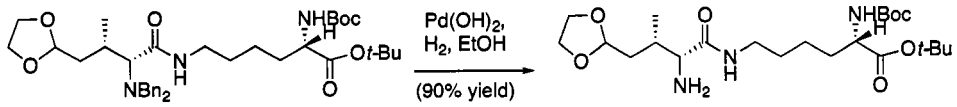
Preparation of Protected Dipeptide 261:



To a suspension of the amine hydrochloride **256** (200 mg, 0.59 mmol) in dry acetonitrile (3 mL) was added a solution of the acid **255** (108 mg, 0.30 mmol) in dry DCM (1.5 mL). The mixture was cooled to 0°C and BOP reagent (140 mg, 0.32 mmol) was added all at once, finally *N,N*-diisopropylethylamine (0.21 mL, 1.20 mmol) was introduced dropwise and the reaction mixture was warmed to room temperature. After 2 d, the reaction mixture was partitioned between ether and NH_4Cl (saturated in water) and the organic phase was washed with $NaHCO_3$ (saturated in water) and NaCl (saturated in water), dried over Na_2SO_4, filtered and rotary evaporated. The residue was purified by

flash chromatography (2% MeOH/DCM) to yield the title compound **261** (170 mg, 87% yield) as a colorless oil: (mixture of two isomers) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.21 (m, 10H), 5.58 (t, J = 5.5 Hz, 1H), 4.87-4.85 (m, 1H), 4.16 (br s, 1H), 4.07-4.02 (m, 2H), 3.91-3.86 (m, 2H), 3.81-3.75 (m, 2H), 3.66 (t, J = 5.2 Hz, 0.5 H), 3.56 (t, J = 5.2 Hz, 0.5H), 3.45 (d, J = 14.4 Hz, 2H), 3.35-3.22 (m, 2H), 2.74 (t, J = 10.0 Hz, 1H), 2.42-2.35 (m, 1H), 1.83 (s, 1H), 1.80-1.72 (m, 1H), 1.68-1.52 (m, 4H), 1.48-1.40 (m, 22H), 1.18 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.30, 170.98, 155.87, 140.17, 128.83, 127.34, 103.85, 82.19, 80.02, 73.48, 71.72, 69.53, 68.17, 68.05, 65.23, 64.76, 61.66, 54.78, 54.28, 39.21, 38.04, 37.93, 33.01, 30.07, 29.91, 28.98, 28.93, 28.83, 28.74, 28.51, 28.43, 27.88, 27.88, 23.22, 22.76, 17.27; IR (thin layer, NaCl) 3341 (br, m), 3029 (m), 2977 (m), 2833 (m), 2723 (w), 1715 (sh, s), 1659 (sh, s), 1517 (sh, s), 1454 (m), 1367 (m), 1153 (m), 1167 (m), 1028 (w) cm^{-1}; HRMS (FAB) *m/z* found 654.41, calc'd for $C_{37}H_{55}N_3O_7$ [M+H]: 654.40.

Preparation of amine 262:

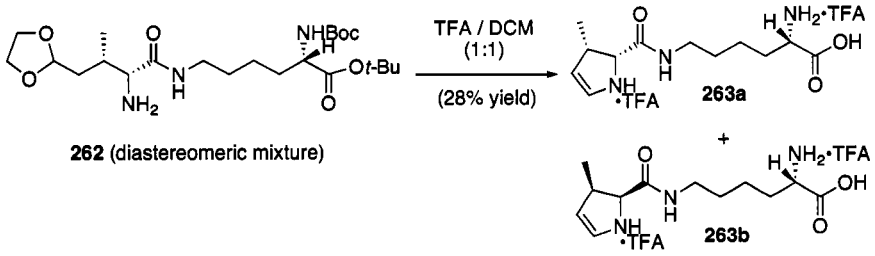


261 (diastereomeric mixture) **262** (diastereomeric mixture)

To a solution of the benzylated amine **261** (170 mg, 0.26 mmol) in EtOH (15 mL) was added Pearlman's catalyst (150 mg, 20 wt % on carbon). The mixture was stirred under an atmosphere of hydrogen for 12 h. The suspension was filtered throught celite under an atmosphere of nitrogen and rinsed several times with EtOH and the filtrate was rotary evaporated. The residue was used without further purification to yield the title compound **262** (122 mg, 90% yield) as a colorless oil: (mixture of two isomers) ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.43 (br s, 1H), 5.09 (t, J = 7.4 Hz, 1H), 4.91 (t, J = 4.4 Hz, 1H), 4.40 (br s, 1H), 4.00-3.95 (m, 2H), 3.87-3.82 (m, 2H), 3.50 (br s, 1H), 3.27- 3.18 (m, 2H), 2.65 (d, J = 9.3 Hz, 1H), 2.52-2.44 (m, 1H), 1.83-1.50 (m, 6H), 1.46 (s, 9H), 1.44 (s, 9H), 1.44-1.30 (m, 4H), 0.86 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ. 172.20, 172.34, 155.83, 104.04, 82.15, 79.95, 65.25, 64.97, 58.19, 54.21, 39.13, 37.76, 32.90, 32.21, 29.67, 28.72, 28.38, 22.99, 14.62; IR (thin layer, NaCl) 3307 (br, s), 2977 (m), 2934 (m), 2872 (w), 1714 (s), 1507 (m), 1457 (w), 1392 (w), 1367 (w), 1252 (w), 1155 (m), 1054 (w) cm^{-1}; HRMS (FAB) *m/z* found 474.32, calc'd for $C_{23}H_{43}N_3O_7$ [M+H]: 474.31.

Preparation of Pyrrolynes 263a-b :

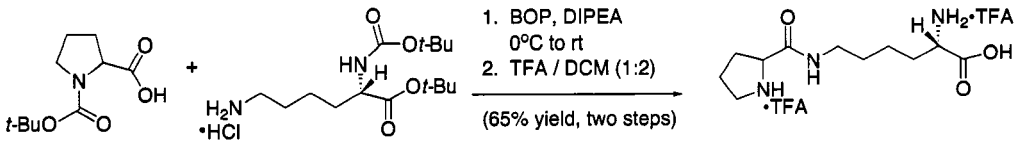


262 (diastereomeric mixture)

The amine **262** (20 mg, 0.042 mmol) was stirred for 7 h in a mixture of TFA (2 mL) and DCM (2 mL). The solvents were rotary evaporated and the residue were purified by reverse phase HPLC (gradient elution, 100→30% water/CH_3CN, in 30 minutes) to yield the title compounds **263a-b** (3 mg, 28% yield) as a white foam: ^1H NMR (400 MHz, CD_3OD) δ. 6.21 (dd, J = 7.9, 3.2 Hz, 1H), 5.04 (dd, J = 7.8, 2.0 Hz, 1H), 3.92-3.88 (m, 2H), 3.72 (d, J = 14.1 Hz, 1H), 3.65-3.54 (m, 2H), 3.49-3.37 (m, 2H), 3.27-3.17 (m, 1H), 2.76-2.68 (m, 1H), 1.93-1.82 (m, 2H), 1.64-1.57 (m, 2H), 1.44-1.39 (m, 2H), 1.22 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ. 172.76, 166.62,

130.14, 112.72, 79.87, 58.35, 57.07, 54.04, 47.34, 32.52, 31.66, 29.18, 28.58, 28.05, 23.74, 23.37, 18.92, 18.77, 18.24; IR (thin layer, NaCl) 3050 (br, w), 2962 (w), 2928 (w), 1673 (br, s), 1514 (w), 1486 (w), 1459 (w), 1437 (w), 1349 (w), 1261 (w), 1204 (m), 1134 (m) cm^{-1}; HRMS (FAB) *m/z* found 256.17, calc'd for $C_{12}H_{22}N_3O_3$ [M+H]: 256.16.

Preparation of L-Pro-L-Lys 267a:



266a : BOC-L-Pro-OH
266b : BOC-D-Pro-OH

256

267a: L-Pro-L-Lys-OH
267b: D-Pro-L-Lys-OH

To a suspension of the amine hydrochloride **256** (130 mg, 0.38 mmol) in dry CH_3CN (4 mL) was added protected L-proline **266a** (55 mg, 0.26 mmol). The mixture was cooled to 0°C and BOP reagent (130 mg, 0.29 mmol) was added all at once, finally *N,N*-diisopropylethylamine (0.18 mL, 1.04 mmol) was introduced dropwise and the reaction mixture was warmed to room temperature. After 12 h, the reaction mixture was partitioned between ether and NH_4Cl (saturated in water) and the organic phase is washed with $NaHCO_3$ (saturated in water) and NaCl (saturated in water), dried over Na_2SO_4, filtered and rotary evaporated. The residue was purified by flash chromatography (2% MeOH/DCM) to yield the protected dipeptide (120 mg, 95% yield) as a colorless oil, this protected dipeptide (120 mg, 0.24 mmol) was stirred 4 h in a mixture of TFA (1 mL) and DCM (2 mL). The solvents were rotary evaporated and the residue was used without further purification. To yield the title compound as a yellow oil **267a** (63 mg, 60% yield) ^1H NMR (400 MHz, D_2O) δ 4.02 (t, J = 7.0 Hz, 1H), 3.70 (t, J = 6.0 Hz, 1H), 3.19-2.89 (m, 5H), 2.20-2.08 (m, 1H), 1.80-1.54 (m, 5H), 1.33-1.02 (m, 5H); ^{13}C NMR (100 MHz,

D_2O) δ 172.83, 169.65, 60.11, 53.41, 46.78, 39.46, 30.15, 29.76, 28.08, 24.12, 21.88; IR (thin layer, NaCl) 3087 (br, w), 3046 (br, s), 2953 (w), 1733 (w), 1674 (br, s), 1575 (m), 1431 (w), 1203 (s), 1137 (s) cm^{-1}; HRMS (ES) *m/z* found 244.17, calc'd for $C_{11}H_{22}N_3O_3$ [M+H]: 244.16.

Preparation of D-Pro-L-Lys 267b:

To a suspension of the amine hydrochloride **256** (75 mg, 0.22 mmol) in CH_3CN (3 mL) was added protected D-proline **266b** (32 mg, 0.30 mmol). The mixture was cooled to 0°C and BOP reagent (73 mg, 0.17 mmol) was added all at once, finally *N,N*-diisopropylethylamine (0.10 mL, 0.6 mmol) was introduced dropwise and the reaction mixture was warmed to room temperature. After 15 min, the reaction mixture was partitioned between ether and NH_4Cl (saturated in water) and the organic phase was washed with $NaHCO_3$ (saturated in water) and NaCl (saturated in water), dried over Na_2SO_4, filtered and rotary evaporated. The residue was purified by flash chromatography (2% MeOH/DCM) to yield the protected dipeptide (80 mg, 95% yield) as a colorless oil, this protected dipeptide (55 mg, 0.11 mmol) was stirred for 4 h in a mixture of TFA (1 mL) and DCM (2 mL). The solvents were rotary evaporated and the residue was used without further purification. To yield the title compound as a yellow oil **267b** (31 mg, 65% yield): ^1H NMR (400 MHz, D_2O) δ 4.11 (t, J = 7.0 Hz, 1H), 3.87 (t, J = 6.2 Hz, 1H), 3.26-2.99 (m, 5H), 2.29-2.18 (m, 1H), 1.90-1.67 (m, 5H), 1.42-1.13 (m, 5H); ^{13}C NMR (100 MHz, D_2O) δ 172.15, 169.54, 60.03, 53.50, 46.73, 39.37, 30.08, 29.54, 27.94, 24.05, 21.77; IR (thin layer, NaCl) 3088 (br, w), 3046 (br, s), 2954 (w), 1675 (br, s), 1575 (m), 1430 (w), 1203 (s), 1137 (s) cm^{-1}; HRMS (ES) *m/z* found 244.17, calc'd for $C_{11}H_{22}N_3O_3$ [M+H]: 244.16.

