ABSTRACT

PROGRESS TOWARD A TOTAL SYNTHESIS OF THE WELWITINDOLINONE ALKALOIDS

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The welwitindolinone alkaloids were recently isolated from blue green algae and found to possess interest biological activities, which included multiple drug resistance reversing activity. Herein are described efforts toward a synthesis of these structurally and biologically interesting natural products.

Toward welwitindolinones C and D, the carbocyclic skeleton of these C(3)-C(4) bridged oxindoles (i.e., **58**) was efficiently prepared in a sequence highlighted by a novel Rh(II)-initiated ring opening reaction in the conversion of **21** → **51**. This sequence allowed for the preparation of **61** which in short order can be converted to isoxazolidines **63**. These products can be advanced to alcohol **84**, which contains a suitably protected bridgehead nitrogen and handles for the construction of the C(12) quaternary center and C(4) spiro ether.

In efforts directed toward a total synthesis of welwitindolinone A isonitrile (**7**) it has been demonstrated that the requisite spirocyclobutane oxindole core can be constructed via an intramolecular palladium-mediated α-arylation (**136** → **138**). A diastereoselective ketene [2+2] cycloaddition allows for the preparation of a [4.2.0] bicyclic system which can be advanced to acetate **178**. This compound can further be elaborated to either acid **244** or epoxide **282**, both of which represent fully functionalized [4.2.0] systems. These systems are suitable intermediates for advancement to welwitindolinone A isonititrile (**7**).

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by
Matthew Mark Weiss

Dissertation Director: Professor John L. Wood

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To My Parents

ACKNOWLEDGEMENTS

I still remember the moment, sitting in Professor John Wood's office asking him the question that Prof. Amos Smith, a week earlier, suggested I ask of him. "What can you and Yale offer me that Amos and the University of Pennsylvania cannot?" After a long uncomfortable silence, which I have since grown rather accustomed to, John replied, "I'm not sure." While I never spent anytime at the University of Pennsylvania, I am sure that there could have been no better environment for my development as a synthetic chemist than the one John provided me here at Yale. John's passion for chemistry has truly been contagious, and I am indebted to him for all of his time and effort over the past four years. However, in addition to being a great advisor to work with, John has also been a good friend, which has the made the past four years all that much better.

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I am also thankful for all the friendships I have made during my stay here at Yale, and will leave with great memories. Last but definitely not least, I want to thank MaryBeth for her unwavering and unconditional support. Her strength and courage has inspired me in ways I never thought possible.

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LIST OF ABBREVIATIONS

ac	acetyl, acetate
AIBN	2,2'-azobisisobutyronitrile
aq.	aqueous
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binapthyl
bn	benzyl
br	broad
BuLi	butyl lithium
calc'd	calculated
cat.	catalytic amount
CI	chemical ionization
csa	camphorsulfonic acid
δ	chemical shift downfield from $(CH_3)_4Si$
d	doublet
dd	doublet of doublets
ddd	doublet of doublet of doublets
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-benzoquinone
dec.	decomposition
DMB	3,4-dimethoxylbenzyl
DMAP	*N,N*-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dt	doublet of triplets
dq	doublet of quartets
EI	electron impact

eq.	equivalent
Et_2O	diethyl ether
EtOAc	ethyl acetate
FAB	fast atom bombardment
FTIR	Fourier transform infrared
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrum
hv	light
Hz	hertz
IR	infrared (spectrum)
J	coupling constant
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
m	multiplet or medium
M	mass
*m*CPBA	*m*-chloroperoxybenzoic acid
MDR	multiple drug resistance
MHz	megahertz
mmol	millimole
mp	melting point
NMR	nuclear magnetic resonance
[O]	oxidation
OAc	acetate
p	pentuplet
p-ABSA	*p*-acetamidobenzenesulfonyl azide
PhH	benzene
pmb	*p*-methoxybenzy
$P(o\text{-}tol)_3$	tri-orthotolylphosphine
PPh_3	triphenylphosphine

ppm	parts per million
p-TSA	*p*-toluenesulfonic acid
py	pyridine
q	quartet
$Rh_2(OAc)_4$	rhodium(II) acetate dimer
$Rh_2(oct)_4$	rhodium(II) octanoate dimer
$Rh_2(tfa)_4$	rhodium(II) trifluoroacetate dimer
rt	room temperature
s	singlet or strong
t	triplet
TBS	t-butyldimethylsilyl
TIPS	tri-isopropylsilyl
tfa	trifluoroacetate
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
w	weak
Δ	heat at reflux

CHAPTER ONE

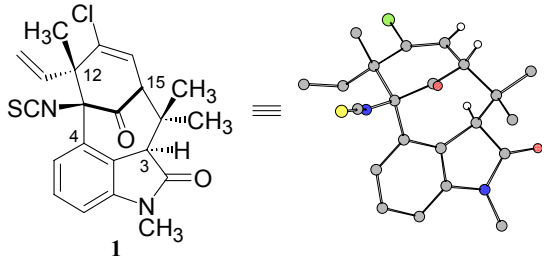
THE 3,4-BRIDGED OXINDOLE WELWITINDOLINONE ALKALOIDS

1.1 Background and Introduction.

1.1.1 Isolation and Biological Activity.

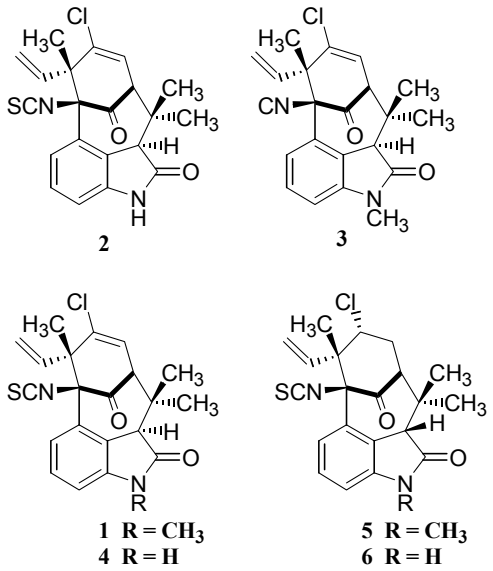
In 1994 Moore and coworkers isolated the welwitindolinone alkaloids (Figures 1.1.1 & 1.1.2) from the lipophilic extracts of the blue green algaes *Hapalosiphon welwitschii* W. & G.S. West (UH strain IC-52-3) and *Westiella intricata* Borzi (UH strain HT-29-1).[1] Biological testing found that this family of alkaloids exhibited multiple drug resistance (MDR) reversing activity, insecticidal activity against blowfish larvae, and antifungal activity against *Aspergillus oryzae*, *Penicillium notatum* and *Saccharomyces cerevisiae*. In particular, the larvacidal and MDR reversing activities were largely associated with *N*-methylwelwitindolinone C isothiocyanate (**1**). Following extensive NMR studies, the structure and absolute configuration of **1** was confirmed using X-ray crystallography techniques (Figure 1.1.1).[1]

Figure 1.1.1



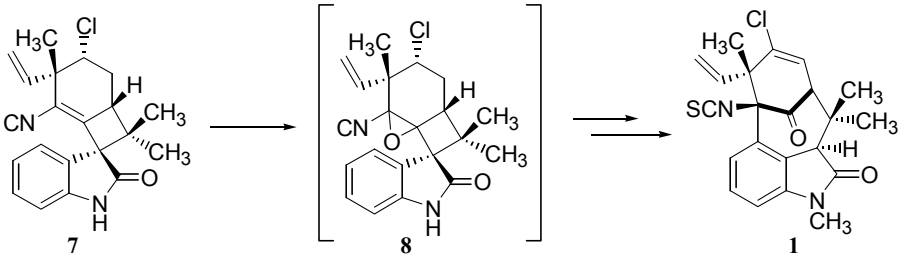
Five additional welwitindolinones (**2**-**6**), all possessing a similarly functionalized 3,4-bridged oxindole core, were also isolated and characterized (Figure 1.1.2).

Figure 1.1.2



In addition to numerous 3,4 bridged oxindoles, a novel spirocyclobutane oxindole, welwitindolinone A isonitrile (**7**) (Scheme 1.1.1), was also identified. This structurally intriguing alkaloid was found to account for much of the antifungal activity associated with the cyanophyte from which it was isolated. It has been postulated that the spiro cyclobutane oxindole core of **7** serves as a biomimetic precursor to the 3,4-bridged oxindole core of welwitindolinones **1**-**6**. Further, it has been speculated that an isocyano epoxide such as **8** might be involved in this process (Scheme 1.1.1).[1,2]

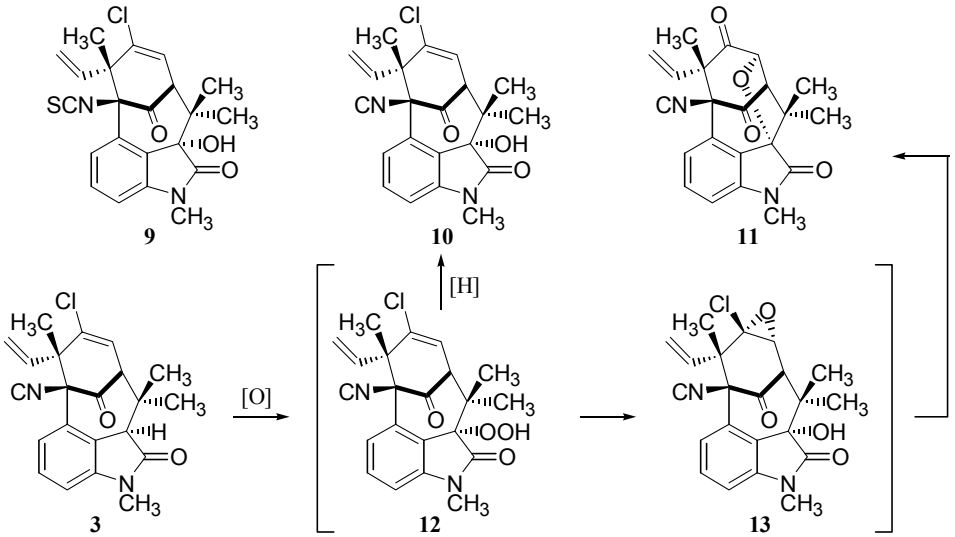
Scheme 1.1.1



1.1.2 The Oxidized Welwitindolinones.

In 1999, Moore and coworkers reported the isolation and characterization of several oxidized welwitindolinones (Scheme 1.1.2, **9-11**).[3] While **9** and **10** are simply the result of oxidation at C(3), *N*-methylwelwitindolinone D isonitrile (**11**) contains an interesting spiro ether functionality. It was postulated that **11** is derived from a photo-oxidation cyclization sequence of **3**.[3] Support for this came when it was found that the irradiation of **3** in the presence of oxygen led to the formation of **10** and **11**. Scheme 1.1.2 illustrates the mechanism proposed for this photo-oxidation. It is believed that this sequence begins with the oxidation of **3** to deliver hydroperoxide **12**. This hydroperoxide can then undergo an intramolecular epoxidation of the vinyl chloride to afford epoxide **13**. The resulting C(3) alcohol can in turn cyclize into the newly formed epoxide. Loss of HCl then gives rise to spiro ether **11**. Alternatively, simple reduction of intermediate hydroperoxide **12** leads to the formation of **10**.

Scheme 1.1.2



1.1.3 Multiple Drug Resistance (MDR)

1.1.3.1 Introduction: MDR.

A major impediment to the successful chemotherapeutic treatment of a wide range of human cancers is an event known as multiple drug resistance (MDR).[4,5] This phenomenon is a protective mechanism that is marked by sudden cellular resistance to a wide array of structurally diverse cytotoxic drugs. Research has identified the onset of MDR as occurring simultaneously with the overexpression of a plasma membrane glycoprotein, P-glycoprotein (Pgp). Further, it is believed that Pgp, which is encoded by the human MDR1 gene, acts as a membrane bound ATP-dependent drug efflux pump in the plasma membranes of tumor cells.[6] This efflux pump serves to actively remove cytotoxic drugs from the cell; thereby reducing their intracellular concentration and thus their cytotoxicity. While other mechanisms have been proposed to account for the activity of Pgp, work has shown that Pgp acting solely as an ATP-dependent drug efflux pump, is sufficient for the onset of multiple drug resistance in tumor cells.[7]

1.1.3.2 MDR-Reversing Agents.

Pharmocological reversal of MDR carries with it major clinical importance. A battery of diverse agents have been found capable of overcoming Pgp-mediated MDR, thereby chemosensitizing resistant tumor cells, and enhancing the accumulation of many chemotherapeutic drugs within the cell.[8,9] These agents include calcium channel

blockers such as verapamil and SR33557,[10,11] antiarrhythmic agents such as quinidine,[12] the immunosuppressant cyclosporin A,[13] and the antiestrogen anticancer drug tamoxifen.[14] Verapamil, one of the most well studied antagonists of Pgp, has been shown to act as an MDR-reversing agent by competing with chemotherapeutic agents for binding to Pgp *in vitro*. The mechanisms by which other MDR-reversing agents operate are unknown but it has been suggested that they may influence MDR by modifying cellular components that regulate Pgp.

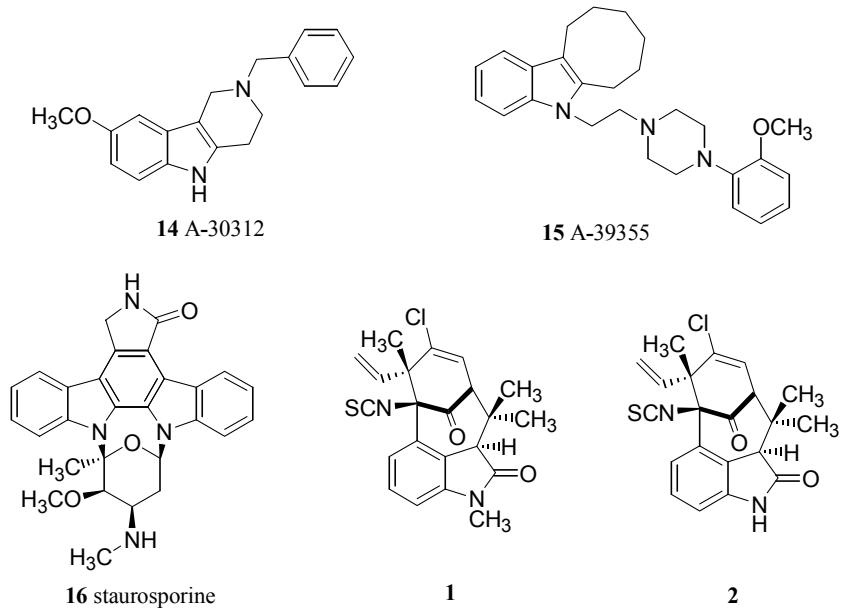
Importantly, however, while many compounds have been identified as MDR-reversing agents, they have not been used clinically because of their dose-limiting toxicicities.[5,6] Thus, efforts are now being directed at the identification of new classes of compounds that inhibit Pgp function and chemosensitize cancer cells to conventional chemotherapy without any undesirable toxilogical effects.

1.1.3.3 Screening for MDR-reversing Agents.

Extensive screening for MDR-reversing agents has been successful in identifying numerous structural classes that act as Pgp antagonists. An examination of the compounds that comprise each of these classes suggests that MDR-reversing agents must be highly hydrophobic and contain multiple (usually aromatic) rings.[5] One of these classes of agents consists of a group of indole alkaloids. Figure 1.1.3 illustrates several members of this class of MDR-reversing agents which include: A-30312 (**14**), A-39355 (**15**), staurosporine (**16**), *N*-methylwelwitindolinone C isothiocyanate (**1**), and

welwitindolinone C isothiocyanate (**2**). The structural diversity that exists among MDR-reversing agents is clearly exemplified by the compounds in Figure 1.1.3.

Figure 1.1.3



1.1.3.4 Welwitindolinones as MDR-Reversing Agents.

Intriguingly, *N*-methylwelwitindolinone C isothiocyanate (**1**) has been identified as being 20-100 times more potent than the best characterized modulator of MDR, verapamil.[4] Biological testing found that **1** chemosensitized drug-resistant breast carcinoma (MCF-7/ADR) cells to anticancer drugs such as taxol, colchicines, and actinomycin at doses as low as 0.1 μM.[4] At this concentration, **1** reduced the IC_{50} values for vinblastin, taxol, and actinomycin D 40-90 fold.

To date, all of the available data suggests that **1** serves as an MDR-reversing agent by binding directly to Pgp. This data includes two key findings. First, it was found that **1** strongly increased the intracellular concentration of both [^{3}H]-vinblastin and [^{3}H]-

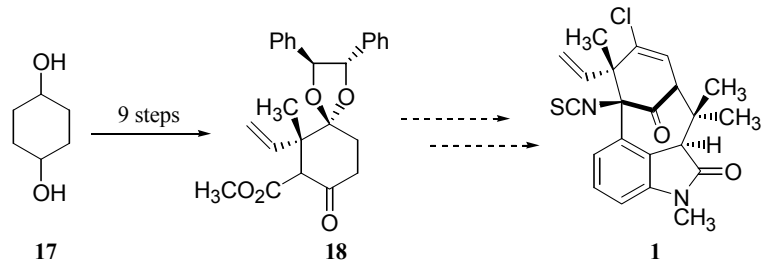
taxol in MDR cells. Second, photoaffinity labeling studies that infer the binding of a compound to Pgp found that **1** was able to reduce Pgp photoaffinity labeling by [^{3}H]-azidopine, suggesting that *N*-methylwelwitindolinone C isothiocyanate (**1**) was indeed binding to Pgp.[4] However, a lack of natural material has precluded the extensive biological testing required to confirm the specific mode of action.

1.2 Previous Synthetic Studies.

1.2.1 Konopelski's Approach to the C(12) Quaternary Center.

The first report of work directed toward a total synthesis of the welwitindolinone alkaloids came in 1998 when Konopelski and coworkers at UC Santa Cruz reported the stereoselective conversion of 1,4-cyclohexanediol (**17**) to β-ketoester **18** (Scheme 1.2.1).[15] It was suggested that **18**, which contains the C(12) quaternary center of the welwitindolinones, could in the future be coupled to an appropriate indole system and advanced toward *N*-methylwelwitindolinone C isothiocyanate (**1**).

Scheme 1.2.1

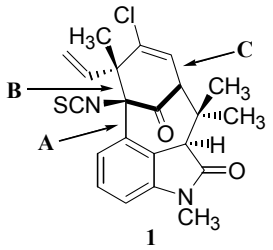


1.2.2 Previous Work from the Wood Group.

1.2.2.1 Introduction and Retrosynthetic Analysis.

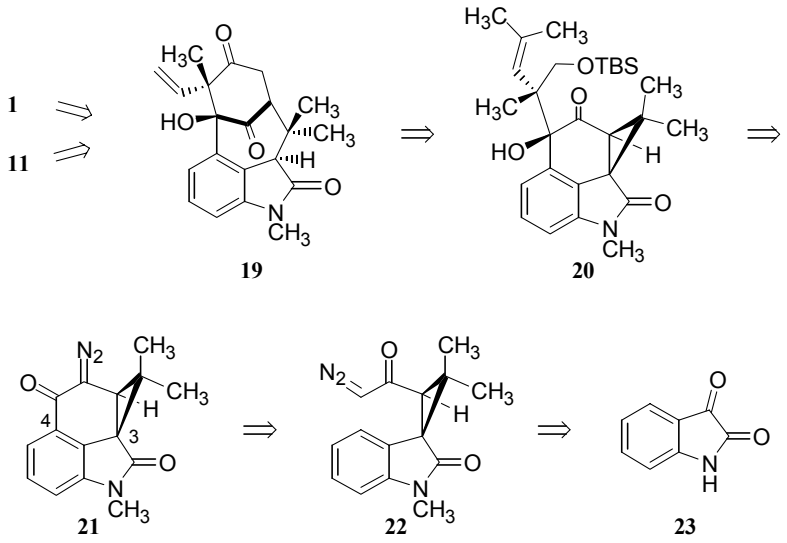
Previous work in these labs focused on syntheses of *N*-methylwelwitindolinone C isothiocyanate (**1**) and *N*-methylwelwitindolinone D isonitrile (**11**).[16,17] A flexible approach was desired that would allow for the elaboration of an advanced intermediate to both **1** and **11**. In surveying the welwitindolinones, 3 bonds were initially targeted for disconnection. Bonds B and C (Figure 1.2.1) target the cyclohexene ring of the welwitindolinones, while bond A targets the 3,4-bridged oxindole core of the molecules. Envisioning disconnection at these three bonds formed the basis for our initial retrosynthetic analysis.

Figure 1.2.1



Thus, diketone **19** was slated as the late-stage common intermediate from which both **1** and **11** could be accessed (Scheme 1.2.2). It was envisioned that the sensitive vinyl chloride and isothiocyanate (and/or isonitrile) functionalities could be derived from a ketone and an amine respectively, the latter arising from an alcohol via Ritter-type chemistry.[18]

Scheme 1.2.2[17]



It was anticipated that common intermediate **19** could be accessed from α-hydroxy ketone **20**, via a process involving cleavage of the cyclopropane and formation of the final six-membered ring. Based on work developed in these laboratories, namely a rhodium-initiated [3,3] rearrangement, it was envisaged that **20** could derive from diazo ketone **21** by coupling to an appropriate allylic alcohol.[19-21] Further disconnections lead to diazo ketone **22**, a carefully engineered intermediate that resulted from extensive experimentation. Finally, isatin (**23**) was identified as a starting point for the synthesis of diazo ketone **22**.[17]

Most work involving the preparation of 3,4-bridged oxindoles (i.e., **21**) relies on the use of a C(4) functionalized aryl ring and builds the bridged system from C(4) to C(3).[22,23] While this approach is often appropriate for the construction of such systems, it requires the preparation of a suitable C(4) substituted oxindole, a task often requiring numerous steps. Thus, the work undertaken in these labs focused on an approach which entailed building the 3,4-bridged oxindole from C(3) to C(4), utilizing an aryl

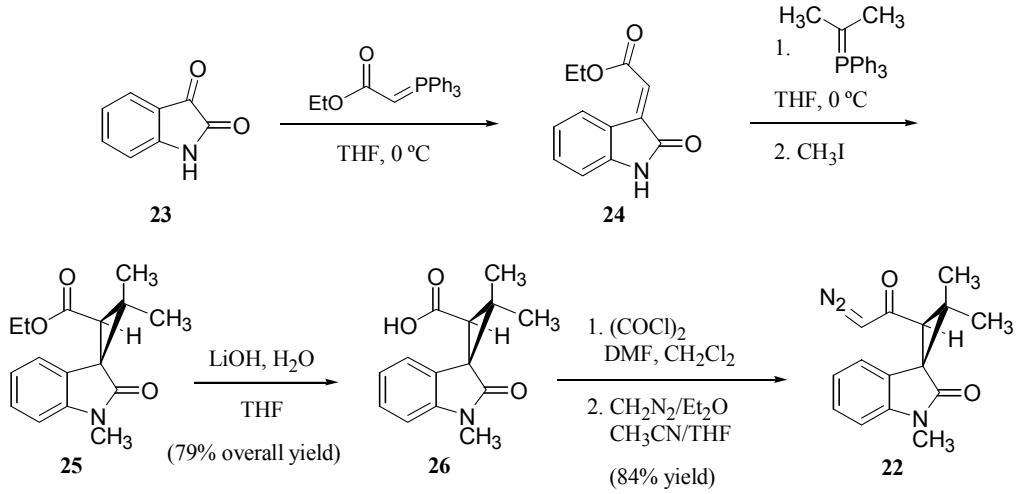
unfunctionalized oxindole. In accord with these goals, the strategy that was ultimately adopted relied upon an aryl C-H insertion reaction to construct the oxindole core of the welwitindolinones (*vide infra)*.[24]

1.2.2.2 Construction of a 3,4 Bridged Oxindole Core.

1.2.2.2.1 Preparation and Elaboration of 22.

Using the above retrosynthetic analysis as a guide, it was found that isatin (**23**) could be advanced to diazo ketone **22** in six steps and excellent overall yield (Scheme 1.2.3).[16]

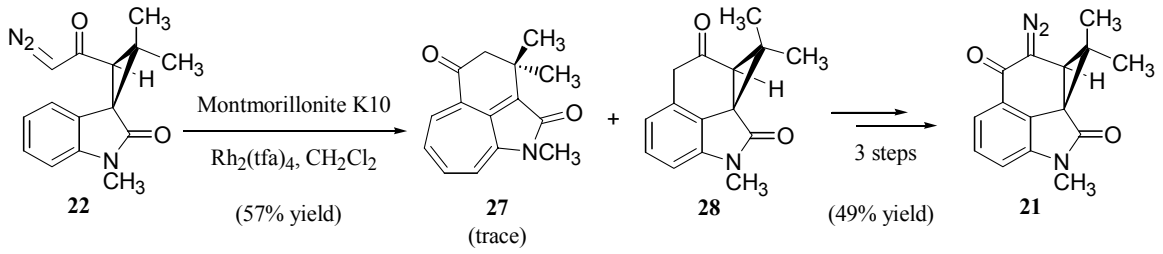
Scheme 1.2.3[17]



Initially, attempts at effecting the aryl C-H insertion reaction proved extremely troublesome. In the event, treatment of diazo ketone **22** with any number of rhodium catalysts led only to minor amounts of the desired ketone **28** contaminated with large amounts of tricycle **27** (Scheme 1.2.4). After considerable experimentation, it was found

that exposure of diazo ketone **22** to rhodium trifluoroacetate dimer ($Rh_2(tfa)_4$) in the presence of thoroughly dried Montmorillonite K10 clay led to the formation of **28** in high yield, with only trace amounts of **27** observed. In a further 3 steps, **28** could efficiently be converted to diazo ketone **21**, thus completing a ten-step protocol for the elaboration of isatin (**23**) to advanced intermediate **21**.

Scheme 1.2.4[17]

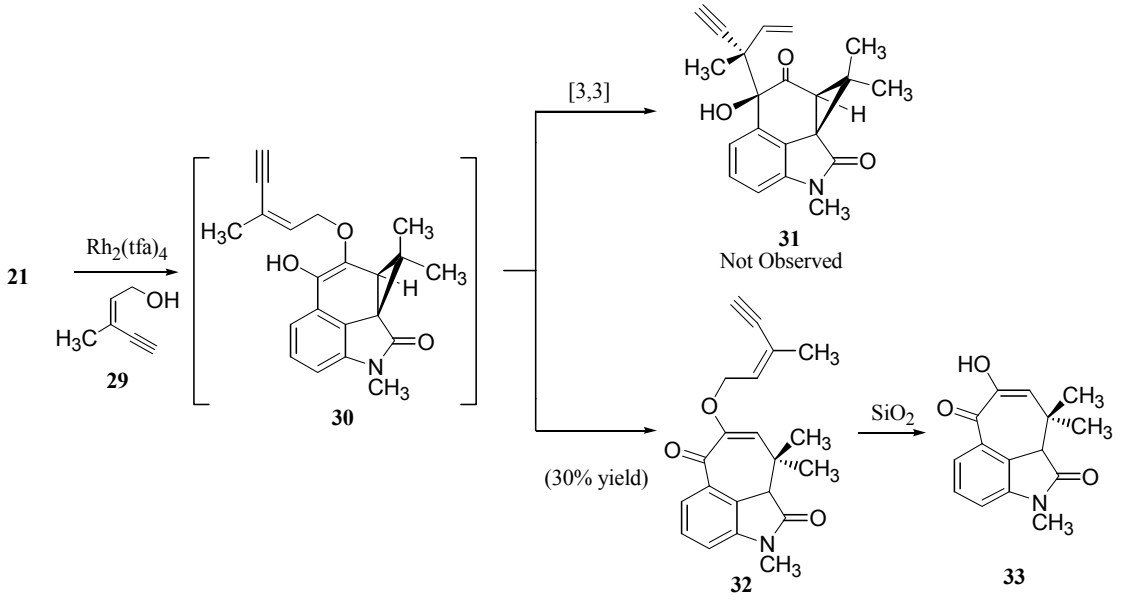


1.2.2.3 Implementation of a Rhodium-Mediated [3,3].

Trouble was once again encountered when **21** was subjected to the conditions for the proposed rhodium-initiated [3,3] rearrangement. It was found that treatment of a solution of diazo ketone **21** and allylic alcohol **29** with a catalytic amount of $Rh_2(tfa)_4$ did not afford the desired α-hydroxy ketone **31**, but rather, gave rise to vicinal diketone **33** in low yield (Scheme 1.2.5). At the time of these findings the unexpected formation of **33** was puzzling; however, subsequent mechanistic work focusing on the rhodium-initiated [3,3] rearrangement has allowed for a rationalization of this reactivity.[16,19,20] It is believed that **33** derives from incipient enol **30**, which preferentially undergoes cleavage of the cyclopropane ring rather than [3,3] rearrangement. Attempted purification of **32** led to hydrolysis of the enol ether and the ultimate formation of enol **33**.

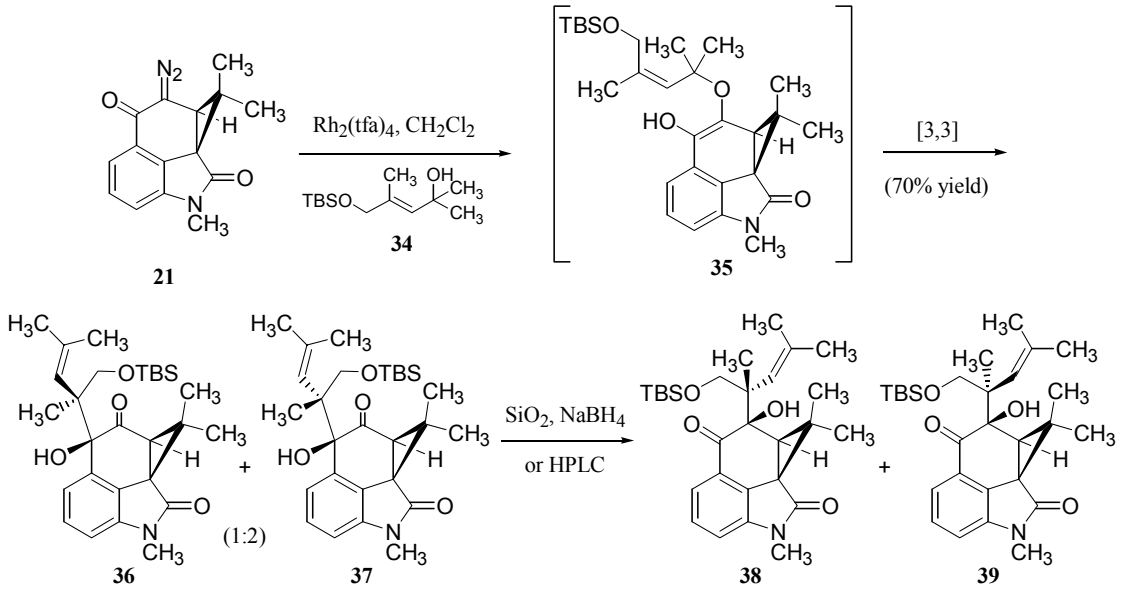
In an effort to circumvent the formation of the undesired byproduct **33**, numerous allylic alcohols were screened as suitable coupling partners to diazo ketone **21**.[17]

Scheme 1.2.5[17]



Interestingly, $Rh_2(tfa)_4$-promoted coupling of diazo ketone **21** and tertiary alcohol **34** led not to a product arising from cleavage of the cyclopropane ring, but rather to the formation of a 1:2 ratio of diastereomeric alcohols **36** and **37** resulting from [3,3] rearrangement (Scheme 1.2.6). Again, recent mechanistic work suggests that this reaction proceeds via enol ether **35**, which undergoes a [3,3] sigmatropic rearrangement to furnish alcohols **36** and **37**, believed to arise from boat- and chair-like transition states, respectively. In this remarkable reaction, two relatively simple compounds were coupled under very mild conditions to furnish two relatively complex molecules each containing the key vicinal quaternary centers found in the welwitindolinones.

Scheme 1.2.6[17]



Unfortunately, this route was plagued by a facile α-ketol rearrangement, giving rise to **38** and **39**. Attempts to advance alcohol **36** and **37** and even efforts to purify these compounds by HPLC were foiled by the deleterious [1,2] shift. Considerable efforts aimed at circumventing this α-ketol rearrangement proved unsuccessful and thus required a modification of this strategy.

1.3 Construction of the Welwitindolinone Carbocyclic Skeleton.

1.3.1 Can a Byproduct Serve as a Key Intermediate?

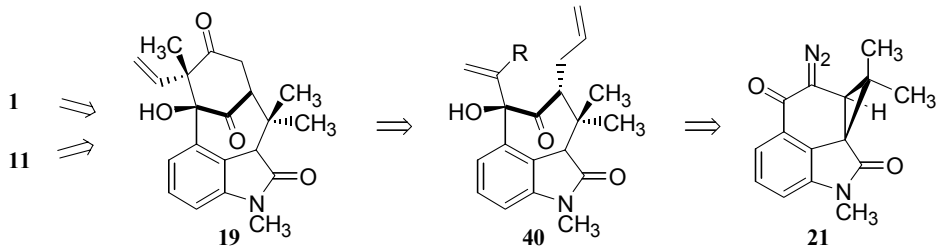
The ease with which large quantities of diazo ketone **21** could be generated, strongly supported its use as an key intermediate in constructing the welwitindolinones. Thus, the challenge clearly lay in: elaborating intermediate **21** to a compound that could

ultimately be advanced to the welwitindolinones. In considering novel ways to manipulate this intermediate, attention shifted from the formation of bond B to construction of bond C, a bond that had remained elusive in prior work (Figure 1.2.1). In contemplating the construction of this bond, the intermediacy of enol ether **32** in the formation of **33** piqued our interest. Of particular note was the fact that enol ether **32** is revealed that it was poised to undergo a [3,3] rearrangement that would result in the construction of the fastidious bond C. It was this disconnection that provided the basis for a modified approach.

1.3.2 Retrosynthetic Analysis.

Consistent with the previous approach developed in this group, it was envisioned that diketone **19** could serve as a common intermediate from which both **1** and **11** could be accessed (Scheme 1.3.1). In this modified approach, it was imagined that the heavily functionalized six-membered ring of the welwitindolinones would be assembled via ring-closing metathesis of a diene of type **40**, a compound that was further envisaged as arising from diazo ketone **21**.

Scheme 1.3.1



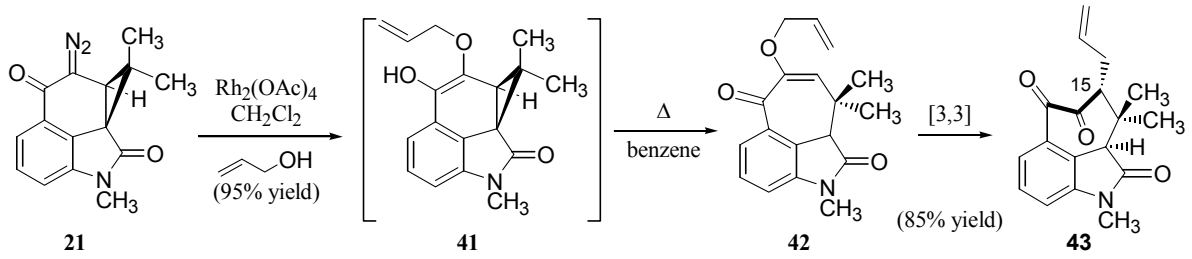
1.3.3 Advancing Intermediate Diazo Ketone 21.

1.3.3.1 Construction of Bond C.

The first task at hand was to advance **21** to a substrate geared to undergo a [3,3] rearrangement in the construction of bond C. Still lacking a mechanistic rationale for the rhodium-initiated [3,3], several alcohols were coupled with **21** in the presence of rhodium (II) catalysts to give a range of products.

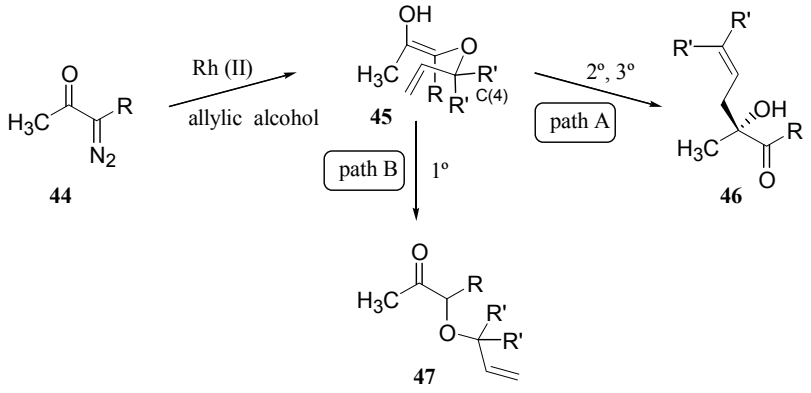
Ultimately, allyl alcohol was chosen as the ideal coupling partner for diazo ketone **21** (Scheme 1.3.2). In the event, treatment of a solution of **21** and excess allyl alcohol with a catalytic amount of rhodium acetate dimer ($Rh_2(OAc)_4$) provided enol ether **42** as the exclusive product in near quantitative yield. Upon heating, enol ether **42** underwent Claisen rearrangement to furnish a single diastereomer of diketone **43**.[25] Gratifyingly, the rearrangement occurred entirely on the α face, generating the correct stereochemistry at C(15). Convinced that this ring-opening/Claisen rearrangement could indeed prove fruitful, efforts were focused on the addition of an appropriate nucleophile to the benzylic ketone of enol ether **42**.

Scheme 1.3.2



Subsequent to the completion of these studies, mechanistic work gave a more thorough understanding of **21**'s reactivity.[20,21] Specifically, it was found that the initial product arising from the rhodium-mediated coupling of an allylic alcohol and an α-diazo ketone is an intermediate enol, and that the rate of the ensuing Claisen rearrangement is highly dependent on the nature of the allylic alcohol. These findings were consistent with previous reports wherein electron-donating groups at the C(4) position of allylic enol ethers accelerate the rearrangement, whereas enol ethers that lack electron-donating substituents at this position undergo rearrangement more slowly (Scheme 11).[26] Thus, in the case of secondary and tertiary allylic alcohols, Claisen rearrangement of the incipient enol (**45**) is fast and gives rise to α-hydroxy ketone products (**46**) (Scheme 1.3.3, path A). However, when the coupling partner is a primary allylic alcohol, the intermediate enol (**45**) undergoes rearrangement much more slowly and tautomerization to the O-H insertion product (**47**) becomes a competitive process (path B).

Scheme 1.3.3



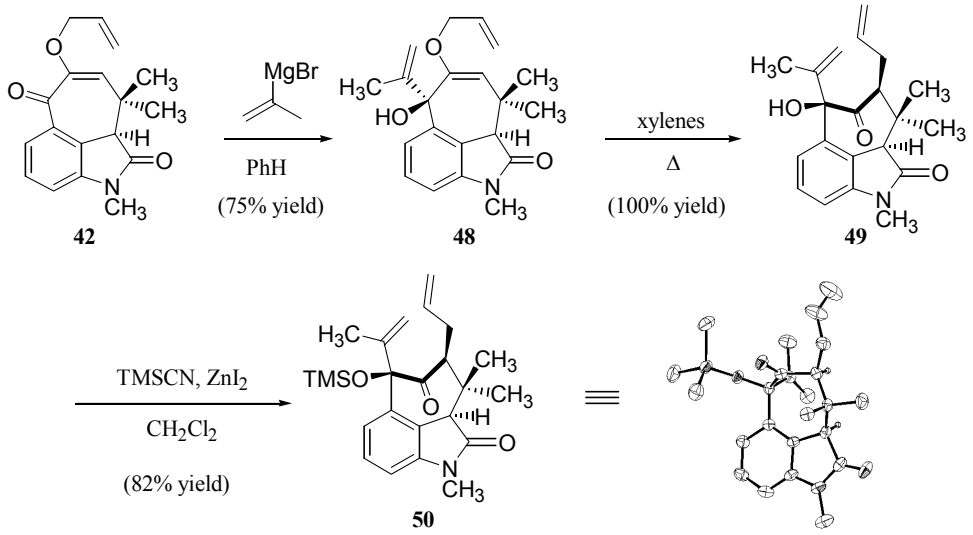
With this mechanistic knowledge in hand, a rationale for the reactivity of **21** could now be offered. In the case of primary allylic alcohol **29**, Claisen rearrangement was slow and the major product resulted from OH insertion and subsequent ring-opening of

the activated cyclopropane (Scheme 1.2.5). However, in the case of tertiary allylic alcohol **34**, rearrangement was fast, hence tautomerization and ring-opening were not competitive processes and cleavage of the cyclopropane was not observed (Scheme 1.2.6).

1.3.3.2 Elaboration of Ketone 42.

Having demonstrated that Bond C could indeed be constructed via a [3,3] rearrangement (**42** → **43**), efforts focused on the addition of an appropriate nucleophile into the benzylic ketone of **42** (Scheme 1.3.4). Initially, propenyl magnesium bromide was targeted as the desired nucleophile. Gratifyingly, treatment of ketone **42** with propenyl Grignard furnished tertiary alcohol **48**, wherein addition occurred almost exclusively from the α-face.[25] As expected, upon heating, enol **48** did indeed undergo Claisen rearrangement; unfortunately, the rearrangement occurred exclusively on the β-face to provide diene **49**. The trans relationship between the two unsaturated sidechains was confirmed following protection of the bridgehead alcohol as its TMS ether to furnish silyl ether **50**, a crystalline solid for which an X-ray structure was obtained (see appendix 2 for the X-ray crystallographic report). The ORTEP of **50** clearly illustrates that the Grignard addition occurred on the α-face while the subsequent rearrangement occurred on the β-face.

Scheme 1.3.4

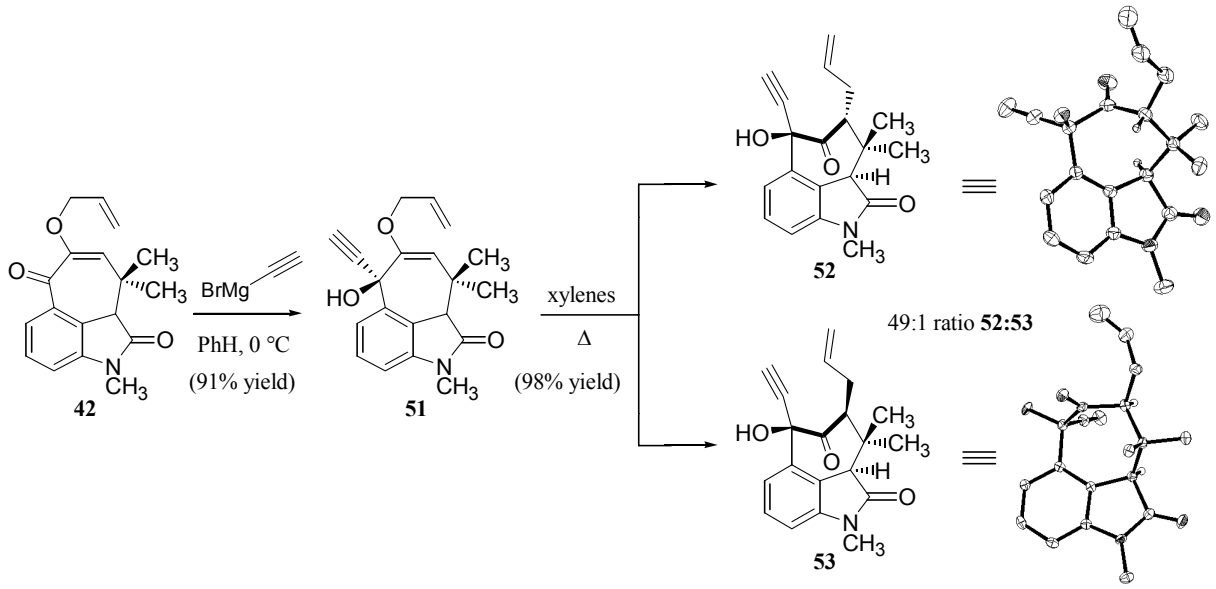


Needing to reverse the diastereoselectivity of the [3,3] rearrangement, the disparity in the facial selectivities observed in the rearrangement of **42** and **48** was noted. While the factors governing this facial selectivity were not obvious, it was speculated that the steric nature of the bulky propenyl moiety forced the rearrangement of **48** to occur on the opposite face, thereby generating a trans-substituted system (i.e., **49**). In the case of **42**, this steric hindrance was absent and rearrangement occurred on the α-face. Thus, it was envisioned that a less sterically demanding nucleophile might provide an enol ether which would behave similar to **42**, and give rise to an adduct containing the required stereochemistry following Claisen rearrangement.

After considerable experimentation, it was found that the addition of ethynyl Grignard to a solution of ketone **42** in benzene occurred stereoselectively to deliver tertiary alcohol **51** (Scheme 1.3.5).[25] Heating a solution of **51** in xylenes effected smooth Claisen rearrangement to provide a 49:1 mixture of ketones **52** and **53**, the structures of which were confirmed by single crystal X-ray analyses (see appendix 2 for the X-ray

crystallographic reports). Pleasingly, the major product (**52**) resulted from Claisen rearrangement on the α-face, providing an adduct with the correct relative stereochemistry between the two unsaturated side chains.

Scheme 1.3.5



1.3.3.3 Ring Closing Metathesis (RCM).

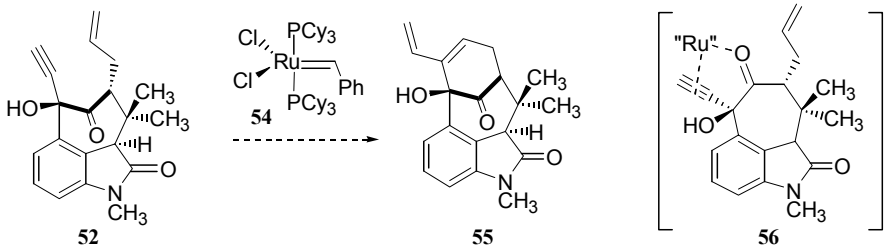
1.3.3.3.1 Attempted Ene-Yne Metathesis.

With ample quantities of ene-yne **52** in hand, efforts were guided toward constructing the final ring of the welwitindolinones via ring-closing metathesis.[27,28] The impetus for examining ethynyl Grignard as a suitable nucleophile was its sterically undemanding nature. Although, of equal importance, was the need for any added nucleophile to serve as an olefinic precursor. However, the presence of the ene-yne system in **52** posed an interesting question regarding the use of ene-yne metathesis for

constructing the final ring of the welwitindolinones.[28] This idea was particularly interesting, as the final product of such a transformation, **55**, would contain the required vinyl substituent needed for the requisite quaternary center.

Unfortunately exposure of ene-yne **52** to Grubbs' catalyst (**54**) under numerous conditions provided only unreacted starting material.[27,29] Interestingly, prolonged exposure of **52** to **54** did not lead to oligomerization, suggesting that the catalyst may be sequestered in the form of an unproductive complex such as **56** (Scheme 1.3.6).[30] Pretreatment of **52** with additives such as $Ti(O^iPr)_4$, known to prevent the formation of chelates such as **56**, proved to no avail.[31]

Scheme 1.3.6

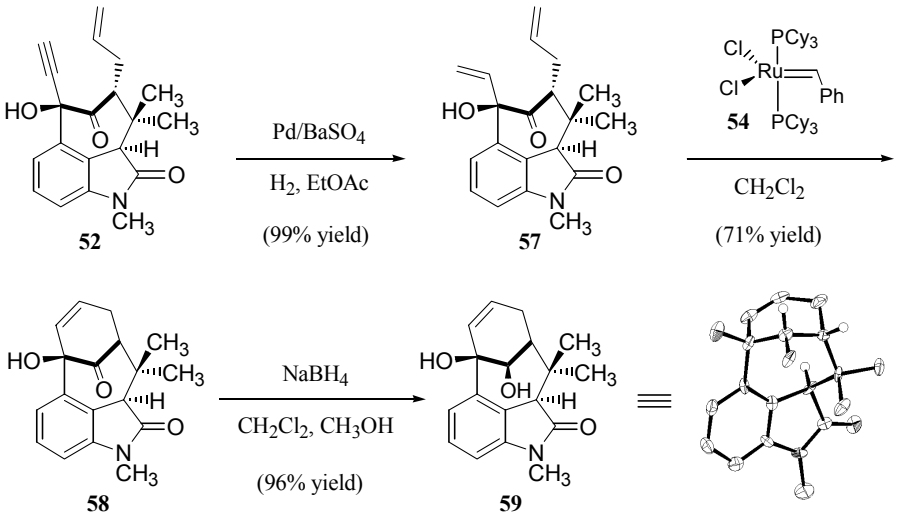


1.3.3.3.2 Attempted Diene Metathesis.

Unable to successfully construct the final ring of the welwitindolinones using ene-yne metathesis, the acetylene moiety was selectively reduced upon exposure to H_2 in the presence of $Pd/BaSO_4$ poisoned with lead to afford diene **57** in excellent yield (Scheme 1.3.7). After considerable optimization, it was found that exposure of diene **57** to 20 mol % Grubbs' catalyst in refluxing CH_2Cl_2 afforded olefin **58** in good yield. This event was confirmed via reduction of ketone **58** which occurred with complete selectively to deliver a single diastereomer of alcohol **59**. Single crystal X-ray analysis of **59** demonstrated

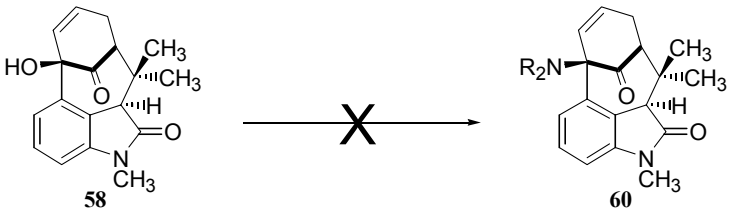
that the complete carbocyclic skeleton of the welwitindolinones had indeed been constructed (see appendix 2 for the X-ray crystallographic report). At the time of its completion, this work provided a rare example of ring-closing metathesis being used in the construction of small or medium sized bridged systems.[32]

Scheme 1.3.7



With the construction of **58**, the carbon framework of the welwitindolinones had been assembled, and attention could be directed to the installation of the bridgehead nitrogen. Unfortunately, all attempts to install the bridgehead nitrogen from the corresponding tertiary alcohol were unsuccessful (Scheme 1.3.8).[33] Concurrent with these findings, an alternative route was developed which allowed for the installation of the bridgehead nitrogen via a nitrone cycloadditon (*vide infra*).

Scheme 1.3.8



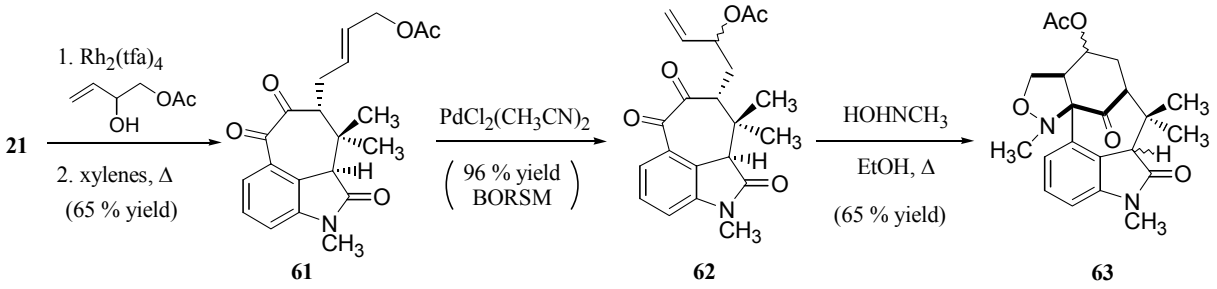
Thus, while this approach did not allow for the installation of the bridgehead nitrogen, it did provide a viable means by which intermediate diazo ketone **21** could be advanced. Namely, the ring-opening/Claisen sequence (*vide supra*) allowed rapid and efficient access to compounds in which bond C had been constructed (i.e., **52**). In addition, difficulties associated with the conversion of the bridgehead alcohol to the corresponding amine suggested that an alternative method be found for the installation of this amine.

1.4 A Modified Approach.

1.4.1 Nitrone [3+2] Cycloaddition.

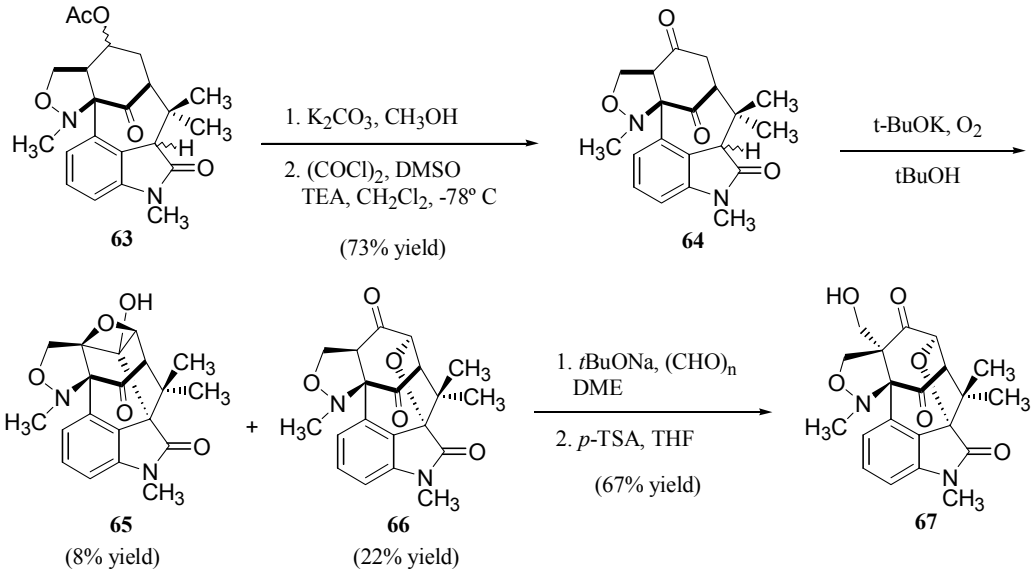
Unable to install the bridgehead nitrogen from the corresponding alcohol, it was found that the chemistry developed in the conversion of diazo ketone **21** to diketone **43**, also allowed for **21** to be advanced to allylic acetate **61**.[17] Following a subsequent allylic transposition vicinal diketone **62** could be obtained as a mixture of diastereomers (Scheme 1.4.1). Exposure of **62** to *N*-methylhydroxylamine led to the regioselective formation of the benzylic nitrone, which upon heating, provided a mixture of products comprised of three diastereomeric nitrone cycloadducts **63**. This transannular [3+2] cycloaddition not only constructs the entire carbon framework of the welwitindolinones, but also simultaneously installs the requisite C(11) nitrogen functionality.

Scheme 1.4.1[17]



Following a substantial amount of work, it was found that cycloadducts **63** could be elaborated in just five steps to alcohol **67** (Scheme 1.4.2).[17] Elaboration of **63** began with hydrolysis of the acetate and subsequent oxidation to furnish ketones **64**, epimeric at C(3). Treatment of **64** with *t*BuOK in the presence of oxygen delivered oxetane **65** and spiro ether **66**. Construction of the quaternary center was achieved by exposure of **66** to *t*BuOK and paraformaldehyde, which, following deprotection of the resulting hemi-acetal, delivered hydroxy ketone **67**. This advanced intermediate contained the C(12) quaternary center, the spiro ether, as well as a handle for the introduction of the isonitrile functionality. However, while **67** was seemingly just steps away from *N*-methylwelwitindolinone D isonitrile (**11**), the bridgehead nitrogen remained to be demethylated, a task which proved to be insurmountable. Unable to advance this late stage intermediate, we were forced to begin exploring other routes.[34]

Scheme 1.4.2[17]

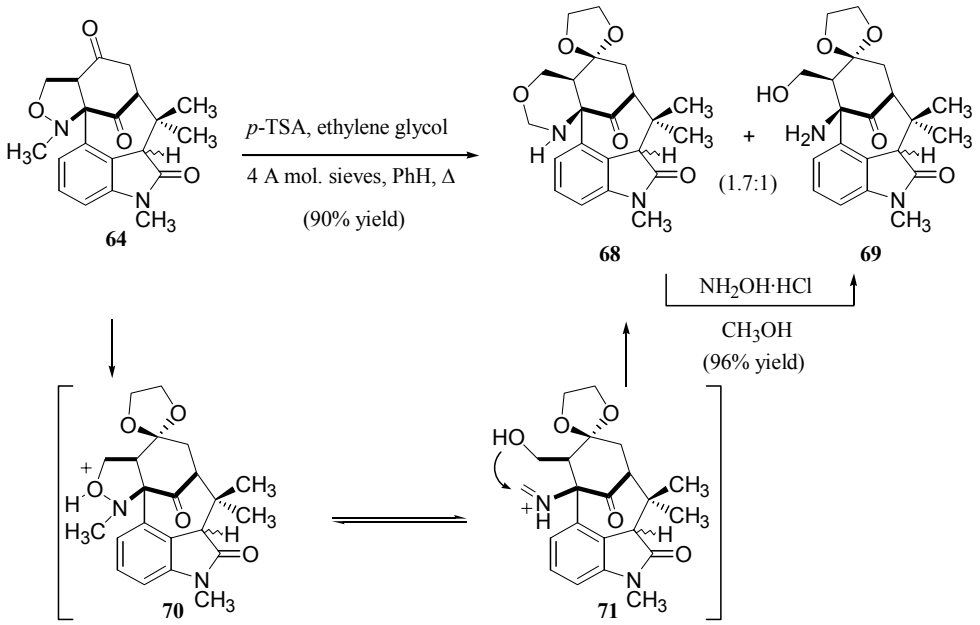


1.5 Building on a Modified Approach.

1.5.1 Deprotection of the Bridgehead Nitrogen.

With the ability to rapidly construct the carbocyclic skeleton of the welwitindolinones with the bridgehead nitrogen intact, the task once again became clear: to establish a protocol for demethylating the bridgehead nitrogen. Following a considerable amount of experimentation, it was found that prolonged exposure of ketones **64** in refluxing benzene to excess ethylene glycol and one equivalent of para-toluenesulphonic acid (*p*-TSA) in the presence of molecular sieves gave rise to a complex mixture of four products (Scheme 1.4.3).[35] After isolation and characterization, these four products were identified as a mixture of aminals **68** and amino alcohols **69**, each epimeric at C(3).

Scheme 1.5.1

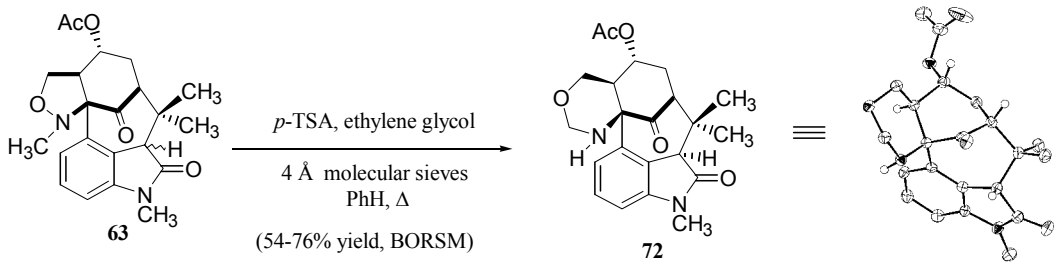


As illustrated in Scheme 1.5.1, it is believed that **68** and **69** arise via initial formation of the acetal (which can be isolated and is observed by TLC) followed by protonation of the oxazoline oxygen, which, pursuant to tautomerization to **71**, undergoes nucleophillic addition to the resulting imminium ion to furnish **68**. Subsequent hydrolysis of the aminal *in situ* delivers **69**. In addition, isolation and subsequent exposure of aminals **68** to hydroxylamine hydrochloride cleanly effected hydrolysis of the aminal to give rise to **69** in good yield. While both **68** and **69** could be elaborated in several directions, difficulties associated with the hydrolysis of the acetal led to the examination of other substrates that would undergo the oxazoline to aminal isomerization (i.e., **64** → **68**).

In the event, treatment of a solution of acetates **63** with one equivalent of *p*-TSA in the presence of molecular sieves led to the formation of a single diastereomer of

aminal **72** in addition to recovered starting material (Scheme 1.5.2). Confirmation of this rearrangement was secured by single crystal X-ray analysis of **72** (see appendix 2 for the X-ray crystallographic report). Attention was next focused on elaboration of **72**.

Scheme 1.5.2



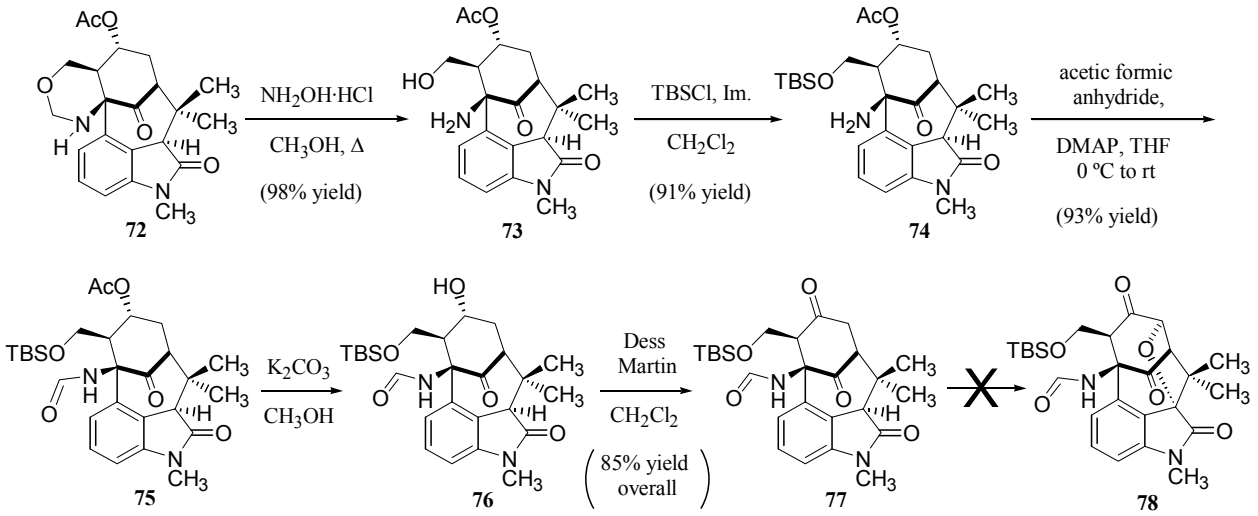
1.5.2 Progress Toward to the Oxidized Welwitindolinones

With the ability to access a fully functionalized carbon framework containing an appropriately protected bridgehead nitrogen, attention could be focused on advancing this core to the welwitindolinones. Following numerous unsuccessful efforts directed at the construction of the C(12) quaternary center, the decision was made to install the spiro ether functionality contained in *N*-methylwelwitindolinone D isonitrile (**11**). It was anticipated that the presence of the spiro ether would greatly simplify efforts aimed at constructing this quaternary center, as previous results suggested that the presence of the spiro ether would allow for the quaternary center to be constructed via a direct alkylation approach (Scheme 1.4.2).[17]

It was anticipated that the strategy outlined in Scheme 1.4.2 could also be employed for the installation of the spiro ether in a more functionalized system. To this end, amino alcohol **73** was chosen as a suitable starting point (Scheme 1.5.3). This

alcohol could be accessed in high yield from aminal **72**. Protection of the primary alcohol as its *t*-butyldimethylsilyl (TBS) ether provided **74**, which, following exposure to acetic formic anhydride, delivered formamide **75** in high yield. This compound could be advanced by hydrolysis of the acetate and oxidation of the resulting alcohol (**76**) to give rise to ketone **77**.[36] With **77** in hand, the stage was set for the formation of the spiro ether. Treatment of **77** with a range of bases in the presence of oxygen led to severe decomposition and resulted in only trace quantities of the desired spiro ether **78**. Unfortunately changes in the reaction conditions also proved to no avail.

Scheme 1.5.3

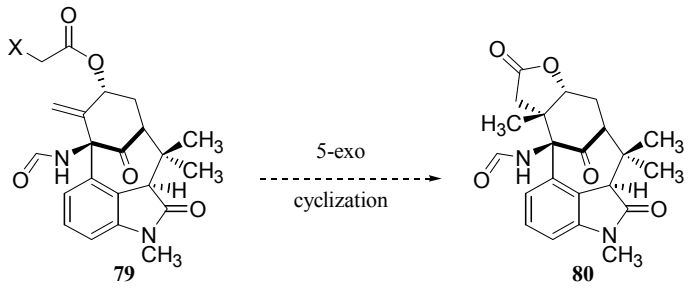


1.5.3 Introduction to Radical Chemistry.

Following unsuccessful attempts to install the spiro-ether, attention once again turned to the construction of the C(12) quaternary center. It was eventually decided that radical chemistry might be ideally suited to complete this task.[37] Importantly, the resident allylic alcohol could serve as a handle for the introduction of a tether that could

participate in an intramolecular radical cyclization. This tether could serve not only to direct the cyclization to the correct face, but to provide the required two carbon atoms needed for the completion of C(12) quaternary center. Thus, it was envisioned that the cyclization of an exocyclic olefin such as **79** in a 5-exo mode would provide access to the desired quaternary center (Scheme 1.5.4).

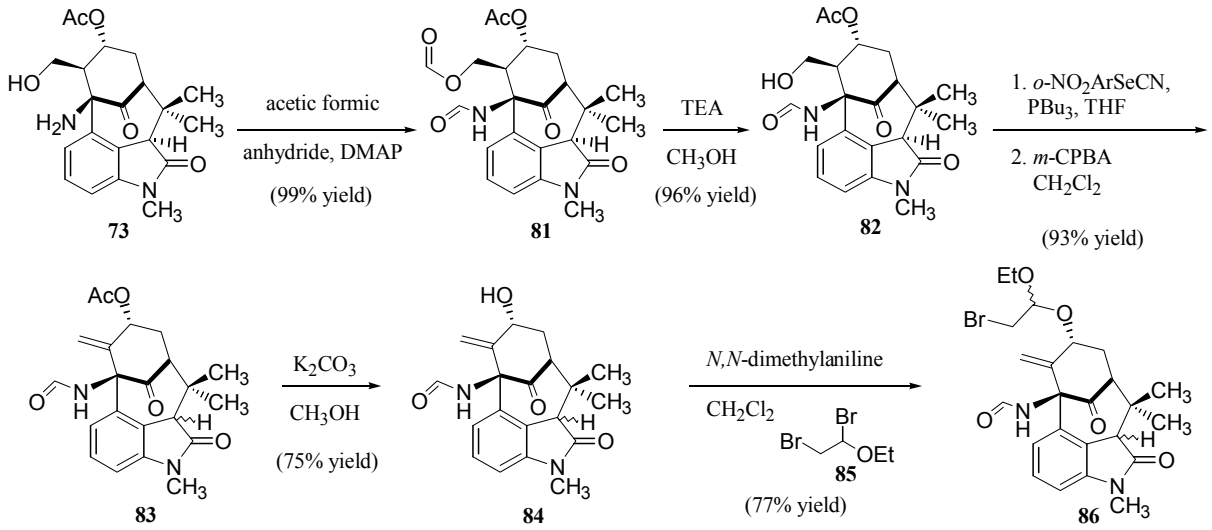
Scheme 1.5.4



1.5.3.1 Efforts Toward Radical Chemistry.

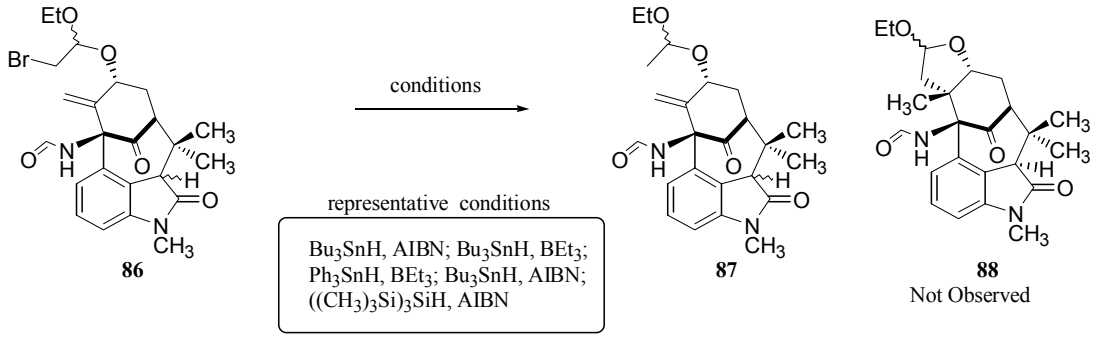
Progress toward cyclization substrate **79** commenced with the bisformylation of amino alcohol **73** to give rise to bis-formylated compound **81**. Exposure of **81** to TEA in methanol led to selective cleavage of the formate ester to deliver formamide **82** (Scheme 1.5.5). Following Grieco's protocol,[38] the primary alcohol was converted to the analogous 2-nitrophenylselenide, which upon exposure to *m*-CPBA underwent oxidation and concomitant elimination to provided olefin **83**. Hydrolysis of the acetate delivers allylic alcohol **84**, which upon treatment with bromide **85** gave rise to a diastereomeric mixture of bromoacetals **86**.[39,40]

Scheme 1.5.5



Having arrived at **86**, an exploration of the 5-exo-trig cyclization of interest was initiated (Scheme 1.5.6). Interestingly, subjection of **86** to numerous reaction conditions did not lead to the desired cyclization product **88**, but led only to reductive cleavage of the bromine to furnish **87**. In no case was the desired cyclization product detected.

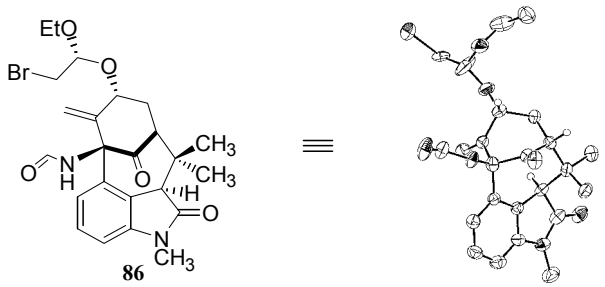
Scheme 1.5.6



In an attempt to understand the stubbornness of **86** to cyclize, a single crystal X-ray analysis was obtained of one of the acetal diastereomers (Figure 1.4.1, see appendix 2 for the X-ray crystallographic report). The ORTEP of **86** suggests the conformation of

this compound was such that the bromoacetal and the olefin are orthogonal to each other, and as a result of this distance the generation of a radical is followed by reduction and not cyclization.

Figure 1.4.1



Attempts to advance **86** via radical chemistry have to date been unsuccessful. However new strategies toward the welwitindolinones focusing on the elaboration of aminal **72** and olefin **84** are currently being explored.

1.6 Conclusion.

A route was developed which allows for the rapid preparation of the 3,4-bridged oxindole skeleton of the welwitindolinones. A tandem OH-insertion/ring opening sequence followed by a thermal subsequent Claisen rearrangement provides access to highly functionalized flexible intermediates which were further advanced in a variety of ways, including ring-closing metathesis and a [3+2] cycloaddition. The intermediates thus obtained could be elaborated to the carbocyclic skeleton of the welwitindolinones.

1.7 Experimental Section.

1.7.1 Materials and Methods.

Unless otherwise stated, all reactions were conducted in flame-dried glassware under a positive pressure of nitrogen using freshly distilled solvents. Tetrahydrofuran (THF), diethyl ether (Et_2O), and dioxane were distilled from sodium metal/benzophenone ketyl. Methylene chloride (CH_2Cl_2), benzene, pentane, pyridine, and triethylamine (TEA) were distilled from calcium hydride. Carbon tetrachloride (CCl_4), 1,2-dichloroethane, titanium tetrachloride ($TiCl_4$), dimethylformamide (DMF), and BF_3•OEt_2 were purchased from the Aldrich Chemical Co. in Sure/Seal™ containers and were used without further purification.

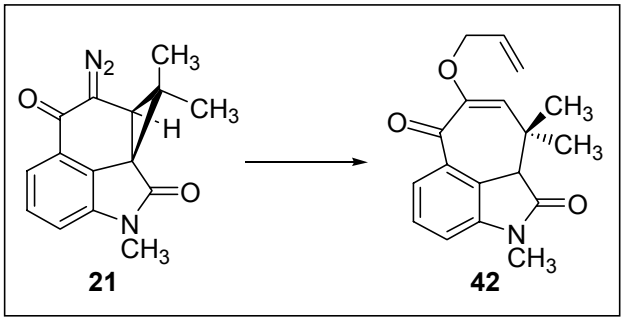
All reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F254 pre-coated plates (0.25-mm). Preparative TLC was also performed using E. Merck silica gel 60 F254 pre-coated plates (0.25-mm). Column and/or flash chromatography was performed with the indicated solvents using silica gel (particle size 0.032-0.063 mm) purchased from Fisher Scientific. Chromatography was performed using the procedures reported by Still.[41]

Melting points were obtained on a Gallenkamp variable temperature melting apparatus (model: MPD350.BM2.1) and are uncorrected. Infrared spectrum (IR) were recorded on a Midac M-1200 FTIR. ^{1}H and ^{13}C spectra were recorded on a Bruker AM-500 or Bruker Advance 400 spectrometers. Chemical shifts are reported relative to chloroform (^{1}H, δ 7.27; ^{13}C, δ 77.0 ppm) or benzene (^{1}H, δ 7.16; ^{13}C, δ 128 ppm). High

resolution mass spectra were performed at The University of Illinois Mass Spectrometry Center. Single-Crystal X-ray analyses were performed by Susan DeGala of Yale University.

1.7.2 Preparative Procedures:

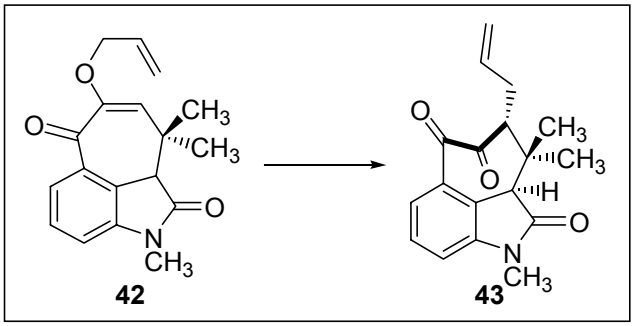
Preparation of Enol ether 42.



Enol ether 42. To a solution of diazo ketone **21** (2.2 g, 8.2 mmol, 1.0 eq.) and allyl alcohol (2.8 mL, 41.2 mmol, 5.0 eq.) in CH_2Cl_2 (82 ml) at ambient temperature was added rhodium acetate dimer (40 mg, 0.09 mmol). The solution was stirred 5 minutes and concentrated under reduced pressure. The resulting residue was subjected to silica gel chromatography (30% EtOAc/hexanes eluent) to afford **42** (2.3 g, 95% yield) as a yellow solid. m.p. 140-142 °C; FTIR (thin film/NaCl) 2943 (w), 2872 (w), 1706 (s), 1689 (m), 1650 (s), 1462 (m), 1341 (m), 1299 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, J = 8.0 Hz, 1H), 7.40 (t, J = 7.9 Hz, 1H), 6.99 (d, J = 7.7 Hz, 1H), 6.07-5.99 (m, 1H), 5.78 (s, 1H), 5.38 (dd, J = 1.5, 17.2 Hz, 1H), 5.23 (dd, J = 1.3, 10.4 Hz, 1H), 4.37 (dd, J = 1.3, 5.5 Hz, 2H), 3.74 (s, 1H), 3.25 (s, 3H), 1.73 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.4, 173.7, 148.5, 143.5, 132.8, 132.7, 128.3, 126.3, 122.0, 117.7,

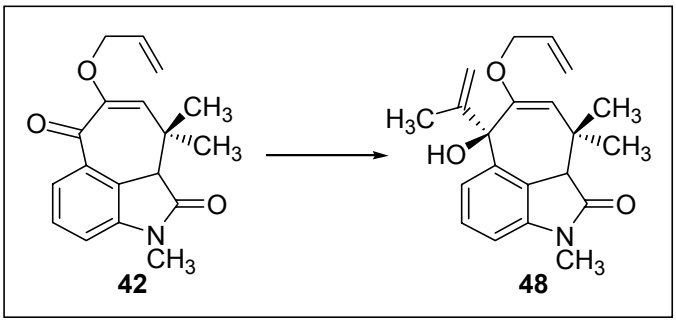
111.0, 70.4, 52.5, 37.7, 28.4, 26.1, 21.6; HRMS (EI) *m/z* 297.1371 [calc'd for $C_{18}H_{19}NO_3$ (M+) 297.1365].

Preparation of Diketone 43.



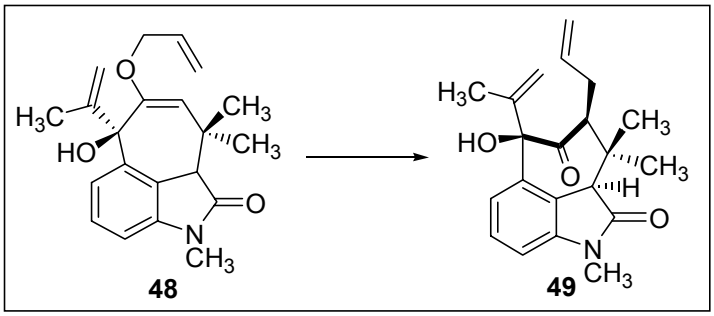
Diketone 43. A solution of enol ether **42** (500 mg, 1.68 mmol, 1.0 eq.) in benzene (25 mL) was heated at reflux for 5 hours before being cooled to room temperature and absorbed onto silica gel. Purification via flash chromatography (30% EtOAc/hexanes eluent) afforded diketone **43** (475 mg, 95% yield) as a yellow solid. m.p. 196-197 °C (dec); FTIR (thin film/NaCl) 3079 (w), 2895 (w), 1706 (s), 1597 (m), 1467 (m), 1408 (w), 1368 (w), 1295 (m), 1269 (m), 1187 (w), 1161 (w), 1019 (m), 986 (m), 789 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 5.59 (dddd, *J* = 6.7, 6.7, 10.3, 17.0 Hz, 1H), 5.02-4.98 (m, 2H), 3.36 (s, 1H), 3.25 (s, 3H), 2.93 (dd, *J* = 2.4, 11.6 Hz, 1H), 2.74 (ddd, *J* = 6.9, 12.2, 13.2 Hz, 1H), 2.18 (ddd, *J* = *1.0,* 6.4, 14.0 Hz, 1H), 1.50 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7, 192.5, 174.3, 145.1, 134.8, 129.6, 129.1, 128.6, 120.7, 117.6, 113.3, 57.2, 53.0, 38.4, 29.9, 26.4, 22.7, 20.9; HRMS (EI) *m/z* 297.1364, [calc'd for $C_{18}H_{19}NO_3$ (M+) 297.1365].

Preparation of Alcohol 48.



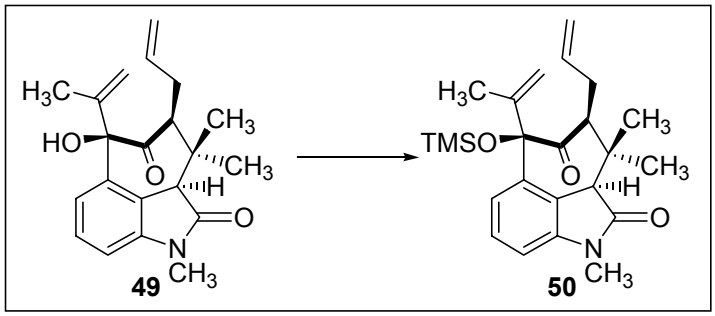
Alcohol 48. To a stirred solution of alcohol **42** (100 mg, 0.33 mmol, 1.0 eq.) in benzene (4 mL) at room temperature was added isopropenyl magnesium bromide (1.0 mL, 0.5 M in THF, 1.5 eq.). The resulting dark blue solution was allowed to stir for 1 hour and subsequently quenched with H_2O (50 mL) and extracted with ethyl acetate (4 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, evaporated to a residue, and purified via silica gel chromatography (25% EtOAc/hexanes eluent) to provide **48** (85 mg, 75% yield) as a yellow oil that solidified upon cooling. m.p. 94.5-96 °C; FTIR (thin film/NaCl) 3553 (m), 2959 (m), 2929 (m), 1705 (s), 1610 (s), 1466 (s), 1369 (m), 1348 (m), 1299 (m), 1194 (m), 1145 (s), 1059 (m), 910 (m), 786 (m), 735 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.1 Hz, 1H), 7.23 (t, *J* = 7.9 Hz, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 5.96-5.87 (m, 1H), 5.27 (dd, *J* = 1.5, 17.4 Hz, 1H), 5.18 (dd, *J* = 1.4, 10.8 Hz, 1H), 5.07 (s, 1H), 4.85 (s, 1H), 4.57 (s, H), 4.21 (d, *J* = 4.2 Hz, 1H), 3.87 (s, 1H), 3.59 (s, 1H), 3.10 (s, 3H), 1.49 (s, 3H), 1.47 (s, 3H), 0.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 148.2, 146.8, 143.6, 138.8, 132.7, 127.6, 123.8, 119.3, 117.9, 113.7, 111.9, 106.4, 78.4, 68.8, 50.8, 36.9, 29.0, 25.9, 23.6, 17.4; HRMS (EI) *m/z* 339.1826 [calc'd for $C_{21}H_{25}NO_3$ (M+) 339.1834].

Preparation of Diene 49.



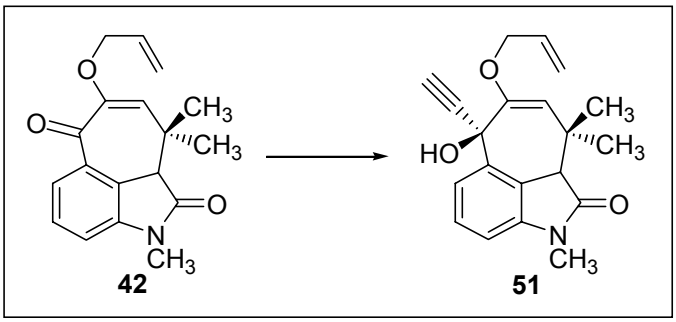
Diene 49. A solution of enol ether **48** (250 mg, 0.74 mmol, 1.0 eq.) in benzene (25 mL) was refluxed for 24 hours resulting in complete conversion of starting material, as judged by TLC. The solution was cooled and evaporated to provide analytically pure diene **49** (250 mg, 100% yield) as a pale yellow oil. FTIR (thin film, NaCl) 3448 (m), 2975 (m), 2934 (w), 1701 (s), 1608 (m), 1466 (m), 1338 (m), 915 (w), 786 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.37 (t, *J* = 8.4 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 5.71-5.65 (m, 1H), 5.16 (t, *J* = 1.3 Hz, 1H), 5.11 (dd, *J* = 1.8, 17.1 Hz, 1H), 5.03 (dt, *J* = 1.2, 10.1 Hz, 1H), 4.62 (s, 1H), 4.56 (s, 1H), 3.47 (s, 1H), 3.22 (dd, *J* = 3.1, 10.4 Hz, 1H), 3.21 (s, 3H), 2.61-2.56 (m, 1H), 2.45-2.34 (m, 1H), 1.79 (s, 3H), 1.67 (s, 3H), 0.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3, 174.6, 143.5, 143.3, 136.3, 136.0, 129.2, 124.2, 119.7, 117.9, 117.7, 107.5, 86.7, 59.6, 56.5, 44.2, 30.9, 26.3, 24.2, 18.9, 16.5; HRMS (EI) *m/z* 339.1831 [calc'd for $C_{21}H_{25}NO_3$ (M+) 339.1834].

Preparation of Diene 50.



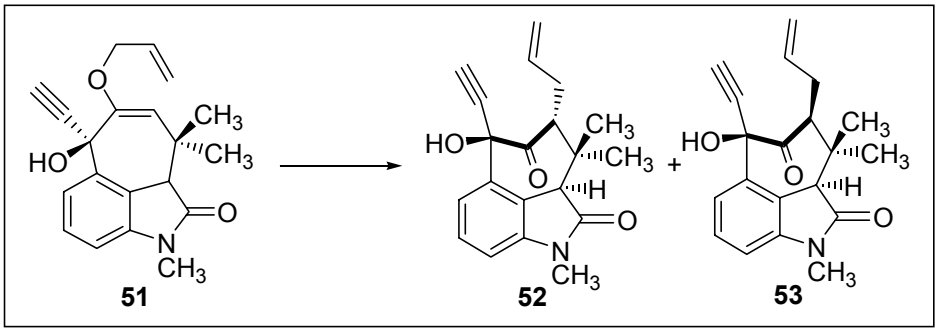
Diene 50. To a solution of alcohol **49** (70 mg, 0.21 mmol, 1.0 eq.) in CH_2Cl_2 (4 mL) was added ZnI_2 (197 mg, 0.62 mmol, 3.0 eq.) followed by trimethylsilyl cyanide (77 μL, 0.62 mmol, 3.0 eq.) immediately resulting in the formation of a white precipitate. The reaction was allowed to stir for 30 minutes at which point the reaction was concentrated *in vacuo* and subjected to flash chromatography (20% EtOAc/hexanes with 2% TEA eluent) to furnish silyl ether **50** (75 mg, 82% yield) as a white solid. Colorless crystals suitable for X-ray crystallography were obtained upon slow evaporation of an ethereal solution. See appendix 2 for X-ray data pertaining to ketone **50**. m.p. 132-135 °C (dec); FTIR (thin film, NaCl) 2955 (w),1710 (s), 1608 (m), 1466 (m), 1337 (w), 1248 (w), 1159 (w), 1083 (w), 843 (m), 783 (w) cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.56 (dd, *J* = 1.0, 7.9 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 6.15 (dd, *J* = 1.0, 7.7 Hz, 1H), 5.73-5.63 (m, 1H), 5.07 (dd, *J* = 1.9, 16.9 Hz, 1H), 5.00-4.96 (m, 1H), 4.78 (t, *J* = 1.4 Hz, 1H), 4.42 (s, 1H), 3.34 (s, 1H), 3.09 (dd, *J* = 3.1, 10.6 Hz, 1H), 2.68 (s, 3H), 2.61-2.53 (m, 1H), 2.22-2.17 (m, 1H), 1.78 (s, 3H), 1.67 (s, 3H), 0.51 (s, 3H), 0.45 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6) δ 208.3, 174.4, 145.9, 144.6, 137.6, 129.4, 124.8, 121.0, 118.4, 116.3, 108.0, 92.6, 60.1, 57.5, 44.1, 32.1, 26.4, 24.9, 20.1, 17.4, 4.1; HRMS (EI) *m/z* 411.2238 [calc'd for $C_{24}H_{33}NO_3Si$ (M+) 411.2238].

Preparation of Ene-yne 51.



Ene-yne 51. To a stirred solution of ketone **42** (1.92 g, 6.5 mmol, 1.0 eq.) in benzene (64 mL) at 0 °C was added a 1.0 M solution of ethynyl Grignard in THF (16.2 mL, 16.2 mmol, 2.5 eq.). The solution was stirred for 10 minutes then diluted with H_2O (250 mL) and extracted with ethyl acetate (4 x 100 mL). The organic layers were combined, washed with brine (100 mL), dried over Na_2SO_4, evaporated to a residue, and purified by silica gel chromatography (25% EtOAc/hexanes eluent) to provide **51** (1.9 g, 91% yield) as a white solid. m.p. 183-185 °C; FTIR (thin film/NaCl) 3488 (bw), 3253 (w), 1691 (s), 1608 (w), 1469 (s), 1355 (w), 1140 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.1 Hz, 1H), 7.34 (t, *J* = 7.9 Hz, 1H), 6.80 (d, *J* = 7.7 Hz, 1H), 6.06-5.99 (m, 1H), 5.39 (dq, *J* = 1.4, 17.3 Hz, 1H), 5.31 (dq, *J* = 1.2, 10.4 Hz, 1H), 4.53 (s, 1H), 4.46 (s, 1H), 4.40 (dd, *J* = 5.6, 12.2 Hz, 1H), 4.31 (dd, *J* = 5.6, 12.2 Hz, 1H), 3.97 (s, 1H), 3.22 (s, 3H), 2.51 (s, 1H), 1.6 (s, 3H), 0.68 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 148.4, 144.1, 138.0, 132.4, 128.4, 124.2, 118.4, 117.5, 113.2, 107.3, 86.1, 71.0, 69.9, 67.6, 51.7, 37.8, 29.1, 26.2, 23.5; HRMS (EI) *m/z* 323.1514 [calc'd for $C_{20}H_{21}NO_3$ (M+) 323.1521].

Preparation of Ketones 52 and 53.

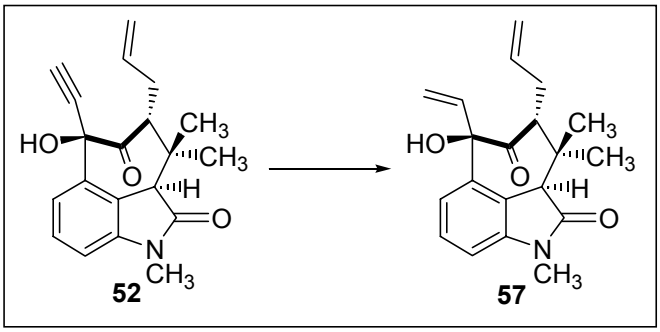


Ketones 52 and 53. A solution of enol ether **51** (900 mg, 2.8 mmol, 1.0 eq.) in xylenes (50 mL) was submersed into an oil bath preheated to 145 °C. The solution was refluxed for 10 minutes, cooled, and concentrated under reduced pressure. The resulting residue was purified via silica gel chromatography (33% EtOAc/hexanes eluent) to afford two compounds.

Ketone 52: The first compound to elute was ketone **52** (860 mg, 96%) as a white solid. X-ray quality crystals were obtained by slow evaporation from CH_2Cl_2. See appendix 2 for X-ray data pertaining to ketone **52**. m.p. 194-196 °C (dec); FTIR (thin film, NaCl) 2972 (bw), 2936 (w), 1693 (s), 1609 (s), 1467 (s), 1347 (m), 1310. w, 915 (w), 732 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 1.0, 8.0 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 7.5 Hz, 1H), 5.69-5.61 (m, 1H), 5.07 (dd, *J* = 1.2, 17.0 Hz, 1H), 4.98 (d, *J* = 10.0 Hz, 1H), 3.26 (s, 1H), 3.20 (s, 1H), 3.15 (s, 3H), 3.03 (dd, *J* = 2.7, 11.6 Hz, 1H), 2.78 (s, 1H), 2.73 (q, *J* = 12.1 Hz, 1H), 2.19 (dd, *J* = 4.9, 12.4 Hz, 1H), 1.43 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.3, 175.1, 144.1, 135.9, 135.7, 129.5, 122.1, 120.0, 117.1, 108.0, 81.1, 78.1, 76.4, 55.1, 51.8, 41.0, 31.2, 26.2, 21.8, 20.6; HRMS (EI) *m/z* 323.1526 [calc'd for $C_{20}H_{21}NO_3$ (M+) 323.1521].

Ketone 53: The second compound to elute was ketone **53** (25 mg, 2%) as a white solid. X-ray quality crystals were obtained by slow evaporation from Et_2O. See appendix 2 for X-ray data pertaining to ketone **53**. m.p. 189-192 °C; FTIR (thin film/NaCl) 2973 (w), 1702 (s), 1604 (m), 1468 (m), 1340 (m), 765 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.1 Hz, 1H), 7.36 (t, *J* = 7.9 Hz, 1H), 6.79 (d, *J* = 7.7 Hz, 1H), 5.74-5.68 (m, 1H), 5.12 (dd, *J* = 1.2, 17.1 Hz, 1H), 5.04 (d, *J* = 10.3 Hz, 1H), 4.40 (s, 1H), 4.12 (dd, *J* = 2.7, 11.1 Hz, 1H), 3.82 (s, 1H), 3.20 (s, 3H), 2.80 (s, 1H), 2.65-2.59 (m, 1H), 2.49-2.44 (m, 1H), 1.72 (s, 3H), 0.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.4, 174.5, 144.3, 135.8, 135.4, 129.4, 123.2, 117.0, 116.9, 108.0, 81.2, 76.8, 76.2, 58.4, 55.4, 44.4, 29.8, 26.4, 24.3, 16.4; HRMS (EI) *m/z* 323.1521 [calc'd for $C_{20}H_{21}NO_3$ (M+) 323.1521].

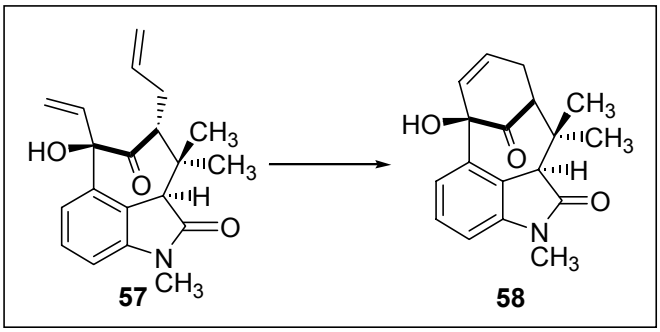
Preparation of Diene 57.



Diene 57. A mixture of acetylene **52** (500 mg, 1.5 mmol, 1.0 eq.) and Lindlar's catalyst (100 mg) in ethyl acetate (30 mL) was placed in a flask and kept under a hydrogen balloon. The reaction was carefully monitored by TLC (25% EtOAc/hexanes eluent) and upon completion was filtered through celite. The filtrate was evaporated and the residue was purified by silica gel chromatography (25% EtOAc/hexanes eluent) to afford diene **57** (495 mg, 99% yield) as a white solid. m.p. 148-149 °C; FTIR (thin

film/NaCl) 2969 (w), 2242 (w), 1717 (s), 1691 (s), 1614 (s), 1464 (m), 1335 (m), 908 (m), 738 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, *J* = 7.9 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 7.7 Hz, 1H), 6.20 (dd, *J* = 10.8, 17.2 Hz, 1H), 5.71-5.63 (m, 1H), 5.29 (d, *J* = 10.8 Hz, 1H), 5.24 (d, *J* = 17.2 Hz, 1H), 5.12 (dd, *J* = 1.1, 16.9 Hz, 1H), 4.98 (d, *J* = 10.0 Hz, 1H), 3.20 (s, 3H), 3.13 (bs, 1H), 3.08 (dd, *J* = 2.4, 11.6 Hz, 1H), 2.68-2.61 (m, 1H), 2.14-2.13 (bs, 1H), 1.21 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.1, 175.3, 144.1, 138.1, 136.5, 136.4, 129.2, 122.6, 120.3, 116.9, 115.3, 107.3, 82.1, 52.1, 41.1, 30.9, 29.7, 26.1, 21.7, 20.5; HRMS (EI) *m/z* 325.1677 [calc'd for $C_{20}H_{23}NO_3$ (M+) 325.1678].

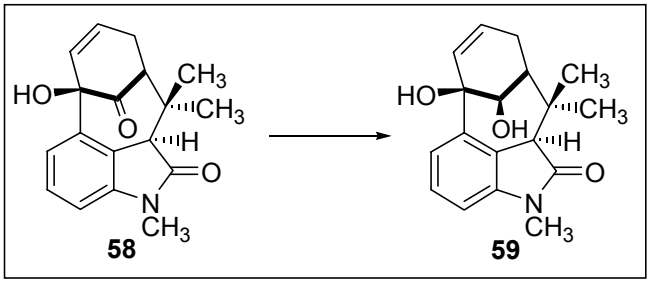
Preparation of Olefin 58.



Olefin 58. To a solution of diene **57** (25 mg, 0.08 mmol, 1.0 eq.) in CH_2Cl_2 (30 mL) was added Grubbs' catalyst (**54**) (13 mg, 0.015 mmol, 0.2 eq.). The resulting solution was refluxed for 24 hours, cooled and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (33% EtOAc/hexanes eluent). The first compound to elute was recovered starting material diene **57** (5.2 mg, 21% yield) and the second compound to elute was the desired olefin **58** (12.9 mg, 56% yield) as a white solid (71% yield based on recovered starting material). m.p. >235 °C (dec); FTIR

(thin film/NaCl) 3032 (w), 2930 (w), 2248 (w), 1708 (2), 1597 (m), 1471 (m), 1340 (m), 1146 (m), 725 (m) cm^{-1};^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.1 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 6.77 (d, *J* = 7.7 Hz, 1H), 5.92 (m, 1H), 5.61 (dd, *J* = 2.6, 9.7 Hz, 1H), 4.24 (s, 1H), 3.78 (s, 1H), 3.20 (s, 3H), 3.03-2.98 (m, 1H), 2.80-2.74 (m, 2H), 1.56 (s, 3H), 0.62 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.6, 175.2, 144.1, 135.8, 130.0, 129.0, 127.2, 126.3, 117.9, 107.6, 77.2, 61.1, 49.7, 40.8, 29.5, 26.3, 26.2, 22.8; HRMS (EI) *m/z* 297.1362 [calc'd for $C_{18}H_{19}N0_3$ (M+) 297.1365].

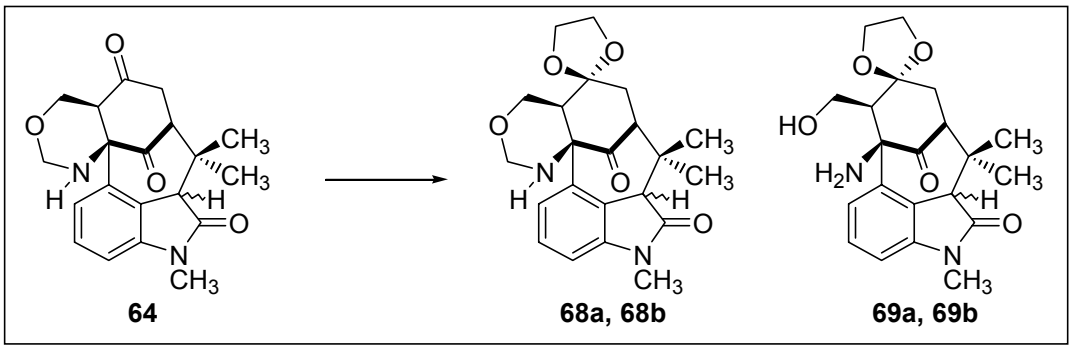
Preparation of Alcohol 59.



Alcohol 59. A solution of ketone **58** (20 mg, 0.067 mmol, 1.0 eq.) in CH_3OH (1 mL) and CH_2Cl_2 (1 mL) was cooled to 0 ºC and treated with $NaBH_4$ (5.5 mg, 0.134 mmol, 2.0 eq.). Following the evolution of H_2, the suspension was stirred for 1 hour at which point TLC indicated the complete consumption of starting material. Absorption onto silica gel and purification by flash chromatography (50% EtOAc/hexanes eluent) furnished alcohol **59** (19.3 mg, 96% yield) as a white solid. X-ray quality crystals were obtained by slow evaporation from Et_2O. See appendix 2 for X-ray data pertaining to alcohol **59**. m.p. >235 °C(dec); FTIR (thin film/NaCl) 2972 (bw), 2936 (w), 1693 (s), 1609 (s), 1467 (s), 1347 (s), 1310 (m), 915 (w), 732 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 1.0, 8.0 Hz, 1H), 7.34 (t, *J* =7.6 Hz, 1H), 6.76 (d, *J* =7.7 Hz, 1H),

5.86 (ddd, J = 9.8, 5.4, 2.0 Hz, 1H), 5.42 (dd, J = 2.8, 9.9 Hz, 1H), 4.31 (t, J = 4.0 Hz, 1H), 3.60 (s, 1H), 3.18 (s, 3H), 2.74 (dd, J = 5.4, 19.2 Hz, 1H), 2.57 (s, 1H), 2.55-2.49 (m, 1H), 2.16 (t, J =5.7 Hz, 1H), 2.10 (d, J = 4.0 Hz, 1H), 1.47 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.3, 144.0, 138.5, 128.5, 128.1, 127.3, 124.8, 119.4, 107.0, 80.0, 75.3, 41.4, 49.8, 37.1, 29.1, 28.3, 26.2, 24.6; HRMS (EI) *m/z* 299.1508 [calc'd for $C_{18}H_{21}NO_3$ (M+) 299.1521].

Preparation of Aminals 68a and 68b and Amino alcohols 69a and 69b.



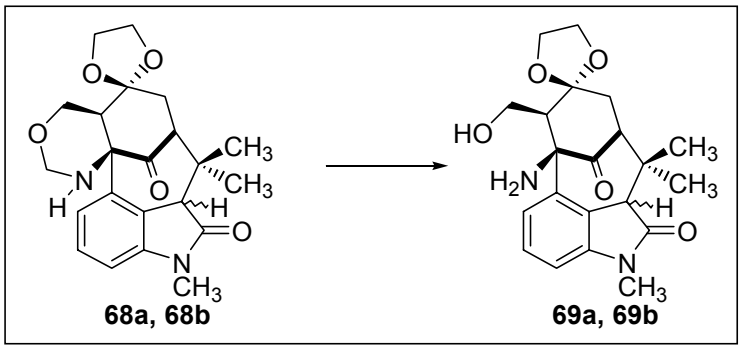
Aminals 68a and 68b and Amino alcohols 69a and 69b. A 100 mL flask equipped with an addition funnel (containing 10 g 4 Å molecular sieves) connected to a reflux condenser was charged with ketones **64** (200 mg, 0.56 mmol, 1.0 eq.), ethylene glycol (1.57 mL, 28.24 mmol, 50.0 eq.), *p*-TSA (108 mg, 0.56 mmol, 1.0 eq.) and benzene (60 mL). The resulting suspension was refluxed in an oil bath heated to 115 °C for 55 hours. The mixture was cooled, quenched with saturated $NaHCO_3$ (250 mL), and extracted with EtOAc (2 x 100 mL). Washing with brine and drying over Na_2SO_4 was followed by concentration and purification by flash chromatography (30-50% EtOAc/hexanes eluent) which furnished four compounds.

Aminal 68a: The first compound to elute was aminal **68a** (77 mg, 39% yield) which was obtained as a tan solid. m.p. dec. >250 °C; FTIR (thin film/NaCl) 2970 (w), 2884 (w), 1706 (s), 1608 (m), 1590 (m), 1472 (m), 1339 (m), 1150 (m), 1054 (m), 1019 (w), 914 (m), 773 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (t, *J* = 7.1 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 7.7 Hz, 1H), 4.76 (d, *J* = 11.2 Hz, 1H), 4.53 (d, *J* = 10.6 Hz, 1H), 4.26-4.21 (m, 2H), 4.08 (t, *J* = 6.7 Hz, 2H), 3.97 (q, *J* = 6.4 Hz, 1H), 3.79 (s, 1H), 3.36 (dd, *J* = 4.1,12.6 Hz, 1H), 3.20 (s, 3H), 2.96 (bs, 1H), 2.74 (dd, *J* = 4.9, 11.0, 1H), 2.39 (d, *J* = 3.8 Hz, 1H), 2.37-2.30 (m, 2H), 1.44 (s, 3H), 0.58 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.3, 174.9, 145.1, 136.3, 129.1, 123.7, 120.9, 107.7, 107.4, 66.5, 65.2, 64.5, 61.4, 61.3, 59.7, 49.8, 45.8, 43.5, 37.1, 26.4, 24.8, 21.8; HRMS (EI) *m/z* 398.1839 [cacl'd for $C_{22}H_{26}N_2O_5$ (M+) 398.1842].

Aminal 68b: The second compound to elute was aminal **68b** (39 mg, 20% yield) which was also obtained as a tan solid. m.p. >215 °C (dec.); FTIR (thin film/NaCl) 2968 (m), 2885 (m), 1706 (s), 1607 (m), 1465 (m), 1339 (m), 1150 (w), 1103 (w), 732 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 7.45 (t, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 8.1 Hz, 1H), 6.80 (d, *J* = 7.4 Hz, 1H), 4.57 (d, *J* = 10.5 Hz, 1H), 4.52 (d, *J* = 10.3 Hz, 1H), 4.01 (dd, *J* = 5.7, 12.2 Hz, 1H), 3.94-3.72 (m, 5H), 3.34 (app t, *J* = 9.1 Hz, 2H), 3.18 (s, 3H), 2.58 (dd, *J* = 8.0, 12.2, 1H), 2.23 (bs, 1H), 1.79 (t, *J* = 14.0 Hz, 1H), 1.71 (dd, *J* = 8.1, 13.9 Hz, 1H), 1.67 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.6, 175.1, 145.0, 140.4, 130.5, 124.1, 119.3, 108.0, 107.9, 66.7, 65.7, 64.8, 64.0, 54.7, 51.8, 49.8, 49.7, 39.2, 34.9, 29.3, 26.6, 20.2; HRMS (EI) *m/z* 398.1838 [cacl'd for $C_{22}H_{26}N_2O_5$ (M+) 398.1842].

Amino alcohols 69a and **69b:** The final two compounds to elute were inseparable amino alcohols **69a** and **69b** (60 mg, 31% yield), epimeric at C(3) as a white solid. m.p. >180 °C (dec.); FTIR (thin film/NaCl) 3409 (s), 2966 (w), 1698 (s), 1650 (m), 1461 (w), 1084 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.37 (m, 4H), 6.78-6.74 (m, 2H), 4.12-3.71 (m, 12H), 3.32 (dd, *J* = 3.7, 7.6 Hz, 1H), 3.27 (dd, *J* = 3.5, 7.2 Hz, 1H), 3.20 (s, 7H), 3.01 (t, *J* = 9.1 Hz, 1H), 2.63 (app t, *J* = 8.8 Hz, 2H), 2.34 (app t, *J* = 8.5 Hz, 2H), 1.76-1.73 (m, 2H), 1.60 (s, 3H), 1.42 (s, 3H), 0.74 (s, 3H), 0.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.0, 209.2, 174.8, 174.3, 144.7, 143.9, 141.9, 138.4, 129.8, 129.0, 122.7, 121.8, 121.2, 117.0, 108.7, 108.0, 107.4, 107.1, 67.1, 66.4, 65.7, 65.3, 64.8, 64.3, 59.6, 59.3, 58.9, 58.8, 54.1, 52.3, 51.5, 49.8, 42.4, 37.7, 35.0, 33.2, 29.2, 26.2, 26.0, 24.5, 21.8, 19.5; HRMS (EI) *m/z* 386.1844 [cacl'd for $C_{21}H_{26}N_2O_5$ (M+) 386.1842].

Preparation of Acetals 69a and 69b.

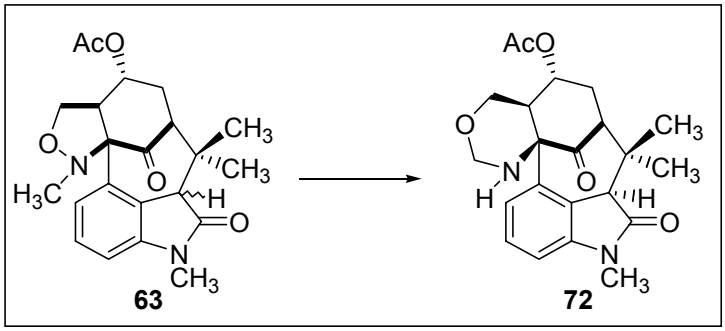


Acetals 69a and 69b. A suspension of aminals **68** (500 mg, 1.22 mmol, 1.0 eq.) and hydroxylamine hydrochloride (847 mg, 12.20 mmol, 10.0 eq.) in CH_3OH (50 mL) was heated to reflux, at which point the reaction became homogeneous. The reaction was kept at this temperature for 20 minutes before being cooled to room temperature and poured into saturated $NaHCO_3$ (150 mL). The volatiles were removed under reduced

pressure and the resulting mixture was diluted with H_2O (100 mL) and extracted with EtOAc (2 x 100 mL). Washing with brine, drying over Na_2SO_4, concentration, and purification by flash chromatography (EtOAc eluent) gave amino alcohols **69a** and **69b**, epimeric at C(3) (466 mg, 96% yield) as a white solid.

Data for amino alcohols **69a** and **69b** can be found above.

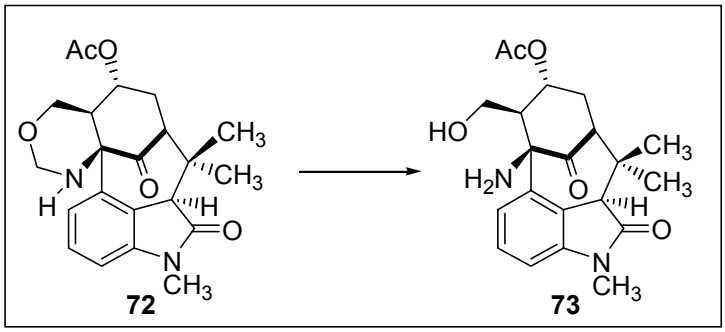
Preparation of Aminal 72.



Aminal 72. A 500 mL flask equipped with an addition funnel (containing 30 g 4 Å molecular sieves) and connected to a reflux condenser was charged with *p*-TSA (85 mg, 0.44 mmol, 1.0 eq.) and benzene (150 mL). The resulting suspension was then heated at reflux for one hour before acetates **63** (175 mg, 0.44 mmol, 1.0 eq.) were introduced as a solid in one portion. The resulting suspension was immersed into an oil bath heated to 110 °C and heated for 48 hours to provide a dark brown reaction mixture containing a small amount of a brown precipitate. The reaction was cooled to 0 ºC and treated with TEA (61 μL, 0.44 mmol, 1.0 eq.). Concentration provided a brown foam that was purified by silica gel chromatography (50-100% EtOAc/hexanes eluent) to afford recovered starting material **63** (11 mg, 11%) and aminal **72** (94 mg, 54% yield, 65% BORSM) as a white solid. X-ray quality crystals were obtained by slow

evaporation from Et_2O. See appendix 2 for X-ray data pertaining to aminal **72**. m.p. 251-254 °C; FTIR (thin film/NaCl) 2967 (bs), 1711 (s), 1606 (m), 1457 (m), 1237 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (t, *J* = 8.1 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 6.83 (d, *J* = 7.7 Hz, 1H), 4.60 (d, *J* = 10.7 Hz, 1H), 4.52 (d, *J* = 10.3 Hz, 1H), 4.34 (ddd, *J* = 5.0, 6.9, 12.5 Hz, 1H), 4.17 (dd, *J* = 5.5, 11.9 Hz, 1H), 3.35 (t, *J* = 12.1 Hz, 1H), 3.32 (s, 1H), 3.19 (s, 3H), 3.12-3.07 (m, 1H), 2.52 (dd, *J* = 7.6, 12.6 Hz, 1H), 2.16 (bs, 1H), 2.00 (s, 3H), 1.89-1.75 (m, 2H), 1.67 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.1, 174.5, 170.3, 144.7, 139.6, 130.2, 123.6, 119.2, 107.8, 77.4, 69.9, 68.1, 66.1, 54.9, 51.3, 45.3, 39.2, 29.7, 28.8, 26.2, 21.1, 19.8; HRMS (EI) *m/z* 398.1839 [cacl'd for $C_{22}H_{26}N_2O_5$ (M+) 398.1842].

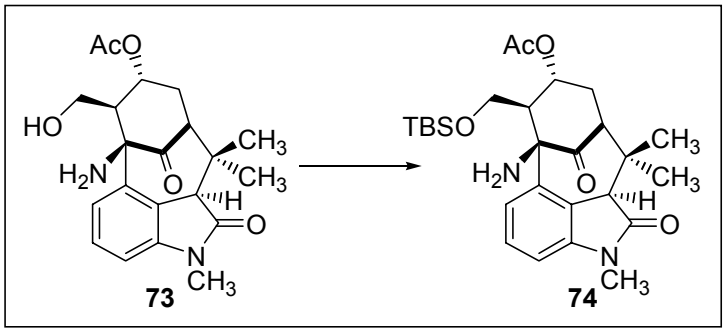
Preparation of Amino alcohol 73.



Amino alcohol 73. A solution of aminal **72** (610 mg, 1.53 mmol, 1.0 eq.) in CH_3OH (100 mL) was treated with hydroxylamine•HCl (1.06 g, 15.33 mmol, 10.0 eq.). The solution that resulted was heated to reflux for 30 minutes before being cooled, concentrated, taken up in EtOAc (200 mL) and quenched with saturated $NaHCO_3$ (250 mL). Separation of the layers and extraction of the aqueous layer with EtOAc (2 x 50 mL) was followed by washing with brine, drying over Na_2SO_4, and concentration under

reduced pressure. The resulting residue was purified using silica gel chromatography (30-100% EtOAc/hexanes eluent) to furnish amino alcohol **73** (577 mg, 98% yield) as a white solid. m.p. dec. >205 °C; FTIR (thin film/NaCl) 3260 (b), 2968 (m), 1715 (s), 1608 (m), 1465 (m), 1240 (m), 1019 (w), 788 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (t, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 4.32-4.27 (m, 1H), 3.58-3.47 (m, 2H), 3.18 (s, 3H), 3.16 (s, 2H), 2.63 (dd, *J* = 7.4, 12.0 Hz, 1H), 2.00 (s, 3H), 1.92-1.86 (m, 1H), 1.78 (q, *J* = 12.6 Hz, 1H), 1.65 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.0, 174.2, 170.4, 144.3, 141.1, 130.2, 121.7, 120.8, 107.4, 68.8, 67.2, 62.1, 54.9, 54.6, 51.3, 38.6, 29.3, 29.2, 26.1, 21.0, 19.6; HRMS (EI) *m/z* 386.1834 [cacl'd for $C_{21}H_{26}N_2O_5$ (M+) 386.1842].

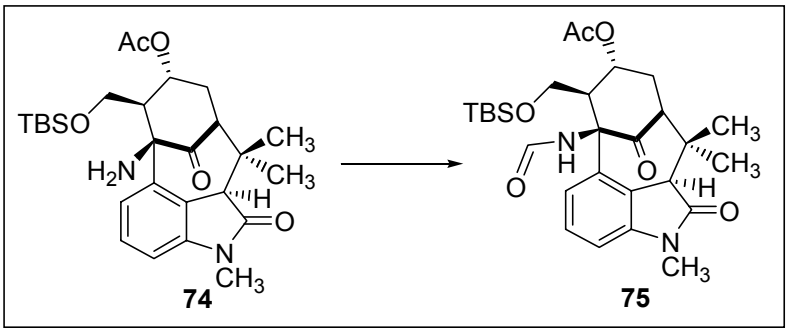
Preparation of Silyl ether 74.



Silyl ether 74. To a solution of alcohol **73** (500 mg, 1.30 mmol, 1.0 eq.) in CH_2Cl_2 (50 mL) was added TBSCl (587 mg, 3.89 mmol, 3.0 eq.), imidazole (265 mg, 3.89 mmol, 3.0 eq.), and DMAP (16 mg, 0.13 mmol, 0.1 eq.) which resulted in the immediate formation of a white precipitate. The suspension was stirred at room temperature for 2 hours before the mixture was concentrated, absorbed onto silica gel and purified by flash chromatography (20-50% EtOAc/hexanes) to furnish silyl ether **74** (590

mg, 91% yield) as a white solid. m.p. 178.5-180 °C; FTIR (thin film/NaCl) 2955 (m), 2930 (m), 1714 (s), 1606 (w), 1463 (m), 1235 (s), 1120 (m), 837 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (t, *J* = 7.4 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 1H), 6.76 (t, *J* = 6.1 Hz, 1H), 4.96-4.91 (m, 1H), 4.22 (dd, *J* = 2.6, 10.2 Hz, 1H), 3.55 (dd, *J* = 2.1, 10.3 Hz, 1H), 3.20 (s, 1H), 3.17 (s, 3H), 2.83 (dt, *J* = 2.1, 4.1 Hz, 1H), 2.61 (dd, *J* = 7.5, 12.3 Hz, 1H), 1.99 (s, 3H), 1.98-1.75 (m, 4H), 1.68 (s, 3H), 0.90 (s, 9H), 0.82 (s, 3H), 0.61 (s, 3H), 0.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.5, 174.7, 170.3, 144.1, 141.7, 129.5, 122.6, 121.9, 107.1, 69.0, 66.9, 59.9, 54.6, 54.2, 51.7, 38.4, 29.4, 29.3, 26.2, 25.6, 21.1, 19.9, 18.1, -5.0, -5.1; HRMS (EI) *m/z* 500.2703 [cacl'd for $C_{27}H_{40}N_2O_5Si$ (M+) 500.2707].

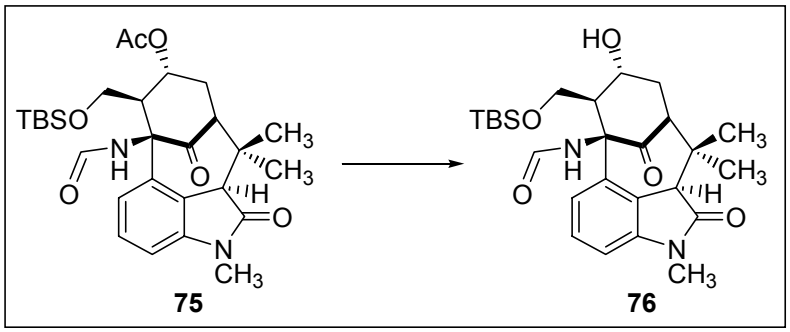
Preparation of Formamide 75.



Formamide 75. A solution of acetic formic anhydride (6 mL), prepared by heating acetic anhydride (3 mL) and formic acid (3 mL) at 65 °C for 1 hour, was added to a solution of amine **74** (580 mg, 1.16 mmol, 1.0 eq.) in THF (50 mL) at 0 °C. After stirring for 10 minutes, the solution was concentrated *in vacuo* to furnish an oil that was chromatographed (50% EtOAc/hexanes eluent) to deliver formamide **75** (570 mg, 93% yield) as a white solid. m.p. >250 °C (dec.); FTIR (thin film/NaCl) 2927 (m), 2852 (m), 1733 (m), 1697 (s), 1669 (m), 1243 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (bs,

1H), 8.04 (d, J = 1.6 Hz, 1H), 7.41 (d, J = 4.4 Hz, 2H), 6.77 (t, J = 4.1 Hz, 1H), 4.57 (ddd, J = 5.0, 7.6, 12.4 Hz, 1H), 3.73-3.65 (m, 2H), 3.32 (dt, J = 2.7, 7.4 Hz, 1H), 3.17 (s, 3H), 2.56 (dd, J = 7.8, 12.2 Hz, 1H), 2.01 (s, 3H), 1.90-1.79 (m, 3H), 1.66 (s, 3H), 0.95 (s, 9H), 0.83 (s, 3H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.5, 174.9, 170.3, 159.5, 143.8, 138.0, 129.1, 124.8, 121.1, 107.4, 68.7, 68.4, 62.5, 54.9, 52.2, 51.8, 38.7, 29.2, 28.9, 26.1, 25.7, 21.0, 20.1, 18.1, -5.6, -5.7; HRMS (EI) *m/z* 528.2647 [cacl'd for $C_{28}H_{40}N_2O_6Si$ (M+) 528.2656].

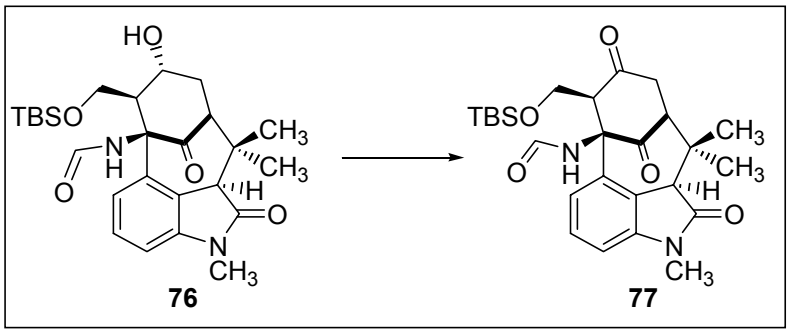
Preparation of Alcohol 76.



Alcohol 76. A solution of acetate **75** (300 mg, 0.57 mmol, 1.0 eq.) in CH_3OH (25 mL) was treated with K_2CO_3 (236 mg, 1.70 mmol, 3.0 eq.). The reaction mixture was stirred for 1 hour before it was quenched with saturated $NaHCO_3$ (50 mL). Removal of the solvent *in vacuo* and dilution with H_2O (100 mL) was followed by extraction with EtOAc (3 x 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The organic concentrate was purified by silica gel chromatography (30% hexanes/EtOAc) to afford alcohol **76** (255 mg, 93% yield) as a white solid. m.p. 186.5-188 °C; FTIR (thin film/NaCl) 3324 (bs), 2955 (m), 2930 (m), 1724 (s), 1707 (s), 1691 (s), 1607 (s), 1464 (m), 1067 (m) cm^{-1}; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 8.18 (bs, 1H), 7.88 (d, *J* = 1.2 Hz, 1H), 7.28 (t, *J* = 8.1 Hz, 1H), 7.24 (t, *J* = 7.7 Hz, 1H), 6.66 (d, *J* = 7.5 Hz, 1H), 3.73-3.62 (m, 2H), 3.57 (s, 1H), 3.15-3.13 (m, 1H), 3.07 (s, 3H), 3.05-3.02 (m, 1H), 2.83 (d, *J* = 4.2 Hz, 1H), 2.37 (dd, *J* = 7.6, 12.2 Hz, 1H), 1.79 (q, *J* = 12.7 Hz, 1H), 1.68-1.62 (m, 1H), 1.53 (s, 3H), 0.87 (s, 9H), 0.74 (s, 3H), 0.65 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.4, 175.1, 159.5, 143.3, 138.3, 129.0, 124.8, 121.7, 107.1, 68.3, 67.6, 63.5, 55.9, 55.3, 51.8, 38.1, 32.9, 28.9, 26.1, 25.6, 20.1, 17.9, -4.4, -4.6; HRMS (EI) *m/z* 486.2560 [cacl'd for $C_{26}H_{38}N_2O_5Si$ (M+) 486.2550].

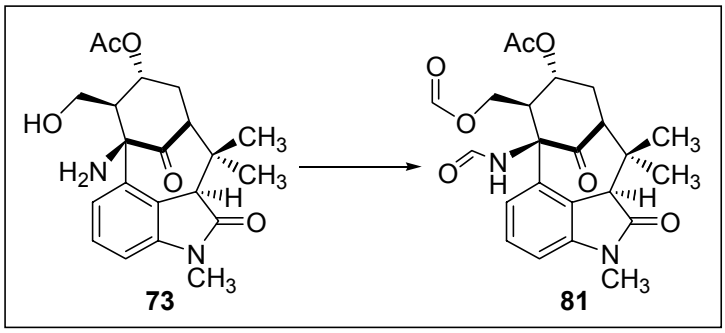
Preparation of Ketone 77.



Ketone 77. A solution of alcohol **76** (250 mg, 0.51 mmol, 1.0 eq.) in CH_2Cl_2 (25 mL) was treated with Dess-Martin periodinane (255 mg, 0.62 mmol, 1.2 eq.) and the resulting suspension was allowed to stir at room temperature for 2 hours (with an additional 255 mg of Dess-Martin periodinane being added after 30 and 60 minutes) before being quenched by the sequential addition of saturated $NaHCO_3$ (150 mL) and saturated $Na_2S_2O_3$ (50 mL). Stirring was continued until both layers were homogeneous and then the aqueous layer was separated and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in*

vacuo to provide a residue that was subjected to flash chromatography (30-50% EtOAc/hexanes eluent) to deliver ketone **77** (225 mg, 91% yield) as a white solid. m.p. 250.5-251.5 °C; FTIR (thin film/NaCl) 2955 (m), 2931 (m), 1712 (s), 1610 (w), 1464 (m), 1252 (m), 1096 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 1.9 Hz, 1H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.59 (bs, 1H), 7.35 (t, *J* = 8.6 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 4.25 (dd, *J* = 1.1, 4.0 Hz, 1H), 4.09 (dd, *J* = 4.3, 10.2 Hz, 1H), 3.82 (dd, *J* = 1.4, 10.3 Hz, 1H), 3.38 (s, 1H), 3.15 (s, 3H), 2.76 (t, *J* = 9.4 Hz, 1H), 2.51 (dd, *J* = 8.8, 17.5 Hz, 1H), 2.36 (dd, *J* = 10.6, 18.0 Hz, 1H), 1.70 (s, 3H), 0.83 (s, 9H), 0.80 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.4, 205.2, 174.2, 159.7, 144.3, 135.7, 129.7, 123.0, 122.3, 108.4, 66.8, 63.0, 58.4, 51.9, 51.5, 42.2, 40.6, 28.8, 26.1, 25.7, 20.3, 18.2, -5.1, -5.2; HRMS (EI) *m/z* 484.2394 [cacl'd for $C_{26}H_{36}N_2O_5Si$ (M+) 484.2389].

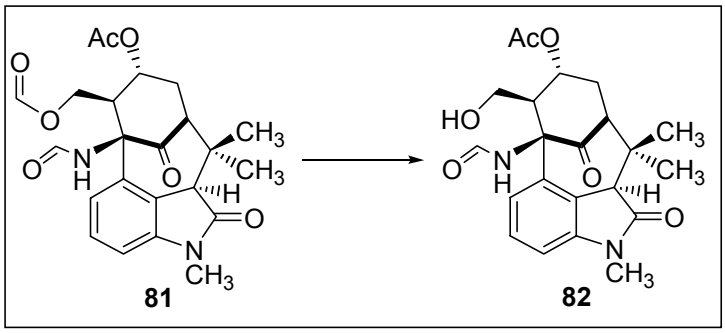
Preparation of Bisformate 81.



Bisformate 81. A solution of amino alcohol **73** (475 mg, 1.23 mmol, 1.0 eq.) in THF (40 mL) at 0 ºC was treated with freshly prepared acetic formic anhydride (6 mL, prepared by heating equal amounts of acetic anhydride and formic acid at 60 ºC for 1 hour). Stirring was continued for 5 minutes at this temperature and then at room temperature for 30 minutes. The reaction was then concentrated under reduced pressure

to furnish a residue that was purified by silica gel chromatography (50% EtOAc/hexanes eluent) to afford formamide **81** (540 mg, 99% yield) as a white foam. m.p. 105-107 °C; FTIR (thin film/NaCl) 3345 (w), 1722 (s), 1717 (s), 1609 (w), 1464 (w), 1243 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 1.4 Hz, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.96 (d, *J* = 1.0 Hz, 1H), 7.44 (t, *J* = 8.7 Hz, 1H), 7.19 (bs, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 4.97 (ddd, *J* = 5.4, 7.0, 12.4 Hz, 1H), 4.52 (dd, *J* = 3.2, 12.2 Hz, 1H), 4.13 (dd, *J* = 3.1, 12.0 Hz, 1H), 3.94 (t, *J* = 3.0 Hz, 1H), 3.24 (s, 1H), 3.17 (s, 3H), 2.70 (dd, *J* = 7.8, 12.4 Hz, 1H), 2.02 (s, 3H), 2.01-1.97 (m, 1H), 1.70 (q, *J* = 12.6 Hz, 1H), 1.69 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.1, 174.3, 170.3, 160.1, 159.9, 144.5, 136.7, 129.5, 122.8, 122.4, 108.5, 68.4, 67.2, 62.6, 53.5, 51.4, 47.2, 40.2, 29.1, 29.0, 26.1, 21.0, 19.6; HRMS (EI) *m/z* 442.1731 [cacl'd for $C_{23}H_{26}N_2O_7$ (M+) 442.1740].

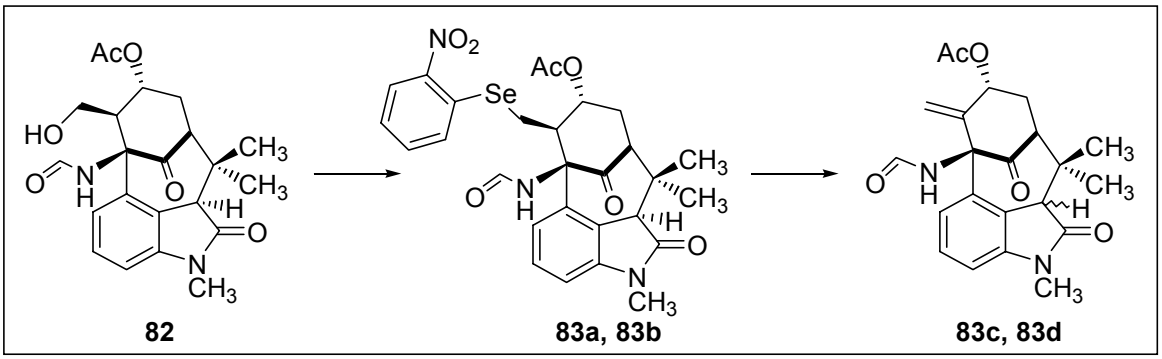
Preparation of Alcohol 82.



Alcohol 82. A solution of formate **81** (140 mg, 0.32 mmol, 1.0 eq.) in CH_3OH (15 mL) at room temperature was treated with TEA (441 μL, 3.17 mmol, 10.0 eq.). The solution was then allowed to stir for 10 minutes, at which point TLC indicated the complete consumption of starting material. Concentration *in vacuo* and purification by flash chromatography (100% EtOAc) furnished alcohol **82** (126 mg, 96% yield) as a pale

yellow foam. m.p. 181-184 °C; FTIR (thin film/NaCl) 3300 (s), 1730 (m), 1694 (m), 1609 (w), 1466 (m), 1236 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (m, 2H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 7.2 Hz, 1H), 4.62 (ddd, *J* = 5.5, 7.6, 12.5 Hz, 1H), 3.79-3.71 (m, 2H), 3.65 (s, 1H), 3.42 (dt, *J* = 3.0, 7.3 Hz, 1H), 3.18 (s, 3H), 2.60 (dd, *J* = 7.9, 12.1 Hz, 1H), 2.49 (t, *J* = 3.7 Hz, 1H), 2.01 (s, 3H), 1.90-1.78 (m, 2H), 1.67 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.8, 175.1, 170.3, 160.2, 143.4, 138.0, 129.1, 124.9, 121.1, 107.3, 68.8, 68.6, 61.7, 55.1, 51.8, 51.7, 38.4, 29.2, 28.8, 26.1, 21.0, 20.0; HRMS (EI) *m/z* 414.1782 [cacl'd for $C_{22}H_{26}N_2O_6$ (M+) 414.1791].

Preparation of Acetates 83c and 83d.

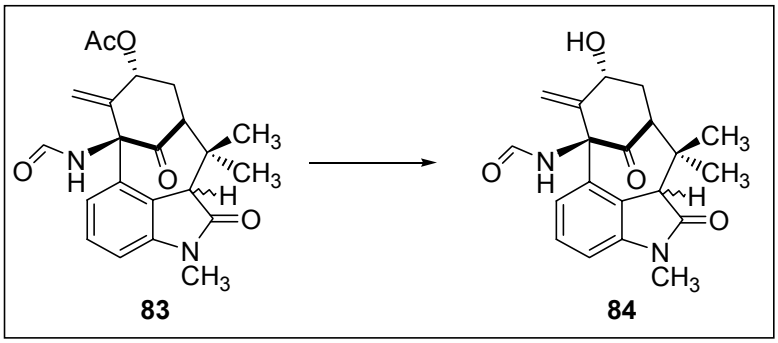


Acetates 83c and 83d. A solution of alcohol **82** (225 mg, 0.54 mmol, 1.0 eq.) in THF (15 mL) was treated with 2-nitroselenocyanate (185 mg, 0.82 mmol, 1.5 eq.). The resulting mixture was stirred until homogeneous (10 minutes), at which point the brown solution was cooled to 0 °C and Bu_3P (203 μl, 0.82 mmol, 1.5 eq.) was added, which resulted in an immediate darkening of the solution. The solution was degassed and backfilled with nitrogen 3 times and allowed to slowly warm up to room temperature and stir at that temperature for 2 hours. The reaction mixture was concentrated and was

routinely carried on to the next step without further purification. An analytical sample of selenides **83a** and **83b** was obtained by flash chromatography (30-100% EtOAc/hexanes) to furnish selenide **83a** and **83b** as a bright yellow solid. m.p. >250 °C (dec.); FTIR (thin film/NaCl) 2968 (w), 1705 (s), 1681 (s), 1606 (w), 1590 (s), 1464 (s), 724 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (dd, *J* = 1.2, 8.0 Hz, 1H), 8.19 (d, *J* = 1.8 Hz, 1H), 8.00 (d, *J* = 10.2 Hz, 1H), 7.75 (dd, *J* = 1.4, 8.3 Hz, 1H), 7.69 (dt, *J* = 1.4, 7.0 Hz, 1H), 7.45 (t, *J* = 8.5 Hz, 1H), 7.39 (dt, *J* = 1.2, 7.0 Hz, 1H), 7.19 (bs, 1H), 6.85 (d, *J* = 7.7 Hz, 1H), 4.71 (dt, *J* = 1.2, 6.4 Hz, 1H), 4.12-4.09 (m, 1H), 3.36 (dd, *J* = 4.3, 12.3 Hz, 1H), 3.20 (s, 1H), 3.18 (s, 3H), 2.68 (dd, *J* = 7.4, 12.3 Hz, 1H), 2.36 (t, *J* = 11.9 Hz, 1H), 2.06-2.01 (m, 1H), 1.78 (s, 3H), 1.67 (s, 3H), 1.65-1.58 (m, 1H), 0.78 (s, 3H), ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.0, 174.2, 169.9, 160.1, 146.7, 144.5, 136.6, 134.0, 132.3, 129.7, 129.5, 126.4, 122.9, 122.5, 122.3, 108.5, 72.9, 69.1, 53.7, 51.2, 44.9, 40.4, 29.4, 28.6, 27.5, 26.2, 21.0, 19.5; HRMS (EI) *m/z* 599.1181 [cacl'd for $C_{28}H_{29}N_3O_7Se$ (M+) 599.1171]. A solution of the derived selenide in CH_2Cl_2 (15 mL) was cooled to 0 °C and treated with *m*-CPBA (187 mg, 1.09 mmol, 2.0 eq.) and $NaHCO_3$ (274 mg, 3.26 mmol, 6.0 eq.). The solution was stirred at 0 °C for 5 minutes then warmed to room temperature and stirred for 1 hour. The reaction mixture was quenched with saturated $NaHCO_3$ (25 mL) and saturated $Na_2S_2O_3$ (15 mL) and stirred vigorously for 15 minutes. Extraction of the aqueous layer with CH_2Cl_2 (3 x 40 mL), washing with brine, and concentration provided a residue that was purified by column chromatography (30-100% EtOAc/hexanes) to afford olefins **83c** and **83d**, epimeric at C(3), (200 mg, 93% overall yield) as a pale yellow foam. m.p. >250 °C (dec.); FTIR (thin film/NaCl) 2972 (w), 1732 (s), 1700 (s), 1605 (m), 1466 (m), 1231 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (bs, 1H), 7.75 (d,

J = 11.8 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.33 (t, *J* = 7.9 Hz, 1H), 7.18 (t, *J* = 8.2 Hz, 2H), 6.86 (d, *J* = 7.7 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 6.21 (bs, 1H), 6.03 (dd, *J* = 11.9 Hz, 1H), 5.80 (d, *J* = 2.6 Hz, 1H), 5.71 (d, *J* = 2.2 Hz, 1H), 5.50 (d, *J* = 2.3 Hz, 1H), 5.42-5.40 (m, 3H), 3.57 (s, 1H), 3.24 (s, 1H), 3.20 (s, 3H), 3.16 (s, 3H), 2.76 (dt, *J* = 7.8, 12.7 Hz, 2H), 2.07 (s, 3H), 2.06 (s, 3H), 2.01-1.71 (m, 4H), 1.68 (s, 3H), 1.67 (s, 3H), 0.85 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (100Hz, $CDCl_3$) δ 206.5, 203.8, 174.7, 174.0, 170.0, 165.1, 160.5, 146.0, 145.5, 144.9, 143.8, 134.1, 134.0, 129.9, 128.6, 125.1, 123.7, 121.5, 121.2, 115.1, 112.7, 108.7, 107.7, 71.6, 71.3, 68.8, 68.5, 55.1, 54.5, 51.6, 51.3, 39.8, 39.1, 28.8, 28.7, 28.6, 28.5, 26.3, 26.1, 20.0, 19.9, 19.5; HRMS (EI) *m/z* 396.1685 [calc'd for $C_{22}H_{24}N_2O_5$ (M+) 398.1685].

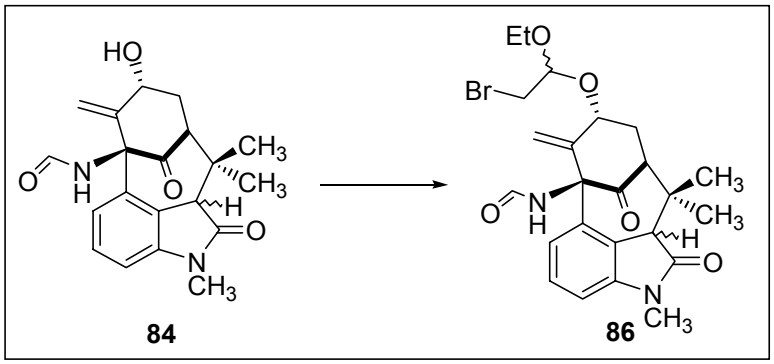
Preparation of Allylic alcohols 84.



Allylic alcohols 84. A 50 mL flask equipped with a reflux condenser was charged with acetate **83** (150 mg, 0.38 mmol, 1.0 eq.), potassium cyanide (30 mg, 0.45 mmol, 1.2 eq.), and ethanol (10 mL). The resulting suspension was slowly heated to a gently reflux over 1 hour, and allowed to stir at this temperature for 5 minutes before being cooled to room temperature and concentrated *in vacuo*. The residue thus obtained was subjected to flash chromatography (50–75% EtOAc/hexanes eluent) to furnish a

mixture of C(3) epimeric alcohols **84** (100 mg, 75% yield) as a white solid. The spectral data that is reported is for the major epimer. m.p. 256-258 °C; FTIR (thin film/NaCl) 3339 (bs), 1710 (m), 1688 (s), 1679 (s), 1469 (m), 1272 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 11.6 Hz, 1H), 7.38 (t, *J* = 10.0 Hz, 1H), 6.99 (d, *J* = 9.5 Hz, 1H), 6.95 (d, *J* = 15.5 Hz, 1H), 6.83 (d, *J* = 9.5 Hz, 1H), 5.84 (d, *J* = 1.8 Hz, 1H), 4.88 (d, *J* = 1.3 Hz, 1H), 4.34 (dd, *J* = 6.0, 12.0 Hz, 1H), 3.66 (s, 1H), 3.20 (s, 3H), 2.79 (dd, *J* = 4.9, 11.2 Hz, 1H), 2.62-2.54 (m, 1H), 2.12 (dt, *J* = 4.8, 12.7 Hz, 1H), 1.61 (bs, 1H), 1.47 (s, 3H), 0.62 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.0, 175.0, 163.7, 149.6, 144.9, 134.4, 129.4, 124.4, 118.5, 114.6, 108.4, 69.5, 68.0, 60.2, 49.7, 43.1, 34.1, 26.4, 24.6, 22.1; HRMS (EI) *m/z* 354.1569 [cacl'd for $C_{20}H_{22}N_2O_4$ (M+) 354.1580].

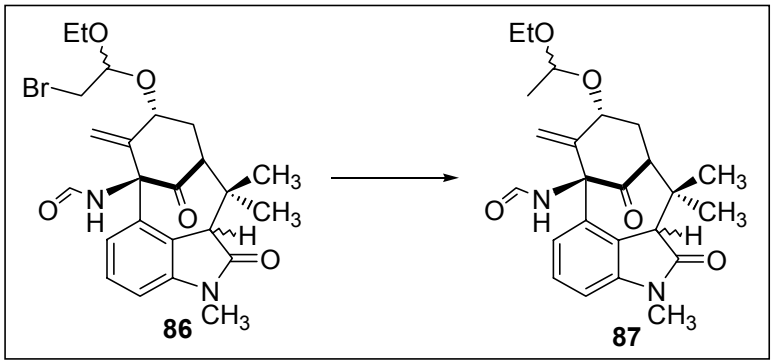
Preparation of Bromoacetals 86.



Bromoacetals 86. To a solution of alcohols **84** (52 mg, 0.15 mmol, 1.0 eq.) in CH_2Cl_2 (1.5 mL) was added bromide **85** (336 μL, 1.46 mmol, 10.0 eq.), *N,N*-dimethylaniline (462 μL, 3.65 mmol, 25.0 eq.), and DMAP (3 mg, 0.02 mmol, 0.15 eq.). The resulting solution was gently refluxed for 15 minutes, at which point the solution turned green and TLC indicated the complete consumption of starting material. Purification was achieved by directly loading the entire reaction mixture onto a column

(30-100% EtOAc /hexanes) which provided acetals **86** (56 mg, 77% yield) as a white foam. The spectral data that is reported is for the major C(3) epimer. X-ray quality crystals for one of the diastereomers was obtained by slow evaporation from EtOAc/hexanes. See appendix 2 for X-ray data pertaining to a single diastereomer of bromoacetal **86**. m.p. >175 °C (dec.); FTIR (thin film/NaCl) 2975 (w), 1692 (s), 1604 (w), 1468 (m), 1115 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (d, *J* = 6.2 Hz, 1H), 8.41 (d, *J* = 6.1 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.37 (t, *J* = 8.1 Hz, 1H), 7.08 (d, *J* = 7.9 Hz, 1H), 7.07 (d, *J* = 8.1 Hz, 1H), 6.87 (dd, *J* = 5.5, 12.2 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 5.94 (d, *J* = 1.7 Hz, 1H), 5.90 (d, *J* = 1.6 Hz, 1H), 4.93 (s, 1H), 4.91 (s, 1H), 4.78 (t, *J* = 5.8 Hz, 1H), 4.69 (t, *J* = 5.7 Hz, 1H), 4.29-4.21 (m, 1H), 3.66-3.37 (m, 13H), 3.20 (s, 6H), 2.82-2.76 (m, 2H), 2.62-2.51 (m, 2H), 2.24-2.12 (m, 2H), 1.48 (s, 6H), 1.23 (t, *J* = 7.3 Hz, 3H), 1.20 (t, *J* = 6.8 Hz, 3H), 0.62 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.7, 202.5, 174.7, 174.6, 163.2, 163.1, 146.7, 146.2, 144.8, 144.7, 134.3, 134.2, 129.4, 129.3, 124.3, 124.2, 118.5, 116.1, 115.9, 108.4, 108.3, 101.4, 100.5, 72.0, 71.3, 69.7, 69.6, 63.1, 62.9, 60.4, 60.3, 49.6, 49.5, 43.1, 43.0, 32.7, 32.2, 31.4, 31.3, 26.3, 24.5, 24.4, 24.3, 22.0, 21.9, 15.2, 15.1, 15.0; HRMS (EI) *m/z* 354.1574 [cacl'd for $C_{24}H_{29}BrN_2O_5$ (M+) 354.1580].

Preparation of Acetal 87.



Acetal 87. To a solution of bromoacetals **86** (6.0 mg, 0.012 mmol, 1.0 eq.) and BEt_3 (35.5 μL, 1M in Et_2O, 3.0 eq.) in toluene (2 mL) cooled to -78 °C was added Bu_3SnH (8.0 μL, 0.030 mmol, 2.5 eq.) followed by air (500 μL). The reaction was allowed to stir at this temperature for 10 minutes at which point TLC indicated the complete consumption of starting material. The solution was absorbed onto silica gel and chromatographed (66% EtOAc/hexanes eluent) to provide acetals **87** (5.0 mg, 100% yield) as a mixture of four diastereomers. The spectral data that is reported is for the major C(3) epimer. FTIR (thin film/NaCl) 2974 (w), 2936 (w), 1695 (s), 1607 (w), 1595 (w), 1472 (w), 1338 (w), 1271 (w), 1131 (w), 1084 (w), 933 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.41 (s, 1H), 7.40(app dt, *J* = 1.8, 8.1 Hz, 2H), 7.10 (app dd, *J* = 1.1, 8.0 Hz, 2H), 6.91 (d, *J* = 12.2 Hz, 1H), 6.85 (t, *J* = 8.1 Hz, 1H), 5.86 (d, *J* = 1.6 Hz, 1H), 5.72 (d, *J* = 1.4 Hz, 1H), 4.94-4.88 (m, 3H), 4.70 (q, *J* = 5.3 Hz, 1H), 4.28 (dd, *J* = 5.8 Hz, 2H), 3.70-3.47 (m, 8H), 3.22 (s, 3H), 3.21 (s, 3H), 2.84-2.77 (m, 2H), 2.59-2.48 (m, 2H), 2.22-2.09 (m, 2H), 1.49 (s, 6H), 1.40 (d, *J* = 5.3 Hz, 3H), 1.34 (d, *J* = 7.0 Hz, 3H), 1.24-1.19 (m, 6H), 0.64 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.9, 202.8, 174.9, 174.8, 163.4, 163.2, 147.7, 147.5, 144.9, 144.8, 134.6, 134.4, 129.4, 129.3, 124.4, 124.3, 118.6, 118.5, 115.7, 115.1, 108.4, 108.3, 99.2, 99.1, 71.1, 69.9, 69.8, 69.4, 61.5, 60.8,

60.7, 60.5, 49.7, 43.1, 32.9, 32.8, 26.4, 26.3, 24.6, 24.5, 24.5, 22.1, 22.0, 20.3, 20.1, 20.0, 15.3, 15.2; HRMS (EI) *m/z* 428.2318 [cacl'd for $C_{24}H_{32}N_2O_5$ (M+) 428.2311].

1.8 Notes and References.

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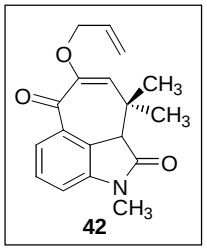
(41) "Rapid chromatographic technique for preparative separations with moderate resolution", Still, W. C.; Kahn, M.; Mitra, A., *Journal of Organic Chemistry* **1978**, *43*, 2923-2925.

APPENDIX ONE: SPECTRA RELEVANT TO CHAPTER ONE



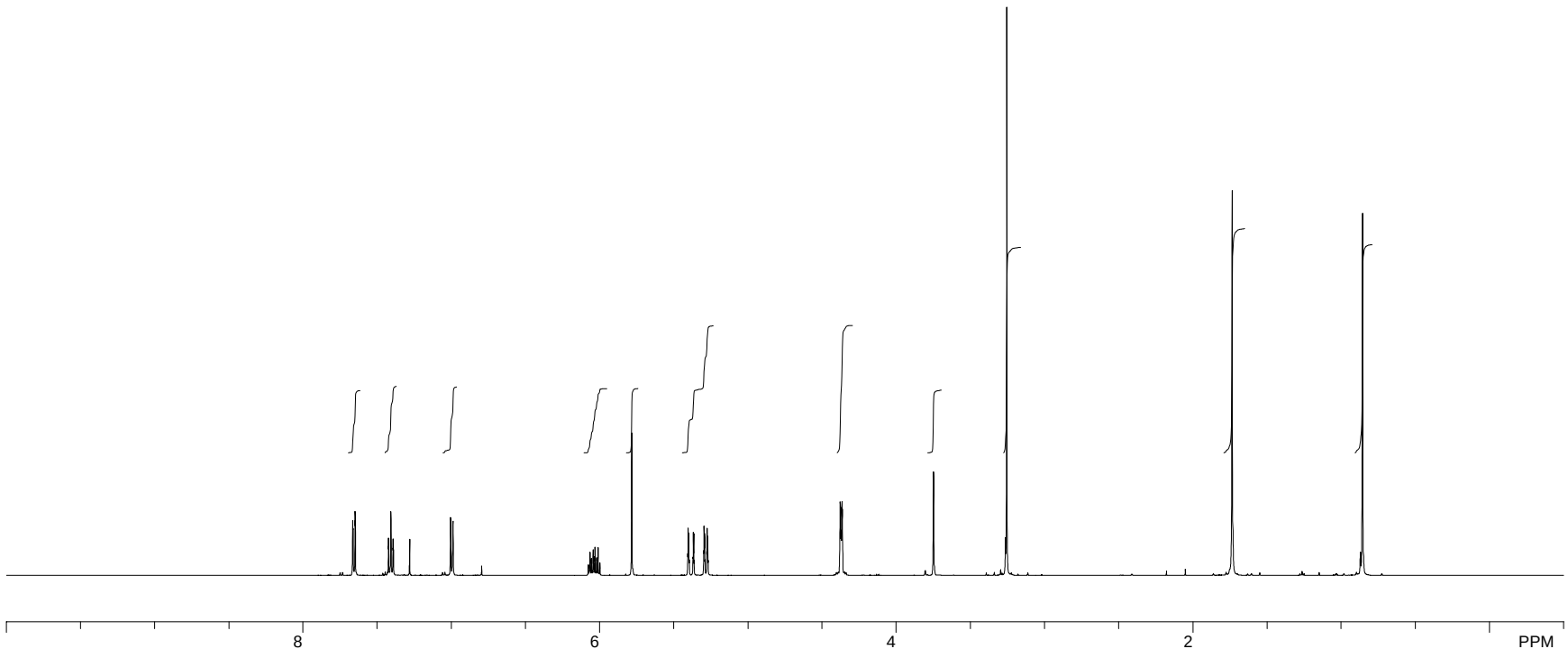


Figure A.1.1 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **42**.

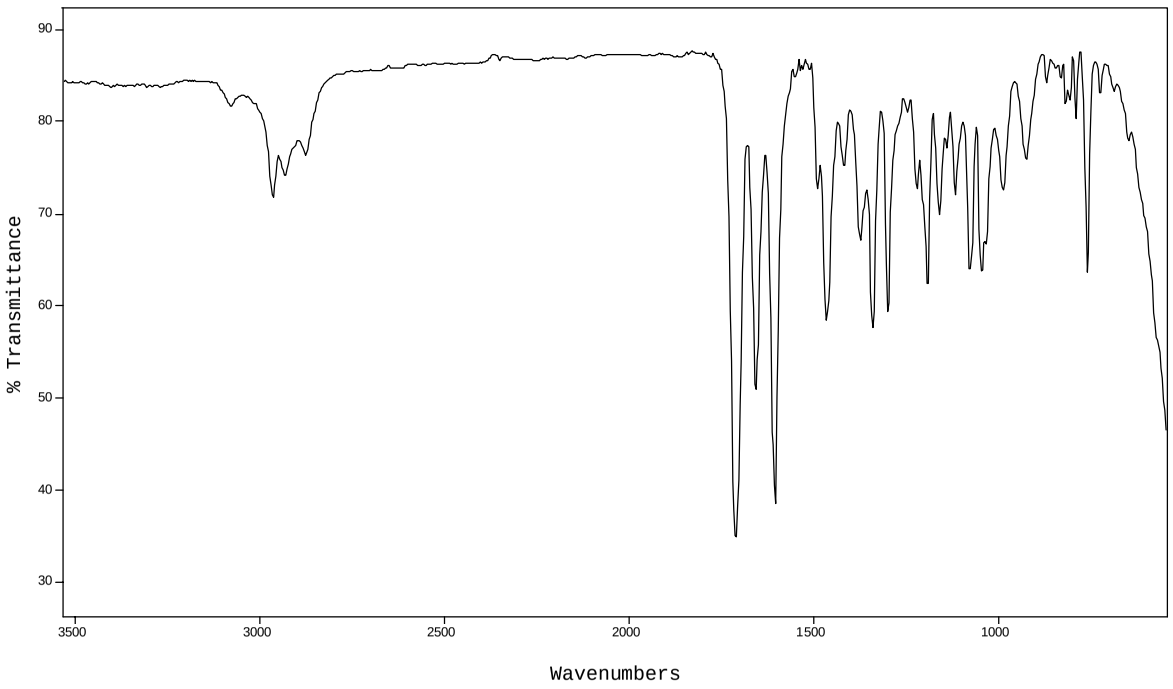


Figure A.1.2 FTIR Spectrum (thin film/NaCl) of Compound **42**.

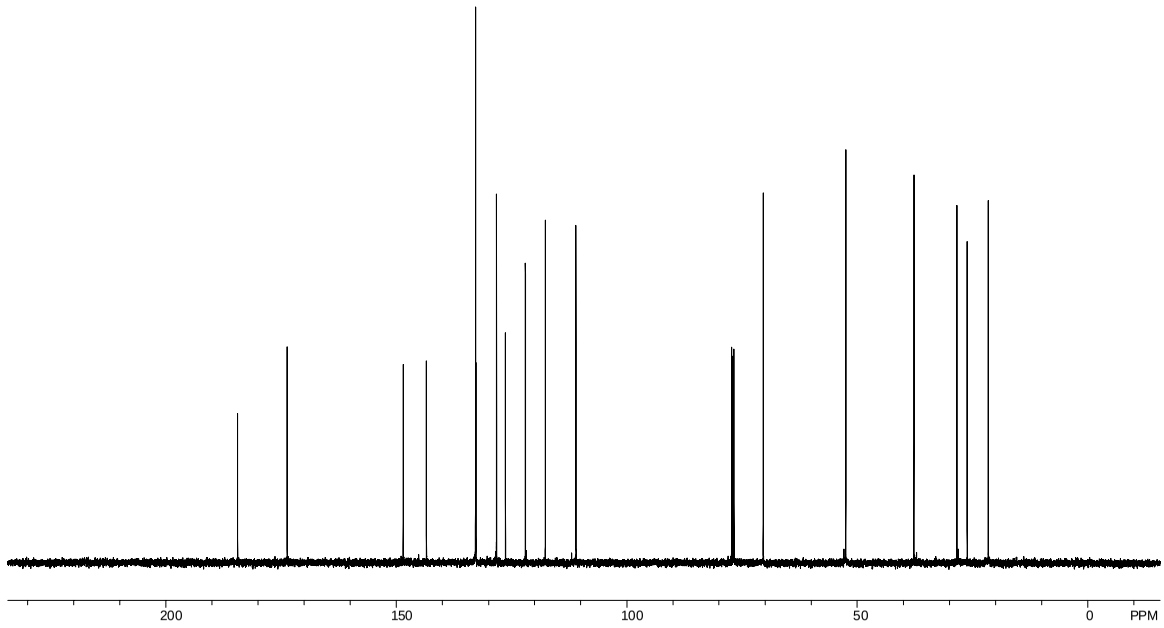


Figure A.1.3 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **42**.

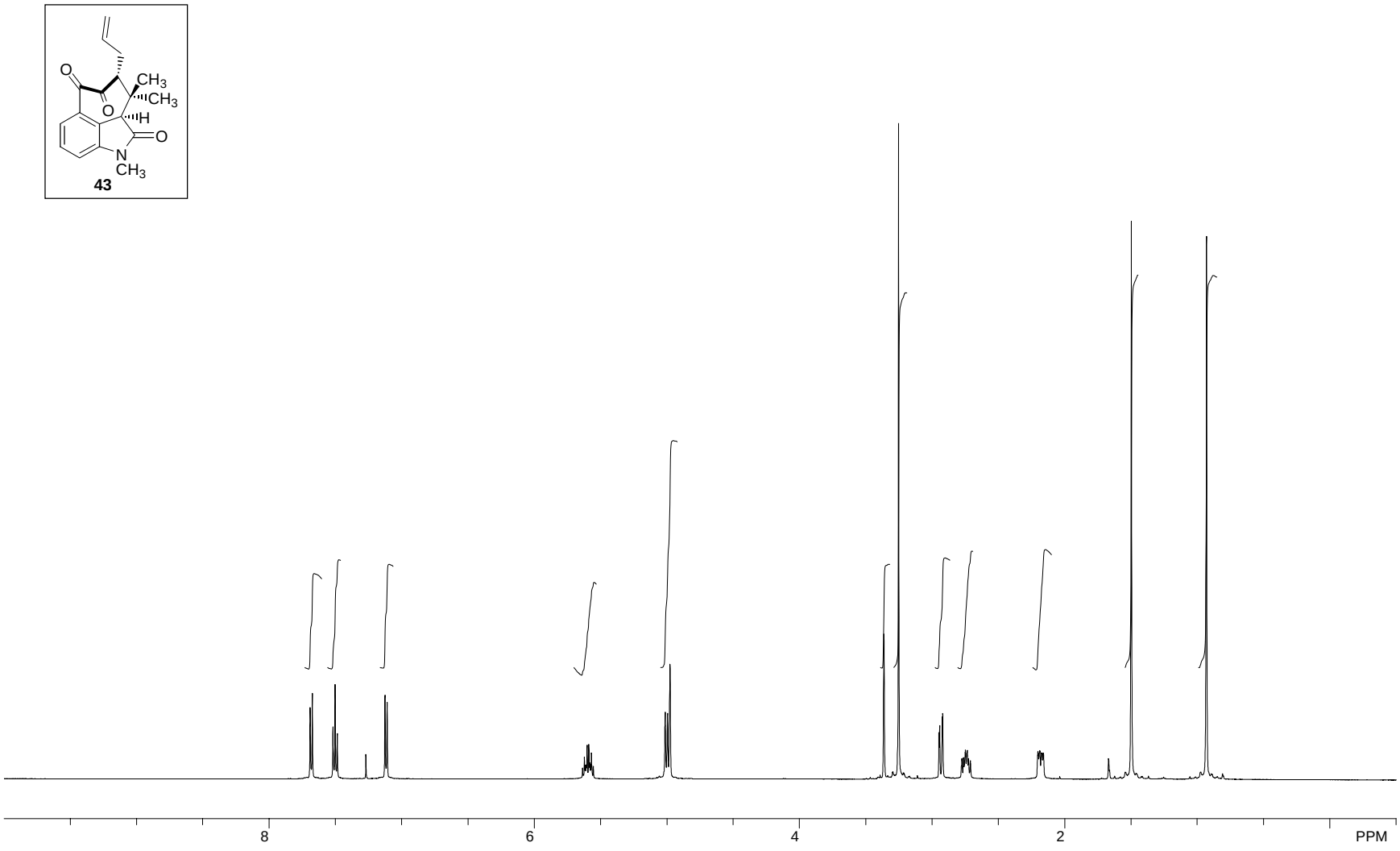


Figure A.1.4 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **43**.

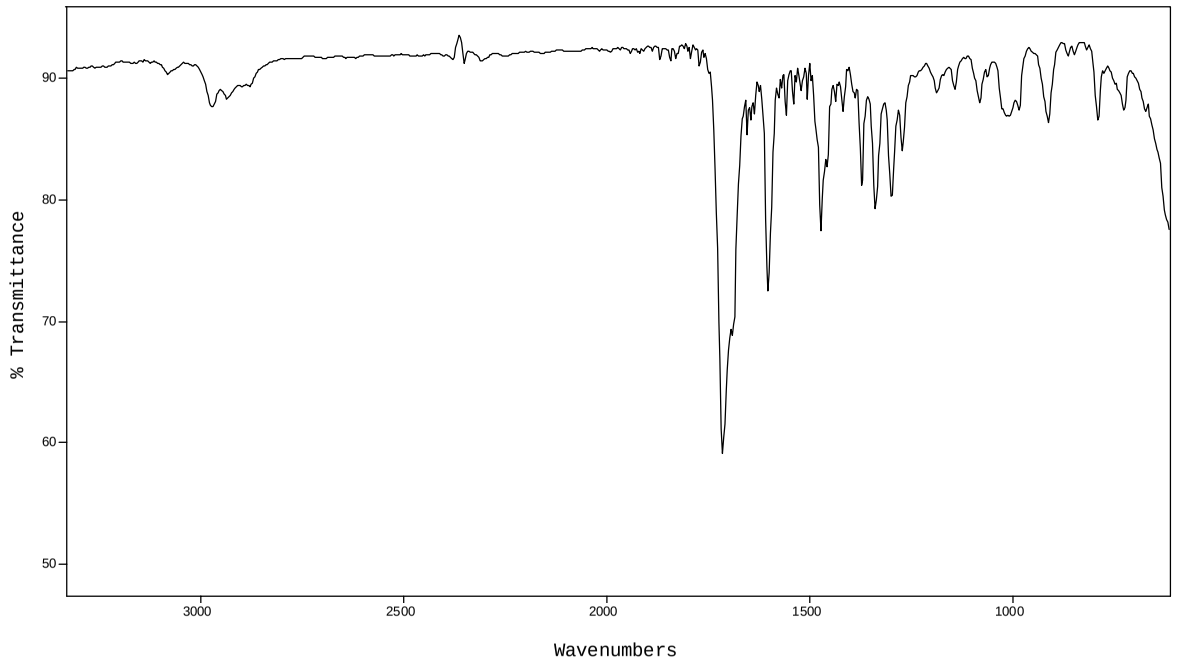


Figure A.1.5 FTIR Spectrum (thin film/NaCl) of Compound **43**.

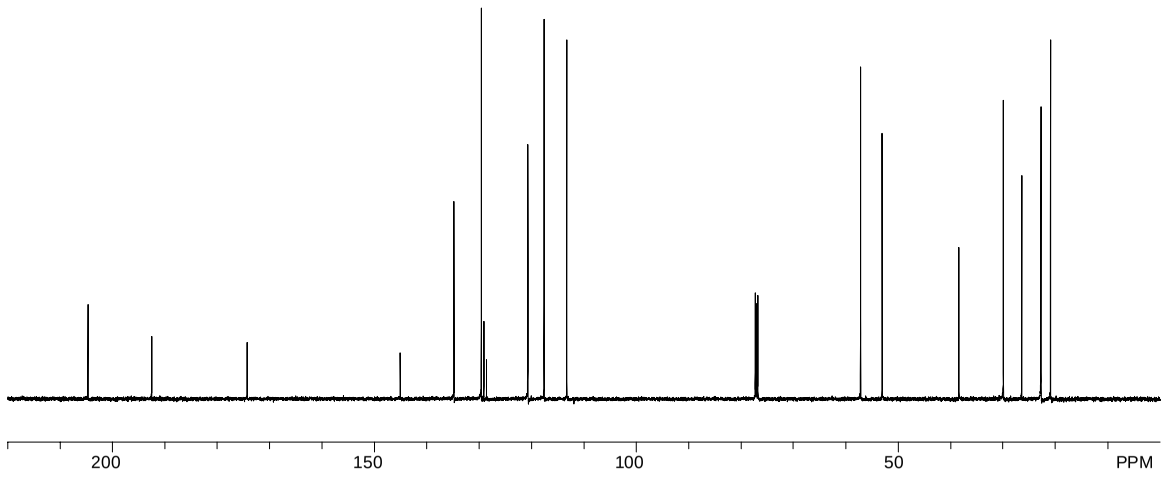


Figure A.1.6 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **43**.

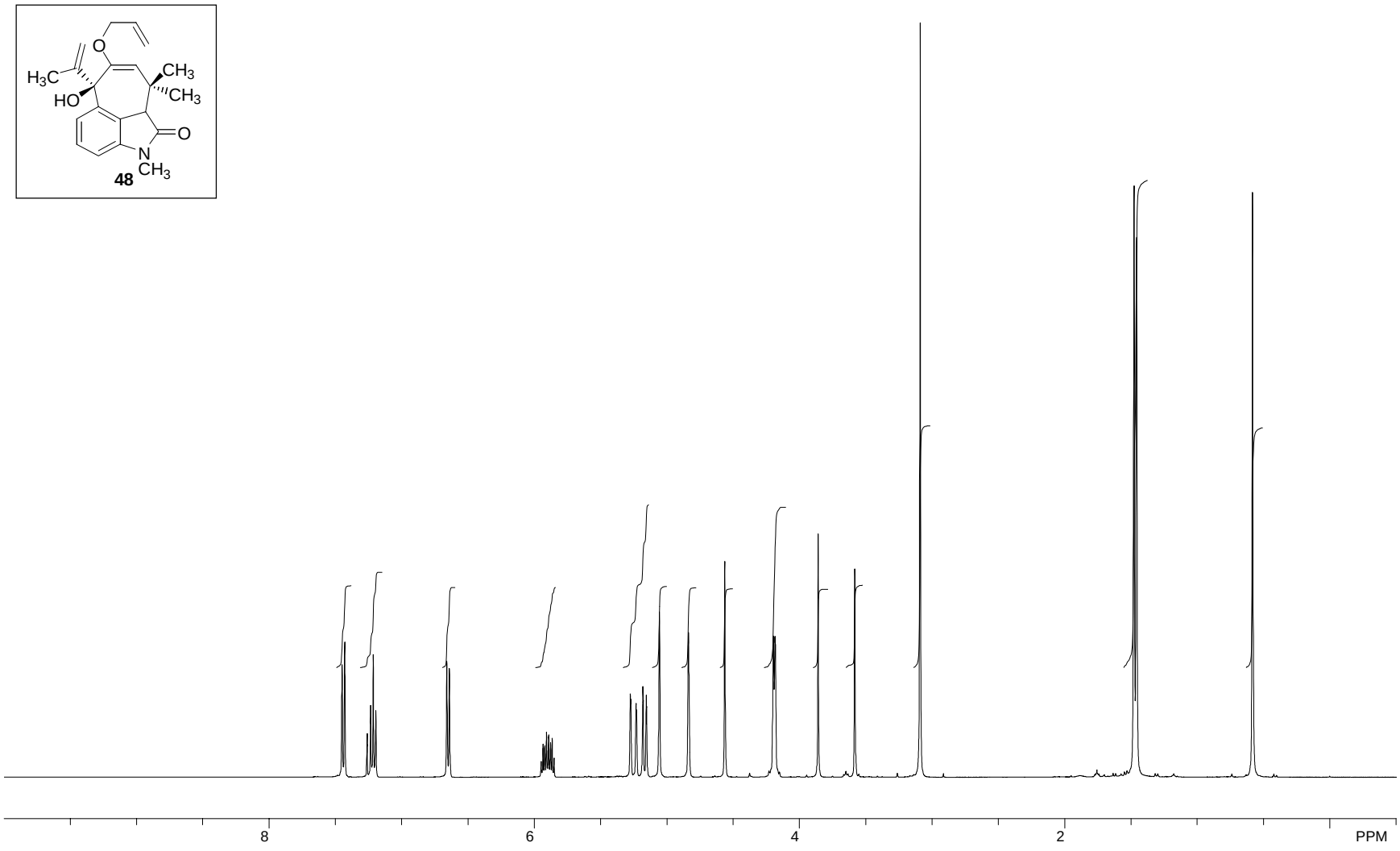


Figure A.1.7 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **48**.

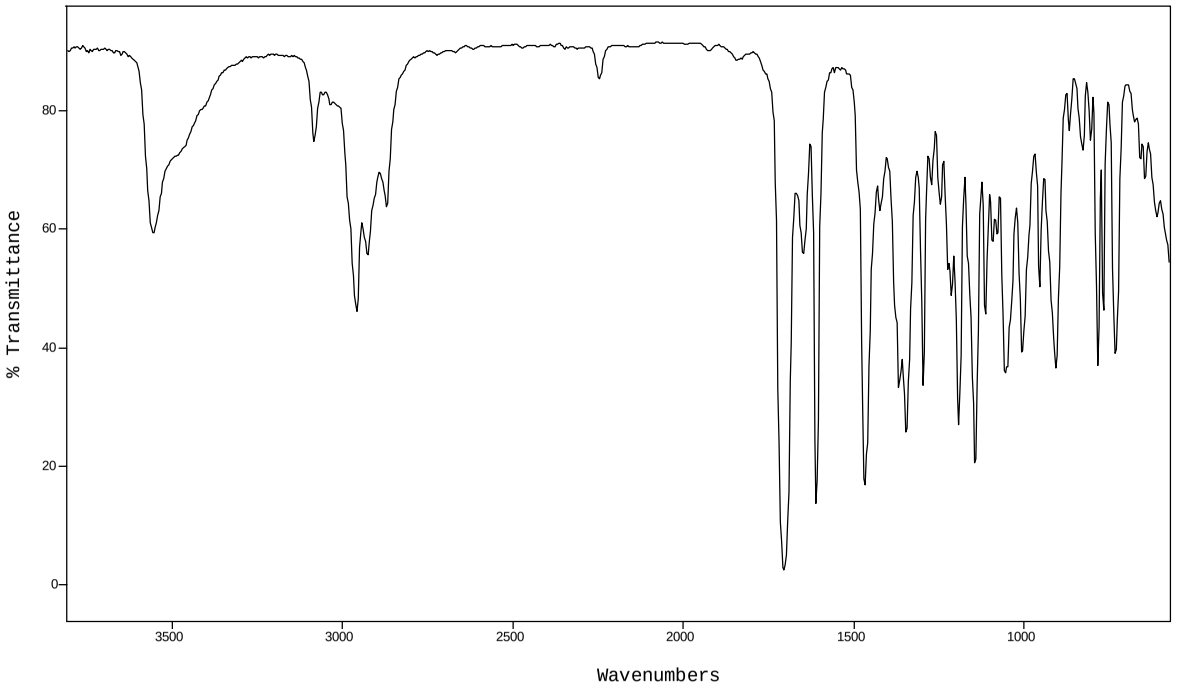


Figure A.1.8 FTIR Spectrum (thin film/NaCl) of Compound **48**.

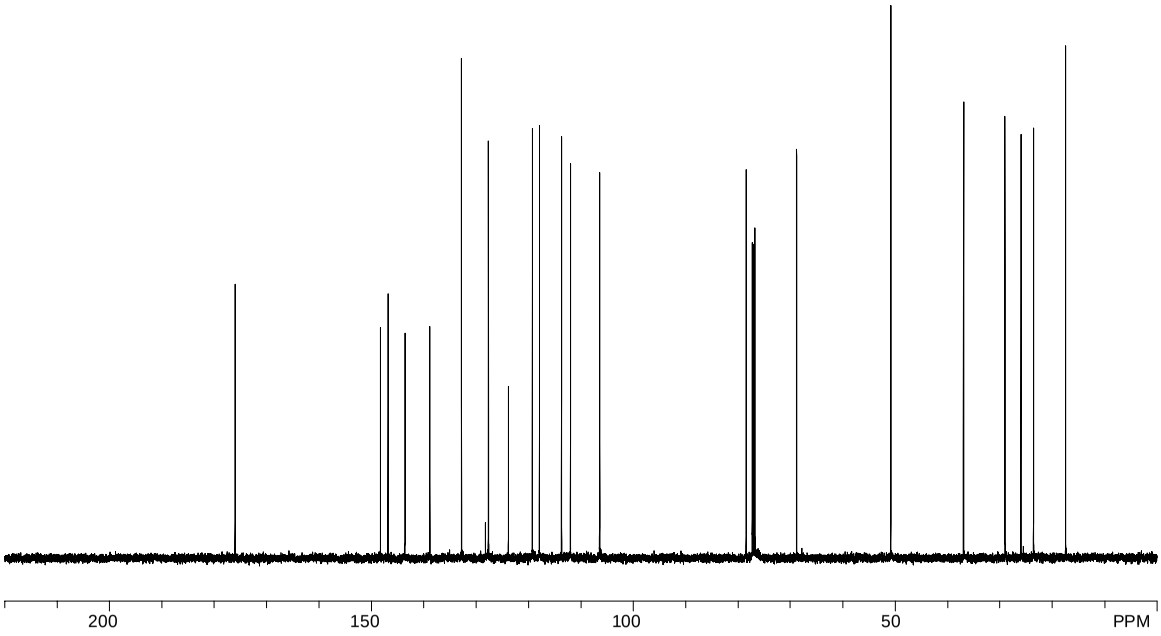


Figure A.1.9 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **48**.

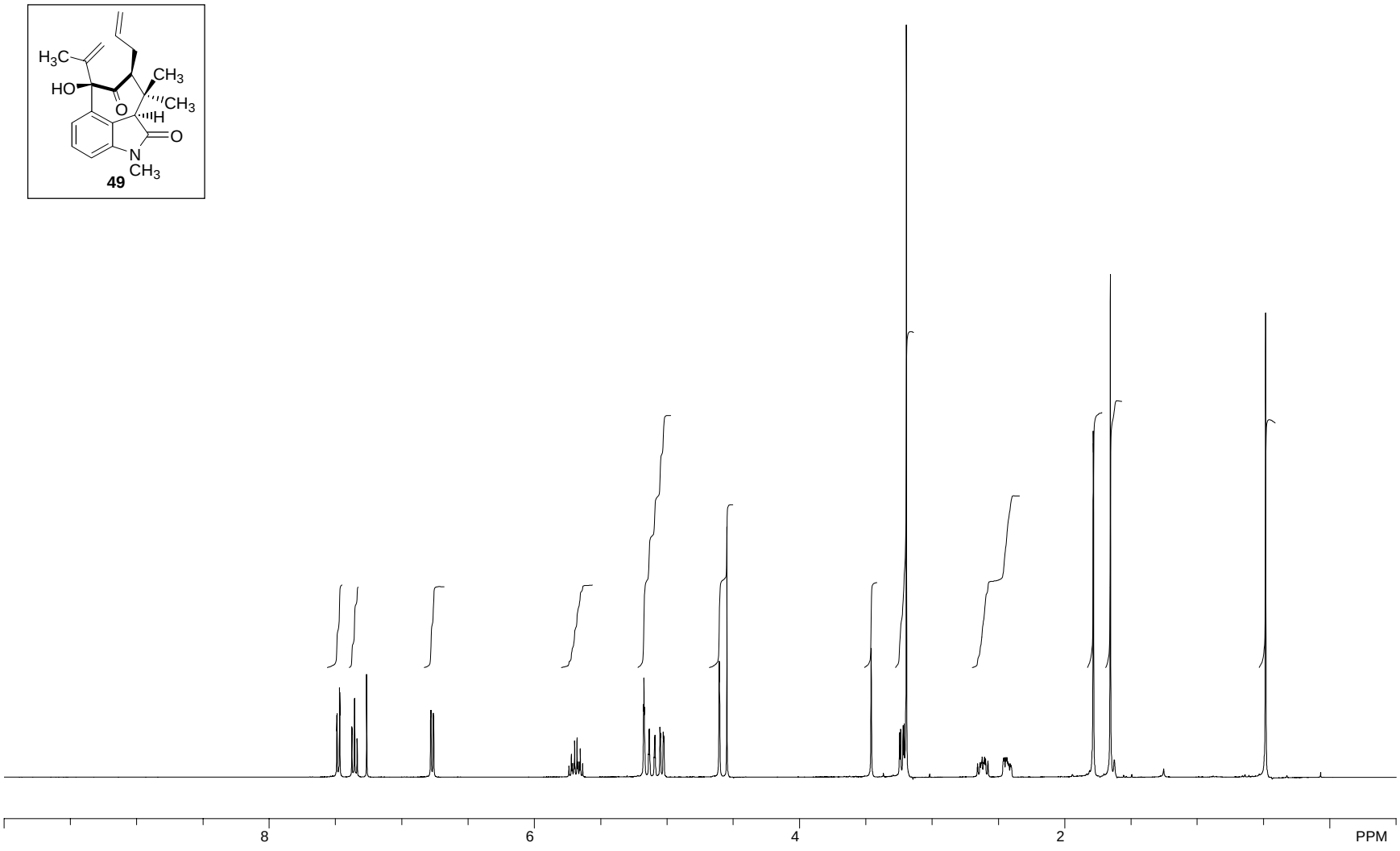


Figure A.1.10 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **49**.

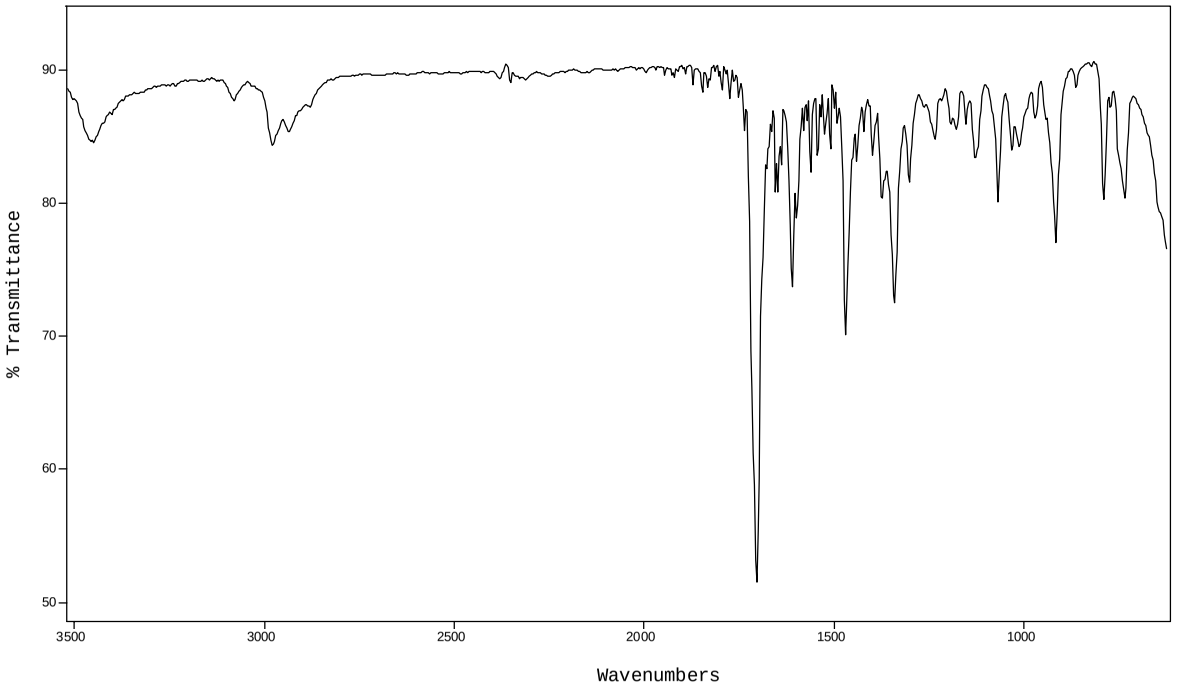


Figure A.1.11 FTIR Spectrum (thin film/NaCl) of Compound **49**.

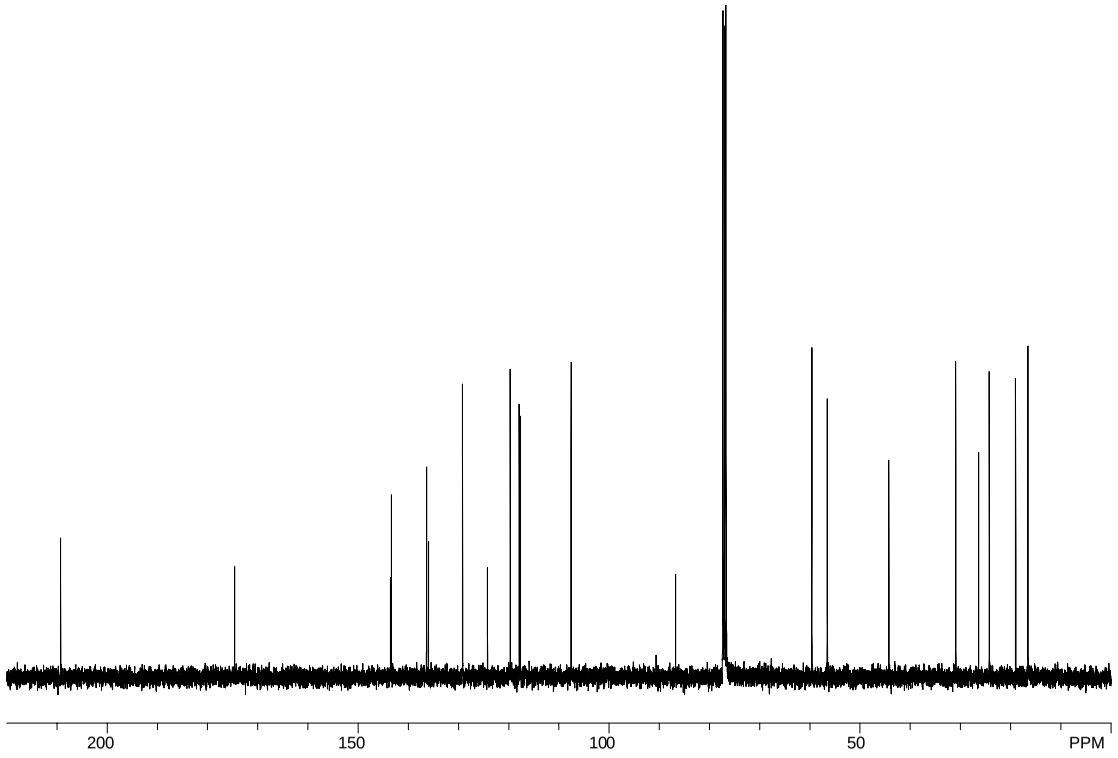


Figure A.1.12 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **49**.

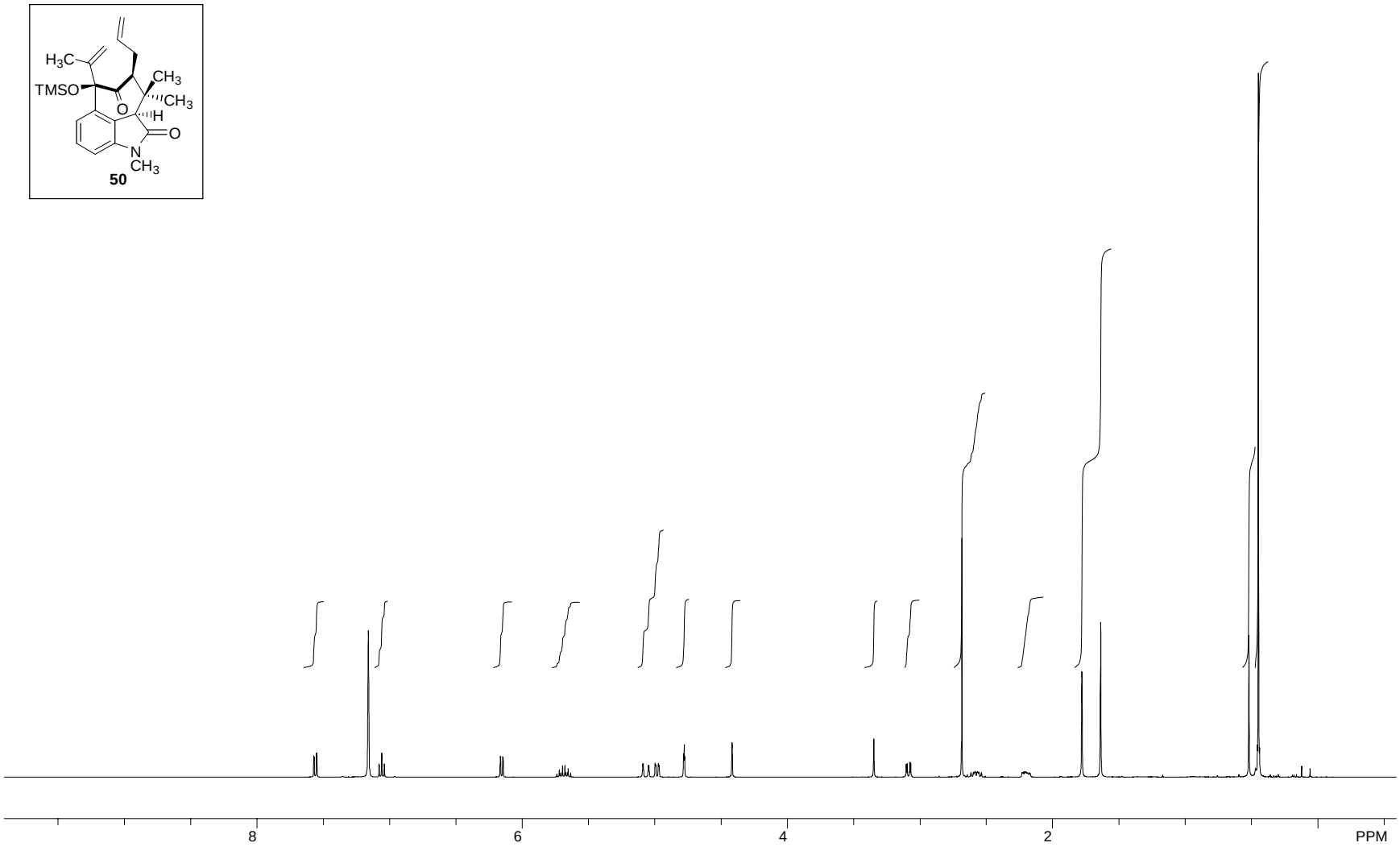


Figure A.1.13 ^{1}H NMR (400 MHz, C_6D_6) of Compound **50**.

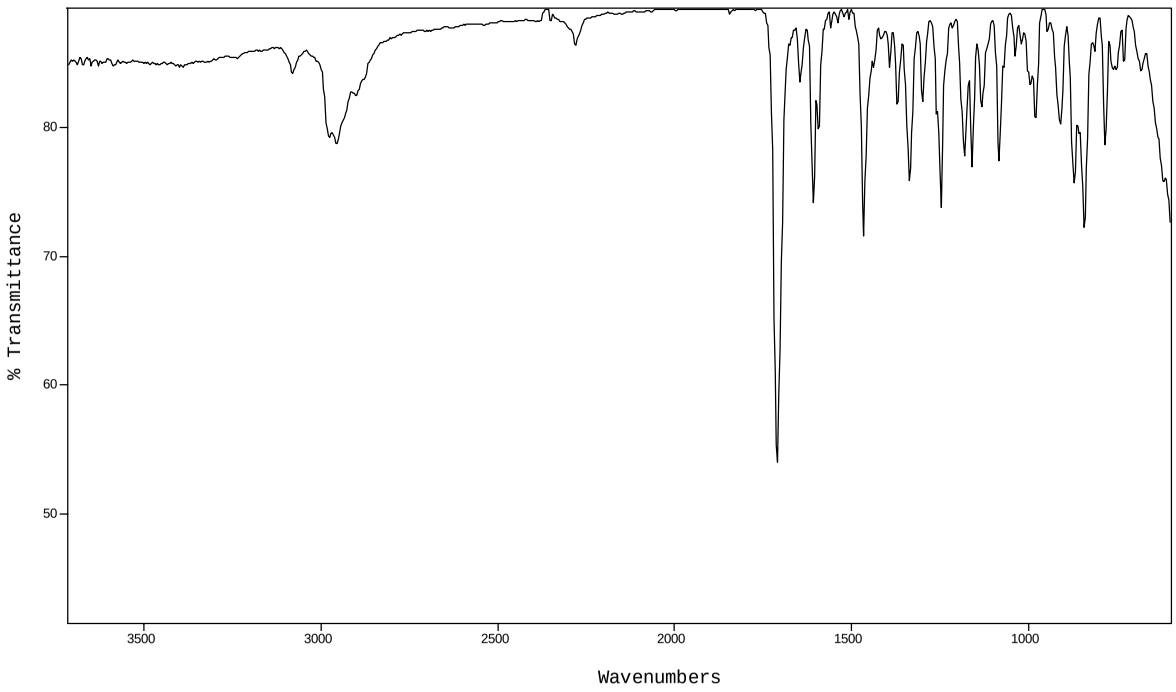


Figure A.1.14 FTIR Spectrum (thin film/NaCl) of Compound **50**.

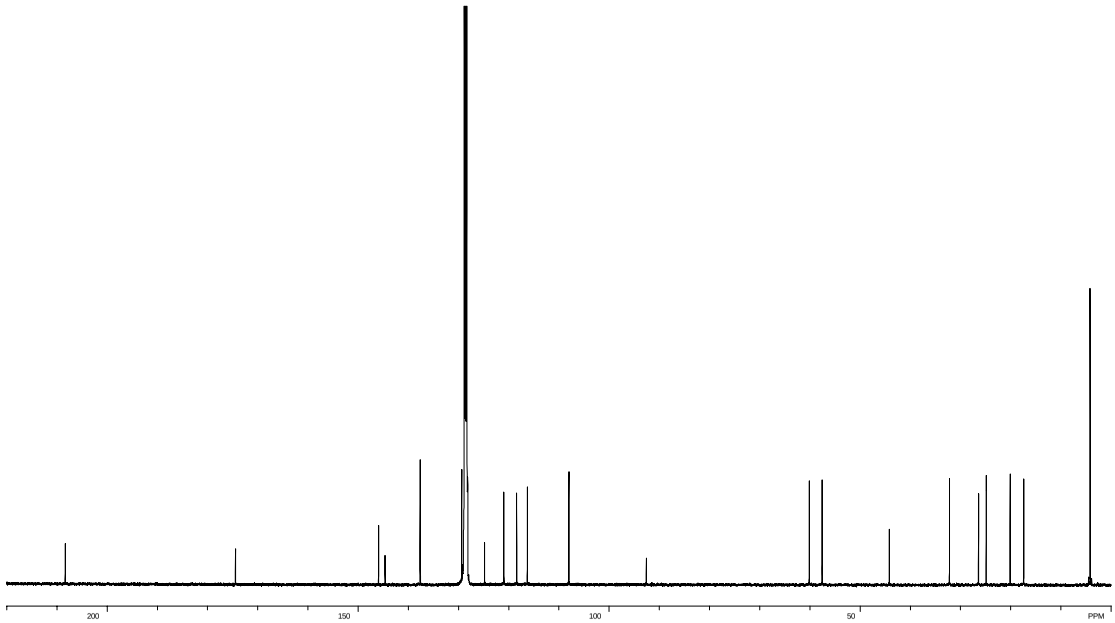


Figure A.1.15 ^{13}C NMR (100 MHz, C_6D_6) of Compound **50**.

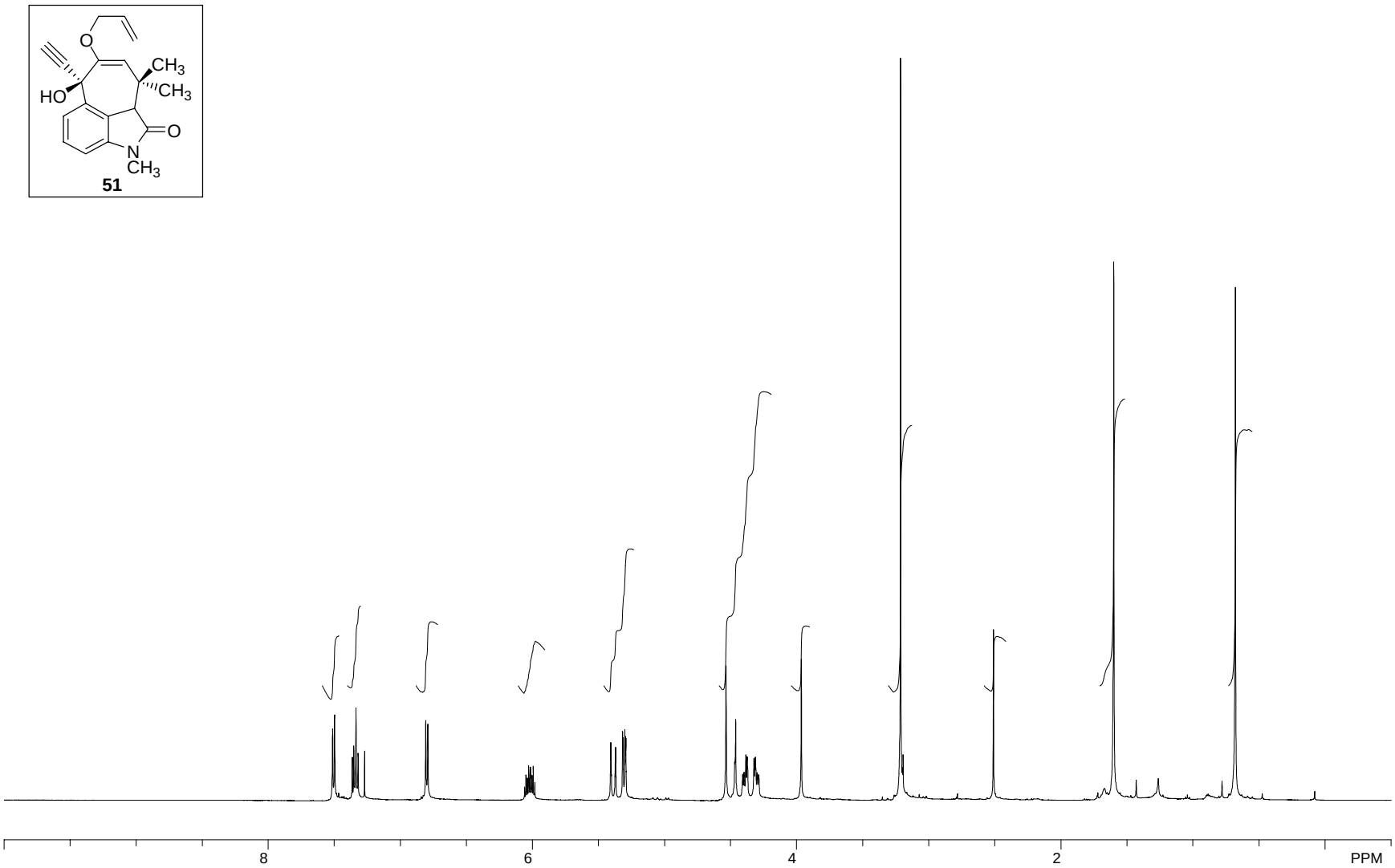


Figure A.1.16 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **51**.

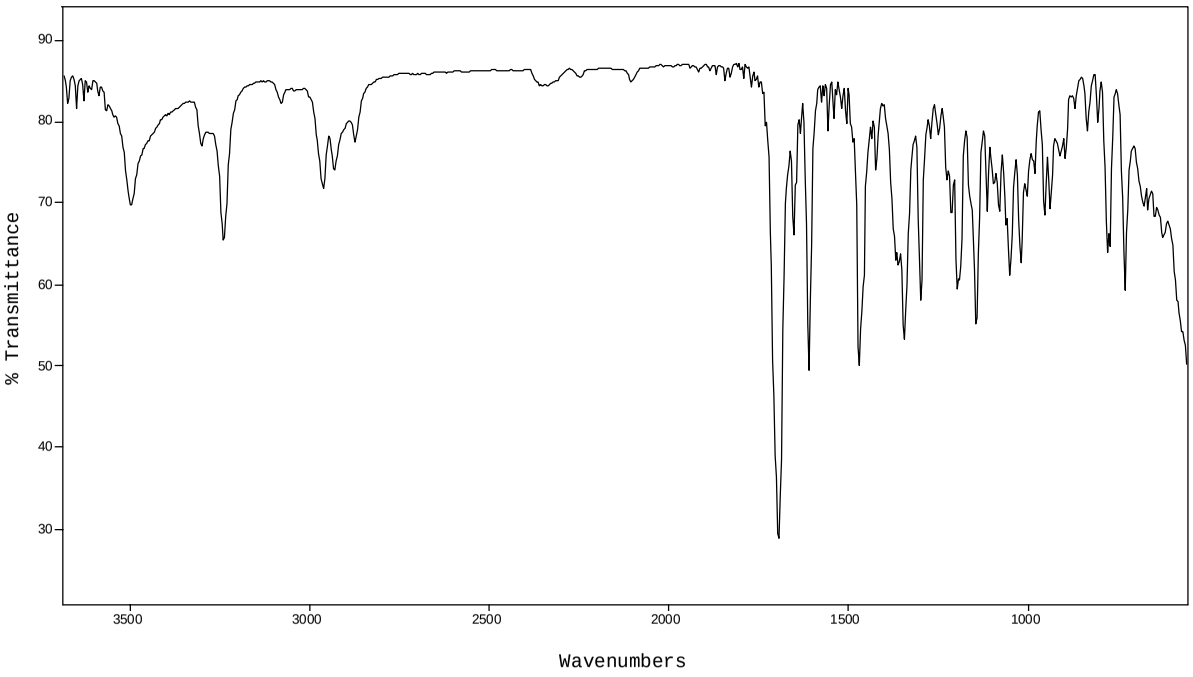


Figure A.1.17 FTIR Spectrum (thin film/NaCl) of Compound **51**.

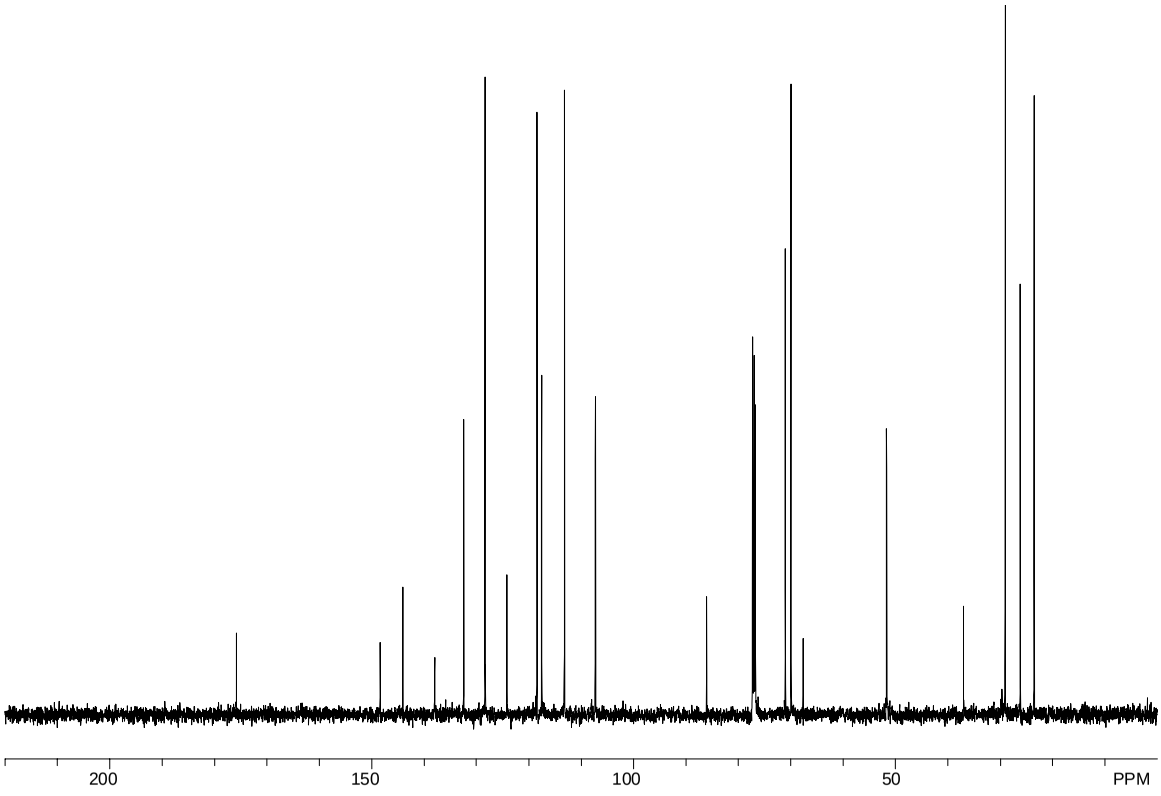


Figure A.1.18 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **51**.

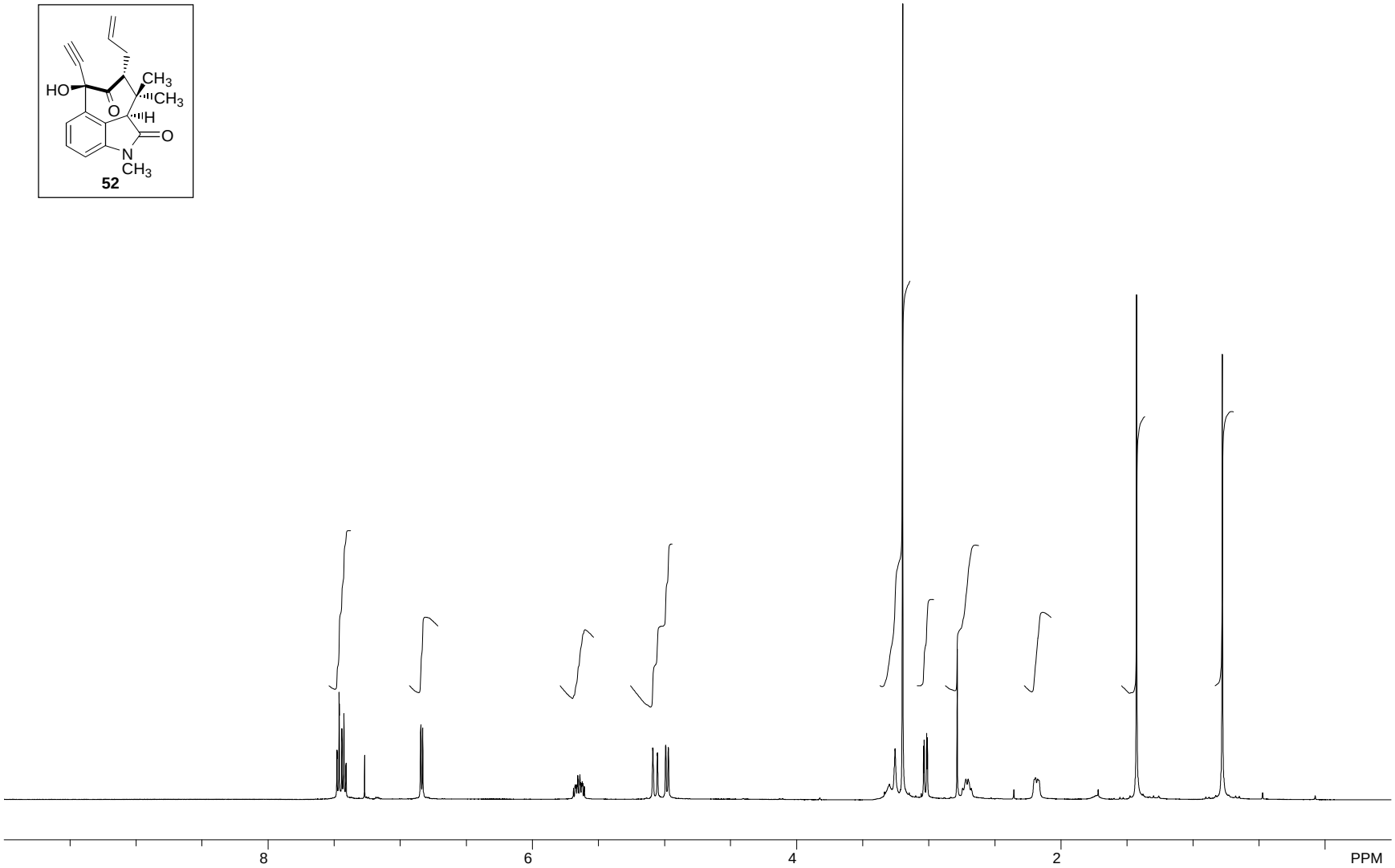


Figure A.1.19 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **52**.

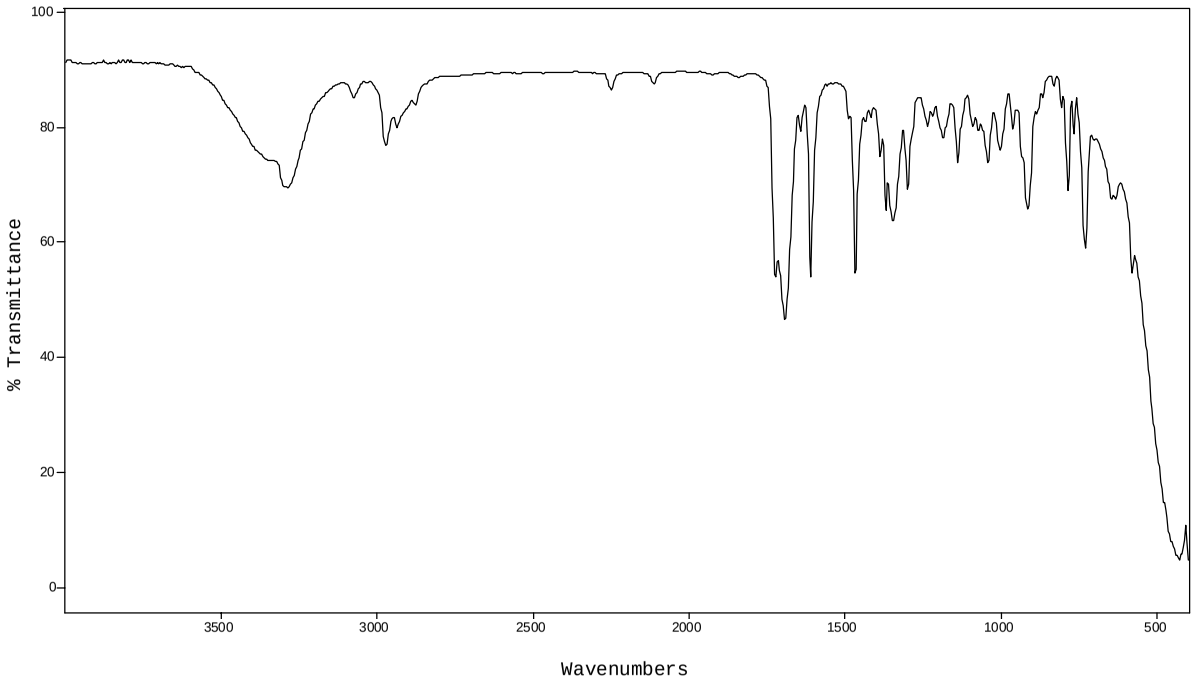


Figure A.1.20 FTIR Spectrum (thin film/NaCl) of Compound **52**.

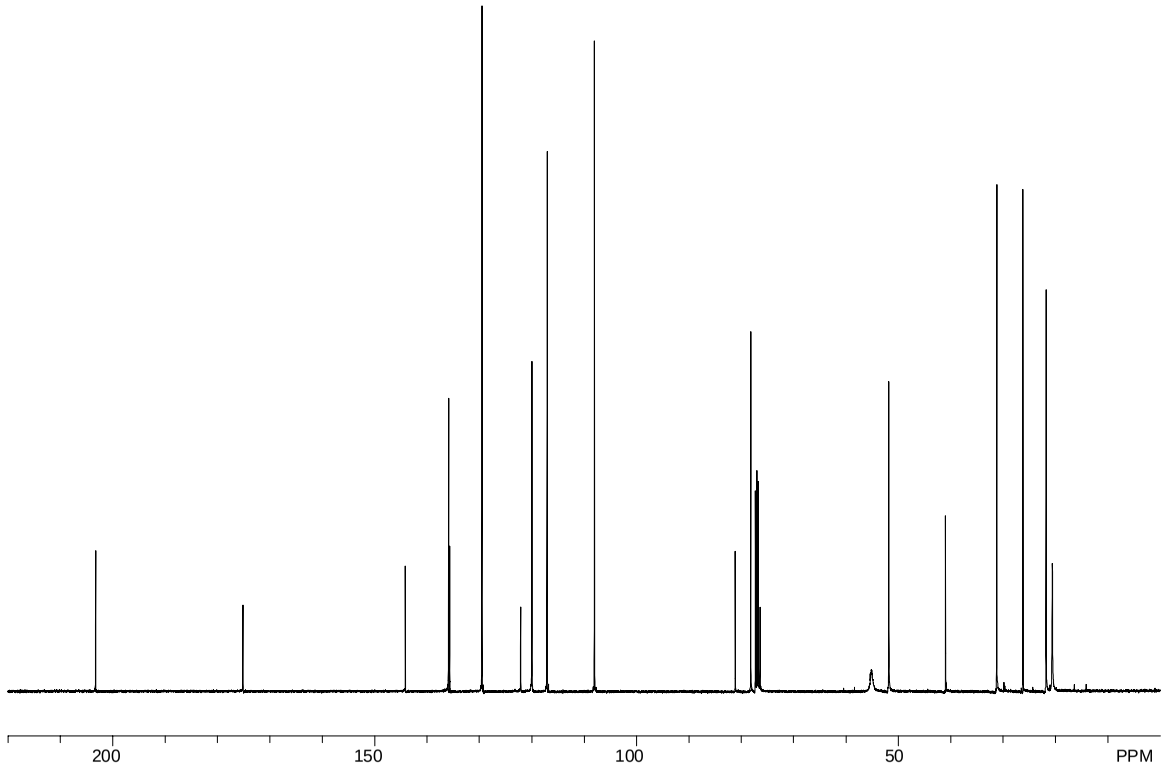


Figure A.1.21 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **52**.

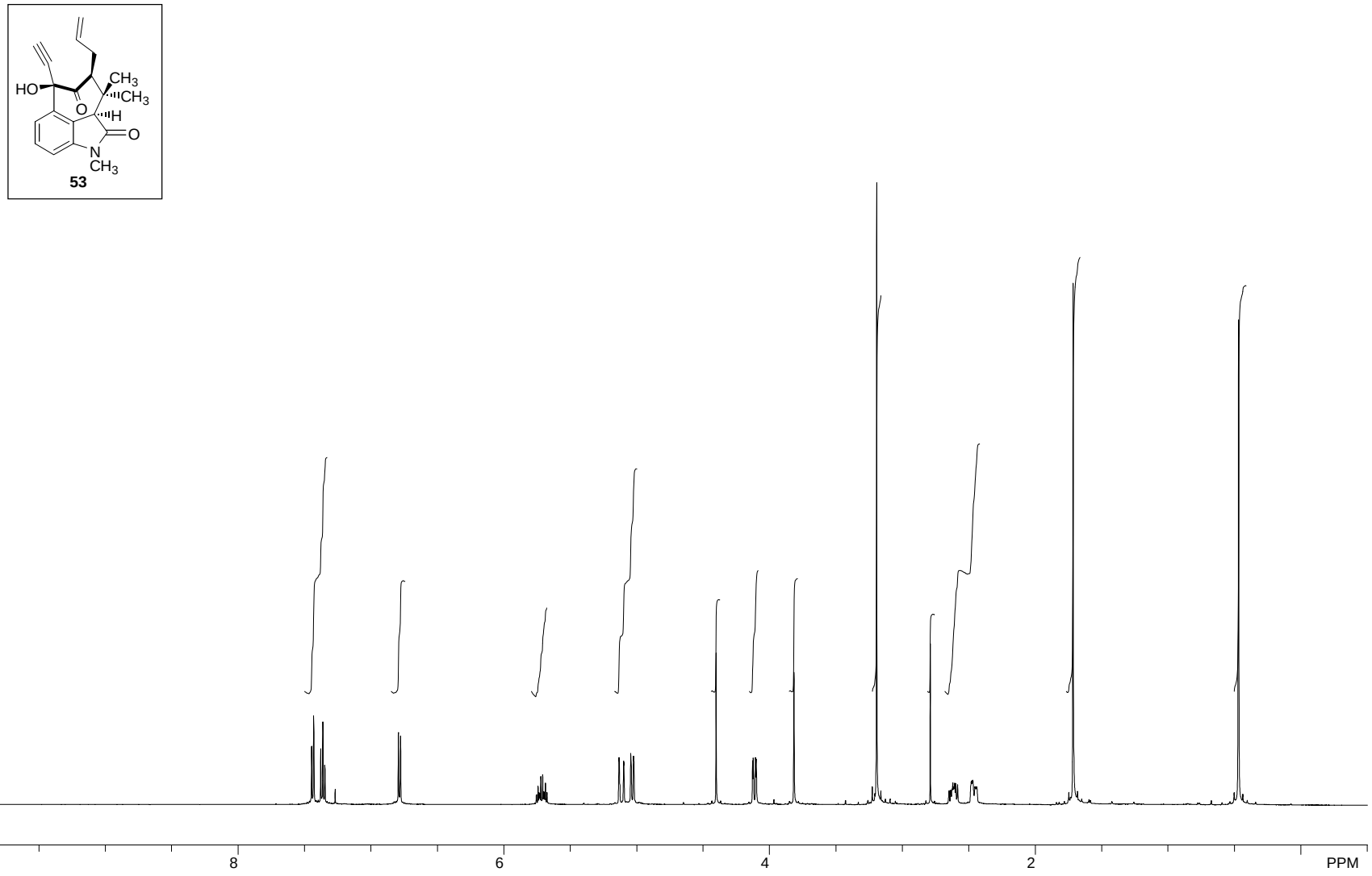


Figure A.1.22 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **53**.

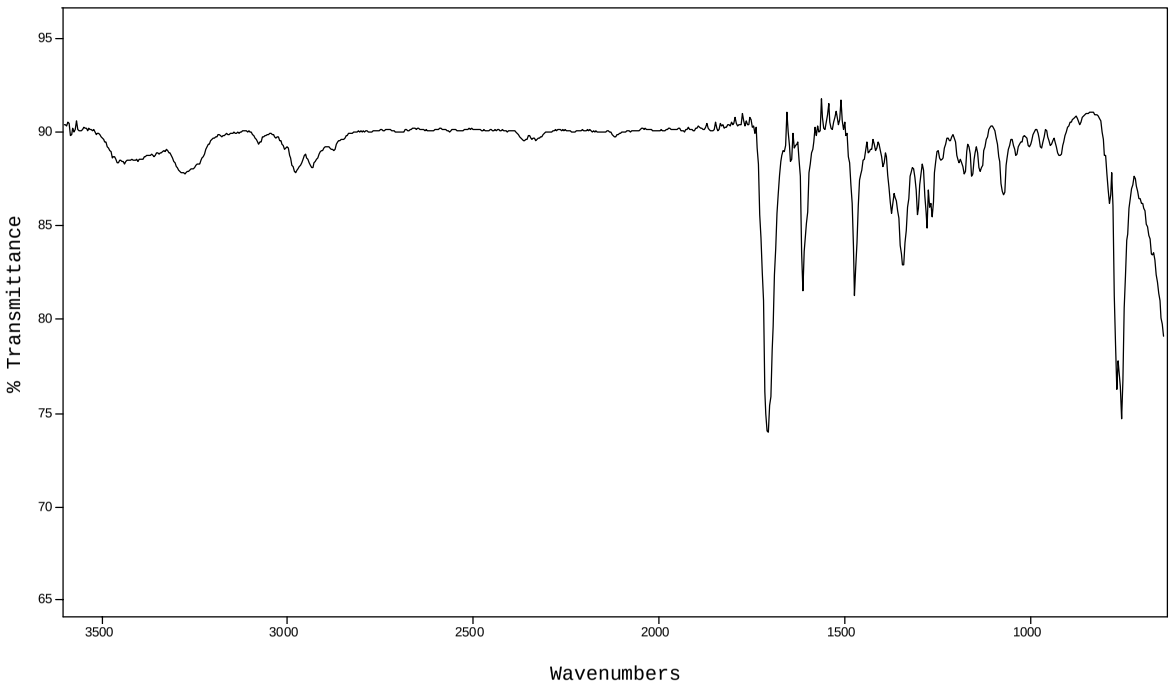


Figure A.23 FTIR Spectrum (thin film/NaCl) of Compound **53**.

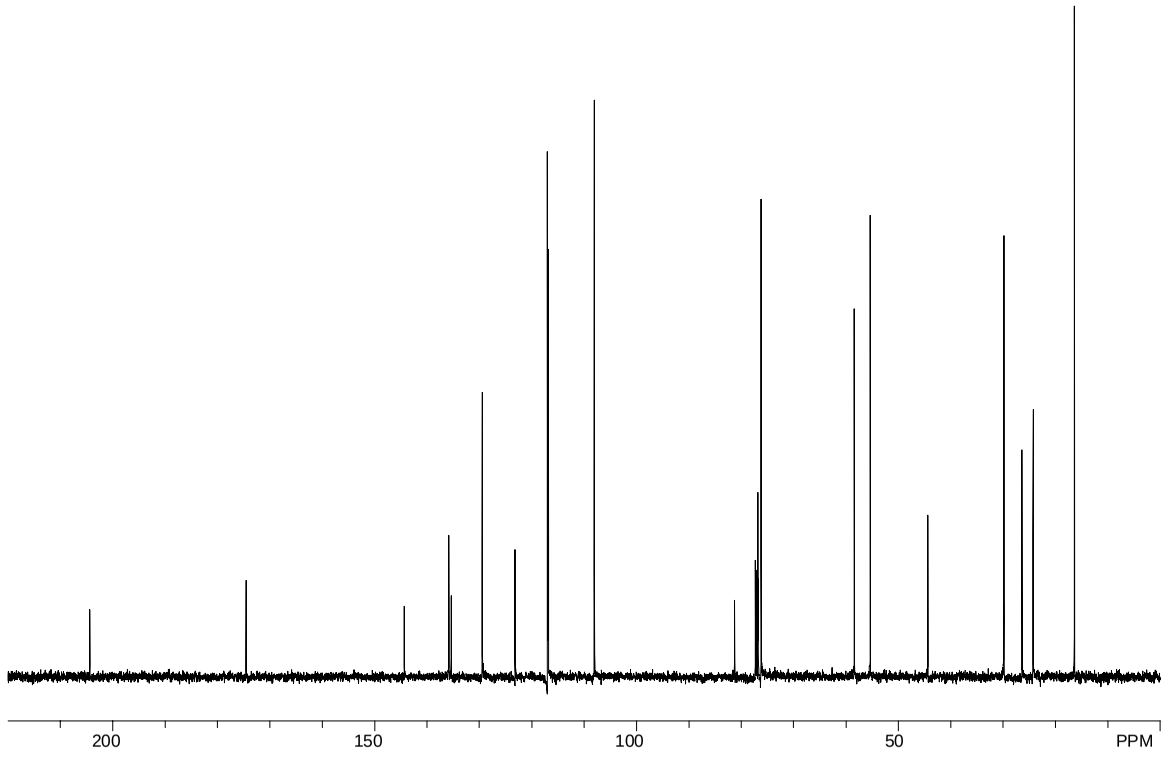


Figure A.1.24 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **53.**

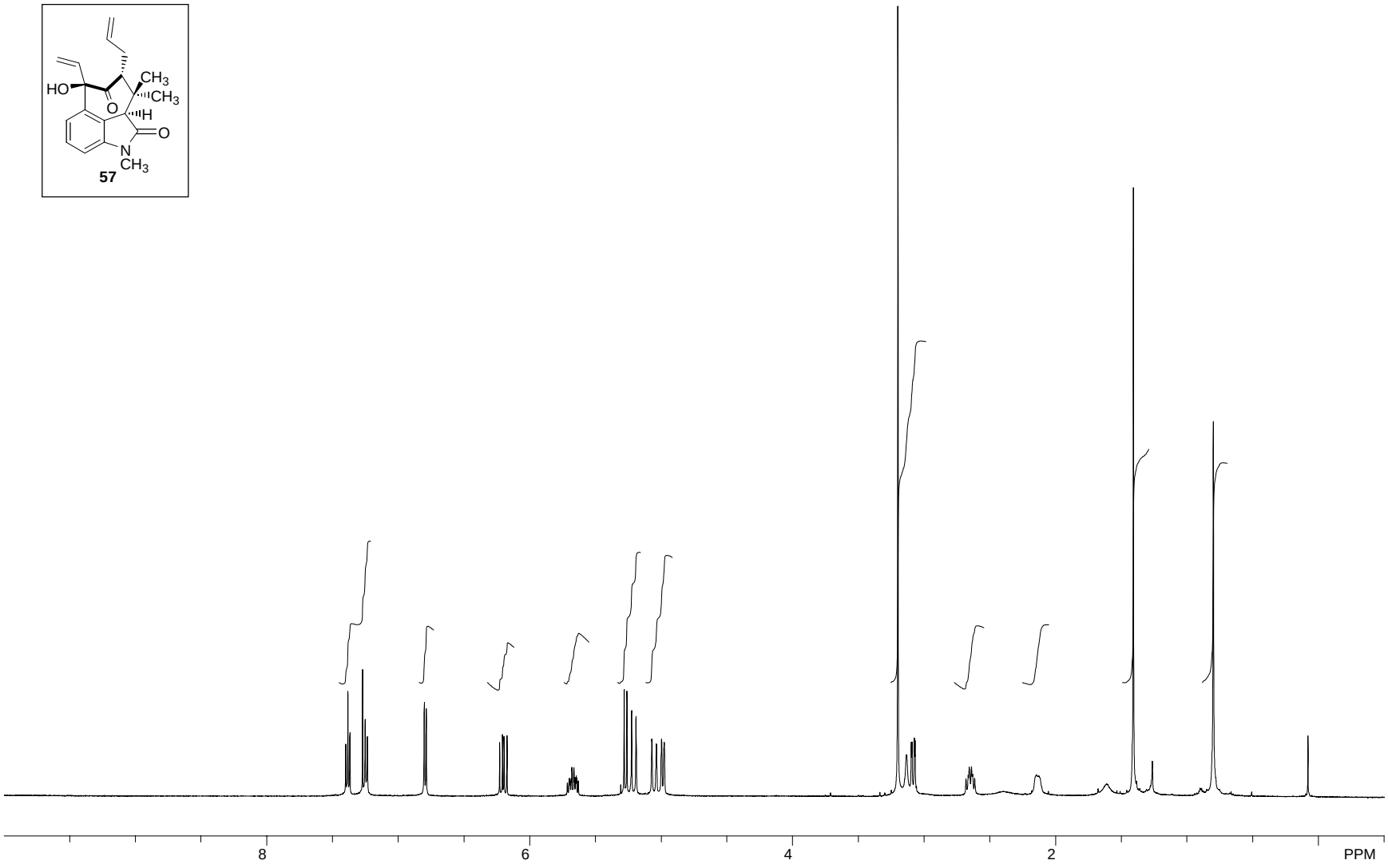


Figure A.1.25 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **57**.

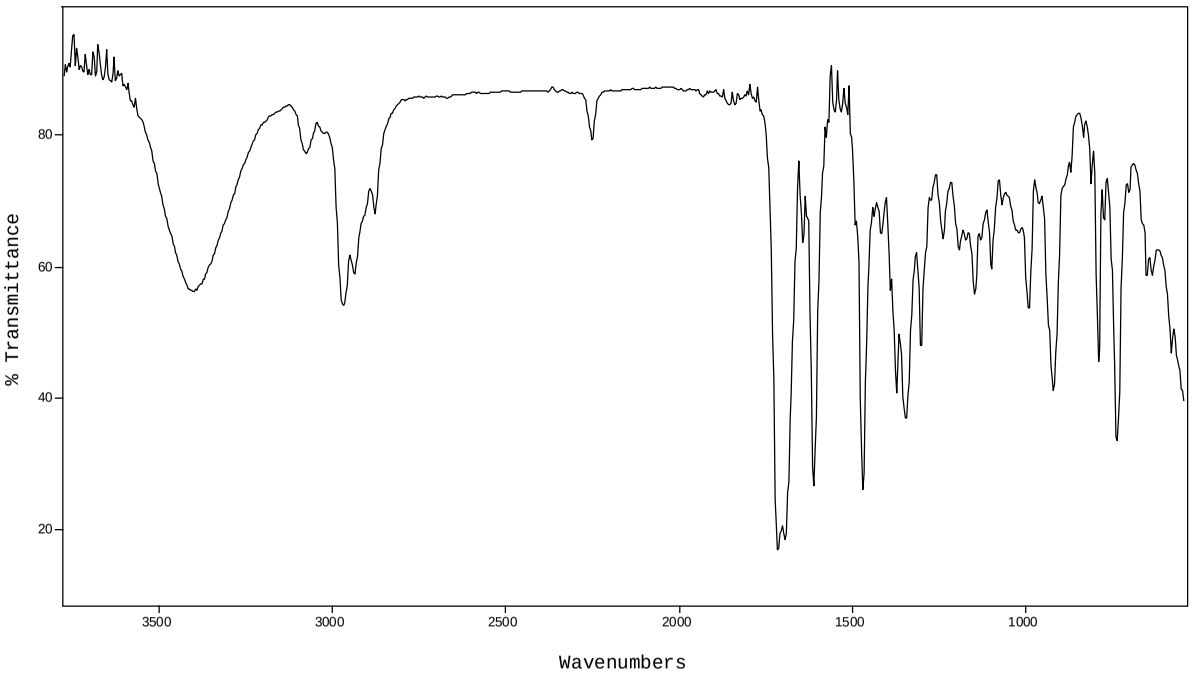


Figure A.1.26 FTIR Spectrum (thin film/NaCl) of Compound **57**.

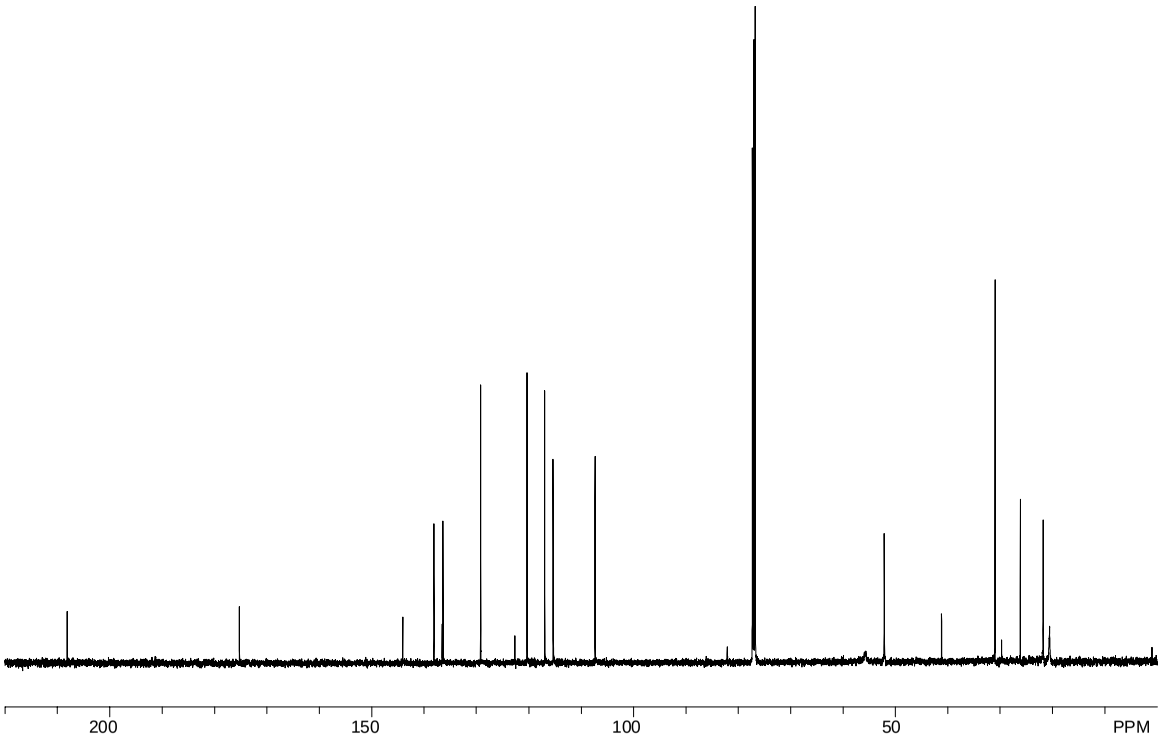


Figure A.1.27 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **57**.

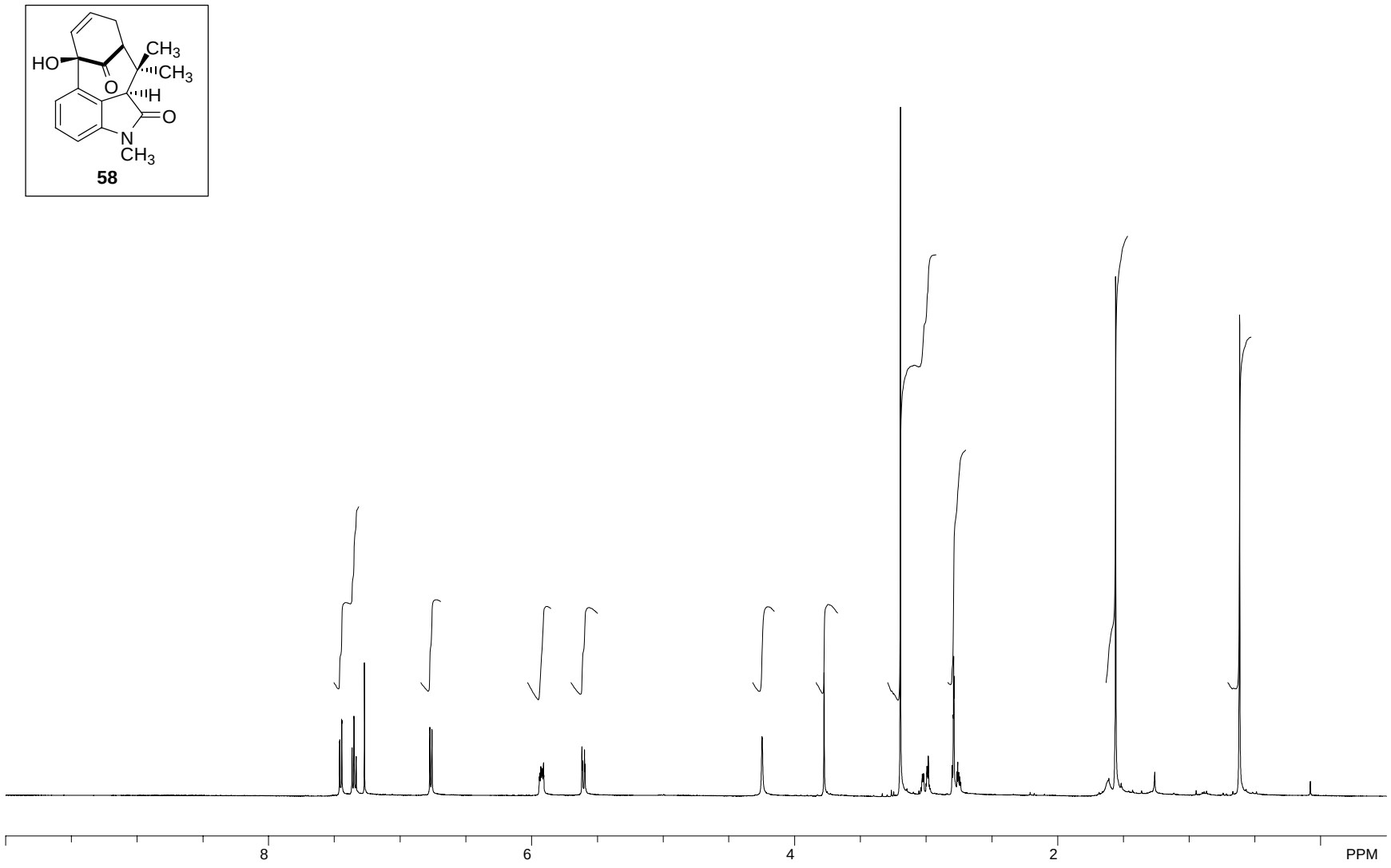


Figure A.1.28 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **58**.

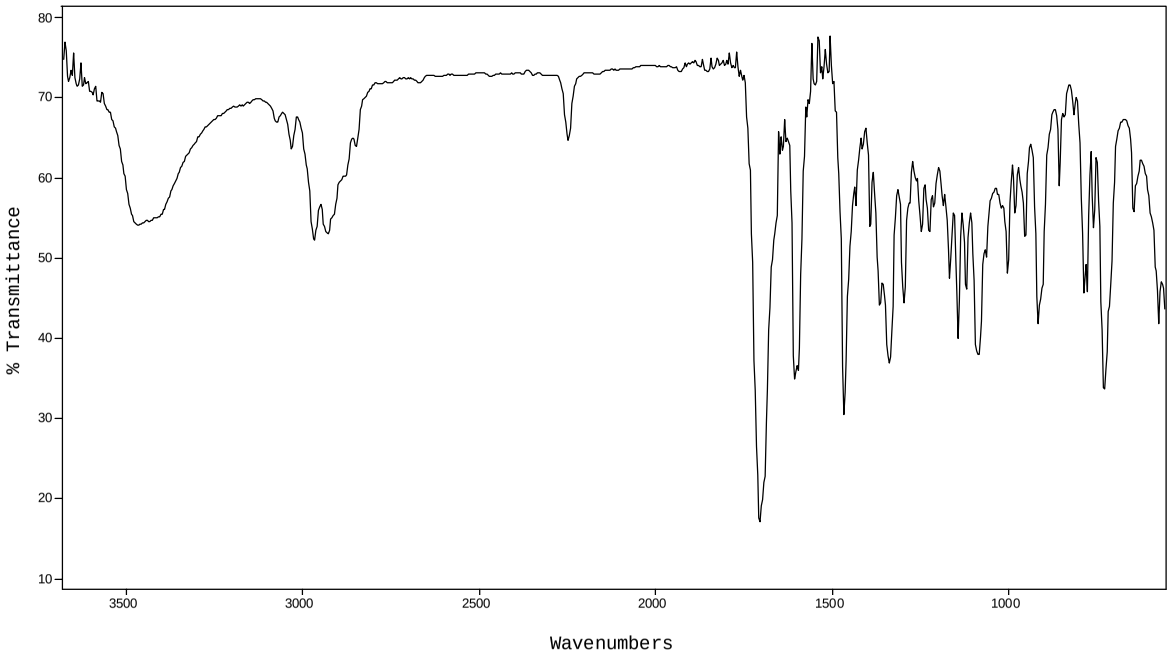


Figure A.1.29 FTIR Spectrum (thin film/NaCl) of Compound **59**.

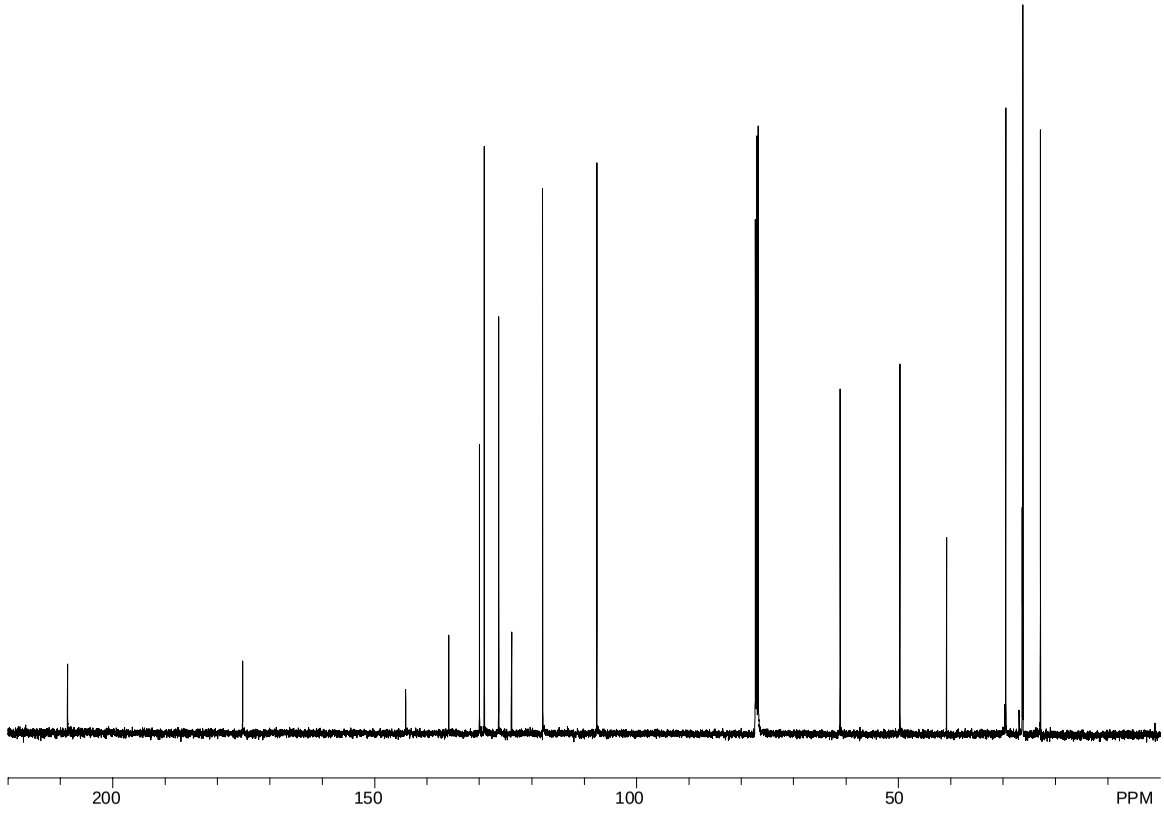


Figure A.1.30 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **59**.

