DISSERTATION

SYNTHETIC STRATEGIES TOWARD THE TOTAL SYNTHESIS OF TETRAPETALONE A

Submitted by

Jennifer Marie Howell

Department of Chemistry

In partial fulfillment of the requirements

For the Degree of Doctor of Philosophy

Colorado State University

Fort Collins, Colorado

Fall 2012

Doctoral Committee:

Advisor: John L. Wood

Alan J. Kennan
Eric M. Ferreira
Amy L. Prieto
Patrick J. Brennan

ABSTRACT

SYNTHETIC STRATIGIES TOWARD THE TOTAL SYNTHESIS OF TETRAPETALONE A

In 2003 Hirota and coworkers reported the isolation of tetrapetalone A (**1**) from the culture filtrate of *Streptomyces* sp. USF-4727, a *Streptomyces* strain isolated from a soil sample taken from Yada, Shizuoka City, Japan. The molecular structure of **1** was initially reported and then revised in a series of two papers which both appeared in 2003. In addition to the interesting molecular architecture, **1** demonstrated inhibition of soybean lipoxygenase (SBL) (IC_{50} of 190 μM) comparable to well-known human lipoxygenase and cyclooxygenase inhibitors. While no total synthesis has been reported to date, the groups of Porco, Hong and Sarpong have disclosed synthetic approaches toward the tetrapetalone core.

Efforts in the Wood group to synthesize **1** are based on highly convergent synthetic strategies, the first of which was directed at constructing an advanced indanone coupling partner via a Stetter reaction. To this end, a route employing a diastereoselective Claisen rearrangement afforded a highly substituted Stetter reaction precursor but we were unable to realize the latter chemistry. We developed a synthetic route employing a Dieckmann condensation to furnish a highly functionalized tetramic acid. Coupling the tetramic acid with *ortho* substituted aryl halides under aryl amidation conditions proved futile. In an effort to promote an intramolecular aryl amidation we pursued an alternative coupling strategy, which relied on an extremely challenging ring closing metathesis. The desired ring closing metathesis product was not realized. Relay ring closing metathesis investigations provide confidence that the desired olefins will engage in metathesis chemistry. Current synthetic efforts are focused on a diastereoselective intramolecular Tsuji-Trost allylation to furnish a highly functionalized indanone, which has proven to be a competent coupling partner with allylamine under Pd(0)-catalyzed aryl amination

conditions. Elaboration of this advanced indanone intermediate is expected to eventually provide a total synthesis of **1**.

ACKNOWLEDGEMENTS

First and foremost I thank Professor John L. Wood for the opportunity to study organic chemistry, specifically the art of total synthesis. It has been an honor and privilege to study under his guidance. His knowledge and passion for organic chemistry will forever be an inspiration. His dedication to teaching is truly contagious. I am grateful to have a mentor that sets no limits and believes in the pursuit of science for science.

To my professors at California State University, Chico, thank you for inspiring me to major in Chemistry. There are no words to express my gratitude for my undergraduate advisor, Professor David B. Ball, for opening my eyes to the world of organic chemistry, supporting my undergraduate research interests and always promoting my educational advances. I must also thank Professor Bruce H. Lipshutz at the University of California, Santa Barbara, where my summer research experience in his lab confirmed that I was just as happy in lab as I was on the beach.

I am very indebted to many past and present Wood group members: Thank you Elnaz, for taking me under your wing.

Barry, for listening through your headphones.

Matt, for advice on Claisen rearrangements and road bike purchases.

Josh, for always talking chemistry with me.

Dave, for being a great roommate, friend and colleague.

Sarah, for helping me get all my paper work filled out.

Ping, for determination;

Brett, for optimism.

Adam, David and Pete for being comrades in class and in lab.

Genessa, be it a day of columns or 13.2 miles, I'm always at your side.

Travis, for reading my rough drafts; I couldn't be happier to leave the tetrapetalone project to you.

Sam, for attention to detail and student seminar snacks.

Jenny, it was an honor to share your first Bud Light Lime.

Aaron, it has been a blast to work alongside you and watch you develop as a chemist and a mountaineer.

Monica, for fresh energy and enthusiasm.

To the many postdocs that I have had the pleasure of working with during my tenure in the Wood Lab: Rishi, Ke, Graham, Matt, Chris, John, Naoto, Taka, and Jonas thank you for your guidance, advice, patience and support. I would not have been able to do this without you. Thank you

Ke, my first lab mate, for being an amazing mentor and role model.

Matt, Team-Tetrapetalone, for your dedication, persistence, imagination, and patience.

Graham, for sharing your knowledge of NMR.

Jonas, for reading my rough drafts and for becoming part of Team-Tetrapetalone, I am excited to see what will come!

I must thank all of my friends for their unending support and patience. Thank you

Kimmie Dawson-Cummings and Annie Youngman, you both inspire me everyday.

Stephen Lathrop for your love and support.

Harit and Heather Vora, for the awesome adventures in Colorado.

The Lathrop and Engel families, for opening your hearts and homes.

Kelly Lathrop, for being my running buddy and a role model.

Dana Lloyd and Rhiannon Haworth, for teaching me that balance is necessary.

To my willpower & grace Family, your tremendous energy and enthusiasm for life has inspired me to accomplish feats I never dreamed possible.

Last but not least, thanks to my family for your unending love, support, encouragement and understanding. Thank you

Mom, for being my first teacher and my best friend.

Dad, for making sure I have my feet on the ground.

Sam, for inspiring me to pursue all my passions.

Jeannie Caton, for your listening ear and healing heart.

My Grandmothers, Lois Burbank and Margaret Jensen, for always supporting my education.

AUTOBIOGRAPHY

The older of two children, Jennifer Marie Howell was born in June of 1984 to Dan and Tracy Howell in Greenville, California. While she was in elementary school the family resided in Taylorsville, CA. As she began middle school her family moved south to Oroville, CA, for a short stint and once more to Gridley, CA, where she graduated from High School in 2002.

Jennifer enrolled in California State University, Chico, in the fall of 2002, as a double major in Biology and Mathematics. During her first general chemistry class she became interested in pursuing Chemistry as a focus of study and it was the organic chemistry series that cemented this decision. Jennifer joined the laboratory of Professor David B. Ball in 2004 and also completed a summer research internship with Bruce H. Lipshutz at the University of California, Santa Barbara in 2005. Her research focused on new conjunctive reagents as cross-coupling partners en route to retinoid-like polyenes and copper-hydride catalyzed asymmetric 1,4-reduction of α,β-unsaturated amides. She was awarded the CSU, Chico Outstanding Graduating Senior in Professional Chemistry in 2006 and graduated with a B.S. in Professional Chemistry with honors in the major and general education.

In the fall of 2006, Jennifer began her studies toward a doctoral degree in chemistry at Colorado State University. She joined the research laboratory of Professor John L. Wood in the spring of 2007 and was invited to participate in the inaugural ACS Organic Division Graduate Research Symposium (Boston, MA) in July 2010. In the fall of 2012, she received her Ph.D. for contributions toward the total synthesis of tetrapetalone A.

Jennifer accepted a post-doctoral position in the laboratory of Professor M. Christina White at the University of Illinois at Urbana-Champaign starting August 2012.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

CHAPTER 3

CHAPTER 4

APPENDIX 1

LIST OF SCHEMES

CHAPTER 1

CHAPTER 2

CHAPTER 3

CHAPTER 5

Chapter 1

Tetrapetalones: Introduction and Background

1.1 Isolation of the Tetrapetalones and Ansaetherone

In 2003, as part of an ongoing effort to discover novel lipoxygenase inhibitors, Hirota and coworkers screened several *Streptomyces* strains using a soybean lipoxygenase inhibitory assay and identified tetrapetalone A (**1**) (Figure 1.1) from the culture filtrate of *Streptomyces* sp. USF-4727, a *Streptomyces* strain isolated from a soil sample taken from Yada, Shizuoka City, Japan. [1,2] In a subsequent report, Hirota and coworkers reported the isolation of three additional congeners that also possess lipoxygenase inhibitory properties from the culture filtrate of the same *Streptomyces*. Structurally these latter compounds were determined to be oxidized variants of **1** and were aptly named tetrapetalone B (**2**), tetrapetalone C (**3**), and tetrapetalone D (**4**).[3]

In 2008, the Hirota group reported efforts wherein a 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay was employed to screen the culture broth of *Streptomyces* sp. USF-4727. These studies resulted in the isolation of ansaetherone (**5**), a radical scavenger that is structurally akin to the previously isolated tetrapetalones. [4]

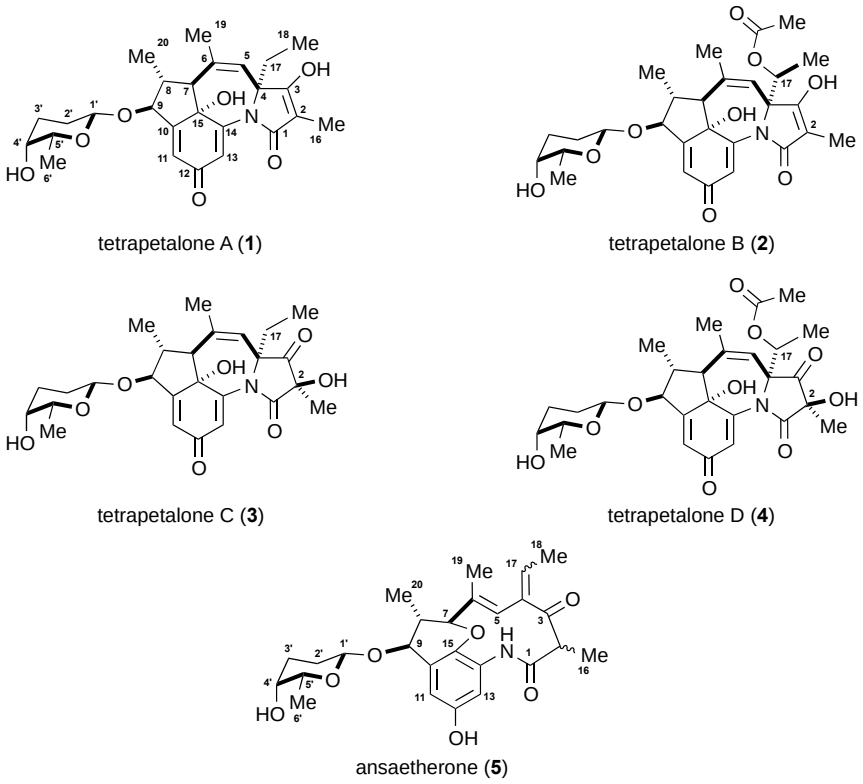


Figure 1.1 Tetrapetalone Series and Ansaetherone

1.2 Tetrapetalone A Structure Elucidation

The molecular structure of tetrapetalone A (**1**) was initially reported and then revised in a series of two papers which both appeared in 2003.[1,5] In the initial report the structure of tetrapetalone A (**1**) was assigned as illustrated as **I** in Figure 1.2 on the basis of spectroscopic studies which included HRFAB mass spectrometry, IR spectroscopy, ^{1}H, ^{13}C NMR, DEPT, ^{1}H-^{1}H COSY, HMQC, ^{1}H-^{13}C HMBC and 2D-INADEQUATE data.[1,5]

Subsequent efforts to confirm the position and substitution pattern of the nitrogen atom led to a ^{1}H-^{15}N HMBC study of the long-range coupling patterns. The latter revealed the presence of an amide nitrogen (due to its chemical shift), which possessed long-range couplings to both 13-H and 17-H. This result was clearly not consistent with the originally assigned structure (i.e., **I**) and led Hirota to propose the actual structure of tetrapetalone A to be that

depicted as **1**, wherein the positions of the amide nitrogen and C(14) oxygen are interchanged (c.f., **I** and **II** in Figure 1.2).

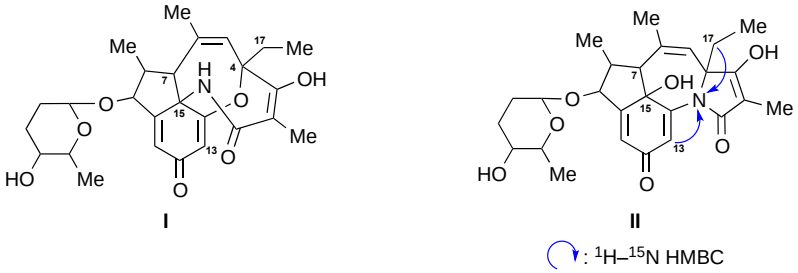


Figure 1.2 Structural Revision of Tetrapetalone A

The stereochemistry of tetrapetalone A (**1**) was assigned on a piece-by-piece basis. The relative stereochemistry of the 2-methyltetrahydropyran unit was initially assigned based on a comparison of ^{1}H NMR derived chemical shift and coupling constant data to that for β-D-rhodinose (**7**) and further supported by ^{1}NOESY correlations observed for 1'-H and 5'-H. The absolute stereochemistry of this ring was determined by a modified Mosher analysis which revealed the absolute stereochemistry at C-4' to be *R*.

The relative stereochemistry of the tetracyclic core was assigned based upon spectroscopic studies of the *O*-methylated derivative **6** (Figure 1.3). Specifically, the *syn* relationship of the C(7)-H, C(9)-H and ethyl group residing at C(4) as well as the 1,3-*syn* relationship of the C(9)-H and C(15)-OH were all assigned based on NOE correlations derived from a NOESY spectrum.[5] The absolute stereochemistry was assigned as illustrated based upon a modified Mosher analysis, which indicated the absolute stereochemistry at C-9 to be of the *S*-configuration.

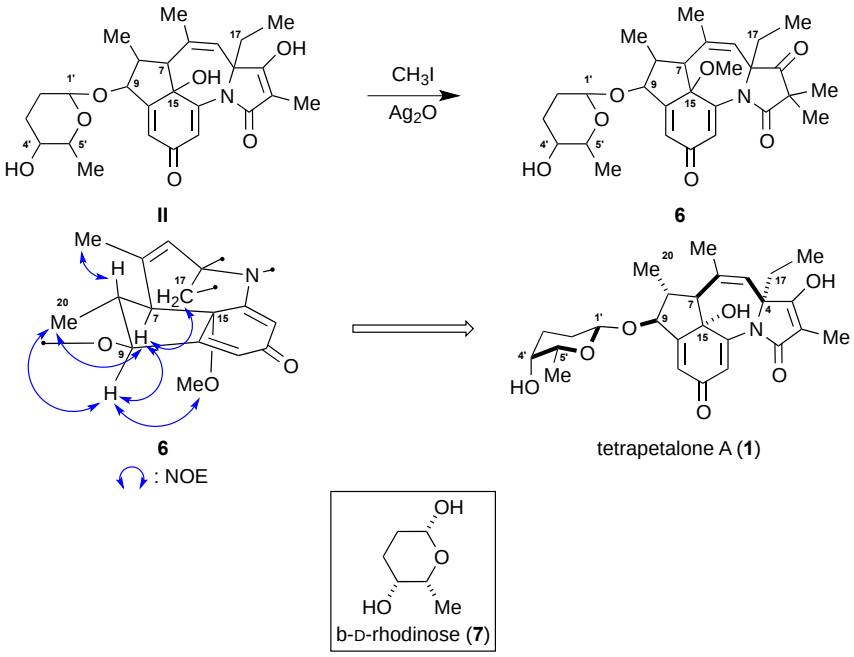


Figure 1.3 Stereochemical Assignment of Tetrapetalone A

1.3 Biological Activity

Tetrapetalone A (**1**) demonstrated inhibition of soybean lipoxygenase (SBL) comparable to the well-known human lipoxygenase and cyclooxygenase inhibitors nordihydroguaiareic acid (NDGA) (**8**) and kojic acid (**9**) (Table 1.1 and Figure 1.4). Interestingly, tetrapetalones B–D (**2-4**) also demonstrated SBL inhibition;[3] however, methylation of tetrapetalone A resulted in a compound (i.e., **10**) that demonstrated very little SBL inhibitory activity.[2] Given that NDGA (**8**) inhibits both human lipoxygenase and cyclooxygenase, there is a possibility that the tetrapetalones (**1**-**4**) may also display inhibitory activity against these latter enzymes.

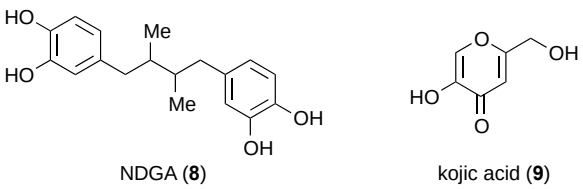
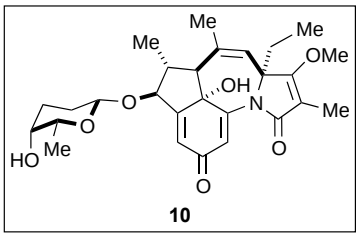


Figure 1.4 Known Lipoxygenase Inhibitors

Table 1.1 Inhibitory Activities against Soybean Lipoxygenase

compound	IC_{50} (mM)
tetrapetalone A (**1**)	190
tetrapetalone B (**2**)	320
tetrapetalone C (**3**)	360
tetrapetalone D (**4**)	340
NDGA (**8**)	110
kojic acid (**9**)	290
tetrapetalone A-Me (**10**)	>1000



10

Human lipoxygenase (HLO) and cyclooxygenase (COX) mediate the metabolism of arachidonic acid (**11**), a key precursor to a large family of hormones that are generally classified as eicosanoids and include the prostaglandins, thromboxanes, prostacyclins and leukotrienes (Figure 1.5).[6] The resulting leukotrienes, lipoxins, and prostaglandins are important signaling molecules that are short-lived and display their effects on cells in proximity to their point of biosynthetic origin. Nevertheless these compounds have been identified as important to the modulation of many biological processes involved in human diseases, including: inflammation, bronchospasm, regulation of blood pressure, congestion, ion transport across membranes, and synaptic transmission.[2,3] Thus, searching for potent inhibitors of these oxygenases continues to be a significant topic in medicinal chemistry.

Cyclooxygenase (COX) has become a major target for the development of anti-inflammatory drugs.[6] Aspirin (**12**), a common anti-inflammatory, anti-pyretic, anti-thrombotic analgesic, has been used for centuries and only in recent years has been shown to irreversibly inhibit cyclooxygenase by acylating a serine residue within the active site. The anti-thrombotic activity of Aspirin (**12**) is a manifestation of the inhibition of thromboxane biosynthesis.

The leukotriene pathway has also become an important target for drug discovery.[6] Overproduction of leukotrienes causes asthmatic attacks, and thus inhibiting the production of these signaling molecules is one target of antiasthmatic drugs such as Prednisone (**13**).

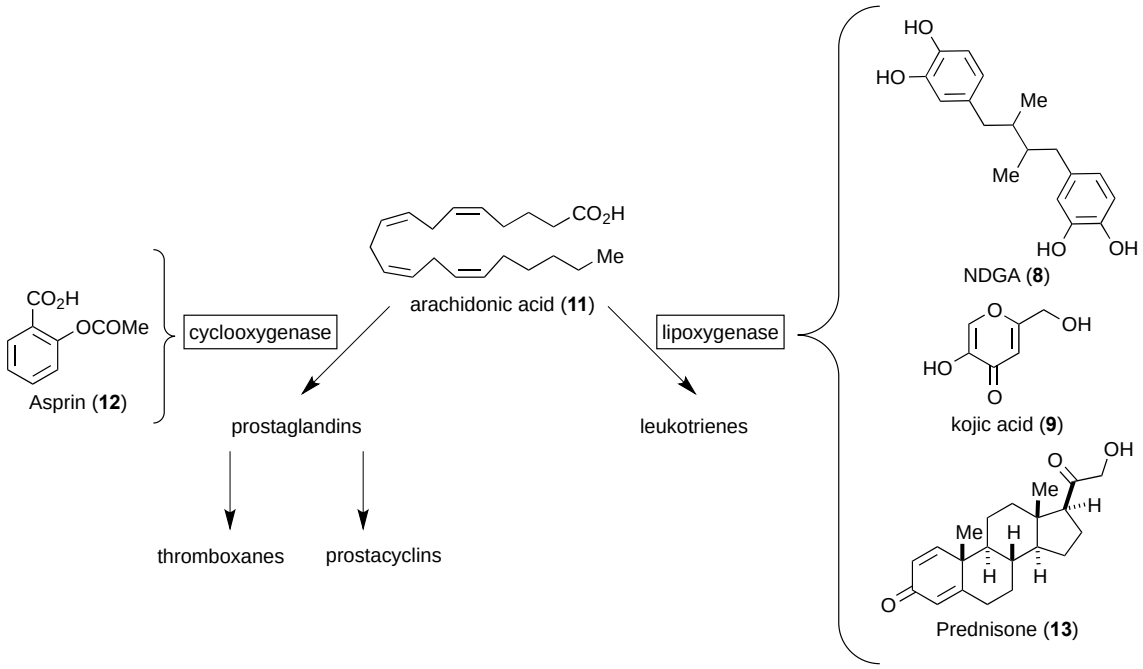


Figure 1.5 General Archidonic Acid Pathway and Known Inhibitors

In contrast to HLO, the role of SBL is to catalyze the oxidation of certain unsaturated fatty acids possessing a *cis*,*cis*-1,4-pentadiene moiety.[7] However, there is homology in the amino acid sequence of the active sites in SBL and human 5-lipoxygenase (5-LO). Although the ideal substrate for SBL is linoleic acid, arachidonic acid (**11**) can also serve as a substrate and undergoes a reaction analogous to 15-lipoxygenase activity.[2] In addition the well-known human lipoxygenase/cyclooxygenase inhibitor NDGA (**8**), a natural product, also has been shown to be a potent inhibitor of SBL. Clearly, given that human and soybean lipoxygenases act on several common substrates, the search for possible inhibitors of these enzymes can be guided by studies on the more abundant and economical enzyme, SBL.

1.4 Biosynthesis

1.4.1 AHBA-Derived Natural Products

3-Amino-5-hydroxybenzoic acid (AHBA) derived natural products are a sizeable group of secondary metabolites produced by microorganisms.[8] They fall, so far, into three structural classes; the great majority represents the family of ansamycins, in which AHBA has served as a starter for a polyketide assembly ultimately resulting in a macrocyclic lactam (Figure 1.6). The ansamycin class can be further segregated based on the incorporation of the AHBA unit into naphthalenic (**14**–**19**) and benzenic (**20**–**25**) ansamycins. The tetrapetalones (**1**–**4**) and ansaetherone (**5**) fall into the benzenic ansamycin structural class. A second class is the mitomycins (**26**), in which AHBA has been combined with an aminosugar moiety to give unique tricyclic structures. A third class can be classified as degraded ansamycins (**27**). In most of the compounds derived from AHBA this starter unit eventually serves as a precursor to a structural "*meta*-C_7N" unit comprised of a six-membered carbocycle, aromatic (naphthalenic/benzenic) or quinoid, functionalized with a carbon and a nitrogen in a meta arrangement (Highlighted in Bold, Figure 1.6).

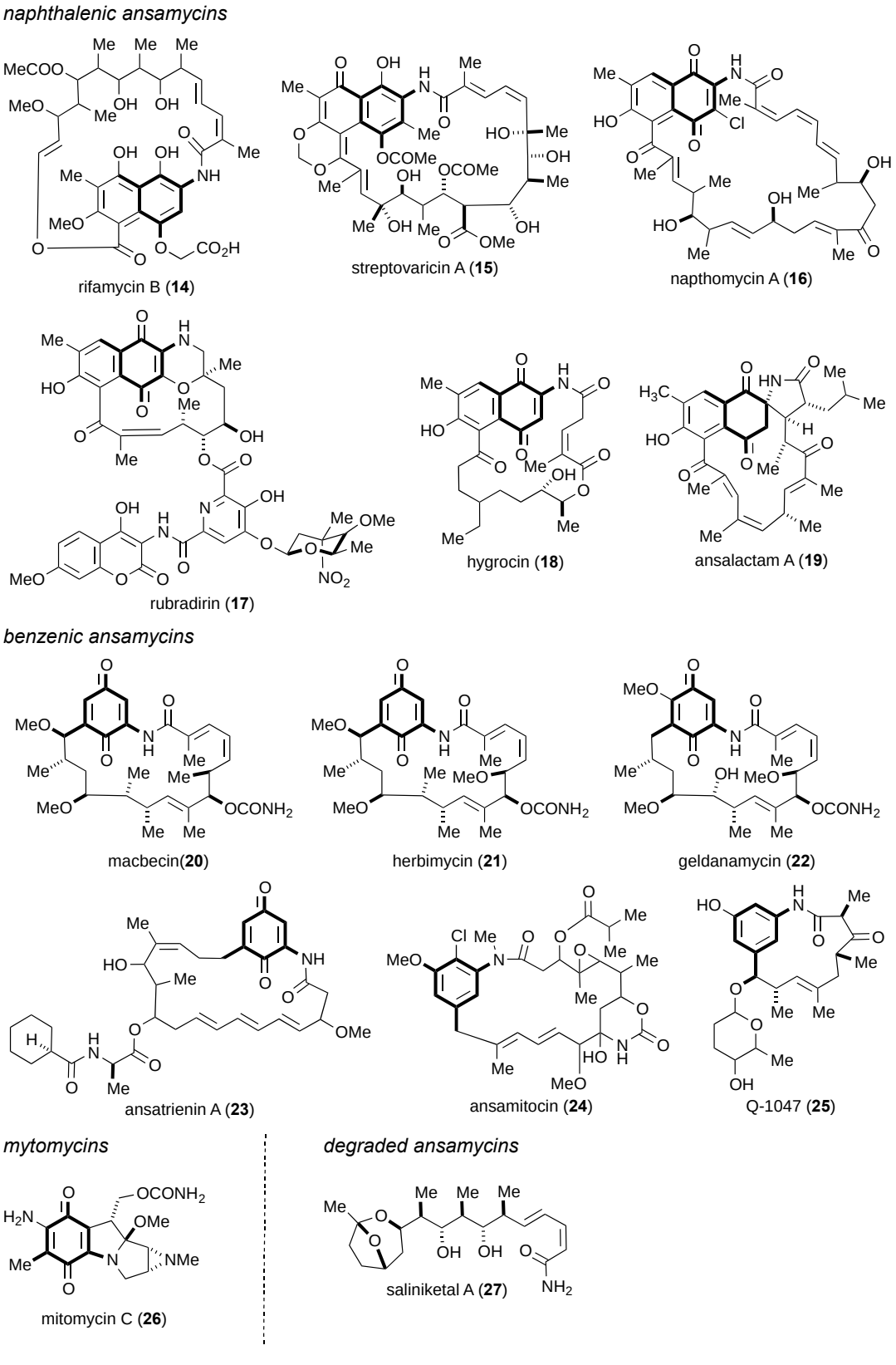
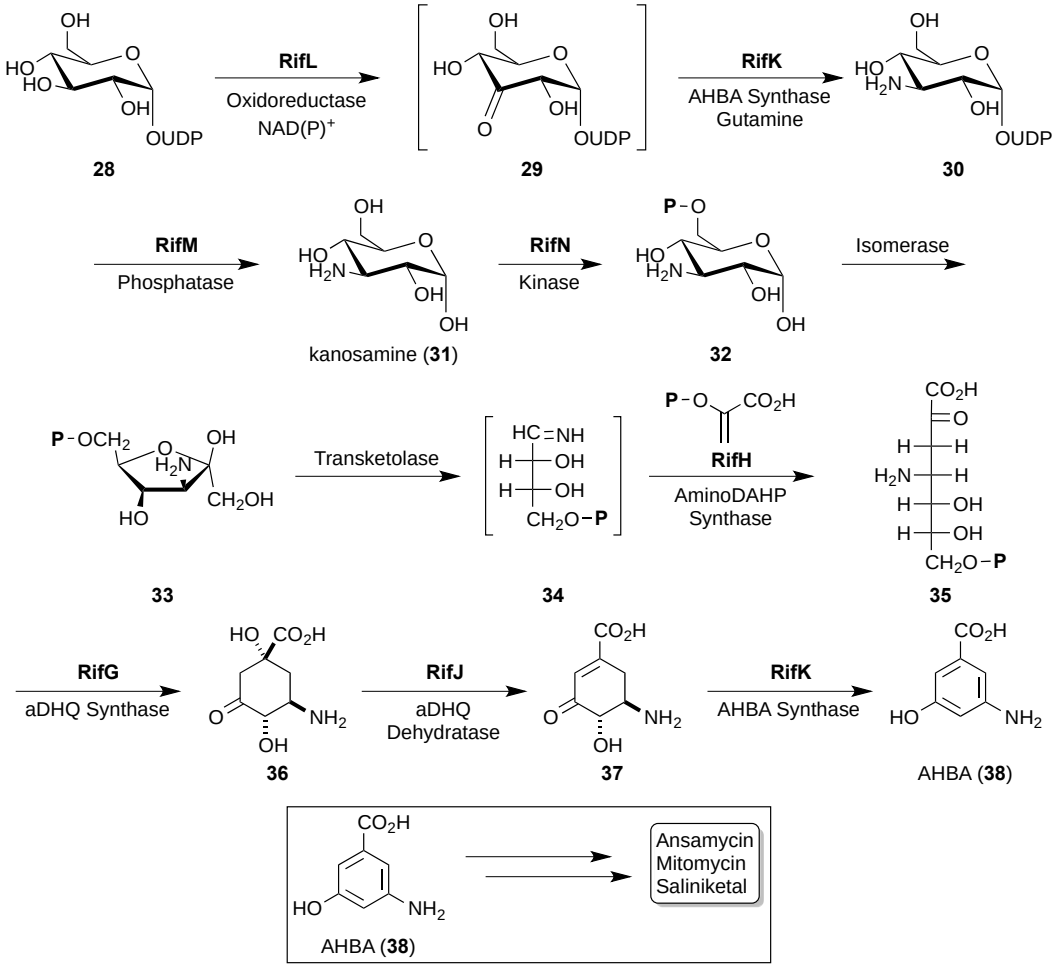


Figure 1.6 Representative AHBA-Derived Natural Products

Prior to its incorporation into the polyketide biosynthetic machinery, AHBA is biosynthesized by a unique amino-shikimate biosynthetic pathway, illustrated in Scheme 1.1.[8,9] In three reactions paralleling the normal shikimate pathway, the imine of erythrose 4-phospate **34** is converted into 5-deoxy-5-amino-dehydroshikimic acid **37**, which is then aromatized to AHBA by the pyriodoxal phosphate-enzyme, AHBA synthase. The origin of the imine **34** was traced to the biosynthesis of kanosamine (**31**), which then undergoes phosphorylation, isomerization and cleavage by transketolase.

Rifamycins were the first group of ansamycins isolated from a microorganism,[8] and accordingly genes responsible for AHBA biosynthesis were first identified as part of the rifamycin biosynthetic gene cluster. Most of the products encoded by these genes are consistent with the proposed AHBA biosynthetic pathway, such as aminoDAHP synthase (RifH), aminoDHQ synthase (RifG), aminoDHQ dehydratase (RifJ), AHBA synthatase (RifK) and those putatively responsible for the early steps in the biosynthesis of imine **34**, including oxidoreductase (RifL) and kinase (RifN) (Scheme 1.1). AHBA synthase catalyzes both the reductive amination of **29** to **30** at the early stage of the pathway and the final dehydration of **37** to AHBA (**38**).



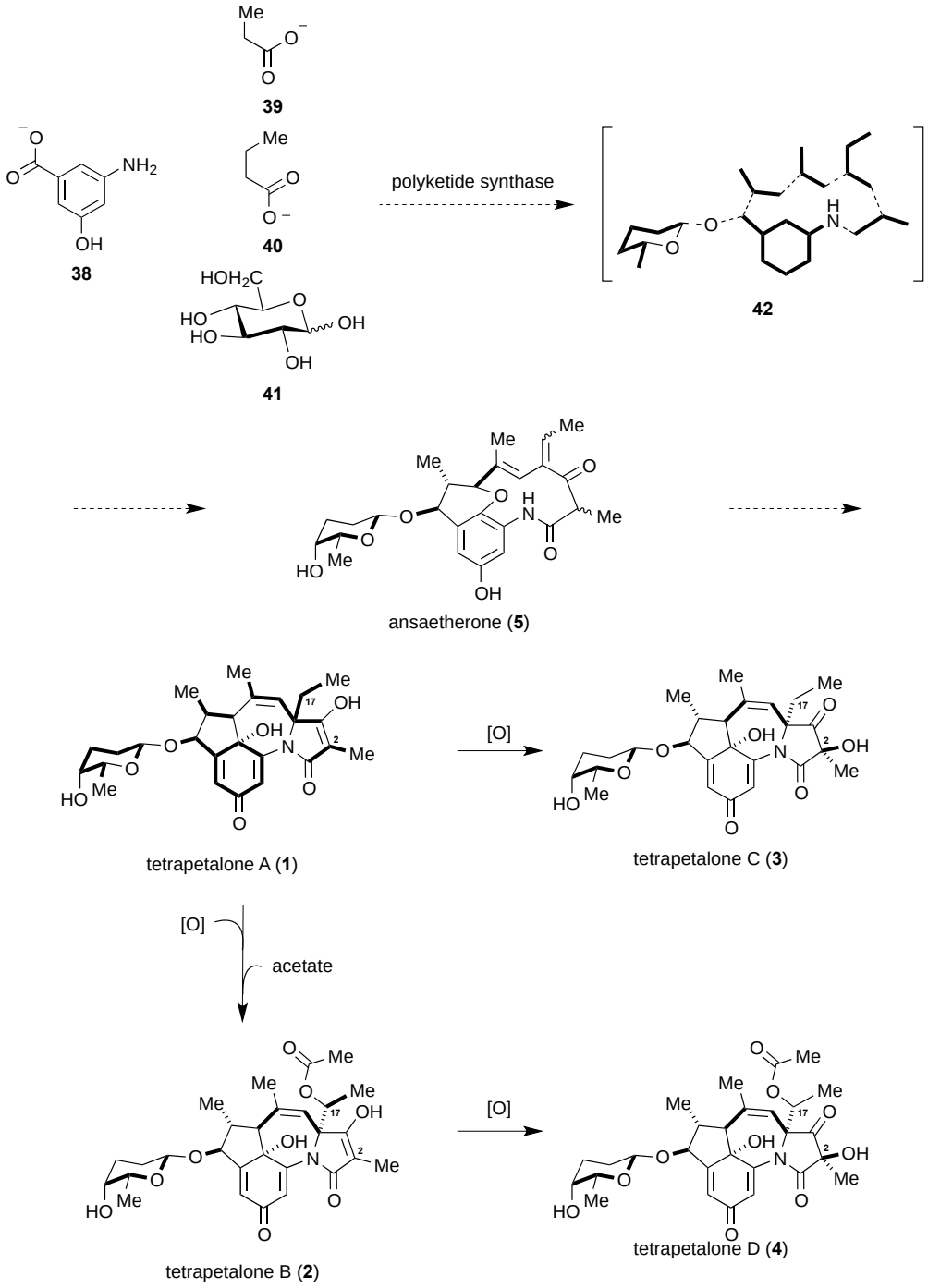
Scheme 1.1 Proposed AHBA Biosynthetic Pathway

1.4.2 Tetrapetalone Biosynthesis

Biosynthesis of the tetrapetalones (**1**–**4**) has, so far, only been studied by feeding experiments with isotope-labeled precursors.[8,10] The feeding experiments indicated that the ansamacrocyclic aglycon of the tetrapetalones is assembled on a polyketide synthase (PKS) using AHBA (**38**) as the starter unit, followed by incorporation of three propionate (**39**) and one butyrate (**40**) extender units (Scheme 1.2). The deoxysugar moiety is derived from glucose (**41**). The acetoxy groups of tetrapetalones B (**2**) and D (**4**) are derived from acetate.

Due to the similar structural features of ansaetherone (**5**), it is proposed to be an intermediate compound in the tetrapetalone biosynthesis (Scheme 1.2).[4] The presence of **5** in the

biosynthetic pathway, suggests that the tetracyclic aglycon of the tetrapetalones is formed after conjunction with the sugar moiety. First, AHBA is synthesized (Scheme 1.1) and employed as a starter unit for constructing an ansa bridge containing intermediate. Second, a sugar moiety derived from a glucose unit (**41**) is attached to the ansa bridge-containing fragment to provide precursor **42**. Precursor **42** is subjected to structural modifications to afford ansaetherone (**5**), from which tetrapetalone A (**1**) is derived. Oxidation of **1** at C-17 to introduce a hydroxyl group and subsequent acetoxylation affords tetrapetalone B (**2**). Tetrapetalone A (**1**) and B (**2**) are oxidized to tetrapetalones C (**3**) and D (**4**), respectively. This oxidation was supported by experimental evidence; exposure of tetrapetalones A (**1**) and B (**2**) to aqueous hydrogen peroxide yielded the oxidized tetrapetalones C (**3**) and D (**4**), respectively.

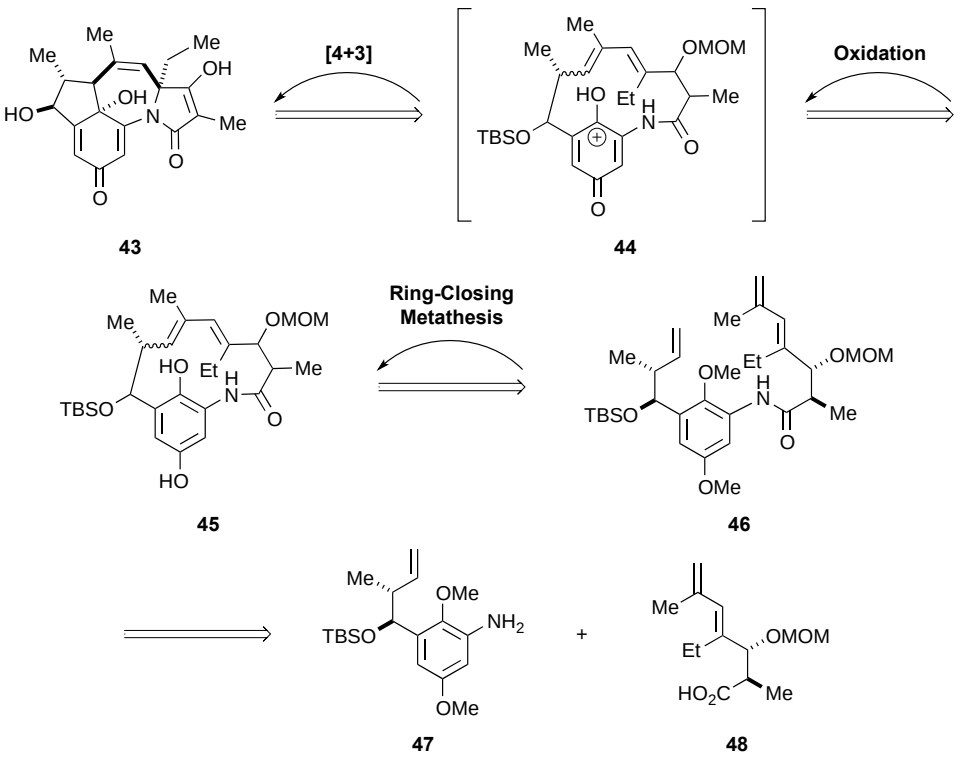


Scheme 1.2 Proposed Biosynthesis of Tetrapetalones

1.5 Previous Synthetic Approaches Towards the Tetrapetalones

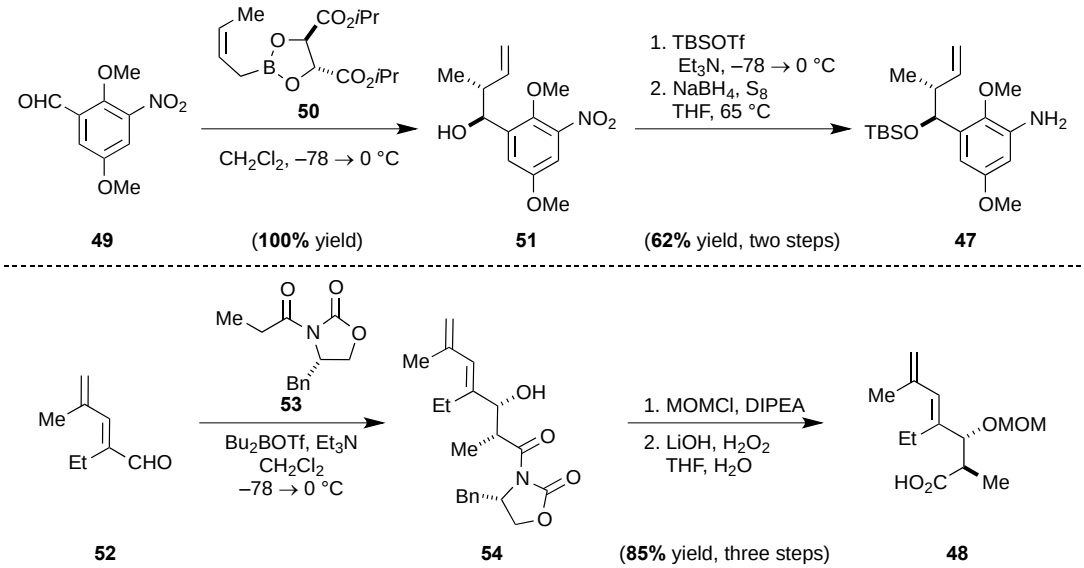
1.5.1 Porco's Approach to the Tetrapetalones

Porco and colleagues at Boston University became interested in the tetrapetalones due to the unique structural features of the tetracyclic core and their similarity to the ansamycin antibiotics.[11] Based on the proposed biosynthesis of the tetrapetalones which involves macrocyclic lactam formation followed by oxidation of the aromatic core, Porco and coworkers envisioned a corresponding synthetic strategy wherein the tetracyclic core of the tetrapetalones (**1**–**4**) would derive from an oxidative transannular [4+3] cyclization process. In the event, oxidation of hydroquinone **45** was expected to provide the arene-derived oxonium ion **44** that would engage the diene fragment and promote subsequent reaction with the amide nitrogen to furnish the tetracyclic skeleton of the tetrapetalones (**43**). Hydroquinone **45** seen as arising from a ring closing metathesis (RCM) reaction of acyclic substrate **46**, which would, in turn, derive from condensation of aniline **47** and carboxylic acid **48**.



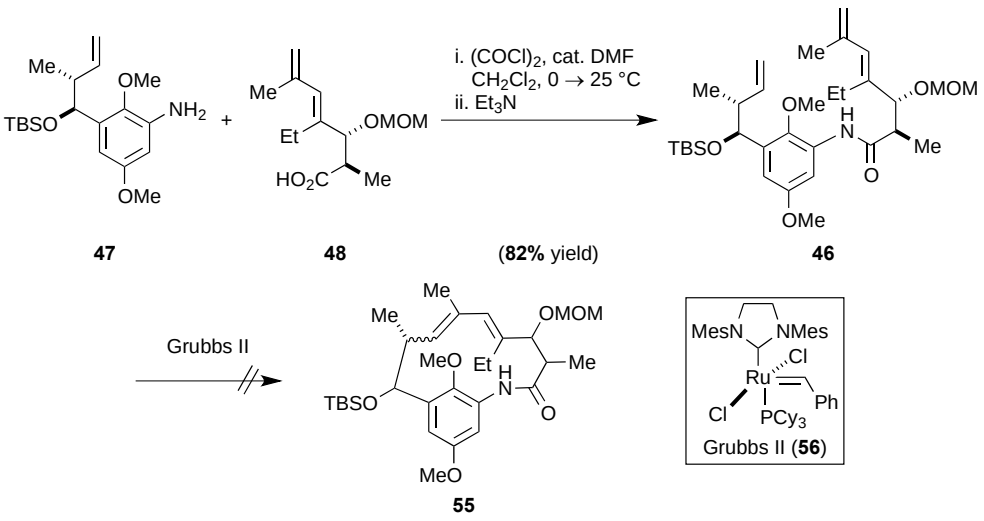
Scheme 1.3 Porco's Retrosynthetic Analysis of Tetrapetalone A Aglycon

Porco initiated his synthesis with an asymmetric crotylation of aldehyde **49** using the chiral cis-crotylboronate derived from L-diisopropyltartrate (**50**) to afford chiral alcohol **51** as a single diastereomer in quantitative yield (Scheme 1.4). Silylation followed by reduction of the nitro group afforded the desired aniline **47** in 62% yield over two steps. Synthesis of the requisite diene acid **48** commenced with an Evans *syn*-aldol condensation of dienal **52** with chiral oxazolidinone **53** to afford chiral alcohol **54** as a single diastereomer. Methoxy methyl protection of the alcohol and hydrolysis of the chiral auxilary afforded carboxylic acid **48** in 85% yield over three steps.



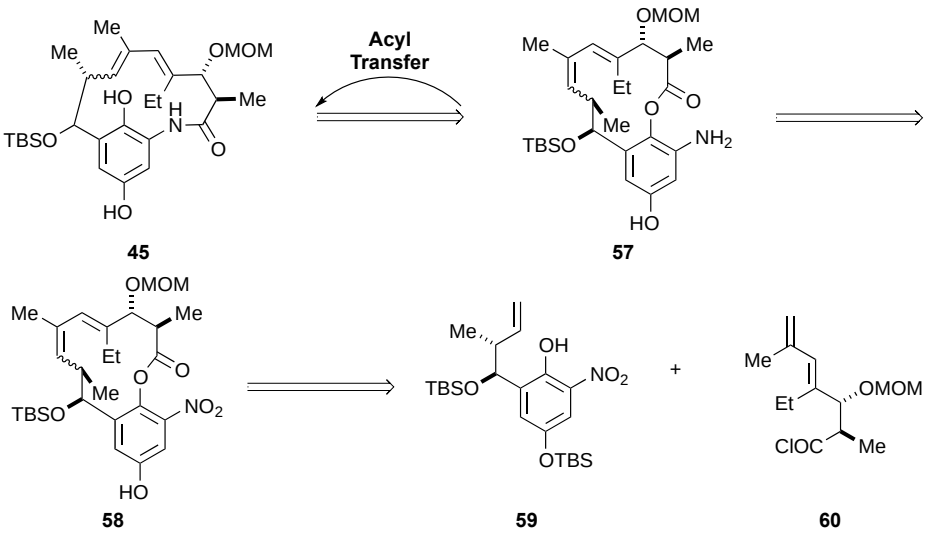
Scheme 1.4 Synthesis of Aniline and Carboxylic Acid Coupling Partners

Coupling of fragments **47** and **48** was achieved via the intermediacy of an acid chloride and provided triene **46** without epimerization (Scheme 1.5). However, treatment of acyclic triene **46** with the Grubbs second-generation catalyst (**56**) did not produce the desired macrocyclic diene **55**. ^{1}H NMR spectroscopic analysis of the crude reaction mixture revealed that the ruthenium catalyst had reacted with the monosubstituted olefin, with no evidence of metathesis of the 1,1-disubstituted olefin. Porco and coworkers propose that this particular reaction, which attempts to incorporate a rather unreactive 1,1-disubstituted olefin into a ring closing metathesis event that would furnish a strained *"meta* bridging" macrocycle **55**, was beyond the scope of the robust RCM reaction.



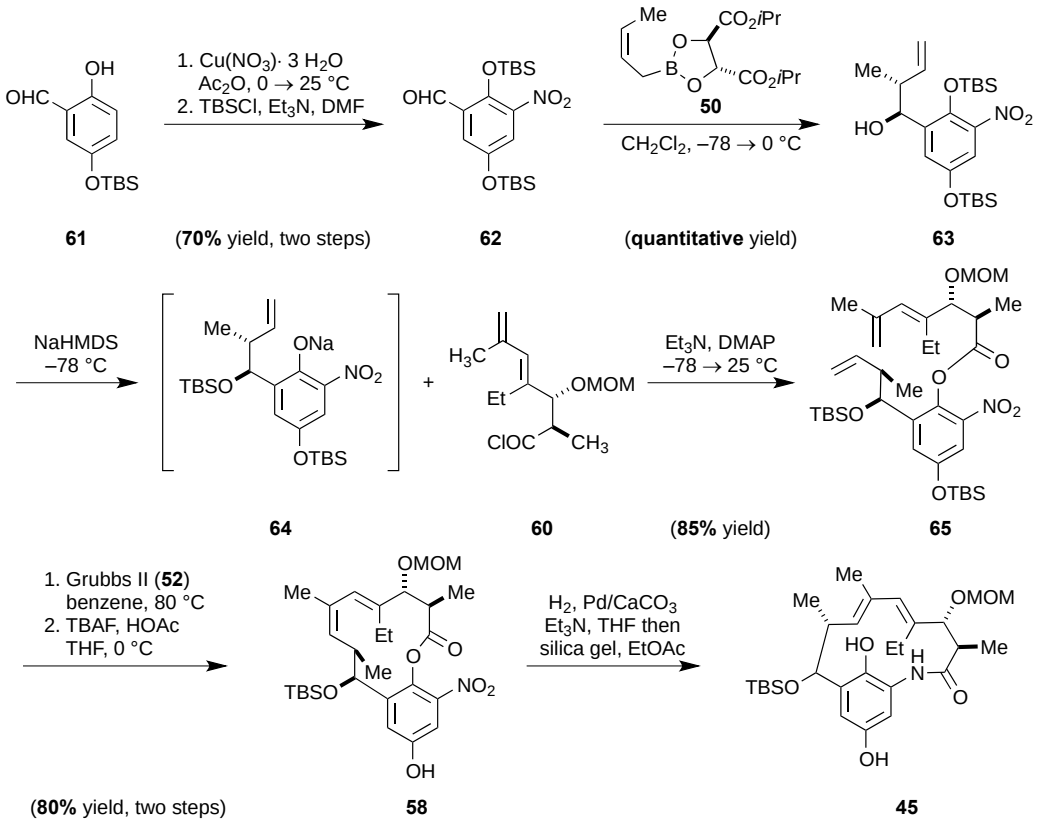
Scheme 1.5 Ring Closing Metathesis Approach to Macrolactam

The failure of the RCM to **45** led Porco and coworkers to next target what they believed would be a less strained and synthetically more accessible "*ortho*-bridge" macrolactone intermediate (i.e., **57**). Subsequent intramolecular acyl transfer was envisioned as giving rise to the ring-expanded macrolactam **45** (Scheme 1.6). Lactone **57** would be prepared via selective reduction of the nitro group of **58**, which would be obtained from a ring closing metathesis reaction applied to the coupling product derived from nitrophenol **59** and acid chloride **60**.



Scheme 1.6 Macrolactam Revised Retrosynthetic Analysis

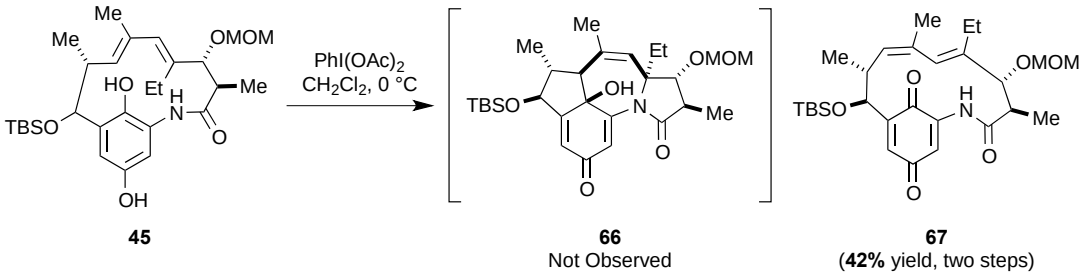
The revised synthesis began with nitration of phenol **61** followed by silylation to afford bis-silylether **62** in 70% yield, over two steps (Scheme 1.7). Asymmetric crotylation of aldehyde **62** using *cis*-crotylboronate **50** provided chiral alcohol **63** as a single diastereomer in quantitative yield. Deprotonation of the secondary alcohol of **63** generated the sodium phenoxide species **64** in situ through intramolecular transfer of a silyl group. Subsequent addition of acid chloride **60** (Et_3N and DMAP) resulted in acylation of **64** to afford ester **65**. Exposure of **65** to Grubbs second-generation catalyst resulted in RCM macrocyclization to afford the cyclic diene, which upon exposure to tetrabutylammonium fluoride (TBAF) underwent selective desilylation to furnish nitrophenol **58**. Chemoselective reduction of the nitro group in **58** was achieved when $Pd/CaCO_3$ was employed as the catalyst in a cosolvent of triethylamine. Filtration of the reaction mixture through silica gel followed by elution with ethyl acetate induced the desired acyl migration to yield macrolactam **45**.



61 62 63 64 60 65 58 45

Scheme 1.7 Synthesis of Macrolactam

With macrolactam **45** in hand, Porco and coworkers next investigated their key step, biomimetic transannular oxidative [4+3] cyclization. It was hypothesized that exposure of hydroquinone **45** to the hypervalent iodine reagent, (diacetoxyiodo)benzene, would result in an arene-derived oxonium ion that could be trapped by the diene fragment, which subsequently could react with the amide nitrogen atom to form the tetracyclic skeleton (Scheme 1.3). Upon first inspection of the oxidized product it was believed that this was indeed the case and Porco published what he believed was an approach to the core ring system;[11] however, a year later, after further spectral analysis, it was realized that the oxidized product was not the tetracyclic skeleton **66** but instead was quinone **67**, the oxidized equivalent of the hydroquinone **45** (Scheme 1.8).[12]

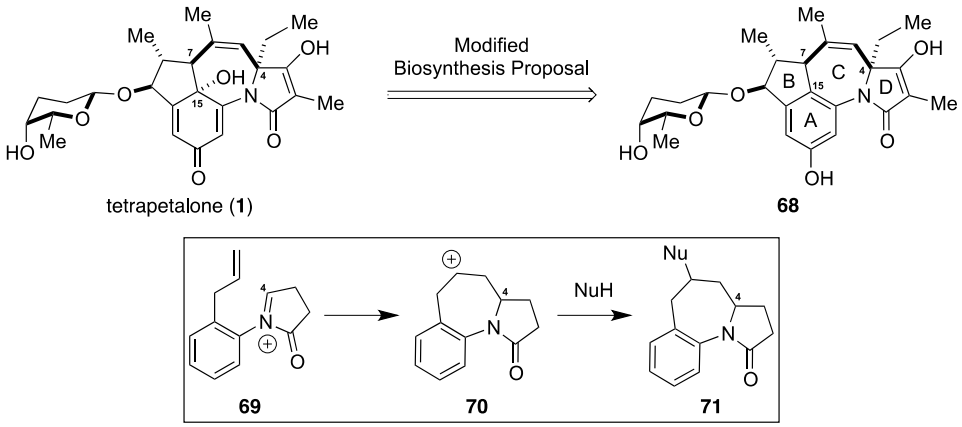


45 **66** Not Observed **67** (**42%** yield, two steps)

Scheme 1.8 Attempted Biomimetic Oxidative Transannular [4+3] Cyclization

1.5.2 Hong's Approach to the Tetrapetalones

Hong and colleagues at the Shanghai Institute of Organic Chemistry became interested in the tetrapetalones and also sought to take advantage of a biomimetic approach.[13] Recognizing that the formation of the fully substituted carbon center (C4) bearing an amide group may have hampered the previous biomimetic endeavor by the Porco group, Hong and coworkers planned to explore an alternate biomimetic approach wherein the cyclohexadienone moiety of **1** was envisaged as arising from a late stage oxidation of an intermediate tetracyclic phenol **68** (Scheme 1.9). This strategy, which calls for formation of the C(7)–C(15) bond prior to introduction of the C(15)-hydroxy group is strategically similar to the biosynthesis of ansamycins. This strategy relies on the proposed ability of singlet oxygen to effect oxidation to the requisite C(15)-alcohol and thus complete the synthesis of tetrapetalone A (**1**).

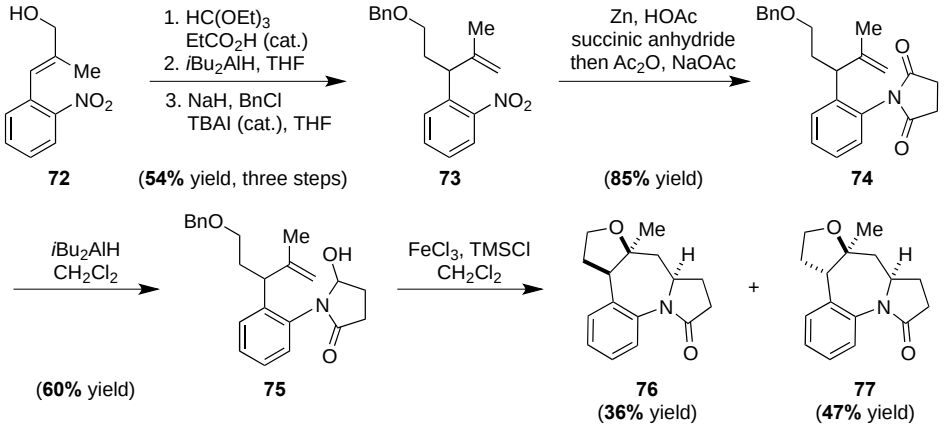


Scheme 1.9 Construction of the 1-Benzazepine via *N*-Acyliminium Ion Cyclization

With an overarching synthetic design in mind, the Hong group began to consider approaches to the requisite 1-benzazepines (C-ring) and proposed generating a reactive *N*-acyliminium ion (**69**) that would engage a pendant olefin in a cyclization reaction to furnish carbocation **70** which, upon nucleophilic quenching, would afford the requisite ring system (e.g., **71**) (Scheme 1.9). Based on seminal contributions from Speckamp and Hiemstra, *N*-acyliminium ion cyclization chemistry has evolved into a powerful reaction that has played a key role in many natural product syntheses;[14] thus, Hong and coworkers had considerable precedents on which to base their proposed construction of the tetracyclic core of the tetrapetalones.

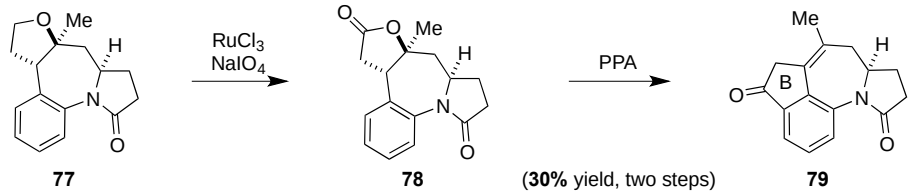
The Hong group initiated their synthetic efforts with a three step sequence that began with exposure of cinnamic alcohol derivative **72** to a Johnson-Claisen rearrangement and was followed by diisobutylaluminum hydride (DIBAL) reduction of the resultant ester, benzyl protection of the resultant primary alcohol afforded 1,1-disubstituted olefin **73** in 54% overall yield (Scheme 1.10). Reduction of the nitro group followed by condensation with succinic anhydride furnished imide **74** which, upon careful treatment with DIBAL, underwent monoreduction to the desired γ-hydroxylactam **75**. Having set the stage for the key *N*-acyliminium cyclization, the γ-hydroxylactam **75** was exposed to a combination of iron

trichloride (catalytic) and trimethylchlorosilane (excess) and found to afford a mixture of diastereomeric products (**76** and **77**).



Scheme 1.10 Speckamp Cyclization

In efforts to further advance the benzazepine intermediates to compounds possessing the tetrapetalone B-ring (Scheme 1.11), Hong and coworkers moved forward with the desired diastereomer **77**. To this end, tetrahydrofuran **77** was oxidized to the corresponding lactone (**78**) which, upon treatment with phosphoric acid, underwent Friedel–Crafts acylation and subsequent dehydration to furnish **79** in 30% yield over two steps.



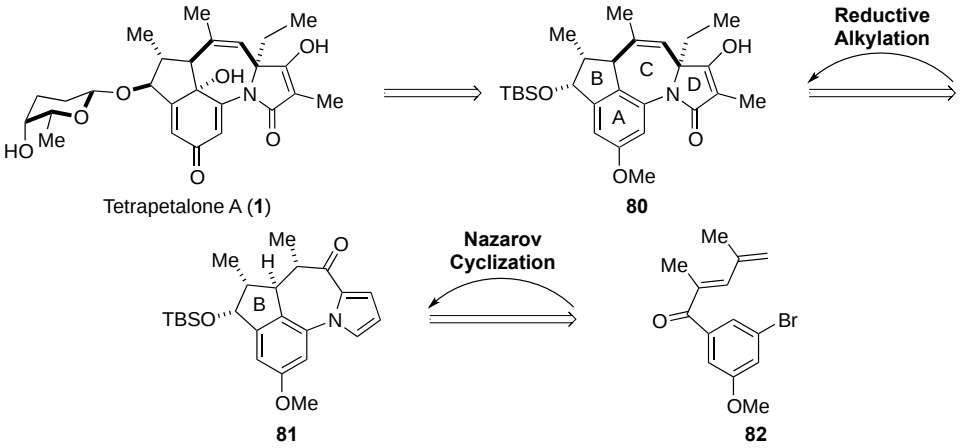
Scheme 1.11 Friedel–Crafts Acylation

Although the Hong group clearly demonstrated that *N*-acyliminium ion cyclization was an effective way to arrive at the 1-benzazepine ring system (Scheme 1.10) and were able to demonstrate that a Friedel–Crafts acylation/dehydration sequence could be employed to construct the B-ring (Scheme 1.11), a considerable amount of the work remains to either advance this relatively under functionalized system or advance more functionalized starting materials. To

date there have been no further publications from the Hong laboratory concerning advancement of this synthetic route.

1.5.3 Sarpong's Approach to the Tetrapetalones

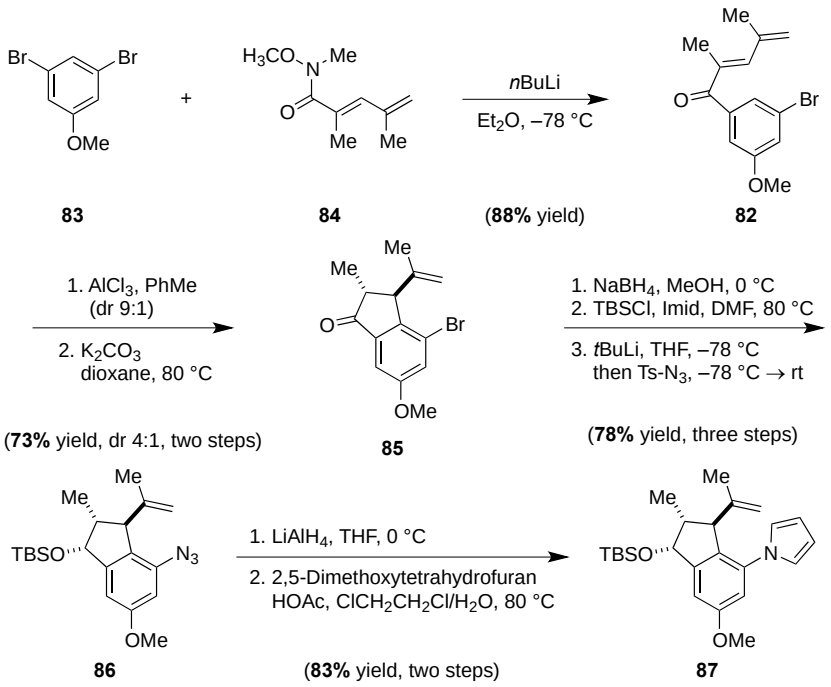
Sarpong and colleagues at the University of California, Berkeley envisioned an approach that in its later stages was somewhat akin to the Hong strategy in that it called for advancing tetracycle **80** via oxidative dearomatization to install the *para*-quinol moiety and the late stage introduction of the β-rhodinose (Scheme 1.12). In contrast to Hong, Sarpong envisioned the tetramic acid moiety as arising from a reductive alkylation reaction of a corresponding acylated pyrrole (**81**). Plans for the early stages of the synthesis were clearly influenced by Sarpong's interest in pentannulation chemistry using the Nazarov cyclization, which led him to propose this transformation as a means of introducing the tetrapetalone B-ring and dienone **82** as his point of departure.[15,16]



Scheme 1.12 Sarpong's Retrosynthetic Analysis of Tetrapetalone A

The Sarpong synthesis commenced with the preparation of dienone **82** via halogen-lithium exchange of dibromide **83** followed by coupling with Weinreb amide **84** (Scheme 1.13). Exposure of dienone **82** to aluminum trichloride effected Nazarov cyclization to afford the desired indanone with good regiocontrol (13:1). The major regioisomer is favored due

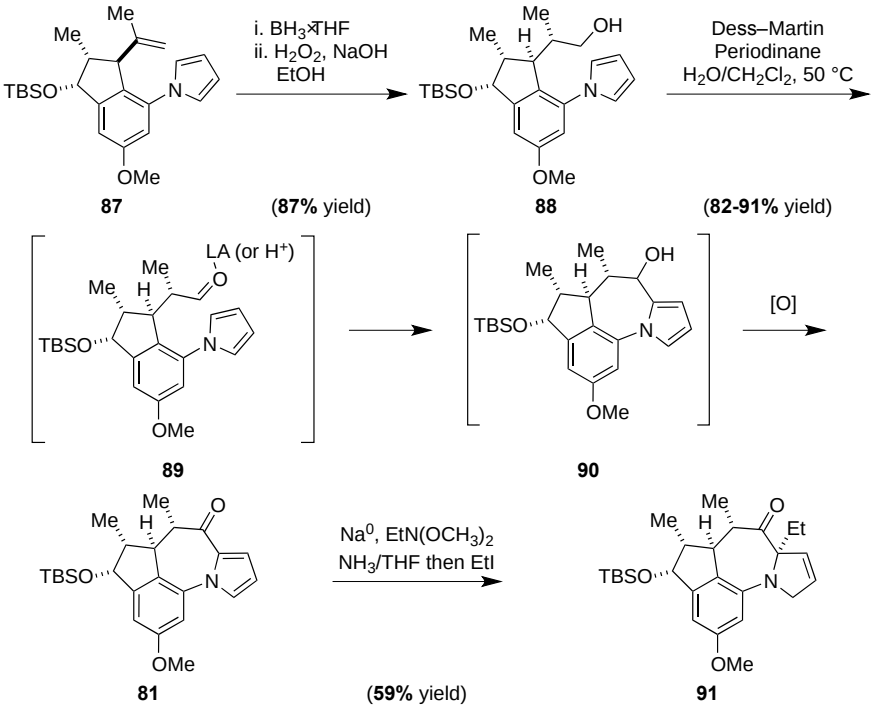
to the dominating *para* directing influence of the methoxy substituent. The indanone was a 9:1 mixture of cis/trans isomers, respectively; thus, it was necessary to effect epimerization to achieve the requisite *trans* relationship between the methyl and isopropenyl substituents. To this end, base mediated epimerization produced the desired indanone **85** as a 4:1 trans/cis mixture, 73% yield, over two steps. Reduction of the ketone in **85** proceeded as anticipated with hydride delivery occurring from the β-face of the indanone and silylation of the resultant hydroxyl group delivered the TBS protected secondary alcohol. At this point a variety of palladium and copper-mediated C–N bond-forming reactions failed to accomplish the desired C–N bond formation. Thus, a more traditional approach for introducing nitrogen was employed that involved halogen-lithium exchange followed by addition of tosyl azide. The resultant azide (**86**) was reduced with lithium aluminum hydride to afford the aniline, which upon exposure to modified Paal–Knorr conditions, yielded pyrrole **87** in 97% yield.



Scheme 1.13 Indanone Synthesis via Nazarov Cyclization

With pyrrole **87** in hand the next challenge of the synthesis was installation of the functionalized azepine ring (Scheme 1.14). To set the stage for this task, terminal olefin **87** was subjected to hydroboration followed by an oxidative workup to afford the primary alcohol **88** (87% yield). Treatment of the primary alcohol **88** with excess Dess–Martin periodinane resulted in formation of tetracycle **81** in excellent yield. Presumably, this transformation proceeds via the intermediate aldehyde **89** followed by activation of the carbonyl group (by the hypervalent iodine species or residual acetic acid), which leads to attack by the proximal pyrrole. The resulting pseudobenzylic secondary hydroxyl group **90** can then undergo further oxidation to produce tetracyclic ketone **81**. This mechanistic scenario is supported by the observation of mixtures of **89**, **90** and **81** when less than two equivalents of the Dess–Martin periodinane was employed. Exposure of the tetracycle **81** to sodium in liquid ammonia/THF in the presence of bis(methoxyethyl)amine followed by quenching with ethyl iodide resulted in the formation of

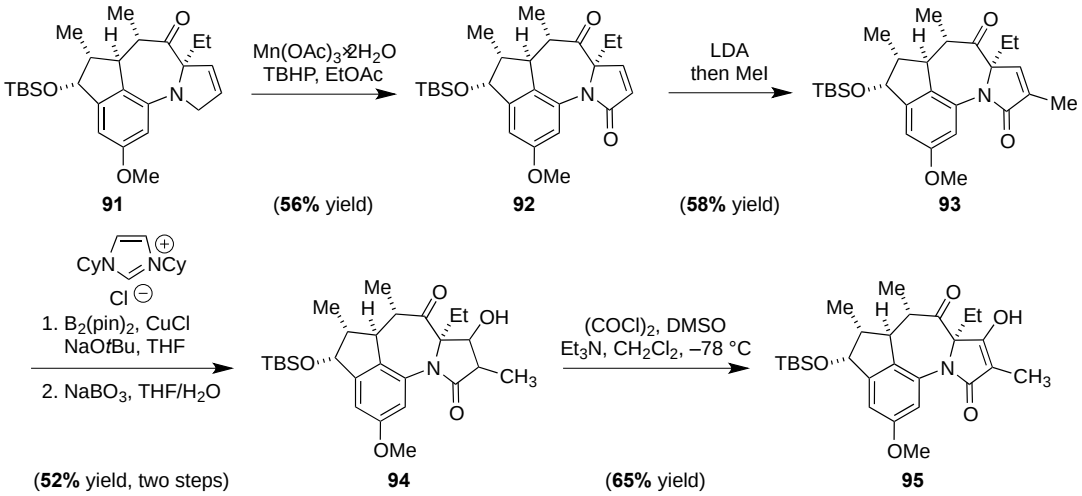
pyrrolidine **91** in 59% yield. Notably, the arene moiety remained intact, and the ethyl group was introduced on the α-face of the tetracycle with excellent diastereocontrol.



Scheme 1.14 An Oxidative Cyclization and Reductive Alkylation of Pyrrole

Focus was then directed to construction of the tetramic acid moiety (Scheme 1.15). Oxidation of pyrrolidine **91** to the corresponding α,β-unsaturated lactam **92** was accomplished with catalytic manganese(III) acetate along with *tert*-butyl hydroperoxide (TBHP) as stoichiometric oxidant (56% yield). Treatment of tetracycle **92** with lithium diisopropylamide (LDA) and iodomethane resulted in methylation of the ene-lactam moiety to provide **91** without competing alpha-methylation of the ketone. Presumably, deprotonation alpha to the ketone group is not favorable due to poor orbital overlap of the C–H bond and the π* of the C=O bond. Conjugate addition of boron pinacolato ester to ene-lactam **93** followed by immediate oxidation of the boronic ester adduct yielded secondary alcohol **94** in 52% yield, over two steps. Swern

oxidation at this stage was employed to install the tetramic acid moiety of tetracycle **95** in 65% yield.



Scheme 1.15 Construction of Tetramic Acid Moiety

Sarpong and coworkers reported the synthesis of a tetracycle (**95**) bearing a tetramic acid en route to tetrapetalone A (Scheme 1.15). This late-stage intermediate contains all the carbons of the aglycon of natural product **1**. Key developments include the use of oxidative conditions for the construction of the tetracyclic core of the tetrapetalones and a reductive alkylation reaction for installation of the angular ethyl group (Scheme 1.14). It appears that the limitation of this approach may be the ketone functionality that is left upon formation of the azepine ring. To date, no work has been published from the Sarpong lab that pertains to the elimination of this ketone. It should also be noted that the relative stereochemistry of the substituents on the B-ring afforded by reduction of the indanone provides the α-hydroxyl group, to obtain the natural product this orientation must be reversed.

References Relevant to Chapter 1

(1) Hirota, A.; Komoda, T.; Sugiyama, Y.; Abe, N.; Imachi, M.; Hirota, H. *Tetrahedron Lett.* **2003**, *44*, 1659.

(2) Komoda, T.; Yoshida, K.; Abe, N.; Sugiyama, Y.; Imachi, M.; Hirota, H.; Koshino, H.; Hirota, A. *Biosci. Biotechnol. Biochem.* **2004**, *68*, 104.

(3) Hirota, A.; Komoda, T.; Kishi, M.; Abe, N.; Sugiyama, Y. *Biosci. Biotechnol. Biochem.* **2004**, *68*, 903.

(4) Komoda, T.; Akasaka, K.; Hirota, A. *Biosci. Biotechnol. Biochem.* **2008**, *72*, 2392.

(5) Komoda, T.; Sugiyama, Y.; Abe, N.; Imachi, M.; Hirota, H.; Koshino, H.; Hirota, A. *Tetrahedron Lett.* **2003**, *44*, 7417.

(6) Nelson, D. L., Cox, M. M. *Principles of Biochemistry*; W. H. Freeman and Company: New York, **2005**; Vol. 4.

(7) Komoda, T.; Morimitsu, Y.; Hirota, H.; Hirota, A. *Biosci. Biotechnol. Biochem.* **1995**, *59*, 924.

(8) Kang, Q.; Shen, Y.; Bai, L. *Nat. Prod. Rep.* **2012**, *29*, 243.

(9) Floss, H. G., Yu, T. W., Arakawa, K. *J. Antibiot.* **2011**, *64*, 35.

(10) Komoda, T.; Sugiyama, Y.; Hirota, A. *Org. Biomol. Chem.* **2007**, *5*, 1615.

(11) Wang, X.; Porco, J. A., Jr. *Angew. Chem. Int. Ed.* **2005**, *44*, 3067.

(12) Wang, X.; Porco, J. A. *Angew. Chem. Int. Ed.* **2006**, *45*, 6607.

(13) Li, C.; Li, X.; Hong, R. *Org. Lett.* **2009**, *11*, 4036.

(14) Ahn, H. R.; Cho, Y. A.; Kim, D. S.; Chin, J.; Gyoung, Y. S.; Lee, S.; Kang, H.; Ham, J. *Org. Lett.* **2009**, *11*, 361.

(15) Marcus, A. P.; Lee, A. S.; Davis, R. L.; Tantillo, D. J.; Sarpong, R. *Angew. Chem. Int. Ed.* **2008**, *47*, 6379.

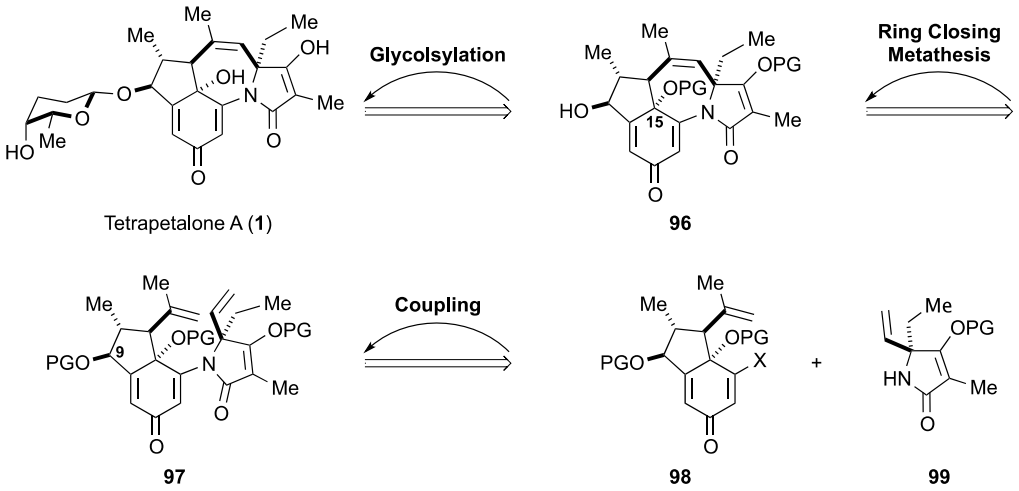
(16) Marcus, A. P.; Sarpong, R. *Org. Lett.* **2010**, *12*, 4560.

Chapter 2

Synthetic Studies Toward a *para*-Quinol Coupling Partner

2.1 Retrosynthetic Analysis

As outlined in Scheme 2.1 our first-generation retrosynthetic analysis of tetrapetalone A (**1**) envisaged completion of the natural product via glycosylation of aglycon **96** followed by subsequent deprotection of the tetramic acid moiety and C(15)-hydroxyl group. Aglycon **96** was envisioned as deriving from a ring closing metathesis (RCM) applied to diene **97** and selective deprotection of the C(9)-hydroxyl group. Diene **97** would be assembled in a convergent manner by the coupling of *para*-quinol **98** and protected tetramic acid **99**. Thus, in accord with this plan our primary objective became the synthesis of coupling partners **98** and **99**. To this end, we began our efforts by developing a synthesis of *para*-quinol **98**.

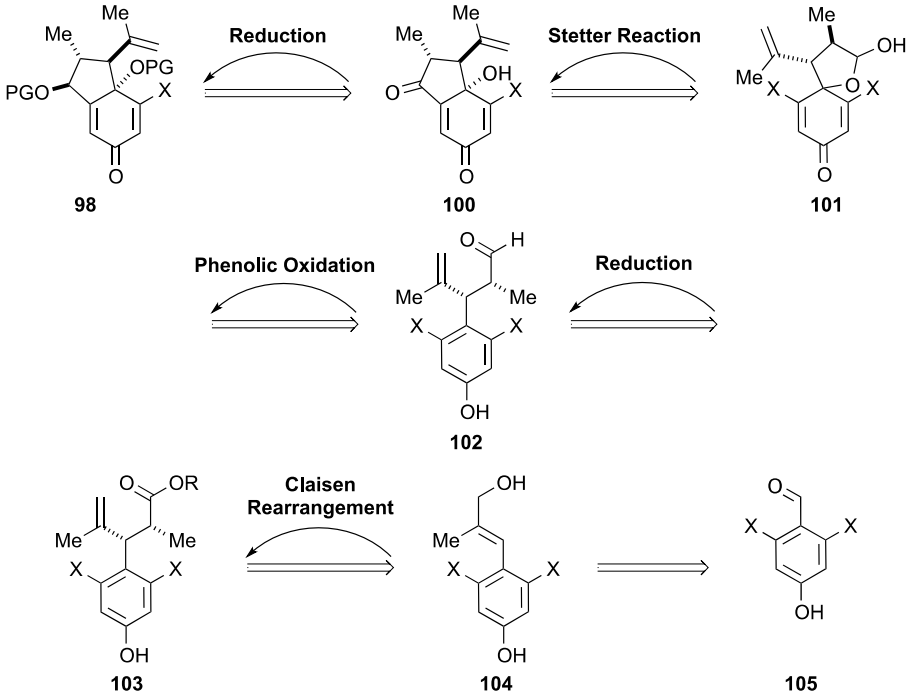


Scheme 2.1 First-Generation Retrosynthetic Analysis of Tetrapetalone A

2.2 Retrosynthetic Analysis of a *para*-Quinol Coupling Partner

Synthesis of *para*-quinol **98** would be completed with a hydroxyl group directed reduction of cyclic β-hydroxy ketone **100** (Scheme 2.2). Intrigued by the application of umpolung reactivity to form C–C bonds, we hypothesized that construction of the last C–C bond

to afford β-hydroxy ketone **100** could be achieved via a Stetter reaction and concomitant elimination from spiro lactol **101**. Spiro lactol **101** would derive from phenolic oxidation of aldehyde **102,** the reduction product of carboxylic acid derivative **103**. Requisite γ,δ-unsaturated carboxylic acid derivative **103** would be prepared via a Claisen rearrangement of allylic alcohol **104** which, in turn would arise from aldehyde **105** via a Horner-Wadsworth-Emmons (HWE) olefination reduction sequence.



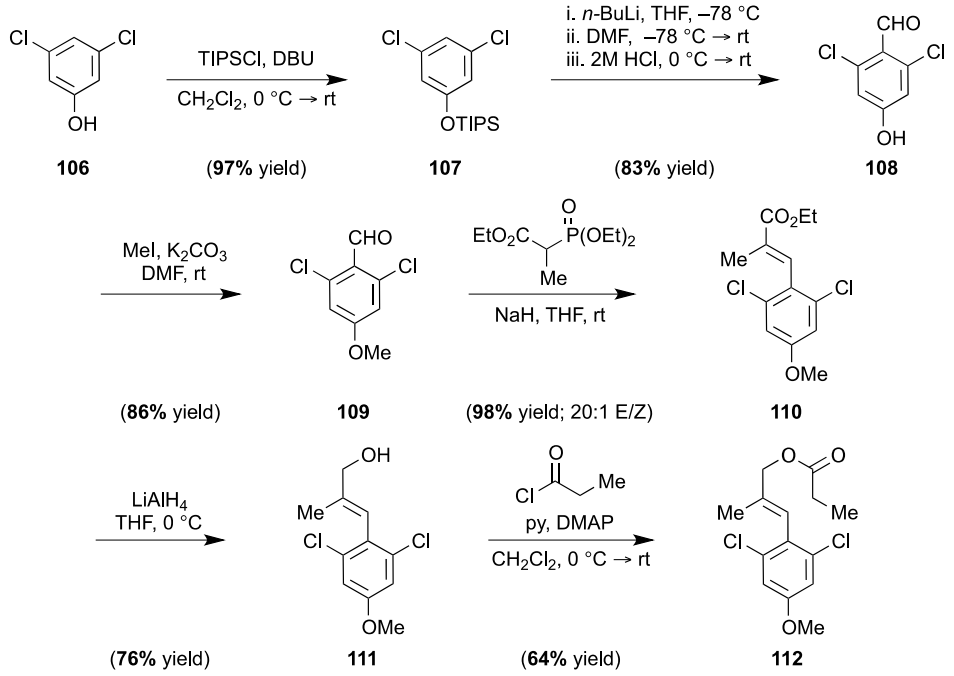
Scheme 2.2 Retrosynthetic Analysis of para-Quinol Coupling Partner

2.3 Dichlorophenol Substrate

2.3.1 Allylic Ester Synthesis

In assessing the viability of the above approach we discovered that a suitable precursor to **105** was known and thus began our synthetic efforts toward **98** with preparation of aldehyde **108** (Scheme2.3).[17] Silylation of commercially available 2,6-dichorophenol (**106**) furnished TIPS-ether **107** which, upon *ortho*-lithiation and trapping of the derived anion with

N,*N*-dimethylformamide followed by acidic hydrolysis, provided aldehyde **108** in excellent yield (81%, two steps). Methylation of the phenol afforded aldehyde **109** and set the stage for a HWE olefination that produced (*E*)-α,β-unsaturated ester **110**. Lithium aluminum hydride mediated reduction of ester **110** provided an allylic alcohol (**111**) that, upon acylation, afforded allylic ester **112**.

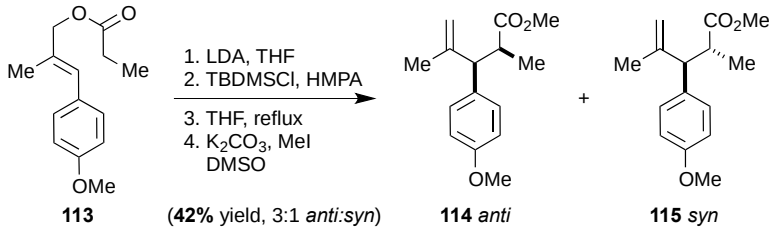


Scheme 2.3 Allylic Ester Synthesis

2.3.2 Ireland-Claisen Rearrangement

In terms of the pending Ireland-Claisen rearrangement that would give rise to the requisite γ,δ-unsaturated carboxylic acid, we took solace in the fact that it has been well documented to provide extremely high diastereoselectivity, an outcome often dependent on the enolization conditions invoked.[18,19] For example, Daub and coworkers have demonstrated that (*E*)-allylic esters (e.g., **113**) participate efficiently in the Ireland-Claisen rearrangement and that enolization of these substrates with lithium diisopropylamide in tetrahydrofuran followed by silylation with *tert*-butyldimethylsilyl chloride in hexamethylphosphoramide affords an

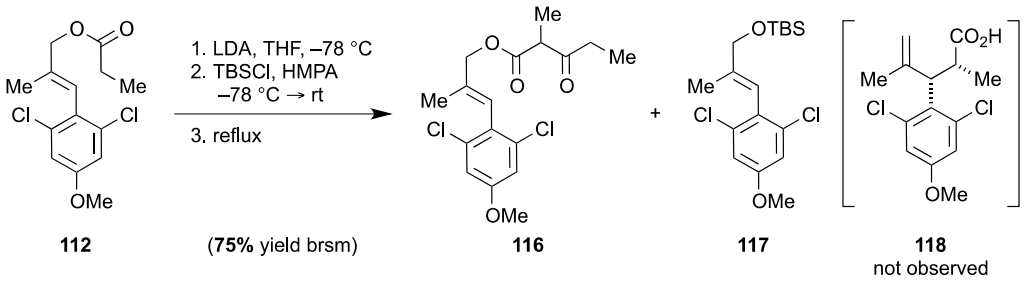
intermediate mixture of silyl ketene acetals wherein the (*E)*-isomer predominates (Scheme 2.4).[20] In this particular example Daub showed that exposure of **113** to these enolization conditions followed by warming to reflux, induces the desired sigmatropic rearrangement. Methylation of the derived carboxylic acids in situ afforded γ,δ-unsaturated ester **114** *anti* and **115** *syn* in moderate yield as a 3:1 *anti:syn* mixture.



113 (**42%** yield, 3:1 *anti:syn*) **114** *anti* **115** *syn*

Scheme 2.4 Daub's Ireland-Claisen Rearrangement of an (*E*)-Allylic Ester

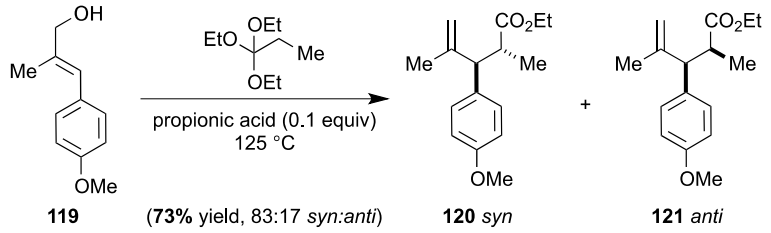
The relative stereochemistry of the methyl and isopropenyl groups in *para*-quinol **98** (Scheme 2.2) would be accessible directly from the *anti* product of an Ireland-Claisen rearrangement, the major isomer observed in Daub's study. Disappointingly, exposure of (*E*)-allylic ester **112** to various Ireland-Claisen rearrangement conditions failed to produce the desired carboxylic acid **118** and resulted only in the formation of β-ketoester **116** and TBS-ether **117** (Scheme 2.5). To avoid undesired Claisen condensation we opted to investigate a Johnson-Claisen rearrangement.



Scheme 2.5 Attempted Ireland-Claisen Rearrangement

2.3.3 Johnson-Claisen Rearrangement

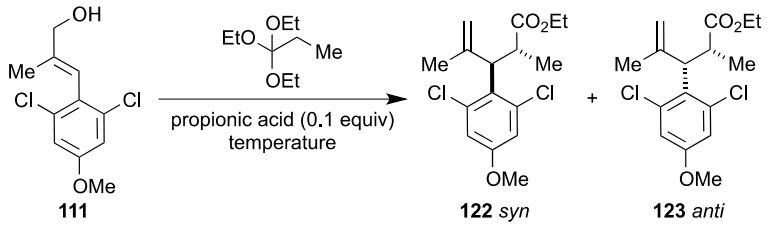
In addition to their work with the Ireland-Claisen reaction, Daub and coworkers have carried out extensive studies concerning acyclic stereoselection of the Johnson-Claisen rearrangement.[20] These latter efforts revealed that Johnson-Claisen rearrangements of trisubstituted allylic alcohols also exhibit significant levels of diastereoselection. In contrast to the Ireland conditions, the reaction of (*E*)-allylic alcohols under Johnson-Claisen rearrangement conditions result in intermediates wherein 1,3-diaxial interactions in the chair-like transition state render the reaction *syn* selective. Daub and coworkers showed that exposure of (*E*)-allylic alcohol **119** to triethyl orthopropionate and catalytic propionic acid affords the δ,γ–unsaturated esters **120** *syn* and **121** *anti* in high yield and good diastereoselectivity (Scheme 2.6).



Scheme 2.6 Daub's Johnson-Claisen Rearrangement

We were excited to find that indeed exposure of (*E*)-allylic alcohol **111** to triethyl orthopropionate and catalytic propionic acid provided access to the δ,γ–unsaturated ester **122** *syn*

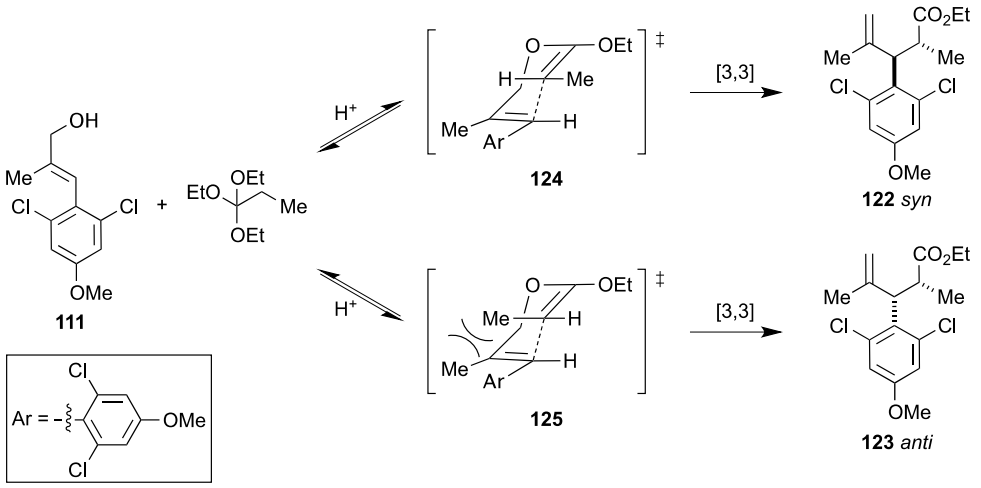
as a single diastereomer, albeit in moderate yield under both thermal and microwave reaction conditions (Scheme 2.7).



temperature (°C)	time (hr)	yield (%)	*syn:anti*
152	4	45	20:1
250 (μwave)	1.5	48	20:1

Scheme 2.7 Johnson-Claisen rearrangement

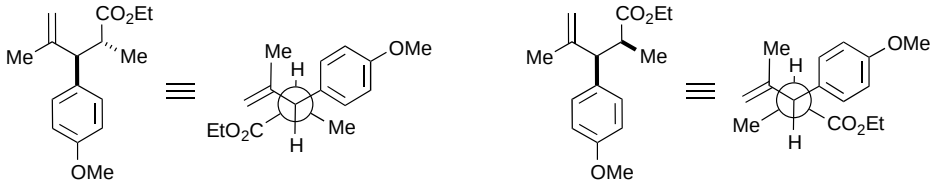
As anticipated by the Daub studies ester **122** *syn* was the expected major diastereomer for the above Johnson-Claisen rearrangement (Scheme 2.7). Analysis of the nonbonding interactions in the corresponding chair-like transition states that would result from the corresponding *E* and *Z* ketene acetals (Scheme 2.8) indicates chair-like transition state **125**, which leads to the *anti* isomer **123**, suffers from 1,3-diaxial interactions. In contrast, *syn* isomer **122** would derive form a lower energy chair-like transition state (i.e., **124**) wherein 1,3-diaxial interactions are minimized.



Scheme 2.8 Stereochemical Model for Johnson-Claisen rearrangement

Relative stereochemistry of δ,γ–unsaturated ester **122** was inferred from ^{1}H NMR spectroscopy via chemical shift trend comparisons with the Johnson-Claisen products reported by Daub and coworkers[20] (Table 2.1). Anisotropy introduced by the aromatic ring led to specific upfield shifts of the alpha methyl group in the *syn* isomer, and correspondingly upfield shifts of the ethyl ester group in the *anti* isomer. Chemical shift trends of δ,γ–unsaturated ester **122** correlate with that of the *syn* isomer **120**.

Table 2.1 Chemical Shift Trend Comparison



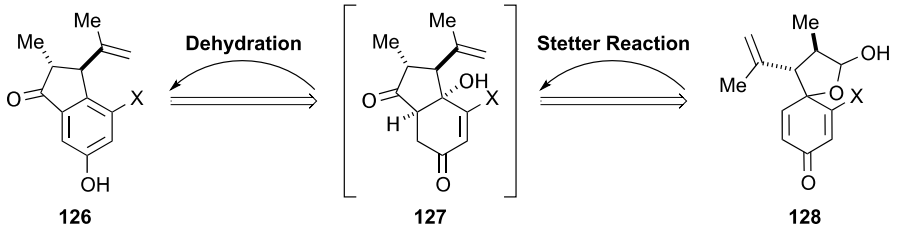
entry	*syn* isomer: chemical shift (d) of ester group (group)	*syn* isomer: chemical shift (d) of a methyl group (group)	*anti* isomer: chemical shift (d) of ester group (group)	*anti* isomer: chemical shift (d) of a methyl group (group)
1[a]	4.13 (CH_2) 1.23 (CH_3)	0.96 (CH_3)	3.89 (CH_2) 0.95 (CH_3)	1.22 (CH_3)
2	4.17 (CH_2) 1.26 (CH_3)	0.93 (CH_3)		

[a]Literature data.

2.4 Retrosynthetic Analysis of an Indanone Coupling Partner

Although at the point we had developed Claisen rearrangement conditions suitable for use on the hindered dichlorophenol, the predominant syn isomer (**123**) derived from rearrangement of **111** possesses the undesired relative stereochemistry. To rectify this problem our first instinct was to prepare the corresponding *Z* isomer of allylic alcohol **111**. Altering the double bond geometry should, in theory, change the course of the reaction such that Johnson-Claisen rearrangement would furnish the desired *anti* isomer.

In addition to correcting the stereochemical outcome of the Claisen rearrangement we also began to consider the subsequent Stetter reaction. To this end, we decided that it maybe advantageous to explore the reactivity of substrates possessing one *ortho* functional group; for example, spiro lactol **128** (Schemes 2.9). Products (i.e. **127**) derived from these substrates would be prone to aromatization; we were intrigued by the issue of chemo/regio-selectivity imposed on the Stetter reaction by the different electronic and steric environments within these substrates.



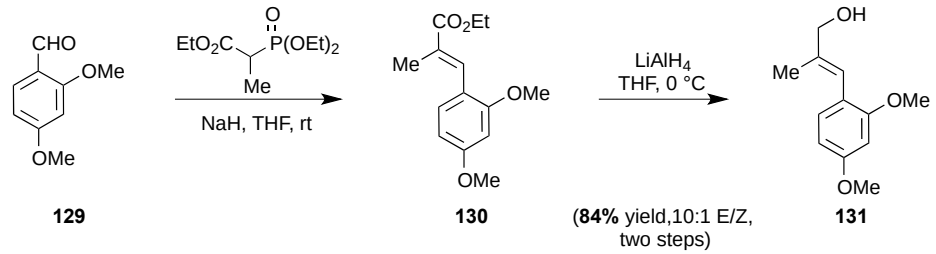
126 127 128

Scheme 2.9 Retrosynthetic Analysis of an Indanone Coupling Partner

2.5 Dimethoxybenzaldehyde Substrate

2.5.1 Allylic Alcohol Synthesis

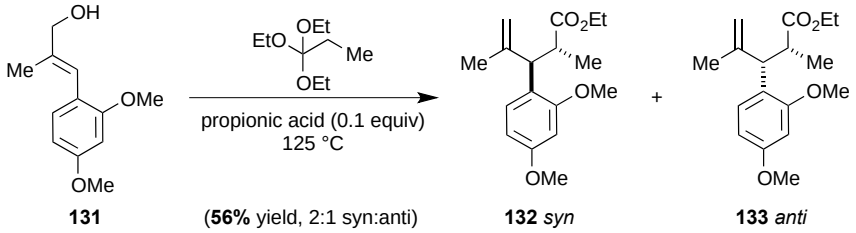
With the notion of exploring Stetter chemistry on a substrate akin to **128**, we initiated our efforts with the HWE olefination of aldehyde **129** (Scheme 2.10). Reduction of the derived enoate (**130**) with lithium aluminum hydride provided allylic alcohol **131** in 84% yield, over two steps**.**



Scheme 2.10 Allylic Alcohol Synthesis

2.5.2 Johnson-Claisen Rearrangement

Given that in our previous efforts Johnson-Claisen rearrangements had proven most successful, our initial studies in this series involved exposure of (*E*)-allylic alcohol **131** to triethyl orthopropionate and catalytic propionic acid under Dean-Stark conditions. As illustrated in Scheme 2.11, this reaction furnished the desired γ,δ-unsaturated esters **132** *syn* and **133** *anti* in 56% yield as a separable mixture (2:1, respectively). As before, the assignment of the stereochemistry illustrated for γ,δ-unsaturated esters **132** *syn* and **133** *anti*, as based upon the comparison of ^{1}H NMR chemical shift trends to those observed by Daub and coworkers.[20]

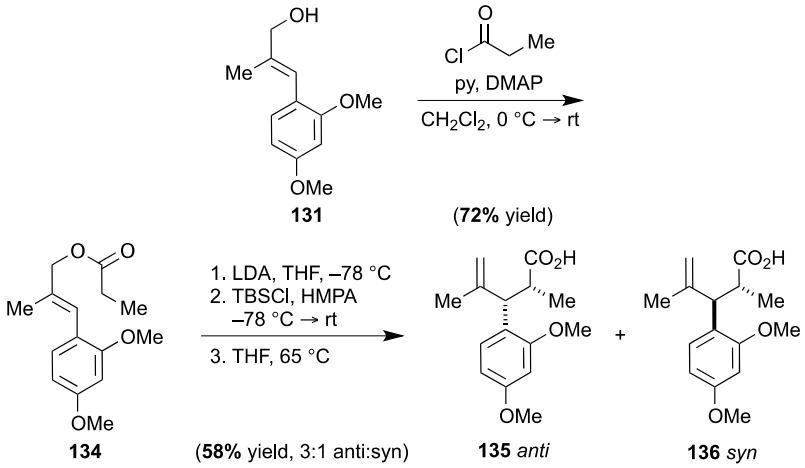


Scheme 2.11 Johnson-Claisen Rearrangement

2.5.3 Ireland-Claisen Rearrangement

Although in our previous studies we had been unsuccessful in efforts to employ the Ireland-Claisen rearrangement we decided to reinvestigate these conditions on the less sterically encumbered substrate **134** (Scheme 2.12) Acylation of allylic alcohol **131** afforded requisite allylic ester **134** in 72% yield. Interestingly, enolization of (*E*)-allylic ester **134** with lithium diisopropylamide in tetrahydrofuran followed by silylation with *tert*-butyldimethylsilyl chloride

in hexamethylphosphoramide and concomitant sigmatropic rearrangement conducted at tetrahydrofuran reflux afforded γ,δ-unsaturated carboxylic acids **135** *anti* and **136** *syn* in 58% yield as a 3:1 *anti:syn* mixture of separable diastereomers. Production of the desired γ,δ-unsaturated ester (**135** *anti*), as the major diastereomer is in accord with the transition state models mentioned above and, provided subsequent studies of the Stetter reaction proved fruitful, would obviate the need for adjusting the olefin geometry of the allylic alcohol.