5.6 Notes and References.

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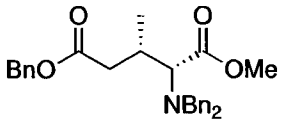
Appendix A6: Spectra Relevant to Chapter 6.



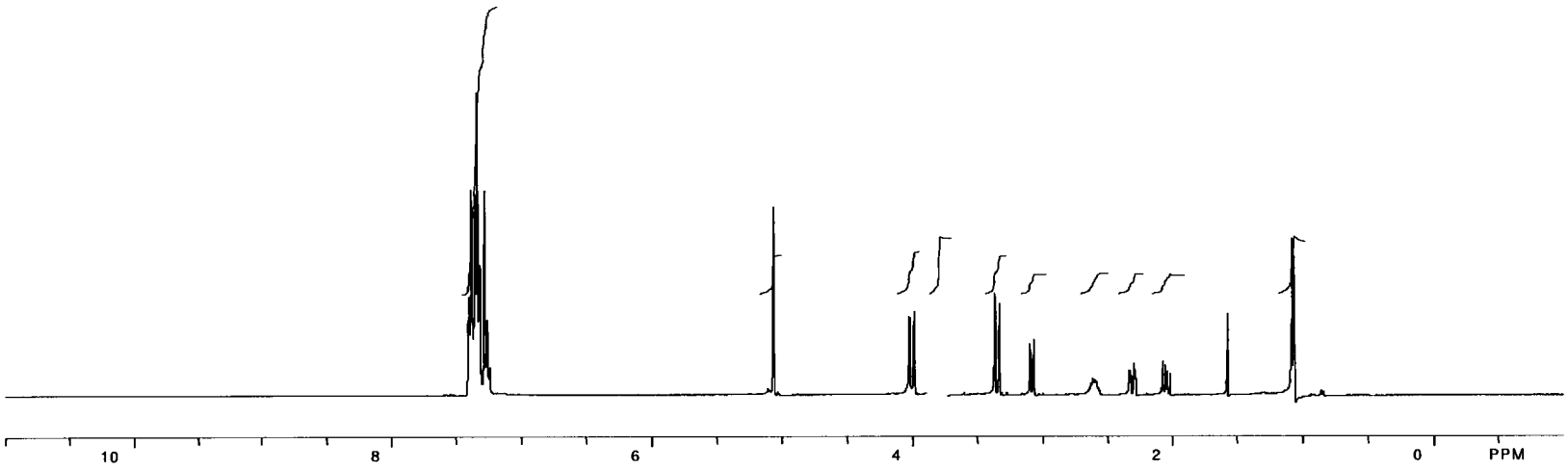


Figure A6.1 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **258**.

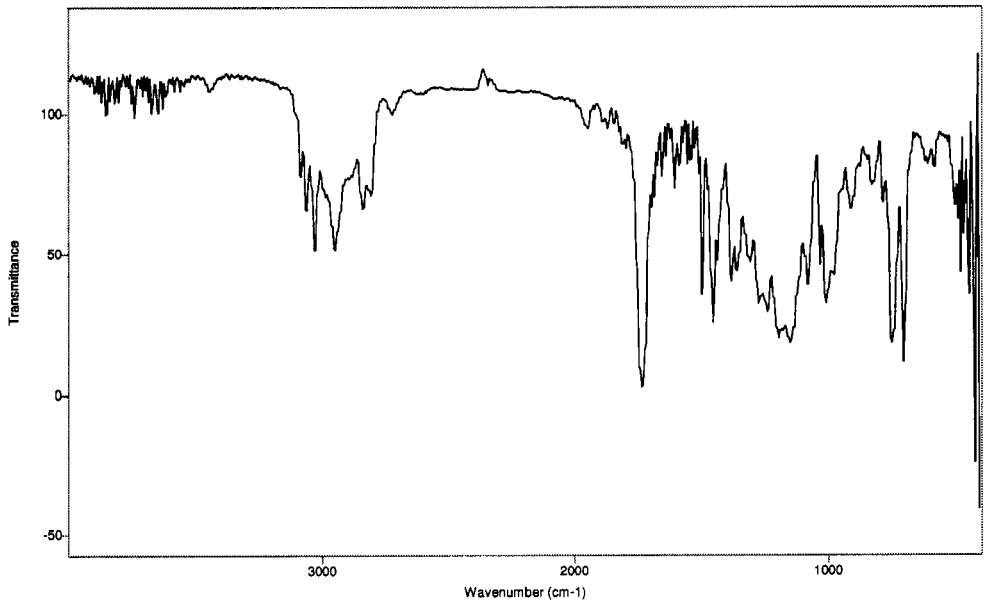


Figure A6.2 IR spectrum (thin film/NaCl) of compound **258**.

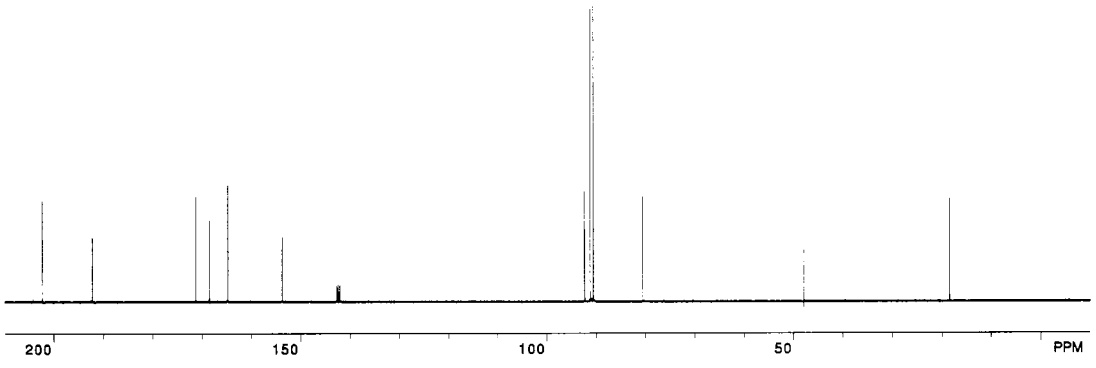


Figure A6.3 ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **258**.

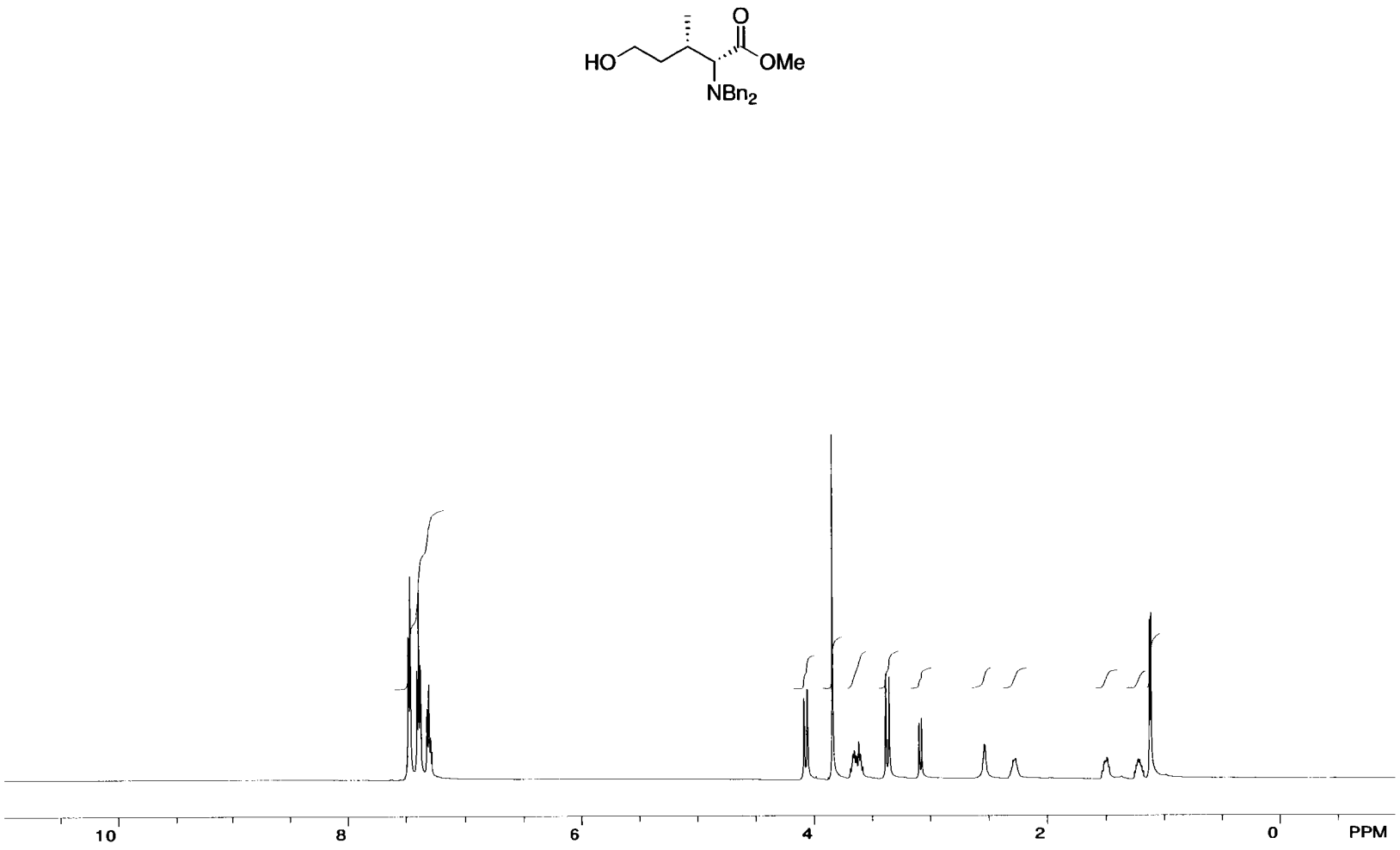


Figure A6.4 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **268**.

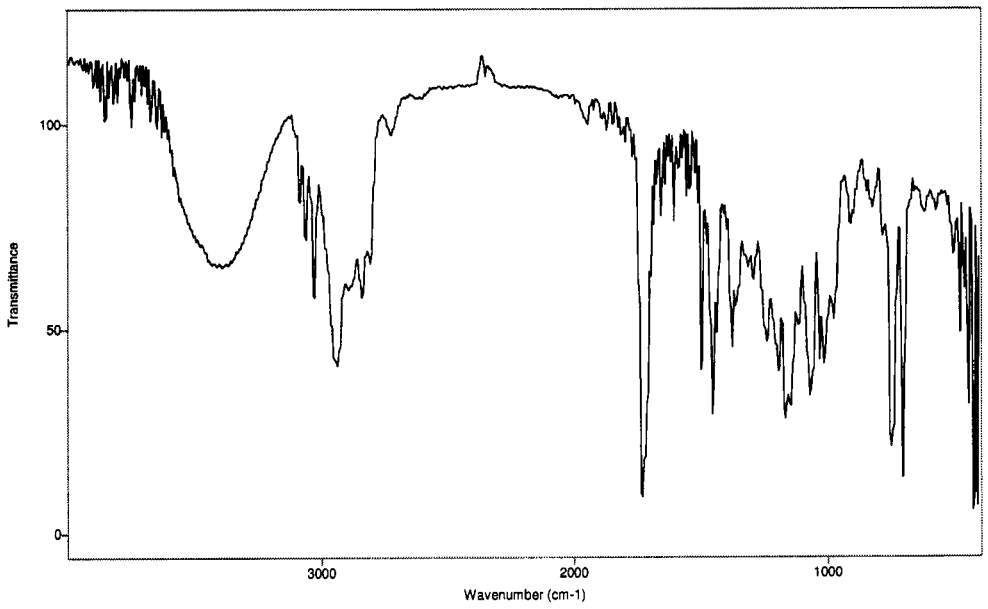


Figure A6.5 IR spectrum (thin film/NaCl) of compound **268**.