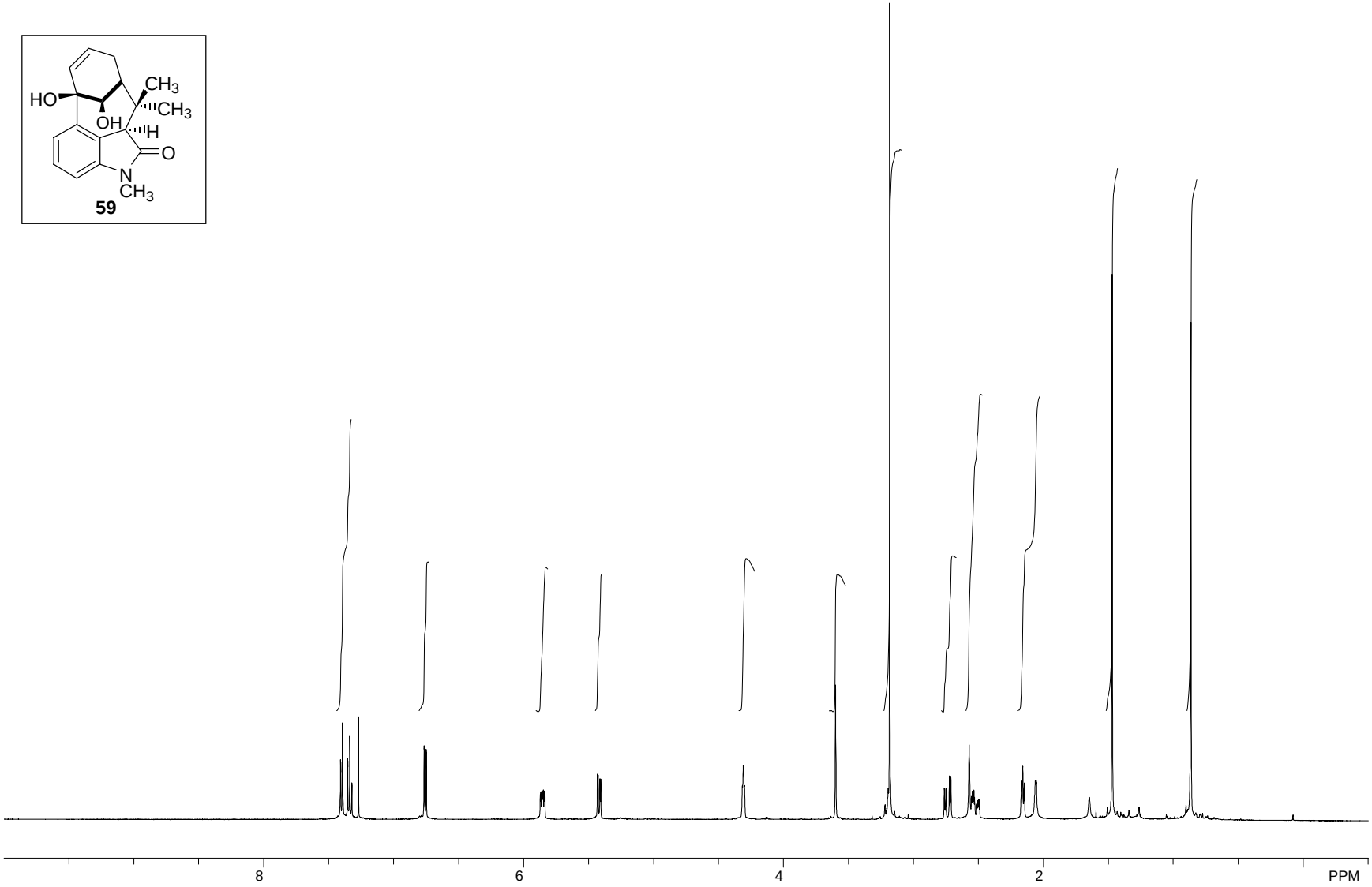


Figure A.1.31 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **59**.

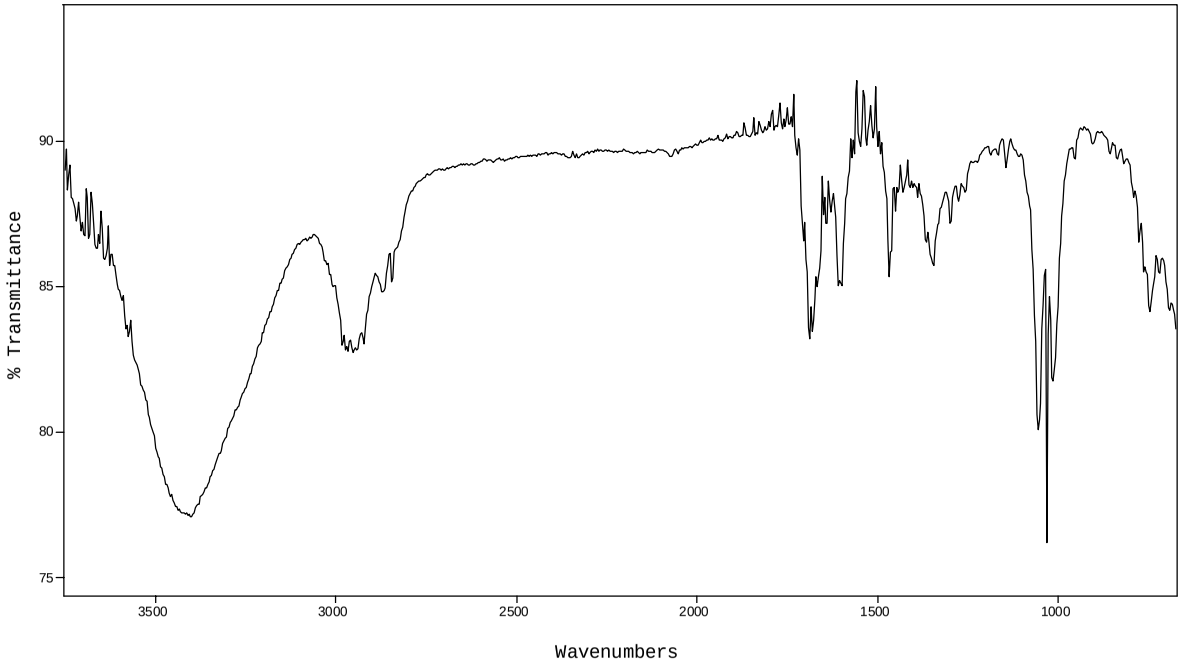


Figure A.1.32 FTIR Spectrum (thin film/NaCl) of Compound **59**.

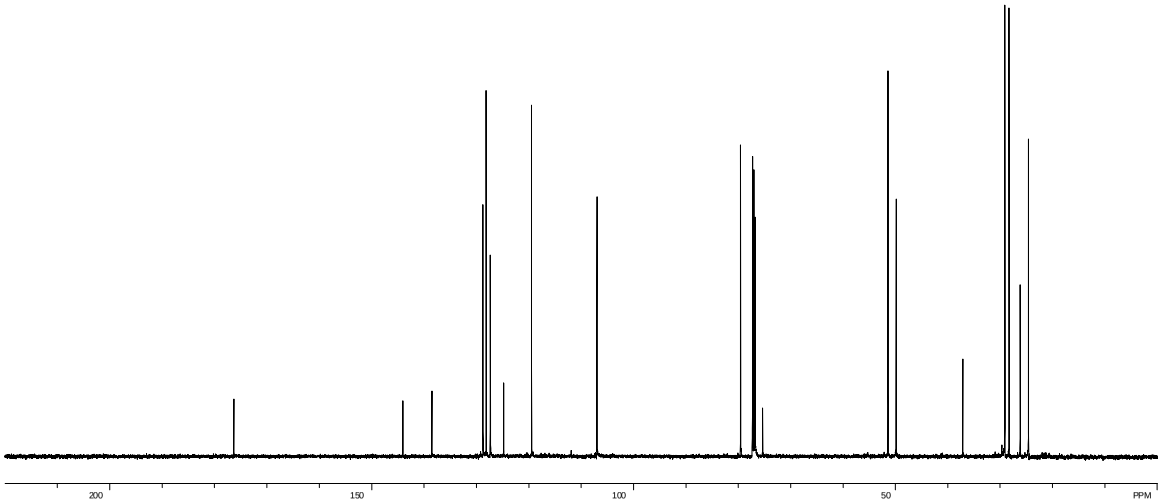


Figure A.1.33 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **59**.

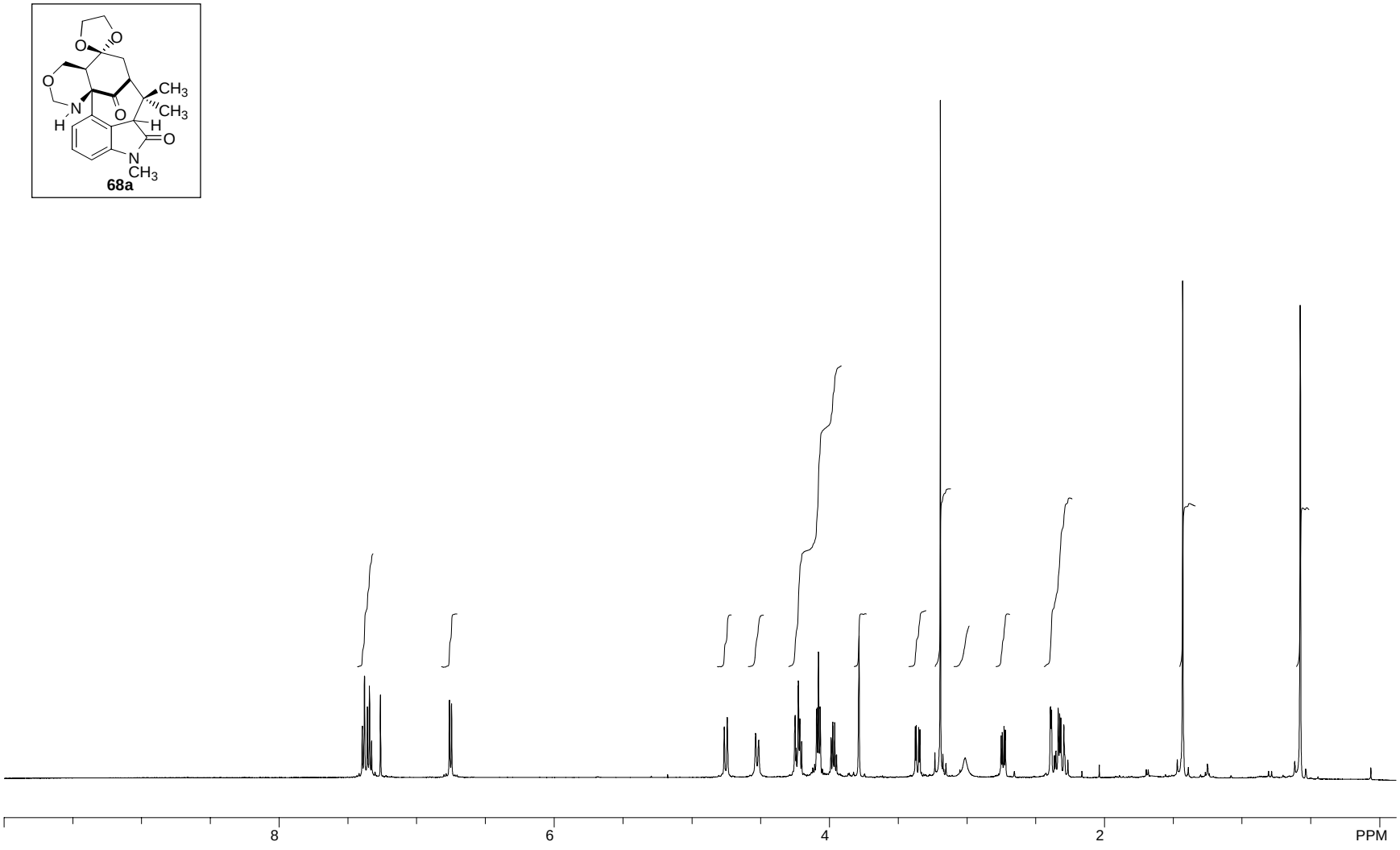


Figure A.1.34 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **68a**.

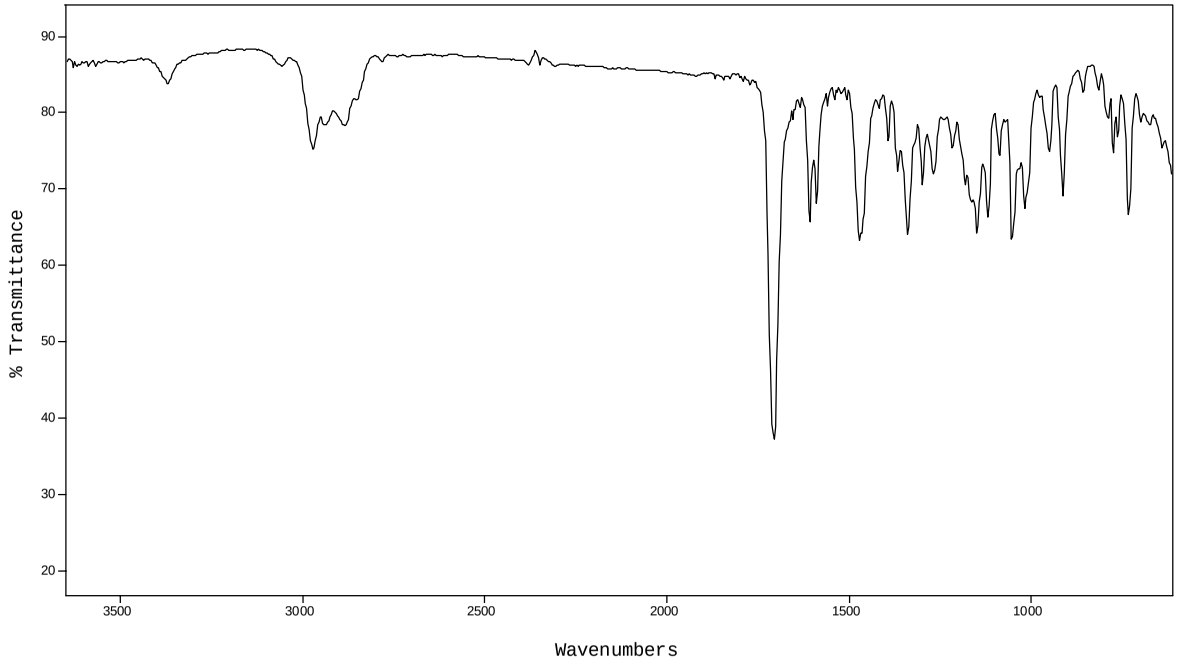


Figure A.1.35 FTIR Spectrum (thin film/NaCl) of Compound **68a**.

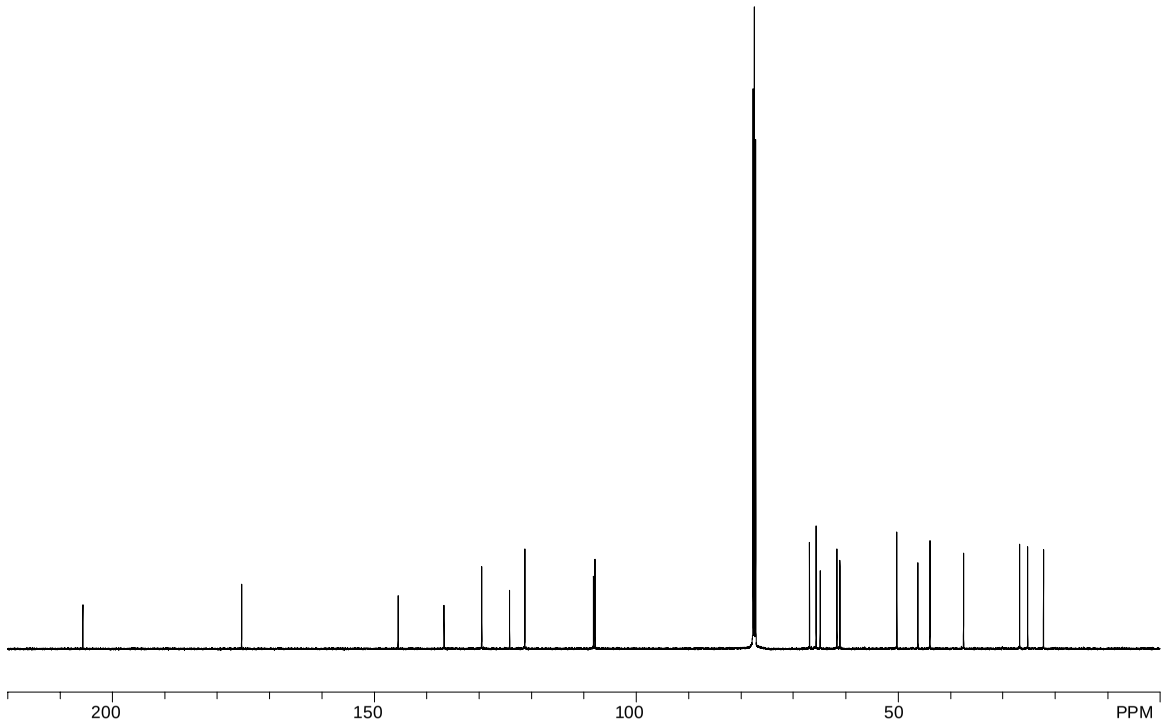


Figure A.1.36 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **68a**.

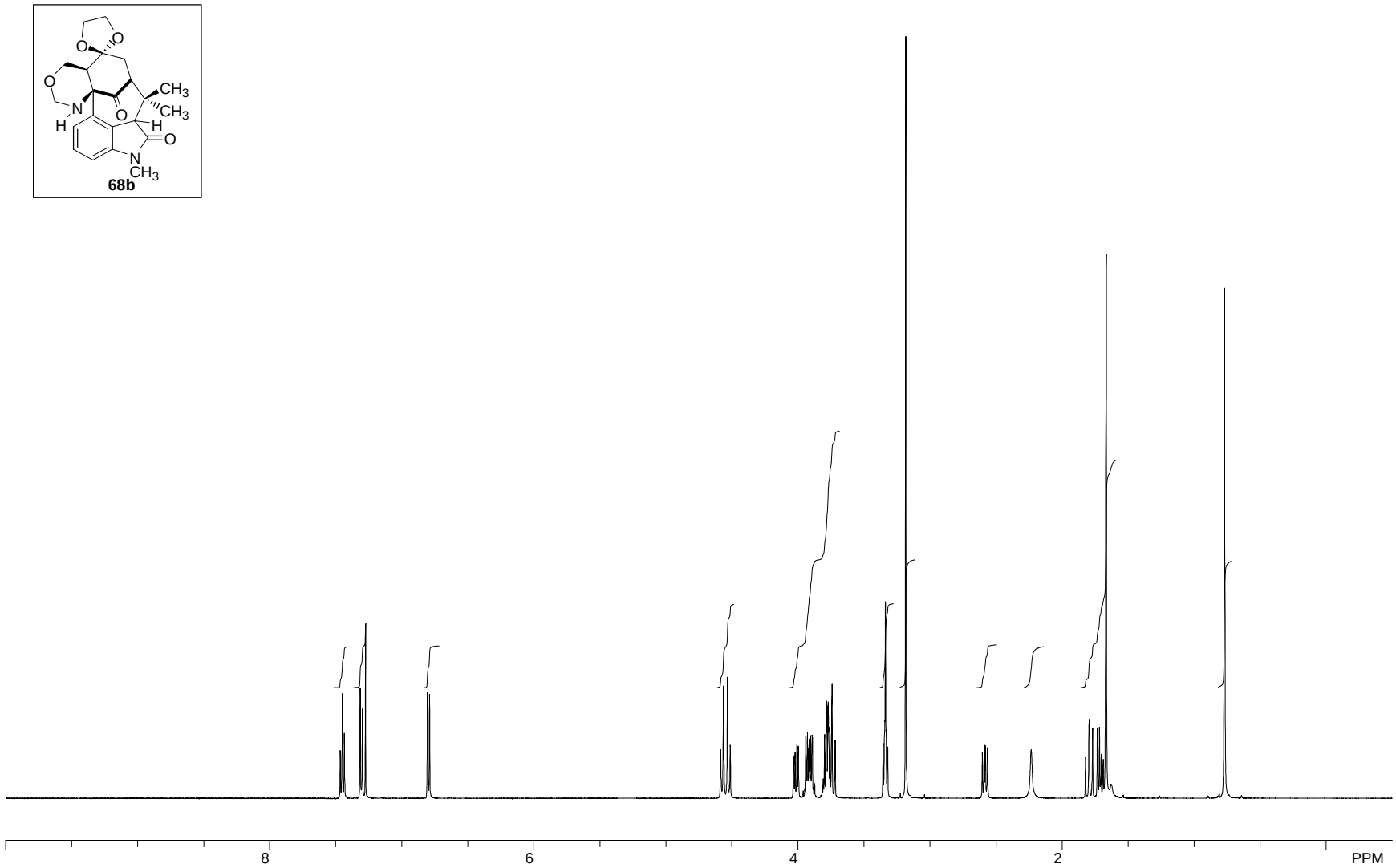


Figure A.1.37 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **68b**.

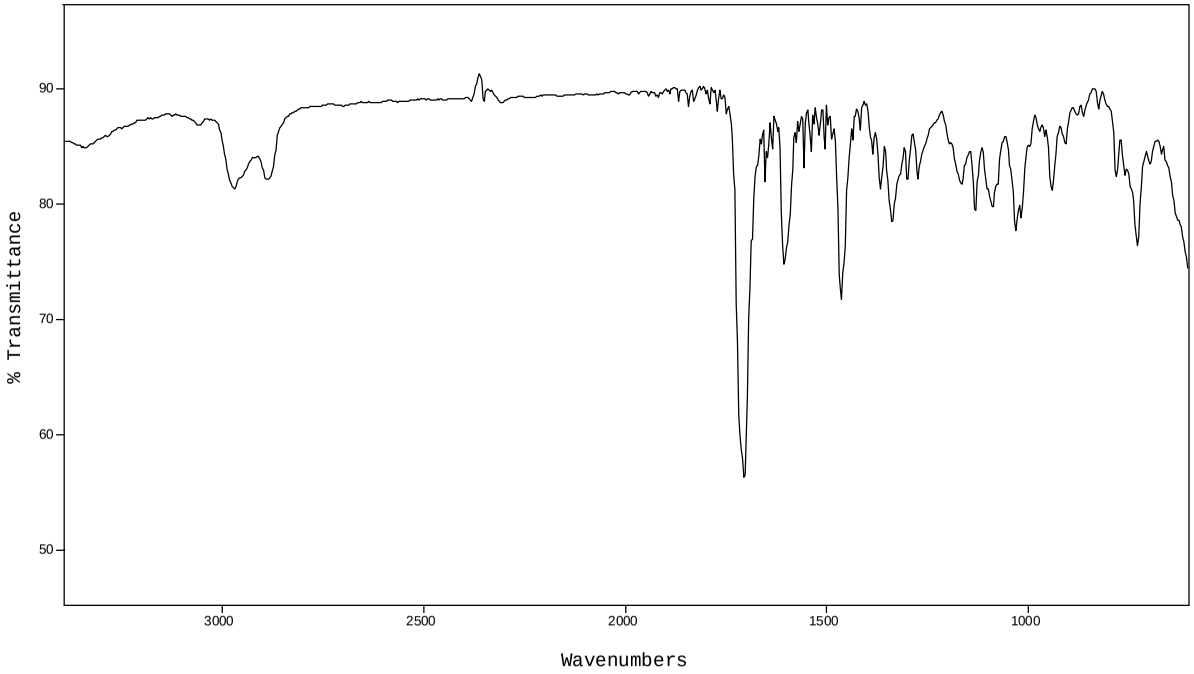


Figure A.1.38 FTIR Spectrum (thin film/NaCl) of Compound **68b**.

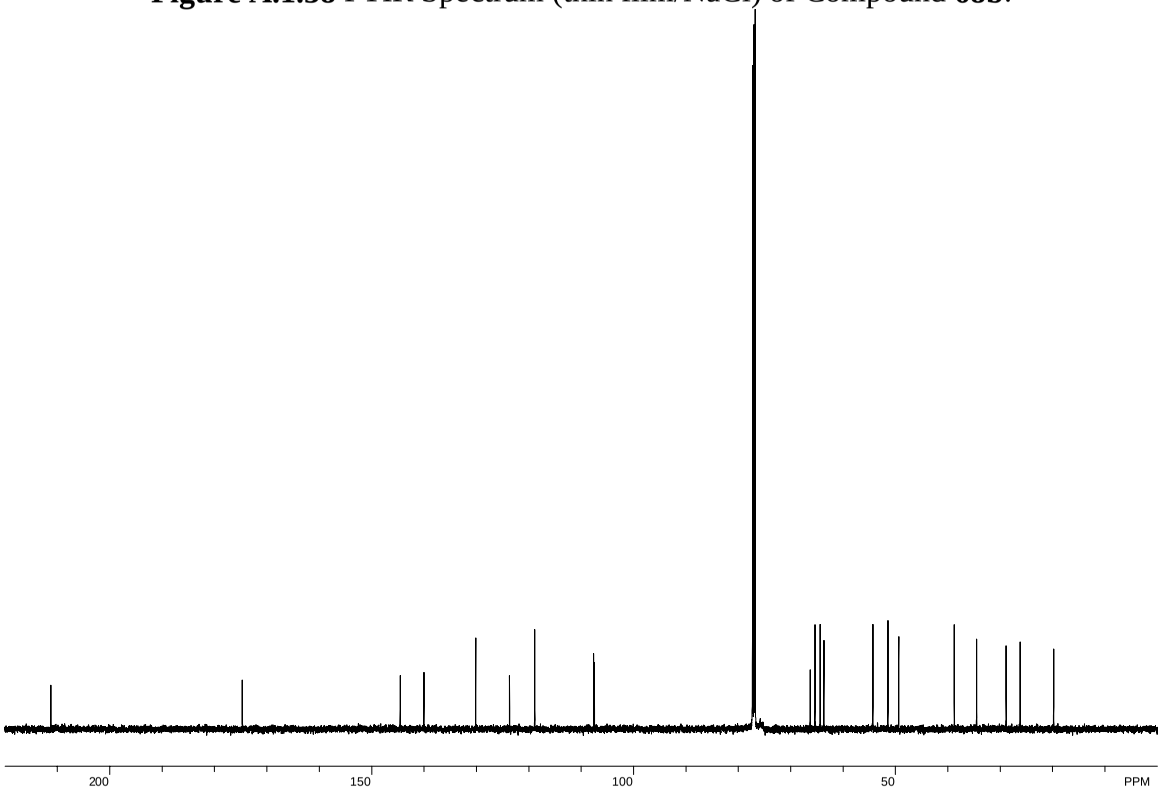


Figure A.1.39 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **68b**.

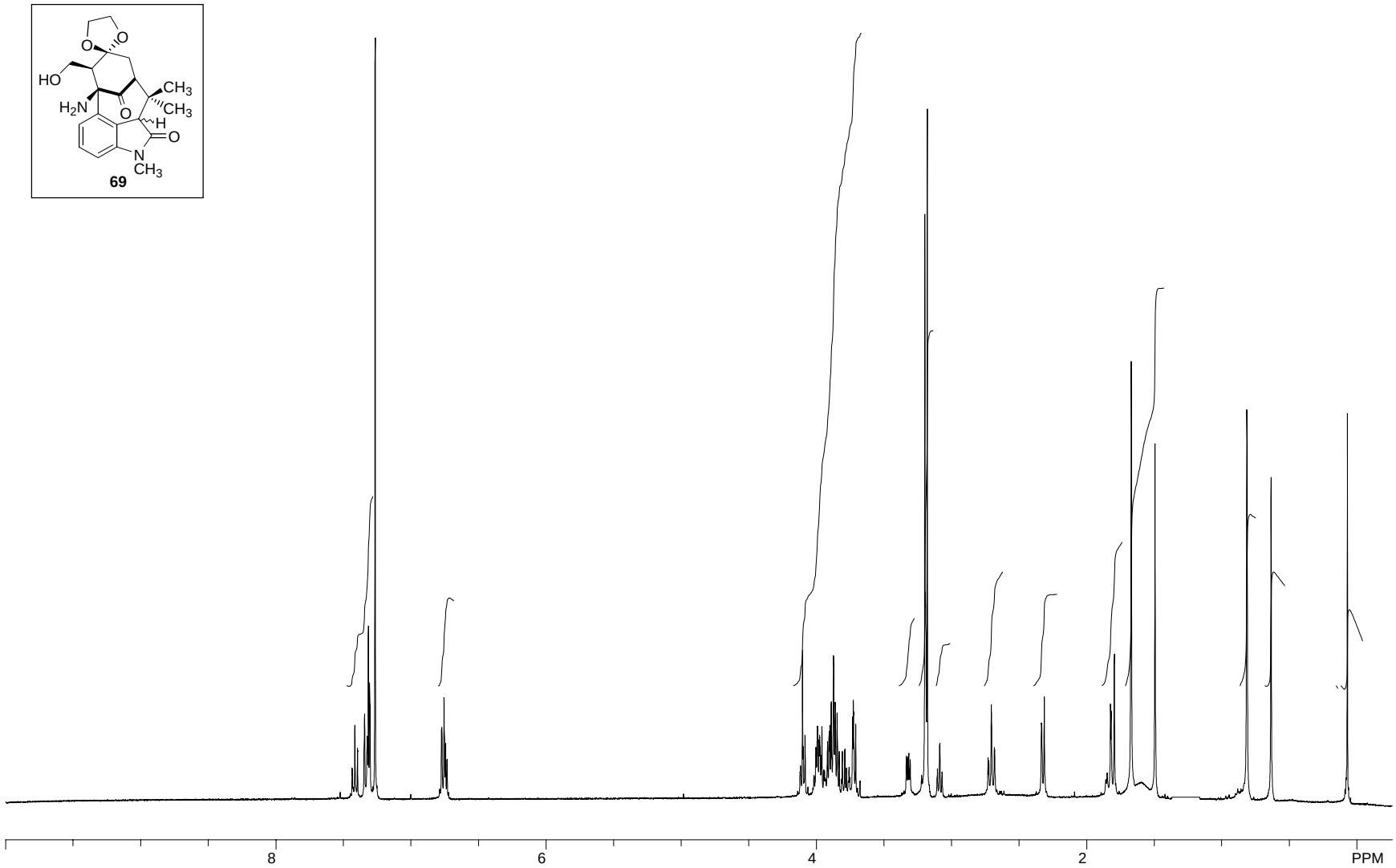


Figure A.1.40 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **69**.

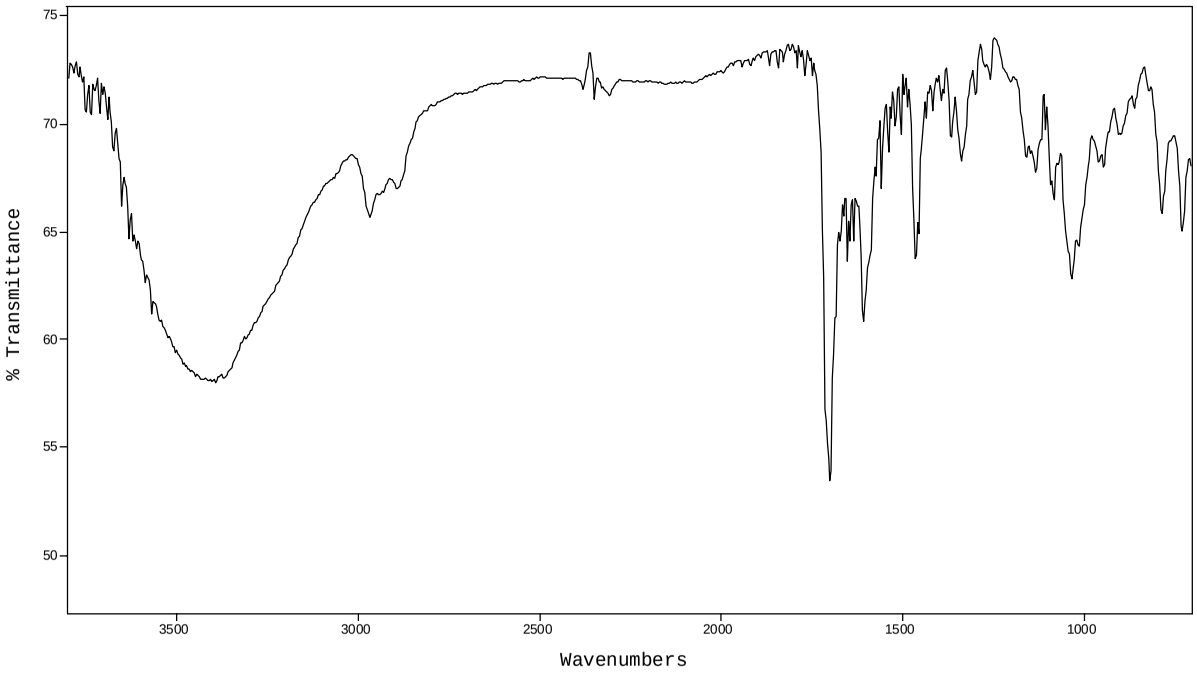


Figure A.1.41 FTIR Spectrum (thin film/NaCl) of Compound **69**.

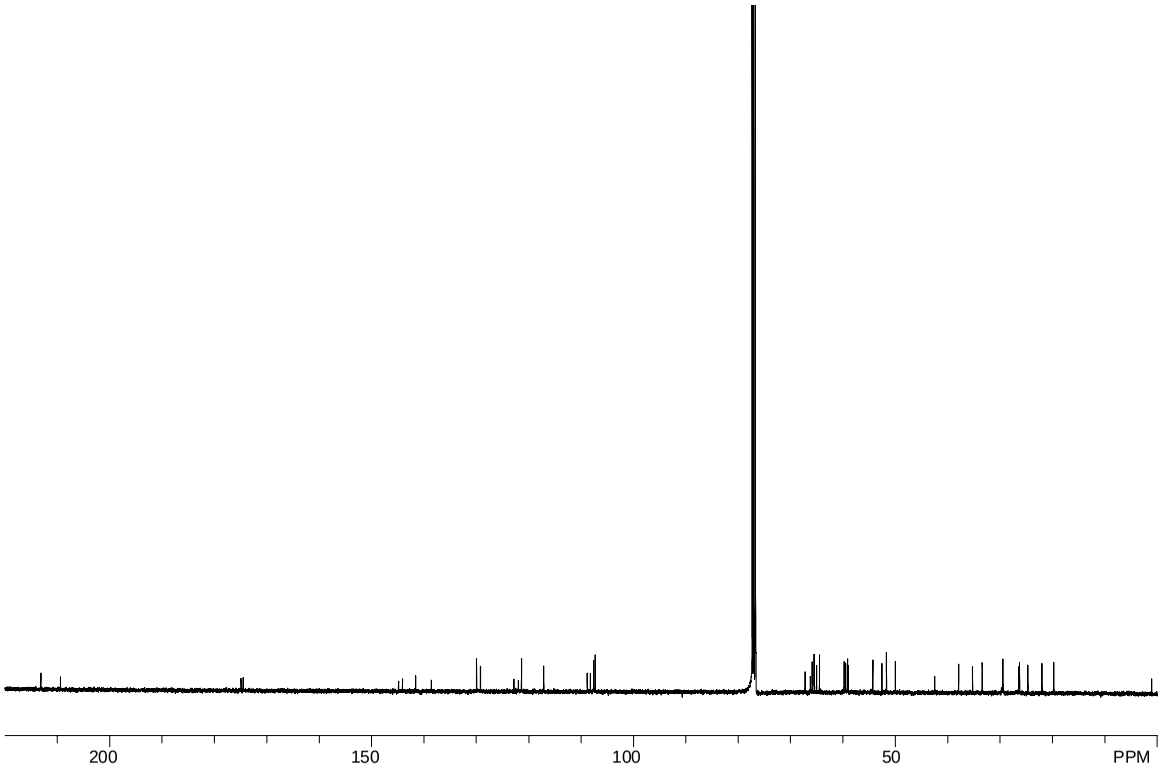


Figure A.1.42 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **69**.

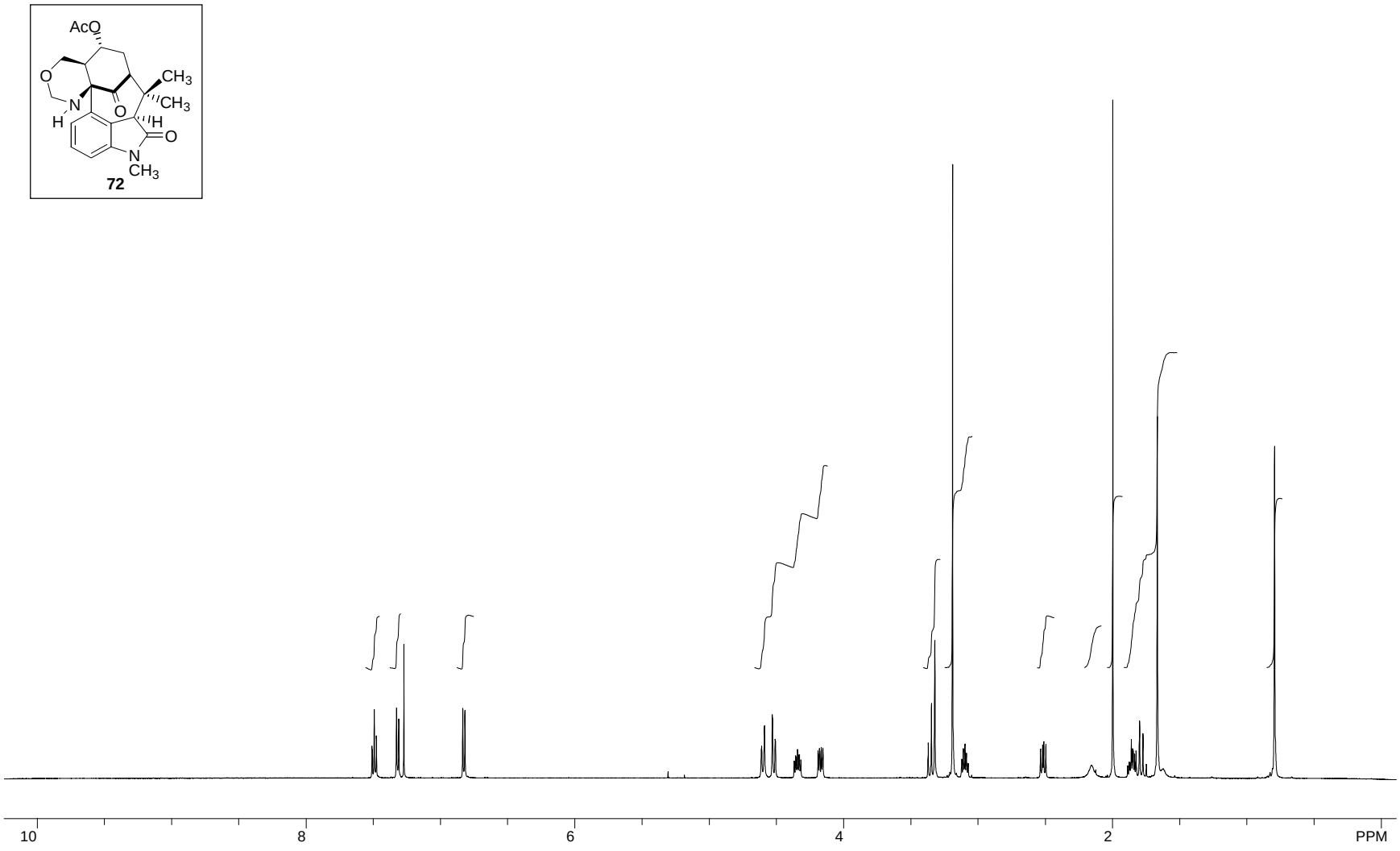


Figure A.1.43 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **72**.

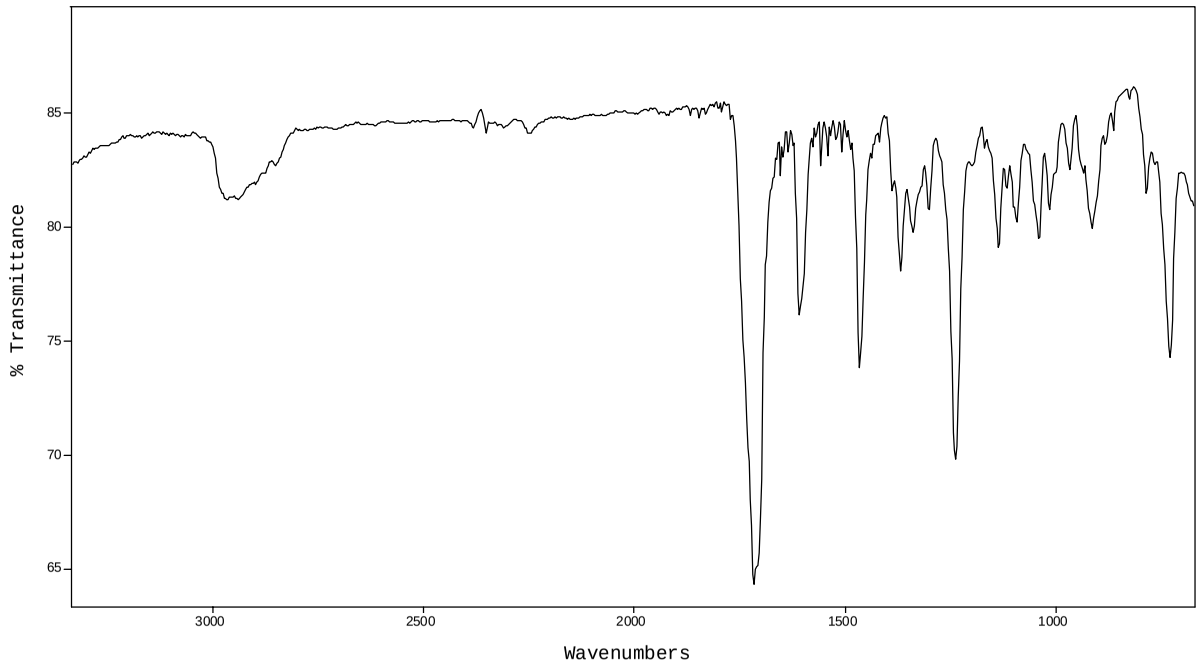


Figure A.1.44 FTIR Spectrum (thin film/NaCl) of Compound **72**.

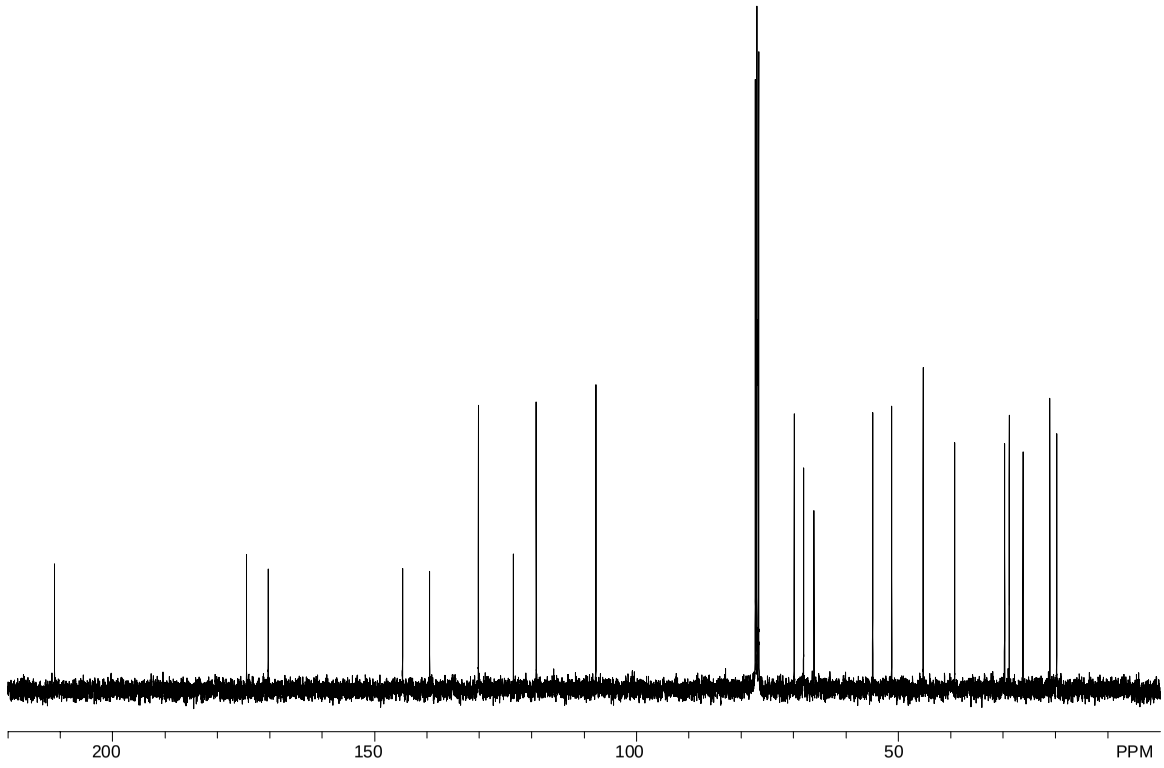


Figure A.1.45 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **72**.

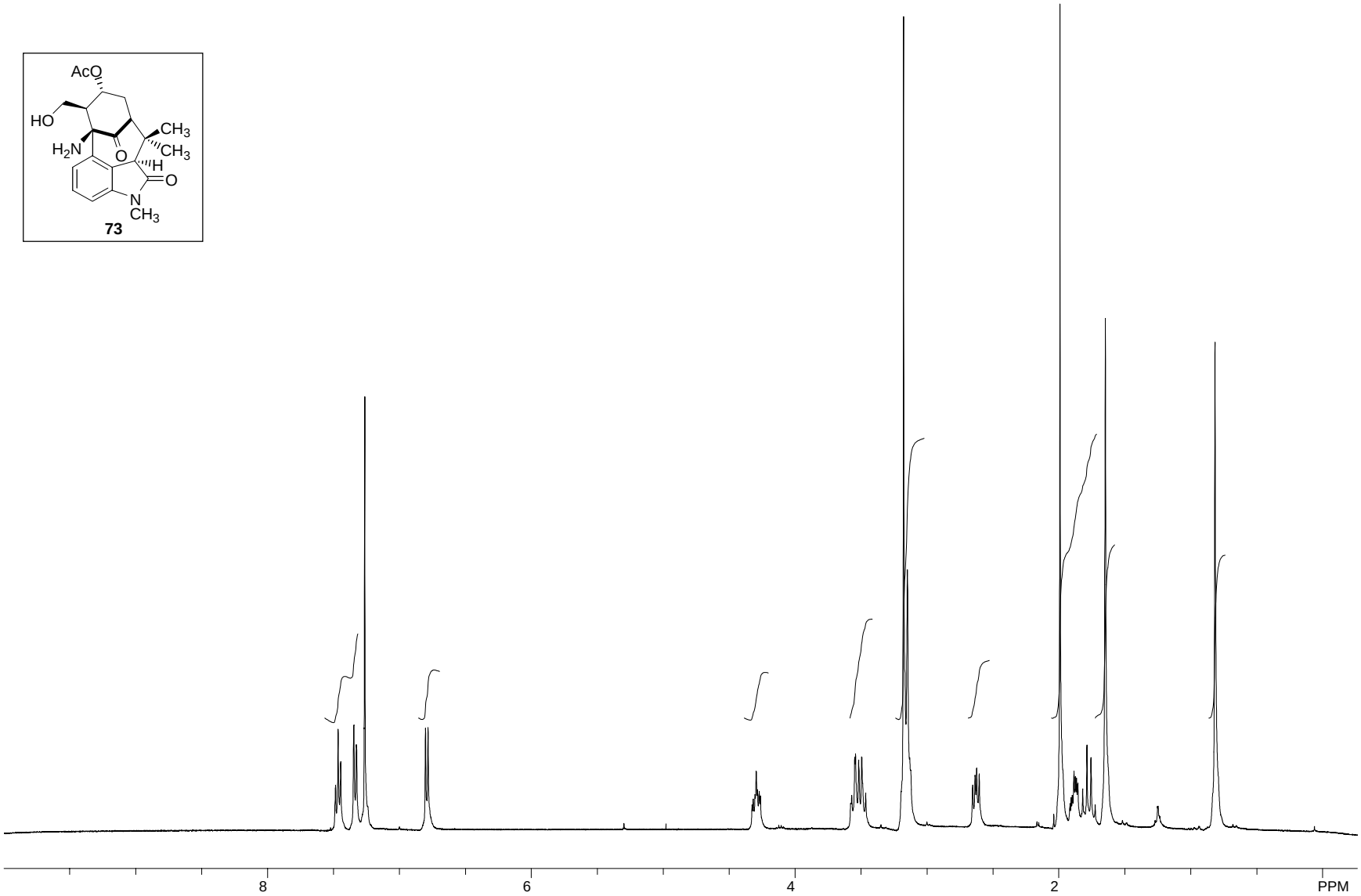


Figure A.1.46 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **73**.

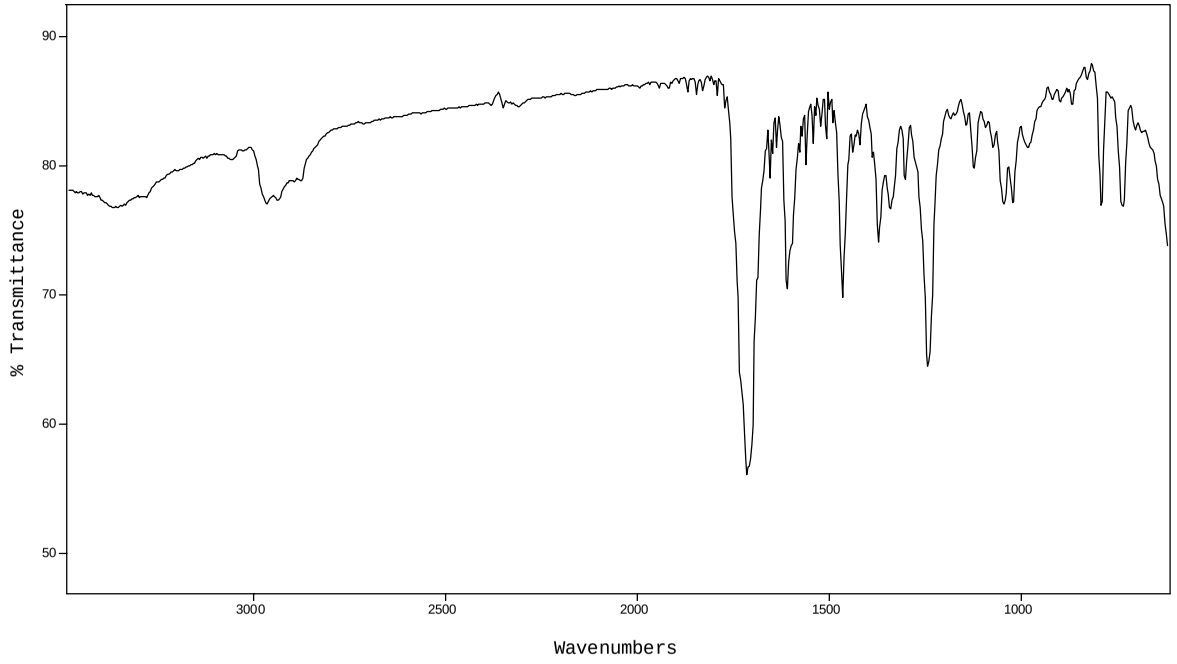


Figure A.1.47 FTIR Spectrum (thin film/NaCl) of Compound **73**.

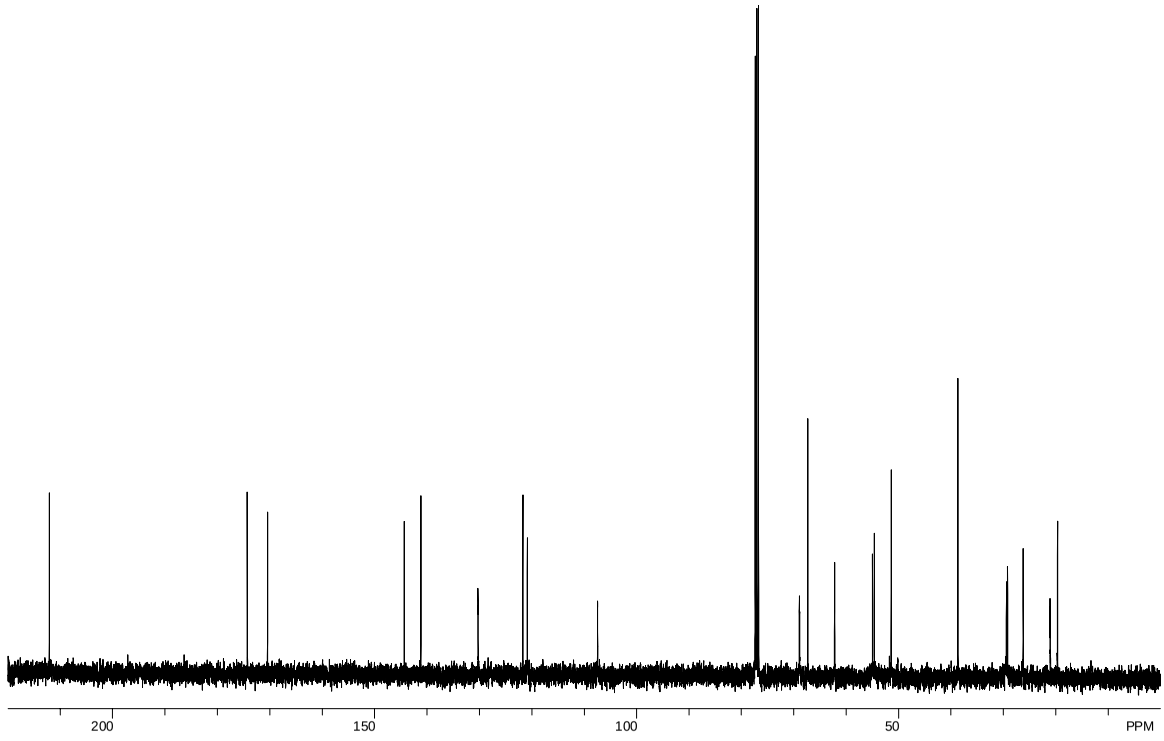


Figure A.1.48 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **73**.

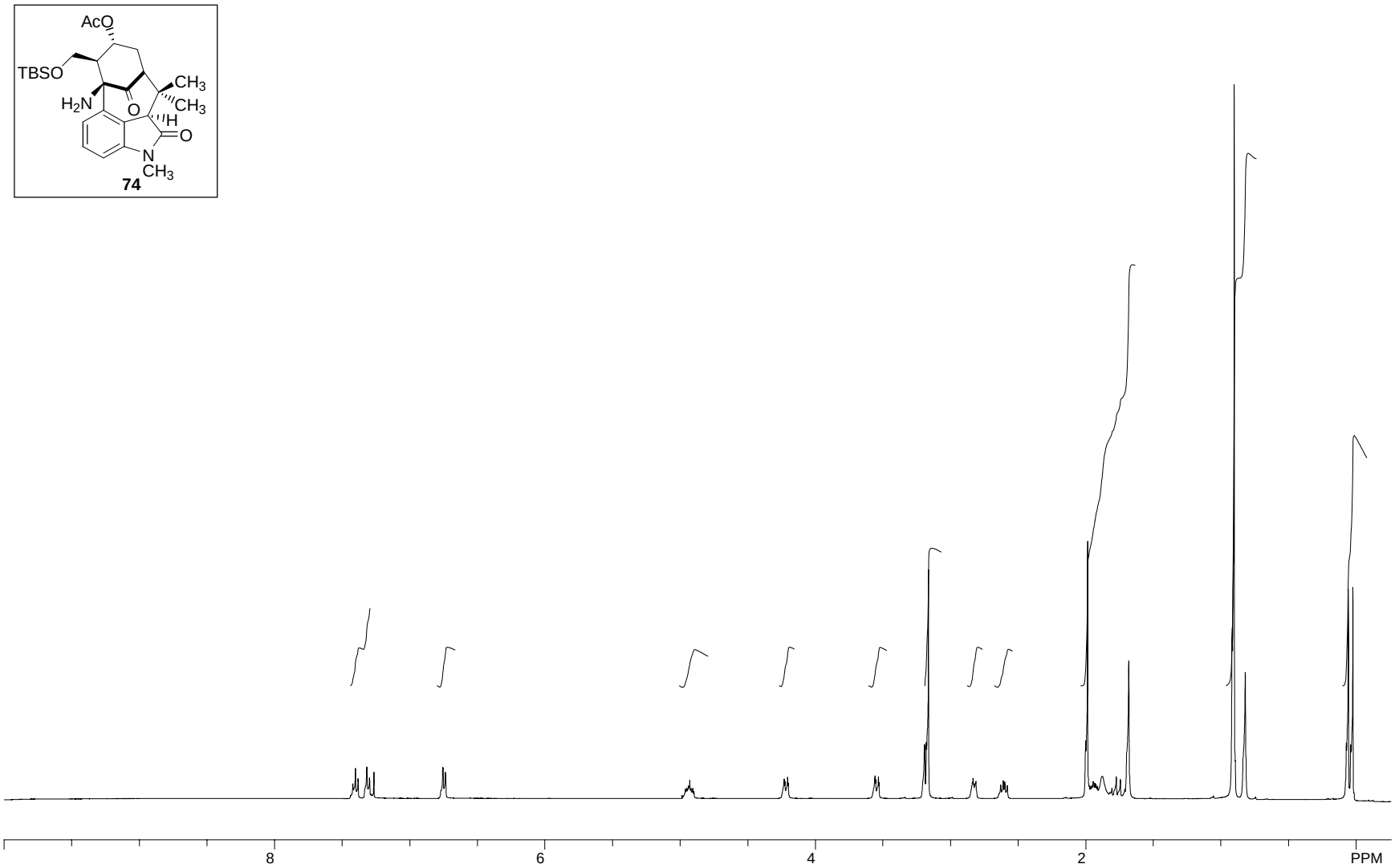


Figure A.1.49 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **74**.

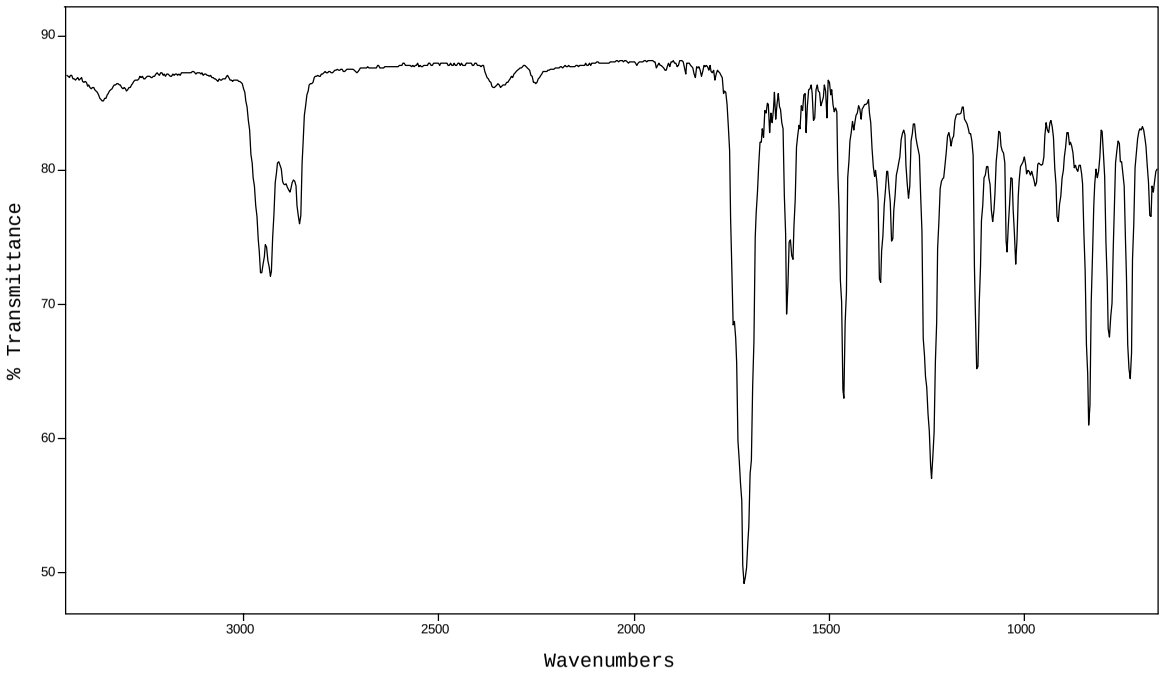


Figure A.1.50 FTIR Spectrum (thin film/NaCl) of Compound **74**.

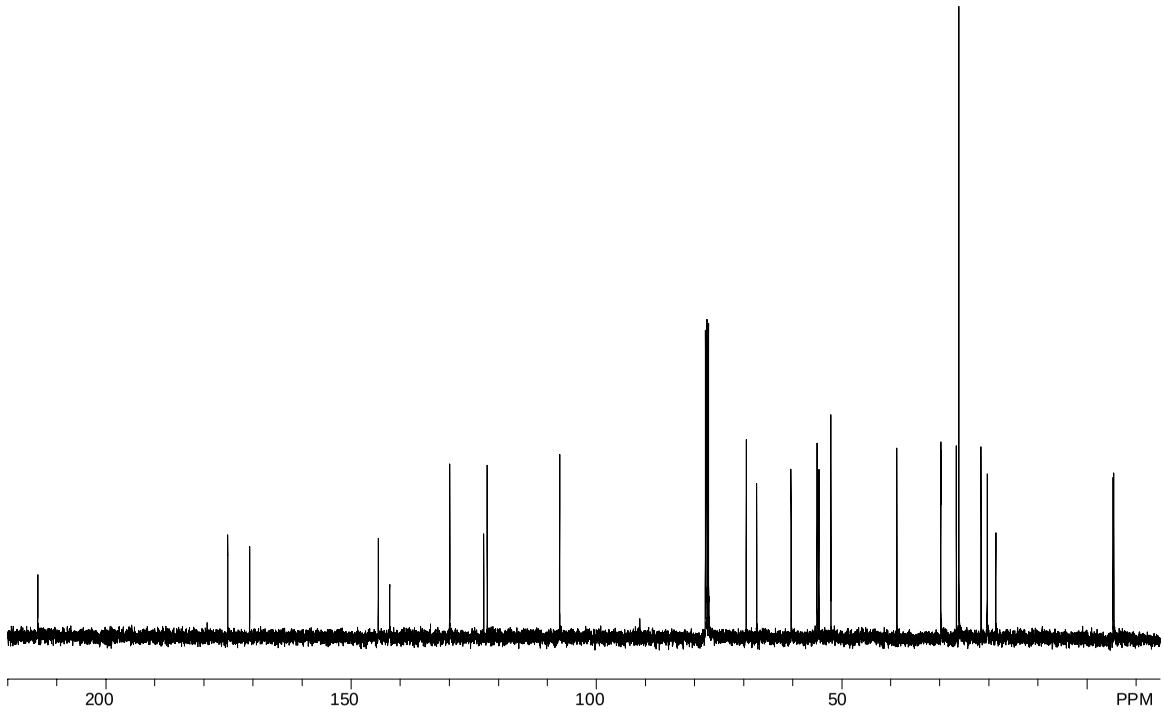


Figure A.1.51 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **74**.

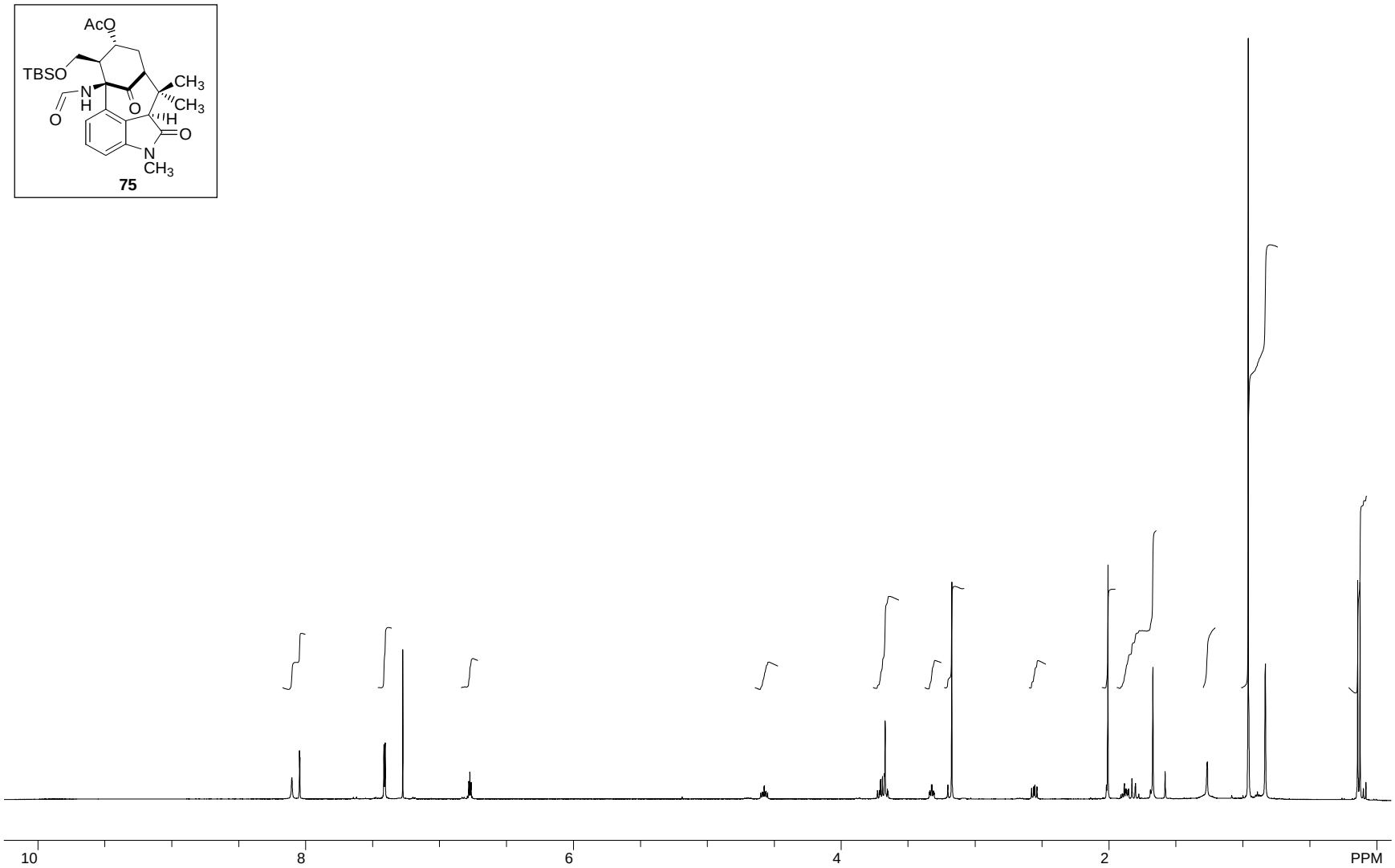


Figure A.1.52 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **75**.

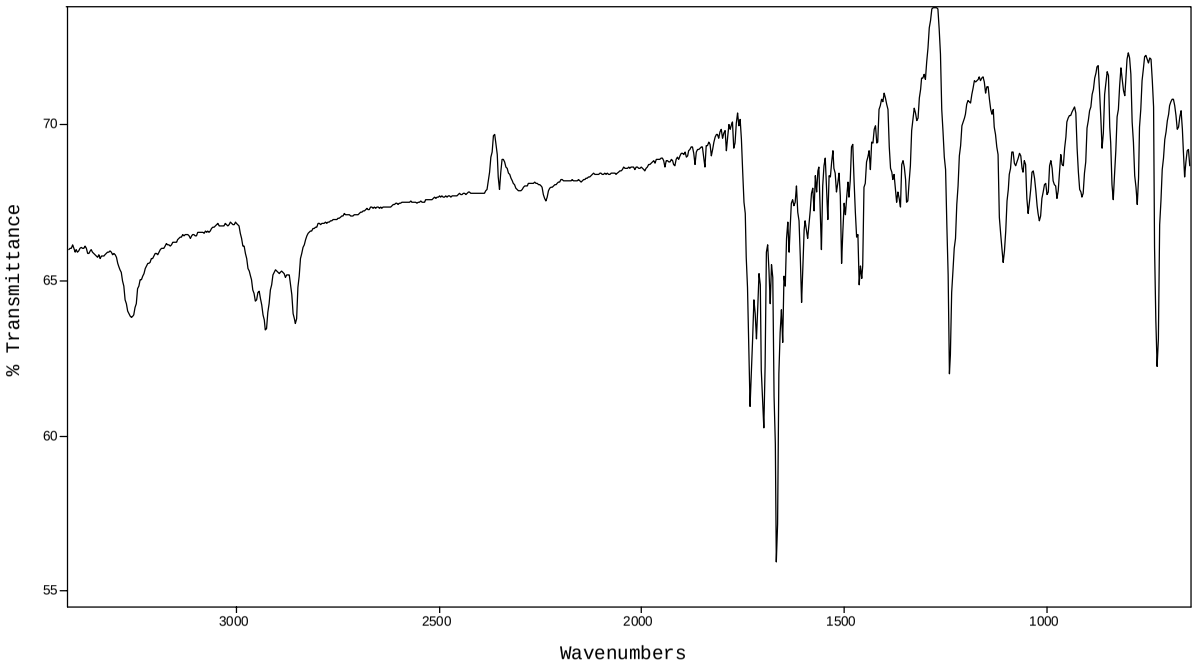


Figure A.1.53 FTIR Spectrum (thin film/NaCl) of Compound **75**.

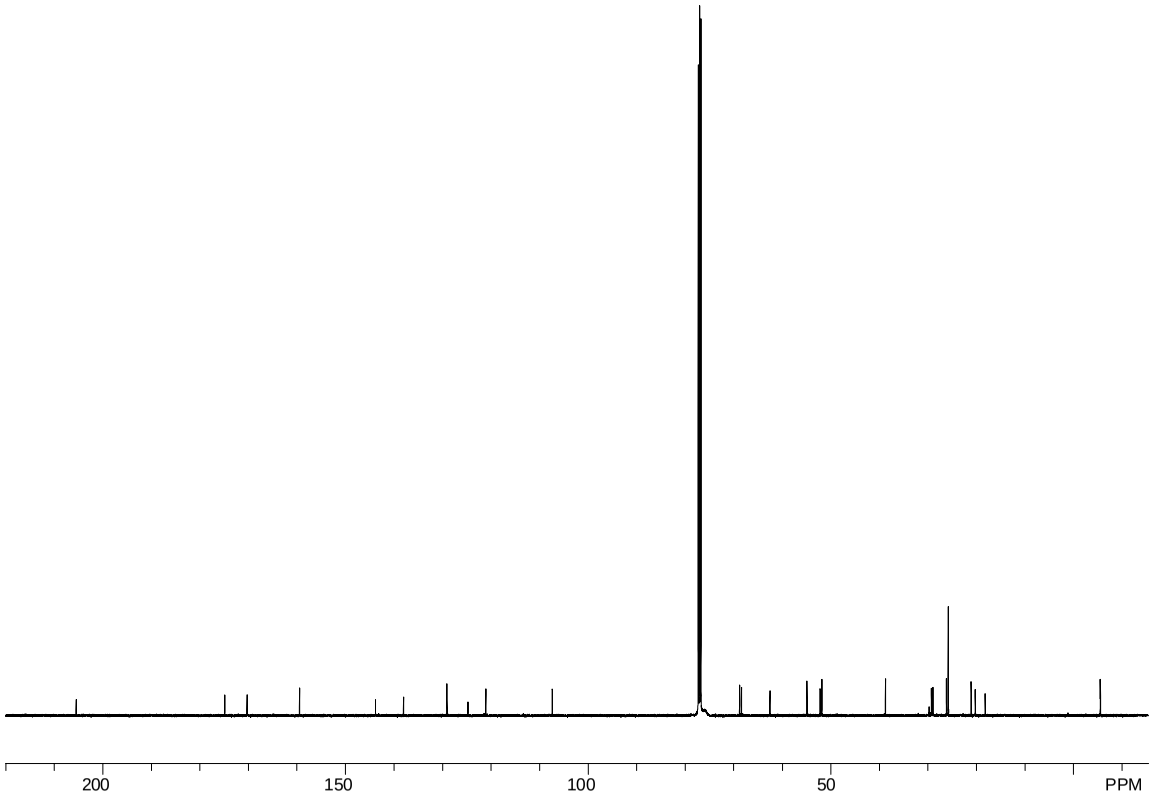


Figure A.1.54 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **75**.

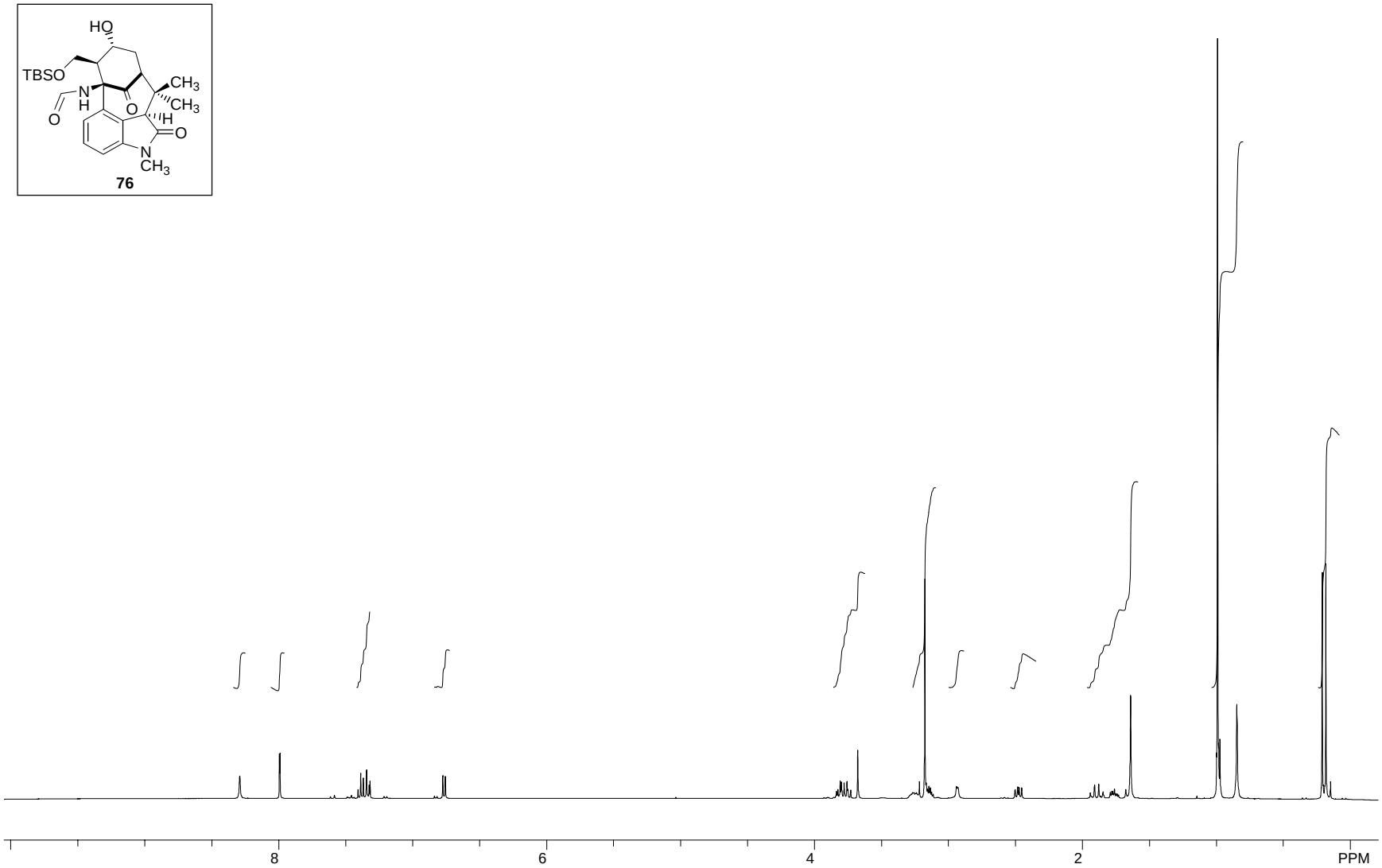


Figure A.1.55 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **76**.

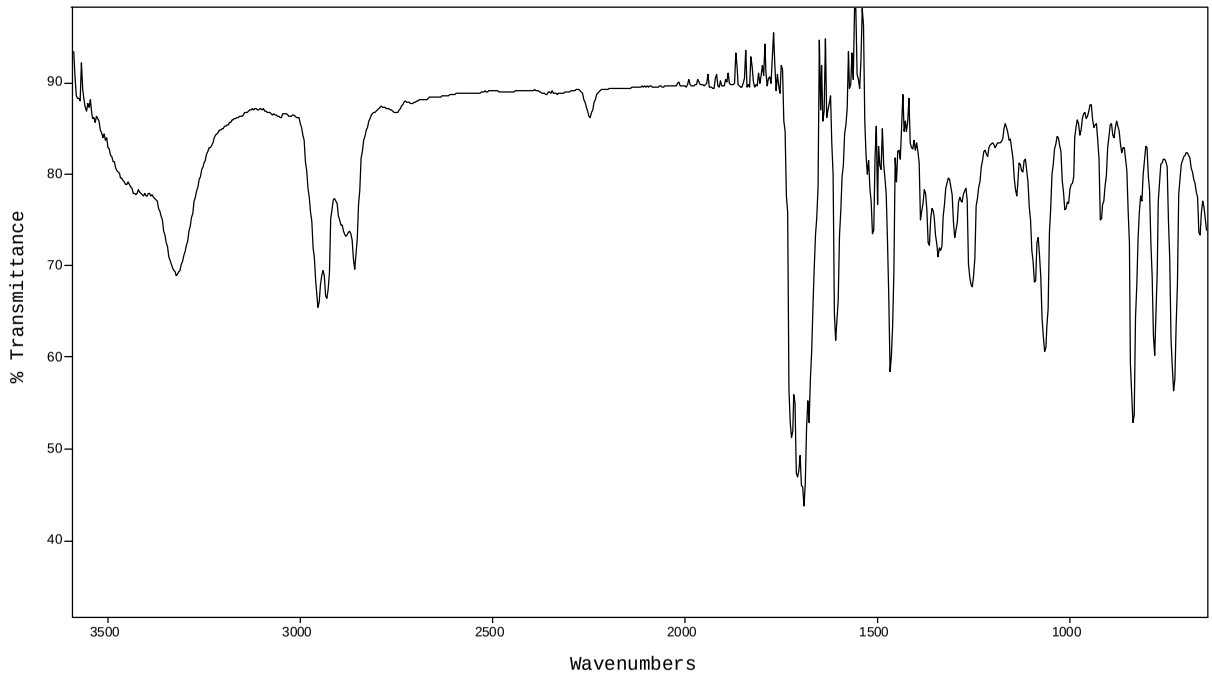


Figure A.56 FTIR Spectrum (thin film/NaCl) of Compound **76**.

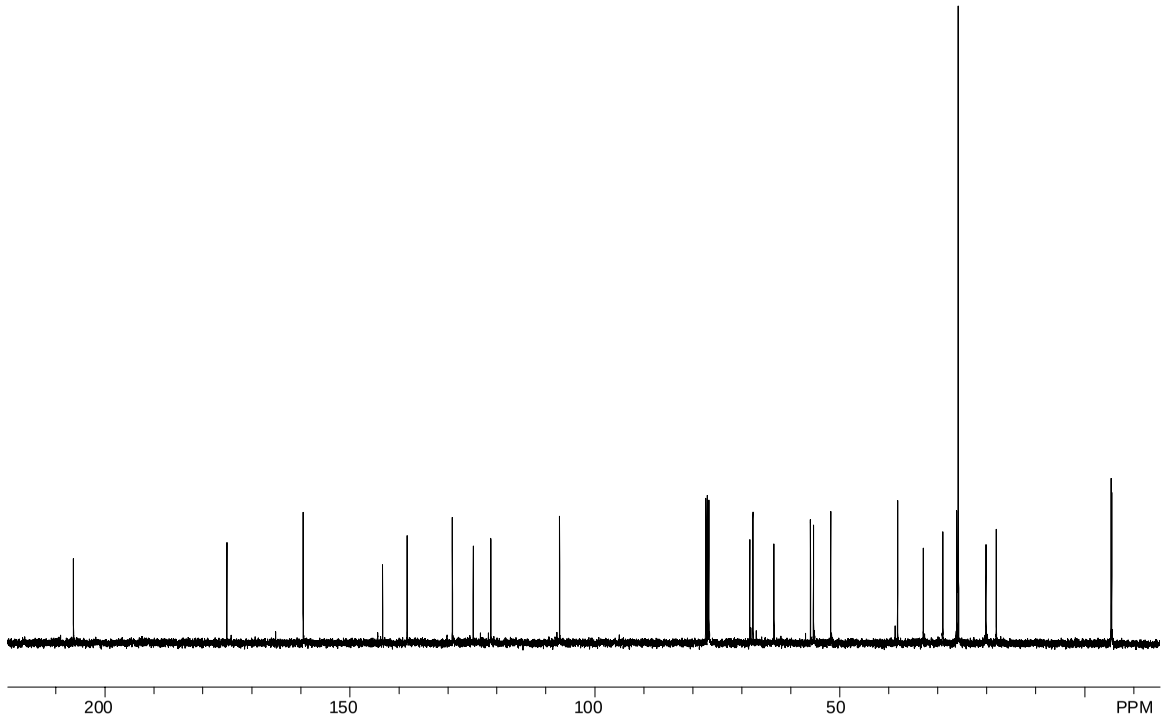


Figure A.1.57 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **76.**

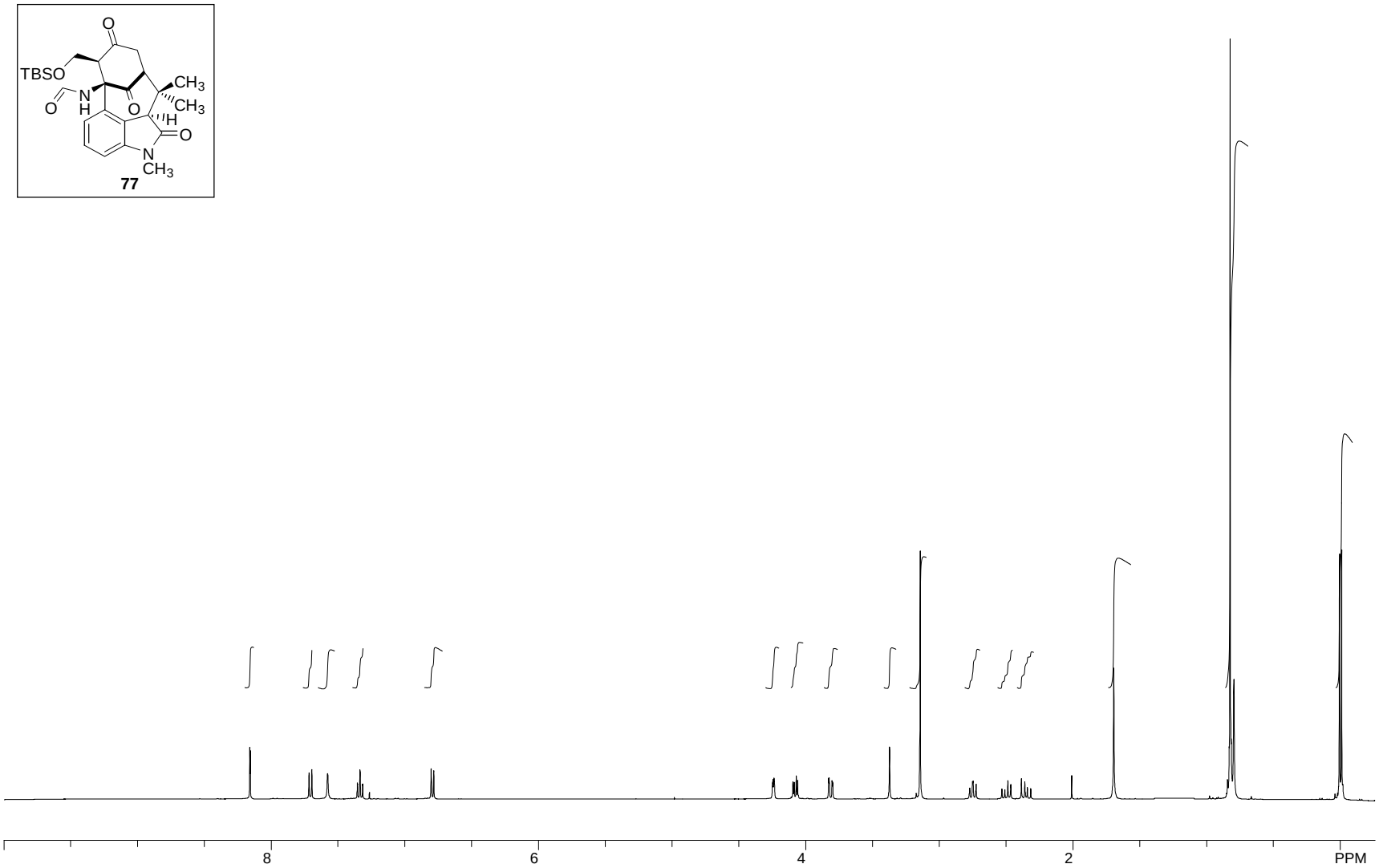


Figure A.1.58 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **77**.

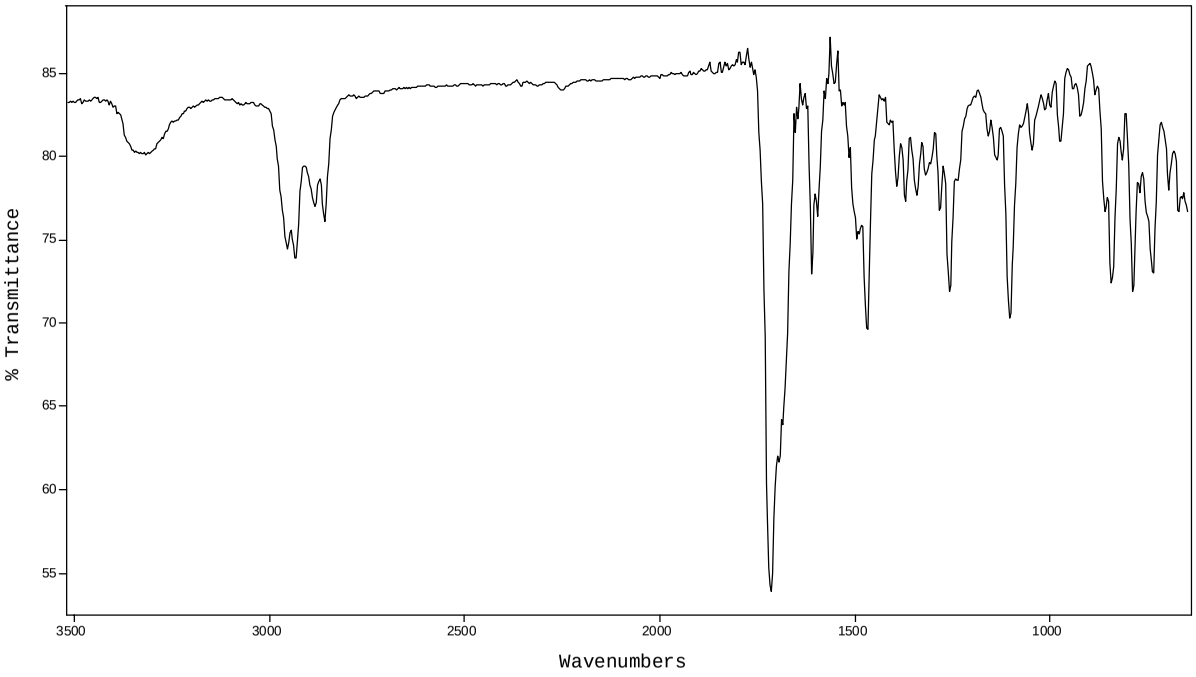


Figure A.1.59 FTIR Spectrum (thin film/NaCl) of Compound **77**.

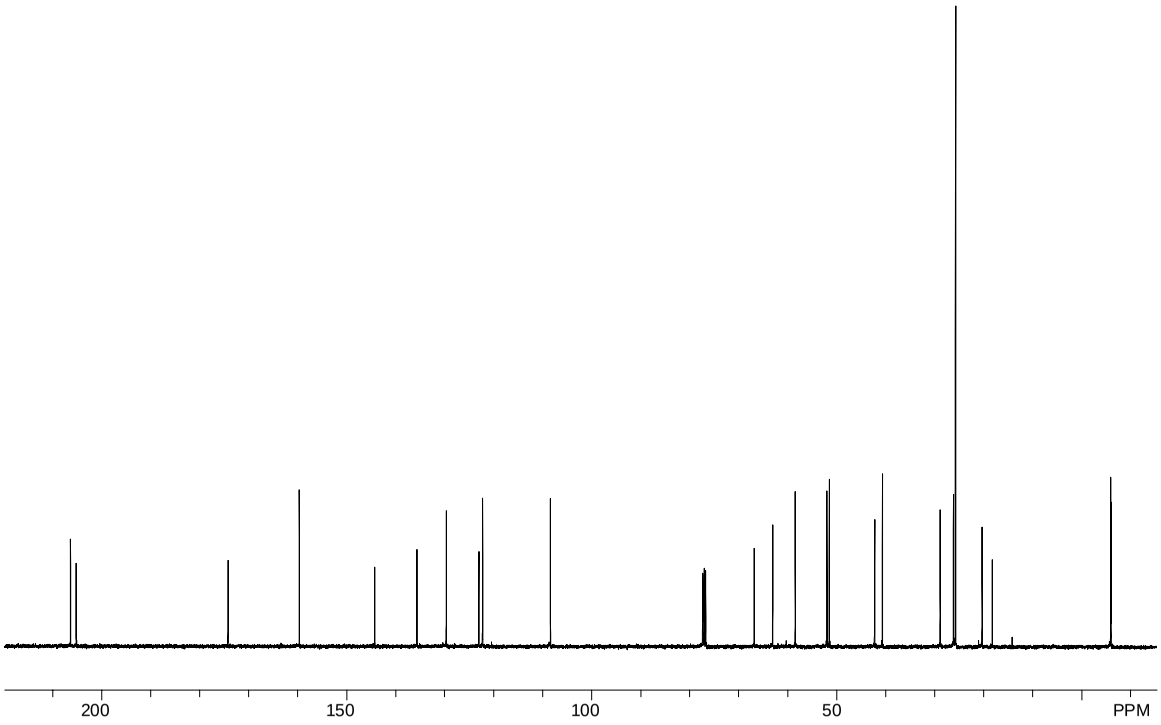


Figure A.1.60 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **77**.

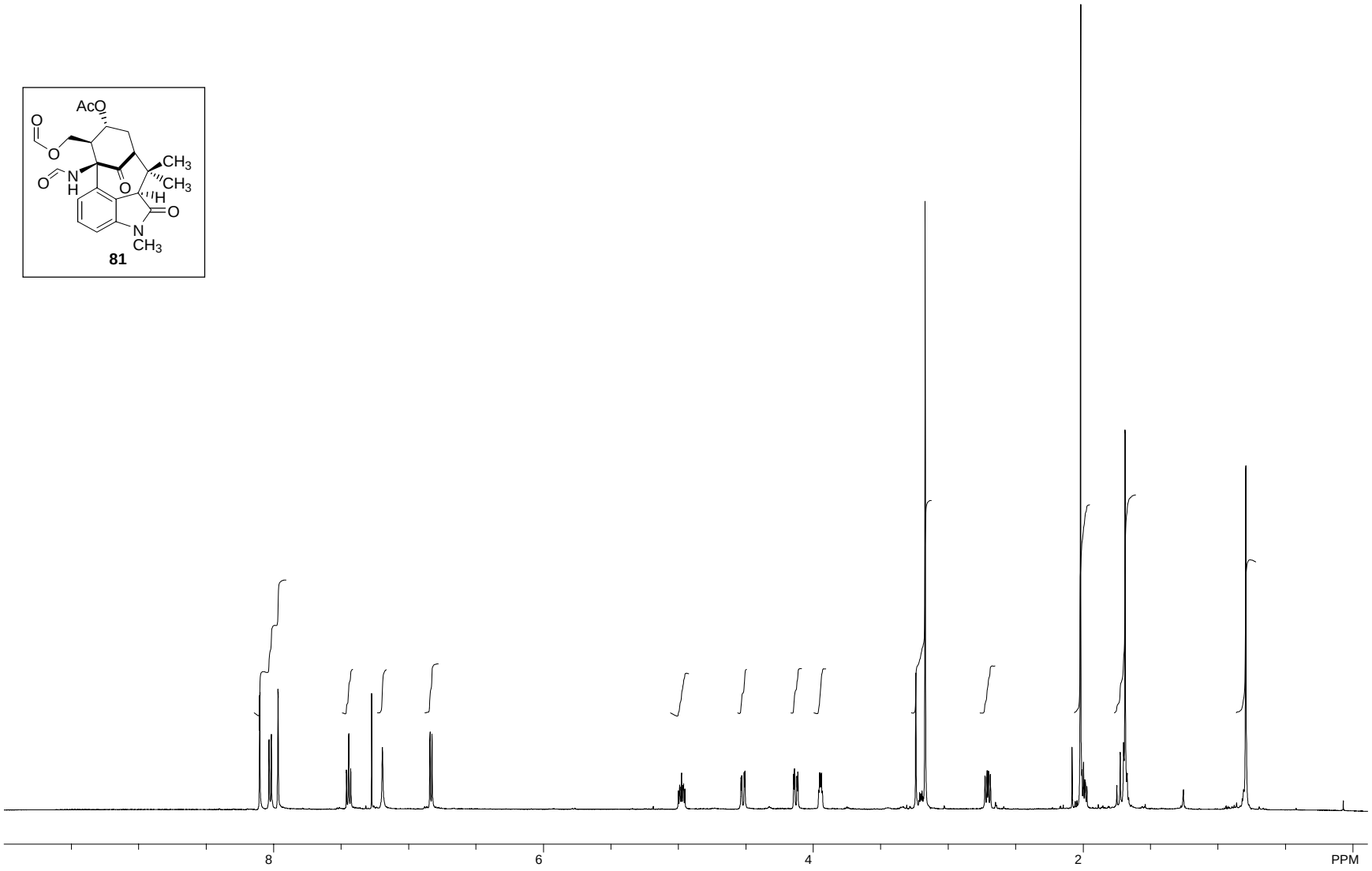


Figure A.1.61 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **81**.

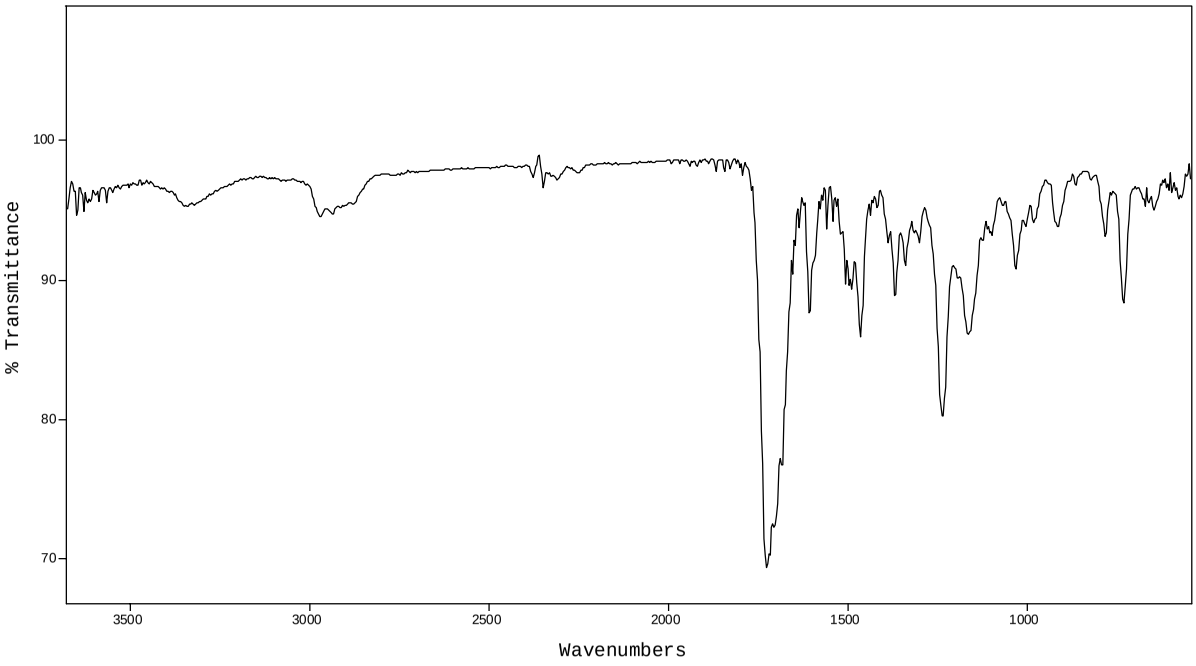


Figure A.1.62 FTIR Spectrum (thin film/NaCl) of Compound **81**.

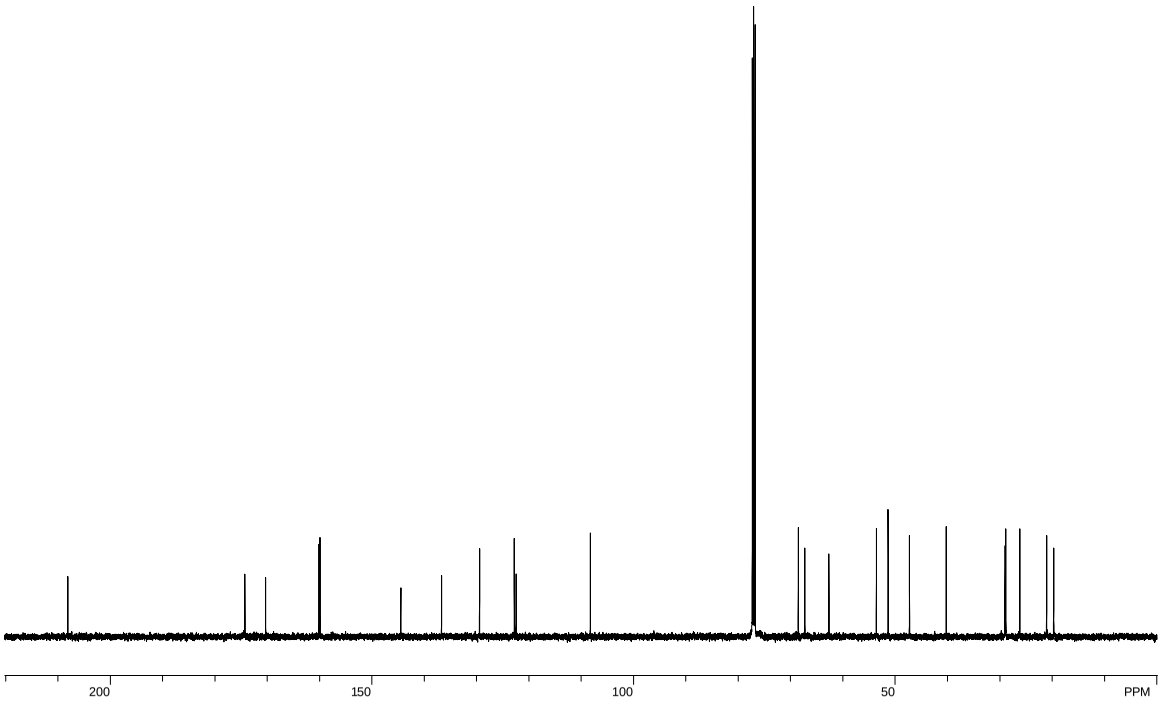


Figure A.1.63 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **81**.

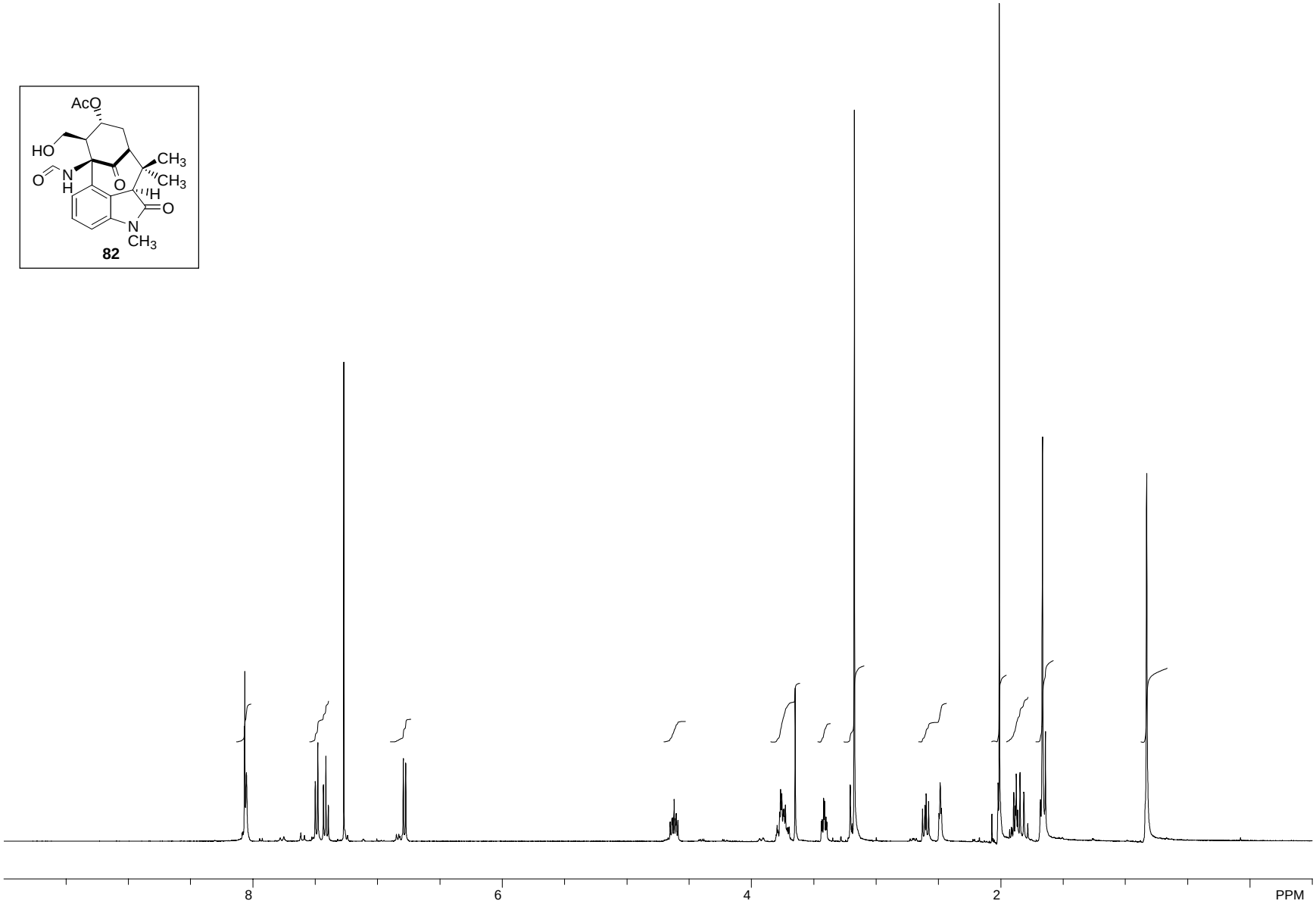


Figure A.1.64 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **82**.

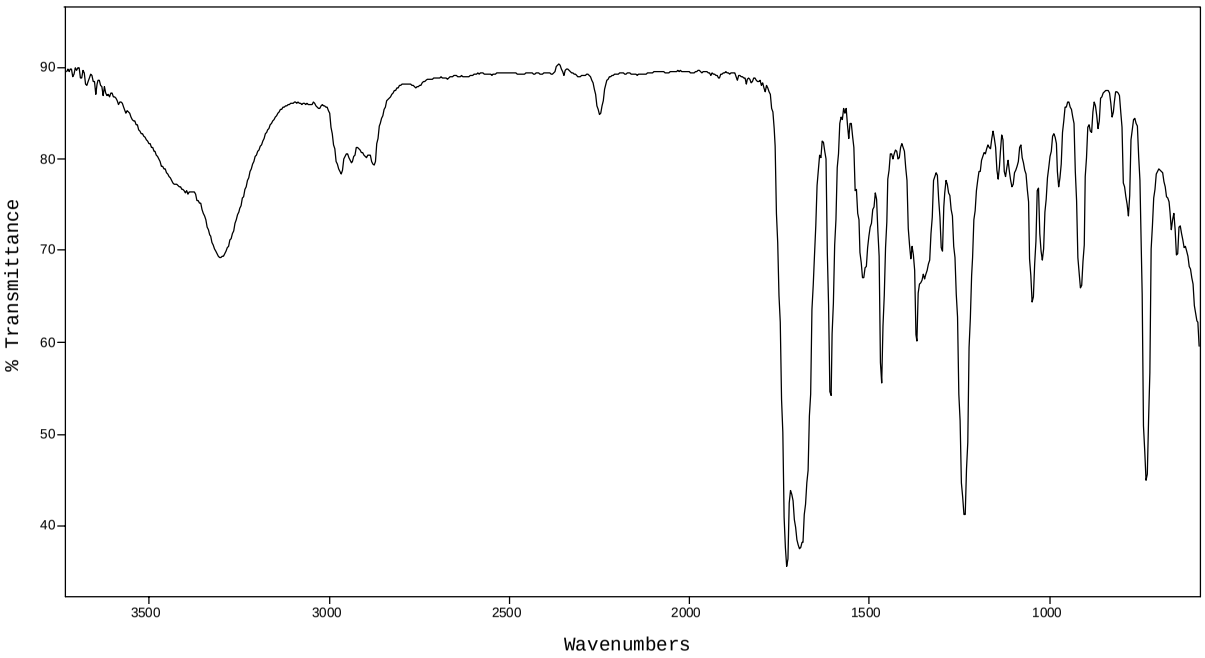


Figure A.1.65 FTIR Spectrum (thin film/NaCl) of Compound **82**.

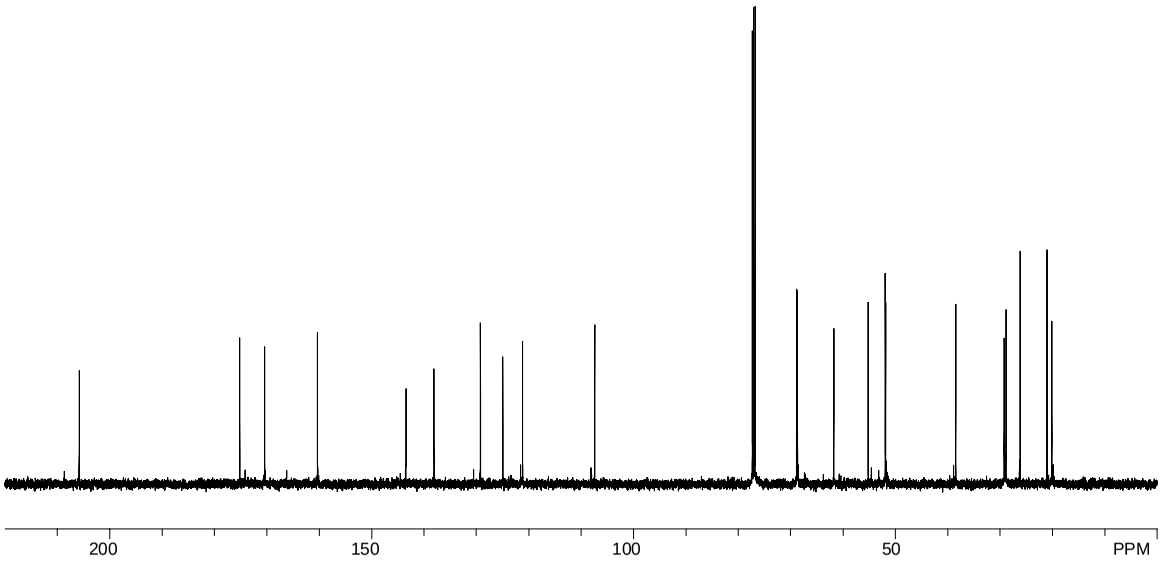


Figure A.1.66 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **82**.

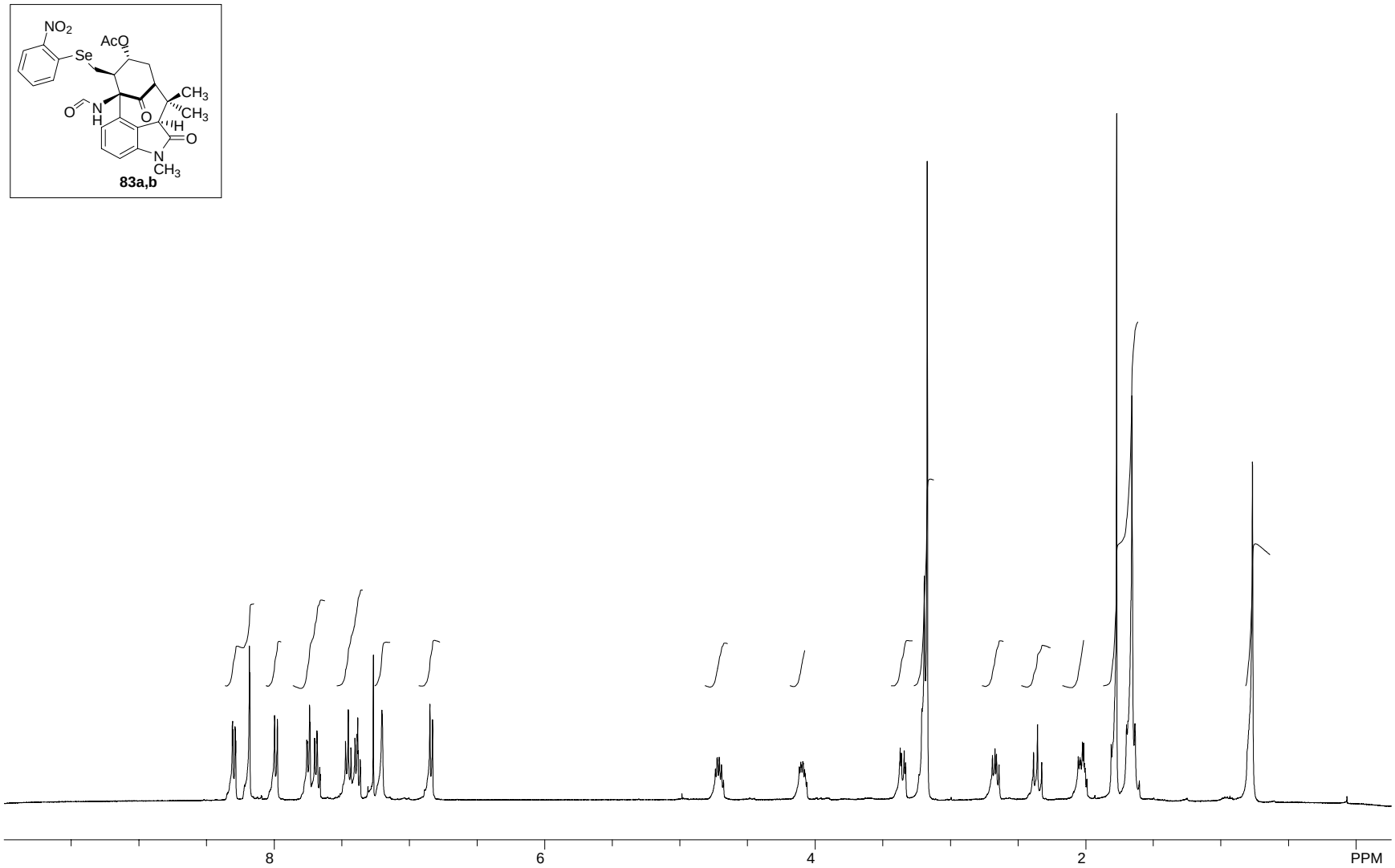


Figure A.1.67 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **83a**.

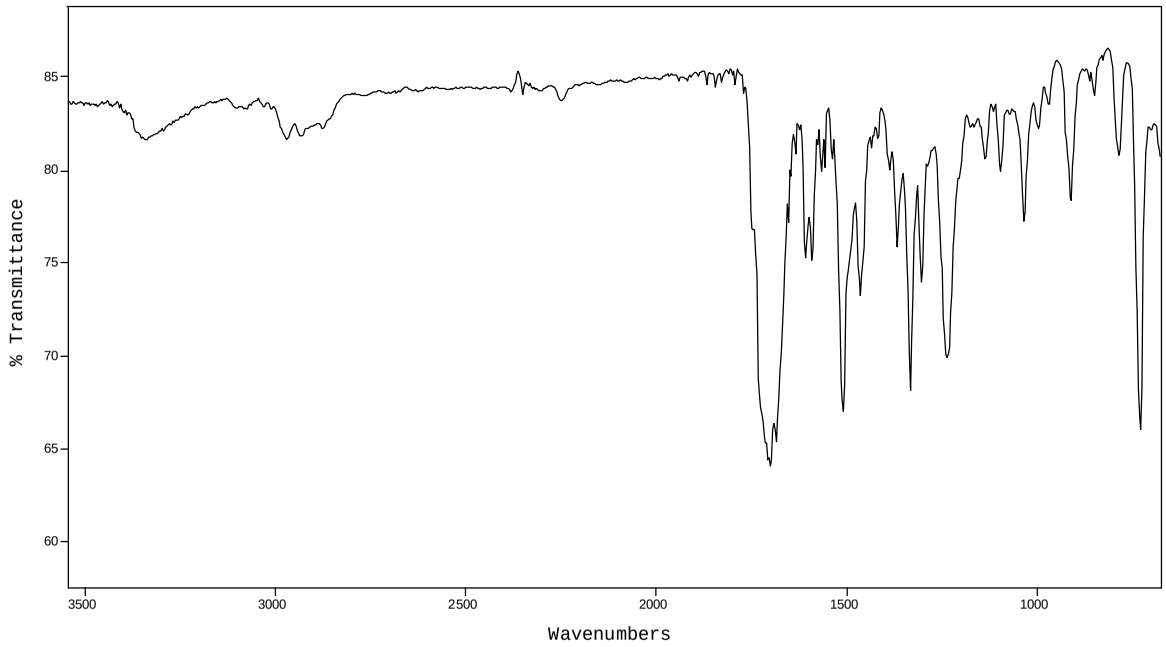


Figure A.68 FTIR Spectrum (thin film/NaCl) of Compound **83a**.

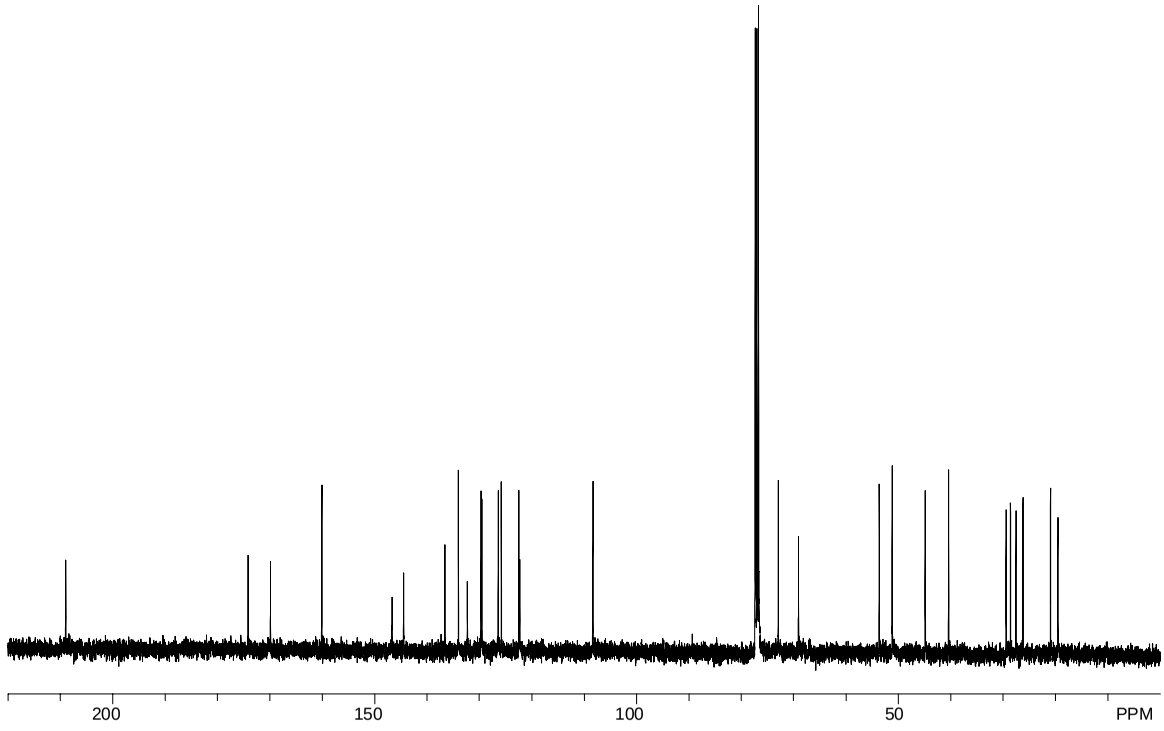


Figure A.1.69 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **83a.**

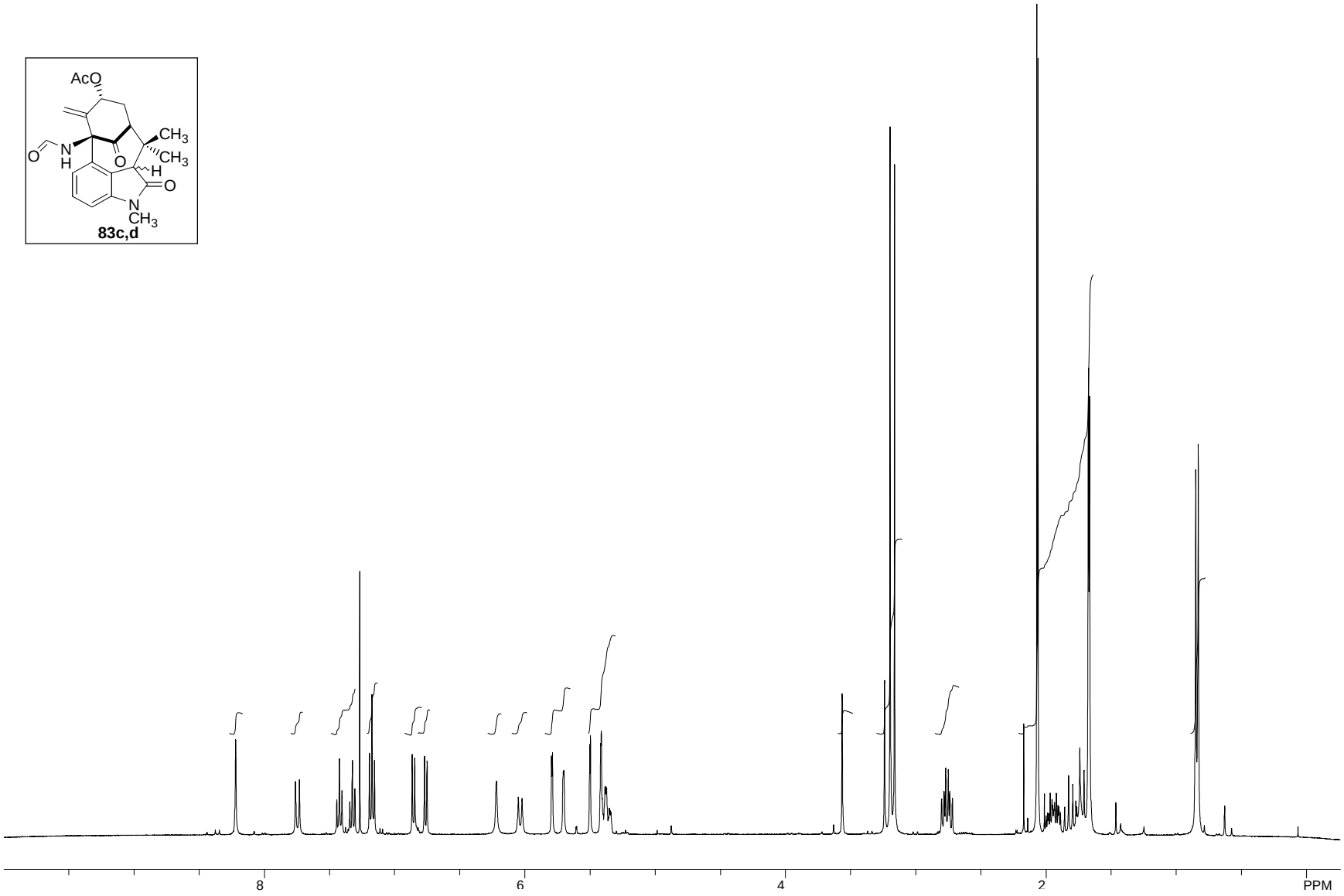


Figure A.1.70 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **83**.

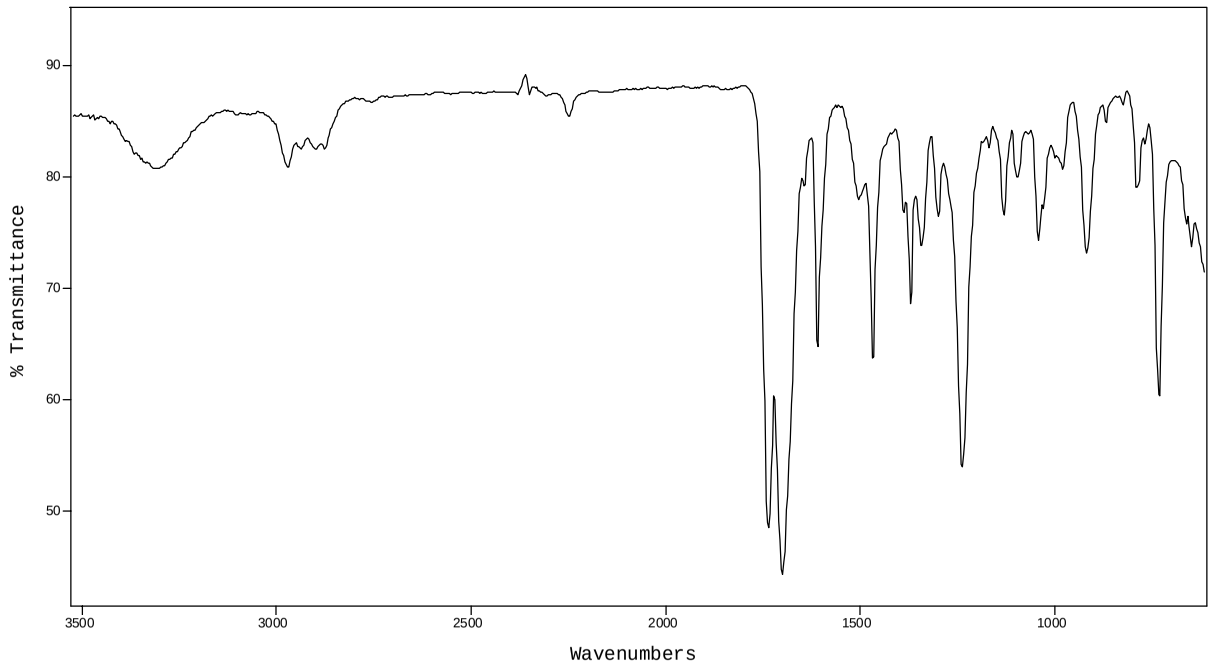


Figure A.1.71 FTIR Spectrum (thin film/NaCl) of Compound **83**.

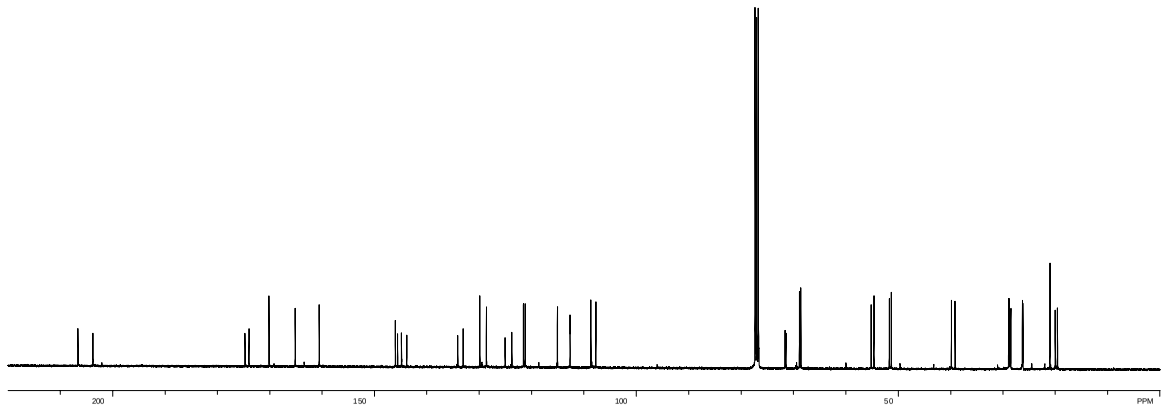


Figure A.1.72 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **83**.

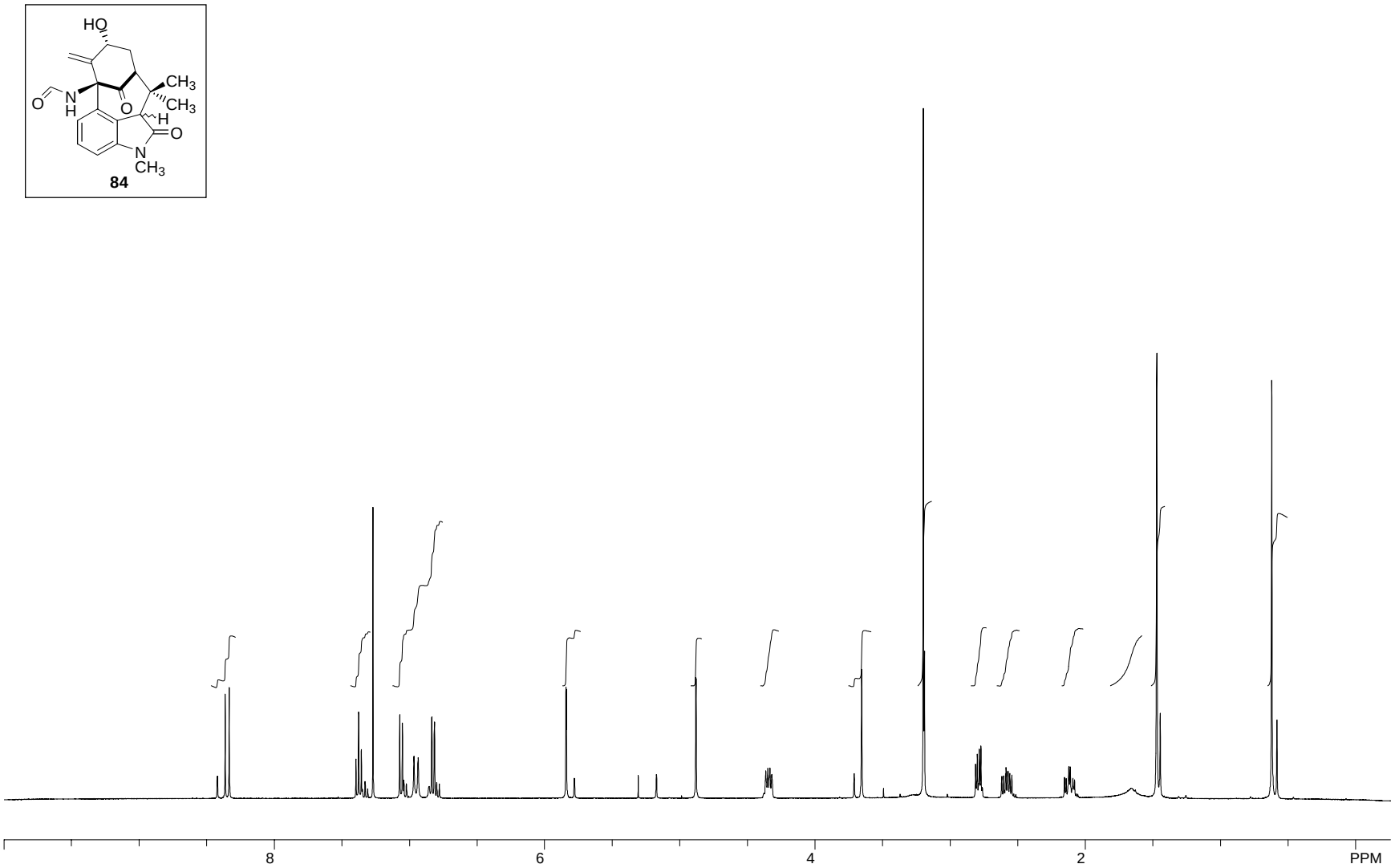


Figure A.1.73 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **84**.

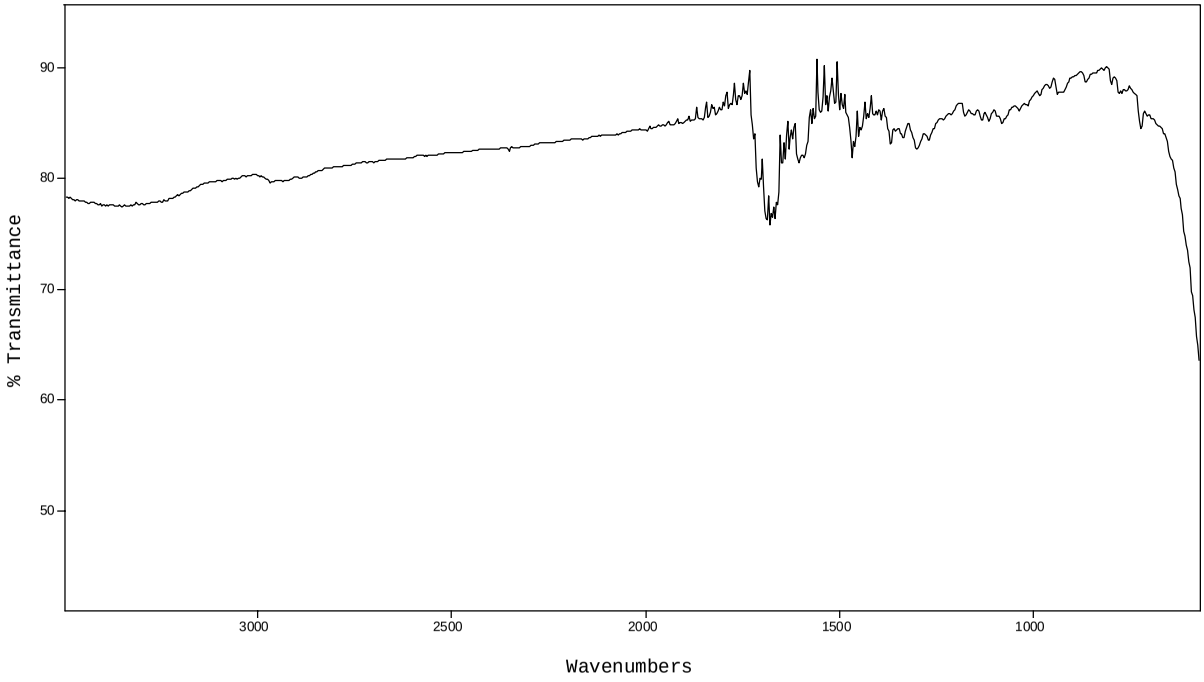


Figure A.1.74 FTIR Spectrum (thin film/NaCl) of Compound **84**.

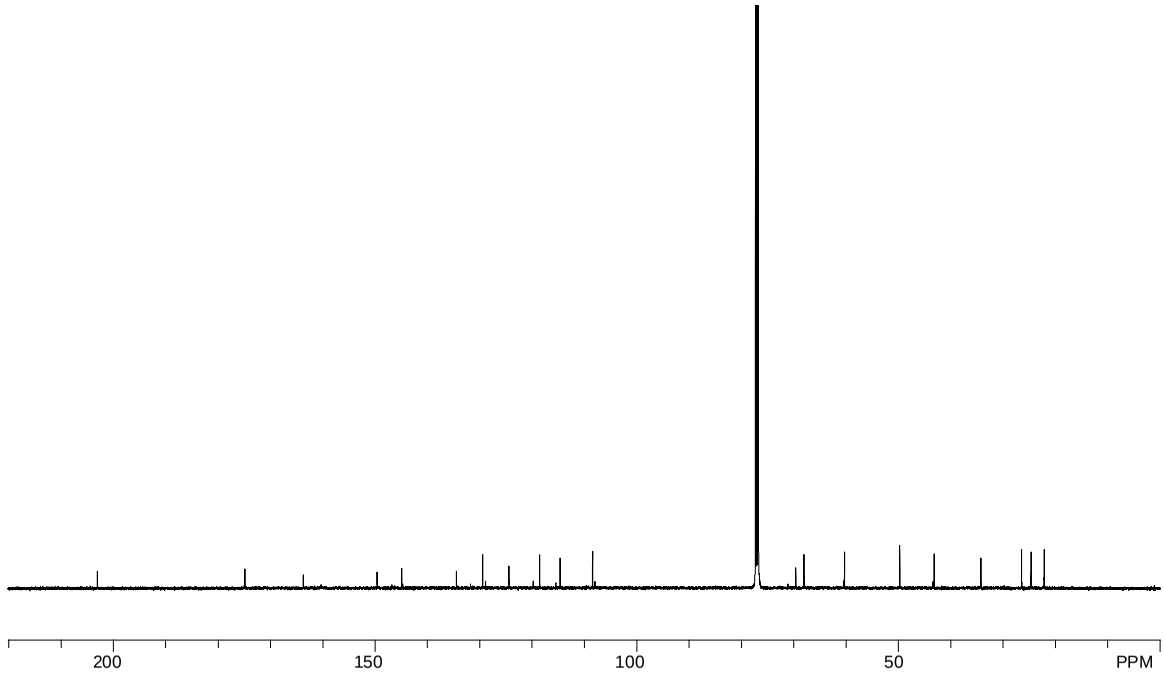


Figure A.1.75 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **84**.

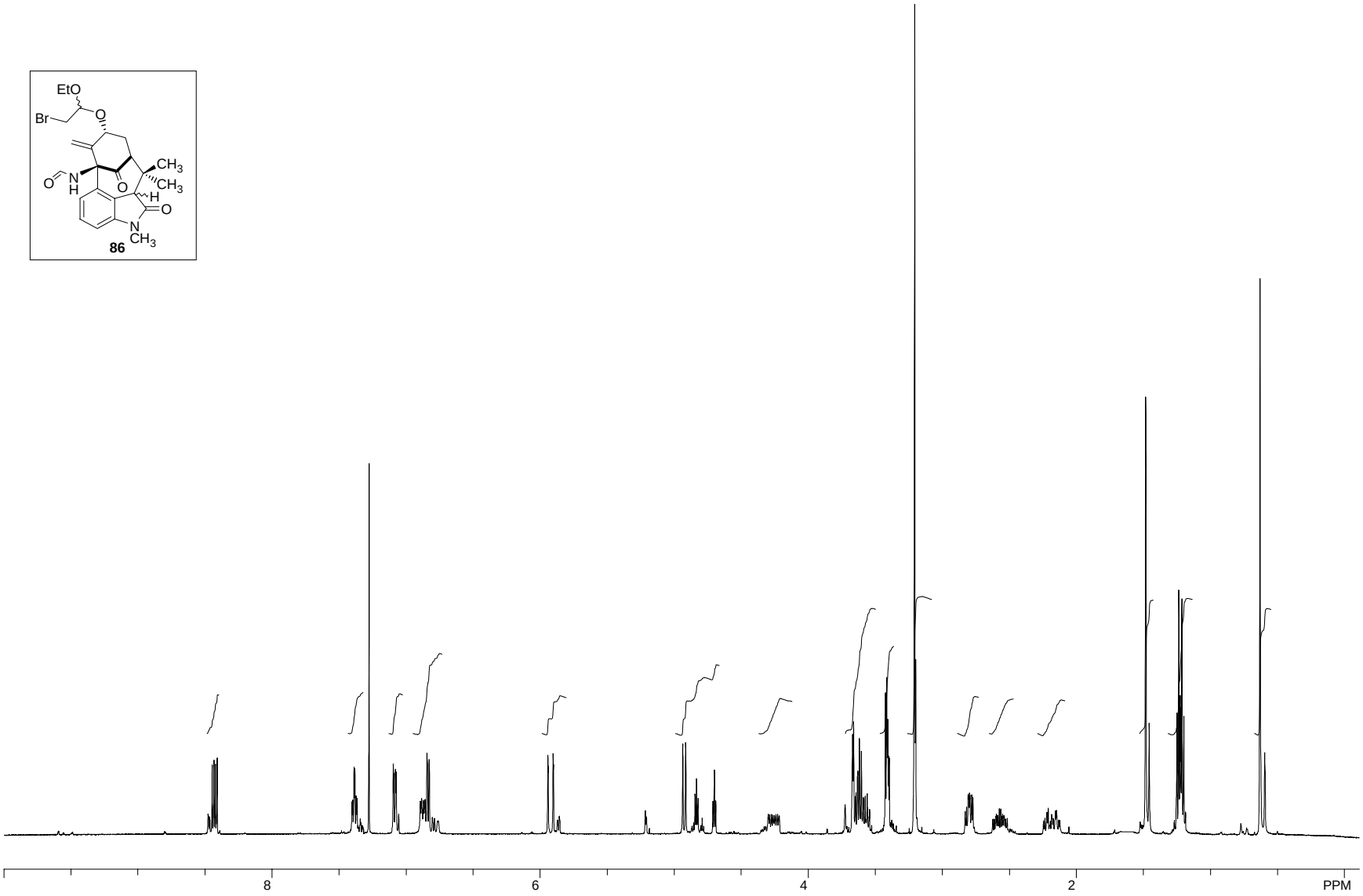


Figure A.1.76 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **86**.

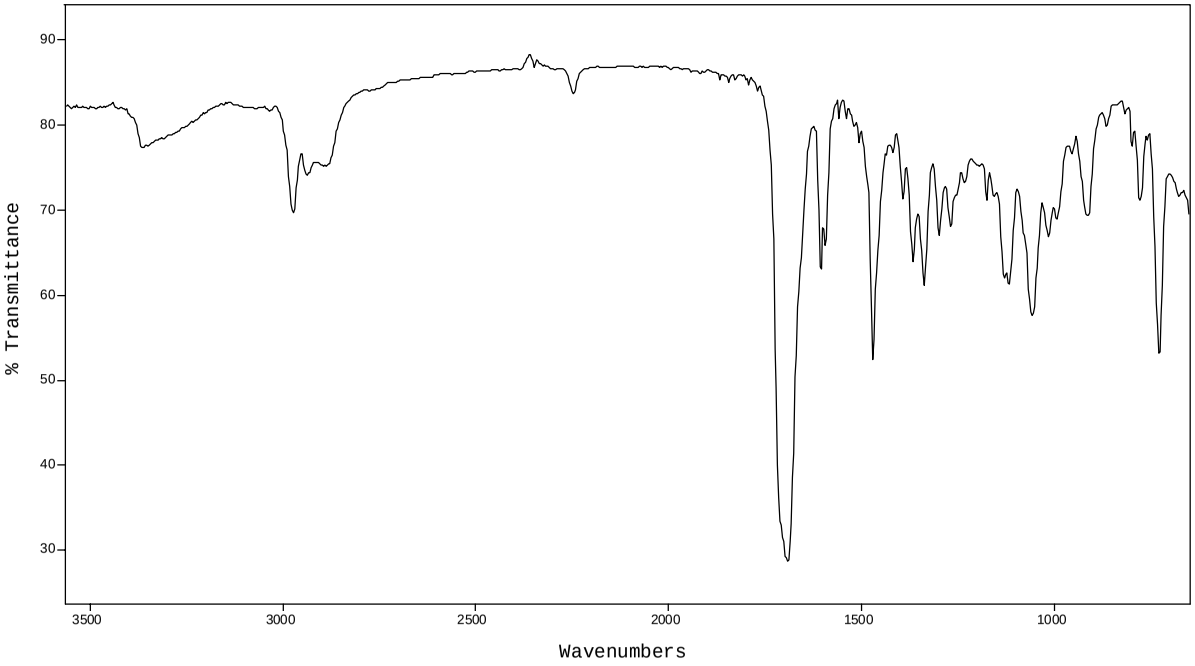


Figure A.1.77 FTIR Spectrum (thin film/NaCl) of Compound **86**.

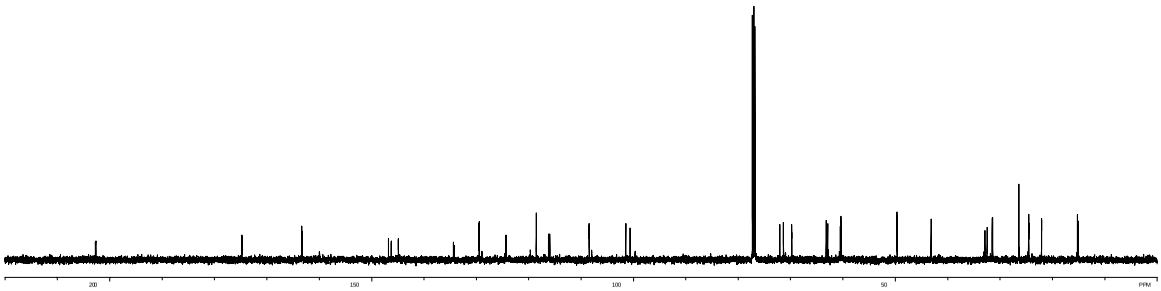


Figure A.1.78 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **86**.

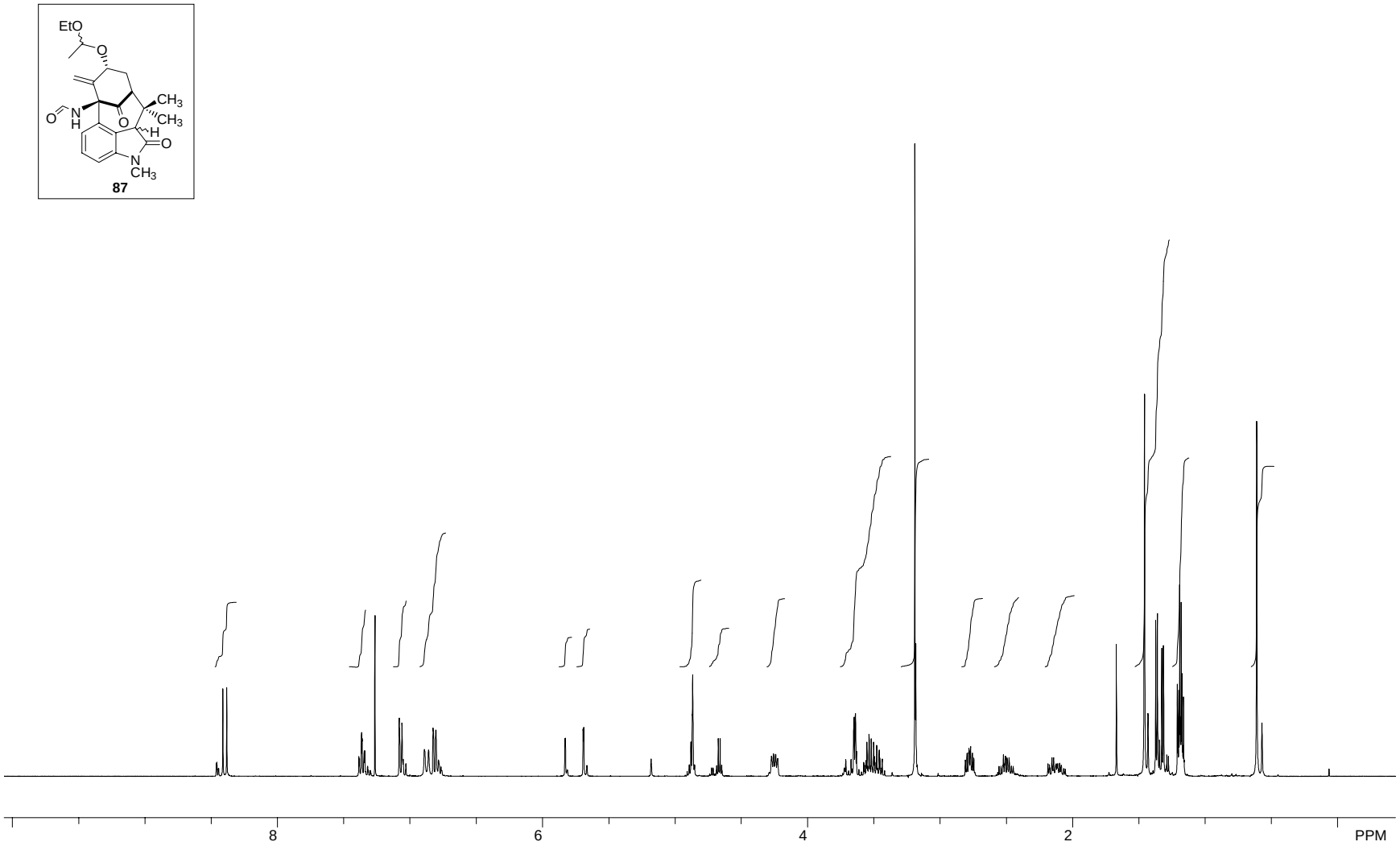


Figure A.1.79 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **87**.

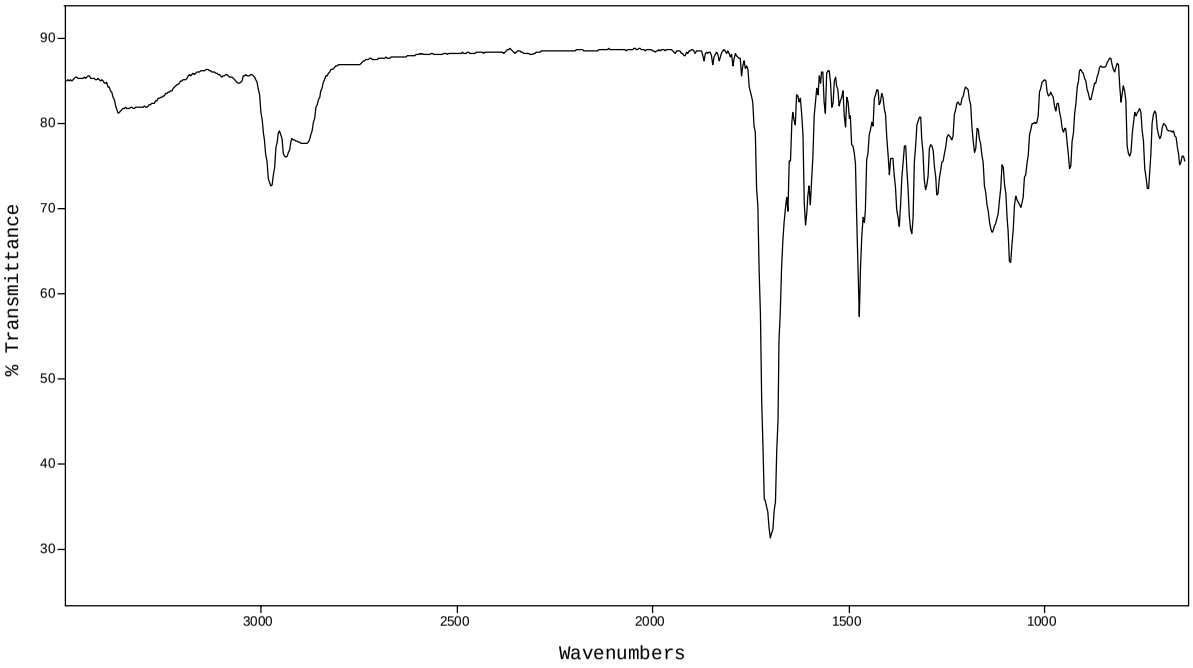


Figure A.1.80 FTIR Spectrum (thin film/NaCl) of Compound **87**.

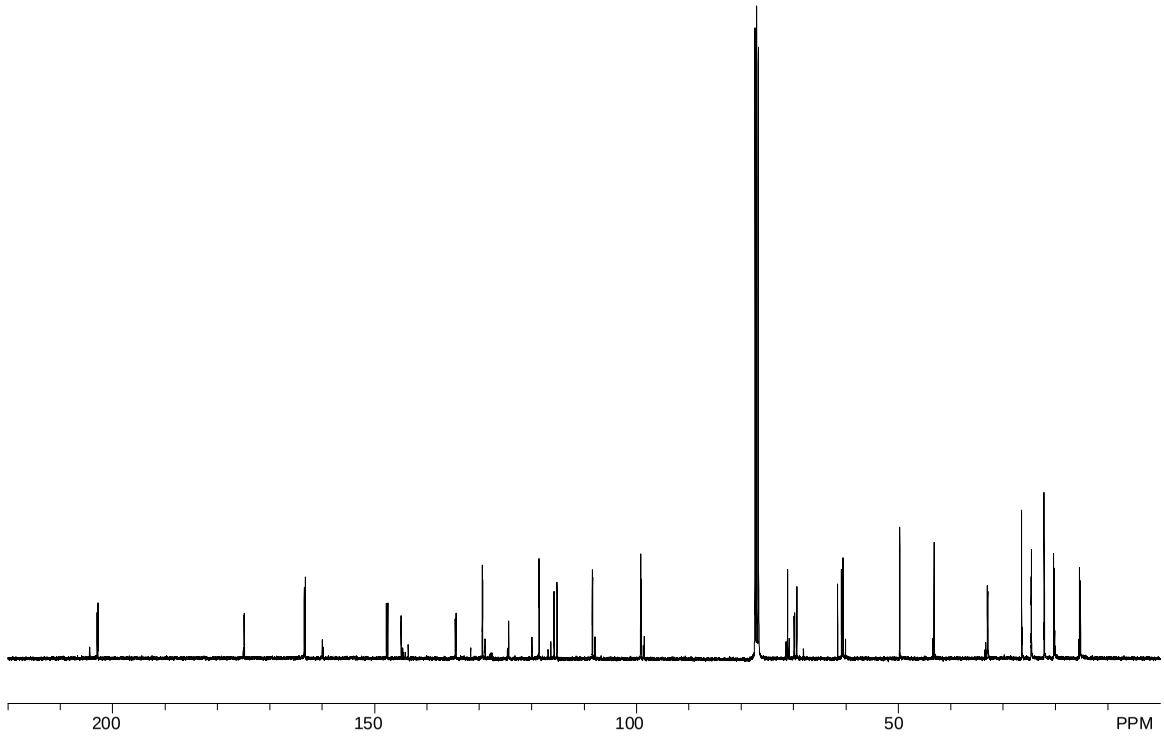
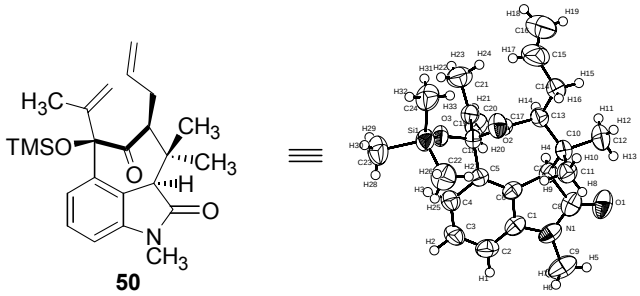


Figure A.1.81 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **87**.

APPENDIX TWO: X-RAY CRYSTALLOGRAPHY REPORTS RELEVANT TO CHAPTER ONE

X-RAY CRYSTALLOGRAPHY REPORT FOR DIENE 50.



Empirical Formula	$C_{24}H_{33}NO_3Si$
Formula Weight	411.62
Crystal Color, Habit	colorless, cut block
Crystal Dimensions	0.10 X 0.23 X 0.27 mm
Crystal System/Lattice Type	triclinic Primitive
No. of Reflections Used for Unit Cell Determination (2θ range)	25 (7.2 - 18.5°)
Omega Scan Peak Width at Half-height	0.18°
Parameters	a = 10.924(5)Å b = 12.592(5) Å c = 9.572(5) Å α = 106.44(4)° β = 105.00(4)° γ = 76.33(3)° V = 1200(1) Å^3
Space Group	P_{-1} (#2)
Z value	2
Dcalc	1.139 g/cm^3
F000	444.00
μ(MoKα)	1.20 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC5S
Radiation	MoKα (λ = 0.71069 Å) graphite monochromated
Attenuator	Zr foil (1.00, 2.28, 5.19, 11.74)
Take-off Angle	6.0°
Detector Aperture	6.0 mm hor./6.0 mm vert.
Crystal to Detector Distance	285 mm
Temperature	23.0°C

Scan Type	ω-2θ
Scan Rate	4.0^{o}/min (in ω) (up to 3 scans)
Scan Width	$(1.21 + 0.30 \tan \theta)^{o}$
$2\theta_{max}$	50.0^{o}
No. of Reflections Measured	Total: 4457 Unique: 4215 (R_{int} = 0.042)
Corrections	Lorentz-polarization

C. Structure Solution and Refinement

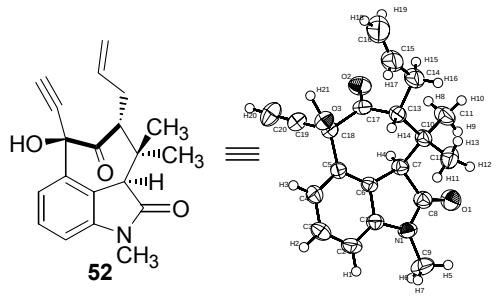
Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma\, w\, (\lvert Fo\rvert - \lvert Fc\rvert)^2$
Least Squares Weights	$1/\sigma^2(Fo) = 4Fo^2/\sigma^2(Fo^2)$
p-factor	0.0200
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	1477
No. Variables	262
Reflection/Parameter Ratio	5.64
Residuals: R; Rw	0.044 ; 0.042
Goodness of Fit Indicator	1.50
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.21 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.15 $e^-/Å^3$

Positional Parameters and B(eq) for 50.

atom	x	y	z	Beq
Si(1)	-0.4165(1)	-0.3212(1)	-1.2176(2)	5.06(4)
O(1)	0.1498(4)	-0.0493(3)	-0.5727(4)	7.2(1)
O(2)	-0.1900(3)	-0.3874(3)	-1.0231(4)	5.2(1)
O(3)	-0.4079(3)	-0.2434(3)	-1.0463(4)	4.37(9)
N(1)	0.0081(4)	0.0287(4)	-0.7523(5)	5.0(1)
C(1)	-0.1083(5)	0.0119(4)	-0.8516(6)	4.3(2)
C(2)	-0.1801(6)	0.0769(4)	-0.9468(7)	5.3(2)
C(3)	-0.2946(6)	0.0465(5)	-1.0330(6)	5.4(2)
C(4)	-0.3339(5)	-0.0464(4)	-1.0231(6)	4.6(1)
C(5)	-0.2600(4)	-0.1135(4)	-0.9250(5)	3.6(1)
C(6)	-0.1452(5)	-0.0826(4)	-0.8377(5)	3.8(1)
C(7)	-0.0474(4)	-0.1284(4)	-0.7141(5)	4.1(1)
C(8)	0.0522(6)	-0.0494(5)	-0.6686(7)	5.1(2)
C(9)	0.0736(6)	0.1205(5)	-0.7349(7)	7.1(2)
C(10)	0.0106(5)	-0.2556(4)	-0.7429(5)	4.1(1)
C(11)	0.0759(5)	-0.2908(4)	-0.8765(6)	5.0(1)

C(12)	0.1117(5)	-0.2789(5)	-0.6057(6)	6.4(2)
C(13)	-0.1001(4)	-0.3225(4)	-0.7672(5)	4.1(1)
C(14)	-0.0509(5)	-0.4483(4)	-0.7662(6)	5.4(2)
C(15)	-0.1535(7)	-0.5105(6)	-0.771(1)	9.5(3)
C(16)	-0.1687(9)	-0.5585(8)	-0.696(1)	12.9(4)
C(17)	-0.1985(5)	-0.3144(4)	-0.9111(6)	3.9(1)
C(18)	-0.3113(4)	-0.2142(4)	-0.9174(5)	3.7(1)
C(19)	-0.3773(5)	-0.1879(4)	-0.7844(6)	4.2(1)
C(20)	-0.3766(5)	-0.0942(5)	-0.6803(6)	5.7(2)
C(21)	-0.4434(5)	-0.2785(5)	-0.7804(7)	6.7(2)
C(22)	-0.2917(6)	-0.3176(5)	-1.3144(6)	7.5(2)
C(23)	-0.5723(6)	-0.2529(5)	-1.3154(7)	7.6(2)
C(24)	-0.4296(5)	-0.4682(4)	-1.2284(7)	7.4(2)
H(1)	-0.1528	0.1408	-0.9547	6.1528
H(2)	-0.3474	0.0904	-1.1000	6.2522
H(3)	-0.4135	-0.0671	-1.0846	5.4619
H(4)	-0.0894	-0.1126	-0.6344	4.6077
H(5)	0.1513	0.1155	-0.6679	8.0077
H(6)	0.0853	0.1205	-0.8307	8.0077
H(7)	0.0172	0.1902	-0.7015	8.0077
H(8)	0.1433	-0.2501	-0.8589	5.5715
H(9)	0.0142	-0.2769	-0.9634	5.5715
H(10)	0.1107	-0.3695	-0.8941	5.5715
H(11)	0.0687	-0.2789	-0.5294	7.0776
H(12)	0.1654	-0.3491	-0.6289	7.0776
H(13)	0.1627	-0.2208	-0.5666	7.0776
H(14)	-0.1447	-0.2900	-0.6887	4.8347
H(15)	0.0115	-0.4528	-0.6761	6.4268
H(16)	-0.0105	-0.4848	-0.8485	6.4268
H(17)	-0.2154	-0.5186	-0.8639	11.5594
H(18)	-0.2424	-0.5925	-0.7187	15.0100
H(19)	-0.1130	-0.5547	-0.5992	15.0100
H(20)	-0.3343	-0.0378	-0.6848	6.7822
H(21)	-0.4185	-0.0827	-0.6004	6.7822
H(22)	-0.4893	-0.3075	-0.8775	8.0208
H(23)	-0.5017	-0.2481	-0.7148	8.0208
H(24)	-0.3809	-0.3373	-0.7463	8.0208
H(25)	-0.3073	-0.2468	-1.3386	8.9530
H(26)	-0.2944	-0.3758	-1.4030	8.9530
H(27)	-0.2092	-0.3284	-1.2511	8.9530
H(28)	-0.5600	-0.1887	-1.3400	9.1451
H(29)	-0.6328	-0.2305	-1.2524	9.1451
H(30)	-0.6039	-0.3046	-1.4039	9.1451
H(31)	-0.4747	-0.4681	-1.1559	8.8681
H(32)	-0.4749	-0.4997	-1.3248	8.8681
H(33)	-0.3458	-0.5116	-1.2102	8.8681

X-RAY CRYSTALLOGRAPHY REPORT FOR DIENE 52.



Empirical Formula	$C_{20}H_{21}NO_3$
Formula Weight	323.39
Crystal Color, Habit	colorless, needle
Crystal Dimensions	0.08 X 0.10 X 0.30 mm
Crystal System	monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 9.2080(3)Å b = 17.282(1) Å c = 11.7397(3) Å β = 111.007(2)^o V = 1744.0(1) Å^3
Space Group	$P2_1/n$ (#14)
Z value	4
Dcalc	1.232 g/cm^3
F000	688.00
μ(MoKα)	0.82 cm^{-1}

B. Intensity Measurements

Diffractometer	Nonius KappaCCD
Radiation	MoKα (λ = 0.71069 Å) graphite monochromated
Take-off Angle	2.8^o
Crystal to Detector Distance	35 mm
Temperature	23.0^{o}C
Scan Width	1°
2θmax	52.9^o
No. of Reflections Measured	Total: 3647
Corrections	Lorentz-polarization Secondary Extinction (coefficient: 4.32691e-06)

C. Structure Solution and Refinement

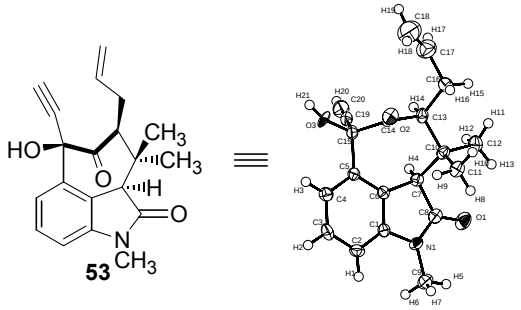
Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma\ w\ (\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$1/\sigma^2(Fo) = 4Fo^2/\sigma^2(Fo^2)$
p-factor	0.0200
Anomalous Dispersion	All non-hydrogen atoms
No. Observations ($I>3.00\sigma(I)$)	2328
No. Variables	217
Reflection/Parameter Ratio	10.73
Residuals: R; Rw	0.049 ; 0.059
Goodness of Fit Indicator	2.47
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.20 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.21 $e^-/Å^3$

Positional Parameters and B(eq) for 52.

atom	x	y	z	B_{eq}
O(1)	-0.8521(2)	0.18270(9)	-0.1605(1)	5.03(4)
O(2)	-0.5085(2)	-0.07631(9)	-0.1597(2)	5.18(4)
O(3)	-0.8089(1)	-0.19198(8)	-0.2968(1)	3.58(3)
N(1)	-1.0320(2)	0.0905(1)	-0.1656(2)	3.67(4)
C(1)	-1.0432(2)	0.0095(1)	-0.1698(2)	3.20(5)
C(2)	-1.1634(2)	-0.0348(1)	-0.1636(2)	4.20(6)
C(3)	-1.1476(2)	-0.1145(1)	-0.1677(2)	4.58(6)
C(4)	-1.0168(2)	-0.1473(1)	-0.1779(2)	3.83(5)
C(5)	-0.8939(2)	-0.1015(1)	-0.1831(2)	2.93(4)
C(6)	-0.9085(2)	-0.0219(1)	-0.1792(2)	2.77(4)
C(7)	-0.8005(2)	0.0438(1)	-0.1808(2)	2.98(4)
C(8)	-0.8913(2)	0.1148(1)	-0.1667(2)	3.55(5)
C(9)	-1.1522(3)	0.1423(1)	-0.1586(2)	5.13(6)
C(10)	-0.7527(2)	0.0497(1)	-0.2959(2)	3.26(5)
C(11)	-0.6098(3)	0.1015(1)	-0.2646(2)	4.74(6)
C(12)	-0.8880(3)	0.0842(1)	-0.4020(2)	4.52(6)
C(13)	-0.7217(2)	-0.0332(1)	-0.3339(2)	3.29(5)
C(14)	-0.6288(3)	-0.0357(1)	-0.4196(2)	4.84(6)
C(15)	-0.6353(4)	-0.1133(2)	-0.4759(2)	5.97(8)
C(16)	-0.5195(5)	-0.1558(2)	-0.4681(3)	8.0(1)
C(17)	-0.6440(2)	-0.0823(1)	-0.2222(2)	3.22(5)
C(18)	-0.7519(2)	-0.1414(1)	-0.1935(2)	2.90(4)
C(19)	-0.6669(2)	-0.1856(1)	-0.0822(2)	3.61(5)
C(20)	-0.5965(3)	-0.2219(1)	0.0043(2)	5.06(6)
H(1)	-1.2538	-0.0120	-0.1568	5.0354
H(2)	-1.2287	-0.1470	-0.1634	5.4946

H(3)	-1.0097	-0.2020	-0.1816	4.5925
H(4)	-0.7086	0.0397	-0.1104	3.5710
H(5)	-1.1408	0.1914	-0.1908	6.1537
H(6)	-1.1431	0.1480	-0.0758	6.1537
H(7)	-1.2515	0.1215	-0.2045	6.1537
H(8)	-0.5232	0.0762	-0.2063	5.6879
H(9)	-0.6290	0.1489	-0.2315	5.6879
H(10)	-0.5879	0.1116	-0.3363	5.6879
H(11)	-0.9832	0.0625	-0.4028	5.4272
H(12)	-0.8901	0.1387	-0.3923	5.4272
H(13)	-0.8747	0.0727	-0.4768	5.4272
H(14)	-0.8202	-0.0559	-0.3766	3.9487
H(15)	-0.5233	-0.0233	-0.3742	5.8031
H(16)	-0.6708	0.0014	-0.4826	5.8031
H(17)	-0.7356	-0.1329	-0.5221	7.1654
H(18)	-0.5355	-0.2047	-0.5074	9.6322
H(19)	-0.4169	-0.1386	-0.4228	9.6322
H(20)	-0.5395	-0.2513	0.0745	6.0743
H(21)	-0.7283	-0.2350	-0.2989	5.9059

X-RAY CRYSTALLOGRAPHY REPORT FOR DIENE 53.



Empirical Formula	$C_{20}H_{25}NO_3$
Formula Weight	327.42
Crystal Color, Habit	colorless, plate
Crystal Dimensions	0.07 X 0.12 X 0.21 mm
Crystal System	monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 13.610(1)Å b = 8.1789(4) Å c = 15.026(1) Å β = 93.319(3)^o V = 1669.8(2) Å^3
Space Group	$P2_1/c$ (#14)
Z value	4
Dcalc	1.302 g/cm^3
F000	704.00
μ(MoKα)	0.87 cm^{-1}

B. Intensity Measurements

Diffractometer	Nonius KappaCCD
Radiation	MoKα (λ = 0.71069 Å) graphite monochromated
Take-off Angle	2.8^o
Crystal to Detector Distance	35 mm
Temperature	-90.0^{o}C
Scan Rate	60sec/frame
Scan Width	1°/frame
2θmax	61.1^o
No. of Reflections Measured	Total: 5403
Corrections	Lorentz-polarization Secondary Extinction

(coeff.: 6.61905e-07)

C. Structure Solution and Refinement

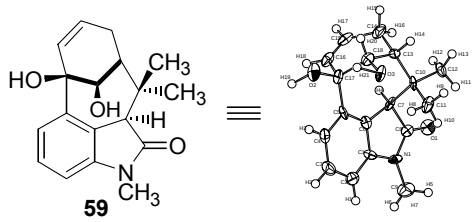
Structure Solution	Direct Methods
Refinement	Full-matrix least-squares
Function Minimized	Σ w (|Fo| - |Fc|)^2
Least Squares Weights	$1/\sigma^2$(Fo)
p-factor	0.0000
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	1644
No. Variables	217
Reflection/Parameter Ratio	7.58
Residuals: R; Rw	0.066 ; 0.061
Goodness of Fit Indicator	2.06
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.49 e^-/Å^3
Minimum peak in Final Diff. Map	-0.38 e^-/Å^3

Positional Parameters and B(eq) for 53.

atom	x	y	z	Beq
O(1)	0.6507(2)	0.8639(3)	0.8499(2)	3.07(8)
O(2)	0.8060(2)	0.1516(3)	0.8364(2)	2.66(8)
O(3)	0.7363(2)	0.0495(2)	0.9867(2)	2.84(8)
N(1)	0.5372(3)	0.6593(3)	0.8511(2)	2.06(9)
C(1)	0.5324(3)	0.4968(4)	0.8818(3)	1.8(1)
C(2)	0.4495(3)	0.4014(4)	0.8830(3)	2.2(1)
C(3)	0.4615(3)	0.2431(4)	0.9164(3)	2.4(1)
C(4)	0.5542(3)	0.1868(4)	0.9454(3)	2.1(1)
C(5)	0.6372(3)	0.2862(4)	0.9431(3)	1.7(1)
C(6)	0.6261(3)	0.4450(4)	0.9103(3)	1.6(1)
C(7)	0.6981(3)	0.5852(4)	0.9020(3)	1.8(1)
C(8)	0.6293(3)	0.7212(5)	0.8654(3)	2.0(1)
C(9)	0.4533(3)	0.7536(4)	0.8178(3)	2.8(1)
C(10)	0.7878(3)	0.5567(4)	0.8426(3)	1.9(1)
C(11)	0.7522(3)	0.5122(4)	0.7485(3)	2.5(1)
C(12)	0.8491(3)	0.7161(4)	0.8425(3)	2.8(1)
C(13)	0.8558(3)	0.4185(4)	0.8870(3)	2.0(1)
C(14)	0.8024(3)	0.2556(4)	0.8932(3)	2.0(1)
C(15)	0.7391(3)	0.2192(4)	0.9725(3)	1.9(1)
C(16)	0.9520(3)	0.3872(4)	0.8407(3)	2.9(1)
C(17)	1.0220(4)	0.2876(6)	0.8992(4)	4.2(1)
C(18)	1.0410(5)	0.1423(7)	0.8969(4)	6.3(2)
C(19)	0.7764(3)	0.2989(4)	1.0562(3)	2.2(1)
C(20)	0.8025(4)	0.3617(5)	1.1237(3)	3.1(1)

H(1)	0.3868	0.4413	0.8621	2.6447
H(2)	0.4060	0.1733	0.9194	2.8513
H(3)	0.5612	0.0781	0.9672	2.5054
H(4)	0.7228	0.6154	0.9601	2.1763
H(5)	0.4724	0.8643	0.8105	3.3658
H(6)	0.4031	0.7479	0.8590	3.3658
H(7)	0.4293	0.7105	0.7620	3.3658
H(8)	0.7141	0.5995	0.7230	2.9573
H(9)	0.7129	0.4163	0.7495	2.9573
H(10)	0.8072	0.4929	0.7138	2.9573
H(11)	0.9115	0.6939	0.8199	3.4085
H(12)	0.8580	0.7568	0.9016	3.4085
H(13)	0.8156	0.7953	0.8059	3.4085
H(14)	0.8735	0.4526	0.9462	2.3483
H(15)	0.9818	0.4891	0.8282	3.4421
H(16)	0.9374	0.3300	0.7866	3.4421
H(17)	1.0570	0.3471	0.9452	5.0438
H(18)	1.0091	0.0746	0.8528	7.5664
H(19)	1.0879	0.0967	0.9392	7.5664
H(20)	0.8236	0.4125	1.1784	3.6808
H(21)	0.7572	-0.0129	1.0190	2.5409

X-RAY CRYSTALLOGRAPHY REPORT FOR DIOL 59.



Empirical Formula	$C_{19}H_{23}NO_3Cl_2$
Formula Weight	384.30
Crystal Color, Habit	colorless, plate
Crystal Dimensions	0.12 X 0.27 X 0.36 mm
Crystal System/Lattice Type	monoclinic/C-centered
No. of Reflections Used for Unit Cell Determination (2θ range)	21 (7.2 - 18.8^o)
Omega Scan Peak Width at Half-height	0.25^o
Lattice Parameters	a = 35.29(1)Å b = 8.897(9) Å c = 11.656(8) Å β = 103.03(5)^o V = 3565(3) Å^3
Space Group	C2/c (#15)
Z value	8
D_{calc}	1.432 g/cm^3
F000	1616.00
μ(MoKα)	3.82 cm^{-1}
B. Intensity Measurements	
Diffractometer	Rigaku AFC5S
Radiation	MoKα (λ = 0.71069 Å) graphite monochromated
Attenuator	Zr foil (1.00, 2.28, 5.19, 11.74)
Take-off Angle	6.0^o
Detector Aperture	6.0 mm hor/6.0 mm vert
Crystal to Detector Distance	285 mm
Temperature	23.0^{o}C
Scan Type	ω-2θ
Scan Rate	4.0^o/min (in ω) (up to 3 scans)
Scan Width	(1.63 + 0.30 tan θ)^o
2θmax	50.0^o

No. of Reflections Measured	Total: 3430 Unique: 3369 (R_{int} = 0.088)
Corrections	Lorentz-polarization

C. Structure Solution and Refinement

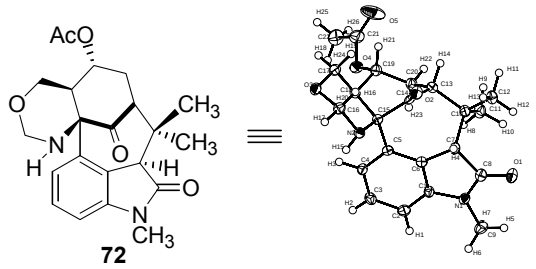
Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma\ w\ (\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$1/\sigma^2(Fo) = 4Fo^2/\sigma^2(Fo^2)$
p-factor	0.0300
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	886
No. Variables	226
Reflection/Parameter Ratio	3.92
Residuals: R; Rw	0.050 ; 0.052
Goodness of Fit Indicator	1.50
Max Shift/Error in Final Cycle	0.01
Maximum peak in Final Diff. Map	0.29 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.26 $e^-/Å^3$

Positional Parameters and B(eq) for 59.

atom	x	y	z	Beq
Cl(1)	0.2424(1)	0.0059(4)	0.6842(3)	6.9(1)
Cl(2)	0.21839(9)	0.1359(4)	0.8827(3)	5.76(10)
O(1)	0.0906(2)	0.7024(7)	0.6499(6)	2.8(2)
O(2)	0.0899(2)	-0.0368(6)	0.4331(5)	2.9(2)
O(3)	0.1041(2)	0.0115(6)	0.6834(5)	2.3(2)
N(1)	0.1407(2)	0.5913(8)	0.5870(6)	2.0(2)
C(1)	0.1475(3)	0.453(1)	0.5358(8)	1.6(2)
C(2)	0.1804(3)	0.414(1)	0.4983(8)	2.4(3)
C(3)	0.1810(3)	0.266(1)	0.4523(8)	3.2(3)
C(4)	0.1497(3)	0.169(1)	0.4482(8)	2.6(3)
C(5)	0.1175(3)	0.213(1)	0.4882(7)	1.8(2)
C(6)	0.1162(3)	0.358(1)	0.5310(7)	1.6(2)
C(7)	0.0862(3)	0.4367(9)	0.5819(7)	1.8(2)
C(8)	0.1053(3)	0.593(1)	0.6120(8)	1.6(2)
C(9)	0.1669(3)	0.719(1)	0.6053(9)	3.7(3)
C(10)	0.0768(3)	0.354(1)	0.6896(7)	1.8(2)
C(11)	0.1155(3)	0.3189(10)	0.7789(7)	2.8(3)
C(12)	0.0526(3)	0.4532(10)	0.7530(8)	2.4(2)
C(13)	0.0530(3)	0.2055(10)	0.6489(8)	1.8(2)
C(14)	0.0141(3)	0.236(1)	0.5583(9)	3.0(3)

C(15)	0.0161(3)	0.227(1)	0.4325(8)	2.6(3)
C(16)	0.0465(3)	0.174(1)	0.3978(7)	2.4(3)
C(17)	0.0820(3)	0.109(1)	0.4778(8)	2.1(3)
C(18)	0.0717(3)	0.075(1)	0.5965(8)	2.1(3)
C(19)	0.2082(3)	0.117(1)	0.731(1)	5.4(4)
H(1)	0.2016	0.4812	0.5028	2.9219
H(2)	0.2028	0.2342	0.4231	3.7936
H(3)	0.1509	0.0706	0.4175	3.1074
H(4)	0.0631	0.4483	0.5230	2.1358
H(5)	0.1730	0.7459	0.6858	4.3763
H(6)	0.1902	0.6935	0.5811	4.3763
H(7)	0.1548	0.8018	0.5593	4.3763
H(8)	0.1300	0.2479	0.7458	3.3641
H(9)	0.1099	0.2787	0.8490	3.3641
H(10)	0.1302	0.4087	0.7973	3.3641
H(11)	0.0684	0.5308	0.7943	2.8901
H(12)	0.0315	0.4956	0.6973	2.8901
H(13)	0.0427	0.3933	0.8075	2.8901
H(14)	0.0461	0.1667	0.7172	2.2063
H(15)	-0.0044	0.1628	0.5717	3.6286
H(16)	0.0053	0.3330	0.5730	3.6286
H(17)	-0.0057	0.2617	0.3744	3.0923
H(18)	0.0455	0.1750	0.3158	2.9082
H(19)	0.0926	0.0113	0.3359	5.1269
H(20)	0.0524	-0.0012	0.5804	2.4624
H(21)	0.1016	-0.0761	0.6174	5.1269
H(22)	0.1834	0.0712	0.7063	6.7873
H(23)	0.2079	0.2133	0.6970	6.7873

X-RAY CRYSTALLOGRAPHY REPORT FOR ACETATE 72.



Empirical Formula	$C_{22}H_{26}N_2O_5$
Formula Weight	398.46
Crystal Color, Habit	colorless, plate
Crystal Dimensions	0.08 X 0.15 X 0.17 mm
Crystal System	triclinic
Lattice Type	Primitive
Lattice Parameters	a = 9.1803(5)Å
	b = 9.237(1) Å
	c = 12.274(1) Å
	α = 90.881(3)^o
	β = 106.438(4)^o
	γ = 93.680(4)^o
	V = 995.6(1) Å^3
Space Group	P_{-1} (#2)
Z value	2
D_{calc}	1.329 g/cm^3
F000	424.00
μ(MoKα)	0.94 cm^{-1}

B. Intensity Measurements

Diffractometer	Nonius KappaCCD
Radiation	MoKα (λ = 0.71069 Å) graphite monochromated
Take-off Angle	2.8^o
Crystal to Detector Distance	33 mm
Temperature	-90.0^{o}C
Scan Rate	40s/frame
Scan Width	2.0^o/frame
2θmax	55.2^o
No. of Reflections Measured	Total: 4550
Corrections	Lorentz-polarization

C. Structure Solution and Refinement

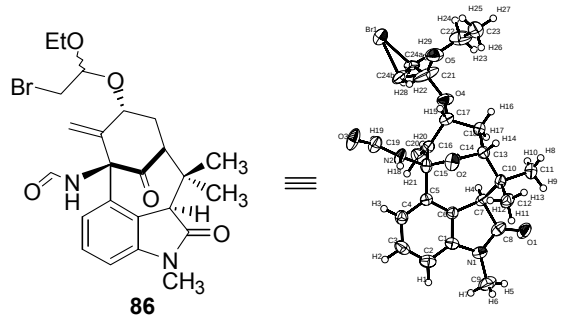
Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma\ w\ (\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$1/\sigma^2(Fo)$
p-factor	0.0200
Anomalous Dispersion	All non-hydrogen atoms
No. Observations ($I>3.00\sigma(I)$)	2390
No. Variables	366
Reflection/Parameter Ratio	6.53
Residuals: R; Rw	0.046 ; 0.045
Goodness of Fit Indicator	1.66
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.29 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.24 $e^-/Å^3$

Positional Parameters and B(eq) for 72.

atom	x	y	z	Beq
O(1)	0.5838(2)	-0.3361(2)	0.8174(1)	2.81(4)
O(2)	1.0608(2)	0.0487(2)	0.8574(1)	2.60(4)
O(3)	1.1043(2)	0.4760(2)	0.9009(1)	2.43(4)
O(4)	0.7539(2)	0.3989(2)	0.5650(1)	2.59(4)
O(5)	0.8583(3)	0.3575(3)	0.4252(2)	6.51(7)
N(1)	0.4667(2)	-0.1291(2)	0.8374(2)	2.28(5)
N(2)	0.9665(2)	0.2761(2)	0.9608(2)	1.97(5)
C(1)	0.5037(2)	0.0215(3)	0.8460(2)	1.98(5)
C(2)	0.4156(3)	0.1299(3)	0.8634(2)	2.51(6)
C(3)	0.4788(3)	0.2715(3)	0.8708(2)	2.47(6)
C(4)	0.6246(2)	0.3028(3)	0.8622(2)	2.04(6)
C(5)	0.7142(2)	0.1926(3)	0.8458(2)	1.73(5)
C(6)	0.6520(2)	0.0498(2)	0.8370(2)	1.82(5)
C(7)	0.7141(3)	-0.0927(3)	0.8194(2)	1.95(5)
C(8)	0.5850(2)	-0.2031(3)	0.8249(2)	2.26(6)
C(9)	0.3217(3)	-0.1972(4)	0.8436(3)	2.99(7)
C(10)	0.7607(2)	-0.1111(3)	0.7066(2)	2.14(5)
C(11)	0.6189(3)	-0.1439(3)	0.6053(2)	2.82(7)
C(12)	0.8643(3)	-0.2366(3)	0.7189(3)	2.82(7)
C(13)	0.8506(2)	0.0327(3)	0.6878(2)	2.18(6)
C(14)	0.9426(2)	0.0979(2)	0.8036(2)	1.96(5)
C(15)	0.8791(2)	0.2301(2)	0.8444(2)	1.78(5)
C(16)	1.1111(3)	0.3541(3)	0.9729(2)	2.28(6)
C(17)	1.0501(3)	0.4236(3)	0.7858(2)	2.34(6)
C(18)	0.8895(2)	0.3495(3)	0.7572(2)	1.91(5)
C(19)	0.8445(3)	0.2914(3)	0.6337(2)	2.16(6)

C(20)	0.7545(3)	0.1454(3)	0.6150(2)	2.36(6)
C(21)	0.7721(3)	0.4222(3)	0.4616(2)	3.29(7)
C(22)	0.6719(4)	0.5332(4)	0.4009(3)	3.80(8)
H(1)	0.314(3)	0.109(3)	0.869(2)	3.0(5)
H(2)	0.425(2)	0.349(2)	0.882(2)	1.9(5)
H(3)	0.666(2)	0.400(3)	0.870(2)	2.2(5)
H(4)	0.797(2)	-0.106(2)	0.878(2)	1.5(5)
H(5)	0.336(3)	-0.298(4)	0.847(3)	6.5(9)
H(6)	0.295(3)	-0.157(3)	0.908(2)	4.8(7)
H(7)	0.243(3)	-0.181(3)	0.774(3)	5.4(7)
H(8)	0.538(2)	-0.069(3)	0.605(2)	3.3(6)
H(9)	0.647(2)	-0.142(3)	0.534(2)	3.3(5)
H(10)	0.572(2)	-0.244(3)	0.615(2)	3.0(5)
H(11)	0.897(2)	-0.250(3)	0.646(2)	3.5(5)
H(13)	0.958(3)	-0.219(3)	0.786(2)	3.2(6)
H(14)	0.928(2)	0.005(2)	0.648(2)	1.8(4)
H(15)	0.909(2)	0.329(2)	0.989(2)	1.7(5)
H(16)	1.180(2)	0.286(2)	0.954(2)	2.2(5)
H(17)	1.150(2)	0.395(2)	1.055(2)	2.3(5)
H(18)	1.049(2)	0.508(3)	0.734(2)	3.7(6)
H(19)	1.125(2)	0.353(2)	0.773(2)	1.6(4)
H(20)	0.823(2)	0.417(2)	0.764(2)	1.1(4)
H(21)	0.938(2)	0.284(2)	0.608(2)	1.8(4)
H(22)	0.728(2)	0.114(2)	0.535(2)	2.4(5)
H(23)	0.654(2)	0.157(2)	0.634(2)	2.4(5)
H(24)	0.597(3)	0.563(3)	0.438(3)	6.0(8)
H(25)	0.727(4)	0.616(4)	0.387(3)	8.4(10)
H(26)	0.616(4)	0.499(4)	0.331(3)	8(1)

X-RAY CRYSTALLOGRAPHY REPORT FOR BROMOACETAL 86.



Empirical Formula	$C_{24}H_{29}N_2O_5Br$
Formula Weight	505.41
Crystal Color, Habit	colorless, plate
Crystal Dimensions	0.08 X 0.11 X 0.15 mm
Crystal System	monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 15.336(1)Å b = 8.548(1) Å c = 17.456(2) Å β = 92.744(5)^o V = 2285.8(3) Å^3
Space Group	$P2_1/a$ (#14)
Z value	4
Dcalc	1.468 g/cm^3
F000	1048.00
μ(MoKα)	18.42 cm^{-1}

B. Intensity Measurements

Diffractometer	Nonius KappaCCD
Radiation	MoKα (λ = 0.71069 Å) graphite monochromated
Take-off Angle	2.8^o
Crystal to Detector Distance	33 mm
Temperature	-90.0^{o}C
Scan Rate	171s/frame
Scan Width	1.9^o/frame
2θmax	50.1^o
No. of Reflections Measured	Total: 4316
Corrections	Lorentz-polarization

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma\ w\ (\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$1/\sigma^2(Fo)$
p-factor	0.0100
Anomalous Dispersion	All non-hydrogen atoms
No. Observations ($I>3.00\sigma(I)$)	1920
No. Variables	298
Reflection/Parameter Ratio	6.44
Residuals: R; Rw	0.051 ; 0.049
Goodness of Fit Indicator	2.12
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.44 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.46 $e^-/Å^3$

Positional Parameters and B(eq) for 86.

atom	x	y	z	Beq
Br(1)	0.00899(5)	-0.26296(8)	0.96571(5)	6.10(2)
O(1)	0.4296(3)	0.4420(5)	0.6282(3)	5.1(1)
O(2)	0.4774(3)	-0.2245(4)	0.7579(3)	4.8(1)
O(3)	0.2449(3)	-0.5653(5)	0.7224(3)	6.6(1)
O(4)	0.2030(3)	-0.0013(5)	0.8751(3)	4.8(1)
O(5)	0.2108(3)	-0.1717(6)	0.9797(3)	5.9(1)
N(1)	0.4027(3)	0.2427(6)	0.5421(3)	4.1(1)
N(2)	0.3219(3)	-0.3418(5)	0.7194(3)	3.9(1)
C(1)	0.3764(4)	0.0858(7)	0.5437(4)	3.4(2)
C(2)	0.3614(4)	-0.0102(9)	0.4820(4)	4.6(2)
C(3)	0.3351(4)	-0.1621(8)	0.4963(4)	4.7(2)
C(4)	0.3258(4)	-0.2152(7)	0.5697(5)	3.9(2)
C(5)	0.3403(3)	-0.1148(7)	0.6320(4)	3.1(2)
C(6)	0.3665(3)	0.0394(6)	0.6184(4)	3.2(2)
C(7)	0.3839(4)	0.1772(6)	0.6719(4)	3.4(2)
C(8)	0.4086(4)	0.3058(7)	0.6139(5)	4.2(2)
C(9)	0.4206(4)	0.3286(8)	0.4728(4)	6.0(2)
C(10)	0.4536(4)	0.1570(6)	0.7380(4)	3.5(2)
C(11)	0.4667(4)	0.3103(7)	0.7848(4)	4.8(2)
C(12)	0.5413(4)	0.1126(7)	0.7054(4)	4.6(2)
C(13)	0.4274(3)	0.0274(6)	0.7957(3)	3.4(2)
C(14)	0.4183(4)	-0.1323(7)	0.7577(4)	3.5(2)
C(15)	0.3302(4)	-0.1695(6)	0.7143(4)	3.7(2)
C(16)	0.2561(4)	-0.0880(6)	0.7538(4)	3.2(2)
C(17)	0.2766(4)	-0.0585(6)	0.8368(4)	3.7(2)
C(18)	0.3469(4)	0.0684(6)	0.8422(4)	3.6(2)

C(19)	0.2492(4)	-0.4216(8)	0.7241(4)	5.0(2)
C(20)	0.1863(4)	-0.0330(7)	0.7168(4)	4.6(2)
C(21)	0.1590(6)	-0.112(2)	0.9195(7)	10.6(4)
C(22)	0.2274(6)	-0.0642(10)	1.0409(6)	7.1(3)
C(23)	0.3115(5)	-0.1054(8)	1.0810(5)	6.3(2)
C(24a)	0.0716(9)	-0.095(1)	0.9230(8)	3.6(4)
C(24b)	0.100(1)	-0.187(2)	0.8893(10)	5.1(5)
H(1)	0.3687	0.0257	0.4312	5.4743
H(2)	0.3232	-0.2311	0.4544	5.6932
H(3)	0.3093	-0.3207	0.5781	4.6818
H(4)	0.3304	0.2062	0.6933	4.1164
H(5)	0.4189	0.4377	0.4830	7.1779
H(6)	0.4768	0.3009	0.4566	7.1779
H(7)	0.3778	0.3033	0.4336	7.1779
H(8)	0.5047	0.2910	0.8284	5.8147
H(9)	0.4917	0.3879	0.7536	5.8147
H(10)	0.4119	0.3459	0.8010	5.8147
H(11)	0.5490	0.1696	0.6595	5.5268
H(12)	0.5419	0.0037	0.6947	5.5268
H(13)	0.5873	0.1371	0.7419	5.5268
H(14)	0.4751	0.0187	0.8322	4.0442
H(15)	0.2978	-0.1516	0.8609	4.4970
H(16)	0.3655	0.0814	0.8945	4.3315
H(17)	0.3224	0.1636	0.8231	4.3315
H(18)	0.3824	-0.4097	0.7034	7.9646
H(19)	0.1966	-0.3648	0.7292	6.0076
H(20)	0.1459	0.0291	0.7430	5.5058
H(21)	0.1762	-0.0551	0.6638	5.5058
H(22)	0.1600	-0.1991	0.8857	12.6689
H(23)	0.2305	0.0390	1.0210	8.5789
H(24)	0.1818	-0.0700	1.0757	8.5789
H(25)	0.3083	-0.2088	1.1007	7.6063
H(26)	0.3570	-0.0996	1.0461	7.6063
H(27)	0.3232	-0.0343	1.1221	7.6063
H(28)	0.0485	-0.0791	0.8721	4.3313
H(29)	0.0615	-0.0044	0.9528	4.3313

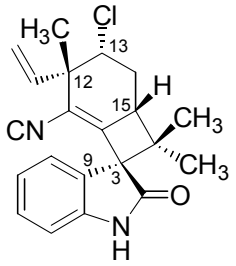
CHAPTER TWO

WELWITINDOLINONE A ISONITRILE: CONSTRUCTION OF THE CARBOCYCLIC SKELETON

2.1 Initial Considerations

Following several years of efforts toward the 3-4 bridged oxindoles, we chose to target the one member of the welwitindolinone family which strayed from the others structurally, welwitindolinone A isonitrile (**7**) (Figure 2.1.1). It was the unique topological complexity of welwitindolinone A (**7**) rather than its modest antifungal activity which served as an impetus for initiating synthetic efforts directed at **7**. The novel spirocyclobutane oxindole framework, the heavily functionalized cyclohexene ring, and the vinyl isonitrile moiety were all features that suggested this alkaloid would prove to be synthetically challenging.

Figure 2.1.1



7

It was believed that the structural disparity between **7** and the other members of the welwitindolinone family warranted an entirely separate synthetic strategy for **7**. At

the outset, we envisioned the major thrust of the project to be two-fold. In addition to developing a method for the construction of the spirocyclobutane oxindole core, a strategy focusing on the heavily functionalized cyclohexene ring would also be required. In contemplating these two tasks, it was decided that efforts should initially focus on establishing a protocol for the preparation of the spirocyclic oxindole framework of **7**.

To date there have been no reports of work directed toward a partial or total synthesis of welwitindolinone A isonitrile (**7**).

2.2 Construction of Spirocyclic Oxindoles.

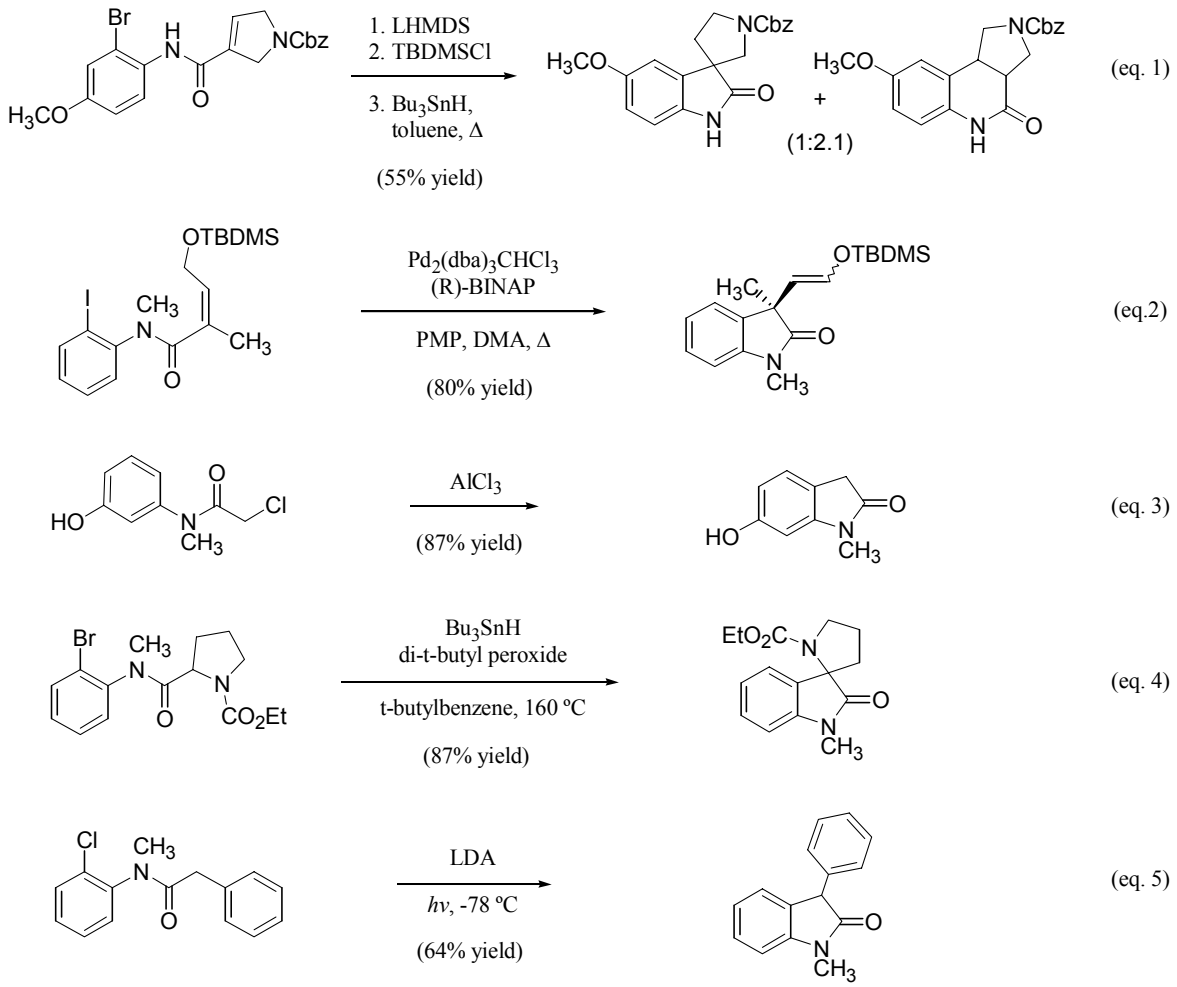
2.2.1 A Review.

An examination of the literature uncovers several existing methodologies available for the construction of oxindoles (Scheme 2.2.1). These methodologies include but are not limited to radical (eq. 1)[1] and Heck cyclizations (eq. 2)[2] of 2-haloacryloylanilide derivatives, Friedel-Crafts cyclizations of 2-haloacetanilides (eq. 3),[3] as well as radical (eq. 4)[4] and photochemical (eq. 5)[5] cyclizations of 2-haloanilide derivatives.

While there are many methods are available for the preparation of oxindoles, a more thorough examination reveals that only a handful of the existing methodologies allow for the efficient construction of 3,3 disubstituted oxindoles. For instance, several of the existing methods involve the cyclization of a reactive intermediate into an olefin, thus mixtures of the desired oxindole and the regioisomeric 3,4-dihydroquinolin-2-one

are often obtained (i.e., Scheme 2.2.1, eq.1). Additionally, when these methods are employed in the synthesis of 3,3-disubstituted oxindoles, a drop in regioselectivity is often observed.

Scheme 2.2.1



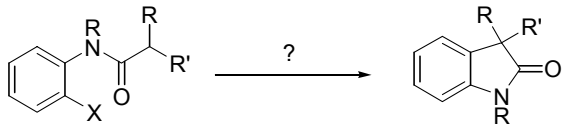
In spite of this, the Heck reaction has emerged as a powerful tool for the construction of 3,3 disubstituted oxindoles.[6-8] However, there are certain instances where the requisite acryloylanilide can be difficult to prepare and/or thermally unstable. In particular, preliminary work in this project found that the cyclobutenes required for the intramolecular Heck reaction were thermally labile and at elevated temperatures

underwent electrocyclic ring-opening.[9-11] With these concerns in mind, a novel method for the construction of spirocyclic oxindoles was sought.

2.2.2 Pd-Mediated Arylation of Amides (Hartwig Chemistry).

In accord with the aforementioned methods for the construction of spirocyclic oxindoles, the C(3)-C(9) bond was targeted as the pivotal bond in the construction of the core of **7**. In contemplating different methods for the construction of this bond, the feasibility of assembling the oxindole ring via the intramolecular arylation of an appropriately substituted amide was considered (Scheme 2.2.2). At the outset of this project, there was no general method for the α-arylation of amides,[12] and the existing methods for the α-arylation of ketones and malonates were limited in scope.[13-20] Thus, a reliable method was desired for the α-arylation of amides, which if carried out in an intramolecular sense would allow for the preparation of spirocyclic oxindoles (Scheme 2.2.2, **89 → 90**).

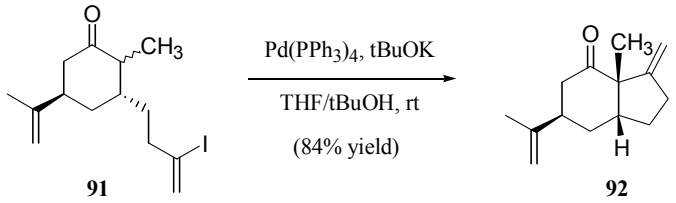
Scheme 2.2.2



89 **90**

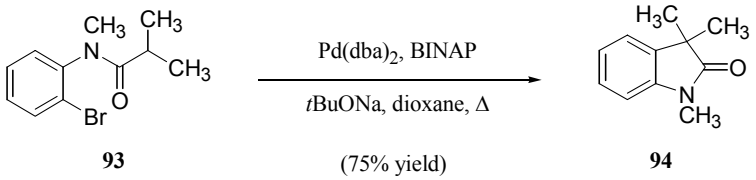
Prior to extensive work focusing on the palladium-catalyzed coupling of aryl and vinyl halides with enolates in the late 1990's,[21-23] there was a single report demonstrating the utility of this reaction.[24,25] This came from the Piers group in their synthesis of crinipellin B, where it was found that upon treatment with Pd(0) and base **91** underwent an intramolecular coupling to provide ketone **92** in good yield.

Scheme 2.2.3



More recently, the groups of Hartwig[21,26] and Buchwald[27,28] have shown that the intermolecular palladium-mediated coupling of ketone and malonate enolates with aryl halides is a versatile process that is broad in scope and proceeds under mild conditions. Thus, it seemed logical that this chemistry could be extended to the α-arylation of amides in the construction of oxindoles. Indeed, in 1998 Hartwig brought this idea to fruition in a report which disclosed a general procedure for the intramolecular arylation of *o*-bromoanilides in the construction of oxindoles (Scheme 2.2.4).[29] This reaction was shown to be suitable for the cyclization of a wide range of anilides providing the corresponding oxindoles in high yields. Perhaps most importantly was that this cyclization proceeded with complete control of regioselectivity, and that the highest yields were observed in the preparation of 3,3-disubstituted oxindoles.

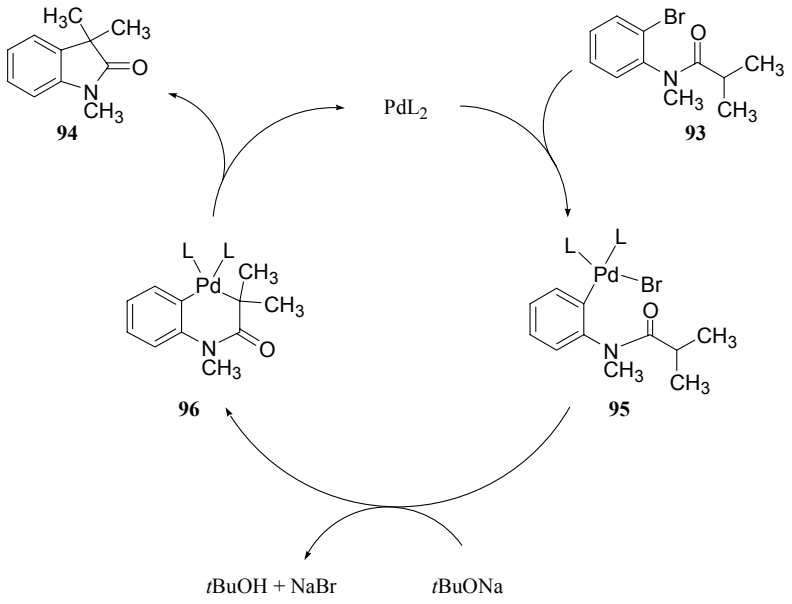
Scheme 2.2.4



2.2.3 Mechanism of the Palladium-Mediated Arylation of Amides.

The mechanism involved in the cyclization of *o*-haloanilides, recently explored by Hartwig,[30] is believed to parallel that involved in the arylation of ketones and malonates. Presumably, the process begins with the oxidative addition of the aryl halide to furnish aryl palladium species **95**. This intermediate then undergoes a based-induced formation of arylpalladium enolate **96**. Subsequent reductive elimination then gives rise to the oxindole (Scheme 2.2.5).

Scheme 2.2.5

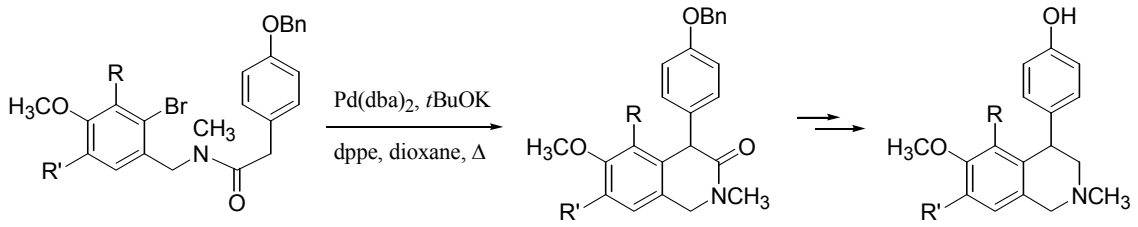


2.2.4 Applications of Pd-Mediated Arylations of Amides in Synthesis.

While there have been no reports describing the use of palladium-mediated arylation in the construction of oxindoles, Honda recently reported the arylation of

lactams **97** and **98** to furnish intermediate isoquinolines **99** and **100** in the synthesis of cherylline (**101**) and latifine (**102**), respectively (Scheme 2.2.6).[32]

Scheme 2.2.6



97 R = H, R' = OBn
98 R = OBn, R' = H

99 R = H, R' = OBn (81% yield) → cherylline **101**
100 R = OBn, R' = H (54% yield) → latifine **102**

2.3 Implementation of Pd-Mediated Arylation.

2.3.1 Initial Model Studies.

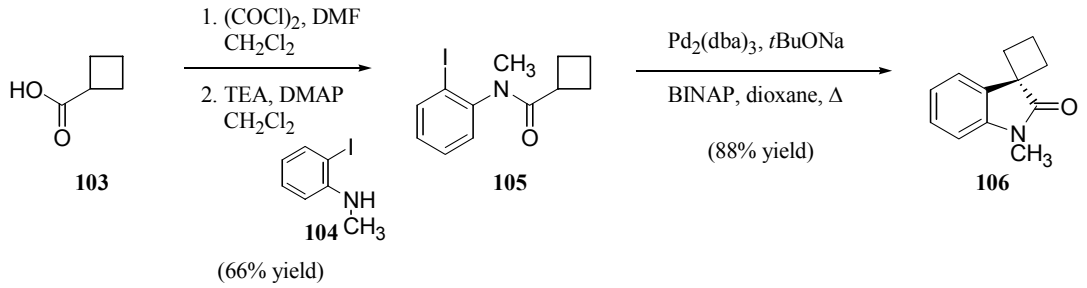
Relying on the initial report from Hartwig,[29] an exploration directed at expanding the scope of this method to include the construction of strained spirocyclobutane oxindoles began. Prudently, before investing considerable time in the preparation of elaborate cyclization substrates that could be elaborated to the natural product, several model studies were first undertaken to test the validity of this method as it pertained to the synthesis of **7**.

2.3.1.1 Cyclization of a Simple Substrate.

The first model study commenced with the coupling of *N*-methyl-2-iodoaniline (**104**)[33] and cyclobutanoyl chloride (derived from commercially available cyclobutane

carboxylic acid (**103**)) to afford anilide **105** (Scheme 2.3.1). Gratifyingly the addition of **105** to a refluxing suspension of *t*BuONa, $Pd_2(dba)_3$, and BINAP in dioxane resulted in the rapid consumption of starting material and formation of oxindole **106** in excellent yield. The efficiency with which this process proceeded suggested that it could indeed be a suitable method for the construction of the oxindole core of **7**.

Scheme 2.3.1

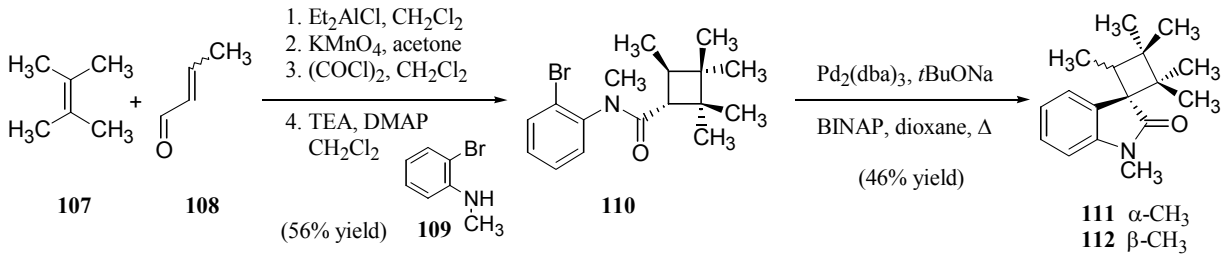


While this result was encouraging, it was deemed necessary to examine another model system before proceeding to more elaborate substrates. In this regard, it was fully expected that much more sterically congested substrates would need to be cyclized *en route* to **7**, thus the construction of a more sterically demanding model substrate was embarked upon.

Eager to test the efficiency of the palladium-mediated cyclization in a more sterically congested environment, anilide **110** was targeted as a cyclization substrate (Scheme 2.3.2). It was found that **110** could rapidly be accessed starting with 2,3-dimethyl-2-butene (**107**), which underwent a Lewis acid catalyzed [2+2] cycloaddition with crotonaldehyde (**108**).[34] The resulting aldehyde was oxidized to the corresponding acid, which following conversion to the analogous acid chloride, was smoothly coupled with *N*-methyl-2-bromoaniline (**109**) to give rise to the desired cyclization substrate

(**110**). Gratifyingly, upon the first attempt, exposure of **110** to the conditions initially reported by Hartwig led to the formation of a diastereomeric mixture of oxindoles **111** and **112** in moderate yield. The stereochemistry of the major product was determined via NOE measurements. (See experimental section for NOE enhancements.)

Scheme 2.3.2



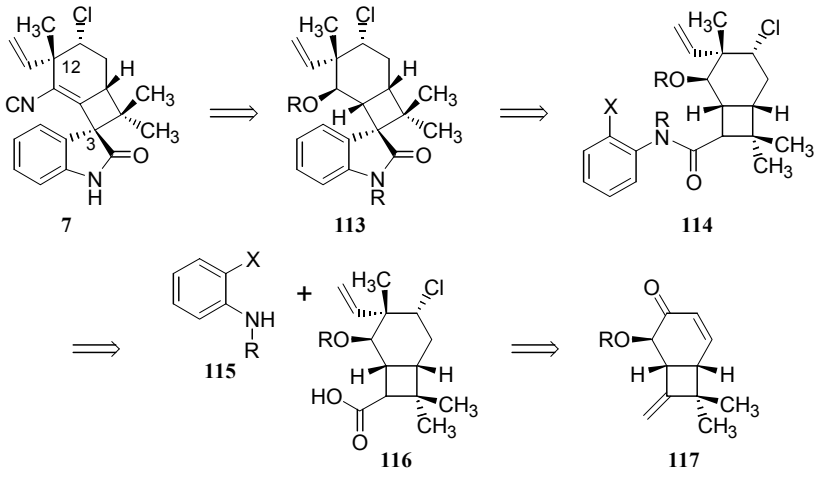
Rather than investing time optimizing this cyclization, the choice was made to move on and prepare more appropriate substrates. However, the importance of the conversion of **110** to **111** and **112** cannot be understated; with the construction of these oxindoles also came the confidence that this methodology would prove useful in the synthesis of **7**.

2.3.2 Retrosynthetic Analysis.

With the successful completion of the two model studies outlined above, a retrosynthetic analysis for **7** was devised using the Pd-mediated arylation as the key disconnection (Scheme 2.3.3). It was envisioned that the sensitive vinyl isonitrile would be unveiled late in the synthesis and would ultimately arise from an alcohol, thereby simplifying the natural product to oxindole **113**. A more detailed discussion pertaining to the preparation of vinyl isonitriles will be presented in Chapter 3.

Confident that the palladium-mediated arylation would prove successful, a bold approach was adopted which entailed construction of the oxindole at a late stage, thereby calling for the preparation and cyclization of a heavily substituted anilide. With this in mind, oxindole **113** was simplified to anilide **114**, which, following cleavage of the amide bond, generates suitably protected *o*-haloaniline derivative **115**, and heavily substituted carboxylic acid **116** as synthetic targets. It was envisaged that ketone **117** would be an appropriate precursor to acid **116**, as several strategies could be imagined for the elaboration of **117**.

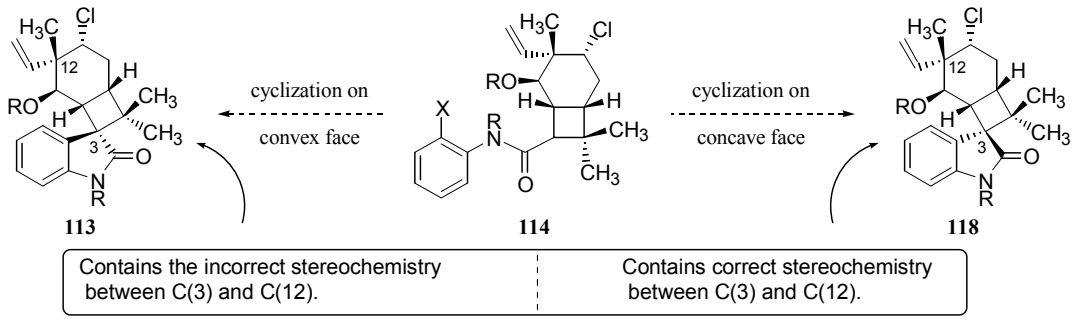
Scheme 2.3.3



Before attempting to take this retrosynthesis from the blackboard to the bench, a closer inspection revealed a possible synthetic pitfall. The point of concern revolved around the facial selectivity for the proposed cyclization of anilide **114** to oxindole **113**. In order to attain the correct relative stereochemistry between the two fully substituted quaternary centers [C(3) and C(12)], the cyclization of **114** must occur on the more hindered concave face of the rigid, heavily functionalized [4.2.0] system (Scheme 2.3.4). Alternatively, cyclization on the convex face would provide oxindole **118**, which

contains the incorrect relative stereochemistry between C(3) and C(12). Realizing that this potential problem could prove disastrous at a late stage this problem was addressed with a model [4.2.0] cyclization precursor (i.e., **114**). Hence, the focus of this model system would be the facial selectivity associated with the cyclization of an anilide containing a [4.2.0] bicyclic system.

Scheme 2.3.4

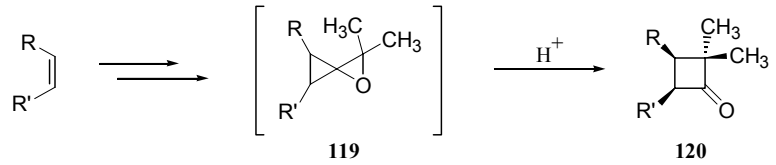


2.4 More Model Studies.

2.4.1 Preparation of a [4.2.0] Bicyclic System.

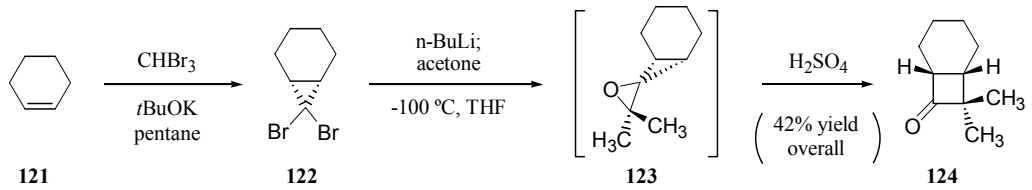
In searching for a quick, simple, and reliable method for the construction of [4.2.0] bicyclic systems it became apparent that chemistry developed by Seebach involving the rearrangement of oxaspiropentanes to the analogous cyclobutanones was a dependable method for the fashioning of gem-dimethyl substituted cyclobutanones (Scheme 2.4.1).[35] This chemistry was attractive, as it was experimentally facile, and the intermediate oxaspiropentanes (**119**), which are known to rapidly rearrange to the corresponding cyclobutane (**120**), can be generated from a wide range of 1,2-cis-substituted olefins.

Scheme 2.4.1



This method proved to be very effective in the preparation of a suitable [4.2.0] bicyclic system (Scheme 2.4.2). Thus, exposure of cyclohexene (**121**) to dibromocarbene generated *in situ* resulted in the formation of *gem*-dibromocyclopropane **122**. Sequential treatment of a cooled solution of **122** with *n*-butyllithium and acetone led to the formation cyclobutanone **124**, presumably by way of intermediate oxaspiropentane **123**.

Scheme 2.4.2

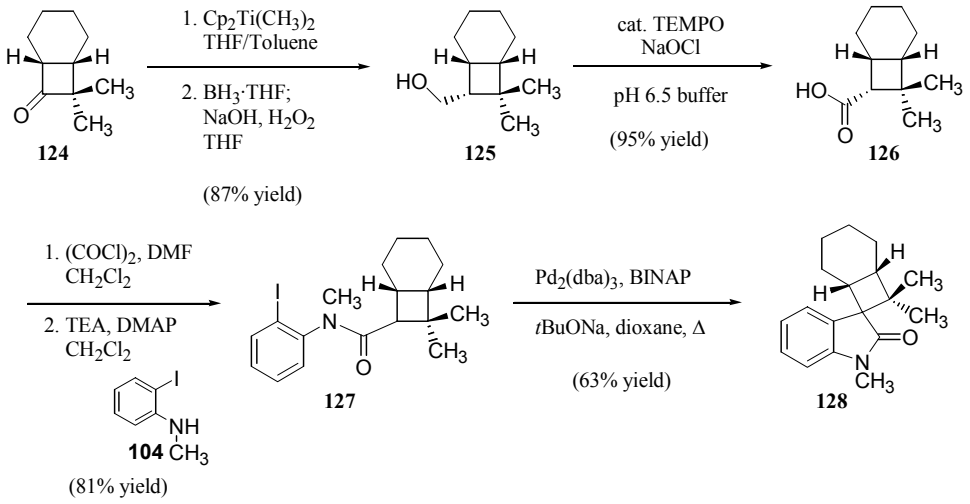


2.4.2 Preparation and Cyclization of Anilide 128.

Elaboration of **124** proceeded via methylenation of the ketone using Petasis' protocol (Scheme 2.4.3).[36,37] The resulting exocyclic methylene cleanly underwent hydroboration/oxidation to furnish primary alcohol **125**, which could be oxidized directly to carboxylic acid **126** using a NaOCl-based oxidation.[38] Conversion of this acid to the analogous acid chloride, and subsequent coupling with *N*-methyl-2-iodoaniline (**104**) furnished anilide **127** in good yield. Pleasingly, exposure of **127** to the cyclization conditions previously employed resulted in smooth cyclization to furnish a single

diastereomer of oxindole **128**, which constitutes the carbocyclic skeleton of welwitindolinone A (**7**).

Scheme 2.4.3



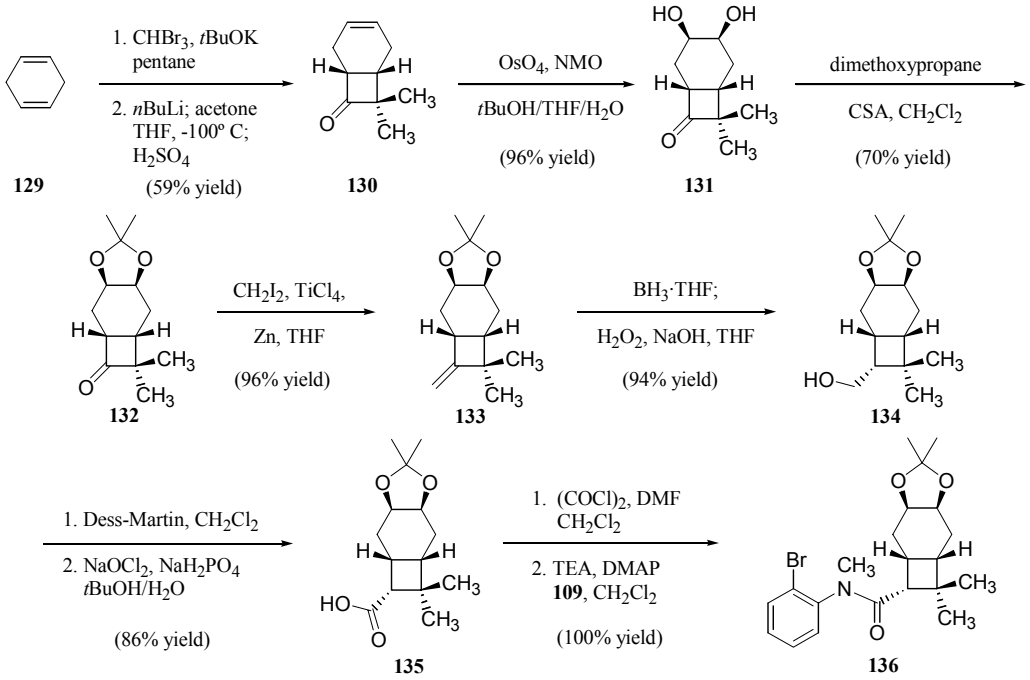
All that remained for the completion of this model study was a determination of the relative stereochemistry of oxindole **128**. Unfortunately, all attempts to unambiguously determine the relative stereochemistry of **128** via X-ray crystallography were unsuccessful and necessitated the need for the construction of a more functionally elaborate product.

In light of the ease and speed with which anilide **127** was prepared, the same method was employed in the construction of a slightly modified substrate. In choosing another cyclization substrate, one which contained a handle for derivatization was desired. This handle would ensure that following construction of the oxindole, a derivative suitable for X-ray crystallographic analysis could be prepared.

2.4.3 Construction and Cyclization of a Slightly Modified [4.2.0] System.

Based on this rationale, cyclohexadiene (**129**) was chosen as a starting point. This substrate, following conversion to the corresponding cyclobutanone, would contain an olefin that could function as the handle for later elaboration. Thus, using the same chemistry employed in the preparation of **127**, 1,4-cyclohexadiene (**129**) was transformed into cyclobutanone **130** (Scheme 2.4.4).[39] To preclude any selectivity issues pursuant to the methylenation of **130**, the olefin was dihydroxylated to furnish a single diastereomer of diol **131**, wherein the oxidation occurred exclusively on the convex face of the molecule.

Scheme 2.4.4

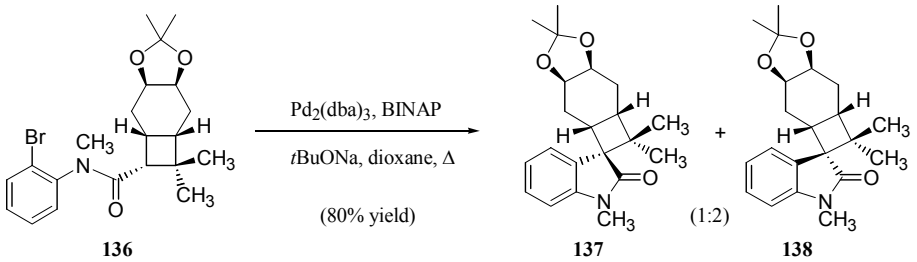


Protection of the diol furnished acetonide **132** a compound now ready for ketone methylenation. Surprisingly, this compound proved resistant to standard homologation procedures. It was found however, that Takai's protocol worked admirably in the

preparation of exocyclic methylene **133**.[40,41] Hydroboration/oxidation gave rise to a single diastereomer of primary alcohol **134**. Two step oxidation then furnished the analogous acid (**135**), which was coupled to *N*-methyl-*o*-bromoaniline (**109**) by means of the intermediate acid chloride, to afford anilide **136**.

Exposure of **136** to the previously employed conditions cleanly led to the formation of two new products (Scheme 2.4.5). After isolation and characterization, these two products were identified as diastereomeric oxindoles **137** and **138** in a 1:2 ratio. Unable to secure X-ray quality crystals of either of these oxindoles, efforts focused on using the protected diol as a handle for the preparation of a crystalline solid suitable for X-ray analysis.

Scheme 2.4.5

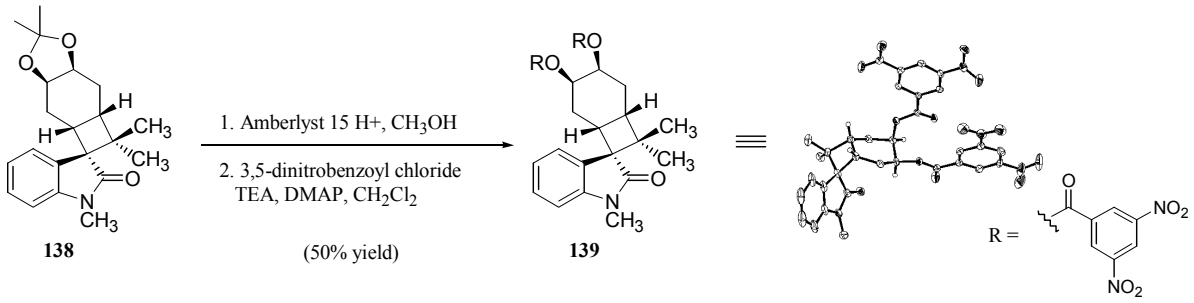


2.4.4 Determining the Relative Stereochemistry of Oxindole 138.

Exposure of the major diastereomer (**138**) to amberlyst 15 H^+ in methanol revealed a diol which, upon conversion to the corresponding bis-3,5-dinitrobenzoate derivative (**139**) provided a crystalline solid (Scheme 2.4.6). X-ray analysis of benzoate **139** illustrated two key points (see Appendix 4 for the X-ray crystallographic report). First, the spirocyclobutane oxindole core of welwitindolinone A was in fact constructed

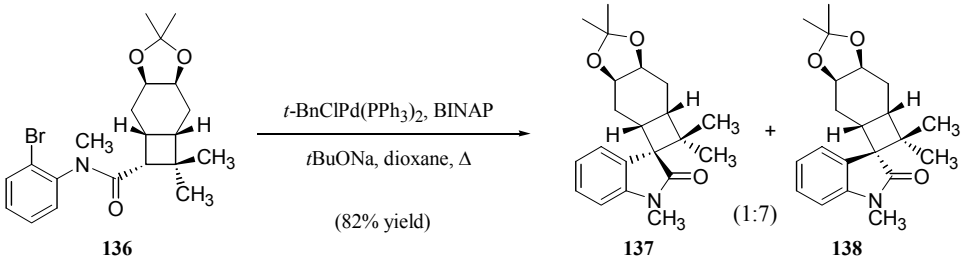
in the palladium-mediated arylation. Second, the X-ray analysis illustrated that the major diastereomer resulted from bond formation on the convex face of the molecule, supporting our initial concerns involving the facial selectivity of the amide arylation.

Scheme 2.4.6



Before reaching any conclusions regarding the intrinsic facial selectivity of this cyclization, an effort was made to improve the low level of diastereoselectivity observed. Following a brief exploration of catalysts and ligands, it was found that changing the catalyst from $Pd_2(dba)_3$ to *t*-ClBnPd$(PPh_3)_2$ [42-44] now provided oxindoles **137** and **138** in a 1:7 ratio, respectively, again in good yield.

Scheme 2.4.7



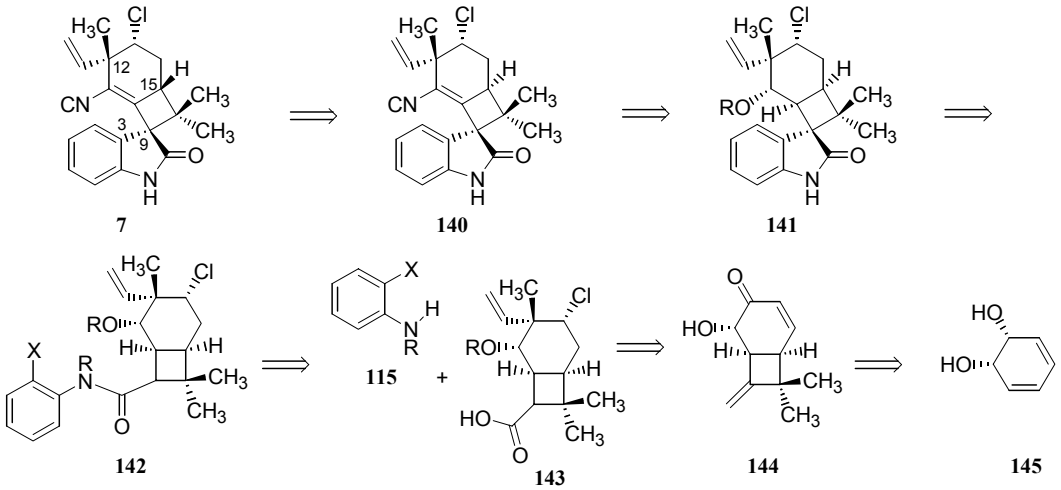
Thus, the foreseen anxiety revolving around the need to direct a cyclization to the concave face of a substrate containing a [4.2.0] system was indeed well founded. While unfortunate, this result was not terribly surprising, and thus forced a modification to the initially devised retrosynthetic analysis.

2.4.5 Revised Retrosynthetic Analysis.

Subsequent retrosynthetic planning was motivated by the facility with which cyclization could be guided to the convex face of the rigid [4.2.0] bicyclic system. As with the previously outlined approach, a fully elaborated [4.2.0] bicyclic system would be generated prior to formation of the oxindole. It was then envisioned that the stereochemistry at the [4.2.0] ring fusion could be used to control the relative stereochemistry established between the two quaternary centers [C(3) and C(12)] in the course of forming the C(3)-C(9) bond. Scheme 2.4.8 illustrates the reworked retrosynthetic analysis. It was anticipated that the immediate precursor to **7** could be its C(15) epimer **140**, thus requiring the inclusion of a late-stage epimerization in the synthesis. Disconnection of the vinyl isonitrile back to a protected hydroxyl group leads to oxindole **141**, which can be unraveled to **142**. Anilide **142** was expected to arise from protected *o*-haloaniline **115** and acid **143**, the latter of which could be simplified to ketone **144**. Finally, meso diene **145**, which is available via an enzymatic oxidation of benzene,[45] was envisioned to be an appropriate starting point.

It is worth noting at this point that in the forward sense, cyclization of **142** via bond formation on the convex face of the [4.2.0] system will generate the correct relative stereochemistry between the two quaternary centers. However, establishing the correct relative stereochemistry between these two centers comes at the cost of generating the incorrect relative stereochemistry at C(15). Epimerization of this position late in the synthesis was expected to provide the natural configuration at this center. This point will be discussed more thoroughly in Chapter 3.

Scheme 2.4.8

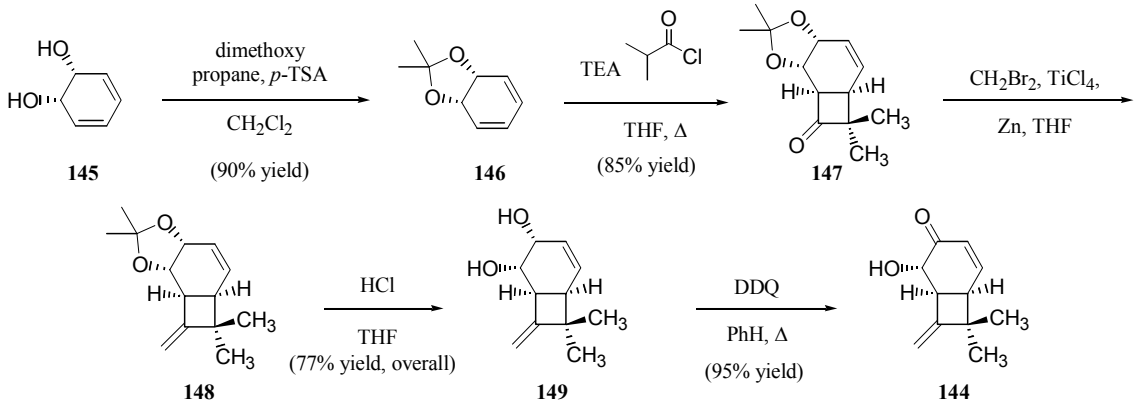


2.5 Initial Approach.

2.5.1 Preparation of Ketone 144.

The literature was once again consulted for a reliable and scaleable method for the construction of [4.2.0] bicyclic systems in order to aid in the preparation of ketone **144**. After surveying the literature, it became apparent that one such method involved the thermal [2+2] cycloaddition of any number of ketenes.[46] Therefore, a cyclohexene unit was required that would allow for rapid elaboration of the [4.2.0] bicyclic system. An examination of the commercially available cyclohexadiene derivatives ultimately led to 3,5-cyclohexadiene-1,2-diol (**145**) as the diene of choice.[47,48] It was soon found that **145** was indeed a suitable starting point for the synthesis of ketone **144** (Scheme 2.5.1).

Scheme 2.5.1



As illustrated in Scheme 2.5.1, acid labile diol **145** could be converted to acetonide **146** following a literature procedure.[49] Slow addition of excess isobutyryl chloride to a refluxing solution of **146** and TEA led to the formation of cyclobutanone **147** in excellent yield. Gratifyingly, the reaction of **146** with *in situ* generated dimethyl diketene, occurred with complete regio- and diastereocontrol to furnish exclusively the desired product **147**. This product could be parleyed into ketone **144** in a three-step sequence involving methylenation of the ketone to provide **148**, hydrolysis of the acetonide to give rise to diol **149**, and selective allylic oxidation to afford ketone **144**. While traditional methods for this allylic oxidation proved unsatisfactory, this final transformation could be achieved by exposure of diol **149** to three equivalents of 2,3-dichloro-5,6-dicyano-benzoquinone (DDQ) in refluxing benzene.[50] Importantly, the conversion of **145** to **144** proceeded in good overall yield and provided access to multi-gram quantities of ketone **144**.

Having gained access to **144**, attention could now shift to the preparation of a fully elaborated [4.2.0] bicyclic system containing the C(12) quaternary center and the

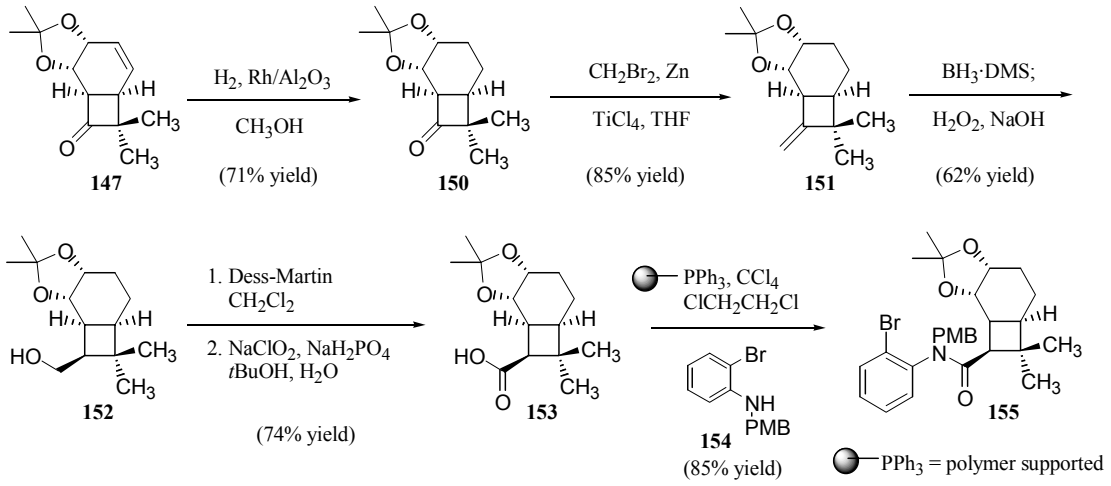
hindered chlorine. However, before advancing to these issues, and with plenty of **144** in hand, a tactful decision was made to investigate the cyclization of one more model substrate which contained a [4.2.0] bicyclic system. Section 2.6 outlines the results of this final study.