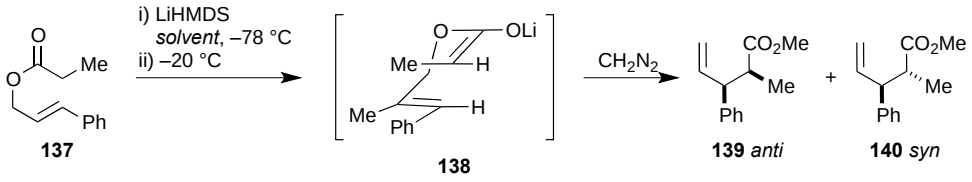


Scheme 2.12 Ireland-Claisen Rearrangement

2.5.4 Lithium Enolate Claisen Rearrangement

Although we were satisfied to move forward with the moderate yield of the Ireland-Claisen rearrangement (Scheme 2.12), we were inspired by the work of Collum and Godenschwager[21] to explore a lithium enolate variant of the Claisen rearrangement. In 2008, Collum and Godenschwager disclosed the lithium enolate Claisen rearrangement of *trans* allylic ester **137** (Scheme 2.13). They reported that enolization of **137** using lithium hexamethyldisilazide (LiHMDS) and triethylamine in toluene at –78 ºC affords an estimated 20:1 preference for enolate **138**. Claisen rearrangement of **138** at –20 ºC affords a 35:1 ratio of **139** *anti* and **140** *syn* in 79% isolated yield. The standard protocol, enolization and rearrangement

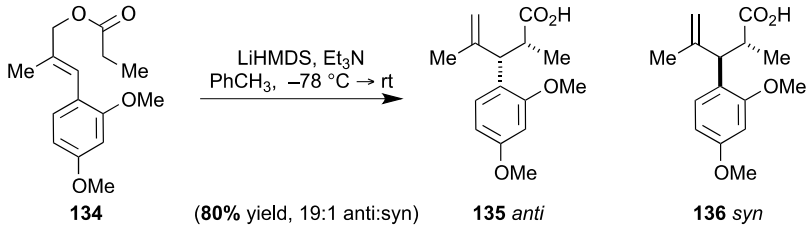
in neat tetrahydrofuran (THF) proceeded in 11% yield. The low yields using LiHMDS/THF are postulated to stem from either a poor enolization or a poor rearrangement from the (*Z*)-isomer as noted by Ireland in a similar silyl Claisen rearrangement.[21,22] Encouraged by this report we opted to investigate the LiHMDS/triethylamine mediated enolization on our trisubstituted allylic ester system.



solvent	*anti:syn* (yield)
Et_3N/toluene	35:1 (79%)
THF	1:5 (11%)

Scheme 2.13 Collum's LiHMDS Mediated Claisen Rearrangement

Gratifyingly, exposure of (*E*)-allylic ester **134** to enolization with LiHMDS and triethylamine in toluene followed by warming to room temperature affords γ,δ-unsaturated carboxylic acid **135** *anti* in excellent yield and diastereoselectivity (Scheme 2.14).

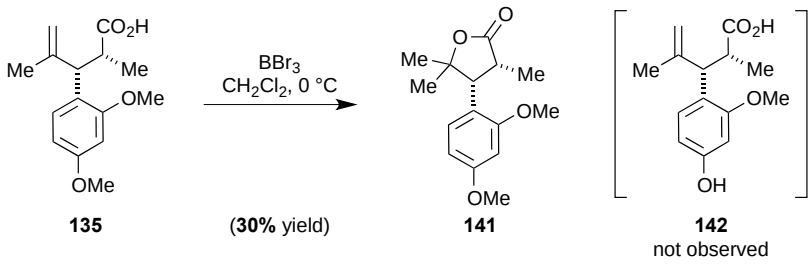


Scheme 2.14 Lithium Enolate Variant of Claisen Rearrangement

2.5.5 Selective Methyl Ether Cleavage

To advance substrate **135** to a spiro lactol (i.e. **128**, Scheme 2.9) we would need to effect a selective demethylation. Exposure of carboxylic acid **135** to boron tribromide afforded a complex mixture of products, the major product being lactone **141** (Scheme 2.15). This failed

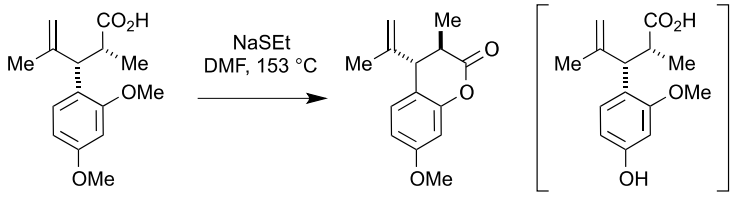
attempt to selectively cleave the *para* methyl ether under Lewis acid conditions prompted us to investigate nucleophilic cleavage reaction conditions.



135 (**30%** yield) **141** **142** not observed

Scheme 2.15 Attempted Lewis acid Mediated Methyl Ether Cleavage

Treatment of carboxylic acid **135** with sodium ethanethiolate in *N*,*N*-dimethyformamide at reflux did indeed provide a selective methyl ether cleavage, unfortunately, the undesired *ortho* methyl ether was cleaved and subsequent lactonization under the reaction conditions afforded lactone **143** (Scheme 2.16). Our failure to identify selective demethylation conditions motivated us to design a synthetic strategy employing an orthogonal protection strategy.



135 (**25%** yield) **143** **142** not observed

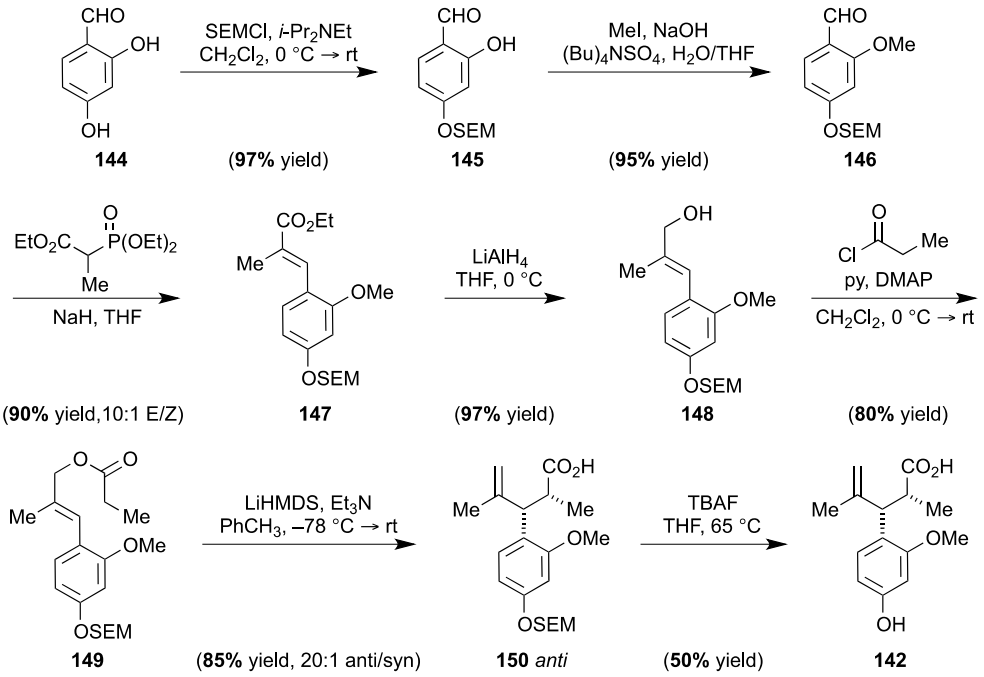
Scheme 2.16 Attempted Nucleophilic Methyl Ether Cleavage

2.6 Dihydroxybenzaldehyde Substrate

2.6.1 Orthogonal Protection

The orthogonal protection strategy began with selective alkylation of the *para*-hydroxyl group of 2,4-dihydroxybenzaldehyde (**144**) to afford SEM-ether **145** which was subsequently methylated to yield orthogonally protected aldehyde **146** in excellent yield over two steps (Scheme 2.17). Horner-Wadsworth-Emmons olefination of **146** provided (*E*)-α,β-unsaturated

ester **147**, lithium aluminum hydride reduction and acylation of the derived alcohol (**148**) with propionyl chloride, furnished Claisen rearrangement precursor **149**. Enolization of allylic ester **149** with LiHMDS and triethylamine in toluene followed by warming to room temperature resulted in [3,3] sigmatropic rearrangement to provide the desired *anti* γ,δ-unsaturated carboxylic acid (**150**) as the major diastereomer in excellent yield. Cleavage of the SEM-ether was achieved upon exposure to tetrabutylammonium fluoride at tetrahydrofuran reflux unveiling phenol **142** in moderate yield.

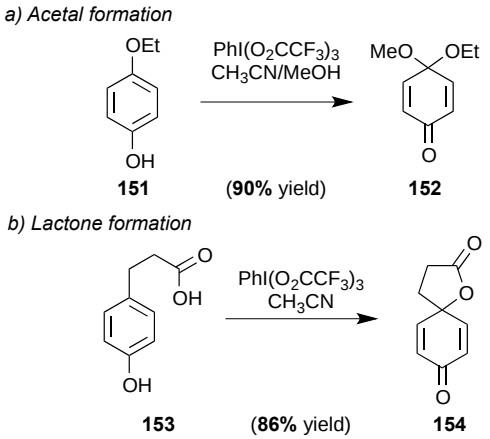


Scheme 2.17 Phenolic Oxidation Precursor via an Orthogonal Protection Strategy

2.6.2 Spiro Lactol Formation via Phenolic Oxidation

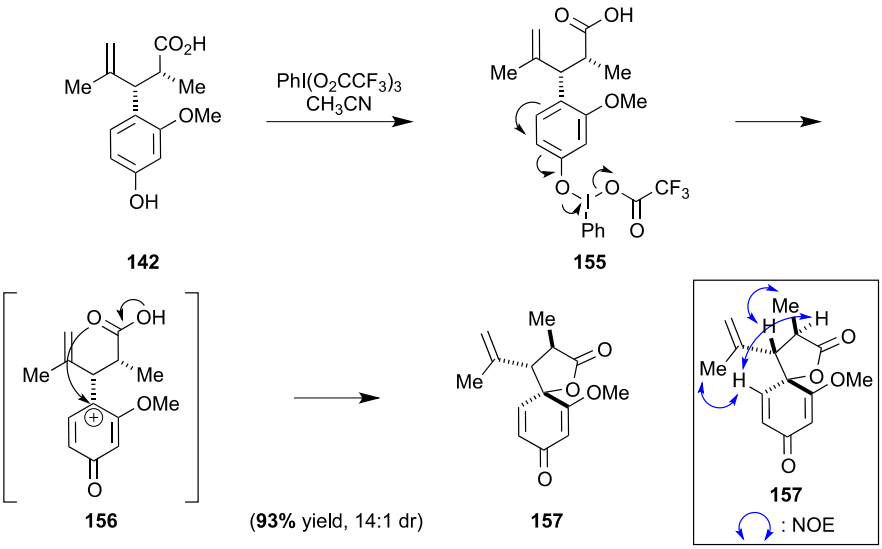
To construct the spiro lactol (i.e. 128, Scheme 2.9) we turned to a 1987 report by Tamura and coworkers wherein a continuation of their study on hypervalent iodine compounds was described as having led them to an efficient oxidant, [bis(trifluoroacetoxy)iodo]benzene, which reacts with various types of *para*-alkoxyphenols to give the *para*-benzoquinone monoacetals in excellent yield under mild reaction conditions (Scheme 2.18a).[23] Oxidation was extended to

intramolecular ipso-trapping by some nucleophiles such as carboxy, amido and hydroxy groups, leading to the corresponding spiro compounds (Scheme 2.18b).



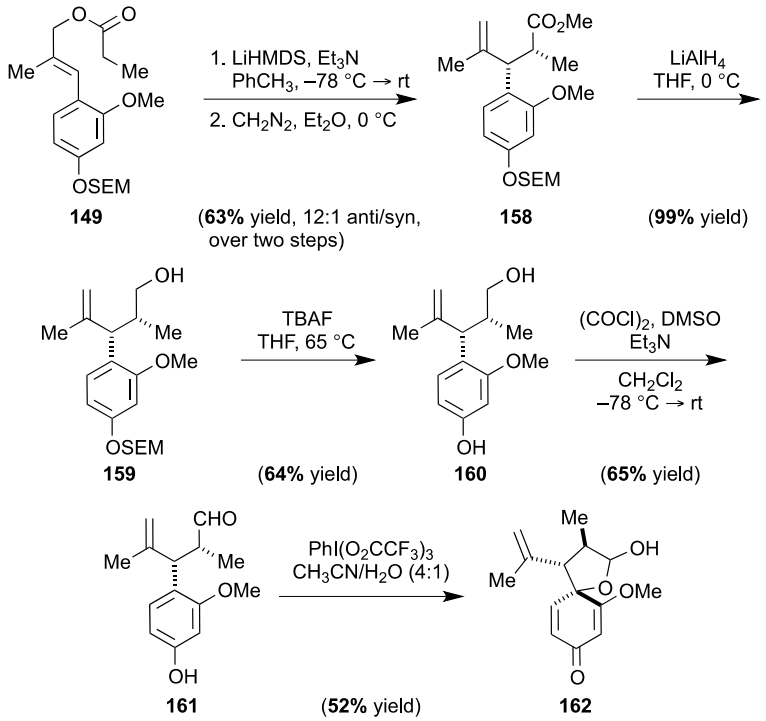
Scheme 2.18 Hypervalent Iodine Mediated Oxidation of *para*-Alkoxyphenols

With carboxylic acid **142** on hand, we were excited to investigate the phenolic oxidation of such a highly functionalized substrate. Exposure of carboxylic acid **142** to [bis(trifluoroacetoxy)iodo]benzene in acetonitrile at room temperature successfully provided access to spiro lactone **157** in high yield and excellent diastereoselectivity (Scheme 2.19). Assignment of the illustrated relative stereochemistry of spiro lactone **157** was based on NOE studies. Attempts to afford a Stetter reaction precursor, spiro lactol (i.e. **128**, Scheme 2.9), via a chemoselective reduction proved to be futile and resulted in both reduction of the lactone and the vinylogous ester of **157**. Unable to selectively reduce the lactone, we considered an alternative strategy wherein reduction of the acid would occur prior to aryl oxidation. The success of our initial phenolic oxidation studies left us hopeful that the derived aldehyde would similarly engage the intermediate cation and directly furnish the desired spiro lactol.



Scheme 2.19 Lactonization via Phenolic Oxidation

Upon scaling up the synthetic route, we found it was advantageous to prepare methyl ester **158**, via diazomethane methylation, directly following lithium enolate Claisen rearrangement (Scheme 2.20). This two-step sequence could be performed using only an aqueous work up of the intermediate carboxylic acid prior to methylation. Reduction of methyl ester **158** was accomplished with lithium aluminum hydride; subsequent tetrabutylammonium fluoride mediated cleavage of SEM-ether **159** provided alcohol **160** and Swern oxidation yielded the desired phenolic aldehyde **161** in modest yield (41%), over three steps. Exposure of phenolic aldehyde **161** to [bis(trifluoroacetoxy)iodo]benzene in a solvent mixture of acetonitrile and water at room temperature successfully provided access to the desired Stetter reaction precursor, spiro lactol **162** in moderate yield.



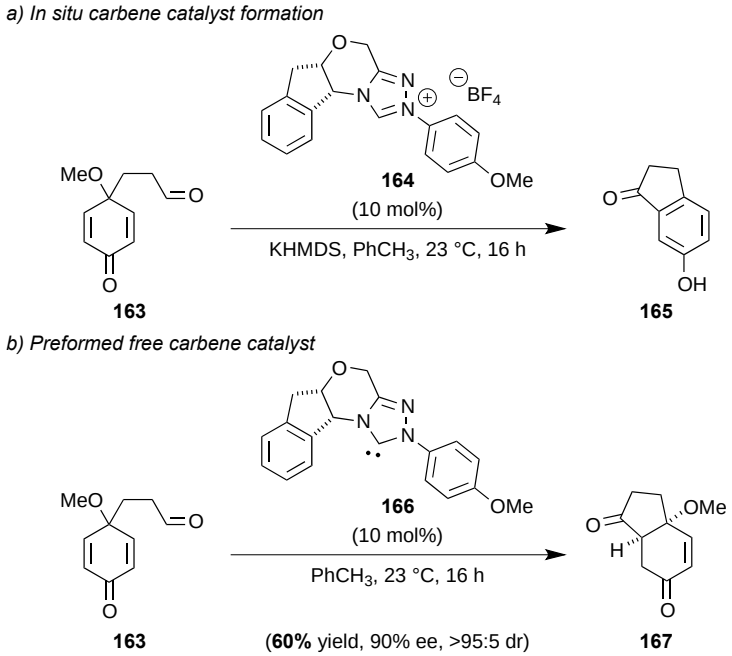
Scheme 2.20 Synthesis of a Spiro Lactol via Phenolic Oxidation

2.6.3 Intramolecular Stetter Reaction with Spiro Lactol Substrates

Umpolung[24,25] reactivity, introduced by E. J. Corey and D. Seebach, is a method in which the normal electron donor and acceptor reactivity of a functional group is inverted to provide complementary reactivity in organic synthesis. The Stetter reaction[26] is an umpolung process in which an acylanion equivalent, generated from an aldehyde in the presence of a nucleophilic catalyst, is added to a Michael acceptor to form a C–C bond.

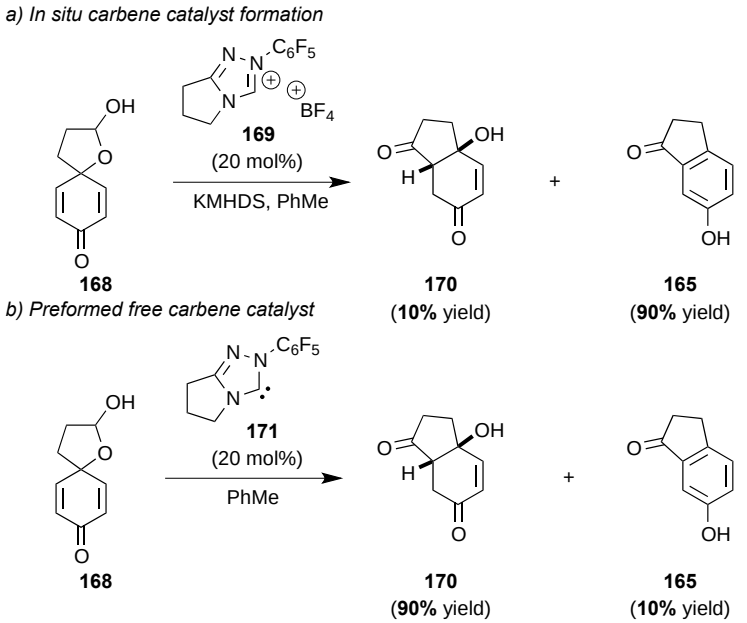
Although, the classic Stetter reaction utilizes sodium cyanide as a catalyst, extensive research has found that carbene catalysts, derived from thiazolium and triazolium salts, can greatly enhance reactivity and also lead to diastereo- and enantiomerically enriched products. Rovis and coworkers have developed a family of triazolium catalysts that promote intramolecular Stetter reactions in excellent enantioselectivities and diastereoselectivities.[27-31] In 2006, Liu and Rovis disclosed that exposure of alicyclic aldehyde **163** to optimized, in situ

carbene catalyst formation reaction conditions afforded only undesired indanone **165** (Scheme 2.21a).[32,33] It was suggested that indanone **165** is derived from the elimination of the expected product under the reaction conditions. It was found that elimination could be avoided if the reaction of alicyclic aldehyde **163** is conducted using the preformed free carbene to provide the desired hydrindane **167** (Scheme 2.21b).



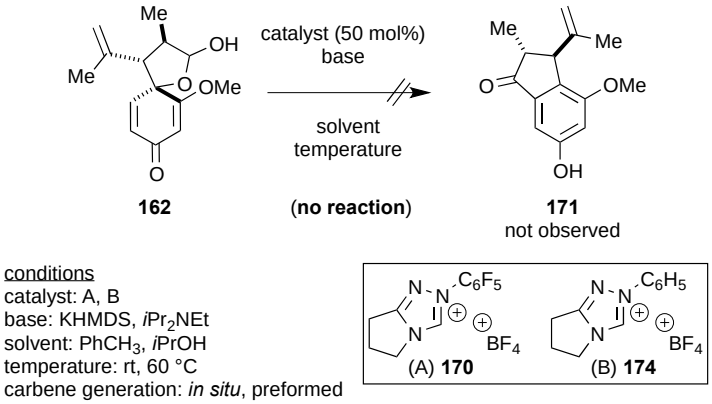
Scheme 2.21 Intramolecular Stetter Reaction of an Alicyclic Substrate

Cullen and Rovis extended the method to spiro lactol **168**. Treatment of **168** with catalyst **169** and potassium bis(trimethylsilyl)amide (KHMDS) in toluene provided the desired Stetter product **170** in low yield, but afforded aromatized product **165** in high yield (Scheme 2.22a). Attributing dehydration to the base in the reaction, it was found that exposure of spiro lactol **169** to catalytic free carbene **171** resulted in a reversal of product ratio, favoring the desired hydrindane **170** (Scheme 2.22b).



Scheme 2.22 Intramolecular Stetter Reaction Applied to a Spiro Lactol Substrate

Unfortunately, we found that spiro lactol **162** does not participate in the Stetter reaction (Scheme 2.23). Surveying reaction conditions proved to be futile and starting material was always recovered from the reaction. Comparison of spiro lactol **162** with the aforementioned Stetter reaction examples led us to propose that spiro lactol **162** does not participate in the Stetter reaction due to the modest adjustment of an α-methyl group that may be hindering attack of the nucleophile.

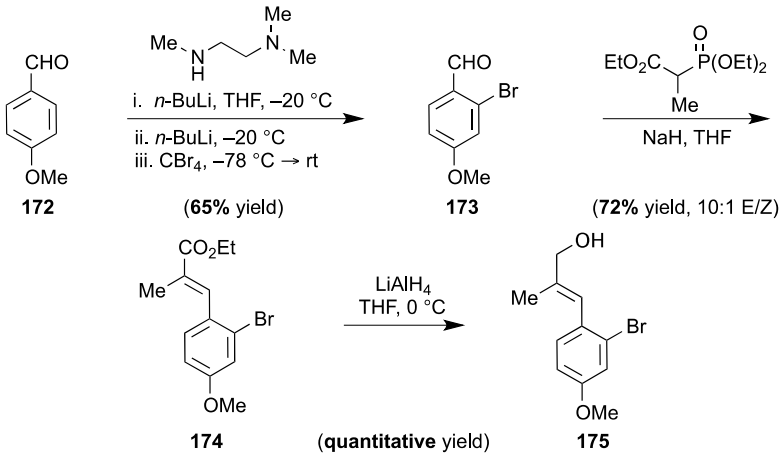


Scheme 2.23 Attempted Stetter Reaction

2.7 Aryl Bromide Substrate Deficient of α-Methyl Group

2.7.1 Allylic Alcohol Synthesis

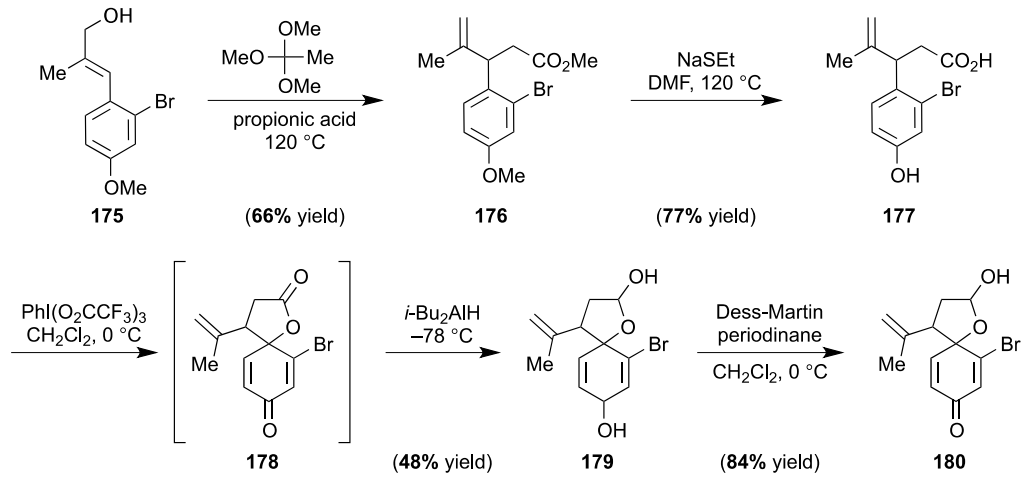
Suspecting that the Stetter reaction did not work because of the α-methyl group we opted to investigate the reactivity of spiro lactol deficient of alpha substituents, while simultaneously exploring the potentially more reactive substrate, which possesses a bromide. To this end *p*-anisaldehyde (**172**) was halogenated using the Comins's α-amino alkoxide directed ortho metalation procedure to afford known aryl bromide **173** in 65% yield (Scheme 2.24).[34-37] Horner-Wadsworth-Emmons olefination of aldehyde **173** gave (*E*)-α,β-unsaturated ester **173**, reduction with lithium aluminum hydride provided access to allylic alcohol **175** in 75% yield, over two steps.



Scheme 2.24 Allylic Alcohol Synthesis

2.7.2 Synthesis of Spiro lactol

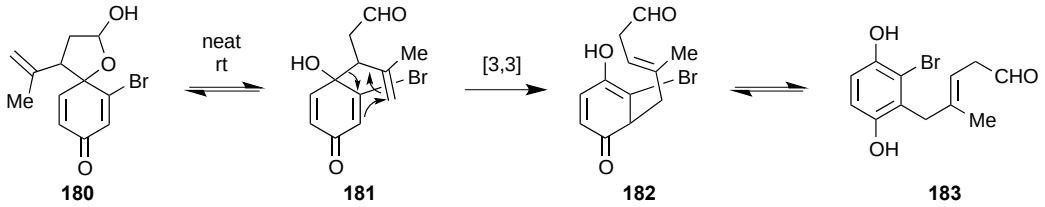
Given our speculation that the methyl group was prohibiting the Stetter reaction we decided to prepare a desmethyl substrate. In a manner analogous to **162**, construction of spiro lactol **180** began with a Johnson-Claisen rearrangement of allylic alcohol **175** to access methyl ester **176** (Scheme 2.25). Simultaneous nucleophilic cleavage of the methyl ester and methyl ether of **176** was achieved upon exposure to sodium ethanethiolate in *N*,*N*-dimethylformamide at reflux. The derived carboxylic acid (**177**) was produced in high yield and when exposed to hypervalent iodine mediated phenolic oxidation underwent conversion to spiro lactone **178**. Immediate diisobutylaluminum hydride (DIBAL) reduction of **178** produced bisallylic alcohol **179** in moderate yield. Dess-Martin periodinane oxidation was employed to achieve a chemoselective oxidation affording the desired dienone **180** in excellent yield.



Scheme 2.25 Synthesis of Desmethyl Spiro Lactol

2.7.3 *oxy*-Cope Rearrangement a Substrate Complication

We found that spiro lactol **180** underwent facile *oxy*-Cope rearrangement to aldehyde **183** at ambient temperature (Scheme 2.26). Aldehyde **183** was also isolated from Stetter reaction attempts with substrate **180**. Spiro lactol **180** thus proved to be incompatible with the Stetter reaction.

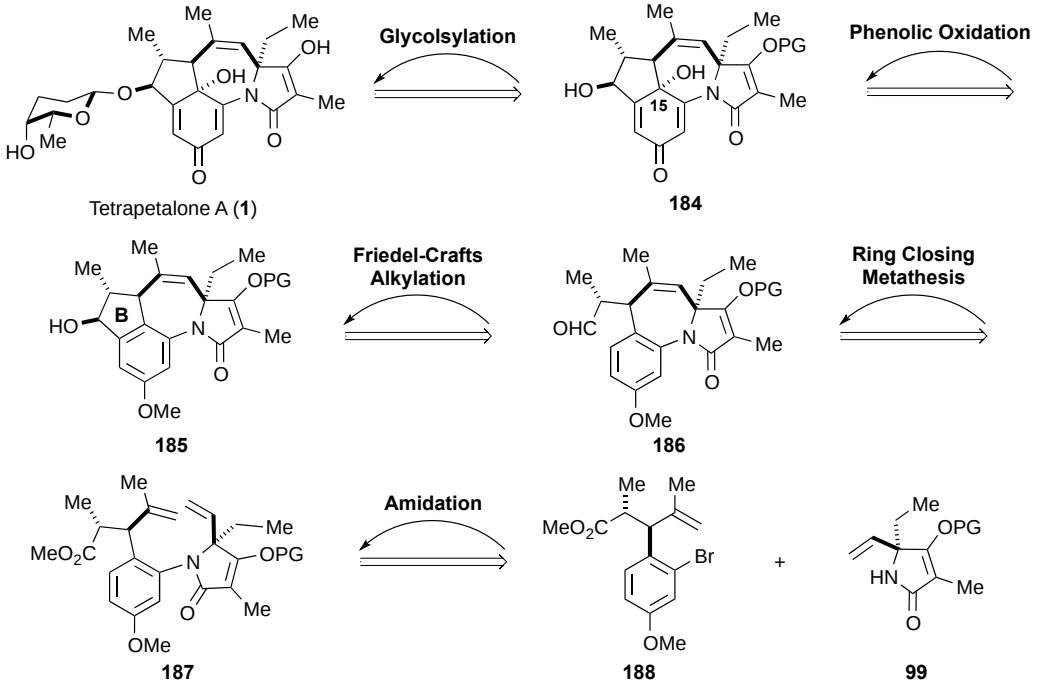


Scheme 2.26 Proposed *oxy*-Cope Rearrangement

2.8 Second-Generation Retrosynthetic Analysis

Unable to realize the desired Stetter reaction to afford an indanone coupling partner (i.e. 126, Scheme 2.9) we redesigned our retrosynthetic analysis of Tetrapetalone A (**1**). Guided by the reactivity issues of our previous Stetter reaction substrates we proposed a retrosynthetic synthetic analysis that would employ a Friedel-Crafts alkylation to afford the B-ring of the tetrapetalone A (**1**) tetracyclic core (Scheme 2.27). Outlined in Scheme 2.27, our second-

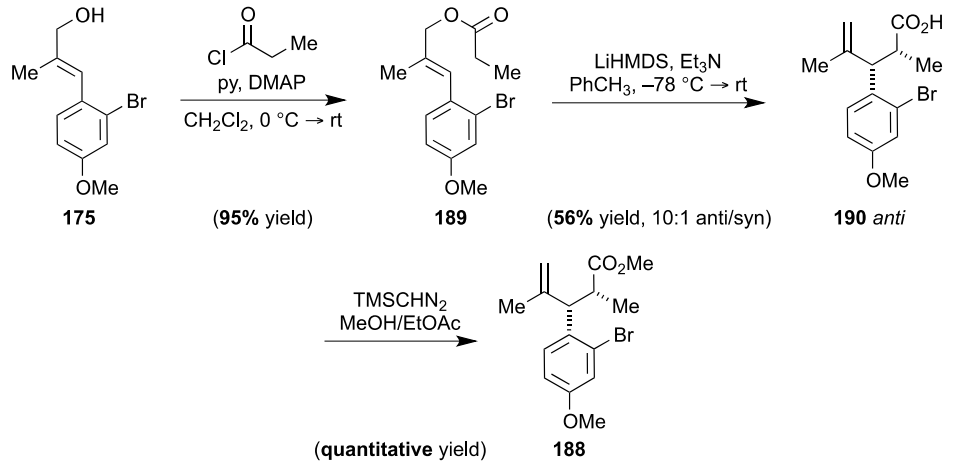
generation retrosynthetic analysis is envisioned to conclude with a glycosylation, deprotection sequence from aglycon **184**. Introduction of the C(15)-hydroxyl group of aglycon **184** would be achieved upon phenolic oxidation of tetracycle **185**. Friedel-Crafts alkylation of benzazepine **186** affords the B ring of desired tetracycle **185**. Following amidation of aryl bromide **188** with protected tetramic acid **99**, ring-closing metathesis of diene **187** would provide benzazepine **186.**



Scheme 2.27 Second-Generation Retrosynthetic Analysis of Tetrapetalone A

2.9 Synthesis of Aryl Bromide Coupling Partner

To this end we synthesized the desired aryl bromide **188**, in a manner analogous to **158**. To set the stage for an enolate Claisen rearrangement allylic alcohol **175** was acylated with propionyl chloride to furnish allylic ester **189** (Scheme 2.28). We were delighted to find that LiHMDS/triethylamine mediated enolization of allylic ester **189** followed by warming to room temperature resulted in [3,3] sigmatropic rearrangement to the desired γ,δ-unsaturated carboxylic acid **190** in modest yield (56%) and good diastereoselectivity. Exposure of carboxylic acid **190** to (trimethylsilyl)diazomethane resulted in methylation to afford the desired methyl ester **188**.



Scheme 2.28 Synthesis of Aryl Bromide Coupling Partner

2.10 Conclusion

In the course of executing a synthetic effort toward an indanone-coupling partner, with the goal of employing an intramolecular Stetter reaction, we sought to investigate the regio/chemo-selectivity that would be imparted by highly functionalized dienone substrates. In the course of exploring these ideas we discovered the inherent limitations of the Stetter reaction and based on this were led to believe that it would likely be unsuitable for this application. Thus, we redevised our synthetic strategy to a route that would employ an aryl bromide and tetramic acid coupling partners (Scheme 2.27), upon aryl amidation we conceived the application of ring closing metathesis technology followed by Friedel-Crafts alkylation would afford an advanced tetracycle containing all requisite carbons of tetrapetalone A (**1**). To this end, we successfully developed a synthetic route to the desired aryl bromide-coupling partner and turned our focus to the synthesis of a tetramic acid coupling partner.

2.11 Experimental Section

2.11.1 Materials and Methods

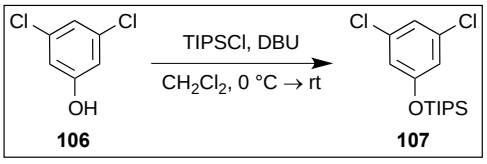
Unless stated otherwise, reactions were performed in flame-dried glassware under a nitrogen atmosphere. Triethylamine, diisopropylamine, and methanol were dried over anhydrous calcium hydride and freshly distilled. 1,4-Dioxane was distilled from sodium, calcium chloride and molecular sieve (0.4 nm). Benzene, tetrahydrofuran, dichloromethane, toluene, and diethyl ether were dried using a solvent purification system manufactured by Glass Contour Solvent Systems, SG Water U.S.A., LLC using technology based upon that originally described by Grubbs *et al*.[38] Anhydrous *N,N*-dimethyformamide, acetonitrile, dimethylsulfoxide, 1,2-dichloroethane was purchased from the Colorado State University Stockroom and supplied by Sigma-Aldrich or Fischer Scientific and stored under nitrogen atmosphere. Commercially available reagents were obtained from Sigma-Aldrich, Strem, TCI, Combi-Blocks, Acros or Alfa-Aesar and were used as received. All known compounds were identified by comparison of NMR spectra to reported in the literature.

Unless otherwise stated, all reactions were monitored by thin layer chromatography (TLC) was using Silicycle glass-backed extra hard layer, 60 Å plates (indicator F-254, 250 μm). Developed TLC plates were visualized using a 254 nm UV lamp and/or with the appropriate stain followed by heating. Typical stains utilized were potassium permanganate, ethanolic anisaldehyde and ceric ammonium molybdate. In general, the flash chromatography guidelines reported by Still *et al*[39] were followed. Silicycle SiliaFlash® P60 (230-400 mesh) silica gel was employed as the stationary phase. When reactions were absorbed onto silica gel, the amount of silica gel used was approximately equal to two times the weight of the reagents.

Infrared spectra were obtained using a Nicolet Avatar 320 FTIR or Bruker Tensor27 FTIR. Samples were analyzed as thin films on NaCl plates (samples was dissolved in CH_2Cl_2 or $CHCl_3$) or potassium bromide pellets, as indicated. IR spectra are presented as transmittance vs. wavenumber (cm^{-1}). Proton (^1H) and carbon (^{13}C) NMR spectra were recorded on a Varian Inova 500, Varian Inova 400, Varian Inova 400 auto sampler, or Varian Inova 300 MHz spectrometer. Spectra were obtained at 22 °C in $CDCl_3$ unless otherwise noted. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to the internal solvent peak. Coupling constants (J) are reported in Hertz (Hz) and are rounded to the nearest 0.1 Hz. Multiplicities are defined as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, br = broad, app = apparent, par = partial. High-resolution mass spectra were obtained from the University of Colorado Central Instrument Facility, performed on an Agilent 6210 TOF LCMS by Donald L. Dick.

2.11.2 Preparative Procedures

Preparation of TIPS-ether 107:



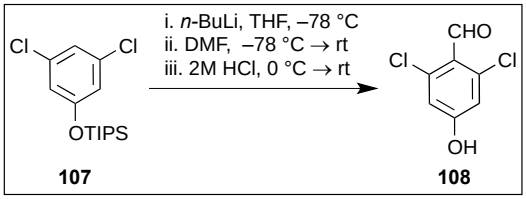
TIPS-ether 107. To a stirred solution of 3,5-dichlorophenol (10.0 g, 61.3 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (18.3 mL, 122.6 mmol) in CH_2Cl_2 (200 mL) was added triisopropylsilyl chloride (19.5 mL, 92.0 mmol) at 0 °C and reaction was warmed to room temperature. Reaction progress was monitored by TLC. TLC plates were developed with 5% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. After hydrolysis with H_2O (100 mL), the organic layer was washed with brine (100 mL), dried over anhydrous $MgSO_4$ and

concentrated under reduced pressure. The crude oil was purified by silica gel chromatography (elution with hexanes) to give **107** (19.0 g, 97% yield) as colorless oil.

TIPS-ether **107** is a known compound, the ^{1}H NMR spectra was obtained and structure was confirmed via comparison with spectra published in the literature.[17]

TIPS-ether 107. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 6.95 (t, *J* = 1.8 Hz, 1H), 6.77 (d, *J* = 1.8 Hz, 2H), 1.31-1.19 (m, *J* = 6.0 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 18H).

Preparation of aldehyde 108:

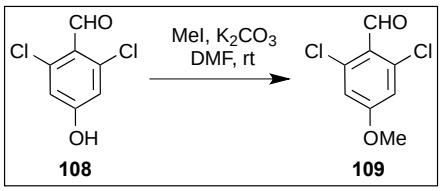


Aldehyde 108. A solution of *n*-butyllithium (1.6 M, 21.2 mL, 33.9 mmol) was added to a stirred solution of TIPS-ether **107** (9.0 g, 28.2 mmol) in THF (150 mL) at –78 °C. The reaction solution was stirred for 45 minutes at –78 °C. Anhydrous *N*,*N*-dimethyformamide (3.3 mL, 42.3 mmol) was added at –78 °C and warmed to room temperature. After addition of 2 M HCl (75 mL, 150 mmol), reaction mixture was stirred vigorously for 1 hour at room temperature. TLC was used to monitor reaction progress at all steps. TLC plates were developed with 5% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Phases were separated (aided by the addition of NaCl), the organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Crude solid was triturated with hexanes to afford aldehyde **108** (4.5 g, 83% yield) as a white solid.

Aldehyde **108** is a known compound, the ^{1}H NMR spectra was obtained and structure was confirmed via comparison with spectra published in the literature.[17]

Aldehyde 108. ^{1}H-NMR (300 MHz; DMSO-d_6): δ 11.47 (s, 1H), 10.24 (s, 1H), 6.94 (s, 2H).

Preparation of methyl ether 109:

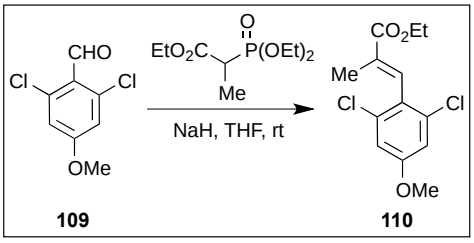


108 **109**

Methyl ether 109. To a stirred solution of phenol **108** (4.0 g, 20.9 mmol) in *N*,*N*-dimethyformamide (70 mL) was added K_2CO_3 and iodomethane (2.6 mL, 41.9 mmol) at room temperature. The reaction solution was stirred over night at room temperature. TLC was used to monitor reaction progress. TLC plates were developed with 10% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Reaction solution was diluted with Et_2O (100 mL) and H_2O (100 mL). Solution was stirred vigorously for 1 hour at room temperature. Phases were separated and organic phase was washed three times with H_2O (100 mL) to remove residual *N*,*N*-dimethyformamide. Organic phase was washed with brine (100 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Methyl ether **109** (4.2 g, 98% yield) was isolated as a white solid and required no further purification.

Methyl ether 109. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 10.42 (s, 1H), 6.91 (s, 2H), 3.88 (s, 4H).

Preparation of α,β-unsaturated ester 110:

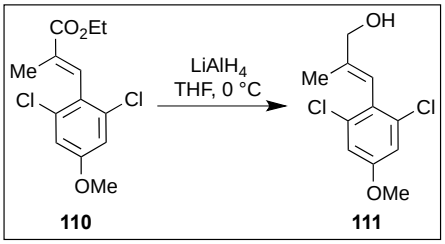


109 **110**

α,β-Unsaturated ester 110. To a stirred heterogeneous solution of sodium hydride (1.3 g, 31.7 mmol) in THF (25 mL) was added triethyl-2-phosphonopropionate (8 mL, 36.5 mmol) at 0 ºC. Aldehyde **109** was added as a solution in THF (25 mL) to the reaction solution via cannula at 0 ºC. Reaction solution was then warmed to room temperature. Reaction progress was monitored by TLC. TLC plates were developed with 10% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Reaction was quenched with saturated NH_4Cl solution. Phases were separated, organic phase was washed with H_2O (50 mL) and brine (50 mL). Dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude oil was purified with silica gel chromatography (gradient elution 5→10% EtOAc/Hex) to yield α,β-unsaturated ester **110** (5.6 g, 80% yield) as colorless oil.

α,β-Unsaturated ester 110. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.41 (q, *J* = 1.3 Hz, 1H), 6.90 (s, 2H), 4.28 (q, *J* = 7.1 Hz, 3H), 3.80 (s, 4H), 1.77 (d, *J* = 1.4 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 4H).

Preparation of allylic alcohol 111:



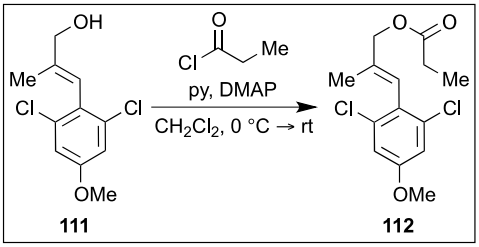
110 **111**

Allylic alcohol 111. To a stirred heterogeneous solution of lithium aluminum hydride (2.0 g, 50.5 mmol) in THF (80 mL) was added α,β-unsaturated ester **110** (7.3 g, 25.3 mmol) as a solution in THF (50 mL) via cannula at 0 °C. Reaction progress was monitored by TLC. TLC plates were developed with 30% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Reaction was quenched with H_2O (2 mL) followed by 15% NaOH (2 mL) and H_2O (6 mL)

at 0 °C. After stirring at 0 °C for 10 minutes reaction was warmed to room temperature and stirred 15 minutes. A scoop of anhydrous $MgSO_4$ was added and stirred for 15 minutes. Solution was filtered through a sand/celite pad. Organic phase was washed with saturated NH_4Cl solution (100 mL), H_2O (100 mL) and brine (100 mL). Organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (eluted with 30% EtOAc/Hex) to afford allylic alcohol **111** (4.7 g, 76% yield) as viscous colorless oil.

Allylic alcohol 111. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 6.89 (s, 2H), 6.24 (q, *J* = 1.3 Hz, 1H), 4.24 (d, *J* = 1.1 Hz, 2H), 1.66 (s, 1H), 1.57 (d, *J* = 1.3 Hz, 3H).

Preparation of allylic ester 112:

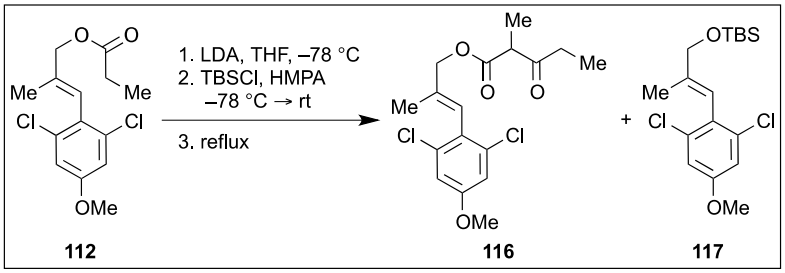


Allylic ester 112. To a stirred solution of allylic alcohol **111** (95.9 mg, 0.39 mmol) and 4-(dimethylamino)pyridine (catalytic amount) in dichloromethane (2 mL) was added pyridine (41 μL, 0.78 mmol) followed by addition of propionyl chloride (53 μL, 0.59 mmol) at 0 ºC. Stirred reaction solution for 30 minutes at 0 ºC and warmed to room temperature. Reaction was stirred over night at room temperature. Reaction progress was monitored by TLC. TLC plates were developed with 30% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Reaction solution was diluted with dichloromethane (5 mL). Organic phase was washed with saturated $CuSO_4$ solution (2 mL), H_2O (2 mL) and brine (2 mL). Organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude oil was purified with silica

gel chromatography (eluted with 30% EtOAc/Hex) to afford allylic ester **112** (76 mg, 64% yield) as colorless oil.

Allylic ester 112. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 6.89 (s, 2H), 6.23 (s, 1H), 4.68 (s, 2H), 3.79 (s, 3H), 2.42 (q, *J* = 7.6 Hz, 2H), 1.57 (s, 3H), 1.19 (t, *J* = 7.6 Hz, 3H).

Attempted Ireland-Claisen rearrangement of allylic ester 112:



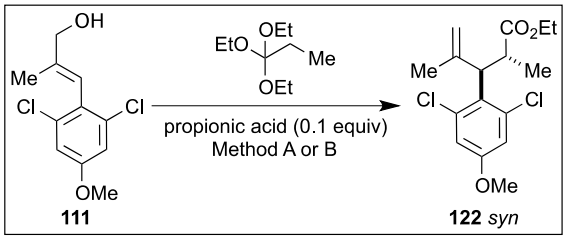
Following the protocol of Daub and *et al*.[20] To a solution of diisopropylamine (0.21 ml, 1.5 mmol) in THF (2 mL) was added *n*-butyllithium (1.6 M, 0.70 mL, 1.1 mmol) at 0 ºC. Reaction solution was stirred 2 minutes at 0 ºC and cooled to –78 ºC. Allylic ester **112** (303 mg, 1 mmol) was added to the reaction solution drop wise over approximately 3 minutes as a solution in THF (1 mL) at –78 ºC; followed by stirring for 2 minutes. *tert*-Butyldimethylsilyl chloride (170 mg, 1.1 mmol) was added as a solution in hexamethylphosphoramide (0.50 mL, 3.0 mmol) at –78 ºC, stirred 2 minutes and warmed to room temperature. Reaction solution was refluxed for 2 hours, oil bath set to 80 ºC. Reaction progress was monitored by TLC. TLC plates were developed with 10% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Reaction was cooled to room temperature and quenched with 10% HCl solution (1 mL); stirred for 1 hour. 15% NaOH solution was added and aqueous phase was extracted three times with diethyl ether (3 mL). Concentrated HCl was added to the aqueous phase, until pH = 3 paper at 0 ºC. Acidic aqueous phase was extracted three times with diethyl ether (3 mL). Organic phase was washed with H_2O (5 mL), brine (5 mL), dried over anhydrous $MgSO_4$ and concentrated under

reduced pressure. By ^{1}H-NMR no desired carboxylic acid was isolated. Basic extract was thus moved forward with. Organic phase was washed with H_2O (5 mL), brine (5 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 5→10% EtOAc/Hex) to afford TBS-ether **117**, allylic ester **112** (75 mg, 25% yield recovered starting material) and β-ketoester **116**.

TBS-ether 117. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 6.89 (s, 2H), 6.25 (s, 1H), 4.22 (s, 2H), 3.79 (s, 3H), 1.50 (s, 3H), 0.95 (s, 9H), 0.13 (s, 6H).

β-ketoester 116. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 6.86 (s, 2H), 6.22 (s, 1H), 4.76 (d, *J* = 12.9 Hz, 1H), 4.66 (d, *J* = 12.9 Hz, 1H), 3.79 (s, 3H), 3.64 (q, *J* = 7.2 Hz, 1H), 2.65 (dq, *J* =7.5 Hz, 1H), 2.57 (dq, *J* =7.5 Hz, 1H), 1.54 (s, 3H), 1.38 (d, *J* = 7.2 Hz, 3H), 1.06 (t, *J* =7.2 Hz, 3H), note data was not available to calculate all J values for dq's at 2.65 and 2.57; ^{13}C APT NMR (100 MHz, $CDCl_3$): δ 206.5, 170.5, 159.2, 136.7, 135.4, 126.8, 122.9, 114.1, 69.3, 55.9, 52.8, 35.1, 16.0, 13.1, 7.9.

Preparation of γ,δ-Unsaturated ester 123:



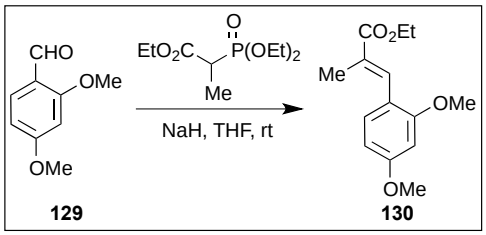
γ,δ-Unsaturated ester 123. (Method A) To a round bottom flask fitted with a magnetic stir bar was added allylic alcohol **111** (589.6 mg, 2.40 mmol), triethyl orthopropionate (5 mL, 24.0 mmol) and propionic acid (18 μL, 0.2 mmol). System was fitted with a short path distillation condenser and collecting round bottom flask. Reaction was heated to 152 °C for 4 hours. Reaction was cooled to room temperature and diluted with Et_2O (20 mL). Organic phase

was washed with 10% HCl (20 mL), $NaHCO_3$ (20 mL), H_2O (20 mL) and brine (20 mL). Organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 10→30% EtOAc/Hex) to afford γ,δ-unsaturated ester **122** *syn* (357 mg, 45% yield) as yellow oil.

γ,δ-Unsaturated ester 122. (Method B) To a microwave reactor tube fitted with a magnetic stir bar was added allylic alcohol **111** (503.0 mg, 2.40 mmol), triethyl orthopropionate (4.1 mL, 20.4 mmol) and propionic acid (15 μL, 0.2 mmol). Reaction was heated in microwave reactor at 250 °C for 1.5 hours, power setting 250. Reaction was cooled to room temperature and diluted with Et_2O (20 mL). Organic phase was washed with 10% HCl (20 mL), $NaHCO_3$ (20 mL), H_2O (20 mL) and brine (20 mL). Organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 10→30% EtOAc/Hex) to afford γ,δ-unsaturated ester **123** *syn* (324 mg, 48% yield) as yellow oil.

γ,δ-Unsaturated ester 123. ^{1}H NMR (400 MHz; $CDCl_3$): δ 6.91 (d, *J* = 2.7 Hz, 1H), 6.79 (d, *J* = 2.7 Hz, 1H), 4.95 (s, 1H), 4.92 (s, 1H), 4.58 (d, *J* = 11.3 Hz, 1H), 4.17 (app dq, *J* = 7.1, 3.0 Hz, 3H), 3.76 (s, 4H), 3.62 (dq, *J* = 11.3, 7.1 Hz, 1H), 1.55 (d, *J* = 0.6 Hz, 4H), 1.26 (t, *J* = 7.1 Hz, 4H), 0.92 (d, *J* = 7.2 Hz, 4H); ^{13}C NMR (101 MHz; CDCl3): δ 176.7, 158.4, 143.1, 138.3, 136.2, 127.4, 116.1, 114.3, 111.8, 60.6, 55.7, 49.4, 39.6, 23.0, 16.7, 14.3; HRMS (EI) *m/z* 331.08622 [calc'd for $C_6H_{21}O_3C_{l2}$ (M+) 331.0855].

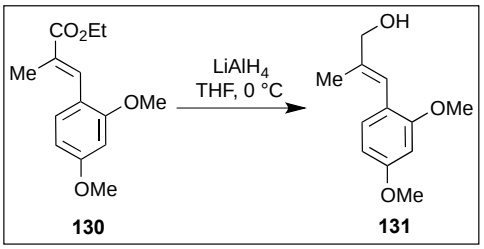
Preparation of α,β-unsaturated ester 130:



α,β-Unsaturated ester 130. To a stirred heterogeneous solution of sodium hydride (53 g, 137.24 mmol) in THF (1 L) was added triethyl 2-phosphonopropionate (35.5 g, 158.35 mmol) at 0 °C. 2,4-Dimethoxybenzaldehyde (**126**) (18 g, 105.57 mmol) was added to reaction solution at 0 °C, followed by immediate warming to room temperature. Reaction was stirred at room temperature over night. Reaction progress was monitored by TLC. TLC plates were developed with 30% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Reaction was quenched with saturated NH_4Cl solution (500 mL) at 0 °C. Quenched solution was warmed to room temperature and diluted with H_2O to dissolve salts. Organic phase was washed with H_2O (500 mL), brine (500 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford α,β-unsaturated ester **130** (>25 g, 10:1 dr) as yellow oil. The crude material was carried on without further purification.

α,β-Unsaturated ester 130. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.80 (br s, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 6.51 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.47 (d, *J* = 2.4 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 6H), 2.06 (d, *J* = 1.5 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H).

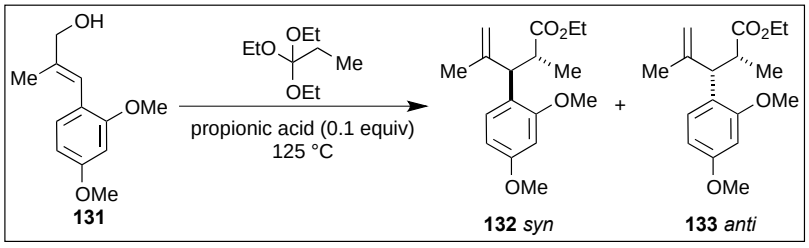
Preparation of allylic alcohol 131:



Allylic alcohol 131. To a heterogeneous stirred solution of lithium aluminum hydride (5.3 g, 138 mmol) in THF (500 mL) was added crude α,β-unsaturated ester **130** (>25 g, 106 mmol) as a solution in THF (50 mL), addition completed via addition funnel, at 0 °C. Reaction progress was monitored by TLC. TLC plates were developed with 20% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Quenched reaction with extremely slow drop wise addition of H_2O (7 mL), 15% NaOH solution (7 mL) and H_2O (21 mL) stirred for 30 minutes at 0 °C. Warmed to room temperature. Added 3 scoops of anhydrous $MgSO_4$ and stirred for 1 hour. Filtered through sand/celite pad. Concentrated to reduce volume. Organic phase was washed with H_2O (200 ml), brine (200 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford allylic alcohol **131** (23.3 g) as oil. Crude material was carried on without further purification.

Allylic alcohol 131. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.16 (d, *J* = 7.9 Hz, 1H), 6.52 (br s, 1H), 6.49 (dd, *J* = 2.5 Hz, 1H), 6.46 (d, *J* = 2.0 Hz, 2H), 4.20 (2, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 1.85 (d, *J* = 1.4 Hz, 3H), 1.61 (s, 1H), note unable to calculate complete *J* values for aromatic region in full due to overlapping chemical shifts.

Preparation of γ,δ-unsaturated esters 132 *syn* and 133 *anti*:



γ,δ-Unsaturated esters 132 *syn* and 133 *anti*. Following the procedure of Daub *et al*.[20] To round bottom flask was added allylic alcohol **131** (378 mg, 1.82 mmol), triethyl orthopropionate (5.5 mL, 27.22 mmol) and propionic acid (14 μL, 0.18 mmol), fitted with a short

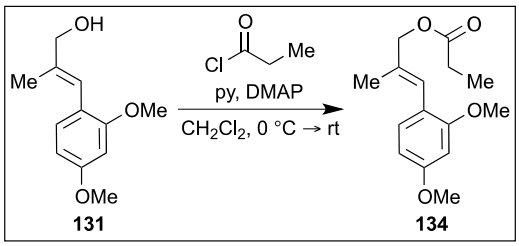
path distillation apparatus and collection round bottom flask, heated oil bath to 150 ºC. Reaction progress was monitored by TLC. TLC plates were developed with 20% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Cooled reaction room temperature and diluted with diethyl ether (10 mL) quenched with 10% HCl (10 mL) and stirred vigorously for 1 hour. Organic phase was washed with saturated $NaHCO_3$ (10 mL), H_2O (15 mL), brine (15 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 1→2→3→4→5→10% EtOAc/Hex) to afford γ,δ-unsaturated esters **132** *syn* and **133** *anti* (combined yield 56%, 2:1 dr) both are colorless oils.

γ,δ-Unsaturated ester 132 *syn*. FTIR (thin film/NaCl): 2977, 2836, 1732, 1646, 1611, 1586, 1505, 1456, 1418, 1373, 1322, 1294, 1261, 1208, 1157, 1123, 1106, 1037, 938, 892, 834; ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.03 (d, *J* = 9.1 Hz, 1H), 6.46 (dd, *J* = 9.0, 2.9 Hz, 1H), 6.44 (d, *J* = 3.5 Hz, 1H), 4.92 (s, 1H), 4.78 (t, *J* = 1.4 Hz, 1H), 4.14 (q, *J* = 6.9 Hz, 2H), 3.96 (d, *J* = 11.5 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 2.97 (dq, *J* = 11.7, 6.9 Hz, 1H), 1.60 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR (101 MHz; CDCl3): δ 176.8, 159.4, 159.1, 147.6, 128.8, 121.6, 109.9, 104.6, 98.6, 60.2, 55.58, 55.42, 46.7, 43.4, 22.4, 16.4, 14.4; HRMS (EI) *m/z* 292.16764 [calc'd for $C_{17}H_{24}O_4$ (M+) 292.16746].

γ,δ-Unsaturated ester 133 *anti*. FTIR (thin film/NaCl): 3076, 2976, 2836, 1733, 1643, 1610, 1586, 1505, 1463, 1418, 1374, 1262, 1208, 1037, 939, 892,834; ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.10 (d, *J* = 9.0 Hz, 1H), 6.41 (dd, *J* = 9.0, 4.8 Hz, 1H), 6.40 (app s, 1H), 4.96 (s, 1H), 4.81 (t, *J* = 1.7 Hz, 1H), 3.94 (d, *J* = 11.7 Hz, 1H), 3.88 (app dd, *J* = 7.1, 4.3 Hz, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 3.08 (dq, *J* = 11.7, 6.8 Hz, 1H), 1.59 (d, *J* = 0.7 Hz, 3H), 1.22 (d, *J* = 6.8 Hz, 3H), 0.96 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (101 MHz; CDCl3): δ 176.1, 159.3, 158.4, 144.8, 128.4,

122.8, 112.7, 103.9, 98.9, 60.0, 55.7, 55.4, 47.8, 41.6, 20.0, 16.8, 14.1; HRMS (EI) *m/z* 292.16779 [calc'd for $C_{17}H_{24}O_4$ (M+) 292.16746].

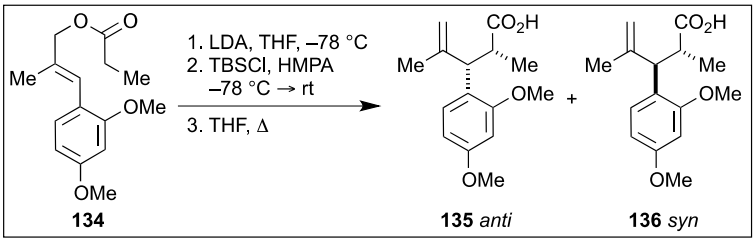
Preparation of allylic ester 134:



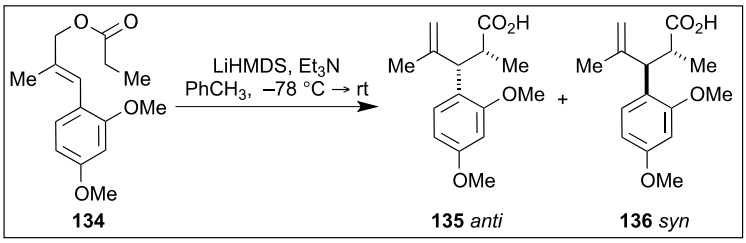
Allylic ester 134. To a solution of allylic alcohol **131** (23.3 g, 110 mmol), 4-(dimethylamino)pyridine (1.4 g, 11 mmol) in dichloromethane (500 mL) was added pyridine (12 mL, 220 mmol) followed by addition of propionyl chloride (25 mL, 275 mmol) at 0 °C. Reaction was warmed to room temperature. Reaction progress was monitored by TLC. TLC plates were developed with 20% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Reaction was quenched with 1M HCl (300 mL). Organic phase was washed with saturated $NaHCO_3$ (300 mL), H_2O (250 mL), brine (250 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 10→15→20→25% EtOAc/Hex) to afford allylic ester **134** (15.8 g, 57% yield, over three steps).

Allylic ester 134. FTIR (thin film/NaCl): 2941, 2837, 1737, 1609, 1579, 1503,1463, 1417, 1341, 1286, 1209, 1124, 1081, 1034, 937, 834; ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.15 (d, *J* = 8.2 Hz, 1H), 6.54 (s, 1H), 6.46 (dd, *J* = 10.2, 2.1 Hz, 1H), 6.45 (d, *J* = 2.2 Hz, 1H), 4.66 (d, *J* = 0.9 Hz, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 2.39 (q, *J* = 7.6 Hz, 2H), 1.84 (d, *J* = 1.4 Hz, 3H), 1.17 (t, *J* = 7.6 Hz, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ 174.4, 160.1, 158.3, 132.0, 131.5, 130.6, 125.8, 123.5, 118.7, 103.8, 98.3, 70.3, 64.4, 55.43, 55.35, 27.7, 21.8, 15.7, 9.2; HRMS (EI) *m/z* 264.13501 [calc'd for $C_{15}H_{20}O_4$ (M+) 264.13616].

Preparation of γ,δ-unsaturated carboxylic acids 135 *anti* and 136 *syn*:



γ,δ-Unsaturated carboxylic acids 135 *anti* and 136 *syn*. Following the protocol of Daub and *et al*.[20] To a solution of diisopropylamine (0.10 ml, 0.68 mmol) in THF (2 mL) was added *n*-butyllithium (1.32 M, 0.33 mL, 0.44 mmol) at 0 ºC. Reaction solution was stirred 2 minutes at 0 ºC and cooled to –78 ºC. Allylic ester **134** (72 mg, 0.27 mmol) was added to the reaction solution drop wise over approximately 3 minutes as a solution in THF (1 mL) at –78 ºC; followed by stirring for 2 minutes. *tert*-Butyldimethylsilyl chloride (45 mg, 0.3 mmol) was added as a solution in hexamethylphosphoramide (0.14 mL, 0.81 mmol) at –78 ºC, stirred 2 minutes and warmed to room temperature. Reaction solution was refluxed for 2 hours; oil bath heat set to 80 ºC. Reaction progress was monitored by TLC. TLC plates were developed with 30% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Reaction was cooled to room temperature and quenched with 10% HCl solution (1 mL); stirred for 1 hour. 15% NaOH solution was added and aqueous phase was extracted three times with diethyl ether (3 mL). Concentrated HCl was added to the aqueous phase, until pH = 3 at 0 ºC. Acidic aqueous phase was extracted three times with diethyl ether (3 mL). Organic phase was washed with H_2O (5 mL), brine (5 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 20→30→50% EtOAc/Hex) to afford γ,δ-unsaturated carboxylic acids **135** *anti* and **136** *syn* (combined 42 mg, 58% yield, 3:1 dr) both colorless oils.



134 **135** *anti* **136** *syn*

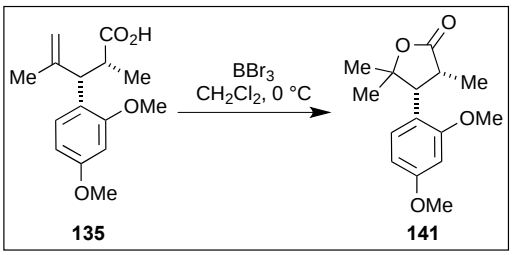
γ,δ-Unsaturated carboxylic acids 135 *anti* and 136 *syn*. Following the procedure of Collum *et al.*[21] To a solution of LiHMDS (1M in toluene, 11.4 mL, 11.34 mmol), triethylamine (16mL, 113.4 mmol) in toluene (40 mL) was added allylic ester **134** (1 g, 3.78 mmol) as a solution in toluene (10 mL) at –78 ºC. Stirred reaction for 1 hour at –78 ºC than warmed to room temperature. TLC was used to monitor reaction progress. TLC plates were developed with 30% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Reaction was basified with 15% NaOH (25 mL). Extracted basified reaction solution with diethyl ether (50 mL). Concentrated HCl was added to the aqueous phase, until pH = 3 at 0 ºC. Extracted acidified aqueous phase three times with diethyl ether (25 mL). Combined organic phase was washed with H_2O (50 mL), brine (50 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to yield γ,δ-unsaturated carboxylic acids **135** *anti* and **136** *syn* (0.80g, 80% yield, 19:1 dr) as white solid. No further purification required.

γ,δ-Unsaturated carboxylic acids 135 *anti*. FTIR (thin film/NaCl) 3077 (br, s), 2969 (s), 2938 (s), 2836 (s), 2660 (br, m), 1708 (s), 1644 (w), 1611 (m), 1586 (m), 1295 (s), 1261 (s), 1036 (m) cm^{-1}; ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.09 (d, *J* = 8.2 Hz, 1H), 6.42 (dd, *J* = 8.0, 2.5 Hz, 1H), 6.39 (t, *J* = 3.0 Hz, 1H), 4.93 (s, 1H), 4.82 (t, *J* = 1.7 Hz, 1H), 3.91 (d, *J* = 11.5 Hz, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.05 (dq, *J* = 11.6, 6.8 Hz, 1H), 1.56 (s, 3H), 1.22 (d, *J* = 6.8 Hz, 4H); ^{13}C-NMR (101 MHz; CDCl3): δ 181.5, 159.4, 158.4, 144.4, 128.1, 122.3, 113.0, 104.0, 99.1,

55.7, 55.4, 47.5, 41.2, 20.0, 16.9; HRMS (EI) *m/z* 264.13637 [calc'd for $C_{15}H_{20}O_4$ (M+) 264.13616].

γ,δ-Unsaturated carboxylic acids 136 *syn*. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.02 (d, *J* = 9.1 Hz, 1H), 6.47 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.45 (d, *J* = 2.4 Hz, 2H), 4.97 (s, 1H), 4.82 (s, 1H), 3.95 (d, *J* = 11.2 Hz, 1H), 3.80 (s, 6H), 3.00 (app dd, *J* = 11.1, 6.8 Hz, 1H), 1.60 (s, 3H), 0.98 (d, *J* = 6.9 Hz, 3H).

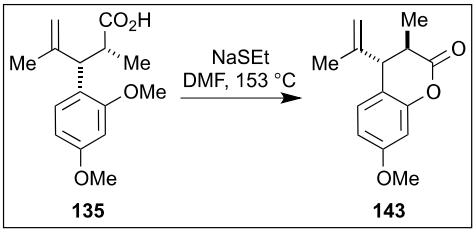
Attempted cleavage of methyl ether 135:



Lactone 141. To a stirred solution of γ,δ-unsaturated carboxylic acid **135** (50 mg, 0.20 mmol) in dichloromethane (2 mL) was added boron tribromide (100 μL, 0.22 mmol) at –78 ºC. Reaction solution was slowly warmed to room temperature. TLC was used to monitor reaction progress. TLC plates were developed with 50% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Reaction was quenched with H_2O (5 mL). Organic phase was washed with brine (5 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 10→20→30→50% EtOAc/Hex) to afford lactone **141** (15 mg, 30% yield) as the major product, white solid.

Lactone 141. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 6.86 (d, *J* = 9.1 Hz, 1H), 6.44 (app s, 1H), 6.41 (dd, *J* = 9.0, 2.5 Hz), 3.80 (s, 3H), 3.73 (s, 3H), 3.45 (br app s, 1H), 3.23-3.13 (m, 1H), 1.52 (s, 3H), 1.06 (s, 3H), 0.94 (d, *J* = 7.1 Hz, 3H).

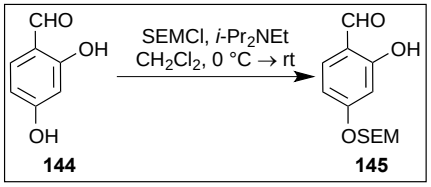
Attempted cleavage of methyl ether 135:



Lactone 143. To a stirred solution of γ,δ-unsaturated carboxylic acid **135** (471 mg, 1.78 mmol) in N,N-dimethylformamide (18 mL) was added sodium ethanethiolate (314 mg, 3.74 mmol). Reaction was heated to reflux (153 ºC) over night. Reaction progress was monitored by TLC. TLC plates were developed with 30% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Reaction was quenched with 10% HCl (10 mL). Diluted with diethyl ether (20 mL). Organic phase was washed three times with H_2O (40 mL), brine (40 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 10→20→30→50% EtOAc/Hex) to afford lactone **143** (112 mg, 25% yield) as a white solid.

Lactone 143. FTIR (thin film/NaCl) 3077 (m), 2975 (s), 2838 (m), 2594 (w), 2416 (w), 2235 (w), 1766 (s), 1623 (s), 1377 (m), 1318 (m), 1260 (m), 1080 (m), 1033 (m), 839 (m); ^{1}H-NMR (400 MHz; $CDCl_3$): δ 6.99 (d, *J* = 8.4 Hz, 1H), 6.66 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.60 (d, *J* = 2.6 Hz, 1H), 5.08 (quintet, *J* = 1.5 Hz, 1H), 4.91 (t, *J* = 0.8 Hz, 1H), 3.78 (s, 3H), 3.38 (d, *J* = 9.9 Hz, 1H), 2.75 (dq, *J* = 9.9, 6.9 Hz, 1H), 1.65 (t, *J* = 0.6 Hz, 3H), 1.25 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR (101 MHz; CDCl3): δ 171.4, 159.9, 152.2, 142.2, 128.7, 116.8, 115.6, 110.6, 102.3, 55.6, 49.1, 37.4, 17.9, 14.2; HRMS (EI) *m/z* 232.10984 [calc'd for $C_{14}H_{16}O_3$ (M+) 232.10994].

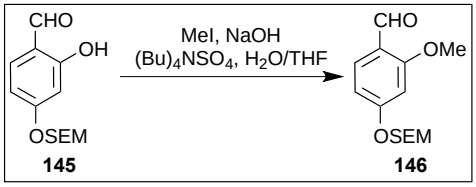
Preparation of SEM-ether 145:



SEM-ether 145. To a stirred heterogeneous solution of 2,4-dihydroxybenzaldehyde (**144**) (5 g, 36.20 mmol) in dichloromethane (250 mL) was added *N*,*N*-diisopropylethylamine (8 mL, 43.44 mmol) and 2-(trimethylsilyl)ethoxymethyl chloride (6.4 mL, 36.20 mmol) at 0 ºC. Reaction was warmed to room temperature. TLC was used to monitor reaction progress. TLC plates were developed with 30% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Quenched reaction with saturated NH_4Cl solution (100 mL) at 0 ºC and warmed to room temperature. Organic phase was washed with H_2O (100 mL), brine (100 mL), dried over anhydrous Na_2SO_4, with stirring. Concentrated under reduced pressure to afford SEM-ether **145** (9.4 g, 97% yield) as oil. No further purification was necessary.

SEM-ether 145. FTIR (thin film/NaCl): 3099, 2954, 2897, 1654, 1577, 1502, 1431, 1361, 1333, 1289, 1249, 1215, 1164, 1119, 1087, 993, 955, 917, 836, 806, 758, 713, 695, 653, 613; ^{1}H-NMR (400 MHz; $CDCl_3$): δ 11.38 (s, 1H), 9.74 (d, *J* = 0.5 Hz, 1H), 7.45 (d, *J* = 8.6 Hz, 1H), 6.65 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.61 (d, *J* = 2.3 Hz, 1H), 5.26 (s, 2H), 3.77-3.73 (m, 2H), 0.98-0.93 (m, 2H), 0.00 (s, 9H); ^{13}C-NMR (101 MHz; CDCl3): δ 194.7, 164.7, 164.3, 135.5, 115.9, 109.2, 103.5, 92.7, 67.1, 18.2, -1.3; HRMS (EI) *m/z* 268.1134 [calc'd for $C_{13}H_{20}O_4Si$ (M+) 268.11309].

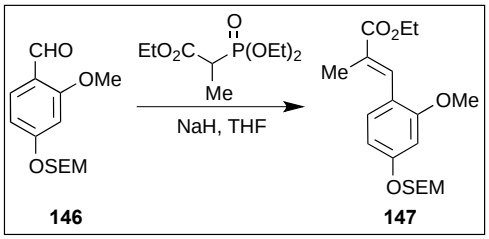
Preparation of methyl ether 146:



Methyl ether 146. To a stirred solution of SEM-ether **145** (9.4 g, 35.02 mmol) in tetrahydrofuran (200 mL) was added tetrabutylammonium hydrogen sulfate (6 g, 17.51 mmol), NaOH solution (2M, 88 mL, 175.10 mmol) and iodomethane (16 mL, 245.14 mmol). Reaction was stirred at room temperature overnight. TLC was used to monitor reaction progress. TLC plates were developed with 30% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Phases were separated. Organic phase was washed with H_2O (200 mL), brine (200 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 5→10→20% EtOAc/Hex) to afford methyl ether **146** (9.4 g, 95% yield) as yellow oil.

Methyl ether 146. FTIR (thin film/NaCl): 3299, 2953, 1679, 1603, 1502, 1466, 1425, 1397, 1315, 1261, 1203, 1165, 1088, 1029, 998, 935, 836, 694; ^{1}H-NMR (400 MHz; $CDCl_3$): δ 10.30 (d, *J* = 0.6 Hz, 1H), 7.78 (d, *J* = 8.7 Hz, 1H), 6.68 (dd, *J* = 8.7, 1.5 Hz, 1H), 6.60 (d, *J* = 2.1 Hz, 1H), 5.27 (s, 2H), 3.89 (s, 3H), 3.77 (dd, *J* = 9.4, 7.3 Hz, 2H), 0.94 (dd, *J* = 9.4, 7.3 Hz, 2H), -0.00 (s, 9H); ^{13}C-NMR (101 MHz; CDCl3): δ 188.6, 164.2, 163.7, 130.7, 119.6, 108.3, 99.5, 92.8, 67.0, 55.8, 18.2, -1.3; HRMS (EI) *m/z* 282.12886 [calc'd for $C_{14}H_{22}O_4Si$ (M+) 282.12874].

Preparation of α,β-unsaturated ester 147:

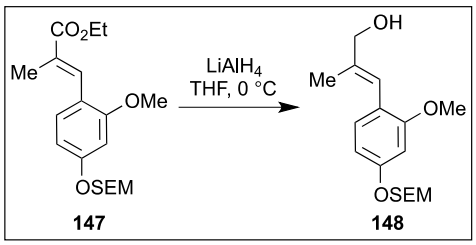


α,β-Unsaturated ester 147. To a stirred heterogeneous solution of sodium hydride (1.8 g, 45.11 mmol) in THF (100 mL) was added triethyl 2-phosphonopropionate (11.4 mL, 52.05 mmol) at 0 °C. Aldehyde **146** (9.8 g, 34.70 mmol) as a solution in THF (30 mL) was added at 0 °C, drop wise via addition funnel, followed by immediate warming to room temperature. TLC was used to monitor reaction progress. TLC plates were developed with 20% EtOAc/Hex solution and visualized by UV lamp and anisaldehyde stain. Reaction was quenched with saturated NH_4Cl solution (100 mL) at 0 °C. Quenched solution was warmed to room temperature and diluted with H_2O to dissolve salts. Organic phase was washed with H_2O (100 mL), brine (100 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 5→7→10→20→50% EtOAc/Hex) to afford α,β-unsaturated ester **147** (11.3 g, 10:1 dr) as yellow oil.

α,β-Unsaturated ester 147. FTIR (thin film/NaCl): 2954, 1702, 1607, 1577, 1501, 1464, 1419, 1366, 1247, 1201, 1087, 1000, 935, 836, 753, 736, 694; ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.79 (s, 1H), 7.24 (d, *J* = 8.5 Hz, 1H), 6.66 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.60 (d, *J* = 2.3 Hz, 1H), 5.24 (s, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 3.77 (dd, *J* = 9.5, 7.2 Hz, 2H), 2.05 (d, *J* = 1.5 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 0.97 (dd, *J* = 9.5, 7.2 Hz, 2H), 0.00 (s, 8H); ^{13}C-NMR (101 MHz; CDCl3): δ 169.0, 159.2, 159.0, 134.2, 131.0, 127.3, 118.6, 107.1, 99.8, 93.0, 66.6, 60.8,

55.7, 18.2, 14.53, 14.43, -1.3; HRMS (EI) *m/z* 366.18651 [calc'd for $C_{19}H_{30}O_5Si$ (M+) 366.18651].

Preparation of allylic alcohol 148:

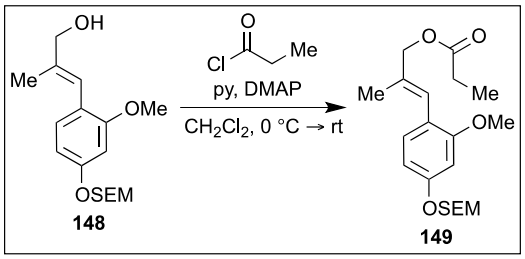


Allylic alcohol 148. To a heterogeneous stirred solution of lithium aluminum hydride (304 mg, 8.02 mmol) in THF (40 mL) was added α,β-unsaturated ester **147** (1.96 g, 5.35 mmol) as a solution in THF (10 mL) at 0 °C. TLC was used to monitor reaction progress. TLC plates were developed with 30% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Quenched reaction with extremely slow drop wise addition of H_2O (1 mL), 15% NaOH solution (1 mL) and H_2O (3 mL) stirred for 30 minutes at 0 °C. Warmed to room temperature. Added 1 scoop of anhydrous $MgSO_4$ and stirred for 1 hour. Filtered through sand/celite pad. Concentrated to reduce volume. Organic phase was washed with H_2O (50 ml), brine (50 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 10→20→30→40→50% EtOAc/Hex) to afford allylic alcohol **148** (1.67 g, 97% yield) as colorless oil.

Allylic alcohol 148. FTIR (thin film/NaCl): 3415, 2953, 1607, 1501, 1464, 1417, 1250, 1198, 1006, 934, 836, 694; ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.14 (d, *J* = 8.3 Hz, 1H), 6.63 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.59 (d, *J* = 2.3 Hz, 1H), 6.52 (s, 1H), 5.23 (s, 2H), 4.19 (s, 2H), 3.80 (s, 3H), 3.77 (t, *J* = 8.4 Hz, 2H), 1.85 (s, 3H), 1.65 (s, 1H), 0.97 (t, *J* = 8.4 Hz, 2H), 0.01 (s, 9H); ^{13}C-NMR (101 MHz; CDCl3): δ 158.2, 157.8, 136.9, 130.7, 120.5, 120.0, 106.9, 99.9, 93.2,

69.4, 66.4, 55.6, 18.2, 15.5, -1.2; HRMS (EI) *m/z* 322.15996 [calc'd for $C_{17}H_{26}O_4Si$ (M+) 322.16004].

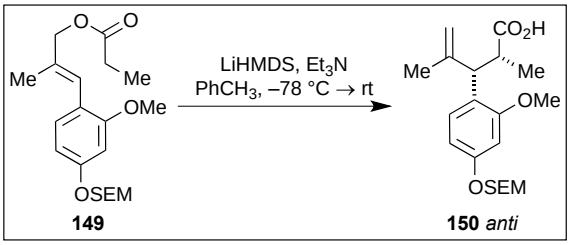
Preparation of allylic ester 149:



Allylic ester 149. To a solution of allylic alcohol **148** (1.67 g, 5.15 mmol), 4-(dimethylamino)pyridine (64 mg, 0.52 mmol) in dichloromethane (50 mL) was added pyridine (400 μL, 7.73 mmol) followed by addition of propionyl chloride (930 μL, 10.3 mmol) at 0 °C. Reaction was warmed to room temperature. TLC was utilized to monitor reaction progress. TLC plates were developed with 50% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Reaction was quenched with 1M HCl (10 mL). Organic phase was washed with saturated $NaHCO_3$ (50 mL), H_2O (50 mL), brine (50 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 5→7→10% EtOAc/Hex) to afford allylic ester **149** (1.57 g, 80% yield) as colorless oil.

Allylic ester 149. FTIR (thin film/NaCl): 3451, 2952, 1737, 1608, 1579, 1502, 1463, 1418, 1279, 1199, 1085, 1010, 935, 836; ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.14 (d, *J* = 8.4 Hz, 1H), 6.63 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.58 (d, *J* = 2.3 Hz, 1H), 6.54 (s, 1H), 5.22 (s, 2H), 4.66 (s, 2H), 3.80 (s, 3H), 3.78 (dd, *J* = 9.5, 7.4 Hz, 2H), 2.40 (q, *J* = 7.6 Hz, 2H), 1.84 (d, *J* = 1.3 Hz, 3H), 1.18 (t, *J* = 7.6 Hz, 3H), 0.95 (dd, *J* = 9.5, 7.4 Hz, 2H), 0.00 (s, 9H); ^{13}C-NMR (101 MHz; CDCl3): δ 174.5, 158.3, 158.0, 131.9, 130.7, 123.6, 119.6, 106.9, 99.9, 93.1, 70.4, 66.5, 55.6, 27.8, 18.2, 15.8, 9.4, -1.2; HRMS (EI) *m/z* 380.20201 [calc'd for $C_{20}H_{32}O_5Si$ (M+) 380.2019].

Preparation of γ,δ-unsaturated carboxylic acid 150:



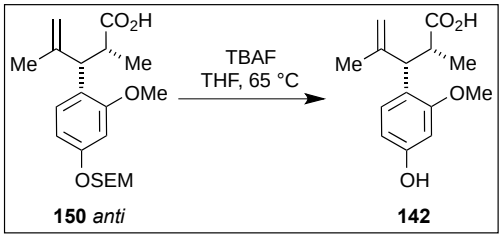
149 **150** *anti*

γ,δ-Unsaturated carboxylic acid 150. Following the procedure of Collum *et al*.[21] A solution of lithium bis(trimethylsilyl)amide (1M in toluene, 16 mL, 15.77 mmol) and triethylamine (22 mL, 157.80 mmol) in toluene (40 mL) was stirred for 10 minutes at room temperature; followed by cooling to –78 ºC. A precooled solution of allylic ester **149** (2 g, 5.26 mmol) in toluene (25 mL) was added over 1 hour to the reaction solution at –78 ºC. Upon complete addition reaction solution was stirred for 10 minutes at –78 ºC prior to warming to room temperature. TLC was utilized to monitor reaction progress. TLC plates were developed with 20% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Quenched reaction with 1M HCl (80 mL) at 0 ºC. Organic phase was washed with H_2O (100 mL), brine (100 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 5→7→10% EtOAc/Hex; doped eluent with 1% AcOH) to afford γ,δ-unsaturated carboxylic acid **150** (1.7g; 85% yield, 20:1 dr) as oil.

γ,δ-Unsaturated carboxylic acid 150. FTIR (thin film/NaCl) 2952 (br s), 1708 (s), 1609 (m), 1503 (m), 1250 (m), 1198 (m), 1163 (m), 1140 (m), 1086 (m), 1013 (s), 937 (m), 859 (m), 836 (s); ^{1}H-NMR (400 MHz; CDCl3): δ 7.07 (d, *J* = 8.4 Hz, 1H), 6.55 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.52 (d, *J* = 2.3 Hz, 1H), 5.19 (d, *J* = 6.9 Hz, 1H), 5.17 (d, *J* = 7.0 Hz, 1H), 4.94 (s, 1H), 4.82 (s, 1H), 3.93 (d, *J* = 11.5 Hz, 1H), 3.77-3.73 (t, *J* = 8.4 Hz, 2H), 3.74 (s, 3H), 3.06 (dq, *J* = 12.1, 6.3 Hz, 1H), 1.56 (s, 3H), 1.22 (d, *J* = 6.8 Hz, 3H), 0.96 (t, *J* = 8.4 Hz, 2H), -0.00 (s, 9H); ^{13}C-NMR

(101 MHz; CDCl3): δ 181.0, 158.3, 157.3, 144.4, 128.1, 123.3, 113.2, 107.1, 100.6, 93.2, 66.4, 55.7, 47.5, 41.0, 19.9, 18.2, 16.9, -1.2; HRMS (EI) *m/z* 381.2092 [calc'd for $C_{20}H_{32}O_5Si$ (M+H)+ 380.2019].

Preparation of phenol 142:

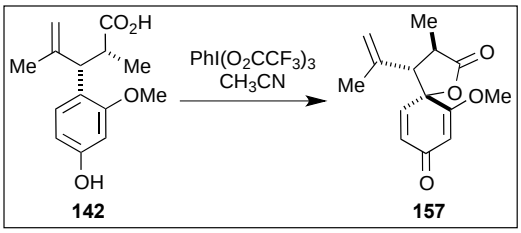


150 *anti* **142**

Phenol 142. To a stirred solution of γ,δ-unsaturated carboxylic acid **150** (1.7 g, 4.47 mmol) in tetrahydrofuran (7 mL) was added tetrabutylammonium fluoride (1M in THF, 23 mL, 22.33 mmol). Reaction was refluxed (65 ºC). Aliquots of the reaction were taken and analyzed by ^{1}H NMR to monitor progress. Quenched with 1M HCl (20 mL). Organic phase was washed with H_2O (15 mL), brine (15 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was triturated with chloroform to afford phenol **142** (549 mg, 50% yield) as a white powder.

Phenol 142. FTIR (thin film/NaCl): 3327, 2969, 1708, 1613, 1506, 1457, 1290, 1198; ^{1}H-NMR (400 MHz; DMSO-d_6): δ 11.75 (s, 2H), 9.21 (s, 2H), 6.97 (d, *J* = 8.3 Hz, 1H), 6.31 (d, *J* = 2.3 Hz, 1H), 6.26 (dd, *J* = 8.3, 2.3 Hz, 1H), 4.86 (s, 1H), 4.72 (s, 1H), 3.77 (d, *J* = 11.6 Hz, 1H), 3.67 (s, 3H), 2.94 (dq, *J* = 12.2, 6.4 Hz, 1H), 1.49 (s, 3H), 1.07 (d, *J* = 6.8 Hz, 3H); ^{13}C- NMR (101 MHz; DMSO-d_6): δ 176.6, 157.9, 156.8, 144.6, 127.7, 120.1, 112.5, 106.3, 99.1, 55.2, 47.1, 19.2, 16.8; HRMS (EI) *m/z* 249.1132 [calc'd for $C_{14}H_{18}O_4$ (M-H)- 250.1205].

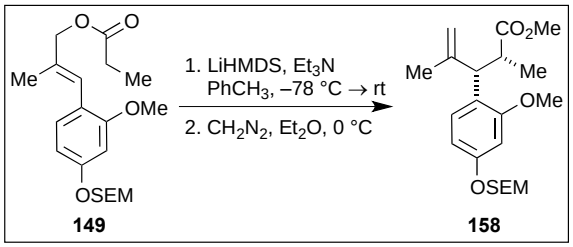
Preparation of spiro lactone 157:



Spiro lactone 157. To a stirred solution of [bis(trifluoroacetoxy)iodo]benzene (120 mg, 0.28 mmol) in acetonitrile (8.2 mL) was added phenol **142** (58 mg, 0.23 mmol) as a solution in acetonitrile (1 mL) at room temperature. TLC was utilized to monitor reaction progress. TLC plates were developed with 20% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Reaction solution was concentrated under reduced pressure and purified with silica gel chromatography (gradient elution 20→30→50% EtOAc/Hex) to afford spiro lactone **157** (52.9 mg, 93% yield, 14:1 dr) as white solid.

Spiro lactone 157. FTIR (thin film/NaCl) 2939 (w), 1787 (s), 1667 (s), 1606 (m), 1455 (w), 1373 (w), 1314 (w), 1228 (m), 1180 (w), 1070 (w), 975 (w), 858 (w), 646 (w); ^{1}H-NMR (300 MHz; $CDCl_3$): δ 6.50 (d, *J* = 10.1 Hz, 1H), 6.21 (dd, *J* = 10.1, 1.7 Hz, 1H), 5.67 (d, *J* = 1.7 Hz, 1H), 5.04 (s, 1H), 4.80 (s, 1H), 3.84 (s, 3H), 3.28 (d, *J* = 12.9 Hz, 1H), 2.95 (dq, *J* = 13.1, 6.6 Hz, 1H), 1.61 (s, 3H), 1.32 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR (101 MHz; CDCl3): δ 186.0, 169.7, 169.3, 139.2, 137.4, 129.8, 115.2, 104.2, 56.5, 55.9, 37.0, 22.2, 13.9.

Preparation of methyl ester 158:



Methyl ester 158. Following the procedure of Collum *et al*.[21] A solution of lithium bis(trimethylsilyl)amide (1M in toluene, 40 mL, 39.41 mmol) and triethylamine (55 mL, 394.20 mmol) in toluene (95 mL) was stirred for 15 minutes at room temperature; followed by cooling to –78 ºC. A precooled solution of allylic ester **149** (5 g, 5.26 mmol) in toluene (75 mL) was added over 1 hour to the reaction solution at –78 ºC. Upon complete addition reaction solution was stirred for 15 minutes at –78 ºC prior to warming to room temperature. Reaction was warmed to 30 ºC and stirred for 12 hours. TLC was utilized to monitor reaction progress. TLC plates were developed with 25% EtOAc/Hex solution and visualized by UV lamp and anisaldehyde stain. Quenched reaction with 1M HCl (125 mL) at 0 ºC. Organic phase was washed with 1M HCl (250 mL), H_2O (500 mL), brine (100 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford crude γ,δ-unsaturated carboxylic acid (4.6 g; crude yield 92%). Crude material was taken on directly to methylation.

Diazomethane was prepared from Diazald, using Aldrich Diazald apparatus.[40]

For an alcohol-containing ethereal solution:

Condenser was filled with dry ice, isopropanol was added slowly until cold-finger was approximately one-third full. Ethanol (95%, 10 mL) was added to a solution of potassium hydroxide (5 g) in water (8 mL) in the reaction vessel. Receiving flask (100 mL) was attached to condenser and cooled in a dry ice/isopropanol bath.

A separatory funnel was place over the reaction vessel and charged with a solution of Diazald (5.0 g, 23 mmol) in ether (45 mL). The reaction vessel was warmed to 65 ºC with a H_2O bath. Diazald solution was added over a period of 20 minutes. The rate of distillation should approximate the rate of addition. Cold-finger was replenished as necessary with dry ice. When all the Diazald was used up, diethyl ether (10 mL) was added, slowly, and distillation was

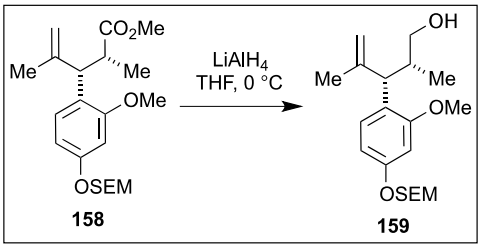
continued until distillate was colorless; process continued until distillate colorless. The ether solution contains approximately 700 mg (16.6 mmol) of diazomethane.

Note: All glassware used must be clear-seal joint type. Pipettes are flame polished prior to use.

To a stirred solution of crude γ,δ-unsaturated carboxylic acid (4.6 g, 13.14 mmol) in diethyl ether (30 mL) was added diazomethane solution at 0 ºC. Addition was continued until reaction solution remained yellow. TLC was utilized to monitor reaction progress. TLC plates were developed with 25% EtOAc/Hex solution and visualized by UV lamp and anisaldehyde stain. Quenched reaction with 3M AcOH in ethyl acetate, colorless solution. Concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 7→10→20→50% EtOAc/Hex) to afford methyl ester **158** (2.9 g; 56% yield, 12:1 dr, over two steps).

Methyl ester 158. FTIR (thin film/NaCl): 2952, 1739, 1609, 1587, 1504, 1455, 1249, 1197, 1162, 1087, 1013, 859, 836; ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.06 (d, *J* = 8.2 Hz, 1H), 6.55 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.53 (d, *J* = 2.2 Hz, 1H), 5.17 (s, 2H), 4.95 (t, *J* = 1.0 Hz, 1H), 4.81 (dd, *J* = 1.8, 1.6 Hz, 1H), 3.95 (d, *J* = 11.6 Hz, 1H), 3.78 (s, 3H), 3.75 (d, *J* = 7.3 Hz, 1H), 3.73 (d, *J* = 7.2 Hz, 1H), 3.42 (s, 3H), 3.10 (dq, *J* = 11.6, 6.8 Hz, 1H), 1.57 (s, 3H), 1.21 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 7.3 Hz, 1H), 0.93 (d, *J* = 7.3 Hz, 1H), -0.01 (s, 9H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ 176.5, 158.2, 157.2, 144.5, 128.0, 123.4, 112.8, 107.0, 100.5, 93.1, 66.3, 55.7, 51.4, 47.7, 41.3, 20.0, 18.1, 16.8, -1.3; HRMS (EI) *m/z* 417.2068 [calc'd for $C_{21}H_{34}O_5Si$ (M+Na)+ 394.2176].

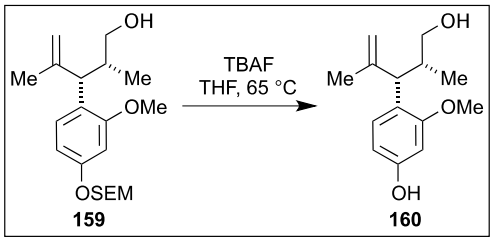
Preparation of alcohol 159:



Alcohol 159. To a stirred heterogeneous solution of lithium aluminum hydride (0.83 g, 31.90 mmol) in tetrahydrofuran (150 mL) was added methyl ester **158** (7.2 g, 18.25 mmol) as a tetrahydrofuran (30 mL) solution at 0 ºC. Stirred at 0 ºC for 1 hour and followed by warming to room temperature, stirred 15 minutes. TLC was utilized to monitor reaction progress. TLC plates were developed with 25% EtOAc/Hex solution and visualized by UV lamp and anisaldehyde stain. Quenched reaction with H_2O (2 mL), 15% NaOH (2 mL) and H_2O (6 mL); stirred 30 minutes at 0 ºC. Added 1 scoop of anhydrous $MgSO_4$. Warmed to room temperature. Filtered through sand/celite pad and concentrated under reduced pressure. Organic phase was washed with H_2O (100 mL), brine (100 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford alcohol **159** (6.6 g, 99% yield), viscous colorless oil. No further purification was necessary.

Alcohol 159. FTIR (thin film/NaCl): 3420, 3076, 2890, 1683, 1644, 1607, 1502, 1373, 1332, 1261, 1080, 936, 850, 757, 694, 664; ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.11 (d, *J* = 8.3 Hz, 1H), 6.63 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.60 (d, *J* = 2.4 Hz, 1H), 5.20 (s, 2H), 4.94 (s, 1H), 4.88 (t, *J* = 1.5 Hz, 1H), 3.83 (s, 3H), 3.76 (t, *J* = 8.3 Hz, 3H), 3.55 (d, *J* = 11.5 Hz, 1H), 3.37 (dd, *J* = 11.2, 3.1 Hz, 1H), 3.24 (dd, *J* = 11.2, 4.6 Hz, 1H), 2.11-2.00 (m, 1H), 1.72 (br s, 1H), 1.61 (s, 3H), 1.11 (d, *J* = 6.6 Hz, 3H), 0.96 (t, *J* = 8.4 Hz, 3H), 0.00 (s, 9H).

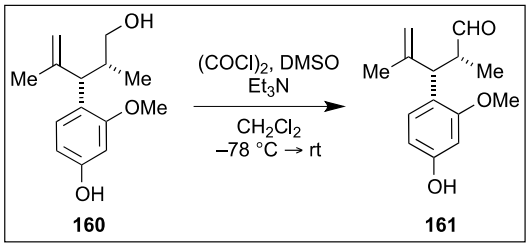
Preparation of phenol 160:



Phenol 160. To a stirred solution of alcohol **159** (6.1 g, 16.64 mmol) in tetrahydrofuran (117 mL) was added tetrabutylammonium fluoride (1M in THF, 117 mL, 116.50 mmol). Reaction was refluxed (65 ºC). Aliquots of the reaction were taken and analyzed by ^{1}H NMR to monitor progress. Quenched with saturated NH_4Cl (50 mL). Organic phase was washed with H_2O (50 mL), brine (50 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 20→30→20→50→100% EtOAc/Hex) to afford phenol **160** (2.5 g, 64% yield), viscous oil.

Phenol 160. FTIR (thin film/NaCl): 3322, 3054, 2965, 2723, 1721, 1644, 1596, 1505, 1465, 1373, 1265, 1197, 1108, 1034, 958, 894, 836, 737, 703; ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.05 (d, *J* = 8.2 Hz, 1H), 6.39 (d, *J* = 2.4 Hz, 1H), 6.37 (dd, *J* = 8.2, 2.4 Hz, 1H), 5.46 (s, 1H), 4.94 (s, 1H), 4.89 (t, *J* = 1.5 Hz, 1H), 3.79 (s, 3H), 3.52 (d, *J* = 11.5 Hz, 1H), 3.42-3.39 (dd, *J* = 11.1, 4.4 Hz, 1H), 3.27 (dd, *J* = 11.1, 4.4 Hz, 1H), 2.10-2.04 (m, 1H), 1.91 (br s, 1H), 1.60 (s, 3H), 1.11 (d, *J* = 6.6 Hz, 3H); ^{13}C-NMR (101 MHz; CDCl3): δ 158.2, 155.4, 146.4, 128.9, 122.6, 111.1, 107.8, 99.3, 66.9, 55.9, 46.0, 37.7, 22.2, 16.4; HRMS (EI) *m/z* 236.14099 [calc'd for $C_{14}H_{20}O_3$ (M+) 236.14124].