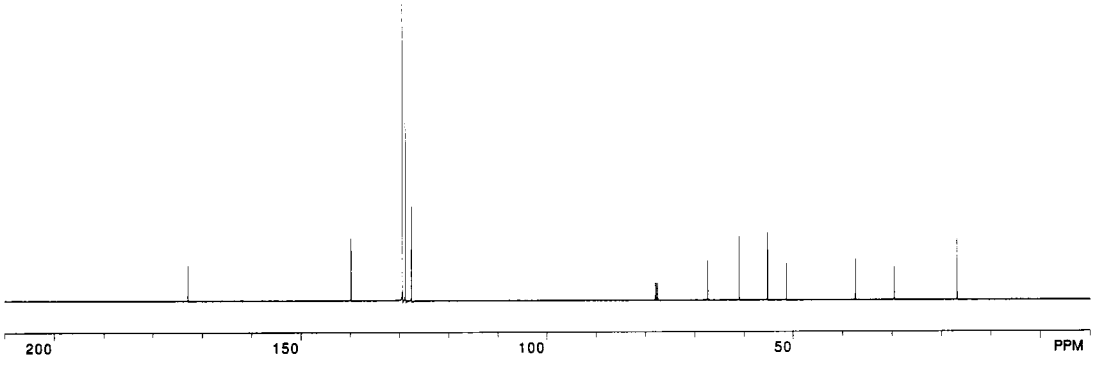


Figure A6.6 ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **268**.

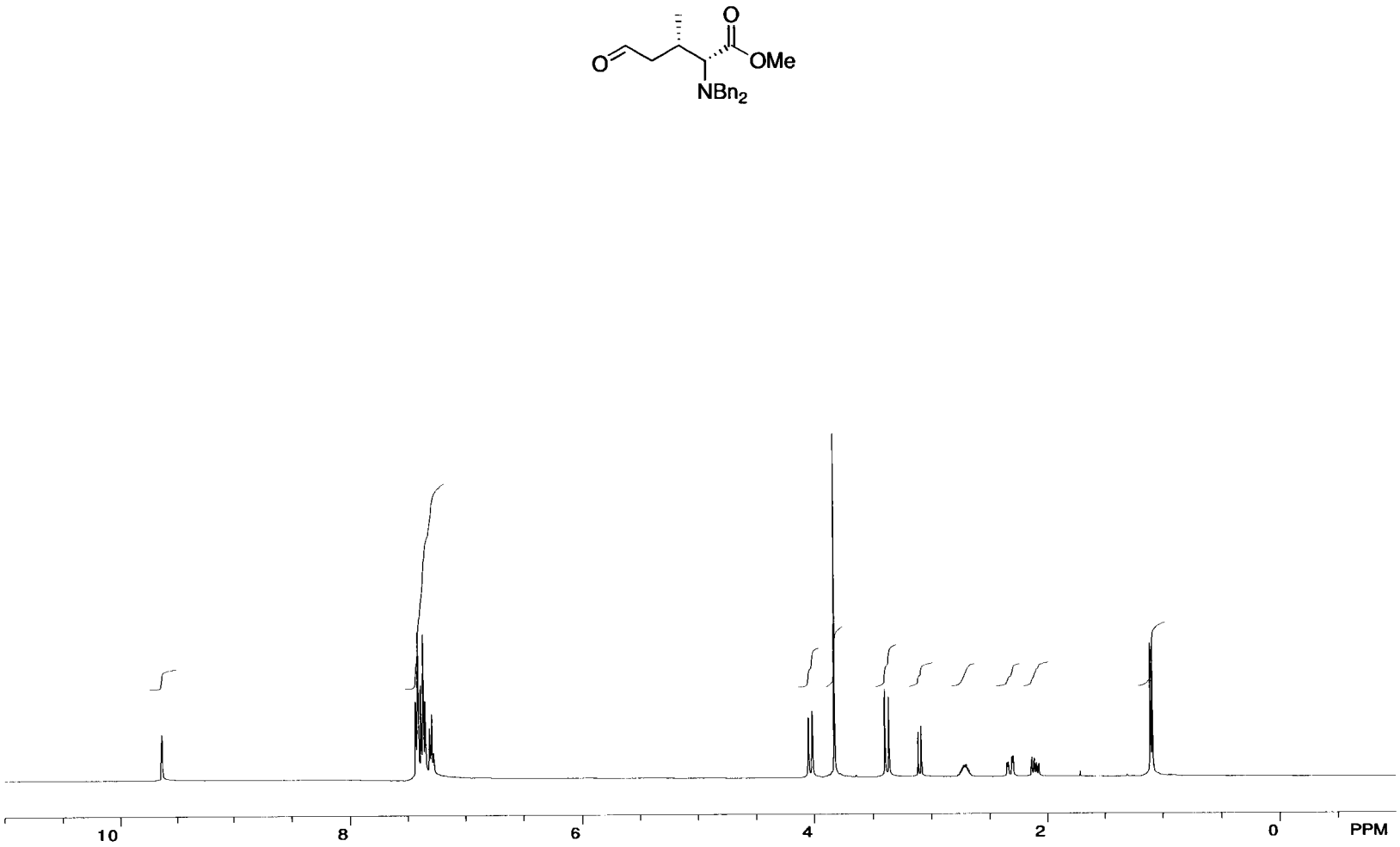


Figure A6.7 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **259**.

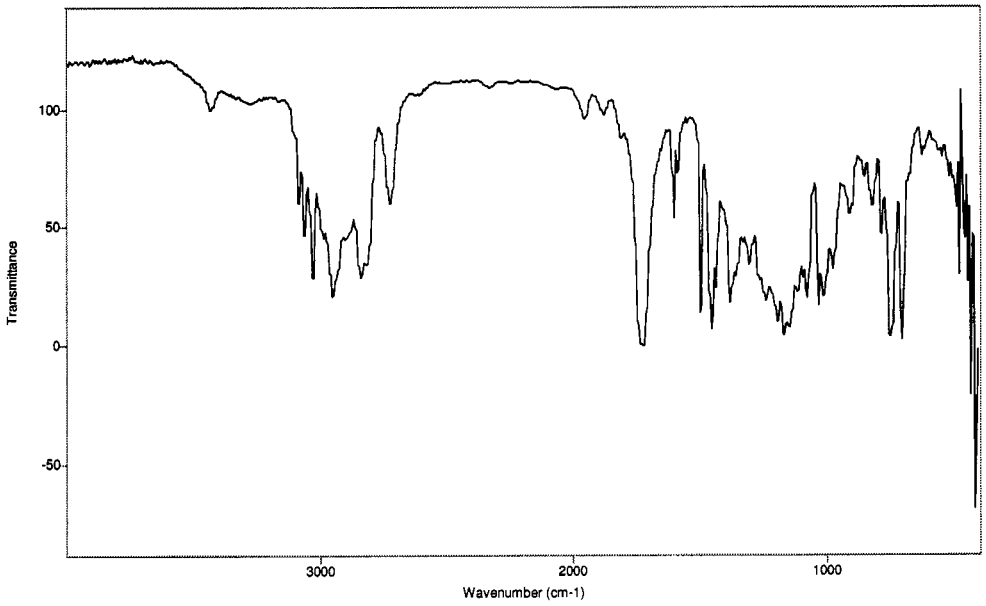


Figure A6.8 IR spectrum (thin film/NaCl) of compound **259**.

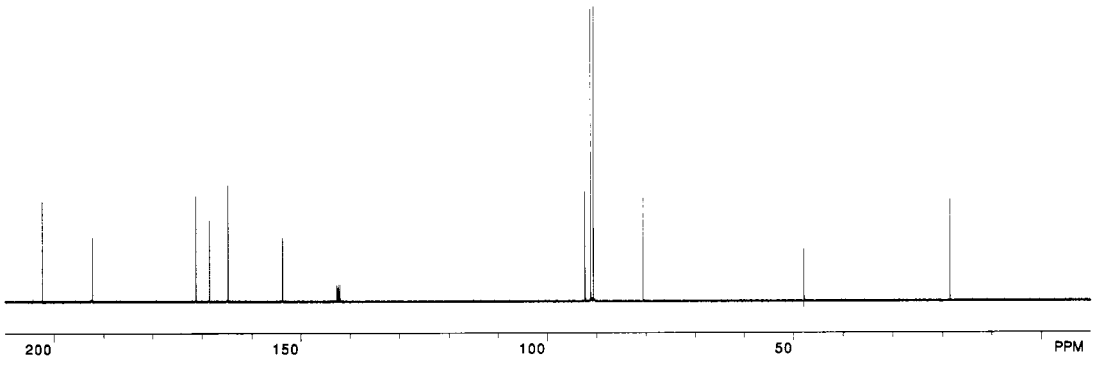


Figure A6.9 ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **259**.

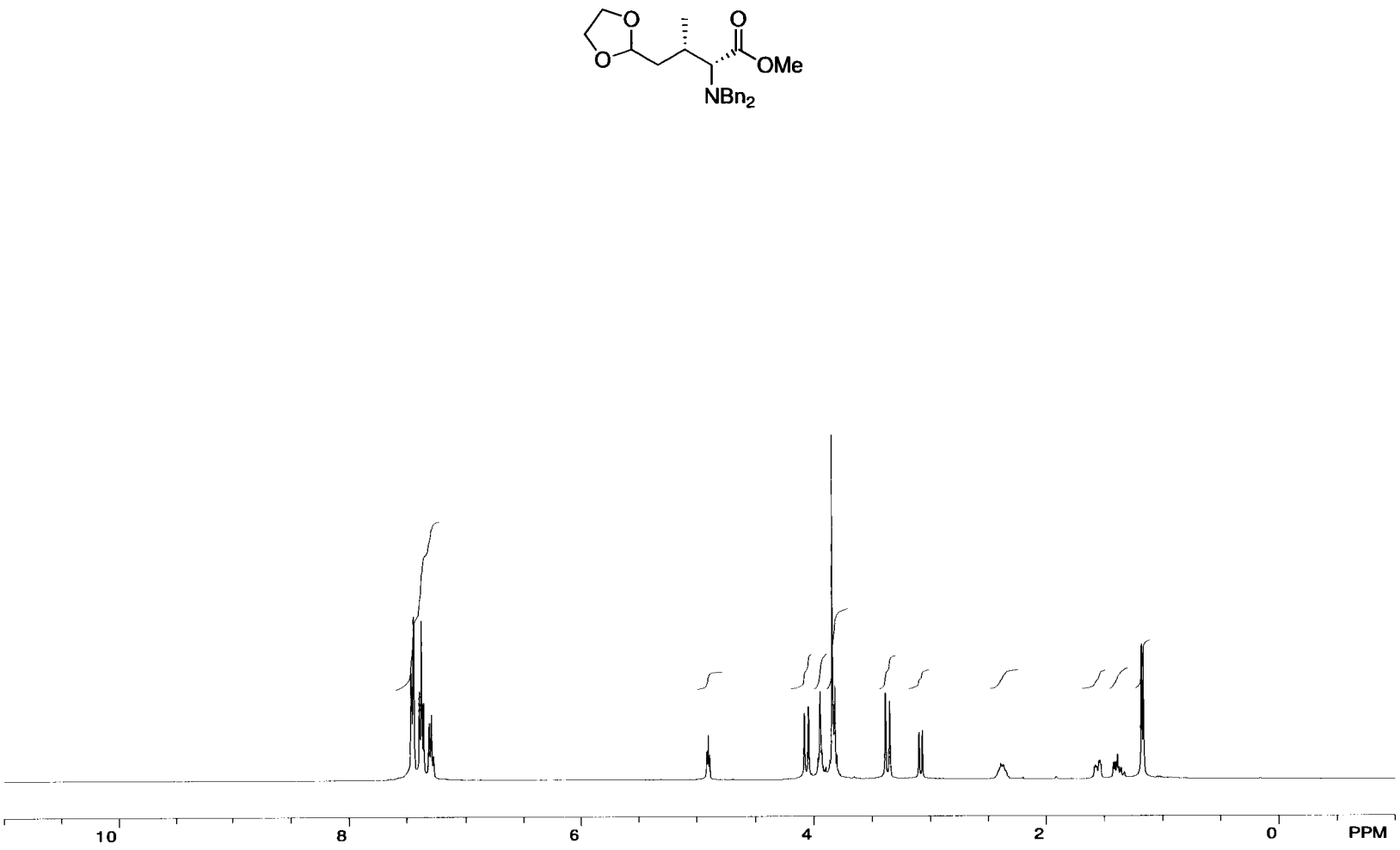


Figure A6.10 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **260**.