2.6 One Last Model Study.

2.6.1 Construction of Anilide 155.

In an effort to expedite the final model study, cyclobutanone **147** was selected as a precursor to the cyclization substrate. Cyclobutanone **147** could be advanced by hydrogenation to ketone **150**, which, following methylenation using Takai's protocol, furnished olefin **151** (Scheme 2.6.1). Hydroboration/oxidation proceeded smoothly to provide **152** which was advanced by a two-step oxidation sequence to afford acid **153** in good overall yield. Previous model studies were conducted with an *N*-methyl protected aniline, thus the choice was made to use this opportunity to choose an aniline with a more labile protecting group. Coupling of acid **153** to *p*-methoxybenzyl (PMB)-protected *o*-bromoaniline **154**,[51] proved somewhat troublesome under the conditions used previously. This coupling was ultimately effected by exposure of **153** and **154** to polymer supported triphenylphosphine (PPh_3) in the presence of carbon tetrachloride, providing the desired anilide **155** in high yield.[52-55]

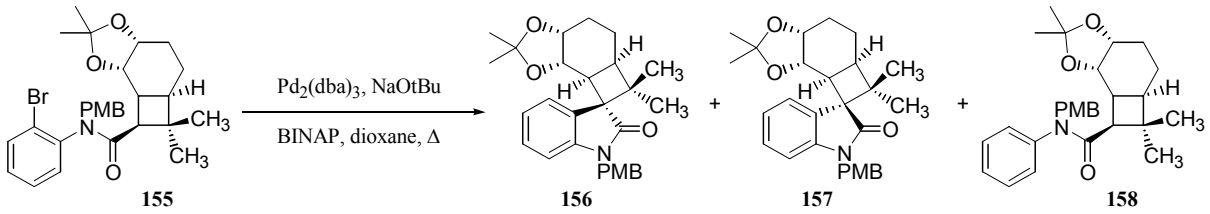
Scheme 2.6.1



2.6.2 Cyclization of Anilide 155.

The first conditions examined for the cyclization of anilide **155** again were those originally reported by Hartwig, as these conditions had thus far proven very efficient for the construction of spirocyclic oxindoles.[29] Treatment of **155** with $Pd_2(dba)_3$, BINAP and *t*BuONa (Table 2.6.1, entry 1) furnished a 1:6 mixture of diastereomeric oxindoles **156** and **157**, respectively, in a 29% overall yield (Scheme 2.6.2). The stereochemistry of each of the products was determined using NOE methods. (See experimental section for NOE enhancements). In addition to these diastereomeric oxindoles, the product of hydrodebromination (**158**) was also isolated in 9% yield.

Scheme 2.6.2



While comforted by the moderate level of diastereoselectivity, which again favored cyclization from the convex face, the low overall yield did cause concern and led to a survey of numerous catalysts and ligands. The results obtained from this investigation are reported in Table 2.6.1. As seen in this table, very high levels of diastereoselectivity can be achieved upon varying both the source of palladium and the ligand.

Table 2.6.1

entry	Pd (mol%)	Ligand (mol%)	Time (hr.)	Conv. (%)	156 (%)	157 (%)	158 (%)
1.	$Pd_2(dba)_3$ (30)	BINAP (45)	7	88	4	25	9
2.	$Pd_2(dba)_3$ (40)	BINAP (30)	6	100	16	18	0
3.	$Pd_2(dba)_3$ (70)	BINAP (100)	5	100	2	26	10
4.	$Pd(OAc)_2$ (30)	PCy_3 (30)	6	32	0	0	6
5.	$Pd(OAc)_2$ (30)	PCy_3 (30)	20	60	0	0	22
6.	t-BnClPd$(PPh_3)_2$ (40)	BINAP (40)	5	100	6	59	5
7.	t-BnClPd$(PPh_3)_2$ (40)	dppe (40)	5	100	3	59	5
8.	t-BnClPd$(PPh_3)_2$ (20)	dppe (20)	3	100	2	54	7
9.	t-BnClPd$(PPh_3)_2$ (30)	---	5	100	8	77	8
10.	$Pd(PPh_3)_4$ (30)	---	7	100	10	65	8

Interestingly, when the reaction was conducted with *t*-BnClPd$(PPh_3)_2$ with no additional ligand the reaction proceeded in excellent yield and with a good level of selectivity (entry 9). Further, it was intriguing to find that the reaction also proceeded in

good yield and with high levels of selectivity when conducted in the presence of $Pd(PPh_3)_4$ (entry 10).

2.7 Conclusion.

The palladium-mediated cyclization of α-haloanilides has been employed in the construction of spirocyclobutane oxindoles, and has proven suitable for the cyclization of heavily substituted cyclobutanes. This method was employed in the cyclization of anilides **136** and **155** each of which provided oxindoles that constitute the complete carbocyclic skeleton of welwitindolinone A isonitrile (**7**). Additionally, several model studies have shown that this cyclization can be guided to the convex face of the [4.2.0] bicyclic system, thereby supporting the approach outlined in Scheme 2.4.8.

2.8 Experimental Section.

2.8.1 Materials and Methods.

Unless otherwise stated, all reactions were conducted in flame-dried glassware under a positive pressure of nitrogen using freshly distilled solvents. Tetrahydrofuran (THF), diethyl ether (Et_2O), and dioxane were distilled from sodium metal/benzophenone ketyl. Methylene chloride (CH_2Cl_2), benzene, pentane, pyridine, and triethylamine (TEA) were distilled from calcium hydride. Carbon tetrachloride (CCl_4), 1,2-dichloroethane, titanium tetrachloride ($TiCl_4$), dimethylformamide (DMF), and BF_3•OEt_2

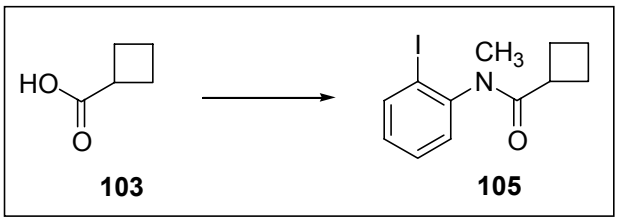
were purchased from the Aldrich Chemical Co. in Sure/Seal™ containers and were used without further purification.

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). Preparative TLC was also performed using E. Merck silica gel 60 F254 pre-coated plates (0.25-mm). Column and/or flash chromatography was performed with the indicated solvents using silica gel (particle size 0.032-0.063 mm) purchased from Fisher Scientific. Chromatography was performed using the procedures reported by Still.[56]

Melting points were obtained on a Gallenkamp variable temperature melting apparatus (model: MPD350.BM2.1) and are uncorrected. Infrared spectrum (IR) were recorded on a Midac M-1200 FTIR. ^{1}H and ^{13}C spectra were recorded on a Bruker AM-500 or Bruker Advance 400 spectrometers. Chemical shifts are reported relative to chloroform (^{1}H, δ 7.27; ^{13}C, δ 77.0 ppm) or benzene (^{1}H, δ 7.16; ^{13}C, δ 128 ppm). High resolution mass spectra were performed at The University of Illinois Mass Spectrometry Center. Single-Crystal X-ray analyses were performed by Susan DeGala of Yale University.

2.8.2 Preparative Procedures:

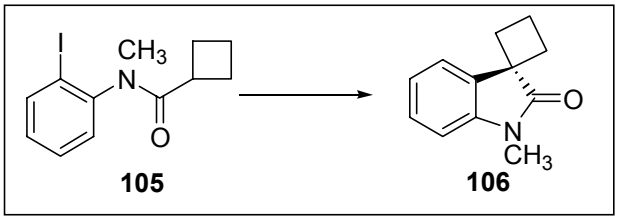
Preparation of Anilide 105.



Anilide 105. A solution of acid **103** (1.00 g, 9.98 mmol, 1.0 eq.) and oxalyl chloride (1.31 mL, 14.98 mmol, 1.5 eq.) in CH_2Cl_2 (100 mL) at 0 °C was treated with DMF (100 μL), which resulted in the immediate evolution of gas. The resulting solution was allowed to stir at 0 °C for 1 hour before being concentrated under reduced pressure (rotary evaporator) at 0 °C. The derived residue was taken up in CH_2Cl_2 (90 mL) and cooled to 0 °C before a solution of aniline **104** (2.3 g, 9.98 mmol, 1.0 eq.) in CH_2Cl_2 (10 mL) was added dropwise. A catalytic amount of DMAP (50 mg) was added and the reaction was removed from the ice-bath and stirred at room temperature for 30 minutes. The mixture was absorbed onto silica gel and subjected to flash chromatography (15% EtOAc/hexanes eluent) to provide anilide **105** (2.2 g, 66% yield) as a white solid. m.p. 79-82 °C; FTIR (thin film/NaCl) 2986 (w), 2945 (m), 1655 (s), 1469 (m), 1428 (m), 1377 (m) 1128 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, J = 1.5, 8.0 Hz, 1H), 7.31 (dt, J = 1.5, 8.0 Hz, 1H), 7.09 (dd, J = 1.5, 7.5 Hz, 1H), 6.97 (dt, J = 1.5, 8.0 Hz, 1H), 3.04 (s, 3H), 2.71 (q, J = 9.5 Hz, 1H), 2.35-2.30 (m, 1H), 2.13-2.08 (m, 1H), 1.67-1.57 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 145.4, 139.6, 129.3, 129.2, 129.0, 99.6,

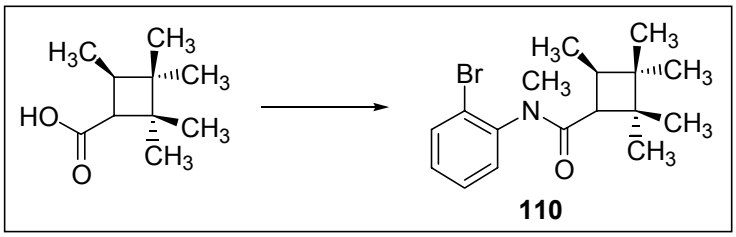
37.8, 35.7, 26.0, 24.5, 17.6; HRMS (EI) *m/z* 316.0196 [cacl'd for $C_{12}H_{14}INO$ (M+H) 316.0198].

Preparation of Oxindole 106.



Oxindole 106. A flame dried 25 mL flask was charged with $Pd_2(dba)_3$ (37 mg, 0.04 mmol, 0.05 eq.), BINAP (39 mg, 0.06 mmol, 0.75 eq.), *t*BuONa (120 mg, 1.25 mmol, 1.5 eq.), and freshly distilled dioxane (4 mL). To this dark red suspension was added a solution of anilide **105** (250 mg, 0.83 mmol, 1.0 eq.) in dioxane (4 mL). The resulting suspension was submersed into an oil bath and refluxed for 2 hours, at which point the reaction was cooled to room temperature diluted with Et_2O (10 mL) and poured into saturated NH_4Cl (25 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 15 mL), washed with brine, and dried over $MgSO_4$. Concentration followed by absorption of the derived residue on silica gel was followed by flash chromatography (30% EtOAc/hexanes eluent) to afford oxindole **106** (135 mg, 88% yield) as a pale yellow oil. FTIR (thin film/NaCl) 2934 (w), 1713 (s), 1699 (s), 1613 (m), 1471 (w), 1350 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 1.0, 8.0 Hz, 1H), 7.27 (t, *J* = 7.0 Hz, 1H), 7.11 (dt, *J* = 1.0, 7.5 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 3.20 (s, 3H), 2.60-2.56 (m, 2H), 2.31-2.16 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.2, 143.0, 134.4, 127.8, 122.5, 122.2, 107.6, 48.1, 31.2, 26.2, 16.8; HRMS (EI) *m/z* 187.0990 [cacl'd for $C_{12}H_{13}NO$ (M+) 187.0997].

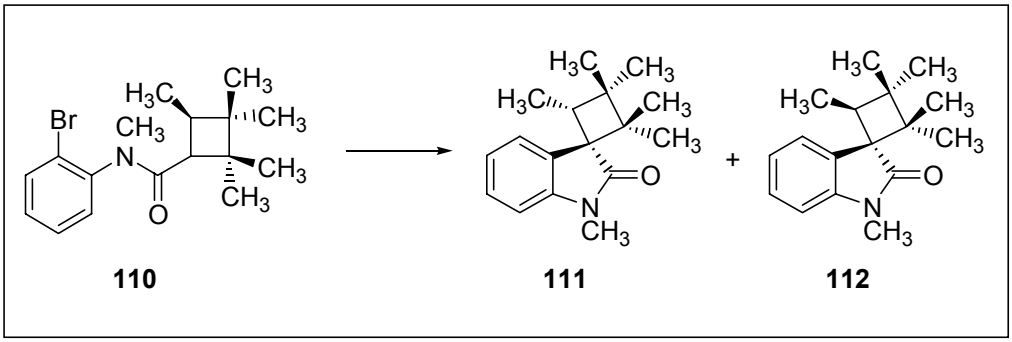
Preparation of Anilide 110.



Anilide 110. To a solution of 2,2-3,3-4-pentamethylcyclobutane-1-carboxylic acid prepared according to the procedure of Snyder[34] (90 mg, 0.53 mmol, 1.0 eq.) in CH_2Cl_2 (5 mL) was added oxalyl chloride (69 μL, 0.79 mmol, 1.5 eq.) followed by a catalytic amount of DMF (2 μL), which resulted in the immediate evolution of gas. The resulting solution was allowed to stir for 30 minutes before being concentrated under reduced pressure. The derived residue was taken up in CH_2Cl_2 (5 mL) and cooled to 0 °C before a solution of aniline **109** (130 mg, 0.69 mmol, 1.3 eq.) in CH_2Cl_2 (1 mL) was added dropwise. A catalytic amount of DMAP (1 mg) was added and the reaction was allowed to slowly warm to room temperature and stir overnight. The mixture was absorbed onto silica gel and subjected to flash chromatography (20% EtOAc/hexanes eluent) to afford anilide **110** (170 mg, 94% yield) as a white solid. m.p. 79-80 °C; FTIR (thin film/NaCl) 2956 (s), 2868 (w), 1661 (s), 1474 (s), 1418 (m), 1367 (w), 1278 (w), 1142 (w), 1025 (w), 764 (w), 730 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67-7.64 (m, 2H), 7.39-7.34 (m, 2H), 7.24-7.17 (m, 4H), 3.20 (s, 3H), 3.17 (s, 3H), 2.59-2.45 (m, 2H), 2.39 (d, J = 10.2 Hz, 1H), 2.12 (d, J = 10.0 Hz, 1H), 1.03 (s, 3H), 0.99 (s, 3H), 0.80-0.76 (m, 12H), 0.67 (s, 3H), 0.66 (s, 3H), 0.49 (s, 3H), 0.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 172.0, 142.8, 142.6, 133.9, 133.6, 131.2, 130.7, 129.5, 129.3, 128.5, 128.4, 123.8, 123.7, 51.7, 50.8, 41.9, 41.5, 38.4, 37.1, 36.9, 36.1, 36.0, 24.0, 23.4, 23.1,

23.0, 21.2, 20.3, 19.7, 19.6, 12.9, 12.6; HRMS (EI) *m/z* 337.1038 [calc'd for $C_{17}H_{24}BrNO$ (M+) 337.1041].

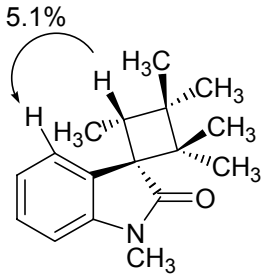
Preparation of Oxindoles 111 and 112.



Preparation of Oxindoles 111 and 112. A flame dried flask was charged with $Pd_2(dba)_3$ (27 mg, 0.03 mmol, 0.10 eq.), BINAP (18 mg, 0.03 mmol, 0.10 eq.), and *t*BuONa (36 mg, 0.44 mmol, 1.5 eq.). The flask was then evacuated and kept under high vac. for 30 minutes. After backfilling the flask with nitrogen, freshly distilled dioxane (3 mL) was introduced to provide a deep red suspension. This suspension was then degassed by repeated several cycles of evacuation the flask and then backfilling it with nitrogen (x 4). A solution of amide **110** (100 mg, 0.30 mmol, 1.0 eq.) in freshly distilled dioxane (3 mL) was then introduced into the flask via syringe addition. The resulting red suspension was then immersed into an oil bath preheated to 110 ºC. Over a period of three hours, the red suspension gradually faded in color and ultimately turned into a pale yellow suspension. The reaction was heated in dioxane for a total of 12 hours, at which point TLC indicated the complete consumption of starting material and formation of higher R_f products. The reaction was removed from the oil bath and allowed to cool to room temperature before being diluted with Et_2O (10 mL) and poured into saturated

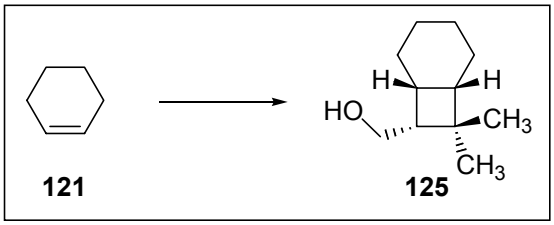
NH_4Cl (15 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Concentration followed by absorption of the derived residue on silica gel was followed by flash chromatography (30% EtOAc/hexanes eluent) to furnish an 10:1 mixture of oxindoles **111** and **112**, respectively. (Only the major product **111** was characterized.) The first compound to elute was oxindole **111** (29 mg, 38% yield) as a white solid. m.p. 121.5-123.5 ºC; FTIR 2950 (m), 2925 (m), 1697 (s), 1611 (m), 1475 (w), 1345 (w), 1092 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.3 Hz, 1H), 7.23 (dt, *J* = 1.5, 7.8 Hz, 1H), 7.03 (dt, *J* = 1.0, 7.5 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 3.14 (s, 3H), 2.63 (q, *J* = 7.0 Hz, 1H), 1.38 (s, 3H), 1.12 (s, 3H), 1.07 (s, 3H), 0.98 (s, 3H), 0.87 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 144.1, 130.0, 127.2, 125.0, 121.0, 106.9, 58.3, 44.5, 43.5, 38.4, 25.7, 25.6, 24.8, 20.3, 19.1, 8.5; HRMS (EI) *m/z* 257.1778 [cacl'd for $C_{17}H_{23}NO$ (M+) 257.1780].

NOE enhancements
^1H 400 MHz, $CDCl_3$



111

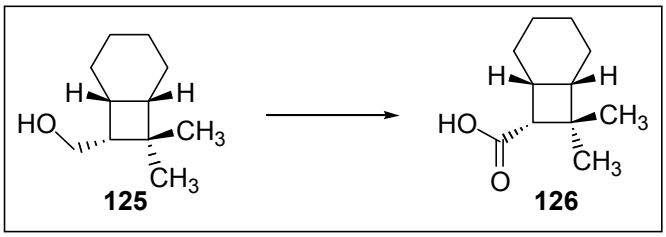
Preparation of Alcohol 125.



Alcohol 125. To a 500 mL 3 neck flask equipped with an additional funnel was added cyclohexene (6.90 g, 84.00 mmol, 1.0 eq.) and pentane (100 mL). To this solution was added *t*BuOK (10.18 g, 90.71 mmol, 1.08 eq.) in one batch. The resulting suspension was cooled to –15 °C and bromoform (21.23 g, 84.00 mmol, 1.0 eq.) in pentane (10 mL) was added via an addition funnel over 2 hours. The solution was then allowed to warm to room temperature over 1 hour and was quenched with H_2O (750 mL) and extracted with pentane (2 x 250 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to provide pure dibromide **122** (18.41g, 86% yield) as a colorless oil that was carried on without further purification. A solution of dibromide **122** (3.0 g, 11.80 mmol, 1.0 eq.) in THF (60 mL) was cooled to –100 °C and treated with *n*BuLi (2.25 M in hexanes, 11.80 mmol, 1.0 eq.). Stirring was continued at this temperature for 1 hour before freshly distilled acetone (0.68 g, 11.80 mmol, 1.0 eq.) was added dropwise over 10 minutes. The mixture was maintained at this temperature for 3 hours before being allowed to warm to room temperature and stir for an additional 15 hours. The solution was then poured into 0.5 N H_2SO_4 (250 mL) and stirred vigorously for 10 minutes. Separation of the layers was followed by extraction of the aqueous layer with ether (5 x 20 mL), washing with brine and drying over $MgSO_4$. Concentration *in vacuo* furnished an oil which was subjected to flash chromatography (5% EtOAc/hexanes eluent) to provide cyclobutanone **124** (735 mg, 42% yield) as a

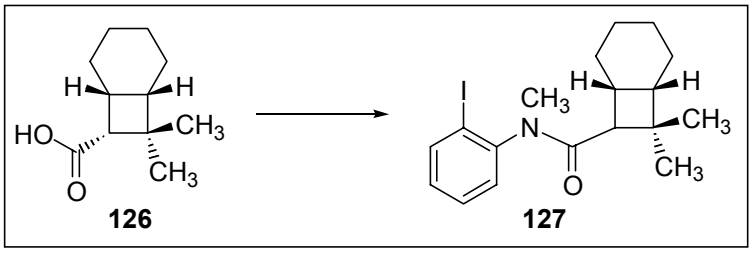
colorless oil which was immediately carried on to the next step. To a solution of ketone **124** (735 mg, 4.84 mmol, 1.0 eq.) in toluene/THF (3:1 10 mL) was added $Cp_2Ti(CH_3)_2$ (0.24 M in 3:1 toluene/THF, 60.3 mL, 3.0 eq.). The orange solution was covered with foil and heated to 65 °C for 18 hours before being reduced to approximately half the original volume. The solution was cooled to 0 °C and hexanes was added to precipitate an orange solid. The whole was filtered through a short plug of silica gel with hexanes to furnish the crude olefin as a colorless oil that was carried on without further purification. This olefin was taken up in THF (25 mL) and treated with BH_3•THF (1.0 M in THF, 4.83 mL, 1.0 eq.) while at 0 °C. The solution was allowed to slowly warm to room temperature over 2 hours and stir for an additional 2 hours. The solution was recooled to 0 °C and 2 N NaOH (4.0 mL) and 30% H_2O_2 (4.0 mL) were added sequentially. The solution was stirred for 30 minutes before being diluted with saturated $NaHCO_3$ (10 mL). The aqueous layer was extracted with Et_2O, washed with brine, dried over Na_2SO_4, and concentrated to provide an oil that was purified by column chromatography (20% EtOAc/hexanes eluent) to provide alcohol **125** (703 mg, 87% yield) as a colorless oil. FTIR (thin film/NaCl) 3330 (bs), 2927 (s), 1453 (m), 1364 (m), 1016 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.81-3.74 (m, 2H), 2.41 (p, J = 8.9 Hz, 1H), 2.22 (q, J = 8.0 Hz, 1H), 2.04-1.99 (m, 1H), 1.62-1.36 (m, 7H), 1.22-1.12 (m, 2H), 1.10 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 61.2, 48.2, 39.6, 39.2, 33.0, 30.3, 22.5, 22.4, 22.1, 21.3, 19.8; HRMS (EI) *m/z* 168.1513 [cacl'd for $C_{11}H_{20}O$ (M+) 168.1514].

Preparation of Acid 126.



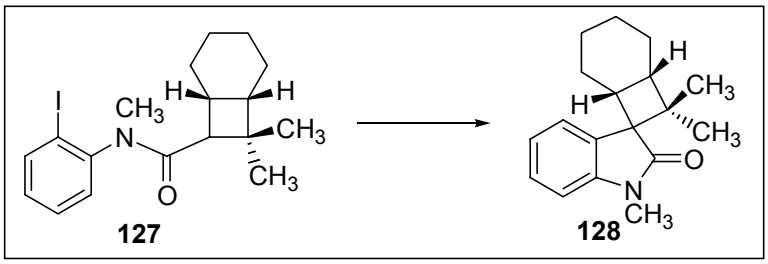
Acid 126. A mixture of alcohol **125** (348 mg, 2.04 mmol, 1.0 eq.), TEMPO (22.6 mg, 0.14 mmol, 0.07 eq.), CH_3CN (10 mL) and sodium phosphate buffer (0.67 M, 9 mL, pH = 6.7) was heated to 35 °C. To this solution was then added $NaClO_2$ (478 mg, 4.14 mmol, 2 eq.) in H_2O (2.1 mL) followed by aqueous NaOCl (5.25%, 54 μL in 1 mL H_2O). The solution was maintained at this temperature for 4 hours before being cooled to room temperature and adjusting the pH to 9 with 2 N NaOH. The reaction was quenched upon its addition to a saturated solution of Na_2SO_3 (5 mL), which was followed by stirring for 20 minutes. The aqueous layer was washed with Et_2O (2 x 5 mL) then acidified with 1 N HCl and extracted again with Et_2O (4 x 10 mL). Washing of the combined organic layers was followed by drying over Na_2SO_4 and concentration *in vacuo* to afford acid **126** (359 mg, 95% yield) as a white solid. m.p. 76-79 °C; FTIR (thin film/NaCl) 2936 (bs), 1696 (s), 1417 (w), 1261 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.00 (d, *J* = 8.6 Hz, 1H), 2.59-2.52 (m, 1H), 2.11-2.07 (m, 1H), 1.95-1.89 (m, 1H), 1.70-1.62 (m, 3H), 1.47-1.40 (m, 3H), 1.28 (s, 3H), 1.17 (s, 3H), 1.13-1.02 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.5, 50.4, 42.3, 39.1, 32.6, 31.8, 25.0, 22.7, 22.3, 21.3, 21.1; HRMS (EI) *m/z* 182.1306 [cacl'd for $C_{11}H_{18}O_2$ (M+) 182.1307].

Preparation of Anilide 127.



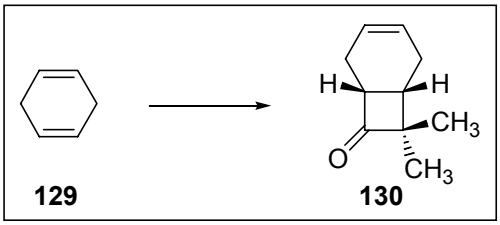
Anilide 127. A solution of acid **127** (237 mg, 1.30 mmol, 1.0 eq.) in CH_2Cl_2 (5 mL) was treated with oxalyl chloride (227 μL, 2.60 mmol, 2.0 eq.) and a catalytic amount of DMF (1 μL). Stirring was continued for 30 minutes before the solution was concentrated under reduced pressure to furnish a pale yellow residue. This residue was dissolved in CH_2Cl_2 (15 mL) and treated with a solution of *N*-methyl-2-iodoaniline (606 mg, 2.60 mmol, 2.0 eq.) in CH_2Cl_2 (5 mL). Stirring was continued at room temperature overnight before the whole was absorbed onto silica gel and subjected to flash chromatography (10% EtOAc/hexanes eluent) to provide anilide **127** as a mixture of rotamers (417 mg, 81% yield) as a white solid. m.p. 96-98 °C; FTIR (thin film/NaCl) 2932 (m), 1655 (s), 1469 (m), 1274 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.94 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.41 (app dt, *J* = 1.1, 7.4 Hz, 2H), 7.19-7.05 (m, 4H), 3.15 (s, 3H), 3.12 (s, 3H), 2.63 (d, *J* = 9.1 Hz, 1H), 2.54 (d, *J* = 8.2 Hz, 1H), 2.46 (p, *J* = 8.5 Hz, 1H), 2.34-2.24 (m, 1H), 2.03-1.23 (m, 16H), 1.59 (s, 3H), 1.23 (s, 3H), 1.12-0.97 (m, 2H), 1.04 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 171.7, 146.9, 146.2, 140.1, 140.0, 129.6, 129.5, 129.4, 129.3, 128.9, 100.4, 100.3, 49.2, 48.0, 41.5, 41.4, 40.4, 35.8, 35.6, 33.9, 32.9, 32.6, 32.1, 23.3, 22.2, 22.0, 21.8, 21.7, 21.5, 21.1, 20.6; HRMS (EI) *m/z* 397.0901 [cacl'd for $C_{18}H_{24}INO$ (M+) 397.0903].

Preparation of Oxindole 128.



Oxindole 128. A 5 mL flask was charged with $Pd_2(dba)_3$ (1.7 mg, 0.0018 mmol, 0.05 eq.), BINAP (1.2 mg, 0.0019 mmol, 0.075 eq.), *t*BuONa (4.60 mg, 0.0566 mmol, 1.5 eq.), and dioxane (1 mL). To this purple suspension was then added a solution of anilide **127** (15.0 mg, 0.0378 mmol, 1.0 eq.) in dioxane (1 mL). The resulting suspension was allowed to reflux for 4 hours at which point a yellow solution had resulted. Additional *t*BuONa (4.60 mg, 0.0566 mmol, 1.5 eq.) was added and heating was continued for a further 5 hours. The reaction was cooled to room temperature, diluted with Et_2O (10 mL) and quenched with NH_4Cl (10 mL). The aqueous layer was extracted with Et_2O (2 x 10 mL). The organic layers were washed with brine, dried over Na_2SO_4 and concentrated to provide a residue that was purified by flash chromatography (10% EtOAc/hexanes eluent) to afford oxindole **128** (6.4 mg, 63% yield) as a white solid. m.p. 116-120 °C; FTIR (thin film/NaCl) 2929 (m), 1702 (s), 1608 (m), 1468 (m), 1335 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.5 Hz, 1H), 7.25 (t, *J* = 7.9 Hz, 1H), 7.05 (t, *J* = 7.3 Hz, 1H), 6.76 (d, *J* = 7.7 Hz, 1H), 3.16 (s, 3H), 2.83 (q, *J* = 8.8 Hz, 1H), 2.28-2.01 (m, 3H), 1.77-1.22 (m, 6H), 1.18 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 143.6, 131.8, 127.7, 124.7, 121.3, 107.1, 43.8, 40.1, 37.0, 29.9, 29.2, 25.8, 21.2, 21.1, 20.7, 20.6, 20.2; HRMS (EI) *m/z* 269.1777 [cacl'd for $C_{18}H_{23}NO$ (M+) 269.1780].

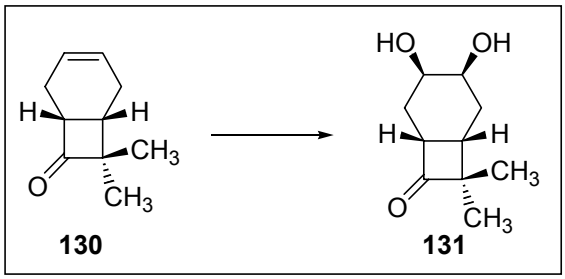
Preparation of Cyclobutanone 130.



Cyclobutanone 130. Following the procedure of Hofmann, 1,4-cyclohexadiene (**129**) was converted to the corresponding geminal dibromo-cyclopropane.[39] To a solution of this dibromide (5.0 g, 19.8 mmol, 1.0 eq.) in THF (90 mL) at –100 °C was added *n*-BuLi (8.13 mL, 2.44 M in hexanes, 1.0 eq.) dropwise at such a rate that the temperature of the reaction did not exceed –90 °C. The resulting solution was allowed to stir at this temperature for 45 minutes before freshly distilled acetone (1.46 mL, 19.8 mol, 1.0 eq.) was added dropwise over 15 minutes. The reaction was maintained at –95 °C for 2 hours, at which point it was allowed to slowly warm to room temperature and stir overnight. The entire reaction mixture was then poured into a 2-L flask containing 0.5 M H_2SO_4 (500 mL) and stirred for 10 minutes, at which point the layers were separated and the aqueous layer was extracted with Et_2O (3 x 250 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated to an oil which was subjected to silica gel chromatography (20% EtOAc/hexanes eluent) to deliver cyclobutanone **130** (1.75 g, 59% yield) as a colorless oil. FTIR (thin film/NaCl) 3026 (s), 2934 (s), 1768 (s), 1459 (m), 1357 (m), 993 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.87-5.82 (m, 2H), 3.65 (dt, J = 2.1, 7.3 Hz, 1H), 2.48-2.43 (m, 1H), 2.40 (dd, J = 2.2, 5.4 Hz, 1H), 2.27-2.17 (m, 2H), 2.06-2.01 (m, 1H), 1.25 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (125

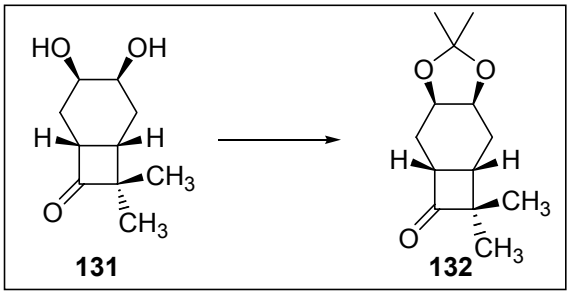
MHz, $CDCl_3$) δ 220.3, 128.2, 127.2, 59.4, 52.8, 35.1, 25.4, 22.2, 21.3, 15.4; HRMS (EI) *m/z* 150.1048 [cacl'd for $C_{10}H_{14}O$ (M+) 150.1045].

Preparation of Diol 131.



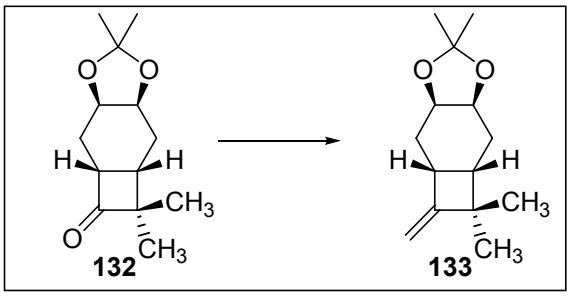
Diol 131. A solution of olefin **130** (2.5 g, 16.66 mmol, 1.0 eq.) in a 5:5:1 mixture of THF:^{t}BuOH:H_2O (150 mL) was cooled to 0 °C and treated with *N*-methylmorpholine-*N*-oxide (NMO) (2.14 g, 18.33 mmol, 1.1 eq.) followed by OsO_4 (2.5%, 1.68 mL, 0.01 eq.). The solution was stirred at 0 °C for 5 minutes then allowed to warm to room temperature and stir for 1.5 hours. The reaction was quenched by the addition of Na_2SO_3 (10 g) and H_2O (40 mL) which was followed by 10 minutes of vigorous stirring. Extraction with EtOAc (3 x 150 mL) was followed by washing with brine, drying over Na_2SO_4, and concentration *in vacuo*. The residue thus obtained was purified by filtration through a small plug of silica gel (50% EtOAc/hexanes eluent) to furnish diol **131** (2.95 g, 96% yield) as a white solid. m.p. 108.5-109.5 °C; FTIR (thin film/NaCl) 3416 (bs), 1752 (m), 1652 (m), 1065 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.95-3.93 (m, 1H), 3.78 (t, *J* = 9.4 Hz, 1H), 3.65 (ddd, *J* = 2.3, 5.9, 10.0 Hz, 1H), 2.34 (q, *J* = 7.8 Hz, 1H), 2.21-2.10 (m, 2H), 1.73 (dt, *J* = 9.2, 13.9 Hz, 1H), 1.37 (s, 3H), 1.36-1.32 (m, 1H), 1.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.4, 68.8, 68.7, 60.6, 52.5, 30.0, 28.6, 26.3, 24.3, 16.9; HRMS (EI) *m/z* 184.1100 [cacl'd for $C_{10}H_{16}O_3$ (M+) 184.1099].

Preparation of Acetonide 132.



Acetonide 132. A solution of diol **131** (2.7 g, 14.67 mmol, 1.0 eq) in CH_2Cl_2 (80 mL) was treated with dimethoxypropane (2.16 mL, 17.61 mmol, 1.2 eq.) and CSA (341 mg, 1.47 mmol, 0.1 eq.). The resulting solution was stirred at room temperature for 2 hours before being absorbed onto silica gel and purified by flash chromatography (30% EtOAc/hexanes eluent) to furnish acetonide **132** (2.28 g, 70% yield) as a white solid. m.p. 82-84 °C; FTIR (thin film/NaCl) 2963 (m), 2962 (m), 1763 (s), 1375 (m), 1249 (m), 1214 (m), 1024 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.42 (dt, *J* = 2.6, 7.8 Hz, 1H), 4.37 (dt, *J* = 2.6, 7.6 Hz, 1H), 3.62 (q, *J* = 10.5 Hz, 1H), 2.24 (ddd, *J* = 5.3, 10.4, 15.6 Hz, 1H), 2.08 (ddd, *J* = 2.8, 8.7, 15.0 Hz, 1H), 1.95-1.90 (m, 1H), 1.51 (ddd, *J* = 2.5, 10.8, 15.0 Hz, 1H), 1.44 (s, 3H), 1.30 (s, 3H), 1.29 (s, 3H), 1.21-1.15 (m, 1H), 1.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.3, 107.0, 72.0, 71.2, 60.7, 48.9, 28.9, 25.9, 25.4, 23.5, 22.1, 16.5; HRMS (EI) *m/z* 224.1410 [cacl'd for $C_{13}H_{20}O_3$ (M+) 224.1412].

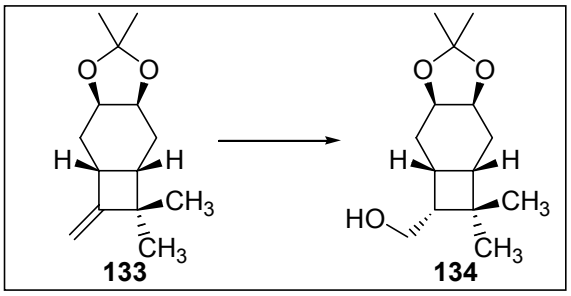
Preparation of Olefin 133.



Olefin 133. To a suspension of Zn (25 g, 383 mmol, 40.0 eq.) in THF (100 mL) was added CH_2Br_2 (12.0 mL, 192 mmol, 20.0 eq.). The mixture was stirred for 5 minutes then cooled to -78 °C and a solution of $TiCl_4$ (10.3 mL, 96 mmol, 10.0 eq.) in CH_2Cl_2 (150 mL) was added via an addition funnel over 30 minutes. After the addition was complete, the reaction was allowed to warm to 0 °C and stirred for 1 hour before ketone **132** (2.15 g, 9.60 mmol, 1.0 eq.) in THF (50 mL) was added via an addition funnel over 30 minutes. The reaction was allowed to warm up to room temperature and stir for an additional 2 hours. The reaction was quenched by cooling to 0 °C and slowly adding saturated $NaHCO_3$ (500 mL). The entire mixture was diluted with Et_2O (300 mL) and poured into saturated $NaHCO_3$ (400 mL) and extracted with Et_2O (2 x 500 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated to furnish a yellow oil. The organic concentrate was subjected to flash chromatography (20% EtOAc/hexanes eluent) to afford olefin **133** (2.05 g, 96% yield) as a colorless oil. FTIR (thin film/NaCl) 2943 (s), 1671 (m), 1454 (m), 1377 (s), 1248 (s), 1207 (s), 1027 (s), 867 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.74 (d, J = 2.7 Hz, 1H), 4.69 (d, J = 2.3 Hz, 1H), 4.43-4.37 (m, 2H), 3.22-3.16 (m, 1H), 2.19-2.12 (m, 2H), 1.78 (ddd, J = 2.5, 5.4, 14.3 Hz, 1H), 1.56-1.36 (m, 5H), 1.32 (s, 3H), 1.24 (s, 3H), 1.01 (s, 3H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 164.9, 106.7, 101.8, 72.4, 72.2, 44.7, 34.4, 32.9, 29.6, 27.3, 26.0, 25.1, 23.6, 21.3; HRMS (EI) *m/z* 222.1620 [cacl'd for $C_{14}H_{22}O_2$ (M+) 222.1620].

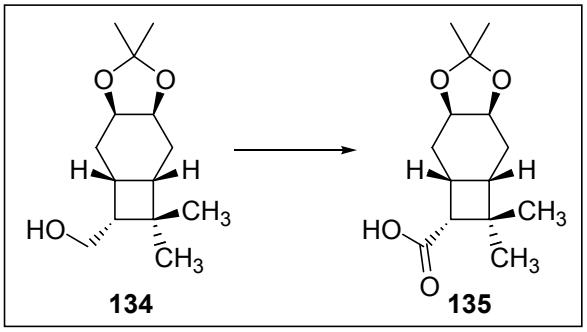
Preparation of Alcohol 134.



Alcohol 134. To a solution of olefin **133** (315 mg, 14.19 mmol, 1.0 eq.) in THF (15 mL) at 0 °C was added BH_3•THF. The reaction was slowly allowed to warm to room temperature over 1 hr and then allowed to stir for an additional 30 minutes. Cooling of the reaction to 0 °C was followed by the addition of 6 N NaOH (1 mL) and H_2O_2 (30%, 1.5 mL). The reaction was stirred for 15 minutes then poured into a separatory funnel containing saturated $NaHCO_3$ (50 mL). The aqueous layer was separated and extracted with Et_2O (4 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to an oil that subjected to silica gel chromatography (30-50% EtOAc/hexanes eluent) to provide alcohol **134** (319 mg, 94% yield) as a colorless oil. FTIR (thin film/NaCl) 3422 (bs), 2932 (s), 1455 (s), 1378 (s), 1256 (s), 1208 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.39 (s, 2H), 3.39 (d, *J* = 1.0 Hz, 1H), 3.36 (d, *J* = 1.0 Hz, 1H), 2.61-2.54 (m, 1H), 2.26 (q, *J* = 8.1 Hz, 1H), 2.19 (ddd, *J* = 7.3, 9.5, 16.8 Hz, 1H), 1.76 (dd, *J* = 6.4, 15.2 Hz, 2H), 1.53-1.43 (m, 2H), 1.41 (s, 3H), 1.28 (s, 3H), 1.15 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 106.9, 72.4, 72.1, 61.1, 46.8, 37.3,

34.5, 33.2, 25.9, 24.0, 23.6, 23.3, 23.0, 19.7; HRMS (EI) *m/z* 240.1729 [cacl'd for $C_{14}H_{24}O_3$ (M+) 240.1725].

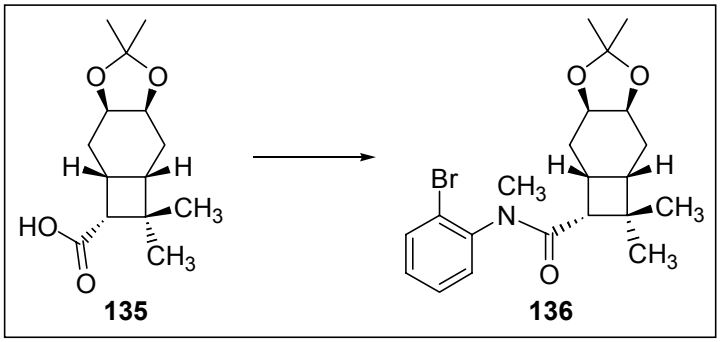
Preparation of Ester 135.



Ester 135. A solution of DMSO (733 μL, 10.35 mmol, 2.2 eq.) in CH_2Cl_2 (30 mL) was cooled to -78 °C and oxalyl chloride (493 μL, 5.65 mmol, 1.2 eq.) was added dropwise. The resulting solution was stirred for 20 minutes before alcohol **134** (1.13 g, 4.71 mmol, 1.0 eq.) in CH_2Cl_2 (20 mL) was added dropwise. Stirring was continued for an additional 20 minutes before TEA (2.62 mL, 18.83 mmol, 4.0 eq.) was added and the reaction was allowed to slowly warm to room temperature over 1 hour. Concentration of the mixture and absoprtion on silica gel was followed by purification by flash chromatography (1.03 g, 92% yield) to furnish an intermediate aldehyde as a colorless oil. A solution of this aldehyde (1.2 g, 5.00 mmol, 1.0 eq) and 2,3-dimethyl-2-butene (5.94 mL, 50 mmol, 10 eq.) in *t*BuOH (21 mL) was treated with a solution of $NaClO_2$ (565 mg, 6.25 mmol, 1.25 eq.) and NaH_2PO_4 (587 mg, 4.25 mmol, 0.85 eq.) in H_2O (5 mL). Stirring was continued for 8 hours at which point the reaction was poured into saturated $NaHCO_3$ (30 mL). The aqeuous layer was washed with CH_2Cl_2 (2 x 20 mL), acidified with 1 N HCl and extracted with CH_2Cl_2 (5 x 25 mL). The combined organic

layers were washed with brine, dried over Na_2SO_4 and concentrated to furnish acid **135** (1.2 g, 94% yield) as a colorless oil. The acid was characterized by conversion to the corresponding methyl ester. This was accomplished by treating a solution of acid **135** (20 mg, 0.08 mmol, 1.0 eq.) in methanol (2 mL) at 0 °C with ethereal CH_2N_2 (1 mL). Stirring was continued for 10 minutes before the yellow solution was concentrated, absorbed onto silica gel and purified by column chromatography (20% EtOAc/hexanes eluent) to provide the methyl ester of acid **135** (21 mg, 100% yield) as a colorless oil. FTIR (thin film/NaCl) 2930 (s), 1724 (s), 1431 (s), 1378 (s), 1257 (s), 1167 (s), 846 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.45 (s, 2H), 3.63 (s, 3H), 3.03 (d, J = 9.5 Hz, 1H), 2.81-2.74 (m, 1H), 2.28-2.23 (m, 1H), 1.96-1.72 (m, 4H), 1.44 (s, 3H), 1.31 (s, 3H), 1.27 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 106.8, 72.5, 72.1, 50.6, 49.3, 39.4, 35.0, 32.7, 26.0, 24.5, 23.9, 23.6, 23.2, 20.8; HRMS (EI) *m/z* 268.1680 [cacl'd for $C_{15}H_{24}O_4$ (M+) 268.1675].

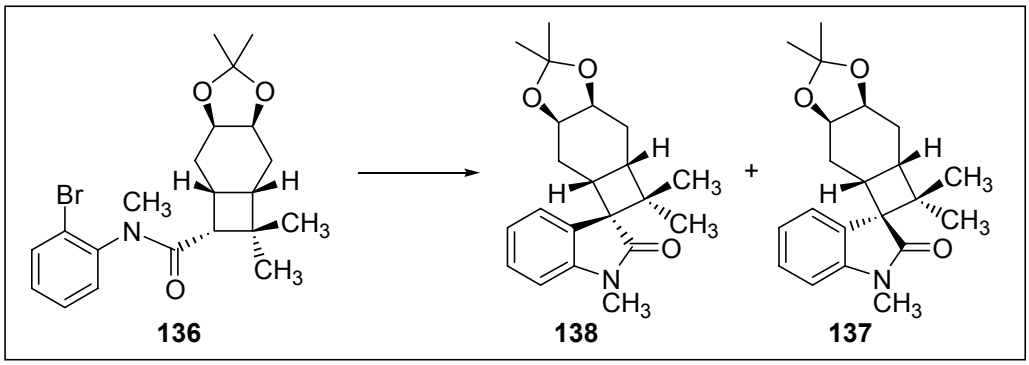
Preparation of Anilide 136.



Anilide 136. A solution of acid **135** (650 mg, 2.55 mmol, 1.0 eq.) in CH_2Cl_2 (25 mL) was treated with oxalyl chloride (289 μL, 3.31 mmol, 1.3 eq.) and a catalytic amount of DMF (10 μL). Stirring was continued for 15 minutes before the solution was

concentrated *in vacuo*. The derived oil was dissolved in CH_2Cl_2 (25 mL) and to this solution was added *N*-methyl-2-bromoaniline (583 mg, 3.19 mmol. 1.25 eq.), TEA (444 μL, 3.19 mmol, 1.25 eq.) and DMAP (31 mg, 0.25 mmol, 0.1 eq.). The resulting solution was stirred for 2 hours then absorbed onto silica gel and chromatographed (30% EtOAc/hexanes eluent) to afford anilide **136**, which existed as a mixture of rotamers, (1.12 g, 100% yield) as a colorless solid. m.p. 107-111 °C; FTIR (thin film/NaCl) 2982 (m), 2932 (s), 1654 (s), 1377 (m), 1254 (m), 1204 (m), 1031 (s), 762 (w), 727 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.60 (app dd, *J* = 4.6, 7.7 Hz, 2H), 7.38-7.32 (m, 2H), 7.23 (app t, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 7.7 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 4.43 (bs, 4H), 3.15 (s, 3H), 3.14 (s, 3H), 2.76-2.51 (m, 4H), 2.39 (dt, *J* = 1.3, 13.7 Hz, 1H), 2.13-1.98 (m, 5H), 1.76-1.59 (m, 4H), 1.39 (s, 3H), 1.38 (s, 3H), 1.29 (s, 6H), 1.15 (s, 3H), 1.05 (s, 3H), 1.03 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 143.4, 143.2, 133.8, 133.7, 129.9, 129.7, 129.5, 129.4, 128.9, 128.7, 123.7, 123.3, 106.7, 106.6, 72.9, 72.7, 72.3, 72.2, 48.2, 47.5, 38.5, 38.4, 35.6, 35.4, 35.1, 34.9, 33.7, 32.5, 26.0, 25.9, 24.3, 24.1, 24.0, 23.8, 23.6, 23.4, 21.9, 20.3, 19.9; HRMS (EI) *m/z* 421.1261 [cacl'd for $C_{21}H_{28}BrNO_3$ (M+) 421.1253].

Preparation of Oxindoles 137 and 138.



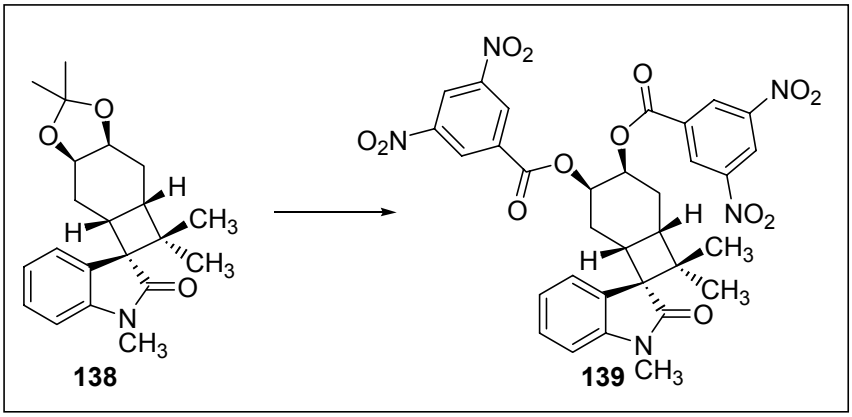
Oxindoles 137 and 138. To a suspension of *t*BuONa (85 mg, 0.89 mmol, 1.5 eq.), $Pd_2(dba)_3$ (54 mg, 0.06 mmol, 0.1 eq) and BINAP (55 mg, 0.09 mmol, 0.15 eq.) in dioxane (2 mL) at room temperature was added a solution of anilide **136** (250 mg, 0.59 mmol, 1.0 eq.) in dioxane (2 mL). The resulting purple suspension was refluxed for 4 hours before being cooled and filtered through a small plug of silica gel. Concentration followed absorption of the derived residue onto silica gel was followed by chromatographic purification (30% EtOAc/hexanes eluent).

Oxindole 138: The first compound to elute was oxindole **138** (108 mg, 53% yield) as a yellow solid. m.p. 178-180 °C; FTIR (thin film/NaCl) 2931 (m), 1697 (s), 1608 (m), 1466 (m), 1378 (m), 1034 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 6.9 Hz, 1H), 7.24 (dt, *J* = 1.1, 7.7 Hz, 1H), 7.05 (dt, *J* = 1.0, 7.6 Hz, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 4.51 (dt, *J* = 2.5, 7.8 Hz, 1H), 4.45 (dt, *J* = 2.6, 7.8 Hz, 1H), 3.15 (s, 3H), 3.15-3.10 (m, 1H), 2.54 (dt, *J* = 3.0, 13.8 Hz, 1H), 2.23 (ddd, *J* = 5.3, 10.0, 15.3 Hz, 1H), 2.18-2.12 (m, 1H), 1.74 (ddd, *J* = 2.1, 5.2, 14.1 Hz, 1H), 1.59 (ddd, *J* = 2.8, 7.9, 14.6 Hz, 1H), 1.49(s, 3H), 1.32 (s, 3H), 1,23 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 143.5, 130.5, 127.4, 125.2, 121.4, 107.2, 106.7, 72.6, 72.3, 57.5, 42.4, 34.2, 30.6, 29.7, 26.0, 25.8, 24.3, 23.5, 20.8, 19.9; HRMS (EI) *m/z* 341.1994 [cacl'd for $C_{21}H_{27}NO_3$ (M+) 341.1991].

Oxindole 137: The second compound to elute was oxindole **137** (55 mg, 27% yield) as a white solid. m.p. 187-191 °C; FTIR (thin film/NaCl) 2932 (m), 1704 (s), 1608 (m), 1468 (m), 1373 (m), 1253 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.4 Hz, 1H),

7.27 (dt, J = 1.3, 7.8 Hz, 1H), 7.01 (dt, J = 1.0, 7.5 Hz, 1H), 6.81 (d, J = 7.8 Hz, 1H), 4.53 (dt, J = 2.6, 7.9 Hz, 1H), 4.46 (dt, J = 2.7, 7.8 Hz, 1H), 3.18 (s, 3H), 3.03 (ddd, J = 6.4, 10.1, 16.6 Hz, 1H), 2.76 (ddd, J = 7.2, 10.3, 17.4 Hz, 1H), 1.97-1.91 (m, 2H), 1.72 (dt, J = 2.7, 12.6 Hz, 1H), 1.63 (ddd, J = 2.6, 6.3, 14.6 Hz, 1H), 1.48 (s, 3H), 1.32 (s, 3H), 1.23 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.3, 144.8, 127.6, 127.3, 126.7, 120.9, 107.8, 107.3, 72.3, 72.1, 56.5, 43.2, 33.7, 30.2, 27.3, 26.1, 26.0, 25.0, 23.7, 23.6, 23.2; HRMS (EI) *m/z* 341.1996 [cacl'd for $C_{21}H_{27}NO_3$ (M+) 341.1991].

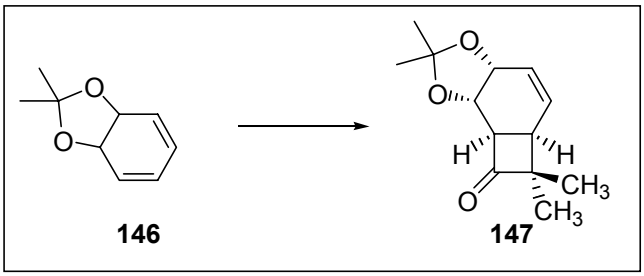
Preparation of Dibenzoate 139.



Dibenzoate 139. A solution of acetonide **138** (30 mg, 0.09 mmol, 1.0 eq.) in undistilled CH_3OH (3 mL) was treated with Amberlyst 15 H^+ (~ 25 mg). The suspension was refluxed 2 hours, cooled, concentrated, and filtered through a small plug of silica gel with EtOAc. The crude diol was carried on without further purification. The derived diol was dissolved in CH_2Cl_2 (2 mL) and treated with 3,5-dinitrobenzoyl chloride (44 mg, 0.19 mmol, 2.2 eq.) and TEA (37 μL, 0.26 mmol, 3.0 eq.). The solution was refluxed for 3 hours, at which point TLC indicated the complete consumption of starting material. Concentration and purification by flash chromatography provided benzoate **139** (30 mg,

50% overall yield) as a yellow crystalline solid. Slow evaporation from EtOAc provided crystals suitable for X-ray analysis. See Appendix 7 for X-ray report. m.p. 226-228 °C; FTIR (thin film/NaCl) 3104 (w), 2926 (m), 1730 (m), 1692 (m), 1544 (s), 1343 (s), 1287 (m), 1168 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.29 (t, *J* = 1.8 Hz, 1H), 9.19 (t, *J* = 2.0 Hz, 1H), 9.16 (d, *J* = 2.0 Hz, 1H), 9.00 (d, *J* = 2.0 Hz, 1H), 7.48 (d, *J* = 7.4 Hz, 2H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.12 (t, *J* = 7.4 Hz, 1H), 6.83 (d, *J* = 7.7 Hz, 1H), 6.16 (t, *J* = 7.3 Hz, 1H), 5.98 (t, *J* = 2.4 Hz, 1H), 3.50 (dt, *J* = 3.1, 10.6 Hz, 1H), 3.24 (s, 3H), 3.18 (t, *J* = 12.1 Hz, 1H), 2.47 (q, *J* = 9.2 Hz, 1H), 2.36-2.30 (m, 1H), 2.07-2.04 (m, 1H), 1.37 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8, 162.2, 161.6, 148.9, 148.6, 143.9, 133.9, 133.8, 129.3, 129.1, 128.4, 125.0, 122.7, 122.4, 122.0, 107.7, 73.2, 73.1, 59.2, 42.4, 36.1, 34.1, 29.7, 29.3, 26.2, 25.9, 25.3, 20.0; HRMS (EI) *m/z* 690.1687 [cacl'd for $C_{32}H_{27}N_5O_{13}$ (M+H) 690.1684].

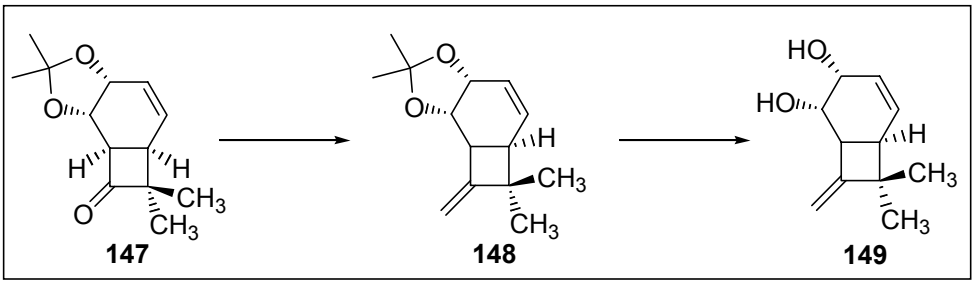
Preparation of Cyclobutanone 147.



Cyclobutanone 147. A solution of diene **146** (8.22 g, 54.1 mmol, 1.0 eq.)[49] and TEA (54.0 mL, 387 mmol, 7.1 eq.) in THF (210 mL) was brought to reflux and maintained at this temperature while isobutyryl chloride (40.0 mL, 382 mmol, 7.1 eq.) was introduced over a period of 15 hours. Immediately upon the addition of isobutyryl chloride a white precipitate began to form. The mixture was allowed to reflux for an

additional 12 hours before the reaction was cooled to room temperature and filtered to remove the triethylamine hydrochloride salt. The solution was then concentrated under reduced pressure (rotary evaporator) keeping the temperature under 10 °C to provide an orange oil containing a large amount of a white precipitate. To this mixture was added 750 mL of a 20% EtOAc/hexanes solution. Following removal of approximately half of this volume under reduced pressure, an additional 300 mL of hexanes was introduced and the mixture was filtered to remove the white precipitate, which consisted entirely of 2,2,4,4-tetramethyl-cyclobutane-1,3-dione, resulting from the dimerization of dimethyl diketene. This precipitate was washed well with hexanes, and the resulting filtrate was concentrated. The resulting residue was subjected to silica gel chromatography (2-10% EtOAc/hexanes eluent) to provide cyclobutanone **147** (10.21 g, 85% yield) as a white solid. m.p. 93.5-95.5 °C; FTIR (thin film/NaCl) 3056 (w), 2993 (m), 1773 (s), 1262 (s), 1053 (m), 736 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80-5.72 (m, 2H), 4.60 (dd, *J* = 1.9, 5.1 Hz, 1H), 4.42 (dd, *J* = 1.1, 5.7 Hz, 1H), 4.14 (dd, *J* = 2.2, 9.3 Hz, 1H), 2.73-2.70 (m, 1H), 1.38 (s, 6H), 1.35 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.3, 128.3, 125.6, 108.9, 69.6, 69.5, 63.3, 53.3, 33.8, 28.0, 26.4, 24.8, 17.0; HRMS (EI) *m/z* 222.1255 [cacl'd for $C_{13}H_{18}O_3$ (M+) 222.1256].

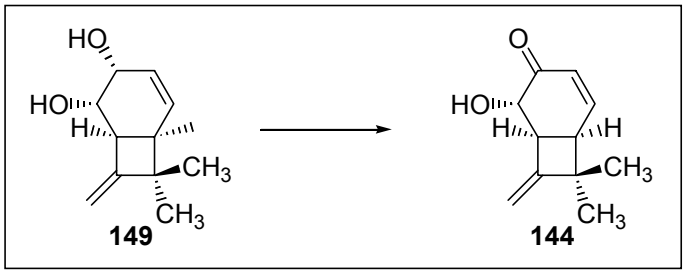
Preparation of Diene 149.



Diene 149. To a suspension of Zn (16.22 g, 248.18 mmol, 9.1 eq.) and $PbCl_2$ (~ 50 mg) in THF (280 mL) was added CH_2Br_2 (8.81 mL, 125.45 mmol, 4.6 eq.). The suspension was heated with a heat gun for 2 minutes and then allowed to stir at room temperature for 15 minutes. The mixture was cooled to 0 °C and $TiCl_4$ was added over 1 minute. The ice bath was removed, and the whole was stirred for an additional 30 minutes. To the resulting dark blue/black suspension was added ketone **147** (6.0 g, 27.27 mmol, 1.0 eq.) in THF (40 mL) via cannula over 10 minutes. After stirring at room temperature for 3 hours, the reaction was carefully quenched (CAUTION!!!) with cold H_2O (250 mL). The mixture was then poured in 1 N HCl (750 mL) and extracted with EtOAc (3 x 250 mL). Concentration *in vacuo* provided a yellow oil that was routinely carried on to the next step without further purification. However, purification could be achieved by column chromatography (10-20% EtOAc/heanes eluent) to furnish olefin **148** (5.60 g, 94% yield) as a pale yellow solid. m.p. 94-97.5 °C; FTIR (thin film/NaCl) 2983 (m), 2960 (m), 2923 (m), 1668 (w), 1457 (m), 1367 (m), 1261 (s), 1051 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.73-5.64 (m, 2H), 4.83 (d, J = 2.4 Hz, 1H), 4.78 (d, J = 2.9 Hz, 1H), 4.49 (s, 2H), 3.70 (d, J = 8.2 Hz, 1H), 2.54 (dd, J = 4.1, 7.7 Hz, 1H), 1.40 (s, 3H), 1.38 (s, 3H), 1.31 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4, 126.9, 108.8, 102.6, 72.7, 70.2, 47.3, 38.9, 37.3, 28.6, 28.3, 26.8, 21.4; HRMS (EI) *m/z* 219.1381 [cacl'd for $C_{14}H_{20}O_2$ (M+) 219.1385]. The derived oil was dissolved in undistilled THF (180 mL) and was treated with 1 N HCl (100 mL). The reaction mixture was stirred at room temperature for 24 hours when the reaction was reduced to half of its volume and the pH was adjusted to 8 with saturated $NaHCO_3$. Extraction with EtOAc (2 x 250 mL) was followed by washing with brine and drying over Na_2SO_4. Concentration

in vacuo was followed by recrystallization from hexanes/EtOAc to provide diol **149** (3.75 g, 77% overall yield) as a white powder. Concentration of the mother liquor followed by absorption onto silica gel and purification by flash chromatography provided additional diol **149** (350 mg, 7% overall yield, 84% combined yield). m.p. 110.5-112 °C; FTIR (thin film/NaCl) 3404 (bs), 2919 (w), 1669 (m), 1037 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89-5.86 (m, 1H), 5.71 (d, *J* = 10.4 Hz, 1H), 4.82 (d, *J* = 2.8 Hz, 1H), 4.80 (d, *J* = 2.1 Hz, 1H), 4.36 (bs, 1H), 4.14 (bs, 1H), 3.60-3.58 (m, 1H), 2.57 (t, *J* = 6.5 Hz, 1H), 1.77 (bs, 2H), 1.30 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 129.2, 129.1, 103.2, 68.3, 65.7, 46.6, 41.9, 39.8, 29.2, 22.1; HRMS (EI) *m/z* 162.1039 [cacl'd for $C_{11}H_{14}O$ (M-H) 162.1045].

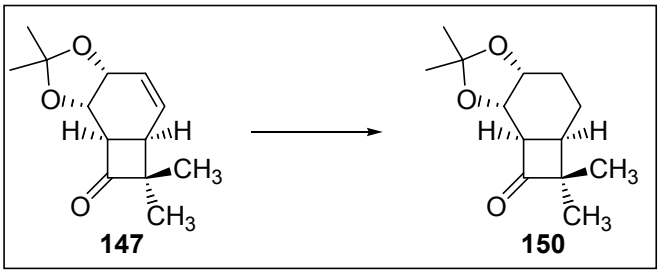
Preparation of Alcohol 144.



Alcohol 144. A solution of diol **149** (5.0 g, 22.52 mmol, 1.0 eq.) in benzene (200 mL) was treated with DDQ (15.32 g, 67.54 mmol, 3.0 eq.). The resulting orange mixture was refluxed for 5-6 hours, until TLC showed the complete consumption of starting material. The solvent was removed under reduced pressure and to the resulting orange solid was added pentane (600 mL). The derived mixture was placed in the refrigerator overnight before the solvent was decanted. Additional pentane (200 mL) was added and the mixture was stirred vigorously for 5 minutes before being decanted again. This

process was repeated numerous times (5-10) until TLC analysis did not show the presence of the desired ketone. Concentration of the combined pentane washings followed by purification by flash chromatography (30–50% EtOAc/hexanes eluent) furnished ketone **144** (4.70 g, 95% yield) as a light yellow solid. m.p. 66.5-67.5 °C; FTIR (thin film/NaCl) 3385 (bs), 2962 (s), 1678 (s), 1386 (s), 1246 (s), 881 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 (dd, *J* = 4.1, 10.2 Hz, 1H), 6.18 (dd, *J* = 1.7, 10.2 Hz, 1H), 5.06 (d, *J* = 1.0 Hz, 1H), 4.95 (d, *J* = 2.5 Hz, 1H), 4.32 (dd, *J* = 1.7, 7.6 Hz, 1H), 3.38-3.34 (m, 1H), 3.24 (bs, 1H), 2.99 (ddd, *J* = 1.7, 4.1, 8.9 Hz, 1H), 1.36 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.9, 157.4, 148.8, 127.3, 105.6, 73.8, 47.5, 44.4, 42.6, 28.7, 23.8; HRMS (EI) *m/z* 178.0995 [cacl'd for $C_{11}H_{14}O_2$ (M+) 178.0994].

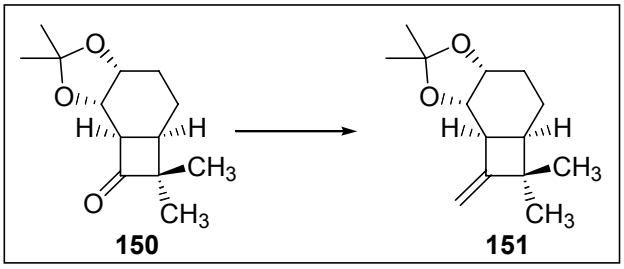
Preparation of Ketone 150.



Ketone 150. A solution of olefin **147** (2.00 g, 9.01 mmol, 1.0 eq.) in CH_3OH (60 mL) was treated with Rh on Al_2O_3 (10% Rh, 250 mg). The resulting suspension was purged with H_2 and then allowed to stir under 1 atm of H_2 (balloon) overnight at which point TLC indicated the complete consumption of starting material. The suspension was filtered through a small plug of celite, that was subsequently washed well with EtOAc. Concentration under reduced pressure was followed by purification via flash chromatography (2–5% EtOAc/hexanes eluent) to provide ketone **150** (1.43 g, 71%

yield) as a white solid. m.p. 85-87 °C; FTIR (thin film/NaCl) 2937 (m), 2890 (m), 1757 (s), 1446 (w), 1376 (m), 1364 (m), 1204 (w), 1169 (m), 866 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58 (dd, *J* = 1.9, 7.3 Hz, 1H), 4.27 (p, *J* = 3.9 Hz, 1H), 3.91 (dd, *J* = 1.5, 9.9 Hz, 1H), 2.30-2.25 (m, 1H), 2.05-1.96 (m, 1H), 1.62-1.55 (m, 1H), 1.52-1.38 (m, 2H), 1.47 (s, 3H), 1.33 (s, 6H), 1.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.2, 107.1, 71.6, 70.5, 60.0, 55.8, 32.8, 26.6, 26.2, 24.4, 24.0, 17.5, 16.6; HRMS (EI) *m/z* 224.1411[cacl'd for $C_{13}H_{20}O_3$ (M+) 224.1412].

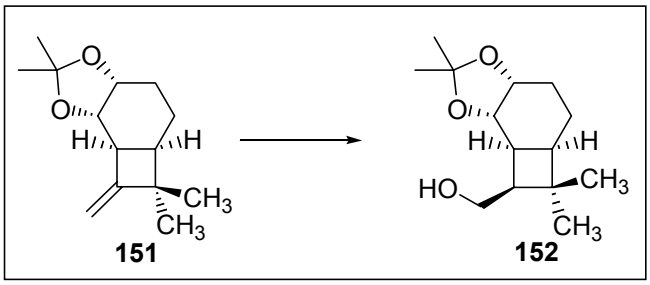
Preparation of Olefin 151.



Olefin 151. A suspension of Zn (3.39 g, 51.9 mmol, 9.0 eq.), CH_2I_2 (2.10 mL, 26.1 mmol, 4.5 eq.), and a catalytic amount of $PbCl_2$ (25 mg) in THF (45 mL) was stirred for 15 minutes, during which time a slightly exothermic reaction occurred. [In the event that this slightly exothermic reaction was not observed, the reaction was heated with a heat gun for 2-3 minutes.] This suspension was cooled to 0 °C and $TiCl_4$ (670 μL, 6.10 mmol, 1.06 eq.) was slowly added, resulting in a very exothermic reaction. The cold bath was removed and the resulting dark brown suspension was stirred at room temperature for 30 minutes, at which point a solution of ketone **150** (1.29 g, 5.76 mmol, 1.0 eq.) was introduced dropwise via cannula addition over 7 minutes. The reaction was allowed to stir at room temperature for 2 hours before being cooled to 0 °C and carefully quenched

by the addition of 1 N HCl (100 mL) (Caution!). The entire mixture was then poured into a separatory funnel containing additional 1 N HCl (250 mL) and EtOAc (100 mL). The layers are separated and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were then washed with 0.5 N HCl (50 mL), 50% $NaHCO_3$ (50 mL), H_2O (50 mL), and brine. Drying over Na_2SO_4 was followed by concentration *in vacuo* and purification by silica gel chromatography (2.5-3% EtOAc/hexanes eluent) to afford olefin **151** (1.09 g, 85% yield) as a pale yellow oil. FTIR (thin film/NaCl) 2979 (m), 2950 (s), 2937 (s), 2865 (m), 1671 (w), 1447 (w), 1366 (m), 1262 (s), 1208 (m), 1046 (s), 1036 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.75 (d, J = 3.2 Hz, 1H), 4.72 (d, J = 2.4 Hz, 1H), 4.41 (dd, J = 2.1, 7.5 Hz, 1H), 4.26 (p, J = 4.2 Hz, 1H), 3.47 (dq, J = 2.7, 8.8 Hz, 1H), 2.08-2.05 (m, 1H), 1.85-1.77 (m, 2H), 1.48-1.36 (m, 2H), 1.46 (s, 3H), 1.34 (s, 3H), 1.22 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 179.0, 106.1, 74.7, 73.9, 50.7, 41.7, 39.0, 31.9, 31.7, 28.1, 26.8, 25.7, 20.1, 20.0; HRMS (FAB) *m/z* 221.1549 [calc'd for $C_{14}H_{22}O_2$(M+) 221.1542].

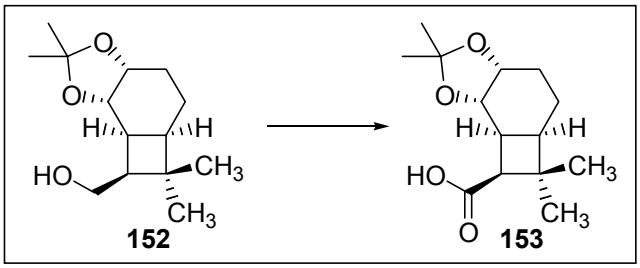
Preparation of Alcohol 152.



Alcohol 152. BH_3•DMS (5.00 mL, 1.0 M in CH_2Cl_2, 1.13 eq.) was added dropwise over 10 minutes to a solution of olefin **151** (977 mg, 4.40 mmol, 1.0 eq.) in THF (15 mL) at 0 °C. The solution was allowed to slowly warm to room temperature

and stir overnight. The solution was then diluted with THF (15 mL) recooled to 0 °C and treated simultaneously with 2N NaOH (3.5 mL) and 30% H_2O_2 (3.5 mL). Stirring was continued at this temperature for 2 hours before the reaction was quenched with 1 N HCl (25 mL), extracted with EtOAc (3 x 25 mL), washed with 5% $Na_2S_2O_3$ (25 mL), H_2O (20 mL), and then brine. Following drying over Na_2SO_4 and concentration, the derived residue was purified by flash chromatography (8-10% EtOAc/hexanes eluent) to provide olefin **152** (660 mg, 62% yield) as a white solid. mp. 58-60 °C; FTIR (thin film/NaCl) 3452 (b), 2940 (s), 1456 (m), 1369 (s), 1250 (s), 1216 (s), 1165 (m), 1054 (s), 868 (m), 795 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.41 (t, *J* = 7.0 Hz, 1H), 4.26 (dt, *J* = 6.8, 9.1 Hz, 1H), 3.81 (dd, *J* = 9.9, 11.5 Hz, 1H), 3.67 (dd, *J* = 6.1, 11.3 Hz, 1H), 2.47-2.36 (m, 2H), 2.21 (q, *J* = 10.2 Hz, 1H), 2.09 (bs, 1H), 2.04-1.98 (m, 1H), 1.53-1.46 (m, 1H), 1.40 (s, 3H), 1.30 (s, 3H), 1.26-1.08 (m, 2H), 1.12 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.9, 74.5, 73.2, 60.0, 46.0, 41.3, 37.8, 33.3, 32.2, 28.0, 26.5, 25.5, 19.6, 18.1; HRMS (EI) *m/z* 240.1722 [calc'd for $C_{14}H_{24}O_3$(M+) 240.1725].

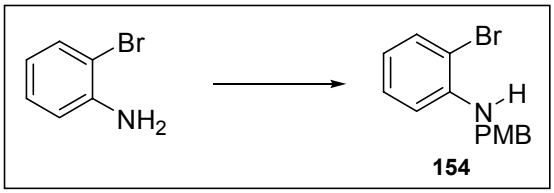
Preparation of Acid 153.



Preparation of Acid 153. To a solution of alcohol **152** (350 mg, 1.46 mmol, 1.0 eq.) in CH_2Cl_2 (12 mL) at 0 °C was added pyridine (118 μL, 1.46 mmol, 1.0 eq.) followed by Dess-Martin Periodinane (742 mg, 1.75 mmol, 1.2 eq.). The resulting

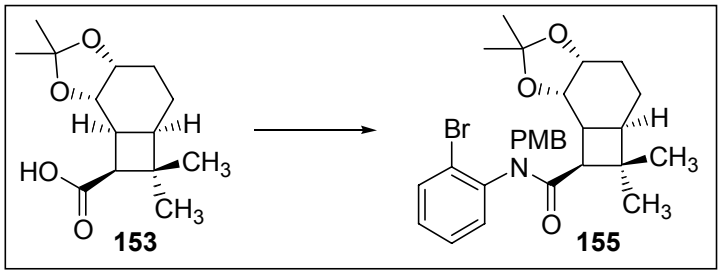
suspension was allowed to stir for 2 hours before being quenched by the addition of 10% $Na_2S_2O_3$ (10 mL) and saturated $NaHCO_3$ (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with H_2O (15 mL) and brine, dried over Na_2SO_4, and concentrated to provide a residue that was filtered through a plug of silica gel (10% EtOAc/hexanes eluent) to provide an aldehyde that was carried on without further purification. To a solution of the derived aldehyde in a mixture of *t*BuOH (19 mL) and 2,3-dimethyl-2-butene (4.5 mL) at room temperature was added a solution of $NaClO_2$ (824 mg, 9.11 mmol, 6.25 eq.) and NaH_2PO_4 (805 mg, 5.83 mmol, 4.0 eq.) in H_2O (8 mL). The colorless solution quickly became yellow and was allowed to stir at room temperature for 1 hour, at which time 1 N HCl (10 mL) was added and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed successively with 5% $Na_2S_2O_3$ (25 mL), H_2O (25 mL), and brine before being dried over Na_2SO_4 and concentrated to furnish acid **153** (274 mg, 74% yield) as a white solid. Recrystallization from EtOAc/hexanes provided colorless crystals. mp. 155-156 °C; FTIR (thin film/NaCl) 2932 (b), 2903 (s), 2978 (s), 2755 (m), 1682 (s), 1451 (w), 1428 (s), 1368 (s), 1343 (m), 1234 (s), 1061 (m), 1047 (m), 879 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.42-4.35 (m, 2H), 3.06-3.00 (m, 2H), 2.12-2.05 (m, 1H), 1.87-1.82 (m, 1H), 1.63-1.50 (m, 2H), 1.45 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H), 1.20-1.10 (m, 1H), 1.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0, 106.1, 74.7, 73.9, 50.8, 41.8, 39.0, 31.9, 31.7, 28.2, 26.8, 25.7, 20.1, 20.0; HRMS (FAB) *m/z* 255.1595 [calc'd for $C_{14}H_{23}O_4$ (M+H) 255.1596].

Preparation of Aniline 154.



Aniline 154. To a solution of 2-bromoaniline (5.0 g, 29.1 mmol, 1.0 eq.) in THF (90 mL) at –78 °C was added *n*BuLi (2.4 M, 12.2 mL, 1.0 eq.) over 5 minutes. The resulting suspension was allowed to stir for 5 minutes before *p*-methoxybezyl chloride (4.0 ml, 29.5 mmol ,1.0 eq.) (PMBCl) was added dropwise over 5 minutes. After stirring at this temperature for 15 minutes, the bath was removed and the resulting mixture was allowed to warm to room temperature and stir overnight, at which point a brown solution remained. The reaction was quenched with 0.5 N NaOH (500 mL) and subsequently extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with H_2O (100 mL) then brine, dried over Na_2SO_4 and subjected to flash chromatography (2-5% EtOAc/hexanes eluent) to provide aniline **154** (7.01 g, 83% yield) as an orange solid. An analytical sample was obtained by recrystallization from pentane/EtOAc to furnish colorless crystals. mp. 68-70 °C; FTIR (thin film/NaCl) 3399 (m), 2962 (w), 1588 (m), 1511 (m), 1425 (m), 1028 (m), 745 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 1.5, 7.9 Hz, 1H), 7.32-7.30 (m, 2H), 7.16 (dt, *J* = 1.7, 7.3 Hz, 1H), 6.92-6.91 (m, 2H), 6.65 (dd, *J* = 1.0, 7.8 Hz, 1H), 6.60 (dt, *J* = 1.1, 7.2 Hz, 1H), 4.71 (bs, 1H), 4.34 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 144.8, 132.3, 130.6, 128.5, 128.4, 117.9, 114.1, 111.6, 109.7, 55.3, 47.5; HRMS (FAB) *m/z* 291.0262 [calc'd for $C_{14}H_{14}NOBr$ (M+) 291.0259].

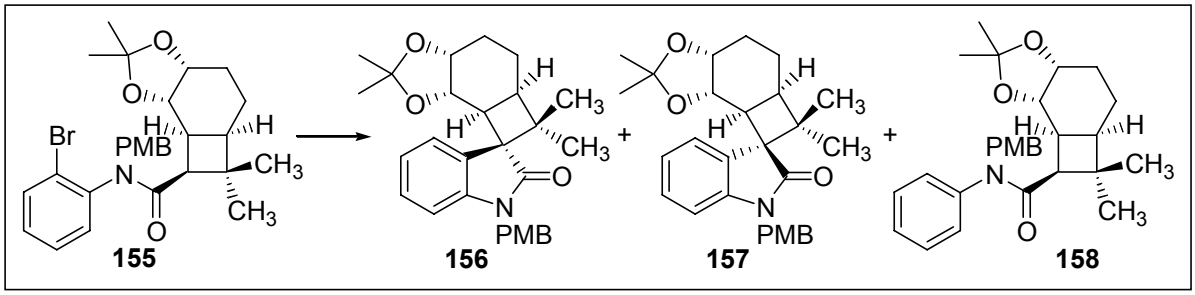
Preparation of Anilide 155.



Anilide 155. To a suspension of aniline **154** (310 mg, 1.06 mmol, 2.0 eq.) and acid **153** (135 mg, 0.531 mmol, 1.0 eq.) in CCl_4 (1.5 mL) and $ClCH_2CH_2Cl$ (13.5 mL) was added polymer supported PPh_3 (3 mmol/g, 531 mg, 3 eq.). The resulting suspension was allowed to reflux overnight, at which point the reaction was cooled to room temperature, concentrated under reduced pressure, and filtered. Concentration and purification by flash chromatography (10-15% EtOAc/hexanes eluent) provided anilide **155** (260 mg, 93% yield), as a viscous colorless foam that existed as a mixture of rotamers. M.m 38-41 ºC; FTIR (thin film/NaCl) 2981 (s), 2934 (s), 1658 (s), 1612 (m), 1584 (w), 1474 (s), 1441 (s), 1401 (s), 1244 (s), 1214 (s), 1046 (s), 880 (m), 730 (m), 604 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$ (for major rotamer) δ 7.65 (dd, *J* = 1.5, 7.2 Hz, 1H), 7.18-7.10 (m, 2H), 7.06 (app d, *J* = 8.8 Hz, 2H), 6.75 (app. d, *J* = 8.7 Hz, 2H), 6.54 (dd, *J* = 2.0, 7.4 Hz, 1H), 5.68 (d, *J* = 14.2 Hz, 1H), 4.63 (p, *J* = 5.3 Hz, 1H), 4.28 (d, *J* = 5.4 Hz, 1H), 3.81 (d, *J* = 14.1 Hz, 1H), 3.70 (s, 3H), 2.91 (t, *J* = 9.6 Hz, 1H), 2.62 (dd, *J* = 1.5, 10.2 Hz, 1H), 2.08-1.86 (m, 4H), 1.54-1.49 (m, 1H), 1.40 (s, 3H), 1.32 (s, 3H), 0.95 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 171.6, 158.9, 158.8, 140.7, 133.6, 133.5, 131.8, 131.7, 130.5, 130.4, 129.5, 129.5, 129.4, 129.3, 128.0, 127.7, 123.9, 123.3, 113.6, 113.5, 105.9, 15.4, 74.9, 74.8, 74.5, 74.4, 55.1, 50.2, 50.1, 48.6, 42.0, 41.7,

38.4, 37.9, 33.6, 32.7, 32.0, 31.0, 28.4, 28.1, 27.3, 27.0, 25.9, 25.5, 20.3, 20.2, 19.8, 19.1; HRMS (FAB) *m/z* 528.1748 [calc'd for $C_{28}H_{35}BrNO_4$(M+H) 528.1749].

Preparation of Oxindoles 156 and 157.

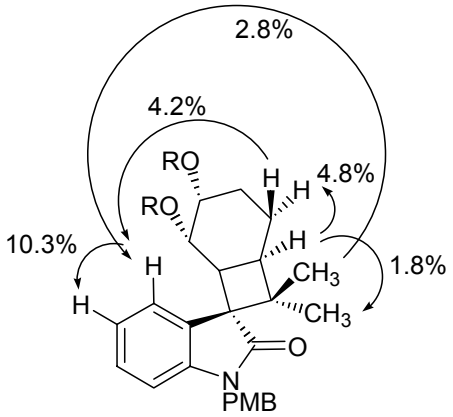


Oxindoles 156 and 157. To a flask charged with *t*-BnClPd$(PPh_3)_2$ (13 mg, 0.017 mmol, 0.3 eq.), $(o\text{-Tol})_3P$ (5.2 mg, 0.017 mmol, 0.3 eq.), *t*BuONa (8.2 mg, 0.085 mmol, 1.5 eq.), and anilide **155** (30 mg, 0.056 mmol, 1.0 eq.) at room temperature was added dioxane (3.8 mL). The yellow/green mixture that resulted was refluxed for 4 hours during which period it turned into a slightly cloudy yellow mixture. The reaction was cooled to room temperature and quenched with saturated NH_4Cl (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with H_2O (10 mL) then brine and dried over Na_2SO_4. Concentration and purification by preparative TLC (15% EtOAc/hexanes eluent x 4) provided three products.

Oxindole 156: The least polar compound isolated was oxindole **156** (1.0 mg, 4% yield) as a colorless oil. FTIR (thin film/NaCl) 2984 (s), 2941 (s), 2870 (m), 1703 (s), 1611 (s), 1513 (s), 1486 (m), 1465 (s), 1358 (m), 1243 (m), 1179 (s), 1050 (m), 748 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 8.6 Hz, 2H), 7.17 (t, *J* =

7.3 Hz, 1H), 7.03 (dt, J = 1.1, 7.5 Hz, 1H), 6.83 (d, J = 8.7 Hz, 2H), 6.72 (d, J = 7.6 Hz, 1H), 5.15 (d, J = 15.5 Hz, 1H), 4.53 (d, J = 15.8 Hz, 1H), 4.32-4.30 (m, 2H), 3.77 (s, 3H), 3.26 (dd, J = 6.7, 10.7 Hz, 1H), 2.77-2.71 (m, 1H), 2.09-2.05 (m, 1H), 1.81-1.75 (m, 1H), 1.48 (dq, J = 2.1, 14.4 Hz, 1H), 1.39 (s, 3H), 1.36-1.26 (m, 1H), 1.29 (s, 3H), 1.22 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.5, 158.9, 143.9, 128.3, 127.8, 127.1, 125.8, 121.4, 114.1, 109.0, 107.0, 74.7, 73.2, 56.5, 55.2, 43.9, 43.2, 40.4, 39.4, 27.9, 27.1, 27.1, 26.9, 25.3, 22.6, 19.3; HRMS (EI) *m/z* 447.2411 [calc'd for $C_{28}H_{33}NO_4$(M+H) 447.2410].

NOE enhancements
^{1}H NMR 500 MHz, $CDCl_3$

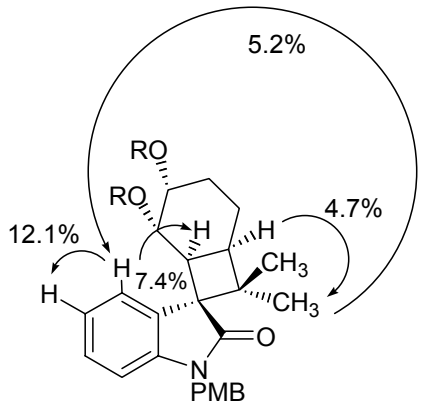


156

Oxindole 157: The second compound to elute was oxindole **157** (20 mg, 79% yield) as a colorless oil. FTIR (thin film/NaCl) 2981 (s), 2932 (s), 2866 (m), 1699 (s), 1611 (s), 1513 (s), 1465 (s), 1249 (s), 1218 (m), 1173 (m), 1052 (s), 878 (m), 746 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (dd, J = 1.1, 7.6 Hz, 1H), 7.21 (d, J = 8.9 Hz, 2H), 7.18 (dt, J = 1.0, 7.3 Hz, 1H), 7.03 (dt, J = 1.0, 7.5 Hz, 1H), 6.84 (d, J = 9.0 Hz, 2H), 6.72 (d, J = 7.6 Hz, 1H), 5.01 (d, J = 15.6 Hz, 1H), 4.61 (d, J = 15.6 Hz, 1H), 4.47 (p, J = 5.3 Hz,

1H), 3.82 (d, J = 5.5 Hz, 1H), 3.77 (s, 3H), 3.34 (d, J = 9.6 Hz, 1H), 2.46 (q, J = 13.8 Hz, 1H), 2.18 (ddd, J = 7.7, 10.0, 12.3 Hz, 1H), 1.95-1.90 (m, 1H), 1.70-1.64 (m, 1H), 1.43 (s, 3H), 1.26 (s, 3H), 1.21 (s, 3H), 1.16 (q, J = 12.3 Hz, 1H), 1.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.9, 159.0, 143.1, 129.3, 128.6, 128.3, 128.0, 125.5, 121.8, 114.1, 108.4, 105.6, 75.1, 74.3, 58.8, 55.2, 43.0, 42.4, 40.6, 38.4, 29.3, 28.3, 27.4, 26.0, 19.9, 19.8; HRMS (EI) *m/z* 447.2411 [calc'd for $C_{28}H_{33}NO_4$(M+H) 447.2410].

NOE enhancements
^{1}H NMR 500 MHz, $CDCl_3$



157

Anilide 158: The last compound to elute was anilide **158** (1.3 mg, 5% yield) also as a colorless oil. FTIR (thin film/NaCl) 2981 (s), 2954 (s), 2933 (s), 1649 (s), 1594 (s), 1512 (s), 1494 (s), 1403 (s), 1386 (s), 1244 (s), 1214 (s), 1165 (m), 860 (m), 701 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.27 (m, 3H), 7.09 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 6.3 Hz, 2H), 6.77 (d, J = 6.8 Hz, 2H), 4.95 (d, J = 13.7 Hz, 1H), 4.70 (d, J = 14.4 Hz, 1H), 4.62 (p, J = 3.7 Hz, 1H), 4.21 (d, J = 5.5 Hz, 1H), 3.77 (s, 3H), 2.89-2.83 (m, 3H), 2.05-1.88 (m, 3H), 1.56-1.51 (s, 1H), 1.43 (s, 3H), 1.34 (s, 3H), 1.02 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 158.8, 142.4, 130.2, 129.9, 129.3, 128.8, 127.8, 113.6,

105.6, 75.1, 74.8, 55.1, 74.8, 55.1, 52.1, 49.7, 42.1, 38.0, 32.5, 31.1, 28.4, 27.4, 26.0, 20.2, 20.1; HRMS (EI) *m/z* 449.2564 [calc'd for $C_{28}H_{35}NO_4$(M+) 449.2562].

2.9 **Notes and References**.

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APPENDIX THREE: SPECTRA RELEVANT TO CHAPTER TWO

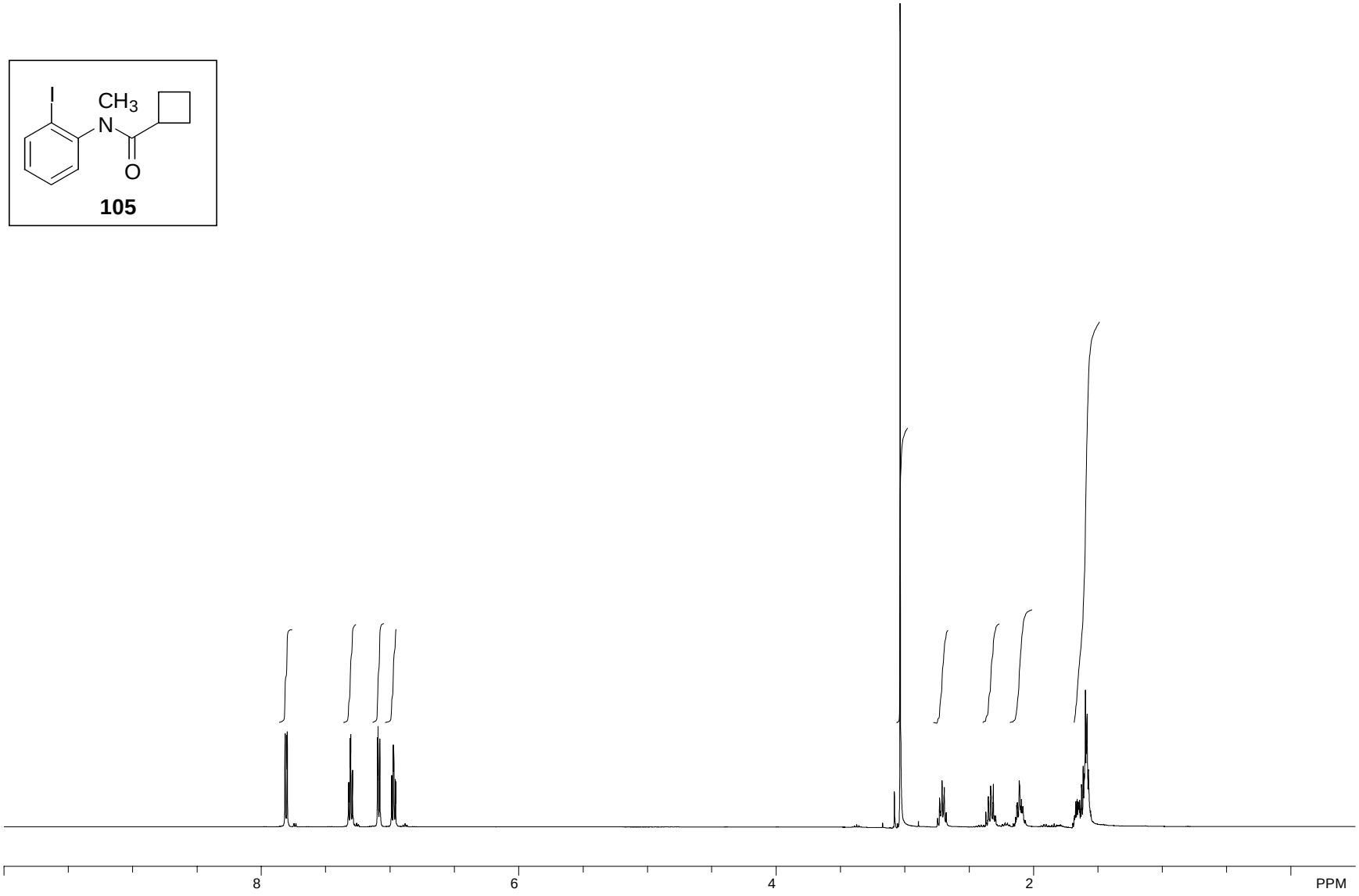


Figure A.3.1 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **105**.

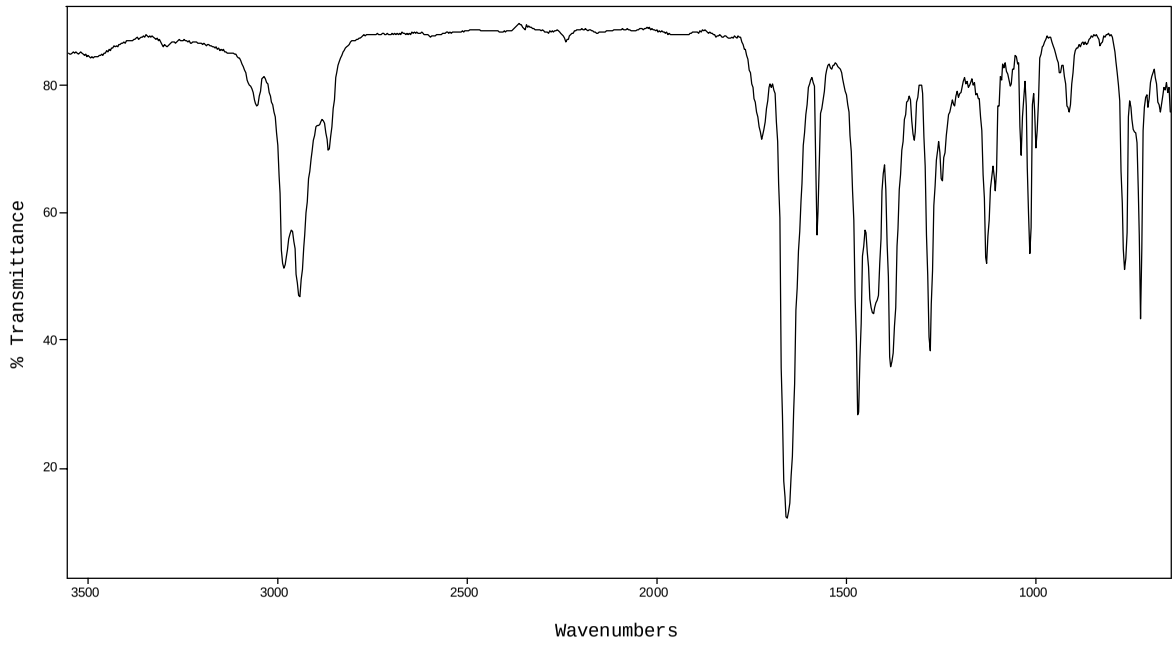


Figure A.3.2 FTIR Spectrum (thin film/NaCl) of Compound **105**.

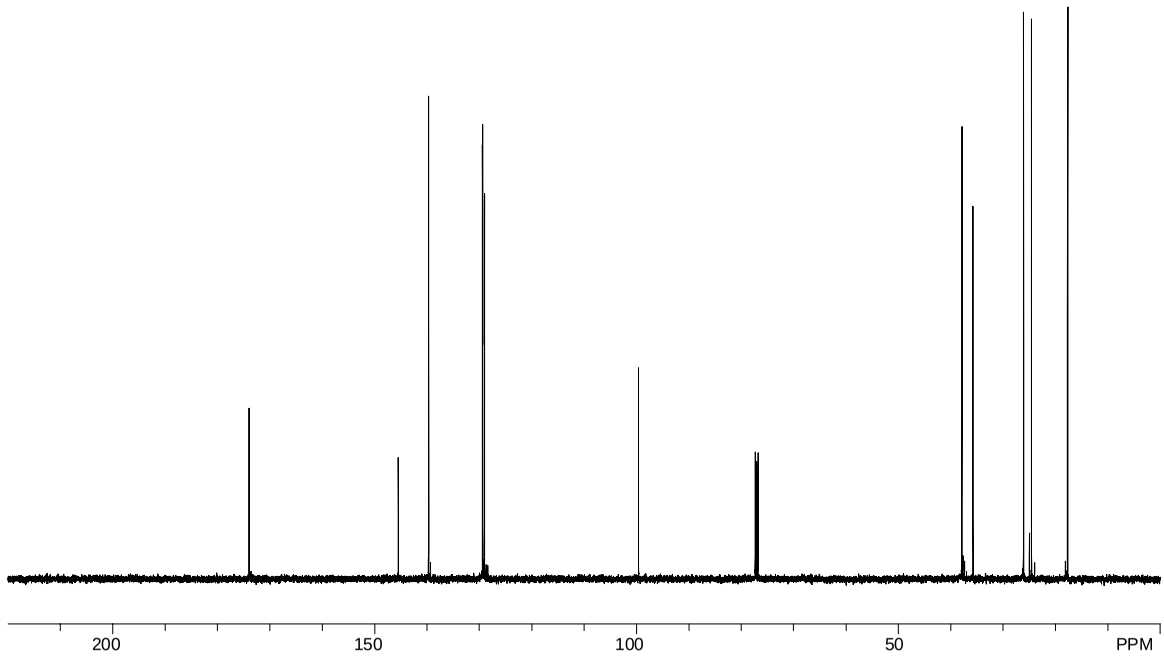


Figure A.3.3 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **105**.

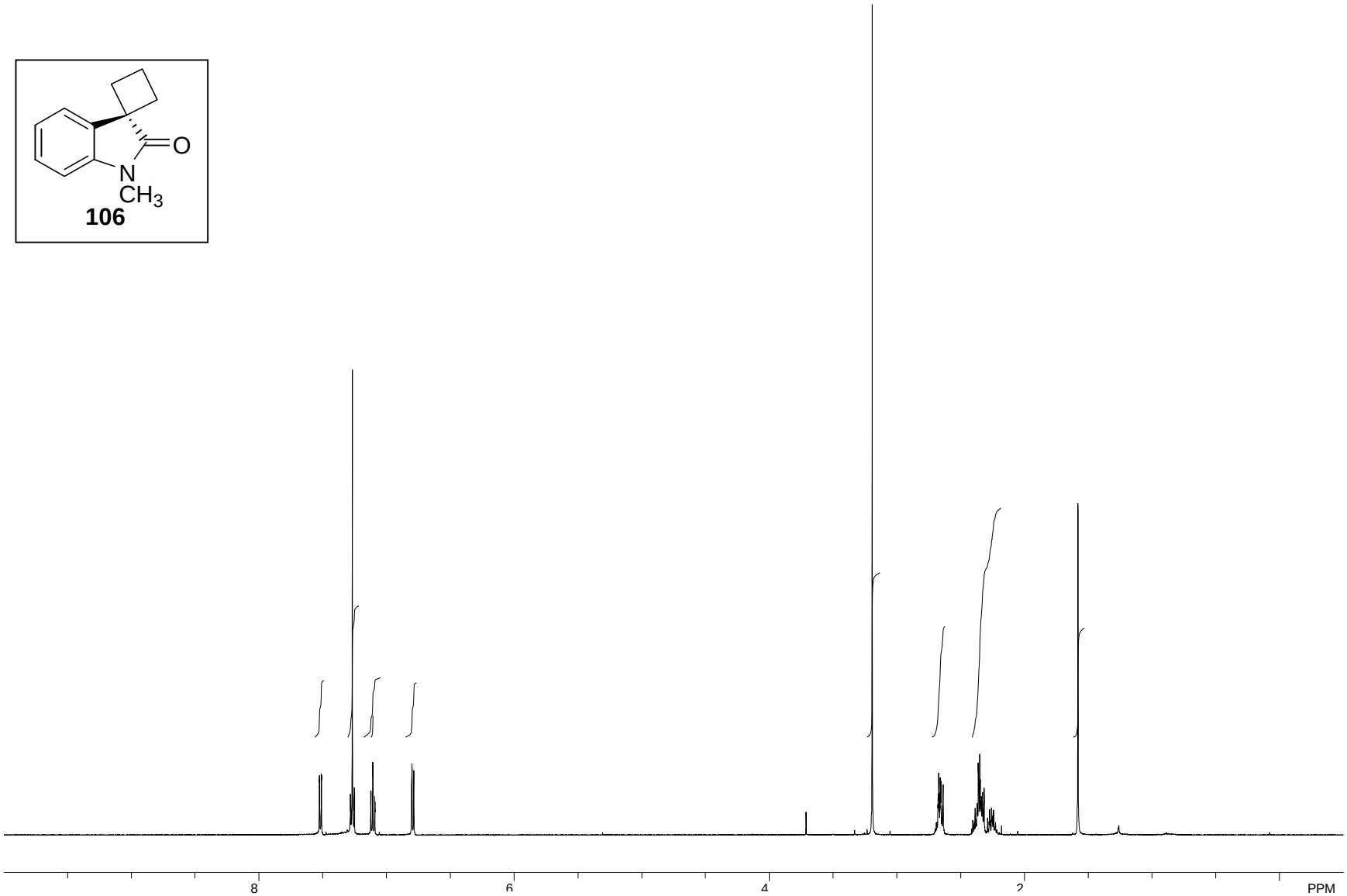


Figure A.3.4 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **106**.

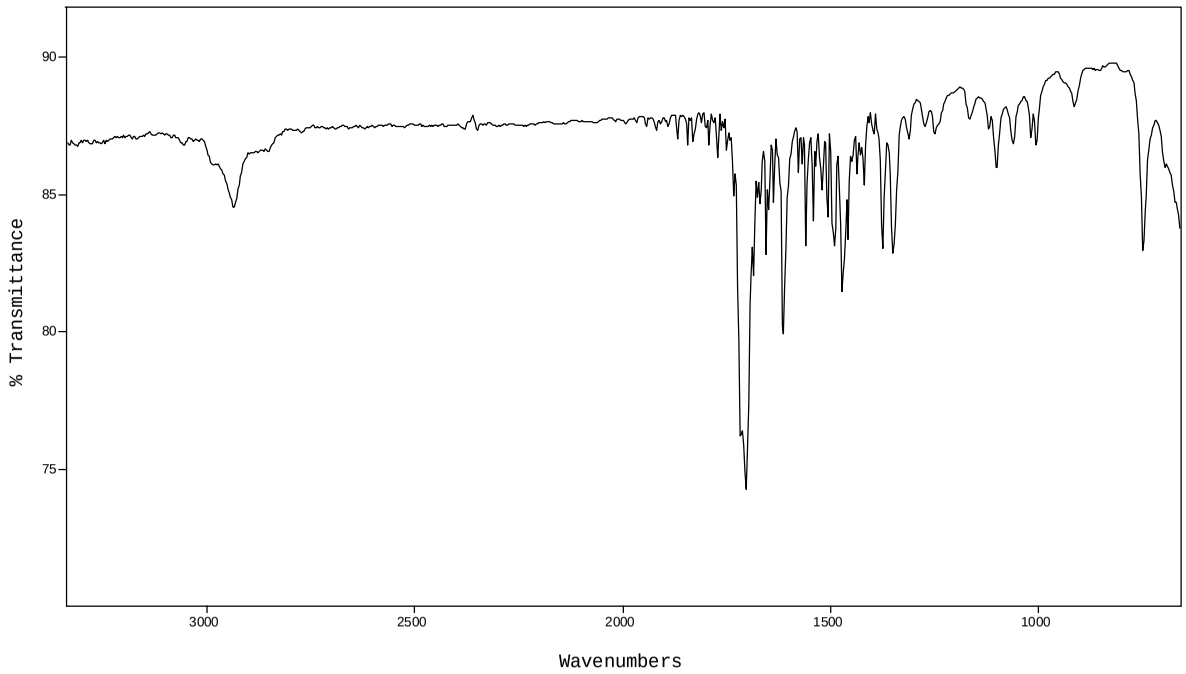


Figure A.3.5 FTIR Spectrum (thin film/NaCl) of Compound **106**.

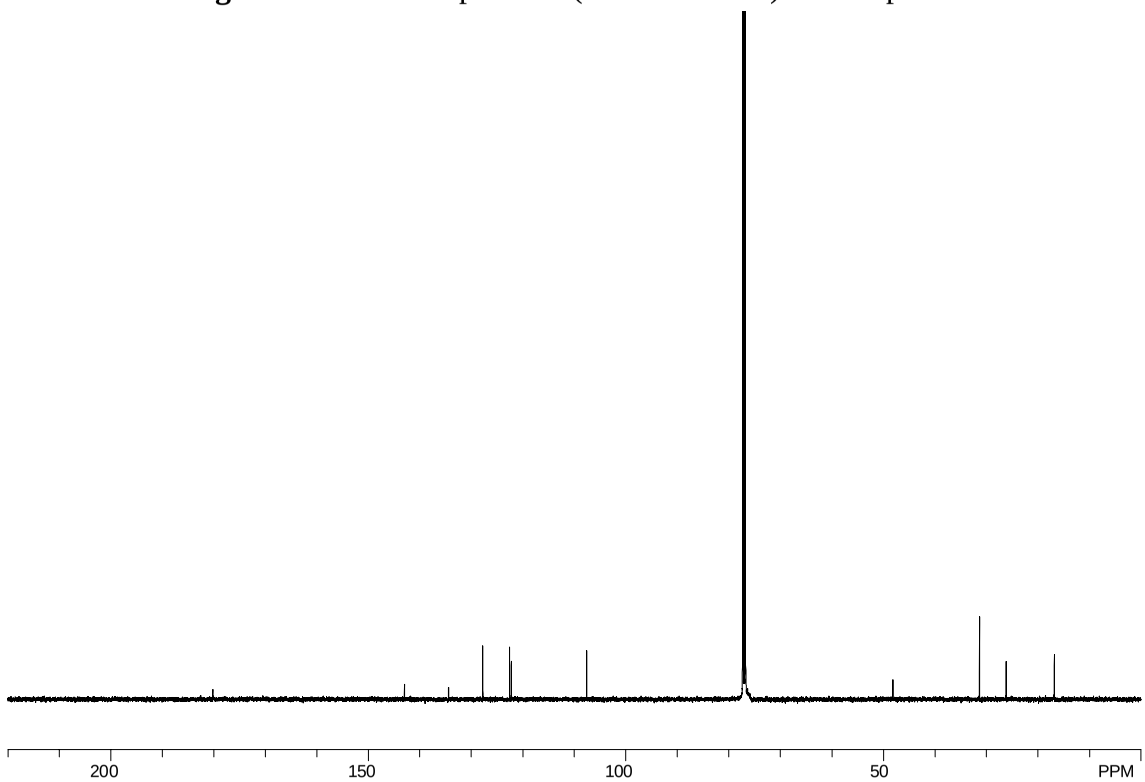
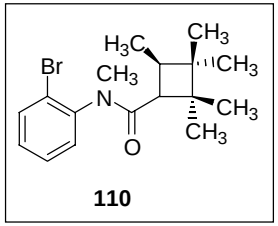


Figure A.3.6 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **106**.



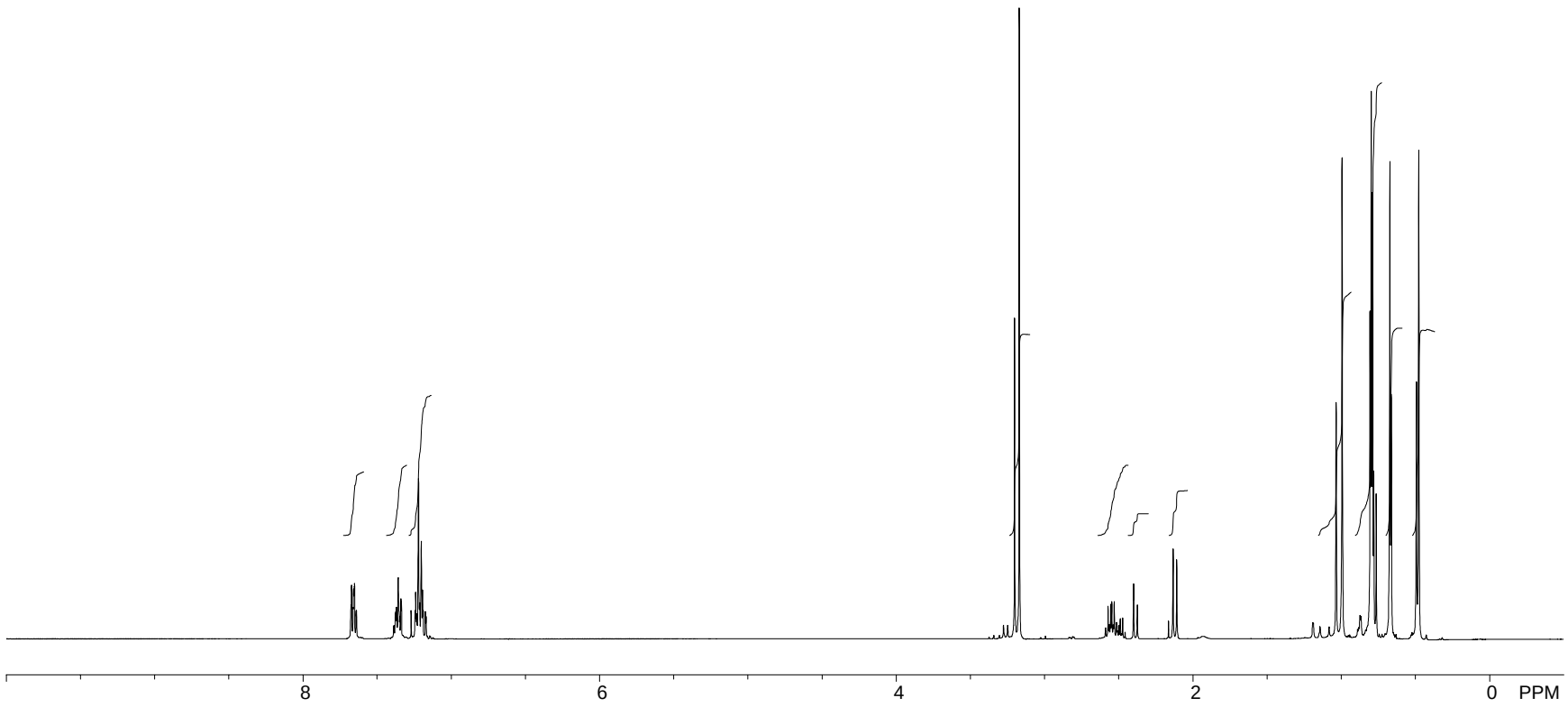


Figure A.3.7 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **110**.

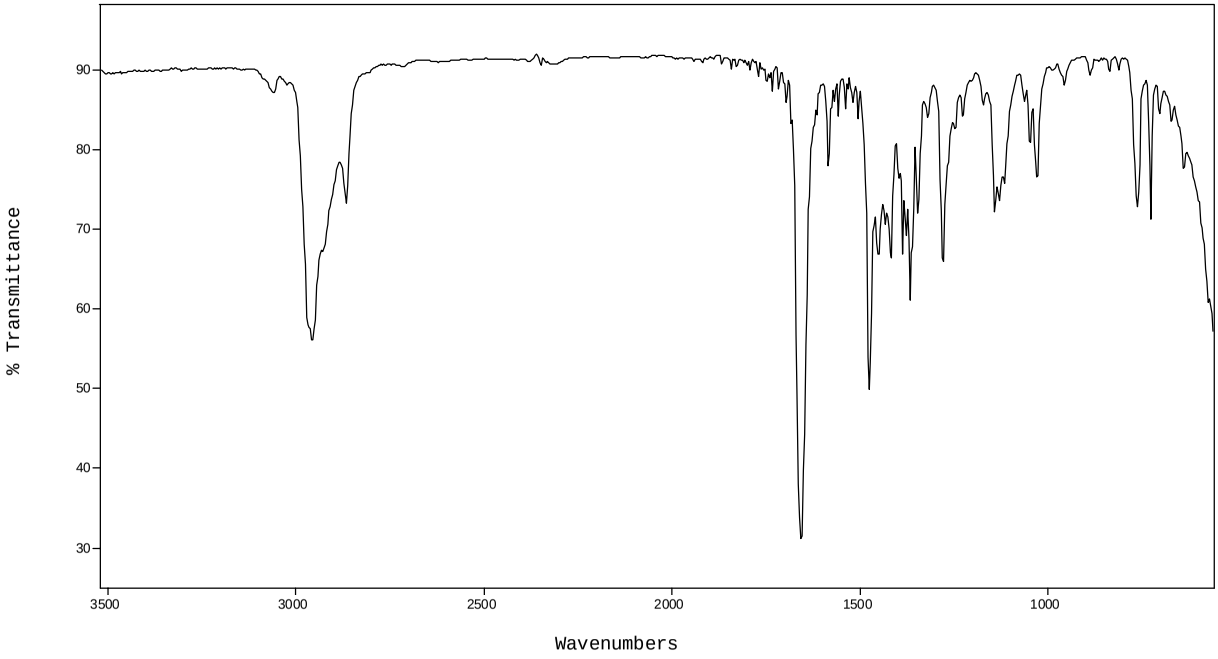


Figure A.3.8 FTIR Spectrum (thin film/NaCl) of Compound **110**.

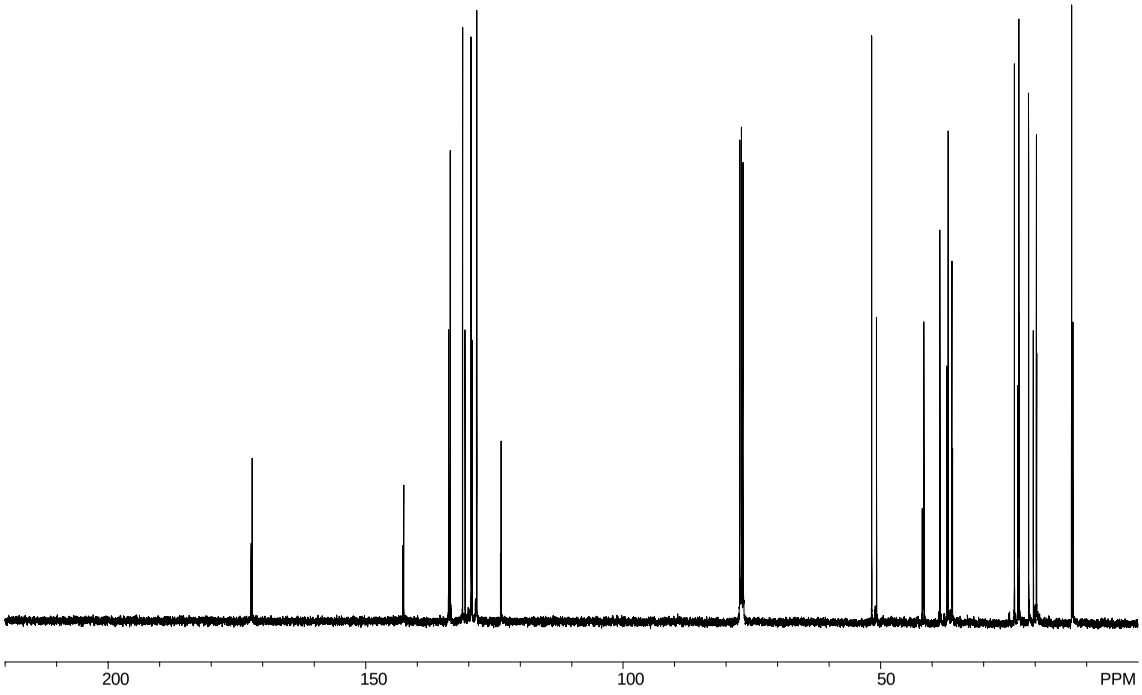
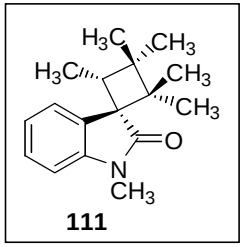


Figure A.3.9 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **110**.



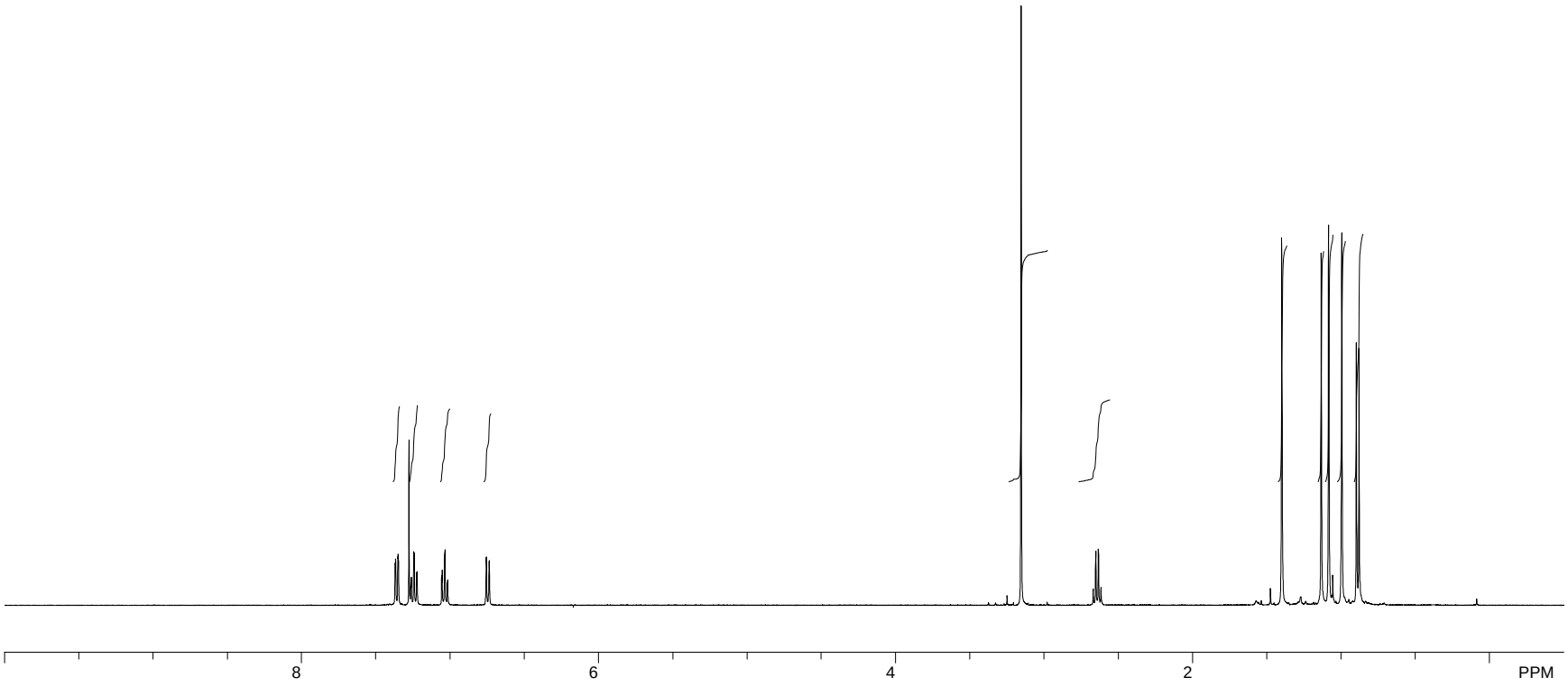


Figure A.3.10 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **111**.

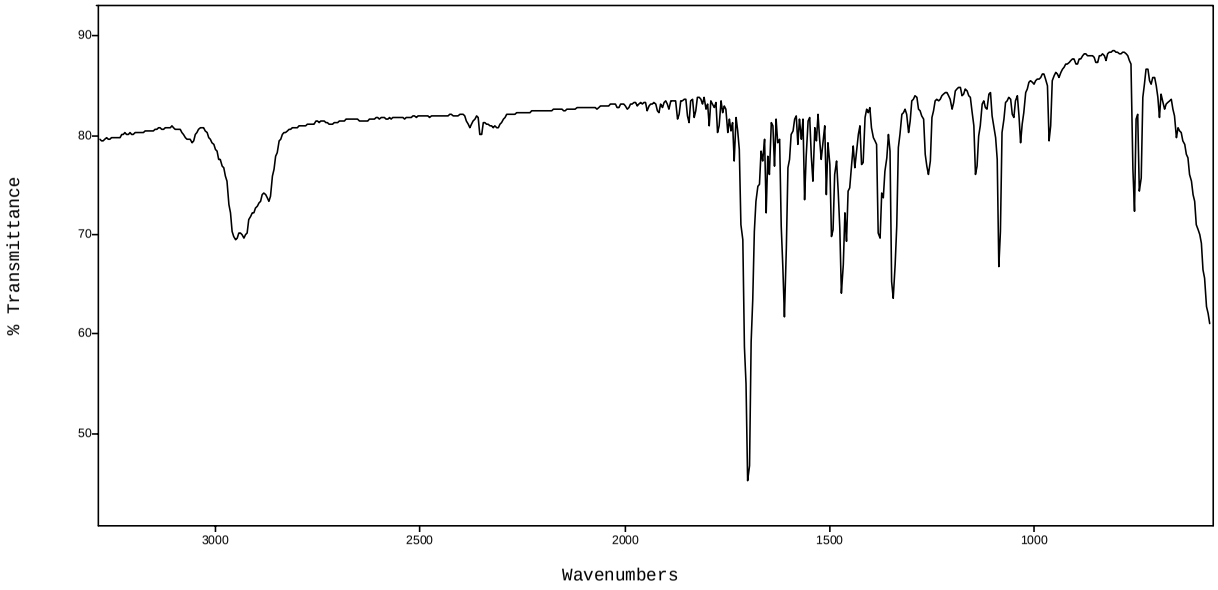


Figure A.3.11 FTIR Spectrum (thin film/NaCl) of Compound **111**.

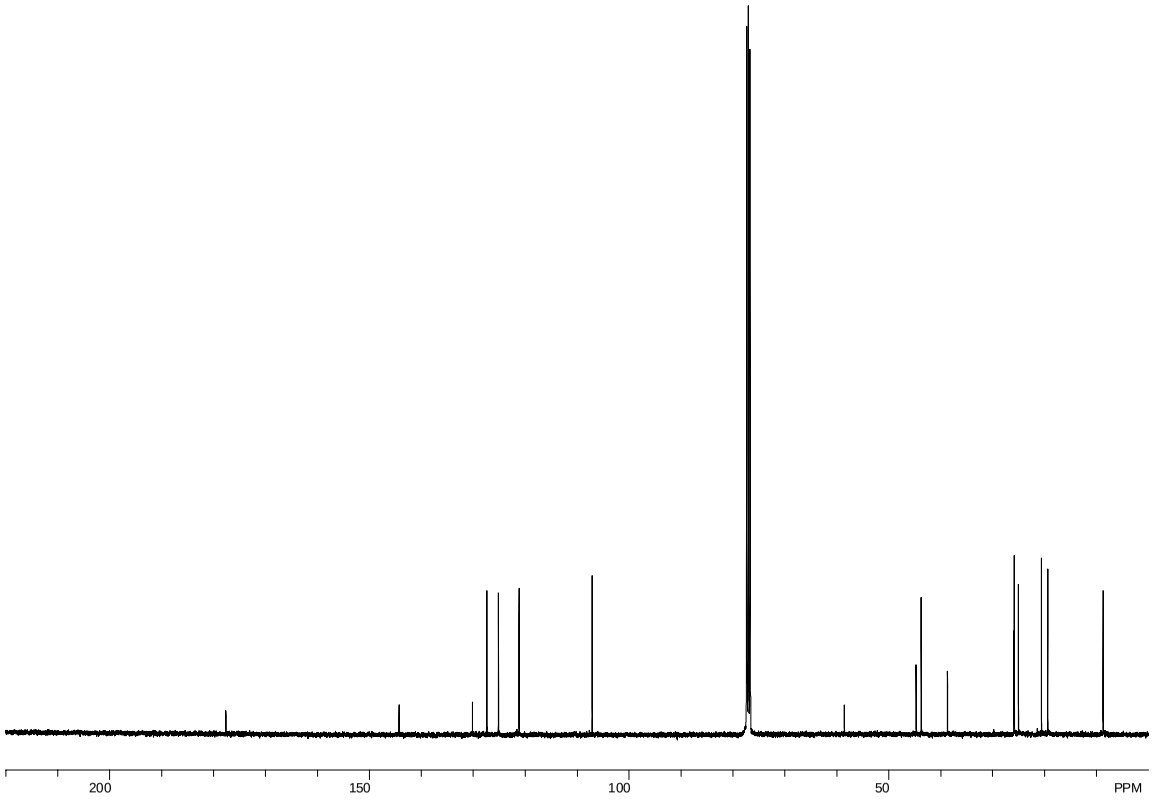


Figure A.3.12 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **111**.

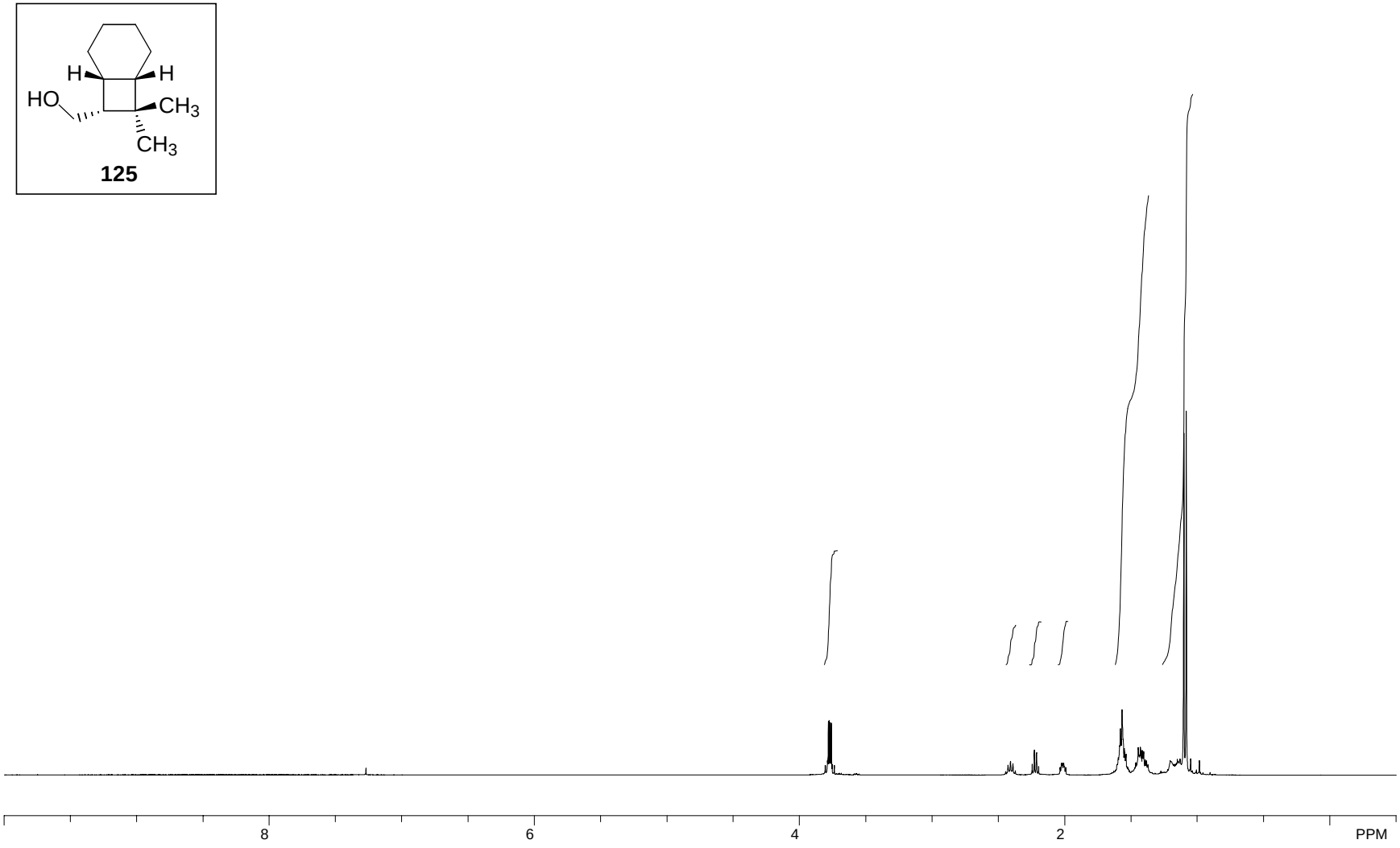


Figure A.3.13 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **125**.

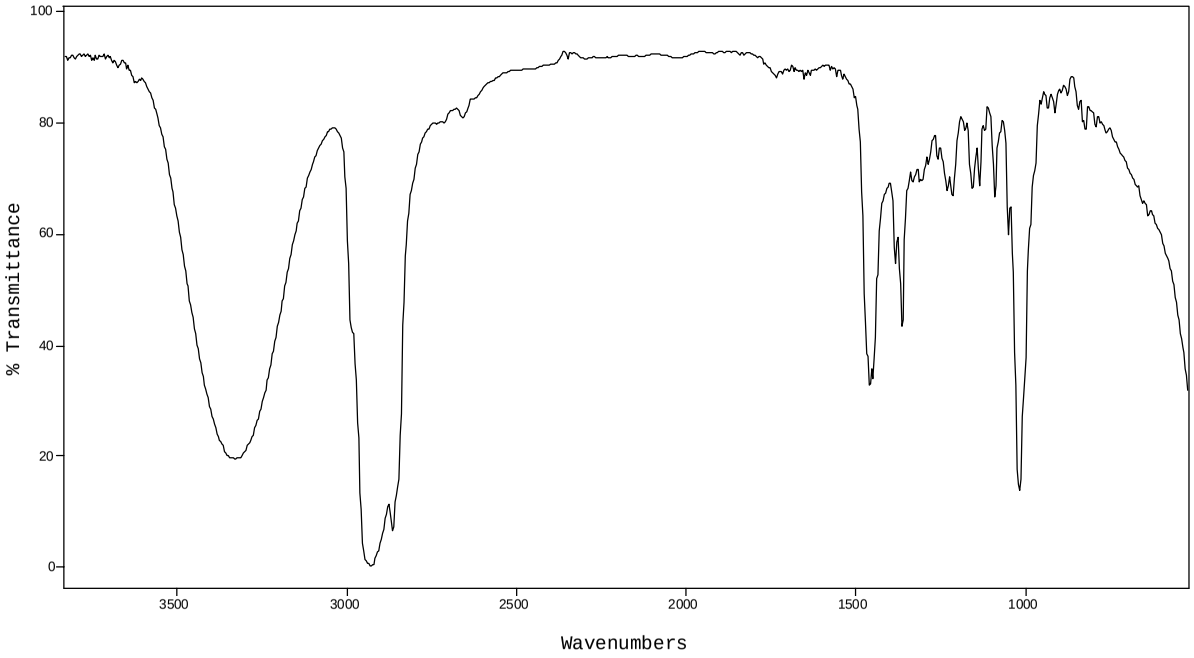


Figure A.3.14 FTIR Spectrum (thin film/NaCl) of Compound **125**.

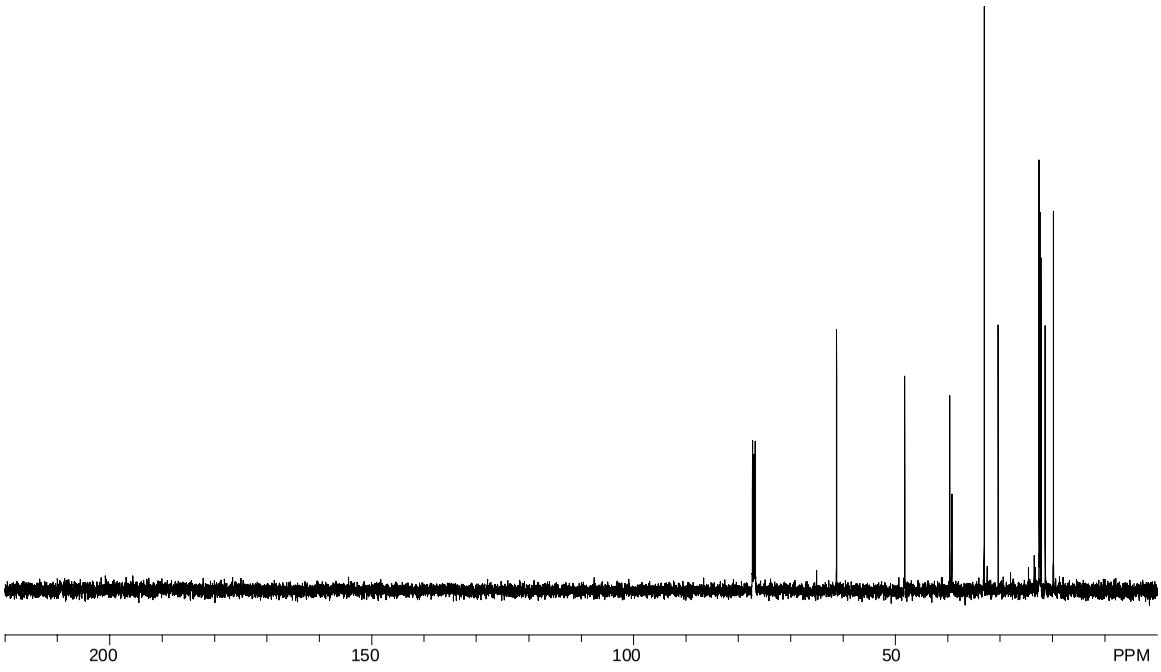


Figure A.3.15 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **125**.

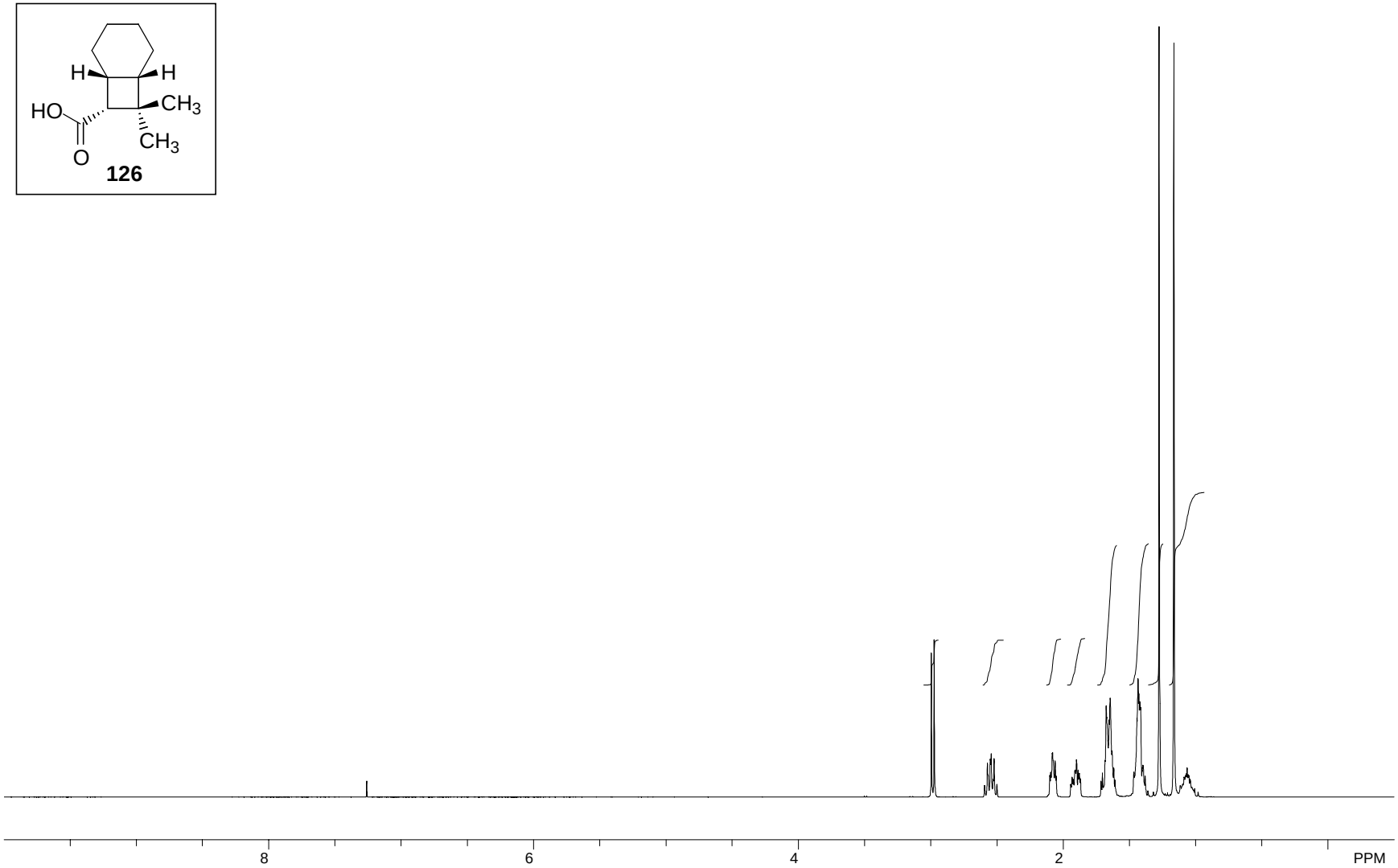


Figure A.3.16 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **126**.

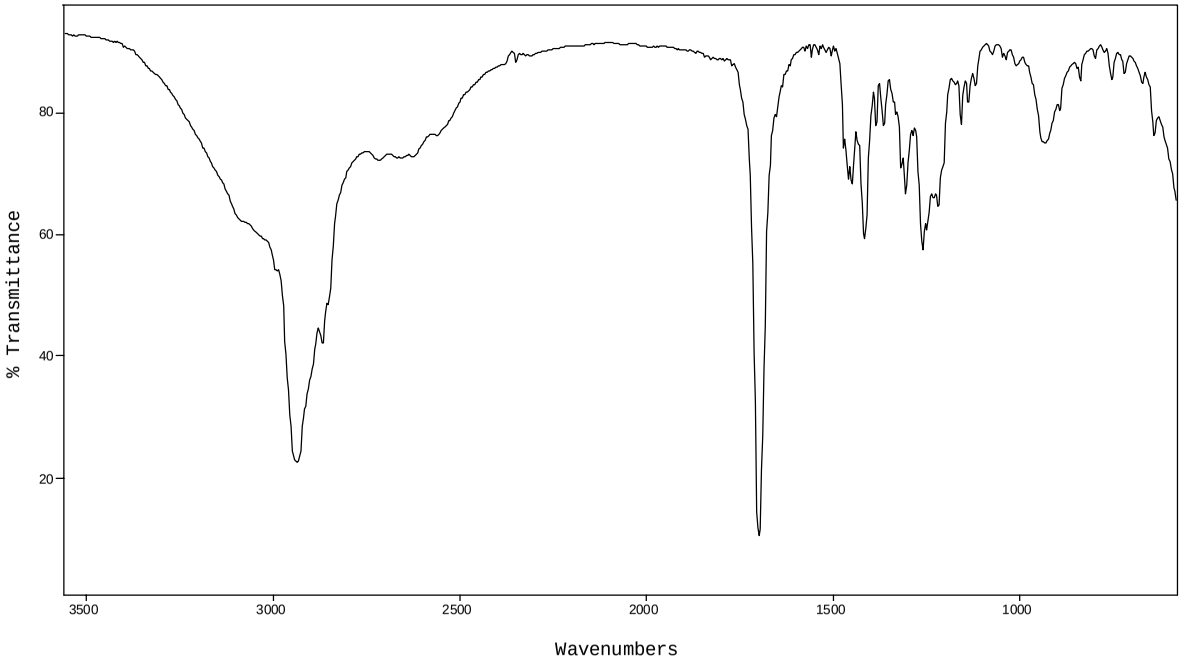


Figure A.3.17 FTIR Spectrum (thin film/NaCl) of Compound **126**.

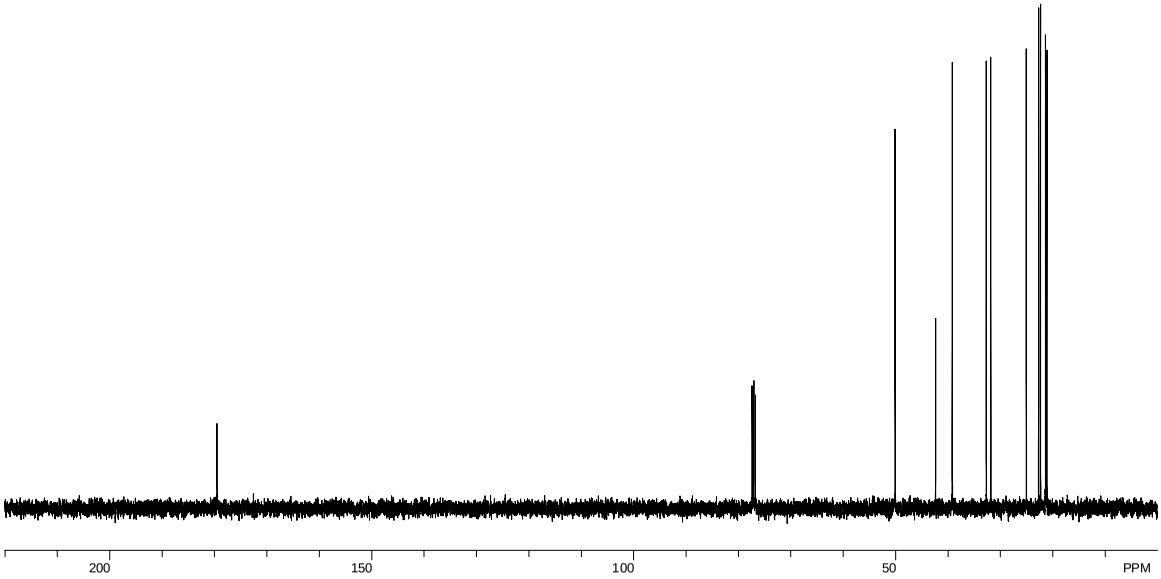
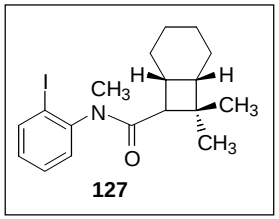


Figure A.3.18 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **126**.



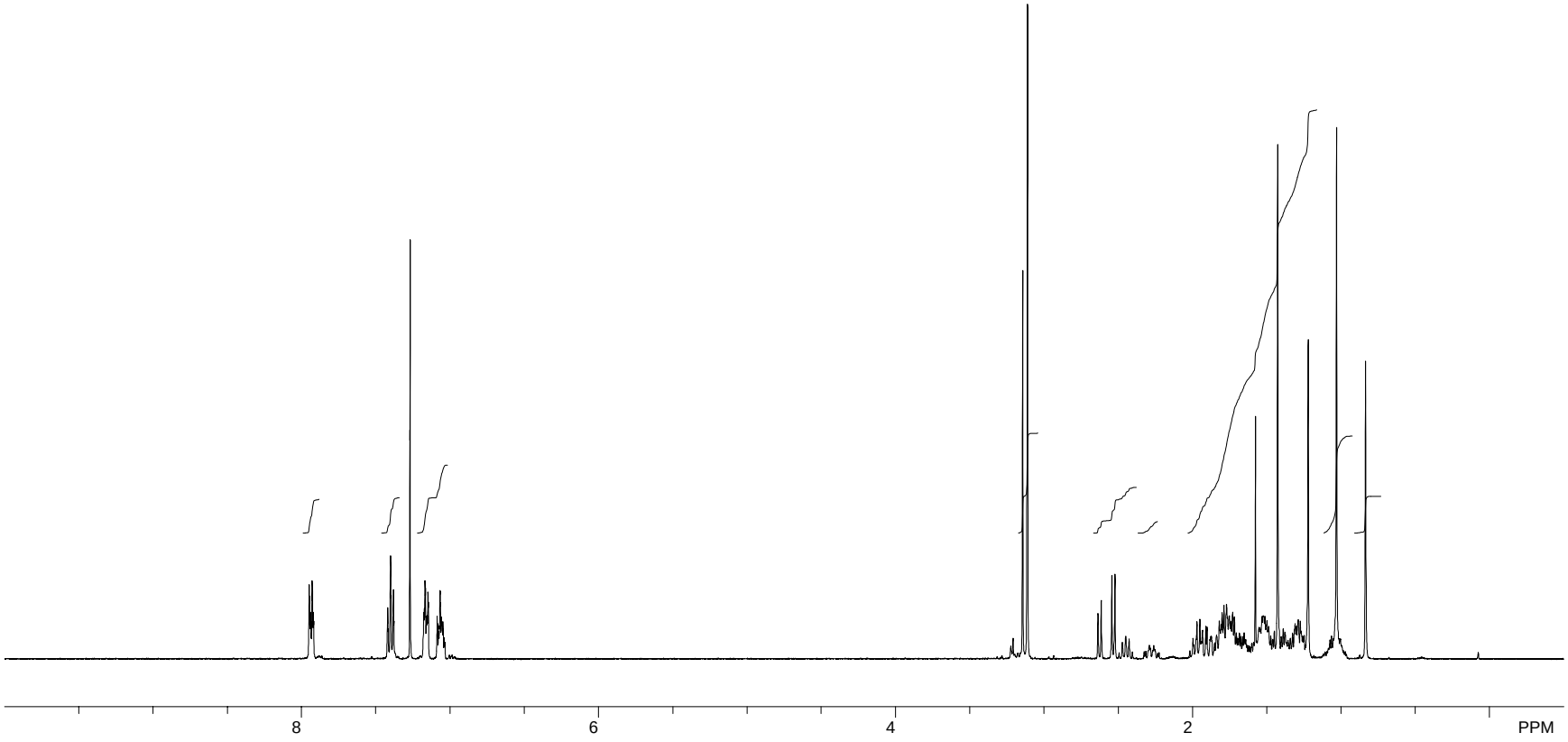


Figure A.3.19 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **127**.

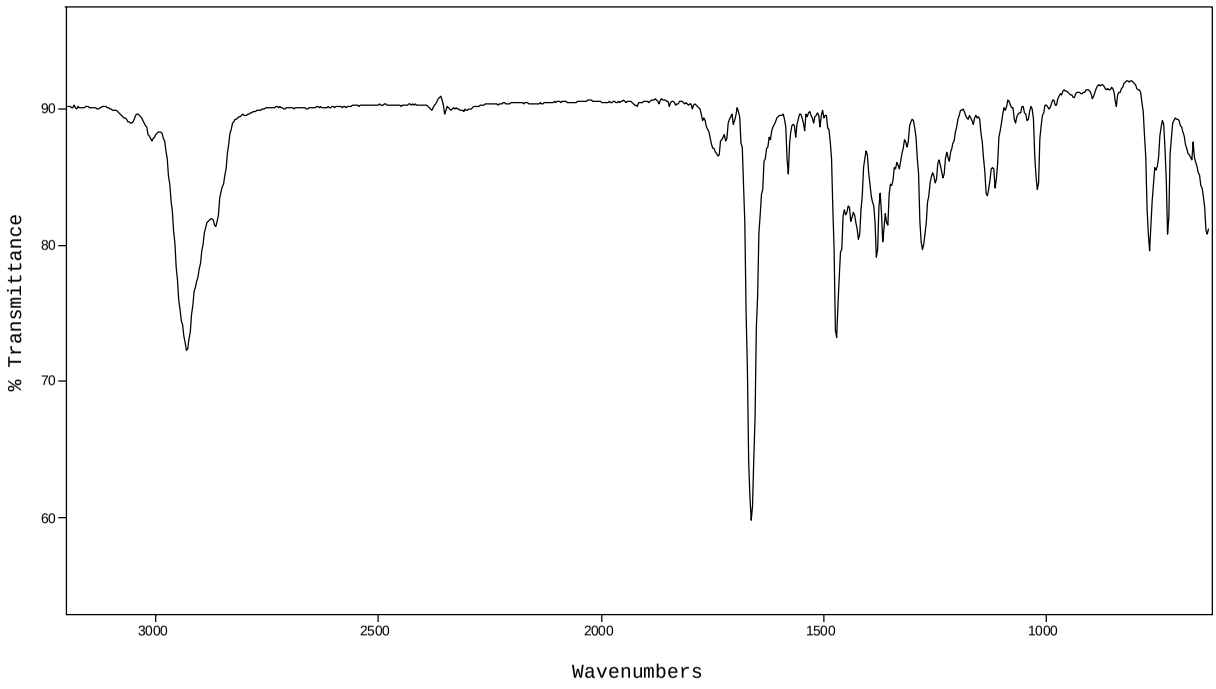


Figure A.3.20 FTIR Spectrum (thin film/NaCl) of Compound **127**.

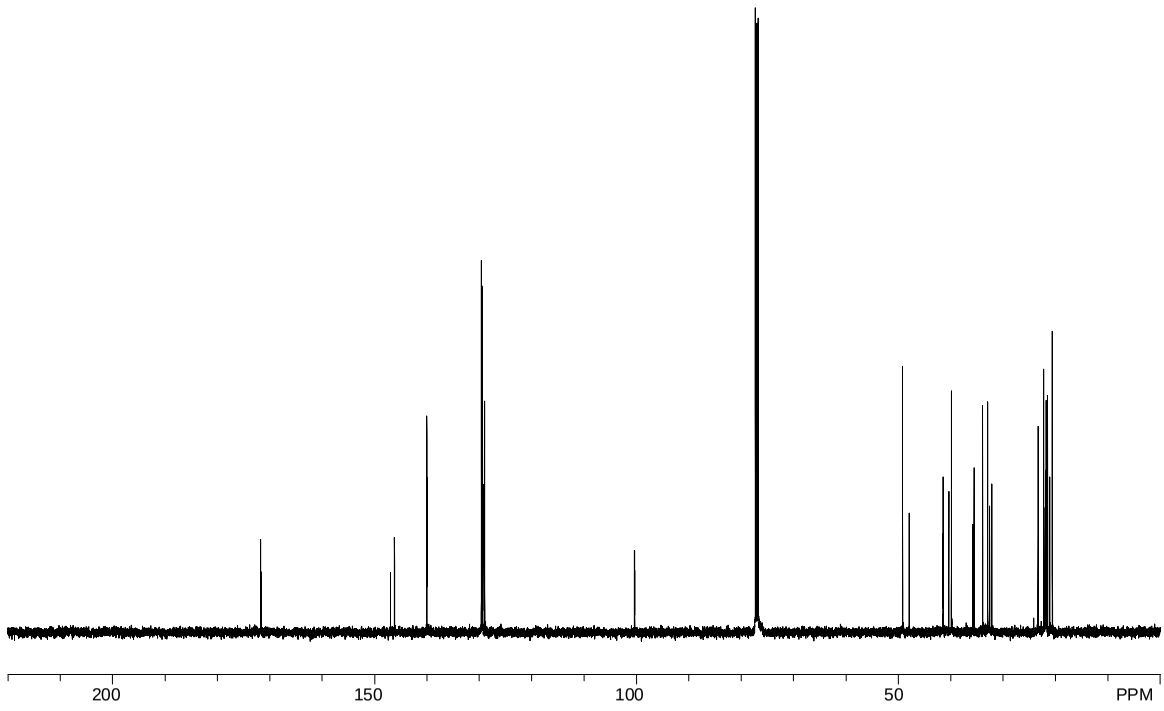


Figure A.3.21 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **127**.

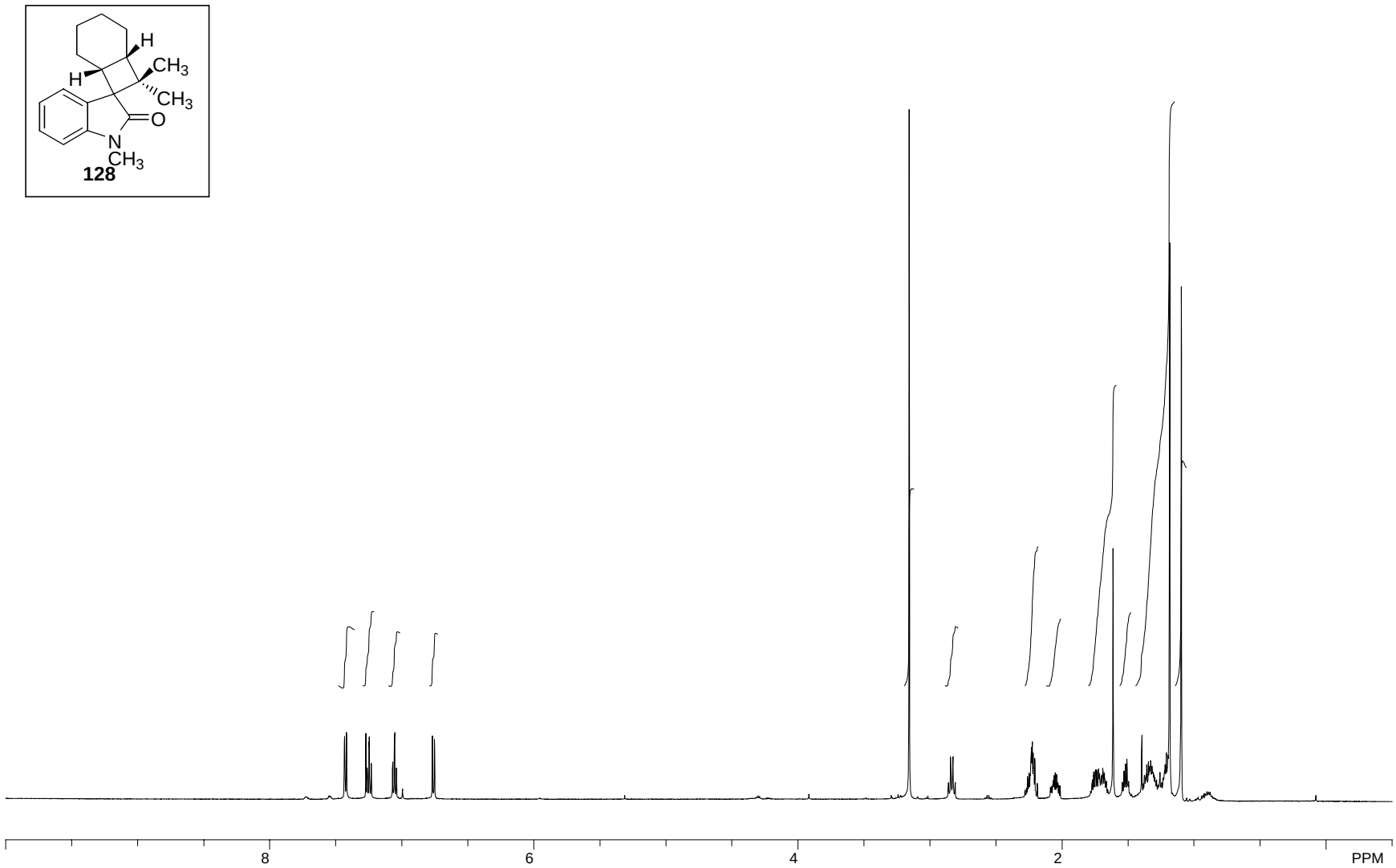


Figure A.3.22 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **128**.

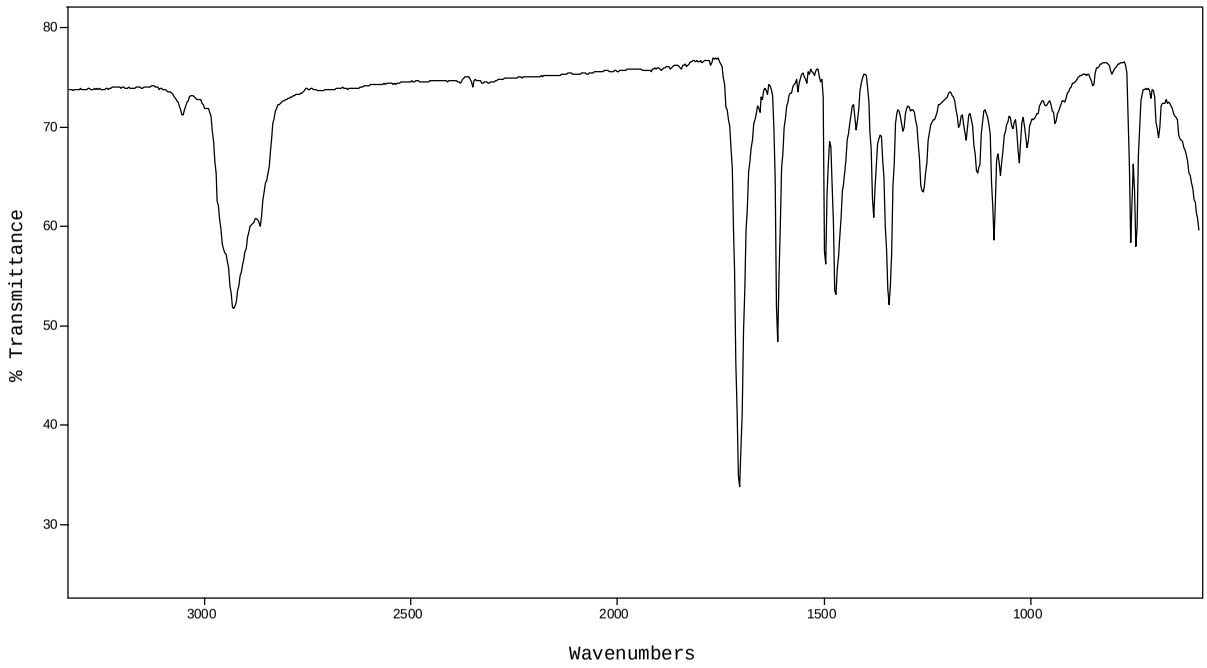


Figure A.3.23 FTIR Spectrum (thin film/NaCl) of Compound **128**.

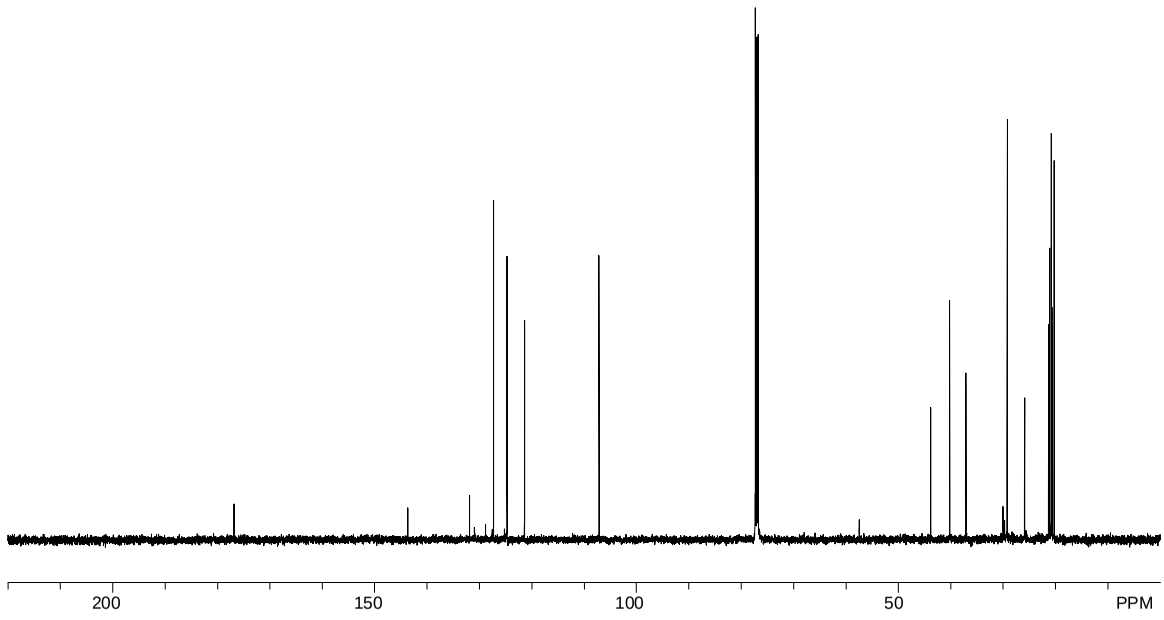


Figure A.3.24 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **128**.

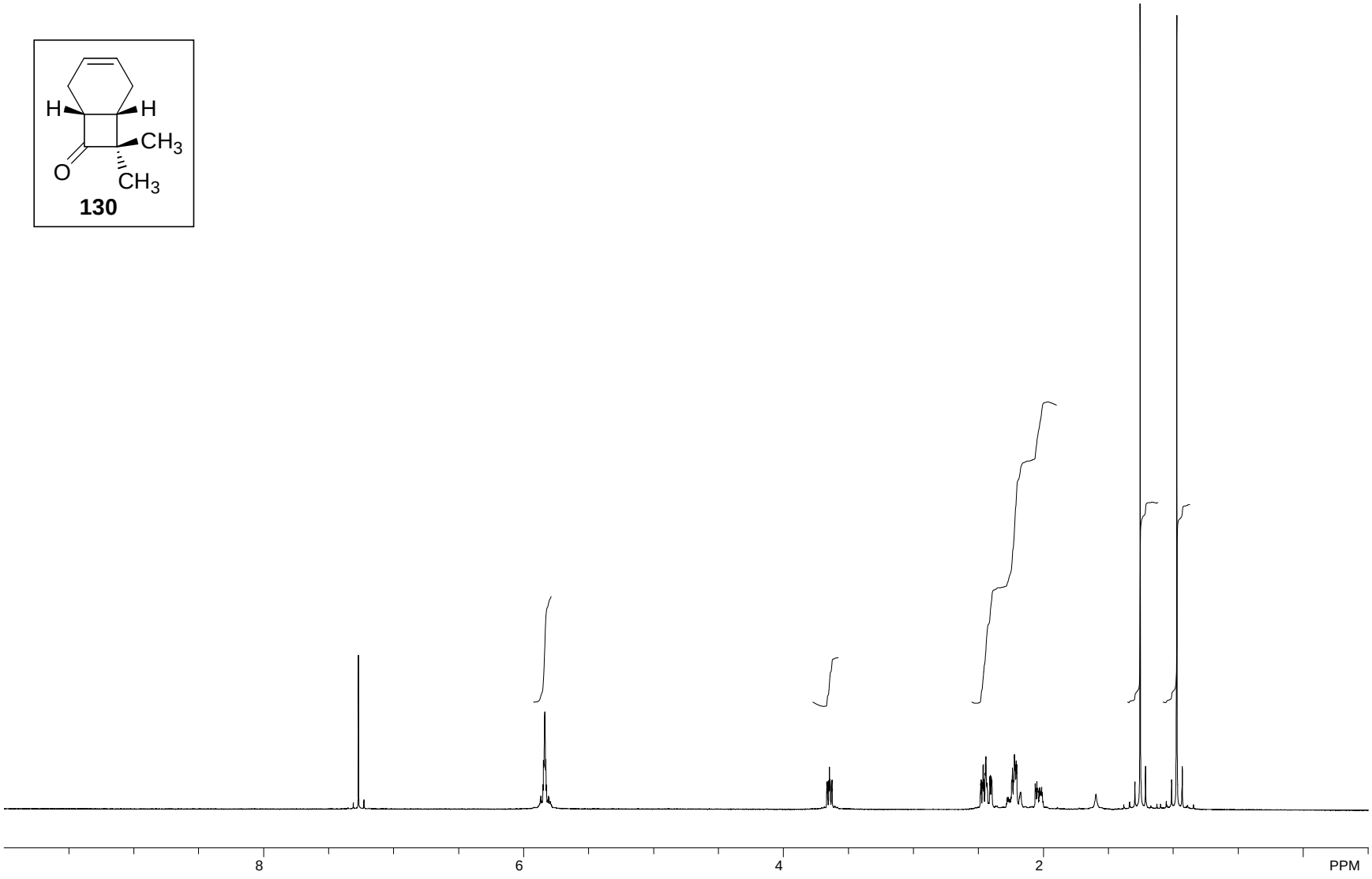


Figure A.3.25 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **130**.

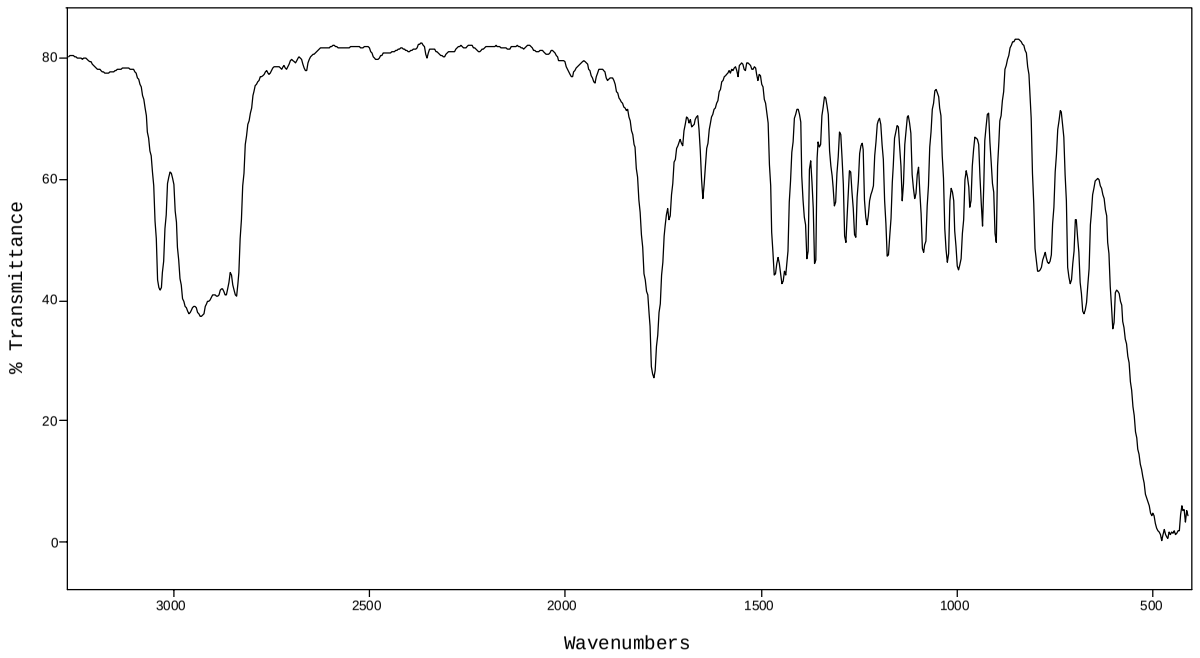


Figure A.3.26 FTIR Spectrum (thin film/NaCl) of Compound **130**.

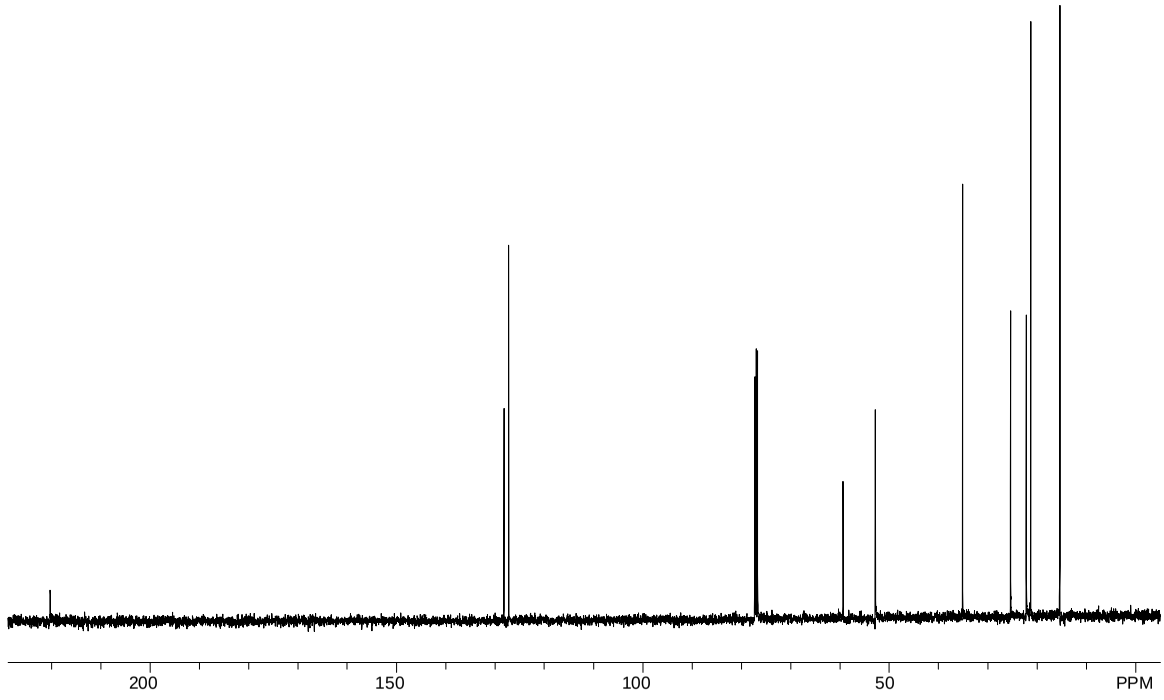


Figure A.3.27 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **130**.

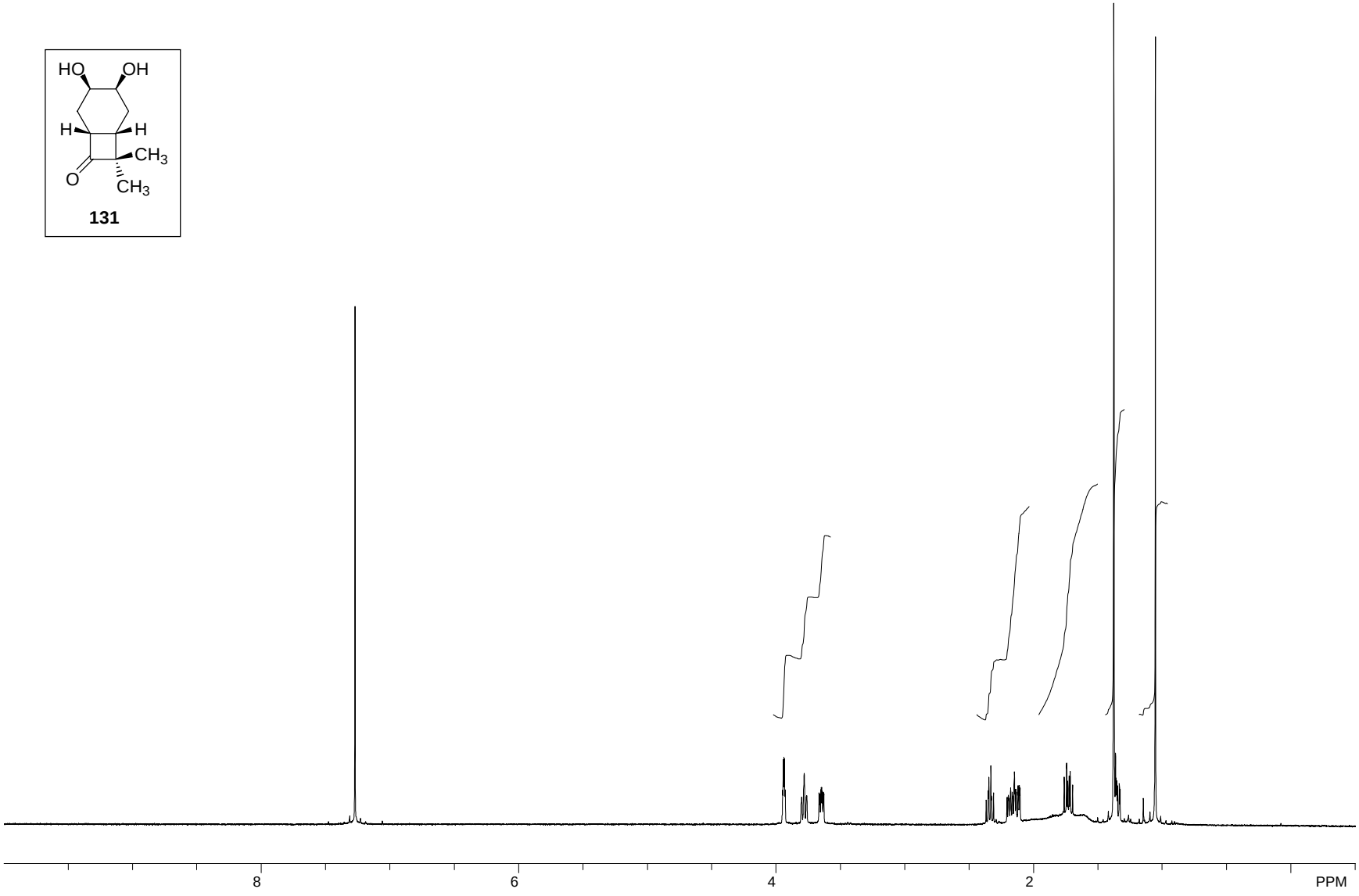


Figure A.3.28 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **131**.

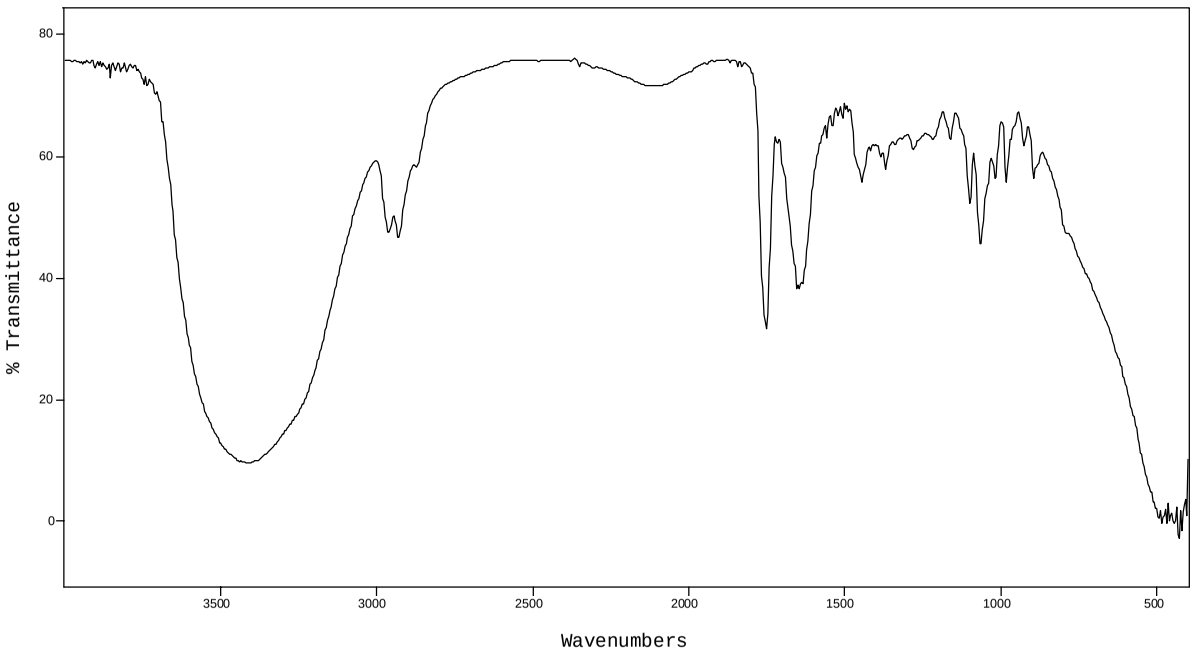


Figure A.3.29 FTIR Spectrum (thin film/NaCl) of Compound **131**.

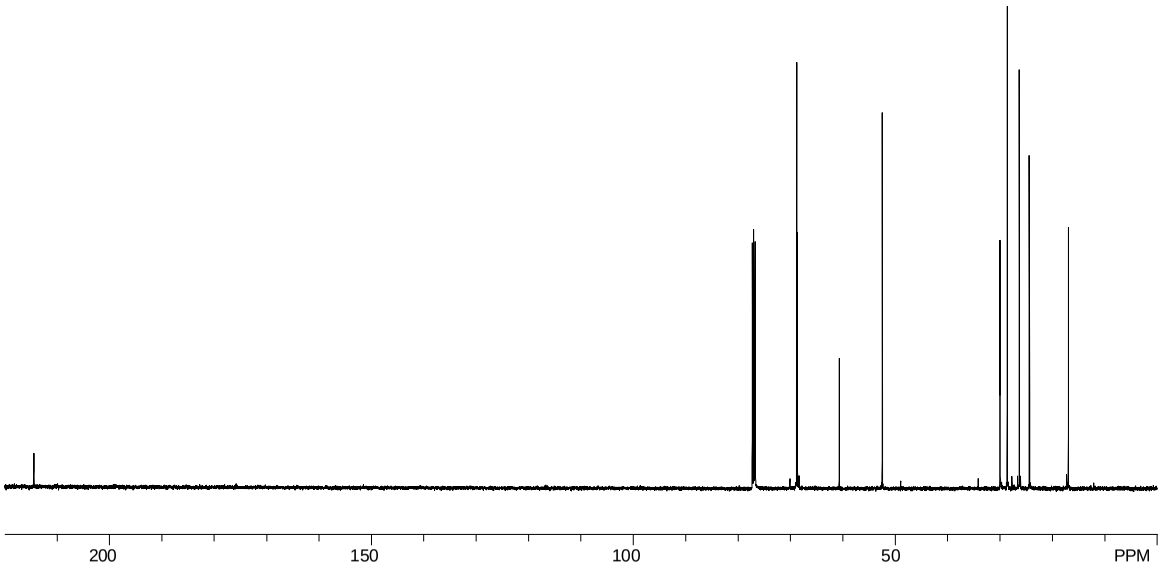


Figure A.3.30 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **131**.

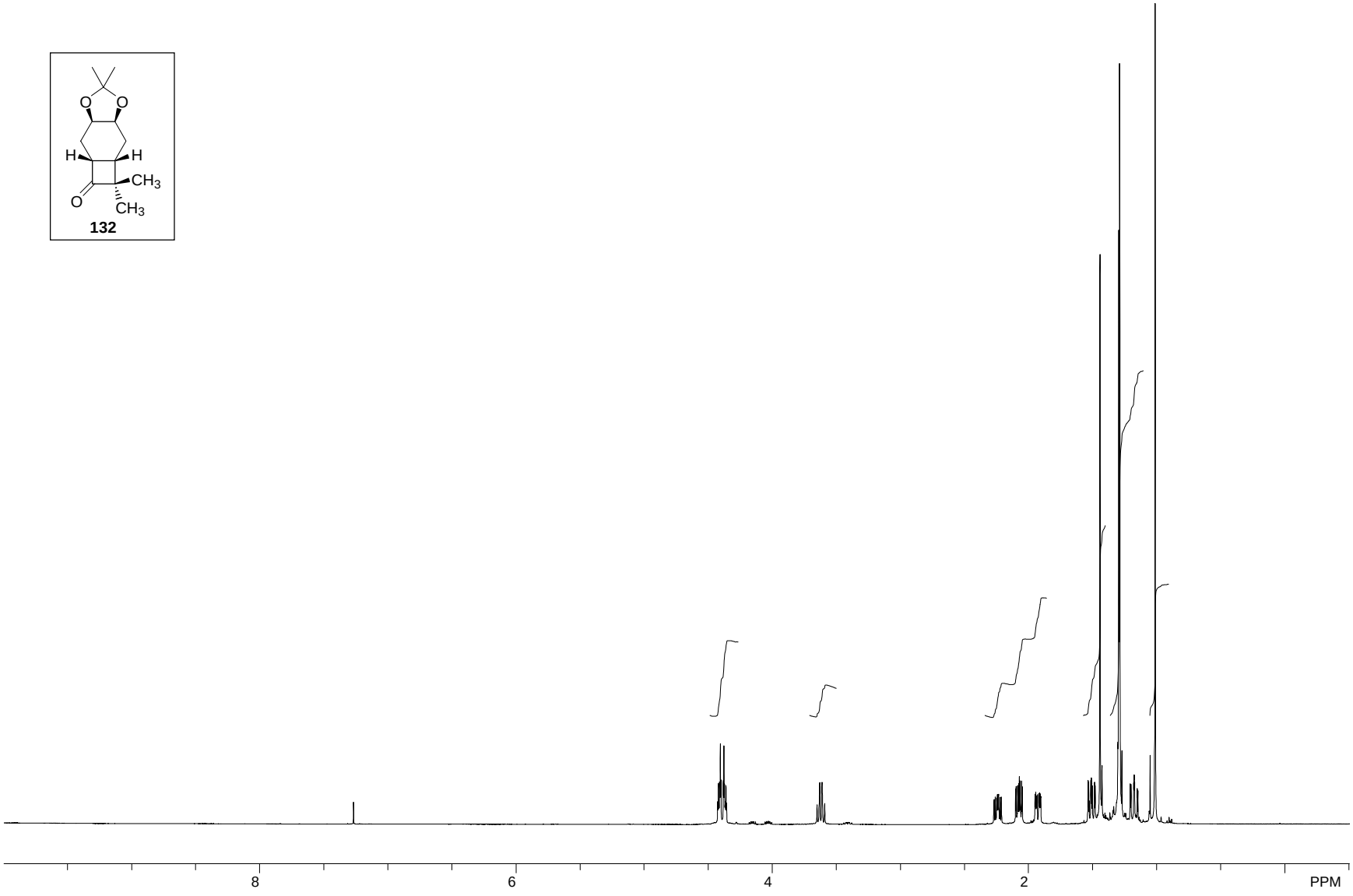


Figure A.3.31 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **132**.

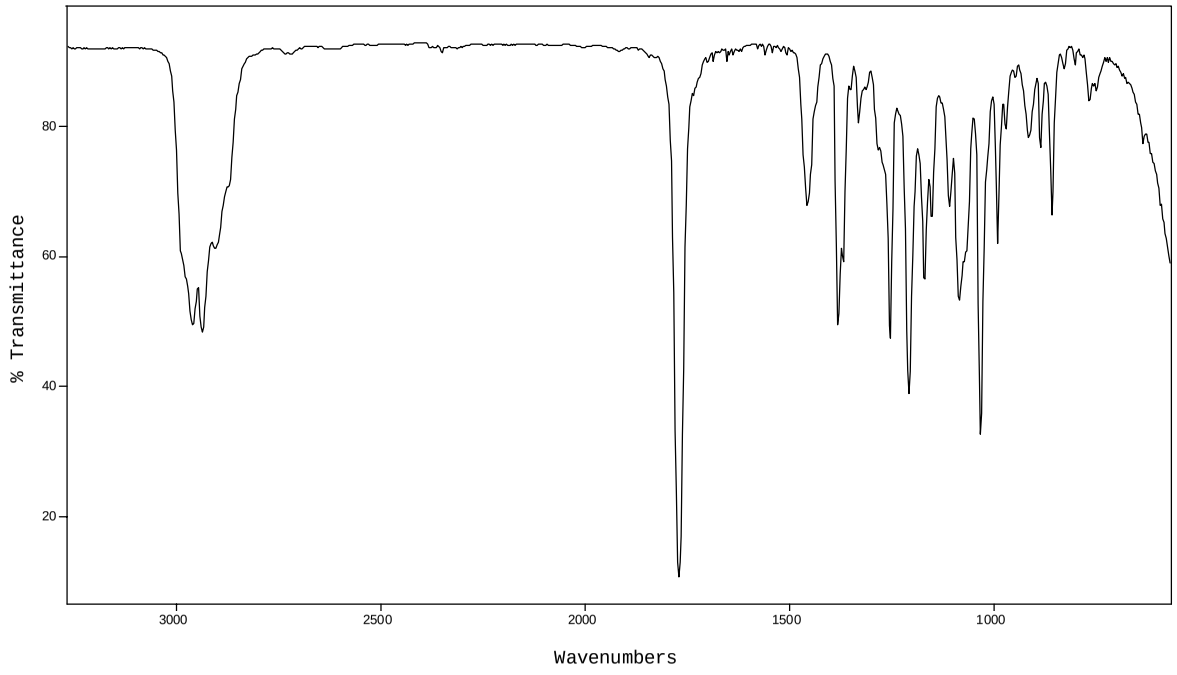


Figure A.3.32 FTIR Spectrum (thin film/NaCl) of Compound **132**.

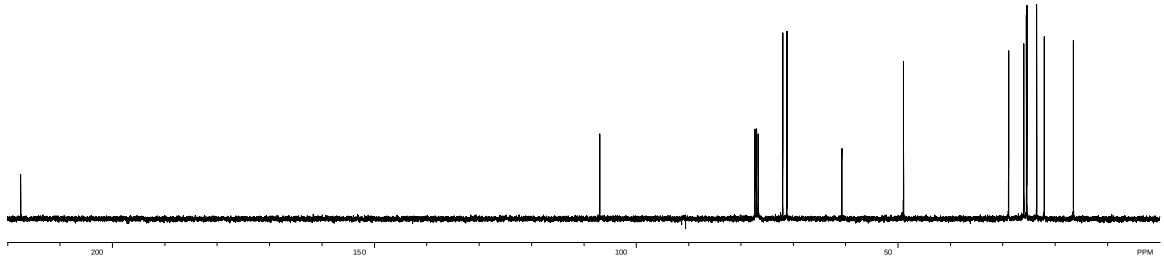


Figure A.3.33 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **132**.

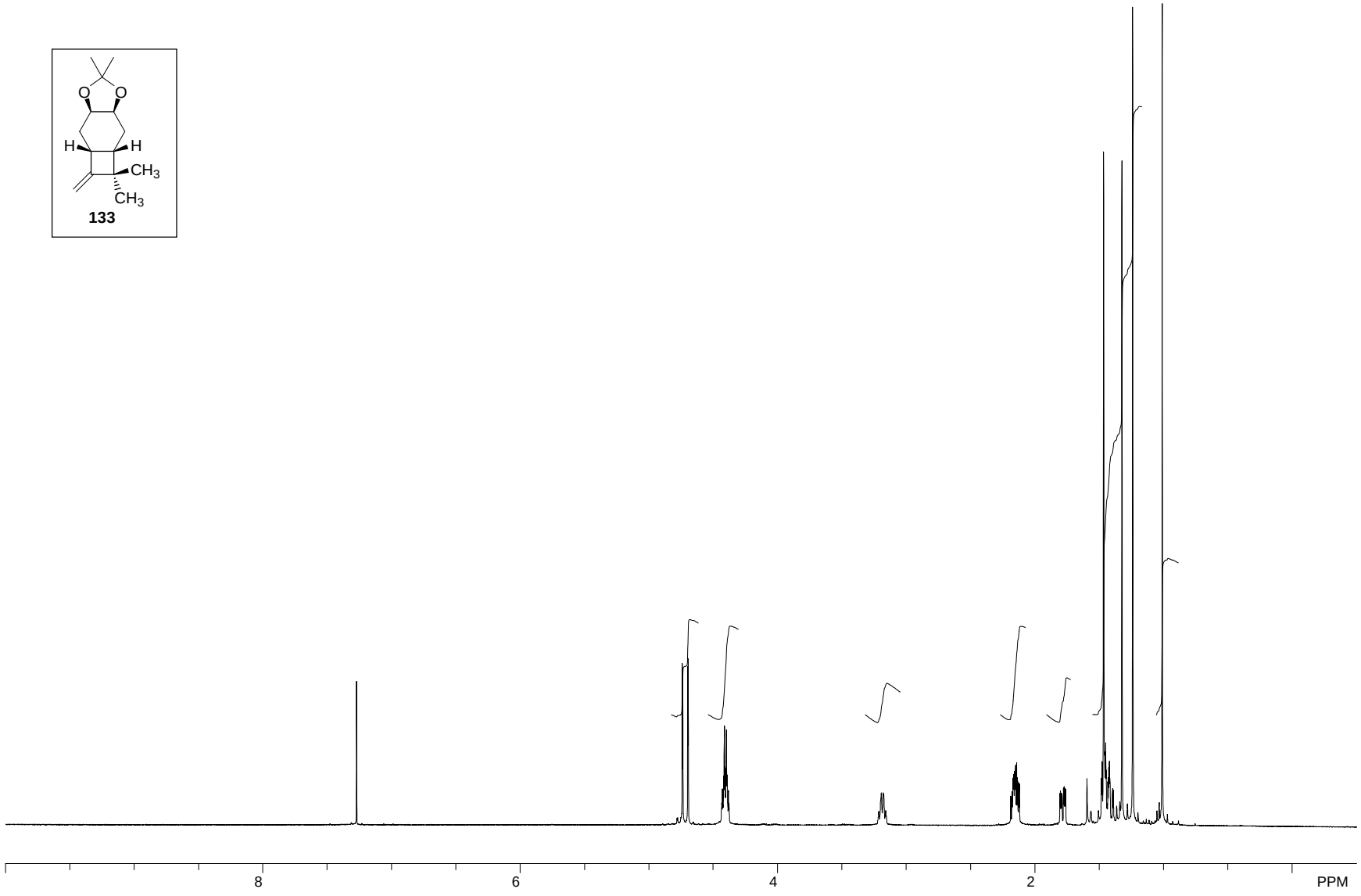


Figure A.3.34 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **133.**

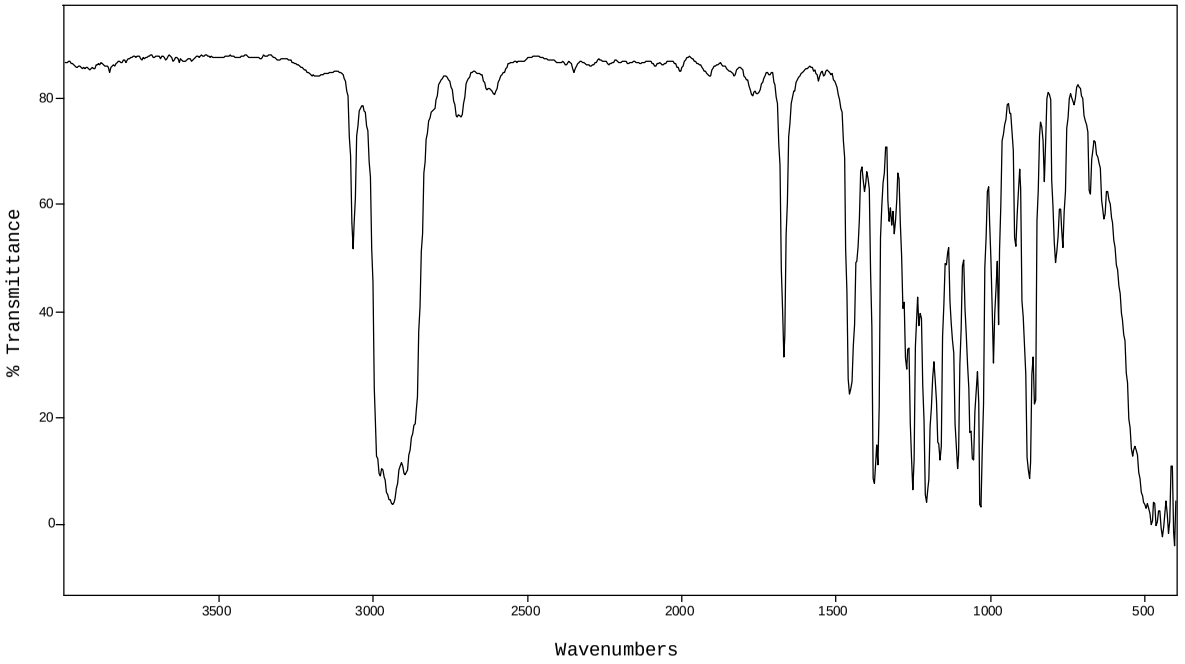


Figure A.3.35 FTIR Spectrum (thin film/NaCl) of Compound **133**.

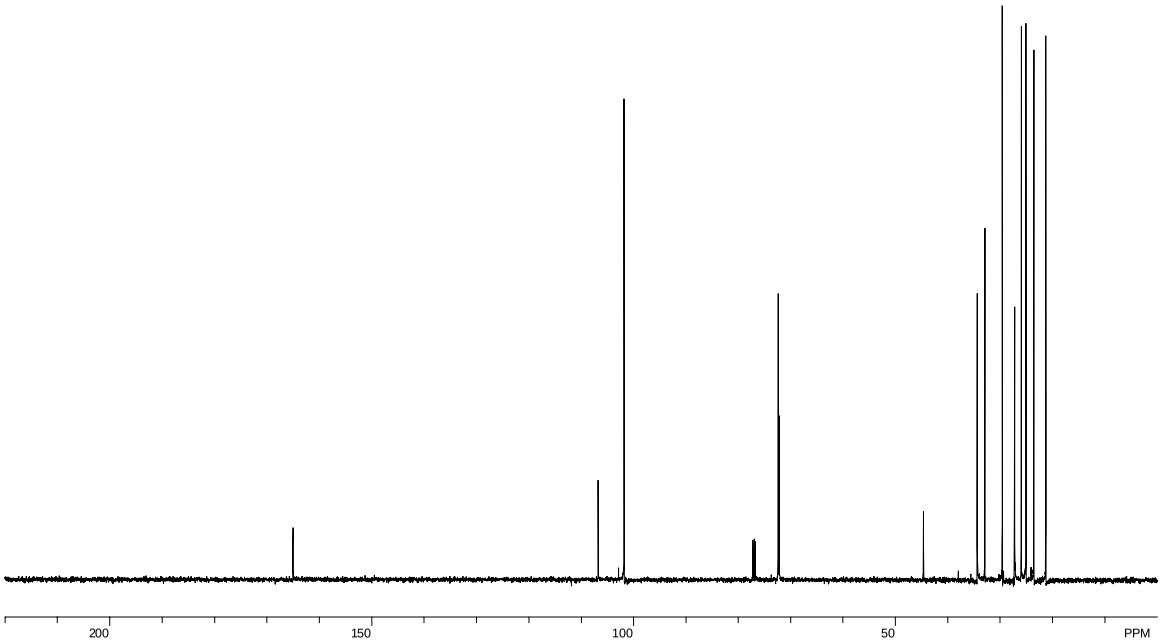
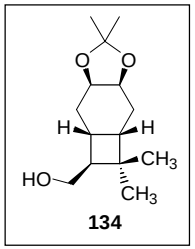


Figure A.3.36 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **133**.



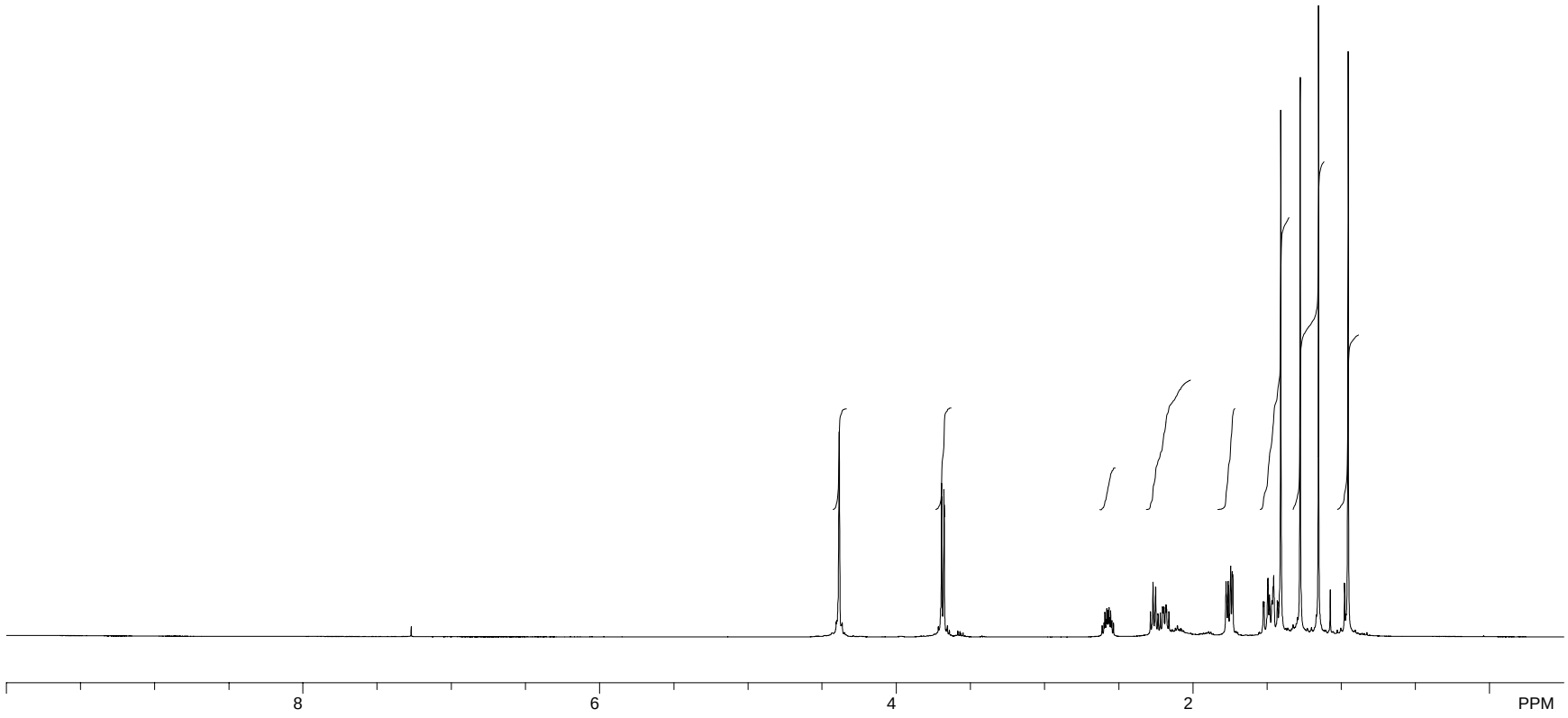


Figure A.3.37 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **134**.

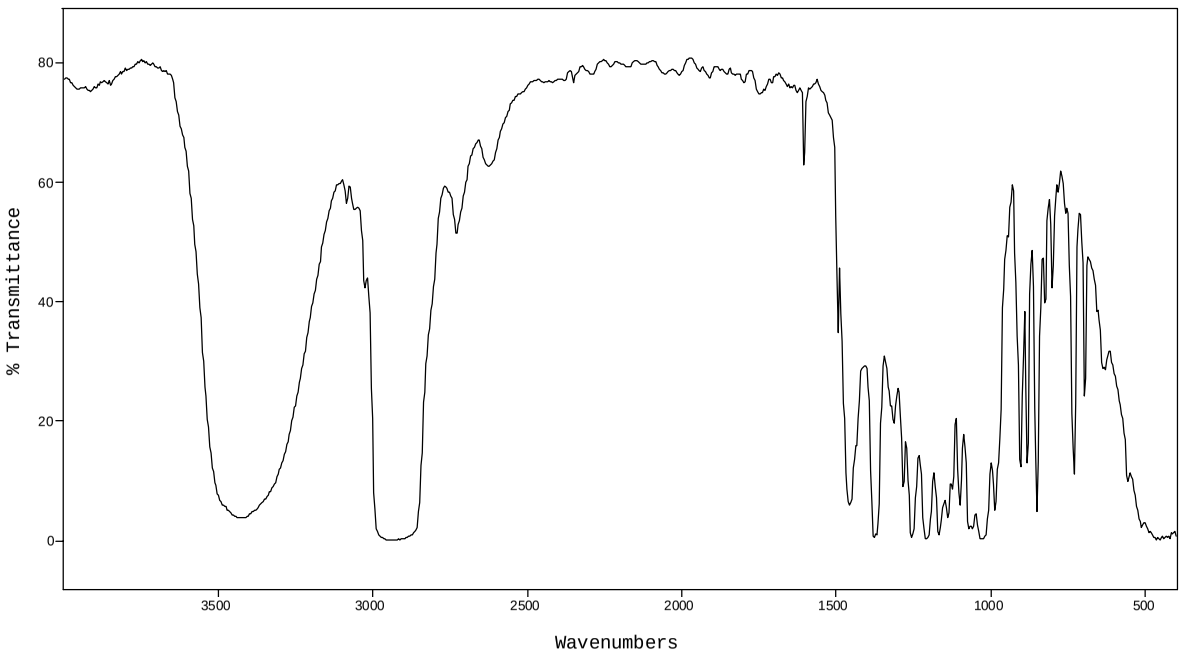


Figure A.3.38 FTIR Spectrum (thin film/NaCl) of Compound **134**.

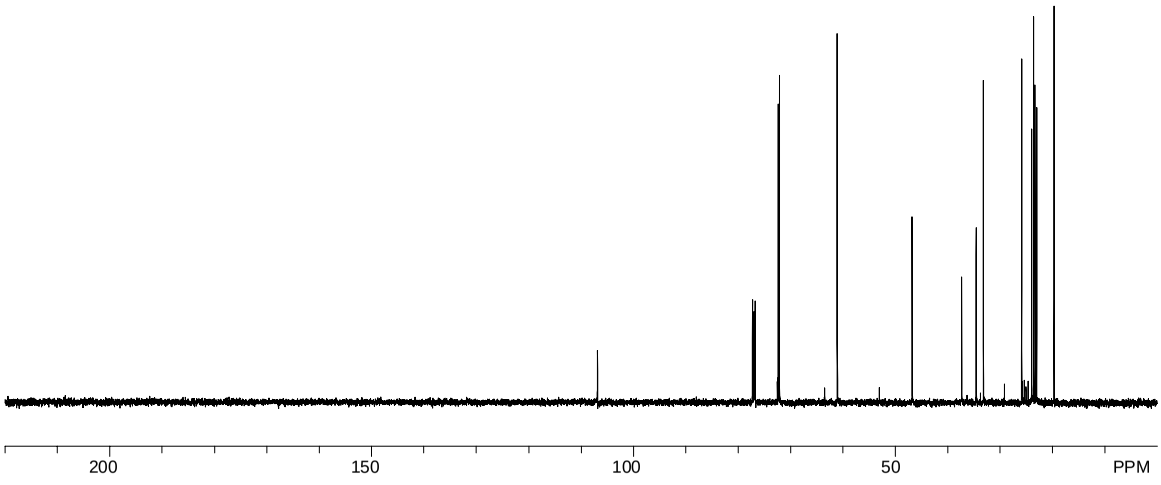


Figure A.3.39 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **134.**

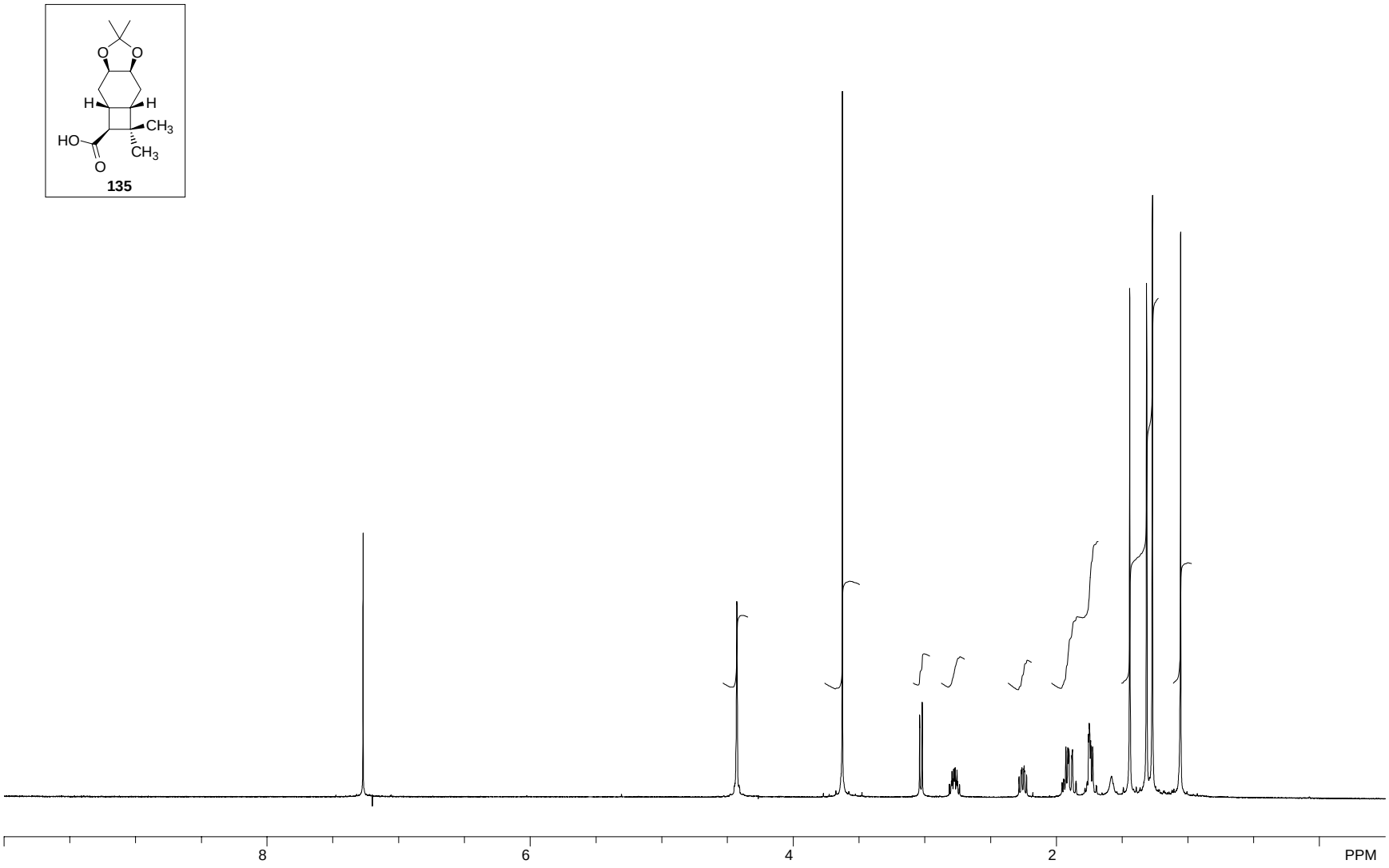


Figure A.3.40 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **135**.

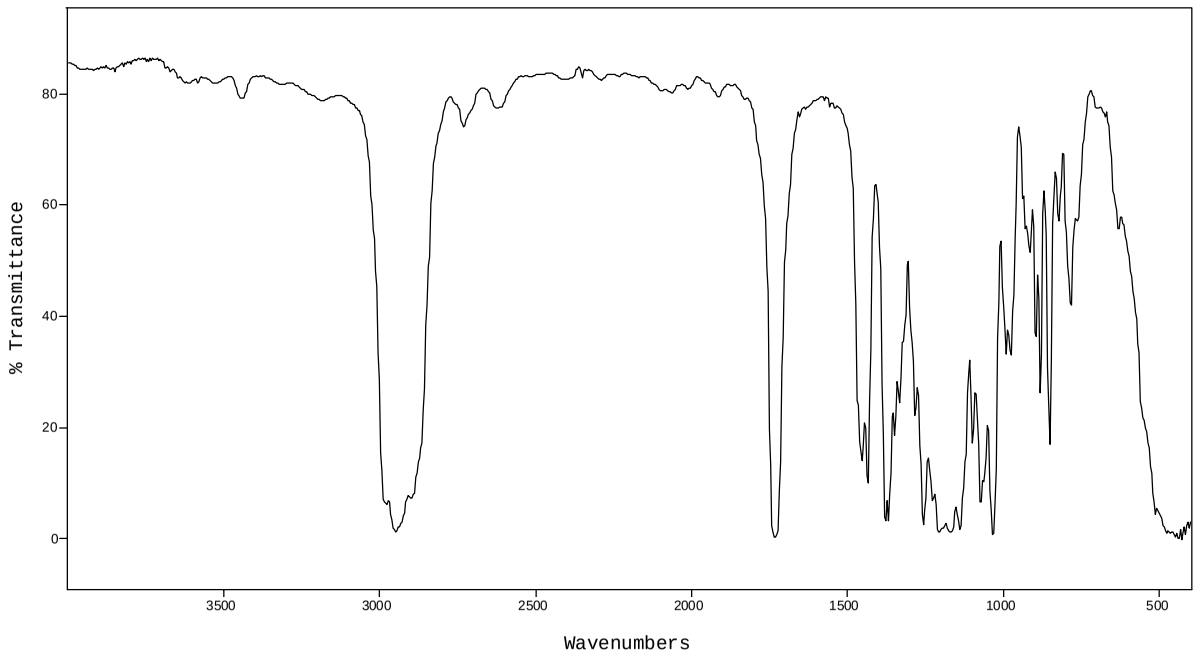


Figure A.3.41 FTIR Spectrum (thin film/NaCl) of Compound **135**.

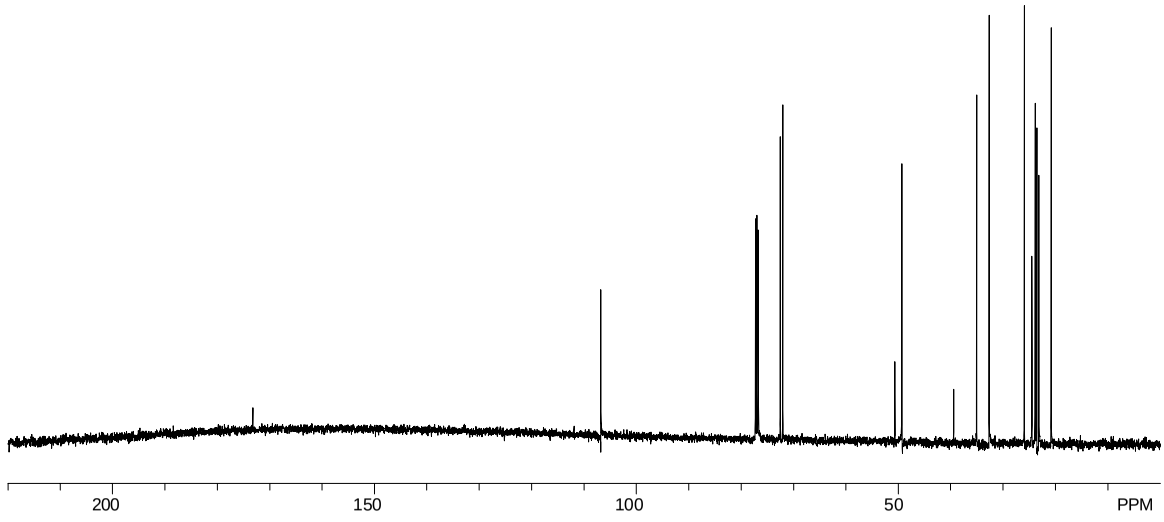


Figure A.3.42 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **135**.

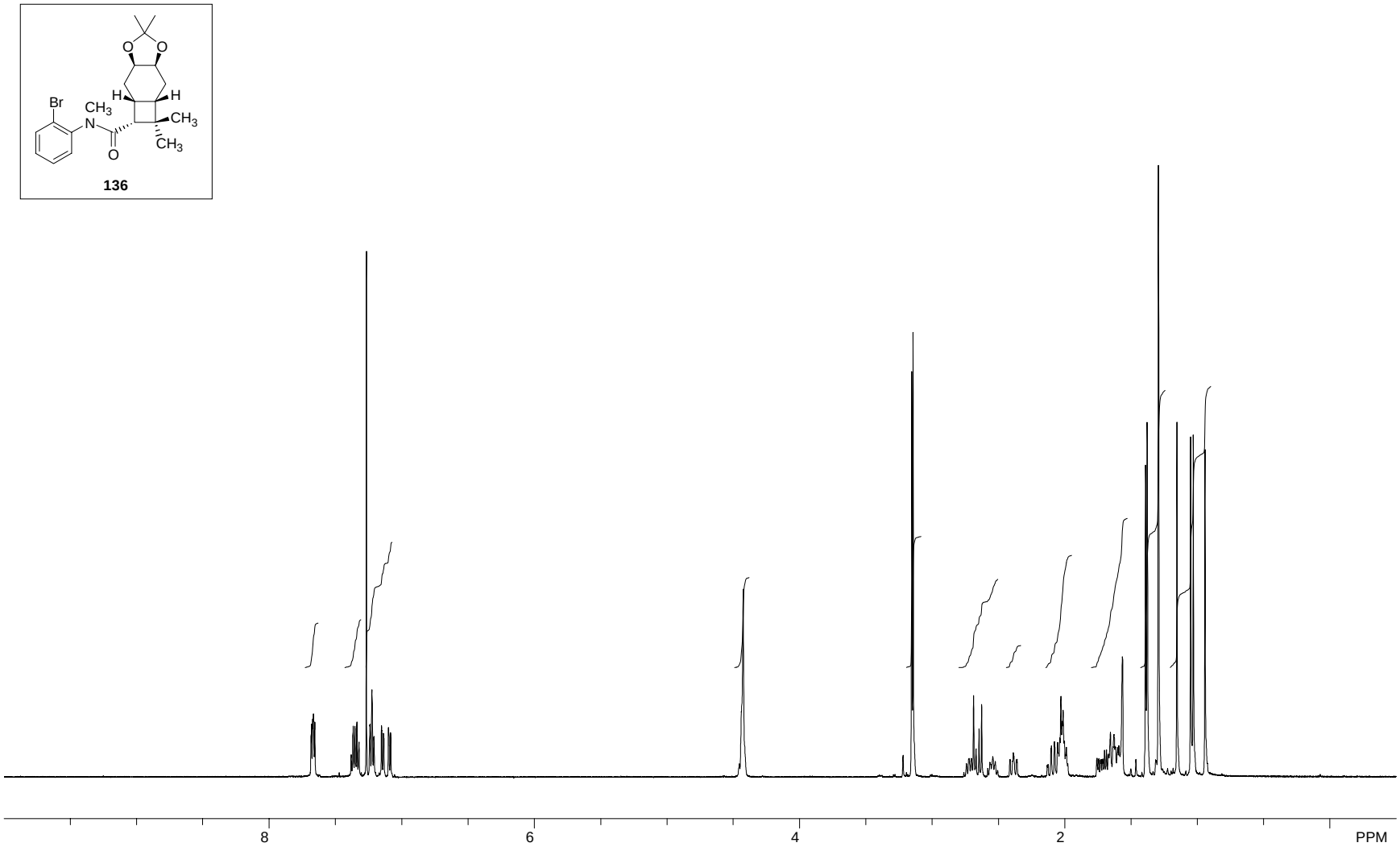


Figure A.3.43 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **136**.

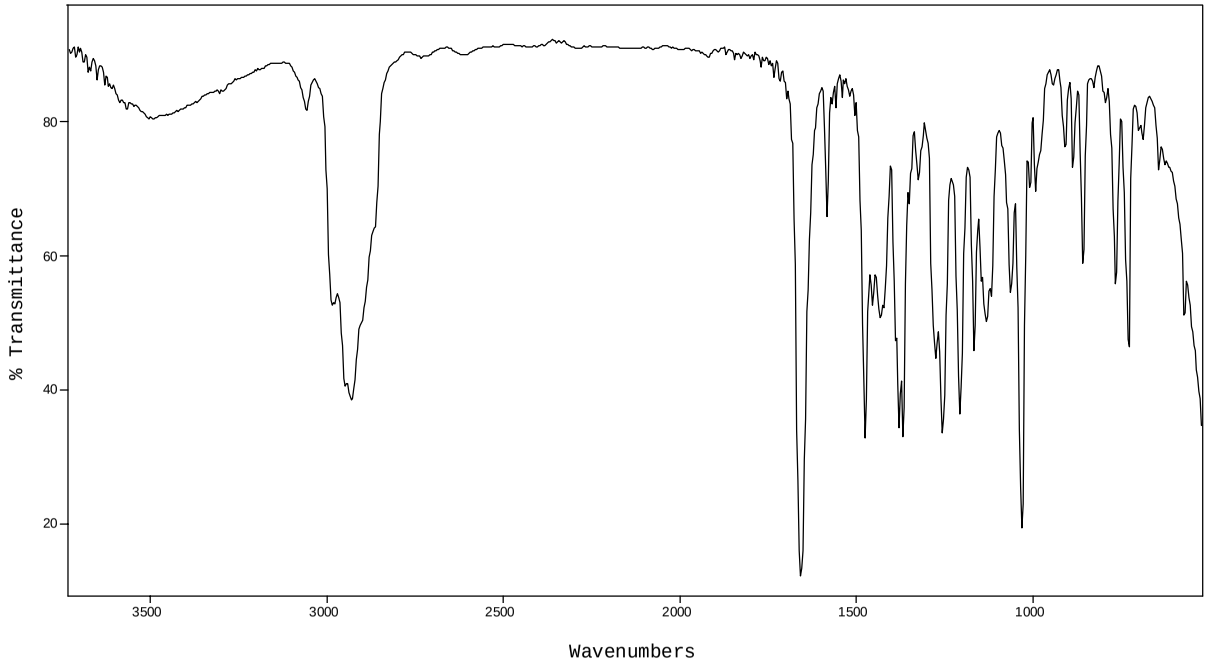


Figure A.3.44 FTIR Spectrum (thin film/NaCl) of Compound **136**.

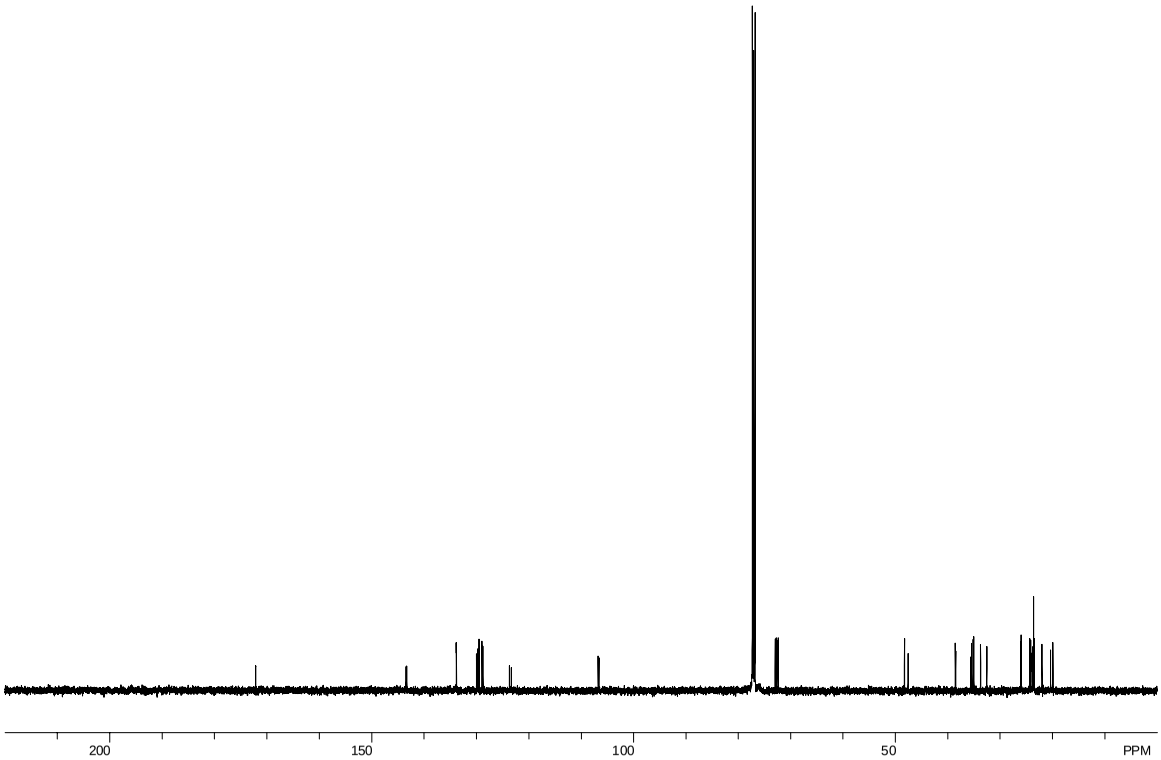


Figure A.3.45 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **136**.

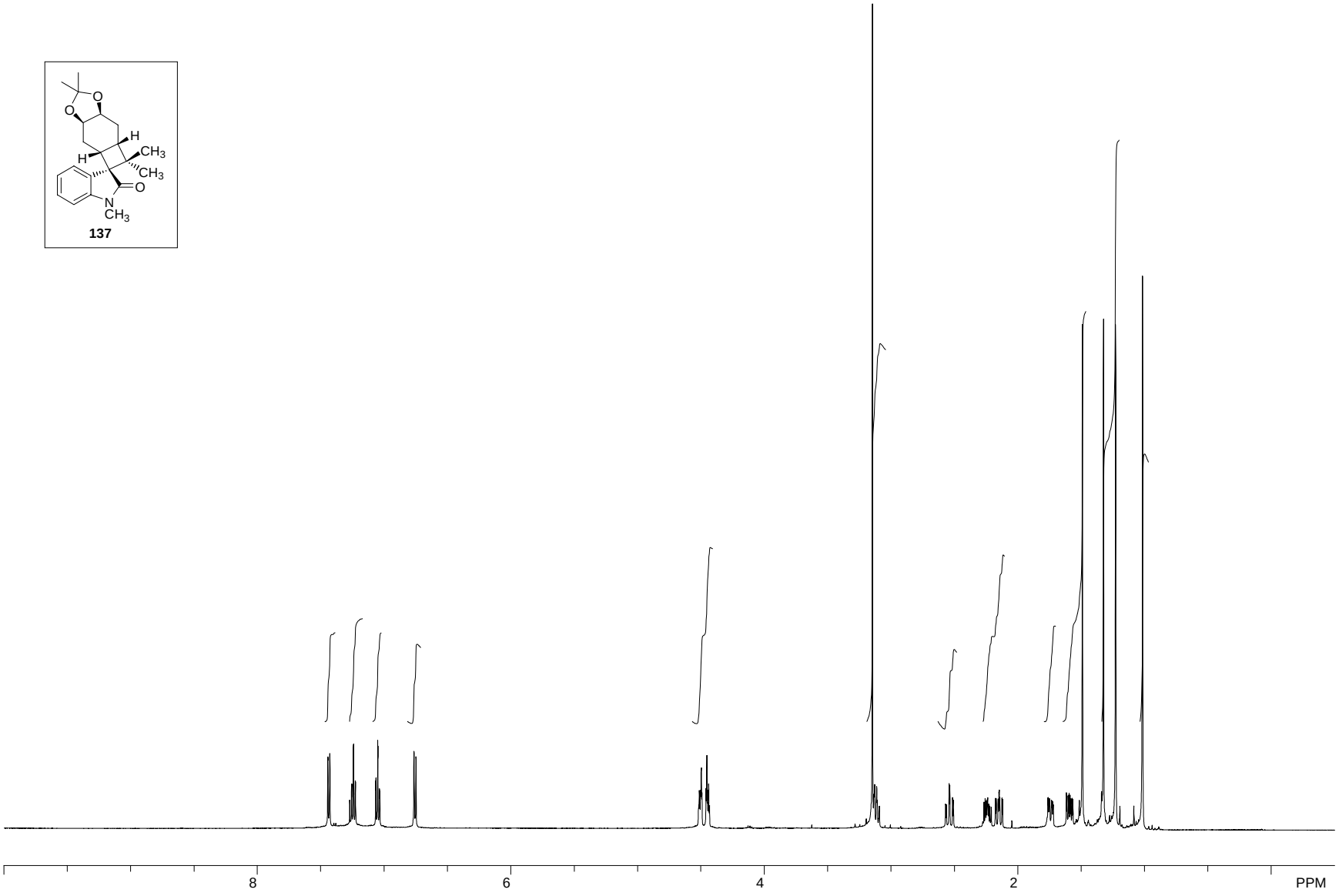


Figure A.3.46 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **137**.

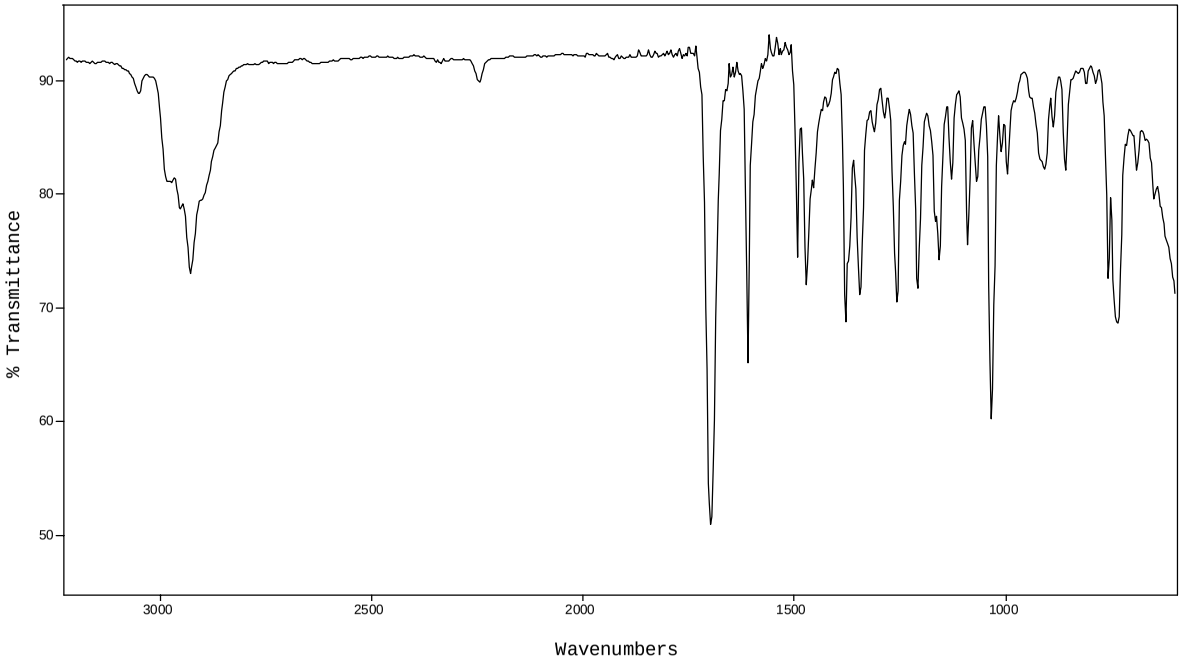


Figure A.3.47 FTIR Spectrum (thin film/NaCl) of Compound **137**.

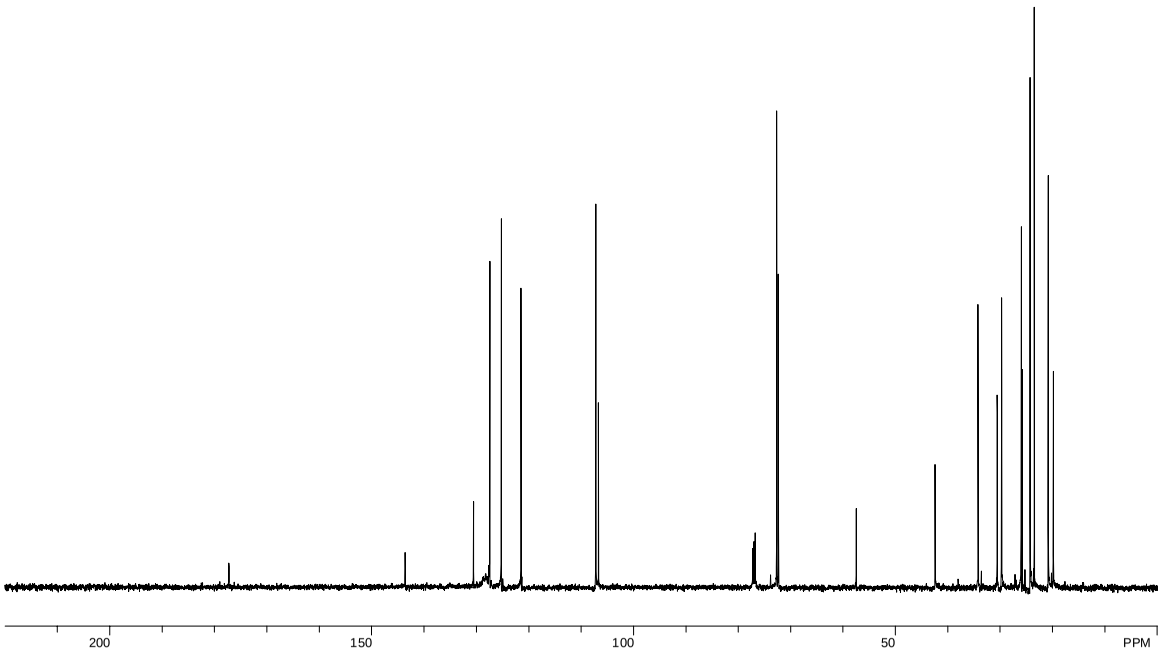


Figure A.3.48 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **137**.

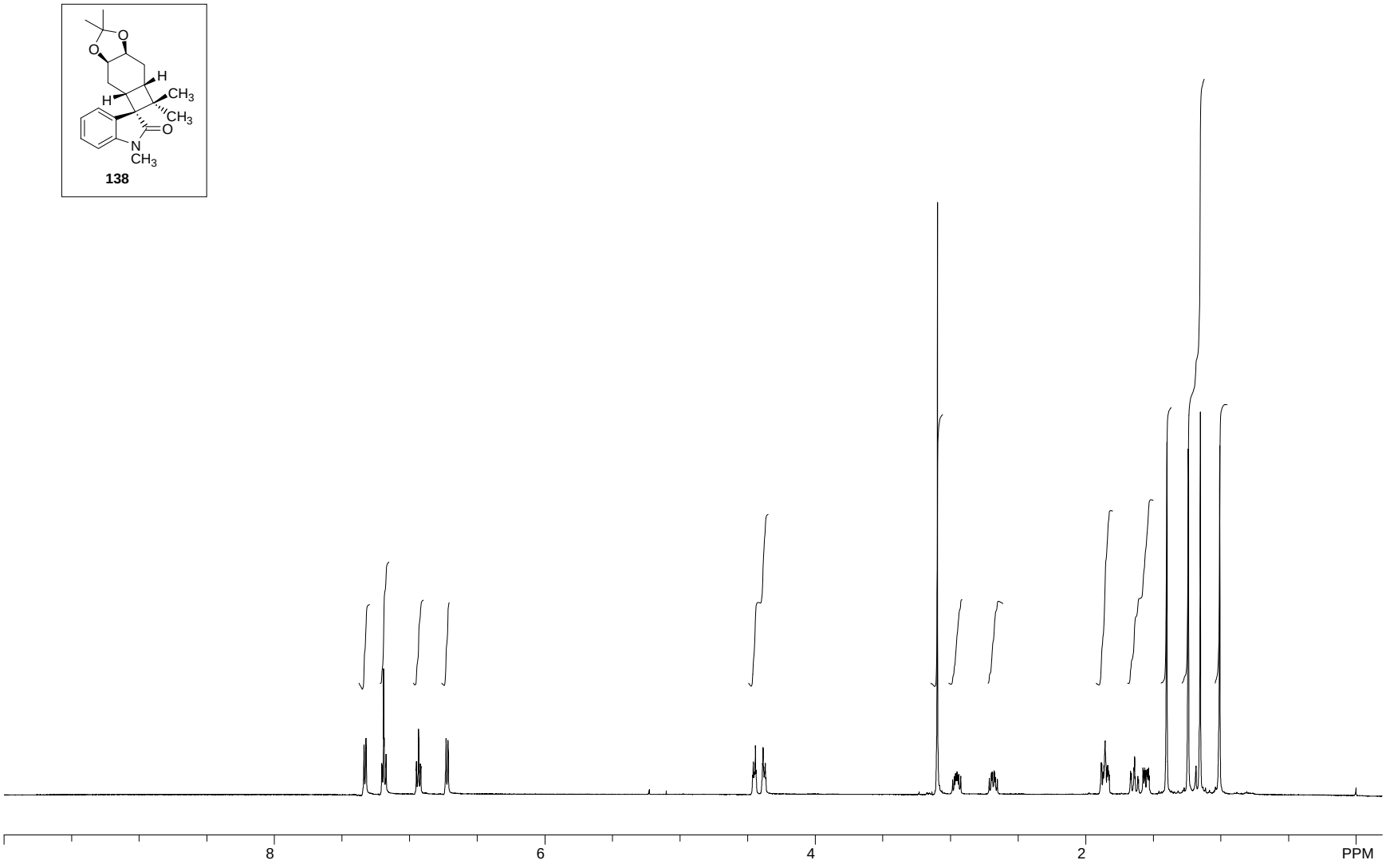


Figure A.3.49 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **138**.

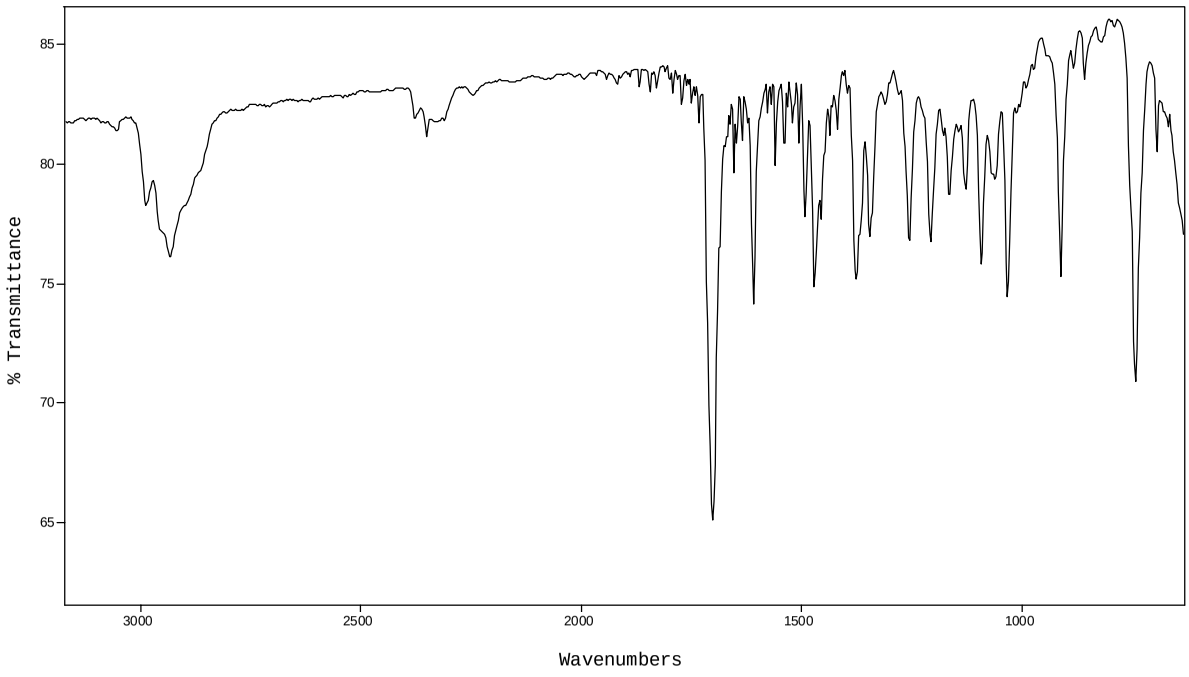


Figure A.3.50 FTIR Spectrum (thin film/NaCl) of Compound **138**.