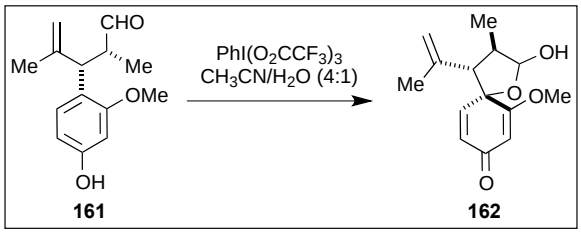
Preparation of aldehyde 161:



Aldehyde 161. To a solution of dimethylsulfoxide (1.5 mL, 21.16 mmol) in dichloromethane (80 mL) was added oxalyl chloride (0.9 mL, 10.58 mmol) at –78 ºC, drop wise, solution stirred for 20 minutes. A solution of alcohol **160** (1.25 g, 5.29 mmol) and triethylamine (3.69 mL, 26.45 mmol) in dichloromethane (20 mL) was added via cannula at –78 ºC. Reaction was stirred for 1 hour at –78 ºC and warmed to room temperature. TLC was used to monitor reaction progress. TLC plates were developed with 50% EtOAc/Hex solution and visualized by UV lamp and anisaldehyde stain. Reaction was quenched with saturated $NaHCO_3$ (100 mL). Organic phase was washed with H_2O (100 mL), brine (100 mL), dried over anhydrous MgSO4 and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 7→10→20→50→100% EtOAc/Hex) to afford aldehyde **161** (800 mg, 65% yield).

Aldehyde 161. FTIR (thin film/NaCl): 3853, 3733, 3583, 3412, 2925, 1716, 1646, 1614, 1596, 1559, 1540, 1506, 1465, 1456, 1434, 1374, 1294, 1197, 1158, 1120, 1036, 454, 426, 410; ^{1}H-NMR (300 MHz; $CDCl_3$): δ 9.35 (d, *J* = 3.6 Hz, 1H), 6.98 (d, *J* = 8.3 Hz, 1H), 6.37 (d, *J* = 2.5 Hz, 1H), 6.31 (dd, *J* = 8.3, 2.5 Hz, 1H), 5.08 (s, 1H), 4.92 (t, *J* = 0.8 Hz, 1H), 4.91 (t, *J* = 1.6 Hz, 1H), 3.88 (d, *J* = 10.9 Hz, 1H), 3.77 (s, 3H), 2.91 (dtt, *J* = 14.1, 6.9, 3.5 Hz, 1H), 1.61 (dd, *J* = 1.3, 0.8 Hz, 3H), 1.12 (d, *J* = 6.8 Hz, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ 205.1, 155.4, 146.3, 129.0, 120.5, 115.4, 111.8, 106.9, 98.9, 55.4, 48.7, 44.4, 22.3, 12.5; HRMS (EI) *m/z* 233.1183 [calc'd for $C_{14}H_{18}O_3$ (M-H)- 234.1256].

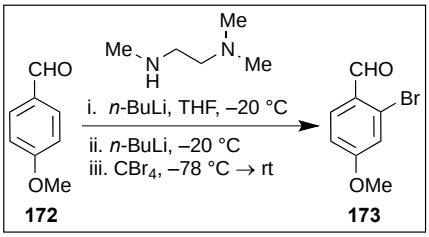
Preparation of spiro lactol 162:



Spiro lactol 162. To a stirred solution of [bis(trifluoroacetoxy)iodo]benzene (151 mg, 0.35 mmol) in acetonitrile (3 mL) and H_2O (1 mL) was added phenol **161** (55 mg, 0.23 mmol) as a solution in acetonitrile (1 mL) at room temperature. TLC was used to monitor reaction progress. TLC plates were developed with 50% EtOAc/Hex solution and visualized by UV lamp and anisaldehyde stain. Acetonitrile was removed under reduced pressure. Diluted with dichloromethane (5 mL). Organic phase was washed with H_2O (2 mL), brine (2 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 20→25→30→50→100% EtOAc/Hex) to afford spiro lactone **162** (30 mg, 52% yield, 1:1 dr) as white solid.

Spiro lactol 162. FTIR (thin film/NaCl): 3395, 2936, 1720, 1662, 1596, 1508, 1456, 1369, 1326, 1274, 1228, 1173, 1057, 973, 897, 856, 736; ^{1}H-NMR (400 MHz; $CDCl_3$): δ 6.72 (d, *J* = 10.1 Hz, 1H), 6.45 (d, *J* = 10.1 Hz, 1H), 6.04 (dd, *J* = 4.2, 1.7 Hz, 1H), 6.02 (dd, *J* = 4.2, 1.7 Hz, 1H), 5.59 (d, *J* = 1.6 Hz, 1H), 5.55 (d, *J* = 1.7 Hz, 1H), 5.43 (dd, *J* = 7.1, 4.7 Hz, 1H), 5.32 (d, *J* = 5.4 Hz, 1H), 4.95 (s, 1H), 4.92 (s, 1H), 4.72 (s, 1H), 4.70 (s, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.02 (app t, *J* = 12.5 Hz, 2H), 2.90 (d, *J* = 7.5 Hz, 1H), 2.55-2.46 (m, 1H), 2.39 (dquintet, *J* = 12.6, 6.4 Hz, 1H), 1.57 (s, 4H), 1.56 (s, 3H), 1.13 (d, *J* = 6.6 Hz, 3H), 1.07 (d, *J* = 6.6 Hz, 3H); HRMS (EI) *m/z* 250.1210 [calc'd for $C_{14}H_{18}O_4$ (M+) 250.1251].

Preparation of bromide 173:

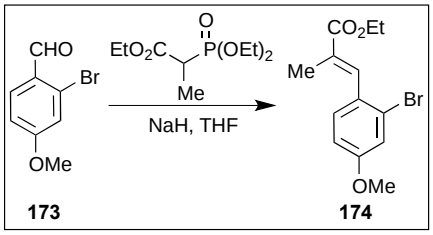


Aryl bromide 173. Following the procedure of Durst and Lear.[37] To a stirred solution of *N*,*N*,*N*′-trimethylethylenediamine (0.71 mL, 5.50 mmol) in tetrahydrofuran (12 mL) was added *n*-butyllithium (1.5 M, 3.3 mL, 5.00 mmol) at –20 ºC, stirred 20 minutes. *p*-Anisaldehyde (**172**) (0.61 mL, 5.00 mmol) was added at –20 ºC, stirred 20 minutes. *n*-Butyllithium (1.5 M, 10.0 mL, 15.00 mmol) at –20 ºC, stirred 45 minutes. Placed in fridge (–20 ºC) for 23 hours. Removed reaction solution from fridge and cooled to–78 ºC. Carbon tetrabromide (5.00 g, 15.00 mmol) was added as a solution in tetrahydrofuran (12 mL). Warmed to room temperature. TLC was utilized to monitor reaction progress. TLC plates were developed with 20% EtOAc/Hex solution and visualized by UV lamp and anisaldehyde stain. Quenched reaction with 10% HCl (25 mL) at 0 ºC, warmed to room temperature. Aqueous phase was extracted with diethyl ether (10 mL) three times. Organic phase was washed with saturated Na_2SO_3 (75 mL) three times, H_2O (100 mL), brine (100 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 5→7→10→20% EtOAc/Hex) to afford aryl bromide **173** (700 mg, 65% yield) as white solid.

Aryl bromide **173** is a known compound, the ^{1}H NMR spectra was obtained and structure was confirmed by comparison with spectra published in the literature.[37]

Aryl bromide 173. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 10.22 (s, 1H), 7.89 (d, *J* = 8.7 Hz, 1H), 7.14 (d, *J* = 2.4 Hz, 1H), 6.94 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.88 (s, 3H).

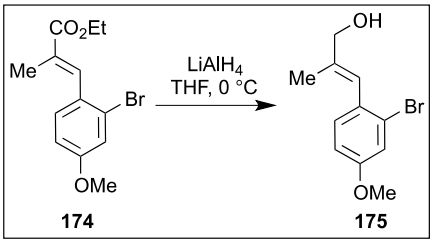
Preparation of α,β-unsaturated ester 174:



α,β-Unsaturated ester 174. To a stirred heterogeneous solution of sodium hydride (156 mg, 3.91 mmol) in tetrahydrofuran (12 mL) was added triethyl-2-phosphonopropionate (0.86 mL, 3.91 mmol) at 0 ºC. Aldehyde **173** (700 mg, 3.26 mmol) was added as a solution in tetrahydrofuran (10 mL) at 0 ºC. Reaction was warmed to room temperature and stirred over night. TLC was utilized to monitor reaction progress. TLC plates were developed with 10% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Reaction was diluted with ethyl acetate (20 mL) and quenched with saturated NH_4Cl solution (20 mL). Organic phase was washed with H_2O (20 mL), brine (20 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 5→7→10% EtOAc/Hex) to afford α,β-unsaturated ester **174** (975 mg, 72% yield, 10:1 E/Z) as colorless oil.

α,β-Unsaturated ester 174. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.68 (d, *J* = 1.5 Hz, 1H), 7.25 (d, *J* = 8.1 Hz, 1H), 7.17 (d, *J* = 2.6 Hz, 1H), 6.87 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 1.99 (d, *J* = 1.5 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H).

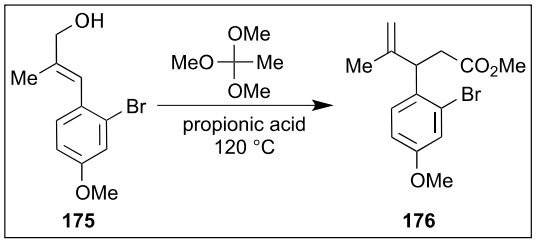
Preparation of allylic alcohol 175:



Allylic alcohol 175. To a stirred heterogeneous solution of lithium aluminum hydride (133 mg, 3.51 mmol) in tetrahydrofuran (11 mL) was added α,β-unsaturated ester **174** (700 mg, 2.34 mmol) as a solution in tetrahydrofuran (5 mL) at 0 ºC, upon complete addition the reaction was warmed to room temperature. TLC was utilized to monitor reaction progress. TLC plates were developed with 10% EtOAc/Hex solution and visualized by UV lamp and anisaldehyde stain. Reaction was quenched with H_2O (1 mL), 15% NaOH (1 mL), and H_2O (3 mL) at 0 ºC. Added 1 scoop of anhydrous $MgSO_4$ and warmed to room temperature. Filtered through celite/sand pad, rinsed with diethyl ether. Organic phase was washed with H_2O (40 mL), brine (40 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford allylic alcohol **175** (602 mg, quantitative yield) as colorless oil. No further purification was necessary.

Allylic alcohol 175. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.19 (d, *J* = 8.6 Hz, 1H), 7.14 (d, *J* = 2.6 Hz, 1H), 6.84 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.47 (br s, 1H), 4.22 (d, *J* = 6.2 Hz, 2H), 3.80 (s, 3H), 1.78 (d, *J* = 1.4 Hz, 3H), 1.53 (d, *J* = 6.3 Hz, 1H).

Preparation of γ,δ-unsaturated ester 176:

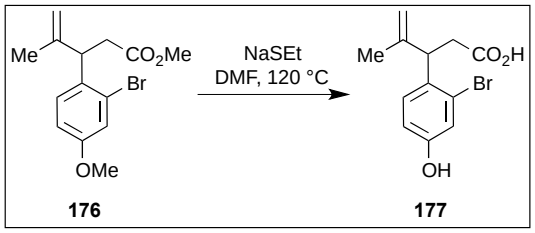


γ,δ-Unsaturated ester 176. A solution of allylic alcohol **175** (0.817 mg, 3.18 mmol) and propionic acid (0.15 mL) in trimethyl orthoacetate (35 mL) was heated to 120 °C and after 24 hours additional propionic acid (0.15 mL) was added and maintained at reflux for an additional 24 hours. All volatiles were removed under reduced pressure and the crude oil was purified with

silica gel chromatography (10% EtOAc/hexanes) to afford γ,δ-unsaturated ester **176** (0.660 g, 2.11 mmol, 66.3% yield) as colorless oil.

γ,δ-Unsaturated ester 176. FTIR (thin film/NaCl): 3083 (m), 2995 (s), 2950 (s), 2915 (s), 2838 (s), 1746 (s), 1649 (s), 1602 (s), 1565 (s), 1489 (s), 1436 (s), 1369 (s), 1374 (s), 1360 (s), 1335 (s), 1259 (s), 1158 (s), 1036 (s); ^{1}H-NMR (500 MHz; $CDCl_3$): δ 7.10 (d, *J* = 2.3 Hz, 1H), 7.10 (d, *J* = 8.7 Hz, 1H), 6.81 (dd, *J* = 8.7, 2.6 Hz, 1H), 4.93 (s, 1H), 4.86 (s, 1H), 4.25 (t, *J* = 7.8 Hz, 1H), 3.77 (s, 3H), 3.63 (s, 3H), 2.76 (dd, *J* = 15.5, 8.7 Hz, 1H), 2.67 (dd, *J* = 15.5, 7.0 Hz, 1H), 1.64 (s, 3H); ^{13}C-NMR (126 MHz; CDCl3): δ 172.14, 158.58, 145.95, 132.88, 128.52, 125.24, 117.94, 113.88, 110.86, 55.42, 51.62, 45.92, 38.63, 22.16; HRMS (EI) *m/z* 312.0354 [calc'd for $C_{14}H_{17}BrO_3$ (M+) 312.0361].

Preparation of carboxylic acid 177:

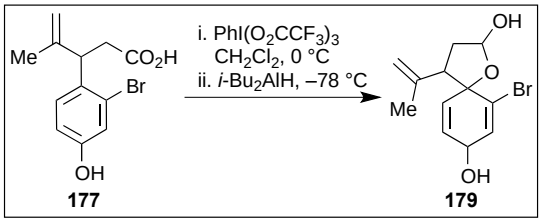


176 **177**

Carboxylic acid 177. To a stirred solution of γ,δ-unsaturated ester **176** (0.195 g, 0.623 mmol) in *N*,*N*-dimethylformamide (6.39 mL) was added a premixed solution of sodium ethanethiolate (0.142 mL, 1.92 mmol) and sodium hydride (0.0768 g, 60% w/w in mineral oil, 1.92 mmol) in *N*,*N*-dimethylformamide (1.92 mL). Reaction solution was heated to 100 °C and maintained overnight. Reaction was quenched with 10% HCl (20 mL) and diluted with ethyl acetate (20 mL). Phases were separated. Aqueous phase was washed with ethyl aceate (2 x 20 mL). Combined organic phase was dried over anhydrous $MgSO_4$ and concentrated reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 25→50% EtOAc/Hex) to afford carboxylic acid **177** (0.137 g, 0.480 mmol, 77.2%) as colorless oil.

Carboxylic acid 177. FTIR (thin film/NaCl): 3263 (br), 3085 (m), 2968 (m), 2937 (m), 1708 (s), 1648 (m), 1606 (s), 1584 (m), 1491 (s), 1432 (s), 1378 (m), 1252 (s), 1214 (s), 1029 (m); ^{1}H-NMR (500 MHz; $CDCl_3$): δ 7.07 (d, *J* = 2.6 Hz, 1H), 7.05 (d, *J* = 8.5 Hz, 1H), 6.73 (dd, *J* = 8.5, 2.6 Hz, 1H), 4.96 (s, 1H), 4.88 (s, 1H), 4.23 (t, *J* = 7.8 Hz, 1H), 2.78 (dd, *J* = 15.9, 8.8 Hz, 1H), 2.71 (dd, *J* = 15.9, 6.9 Hz, 1H), 1.65 (s, 3H); ^{13}C-NMR (126 MHz; CDCl3): δ 177.44, 154.76, 145.65, 132.75, 128.78, 125.21, 119.86, 115.05, 111.20, 45.72, 38.48, 22.22; HRMS (EI) *m/z* 284.0047 [calc'd for $C_{12}H_{13}BrO_3$ (M+) 284.0048].

Preparation of bisallylic alcohol 179:

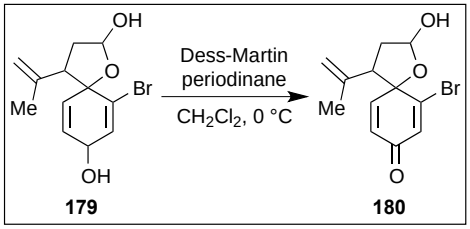


Bisallylic alcohol 179. To a stirred solution of carboxylic acid **177** (0.060 g, 0.210 mmol) in dichloromethane (5 mL) was added [bis(trifluoroacetoxy)iodo]benzene (0.104 g, 0.242 mmol) at 0 °C, approximately 10 minutes. TLC was utilized to monitor reaction progress. TLC plates were developed with 50% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain.

Reaction mixture was cooled to -78 °C and diisobutylaluminum hydride (1.05 mL, 1.0 M, 1.05 mmol) was added and maintained for 15 minutes at -78 °C. Reaction was quenched with saturated Rochelle's salt solution (10 mL) and stirred vigorously for 12 hours. Phases were separated and the aqueous phase was extracted with dichloromethane (2 x 5 mL). Combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (20% EtOAc/hexanes) to yield bisallylic alcohol **179** (0.029 g, 0.101 mmol, 48%) as a complex mixture of diastereomers, colorless oil.

Bisallylic alcohol 179. FTIR (thin film/NaCl): 3384 (br), 2923 (m), 2854 (m), 1672 (m), 1640 (m), 1447 (s), 1377 (s), 1349 (s), 1261 (s), 1241 (s), 1186 (s), 1128 (s), 1086 (s), 1044 (s), 1000 (s); ^{1}H-NMR (500 MHz; CDCl3): δ 6.60 (dd, *J* = 4.1, 1.9 Hz, 1H), 6.57 (dd, *J* = 3.6, 1.9 Hz, 1H), 6.55 (dd, *J* = 4.3, 1.8 Hz, 1H), 6.50 (dd, *J* = 3.6, 1.8 Hz, 1H), 6.09 (dd, *J* = 10.1, 0.8 Hz, 1H), 6.00-5.99 (m, 1H), 5.99-5.98 (m, 2H), 5.96 (dt, *J* = 3.4, 1.5 Hz, 2H), 5.95 (t, *J* = 1.6 Hz, 1H), 5.93 (dd, *J* = 3.1, 2.0 Hz, 1H), 5.75 (dd, *J* = 10.1, 1.0 Hz, 2H), 5.74-5.71 (m, 3H), 5.66 (dd, *J* = 10.0, 1.3 Hz, 2H), 5.59 (t, *J* = 4.8 Hz, 1H), 5.56 (t, *J* = 4.7 Hz, 2H), 4.94 (d, *J* = 0.9 Hz, 1H), 4.93 (d, *J* = 1.1 Hz, 1H), 4.86 (d, *J* = 1.1 Hz, 1H), 4.85 (d, *J* = 1.3 Hz, 2H), 4.79 (s, 1H), 4.78 (s, 1H), 4.76 (s, 1H), 4.74 (s, 2H), 4.52-4.46 (m, 2H), 4.41 (s, 3H), 3.63-3.61 (m, 1H), 3.59 (d, *J* = 6.4 Hz, 1H), 3.57 (d, *J* = 6.4 Hz, 1H), 3.54 (d, *J* = 5.8 Hz, 2H), 3.39 (dd, *J* = 13.0, 7.6 Hz, 1H), 3.35 (dd, *J* = 12.7, 7.3 Hz, 1H), 3.25 (d, *J* = 3.1 Hz, 1H), 3.17 (d, *J* = 4.4 Hz, 2H), 2.87-2.86 (m, 1H), 2.43 (dddd, *J* = 28.2, 13.1, 7.6, 5.4 Hz, 3H), 2.34 (d, *J* = 4.9 Hz, 1H), 2.31 (d, *J* = 4.4 Hz, 3H), 2.29 (s, 1H), 2.28 (s, 1H), 2.26 (s, 1H), 2.21 (d, *J* = 6.5 Hz, 1H), 2.18 (d, *J* = 6.4 Hz, 1H), 2.14 (d, *J* = 6.3 Hz, 1H), 2.12 (d, *J* = 6.3 Hz, 1H), 2.10 (d, *J* = 6.2 Hz, 1H), 2.07 (d, *J* = 6.3 Hz, 1H), 1.71 (s, 2H), 1.70 (s, 3H), 1.61 (s, 11H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.27, 140.52, 135.53, 135.38, 134.90, 134.71, 130.81, 130.08, 130.01, 129.43, 128.88, 128.28, 128.23, 128.04, 127.93, 127.86, 113.70, 113.25, 112.76, 110.00, 99.07, 98.75, 97.42, 97.09, 82.13, 81.65, 80.82, 77.20, 64.75, 64.66, 64.51, 64.43, 52.45, 51.92, 49.33, 49.04, 37.15, 36.87, 36.82, 36.71, 22.05, 22.03; HRMS (EI) *m/z* 269.0164 [calc'd for $C_{12}H_{13}BrO_2$ [$C_{12}H_{15}BrO_3$(–H_2O)] (M+H)+ 268.009].

Preparation of dienone 180:

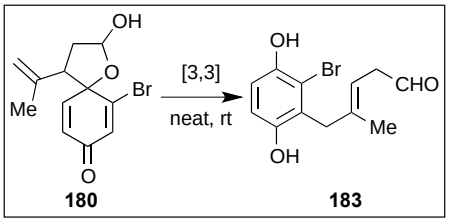


179 180

Dienone 180. To a stirred solution of bisallylic alcohol **179** (0.019 g, 0.0662 mmol) in dichloromethane (3 mL) was added Dess-Martin reagent (0.0337 g, 0.0794 mmol) at 0 °C. Reaction progress was monitored by TLC. TLC plates were developed with 20% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. After approximately 10 minutes saturated $NaHCO_3$ solution (5 mL) was added. Reaction mixture extracted with diethyl ether (3 x 5 mL). Combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (10% EtOAc/Hex) to afford dienone **180** (0.016 g, 84% yield) as an inseparable mixture of diastereomers and colorless oil.

Dienone 180. FTIR (thin film/NaCl): 3385 (br), 2924 (m), 2852 (m), 1718 (m), 1671 (m), 1649 (s), 1623 (m), 1598 (m), 1490 (m), 1437 (s), 1380 (m), 1299 (s), 1262 (m), 1176 (s), 1117 (m), 1097 (m), 1058 (m), 1012 (s); ^{1}H-NMR (500 MHz; $CDCl_3$): δ 7.13 (d, *J* = 10.2 Hz, 1H), 6.74 (d, *J* = 10.0 Hz, 2H), 6.17 (dd, *J* = 14.8, 10.5 Hz, 2H), 5.88 (t, *J* = 4.7 Hz, 1H), 5.73 (s, 1H), 4.91 (d, *J* = 7.3 Hz, 3H), 4.84 (s, 1H), 4.79 (s, 1H), 3.72 (dd, *J* = 13.5, 6.2 Hz, 1H), 3.47 (t, *J* = 9.9 Hz, 1H), 3.34-3.22 (m, 2H), 2.95 (s, 1H), 2.57 (dt, *J* = 13.4, 6.6 Hz, 1H), 2.44 (td, *J* = 13.1, 4.7 Hz, 2H), 2.31 (td, *J* = 12.8, 5.9 Hz, 1H), 2.24 (dd, *J* = 13.0, 6.2 Hz, 2H), 1.62 (s, 7H), 1.25 (d, *J* = 0.4 Hz, 1H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 199.56, 183.25, 183.15, 150.60, 150.48, 147.81, 146.79, 146.61, 138.85, 138.66, 138.37, 134.57, 134.12, 126.79, 126.72, 125.28, 116.64, 114.87, 114.82, 114.31, 114.21, 113.88, 99.91, 98.42, 83.64, 54.42, 51.65, 43.11, 40.25, 37.40, 37.20, 22.07, 22.01, 16.69; HRMS (EI) *m/z* 267.0015 [calc'd for $C_{12}H_{11}BrO_2$ [$C_{12}H_{13}BrO_3$(–H_2O)] (M+H)+ 265.9941]. Note dienone **180** is contaminated with aldehyde **183**.

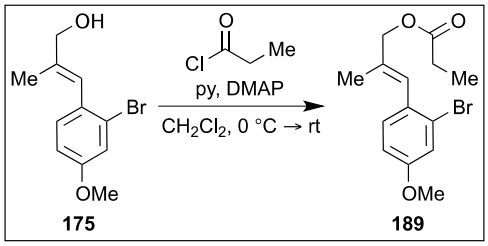
Preparation of aldehyde 183:



Aldehyde 183. It was observed that dienone **180** undergoes facile [3,3]-sigmatropic rearrangement at room temperature to afford aldehyde **183** (quantitative).

Aldehyde 183. FTIR (thin film/NaCl): 3385 (br), 2924 (m), 2853 (m), 1710 (s), 1664 (m), 1589 (m), 1488 (s), 1436 (s), 1176 (s), 1078 (m), 1023 (m); ^{1}H-NMR (500 MHz; $CDCl_3$): δ 9.64 (s, 1H), 6.86 (d, *J* = 8.7 Hz, 1H), 6.77 (d, *J* = 8.7 Hz, 1H), 5.32 (t, *J* = 7.3 Hz, 1H), 5.25 (s, 1H), 4.99 (s, 1H), 3.64 (s, 2H), 3.19 (d, *J* = 6.8 Hz, 2H), 1.69 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.47, 148.53, 146.81, 138.37, 125.26, 116.69, 114.91, 114.33, 43.11, 40.32, 16.67; HRMS (EI) *m/z* 282.9975 [calc'd for $C_{12}H_{13}BrO_3$ (M-H)- 284.0047].

Preparation of allylic ester 189:

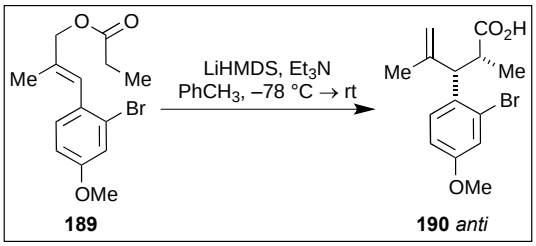


Allylic ester 189. To a stirred solution of allylic alcohol **175** (602 mg, 2.34 mmol), 4-(dimethylamino)pyridine (28 mg, 0.23 mmol), pyridine (0.18 mL, 3.51 mmol) in dichloromethane (16 mL) was added propionyl chloride (0.42 mL, 4.68 mmol) at 0 ºC. Reaction was warmed to room temperature. TLC was used to monitor reaction progress. TLC plates were developed with 20% EtOAc/Hex solution and visualized by UV lamp and anisaldehyde stain. Reaction was quenched with 1M HCl (20 mL). Organic phase was washed with saturated

$NaHCO_3$ solution (20 mL) two times, H_2O (50 mL), brine (50 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 7→10→20% EtOAc/Hex) to afford allylic ester **189** (700 mg, 95% yield) as yellow oil.

Allylic ester 189. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.19 (d, *J* = 8.6 Hz, 1H), 7.14 (d, *J* = 2.6 Hz, 1H), 6.84 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.47 (br s, 1H), 4.67 (d, *J* = 1.0 Hz, 2H), 3.80 (s, 4H), 2.42 (q, *J* = 7.6 Hz, 2H), 1.77 (d, *J* = 1.4 Hz, 3H), 1.19 (t, *J* = 7.6 Hz, 3H).

Preparation of γ,δ-unsaturated carboxylic acid 190:



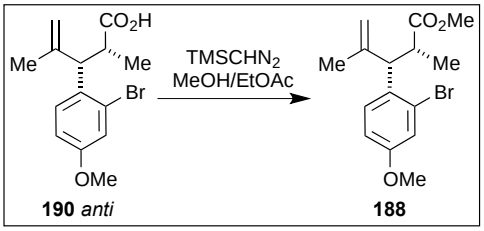
189 **190** *anti*

γ,δ-Unsaturated carboxylic acid 190. Following the procedure of Collum *et al*.[21] A solution of lithium bis(trimethylsilyl)amide (1.2 g, 7.02 mmol) and triethylamine (9.3 mL, 70.2 mmol) in toluene (30 mL) was stirred for 15 minutes at room temperature; followed by cooling to –78 ºC. A precooled solution of allylic ester **189** (733 mg, 2.34 mmol) in toluene (10 mL) was added over 1 hour to the reaction solution at –78 ºC, upon complete addition reaction solution was stirred for 15 minutes at –78 ºC prior to warming to 30 ºC and stirred for 12 hours. TLC was utilized to monitor reaction progress. TLC plates were developed with 20% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Reaction was basified with 15% NaOH (25 mL). Extracted basified reaction solution with diethyl ether (25 mL) two times. Concentrated HCl was added to the aqueous phase, until pH = 3 at 0 ºC. Extracted acidified aqueous phase with diethyl ether (25 mL) three times. Combined organic phase was washed with H_2O (50 mL), brine (50

mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to yield γ,δ-unsaturated carboxylic acids **190** (411 mg, 56% yield, 10:1 dr) as orange foam. No further purification required.

γ,δ-Unsaturated carboxylic acid 190. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 11.00 (br s, 1H), 7.19 (d, *J* = 8.7 Hz, 1H), 7.09 (d, *J* = 2.7 Hz, 1H), 6.81 (dd, *J* = 8.7, 2.7 Hz, 1H), 5.07 (d, *J* = 0.6 Hz, 1H), 4.92 (t, *J* = 1.5 Hz, 1H), 4.01 (d, *J* = 11.3 Hz, 1H), 3.77 (s, 3H), 3.04 (dq, *J* = 11.3, 6.8 Hz, 1H), 2.07 (s, 2H), 1.56 (s, 3H), 1.27 (d, *J* = 6.9 Hz, 3H).

Preparation of methyl ester 188:



190 *anti* **188**

Methyl ester 188. To a stirred solution of carboxylic acid **190** (500 mg, 1.6 mmol) in methanol (11 mL) and ethyl acetate (4 mL) was added (trimethylsilyl)diazomethane (0.96 mL, 1.20 mmol) at room temperature. TLC was used to monitor reaction progress. TLC plates were developed with 20% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Reaction was quenched with 3M acetic acid solution in ethyl acetate (15 mL). Solution was concentrated under reduced pressure to afford methyl ester **188** (556 mg, quantitative yield) as orange oil. No further purification was necessary.

Methyl ester 188. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.18 (d, *J* = 8.7 Hz, 1H), 7.08 (d, *J* = 2.7 Hz, 1H), 6.81 (dd, *J* = 8.8, 2.7 Hz, 1H), 5.07 (d, *J* = 0.8 Hz, 1H), 4.91 (t, *J* = 1.5 Hz, 1H), 4.03 (d, *J* = 11.4 Hz, 1H), 3.76 (s, 3H), 3.45 (s, 3H), 3.06 (dq, *J* = 11.4, 6.8 Hz, 1H), 1.59 (t, *J* = 0.7 Hz, 3H), 1.25 (d, *J* = 6.8 Hz, 3H).

References Relevant to Chapter 2

(17) von Hirschheydt, T.; Voss, E. *Synthesis* **2004**, 2062.

(18) Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939.

(19) Pereira, S., Srebnik, M. *Aldrichimica Acta* **1993**, *26*, 17.

(20) Daub, G. W.; Edwards, J. P.; Okada, C. R.; Allen, J. W.; Maxey, C. T.; Wells, M. S.; Goldstein, A. S.; Dibley, M. J.; Wang, C. J.; Ostercamp, D. P.; Chung, S.; Cunningham, P. S.; Berliner, M. A. *J. Org. Chem.* **1997**, *62*, 1976.

(21) Godenschwager, P. F.; Collum, D. B. *J. Am. Chem. Soc.* **2008**, *130*, 8726.

(22) Ireland, R. E.; Wipf, P.; Armstrong, J. D. *J. Org. Chem.* **1991**, *56*, 650.

(23) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927.

(24) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231.

(25) Seebach, D. *Angew. Chem. Int. Ed.* **1979**, *18*, 239.

(26) Stetter, H. *Angew. Chem. Int. Ed.* **1976**, *15*, 639.

(27) Kerr, M. S.; de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298.

(28) Kerr, M. S.; Rovis, T. *Synlett* **2003**, 1934.

(29) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876.

(30) Reynolds, N. T.; Rovis, T. *Tetrahedron* **2005**, *61*, 6368.

(31) Moore, J. L.; Keff, M. S.; Rovis, T. *Tetrahedron* **2006**, *62*, 11477.

(32) Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2552.

(33) Liu, Q.; Rovis, T. *Org. Process. Res. Dev.* **2007**, *11*, 598.

(34) Comins, D. L. *Synlett* **1992**, 615.

(35) Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1984**, *49*, 1078.

(36) Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1987**, *52*, 104.

(37) Lear, Y.; Durst, T. *Can. J. Chem.* **1997**, *75*, 817.

(38) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

(39) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

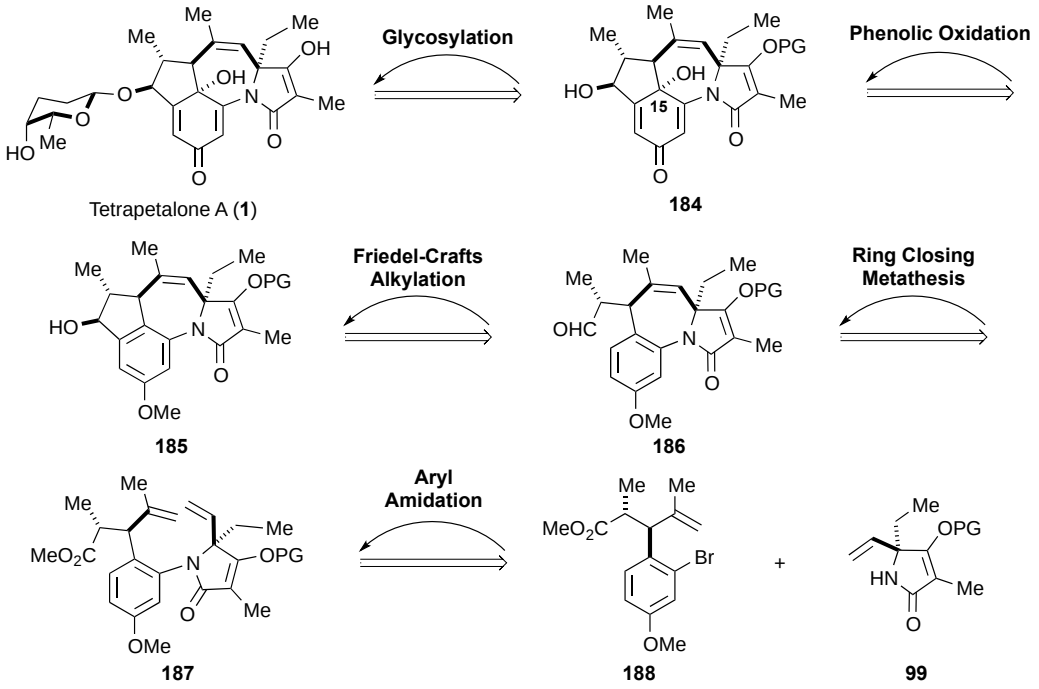
(40) Black, T. H. *Aldrichimica Acta* **1983**, *16*, 3.

Chapter 3

Synthesis of a Tetramic Acid

3.1 Second-Generation Retrosynthetic Analysis

As outlined in Scheme 3.1 our second-generation retrosynthetic analysis of tetrapetalone A (1) envisaged completion of the natural product via glycosylation of aglycon **184** followed by subsequent deprotection of the tetramic acid moiety. Aglycon **184** was envisioned as deriving from phenolic oxidation applied to tetracycle **185**, a compound seen arising from diene **187** via a ring closing metathesis and subsequent Friedel-Crafts alkylation. Diene **187** would be assembled in a convergent manner by amidation of aryl bromide **188** with protected tetramic acid **99**. Having successfully established a synthetic route to aryl bromide **188**, our primary objective became the synthesis of protected tetramic acid **99**. To this end, we began our efforts by developing a synthesis of protected tetramic acid **99**.



Scheme 3.1 Second-Generation Retrosynthetic Analysis of Tetrapetalone A

3.2 Tetramic Acid Introduction

3.2.1 Naturally Occurring Tetramic Acids

The tetramic acid (2,4-pyrrolidinedione) ring system **191** has been known since the early twentieth century when the first simple derivatives were prepared.[41,42] It was not until the 1960s that this heterocycle was found to be a key structural unit in many natural products (Figure 3.1). Pyrrolidine-2,4-diones bearing an acyl substituent at C-3 (i.e. **192–193**) are the most commonly found tetramic acid derivatives in nature; *N*-acyl-4-methoxy-3-pyrrolin-2-ones, in other words the 4-*O*-methyl ethers of *N*-acylated tetramic acids have also been isolated (i.e. **194**–**195**). Naturally occurring tetramic acids have attracted a great deal of interest because the majority of the compounds isolated exhibit some biological function – usually antibiotic or antiviral activity.

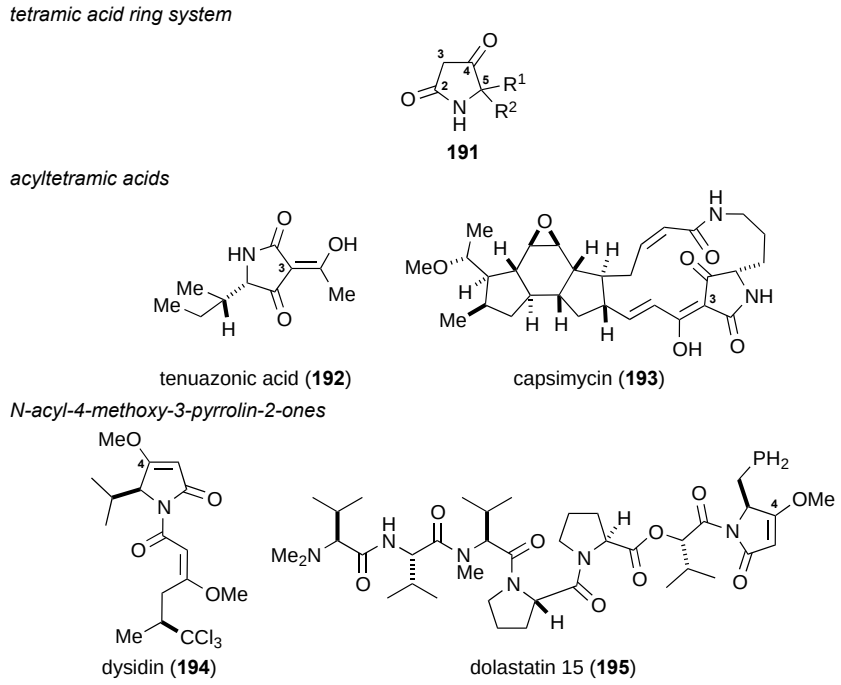


Figure 3.1 Representative Natural Products Containing a Tetramic Acid Moiety

3.2.2 Structure of the Tetramic Acid Ring

Tetramic acid (**196**) was synthesized for the first time by Mulholland and coworkers in 1972;[43] earlier attempts[44,45] were later shown to have resulted only in the formation of the isomer 2-iminotetronic acid (**198**) (Figure 3.2).[46,47] Tetramic acid (**196**) is a much weaker acid (with a pK_a = 6.4 in aqueous solution) than its oxygen analog, tetronic acid (**201**) (with a pK_a = 3.76 in aqueous solution); consequently tetramic acid (**196**) is not highly enolizable and exists primarily as the 2,4-diketo tautomer (**196)**. Tetramic acids bearing acyl (i.e. **199**), or alkoxycarbonyl (i.e. **200**) substituents at C-3 have similar acidity to the tetronic acids. The former have pK_a values in the range of 3.0–3.5 while the latter have values between 2.3 and 2.5.

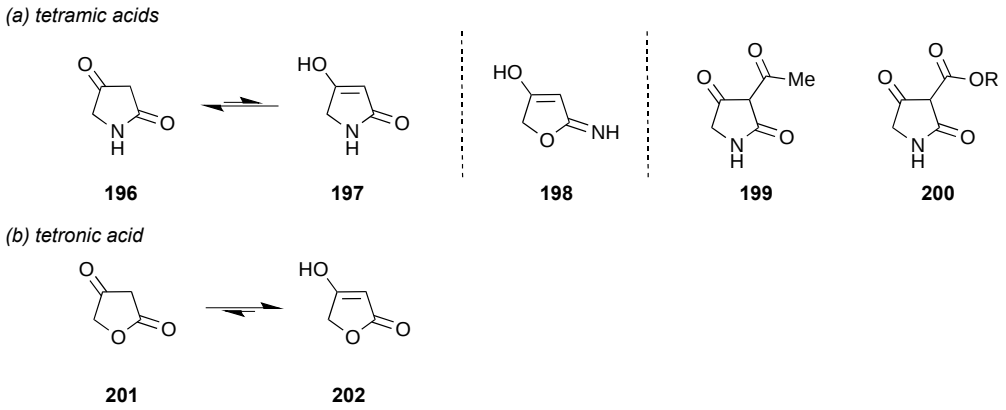
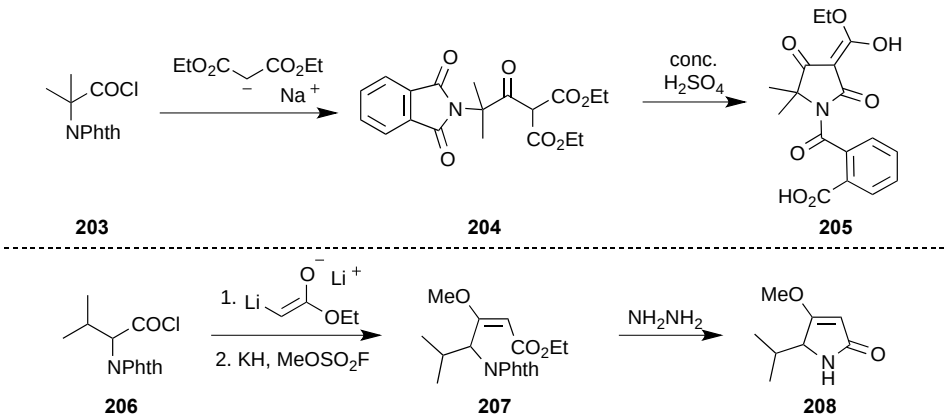


Figure 3.2 Structure of Tetramic Acids and Tetronic Acid

3.2.3 Synthetic Strategies for Construction of Tetramic Acid Derivatives

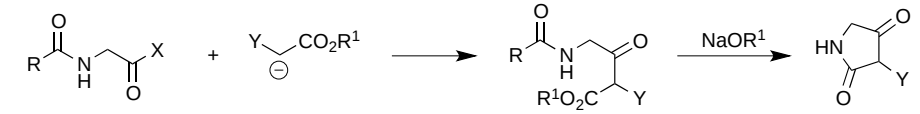
3.2.3.1 Ring Closure by C–N Bond Formation

Gabriel achieved the first reliable synthesis of a tetramic acid derivative in 1941.[41,48,49] In this work he demonstrated that phthalimidoisobutyryl chloride (**203**) with diethyl sodium malonate gave **204**, which upon treatment with concentrated sulfuric acid cyclized to the ethoxycarbonyl tetramic acid **205**. Williard and Laszlo applied similar methodology to the synthesis of dysidin (**194**),[50] wherein the acid chloride of *N*-phthaloylvaline (**206**) was homologated to the intermediate β-ketoester with the dilithium dianion of monoethyl malonate subsequent *O*-methylation afforded **207**. Exposure to hydrazine resulted in cyclization affording *O*-methyltetramic acid **208**.



Scheme 3.2 *N*-Phthalalkylamine Acid Chloride Route

Hippuric and aceturic acid derivatives have been shown by Sandris and coworkers to be versatile building blocks for the synthesis of substituted tetramic acids.[41,51,52] Reaction of a hippuric/aceturic acid derivative **209** with the anion of an active methylene compound **210** provides the corresponding acetyl derivative **211**. Cyclization was performed with excess sodium alkoxide and was observed to proceed with simultaneous deprotection of the amide nitrogen to afford the substituted tetramic acid **212**.

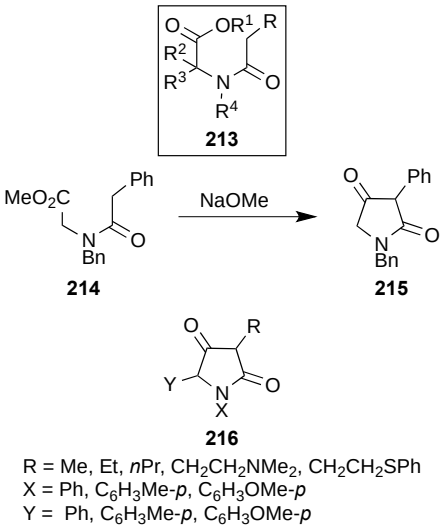


Scheme 3.3 Hippuric and Aceturic Acid Derivatives

3.2.3.2 Dieckmann Cyclization

The base induced Dieckmann cyclization of *N*-acyl-α-amino esters (i.e. **213**), offers a convenient route to tetramic acid rings, which is potentially very versatile in terms of the possible substitution patterns available. The synthesis of 1-benzyl-2-phenyltetramic acid **215** by treatment of **214** with sodium methoxide was reported in 1950 by King and McMillan.[41,53]

Shortly after a series of 3-alkyl-1,5-diaryltetramic acids **216** were reported in a cognate manner.[41]



Scheme 3.4 Dieckmann Cyclization Method for Tetramic Acid Synthesis

3.2.4 Reactions of the Tetramic Acid Ring

Reactions of the tetramic acid ring (**191**) itself can be summarized as follows (Figure 3.3): (a) reaction with electrophilic species (e.g. aldehydes, bromine or nitrating agents) at C-3, (b) with nucleophilic species (e.g. hydrazine) at C-4, (c) acylation at O-4 or, under certain conditions, C-3, and (d) with organometallic bases (e.g. *n*-butyllithium) metalation occurs at C-3.[54]

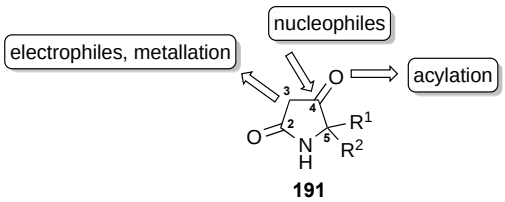
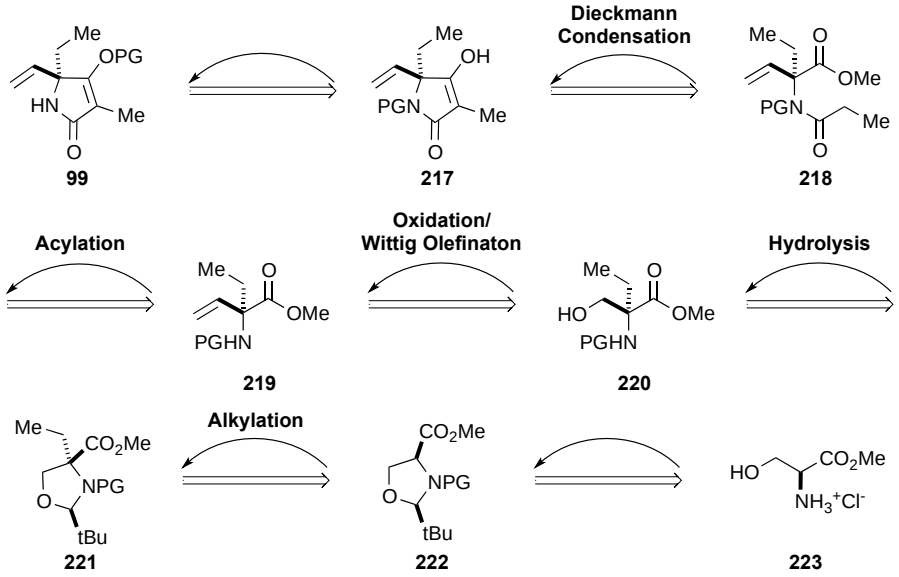


Figure 3.3 Reactions of the Tetramic Acid Ring

3.3 Retrosynthetic Analysis of Tetramic Acid Coupling Partner

Synthesis of protected tetramic acid **99** would be completed with a Dieckmann cyclization of *N*-acyl-α-amino ester **218** followed by protection of the vinylogous acid moiety and deprotection of the amide. Dieckmann cyclization precursor **218** would be produced via acylation of α-amino ester **219**, derived from oxidation and Wittig olefination of the amino alcohol **220**. The requisite serine derivative **220** would be prepared via alkylation and subsequent hydrolysis of oxazolidine **222**, derived from serine methyl ester hydrochloride (**223**).



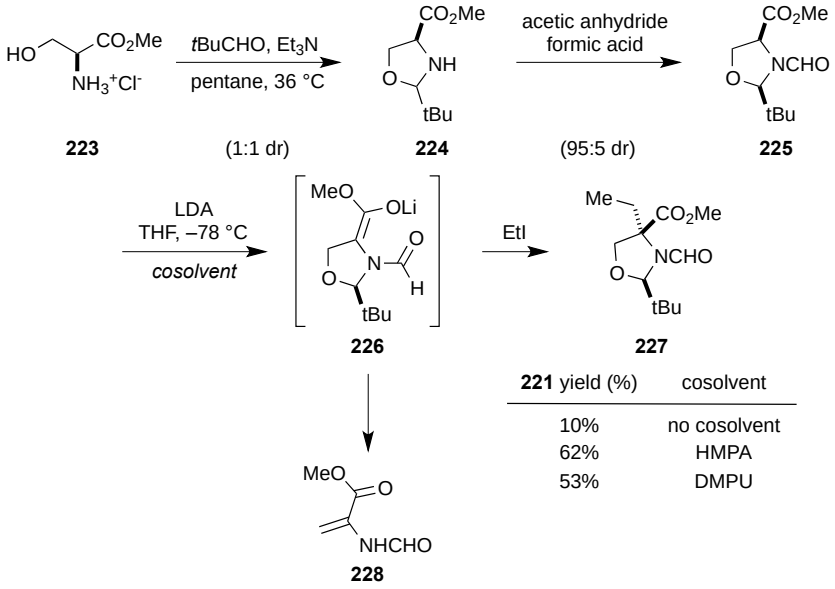
Scheme 3.5 Retrosynthetic Analysis of Tetramic Acid Coupling Partner

3.4 Benzyl Protected Amide Series

3.4.1 α-Vinyl, α-Alkyl Quaternary α-Amino Ester Synthesis

In 1984, Seebach and Aebi disclosed a method for the α-alkylation of serine with self-reproduction of the center of chirality (Scheme 3.6).[55] It was realized that serine methyl ester hydrochloride (**223**) furnishes the oxazolidine **224** as a mixture of diastereomers (1:1 dr) when heated with pivalaldehyde and triethylamine in pentane, with continuous removal of water. Formylation of oxazolidine **224** affords the *N*-formyl heterocycles in a diastereomeric ratio of

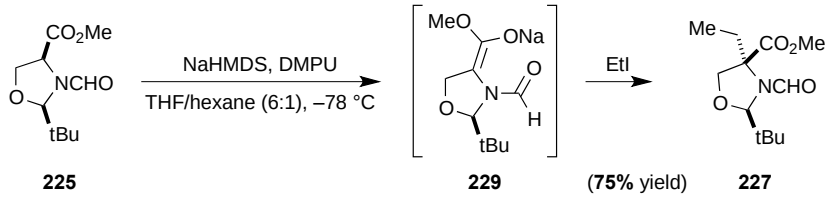
95:5; the major *cis* diastereomer **225** can be obtained in pure form by recrystallization. Alkylation of lithium enolate **226** proceeds with 1,3-asymmetric induction to afford **227**, as a single diastereomer but in low yield even when lithium-coordinating cosolvents were employed. The poor yield of alkylated product is primarily due to a concurrent elimination reaction of the enolate leading to the deprotected α,β-unsaturated ester **228**.



221 yield (%)	cosolvent
10%	no cosolvent
62%	HMPA
53%	DMPU

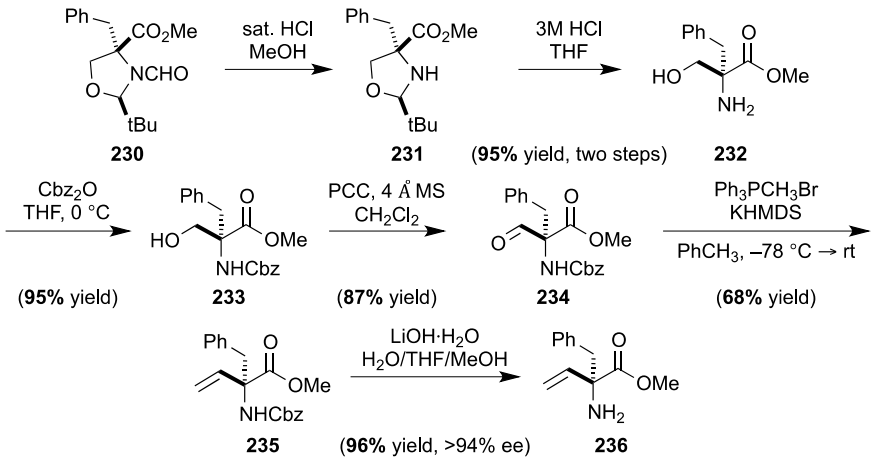
Scheme 3.6 Seebach's α-Alkylation of Serine

Colombo and coworkers were able to improve Seebach's alkylation protocol (Scheme 3.6), increasing the yield of α-alkylation product **227** by employing sodium bis(trimethylsilyl)amide to generate enolate **229** (Scheme 3.7).[56] The sodium counterion of the enolate **229** promotes formation of less tight ion-pairs, making the enolate more reactive toward electrophiles.



Scheme 3.7 Colombo's Modification an Improved α-Alkylation of Serine

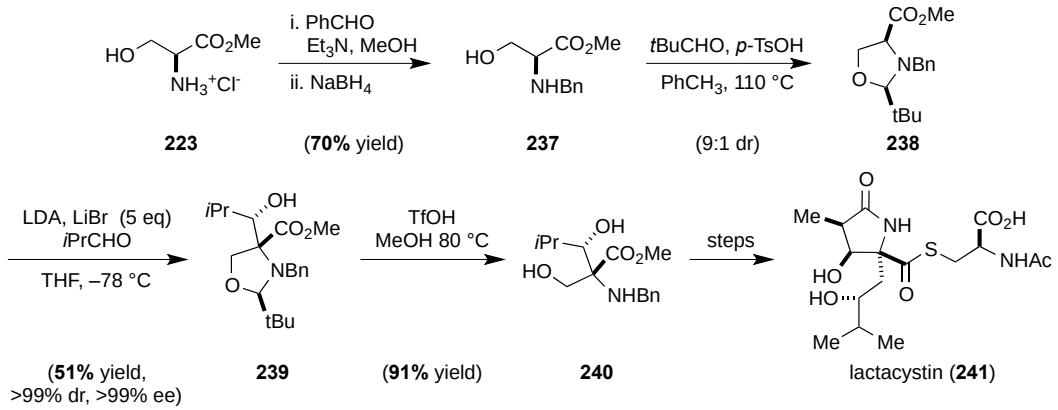
In the same report, Colombo and coworkers disclosed a practical synthetic method for the enantioselective synthesis of α-vinyl, α-alkyl, quaternary α-amino acids (Scheme 3.8).[56] Alkylation product **230** was advanced to amino alcohol **232** via deformylation and hydrolysis of oxazolidine **231**. The synthetic route required primary amine **232** to be protected as benzyloxycarbamate **233**. Pyridinium chlorochromate mediated oxidation of alcohol **233** provided aldehyde **234**, exposure to Wittig olefination conditions afforded alkene **235**, subsequent hydrolysis of the benzyloxycarbamate **235** afforded the desired α-vinyl α-benzyl quaternary α-amino acid **236** in excellent yield and >94% enantiomeric excess.



Scheme 3.8 Enantioselective Synthesis of α-Vinyl, α-Alkyl Quaternary α-Amino Acids

In 1992, Corey and Reichard utilized an aldol reaction with the *N*-benzylserine derived oxazolidine **238** en route to the synthesis of lactacystin (**241**).[57] Reductive amination of serine methyl ester hydrochloride (**223**) with benzaldehyde afforded *N*-benzylserine **237**[58] which upon

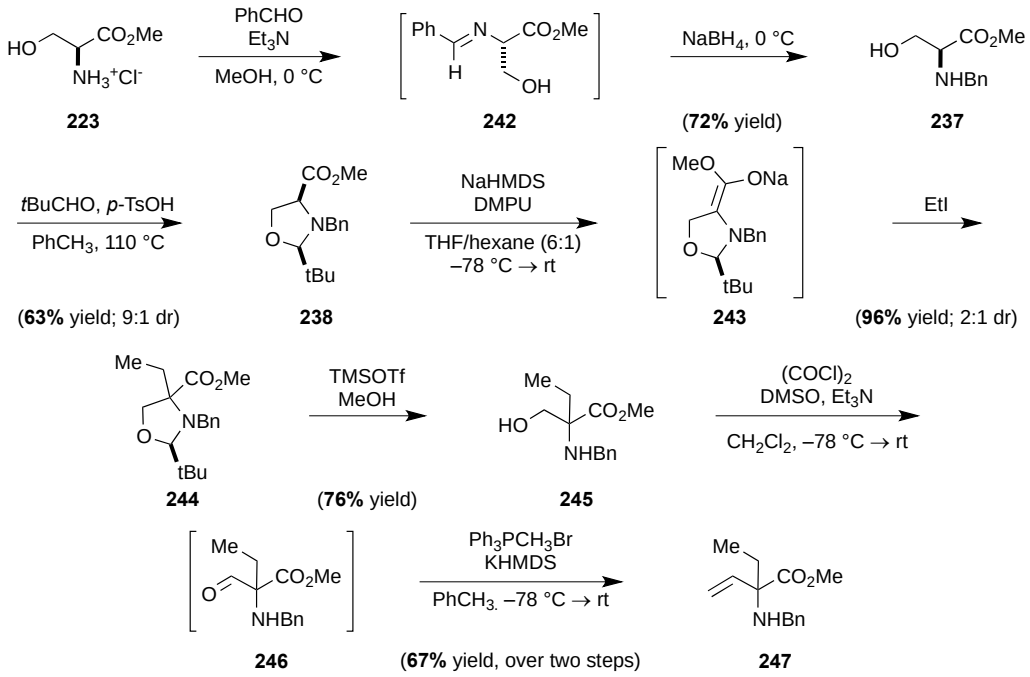
exposure to pivalaldehyde in the presence *para*-toluenesulfonic acid in toluene, with continuous removal of water, provided oxazolidine **238**, as a 9:1 mixture of diastereomers. The 9:1 mixture was converted via the lithium enolate-lithium bromide complex with isobutyraldehyde to aldol product **239**, which was obtained in 77% yield and >98% diastereomeric purity; recrystallization from pentane afforded diastereo- and enantiomerically pure **239** in 51% yield. Aminal cleavage was achieved upon exposure to trifluoromethanesulfonic acid in methanol affording amino alcohol **240** in excellent yield (91%).



Scheme 3.9 Corey's *N*-Benzylserine Derived Oxazolidine

Adopting Corey's 1,3-oxazolidine **238** (Scheme 3.10) as the chiral template in our studies, we focused our synthetic endeavors on the preparation of the requisite α-vinyl, α-ethyl, quaternary α-amino ester **247**. Following the procedure of Thompson and coworkers,[58] reductive amination of benzaldehyde with serine methyl ester hydrochloride **223** afforded *N*-benzyl serine methyl ester **237**. Employing the protocol developed by Seebach and coworkers,[59,60] condensation with pivalaldehyde in the presence of catalytic *para*-toluenesulfonic acid at toluene reflux, with continuous removal of water, afforded the desired *N*-benzyl 1,3-oxazolidine **238** in modest yield (63%), as a 9:1 mixture of diastereomers. The 9:1 mixture of diastereomers was carried on through the α-alkylation conditions developed by Colombo and coworkers.[56]

Alkylation of *N*-benzyl 1,3-oxazolidine **238** with iodoethane proceeded in excellent yield (96%) unfortunately; we observed an erosion in the diastereomeric ratio upon alkylation, realizing a 2:1 mixture of diastereomers. The resulting diastereomers proved difficult to separate by silica gel chromatography and thus, the material was carried forward as a mixture of diastereomers. *N*-Benzyl α-ethyl 1,3-oxazolidine **244** engaged in methanolysis upon treatment with trimethylsilyl trifluoromethanesulfonate in methanol to reveal amino alcohol **245** in good yield (67%), Swern oxidation provided aldehyde **246** which was immediately carried directly into Wittig olefination affording the desired α-vinyl amino ester **247** in modest yield (67%), over two steps.

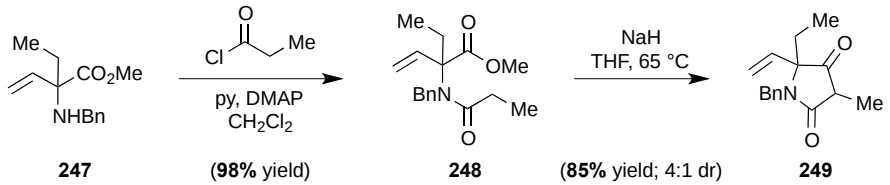


Scheme 3.10 Synthesis of α-Vinyl, α-Alkyl Quaternary *N*-Benzyl α-Amino Ester

3.4.2 Dieckmann Cyclization

With methyl ester **247** on hand we were excited to investigate the key Dieckmann cyclization to afford *N*-benzyl tetramic acid **249**. To this end, acylation with propionyl chloride afforded amide **248**. Gratifyingly, amide **248** engaged in the desired cyclization upon exposure

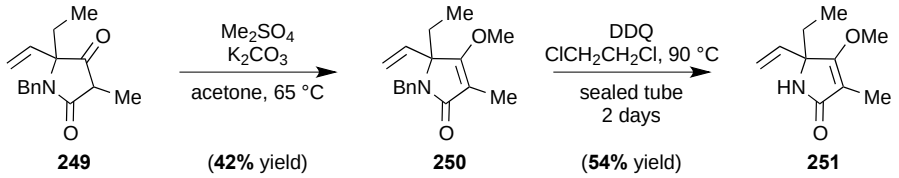
to sodium hydride in refluxing tetrahydrofuran to provide *N*-benzyl tetramic acid **249** in excellent yield (85%), as a 4:1 mixture of diastereomers.



Scheme 3.11 Dieckmann Cyclization

3.4.3 Unveiling of the Amide via Cleavage of the Benzyl Protecting Group

Prior to investigating an amidation strategy (i.e. Scheme 3.1) we decided to protect the tetramic acid moiety as the vinylogous ester, predicting that elimination of the acidic proton would prove beneficial. *O*-Methylation of tetramic acid **249** was achieved upon treatment with potassium carbonate and dimethyl sulfate in refluxing acetone providing vinylogous ester **250** in low yield (42%). Cleavage of the benzyl amide proved to be more difficult then predicted and upon surveying oxidative cleavage conditions we were delighted to realize that exposure of benzyl amide **250** to excess 2,3-dichloro-5,6-dicyano-*p*-benzoquinone in 1,2-dichloroethane at 90 °C, in a sealed tube, after two days afforded the desired tetramic acid **251** in moderate yield (54%). Attempts to optimize the amide deprotection were not fruitful and although the mass balance of the reaction was starting material we opted to investigate alternate protecting groups for the amide nitrogen. Specifically, we choose to replace the benzyl with the more electron rich *para*-methoxybenzyl, as in theory it should be applicable with all the same chemistry, and more facially cleaved under oxidative conditions

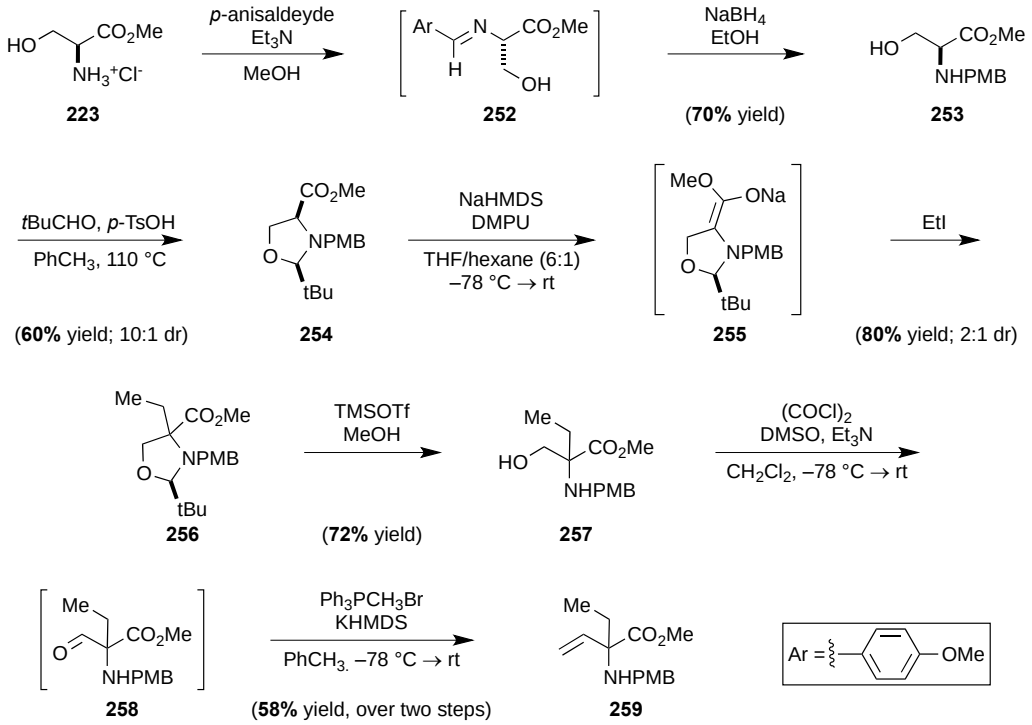


Scheme 3.12 *O*-Alkylation and Benzyl Amide Cleavage

3.5 *para*-Methoxybenzyl Protected Amide Series

3.5.1 α-Vinyl, α-Alkyl Quaternary α-Amino Ester Synthesis

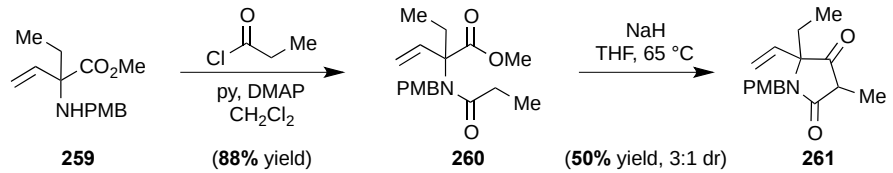
In a manner analogous to that of the *N*-benzyl amide series (i.e. Scheme 3.10) we prepared the desired *N-para*-methoxybenzyl α-amino methyl ester **259**. Reductive amination was conducted in a scalable two-step one pot procedure; condensation of L-serine methyl ester hydrochloride (**223**) with *para*-anisaldehyde in the presence of triethylamine in methanol subsequent concentration under reduced pressure provided imine **252**, which was suspended in ethanol and exposed to sodium borohydride to afford the desired *N-para*-methoxybenzyl serine methyl ester **253** in good yield (70%). Following the protocol developed by Seebach and coworkers,[59] *N-para*-methoxybenzyl serine methyl ester was condensed onto pivalaldehyde upon exposure to catalytic *para*-toluenesulfonic acid at toluene reflux, with continuous removal of water, to yield 1,3-oxazolidine **254** in modest yield (60%), as a 10:1 mixture of diastereomers, in preference of the thermodynamically more stable *cis* isomer. Oxazolidine **254** was carried on as the mixture, employing the α-alkylation conditions developed by Colombo and coworkers.[56] Enolization with sodium bis(trimethylsilyl)amide in the presence of iodoethane furnished α-ethyl 1,3-oxazolidene **256** in excellent yield (80%), albeit with poor diastereoselectivity (2:1 dr). Amino alcohol **257** was accessed via methanolysis and engaged in Swern oxidation to afford aldehyde **258**, which was immediately subjected to Wittig olefination to provide the desired α-vinyl, α-amino ester **259** in good yield (42%) over three steps.



Scheme 3.13 Synthesis of α-Vinyl, α-Ethyl, α-Amino Ester

3.5.2 Dieckmann Cyclization

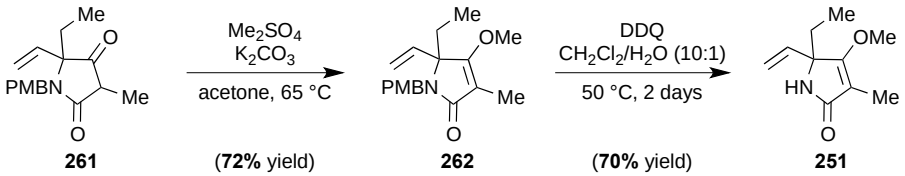
With amine **252** in hand we were enthusiastic to investigate the Dieckmann cyclization. To this end, amine **259** was acylated upon exposure to propionyl chloride providing the requisite amide **260**. We were delighted to find that indeed amide **260** engaged in the desired cyclization to furnish *N-para*-methoxybenzyl tetramic acid **261** in moderate yield (50%), **261** was obtained as a 3:1 mixture of diastereomers.



Scheme 3.14 Dieckmann Cyclization

3.5.3 Unveiling of the Amide via Cleavage of the *N-para*-Methoxybenzyl Protecting Group

As mentioned above in Scheme 3.12, *O*-methylation of *N-para*-methoxybenzyl tetramic acid **261** was achieved upon treatment with dimethyl sulfate and potassium carbonate in refluxing acetone to provide vinylogous ester **262** in good yield (72%) (Scheme 3.15). Oxidative cleavage of the *N-para*-methoxybenzyl amide **262** proved to be much more efficient than the benzyl series, exposure to 2,3-dichloro-5,6-dicyano-*p*-benzoquinone and water in refluxing dichloromethane provided tetramic acid **251** in good yield (70%) .

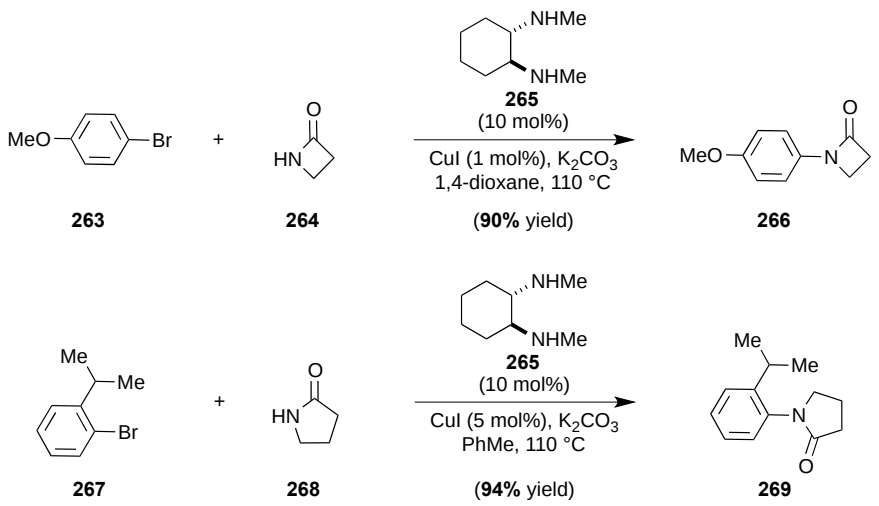


Scheme 3.15 *O*-Alkylation and *N-para*-Methoxybenzyl Amide Cleavage

3.6 Intermolecular Aryl Amidation Strategy

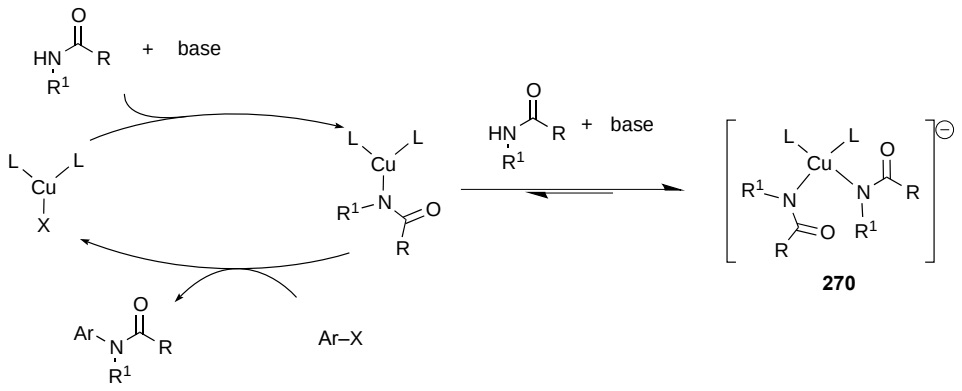
3.6.1 Copper Catalyzed Aryl Amidation Reactions

In 2001 Buchwald and coworkers disclosed that the use of diamine ligands allows the Goldberg reaction (copper-catalyzed *N*-arylation of amides) of aryl halides to be performed under mild conditions, employing a weak base and non-polar solvent (Scheme 3.16).[61-63]



Scheme 3.16 Diamine Ligands in Copper Catalyzed Amidation of Aryl Halides

Buchwald's early reports established parameters for applying these catalyst systems. The best solvents proved to be toluene and 1,4-dioxane, although *N*,*N*-dimethylformamide proved optimal for very polar amides. Copper iodide gives the highest yields and the advantage of being cheap and air stable. The choice of base proved to be of extreme importance in these reactions; for aryl iodides potassium phosphate proved to be the best and reactions performed using potassium carbonate were found to be much slower. With aryl bromides, which generally react more slowly than aryl iodides, potassium phosphate is often unsuccessful but potassium carbonate is effective. This disparity is thought to result from the need to match the rate of deprotonation of the amide and the rate of the C–N bond formation. If the rate of the deprotonation is relatively too high, then deprotonated amide accumulates and forms an unreactive cuprate complex **270** (Scheme 3.17). Evidence to support this hypothesis comes from the observation that strong bases such as potassium bis(trimethylsilyl)amide are only efficacious if added slowly to the reaction mixture. Potassium phosphate and potassium carbonate both behave as strong bases in aprotic solvents, but their low solubility ensures slow formation of the deprotonated amides.



Scheme 3.17 Copper Catalyzed Aryl Amidation

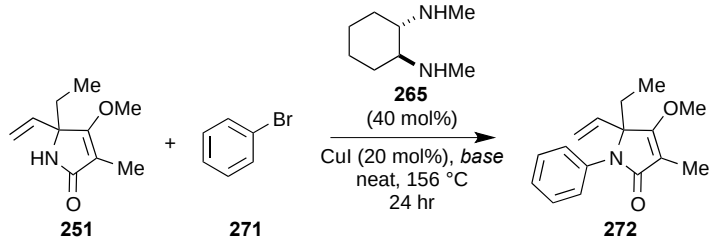
Ligands based on ethylenediamine or cyclohexanediamine provide favorable reactivity. Unsubstituted diamines can be used in some cases, however, *N,N'*-dimethyl-substituted ligands generally provide higher rates and avoid undesired *N*-arylation of the ligand under the reaction conditions. Kinetic studies have indicated that the role of the ligand is to prevent the formation of the less reactive, multiply ligated cuprate structures.

The reaction is applicable to a range of electron-rich and electron-deficient aryl and heteroaryl bromides, iodides, and in some cases aryl chlorides. Carbamates are also suitable coupling partners, but the reaction remains most suitable for lactams and primary amides. Acyclic secondary amides are much more challenging, an efficient reaction can only be realized for *N*-aryl or *N*-methyl amides, except in the case of formamides.

3.6.2 Lessons from Model Aryl Bromide Substrates

Although precedent for an aryl amidation with a γ-substituted lactam proved to be deficient in the literature, we were enthusiastic to explore the reactivity of tetramic acid **251** in an aryl amidation and push the forefront of the diamine copper catalyst system. To this end we screened bases in the aryl amidation of bromobenzene (**271**) with tetramic acid **251** in the presence of catalytic copper iodide and *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine (**265**) in

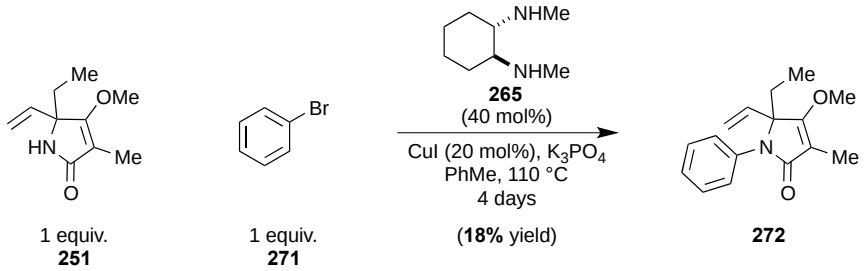
neat bromobenzene (Scheme 3.18). Potassium phosphate afforded amide **272** in the highest yield (26%) after twenty-four hours.



base	yield (%)
K_2CO_3	2
Cs_2CO_3	19
K_3PO_4	26
KHMDS	7

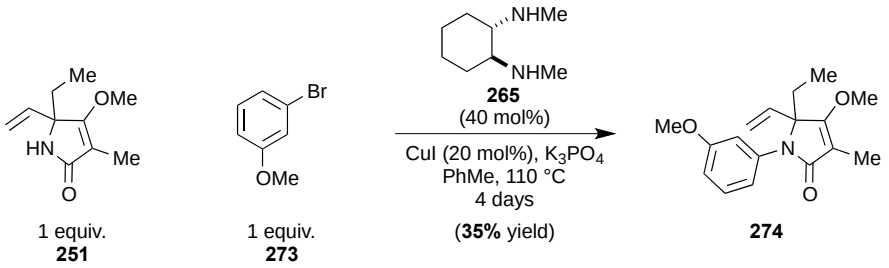
Scheme 3.18 Aryl Amidation Base Screen

We were extremely gratified to find that we could reduce the amount of bromobenzene (**271**), 1:1 stoichiometry, and effectively couple with tetramic acid **251** albeit, in low yield (18%) and extended reaction times (Scheme 3.19).



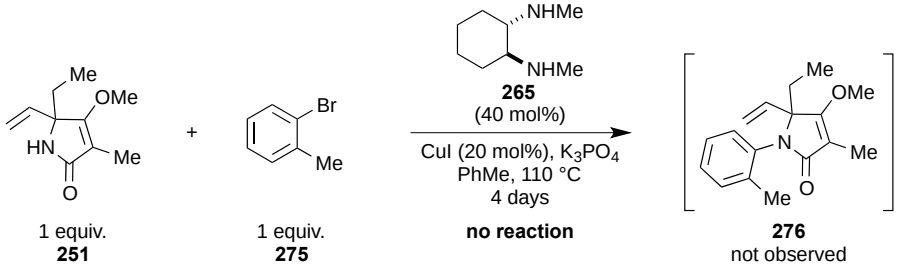
Scheme 3.19 Stoichiometric Aryl Amidation with Tetramic Acid Coupling Partner

Aryl amidation with an electron rich aryl bromide proved to be advantageous. Exposure of 3-bromoanisole (**273**) and tetramic acid **251** to coupling reaction conditions provided product **274** in modest yield (35%), after four days (Scheme 3.20). This result delivered confidence that aryl bromide **188** (Scheme 3.1) would prove to be an effective coupling partner with tetramic acid **251** provided, of course, that the *ortho*-substitution did not interfere.



Scheme 3.20 Amidation of an Electron Rich Aryl Bromide

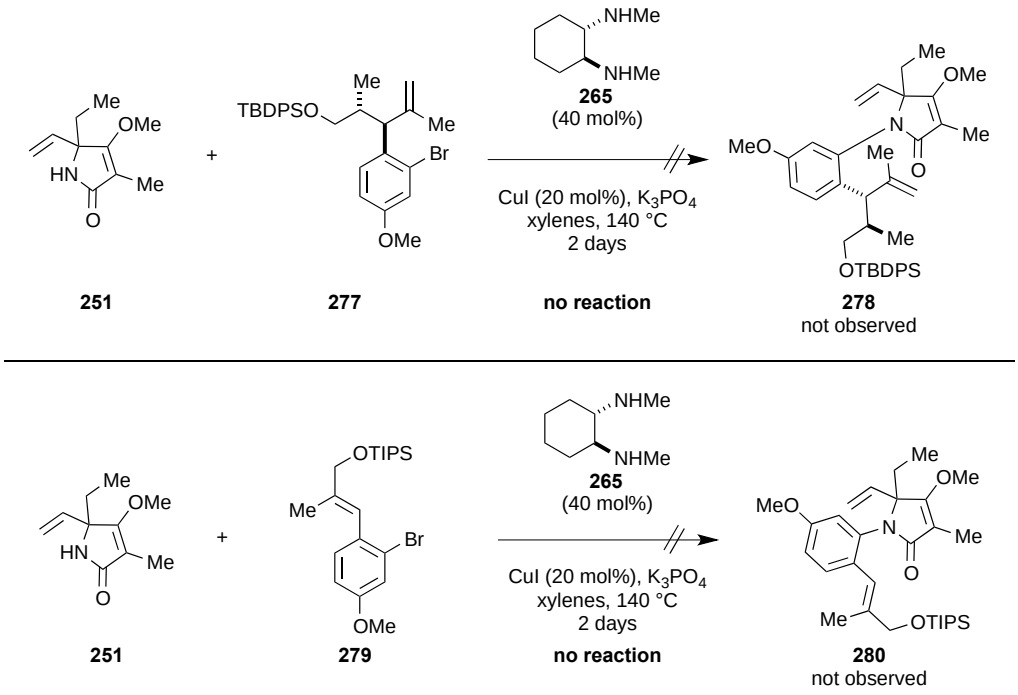
To this end, we probed the aryl amidation of 2-bromotoluene (**275**) and tetramic acid **251** (Scheme 3.21). Unfortunately, this aryl amidation was to no avail and coupling product **276** was not realized. We propose that this coupling was prohibited by the sterics of each coupling partner. Although disheartening, this reaction provided insight into the reactivity of tetramic acid **251** and in general that of γ-substituted lactams. It appears that the success of an aryl amidation between an aryl bromide and lactam is greatly influenced by the steric environments of both coupling partners.



Scheme 3.21 Attempted Amidation of *ortho*-Bromotoluene

3.6.3 Sterically Encumbered Aryl Bromide Substrates

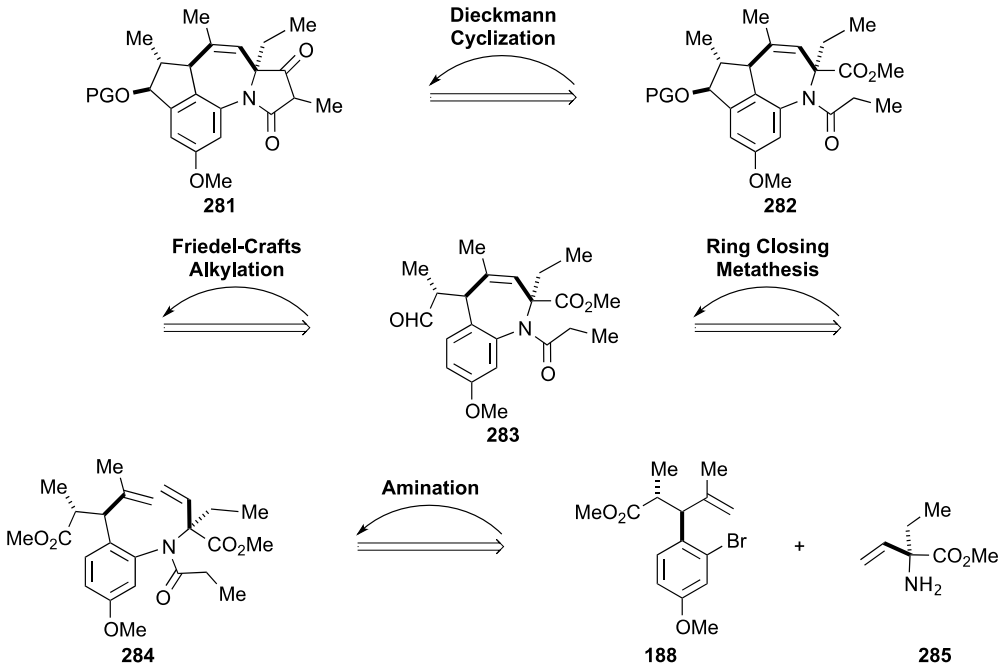
Indeed, our aryl amidation observations in the model system held true as we probed more advanced aryl bromide substrates (i.e. **277** and **279**)[64] (Scheme 3.22). This prompted us to investigate an alternative nitrogen nucleophile as a coupling partner with our prepared aryl bromides.



Scheme 3.22 Aryl Amidations with *Ortho*-Substituted Aryl Bromide Substrates

3.7 Third-Generation Retrosynthetic Analysis

At this point, we were motivated to investigate the reactivity of aryl bromide **188** toward aryl amination cross-coupling methods and revised our retrosynthetic analysis. In an effort to reduce the impact of sterics in constructing the C–N bond, we turned to a route wherein the tetracycle **281** would arise by Dieckmann cyclization of amide **282** which would, in turn, derive from a Friedel-Crafts alkylation of benzazepine **283,** the product of a ring closing metathesis applied to diene **284**. The requisite diene would be furnished by a cross-coupling reaction of aryl bromide **188** and amine **285**.



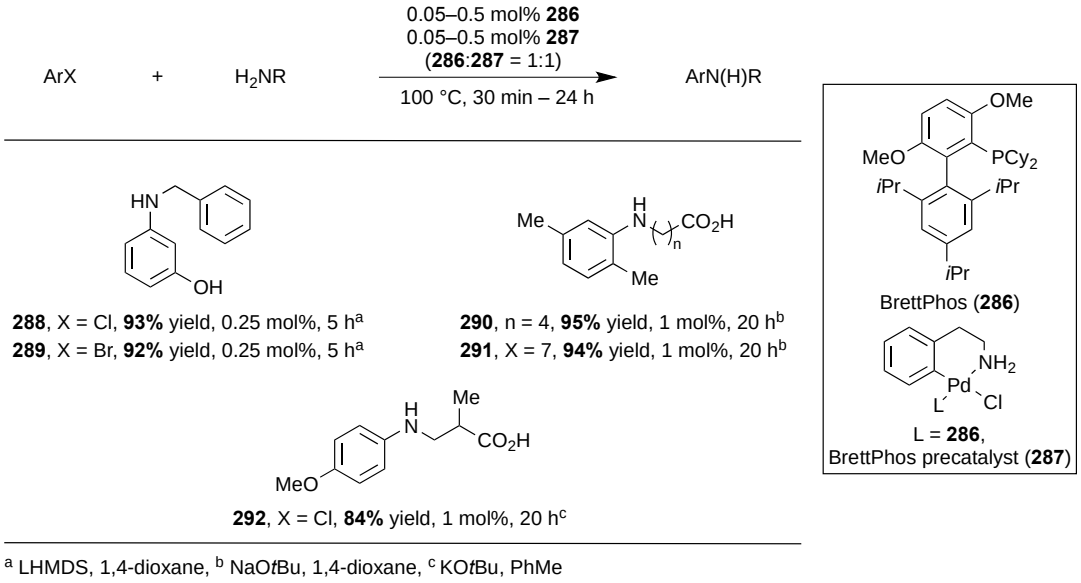
Scheme 3.23 Third Generation Retrosynthetic Analysis

3.8 Intermolecular Aryl Amination Strategy

The palladium-catalyzed amination of aryl halides allows the conceptually simple, yet powerful, disconnection of an aromatic amine to an aryl halide or pseudo halide and a nitrogen nucleophile.[65,66] The first palladium-catalyzed formation of aryl C–N bonds was disclosed by Migita and coworkers in 1983.[67] More than a decade later Buchwald and coworkers reported a new catalytic procedure based on Migita's amination procedure.[68] The disadvantage of these early methods was that both procedures utilized stoichiometric amounts of heat- and moisture sensitive tributyltin amides as coupling partners. In 1995 Buchwald[68] and Hartwig[69] concurrently discovered that the aminotin species could be replaced with the free amine when a strong base (e.g. sodium *tert*-butoxide or lithium bis(trimethylsilyl) amide) was employed to generate the corresponding sodium amide *in situ* by deprotonating the palladium-coordinated amine. Since these initial discoveries there has been great interest in this area and significant improvements in substrate scope and catalyst loadings have been realized. Advancements in this area have

typically been driven by the implementation of new classes of ligands; i.e. chelating diphenylphosphino ligands such as BINAP, dppf, and Xantphos, more electron-rich chelating phosphines such as Josiphos, *N*-heterocyclic carbenes and trialkylphosphines that have served to continually increase the substrate scope and to render the reactions more efficient. Despite the plethora of systems currently available for palladium-catalyzed C–N couplings, only a limited group has seen extensive practical application, reflecting on a combination of the ease of use of a catalyst system, its robustness, availability of ligands and substrate scope. Catalysts based on dialkylbiaryl phosphines, first described for palladium-catalyzed cross-coupling reactions in 1998 by Buchwald, compare favorably with other systems in this regard and have been extensively applied in the synthesis of biologically active molecules. A catalyst composed of the BrettPhos ligand (**286**) (Table 3.1) has demonstrated excellent reactivity and stability in C–N cross-coupling reactions and overcomes many restrictions that previous catalyst systems have possessed.[70] The palladium precatalyst system (**287**), based on the BrettPhos ligand (**286**), has been shown to quantitatively form the active monoligated palladium(0) complex under the reaction conditions,[71] and has demonstrated the widest scope for primary amines to date.

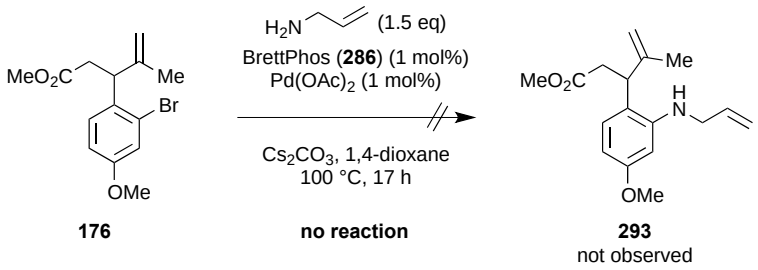
Table 3.1 Cross-Coupling of Aryl Halides and Primary Amines



[a] LHMDS, 1,4-dioxane, [b] NaO*t*Bu, 1,4-dioxane, [c] KO*t*Bu, PhMe

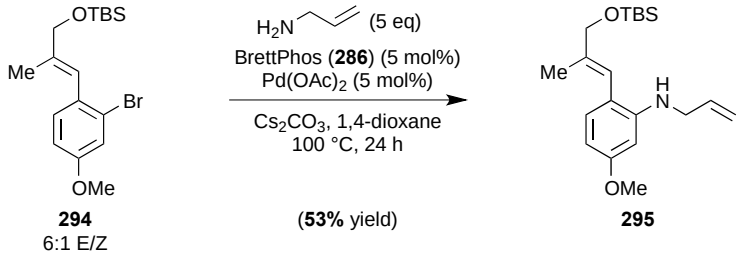
3.8.1 Allylamine as an Effective Coupling Partner

To probe the reactivity of aryl bromide **188** towards a palladium-catalyzed C–N cross-coupling reaction we conducted studies utilizing allylamine. Exposure of aryl bromide **176** and allylamine to a catalyst system derived from palladium acetate and BrettPhos (**286**) resulted in no reaction and the aryl bromide **176** was recovered. This outcome leads to the proposal that the *ortho*-substitution of aryl bromide **176** was preventing engagement in the desired aryl amination. Thus, we sought to investigate an aryl amination of an aryl bromide possessing less steric encumbrance.



Scheme 3.24 Cross-Coupling Reaction of *ortho*-Substituted Aryl Bromide and Allylamine

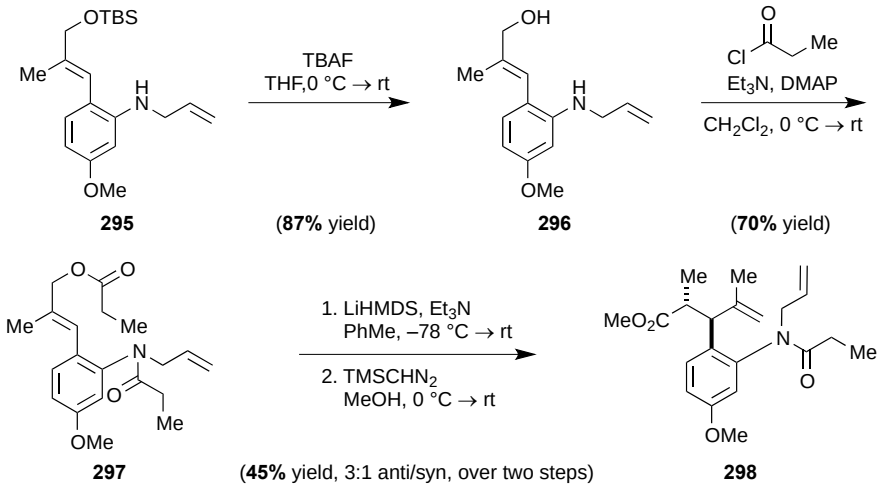
In this light, we explored the amination of aryl bromide **294** (Scheme 3.25). Indeed, treatment of aryl bromide **294** and allylamine with a catalyst system derived from palladium acetate and BrettPhos (**286**) afforded the desired amine **295** in modest yield (53%). We were excited to realize this C–N cross-coupling product, as **295** could be a viable synthetic intermediate for tetrapetalone A (**1**).



Scheme 3.25 Cross-Coupling Reaction of a Simplified Aryl Bromide and Allylamine

3.8.2 Lithium Enolate Claisen Rearrangement

Allylic alcohol **296** was unveiled upon subjecting **295** to fluoride mediated silyl ether cleavage; subsequent acylation smoothly provided allylic ester **297** in good yield (60%), over two steps. We were delighted to find that allylic ester **297** engaged in the desired Claisen rearrangement upon enolization with lithium bis(trimethylsilyl)amide/triethylamine and warming to room temperature. Treatment of the intermediate carboxylic acid with trimethylsilyldiazomethane afforded γ,δ-unsaturated methyl ester **298** in modest yield (45%) as a 3:1 mixture of anti/syn isomers.



Scheme 3.26 Lithium Enolate Claisen Rearrangement

3.8.3 A Problematic Ring Closing Metathesis

The formation of carbon–carbon bonds by olefin metathesis has become one of the most powerful and broadly applicable methods of modern synthetic chemistry. In particular, ring closing metathesis (RCM) reactions promoted by ruthenium based catalysts have been widely utilized in the construction of small, medium and large ring systems from acyclic precursors. Construction of cyclic, disubstituted olefins from terminal dienes has shown to be effectively catalyzed by diphosphine ruthenium complexes such as **299** (Figure 3.4). Synthesis of cyclic trisubstituted olefins can be readily achieved using second-generation systems such as **300** and the construction of cyclic tetrasubstituted olefins by ring closing metathesis is effectively catalyzed by second-generation systems such as **302**.[72]

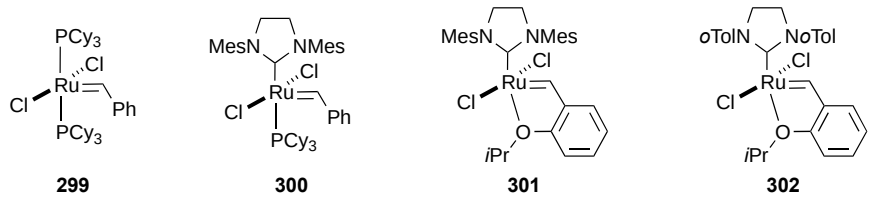
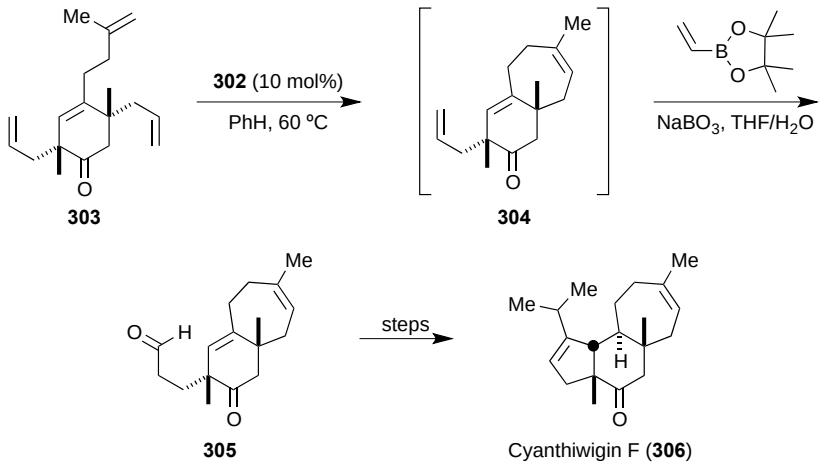


Figure 3.4 Ruthenium Based Olefin Metathesis Catalysts

In their total synthesis of (–)-cyanthiwigin F (**306**), Enquist and Stoltz realized a facile ring closing metathesis to afford a trisubstituted olefin of a seven membered carbocycle (**304**) by employing the unhindered Hoveyda-Grubbs catalyst **302** (Scheme 3.27).[73]



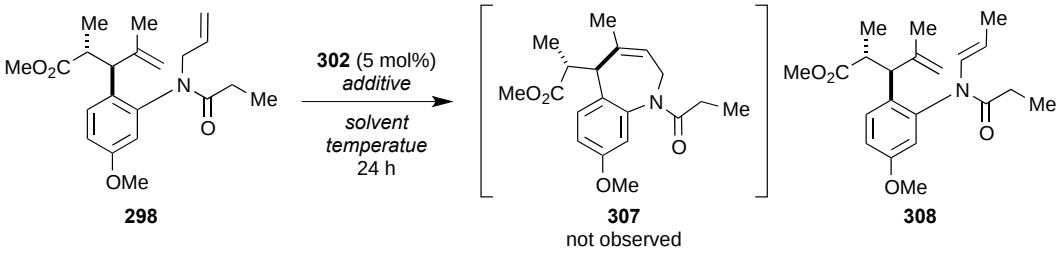
Scheme 3.27 (–)-Cyanthiwigin F Ring Closing Metathesis

With diene **298** on hand, we investigated construction of the benzazepine ring system by ring closing metathesis. No reaction was observed upon exposure of diene **298** to catalyst **302** at 60 ºC (Table 3.2, entry 1). Increasing the reaction temperature (110 ºC) did not afford the desired benzazepine **307**; instead enamide **308** was isolated in excellent yield (80%).