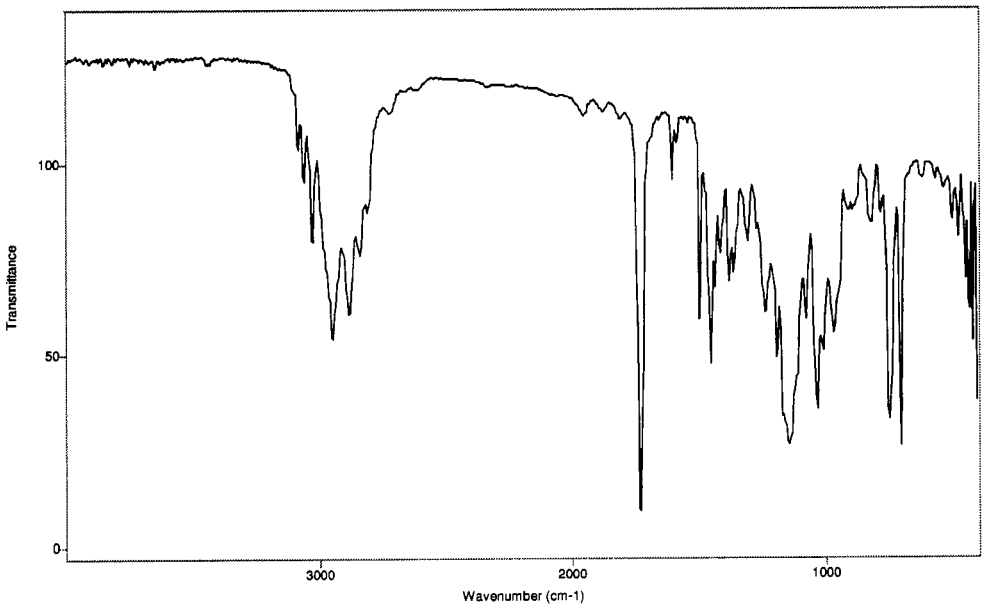


Figure A6.11 IR spectrum (thin film/NaCl) of compound **260**.

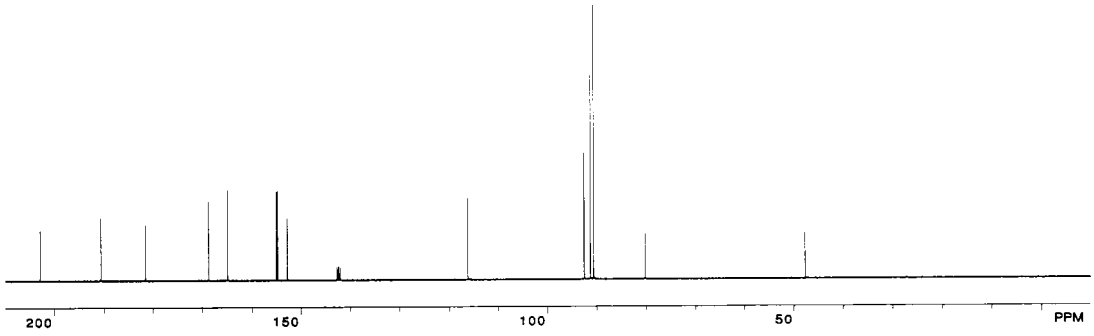


Figure A6.12 ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **260**.

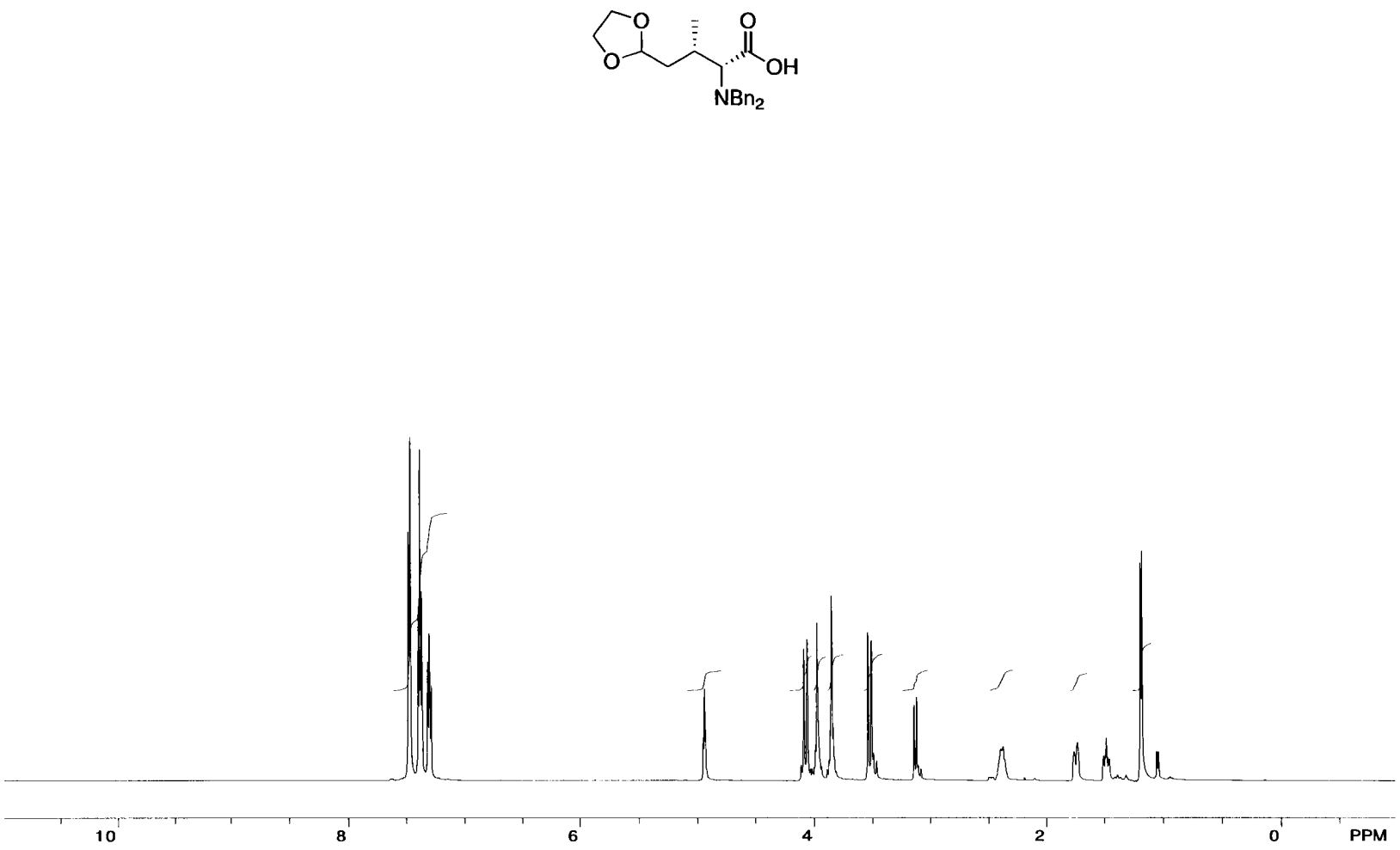


Figure A6.13 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **255**.

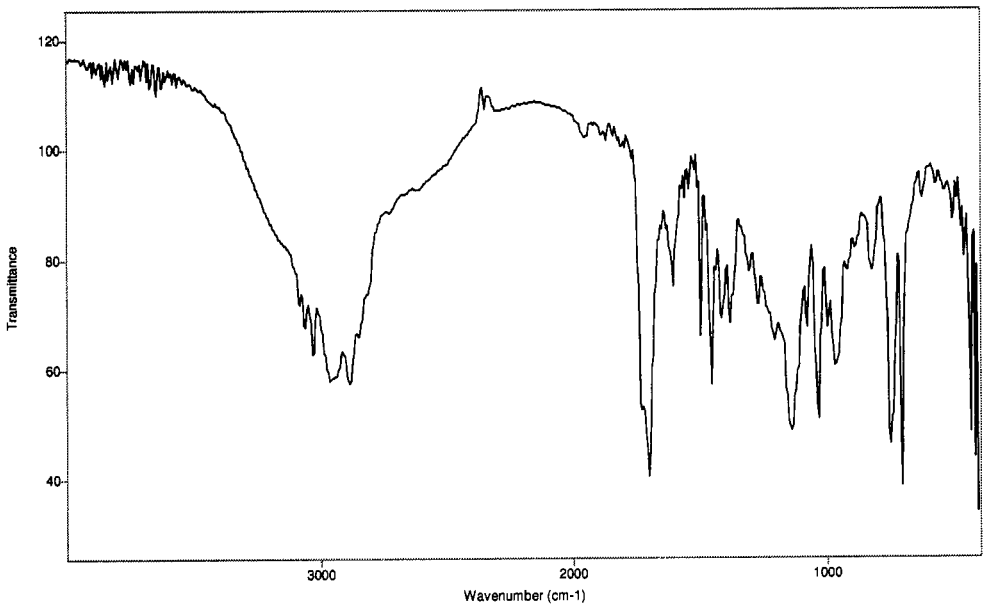


Figure A6.14 IR spectrum (thin film/NaCl) of compound **255**.

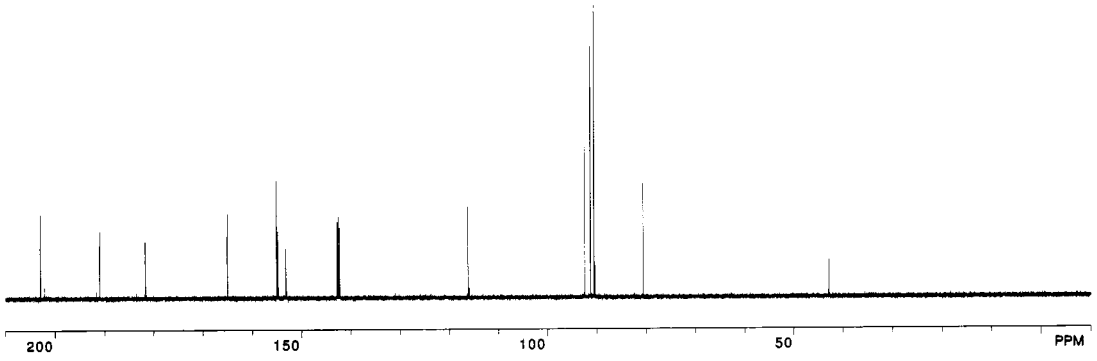


Figure A6.15 ^{13}C NMR spectrum (125 MHz, $CDCl_3$) of compound **255**.