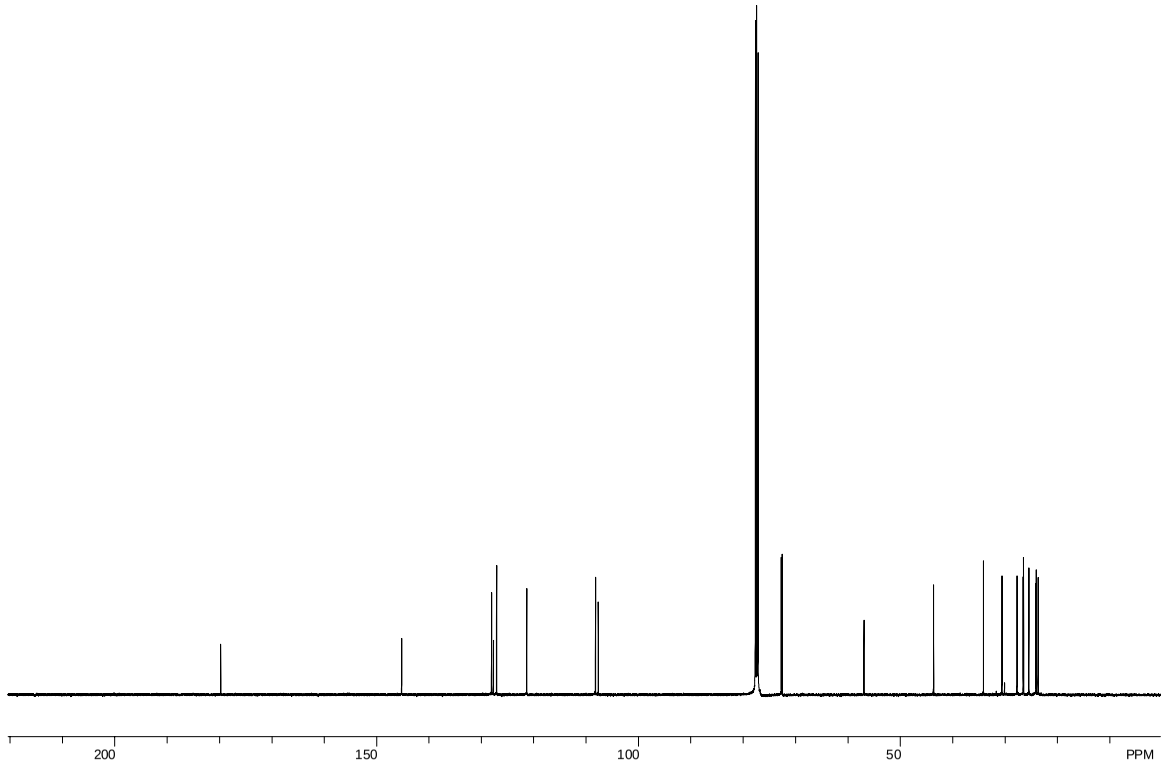


Figure A.3.51 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **138**.

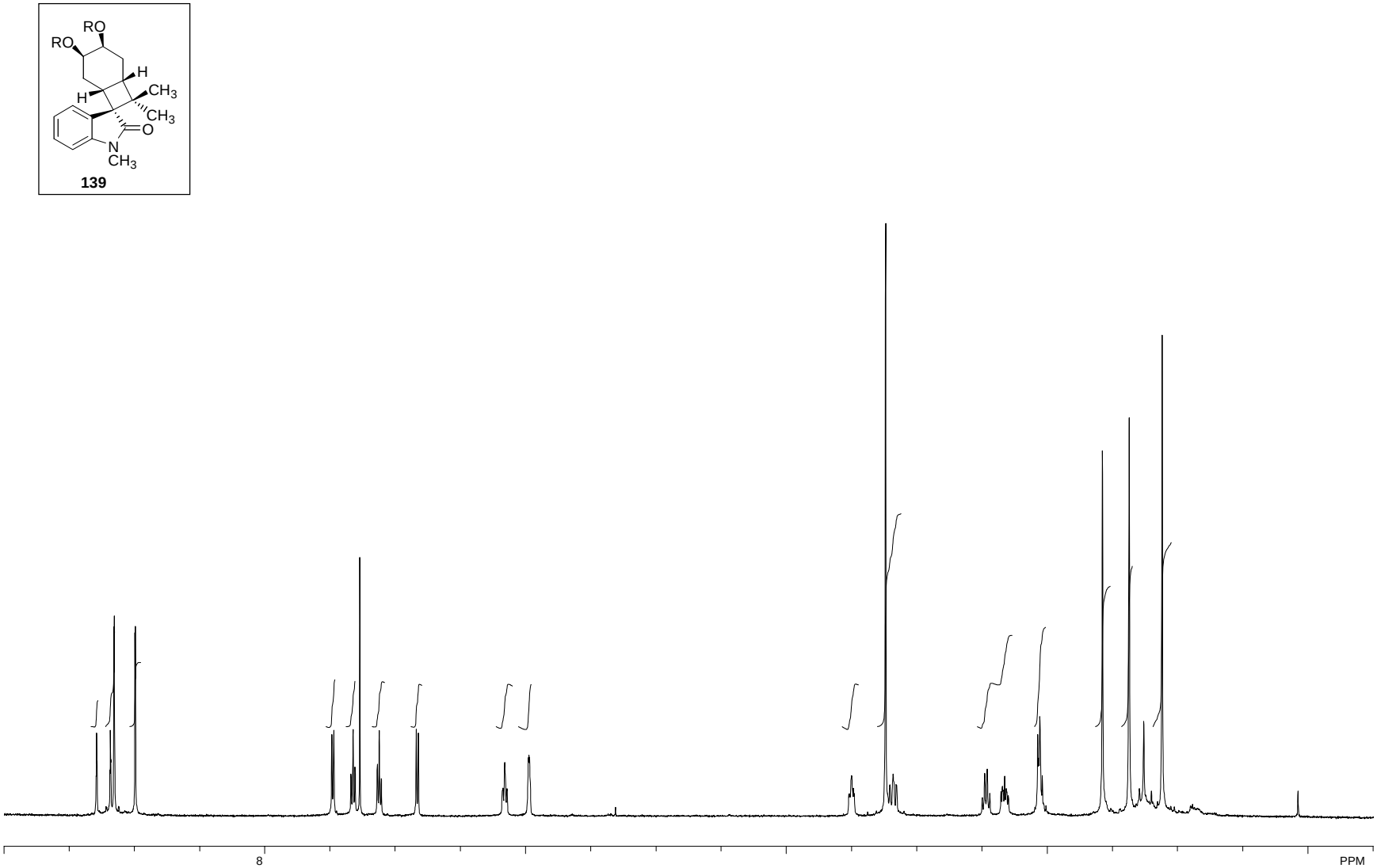


Figure A.3.52 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **139**.

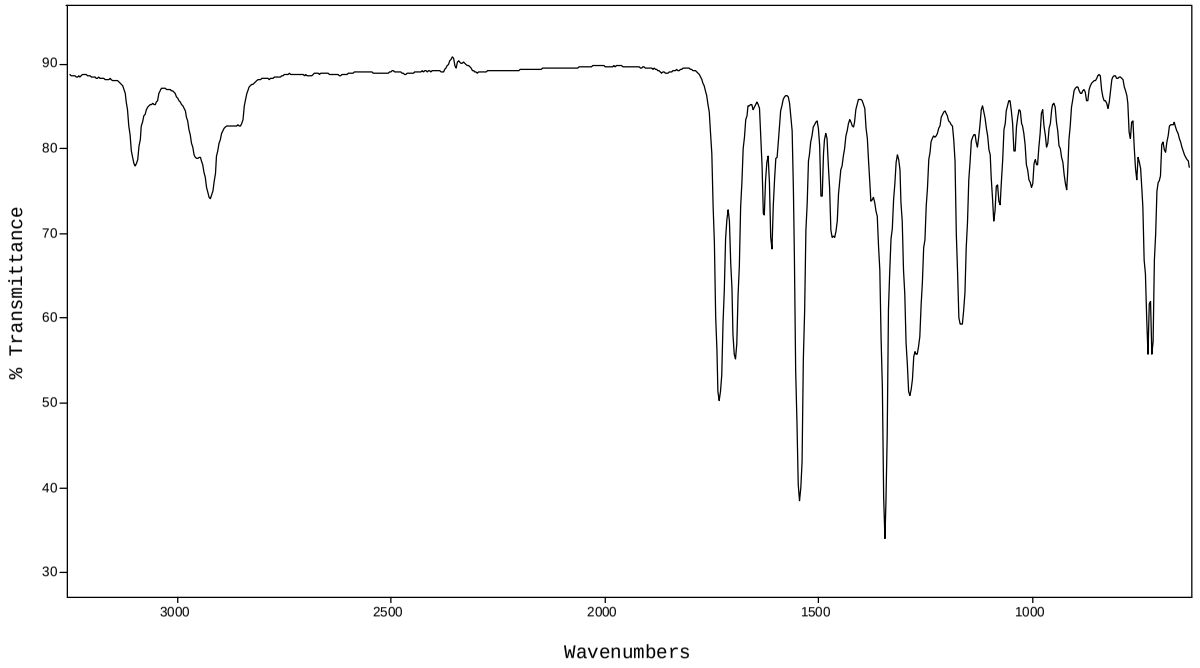


Figure A.3.53 FTIR Spectrum (thin film/NaCl) of Compound **139**.

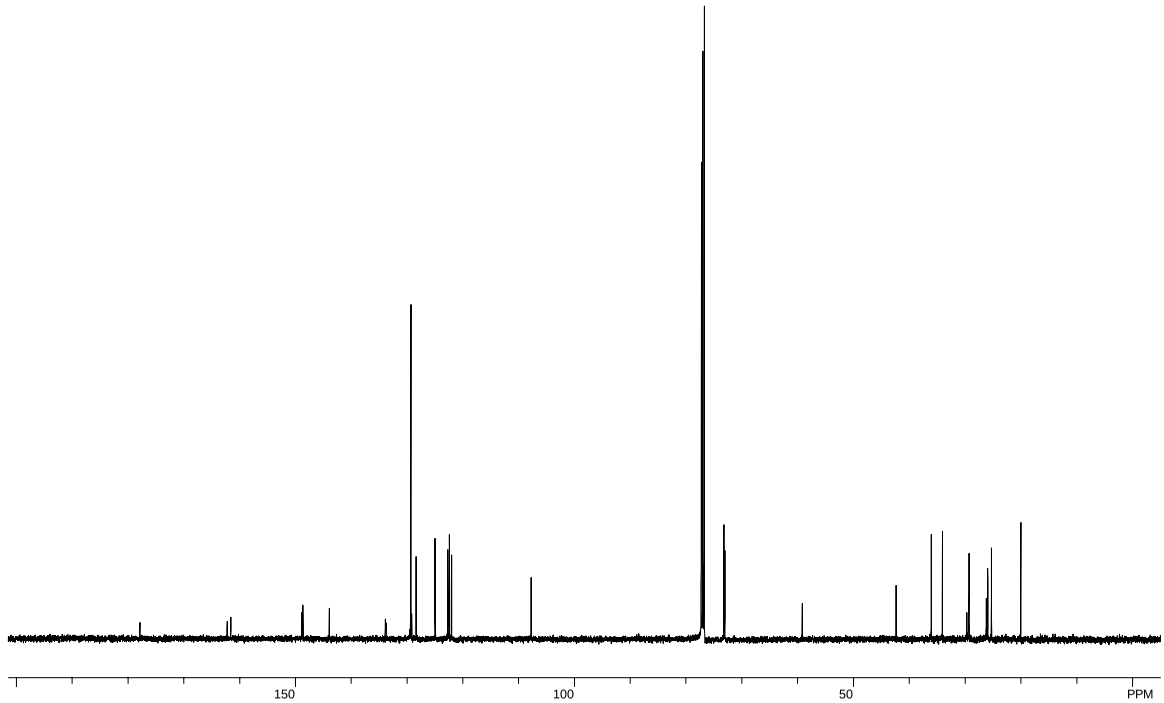


Figure A.3.54 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **139**.

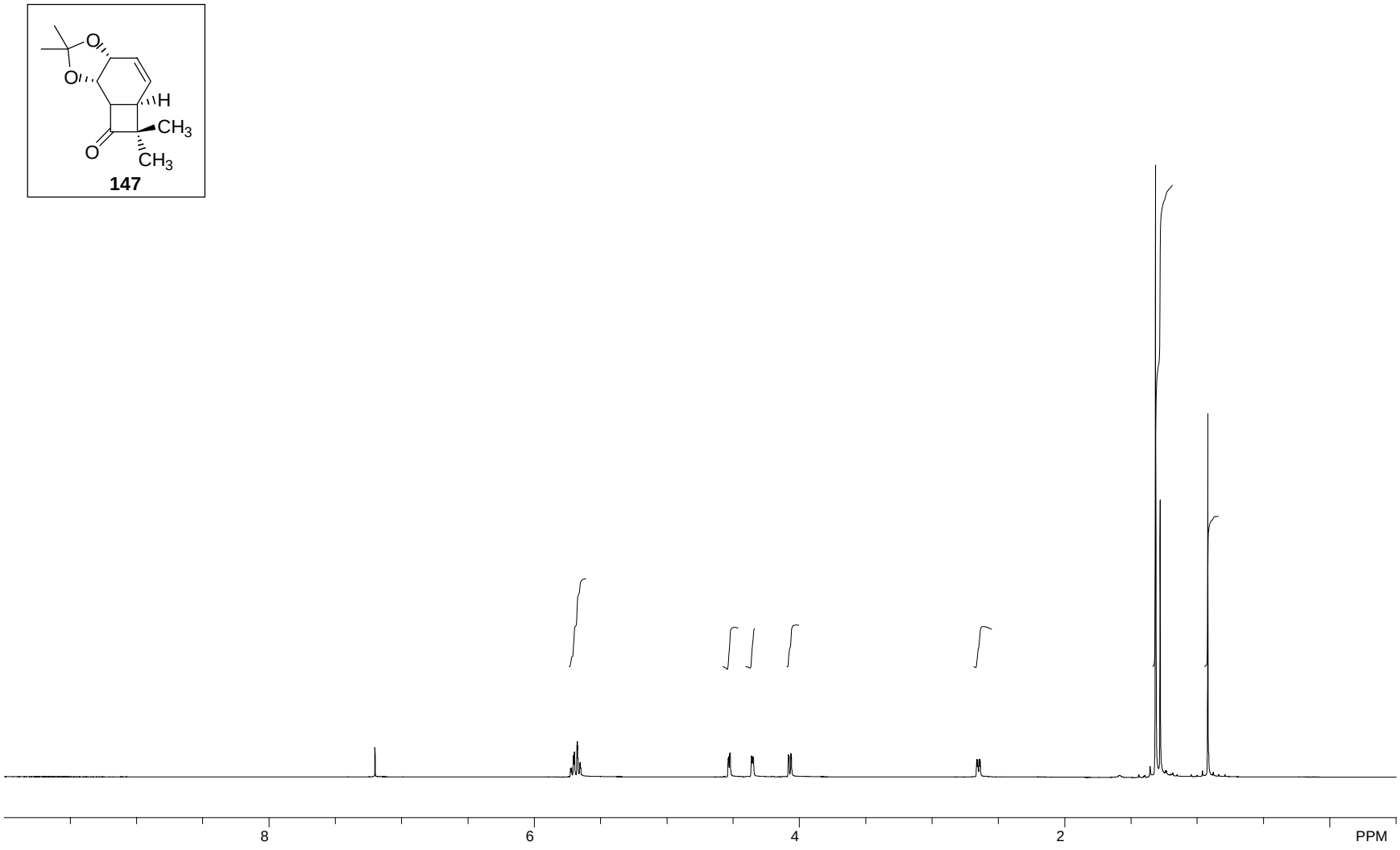


Figure A.3.55 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **147**.

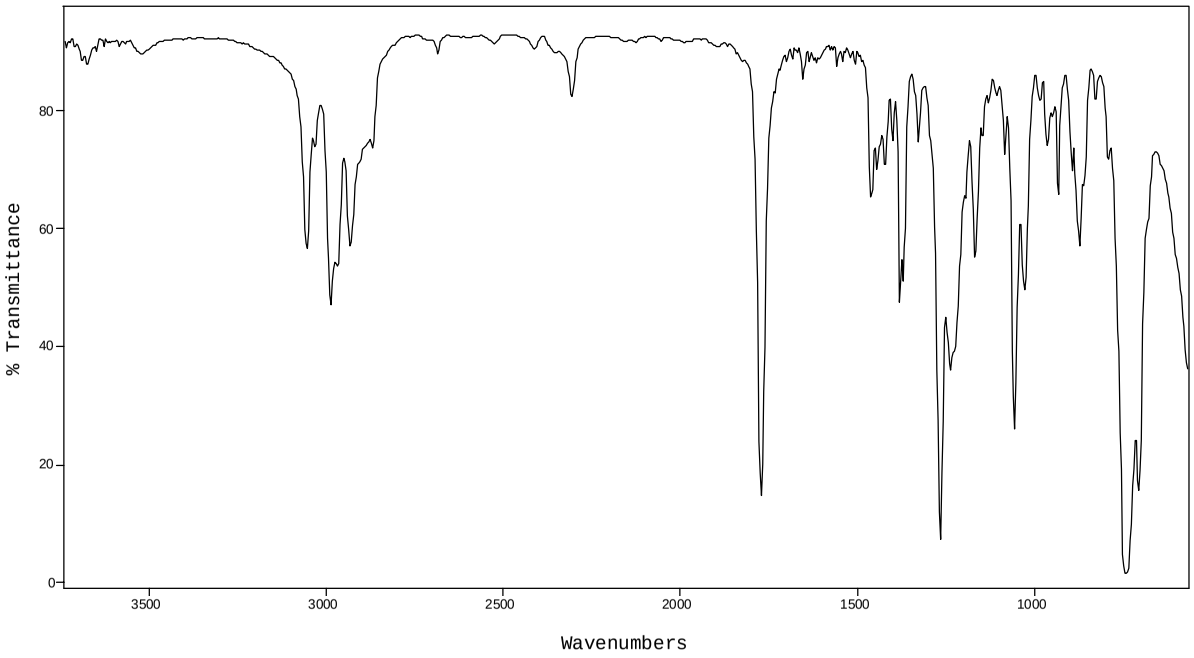


Figure A.3.56 FTIR Spectrum (thin film/NaCl) of Compound **147**.

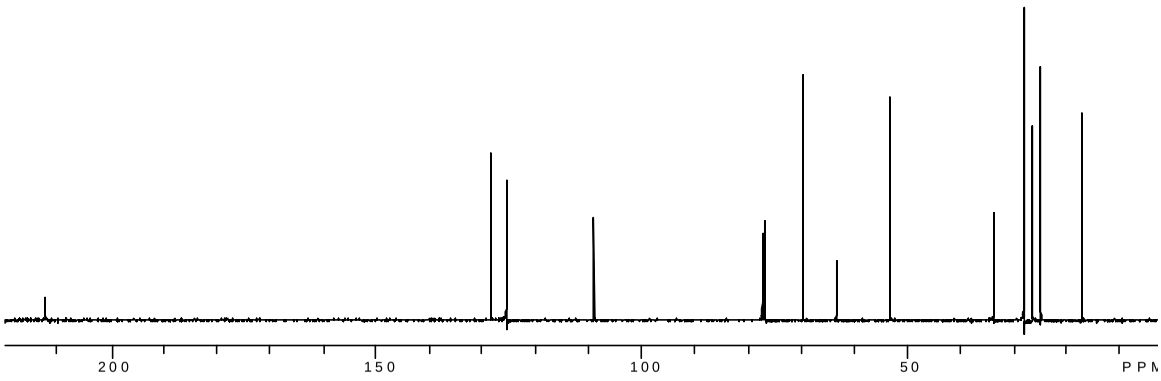


Figure A.3.57 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **147**.

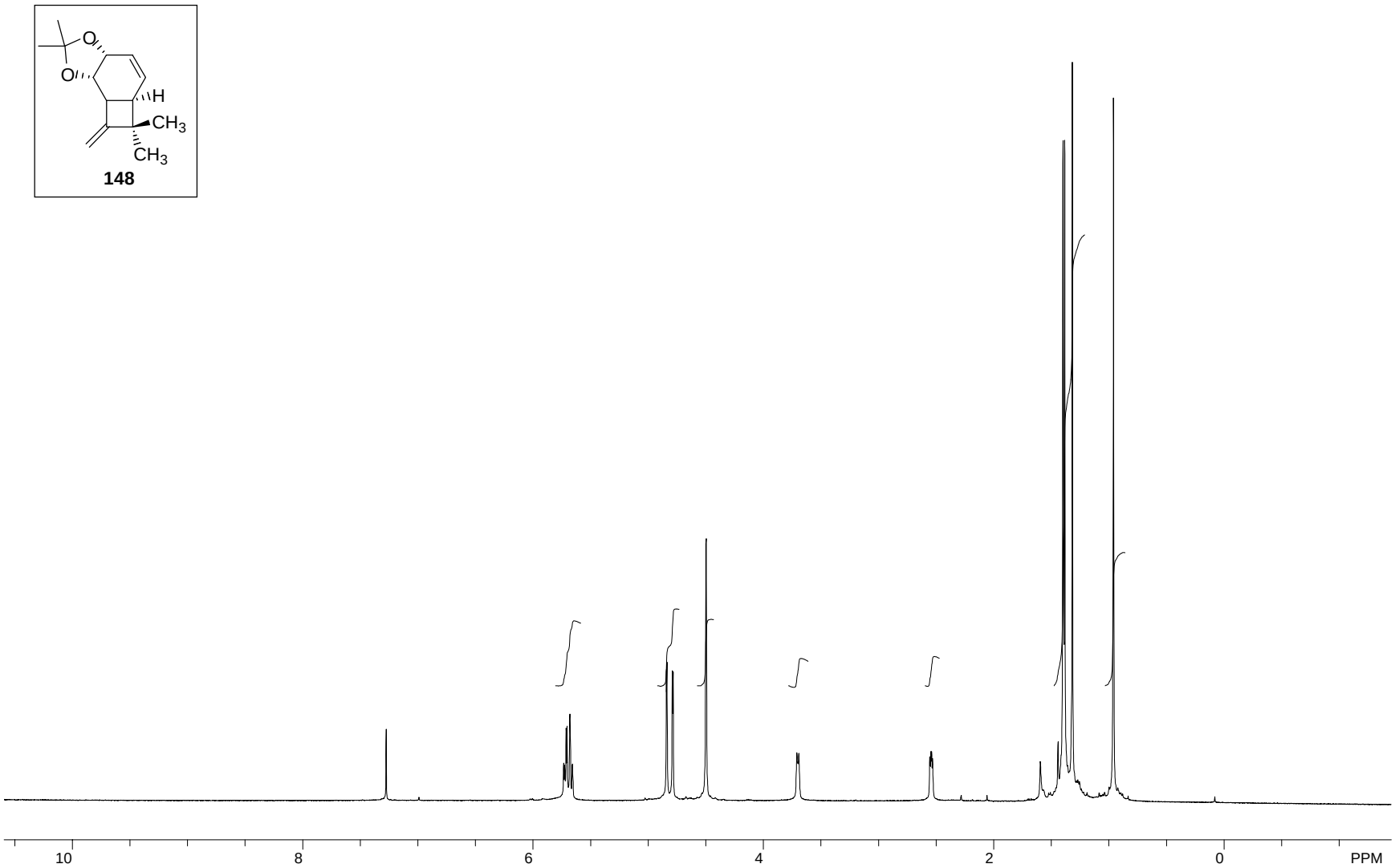


Figure A.3.58 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **148**.

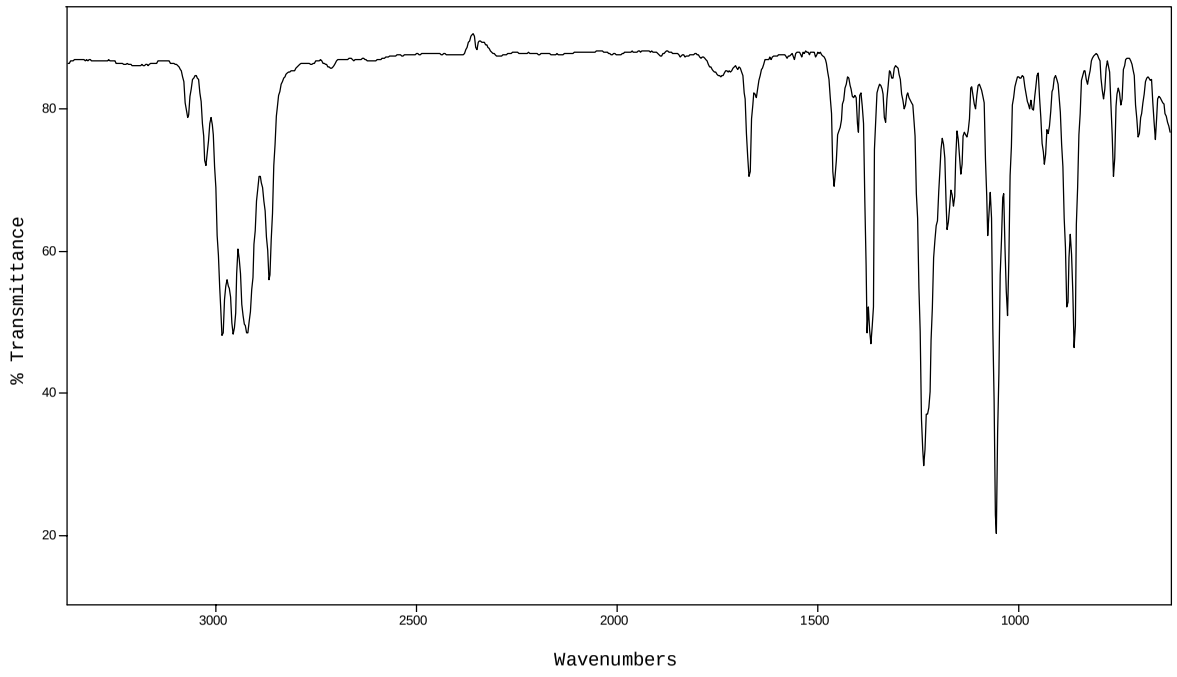


Figure A.3.59 FTIR Spectrum (thin film/NaCl) of Compound **148**.

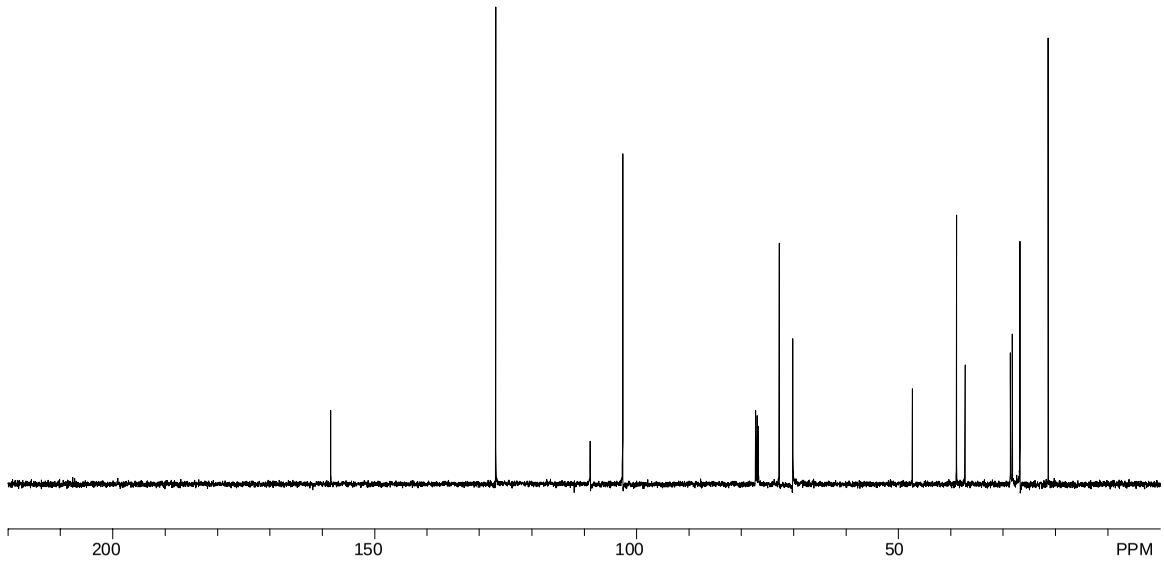


Figure A.3.60 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **148**.

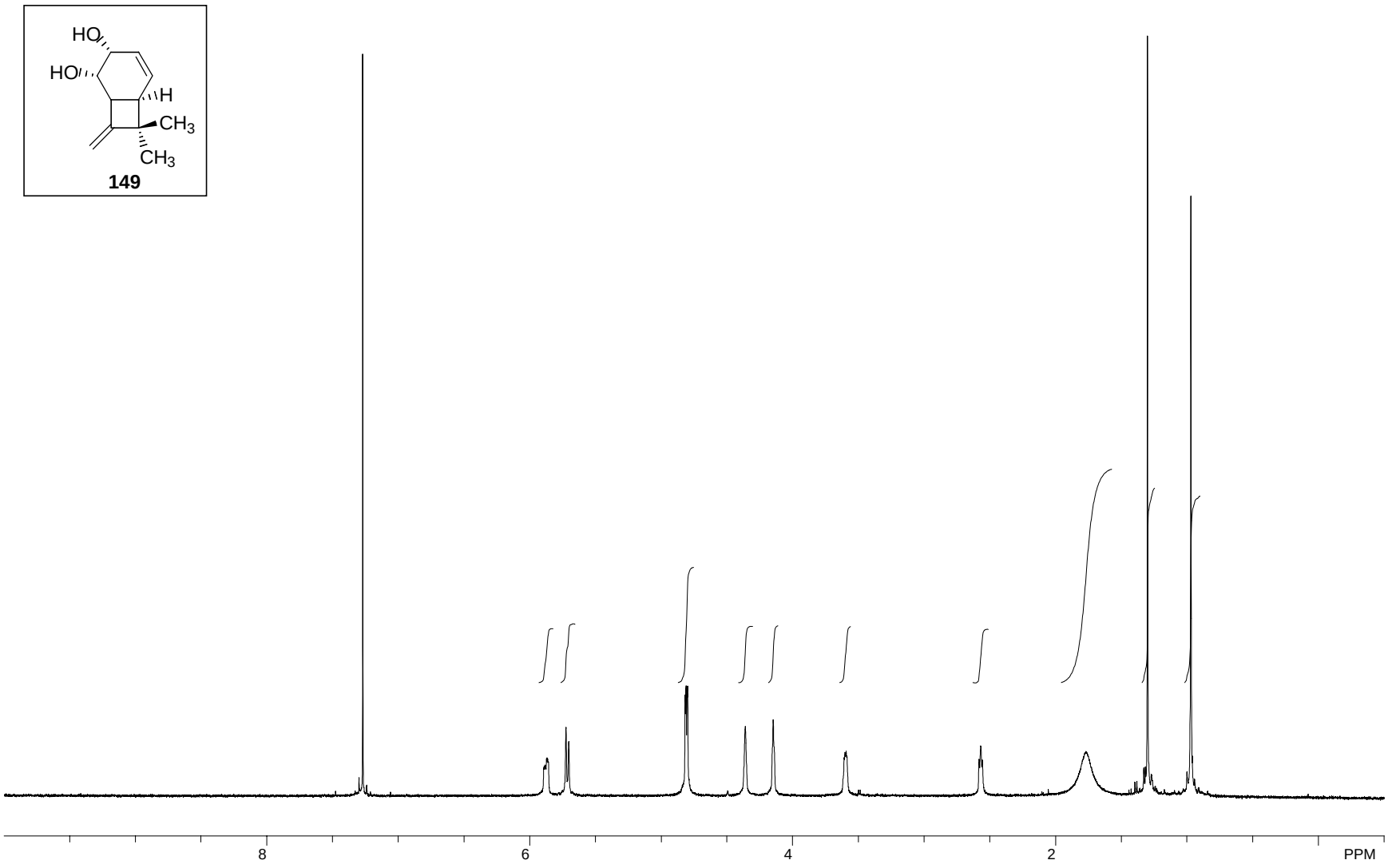


Figure A.3.61 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **149**.

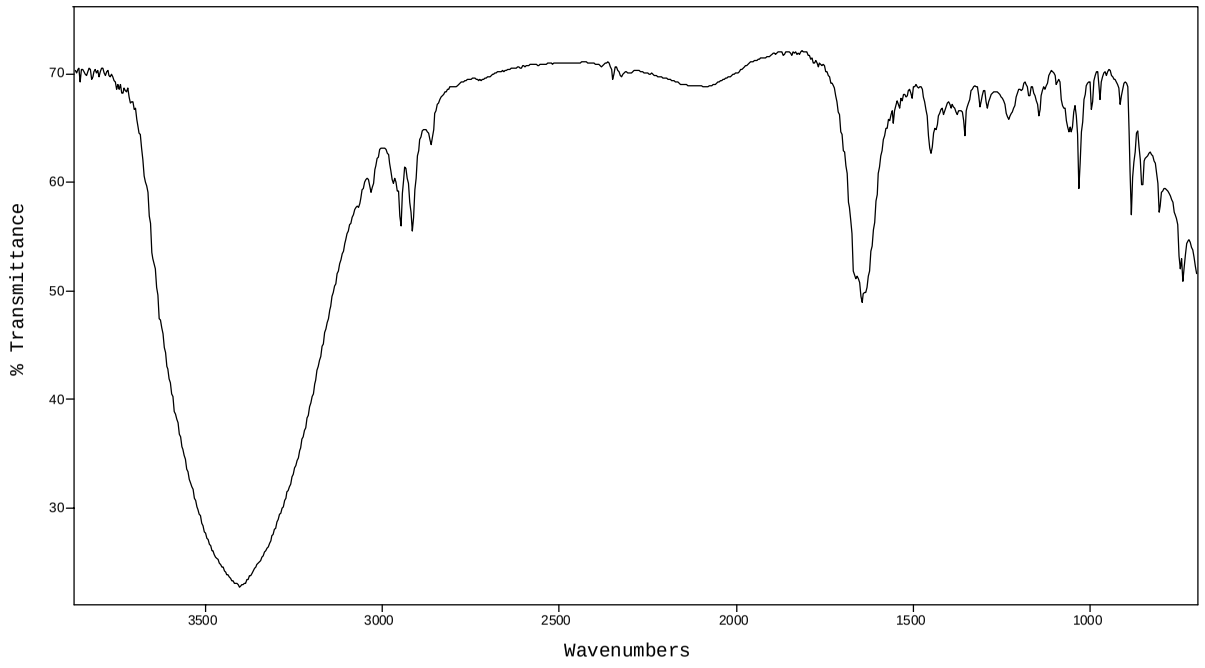


Figure A.3.62 FTIR Spectrum (thin film/NaCl) of Compound **149**.

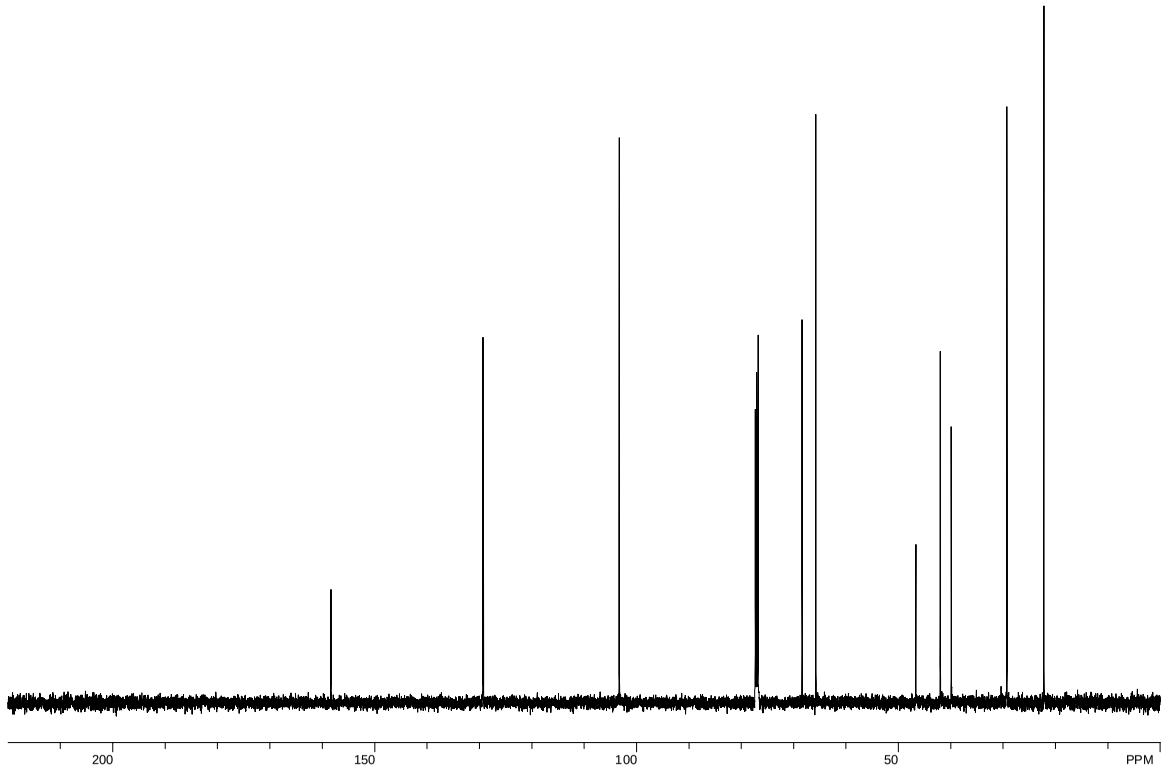


Figure A.3.63 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **149**.

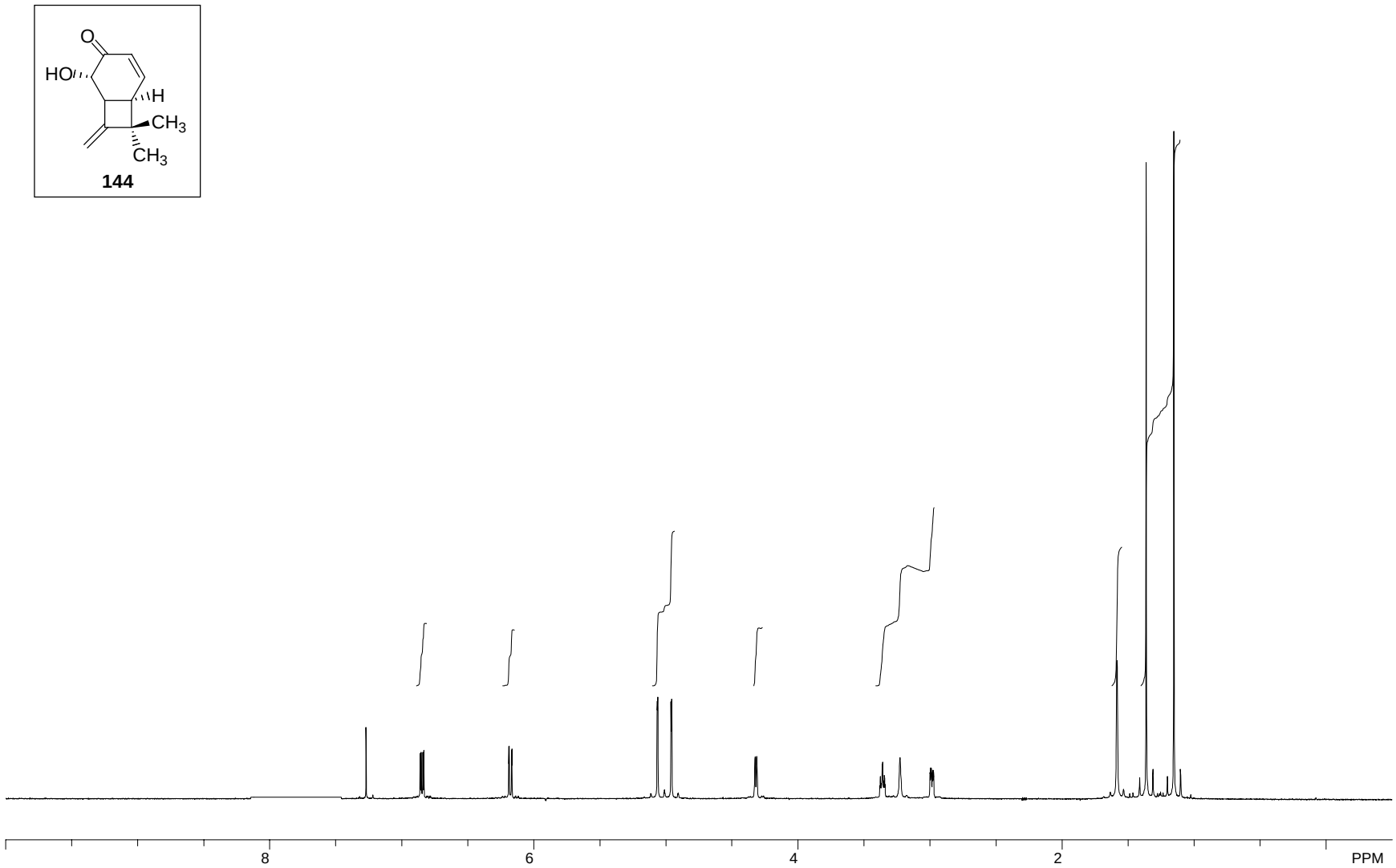


Figure A.3.64 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **144**.

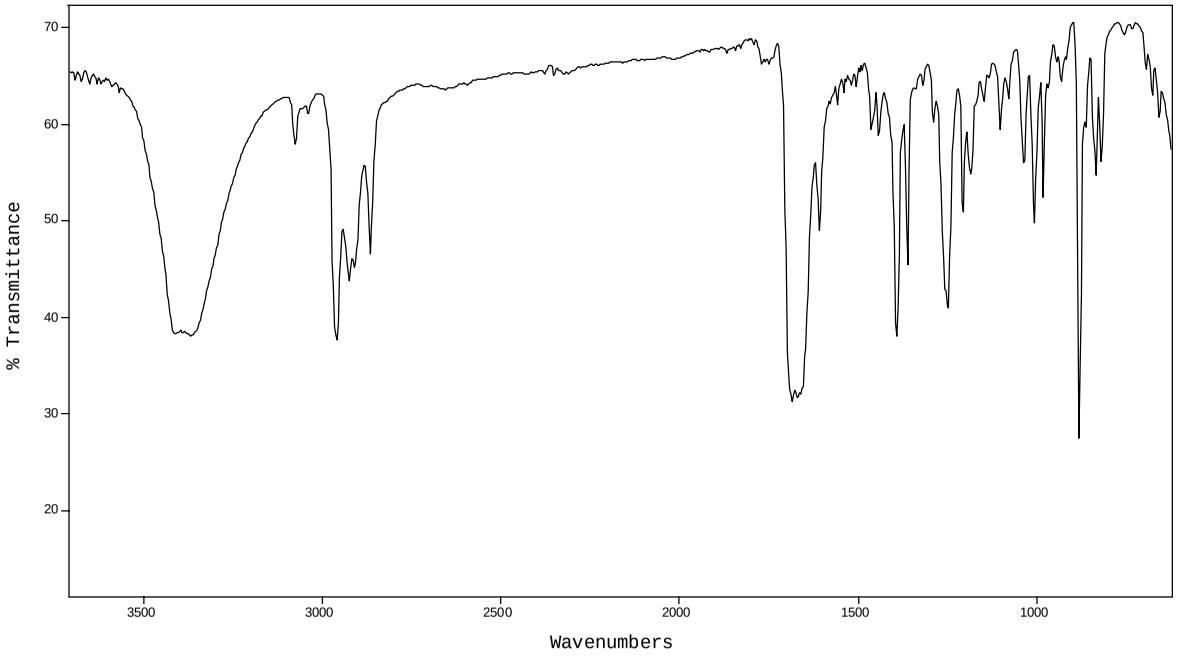


Figure A.3.65 FTIR Spectrum (thin film/NaCl) of Compound **144**.

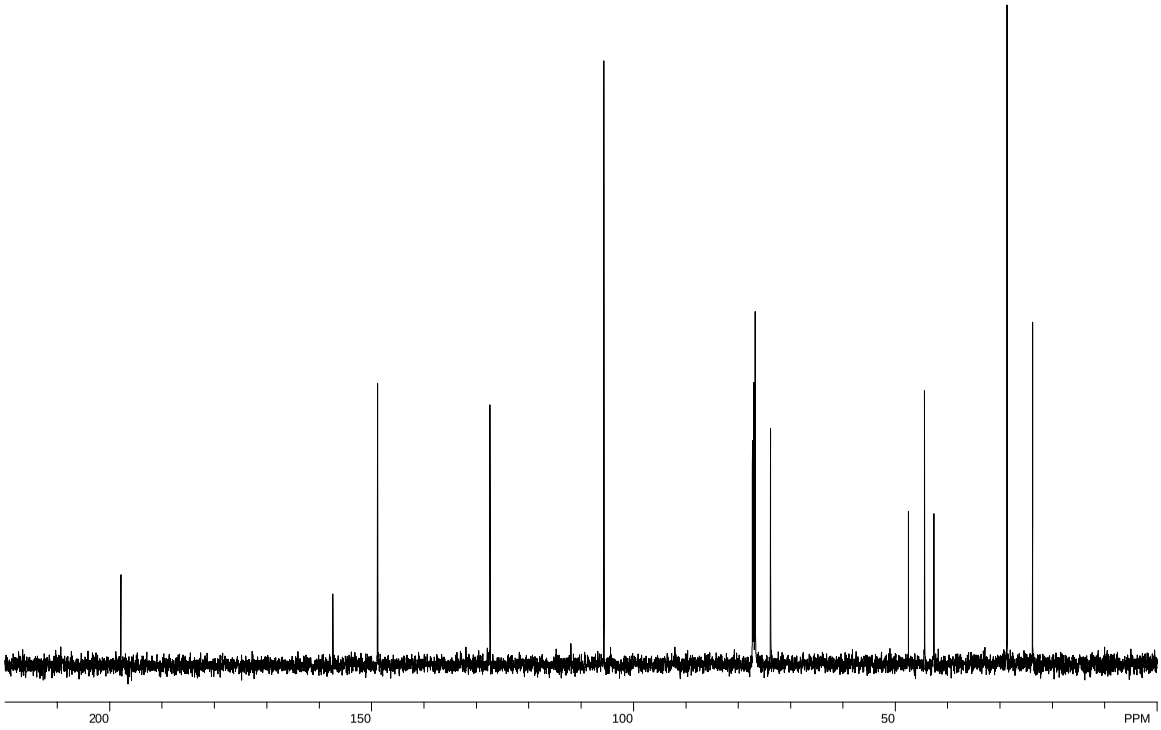


Figure A.3.66 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **144.**

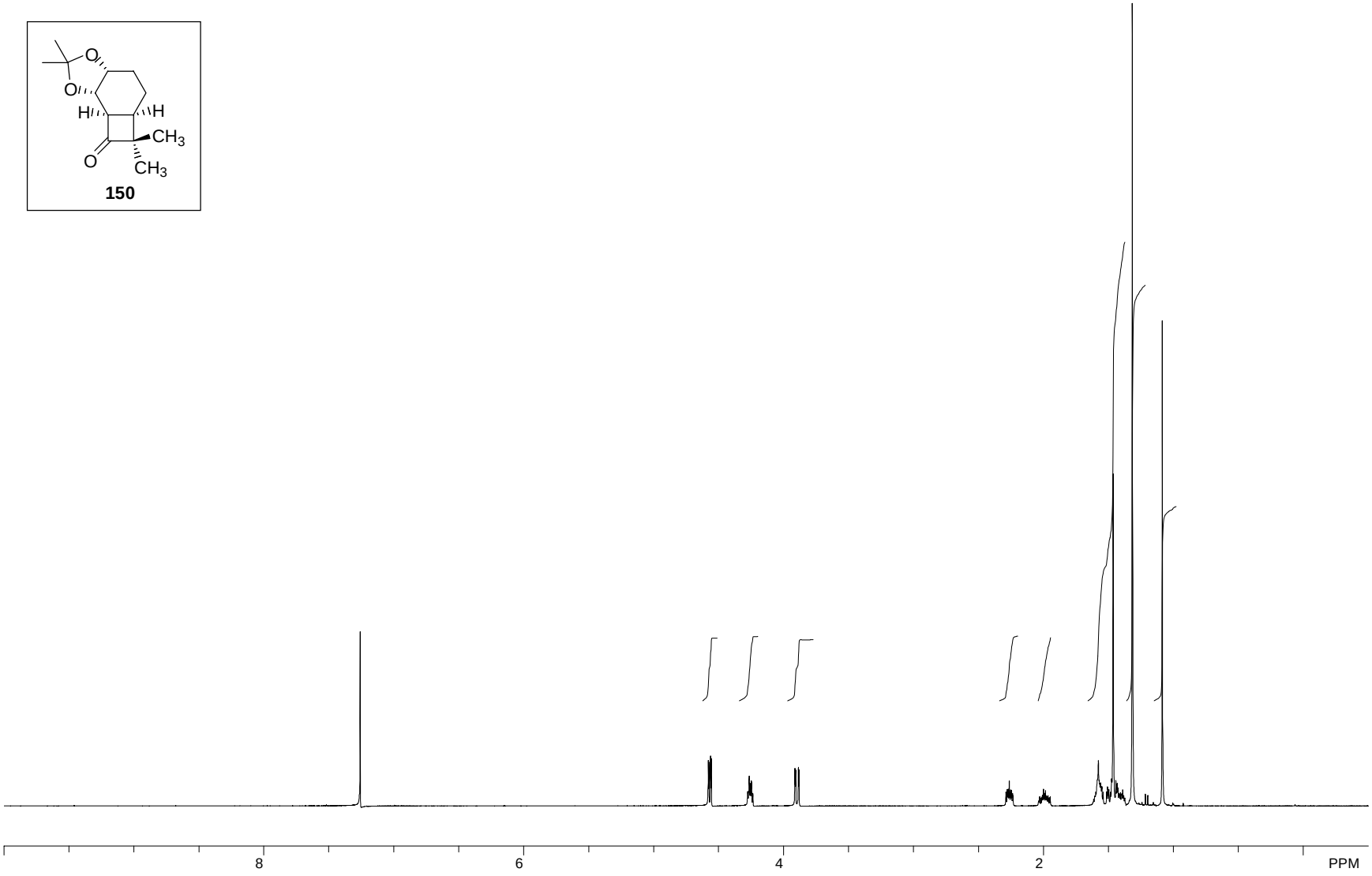


Figure A.3.67 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **150**.

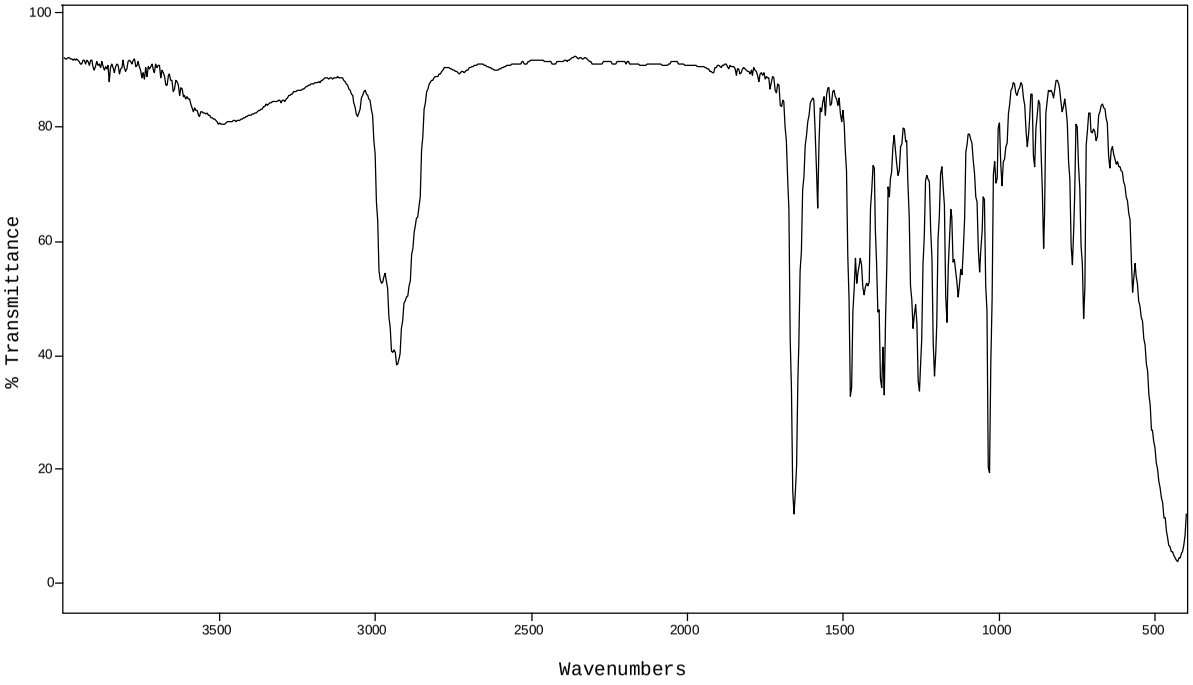


Figure A.3.68 FTIR Spectrum (thin film/NaCl) of Compound **150**.

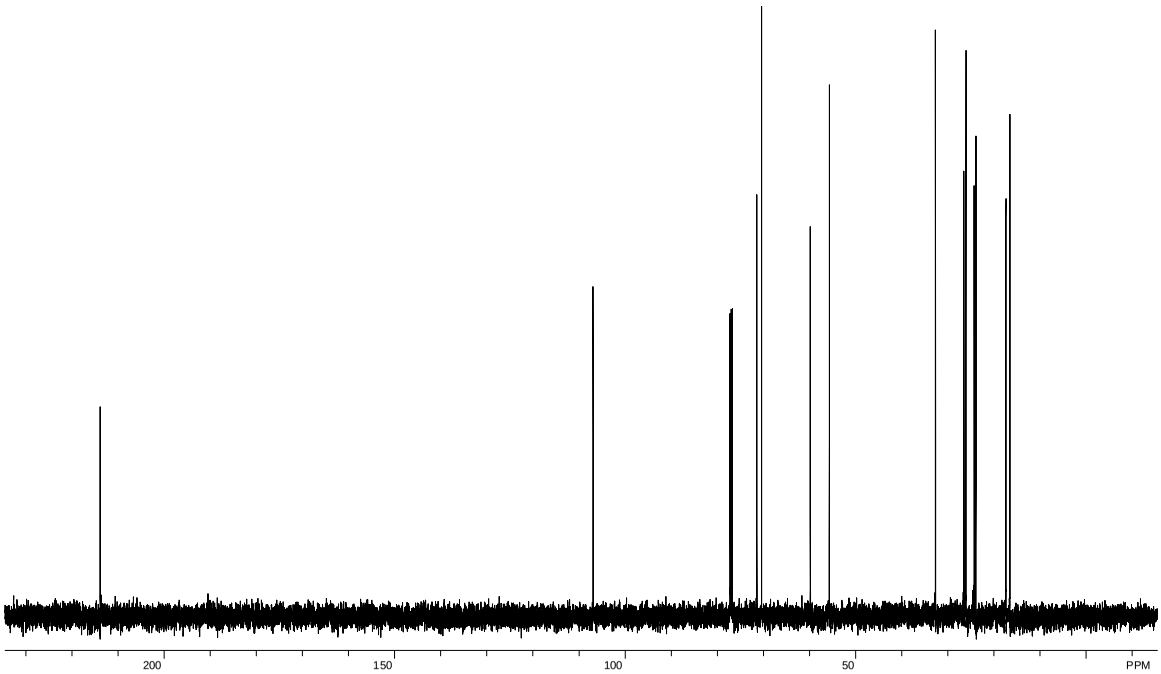


Figure A.3.69 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **150**.

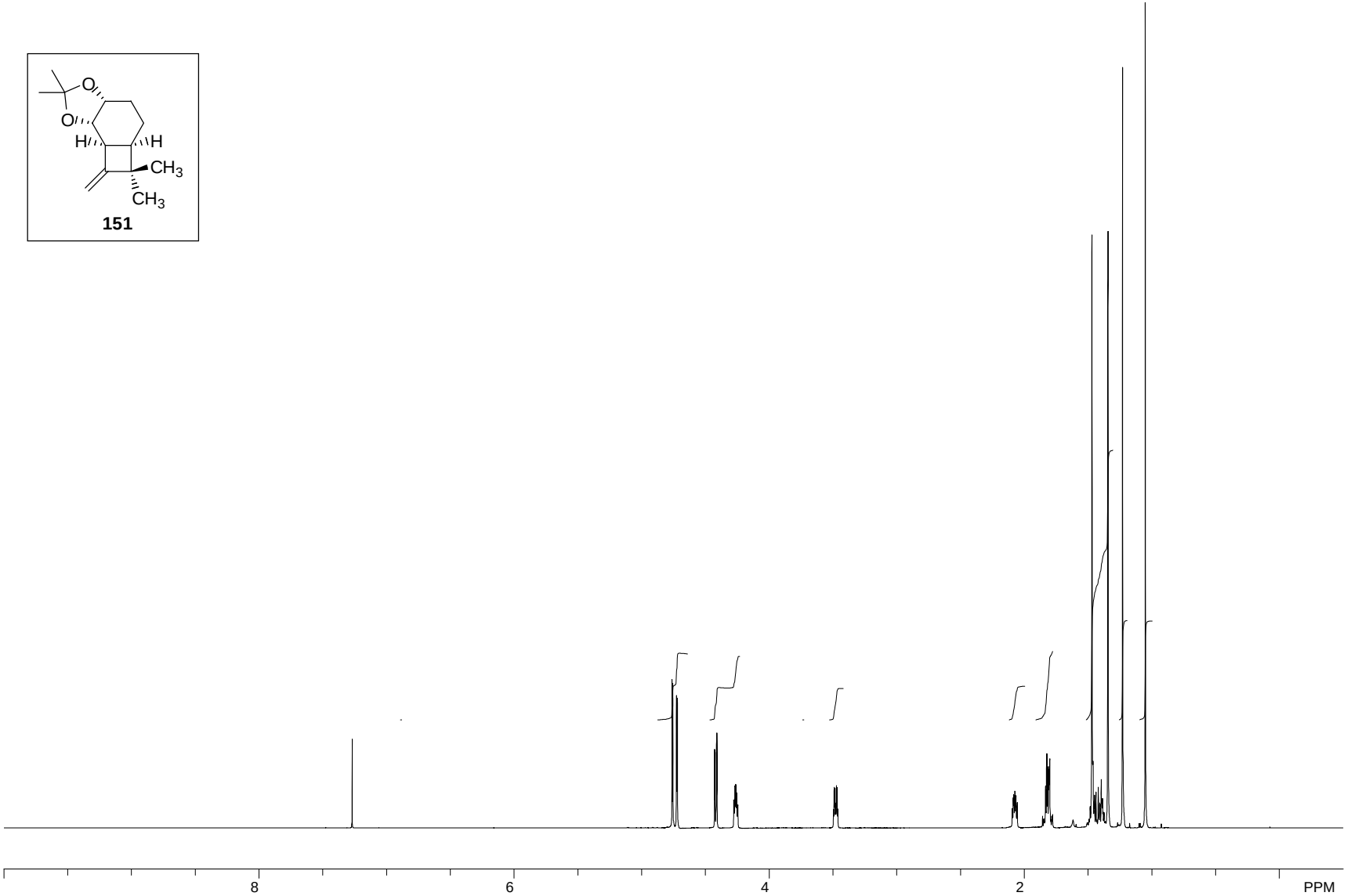


Figure A.3.70 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **151**.

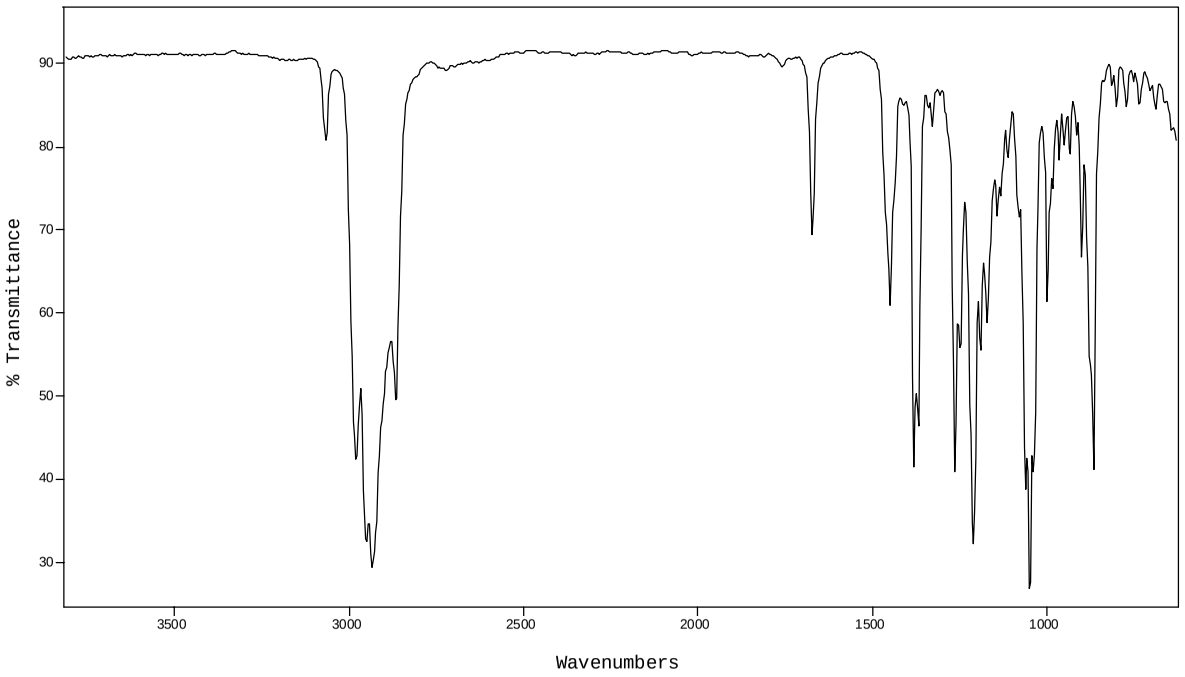


Figure A.3.71 FTIR Spectrum (thin film/NaCl) of Compound **151**.

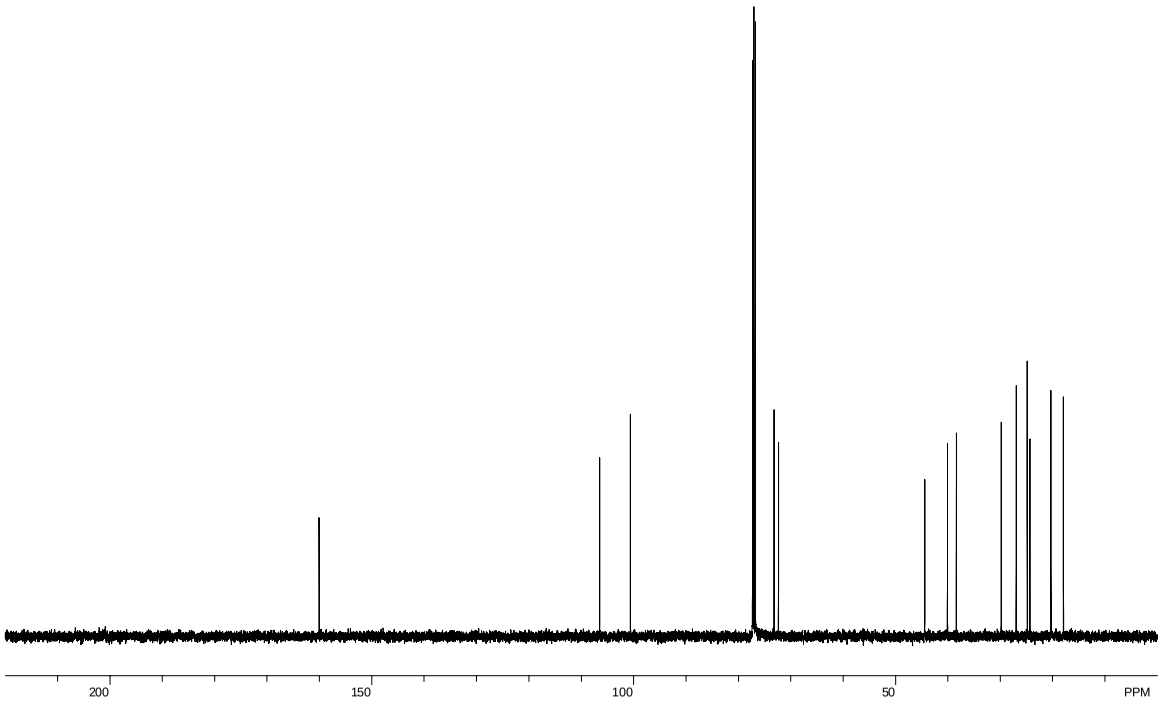


Figure A.3.72 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **151.**

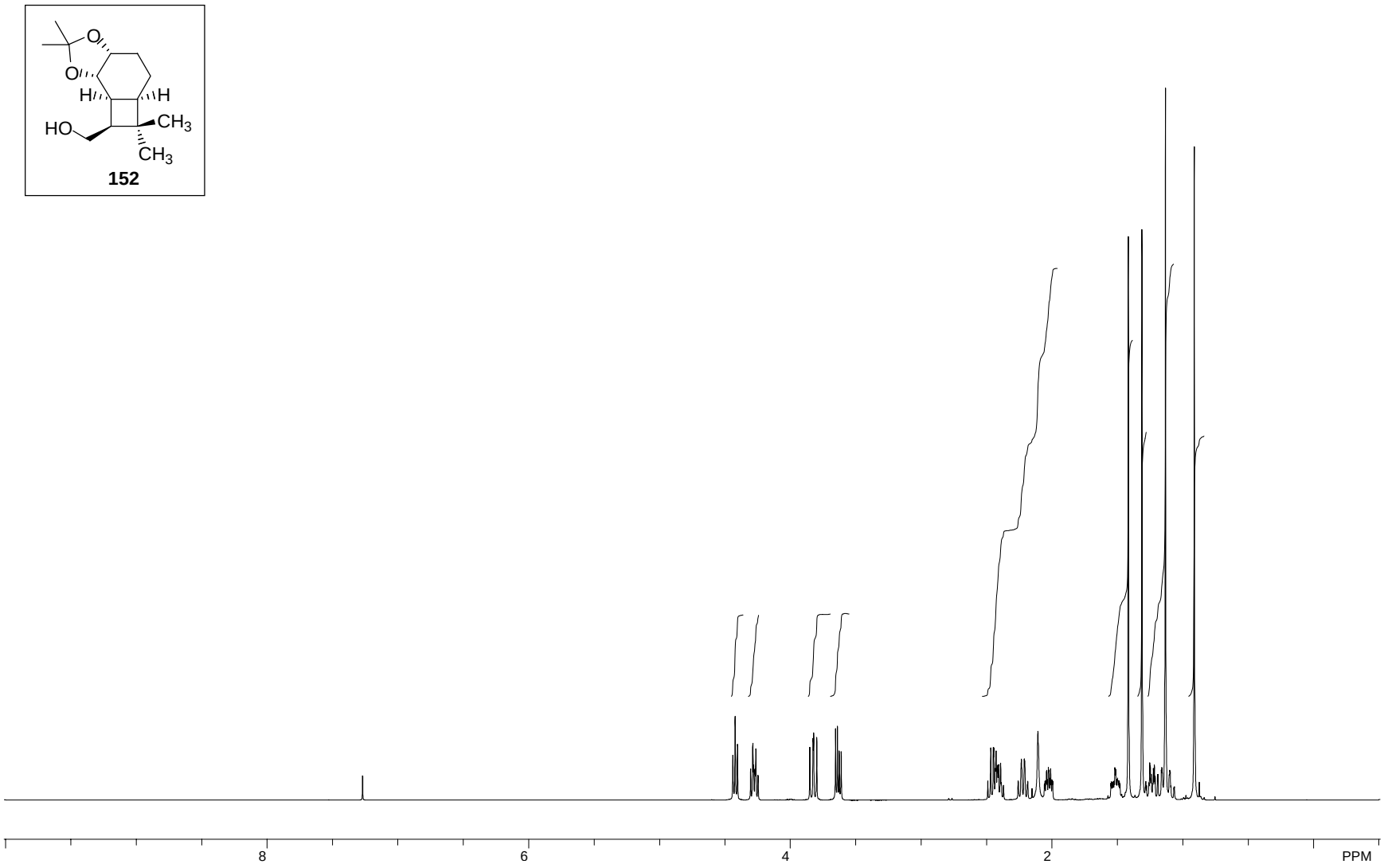


Figure A.3.73 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **152**.

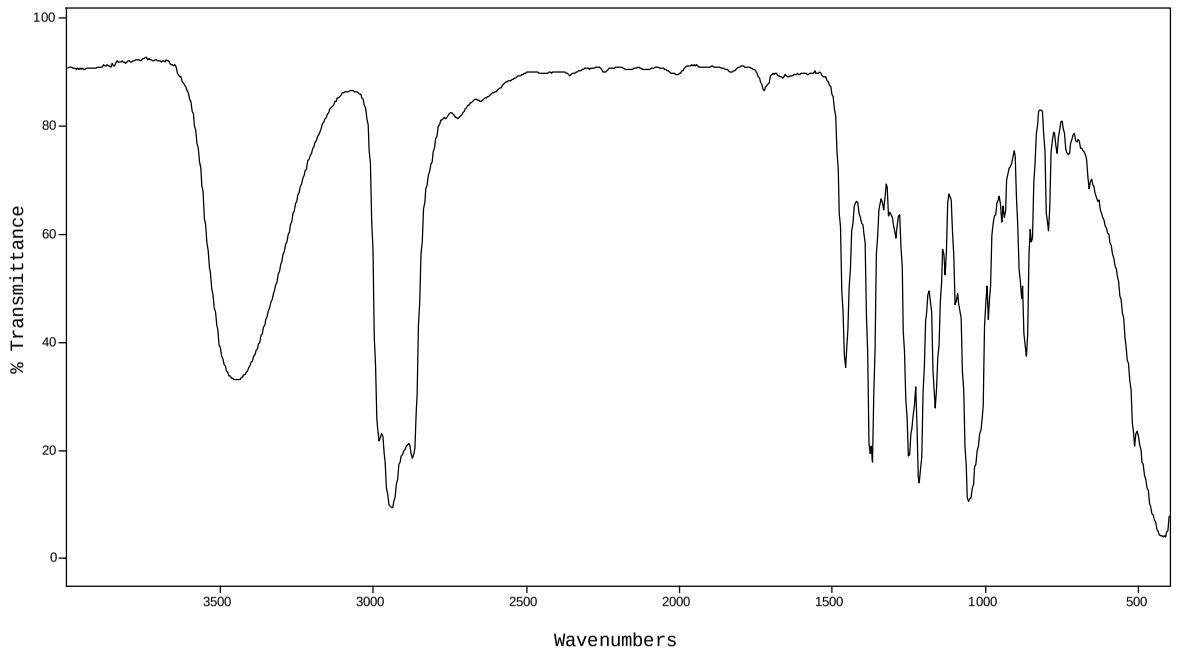


Figure A.3.74 FTIR Spectrum (thin film/NaCl) of Compound **152**.

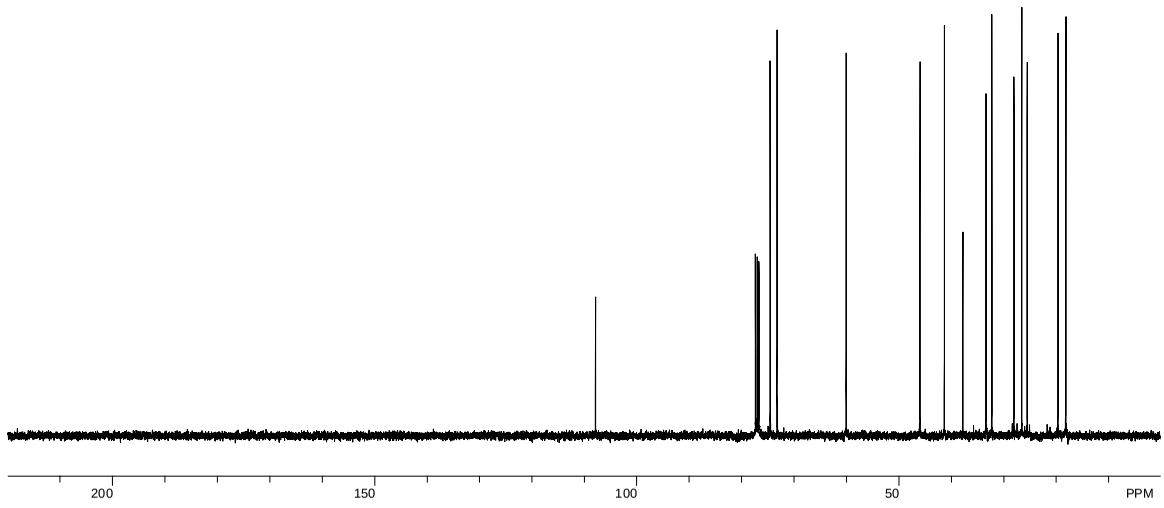


Figure A.3.75 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **152.**

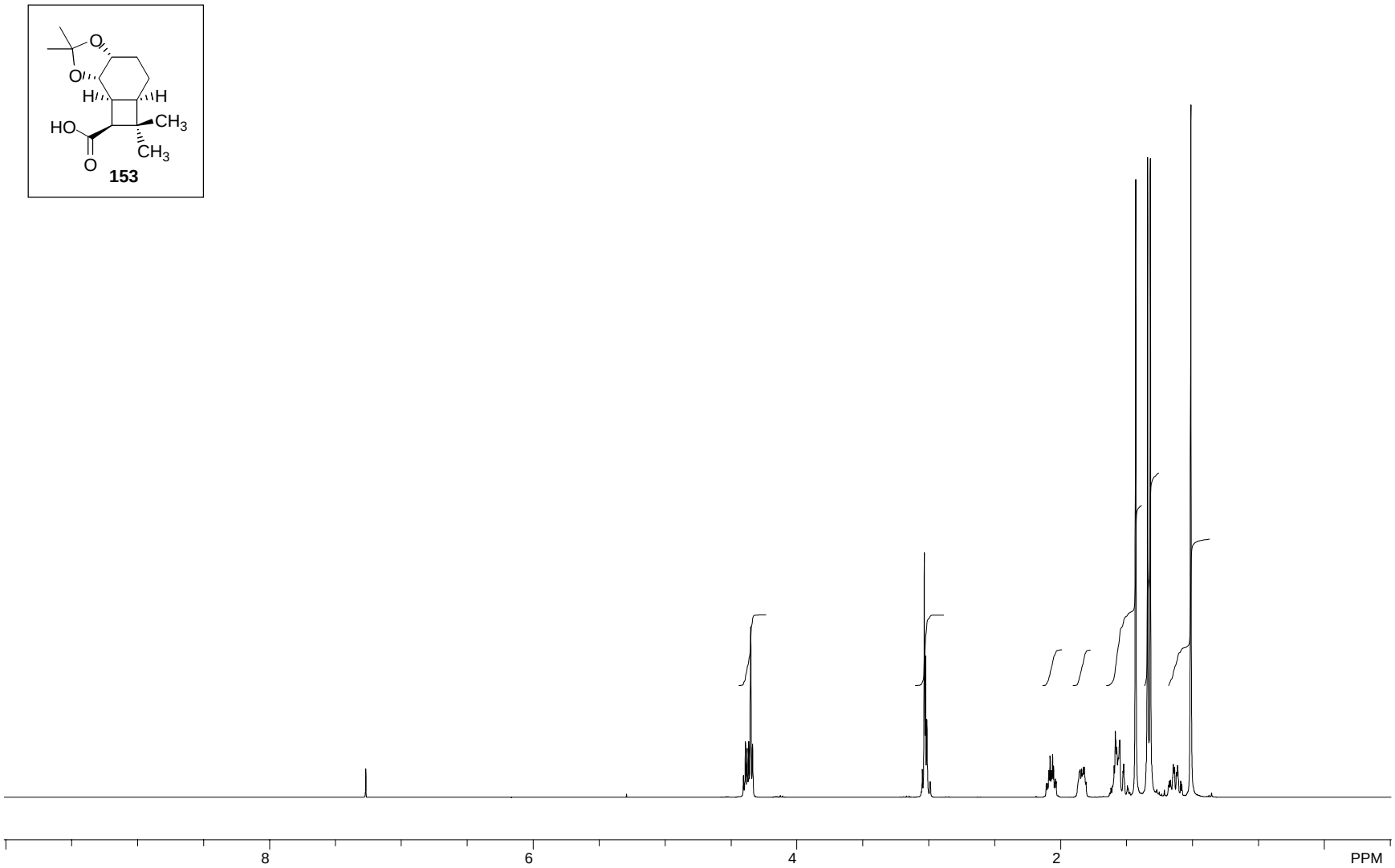


Figure A.3.76 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **153**.

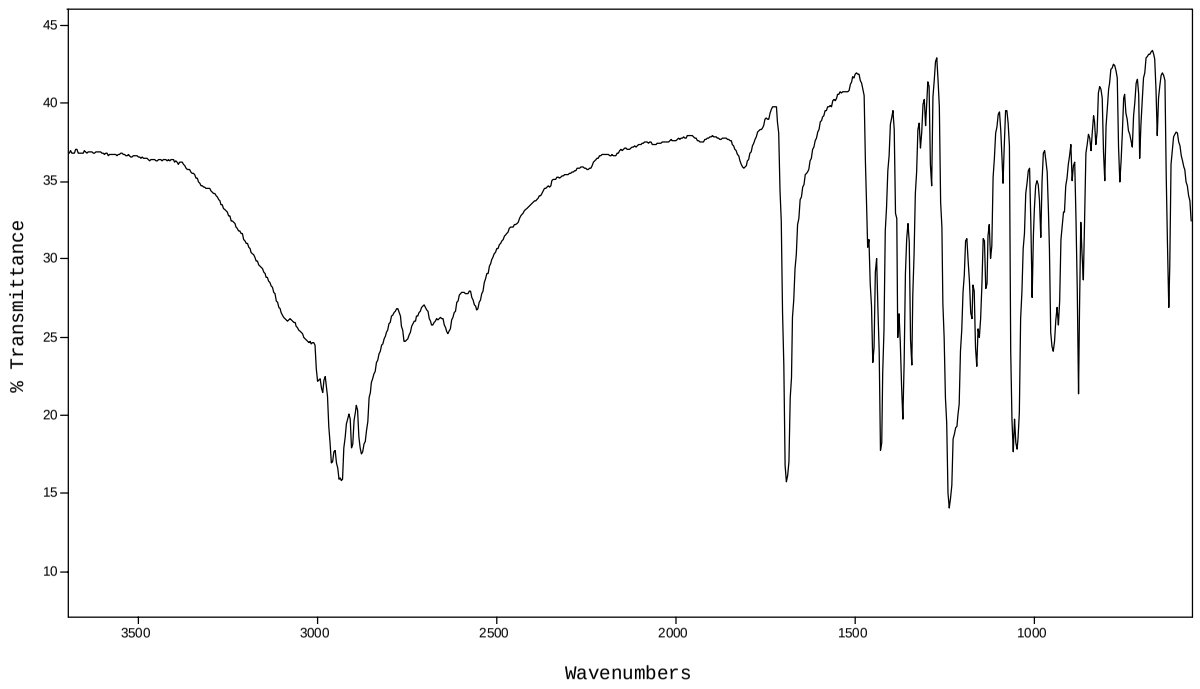


Figure A.3.77 FTIR Spectrum (thin film/NaCl) of Compound **153**.

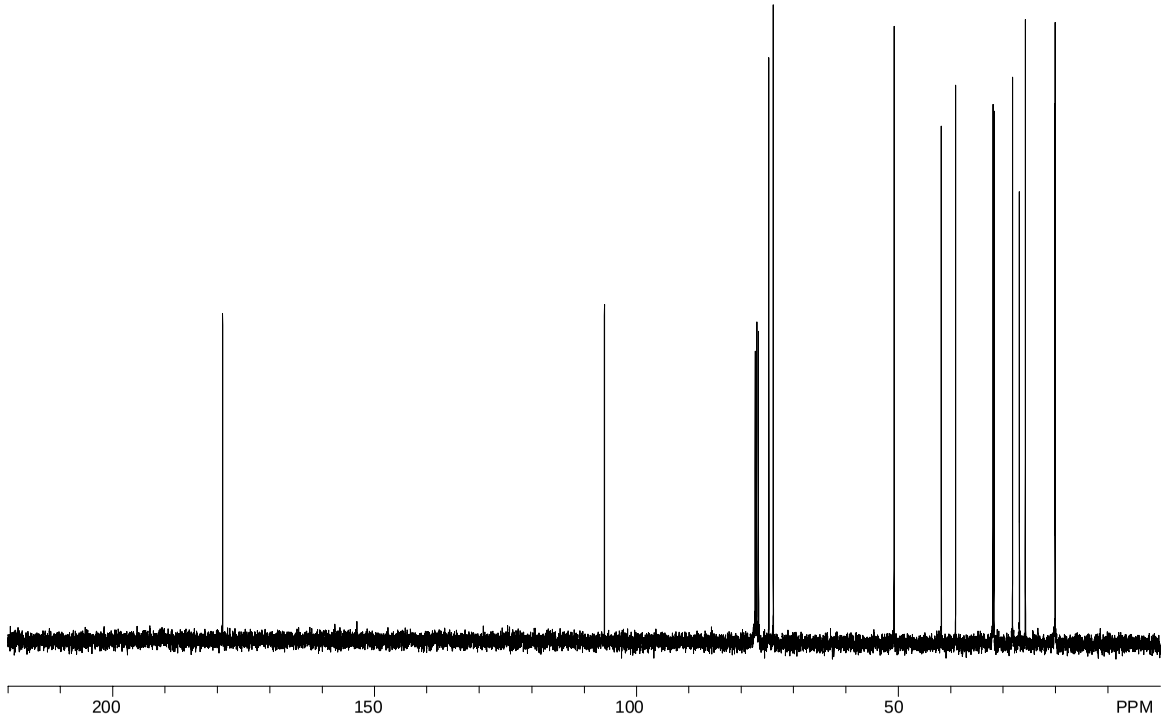


Figure A.3.78 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **153**.

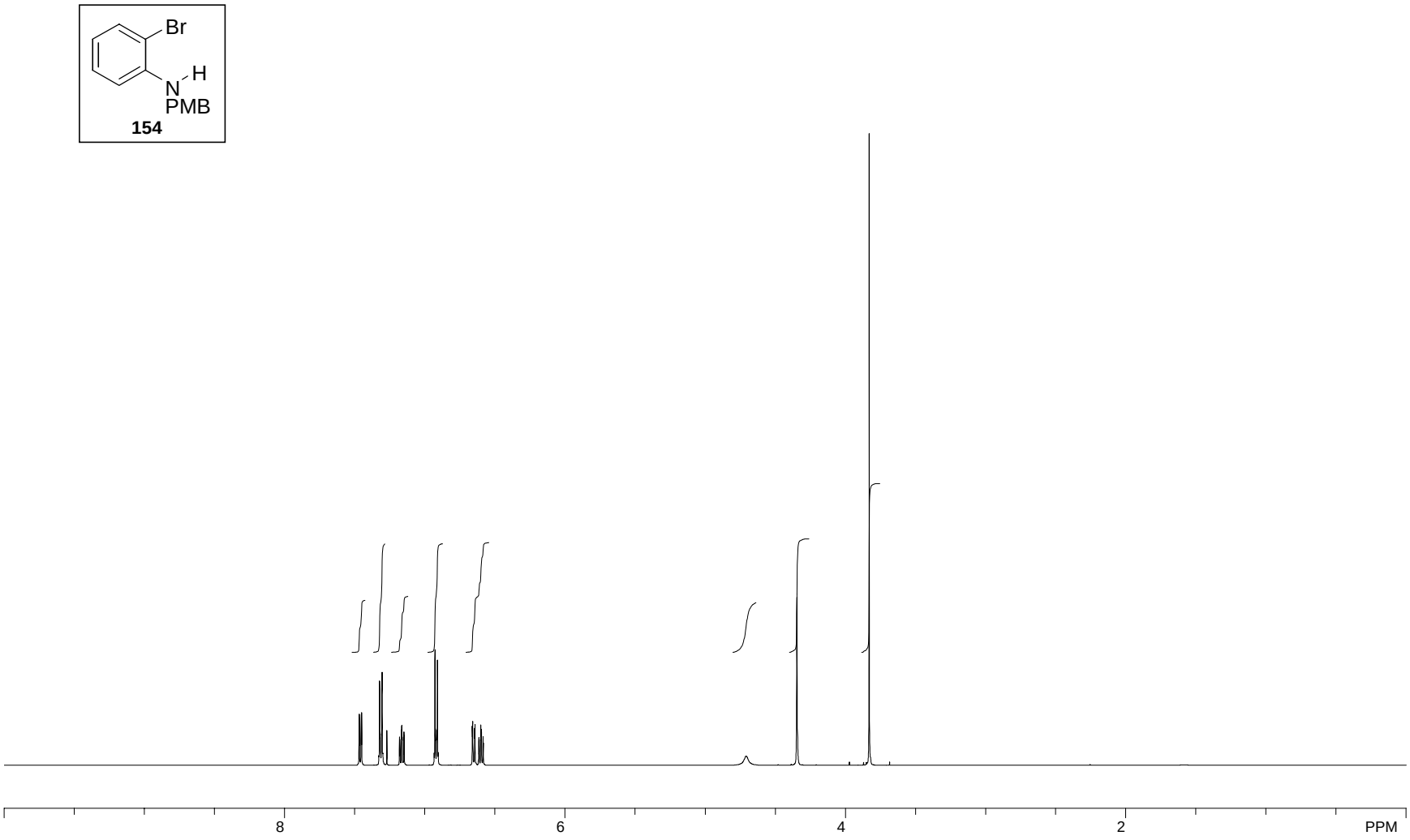


Figure A.3.79 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **154**.

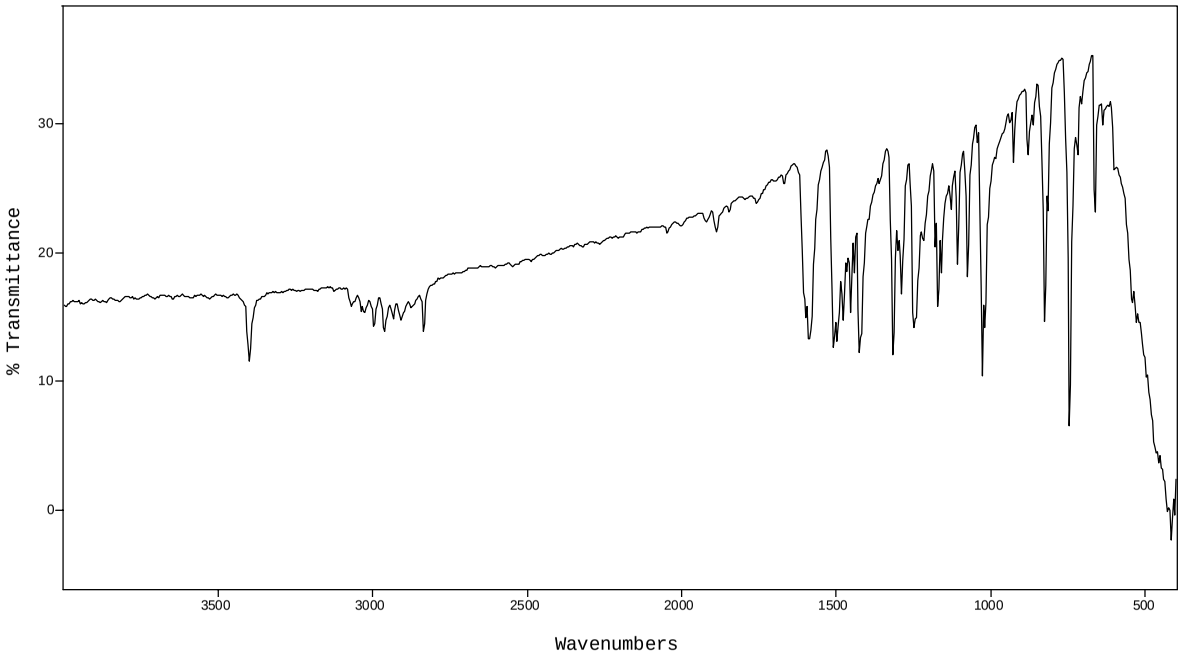


Figure A.3.80 FTIR Spectrum (thin film/NaCl) of Compound **154**.

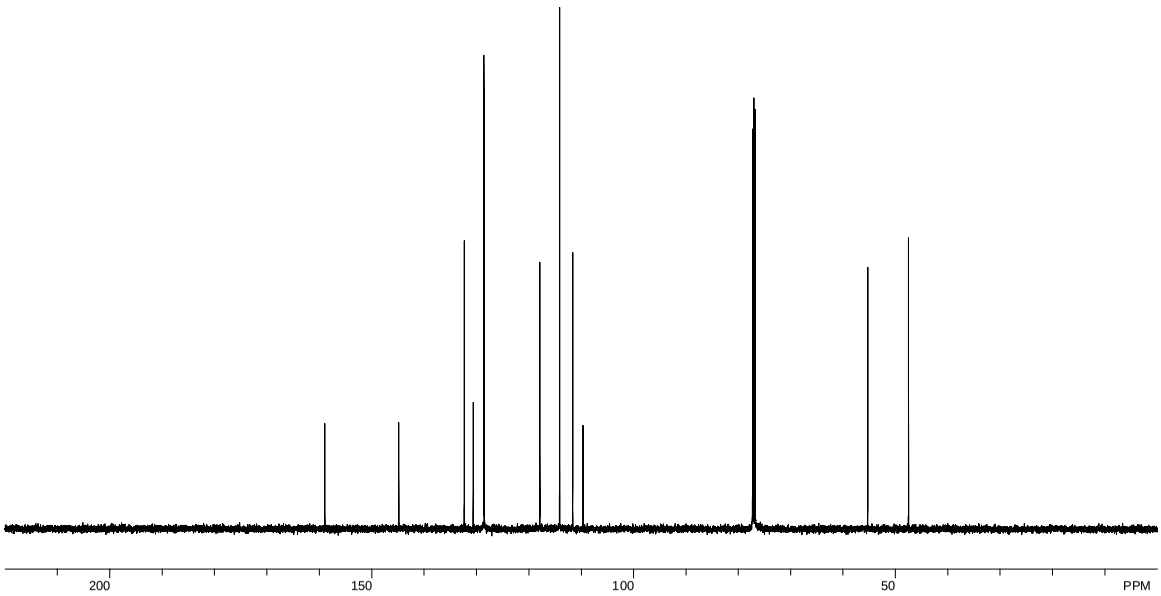


Figure A.3.81 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **154**.

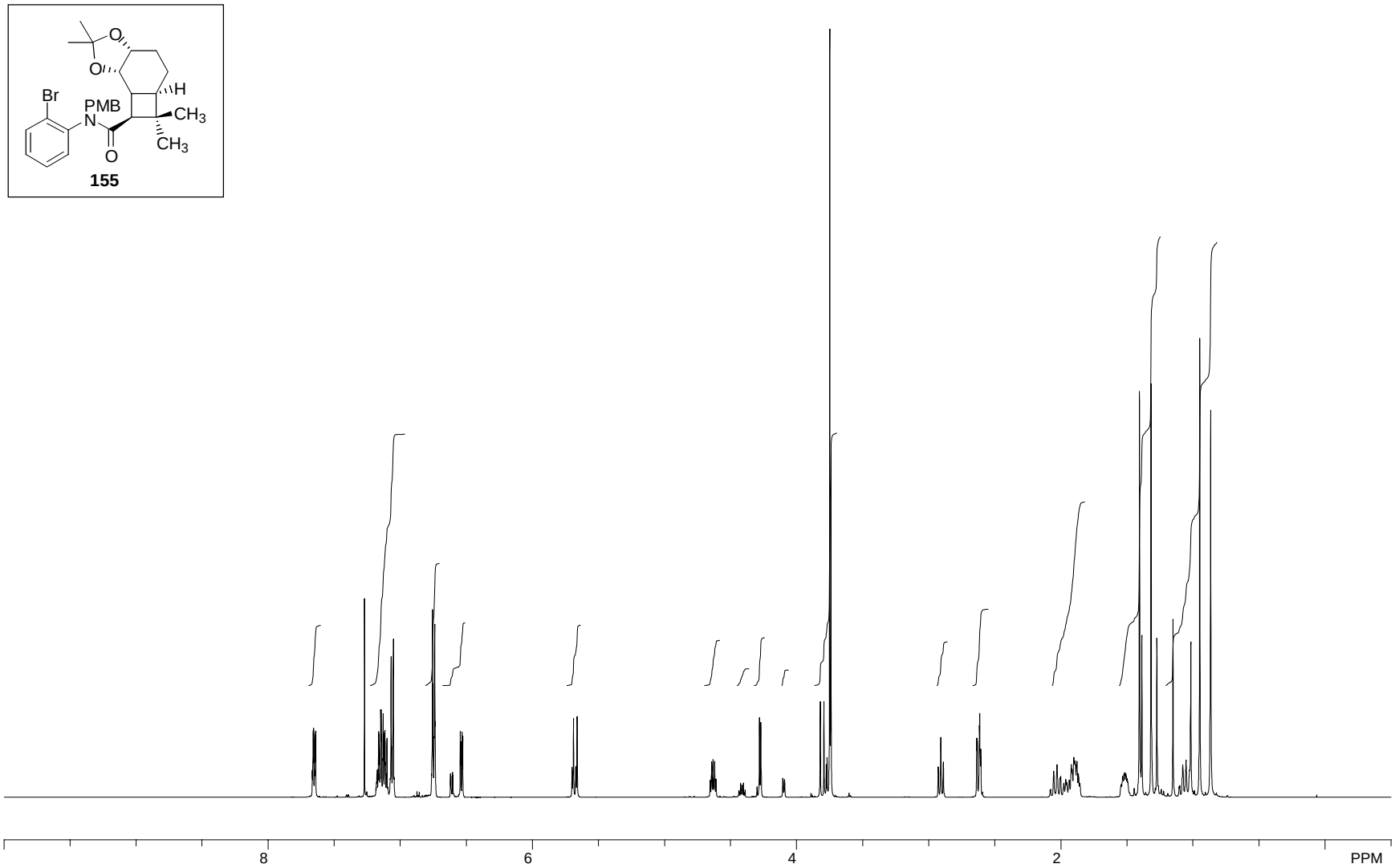


Figure A.3.82 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **155**.

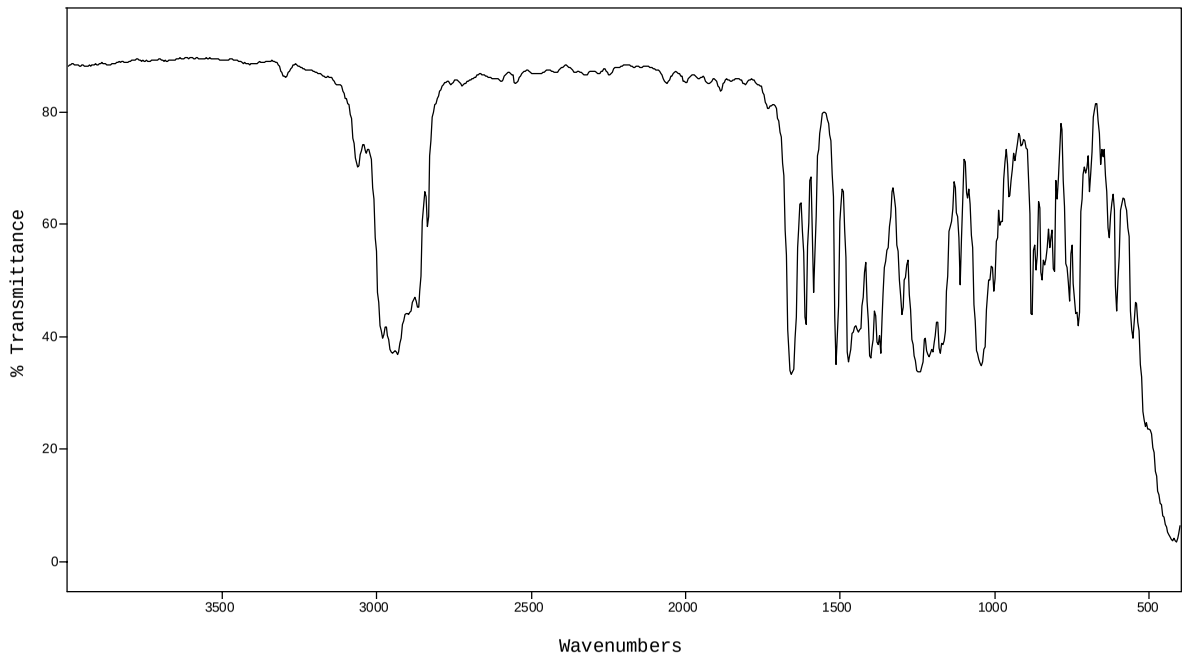


Figure A.3.83 FTIR Spectrum (thin film/NaCl) of Compound **155**.

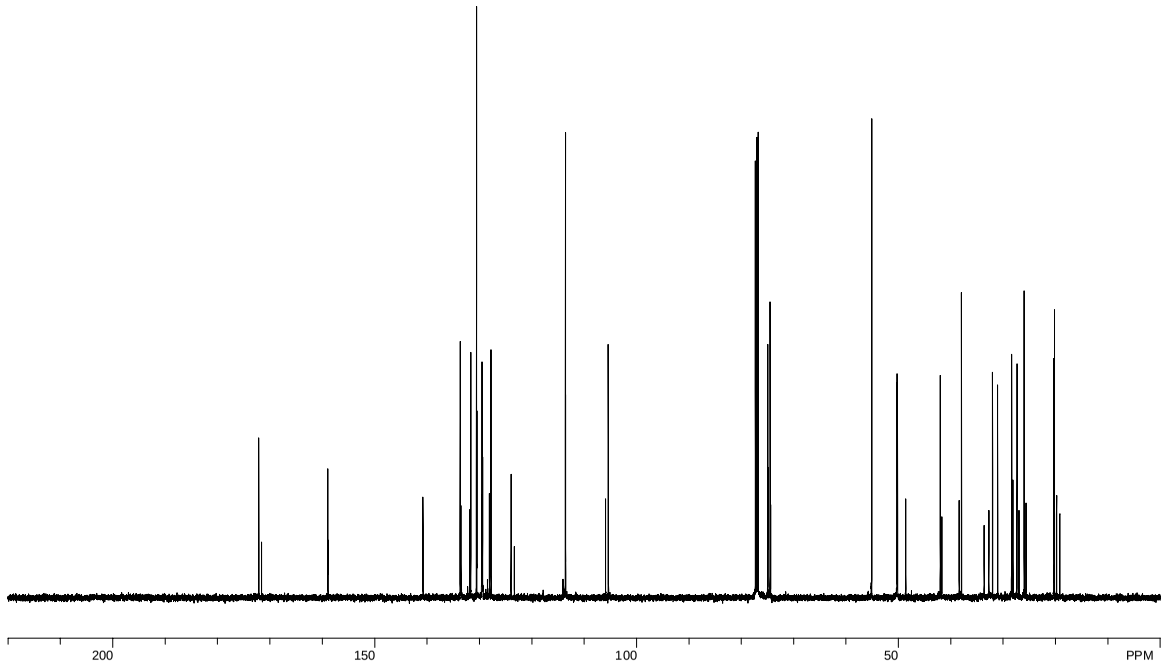


Figure A.3.84 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **155**.

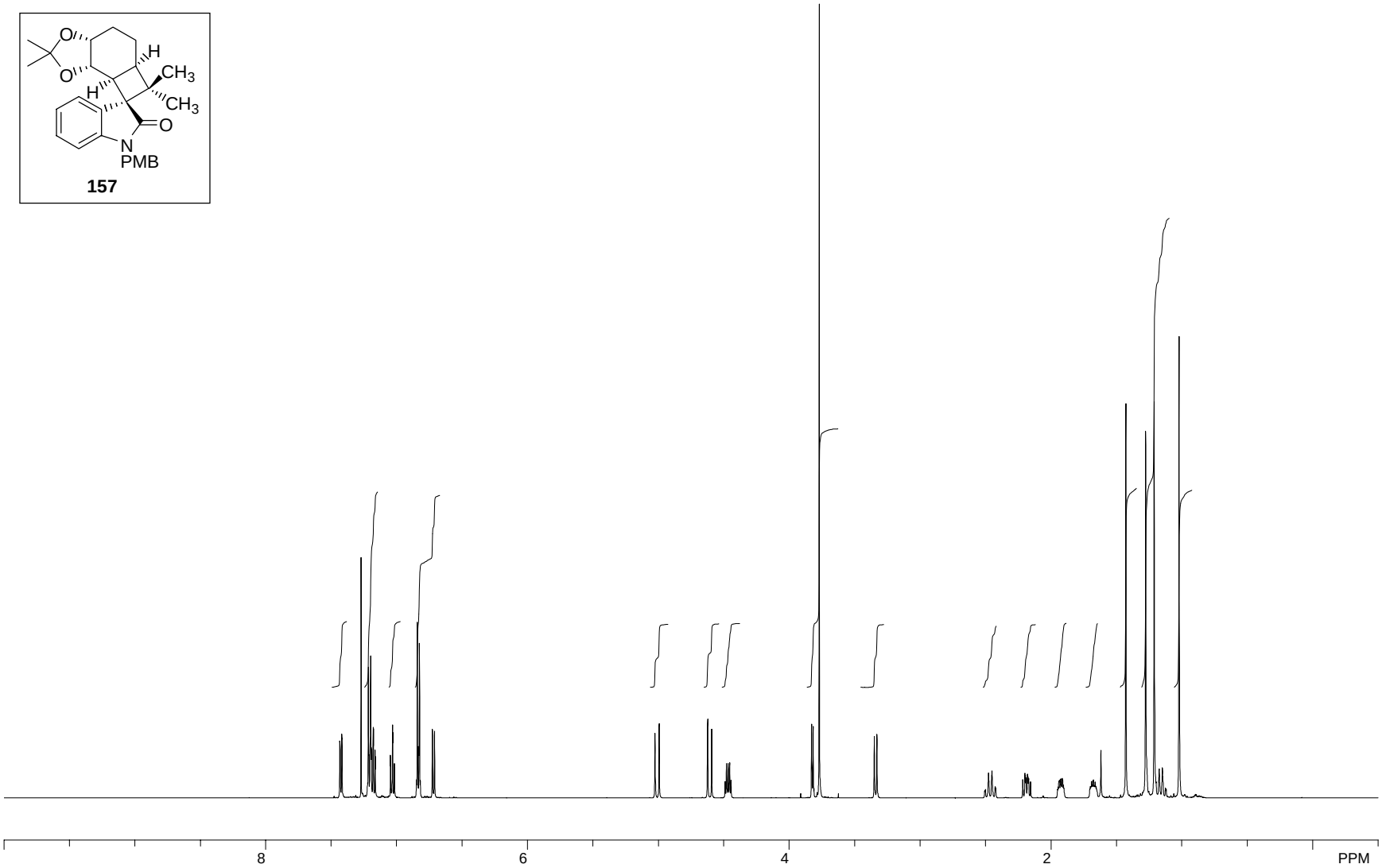


Figure A.3.85 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **157**.

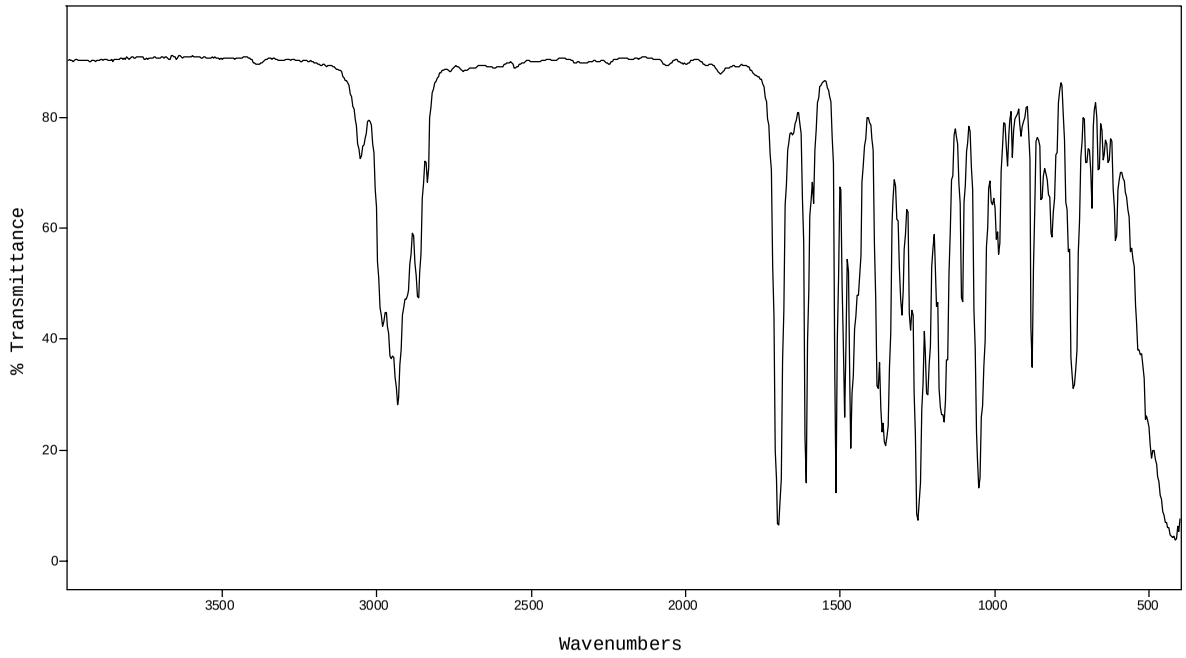


Figure A.3.86 FTIR Spectrum (thin film/NaCl) of Compound **157**.

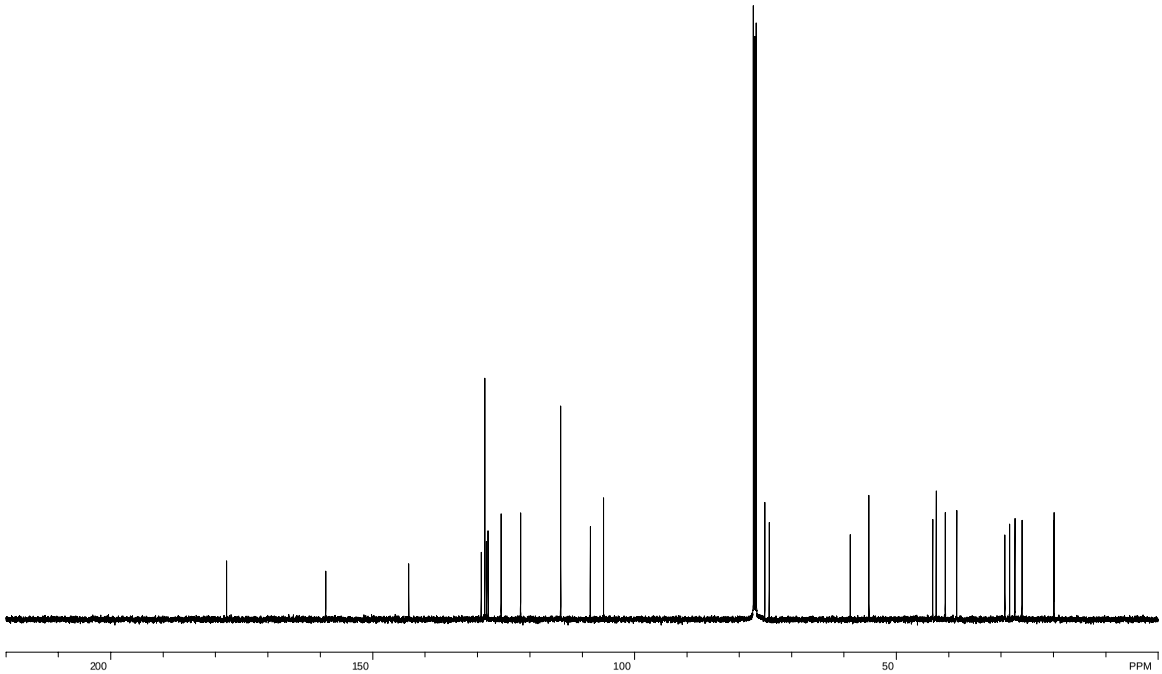


Figure A.3.87 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **157**.

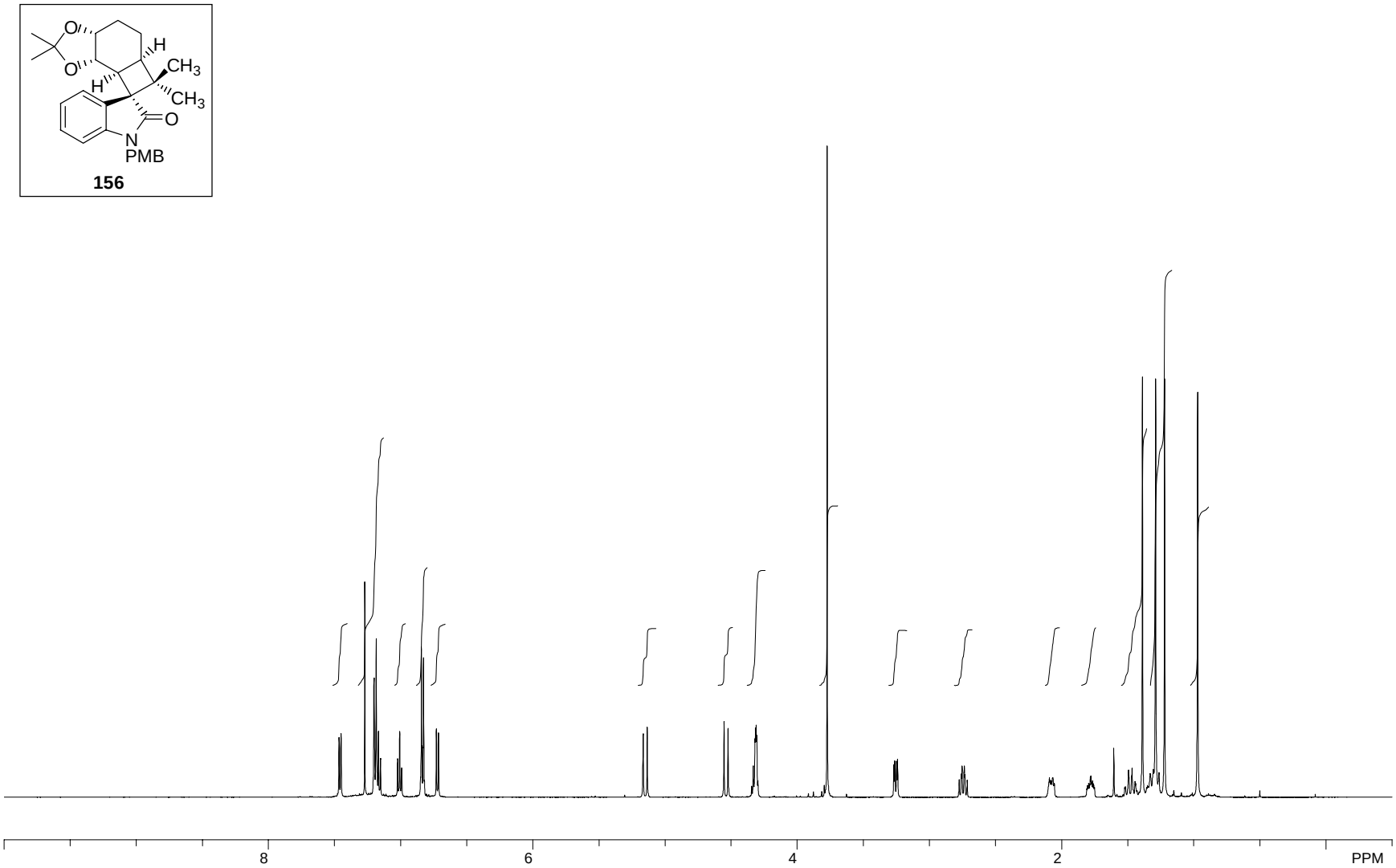


Figure A.3.88 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **156**.

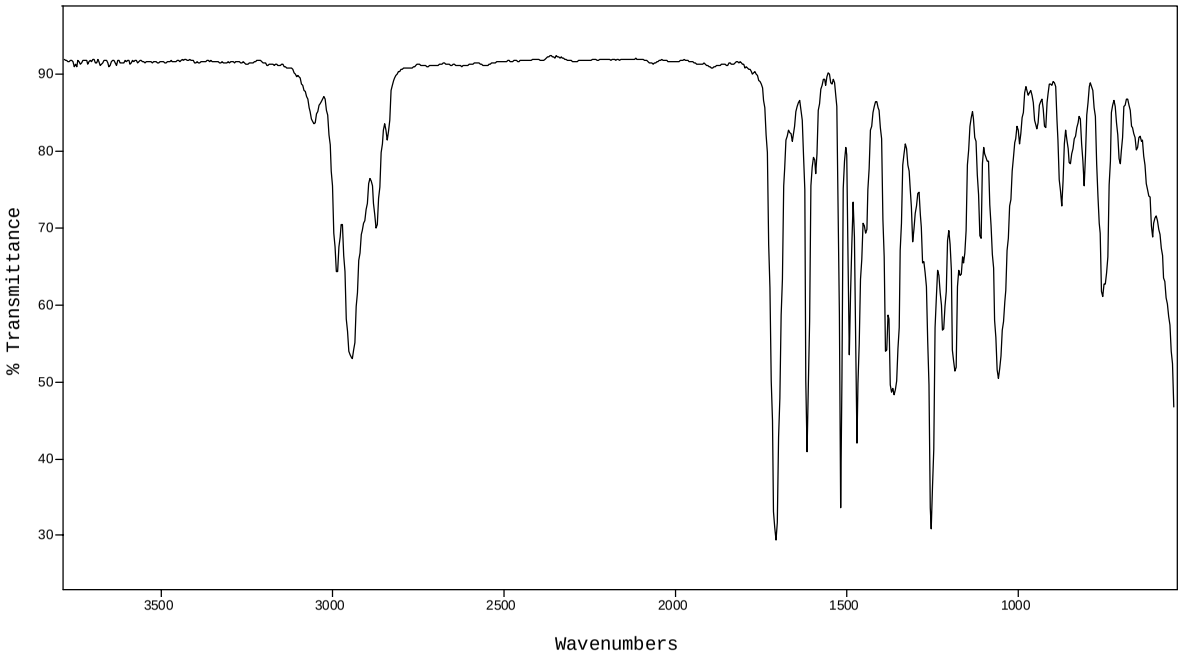


Figure A.3.89 FTIR Spectrum (thin film/NaCl) of Compound **156**.

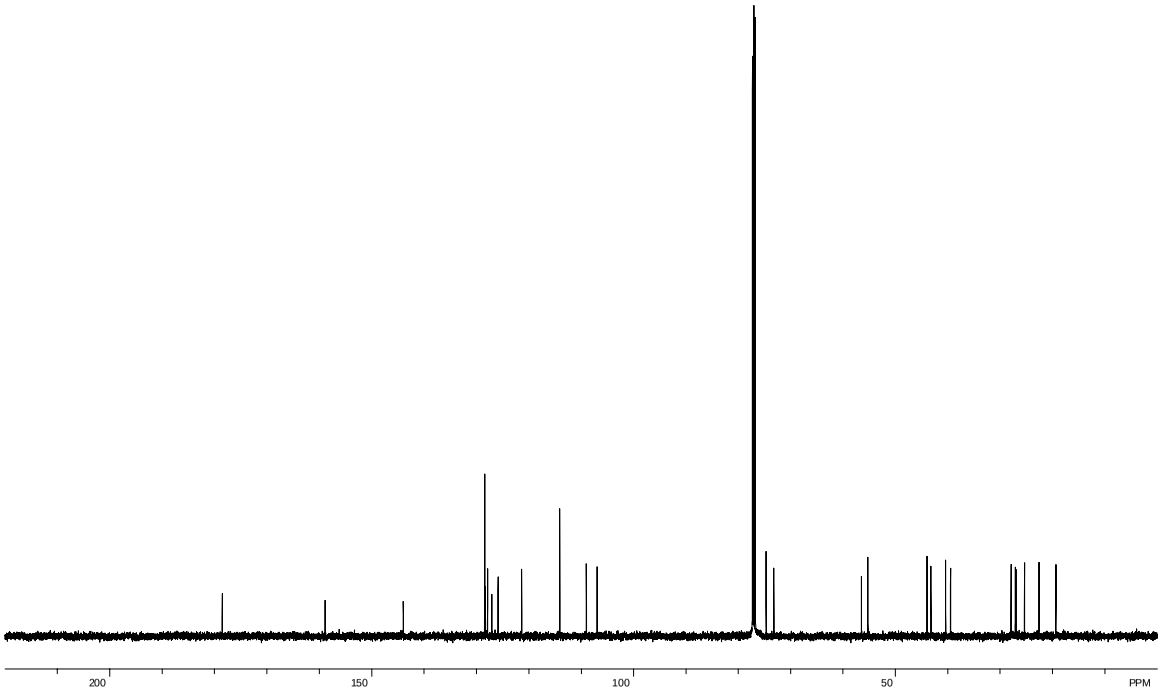


Figure A.3.90 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **156**.

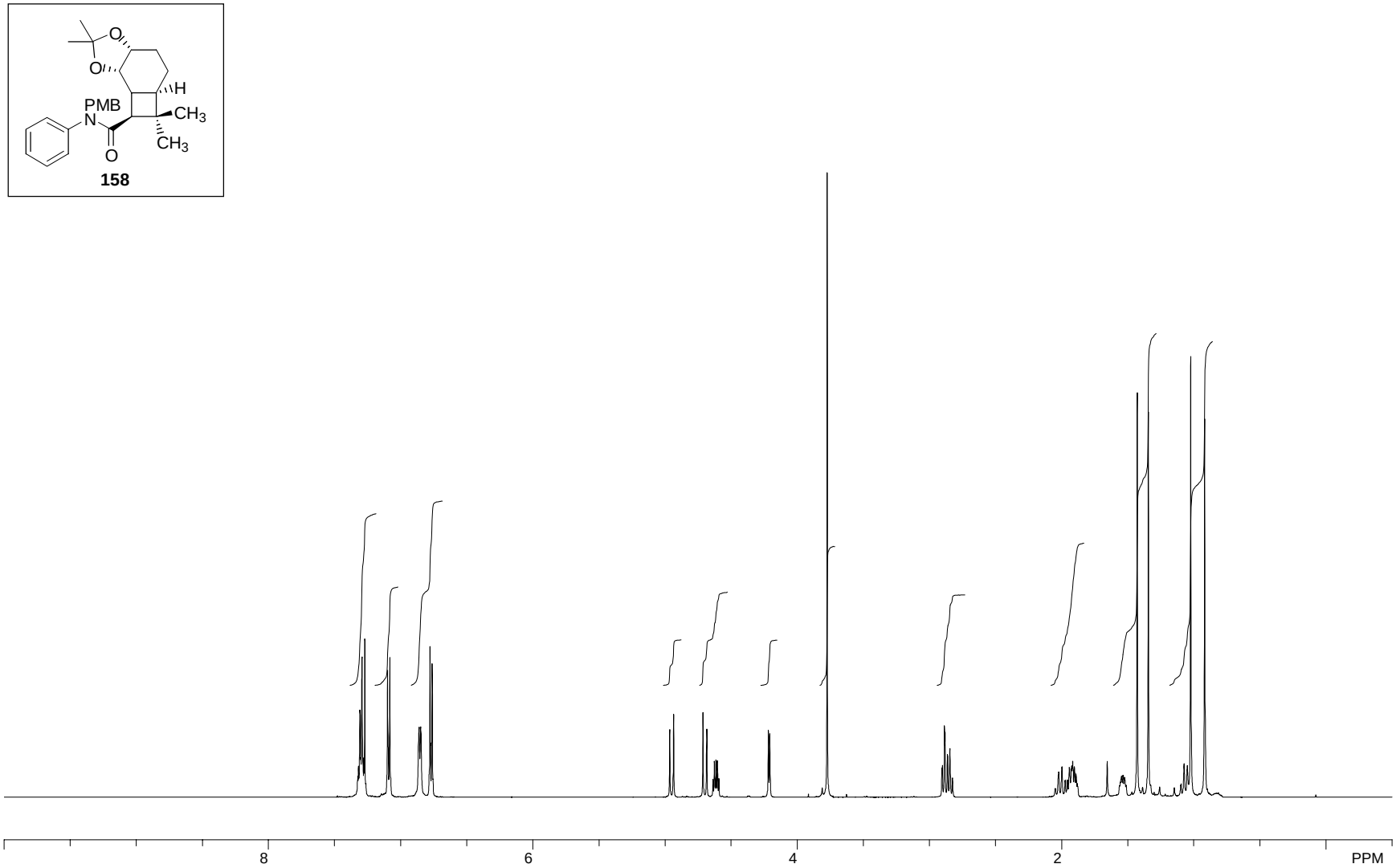


Figure A.3.91 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **158**.

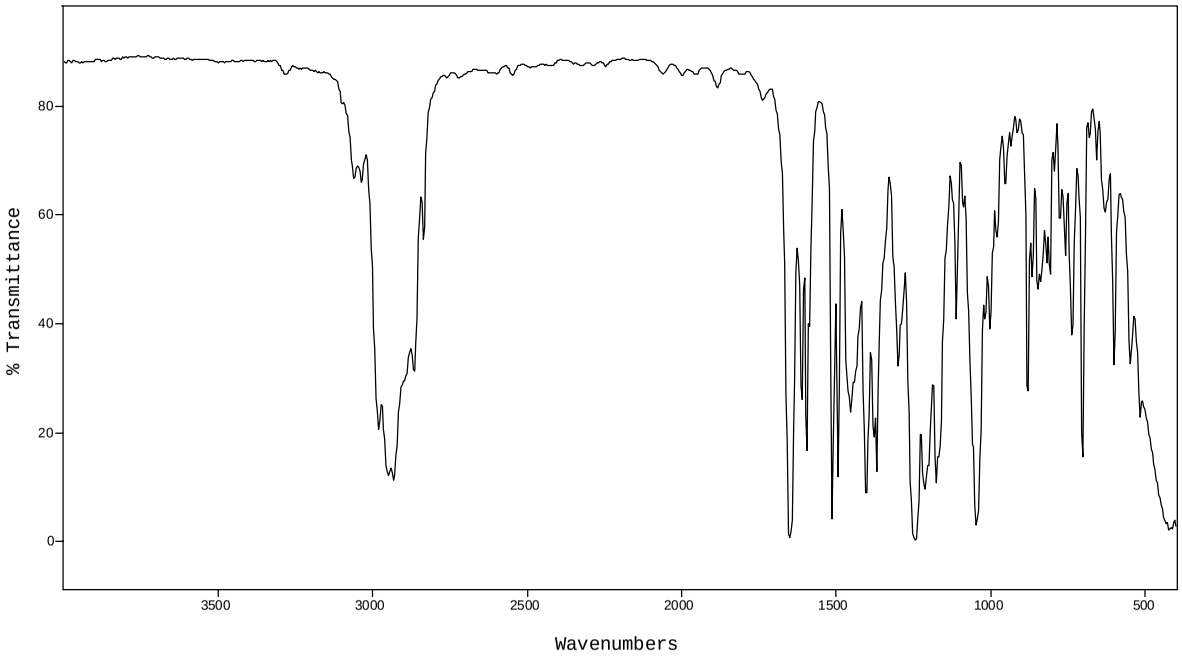


Figure A.3.92 FTIR Spectrum (thin film/NaCl) of Compound **158**.

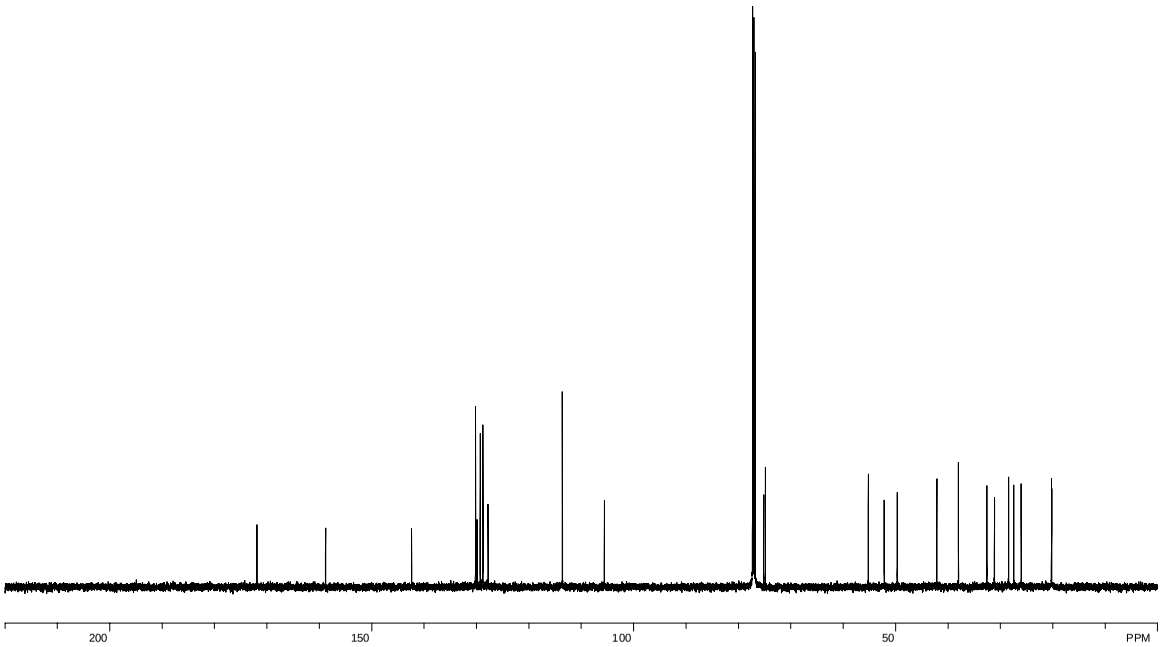
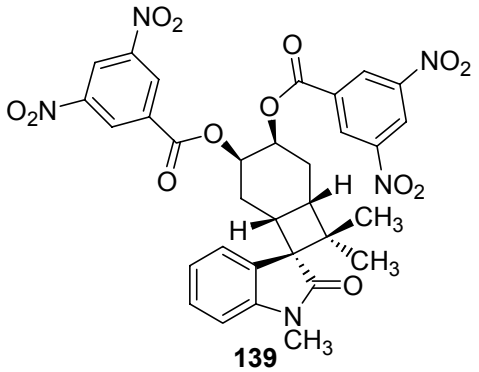


Figure A.3.93 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **158**.

APPENDIX FOUR: X-RAY CRYSTALLOGRAPHY REPORTS RELEVANT TO CHAPTER TWO

X-RAY CRYSTALLOGRAPHY REPORT FOR OXINDOLE 139.



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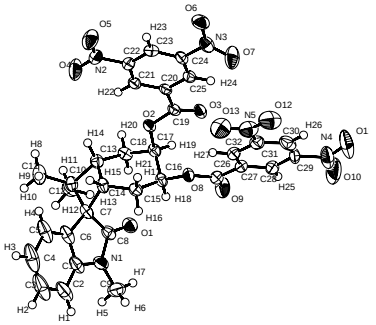


Empirical Formula	$C_{32}H_{27}N_5O_{13}$
Formula Weight	689.59
Crystal Color, Habit	yellow, cut hexagonal plate
Crystal Dimensions	0.20 X 0.15 X 0.08 mm
Crystal System	monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 16.355(1)Å
	b = 10.2544(3) Å
	c = 18.715(1) Å
	β = 95.765(2)^o
	V = 3122.9(2) Å^3
Space Group	$P2_1/n$ (#14)
Z value	4
Dcalc	1.467 g/cm^3
F000	1432.00
μ(MoKα)	1.16 cm^{-1}

B. Intensity Measurements

Diffractometer	Nonius KappaCCD
Radiation	MoKα (λ = 0.71069 Å)
	graphite monochromated
Take-off Angle	2.8^o
Crystal to Detector Distance	35 mm
Temperature	-90.0^{o}C
Scan Rate	90sec/frame
Scan Width	1°/frame
2θmax	52.7^o
No. of Reflections Measured	Total: 6738

Corrections	Lorentz-polarization

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma\ w\ (\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$1/\sigma^2(Fo) = 4Fo^2/\sigma^2(Fo^2)$
p-factor	0.0100
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>4.00σ(I))	3207
No. Variables	451
Reflection/Parameter Ratio	7.11
Residuals: R; Rw	0.050 ; 0.052
Goodness of Fit Indicator	2.28
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.32 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.35 $e^-/Å^3$

Postional Parameters and B(eq) for 139.

atom	x	y	z	Beq
O(1)	1.3253(1)	0.0560(2)	1.1589(1)	3.39(5)
O(2)	1.1515(1)	0.4386(2)	1.17827(10)	2.57(5)
O(3)	1.0365(1)	0.3981(2)	1.2332(1)	3.01(5)
O(4)	1.1854(2)	0.8466(2)	1.0619(2)	5.83(7)
O(5)	1.0825(1)	0.9713(2)	1.0337(1)	5.21(7)
O(6)	0.8144(1)	0.8558(2)	1.1044(1)	4.22(6)
O(7)	0.7932(1)	0.6510(2)	1.1249(1)	5.32(7)
O(8)	1.0746(1)	0.2097(2)	1.12899(10)	2.51(5)
O(9)	1.0660(1)	0.0581(2)	1.2149(1)	4.60(6)
O(10)	0.7859(2)	-0.0543(3)	1.2710(2)	7.8(1)
O(11)	0.6834(2)	0.0666(3)	1.2319(1)	7.91(10)
O(12)	0.7166(2)	0.3849(2)	1.0477(1)	6.03(8)
O(13)	0.8397(2)	0.4329(2)	1.0207(1)	5.68(8)
N(1)	1.3733(1)	0.0016(3)	1.0526(1)	3.65(7)
N(2)	1.1129(2)	0.8732(3)	1.0610(1)	3.46(7)
N(3)	0.8382(2)	0.7445(3)	1.1173(1)	3.31(7)
N(4)	0.7563(2)	0.0345(4)	1.2347(2)	6.0(1)
N(5)	0.7915(2)	0.3713(3)	1.0540(2)	4.43(9)
C(1)	1.3923(2)	0.0650(4)	0.9902(2)	3.99(9)
C(2)	1.4143(2)	0.0083(5)	0.9278(2)	6.2(1)
C(3)	1.4269(3)	0.0921(7)	0.8716(2)	8.0(2)
C(4)	1.4176(3)	0.2244(6)	0.8776(2)	6.7(1)
C(5)	1.3944(2)	0.2793(4)	0.9407(2)	4.9(1)
C(6)	1.3831(2)	0.1989(4)	0.9977(2)	3.58(9)

C(7)	1.3555(2)	0.2266(3)	1.0708(1)	2.58(7)
C(8)	1.3484(2)	0.0882(3)	1.1012(2)	2.88(8)
C(9)	1.3750(2)	-0.1388(3)	1.0627(2)	5.5(1)
C(10)	1.4017(2)	0.3281(3)	1.1260(1)	2.67(7)
C(11)	1.4470(2)	0.4338(3)	1.0885(2)	4.22(9)
C(12)	1.4597(2)	0.2711(3)	1.1864(2)	3.38(8)
C(13)	1.3156(2)	0.3795(3)	1.1435(2)	2.73(7)
C(14)	1.2774(2)	0.3134(3)	1.0734(1)	2.56(7)
C(15)	1.1920(2)	0.2548(3)	1.0700(1)	2.57(7)
C(16)	1.1646(2)	0.2156(3)	1.1419(2)	2.45(7)
C(17)	1.1888(2)	0.3135(3)	1.2008(1)	2.46(7)
C(18)	1.2807(2)	0.3311(3)	1.2115(2)	2.77(7)
C(19)	1.0756(2)	0.4632(3)	1.1951(2)	2.47(7)
C(20)	1.0423(2)	0.5842(3)	1.1577(1)	2.37(7)
C(21)	1.0934(2)	0.6711(3)	1.1263(2)	2.54(7)
C(22)	1.0588(2)	0.7810(3)	1.0943(2)	2.63(7)
C(23)	0.9761(2)	0.8086(3)	1.0908(2)	2.70(7)
C(24)	0.9275(2)	0.7190(3)	1.1213(2)	2.47(7)
C(25)	0.9582(2)	0.6082(3)	1.1552(1)	2.52(7)
C(26)	1.0347(2)	0.1344(3)	1.1719(2)	2.92(8)
C(27)	0.9439(2)	0.1574(3)	1.1602(2)	2.60(7)
C(28)	0.8929(2)	0.0857(3)	1.2002(2)	3.24(8)
C(29)	0.8096(2)	0.1112(3)	1.1917(2)	3.64(9)
C(30)	0.7749(2)	0.2036(3)	1.1450(2)	3.86(9)
C(31)	0.8265(2)	0.2717(3)	1.1055(2)	3.34(8)
C(32)	0.9101(2)	0.2512(3)	1.1124(2)	2.87(8)
H(1)	1.4204	-0.0834	0.9236	7.4382
H(2)	1.4423	0.0568	0.8280	9.5933
H(3)	1.4272	0.2792	0.8384	8.0491
H(4)	1.3864	0.3708	0.9443	5.8538
H(5)	1.4296	-0.1697	1.0614	6.5839
H(6)	1.3401	-0.1791	1.0255	6.5839
H(7)	1.3565	-0.1594	1.1078	6.5839
H(8)	1.4532	0.5088	1.1184	5.0652
H(9)	1.4165	0.4560	1.0443	5.0652
H(10)	1.4997	0.4025	1.0795	5.0652
H(11)	1.4779	0.3383	1.2191	4.0516
H(12)	1.5057	0.2331	1.1671	4.0516
H(13)	1.4318	0.2062	1.2108	4.0516
H(14)	1.3126	0.4718	1.1399	3.2720
H(15)	1.2773	0.3758	1.0359	3.0708
H(16)	1.1910	0.1793	1.0405	3.0821
H(17)	1.1541	0.3172	1.0488	3.0821
H(18)	1.1859	0.1320	1.1554	2.9432
H(19)	1.1691	0.2858	1.2444	2.9525
H(20)	1.2936	0.3929	1.2488	3.3272

H(21)	1.3055	0.2498	1.2250	3.3272
H(22)	1.1507	0.6547	1.1270	3.0494
H(23)	0.9537	0.8858	1.0686	3.2383
H(24)	0.9230	0.5492	1.1765	3.0252
H(25)	0.9148	0.0205	1.2327	3.8905
H(26)	0.7174	0.2197	1.1403	4.6266
H(27)	0.9444	0.3008	1.0847	3.4478

CHAPTER THREE

WELWITINDOLINONE A ISONITRILE: INITIAL EFFORTS TOWARD A FULLY ELABORATED [4.2.0] BICYCLIC SYSTEM

3.1 Constructing a Fully Elaborated [4.2.0] Bicyclic System.

3.1.1 Initial Concerns.

Satisfied that a reliable method had been realized for the construction of the spirocyclobutane oxindole framework of **7**, and confident that the stereochemical outcome of the key palladium-mediated arylation would be substrate directed, efforts shifted to the preparation of a fully elaborated [4.2.0] bicyclic system. Prior to a detailed account of the work focusing on the construction of advanced [4.2.0] systems, a brief discussion concerning vinyl isonitriles will be offered.

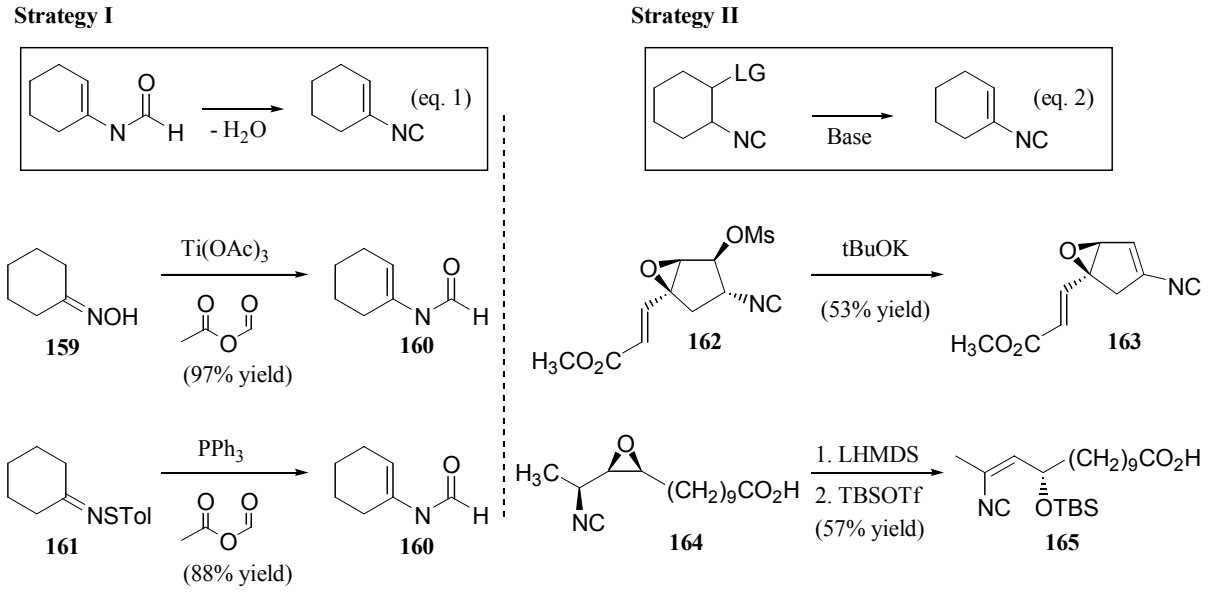
3.1.1.1 Addressing the Vinyl Isonitrile.

One of the salient features of **7** is the vinyl isonitrile moiety. While there is an abundance of isolated natural products which contain the isonitrile functionality, natural products which contain a vinyl isonitrile are rarities. Presumably this observation, along with their inherent instability, has led to a dearth of research regarding their preparation, the few methods that are available are discussed below.

3.1.1.1.1 Preparation of Vinyl Isonitriles.

The methods that do exist for the preparation of vinyl isonitriles can be divided into two categories, each of which is illustrated in Scheme 3.1.1.[1] The first approach (Strategy I) calls for the preparation of a vinyl formamide, which in a subsequent step can be dehydrated to provide the vinyl isonitrile (eq. 1).[2] This method relies on the observation that vinyl formamides behave much like their aliphatic counterparts in that they can be dehydrated to the corresponding isonitriles under a range of conditions.[3] To this end, two procedures have been developed and applied in the preparation of vinyl formamides. The first of these, developed by Barton,[4] involves the reductive formylation of an oxime (**159**) with titanium (III) acetate. The second procedure, reported by Baldwin,[3] consists of the reduction of a thiooxime (**161**) with PPh_3 in the presence of benzoic formic anhydride. Both of these methods allow for the construction of vinyl formamides using mild conditions.

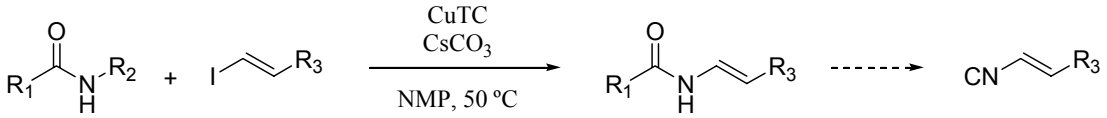
Scheme 3.1.1



Alternatively, the second strategy developed for the synthesis of vinyl isonitriles involves the preparation of an aliphatic isonitrile, which contains a leaving group in the β-position (eq. 2); upon treatment with base, the leaving group is expelled, thereby directly generating the vinyl isonitrile. Leaving groups which have proven to be suitable for this chemistry include mesylates (**162 → 162**),[5] halogens,[6] and epoxides (**164 → 165**).[1] Both of the strategies outlined in Scheme 3.1.1 have been employed in the synthesis of vinyl isonitriles *en route* to natural products.[3,5]

In addition to the two strategies outlined above, recent work by Porco involving the Cu(II)-catalyzed coupling of vinyl iodides and amides to furnish enamides suggests a third strategy for the preparation of vinyl formamides (Scheme 3.1.2).[7] The preliminary communication describing this methodology did not report the preparation of unprotected vinyl formamides, however it seems to be a logical extension of this work.

Scheme 3.1.2

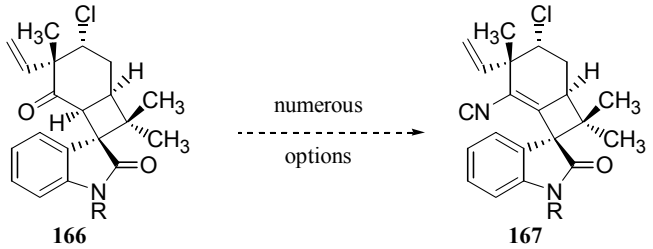


R_1 = Ph , R_2 = H , R_3 = C_5H_{11} 71% yield

R_1 = H, R_2 = CH_3, R_3 = C_5H_{11} 75% yield

As noted in the retrosynthetic analysis presented in Section 2.4, it was envisioned that the vinyl isonitrile would ultimately arise from an alcohol (Scheme 3.1.3). This disconnection allows for each of the aforementioned strategies to be examined, as the precursors required for each of these strategies can be accessed from a ketone.

Scheme 3.1.3

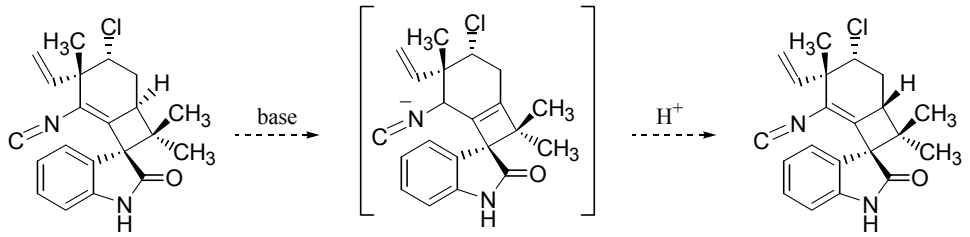


3.1.1.2 Stereochemical Issues

Having demonstrated that the rigid nature of the [4.2.0] bicyclic system could be used to direct the Pd-catalyzed arylation to the convex face, we opted initially to pursue a route that would require late-stage epimerization at C(15) (Scheme 3.1.4). While the decision to adopt this approach derived largely from our ability to control the diastereoselectivity observed in the cyclization of numerous anilides, it was also believed that the structural motifs present in both **166** and **167** were conducive to such an

approach. For example, in **167**, the C(15) hydrogen lies in conjugation with the vinyl isonitrile raising the question as to whether the penultimate intermediate in the synthesis of **7** could be C(15)-epi-welwitindolinone A isonitrile (**140**). Extensive work regarding the reactivity of vinyl isonitriles remains to be done, however, it has been demonstrated that aliphatic isonitriles can efficiently be alkylated.[8,9] Thus, it is clear that upon treatment with a suitable base, isonitriles can be deprotonated. The concept of vinylogy would therefore suggest that vinyl isonitriles would behave similarly. Thus it seems plausible that epi-welwitindolinone A (**140**) could indeed be an intermediate *en route* to **7**.

Scheme 3.1.4

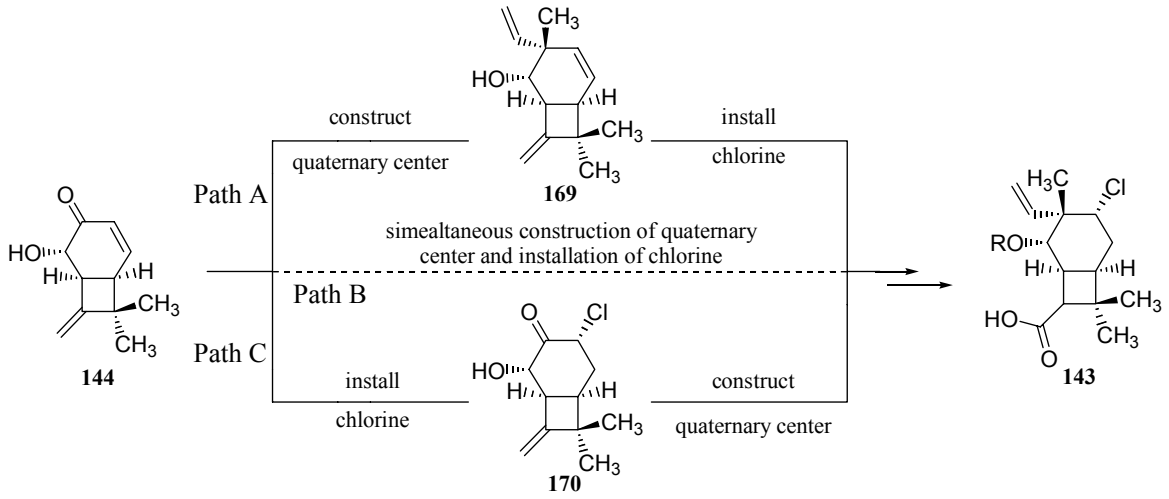


Alternatively, ketone **166**, which has been targeted as the immediate precursor to the vinyl isonitrile, also provides several options by which the C(15) hydrogen could be epimerized. Most obvious would be the conversion of this ketone to its α,β-unsaturated counterpart, which opens up several possibilities for obtaining the correct stereochemistry at C(15).

3.1.2 Initial Considerations for the Advancement of Ketone 144.

With ample quantities of ketone **144** in hand, efforts could focus on the transformation of this intermediate to a fully functionalized [4.2.0] system (i.e. **143**). Scheme 3.1.5 illustrates the three paths that were seen as options for the elaboration of **144**. Path A involves the initial construction of the quaternary center followed by the subsequent installation of the chlorine. Alternatively, Path C calls for these tasks to be reversed in the preliminary preparation of chloroketone **170**. Finally, Path B involves the simultaneous creation of the quaternary center and installation of chlorine moiety. A cautious, stepwise approach was first adopted and is outlined below.

Scheme 3.1.5



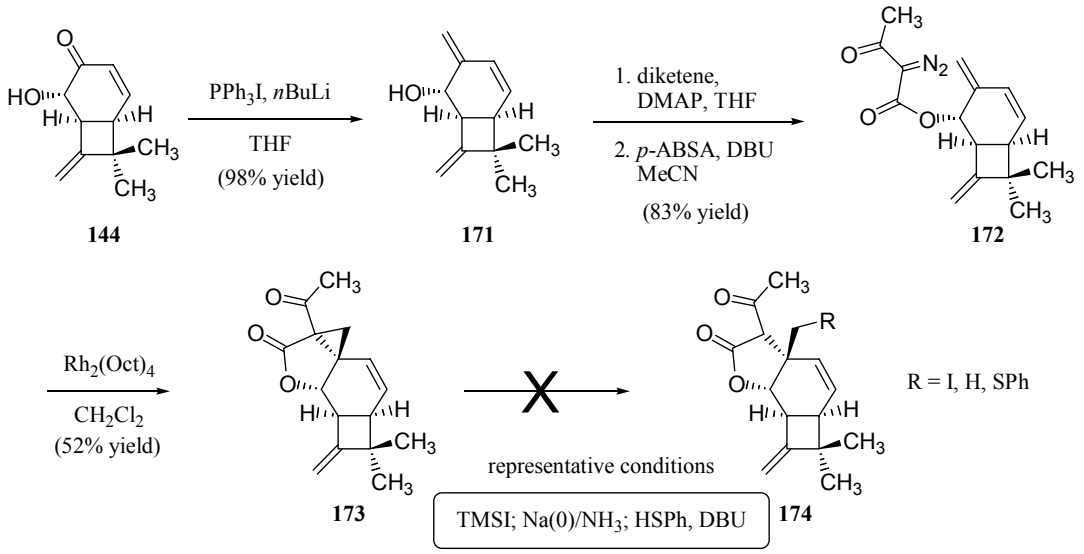
3.2 Approach I: Construction of the C(12) Quaternary Center via an Intramolecular Cyclopropanation.

Recent work has led to the development of a plethora of conditions suitable for cyclopropanating a range of olefins.[10] Accordingly, there are numerous methods

available for both the oxidative and reductive cleavage of activated cyclopropanes.[11] Hence, the first approach directed at the construction of the C(12) quaternary center involved an intramolecular cyclopropanation/ring-opening strategy to unmask the quaternary center.

Toward this end, a one-carbon homologation proceeded smoothly in the conversion of ketone **144** to triene **171** (Scheme 3.2.1). Acylation with diketene followed by diazotization of the resulting β-ketoester gave rise to diazo ketone **172**. Exposure of a thoroughly dried solution of **172** in CH_2Cl_2 to a catalytic amount of rhodium octanoate dimer [$Rh_2(oct)_4$] led to the formation of cyclopropane **173**. Unfortunately, attempts to unmask the quaternary center using both oxidative and reductive conditions proved inadequate. Hence, another strategy was needed for the advancement of ketone **144**.

Scheme 3.2.1

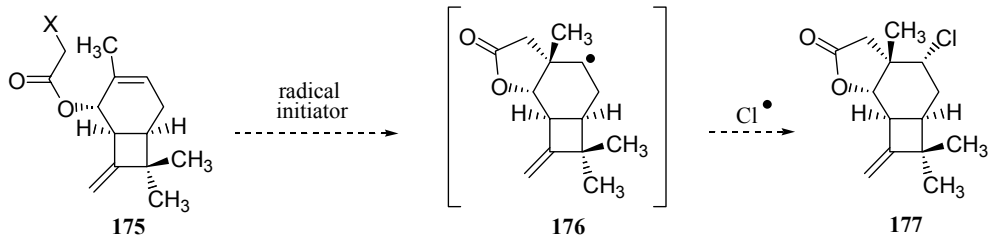


3.3 Approach II: Construction of the C(12) Quaternary Center via Radical Chemistry.

3.3.1 Tandem Installation of the Quaternary Center and Chlorine.

Unable to unmask the quaternary center contained in cyclopropane **173**, a revised strategy was needed. The next approach that was exploited called for the simultaneous construction of the quaternary center and installation of the hindered chlorine functionality (Scheme 3.3.1). To this end, α halo-ester **175** was targeted as a key intermediate. It was envisioned that upon treatment with a suitable radical initiator, **175** would undergo a 5-exo-trig cyclization resulting in the formation of a fleeting secondary radical (**176**), which could then be trapped by a source of Cl• to furnish lactone **177**.[12] Importantly, it was anticipated that Cl• would trap **177** from the convex face of the rigid [4.2.0] bicyclic system, thereby generating the required trans relationship between the chlorine and the adjacent methyl group.

Scheme 3.3.1



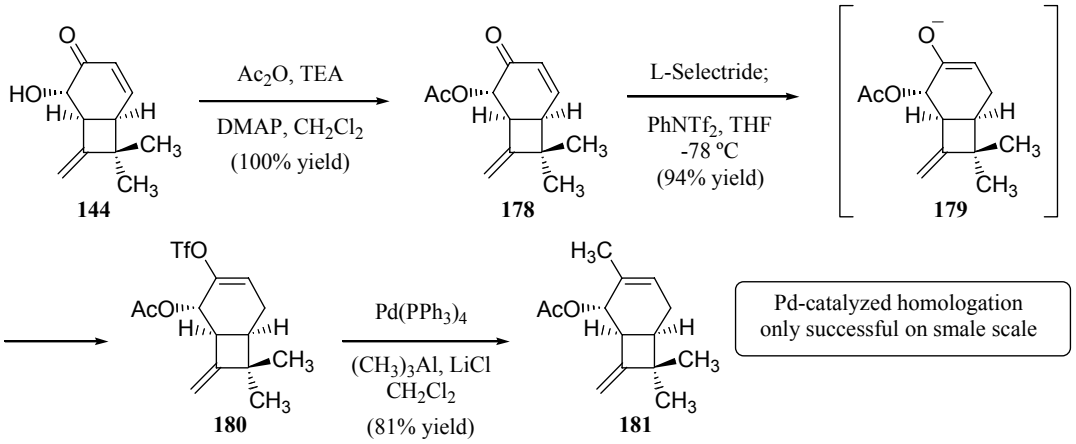
In considering methods for the conversion of **175** → **177**, the most obvious route would involve a radical transfer, wherein X = Cl. Indeed, the use of halogen atom transfers to mediate free-radical reactions has emerged as a powerful tool.[13-16] However,

the generality of this reaction is highly dependent on the halogen involved. In cases involving chlorine, the scope is much more limited, the reactions are less efficient, and the conditions are more forcing often requiring high pressures and temperatures in excess of 150 ºC.[17-23] In light of this, it was envisioned that the source of Cl• could derive from an external additive, as the trapping of transient radicals is not without precedence. Pioneering work by Stork demonstrated that carbon-centered radicals generated from 5-exo cyclizations could be trapped with numerous reagents, including activated olefins and cyano radicals.[24-26]

3.3.2 Construction of a Radical Cyclization Substrate.

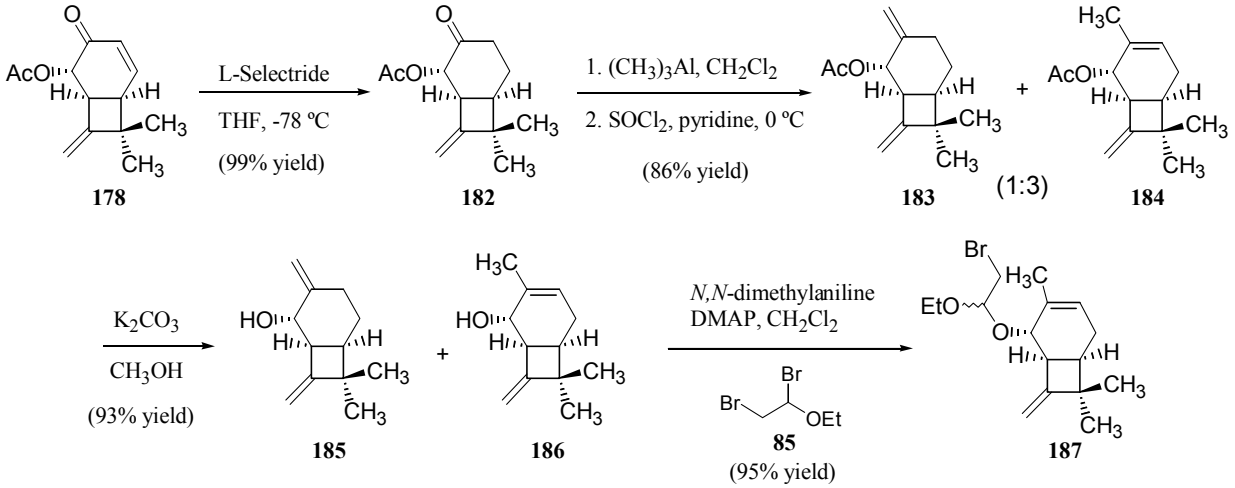
Turning next to the preparation of the requisite radical cyclization substrate (i.e., **175**), acylation of **144** proceeded smoothly to furnish ketone **178**. Following considerable experimentation, it was found that upon treatment with L-Selectride ketone **178** underwent a selective 1,4 reduction to furnish intermediate enolate **179**, upon exposure to *N*-phenyltriflimide this enolate was efficiently trapped as the corresponding enol triflate to furnish **180** in excellent yield (Scheme 3.3.2). The necessary one carbon homologation of triflate **180** to diene **181** could be achieved by treatment with trimethyl aluminum and a catalytic amount of Pd(0) in the presence of LiCl.[27] This reaction yielded admirable results on small scale (<50 mg), however attempts to effect this transformation on a larger scale led to diminished yields, requiring an alternative method for the construction of diene **181**.

Scheme 3.3.2



An alternative route to **181** was quickly found, and began with conjugate reduction of **178** to furnish ketone **182** (Scheme 3.3.3). Exposure of **182** to trimethyl aluminum provided a mixture of alcohols, which, upon exposure to thionyl chloride in pyridine, furnished a 1:3 mixture of olefins **183** and **184**. This inseparable mixture was advanced by hydrolysis of the acetate to afford a mixture of allylic alcohols **185** and **186** that could easily be separated by silica gel chromatography. The desired endocyclic olefin **186** was converted without incident to a diastereomeric mixture of α-bromoacetals **187**.

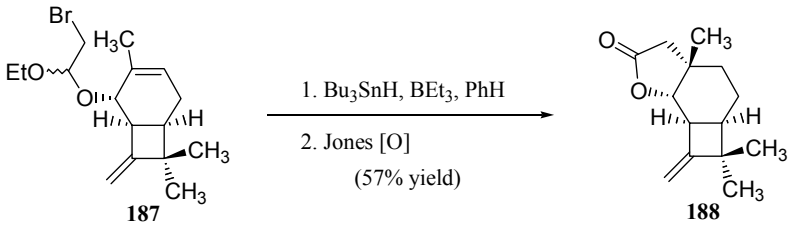
Scheme 3.3.3



3.3.3 Cyclization of Bromoacetals 187.

With ample quantities of **187** in hand, the pivotal radical cyclization/trapping sequence could be examined. Prior to screening additives that could act as a source of Cl•, the desired 5-exo-trig cyclization was first examined (Scheme 3.3.4). Encouragingly, exposure of **187** to standard radical initiating conditions led, after hydrolysis and oxidation, to lactone **188**.

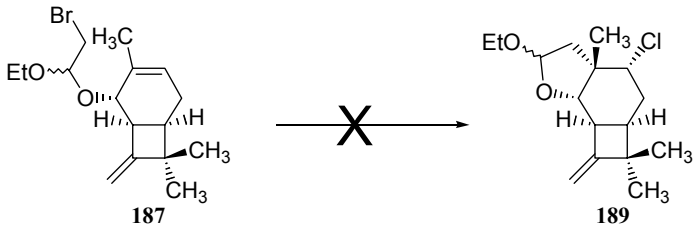
Scheme 3.3.4



Unfortunately, a suitable combination between a radical initiator (BEt_3, AIBN), propagator [$(Bu_3Sn)_2$, $(Ph_3Sn)_2$, Ph_3SnH], and additive (NCS, LiCl, CCl_4) which would

allow for the preparation of **189** could not be realized (Scheme 3.3.5). Presumably the inability to effect the conversion of **187** → **189** derives from an incompatibility between the additives and the radical propagator. While this strategy did not allow for the concurrent installation of both the quaternary center and installation of the chlorine, it demonstrated that the C(12) quaternary center could be fashioned using radical chemistry.

Scheme 3.3.5



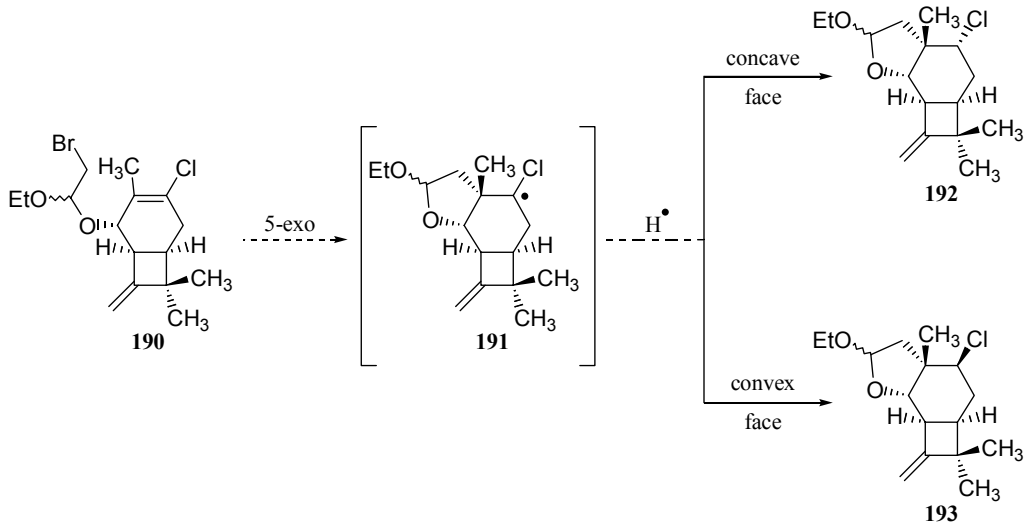
3.3.4 Cyclization of a Vinyl Chloride?

Forced to modify the approach, a stepwise route was again devised. The strategy adopted called for the preliminary installation of the chlorine with the construction of the quaternary center via a 5-exo-trig cyclization to follow (*vide infra*). In an effort to accommodate this strategy, vinyl chloride **190** was targeted.

In considering the cyclization of **190**, it was recognized that there were two possible stereochemical outcomes that could result from a 5-exo-trig cyclization (Scheme 3.3.6). Intermediate radical **191** could be quenched with H• from either the concave or convex face, only the former outcome generating the correct relative stereochemistry between the chlorine and the adjacent quaternary center. While there was uncertainty as to what the stereochemical outcome of such a reaction would be, the idea was intriguing.

A review of the literature revealed only three examples of intramolecular 5-exo-trig cyclizations into vinyl chlorides, each involving aryl or vinyl radicals.[28-30] There were no reports of the analogous reaction wherein the initial radical was aliphatic (i.e., **190**). Eager to investigate the feasibility of such a cyclization, focus quickly shifted to the installation of the chlorine.

Scheme 3.3.6

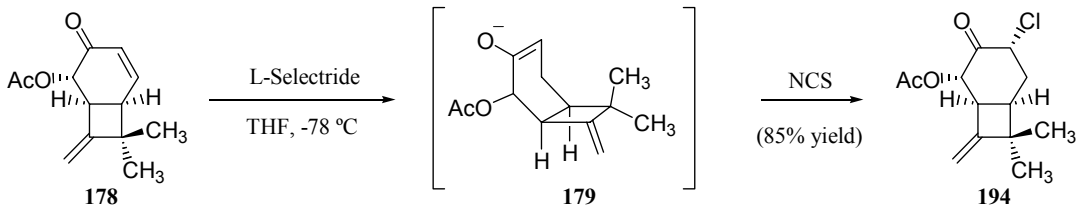


3.3.4.1 Installation of the Chlorine.

With the recognition that enolate **179** could selectively be generated upon 1,4 reduction of **178**, the opportunity to employ a similar strategy for the installation of the chlorine presented itself. The success of this approach hinged upon the selection of an appropriate electrophilic source of chlorine. Eventually, it was found that enolate **179**, generated upon conjugate reduction of **178** was effectively trapped when treated with several equivalents of *N*-chlorosuccinimide (NCS) at –78 °C (Scheme 3.3.7).

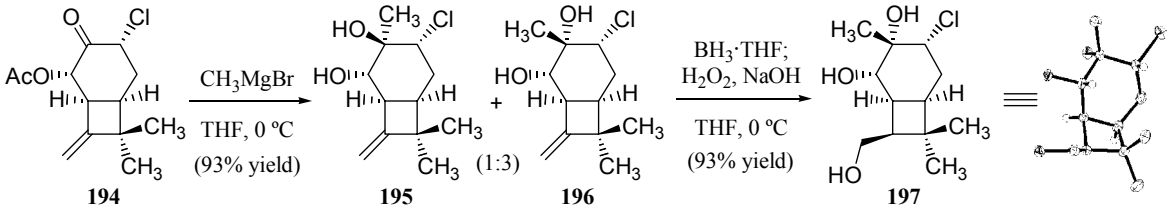
Rewardingly, this reaction proceeded with complete diastereoselectivity to yield chloroketone **194** exclusively.

Scheme 3.3.7



The relative stereochemistry of **194** was tentatively assigned as that illustrated in Scheme 3.3.8, as it was speculated that the trapping would proceed on the convex face of the [4.2.0] bicyclic system. This assignment was confirmed by the addition of methyl Grignard to provide diols **195** and **196** in a 1:3 ratio (Scheme 3.3.8). Interestingly, the major product resulted from addition to the more hindered concave face of the [4.2.0] system. These diastereomers were separated and the major diastereomer (**196**) was carried on via hydroboration/oxidation to deliver triol **197** as a crystalline solid. The relative stereochemistry was unambiguously determined by single crystal X-ray analysis of **197**, confirming that **179** was chlorinated exclusively on the convex face (see appendix 6 for the X-ray crystallographic data).

Scheme 3.3.8

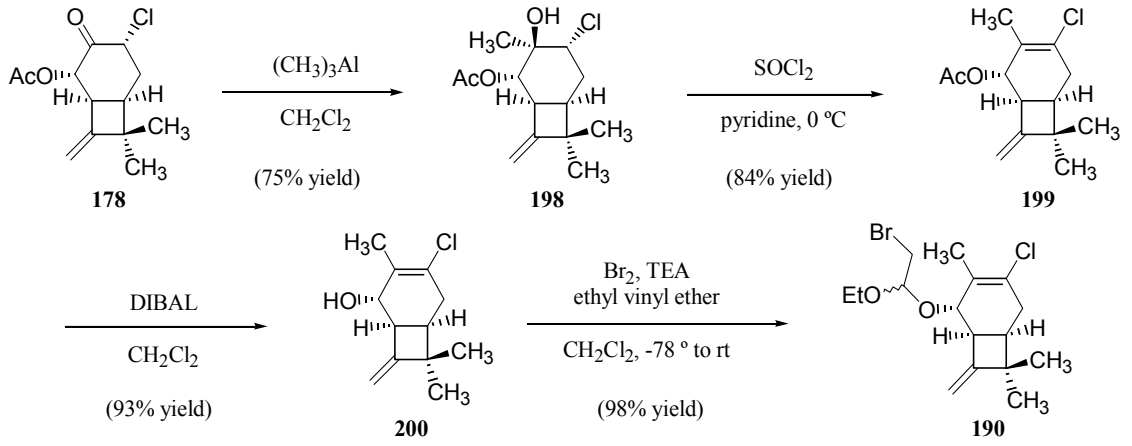


3.3.4.2 Preparation of Vinyl Chloride 190.

Excited by the ability to install the chlorine in an extremely efficient manner, it was imagined that vinyl chloride **190** could be rapidly accessed. Unexpectedly, chloroketone **194** proved somewhat difficult to advance. Both attempts to convert the ketone to the corresponding enol triflate and more direct procedures for the homologation of this ketone led only to extensive decomposition.[31] Fortunately, exposure of **178** to trimethylaluminum led to the formation of tertiary alcohol **198** in high yield and with good diastereoselectivity (Scheme 3.3.9).[32] In contrast to the case with methyl Grignard, addition of trimethylaluminum occurred exclusively from the convex face. Presumably, this discrepancy results from the Grignard addition initially removing the acetate (which is observed by TLC), thereby generating the corresponding alkoxide. This alkoxide could be associated with a solvated counterion, and this ion pair may exist as either monomeric or aggregate forms. In light of their size, the solvated counterion could block the *syn* approach of the Grignard reagent.[33]

Numerous dehydrating conditions were examined before it was found that exposure of a cooled solution of **198** in pyridine to thionyl chloride resulted in the exclusive formation of vinyl chloride **199**. Cleavage of the acetate provided the corresponding allylic alcohol (**200**), which was converted to bromoacetals **190**.

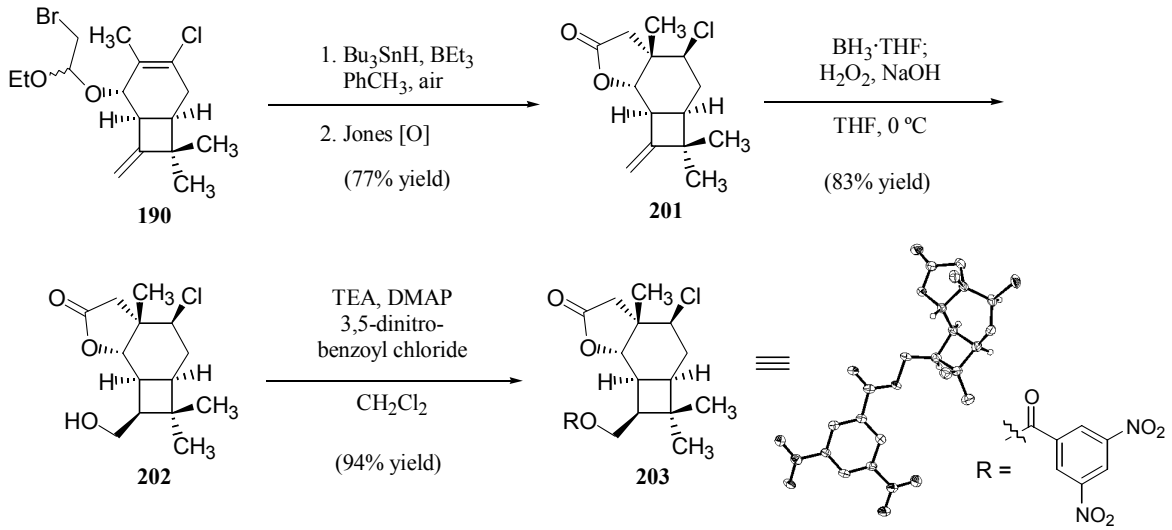
Scheme 3.3.9



3.3.4.3 Radical Cyclization of Vinyl Chloride 190.

Owing to the success observed in the cyclization of bromoacetals **187**, it was anticipated that **190** would behave in a similar fashion. Toward this end, treatment of **190** with BEt_3 and Bu_3SnH in the presence of a small amount of air led to the rapid formation of a mixture of products (Scheme 3.3.10). This mixture was subjected directly to oxidation Jones reagent thereby giving rise to lactone **201**. The relative stereochemistry of **201** was determined by hydroboration/oxidation of the exocyclic methylene to provide the corresponding alcohol (**202**). Derivatization of this alcohol gave rise to benzoate **203** for which an X-ray structure was obtained (see Appendix 6 for X-ray crystal data). An examination of the ORTEP shows two important points. First, it illustrates that 5-exo-trig cyclizations of aliphatic radicals into vinyl chlorides are indeed a viable mode of cyclization. Unfortunately, the ORTEP also reveals that the cyclization adduct contains the incorrect relative stereochemistry between the chlorine and the adjacent quaternary center. Thus, the intermediate radical generated following the 5-exo-trig cyclization was quenched with H• from convex face of the molecule.

Scheme 3.3.10



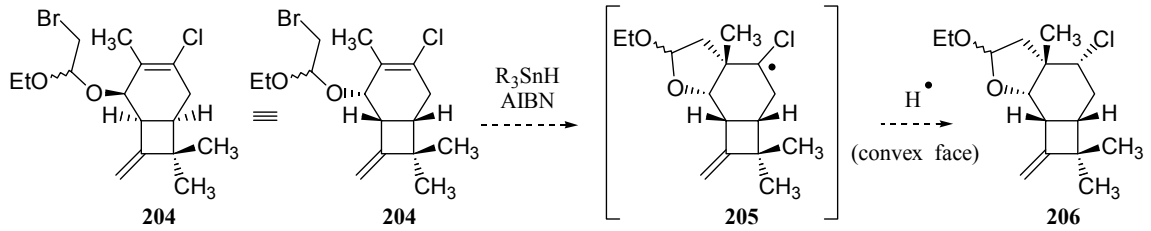
Attempts to alter the diastereoselectivity of this reaction and promote the formation of the desired adduct (**192**) by conducting the cyclization under a range of conditions were of no avail. Thus, the strategy required yet another modification.

3.3.4.4 Can Vinyl Chloride 190 be Tailored to Undergo a 5-exo-trig Cyclization?

While numerous alternative strategies quickly became apparent, we decided to first explore a route requiring only minor adjustments. Realizing that the stereochemistry of the allylic hydroxyl group controlled the facial selectivity of the radical cyclization, it was anticipated that inversion of this stereochemistry should lead to cyclization on the β-face (Scheme 3.3.11), followed by H• quenching from the convex face to provide **206**. The net result of this is the preparation of a [4.2.0] system containing the correct relative stereochemistry between chlorine and the adjacent quaternary center. This modification

seemed logical and could easily be tested, as it required only minor alterations in the synthetic sequence.

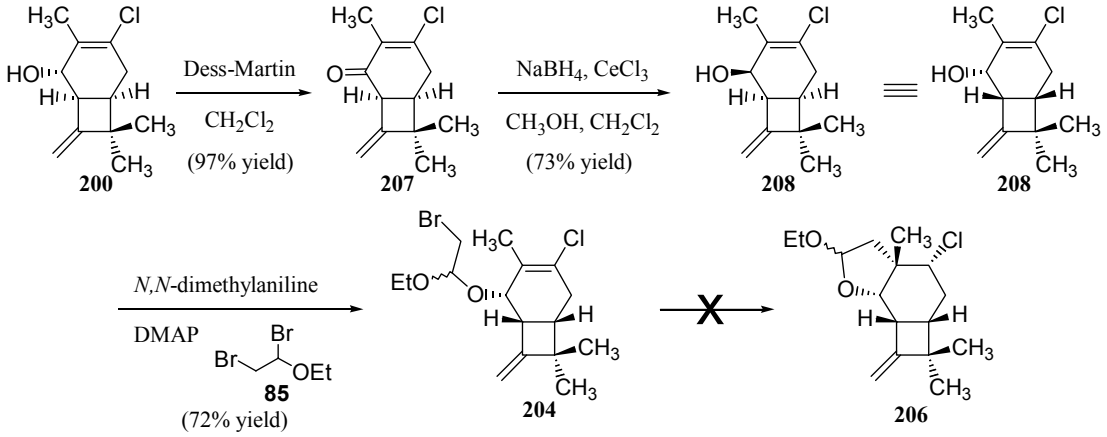
Scheme 3.3.11



3.3.4.5 Preparation of Modified Vinyl Chlorides.

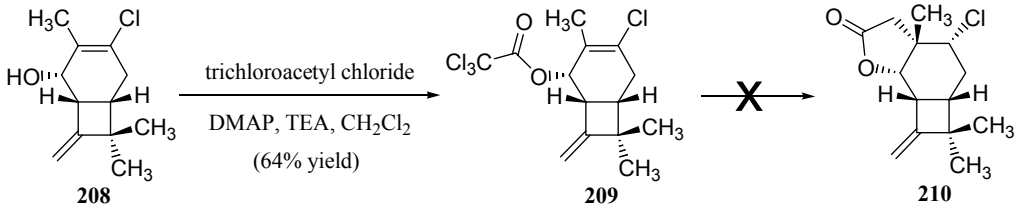
Mitsonobu chemistry proved inadequate for inverting the C(11) alcohol however, a two-step oxidation/reduction sequence was found to deliver alcohol **208** in excellent overall yield (Scheme 3.3.12). Conversion of **208** to **204** proceeded without incident. Surprisingly, the reactivity observed for bromoacetals **204** was in stark contrast to its C(11) epimer (**190**). Specifically, exposure of **204** to numerous radical initiators and propagators did not induce the desired 5-exo-trig cyclization, but rather led to a complex mixture of products. The underlying reasons for the disparity between the reactivity of bromoacetals **190** and **204** are unclear.

Scheme 3.3.12



In accord with the above approach, alcohol **208** was converted to trichloroacetate **209**, which also proved resistant to cyclization and only provided products resulting from reduction (Scheme 3.3.13). Unable to effect the cyclization of either **204** or **209**, another modification was required.

Scheme 3.3.13



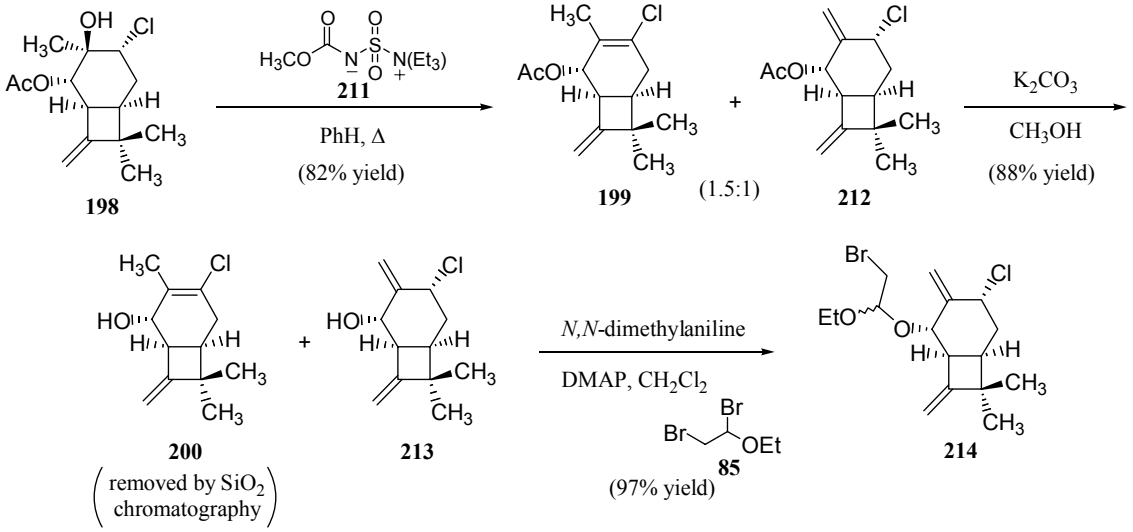
3.3.5 Preparation of an Exocyclic Olefin.

The ability to install the chlorine in a completely stereoselective manner (**178** → **194**) was the guiding factor in the selection of a new approach toward a fully elaborated [4.2.0] bicyclic system. In contrast to the previous approaches, a strategy was adopted which retained the stereochemistry set in the preparation of α-chloroketone **194**. This

approach called for the preparation of exocyclic methylene **214**, which, following a 5-exo-trig cyclization, would contain the much sought after trans relationship between the chlorine and the adjacent methyl group (*vide infra*).

As mentioned earlier, chloroketone **194** proved somewhat difficult to handle. In particular, the ketone proved resistant to methylenation under a barrage of conditions, thereby forcing us to explore the conversion of tertiary alcohol **198** to the desired exocyclic olefin (**212**). It was illustrated earlier (Scheme 3.3.9) that dehydration of **198** with thionyl chloride provided exclusively the endocyclic olefin (**199**). In an effort to redirect the course of this reaction, several dehydrating agents were screened. After considerable experimentation, the most promising results were observed when a refluxing solution of **198** was treated with several equivalents of Burgess's Reagent (**211**) (Scheme 3.3.14).[34] This reaction proceeded with good efficiency to provide an inseparable 1.5:1 mixture of olefins **199** and **212**, respectively. While the selectivity of this reaction was poor it did allow for the preparation of enough material to investigate the cyclization of interest. Hydrolysis of the acetate furnished alcohols **200** and **213**, which were separable by silica gel chromatography. Finally, the conversion of **213** to bromoacetals **214** proceeded smoothly.

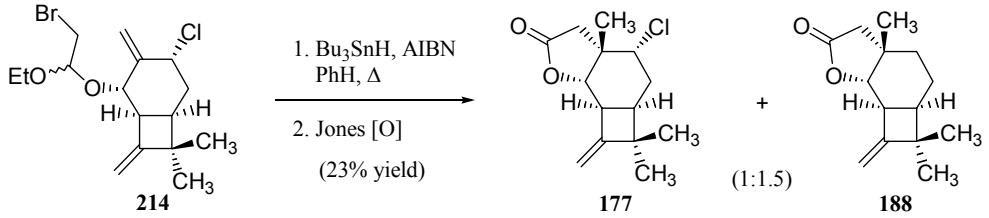
Scheme 3.3.14



3.3.5.1 Cyclization of exocyclic olefin 214.

Having gained access to bromoacetals **214**, an examination of the cyclization of interest could begin. In the event, exposure of **214** to Bu_3SnH and AIBN led to a complex mixture of products that, following exposure to Jones Reagent, gave rise to a mixture of lactones **177** and **188** in low yield (Scheme 3.3.15). Efforts to optimize this reaction by varying the radical initiator, solvent, temperature, and concentration proved fruitless.

Scheme 3.3.15



Hence, while this approach did enable for the construction of **177**, which contained the desired relative stereochemistry between the chlorine and the adjacent quaternary center, the low yield of the cyclization, in addition to the poor selectivity in the dehydration of **198**, forced further modifications to the strategy.

3.3.5.1 Conclusion.

A fully elaborated [4.2.0] bicyclic system, containing both the C(12) quaternary center and the adjacent chlorine was constructed. An efficient and selective method was developed for the installation of the chlorine (**178** → **194**). Chloroketone **194** could be elaborated to bromoacetals **190** in an efficient four-step sequence. Exposure of **190** to Bu_3SnH led to a novel 5-exo-trig cyclization into the vinyl chloride to furnish, after oxidation, **201**. Unfortunately, X-ray crystallography revealed that **201** contained the incorrect relative stereochemistry. In light of this, **194** was converted to exocyclic olefin **212** which following a 5-exo-trig cyclization and subsequent oxidation furnished **177**. While **177** represents a fully elaborated [4.2.0] bicyclic system, difficulties associated with the preparation of exocyclic olefin **212**, in addition to the low yield observed in the cyclization of **214**, forced further modifications.

3.5 Experimental Section.

3.5.1 Materials and Methods.

Unless otherwise stated, all reactions were conducted in flame-dried glassware under a positive pressure of nitrogen using freshly distilled solvents. Tetrahydrofuran (THF), diethyl ether (Et_2O), and dioxane were distilled from sodium metal/benzophenone ketyl. Methylene chloride (CH_2Cl_2), benzene, pentane, pyridine, and triethylamine (TEA) were distilled from calcium hydride. Carbon tetrachloride (CCl_4), 1,2-dichloroethane, titanium tetrachloride ($TiCl_4$), dimethylformamide (DMF), and BF_3•OEt_2 were purchased from the Aldrich Chemical Co. in Sure/Seal™ containers and were used without further purification.

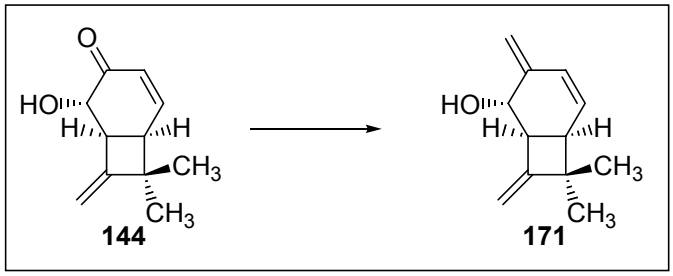
All reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F254 pre-coated plates (0.25-mm). Preparative TLC was also performed using E. Merck silica gel 60 F254 pre-coated plates (0.25-mm). Column and/or flash chromatography was performed with the indicated solvents using silica gel (particle size 0.032-0.063 mm) purchased from Fisher Scientific. Chromatography was performed using the procedures reported by Still.[35]

Melting points were obtained on a Gallenkamp variable temperature melting apparatus (model: MPD350.BM2.1) and are uncorrected. Infrared spectrum (IR) were recorded on a Midac M-1200 FTIR. ^{1}H and ^{13}C spectra were recorded on a Bruker AM-500 or Bruker Advance 400 spectrometers. Chemical shifts are reported relative to chloroform (^{1}H, δ 7.27; ^{13}C, δ 77.0 ppm) or benzene (^{1}H, δ 7.16; ^{13}C, δ 128 ppm). High

resolution mass spectra were performed at The University of Illinois Mass Spectrometry Center. Single-Crystal X-ray analyses were performed by Susan DeGala of Yale University.

3.5.2 Preparative Procedures:

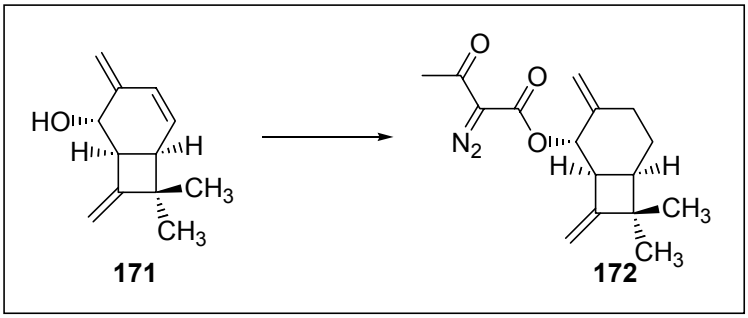
Preparation of Triene 171.



Triene 171. The ylide derived from triphenylphosphonium bromide was prepared by adding *n*-BuLi (2.3 M in hexanes, 6.77 mL, 3.0 eq.) to a suspension of trimethylphosphonium bromide (5.57 g, 15.59 mmol, 3.0 eq.) in THF (45 mL) at 0 °C. The suspension was allowed to stir for 15 minutes during which time it turned to a deep orange solution. The solution was maintained at 0 °C while ketone **144** (925 mg, 5.20 mmol, 1.0 eq.) was added as a solution in THF (15 mL). Stirring was continued for 15 minutes before it was quenched with saturated NH_4Cl (250 mL). The aqueous layer was extracted with EtOAc (2 x 50 mL), washed with brine, dried over Na_2SO_4, and concentrated *in vacou*. The derived oil was purified by silica gel chromatography (50% EtOAc/hexanes) to provide triene **171** (900 mg, 98% yield) as a colorless oil. FTIR (thin film/NaCl) 3369 (bs), 1652 (w), 1556 (w), 1456 (w), 1010 (m), 913 (s), 744 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.23 (d, J = 10.1 Hz, 1H), 5.84 (dd, J = 4.5, 9.9 Hz, 1H), 5.08

(s, 1H), 5.05 (s, 1H), 4.78 (d, J = 2.8 Hz, 1H), 4.73 (d, J = 2.6 Hz, 1H), 4.41 (bs, 1H), 3.59-3.57 (m, 1H), 2.66 (dd, J = 4.5, 8.0 Hz, 1H), 1.53 (bs, 1H), 1.33 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 142.9, 130.2, 126.4, 115.2, 103.1, 69.9, 47.5, 44.1, 40.2, 29.0, 21.9; HRMS (EI) *m/z* 176.1205 [cacl'd for $C_{12}H_{16}O$ (M+) 176.1201].

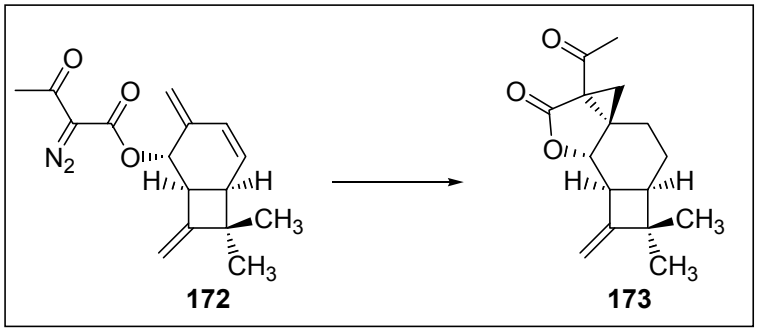
Preparation of Diazo ketone 172.



Diazo ketone 172. Diketene (64 μL, 0.83 mmol, 1.2 eq.) and DMAP (21 mg, 0.17 mmol, 0.25 eq.) were sequentially added to a solution of alcohol **171** (122 mg, 0.69 mmol, 1.0 eq.) in THF (8 mL) that was cooled to 0 °C. The resulting solution was stirred at 0 °C for 5 minutes then allowed to warm to room temperature where it was stirred for an additional 10 minutes. Concentration provided a residue that was carried to the next step without further purification. To a solution of the derived ester in CH_3CN (7 mL) was added *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) (200 mg, 0.83 mmol, 1.2 eq.) to furnish a colorless solution. DBU (124 μL, 0.83 mmol, 1.2 eq.) was added, which resulted in the immediate formation of a bright yellow solution. Concentration, and absorption onto silica gel was followed by purification on silica gel (25% EtOAc/hexanes eluent) to afford diazo ketone **172** (165 mg, 83% overall yield) as a yellow crystalline solid. m.p. 42-44 °C; FTIR (thin film/NaCl) 2960 (w), 2140 (s), 1711 (s), 1659 (s), 1327

(s), 1297 (m), 1150 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.20 (d, *J* = 10.3 Hz, 1H), 5.83 (dd, *J* = 4.3, 10.3 Hz, 1H), 5.71 (d, *J* = 2.8 Hz, 1H), 5.20 (s, 2H), 4.84 (d, *J* = 2.9 Hz, 1H), 4.81 (d, *J* = 2.5 Hz, 1H), 3.65-3.63 (m, 1H), 2.61 (dd, *J* = 4.4, 7.7 Hz, 1H), 2.46 (s, 3H), 1.33 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.2, 161.2, 156.4, 137.6, 130.1, 126.9, 118.7, 104.3, 72.5, 48.0, 42.1, 40.1, 29.0, 28.4, 22.0; HRMS (EI) *m/z* 287.1407 [cacl'd for $C_{16}H_{18}N_2O_3$ (M+H) 287.1396].

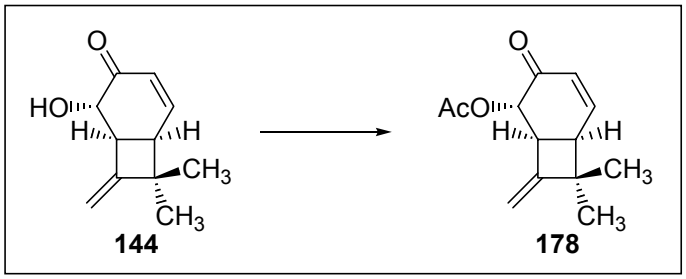
Preparation of Cyclopropane 173.



Cyclopropane 173. A solution of diazo ketone **172** (600 mg, 2.09 mmol, 1.0 eq.) in CH_2Cl_2 (60 mL) was stirred with 4 Å molecular sieves (~ 5 g) for 3 hours before $Rh_2(Oct)_4$ (~ 10 mg) was added, which resulted in the rapid evolution of nitrogen. Stirring was continued for 30 minutes before the reaction was absorbed onto silica gel and purified by flash chromatography (20% EtOAc/hexanes eluent) to deliver cyclopropane **173** (280 mg, 52% yield) as a pale yellow oil. FTIR (thin film/NaCl) 2956 (m), 2927 (w), 1762 (s), 1696 (m), 1361 (m), 997 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.03 (dd, *J* = 3.5, 10.2 Hz, 1H), 5.59 (dd, *J* = 2.6, 10.1 Hz, 1H), 4.98 (d, *J* = 2.0 Hz, 1H), 4.92 (d, *J* = 2.9 Hz, 1H), 4.52 (d, *J* = 4.2 Hz, 1H), 3.27-3.24 (m, 1H), 2.81 (dt, *J* = 2.8, 9.5 Hz, 1H), 2.44 (s, 3H), 2.40 (d, *J* = 4.4 Hz, 1H), 1.68 (d, *J* = 4.5 Hz, 1H), 1.28 (s,

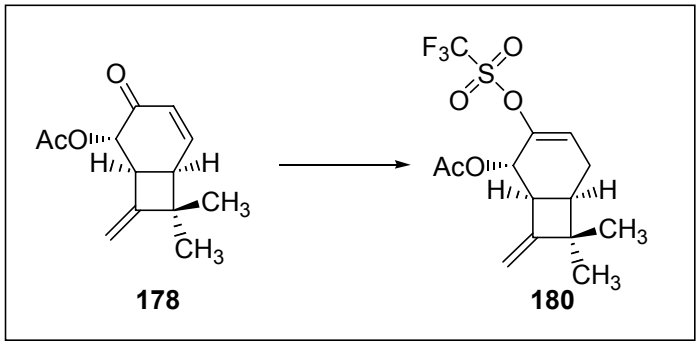
3H), 1.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5, 172.6, 158.5, 132.2, 122.3, 104.9, 80.3, 46.6, 44.7, 42.7, 42.3, 42.0, 29.8, 28.2, 27.6, 2.3.0; HRMS (EI) *m/z* 258.1248 [cacl'd for $C_{16}H_{18}O_3$ (M+) 258.1256]

Preparation of Acetate 178.



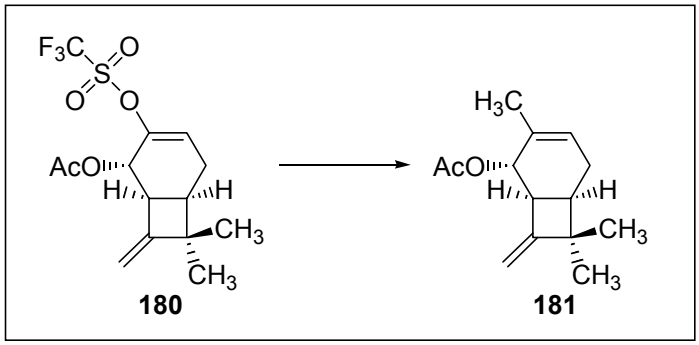
Acetate 178. Acetic anhydride (930 μL, 9.27 mmol, 1.1 eq.), TEA (1.30 mL, 9.27 mmol, 1.1 eq.), and DMAP (103 mg, 0.84 mmol, 0.1 eq.) were added to a solution of alcohol **144** (1.85 g, 8.42 mmol, 1.0 eq.) in CH_2Cl_2 (70 mL) at room temperature. Stirring continued for 2 hours before the solvent was removed *in vacuo* and the derived residue was chromatographed (25% EtOAc/hexanes eluent) to provide acetate **178** (1.85 g, 100% yield) as a light yellow solid. m.p. 68-69.5 °C; FTIR (thin film/NaCl) 2966 (m), 2925 (w), 1744 (s), 1682 (s), 1365 (m), 1225 (s), 1027 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 (dd, J = 3.9, 10.3 Hz, 1H), 6.20 (d, J = 10.1 Hz, 1H), 5.30 (d, J = 4.2 Hz, 1H), 4.98 (s, 1H), 4.92 (s, 1H), 3.66-3.64 (m, 1H), 2.91-2.89 (m, 1H), 2.11 (s, 3H), 1.39 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.7, 169.8, 154.8, 148.8, 128.3, 106.2, 72.6, 48.6, 41.9, 41.6, 28.5, 22.6, 20.9; HRMS (EI) *m/z* 220.1092 [cacl'd for $C_{13}H_{16}O_3$ (M+) 220.1099]

Preparation of Enol triflate 180.



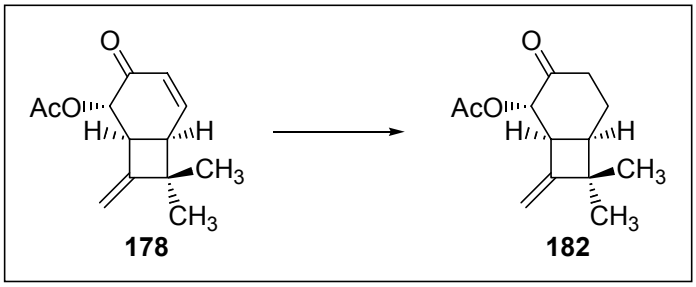
Enol triflate 180. To a solution of L-selectride (9.25 mL, 1.0 M in THF, 1.1 eq.) in THF (60 mL) at –78 ºC was added a solution of ketone **178** (1.85 g, 8.41 mmol, 1.0 eq.) in THF (25 mL) over 10 minutes. The reaction was maintained at this temperature until TLC indicated the complete consumption of starting material, at which point $PhNTf_2$ (3.30 g, 9.25 mmol, 1.1 eq.) was added in one portion as a solid. The resulting suspension was allowed to warm to 0 ºC over 10 minutes, and then stir at this temperature for 1 hour before being quenched with saturated $NaHCO_3$ (200 mL). The aqueous layer was extracted with Et_2O (2 x 150 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The derived residue was purified by column chromatography (0-10% EtOAc/hexanes eluent) to deliver enol triflate **180** (2.80 g, 94% yield) as a colorless oil. FTIR (thin film/NaCl) 2959 (m), 1743 (s), 1419 (s), 1221 (s), 1139 (s), 1061 (m), 874 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.14 (dd, *J* = 2.4, 6.8 Hz, 1H), 5.42 (d, *J* = 1.2 Hz, 1H), 4.94 (d, *J* = 1.8 Hz, 1H), 4.89 (dd, *J* = 1.0, 2.8 Hz, 1H), 3.58-3.56 (m, 1H), 2.57 (dq, *J* = 3.1, 8.5 Hz, 1H), 2.43-2.36 (m, 2H), 2.09 (s, 3H), 1.21 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 156.9, 146.2, 123.7, 117.8 (q, *J* = 319 Hz), 104.3, 68.9, 53.2 44.1, 36.9, 29.9, 22.6, 21.5, 20.9; HRMS (EI) *m/z* 355.0817 [cacl'd for $C_{14}H_{17}F_3O_5S$ (M+H) 355.0827].

Preparation of Diene 181.



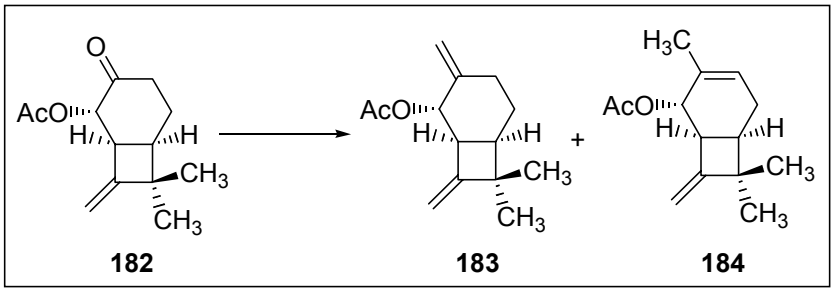
Diene 181. To a suspension of enol triflate **180** (35 mg, 0.099 mmol, 1.0 eq.), $Pd(PPh_3)_4$ (11.0 mg, 0.001 mmol, 0.10 eq.), and LiCl (4.0 mg, 0.099 mmol, 1.0 eq.) in THF (2 mL) at room temperature was added a freshly prepared solution of $(CH_3)_3Al$ (99 μL, 2 M in THF, 2.0 eq.) dropwise over 1 minute. The reaction was allowed to stir at ambient temperature for 24 hours before being cooled to 0 ºC and carefully quenched with saturated $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organic layers were dried washed with brine, dried over Na_2SO_4, and absorbed onto silica gel. Purification by flash chromatography (5% EtOAc/hexanes eluent) provided diene **181** (17 mg, 81% yield) as a colorless oil. FTIR (thin film/NaCl) 2950 (m), 2932 (m), 1735 (s), 1361 (w), 1237 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.75 (dd, *J* = 2.0, 4.0 Hz, 1H), 5.19 (d, *J* = 2.5 Hz, 1H), 4.77 (d, *J* = 2.0 Hz, 1H), 4.74 (d, *J* = 3.0 Hz, 1H), 3.46-3.43 (m, 1H), 2.31-2.27 (m, 2H), 2.13-2.09 (m, 1H), 2.05 (s, 3H), 1.74 (bs, 3H), 1.18 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 159.8, 133.2, 126.6, 102.1, 72.0, 43.8, 42.4, 37.4, 30.3, 22.7, 22.6, 21.4, 21.2; HRMS (EI) *m/z* 220.1464 [cacl'd for $C_{14}H_{20}O_2$ (M+) 220.1463].

Preparation of Ketone 182.



Ketone 182. A solution of ketone **178** (250 mg, 1.13 mmol, 1.0 eq.) in THF (15 mL) at -78 °C was treated dropwise with a solution of L-Selectride (1.30 mL, 1.0 M in THF, 1.15 eq.). TLC indicated completion of the reaction in 10 minutes, at which point the reaction was diluted with Et_2O (15 mL) and quenched with the addition of saturated $NaHCO_3$ (25 mL). Separation of the layers and extraction of the aqueous layer with Et_2O (2 x 15 mL) was followed by washing with brine and drying over Na_2SO_4. Absorption onto silica gel and purification via flash chromatography (30% EtOAc/hexanes eluent) provided ketone **182** (250 mg, 99% yield) as a white solid. m.p. 64-66 °C; FTIR (thin film/NaCl) 2956 (m), 1747 (s), 1728 (s), 1368 (w), 1236 (m), 1054 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.46 (d, *J* = 9.3 Hz, 1H), 4.90 (t, *J* = 3.1 Hz, 2H), 3.25 (dt, *J* = 2.2, 9.5 Hz, 1H), 2.62 (ddd, *J* = 2.3, 4.6, 19.2 Hz, 1H), 2.32-2.23 (m, 2H), 2.19 (s, 3H), 2.16 (dq, *J* = 4.7, 13.4 Hz, 1H), 1.89-1.84 (m, 1H), 1.27 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7, 169.9, 160.0, 104.6, 79.9, 44.8, 41.3, 40.7, 37.3, 29.3, 21.4, 20.6, 20.1; HRMS (EI) *m/z* 222.1261 [cacl'd for $C_{13}H_{18}O_3$ (M+) 222.1256].

Preparation of Dienes 183 and 184.



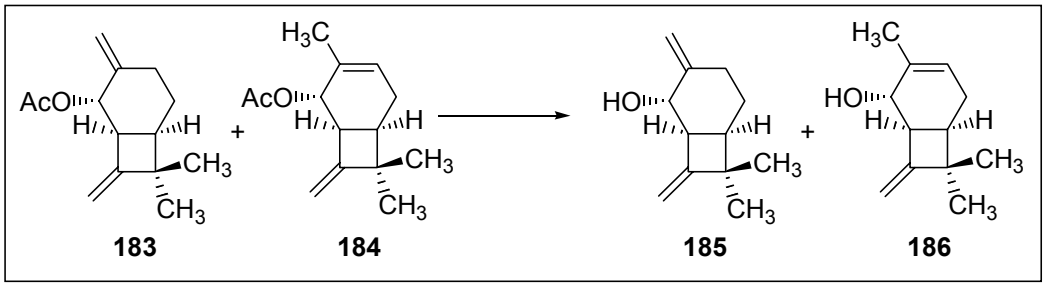
Dienes 183 and 184. To a solution of ketone **182** (500 mg, 2.2 mmol, 1.0 eq) in CH_2Cl_2 (22 mL) at room temperature was added a solution of $(CH_3)_3Al$ (3.3 mL, 1.0 M in toluene, 1.5 eq.) and the solution that resulted was allowed to stir for 5 hour. The reaction was then quenched by being cooled to 0 ºC and treated slowly (CAUTION!) with 1 N HCl (50 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to provide 500 mg of a yellow oil. This oil was carried on without further purification. A solution of the derived alcohol (500 mg, 2.12 mmol, 1.0 eq.) in pyridine (10 mL) was cooled to 0 °C and treated with thionyl chloride (309 μL, 4.24 mmol, 2.0 eq.) which resulted in the immediate formation of a yellow precipitate. After stirring for 15 minutes at 0 °C the reaction mixture was allowed to warm to room temperature and stir for 1 hour before being quenched with 1 N HCl (200 mL). The aqueous layer was extracted with EtOAc (100 mL), washed with brine, and dried over Na_2SO_4. Concentration *in vacuo* provided a residue that was subjected to silica gel chromatography (5-10% EtOAc/hexanes eluent) to furnish an inseparable 3:1 mixture of olefins **184** and **183** (400 mg, 86% yield) as a colorless oil. A characterization quality spectrum was obtained for each of the isomers following hydrolysis of the acetate

(K_2CO_3, CH_3OH), separation of the isomers (20% EtOAc/hexanes eluent) and reacetylation (Ac_2O, TEA, CH_2Cl_2) to furnish analytically pure compounds.

Diene 183: Exocyclic olefin **183** was obtained as a colorless oil. FTIR (thin film/NaCl) 2950 (m), 2932 (m), 1735 (s), 1361 (w), 1237 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.75 (dd, *J* = 2.0, 4.0 Hz, 1H), 5.19 (d, *J* = 2.5 Hz, 1H), 4.77 (d, *J* = 2.0 Hz, 1H), 4.74 (d, *J* = 3.0 Hz, 1H), 3.46-3.43 (m, 1H), 2.31-2.27 (m, 2H), 2.13-2.09 (m, 1H), 2.05 (s, 3H), 1.74 (bs, 3H), 1.18 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 159.8, 133.2, 126.6, 102.1, 72.0, 43.8, 42.4, 37.4, 30.3, 22.7, 22.6, 21.4, 21.2; HRMS (EI) *m/z* 220.1464 [cacl'd for $C_{14}H_{20}O_2$ (M+) 220.1463].

Diene 184: Endocyclic olefin **184** was obtained as a colorless oil. FTIR (thin film/NaCl) 2935 (m), 1737 (s), 1366 (w), 1233 (s), 911 (m), 743 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.48 (d, *J* = 5.0 Hz, 1H), 4.94 (t, *J* = 1.3 Hz, 1H), 4.91 (t, *J* = 1.4 Hz, 1H), 4.79 (d, *J* = 2.3 Hz, 2H), 3.23-3.20 (m, 1H), 2.40-2.24 (m, 2H), 2.14 (dq, *J* = 6.7, 9.5 Hz, 1H), 2.09 (s, 3H), 1.78-1.56 (m, 2H), 1.24 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 158.9, 143.8, 111.3, 102.5, 74.1, 45.2, 44.5, 40.0, 29.2, 28.5, 22.9, 21.4, 20.9; HRMS (EI) *m/z* 220.1454 [cacl'd for $C_{14}H_{20}O_2$ (M+) 220.1463].

Preparation of Alcohols 185 and 186.

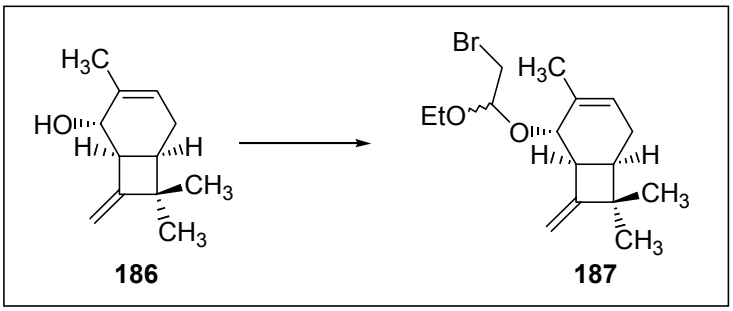


Alcohols 185 and 186. A mixture of acetates **183** and **184** (400 mg, 1.82 mmol, 1.0 eq.) was dissolved in CH_3OH (15 mL) and treated with K_2CO_3 (754 mg, 5.45 mmol, 3.0 eq.). The suspension was stirred at room temperature overnight before being quenched with saturated NH_4Cl (50 mL). The organic layer was removed in vacuo and the remaining aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to furnish an oil. This oil was purified by flash chromatography (20% EtOAc/hexanes eluent) to provide two products.

Alcohol 185: The first compound to elute was exocyclic alcohol **185** (75 mg, 23% yield) as a colorless oil. FTIR (thin film/NaCl) 3339 (s), 2931 (s), 1670 (m), 1440 (w), 881 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.01 (t, *J* = 1.8 Hz, 1H), 4.87 (t, *J* = 1.8 Hz, 1H), 4.84 (d, *J* = 2.2 Hz, 1H), 4.78 (d, *J* = 3.0 Hz, 1H), 4.35 (d, *J* = 5.3 Hz, 1H), 3.08 (ddd, *J* = 2.8, 5.2, 11.6 Hz, 1H), 2.40-2.31 (m, 2H), 2.16 (dq, *J* = 6.8, 10.2 Hz, 1H), 1.73-1.55 (m, 2H), 1.24 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.6, 148.8, 108.7, 102.0, 72.8, 47.0, 45.1, 40.4, 29.3, 28.4, 22.5, 21.1; HRMS (EI) *m/z* 178.1349 [cacl'd for $C_{12}H_{18}O$ (M+) 178.1358].

Alcohol 186: The second compound to elute was endocyclic olefin **186** (225 mg, 70% yield) was also isolated as a colorless oil. FTIR (thin film/NaCl) 3310 (bs), 2949 (s), 2927 (s), 1667 (m), 1444 (m), 999 (s), 873 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.61 (t, *J* = 2.5 Hz, 1H), 4.68 (d, *J* = 2.5 Hz, 1H), 4.65 (d, *J* = 2.5 Hz, 1H), 4.03 (d, *J* = 3.0 Hz, 1H), 3.44-3.41(m, 1H), 2.34-2.25 (m, 2H), 2.09 (dd, *J* = 6.0, 15.5 Hz, 1H), 1.78 (bs, 3H), 1.18 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.1, 136.8, 123.8, 101.1, 70.4, 45.1, 43.5, 37.6, 30.4, 22.7, 22.6, 21.1; HRMS (EI) *m/z* 178.1360 [cacl'd for $C_{12}H_{18}O$ (M+) 178.1358].

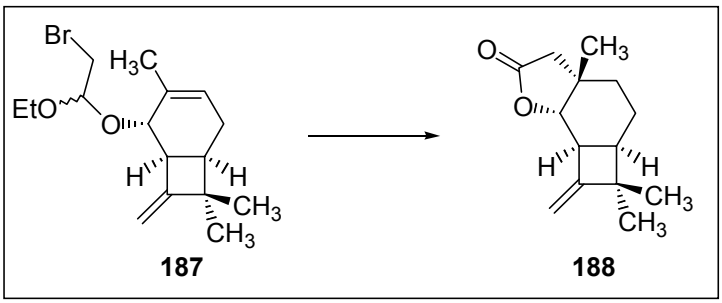
Preparation of Bromoacetals 187.



Bromoacetals 187. To a solution of alcohol **186** (40 mg, 0.22 mmol, 1.0 eq.) in CH_2Cl_2 (2 mL) at room temperature was added bromide **85** (260 mg, 1.12 mmol, 5.0 eq.), *N,N*-dimethylaniline (285 μL, 2.25 mmol, 10.0 eq.), and DMAP (3 mg, 0.02 mmol, 0.1 eq.). After stirring for 10 minutes the solution was diluted with CH_2Cl_2 (15 mL) and washed with 2 N HCl (3 x 15 mL), $NaHCO_3$ (10 ml), and brine. Concentration furnished an oil that was purified by silica gel chromatography (2.5% EtOAc/hexanes eluent) to provide bromoacetals **187** (70 mg, 95% yield) as a colorless oil. FTIR (thin film/NaCl) 2973 (w), 2927 (s), 1667 (m), 1432 (m), 1110 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ

5.74-5.71 (m, 2H), 4.81 (t, J = 5.5 Hz, 1H), 4.74 (t, J = 5.3 Hz, 1H), 4.69 (dd, J = 2.8, 6.4 Hz, 2H), 4.55 (t, J = 2.7 Hz, 2H), 4.02 (d, J = 2.6 Hz, 1H), 4.00 (d, J = 2.7 Hz, 1H), 3.69-3.55 (m, 6H), 3.42-3.34 (m, 4H), 2.35-2.30 (m, 4H), 2.09-2.05 (m, 2H), 1.72 (bs, 6H), 1.28-1.23 (m, 6H), 1.19 (s, 3H), 1.18 (s, 3H), 0.96 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 160.6, 134.4, 134.3, 126.1, 125.7, 101.2, 101.1, 100.6, 99.8, 75.8, 75.4, 61.2, 60.7, 44.7, 44.6, 43.7, 43.3, 43.3, 41.8, 38.0, 37.9, 32.3, 32.2, 30.5, 30.4, 24.0, 23.9, 22.9, 22.8, 15.4, 15.4; HRMS (EI) *m/z* 328.1031 [cacl'd for $C_{16}H_{25}BrO$ (M+) 328.1038].

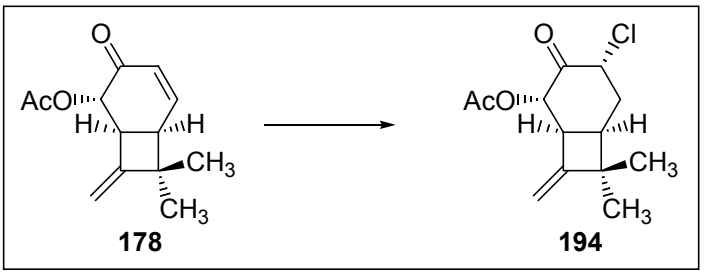
Preparation of Lactone 188.



Lactone 188. To a solution of bromoacetals **187** (40 mg, 0.12 mmol, 1.0 eq.) in benzene (4 mL) at room temperature was added Bu_3SnH (48 μL, 0.18 mmol, 1.5 eq.). To this colorless solution was then introduced BEt_3 (360 μL, 1 M in hexanes, 3.0 eq.) over a 30 second period. Stirring was continued for one minute before a small amount of air (1 mL) was introduced into the reaction mixture via syringe. The resulting solution was then allowed to stir at room temperature for 10 minutes at which point TLC indicated the complete consumption of starting material. The solution was concentrated to provide a colorless oil. This oil was taken up in acetone (4 mL) and cooled to 0 ºC. The solution was then treated with Jones reagent (1 mL) and slowly allowed to warm to room

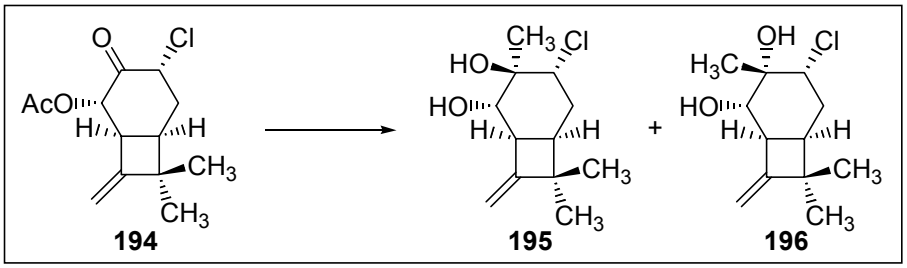
temperature. Stirring was continued for 2 hours before the reaction was quenched with isopropyl alcohol (1 mL). The reaction was allowed to stir for 10 minutes, during which time the reddish-orange dissipated to a dark green suspension. The reaction mixture was cooled to 0 ºC and treated with saturated $NaHCO_3$ (10 mL) and EtOAc (25 mL). The whole was then poured into a separatory flask containing saturated $NaHCO_3$ (200 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 25 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. Concentration *in vacuo* and purification of the resulting residue by silica gel chromatography (10% EtOAc/hexanes) furnished lactone **188** (17 mg, 57% yield) as a white solid. m.p. 73-75 °C; FTIR (thin film/NaCl) 2961 (m), 2924 (w), 1778 (s), 1172 (w), 1010 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.82 (d, J = 3.1 Hz, 1H), 4.78 (d, J = 2.4 Hz, 1H), 4.40 (d, J = 1.2 Hz, 1H), 3.55-3.53 (m, 1H), 2.49 (d, J = 17.4 Hz, 1H), 2.39-2.34 (d, J = 17.1 Hz, 1H), 2.14 (dd, J = 17.6 Hz, 1H), 1.65-1.31 (m, 4H), 1.26 (s, 3H), 1.23 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.3, 159.1, 101.7, 83.7, 45.4, 45.3, 40.3, 38.8, 37.5, 31.4, 28.8, 24.9, 20.7, 18.9; HRMS (EI) *m/z* 220.1462 [cacl'd for $C_{14}H_{20}O_2$ (M+) 220.1463].

Preparation of Chloroketone 194.



Chloroketone 194. A solution of L-Selectride (1.0 M in THF, 9.9 mL, 1.1 eq.) in THF (20 mL) was cooled to –78 °C, at which point ketone **178** (2.0 g, 9.09 mmol, 1.0 eq.) was added as a solution in THF (20 mL). Upon the disappearance of starting material, as visualized by TLC, a solution of NCS (8.46 g, 63.64 mmol, 7.0 eq.) in THF (10 mL) was added. The resulting suspension was stirred for 10 minutes before being diluted Et_2O (300 mL) and quenched with saturated $NaHCO_3$ (300 mL). Separation of the layers and extraction of the aqueous layer with Et_2O (200 mL) followed by washing with brine, drying over $MgSO_4$, and concentration provided a white solid. Addition of hexanes (300 mL) and filtration of the solid followed by thorough washing of the solid with cold hexanes provided chloroketone **194** (1.97 g, 85% yield) as a white solid. m.p. 72-74 °C; FTIR (thin film/NaCl) 2957 (m), 1755 (s), 1369 (w), 1277 (s), 1051 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.43 (d, *J* = 8.8 Hz, 1H), 4.94 (d, *J* = 2.2 Hz, 1H), 4.93 (d, *J* = 1.8 Hz, 1H), 4.60 (t, *J* = 4.0 Hz, 1H), 3.36-3.33 (m, 1H), 2.64-2.59 (m, 2H), 2.27-2.24 (m, 1H), 2.19 (s, 3H), 1.30 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5, 169.9, 159.2, 105.1, 76.8, 57.7, 44.6, 41.0, 37.1, 30.8, 29.3, 21.8, 20.5; HRMS (EI) *m/z* 256.0877 [cacl'd for $C_{13}H_{17}ClO_3$ (M+) 256.0866].

Preparation of Alcohols 195 and 196.

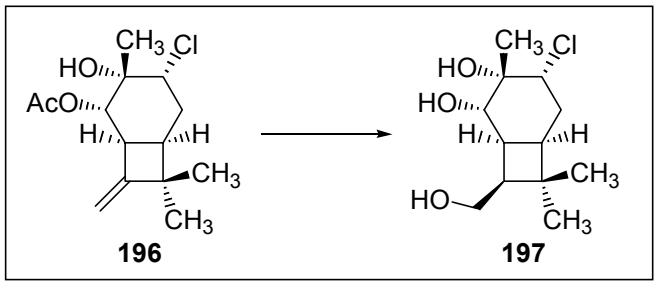


Alcohols 195 and 196. A solution of methyl magnesium bromide (1.96 mL, 3.0 M in Et_2O, 5.0 eq.) was added to a cooled solution (0 °C) of ketone **194** (300 mg, 1.17 mmol, 1.0 eq.) in THF (11 mL). The reaction was maintained at 0 °C for 1 hour at which point the reaction was quenched by the slow addition of saturated $NaHCO_3$ (50 mL). The resulting mixture was diluted with H_2O (50 mL) and extracted with Et_2O (4 x 50 mL). The combined organic layers were washed with brine dried over Na_2SO_4 and concentrated in vacuo. The derived residue was subjected to silica gel chromatography (25% EtOAc/hexanes eluent).

Alcohol 195: The first compound to elute was alcohol **195** (63 mg, 23% yield) as a colorless oil. m.p. 72-74 °C; FTIR (thin film/NaCl) 3429 (bs), 2962 (s), 1670 (m), 1456 (m), 1370 (m), 1027 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.96 (d, *J* = 2.1 Hz, 1H), 4.88 (d, *J* = 2.8 Hz, 1H), 4.13 (dd, *J* = 4.5, 12.1 Hz, 1H), 3.98 (d, *J* = 4.3 Hz, 1H), 3.15-3.12 (m, 1H), 2.35 (bs, 1H), 2.30-2.02 (m, 3H), 1.95 (bs, 1H), 1.35 (s, 3H), 1.26 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.3, 103.4, 74.5, 74.0, 64.8, 45.8, 43.7, 39.3, 29.8, 28.8, 23.9, 21.5; HRMS (EI) *m/z* 230.1071 [cacl'd for $C_{12}H_{19}ClO_2$ (M+) 230.1074].

Alcohol 196: The second compound to elute was alcohol **196** (188 mg, 70% yield) as a white solid. m.p. 139-141 °C; FTIR (thin film/NaCl) 3324 (bs), 2921 (s), 1732 (m), 1450 (m), 1051 (w), 875 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.91 (d, *J* = 2.0 Hz, 1H), 4.84 (d, *J* = 2.4 Hz, 1H), 4.17 (dd, *J* = 5.1, 8.9 Hz, 1H), 3.62 (d, *J* = 5.7 Hz, 1H), 3.13-3.10 (m, 1H), 2.44 (dt, *J* = 5.2, 8.8 Hz, 1H), 2.37 (bs, 1H), 2.18-2.02 (m, 3H), 1.43 (s, 3H), 1.20 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4, 103.2, 76.6, 72.6, 67.0, 45.4, 45.0, 38.3, 29.5, 29.0, 25.1, 22.6; HRMS (EI) *m/z* 230.1075 [cacl'd for $C_{12}H_{19}ClO_2$ (M+) 230.1074]

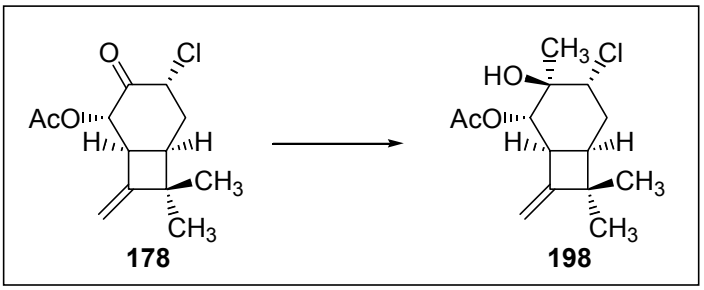
Preparation of Triol 197.



Triol 197. To a solution of olefin **196** (10.0 mg, 0.043 mmol, 1.0 eq.) cooled to 0 ºC was added BH_3•THF (1.0 M in THF, 87 μL, 2.0 eq.) over 2 minutes. The resulting solution was allowed to warm to room temperature over a period of 1 hour and then allowed to stir at this temperature for an additional 2 hours. At this point, TLC indicated remaining starting material, so the solution was recooled to 0 ºC and additional BH_3•THF (1.0 M in THF, 87 μL, 2.0 eq.) was added over 2 minutes. After stirring at this temperature for two hours, 2N NaOH (250 μL) and H_2O_2 (250 μL) were sequentially added. Stirring was continued for 10 minutes before being quenched with 1 N HCl (10 mL). Extraction with EtOAc (3 x 10 mL) was followed by sequential washing with

$Na_2S_2O_3$ (10 mL), H_2O (10 mL), and brine. Drying over Na_2SO_4 was followed by concentration and purification by silica gel chromatography (50-75% EtOAc/hexanes) to furnish triol **197** (10.0 mg, 93% yield) as a white solid. X-ray quality crystals were obtained by slow evaporation from CH_2Cl_2 to provide colorless crystals. See appendix 6 for X-ray report. m.p. 134-135 °C; FTIR (thin film/NaCl) 3391 (bs), 2932 (s), 1722 (m), 1420 (m), 13690 (w), 1211 (s), 1141 (w), 1045 (w), 1014 (w), 739 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.07 (dd, J = 6.4, 11.6 Hz, 1H), 3.91 (d, J = 8.8 Hz, 1H), 3.86 (t, J = 11.4 Hz, 1H), 3.65 (dd, J = 5.7, 11.6 Hz, 1H), 2.54-1.95 (m, 8H), 1.50 (s, 3H), 1.06 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.9, 73.2, 66.6, 59.1, 45.5, 39.9, 39.5, 37.4, 32.1, 29.1, 23.9, 19.9; HRMS (EI) *m/z* 249.1258 [cacl'd for $C_{12}H_{21}ClO_3$ (M+H) 249.1257].

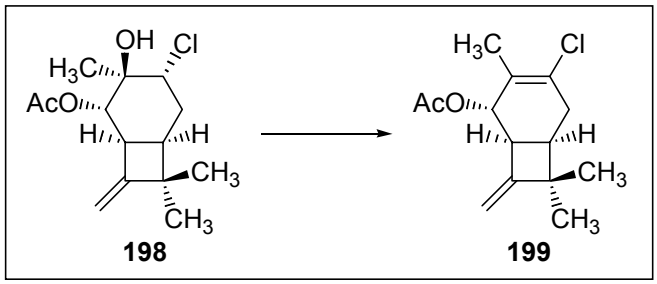
Preparation of Tertiary alcohol 198.



Tertiary alcohol 198. A solution of ketone **178** (1.6 g, 6.27 mmol, 1.0 eq) in CH_2Cl_2 (60 mL) at 0 °C was treated with $(CH_3)_3Al$ (2.4 mL, 25.10 mmol, 4.0 eq.). The resulting yellow solution was allowed to slowly warm up to room temperature over a period of 1 hour. The reaction mixture was cooled to 0 °C and carefully quenched (CAUTION!!) with 1 N HCl (100 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed

with brine and dried over Na_2SO_4. Concentration and purification by flash chromatography (20-50% EtOAc/hexanes) afforded alcohol **198** (1.0 g, 75% yield BORSM) as a white solid and recovered ketone **178** (350 mg). m.p. 67.5-70.0 °C; FTIR (thin film/NaCl) 3493 (bs), 2955 (s), 1731 (s), 1373 (s), 1235 (s), 1028 (s), 880 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.06 (d, *J* = 7.4 Hz, 1H), 4.81 (d, *J* = 2.5 Hz, 1H), 4.80 (d, *J* = 1.8 Hz, 1H), 4.18 (t, *J* = 6.6 Hz, 1H), 3.20-3.16 (m, 1H), 2.52-2.47 (m, 1H), 2.15 (s, 3H), 2.10 (dt, *J* = 5.2, 7.9 Hz, 2H), 1.29 (s, 3H), 1.17 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 159.1, 104.1, 77.2, 72.5, 66.1, 45.2, 42.4, 38.4, 29.7, 28.9, 24.3, 22.6, 21.1; HRMS (EI) *m/z* 273.1261 [cacl'd for $C_{14}H_{21}ClO_3$ (M+H) 273.1257].

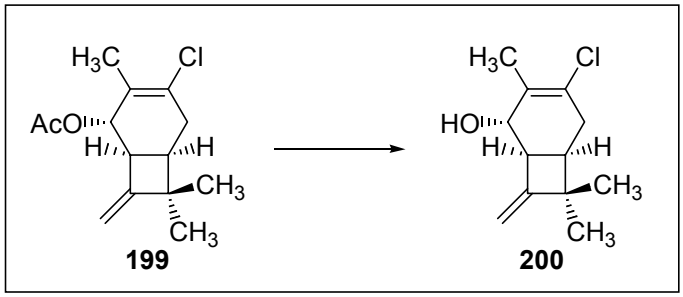
Preparation of Vinyl Chloride 199.



Vinyl Chloride 199. To a solution of alcohol **198** (960 mg, 3.54 mmol, 1.0 eq.) in pyridine (14 mL) at 0 °C was added thionyl chloride (517 μL, 7.08 mmol, 2.0 eq.) which immediately resulted in the formation of a white precipitate. Stirring was continued for 30 minutes before the reaction mixture was diluted with EtOAc (100 mL) and the whole was washed sequentially with 1 N HCl (100 mL) then saturated $NaHCO_3$ (100 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* was followed by purification via silica gel chromatography (25% EtOAc/hexanes eluent) to afford olefin **199** (760 mg, 84% yield)

as a colorless oil. FTIR (thin film/NaCl) 2952 (m), 1739 (s), 1372 (w), 1235 (s), 964 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.33 (d, *J* = 2.5 Hz, 1H), 4.78 (dd, *J* = 1.0, 3.0 Hz, 1H), 4.77 (dd, *J* = 1.0, 2.0 Hz, 1H), 3.46-3.42 (m, 1H), 2.82-2.76 (m, 1H), 2.34-2.30 (m, 2H), 1.97 (s, 3H), 1.79 (bs, 3H), 1.12 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 158.5, 132.8, 128.6, 103.0, 73.8, 44.3, 41.7, 39.5, 32.3, 30.2, 21.4, 21.0, 19.8; HRMS (EI) *m/z* 254.1075 [cacl'd for $C_{14}H_{19}ClO_2$ (M+) 254.1074].

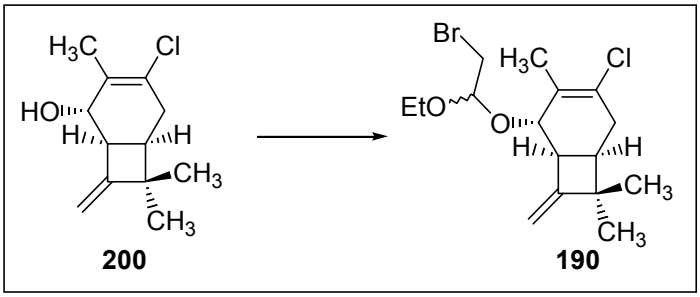
Preparation of Alcohol 200.



Alcohol 200.A solution of acetate **199** (670 mg, 2.63 mmol, 1.0 eq.) in CH_2Cl_2 (10 mL) was added to a solution of DIBAL (1.0 M in CH_2Cl_2 , 5.8 mL, 2.2 eq.) in CH_2Cl_2 (20 mL) at 0 °C. Stirring was continued for 20 minutes until TLC indicated no remaining starting material. The reaction was quenched by the addition of 1 M Rochelle's salt (25 mL). Vigorous stirring was continued for 30 at room temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 25 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The crude organic concentrate was subjected to silica gel chromatography (25% EtOAc/hexanes eluent) to furnish alcohol **200** (520 mg, 93% yield) as a white solid. m.p. 76-78 °C; FTIR (thin film/NaCl) 3290 (bs), 2954 (s), 1667 (m), 1443 (w), 987 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.74 (d, *J* = 2.8 Hz, 1H), 4.67 (d, *J* = 2.2 Hz, 1H), 4.23 (d, *J* = 2.6 Hz,

1H), 3.45-3.43 (m, 1H), 2.82-2.76 (m, 1H), 2.45 (t, J = 8.7 Hz, 1H), 2.41 (t, J = 17.2 Hz, 1H), 1.92 (d, J = 2.7 Hz, 3H), 1.55 (bs, 1H), 1.21 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 131.5, 130.6, 102.0, 72.9, 44.3, 44.1, 40.0, 32.1, 30.2, 21.0, 19.6; HRMS (EI) *m/z* 212.0964 [cacl'd for $C_{12}H_{17}ClO_3$ (M+) 212.0968].

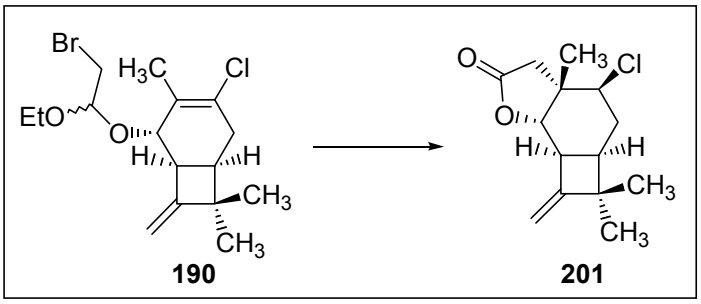
Preparation of Bromoacetals 190.



Bromoacetals 190. Bromine (175 µl, 3.38 mmol, 4.0 eq.) was added to a solution of ethyl vinyl ether (404 µL, 4.22 mmol, 5.0 eq) in CH_2Cl_2 (6 mL) at –78 °C over a period of 1 minute. The resulting colorless solution was stirred at –78 °C for 10 minutes then allowed to warm to room temperature and stir for an additional 10 minutes. The solution was recooled to –78 °C and a solution of alcohol **200** (180 mg, 0.85 mmol, 1.0 eq.) and TEA (707 µL, 5.07 mmol, 6.0 eq.) in CH_2Cl_2 (4 mL) was added over 5 minutes. The solution was allowed to slowly warm to room temperature over 2 hours then stir at this temperature for an additional 4 hours. The mixture was concentrated and purified by silica gel chromatography to furnish bromoacetals **190** (300 mg, 98% yield) as a colorless oil. FTIR (thin film/NaCl) 2979 (m), 2975 (m), 1724 (m), 1104 (m), 989 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.78 (t, J = 5.4 Hz, 1H), 4.74 (dt, J = 1.0, 3.2 Hz, 2H), 4.71 (t, J = 5.5 Hz, 1H), 4.64 (dd, J = 1.0, 2.4 Hz, 2H), 4.23 (d, J = 3.0 Hz, 1H),

4.15 (d, J = 2.5 Hz, 1H), 3.66-3.55 (m, 6H), 3.41-3.30 (m, 4H), 2.89-2.80 (m, 2H), 2.44-2.39 (m, 2H), 2.37 (s, 3H), 2.33 (s, 3H), 1.92 (s, 3H), 1.90 (s, 3H), 1.27 (t, J = 7.0 Hz, 3H), 1.25 (t, J = 6.5 Hz, 3H), 1.22 (s, 3H), 1.21 (s, 3H), 1.01 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 159.3, 132.0, 131.6, 129.6, 129.5, 102.1, 102.0, 100.4, 99.9, 77.7, 77.3, 61.2, 60.6, 44.2, 44.1, 42.8, 41.3, 40.1, 40.0, 32.5, 32.4, 32.0, 31.9, 30.4, 30.3, 21.1, 21.0, 20.9, 20.4, 15.3, 15.2; HRMS (EI) *m/z* 362.0655 [calc'd for $C_{16}H_{24}BrClO_2$ (M+) 362.0648].

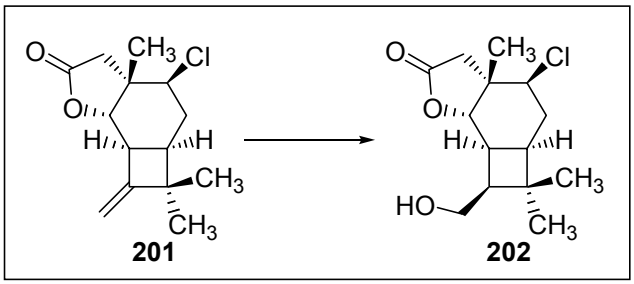
Preparation of Lactone 201.