If chelation of the evolving carbene with the amide moiety in **298** occurs to form a stable six-membered chelate (i.e. **313**, Scheme 3.28, bottom) the catalyst is effectively sequestered, in an unproductive complex, rendering the ring closing metathesis ineffective. Furstner and coworkers have demonstrated that if the ruthenium is too tightly complexed by polar functional groups (such as five- or six-membered chelates), the metathesis reaction can be inhibited and that a mild Lewis acid (such as titanium isopropoxide), can be used to compete with the ruthenium for chelation of the polar group to effectively release the ruthenium and afford a productive RCM.[74] In order to destabilize the presumed unproductive chelate **313**, we ran the cyclization of

298 in the presence of excess titanium isopropoxide (Table 3.2, entry 3) unfortunately; we again realized enamide **308** in excellent yield (89%).

Table 3.2 Attempts to from Benzazepine System by Ring Closing Metathesis

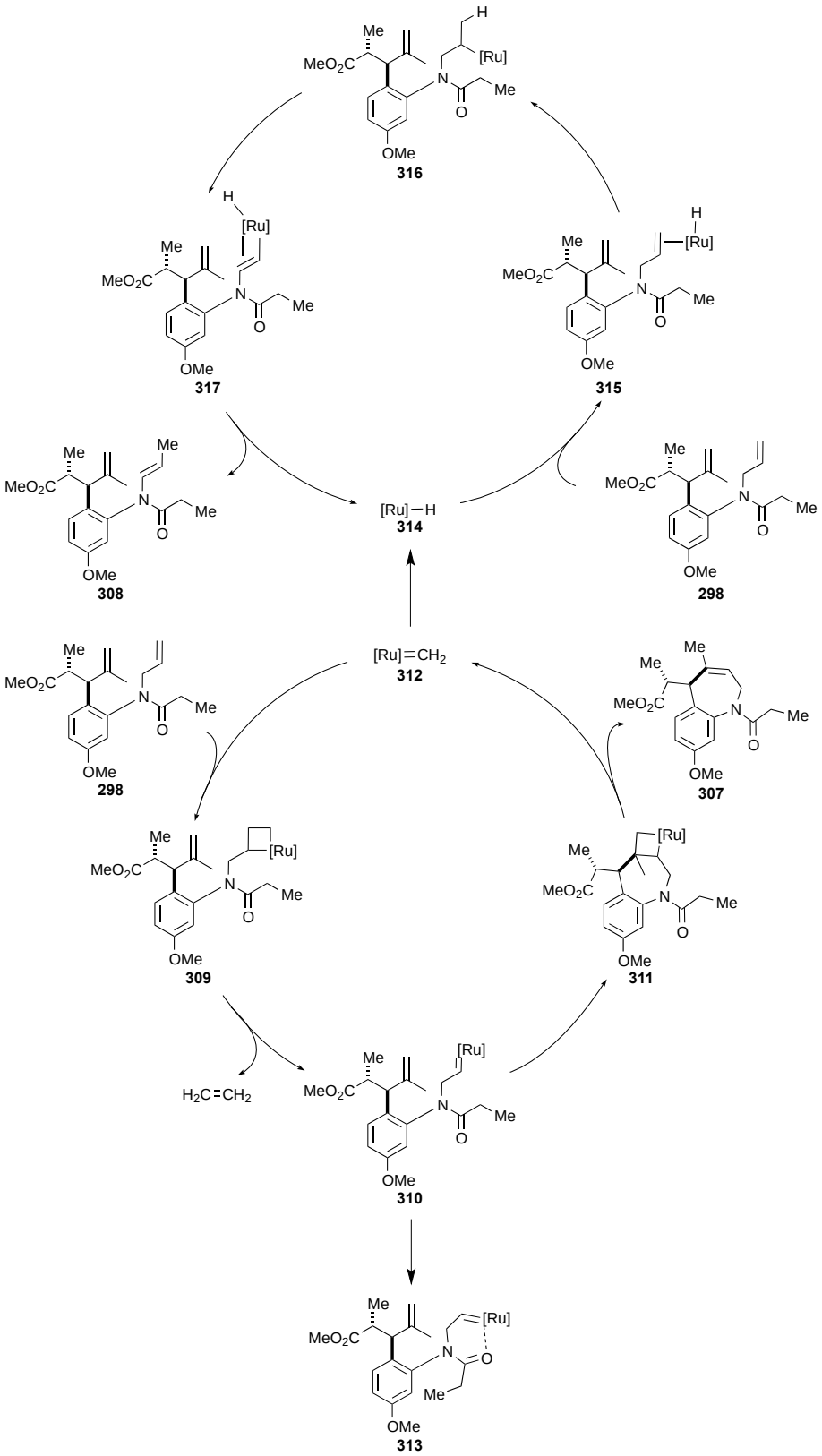


entry	additive	solvent	temperature (°C)	**product** (% yield)
1	–	PhMe (0.001 M)	60	**no reaction**
2	–	PhMe (0.01 M)	110	**308** (**80%** yield, 1.5:1 dr)
3	Ti(O*i*Pr)$_4$ (2 eq)	PhMe (0.01 M)	110	**308** (**89%** yield, 2:1 dr)
4	Ti(O*i*Pr)$_4$ (2 eq) benzoquinone (50 mol%)	1,2-dichloroethane (0.01 M)	83	**no reaction**

Enamide **308** is proposed to arise from an olefin isomerization event (Scheme 3.28, top), via a hydrometalation/β-hydride sequence, which requires the presence of a coordinately unsaturated ruthenium hydride species **314**. Coordination of the monosubstituted terminal alkene gives the π-complex **315**, which undergoes a migratory insertion (hydrometalation) to provide the σ-alkyl complex **316**. β-Hydride elimination leads to π-complex **317**, from which the catalytically active species **314** is regenerated by dissociation of the isomerized alkene **308**.

Ruthenium hydride complexes are formed in some cases as byproducts during the preparation of second-generation metathesis catalysts.[75] If these are present as an impurity in the metathesis catalyst, they may be responsible for the observed isomerization reactions. Alternatively, ruthenium hydride species may be formed by decomposition of the ruthenium carbene species under the reaction conditions. To inhibit the olefin isomerization reaction

pathway we ran the cyclization of **298** in 1,2-dichloroethane,[76] and catalytic 1,4-benzoquinone;[77] to this end the formation of enamide **308** was effectively suppressed, but the desired benzazepine **307** was not realized.



Scheme 3.28 Proposed Mechanisms for RCM and Double Bond Isomerization

3.9 Conclusion

The successful synthesis of a highly functionalized tetramic acid enabled us to investigate construction of the desired aryl C–N bond via a copper-catalyzed cross-coupling reaction. The tetramic acid proved competent in aryl amidation reactions with simple aryl bromides but the introduction of *ortho*-substitution into the aryl bromide-coupling partner thwarted the desired cross-coupling reaction.

Advanced *ortho*-substituted aryl bromide intermediates proved to be competent coupling partners with primary amines under palladium-catalyzed reaction conditions. This allowed the synthesis of a highly functionalized diene. Unfortunately, the diene did not engage in ring closing metathesis to afford the benzazepine system.

3.10 Experimental Section

3.10.1 Materials and Methods

Unless stated otherwise, reactions were performed in flame-dried glassware under a nitrogen atmosphere. Triethylamine, diisopropylamine, and methanol were dried over anhydrous calcium hydride and freshly distilled. 1,4-Dioxane was distilled from sodium, calcium chloride and molecular sieve (0.4 nm). Benzene, tetrahydrofuran, dichloromethane, toluene, and diethyl ether were dried using a solvent purification system manufactured by Glass Contour Solvent Systems, SG Water U.S.A., LLC using technology based upon that originally described by Grubbs *et al.*[78] Anhydrous *N*,*N*-dimethyformamide, acetonitrile, dimethylsulfoxide, 1,2-dichloroethane was purchased from the Colorado State University Stockroom and supplied by Sigma-Aldrich or Fischer Scientific and stored under nitrogen atmosphere. Commercially available reagents were obtained from Sigma-Aldrich, Strem, TCI, Combi-Blocks, Acros or

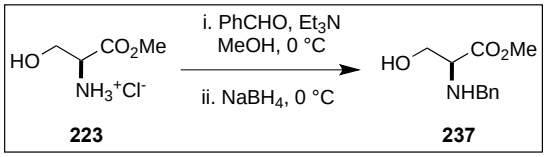
Alfa-Aesar and were used as received. All known compounds were identified by comparison of NMR spectra to reported in the literature.

Unless otherwise stated, all reactions were monitored by thin layer chromatography (TLC) was using Silicycle glass-backed extra hard layer, 60 Å plates (indicator F-254, 250 μm). Developed TLC plates were visualized using a 254 nm UV lamp and/or with the appropriate stain followed by heating. Typical stains utilized were potassium permanganate, ethanolic anisaldehyde and ceric ammonium molybdate. In general, the flash chromatography guidelines reported by Still *et al*[79] were followed. Silicycle SiliaFlash® P60 (230-400 mesh) silica gel as the stationary phase. When reactions were absorbed onto silica gel, the amount of silica gel used was equal to two times the weight of the reagents.

Infrared spectra were obtained using a Nicolet Avatar 320 FTIR or Bruker Tensor27 FTIR. Samples were analyzed as thin films on NaCl plates (samples was dissolved in CH_2Cl_2 or $CHCl_3$) or potassium bromide pellets, as indicated. IR spectra are presented as transmittance vs. wavenumber (cm^{-1}). Proton (^1H) and carbon (^{13}C) NMR spectra were recorded on a Varian Inova 500, Varian Inova 400, Varian Inova 400 auto sampler, or Varian Inova 300 MHz spectrometer. Spectra were obtained at 22 °C in $CDCl_3$ unless otherwise noted. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to the internal solvent peak. Coupling constants (J) are reported in Hertz (Hz) and are rounded to the nearest 0.1 Hz. Multiplicities are defined as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, br = broad, app = apparent, par = partial. High-resolution mass spectra were obtained from the University of Colorado Central Instrument Facility, performed on an Agilent 6210 TOF LCMS by Donald L. Dick.

3.10.2 Preparative Procedures

Preparation of *N*-benzylserine methyl ester 237:

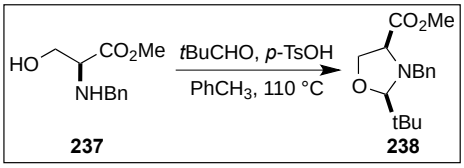


***N*-benzylserine methyl ester 237**. Following the procedure of Thompson *et al*[58] *N*-benzylserine methyl ester was prepared. *L*-Serine methyl ester hydrochloride (**223**) (15.2 g, 97.70 mmol) was dissolved in methanol (40 mL) and cooled to 0 ºC. Triethylamine (14.3 mL, 102.58 mmol) was added and the reaction was stirred for 10 minutes and benzaldehyde (10.4 mL, 102.58 mmol) was added. The reaction mixture was stirred for 3 hours, at which time sodium borohydride was added portion wise to the reaction mixture, via addition funnel, over a period of 1 hour. TLC was used to monitor reaction progress. TLC plates were developed with 100% diethyl ether and visualized by UV lamp and $KMnO_4$ stain. The reaction was then partitioned between 20% HCl (75 mL) and diethyl ether (20 mL). The organic phase was extracted with 20% HCl (2x with 80 mL). The combined aqueous phase was washed with diethyl ether (50 mL). The aqueous layer was then cautiously neutralized with solid $NaHCO_3$. The neutral aqueous phase was then extracted with diethyl ether (3x with 80 mL). The combined organic phase was washed with H_2O (250 mL), brine (250 mL), dried over anhydrous $MgSO_4$ and concentrated to afford **237** (14.6 g, 72% yield) as colorless oil. No further purification was necessary.

***N*-benzylserine methyl ester 237** is a known compound, the ^1H NMR spectra was obtained and structure was confirmed by comparison with spectra published in the literature.[58]

***N*-benzylserine methyl ester 237**. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.39-7.26 (m, 5H), 3.88 (d, *J* = 13.0 Hz, 1H), 3.81-3.77 (dd, *J* = 10.7, 6.4 Hz, 1H), 3.74 (s, 3H), 3.76-3.71 (d, *J* = 13.0 Hz, 1H), 3.62 (dd, *J* = 10.7, 6.4 Hz, 1H), 3.44 (dd, *J* = 6.3, 4.5 Hz, 1H), 2.48 (s, 2H).

Preparation of *N*-benzyl 1,3-oxazolidine 238:



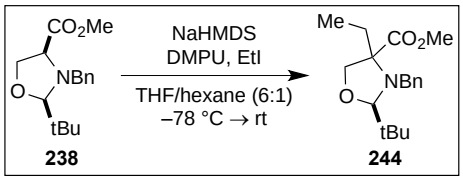
***N*-Benzyl 1,3-oxazolidine 238**. To a stirred solution of *N*-benzyl serine methyl ester **237** (14.6 g, 69.78 mmol) in toluene (125 mL) was added pivalaldehyde (15.2 mL, 139.56 mmol), *para*-toluenesulfonic acid (0.7 g, 3.49 mmol). Round bottom flask was fitted with a reflux condenser and Dean-Stark trap; reaction was heated to 95 ºC for 24 hours. TLC was used to monitor reaction progress. TLC plates were developed with 20% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Reaction was diluted with ethyl acetate (100 mL) and the washed with saturated $NaHCO_3$ solution (250 mL), H_2O (250 mL), brine (250 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 5→7→10% EtOAc/Hex) to afford 1,3-oxazolidine **238** (12.3 g, 63% yield, 9:1cis/trans) as colorless oil.

***N*-Benzyl 1,3-oxazolidine 238** is a known compound, the ^{1}H NMR spectra was obtained and structure was confirmed by comparison with spectra published in the literature.[57,59,60]

***N*-Benzyl 1,3-oxazolidine 238**. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.44 (d, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 2H), 7.24 (d, *J* = 7.2 Hz, 1H), 4.23 (dd, *J* = 8.5, 3.9 Hz, 1H), 4.15 (s, 1H), 4.08 (d, *J* = 14.0 Hz, 1H), 3.91 (dd, *J* = 8.4, 6.8 Hz, 1H), 3.71 (d, *J* = 14.0 Hz, 1H), 3.50 (dd, *J* = 6.8, 3.4 Hz, 1H), 3.48 (s, 3H), 1.00 (s, 9H); ^{13}C-NMR (101 MHz; CDCl3): δ 172.8, 138.6, 128.9,

128.3, 127.4, 105.4, 68.3, 66.3, 61.2, 51.8, 36.8, 25.5; HRMS (EI) *m/z* 278.1751 [calc'd for $C_{16}H_{23}NO_3$ (M+H)+ 278.1758].

Preparation of *N*-benzyl α-ethyl 1,3-oxazolidine 244:

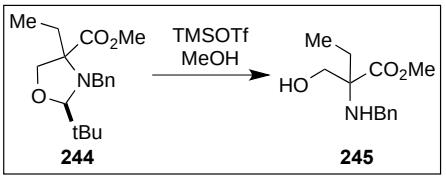


***N*-benzyl α-ethyl 1,3-oxazolidine 244**. Following the procedure of Colombo *et al*.[56] To a stirred 0.2 M solution of 1,3-oxazolidine **238** (5.0 g, 18.03 mmol) in tetrahydrofuran (90 mL) was added in sequence; 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (15 mL), iodomethane (5.8 mL), and hexanes (15 mL). The resulting solution was cooled to –78 °C and sodium bis(trimethylsilyl)amide (NaHMDS) (27.10 mL, 27.05 mmol) was added drop wise, two 20 mL syringes were loaded with NaHMDS (13.5 mL) and set for a addition rate of rate of 0.26 mL/min with a syringe pump, approximately 52 minutes for complete addition. Reaction turned a pale yellow upon addition of NaHMDS. TLC was used to monitor reaction progress. TLC plates were developed with 7% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Note the reaction is a product is a mixture of diastereomers and the lower R_f diastereomer co-spots with t starting material. Reaction solution was stirred for 30 minutes at –78 °C and then warmed to room temperature and stirred overnight; no change by TLC upon stirring over night at room temperature. Quenched with saturated NH_4Cl (100 mL), diluted with H_2O to dissolve salts and separated phases. Organic phase was washed with saturated LiCl solution (3 x 50 mL), H_2O (200 mL) and brine (200 mL). Dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford *N*-benzyl α-ethyl 1,3-oxazolidine **244** (5.3 g, 96% yield, 2:1 dr) yellow oil. Diastereomers proved difficult to separate and thus moved were moved forward together.

***N*-benzyl α-ethyl 1,3-oxazolidine 244a** (first diastereomer to elute off silica gel column). ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.46 (d, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 4.57 (d, *J* = 8.3 Hz, 1H), 4.25 (d, *J* = 16.5 Hz, 1H), 4.17 (s, 1H), 3.83 (d, *J* = 16.5 Hz, 1H), 3.59 (d, *J* = 8.3 Hz, 1H), 3.48 (s, 3H), 1.78 (app quintet, *J* = 7.4 Hz, 2H), 0.94 (s, 9H), 0.77 (t, *J* = 7.5 Hz, 3H); ^{13}C-NMR (101 MHz; CDCl3): δ 173.6, 140.7, 128.1, 127.6, 126.7, 105.4, 72.7, 71.7, 53.3, 51.6, 37.1, 25.5, 23.5, 9.8; HRMS (EI) *m/z* 306.2064 [calc'd for $C_{18}H_{27}NO_3$ (M+H)+ 306.2063].

***N*-benzyl α-ethyl 1,3-oxazolidine 244b** (second diastereomer to elute off silica gel column). ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.38-7.19 (m, 5H), 4.32 (s, 1H), 4.13 (d, *J* = 8.4 Hz, 1H), 3.97 (d, *J* = 16.5 Hz, 1H), 3.84 (d, *J* = 8.4 Hz, 1H), 3.79 (s, 3H), 3.80-3.74 (d, *J* = 16.4 Hz, 1H), 1.65 (dq, *J* = 14.2, 7.2 Hz, 1H), 1.39 (dq, *J* = 14.4, 7.2 Hz, 1H), 0.96 (s, 9H), 0.73 (t, *J* = 7.5 Hz, 3H).

Preparation of amino alcohol 245:

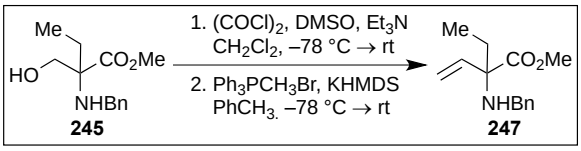


Amino alcohol 245. To a stirred solution of *N*-benzyl α-ethyl 1,3-oxazolidine **244** (4.8 g, 15.72 mmol) in methanol (160 mL) was added trimethylsilyl trifluoromethanesulfonate (11.4 mL, 62.87 mmol) at room temperature. TLC was used to monitor reaction progress. TLC plates were developed with 50% EtOAc/Hex solution doped with 1% triethylamine and visualized by UV lamp and $KMnO_4$ stain. Reaction was complete after approximately 1 hour. Neutralized reaction solution slowly with saturated $NaHCO_3$ solution. Extracted with diethyl ether (3 x 100 mL). Combined organic phase was washed with H_2O (150 mL), brine (150 mL), dried over

anhydrous Na_2SO_4 and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 30→50% EtOAc/Hex, doped with 1% triethylamine) to afford amino alcohol **245** (3.1 g, 76% yield) as a white solid. Note the amino alcohol **245** can also be purified by recrystallization from diethyl ether/pentane.

Amino alcohol 245. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.34 (d, *J* = 4.4 Hz, 3H), 7.28 (t, *J* = 4.3 Hz, 2H), 3.81 (d, *J* = 7.7 Hz, 1H), 3.77 (s, 3H), 3.66 (d, *J* = 12.1 Hz, 1H), 3.65 (d, *J* = 7.7 Hz, 1H), 3.61 (d, *J* = 12.1 Hz, 1H), 2.74 (s, 1H), 2.00 (s, 1H), 1.73 (dtt, *J* = 22.2, 14.8, 7.4 Hz, 2H), 0.89 (t, *J* = 7.5 Hz, 3H); ^{13}C-NMR (101 MHz; CDCl3): δ 174.8, 139.9, 128.7, 128.3, 127.5, 66.9, 62.0, 52.2, 46.9, 26.4, 8.2; HRMS (EI) *m/z* 238.1438 [calc'd for $C_{13}H_{19}NO_3$ (M+H)+ 238.1437].

Preparation of α-vinyl amino ester 247:



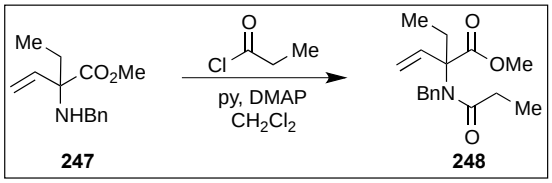
α-Vinyl amino ester 247. *Swern oxidation protocol*: To a stirred solution of dimethylsulfoxide (2.2 mL, 30.36 mmol) in dichloromethane (60 mL) was added oxalyl chloride (1.3 mL, 15.17 mmol) at –78 °C, slowly. Reaction solution was stirred for 20 minutes at –78 °C. A solution of amino alcohol **245** (1.8 g, 7.59 mmol) and triethylamine (5.3 mL, 37.95 mmol) in dichloromethane (15 mL) was added via cannula at –78 °C. Reaction was stirred at –78 °C for 1 hour and warmed to room temperature. TLC was used to monitor reaction progress. TLC plates were developed with gradient elution 20→30% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Quenched reaction with saturated $NaHCO_3$ solution (50 mL). Organic phase was washed with H_2O (100 mL), brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated

under reduced pressure to crude yellow oil. Crude material was carried directly into Wittig olefination protocol.

Wittig olefination protocol: Methyltriphenylphosphonium bromide (5.4 g, 15.18 mmol) was dried over night under high vacuum and heated to 110 °C. To a stirred heterogeneous solution of methyltriphenylphosphonium bromide (5.4 g, 15.18 mmol) in toluene (26 mL) was added potassium bis(trimethylsilyl)amide (1.0 M in toluene, 14.4 mL, 14.42 mmol) at room temperature. Reaction solution was stirred for 1.5 hours at room temperature; bright yellow colored solution. Crude aldehyde (7.59 mmol) as a solution in toluene (10 mL) was added to the ylide solution at –78 °C via cannula addition. Reaction solution turned a dark orange color. Reaction was stirred for 1 hour at –78 °C upon complete addition of aldehyde and warmed to room temperature. Stirred 2 hours at room temperature. TLC was used to monitor reaction progress. TLC plates were developed with gradient elution 20% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Quenched reaction with saturated NH_4Cl solution (50 mL) and organic phases were separated. Organic phase was washed with H_2O (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 3→4→5→6% Hex/EtOAc solution) to afford α-vinyl amino ester **247** (1.2 g, 67% yield, over two steps) as yellow oil.

α-Vinyl amino ester 247. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.37 (d, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.25 (t, *J* = 7.1 Hz, 1H), 6.01 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.43 (d, *J* = 17.5 Hz, 1H), 5.30 (d, *J* = 10.8 Hz, 1H), 3.76 (s, 3H), 3.62 (d, *J* = 12.2 Hz, 1H), 3.57 (d, *J* = 12.2 Hz, 1H), 1.86 (qq, *J* = 12.9, 6.6 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR (101 MHz; CDCl3): δ 175.3, 140.7, 138.1, 128.53, 128.37, 127.1, 116.2, 67.5, 52.2, 47.9, 30.1, 8.0; HRMS (EI) *m/z* 234.1498 [calc'd for $C_{14}H_{19}NO_2$ (M+H)+ 234.1486].

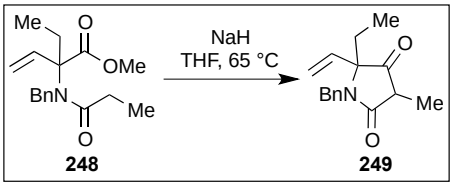
Preparation of amide 248:



Amide 248. To a stirred solution of amine **247** (703 mg, 3.01 mmol), pyridine (0.50 mL, 6.03 mL), 4-(dimethylamino)pyridine (18 mg, 0.15 mmol) in dichloromethane (15 mL) was added propionyl chloride (0.40 mL, 4.52 mmol) at 0 °C. Reaction solution was warmed to room temperature, fitted with a reflux condenser and refluxed (40 °C). TLC was used to monitor reaction progress. TLC plates were developed with gradient elution 50% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Quenched reaction with 1M HCl (20 mL) and separated phases. Organic phase was washed with 15% NaOH (20 mL), H_2O (25 mL), brine (25 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 20→25→30% EtOAc/Hex) to afford Dieckmann cyclization precursor **248** (766 mg, 88% yield) as colorless oil.

Amide 248. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.51 (d, *J* = 7.3 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.30-7.26 (m, 1H), 6.03 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.25 (d, *J* = 17.1 Hz, 2H), 5.23 (d, *J* = 11.3 Hz, 1H), 4.60 (d, *J* = 19.0 Hz, 1H), 4.52 (d, *J* = 19.0 Hz, 1H), 3.78 (s, 3H), 2.40-2.01 (m, 4H), 1.05 (t, *J* = 7.4 Hz, 3H), 0.86 (t, *J* = 7.5 Hz, 3H); HRMS (EI) *m/z* 290.1751 [calc'd for $C_{17}H_{23}NO_3$ (M+H)+ 290.1754].

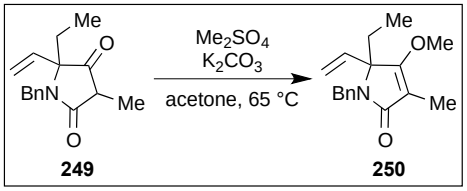
Preparation of *N*-benzyl tetramic acid 249:



***N*-Benzyl tetramic acid 249**. To a refluxing suspension of sodium hydride (60% dispersion in mineral oil) (412 mg, 10.30 mmol) in tetrahydrofuran (35 mL), was added dropwise a solution of amide **248** (1.5 g, 5.15 mmol), in tetrahydrofuran (15 mL). Reaction was refluxed for 2 days. TLC was used to monitor reaction progress. TLC plates were developed with gradient elution 25→30% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Checking conversion by ^{1}H NMR also monitored reaction progress; aliquots were from the reaction every 24 hours. Reaction was quenched with addition of saturated NH_4Cl solution (25 mL) and phases were separated. The aqueous phase was extracted with ethyl acetate (2 x 20 mL). Combined organic phase was washed with H_2O (100 mL), brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford N-benzyl tetramic acid **249** (1.1 g, 85% yield, 4:1 dr) as a yellow solid. No further purification was necessary and material was carried on directly to methylation.

***N*-Benzyl tetramic acid 249**. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.41-7.38 (m, 2H), 7.33-7.27 (m, 3H), 5.63 (dd, *J* = 17.4, 10.6 Hz, 1H), 5.27-5.21 (d, *J* = 10.6 Hz, 1H), 5.20 (d, *J* = 17.4 Hz, 1H), 4.73 (d, *J* = 14.9 Hz, 1H), 4.35 (d, *J* = 14.9 Hz, 1H), 2.99 (q, *J* = 7.6 Hz, 1H), 2.13-1.97 (m, 1H), 1.80-1.63 (m, 1H), 1.32 (d, *J* = 7.6 Hz, 3H), 0.41 (t, *J* = 7.3 Hz, 3H), 7.41-7.38 (m, 2H), 7.33-7.27 (m, 3H), 5.64 (dd, *J* = 17.4, 10.7 Hz, 3H), 5.31 (d, *J* = 10.8 Hz, 1H), 5.23 (d, *J* = 17.4 Hz, 1H), 4.87 (d, *J* = 14.9 Hz, 1H), 4.21 (d, *J* = 14.9 Hz, 1H), 2.77 (q, *J* = 7.8 Hz, 1H), 2.13-1.97 (m, 1H), 1.80-1.63 (m, 1H), 1.38 (d, *J* = 7.8 Hz, 3H), 0.48 (t, *J* = 7.4 Hz, 3H). HRMS (EI) *m/z* 258.1489 [calc'd for $C_{16}H_{19}NO_2$ (M+H)+ 258.1494].

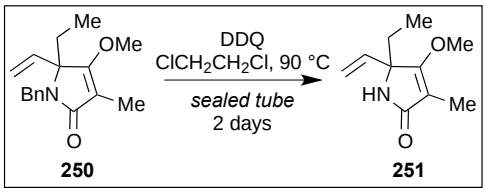
Preparation of vinylogous ester 250:



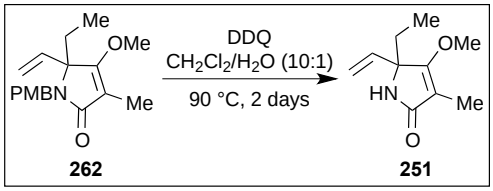
Vinylogous ester 250. To a stirred heterogeneous solution of *N*-benzyl tetramic acid **249** (1.1 g, 4.27 mmol), potassium carbonate (708 mg, 5.12 mmol) in acetone (43 mL), was added dimethyl sulfate (0.44 mL). Reaction was fitted with a reflux condenser and refluxed (56 °C) overnight. TLC was used to monitor reaction progress. TLC plates were developed with gradient elution 25→30% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Note starting material and product have very similar R_f. Conversion was checked ^{1}H NMR after 24 hours. Reaction was cooled to room temperature and partitioned between ethyl acetate (40 mL) and 2M NaOH (40 mL). Aqueous phase was extracted with ethyl acetate (2 x 40 mL). Combined organic phase was washed with H_2O (150 mL), brine (150 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 25→30% EtOAc/Hex) to afford vinylogous ester **250** (0.5 g, 42% yield) as colorless oil.

Vinylogous ester 250. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.35 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.28-7.20 (m, 3H), 5.48 (dd, *J* = 18.0, 10.0 Hz, 1H), 5.24 (d, *J* = 1.0 Hz, 1H), 5.21-5.19 (m, 1H), 4.59 (d, *J* = 15.3 Hz, 1H), 4.18 (d, *J* = 15.1 Hz, 1H), 4.00 (s, 3H), 2.05 (s, 3H), 1.82 (dq, *J* = 14.3, 7.2 Hz, 1H), 1.59 (dt, *J* = 14.2, 7.1 Hz, 1H), 0.37 (t, *J* = 7.3 Hz, 3H); HRMS (EI) *m/z* 272.1645 [calc'd for $C_{16}H_{19}NO_2$ (M+H)+ 272.1646].

Preparation of tetramic acid 251:



Tetramic acid 251. *DDQ mediated benzyl amide cleavage protocol*: To a vial equipped with a magnetic stir bar was added in sequence *N*-benzyl tetramic acid **250** (20 mg, 0.07 mmol), 1,2-dichloroethane (1.4 mL) and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) (80 mg, 0.35 mmol). Reaction vial was sealed and heated to 90 °C for two days. TLC was used to monitor reaction progress. TLC plates were developed with 80% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Reaction was cooled to room temperature and quenched with saturated $NaHCO_3$ (3 mL) and phases were separated. Organic phase was concentrated under reduced pressure and purified with silica gel chromatography (gradient elution 20→50→80% EtOAc/Hex) to afford tetramic acid **251** (7 mg, 54% yield) as tan solid.

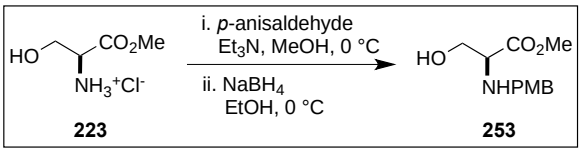


DDQ mediated para-methoxybenzyl amide cleavage protocol: To a round bottom flask equipped with a magnetic stir bar was added in sequence: *N-para*-methoxybenzyl tetramic acid **262** (322 mg, 1.07 mmol), dichloromethane (20 mL), H_2O (2 mL) and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) (1.2 g, 5.34 mmol), fitted with a west condenser and reaction was refluxed (50 °C) for two days. TLC was used to monitor reaction progress. TLC plates were developed with 80% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Reaction was cooled to room temperature, diluted with dichloromethane (20 mL); quenched with

saturated $NaHCO_3$ (20 mL) and phases were separated. Aqueous phase was extracted with dichloromethane (2 x 10 mL). Combined organic phase was washed with H_2O (75 mL), brine (75 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Crude material was and purified with silica gel chromatography (gradient elution 20→50→80% EtOAc/Hex) to afford tetramic acid **251** (129 mg, 70% yield) as white solid.

Tetramic acid 251. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 5.83 (dd, *J* = 17.3, 10.5 Hz, 1H), 5.34 (s, 1H), 5.26 (dd, *J* = 17.3, 0.8 Hz, 1H), 5.13 (dd, *J* = 10.5, 0.8 Hz, 1H), 4.04 (s, 3H), 1.97 (s, 3H), 1.71 (app septuplet, *J* = 7.5 Hz, 2H), 0.80 (t, *J* = 7.4 Hz, 3H).

Preparation of *para*-methoxybenzyl serine methyl ester 253:

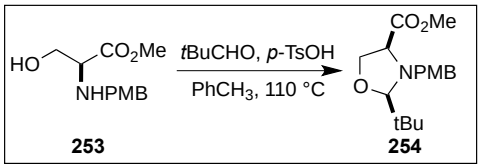


***para*-Methoxybenzyl serine methyl ester 253**. To a stirred solution of L-serine methyl ester hydrochloride (**223**) (50.0 g, 321.38 mmol) in methanol (640 mL) was added triethylamine (45 mL, 321.38 mmol) and *p*-anisaldehyde (27 mL, 224.97 mmol) at room temperature. The reaction solution was stirred at room temperature for 1 hour and concentrated under reduced pressure to yield the crude imine as a white solid. The imine was suspended in ethanol (500 mL) and sodium borohydride (12 g, 321.38 mmol) was added portion wise via addition funnel over 30 minutes at room temperature. The heterogeneous reaction mixture was stirred at room temperature for 24 hours. TLC was used to monitor reaction progress. TLC plates were developed with 100% Et_2O and visualized by UV lamp and $KMnO_4$ stain. Ethanol was removed under reduced pressure and the residue was dissolved in 1M HCl (500 mL) at 0 °C. The acidic solution was washed with ethyl acetate (250 mL). The acidic phase was then brought to ph = 10 with 10M NaOH. Basic solution was extracted with dichloromethane (3 x 250 mL). Combined

organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford *N-para*-methoxybenzylserine methyl ester **253** (51.8, 70% yield) as orange oil. No further purification was necessary.

***N-para*-Methoxybenzyl serine methyl ester 253**. FTIR (thin film/NaCl): 3404, 2999, 2953, 2837, 1737, 1643, 1613, 1585, 1513, 1464, 1421, 1321, 1303, 1249, 1177, 1106, 1058, 1033, 810, 734; ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.23 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 3.80 (d, *J* = 12.7 Hz, 1H), 3.79 (s, 3H), 3.76 (dd, *J* = 10.7, 6.4 Hz, 1H), 3.74 (s, 3H), 3.66 (d, *J* = 12.7 Hz, 1H), 3.59 (dd, *J* = 10.7, 6.4 Hz, 1H), 3.42 (dd, *J* = 6.4, 4.5 Hz, 1H), 2.53 (br s, 2H); HRMS (EI) *m/z* 240.123 [calc'd for $C_{12}H_{17}NO_4$ (M+H)+ 239.1158].

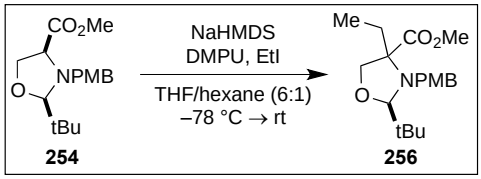
Preparation of *N-para*-methoxybenzyl 1,3-oxazolidine 254:



***N-para*-Methoxybenzyl 1,3-oxazolidine 254**. To a stirred solution of *N-para*-methoxybenzyl serine methyl ester **253** (53 g, 222.70 mmol) in toluene (450 mL) was added pivalaldehyde (48 mL, 445.40 mmol), *para*-toluenesulfonic acid (2.1 g, 11.14 mmol). Round bottom flask was fitted with a reflux condenser and Dean-Stark trap; reaction was heated to 160 ºC for 24 hours. TLC was used to monitor reaction progress. TLC plates were developed with 5% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Reaction was washed with saturated $NaHCO_3$ solution (500 mL), H_2O (500 mL), brine (500 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (eluent 5% EtOAc/Hex) to afford *N-para*-methoxybenzyl 1,3-oxazolidine **254** (40.8 g, 60% yield, 9:1cis/trans) as colorless oil.

***N-para*-Methoxybenzyl 1,3-oxazolidine 254**. FTIR (thin film/NaCl): 2954, 1735, 1612, 1585, 1512, 1484, 1463, 1396, 1359, 1244, 1085, 1059, 1035, 970, 887, 823; ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.34 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 4.20 (dd, *J* = 8.5, 3.9 Hz, 1H), 4.11 (s, 1H), 3.99 (d, *J* = 13.8 Hz, 1H), 3.87 (dd, *J* = 8.5, 6.8 Hz, 1H), 3.77 (s, 3H), 3.62 (d, *J* = 12.7 Hz, 1H), 3.48 (app q, *J* = 3.6 Hz, 1H), 3.48 (s, 3H), 0.99 (s, 9H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ 172.7, 158.9, 130.5, 130.0, 113.5, 105.1, 68.1, 65.9, 60.4, 55.2, 51.6, 36.7, 25.4; HRMS (EI) *m/z* 308.1856 [calc'd for $C_{17}H_{25}NO_4$ (M+H)+ 307.1784].

Preparation of *N-para*-methoxybenzyl α-ethyl 1,3-oxazolidine 256:

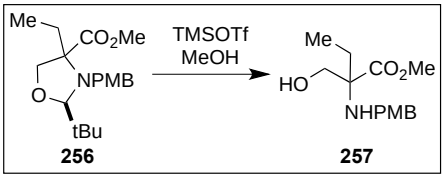


***N-para*-Methoxybenzyl α-ethyl 1,3-oxazolidine 256**. Following the procedure of Colombo *et al.*[56] To a stirred 0.5 M solution of 1,3-oxazolidine **254** (62 g, 201.70 mmol) in tetrahydrofuran (400 mL) was added in sequence: 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (60 mL), iodoethane (65 mL, 806.8 mmol), and hexanes (60 mL). The resulting solution was cooled to –78 °C and sodium bis(trimethylsilyl)amide (NaHMDS) (1 M in THF, 303 mL, 302.55 mmol) was added dropwise with an addition funnel. Reaction turned a pale yellow upon complete addition of NaHMDS. TLC was used to monitor reaction progress. TLC plates were developed with 20% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Note: reaction product is a mixture of two diastereomers, the lower R_f diastereomer co-spots, just above, starting material. Upon complete addition of NaHMDS reaction solution was stirred for 30 minutes at –78 °C then warmed to room temperature and stirred overnight. Quenched with saturated NH_4Cl (250 mL), diluted with H_2O (250 mL) to dissolve salts and

separated phases. Aqueous phase was extracted with ethyl acetate (3 x 200 mL) Combined organic phase was washed with saturated LiCl solution (200 mL), H_2O (250 mL) and brine (250 mL). Dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford *N-para*-methoxybenzyl α-ethyl 1,3-oxazolidine **256** (59.6 g, 88% yield, 2:1 dr) yellow oil. Diastereomers proved difficult to separate and were moved forward together, with no further purification.

***N-para*-Methoxybenzyl α-ethyl 1,3-oxazolidine 256** (2:1 mixture of diastereomers). FTIR (thin film/NaCl): 2958, 1728, 1612, 1585, 1510, 1460, 1394, 1359, 1300, 1243, 1036, 968, 930, 886, 862, 823, 753; HRMS (EI) *m/z* 336.2169 [calc'd for $C_{19}H_{29}NO_4$ (M+H)+ 335.2097].

Preparation of amino alcohol 257:

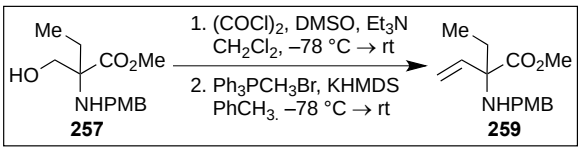


Amino alcohol 257. To a stirred solution of *N-para*-methoxybenzyl α-ethyl 1,3-oxazolidine **256** (13 g, 37.40 mmol) in methanol (60 mL) was added trimethylsilyl trifluoromethanesulfonate (14 mL, 74.80 mmol) at room temperature. Reaction was stirred at room temperature overnight. TLC was used to monitor reaction progress. TLC plates were developed with 80% EtOAc/Hex solution doped with 1% triethylamine and visualized by UV lamp and $KMnO_4$ stain. Neutralized reaction solution slowly with saturated $NaHCO_3$ solution (100 mL). Extracted with diethyl ether (3 x 75 mL). Combined organic phase was washed with H_2O (100 mL), brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 40→80%

EtOAc/Hex, doped with 1% triethylamine) to afford amino alcohol **257** (7.2 g, 72% yield) as a white solid.

Amino alcohol 257. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.25 (d, *J* = 5.5 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 3.80 (s, 3H), 3.78-3.76 (m, 1H), 3.76 (s, 3H), 3.62-3.48 (m, 3H), 2.78 (br s, 1H), 1.92 (br s, 1H), 1.81-1.61 (m, 2H), 0.87 (t, *J* = 7.5 Hz, 3H).

Preparation of α-vinyl amino ester 259:



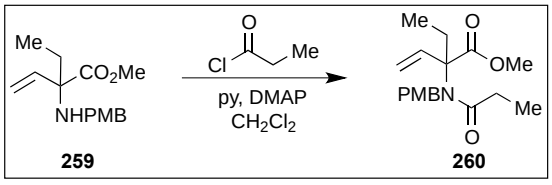
α-Vinyl amino ester 259. *Swern oxidation protocol*: To a stirred solution of dimethylsulfoxide (7.4 mL, 104.76 mmol) in dichloromethane (200 mL) was added oxalyl chloride (4.4 mL, 52.38 mmol) at –78 °C, slowly. Reaction solution was stirred for 20 minutes at –78 °C. A solution of amino alcohol **257** (7.0 g, 26.19 mmol) and triethylamine (18.4 mL, 130.95 mmol) in dichloromethane (30 mL) was added via cannula at –78 °C. Reaction was stirred at –78 °C for 1 hour and warmed to room temperature. TLC was used to monitor reaction progress. TLC plates were developed with gradient elution 80% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Quenched reaction with saturated $NaHCO_3$ solution (200 mL). Organic phase was washed with H_2O (200 mL), brine (200 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to crude yellow oil. Crude material was carried directly into Wittig olefination protocol.

Wittig olefination protocol: Methyltriphenylphosphonium bromide (14.0 g, 39.29 mmol) was dried over night under high vacuum and heated to 110 °C. To a stirred heterogeneous solution of methyltriphenylphosphonium bromide (14.0 g, 39.29 mmol) in toluene (100 mL) was

added potassium bis(trimethylsilyl)amide (0.5 M in toluene, 73 mL, 36.67 mmol) at room temperature. Reaction solution was stirred for 1.5 hours at room temperature; bright yellow colored solution. Crude aldehyde (26.19 mmol) as a solution in toluene (30 mL) was added to the ylide solution at –78 °C via cannula addition. Reaction solution turned a dark orange color. Reaction was stirred for 1 hour at –78 °C upon complete addition of aldehyde and warmed to room temperature. Stirred 2 hours at room temperature. TLC was used to monitor reaction progress. TLC plates were developed with gradient elution 35% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Quenched reaction with saturated NH_4Cl solution (100 mL) and organic phases were separated. Organic phase was washed with H_2O (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 5→10→15% Hex/EtOAc solution; doped with 1% triethylamine) to afford α-vinyl amino ester **259** (4.0 g, 58% yield, over two steps) as yellow oil.

α-Vinyl amino ester 259. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.28 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.00 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.41 (dd, *J* = 17.5, 1.3 Hz, 1H), 5.29 (dd, *J* = 10.8, 1.3 Hz, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.54 (d, *J* = 11.9 Hz, 1H), 3.49 (d, *J* = 11.8 Hz, 1H), 1.87 (tt, *J* = 14.3, 7.2 Hz, 2H), 0.88 (t, *J* = 7.4 Hz, 3H).

Preparation of amide 260:

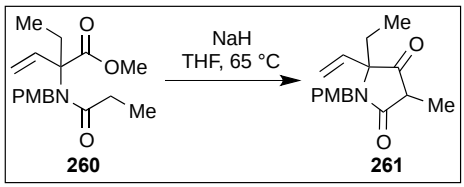


Amide 260. To a stirred solution of amine **259** (3.4 g, 12.91 mmol), pyridine (2.1 mL, 25.85 mmol), 4-(dimethylamino)pyridine (79 mg, 0.65 mmol) in dichloromethane (57 mL) was

added propionyl chloride (1.70 mL, 19.37 mmol) at 0 °C. Reaction solution was warmed to room temperature, and stirred for two days. TLC was used to monitor reaction progress. TLC plates were developed with gradient elution 40% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Quenched reaction with 1M HCl (75 mL) and separated phases. Organic phase was washed with 15% NaOH (75 mL), H_2O (75 mL), brine (75 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 25→30→35% EtOAc/Hex) to afford amide **260** (3.4 g, 88% yield) as colorless oil.

Amide 260. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.43 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.03 (dd, *J* = 17.6, 10.7 Hz, 1H), 5.26 (d, *J* = 15.4 Hz, 1H), 5.23 (d, *J* = 11.0 Hz, 1H), 4.54 (d, *J* = 17.6 Hz, 1H), 4.50 (d, *J* = 17.7 Hz, 1H), 3.81 (s, 3H), 3.77 (s, 2H), 2.39-2.01 (m, 4H), 1.05 (t, *J* = 7.4 Hz, 3H), 0.85 (t, *J* = 7.5 Hz, 3H).

Preparation of *N*-*para*-methoxybenzyl tetramic acid 261:

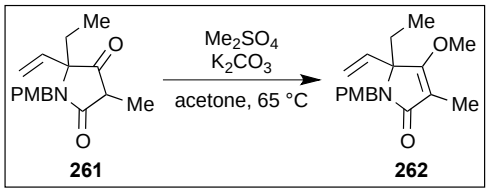


***N*-*para*-Methoxybenzyl tetramic acid 261**. To a refluxing suspension of sodium hydride (60% dispersion in mineral oil) (1.8 g, 45.57 mmol) in tetrahydrofuran (50 mL), was added dropwise a solution of amide **260** (5.1 g, 15.19 mmol), in tetrahydrofuran (50 mL). Reaction was refluxed for 2 days. TLC was used to monitor reaction progress. TLC plates were developed with gradient elution 25→50% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Checking conversion by ^{1}H NMR also monitored reaction progress; aliquots were from the reaction every 24 hours. Reaction was quenched with addition of saturated NH_4Cl solution (50

mL) and phases were separated. The aqueous phase was extracted with ethyl acetate (2 x 50 mL). Combined organic phase was washed with H_2O (200 mL), brine (200 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 10→30→50% EtOAc/Hex) followed by trituration with hexanes to afford *N-para*-Methoxybenzyl tetramic acid **261** (2.12 g, 50% yield, 3:1 dr) as a white solid.

***N-para*-Methoxybenzyl tetramic acid 261**. FTIR (thin film/NaCl): 2935, 2836, 2708, 1770, 1612, 1513, 1431, 1405, 1353, 1302, 1246, 1218, 1176, 1145, 1111, 1096, 1039, 1013, 992, 964, 927, 861, 845, 821, 791, 767, 734, 616, 591, 541; ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.32 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 5.62 (dd, *J* = 17.4, 10.6 Hz, 1H), 5.24 (d, *J* = 10.6 Hz, 1H), 5.17 (d, *J* = 17.4 Hz, 1H), 4.65 (d, *J* = 14.8 Hz, 1H), 4.30 (d, *J* = 14.8 Hz, 1H), 3.78 (s, 3H), 2.96 (q, *J* = 7.6 Hz, 1H), 2.07 (dq, *J* = 14.6, 7.3 Hz, 1H), 1.70 (dq, *J* = 14.6, 7.3 Hz, 3H), 1.29 (d, *J* = 7.6 Hz, 3H), 0.41 (t, *J* = 7.3 Hz, 3H); 7.31 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 5.63 (dd, *J* = 17.4, 10.7 Hz, 1H), 5.30 (d, *J* = 10.7 Hz, 1H), 5.21 (d, *J* = 17.4 Hz, 1H), 4.80 (d, *J* = 14.8 Hz, 1H), 4.15 (d, *J* = 14.8 Hz, 1H), 3.78 (s, 3H), 2.74 (q, *J* = 7.8 Hz, 1H), 2.00 (dq, *J* = 14.5, 7.3 Hz, 1H), 1.69 (dq, *J* = 14.6, 7.3 Hz, 1H), 1.35 (d, *J* = 7.8 Hz, 3H), 0.48 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ 210.8, 209.6, 173.6, 173.3, 159.1, 136.4, 135.9, 130.47, 130.38, 129.9, 118.6, 118.1, 113.9, 55.3, 44.9, 43.45, 43.34, 43.19, 27.0, 26.3, 12.7, 9.7, 7.96, 7.77; HRMS (EI) *m/z* 288.1594 [calc'd for $C_{17}H_{21}NO_3$ (M+H)+ 287.1521].

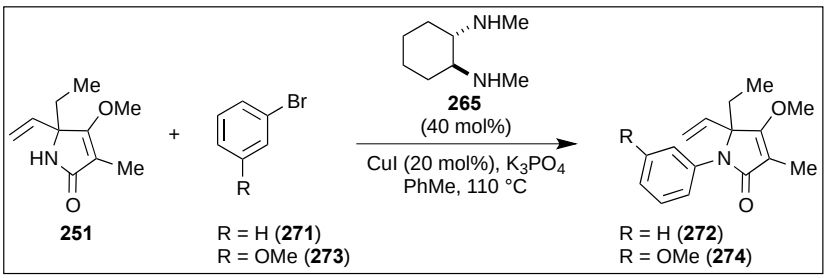
Preparation of vinylogous ester 262:



Vinylogous ester 262. To a stirred heterogeneous solution of *N-para*-methoxybenzyl tetramic acid **261** (2.8 g, 9.74 mmol), potassium carbonate (1.62 g, 11.69 mmol) in acetone (195 mL), was added dimethyl sulfate (1.1 mL, 11.69 mmol). Reaction was fitted with a reflux condenser and refluxed (56 °C) 24 hours. TLC was used to monitor reaction progress. TLC plates were developed with gradient elution 25→35→40% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Note starting material and product have very similar R_f, product has lower R_f then starting material. Conversion was checked ^{1}H NMR after 12 hours. Reaction was cooled to room temperature and volume of acetone reduced under pressure. Residue was partitioned between ethyl acetate (50 mL) and 2M NaOH (50 mL). Aqueous phase was extracted with ethyl acetate (3 x 25 mL). Combined organic phase was washed with H_2O (100 mL), brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 20→50→80% EtOAc/Hex) to afford vinylogous ester **262** (2.1 g, 72% yield) as yellow oil.

Vinylogous ester 262. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.29-7.26 (d, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 5.47 (dd, *J* = 17.0, 11.0 Hz, 1H), 5.25-5.18 (d, *J* = 17.0 Hz, 1H), 5.20 (d, *J* = 9.1 Hz, 1H), 4.54 (d, *J* = 15.1 Hz, 1H), 4.12 (d, *J* = 15.1 Hz, 1H), 3.99 (s, 3H), 3.78 (s, 3H), 2.04 (s, 3H), 1.80 (app tq, *J* = 14.3, 7.2 Hz, 1H), 1.59 (dq, *J* = 14.2, 7.2 Hz, 1H), 0.37 (t, *J* = 7.3 Hz, 3H).

Preparation of Aryl Amides 272 and 274:



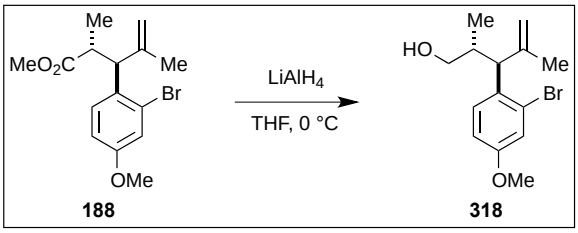
Base Screen. A vial equipped with a magnetic stir bar was charged with tetramic acid **251** (42 mg, 0.23 mmol), copper iodide (10 mg, 0.05 mmol), *trans*-*N,N'*-dimethyl-cyclohexane-1,2-diamine (**265**) (14 μL, 0.09 mmol), base [K_2CO_3 (64 mg, 0.46 mmol) or Cs_2CO_3 (150 mg, 0.46 mmol) or K_3PO_4 (98 mg, 0.46 mmol)], and bromobenzene (**271**) (0.5 M, 0.50 mL), briefly evacuated, and backfilled with nitrogen. Vial was quickly sealed, minimizing exposure to external atmosphere, and reaction was stirred at 156 °C for 24 hours. The reaction solution was cooled to room temperature and then filtered through a pad of silica gel and sand prepared in a medium pipette, eluting with 1:1 ethyl acetate-dichloromethane (5 mL). The filtrate was concentrated under reduced pressure and purified with silica gel chromatography (gradient elution 5→10→20% EtOAc/Hex) to afford aryl amide **272** [K_2CO_3 (1.2 mg, 2% yield); Cs_2CO_3 (11.1 mg, 19 % yield); K_3PO_4 (15.1 mg, 26% yield)] as colorless oil.

General Aryl Amidation Procedure. Following the procedure of Buchwald *et al.*[62] A vial equipped with a magnetic stir bar was charged with tetramic acid **251** (50 mg, 0.28 mmol), copper iodide (12 mg, 0.06 mmol), K_3PO_4 (119 mg, 0.56 mmol), briefly evacuated, and backfilled with nitrogen. *trans*-*N,N'*-Dimethyl-cyclohexane-1,2-diamine (**265**) (19 μL, 0.12 mmol) was added a solution in toluene (0.3 mL) followed by the addition of aryl bromide (**271** or **273**) (0.28 mmol). Vial was quickly sealed, minimizing exposure to external atmosphere, and reaction was stirred at 156 °C for 24 hours. The reaction solution was cooled to room temperature and then filtered through a pad of silica gel and sand prepared in a medium pipette, eluting with 1:1 ethyl acetate-dichloromethane (5 mL). The filtrate was concentrated under reduced pressure and purified with silica gel chromatography (gradient elution 5→10→20% EtOAc/Hex) to afford aryl amide **272** (13 mg, 18% yield) as a colorless oil or aryl amide **274** (28 mg, 35% yield) as colorless oil, respectively.

Aryl amide 272. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.45 (d, *J* = 8.2 Hz, 2H), 7.31 (t, *J* = 7.9 Hz, 2H), 7.15 (t, *J* = 7.3 Hz, 1H), 5.87 (dd, *J* = 17.4, 10.9 Hz, 1H), 5.31 (d, *J* = 10.3 Hz, 1H), 5.33-5.27 (d, *J* = 17.4 Hz, 1H), 4.07 (s, 3H), 2.09 (s, 3H), 2.00 (dq, *J* = 14.4, 7.2 Hz, 1H), 1.76 (dq, *J* = 14.3, 7.1 Hz, 1H), 0.67 (t, *J* = 7.3 Hz, 3H).

Aryl amide 274. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.20 (t, *J* = 8.1 Hz, 1H), 7.13 (t, *J* = 2.2 Hz, 1H), 7.06 (ddd, *J* = 8.1, 2.0, 0.9 Hz, 1H), 6.70 (ddd, *J* = 8.2, 2.5, 0.9 Hz, 1H), 5.88 (dd, *J* = 17.8, 10.5 Hz, 1H), 5.32 (d, *J* = 11.3 Hz, 1H), 5.31 (dd, *J* = 17.0 Hz, 1H), 4.07 (s, 3H), 3.77 (s, 3H), 2.08 (s, 3H), 1.99 (dt, *J* = 14.4, 7.2 Hz, 1H), 1.82 (dq, *J* = 14.3, 7.2 Hz, 1H), 0.65 (t, *J* = 7.3 Hz, 3H).

Preparation of alcohol 318:

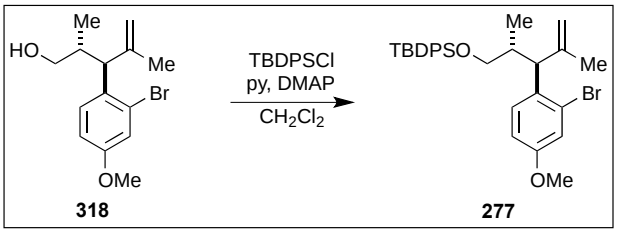


Alcohol 318. To a stirred heterogeneous solution of lithium aluminum hydride (78 mg, 2.04 mmol) in tetrahydrofuran (10 mL) was added methyl ester **188** (556 mg, 1.70 mmol) was a solution in tetrahydrofuran (7 mL), dropwise via cannula, at 0 °C. Upon complete addition reaction was warmed to room temperature. TLC was used to monitor reaction progress. TLC plates were developed with gradient elution 40% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Upon completion reaction was cooled to 0 °C and very slowly quenched with H_2O (100 μL), 15% NaOH (100 μL) and H_2O (300 μL), stirred for 30 minutes. Added a scoop of anhydrous $MgSO_4$, warmed to room temperature and stirred for 45 minutes. Filtered solution through a celite/sand pad, filtrated was washed with saturated NH_4Cl solution (20 mL), H_2O (20 mL), brine (20 mL). Organic phase was dried over anhydrous $MgSO_4$ and concentrated

under reduced pressure to afford alcohol **318** (500 mg, 98% yield) as colorless oil. No further purification was necessary.

Alcohol 318. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.20 (d, *J* = 8.7 Hz, 1H), 7.09 (d, *J* = 2.7 Hz, 1H), 6.84 (dd, *J* = 8.7, 2.7 Hz, 1H), 5.03 (d, *J* = 0.7 Hz, 1H), 4.87 (dd, *J* = 2.7, 1.3 Hz, 1H), 3.77 (s, 3H), 3.62 (d, *J* = 11.4 Hz, 1H), 3.41 (d, *J* = 10.2 Hz, 1H), 3.25 (t, *J* = 8.5 Hz, 1H), 2.25-2.12 (m, 1H), 1.62 (s, 3H), 1.19 (br s, 1H), 1.10 (d, *J* = 6.6 Hz, 3H).

Preparation of TBDPS-ether 277:

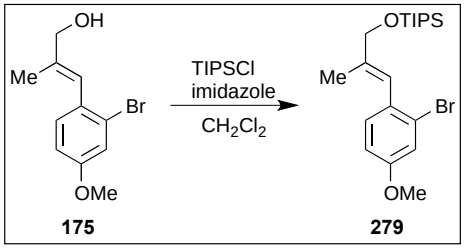


TBDPS-ether 277. To a stirred solution of alcohol **318** (500 mg, 1.67 mmol), 4-(dimethylamino)pyridine (21 mg, 0.17 mmol) and pyridine (0.27 mL, 3.34 mmol) in dichloromethane (7.4 mL) was added *tert*-butyl(chloro)diphenylsilane (0.65 mL, 2.51 mmol) at room temperature. Stirred for 24 hours at room temperature. TLC was used to monitor reaction progress. TLC plates were developed with gradient elution 20% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Reaction did not go to completion but was quenched with 1 M HCl (10 mL) after 24 hours. Organic phase was washed with H_2O (15 mL), brine (15 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 1→2→3% EtOAc/Hex) to afford TBDPS-ether **277** (194 mg, 22% yield) as colorless oil.

TBDPS-ether 277. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.63-7.60 (m, 2H), 7.47 (dd, *J* = 7.9, 1.4 Hz, 4H), 7.42-7.35 (m, 4H), 7.31 (t, *J* = 6.0 Hz, 2H), 7.09 (d, *J* = 2.7 Hz, 1H), 6.97 (d, *J* = 8.7 Hz, 1H), 6.71 (dd, *J* = 8.7, 2.7 Hz, 1H), 5.06 (d, *J* = 1.4 Hz, 1H), 4.86 (t, *J* = 1.5 Hz, 1H), 3.78 (s,

3H), 3.74 (d, *J* = 11.3 Hz, 1H), 3.41 (dd, *J* = 10.0, 3.5 Hz, 1H), 3.39-3.34 (m, 1H), 2.26-2.13 (m, 1H), 1.58 (s, 3H), 1.16 (d, *J* = 6.5 Hz, 3H), 1.03 (s, 9H).

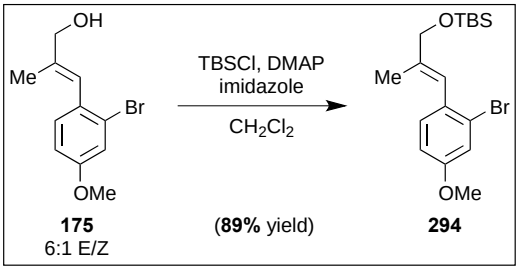
Preparation of TIPS-ether 279:



TIPS-ether 279. To a stirred solution of allylic alcohol **175** (86 mg, 0.33 mmol), imidazole (228 mg, 3.34 mmol) in dichloromethane (3 mL) was added triisopropylsilyl chloride (0.22 mL, 1.00 mmol) at room temperature. Reaction was stirred overnight at room temperature. TLC was used to monitor reaction progress. TLC plates were developed with gradient elution 2% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Quenched with saturated NH_4Cl solution (5 mL), diluted with H_2O (2 mL) and separated phases. Aqueous phase was extracted with diethyl ether (2 x 5 mL). Combined organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution Hex$\rightarrow$1$\rightarrow$2% EtOAc/Hex) to afford TIPS-ether **279** (121 mg, 98% yield) as colorless oil.

TIPS-ether 279. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.20 (d, *J* = 8.5 Hz, 1H), 7.13 (d, *J* = 2.6 Hz, 1H), 6.83 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.58 (s, 1H), 4.28 (s, 2H), 3.79 (s, 3H), 1.71 (s, 3H), 1.22-1.19 (m, 3H), 1.11 (d, *J* = 5.0 Hz, 18H).

Preparation of TBS-ether 294:

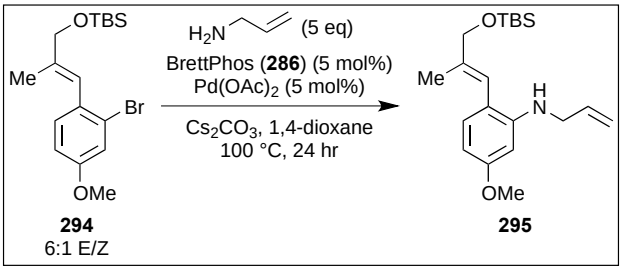


TBS-ether 294. To a stirred solution of allylic alcohol **175** (6:1 E/Z) (500 mg, 1.94 mmol), 4-(dimethylamino)pyridine (24 mg, 0.19 mmol), imidazole (264 mg, 3.88 mmol) in dichloromethane (2 mL) was added *tert*-butyldimethylsilyl chloride (440 mg, 2.92 mmol) at room temperature. TLC was used to monitor reaction progress. TLC plates were developed with gradient elution 2% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Reaction was stirred at room temperature for 3 hours. Reaction was diluted with dichloromethane (2 mL) followed by hydrolysis with H_2O (5 mL) and separation of phases. Organic phase was washed with brine (5 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure directly onto silica gel (approximately 1.5 g). Purified with silica gel chromatography (gradient elution1→2% EtOAc/Hex) to afford TBS-ether **294** (643 mg, 89% yield, 6:1 E/Z) as colorless oil.

TBS-ether 294. FTIR (thin film/NaCl): 2925, 1688, 1597, 1566, 1462, 1389, 1361, 1235, 1181, 1086, 939, 841, 777, 669; ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.19 (d, *J* = 8.6 Hz, 1H), 7.14 (d, *J* = 2.6 Hz, 1H), 6.83 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.50 (s, 1H), 4.20 (s, 2H), 3.80 (s, 3H), 1.71 (d, *J* = 1.4 Hz, 3H), 0.95 (s, 9H), 0.13 (s, 6H); 7.43 (d, *J* = 8.6 Hz, 1H), 7.07 (d, *J* = 2.6 Hz, 1H), 6.88 (dd, *J* = 8.6, 2.6 Hz, 1H), 4.13 (s, 2H), 3.79 (s, 3H), 1.96 (d, *J* = 1.5 Hz, 3H), 0.89 (s, 9H), 0.12 (s, 6H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ 158.7, 138.1, 131.6, 131.3, 130.5, 128.6, 126.2,

124.8, 123.0, 117.7, 113.4, 113.22, 113.15, 68.2, 64.4, 62.8, 55.7, 26.15, 26.08, 21.6, 18.6, 15.0, -5.05, -5.12; HRMS (EI) *m/z* 389.0967 [calc'd for $C_{17}H_{27}BrO_3Si$ (M+H)+ 386.0913].

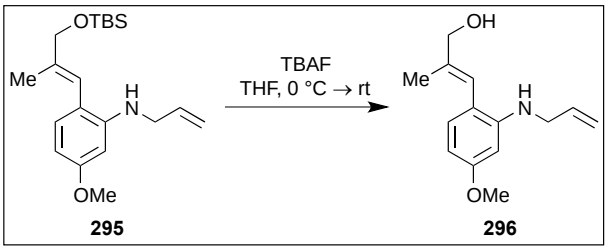
Preparation of aryl amine 295:



Aryl amine 295. A sealed tube reaction vessel equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (7 mg, 0.03 mmol), BrettPhos (**286**) (16 mg, 0.03 mmol) and Cs_2CO_3 (352 mg, 1.08 mmol), briefly evacuated, and backfilled with nitrogen. 1,4,-Dioxane (2 mL) (deoxygenated prior to use by sparging with nitrogen for 1 hour) was added followed by the addition of allylamine (0.21 mL, 2.69 mmol) and aryl bromide **294** (200 mg, 0.54 mmol) as a solution in 1,4-dioxane (2 mL). Reaction vessel was sealed with minimal exposure of reaction solution to external atmosphere and heated to 100 °C. TLC was used to monitor reaction progress. TLC plates were developed with gradient elution 2% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Reaction was cooled to room temperature after 24 hours diluted with dichloromethane (10 mL) and quenched with saturated NH_4Cl solution (10 mL) followed by separation of the phases. Organic layer was washed with H_2O (10 mL), brine (10 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure directly onto silica gel (approximately 300 mg). Purified with silica gel chromatography (gradient elution 1→2→5% EtOAc/Hex) to afford aryl amine **295** (100 mg, 53% yield) as yellow oil. Crude material was also successfully be advanced to cleavage of TBS-ether and purified there after.

Aryl amine 295. Spectral data was for aryl amine **295** was lost.

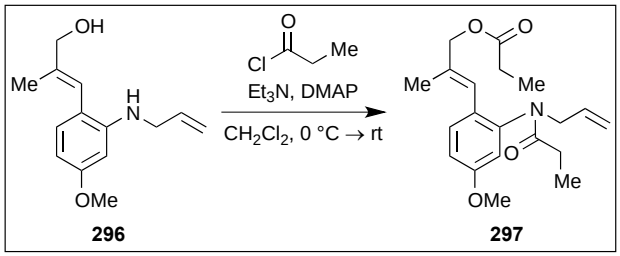
Preparation of allylic alcohol 296:



Allylic alcohol 296. To a stirred solution of TBS-ether **295** (344 mg, 0.99 mmol) in tetrahydrofuran (2 mL) was added tetrabutylammonium fluoride (1 M in THF, 1.5 mL, 1.46 mmol) at 0 °C and stirred for 1 hour. Reaction was warmed to room temperature and stirred over night. TLC was used to monitor reaction progress. TLC plates were developed with gradient elution 40% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Reaction was diluted with ethyl acetate (10 mL) and quenched with saturated NH_4Cl solution (10 mL), phase were separated. Organic phase was washed with brine (20 mL), dried over anhydrous $MgSO_4$ and absorbed directly onto silica gel (approximately 350 mg) under reduced pressure. Purified with silica gel chromatography (gradient elution 25→50% EtOAc/Hex) to afford allylic alcohol **296** (200 mg, 87% yield) as colorless oil.

Allylic alcohol 296. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 6.94 (d, *J* = 8.2 Hz, 1H), 6.27 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.21 (d, *J* = 2.4 Hz, 1H), 5.99-5.89 (m, 1H), 5.27 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.16 (dd, *J* = 10.3, 1.4 Hz, 1H), 4.20 (s, 2H), 3.79 (s, 3H), 1.75 (s, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ 160.0, 146.9, 139.5, 135.4, 130.4, 120.5, 116.3, 116.0, 101.1, 97.3, 68.5, 55.2, 46.5, 15.3; HRMS (EI) *m/z* 234.1491 [calc'd for $C_{14}H_{19}NO_2$ (M+H)+ 234.1489].

Preparation of allylic ester 297:

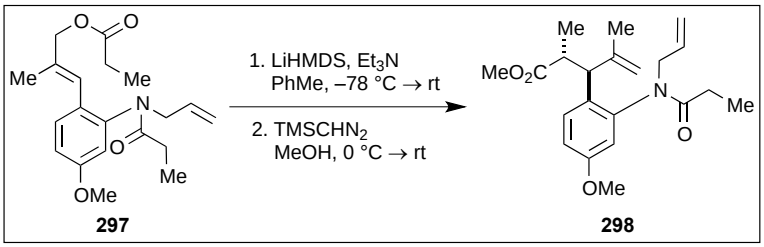


Allylic ester 297. To a stirred solution of allylic alcohol **296** (200 mg, 0.86 mmol), 4-(dimethylamino)pyridine (catalytic quantity, flake), triethylamine (0.5 mL, 3.43 mmol) in dichloromethane (8 mL) was added propionyl chloride (0.2 mL, 2.15 mmol) at 0 °C, stirred for 5 minutes. Reaction was warmed to room temperature and stirred. TLC was used to monitor reaction progress. TLC plates were developed with gradient elution 10% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Quenched with saturated NH_4Cl solution (10 mL) and separated phases. Organic phase was washed with H_2O (10 mL) and brine (10 mL), dried over anhydrous $MgSO_4$ and filtered. Filtrated was absorbed directly onto silica gel (approximately 200 mg) under reduced pressure. Purified with silica gel chromatography (gradient elution 10→20→30% EtOAc/Hex) to afford allylic ester **297** (200 mg, 70 % yield) as colorless oil.

Allylic ester 297. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.26 (d, *J* = 8.4 Hz, 1H), 6.87 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.63 (d, *J* = 2.7 Hz, 1H), 6.24 (s, 1H), 5.83 (tdd, *J* = 11.7, 11.0, 6.1 Hz, 1H), 5.05 (d, *J* = 8.7 Hz, 1H), 5.02 (d, *J* = 15.6 Hz, 1H), 4.57 (s, 2H), 4.53 (dd, *J* = 14.5, 6.1 Hz, 1H), 3.79 (s, 3H), 3.77-3.74 (dd, *J* = 14.5, 6.1 Hz, 1H), 2.36 (q, *J* = 7.6 Hz, 2H), 1.99 (dq, *J* = 15.8, 7.8 Hz, 1H), 1.88 (dq, *J* = 15.7, 7.7 Hz, 1H), 1.79 (s, 2H), 1.15 (t, *J* = 7.6 Hz, 3H), 1.00 (t, *J* = 7.5 Hz, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ 174.2, 173.5, 159.3, 142.1, 134.3, 133.3, 131.6,

127.7, 123.4, 118.2, 115.0, 113.3, 69.3, 55.6, 51.7, 27.7, 27.4, 15.5, 9.5, 9.3; HRMS (EI) *m/z* 346.202 [calc'd for $C_{20}H_{27}NO_4$ (M+H)+ 346.2013].

Preparation of γ,δ-unsaturated methyl ester 298:



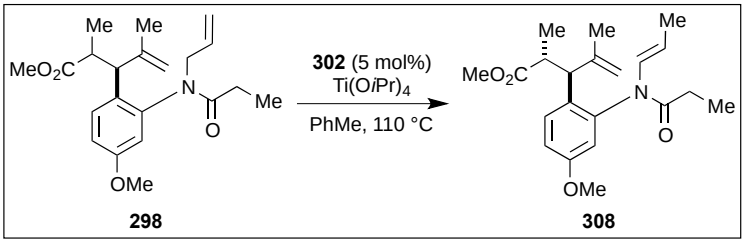
γ,δ-Unsaturated methyl ester 298. A vial fitted with a magnetic stir bar was charged with lithium bis(trimethylsilyl)amide (60 mg, 0.36 mmol), toluene (1 mL) and triethylamine (0.5 mL, 3.60 mmol), solution was cooled to –78 °C and allylic ester **297** (20 mg, 0.06 mmol) was added a solution in toluene (200 μL), dropwise. Reaction was warmed to room temperature and allowed to stir overnight. TLC was used to monitor reaction progress. TLC plates were developed with 50% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Reaction was hydrolyzed with H_2O (1 mL), stirring vigorously. Solution was acidified with 12 M HCl to pH = 1. Acidic solution Acidic solution was extracted with ethyl acetate (3 x 2 mL). Combined organic phase was washed with brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated to crude oil.

To a stirred solution of crude carboxylic acid (0.06 mmol) in methanol (0.5 mL) was added trimethylsilyldiazomethane (2 M in hexanes, 0.10 mL, 0.18 mmol), dropwise, at 0 °C. Reaction was stirred for 15 minutes at 0 °C. Reaction was warmed to room temperature and stirred for 1 hour. Reaction was warmed to room temperature and allowed to stir overnight. TLC was used to monitor reaction progress. TLC plates were developed with 50% EtOAc/Hex solution and visualized by UV lamp and $KMnO_4$ stain. Quenched with 3 M AcOH in EtOAc (2

mL) and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 10→25% EtOAc/Hex) to afford γ,δ-unsaturated methyl ester **298** (10 mg, 45% yield, 3:1 anti/syn, over two steps).

γ,δ-Unsaturated methyl ester 298. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.28 (d, *J* = 5.3 Hz, 1H), 6.86 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.52 (d, *J* = 2.7 Hz, 1H), 5.98-5.90 (m, 1H), 5.12 (d, *J* = 9.0 Hz, 1H), 5.09 (d, *J* = 14.3 Hz, 1H), 4.86 (s, 1H), 4.80 (s, 1H), 3.77 (s, 3H), 3.60 (d, *J* = 11.9 Hz, 1H), 3.48 (s, 3H), 3.06 (ddd, *J* = 19.8, 12.9, 6.9 Hz, 1H), 1.89 (dq, *J* = 15.9, 7.8 Hz, 1H), 1.67 (dq, *J* = 15.9, 7.8 Hz, 1H), 1.50 (s, 3H), 1.20 (d, *J* = 6.9 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H), 7.30 (d, *J* = 8.7 Hz, 1H), 6.86 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.60 (d, *J* = 2.7 Hz, 1H), 5.98-5.90 (m, 1H), 5.07 (d, *J* = 14.4 Hz, 1H), 5.05 (d, *J* = 5.3 Hz, 1H), 4.94 (s, 1H), 4.92 (s, 1H), 3.77 (s, 3H), 3.62 (d, *J* = 14.7 Hz, 1H), 3.48 (s, 3H), 3.06 (ddd, *J* = 19.8, 12.9, 6.9 Hz, 6H), 2.20 (dq, *J* = 16.0, 7.8 Hz, 1H), 2.00 (dt, *J* = 16.0, 7.8 Hz, 1H), 1.49 (s, 3H), 1.19 (d, *J* = 6.7 Hz, 3H), 1.10 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR (101 MHz; CDCl3): δ 176.13, 176.05, 174.34, 174.24, 158.48, 158.41, 142.8, 142.5, 142.20, 142.04, 133.8, 133.4, 130.6, 130.2, 129.1, 128.7, 118.33, 118.15, 116.68, 116.52, 116.1, 115.8, 113.41, 113.33, 55.5, 52.8, 51.73, 51.70, 51.2, 50.71, 50.54, 40.90, 40.71, 28.3, 27.5, 20.8, 18.4, 17.6, 17.34, 17.20, 14.4, 9.7, 9.5.

Preparation of enamide 308:



Enamide 308. Toluene used in procedure was pulled fresh from the still and deoxygenated immediately prior to use by sparging with nitrogen for 1 hour. To a stirred solution of diene **298** (6.5 mg, 0.02 mmol) in toluene (1 mL) was added titanium(IV) isopropoxide (12

μL, 0.04 mmol) at room temperature and stirred for 5 minutes. Diene/titanium(IV) isopropoxide/toluene solution was transferred to a stirred solution of precatalyst **302** (1 mg, 0.001 mmol) in toluene (1 mL) and reaction was refluxed (110 °C) for 24 hours. Reaction was cooled to room temperature and concentrated under reduced pressure. Residue was purified with silica gel chromatography (gradient elution 5→10→15→20% EtOAc/Hex) to afford enamide **308** (6 mg, 89% yield, 2:1 dr) as colorless residue.

Enamide 308. FTIR (thin film/NaCl): 3380, 2939, 1736, 1675, 1610, 1577, 1501, 1457, 1372, 1243, 1227, 1164, 1089, 1059, 1037; ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.44 (d, *J* = 14.3 Hz, 1H), 7.38 (d, *J* = 8.6 Hz, 1H), 6.92 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.57 (d, *J* = 2.5 Hz, 1H), 4.81 (s, 2H), 4.41 (dq, *J* = 14.0, 6.9 Hz, 1H), 3.79 (s, 3H), 3.54 (d, *J* = 11.7 Hz, 1H), 3.47 (s, 3H), 3.05 (tt, *J* = 13.0, 6.6 Hz, 2H), 1.87 (dq, *J* = 16.0, 7.8 Hz, 2H), 1.69 (d, *J* = 6.6 Hz, 3H), 1.45 (s, 3H), 1.15 (d, *J* = 6.8 Hz, 3H), 0.96 (t, *J* = 7.3 Hz, 3H); 7.38 (d, *J* = 8.6 Hz, 1H), 7.33 (d, *J* = 16.4 Hz, 1H), 6.92 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.59 (d, *J* = 2.6 Hz, 1H), 4.81 (s, 1H), 4.74 (s, 1H), 4.14 (td, *J* = 13.8, 7.1 Hz, 1H), 3.79 (s, 3H), 3.47 (d, *J* = 5.3 Hz, 1H), 3.47 (s, 3H), 3.05 (tt, *J* = 13.0, 6.6 Hz, 3H), 2.20 (td, *J* = 15.6, 8.1 Hz, 1H), 2.01 (dt, *J* = 16.0, 7.8 Hz, 1H), 1.69 (d, *J* = 6.6 Hz, 3H), 1.45 (s, 3H), 1.15 (d, *J* = 6.8 Hz, 3H), 0.96 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 175.8, 172.2, 159.2, 158.6, 142.1, 130.6, 129.2, 127.1, 116.1, 115.8, 114.0, 109.0, 55.5, 51.6, 50.4, 40.4, 28.9, 17.7, 17.0, 15.4, 9.3; HRMS (EI) *m/z* 360.2175 [calc'd for $C_{21}H_{29}NO_4$ (M+H)+ 360.2169]

References Relevant to Chapter 3

(41) Royles, B. J. L. *Chem. Rev.* **1995**, *95*, 1981.

(42) Schobert, R.; Schlenk, A. *Bioorgan. Med. Chem.* **2008**, *16*, 4203.

(43) Mulholla.Tp; Foster, R.; Haydock, D. B. *J. Chem. Soc. Perk. Trans. 1*. **1972**, 2121.

(44) Benary, E. *Ber. Dtsch. Chem. Ges.* **1907**, *40*, 1079.

(45) Benary, E. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 1759.

(46) Benary, E. *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 3682.

(47) Anschutz, R. *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 2374.

(48) Gabriel, S. *Ber. Dtsch. Chem. Ges.* **1913**, *46*, 1319.

(49) Gabriel, S. *Ber. Dtsch. Chem. Ges.* **1914**, *47*, 3033.

(50) Willard, P. G.; Delaszlo, S. E. *J. Org. Chem.* **1984**, *49*, 3489.

(51) Igglessimarkopoulou, O.; Sandris, C. *J. Heterocyclic Chem.* **1982**, *19*, 883.

(52) Igglessimarkopoulou, O.; Sandris, C. *J. Heterocyclic Chem.* **1985**, *22*, 1599.

(53) King, J. A.; Mcmillan, F. H. *J. Am. Chem. Soc.* **1950**, *72*, 1236.

(54) Henning, H. G.; Gelbin, A. *Adv. Heterocycl. Chem.* **1993**, *57*, 139.

(55) Seebach, D.; Aebi, J. D. *Tetrahedron Lett.* **1984**, *25*, 2545.

(56) Di Giacomo, M.; Vinci, V.; Serra, M.; Colombo, L. *Tetrahedron-Asymmetry* **2008**, *19*, 247.

(57) Corey, E. J.; Reichard, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 10677.

(58) Thompson, C. M.; Frick, J. A.; Green, D. L. C. *J. Org. Chem.* **1990**, *55*, 111.

(59) Seebach, D.; Aebi, J. D.; Gandercoquoz, M.; Naef, R. *Helv. Chim. Acta.* **1987**, *70*, 1194.

(60) Loh, T. P.; Chok, Y. K.; Yin, Z. *Tetrahedron Lett.* **2001**, *42*, 7893.

(61) Klapars, A.; Antilla, J. C.; Huang, X. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727.

(62) Klapars, A.; Huang, X. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421.

(63) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2010**, *1*, 13.

(64) For preparation of aryl bromides **270** and **272** see Appendix 2.

(65) Maiti, D.; Fors, B. P.; Henderson, J. L.; Nakamura, Y.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 57.

(66) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27.

(67) Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, 927.

(68) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901.

(69) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609.

(70) Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 13552.

(71) Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 6686.

(72) Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Schrodi, Y. *Org. Lett.* **2007**, *9*, 1589.

(73) Enquist, J. A.; Stoltz, B. M. *Nature* **2008**, *453*, 1228.

(74) Furstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130.

(75) Furstner, A.; Ackermann, L.; Gabor, B.; Goddard, R.; Lehmann, C. W.; Mynott, R.; Stelzer, F.; Thiel, O. R. *Chem. Eur. J.* **2001**, *7*, 3236.

(76) Campbell, M. J.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 10370.

(77) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160.

(78) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

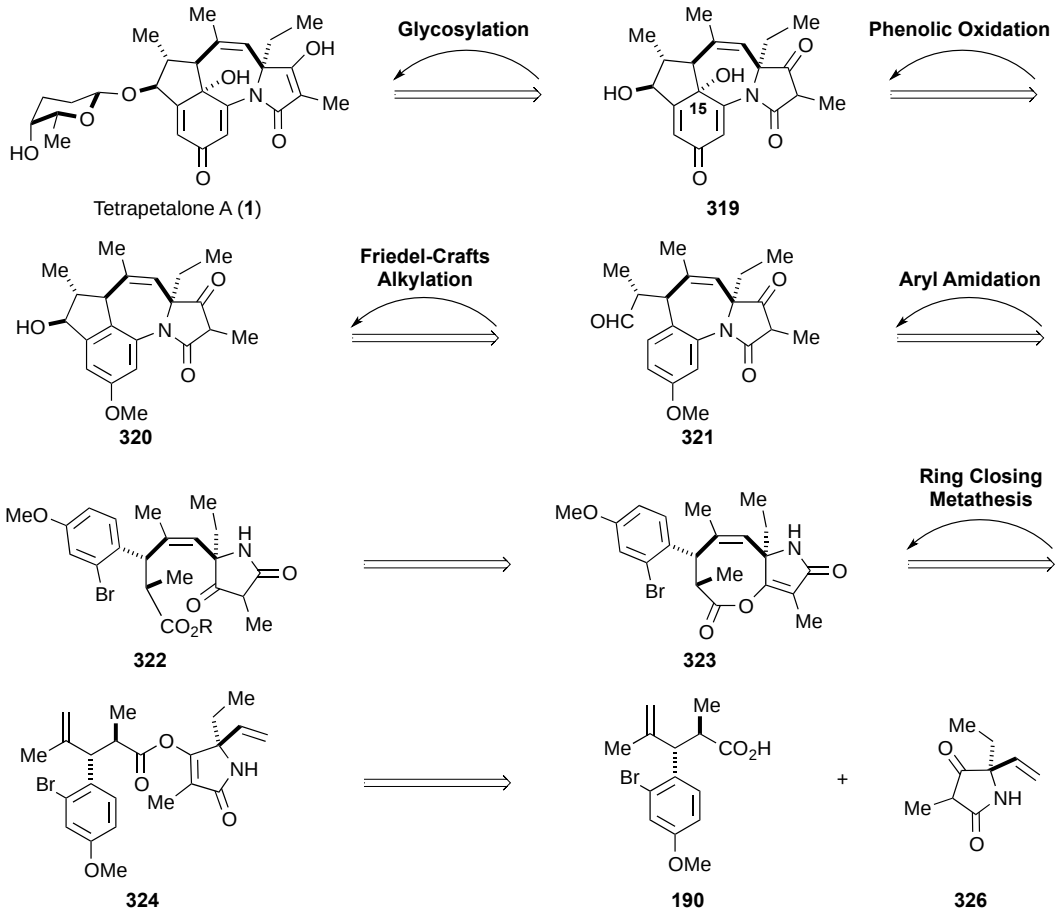
(79) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Chapter 4

Turning to Ring Closing Metathesis

4.1 Fourth-Generation Retrosynthetic Analysis

As outlined in Scheme 4.1, our fourth-generation retrosynthetic analysis of tetrapetalone A (**1**) envisaged completion of the natural product via glycosylation of aglycon **319**. Aglycon **319** was envisioned as deriving from a Friedel-Crafts alkylation applied to aldehyde **321** and phenolic oxidation to install the C(15)-hydroxyl group. Construction of the C–N bond of benzazepine **321** would be achieved by application of an intramolecular cross-coupling reaction applied to tetramic acid **322**. Tetramic acid **322** would derive from hydrolysis of lactone **323** subsequent to implementation of ring closing metathesis applied to diene **324**. Diene **324** would be procured by coupling carboxylic acid **190** and tetramic acid **326**.



Scheme 4.1 Fourth-Generation Retrosynthetic Analysis

4.2 Olefin Metathesis

4.2.1 Olefin Types and Rules for Selectivity as Derived from Cross Metathesis

Olefin cross metathesis is a convenient route to functionalized and higher olefins from simple alkene substrates.[80] Olefin cross metathesis has gained prominence due to the availability of catalysts with varied activities. These catalysts have expanded the variety of olefin types and functional groups that are amenable to olefin metathesis and have demonstrated the ability to prepare highly substituted olefins.

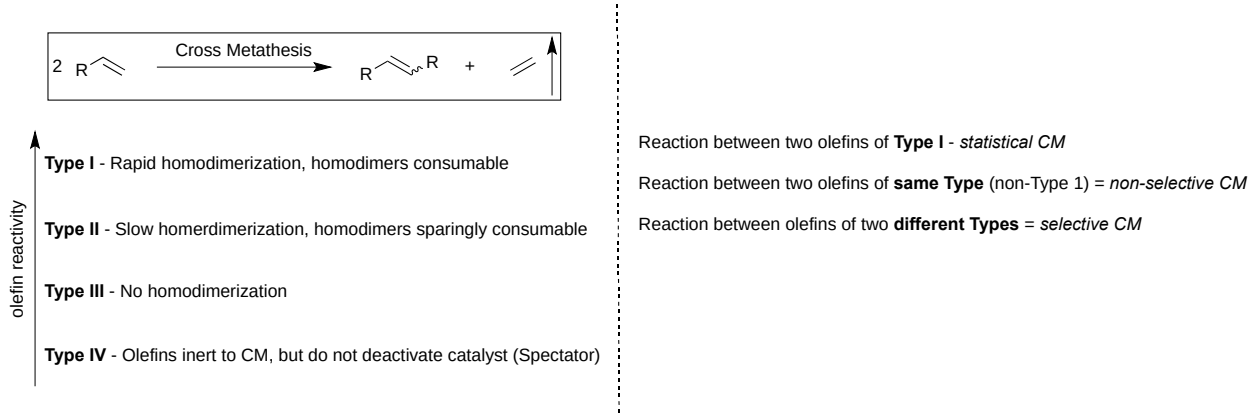
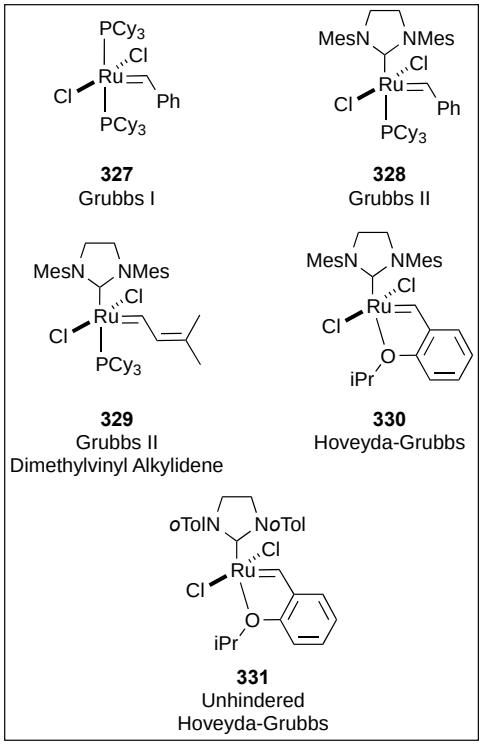


Figure 4.1 Olefin Categorization and Rules for Selectivity

A growing body of empirical evidence has allowed the prediction of olefin reactivity, described as a gradient scale of the *relative* propensity for an olefin to undergo homodimerization, along with the subsequent reactivity of the resulting homodimers. The general model for olefin metathesis is comprised of four distinct olefin types, which can be used to predict both selective and nonselective cross metathesis reactions (Figure 4.1). In general, a reactivity gradient exists from most active olefin type (Type I olefin) to least active olefin Type (Type IV), with sterically unhindered electron-rich olefins categorized as Type I and increasingly sterically hindered/or electron-deficient olefins falling into Types II through IV. Grubbs and coworkers have disclosed a general model based on the categorization of olefin reactivity, which can be utilized to predict both selective and nonselective cross metathesis reactions for a number of commercially available metathesis catalysts with varying activities and has been described specifically for catalyst **328** (Table 4.1).[80]

Table 4.1 Olefin Categories for Selective Cross Metathesis with Grubbs II Catalyst

olefin type	**328**
Type I	terminal olefins 1° allylic alcohols, esters allyl boronate esters allyl halides styrenes (no large *o*-substit.) allyl phosphonates allyl silanes allyl phosphine oxides allyl sulfides protected allyl amines
Type II	styrenes (large *o*-substit.) acrylates acrylamide acrylic acide acrolein vinyl ketones unprotected 3º allylic alcohols vinyl epoxides 2º allylic alcohols perfluorinated alkane olefins
Type III	1,1-disubstituted olefins non-bulky trisub. olefins vinyl phosphonates phenyl vinyl sulfone 4º allylic carbons (all alkyl substit.) 3º allylic alcohols (protected)
Type IV	vinyl nitro olefins trisubstituted allyl alcohols (protected)



327
Grubbs I

328
Grubbs II

329
Grubbs II
Dimethylvinyl Alkylidene

330
Hoveyda-Grubbs

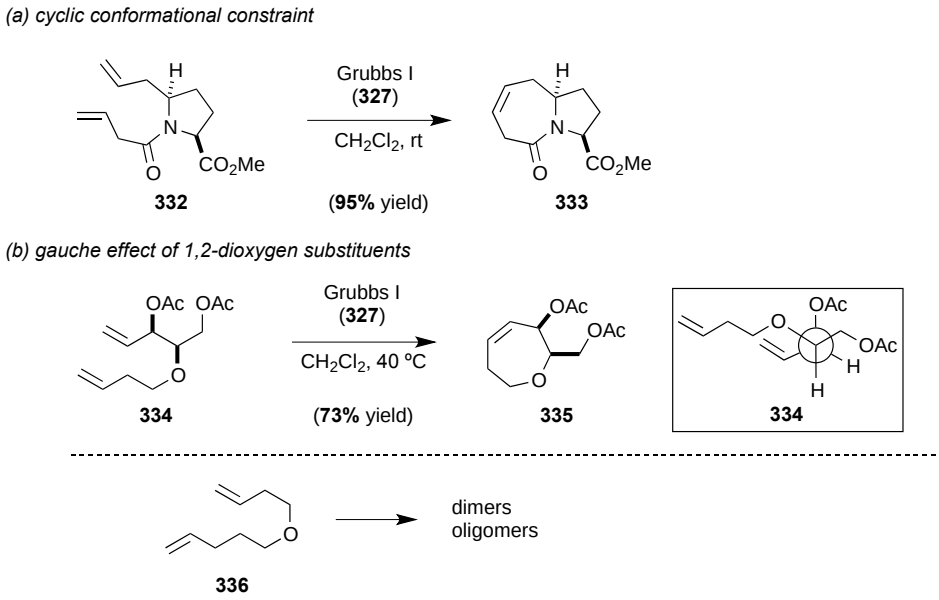
331
Unhindered
Hoveyda-Grubbs

4.2.2 Construction of Medium-Sized Rings by Ring Closing Metathesis

Not every ring size is accessible with the same ease because of enthalpic (increasing ring strain in the transition state) and entropic influences (probability of the chain ends meeting).[81] Medium-sized rings are the most difficult to prepare. Among the many cyclization reactions available, olefin metathesis (ring closing metathesis) has gained tremendous popularity due in part to the involvement of relatively stable double bonds. This advantage facilitates synthesis and handling of the cyclization precursors.

To date there are many elegant applications of ring closing metathesis to the synthesis of macrocycles. In contrast, successful RCM reactions for medium-sized ring construction are

much more limited.[81] For medium-sized rings, it is beneficial to use conformational constraints or stereoelectronic effects to promote cyclization. These constraints are achieved either by using preexisting rings (cyclic conformational constraints) or acyclic conformational constraints. (*gauche* effect). For example, Westermann and coworkers demonstrated that the attachment of olefinic side chains to lactams facilitates RCM cyclization. Specifically, they found that the seven membered bicyclic lactam **333** was produced in excellent yield (95%) upon exposure of **332** to Grubbs I (**327**) catalyst in dichloromethane at room temperature (Scheme 4.2a).[82] Besides using a ring in order to limit the conformational freedom of a chain, appropriately positioning substituents on an acyclic chain can increase propinquity of the two olefinic groups and improve the cyclization. Crimmins and coworkers reported on the use of the gauche effect of 1,2-dioxygen substituents to facilitate ring closure, exposure of **334** to Grubbs I (**327**) in dichloromethane at 40 ºC provided cyclic ether **335** while, ether **336** only afforded dimers and oligomers (Scheme 4.2b).[83]

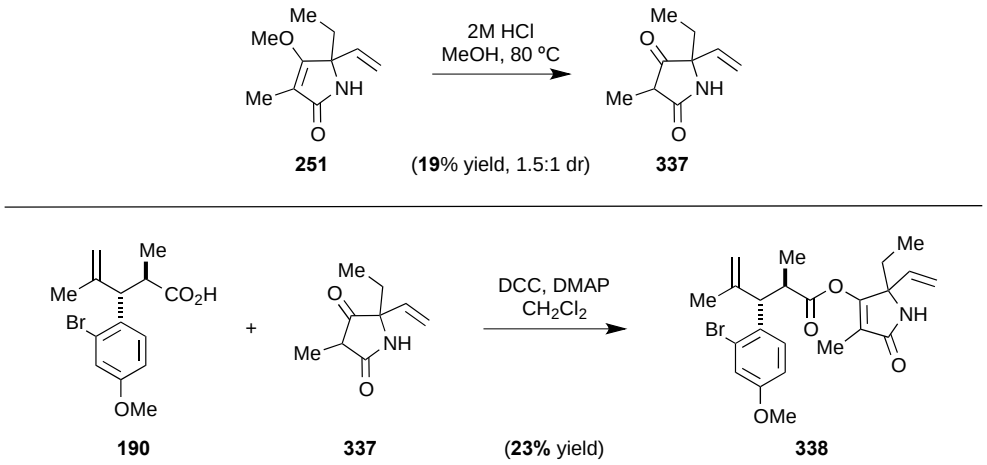


Scheme 4.2 Conformational Control Employed for Construction of Medium-Sized Rings

4.3 Initial Ring Closing Metathesis Inquiry

4.3.1 Secondary Amide Substrate

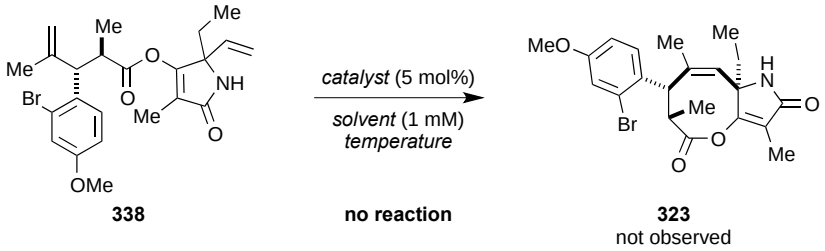
The proposed cyclization of diene **324** (Scheme 4.1) by ring closing metathesis represents an extremely challenging scenario as both olefins are Type III (1,1-disubstituted and fully substituted allylic carbons, respectively) but having the synthetic precursors on hand we felt that this cyclization was worth investigating. To this end vinylogous ester **251** was hydrolyzed to the requisite tetramic acid **337** and subjected to dicyclohexylcarbodiimide (DCC) mediated esterification of carboxylic acid **190** to afford the desired diene **338** in low yield (5%), over two steps.



Scheme 4.3 Diene Synthesis

Exposure of diene **338** to Grubbs II catalyst (**328**) or Hoveyda-Grubbs catalyst (**330**) did not afford lactone **323** and only starting material was observed (Table 4.2). Variation of the reaction conditions (temperature, solvent and reaction concentration) did not alter the outcome. To ensure that the catalyst was not being sequestered by the amide moiety of diene **338**, we opted to investigate a diene in which the amide was protected.

Table 4.2 Attempted Cyclization by Ring Closing Metathesis



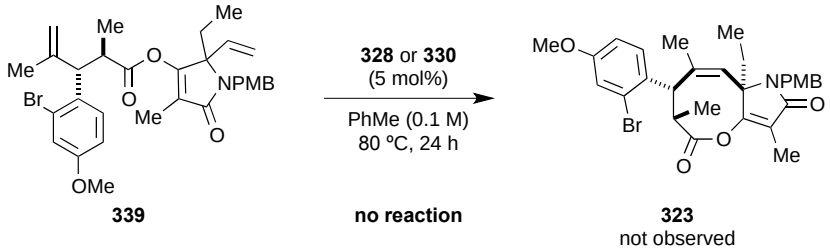
entry	catalyst	solvent	temperatue (ºC)	Time (h)
1	**328**	PhMe	rt	48
2	**328**	PhMe (0.05 M)	80	24
3	**330**	PhMe	rt	48
4	**330**	PhMe (0.05 M)	80	24
5	**328**	CH_2Cl_2	rt	48
6	**330**	CH_2Cl_2	rt	48

4.3.2 Tertiary Amide Substrate

Carboxylic acid **190** was subjected to DCC mediated esterification with *N-para*-methoxybenzyl tetramic acid **261** to provide diene **339** in moderate yield (49%) (Scheme 4.4).