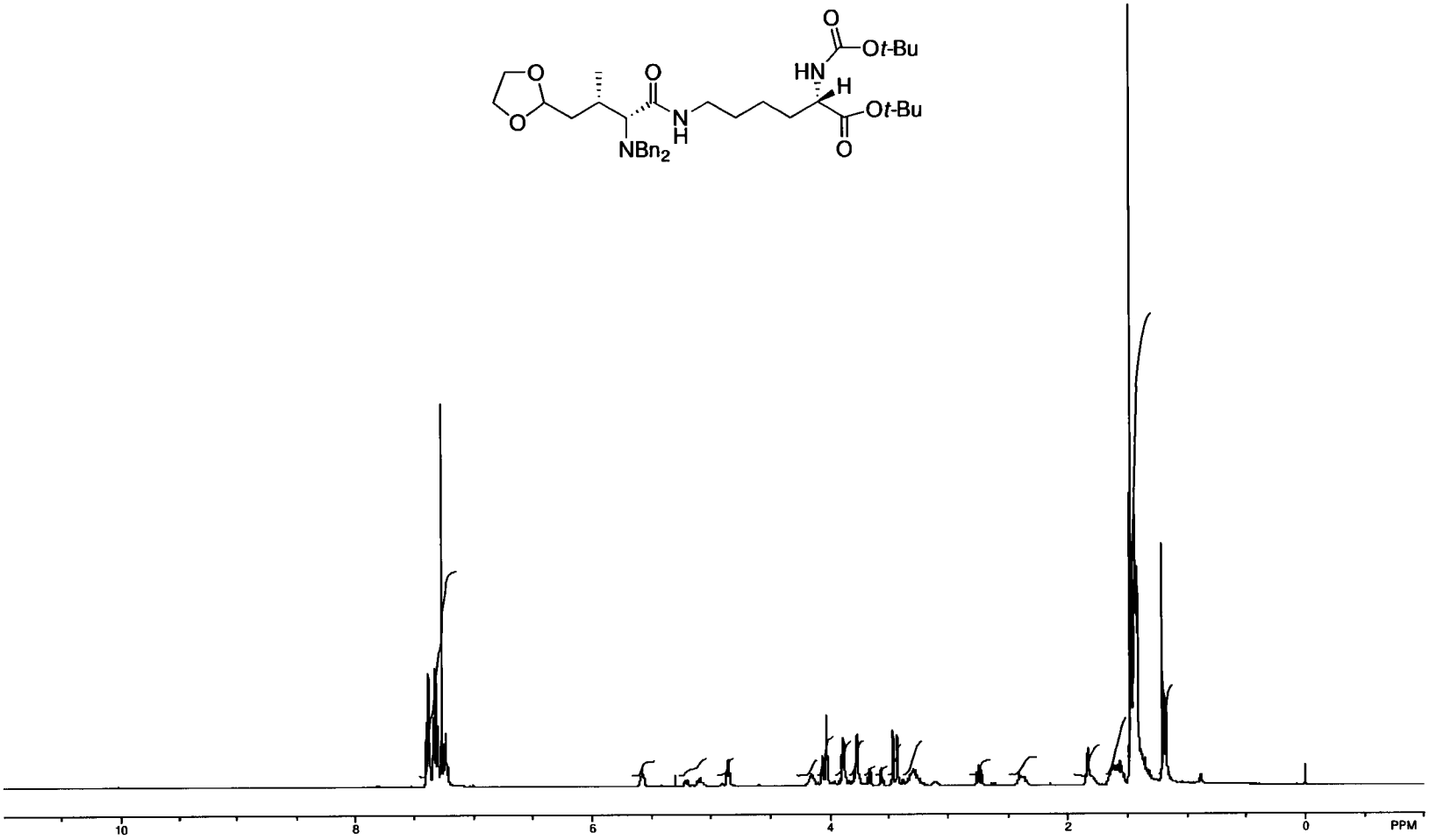


Figure A6.16 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **261**.

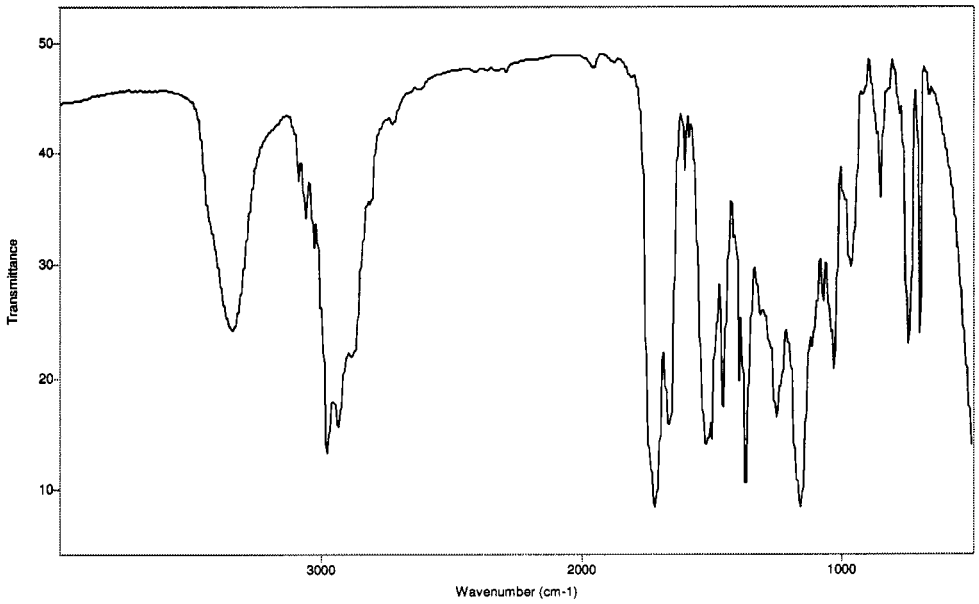


Figure A6.17 IR spectrum (thin film/NaCl) of compound **261**.

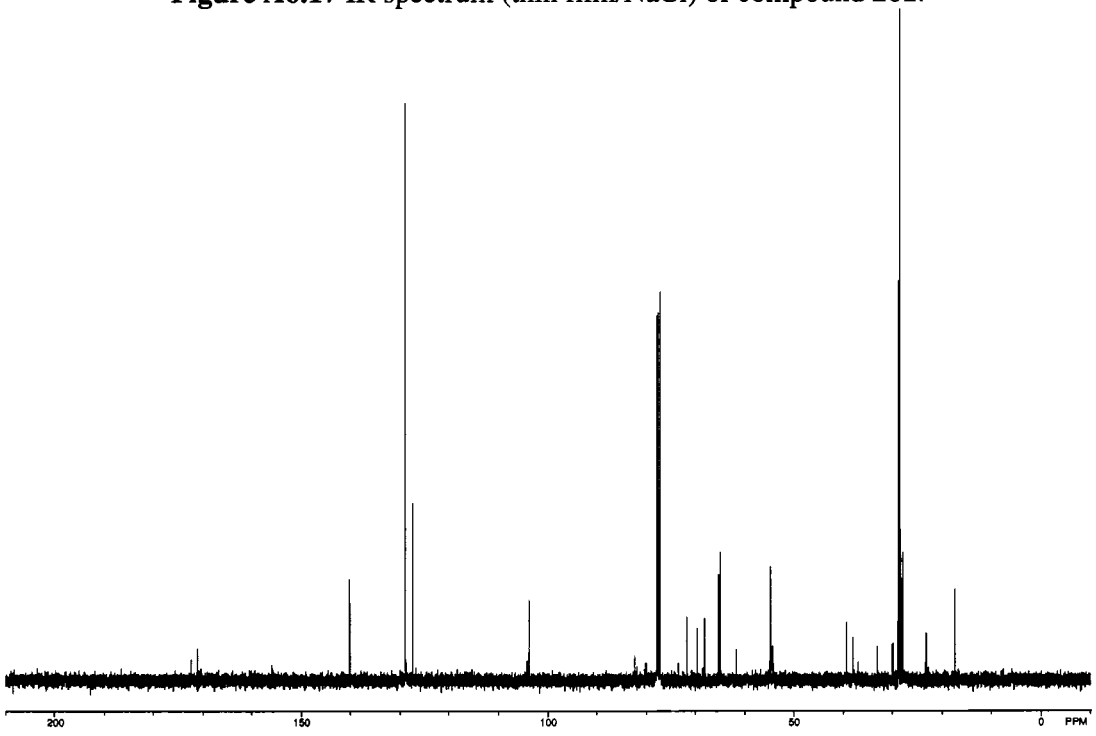


Figure A6.18 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **261**.

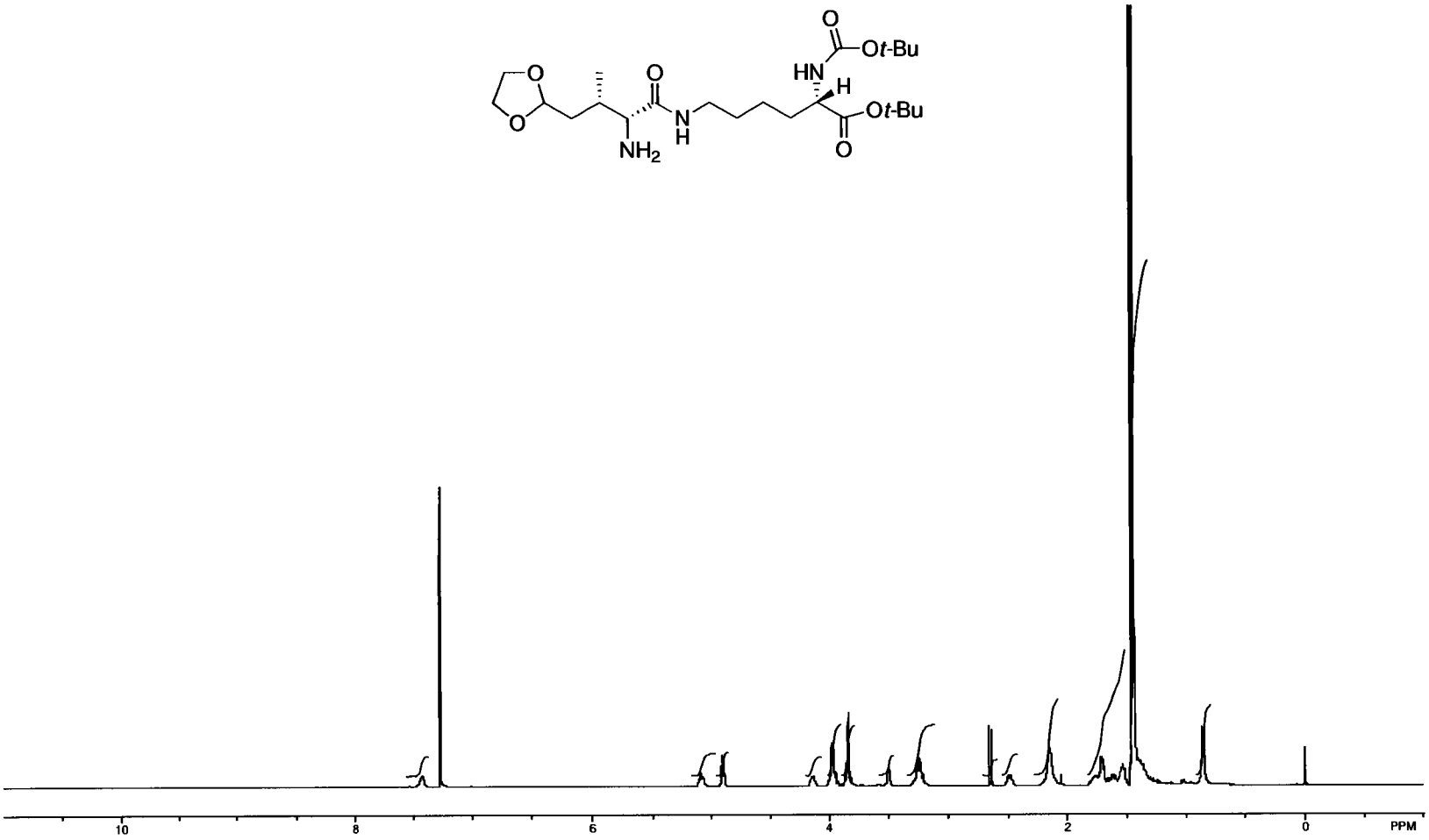


Figure A6.19 ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **262**.