Lactone 201. A solution of bromoacetals **190** (13 mg, 0.04 mmol, 1.0 eq.) in toluene (4 mL) at room temperature was treated with Bu_3SnH (11 μL, 0.04 mmol, 1.2 eq.), BEt_3 (1.0 M in hexanes, 142 μL, 4.0 eq.), and air (1 mL). Stirring was continued for 10 minutes before the solution was concentrated *in vacuo*, providing a residue that was dissolved in Et_2O (10 mL). To this ethereal solution was added DBU (16 μL, 0.11 mmol, 3 eq.), which resulted in the immediate formation of a white precipitate. Filtration through a small plug of silica gel afforded a mixture of crude acetals as a colorless oil that was carried directly to the next step. The derived oil was dissolved in acetone (4 mL) and treated with Jones reagent (~ 250 μL). Stirring was continued for 1 hour before

dilution with saturated $NaHCO_3$ (10 mL) and extraction with EtOAc (2 x 10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. Concentration *in vacuo* provided an residue that was purified by column chromatography (5% EtOAc/hexanes eluent) to furnish lactone **201** (7 mg, 77% yield) as a white solid. m.p. 99-102 °C; FTIR (thin film/NaCl) 2959 (bs), 2921 (bs), 1783 (s), 1001 (s), 909 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.89 (d, J = 3.2 Hz, 1H), 4.84 (d, J = 2.6 Hz, 1H), 4.58 (s, 1H), 3.86 (dd, J = 3.0, 11.7 Hz, 1H), 3.55 (d, J = 8.2 Hz, 1H), 2.94 (d, J = 17.6 Hz, 1H), 2.43 (d, J = 17.7 Hz, 1H), 2.33-2.28 (m, 1H), 2.09-1.92 (m, 2H), 1.33 (s, 3H), 1.25 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8, 157.7, 102.7, 84.3, 62.0, 46.3, 44.4, 43.1, 41.4, 39.1, 29.7, 28.1, 20.8, 18.0; HRMS (EI) *m/z* 254.1081 [calc'd for $C_{14}H_{19}ClO_2$ (M+) 254.1074].

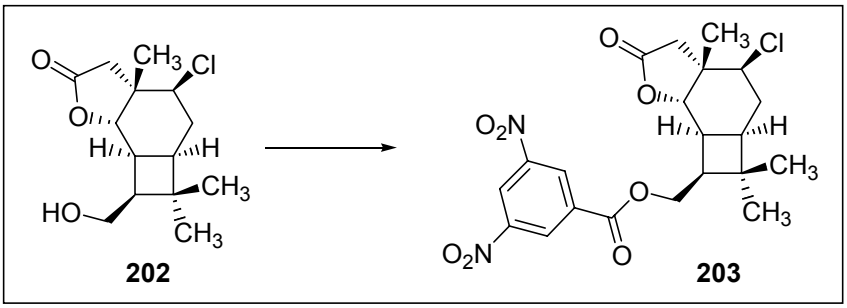
Preparation of Alcohol 202.



Alcohol 202. A solution of olefin **201** (12 mg, .05 mmol, 1.0 eq.) in CH_2Cl_2 (2 mL) at 0 °C was treated with BH_3•DMS (1.0 M in CH_2Cl_2 , 56 μL, 1.2 eq.). The resulting colorless solution was allowed to slowly up to room temperature, and stir at that temperature for 3 hours, at which point additional BH_3•DMS (1.0 M in CH_2Cl_2, 28 μL, 0.6 eq.) was added. After stirring for an additional 30 minutes, TLC indicated the complete consumption of starting material. Upon cooling the reaction mixture to 0 °C,

THF (2 mL) was added followed by H_2O_2 (265 μL) and 2 N NaOH (250 μL). After stirring vigorously for 30 minutes, the reaction was diluted with saturated $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Absorption onto silica gel was followed by purification by flash chromatography (50–75% EtOAc/hexanes eluent) to furnish alcohol **202** (10 mg, 83% yield) as a colorless oil. FTIR (thin film/NaCl) 2954 (bs), 1774 (s), 1171 (w), 1071 (w), 749 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.66 (d, *J* = 9.8 Hz, 1H), 3.89-3.84 (m, 2 H), 3.71 (dd, *J* = 6.9, 11.6 Hz, 1H), 2.55-2.40 (m, 6H), 1.91-1.77 (m, 2H), 1.39 (s, 3H), 1.20 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 85.9, 64.0, 59.5, 46.0, 43.5, 42.0, 40.7, 38.6, 32.9, 32.3, 28.5, 21.7, 19.8; HRMS (EI) *m/z* 273.1251 [calc'd for $C_{14}H_{21}ClO_3$ (M+H) 273.1257].

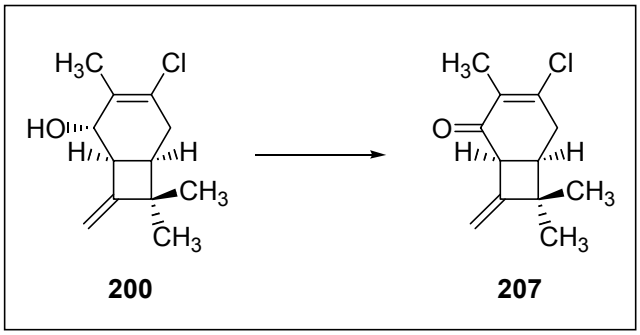
Preparation of Benzoate 203.



Benzoate 203. A solution containing alcohol **202** (10 mg, 0.04 mmol, 1.0 eq.), TEA (26 μL, 0.18 mmol, 5.0 eq.), and DMAP (approx. 1 mg) in CH_2Cl_2 (3 mL) was treated with 3,5-dinitrobenzoyl chloride (17 mg, 0.07 mmol, 2.0 eq.). The resulting solution was refluxed gently for 3 hours before being cooled, absorbed onto silica gel and

purified by flash chromatography (20% EtOAc/hexanes eluent) to afford benzoate **203** (16 mg, 94% yield) as a yellow solid. See appendix 6 for X-ray report. m.p. 103-105 °C; FTIR (thin film/NaCl) 2919 (w), 1778 (m), 1730 (w), 1540 (m), 1343 (m), 912 (s), 738 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (t, *J* = 1.9 Hz, 1H), 9.14 (d, *J* = 2.3 Hz, 2H), 4.67 (dd, *J* = 7.8, 11.4 Hz, 1H), 4.59 (d, *J* = 10.8 Hz, 1H), 4.51 (dd, *J* = 8.2, 11.3 Hz, 1H), 3.87 (dd, *J* = 2.9, 12.9 Hz, 1H), 2.83 (q, *J* = 8.7 Hz, 1H), 2.63 (q, *J* = 10.1 Hz, 1H), 2.52 (s, 2H), 2.47 (q, *J* = 9.1 Hz, 1H), 1.94-1.78 (m, 2H), 1.39 (s, 3H), 1.27 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 162.4, 148.7, 133.7, 129.4, 122.4, 85.5, 63.8, 63.4, 43.6, 42.3, 41.9, 40.7, 39.1, 33.3, 32.3, 28.3, 22.1, 20.2; HRMS (EI) *m/z* 467.1218 [calc'd for $C_{21}H_{23}ClN_2O_8$ (M+) 467.1221].

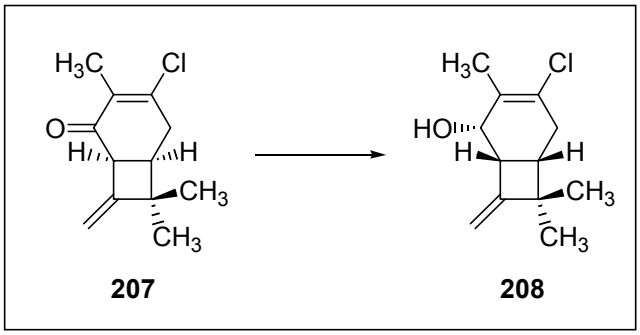
Preparation of Ketone 207.



Ketone 207. To a solution of alcohol **200** (100 mg, 0.47 mmol, 1.0 eq.) in CH_2Cl_2 (10 mL) was added Dess-Martin Periodinane (292 mg, 0.71 mmol, 1.5 eq.). The resulting white mixture was allowed to stir at room temperature for 30 minutes at which point TLC indicated complete consumption of starting material. Saturated $NaHCO_3$ (10 mL) and saturated $Na_2S_2O_3$ (5 mL) were added and the biphasic mixture was allowed to stir until both layers were homogeneous (30 minutes). The layers were separated and the

aqueous layer was extracted with CH_2Cl_2 (30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to a residue that was purified by flash chromatography (20% EtOAc/hexanes eluent) to provide ketone **207** (96 mg, 97% yield) as a colorless oil. FTIR (thin film/NaCl) 2956 (m), 2930 (m), 1674 (s), 1662 (s), 1629 (m), 1325 (m), 1289 (w), 1276 (w), 886 (w), 829 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.94 (dd, *J* = 1.1, 2.5 Hz, 1H), 4.85 (dd, *J* = 1.0, 3.0 Hz, 1H), 3.72 (dt, *J* = 2.6, 9.5 Hz, 1H), 2.92-2.84 (m, 1H), 2.69 (d, *J* = 18.2 Hz, 1H), 2.63 (dd, *J* = 2.1, 9.4 Hz, 1H), 1.88 (dd, *J* = 1.6, 2.5 Hz, 3H), 1.29 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 155.5, 151.4, 132.8, 105.4, 47.1, 46.3, 36.8, 31.8, 29.1, 21.9, 13.0; HRMS (EI) *m/z* 210.0807 [cacl'd for $C_{12}H_{15}ClO$ (M+) 210.0811].

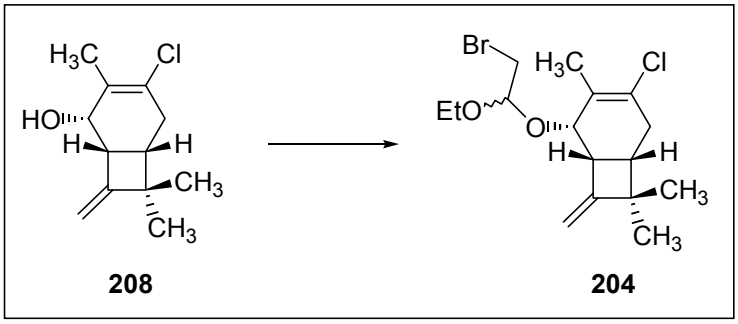
Preparation of Alcohol 208.



Alcohol 208. To a solution of ketone **207** (96 mg, 0.46 mmol, 1.0 eq.) in CH_3OH (1 mL) and CH_2Cl_2 (1mL) at room temperature was added $CeCl_3 \cdot 7\ H_2O$ (850 mg, 2.28 mmol, 5.0 eq.) the resulting solution was allowed to stir for 10 minutes then cooled to 0 ° C, at which point $NaBH_4$ (55 mg, 1.37 mmol, 3.0 eq.) was added in one portion. Stirring was continued at this temperature for 30 minutes before the addition of silica gel (approx. 500 mg). Concentration and purification by silica gel chromatography (20%

EtOAc/hexanes eluent) furnished alcohol **208** (70 mg, 73% yield) as a colorless oil. FTIR (thin film/NaCl) 3450 (bs), 2985 (s), 2975 (s), 2966 (m), 1680 (m), 1675 (m), 1450 (w), 1390 (w), 1310 (w), 1288 (w), 1275 (w), 1100 (m), 1008 (s), 764 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (d, *J* = 2.3 Hz, 1H), 4.83 (d, *J* = 2.6 Hz, 1H), 3.59-3.54 (m, 1H), 2.46-2.25 (m, 3H), 1.92-1.90 (m, 3H), 1.20 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 133.6, 125.3, 104.5, 69.9, 43.7, 43.2, 38.3, 21.2, 30.7, 19.9, 15.5; HRMS (EI) *m/z* 210.0808 [cacl'd for $C_{12}H_{15}ClO$ (M-2H) 210.0811].

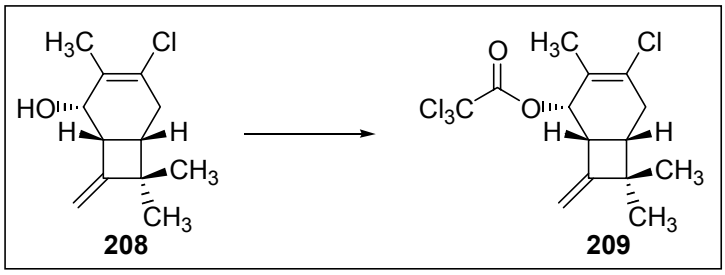
Preparation of Bromoacetals 204.



Bromoacetals 204. A solution of alcohol **208** (26 mg, 0.012 mmol, 1.0 eq.) in CH_2Cl_2 (2 mL) at 0 °C was added bromide **85** (85 mg, 0.37 mmol, 3.0 eq.) and *N,N*-dimethylaniline (78 μL, 0.61 mmol, 5.0 eq.). The resulting colorless solution was allowed to stir at room temperature for 3 hours, at which point the solution had become dark blue. The reaction was quenched by the addition of 1 N HCl (20 mL), extraction of the aqueous layer with EtOAc (3 x 10 mL) was followed by washing the combined organic layers with saturated $NaHCO_3$ (10 mL), H_2O (10 mL), and brine. Drying over Na_2SO_4 and concentration provided a residue that was subjected to silica gel chromatography (7% EtOAc/hexanes eluent) to afford bromoacetals **204** (36 mg, 80%

yield) as a white solid. FTIR (thin film/NaCl) 2952 (s), 2928 (s), 1673 (w), 1442 (m), 1333 (m), 1119 (s), 1056 (s), 1017 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.96 (d, *J* = 2.3 Hz, 1H), 4.94 (d, *J* = 2.2 Hz, 1H), 4.86 (t, *J* = 5.4 Hz, 1H), 4.76 (t, *J* = 5.4 Hz, 1H), 4.71 (t, *J* = 2.2 Hz, 2H), 4.23 (d, *J* = 5.5 Hz, 1H), 4.15 (d, *J* = 5.4 Hz, 1H), 3.70-3.60 (m, 6H), 3.46-3.38 (m, 4H), 2.49-2.36 (m, 4H), 2.23-2.18 (m, 2H), 1.89 (bs, 6H), 1.25 (t, *J* = 6.9 Hz, 3H), 1.24 (t, *J* = 6.9 Hz, 3H), 1.21 (s, 6H), 0.98 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 158.3, 133.6, 133.5, 124.1, 123.9, 103.9, 103.7, 102.4, 99.9, 75.2, 61.6, 61.2, 43.8, 43.7, 42.4, 40.3, 38.3, 38.2, 32.4, 32.3, 31.8, 31.7, 30.5, 30.4, 20.0, 19.9, 16.0, 15.7, 15.2, 15.1; HRMS (EI) *m/z* 362.0649 [cacl'd for $C_{16}H_{24}BrClO_2$ (M+) 362.0648].

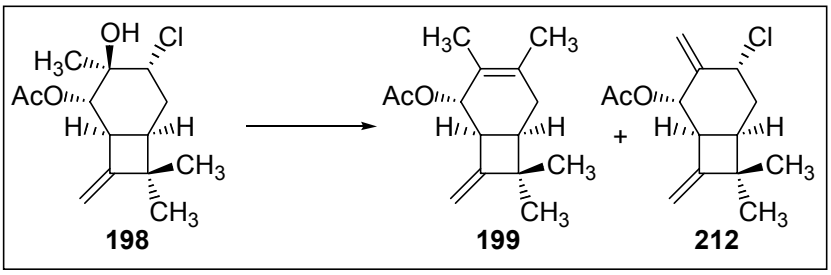
Preparation of Trichloroacetate 209.



Trichloroacetate 209. A solution of alcohol **208** (37 mg, 0.17 mmol, 1.0 eq.) in THF (2 mL) at 0 °C was added pyridine (61 μl, 0.75 mmol, 4.0 eq.), trichloroacetyl chloride (42 μL, 0.38 mmol, 2.0 eq.) and DMAP (3 mg, 0.03 mmol, .15 eq.). The suspension was stirred at this temperature for 1 hour and allowed to warm to room temperature and stir for an additional 1 hour. The reaction was quenched by the addition of 1 N HCl (10 mL), extraction of the aqueous layer with EtOAc (3 x 10 mL) was followed by washing the combined organic layers with saturated $NaHCO_3$ (10 mL), H_2O (10 mL), and brine. Drying over Na_2SO_4 and concentration provided a residue that was

subjected to silica gel chromatography (4% EtOAc/hexanes eluent) to afford trichloroacetate **209** (48 mg, 77% yield) as a white solid. m.p. 105-107 °C; FTIR (thin film/NaCl) 2956 (s), 1759 (s), 1250 (s), 829 (s), 677 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.52 (d, *J* = 6.1 Hz, 1H), 5.02 (d, *J* = 2.2 Hz, 1H), 4.81 (d, *J* = 2.8 Hz, 1H), 3.76-3.72 (m, 1H), 2.59-2.52 (m, 1H), 2.47 (d, *J* = 17.0 Hz, 1H), 2.34 (dt, *J* = 1.8, 7.8 Hz, 1H), 1.88 (bs, 3H), 1.22 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.3, 156.6, 129.6, 126.9, 105.2, 90.0, 78.0, 44.0, 40.5, 37.8, 32.3, 30.3, 20.1, 15.5; HRMS (FAB) *m/z* 355.9902 [cacl'd for $C_{14}H_{16}ClO_2$ (M+) 355.9904].

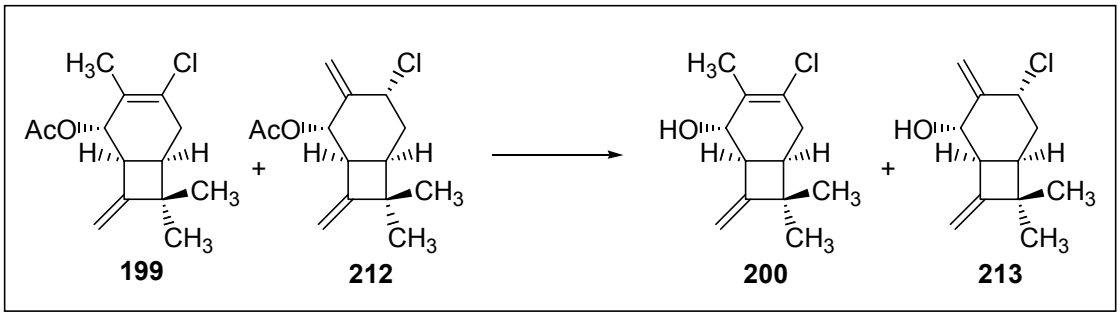
Preparation of Acetate 212.



Acetate 212. A solution of alcohol **198** (350 mg, 1.29 mmol, 1.0 eq.) in benzene (26 mL) was treated with Burgess Reagent (**211**) (922 mg, 3.87 mmol, 3.0 eq.). The solution that resulted was heated to reflux for 3 hours before being cooled, concentrated, and absorbed onto silica gel for purification (20% EtOAc/hexanes eluent) which provided a 1.5:1 inseparable mixture of olefins **199** and **212** (270 mg, 82% yield) as a colorless oil. A pure sample of **212** was obtained following hydrolysis of the acetates (K_2CO_3, CH_3OH), separation of the resulting diols by silica gel chromatography (20% EtOAc/hexanes eluent), and subsequent acylation (Ac_2O, TEA, DMAP, CH_2Cl_2) to furnish acetate **57** as a colorless oil. FTIR (thin film/NaCl) 2954 (m), 1736 (s), 1367 (m),

1233 (s), 1047 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.54 (d, *J* = 5.5 Hz, 1H), 5.44 (s, 1H), 5.30 (s, 1H), 4.90 (t, *J* = 1.0 Hz, 1H), 4.82 (dd, *J* = 2.5, 8.0 Hz, 1H), 3.31-3.28 (m, 1H), 2.51 (q, *J* = 6.3 Hz, 1H), 2.16-2.10 (m, 6H), 1.27 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 158.3, 142.9, 118.0, 103.6, 72.6, 58.0, 44.7, 42.9, 37.4, 31.6, 29.3, 21.5, 21.3; HRMS (EI) *m/z* 254.1072 [cacl'd for $C_{14}H_{19}ClO_2$ (M+) 254.1074].

Preparation of Allylic alcohol 213.



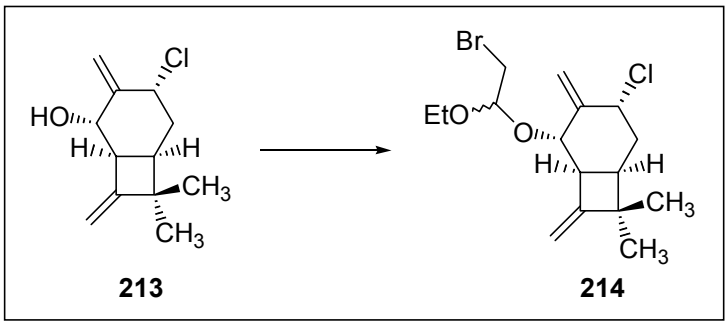
Allylic alcohol 213. A solution of acetates **199** and **212** (618 mg, 2.42 mmol, 1.0 eq.) in CH_3OH (30 mL) was cooled to 0 °C and treated with K_2CO_3 (436 mg, 3.16 mmol, 1.3 eq.). The suspension was slowly allowed to warm to room temperature and stir at that temperature for 2 hours before being quenched with silica gel (10 g), concentrated and purified by flash chromatography (20% EtOAc/hexanes).

Allylic alcohol 213: The first compound to elute was exocyclic olefin **213** (167 mg, 32% yield) as a colorless oil FTIR (thin film/NaCl) 3337 (bs), 2953 (s), 1672 (m), 1444 (w), 1064 (m), 909 (m), 879 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.40 (s, 2H), 4.91 (t, *J* = 4.2 Hz, 1H), 4.85 (d, *J* = 2.2 Hz, 1H), 4.81 (d, *J* = 2.6 Hz, 1H), 4.34 (d, *J* = 5.8 Hz, 1H), 3.24-3.20 (m, 1H), 2.54 (dt, *J* = 6.6, 9.5 Hz, 1H), 2.17-2.00 (m, 2H), 1.85 (bs, 1H), 1.28

(s, 3H), 1.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 147.3, 115.9, 102.9, 71.9, 59.1, 46.0, 44.7, 37.2, 31.3, 29.2, 21.7; HRMS (EI) *m/z* 212.0970 [cacl'd for $C_{12}H_{17}ClO$ (M+) 212.0968].

Alcohol 200: The second compound to elute was endocyclic olefin **200** (290 mg, 56% yield). The spectral data for **200** can be found above.

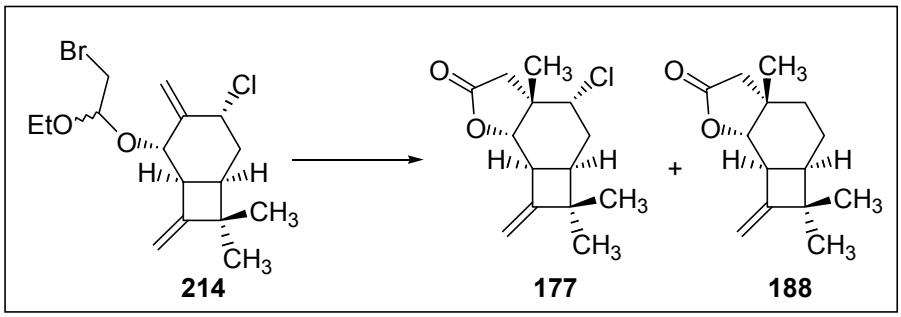
Preparation of Bromoacetals 214.



Bromoacetals 214. Bromide **85** (354 mg, 1.53 mmol, 2.5 eq.), *N,N*-dimethylaniline, (388 μL, 3.05 mmol, 5.0 eq.) and DMAP (7 mg, 0.06 mmol, .01 eq.) were added to a solution of alcohol **213** (130 mg, 0.61 mmol, 1.0 eq.) in CH_2Cl_2 (2 mL). After stirring for 30 minutes, the resulting green solution was washed with 2 N HCl (3 x 15 mL), saturated $NaHCO_3$ (10 mL) and brine. Drying over Na_2SO_4 was followed by concentration and purification by flash chromatography (5% EtOAc/hexanes eluent) to furnish bromoacetals **214** (215 mg, 97% yield) as a colorless oil. FTIR (thin film/NaCl) 2963 (s), 2927 (s), 1674 (m), 1368 (w), 1119 (s), 1060 (s), 1021 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.53 (s, 1H), 5.51 (d, J = 1.0 Hz, 1H), 5.41 (d, J = 1.0 Hz, 1H), 5.29 (s, 1H), 4.84-4.77 (m, 7H), 4.72 (d, J = 2.5 Hz, 1H), 4.35 (d, *J* = 4.0 Hz, 1H), 4.27 (d, *J* = 5.5

Hz, 1H), 3.72-3.36 (m, 10H), 2.40-2.08 (m, 6H), 1.25 (t, J = 7.2 Hz, 3H), 1.24 (s, 3H), 1.23 (s, 3H), 1.19 (t, J = 6.8 Hz, 3H), 1.06 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 158.1, 144.4, 142.5, 120.0, 118.1, 103.6, 103.2, 100.4, 98.2, 76.3, 76.2, 62.4, 60.7, 57.4, 57.0, 44.7, 44.5, 44.2, 44.1, 38.3, 37.9, 32.5, 32.4, 32.1, 31.8, 29.6, 29.5, 21.6, 21.4, 15.3, 15.1; HRMS (EI) *m/z* 362.0646 [cacl'd for $C_{16}H_{24}BrClO_2$ (M+) 362.0648].

Preparation of Lactones 177 and 188.



Lactones 177 and 188. A solution of bromoacetals **214** (35 mg, 0.11 mmol, 1.0 eq.) in benzene (8 mL) was degassed well with Argon before it was heated to reflux and a solution of Bu_3SnH (30 μL, 0.12 mmol, 1.1 eq.) and AIBN (4 mg, 0.03 mmol, 0.25 eq.) in benzene (2 mL) was added via a syringe pump over 2 hours. A second solution of Bu_3SnH (30 μL, 0.12 mmol, 1.1 eq.) and AIBN (4 mg, 0.03 mmol, 0.25 eq.) in benzene (2 mL) was added via a syringe pump over 2 hours and the resulting solution was refluxed overnight. The reaction was cooled to room temperature, diluted with Et_2O (10 mL) and treated with DBU (44 μL, 0.32 mmol, 3 eq.). The white suspension that resulted was then titrated with a saturated ethereal solution of iodine until the yellow color persisted. Filtration of the reaction mixture through a small plug of silica gel eluting with

Et_2O was followed by concentration of the reaction mixture to provide a colorless oil which was carried on without further purification. The derived oil was taken up in acetone (5 mL) cooled to 0 °C and treated with Jones Reagent (10 drops). The solution was allowed to warm to room temperature and was stirred for 30 minutes before the addition of isopropyl alcohol (5 drops) and saturated $NaHCO_3$ (5 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL), washed with brine, and dried over Na_2SO_4. Removal of the solvent *in vacuo* provided an oil that was subjected to flash chromatography (20% EtOAc/hexanes eluent).

Lactone 177: The first compound to elute was lactone **177** (2.5, 9% yield) as a colorless oil. FTIR (thin film/NaCl) 2957 (m), 2931 (w), 1775 (s), 1196 (w), 1011 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.90 (dd, *J* = 1.0, 2.9 Hz, 1H), 4.83 (dd, *J* = 1.1, 2.4 Hz, 1H), 4.60 (d, *J* = 2.5 Hz, 1H), 4.36 (dd, *J* = 3.2, 11.7 Hz, 1H), 3.64-3.61 (m, 1H), 3.05 (d, *J* = 18.9 Hz, 1H), 2.37 (d, *J* = 18.9 Hz, 1H), 2.33-2.29 (m, 1H), 2.11 (dt, *J* = 3.5, 14.4 Hz, 1H), 2.04-1.97 (m, 1H), 1.44 (s, 3H), 1.28 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 158.1, 102.7, 85.0, 62.8, 44.6, 42.5, 39.9, 39.5, 38.9, 30.1, 29.6, 28.7, 20.9; HRMS (EI) *m/z* 254.1073 [cacl'd for $C_{14}H_{19}ClO_2$ (M+) 254.1074].

Lactone 188: The second compound to elute was lactone **188** (3.7 mg, 14% yield). The spectral data for **188** can be found above.

3.6 Notes and References.

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(31) The methylenating reagents examined included: $Cp_2Ti(CH_3)_2$; Zn, $TiCl_4$, CH_2Br_2; $LiCH_2TMS$; Tebbe reagent.

(32) The stereochemistry of **198** was determined by its conversion to diol **195**.

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APPENDIX FIVE: SPECTRA RELEVANT TO CHAPTER THREE

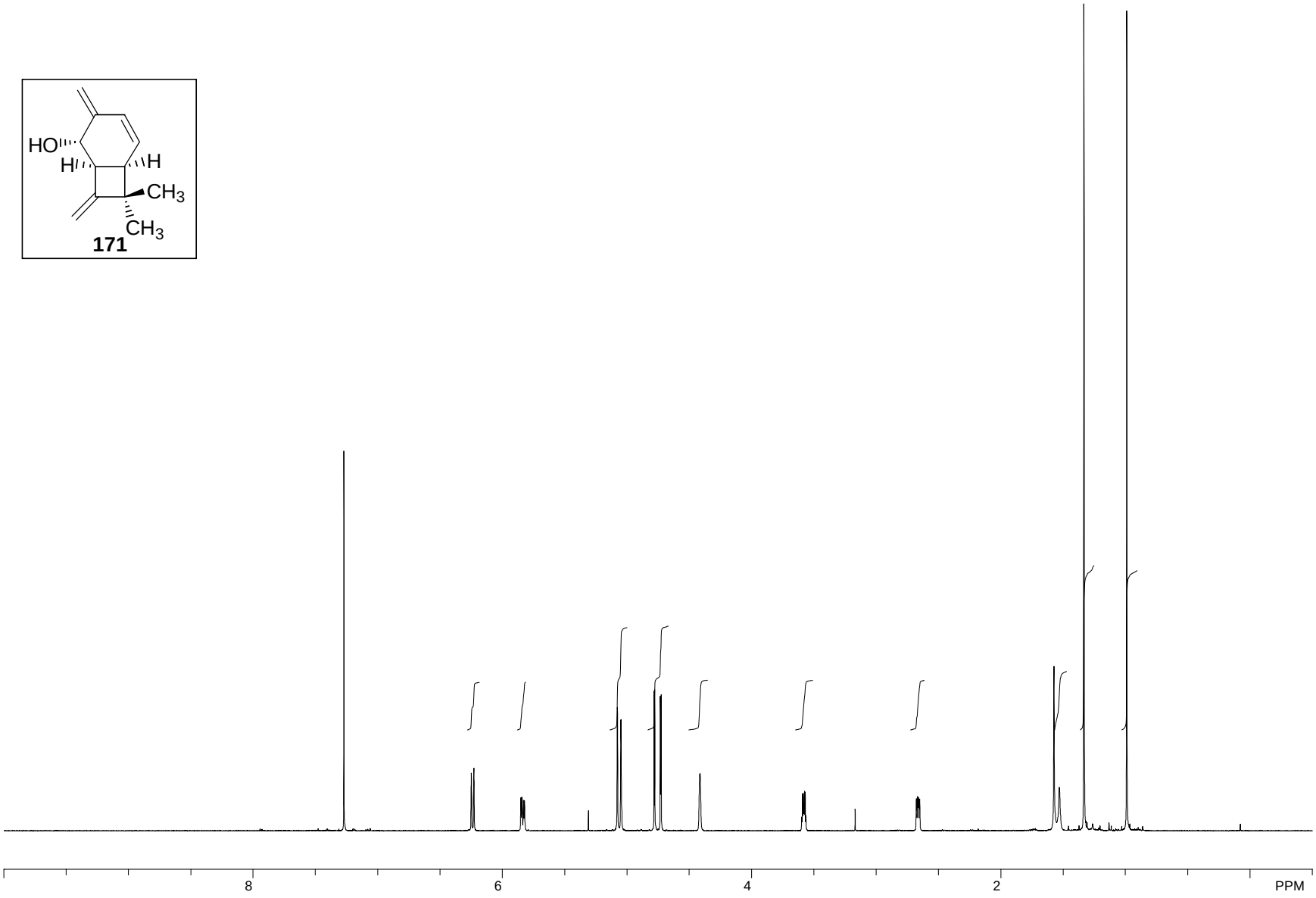


Figure A.5.1 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **171**.

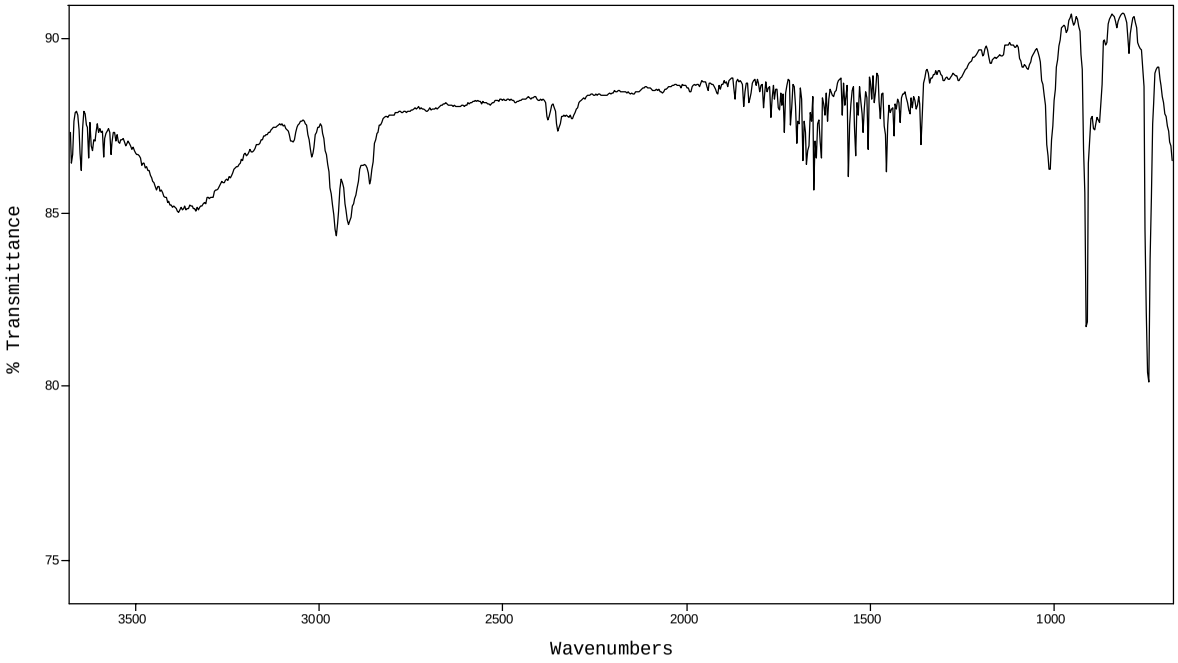


Figure A.5.2 FTIR Spectrum (thin film/NaCl) of Compound **171**.

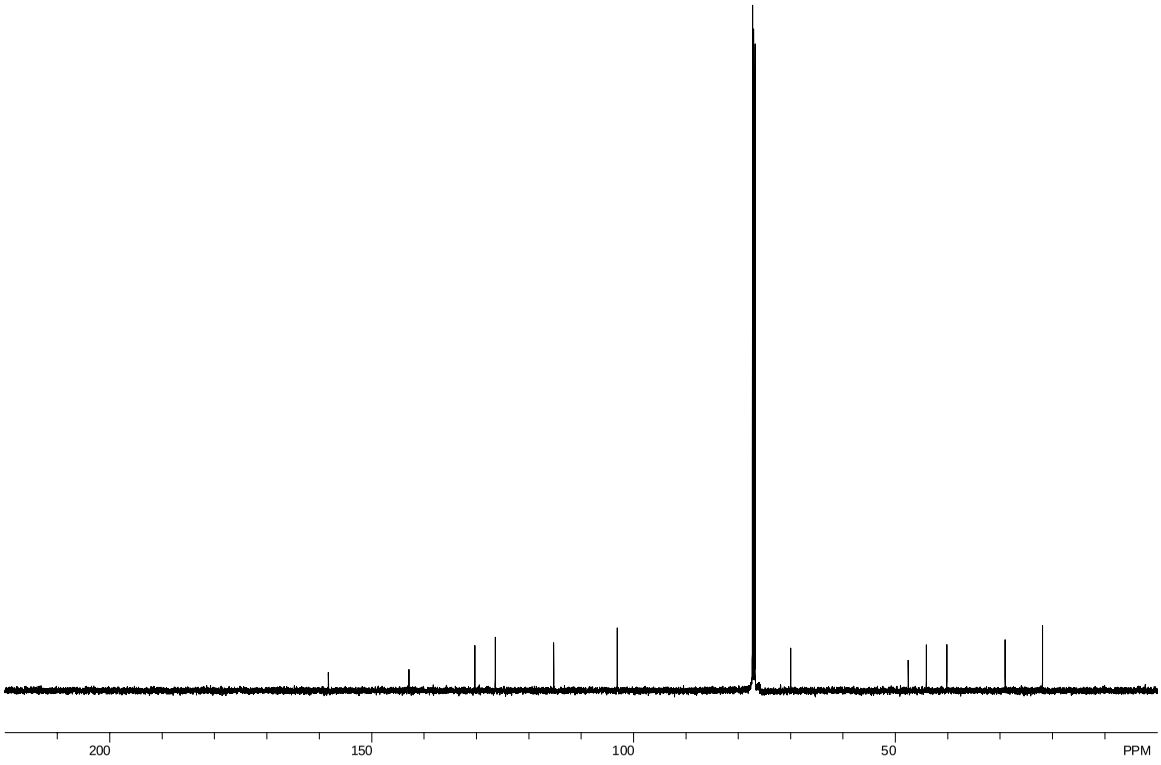


Figure A.5.3 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **171**.

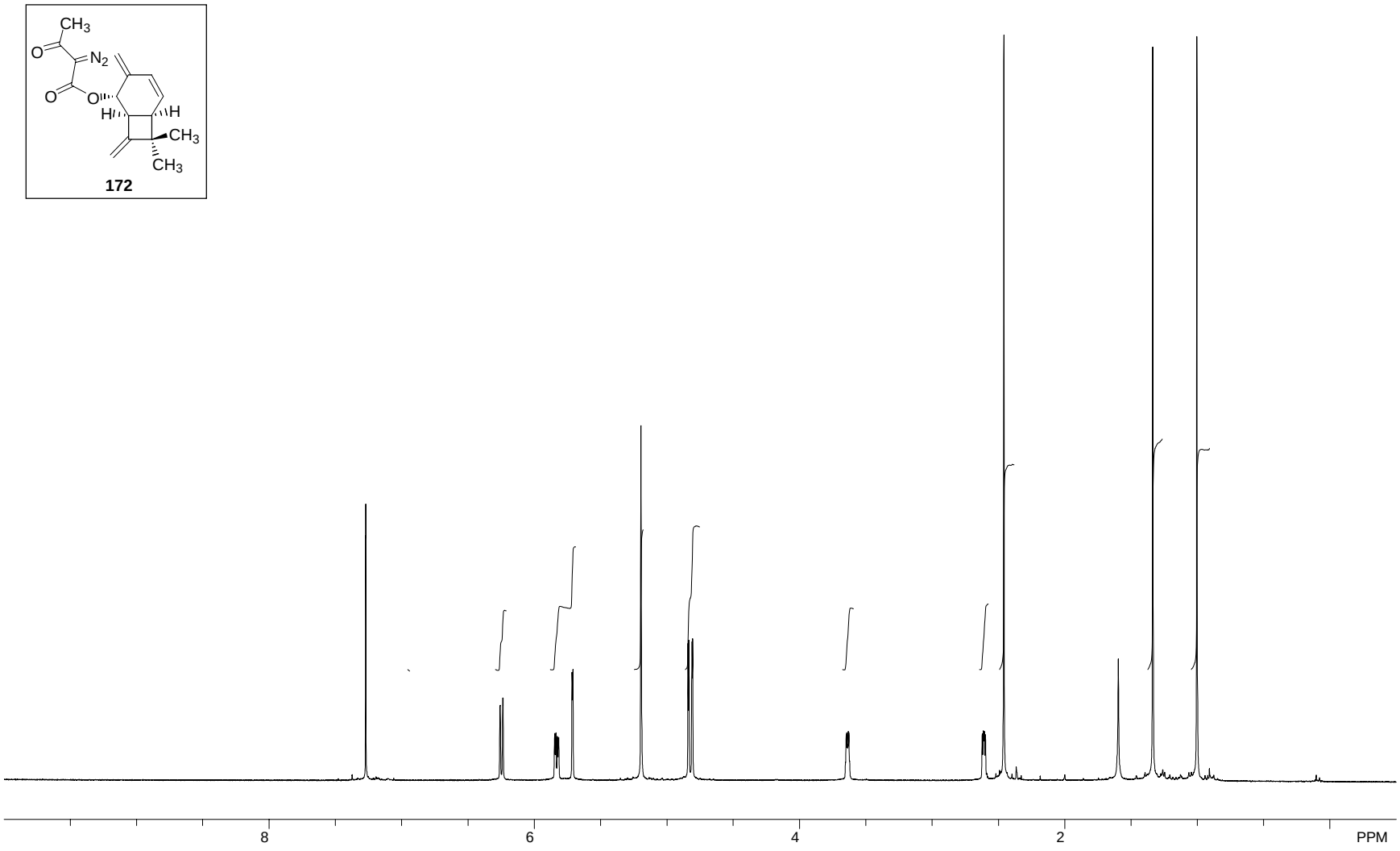


Figure A.5.4 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **172**.

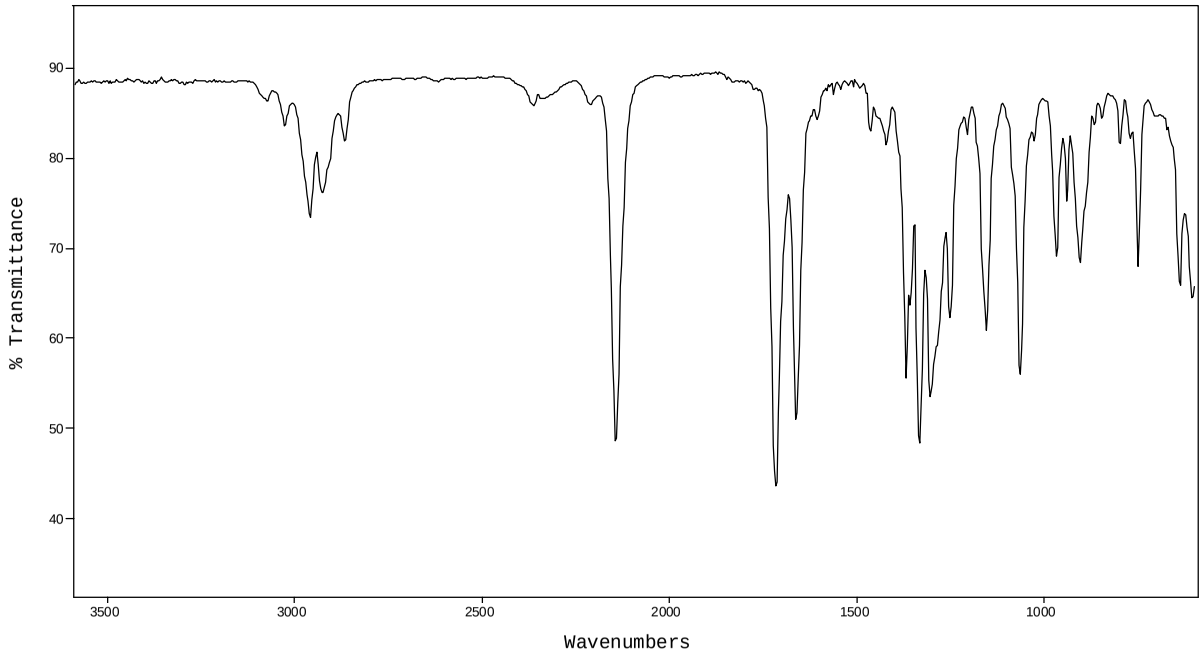


Figure A.5.5 FTIR Spectrum (thin film/NaCl) of Compound **172**.

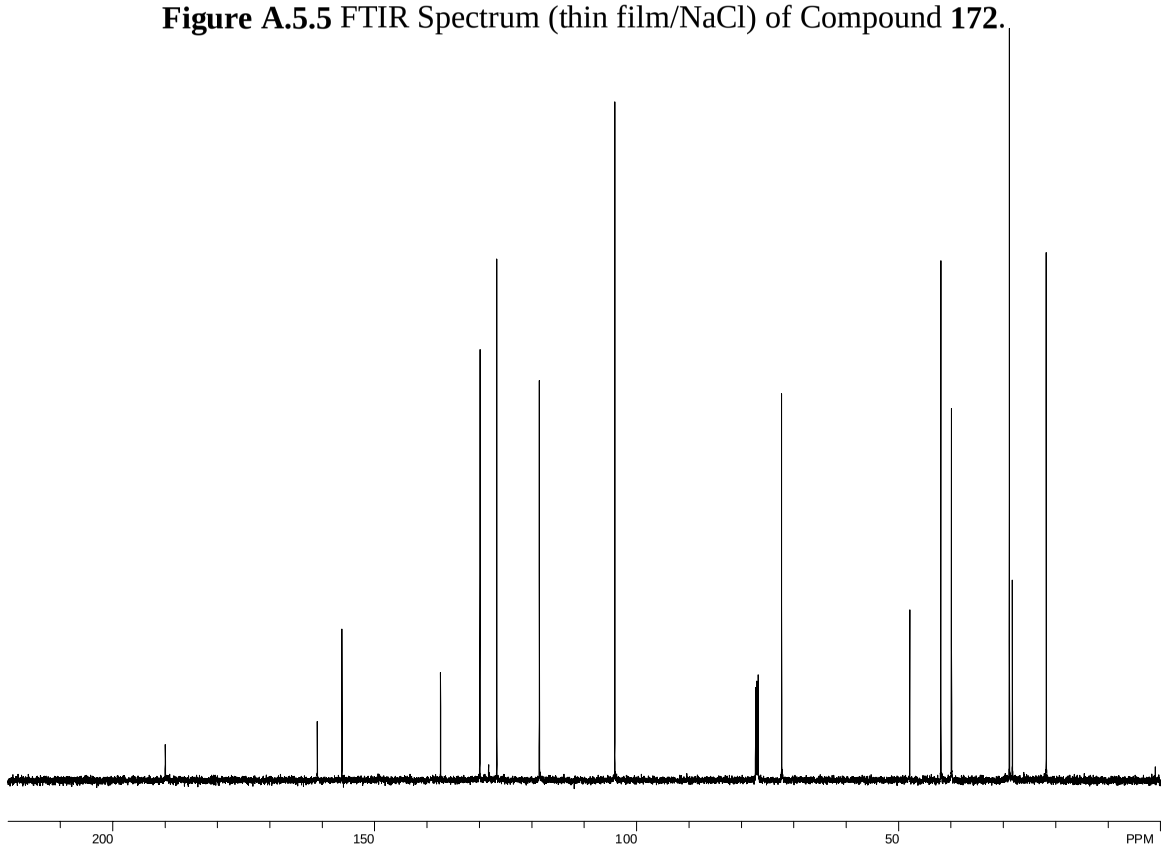


Figure A.5.6 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **172**.

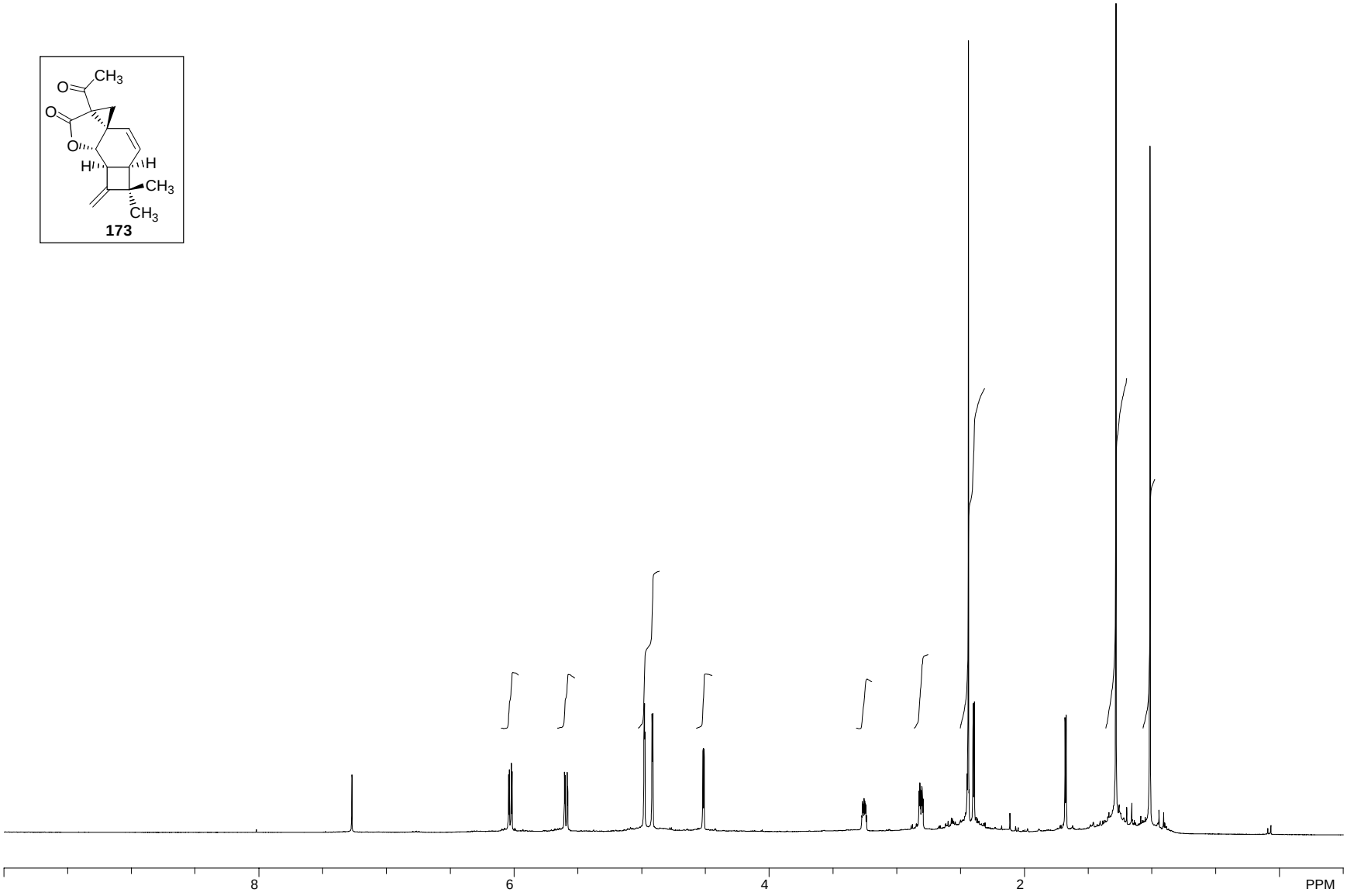


Figure A.5.7 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **173**.

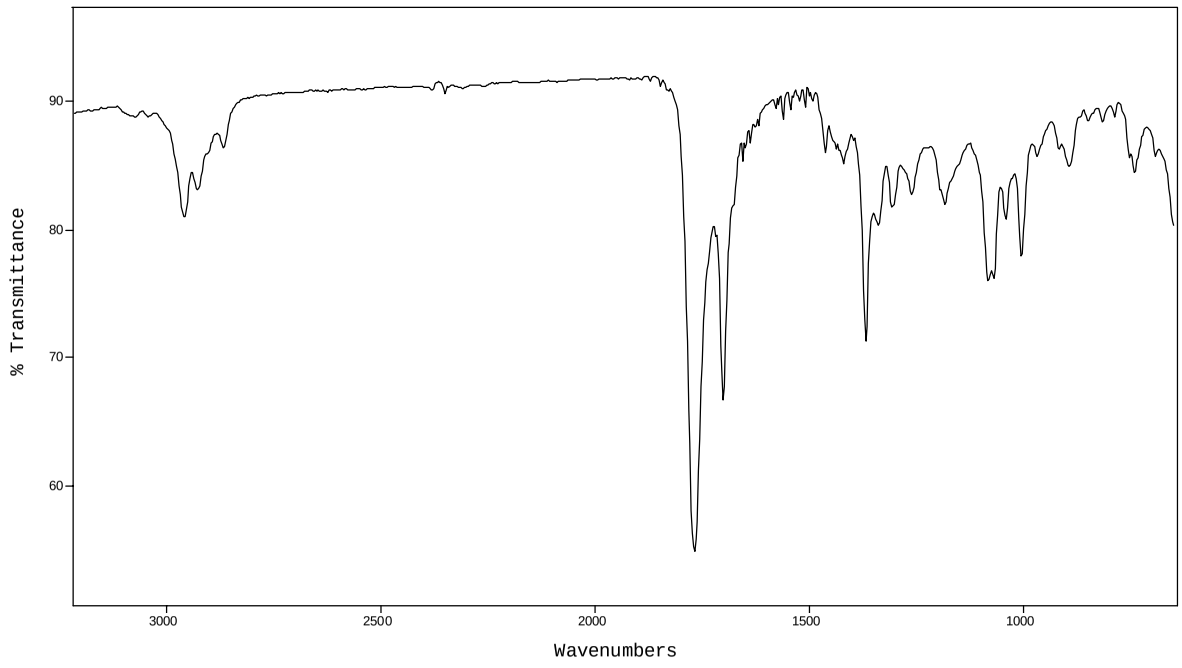


Figure A.5.8 FTIR Spectrum (thin film/NaCl) of Compound **173**.

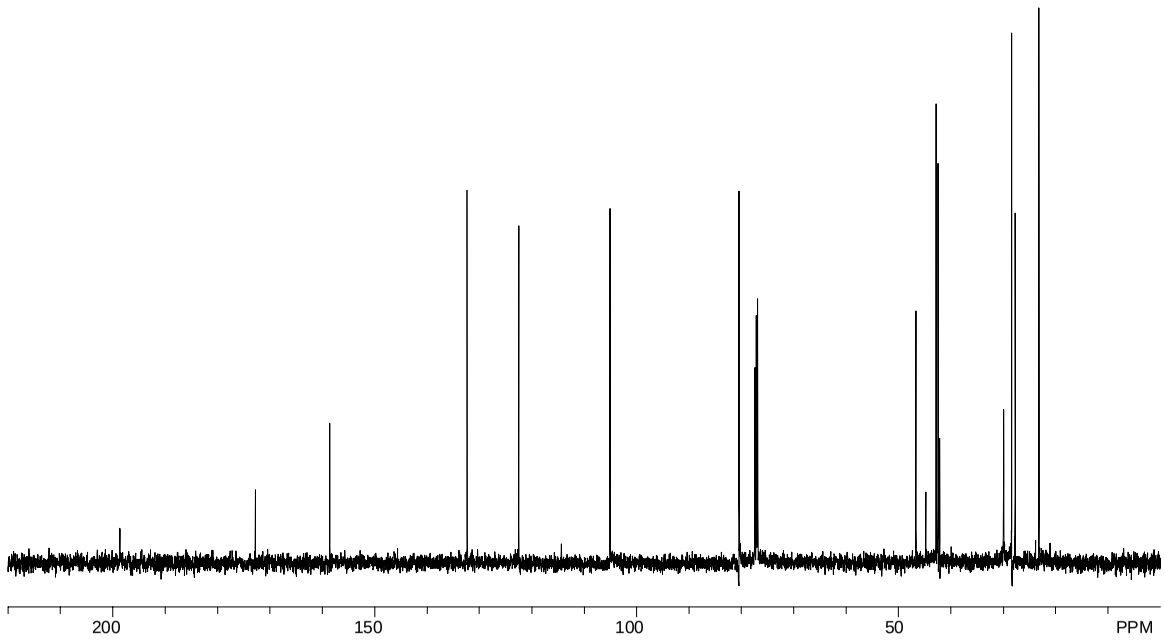


Figure A.5.9 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **173**.

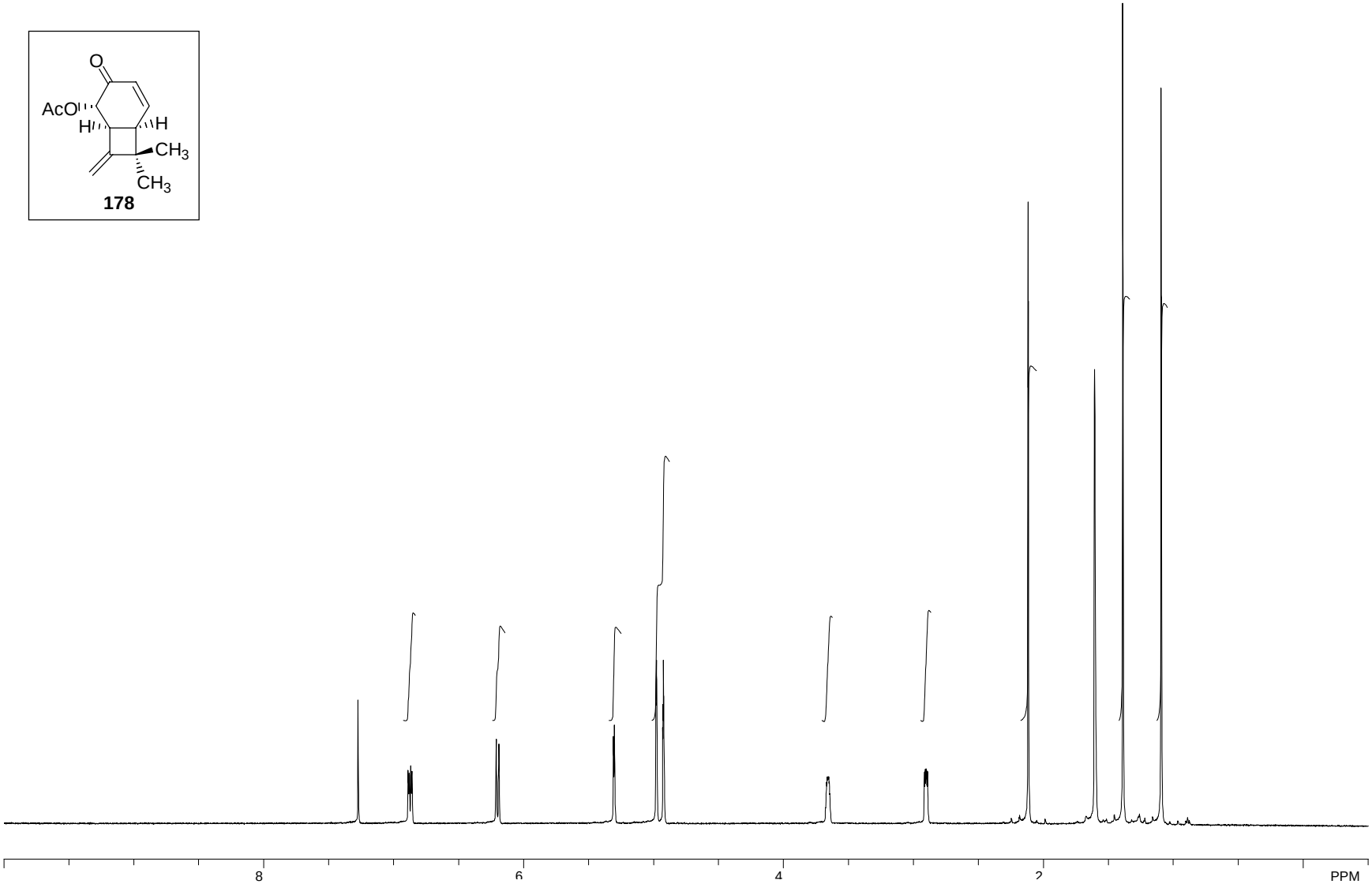


Figure A.5.10 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **178**.

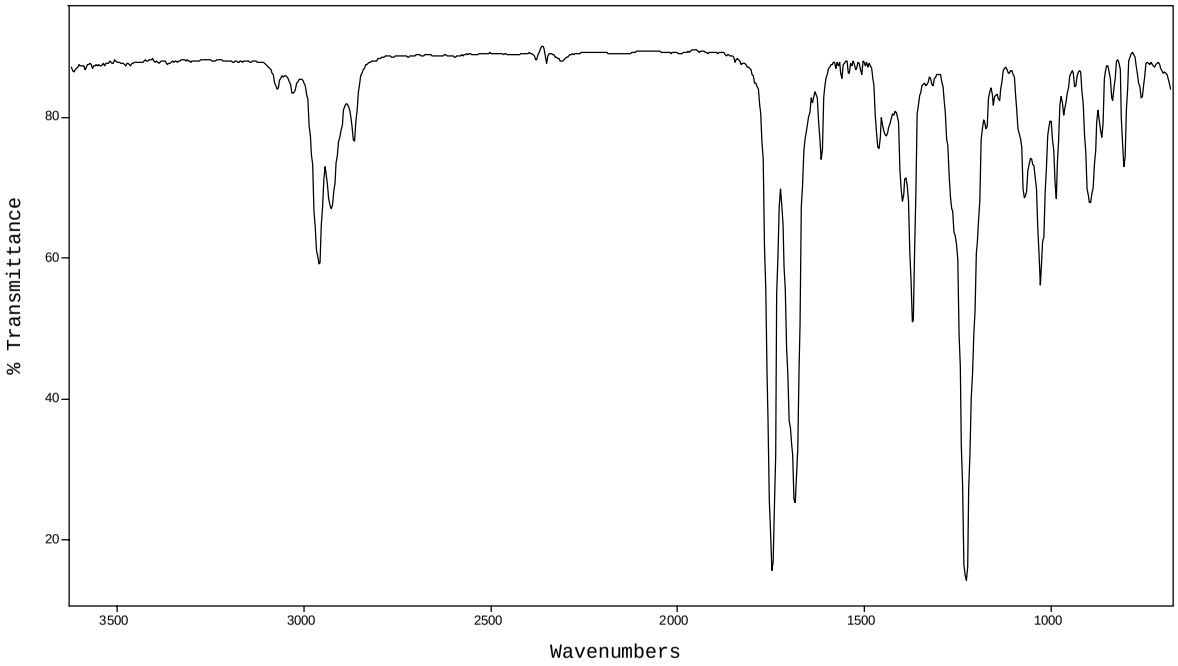


Figure A.5.11 FTIR Spectrum (thin film/NaCl) of Compound **178**.

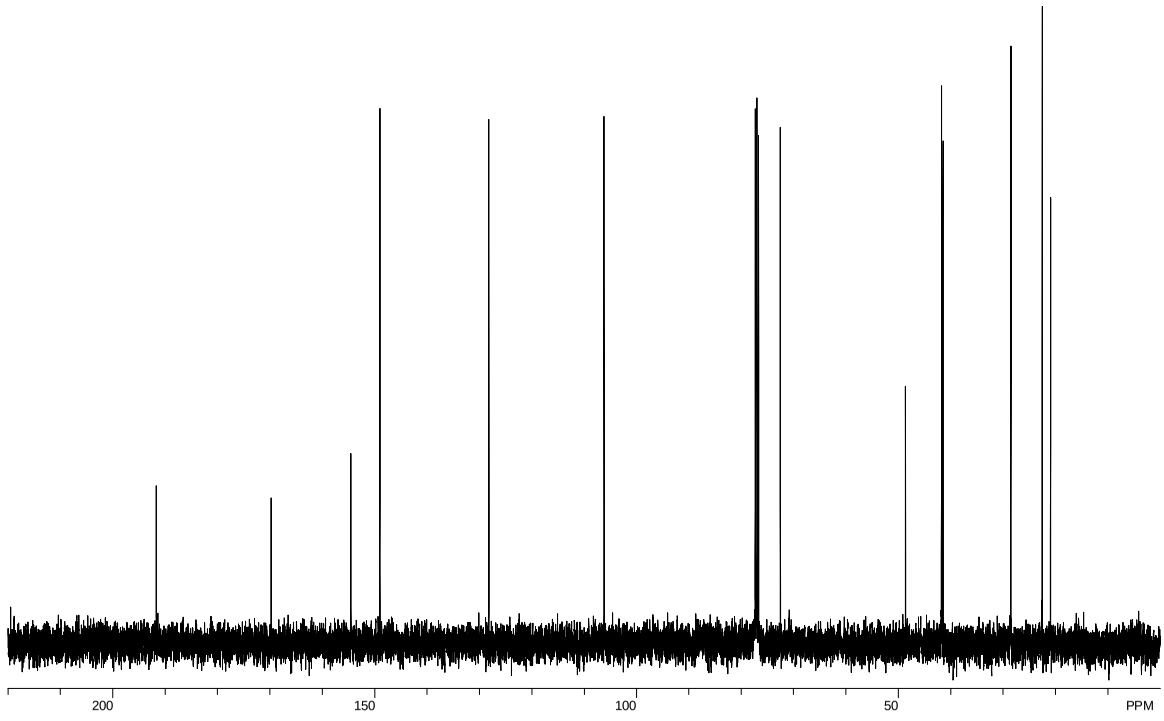


Figure A.5.12 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **178**.

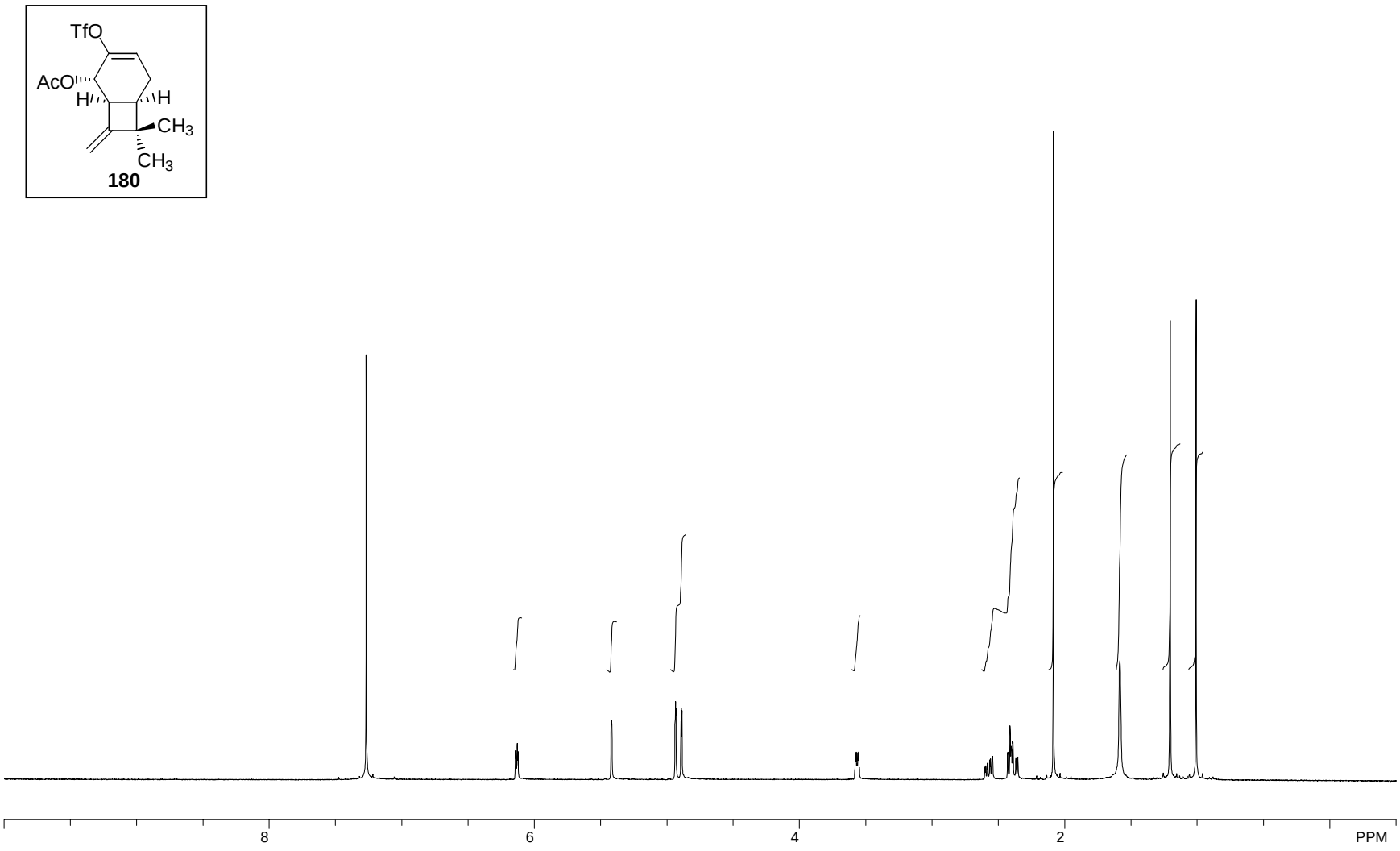


Figure A.5.13 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **180**.

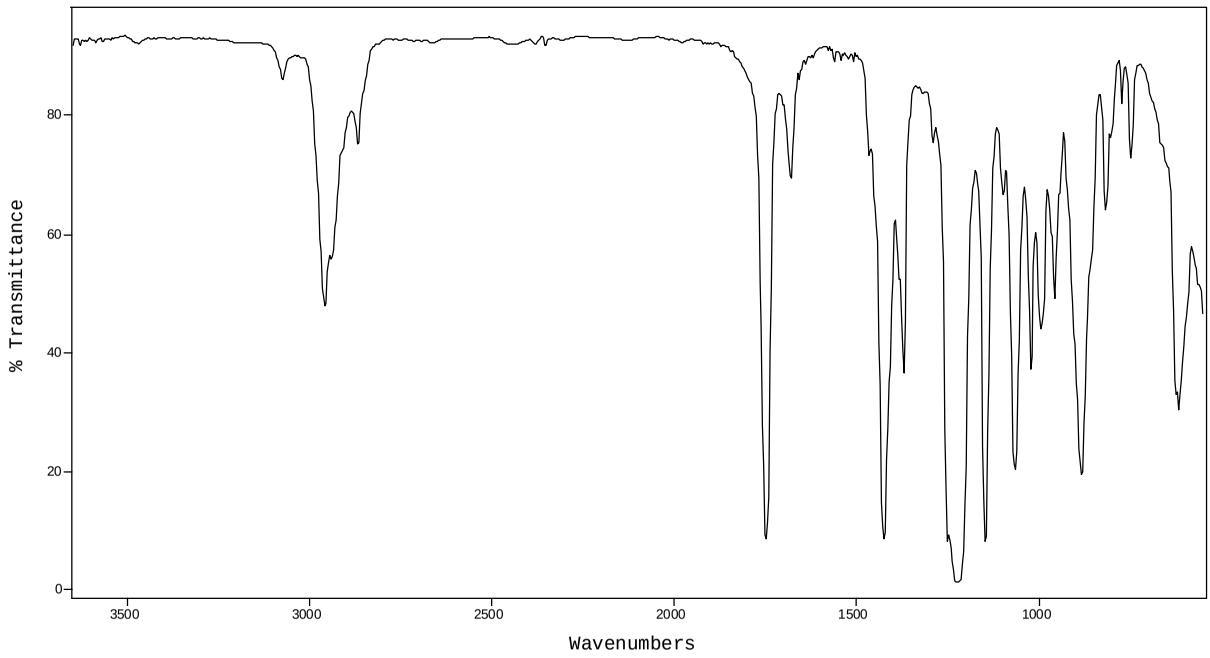


Figure A.5.14 FTIR Spectrum (thin film/NaCl) of Compound **180**.

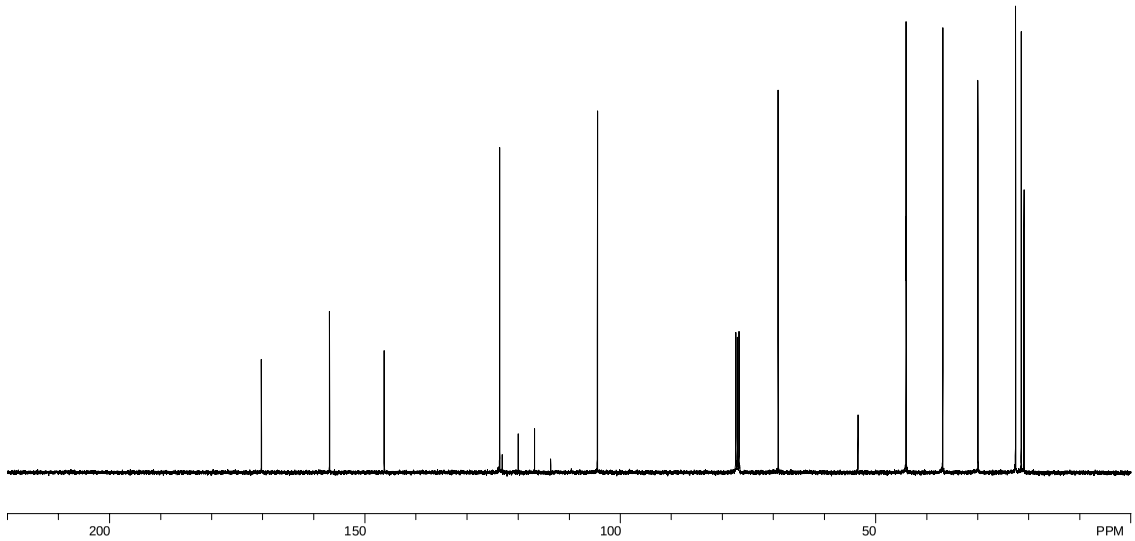


Figure A.5.15 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **180**.

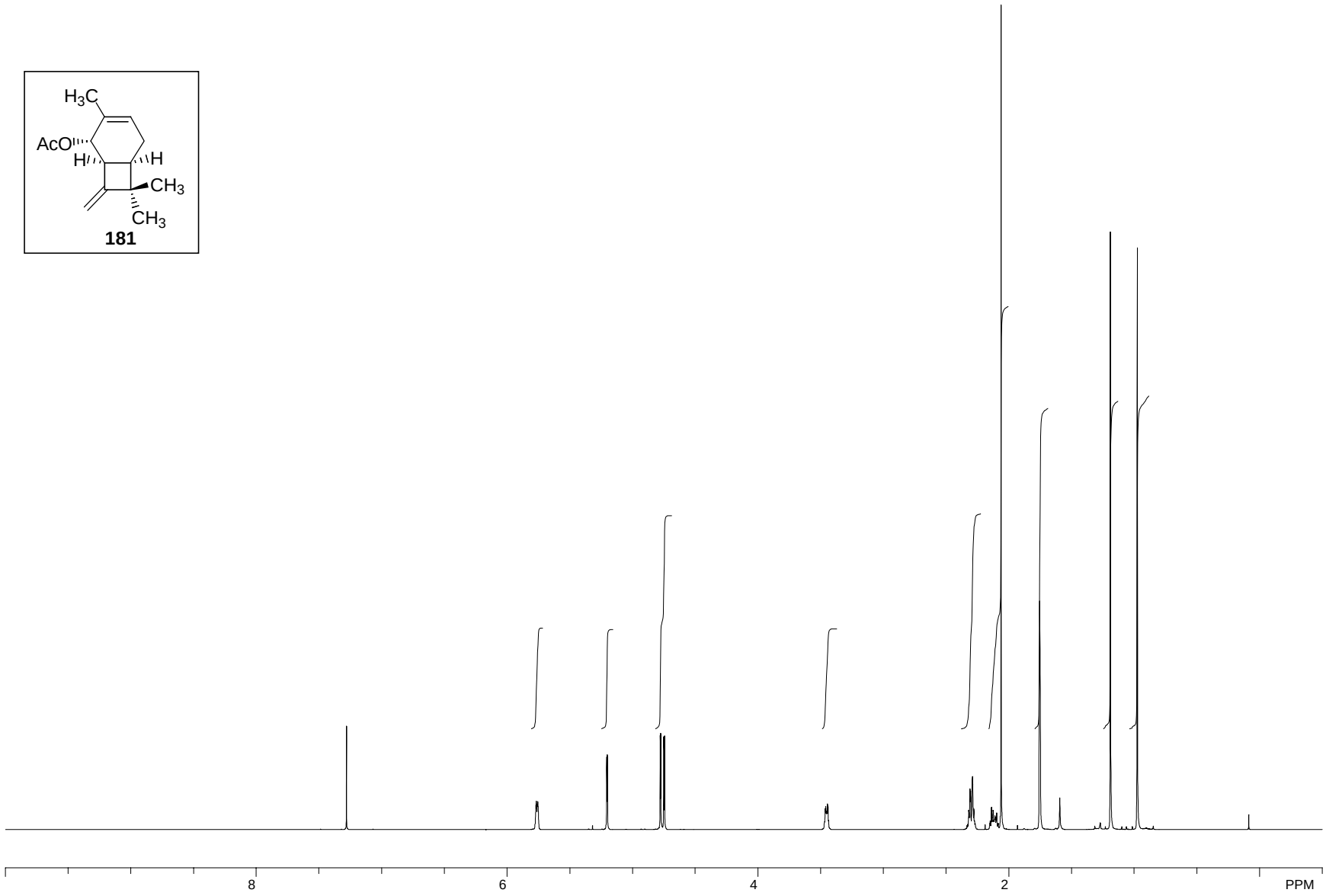


Figure A.5.16 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **181**.

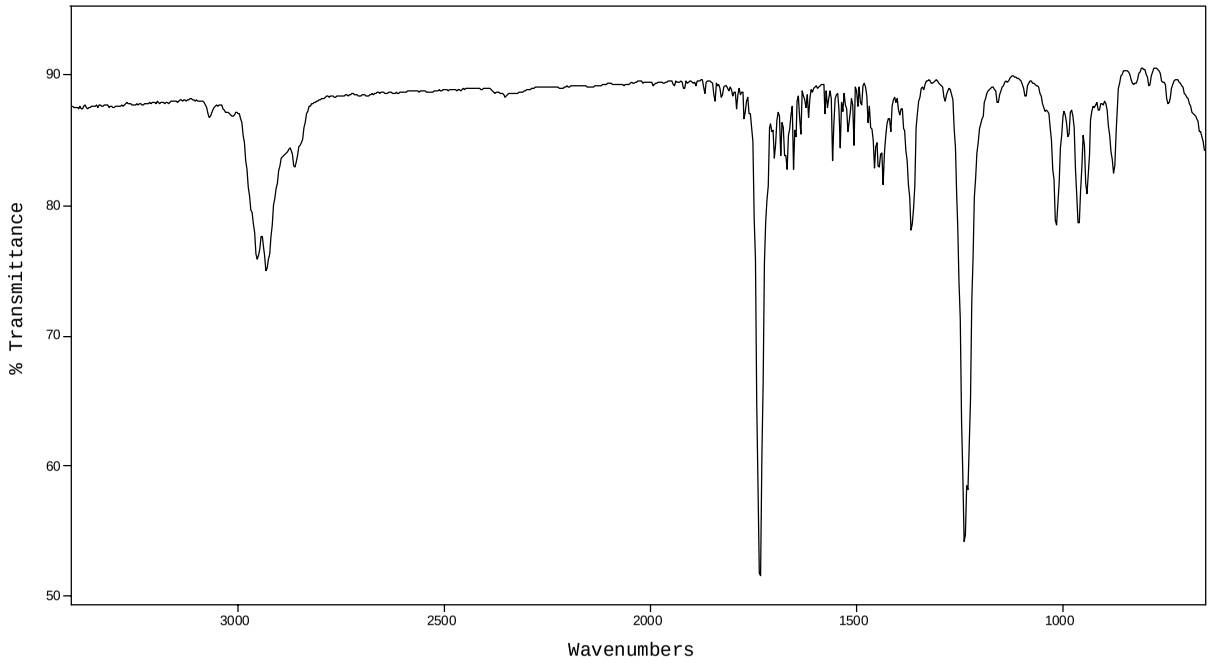


Figure A.5.17 FTIR Spectrum (thin film/NaCl) of Compound **181**.

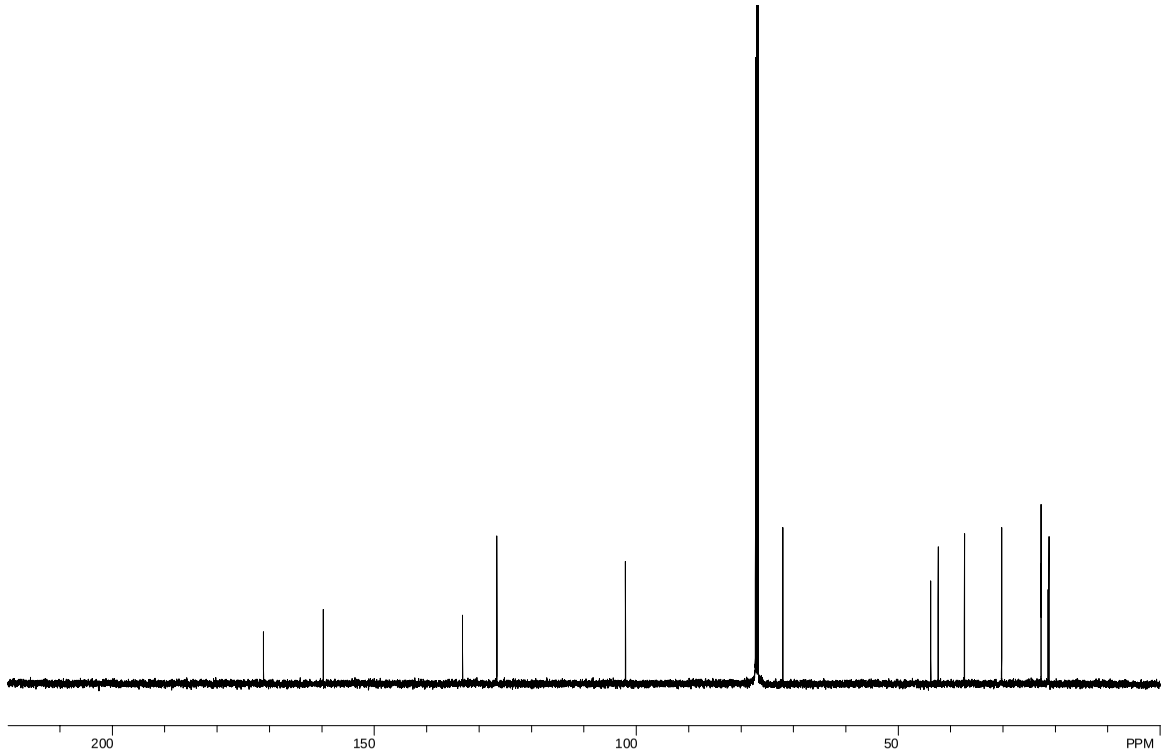


Figure A.5.18 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **181**.

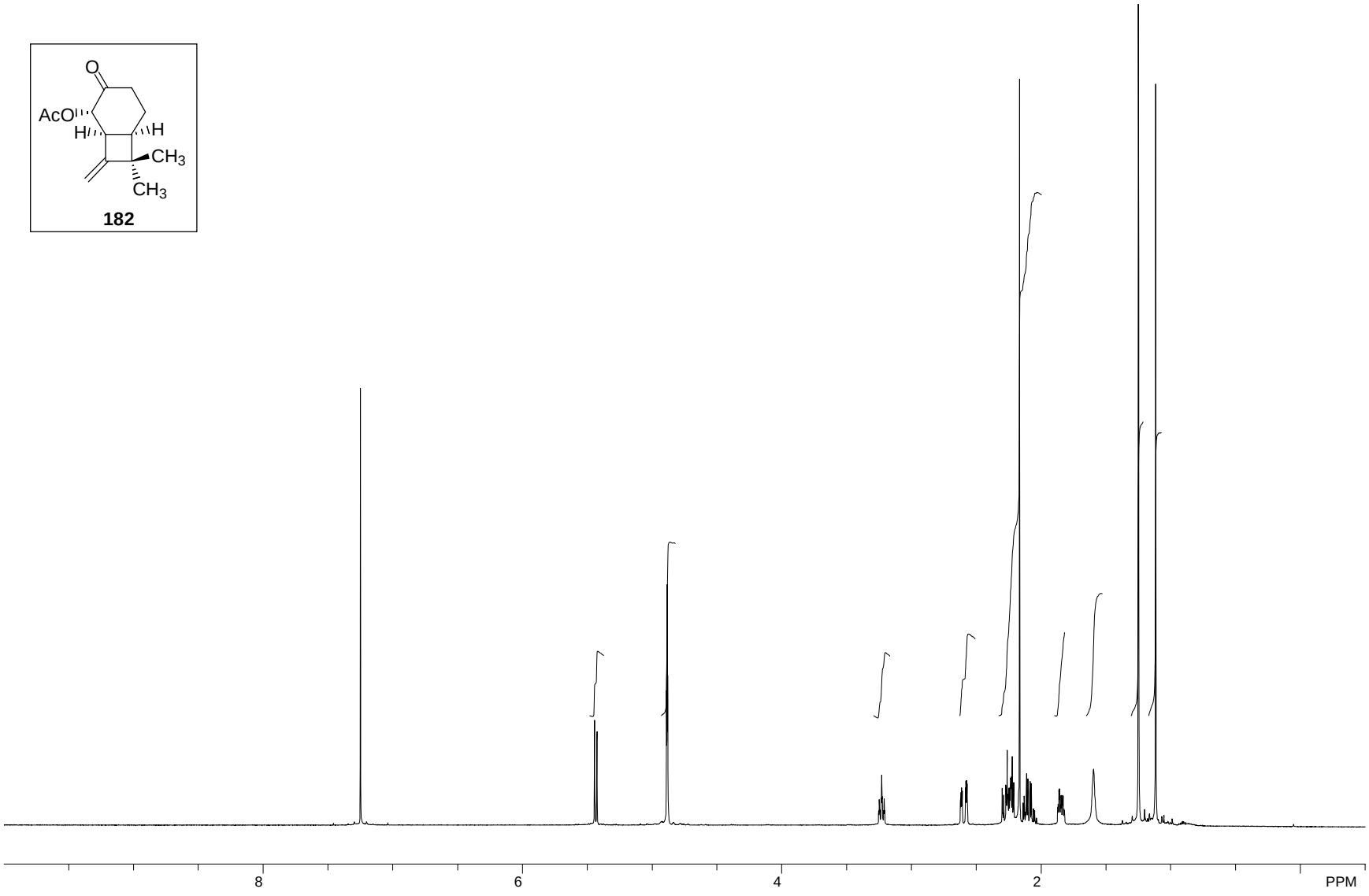


Figure A.5.19 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **182**.

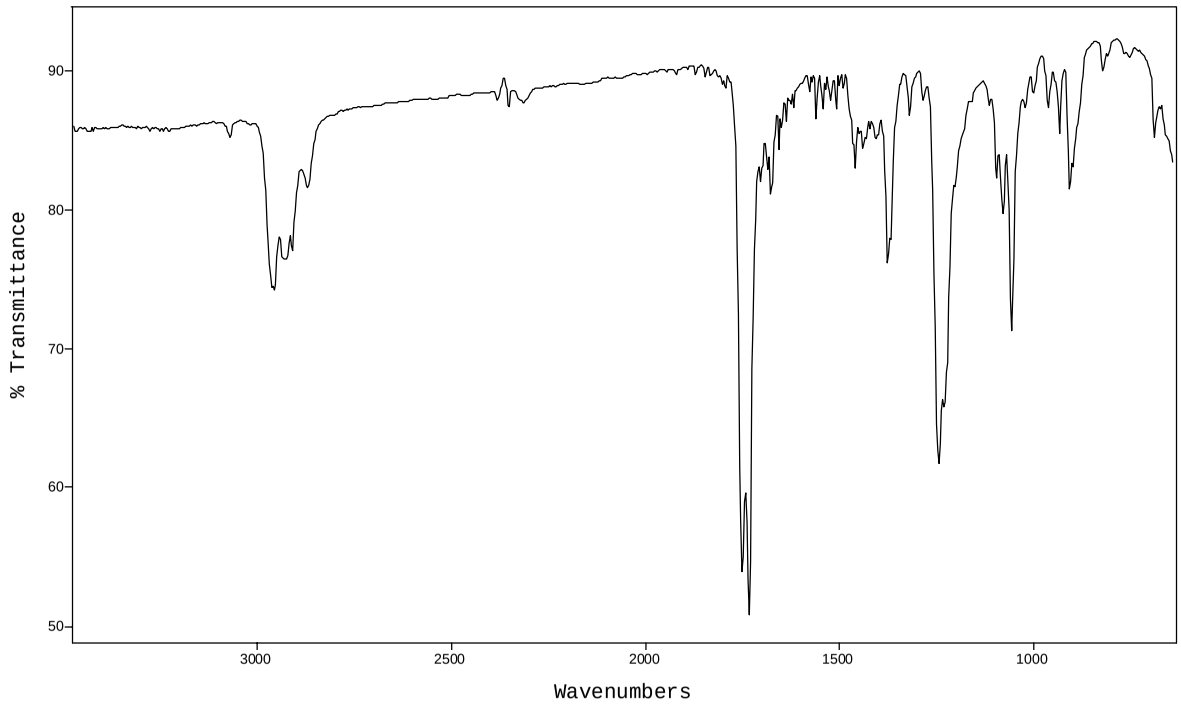


Figure A.5.20 FTIR Spectrum (thin film/NaCl) of Compound **182**.

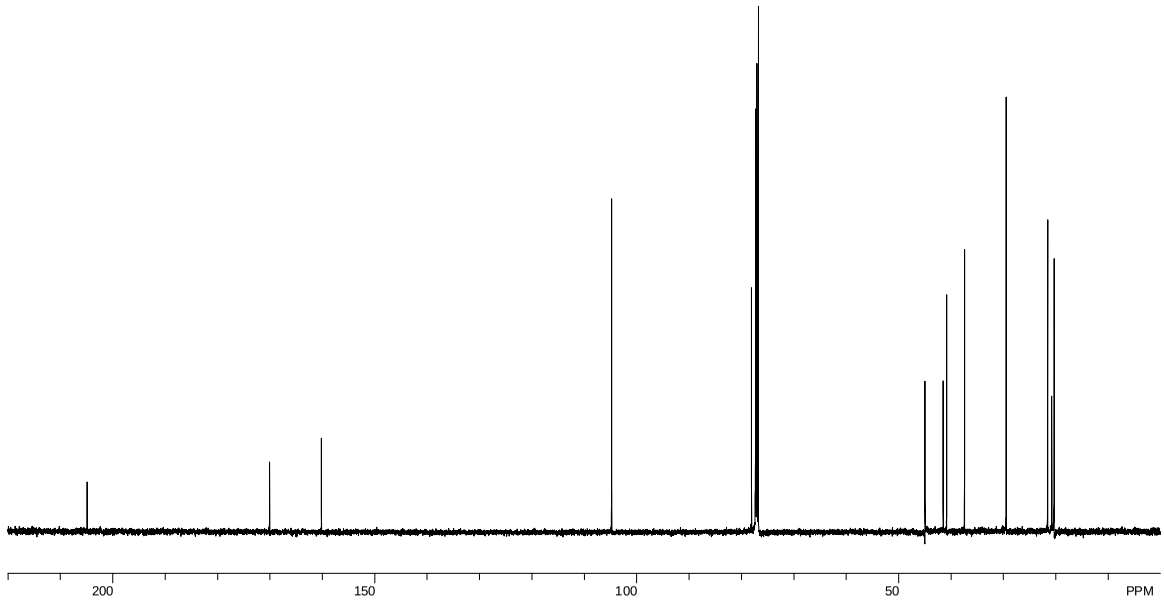


Figure A.5.21 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **182**.

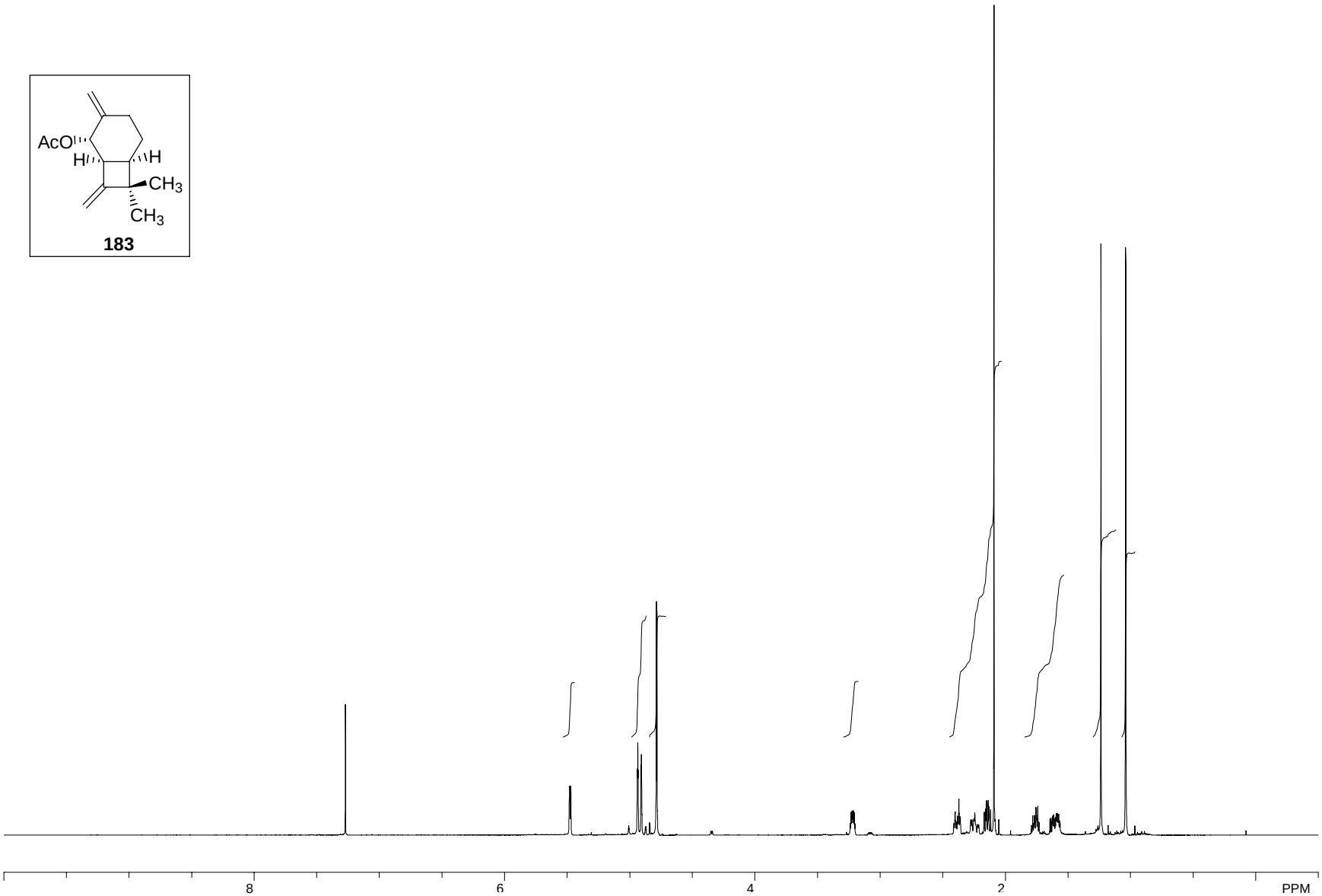


Figure A.5.22 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **183**.

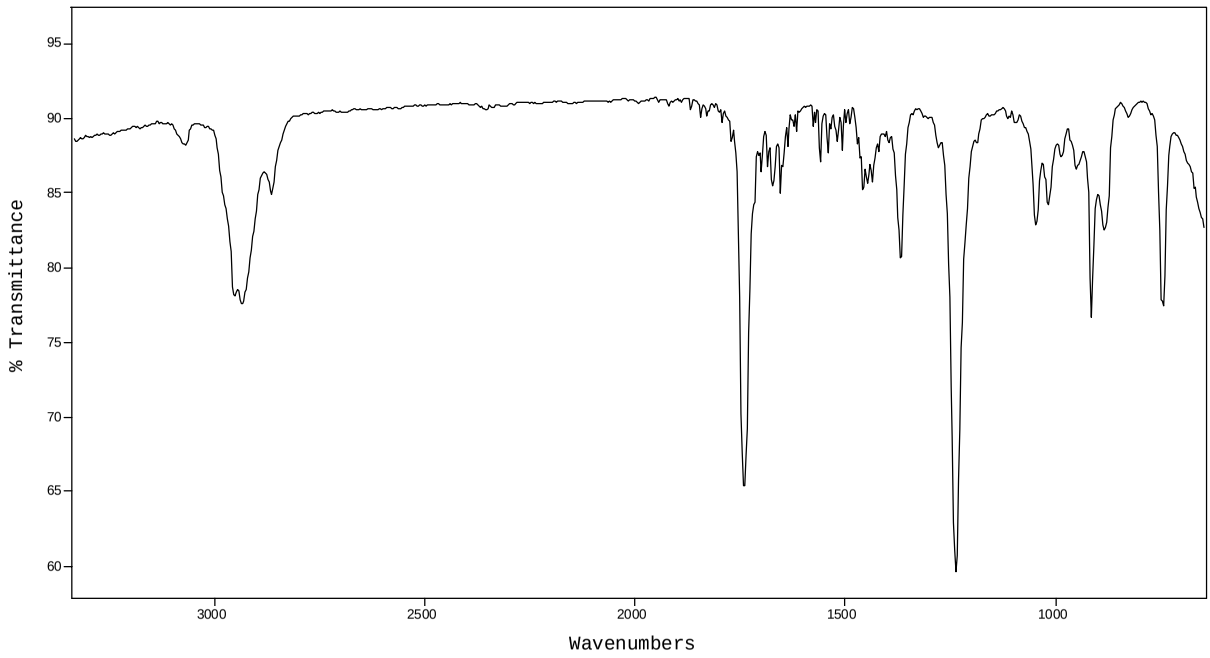


Figure A.5.23 FTIR Spectrum (thin film/NaCl) of Compound **183**.

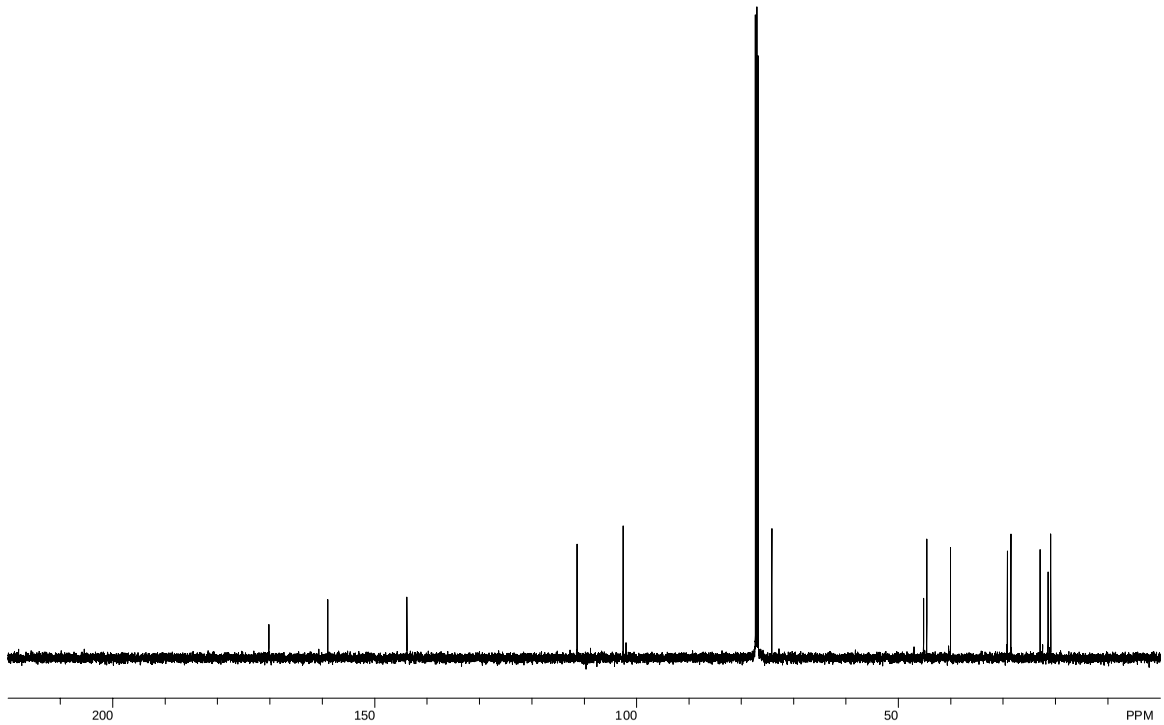


Figure A.5.24 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **183**.

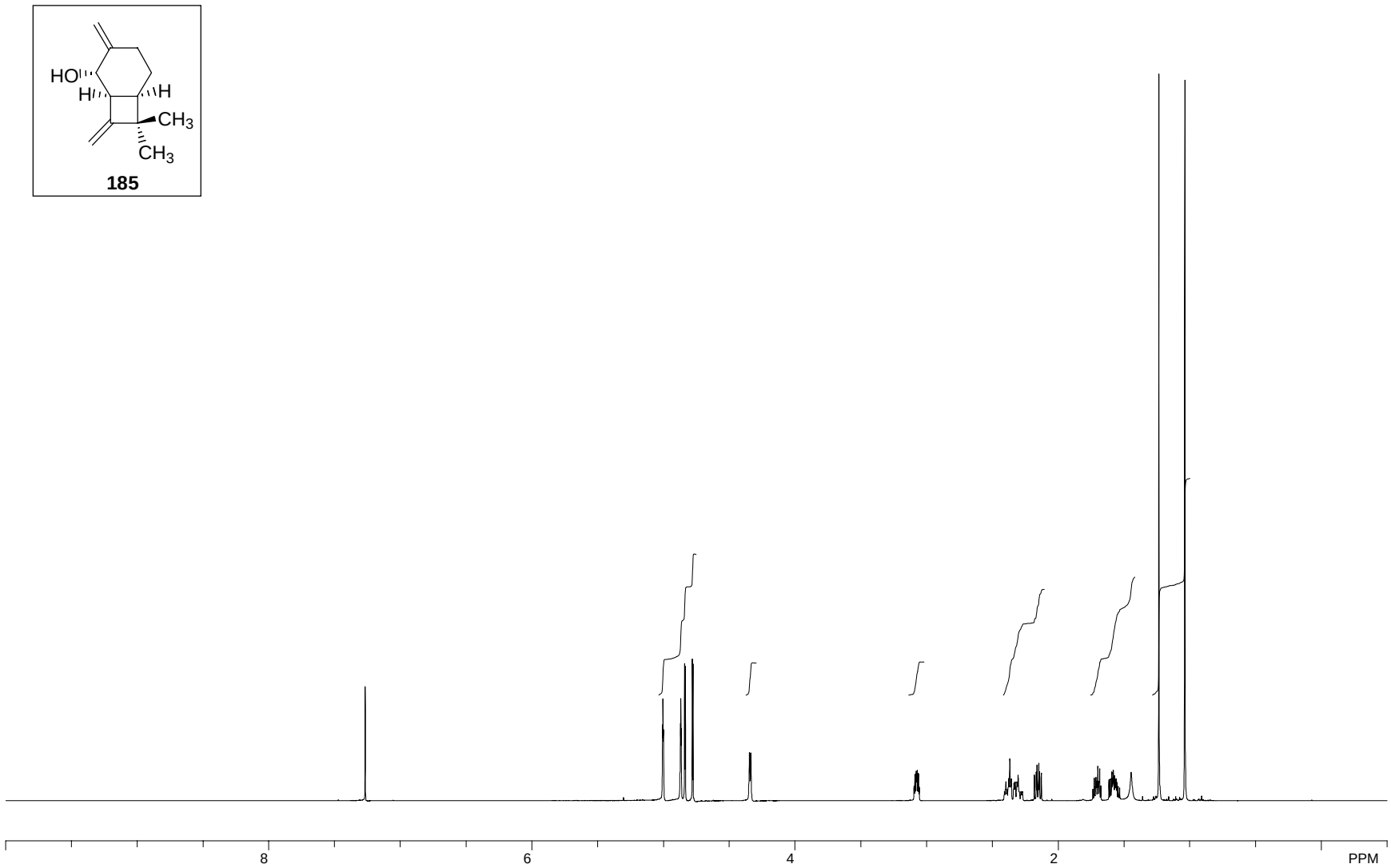


Figure A.5.25 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **185**.

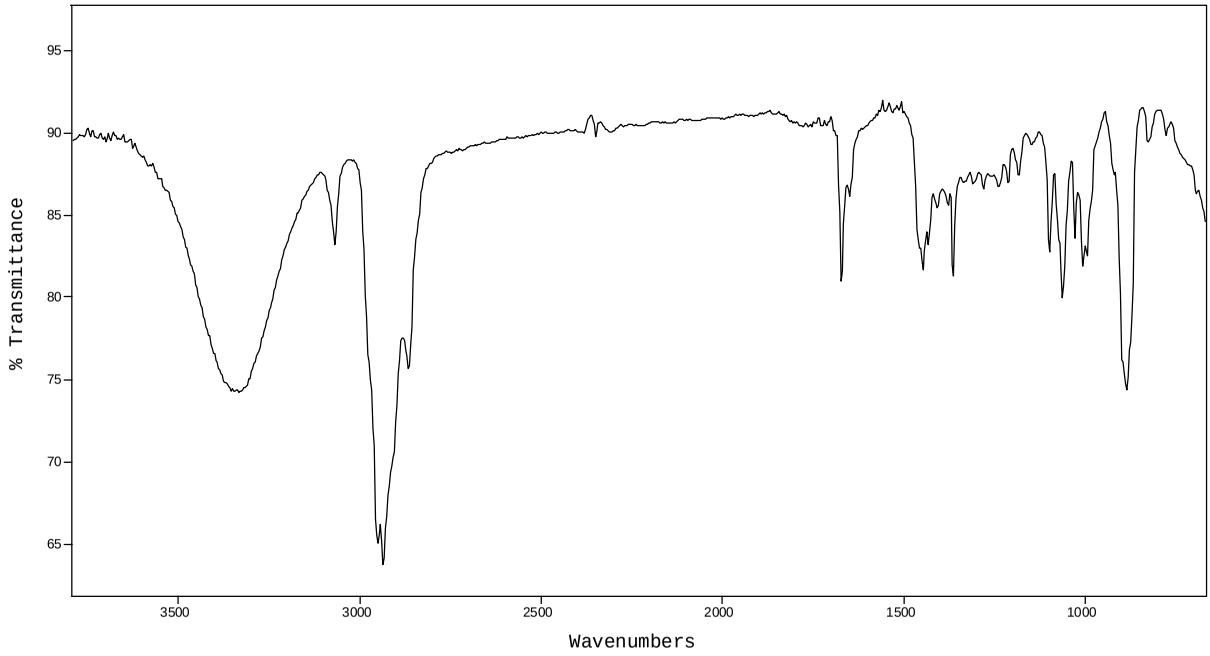


Figure A.5.26 FTIR Spectrum (thin film/NaCl) of Compound **185**.

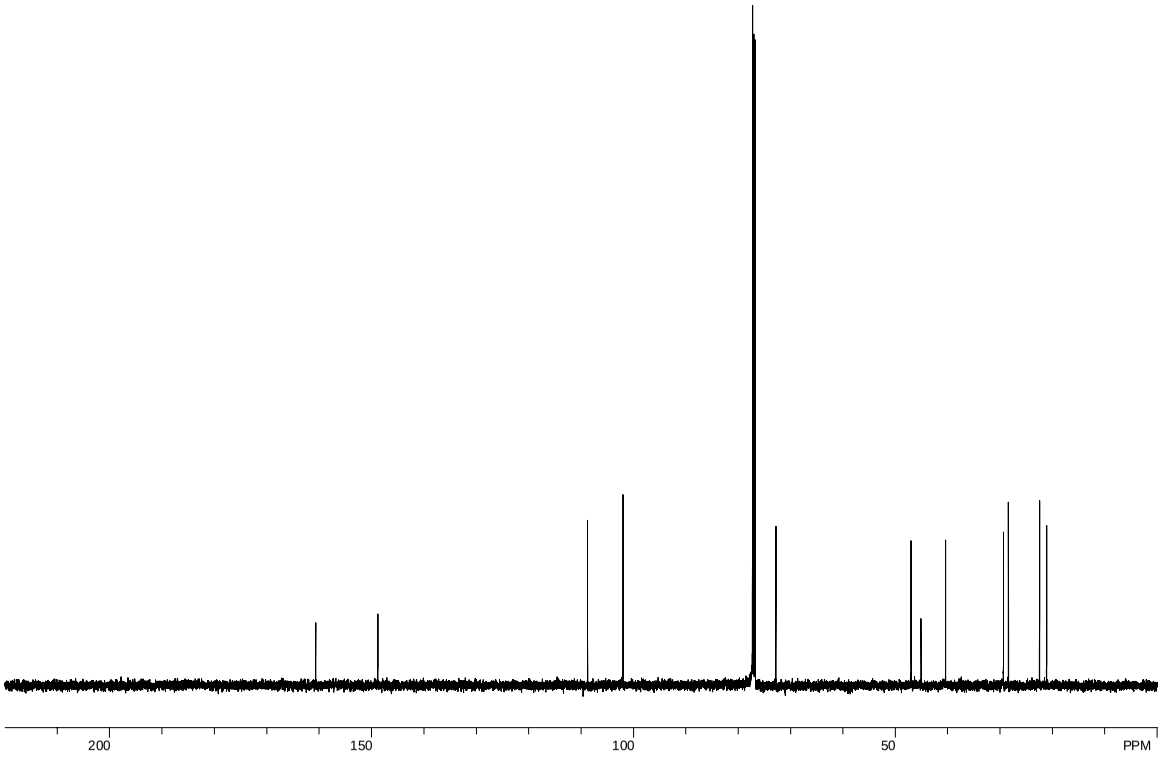


Figure A.5.27 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **185.**

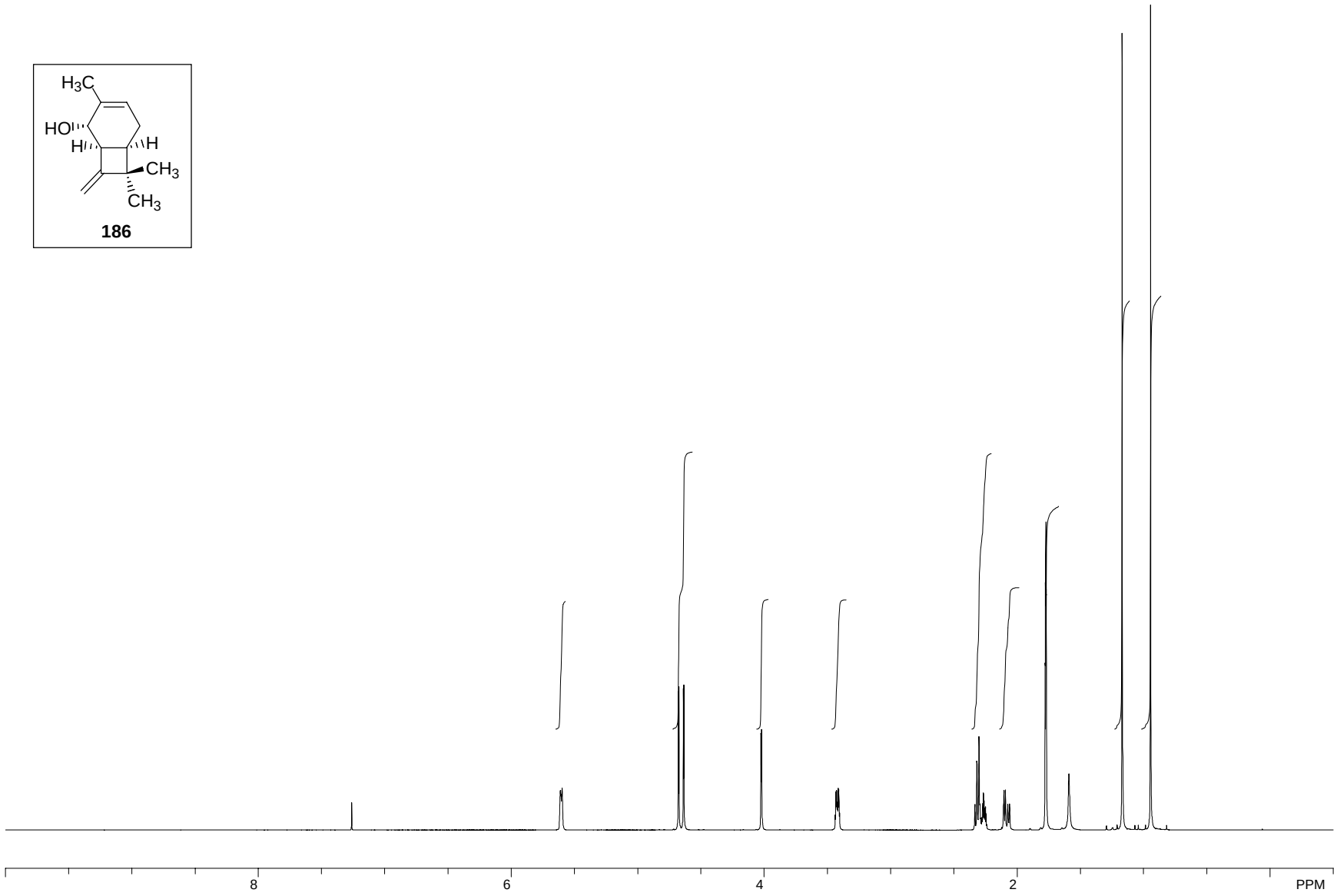


Figure A.5.28 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **186**.

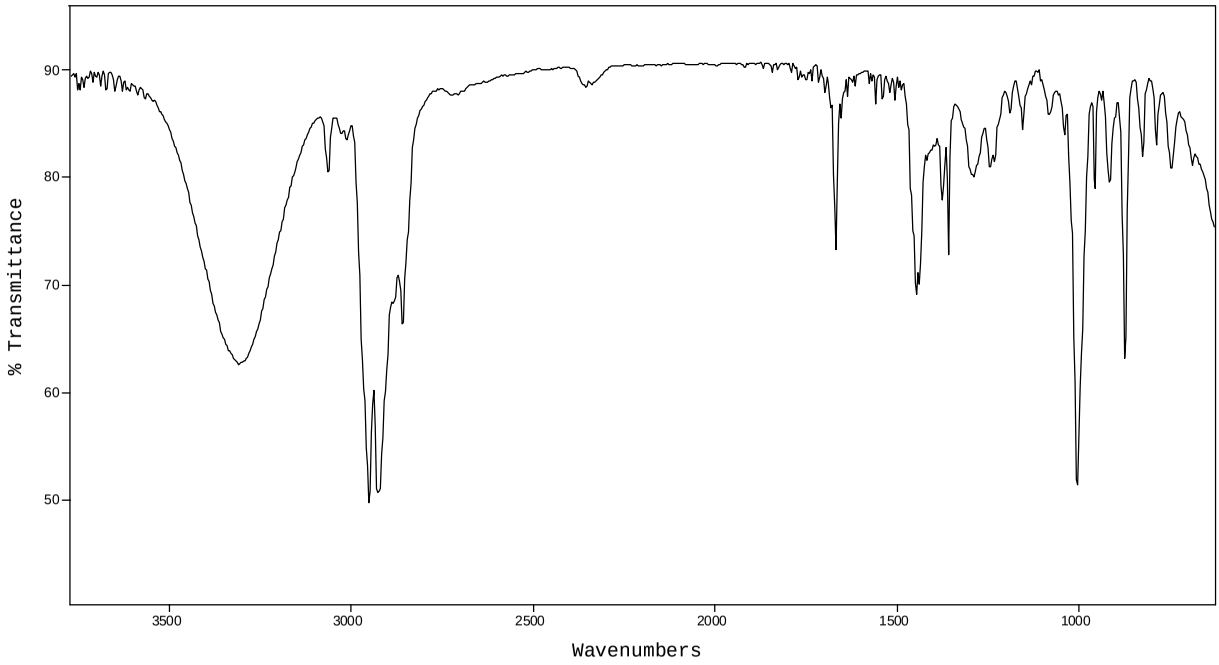


Figure A.5.29 FTIR Spectrum (thin film/NaCl) of Compound **186**.

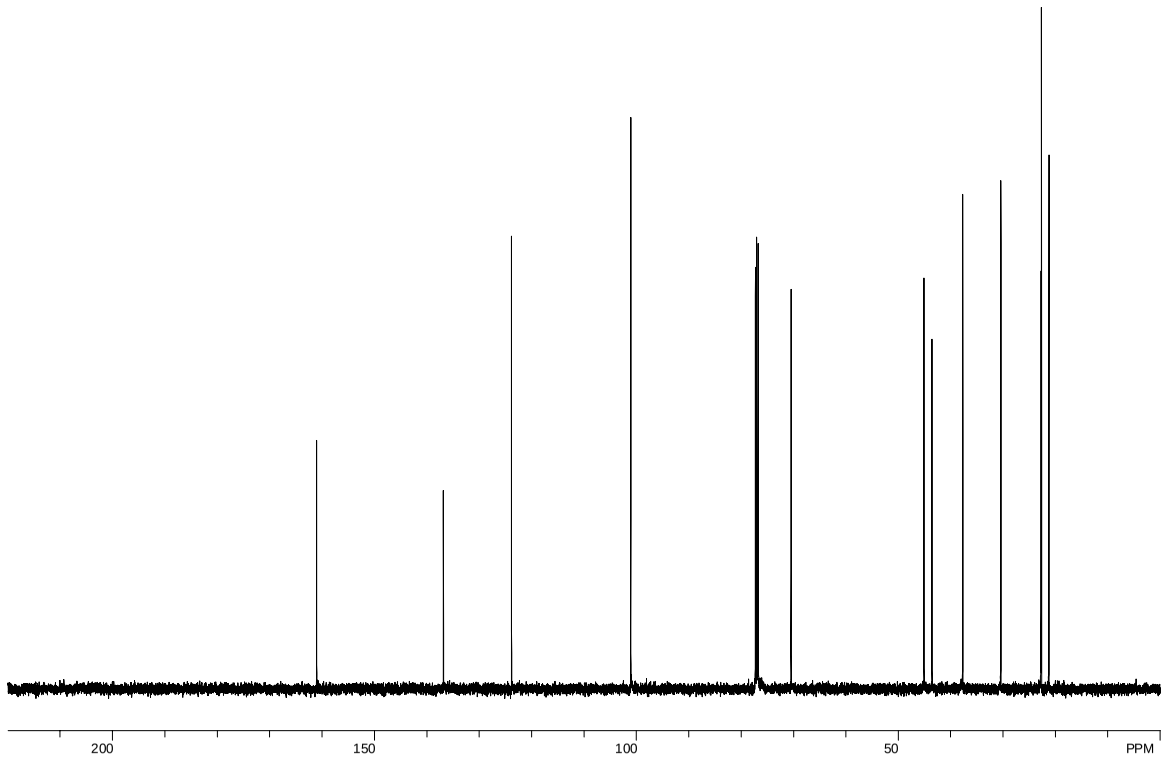


Figure A.5.30 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **186**.

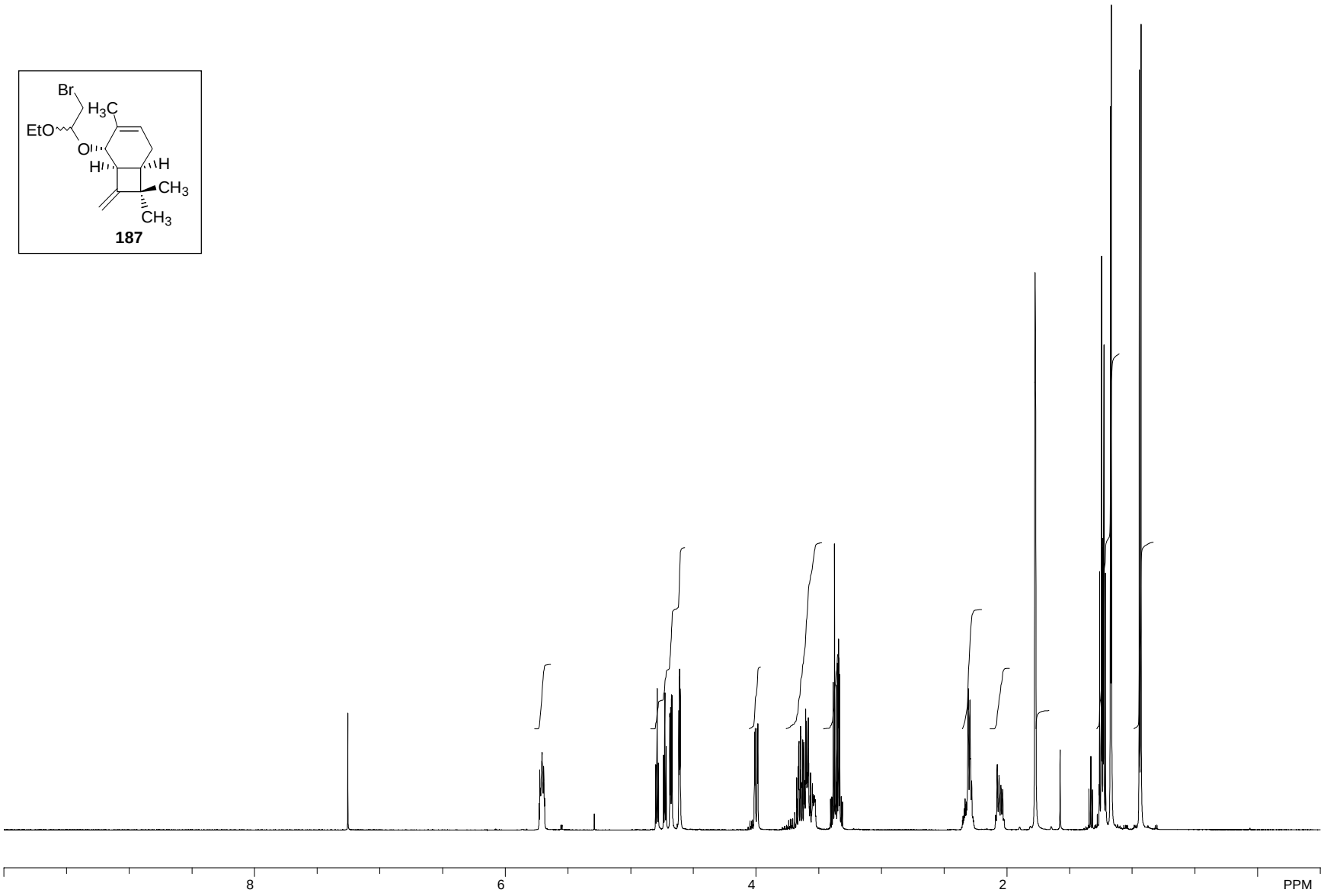


Figure A.5.31 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **187**.

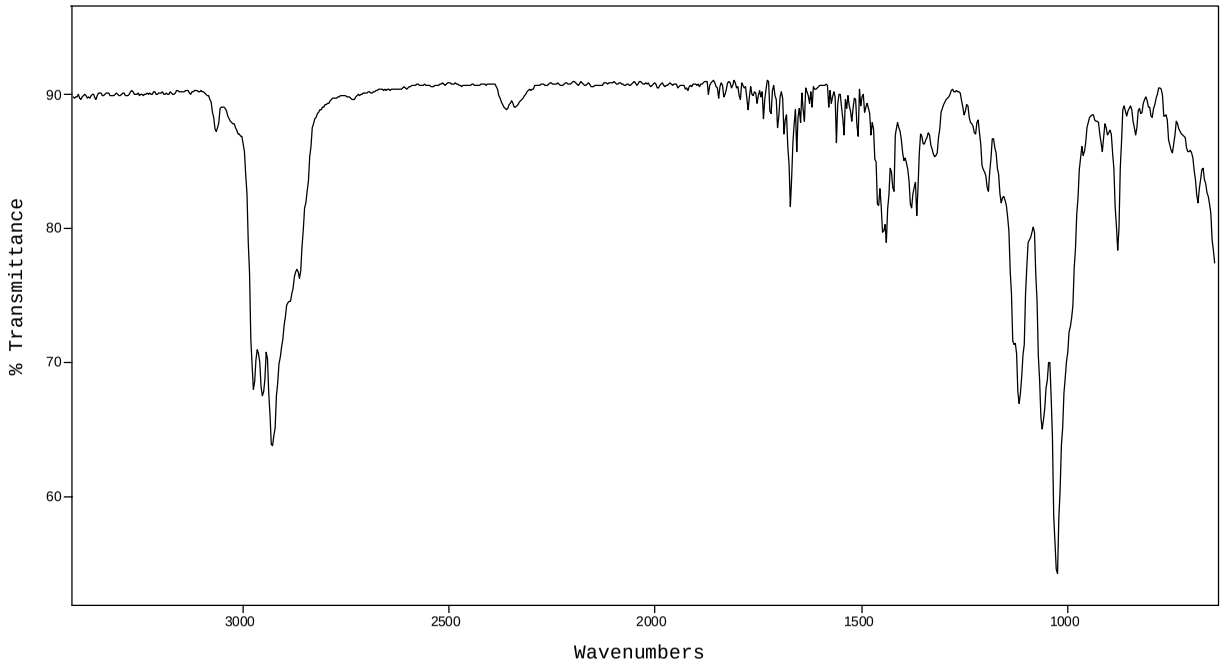


Figure A.5.32 FTIR Spectrum (thin film/NaCl) of Compound **187**.

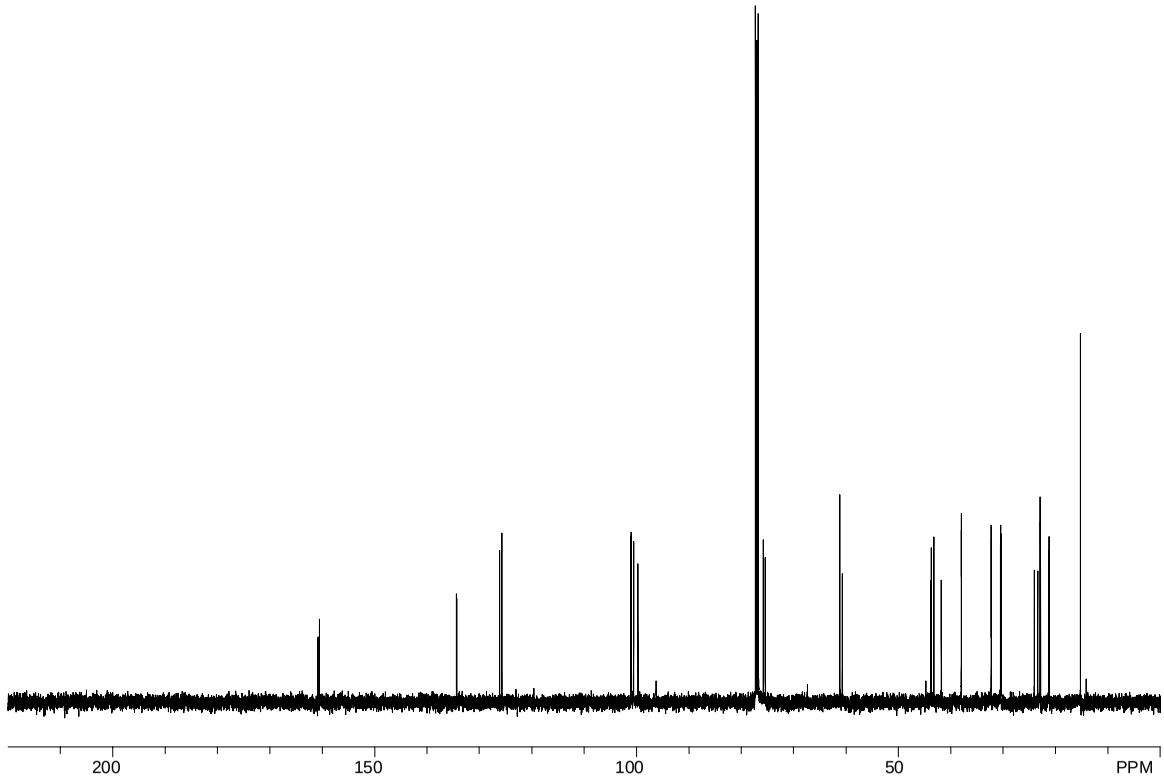
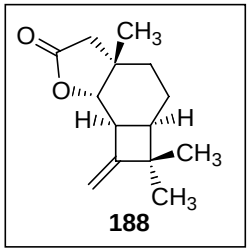


Figure A.5.33 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **187**.



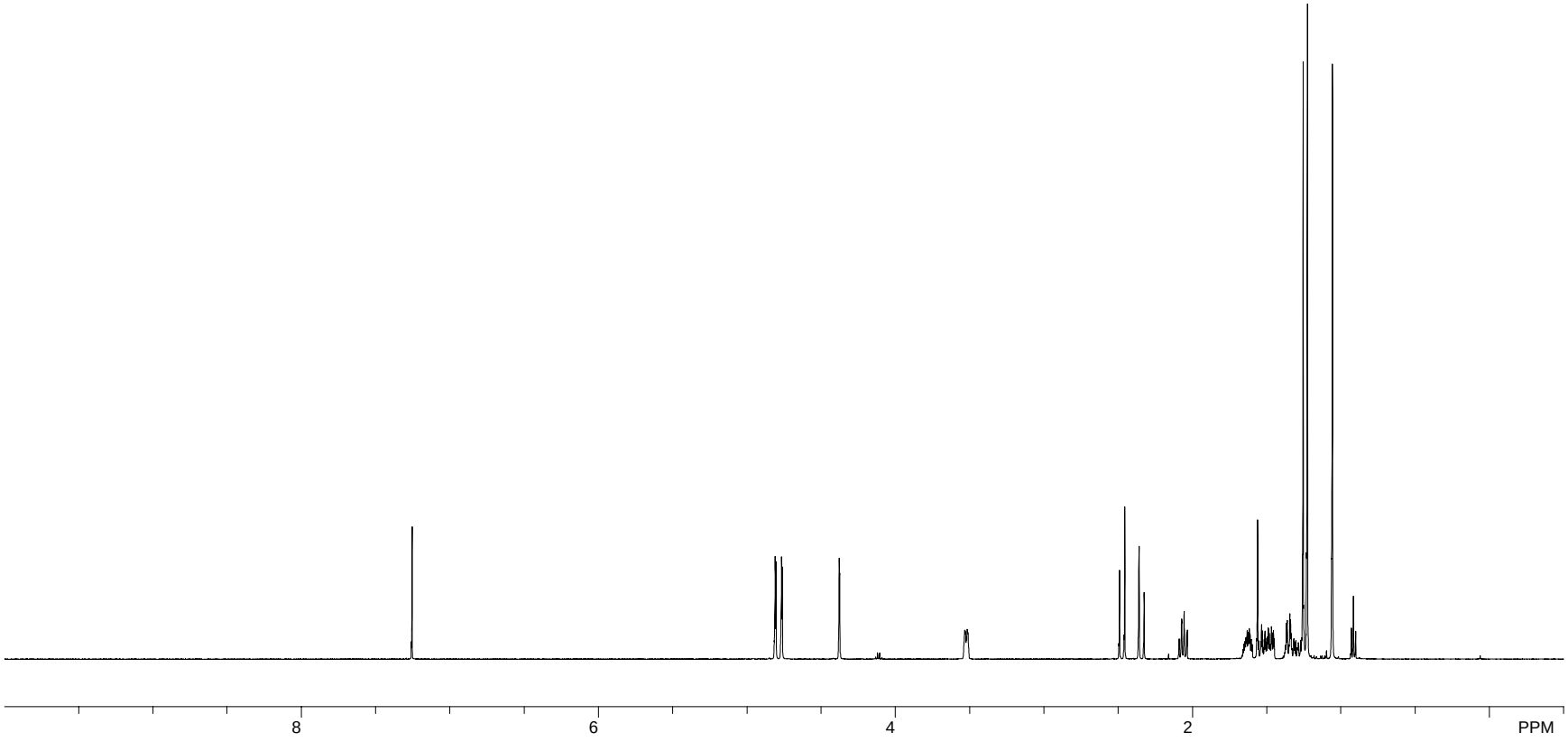


Figure A.5.34 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **188**.

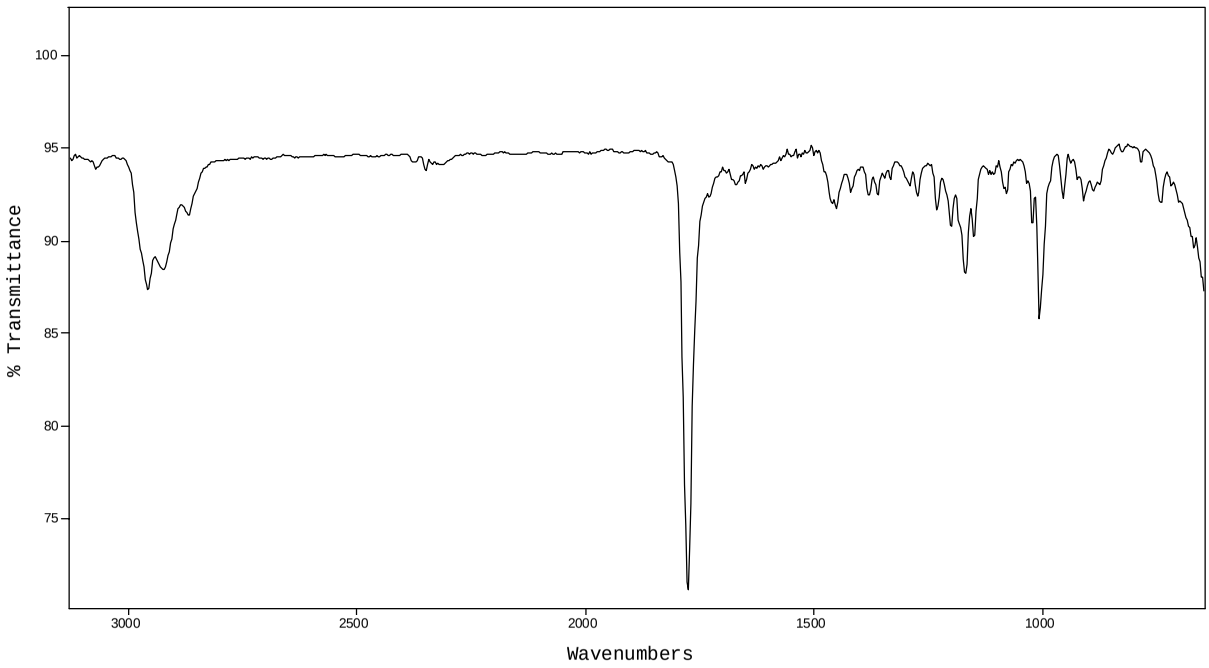


Figure A.5.35 FTIR Spectrum (thin film/NaCl) of Compound **188**.

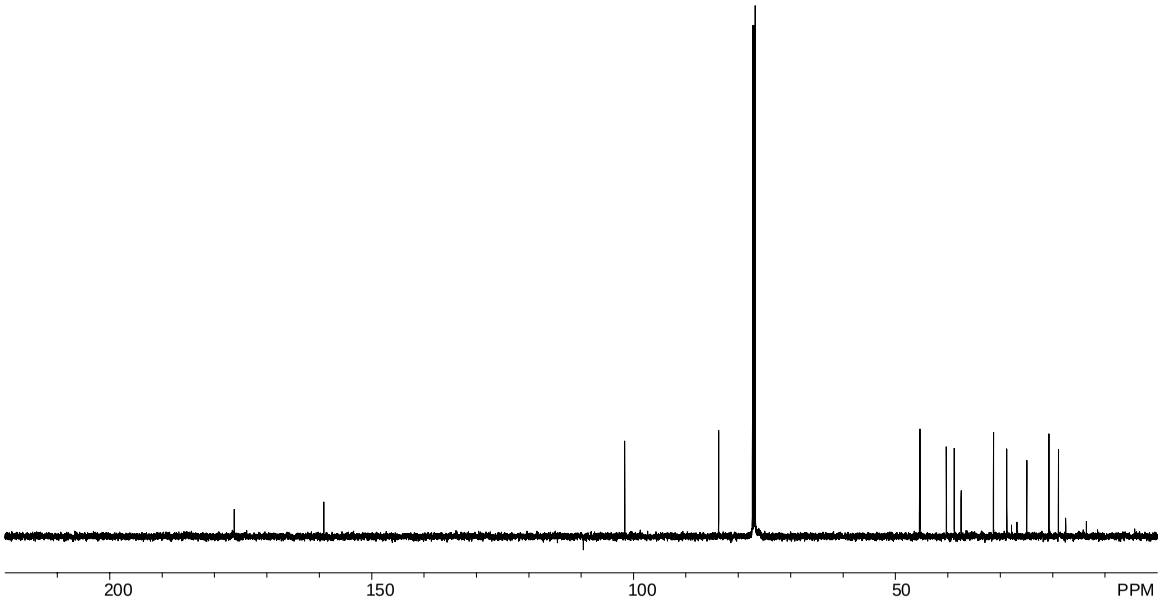


Figure A.5.36 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **188**.

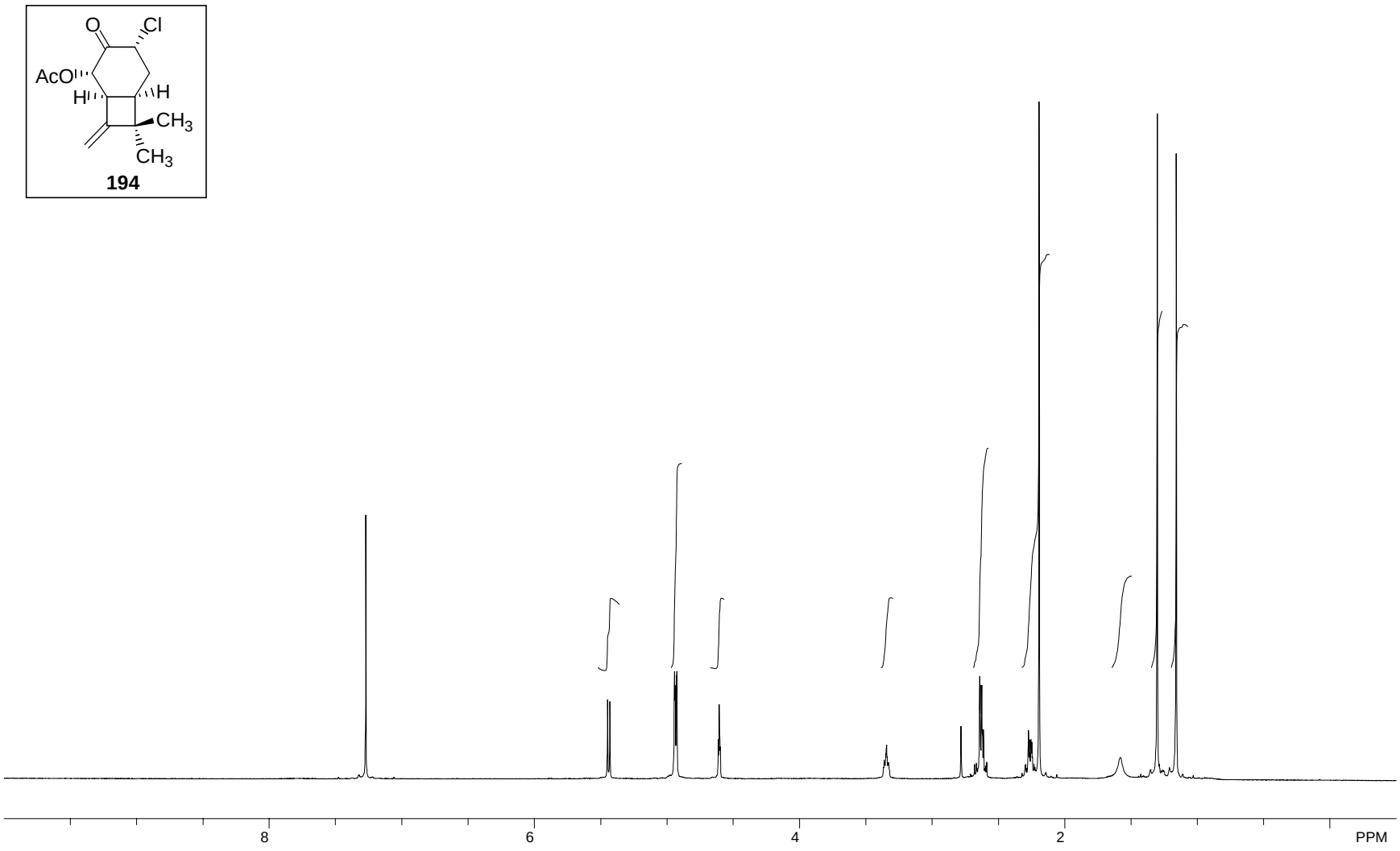


Figure A.5.37 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **194**.

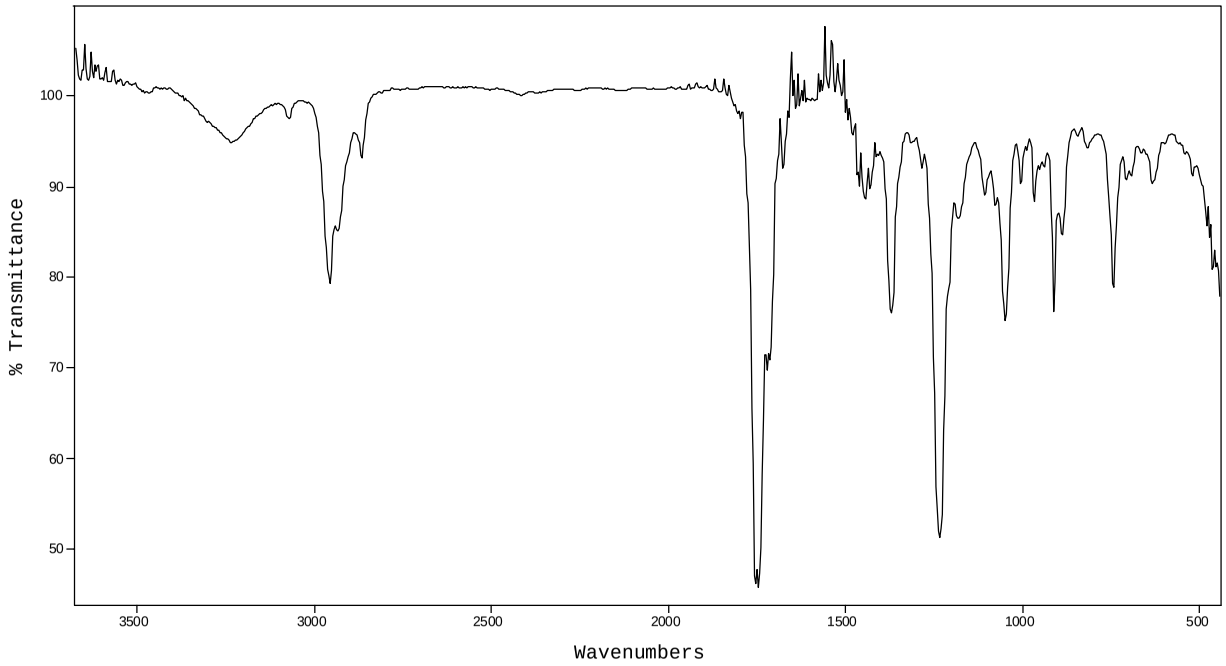


Figure A.5.38 FTIR Spectrum (thin film/NaCl) of Compound **194**.

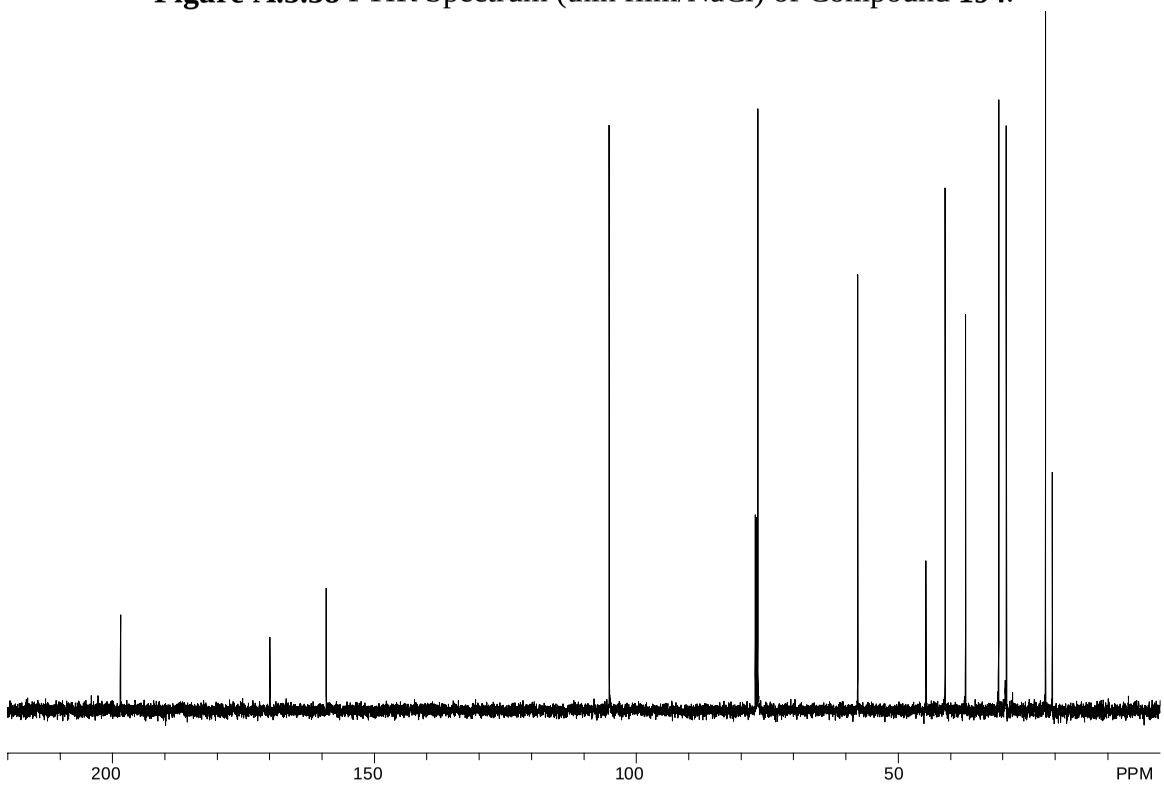


Figure A.5.39 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **194**.

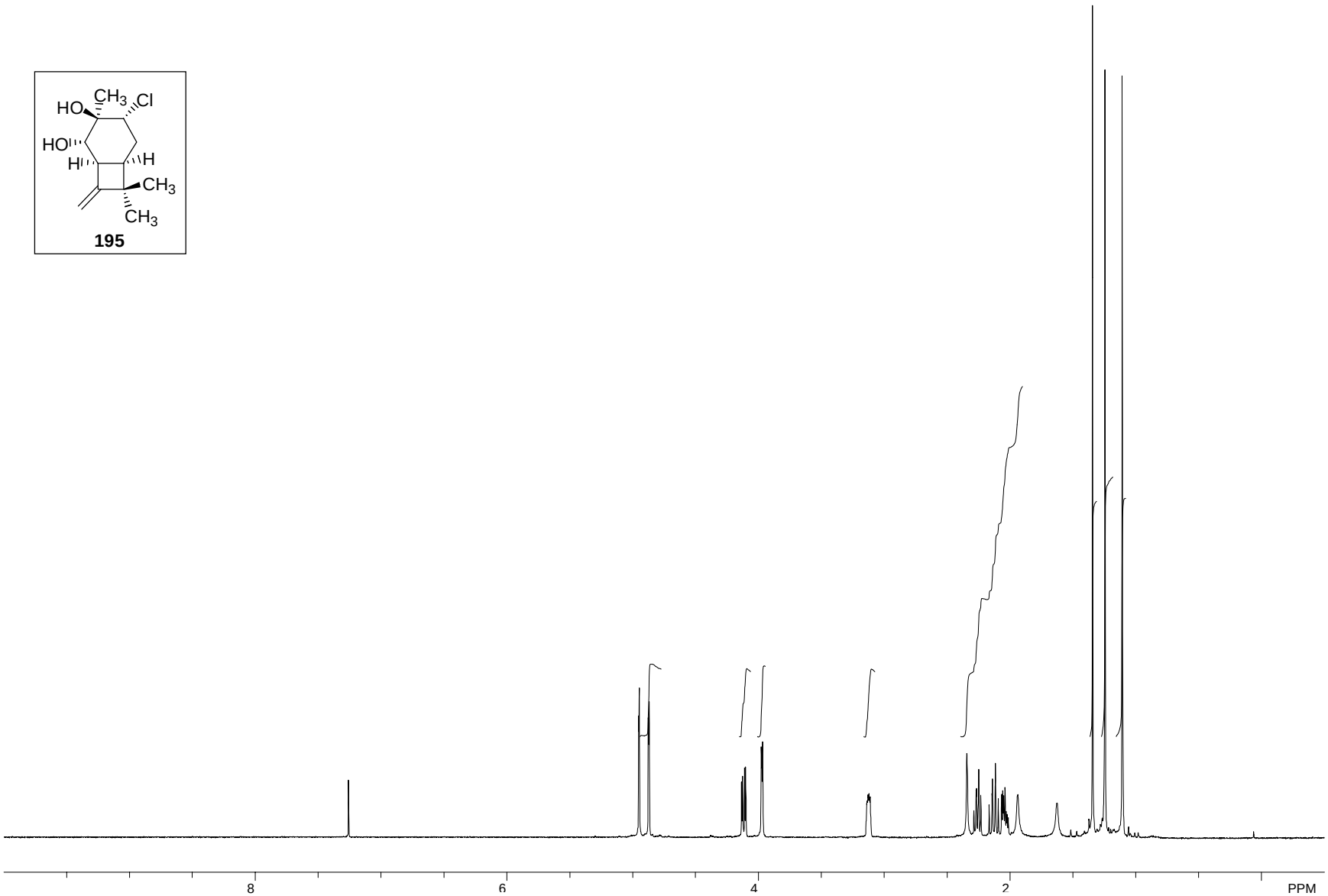


Figure A.5.40 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **195**.

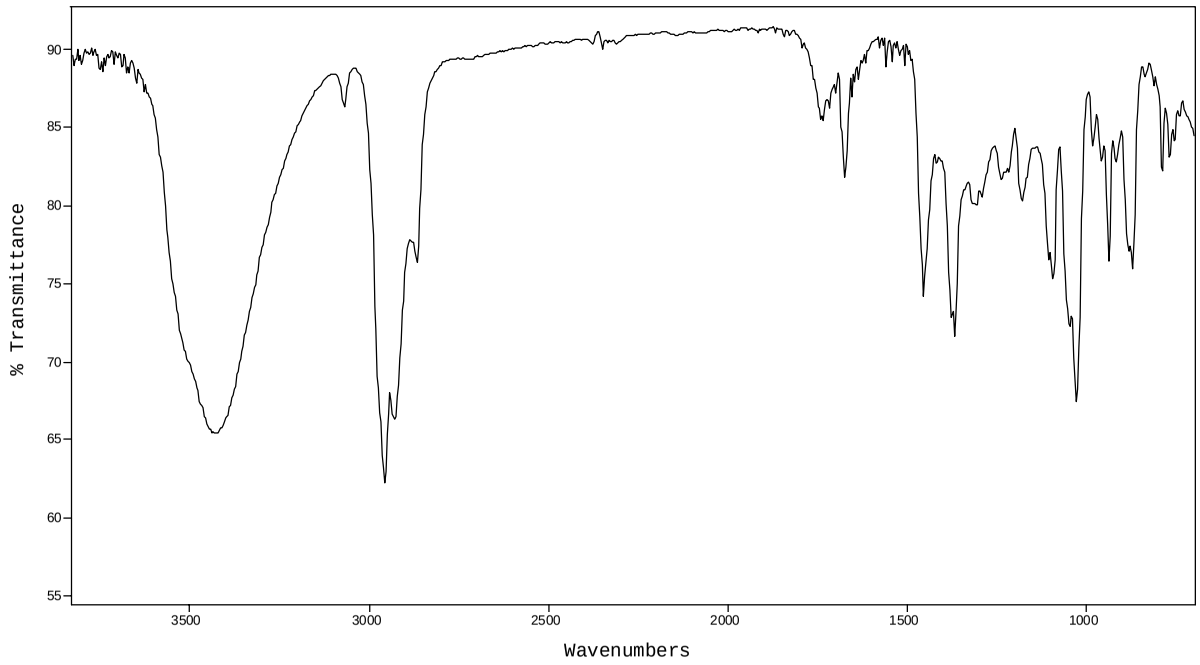


Figure A.5.41 FTIR Spectrum (thin film/NaCl) of Compound **195**.

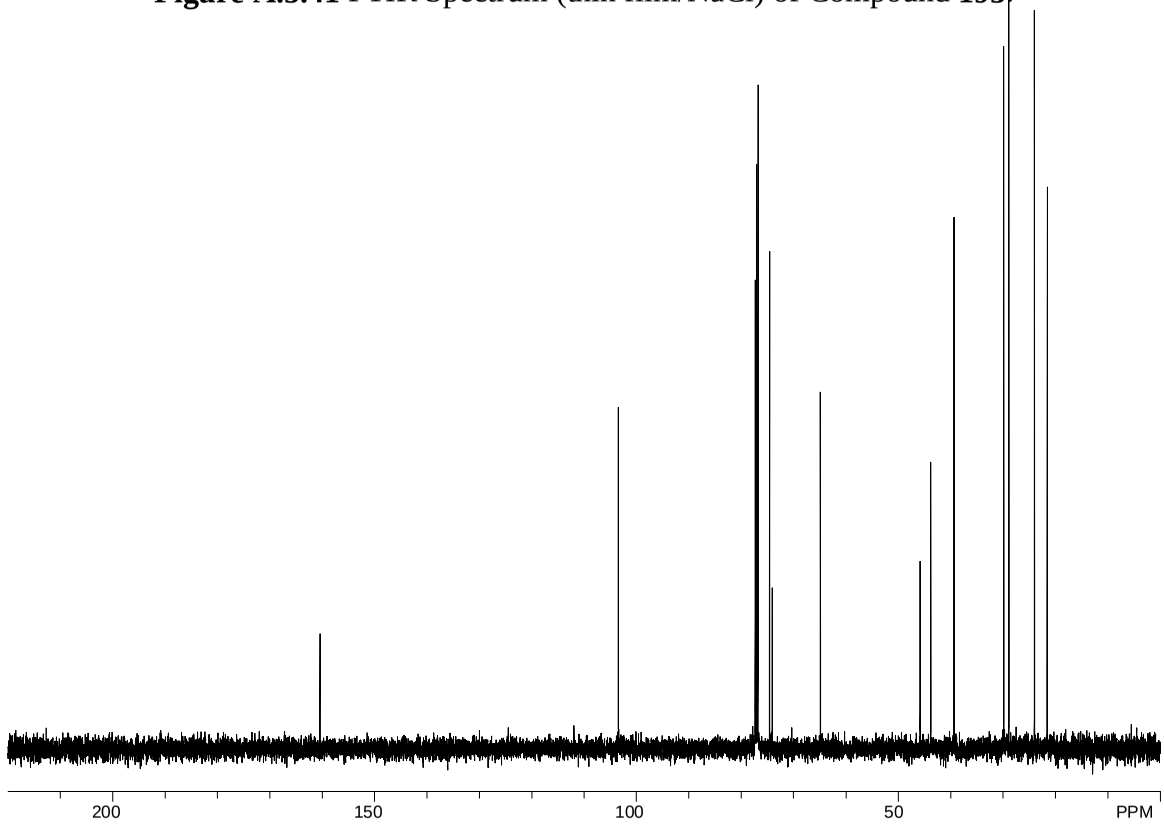


Figure A.5.42 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **195**.

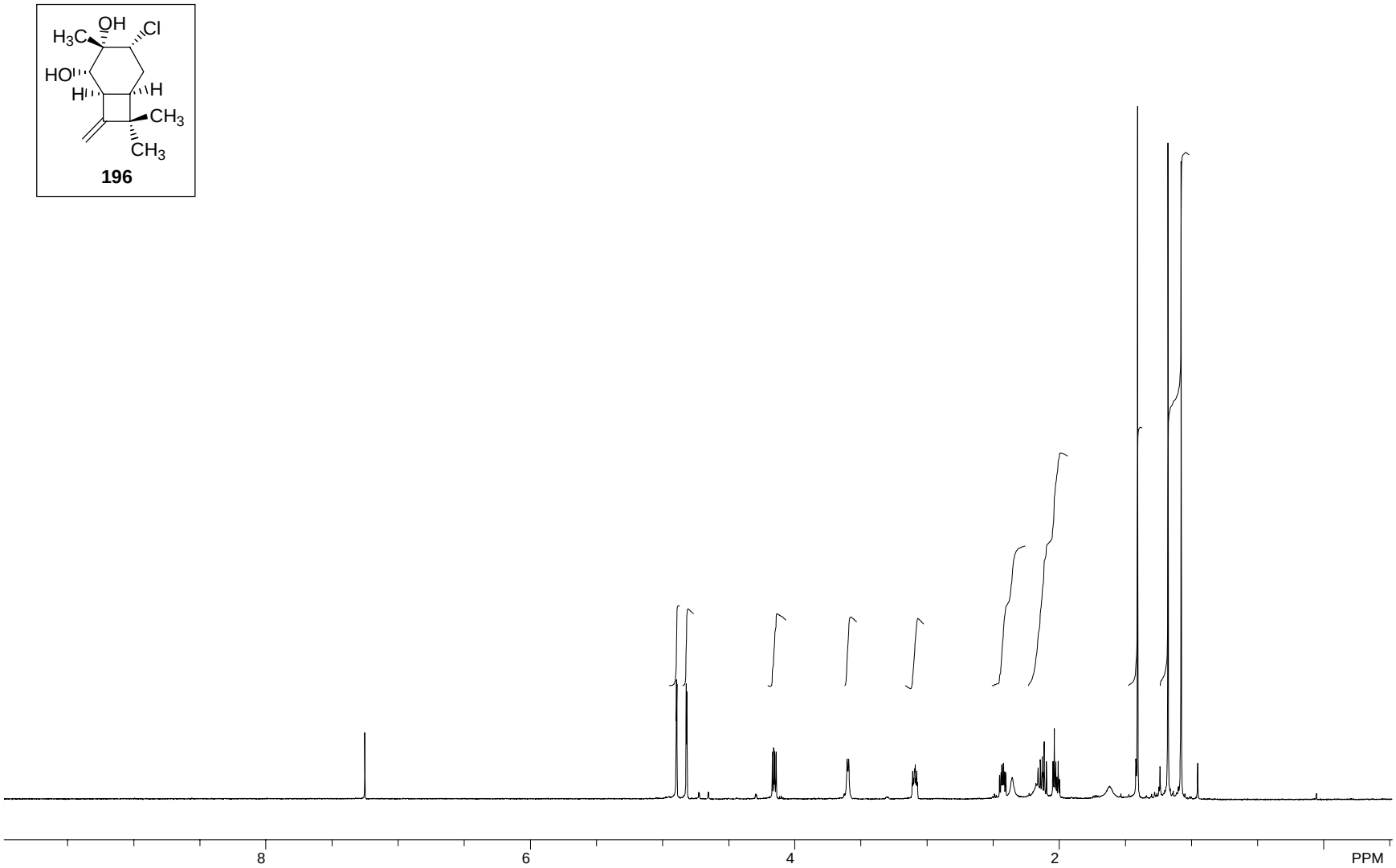


Figure A.5.43 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **196**.

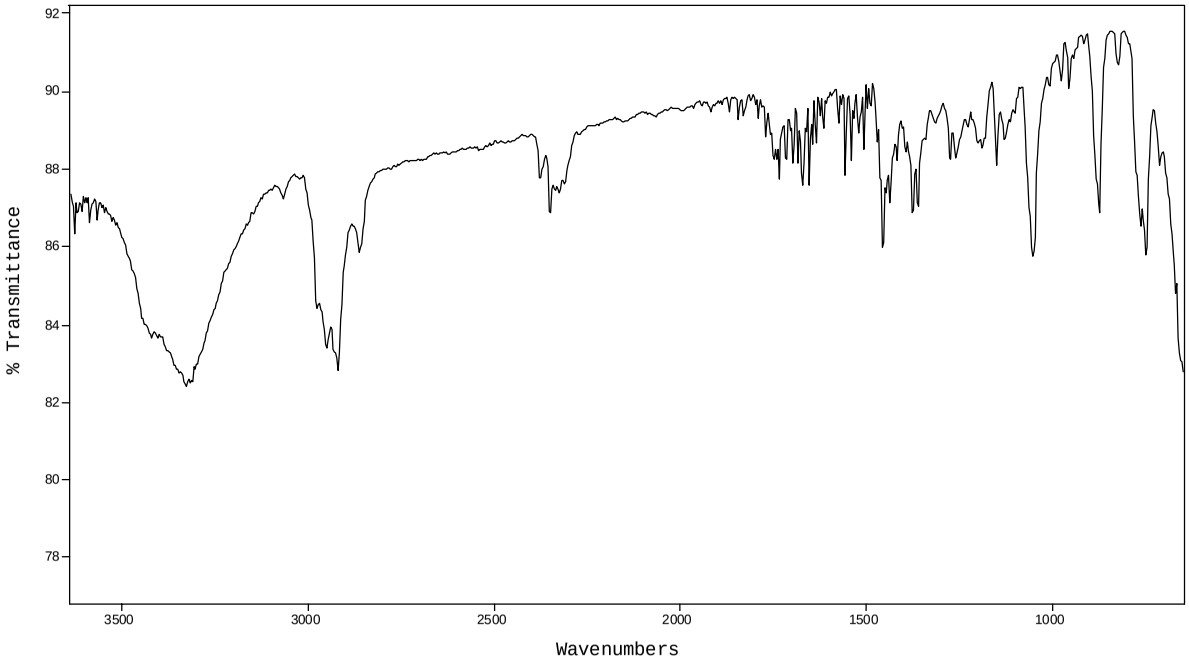


Figure A.5.44 FTIR Spectrum (thin film/NaCl) of Compound **196**.

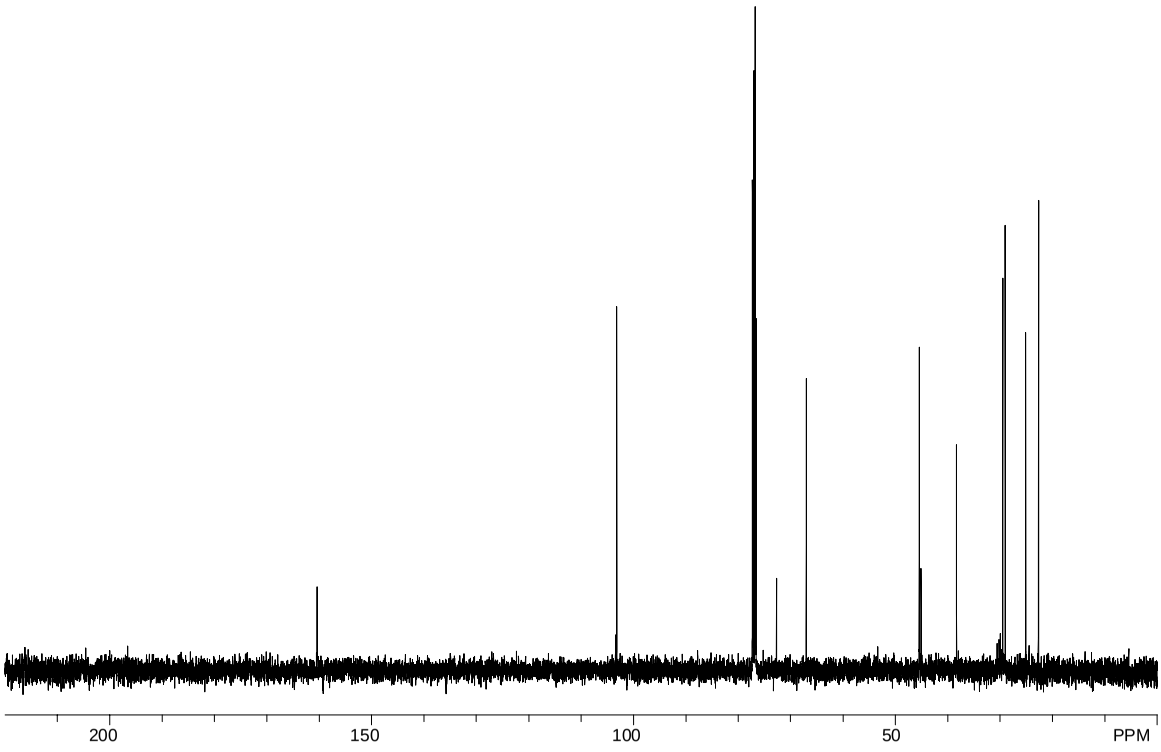


Figure A.5.45 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **196**.

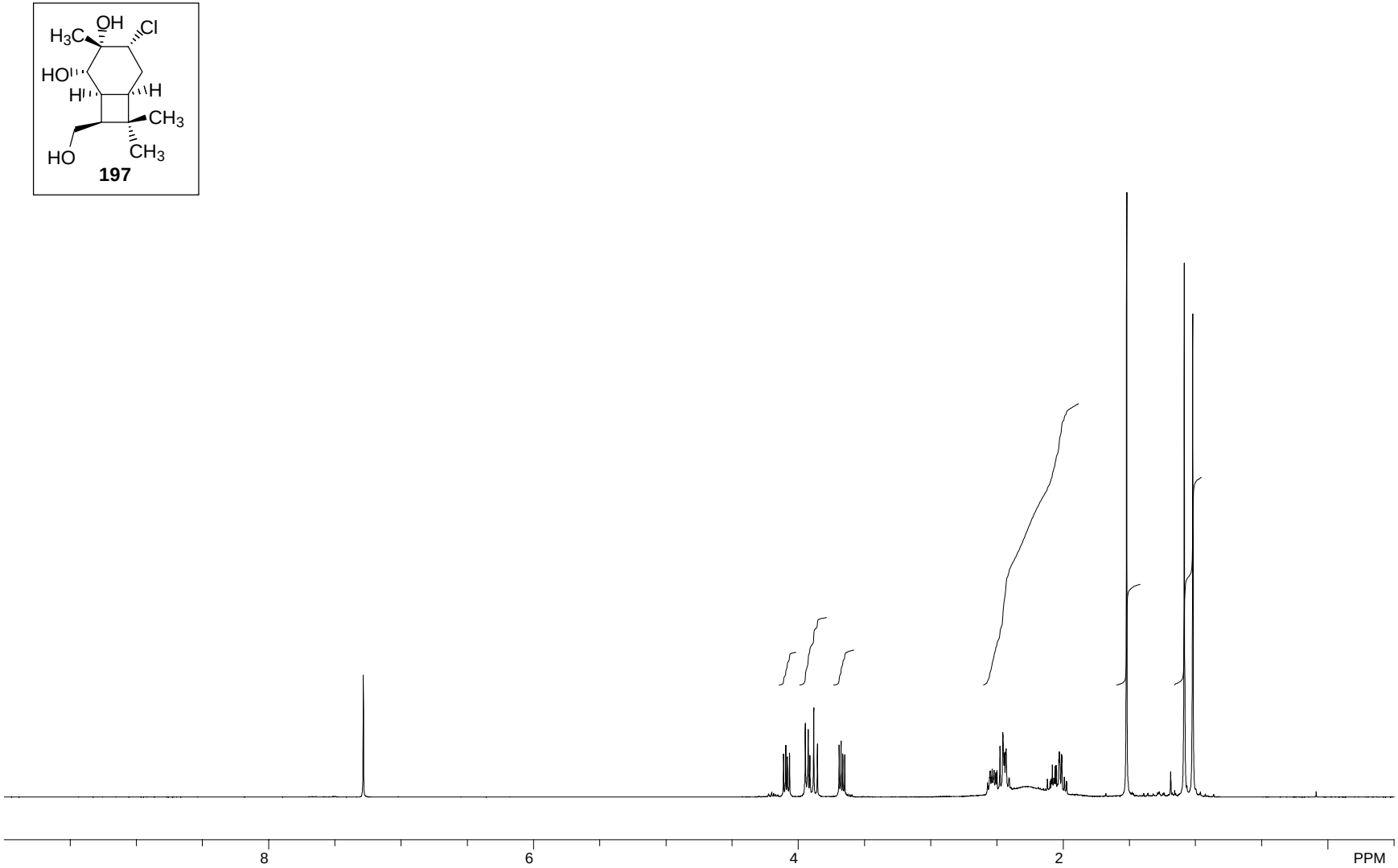


Figure A.5.46 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **197**.

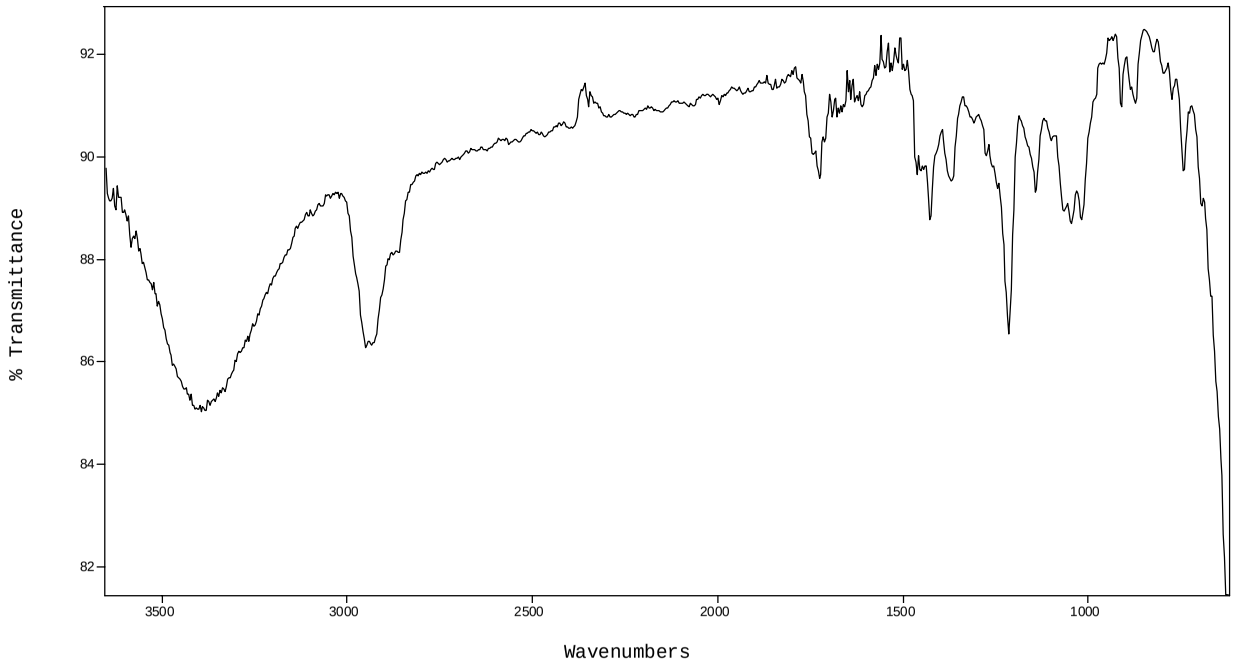


Figure A.5.47 FTIR Spectrum (thin film/NaCl) of Compound **197**.

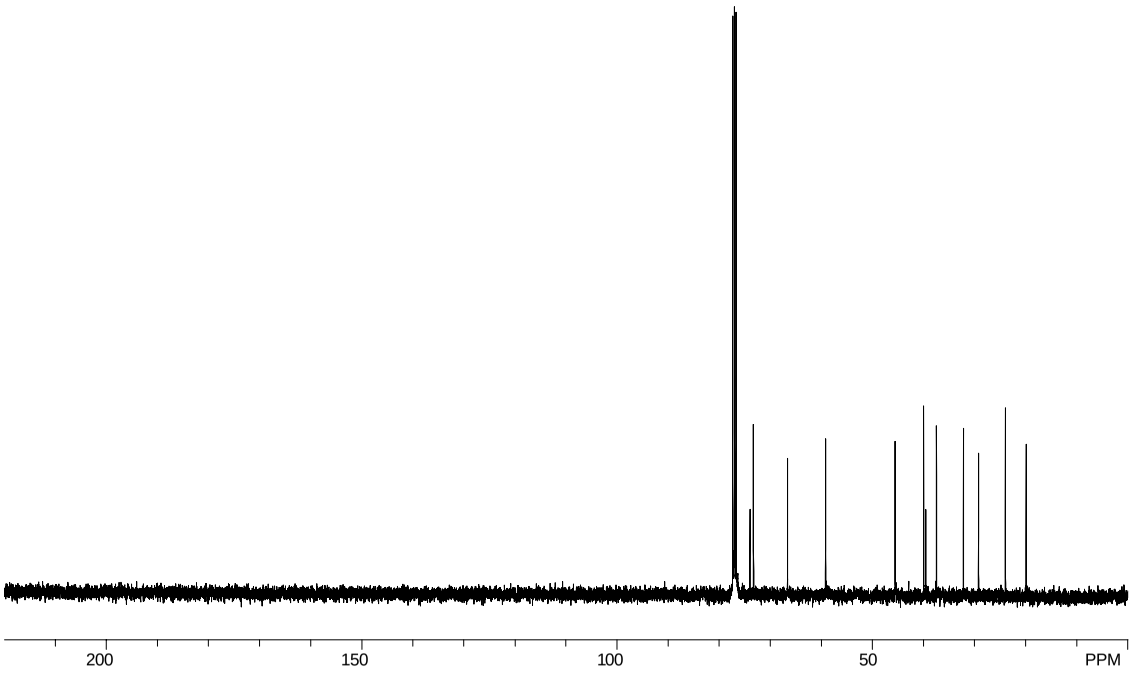


Figure A.5.48 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **197**.

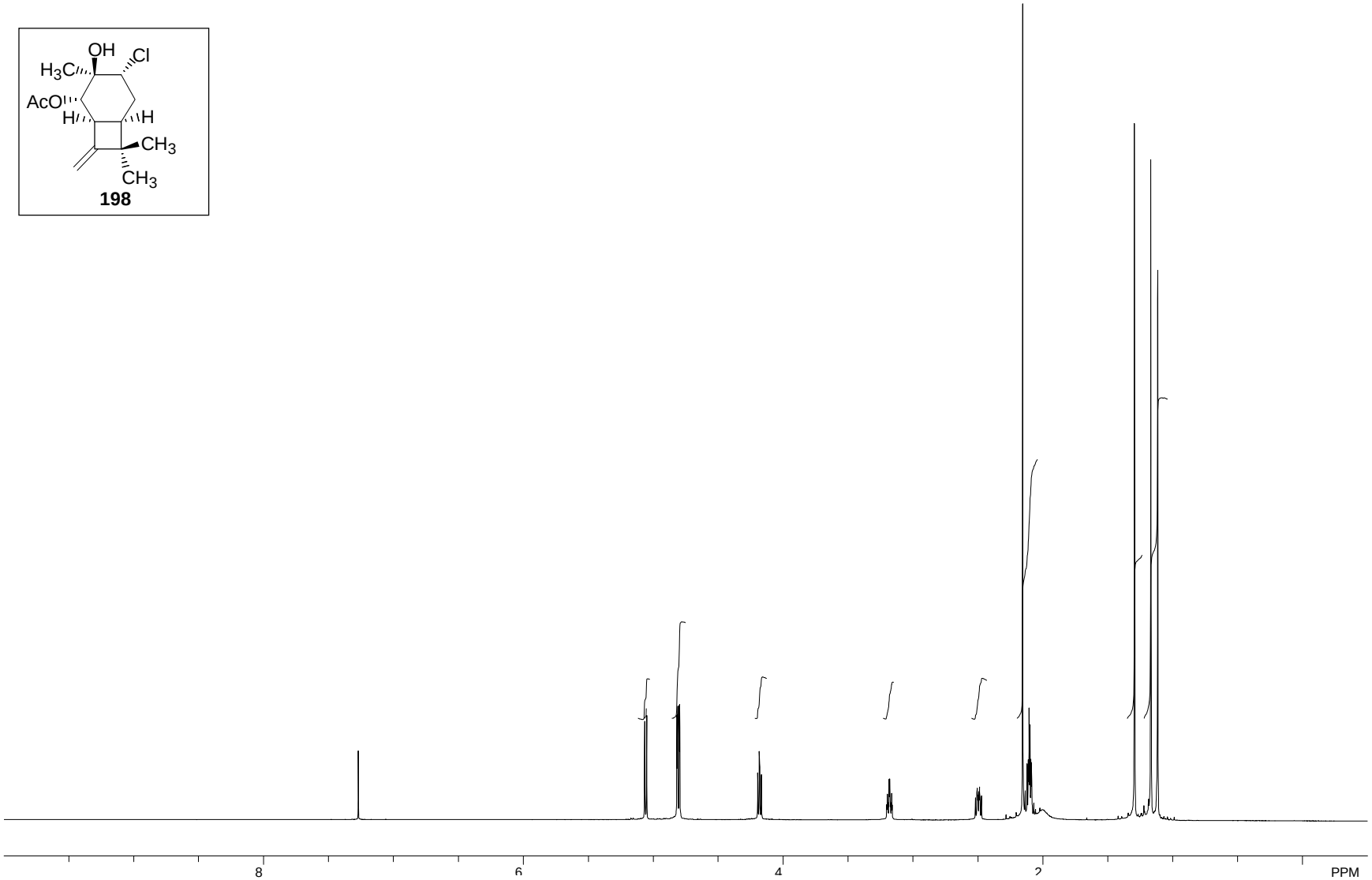


Figure A.5.49 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **198**.

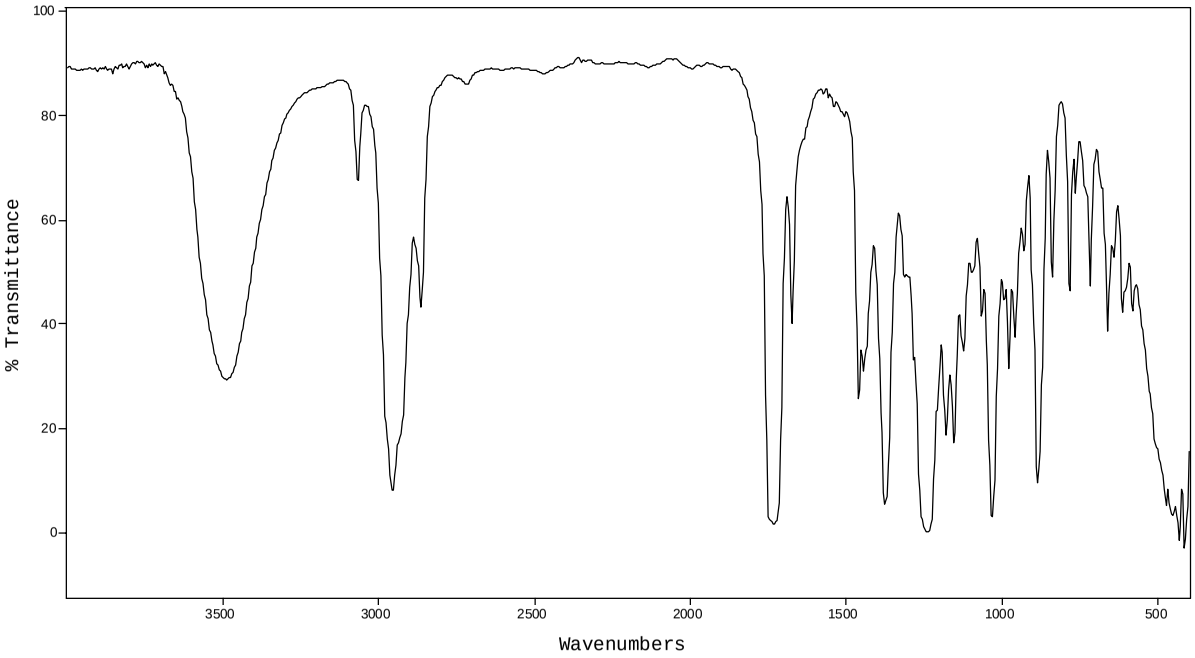


Figure A.5.50 FTIR Spectrum (thin film/NaCl) of Compound **198**.

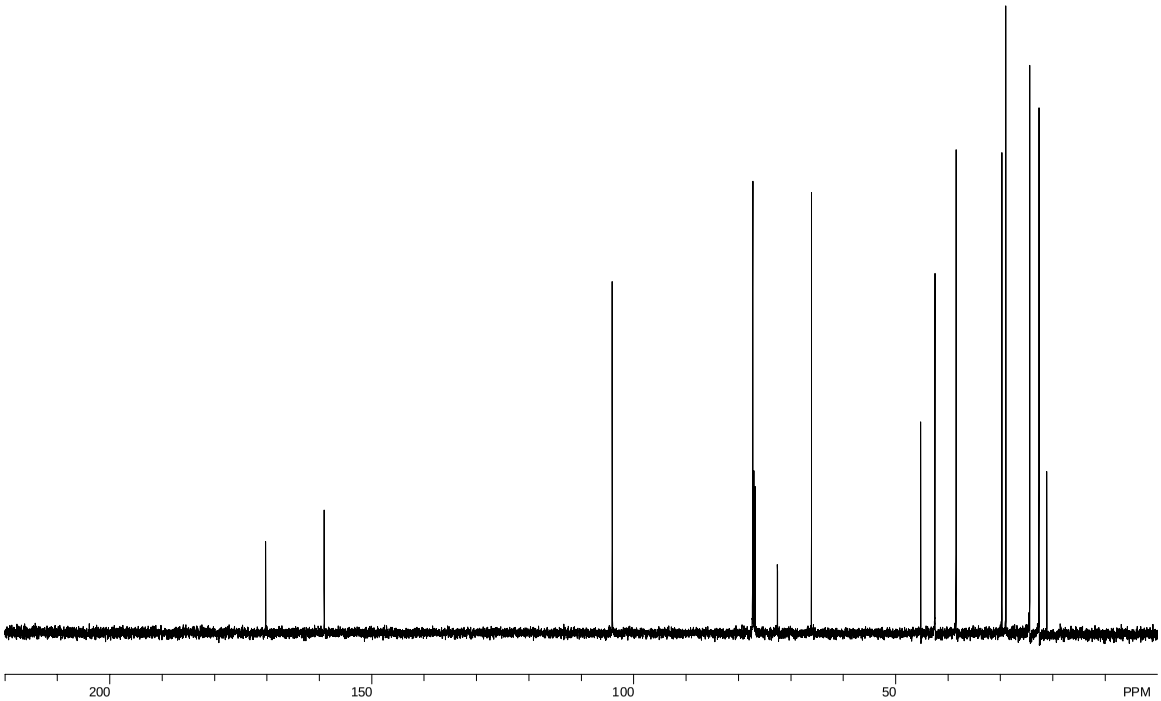


Figure A.5.51 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **198**.

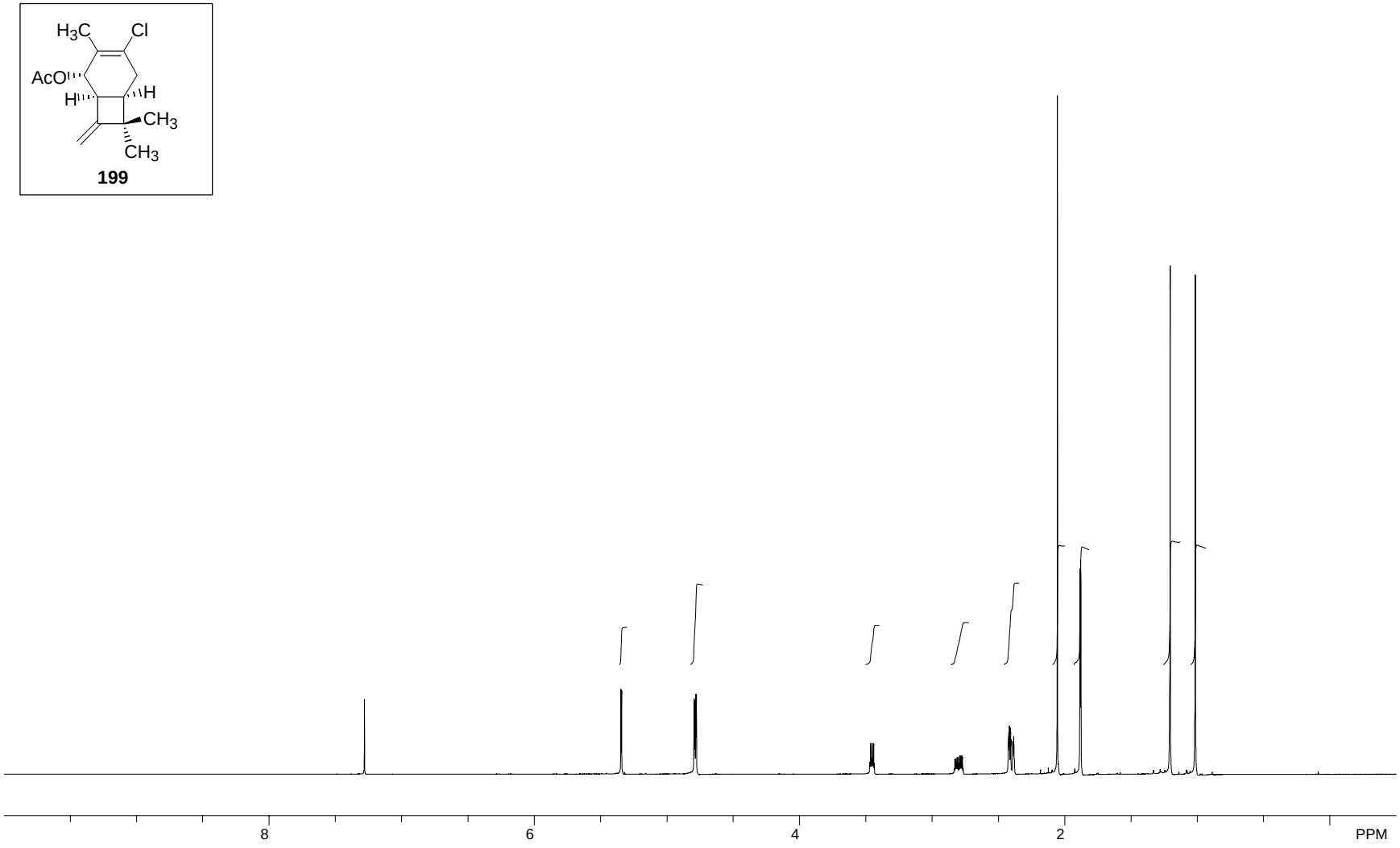


Figure A.5.52 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **199**.

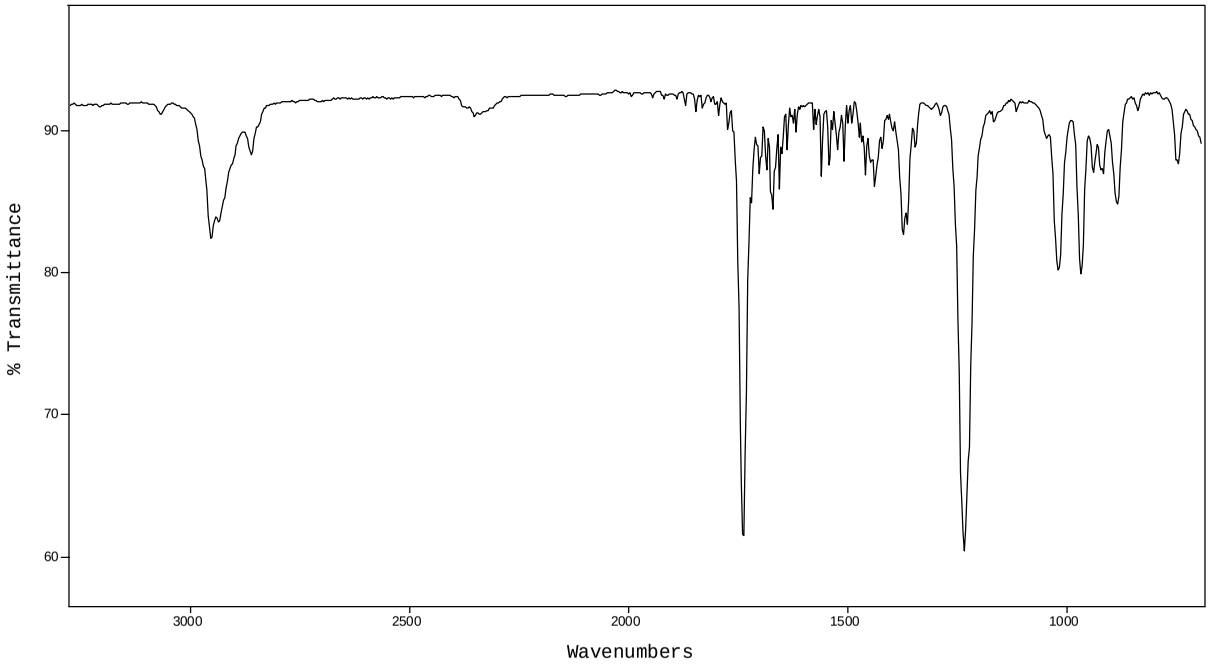


Figure A.5.53 FTIR Spectrum (thin film/NaCl) of Compound **199**.

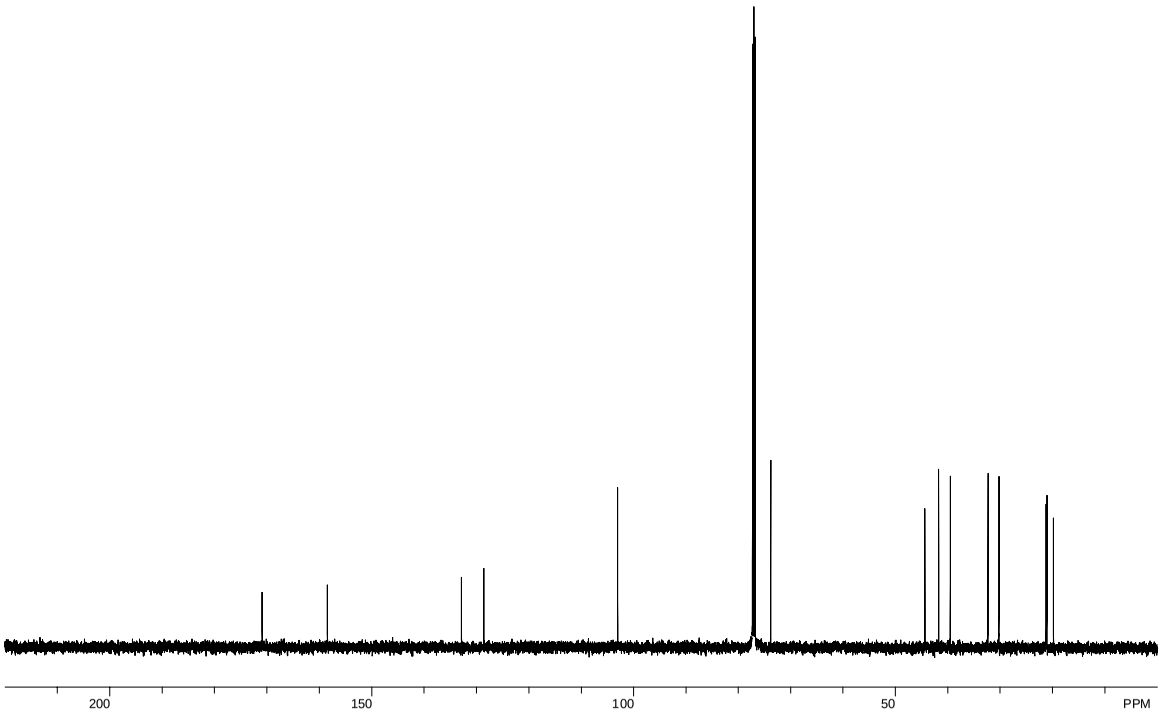


Figure A.5.54 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **199**.

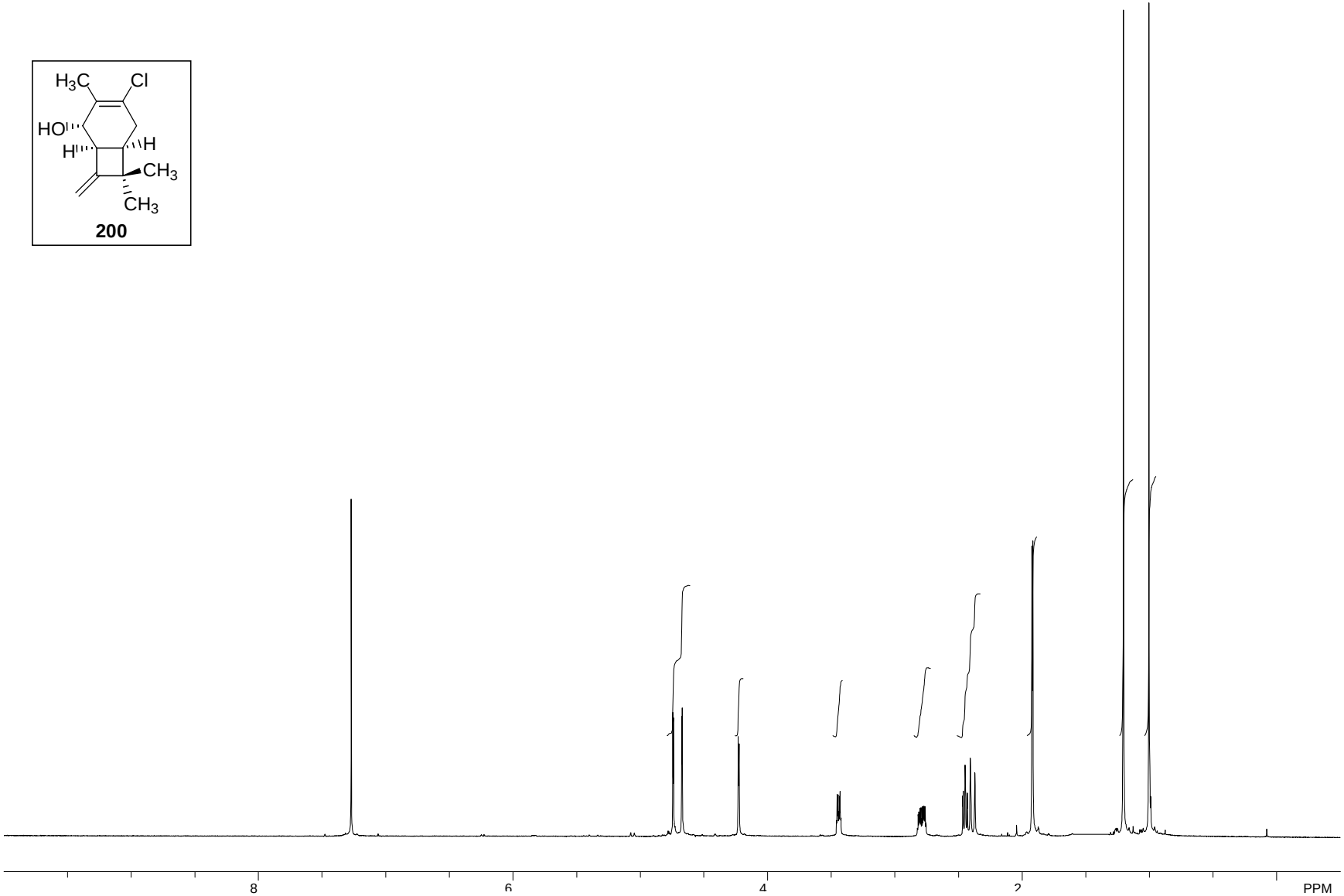


Figure A.5.55 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **200**.

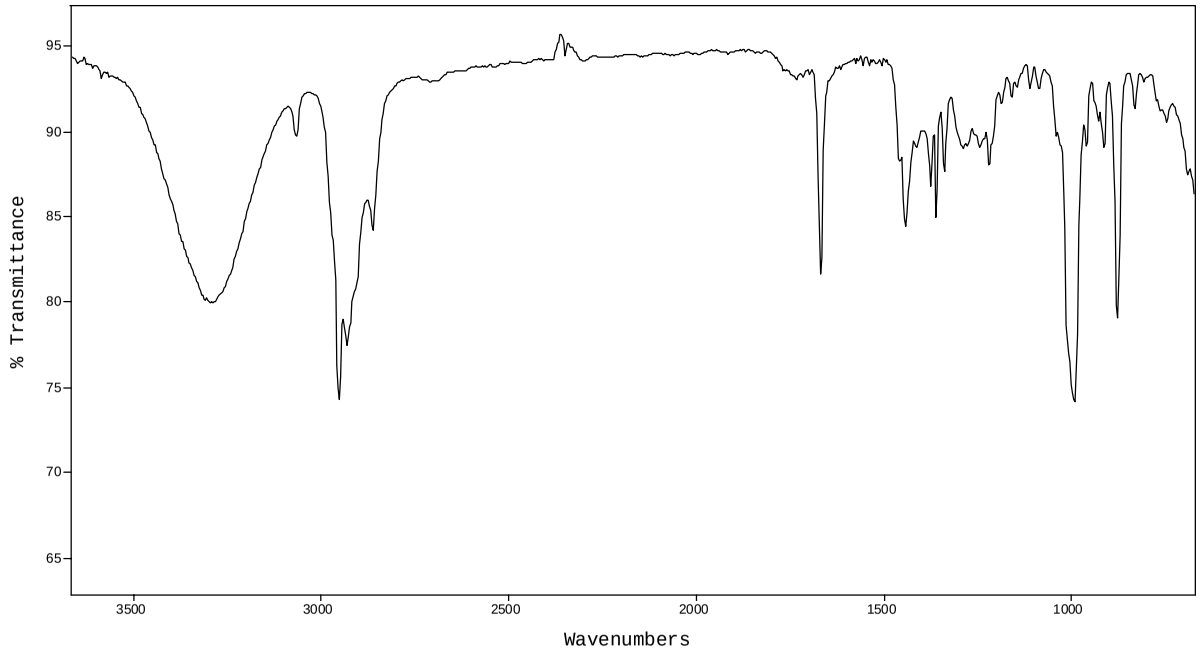


Figure A.5.56 FTIR Spectrum (thin film/NaCl) of Compound **200**.

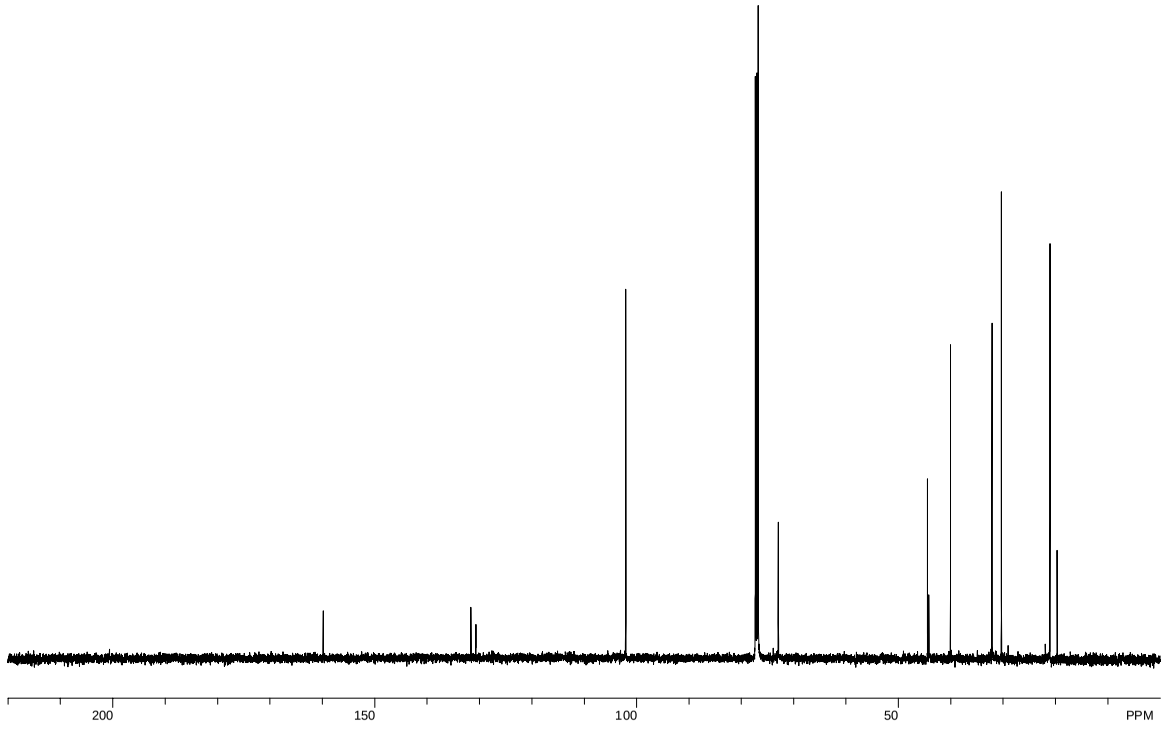


Figure A.5.57 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **200**.

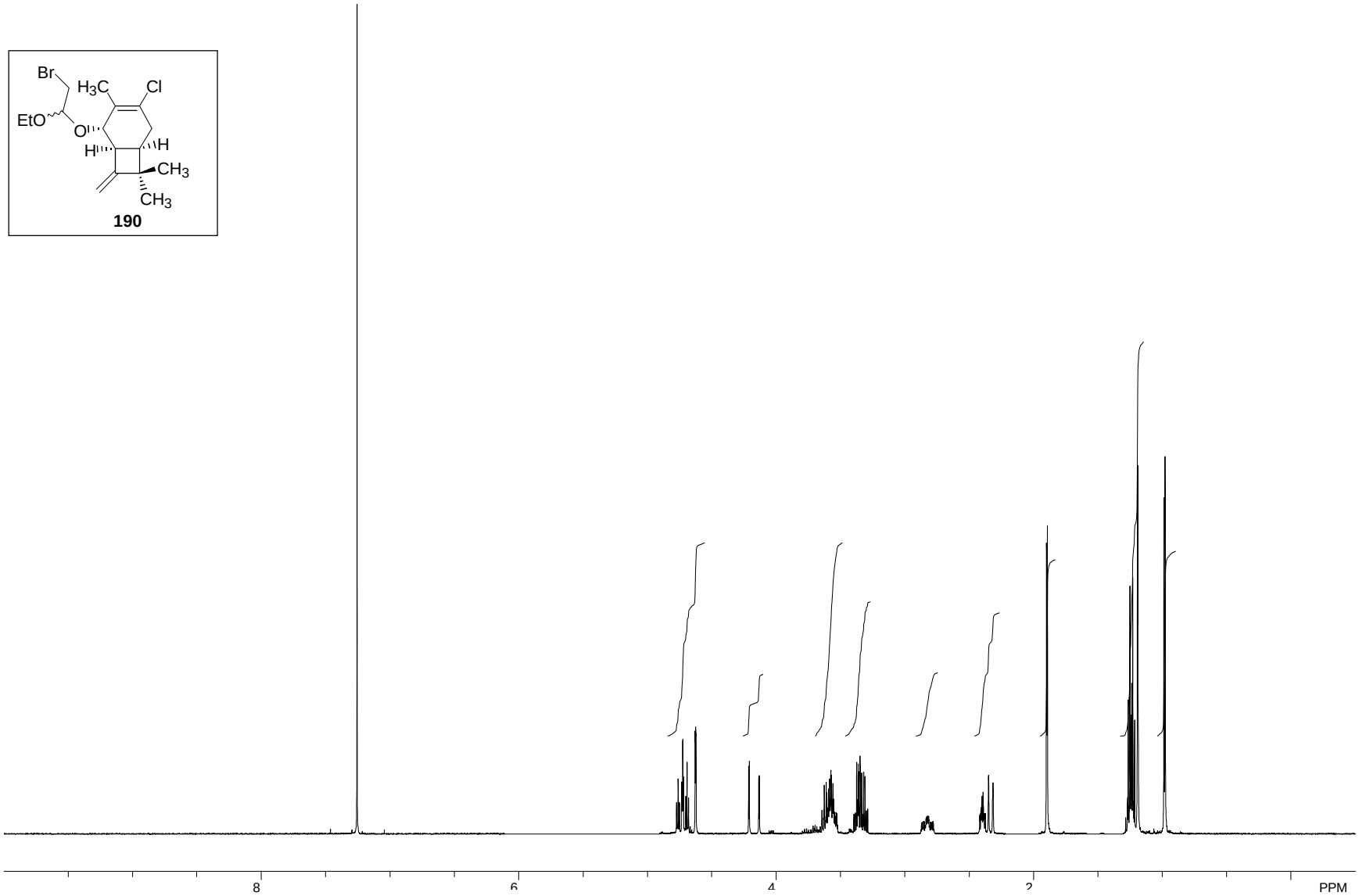


Figure A.5.58 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **190**.

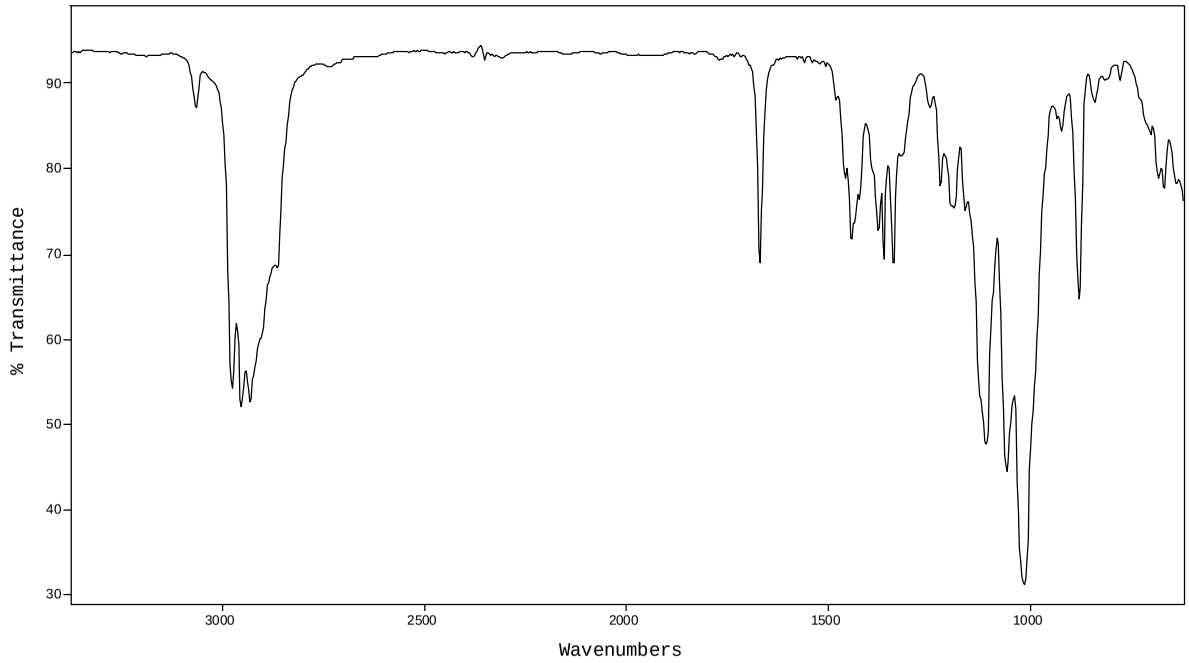


Figure A.5.59 FTIR Spectrum (thin film/NaCl) of Compound **190**.

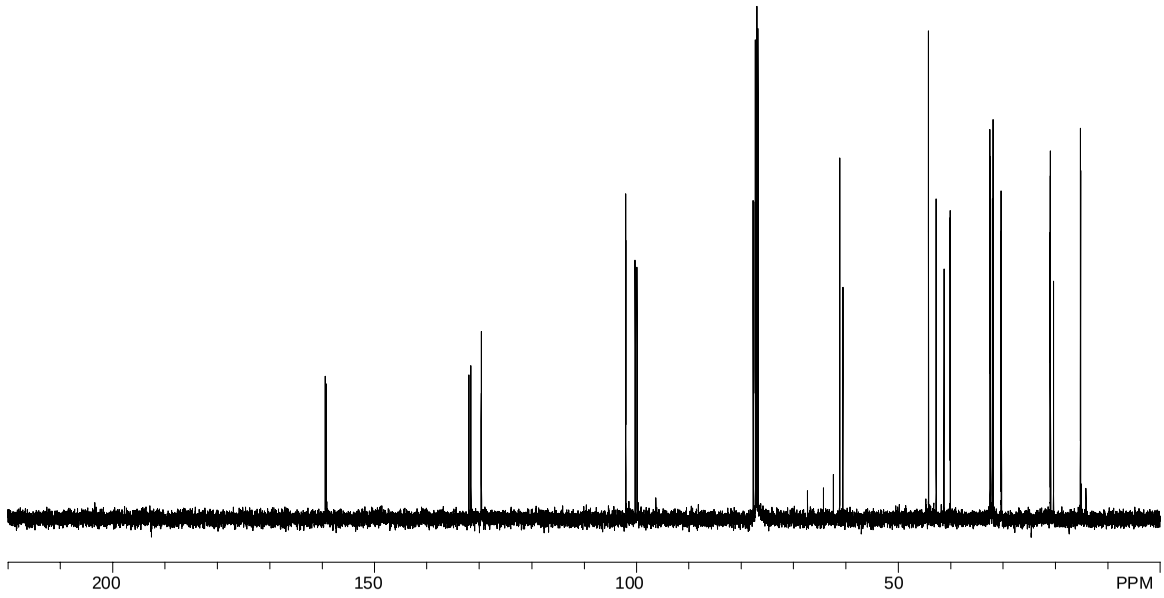


Figure A.5.60 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **190**.

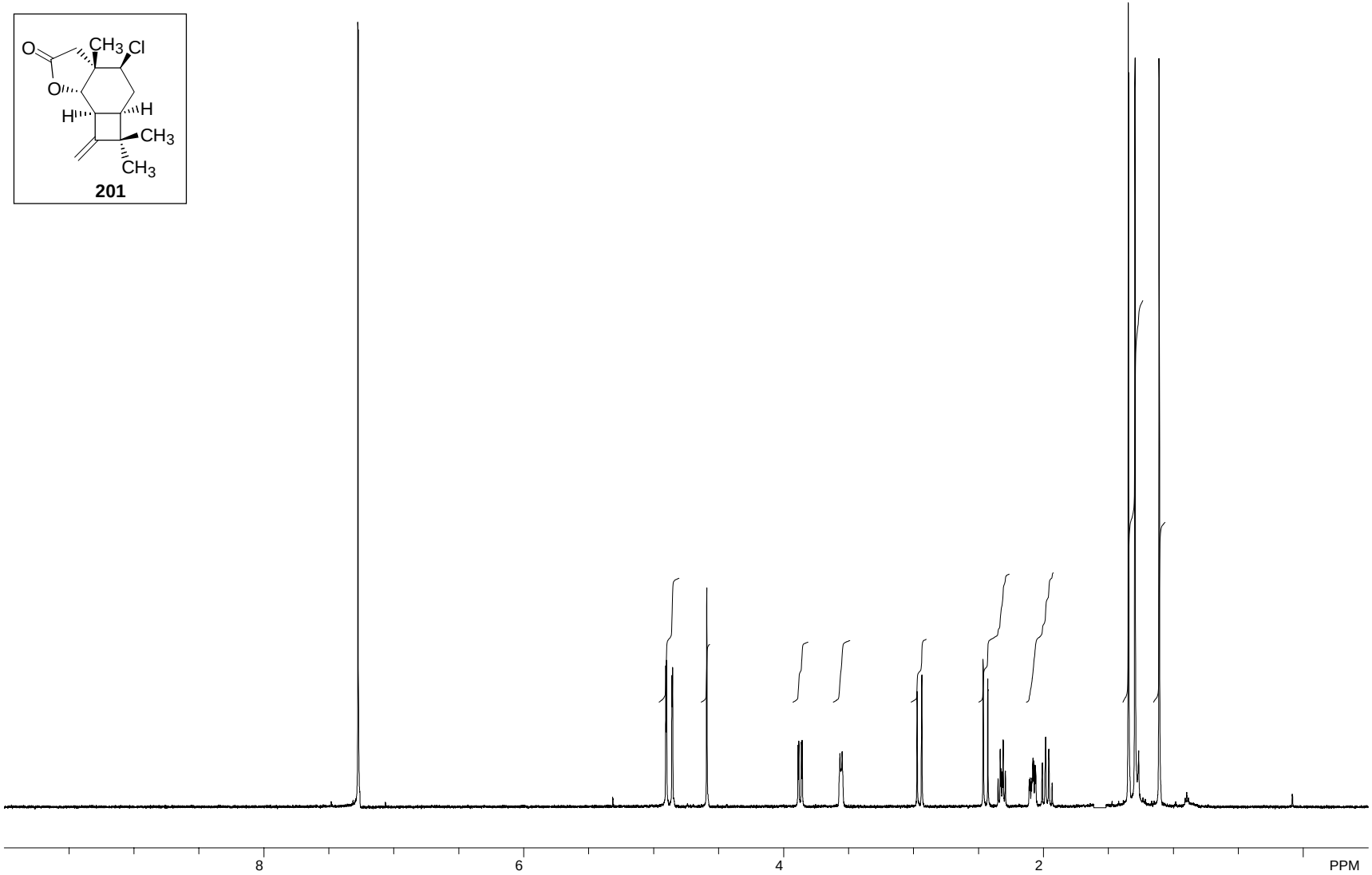


Figure A.5.61 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **201**.

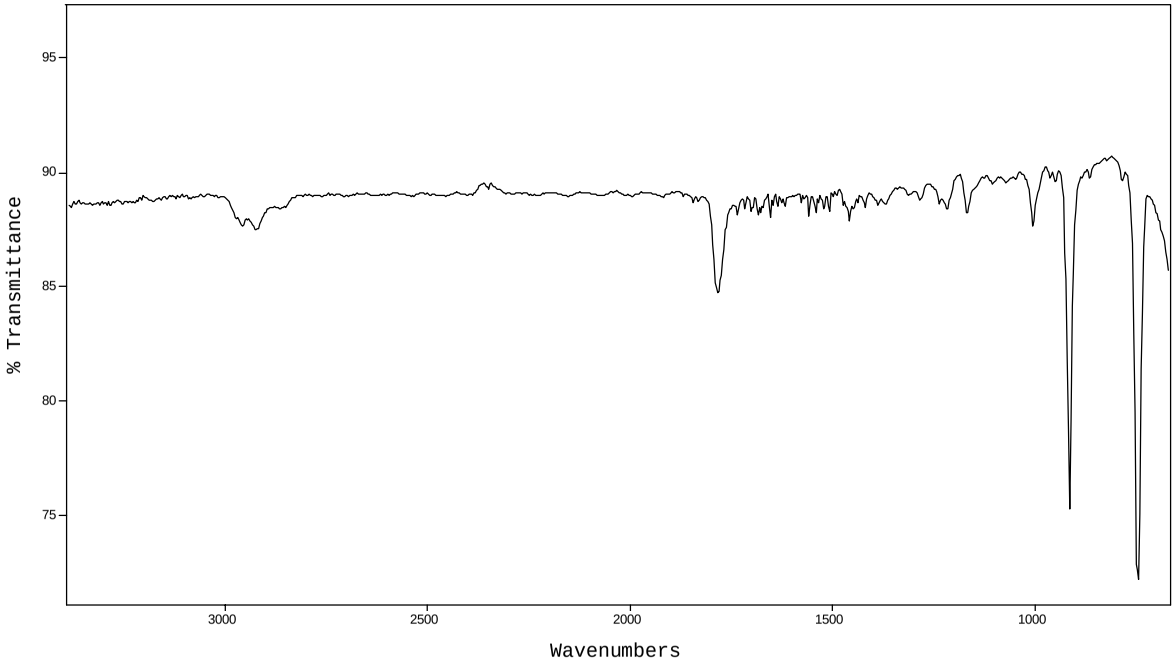


Figure A.5.62 FTIR Spectrum (thin film/NaCl) of Compound **201**.

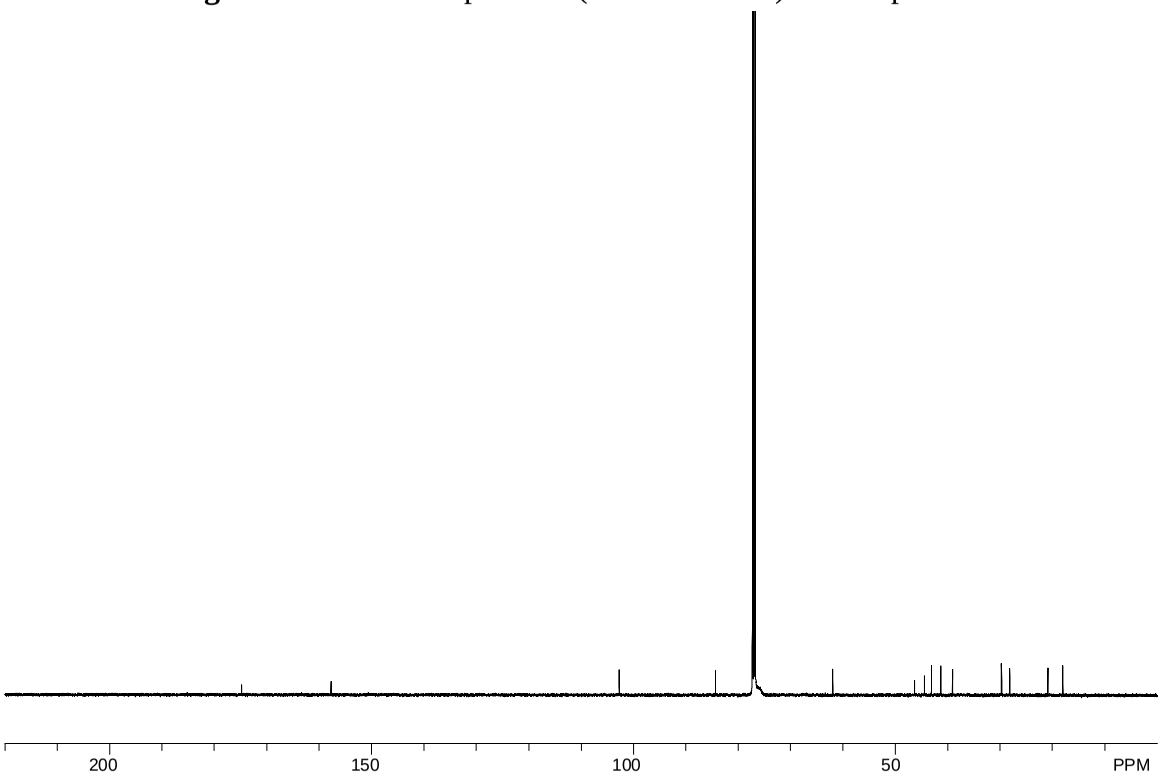


Figure A.5.63 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **201**.

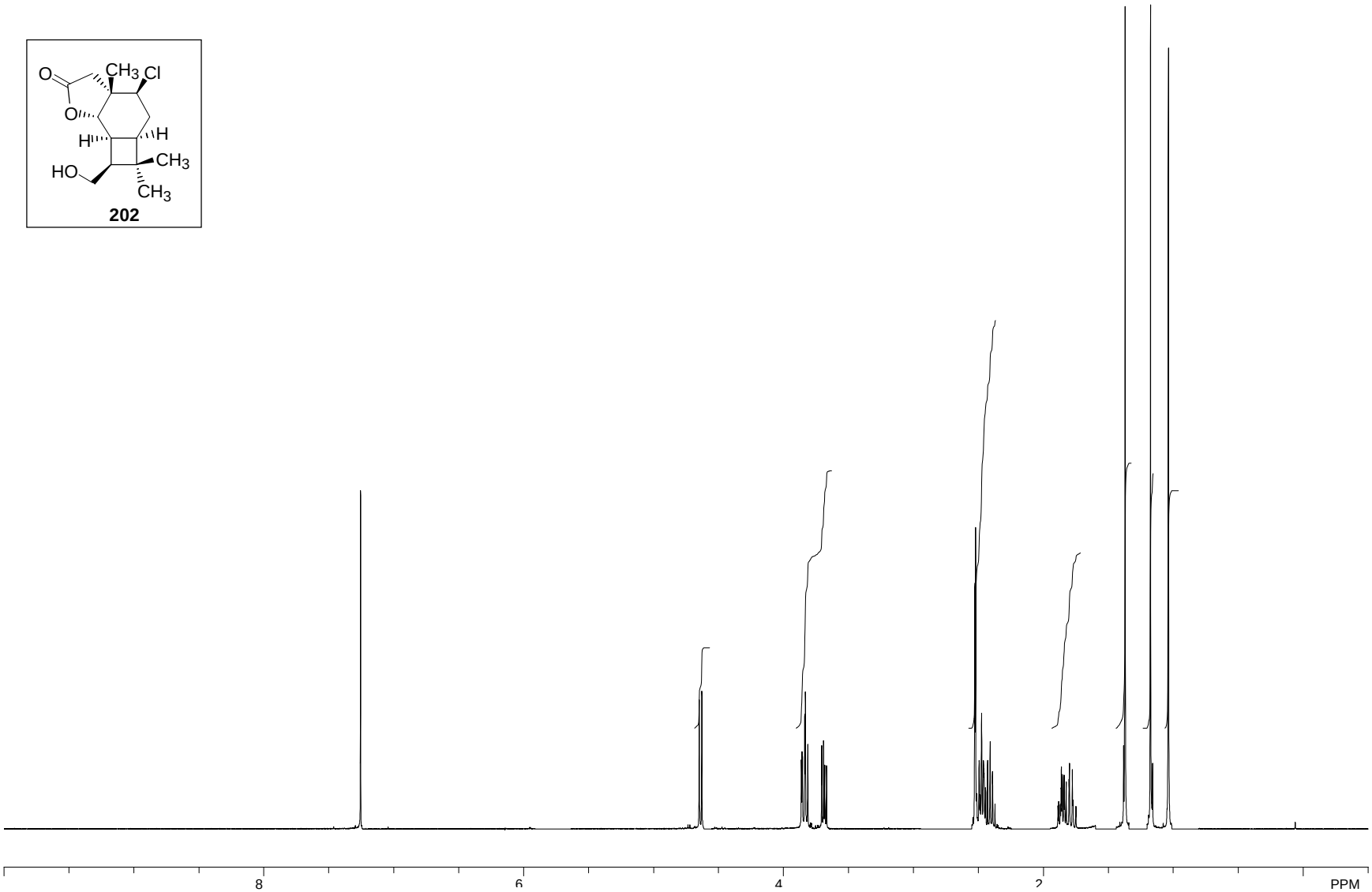


Figure A.5.64 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **202**.

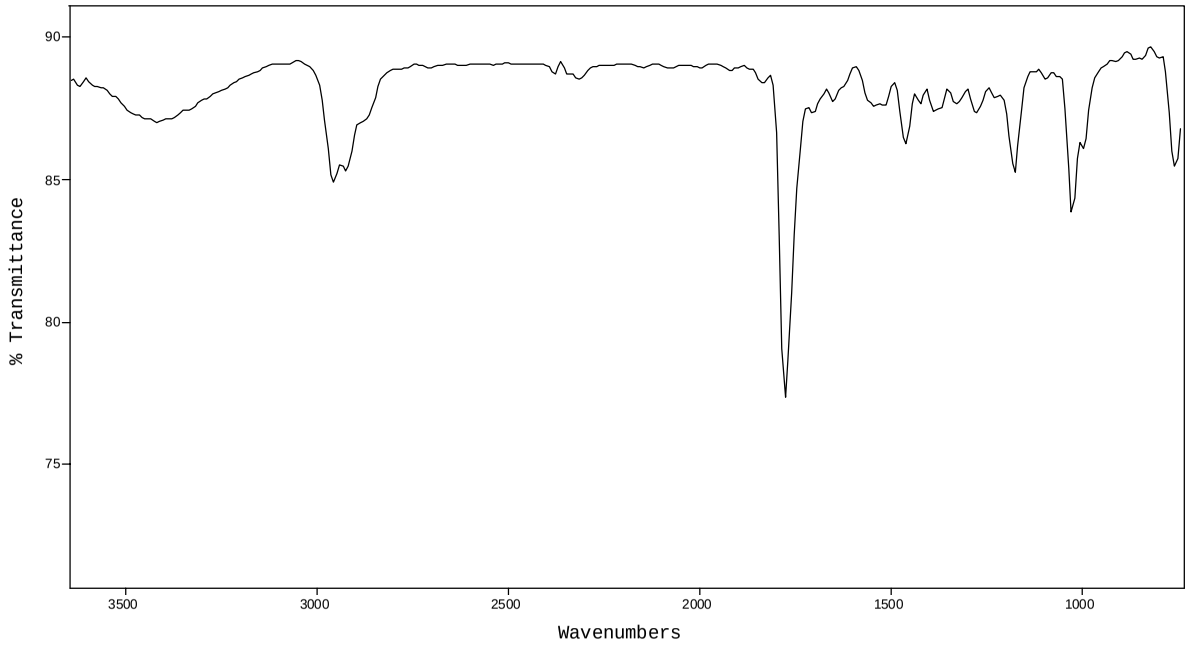


Figure A.5.65 FTIR Spectrum (thin film/NaCl) of Compound **202**.

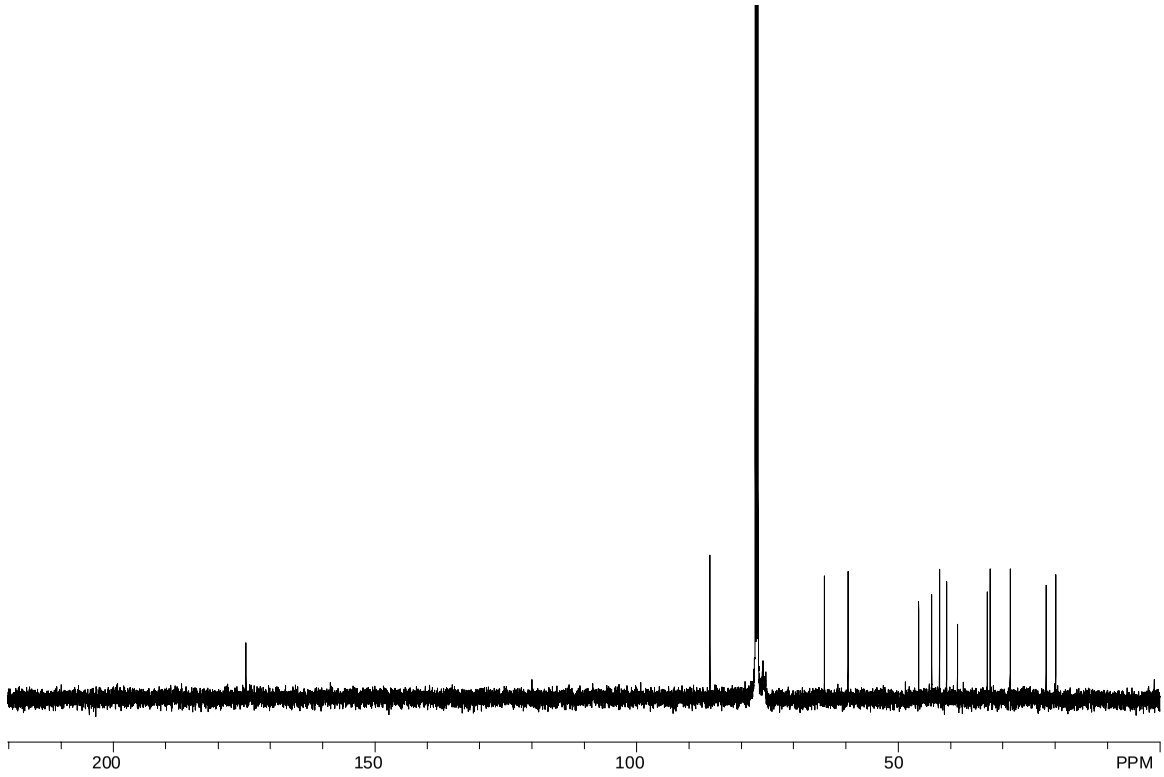


Figure A.5.66 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **202.**

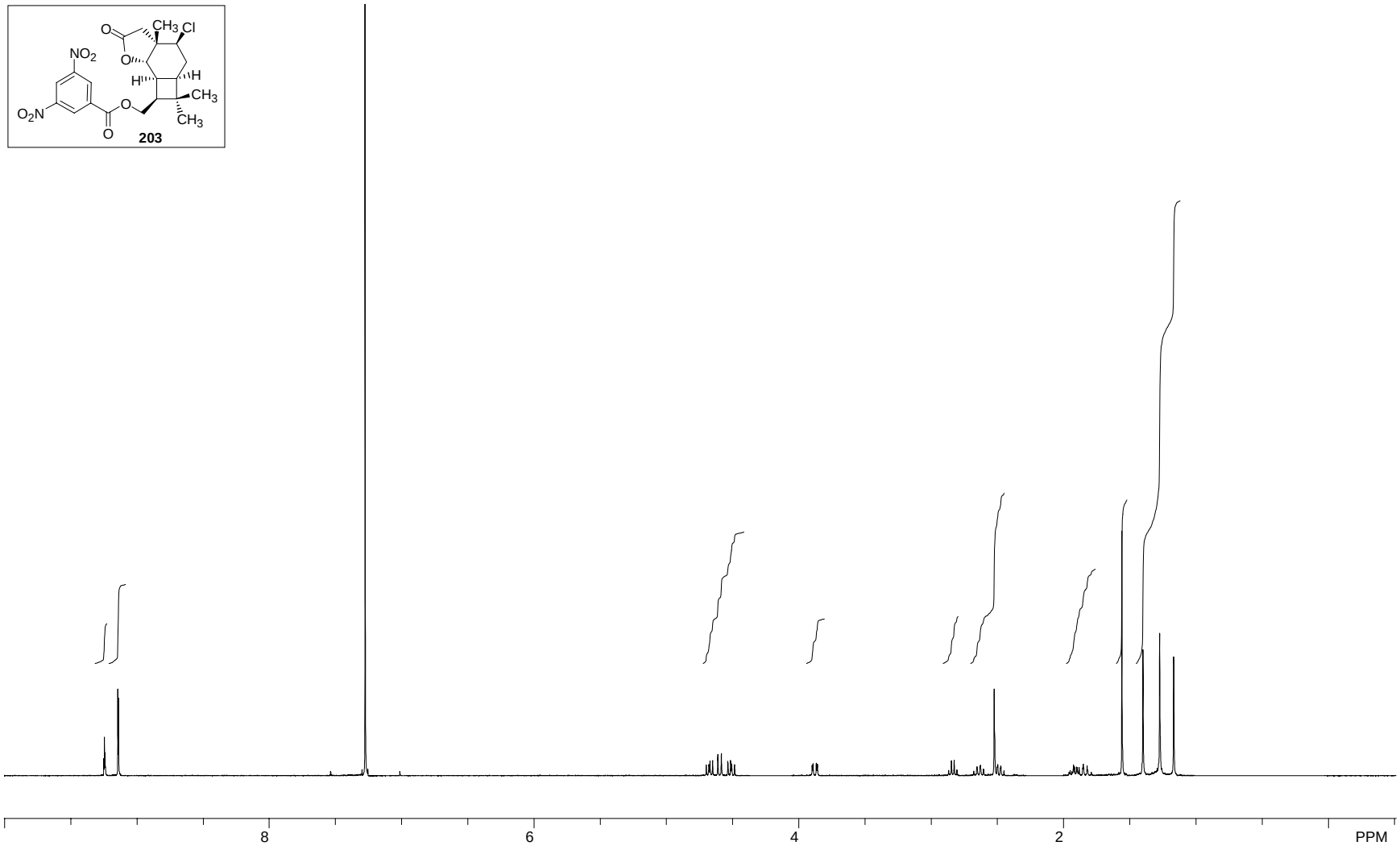


Figure A.5.67 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **203**.

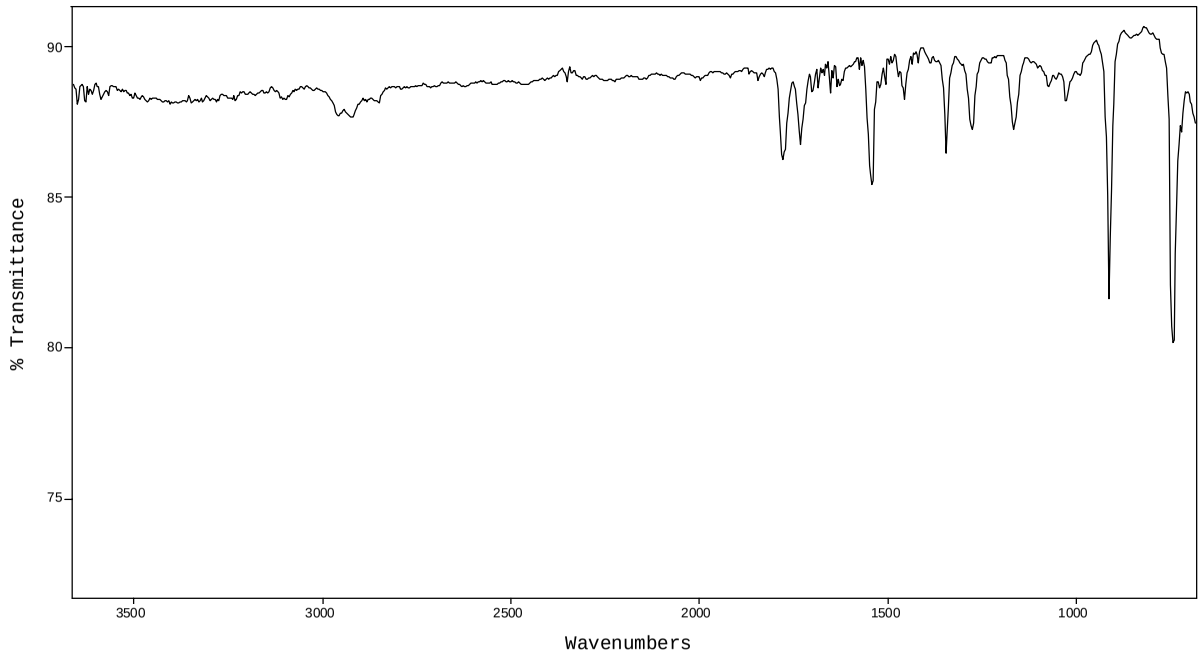


Figure A.5.68 FTIR Spectrum (thin film/NaCl) of Compound **203**.