Scheme 4.4 DCC Mediated Esterification

Diene **339**, when subjected to Grubbs II catalyst (**328**) or the Hoveyda-Grubbs catalyst (**330**) in toluene at 80 ºC, did not engage in the desired cyclization to afford lactone **323**. Recognizing the difficulty of initiating the catalytic process on either of the Type III olefins of diene **338** and **339** we decided to investigate a relay ring closing metathesis strategy.



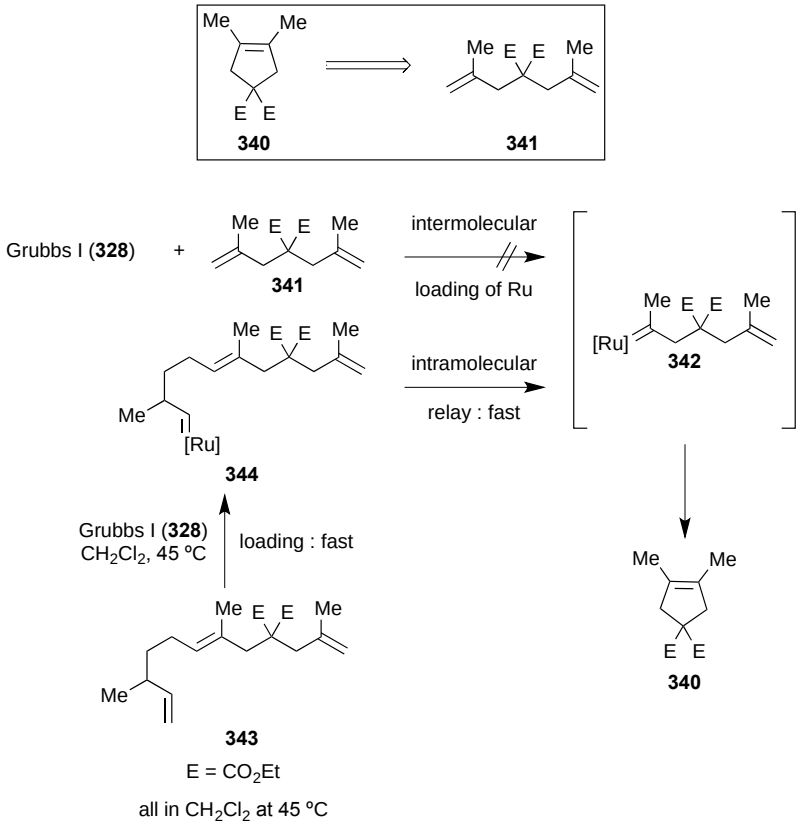
Scheme 4.5 Attempted Cyclization by Ring Closing Metathesis

4.4 Relay Ring Closing Metathesis

Despite the many successful applications, in some cases cyclization by ring closing metathesis can be less than satisfactory, due to low reactivity and/or low selectivity. The development of methods to overcome these shortcomings is ongoing in many laboratories, and relay ring closing metathesis (RRCM) is one such development.[84]

The foundation of this strategy rests on the fact that although initiation of the catalytic cycle with a sterically demanding olefin is a challenge (e.g., **341** to **342**, Scheme 4.6), the

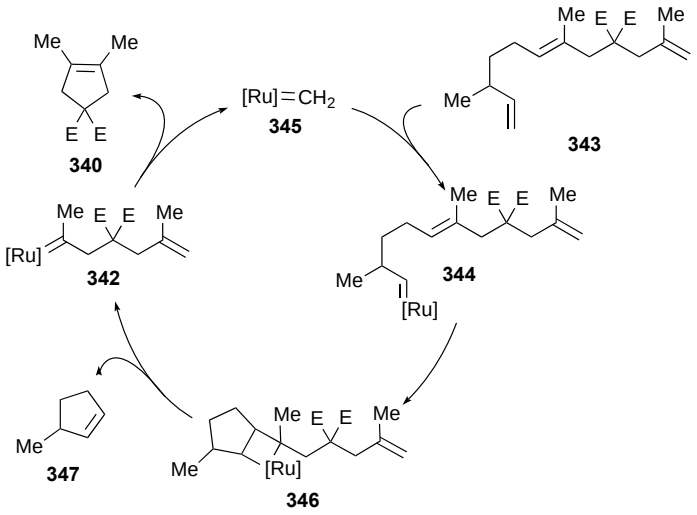
intramolecular reaction of a ruthenium alkylidene onto such an alkene is often attainable (i.e. **344** to **342**), as is the subsequent intramolecular reaction of the previously inaccessible alkylidene (i.e. **342** to **340**). Thus, in this scenario the term relay refers to the intermolecular generation of an accessible alkylidene followed by its intramolecular relay to an inaccessible but desired alkylidene from which ring closing metathesis of interest proceeds (i.e. **343** to **344**).[85]



Scheme 4.6 Relay Ring Closing Metathesis to afford Tetrasubstituted Olefin

The relay RCM strategy employs a temporary tether containing a sterically unencumbered olefin; the Type I olefin provides a site for the catalytic cycle to initiate (i.e. **343** to **344**) (Scheme 4.7). The Type I olefin is positioned such that a kinetically favored five-membered metallacycle (**346**) forms and sets the stage for ruthenium delivery onto the sterically hindered position (Type III olefin). The resultant alkylidene (**342**) forms with

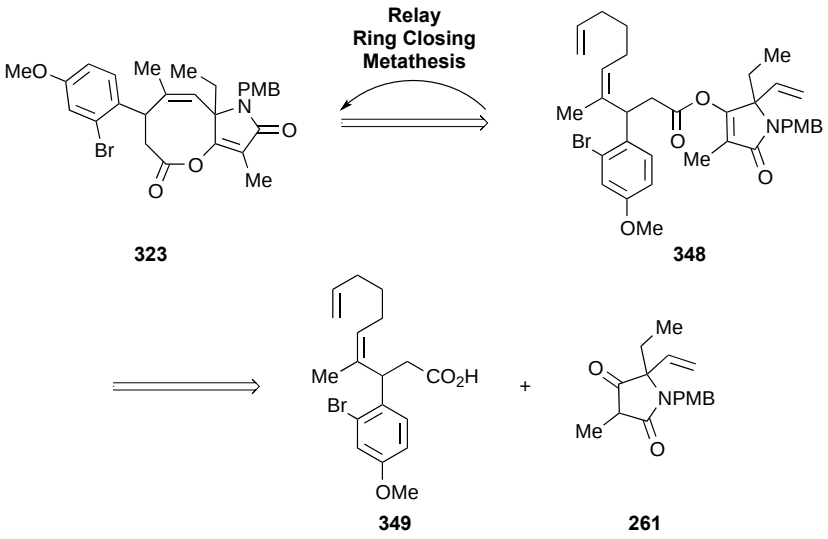
concomitant extrusion of cyclopentene **347** and then undergoes the desired ring closing metathesis to afford tetrasubstituted olefin **340**.



Scheme 4.7 Relay Ring Closing Metathesis to Afford a Tetrasubstituted Olefin

4.5 Relay RCM Investigation to Afford Eight-Membered Lactone

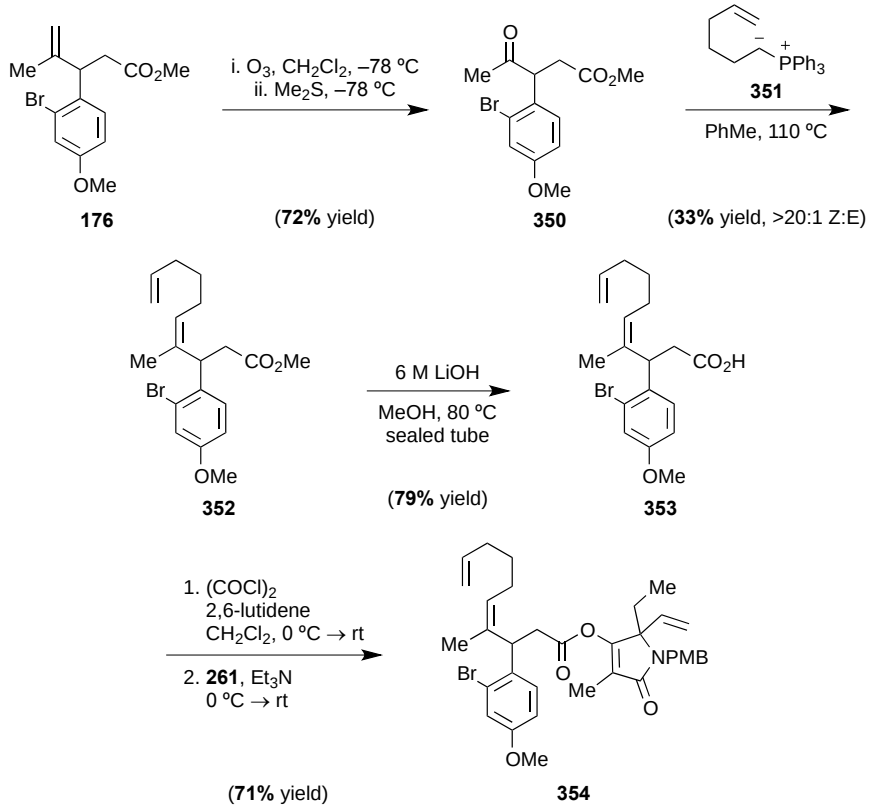
We envisaged constructing the desired lactone **323** via relay ring closing metathesis applied to triene **348** (Scheme 4.8). Triene **348** would be prepared by the coupling of carboxylic acid **349** and tetramic acid **261**. Thus, we turned our attention to the synthesis of triene **348**.



Scheme 4.8 Lactone Retrosynthetic Analysis

4.5.1 Synthesis of Relay Ring Closing Metathesis Triene

Ozonolysis of olefin **176** followed by subsequent dimethylsulfide mediated reduction afforded ketone **350** in good yield (72%) (Scheme 4.9). Installation of the tether required for relay metathesis was achieved by employing ylide **351**[86] in a salt free Wittig olefination of ketone **350** to provide diene **352**, albeit in low yield (33%) but with excellent stereoselectivity (>20:1 Z:E). Saponification proceeded smoothly to furnish carboxylic acid **353** which upon exposure to oxalyl chloride gave rise to an intermediate acid chloride that underwent base mediated coupling with tetramic acid **261** to provide triene **354** in good yield (71%).

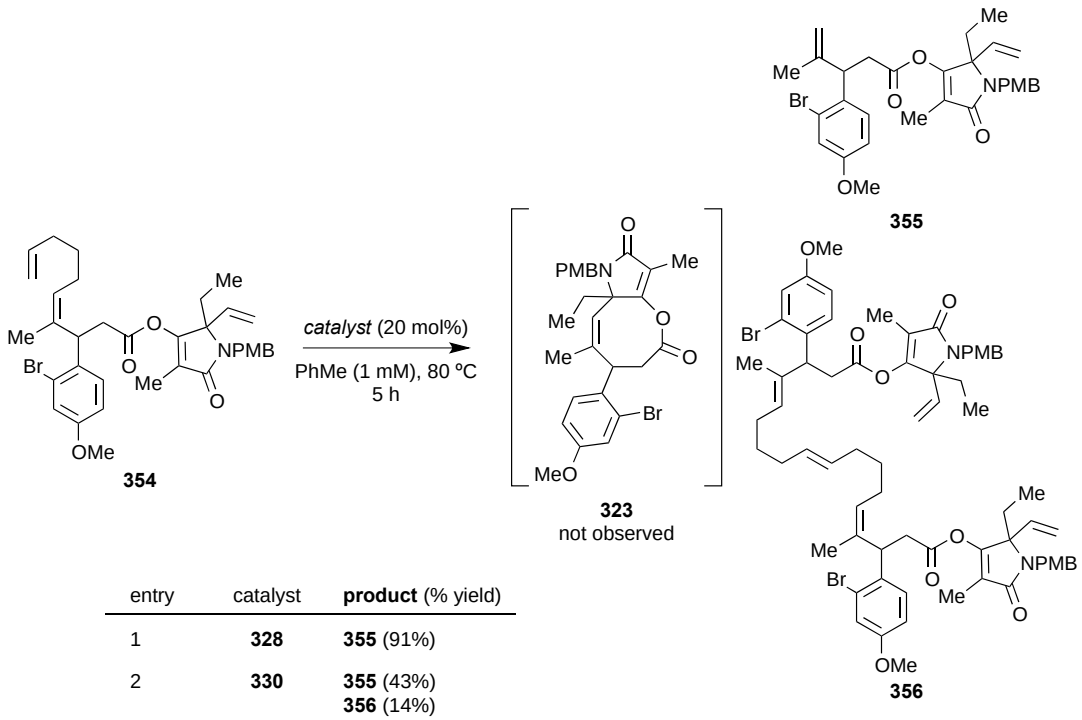


Scheme 4.9 Installation of Tether at 1,1-Disubstituted Olefin Site

4.5.2 Relay Ring Closing Metathesis Investigation

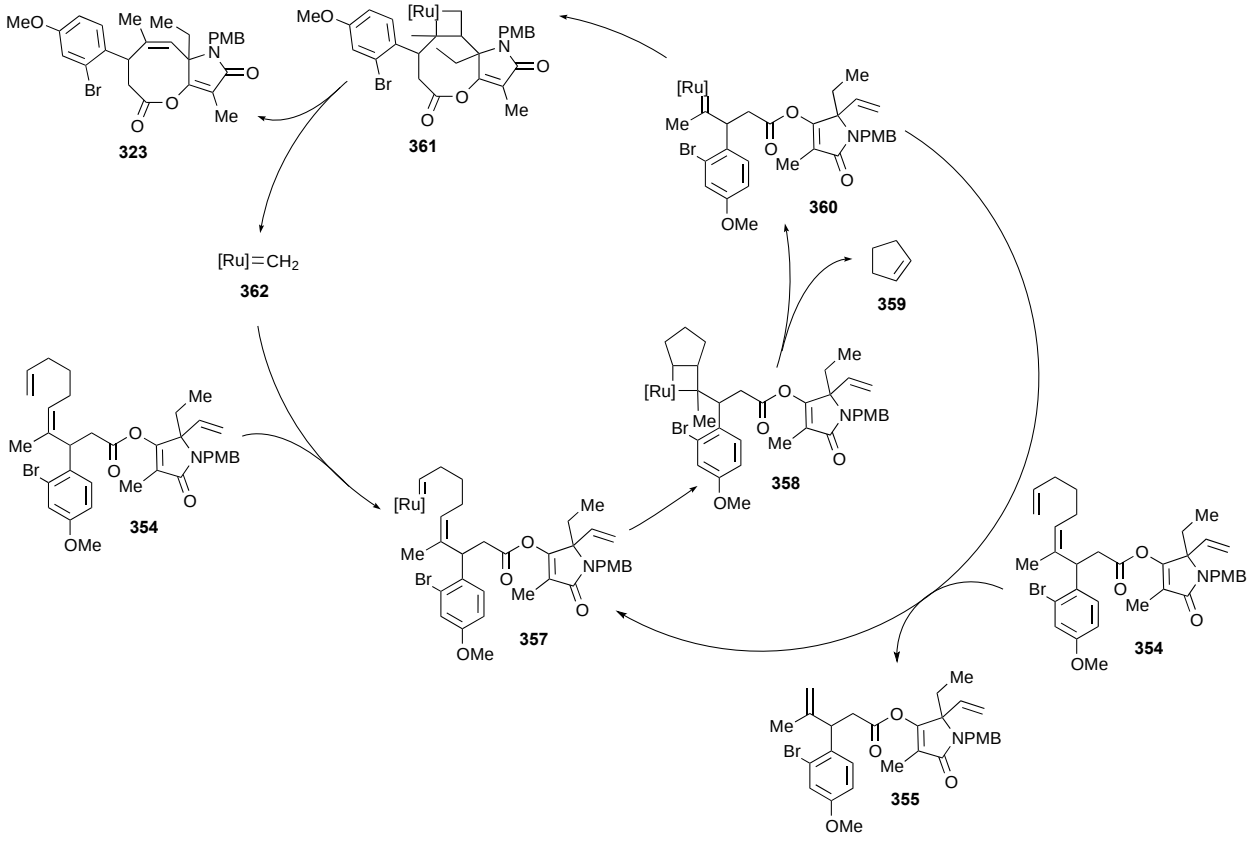
With triene **354** in hand we were excited to investigate a relay ring-closing metathesis strategy to achieve lactone **323** (Scheme 4.8). Upon exposure to various metathesis catalysts it was observed that triene **354** did not engage in the desired ring closing metathesis event to afford the lactone **323** (Table 4.3). Instead, we observed loss of the tether to afford diene **355,** and dimerization of the starting triene to provide dimer **356**. Observation of the truncated product, diene **355**, indicates that the relay ring closing metathesis was successful but that the desired ring closing metathesis leading to the eight-membered lactone **323** did not occur.

Table 4.3 Relay RCM Catalyst Survey



entry	catalyst	**product** (% yield)
1	**328**	**355** (91%)
2	**330**	**355** (43%) **356** (14%)
3	**331**	**355** (90%)

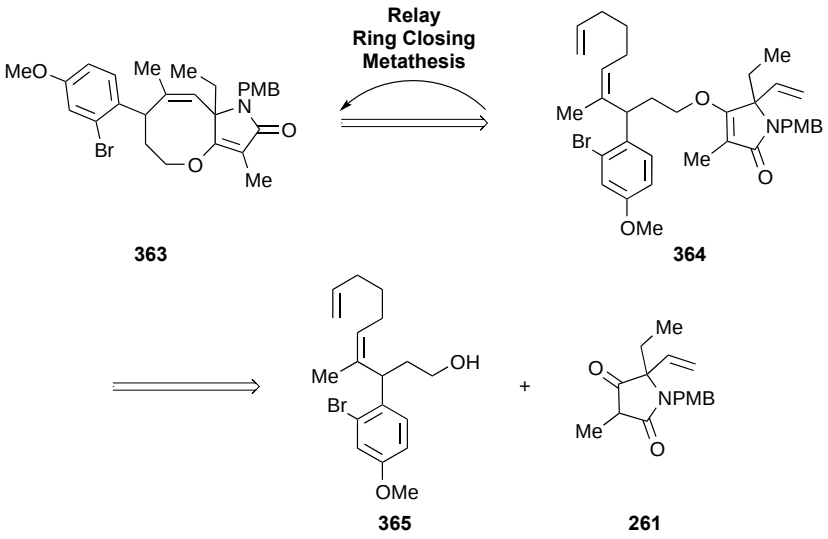
In a productive scenario the initial cross metathesis of the ruthenium alkylidene with the Type I olefin of triene **354** provides carbene **357** which subsequently undergoes ring closing metathesis to afford the desired 1,1-disubstitued carbene **360** with concomitant expulsion of cyclopentene (**359**) (Scheme 4.10). An intramolecular engagement of carbene **360** in ring closing metathesis would afford lactone **323** via metallacycle **361**. Alternatively, carbene **360** can participate in cross metathesis with the Type I olefin of triene **354** to deliver diene **355** and carbene **357**. In theory, the intramolecular process should be faster than the intermolecular process. Thus, we propose that carbene **361** may be unable to adopt a productive conformation allowing formation of metallacycle **361** and subsequently lactone **323**.



Scheme 4.10 Proposed Mechanism for Formation of Lactone and Diene Side Product

4.6 Relay RCM to Afford an Eight-Membered Cyclic Ether

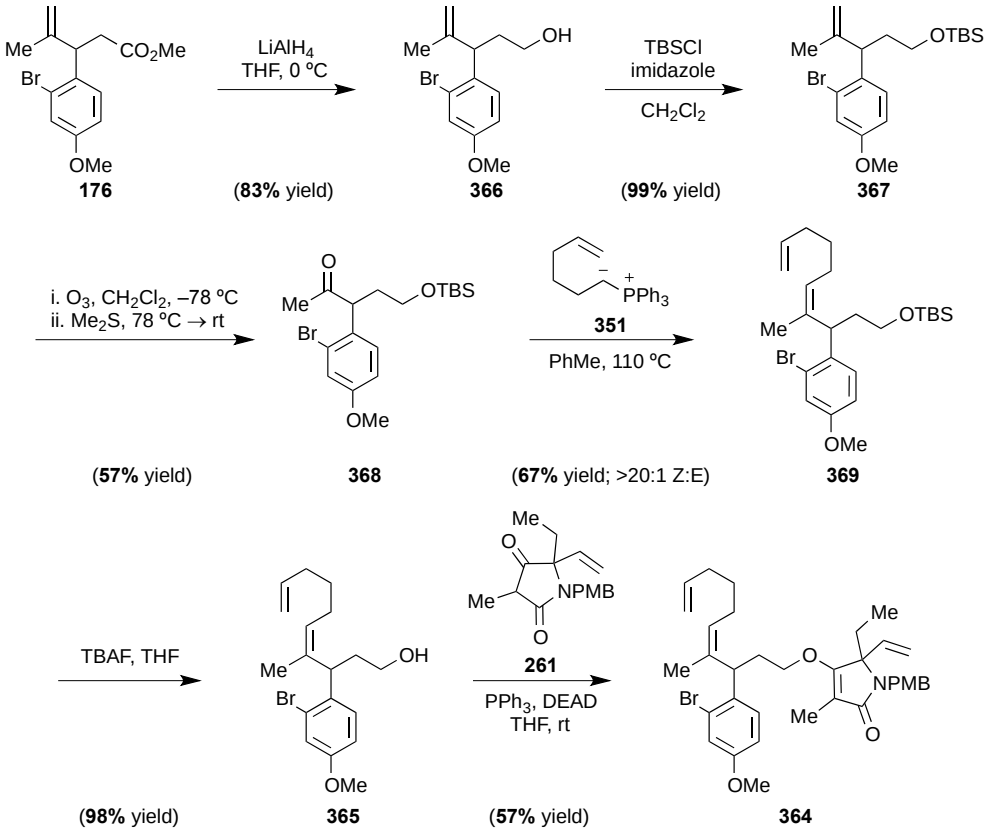
To introduce greater conformational freedom during the ring closing metathesis event we decided to investigate a system wherein an ether linkage would reside in backbone connecting the two olefin moieties (e.g. 364, Scheme 4.11). The latter was seen as arising from the ring closing metathesis of triene **364**, which in turn, would be derived via coupling of tetramic acid **261** with alcohol **365** under Mitsunobu conditions. To this end our synthetic endeavors focused on preparing the requisite components.



Scheme 4.11 Ether Linked Triene Retrosynthetic Analysis

4.6.1 Synthesis of Relay Ring Closing Metathesis Triene

To arrive at triene **364**, methyl ester **176** was advanced via lithium aluminum hydride mediated reduction to the primary alcohol **366** followed by subsequent silylation to furnish TBS-ether **367** which, upon exposure to ozone followed by dimethylsulfide, underwent oxidative cleavage to afford ketone **368** in good yield (47%) over three steps (Scheme 4.12). Installation of the relay metathesis tether was achieved by employing phosphorus ylide **351**[87] in a salt free Wittig olefination of ketone **368** to provide diene **369** in good yield (67%) as essentially a single olefin isomer (>20:1 Z:E). Exposure of **369** to tetrabutylammonium fluoride unveiled the primary alcohol **365**, which upon coupling with tetramic acid **261** under Mitsunobu conditions (i.e., diethyl azodicarboxylate and triphenylphosphine), furnished ether **364** in moderate yield (56%) over two steps.



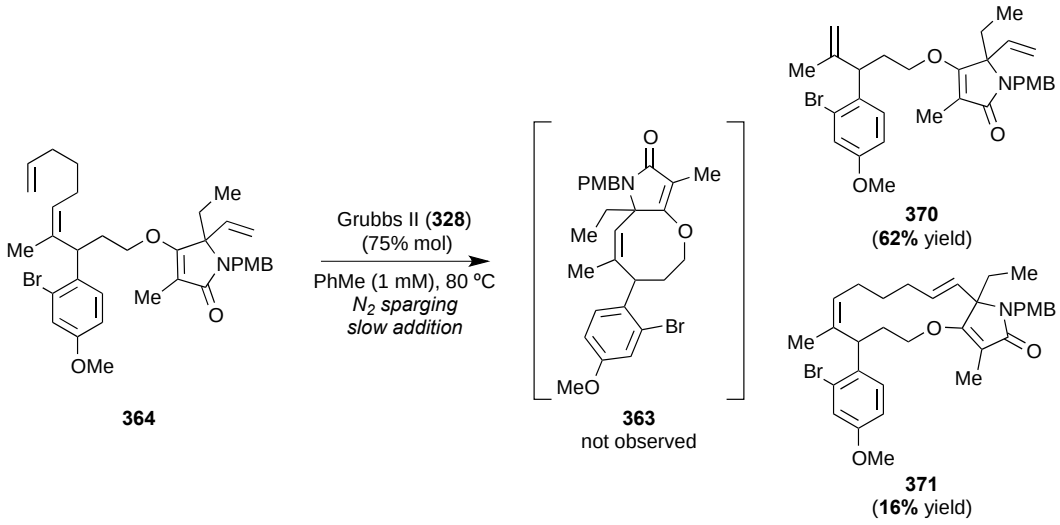
Scheme 4.12 Synthesis of Triene with an Ether Backbone

4.6.2 Relay Ring Closing Metathesis Investigation

In a productive scenario the initial cross metathesis of the ruthenium alkylidene species with the Type I olefin of triene **364** provides carbene **373** which upon ring closing metathesis affords the 1,1-disubstitued carbene **375** with concomitant expulsion of cyclopentene (**359**) (Scheme 4.14). Carbene **375** can engage in ring closing metathesis via metallacycle **376** to afford the desired cyclic ether **363**. Alternatively, carbene **375** can participate in an undesired competing pathway, cross metathesis with the Type I olefin of triene **364** to deliver a truncated product, diene **370,** and regenerate carbene **373**. The latter was the favored pathway with ester-linked triene **354** (Table 4.3 and Scheme 4.10).

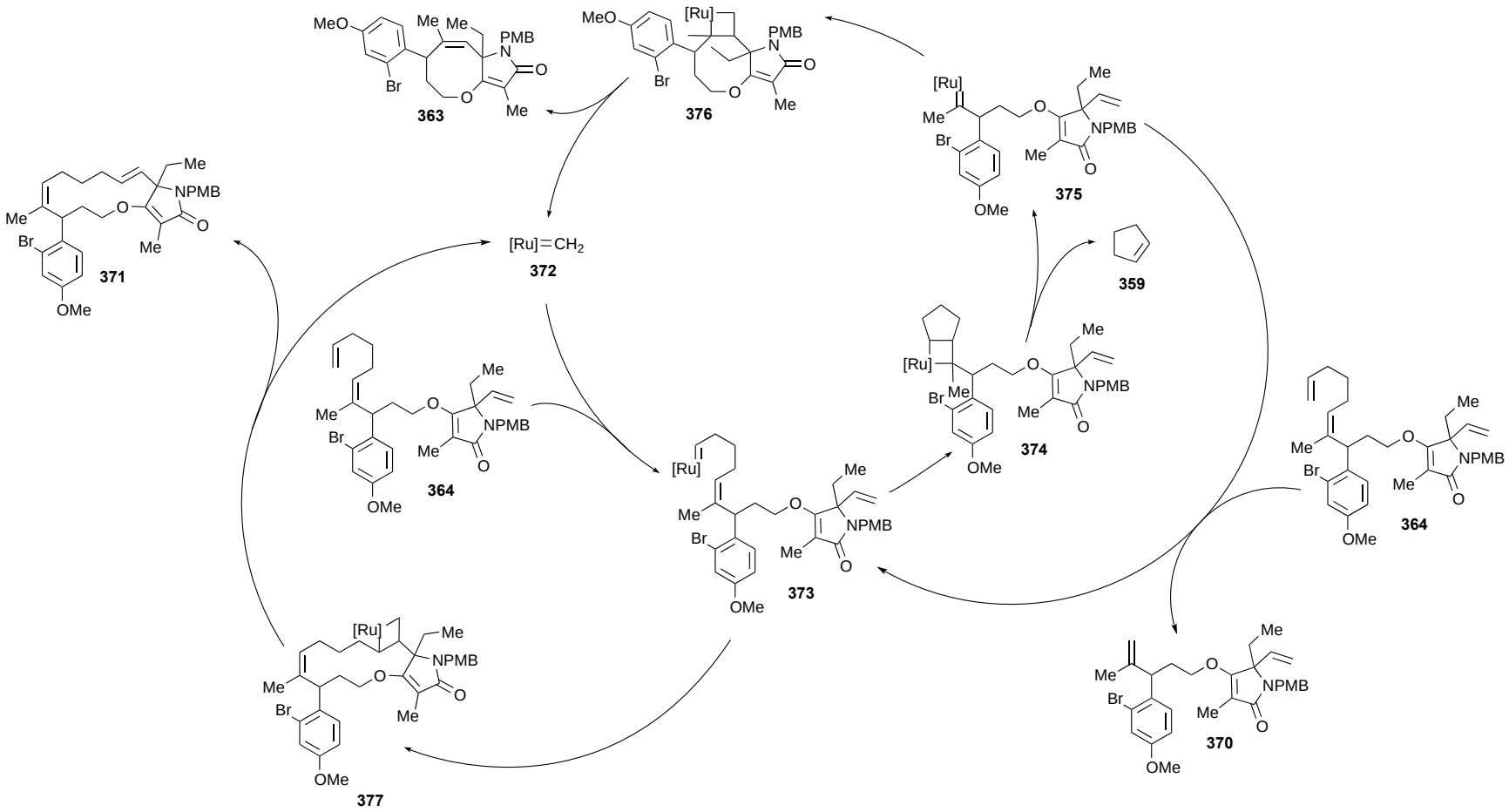
With triene **364** in hand, we were excited to investigate a relay ring closing metathesis approach to afford cyclic ether **363** (Scheme 4.11). Unfortunately, after a survey of metathesis

catalysts and reaction conditions we were unable to realize the desired ether **363**. As in the previous substrate (i.e. **354)** (Table 4.3 and Scheme 4.10), we observed formation of a truncated product, diene **370** indicating that the relay metathesis is successful but that the desired ring closing metathesis to afford the eight-membered cyclic ether **363** does not occur (Scheme 4.13).



Scheme 4.13 Macrocyclization by Ring Closing Metathesis

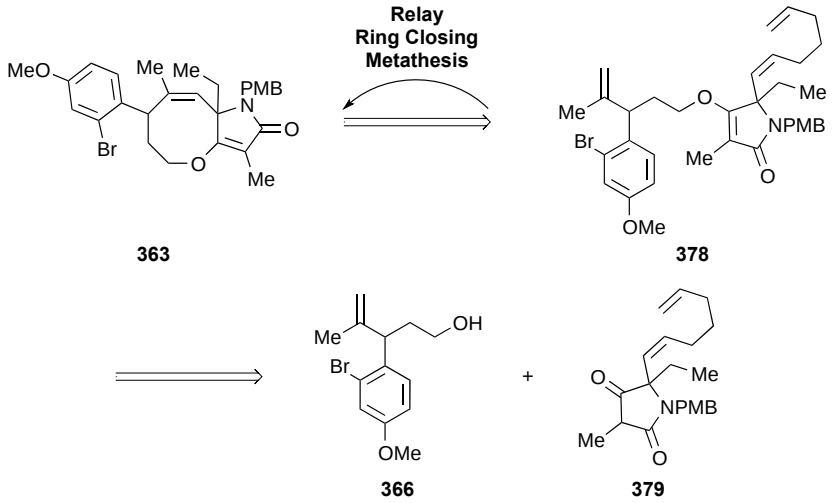
Surprisingly, exposure of triene **364** to Grubbs II catalyst (**328**) afforded the thirteen-membered macrocycle **371**, albeit in low yield (16%) (Scheme 4.13). Indicating that in this system there is a competing pathway carbene **373** can undergo a macrocyclization via metallacycle **377** to afford the thirteen-membered cyclic ether **371**. Although, macrocycle **371** was an undesired product it demonstrated that the hindered, Type III olefin attached to the tetramic acid moiety of triene **364** was capable of engaging in a productive ring closing metathesis event. Clearly, the ether backbone was having a positive influence on cyclization as a macrocyclization product was not observed in our previous substrate (**354**) (Table 4.4 and Scheme 4.10).



Scheme 4.14 Proposed Mechanism for Formation of Cyclic Ether, Diene and Macrocycle

4.7 Relay RCM – Focusing on the Tetramic Acid Olefin

An alternate synthetic route to the desired cyclic ether **363** (Scheme 4.15) was envisaged wherein the application of a relay ring closing metathesis would be applied to triene **378**. The latter would derive from the coupling of alcohol **366** with tetramic acid **379** under Mitsunobu conditions.

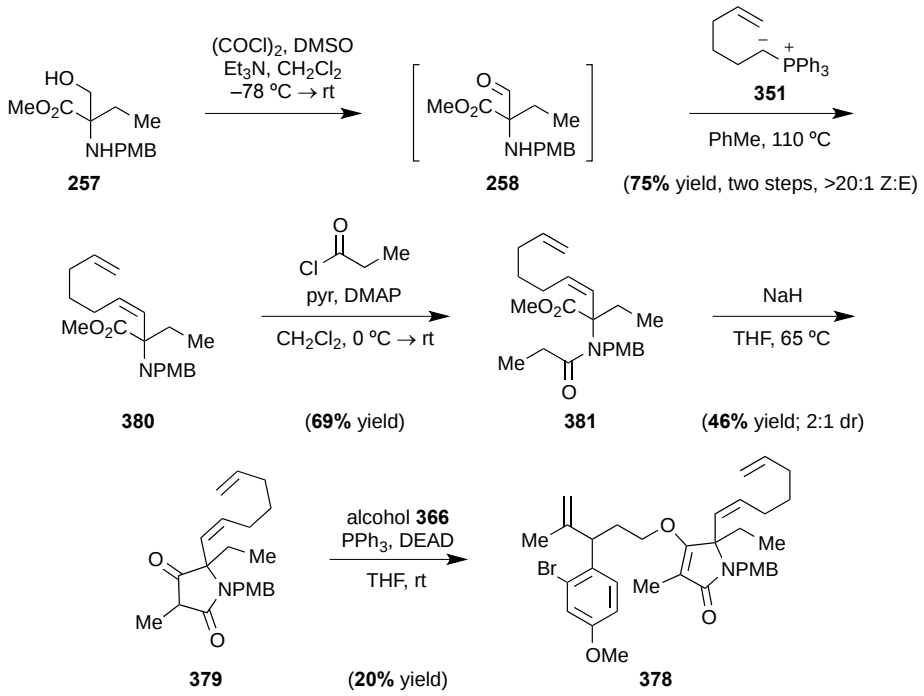


Scheme 4.15 Retrosynthetic Analysis - Tether Attached to Tetramic Acid Moiety

4.7.1 Synthesis of Relay Ring Closing Metathesis Triene

In a manner analogous to that described in Chapter 3, the desired tetramic acid **379** was prepared from alcohol **257** which, when subjected to Swern oxidation furnishes aldehyde **258**. Immediate exposure of **258** to phosphorus ylide **351** in toluene at reflux produces diene **380** in excellent yield (75%), as essentially one olefin isomer (>20:1 Z/E), over two steps (Scheme 4.16). Acylation of amine **380** with propionyl chloride provided amide **381** and subsequent treatment with sodium hydride in tetrahydrofuran at reflux induces Dieckmann cyclization to provide tetramic acid **379** in modest yield (32%) over two steps, as a mixture of two diastereomers (2:1 dr). A diethyl azodicarboxylate (DEAD) and triphenylphosphine mediated

Mitsunobu alkylation of tetramic acid **379** with primary alcohol **366** afforded triene **378** in low yield (20%) but provided enough material to investigate the relay ring closing metathesis.



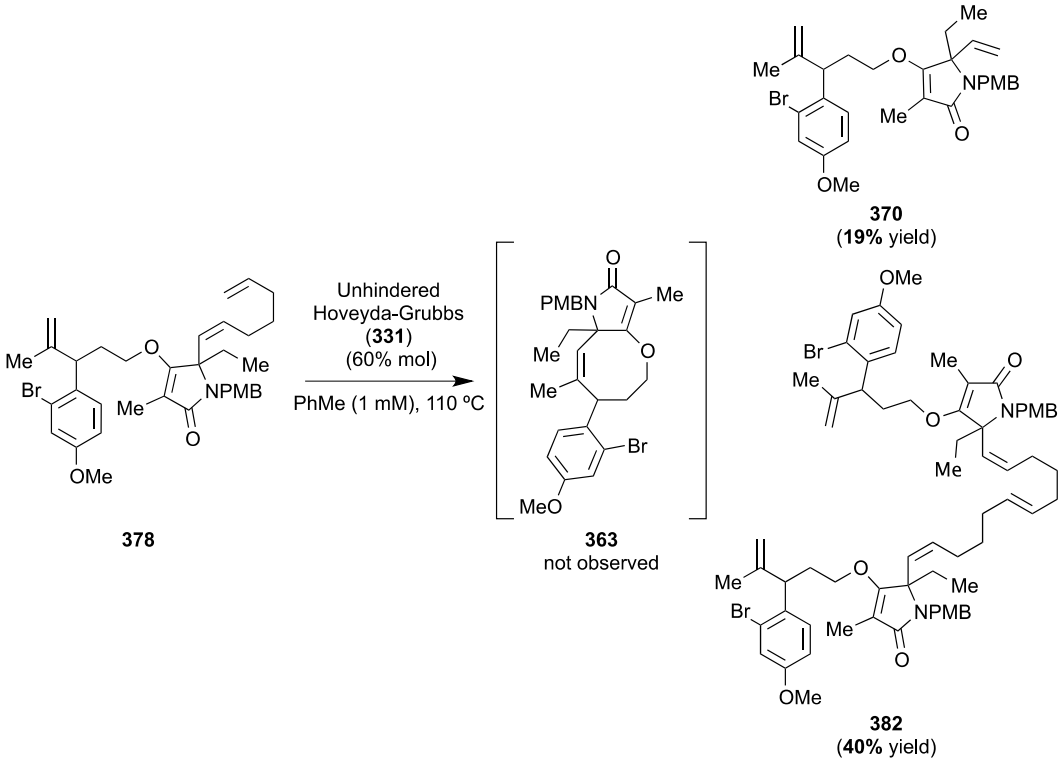
Scheme 4.16 Synthesis of Triene with Tether Attached to Tetramic Acid Moiety

4.7.2 Relay Ring Closing Metathesis Investigation

In a productive scenario the initial cross metathesis of the ruthenium alkylidene species with the Type I olefin of triene **378** provides carbene **384,** subsequent ring closing metathesis proceeding via metallacycle **385** affords the directly inaccessible carbene **386** upon concomitant expulsion of cyclopentene (**359**) (Scheme 4.18). Cyclization of carbene **386** via metallacycle **387** would afford the desired cyclic ether **363**.

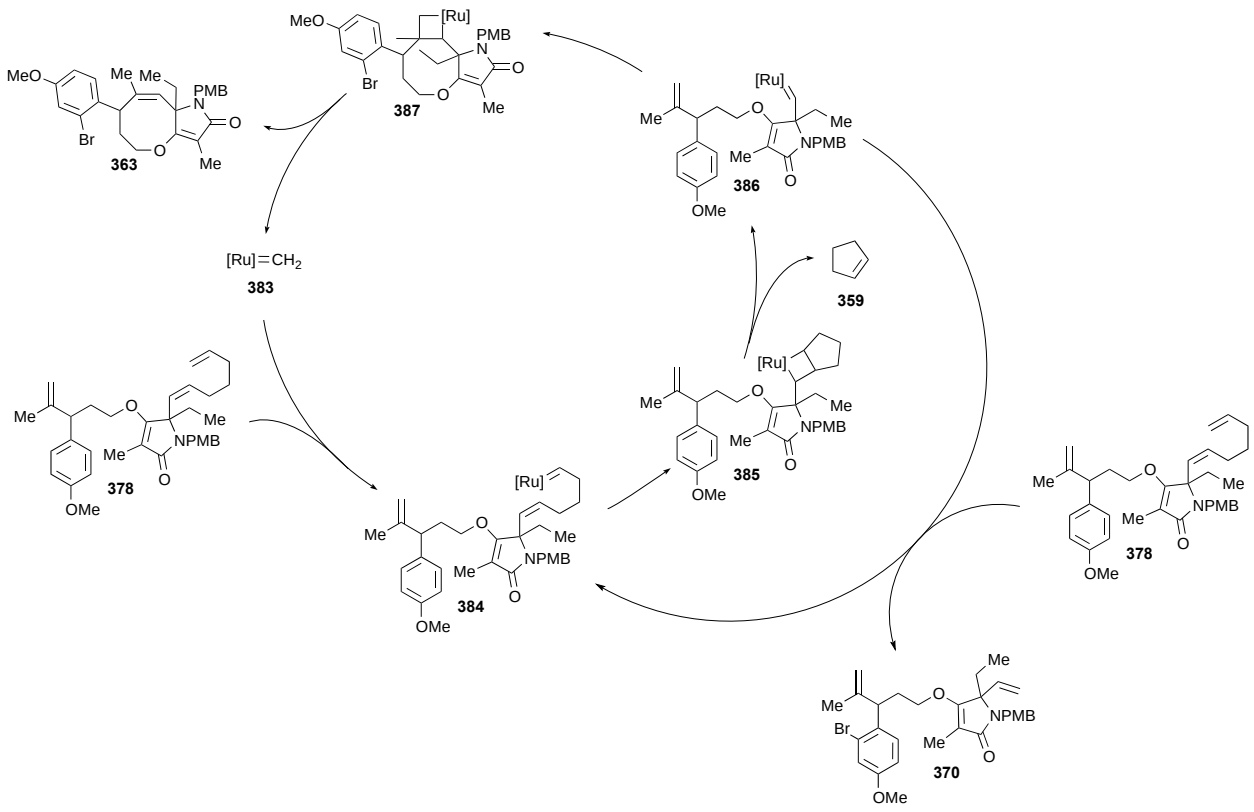
With triene **378** in hand we were excited to investigate a relay ring closing metathesis approach to afford cyclic ether **363** (Scheme 4.15). Unfortunately, exposure of triene **378** to the unhindered Hoveyda-Grubbs catalyst (**331**) did not afford the desired cyclic ether **363**; only the diene **370** (19% yield) and starting material dimer **382** (40% yield) were obtained (Scheme 4.17). Diene **370** indicates that the relay ring closing metathesis is successful in this system, affording

the initially inaccessible carbene **386** but that the desired cyclization to afford the eight-membered cyclic ether **363** does not occur (Scheme 4.18).



Scheme 4.17 Attempted Relay Ring Closing Metathesis

Unfortunately, as was observed with the two previous substrates (i.e., **354** and **364**) the preferred pathway for carbene **386** is not the desired ring closing metathesis but an unproductive cross metathesis with the Type I olefin of triene **378** to afford the undesired diene **370**. We propose that the desired pathway is prohibitively high in energy and or that carbene **386** does not have enough conformational freedom to adopt a productive conformation that allows for the formation of metallacycle **387** and thus cyclic ether **363.**



Scheme 4.18 Proposed Mechanism for Formation of Cyclic Ether and Diene

4.8 Conclusion

Although the desired ring closing metathesis to afford an eight-membered lactone or ether was not realized the relay ring closing metathesis investigations provided insight into the reactivity of the olefin moieties attached to the aryl bromide and tetramic acid coupling partners. The relay ring closing metathesis experiments demonstrated that both olefins are capable of participating in a ring closing metathesis. We propose that the desired ring closing metathesis events did not occur due to a conformation constraint that prohibited formation of the desired eight-membered ring. Thus, we propose that a successful ring closing metathesis may be realized upon synthesis of a substrate that employs a higher order of conformational control forcing the olefinic side chains to reside in the same space. Relay ring closing metathesis is an extremely

valuable and reliable synthetic strategy to initiate the catalytic cycle and control the site of initiation.

4.9 Experimental Section

4.9.1 Materials and Methods

Unless stated otherwise, reactions were performed in flame-dried glassware under a nitrogen atmosphere. Triethylamine, diisopropylamine, and methanol were dried over anhydrous calcium hydride and freshly distilled. 1,4-Dioxane was distilled from sodium, calcium chloride and molecular sieve (0.4 nm). Benzene, tetrahydrofuran, dichloromethane, toluene, and diethyl ether were dried using a solvent purification system manufactured by Glass Contour Solvent Systems, SG Water U.S.A., LLC using technology based upon that originally described by Grubbs *et al*.[88] Anhydrous *N*,*N*-dimethyformamide, acetonitrile, dimethylsulfoxide, 1,2-dichloroethane was purchased from the Colorado State University Stockroom and supplied by Sigma-Aldrich or Fischer Scientific and stored under nitrogen atmosphere. Commercially available reagents were obtained from Sigma-Aldrich, Strem, TCI, Combi-Blocks, Acros or Alfa-Aesar and were used as received. All known compounds were identified by comparison of NMR spectra to reported in the literature.

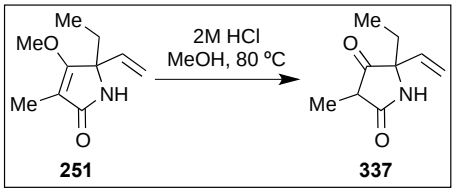
Unless otherwise stated, all reactions were monitored by thin layer chromatography (TLC) was using Silicycle glass-backed extra hard layer, 60 Å plates (indicator F-254, 250 μm). Developed TLC plates were visualized using a 254 nm UV lamp and/or with the appropriate stain followed by heating. Typical stains utilized were potassium permanganate, ethanolic anisaldehyde and ceric ammonium molybdate. In general, the flash chromatography guidelines reported by Still *et al*[89] were followed. Silicycle SiliaFlash® P60 (230-400 mesh) silica gel as the

stationary phase. When reactions were absorbed onto silica gel, the amount of silica gel used was equal to two times the weight of the reagents.

Infrared spectra were obtained using a Nicolet Avatar 320 FTIR or Bruker Tensor27 FTIR. Samples were analyzed as thin films on NaCl plates (samples was dissolved in CH_2Cl_2 or $CHCl_3$) or potassium bromide pellets, as indicated. IR spectra are presented as transmittance vs. wavenumber (cm^{-1}). Proton (^1H) and carbon (^{13}C) NMR spectra were recorded on a Varian Inova 500, Varian Inova 400, Varian Inova 400 auto sampler, or Varian Inova 300 MHz spectrometer. Spectra were obtained at 22 °C in $CDCl_3$ unless otherwise noted. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to the internal solvent peak. Coupling constants (J) are reported in Hertz (Hz) and are rounded to the nearest 0.1 Hz. Multiplicities are defined as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, br = broad, app = apparent, par = partial. High-resolution mass spectra were obtained from the University of Colorado Central Instrument Facility, performed on an Agilent 6210 TOF LCMS by Donald L. Dick.

4.9.2 Preparative Procedures

Preparation of tetramic acid 337:



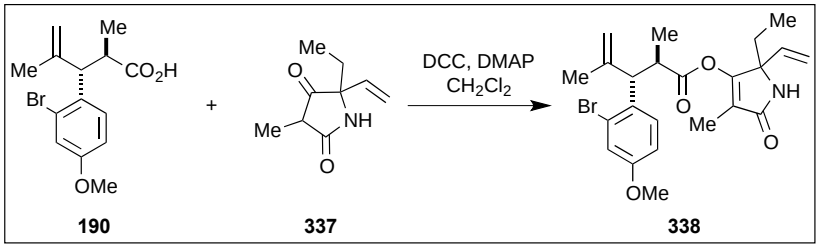
251 **337**

Tetramic acid 337. To a stirred solution of vinylogous ester **251** (50 mg, 0.28 mmol) in methanol (4.2 mL) was added 2 M HCl (1.4 mL, 2.80 mmol) at room temperature. Reaction was heated to reflux (80 ºC). TLC was used to monitor reaction progress. TLC plates were developed

with 80% EtOAc/Hex and visualized by UV lamp and $KMnO_4$ stain. Reaction was cooled to room temperature and diluted with dichloromethane (4 mL). Organic phase was washed with saturated $NaHCO_3$ (5 mL), brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated to yield tetramic acid **337** (14 mg, 19% yield, 1.5:1 dr) as yellow oil. No further purification necessary.

Tetramic acid 337. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 6.90 (s, 1H), 5.84 (dd, *J* = 17.1, 10.4 Hz, 1H), 5.38 (d, *J* = 18.8 Hz, 1H), 5.29 (d, *J* = 10.4 Hz, 1H), 2.94 (q, *J* = 7.7 Hz, 1H), 1.92 (dq, *J* = 19.5, 6.0 Hz, 1H), 1.75 (dq, *J* = 14.7, 7.3 Hz, 1H), 1.29 (d, *J* = 7.7 Hz, 3H), 0.85 (t, *J* = 7.5 Hz, 3H).; 6.98 (s, 1H), 5.91 (dd, *J* = 17.2, 10.5 Hz, 1H), 5.38 (d, *J* = 17.1 Hz, 1H), 5.27 (d, *J* = 10.6 Hz, 1H), 2.77 (q, *J* = 7.8 Hz, 1H), 1.92 (dq, *J* = 19.5, 6.0 Hz, 1H), 1.75 (dq, *J* = 14.7, 7.3 Hz, 1H), 1.33 (d, *J* = 7.8 Hz, 3H), 0.91 (t, *J* = 7.5 Hz, 3H).

Preparation of diene 338:

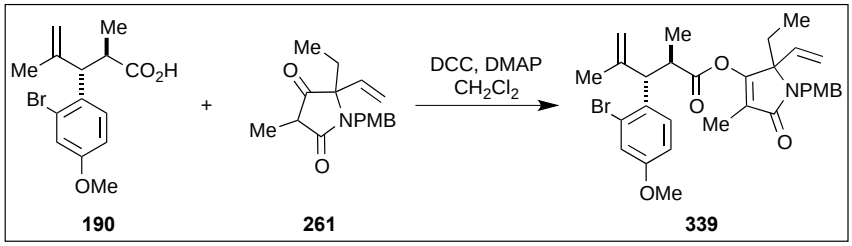


Diene 338. To a stirred solution of carboxylic acid **190** (28 mg, 0.09 mmol), tetramic acid **337** (14 mg, 0.08 mmol) and 4-(dimethylamino)pyridine (3 mg, 0.02 mmol) in dichloromethane (0.8 mL) was added dicyclohexylcarbodiimide (21 mg, 0.10 mmol) at 0 ºC. Reaction was stirred for 10 minutes at 0 ºC, warmed to room temperature and stirred over night. TLC was used to monitor reaction progress. TLC plates were developed with 35% EtOAc/Hex; visualized by UV lamp and $KMnO_4$ stain. Reaction was diluted with dichloromethane (2 mL) and quenched with saturated NH_4Cl (2 mL). Organic phase was washed with H_2O (2 mL), brine (2 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Crude material was purified with

silica gel chromatography (gradient elution 1→5→10→15→20→25→30→35% EtOAc/Hex) to afford diene **338** (8.5 mg; 23% yield) as colorless oil.

Diene 338. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.24 (d, *J* = 8.9 Hz, 1H), 7.11 (d, *J* = 3.5 Hz, 1H), 6.85 (dd, *J* = 8.7, 2.3 Hz, 1H), 5.79 (s, 1H), 5.53 (dd, *J* = 17.3, 10.6 Hz, 1H), 5.19 (d, *J* = 17.3 Hz, 1H), 5.13 (d, *J* = 2.7 Hz, 1H), 5.00 (d, *J* = 10.5 Hz, 1H), 4.96 (s, 1H), 4.10 (d, *J* = 11.6 Hz, 1H), 3.76 (s, 3H), 3.25 (td, *J* = 12.5, 5.7 Hz, 1H), 1.61 (s, 3H), 1.60 (q, *J* = 11.0 Hz, 1H), 1.47 (q, *J* = 7.1 Hz, 1H), 1.26 (s, 3H), 0.70 (td, *J* = 7.4, 3.8 Hz, 3H); ^{13}C-NMR (101 MHz; CDCl3): δ 172.3, 170.0, 161.0, 159.0, 142.4, 136.36, 136.25, 131.86, 131.81, 128.7, 126.07, 125.98, 118.73, 118.66, 115.82, 115.65, 115.1, 114.9, 113.8, 65.4, 55.7, 53.2, 42.56, 42.38, 27.5, 19.5, 19.3, 17.1, 7.78, 7.60, 7.54; HRMS (EI) *m/z* 462.1273 [calc'd for $C_{23}H_{28}BrNO_4$ (M+H)+ 462.1274].

Preparation of diene 339:

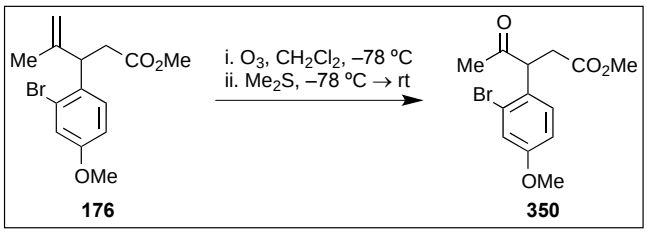


Diene 339. To a stirred solution of carboxylic acid **190** (50 mg, 0.16 mmol), tetramic acid **261** (30 mg, 0.18 mmol) and 4-(dimethylamino)pyridine (3 mg, 0.02 mmol) in dichloromethane (1.6 mL) was added dicyclohexylcarbodiimide (37 mg, 0.18 mmol) at 0 ºC. Reaction was stirred for 10 minutes at 0 ºC, warmed to room temperature and stirred over night. TLC was used to monitor reaction progress. TLC plates were developed by gradient elution 15→40% EtOAc/Hex; visualized by UV lamp and $KMnO_4$ stain. Reaction was diluted with dichloromethane (2 mL) and quenched with saturated NH_4Cl (4 mL). Organic phase was washed with H_2O (4 mL), brine

(4 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 10→20→40% EtOAc/Hex) to afford diene **339** (46 mg; 49% yield) as colorless oil.

Diene 339. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.24-7.18 (m, 3H), 7.11-7.06 (m, 1H), 6.83-6.75 (m, 3H), 5.28-4.93 (m, 5H), 4.39 (dd, *J* = 15.0, 1.5 Hz, 1H), 4.18 (dd, *J* = 15.1, 7.1 Hz, 1H), 4.04 (dd, *J* = 11.6, 2.0 Hz, 1H), 3.78 (d, *J* = 0.9 Hz, 1H), 3.76 (s, 6H), 3.75 (d, *J* = 1.6 Hz, 3H), 3.24-3.13 (m, 1H), 1.58 (s, 3H), 1.61-1.50 (m, 2H), 1.32 (dd, *J* = 6.8, 2.4 Hz, 3H), 1.24 (s, 3H), 0.32 (q, *J* = 7.7 Hz, 3H).

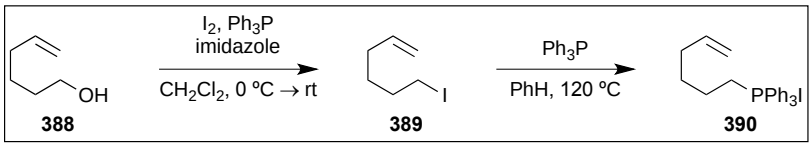
Preparation of ketone 350:



Ketone 350. Alkene **176** (250 mg, 0.798 mmol) was dissolved in dichloromethane (8 mL) and cooled to –78 ºC. Ozone was bubble through solution until saturation was achieved. TLC was used to monitor reaction progress. TLC plates were developed with 15% EtOAc/Hex; visualized by UV lamp and $KMnO_4$ stain. Oxygen was bubbled through solution for 10 minutes and dimethylsulfide (1.17 mL, 16.0 mmol) was added to solution. Reaction was warmed to room temperature and stirred overnight. Solution was concentrated under reduced pressure and crude material was purified with silica gel chromatography (eluent 5% EtOAc/Hex) to afford ketone **350** (175 mg, 72% yield) as colorless oil.

Ketone 350. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.16 (d, *J* = 2.6 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 1H), 6.82 (dd, *J* = 8.7, 2.6 Hz, 1H), 4.66 (dd, *J* = 9.7, 4.9 Hz, 1H), 3.79 (s, 3H), 3.66 (s, 3H), 3.11 (dd, *J* = 16.9, 9.8 Hz, 1H), 2.50 (dd, *J* = 17.0, 4.9 Hz, 1H), 2.12 (s, 3H).

Preparation of (5-Hexen-1-yl)triphenylphosphonium iodide 390:



Alkyl iodide 389. Following the procedure of Hiersemann and Helmboldt.[90] To a stirred solution of triphenylphosphine (83 g, 314.78 mmol) in dichloromethane (200 mL) at 0 ºC was added iodine (80 g, 314.78 mmol) and imidazole (21.4 g, 314.78 mmol). After being stirred for 15 minutes, 5-hexen-1-ol (**388**) (10 g, 99.84 mmol) was added dropwise at 0 ºC to the reaction mixture and stirring was continued at room temperature for 4 hours. TLC was used to monitor reaction progress. TLC plates were developed with 5% EtOAc/Hex; visualized by $KMnO_4$ stain. Dichloromethane was evaporated under reduced pressure and the residue diluted with pentane. The resulting suspension was filtered through celite; and the celite was carefully rinsed with pentane. The filtrate was concentrated under reduced pressure and purified with silica chromatography (gradient elution pentane→1% Et_2O/pentane) to afford alkyl iodide **3389** (16 g, 76% yield) as colorless oil.

Alkyl iodide **389** is a known compound ^{1}H-NMR was compared to that reported in the literature.[90]

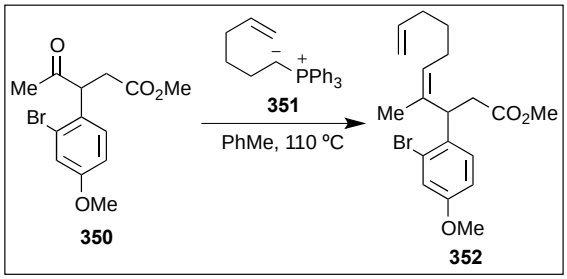
Alkyl iodide 389. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 5.79 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 5.06-4.99 (m, 1H), 4.99-4.95 (m, 1H), 3.20 (t, *J* = 7.0 Hz, 2H), 2.08 (q, *J* = 7.1 Hz, 2H), 1.84 (dt, *J* = 14.8, 7.3 Hz, 2H), 1.50 (quintet, *J* = 7.4 Hz, 2H).

(5-Hexen-1-yl)triphenylphosphonium iodide 390. A solution of alkyl iodide **389** (3.0 g, 14.28 mmol) and triphenylphosphine (3.6 g, 13.57 mmol) in benzene (15 mL) in a commercially available glass pressure tube with a Teflon screw-cap was heated to 120 ºC for 12 hours. Reaction was cooled to room temperature and the resulting solid was filtered off and rinsed with

a small quantity of benzene to afford the Wittig salt **390** (6.0 g, 90% yield) as yellowish white solid.

(5-Hexen-1-yl)triphenylphosphonium iodide 390. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.87-7.78 (m, 10H), 7.73-7.68 (m, 5H), 5.68 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 4.96-4.91 (m, 1H), 4.91-4.87 (m, 1H), 3.80-3.72 (m, 2H), 2.09 (q, *J* = 7.0 Hz, 2H), 1.79 (dt, *J* = 14.8, 7.3 Hz, 2H), 1.69-1.59 (m, 2H); ^{13}C-NMR (101 MHz; CDCl3): δ 137.8, 135.2, 133.96, 133.87, 130.70, 130.57, 118.8, 118.0, 115.5, 33.1, 29.40, 29.26, 23.4, 22.9, 21.97, 21.92.

Preparation of diene 352:



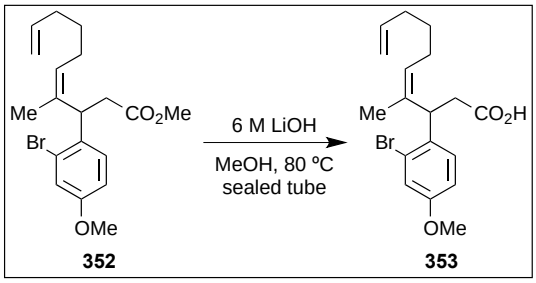
Diene 352. Ylide **351** solution in toluene (0.1 M). To a stirred solution of Wittig salt **390** (1.0 g, 2.12 mmol) in toluene (13.6 mL) was added potassium bis(trimethylsilyl)amide (0.5 M in toluene, 3.4 mL, 1.70 mmol) at –78 ºC. Reaction mixture was stirred for 5 minutes at –78 ºC, warmed to room temperature and stirred 90 minutes. Solution turned orange upon warming. Allowed solution to stand with out stirring so that potassium iodide settled on the bottom of the round bottom flask.

To a stirred solution of ketone **350** (262 mg, 0.83 mmol) in toluene (29 mL) was added ylide **351** (0.1 M in toluene, 12.5 mL, 1.25 mmol) in a commercially available glass pressure tube with a Teflon screw-cap and heated to 120 ºC for 12 hours. Reaction mixture was cooled to room temperature and quenched with saturated NH_4Cl solution (15 mL). Organic phase was washed with H_2O (30 mL), brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated under

reduced pressure. TLC plates were developed with 15% EtOAc/Hex; visualized by UV lamp and CAM stain. Crude material was purified with silica gel chromatography (gradient elution 5→10→15% EtOAc/Hex) to afford diene **352** (105 mg, 33% yield, >20:1 Z:E) as colorless oil.

Diene 352. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.10 (d, *J* = 2.6 Hz, 1H), 7.07 (d, *J* = 8.7 Hz, 1H), 6.81 (dd, *J* = 8.6, 2.7 Hz, 1H), 5.81 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 5.31 (t, *J* = 7.2 Hz, 1H), 5.00 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.96-4.93 (m, 1H), 4.22 (t, *J* = 8.0 Hz, 1H), 3.78 (s, 3H), 3.63 (s, 3H), 2.74 (dd, *J* = 15.3, 8.9 Hz, 1H), 2.65 (dd, *J* = 15.3, 7.1 Hz, 1H), 2.08-2.02 (m, 4H), 1.50 (s, 3H), 1.46 (t, *J* = 7.4 Hz, 2H).

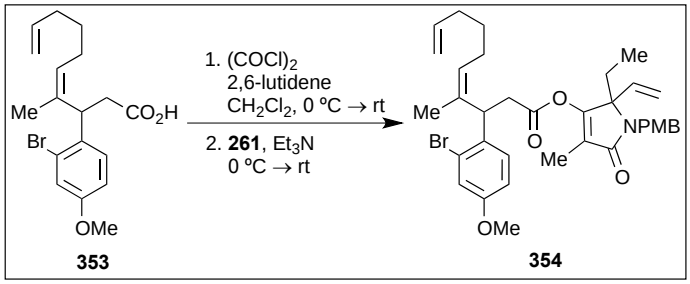
Preparation of carboxylic acid 353:



Carboxylic acid 353. Methyl ester **352** (34 mg, 0.09 mmol) was dissolved in methanol (3 mL) and lithium hydroxide (3.5 M in H_2O, 3 mL) was added. Vial was sealed and heated to 80 ºC for 24 hours. Reaction solution was cooled to room temperature and acidified. The acidic aqueous phase was extracted with diethyl ether (3 x 3 mL). Combined organic phase was dried over anhydrous Na_2SO_4 and concentrated to yield carboxylic acid **353** (26 mg, 79% yield).

Carboxylic acid 353. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.10 (d, *J* = 2.6 Hz, 1H), 7.07 (d, *J* = 8.7 Hz, 1H), 6.81 (dd, *J* = 8.7, 2.7 Hz, 1H), 5.87-5.75 (m, 1H), 5.33 (t, *J* = 7.1 Hz, 1H), 5.03-4.96 (m, 1H), 4.95-4.92 (m, 1H), 4.19 (t, *J* = 7.9 Hz, 1H), 3.77 (s, 3H), 2.71 (t, *J* = 7.4 Hz, 2H), 2.09-2.00 (m, 4H), 1.50 (s, 3H), 1.46 (t, *J* = 7.4 Hz, 3H).

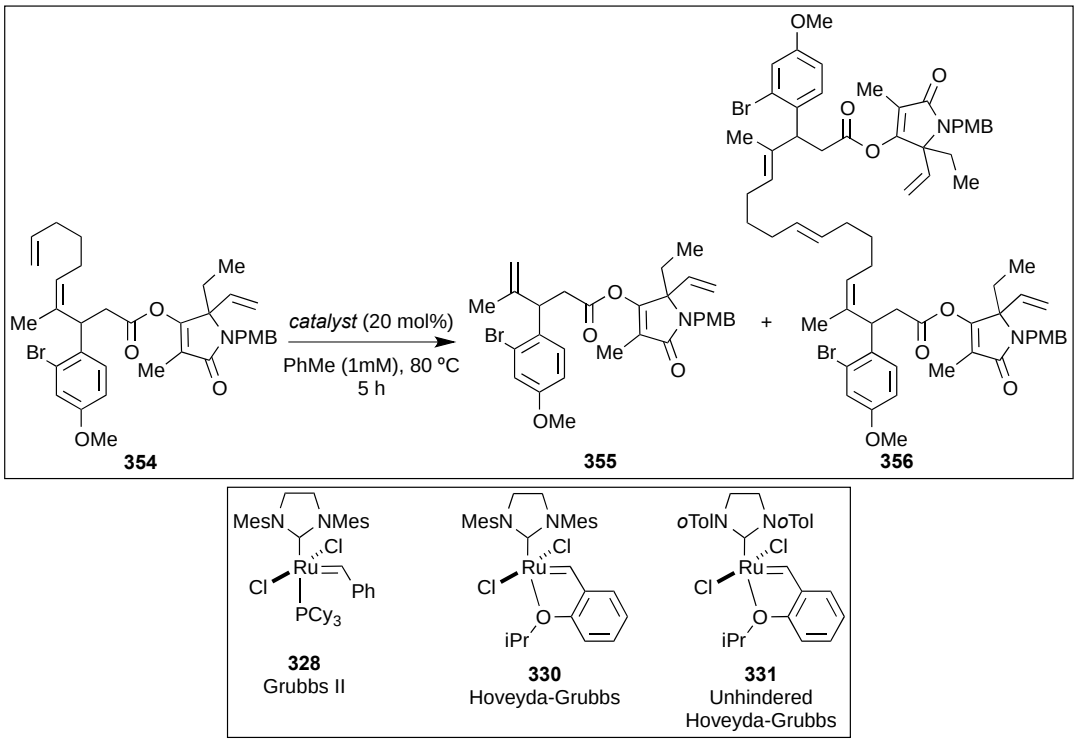
Preparation of triene 354:



Triene 354. To a stirred solution of carboxylic acid **353** (113 mg, 0.31 mmol) and 2,6-lutidene (43 μL, 0.37 mmol) in dichloromethane (2 mL) was added oxalyl chloride (28.6 μL, 0.34 mmol) at 0 ºC. Warmed to room temperature and stirred 2 hours. Reaction solution was cooled to 0 ºC and a solution of tetramic acid **261** (177 mg, 0.62 mmol) and triethylamine (172 μL, 1.23 mmol) in dichloromethane (2 mL). Reaction mixture was warmed to room temperature and stirred 4 hours. TLC was used to monitor reaction progress. TLC plates were developed with 15% EtOAc/Hex; visualized by UV lamp and $KMnO_4$ stain. Reaction mixture was quenched with saturated NH_4Cl solution (5 mL). Organic phase was washed with H_2O (5 mL), brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 5→10→20% EtOAc/Hex) to afford triene **354** (140 mg, 71% yield).

Triene 354. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.26 (s, 3H), 7.11-7.06 (m, 2H), 6.79-6.76 (m, 3H), 5.79 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 5.40-5.29 (m, 2H), 5.18-5.08 (m, 2H), 5.02-4.92 (m, 2H), 4.44 (d, *J* = 14.8 Hz, 1H), 4.26-4.20 (m, 2H), 3.77 (s, 6H), 2.85 (dt, *J* = 8.1, 4.1 Hz, 2H), 2.04 (q, *J* = 6.0 Hz, 4H), 1.67-1.57 (m, 6H), 1.52-1.42 (m, 6H), 0.40-0.35 (m, 3H).

Preparation of alkene 355 and dimer 356:



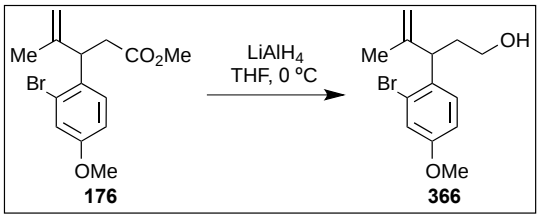
Alkene 355 and dimer 356. Prior to use toluene was pulled freshly from solvent system and then deoxygenated by sparging with nitrogen at reflux for 30 minutes. To a round bottom flask was added catalyst (5 mg, 0.008 mmol), toluene (39 mL) and substrate and substrate as a solution in toluene (1 mL). Round bottom flask was fitted with a condenser, a needle attached to nitrogen line was inserted through septum down condenser into the reaction solution and a vent needle was inserted into septum. Nitrogen pressure was increased to establish a slow and steady bubbling of nitrogen through reaction solution and heated to 80 ºC. TLC was used to monitor reaction progress. TLC plates were developed with 40% EtOAc/Hex; visualized by UV lamp and $KMnO_4$ stain. Reaction was cooled to room temperature and quenched with dimethylsulfoxide (50 equivalents, 27 μL, 0.385 mmol) stirred for 12 hours. Reaction solution was concentrated

under reduced pressure and resulting residue purified with silica gel chromatography (gradient elution 20→40% EtOAc/Hex) to afford alkene **355** and dimer **356**.

Alkene 355. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.26-7.23 (m, 3H), 7.11-7.08 (m, 2H), 6.83-6.76 (m, 3H), 5.35 (dd, *J* = 18.0, 9.9 Hz, 1H), 5.35 (dd, *J* = 18.1, 9.9 Hz, 1H), 5.19-5.13 (d, *J* = 18.4 Hz, 1H), 5.13 (d, *J* = 9.3 Hz, 1H), 4.96 (s, 1H), 4.87 (d, *J* = 4.1 Hz, 1H), 4.44 (d, *J* = 15.0 Hz, 1H), 4.26 (t, *J* = 8.0 Hz, 1H), 4.26-4.21 (d, *J* = 15.0 Hz, 1H), 3.77 (s, 6H), 2.95-2.78 (m, 2H), 1.80-1.59 (m, 2H), 1.65 (s, 3H), 1.62-1.61 (d, *J* = 4.6 Hz, 3H), 0.38 (td, *J* = 7.2, 2.9 Hz, 3H); HRMS (EI) *m/z* 568.1695 [calc'd for $C_{30}H_{34}BrNO_5$ (M+H)+ 568.1693].

Dimer 356. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.26-7.23 (m, 7H), 7.08 (d, *J* = 10.8 Hz, 4H), 6.78 (d, *J* = 8.4 Hz, 6H), 5.39-5.28 (m, 4H), 5.18-5.07 (m, 4H), 4.46-4.41 (m, 2H), 4.24-4.19 (m, 4H), 3.77 (s, 12H), 2.85-2.82 (m, 4H), 1.61-1.58 (m, 10H), 1.51 (s, 6H), 0.39-0.34 (m, 4H); HRMS (EI) *m/z* 1243.4252 [calc'd for $C_{68}H_{80}Br_2N_2O_{10}$ (M+H)+ 1243.4252].

Preparation of alcohol 366:

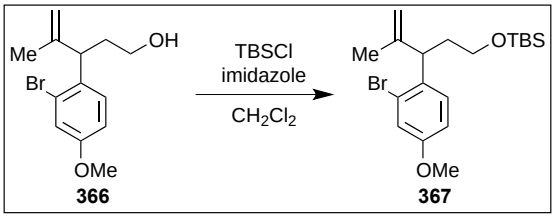


Alcohol 366. To a stirred heterogeneous solution of lithium aluminum hydride (160 mg, 3.51 mmol) in tetrahydrofuran (27.5 mL) was added methyl ester **176** (1.1 g, 3.51 mmol) as a solution in tetrahydrofuran (7.5 mL) over 40 minutes with a syringe pump. TLC was used to monitor reaction progress. TLC plates were developed with 15% EtOAc/Hex; visualized by UV lamp and $KMnO_4$ stain. Reaction was quenched with H_2O (0.2 mL), 15% NaOH (0.2 mL) and

H_2O (0.6 mL) at 0 ºC. Anhydrous $MgSO_4$ (2 scoops) was added, warmed to room temperature and stirred over night. Solution was filtered through a sand/celite pad and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (eluent 10% EtOAc/Hex) to afford alcohol **366** (800 mg, 80% yield) as colorless oil).

Alcohol 366. FTIR (thin film/NaCl): 3362, 2940, 1645, 1602, 1565, 1490, 1439, 1373, 1283, 1236, 1181, 1037, 894, 857, 839, 816; ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.12 (d, *J* = 8.7 Hz, 1H), 7.10 (d, *J* = 2.7 Hz, 1H), 6.83 (dd, *J* = 8.7, 2.7 Hz, 1H), 4.93 (d, *J* = 0.7 Hz, 1H), 4.91 (dd, *J* = 2.2, 1.4 Hz, 1H), 3.89-3.85 (m, 1H), 3.78 (s, 3H), 3.59 (dd, *J* = 5.4, 1.5 Hz, 1H), 3.57-3.56 (m, 1H), 2.14 (dq, *J* = 13.5, 6.8 Hz, 1H), 1.87 (ddt, *J* = 13.6, 8.9, 6.0 Hz, 1H), 1.61 (s, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 158.5, 147.2, 134.2, 128.9, 125.7, 117.7, 114.4, 110.8, 61.2, 55.6, 46.1, 36.9, 22.0; HRMS (EI) *m/z* 285.0474 [calc'd for $C_{13}H_{17}BrO_2$ (M+H)+ 284.0412].

Preparation of TBS-ether 367:

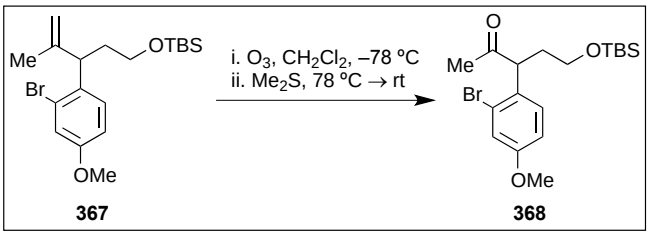


TBS-ether 367. To a stirred solution of alcohol **366** (500 mg, 285.18 mmol) and imidazole (238 mg, 3.50 mmol) in dichloromethane (4 mL) was added *tert*-butyldimethylsilyl chloride (396 mg, 2.63 mmol) at room temperature. TLC was used to monitor reaction progress. TLC plates were developed with 40% EtOAc/Hex; visualized by UV lamp and $KMnO_4$ stain. Reaction solution was hydrolyzed with H_2O (5 mL) and phases were separated. Organic phase was washed with brine (5 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced

pressure to afford TBS-ether **367** (697 mg, 99% yield). Crude material was advanced directly to ozonolysis with no further purification.

TBS-ether 367. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.12 (d, *J* = 8.7 Hz, 1H), 7.09 (d, *J* = 2.7 Hz, 1H), 6.82 (dd, *J* = 8.7, 2.6 Hz, 1H), 4.88 (dd, *J* = 1.6, 0.9 Hz, 2H), 3.85 (t, *J* = 7.2 Hz, 2H), 3.78 (s, 3H), 3.62-3.48 (m, 3H), 2.05 (td, *J* = 13.4, 7.3 Hz, 1H), 1.93-1.83 (m, 1H), 1.61 (s, 2H), 0.87 (s, 9H), 0.00 (s, 6H).

Preparation of ketone 368:

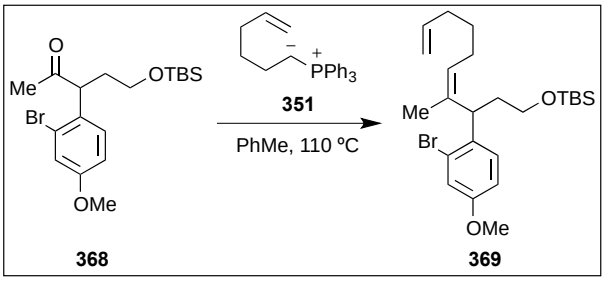


367 **368**

Ketone 368: Alkene **367** (697 mg, 1.75 mmol) was dissolved in dichloromethane (20 mL) and cooled to –78 ºC. Ozone was bubble through solution until saturation was achieved. TLC was used to monitor reaction progress. TLC plates were developed with 5% EtOAc/Hex; visualized by UV lamp and $KMnO_4$ stain. Oxygen was bubbled through solution for 10 minutes and dimethylsulfide (1.00 mL, 8.75 mmol) was added to solution. Reaction was warmed to room temperature and stirred overnight. Solution was concentrated under reduced pressure and crude material was purified with silica gel chromatography (gradient elution 2→3→4% EtOAc/Hex) to afford ketone **368** (400 mg, 57% yield) as colorless oil.

Ketone 368. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.14 (d, *J* = 2.6 Hz, 1H), 7.05 (d, *J* = 8.7 Hz, 1H), 6.83 (dd, *J* = 8.6, 2.7 Hz, 1H), 4.40 (t, *J* = 7.1 Hz, 1H), 3.79 (s, 3H), 3.59-3.46 (m, 2H), 2.26 (td, *J* = 13.7, 6.0 Hz, 1H), 2.08 (s, 3H), 1.78 (td, *J* = 13.1, 6.8 Hz, 1H), 0.88 (s, 9H), 0.00 (s, 6H).

Preparation of diene 369:

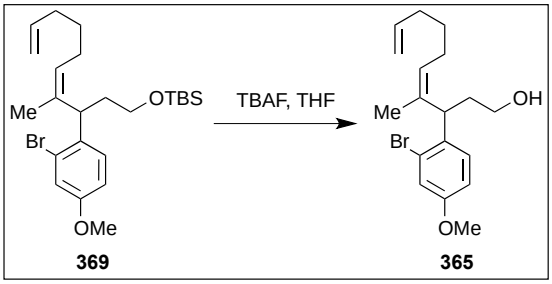


Diene 369. Ylide **351** (0.1 M in toluene): To a stirred solution of Wittig salt **390** (289 mg, 0.61 mmol) in toluene (4.8 mL) was added potassium bis(trimethylsilyl)amide (0.5 M in toluene, 1.2 mL, 0.60 mmol) at –78 ºC. Reaction mixture was stirred for 5 minutes at –78 ºC, warmed to room temperature and stirred 2 hours. Solution turned orange upon warming. Allowed solution to stand with out stirring so that potassium iodide settled on the bottom of the vial.

To ketone **368** (50 mg, 0.12 mmol) was added ylide **351** (0.1 M in toluene, 2.4 mL, 0.24 mmol) in a commercially available glass pressure tube with a Teflon screw-cap and heated to 110 ºC for 12 hours. Reaction mixture was cooled to room temperature and quenched with saturated NH_4Cl solution (3 mL). Organic phase was washed with H_2O (3 mL), brine (3 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. TLC plates were developed with 5% EtOAc/Hex; visualized by UV lamp and CAM stain. Crude material was purified with silica gel chromatography (gradient elution 1→2% EtOAc/Hex) to afford diene **369** (37.3 mg, 67% yield, >20:1 Z:E) as colorless oil.

Diene 369. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.11 (d, *J* = 9.1 Hz, 1H), 7.09 (d, *J* = 2.9 Hz, 1H), 6.82 (dd, *J* = 8.6, 2.6 Hz, 1H), 5.82 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 5.35 (t, *J* = 7.2 Hz, 1H), 5.04-4.88 (m, 2H), 3.78 (s, 3H), 3.63-3.48 (m, 2H), 2.10-1.98 (m, 5H), 1.90-1.79 (m, 2H), 1.52-1.42 (m, 2H), 1.47 (s, 3H), 0.88 (s, 9H), 0.01 (s, 6H).

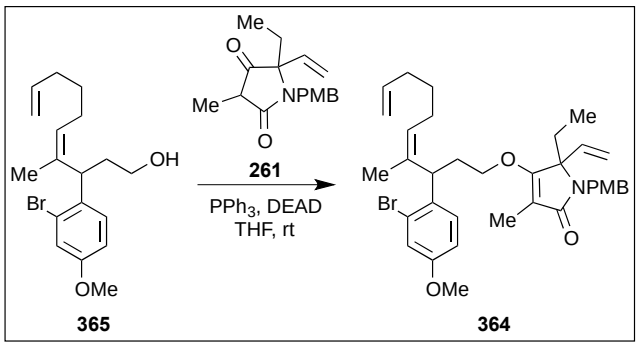
Preparation of alcohol 365:



Alcohol 365. To a stirred solution of TBS-ether **369** (37.3 mg, 0.08 mmol) in tetrahydrofuran (0.68 mL) was added tetrabutylammonium fluoride (1 M in tetrahydrofuran, 0.32 mL, 0.28 mmol) at room temperature. TLC was used to monitor reaction progress. TLC plates were developed with 20% EtOAc/Hex; visualized by UV lamp and $KMnO_4$ stain. Reaction was quenched with saturated NH_4Cl solution (1 mL) and phases were separated. Organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Residue was purified with silica gel chromatography (eluent 20% EtOAc/Hex) to afford alcohol **365** (28 mg, 99% yield) as colorless oil.

Alcohol 365. FTIR (thin film/NaCl): 3943, 3436, 3054, 2940, 2839, 2253, 1639, 1603, 1565, 1491, 1464, 1440, 1422, 1265, 1235, 1182, 1036, 909, 862, 843, 735, 705, 650, 427; ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.09 (d, *J* = 8.8 Hz, 1H), 7.08 (d, *J* = 2.8 Hz, 1H), 6.82 (dd, *J* = 8.7, 2.7 Hz, 1H), 5.80 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.38 (t, *J* = 7.2 Hz, 1H), 4.99 (dq, *J* = 17.1, 1.8 Hz, 1H), 4.94 (ddt, *J* = 10.2, 2.1, 1.1 Hz, 1H), 3.78-3.76 (m, 1H), 3.76 (s, 3H), 3.56 (t, *J* = 6.6 Hz, 2H), 2.17-2.01 (m, 6H), 1.88-1.79 (m, 1H), 1.60-1.43 (m, 2H), 1.46 (s, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 158.3, 139.0, 136.3, 134.6, 128.9, 125.7, 125.4, 117.7, 114.6, 114.0, 61.3, 55.6, 47.4, 36.5, 33.5, 29.1, 27.4, 15.4.

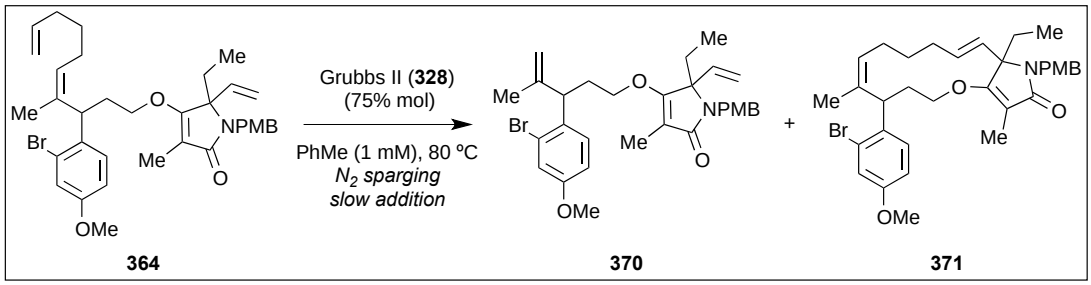
Preparation of triene 364:



Triene 364. Alcohol **365** (20 mg, 0.057 mg) and triphenylphosphine (22 mg, 0.085 mmol) were dissolved in tetrahydrofuran (0.6 mL) and diethyl azodicarboxylate (DEAD) (40% solution in toluene, 39 μl, 0.085 mmol) was added at room temperature and stirred for 10 minutes. Tetramic acid **261** (24.4 mg, 0.085 mmol) was added as a solution in tetrahydrofuran at room temperature and stirred overnight. TLC was used to monitor reaction progress. TLC plates were developed with 40% EtOAc/Hex; visualized by UV lamp and $KMnO_4$ stain. Tetrahydrofuran was evaporated under reduced pressure and residue was purified with silica gel chromatography (eluent 20% EtOAc/Hex) to afford triene **364** (21 mg, 57% yield) as colorless oil.

Triene 364. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.28-7.16 (m, 3H), 7.07 (dd, *J* = 4.7, 3.5 Hz, 1H), 6.83-6.76 (m, 3H), 5.80 (ddtd, *J* = 17.0, 10.2, 6.8, 0.9 Hz, 1H), 5.46 (dd, *J* = 17.8, 10.3 Hz, 1H), 5.33 (q, *J* = 5.7 Hz, 1H), 5.24-5.16 (m, 2H), 5.02-4.92 (m, 2H), 4.53 (dd, *J* = 15.1, 4.7 Hz, 1H), 4.22 (t, *J* = 7.8 Hz, 1H), 4.12 (dt, *J* = 14.7, 7.1 Hz, 2H), 3.83 (d, *J* = 7.0 Hz, 1H), 3.77 (s, 3H), 3.77 (s, 3H), 2.13-2.01 (m, 2H), 2.04 (q, *J* = 7.1 Hz, 4H), 1.92 (d, *J* = 0.9 Hz, 3H), 1.95-1.82 (m, 2H), 1.58 (dt, *J* = 14.0, 7.0 Hz, 1H), 1.50-1.43 (m, 1H), 1.43 (s, 3H), 0.34 (d, *J* = 1.0 Hz, 3H); HRMS (EI) *m/z* 622.2526 [calc'd for $C_{35}H_{44}BrNO_4$ (M+H)+ 622.2526].

Preparation of alkene 370 and macrocycle 371:



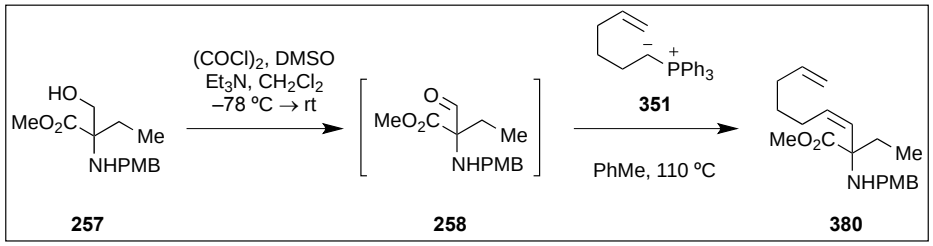
Alkene 370 and macrocycle 371. Toluene was pulled fresh from solvent still and degassed prior to use by sparging with nitrogen for 2 hours. To a 3-neck round bottom flask was added Grubbs II (**328**) (22 mg, 0.025 mmol) and system was flushed with nitrogen, toluene (35 mL) was added, nitrogen sparging of the solution was initiated and heated to 80 ºC. At 80 ºC triene **364** (21 mg, 0.034 mmol) was added as a solution in toluene (1.8 mL) by slow addition (syringe pump, 0.03 mL/min). TLC was used to monitor reaction progress. TLC plates were developed with 40% EtOAc/Hex; visualized by UV lamp and ceric ammonium molybdate (CAM) stain. After 60 minutes, (complete addition of triene **364**) conversion to two new compounds was observed. Reaction was cooled to room temperature and stirred open to external atmosphere over night. Toluene volume was reduced under pressure and solution was purified directly with silica gel chromatography (gradient elution 5→10→15→20→25% EtOAc/Hex) to afford alkene **370** (11.5 mg, 62% yield) and thirteen-membered macrocycle **371** (3.3 mg, 16% yield).

Alkene 370. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.27 (d, *J* = 8.6 Hz, 2H), 7.11-7.09 (m, 2H), 6.84-6.81 (m, 1H), 6.78 (d, *J* = 8.6 Hz, 2H), 5.51-5.42 (m, 1H), 5.23-5.17 (m, 2H), 4.93 (s, 1H), 4.88 (d, *J* = 5.5 Hz, 1H), 4.53 (dd, *J* = 15.1, 8.5 Hz, 1H), 4.26-4.20 (m, 1H), 4.18-4.09 (m, 2H), 3.87 (t, *J* = 7.5 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 2.14 (dddd, *J* = 13.4, 10.0, 6.8, 3.3 Hz, 2H),

2.01-1.94 (m, 1H), 1.92 (s, 3H), 1.88-1.82 (m, 1H), 1.58 (s, 3H), 0.35 (td, *J* = 7.2, 2.8 Hz, 3H); HRMS (EI) *m/z* 554.1897 [calc'd for $C_{30}H_{37}BrNO_4$ (M+H)+ 554.19].

Macrocycle 371. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.26 (d, *J* = 8.5 Hz, 2H), 7.11 (d, *J* = 4.4 Hz, 1H), 7.10 (d, *J* = 1.4 Hz, 1H), 6.83-6.79 (m, 1H), 6.78 (d, *J* = 8.5 Hz, 2H), 5.63 (dt, *J* = 14.6, 7.4 Hz, 2H), 5.06 (d, *J* = 15.8 Hz, 1H), 4.47 (ddd, *J* = 9.2, 5.3, 3.7 Hz, 1H), 4.40 (d, *J* = 15.1 Hz, 1H), 4.25 (d, *J* = 15.1 Hz, 1H), 4.00 (dd, *J* = 11.7, 3.6 Hz, 1H), 3.81 (dd, *J* = 9.5, 4.1 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 2.19-2.10 (m, 4H), 2.07-2.04 (m, 1H), 2.03-1.97 (m, 3H), 1.93 (t, *J* = 7.0 Hz, 1H), 1.89 (s, 3H), 1.64 (t, *J* = 7.0 Hz, 1H), 1.38 (s, 3H), 0.46 (t, *J* = 7.2 Hz, 3H); HRMS (EI) *m/z* 594.2212 [calc'd for $C_{33}H_{41}BrNO_4$ (M+H)+ 594.2213].

Preparation of diene 380:



Diene 380. *Swern Oxidation*: To a stirred solution of dimethylsulfoxide (0.8 mL, 11.24 mmol) in dichloromethane (20 mL) was added oxalyl chloride (0.47 mL, 5.61 mmol) at –78 ºC. Reaction solution was stirred for 20 minutes and alcohol **257** (750 mg, 2.81 mmol) as a solution in dichloromethane (5 mL) dropwise via cannula. Reaction solution was stirred for 1 hour at –78 ºC and then warmed to room temperature. TLC was used to monitor reaction progress. TLC plates were developed with 30% EtOAc/Hex; visualized by UV lamp and $KMnO_4$ stain. Reaction solution was quenched with saturated $NaHCO_3$ solution (50 mL) and phases were separated. Organic phase was washed with H_2O (100 mL), brine (100 mL), dried over anhydrous

Na_2SO_4 and concentrated to afford aldehyde **258** as yellow oil, which was immediately carried into the Wittig olefination.

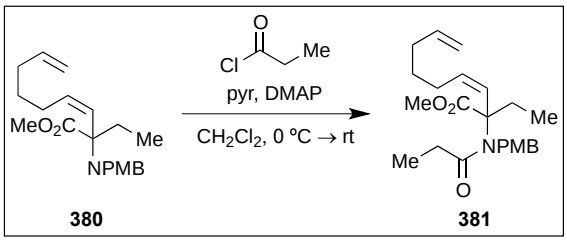
*Ylide **351** preparation*: To a stirred heterogeneous solution of phosphonium salt **390** (3.8 g, 8.00 mmol) in toluene (50 mL) was added potassium bis(trimethylsilyl)amide (0.5 M in toluene, 12.8 mL, 6.4 mmol) at room temperature. Solution was stirred for 3 hours. Stirring was stopped and potassium iodide salts and excess phosphonium salt **390** were allowed to settle to the bottom of the round bottom flask to yield a homogenous, red/orange solution of ylide **351** (0.1 M in toluene).

Wittig olefination: To a stirred solution of ylide **351** (0.1 M in toluene, 57 mL, 5.62 mmol) was added aldehyde **258** (2.81 mmol) as a solution in toluene (84 mL) dropwise via cannula at –78 ºC. Reaction was stirred and warmed to room temperature. TLC was used to monitor reaction progress. TLC plates were developed with 30% EtOAc/Hex; visualized by UV lamp and $KMnO_4$ stain. Reaction was diluted with ethyl acetate (100 mL) and quenched with saturated $NaHCO_3$ solution (100 mL) followed by separation of the phases. Aqueous phase was extracted with ethyl acetate (2 x 50 mL). Combined organic phase was washed with H_2O (100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (eluent 15% EtOAc/Hex) to yield diene **380** (697 mg, 75% yield, over two steps, >20:1 Z:E) as colorless oil.

Diene 380. FTIR (thin film/NaCl): 3074, 2932, 2836, 1730, 1640, 1612, 1585, 1512, 1458, 1441, 1301, 1247, 1173, 1126, 1037, 995, 911, 823, 808, 410; ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.25 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.80 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 5.56 (d, *J* = 4.5 Hz, 1H), 5.55 (d, *J* = 4.3 Hz, 1H), 5.00 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.94 (dt,

J = 10.2, 0.9 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 3.54 (d, *J* = 11.9 Hz, 1H), 3.48 (d, *J* = 11.9 Hz, 1H), 2.29 (dd, *J* = 13.6, 5.8 Hz, 2H), 2.06 (q, *J* = 7.4 Hz, 2H), 1.93 (dq, *J* = 14.4, 7.2 Hz, 1H), 1.83 (dt, *J* = 14.1, 7.1 Hz, 1H), 1.78 (br s, 1H), 1.45 (quintet, *J* = 7.6 Hz, 2H), 0.86 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 176.1, 158.7, 138.8, 134.3, 132.9, 129.5, 129.0, 114.7, 113.9, 66.5, 55.4, 52.1, 47.5, 33.7, 31.5, 29.0, 28.0, 8.4; HRMS (EI) *m/z* 332.2216 [calc'd for $C_{20}H_{29}NO_3$ (M+H)+ 332.222].

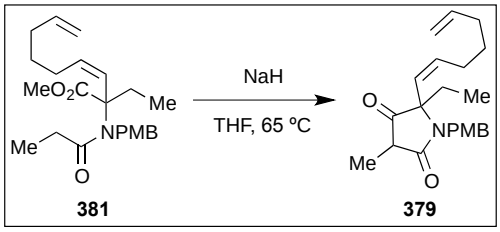
Preparation of amide 381:



Amide 381. To a stirred solution of amine **380** (1.3 g, 3.92 mmol), pyridine (1.6 mL, 19.60 mmol), 4-(dimethylamino)pyridine (24 mg, 0.19 mmol) in dichloromethane (5 mL) was added propionyl chloride (1.4 mL, 15.68 mmol) at 0 ºC. Reaction was stirred 20 minutes at 0 ºC prior to warming to room temperature. Stirred 2 ½ days at room temperature. TLC was used to monitor reaction progress. TLC plates were developed with 30% EtOAc/Hex; visualized by UV lamp and $KMnO_4$ stain. Reaction solution was diluted with dichloromethane (5 mL) and quenched with saturated $NaHCO_3$ solution (5 mL) followed by separation of the phases. Aqueous phase was extracted with dichloromethane (3 x 5 mL). Combined organic phase was washed with H_2O (50 mL), brine (50 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 10→20→30% EtOAc/Hex) to yield amide **381** (1.04 g, 69% yield) as yellow oil.

Amide 381. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.40 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 5.76 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 5.59 (d, *J* = 12.5 Hz, 1H), 5.38 (dt, *J* = 12.4, 7.1 Hz, 1H), 5.02-4.92 (m, 2H), 4.64 (d, *J* = 18.2 Hz, 1H), 4.58 (d, *J* = 18.3 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 2.35-1.98 (m, 8H), 1.41 (quintet, *J* = 7.5 Hz, 2H), 1.02 (t, *J* = 7.4 Hz, 3H), 0.87 (t, *J* = 7.5 Hz, 3H); HRMS (EI) *m/z* 388.2477[calc'd for $C_{23}H_{33}NO_4$ (M+H)+ 388.2482].

Preparation of tetramic acid 379:

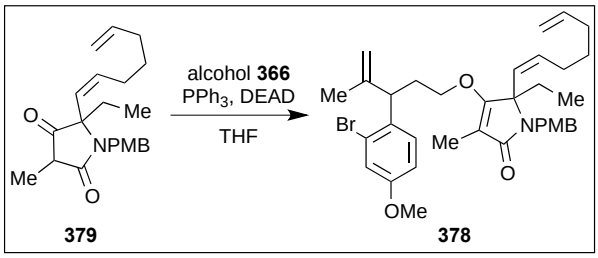


381 **379**

Tetramic acid 379. Sodium hydride (60% in mineral oil) was washed with pentane (3 x 2 mL) and dried under high vacuum. To a stirred heterogeneous solution of washed sodium hydride (75 mg, 1.83 mmol) in tetrahydrofuran (5 mL) was added amide **381** (177 mg, 0.46 mmol) as a solution in tetrahydrofuran (5 mL) at 65 ºC down interior of condenser. TLC was used to monitor reaction progress. TLC plates were developed with 40% EtOAc/Hex; visualized by UV lamp and $KMnO_4$ stain. After 24 hours reaction was cooled to room temperature and diluted with ethyl acetate (10 mL), quenched with saturated NH_4Cl solution (10 mL) and phases were separated. Organic phase was washed with H_2O (20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 5→10→15→20% EtOAc/PhMe) to afford tetramic acid **379** (76 mg, 46% yield, 2:1 dr) as yellow foam.

Tetramic acid 379. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.32 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 5.79-5.62 (m, 1H), 5.54 (dt, *J* = 11.6, 7.3 Hz, 1H), 5.25 (dt, *J* = 11.3, 1.9 Hz, 1H), 5.02-4.90 (m, 3H), 3.99 (d, *J* = 14.6 Hz, 1H), 3.79 (s, 3H), 2.85 (q, *J* = 7.5 Hz, 1H), 1.97 (q, *J* = 7.3 Hz, 4H), 1.74-1.50 (m, 4H), 1.37 (d, *J* = 7.5 Hz, 3H), 0.53 (t, *J* = 7.4 Hz, 3H); 7.34 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 9.2 Hz, 2H), 5.79-5.62 (m, 1H), 5.54 (dd, *J* = 14.6, 11.6 Hz, 1H), 5.18 (dt, *J* = 8.3, 1.9 Hz, 1H), 4.98-4.93 (m, 2H), 4.71 (d, *J* = 14.5 Hz, 1H), 4.20 (d, *J* = 14.7 Hz, 1H), 3.79 (s, 3H), 2.95 (q, *J* = 7.7 Hz, 1H), 1.90-1.81 (m, 4H), 1.74-1.50 (m, 4H), 1.33 (d, *J* = 7.7 Hz, 3H), 0.40 (t, *J* = 7.3 Hz, 3H); HRMS (EI) *m/z* 356.2215 [calc'd for $C_{22}H_{29}NO_3$ (M+H)+ 356.222].