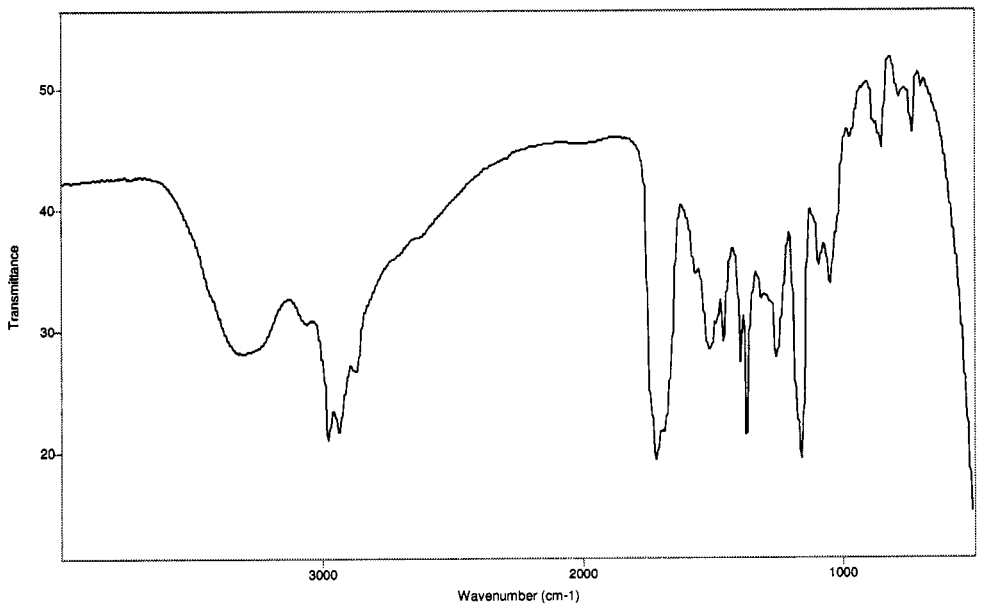


Figure A6.20 IR spectrum (thin film/NaCl) of compound **262**.

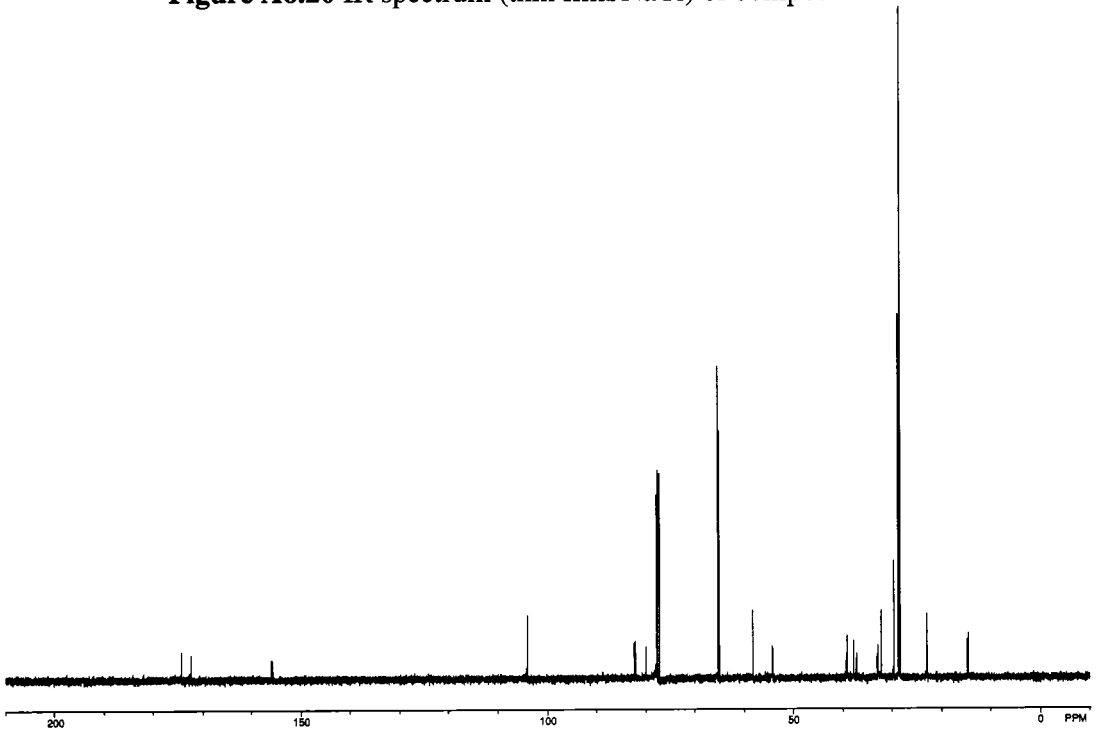


Figure A6.21 ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **262**.

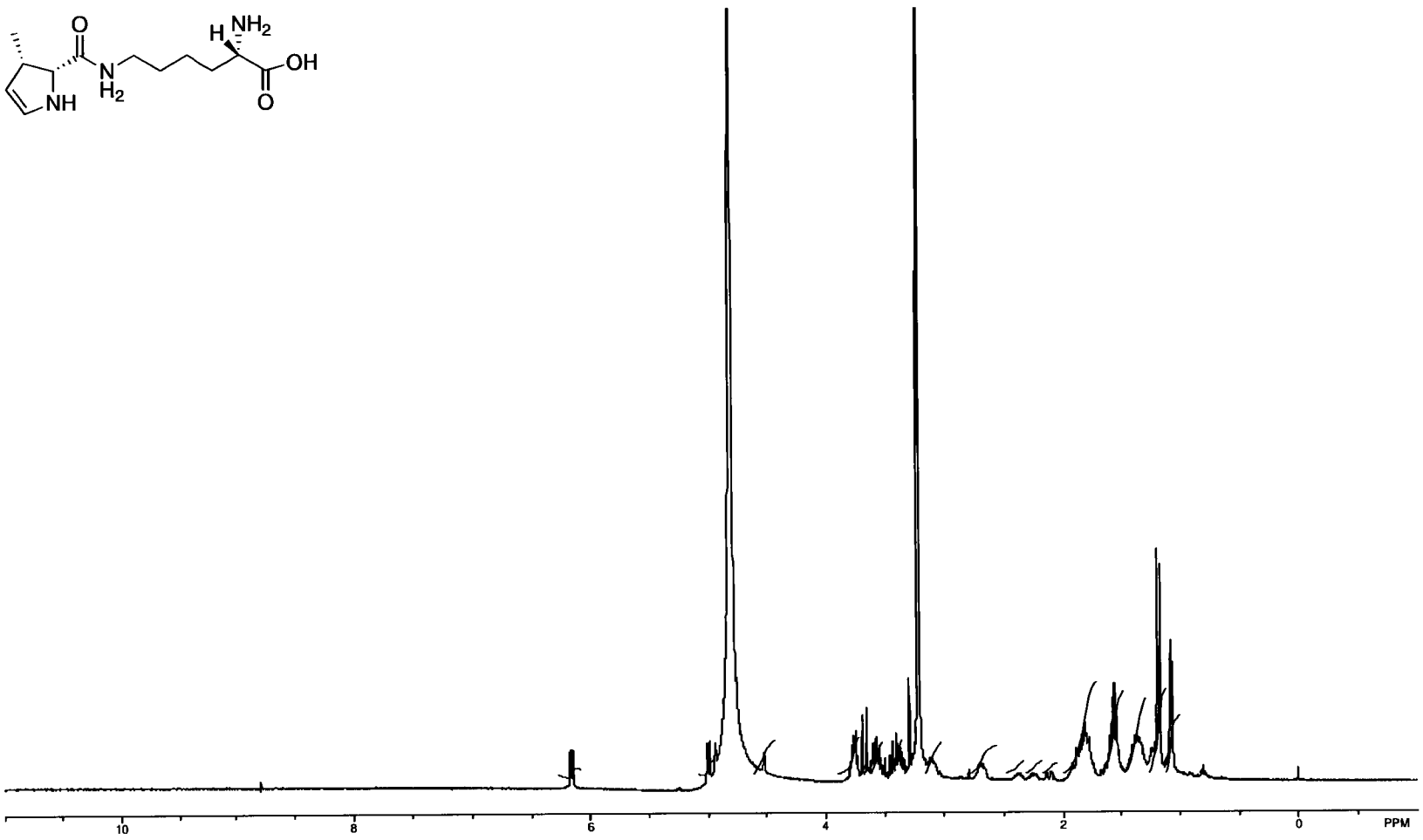


Figure A6.22 ^{1}H NMR spectrum (400 MHz, CD_3OD) of compound **263a-b**.

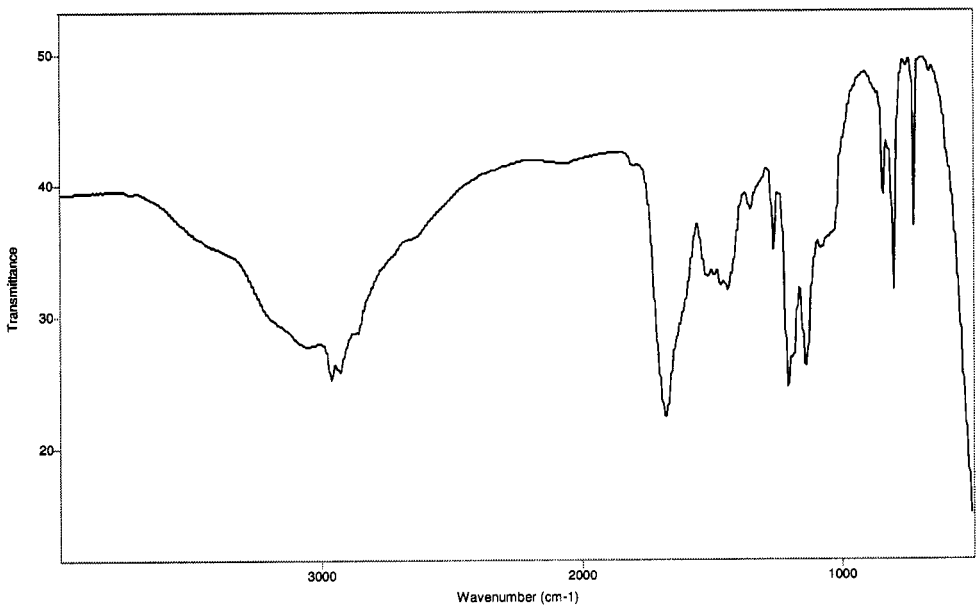


Figure A6.23 IR spectrum (thin film/NaCl) of compound **263a-b**.