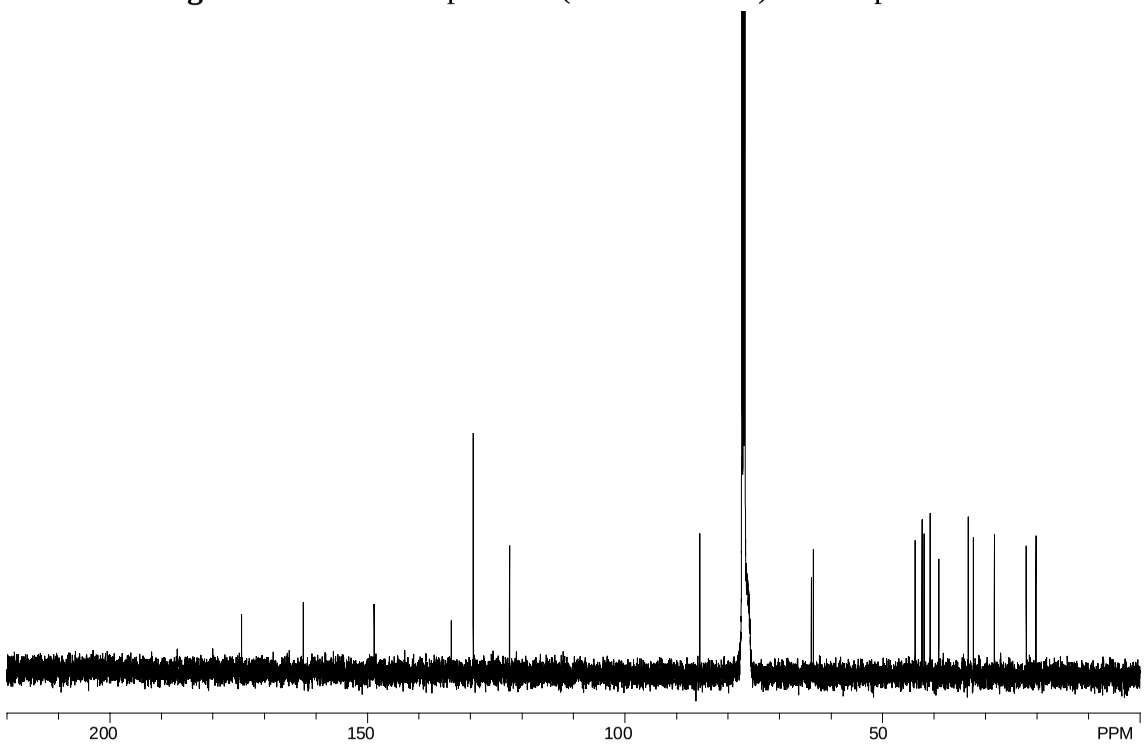
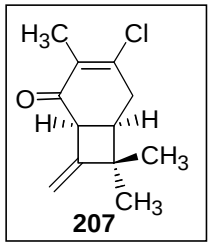


Figure A.5.69 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **203**.



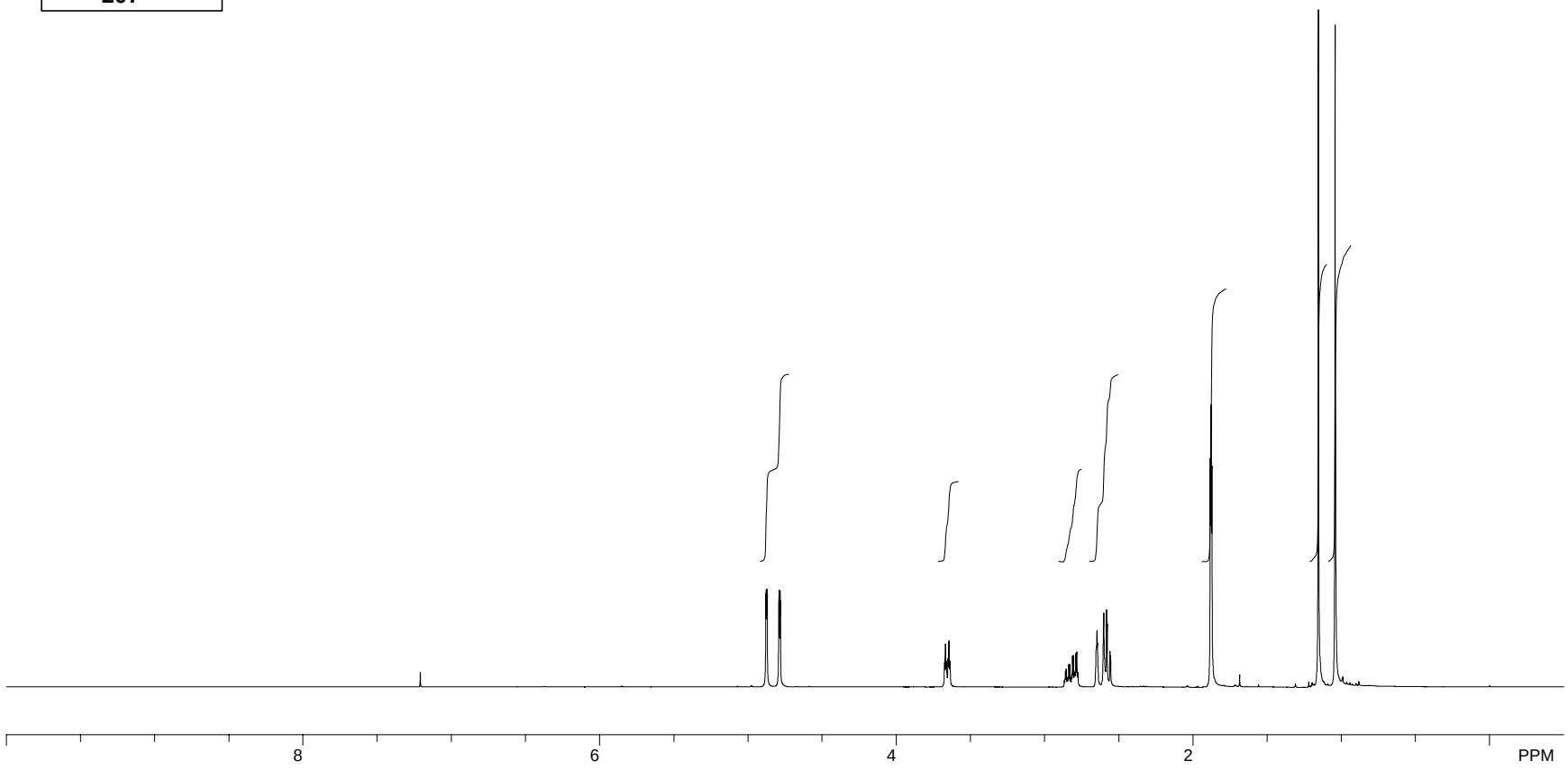


Figure A.5.70 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **207**.

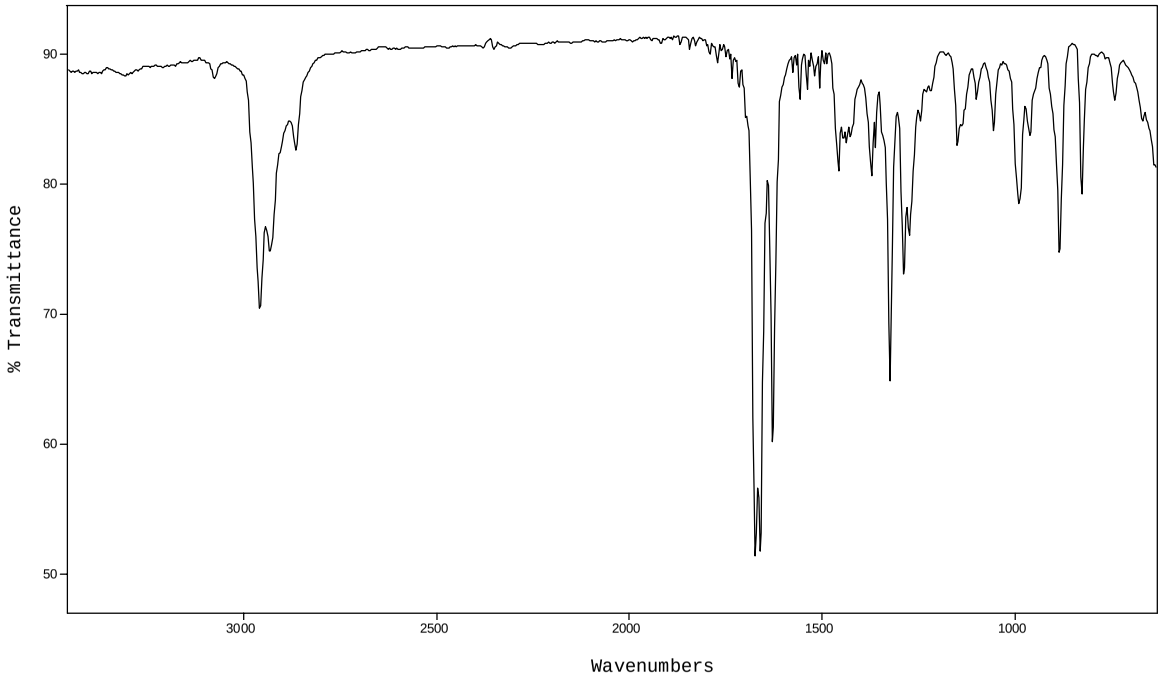


Figure A.5.71 FTIR Spectrum (thin film/NaCl) of Compound **207**.

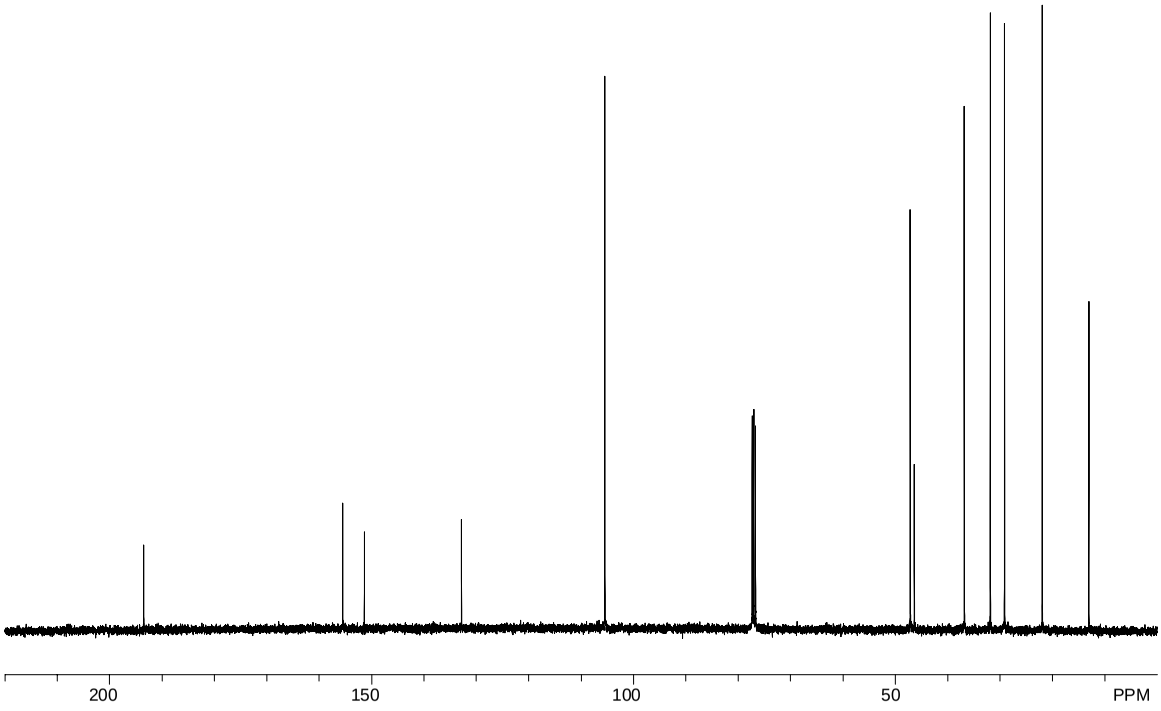


Figure A.5.72 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **207.**

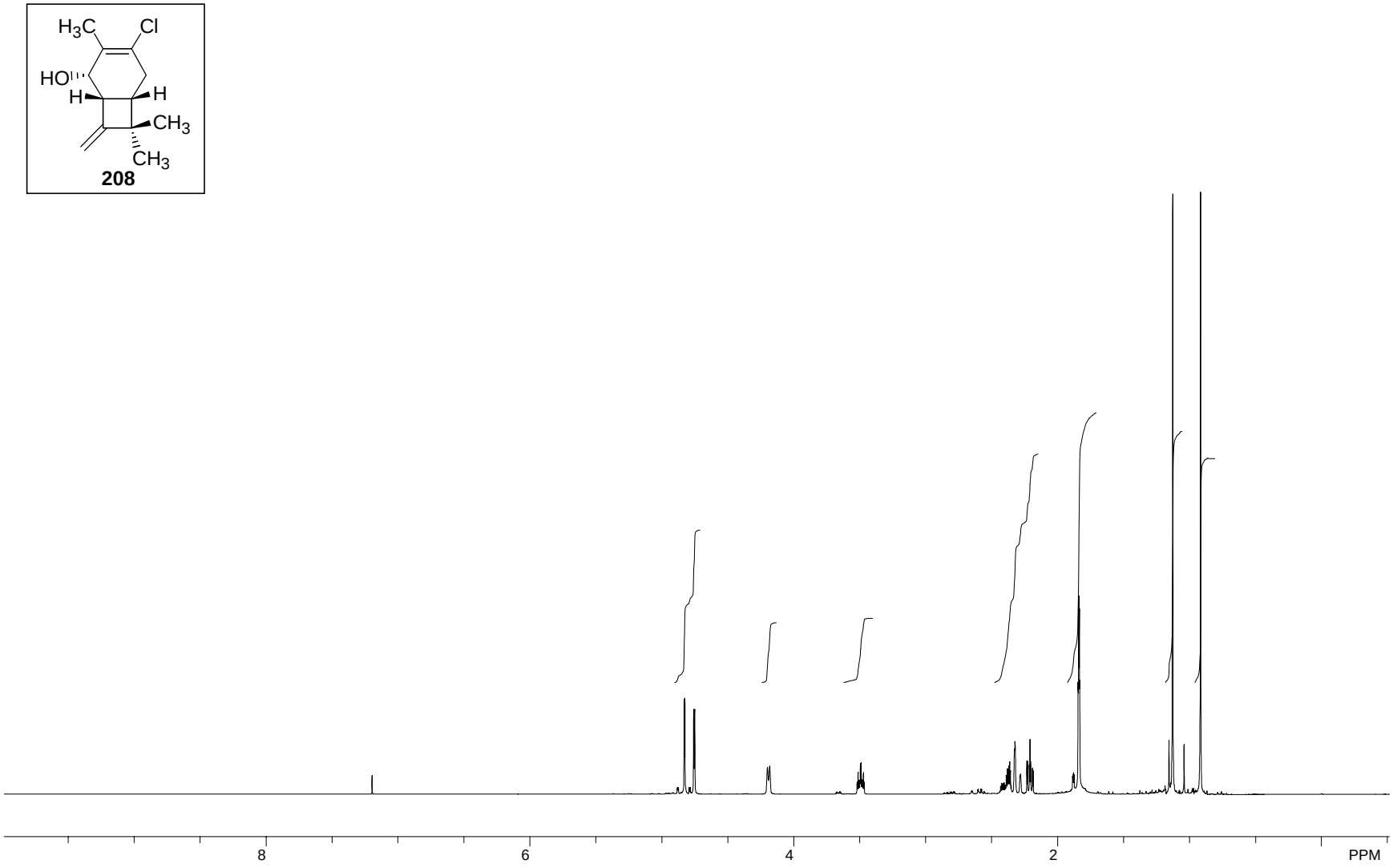


Figure A.5.73 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **208**.

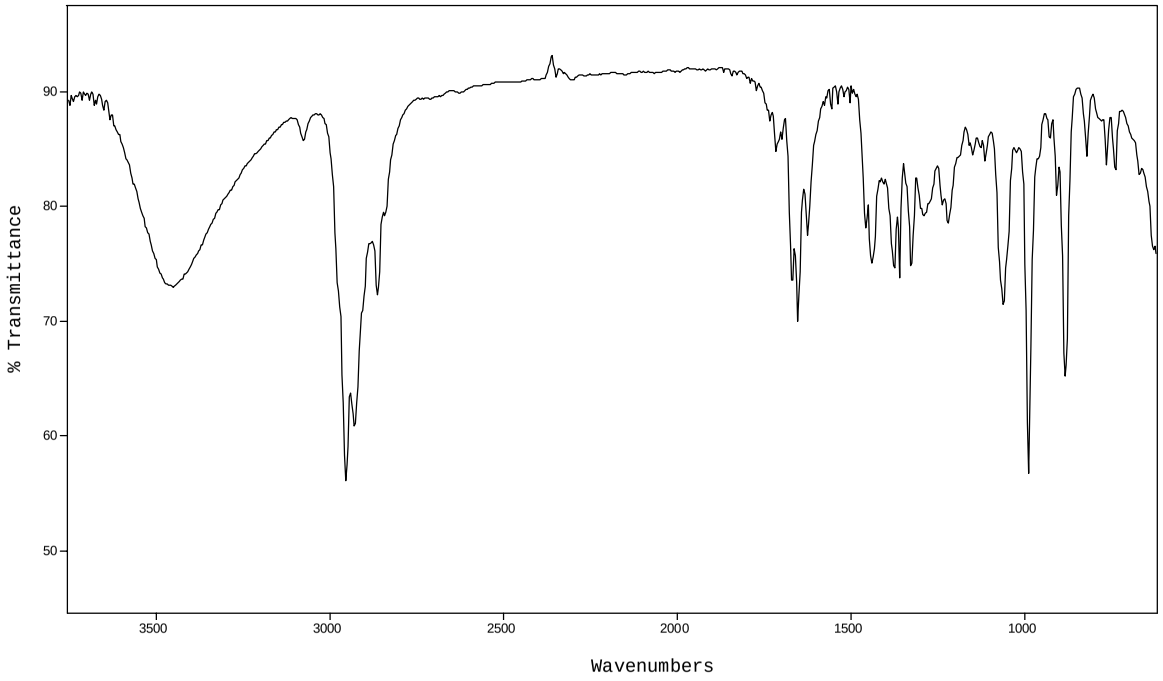


Figure A.5.74 FTIR Spectrum (thin film/NaCl) of Compound **208**.

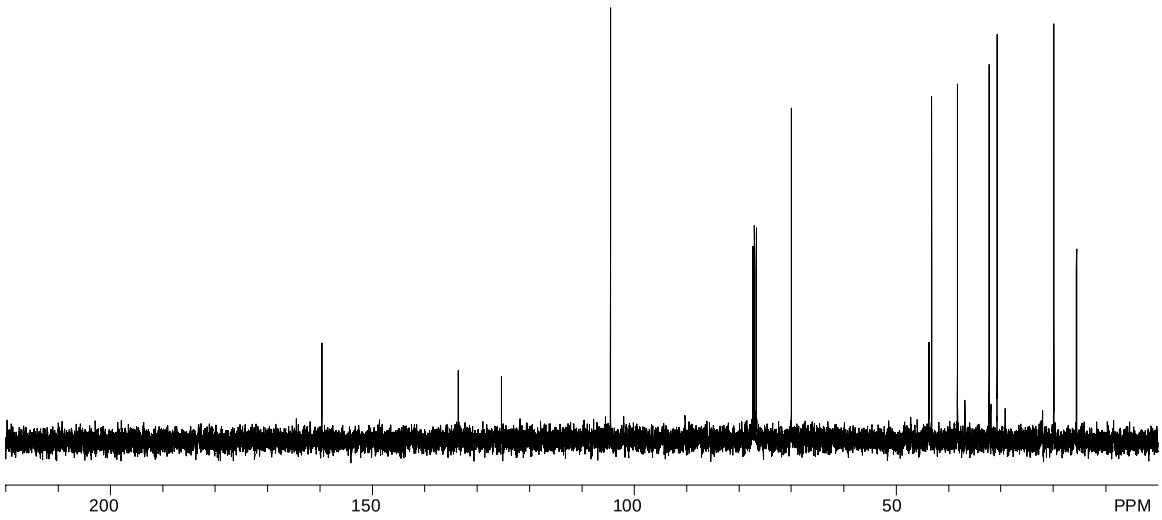


Figure A.5.75 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **208.**

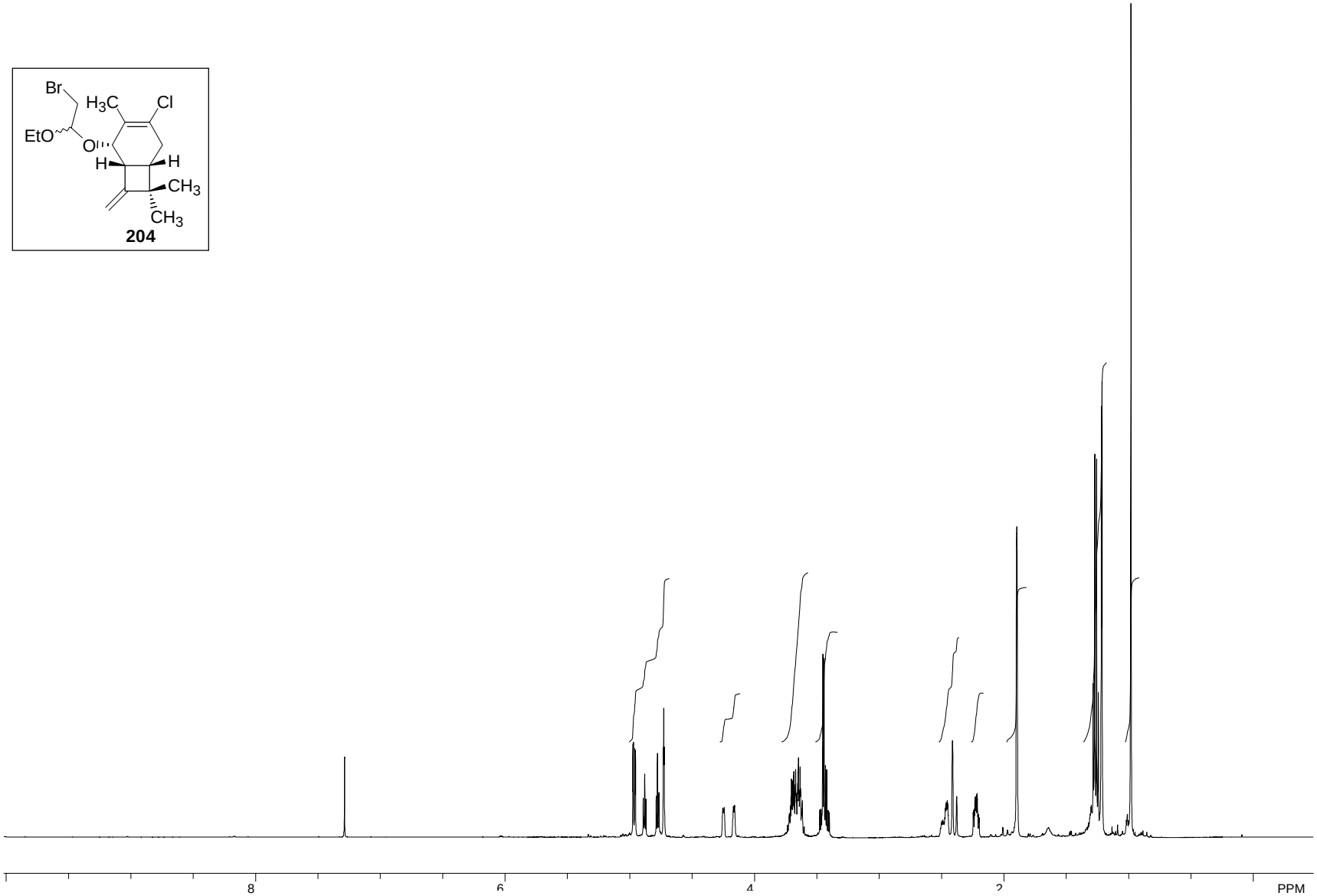


Figure A.5.76 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **204**.

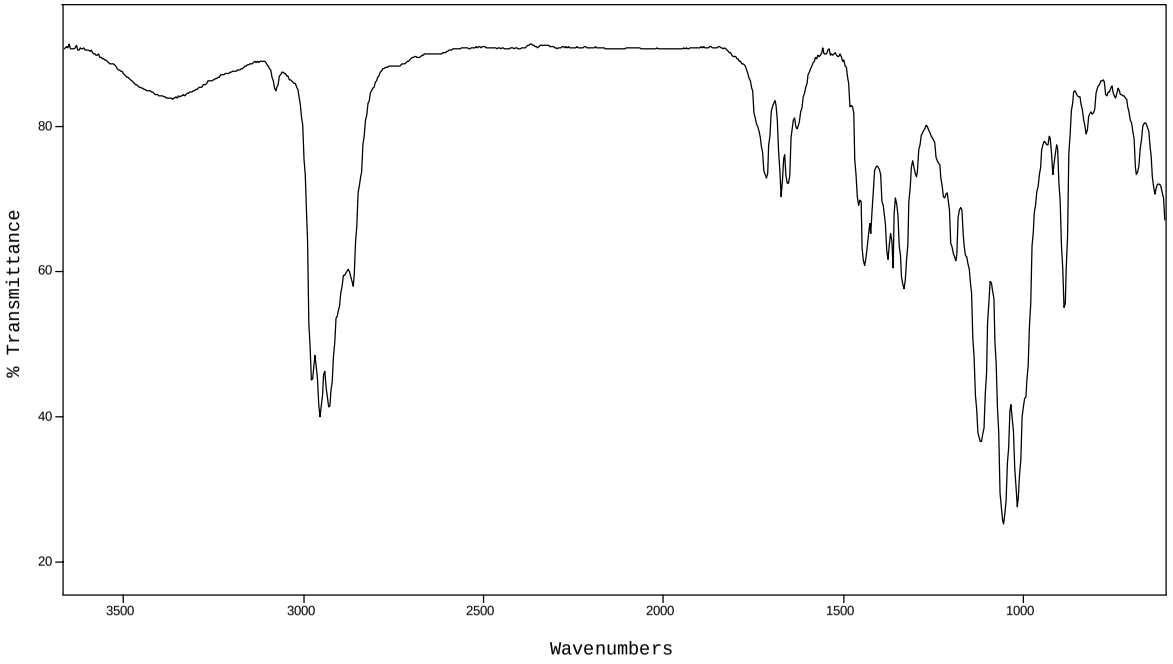


Figure A.5.77 FTIR Spectrum (thin film/NaCl) of Compound **204**.

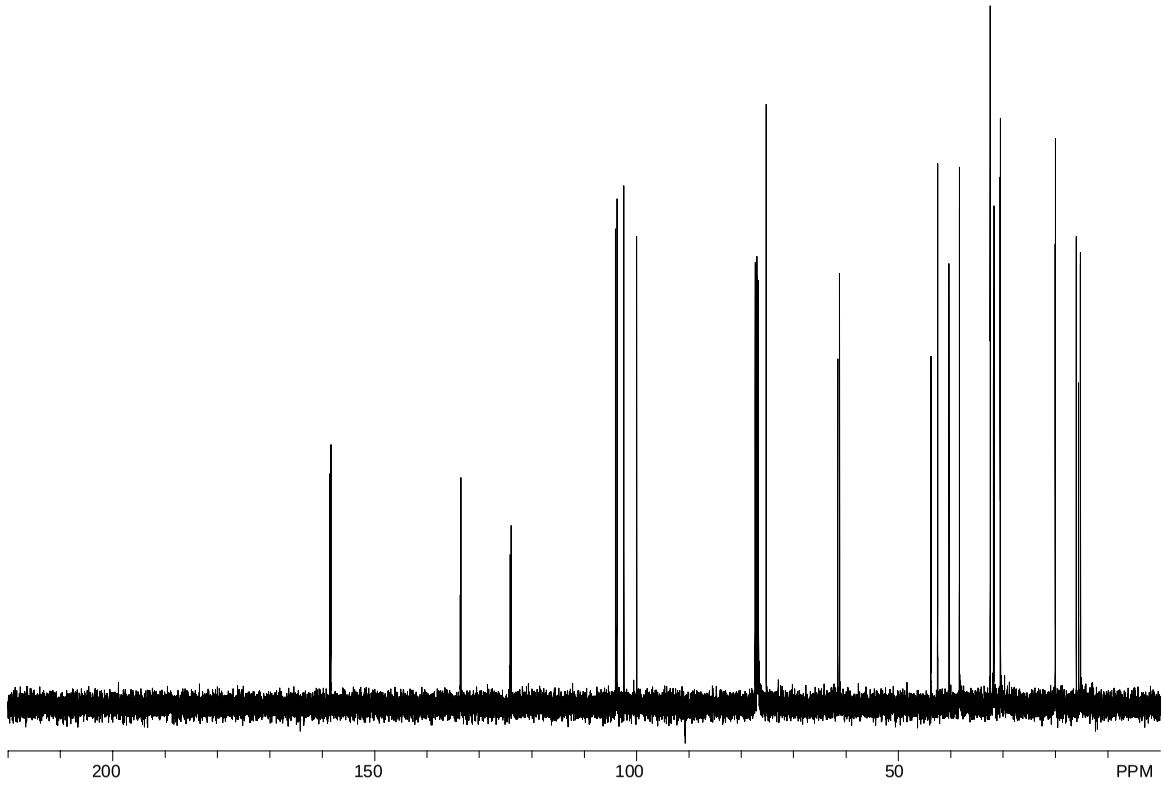


Figure A.5.78 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **204**.

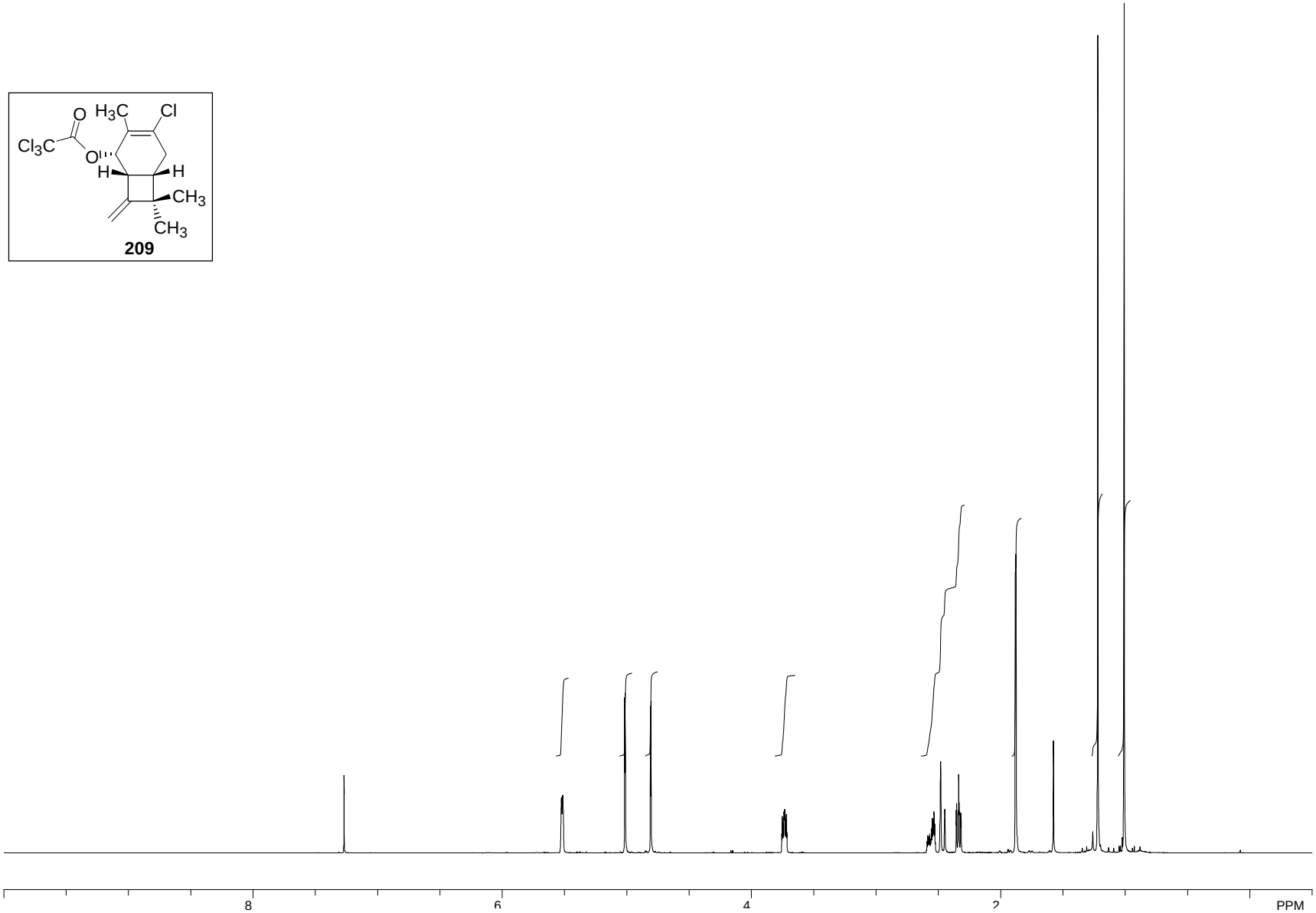


Figure A.5.79 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **209**.

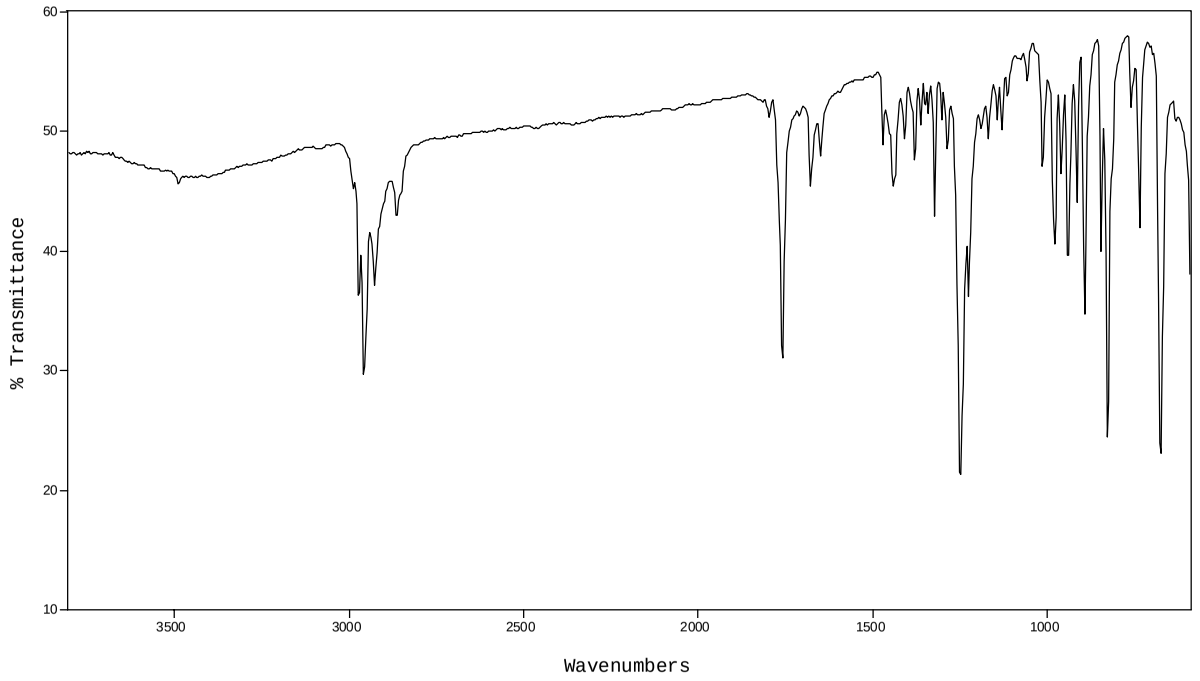


Figure A.5.80 FTIR Spectrum (thin film/NaCl) of Compound **209**.

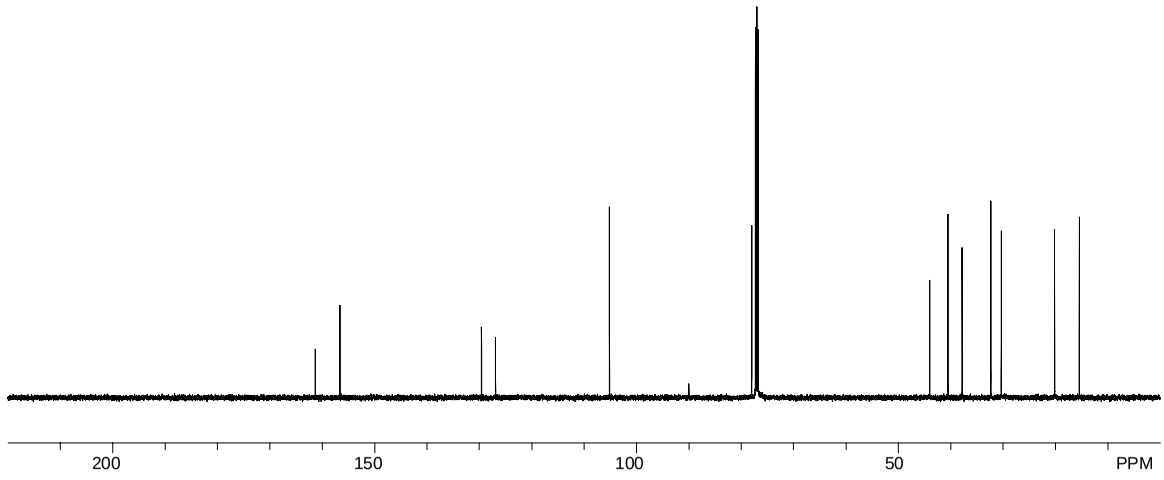


Figure A.5.81 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **209.**

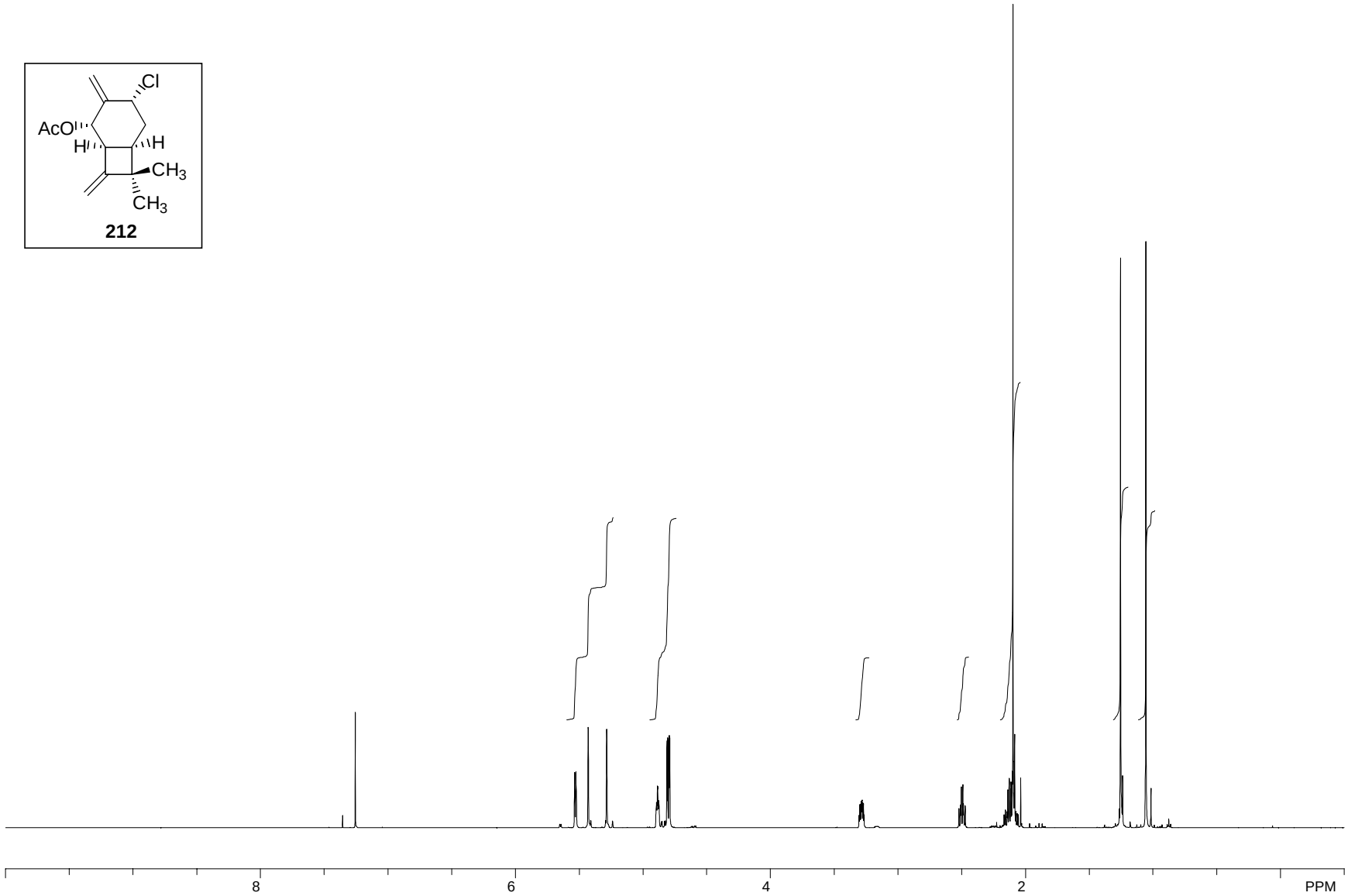


Figure A.5.82 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **212**.

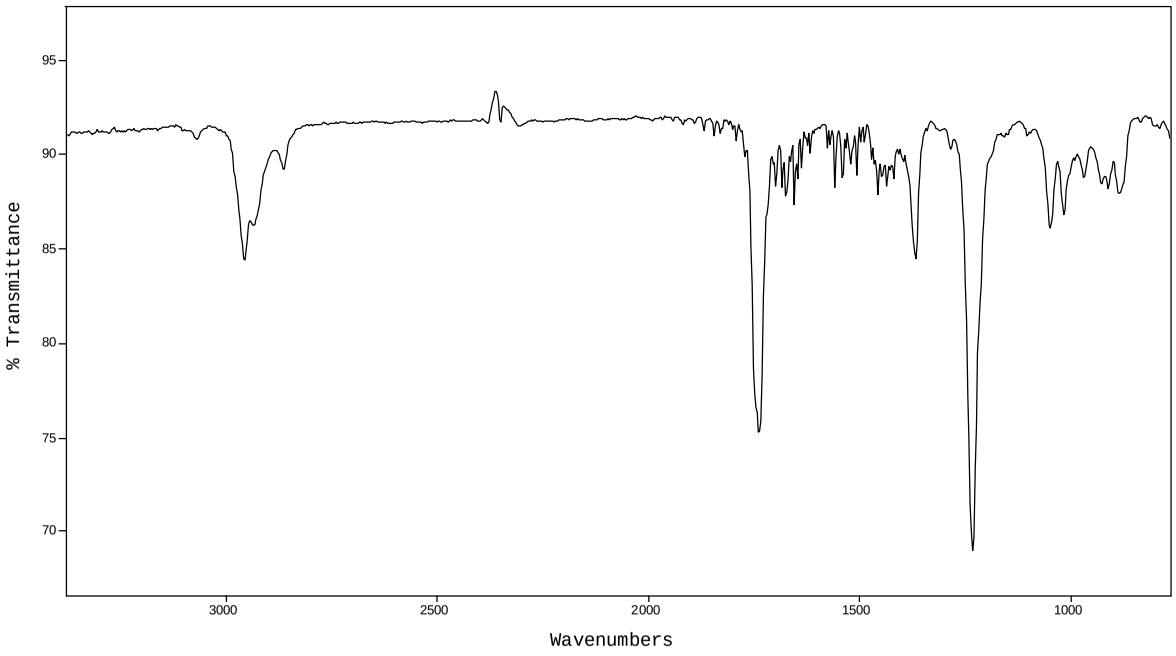


Figure A.5.83 FTIR Spectrum (thin film/NaCl) of Compound **212**.

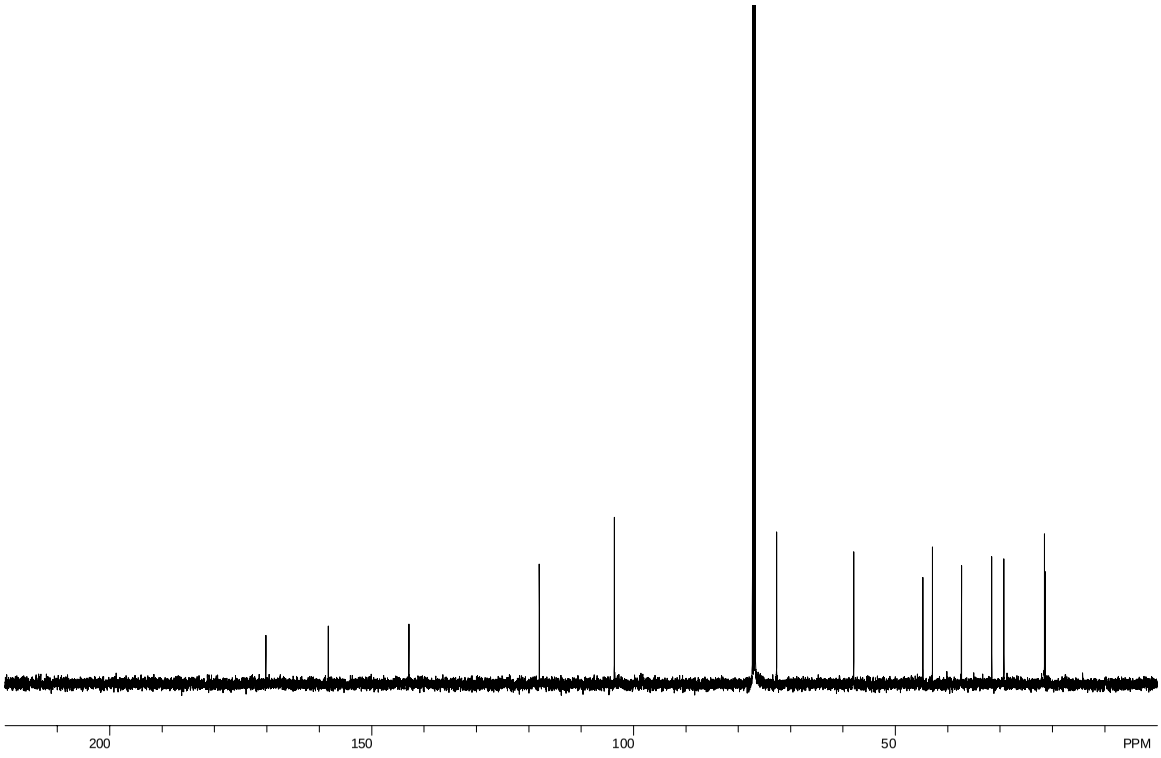


Figure A.5.84 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **212**.

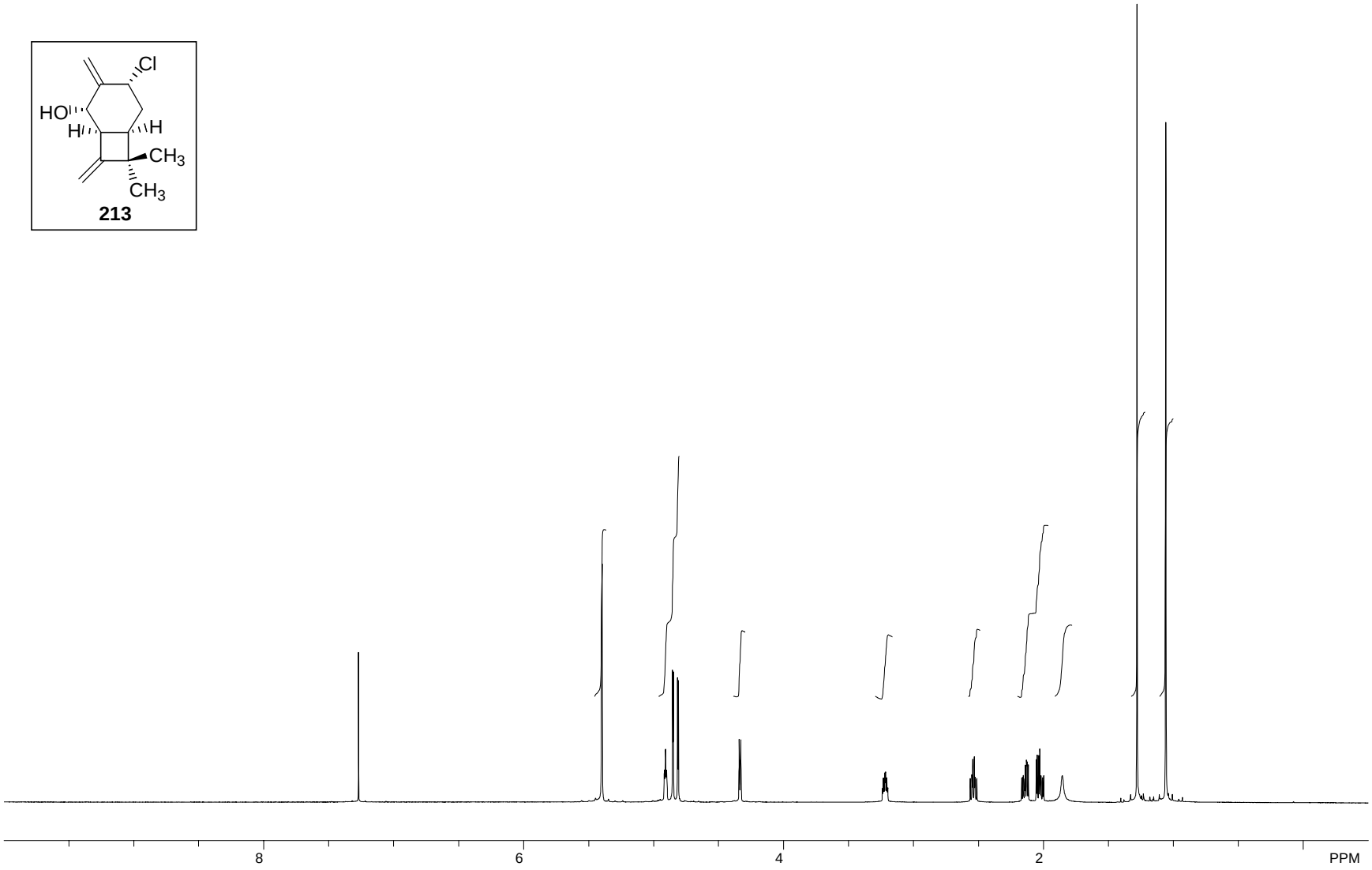


Figure A.5.85 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **213**.

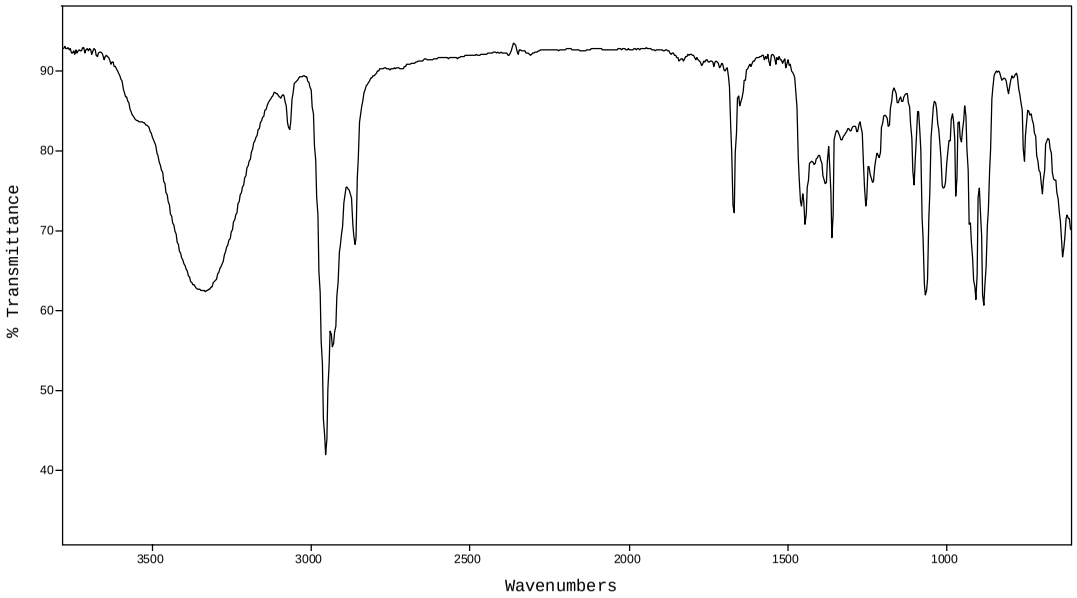


Figure A.5.86 FTIR Spectrum (thin film/NaCl) of Compound **213**.

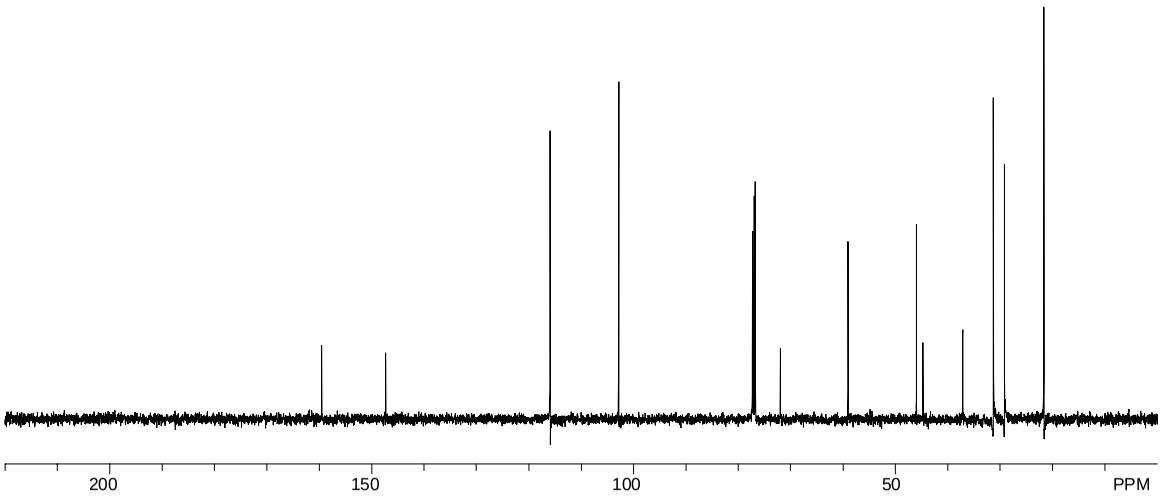


Figure A.5.87 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **213**.

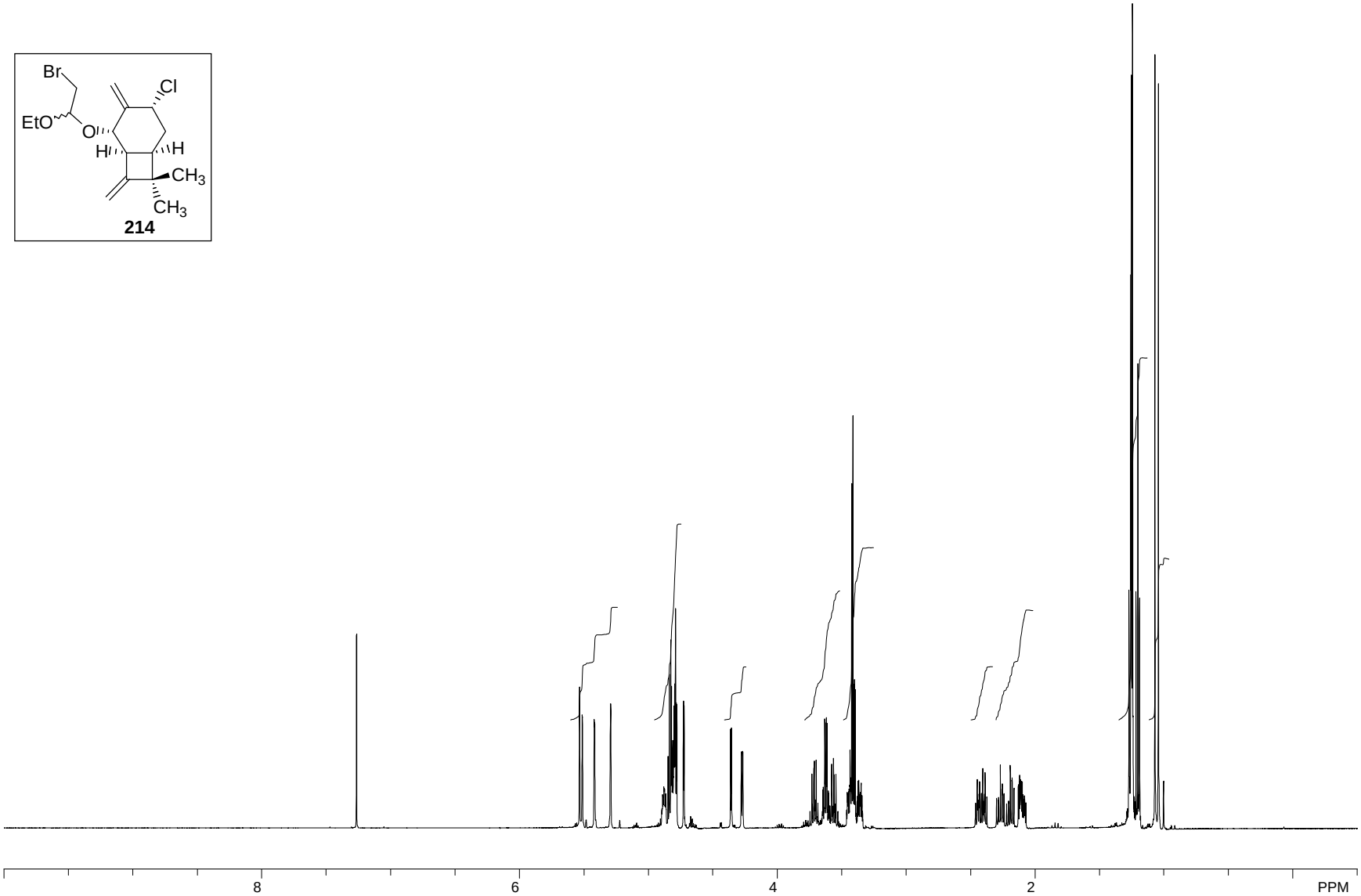


Figure A.5.88 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **214**.

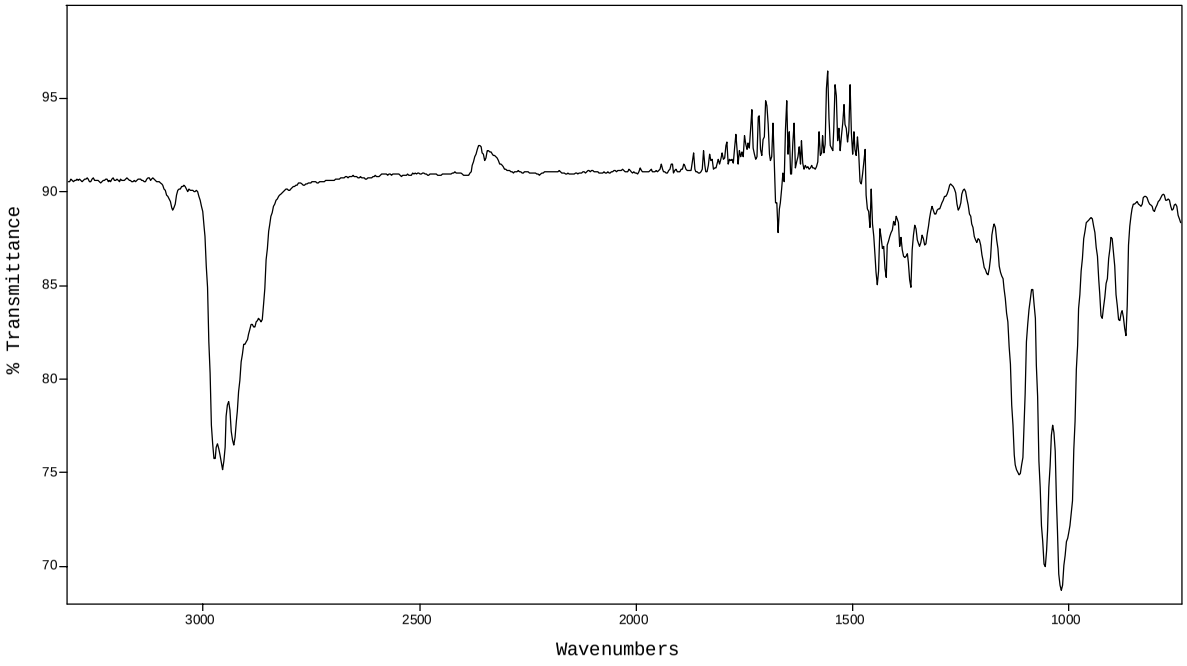


Figure A.5.89 FTIR Spectrum (thin film/NaCl) of Compound **214**.

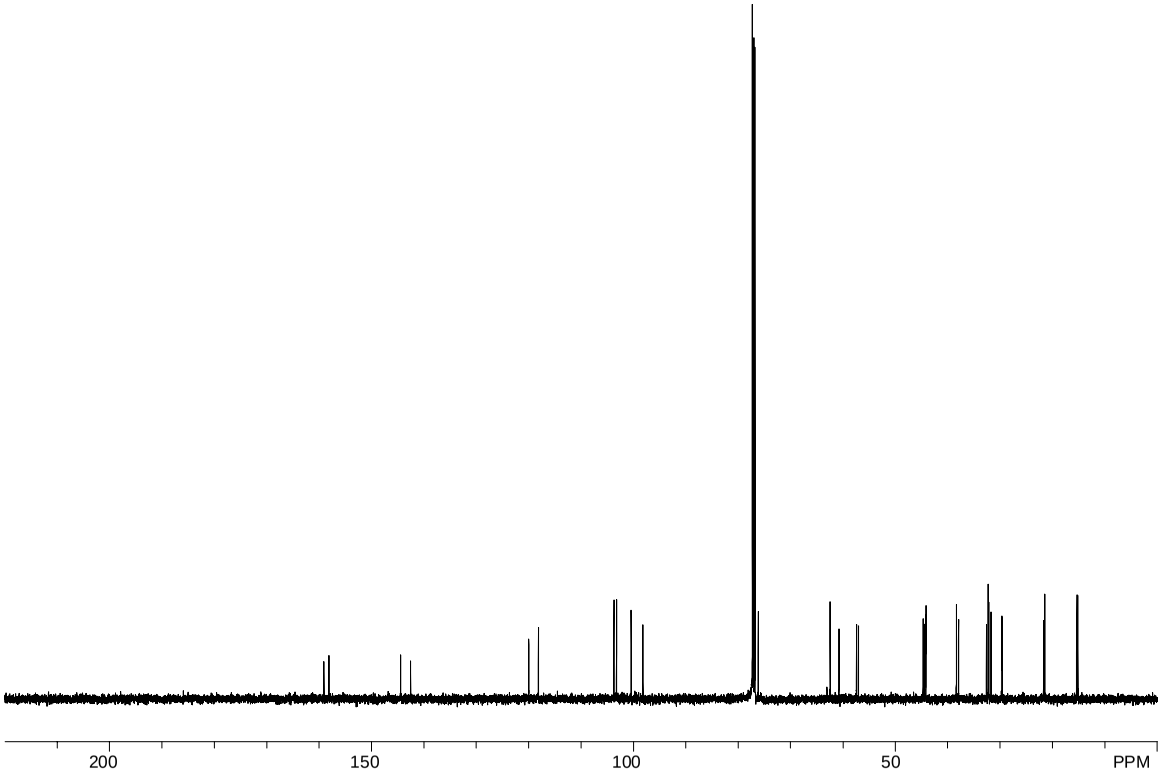


Figure A.5.90 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **214**.

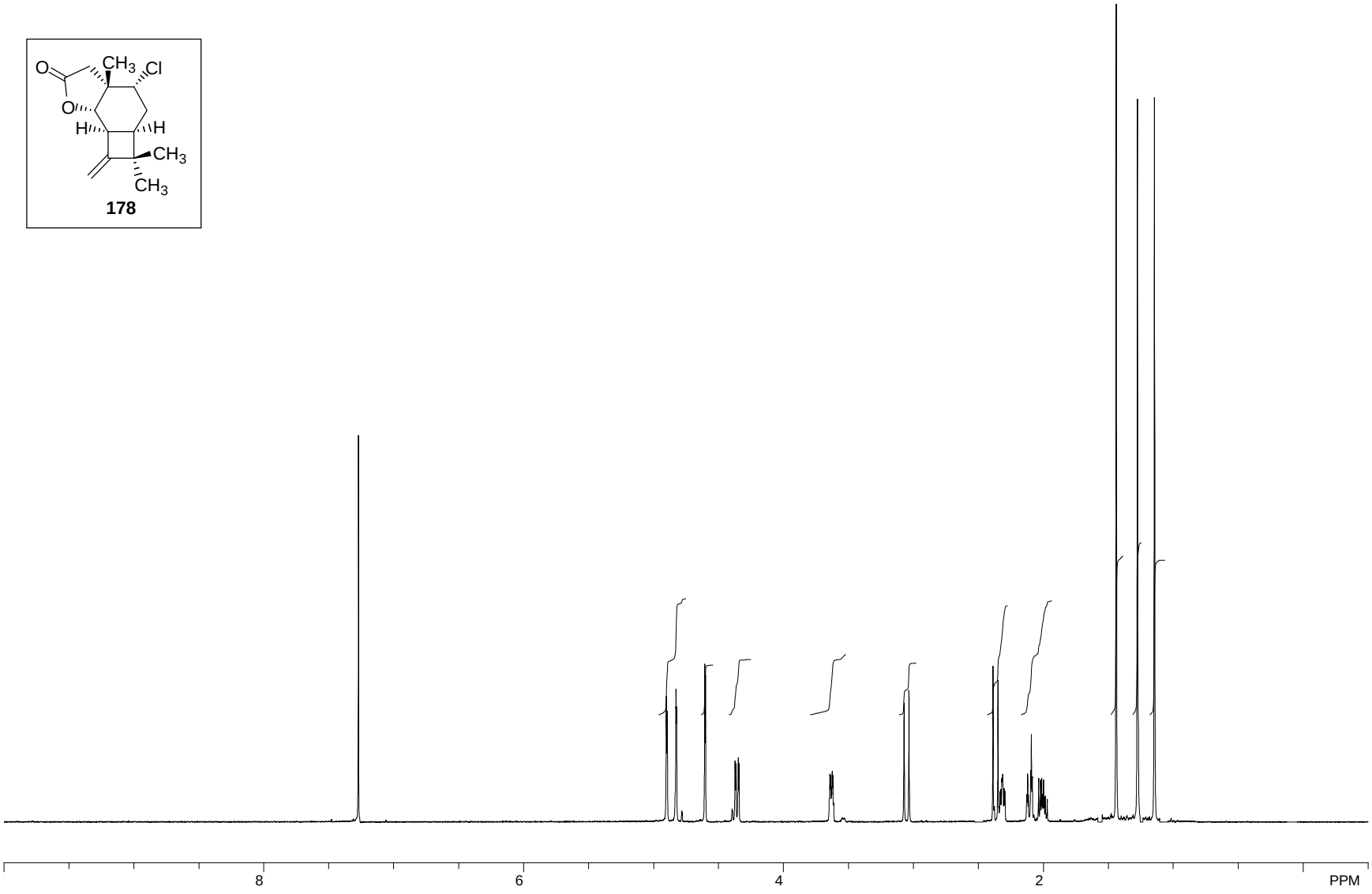


Figure A.5.91 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **178**.

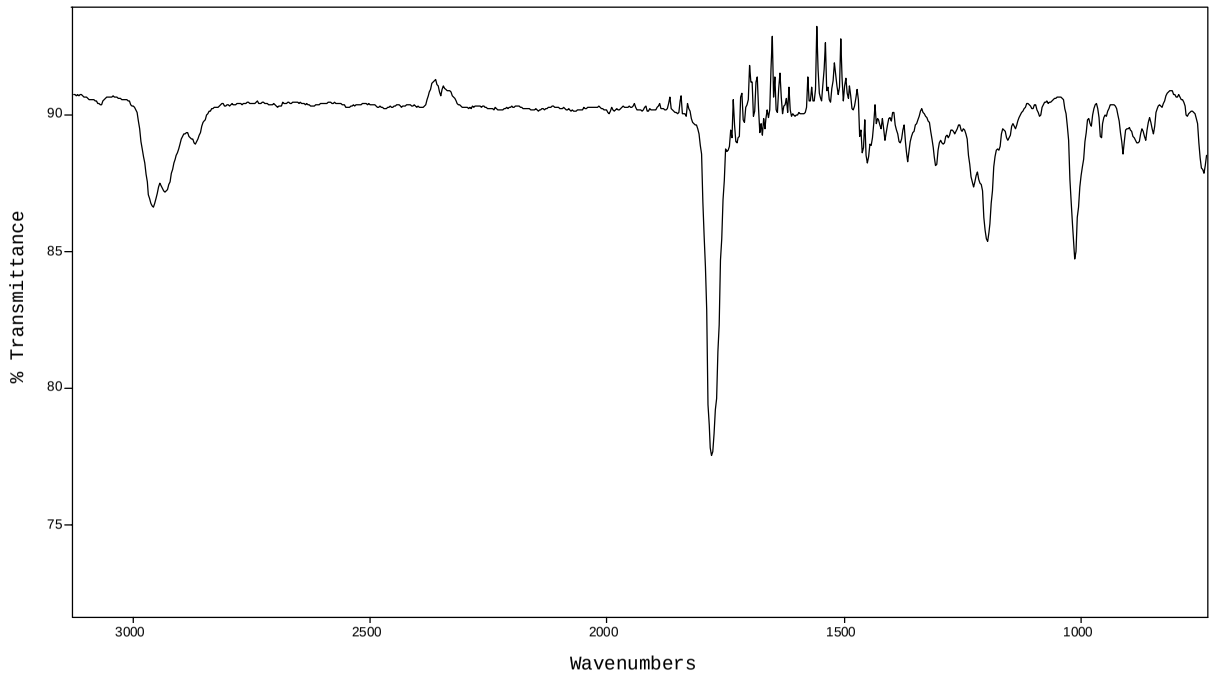


Figure A.5.92 FTIR Spectrum (thin film/NaCl) of Compound **178**.

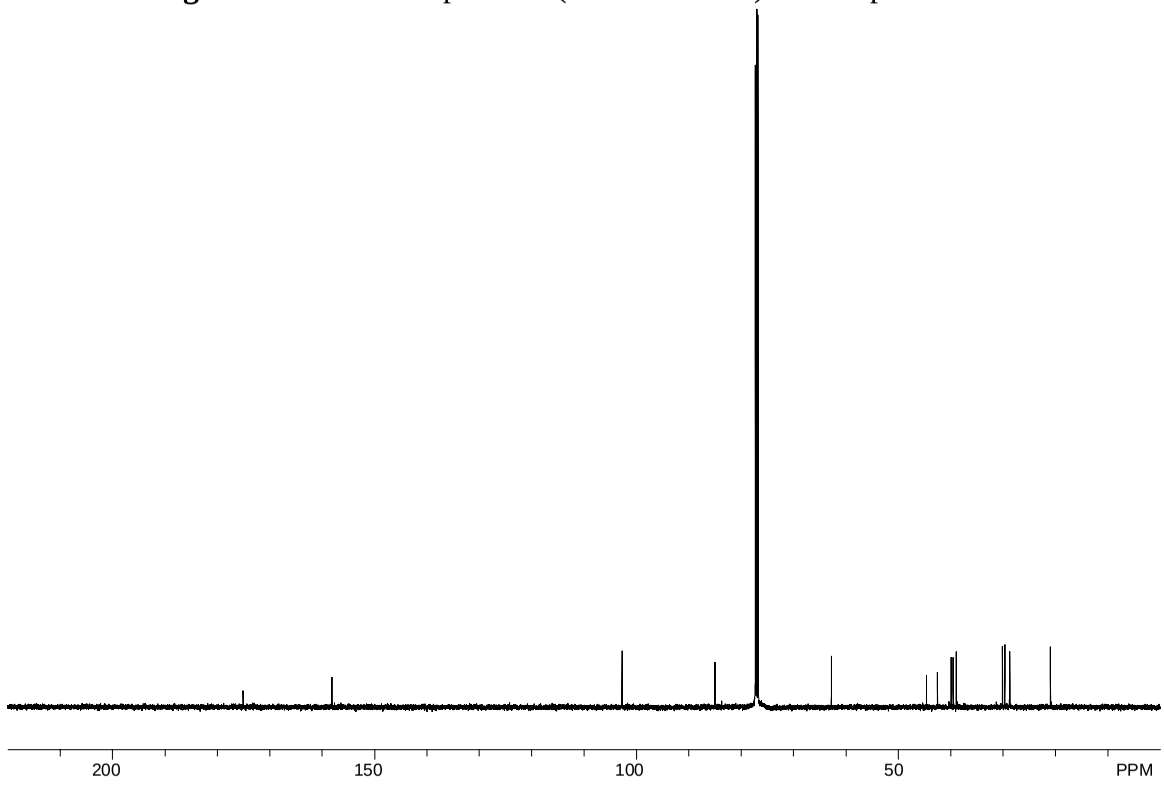
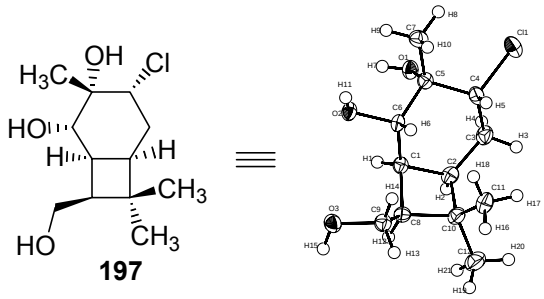


Figure A.5.93 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **178**.

APPENDIX SIX: X-RAY CRYSTALLOGRAPHY REPORTS RELEVANT TO CHAPTER THREE

X-RAY CRYSTALLOGRAPHY REPORT FOR TRIOL 197.



Empirical Formula	$C_{12}H_{21}O_3Cl \cdot H_2O$
Formula Weight	266.76
Crystal Color, Habit	colorless, plate
Crystal Dimensions	0.12 X 0.22 X 0.26 mm
Crystal System	triclinic
Lattice Type	Primitive
Lattice Parameters	a = 7.1526(4)Å
	b = 7.4101(4) Å
	c = 13.464(1) Å
	α = 81.912(4)^o
	β = 76.020(4)^o
	γ = 87.129(4)^o
	V = 685.50(7) Å^3
Space Group	P_{-1} (#2)
Z value	2
Dcalc	1.292 g/cm^3
F000	288.00
μ(MoKα)	2.80 cm^{-1}

B. Intensity Measurements

Diffractometer	Nonius KappaCCD
Radiation	MoKα (λ = 0.71069 Å)
	graphite monochromated
Take-off Angle	2.8^o
Crystal to Detector Distance	35 mm
Temperature	-90.0^{o}C
Scan Rate	60sec/frame
Scan Width	2°/frame
2θmax	55.0^o

No. of Reflections Measured	Total: 3027
Corrections	Lorentz-polarization

C. Structure Solution and Refinement

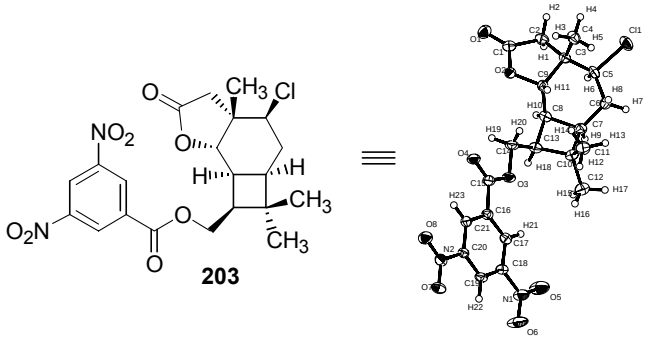
Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma\ w\ (\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$1/\sigma^2(Fo)$
p-factor	0.0100
Anomalous Dispersion	All non-hydrogen atoms
No. Observations ($I>3.00\sigma(I)$)	2408
No. Variables	246
Reflection/Parameter Ratio	9.79
Residuals: R; Rw	0.034 ; 0.045
Goodness of Fit Indicator	2.02
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.25 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.26 $e^-/Å^3$

Positional Parameters and B(eq) for 197.

atom	x	y	z	Beq
Cl(1)	-0.24677(6)	-0.67800(6)	-0.67270(3)	3.18(1)
O(1)	-0.4540(1)	-0.6332(1)	-0.85255(9)	2.03(2)
O(2)	-0.4940(2)	-0.2719(1)	-0.96464(7)	1.93(2)
O(3)	-0.8176(2)	0.0751(1)	-0.91658(8)	2.29(2)
O(4)	-0.2028(2)	0.0708(2)	-0.8978(1)	2.69(3)
C(1)	-0.7201(2)	-0.3308(2)	-0.8034(1)	1.65(3)
C(2)	-0.7616(2)	-0.4161(2)	-0.6883(1)	1.88(3)
C(3)	-0.6085(2)	-0.5392(2)	-0.6507(1)	2.26(3)
C(4)	-0.4038(2)	-0.4957(2)	-0.7121(1)	2.03(3)
C(5)	-0.3823(2)	-0.4713(2)	-0.8290(1)	1.70(3)
C(6)	-0.5086(2)	-0.3045(2)	-0.8554(1)	1.60(3)
C(7)	-0.1747(2)	-0.4415(2)	-0.8889(1)	2.36(3)
C(8)	-0.8396(2)	-0.1595(2)	-0.7667(1)	1.79(3)
C(9)	-0.7799(2)	0.0314(2)	-0.8156(1)	2.02(3)
C(10)	-0.8199(2)	-0.2241(2)	-0.6540(1)	2.05(3)
C(11)	-0.6626(3)	-0.1285(2)	-0.6229(1)	2.52(4)
C(12)	-1.0073(3)	-0.2190(3)	-0.5712(1)	2.97(4)
H(1)	-0.773(2)	-0.390(2)	-0.845(1)	1.3(3)
H(2)	-0.874(2)	-0.486(2)	-0.674(1)	1.4(3)
H(3)	-0.618(2)	-0.530(2)	-0.579(1)	2.8(3)
H(4)	-0.633(2)	-0.671(2)	-0.657(1)	2.3(3)
H(5)	-0.356(2)	-0.387(2)	-0.698(1)	1.9(3)
H(6)	-0.454(2)	-0.196(2)	-0.835(1)	1.5(3)
H(7)	-0.459(3)	-0.612(2)	-0.912(2)	3.6(4)

H(8)	-0.088(2)	-0.543(2)	-0.868(1)	3.1(3)
H(9)	-0.171(2)	-0.436(2)	-0.961(1)	3.0(4)
H(10)	-0.127(2)	-0.325(2)	-0.875(1)	2.6(3)
H(11)	-0.400(3)	-0.220(3)	-0.992(2)	4.1(5)
H(12)	-0.971(2)	-0.173(2)	-0.7686(10)	1.3(3)
H(13)	-0.848(2)	0.122(2)	-0.772(1)	2.3(3)
H(14)	-0.643(2)	0.050(2)	-0.825(1)	1.5(3)
H(15)	-0.941(4)	0.088(3)	-0.910(2)	5.6(5)
H(16)	-0.706(2)	-0.010(2)	-0.608(1)	3.1(4)
H(17)	-0.628(3)	-0.191(3)	-0.562(2)	3.9(4)
H(18)	-0.543(2)	-0.114(2)	-0.674(1)	2.4(3)
H(19)	-1.059(3)	-0.096(3)	-0.568(1)	3.4(4)
H(20)	-0.989(2)	-0.269(2)	-0.503(1)	3.3(4)
H(21)	-1.117(3)	-0.289(3)	-0.589(1)	4.1(4)
H(22)	-0.272(3)	0.168(3)	-0.875(2)	4.5(5)
H(23)	-0.226(3)	0.059(3)	-0.955(2)	3.7(4)

X-RAY CRYSTALLOGRAPHY REPORT FOR LACTONE 203.



Empirical Formula	$C_{21.50}H_{24}N_2O_8Cl_2$
Formula Weight	509.34
Crystal Color, Habit	colorless, plate
Crystal Dimensions	0.04 X 0.08 X 0.15 mm
Crystal System	monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 12.308(1)Å
	b = 9.9565(5) Å
	c = 19.721(1) Å
	β = 105.891(2)^o
	V = 2324.4(2) Å^3
Space Group	P2/n (#13)
Z value	4
D_{calc}	1.455 g/cm^3
F000	1060.00
μ(MoKα)	3.30 cm^{-1}

B. Intensity Measurements

Diffractometer	Nonius KappaCCD
Radiation	MoKα (λ = 0.71069 Å)
	graphite monochromated
Take-off Angle	2.8^o
Crystal to Detector Distance	33 mm
Temperature	-90.0^{o}C
Scan Type	ω
Scan Rate	180s/frame
Scan Width	2.0^o/frame
2θmax	49.9^o
No. of Reflections Measured	Total: 4335
Corrections	Lorentz-polarization

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma\ w\ (\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$1/\sigma^2(Fo)$
p-factor	0.0100
Anomalous Dispersion	All non-hydrogen atoms
No. Observations ($I>3.00\sigma(I)$)	2075
No. Variables	321
Reflection/Parameter Ratio	6.46
Residuals: R; Rw	0.045 ; 0.041
Goodness of Fit Indicator	1.97
Max Shift/Error in Final Cycle	0.10
Maximum peak in Final Diff. Map	0.28 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.31 $e^-/Å^3$

Positional Parameters and B(eq) for 203.

atom	x	y	z	Beq
Cl(1)	0.30687(9)	-0.0200(1)	-0.15862(5)	4.20(3)
Cl(2a)	-0.338(1)	-0.436(1)	0.1871(6)	8.5(2)
Cl(2b)	-0.2998(10)	-0.372(1)	0.1740(4)	7.7(2)
Cl(2c)	-0.348(2)	-0.394(5)	0.193(1)	9.9(7)
O(1)	-0.0743(2)	0.2401(3)	-0.0780(1)	4.31(8)
O(2)	-0.0596(2)	0.0189(3)	-0.0828(1)	2.90(7)
O(3)	-0.2251(2)	-0.4089(2)	-0.0944(1)	3.26(7)
O(4)	-0.2630(2)	-0.3568(2)	0.0077(1)	3.30(7)
O(5)	-0.3452(3)	-0.8251(3)	-0.2117(2)	6.5(1)
O(6)	-0.4476(3)	-0.9623(3)	-0.1738(2)	6.8(1)
O(7)	-0.5487(2)	-0.8637(3)	0.0418(1)	3.87(8)
O(8)	-0.4910(2)	-0.6786(3)	0.0980(1)	4.10(8)
N(1)	-0.3941(3)	-0.8588(4)	-0.1692(2)	4.1(1)
N(2)	-0.4971(3)	-0.7572(4)	0.0491(2)	3.23(9)
C(1)	-0.0271(4)	0.1447(4)	-0.0938(2)	3.1(1)
C(2)	0.0700(4)	0.1373(4)	-0.1256(2)	3.4(1)
C(3)	0.1183(3)	-0.0038(4)	-0.1093(2)	2.59(9)
C(4)	0.2050(3)	-0.0052(4)	-0.0375(2)	3.6(1)
C(5)	0.1618(3)	-0.0687(4)	-0.1670(2)	3.0(1)
C(6)	0.1509(4)	-0.2205(4)	-0.1684(2)	3.2(1)
C(7)	0.0255(3)	-0.2544(4)	-0.1937(2)	3.1(1)
C(8)	-0.0524(3)	-0.1552(4)	-0.1676(2)	2.61(10)
C(9)	0.0121(3)	-0.0826(4)	-0.1020(2)	2.53(10)
C(10)	-0.0281(3)	-0.3749(4)	-0.1642(2)	3.2(1)
C(11)	0.0441(4)	-0.4346(4)	-0.0954(2)	4.0(1)

C(12)	-0.0692(4)	-0.4891(4)	-0.2170(2)	4.6(1)
C(13)	-0.1242(3)	-0.2780(4)	-0.1564(2)	3.0(1)
C(14)	-0.1666(4)	-0.2811(4)	-0.0923(2)	3.3(1)
C(15)	-0.2687(3)	-0.4325(4)	-0.0407(2)	3.0(1)
C(16)	-0.3271(3)	-0.5656(4)	-0.0481(2)	2.59(10)
C(17)	-0.3299(3)	-0.6515(4)	-0.1039(2)	2.8(1)
C(18)	-0.3893(3)	-0.7700(4)	-0.1082(2)	2.7(1)
C(19)	-0.4449(3)	-0.8074(4)	-0.0598(2)	2.74(10)
C(20)	-0.4395(3)	-0.7211(4)	-0.0046(2)	2.50(10)
C(21)	-0.3814(3)	-0.6011(4)	0.0022(2)	2.73(10)
C(22)	-0.2500	-0.3248(9)	0.2500	10.5(4)
H(1)	0.0447	0.1512	-0.1751	4.0902
H(2)	0.1253	0.2028	-0.1050	4.0902
H(3)	0.1676	0.0048	-0.0015	4.3758
H(4)	0.2567	0.0667	-0.0348	4.3758
H(5)	0.2448	-0.0881	-0.0313	4.3758
H(6)	0.1170	-0.0357	-0.2110	3.6421
H(7)	0.1893	-0.2575	-0.1999	3.8916
H(8)	0.1823	-0.2560	-0.1225	3.8916
H(9)	0.0027	-0.2573	-0.2438	3.7592
H(10)	-0.0928	-0.0961	-0.2035	3.1376
H(11)	0.0349	-0.1455	-0.0646	3.0374
H(12)	0.0100	-0.5149	-0.0852	4.8028
H(13)	0.1174	-0.4541	-0.0999	4.8028
H(14)	0.0500	-0.3720	-0.0582	4.8028
H(15)	-0.1217	-0.4549	-0.2580	5.5254
H(16)	-0.1048	-0.5561	-0.1962	5.5254
H(17)	-0.0067	-0.5273	-0.2295	5.5254
H(18)	-0.1868	-0.2873	-0.1968	3.6289
H(19)	-0.2172	-0.2086	-0.0933	3.9925
H(20)	-0.1053	-0.2754	-0.0509	3.9925
H(21)	-0.2917	-0.6293	-0.1382	3.3503
H(22)	-0.4856	-0.8895	-0.0642	3.2922
H(23)	-0.3787	-0.5434	0.0410	3.2728
H(24)	-0.2069	-0.2623	0.2277	12.0853

CHAPTER FOUR

WELWITINDOLINONE A ISONITRILE: CONSTRUCTION OF A FULLY ELABORATED [4.2.0] BICYCLIC SYSTEM

4.1 Initial Concerns.

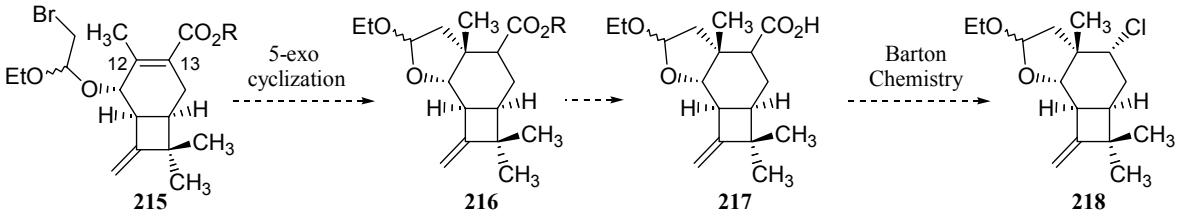
While the results presented in Chapter 3 did not allow for an efficient preparation of a fully elaborate [4.2.0] bicyclic system, the pitfalls that were encountered during this work provided invaluable information. Determined to use this information in devising a final strategy for an efficient construction of a fully elaborate [4.2.0] system, our revised tactics were guided by three findings. First, it was shown that enolate **179** could selectively be generated upon conjugate reduction of ketone **178**, and that this enolate was efficiently chlorinated upon treatment with NCS. Second, the C(12) quaternary center could be constructed via a 5-exo-trig radical cyclization. Finally, in the conversion of **190** → **201**, it was demonstrated that a radical produced at C(13) had a tendency to be trapped exclusively from the convex face. These observations ultimately culminated into the strategy outlined below (Scheme 4.1.1).

4.1.1 Formulating a New Strategy.

In view of the previous results, ester **215** was initially targeted as a key intermediate (Scheme 4.1.1). Several features made this an attractive target. First, it was

envisaged that the protocol established for the installation of the chlorine (i.e., **178** → **194**) would be amenable for the construction of **215**. It was believed that the C(13) ester would serve both to activate the tetrasubsituted olefin for the 5-exo-trig cyclization and would act as a handle for the late introduction of the chlorine. Specifically, it was envisioned that the corresponding acid (**217**) would allow for the introduction of the chlorine via a halogenative decarboxylation. It was this last feature which piqued our interest, as it had already been demonstrated in one system (**190** → **201**) that a radical generated at C(13) was quenched exclusively from the convex face. Further, the halogenative decarboxylation methodology developed by Barton and Crich has been shown to be very effective for the introduction of hindered chlorines.[1,2]

Scheme 4.1.1



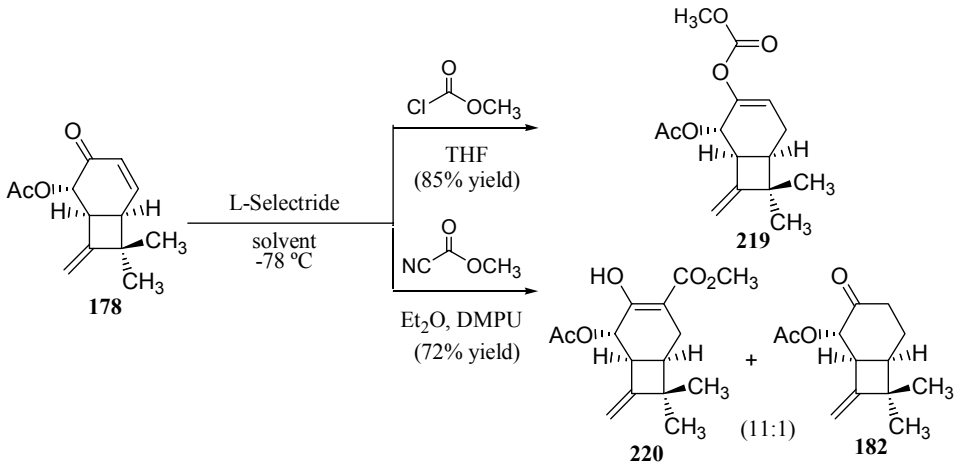
4.2 Preparation and Radical Cyclization of a Modified Substrate.

4.2.1 Installation of the Carboxyl Group.

Anticipating that the protocol which allowed for the conversion of **178** → **194** would also allow for the installation of the ester, **178** was treated sequentially with L-Selectride and methyl chloroformate (Scheme 4.2.1). This reaction sequence led solely to the formation of enol carbonate **219**, which arises from O-alkylation of the intermediate enolate. Methyl chloroformate was replaced with methyl cyanoformate in

an effort to redirect the course of the reaction to favor C-alkylation.[3,4] This alteration did indeed lead to the formation of β-ketoester **220**, however, it was accompanied by an equimolar amount of ketone **182**. Eventually it was found that the best results were obtained when the reaction was performed in Et_2O and 1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone (DMPU) was used as a cosolvent. This procedure allowed for the preparation of β-ketoester **220** in good yield with only minor amounts of ketone **182**.

Scheme 4.2.1

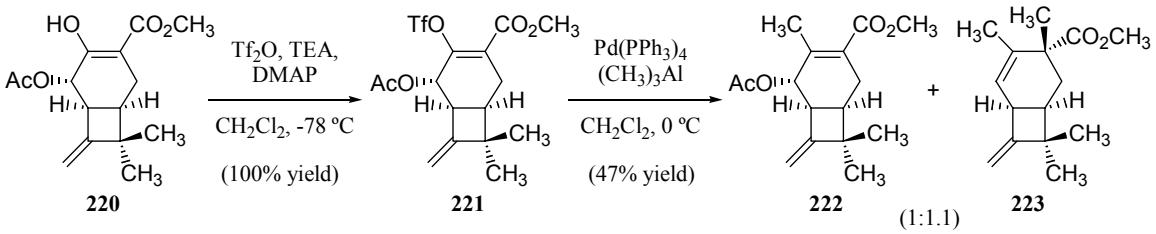


4.2.2 Homologation of the Ketone.

Enol triflate **221** was efficiently prepared from **220** with the intent of using palladium chemistry for the introduction of the requisite C(12) methyl group; however, further elaboration proved more difficult than expected (Scheme 4.2.2). Upon treatment with Pd(0) and trimethyl aluminum, **221** was converted to a mixture of the desired diene (**222**) as well as a single diastereomer of diene **223**. It is believed that **223** arises via palladium-catalyzed allylic substitution.[5-9] It was speculated that the deprotection of the

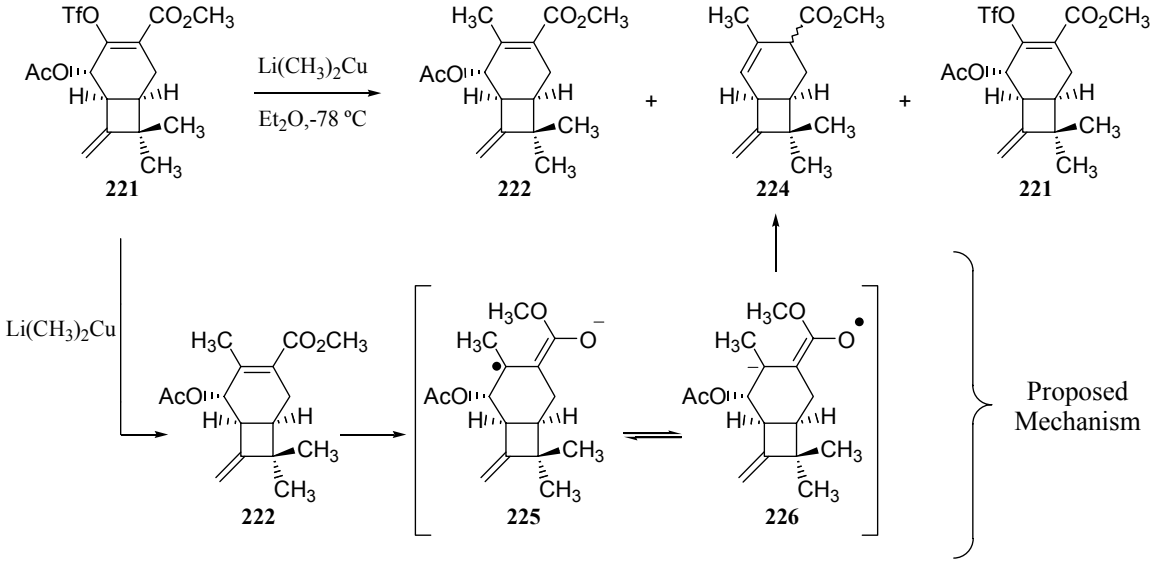
acetate could prevent the formation of products arising from π-allyl chemistry, however, initial efforts at the hydrolysis of this acetate were met with little success.

Scheme 4.2.2



Unable to efficiently construct diene **222** using Pd chemistry, attention shifted to the use of cuprate chemistry to effect the desired homologation of enol triflate **221** (Scheme 4.2.3).[10,11] Toward this end, the addition of an ethereal solution of **221** to $Li(CH_3)_2Cu$ did afford the desired product **222**,[12,13] yet this product was contaminated with recovered starting material **221** as well as a diastereomeric mixture of olefins **224**. This latter result is not without precedence: it has previously been demonstrated that α,β-enones which possess leaving groups in the γ position display more complex reactivity towards lithium dialkyl cuprates that do normal α,β-enones.[14-17] Depending on the nature of the leaving group, reductive cleavage of the γ-heteroatom can occur giving rise to β,γ-unsaturated ketones.[18] This process is believed to occur via a one electron transfer from copper to the enone to produce a radical anion which can undergo a subsequent 1,2 elimination to expel the γ leaving group.[14,19-21] Presumably, it is this mechanism that is in play in the formation of dienes **224**; whereby an initial Michael addition/β-elimination sequence gives rise to the desired product **222**. Excess reagent can then produce tautomeric radical anions **225** and **226** which go on to furnish **224**.

Scheme 4.2.3



With this knowledge in hand, an examination of the reaction parameters began in an effort to maximize the formation of the desired homologation product (**222**). The results of some of these efforts are summarized in Table 4.2.1. It was found that by minimizing the amount of $Li(CH_3)_2Cu$ employed in the reaction, the production of **224** could be curtailed; however this also led to incomplete consumption of starting material.

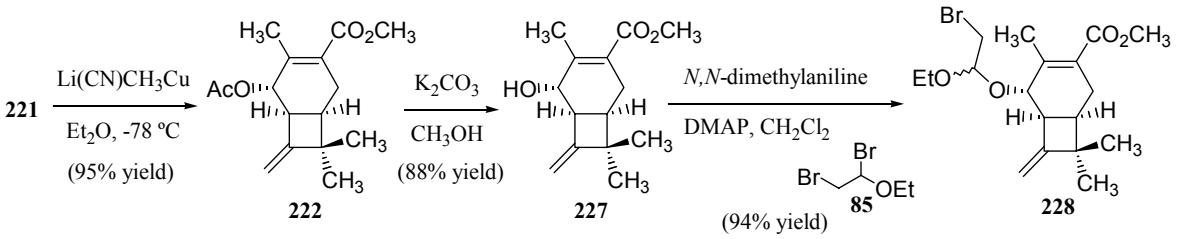
Table 4.2.1

Entry	Cuprate (eq.)	**221** (%)	**222** (%)	**224** (%)
1	$Li(CH_3)_2Cu$ (2.5)	-	43	34
2	$Li(CH_3)_2Cu$ (1.6)	4	65	29
3	$Li(CH_3)_2Cu$ (1.5)	13	64	17
4	$Li(CH_3)_2Cu$ (1.0)	54	36	-
5	$Li(CN)CH_3Cu$ (3.0)	-	95	-

Ultimately, the solution to this problem involved the use of a mixed cuprate (entry 5). Exposure of **221** to three equivalents of $Li(CN)CH_3Cu$ at –78 ºC led to the near

quantitative formation of diene **222** (Scheme 4.2.4).[18,22,23] Subsequent hydrolysis of the acetate delivered alcohol **227** which was efficiently converted to bromoacetals **228**.

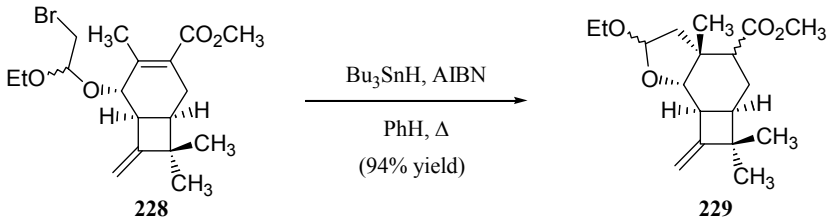
Scheme 4.2.4



4.2.4 Cyclization of 228.

With **228** in hand, the 5-exo-trig cyclization into the tetrasubstituted olefin could be examined. All expectations that the ester would serve to activate the olefin toward cyclization were met, as the slow addition of Bu_3SnH and AIBN to a refluxing solution of **228** resulted in the formation of four diastereomeric esters **229** in excellent yield (Scheme 4.2.5).

Scheme 4.2.5

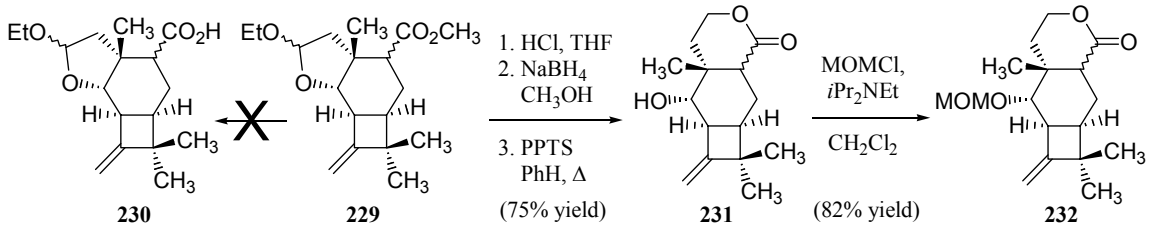


4.3 A Fully Functionalized [4.2.0] Bicyclic System.

4.3.1 Elaboration of 229.

Eager to explore the use of Barton chemistry for the installation of the C(13) chlorine, sights were set on the saponification of esters **229**. Surprisingly, this seemingly simple transformation proved extremely troublesome, and no conditions were found that would allow for the preparation of acids **230** (Scheme 4.3.1).

Scheme 4.3.1

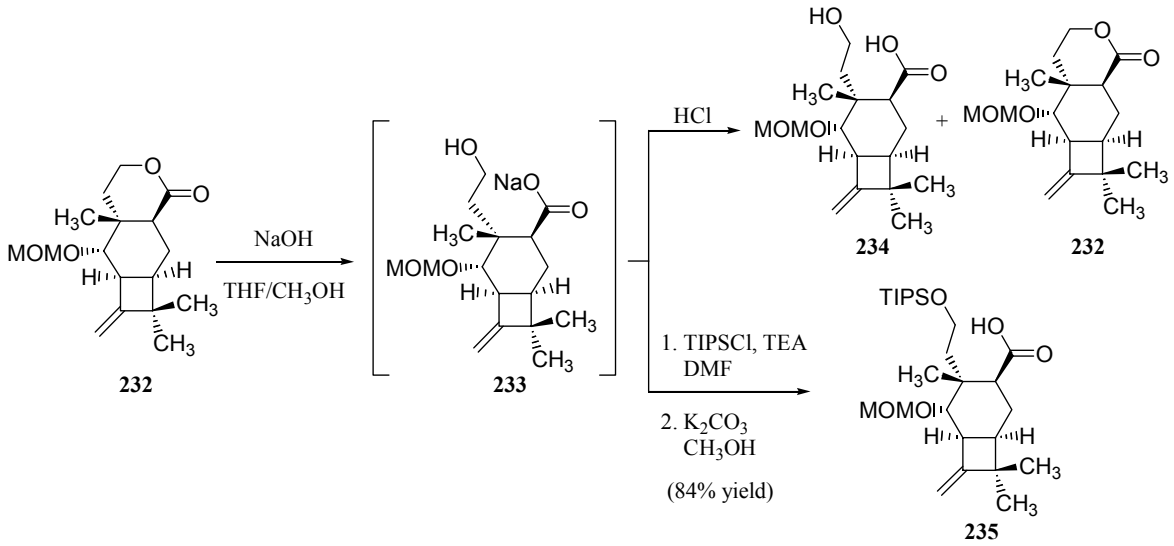


Unable to advance **229** to the corresponding acids presumably due to steric effects, efforts focused on manipulating the acetal portion of the molecule. It was speculated that subsequent structural alterations would lead to a conformational change that would ultimately allow for the hydrolysis of this ester. To this end, **229** could be parlayed to lactone **232** in a four-step sequence (Scheme 4.3.1). This process involved hydrolysis of the acetal, and reduction of the resulting aldehyde to the corresponding diol. Heating this diol in the presence of a catalytic amount of *p*-pyridiniumtoluene sulfonate (*p*PTS) resulted in an intramolecular lactonization to afford a mixture of lactones **231**. Protection of the remaining alcohol as its methoxymethyl ether (MOM) delivered lactones **232**. A single diastereomer of this lactone containing the β stereochemistry at

C(13), could be isolated by recrystallization. However, **232** was usually carried on as a mixture of diastereomers, as it was found that this did not affect the subsequent halogenative decarboxylation.

Interestingly, saponification of lactones **232** with one equivalent of NaOH proceeded smoothly at room temperature to effect complete conversion to carboxylate salt **233** (Scheme 4.3.2). Conventional acid-workup provided the desired hydroxy acid **234**, in addition to recovered starting material, the latter presumably arising via acid-catalyzed cyclization of **234**. While the cyclization of **234** → **232** could not be prevented, this problem could be overcome by treatment of the intermediate carboxylate salt (**233**) with excess tri-isopropylsilyl chloride (TIPSCl) leading to protection of both the primary alcohol and the carboxylic acid. Selective hydrolysis of the silyl ester with K_2CO_3 in methanol furnished acid **235** in good yield.

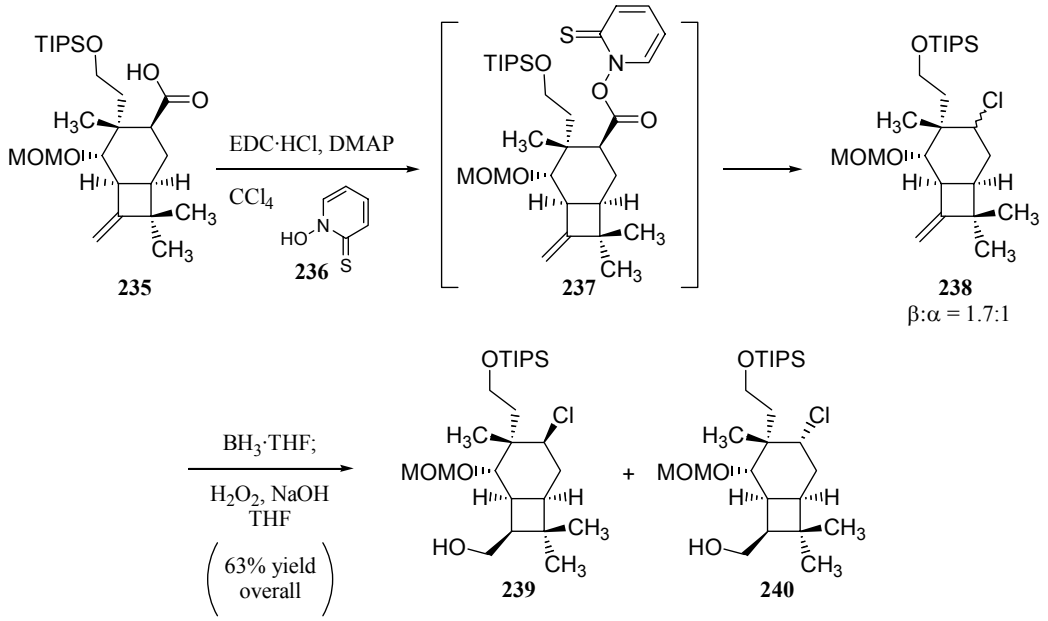
Scheme 4.3.2



4.3.2 Investigating the Halogenative Decarboxylation.

As was evident in the cyclization of **228**, the inclusion of the C(13) ester had proven a useful modification. This functionality now needed to serve as a handle for the introduction of the C(13) chlorine (Scheme 4.3.3). Toward this end, a thoroughly degassed solution of acid **235**, mercaptan **236**, and DMAP in CCl_4 was added to a suspension of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC•HCl) in degassed CCl_4.[2,24] The resulting suspension (whose yellow color presumably indicated the formation of intermediate thiohydroxamic esters **237**) was allowed to stir under an atmosphere of argon until the yellow color dissipated (~12 hours), at which point TLC analysis revealed the disappearance of starting material and the formation of higher R_f products. A ^{1}H spectrum of the crude reaction mixture indicated the clean conversion of **235** to two new products in a 1.7:1 ratio (**238**).[25] This inseparable mixture was carried on and subjected to a hydroboration/oxidation sequence to furnish alcohols **239** and **240**. The stereochemical assignment of each of these structures was determined using NOE methods (See experimental section for NOE enhancements).

Scheme 4.3.3

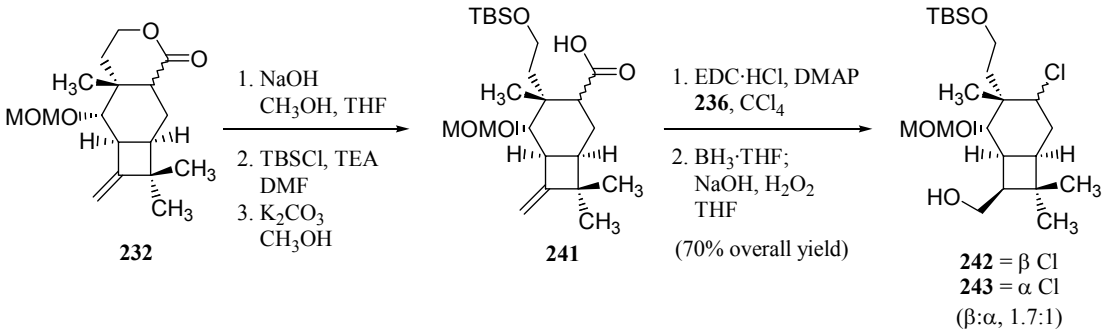


Unfortunately, the major product formed in the chlorinative decarboxylation resulted from chlorine installation on the concave face, hence containing the incorrect relative stereochemistry. This result was surprising, especially in light of previous findings (**190** → **201**) which suggested that a radical produced at C(13) would preferentially be quenched from the convex face. Thus, while the conversion of **235** → **239** and **240** proceeded with good overall efficiency, the diastereoselectivity of the chlorination was poor and favored the undesired product.

In an effort to improve the selectivity observed in the introduction of the chlorine, the silyl protecting group was altered. (Scheme 4.3.4). Following the previously described procedure, lactones **232** were efficiently converted to acids **241** in which case the primary alcohol was protected as a *t*-butyldimethylsilyl ether (TBS). Following the two-step protocol, this acid was subjected to the halogenative decarboxylation followed by a subsequent hydroboration/oxidation sequence to give rise to a mixture of alcohols

242 and **243**, epimeric at C(13). This sequence occurred with better efficiency than previously, however, the selectivity observed in the installation of the chlorine was not effected.[26,27] (See experimental section for NOE enhancements). In addition, a similar level of selectivity was also observed when the primary alcohol was protected as a triethylsilyl ether.

Scheme 4.3.4



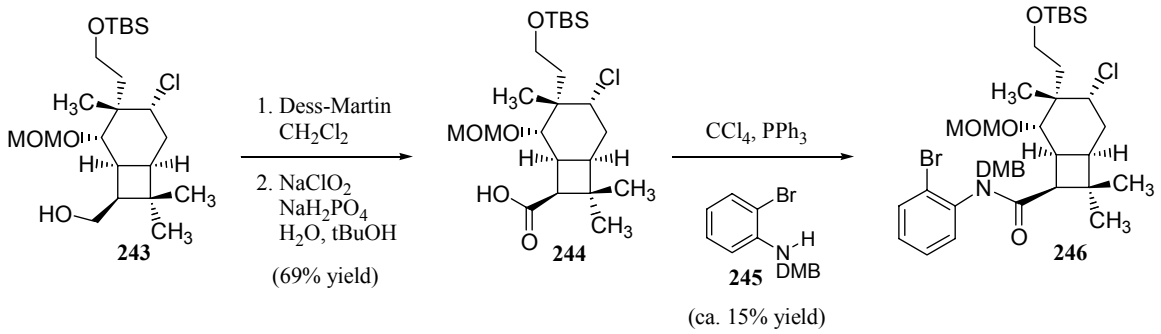
Having finally obtained a fully elaborated [4.2.0] bicyclic system, we chose to tentatively accept the poor selectivity observed in the installation of the chlorine, hoping that the crucial palladium-mediated cyclization of a fully elaborated substrate could soon be explored.

4.3.3 Attempted Elaboration of 243.

Alcohol **243**, could be converted to the analogous acid (**244**) via a two-step oxidation sequence (Scheme 4.3.5). Unexpectedly, coupling of this acid to a suitably protected *o*-bromoaniline proved to be very difficult. The best results obtained allowed for the coupling of **244** and *N*-dimethoxybenzyl-*o*-bromoaniline (**245**) in very low yield

to provide only minute quantities of anilide **246**.[28] Initial attempts to effect the cyclization of **246** were met with no success and led only to the formation of complex mixtures of products. Unable to access sizeable quantities of **246** that would allow for a thorough examination of its cyclization, another modification was sought.

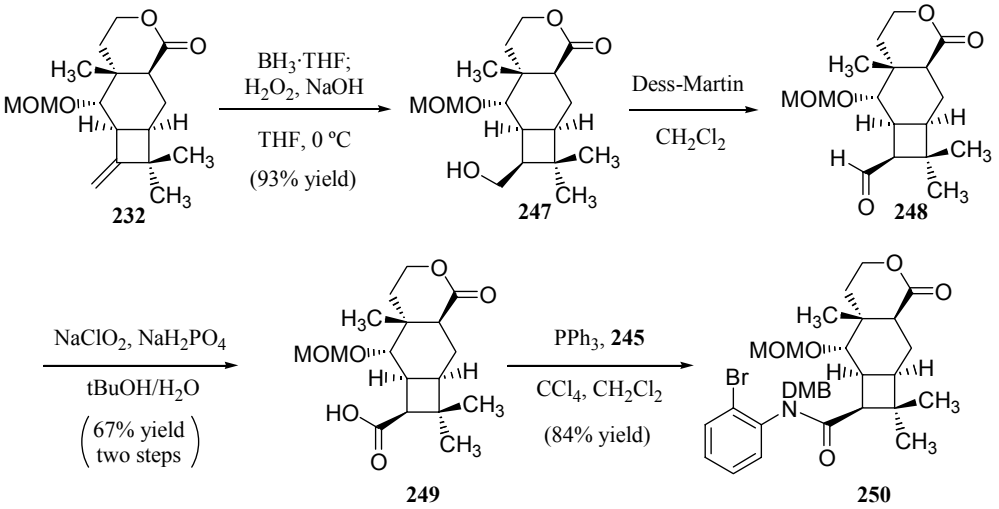
Scheme 4.3.5



4.3.4 Elaboration of Lactone 232 via an Alternative Route.

Difficulties associated with advancing **244**, along with the poor diastereoselectivity involved in the installation of the chlorine, spurred interests in advancing **232** via a slightly amended route (Scheme 4.3.6). It was eventually found that **232** could be advanced to anilide **249** in short order and good yield. Thus, hydroboration/oxidation of **232** provided primary alcohol **247**. Following a two-step oxidation, carboxylic acid **249** could be obtained. Coupling of this acid with DMP-*o*-bromoaniline (**249**) occurred with surprising efficiency to deliver anilide **250** in high yield.

Scheme 4.3.6



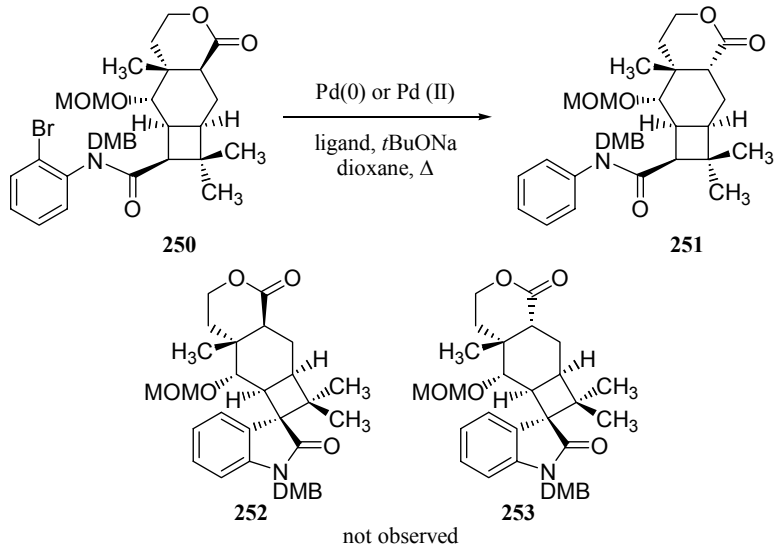
With the ability to access large quantities of anilide **249**, attention quickly shifted to an examination of conditions suitable for its cyclization to the corresponding oxindole.

4.3.5 Attempted Cyclization of 250.

Only one step away from a fully substituted carbocyclic skeleton of **7**, the cyclization of **250** was of prime interest. At the outset, it was not apparent whether or not the presence of another acidic proton would interfere with the desired cyclization. In the event, treatment of **250** with a wide array of ligands and palladium catalysts did not lead to the desired oxindole **252** or its C(13) epimer **253** (Scheme 4.3.7). The only product that could be isolated in the attempted cyclization reaction was **251**, which resulted from hydrodebromination and epimerization at C(13). The exact mechanism by which **251** is formed, as well as the source of the hydrogen leading to the formation of **251** are unclear.

The stereochemistry of **251** was confirmed following extensive NOE measurements. (See Experimental Section for NOE enhancements.)

Scheme 4.3.7



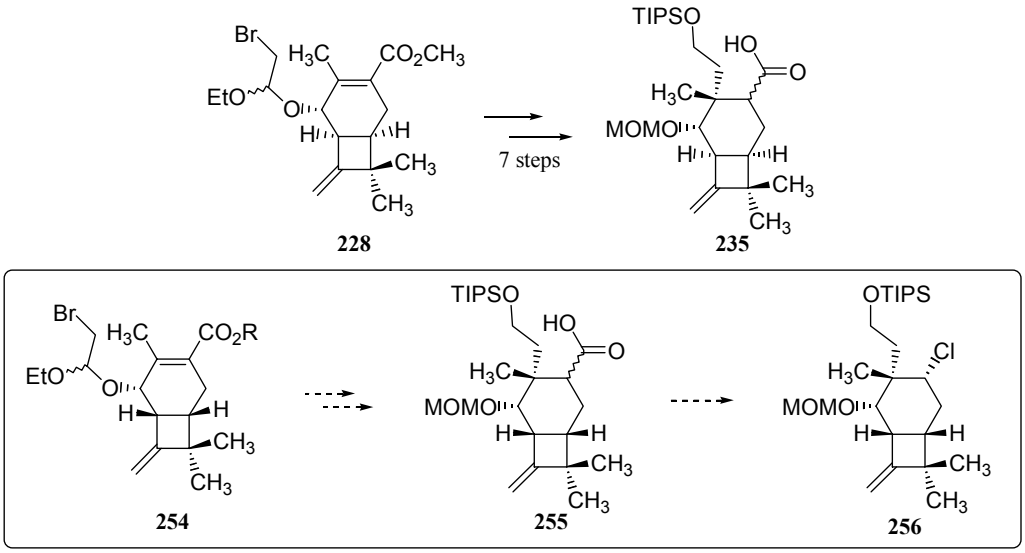
4.4 One Final Modification.

4.4.1 Initial Considerations.

The low levels of diastereoselectivity in the aforementioned Barton Chemistry and the observation that this reaction favored installation of the chlorine on the concave face of the [4.2.0] system brought with it much concern and was the impetus for one final modification (Scheme 4.4.1). It was speculated that the sequence employed in the conversion of **228** → **235** would also allow for the elaboration of **254** → **255** (Scheme 4.4.1). Based on previous findings, it was expected that the ensuing halogenative

decarboxylation would then proceed to furnish chlorine **256**, wherein the chlorine has been installed on the concave face, as the major product.

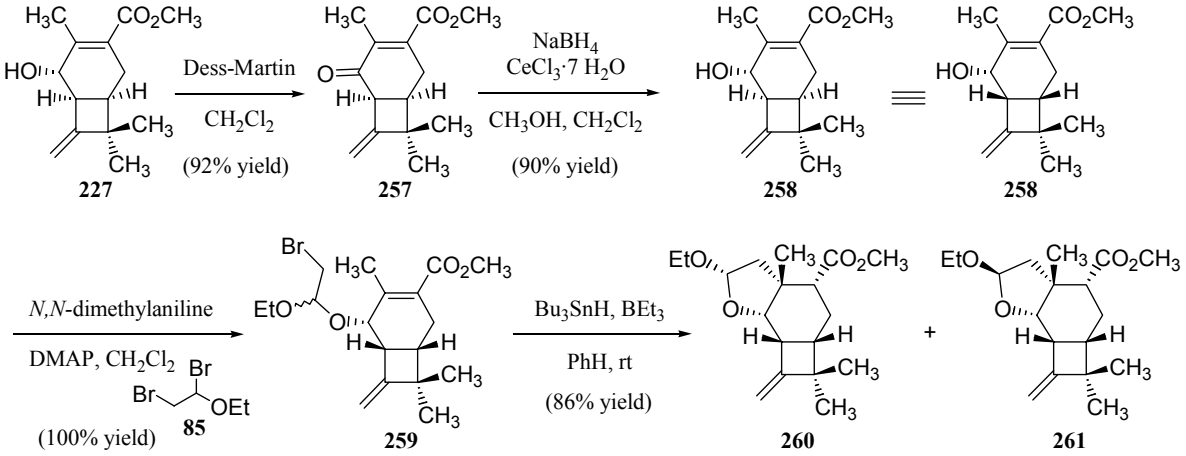
Scheme 4.4.1



4.4.2 Cyclization of a Modified Substrate.

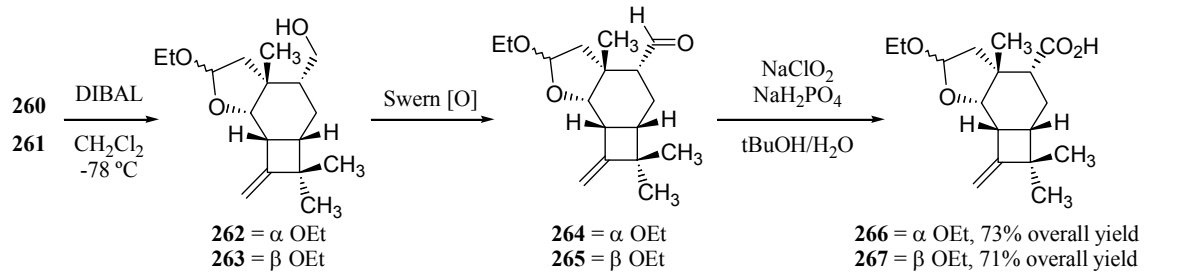
With alcohol **227** as a starting point, it was found that oxidation to the corresponding ketone (**257**) could be followed by Luche reduction to furnish alcohol **259** in good overall yield (Scheme 4.4.2). Able to effectively invert the stereochemistry of this hydroxyl group, **258** was converted to bromoacetals **259** without incident. Rewardingly, **259** cyclized in an efficient manner to give rise to a diastereomeric mixture of easily separable acetals **260** and **261**.

Scheme 4.4.2



In accord with the previous approach, both **260** and **261** proved to be impervious to saponification, leading only to recovered starting material. Borrowing from the chemistry uncovered in the previous approach, namely the ability to saponify lactones **232**, efforts focused on advancing **260** and **261** in a similar manner. This approach was quickly abandoned as suitable conditions for the hydrolysis of these acetals could not be realized. Each of the acetals was, however, individually advanced by reduction to the primary alcohol (**262**, **263**) which, following oxidation, furnished the corresponding aldehyde (**264** and **265**, Scheme 4.4.3). A subsequent oxidation then delivered acids **266** and **267**.

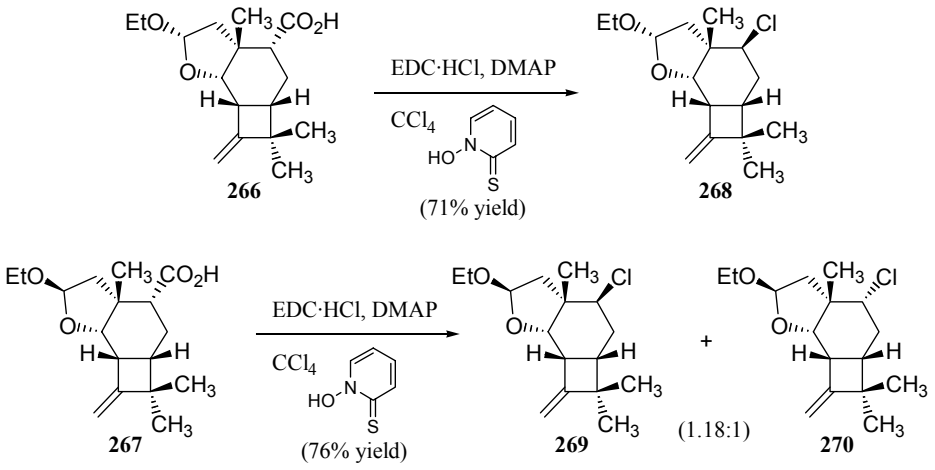
Scheme 4.4.3



4.4.3 Installation of the Chlorine.

Acids **266** and **267** were then individually subjected to the conditions previously employed for the installation of the C(13) chlorine atom (Scheme 4.4.4). Following full characterization of each of the products, including extensive NOE work, the products were identified as chlorines **268-270**. (See experimental section for NOE enhancements). In the case of **266**, only a single diastereomer (**268**) was formed and it contained the incorrect relative stereochemistry between the chlorine and the adjacent quaternary center. However, the reaction involving **267** gave rise to a nearly equimolar mixture of products arising from installation of the chlorine on the convex (**269**) and concave (**270**) faces. These results were encouraging, and spurred interests in developing a more efficient means by which **267** could be accessed.

Scheme 4.4.4

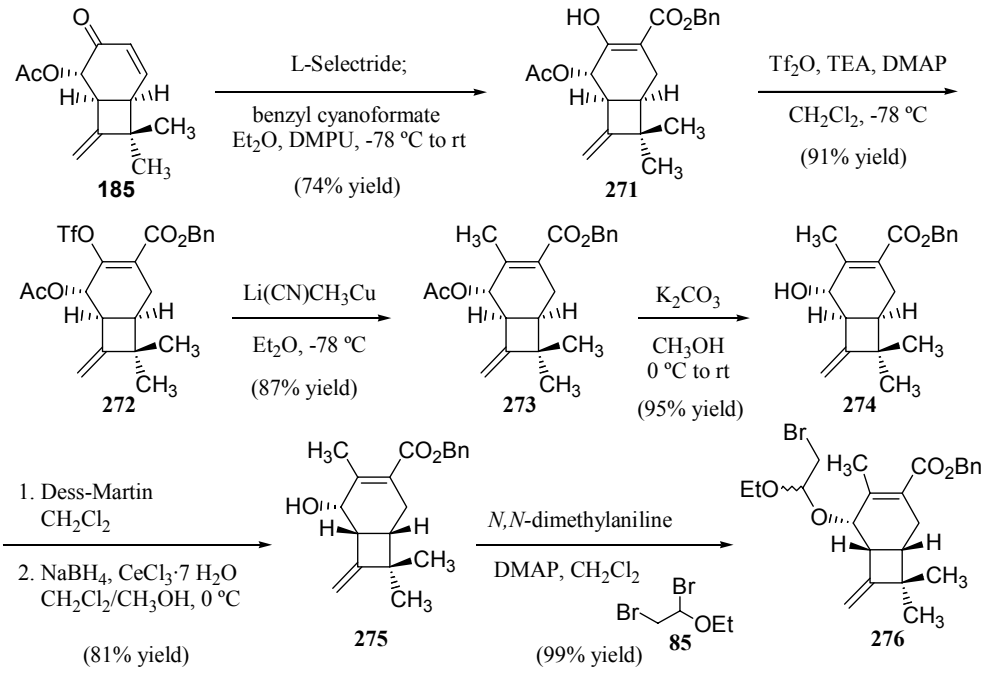


4.4.4 Revised Route to Acid 267.

4.4.4.1 Installation of a Benzyl Ester.

Realizing that the major stumbling block encountered in the preparation of **267** was the inability to hydrolyze the C(13) ester, the revised route called for the preparation of a substrate containing an ester which could be deprotected by methods other than conventional hydrolysis. With this in mind, the benzyl ester was chosen as a suitable alternative. Toward this end, ketone **185** was advanced to β-ketoester **271** by utilizing benzyl cyanoformate in the reduction/trapping sequence (Scheme 4.4.5). Relying on the previously developed chemistry, **271** could be converted to enol triflate **272**, which following the optimized conditions for the one-carbon homologation, was advanced to diene **273** in excellent yield. This compound was further elaborated to bromoacetals **276** as described previously.

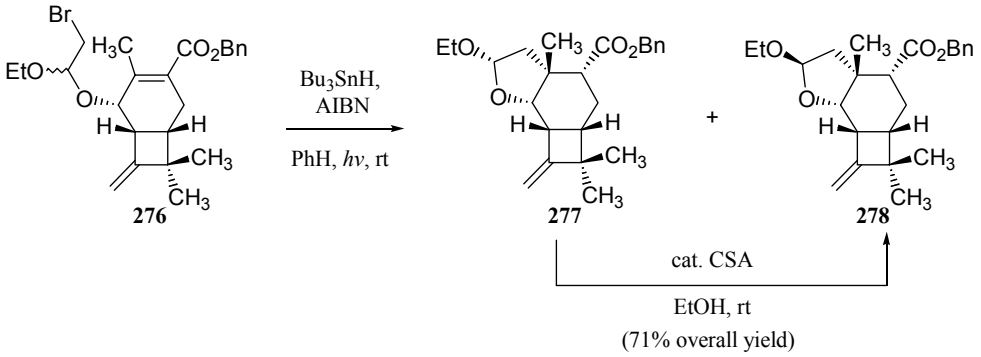
Scheme 4.4.5



4.4.4.2 Cyclization and Subsequent Elaboration of 276.

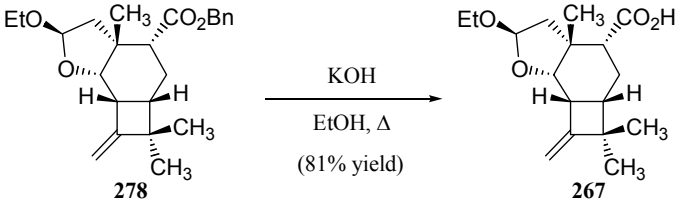
Able to access large quantities of bromoacetals **276**, efforts could now focus on its cyclization. In the event, irradiation of a solution of **276**, Bu_3SnH, and one equivalent of AIBN at room temperature led to the formation of a separable mixture of acetals **277** and **278** in superb yield (Scheme 4.4.6). Gratifyingly, the undesired diastereomer (**277**) could be equilibrated to **278** upon exposure to camphorsulphonic acid (CSA) in ethanol.

Scheme 4.4.6



Surprisingly, exposure of **278** to KOH in refluxing ethanol proceeded smoothly to provide acid **267** in high yield (Scheme 4.4.7). Thus, a three step protocol allowed for the conversion of bromoacetals **276** to a single diastereomer of **267** in good overall yield.

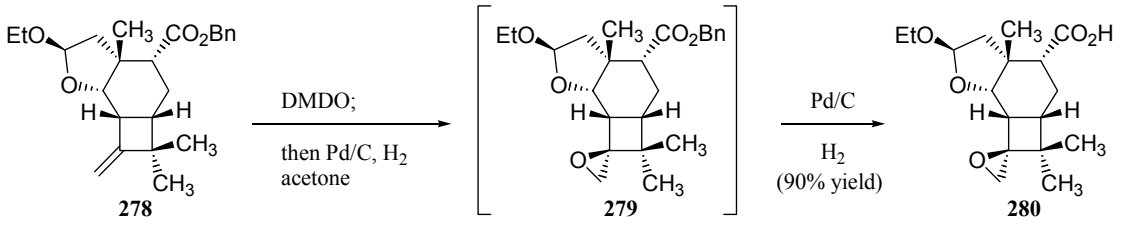
Scheme 4.4.7



4.4.4.3 Installation of the Chlorine.

With the ability to access sizeable quantities of acid **267**, efforts focused on improving the diastereoselecitivity observed in the installation of the chlorine. Unfortunately, changes in the reaction parameters (i.e., coupling reagent, concentration and temperature) had no affect on the diastereoselectivity. However, promising results were seen when subtle changes were made to the structure of **267** (Scheme 4.4.8). Particularly interesting was the reactivity of epoxy acid **280**. This compound could be accessed in excellent yield via a one-pot epoxidation/hydrogenolysis procedure. This one-pot procedure was required, as the intermediate epoxide (**279**) was surprisingly unstable, and even upon concentration underwent substantial decomposition. This problem could be avoided however, if subsequent to the formation of epoxide **279**,[29] Pd/C was directly introduced and the reaction was maintained under an atmosphere of H_2. This procedure allowed for the construction of **280** in excellent overall yield.

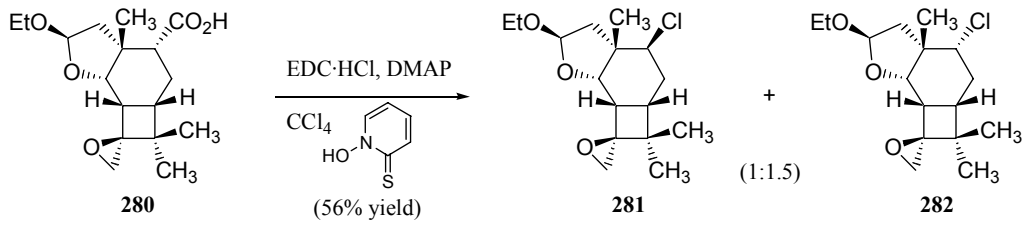
Scheme 4.4.8



Subjection of **280** to the chlorinative decarboxylation conditions furnished adducts **281** and **282** in a 1:1.5 ratio (Scheme 4.4.9). The relative stereochemistry of the major product was determined using NOE methods. (See experimental section for NOE

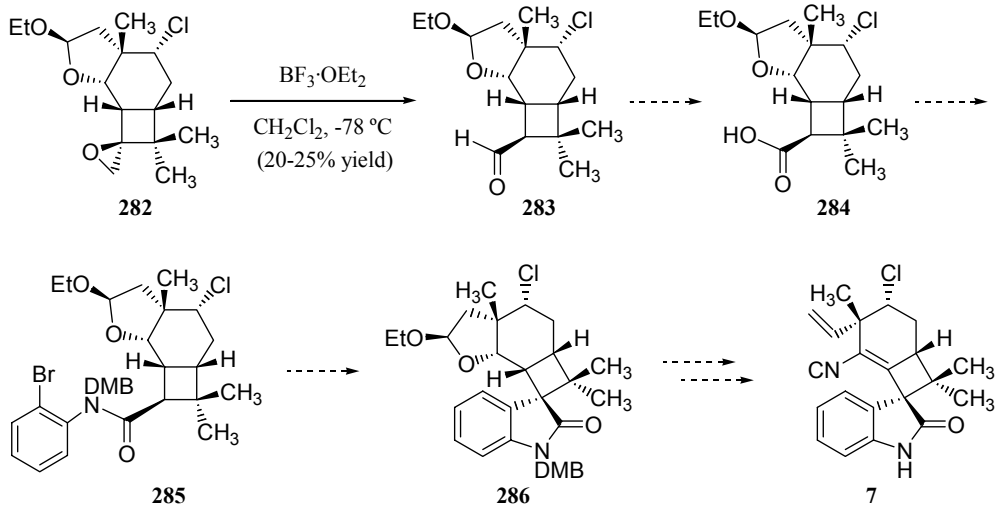
enhancements). Gratifyingly, the major product resulted from chlorine installation on the concave face and hence contained the correct relative stereochemistry.

Scheme 4.4.9



Willing to accept this rather modest selectivity, all that remained was rearrangement of the epoxide to the corresponding aldehyde (**283**, Scheme 4.4.10).[30,31] Preliminary results have demonstrated that **282** can indeed be converted to aldehyde **283**, albeit in low yield. Currently, endeavors are focused upon the elaboration of aldehyde **283** and olefin **270** to an anilide poised to undergo an intramolecular arylation. Additionally, work is being directed at the cyclization of anilide of **249**. Either of these routes are capable of yielding highly functionalized oxindoles which can in turn be advanced toward welwitindolinone A isonitrile (**7**).

Scheme 4.4.10



4.5 Conclusion.

In conclusion, based on findings presented in the previous chapters, anilides **228** and **276** were prepared in an efficient manner. In five steps, **228** could be converted to lactones **232**, which have been advanced in two directions. First, **232** could be parleyed into acids **241** which underwent a high-yield Barton chlorinative decarboxylation and subsequent hydroboration/oxidation to furnish a mixture of chlorines **242** and **243**, the latter of which constitutes a fully functionalized [4.2.0] bicyclic core. Alternatively, **232** could be advanced in four steps to anilide **250**. While initial attempts at the cyclization of **249** have proven unsuccessful, there is still a range of catalyst and ligand combinations that can be explored.

With respect to **276**, in six steps, this mixture of bromoacetals could be advanced to a mixture of chlorines **281** and **282**. Introductory work has shown that the spirocyclic epoxide **282** can indeed serve as precursor to the aldehyde (**283**), which in turn will allow for the construction of anilide **285**.

4.6 Experimental Section.

4.6.1 Materials and Methods.

Unless otherwise stated, all reactions were conducted in flame-dried glassware under a positive pressure of nitrogen using freshly distilled solvents. Tetrahydrofuran (THF), diethyl ether (Et_2O), and dioxane were distilled from sodium metal/benzophenone

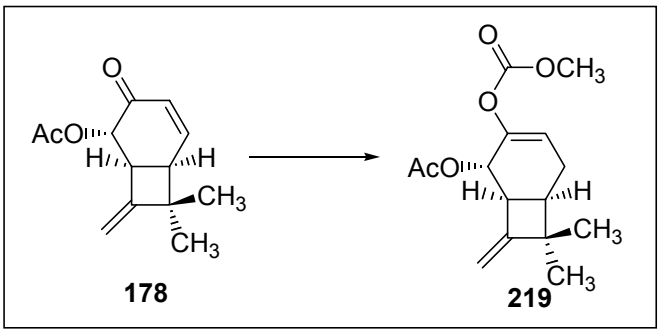
ketyl. Methylene chloride (CH_2Cl_2), benzene, pentane, pyridine, and triethylamine (TEA) were distilled from calcium hydride. Carbon tetrachloride (CCl_4), 1,2-dichloroethane, titanium tetrachloride ($TiCl_4$), dimethylformamide (DMF), and BF_3•OEt_2 were purchased from the Aldrich Chemical Co. in Sure/Seal™ containers and were used without further purification.

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). Preparative TLC was also performed using E. Merck silica gel 60 F254 pre-coated plates (0.25-mm). Column and/or flash chromatography was performed with the indicated solvents using silica gel (particle size 0.032-0.063 mm) purchased from Fisher Scientific. Chromatography was performed using the procedures reported by Still.[32]

Melting points were obtained on a Gallenkamp variable temperature melting apparatus (model: MPD350.BM2.1) and are uncorrected. Infrared spectrum (IR) were recorded on a Midac M-1200 FTIR. ^{1}H and ^{13}C spectra were recorded on a Bruker AM-500 or Bruker Advance 400 spectrometers. Chemical shifts are reported relative to chloroform (^{1}H, δ 7.27; ^{13}C, δ 77.0 ppm) or benzene (^{1}H, δ 7.16; ^{13}C, δ 128 ppm). High resolution mass spectra were performed at The University of Illinois Mass Spectrometry Center. Single-Crystal X-ray analyses were performed by Susan DeGala of Yale University.

4.6.2 Preparative Procedures:

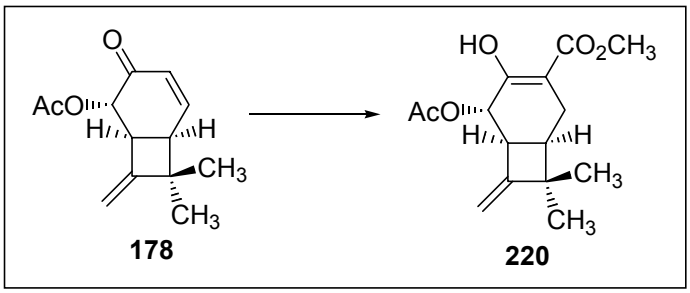
Preparation of Carbonate 219.



Carbonate 219. A suspension of ketone **178** (80 mg, 0.36 mmol, 1.0 eq.) in Et_2O was cooled to –78 °C and treated with L-selectride (1.0 M in THF, 440 μL, 1.2 eq.). After stirring at this temperature for 10 minutes, TLC analysis revealed the complete consumption of starting material, at which point methyl chloroformate (80 μL, 1.0 mmol, 2.8 eq.) was added dropwise over 1 minute and the resulting solution was allowed to slowly warm to room temperature and stir an additional 4 hours. The reaction was quenched by the addition of 1 N HCl (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed successively with saturated $NaHCO_3$ (10 mL), H_2O (10 mL), and brine. Drying over Na_2SO_4 and concentration afforded a residue that was purified by column chromatography (3-8% EtOAc/hexanes eluent) to provide enol acetate **219** (87 mg, 85% yield) as a colorless oil. FTIR (thin film/NaCl) 2955 (s), 2933 (s), 1765 (s), 1739 (s), 1259 (s), 1161 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.84 (dd, *J* = 2.3, 5.9 Hz, 1H), 5.40 (d, *J* = 1.0 Hz, 1H), 4.89 (d, *J* = 12.3 Hz, 1H), 4.85 (d, *J* = 2.9 Hz, 1H), 3.79 (s, 3H), 3.51 (dq, *J* = 2.7, 8.9 Hz, 1H), 2.50 (ddd, *J* = 2.6, 8.1, 17.3 Hz, 1H), 2.38 (t, *J* = 8.9 Hz, 1H), 2.28 (dd, *J* = 6.9, 17.4 Hz,

1H), 2.40 (s, 3H), 1.18 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 157.7, 153.6, 146.0, 119.0, 103.8, 69.0, 55.0, 43.8, 43.6, 37.0, 30.0, 21.9, 21.4, 21.1; HRMS (EI) *m/z* 280.1304 [cacl'd for $C_{15}H_{20}O_5$ (M+) 280.1311].

Preparation of β-ketoester 220.

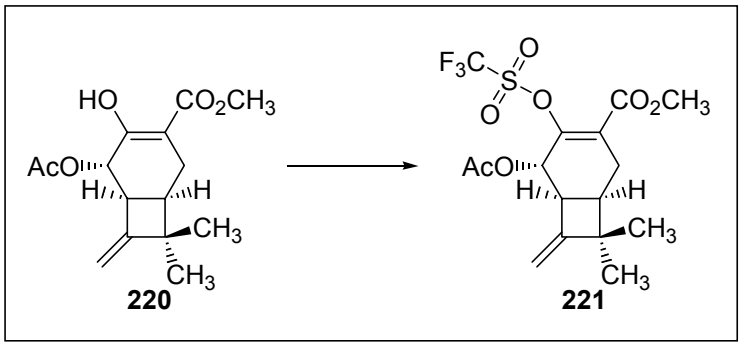


β-ketoester 220. A suspension of ketone **178** (1.45g, 6.59 mmol, 1.0 eq.) in Et_2O (50 mL) at – 78 °C was treated with L-Selectride (1.0 M in THF, 7.91 mL, 1.2 eq.), resulting in the formation of a homogeneous solution. Stirring was continued for 15 minutes before the slow addition of DMPU (50 mL) over 5 minutes. After stirring for an additional 5 minutes, methyl cyanoformate (1.50 mL, 18.90 mmol, 2.9 eq.) was added over 1 minute. The reaction was slowly allowed to warm to room temperature over 2 hours and then allowed to stir at this temperature for an additional 3 hours, at which point TLC indicated the complete consumption of starting material. The reaction mixture was cooled to 0 °C and quenched by the slow addition of 1 N HCl (10 mL). The reaction was diluted with EtOAc (300 mL) and poured into 1 N HCl (150 mL). Extraction of the aqueous layer with EtOAc (2 x 120 mL), washing with 1 N HCl (100 mL), H_2O (2 x 100 mL), brine and drying over Na_2SO_4 was followed by concentration and purification by flash chromatography (2-5% EtOAc/hexanes eluent).

β-ketoester 220: The first compound to elute was β-ketoester **220** (1.33 g, 72% yield) as a colorless solid. m.p. 68-70 °C; FTIR (thin film/NaCl) 2954 (bs), 1745 (s), 1663 (s), 1444 (m), 1216 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.90 (s, 1H), 5.36 (d, *J* = 3.7 Hz, 1H), 4.80 (dd, *J* = 1.1, 2.6 Hz, 1H), 4.77 (dd, *J* = 1.0, 2.9 Hz, 1H), 3.78 (s, 3H), 3.53 (dq, *J* = 2.8, 8.9 Hz, 1H), 2.54 (dd, *J* = 2.6, 16.0 Hz, 1H), 2.40 (dd, *J* = 7.2, 16.0 Hz, 1H), 2.28 (dt, *J* = 3.0, 7.2 Hz, 1H), 2.07 (s, 3H), 1.18 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 170.1, 167.7, 157.4, 103.7, 99.0, 70.5, 51.8, 43.9, 42.3, 37.8, 30.2, 20.9, 20.7, 19.9; HRMS (EI) *m/z* 289.1310 [cacl'd for $C_{15}H_{20}O_5$ (M+) 280.1311].

Ketone 182: The second compound to elute was ketone **182** (112 mg, 6% yield) as a colorless oil. The spectral data for **182** can be found in Chapter 3.

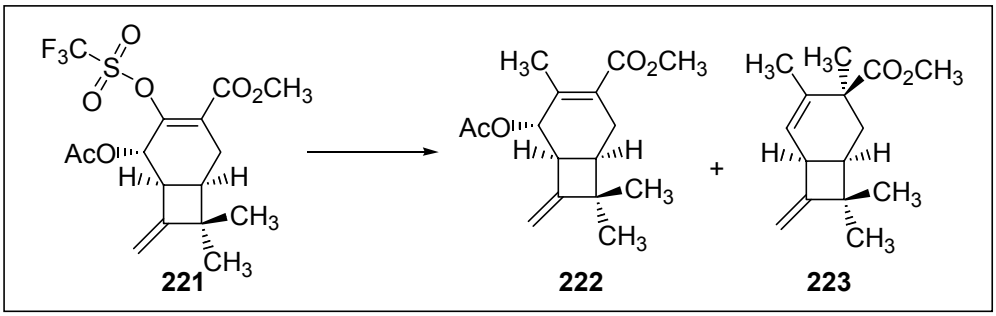
Preparation of Enol triflate 221.



Enol triflate 221. A solution of enol **220** (1.7 g, 6.12 mmol, 1.0 eq.) in CH_2Cl_2 (60 mL) at room temperature was treated with TEA (2.56 mL, 18.34 mmol, 3.0 eq.) and DMAP (75 mg, 0.61 mmol, 0.1 eq.). The resulting solution was stirred for 1 hour before it was cooled to –78 °C and triflic anhydride was added dropwise over 2 minutes. Stirring was continued for 20 minutes before the addition of saturated NH_4Cl (250 mL).

The aqueous layer was extracted with EtOAc (3 x 150 mL) and the combined organic layers were washed with 1 N HCl (100 mL), saturated $NaHCO_3$ (100 mL), H_2O (100 mL), and brine. Drying over Na_2SO_4 and concentration under reduced pressure provided an oil which was purified by flash chromatography (10% EtOAc/hexanes eluent) to furnish enol triflate **221** (2.5 g, 100% yield) as a colorless oil. FTIR (thin film/NaCl) 2957 (m), 1749 (s), 1732 (s), 1426 (s), 1217 (s), 1141 (s), 882 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.47 (d, *J* = 3.0 Hz, 1H), 4.91 (s, 1H), 4.90 (s, 1H), 3.85 (s, 3H), 3.61 (dq, *J* = 2.3, 8.5 Hz, 1H), 2.82 (dd, *J* = 1.8, 17.2 Hz, 1H), 2.70 (dd, *J* = 7.7, 17.2 Hz, 1H), 2.43 (dt, *J* = 1.9, 7.6 Hz, 1H), 2.08 (s, 3H), 1.21 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 164.4, 155.9, 147.9, 126.7, 118.2 (q, *J* = 118 ppm), 105.4, 70.3, 52.5, 44.1, 43.5, 37.0, 30.2, 24.9, 21.0, 20.7; HRMS (FAB) *m/z* 413.0881 [cacl'd for $C_{16}H_{19}F_3O_7S$ (M+) 413.0882].

Preparation of Esters 222 and 223.



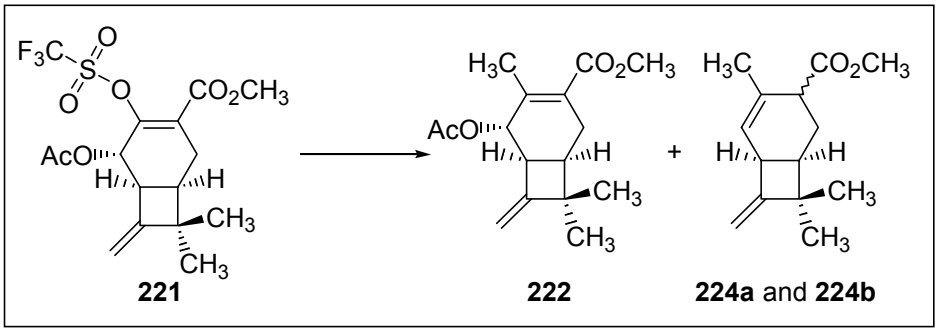
Esters 222 and 223. A solution of enol triflate **221** (17 mg, 0.041 mmol, 1.0 eq.) and $Pd(PPh_3)_4$ (20 mg, 0.017 mmol, 0.42 eq.) in THF (2.5 mL) was cooled to 0 ºC and treated with $(CH_3)_3Al$ (2.0 M in hexanes, 41 μL, 1.0 eq.). The resulting solution was allowed to stir at this temperature for 5 minutes and then the removed from the ice-bath

and stirred at ambient temperature for an additional 3 hours. The reaction was quenched by cooling to 0 ºC and the slow addition of saturated $NaHCO_3$ (10 mL). The whole was poured into H_2O (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with 1 N HCl (15 mL), H_2O (2 x 10 mL), brine, and then dried over Na_2SO_4. Purification by preparative TLC (7% EtOAc/hexanes x 5 developments) provided two products.

Ester 222 The higher Rf band provided diene **222** (4.7 mg, 41% yield) as a colorless oil. FTIR (thin film/NaCl) 2952 (s), 2930 (s), 1739 (s), 1717 (s), 1233 (s), 1217 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.30 (d, *J* = 3.9 Hz, 1H), 4.77-4.76 (m, 2H), 3.77 (s, 3H), 3.44-3.40 (m, 2H), 3.42 (dq, *J* = 2.6, 9.3 Hz, 1H), 2.30 (dt, *J* = 5.3, 9.3 Hz, 1H), 2.08 (t, *J* = 1.7 Hz, 3H), 2.06 (s, 3H), 1.19 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 168.7, 158.6, 144.1, 128.4, 103.2, 74.2, 51.5, 44.0, 41.9, 37.9, 30.4, 24.3, 21.1, 20.8, 20.7; HRMS (FAB) *m/z* 278.1516 [cacl'd for $C_{16}H_{22}O_4$ (M+) 278.1518].

Ester 223: The lower Rf band provided ester **223** (4.3 mg, 45% yield) as a colorless oil. FTIR (thin film/NaCl) 2952 (s), 2924 (s), 1731 (s), 1447 (w), 1166 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.64 (dd, *J* = 1.2, 3.8 Hz, 1H), 4.73 (d, *J* = 2.7 Hz, 1H), 4.70 (d, *J* = 2.4 Hz, 1H), 3.67 (s, 3H), 3.44-3.42 (m, 1H), 2.16-2.05 (m, 2H), 1.57 (s, 3H), 1.43 (t, *J* = 12.6 Hz, 1H), 1.33 (s, 3H) 1.26 (s, 6H), 1.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 162.6, 136.0, 124.1, 101.6, 51.9, 45.2, 44.9, 40.2, 37.9, 36.2, 29.0, 24.5, 20.6, 20.4; HRMS (FAB) *m/z* 233.1452 [cacl'd for $C_{15}H_{20}O_2$ (M+) 233.1542].

Preparation of Esters 222 and 224.

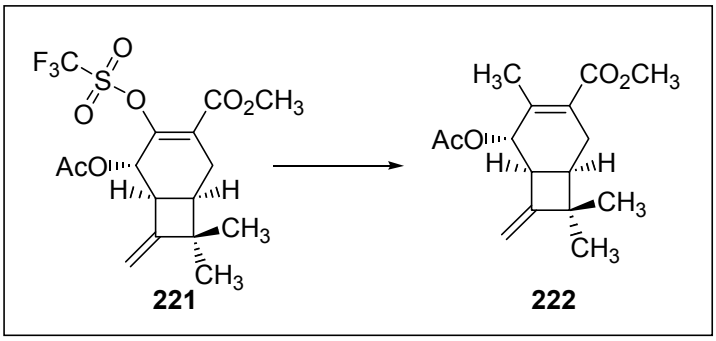


Esters 222 and 224. To a suspension of CuI (36 mg, 0.18 mmol, 2.5 eq.) in Et_2O (3 mL) at –5 °C was added CH_3Li (1.4 M in Et_2O, 270 μL, 5.0 eq.) dropwise over 1 minute. The suspension was allowed to stir at this temperature for 20 minutes, during which time it became a colorless solution. The solution of the derived cuprate was cooled to –78 °C and a solution of triflate **221** (31 mg, 0.07 mmol, 1.0 eq.) in Et_2O (2 mL) was added dropwise resulting in the immediate formation of a yellow precipitate. The reaction was maintained at –78 °C for 30 minutes and then warmed to room temperature and stirred for an additional 30 minutes before being quenched with 1 N HCl (25 mL). Extraction into EtOAc (2 x 15 mL) was followed by washing with saturated $NaHCO_3$ (10 mL), $Na_2S_2O_3$ (10 mL), H_2O (10 mL), and brine. Drying over Na_2SO_4, concentration *in vacuo* and purification by silica gel chromatography (3-4% EtOAc/hexanes) provided two compounds.

Ester 222: The first compound to elute was diene **222** (9.0 mg, 43% yield) as a colorless oil. The spectral data for **222** can be found above.

Esters 224a and 224b: The second compounds to elute were a 1:1 mixture of esters **224a** and **224b** (5.7 mg, 34% yield) as a colorless oil. FTIR (thin film/NaCl) 2953 (s), 1738 (s), 1444 (w), 1164 (m), 874 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.68 (d, *J* = 3.0 Hz, 1H), 5.61 (t, *J* = 1.0 Hz, 1H), 4.74-4.70 (m, 4H), 3.71 (s, 3H), 3.69 (s, 3H), 3.49-3.44 (m, 2H), 2.98-2.95 (m, 2H), 2.21-2.17 (m, 1H), 2.10 (ddd, *J* = 3.0, 6.5, 13.0 Hz, 1H), 2.05-2.01 (m, 1H), 1.94 (ddd, *J* = 3.5, 7.0, 12.5 Hz, 1H), 1.81 (s, 3H), 1.77 (q, *J* = 12.5 Hz, 1H), 1.68 (s, 3H), 1.64 (dt, *J* = 5.0, 12.5 Hz, 1H), 1.57 (s, 6H), 1.03 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 174.1, 162.4, 162.1, 132.0, 131.9, 123.6, 123.0, 101.9, 101.5, 51.7, 51.5, 45.2, 45.1, 44.5, 44.4, 40.2, 39.9, 39.2, 36.5, 29.1, 28.9, 27.6, 26.0, 23.7, 23.6, 20.9, 20.5; HRMS (EI) *m/z* 220.1463[cacl'd for $C_{14}H_{20}O_2$ (M+) 220.1463].

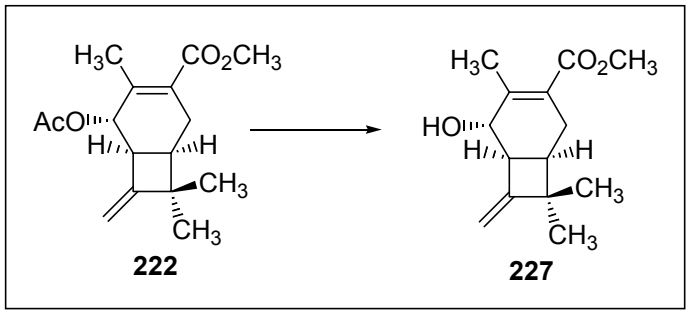
Preparation of Diene 222.



Diene 222. A suspension of CuCN (1.13 g, 12.58 mmol, 3.05 eq.) in Et_2O (50 mL) was cooled to –25 °C at which time CH_3Li (1.0 M in Et_2O , 12.4 mL, 3.0 eq.) was added dropwise over a period of 3 minutes to give rise to a colorless solution. After stirring for 20 minutes, the solution was cooled to –78 °C and a solution of enol triflate

221 (1.7 g, 4.13 mmol, 1.0 eq.) in Et_2O (20 mL) was added dropwise. The yellow suspension that resulted was stirred for 20 minutes before being quenched by the addition of saturated NH_4Cl (350 mL). Extraction with EtOAc (2 x 150 mL) and washing of the combined organic layers with 1 N HCl (100 mL), saturated $NaHCO_3$ (100 mL) and brine was followed by drying over Na_2SO_4 and concentration *in vacuo*. The organic concentrate was absorbed onto silica gel and purified by column chromatography (10% EtOAc/hexanes eluent) to afford unsaturated ester **222** (1.08 g, 95% yield) as a colorless oil. The spectral data for **222** can be found above.

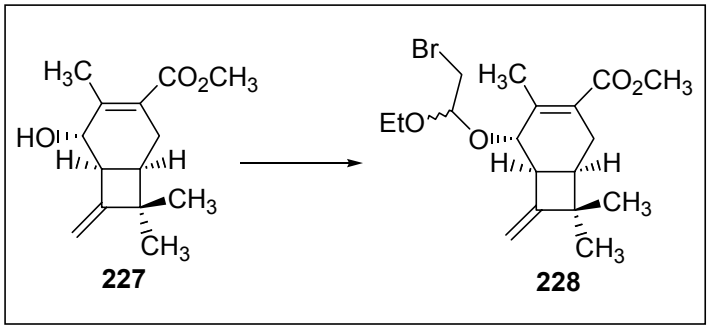
Preparation of Allylic alcohol 227.



Allylic alcohol 227. A mixture of acetate **222** (1.35 g, 4.86 mmol, 1.0 eq.) and K_2CO_3 (1.01 g, 7.28 mmol, 1.5, eq.) in CH_3OH (50 mL) was stirred at room temperature for 3 hours before the reaction was diluted with saturated NH_4Cl (250 mL) and the organics were removed *in vacuo*. Extraction of the aqueous layer with EtOAc (3 x 100 mL), washing with brine, drying over Na_2SO_4, and concentration provided an oil that was subjected to column chromatography (25–30% EtOAc/hexanes eluent) to furnish alcohol **227** (1.01 g, 88% yield) as a colorless oil. FTIR (thin film/NaCl) 3412 (bs), 2951 (s), 1713 (s), 1216 (s), 1065 (m), 880 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.72-4.71 (m, 2H), 4.15 (d, J = 4.0 Hz, 1H), 3.73 (s, 3H), 3.31-3.27 (m, 1H), 2.54-2.49 (m, 1H), 2.40

(dd, J = 3.3, 16.5 Hz, 1H), 2.28 (ddd, J = 3.8, 7.1, 11.3 Hz, 1H), 2.11 (s, 3H), 1.95 (bs, 1H), 1.18 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 160.1, 148.2, 126.0, 102.4, 73.4, 51.4, 44.5, 43.6, 38.4, 30.4, 23.9, 20.9, 20.0; HRMS (FAB) 237.1490 [cacl'd for $C_{14}H_{20}O_3$ (M+) 237.1491].

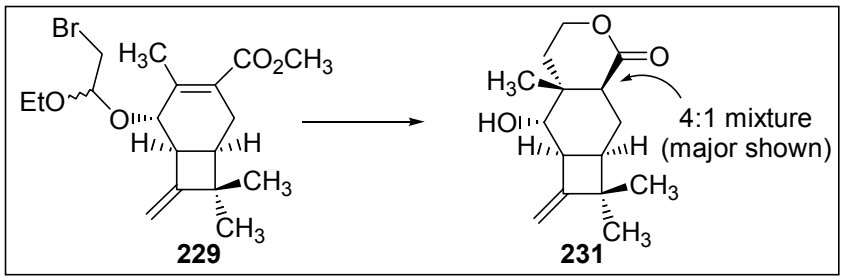
Preparation of Bromoacetals 228.



Bromoacetals 228. To a solution of alcohol **227** (1.87 g, 7.92 mmol, 1.0 eq.) in CH_2Cl_2 (160 mL) at 0 °C was added *N,N*-dimethylaniline (6.02 mL, 47.4 mmol, 6.0 eq.) followed by a solution of bromide **85** (5.13 g, 23.7 mmol, 3.0 eq.) in CH_2Cl_2 (30 mL). The resulting yellow solution was allowed to slowly warm to rt and stir overnight, at which time the reaction had turned a deep green color. The reaction was poured into a cold solution of 1N HCl (300 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with saturated $NaHCO_3$ (100 mL), H_2O (100 mL), brine and then dried over Na_2SO_4. Concentration and purification by silica gel chromatography (1-2.5% EtOAc/hexanes eluent) provided bromoacetals **228** (2.90 g, 94% yield) as a colorless oil. FTIR (thin film/NaCl) 2976 (m), 2975 (s), 2950 (s), 2929 (s), 1714 (s), 1670 (s), 1434 (s), 1361 (m), 1321 (w), 1254 (s), 1217 (s), 1112 (s), 1066 (s), 1021 (s), 880 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.80 (t, J = 5.5 Hz, 1H), 4.72-

4.69 (m, 3H), 4.63 (app. dd, J = 1.9, 4.4 Hz, 2H), 4.18 (d, J = 3.5 Hz, 1H), 4.09 (d, J = 3.4 Hz, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3.67-3.51 (m, 6H), 3.40-3.29 (m, 4H), 2.60-2.46 (m, 4H), 2.34-2.30 (m, 2H), 2.12 (bs, 6H), 1.25 (t, J = 6.7 Hz, 3H), 1.21 (t, J = 6.8 Hz, 3H), 1.19 (s, 3H), 1.18 (s, 3H), 0.92 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 168.7, 159.5, 159.2, 145.7, 145.6, 128.0, 127.4, 102.3, 102.2, 100.4, 100.2, 78.1, 77.6, 61.2, 60.7, 51.4, 51.3, 44.0, 43.9, 42.8, 41.5, 38.3, 38.2, 31.9, 31.8, 30.6, 30.5, 24.3, 24.2, 22.8, 21.8, 20.8, 20.7, 15.2, 15.1; HRMS (FAB) *m/z* 355.0916 [calc'd for $C_{17}H_{24}BrO_3$ (M-CH_3OH) 355.0909].

Preparation of Lactone 231.

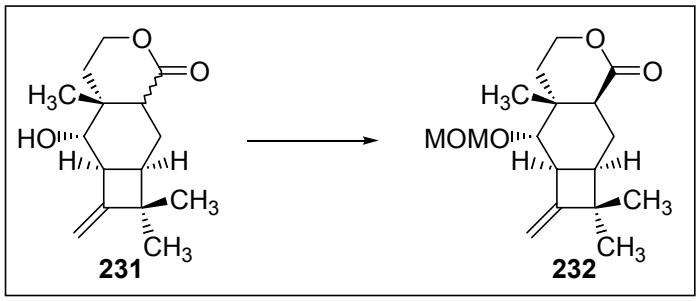


Lactone 231. A solution of bromoacetals **229** (513 mg, 1.33 mmol, 1.0 eq.) in benzene (60 mL) was degassed by purging the solution with argon for 15 minutes. This solution was then brought to reflux, at which time a degassed solution of AIBN (26 mg, 0.158 mmol, 0.12 eq.) and Bu_3SnH (465 μL, 1.73 mmol, 1.3 eq.) in benzene (8 mL) was added over 3 hours via syringe pump. Upon completion, the resulting solution was allowed to cool to room temperature and was diluted with Et_2O (65 mL). DBU (340 μL, 2.27 mmol, 1.70 eq.) was added to this solution, which resulted in the immediate formation of a white precipitate. Stirring was continued for 7 minutes before the whole was filtered through a small plug of silica gel (10 g) to remove the tin precipitate. The

plug of silica gel was rinsed with Et_2O (100 mL) and the resulting filtrate was concentrated and subjected to silica gel chromatography (2-3% EtOAc/hexanes eluent) to provide a colorless oil (378 mg, 93% yield) consisting of 4 diastereomeric adducts resulting from 5-exo cyclization. A solution of the derived adducts (476 mg, 1.55 mmol, 1.0 eq.) in undistilled THF (18 mL) was treated with aqueous HCl (3.7%, 18 mL). The mixture was vigorously stirred for 24 hours, at which point TLC indicated the complete consumption of starting material. The THF was then removed *in vacuo*, and the aqueous layer was diluted with H_2O (50 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with H_2O (2 x 25 mL) and then brine, dried over Na_2SO_4, and concentrated to provide a colorless oil that was carried on without further purification. The derived oil was dissolved in CH_3OH (20 mL) and cooled to 0 ºC. To this solution was then added $NaBH_4$ (1.76 g, 46.4 mmol, 30 eq.) in approximately 100 mg batches over 30 minutes. Upon completion, the reaction was quenched at 0 ºC with cold 1 N HCl (150 mL). Extraction with EtOAc (3 x 70 mL) was followed by washing of the combined organic layers with H_2O (2 x 100 mL) and brine. The solution was then dried over Na_2SO_4 and concentrated to an oil which was carried on to the next step crude. A solution of the crude diol and *p*PTS (59 mg, 0.23 mmol, 0.15 eq.) in benzene (10 mL) was allowed to reflux overnight before being cooled to room temperature and poured in H_2O (100 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organic layers were washed with H_2O (25 mL) and brine. Drying over Na_2SO_4 and concentration was followed by flash chromatography to provide a 4:1 mixture of lactones **231**, epimeric at C(13), (292 mg, 70% yield over four steps) as a colorless oil. The ^1H spectral data reported is for the major epimer. FTIR (thin film/NaCl) 3458 (b),

2954 (s), 2922 (s), 1725 (s), 1453 (w), 1395 (m), 1267 (m), 1201 (m), 1137 (w), 1030 (m), 875 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.71 (d, *J* = 3.2 Hz, 1H), 4.65 (d, *J* = 2.9 Hz, 1H), 4.28-4.19 (m, 2H), 3.73 (d, *J* = 1.2 Hz, 1H), 3.21 (d, *J* = 9.0 Hz, 1H), 2.89 (bs, 1H), 2.70 (dd, *J* = 2.9, 12.6 Hz, 1H), 2.34 (dt, *J* = 4.4, 14.5 Hz, 1H), 2.19 (q, *J* = 9.2 Hz, 1H), 1.98 (dt, *J* = 3.0 12.3 Hz, 1H), 1.64-1.54 (m, 1H), 1.44 (p, *J* = 7.3 Hz, 1H), 1.18 (s, 3H), 1.02 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 174.4, 161.2, 161.1, 103.6, 102.1, 77.4, 72.2, 66.3, 65.1, 46.2, 45.3, 44.5, 44.4, 41.3, 38,,8, 38.5, 38.4, 37.7, 36.1, 34.7, 29.5, 29.4, 29.1, 26.8, 22.9, 22.4, 21.0, 19.9, 19.7; HRMS (EI) *m/z* 250.1567 [calc'd for $C_{15}H_{22}O_3$(M+) 250.1569].

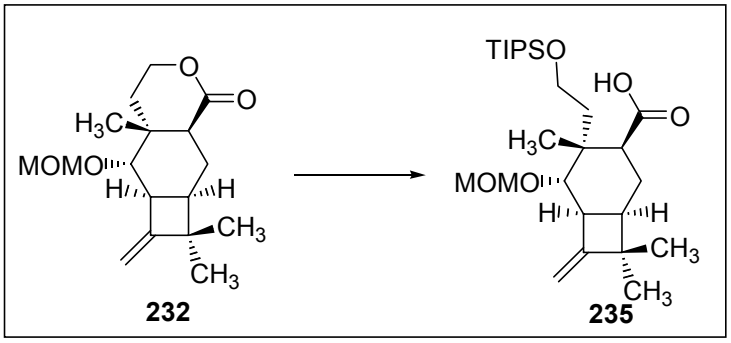
Preparation of Ether 232.



Ether 232. A solution of alcohols **231** (290 mg, 1.16 mmol, 1.0 eq.) in CH_2Cl_2 (13 mL) cooled to 0º C was treated sequentially with $^{i}Pr_2NEt$ (1.62 mL, 9.30 mmol, 8.0 eq.) and MOMCl (440 μL, 5.79 mmol, 5.0 eq.). The solution was allowed to slowly warm to ambient temperature and stir overnight, at which time TLC indicated remaining starting material. Additional $^{i}Pr_2NEt$ (1.62 mL, 9.30 mmol, 8.0 eq.) then MOMCl (440 μL, 5.79 mmol, 5.0 eq.) were introduced and the whole was allowed to stir for an additional 24 hours. The solution was then concentrated to provide a yellow solid that

was recrystallized from EtOAc/hexanes to furnish a single diastereomer of lactone **232** (183 mg, 54% yield) as a colorless solid. The mother liquor was concentrated and subjected to silica gel chromatography (20-30% EtOAC/hexanes eluent) to provide a 1:1 mixture of diastereomeric lactones (95 mg, 28% yield, combined 82% yield). The spectral data reported is for a single diastereomer recrystallized from hexanes/EtOAc to afford colorless crystals. m.p. 110-111 °C; FTIR (thin film/NaCl) 2942 (s), 2924 (s), 1740 (s), 1389 (w), 1055 (m), 1036 (s), 919 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.78 (d, *J* = 3.2 Hz, 1H), 4.74 (d, *J* = 6.9 Hz, 1H), 4.71 (d, *J* = 2.7 Hz, 1H), 4.59 (d, *J* = 6.9 Hz, 1H), 4.29 (dd, *J* = 4.8, 6.9 Hz, 2H), 3.61 (s, 1H), 3.39 (s, 3H), 3.30 (d, *J* = 9.0 Hz, 1H), 2.67 (dd, *J* = 3.1, 13.1 Hz, 1H), 2.32 (dt, *J* = 4.6, 14.2 Hz, 1H), 2.22 (q, *J* = 9.3 Hz, 1H), 2.13-2.06 (m, 1H), 1.68 (q, *J* = 12.9 Hz, 1H), 1.43 (p, *J* = 7.1 Hz, 1H), 1.26 (s, 3H), 1.09 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 161.5, 102.3, 95.8, 79.0, 66.1, 56.1, 44.7, 41.5, 39.4, 39.1, 37.6, 35.2, 29.7, 23.1, 21.2, 19.6; HRMS (EI) *m/z* 294.1826 [cacl'd for $C_{17}H_{26}O_4$ (M+) 294.1831].

Preparation of Lactones 235.

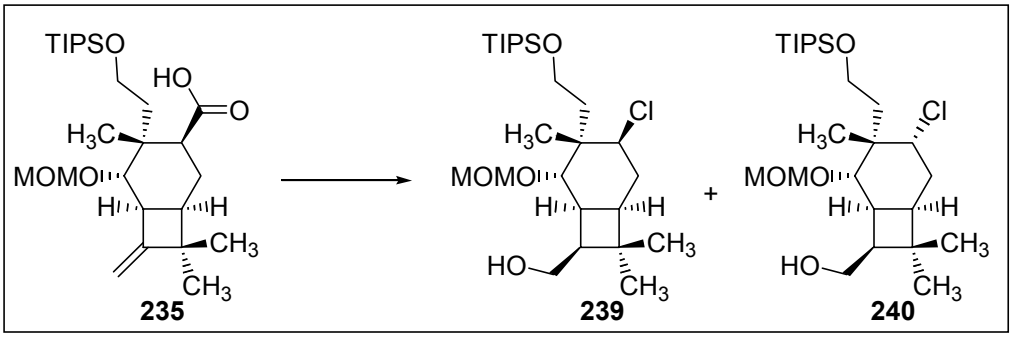


Lactones 235. A solution of lactone **232** (120 mg, 0.408 mmol, 1.0 eq.) in a 1:1 mixture of THF:CH_3OH (3.5 mL) was treated with aqueous NaOH (1 N, 420 μL, 1.03

eq.). The solution was allowed to stir for 12 hours at which point the mixture was concentrated *in vacuo* to provide an off-white solid that was azeotroped with toluene (2 x 5 mL) then benzene (3 x 5 mL) and dried under high vacuum for 2 hours. The resulting solid was dissolved in DMF (5.0 mL), cooled to 0 ºC and treated sequentially with TEA (570 μL, 4.12 mmol, 10 eq.) and TIPSCl (440 μL, 2.06 mmol, 5.0 eq.). The solution was allowed to slowly warm to room temperature and stir at that temperature overnight. The reaction was quenched upon the addition of 0.5 N HCl (25 mL). The aqueous layer was extracted with EtOAc (3 x 25 mL) and washed with H_2O (3 x 100 mL) and brine. Drying of the solution over Na_2SO_4 was followed by concentration to provide a colorless oil. This oil was dissolved in a 3:1 mixture of THF:CH_3OH (4.5 mL) and treated with K_2CO_3 (132 mg, 0.95 mmol, 2.3 eq.). The resulting mixture was allowed to stir for 3 hours. Upon completion the reaction was poured into 1N HCl (20 mL) and extracted with EtOAc (3 x 25 mL). The organic layers were washed with H_2O (3 x 20 mL) and brine and dried over Na_2SO_4. Concentration and purification of the resulting oil by flash chromatography (6-25% EtOAc/hexanes eluent) provided acid **235** (161 mg, 84% yield) as a colorless oil. FTIR (thin film/NaCl) 2944 (bs), 2886 (s), 1730 (s), 1463 (s), 1382 (w), 1218 (w), 1146 (m), 1099 (s), 1042 (s), 883 (m), 682 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.98 (d, *J* = 2.1 Hz, 1H), 4.82 (d, *J* = 2.8 Hz, 1H), 4.77 (d, *J* = 6.7 Hz, 1H), 4.64 (d, *J* = 7.1 Hz, 1H), 3.87 (app t, *J* = 6.8 Hz, 2H), 3.63 (d, *J* = 7.2 Hz, 1H), 3.37 (s, 3H), 3.15-3.11 (m, 1H), 2.77 (dd, *J* = 4.8, 13.0 Hz, 1H), 2.15-2.10 (m, 1H), 1.99 (p, *J* = 6.7 Hz, 1H), 1.83 (q, *J* = 13.2 Hz, 1H), 1.67-1.57 (m, 2H), 1.23 (s, 3H), 1.12-1.02 (m, 27 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1, 161.2, 103.7, 81.9, 60.2, 55.7, 47.9, 45.0, 43.3,

40.1, 39.5, 38.2, 29.2, 23.3, 21.0, 20.5, 18.0, 11.9, 11.8; HRMS (FAB) *m/z* 469.3350 [cacl'd for $C_{26}H_{49}O_5Si$ (M+H) 469.3349].

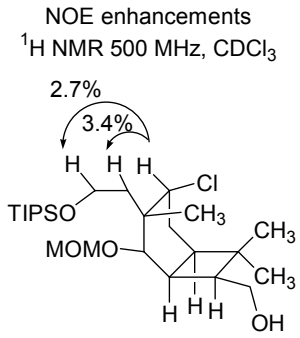
Preparation of Chlorines 239 and 240.



Chlorines 239 and 240. A solution of acid **235** (155 mg, 0.331 mmol, 1.0 eq.), DMAP (12 mg, 0.098 mmol, 0.3 eq.), and 2-mercapto-pyridine-*N*-oxide (**236**) (55 mg, 0.432 mmol, 1.3 eq.) in CCl_4 (7.5 mL) was purged with argon for 45 minutes. This solution was added via cannula to a degassed suspension of EDC•HCl (127 mg, 0.662 mmol, 1.2 eq.) in CCl_4 (2.5 mL). The resulting suspension, which immediately turned bright yellow, was allowed to stir at 50 ºC overnight, at which point a colorless reaction mixture remained. The solvent was removed and the resulting residue was purified by silica gel chromatography (2.5-8% EtOAc/hexanes eluent) to provide an inseparable 1.8:1 mixture of adducts (101 mg, 67 % yield) as a colorless oil. The derived oil was dissolved in THF (2.2 mL) and cooled to 0 ºC before BH_3•THF (1.0 M in THF, 250 μL, 1.15 eq.) was added dropwise over 5 minutes. Stirring was continued at this temperature for 2 hours before the reaction was diluted with THF (10 mL) and treated simultaneously with 2N NaOH (300 μL) and 30% H_2O_2 (300 μL). After stirring for 30 minutes the reaction was poured into 0.5 N HCl (25 mL) and extracted with EtOAc (3 x 25 mL). The

combined organic layers were washed with 2% $Na_2S_2O_3$ (50 mL), H_2O (25 mL), and brine before being dried over Na_2SO_4. The resulting residue was subjected to silica gel chromatography (5-25% EtOAc/hexanes eluent).

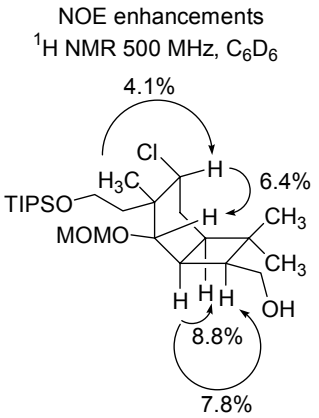
Chlorine 239: The first compound to elute was alcohol **239** (32.1 mg, 31% yield) as a colorless oil. FTIR (thin film/NaCl) 3445 (bs), 2943 (bs), 2866 (s), 1463 (s), 1383 (w), 1366 (w), 1145 (m), 1100 (w), 1043 (s), 882 (m), 682 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.73 (d, *J* = 6.8 Hz, 1H), 4.70 (d, *J* = 6.6 Hz, 1H), 4.50 (t, *J* = 7.0 Hz, 1H), 3.99 (dt, *J* = 2.0, 12.0 Hz, 1H), 3.90 (d, *J* = 9.2 Hz, 1H), 3.86-3.81 (m, 2H), 3.66-3.61 (m, 1H), 3.40 (s, 3H), 3.33 (dd, *J* = 2.9, 9.6 Hz, 1H), 2.64 (q, *J* = 9.2 Hz, 1H), 2.37 (dq, *J* = 4.4, 9.0 Hz, 1H), 2.32 (q, *J* = 8.8 Hz, 1H), 2.21-2.15 (m, 1H), 1.92-1.88 (m, 2H), 1.66 (bs, 1H), 1.58-1.53 (m, 1H), 1.21 (s, 3H), 1.19 (s, 3H), 1.07 (s, 17H), 1.06 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 97.2, 80.1, 66.1, 60.5, 60.2, 55.6, 48.3, 42.4, 40.2, 37.0, 36.2, 35.1, 32.9, 30.3, 22.7, 19.2, 18.0, 11.9; HRMS (FAB) *m/z* 477.3167 [cacl'd for $C_{25}H_{50}O_4Si$ (M+H) 477.3167].



239

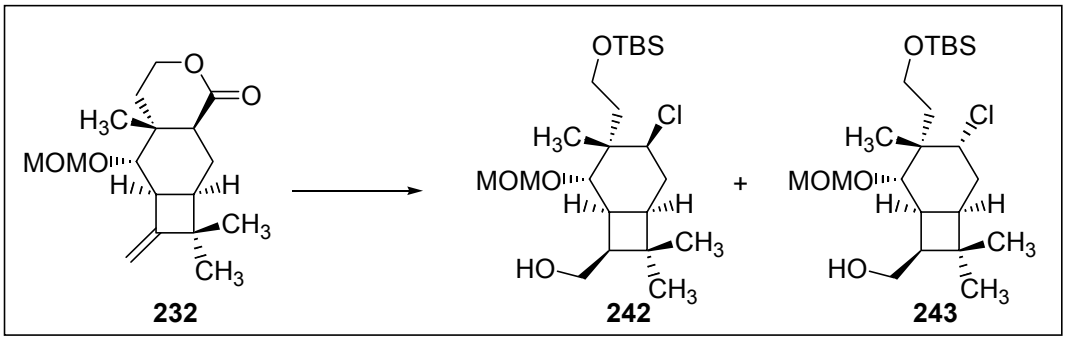
Chlorine 240: The second compound to elute was alcohol **240** (33.2 mg, 32% yield) as a colorless oil. FTIR (thin film/NaCl) 3444 (b), 2943 (b), 2865 (s), 1464 (s), 1146 (w),

1095 (m), 1042 (s), 882 (w), 680 (w) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 4.37 (d, *J* = 6.5 Hz, 1H), 4.31 (d, *J* = 6.8 Hz, 1H), 4.17 (ddd, *J* = 5.3, 9.8, 15.2 Hz, 1H), 4.06 (ddd, *J* = 5.4, 10.5, 16.3 Hz, 1H), 3.79-3.75 (m, 1H), 3.61 (dd, *J* = 9.2, 11.9 Hz, 1H), 3.48 (dd, *J* = 5.3, 11.8 Hz, 1H), 3.31 (d, *J* = 9.6 Hz, 1H), 3.06 (s, 3H), 2.58 (bs, 1H), 2.44 (q, *J* = 9.6 Hz, 1H), 2.24 (dt, *J* = 5.4, 8.9 Hz, 1H), 2.04-1.88 (m, 3H), 1.79-1.75 (m, 2H), 1.20 (s, 3H), 1.19 (s, 18H), 1.16 (s, 3H), 0.78 (s, 3H), 0.63 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 98.8, 86.8, 68.1, 60.4, 58.9, 56.0, 47.4, 43.6, 39.9, 39.0, 37.5, 31.7, 31.6, 29.3, 22.7, 19.2, 18.0, 12.0; HRMS (FAB) *m/z* 477.3167 [cacl'd for $C_{25}H_{50}O_4Si$ (M+H) 477.3167].



240

Preparation of Alcohols 242 and 243.



Alcohols 242 and 243. A solution of lactone **232** (300 mg, 1.02 mmol, 1.0 eq.) was dissolved in CH_3OH (3.0 mL) and THF (3.0 mL). To this solution was added 1 N

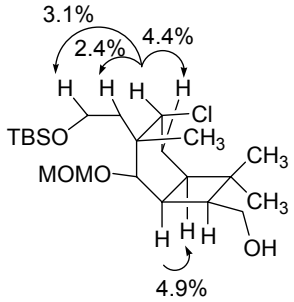
NaOH (1.09 mL). The resulting solution was allowed to stir at room temperature for 6 hours before being concentrated *in vacuo*. The solid that was thus obtained was azeotropped with toluene (2 x 5 mL) and benzene (2 x 5 mL) before being dried under high vacuum for 1.5 hours. The derived solid in DMF (10 mL) was treated with TEA (1.42 mL, 20.20 mmol, 10.0 eq.) and TBSCl (769 mg, 5.10 mmol, 5.0 eq.). The solution was allowed to stir at room temperature overnight, at which point it was poured into 0.5 N HCl (50 mL). Extraction with EtOAc (3 x 25 mL) was followed by washing of the combined organic layers with H_2O (3 x 100 mL) and brine. Drying over Na_2SO_4 and concentration provided the intermediate silyl ester as a colorless oil. A solution of this ester in CH_3OH (5.0 mL) and THF (5.0 mL) was treated with K_2CO_3 (240 mg, 1.74 mmol, 1.7 eq.) and allowed to stir at room temperature for 1 hour. The reaction was then poured into 1 N HCl (25 mL) and extracted with EtOAc (3 x 25 mL). The organic layers were combined, washed with brine, and dried over Na_2SO_4. Concentration provided acids **241** (416 mg, 96% yield) as a colorless oil that was used without further purification. A solution of **241** (416 mg, 0.977 mmol, 1.0 eq.), DMAP (35.8 mg, 0.029 mmol, 0.3 eq.), and 2-mercapto-pyridine-*N*-oxide (**236**) (162 mg, 1.27 mmol, 1.3 eq.) in CCl_4 (20 mL) was purged with argon for 20 minutes. In a separate flask, a suspension of EDC•HCl (375 mg, 1.96 mmol, 2.0 eq.) in CCl_4 (8 mL) was also purged with argon for 20 minutes. The solution containing the acid was transferred via cannula to the suspension of EDC•HCl. Upon complete addition (~ 5 minutes), the reaction mixture turned bright yellow, indicating the formation of the intermediate thiohydroxamic ester. The reaction was allowed to stir at room temperature under an atmosphere of argon for 20 hours. The reaction mixture, which was still yellow in color, was heated to 40 ºC for 2

hours, resulting in the formation of a colorless solution containing a large amount of a white precipitate, indicating completion of the reaction. The reaction was poured into 0.3 N HCl (25 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with H_2O (25 mL) and brine and dried over Na_2SO_4. Concentration and purification by silica gel chromatography (2-5% EtOAc/hexanes eluent) provided the intermediate chlorines (298 mg, 73% yield) as an inseparable mixture. ^{1}H NMR of the crude reaction mixture indicated a 1.7:1 mixture of adducts. A solution of the derived chlorine adducts (298 mg, 0.715 mmol) in THF (4.0 mL) was cooled to 0 ºC and treated with BH_3•DMS (1.0 M in THF, 720 μL, 1.0 eq.) dropwise over 15 minutes. Stirring was continued at this temperature for 4.5 hours at which time the reaction was diluted with THF (12 mL) and treated simultaneously with 2 N NaOH (1.45 mL) and 30% H_2O_2 (1.45 mL). The heterogeneous mixture was stirred at 0 ºC for 2 hours before being poured into H_2O (50 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with 2% $Na_2S_2O_3$ (50 mL), H_2O (50 mL), and brine. Drying over Na_2SO_4 was followed by concentration and purification by flash chromatography (10-30% EtOAc/hexanes eluent).

Alcohol 242: The first compound to elute was alcohol **242** (119 mg, 38% yield) as a colorless oil. FTIR (thin film/NaCl) 3446 (bs), 2952 (s), 2930 (s), 1763 (w), 1470 (w), 1097 (m), 1043 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.71 (d, *J* = 6.4 Hz, 1H), 4.67 (d, *J* = 6.5 Hz, 1H), 4.43 (t, *J* = 7.0 Hz, 1H), 3.97 (t, *J* = 11.2 Hz, 1H), 3.87 (d, *J* = 9.4 Hz, 1H), 3.74-3.71 (m, 2H), 3.61 (dd, *J* = 4.4, 12.0 Hz, 1H), 3.38 (s, 3H), 2.64 (q, *J* = 9.8 Hz, 1H), 2.34 (dt, *J* = 4.0, 9.2 Hz, 1H), 2.29 (q, *J* = 9.1 Hz, 1H), 2.18-2.12 (m, 1H), 1.90-1.77

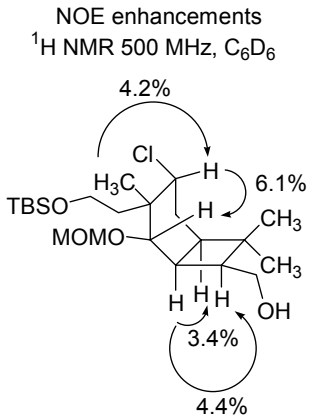
(m, 2H), 1.50 (p, J = 6.8 Hz, 1H), 1.17 (s, 6H), 0.94 (s, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 97.2, 80.1, 66.0, 60.5, 59.8, 55.6, 48.3, 42.5, 40.2, 37.0, 36.1, 35.0, 32.9, 30.4, 25.9, 22.6, 19.2, 18.2, -5.4, -5.5; HRMS (FAB) *m/z* 435.2697 [cacl'd for $C_{22}H_{43}ClO_4Si$ (M+) 435.2697].

NOE enhancements
^{1}H NMR 500 MHz, $CDCl_3$



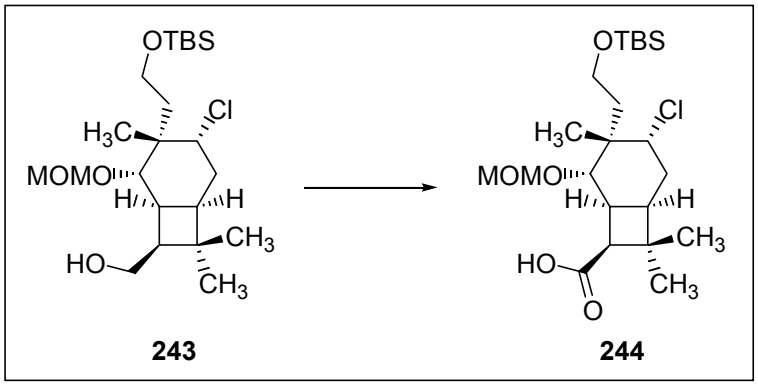
242

Alcohol 243: The second compound to elute was chlorine **243** (72.4 mg, 23% yield, 73% combined yield) as a colorless oil. FTIR (thin film/NaCl) 3455 (bs), 2953 (s), 2929 (s), 1464 (w), 1254 (w), 1083 (m), 1041 (m), 836 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.75 (d, J = 6.3 Hz, 1H), 4.69 (d, J = 6.3 Hz, 1H), 3.93-3.71 (m, 4H), 3.63 (d, J = 9.5 Hz, 1H), 3.54 (dd, J = 4.2, 12.4 Hz, 1H), 3.40 (s, 3H), 3.19 (bs, 1H), 2.61 (q, J = 9.1 Hz, 1H), 2.47-2.40 (m, 2H), 1.95-1.87 (m, 2H), 1.69 (t, J = 8.3 Hz, 2H), 1.18 (s, 3H), 1.05 (s, 3H), 1.00 (s, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 98.8, 86.7, 68.1, 60.3, 58.9, 55.9, 47.5, 43.6, 39.9, 39.1, 37.5, 31.7, 31.6, 29.3, 26.0, 22.6, 19.2, 18.4, -5.1, -5.2; HRMS (FAB) *m/z* 435.2697 [cacl'd for $C_{22}H_{43}ClO_4Si$ (M+) 435.2697].



243

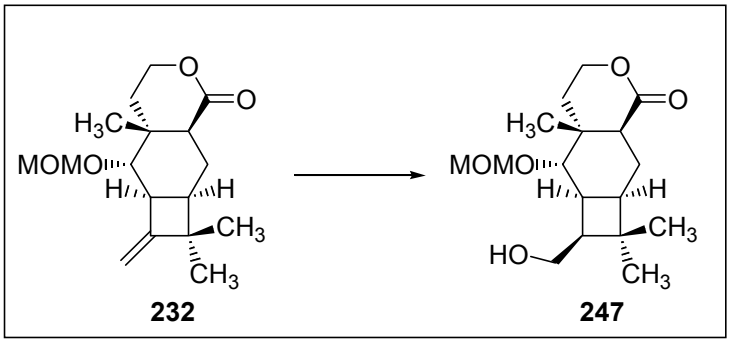
Preparation of Acid 244.



Acid 244. A solution of alcohol **243** (44 mg, 0.10 mmol, 1.0 eq.) in CH_2Cl_2 (4.0 mL) was treated sequentially with pyridine (15 μL, 0.18 mmol, 1.8 eq.) and Dess-Martin (60 mg, 0.14 mmol, 1.4 eq.) and the resulting suspension was allowed to stir at room temperature for 3 hours. The reaction was quenched with the addition of saturated $NaHCO_3$ (10 mL) and 10% $Na_2S_2O_3$ (10 mL). The layers were separated and the organic layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with 1 N HCl (25 mL), saturated $NaHCO_3$ (25 mL), H_2O (25 mL), and brine. Concentration and filtration through a small plug of silica gel (10% EtOAc/hexanes eluent) provided an intermediate aldehyde that was carried onto the next step without

further purification. A solution of the derived aldehyde in tBuOH (1.9 mL) and 2-methyl-2-butene (500 μL) was treated with a solution of $NaClO_2$ (23 mg, 0.25 mmol, 4.0 eq.) and NaH_2PO_4 (17 mg, 0.13 mmol, 2.0 eq.) in H_2O (1.0 mL). The resulting solution was allowed to stir at room temperature for 4 hours before TLC indicated the complete consumption of starting material. The reaction was treated with 0.5 N HCl (20 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with 2% $Na_2S_2O_3$ (10 mL), H_2O (10 mL), and brine. Drying over Na_2SO_4 and concentration was followed by purification via silica gel chromatography (2.5% 7:3 (CH_2Cl_2:hexanes)/CH_3OH eluent) to provide acid **244** (31 mg, 69% overall yield) as a colorless oil. FTIR (thin film/NaCl) 2953 (s), 2929 (s), 1464 (w), 1254 (w), 1083 (m), 1041 (m), 836 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.64 (d, *J* = 6.4 Hz, 1H), 4.56 (d, *J* = 6.7 Hz, 1H), 4.10 (d, *J* = 9.0 Hz, 1H), 3.95 (dd, *J* = 6.2, 12.0 Hz, 1H), 3.90-3.68 (m, 2H), 3.28 (s, 3H), 3.07 (d, *J* = 8.9 Hz, 1H), 2.70 (q, *J* = 10.4 Hz, 1H), 2.50 (t, *J* = 10.2 Hz, 1H), 2.00-1.80 (m, 2H), 1.69-1.61 (m, 2H),1.18 (s, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.4, 98.3, 84.0, 68.0, 60.6, 55.7, 47.5, 43.0, 40.8, 40.0, 37.7, 32.1, 31.7, 29.3, 26.1, 26.0, 25.9, 22.3, 20.1, 18.4, -5.5, -5.1; HRMS (FAB) *m/z* 448.2419[cacl'd for $C_{22}H_{41}ClO_5SiCl$ (M+) 448.2419].

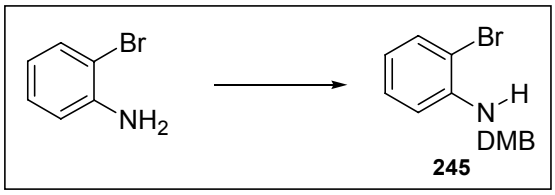
Preparation of Alcohol 247.



Alcohol 247. A solution of acid **232** (101 mg, 0.344 mmol, 1.0 eq.) in THF (1.4 mL) was cooled to 0 ºC and treated with BH_3•DMS (2.0 M in THF, 210 μL, 1.2 eq.) over 7 minutes. The solution was allowed to warm to room temperature over a period of 1 hour, at which point TLC indicated the complete consumption of starting material. The solution was diluted with THF (3.5 mL) and then recooled to 0 ºC, whereupon 2 N NaOH (280 μL) and 30% H_2O_2 (280 μL) were added over a period of one minute. Stirring was continued at 0 ºC for 1 hour before the reaction was poured into 1 N HCl (25 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with 5% $Na_2S_2O_3$ (25 mL), H_2O (25 mL), and brine. The solution was dried over Na_2SO_4, concentrated, and purified by flash chromatography (2-3% (70% CH_2Cl_2/hexanes)/CH_3OH eluent) to provide alcohol **247** (100 mg, 93% yield) as a colorless oil. FTIR (thin film/NaCl) 3485 (b), 2951 (s), 1746 (s), 1459 (w), 1405 (w), 1272 (w), 1146 (w), 1038 (m), 921 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.71 (d, *J* = 6.6 Hz, 1H), 4.66 (d, *J* = 6.1 Hz, 1H), 4.41 (ddd, *J* = 3.7, 8.4, 12.2 Hz, 1H), 4.27 (dt, *J* = 8.3, 11.9 Hz, 1H), 3.79 (d, *J* = 10.5 Hz, 1H), 3.65 (t, *J* = 11.4 Hz, 1H), 3.51-3.50 (m, 1H), 3.37 (s, 3H), 2.44-2.29 (m, 5H), 2.09 (ddd, *J* = 4.2, 8.4, 13.7 Hz, 1H), 1.80 (ddd, *J* = 1.7, 8.6, 10.3 Hz, 1H), 1.73 (dt, *J* = 8.3, 13.7 Hz, 1H), 1.38-1.28

(m, 1H), 1.18 (s, 3H), 1.09 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 98.6, 85.3, 65.4, 58.9, 56.5, 46.2, 46.0, 42.3, 37.7, 37.5, 34.0, 32.1, 29.6, 24.3, 20.1, 16.3; HRMS (EI) *m/z* 313.2014 [cacl'd for $C_{17}H_{29}O_5$ (M+H) 313.2015].

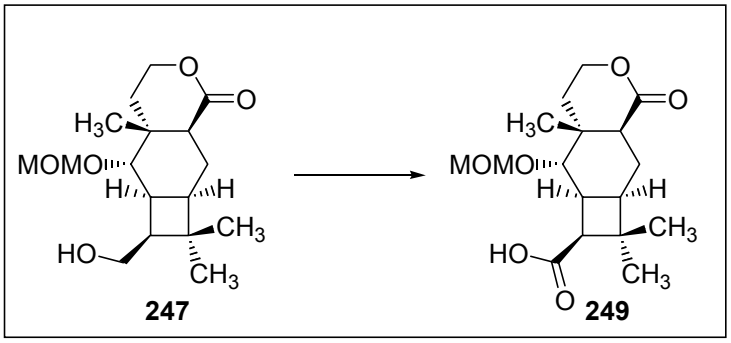
Preparation of Aniline 245.



Aniline 245. A solution of 2-bromoaniline (2.0 g, 11.6 mmol, 1.0 eq.) and 3,4-dimethoxybenzaldehyde (1.90 g, 11.4 mmol, 1.0 eq.) in benzene (35 mL) was fitted with a Dean Stark trap and allowed to reflux overnight.[33] The resulting solution was allowed to cool to room temperature and concentrated under reduced pressure. The derived residue was dissolved in CH_3OH (25 mL) and cooled to 0 °C at which point $NaBH_4$ (440 mg, 11.6 mmol, 1.0 eq.) was added in approximately 50 mg batches over 5 minutes. The solution was then allowed to warm to room temperature and stir for 1.5 hours before additional $NaBH_4$ (440 mg, 11.6 mmol, 1.0 eq.) was added in one portion. Stirring was continued for 2 hours before the reaction was quenched with the addition of 0.5 N HCl (250 mL). Extraction with EtOAc (3 x 150 mL) was followed by washing with H_2O (100 mL) and brine. The solution was dried over Na_2SO_4 and concentrated to provide an oil that was purified by silica gel chromatography (10-15% EtOAc/hexanes eluent) to provide aniline **245** (2.35 g, 64% yield) as a yellow solid. Recrystallization from EtOAc/hexanes provided analytically pure **245** (2.1g, 57% yield) as colorless crystals. m.p. 68-70 °C; FTIR (thin film/NaCl) 3406 (w), 2952 (m), 2933 (m), 2833 (w), 1595 (s),

1151 (s), 1460 (m), 1316 (w), 1263 (s), 1237 (s), 1024 (s), 743 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 1.9, 7.9 Hz, 1H), 7.16 (dt, *J* = 1.1, 7.9 Hz, 1H), 6.93-6.92 (m, 2H), 6.65 (dd, *J* = 1.1, 7.9 Hz, 1H), 6.59 (dt, *J* = 1.4, 7.7 Hz, 1H), 4.72 (bs, 1H), 4.34 (s, 2H), 3.89 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.2, 148.3, 144.8, 132.3, 131.1, 128.5, 119.4, 118.0, 111.7, 111.3, 110.5, 109.7, 55.9, 55.8, 47.9; HRMS (FAB) *m/z* 321.0363 [calc'd for $C_{15}H_{16}NO_2Br$ (M+) 321.0364].

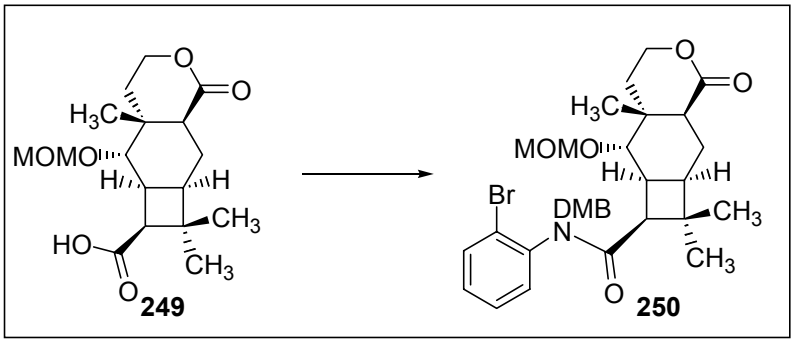
Preparation of Acid 249.



Acid 249. To a solution of alcohol **247** (100 mg, 0.321 mmol, 1.0 eq.) in undistilled CH_2Cl_2 (9.0 mL) was added Dess-Martin (163 mg, 0.384 mmol, 1.2 eq.). The resulting cloudy white mixture was allowed to stir at room temperature for 6 hours before being quenched with the addition of saturated $NaHCO_3$ (15 mL) and 10% $Na_2S_2O_3$ (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with H_2O (30 mL) and brine then dried over Na_2SO_4. Concentration and purification of the resulting residue by silica gel chromatography (30-50% EtOAc/hexanes eluent) afforded aldehyde **248** as a colorless oil, which was immediately carried on to the next step. The derived aldehyde was dissolved in ^{t}BuOH (5.0 mL) and 2-methyl-2-butene (1.2 mL). To this solution was

added a solution of $NaClO_2$ (145 mg, 1.60 mmol, 5.0 eq.) and NaH_2PO_4 (155 mg, 1.12 mmol, 3.5 eq.) in H_2O (2.0 mL). After 30 minutes, additional $NaClO_2$ (48 mg, 0.53 mmol, 1.6 eq.) and NaH_2PO_4 (52 mg, 0.37 mmol, 1.1 eq.) were added as a solution in H_2O (0.5 mL). Stirring was continued for 30 minutes before the reaction was poured into 1 N HCl (25 mL). Extraction with EtOAc (3 x 10 mL) was followed by washing of the combined organic layers with 5% $Na_2S_2O_3$ (20 mL), H_2O (25 mL), and brine. Drying over Na_2SO_4 and concentration provided a residue that was subjected to silica gel chromatography (2-3% (70% CH_2Cl_2/CH_3OH)/hexanes eluent) to afford acid **249** (70 mg, 67% yield) as a white solid. m.p. 145-147 ºC; FTIR (thin film/NaCl) 3168 (s), 2955 (s), 1738 (s), 1458 (w), 1406 (w), 1149 (m), 1102 (m), 1037 (s), 921 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.68 (d, *J* = 6.9 Hz, 1H), 4.58 (d, *J* = 6.9 Hz, 1H), 4.41 (ddd, *J* = 4.5, 7.9, 12.9 Hz, 1H), 4.32-4.26 (m, 1H), 4.04 (d, *J* = 9.8 Hz, 1H), 3.34 (s, 3H), 3.10 (d, *J* = 9.3 Hz, 1H), 2.63 (q, *J* = 9.3 Hz, 1H), 2.42 (q, *J* = 10.5 Hz, 1H), 2.32 (dd, *J* = 1.6, 12.0 Hz, 1H), 2.13 (ddd, *J* = 4.5, 7.5, 13.6 Hz, 1H), 1.87 (ddd, *J* = 2.0, 9.1, 11.0 Hz, 1H), 1.77 (dt, *J* = 8.1, 13.8 Hz, 1H), 1.50-1.43 (m, 1H), 1.24 (s, 3H), 1.19 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 174.3, 99.2, 83.8, 65.8, 56.3, 47.3, 45.1, 41.8, 39.8, 37.7, 35.1, 32.5, 30.9, 23.8, 21.3, 17.0; HRMS (EI) *m/z* 327.1808 [cacl'd for $C_{17}H_{26}O_6$ (M+) 327.1808].

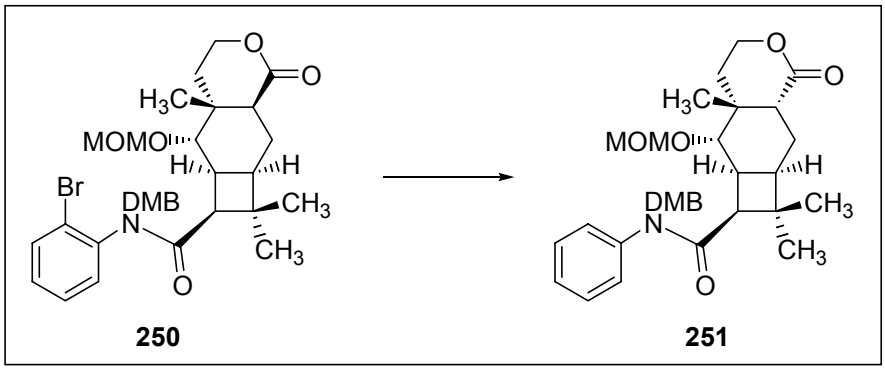
Preparation of Anilide 250.



Anilide 250. A flame dried 50 mL flask was charged with acid **249** (190 mg, 0.583 mmol, 1.0 eq.), DMB-*o*-bromoaniline (**245**) (319 mg, 0.991 mmol, 1.7 eq.). This mixture was dissolved in CH_2Cl_2 (14.0 mL) and CCl_4 (2.0 mL). The resulting solution was cooled to 0 ºC and PPh_3 (229 mg, 0.873 mmol, 1.5 eq.) was added. The cold bath was removed and the reaction was allowed to warm to ambient temperature and stir for 8 hours. The resulting mixture was then poured into $NaHCO_3$ (30 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with H_2O (25 mL) and brine and dried over Na_2SO_4. Concentration and purification by flash chromatography (2-5% (70% CH_2Cl_2/CH_3OH)/hexanes eluent) afforded a pale yellow oil that was further purified by preparative TLC (2% (70% CH_2Cl_2/hexanes)/CH_3OH eluent) to afford anilide **250** (309 mg, 84% yield) as a colorless foam. m.p. 68-70 ºC; FTIR (thin film/NaCl) 2954 (s), 1748 (s), 1656 (s), 1515 (s), 1474 (s), 1405 (m), 1264 (s), 1238 (s), 1142 (s), 1035 (s), 731 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 1.9, 7.7 Hz, 1H), 4.67 (dd, *J* = 2.1, 7.5 Hz, 1H), 7.29-7.23 (m, 3H), 7.20-7.14 (m, 1H), 7.00 (dd, *J* = 2.3, 7.3 Hz, 1H), 6.80 (d, *J* = 1.9 Hz, 1H), 6.70-6.69 (m, 3H), 6.63 (s, 1H), 6.59 (app. dt, *J* = 1.9, 7.5 Hz, 2H), 5.55 (d, *J* = 14.2 Hz, 1H), 5.20 (d, *J* = 13.8 Hz, 1H), 4.91 (d, *J* = 6.5 Hz, 1H), 4.62 (d, *J* = 6.7

Hz, 1H), 4.47 (d, J = 7.3 Hz, 1H), 4.45-4.36 (m, 2H), 4.28-4.18 (m, 2H), 4.08 (app. d, J = 12.2 Hz, 4H), 3.84 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 3.73 (s, 3H), 3.38 (s, 3H), 3.19 (s, 3H), 2.75 (d, J = 8.9 Hz, 1H), 2.52 (d, J = 8.6 Hz, 1H), 2.43 (q, J = 6.0 Hz, 1H), 2.19-1.92 (m, 7H), 1.84-1.72 (m, 5H), 1.45-1.36 (m, 2H), 1.35 (s, 3H), 1.28 (s, 3H), 1.22 (s, 3H), 1.20 (s, 3H), 1.01 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 174.2, 170.3, 170.1, 148.8, 148.4, 148.3, 141.1, 140.8, 133.8, 133.7, 132.2, 131.8, 129.9, 129.7, 129.5, 129.3, 127.9, 127.8, 124.2, 123.4, 122.6, 121.5, 113.5, 112.1, 110.6, 99.9, 99.2, 84.8, 82.5, 65.9, 65.7, 56.1, 55.8, 55.7, 51.1, 50.7, 46.2, 45.2, 44.5, 42.1, 42.0, 40.1, 40.0, 37.9, 37.7, 37.2, 36.5, 33.4, 31.8, 30.5, 30.1, 23.9, 23.2, 21.9, 21.8, 16.8, 16.5; HRMS (FAB) *m/z* 630.2065 [cacl'd for $C_{32}H_{41}NO_7Br$ (M+H) 630.2066].

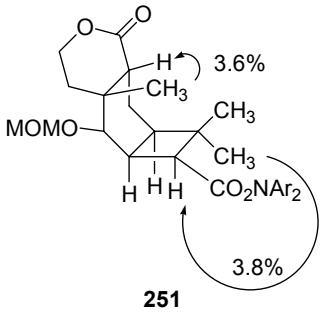
Preparation of Anilide 251.



Anilide 251. To a flame dried flask was added t-BnClPd(PPh_3)$_2$ (8.4 mg, 0.012 mmol, 0.3 eq.), *t*BuONa (9.6 mg, 0.10 mmol, 2.5 eq.), followed by a solution of anilide **250** (25.0 mg, 0.04 mmol, 1.0 eq.) in dioxane (2.5 mL). The resulting red suspension was then heated to reflux for 8 hours at which time a yellow suspension resulted. Following cooling of the solution to room temperature, the reaction was diluted with Et_2O (5 mL) and quenched with saturated NH_4Cl (15 mL). The layers were separated and the aqueous

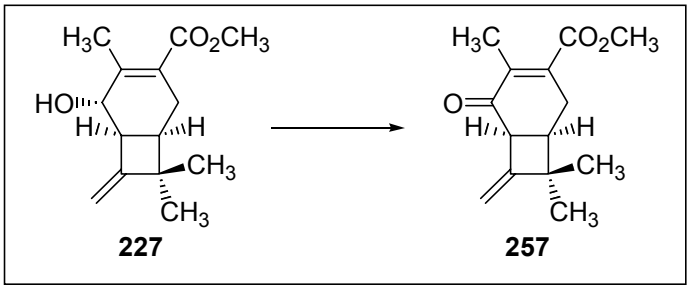
layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4 before being concentrated under reduced pressure. The derived residue was purified by preparative TLC (2% (70% CH_2Cl_2/hexanes)/CH_3OH eluent) to furnish anilide **251** (8.6 mg, 39% yield) as a colorless oil. FTIR (thin film/NaCl) 2952 (s), 2930 (s), 1725 (s), 1644 (s), 1594 (s), 1515 (s), 1463 (m), 1402 (m), 1291 (m), 1237 (m), 1142 (m), 1043 (w), 703 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32-7.28 (m, 3H), 6.92 (bs, 2H), 6.83 (d, *J* = 1.9 Hz, 1H), 6.69 (d, *J* = 8.2 Hz, 1H), 6.61 (dd, *J* = 8.1 Hz, 1H), 5.14 (d, *J* = 14.0 Hz, 1H), 4.72 (d, *J* = 8.6 Hz, 1H), 4.59 (d, *J* = 6.7 Hz, 1H), 4.54 (d, *J* = 6.7 Hz, 1H), 4.48 (d, *J* = 14.3 Hz, 1H), 4.40-4.30 (m, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 3.27 (s, 3H), 2.84 (d, *J* = 8.6 Hz, 1H), 2.61-2.55 (m, 2H), 2.44 (q, *J* = 9.8 Hz, 1H), 2.00-1.94 (m, 2H), 1.78-1.64 (m, 2H), 1.29 (s, 3H), 1.07 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8, 171.8, 148.8, 148.2, 142.5, 130.3, 129.2, 128.8, 127.7, 121.3, 112.0, 110.5, 97.2, 78.9, 65.5, 55.8, 55.7, 55.3, 52.6, 47.4, 46.6, 40.5, 38.0, 36.1, 34.7, 31.3, 28.8, 27.4, 22.9, 19.8; HRMS (EI) *m/z* [cacl'd for $C_{32}H_{41}NO_7$ (M+)].

NOE enhancements
^1H NMR 500 MHz, $CDCl_3$



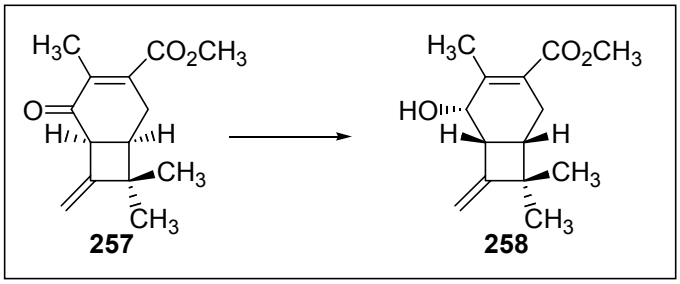
251

Preparation of Ketone 257.



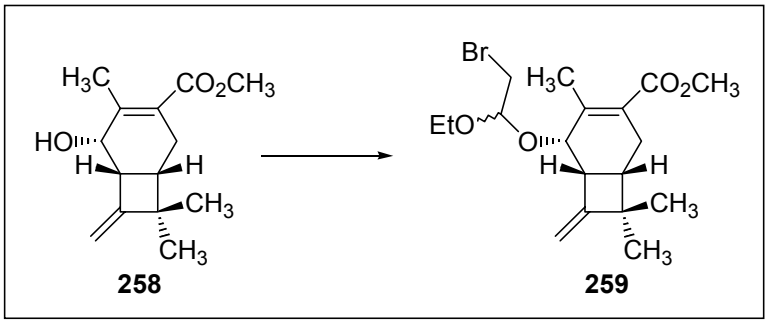
Ketone 257. To a solution of alcohol **227** (450 mg, 1.91 mmol, 1.0 eq.) in CH_2Cl_2 (60 mL) was added Dess-Martin periodinane (1.58 g, 3.81 mmol, 2.0 eq.). Stirring was continued for 1 hour before saturated $NaHCO_3$ (100 mL) and saturated $Na_2S_2O_3$ (25 mL) were added. Vigorous stirring was continued for 30 minutes before the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The derived oil was chromatographed (25% EtOAc/hexanes eluent) to furnish ketone **257** (404 mg, 92% yield) as a colorless oil. FTIR (thin film/NaCl) 2954 (m), 1725 (s), 1677 (s), 1435 (w), 1225 (s), 1045 (m), 887 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.90 (dd, *J* = 1.5, 2.5 Hz, 1H), 4.86 (dd, *J* = 1.0, 3.0 Hz, 1H), 3.83 (s, 3H), 3.78 (d, *J* = 9.0 Hz, 1H), 2.65-2.55 (m, 3H), 1.96 (bs, 3H), 1.24 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7, 168.6, 155.3, 141.5, 137.2, 105.3, 52.0, 47.8, 46.3, 37.1, 29.3, 24.0, 21.6, 13.6; HRMS (EI) *m/z* 234.1262 [cacl'd for $C_{14}H_{18}O_3$ (M+) 234.1256]

Preparation of Alcohol 258.



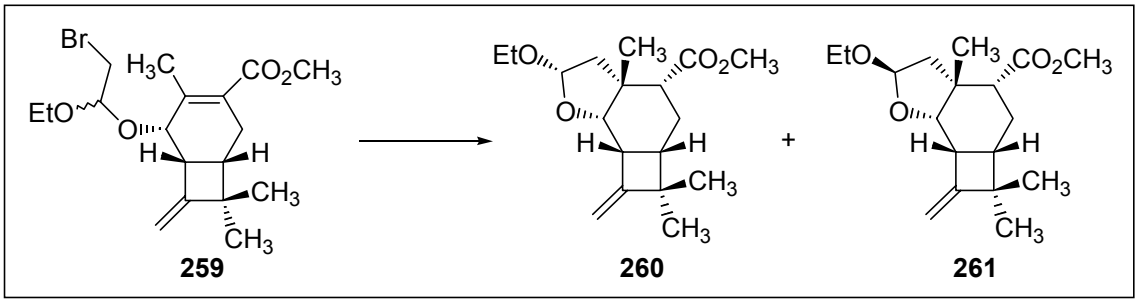
Alcohol 258. A solution of ketone **257** (400 mg, 1.71 mmol, 1.0 eq.) and $CeCl_3$•7 H_2O (3.18 g, 8.55 mmol, 5.0 eq.) in CH_3OH (15 mL) and CH_2Cl_2 (15 mL) was stirred for 5 minutes before being cooled to 0 °C and treated with $NaBH_4$ (137 mg, 3.42 mmol, 2.0 eq.). The suspension was allowed to warm to room temperature and stir at that temperature for 1 hour before being quenched with silica gel (~ 8 g). Concentration and purification by silica gel chromatography (20% EtOAc/hexanes eluent) provided alcohol **258** (365 mg, 90% yield) as an oil which upon cooling solidified to a white solid. m.p. 97-98 °C; FTIR (thin film/NaCl) 3490 (s), 1691 (s), 1434 (w), 1261 (m), 1208 (m), 1026 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.85 (d, *J* = 2.2 Hz, 1H), 4.72 (d, *J* = 2.4 Hz, 1H), 4.24 (d, *J* = 6.0 Hz, 1H), 3.74 (s, 3H), 3.56-3.52 (m, 1H), 2.66 (d, *J* = 15.6 Hz, 1H), 2.26-2.21 (m, 1H), 2.15 (s, 3H), 2.14-2.09 (m, 1H), 1.17 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 159.7, 151.6, 123.8, 103.6, 71.1, 51.4, 43.9, 43.5, 38.3, 31.0, 24.5, 19.3, 16.4; HRMS (EI) *m/z* 236.1403 for $C_{14}H_{20}O_3$ (M+) 236.1412

Preparation of Bromoacetals 259.



Bromoacetals 259. A solution of alcohol **589** (350 mg, 1.48 mmol, 1.0 eq.) in CH_2Cl_2 (6 mL) was treated with bromide **85** (60 mg, 3.71 mmol, 2.5 eq.), *N,N*-dimethylaniline (935 μL, 7.41 mmol, 5.0 eq.), and DMAP (18 mg, 0.15 mmol, 0.1 eq.). After stirring overnight, the resulting dark green solution was washed with 2 N HCl (3 x 30 mL), saturated $NaHCO_3$ (30 mL), and brine before being dried over Na_2SO_4. Concentration *in vacuo* was followed by flash chromatography (2.5–3.0% EtOAc/hexanes eluent) to furnish a 1:1 diastereomeric mixture of bromoacetals **259** (575 mg, 100% yield) as a colorless oil. FTIR (thin film/NaCl) 2978 (m), 2952 (m), 1707 (s), 1429 (w), 1258 (m), 1031 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.92-4.90 (m, 2H), 4.78 (t, *J* = 5.4 Hz, 1H), 4.66 (dd, *J* = 1.1, 2.2 Hz, 2H), 4.21 (d, *J* = 5.1 Hz, 1H), 4.12 (d, *J* = 5.6 Hz, 1H), 3.75 (s, 3H), 3.71-3.60 (m, 7H), 3.48-3.42 (m, 4H), 2.75 (d, *J* = 2.7 Hz, 1H), 2.71 (d, *J* = 2.1 Hz, 1H), 2.23-2.20 (m, 2H), 2.14 (bs, 3H), 2.13-1.98 (m, 2H), 1.26 (t, *J* = 6.9 Hz, 1H), 1.24 (t, *J* = 6.8 Hz, 1H), 1.19 (s, 3H), 1.18 (s, 3H), 0.87 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 168.4, 158.8, 158.6, 151.3, 123.7, 123.5, 103.6, 103.4, 102.4, 99.8, 77.6, 75.8, 61.6, 61.3, 51.4, 43.8, 43.7, 42.6, 40.3, 38.3, 38.2, 31.8, 31.7, 30.9, 30.8, 24.7, 19.4, 19.3, 17.0, 16.6, 15.3, 15.2; HRMS (EI) *m/z* 385.0828 [cacl'd for $C_{18}H_{27}BrO$ (M+) 385.0837].

Preparation of Acetals 260 and 261.



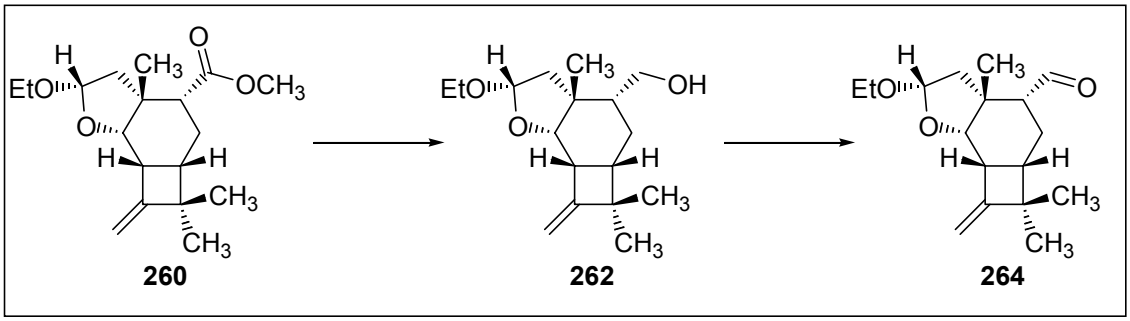
Acetals 260 and 261. A solution of bromoacetals **259** (390 mg, 1.01 mmol, 1.0 eq.) in benzene (50 mL) was degassed with argon for 15 minutes before it was treated with BEt_3 (1.0 M, in hexanes, 3.02 mL, 3.0 eq.), Bu_3SnH (392 μL, 1.51 mmol, 1.5 eq.), and air (5 mL). The reaction mixture was then treated with additional BEt_3 (3.02 mL), Bu_3SnH (392 μL), and air (5 mL) after 1 hour and then again after two hours. The reaction mixture was then diluted with Et_2O (50 mL) and treated with DBU (848 μL, 6.03 mmol, 6.0 eq.) which resulted in the immediate formation of a white precipitate. The white suspension was then titrated with a saturated solution of iodine in Et_2O until the yellow color persisted. Filtration of the reaction mixture through a small pad of silica gel was followed by concentration *in vacuo*. Purification via silica gel chromatography (3–5% EtOAc/hexanes eluent) afforded two compounds.

Acetal 260: The first compound to elute was acetal **260** (100 mg, 41% yield) as a colorless oil. FTIR (thin film/NaCl) 2954 (m), 2901 (m), 1732 (s), 1457 (w), 1438 (w), 1196 (m), 1150 (m), 1026 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.05 (t, J = 5.3 Hz, 1H), 4.92 (d, J = 2.1 Hz, 1H), 4.88 (d, J = 2.6 Hz, 1H), 3.86-3.81(m, 1H), 3.77 (d, J = 6.2 Hz, 1H), 3.68 (s, 3H), 3.56-3.50 (m, 1H), 3.15-3.12 (m, 1H), 2.24-2.07 (m, 3H), 2.05 (dd, J = 5.0, 13.8 Hz, 1H), 1.90 (dd, J = 6.0, 13.9 Hz, 1H), 1.70-1.64 (m, 1H), 1.24 (s, 3H),

1.21 (t, J = 6.8 Hz, 3H), 1.20 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 159.4, 104.4, 103.3, 82.8, 64.5, 51.5, 49.5, 44.6, 43.1, 41.9, 41.4, 38.1, 29.1, 27.9, 21.0, 20.8, 15.2; HRMS (EI) *m/z* 308.1979 [cacl'd for $C_{18}H_{28}O_4$ (M+) 308.1988].

Acetal 261: The second compound to elute was acetal **261** (110 mg, 45% yield) also as a colorless oil. FTIR (thin film/NaCl) 2956 (m), 2905 (m), 1724 (m), 1104 (w), 989 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.11 (dd, J = 1.7, 5.5 Hz, 1H), 4.87 (d, J = 2.5 Hz, 1H), 4.81 (d, J = 1.9 Hz, 1H), 4.00 (d, J = 5.9 Hz, 1H), 3.69 (s, 3H), 3.68-3.63 (m, 1H), 3.45-3.40 (m, 1H), 3.16-3.13 (m, 1H), 2.24 (dd, J = 5.8, 13.8 Hz, 1H), 2.15 (ddd, J = 7.4, 10.0, 11.9 Hz, 1H), 2.05 (dd, J = 2.2, 12.7 Hz, 1H), 1.76 (q, J = 12.3 Hz, 1H), 1.66 (dd, J = 1.8, 14.2 Hz, 1H), 1.62 (ddd, J = 2.3, 7.6, 13.1 Hz, 1H), 1.32 (s, 3H), 1.19 (s, 3H), 1.18 (t, J = 6.0 Hz, 3H), 1.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 159.4, 104.3, 102.2, 81.3, 62.5, 51.4, 49.5, 44.5, 43.6, 42.2, 41.5, 37.3, 30.0, 27.3, 21.2, 21.2, 15.3; HRMS (EI) *m/z* 308.1981 [cacl'd for $C_{18}H_{28}O_4$ (M+) 308.1988].

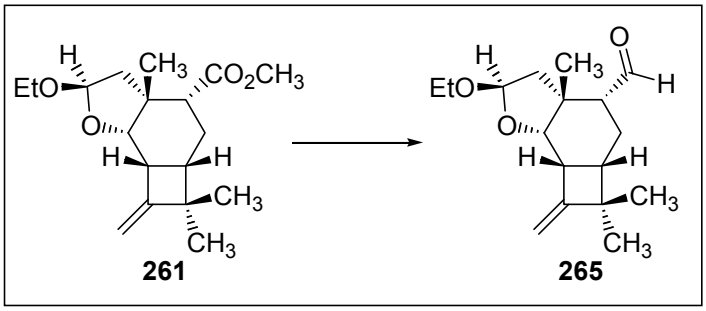
Preparation of Aldehyde 264.



Aldehyde 264. To a solution of ester **260** (85 mg, 0.27 mmol, 1.0 eq.) in CH_2Cl_2 (6 mL) at –78 °C was added DIBAL (1.0 M in toluene, 825 μL, 3.0 eq.). The reaction was maintained at –78 °C for 1 hour before it was quenched with 0.5 N HCl. The reaction was then allowed to warm to room temperature and stir until homogeneous (30 minutes). Extraction with CH_2Cl_2 (4 x 5 mL) was followed by washing with saturated $NaHCO_3$ (25 mL) then brine. Concentration under reduced pressure provided an oil that was purified by flash chromatography (30% EtOAc/hexanes eluent) to provide alcohol **262** (68 mg, 88% yield) as a colorless oil. FTIR (thin film/NaCl) 3405 (bs), 2947 (s), 2868 (s), 1669 (m), 1456 (m), 1376 (m), 1012 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.08 (d, *J* = 6.4 Hz, 1H), 4.89 (d, *J* = 3.0 Hz, 1H), 4.84 (d, *J* = 2.3 Hz, 1H), 3.93-3.87 (m, 1H), 3.79 (d, *J* = 5.0 Hz, 1H), 3.76 (t, *J* = 3.1 Hz, 1H), 3.71-3.67 (m, 1H), 3.54-3.48 (m, 1H), 3.13-3.10 (m, 1H), 3.03 (dd, *J* = 2.5, 7.3 Hz, 1H), 2.25-2.14 (m, 3H), 1.87 (dd, *J* = 6.7, 14.1 Hz, 1H), 1.43-1.31 (m, 2H), 1.20 (s, 3H), 1.19 (t, *J* = 7.0 Hz, 3H), 1.14 (s, 3H) 1.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.5, 104.1, 102.6, 84.3, 63.9, 63.8, 44.6, 44.5, 43.1, 42.2, 40.6, 37.9, 30.2, 27.9, 21.2, 21.0, 14.9; HRMS (EI) *m/z* 280.2048 [cacl'd for $C_{17}H_{28}O_3$ (M+) 280.2038]. To a solution of DMSO (74 μL, 1.05 mmol, 6 eq.) in CH_2Cl_2 (3 mL) at –78 °C was added oxalyl chloride (3 μL, 0.44 mmol, 2.5 eq.). After

stirring for 10 minutes a solution of alcohol **262** (50 mg, 0.18 mmol, 1.0 eq.) in CH_2Cl_2 (2 mL) was added dropwise. Stirring was continued for 10 minutes at –78 ºC before triethylamine (366 μL, 2.6 mmol, 15.0 eq.) was added and the reaction mixture was to slowly warm to room temperature over a period of 2 hours. Removal of the solvent *in vacuo*, absorption of the reaction mixture onto silica gel and flash chromatography (25% EtOAc/hexanes eluent) provided aldehyde **264** (50 mg, 100% yield) as a colorless oil. FTIR (thin film/NaCl) 2951 (s), 2897 (s), 1719 (s), 1455 (w), 1378 (m), 1122 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.77 (d, *J* = 2.3 Hz, 1H), 5.06 (dd, *J* = 3.5, 6.0 Hz, 1H), 4.89 (d, *J* = 2.9 Hz, 1H), 4.86 (d, *J* = 1.7 Hz, 1H), 3.85-3.81 (m, 1H), 3.77 (d, *J* = 5.3 Hz, 1H), 3.53-3.46 (m, 1H), 3.13-3.10 (m, 1H), 2.31 (q, *J* = 12.3 Hz, 1H), 2.20-2.15 (m, 1H), 2.08 (dd, *J* = 3.6, 14.1 Hz, 1H), 1.96 (dd, *J* = 6.5, 14.4 Hz, 1H), 1.88 (dt, *J* = 2.1, 12.8 Hz, 1H), 1.66 (ddd, *J* = 2.9, 7.8, 13.2 Hz, 1H), 1.23 (s, 3H), 1.20 (s, 3H), 1.17 (t, *J* = 7.0 Hz, 3H), 1.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.2, 159.4, 104.6, 103.0, 83.2, 64.3, 55.4, 44.7, 43.2, 41.2, 40.0, 37.9, 30.1, 27.5, 21.1, 18.8, 15.1; HRMS (EI) *m/z* 278.1867 [cacl'd for $C_{17}H_{26}O_3$ (M+) 278.1882].

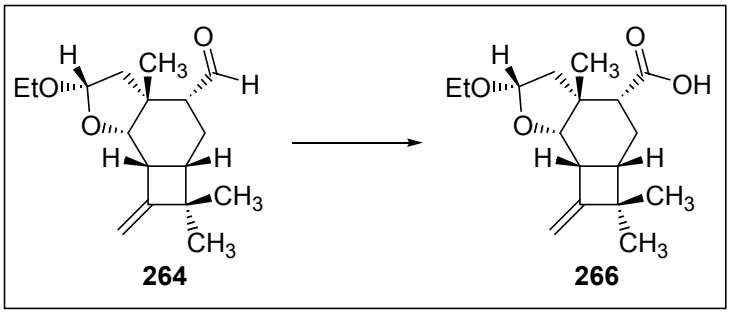
Preparation of Aldehyde 265.



Aldehyde 265. A solution of ester **261** (105 mg, 0.34 mmol, 1.0 eq.) in CH_2Cl_2 (8 mL) was cooled to –78 ºC and treated with DIBAL (1.0 M in toluene, 1.02 mL, 3.0 eq.). The solution was allowed to stir at this temperature for 1 hour before being quenched with the addition of 1 N HCl (25 mL). The resulting mixture was allowed to warm to room temperature and stir for an additional 10 minutes. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4 before being concentrated. The derived residue was purified by silica gel chromatography (20% EtOAc/hexanes eluent) to provide alcohol **263** (71 mg, 74% yield) as a colorless oil that was immediately carried on. A solution of DMSO (106 μL, 1.5 mmol, 6.0 eq.) in CH_2Cl_2 (4 mL) at –78 °C was treated dropwise with oxalyl chloride (54 μL, 0.62 mmol, 2.5 eq.). The solution was stirred for 10 minutes before alcohol **263** (71 mg, 0.25 mmol, 1.0 eq.) in CH_2Cl_2 (2 mL) was added dropwise. After stirring for a further 10 minutes, triethylamine (524 μL, 3.7 mmol, 15.0 eq.) was added and the reaction mixture was allowed to slowly warm to room temperature and stir at that temperature for 30 minutes. Following removal of the solvent *in vacuo* and absorption of the reaction mixture onto silica gel, the aldehyde was purified by flash chromatography (10% EtOAc/hexanes eluent) to furnish aldehyde **265** (71 mg, 100% yield, 74% overall yield) as a colorless oil. FTIR (thin film/NaCl) 2956 (m), 2905 (m), 1725 (s), 1455 (w), 1109 (w), 975 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 5.09 (d, J = 5.2 Hz, 1H), 4.88 (d, J = 2.3 Hz, 1H), 4.80 (d, J = 2.2 Hz, 1H), 3.98 (d, J = 6.3 Hz, 1H), 3.66-3.62 (m, 1H), 3.44-3.38 (m, 1H), 3.18-3.14 (m, 1H), 2.22-2.15 (m, 1H), 2.00 (dd, J = 5.4, 13.6 Hz, 1H), 1.92 (d, J = 11.1 Hz, 1H), 1.81 (d, J = 13.5 Hz, 1H) 1.80-1.74 (m, 1H), 1.47 (q, J = 12.0 Hz, 1H), 1.40 (s, 3H) 1.19 (s, 3H), 1.17 (t, J = 7.2

Hz, 3H), 1.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 159.1, 104.6, 102.1, 81.4, 62.2, 56.9, 44.5, 43.5, 41.6, 40.9, 37.3, 29.9, 27.6, 21.2, 18.1, 15.3; HRMS (EI) *m/z* 278.1880 [cacl'd for $C_{17}H_{26}O_3$ (M+) 278.1882].

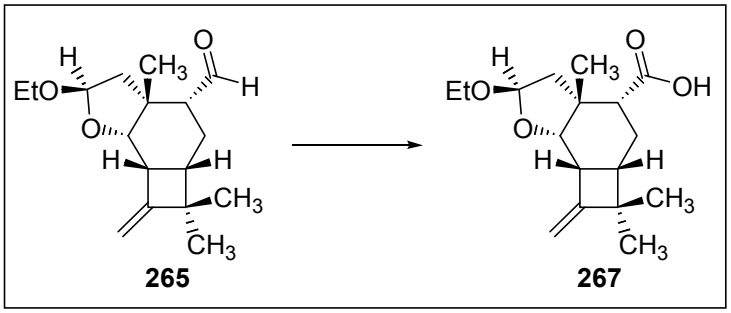
Preparation of Acid 266.



Acid 266. A solution of aldehyde **264** (40 mg, 0.14 mmol, 1.0 eq.) in *t*BuOH (4 mL) and 2,3-dimethyl-2-butene (170 μL, 1.43 mmol, 10.0 eq.) was treated with a solution of $NaClO_2$ (52 mg, 0.57 mmol, 4.0 eq.) and NaH_2PO_4 (40 mg, 0.28 mmol, 2.0 eq.) in H_2O (1 mL). The resulting solution was vigorously stirred for 4 hours before the organic layer was removed under reduced pressure. Dilution with H_2O (15 mL) and basification with 2 N NaOH (3 mL) was followed by extraction with CH_2Cl_2 (3 x 5 mL). Acidification to pH 1 with 1 N HCl and extraction with CH_2Cl_2 (3 x 10 mL) was followed by washing with brine and drying over Na_2SO_4. Concentration *in vacuo* delivered acid **266** (35 mg, 83% yield) as a colorless oil. FTIR (thin film/NaCl) 2950 (m), 2898 (m), 1699 (s), 1378 (w), 1118 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09 (dd, *J* = 3.2, 6.1 Hz, 1H), 4.90 (d, *J* = 2.7 Hz, 1H), 4.88 (d, *J* = 1.9 Hz, 1H), 3.93-3.89 (m, 1H), 3.82 (d, *J* = 5.6 Hz, 1H), 3.59-3.55 (m, 1H), 3.16-3.12 (m, 1H), 2.32-2.10 (m, 4H), 2.01 (dd, *J* = 6.3, 14.2 Hz, 1H), 1.70-1.65 (m, 1H), 1.34 (s, 3H), 1.24 (t, *J* = 5.6 Hz, 3H),

1.21 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 159.3, 104.6, 102.8, 83.4, 64.5, 50.4, 44.7, 43.7, 41.3, 40.7, 37.7, 30.0, 27.5, 21.1, 21.0, 15.0; HRMS (EI) *m/z* 294.1839[cacl'd for $C_{17}H_{26}O_4$ (M+) 294.1831].