Preparation of triene 378:

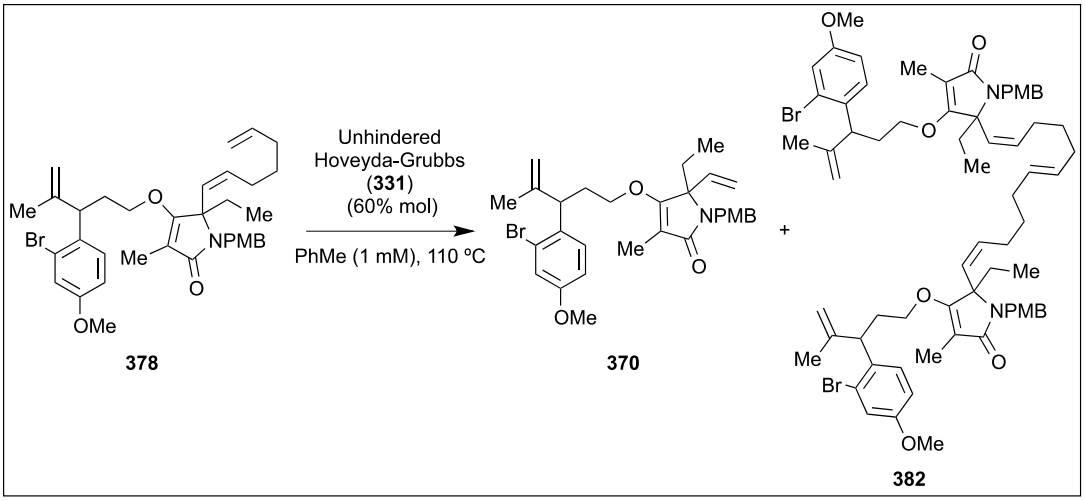


Triene 378. To a stirred solution of triphenylphosphine (504 mg, 1.92 mmol) in tetrahydrofuran (20 mL) was added diethyl azodicarboxylate (DEAD) (40% solution in toluene, 0.80 mL, 1.92 mmol) and alcohol **366** (457 mg, 1.60 mmol) as a solution in tetrahydrofuran (6 mL) and stirred for 10 minutes at room temperature. Tetramic acid **379** (570 mg, 1.60 mmol) was added as a solution in tetrahydrofuran (6 mL) and stirred at room temperature. TLC was used to monitor reaction progress. TLC plates were developed with a gradient elution 100% $CH_2Cl_2 \rightarrow$ 5% EtOAc/CH_2Cl_2; visualized by UV lamp and $KMnO_4$ stain. Reaction solution was concentrated under reduced pressure and purified with silica gel chromatography (gradient elution 1→2→3→4→5% EtOAc/Hex) fractions with new compound were combined and

purified a second time with silica gel chromatography (gradient elution 100% $CH_2Cl_2 \rightarrow$ 5% EtOAc/ CH_2Cl_2) to afford triene **378** (211 mg, 21% yield).

Triene 378. FTIR (thin film/NaCl): 2932, 1663, 1620, 1512, 1491, 1439, 1403, 1334, 1303, 1244, 1035; ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.30 (d, *J* = 8.6 Hz, 2H), 7.09 (dd, *J* = 8.6, 0.7 Hz, 1H), 7.09 (d, *J* = 2.7 Hz, 1H), 6.82 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.77 (d, *J* = 8.7 Hz, 2H), 5.71 (ddq, *J* = 17.0, 10.3, 6.8 Hz, 1H), 5.46 (dt, *J* = 11.5, 7.2 Hz, 1H), 5.10 (dd, *J* = 11.5, 3.0 Hz, 1H), 4.98-4.88 (m, 4H), 4.67 (dd, *J* = 14.9, 4.9 Hz, 1H), 4.26-4.10 (m, 2H), 3.96 (dd, *J* = 14.9, 3.8 Hz, 1H), 3.86 (t, *J* = 7.1 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 2.17 (dq, *J* = 13.9, 6.8 Hz, 1H), 2.02-1.89 (m, 2H), 1.92 (d, *J* = 2.7 Hz, 3H), 1.84-1.66 (m, 2H), 1.58 (d, *J* = 2.9 Hz, 3H), 1.60-1.52 (m, 2H), 1.35-1.22 (m, 3H), 0.27-0.23 (m, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 173.5, 167.7, 158.77, 158.69, 146.2, 136.5, 133.7, 131.2, 130.5, 128.7, 128.1, 125.7, 117.9, 114.8, 114.3, 113.5, 111.2, 102.3, 69.1, 67.8, 55.7, 55.4, 45.87, 45.78, 42.8, 34.10, 34.02, 33.57, 33.54, 29.9, 28.68, 28.66, 26.92, 26.89, 22.01, 21.87, 8.68, 8.66, 6.65, 6.62; HRMS (EI) *m/z* 646.2332 [calc'd for $C_{35}H_{44}BrNO_4$ (M+Na)+ 621.2454].

Preparation of diene 370 and dimer 382:



Diene 370 and dimer 382. Toluene was pulled fresh from solvent still and degassed prior to use by sparging with nitrogen for 2 hours. To a round bottom flask was added toluene (30 mL) followed by the addition of triene **378** (20 mg, 0.032 mmol) as a solution in toluene (1.8 mL); the substrate solution was heated to 80 ºC and catalyst **331** (4 mg, 0.0064 mmol, 20 mol%) was added as a solution in toluene (1 mL). TLC was used to monitor reaction progress. TLC plates were developed with a gradient elution 40% EtOAc/Hex; visualized by UV lamp and $KMnO_4$ stain. After 2 hours at 80 ºC starting material remained by TLC. Reaction was heated to reflux (110 ºC) and catalyst **331** (an additional 40 mol%, 12 mg, 0.021 mmol) as a solution in toluene (3 mL) was added. Stirring at reflux was continued for 15 hours. Reaction solution was cooled to room temperature and concentrated under reduced pressure. Residue was purified by silica gel chromatography (gradient elution 20→40% EtOAc/Hex) to afford recovered starting material **378** (5 mg, 25 % yield), diene **370** (3.4 mg, 19% yield) and dimer **382** (7.4 mg, 40% yield).

Dimer 382. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.29 (d, J = 8.3 Hz, 4H), 7.10-7.07 (m, 4H), 6.82 (dd, J = 8.6, 2.2 Hz, 2H), 6.77 (d, J = 8.7 Hz, 4H), 5.48-5.42 (m, 2H), 5.30-5.23 (m, 2H), 5.12-5.06 (m, 2H), 4.92-4.90 (m, 2H), 4.88-4.86 (m, 2H), 4.72-4.65 (m, 2H), 4.25-4.08 (m, 4H), 3.94-3.88 (m, 2H), 3.87-3.83 (m, 2H), 3.77 (s, 12H), 2.20-2.09 (m, 2H), 1.91 (s, 6H), 2.01-1.67 (m, 12H), 1.57 (s, 6H), 1.57-1.43 (m, 4H), 1.27-1.20 (m, 6H), 0.23 (t, J = 6.8 Hz, 6H); HRMS (EI) *m/z* 1215.4666 [calc'd for $C_{68}H_{84}N_2O_8$ (M+H)+ 1215.4667].

References Relevant to Chapter 4

(80) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

(81) Maier, M. E. *Angew. Chem. Int. Edit.* **2000**, *39*, 2073.

(82) Diedrichs, N.; Westermann, B. *Synlett* **1999**, 1127.

(83) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653.

(84) Wallace, D. J. *Angew. Chem. Int. Edit.* **2005**, *44*, 1912.

(85) Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J. Z.; Zhao, H. Y. *J. Am. Chem. Soc.* **2004**, *126*, 10210.

(86) For preparation of the requisite Wittig salt see Appendix.

(87) For preparation of the requisite Wittig salt see Appendix.

(88) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

(89) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

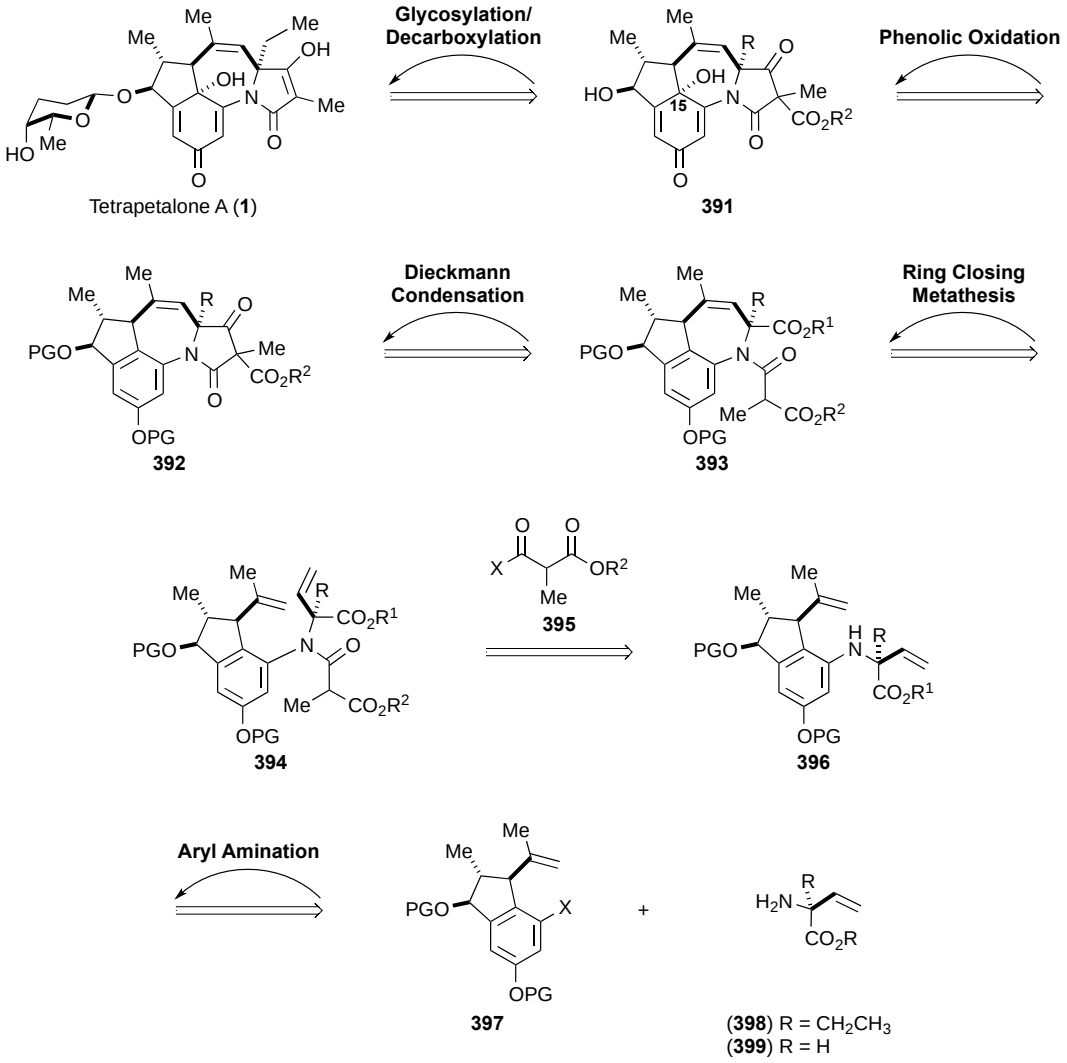
(90) Helmboldt, H.; Hiersemann, M. *J. Org. Chem.* **2009**, *74*, 1698.

Chapter 5

An Indanone Coupling Partner

5.1 Fifth-Generation Retrosynthetic Analysis

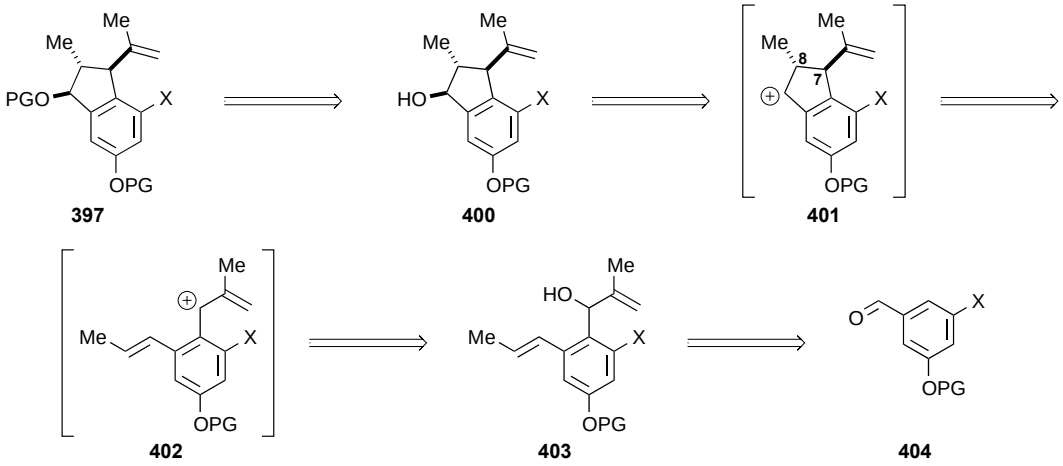
As outlined in Scheme 5.1, our fifth-generation retrosynthetic analysis of tetrapetalone A (**1**) envisaged completion of the natural product via a glycosylation and decarboxylation sequence of aglycon **391**, which was envisioned as deriving from a Dieckmann condensation applied to amide **393** and phenolic oxidation to install the C(15)-hydroxyl group. Benzazepine **393** would be achieved upon application of ring closing metathesis to diene **394** derived from acylation of amine **396**. Construction of the C–N bond of diene **394** conceived to be accomplished by an intermolecular aryl amination between indanol **397** and the appropriately functionalized amine **398** or **399**. With a synthetic route in hand to prepare amine **398** and knowledge that amine **399** had been prepared previously[91,92]; we focused our synthetic endeavors on the synthesis of an indanol coupling partner.



Scheme 5.1 Fifth-Generation Retrosynthetic Analysis

5.1.2 An Indanol Coupling Partner - Retrosynthetic Analysis

Inspired by the work of Snyder and coworkers[93], the synthesis of indanol **397** was seen as proceeding via protection of a secondary alcohol (**400**) that was in turn envisioned as arising from the addition of water to benzylic carbocation **401** (Scheme 5.2). Construction of the C(**7**)-C(**8**) bond of **401** via a cationic cyclization involving intermediate alkene **402**, would be initiated upon ionization of benzylic alcohol **403**. The requisite benzylic alcohol **403** would be accessed from an appropriate benzaldehyde derivative **404**.

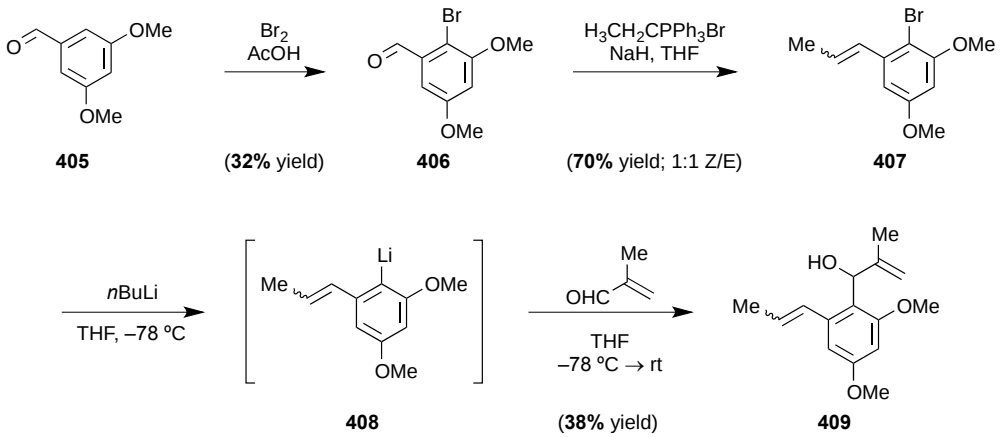


Scheme 5.2 Retrosynthetic Analysis of Indanol Coupling Partner

5.2 Looking into a Cation-Based Cyclization

5.2.1 Synthesis of a Cyclization Substrate

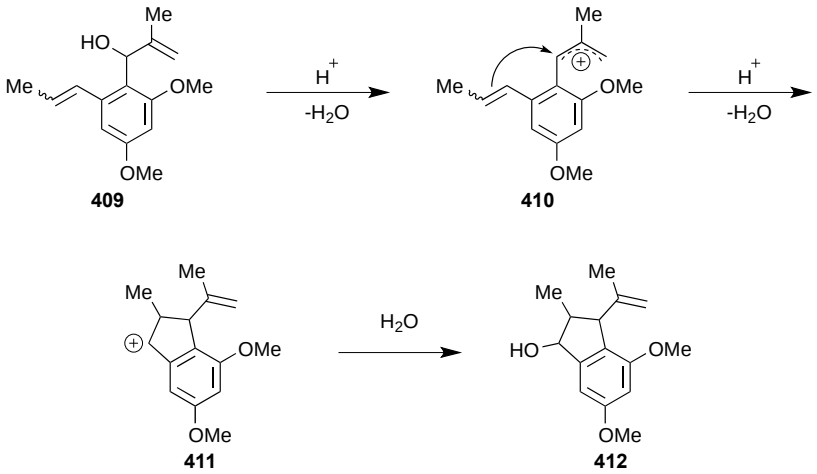
Electrophilic aromatic bromination of commercially available 3,5-dimethoxybenzaldehyde (**405**) furnished aryl bromide **406** in low yield (32%) (Scheme 5.3). Wittig olefination was employed to furnish alkene **407** in good yield (70%) as a 1:1 mixture of olefin isomers. Lithium-halogen exchange followed by trapping of the resultant aryl anion **408** with methacrolein provided the desired benzylic alcohol **409**, although in low yield (38%) provided enough material to investigate the cation-based cyclization.



Scheme 5.3 Synthesis of a Cyclization Precursor

5.2.2 Acid Catalyzed Cyclization

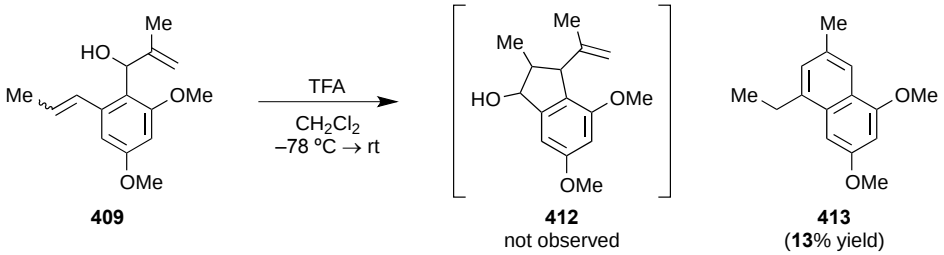
In a productive scenario, acid mediated ionization of benzylic alcohol **409** would furnish carbocation **410** subsequent 5-exo-trig cyclization, favored in accordance with Baldwin's rules, would provide indane **411** concomitant addition of water would afford desired indanol **412** (Scheme 5.4).



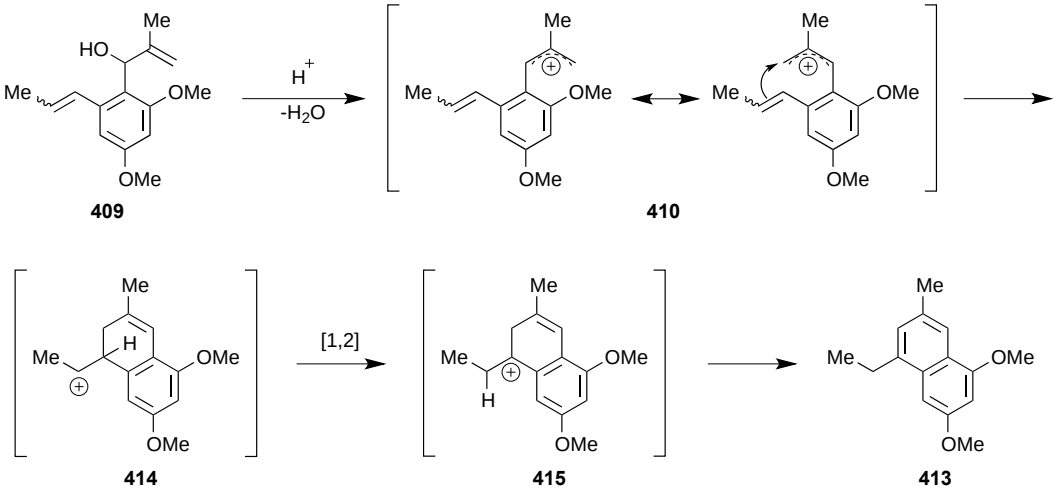
Scheme 5.4 Proposed Cationic Cyclization

Following the cationic cyclization procedure of Snyder *et al.*,[93] benzylic alcohol **409** was exposed to trifluoroacetic acid and slowly warmed to room temperature, unfortunately the cyclization product observed was not the desired indanol **412** but naphthalene **413** (Scheme 5.5).

Acid mediated ionization of benzylic alcohol **409** affords carbocation **410**, which is subsequently trapped in a 6-endo-trig cyclization, favored in accordance with Baldwin's rules, to afford secondary carbocation **414,** which would undergo a facile 1,2-hydride shift and aromatization sequence to furnish naphthalene **413** (Scheme 5.6).



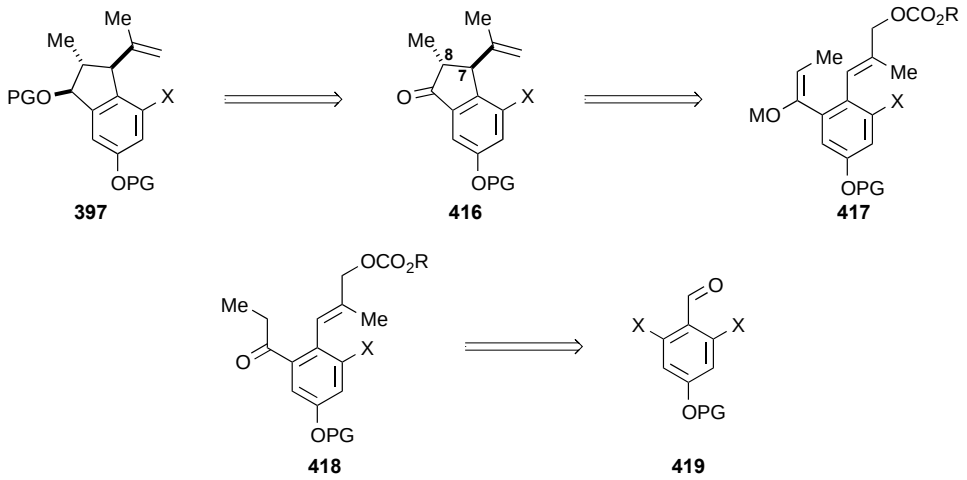
Scheme 5.5 Acid Mediated Cyclization



Scheme 5.6 Proposed Mechanism for Naphthalene Formation

5.3 An Alternative Cyclization Strategy

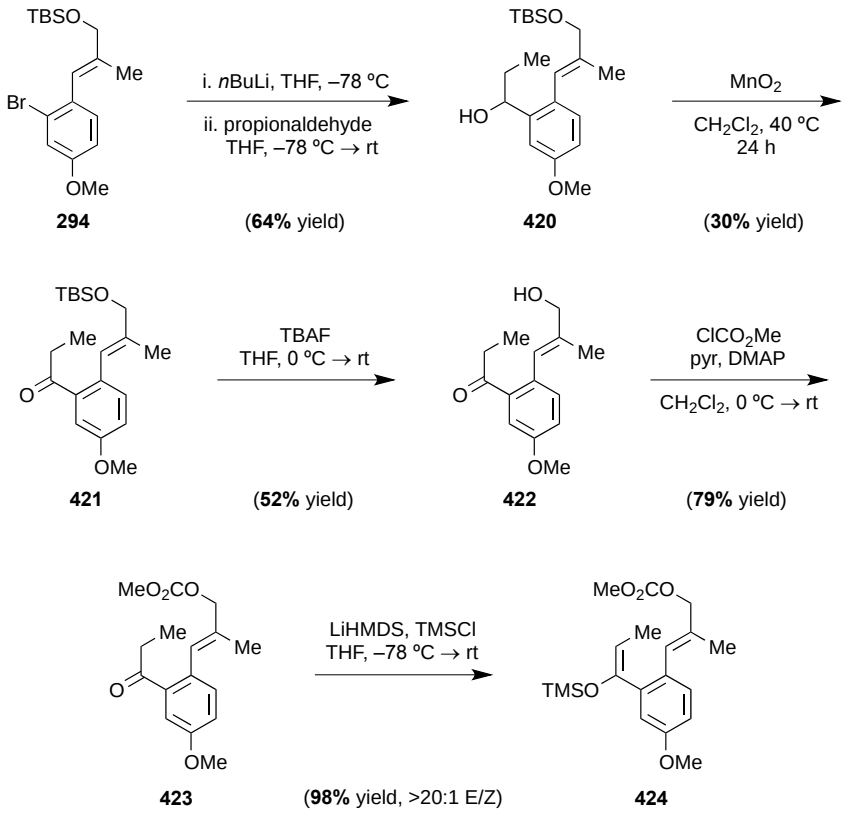
In order to selectively construct the C(**7**)–C(**8**) bond by a cyclization strategy, we turned our attention to the indanone **416**, which upon reduction would provide direct access to the desired indanol coupling partner **397** (Scheme 5.7). We envisaged accessing indanone **416** via S_N2' cyclization of enolate **417** which would derive from ketone **418**, a substrate which appeared accessible from benzaldehyde derivative **419**.



Scheme 5.7 Revised Retrosynthetic Analysis of Indanol Coupling Partner

5.4 Investigation of a Model System

In order to investigate the desired cyclization in an expedient fashion, we opted to start with the previously synthesized aryl bromide **294**, lacking only a halogen from our desired system. En route to cyclization substrate **424**, aryl bromide **294** was subjected to lithium-halogen exchange followed by trapping of the resultant aryl anion with propionaldehyde to furnish benzylic alcohol **420** proceeded in moderate yield (64%.). Subsequent exposure of **420** to manganese dioxide oxidation proved to be slow but effectively provided access to ketone **421**. Tetrabutylammonium fluoride mediated silyl ether cleavage unveiled allylic alcohol **422** which was acylated with methyl chloroformate to provide allylic carbonate **423** in modest yield (41%), over two steps. Lithium bis(trimethylsilyl)amide mediated enolization of ketone **423** in the presence of trimethylsilyl chloride furnished silyl enol ether **424** in excellent yield (98%) as essentially a single olefin isomer.

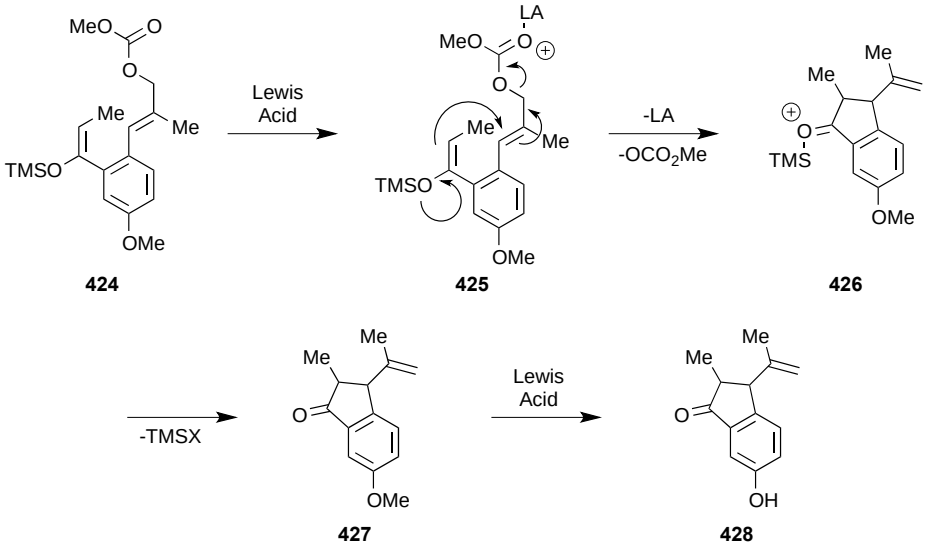


Scheme 5.8 Synthesis of Cyclization Precursor

5.4.1 Lewis Acid Mediated Cyclization

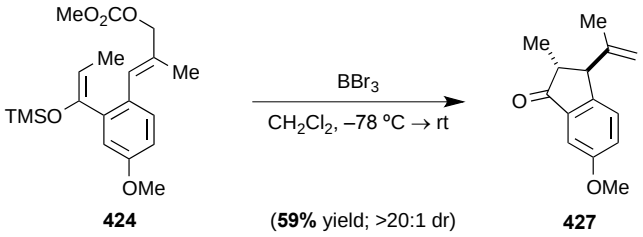
Silyl enol ethers have proven to be extraordinarily versatile substrates for a wide variety of synthetic reactions, including aldol reaction, Michael reactions, [4+2] cycloaddition reactions, alkylations, acylations, oxidative processes, etc.[94] The Lewis acid catalyzed reactions of silyl enol ethers with electrophiles are an extremely important application of silyl enol ethers in organic chemistry. Under the influence of Lewis acids, silyl enol ethers react not only with carbonyl compounds, such as aldehydes and ketones, but also acetals, orthoesters, azomethine functions, and α-halo ethers and sulfides. It is known that allylic bromides, chloromethyl methyl ether, and allylic acetates react with silyl enol ethers in the presence of Lewis acids.[95-97] Lewis acids have been shown to effective reagents for the cleavage of aryl methyl ethers.[98]

In a productive cyclization, we envisioned that activation of the allylic carbonate **425** via Lewis acid coordination would facilitate the intramolecular S_N2' displacement by the silyl enol ether to construct the desired carbon-carbon bond of indanone **427** (Scheme 5.9). One could also conceive concomitant aryl methyl ether cleavage under the reaction conditions to effectively afford phenol **428** in a one-pot procedure.



Scheme 5.9 Proposed Mechanism for Lewis Acid Facilitated Cyclization

With cyclization precursor **424** on hand we were excited to investigate a Lewis acid facilitated cyclization. Gratifyingly, exposure of allylic carbonate **424** to boron tribromide afforded the desired indanone **427** as a single diastereomer, albeit in modest yield (59%) (Scheme 5.10). We were very excited by this result as it proved we could construct the requisite carbon-carbon bond to furnish an indanone core and that upon optimization of the reaction conditions we would be able to develop a one-pot cyclization/demethylation procedure.



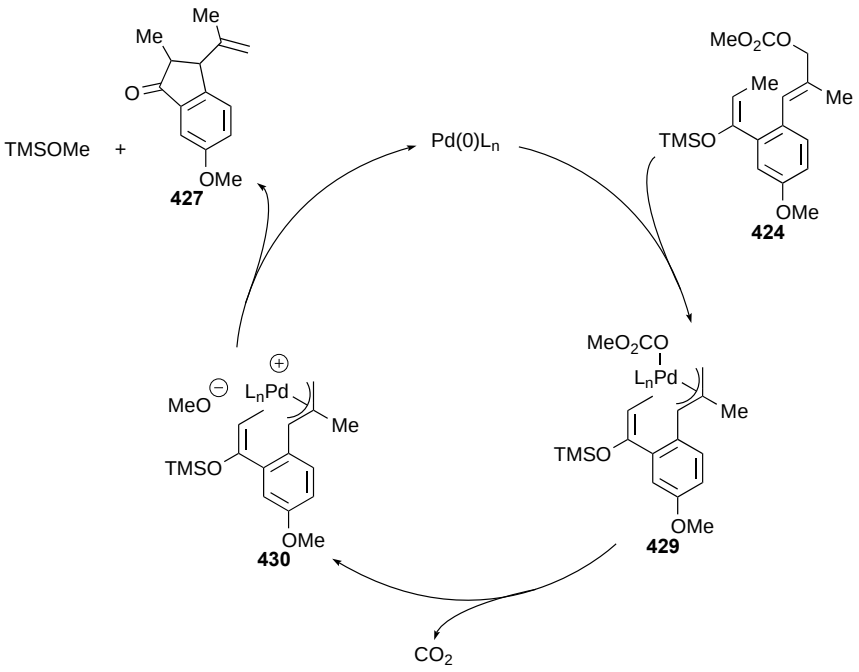
424 (**59%** yield; >20:1 dr) **427**

Scheme 5.10 Lewis Acid Facilitated Cyclization

5.4.2 Tsuji-Trost Allylic Alkylation

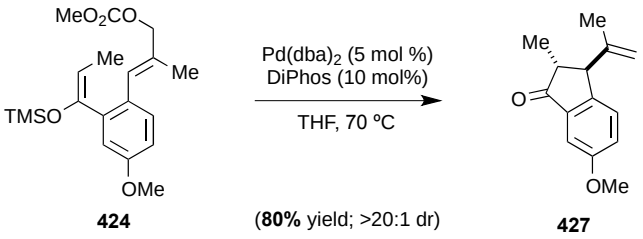
Metal-catalyzed asymmetric allylic substitution, which involves the attack of diverse nucleophiles at an allylic metal intermediate or S_N2'-type allylic substitutions, has been investigated with great intensity. The benefits of this method include high levels of asymmetric induction, tolerance of a wide range of functional groups and a great flexibility in the type of bonds that can be formed. For example, H-, C-, N-, O- and S-centered nucleophiles can be employed. Many ligands have been designed for the benchmark allylic alkylation of diphenylallyl acetate with malonate.[99-108]

In effort to pursue an enantio- and diastereoselective indanone synthesis we decided to investigate an intramolecular Tsuji-Trost allylic alkylation. Under neutral reaction conditions we envisioned cyclization to proceed via oxidative addition of allyl carbonate **424** to palladium(0) to provide π-allylpalladium carbonate **429**, which upon subsequent decarboxylation would afford π-allylpalladium methoxide **430** (Scheme 5.11). Concomitant carbon-carbon bond formation and silyl enol ether cleavage would furnish indanone **427** along with an equivalent of methoxysilane and regeneration of the palladium(0) species.



Scheme 5.11 Proposed Intramolecular Tsuji-Trost Allylic Alkylation

Indeed exposure of allylic carbonate **424** to Tsuji's neutral reaction conditions[109,110] based on a catalytic system derived from palladium tris(dibenzylideneacetone)dipalladium(0) and ethylenebis(diphenylphosphine) (Diphos) afforded the desired indanone in excellent yield (80%), as essentially a single diastereomer (Scheme 5.12). Successful cyclization to afford model indanone **427** prompted us to investigate a system that possessed a handle on the aromatic core (i.e. **397**, Scheme 5.7) that would allow for further functionalization upon cyclization.

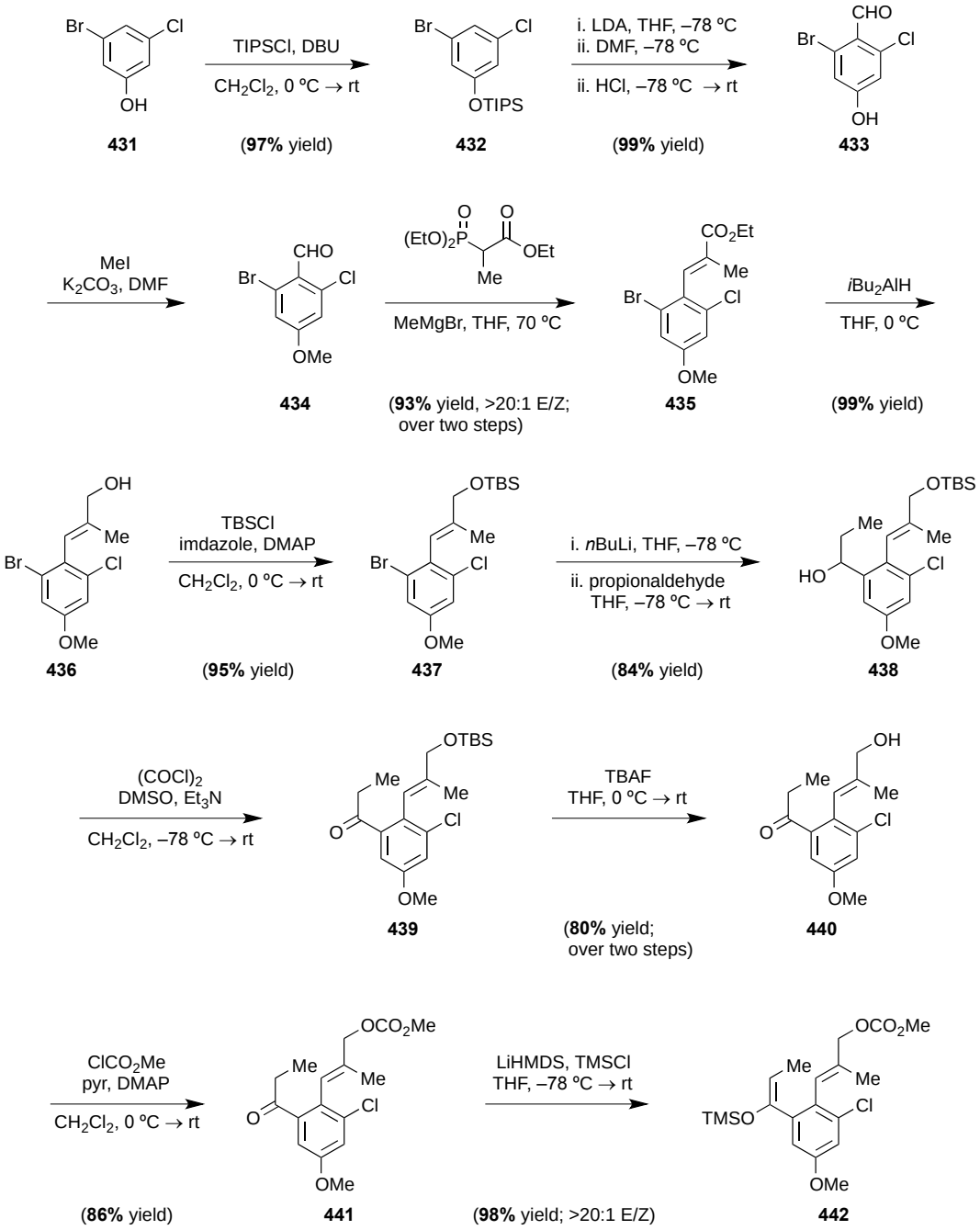


424 (**80%** yield; >20:1 dr) **427**

Scheme 5.12 Intramolecular Tsuji-Trost Allylic Alkylation

5.5 Synthesis of a Highly Functionalized Cyclization Precursor

Silylation of commercially available 3-bromo-5-chlorophenol (**431**) provided TIPS-ether **432,** which underwent *ortho*-lithiation upon exposure to lithium diisopropylamide (LDA) subsequent trapping of the resultant aryl anion with *N*,*N*-dimethylformamide followed by hydrolysis afforded aldehyde **433** in excellent yield (96%) yield over two steps.[111,112] Methylation followed by Horner Wadsorth Emmons olefination furnished α,β-unsaturated ester **435** in high yield (93%), as a single olefin isomer (>20:1 E/Z), over two steps. Diisobutylaluminum hydride mediated reduction furnished allylic alcohol **436**, silylation provided TBS-ether **437** in excellent yield (94%), over two steps. Chemoselective lithium-bromine exchange and subsequent trapping of the resultant aryl anion with propionaldehyde provided benzylic alcohol **438** in high yield (84%). Swern oxidation afforded ketone **439,** subsequent tetrabutylammonium fluoride mediated silyl ether cleavage unveiled allylic alcohol **440** in high yield (80%), over two steps. Acylation of the allylic alcohol smoothly furnished allylic carbonate **442** in 86% yield. Lithium bis(trimethylsilyl)amide mediated enolization in the presence of trimethylsilyl chloride afforded the desired silyl enol ether **442** in excellent yield as a single olefin isomer (>20:1 E:Z).



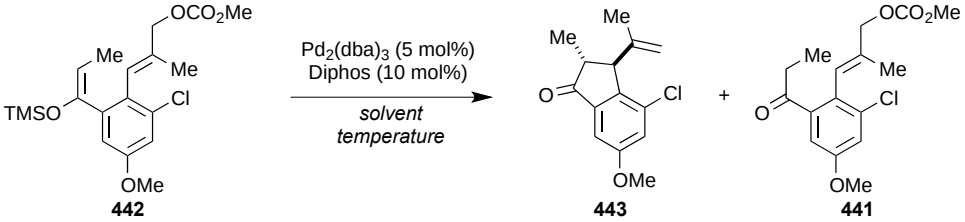
Scheme 5.13 Synthesis of Highly Functionalized Cyclization Precursor

5.5.1 Intramolecular Tsuji-Trost Allylic Alkylation

With the successful application of a Tsuji-Trost allylic alkylation to model system **424** (Scheme 5.12), we were excited to probe the reactivity of **442** in such a reaction. To our dismay the application of previously successful cyclization conditions (entry 1, Table 5.1) to π-allyl

precursor **424** resulted in a 1:1 mixture of starting material (**442**) and ketone **441**. Switching the reaction solvent to 1,4-dioxane and increasing the reaction temperature (entries 2 and 3, Table 5.1) proved successful and afforded the desired indanone **443**, albeit in low yield (23%) yield; as a mixture of diastereomers (5:1 dr). Observing that an increase in reaction temperature proved to be successful with substrate **442** we decided it would be beneficial to run the reaction in a higher boiling solvent. An initial solvent screen proved futile; toluene (entry 4) provided a mixture of starting material **442** and ketone **441** and *N*,*N*-dimethylformamide (entry 5) resulted in complete conversion to ketone **441**.

Table 5.1 Effect of Solvent on the Palladium(0)-Catalyzed Reaction



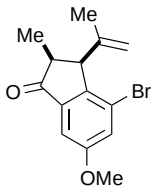
entry	solvent	temperature (ºC)	time (h)	**product** (% yield)
1	THF	65	24	**442** (50%): **441** (50%)[a]
2	1,4-dioxane	80	19	**443** (23%, 5:1 dr)[b]
3	1,4-dioxane	100	21	**443** (24%, 5:1 dr)[b]
4	PhMe	100	18	**442** : **441** mixture[a]
5	DMF	100	15	**441** (100%)[a]

[a]Reaction analyzed by ^{1}H NMR.
[b]Isolated yield.

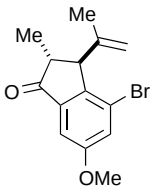
The relative stereochemistry of indanones **427** and **443** was inferred from ^{1}H NMR spectroscopy via chemical shift and splitting pattern comparisons with the indanone **85** reported by Sarpong and coworkers (Table 5.2).[113] From this comparison it was concluded that the

palladium(0)-catalyzed cyclization provides the desired relative stereochemistry, corresponding to that of Tetrapetalone A (**1**), as the major diastereomer.

Table 5.2 Chemical Shift and Splitting Pattern Comparison



syn- **85**



trans- **85**

entry	*syn* isomer: chemical shift (d) of a-hydrogen (*splitting*)	*trans* isomer: chemical shift (d) of a-hydrogen (*splitting*)	*syn* isomer: chemical shift (d) of b-hydrogen (*splitting*)	*trans* isomer: chemical shift (d) of b-hydrogen (*splitting*)
1[a]	4.08 (d, *J* = 8.0 Hz)	3.51 (d, *J* = 3.0 Hz)	2.90 (quint, *J* = 7.5 Hz)	2.50 (dq, *J* = 7.5 Hz, 3.0 Hz)
2[b]	4.15 (d, *J* = 7.7 Hz)	3.57 (d, *J* = 3.1 Hz)	2.89 (quint, *J* = 7.4 Hz)	2.48 (dq, *J* = 7.5 Hz, 3.1 Hz)
3[c]		3.44 (d, *J* = 4.3 Hz)		2.45 (dq, *J* = 7.3 Hz, 4.3 Hz)

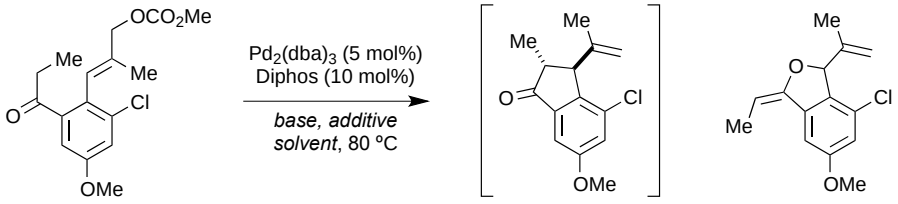
[a]Literature data.
[b]Compound **443**.
[c]Compound **427**.

5.5.2 Intramolecular Tsuji-Trost Allylic Alkylation – Ketone Substrate

Our initial investigations into a palladium(0)-catalyzed cyclization furnished the desired indanone in low yield; however, since the latter is the result of undesired silyl ether hydrolysis and not starting material decomposition we decided to probe an allylic alkylation as applied directly to ketone **441**. Hou and coworkers have demonstrated the intermolecular palladium(0)-catalyzed allylic alkylation of ketone enolates with monosubstituted allyl substrates to proceed with high regio-, diastereo-, and enantioselectivity.[114] Our initial investigation in the reaction of ketone **441** using lithium bis(trimethylsilyl)amide as base and lithium chloride as a stoichiometric additive in the presence of $Pd_2(dba)_3$ and Diphos failed to provide **443** instead we observed the formation of furan **444** in 78% yield (entry 1, Table 5.2). In an attempt to promote *C*-alkylation over *O*-alkylation by employing a less tight ion pair, sodium and potassium

bis(trimethylsilyl)amide (entries 2 and 3, Table 5.2) were employed as base in the reaction of ketone **441**, with both bases complete conversion to furan **444** was observed.

Table 5.3 Pd-Catalyzed Reaction of Ketone with Strong Base

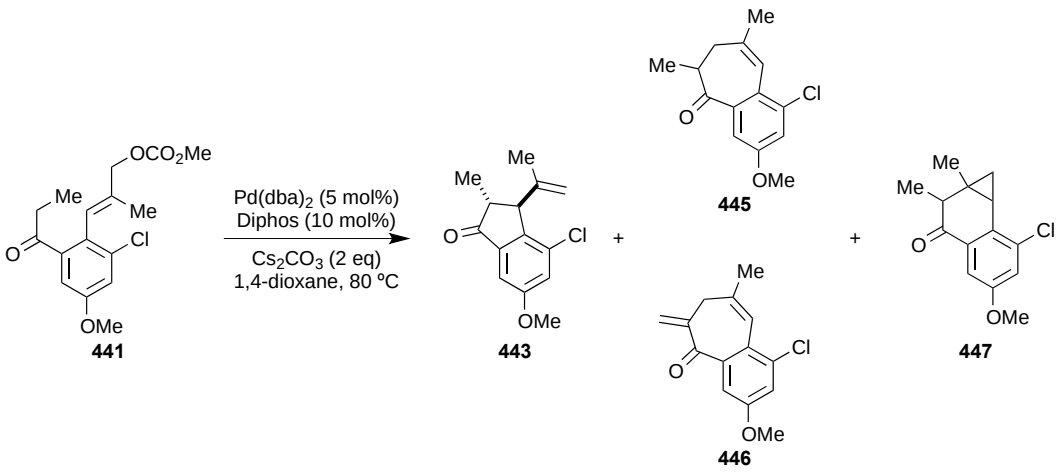


441 **443** **444**

entry	base	solvent	additive	product
1	LiHMDS	DME	LiCl (1 eq)	**446** (76%)[a]
2	NaHMDS	1,4-dioxane	-	**446**[b]
3	KHMDS	1,4-dioxane	-	**446**[b]

[a]Isolated yield.
[b]Complete conversion observed by ^{1}H NMR analysis of crude reaction.

Interestingly when a reversible base was employed in the reaction of ketone **441** we observed only products resulting from *C*-alkylation (Scheme 5.14). Exposure of ketone **441** to cesium carbonate in the presence of $Pd(dba)_2$ and Diphos afforded a complex mixture of products, that consisted of indanone **443,** ketone **445,** enone **446**, and tricycle **447**.

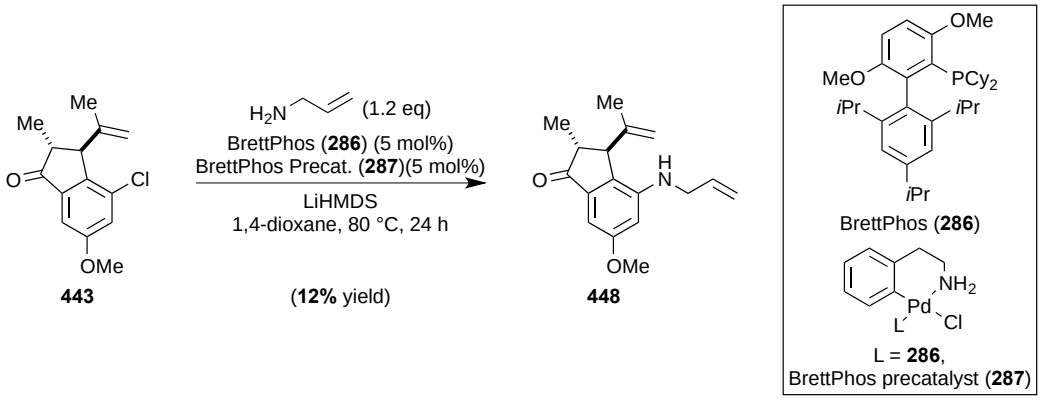


441 **443** **445** **446** **447**

Scheme 5.14 Pd-Catalyzed Reaction of Ketone with Reversible Base

5.6 Successful Aryl Amination with Indanone Coupling Partner

With indanone **443** on hand we were eager to investigate the feasibility of conducting a palladium-catalyzed aryl amination on such an elaborated aryl chloride **443**. To this end an initial exploration proved successful exposure of aryl chloride **443** to a palladium(0)-catalyst derived from BrettPhos (**286**) and BrettPhos precatalyst (**287**) furnished aryl amine **444** in 12% yield, the mass balance of the reaction appears to be indanone **427**. The successful coupling, albeit with much room for improvement, provides confidence that this synthetic route has promise.



Scheme 5.15 Pd-Catalyzed Aryl Amination

5.7 Conclusion

Although still in its infancy, forward progress following the fifth-generation retrosynthetic analysis (Scheme 5.1) has thus far proven to be the most successful. Critically important to decisions to pursue this route further is the direct and high yielding route leading to a highly functionalized cyclization precursor. Initial investigations into a palladium-catalyzed cyclization have proved fruitful, furnishing the desired indanone in low yield; however, since the latter is the result of undesired silyl ether hydrolysis and not starting material decomposition, there is much room for reaction development and optimization. With the advanced aryl chloride we were able to conduct an exploratory aryl amination and to our delight found that we could successfully couple with allyl amine. This provides great confidence that we will be able to

couple a functionalized primary amine with an indanone or indanol coupling partner. As the remainder of the material recovered did not posses the aryl chloride, this suggests that there is a path for reaction optimization.

5.8 Experimental Section

5.8.1 Materials and Methods

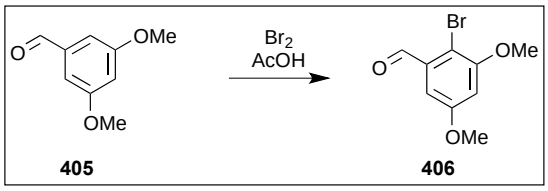
Unless stated otherwise, reactions were performed in flame-dried glassware under a nitrogen atmosphere. Triethylamine, diisopropylamine, and methanol were dried over anhydrous calcium hydride and freshly distilled. 1,4-Dioxane was distilled from sodium, calcium chloride and molecular sieve (0.4 nm). Benzene, tetrahydrofuran, dichloromethane, toluene, and diethyl ether were dried using a solvent purification system manufactured by Glass Contour Solvent Systems, SG Water U.S.A., LLC using technology based upon that originally described by Grubbs *et al*.[115] Anhydrous *N*,*N*-dimethyformamide, acetonitrile, dimethylsulfoxide, 1,2-dichloroethane was purchased from the Colorado State University Stockroom and supplied by Sigma-Aldrich or Fischer Scientific and stored under nitrogen atmosphere. Commercially available reagents were obtained from Sigma-Aldrich, Strem, TCI, Combi-Blocks, Acros or Alfa-Aesar and were used as received. All known compounds were identified by comparison of NMR spectra to reported in the literature.

Unless otherwise stated, all reactions were monitored by thin layer chromatography (TLC) was using Silicycle glass-backed extra hard layer, 60 Å plates (indicator F-254, 250 μm). Developed TLC plates were visualized using a 254 nm UV lamp and/or with the appropriate stain followed by heating. Typical stains utilized were potassium permanganate, ethanolic anisaldehyde and ceric ammonium molybdate. In general, the flash chromatography guidelines reported by Still *et al*[116] were followed. Silicycle SiliaFlash® P60 (230-400 mesh) silica gel as the stationary phase. When reactions were absorbed onto silica gel, the amount of silica gel used was equal to two times the weight of the reagents.

Infrared spectra were obtained using a Nicolet Avatar 320 FTIR or Bruker Tensor27 FTIR. Samples were analyzed as thin films on NaCl plates (samples was dissolved in CH_2Cl_2 or $CHCl_3$) or potassium bromide pellets, as indicated. IR spectra are presented as transmittance vs. wavenumber (cm^{-1}). Proton (^1H) and carbon (^{13}C) NMR spectra were recorded on a Varian Inova 500, Varian Inova 400, Varian Inova 400 auto sampler, or Varian Inova 300 MHz spectrometer. Spectra were obtained at 22 °C in $CDCl_3$ unless otherwise noted. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to the internal solvent peak. Coupling constants (J) are reported in Hertz (Hz) and are rounded to the nearest 0.1 Hz. Multiplicities are defined as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, br = broad, app = apparent, par = partial. High-resolution mass spectra were obtained from the University of Colorado Central Instrument Facility, performed on an Agilent 6210 TOF LCMS by Donald L. Dick.

5.8.2 Preparative Procedures

Preparation of aryl bromide 406:

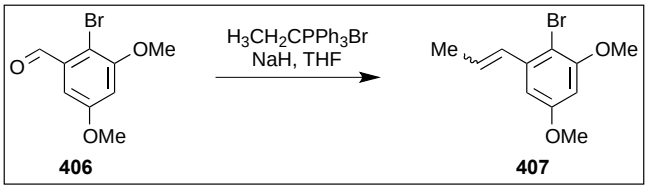


Aryl bromide 406. Following the procedure of Scheidt *et al.*[117] 2,3-Dimethoxybenzaldehyde (**405**) (100 mg, 0.60 mmol) was added to a vial fitted with a magnetic stir bar and dissolved in acetic acid (0.5 mL). The resulting colorless solution was cooled to 0 ºC. A solution of bromine (32 μL, 0.63 mmol) in acetic acid (0.5 mL) was added dropwise at 0 ºC. Once the addition was complete the ice bath was removed. After approximately 5 minutes the

reaction had solidified and water (2 mL) was added. The solid was collected by vacuum filtration and rinsed with water. The solid was then dissolved in dichloromethane (5 mL) and washed with saturated $NaHCO_3$ (5 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (2 x 5 mL). Combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield a white solid composed of both mono- and dibrominated aldehydes. A small amount of ethyl acetate was added to the solid. After standing at 5 ºC, a white solid (the dibrominated aldehyde) had precipitated. The solid was separated from the liquid by vacuum filtration and the filtrate was concentrated to yield the monobrominated aldehyde **406** (50 mg, 32% yield) as white solid.

Aryl bromide 406. FTIR (thin film/NaCl): 3008, 2970, 2941, 1678, 1590, 1450, 1430, 1391, 1290, 1222, 1199, 1182, 1160, 1075, 1021; ^{1}H-NMR (400 MHz; $CDCl_3$): δ 10.42 (s, 1H), 7.05 (d, *J* = 2.8 Hz, 1H), 6.72 (d, *J* = 2.8 Hz, 1H), 3.92 (s, 3H), 3.85 (s, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ 192.1, 160.0, 157.2, 134.8, 109.2, 105.9, 103.5, 56.7, 55.9. Spectral data matched the reported.[117,118]

Preparation of alkene 407:

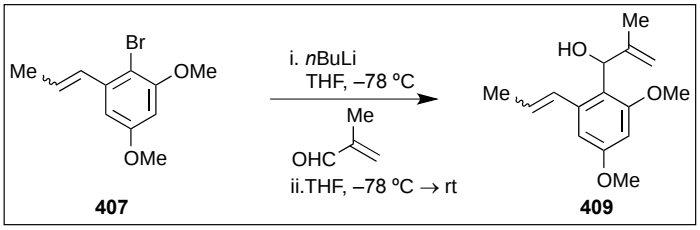


Alkene 407. Following the procedure of Merlic *et al*.[118] To an oven dried vial fitted with a magnetic stir bar was added sodium hydride (60% in mineral oil, 10 mg, 0.24 mmol) and tetrahydrofuran (1 mL), followed by the addition of ethyl triphenylphosphonium bromide (92 mg, 0.25 mmol) at room temperature. Solution was stirred for 15 minutes and aldehyde **406** (47 mg, 0.19 mmol) as a solution in tetrahydrofuran (2 mL) was added at room temperature. TLC

was used to monitor reaction progress. TLC plates were developed with 10% EtOAc/Hex and visualized by UV lamp and $KMnO_4$ stain. Reaction was complete after 5 hours. Quenched reaction with saturated NH_4Cl solution (2 mL) and diluted with ethyl acetate (2 mL). Phases were separated. Organic phase was washed with H_2O (3 mL), brine (3 mL), dried over anhydrous Na_2SO_4 and absorbed directly onto silica gel (150 mg) under reduced pressure. Purified with silica gel chromatography (25:1 silica/crude material, gradient elution 2→5% EtOAc/Hex) to afford alkene **407** (34.3 mg, 70% yield, 1:1 Z/E) as colorless oil.

Alkene 407. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 6.79 (dd, *J* = 15.6, 1.7 Hz, 1H), 6.64 (d, *J* = 2.7 Hz, 1H), 6.47 (td, *J* = 5.7, 2.2 Hz, 2H), 6.41 (d, *J* = 2.7 Hz, 1H), 6.38 (d, *J* = 2.7 Hz, 1H), 6.18 (dq, *J* = 15.6, 6.7 Hz, 1H), 5.87 (dq, *J* = 11.5, 7.0 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 1.93 (dd, *J* = 6.7, 1.7 Hz, 3H), 1.78 (dd, *J* = 7.1, 1.8 Hz, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ 159.6, 159.2, 156.9, 139.5, 139.3, 130.5, 130.0, 129.2, 128.2, 107.3, 104.5, 104.1, 103.1, 98.6, 98.3, 56.5, 55.70, 55.66, 18.8, 14.6.

Preparation of alcohol 409:

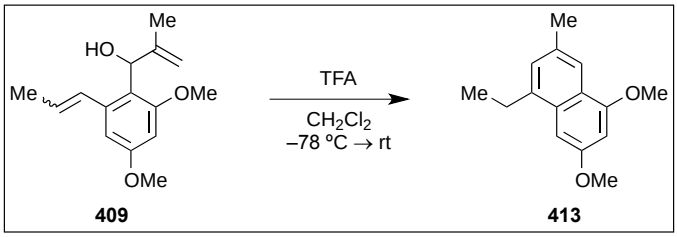


Alcohol 409. Following the procedure of Snyder *et al*.[93] To an oven dried vial fitted with a magnetic stir bar was added aryl bromide **407** (34 mg, 0.13 mmol) and tetrahydrofuran (2 mL), solution was cooled to –78 ºC and *n*-butyllithium (2.1 M in THF, 70 μL, 0.14 mmol) was added dropwise resulting in a yellow reaction solution; reaction was stirred for 20 minutes at –78 ºC. Methacrolein (21 μL, 0.26) as a tetrahydrofuran (1 mL) solution was added dropwise at –78 ºC and reaction was stirred for 40 minutes and warmed slowly to room temperature and stirred over

night. TLC was used to monitor reaction progress. TLC plates were developed with 10% EtOAc/Hex and visualized by UV lamp and $KMnO_4$ stain. Quenched with saturated NH_4Cl solution (3 mL) at room temperature. Phases were separated. Organic phase was washed with H_2O (3 mL) and brine (3 mL), dried over anhydrous Na_2SO_4 and absorbed directly silica gel (100 mg). Purified with silica gel chromatography (25:1 silica/crude material, gradient elution 2→5→10→15→20% EtOAc/Hex) to afford alcohol **409** (12.2 mg, 38% yield) as colorless oil.

Alcohol 409 (1:1 Z/E). ^{1}H-NMR (400 MHz; $CDCl_3$): δ 6.68 (dd, *J* = 15.5, 1.3 Hz, 1H), 6.52 (d, *J* = 2.4 Hz, 1H), 6.50 (d, *J* = 12.0 Hz, 1H), 6.41 (d, *J* = 2.3 Hz, 1H), 6.39 (d, *J* = 2.3 Hz, 1H), 6.32 (d, *J* = 2.2 Hz, 1H), 6.01 (dq, *J* = 15.4, 6.6 Hz, 1H), 5.83 (dq, *J* = 11.4, 6.9 Hz, 1H), 5.39 (d, *J* = 10.1 Hz, 1H), 5.24 (d, *J* = 11.1 Hz, 1H), 4.86 (d, *J* = 0.3 Hz, 2H), 4.83 (d, *J* = 0.8 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.67 (d, *J* = 11.1 Hz, 1H), 3.54 (d, *J* = 10.2 Hz, 1H), 1.86 (dd, *J* = 6.6, 1.6 Hz, 3H), 1.70 (s, 6H), 1.69-1.67 (m, 3H).

Preparation of naphthalene 413:



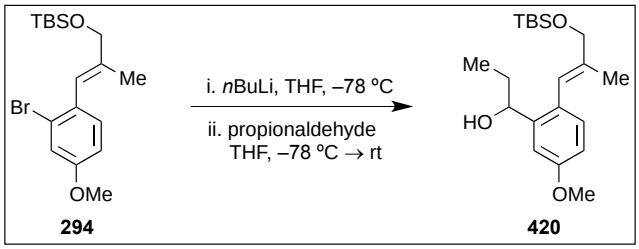
409 **413**

Naphthalene 413. To an oven dried vial fitted with a magnetic stir bar was added alcohol **409** (12 mg, 0.04 mmol) and dichloromethane (3 mL), solution was cooled to –78 ºC and trifluoroacetic acid was added as a single portion. Reaction solution was slowly warmed to room temperature. TLC was used to monitor reaction progress. TLC plates were developed with 10% EtOAc/Hex and visualized by UV lamp and $KMnO_4$ stain. After 1 hour at room temperature the reaction was quenched with potassium carbonate (small scoop), methanol (3 mL) and stirred at room temperature. Reaction solution was concentrated under reduced pressure; residue was

dissolved in ethyl acetate (5 mL). Organic phase was washed with H_2O (2 mL), brine (2 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (eluent 15% EtOAc/Hex) to afford naphthalene **413** (1.2 mg, 13% yield).

Naphthalene 413. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.83 (s, 1H), 7.17 (s, 1H), 6.85 (d, *J* = 2.0 Hz, 1H), 6.50 (d, *J* = 2.1 Hz, 1H), 3.96 (s, 3H), 3.92 (s, 3H), 3.00 (q, *J* = 7.5 Hz, 2H), 2.46 (s, 3H), 1.37 (t, *J* = 7.5 Hz, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ 157.5, 156.8, 138.6, 132.2, 131.5, 128.4, 122.2, 119.3, 97.3, 94.6, 55.7, 55.4, 26.5, 21.8, 14.8; HRMS (EI) *m/z* 231.1377 [calc'd for $C_{15}H_{18}O_2$ (M+H)+ 231.138].

Preparation of alcohol 420:

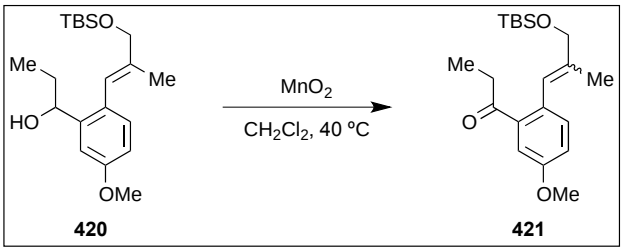


Alcohol 420. To an oven-dried round bottom flask was added aryl bromide **294** (500 mg, 1.34 mmol) and tetrahydrofuran (10 mL), solution was cooled to –78 ºC and *n*-butyllithium (1.6 M in hexanes, 0.92 mL, 1.47 mmol) was added over 10 minutes via syringe pump. Stirred 1 hour at –78 ºC. Propionaldehyde (0.2 mL, 2.68 mmol) as a solution in tetrahydrofuran (2 mL) was added in one portion, stirred at –78 ºC for 1 hour and warmed to room temperature. TLC was used to monitor reaction progress. TLC plates were developed with 10% EtOAc/Hex and visualized by UV lamp and $KMnO_4$ stain. Quenched reaction with saturated NH_4Cl solution (20 mL). Phases were separated. Organic phase was washed with H_2O (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4 and absorbed directly onto to silica gel (500 mg) under reduced

pressure. Purified with silica gel chromatography (gradient elution 10→50 EtOAc/Hex) to afford alcohol **420** (300 mg, 64% yield) as colorless oil.

Alcohol 420. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.07 (d, *J* = 3.3 Hz, 1H), 7.06 (d, *J* = 9.5 Hz, 1H), 6.78 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.52 (s, 1H), 4.79 (td, *J* = 6.3, 2.5 Hz, 1H), 4.18 (s, 2H), 3.83 (s, 3H), 1.76 (s, 1H), 1.69 (dt, *J* = 14.4, 7.3 Hz, 2H), 1.64 (s, 3H), 0.95 (s, 9H), 0.89 (t, *J* = 8.0 Hz, 3H), 0.12 (s, 6H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 158.8, 144.7, 138.1, 131.0, 128.1, 121.2, 112.5, 110.5, 72.5, 68.0, 55.4, 31.2, 27.1, 26.1, 18.6, 15.0, 10.4, -3.1, -5.1; HRMS (EI) *m/z* 373.2171 [calc'd for $C_{20}H_{34}O_3Si$ (M+Na)+ 373.2169].

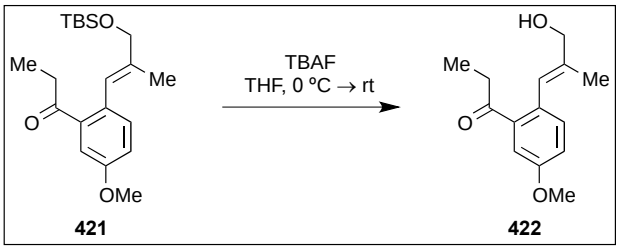
Preparation of ketone 421:



Ketone 421. To a round bottom flask fitted with a magnetic stir bar was added alcohol **420** (280 mg, 0.80 mmol), dichloromethane (16 mL) and manganese dioxide (1.1 g, 12.00 mmol). Round bottom flask was fitted with a condenser and reaction was refluxed (40 ºC). TLC was used to monitor reaction progress. TLC plates were developed with 10% EtOAc/Hex and visualized by UV lamp and $KMnO_4$ stain. After 24 hours starting material remained by TLC but reaction worked up. Cooled reaction solution to room temperature and filtered through a sand/celite pad. Filtrate was absorbed directly on to silica gel (300 mg) under reduced pressure. Purified with silica gel chromatography (50:1 silica/crude material, gradient elution 5→10% EtOAc/Hex) to afford ketone **421** (81 mg, 30% yield) as colorless oil.

Ketone 421. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.16 (d, *J* = 8.5 Hz, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 6.96 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.62 (s, 1H), 4.17 (s, 2H), 3.83 (s, 3H), 2.81 (q, *J* = 7.3 Hz, 2H), 1.63 (s, 3H), 1.12 (t, *J* = 7.3 Hz, 3H), 0.93 (s, 9H), 0.11 (s, 6H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ 206.3, 192.1, 158.2, 140.9, 138.2, 131.9, 131.1, 129.0, 122.5, 116.4, 112.7, 68.2, 55.6, 35.9, 31.1, 27.1, 26.1, 18.5, 15.0, 8.6, -2.4, -5.2; HRMS (EI) *m/z* 371.2013 [calc'd for $C_{20}H_{32}O_3Si$ (M+Na)+ 371.2013].

Preparation of allylic alcohol 422:



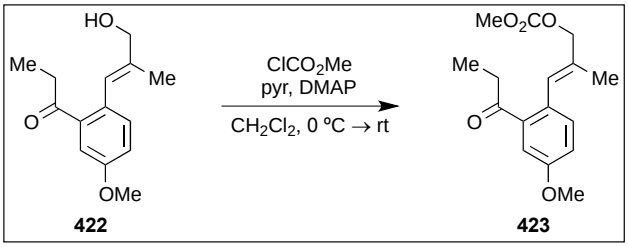
421 **422**

Allylic Alcohol 422. To a vial was added TBS-ether **421** (81 mg, 0.23 mmol), tetrahydrofuran (2 mL); solution was cooled to 0 ºC and tetrabutylammonium fluoride was added (1 M in THF, 0.35 mL, 0.35 mmol). Stirred at 0 ºC for 10 minutes and warmed to room temperature. TLC was used to monitor reaction progress. TLC plates were developed with 50% EtOAc/Hex and visualized by UV lamp and $KMnO_4$ stain. After 3 hours reaction was complete. Quenched with saturated NH_4Cl solution (2 mL) and separated phases. Organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (gradient elution 25→50% EtOAc/Hex) to afford alcohol **422** (28 mg, 52% yield) as yellow oil.

Allylic Alcohol 422. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.18 (d, *J* = 8.5 Hz, 1H), 7.13 (d, *J* = 2.6 Hz, 1H), 6.98 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.65 (s, 1H), 4.19 (d, *J* = 5.5 Hz, 2H), 3.84 (s, 3H), 2.85 (q, *J* = 7.3 Hz, 2H), 1.70 (s, 3H), 1.60 (d, *J* = 5.9 Hz, 1H), 1.15 (t, *J* = 7.3 Hz, 3H);

^{13}C-NMR (101 MHz; $CDCl_3$): δ 205.4, 158.3, 140.0, 137.6, 132.1, 129.0, 124.3, 116.4, 113.6, 68.7, 55.6, 35.3, 15.2, 8.6.

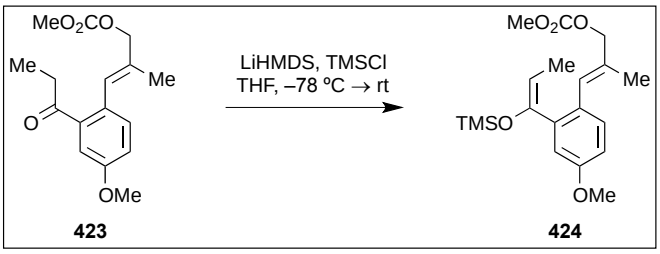
Preparation of allylic carbonate 423:



Allylic carbonate 423. To a stirred solution of allylic alcohol **422** (23 mg, 0.10 mmol), pyridine (16 μL, 0.20 mmol) and 4-(dimethylamino)pyridine (cat., flake) in dichloromethane (2 mL) at 0 ºC was added methyl chloroformate (12 μL, 0.15 mmol). Reaction solution was warmed to room temperature. TLC was used to monitor reaction progress. TLC plates were developed with 25% EtOAc/Hex and visualized by UV lamp and $KMnO_4$ stain. Quenched with saturated $NaHCO_3$ solution (2 mL) and phases were separated. Organic phase was washed with H_2O (2 mL), brine (2 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Crude material was purified with silica gel chromatography (eluent 25% EtOAc/Hex) to afford allylic carbonate **423** (23 mg, 17% yield) as colorless oil.

Allylic carbonate 423. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.17 (d, *J* = 8.5 Hz, 1H), 7.13 (d, *J* = 2.7 Hz, 1H), 6.98 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.70 (s, 1H), 4.70 (d, *J* = 1.0 Hz, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 2.83 (q, *J* = 7.3 Hz, 2H), 1.72 (d, *J* = 1.4 Hz, 3H), 1.14 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 205.0, 191.2, 158.4, 155.7, 139.9, 132.1, 131.8, 128.0, 116.2, 113.4, 73.2, 55.4, 54.8, 35.2, 15.2, 8.3.

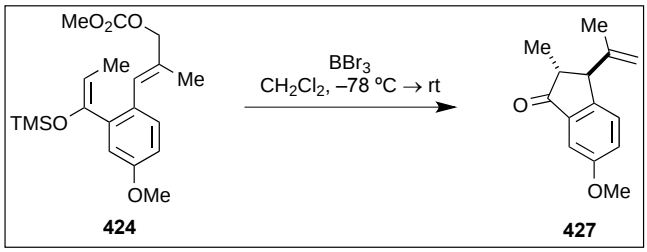
Preparation of silyl enol ether 424:



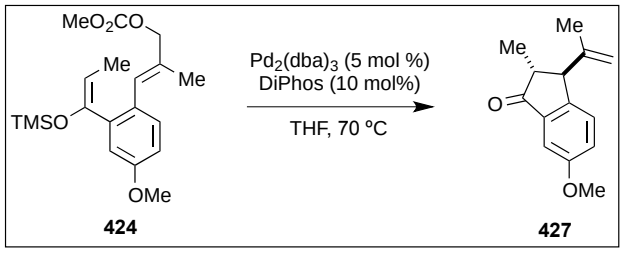
Silyl enol ether 424. To a solution of lithium bis(trimethylsilyl)amide (32 mg, 0.19 mmol) and trimethylsilyl chloride (27 μL, 0.21 mmol) in tetrahydrofuran (1 mL) at –78 ºC was added ketone **423** (50 mg, 0.17 mmol) as a solution in tetrahydrofuran (1 mL) and warmed to room temperature. TLC was used to monitor reaction progress. TLC plates were developed with 25% EtOAc/Hex and visualized by UV lamp and $KMnO_4$. Reaction solution was diluted with ethyl acetate (2 mL) and the washed with saturated $NaHCO_3$ solution (4 mL). Organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford silyl enol ether **424** (61 mg, 98% yield). No further purification necessary but silyl enol ether **424** is stable to silica gel chromatography.

Silyl enol ether 424. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.16 (d, *J* = 8.5 Hz, 1H), 6.93 (d, *J* = 2.8 Hz, 1H), 6.78 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.55 (s, 1H), 4.91 (q, *J* = 6.8 Hz, 1H), 4.70 (d, *J* = 0.9 Hz, 2H), 3.81 (s, 3H), 3.81 (s, 3H), 1.86 (d, *J* = 1.4 Hz, 3H), 1.70 (d, *J* = 6.8 Hz, 3H), 0.02 (s, 9H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 190.9, 157.9, 155.5, 148.0, 140.4, 130.6, 129.2, 128.8, 126.4, 112.9, 112.4, 109.8, 98.2, 77.0, 76.7, 76.3, 73.8, 54.9, 54.4, 15.1, 11.0, -0.0.

Preparation of indanone 427:



Indanone 427. *Lewis acid mediated cyclization*: To an oven dried vial fitted with a magnetic stir bar was added silyl enol ether **424** (3.6 mg, 0.01 mmol) and dichloromethane (1 mL), solution was cooled to –78 ºC. Boron tribromide (10 μL, 0.10 mmol) was added at –78 ºC, reaction solution turned bright orange. TLC was used to monitor reaction progress. TLC plates were developed with 10% EtOAc/Hex and visualized by UV lamp and $KMnO_4$. After 30 minutes reaction was quenched with saturated NH_4Cl solution (1 mL) at –78 ºC and allowed to warm to room temperature. Phases were separated. Organic phase was washed with brine (1 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Crude material was purified with silica gel chromatograph (gradient elution 10→50% EtOAc/Hex) to afford indanone **427** (1.3 mg 59% yield, >20:1 dr).

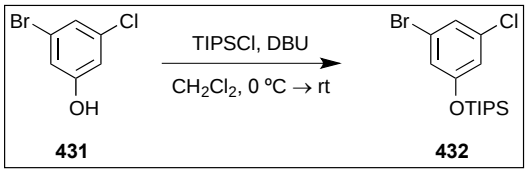


Palladium(0)-catalyzed cyclization: To an oven dried vial fitted with a magnetic stir bar was added tris(dibenzylideneacetone)dipalladium(0) (3 mg, 0.005 mmol) and ethylenebis(diphenylphosphine) (4 mg, 0.009 mmol) and silyl enol ether **424** (32 mg, 0.09 mmol) as a solution in tetrahydrofuran (2 mL), vial was sealed and reaction was heated to 70 ºC.

After two days reaction was cooled to room temperature and purified with silica gel chromatography (gradient elution 10→50% EtOAc/Hex) to afford indanone **427** (15 mg 80% yield; >20:1 dr).

Indanone 427. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.22-7.20 (m, 1H), 7.14 (d, *J* = 2.5 Hz, 1H), 7.12 (d, *J* = 2.7 Hz, 1H), 4.89 (d, *J* = 0.7 Hz, 1H), 4.87 (quintet, *J* = 1.6 Hz, 1H), 3.78 (s, 3H), 3.44 (d, *J* = 4.3 Hz, 1H), 2.45 (qd, *J* = 7.3, 4.3 Hz, 1H), 1.50 (t, *J* = 1.0 Hz, 3H), 1.25 (d, *J* = 7.4 Hz, 3H); HRMS (EI) *m/z* 217.1221 [calc'd for $C_{14}H_{16}O_2$ (M+H)+ 217.1223].

Preparation of TIPS-ether 432:

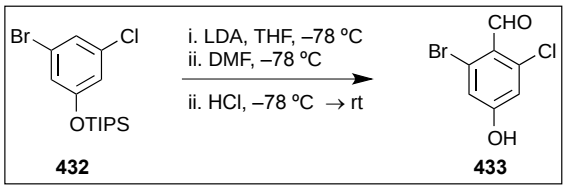


TIPS-ether 432. To a flame dried round bottom flask fitted with a magnetic stir bar was added 3-bromo-5-chlorophenol (**431**) (25 g, 120.5 mmol) and dichloromethane (120 mL) the resulting solution was cooled to 0 ºC with an ice bath. To the stirred solution was added 1,8-diazabicyclo[5.4.0]undec-7-ene (22 mL, 144.6 mmol) and triisopropylsilyl chloride (27 mL, 126.2 mmol) at 0 ºC. Reaction was stirred at 0 ºC for 20 minutes and then warmed to room temperature. TLC was used to monitor reaction progress. TLC plates were developed with 10% EtOAc/Hex and visualized by UV lamp and $KMnO_4$. Reaction solution was diluted with dichloromethane (120 mL) and hydrolyzed with H_2O (250 mL). Phases were separated and the organic phase was washed with brine (250 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude oil was purified with silica gel chromatography (20:1 silica/crude material, eluent 100% Hexanes) to afford TIPS-ether **432** (39.7 g, 91% yield) as colorless oil.

TIPS-ether 432. FTIR (thin film/NaCl): 2946, 2868, 1582, 1559, 1463, 1434, 1385, 1273, 1092, 993, 968, 882, 837, 777, 749, 685, 670; ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.10 (t, *J* =

1.7 Hz, 1H), 6.93 (t, *J* = 1.9 Hz, 1H), 6.80 (t, *J* = 2.0 Hz, 1H), 1.29-1.20 (m, 3H), 1.10 (d, *J* = 7.2 Hz, 18H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ 157.5, 135.3, 124.3, 122.7, 121.9, 119.4, 18.0, 12.7; HRMS (EI) *m/z* 382.0785 [calc'd for $C_{15}H_{24}BrClOSi$ $(M+NH_4)+$ 362.0468].

Preparation of aldehyde 433:



432 **433**

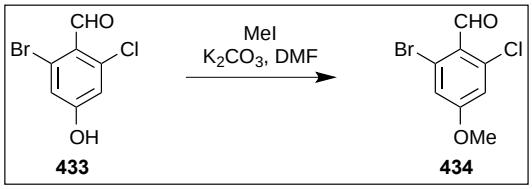
Aldehyde 433. Following the procedure of Serwatoski *et al*.[111,112] *Preparation of lithium diisopropylamide (LDA) solution* (0.5 M in THF): To a flame dried round bottom flask fitted with a magnetic stir bar was added tetrahydrofuran (200 mL) and diisopropylamine (23 mL, 163.7 mmol) solution was cooled to –78 ºC and *n*-butyllithium (1.6 M in THF, 102 mL, 163.7 mmol) was added. Stirred for 30 minutes at –78 ºC prior to use.

To a stirred solution of TIPS-ether **432** (39.7 g, 109.1 mmol) in tetrahydrofuran (220 mL) was added LDA solution (0.5 M in THF, 325 mL), moderate pace via cannula, at –78 ºC. Upon complete addition the reaction solution was stirred 45 minutes at –78 ºC. *N*,*N*-Dimethylformamide (17 mL) was added at –78 ºC and stirred for 45 minutes. TLC was used to monitor reaction progress. TLC plates were developed with 10% EtOAc/Hex and visualized by UV lamp and $KMnO_4$. Quenched with 1 M HCl (550 mL) at –78 ºC followed by warming to room temperature. TLC was used to monitor hydrolysis of the TIPS-ether. TLC plates were developed with 10% EtOAc/Hex and visualized by UV lamp and $KMnO_4$. Upon warming to room temperature the solution was further acidified to pH = 1 with 6 M HCl. Phases were separated. Aqueous phase was extracted with diethyl ether (3 x 250 mL). Combined organic phase was washed with saturated $NaHCO_3$ (500 mL), H_2O (500 mL), brine (500 mL). Organic

phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford a crude solid. Crude material was purified with silica gel chromatography (5→10→15→20→25% EtOAc/Hex) to afford aldehyde **433** (24.1 g, 94% yield) as a pink solid.

Aldehyde 433. FTIR (KBr pellet): 3234, 1667, 1552, 1439, 1410, 1245, 1057, 948, 862, 809, 759, 641, 504; ^{1}H-NMR (400 MHz; DMSO-d_6): δ 11.43 (br s, 1H), 10.14 (s, 1H), 7.13 (d, *J* = 2.3 Hz, 1H), 6.97 (d, *J* = 2.3 Hz, 1H); 13-C NMR (101 MHz; DMSO-d_6): δ 188.6, 162.2, 137.6, 126.5, 121.7, 120.4, 117.6; HRMS (EI) *m/z* 234.8988 [calc'd for $C_7H_4BrClO_2$ (M-H)- 233.9083].

Preparation of methyl ether 434:

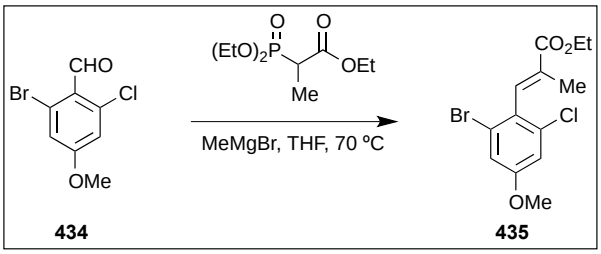


433 **434**

Methyl ether 434. To a stirred solution of phenol **433** (24.1 g, 102.35 mmol) in *N*,*N*-dimethylformamide (DMF) (100 mL) was added potassium carbonate (28.3 g, 204.7 mmol) and iodomethane (7.6 mL, 122.82 mmol) at room temperature. TLC was used to monitor reaction progress. TLC plates were developed with 20% EtOAc/Hex and visualized by UV lamp and $KMnO_4$. Reaction was complete after 14 hours. Reaction was diluted with diethyl ether (200 mL) and H_2O (200 mL) followed by separating phases. Aqueous phase was extracted with diethyl ether (3 x 200 mL). Combined organic phase was washed with H_2O (3 x 200 mL) and brine (200 mL). During workup ethyl acetate was added sparingly to help product dissolve. Organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was triturated with hexanes, solid with hexanes until filtrate was colorless, to afford methyl ether **434** (14.7 g, 58 % yield) as light pink needle solid.

Methyl ether 434. FTIR (thin film/NaCl): 1769, 1696, 1591, 1539, 1468, 1431, 1395, 1296, 1254, 1169, 1179, 1055, 1030, 908, 868, 845, 809; ^{1}H-NMR (400 MHz; $CDCl_3$): δ 10.31 (s, 1H), 7.13 (d, *J* = 2.5 Hz, 1H), 6.95 (d, *J* = 2.4 Hz, 1H), 3.87 (s, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ 189.1, 162.9, 139.1, 127.2, 123.9, 119.3, 116.5, 56.3; HRMS (EI) *m/z* 250.929 [calc'd for $C_8H_6BrClO_2$ (M+H)+ 247.924].

Preparation of γ,δ-unsaturated ester 435:



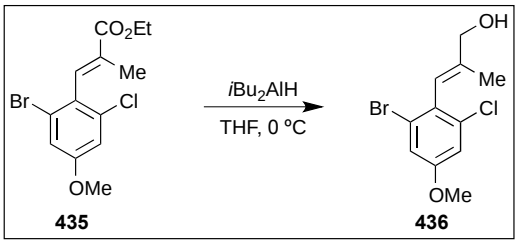
434 **435**

γ,δ-Unsaturated ester 435. Following the procedure of Davies *et al*.[119] To a flame dried round bottom flask equipped with a reflux condenser and a magnetic stir bar was added tetrahydrofuran (15 mL), triethyl-2-phosphonopropionate (0.83 mL, 3.85 mmol) and methylmagnesium bromide solution (3.0 M in Et_2O, 1.3 mL, 3.85 mmol). Addition of methylmagnesium bromide is exothermic. Deprotonation was stirred for 15 minutes at room temperature. Aldehyde **434** (800 mg, 3.21 mmol) as a solution in tetrahydrofuran (15 mL) was added to the ylide solution at room temperature. Reaction was transferred to a preheated oil bath (75 ºC) and refluxed for 24 hours. TLC was used to monitor reaction progress. TLC plates were developed with 10% EtOAc/Hex and visualized by UV lamp and $KMnO_4$. Reaction solution was cooled to room temperature and quenched with saturated NH_4Cl solution (50 mL) followed by diluting with ethyl acetate (30 mL). Phases were separated. Aqueous phase was extracted with ethyl acetate (1 x 50 mL). Combined organic phase was washed with H_2O (60 mL) and brine (60 mL). Organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure.

Crude material was absorbed directly onto silica gel (1 g) and purified with silica gel chromatography (20:1 silica/crude material; gradient elution 5→10% EtOAc/Hex) to afford γ,δ-unsaturated ester **435** (1.0 g, 93% yield) as yellow oil.

γ,δ-Unsaturated ester 435. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.39 (d, *J* = 1.4 Hz, 1H), 7.10 (d, *J* = 2.5 Hz, 1H), 6.95 (d, *J* = 2.5 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 1.76 (d, *J* = 1.4 Hz, 3H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ 167.6, 159.7, 135.6, 134.5, 133.3, 128.0, 124.2, 117.3, 114.8, 61.1, 55.9, 14.62, 14.43.

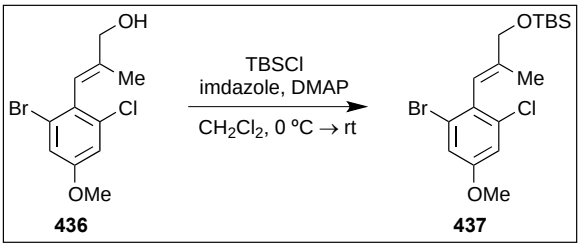
Preparation of allylic alcohol 436:



Allylic alcohol 436. To a flame dried round bottom flask equipped with a magnetic stir bar was added γ,δ-unsaturated ester **435** (1.7 g, 5.10 mmol) and tetrahydrofuran (45 mL). The resulting solution was cooled to 0 ºC and diisobutylaluminum hydride (1 M in hexanes, 10.4 mL, 10.80 mmol) was added. TLC was used to monitor reaction progress. TLC plates were developed with 10% EtOAc/Hex and visualized by UV lamp and $KMnO_4$. Quenched with saturated Rochelle salt solution (30 mL) at 0 ºC and warmed to room temperature, stirred over night. Phases were separated. Organic phase was washed with H_2O (25 mL) and brine (25 mL). Organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was absorbed onto silica gel (2 g) under reduced pressure and purified with silica gel chromatography (50:1 silica/crude material, gradient elution 10→20→30% EtOAc/Hex) to afford allylic alcohol **436** (1.6 g, quantitative) as colorless oil.

Allylic alcohol 436. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.08 (d, *J* = 2.5 Hz, 1H), 6.93 (d, *J* = 2.5 Hz, 1H), 6.23 (d, *J* = 1.3 Hz, 1H), 4.23 (d, *J* = 5.5 Hz, 2H), 3.78 (s, 3H), 1.75 (t, *J* = 6.2 Hz, 1H), 1.56 (d, *J* = 1.0 Hz, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ 159.0, 141.7, 135.1, 129.2, 125.2, 121.5, 117.1, 114.6, 67.6, 55.9, 15.4.

Preparation of TBS-ether 437:

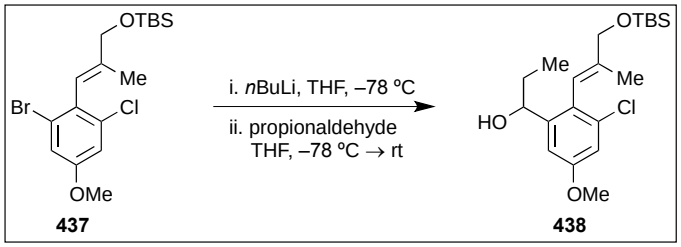


TBS-ether 437. To a flame dried round bottom flask equipped with a magnetic stir bar was added allylic alcohol **436** (1.5 g, 5.20 mmol), dichloromethane (10 mL), 4-(dimethylamino)pyridine (62 mg, 0.51 mmol) and imidazole (690 mg, 10.20 mmol). The resulting solution was cooled to 0 ºC with an ice bath and *tert*-butyldimethylsilyl chloride (850 mg, 5.61 mmol) was added. Reaction was stirred for 30 minutes at 0 ºC after which the ice bath was removed and the reaction was warmed to room temperature. TLC was used to monitor reaction progress. TLC plates were developed with 5% EtOAc/Hex and visualized by UV lamp and $KMnO_4$. Quenched with saturated NH_4Cl solution (10 mL). Phases were separated. Organic phase was washed with H_2O (10 mL) and brine (10 mL). Organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was absorbed directly onto silica gel (2 g) under reduced pressure and purified with silica gel chromatography (25:1 silica/crude material, gradient elution 2→5→10% EtOAc/Hex) to afford TBS-ether **437** (2.0 g, 95% yield) as colorless oil.

TBS-ether 437. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.08 (d, *J* = 2.6 Hz, 1H), 6.93 (d, *J* = 2.5 Hz, 1H), 6.23 (d, *J* = 1.4 Hz, 1H), 4.22 (d, *J* = 1.1 Hz, 2H), 3.79 (s, 3H), 1.49 (d, *J* = 1.1 Hz, 3H),

0.95 (s, 9H), 0.13 (s, 6H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ 158.8, 141.3, 135.2, 129.9, 125.4, 120.2, 117.0, 114.6, 67.2, 55.9, 26.1, 18.6, 15.2, -5.1.

Preparation of alcohol 438:

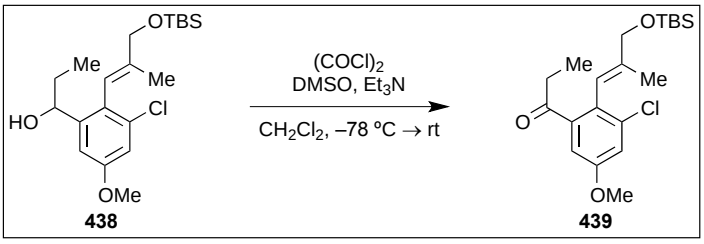


Alcohol 438. To a flame dried round bottom flask equipped with a magnetic stir bar was added aryl bromide **437** (250 mg, 0.62 mmol, and tetrahydrofuran (12 mL). The resulting solution was cooled to –78 ºC. *n*-Butyllithium (1.6 M in THF, 0.47 mL, 0.74 mmol) was added at a moderate rate at –78 ºC. Reaction was stirred for 30 minutes at –78 ºC. Propionaldehyde (90 μL, 1.24 mmol) as a solution in tetrahydrofuran (2 mL) was added in one portion at –78 ºC. Reaction was stirred for 1 hour at –78 ºC. TLC was used to monitor reaction progress. TLC plates were developed with 10% EtOAc/Hex and visualized by UV lamp and $KMnO_4$. Quenched with saturated NH_4Cl solution (3 mL) and warmed to room temperature. Phases were separated. Organic phase was washed with H_2O (6 mL) and brine (6 mL). Organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was absorbed onto silica gel (500 mg) and purified with silica gel chromatography (20:1 silica/crude material, gradient elution 2→10% EtOAc/Hex) to afford alcohol **438** (200 mg, 84% yield) as colorless oil.

Alcohol 438. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.00 (d, *J* = 2.6 Hz, 1H), 6.88 (d, *J* = 2.6 Hz, 1H), 6.25 (s, 1H), 4.72 (td, *J* = 6.2, 3.6 Hz, 1H), 4.20 (s, 2H), 3.81 (s, 3H), 1.78 (d, *J* = 0.6 Hz, 1H), 1.64 (t, *J* = 5.7 Hz, 2H), 1.45 (s, 3H), 0.94 (s, 9H), 0.91 (t, *J* = 7.4 Hz, 3H), 0.12 (s, 6H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ 159.1, 134.5, 126.8, 118.3, 113.6, 109.9, 104.8, 98.7, 72.8,

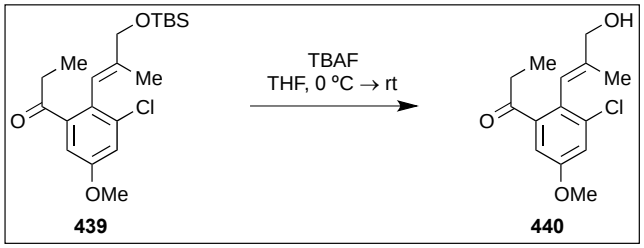
67.3, 55.6, 26.1, 18.6, 15.1, 10.3, -5.1; HRMS (EI) *m/z* 385.1969 [calc'd for $C_{20}H_{33}ClO_3Si$ (M+H)+ 385.196].

Preparation of ketone 439:



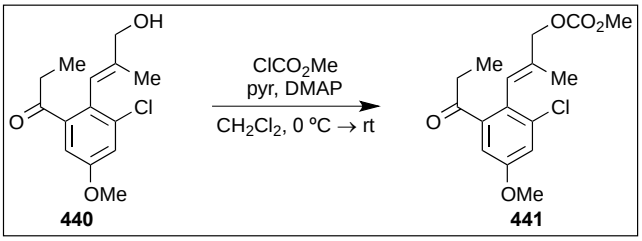
Ketone 439. To a flame dried round bottom flask equipped with a magnetic stir bar was added dichloromethane (25 mL) and dimethylsulfoxide (1 mL, 13.6 mmol). The resulting solution was cooled to –78 ºC. Oxalyl chloride (0.6 mL, 6.80 mmol) was added at –78 ºC and reaction was stirred for 20 minutes. Alcohol **438** (1.3 g, 3.40 mmol) and triethylamine (2.4 mL, 17.00 mmol) as a solution is dichloromethane (5 mL) were added via cannula at –78 ºC followed by stirring for 1 hour. Reaction solution was warmed to room temperature. TLC was used to monitor reaction progress. TLC plates were developed with gradient elution 10→20% EtOAc/Hex and visualized by UV lamp and $KMnO_4$. Reaction solution was diluted with dichloromethane (20 mL) and washed with saturated $NaHCO_3$ solution (60 mL), H_2O (60 mL) and brine (100 mL). Organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford crude ketone **439** (1.4 g, quantitative) as yellow oil. Crude material was taken directly into desilylation.

Preparation of allylic alcohol 440:



Allylic alcohol 440. To a flame dried round bottom flask was added TBS-ether **439** (1.4 g, 3.40 mmol) and tetrahydrofuran (12 mL). The resulting solution was cooled to 0 ºC. Tetrabutylammonium fluoride solution (1 M in THF, 5.1 mL) was added at 0 ºC. Reaction was warmed to room temperature. TLC was used to monitor reaction progress. TLC plates were developed with 20% EtOAc/Hex and visualized by UV lamp and $KMnO_4$. Quenched with saturated NH_4Cl solution (50 mL). Phases were separated. Organic phase was washed with H_2O (50 mL) and brine (50 mL). Organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford allylic alcohol **440** (1.1 g, quantitative) as oil. Crude material was carried on directly to acylation.

Preparation of allylic carbonate 441:



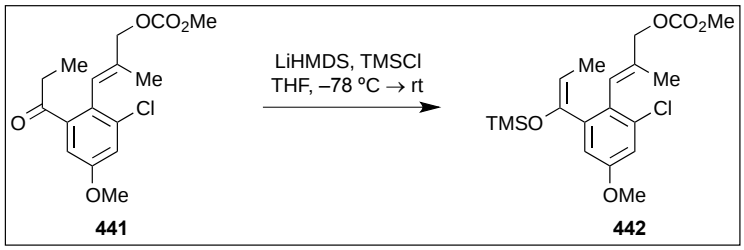
440 **441**

Allylic carbonate 441. To an oven dried round bottom flask equipped with a magnetic stir bar was added allylic alcohol **440** (800 mg, 2.98 mmol), dichloromethane (60 mL), 4-(dimethylamino)pyridine (40 mg, 0.30 mmol) and pyridine (0.50 mL, 5.96 mmol). The resulting solution was cooled to 0 ºC. Methyl chloroformate (0.35 mL, 4.48 mmol) was added at 0 ºC and stirred for 60 minutes. Reaction was warmed to room temperature. TLC was used to monitor reaction progress. TLC plates were developed with 30% EtOAc/Hex and visualized by UV lamp and $KMnO_4$. Reaction was complete after 8 hours at room temperature. Quenched with saturated NH_4Cl solution (50 mL). Phases were separated. Organic phase was washed with H_2O (50 mL) and brine (50 mL). Organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Crude material was absorbed onto silica gel (1 g) and purified with silica

gel chromatography (20:1 silica/crude material, gradient elution 10→20% EtOAc/Hex) to afford allylic carbonate **441** (800 mg, 86% yield) as yellow oil.

Allylic carbonate 441. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.04 (d, *J* = 2.6 Hz, 1H), 6.88 (d, *J* = 2.6 Hz, 1H), 6.51 (d, *J* = 1.3 Hz, 1H), 4.69 (d, *J* = 1.0 Hz, 2H), 3.81 (s, 3H), 3.81 (s, 3H), 2.71 (d, *J* = 6.8 Hz, 2H), 1.47 (d, *J* = 1.3 Hz, 3H), 1.09 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ 205.9, 159.1, 155.8, 143.5, 136.4, 135.4, 125.4, 124.2, 117.0, 111.6, 72.0, 55.8, 55.0, 35.8, 15.4, 8.6.