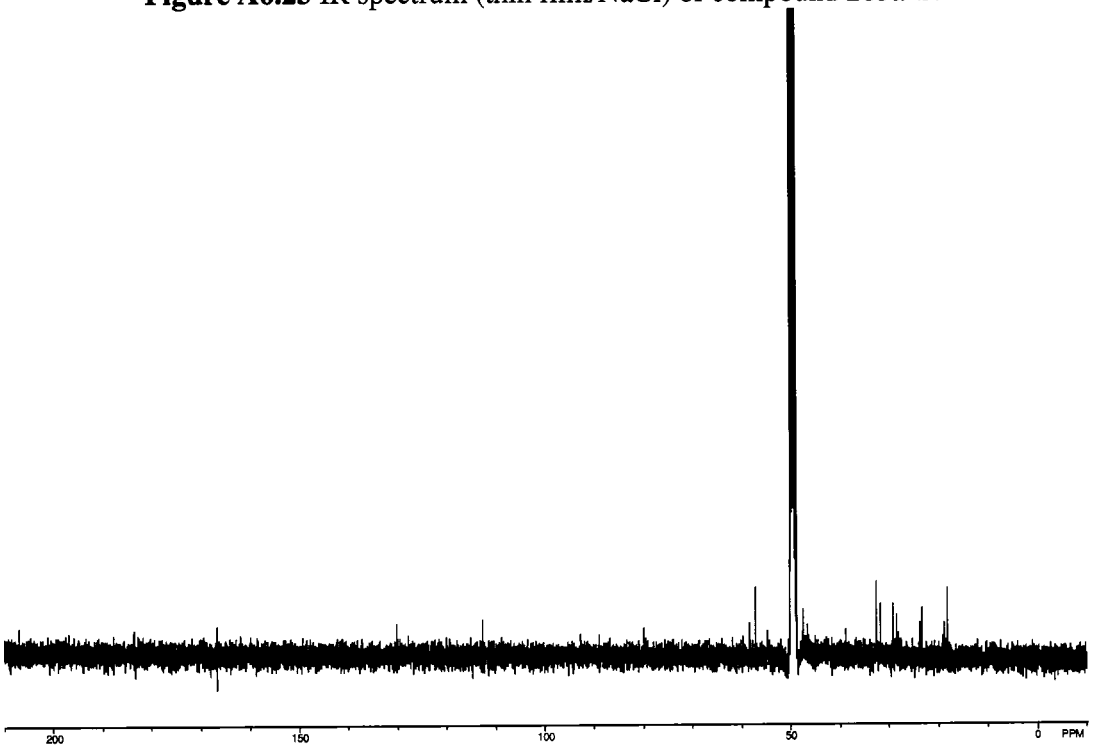


Figure A6.24 ^{13}C NMR spectrum (100 MHz, CD_3OD) of compound **263a-b**.

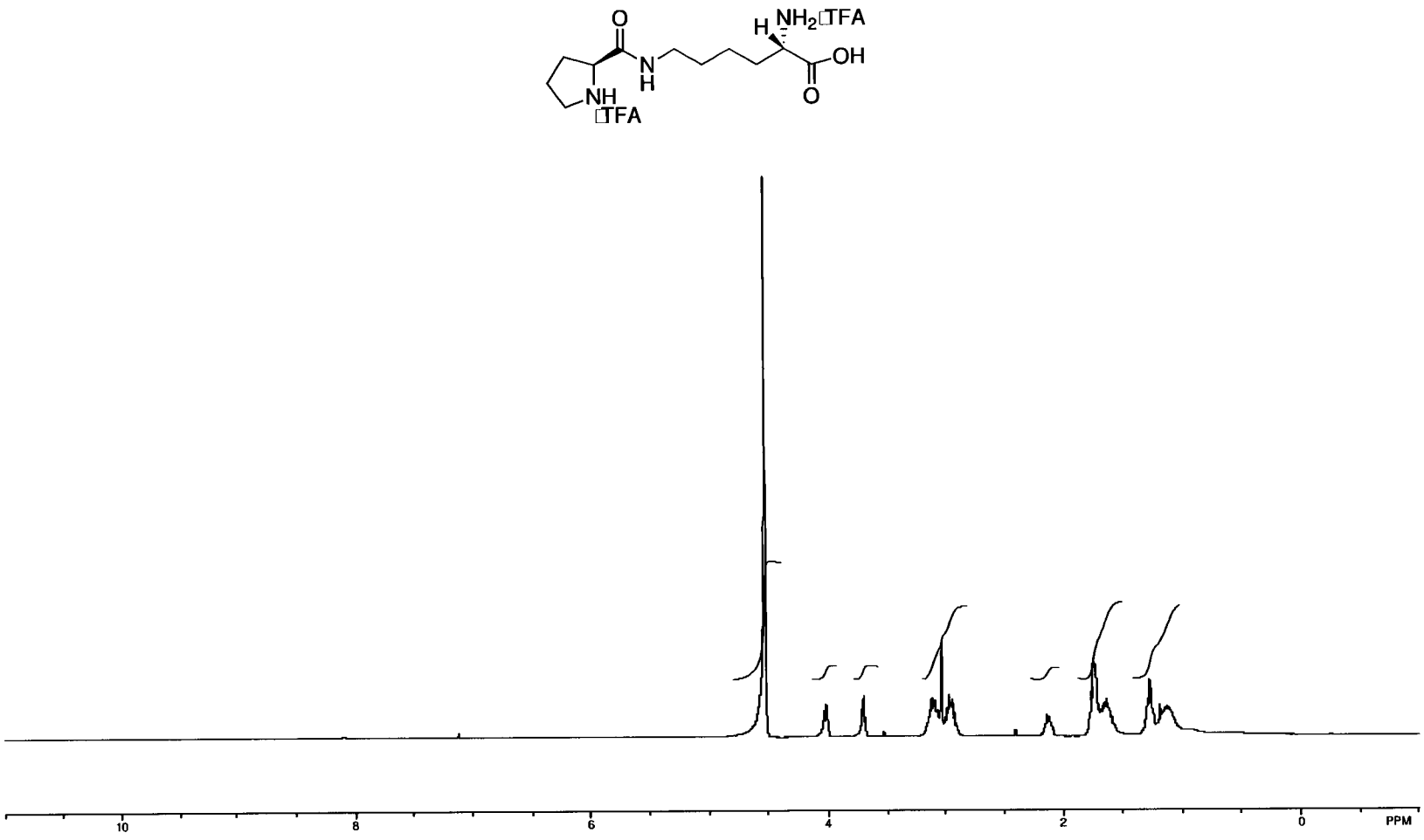


Figure A6.25 ^{1}H NMR spectrum (400 MHz, D_2O) of compound **267a**.

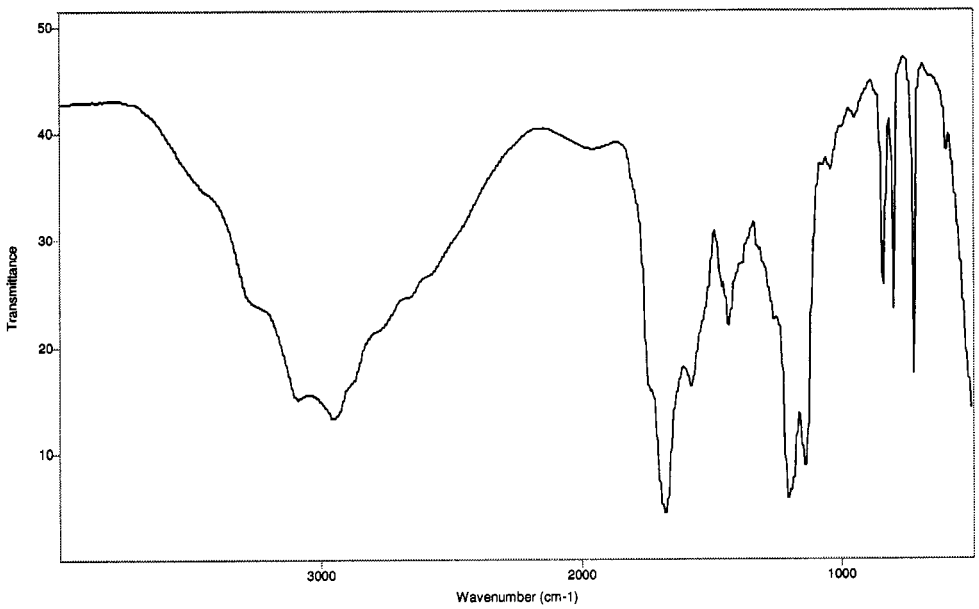


Figure A6.26 IR spectrum (thin film/NaCl) of compound **267a**.

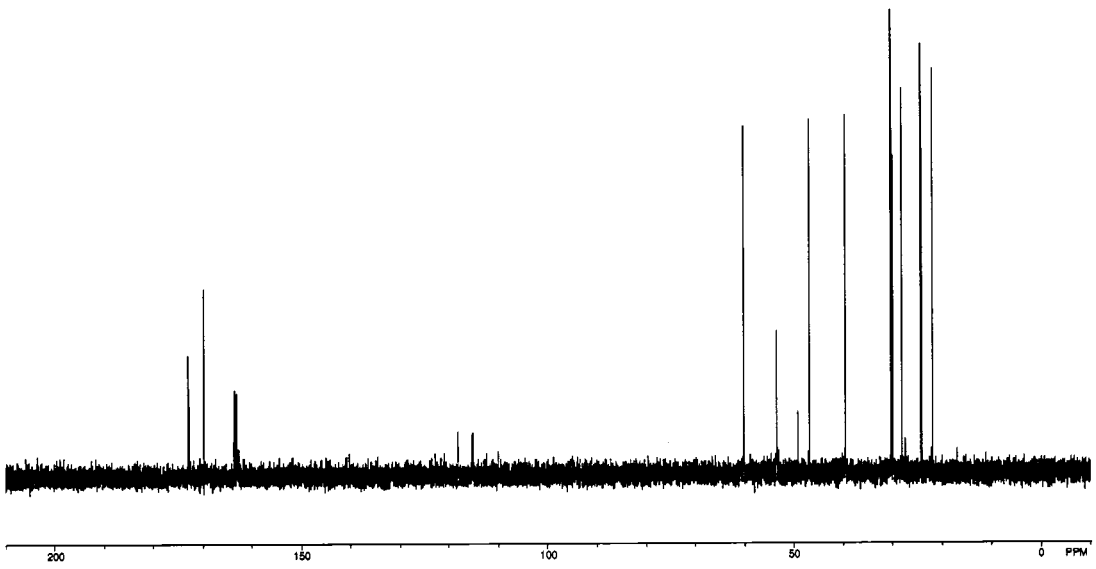


Figure A6.27 ^{13}C NMR spectrum (100 MHz, D_2O) of compound **267a**.