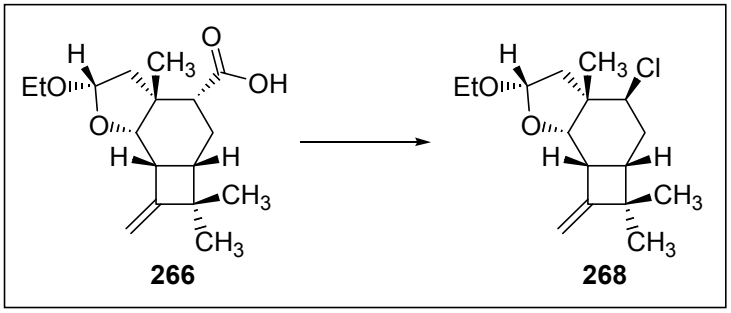
Preparation of Acid 267.



Acid 267. To a solution of aldehyde **265** (25 mg, 0.08 mmol, 1.0 eq.) and 2,3-dimethyl-2-butene (107 μL, 0.89 mmol, 10.0 eq.) in *t*BuOH (4 mL) was added a solution of $NaClO_2$ (32 mg, 0.36 mmol, 4.0 eq.) and NaH_2PO_4 (25 mg, 0.18 mmol, 2.0 eq.) in H_2O (1 mL). Stirring was continued for 3 hours, at which point TLC indicated no remaining starting material. Following removal of the organic phase under reduced pressure, the aq. layer was basified with 2 N NaOH and extracted with CH_2Cl_2 (3 x 5 mL). Acidification to pH 1 with 1 N HCl was followed by extraction with CH_2Cl_2 (3 x 15 mL) and washing of the combined organic layers with brine. Drying over Na_2SO_4 and removal of the solvent *in vacuo* provided acid **267** (25 mg, 96% yield) as a white solid. m.p. 116-117 °C; FTIR (thin film/NaCl) 3331 (bs), 2954 (s), 1672 (m), 1447 (m), 1068 (m), 886 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.13 (dd, *J* = 1.1, 5.1 Hz, 1H), 4.87 (d, *J* = 2.4 Hz, 1H), 4.81 (d, *J* = 2.1 Hz, 1H), 4.02 (d, *J* = 6.0 Hz, 1H), 3.68-3.65 (m, 1H), 3.44-3.41 (m, 1H), 3.17-3.14 (m, 1H), 2.30 (dd, *J* = 5.5, 14.0 Hz, 1H), 2.20-2.14 (m, 1H),

2.08 (dd, J = 2.0, 12.3 Hz, 1H), 1.78-1.66 (m, 3H), 1.36 (s, 3H), 1.20 (s, 3H), 1.18 (t, J = 7.0 Hz, 3H), 1.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.7, 159.3, 104.4, 102.1, 81.4, 62.5, 49.4, 44.5, 43.6, 42.1, 41.4, 37.2, 30.0, 27.2, 21.2, 20.9, 15.3; HRMS (EI) *m/z* 294.1824 [cacl'd for $C_{17}H_{26}O_4$ (M+) 294.1831].

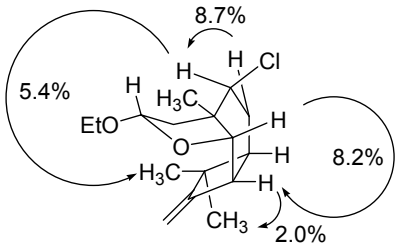
Preparation of Chlorine 268.



Chlorine 268. A solution of acid **266** (22 mg, 0.07 mmol, 1.0 eq.), 2-mercapto-pyridine-*N*-oxide (**236**) (12 mg, 0.10 mmol, 1.3 eq.), and DMAP (3 mg, 0.02 mmol, 0.3 eq.) in CCl_4 (6 mL) was thoroughly degassed with argon before being added via cannula to a flask containing EDC•HCl (29 mg, 0.15 mmol, 2.0 eq.). The resulting suspension, which quickly turned bright yellow, was allowed to stir at room temperature under argon overnight. The completion of the reaction was marked by the gradual fading of the yellow color to a colorless solution. The reaction mixture was absorbed onto silica gel and purified by flash chromatography (1% EtOAc/hexanes eluent) to deliver chlorine **268** (15 mg, 71% yield) as a colorless oil. FTIR (thin film/NaCl) 2956 (s), 2931 (s), 1452 (m), 1377 (m), 1031 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.57 (d, J = 2.5 Hz, 1H), 4.98 (dd, J = 5.4, 6.3 Hz, 1H), 4.83 (d, J = 2.9 Hz, 1H), 4.79-4.74 (m, 1H), 3.83 (dq, J = 7.2, 9.4 Hz, 1H), 3.65 (d, J = 7.3 Hz, 1H), 3.37 (dq, J = 7.2, 9.4 Hz, 1H), 3.32-3.27 (m,

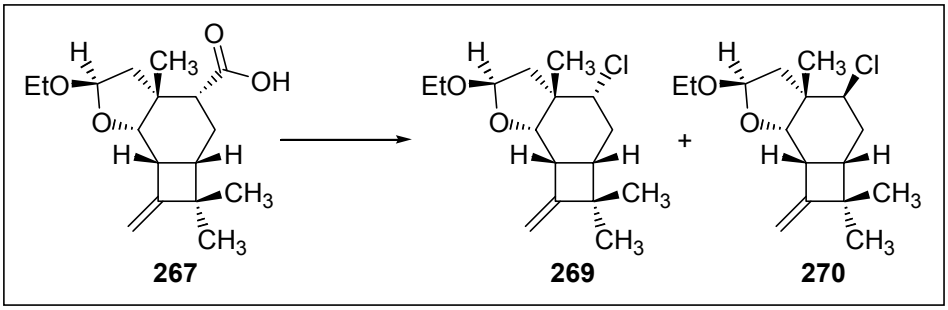
1H), 2.15 (dd, J = 6.2, 12.6 Hz, 1H), 1.98-1.93 (m, 2H), 1.78-1.71 (m, 2H), 1.11 (t, J = 6.5 Hz, 3H), 1.04 (s, 3H), 1.02 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 103.9, 103.4, 84.7, 76.9, 64.9, 64.8, 47.4, 44.7, 44.3, 39.7, 39.6, 30.5, 21.9, 20.8, 15.4; HRMS (EI) *m/z* 283.1466 [calc'd for $C_{16}H_{25}ClO_2$ (M+) 283.1465].

NOE enhancements
^{1}H NMR 500 MHz, C_6D_6



268

Preparation of Chlorines 269 and 270.

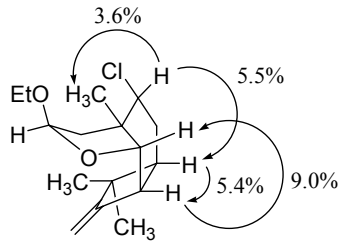


A solution of acid **267** (20 mg, 0.07 mmol, 1.0 eq.), 2-mercapto-pyridine-*N*-oxide (**236**) (11 mg, 0.09 mmol, 1.3 eq.) and DMAP (2 mg, 0.02 mmol, 0.3 eq.) in CCl_4 (6 mL) was degassed by bubbling argon through the solution for 45 minutes. The derived solution was then added via cannula transfer to a flask containing EDC•HCl (26 mg, 0.14 mmol, 2.0 eq.). The resulting suspension quickly turned yellow and was allowed to stir at room temperature under argon overnight. Completion of the reaction was indicated by the disappearance of the bright yellow color and the formation of a colorless reaction

mixture. The reaction was absorbed onto silica gel and purified by flash chromatography (1% EtOAc/hexanes).

Chlorine 269: The first compound to elute was chlorine **269** (6 mg, 32% yield) as a colorless oil. FTIR (thin film/NaCl) 2956 (s), 2907 (s), 2870 (m), 1673 (w), 1448 (m), 1373 (m), 1328 (w), 1102 (s), 1046 (s), 990 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.13 (d, *J* = 5.1 Hz, 1H), 4.88 (d, *J* = 2.5 Hz, 1H), 4.80 (d, *J* = 2.0 Hz, 1H), 4.08 (d, *J* = 5.5 Hz, 1H), 3.69-3.62 (m, 2H), 3.43 (dq, *J* = 7.6, 10.0 Hz, 1H), 3.15-3.07 (m, 1H), 2.56 (dd, *J* = 5.4, 14.0 Hz, 1H), 2.32 (ddd, *J* = 8.0, 10.1, 11.6 Hz, 1H), 1.96 (q, *J* = 11.6 Hz, 1H), 1.78 (ddd, *J* = 2.5, 7.9, 10.4 Hz, 1H), 1.70 (dd, *J* = 1.0, 14.0 Hz, 1H), 1.31 (s, 3H),1.19 (t, *J* = 7.4 Hz, 3H), 1.18 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 104.7, 101.9, 81.7, 68.2, 62.2, 45.9, 44.7, 43.5, 42.7, 36.6, 29.9, 29.0, 26.3, 21.3, 15.3; HRMS (EI) *m/z*. 284.1537 [cacl'd for $C_{16}H_{25}ClO_2$ (M-H) 284.1543].

NOE enhancements
^{1}H NMR 500 MHz, 2:1 C_6D_6:$CDCl_3$

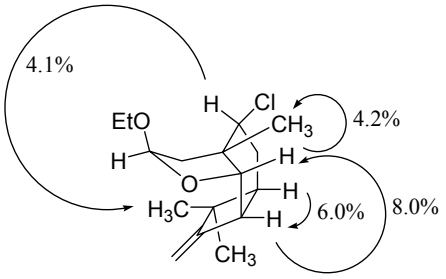


269

Chlorine 270: The second compound to elute was chlorine **270** (9 mg, 47% yield) as a pale yellow oil. FTIR (thin film/NaCl) 2928 (s), 1453 (m), 1089 (m), 1046 (m), 999 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.16 (d, *J* = 5.0 Hz, 1H), 4.99 (d, *J* = 2.5 Hz, 1H),

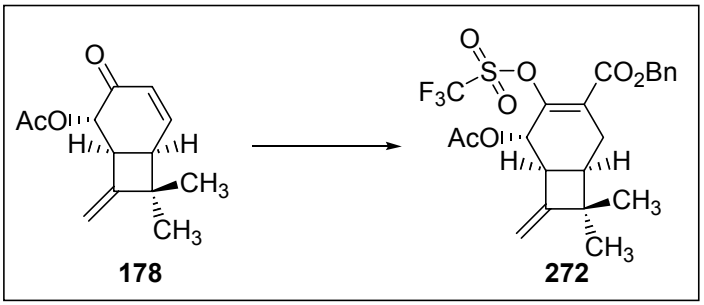
4.74 (d, J = 2.5 Hz, 1H), 4.48 (dd, J = 4.5, 10.5 Hz, 1H), 4.08 (d, J = 7.5 Hz, 1H), 3.75-3.71 (m, 1H), 3.56-3.55 (m, 1H), 3.46-3.42 (m, 1H), 2.20-2.17 (m, 1H), 2.04-1.95 (m, 4H), 1.35 (s, 3H), 1.27 (s, 3H), 1.21 (t, J = 7.0 Hz, 3H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.1, 102.9, 102.6, 84.9, 66.1, 62.5, 48.6, 45.3, 44.2, 39.3, 38.9, 30.4, 30.3, 22.3, 21.0, 15.3; HRMS (EI) *m/z* 284.1537 [cacl'd for $C_{16}H_{25}ClO_2$ (M+) 284.1543].

NOE enhancements
^{1}H NMR 500 MHz, $CDCl_3$



270

Preparation of Enol triflate 272.

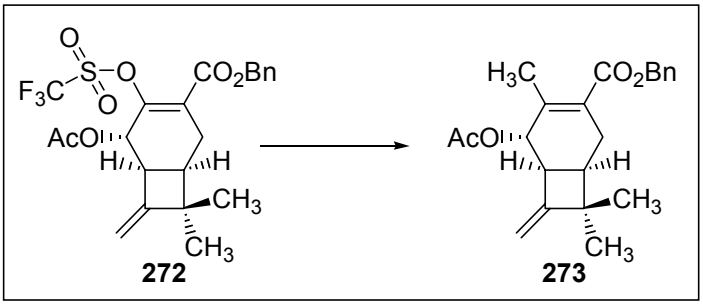


Enol triflate 272. To a solution of ketone **178** (1.5 g, 6.81 mmol, 1.0 eq.) in Et_2O (45 mL) at –78 ºC was added L-Selectride (1.0 M in THF, 8.18 mL, 1.2 eq.) over 1 minute. The resulting solution was allowed to stir for an additional 2 minutes, at which point TLC indicated the complete consumption of starting material. DMPU (45 mL) was added over a period of 2 minutes and the solution was allowed to stir for 5 minutes

before benzyl cyanoformate (2.94 mmol, 20.45 mmol, 3.0 eq.) was added. The solution was allowed to slowly warm to room temperature over a period of 3 hours and then stir for an additional 3 hours. The reaction was quenched by pouring it into 1 N HCl (250 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 200 mL) and washed successively with 1 N HCl (2 x 200 mL), H_2O (3 x 300 mL), $NaHCO_3$ (200 mL), and brine. Drying over Na_2SO_4 was followed by concentration and purification by silica gel chromatography (5-10% EtOAc/hexanes eluent) to provide β-ketoester **271** (1.8 g, 74% yield) as a colorless oil that was typically used immediately in the next step. [The yield of this reaction was found to drop when performed on scales > 7 mmol of ketone **178**.] A solution of enol **271** (3.4 g, 9.5 mmol, 1.0 eq.) in CH_2Cl_2 (100 mL) was treated with triethylamine (4.0 mL, 28.7 mmol, 3 eq.) and DMAP (117 mg, .9 mmol, .1 eq.). The resulting solution was stirred at room temperature for 30 minutes and then cooled to –78 °C. While at -78 °C triflic anhydride (3.38 mL, 19.2 mmol, 2 eq.) was added dropwise over 1 minute. After stirring at -78 °C for 20 minutes the reaction was quenched by the addition of saturated NH_4Cl (200 mL). The reaction mixture was then poured into additional saturated NH_4Cl (250 mL) and extracted with EtOAc (2 x 250 mL). The combined organic layers were washed with 1 N HCl (200 mL), saturated $NaHCO_3$ (200 mL), brine and dried over Na_2SO_4 and concentrated to furnish a yellow oil. Flash chromatography (5-10% EtOAc/ hexanes eluent) provided enol triflate **272**(4.1 g, 91% yield) as a colorless oil. FTIR (thin film/NaCl) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.35 (m, 5H), 5.48 (d, J = 2.6 Hz, 1H), 5.31 (d, J = 12.1 Hz, 1H), 5.28 (d, J = 12.1 Hz, 1H), 4.91-4.90 (m, 2H), 3.60 (dq, J = 2.8, 9.3 Hz, 1H), 2.81 (dd, J = 1.7, 17.2 Hz, 1H), 2.70 (dd, J = 7.6, 17.2 Hz, 1H), 2.42 (dt, J = 2.0, 7.7 Hz, 1H), 2.08 (s, 3H), 1.20 (s,

3H), 0.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 163.9, 155.9, 147.9, 135.0, 128.7, 128.6, 128.5, 127.0, 117.8 (q, *J* = 118 Hz), 105.6, 70.3, 67.6, 44.1, 43.6, 37.1, 30.2, 25.0, 21.0, 20.8; HRMS (EI) *m/z* 488.1120 [calc'd for $C_{22}H_{23}F_3O_6S$ (M+) 488.1117].

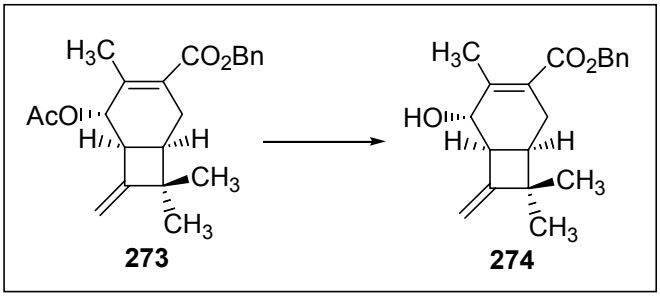
Preparation of Diene 273.



Diene 273. A suspension of CuCN (2.35 g, 26.3 mmol, 3.1 eq.) was cooled to -25 °C before CH_3Li (1.4 M in Et_2O, 18.0 mL, 3.0 eq.) was added dropwise over 5 minutes. The reaction mixture initially became bright yellow gradually turned into a colorless solution. After stirring for 20 minutes at -25 °C, the colorless solution was cooled to -78 °C and a solution of enol triflate **272** (4.0 g, 8.4 mmol, 1.0 eq.) was added via cannula over 5 minutes. The colorless solution immediately turned bright yellow. After stirring for 20 minutes, the reaction was quenched by the addition of saturated NH_4Cl (200 mL). The entire reaction mixture was poured into an additional 200 ml saturated NH_4Cl, extracted with EtOAc (3 x 200 mL), washed with 1N HCl (200 mL), saturated $NaHCO_3$ (200 mL) and brine. Drying over Na_2SO_4 and concentration provided an oil which was chromatographed (3-10% EtOAc/hexanes eluent) to furnish unsaturated ester **273** (2.60 g, 87% yield) as a colorless oil. FTIR (thin film/NaCl) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.34 (m, 5H), 5.31 (d, *J* = 4.1 Hz, 1H), 5.25 (d, *J* = 12.7 Hz, 1H), 5.20 (d, *J* = 12.8

Hz, 1H), 4.77-4.76 (m, 2H), 3.43 (dq, J = 2.4, 6.4 Hz, 1H), 2.56-2.53 (m, 2H), 2.31 (ddd, J = 4.0, 6.9, 10.4 Hz, 1H), 2.10-2.09 (m, 3H), 2.07 (s, 3H), 1.12 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 168.0, 158.6, 144.7, 136.1, 128.5, 128.4, 128.1, 103.4, 74.3, 66.3, 49.3, 44.0, 41.9, 37.9, 30.4, 24.3, 21.2, 21.0, 20.8; HRMS (EI) *m/z* 354.1834 [calc'd for $C_{22}H_{26}O_4$ (M+) 354.1831].

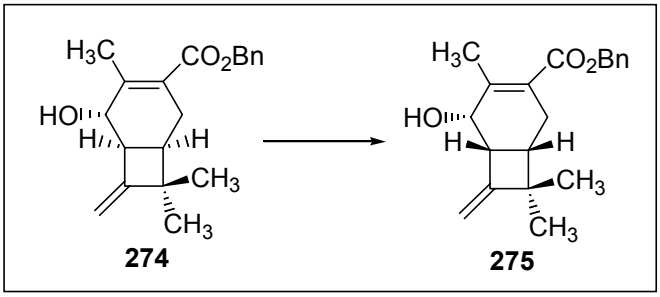
Preparation of Alcohol 274.



Alcohol 274. To a solution of acetate **273** (4.00 g, 11.29 mmol, 1.0 eq.) in CH_3OH (100 mL) at 0 ºC was added K_2CO_3 (1.56 g, 11.29 mmol, 1.0 eq.). The reaction was allowed to warm to room temperature over a period of 1 hour, during which time the reaction gradually turned from colorless to yellow. After stirring at room temperature for an additional 30 minutes, the reaction was quenched with saturated NH_4Cl (250 mL). The volatiles were removed *in vacuo* and the remaining aqueous layer was extracted with Et_2O (2 x 200 mL). Washing with brine and drying over Na_2SO_4 was followed by concentration and purification by flash chromatography (25-30% EtOAc/hexanes eluent) to furnish alcohol **274** (3.35 g, 95% yield) as a colorless oil. FTIR (thin film/NaCl) 3404 (b), 2950 (s), 2864 (s), 1701 (s), 1455 (m), 1374 (m), 1252 (s), 1213 (s), 1059 (m), 1029 (m), 880 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.33 (m, 5H), 5.25 (d, J = 12.6 Hz, 1H), 5.19 (d, J = 12.3 Hz, 1H), 4.75 (d, J = 2.7 Hz, 1H), 4.74 (d, J = 2.3 Hz, 1H),

4.19 (d, J = 4.3 Hz, 1H), 3.35-3.30 (m, 1H), 2.60-2.46 (m, 2H), 2.32 (ddd, J = 4.0, 7.3, 9.4 Hz, 1H), 2.17 (s, 3H), 1.21 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 160.0, 148.9, 136.0, 128.4, 127.9, 125.8, 102.4, 73.3, 66.1, 44.3, 43.6, 38.3, 30.3, 28.9, 20.9, 20.2; HRMS (EI) *m/z* 312.1724 [calc'd for $C_{20}H_{24}O_3$(M+) 312.1725].

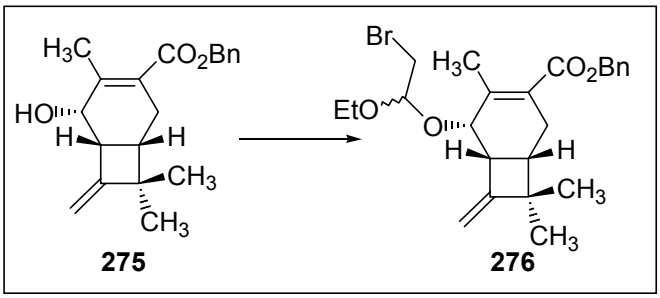
Preparation of Alcohol 275.



Alcohol 275. To a solution of alcohol **274** (1.8, 5.77, 1.0 eq.) in CH_2Cl_2 (50 mL) was added Dess-Martin periodinane (2.86 g, 6.92 mmol, 1.2 eq.). The resulting suspension was stirred for 10 minutes before being quenched by the addition of saturated $NaHCO_3$ (150 mL) and saturated $Na_2S_2O_3$ (50 mL). Stirring was continued for 30 minutes, at which point both the aqueous and organic layers were homogenous. The aqueous layer was then extracted with CH_2Cl_2 (3 x 150 mL). Washing with brine and drying over Na_2SO_4 was followed by concentration *in vacuo* to provide an oil that was carried on without further purification. The crude ketone was dissolved in a 1:1 mixture of CH_2Cl_2/CH_3OH (50 mL) and was treated with $CeCl_3$ x 7 H_2O (10.74 g, 28.84 mmol, 5.0 eq.) and allowed to stir at room temperature for 5 minutes before being cooled to 0 ºC. Once at 0 ºC, the reaction mixture was treated with $NaBH_4$ (461 mg, 11.54 mmol, 2.0 eq.). Stirring was continued for 1 hour before the reaction was quenched by the addition of silica gel (approx. 10 g). Removal of the solvent and column chromatography (20%

EtOAc/hexanes eluent) afforded alcohol **275** (1.45 g, 81% yield) as a colorless oil. FTIR (thin film/NaCl) 3497 (bs), 2952 (s), 1691 (s), 1252 (s), 1204 (s), 1020 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.32 (m, 5H), 5.25 (d, *J* = 12.3 Hz, 1H), 5.18 (d, *J* = 12.8 Hz, 1H), 4.86 (d, *J* = 1.7 Hz, 1H), 4.74 (d, *J* = 2.3 Hz, 1H), 4.25 (d, *J* = 5.5 Hz, 1H), 3.64-3.53 (m, 1H), 2.73 (d, *J* = 16.3 Hz, 1H), 2.25 (dt, *J* = 1.3, 8.0 Hz, 1H), 2.18 (s, 3H), 2.18-2.13 (m, 1H), 1.72 (bs, 1H), 1.19 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 159.5, 152.6, 136.2, 128.4, 127.9, 123.4, 103.5, 71.1, 65.9, 43.9, 43.4, 38.2, 30.8, 24.5, 19.2, 16.3; HRMS (EI) *m/z* 310.1575 [calc'd for $C_{20}H_{22}O_3$(M+) 310.1569].

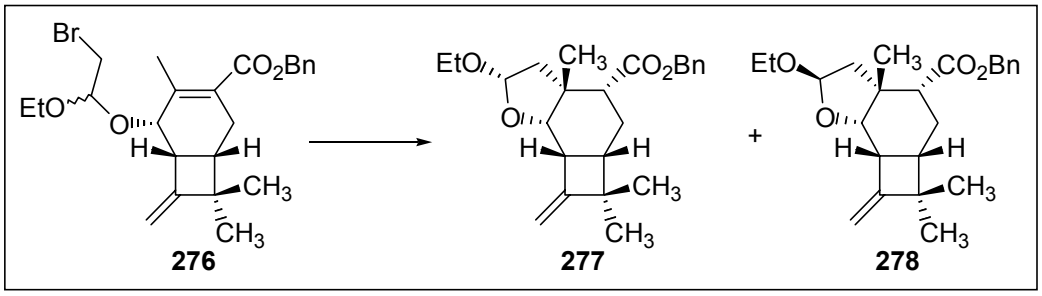
Preparation of Bromoacetals 276.



B**romoacetals 276.** A solution of alcohol **275** (1.1 g, 3.53 mmol, 1.0 eq.), *N,N*-dimethylaniline (2.68 mL, 21.15 mmol, 6.0 eq.) and DMAP (86 mg, 0.71 mmol, 0.2 eq.) in CH_2Cl_2 (12 mL) was treated with bromide **85** (2.45 g, 10.58 mmol, 3.0 eq.). The resulting yellow solution was allowed to stir at room temperature for 3 hours, during which time the solution gradually turned to a deep green color. The reaction was diluted with CH_2Cl_2 (50 mL) washed with 2 N HCl (3 x 50 mL), saturated $NaHCO_3$ (50 mL), and brine. Drying over Na_2SO_4 was followed by concentration *in vacuo* and purification by column chromatography (2-5% EtOAc/hexanes eluent) to furnish a 1:1 mixture of diastereomeric bromoacetals **276** (1.62 g, 99% yield) as a colorless oil. FTIR (thin

film/NaCl) 2976 (m), 2952 (m), 1706 (s), 1257 ms), 1202 (s), 1028 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.32 (m, 10H), 5.26 (d, *J* = 12.7 Hz, 2H), 5.18 (d, *J* = 12.4 Hz, 2H), 4.92-4.90 (m, 3H), 4.79 (t, *J* = 5.4 Hz, 1H), 4.66 (app t, *J* = 1.8 Hz, 2H), 4.22-4.21 (m, 1H), 4.13-4,12 (m, 1H), 3.73-3.60 (m, 4H), 3.49-3.41 (m, 4H), 2.81 (d, *J* = 2.9 Hz, 1H), 2.72 (d, *J* = 2.4 Hz, 1H), 2.55-2.09 (m, 6H), 1.56 (s, 6H), 1.27 (t, *J* = 7.0 Hz, 3H), 1.24 (t, *J* = 6.8 Hz, 3H), 1.19 (s, 3H), 1.18 (s, 3H), 0.87 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 158.8, 158.6, 152.0, 151.9, 136.3, 128.5, 128.0, 127.9, 123.5, 123.3, 103.7, 103.3, 102.4, 99.8, 77.6, 75.9, 66.1, 66.0, 61.6, 61.3, 43.8, 43.7, 42.7, 40.3, 38.3, 38.2, 31.8, 31.7, 30.9, 30.8, 24.7, 24.6, 19.4, 19.3, 16.9, 16.5, 15.2, 15.1; HRMS (EI) *m/z* [calc'd for $C_{24}H_{31}BrO_4$(M+)].

Preparation of Acetals 277 and 278.



Acetals 277 and 278. A solution of bromoacetals **276** (1.10 g, 2.37 mmol, 1.0 eq.), Bu_3SnH (927 μL, 3.56 mmol, 1.5 eq.), and AIBN (428 mg, 2.61 mmol, 1.1 eq.) in benzene (237 mL) was degassed with argon for 30 minutes before being irradiated for 5 hours with a Tungsten 300 W bulb. At this point additional Bu_3SnH (231 μL, 0.89 mmol, 0.37 eq.) and AIBN (107 mg, 0.65 mmol, 0.27 eq.) were added and the reaction was irradiated for an additional 1 hour. The volatiles were removed *in vacuo* and the derived oil dissolved in Et_2O (300 mL). To this solution at room temperature was added

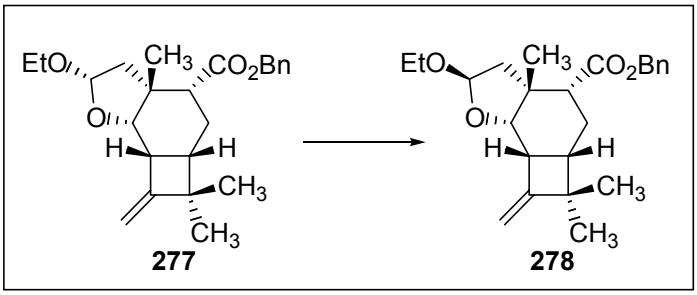
DBU (709 μL, 4.75 mmol, 2.0 eq.) which resulted in the immediate formation of a white precipitate. This suspension was filtered through a plug of silica gel which was subsequently washed well with Et_2O. Concentration provided a residue that was subjected to silica gel chromatography (2-10% EtOAc/hexanes eluent).

Acetal 278: The first compound to elute was acetal **278** (420 mg, 46% yield) as a colorless oil. FTIR (thin film/NaCl) 2955 (m), 1730 (s), 1146 (w), 918 (m), 747 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.34 (m, 5H), 5.16 (d, *J* = 12.2 Hz, 1H), 5.11 (d, *J* = 12.4 Hz, 1H), 5.04 (t, *J* = 5.4 Hz, 1H), 4.91 (d, *J* = 2.2 Hz, 1H), 4.87 (d, *J* = 2.6 Hz, 1H), 3.83 (dq, *J* = 7.1, 9.4 Hz, 1H), 3.77 (d, *J* = 5.9 Hz, 1H), 3.52 (dq, *J* = 7.1, 9.2 Hz, 1H), 3.15-3.11 (m, 1H), 2.37-2.06 (m, 4H), 1.88 (dd, *J* = 6.1, 13.9 Hz, 1H), 1.71-1.66 (m, 1H), 1.24 (s, 3H), 1.20 (t, *J* = 7.2, 3H), 1.19 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 159.5, 136.1, 128.6, 128.5, 128.1, 104.4, 103.3, 82.9, 66.1, 64.4, 49.5, 44.6, 43.0, 41.8, 41.5, 38.1, 29.9, 27.9, 21.0, 20.7, 15.2; HRMS (EI) *m/z* 384.2303 [calc'd for $C_{24}H_{32}O_4$ (M+) 384.2301].

Acetal 277: The second compound to elute was acetal **277** (322 mg, 35% yield) also as a colorless oil (combined 81% yield). FTIR (thin film/NaCl) 2955 (m), 1729 (s), 1453 (w), 912 (w), 738 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.35 (m, 5H), 5.17 (d, *J* = 12.2 Hz, 1H), 5.10-5.07 (m, 2H), 4.87 (d, *J* = 2.6 Hz, 1H), 4.80 (d, *J* = 1.9 Hz, 1H), 3.98 (d, *J* = 5.8 Hz, 1H), 3.65 (dq, *J* = 7.1, 10.0 Hz, 1H), 3.40 (dq, *J* = 7.1, 9.9 Hz, 1H), 3.16-3.11 (m, 1H), 2.24 (dd, *J* = 5.4, 13.8 Hz, 1H), 2.17-2.13 (m, 1H), 2.09 (dd, *J* = 2.4, 12.8 Hz, 1H), 1.77 (q, *J* = 12.6 Hz, 1H), 1.67-1.59 (m, 2H), 1.31 (s, 3H), 1.18 (s, 3H), 1.17 (t,

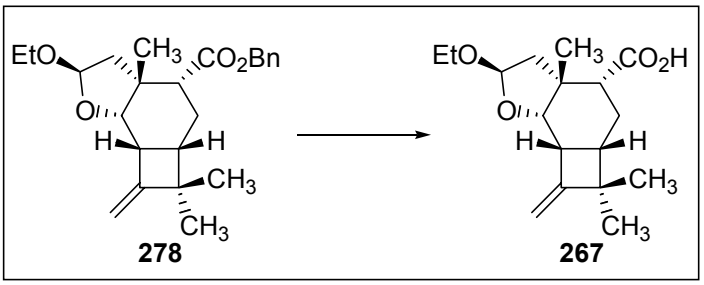
J = 6.8 Hz, 3H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 159.4, 136.0, 128.6, 128.3, 128.2, 104.3, 102.2, 81.3, 66.2, 62.4, 49.6, 44.5, 43.5, 42.2, 41.5, 37.2, 30.0, 27.4, 21.2, 21.1, 15.3; HRMS (EI) *m/z* 384.2299 [calc'd for $C_{24}H_{32}O_4$ (M+) 384.2301].

Equilibration of 277 to 278.



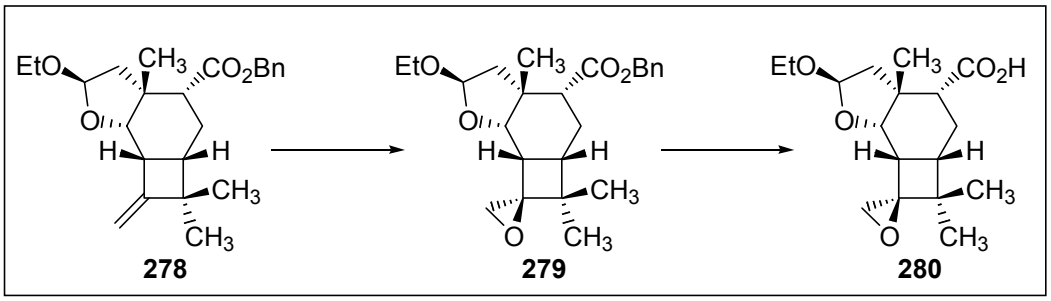
A solution of acetals **277** (340 mg, 0.885 mmol, 1.0 eq.) in EtOH (9.0 mL) was treated with CSA (30.8 mg, 0.132 mmol, 0.15 eq.) and allowed to stir at room temperature for 24 hours. The reaction was quenched with saturated $NaHCO_3$ (5 mL) and concentrated *in vacuo* to provide a thick white paste. This paste was diluted with H_2O (15 mL) and extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine, and dried over Na_2SO_4. Concentration and purification by silica gel chromatography (2-5% EtOAc/hexanes eluent) furnished acetal **278** (300 mg, 88% yield) as a colorless oil. The spectral data for acetal **278** is reported above.

Revised preparation of Acid 267.



Acid 267. A solution of ester **278** (1.1 g, 2.86 mmol, 1.0 eq.) in EtOH (38 mL) was treated with KOH (3 M, 38 mL, 40 eq.). The reaction was immersed into an oil bath and slowly heated to reflux. The reaction remained at that temperature for 1 hour before being cooled to room temperature, diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The remaining aqueous layer was acidified to pH 1 with 1 N HCl and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to provide acid **267** (686 mg, 81% yield) as a white solid. The spectral data for **267** can be found above.

Preparation of Epoxide 279.

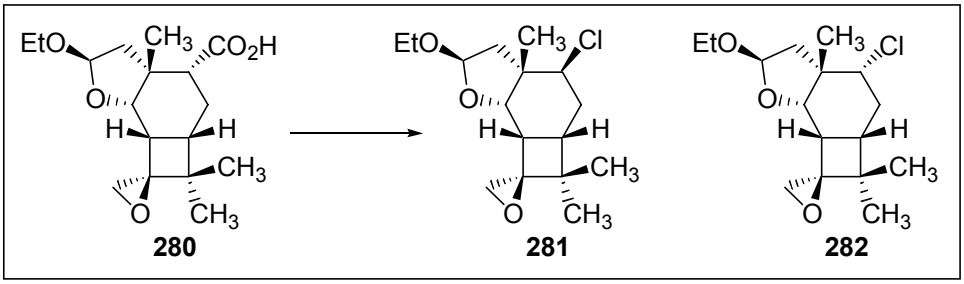


Epoxide 279. A solution of olefin **278** (410 mg, 1.07 mmol, 1.0 eq.) in acetone (10 mL) was treated with a solution of dimethyldioxirane (26 mL, 0.08 M in acetone, 2.0 eq.). The reaction was allowed to stir at room temperature until judged to be complete by

TLC (approx. 1 hour). The resulting epoxide was carried on crude, without concentration or purification. [An analytically pure sample of the epoxide could be obtained by absorption onto silica gel and purification by flash chromatography (40% EtOAc/hexanes eluent) to provide epoxide **279** as a colorless oil.] FTIR (thin film/NaCl) 2955 (m), 2929 (m), 2899 (m), 2868 (w), 1725 (s), 1453 (w), 1374 (w), 1170 (m), 1140 (m), 1102 (m), 981 (s), 909 (w), 740 (w), 694 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.33 (m, 5H), 5.18 (d, *J* = 12.2 Hz, 1H), 5.10 (d, *J* = 12.4 Hz, 1H), 5.09 (d, *J* = 2.4, Hz, 1H), 3.82 (d, *J* = 5.3 Hz, 1H), 3.62 (dq, *J* = 7.0, 9.8 Hz, 1H), 3.41 (dq, *J* = 7.4, 9.7 Hz, 1H), 2.77-2.74 (m, 2H), 2.68 (d, *J* = 4.2 Hz, 1H), 2.24-2.18 (m, 2H), 2.11 (dd, *J* = 2.6, 12.8 Hz, 1H), 1.81 (q, *J* = 12.7 Hz, 1H), 1.67 (ddd, *J* = 2.0, 7.3, 12.9 Hz, 1H), 1.62 (dd, *J* = 2.6 11.7 Hz, 1H), 1.27 (s, 3H), 1.17 (t, *J* = 6.9, 3H), 1.08 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8, 136.3, 128.9, 128.8, 128.7, 102.5, 80.3, 67.4, 66.7, 63.0, 50.1, 49.9, 44.3, 43.0, 41.4, 39.5, 37.3, 27.4, 25.7, 21.5, 19.6, 15.7; HRMS (EI) *m/z* 400.2256 [calc'd for $C_{24}H_{32}O_5$ (M+) 400.2250]. The derived epoxide in solution was advanced by the direct addition of Pd/C (15 wt.%, 410 mg). The suspension was purged with hydrogen for 5 minutes and kept under 1 atm of hydrogen for an additional 1 hour. Filtration over celite was followed by washing with EtOAc and concentration to provide acid **280** (330 mg, 100% yield) judged to be 90% pure by ^{1}H NMR. An analytically pure sample of **280** could be obtained by chromatography (30% EtOAc/hexanes eluent) to afford acid **280** as a colorless oil. FTIR (thin film/NaCl) 3156 (b), 2958 (s), 2930 (s), 2873 (s), 1729 (m), 1693 (s), 1453 (w), 1373 (w), 1106 (m), 977 (m), 912 (m), 735 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 (d, *J* = 3.2 Hz, 1H), 3.85 (d, *J* = 5.2 Hz, 1H), 3.63 (dq, *J* = 7.0, 9.5 Hz, 1H), 3.42 (dq, *J* = 7.1, 9.5 Hz, 1H), 2.78 (app. d, *J* = 5.1 Hz,

2H), 2.69 (d, J = 4.6 Hz, 1H), 2.31 (dd, J = 5.8, 14.2 Hz, 1H), 2.22 (dt, J = 7.5, 11.6 Hz, 1H), 2.09 (dd, J = 2.6, 12.6 Hz, 1H), 1.70-167 (m, 3H), 1.31 (s, 3H), 1.18 (t, J = 7.6, 3H), 1.08 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1, 102.0, 79.8, 67.1, 62.7, 49.5, 49.4, 44.0, 42.5, 41.0, 38.9, 36.8, 26.8, 25.3, 20.8, 19.2, 15.3; HRMS (EI) *m/z* 309.1706 [calc'd for $C_{17}H_{26}O_5$ (M+) 309.1702].

Preparation of Chlorines 281 and 282.

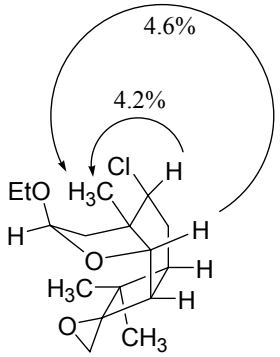


Chlorines 281 and 282. A solution of acid **280** (75 mg, 0.24 mmol, 1.0 eq.), 2-mercapto-pyridine-*N*-oxide (**236**) (38 mg, 0.30 mmol, 1.25 eq.) and DMAP (9 mg, 0.07 mmol, 0.3 eq.) in CCl_4 (5 mL) was degassed with argon for 45 minutes. This solution was then added dropwise via cannula addition over 10 minutes to a thoroughly degassed suspension of EDC•HCl (93 mg, 0.48 mmol, 2.0 eq.) in CCl_4 (1 mL). The reaction, which quickly became deep yellow in color, was maintained under an argon atmosphere. Stirring continued overnight, leading to a colorless solution containing a white precipitate. Silica gel was added directly to the reaction mixture which was followed by concentration and purification by flash chromatography.

Chlorine 282: The first compound to elute was epoxide **282** (25 mg, 34% yield) as a white solid. FTIR (thin film/NaCl) 2963 (b), 2924 (m), 2874 (m), 1557 (w), 1455 (w),

1105 (w), 1059 (m), 982 (w), 924 (w), 844 (w) cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 4.80 (d, *J* = 5.2 Hz, 1H), 3.66 (d, *J* = 5.2 Hz, 2H), 3.44-3.36 (m, 1H), 3.27 (dd, *J* = 2.6, 12.7 Hz, 1H), 3.15-3.07 (m, 1H), 2.62 (d, *J* = 4.7 Hz, 1H), 2.58-2.52 (m, 2H), 2.37 (dd, *J* = 5.3, 11.0 Hz, 1H), 1.96-1.70 (m, 2H), 1.57-1.51 (m, 1H), 1.09 (s, 6H), 1.02 (t, *J* = 7.1 Hz, 3H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 101.9, 80.3, 67.8, 67.7, 62.3, 49.3, 46.0, 43.5, 41.2, 40.6, 36.4, 28.9, 25.8, 25.2, 19.3, 15.3; HRMS (EI) *m/z* 300.1496 [calc'd for $C_{16}H_{25}ClO_3$ (M+) 300.1492].

NOE enhancements
^{1}H NMR 500 MHz, 1:1 C_6D_6:$CDCl_3$

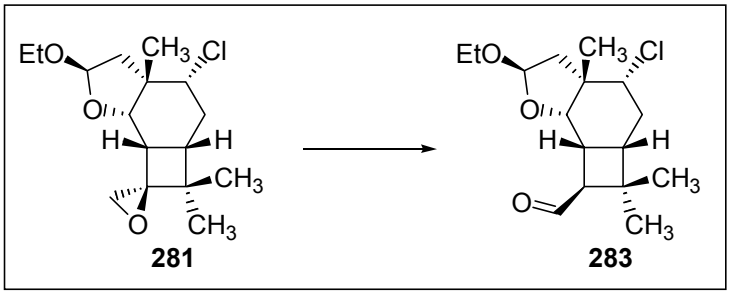


281

Chlorine 281: The second compound to elute was epoxide **282** (16 mg, 22% yield) as a colorless oil (combined yield 56% yield). FTIR (thin film/NaCl) 3048 (b), 2996 (b), 2993 (w), 1568 (s), 1448 (s), 1418 (s), 1370 (w), 1112 (m), 1038 (m), 986 (m), 799 (s), 754 (s), 728 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.09 (d, *J* = 4.1 Hz, 1H), 4.18 (app dd, *J* = 5.5, 8.9 Hz, 1H), 3.97 (d, *J* = 7.7 Hz, 1H), 3.66 (dq, *J* = 7.0, 9.8 Hz, 1H), 3.39 (dq, *J* = 6.8, 9.6, 1H), 3.30 (dd, *J* = 7.6, 9.9 Hz, 1H), 3.06 (d, *J* = 8.6 HZ, 1H), 2.64 (d, *J* = 5.4 Hz, 1H), 2.29-2.25 (m, 1H), 2.02-1.95 (m, 4H), 1.31 (s, 3H), 1.19 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H), 0.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 101.7, 81.7, 67.2, 66.8, 62.5, 48.5,

48.3, 44.7, 41.3, 36.8, 35.6, 28.7, 25.3, 21.8, 19.6, 15.2; HRMS (EI) *m/z* 300.1496 [calc'd for $C_{16}H_{25}ClO_3$ (M+) 300.1492].

Preparation of Aldehyde 283.



Aldehyde 283. To a solution of epoxide **281** (25 mg, 0.083 mmol, 1.0 eq.) in CH_2Cl_2 (3 mL) cooled to –78 ºC was added $BF_3{\cdot}OEt_2$ (16 µL, 0.12 mmol, 1.5 eq.) over 30 seconds. The resulting solution was allowed to stir for 30 minutes before being quenched with silica gel and purified by silica gel chromatography (20% EtOAc/hexanes eluent) to provide aldehyde **283** (6.3 mg, 25% yield) as a colorless oil. FTIR (thin film/NaCl) 2955 (m), 2931 (m), 1716 (s), 1455 (m), 1114 (m), 1050 (s), 990 (s), 9111 (s), 748 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.86 (d, *J* = 1.0 Hz, 1H), 5.19 (d, *J* = 5.2 Hz, 1H), 3.97 (d, *J* = 5.7 Hz, 1H), 3.72-3.62 (m, 2H), 3.45 (dq, *J* = 7.0, 9.9 Hz, 1H), 3.29 (dt, *J* = 1.2, 6.1 Hz, 1H), 3.03 (dt, *J* = 6.0, 10.6 Hz, 1H), 2.61 (dd, *J* = 5.6, 14.1 Hz, 1H), 2.29-2.21 (m, 1H), 3.98 (q, *J* = 12.6 Hz, 1H), 1.79-1.73 (m, 2H), 1.30 (s, 6H), 1.27 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.3, 101.9, 81.1, 67.5, 62.3, 54.8, 46.3, 43.7, 42.8, 29.1, 27.0, 26.4, 24.6, 15.2; HRMS (EI) *m/z* 300.1492 [calc'd for $C_{16}H_{25}ClO_3$ (M+) 300.1492].

4.7 Notes and References.

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(5) The stereochemistry of **233** was not confirmed, but is consistent with the inversion mechanism often observed in palladium-mediated allylic substitutions involving "hard" nucleophile. See Refs. 7 and 8.

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reaction of lithium dimethylcuprate(I) with 10-methyl-δ-1,9-2-octalone", Bertz, S. H.; Smith, R. A. J., *Journal of the American Chemical Society* **1989**, *111*, 8276-8277.

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(14) "Mechanism of $LiMe_2Cu$ addition to conjugated enones", Ruden, R. A.; Litterer, W. E., *Tetrahedron Letters* **1975**, 2043-2044.

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(25) This ratio was obtained regardless of the diastereomeric purity of the starting acid.

(26) The use of a diastereomeric mixture of acids **241**, epimeric at C(13) did not effect the diastereoselectivity observed in the chlorinative decarboxylation. The same ratio of products was obtained when a single epimer of **241** was carried through the reaction sequence.

(27) The relative stereochemistry of both **242** and **243** was deduced using NOE enhancements.

(28) Anilide **246** was not fully characterized and its structure was assigned on the basis of its ^{1}H NMR spectrum, which was fully consistent with the structure drawn.

(29) The diastereoselectivity observed in the epoxidation was >15:1.

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APPENDIX SEVEN: SPECTRA RELEVANT TO CHAPTER FOUR

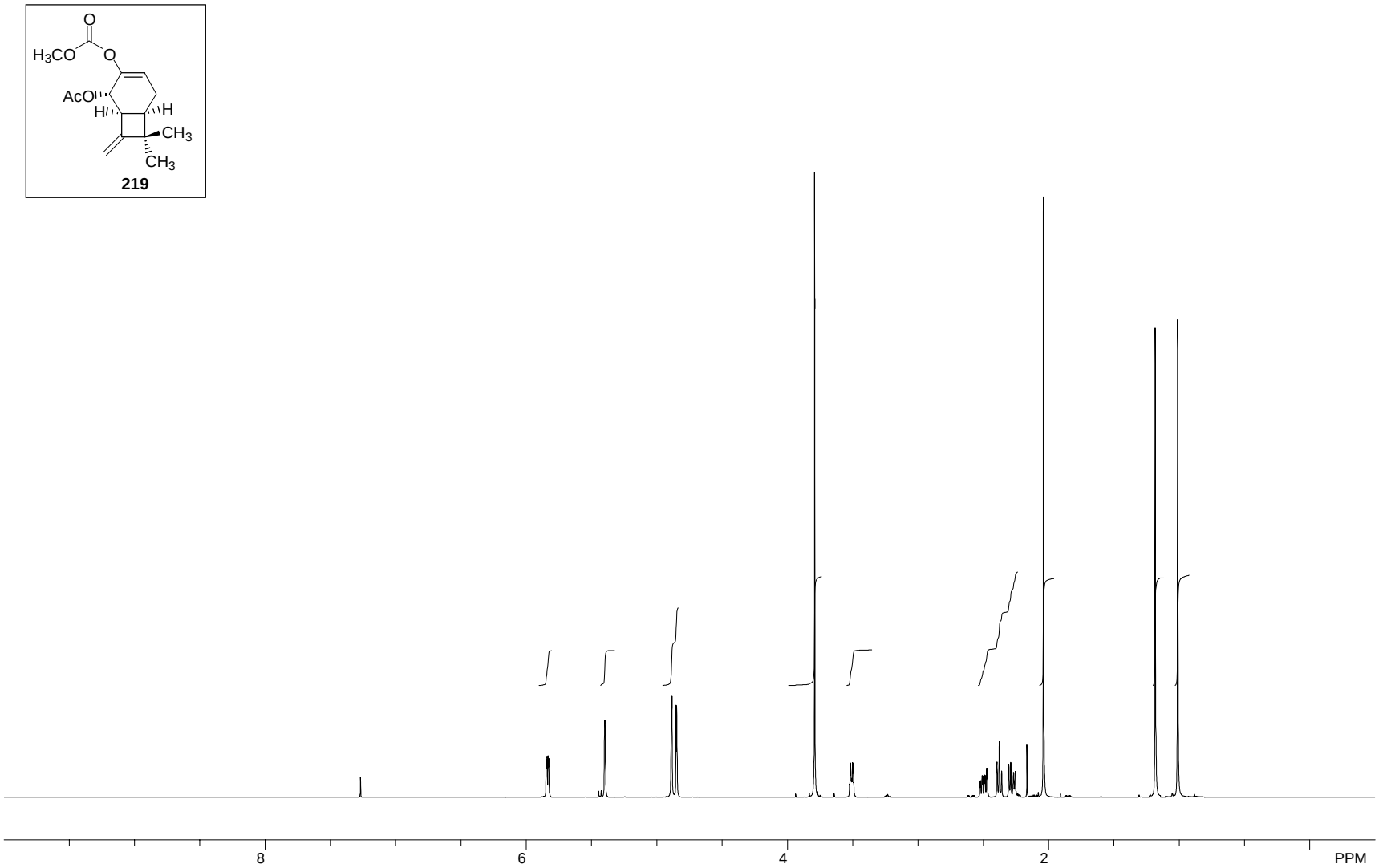


Figure A.7.1 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **219**.

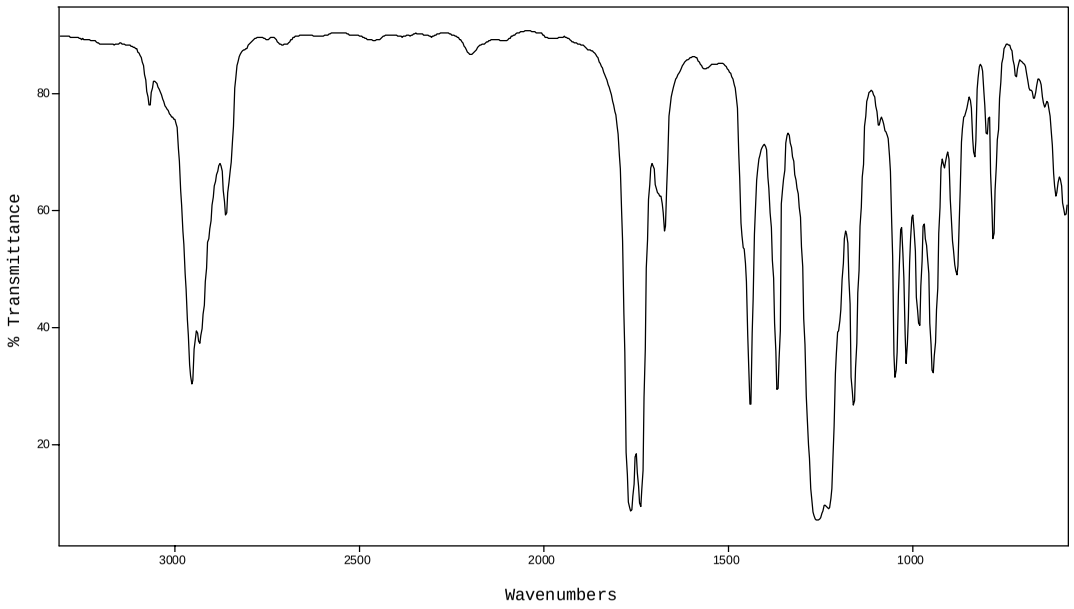


Figure A.7.2 FTIR Spectrum (thin film/NaCl) of Compound **219**.

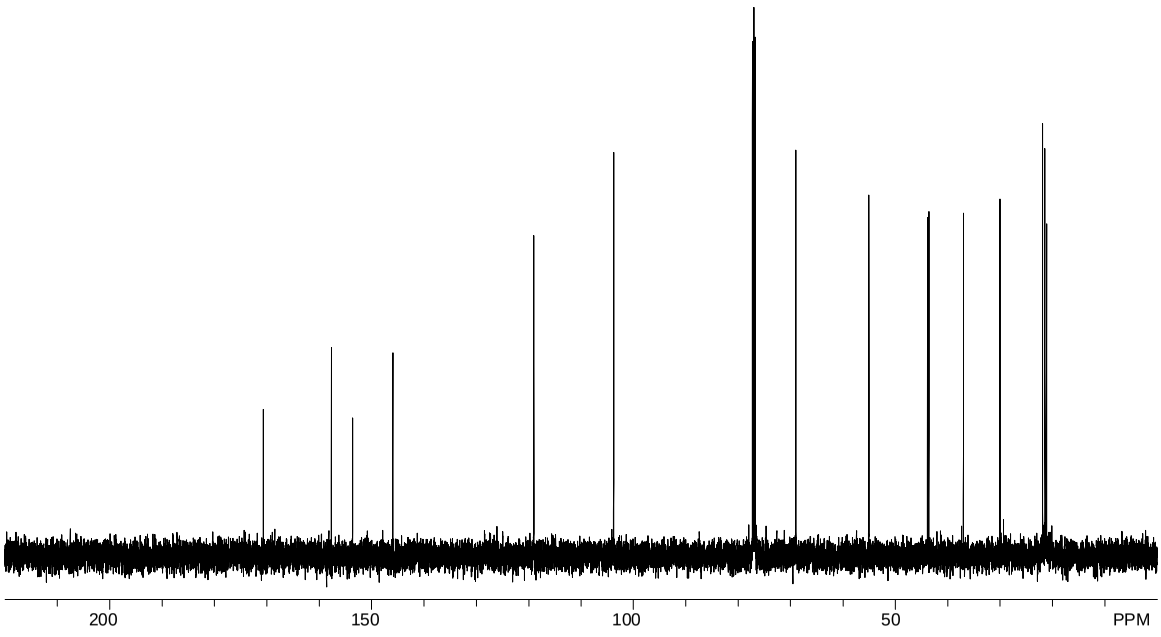


Figure A.7.3 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **219**.

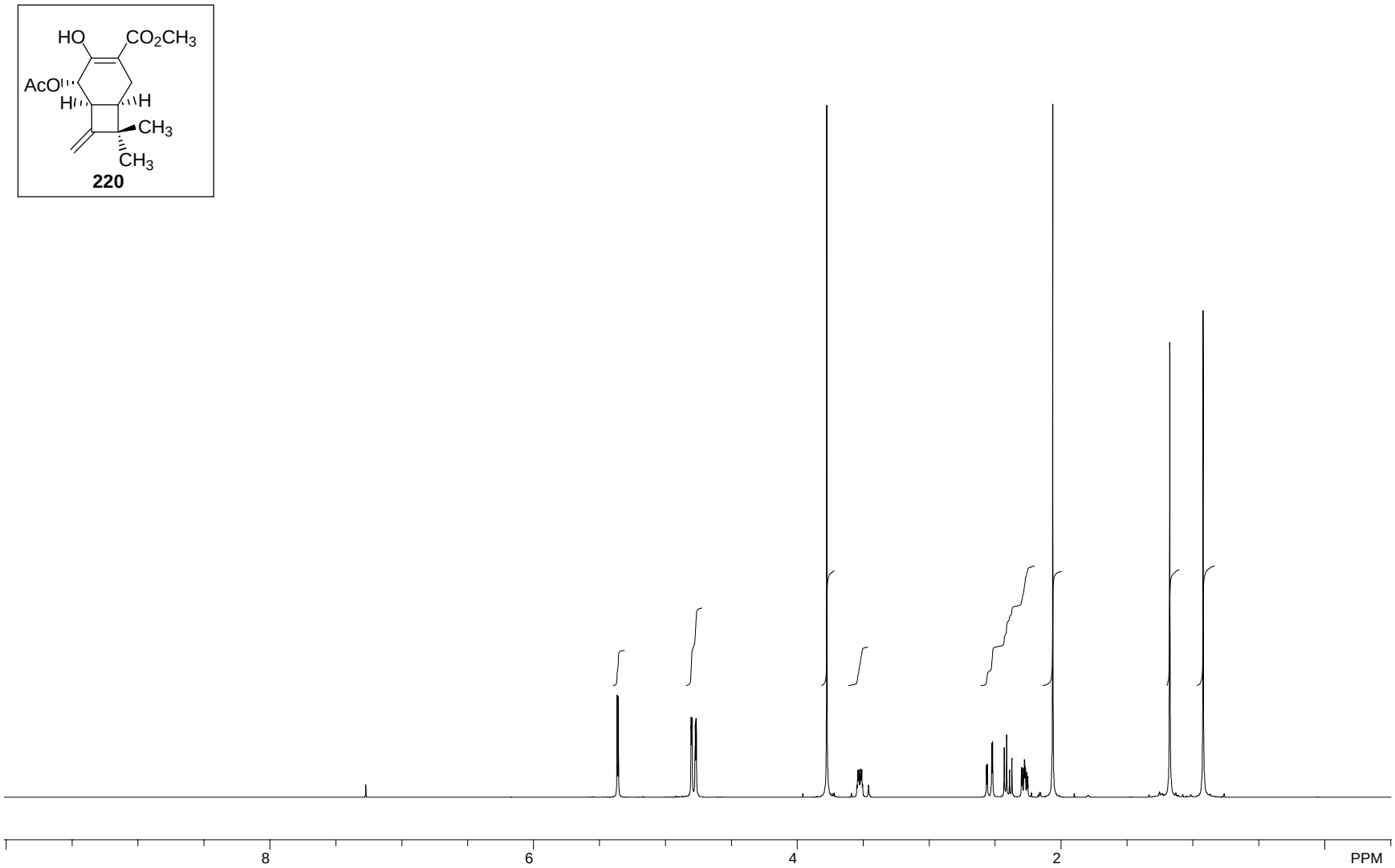


Figure A.7.4 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **220**.

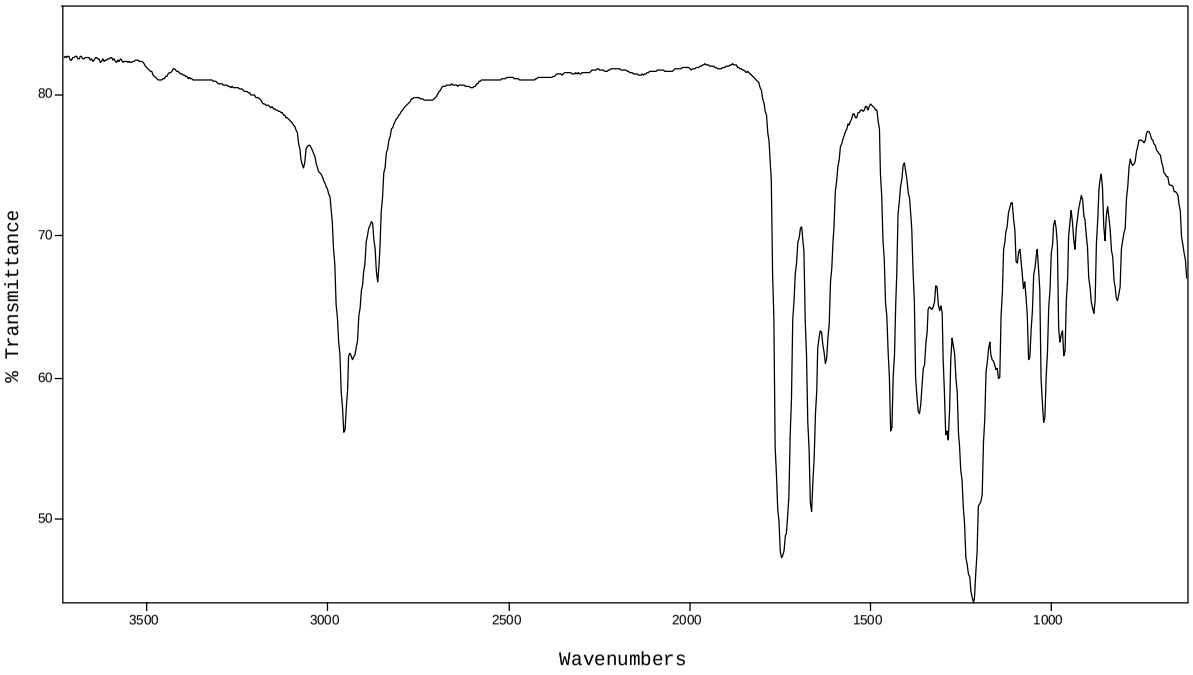


Figure A.7.5 FTIR Spectrum (thin film/NaCl) of Compound **220**.

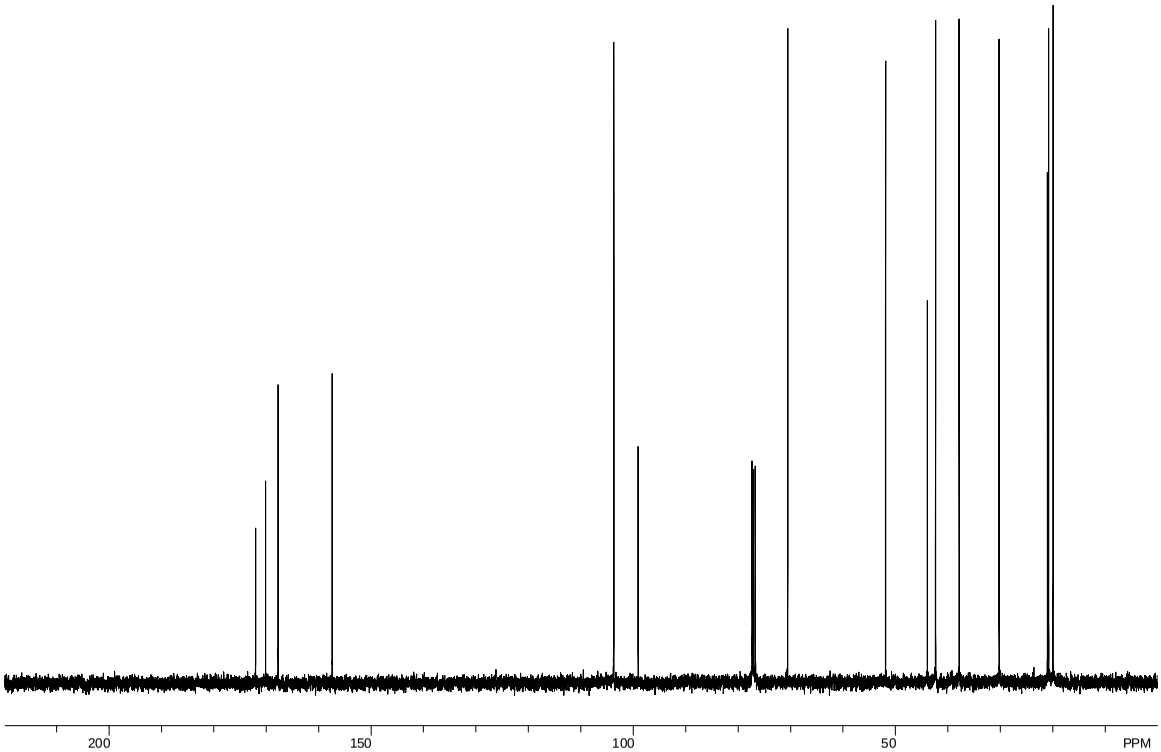


Figure A.7.6 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **220**.

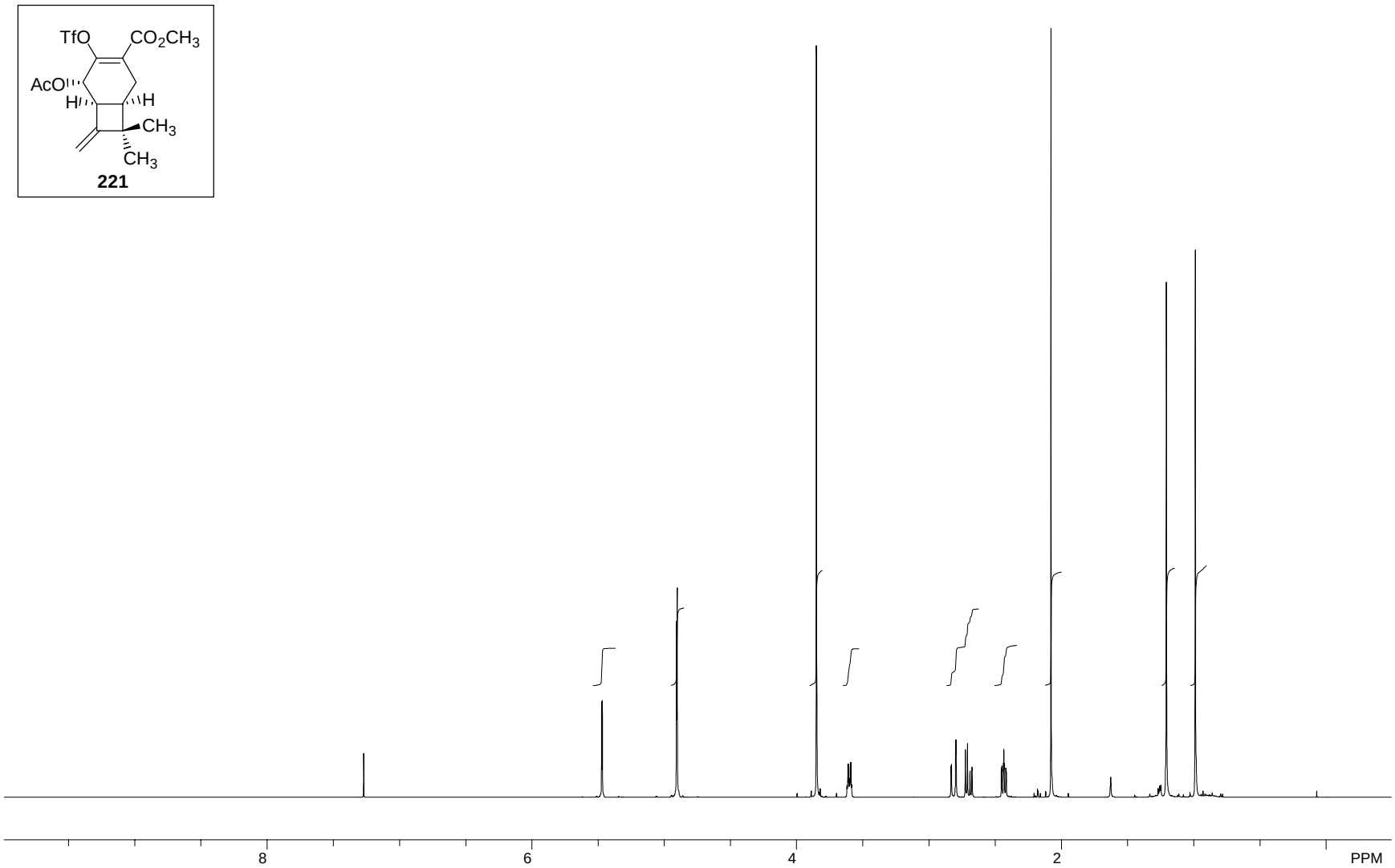


Figure A.7.7 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **221**.

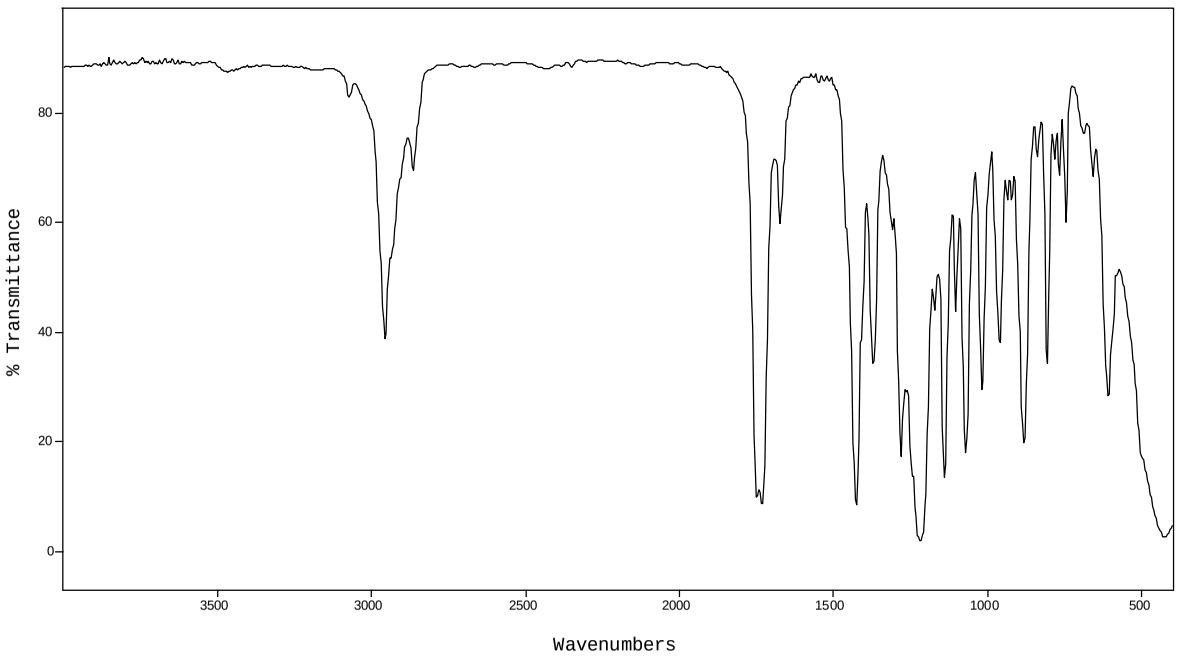


Figure A.7.8 FTIR Spectrum (thin film/NaCl) of Compound **221**.

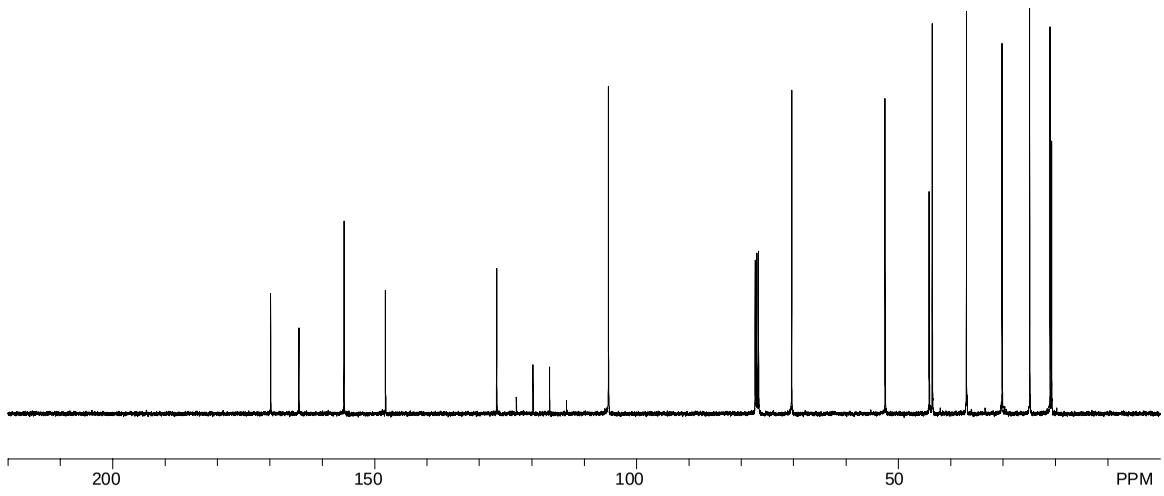


Figure A.7.9 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **221**.

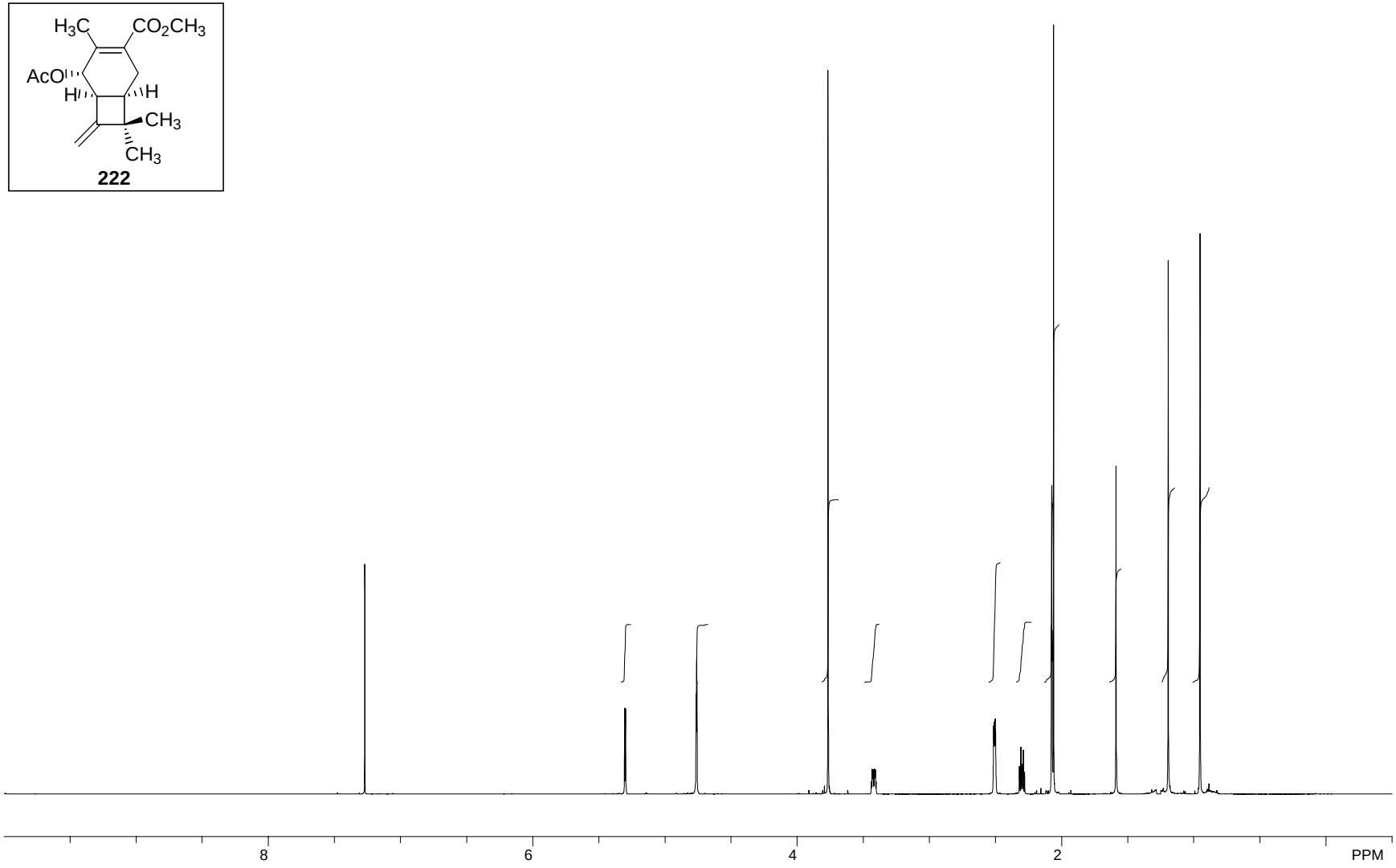


Figure A.7.10 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **222**.

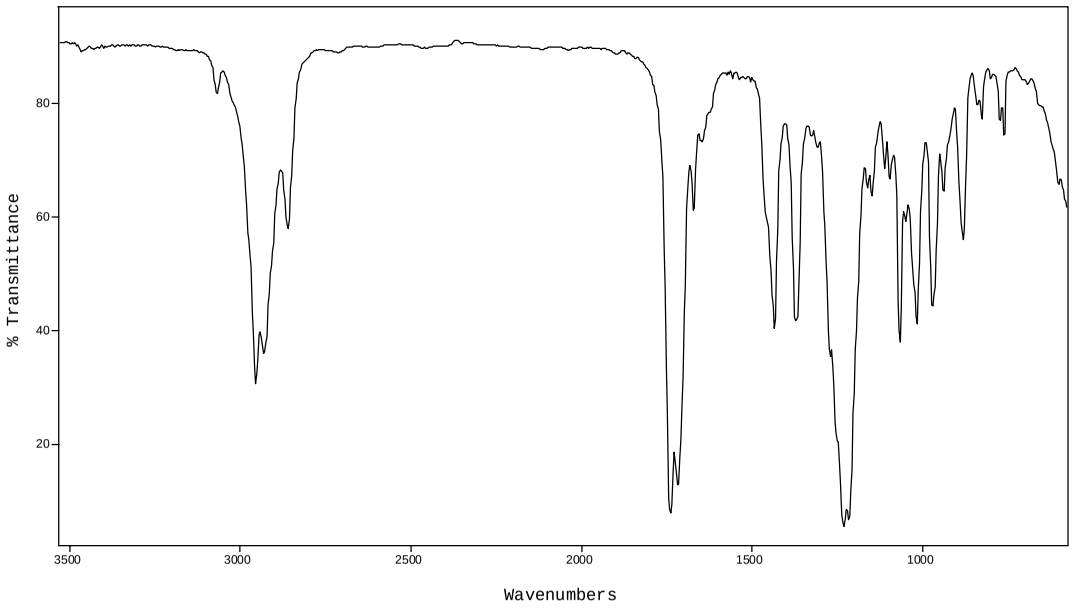


Figure A.7.11 FTIR Spectrum (thin film/NaCl) of Compound **222**.

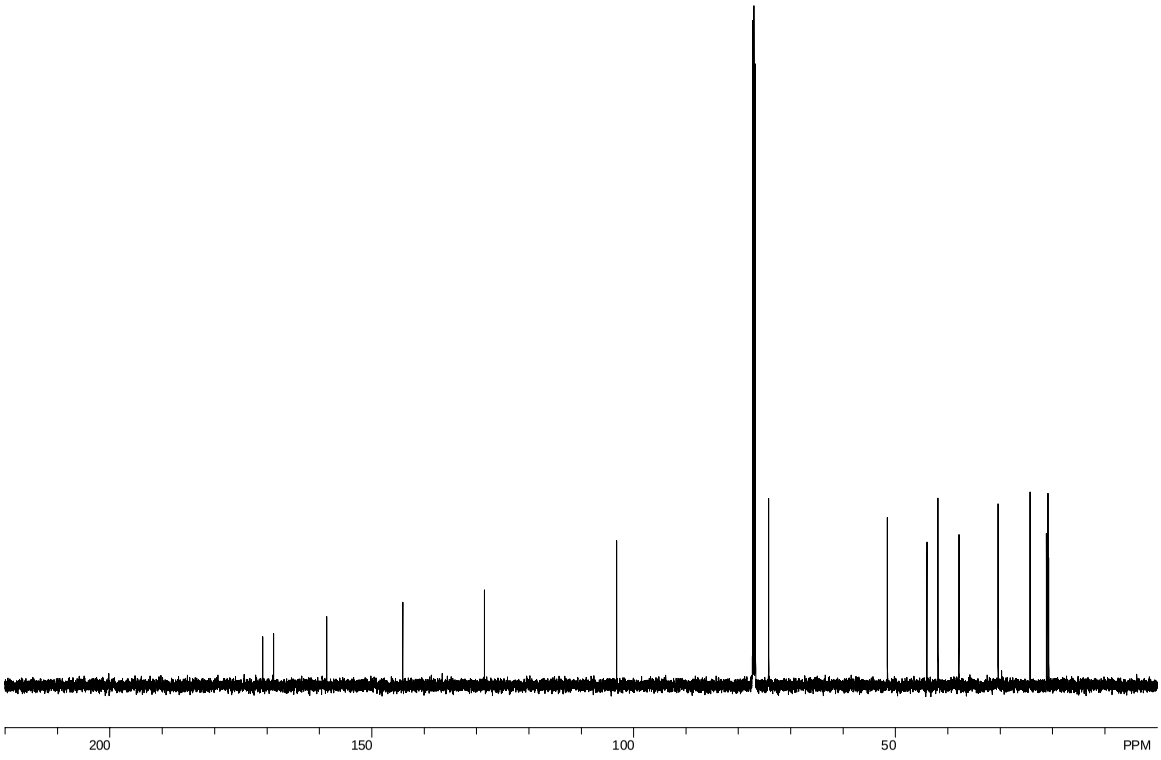


Figure A.7.12 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **222**.

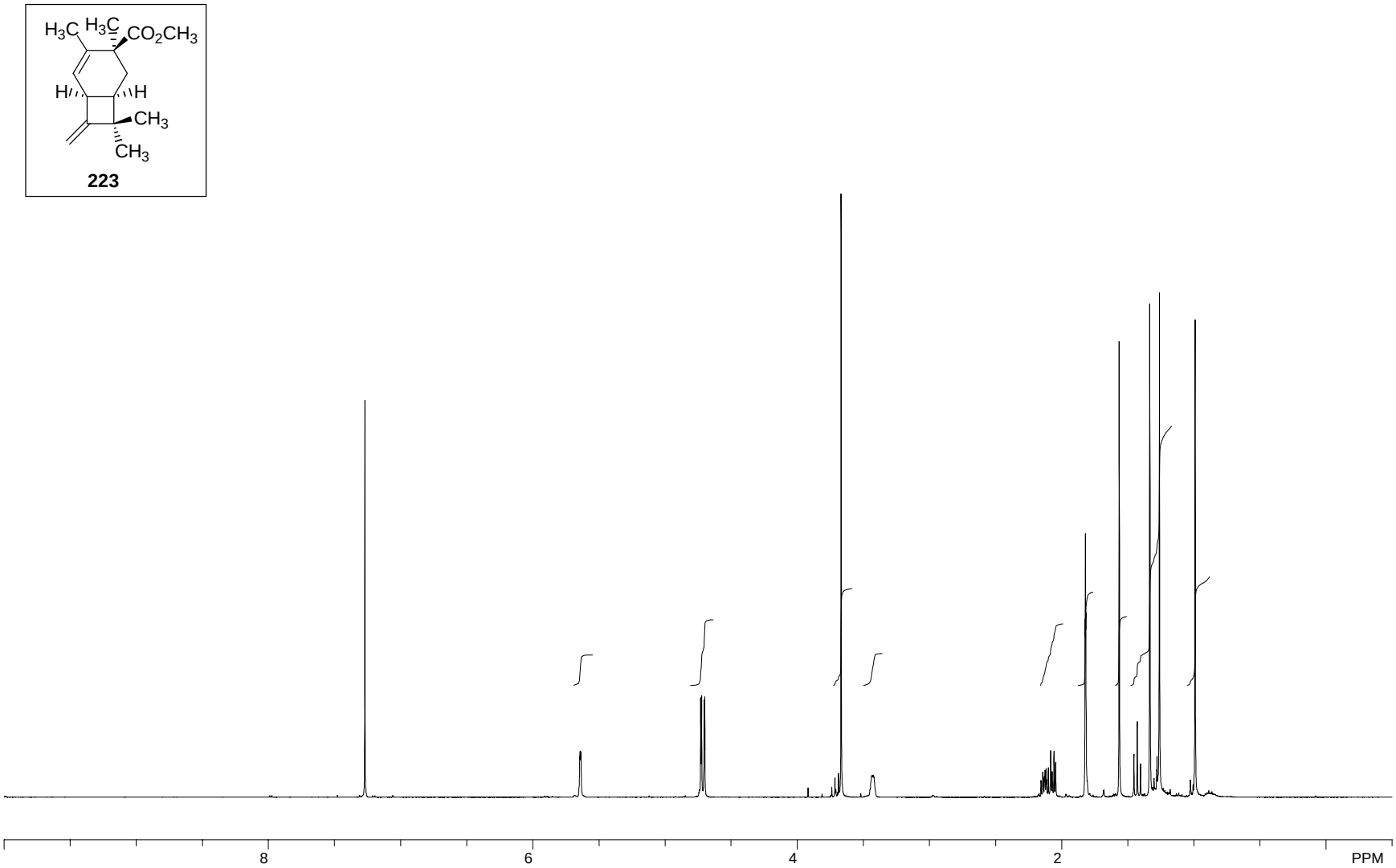


Figure A.7.13 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **223**.

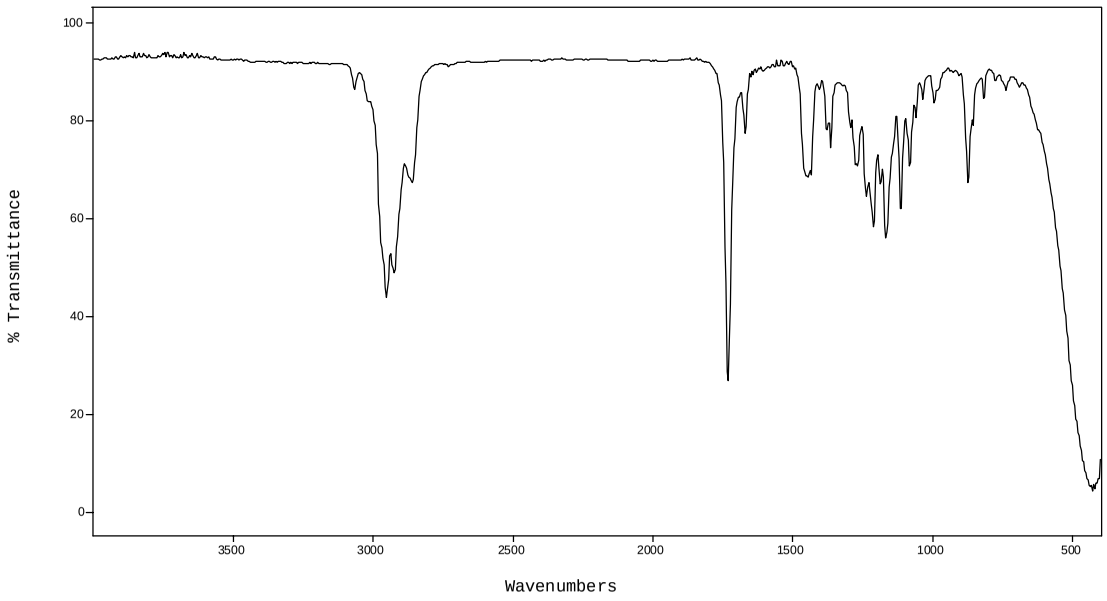


Figure A.7.14 FTIR Spectrum (thin film/NaCl) of Compound **223**.

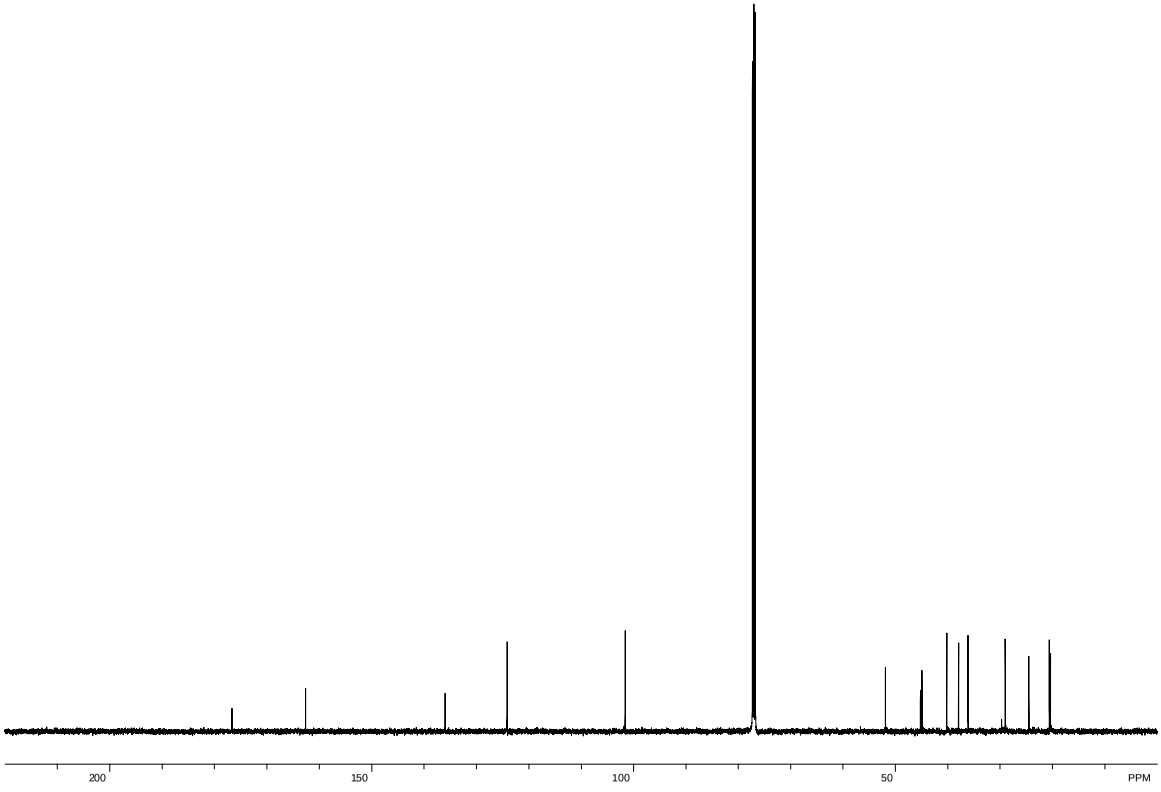


Figure A.7.15 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **223**.

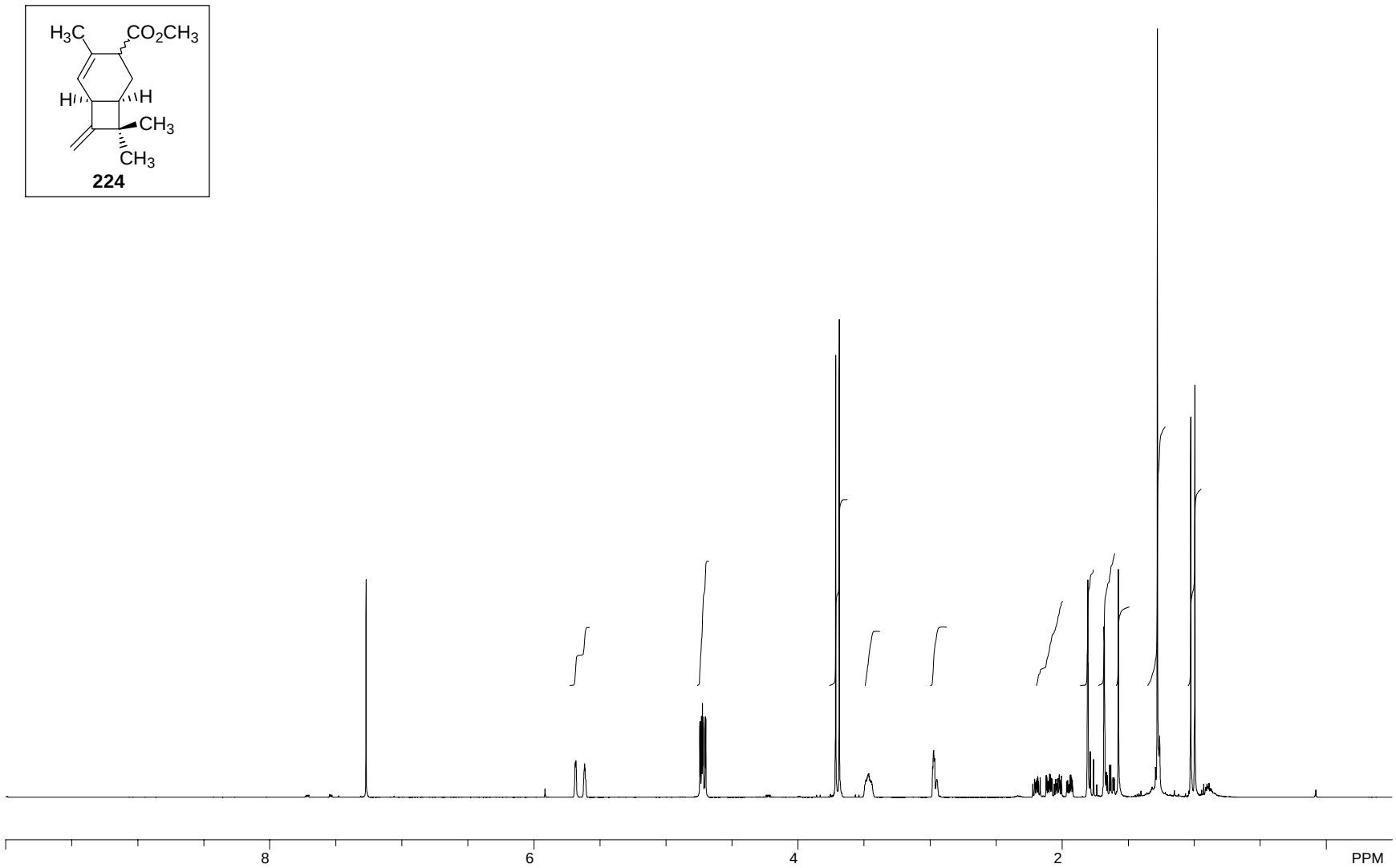


Figure A.7.16 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **224**.

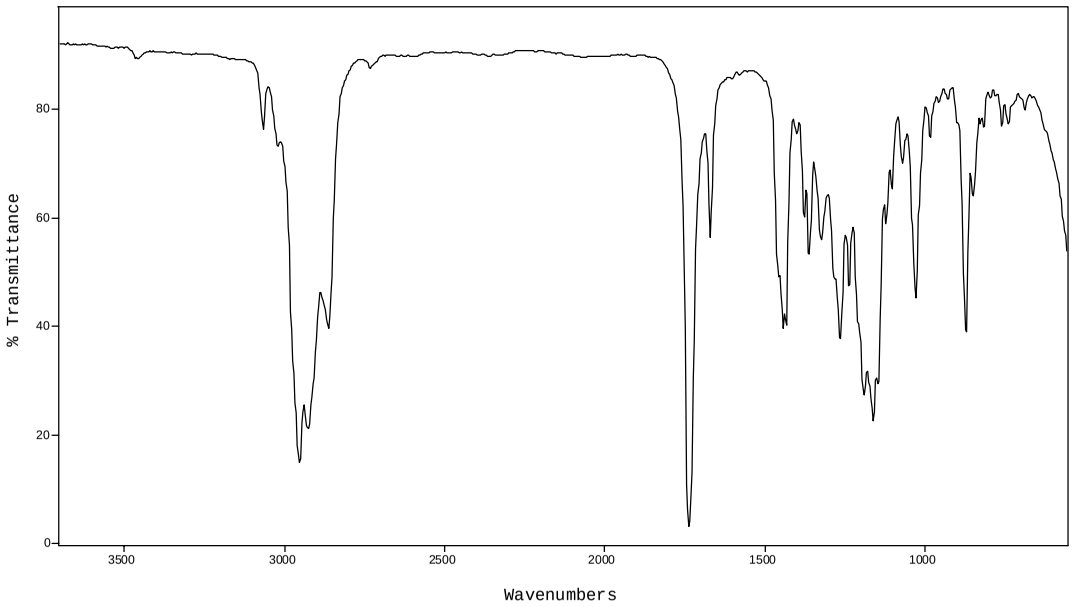


Figure A.7.17 FTIR Spectrum (thin film/NaCl) of Compound **224**.

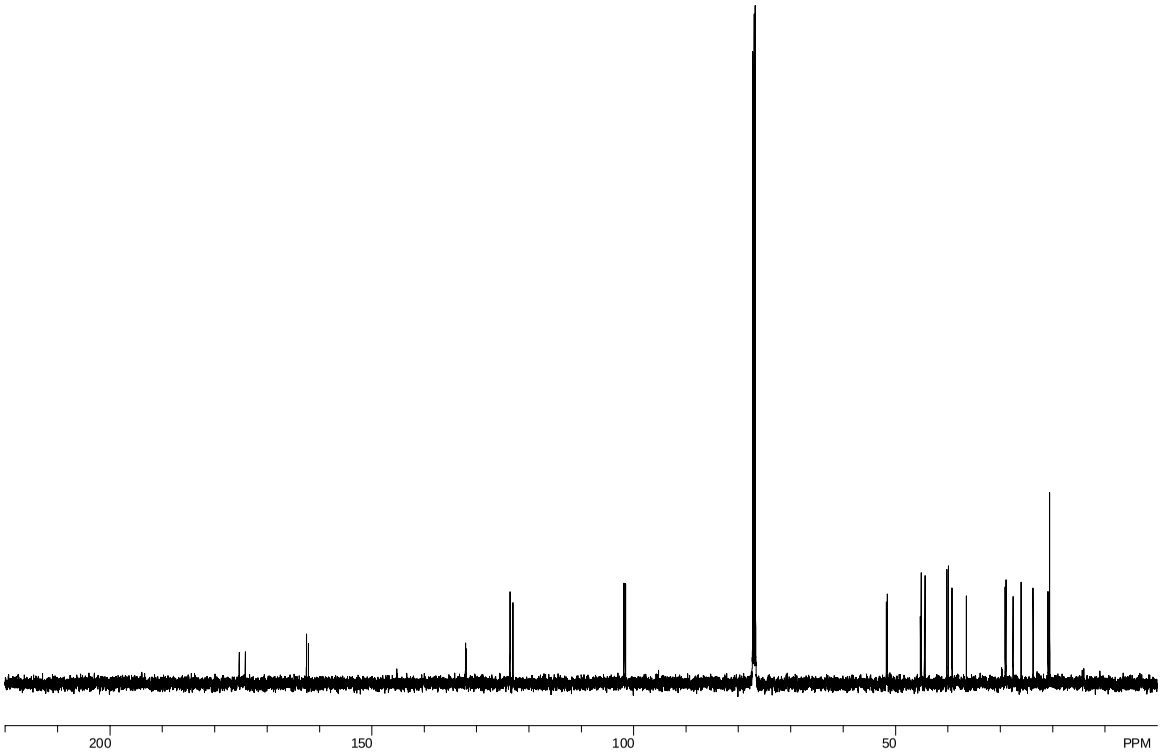


Figure A.7.18 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **224**.

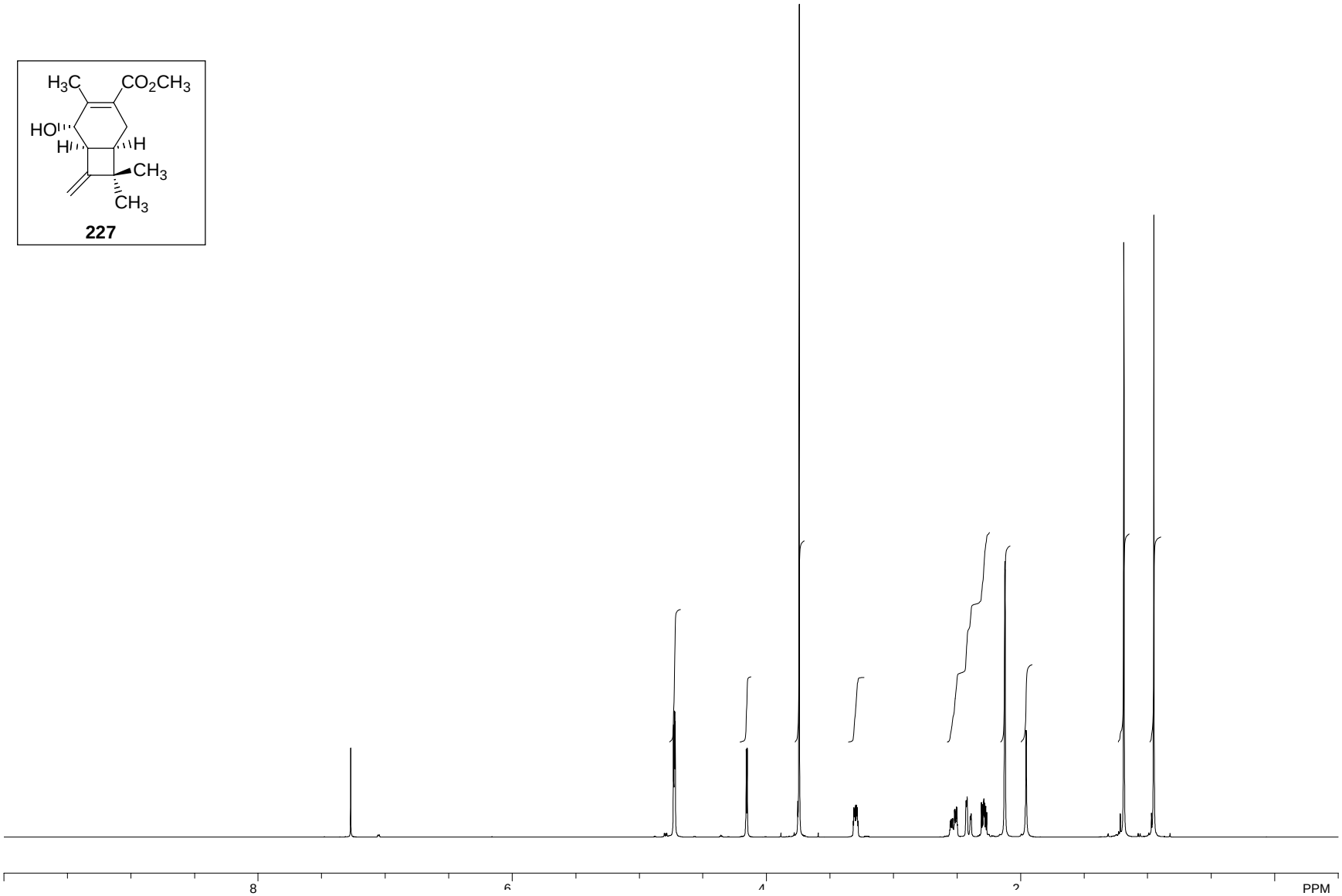


Figure A.7.19 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **227**.

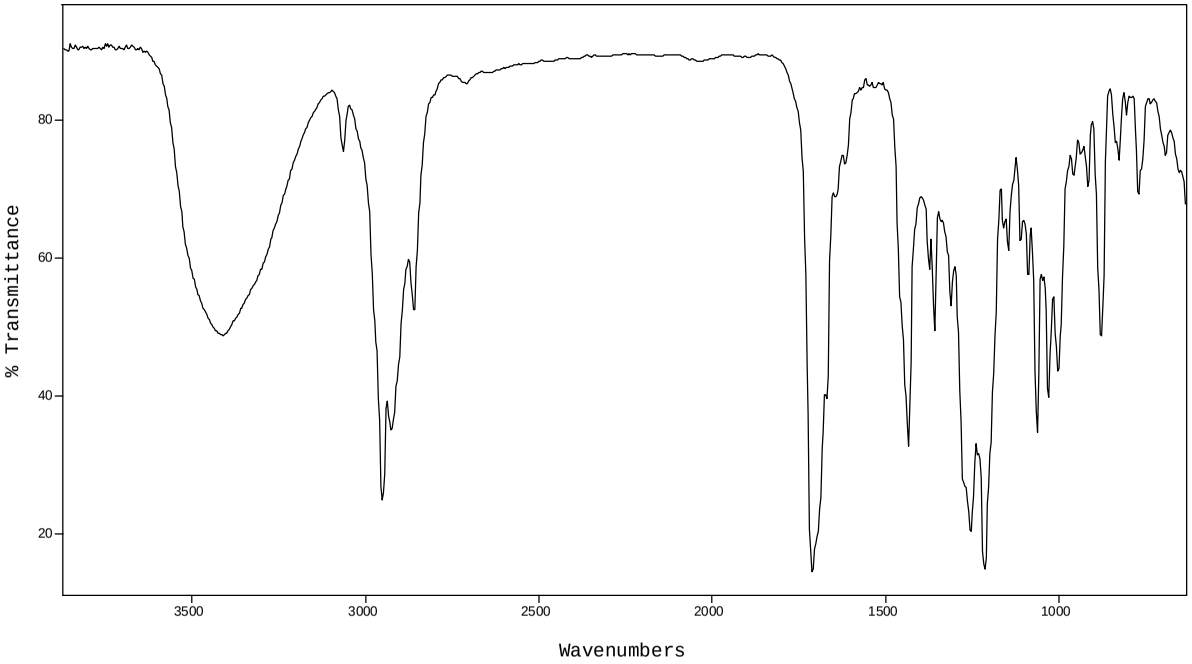


Figure A.7.20 FTIR Spectrum (thin film/NaCl) of Compound **227**.

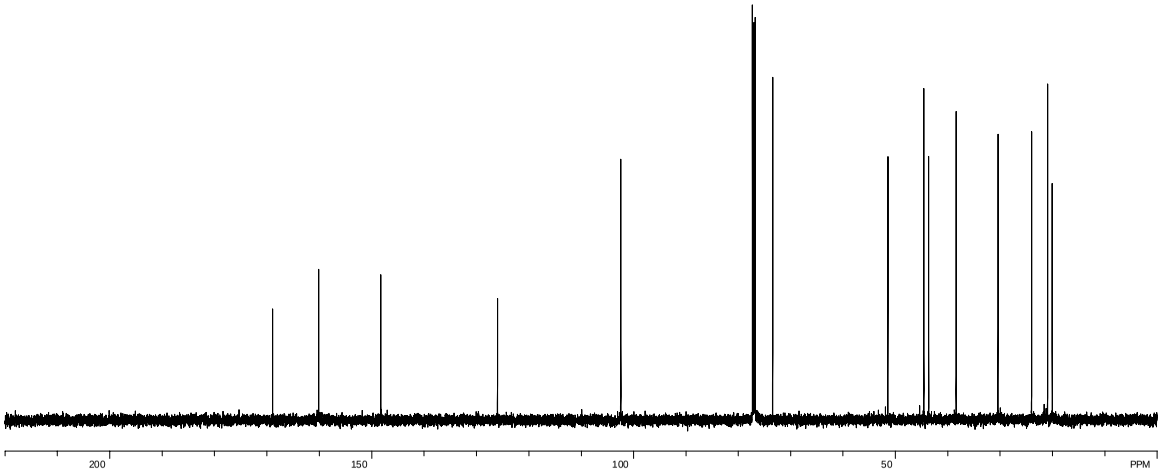


Figure A.7.21 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **227**.

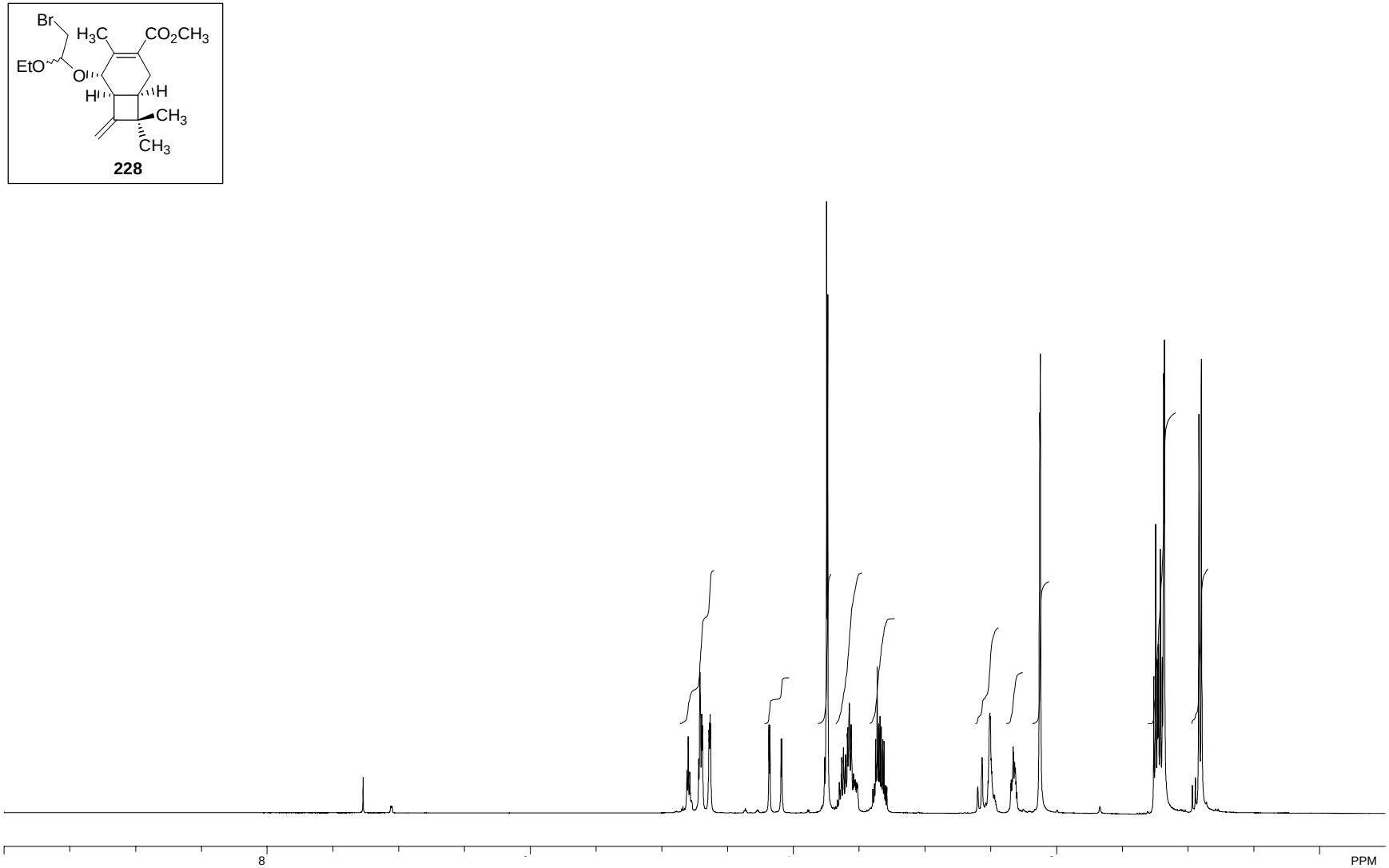


Figure A.7.22 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **228**.

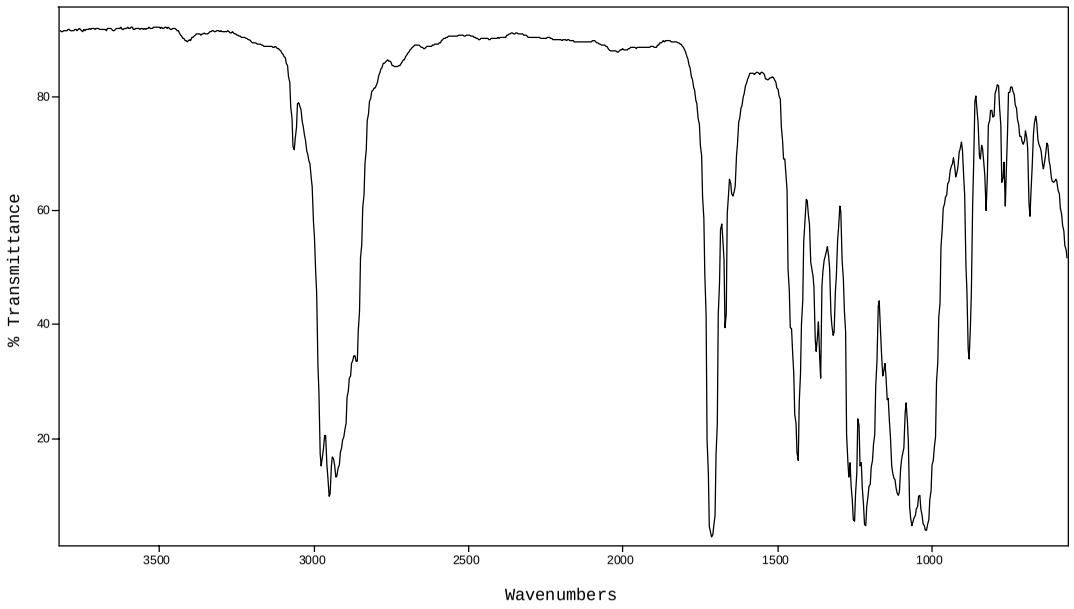


Figure A.7.23 FTIR Spectrum (thin film/NaCl) of Compound **228**.

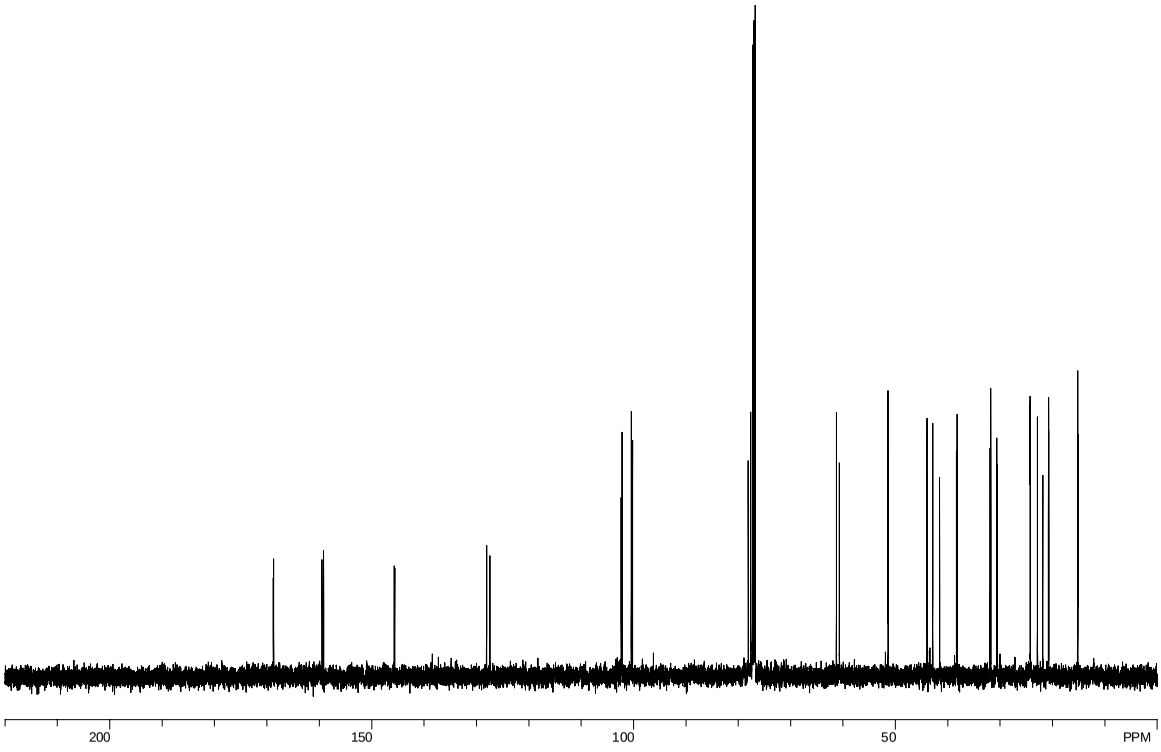


Figure A.7.24 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **2228.**

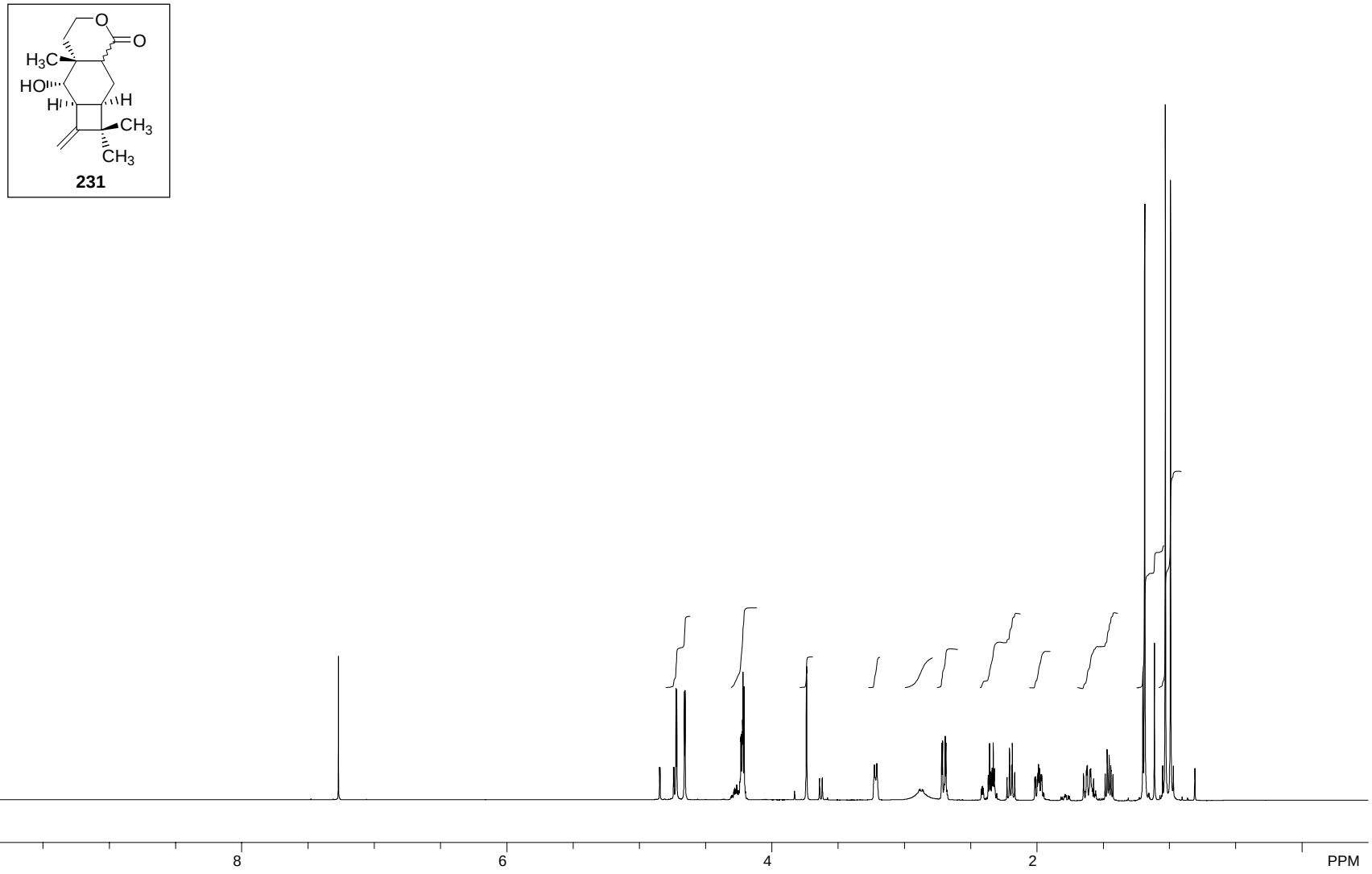


Figure A.7.25 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **231**.

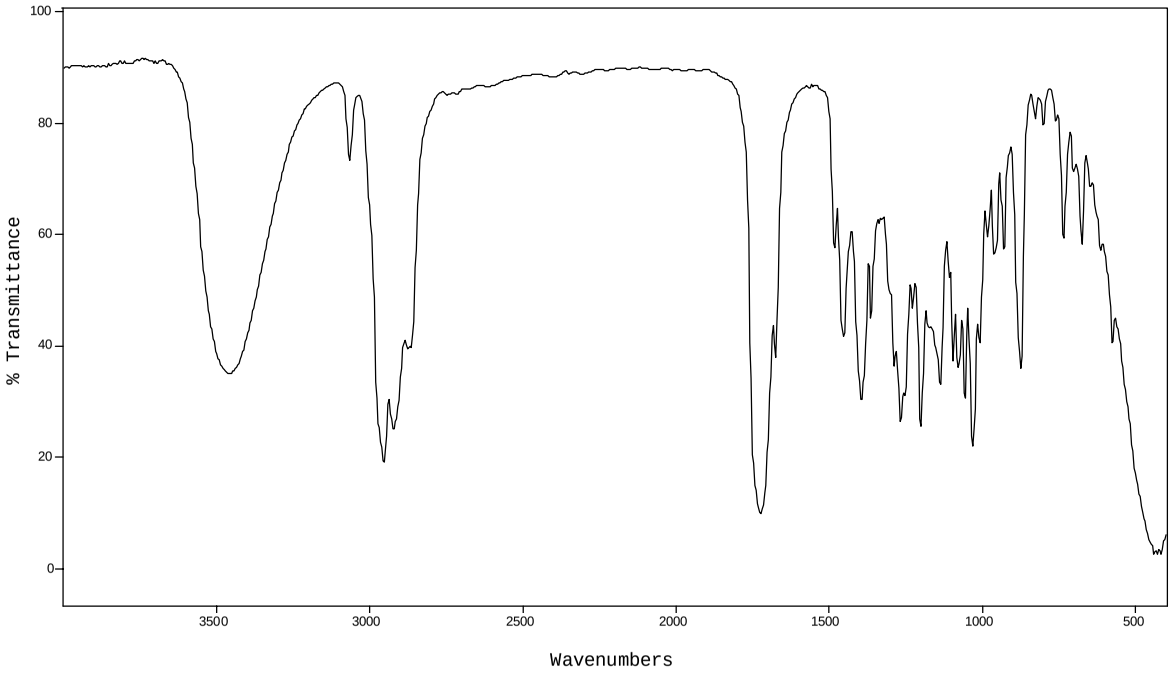


Figure A.7.26 FTIR Spectrum (thin film/NaCl) of Compound **231**.

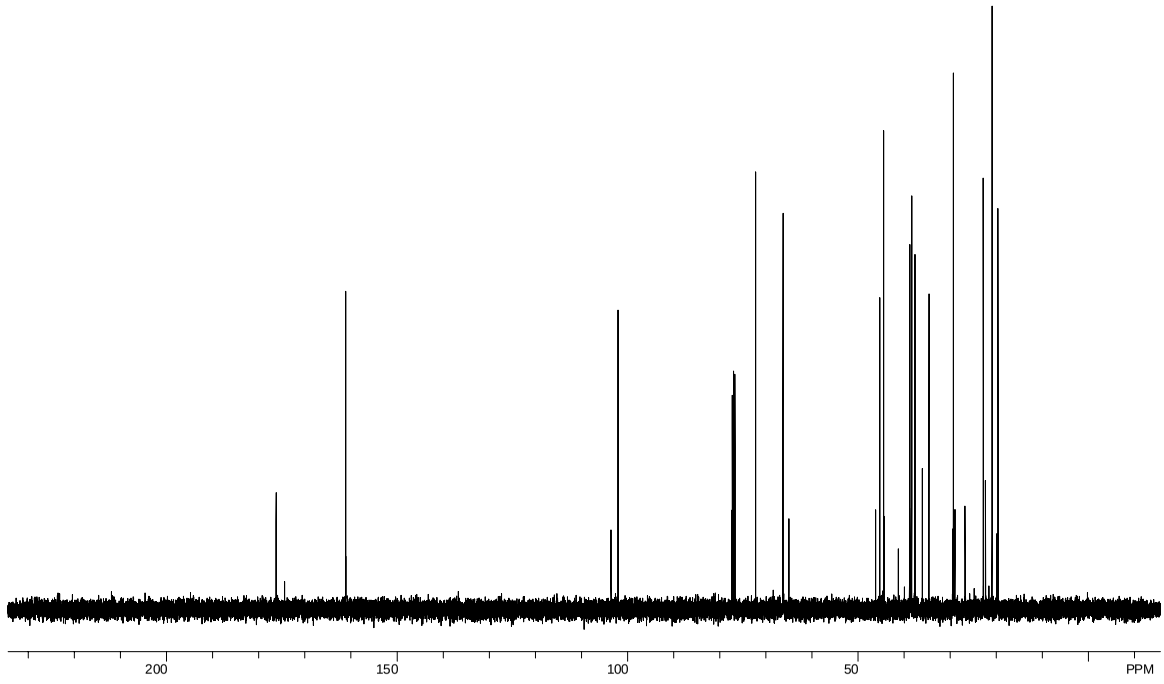


Figure A.7.27 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **231**.

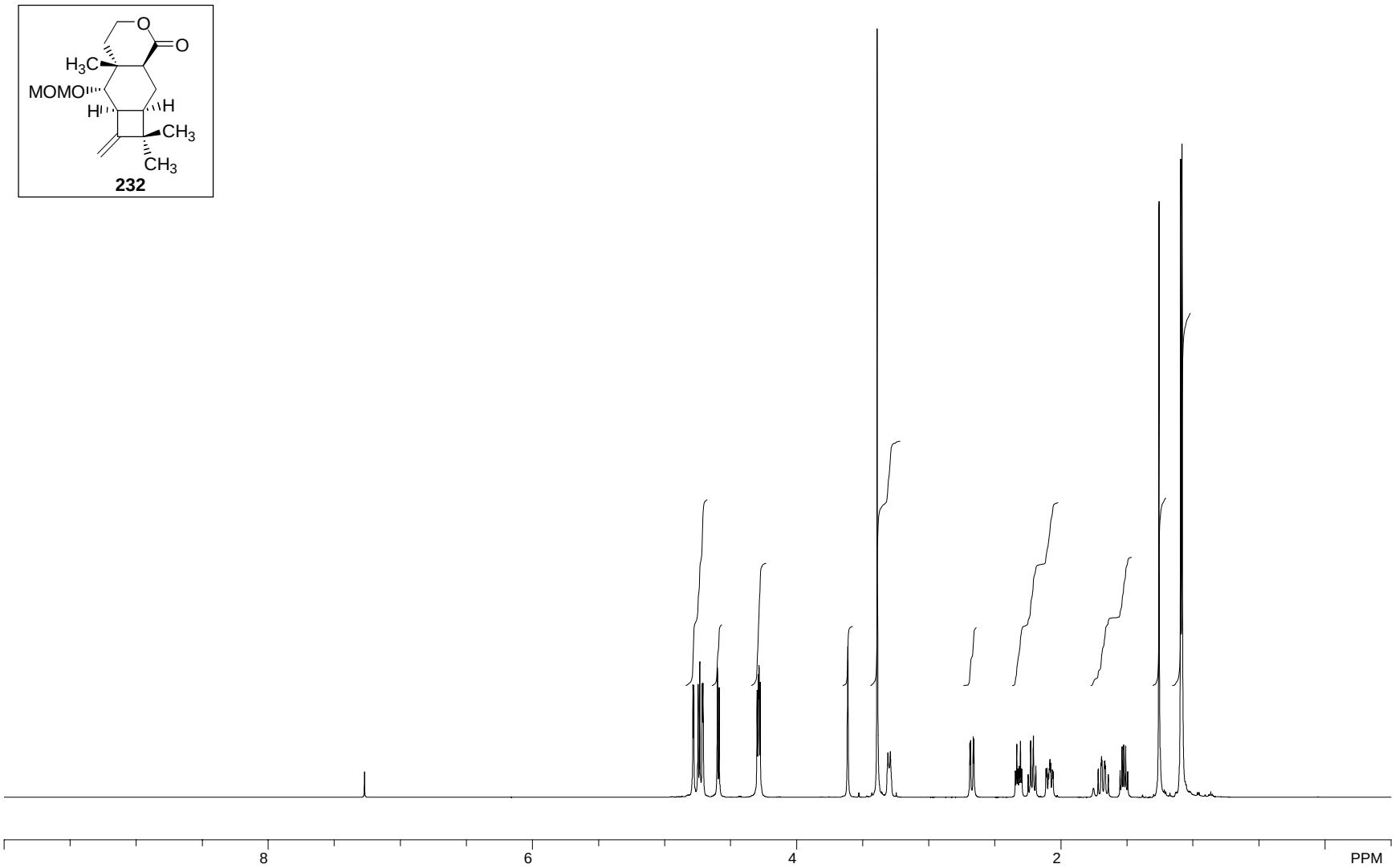


Figure A.7.28 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **232**.

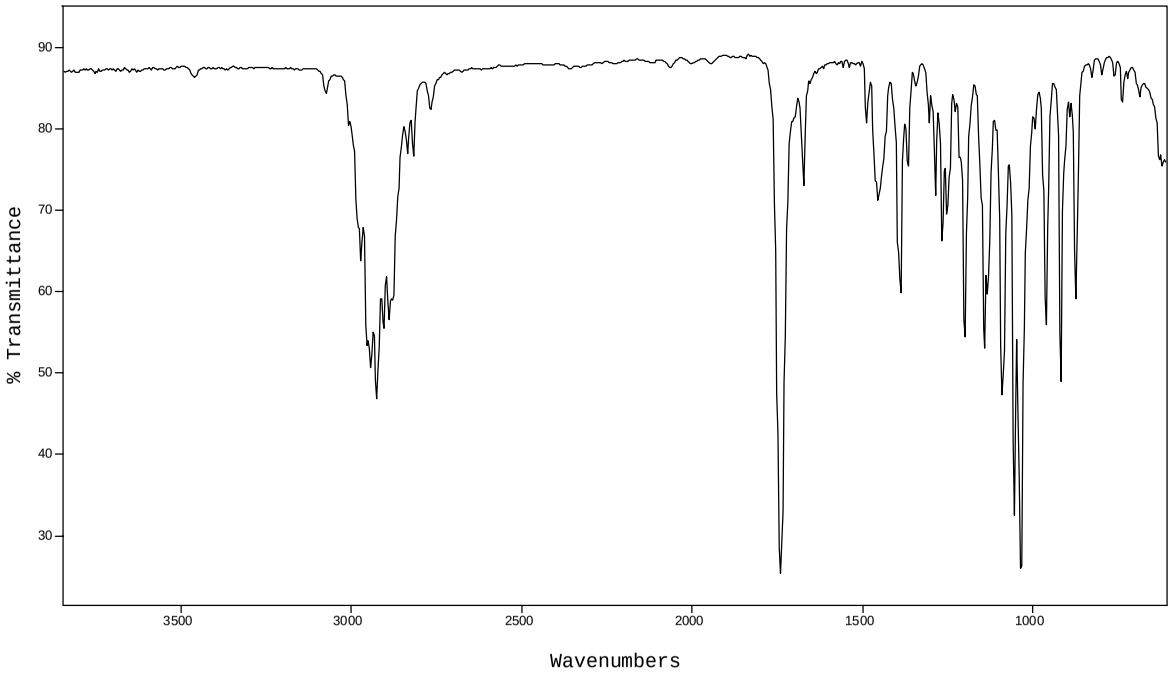


Figure A.7.29 FTIR Spectrum (thin film/NaCl) of Compound **232**.

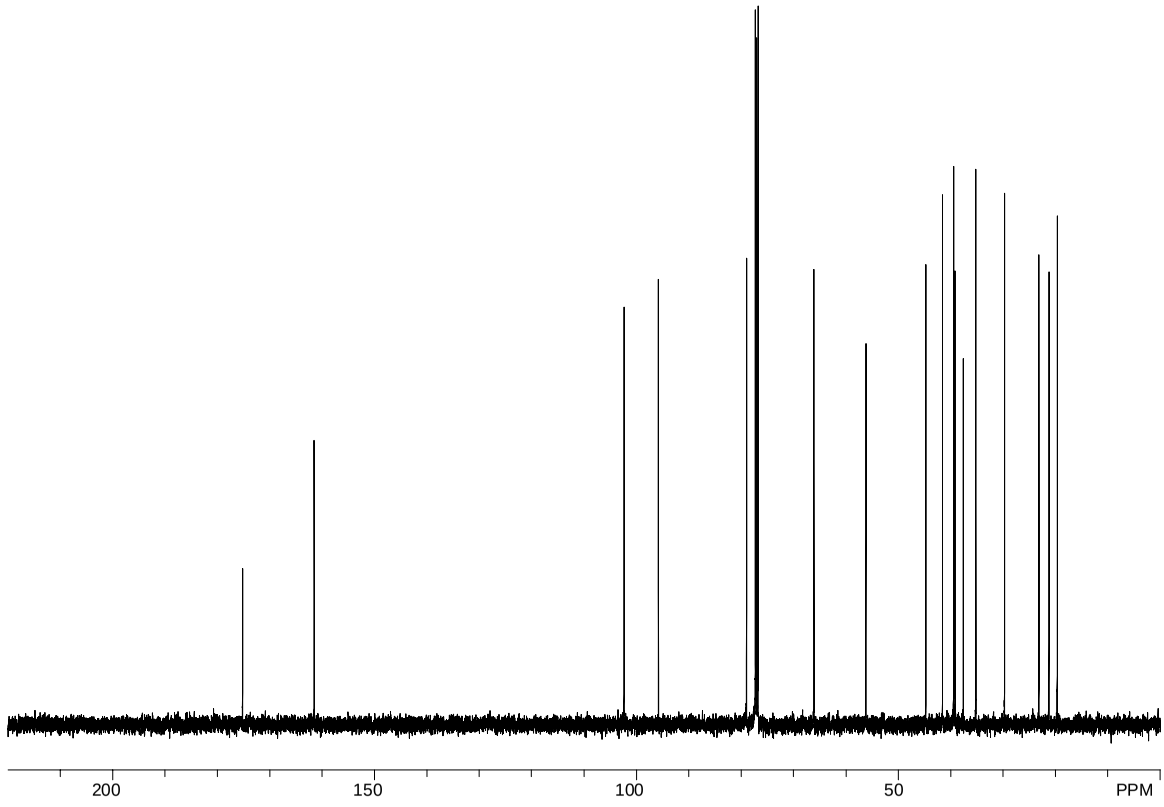


Figure A.7.30 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **232**.

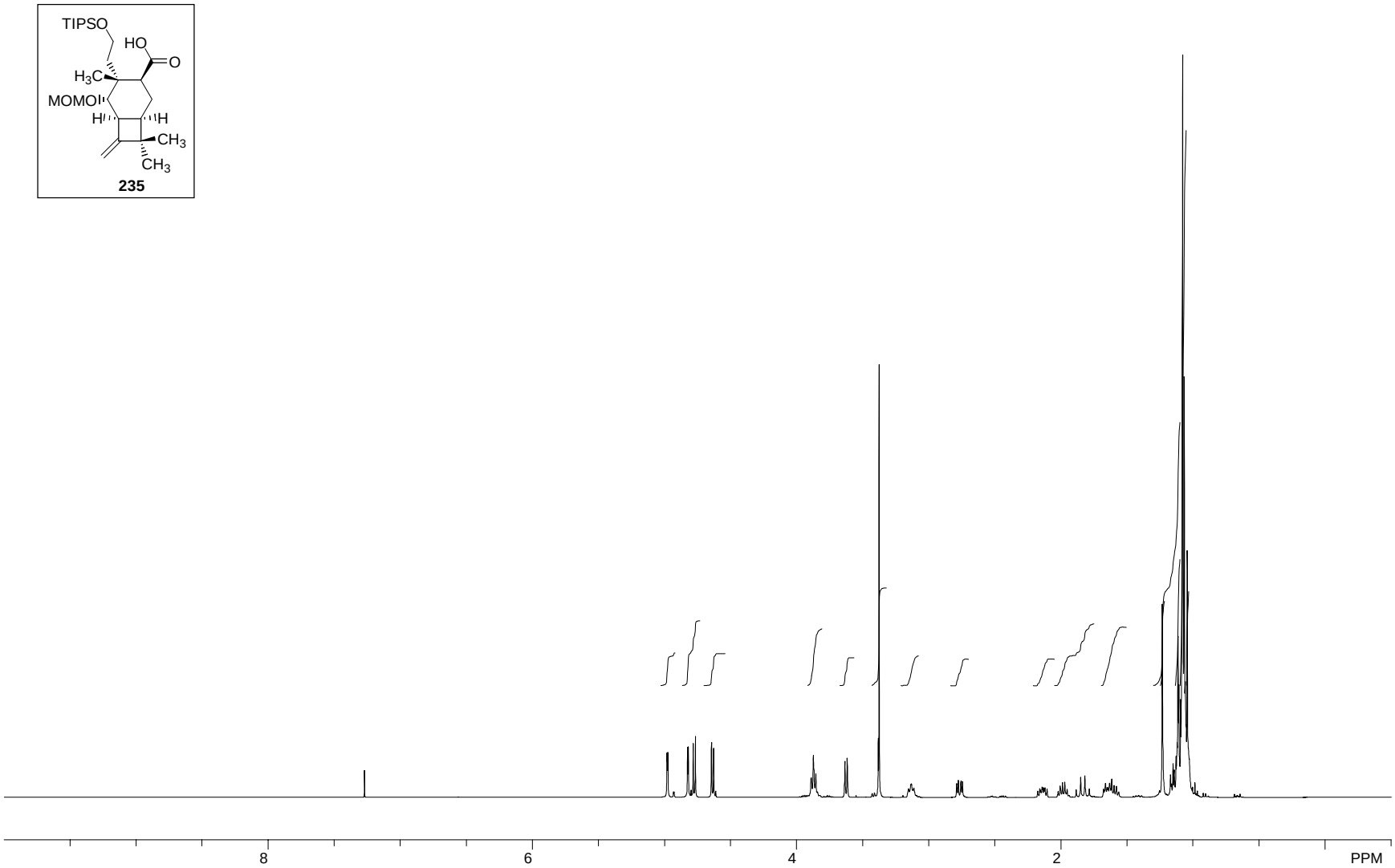


Figure A.7.31 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **235**.

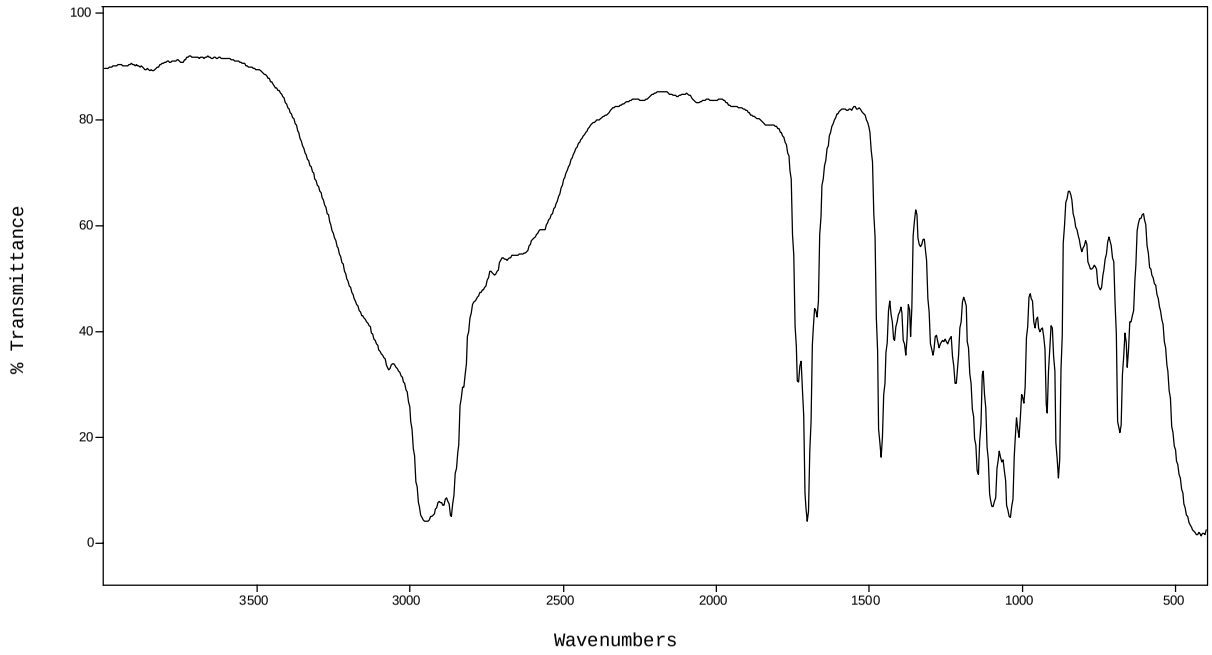


Figure A.7.32 FTIR Spectrum (thin film/NaCl) of Compound **235**.

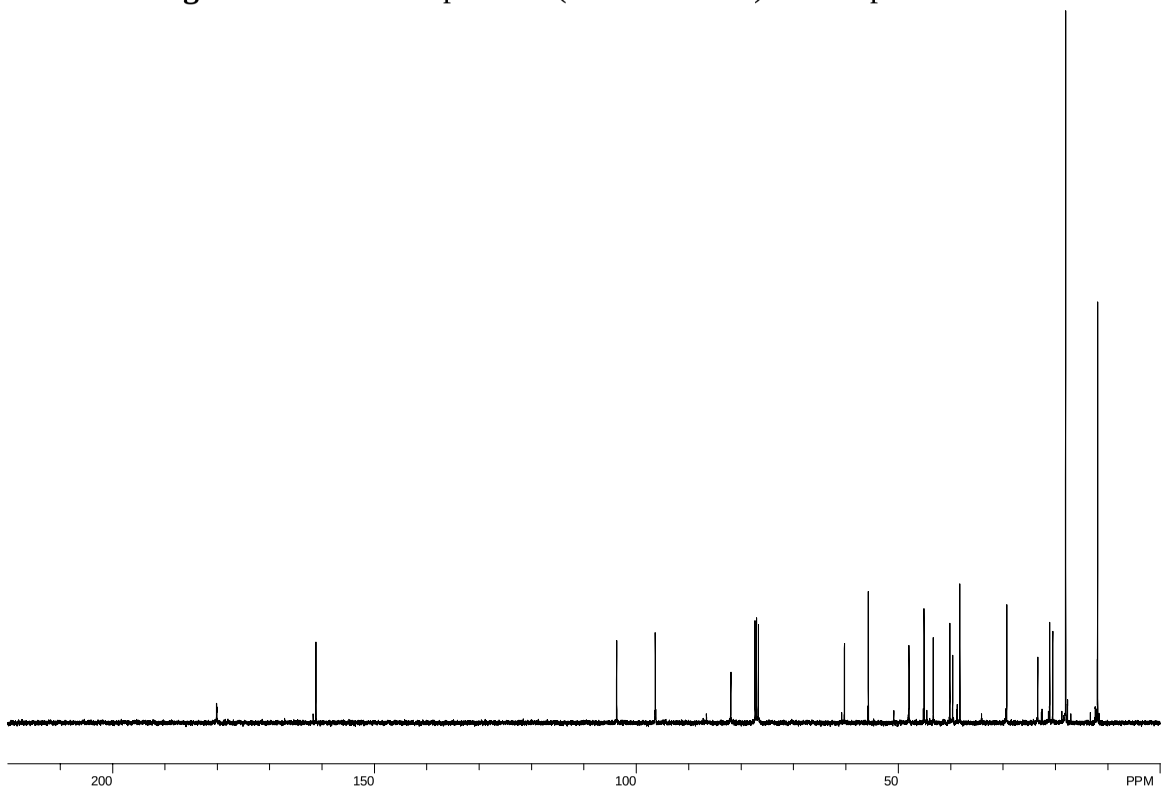


Figure A.7.33 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **235**.

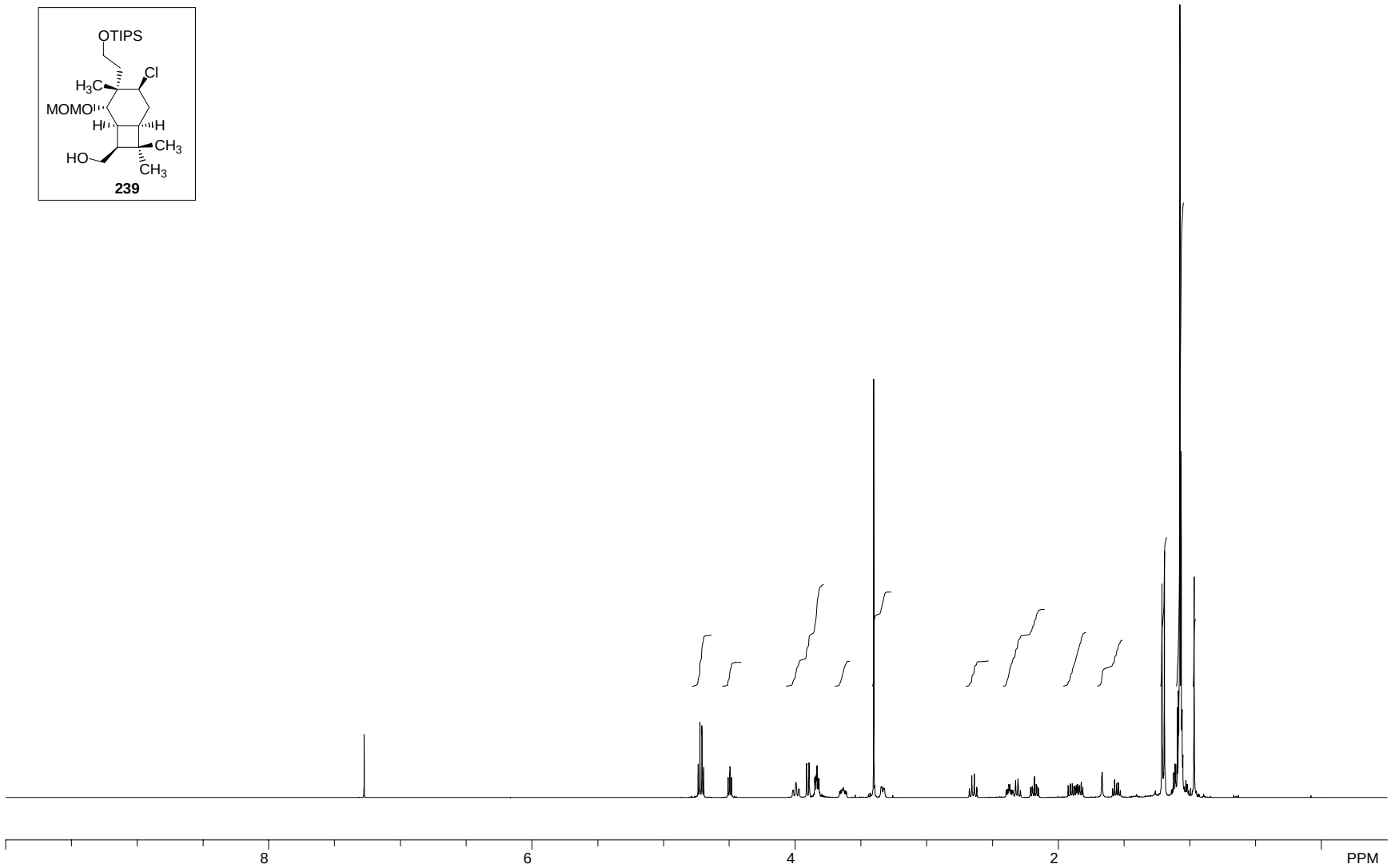


Figure A.7.34 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **239**.

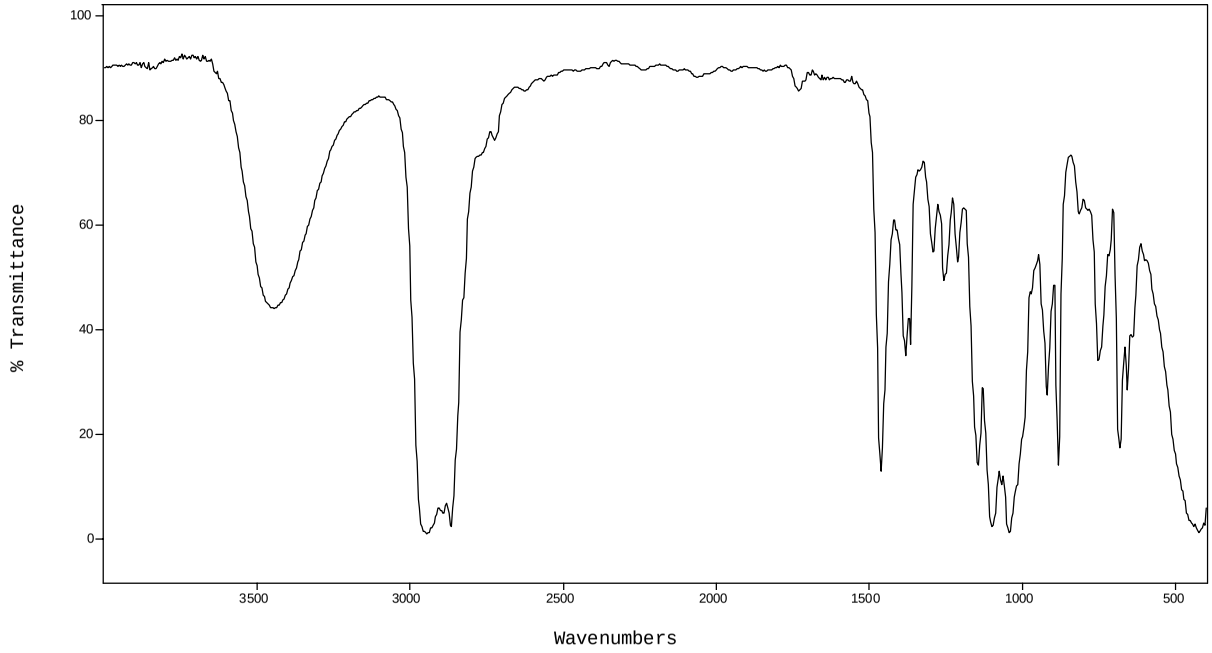


Figure A.7.35 FTIR Spectrum (thin film/NaCl) of Compound **239**.

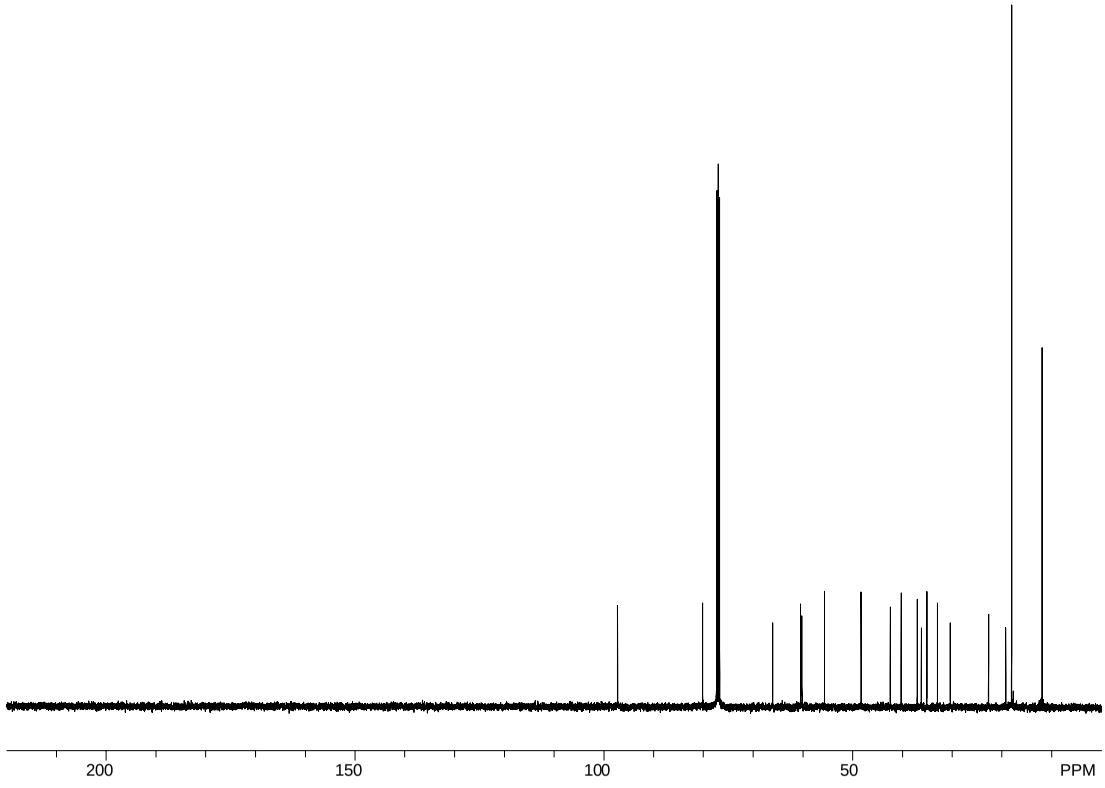


Figure A.7.36 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **239**.

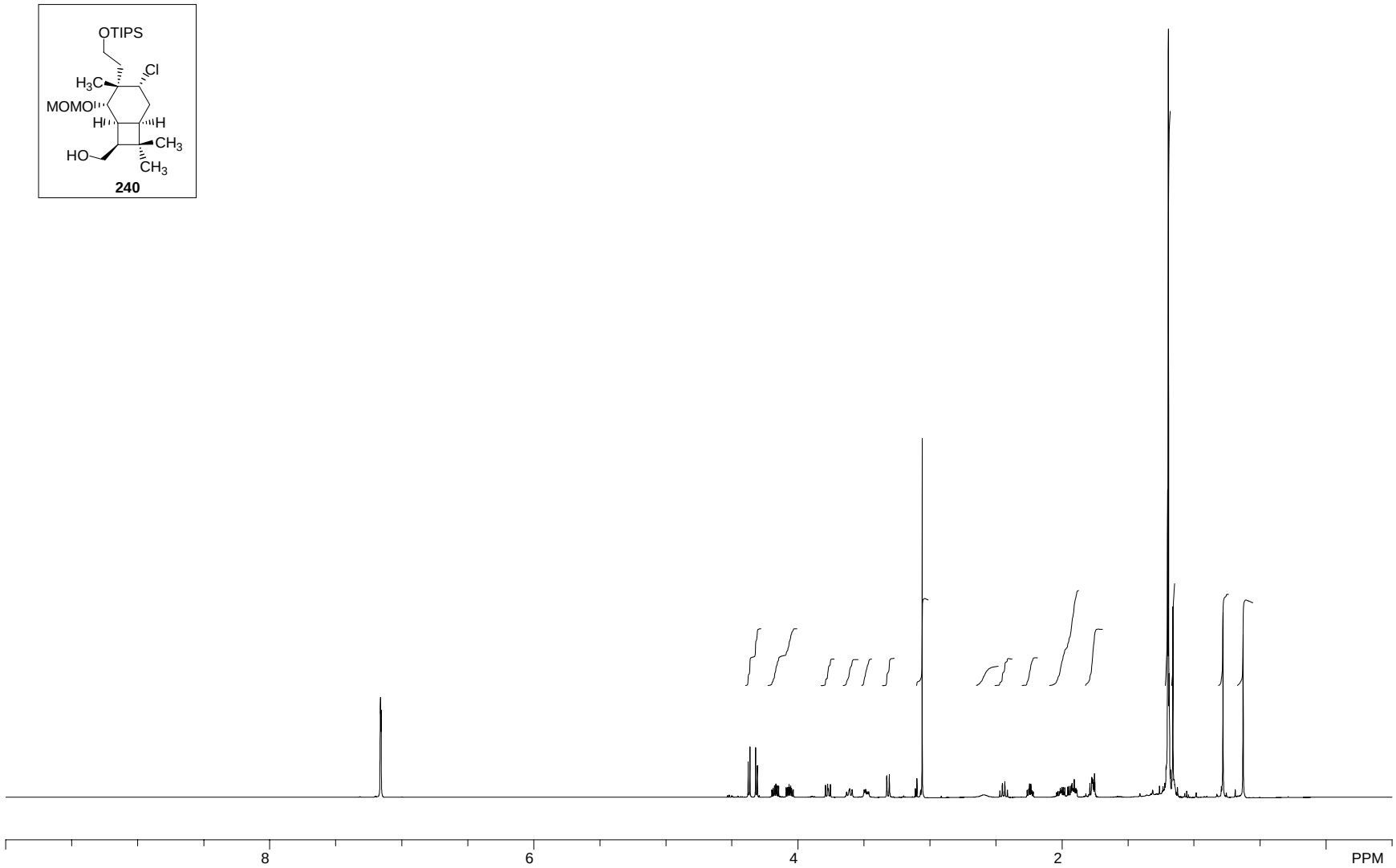


Figure A.7.37 ^{1}H NMR (500 MHz, C_6D_6) of Compound **240**.

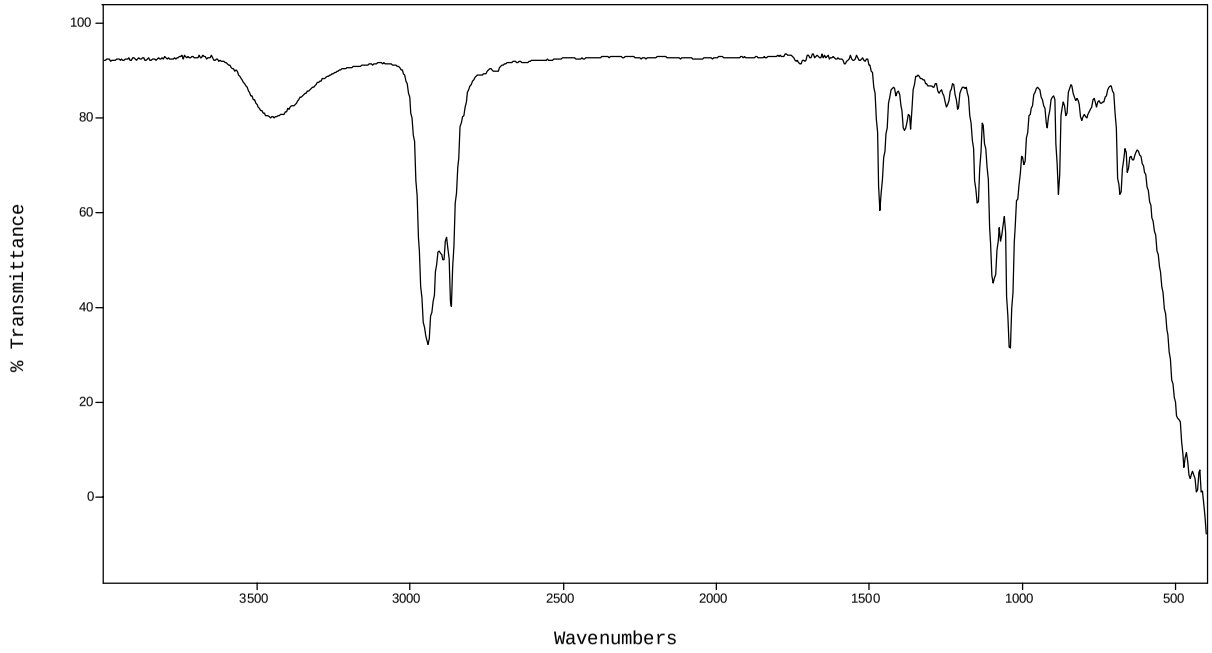


Figure A.7.38 FTIR Spectrum (thin film/NaCl) of Compound **240**.

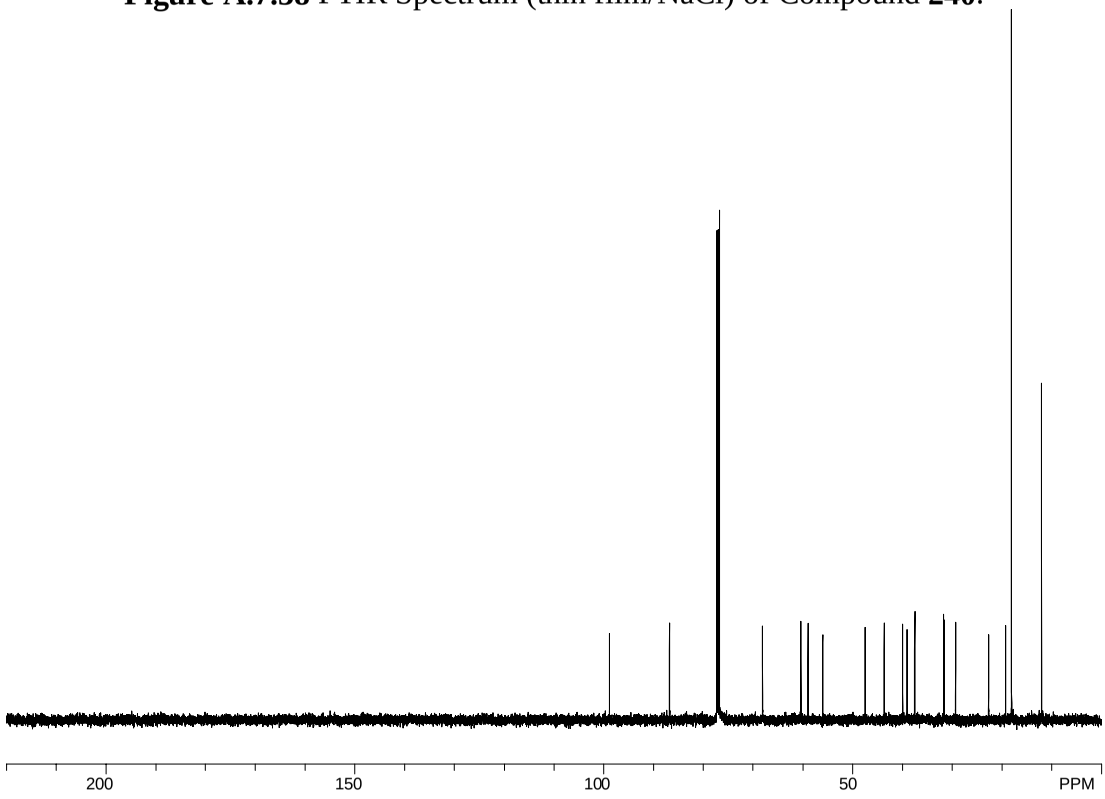


Figure A.7.39 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **240**.

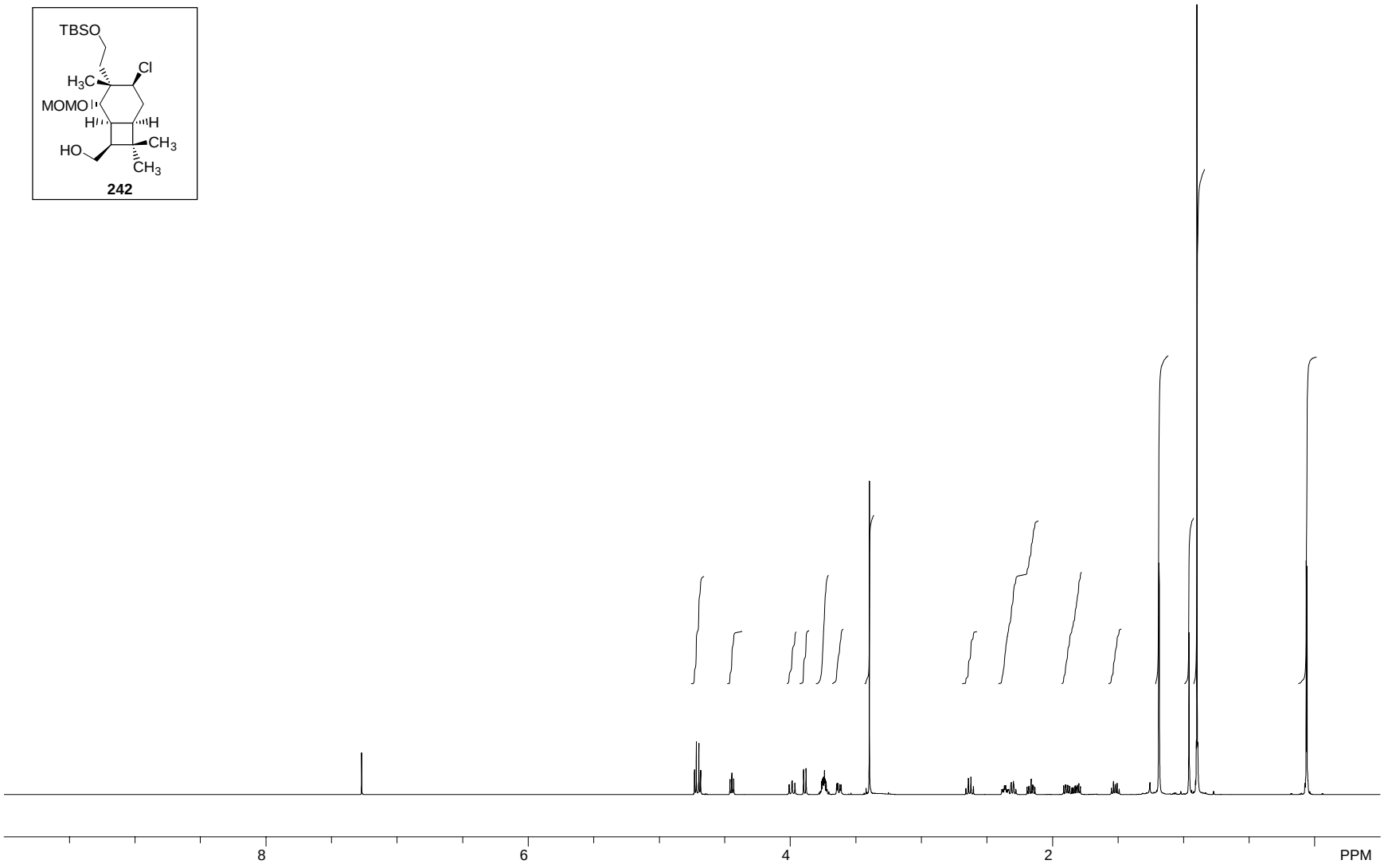


Figure A.7.40 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **242**.

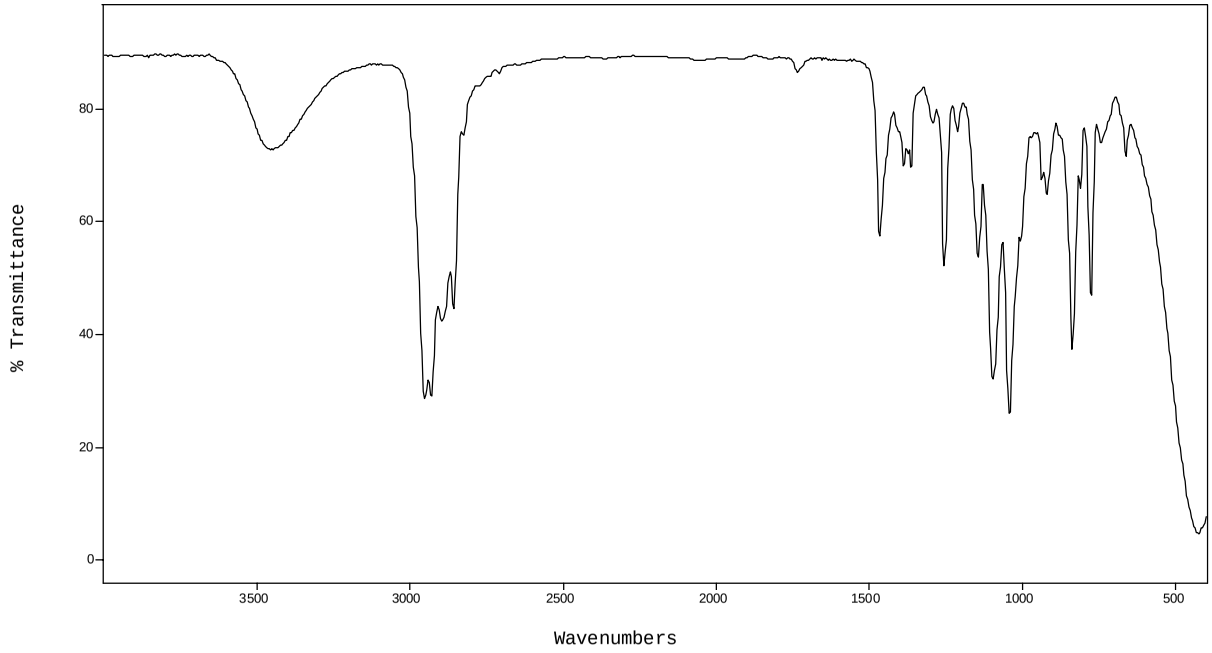


Figure A.7.41 FTIR Spectrum (thin film/NaCl) of Compound **242**.

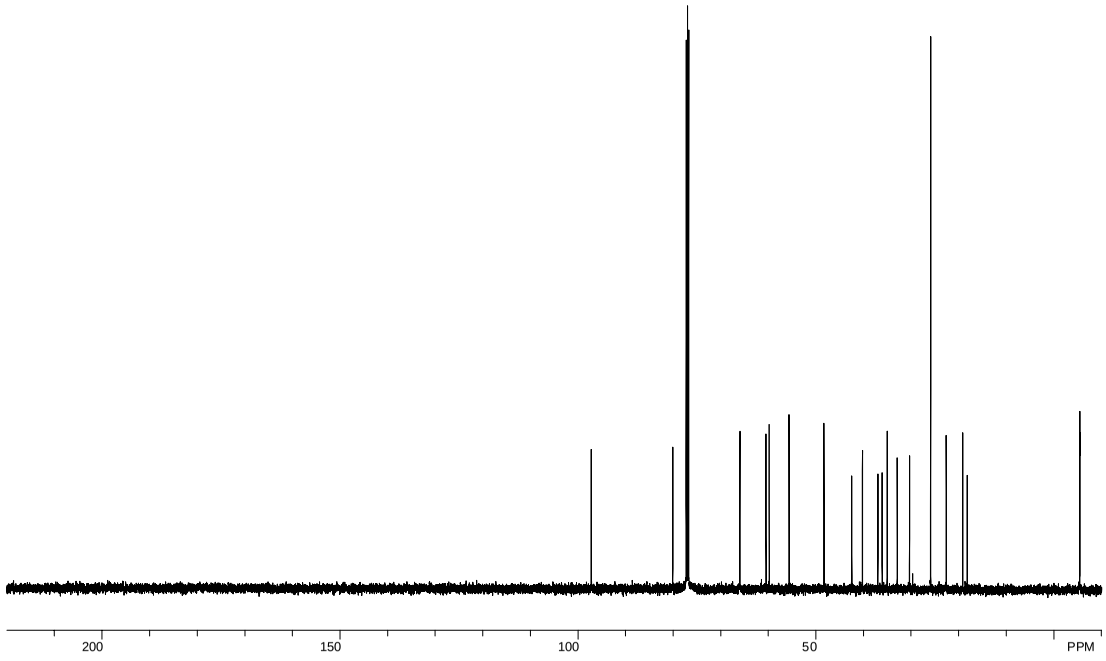


Figure A.7.42 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **242**.

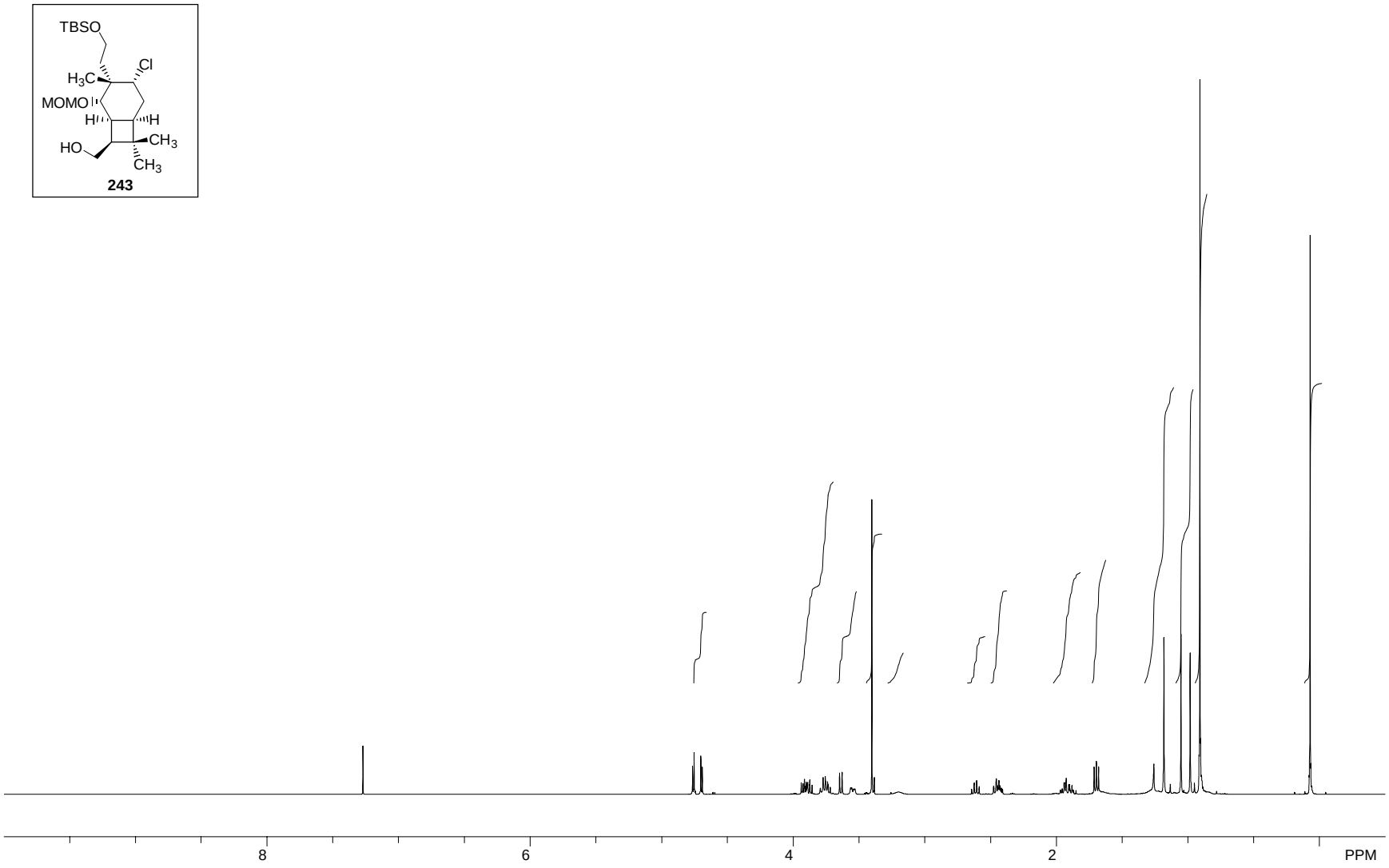


Figure A.7.43 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **243**.

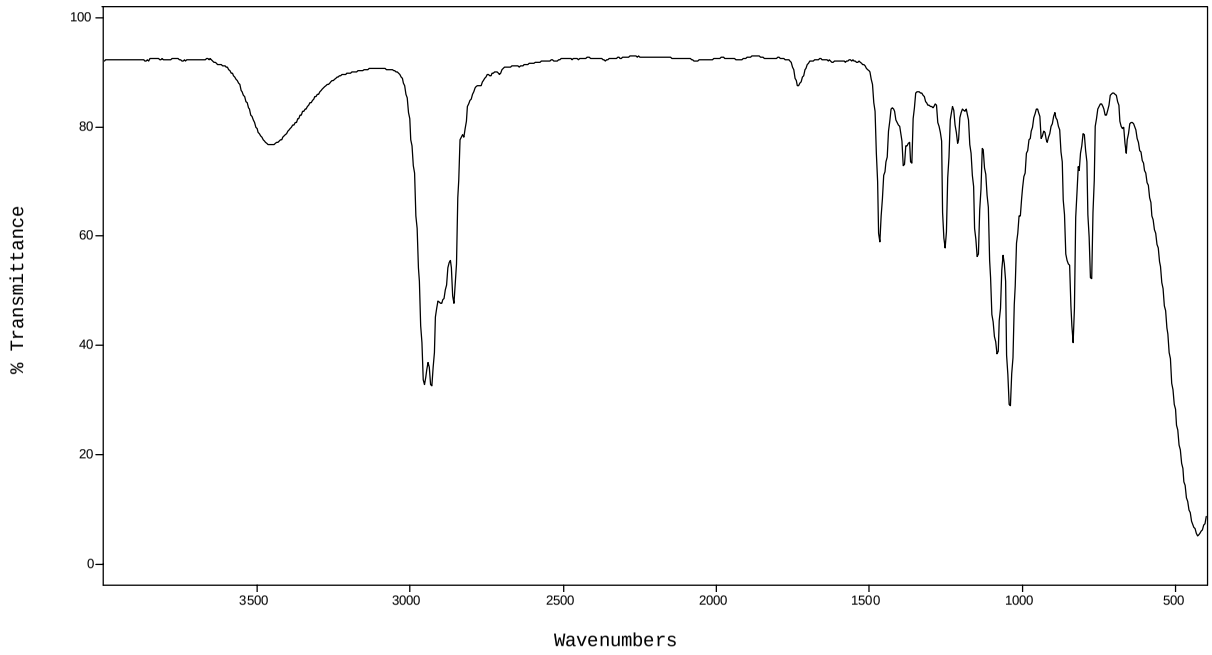


Figure A.7.44 FTIR Spectrum (thin film/NaCl) of Compound **243**.

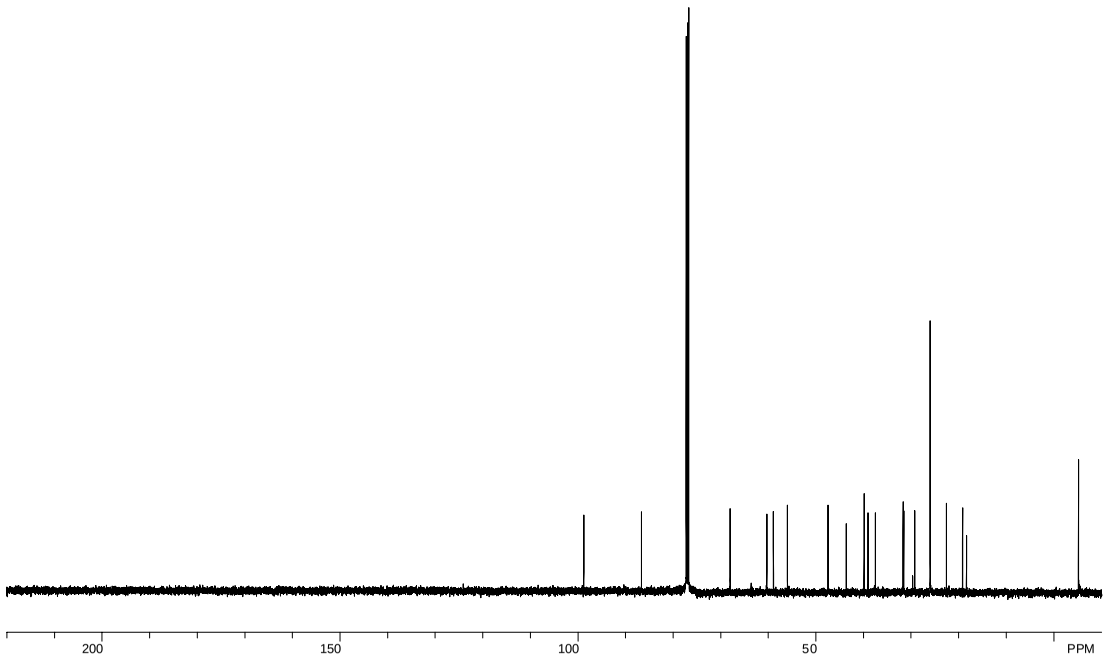


Figure A.7.45 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **243**.

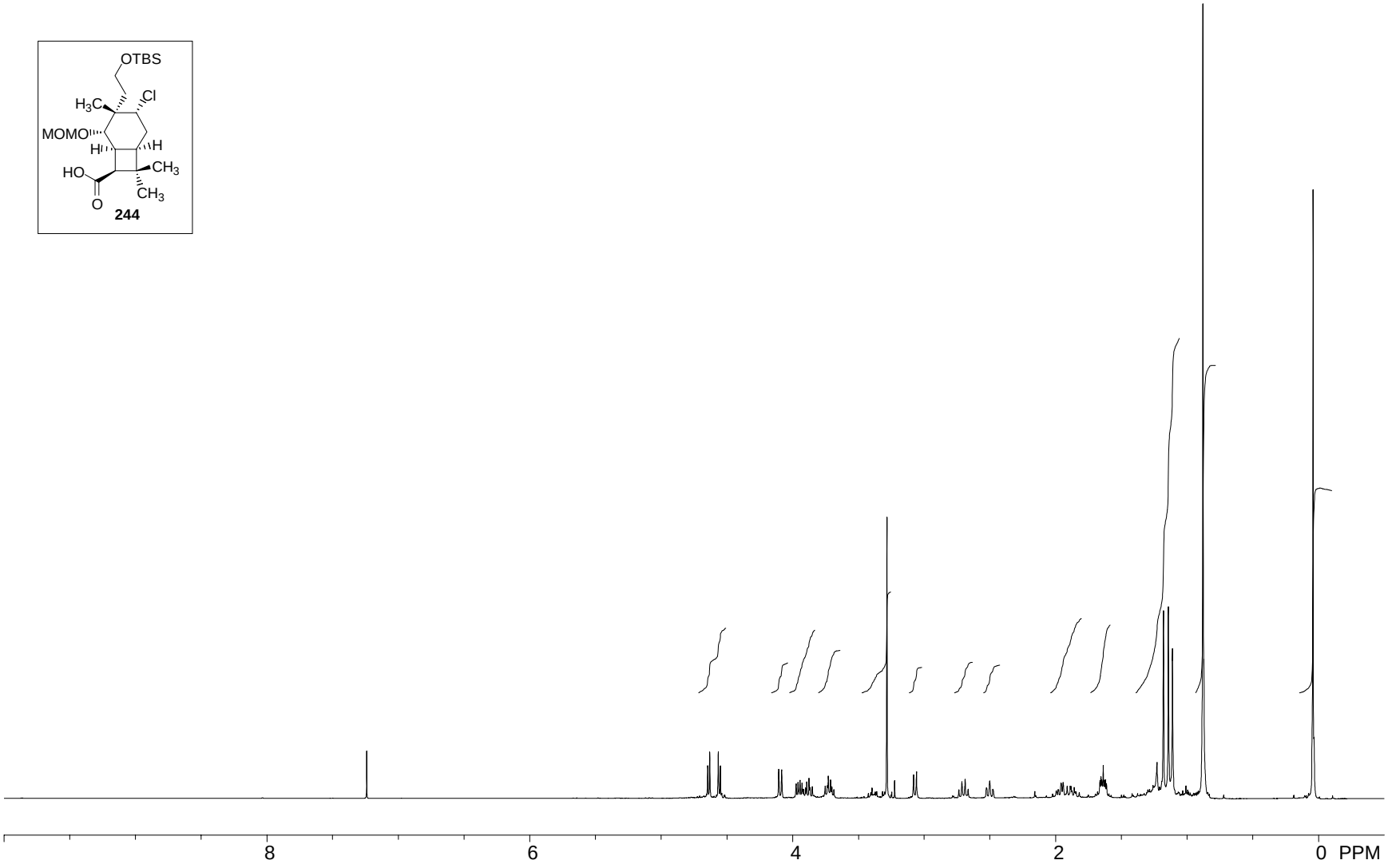


Figure A.7.46 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **244**.

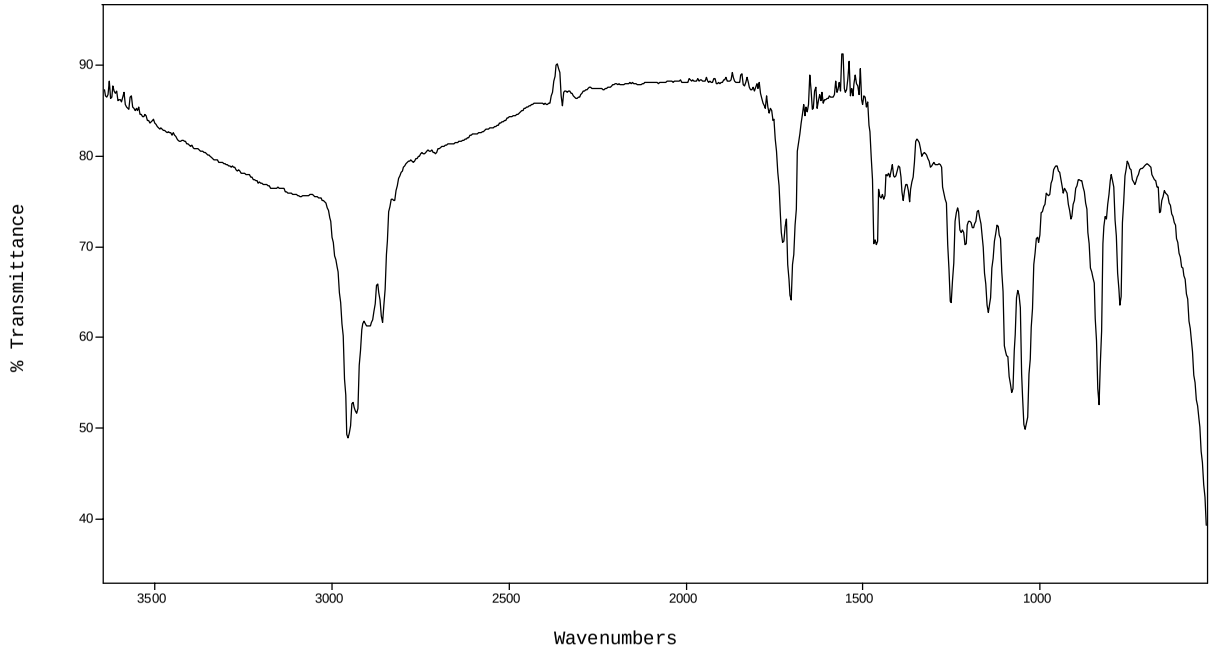


Figure A.7.47 FTIR Spectrum (thin film/NaCl) of Compound **244**.

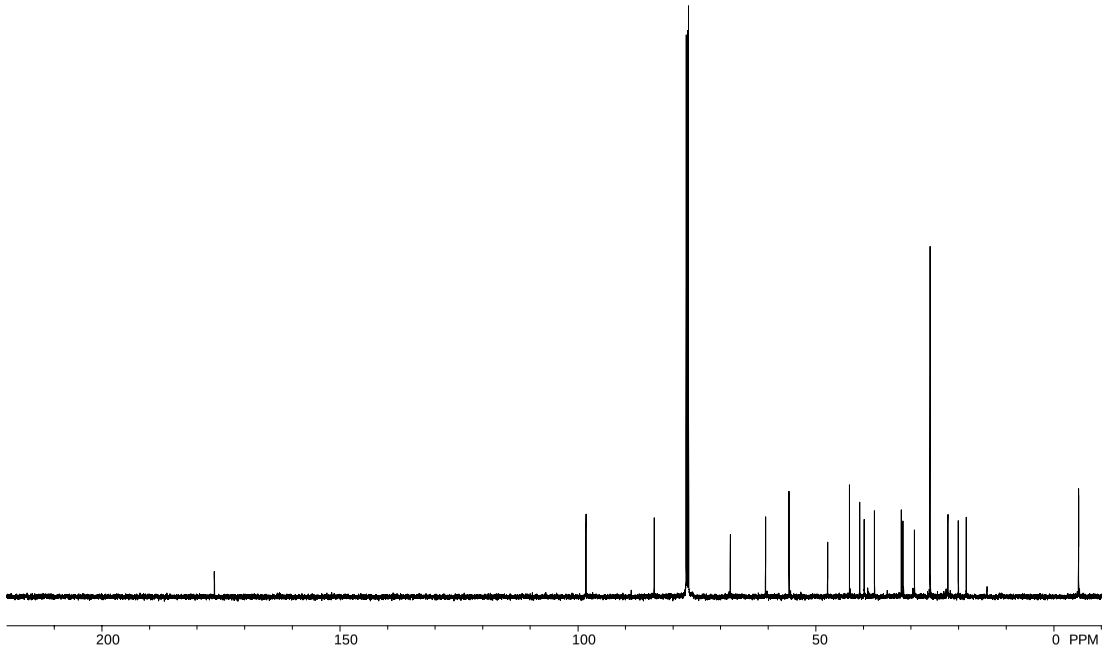


Figure A.7.48 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **244**.

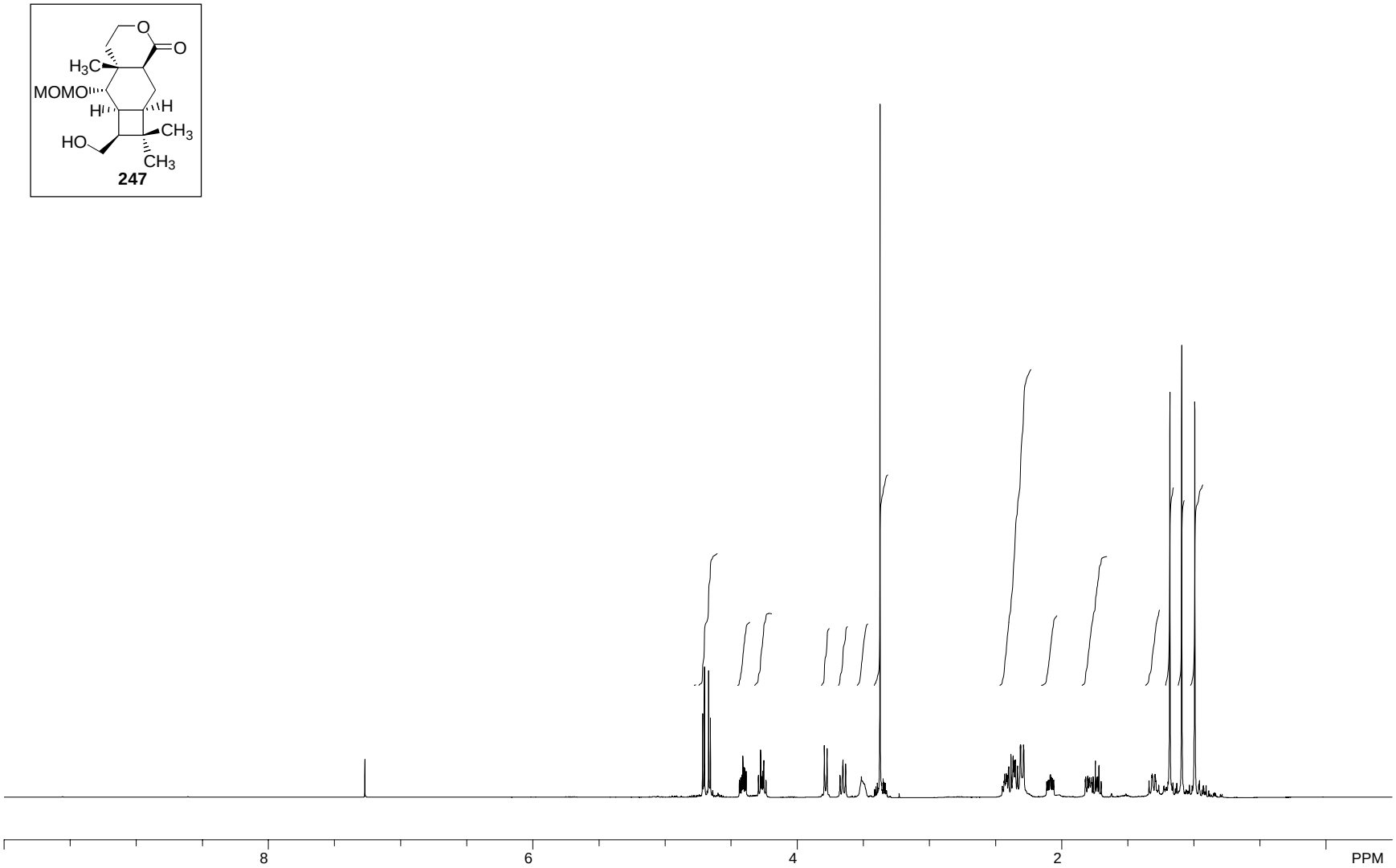


Figure A.7.49 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **247.**

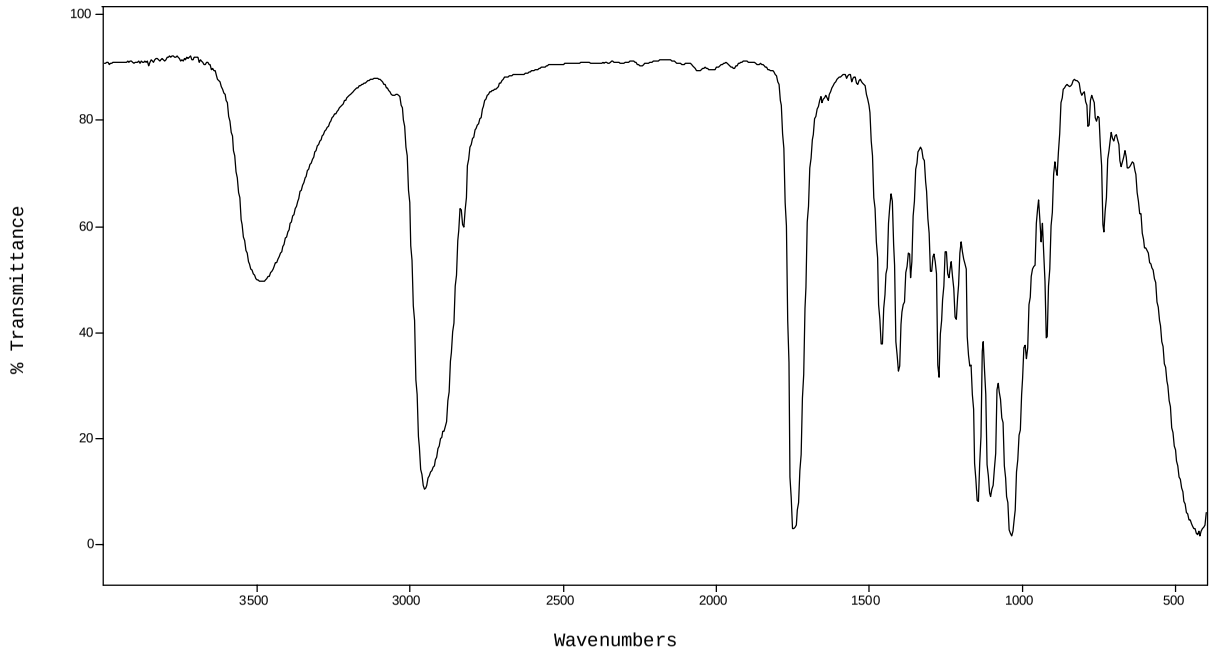


Figure A.7.50 FTIR Spectrum (thin film/NaCl) of Compound **247**.

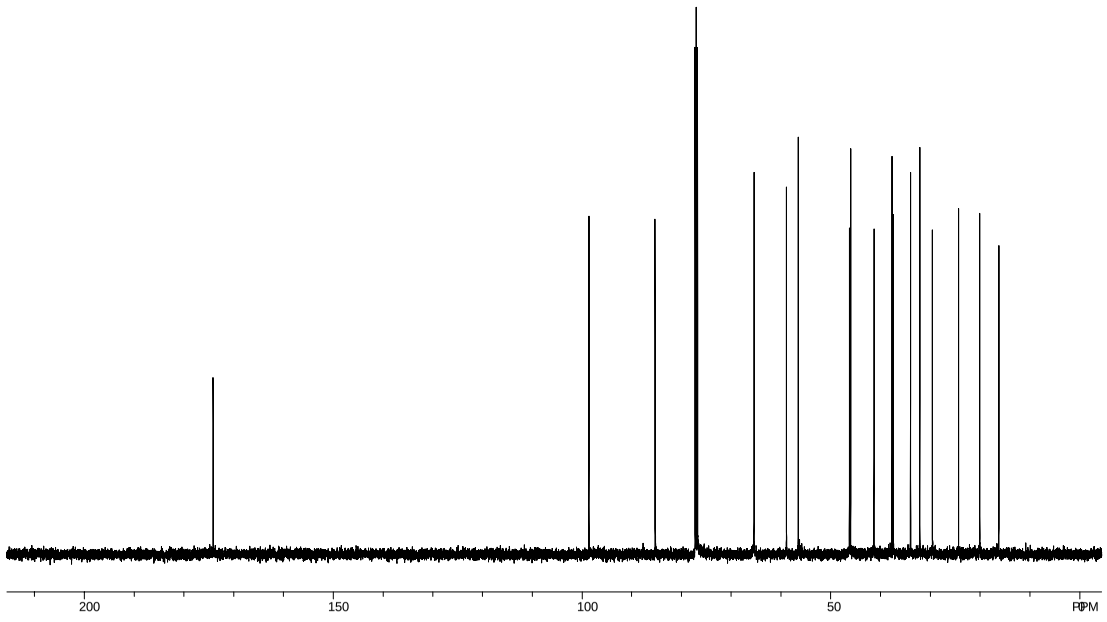


Figure A.7.51 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **247**.

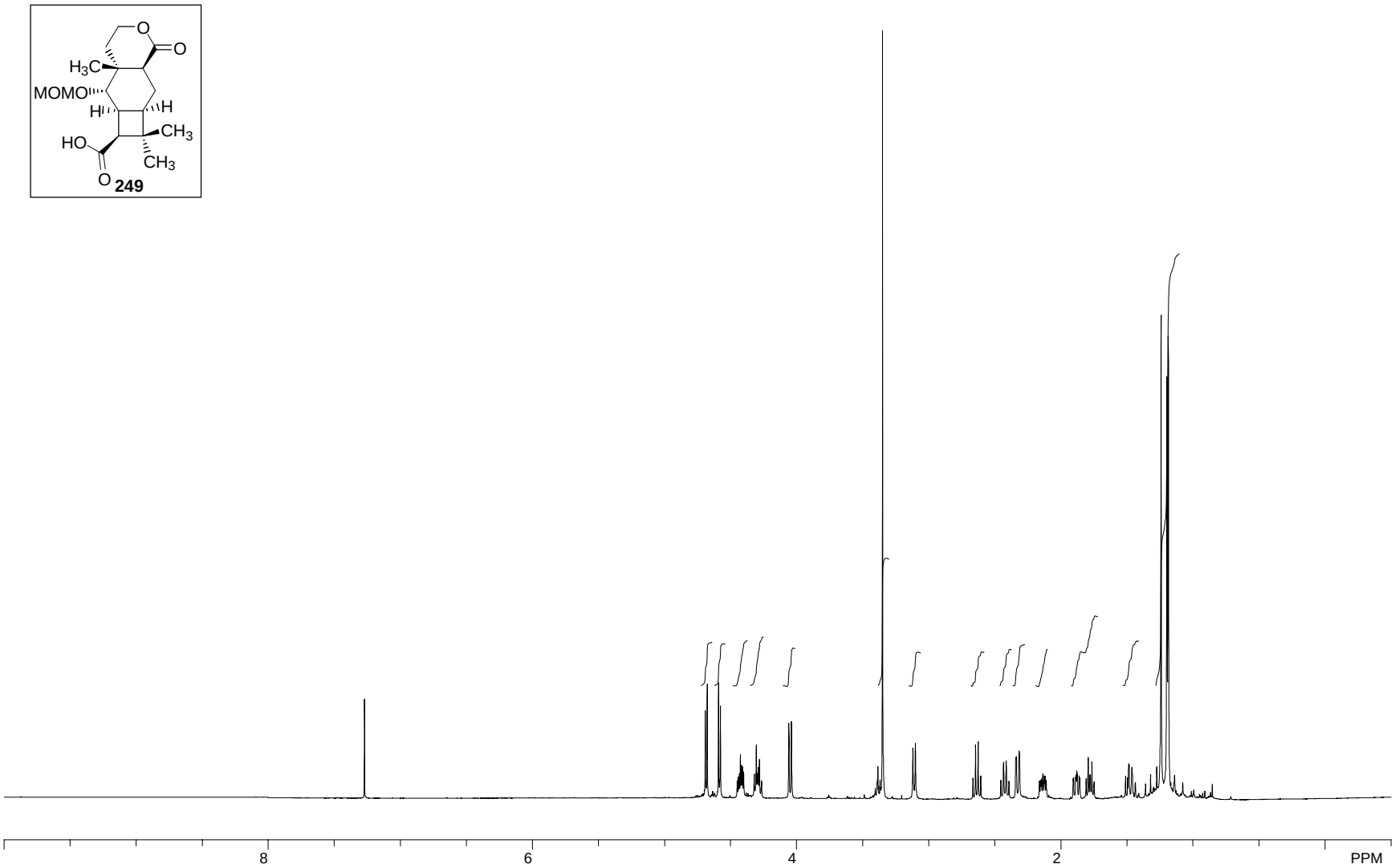


Figure A.7.52 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **249**.

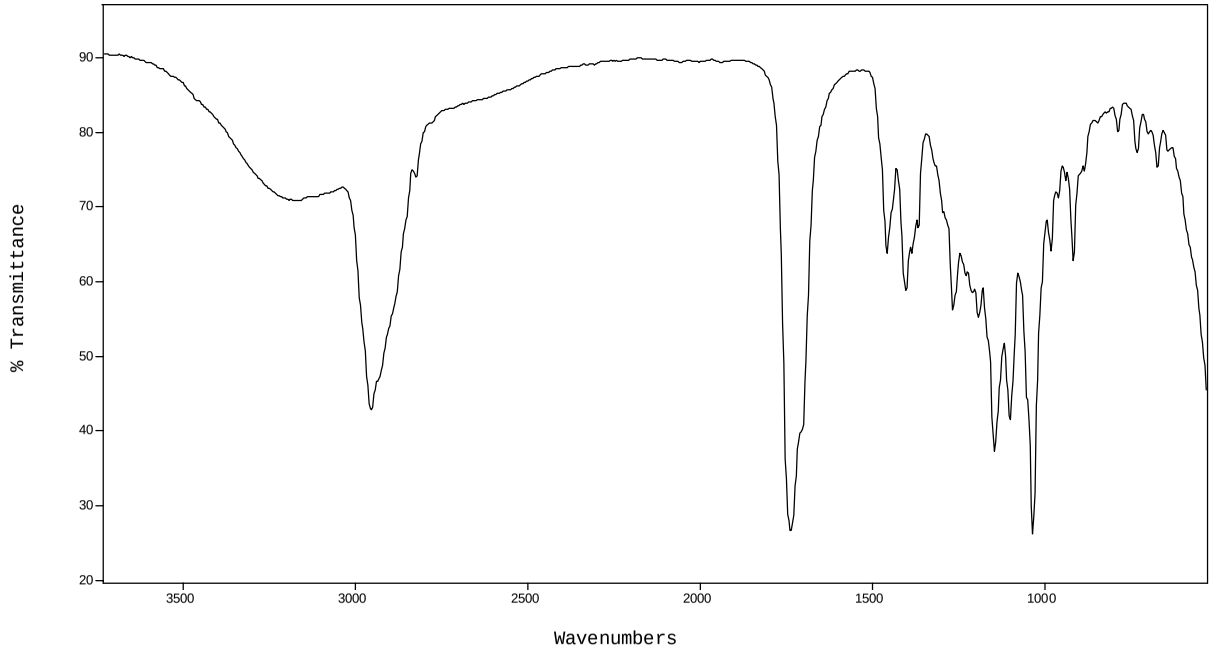


Figure A.7.53 FTIR Spectrum (thin film/NaCl) of Compound **249**.

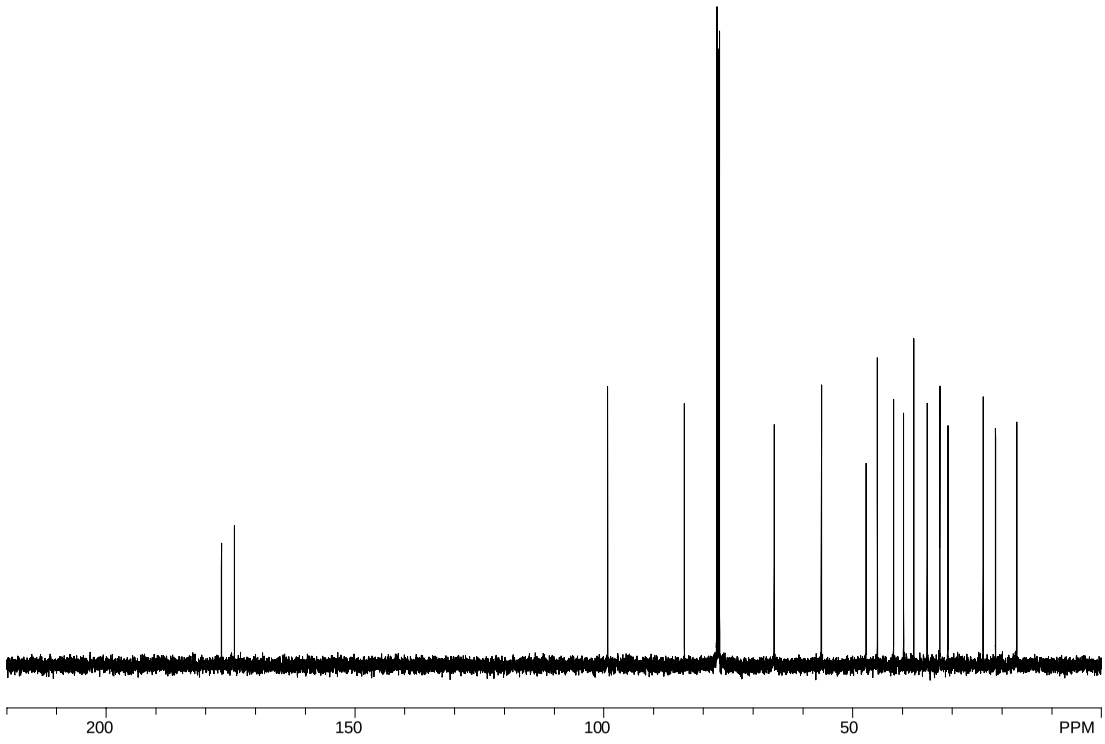


Figure A.7.54 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **249**.

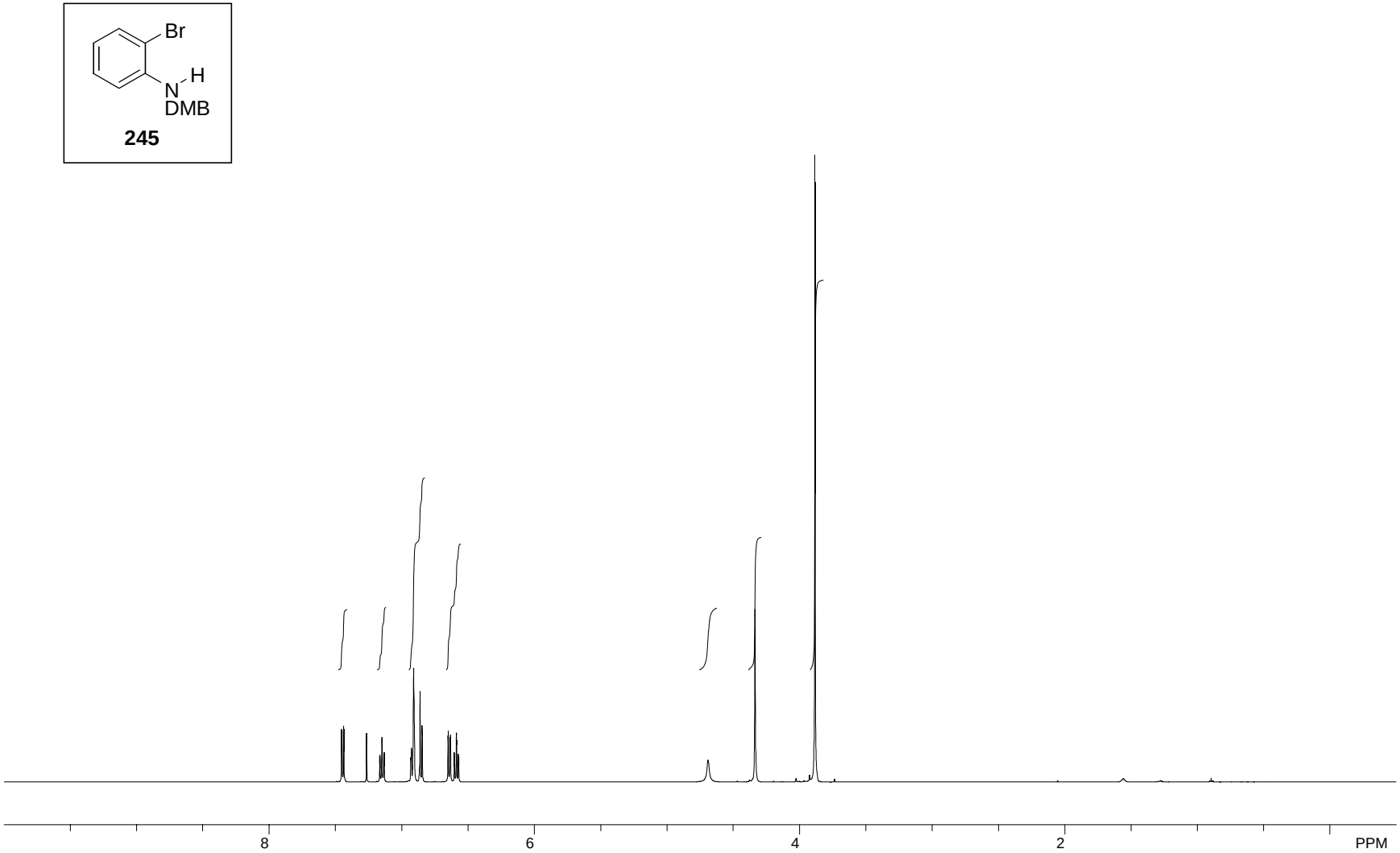


Figure A.7.55 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **245**.

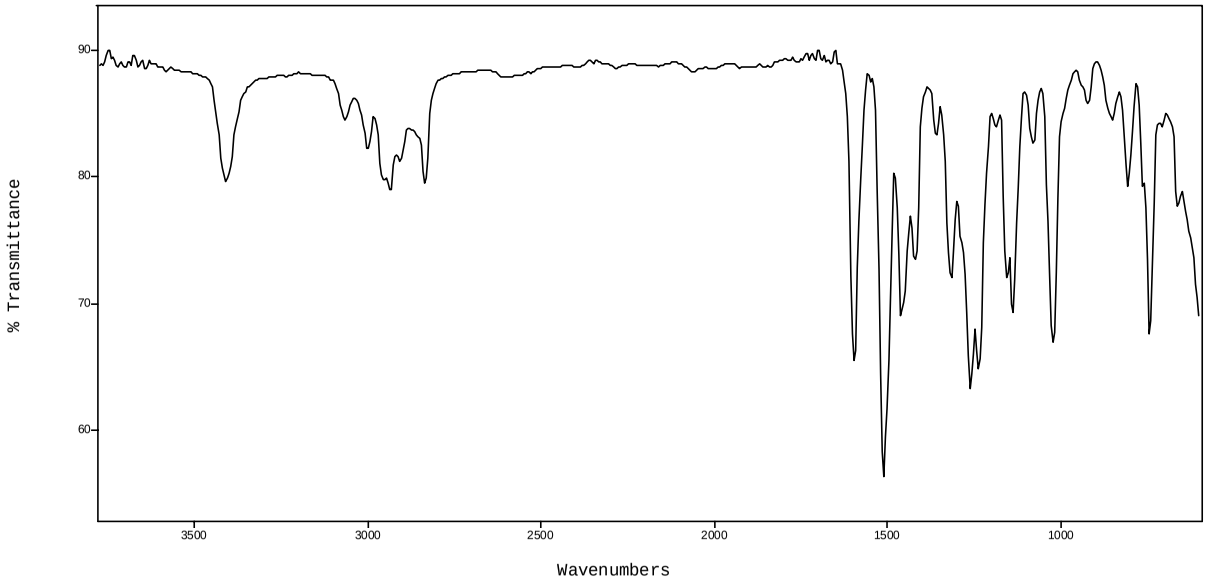


Figure A.7.56 FTIR Spectrum (thin film/NaCl) of Compound **245**.

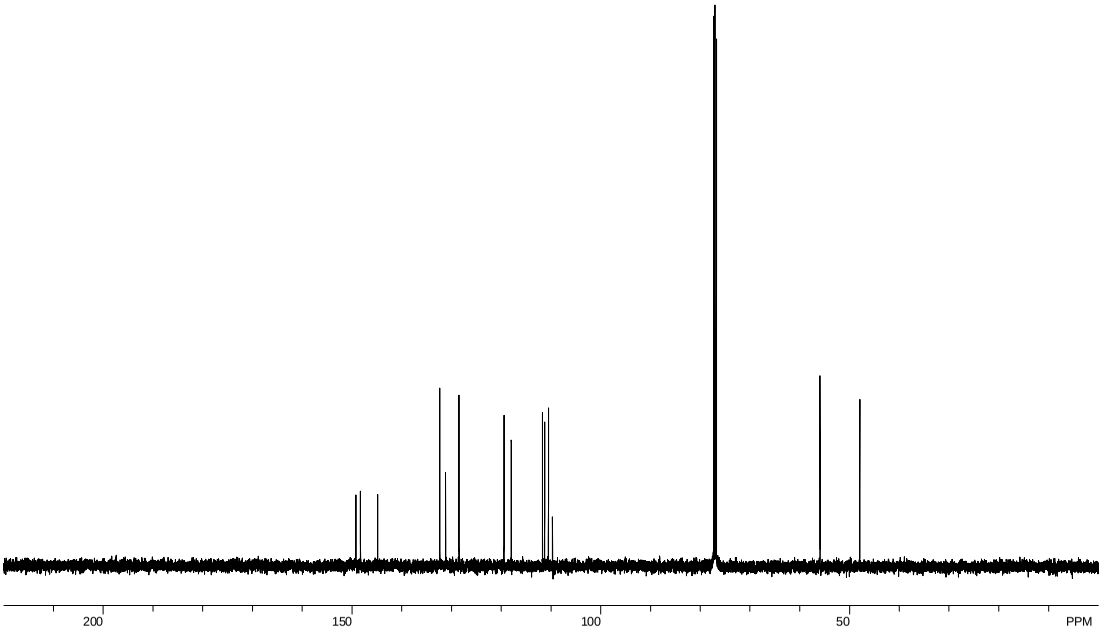


Figure A.7.57 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **245**.

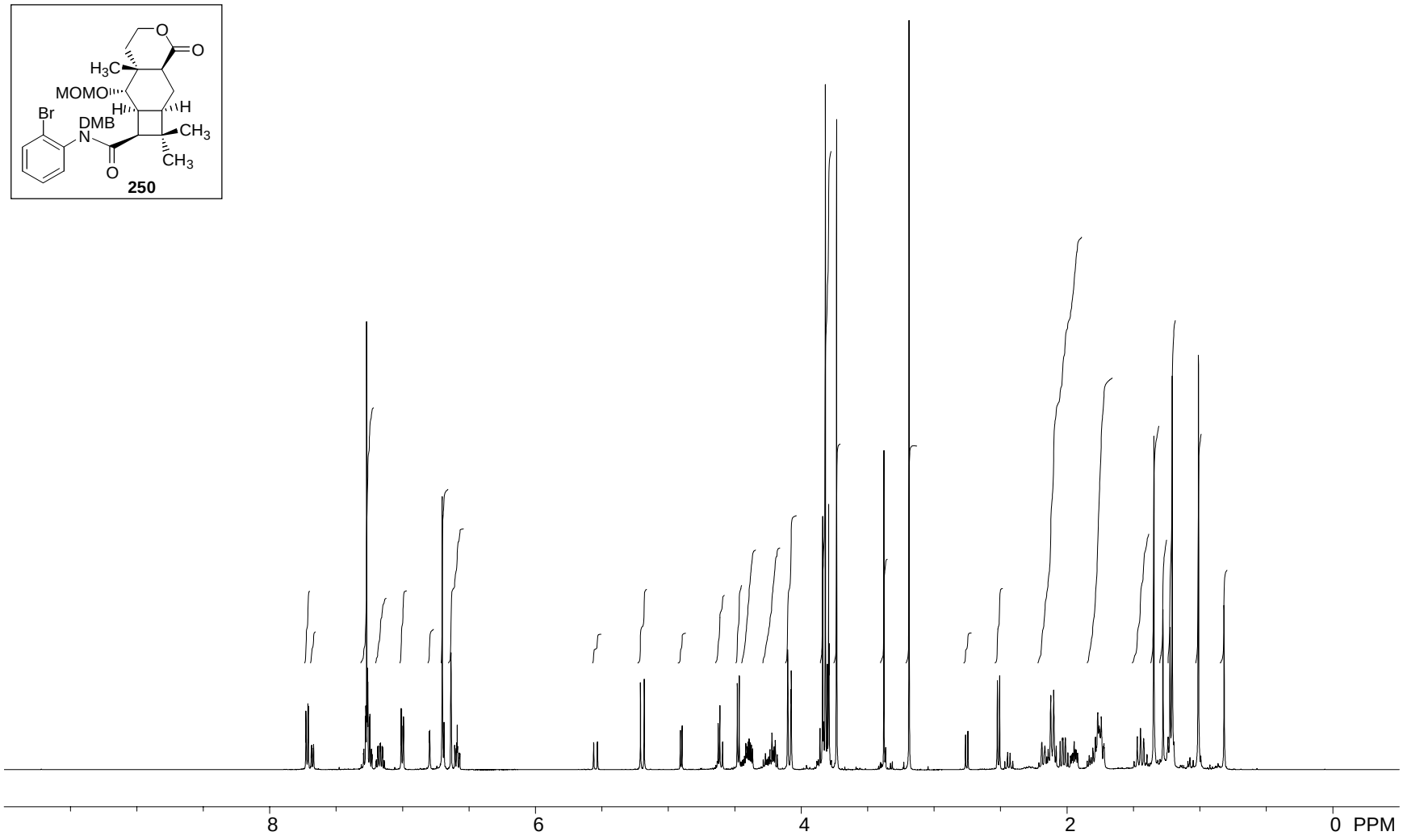


Figure A.7.58 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **250**.

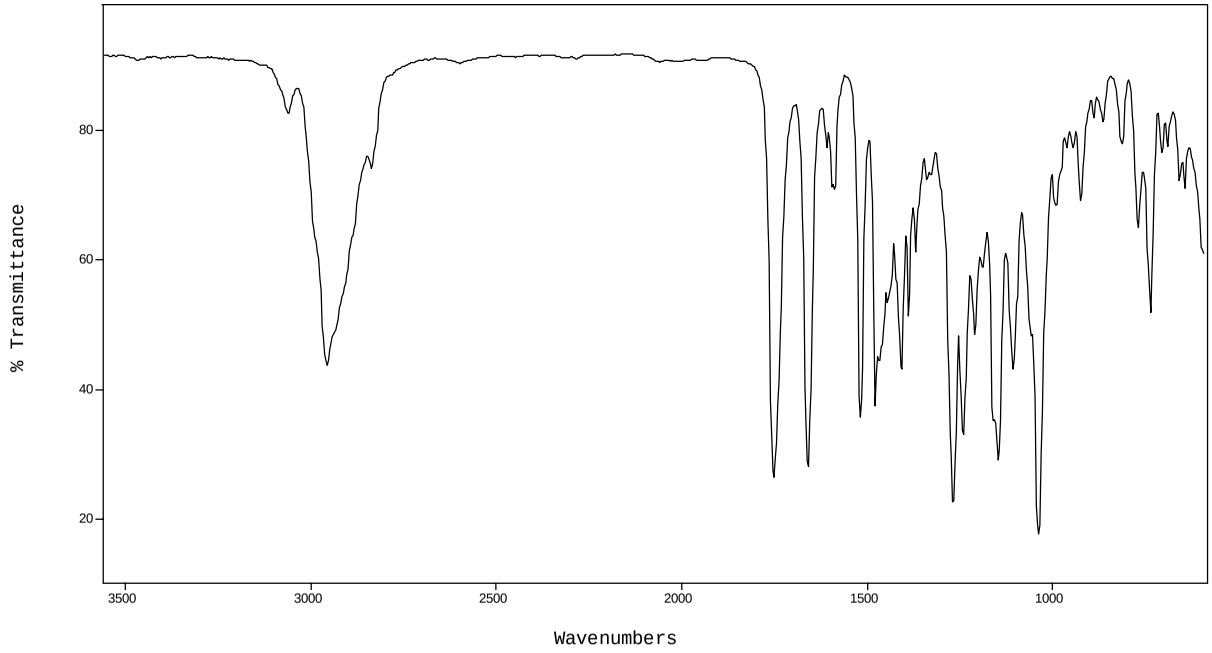


Figure A.7.59 FTIR Spectrum (thin film/NaCl) of Compound **250**.

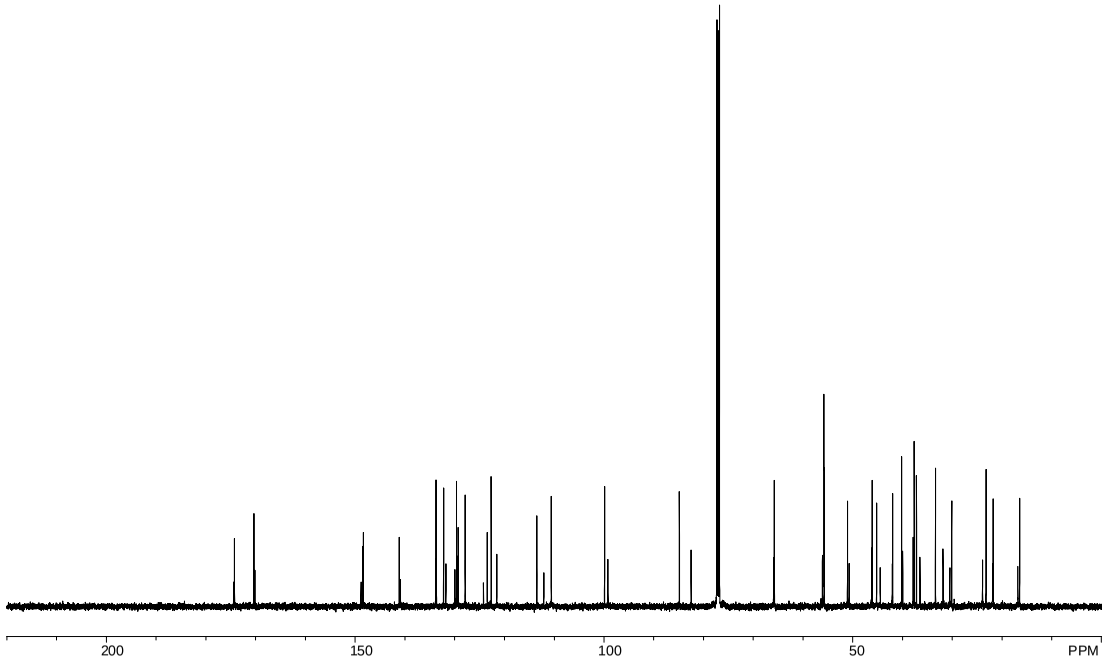


Figure A.7.60 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **250**.

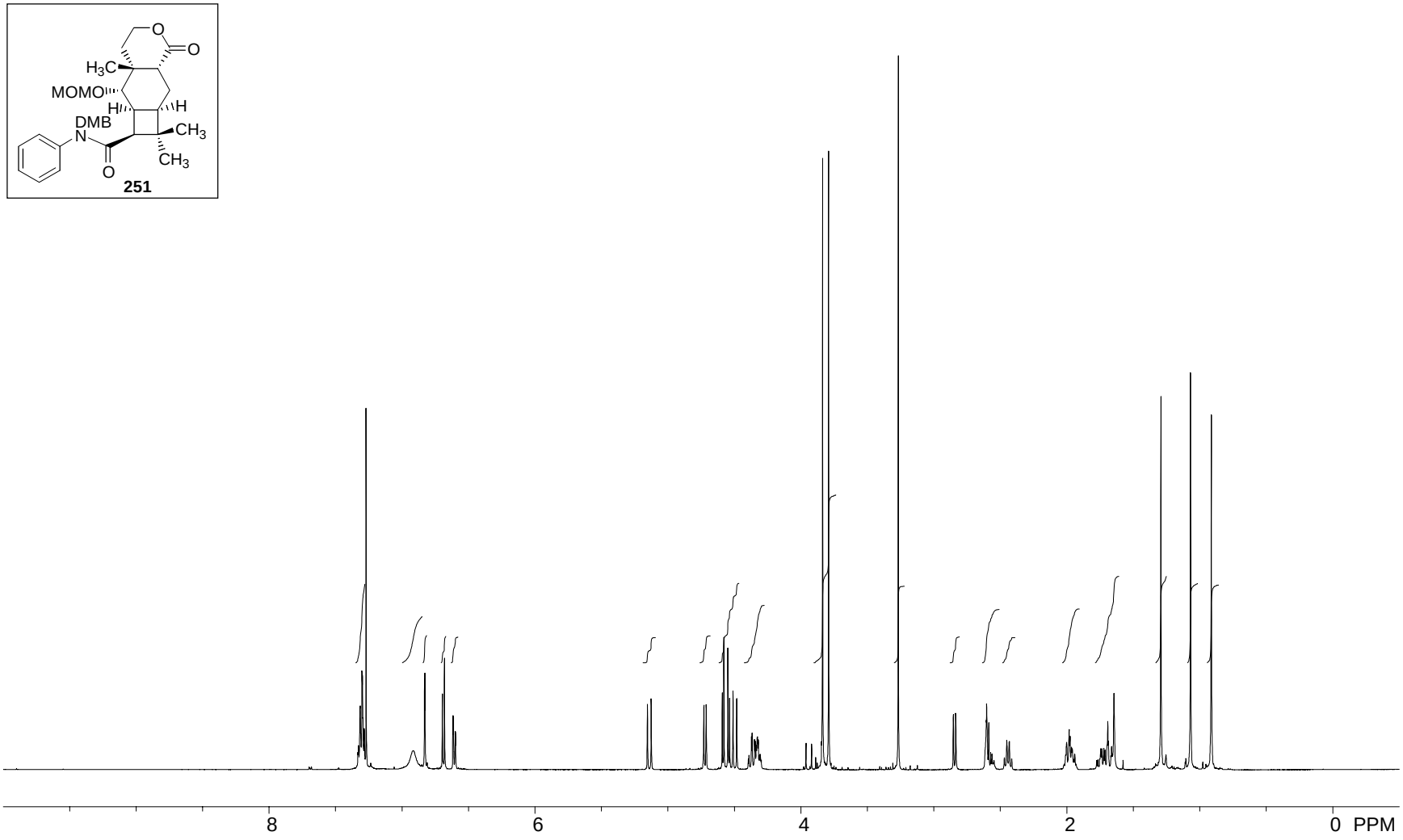


Figure A.7.61 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **251**.

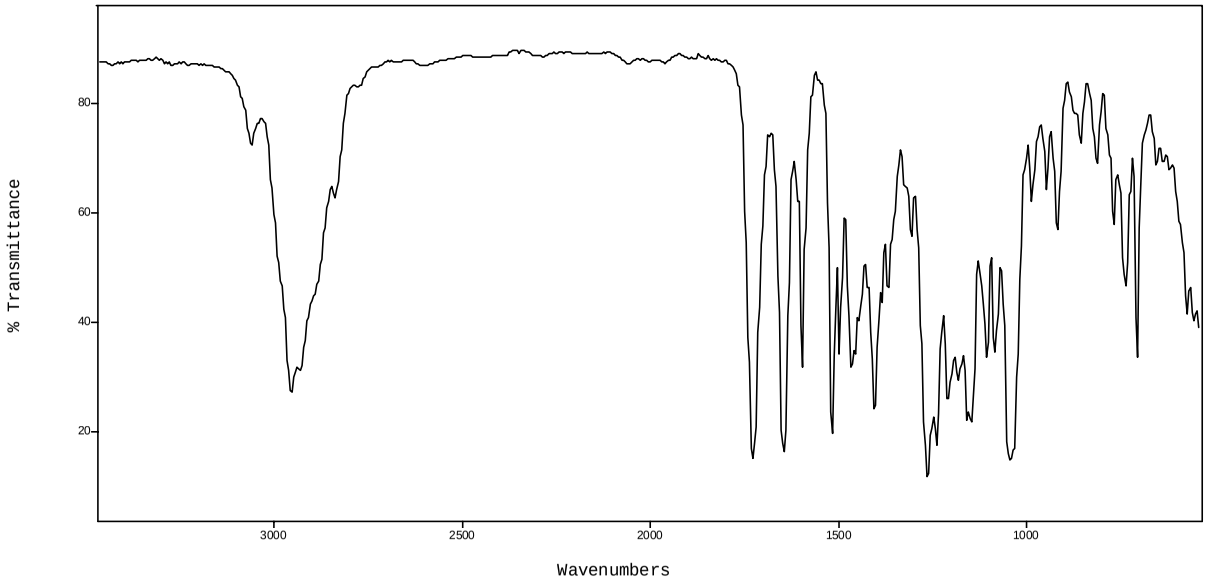


Figure A.7.62 FTIR Spectrum (thin film/NaCl) of Compound **251**.

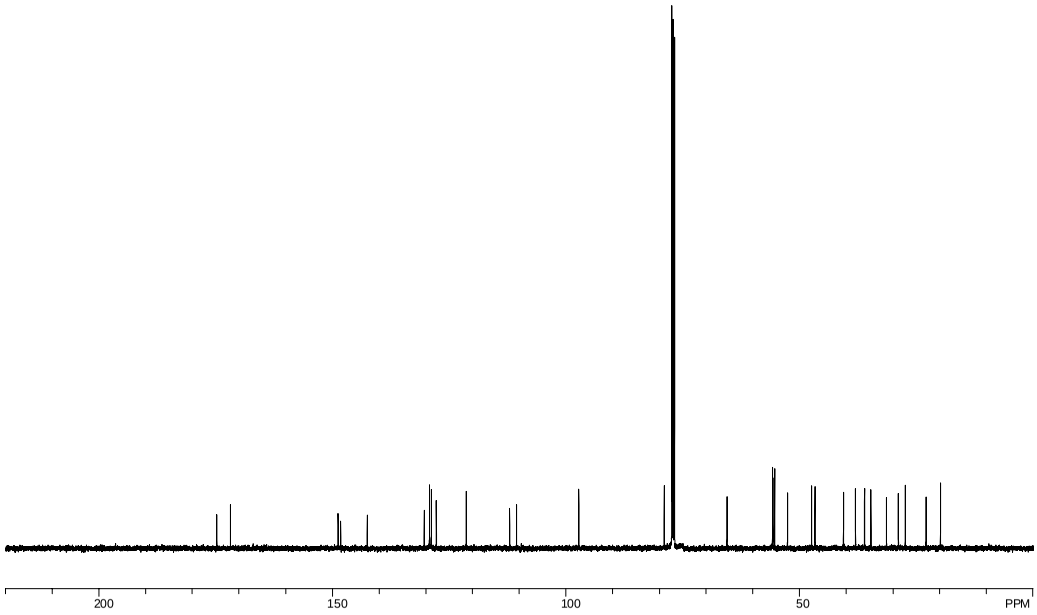


Figure A.7.63 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **251**.

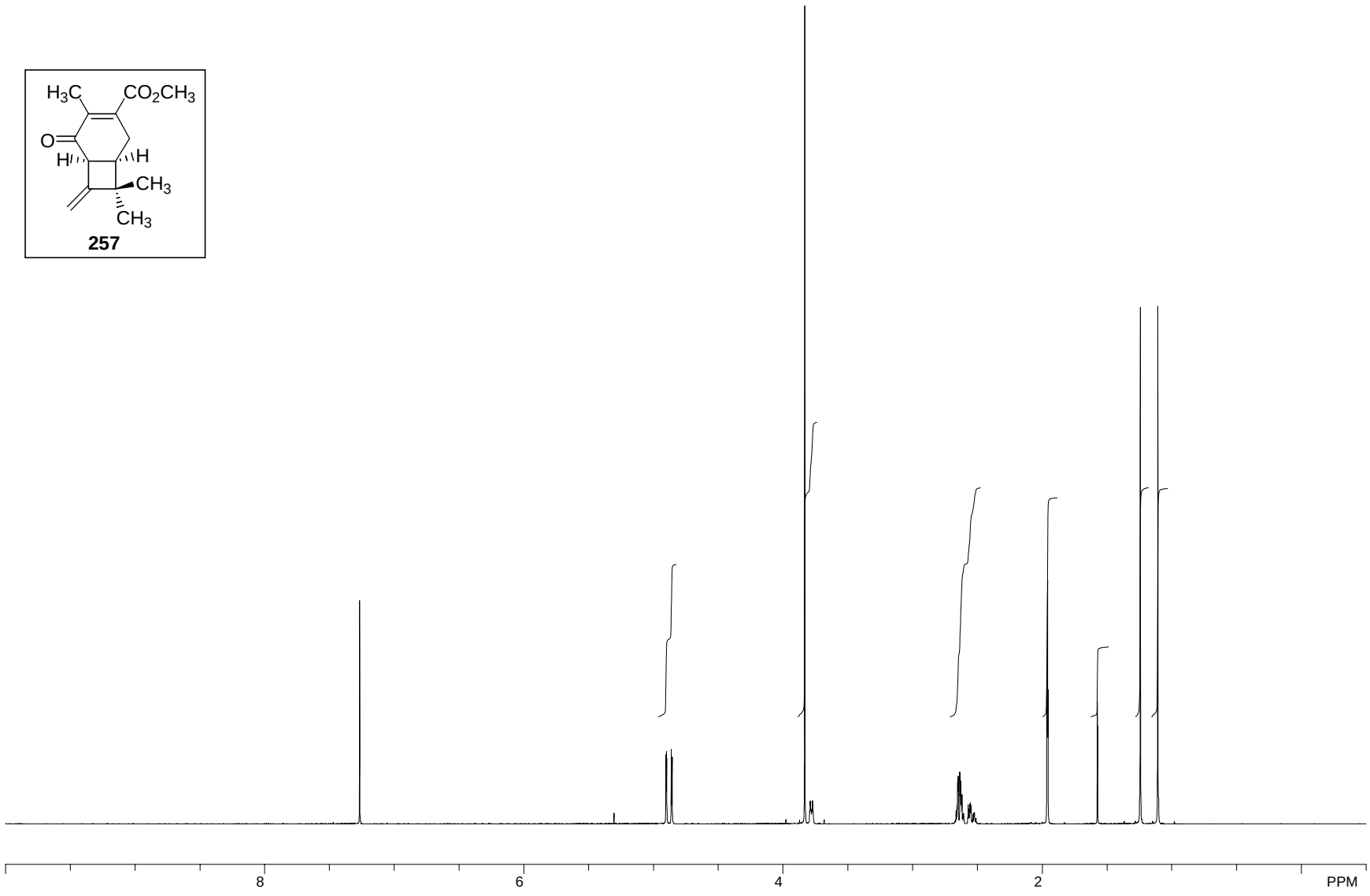


Figure A.7.64 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **257**.