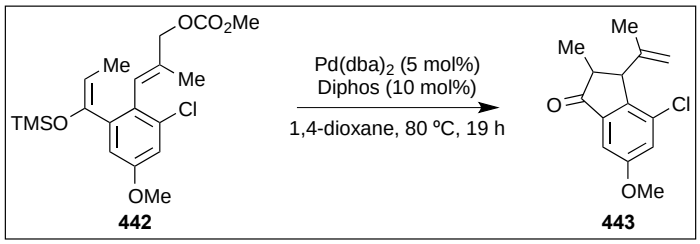
Preparation of silyl enol ether 442:



Silyl enol ether 442. To a flame dried round bottom flask equipped with a magnetic stir bar was added ketone **441** (419 mg, 1.28 mmol), tetrahydrofuran (9 mL) and trimethylsilyl chloride (325 μL, 2.56 mmol). The resulting solution was cooled to –78 ºC. Lithium bis(trimethylsilyl)amide (0.5 M solution in DME, 3.8 mL, 1.92 mmol) was added at –78 ºC. Reaction was stirred at –78 ºC for 1 hour followed by warming to room temperature. Reaction was stirred overnight at room temperature. TLC was used to monitor reaction progress. TLC plates were developed with 15% EtOAc/Hex and visualized by UV lamp and *p*-anisaldehyde. Reaction solution was washed with saturated $NaHCO_3$ solution (10 mL). Organic phase was dried over anhydrous Na_2SO_4. Crude material was purified with silica gel chromatography (20:1 silica/crude material, gradient elution 10→20% EtOAc/Hex) to afford silyl enol ether **442** (500 mg, 98% yield, >20:1 E/Z) as colorless oil.

Silyl enol ether 442. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 6.88 (d, *J* = 2.7 Hz, 1H), 6.84 (d, *J* = 2.7 Hz, 1H), 6.33 (d, *J* = 1.2 Hz, 1H), 4.93 (q, *J* = 6.8 Hz, 1H), 4.70 (d, *J* = 0.9 Hz, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 1.65 (d, *J* = 6.8 Hz, 3H), 1.55 (d, *J* = 1.3 Hz, 3H), 0.03 (s, 9H); ^{13}C-NMR (101 MHz; cdcl3): δ 158.6, 155.9, 148.6, 142.4, 134.7, 134.1, 126.0, 125.6, 114.0, 113.1, 109.8, 72.7, 55.6, 54.9, 15.8, 11.5, 0.5.

Preparation of Indanone 443:

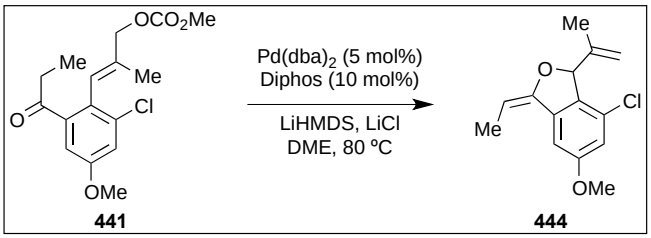


442 **443**

Indanone 443. To an oven dried vial equipped with a magnetic stir bar was added $Pd(dba)_2$ (4 mg, 0.007 mmol) and Diphos (5 mg, 0.013 mmol); system was purged with a stream of nitrogen prior to the addition of 1,4-dioxane (0.5 mL). Catalyst solution was premixed for 30 minutes at room temperature. π-Allyl precursor **442** (50 mg, 0.13 mmol) was added as a solution in 1,4-dioxane (1 mL) and reaction solution was transferred to a preheated (80 ºC) oil bath. After 19 hours reaction solution was cooled to room temperature. TLC was used to monitor reaction progress after 19 hours but reaction was not monitored until this point. TLC plates were developed with 15% EtOAc/Hex and visualized by UV lamp and *p*-anisaldehyde. Indanone **443** and silyl enol ether **442** have very close R_f's under the TLC conditions; indanone **443** stains green and silyl enol ether stains brown with *p*-anisaldehyde. Reaction solution was concentrated and purified with silica gel chromatography (50:1 silica/reaction mixture, gradient elution 1→2→3→4→5% EtOAc/Hex) to afford indanone **443** (7 mg, 23% yield) as a 5:1 mixture of diastereomers.

Indanone 443. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.20 (d, *J* = 2.3 Hz, 1H), 7.14 (d, *J* = 2.3 Hz, 1H), 4.88 (t, *J* = 1.5 Hz, 1H), 4.79 (d, *J* = 0.7 Hz, 1H), 3.85 (s, 3H), 3.57 (d, *J* = 3.1 Hz, 1H), 2.48 (qd, *J* = 7.5, 3.1 Hz, 1H), 1.60 (d, *J* = 0.5 Hz, 3H), 1.32 (d, *J* = 7.5 Hz, 3H); 7.18 (d, *J* = 2.4 Hz, 1H), 7.14 (d, *J* = 2.3 Hz, 1H), 5.00 (t, *J* = 1.5 Hz, 1H), 4.69 (s, 1H), 4.15 (d, *J* = 7.7 Hz, 1H), 3.85 (s, 3H), 2.89 (quintet, *J* = 7.4 Hz, 1H), 1.59 (s, 3H), 1.20 (d, *J* = 7.3 Hz, 3H).

Preparation of furan 444:

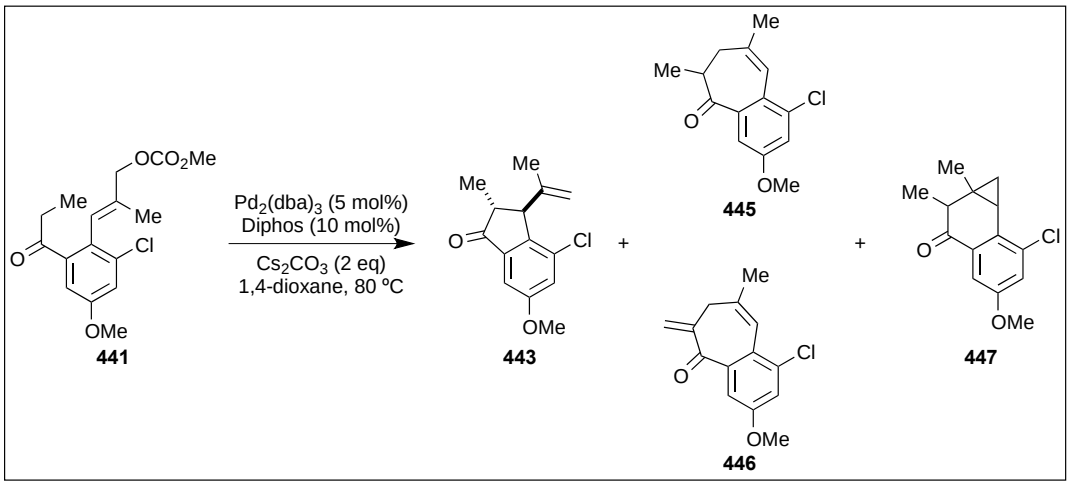


Furan 444. To a flame dried schlenk tube was added lithium chloride (6 mg, 0.15 mmol) and flame dried under vacuum. To lithium chloride was added ketone **441** (50 mg, 0.15 mmol) as a solution in 1,2-dimethoxyethane (DME) (1 mL); followed by the addition of lithium bis(trimethylsilyl)amide (0.5 M solution in DME, 0.3 mL, 0.15 mmol) at room temperature, allowed enolization to stir at room temperature for 30 minutes. $Pd(dba)_2$ (4 mg, 0.008 mmol) and Diphos (6 mg, 0.015 mmol) were premixed in DME (0.5 mL) and stirred for 30 minutes at room temperature. Catalyst solution was transferred to enolate solution and the reaction solution was immediately transferred to a preheated oil bath (80 ºC). After 16 hours reaction was cooled to room temperature. TLC was used to monitor reaction progress after 16 hours but reaction was not monitored until this point. TLC plates were developed with 15% EtOAc/Hex and visualized by UV lamp and *p*-anisaldehyde. Quenched with H_2O (1 mL) and phases were separated. Aqueous phase was extracted with diethyl ether (3 x 1 mL). Combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Crude material was purified

with silica gel chromatography (gradient elution 1→2→3→4→5→10→15% EtOAc/Hex) to afford furan **444** (29 mg, 76% yield).

Furan 444. FTIR (thin film/NaCl): 3452, 3088, 2972, 2939, 1771, 1607, 1487, 1436, 1377, 1333, 1309, 1280, 1230, 1196, 1134, 1069, 1032, 858; ^{1}H-NMR (400 MHz; $CDCl_3$): δ 6.80 (d, *J* = 2.0 Hz, 1H), 6.78 (d, *J* = 2.1 Hz, 1H), 5.81 (s, 1H), 5.23 (s, 1H), 5.10 (t, *J* = 1.5 Hz, 1H), 4.93 (q, *J* = 7.1 Hz, 1H), 3.82 (s, 3H), 1.80 (d, *J* = 7.0 Hz, 3H), 1.49 (d, *J* = 0.4 Hz, 3H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ 161.2, 154.8, 141.9, 138.2, 130.3, 129.6, 116.8, 115.5, 102.7, 91.2, 88.0, 56.0, 16.2, 10.4.

Palladium(0)-Catalyzed Cyclization with Cesium Carbonate as Base:



Palladium(0)-Catalyzed Cyclization with Cesium Carbonate as Base: To an oven dried vial equipped with a magnetic stir bar was added $Pd(dba)_2$ (4 mg, 0.008 mmol), Diphos (6 mg, 0.015 mmol) and cesium carbonate (98 mg, 0.30 mmol); the system was purged with a stream of nitrogen prior to the addition of 1,4-dioxane (0.5 mL). Catalyst and base solution was premixed for 30 minutes at room temperature. Ketone **441** (50 mg, 0.13 mmol) was added as a solution in 1,4-dioxane (1 mL) and reaction solution was transferred to a preheated (80 ºC) oil bath. After 21 hours the reaction solution was cooled to room temperature. TLC was used to

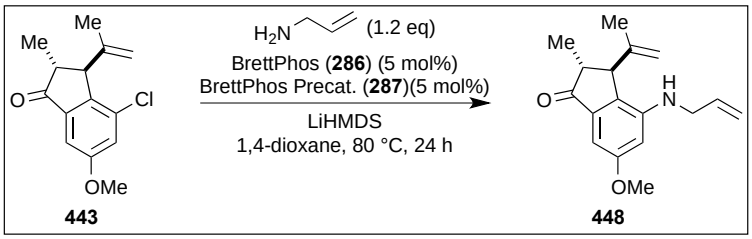
monitor reaction progress after 21 hours but reaction was not monitored until this point. TLC plates were developed with 15% EtOAc/Hex and visualized by UV lamp and *p*-anisaldehyde. Quenched with 1 M HCl (2 mL) and phases were separated. Aqueous phase was extracted with diethyl ether (3 x 1 mL). Combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Reaction solution was concentrated and purified with silica gel chromatography (50:1 silica/reaction mixture, gradient elution 1→2→3→4→5% EtOAc/Hex) to afford indanone **443**, ketone **445**, enone **446** and tricycle **447**. The yield of each product was sacrificed in order to isolate each component as cleanly as possible for characterization.

Ketone 445: ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.06 (d, *J* = 2.8 Hz, 1H), 7.03 (d, *J* = 2.7 Hz, 1H), 6.51 (t, *J* = 0.7 Hz, 1H), 3.82 (s, 3H), 3.03 (dqd, *J* = 9.2, 7.1, 5.1 Hz, 1H), 2.36 (d, *J* = 9.2 Hz, 1H), 2.35 (d, *J* = 5.1 Hz, 1H), 2.02 (d, *J* = 1.5 Hz, 3H), 1.25 (d, *J* = 7.1 Hz, 4H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ 207.1, 190.3, 141.0, 140.3, 126.9, 121.4, 119.0, 112.4, 55.8, 48.8, 36.9, 26.3, 17.4.

Enone 446. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.29 (d, *J* = 2.2 Hz, 1H), 7.20 (d, *J* = 2.2 Hz, 1H), 5.82 (s, 1H), 5.36 (s, 1H), 5.27 (quintet, *J* = 1.4 Hz, 1H), 3.88 (s, 3H), 1.47 (t, *J* = 1.2 Hz, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 169.5, 161.9, 138.3, 137.1, 130.2, 122.9, 119.8, 107.2, 84.6, 56.3, 16.2.

Tricycle 447. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.25 (d, *J* = 2.7 Hz, 1H), 7.14 (d, *J* = 2.7 Hz, 1H), 3.80 (s, 3H), 2.59 (qd, *J* = 6.6, 1.2 Hz, 1H), 2.38 (dd, *J* = 8.6, 4.6 Hz, 1H), 1.40 (d, *J* = 6.6 Hz, 3H), 1.35 (s, 3H), 1.20 (ddd, *J* = 8.6, 4.8, 1.3 Hz, 1H), 0.05 (t, *J* = 4.7 Hz, 1H); ^{13}C-NMR (101 MHz; $CDCl_3$): δ 198.5, 157.5, 135.8, 133.9, 131.4, 121.3, 109.9, 55.9, 44.3, 25.7, 24.4, 21.5, 20.6, 12.5; HRMS (EI) *m/z* 251.0833 [calc'd for $C_{14}H_{15}ClO_2$ (M+H)+ 250.0761].

Preparation of amine of amine 455:



Amine 455. To an oven dried vial equipped with a magnetic stir bar was added aryl chloride (16 mg, 0.06 mmol), BrettPhos (286) (2 mg, 0.003 mmol), BrettPhos precatalyst (**287**) (2 mg, 0.003 mmol); the system was evacuated and backfilled with nitrogen (3 x). To the vial was added 1,4-Dioxane (0.7 mL), allylamine (6 μL, 0.07 mmol) and lithium bis(trimethylsilyl)amide (0.5 M in 1,4-dioxane, 0.3 mL, 0.15 mmol). Vial was immediately placed in a preheated oil bath (80 ºC). After 24 hours the reaction solution was cooled to room temperature. TLC was used to monitor reaction progress after 24 hours but reaction was not monitored until this point. TLC plates were developed with 10% EtOAc/Hex and visualized by UV lamp and *p*-anisaldehyde. Reaction solution was quenched with saturated NH_4Cl solution (1 mL) and diluted with dichloromethane (2 mL). Phases were separated and the organic layer was dried over anhydrous $MgSO_4$ and concentrated. Crude residue was purified with silica gel chromatography (gradient elution 1→5→10→20% EtOAc/Hex) to afford amine **455** (2 mg, 12% yield) the mass balance of the material appears correspond to loss of the chloride and the ^{1}H NMR spectra matches that of indanone **427**.

Amine 455. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 6.59 (d, *J* = 2.2 Hz, 1H), 6.33 (d, *J* = 2.3 Hz, 1H), 5.97-5.84 (m, 1H), 5.24 (dd, *J* = 17.3, 1.4 Hz, 1H), 5.18 (dd, *J* = 10.3, 1.5 Hz, 1H), 5.11 (dt, *J* = 1.2, 0.6 Hz, 1H), 4.99-4.98 (m, 1H), 3.81 (s, 3H), 3.43 (d, *J* = 3.4 Hz, 1H), 2.48-2.39 (m, 1H), 1.57 (t, *J* = 0.7 Hz, 3H), 1.31 (d, *J* = 7.4 Hz, 3H).

References Relevant to Chapter 5

(91) Abell, A. D. C., James Morriss; Jones, Matthew Alan; McNabb, Stephen Brian; Neffe, Axel Thomas; Aitken, Steven Geoffrey; Stuart, Blair Gibb; Nikkel, Janna Marie; Duncan, Joanna Kimberley; Klanchantra, Mutita; Morton, James David; Bickerstaffe, Roy; Robertson, Lucinda Jane Goodricke; Lee, Hannah Yun Young; Muir, Matthew Stewart; Lincoln University, N. Z.; Canterprise Limited: **2008**; Vol. Apr 24, 2008
WO 2008048121 A2.

(92) Boumendjel, A.; Miller, S. P. F. *Tetrahedron Lett.* **1994**, *35*, 819.

(93) Snyder, S. A.; Breazzano, S. P.; Ross, A. G.; Lin, Y. Q.; Zografos, A. L. *J. Am. Chem. Soc.* **2009**, *131*, 1753.

(94) Kobayashi, S. M., K.; Ishitani, H.; Matsuo, J.-I. *Science of Synthesis* **2002**, *4*, 317.

(95) Reetz, M. T.; Huttenhain, S.; Hubner, F. *Synthetic Commun.* **1981**, *11*, 217.

(96) Paterson, I. *Tetrahedron Lett.* **1979**, 1519.

(97) Shono, T.; Nishiguchi, I.; Komamura, T.; Sasaki, M. *J. Am. Chem. Soc.* **1979**, *101*, 984.

(98) Greene, T. W., Wuts, P.G.M *Protective Groups in Organic Synthesis, Third Edition*; John Wiley & Sons, Inc., **1999**.

(99) Lu, Z.; Ma, S. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 258.

(100) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813.

(101) Graening, T.; Schmalz, H. G. *Angew. Chem. Int. Ed.* **2003**, *42*, 2580.

(102) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1.

(103) Helmchen, G. *J Organomet. Chem.* **1999**, *576*, 203.

(104) Trost, B. M.; VanVranken, D. L. *Chem. Rev.* **1996**, *96*, 395.

(105) Trost, B. M. *Accounts Chem. Res.* **1996**, *29*, 355.

(106) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

(107) Consiglio, G.; Waymouth, R. M. *Chem. Rev.* **1989**, *89*, 257.

(108) Braun, M.; Meier, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 6952.

(109) Tsuji, J.; Minami, I.; Shimizu, I. *Chem. Lett.* **1983**, 1325.

(110) Tsuji, J. *Tetrahedron* **1986**, *42*, 4361.

(111) Dabrowski, M.; Kubicka, J.; Lulinski, S.; Serwatowski, J. *Tetrahedron Lett.* **2005**, *46*, 4175.

(112) von Hirschheydt, T.; Voss, E. *Synthesis-Stuttgart* **2004**, 2062.

(113) Sarpong, R.; Marcus, A. P. *Org. Lett.* **2010**, *12*, 4560.

(114) Zheng, W. H.; Zheng, B. H.; Zhang, Y.; Hou, X. L. *J. Am. Chem. Soc.* **2007**, *129*, 7718.

(115) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

(116) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(117) Mattson, A. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 4508.

(118) Merlic, C. A.; Aldrich, C. C.; Albaneze-Walker, J.; Saghatelian, A.; Mammen, J. *J. Org. Chem.* **2001**, *66*, 1297.

(119) Claridge, T. D. W.; Davies, S. G.; Lee, J. A.; Nicholson, R. L.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Toms, S. M. *Org. Lett.* **2008**, *10*, 5437.