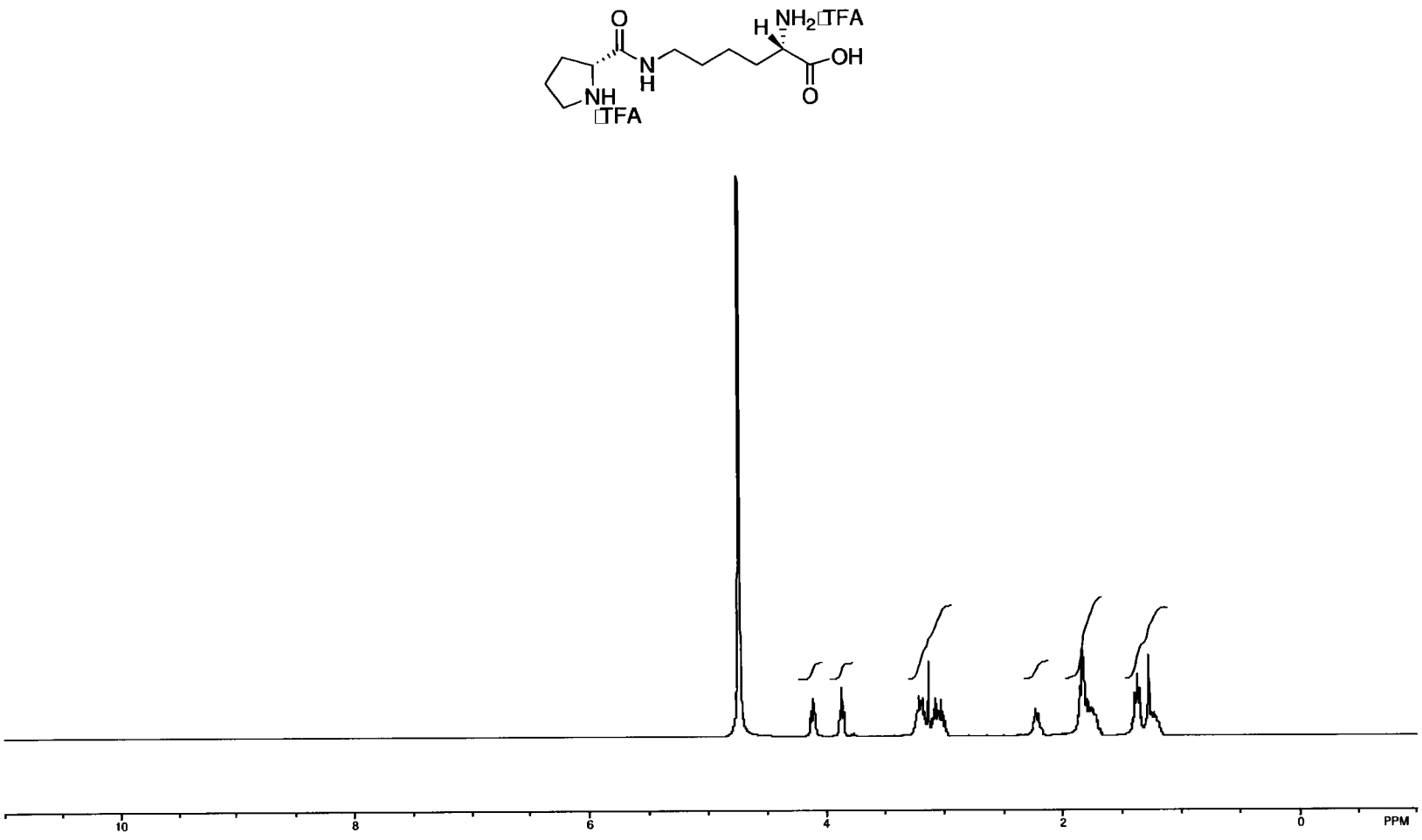


Figure A6.28 ^{1}H NMR spectrum (400 MHz, D_2O) of compound **267b**.

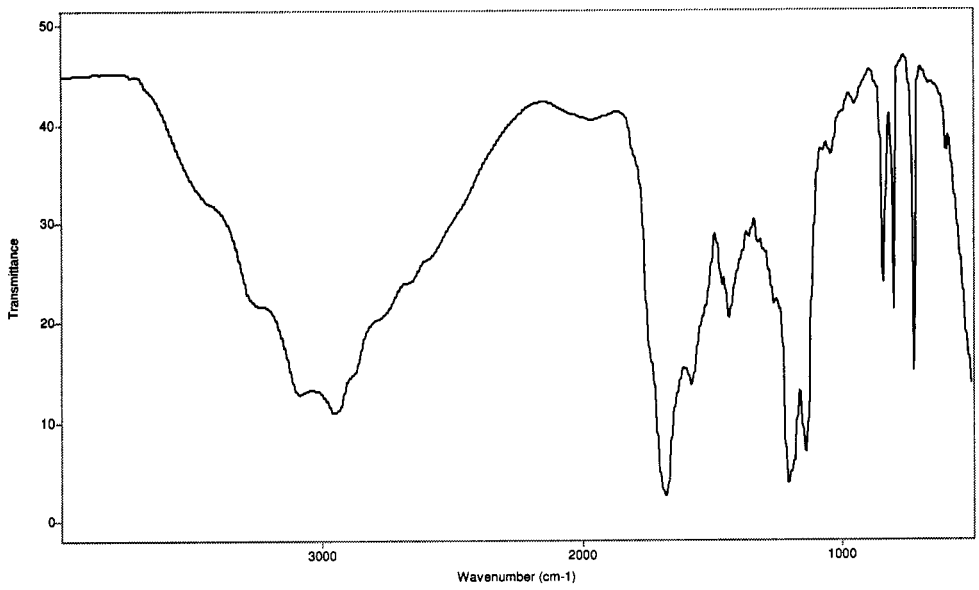


Figure A6.29 IR spectrum (thin film/NaCl) of compound **267b**.

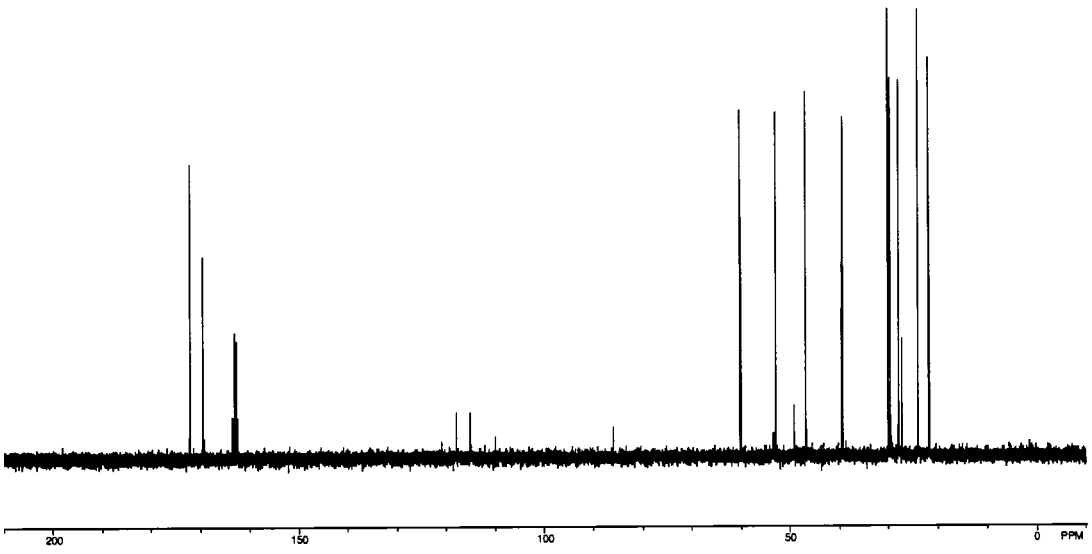


Figure A6.30 ^{13}C NMR spectrum (100 MHz, D_2O) of compound **267b**.

Appendix 7

Notebook Cross Reference

The following notebook cross reference has been included to facilitate access to the original spectroscopic data obtained for the compounds present in this work. For each compound a folder name is given which corresponds to an original notebook reference. References beginning with AB refer to Amélie Bérubé's notebooks, and references beginning with SW refer to SusAnn Winbush's notebook. All spectroscopic data for a given compound is organized by its original notebook reference in the Wood group archives.

Table A7.1 Compounds Appearing in Chapter 1

Cmpd	Notebook		Cmpd	Notebook
51	AB-VII-41		**57**	AB-VII-65
52	AB-VII-54		**58**	AB-VII-67
53	AB-VII-58		**59**	AB-VII-82
54	AB-VII-60		**43**	AB-VII-84
55	AB-VII-63		**66**	AB-VII-86
56	AB-VI-71			

Table A7.2 Compounds Appearing in Chapter 2

Cmpd	Notebook		Cmpd	Notebook		Cmpd	Notebook
72	AB-VI-208		**88**	AB-VI-165		**103**	AB-VII-232A
73	AB-VI-209		**89**	AB-VI-166		**104**	AB-VII-232B
74	AB-VI-210		**90**	AB-VII-17		**106**	AB-VII-201

75	AB-VI-211		**91**	AB-VII-18		**107**	AB-VII-204
70	AB-VI-213		**82**	AB-VII-19		**108**	AB-VII-206
69	AB-VI-214		**96**	AB-VII-100		**109**	AB-VII-207
76	AB-VI-234		**99**	AB-VII-184		**110**	AB-VII-209
85	AB-VI-159		**100**	AB-VII-187A		**111**	AB-VII-210
86	AB-VI-160		**101**	AB-VII-187B		**112**	AB-VII-230
87	AB-VI-163		**102**	AB-VII-188		**113**	AB-VII-235

Table A7.3 Compounds Appearing in Chapter 3

Cmpd	Notebook		Cmpd	Notebook
124	AB-VIII-83		**128**	AB-VIII-96
126	AB-VIII-84		**129**	AB-VIII-97
127	AB-VIII-85		**144**	AB-VIII-243

Table A7.4 Compounds Appearing in Chapter 4

Cmpd	Notebook		Cmpd	Notebook
204	AB-II-216		**196/197**	AB-VIII-253
205	AB-II-292		**216a/217a**	AB-III-107
195	AB-II-209		**216b-c/217b**	AB-III-108
209	AB-VIII-251		**218**	AB-III-56
210	AB-VIII-252		**224**	AB-VIII-255

Table A7.5 Compounds Appearing in Chapter 5

Cmpd	Notebook		Cmpd	Notebook
258	SW-I-217		**261**	AB-V-99
268	SW-I-219		**262**	AB-V-102
259	AB-V-53		**263a-b**	AB-V-103
260	AB-V-54		**267a**	AB-V-101,103
255	AB-V-55		**267b**	AB-VII-70,71

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About the Author

Amélie Bérubé was born on January 26th 1977 in Rimouski, a coastal town on the Saint-Laurence River in Québec, Canada. As a young girl, she moved and traveled around the world with her mother Mona Picard, to settle in 1990 in Montréal with her stepfather Jean Pilon. Her sister, Marie-Hélène, was born in 1991. In Montréal, she attended Collège Regina Assumpta, an all girl secondary school. She enjoyed Science and decided to pursue a DEC^{plus} specialized in general sciences at Collège André-Grasset.

Unlike their American colleagues, students in Québec select their major when they enter the university and take courses related to their field of studies. She chose the chemistry program at the Université de Montréal where she met her husband Louis-David Cantin in 1997 and obtained her B.Sc. in 1999. Early on, she knew that she wanted to pursue a career in chemistry and sought to broaden her knowledge of organic chemistry. Her first mentor was Professor Stephen Hanessian at the Université de Montréal, with whom she completed a summer internship. Subsequently, she also performed a summer internship in an industrial setting at the Montréal Institute of Clinical Research, where Dr. Yvan Guindon supervised her.

She then had the opportunity to further expand her knowledge to the field of physical organic chemistry at Bryn Mawr College, Pennsylvania. In 1999, she completed a Masters degree under the supervision of Professor Frank B. Mallory, working on the synthesis of large phenacenes, a family of graphite ribbons. Her studies at Bryn Mawr also provided her with her first teaching experience. As a teaching assistant she found very fulfilling to share her knowledge with the undergraduate students and help them acquire new laboratory skills.

She then decided to continue her graduate work at Yale University to work on the total synthesis of complex natural products. She joined Professor John Wood's laboratory in 2002, and had the opportunity to work toward the total syntheses of providencin, bacchopetiolone and pyrrolysine. Yale University has given her an ideal setting to learn not only chemistry but also quality teaching. Upon completion of her Ph.D., Amélie will begin her independent academic career at Saint Joseph College in West Hartford, Connecticut.