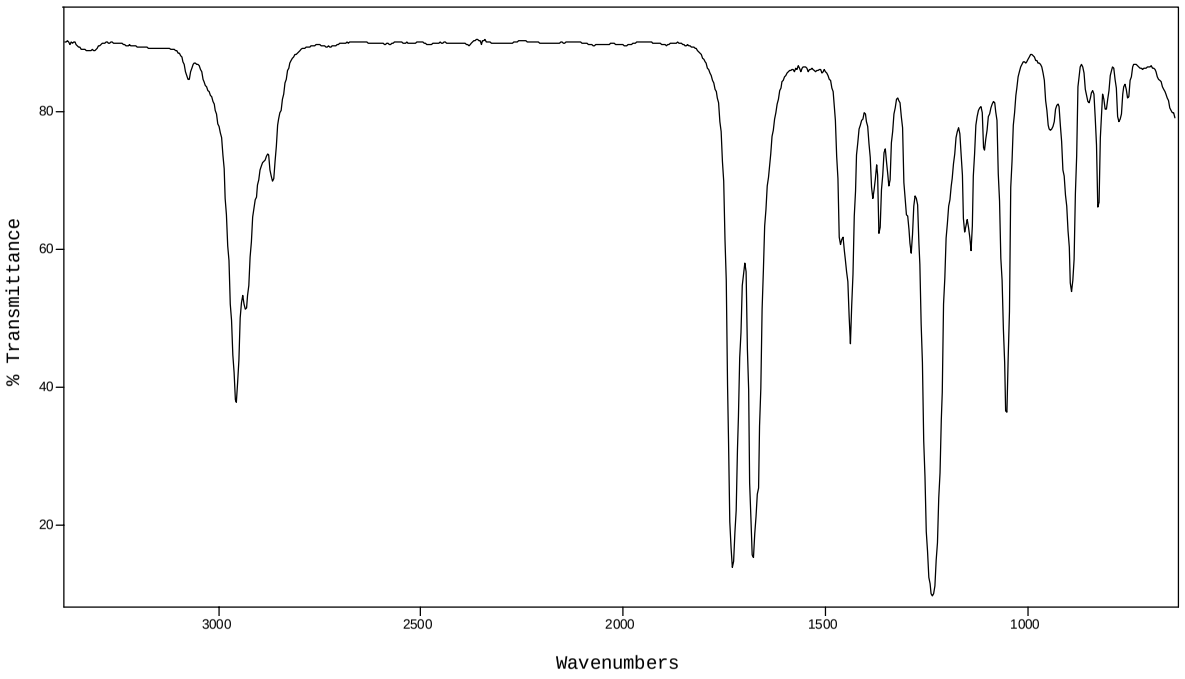


Figure A.7.65 FTIR Spectrum (thin film/NaCl) of Compound **257**.

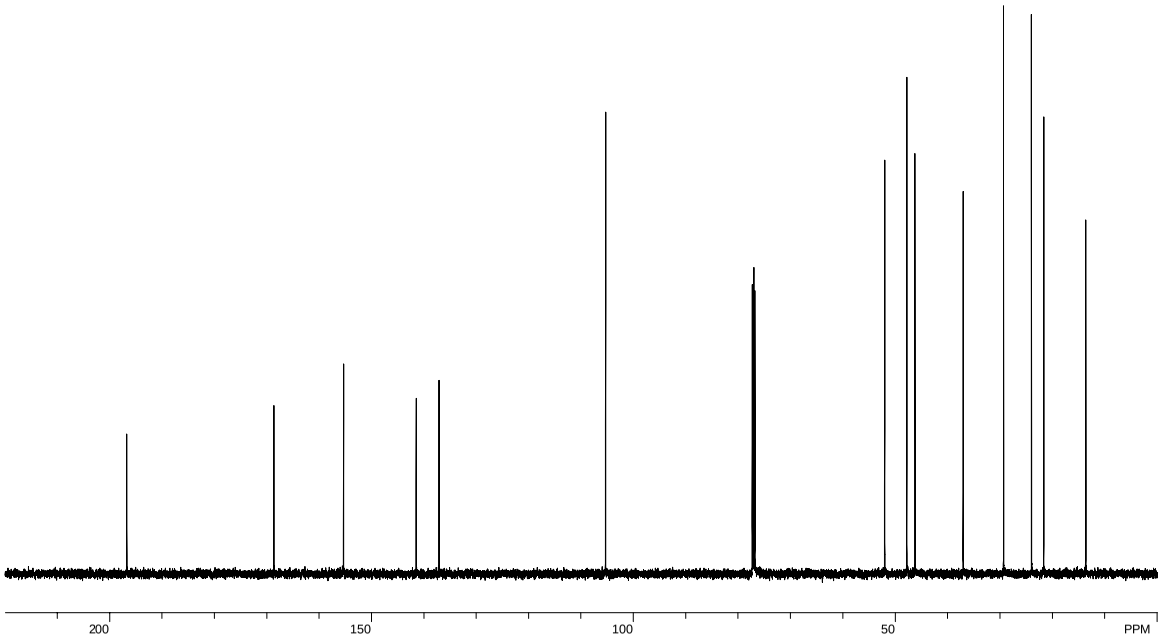


Figure A.7.66 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **257**.

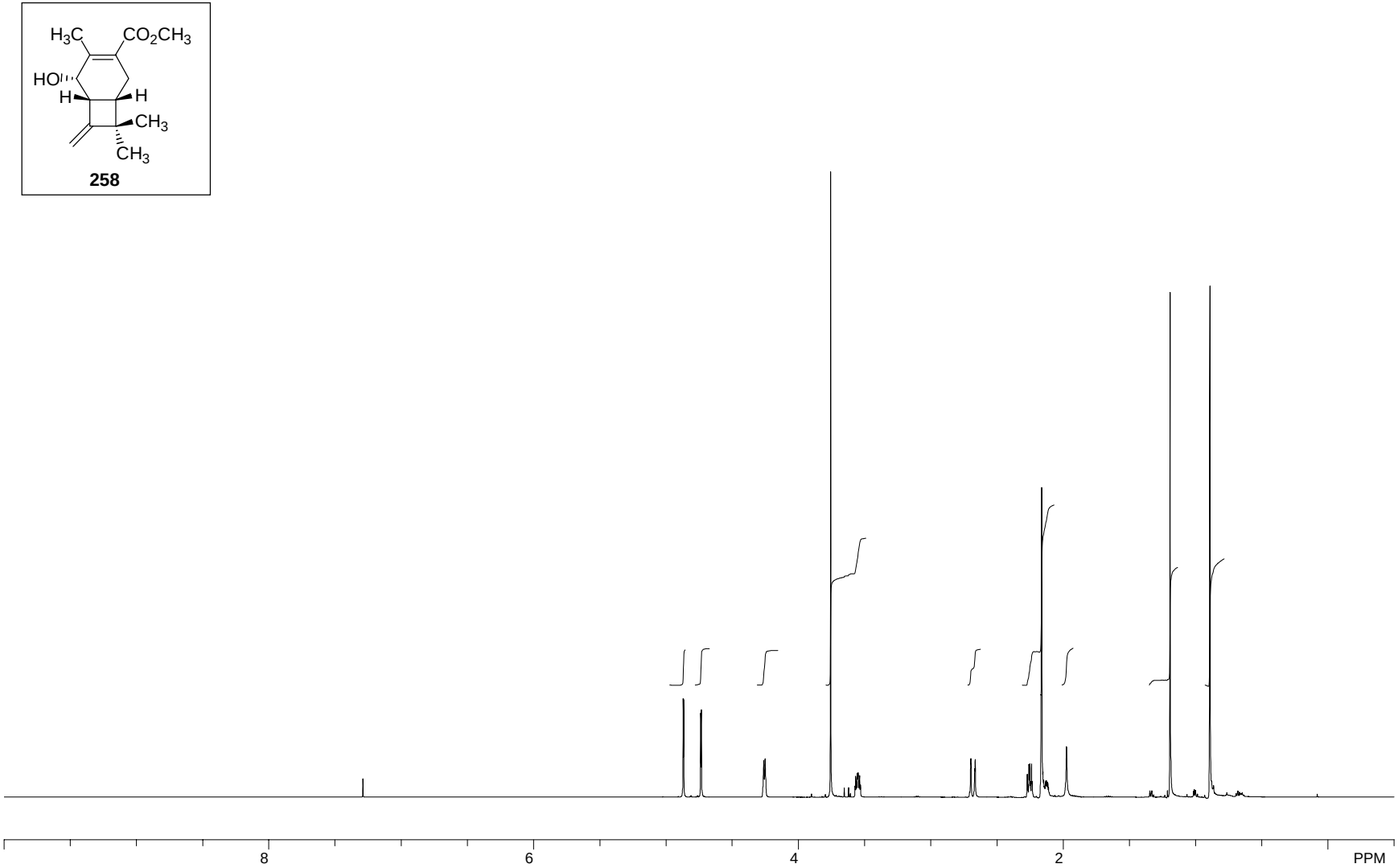


Figure A.7.67 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **258**.

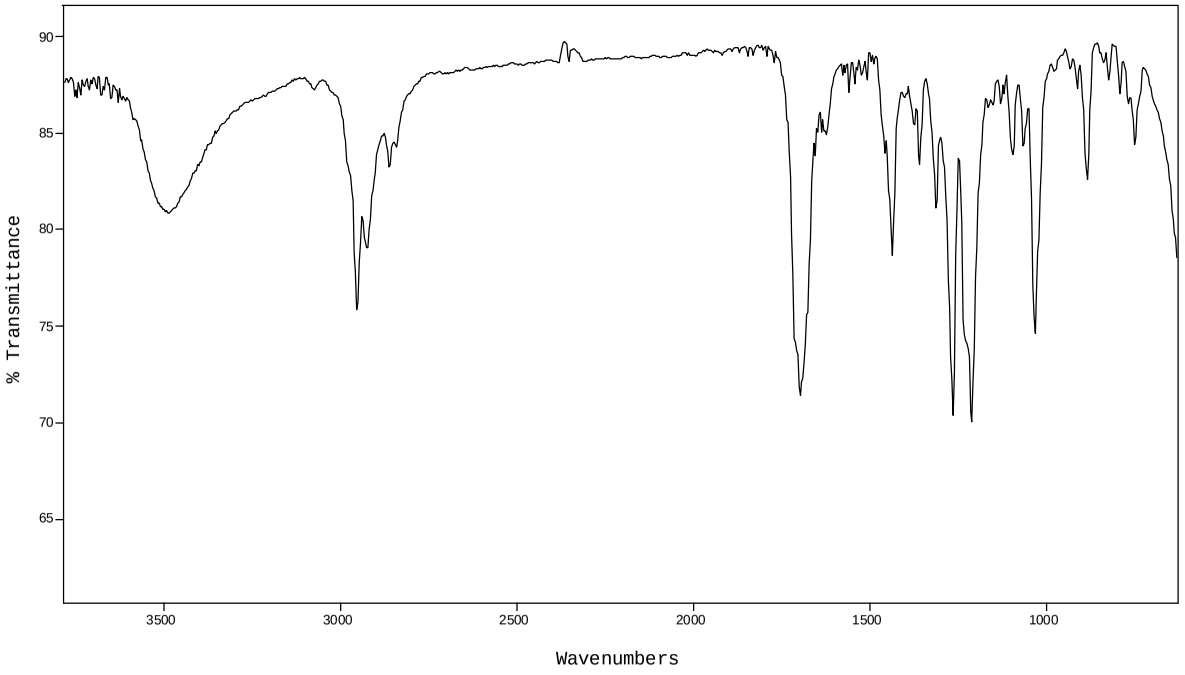


Figure A.7.68 FTIR Spectrum (thin film/NaCl) of Compound **258**.

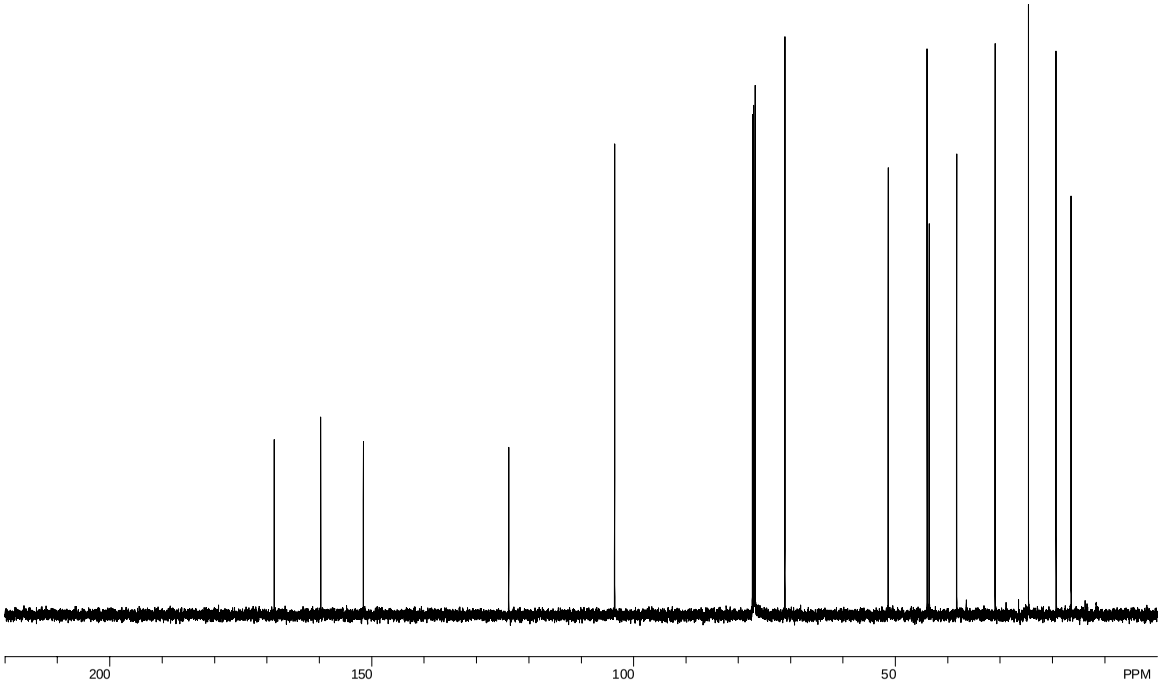


Figure A.7.69 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **258**.

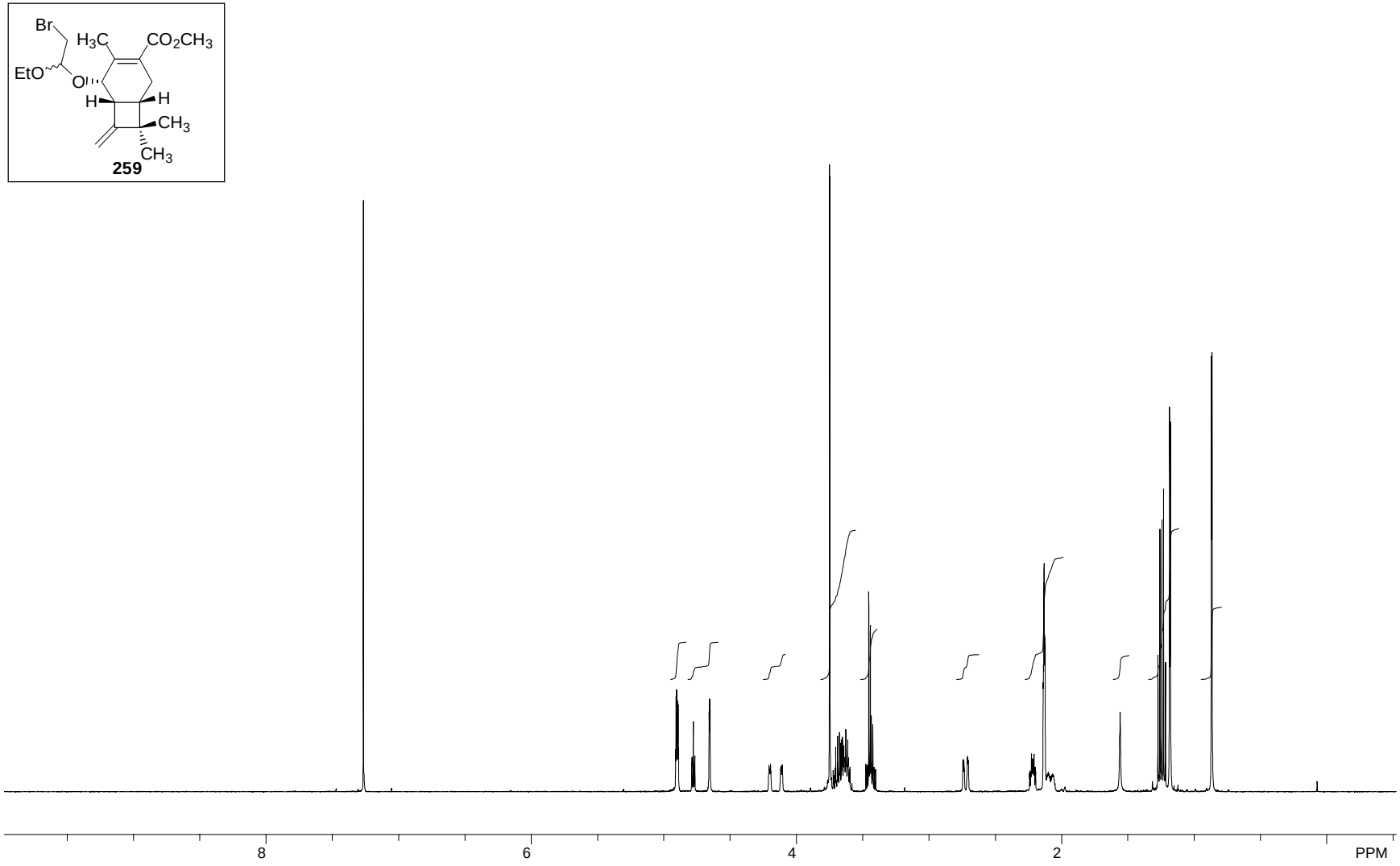


Figure A.7.70 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **259**.

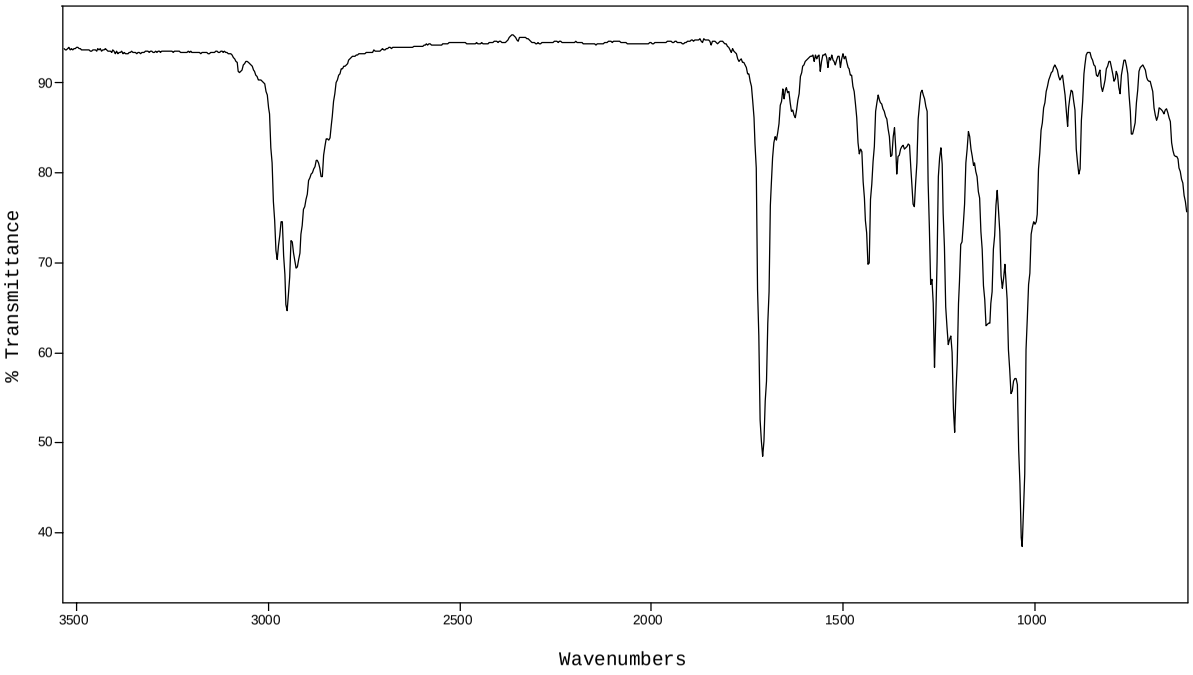


Figure A.7.71 FTIR Spectrum (thin film/NaCl) of Compound **259**.

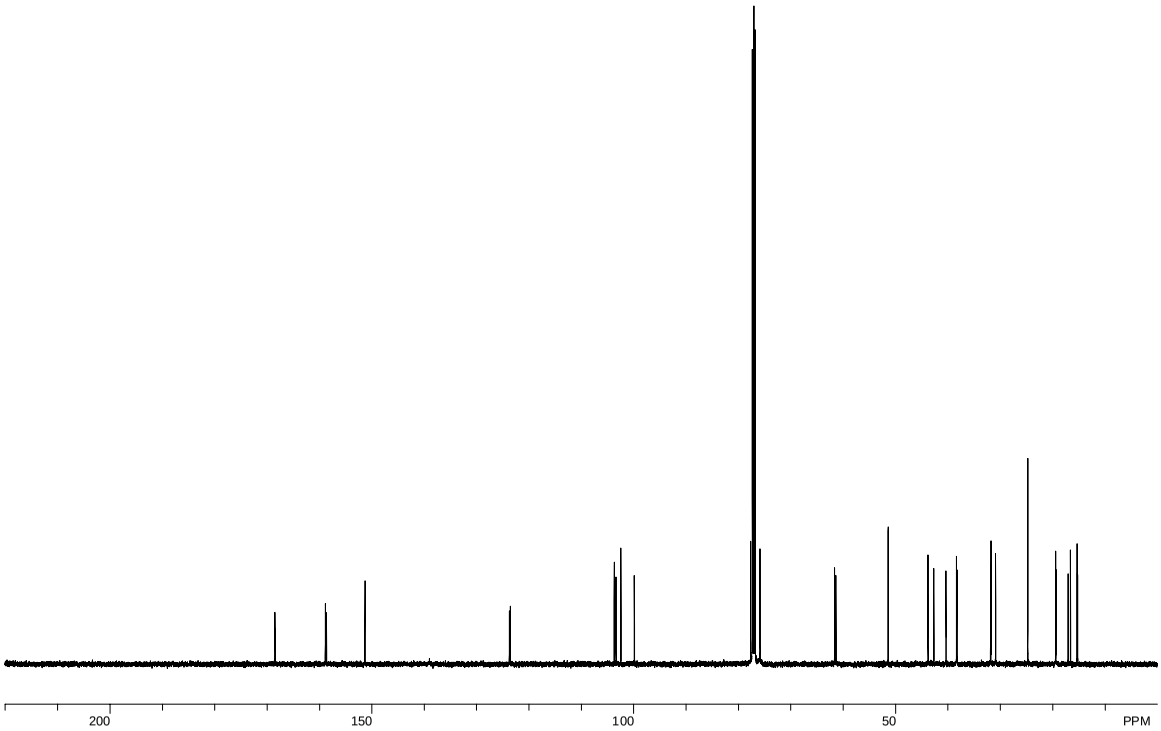


Figure A.7.72 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **259**.

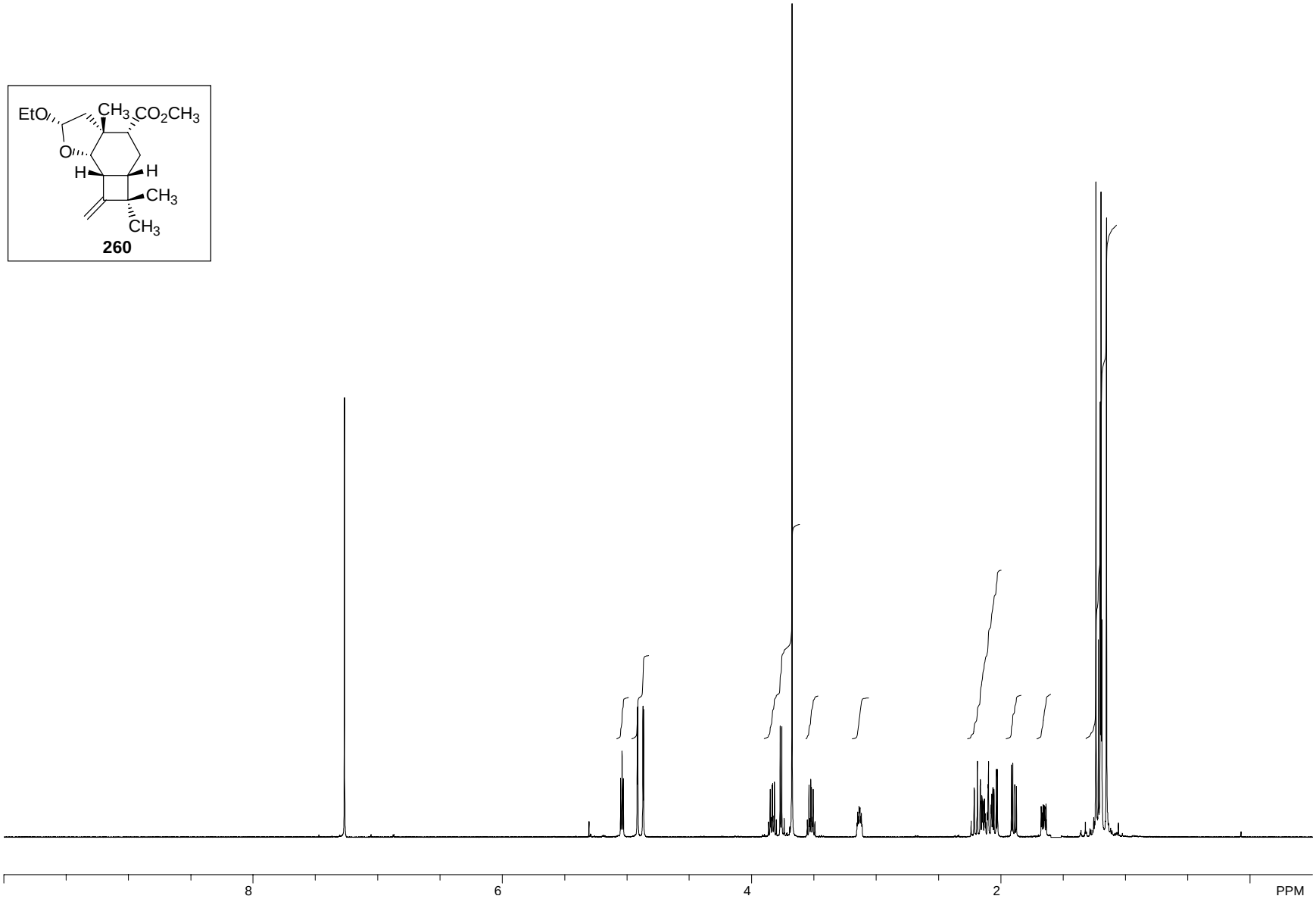


Figure A.7.73 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **260**.

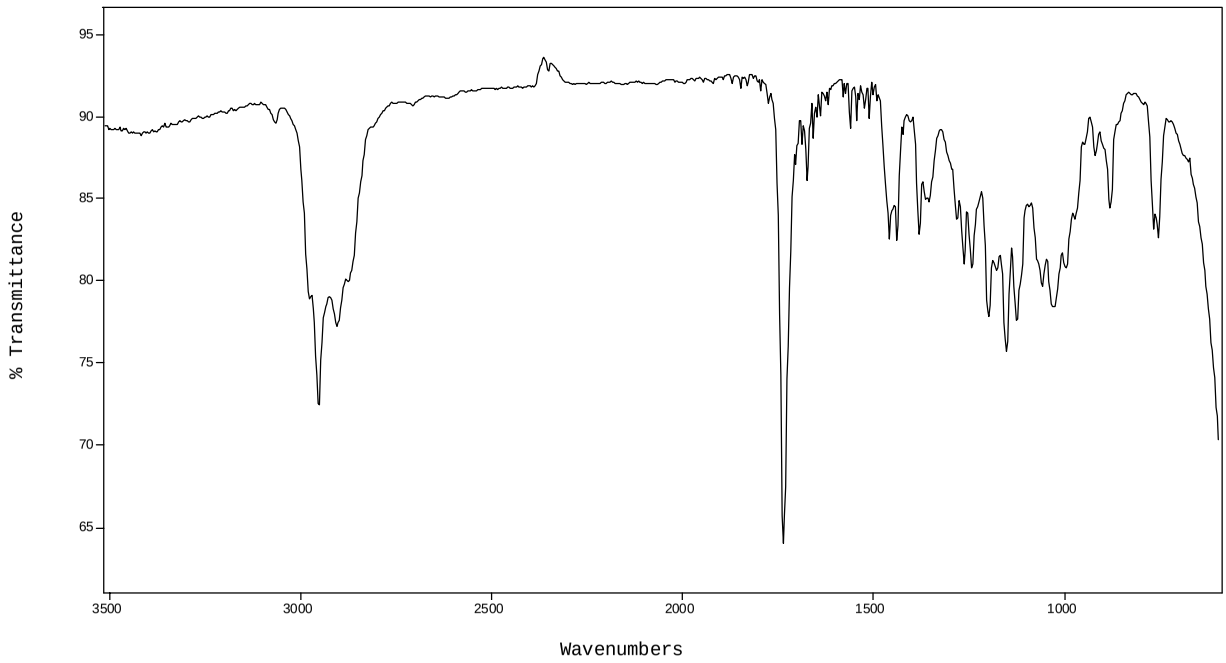


Figure A.7.74 FTIR Spectrum (thin film/NaCl) of Compound **260**.

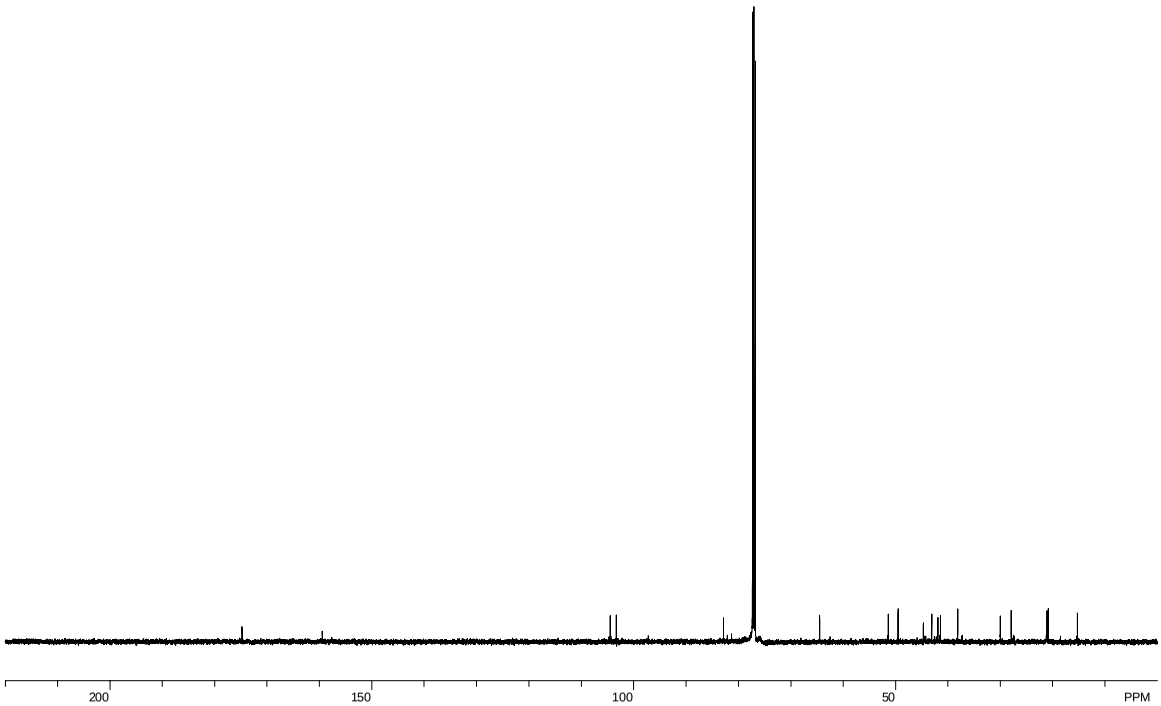


Figure A.7.75 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **260**.

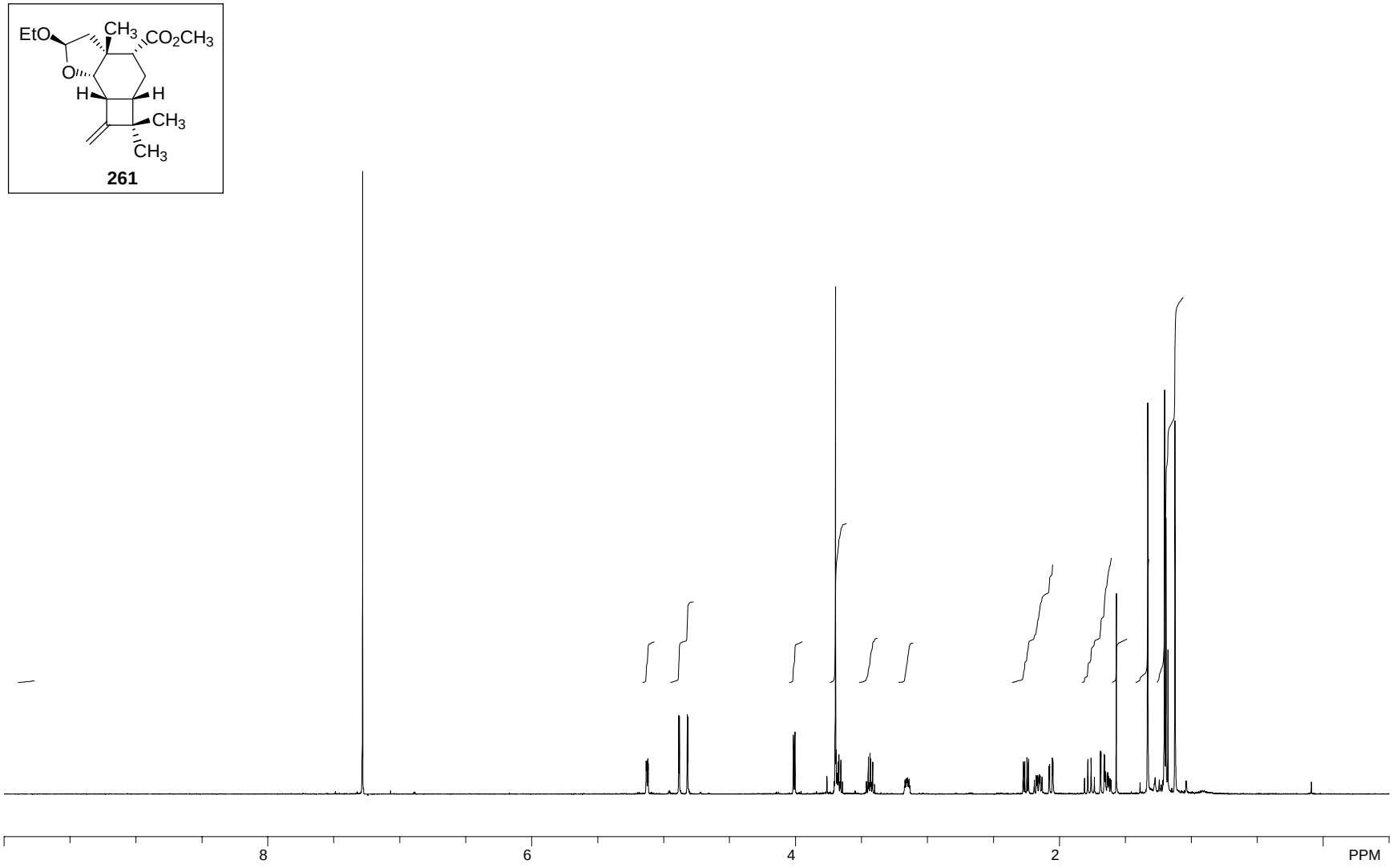


Figure A.7.76 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **261**.

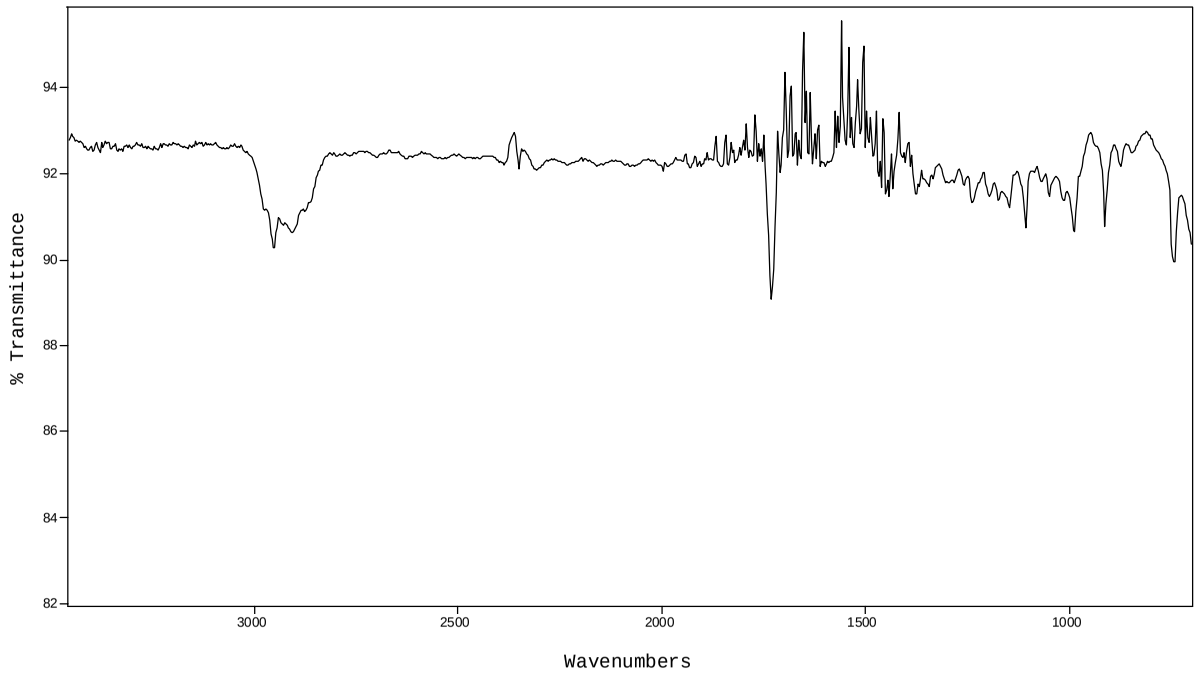


Figure A.7.77 FTIR Spectrum (thin film/NaCl) of Compound **261**.

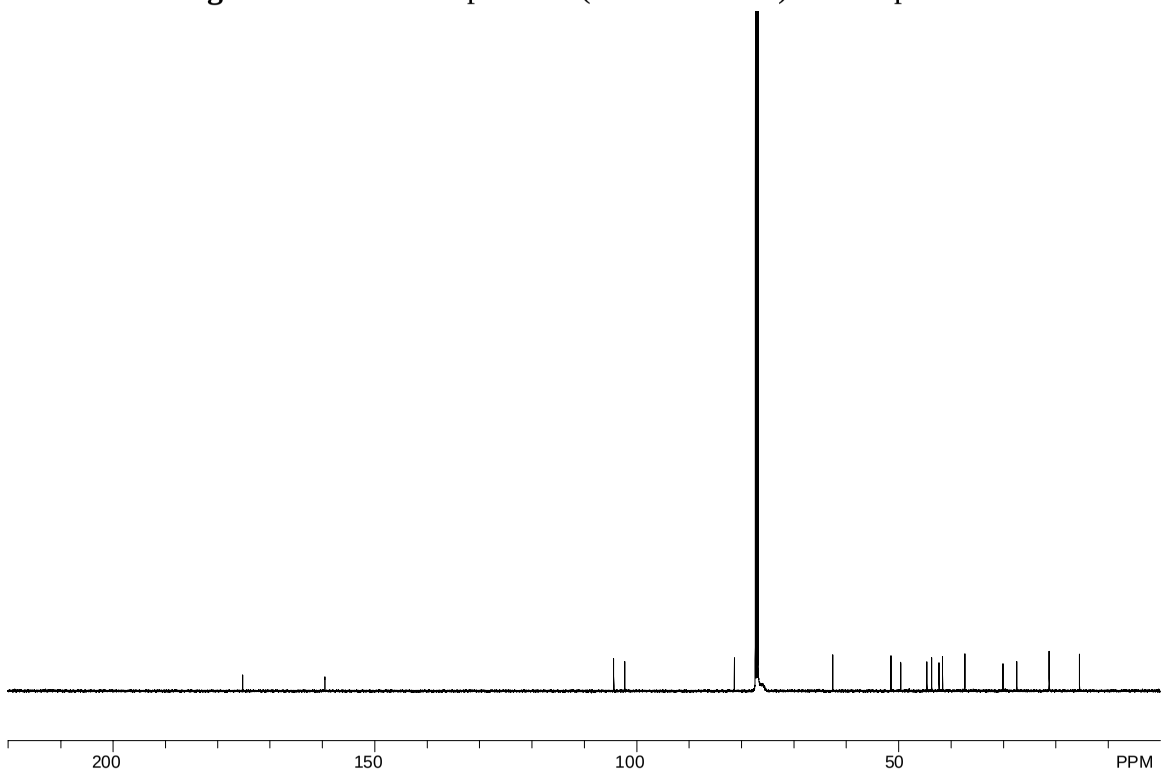


Figure A.7.78 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **261**.

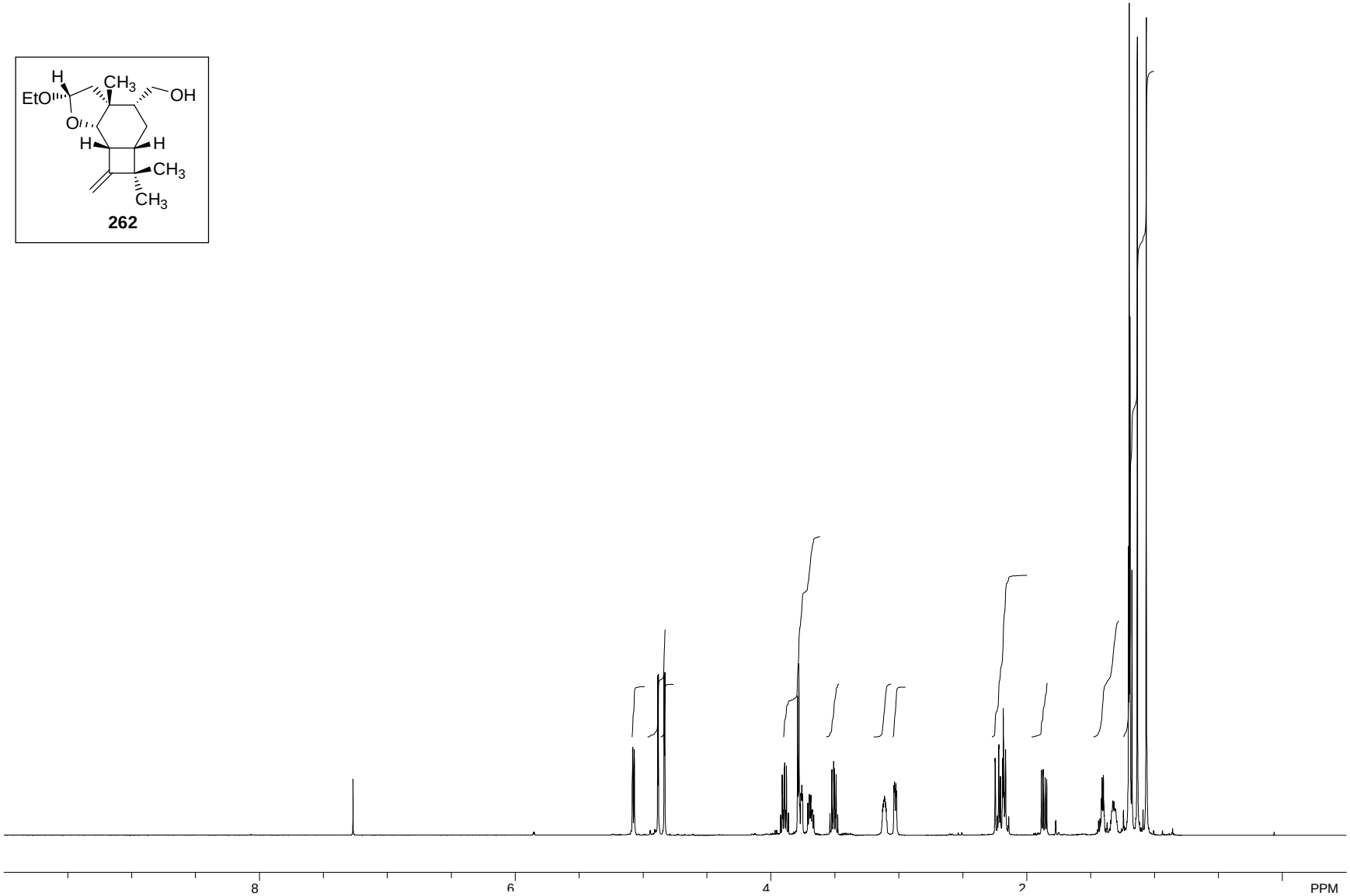


Figure A.7.79 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **262**.

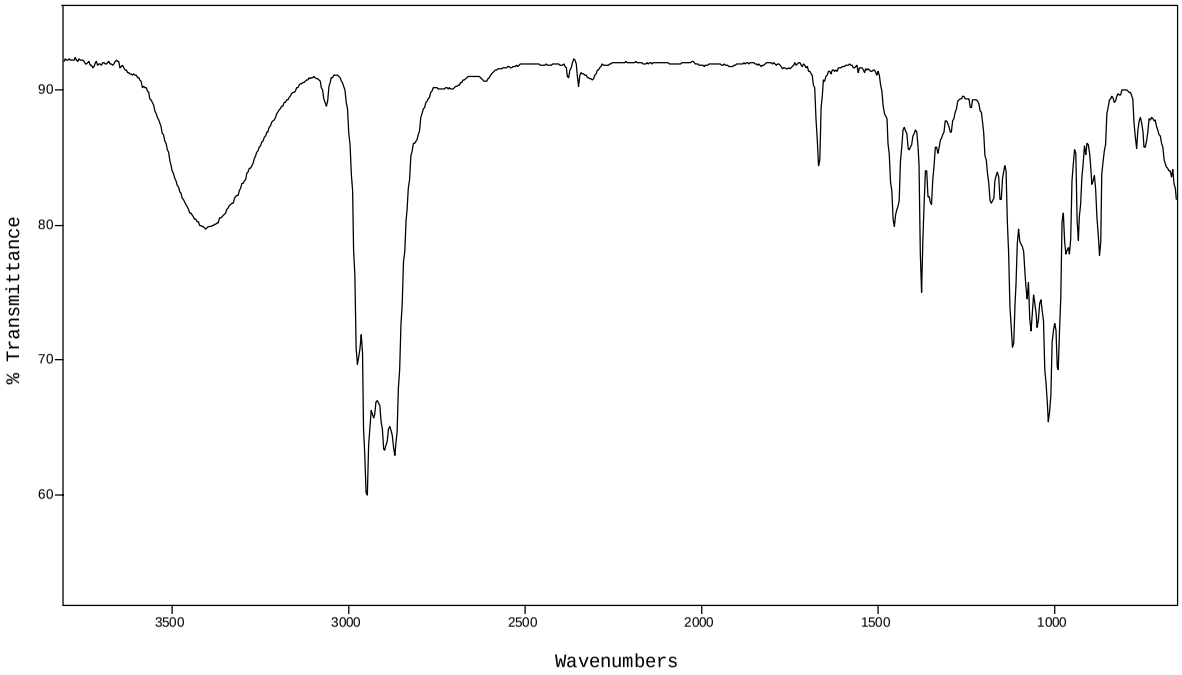


Figure A.7.80 FTIR Spectrum (thin film/NaCl) of Compound **262**.

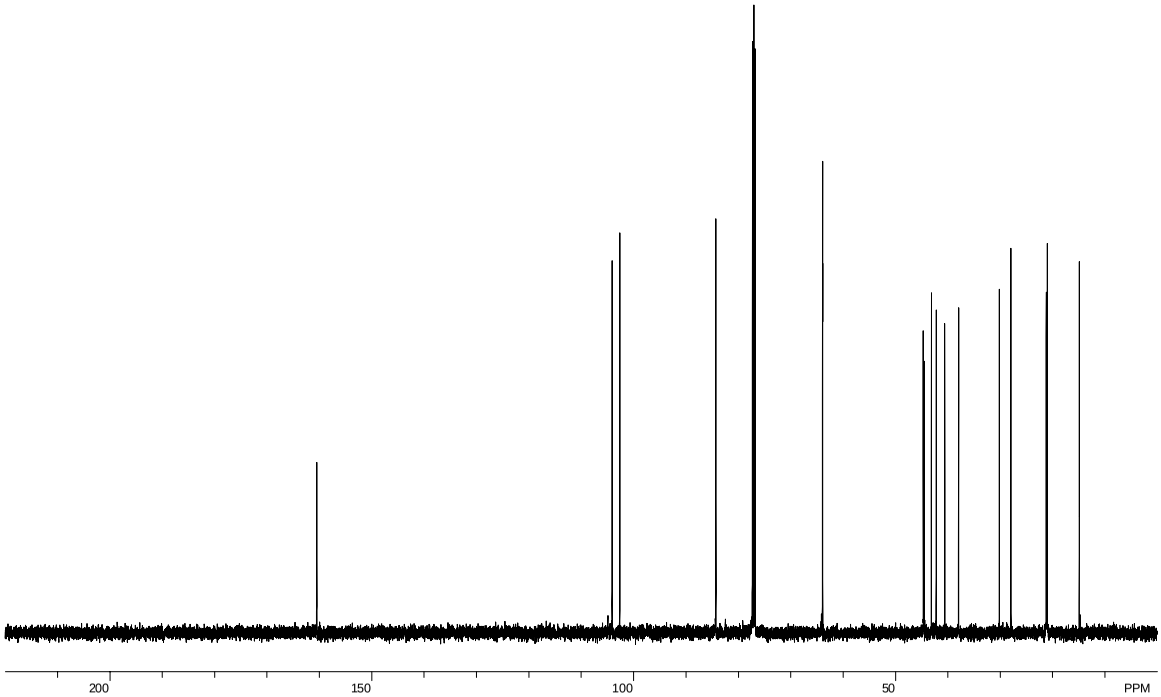


Figure A.7.81 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **262.**

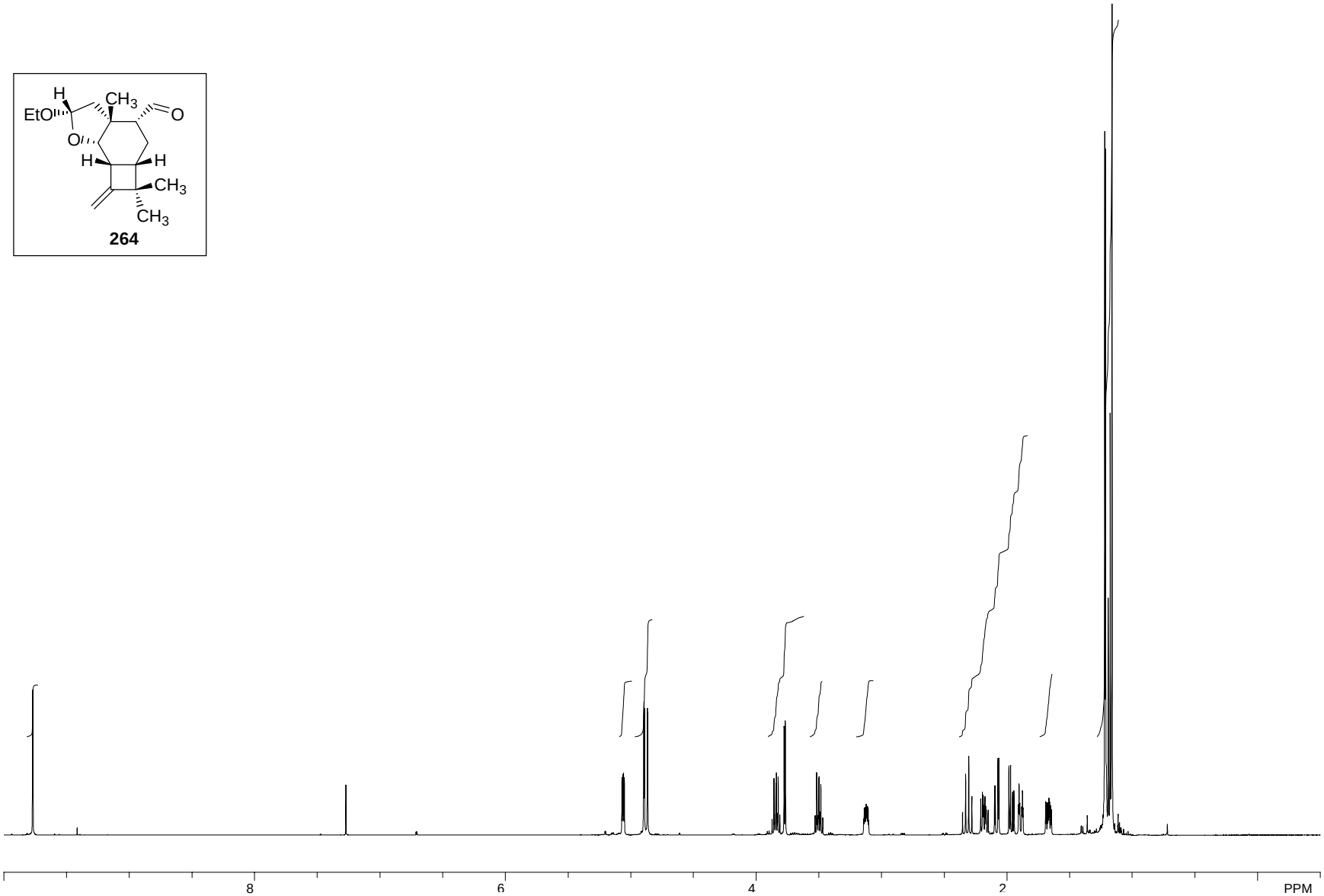


Figure A.7.82 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **264**.

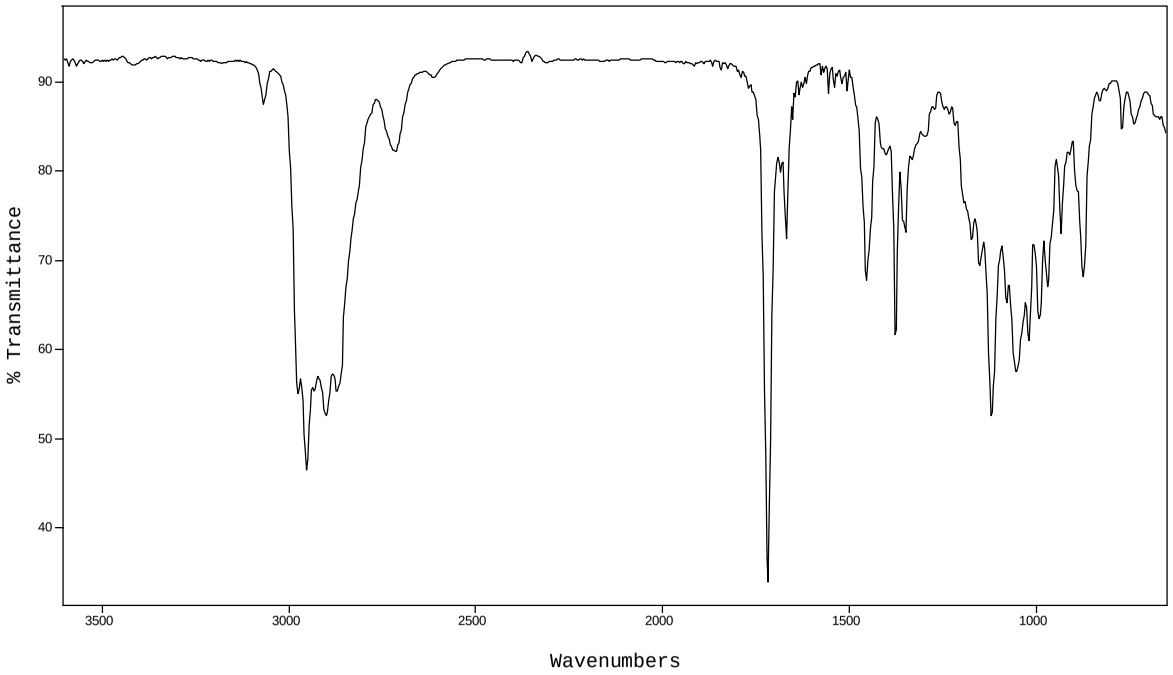


Figure A.7.83 FTIR Spectrum (thin film/NaCl) of Compound **264**.

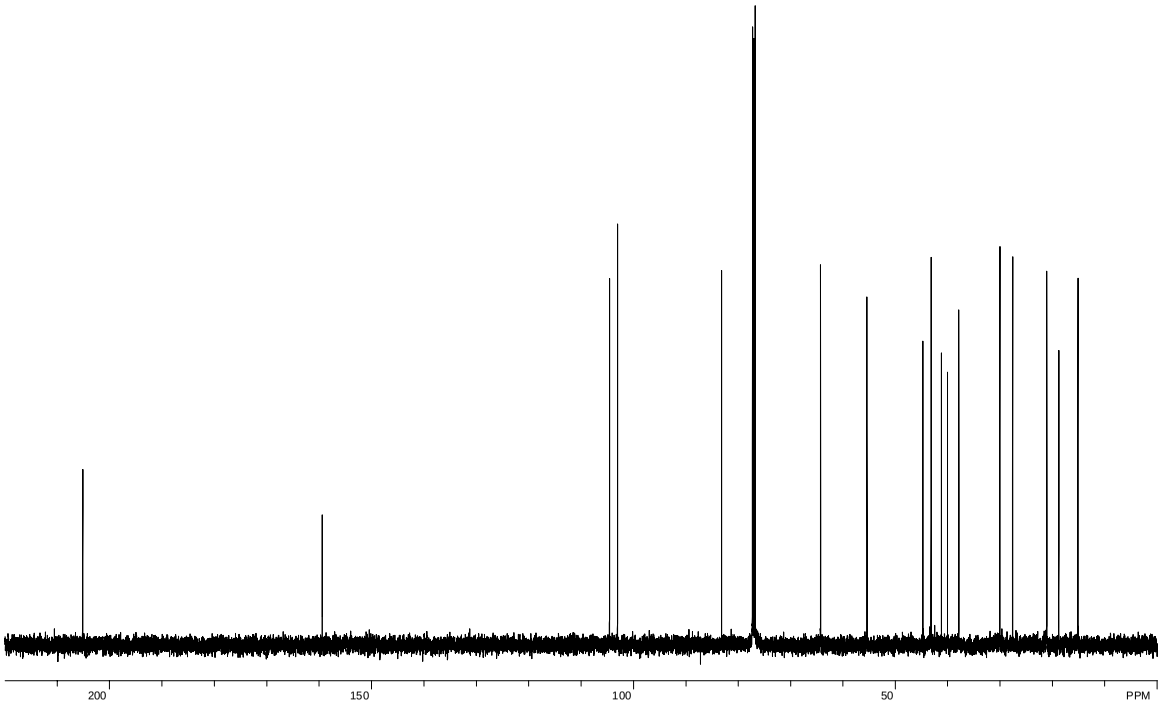


Figure A.7.84 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **264**.

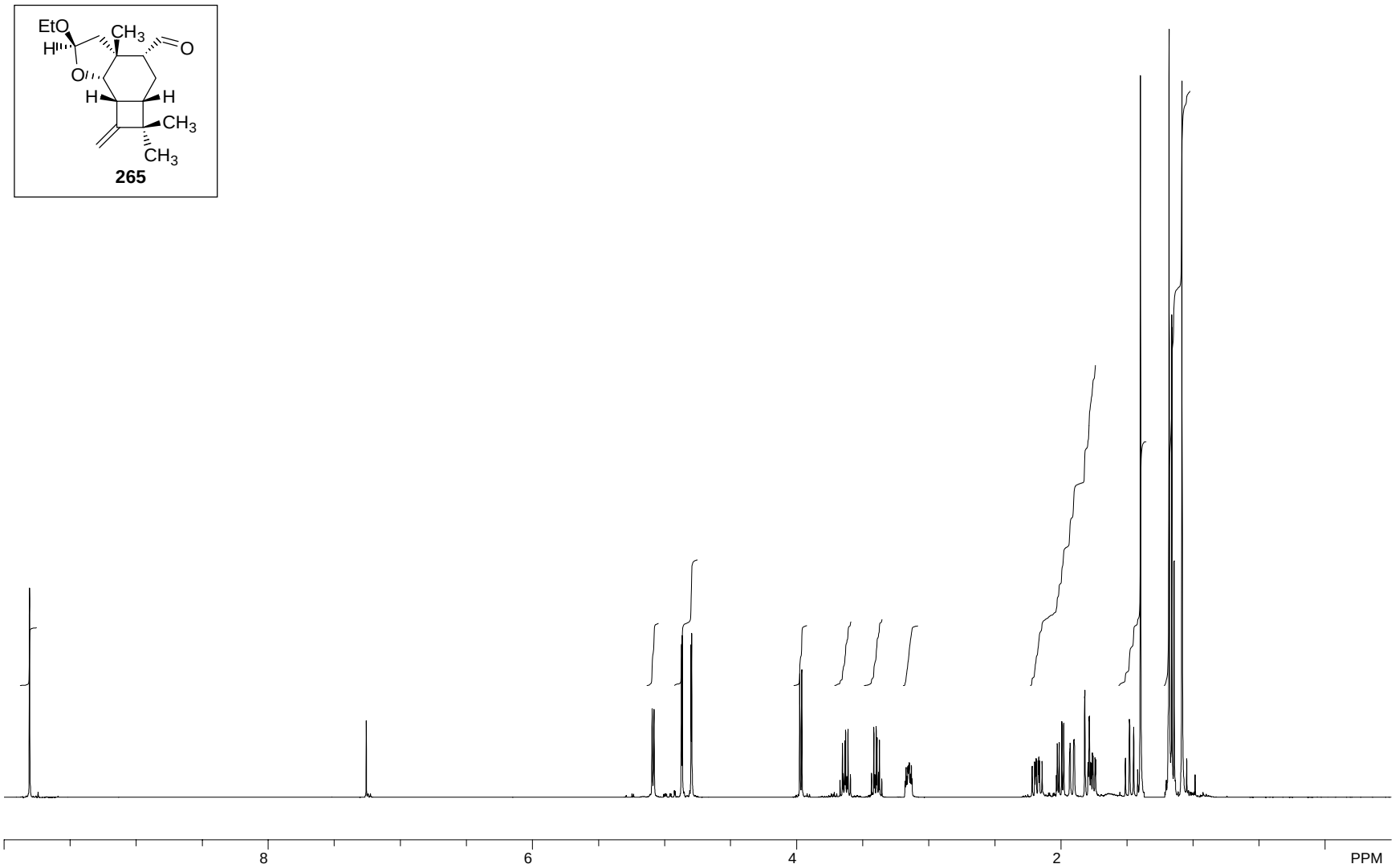


Figure A.7.85 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **265**.

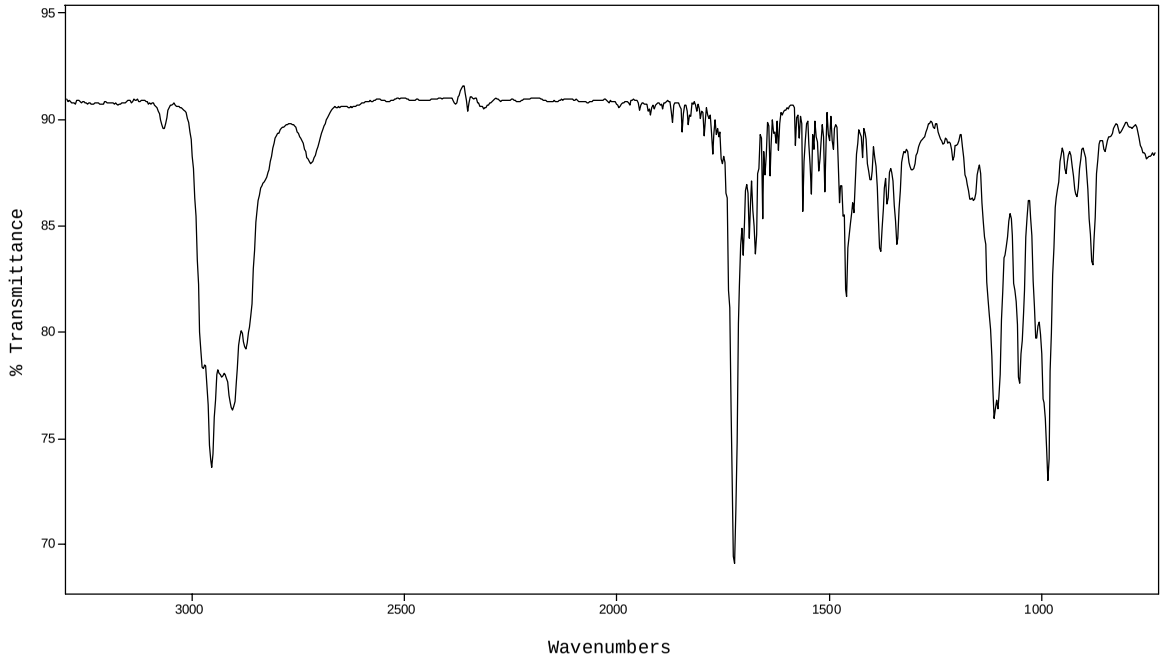


Figure A.7.86 FTIR Spectrum (thin film/NaCl) of Compound **265**.

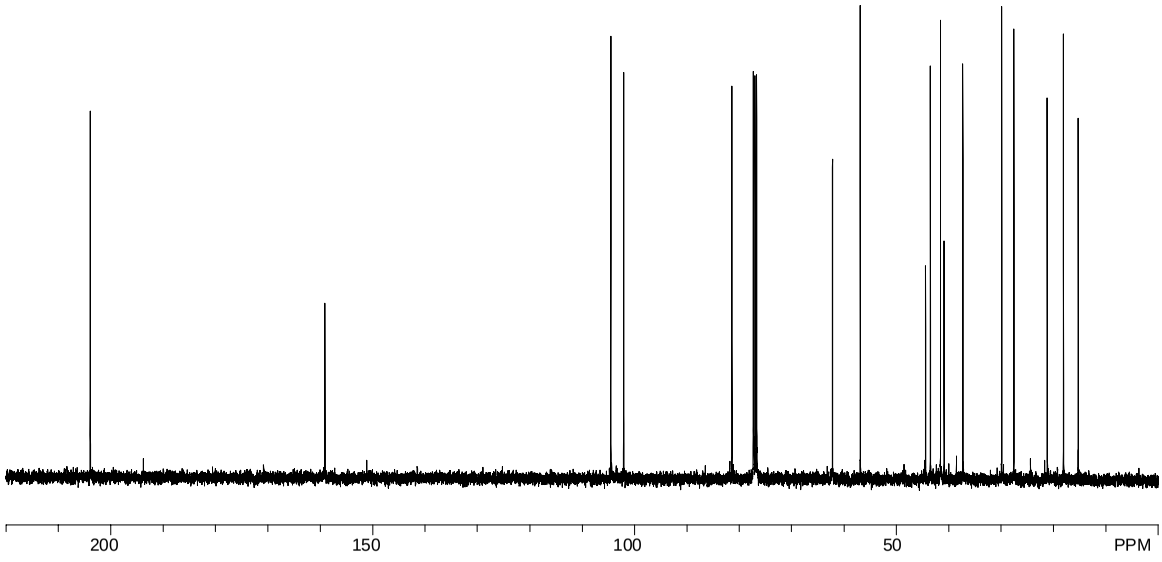


Figure A.7.87 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **265**.

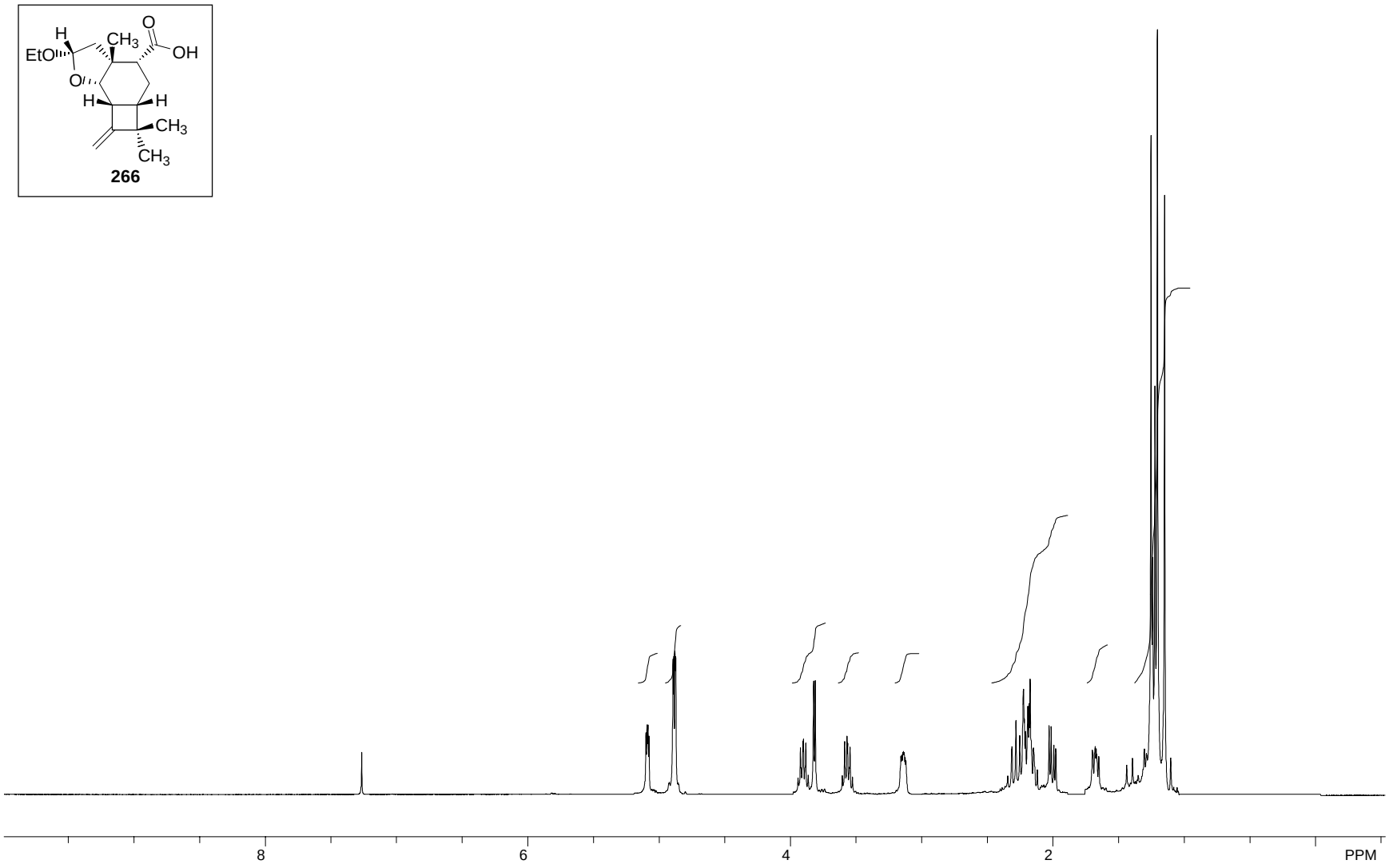


Figure A.7.88 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **266**.

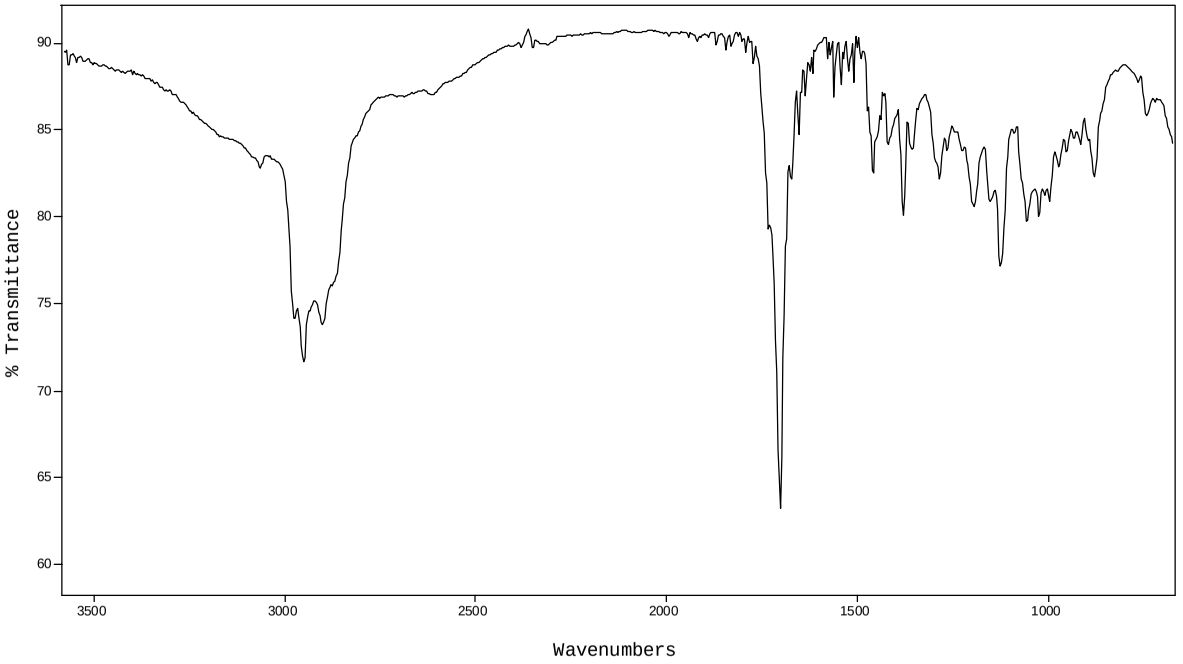


Figure A.7.89 FTIR Spectrum (thin film/NaCl) of Compound **266**.

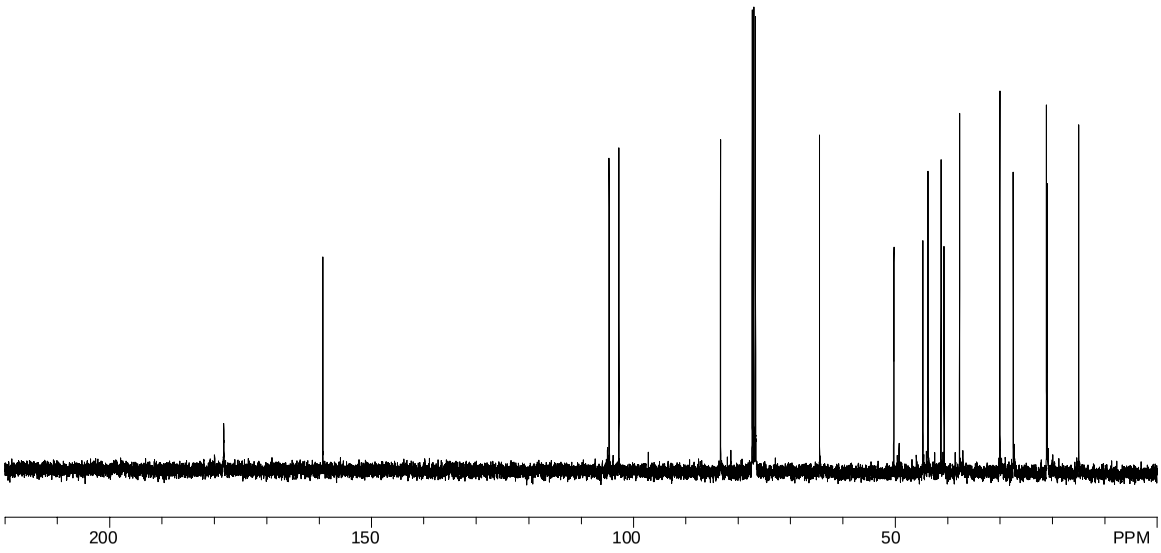


Figure A.7.90 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **266**.

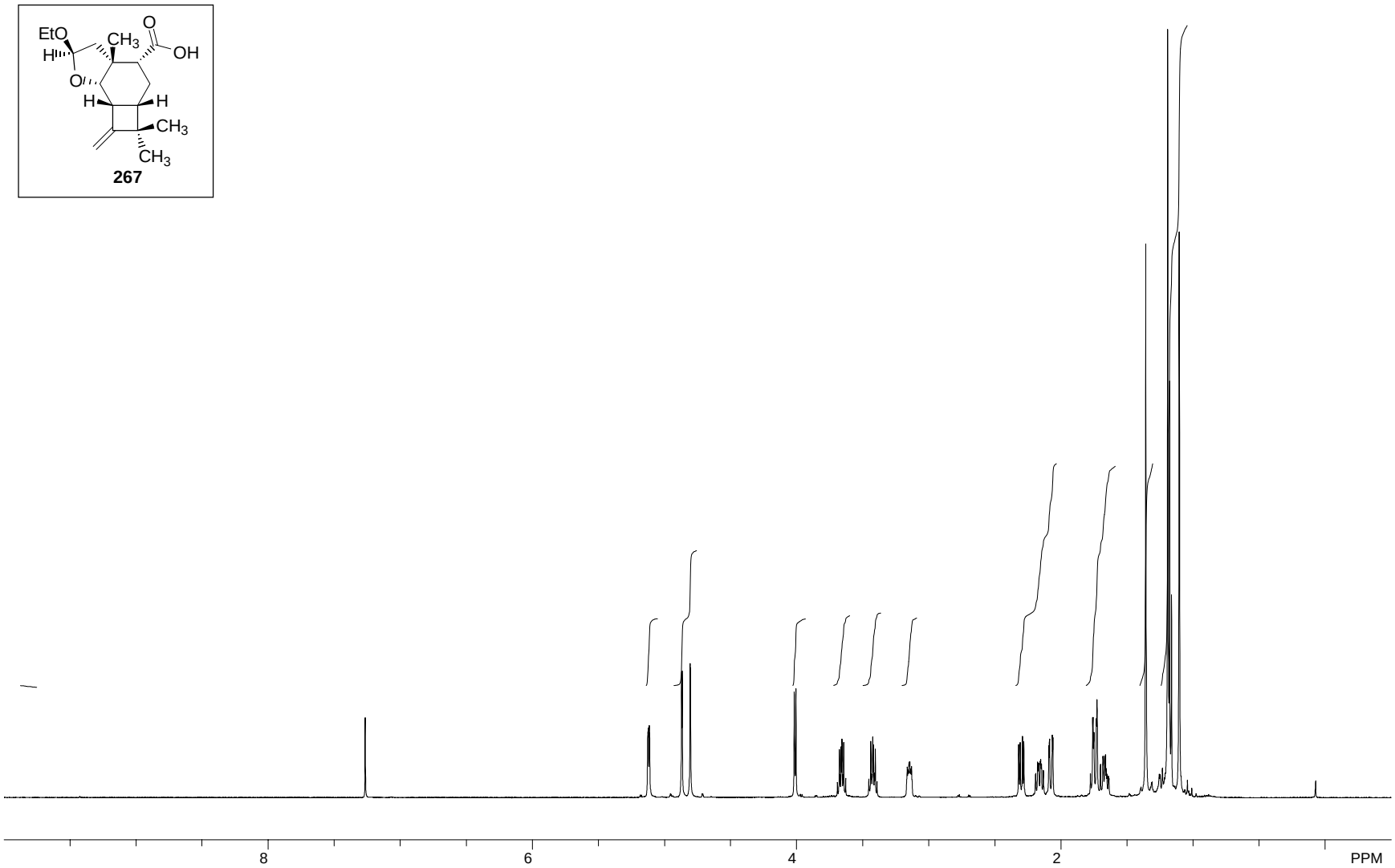


Figure A.7.91 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **267**.

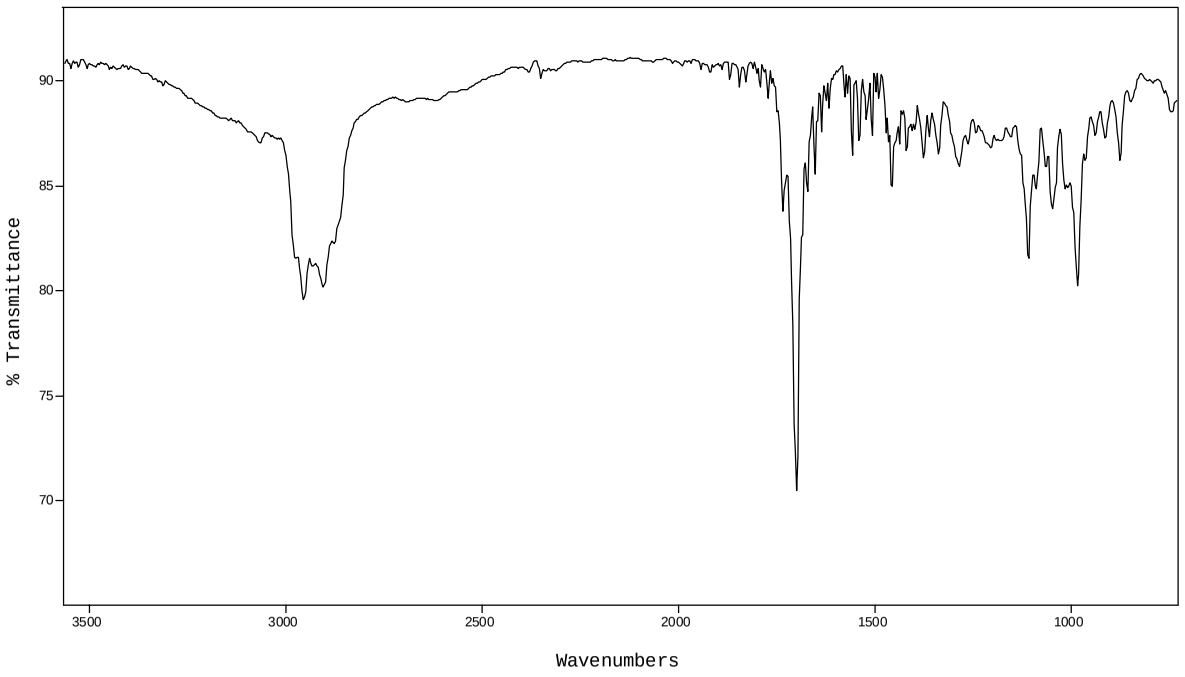


Figure A.7.92 FTIR Spectrum (thin film/NaCl) of Compound **267**.

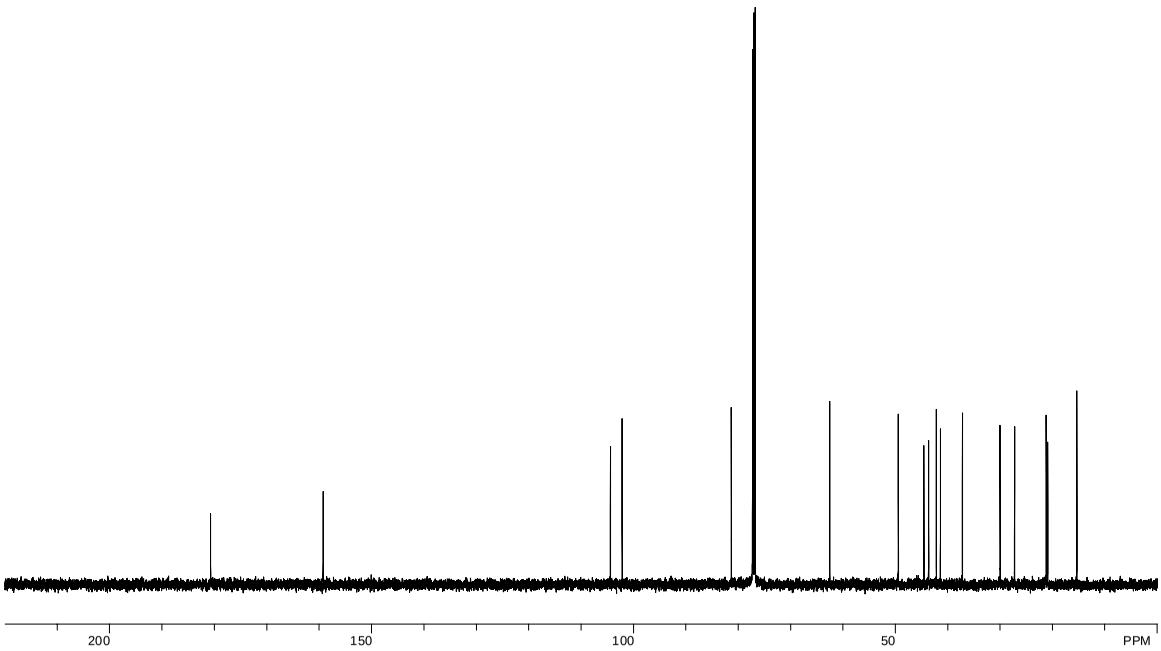


Figure A.7.93 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **267**.

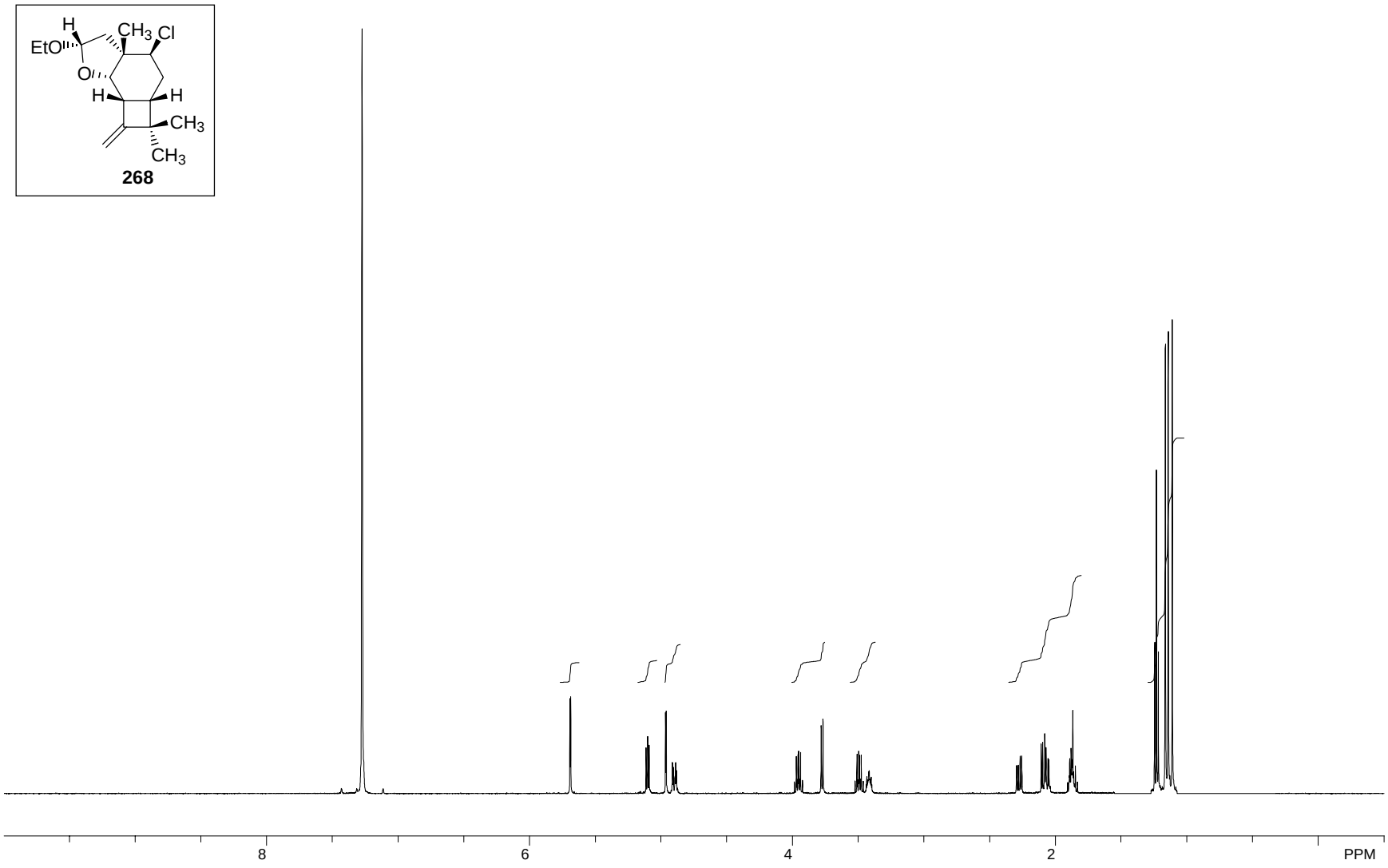


Figure A.7.94 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **268**.

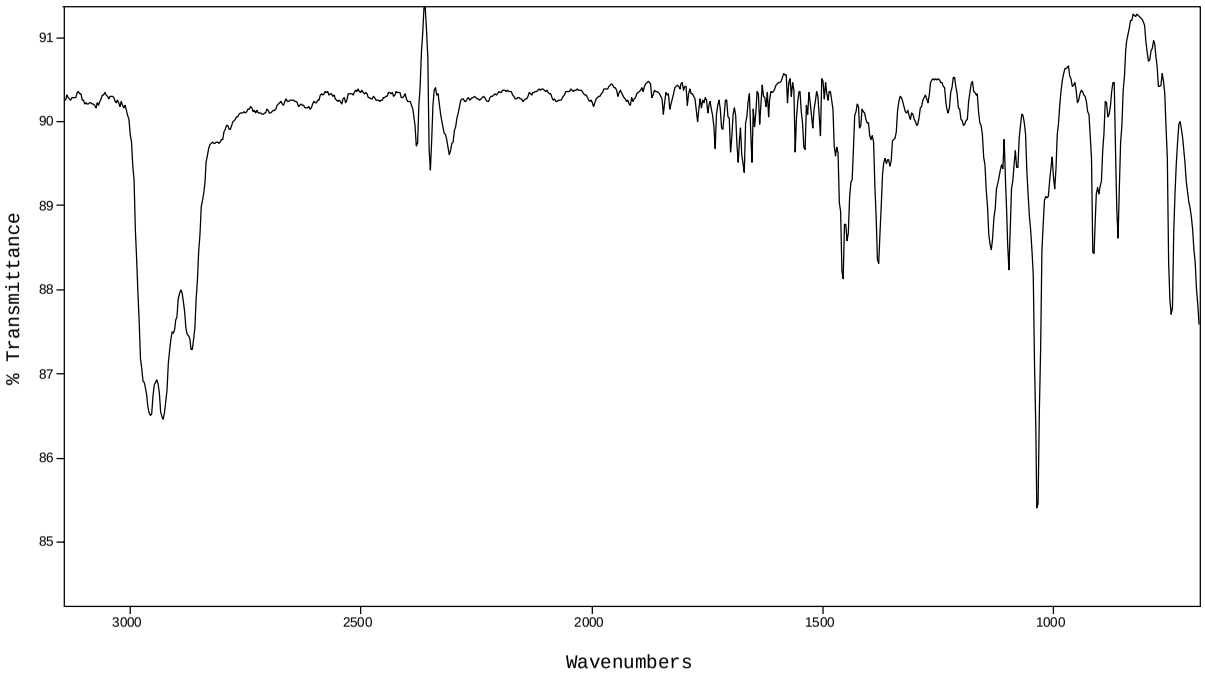


Figure A.7.95 FTIR Spectrum (thin film/NaCl) of Compound **268**.

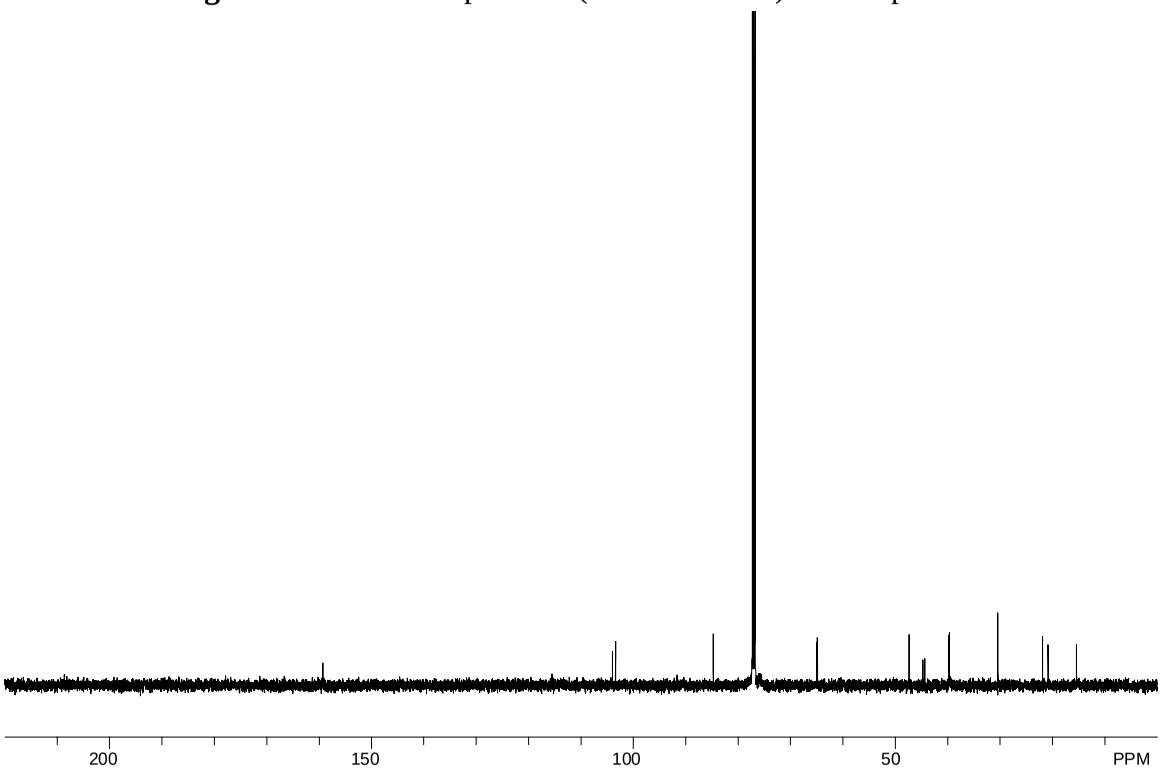


Figure A.7.96 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **268.**

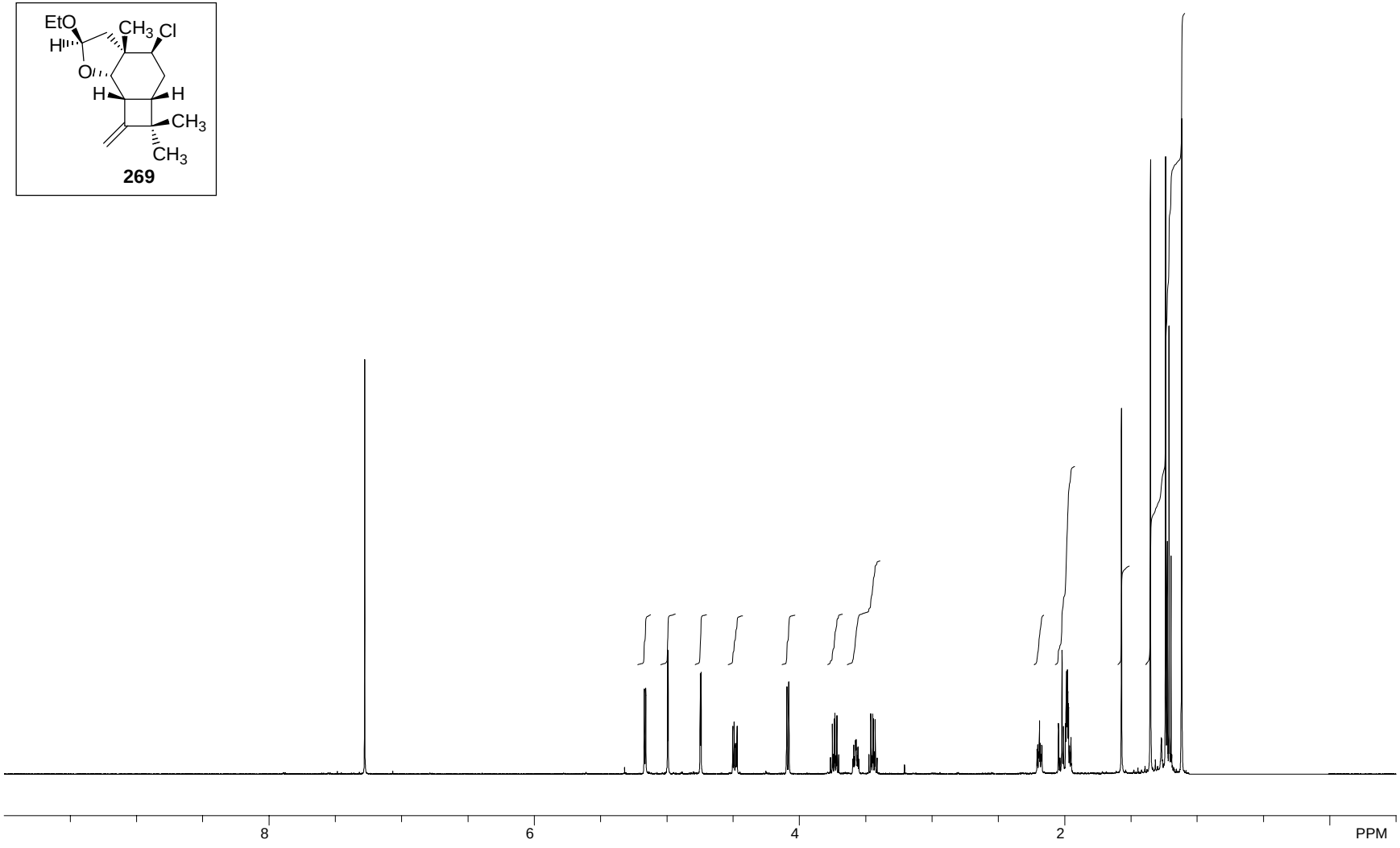


Figure A.7.947 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **269**.

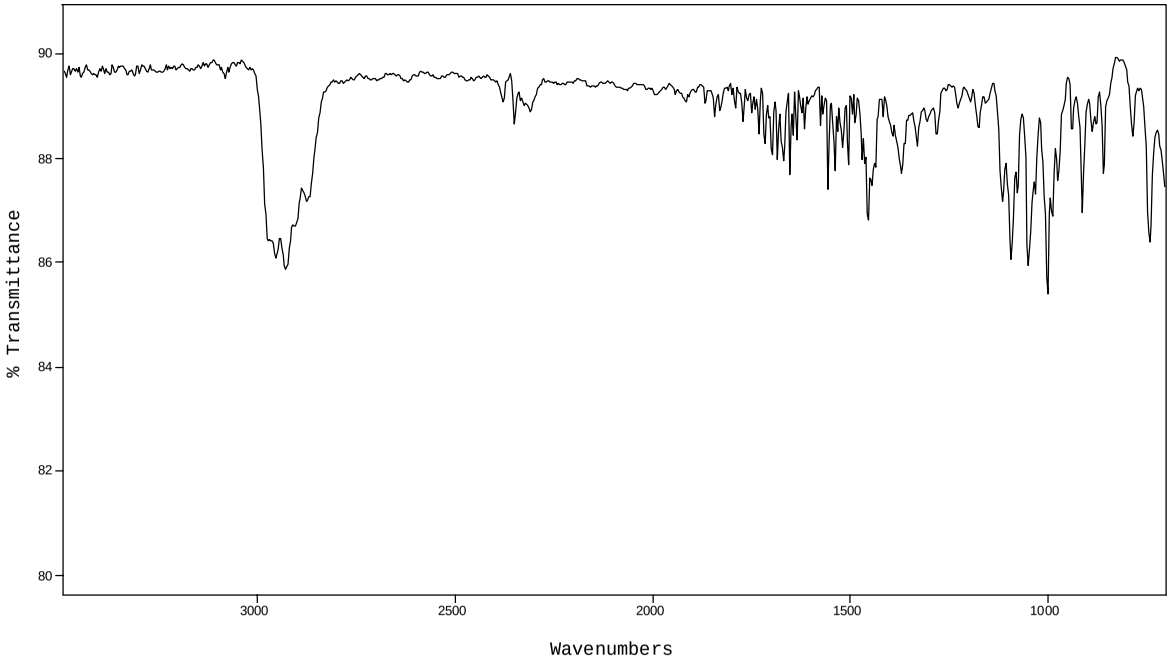


Figure A.7.98 FTIR Spectrum (thin film/NaCl) of Compound **269**.

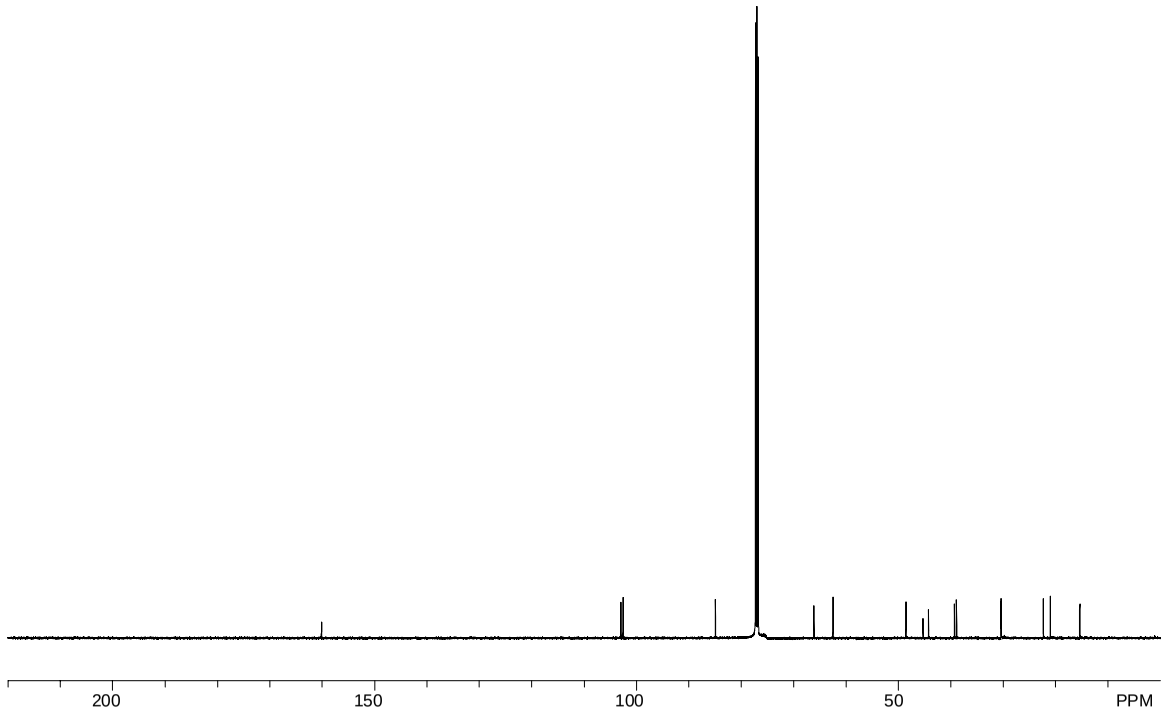


Figure A.7.99 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **269**.

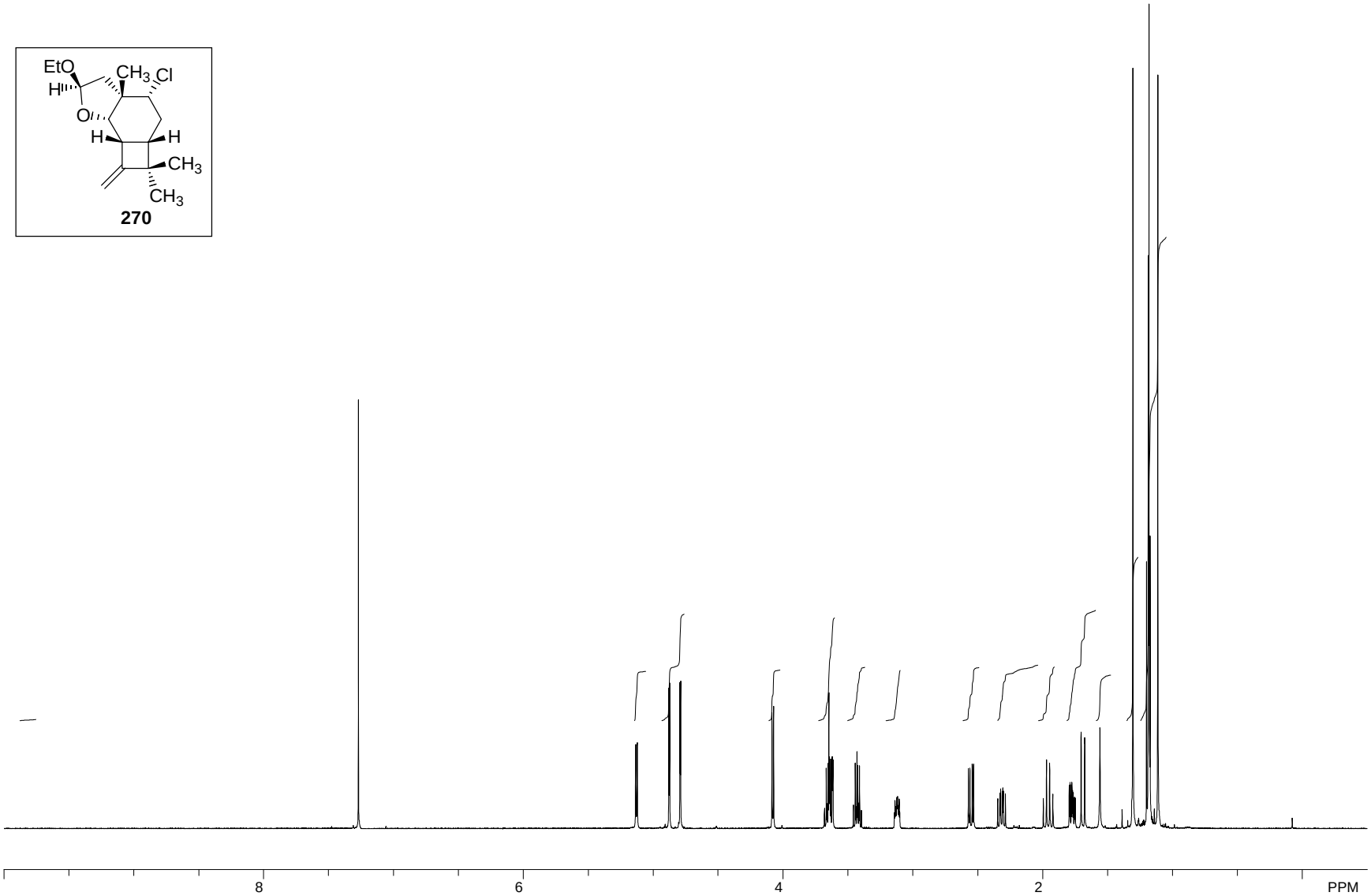


Figure A.7.100 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **270**.

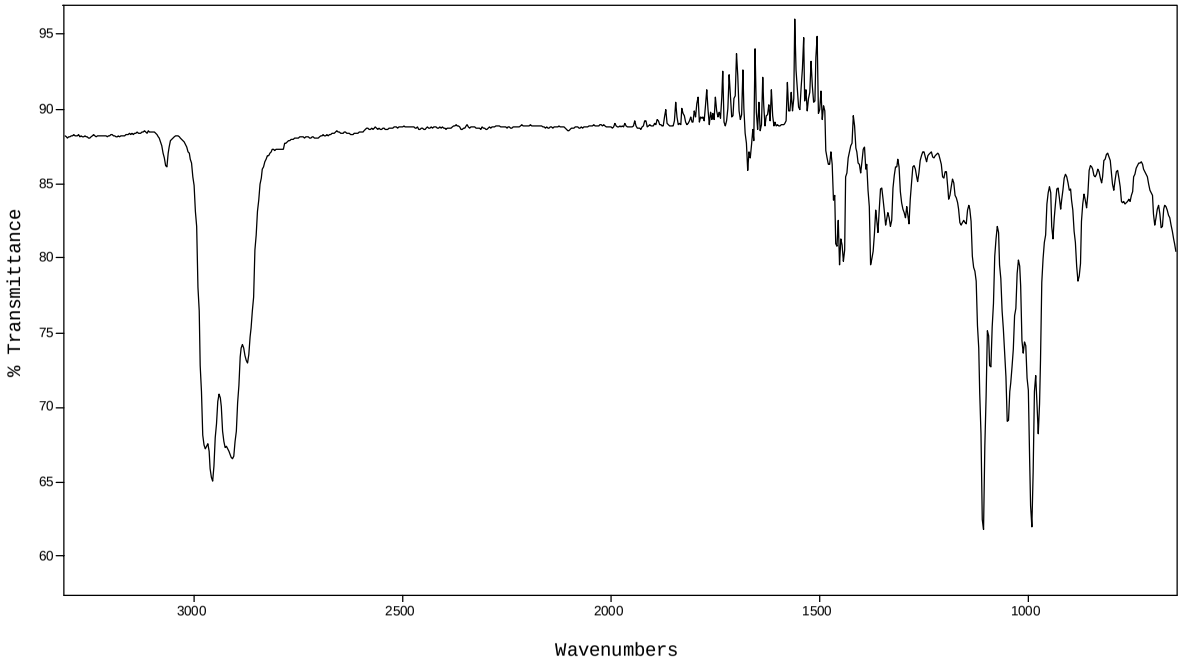


Figure A.7.101 FTIR Spectrum (thin film/NaCl) of Compound **270**.

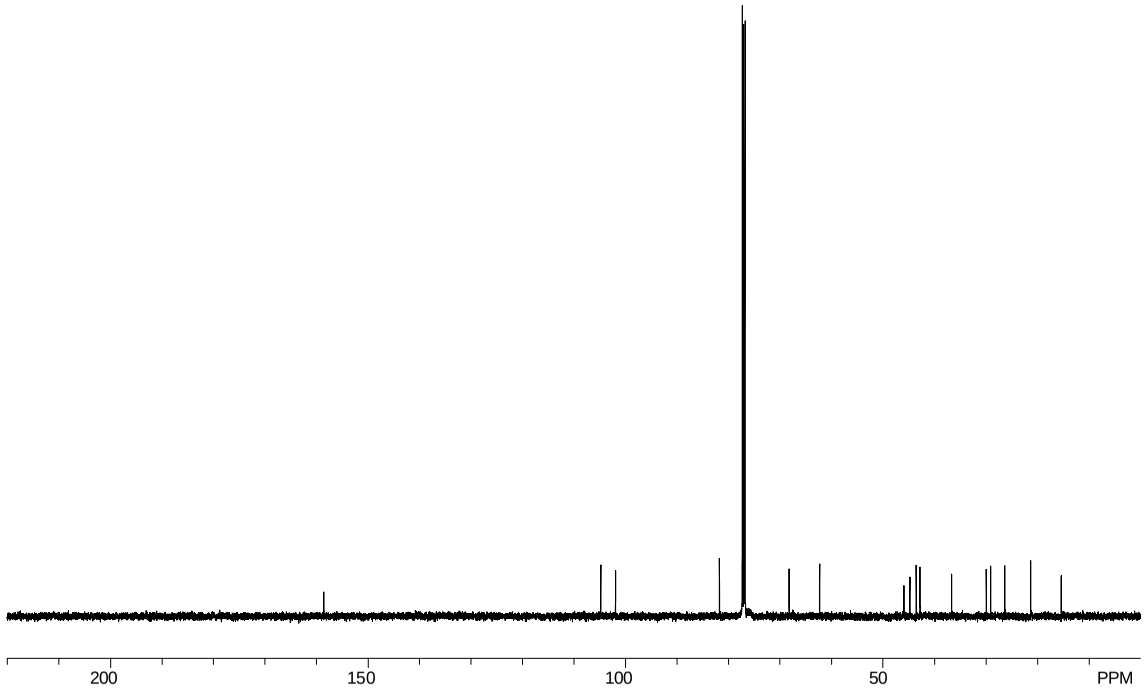


Figure A.7.102 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **270.**

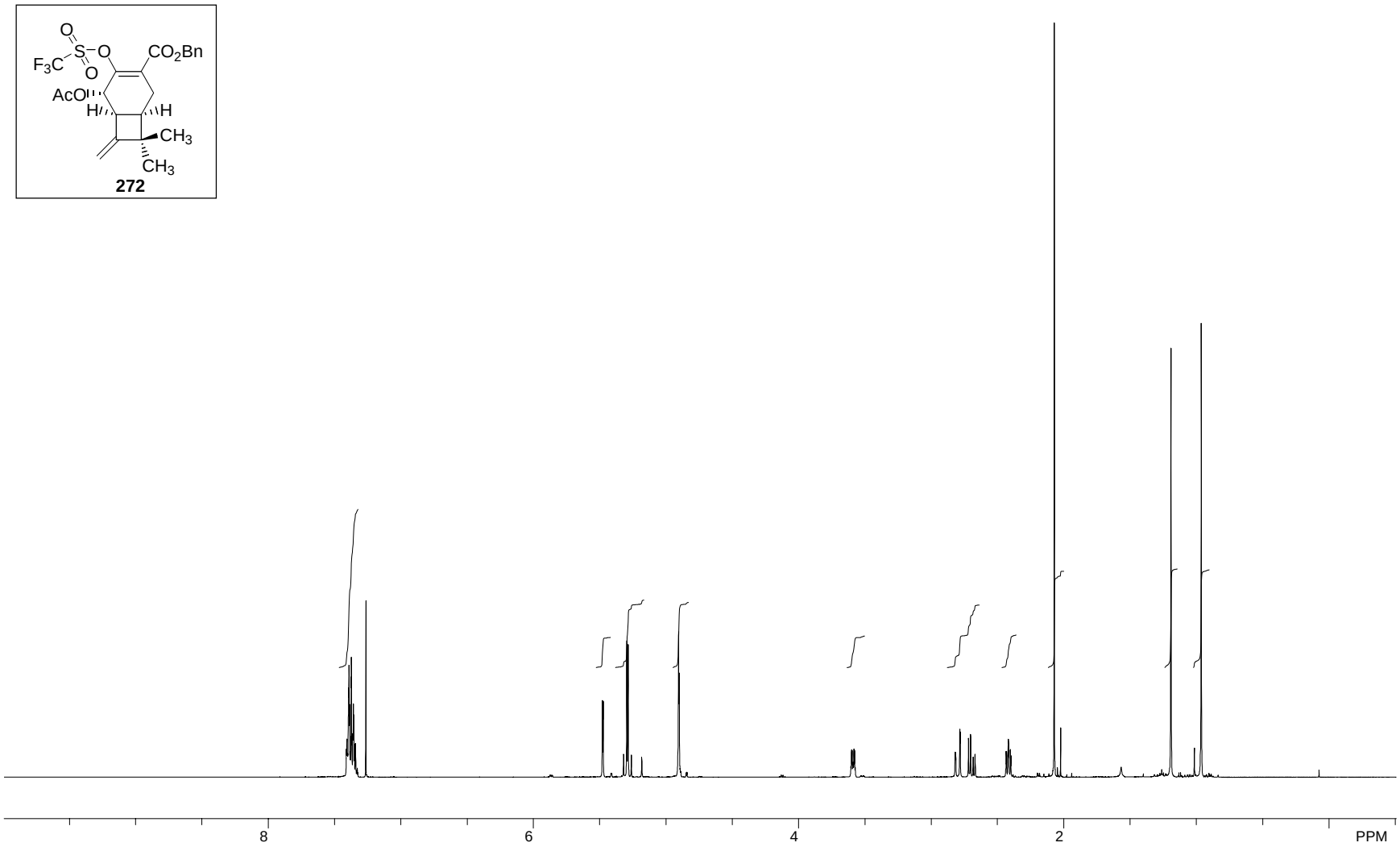


Figure A.7.103 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **272**.

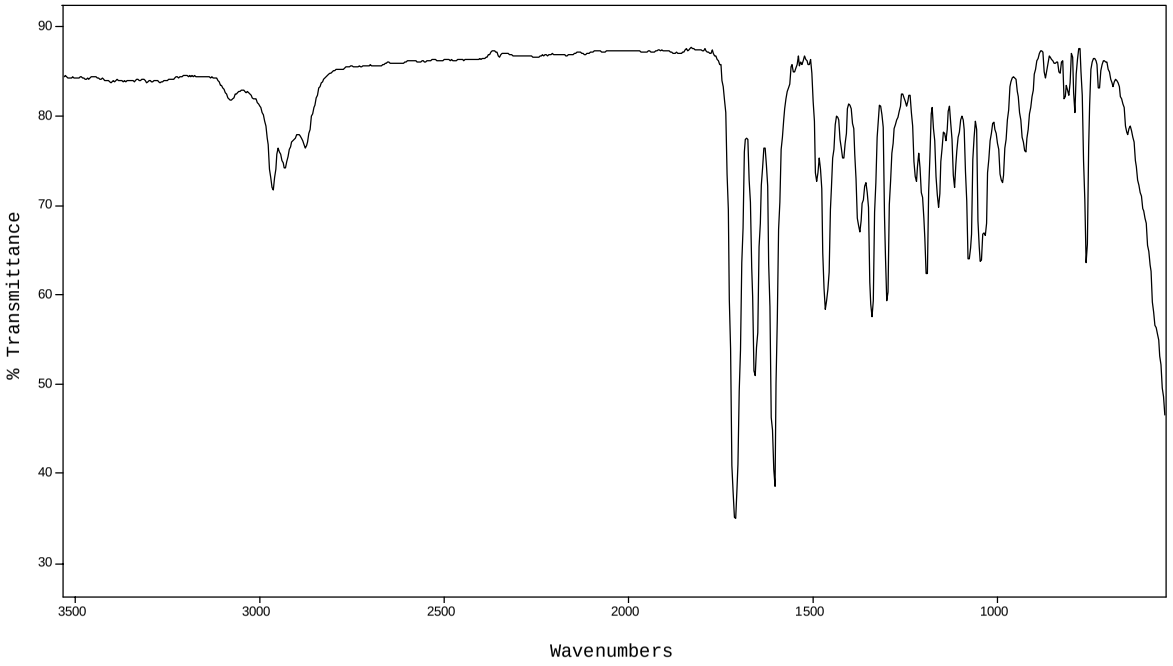


Figure A.7.104 FTIR Spectrum (thin film/NaCl) of Compound **272**.

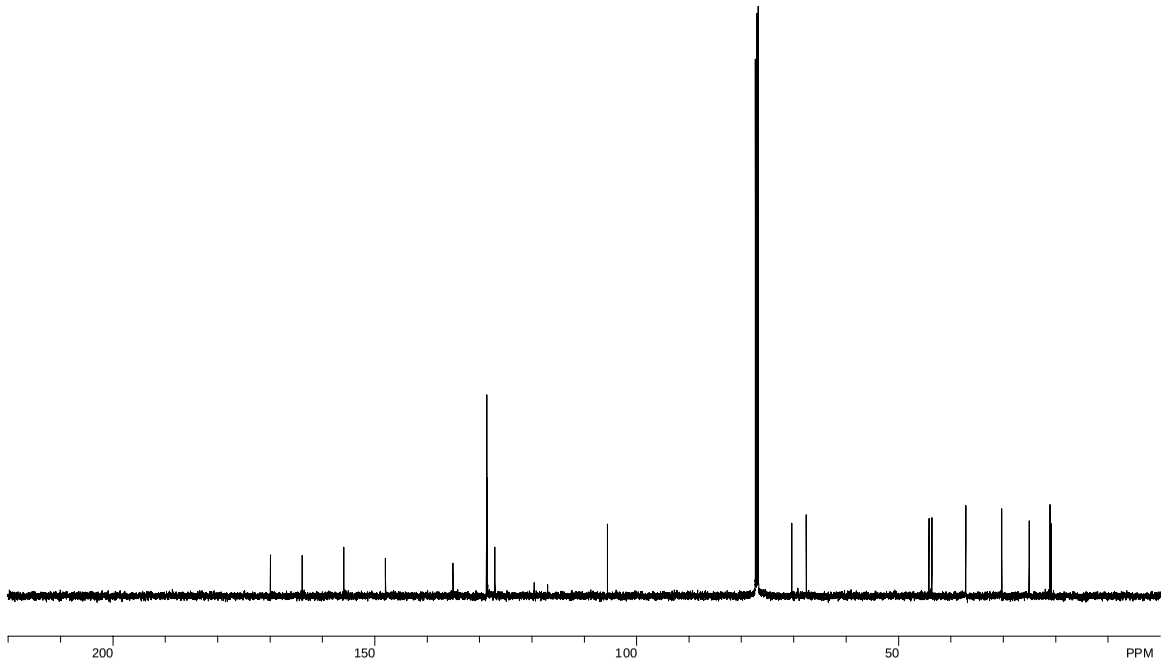


Figure A.7.105 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **272**.

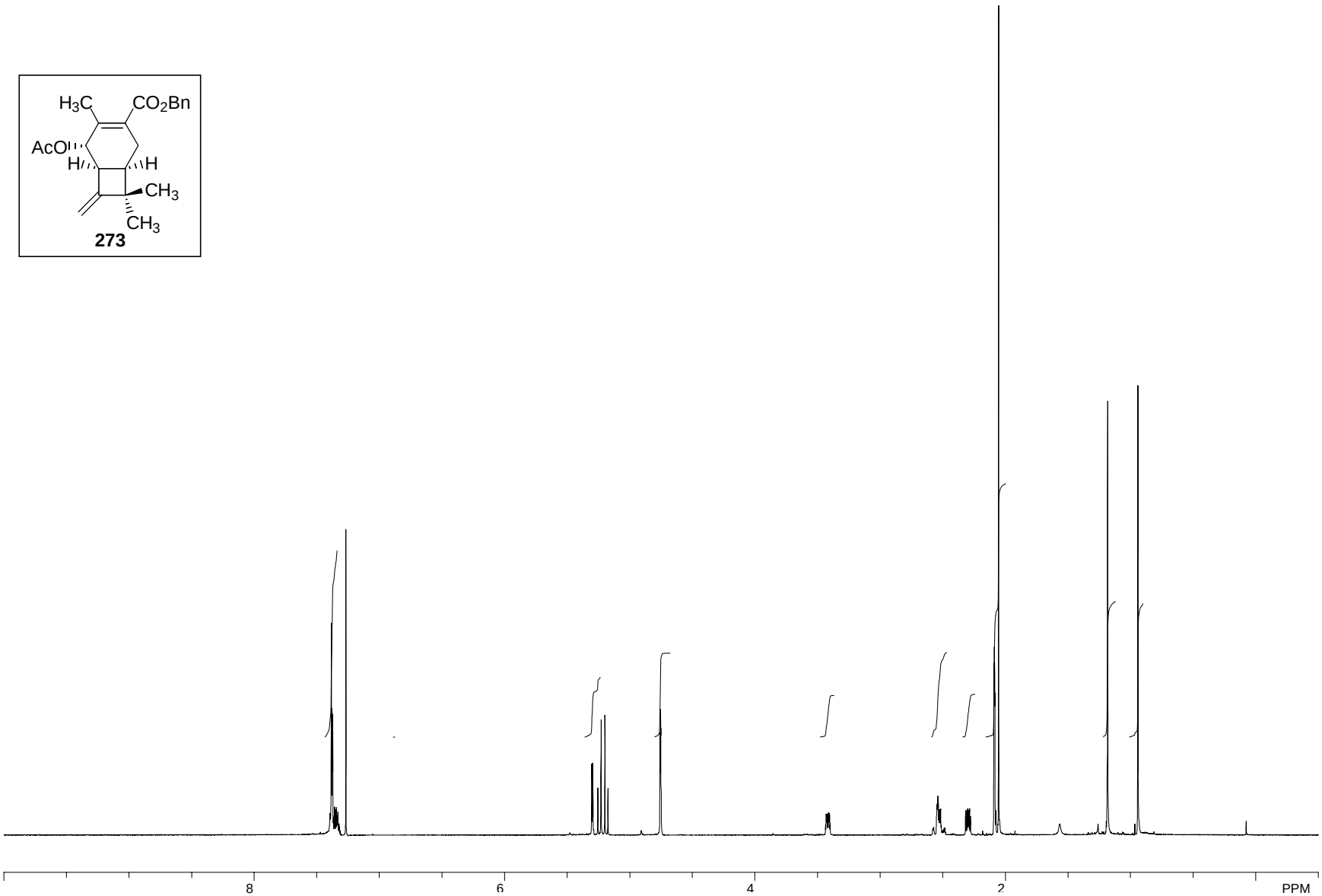


Figure A.7.106 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **273**.

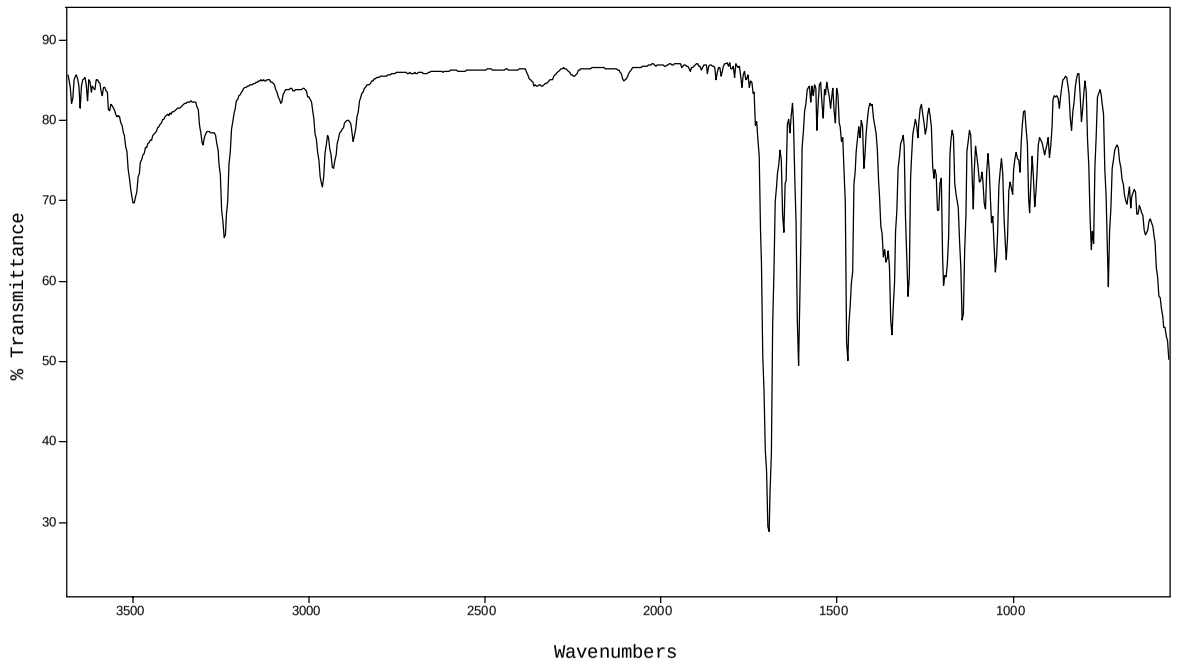


Figure A.7.107 FTIR Spectrum (thin film/NaCl) of Compound **273**.

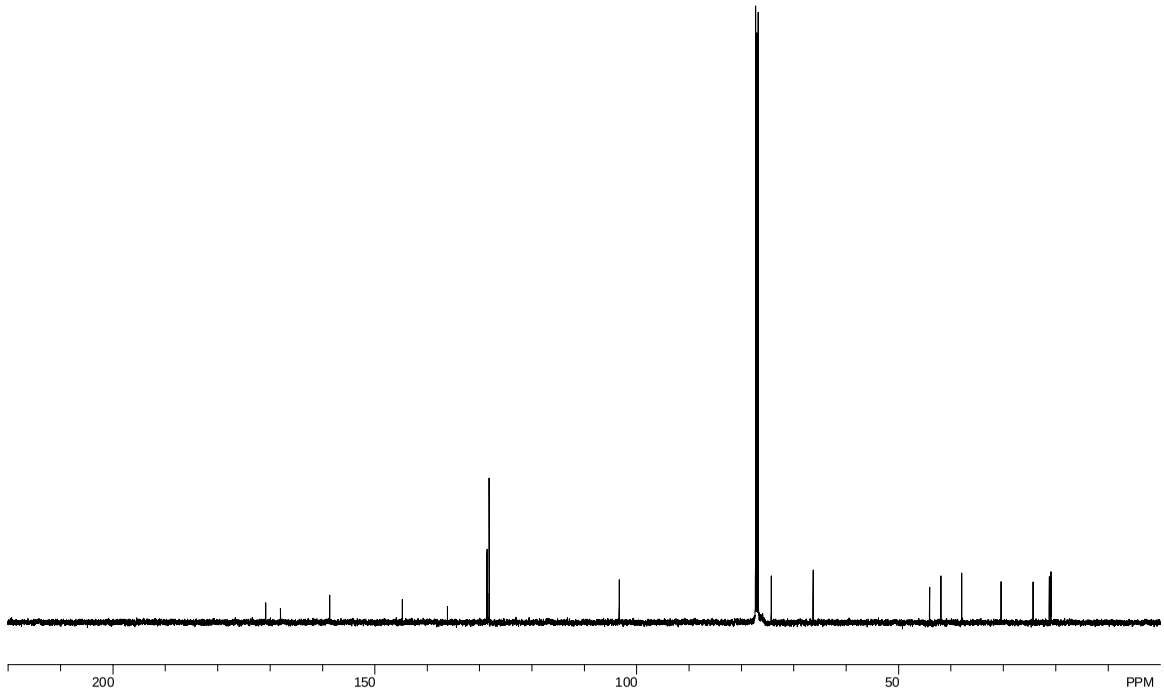
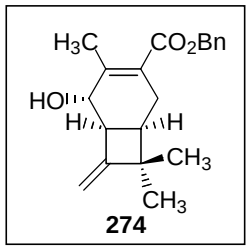


Figure A.7.108 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **273**.



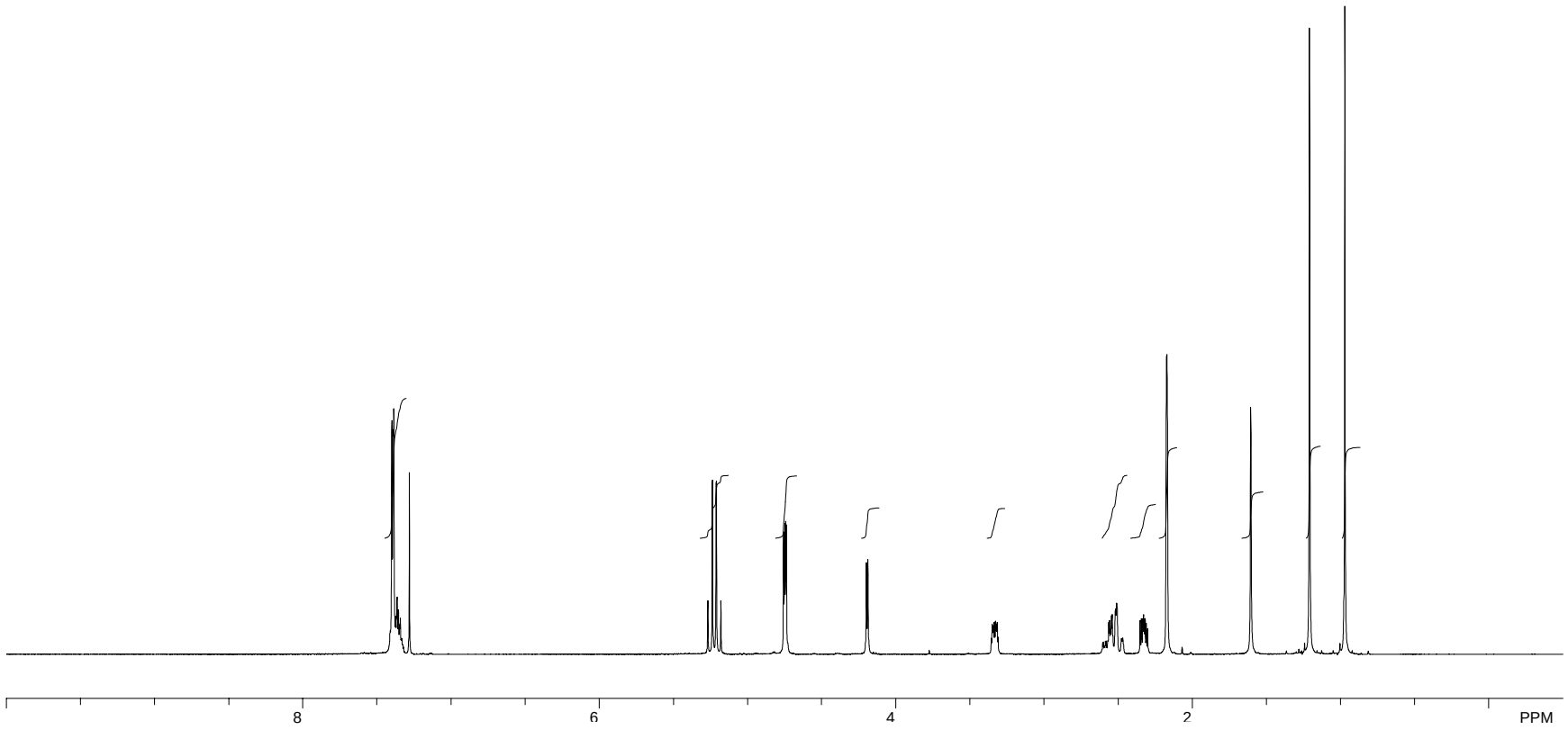


Figure A.7.109 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **274**.

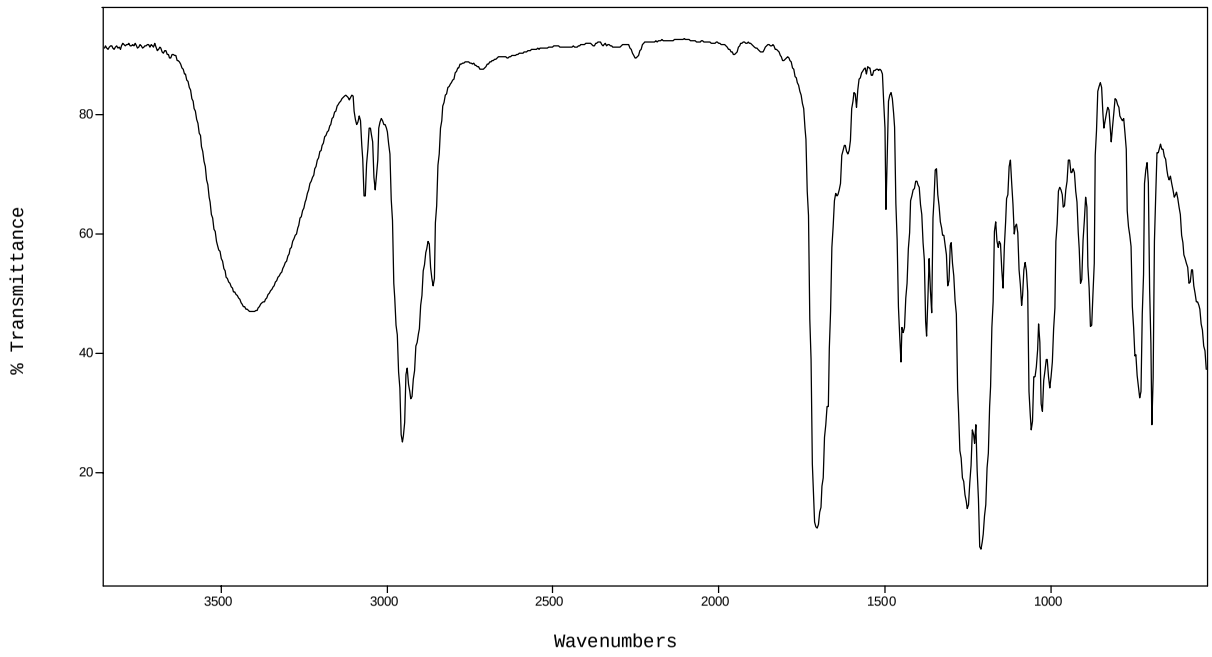


Figure A.7.110 FTIR Spectrum (thin film/NaCl) of Compound **274**.

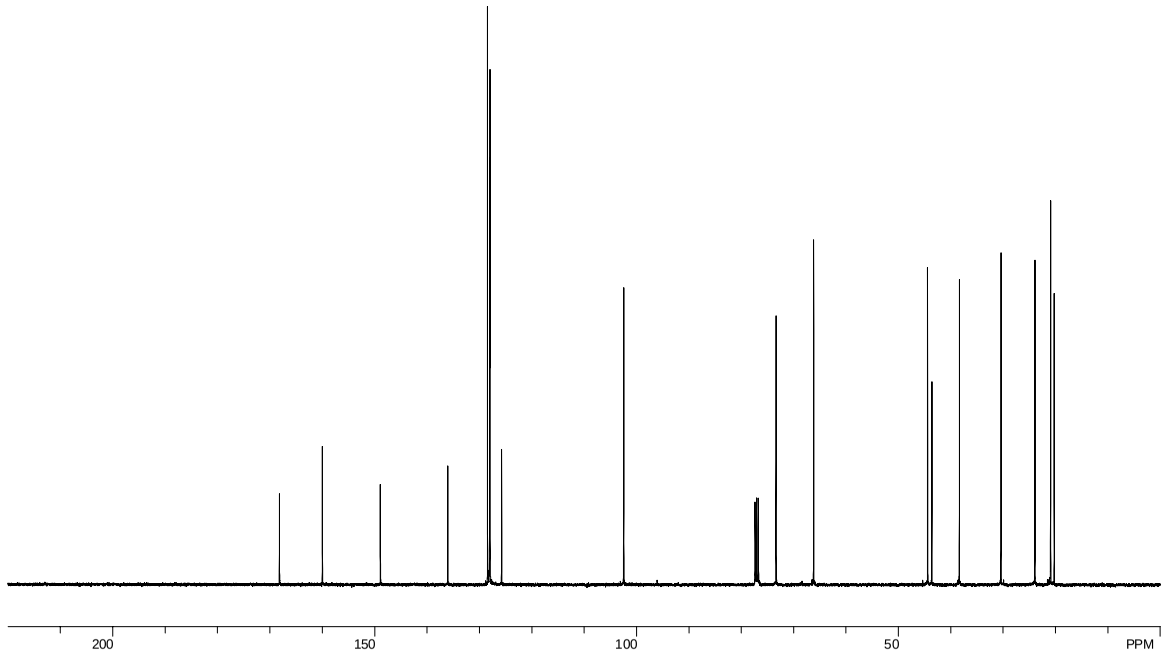


Figure A.7.111 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **274**.

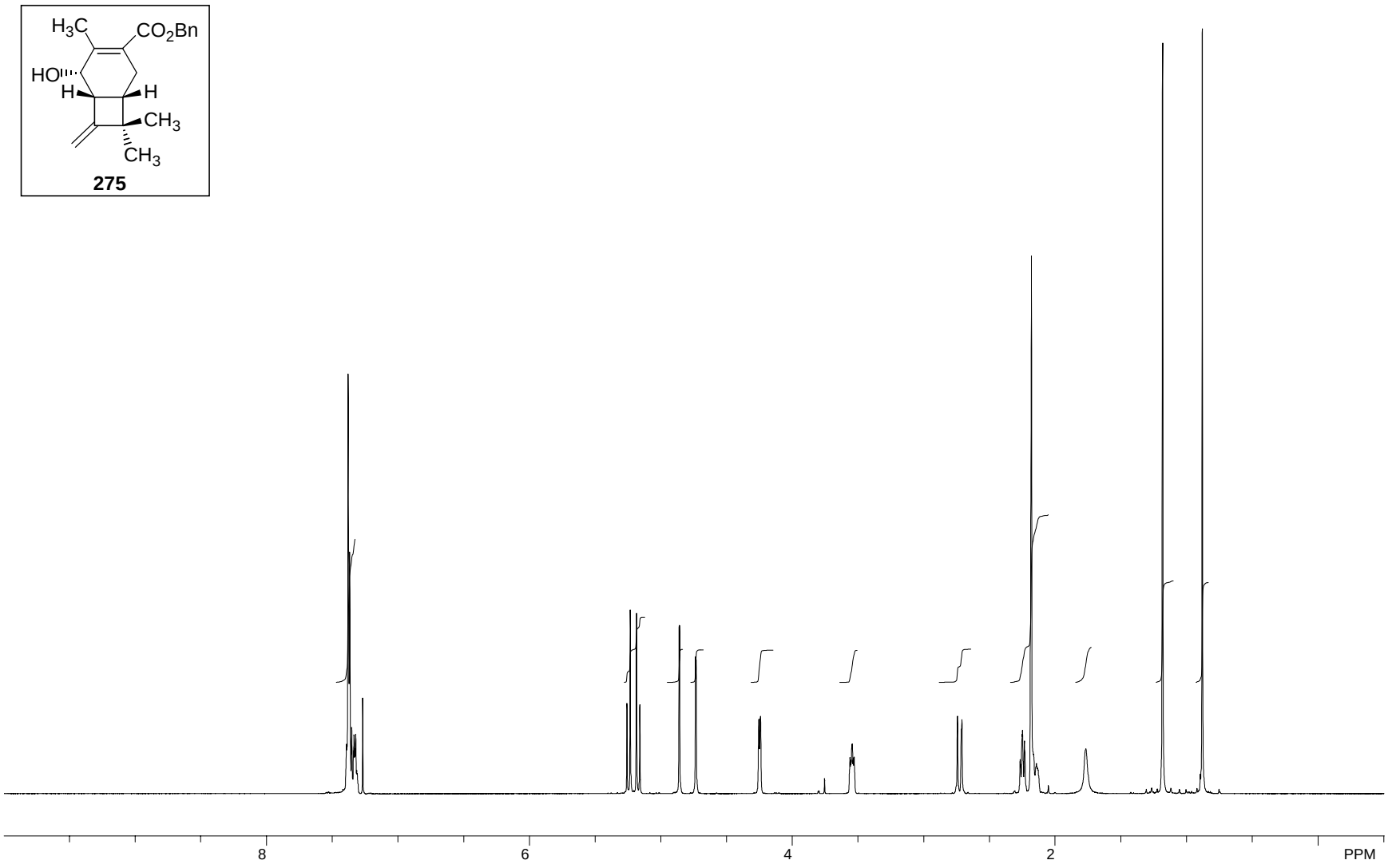


Figure A.7.112 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **275**.

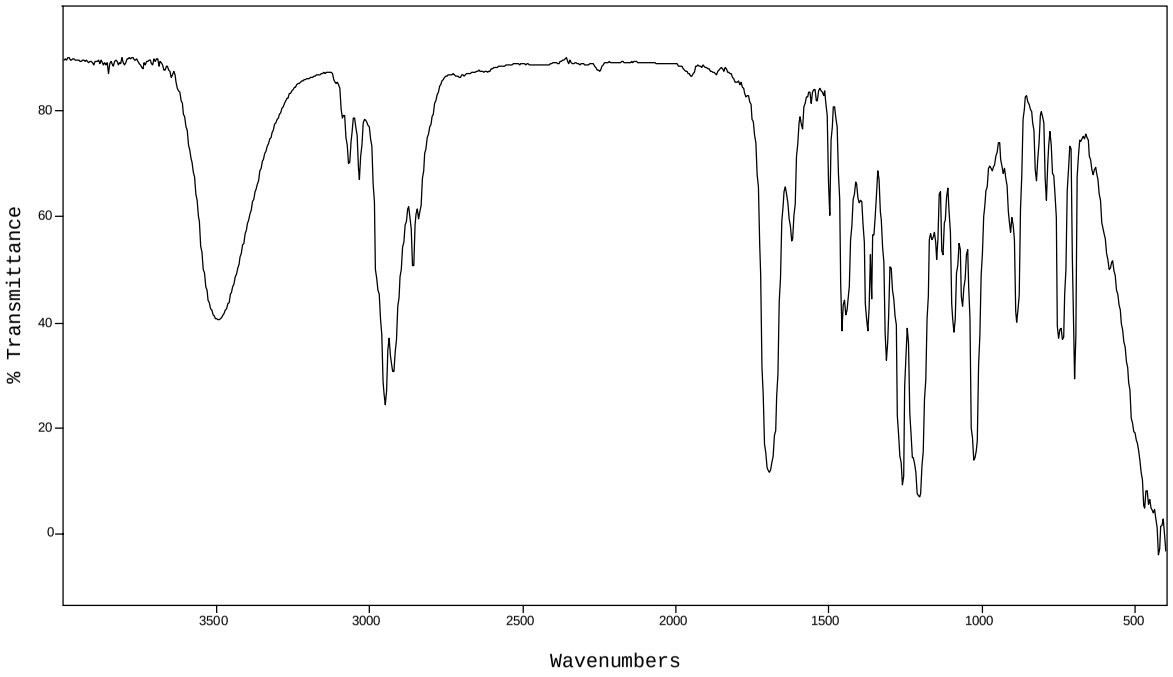


Figure A.7.113 FTIR Spectrum (thin film/NaCl) of Compound **275**.

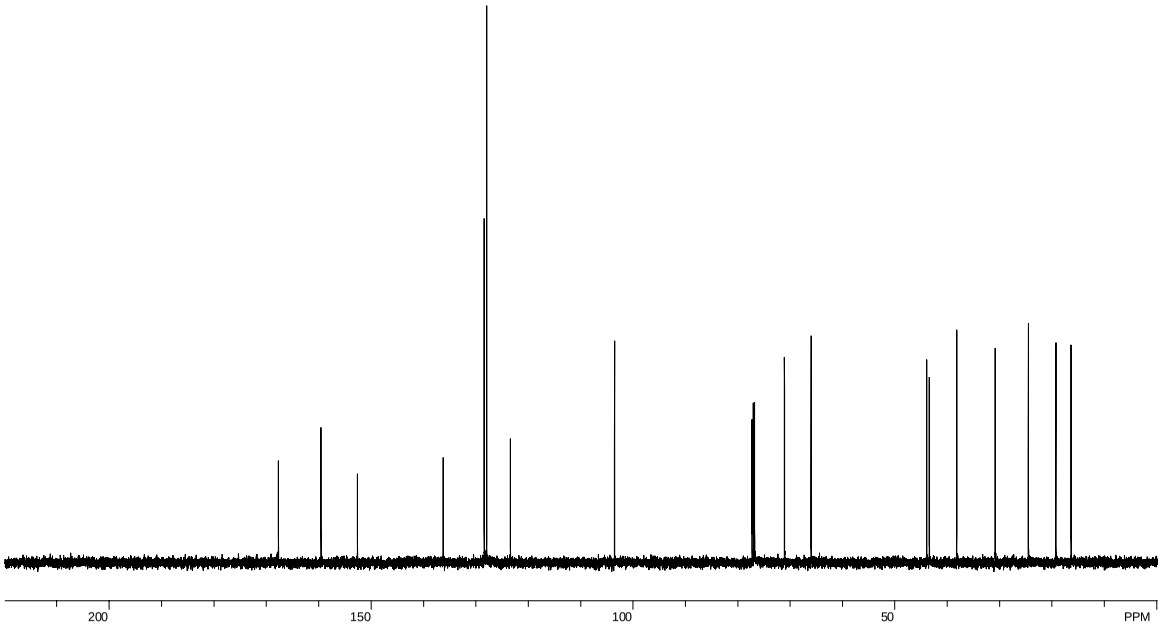


Figure A.7.114 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **275.**

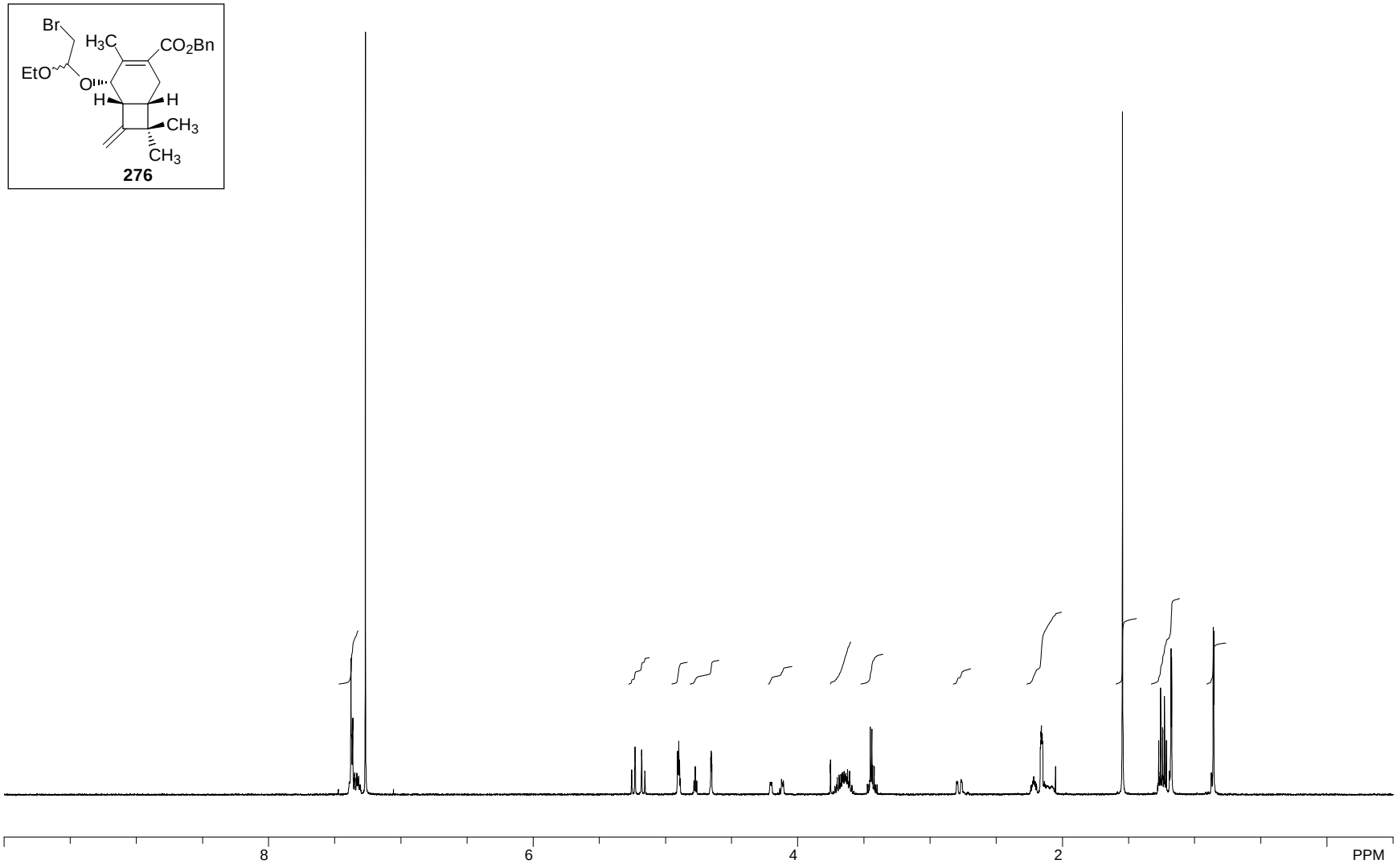


Figure A.7.115 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **276**.

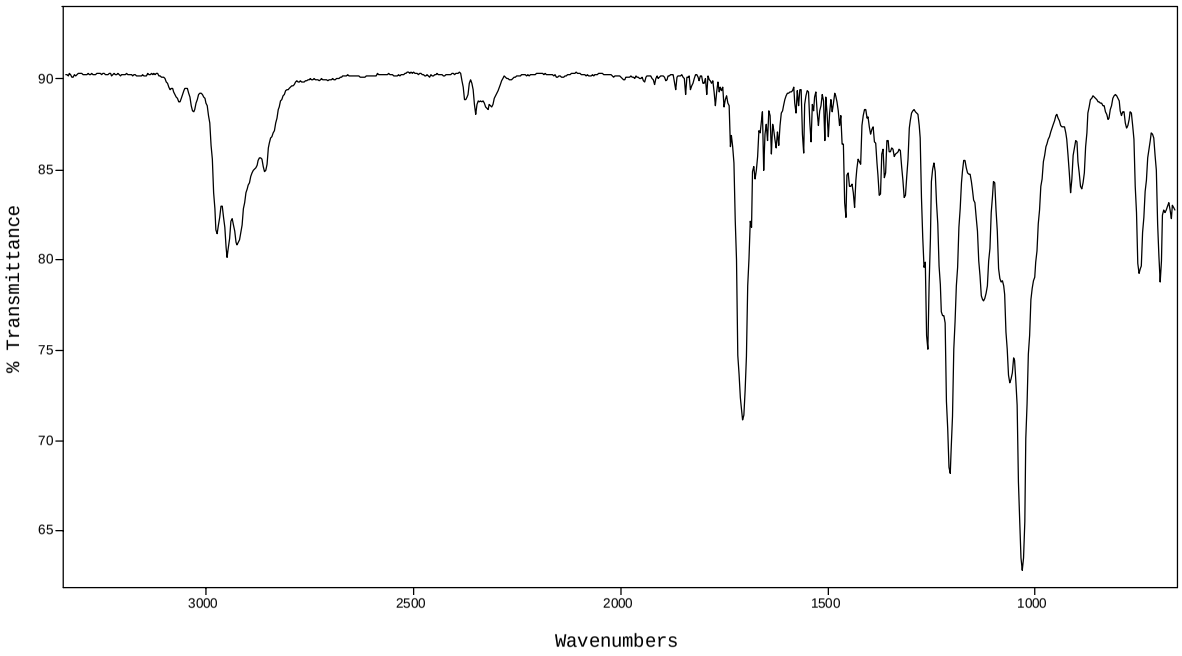


Figure A.7.116 FTIR Spectrum (thin film/NaCl) of Compound **276**.

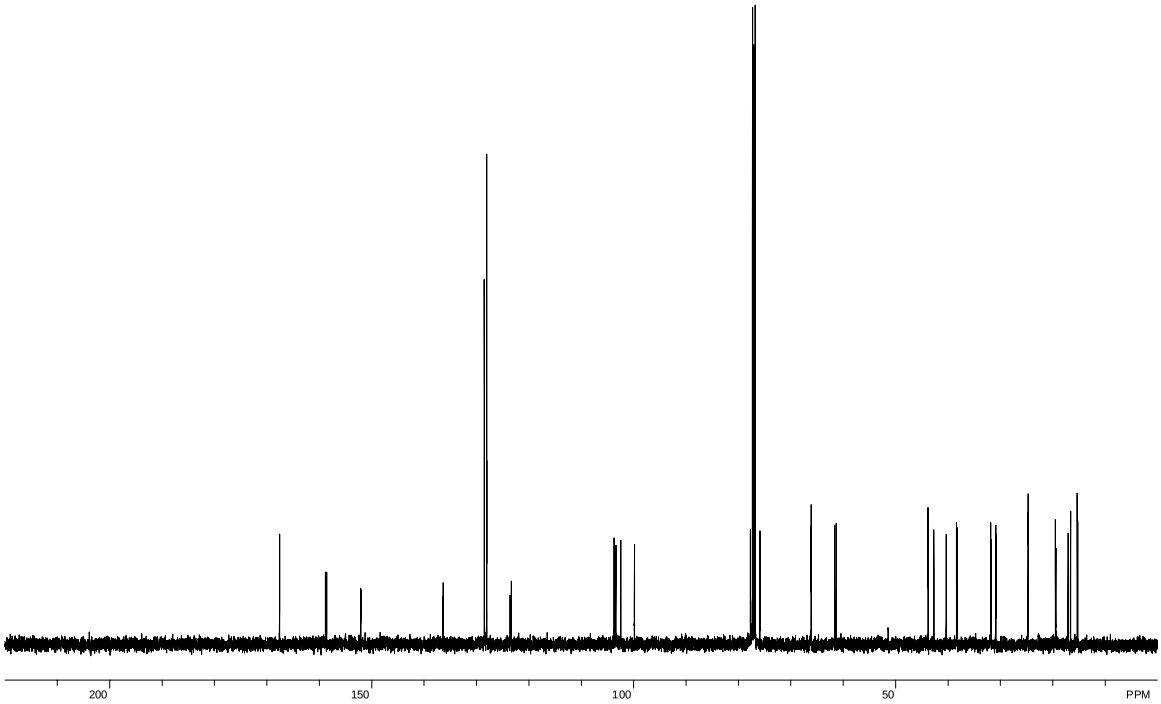


Figure A.7.117 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **276**.

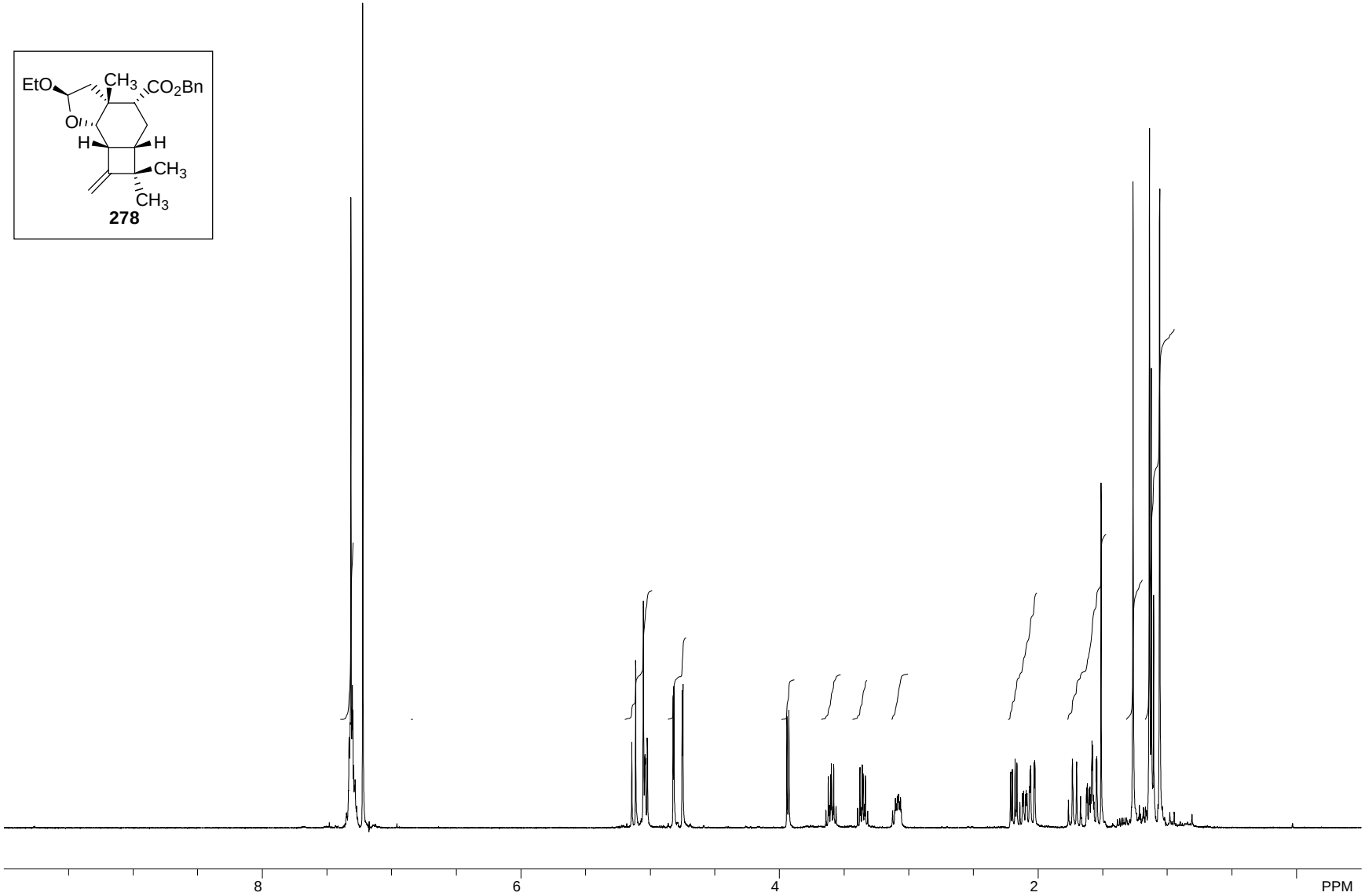


Figure A.7.118 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **278**.

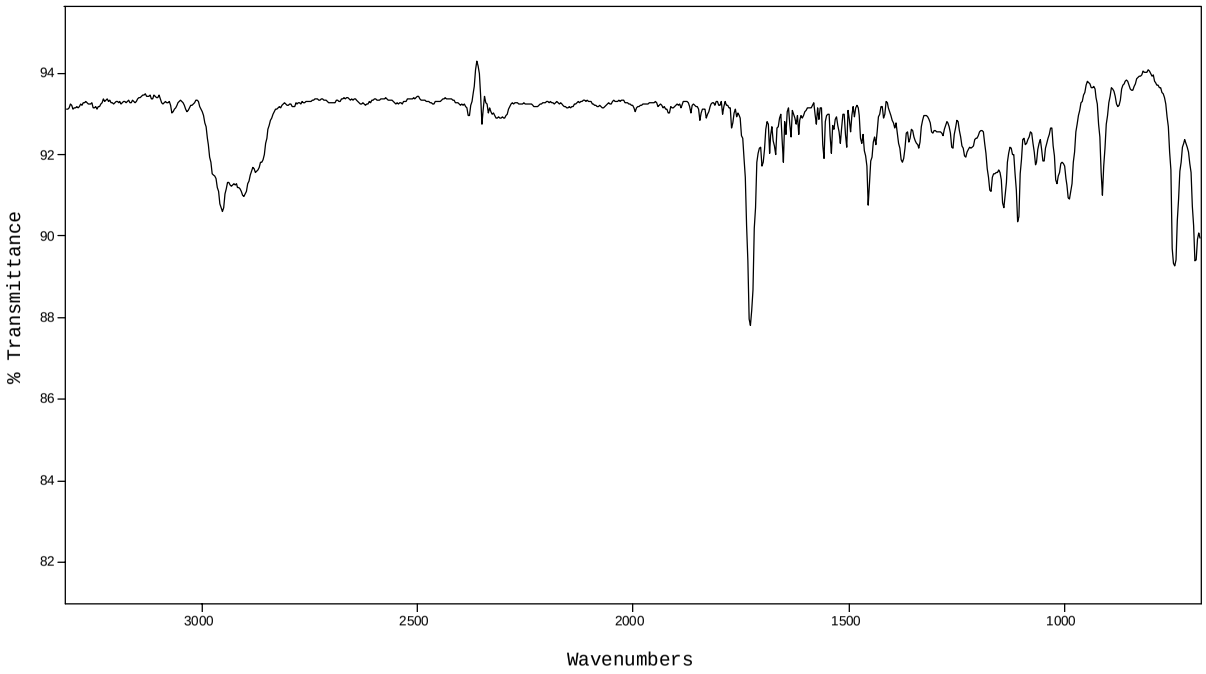


Figure A.7.119 FTIR Spectrum (thin film/NaCl) of Compound **278**.

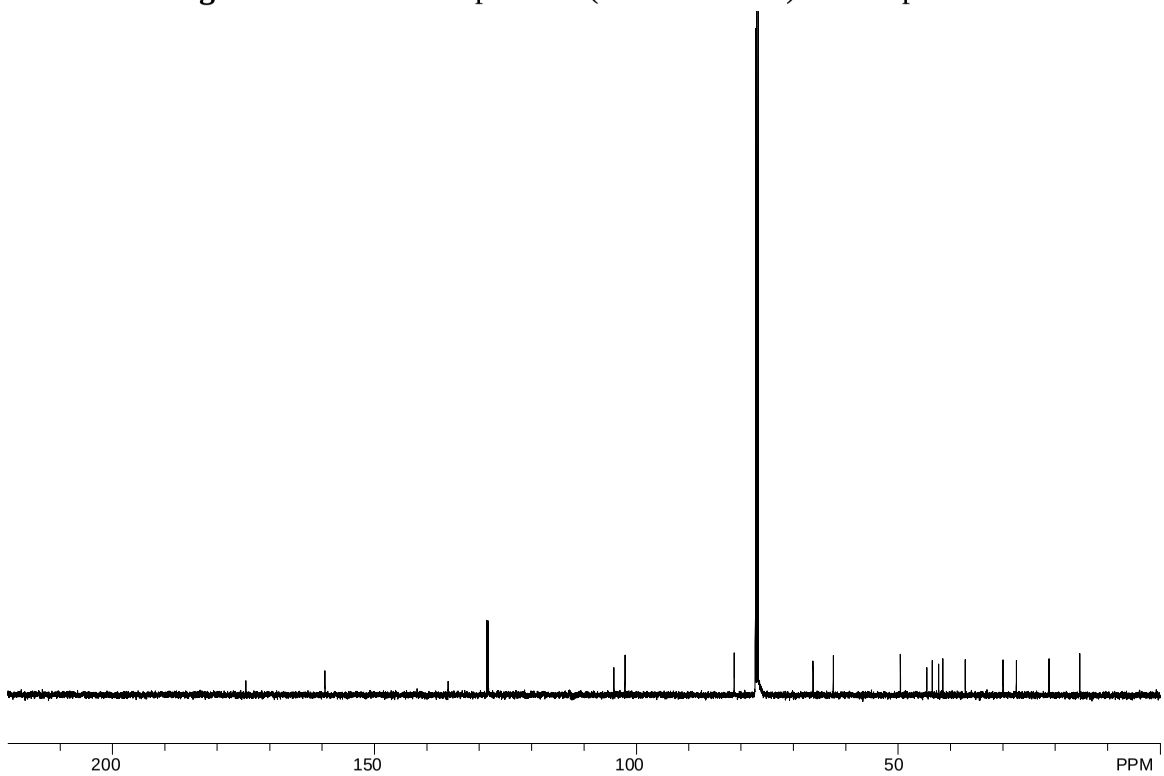


Figure A.7.120 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **278**.

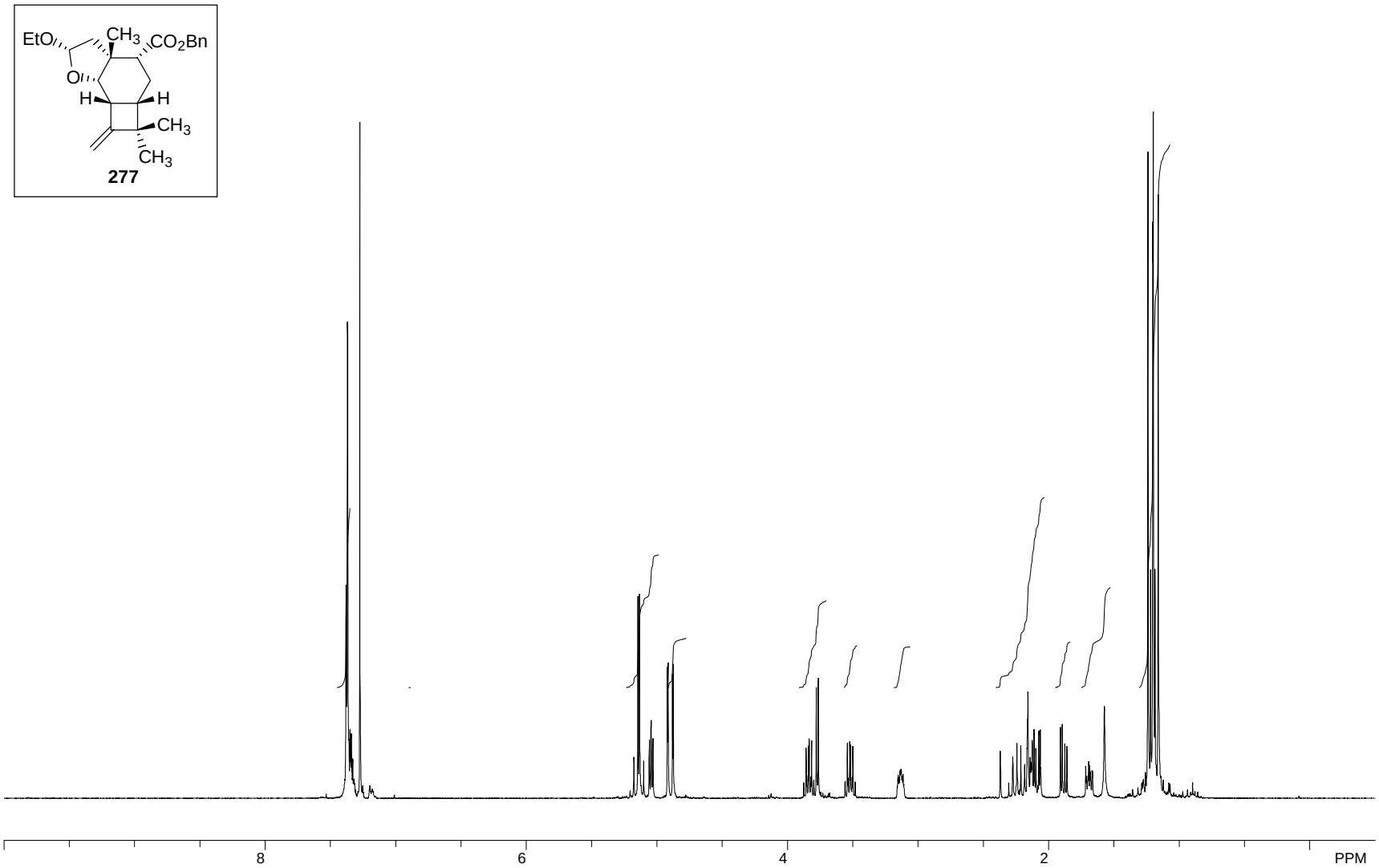


Figure A.7.121 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **277**.

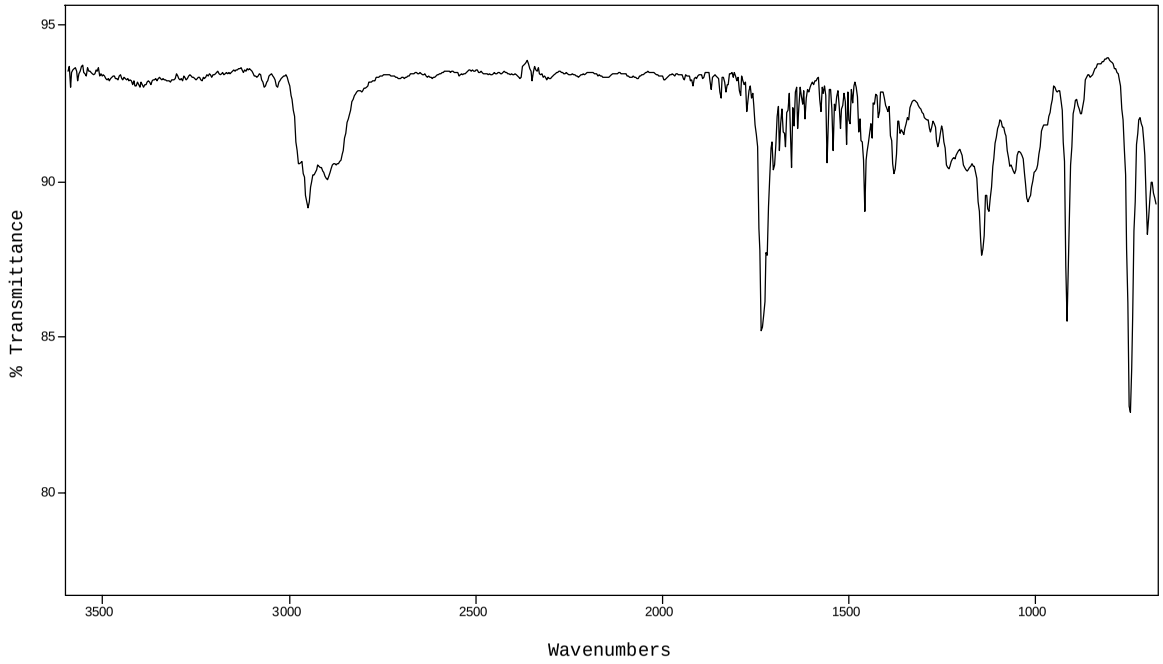


Figure A.7.122 FTIR Spectrum (thin film/NaCl) of Compound **277**.

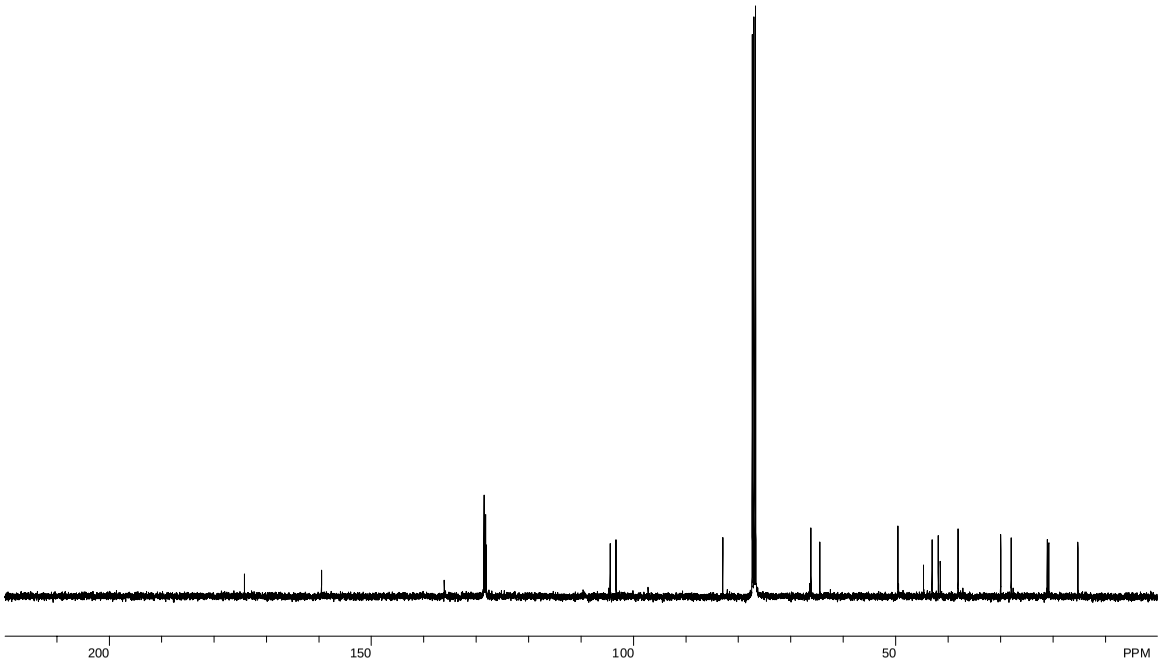


Figure A.7.123 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **277**.

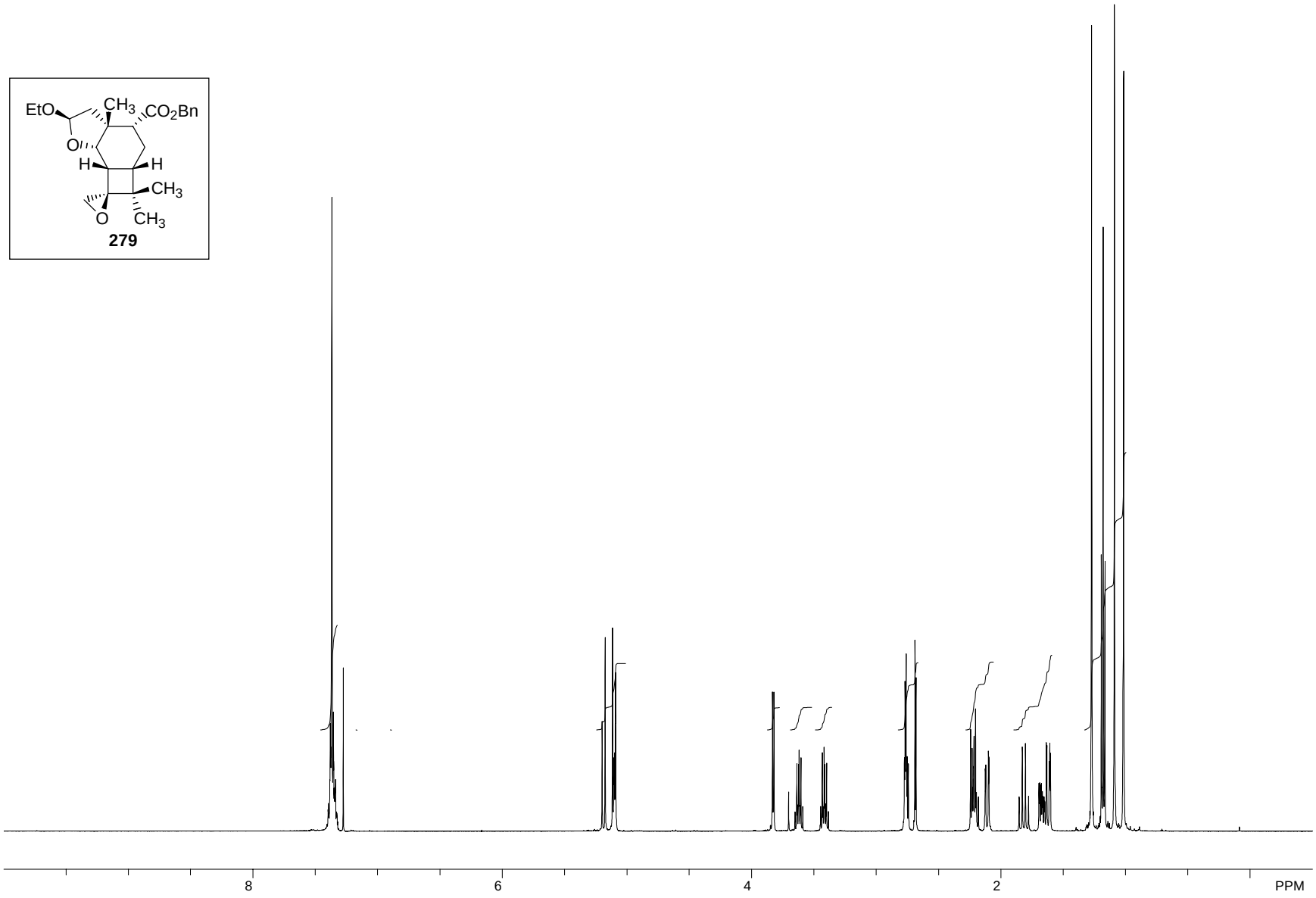


Figure A.7.124 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **279**.

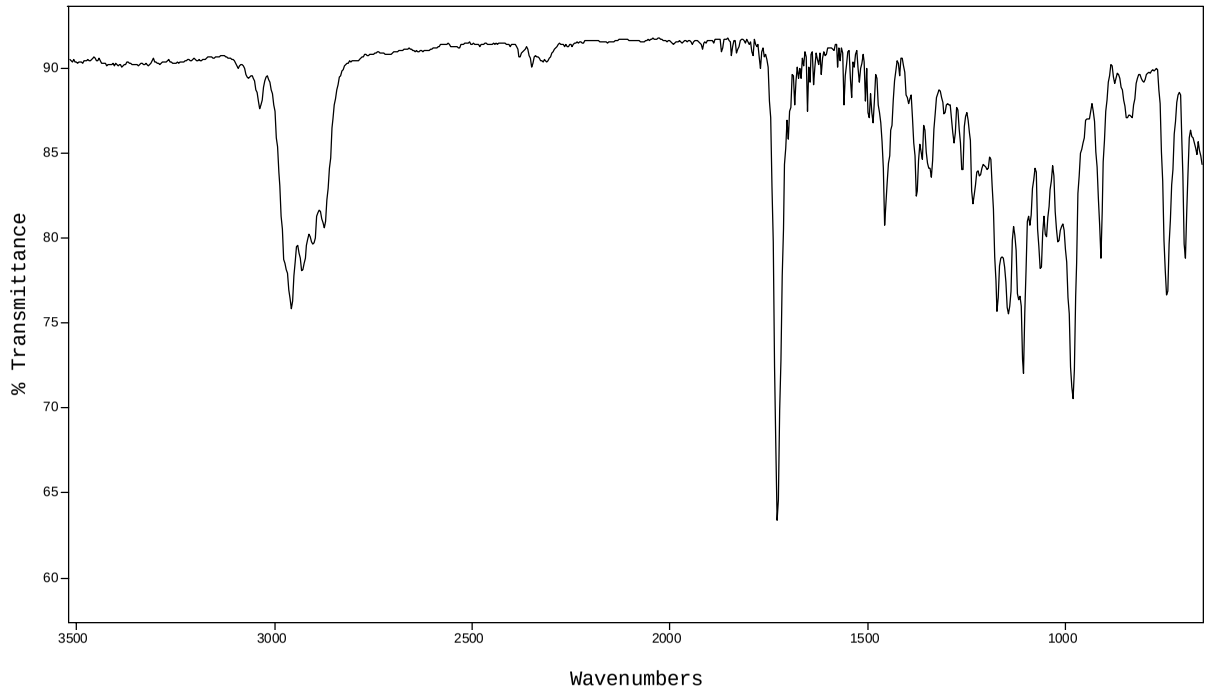


Figure A.7.125 FTIR Spectrum (thin film/NaCl) of Compound **279**.

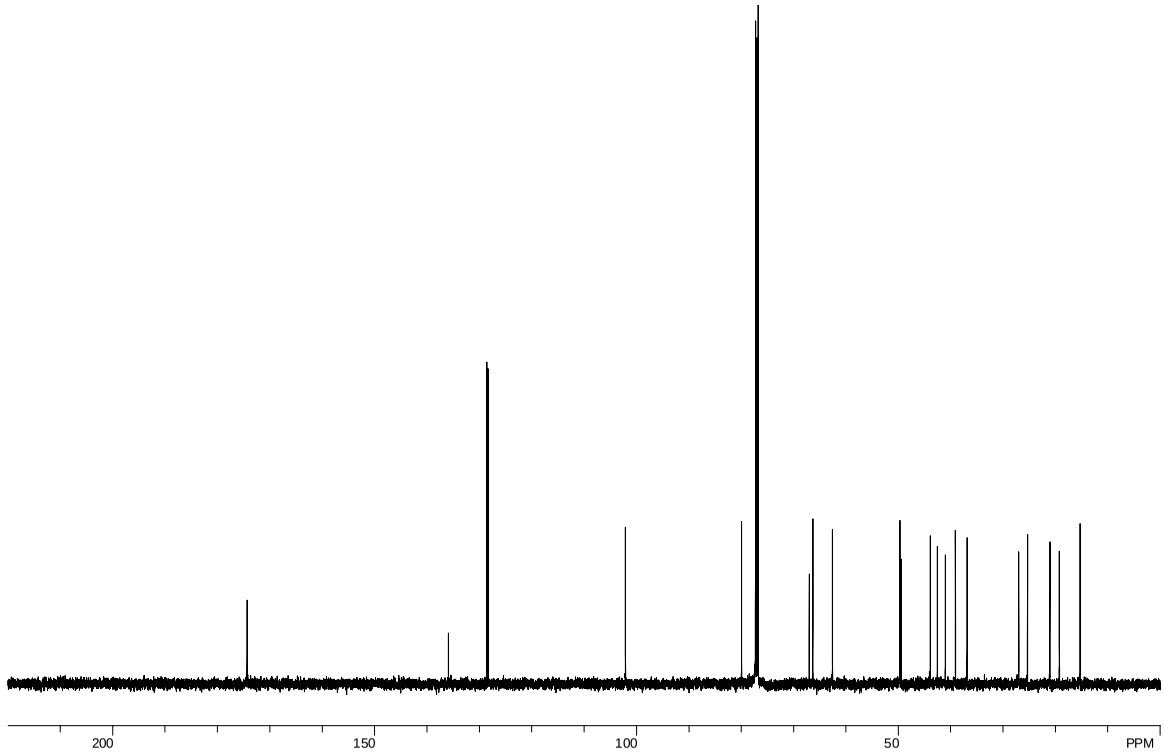


Figure A.7.126 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **279**.

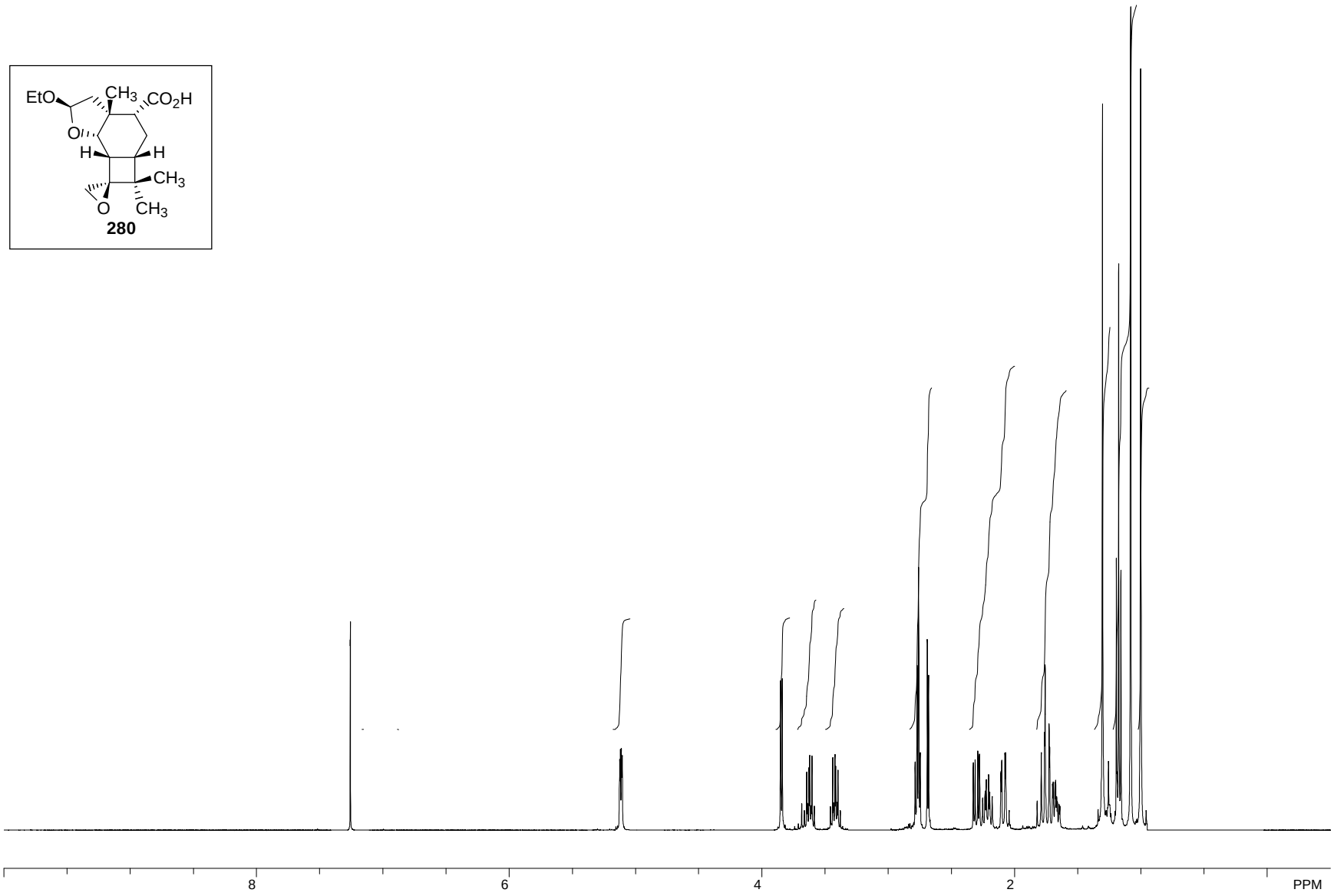


Figure A.7.127 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **280**.

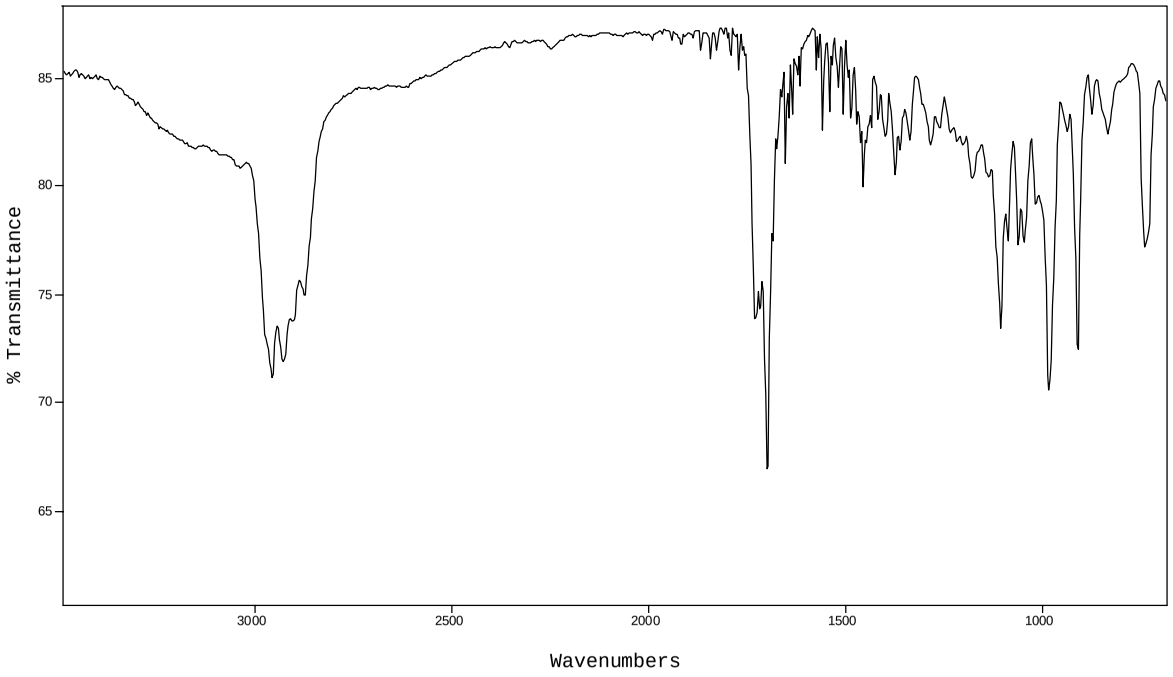


Figure A.7.128 FTIR Spectrum (thin film/NaCl) of Compound **280**.

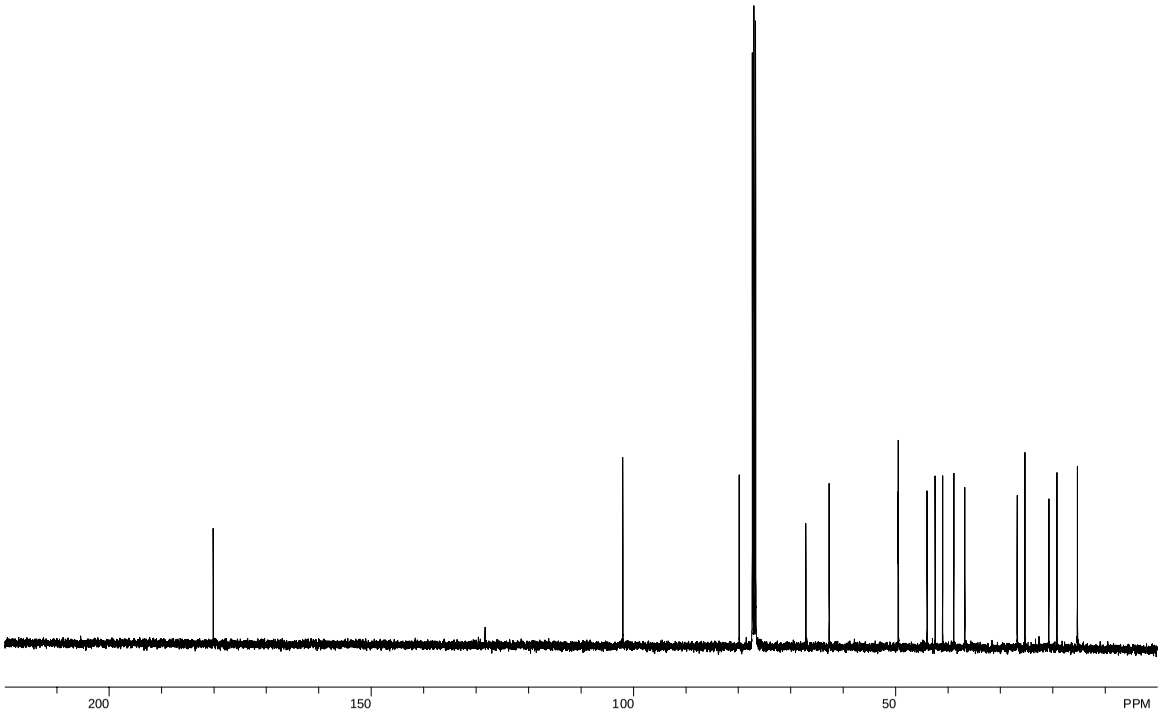


Figure A.7.129 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **280**.

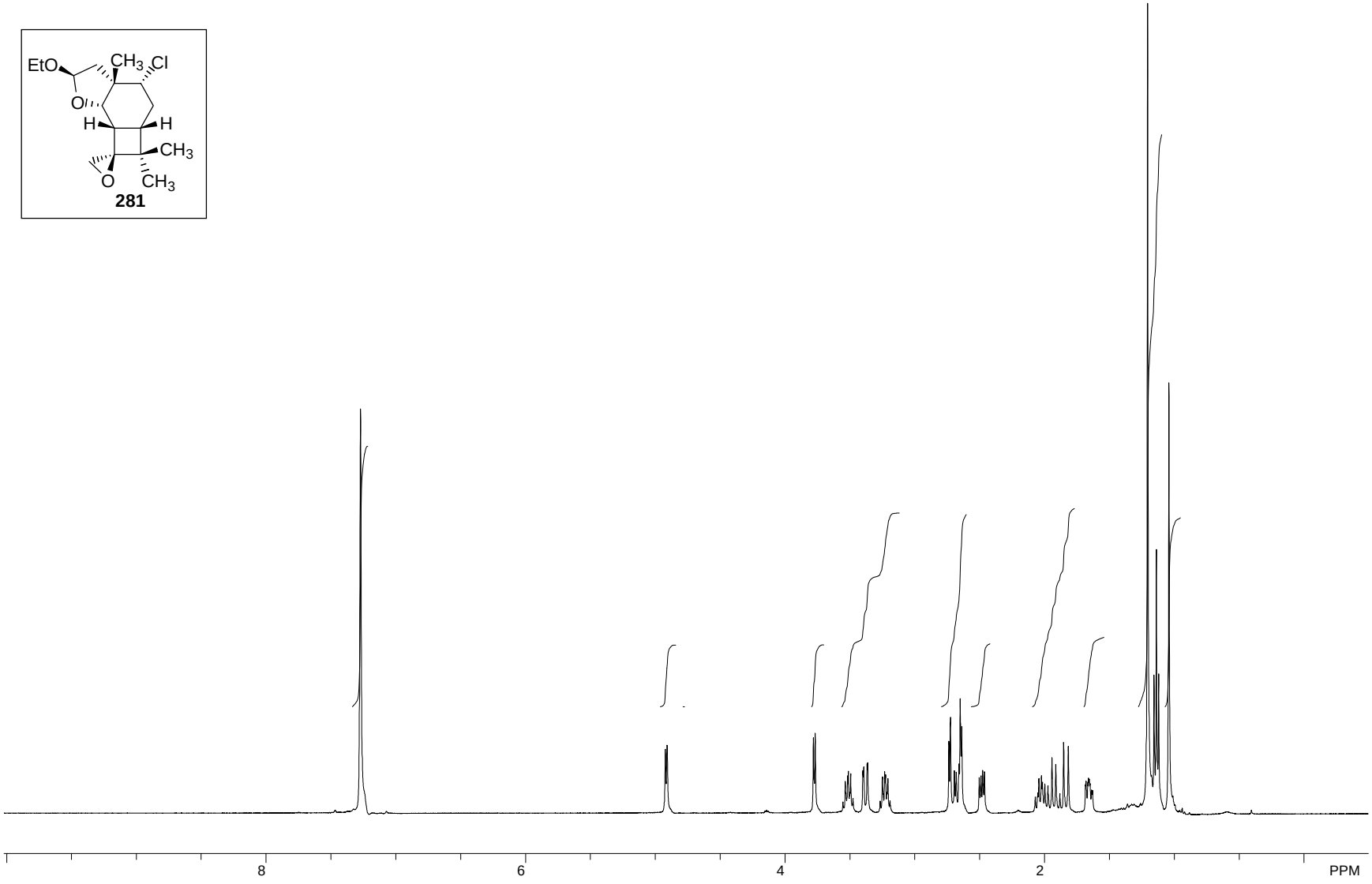


Figure A.7.130 ^{1}H NMR (400 MHz, C_6D_6) of Compound **281**.

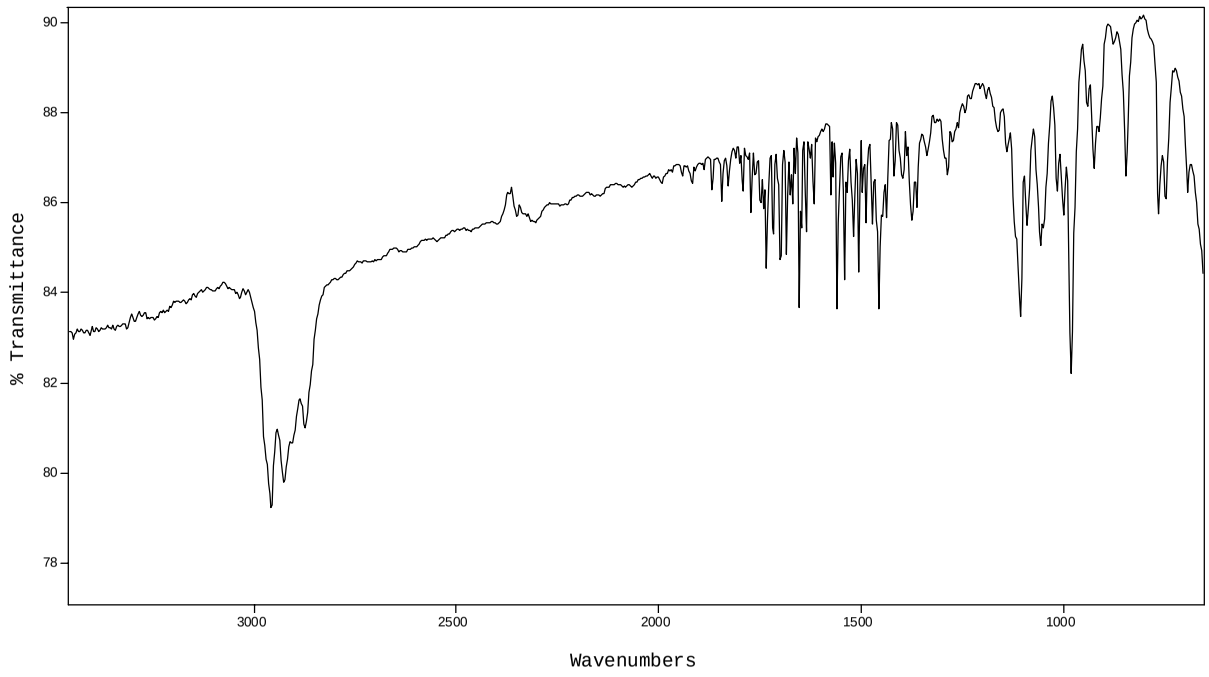


Figure A.7.131 FTIR Spectrum (thin film/NaCl) of Compound **281**.

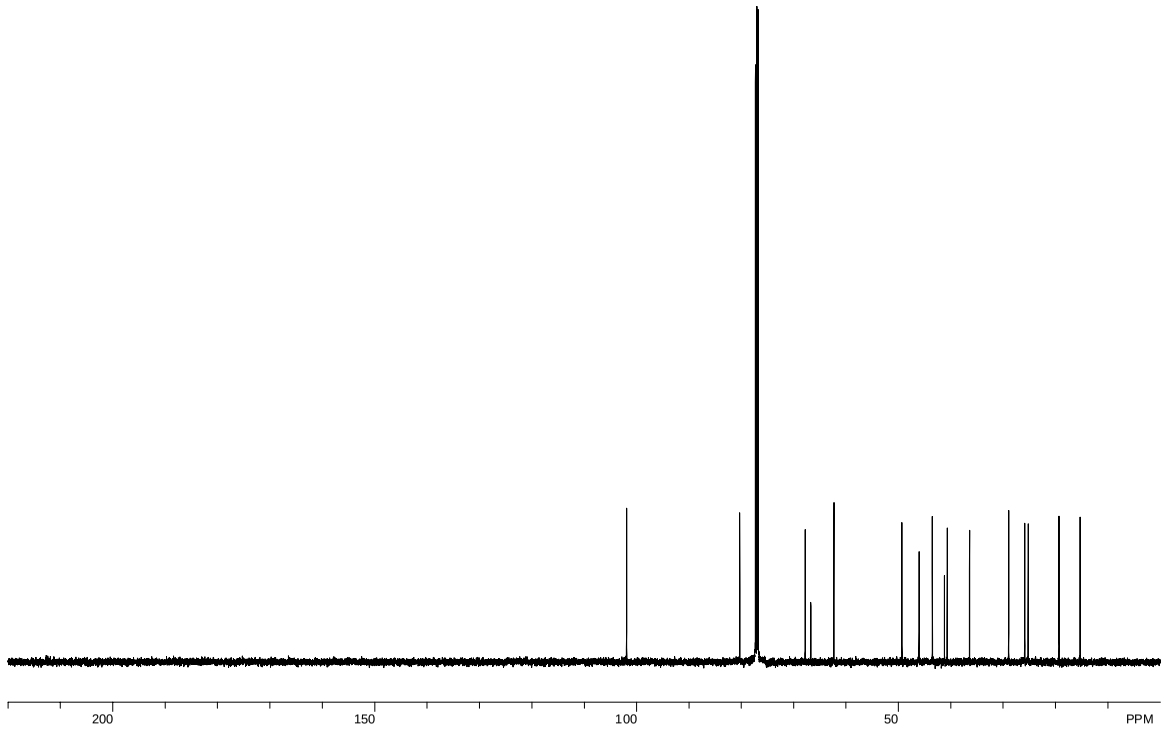


Figure A.7.132 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **281**.

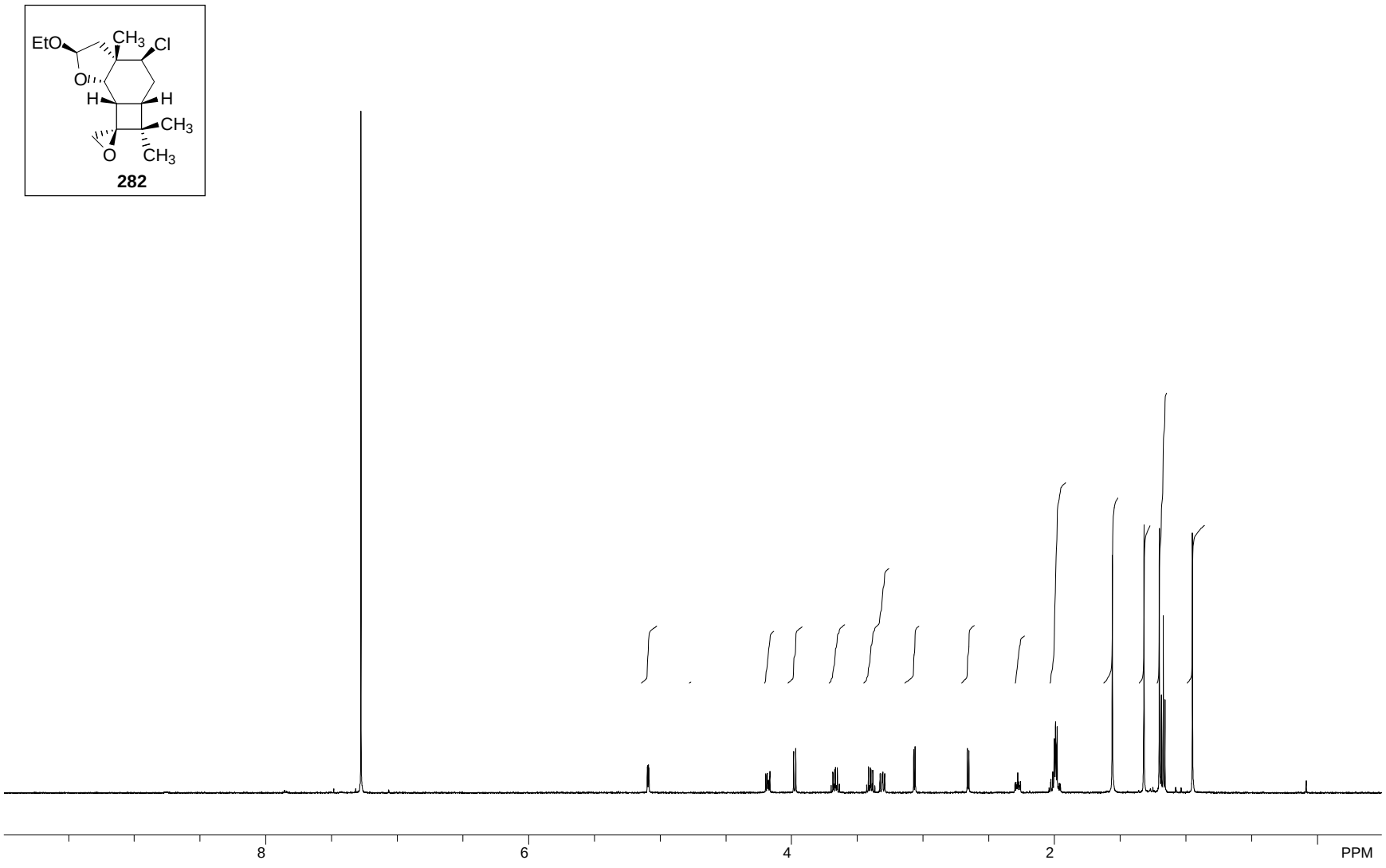


Figure A.7.133 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **282**.

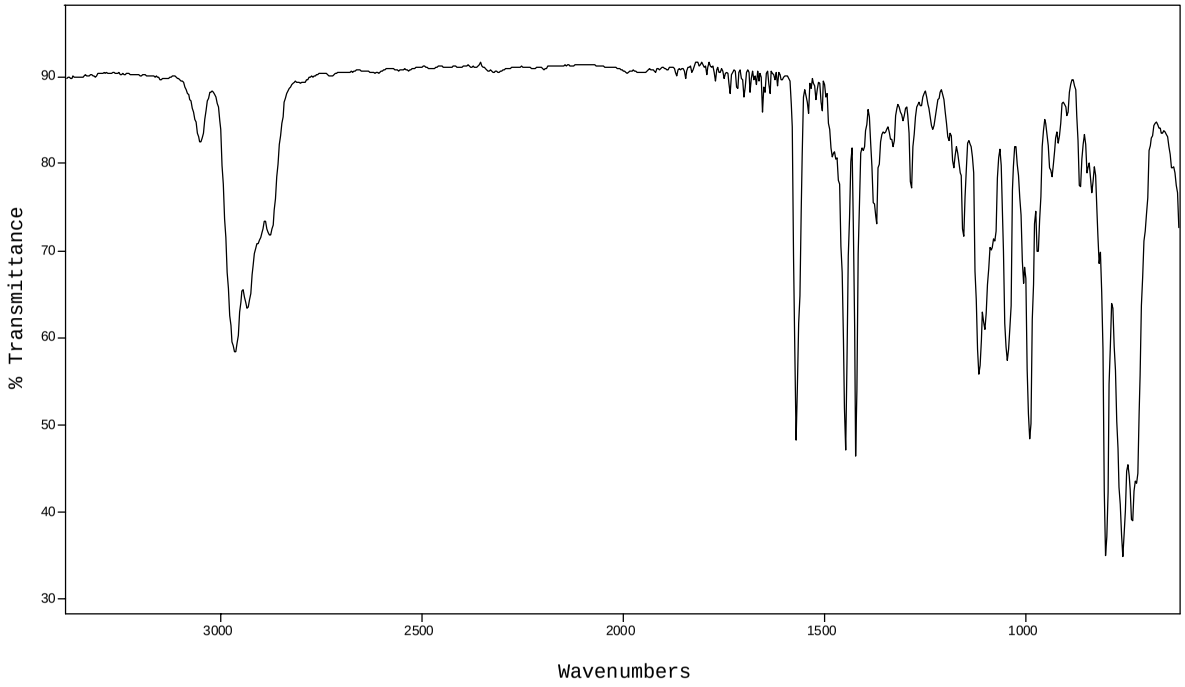


Figure A.7.134 FTIR Spectrum (thin film/NaCl) of Compound **282**.

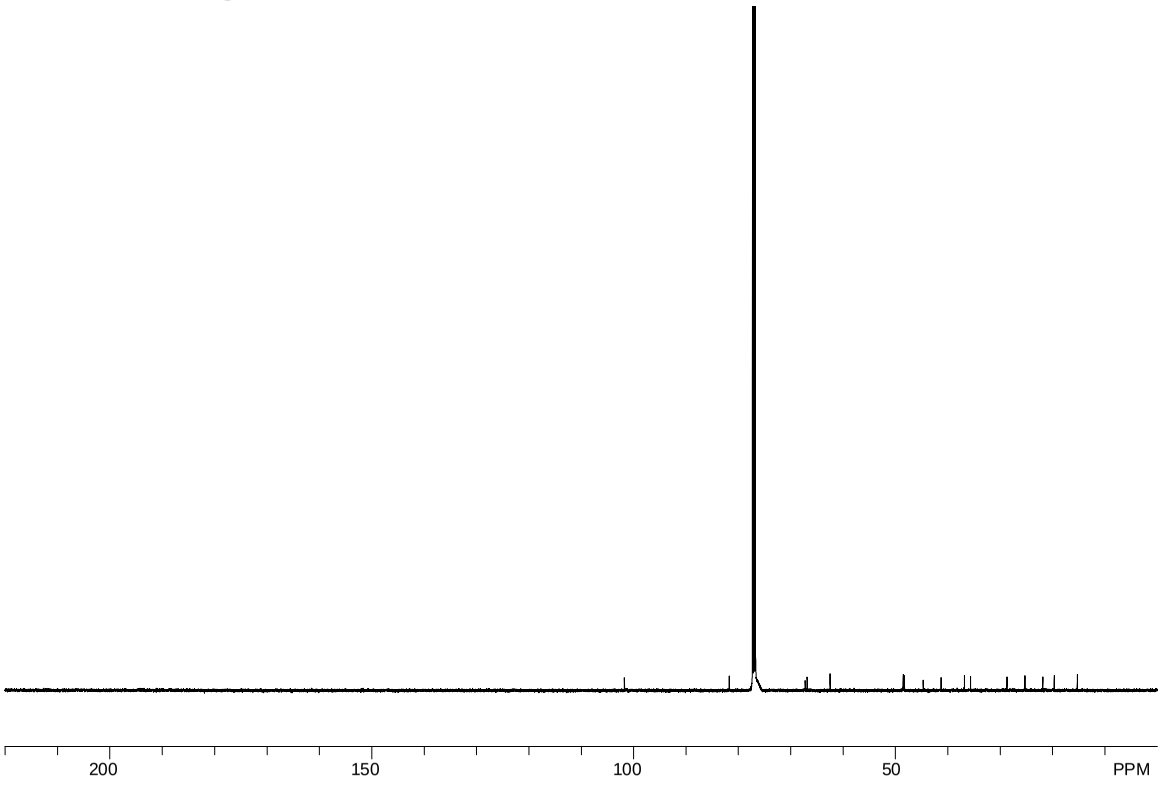


Figure A.7.135 ^{13}C NMR (125 MHz, $CDCl_3$) of Compound **282.**

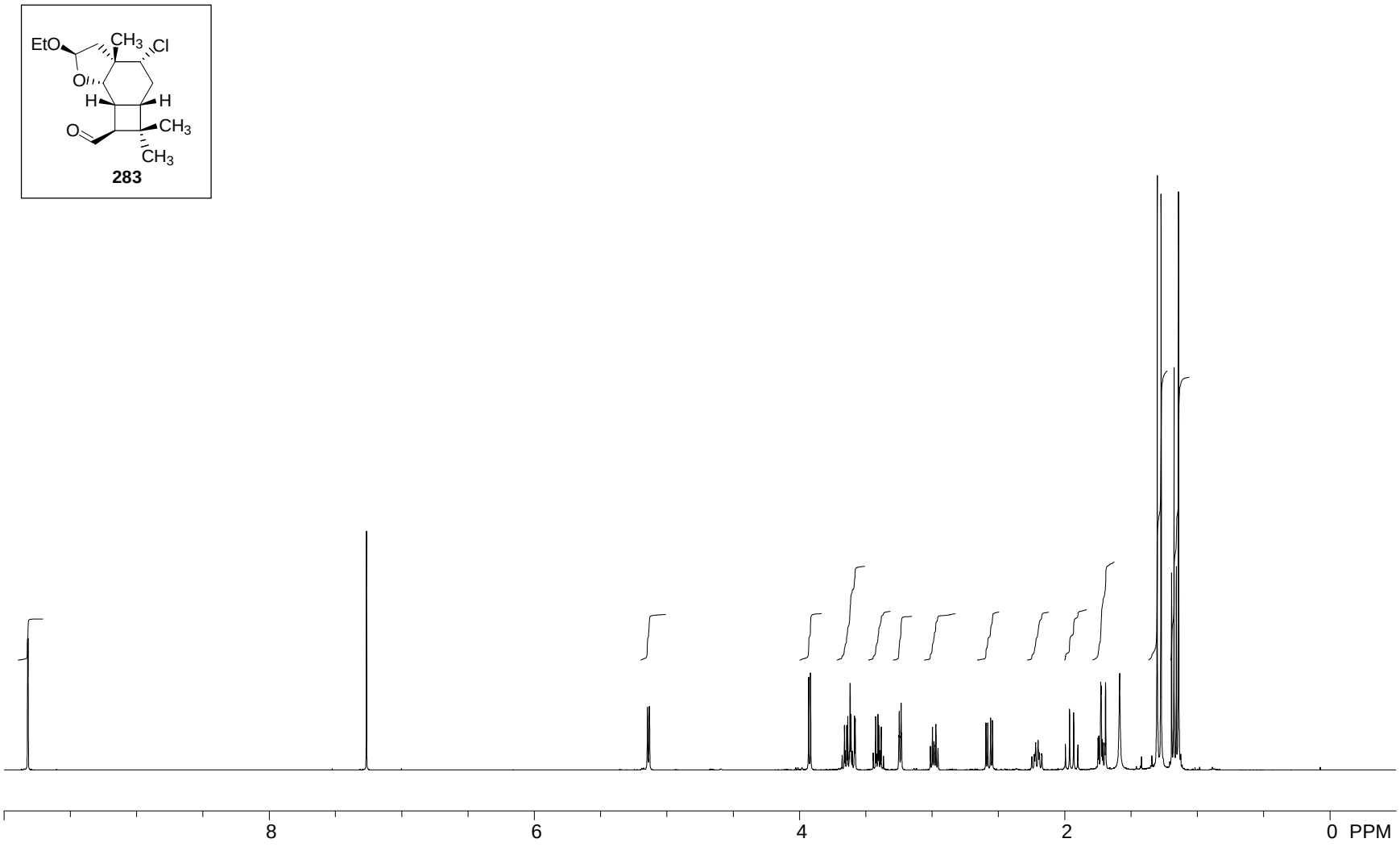


Figure A.7.136 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **283**.

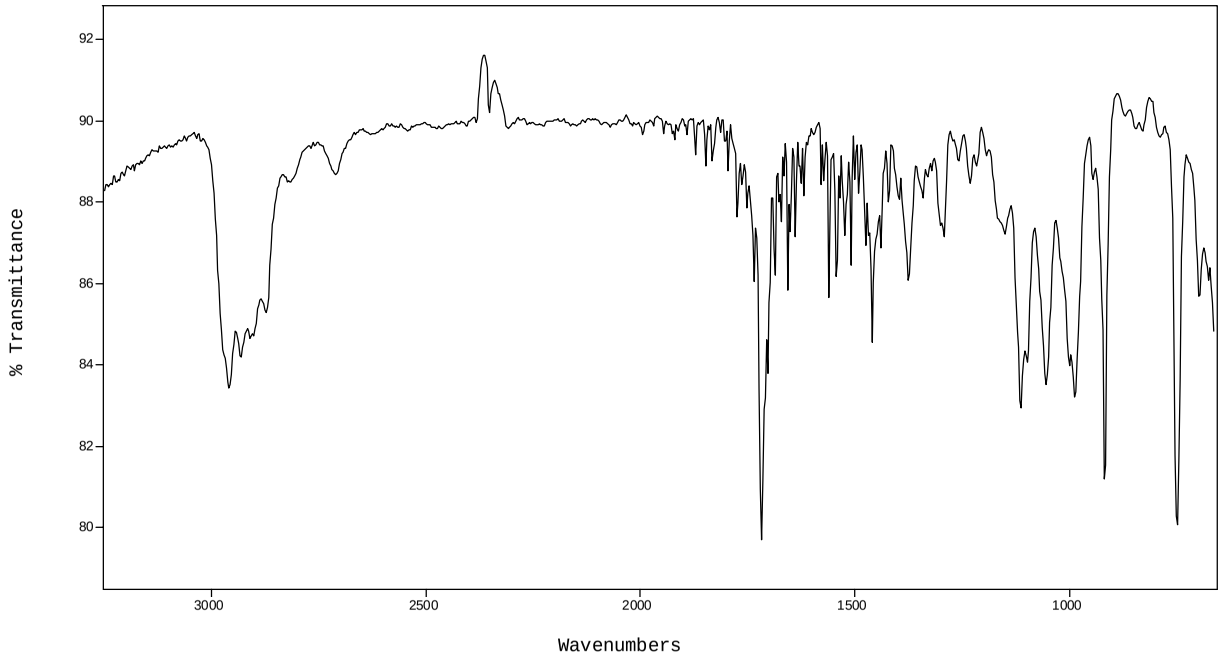


Figure A.7.137 FTIR Spectrum (thin film/NaCl) of Compound **283**.

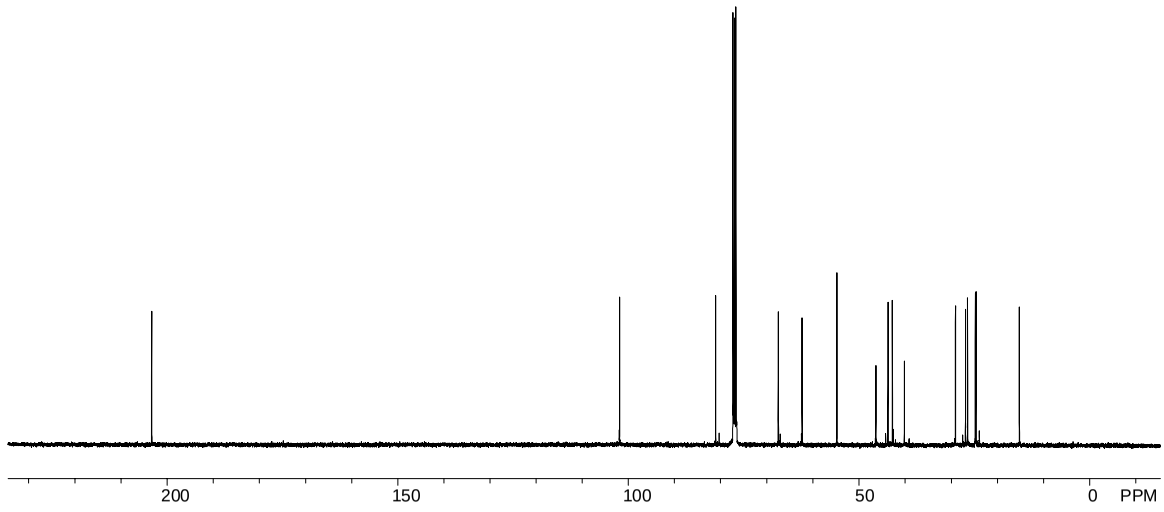


Figure A.7.138 ^{13}C NMR (100 MHz, $CDCl_3$) of Compound **283.**

APPENDIX EIGHT: NOTEBOOK CROSS-REFERENCE

NOTEBOOK CROSS-REFERENCE

The following notebook cross-reference has been included to facilitate access to the original spectroscopic data obtained for the compounds presented in this thesis. For each compound a folder name is given (i.e., MMW12-102) which corresponds to an archived characterization folder hard copy and notebook number (for example, MMW12-102 corresponds to notebook MMW12, page 102). The filenames corresponding to each compound are listed under the appropriate type of spectrum (i.e. ^{1}H NMR, ^{13}C NMR, IR), and these files are stored on ZIP disks and a CD. All notebooks, spectral data, and diskettes are stored in the Wood Group archive.

Compounds Appearing in Chapter One

Compound	Folder	^{1}H NMR	^{13}C NMR	IR
42	MMW5.147	MMW5A.147	MMW5B.147	MMW5r.147
43	MMW11.300	MMW11A.300	MMW11B.300	MMW11r.300
48	MMW17.274	MMW17A.274	MMW17B.274	MMW17r.274
49	MMW17.280	MMW17A.280	MMW17B.280	MMW17r.280
50	MMW17.276	MMW17A.276	MMW17B.276	MMW17r.276
51	MMW5.157	MMW5A.157	MMW5B.157	MMW5r.157
52	MMW5.161	MMW5A.161	MMW5B.161	MMW5r.161
53	MMW11.083	MMW11A.083	MMW11B.083	MMW11r.083
57	MMW5.163	MMW5A.163	MMW5B.163	MMW5r.163
58	MMW5.185	MMW5A.185	MMW5B.185	MMW5r.185
59	MMW11.105	MMW11A.105	MMW11B.105	MMW11r.105
68a	MMW15.237	MMW15A.237	MMW15B.237	MMW15r.137
68b	MMW15.238	MMW15A.238	MMW15B.238	MMW15r.238
69	MMW16.073	MMW16A.073	MMW16B.073	MMW16r.073
72	MMW15.279	MMW15A.279	MMW15B.279	MMW15r.279
73	MMW15.213	MMW15A.213	MMW15B.213	MMW15r.213
74	MMW16.117	MMW16A.117	MMW16B.117	MMW16.117
75	MMW16.118	MMW16A.118	MMW16B.118	MMW16r.118
76	MMW16.131	MMW16A.131	MMW16B.131	MMW16r.131
77	MMW16.124	MMW16A.124	MMW16B.124	MMW16r.124
81	MMW15.281	MMW15A.281	MMW15B.281	MMW15r.281
82	MMW16.275	MMW16A.275	MMW16B.275	MMW16r.275
83a,b	MMW16.182	MMW16A.182	MMW16B.182	MMW16r.182
83c,d	MMW16.182	MMW16A.183	MMW16B.183	MMW16r.183
84	MMW16.255	MMW16A.255	MMW16B.255	MMW16r.255
86	MMW16.256	MMW16A.256	MMW16B.256	MMW16r.256
87	MMW16.238	MMW16A.238	MMW16B.238	MMW16r.238

Compounds Appearing in Chapter Two

Compound	Folder	^{1}H NMR	^{13}C NMR	IR
105	MMW17.056	MMW17A.056	MMW17B.056	MMW17r.056
106	MMW17.056	MMW17C.056	MMW17D.056	MMW17r.057
110	MMW17.217	MMW17A.217	MMW17B.217	MMW17r.217
111	MMW17.280	MMW17C.280	MMW17B.280	MMW17r.280
125	T1.055	T1B.001	T1C.001	T1r.001
126	T1.063	T1C.002	T1D.001	T1r.002
127	T1.069	T1C.003	T1F.001	T1r.003
128	T1.073	T1A.009	T1B.009	T1r.009
130	MMW11.195	MMW11A.195	MMW11B.195	MMW11r.195
131	MMW11.205	MMW11A.205	MMW11B.205	MMW11r.205
132	MMW11.209	MMW11A.209	MMW11B.209	MMW11r.209
133	MMW12.067	MMW12A.067	MMW12B.067	MMW12r.067
134	MMW11.213	MMW11A.213	MMW11B.213	MMW11r.213
135	MMW11.261	MMW11A.261	MMW11B.261	MMW11r.261
136	MMW12.100	MMW12A.100	MMW12B.100	MMW17r.100
137	MMW12.057	MMW12A.057	MMW12B.057	MMW12r.057
138	MMW12.058	MMW12A.058	MMW12B.058	MMW12r.058
139	MMW11.259	MMW11A.259	MMW11B.259	MMW11r.259
147	MMW12.175	MMW12A.175	MMW12B.175	MMW12r.175
148	MMW12.071	MMW12A.071	MMW12B.071	MMW12r.071
149	MMW12.072	MMW12A.072	MMW12B.072	MMW12r.072
144	MMW13.105	MMW13A.105	MMW13B.105	MMW13r.105
150	MMW17.100	MMW17A.100	MMW17B.100	MMW17r.100
151	KT3-069-1	KT3-069-1	KT3-069-1	KT3-069-1
152	KT-3-120-1	KT-3-120-1	KT-3-120-1	KT-3-120-1
153	KT-3-103-1	KT-3-103-1	KT-3-103-1	KT-3-103-1
154	KT-3-019-1	KT-3-019-1	KT-3-019-1	KT-3-019-1
155	KT-3-074-1	KT-3-019-1	KT-3-019-1	KT-3-019-1
156	KT-3-143-2	KT-3-143-2	KT-3-143-2	KT-3-143-2
157	KT-3-132-1	KT-3-132-1	KT-3-132-1	KT-3-132-1
158	KT-3-106-1	KT-3-106-1	KT-3-106-1	KT-3-106-1

Compounds Appearing in Chapter Three

Compound	Folder	^{1}H NMR	^{13}C NMR	IR
171	MMW13.023	MMW13A.023	MMW13B.023	MMW13r.023
172	MMW12.221	MMW12A.221	MMW12B.221	MMW12r.221
173	MMW12.229	MMW12A.229	MMW12B.229	MMW12r.229
178	MMW13.159	MMW13A.159	MMW13B.159	MMW13r.159
180	MMW14.087	MMW14A.087	MMW14C.087	MMW14r.087
181	MMW17.054	MMW17A.054	MMW17B.054	MMW17r.054

182	MMW14.085	MMW14C.085	MMW14D.085	MMW14r.085
183	MMW17.052	MMW17A.052	MMW17B.052	MMW17r.051
185	MMW17.053	MMW17C.053	MMW17D.053	MMW17r.052
186	MMW17.053	MMW17A.053	MMW17B.053	MMW17r.053
187	MMW17.055	MMW17A.055	MMW17B.055	MMW17r.055
188	MMW17.035	MMW17A.035	MMW17B.035	MMW17r.035
194	MMW14.154	MMW14A.154	MMW14B.154	MMW14r.154
195	MMW14.011	MMW14A.011	MMW14B.011	MMW14r.011
196	MMW14.011	MMW14C.011	MMW14D.011	MMW14r.010
197	MMW17.302	MMW17A.302	MMW17B.302	MMW17r.302
198	MMW14.071	MMW14A.071	MMW14B.071	MMW14r.071
199	MMW17.072	MMW17A.072	MMW17B.072	MMW17r.072
200	MMW14.095	MMW14C.095	MMW14D.095	MMW14r.095
190	MMW17.097	MMW17A.097	MMW17B.097	MMW17r.097
201	MMW17.098	MMW17A.098	MMW17B.098	MMW17r.098
202	MMW17.102	MMW17A.102	MMW17B.102	MMW17r.102
203	MMW17.109	MMW17A.109	MMW17B.109	MMW17r.109
207	MMW15.001	MMW15A.001	MMW15B.001	MMW15r.001
208	MMW15.002	MMW15A.002	MMW15B.002	MMW15r.002
204	KT-2-211-2	KT-2-211-2	KT-2-211-2	KT-2-211-2
209	KT-2-222-1	KT-2-222-1	KT-2-222-1	KT-2-222-1
212	MMW17.073	MMW17A.073	MMW17B.073	MMW17r.073
213	MMW14.095	MMW14A.095	MMW14B.095	MMW14r.094
214	MMW17.074	MMW17A.074	MMW17B.074	MMW17r.074
178	MMW17.078	MMW17A.078	MMW17B.078	MMW17r.078

Compounds Appearing in Chapter Four

Compound	Folder	^{1}H NMR	^{13}C NMR	IR
219	KT-2-246-2	KT-2-246-2	KT-2-246-2	KT-2-246-2
220	KT-3-036-1	KT-3-036-1	KT-3-036-1	KT-3-036-1
221	KT-2-233-1	KT-2-233-1	KT-2-233-1	KT-2-233-1
222	KT-2-240-1	KT-2-240-1	KT-2-240-1	KT-2-240-1
223	KT-2-234-1	KT-2-234-1	KT-2-234-1	KT-2-234-1
224	KT-2-239-1	KT-2-239-1	KT-2-239-1	KT-2-239-1
227	KT-3-047-1	KT-3-047-1	KT-3-047-1	KT-3-047-1
228	KT-3-051-1	KT-3-051-1	KT-3-051-1	KT-3-051-1
231	KT-3-056-1	KT-3-056-1	KT-3-056-1	KT-3-056-1
232	KT-2-297-1	KT-2-297-1	KT-2-297-1	KT-2-297-1
235	KT-3-210-1	KT-3-210-1	KT-3-210-1	KT-3-210-1
239	KT-3-211-1	KT-3-211-1	KT-3-211-1	KT-3-211-1
240	KT-3-211-2	KT-3-211-2	KT-3-211-2	KT-3-211-2
242	KT-3-013-1	KT-3-013-1	KT-3-013-1	KT-3-013-1
243	KT-3-013-2	KT-3-013-2	KT-3-013-2	KT-3-013-2

244	KT-3-178-1	KT-3-178-1	KT-3-178-1	KT-3-178-1
245	KT-3-160-1	KT-3-160-1	KT-3-160-1	KT-3-160-1
247	KT-3-227-1	KT-3-227-1	KT-3-227-1	KT-3-227-1
248	KT-3-094-1	KT-3-094-1	KT-3-094-1	KT-3-094-1
249	KT-3-236-2	KT-3-236-2	KT-3-236-2	KT-3-236-2
250	KT-3-279-2	KT-3-279-2	KT-3-279-2	KT-3-279-2
258	MMW17.085	MMW17A.085	MMW17B.085	MMW17r.085
259	MMW17.029	MMW17A.029	MMW17B.029	MMW17r.029
255	MMW17.042	MMW17A.042	MMW17B.042	MMW17r.042
260	MMW17.046	MMW17A.046	MMW17B.046	MMW17r.045
261	MMW17.087	MMW17A.087	MMW17B.087	MMW17r.087
262	MMW17.090	MMW17A.090	MMW17B.090	MMW17r.090
264	MMW17.091	MMW17A.091	MMW17B.091	MMW17r.091
265	MMW17.093	MMW17A.093	MMW17B.093	MMW17r.093
266	MMW17.092	MMW17A.092	MMW17B.092	MMW17r.092
267	MMW17.094	MMW17A.094	MMW17B.094	MMW17r.094
268	MMW17.096	MMW17A.096	MMW17B.096	MMW17r.096
269	MMW17.082	MMW17A.082	MMW17B.082	MMW17r.082
270	MMW17.081	MMW17A.081	MMW17B.081	MMW17r.081
272	MMW17.105	MMW17A.105	MMW17B.105	MMW17r.105
273	MMW17.107	MMW17A.107	MMW17B.107	MMW17r.107
274	MMW17.299	MMW17A.299	MMW17B.299	MMW17r.299
275	MMW17.130	MMW17A.130	MMW17B.130	MMW17r.130
276	MMW17.152	MMW17A.152	MMW17B.152	MMW17r.152
277	MMW17.124	MMW17A.124	MMW17B.124	MMW17r.124
278	MMW17.123	MMW17A.123	MMW17B.123	MMW17r.123
279	MMW17.191	MMW17A.191	MMW17B.191	MMW17r.191
280	MMW17.211	MMW17A.211	MMW17B.211	MMW17r.211
281	MMW17.192	MMW17A.192	MMW17B.192	MMW17r.192
282	MMW17.192	MMW17C.192	MMW17D.192	MMW17.193
283	MMW18.034	MMW18A.034	MMW18B.034	MMW18r.034

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The author, Matthew Mark Weiss was born on November 10, 1974 in Westwood, NJ to Marsha and Larry Weiss. One year later the Weiss family moved to Lubbock, TX where they have remained since. Matt was raised with his two sisters Wendy and Megan. Wendy, four years older than Matt, is married to Rod Lewis and they are raising their two year old daughter Maggie. Megan, two years younger than Matt, is married to Nathan Agnew, and they are expecting their first child next year.

Matt attended Murfee elementary before heading to Evans Junior High and then Monterey High School. During this period, Matt spent most of his free time playing sports. Throughout his time at Monterey he developed an interest in the sciences, particularly biology. After graduating from Monterey in 1993, he decide to leave the state of Texas and head back to the east coast for college. On the advice of his dentist, Matt chose to attend Bowdoin College, in Brunwick, ME where he intended to pursue interests in genetic engineering. In the spring semester of his first year he was required to take Chem. 225, an introduction to organic chemistry. It was this class which piqued his interests in chemistry. Under the tutelage of Professor Richard Broene, Matt began to pursue a major in chemistry. While at Bowdoin, Matt spent two summers performing undergraduate research under the direction of Prof. Broene, working on implementations of metallocene chemistry in the facilitation of natural product synthesis. After graduating from Bowdoin, *Magna Cum Laude*, Matt headed to Yale University in New Haven, CT to pursue graduate studies in organic chemistry.

Matt arrived at Yale in the summer of 1997 to start working in the labs of Prof. John L. Wood. During this period, his growing interests in natural product synthesis and in the fall of 1997 he joined the Wood Group. Matt began his graduate career by joining a project aimed at a total synthesis of welwitindolinone C isothiocyanate. The following spring Matt initiated work directed at a total synthesis of welwitindolinone A isonitrile. In the fall of 1999, he accepted a postdoctoral position in the laboratories of Prof. Larry E. Overman at the University of California in Irvine. Matt received his doctorate in 2001 at which point he headed out to California to begin an NIH-funded postdoc.