Appendix 1

Spectra Relevant to Chapter 2

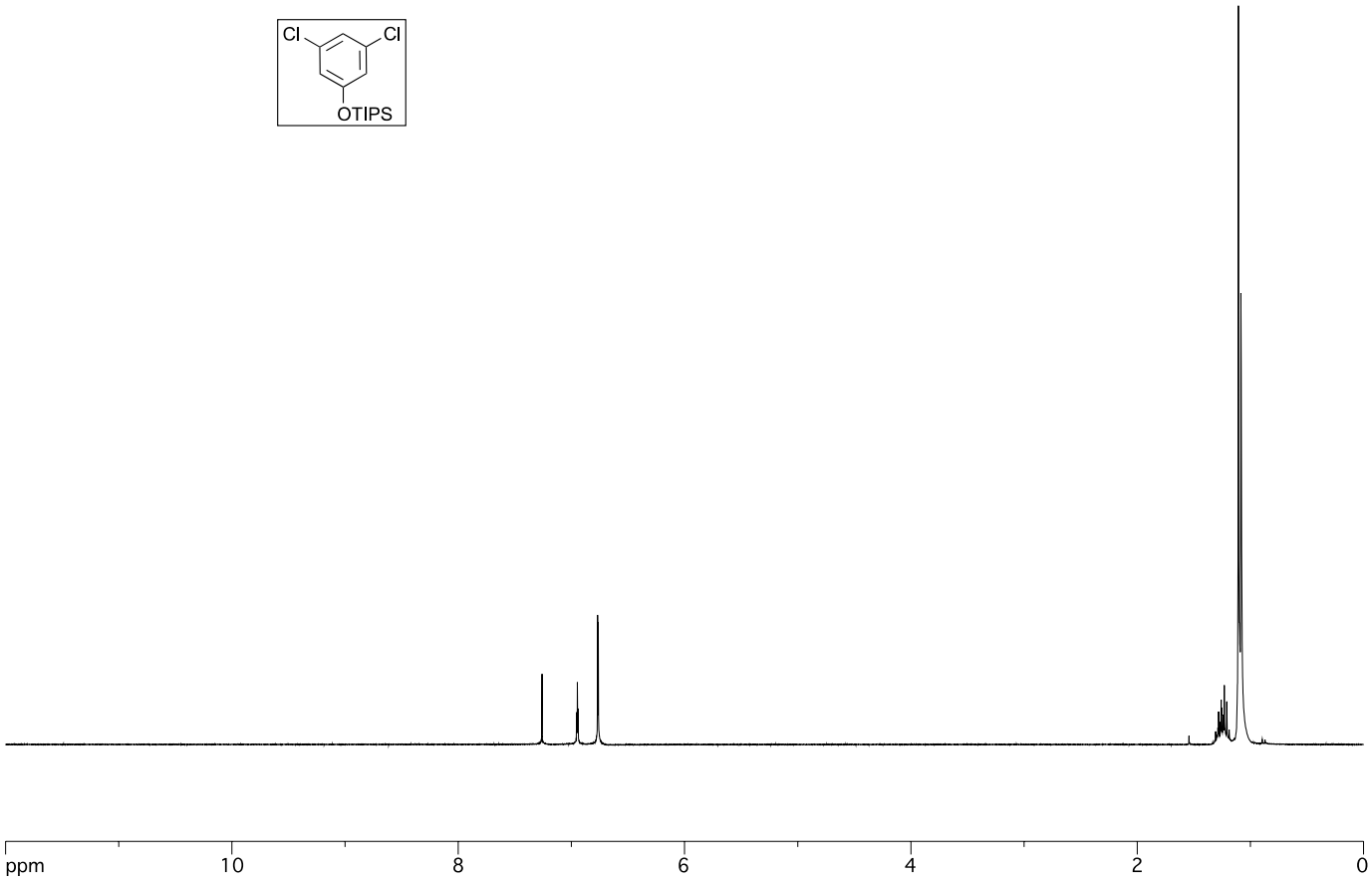


Figure A.1.1 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **107**

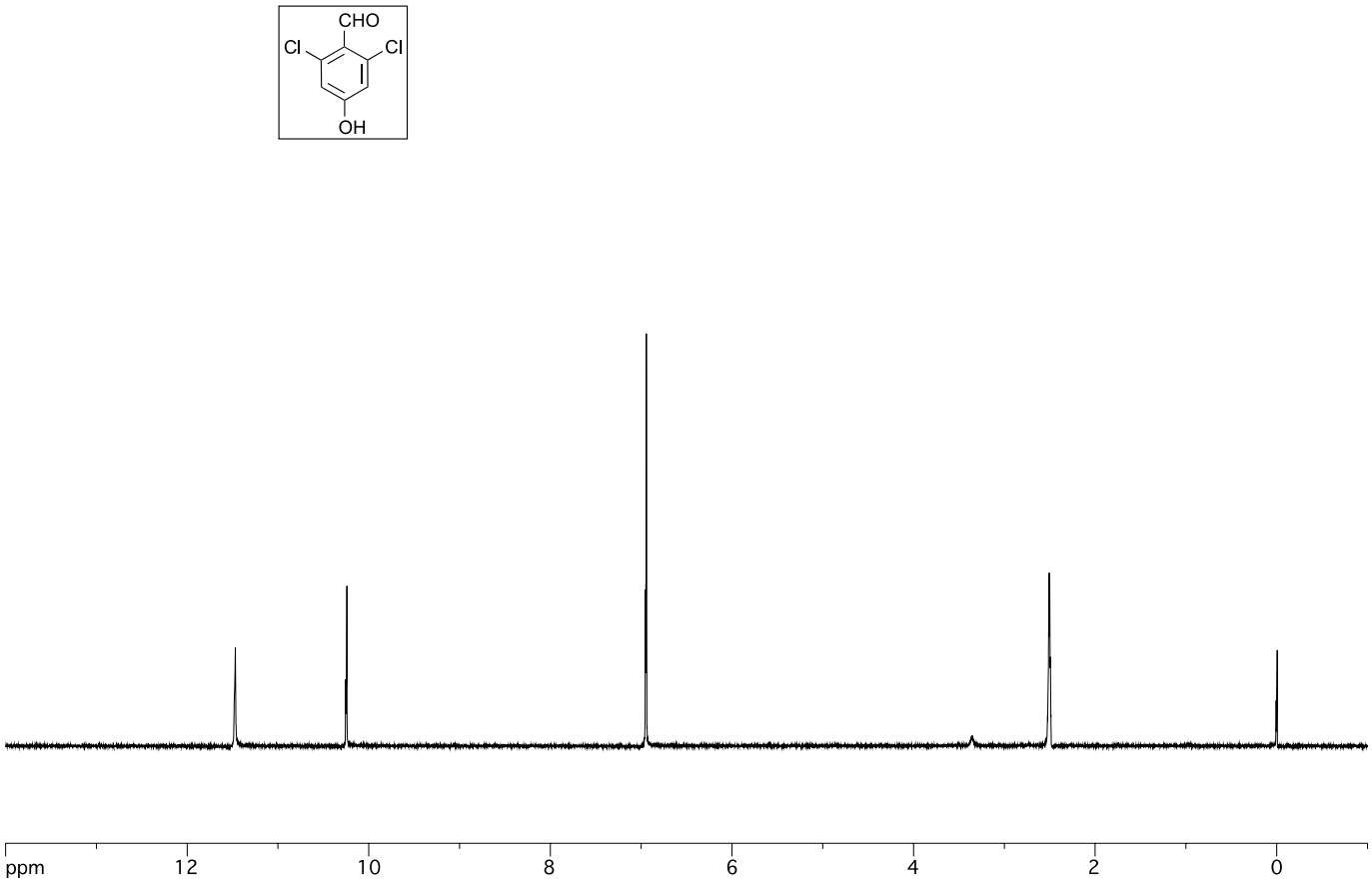


Figure A.1.2 ^{1}H NMR (300 MHz, DMSO-d_6) of Compound **108**

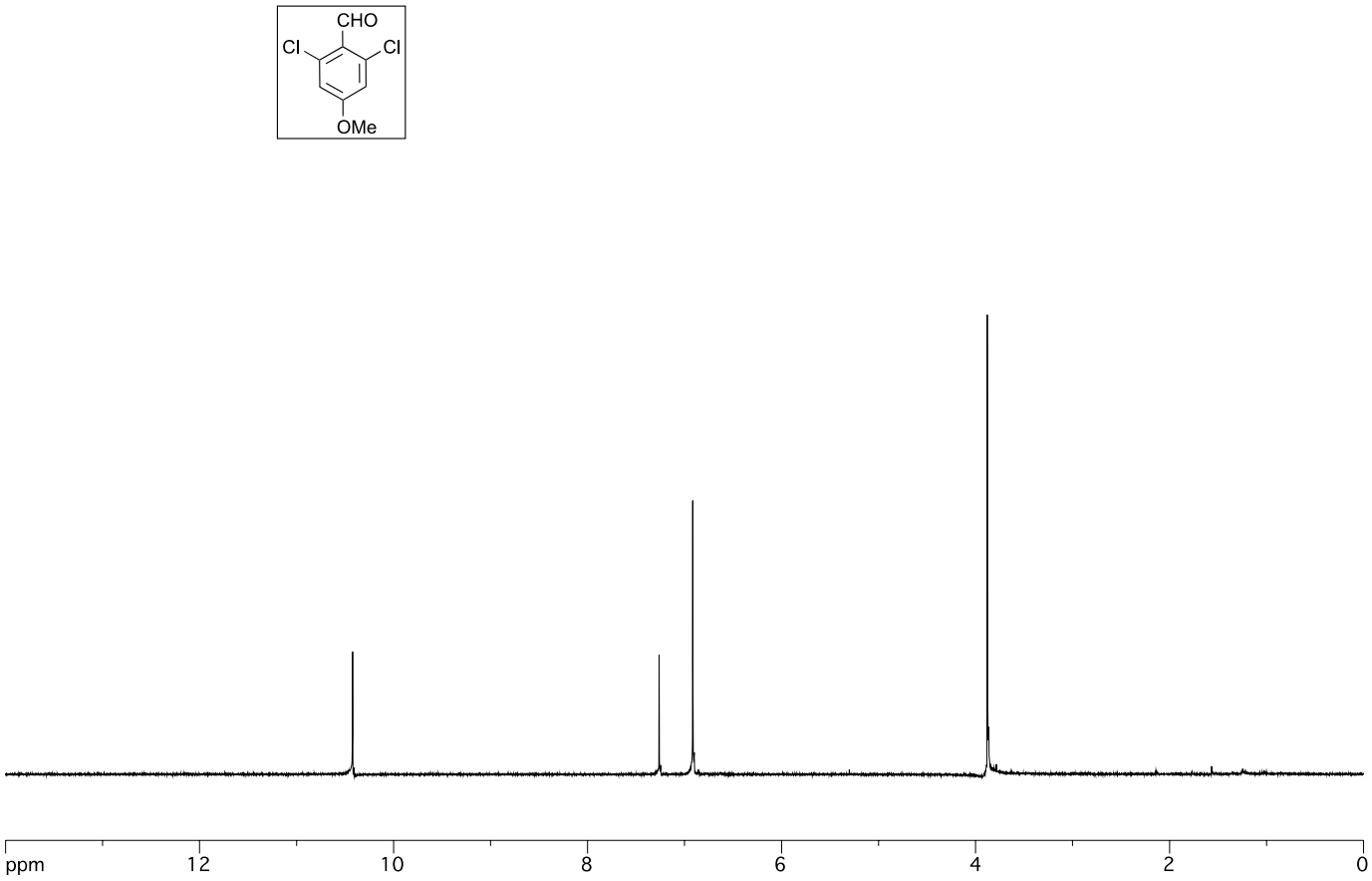


Figure A.1.3 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **109**

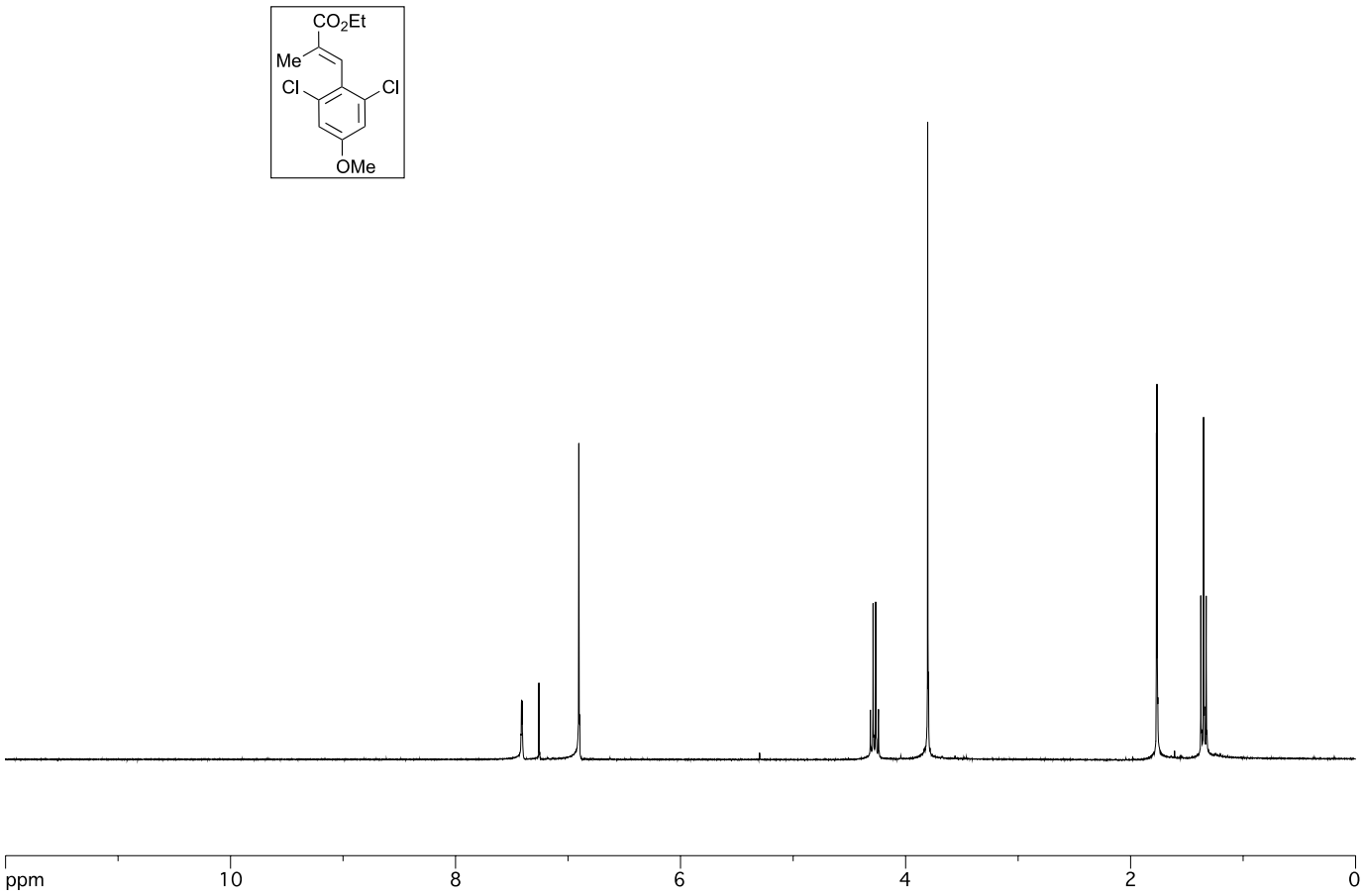


Figure A.1.4 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **110**

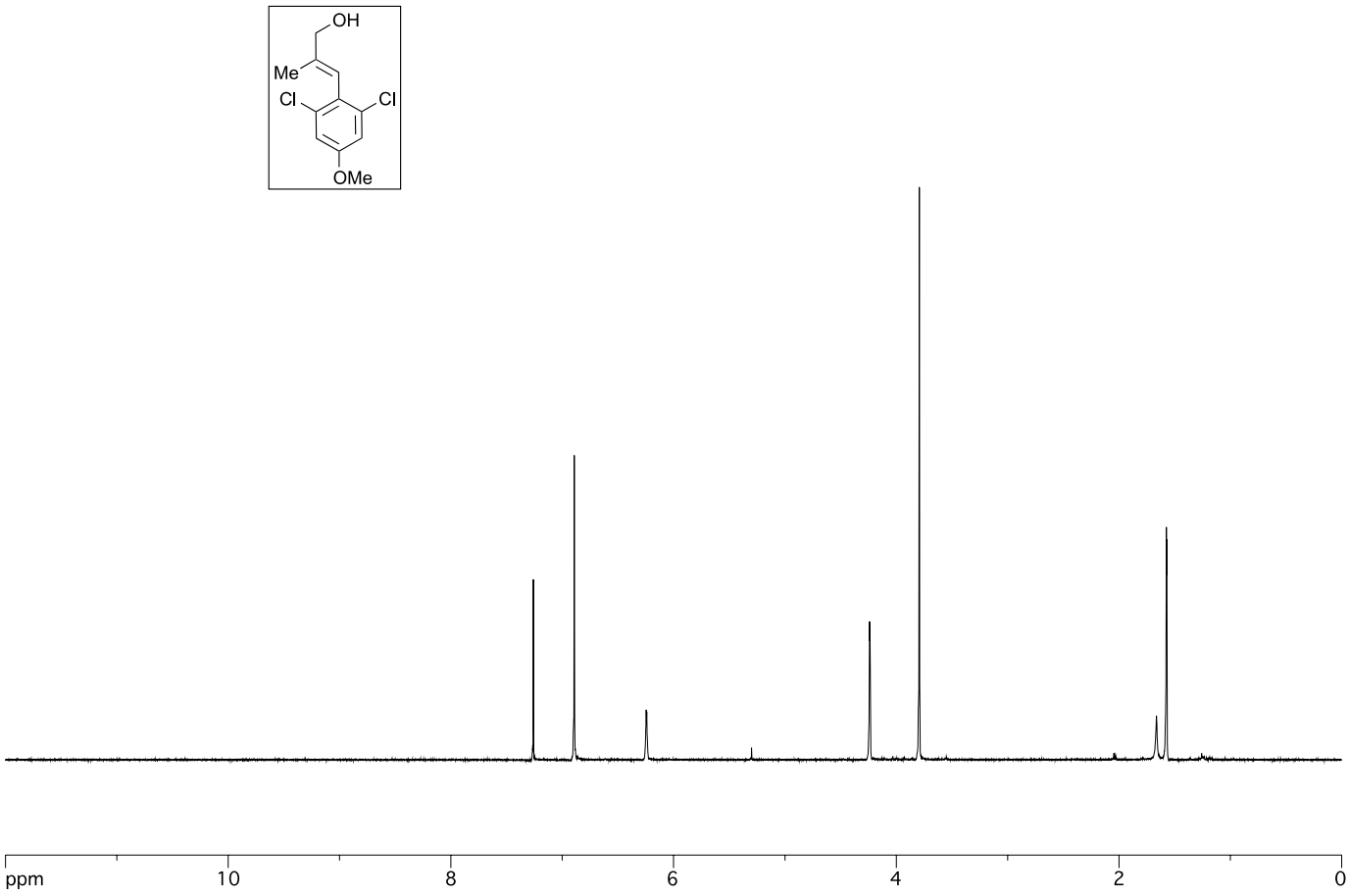


Figure A.1.5 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **111**

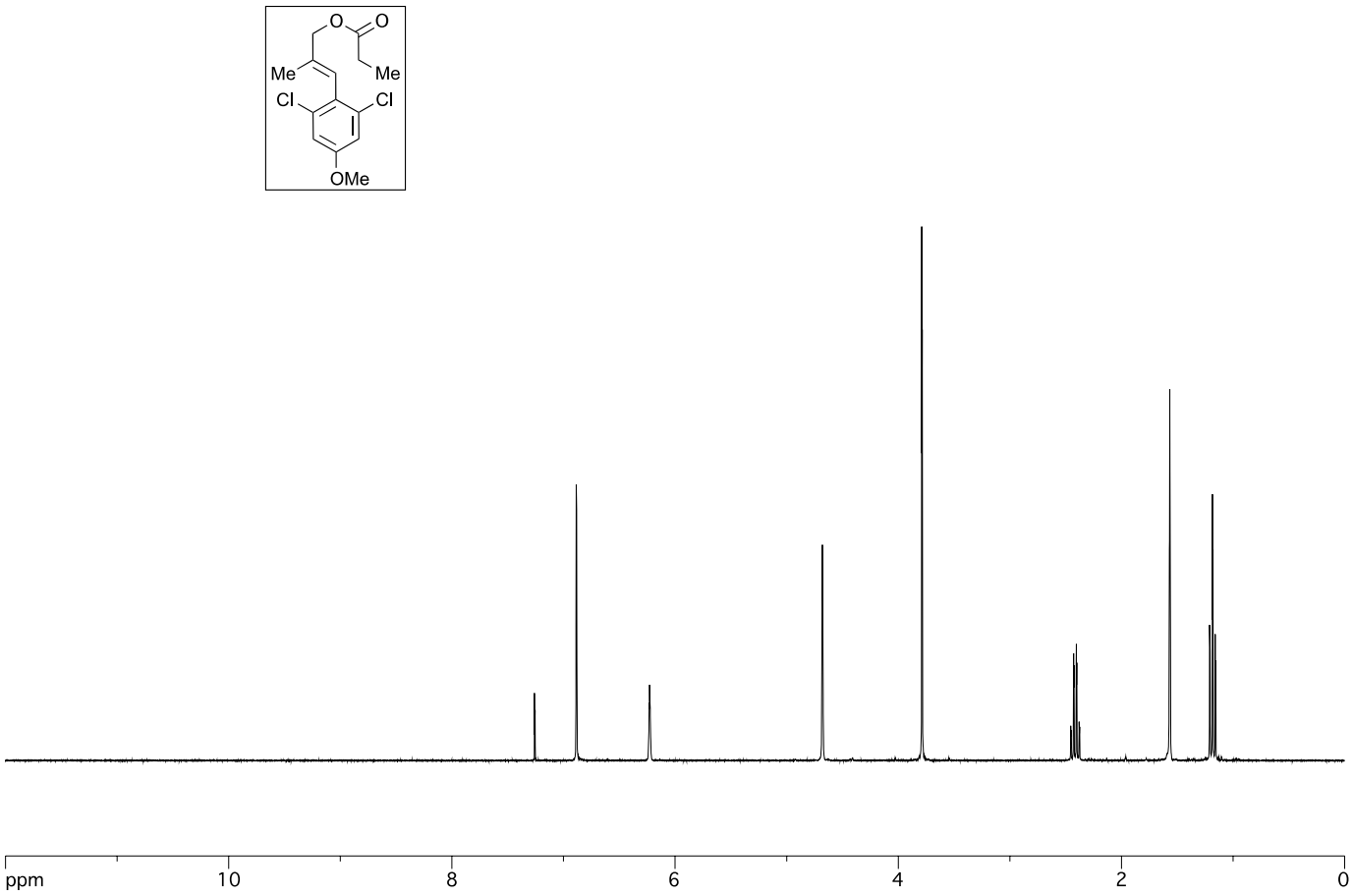


Figure A.1.6 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **112**

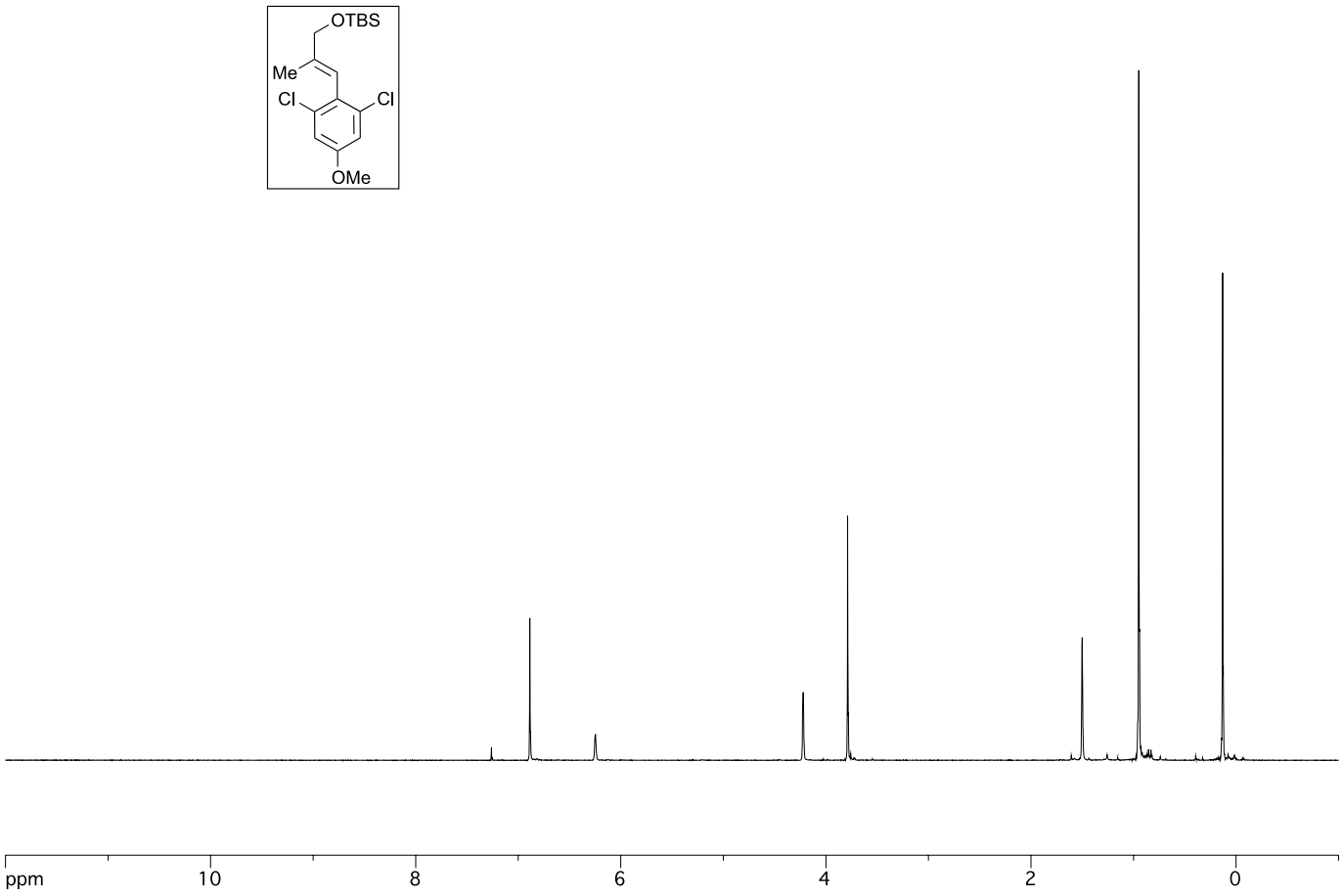


Figure A.1.7 ^{1}H-NMR (300 MHz, $CDCl_3$) of Compound **117**

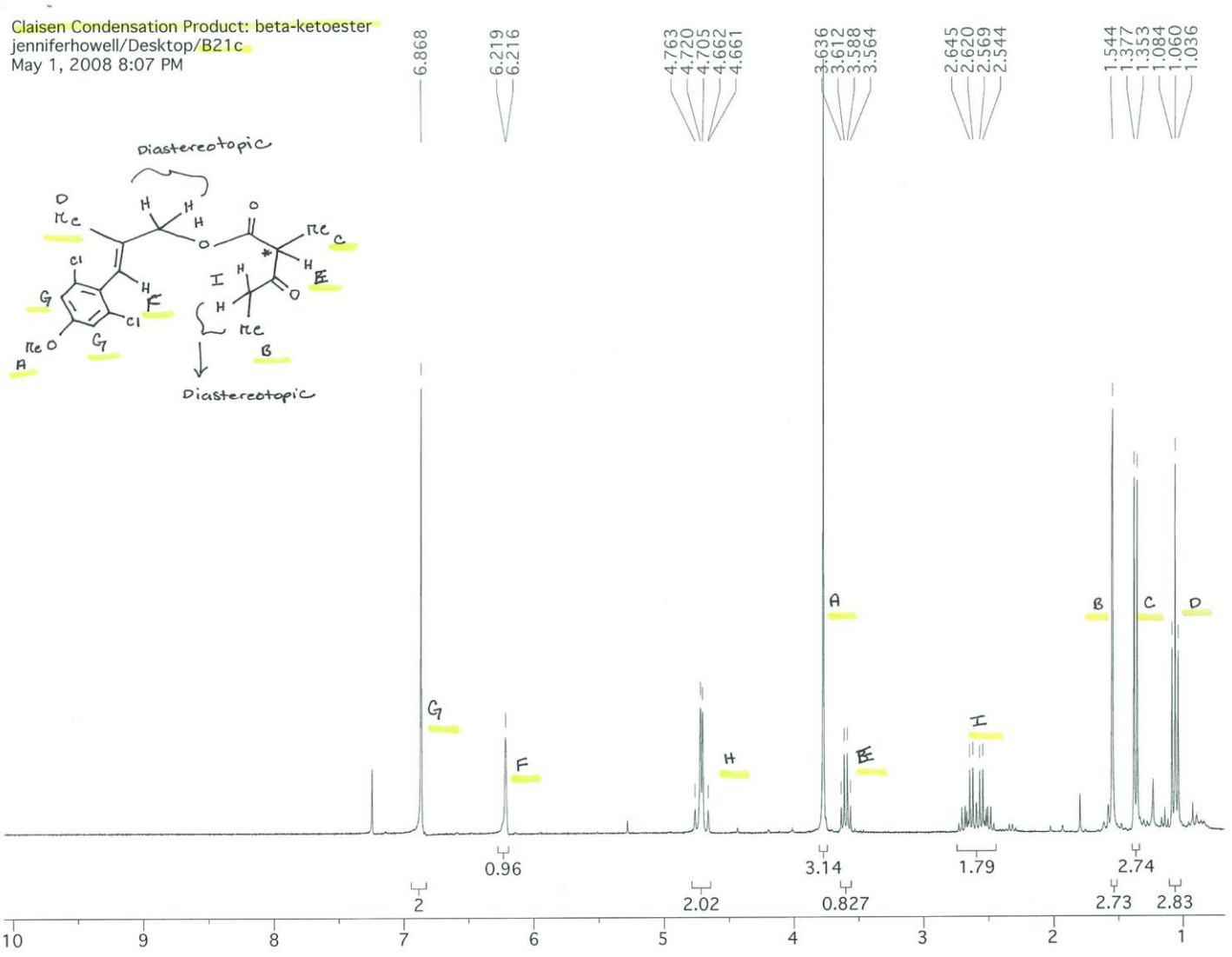


Figure A.1.8 ^{1}H-NMR (300 MHz, $CDCl_3$) of Compound **118**

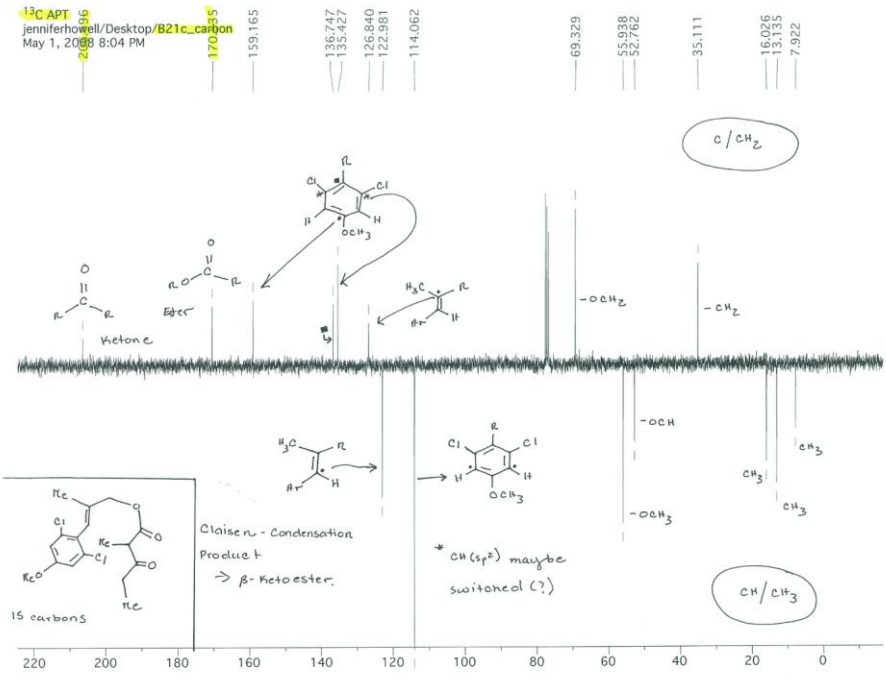


Figure A.1.9 ^{13}C APT (100 MHz, $CDCl_3$) of Compound **118**

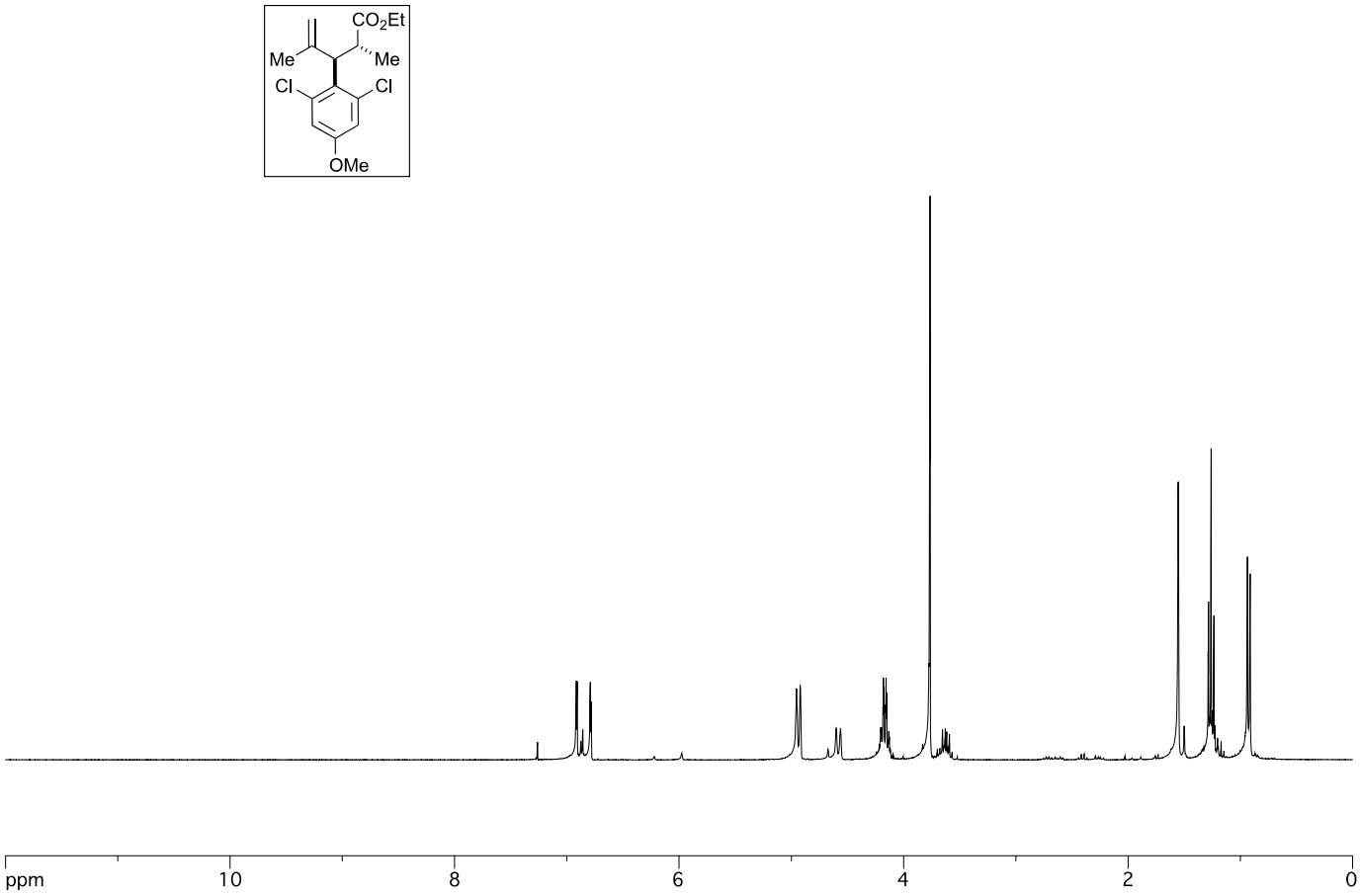


Figure A.1.10 ^{1}H-NMR (400 MHz, $CDCl_3$) of Compound **122**

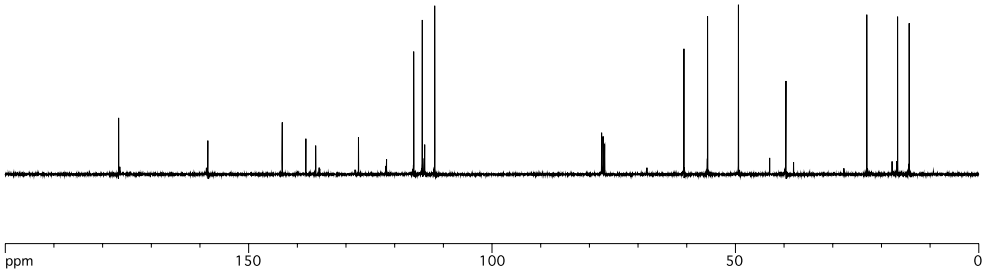


Figure A.1.11 ^{13}C-NMR (101 MHz, $CDCl_3$) of Compound **122**

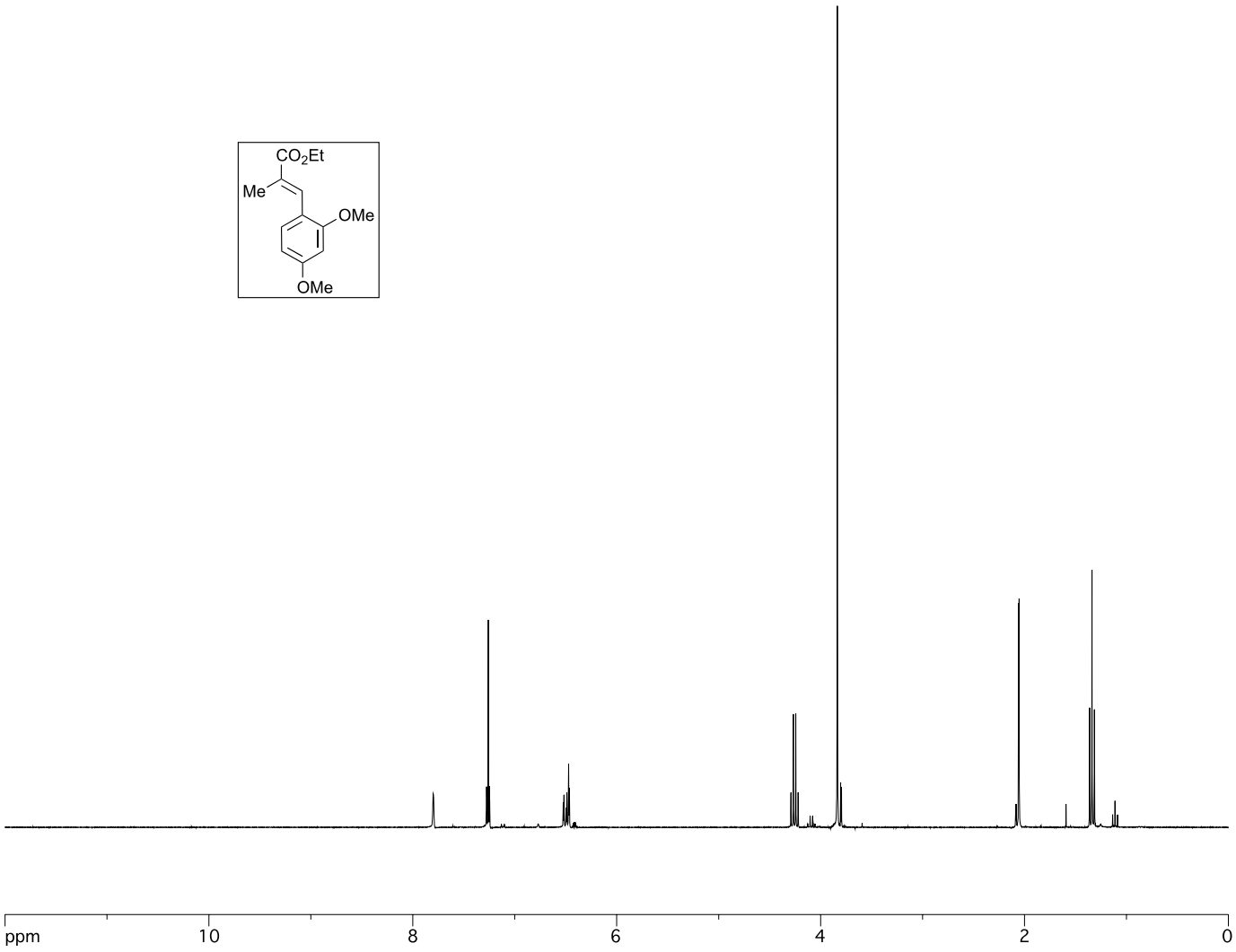


Figure A.1.12 ^{1}H-NMR (300 MHz, $CDCl_3$) of Compound **130**

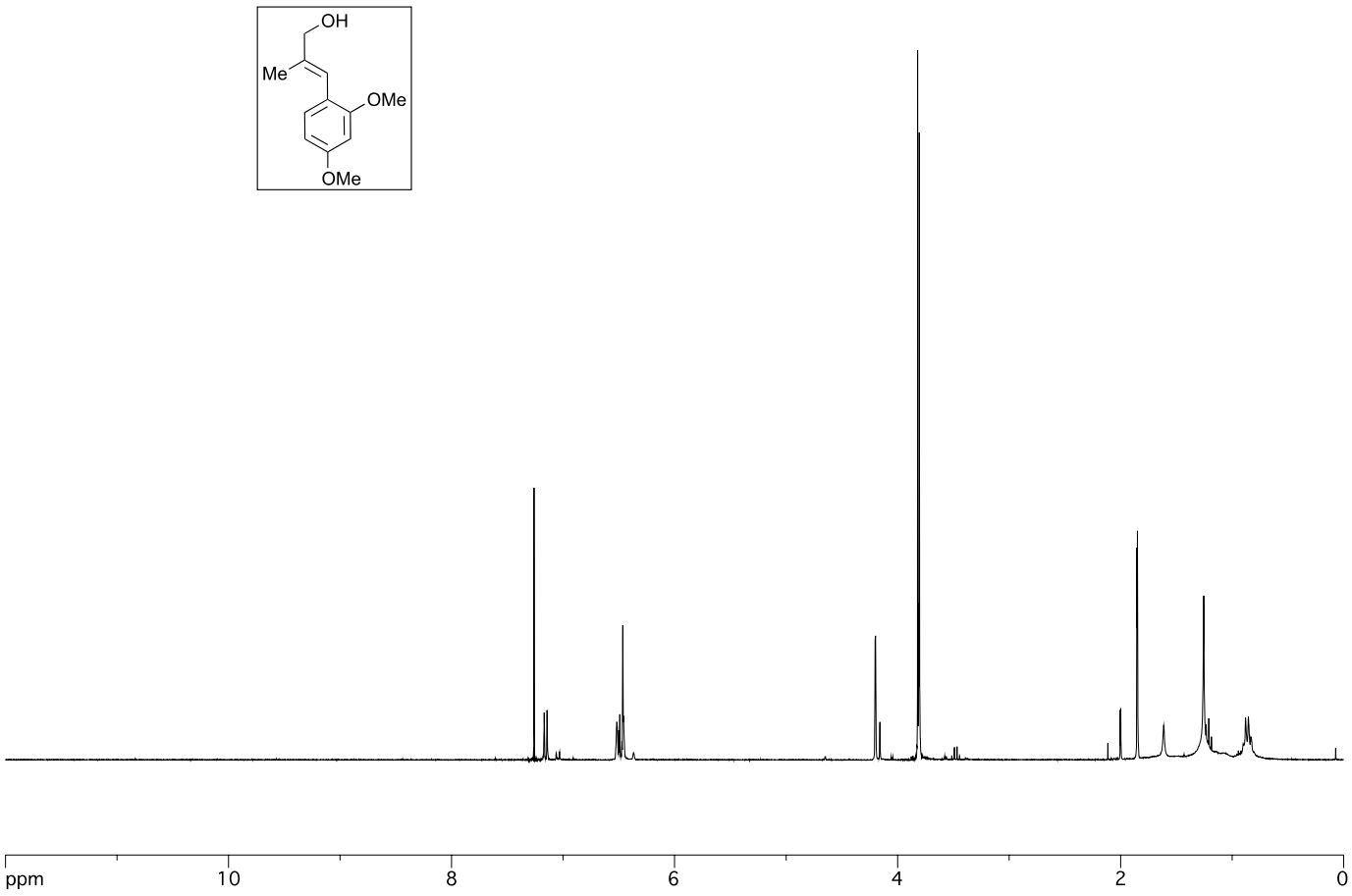


Figure A.1.13 ^{1}H-NMR (300 MHz, $CDCl_3$) of Compound **131**

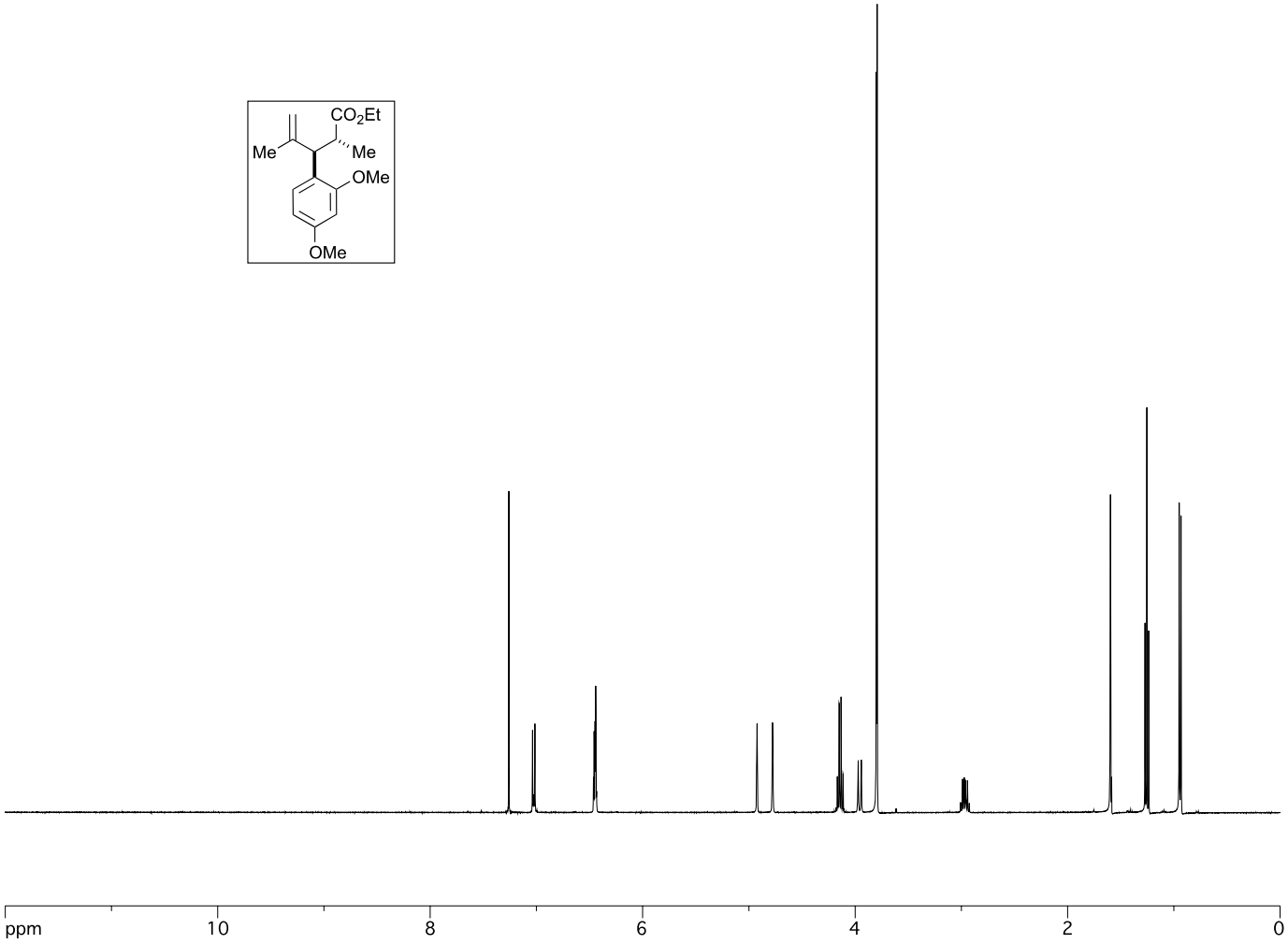


Figure A.1.14 ^{1}H-NMR (400 MHz, $CDCl_3$) of Compound **132**

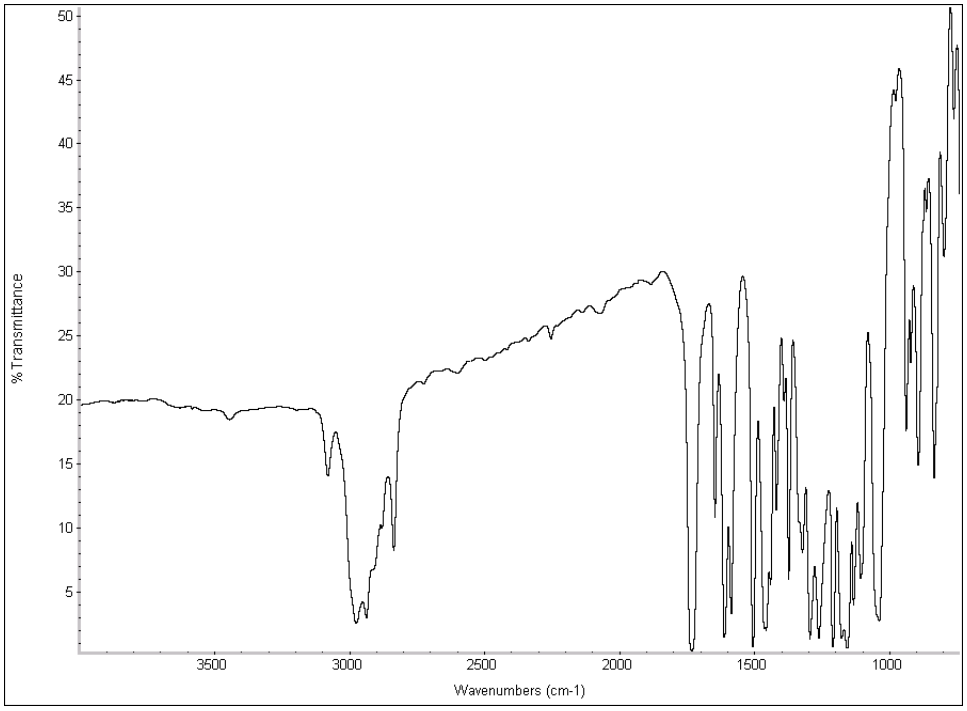


Figure A.1.15 FTIR (thin film/NaCl) Spectrum of Compound **132**

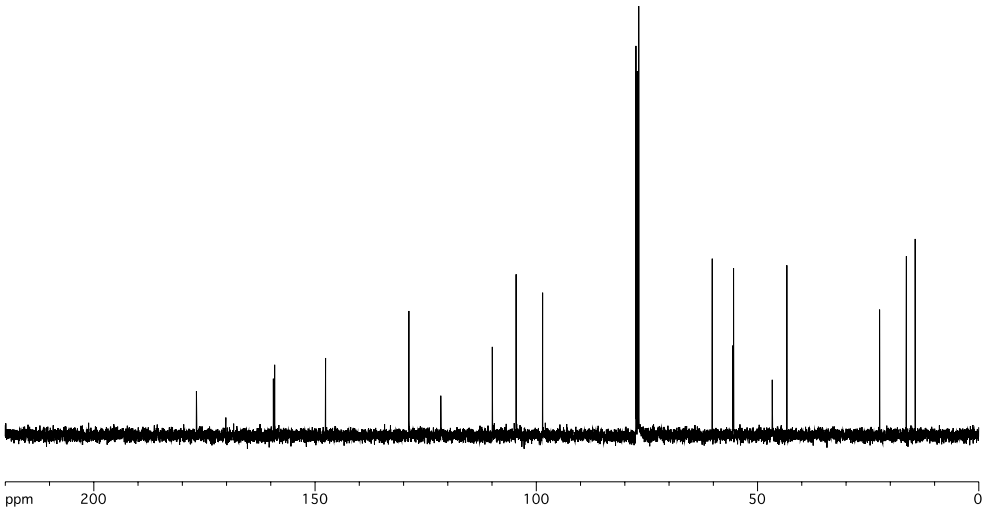


Figure A.1.16 ^{13}C-NMR (101 MHz, $CDCl_3$) of Compound **132**

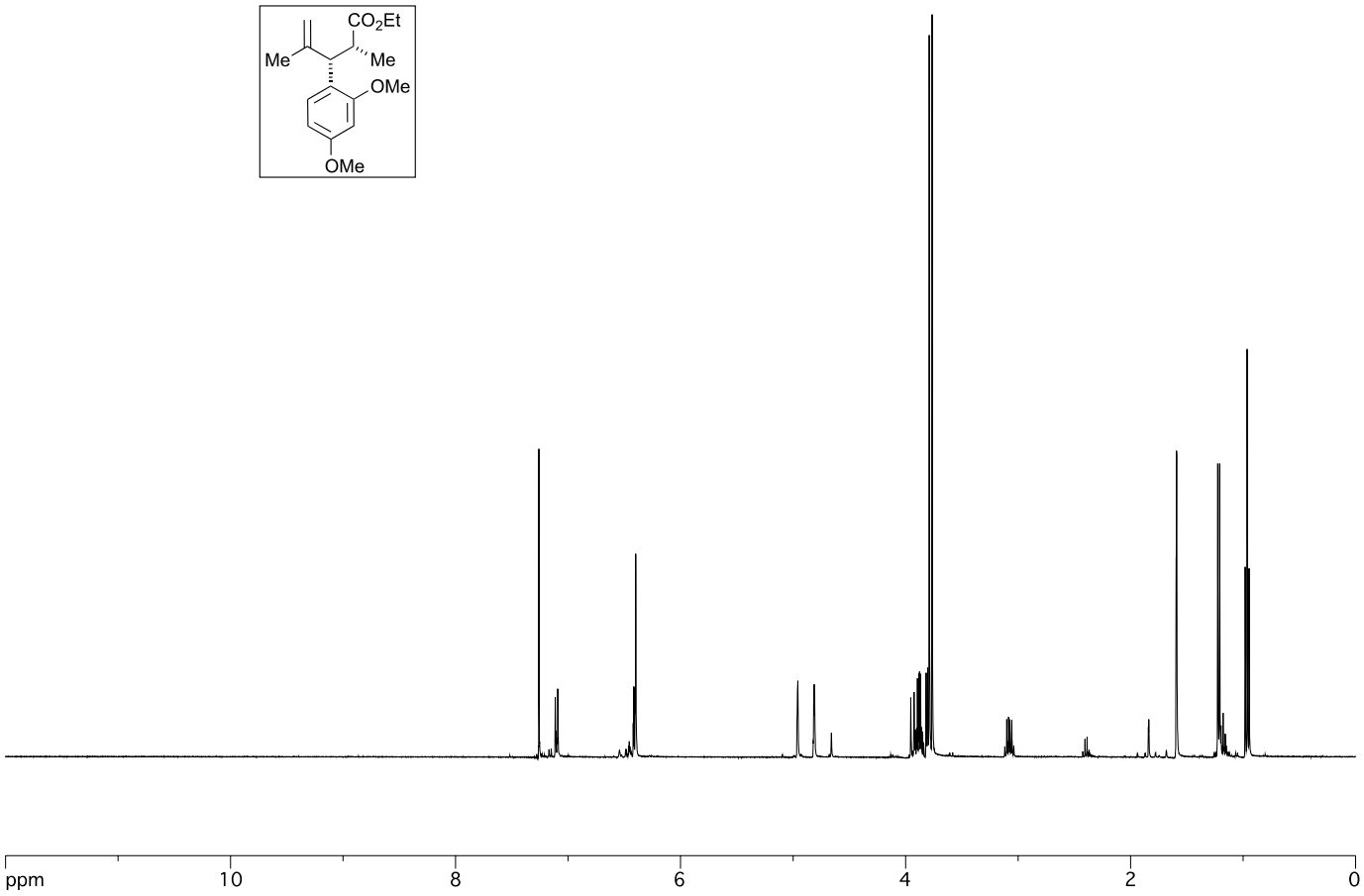


Figure A.1.17 ^{1}H-NMR (400 MHz, $CDCl_3$) of Compound **133**

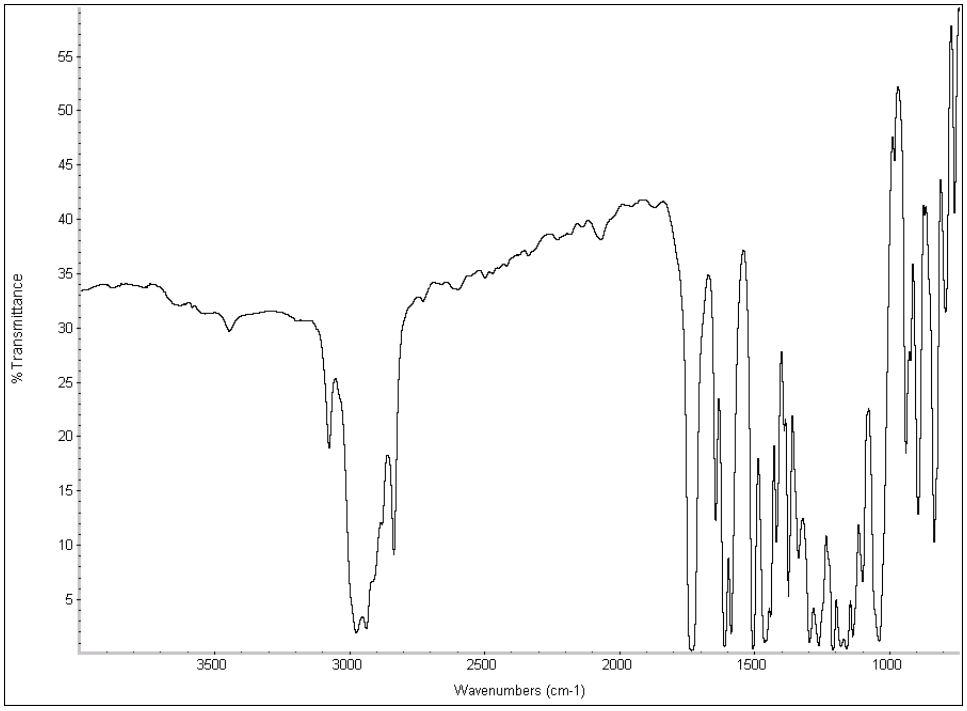


Figure A.1.18 FTIR (thin film/NaCl) Spectrum of Compound **133**

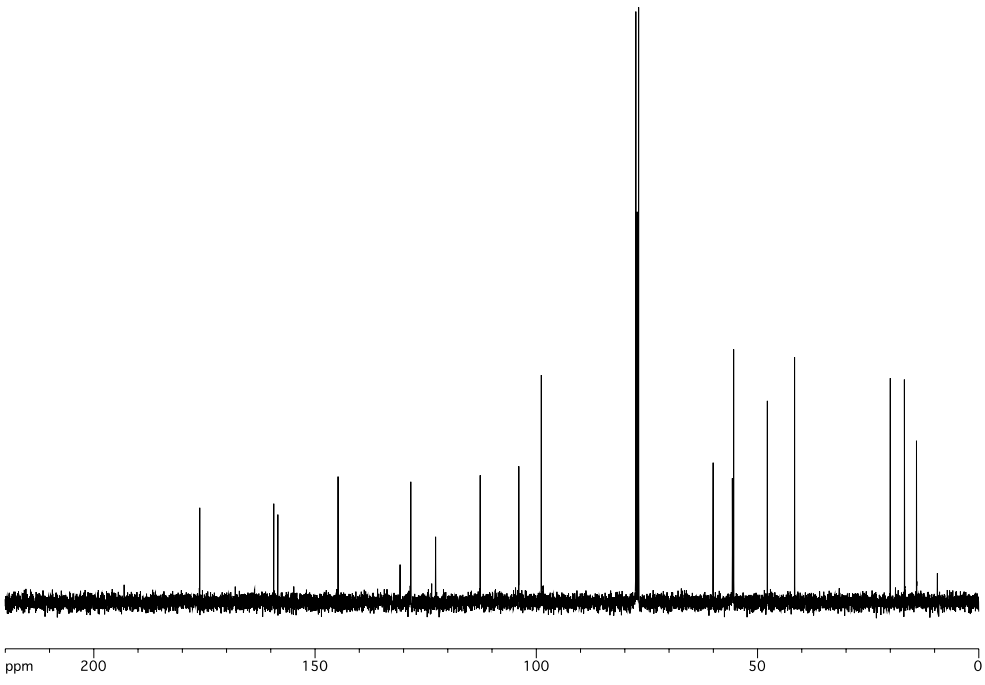


Figure A.1.19 ^{13}C-NMR (101 MHz, $CDCl_3$) of Compound **133**

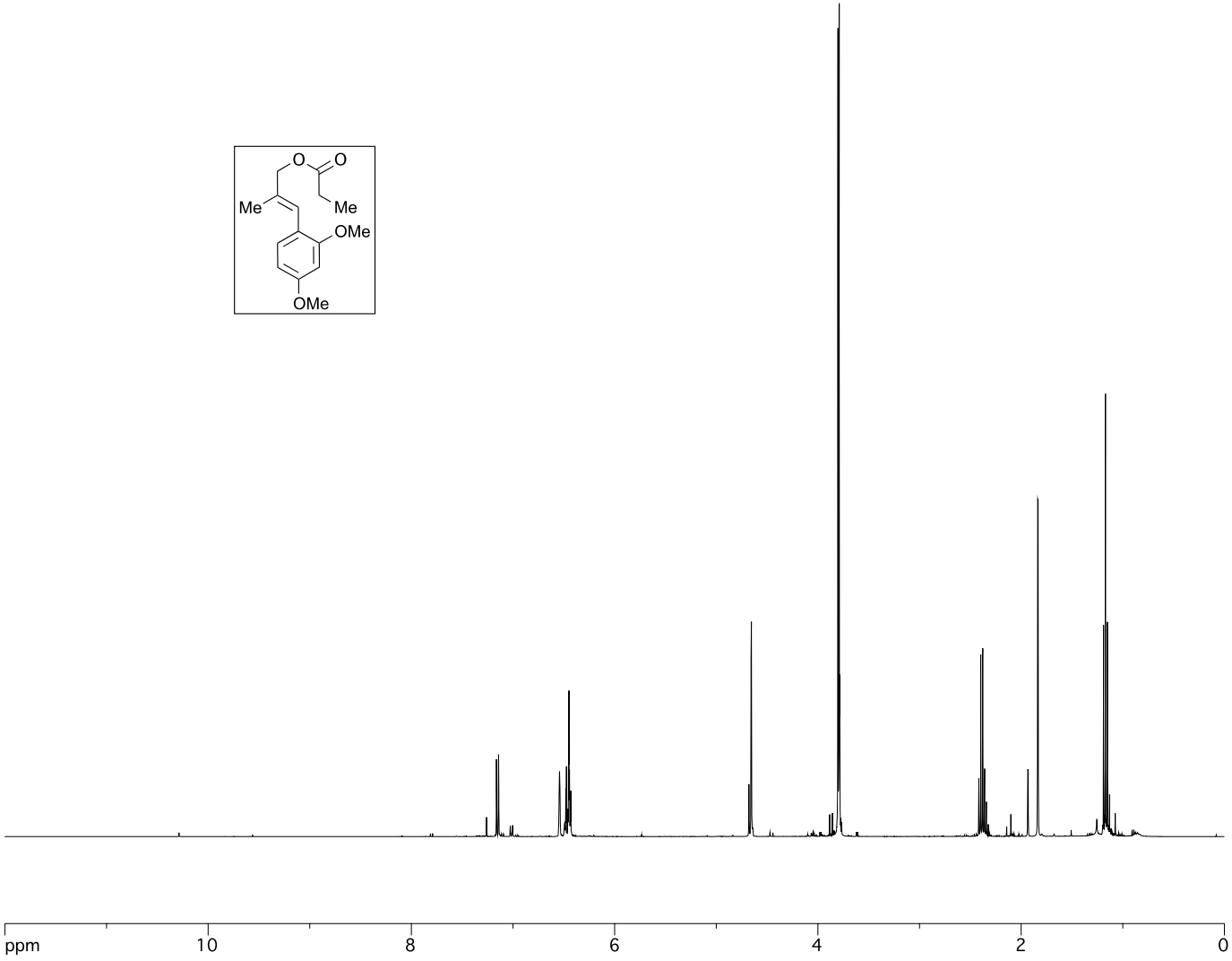


Figure A.1.20 ^{1}H-NMR (400 MHz, $CDCl_3$) of Compound **134**

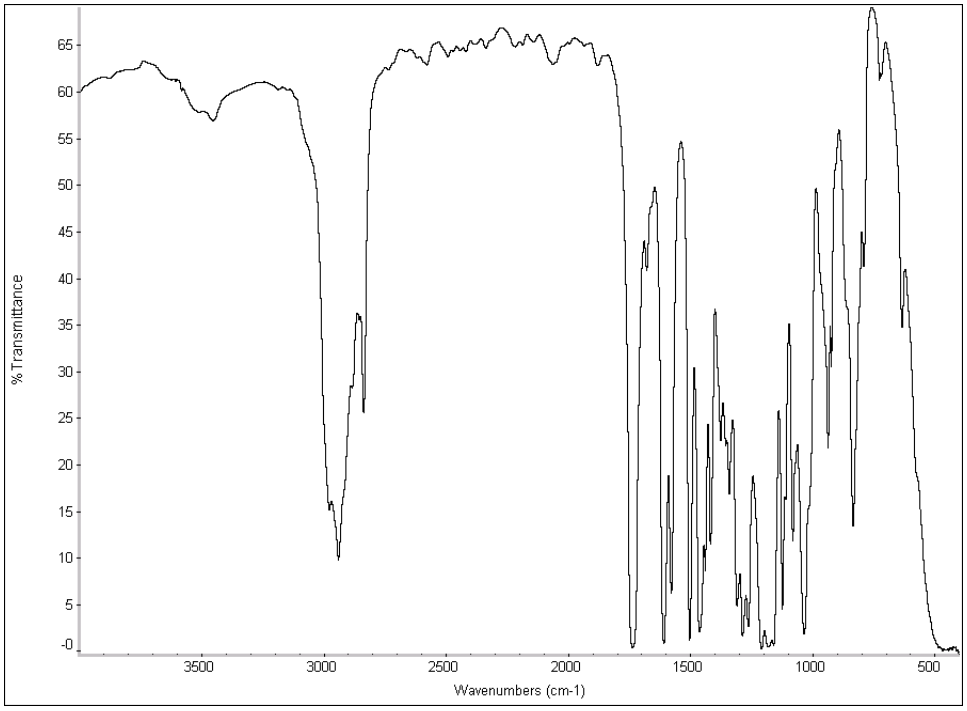


Figure A.1.21 FTIR (thin film/NaCl) Spectrum of Compound **134**

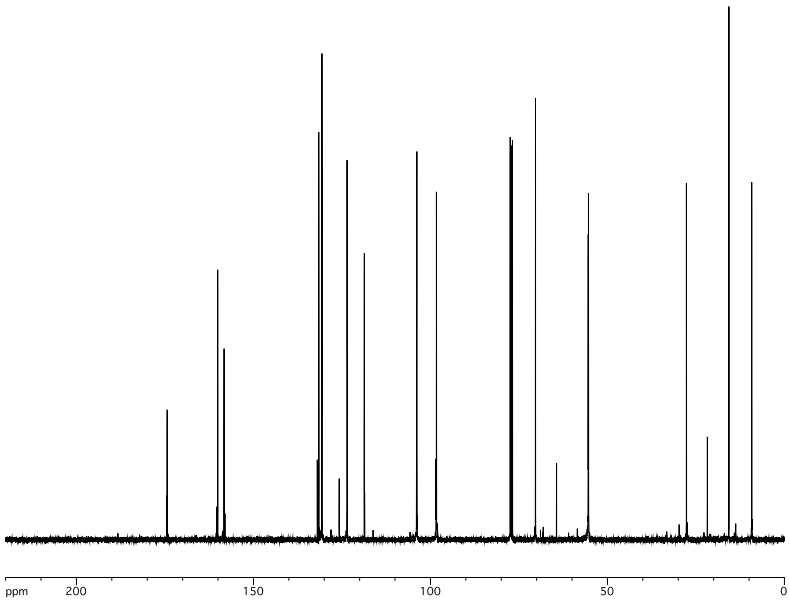


Figure A.1.22 ^{13}C-NMR (101 MHz, $CDCl_3$) of Compound **134**

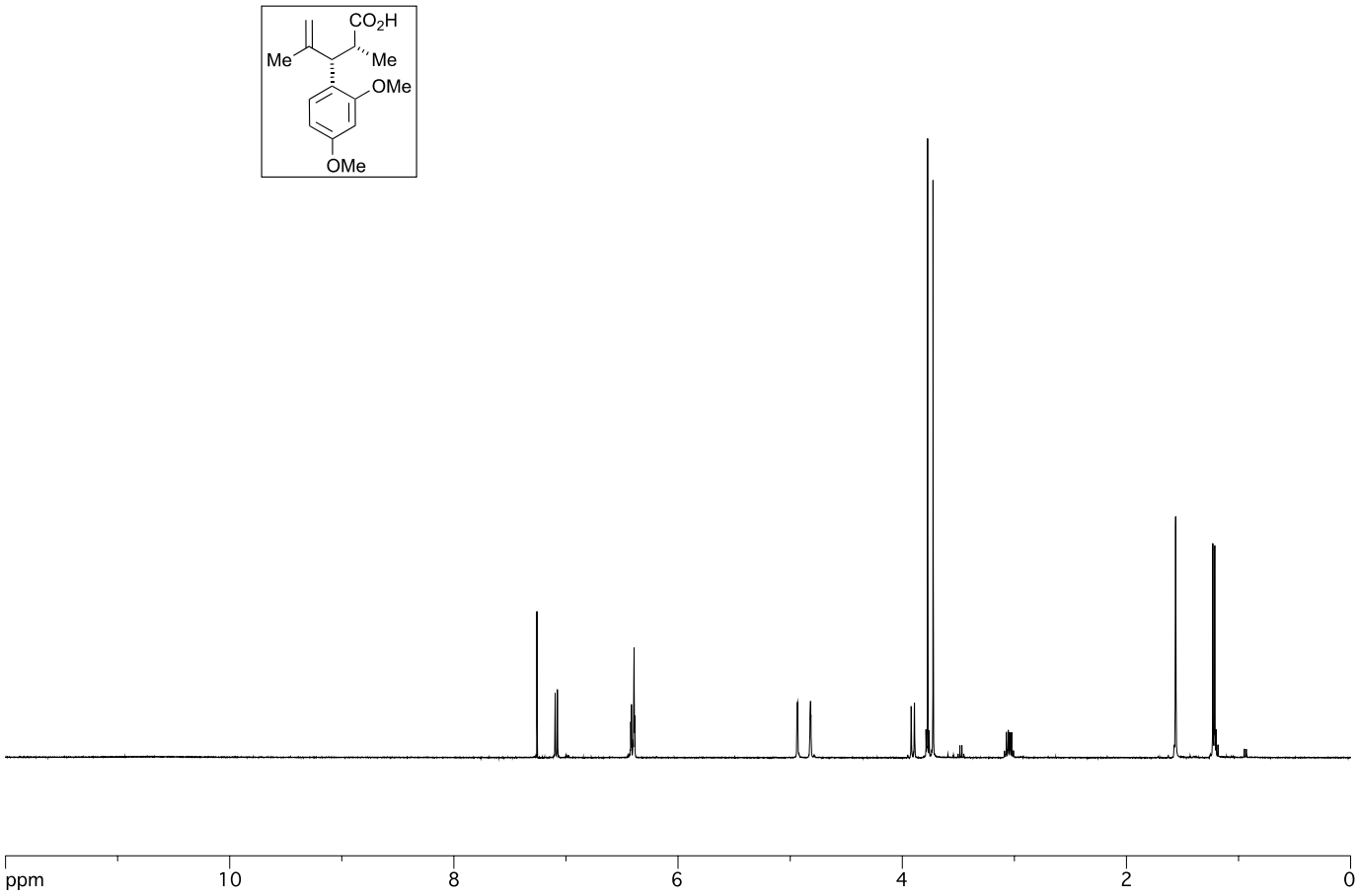


Figure A.1.23 ^{1}H-NMR (300 MHz, $CDCl_3$) of Compound **135**

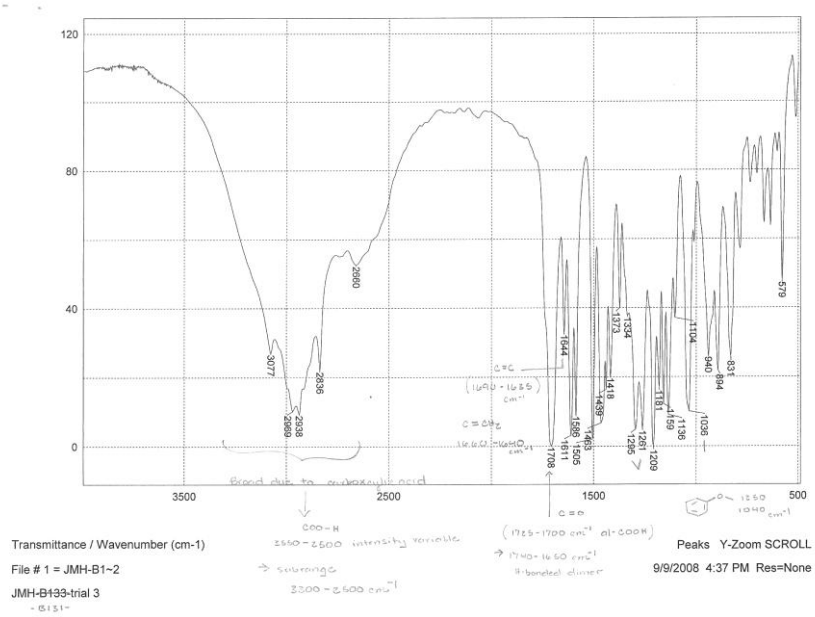


Figure A.1.24 FTIR (thin film/NaCl) Spectrum of Compound **135**

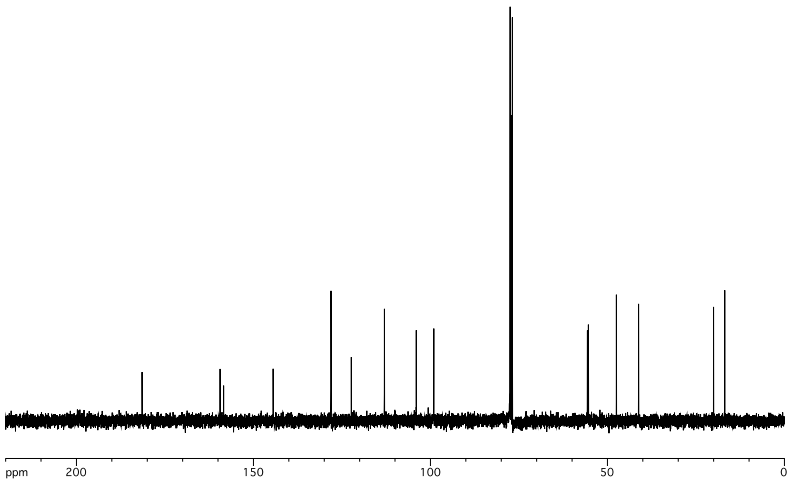


Figure A.1.25 ^{13}C-NMR (101 MHz, $CDCl_3$) of Compound **135**

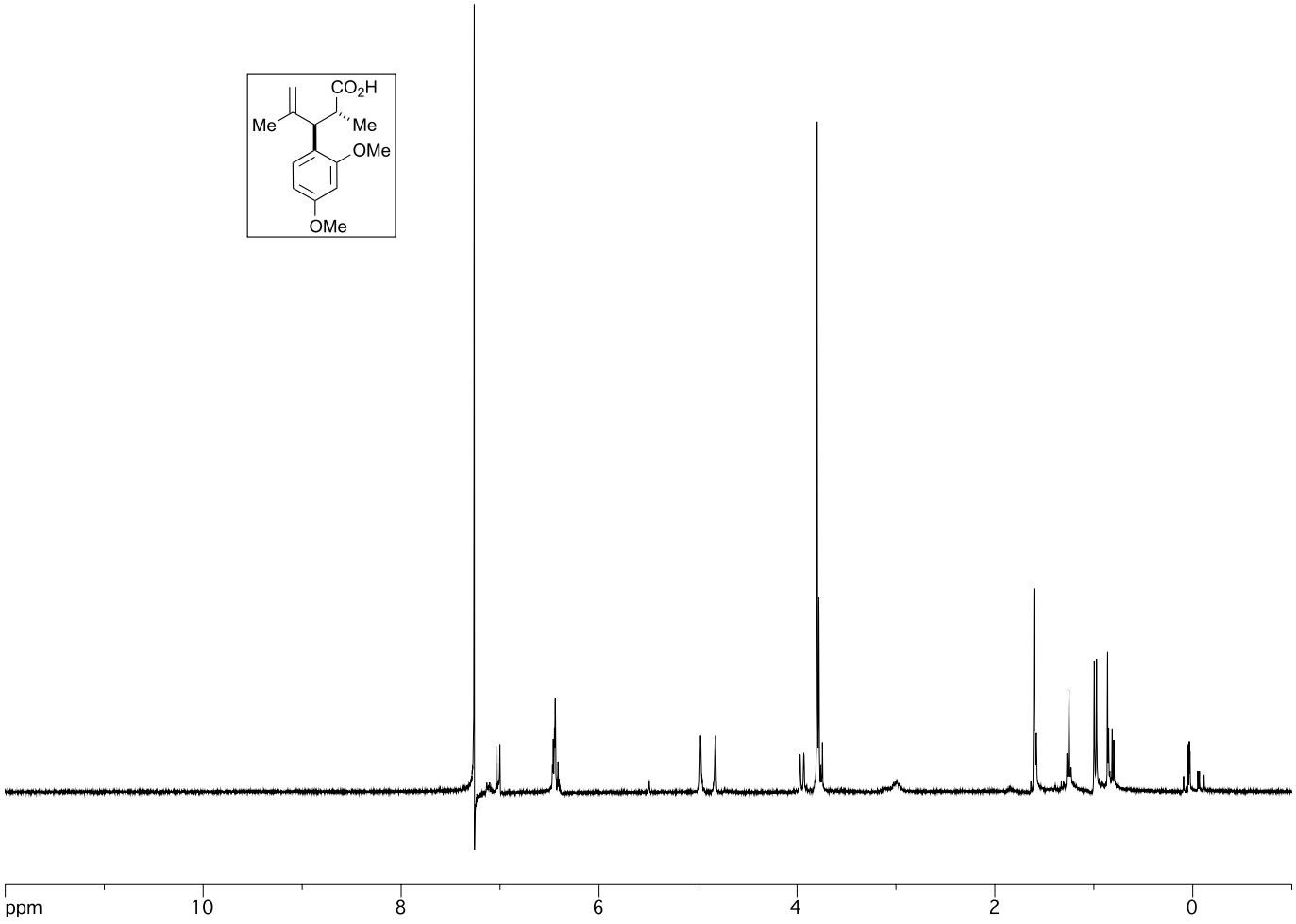


Figure A.1.26 ^{1}H-NMR (300 MHz, $CDCl_3$) of Compound **136**

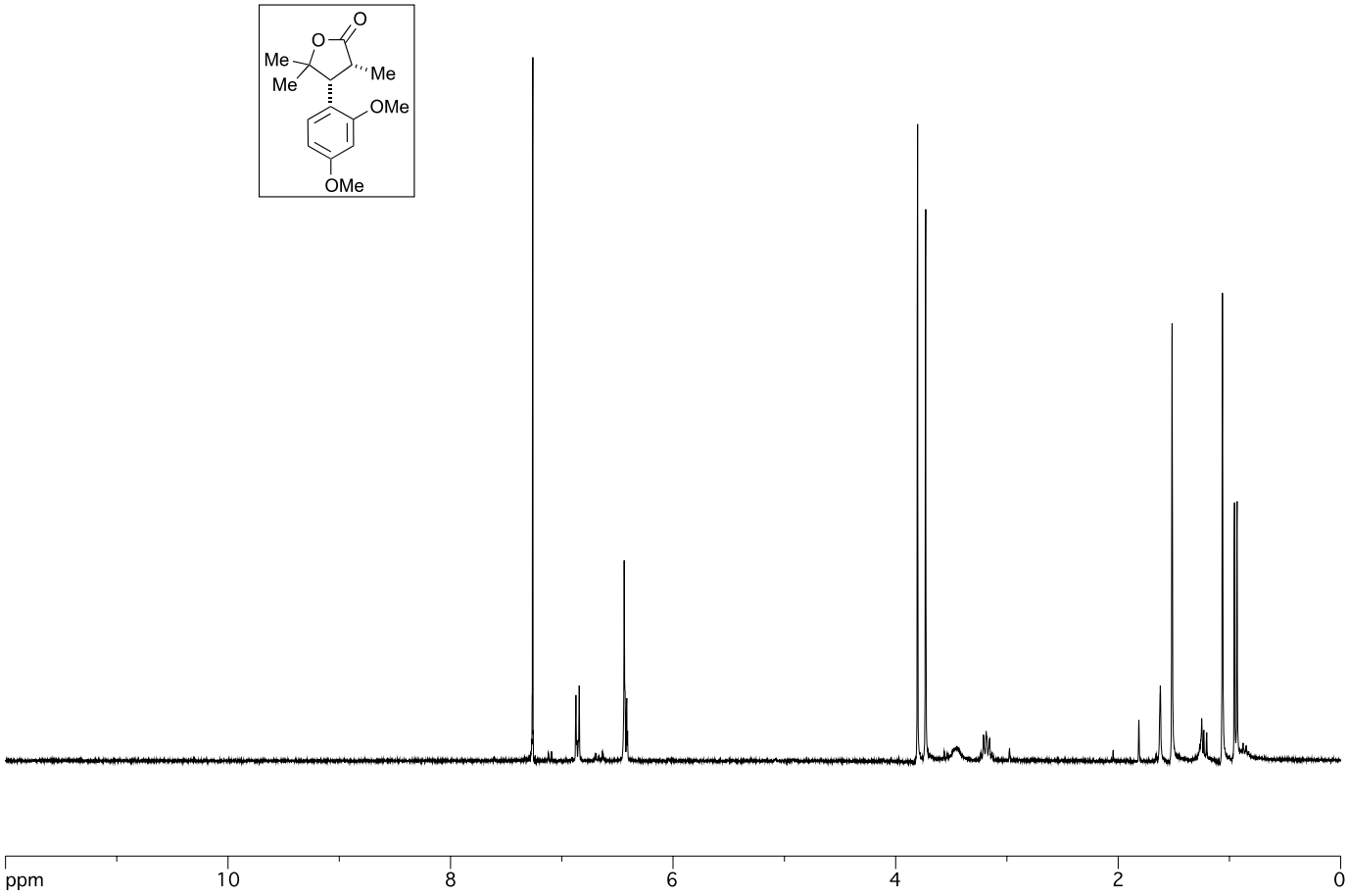


Figure A.1.27 ^{1}H-NMR (300 MHz, $CDCl_3$) of Compound **141**

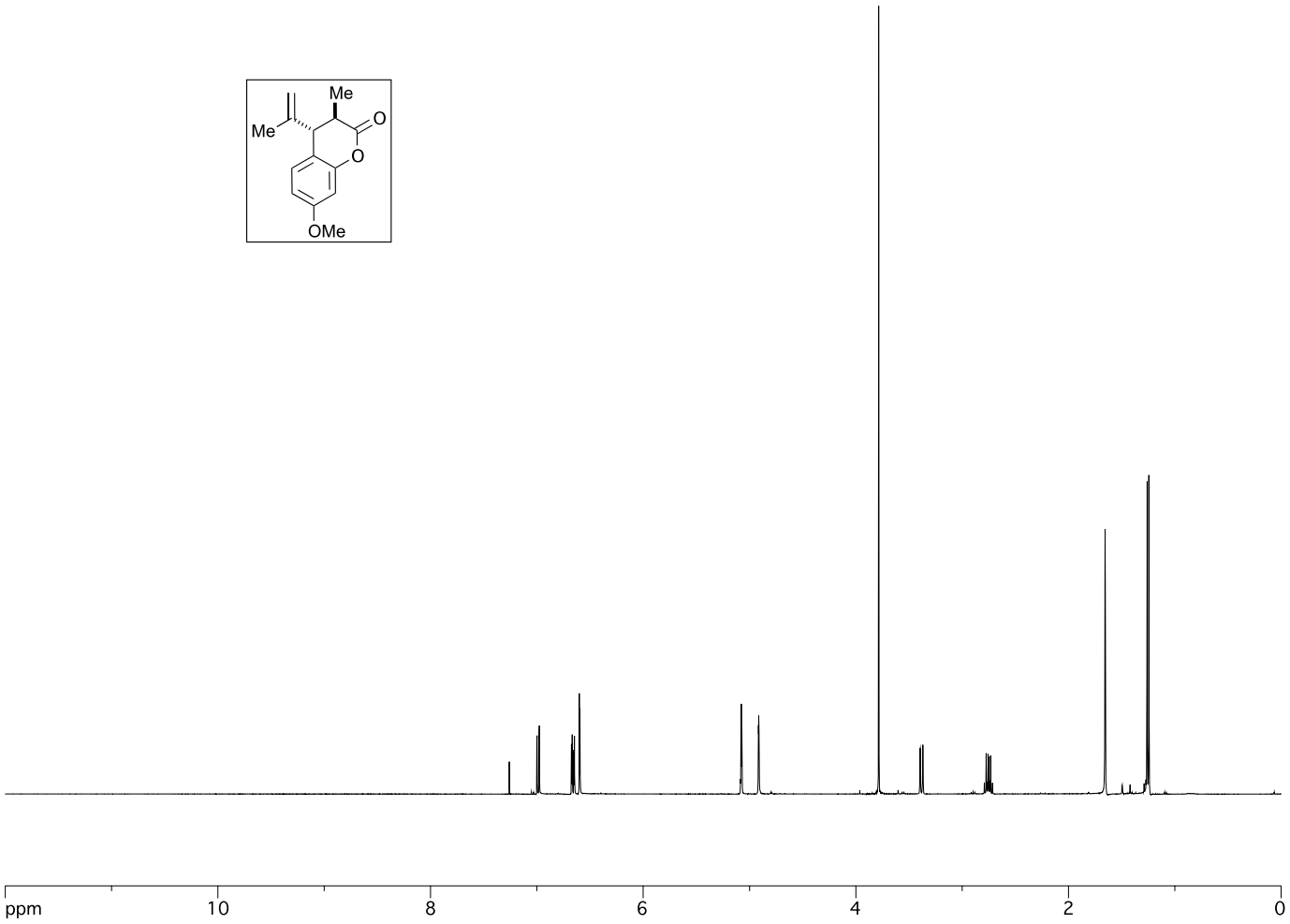


Figure A.1.28 ^{1}H-NMR (400 MHz; $CDCl_3$) of Compound **143**

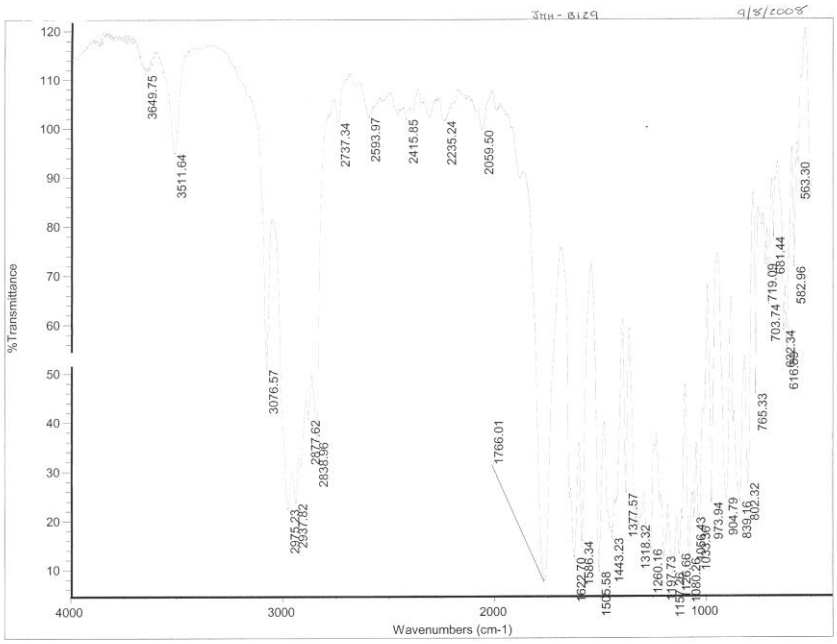


Figure A.1.29 FTIR (thin film/NaCl) Spectrum of Compound **143**

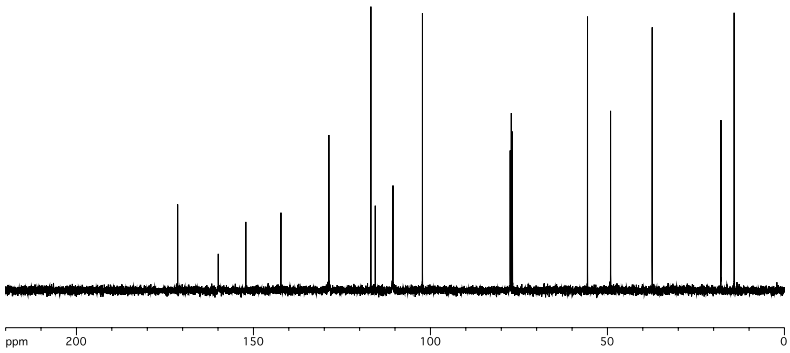


Figure A.1.30 ^{13}C-NMR (101 MHz, $CDCl_3$) of Compound **143**

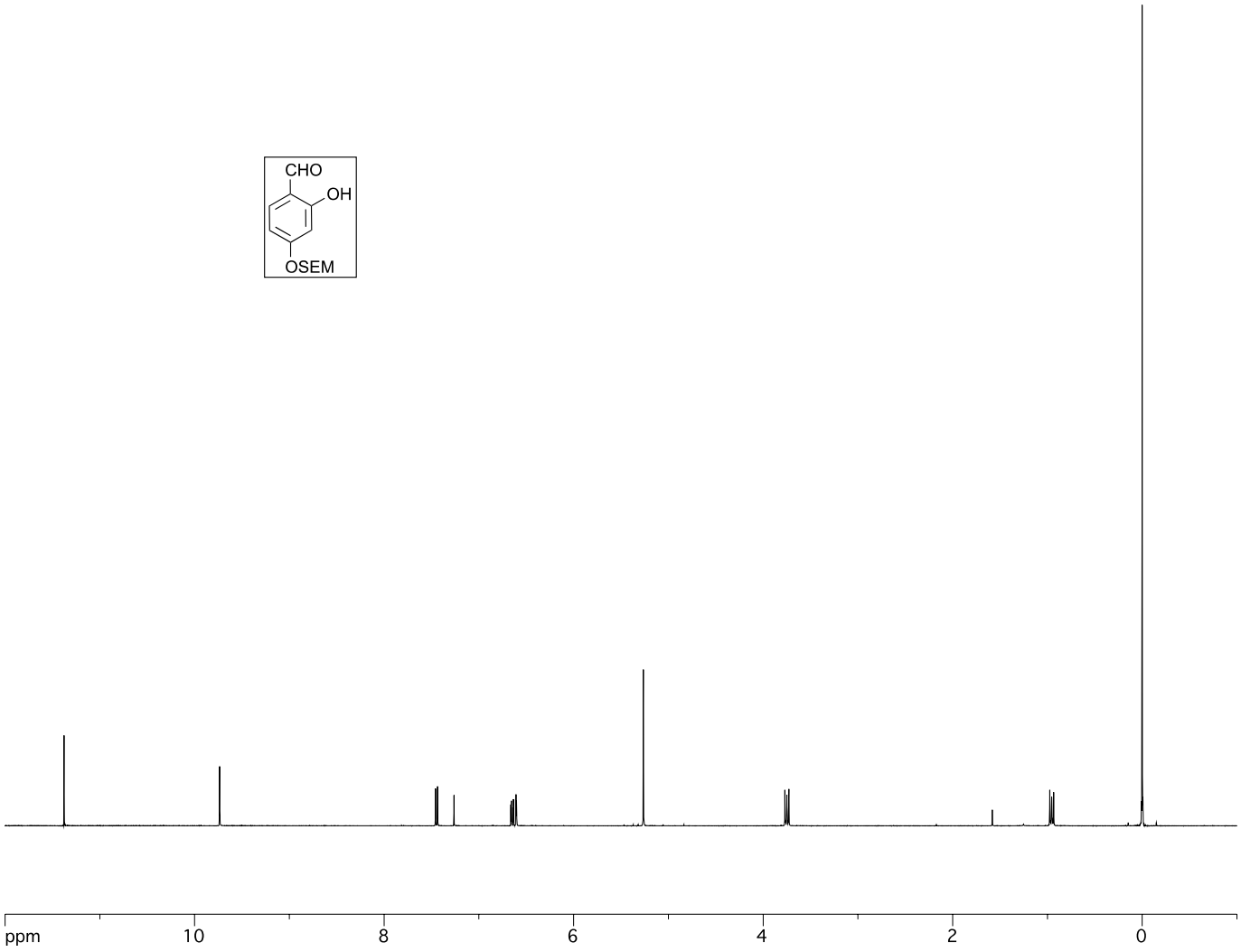


Figure A.1.31 ^{1}H-NMR (400 MHz; $CDCl_3$) of Compound **145**

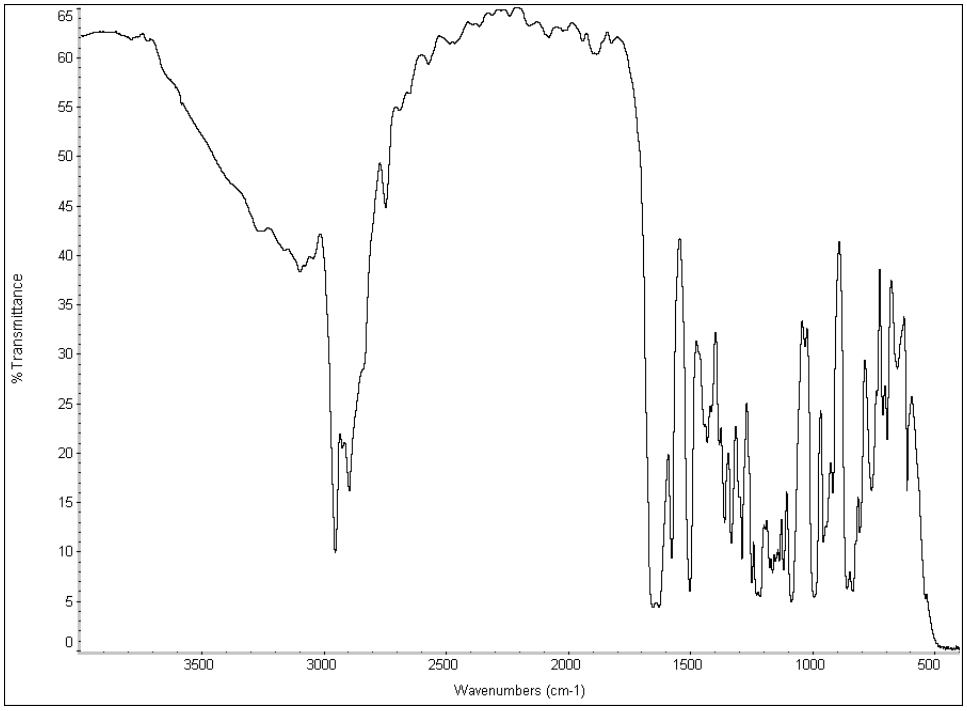


Figure A.1.32 FTIR (thin film/NaCl) of Compound **145**

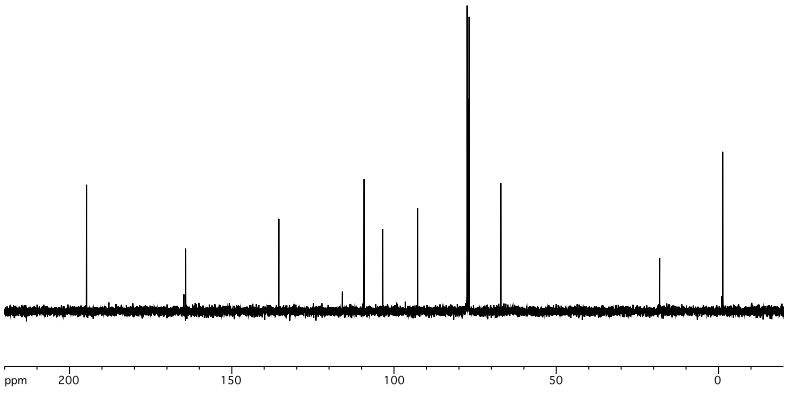


Figure A.1.33 ^{13}C-NMR (101 MHz, $CDCl_3$) of Compound **145**

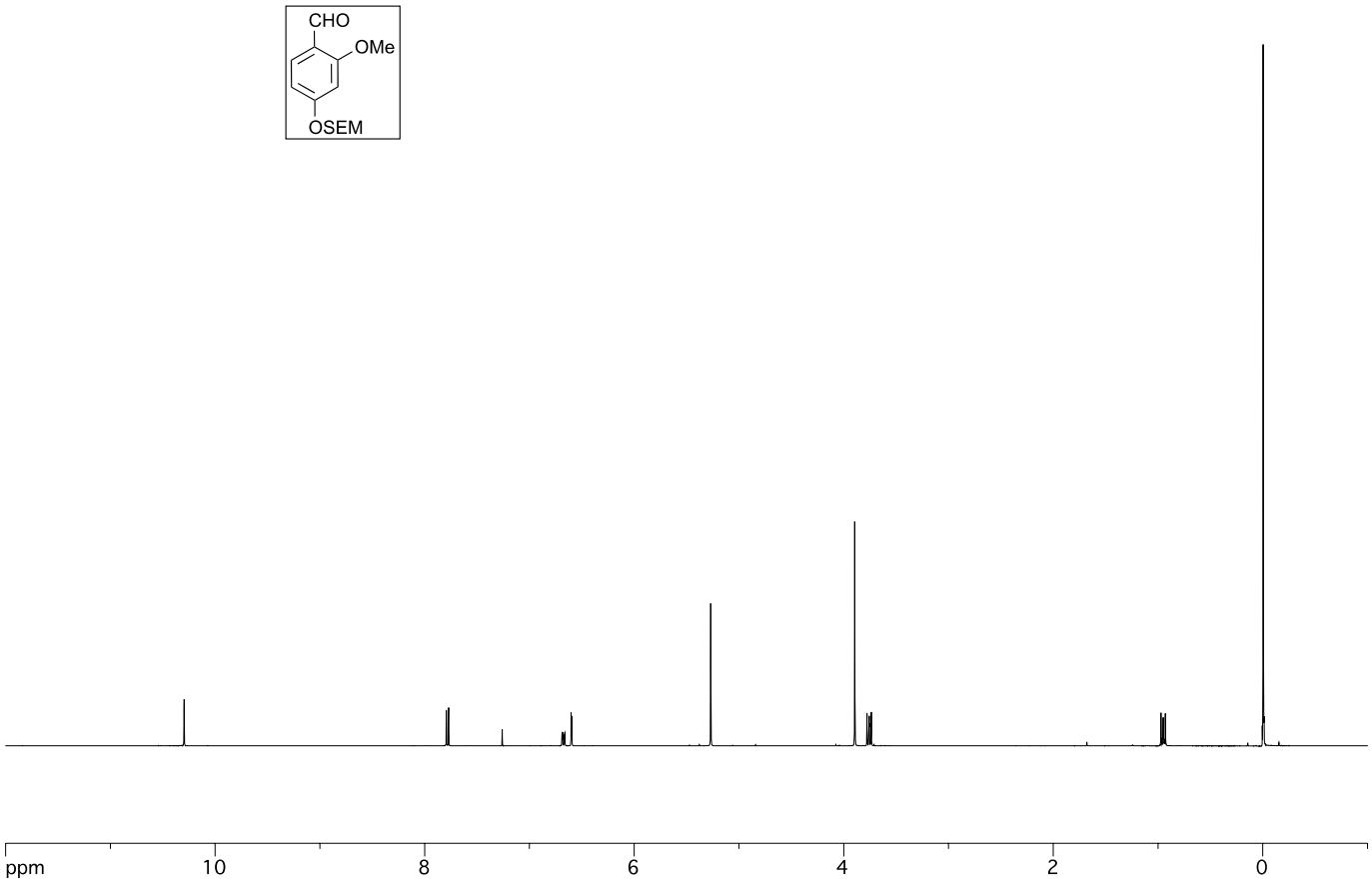


Figure A.1.34 ^{1}H-NMR (400 MHz; $CDCl_3$) of Compound **146**

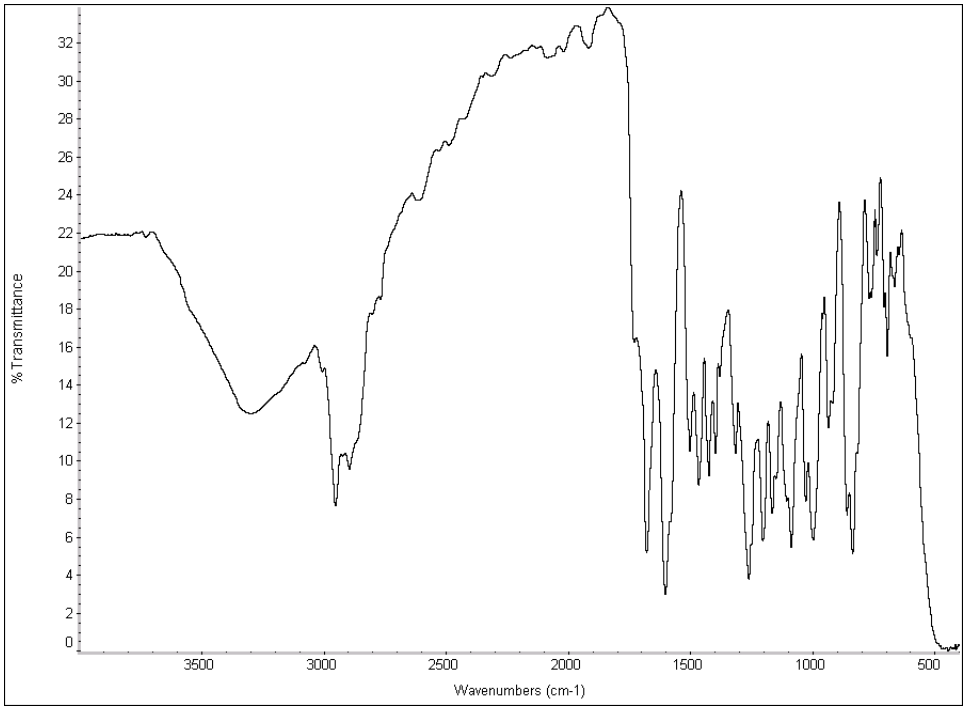


Figure A.1.35 FTIR (thin film/NaCl) of Compound **146**

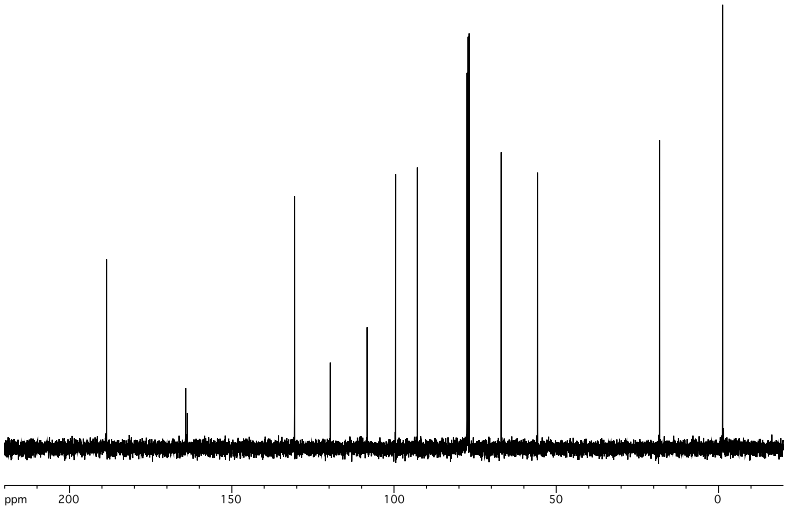


Figure A.1.36 ^{13}C-NMR (101 MHz, $CDCl_3$) of Compound **146**

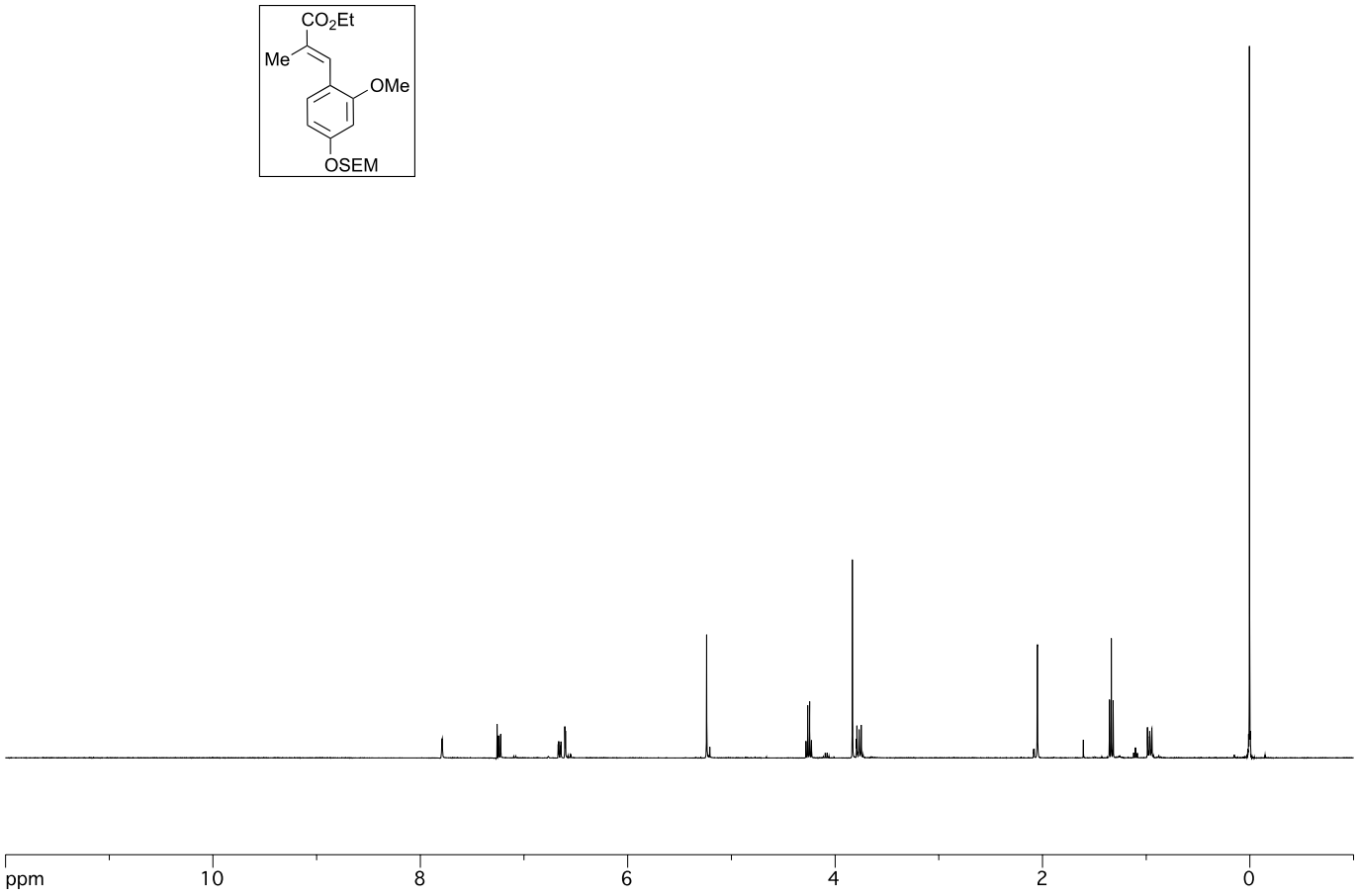


Figure A.1.37 ^{1}H-NMR (400 MHz; $CDCl_3$) of Compound **147**

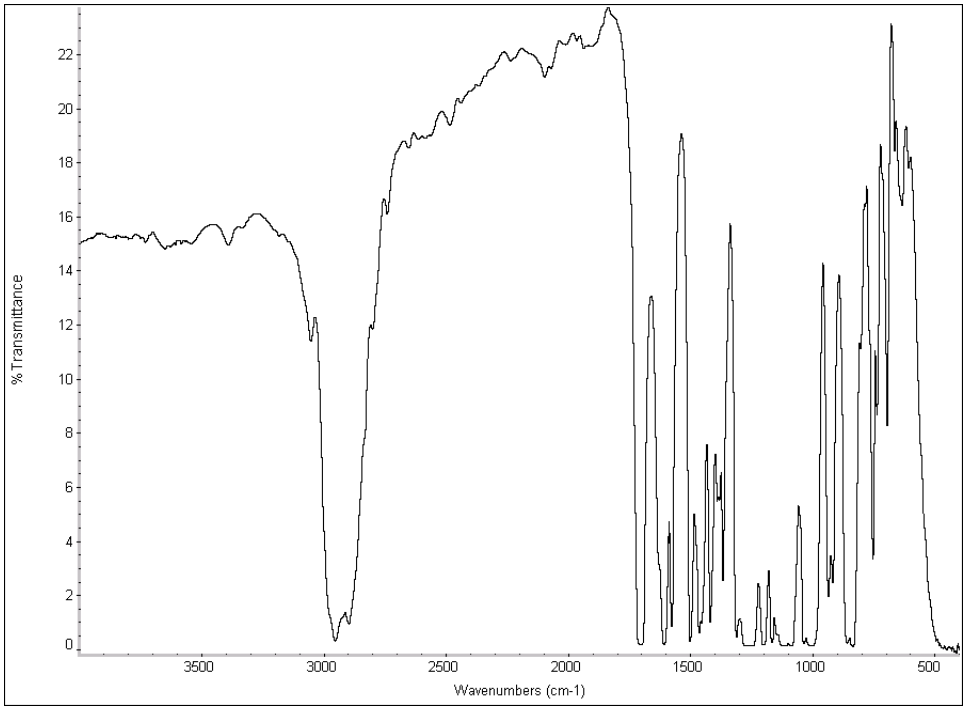


Figure A.1.38 FTIR (thin film/NaCl) of Compound **147**

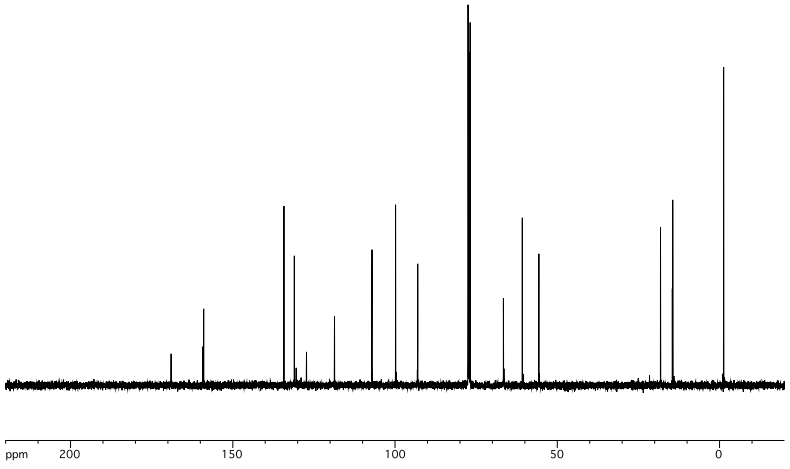


Figure A.1.39 ^{13}C-NMR (101 MHz, $CDCl_3$) of Compound **147**

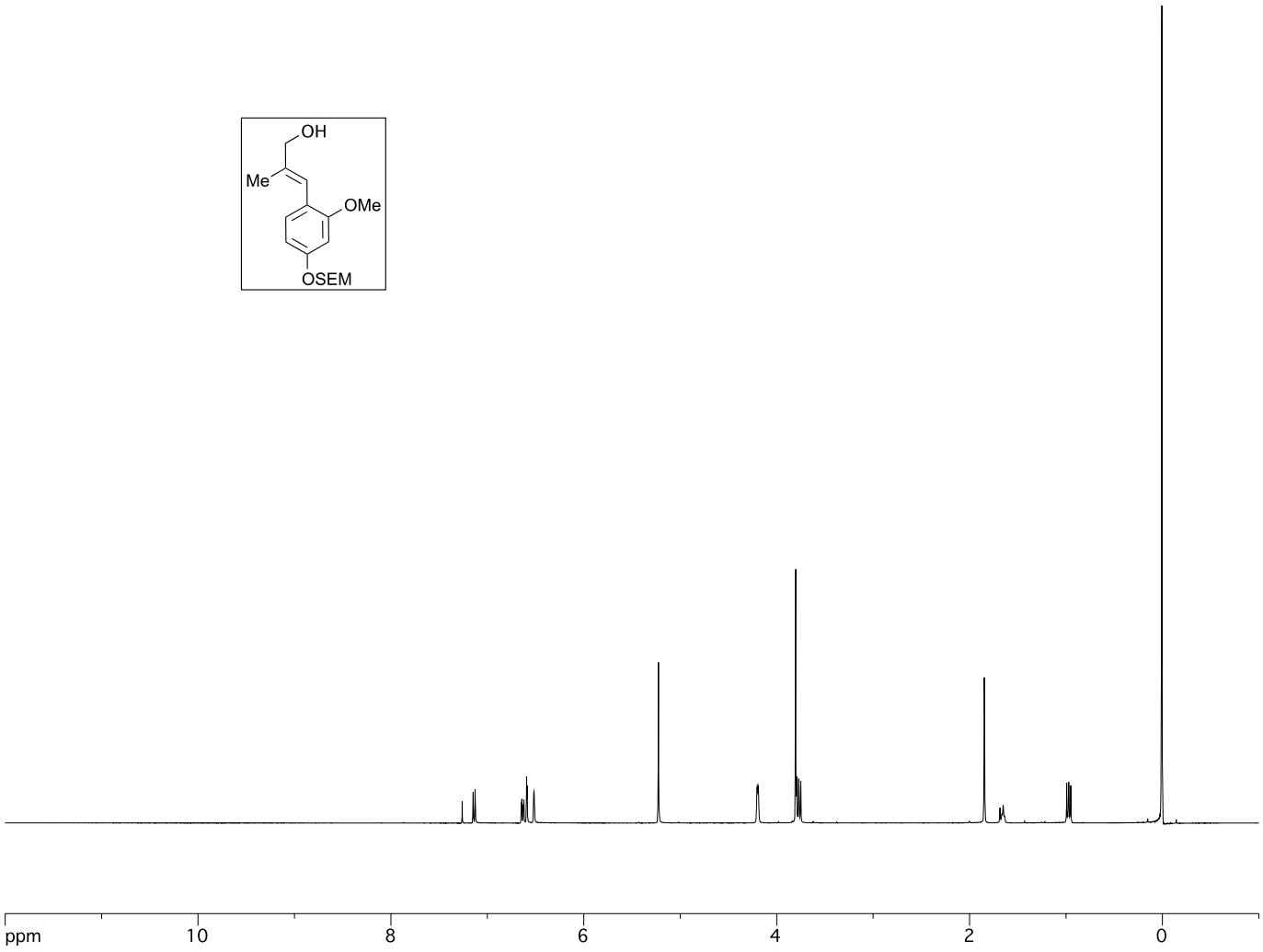


Figure A.1.40 ^{1}H-NMR (400 MHz; $CDCl_3$) of Compound **148**

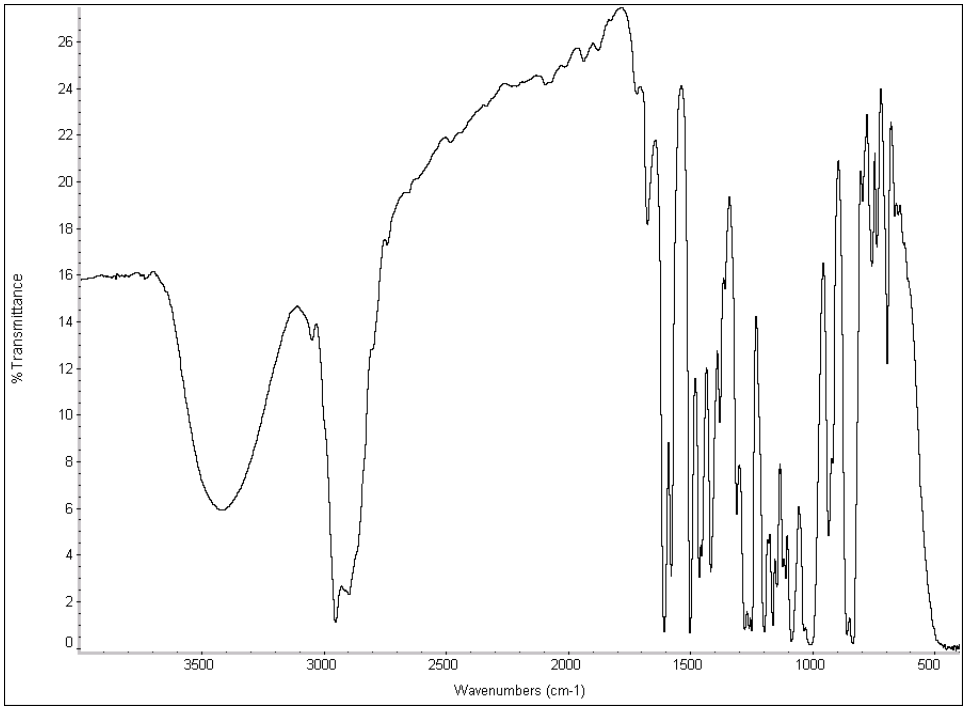


Figure A.1.41 FTIR (thin film/NaCl) of Compound **148**

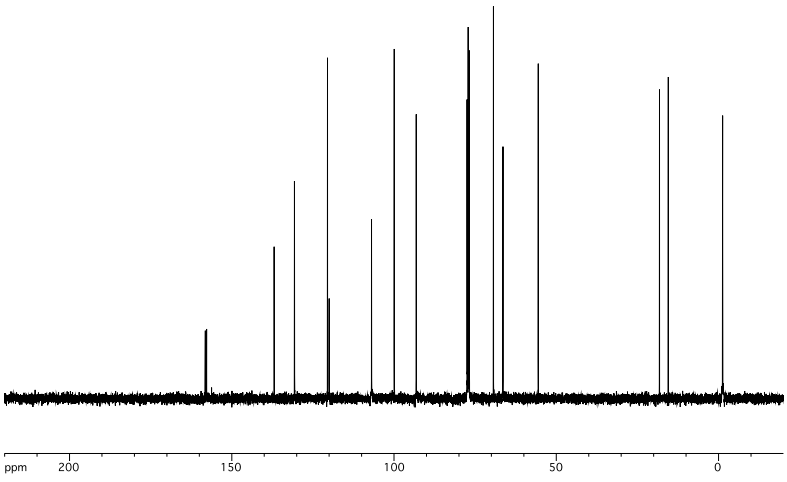


Figure A.1.42 ^{13}C-NMR (101 MHz, $CDCl_3$) of Compound **148**

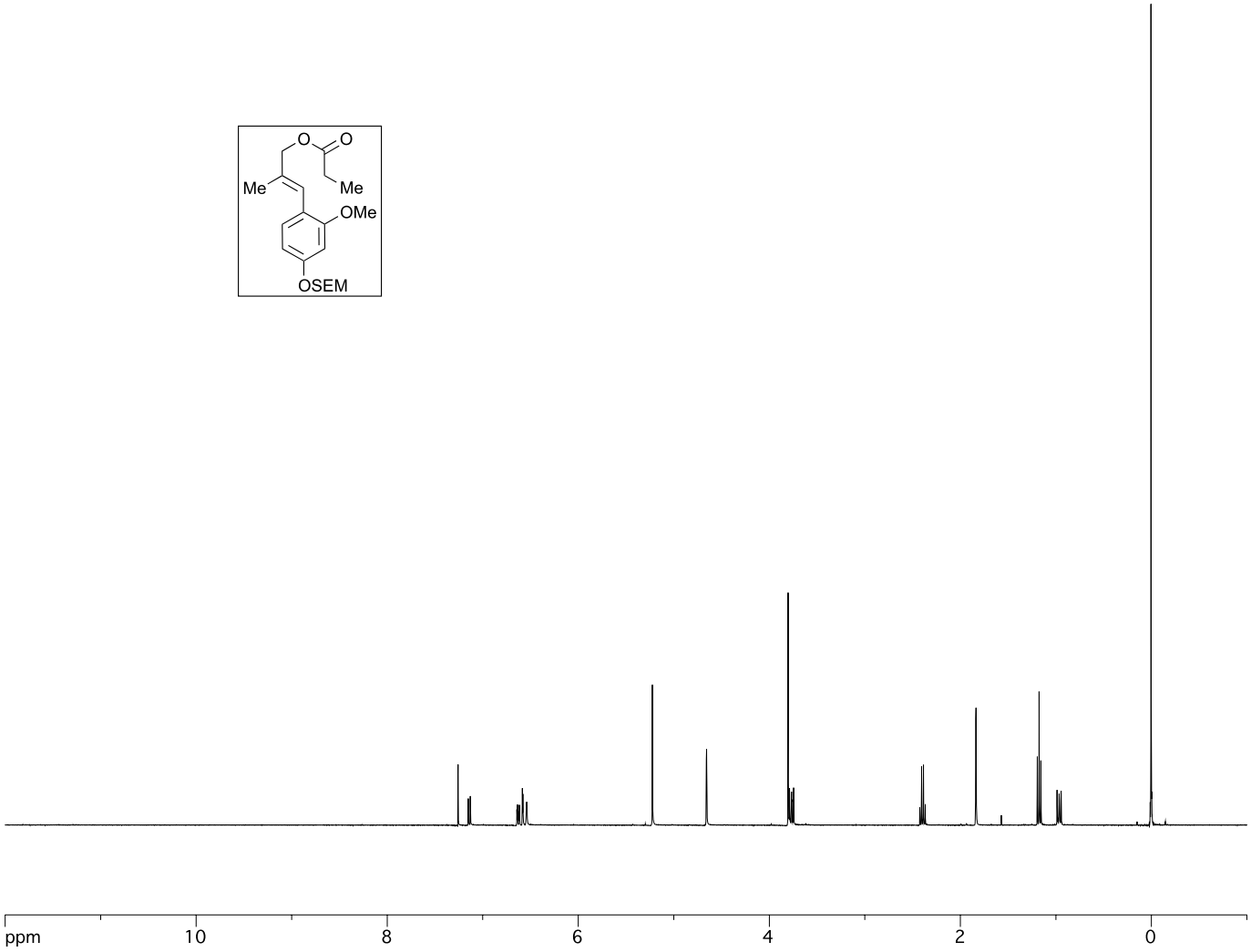


Figure A.1.43 ^{1}H-NMR (400 MHz; $CDCl_3$) of Compound **149**

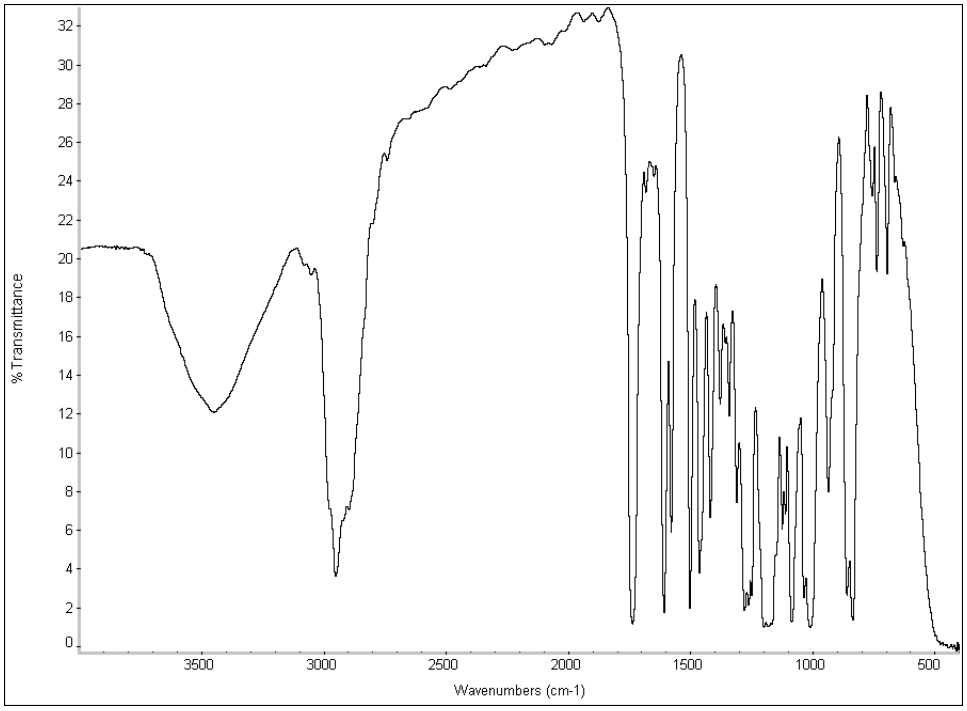


Figure A.1.44 FTIR (thin film/NaCl) of Compound **149**

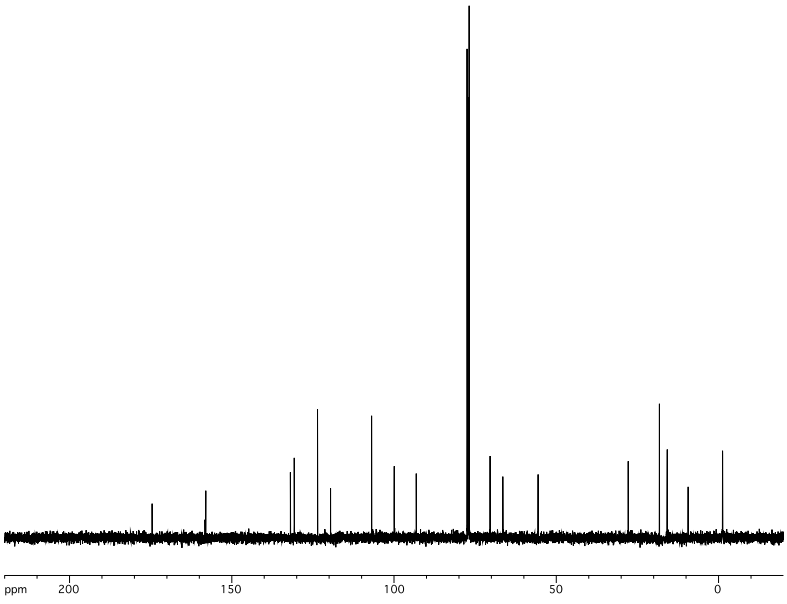


Figure A.1.45 ^{13}C-NMR (101 MHz, $CDCl_3$) of Compound **149**

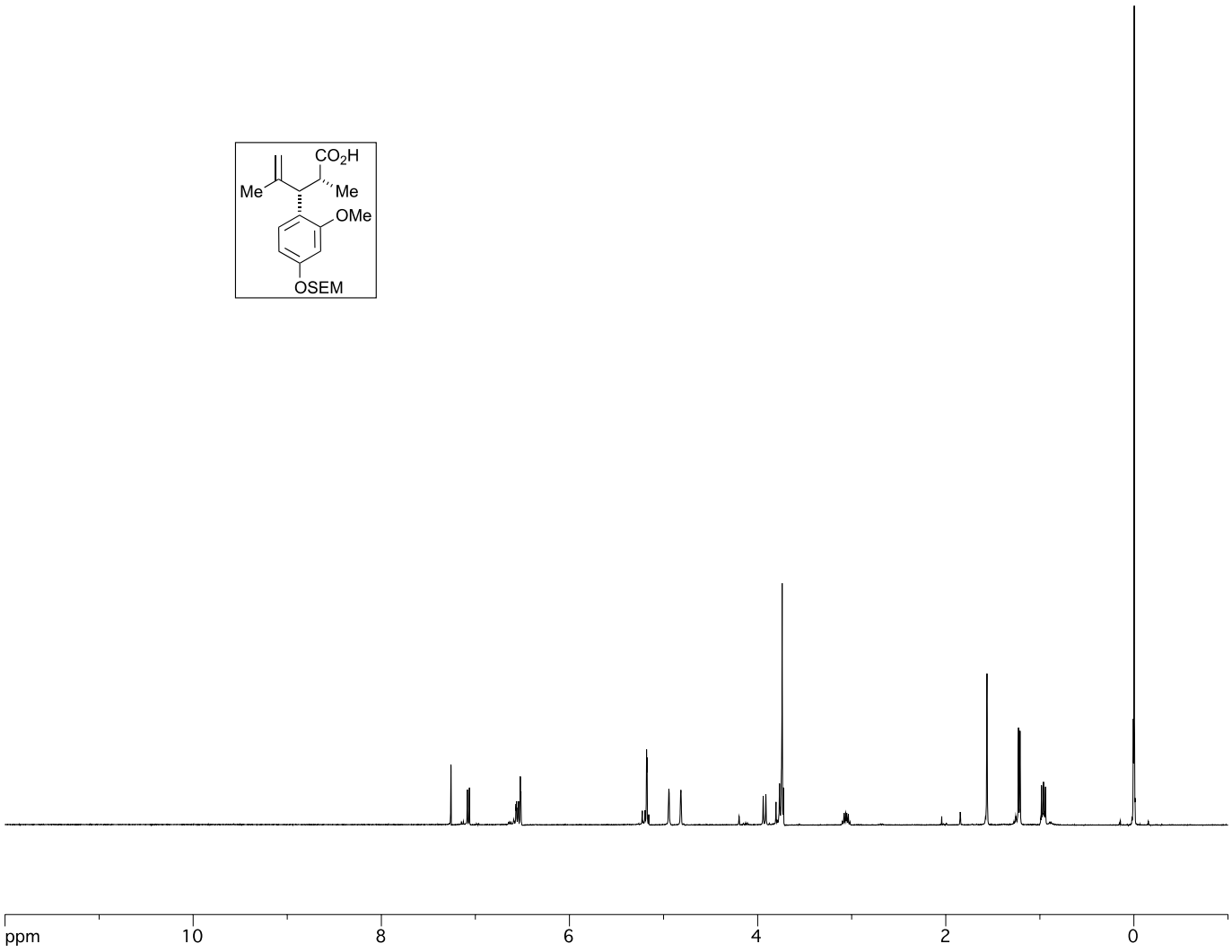


Figure A.1.46 ^{1}H-NMR (400 MHz; $CDCl_3$) of Compound **150**

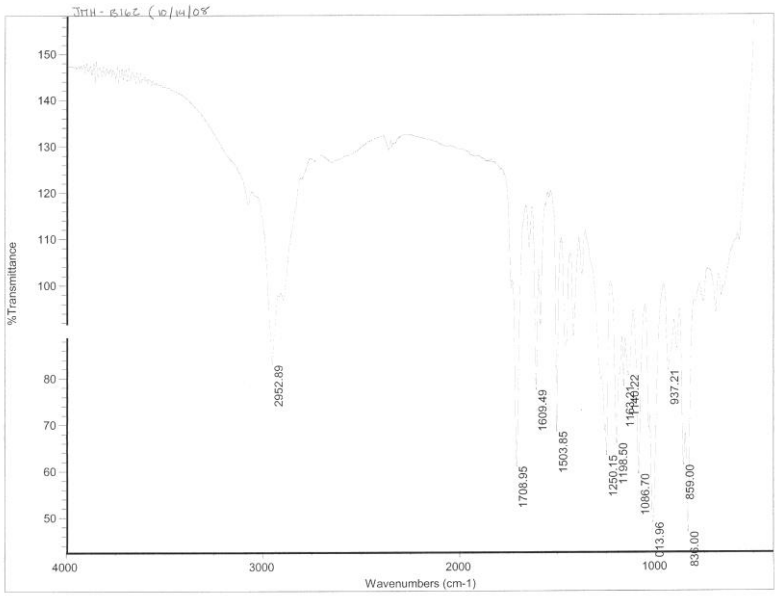


Figure A.1.47 FTIR (thin film/NaCl) Spectrum of Compound **150**

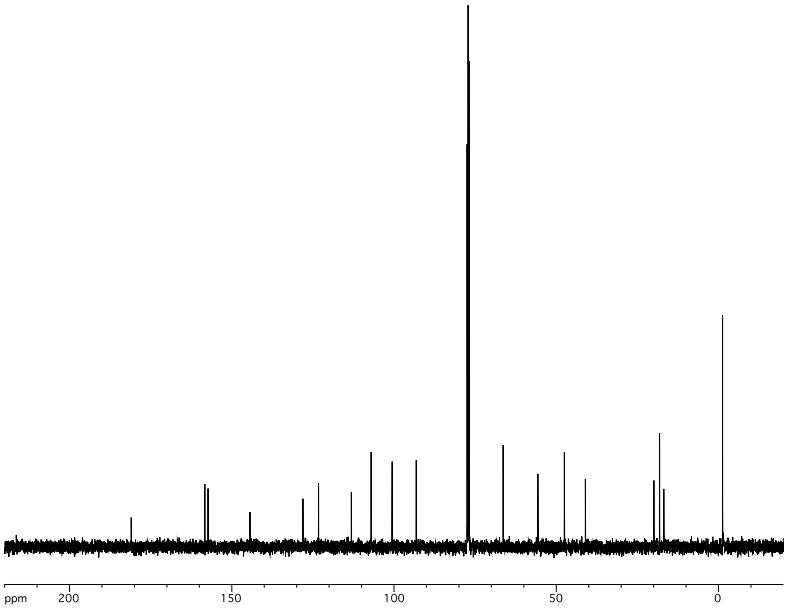


Figure A.1.48 ^{13}C-NMR (101 MHz, $CDCl_3$) of Compound **150**

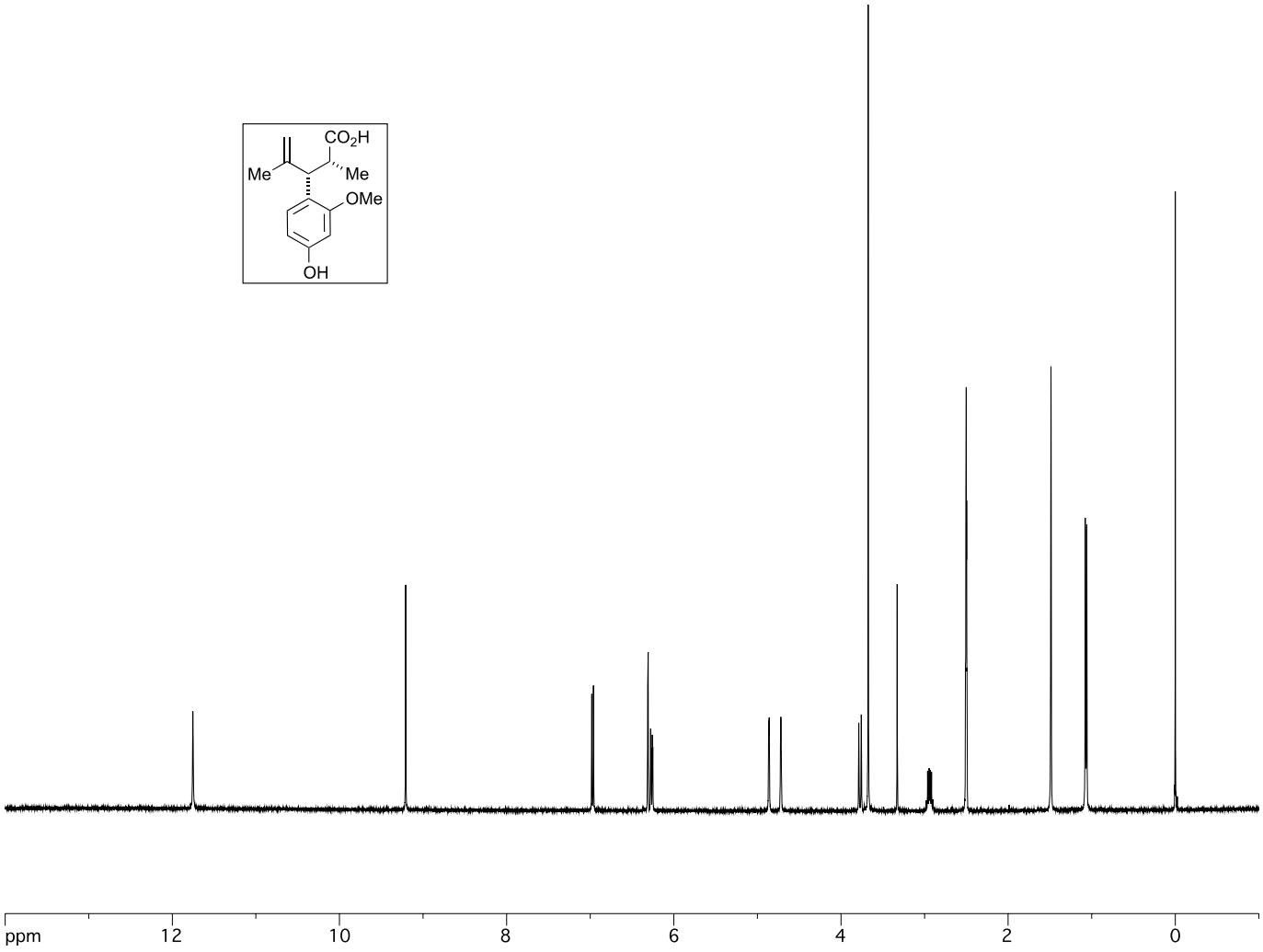


Figure A.1.49 ^{1}H-NMR (400 MHz; DMSO-d_6) of Compound **142**

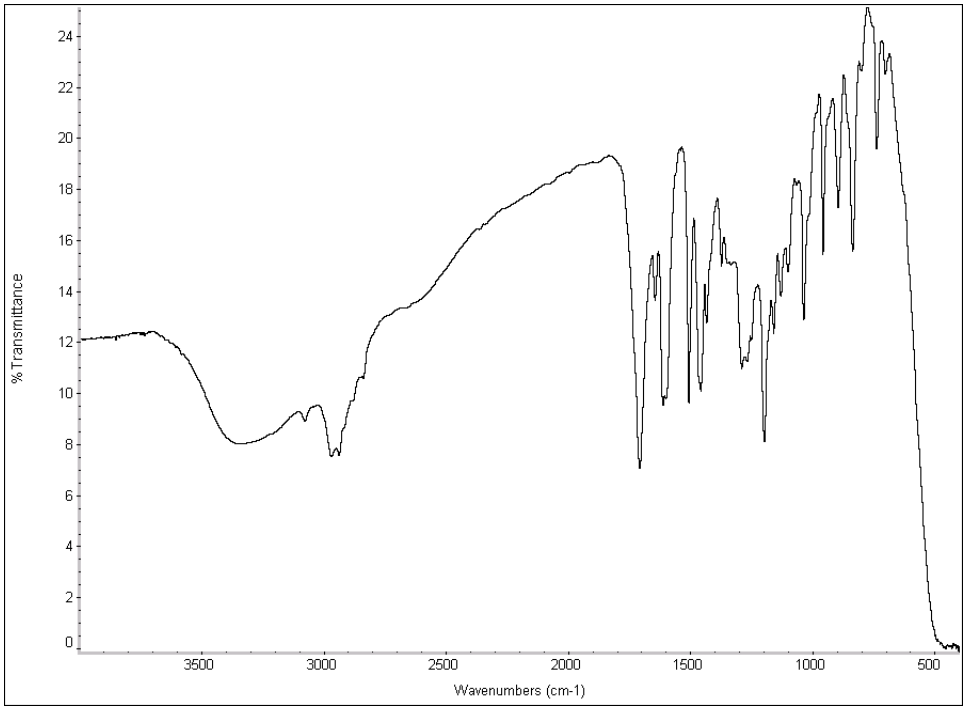


Figure A.1.50 FTIR (thin film/NaCl) of Compound **142**

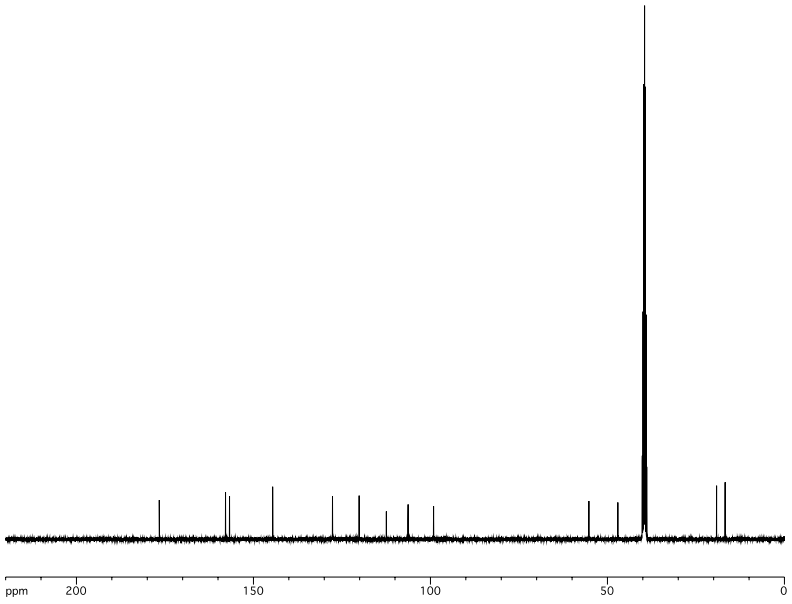


Figure A.1.51 ^{13}C-NMR (101 MHz, $CDCl_3$) of Compound **142**

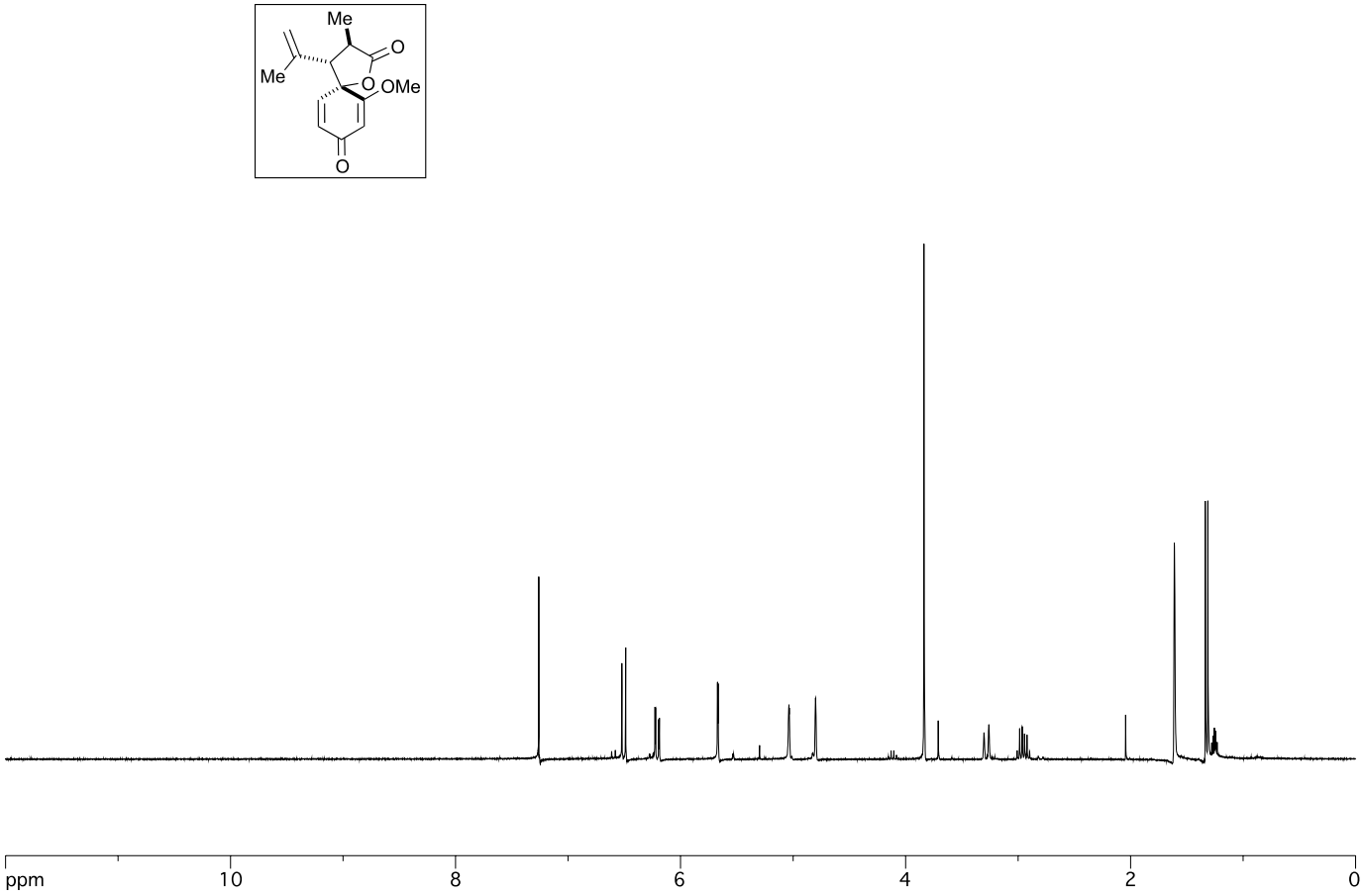


Figure A.1.52 ^{1}H-NMR (300 MHz; $CDCl_3$) of Compound **157**

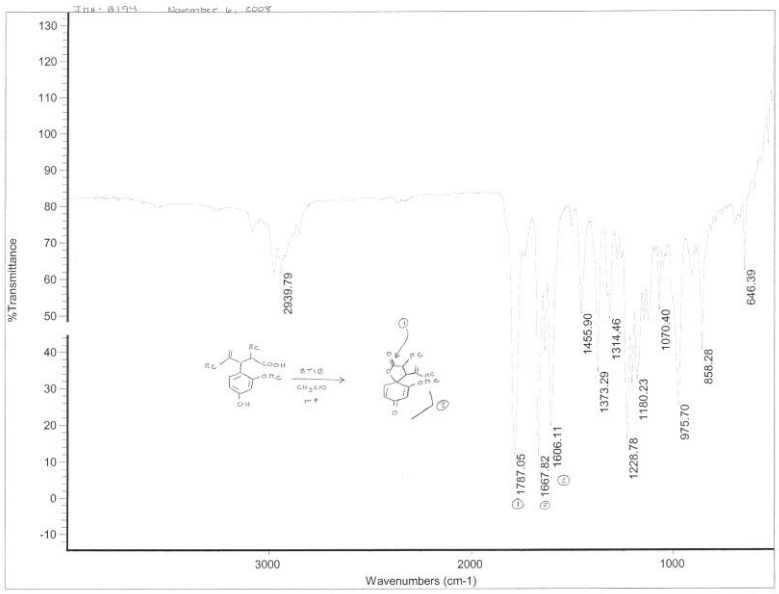


Figure A.1.53 FTIR (thin film/NaCl) Spectrum of Compound **157**

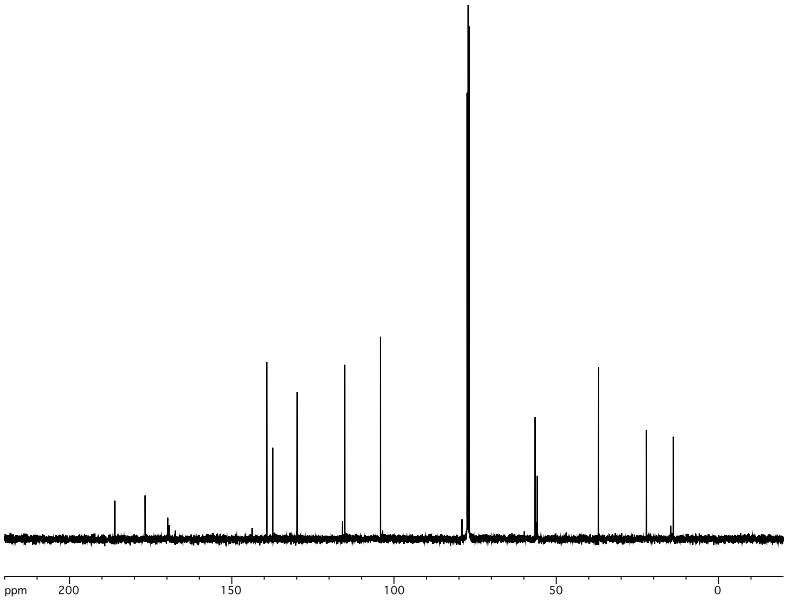


Figure A.1.54 ^{13}C-NMR (101 MHz, $CDCl_3$) of Compound **157**

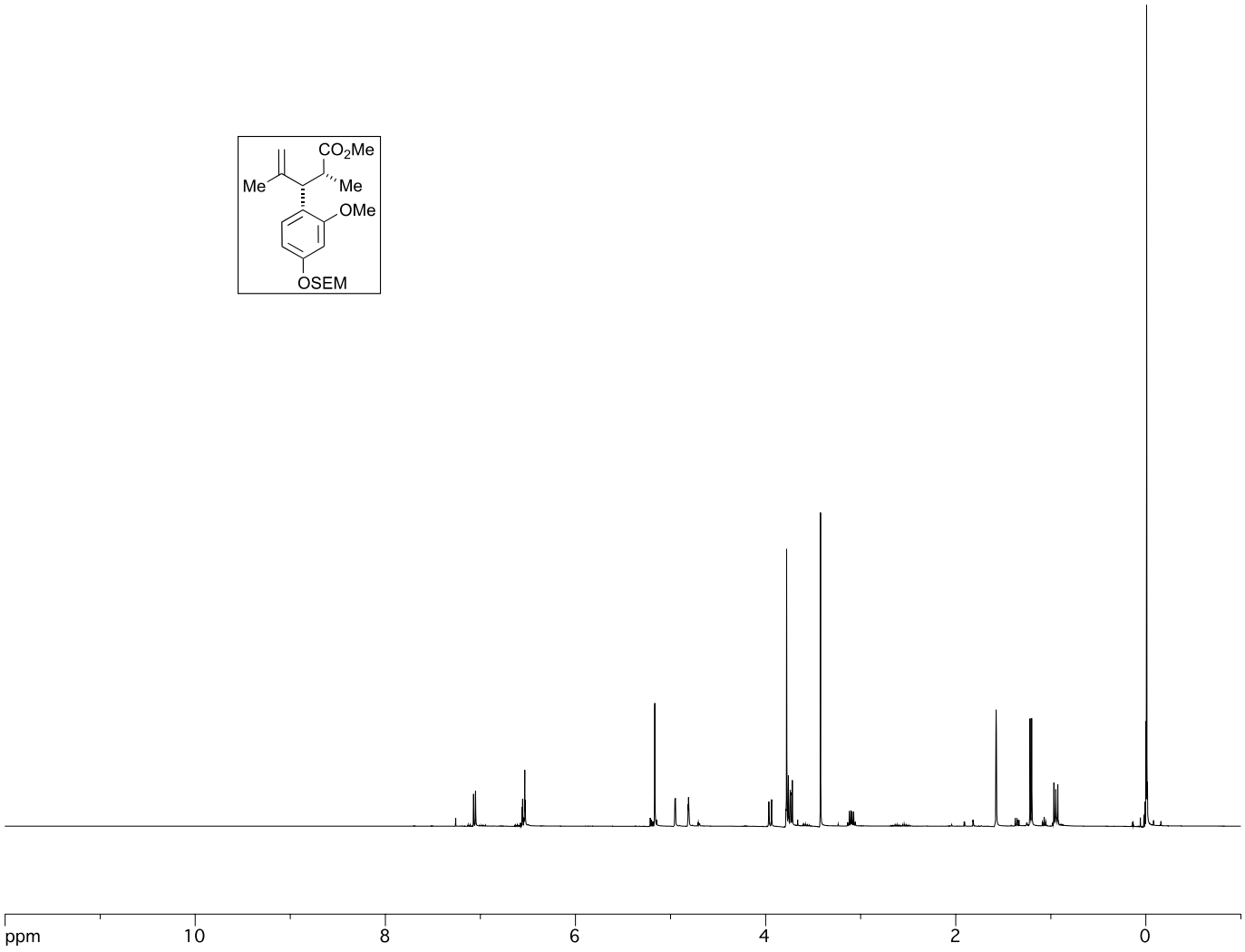


Figure A.1.55 ^{1}H-NMR (400 MHz; $CDCl_3$) of Compound **158**

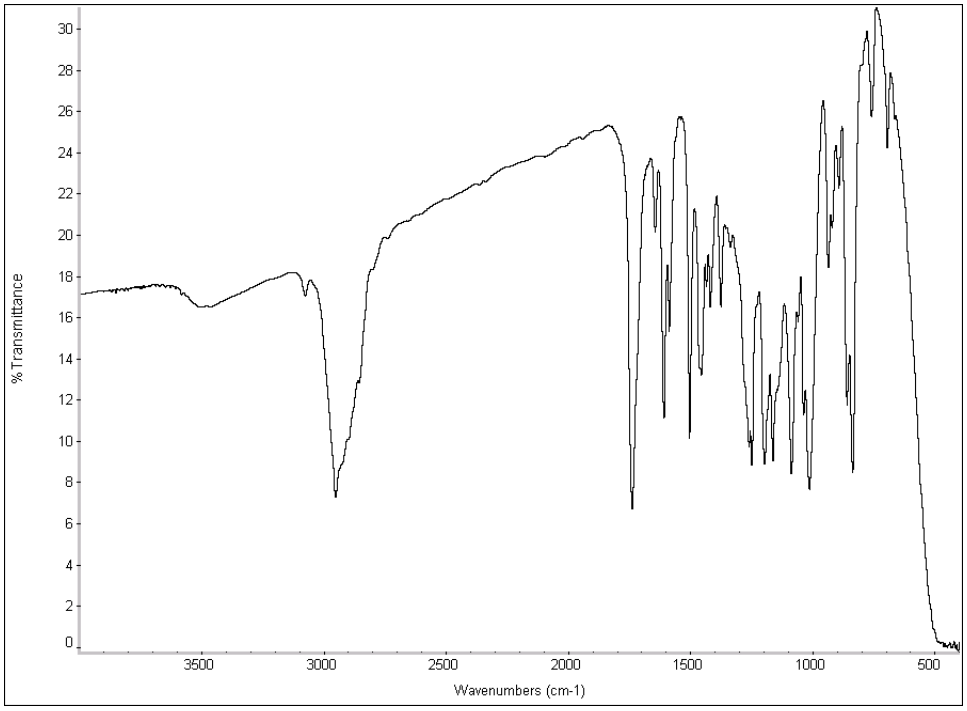


Figure A.1.56 FTIR (thin film/NaCl) of Compound **158**

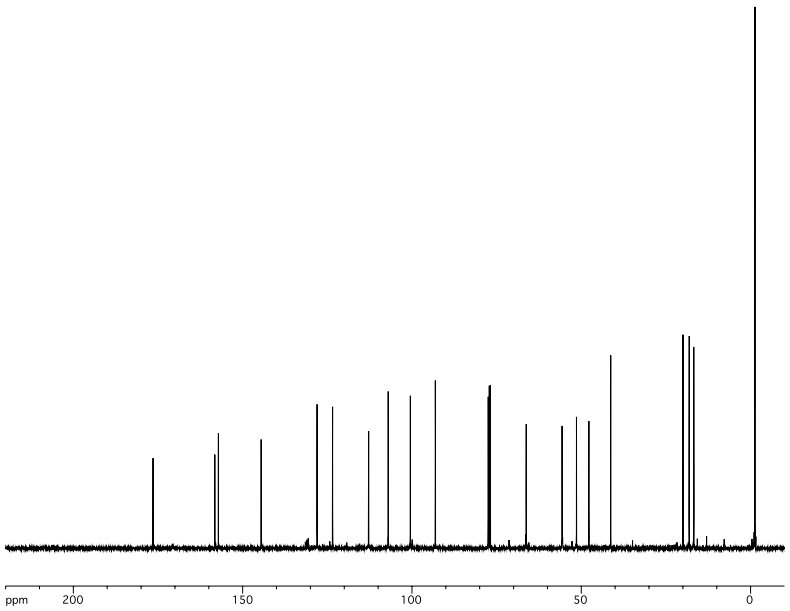


Figure A.1.57 ^{13}C-NMR (101 MHz, $CDCl_3$) of Compound **158**

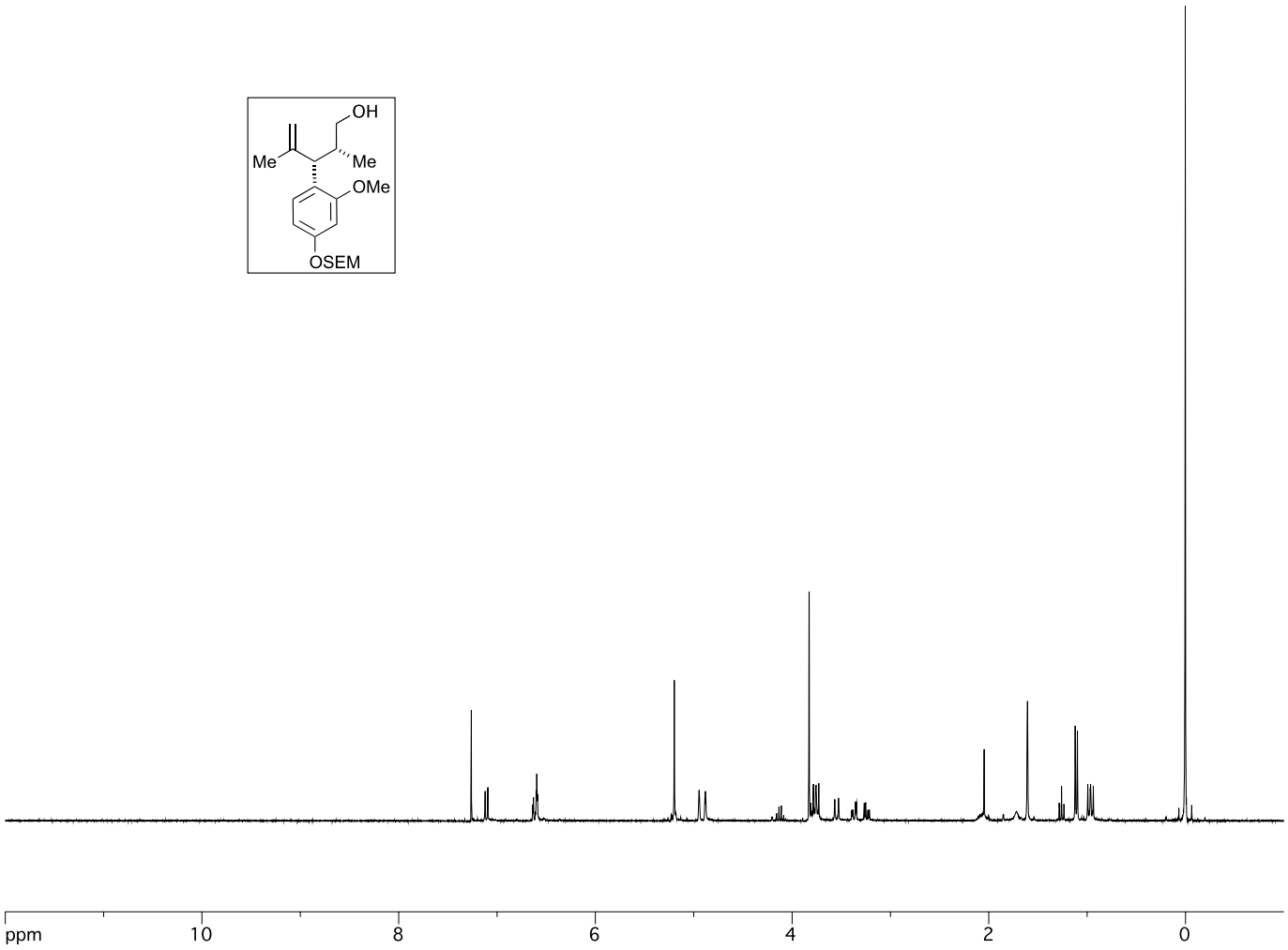


Figure A.1.58 ^{1}H-NMR (300 MHz; $CDCl_3$) of Compound **159**

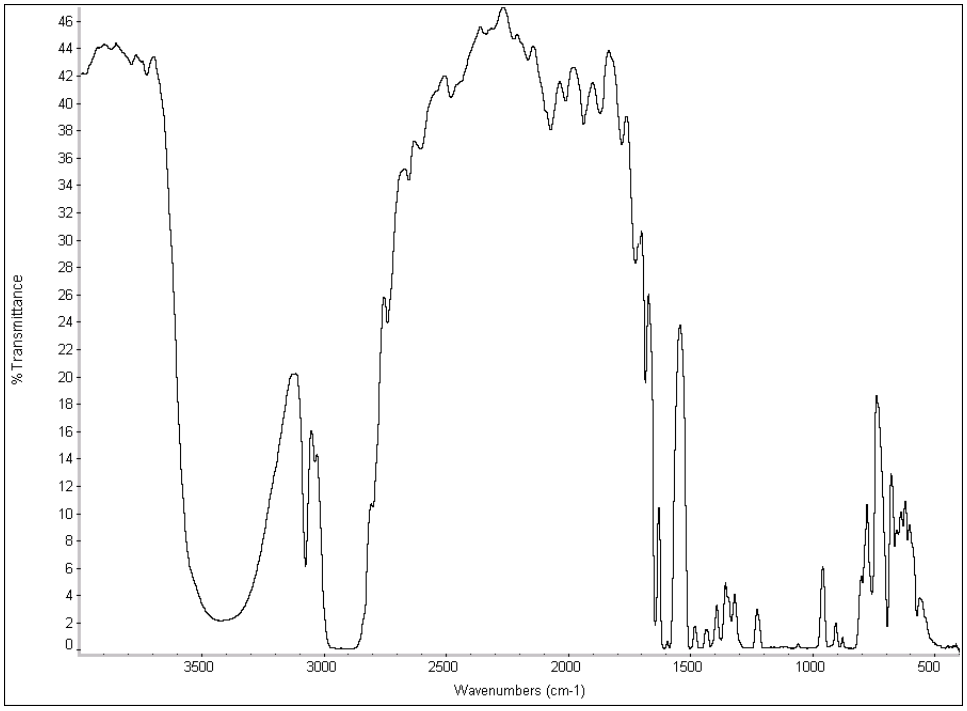


Figure A.1.59 FTIR (thin film/NaCl) of Compound **159**

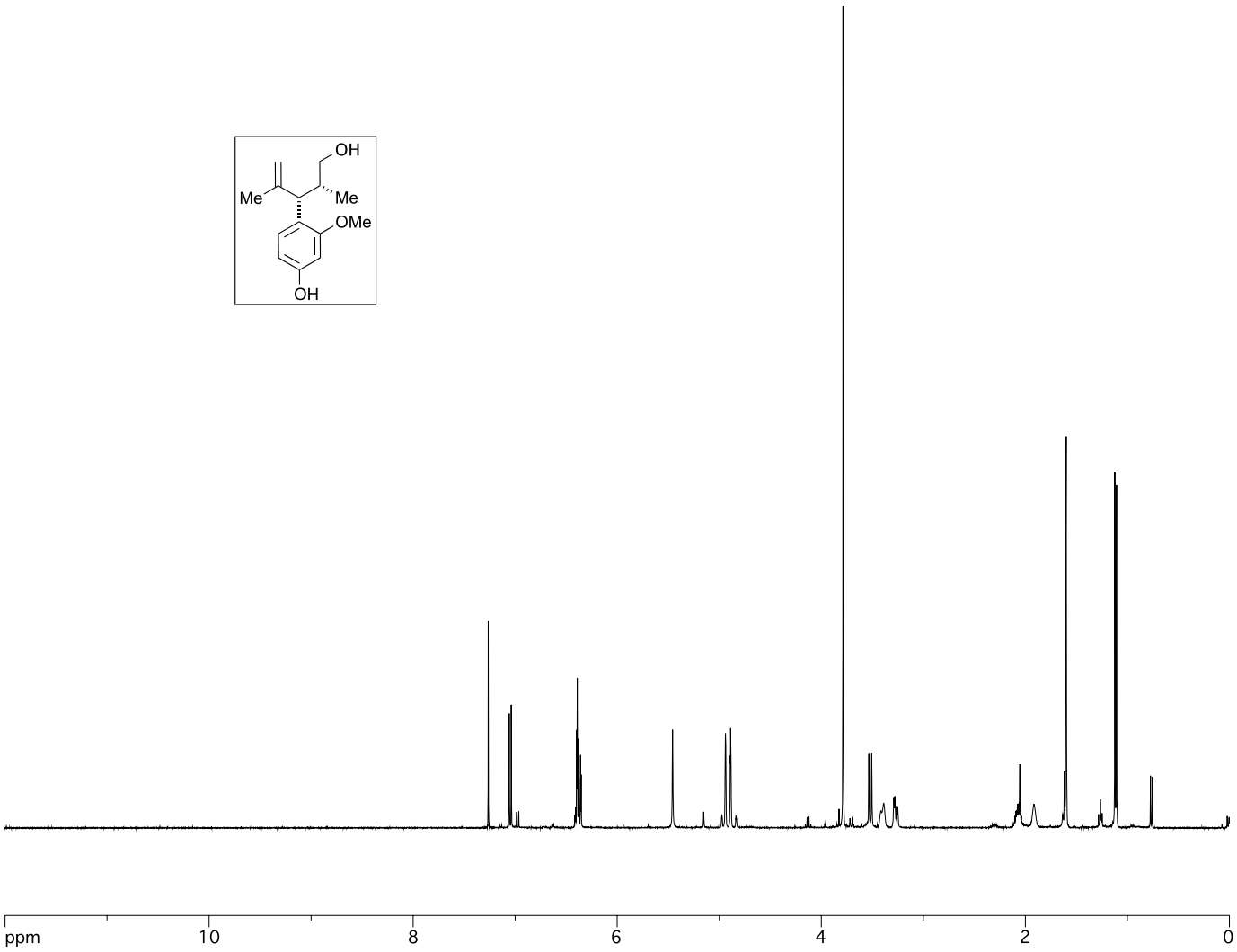


Figure A.1.60 ^{1}H-NMR (400 MHz; $CDCl_3$) of Compound **160**

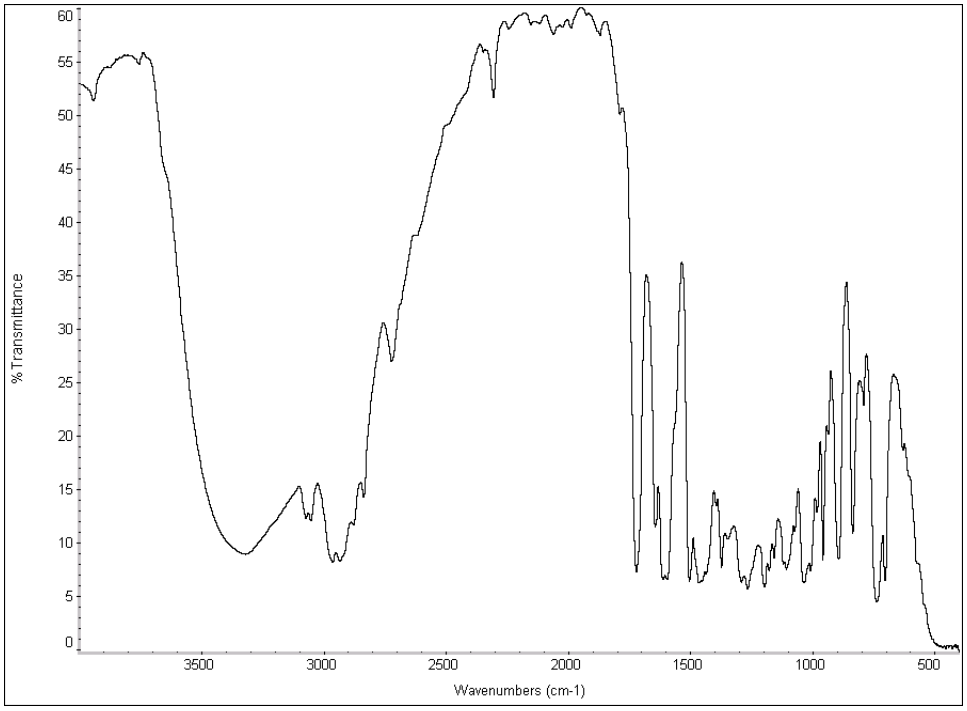


Figure A.1.61 FTIR of Compound **160**

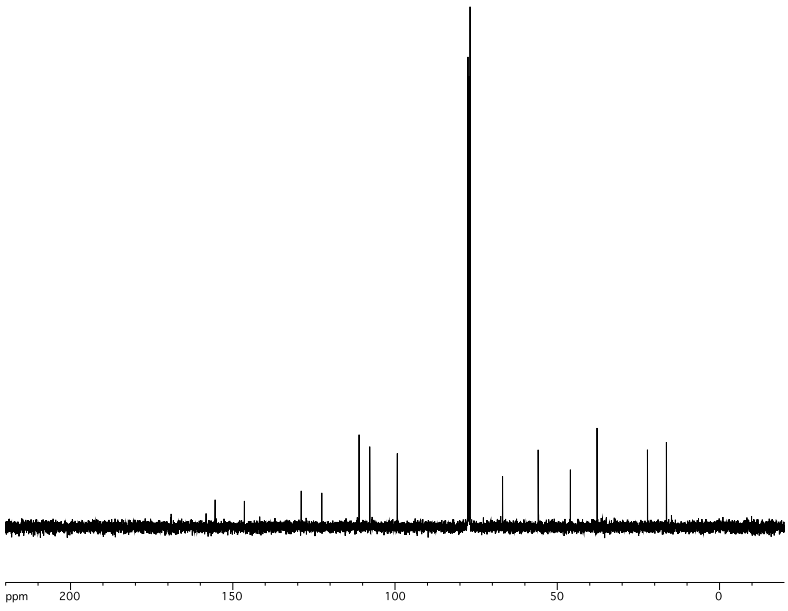


Figure A.1.62 ^{13}C-NMR (101 MHz, $CDCl_3$) of Compound **160**

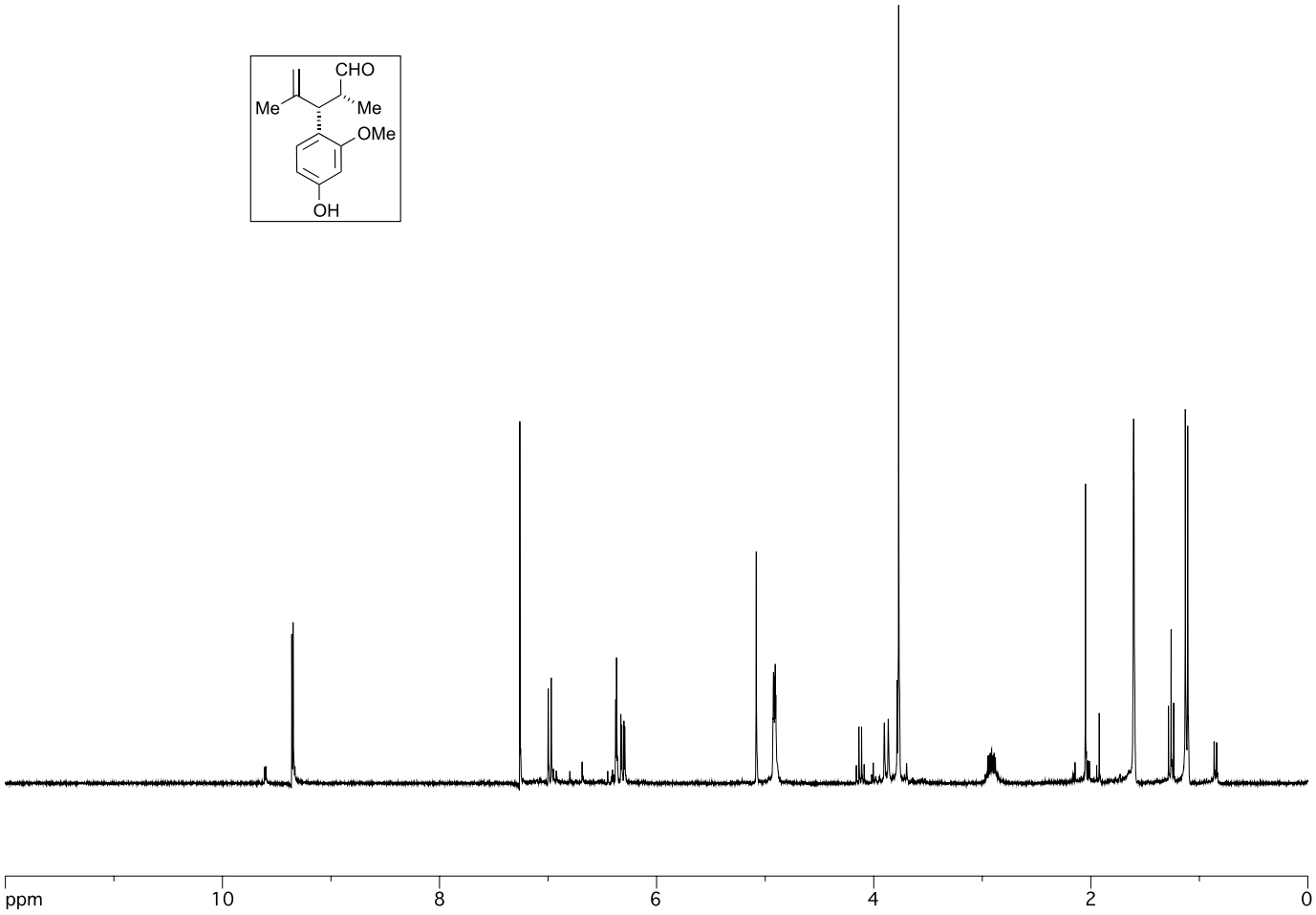


Figure A.1.63 ^{1}H-NMR (300 MHz; $CDCl_3$) of Compound **161**

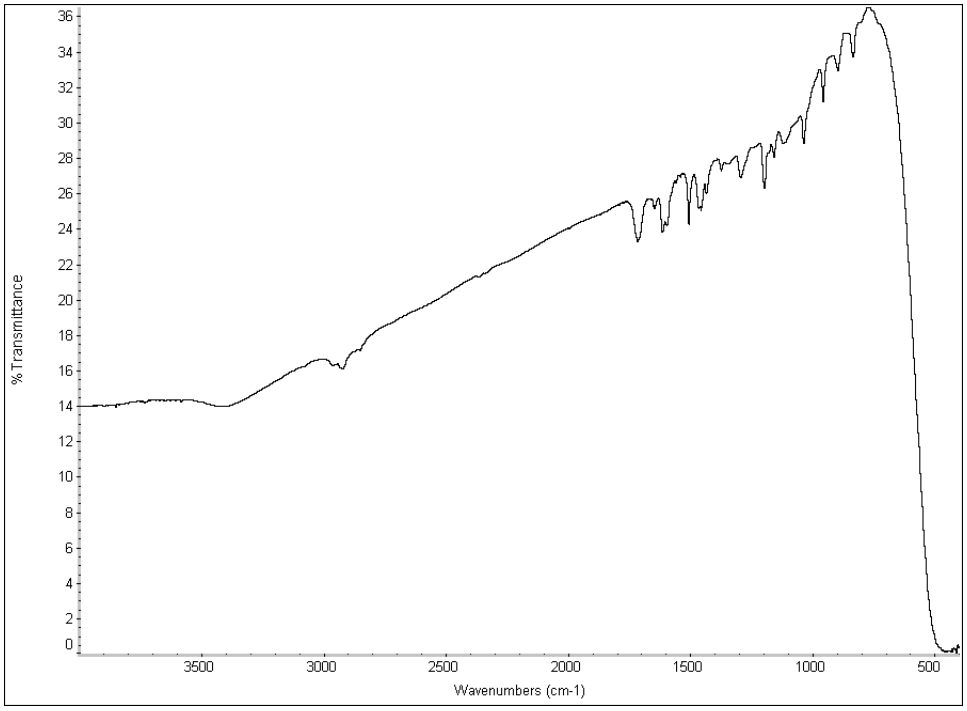


Figure A.1.64 FTIR (thin film/NaCl) of Compound **161**

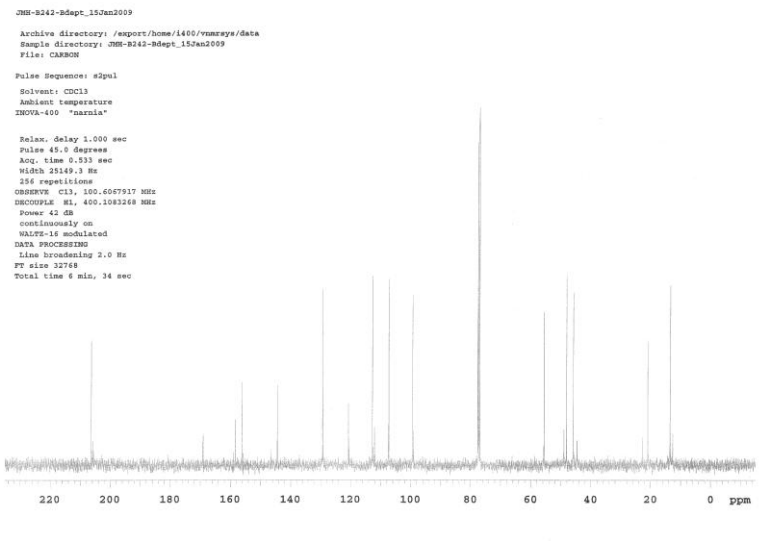


Figure A.1.65 ^{13}C-NMR (101 MHz; $CDCl_3$) of Compound **161**

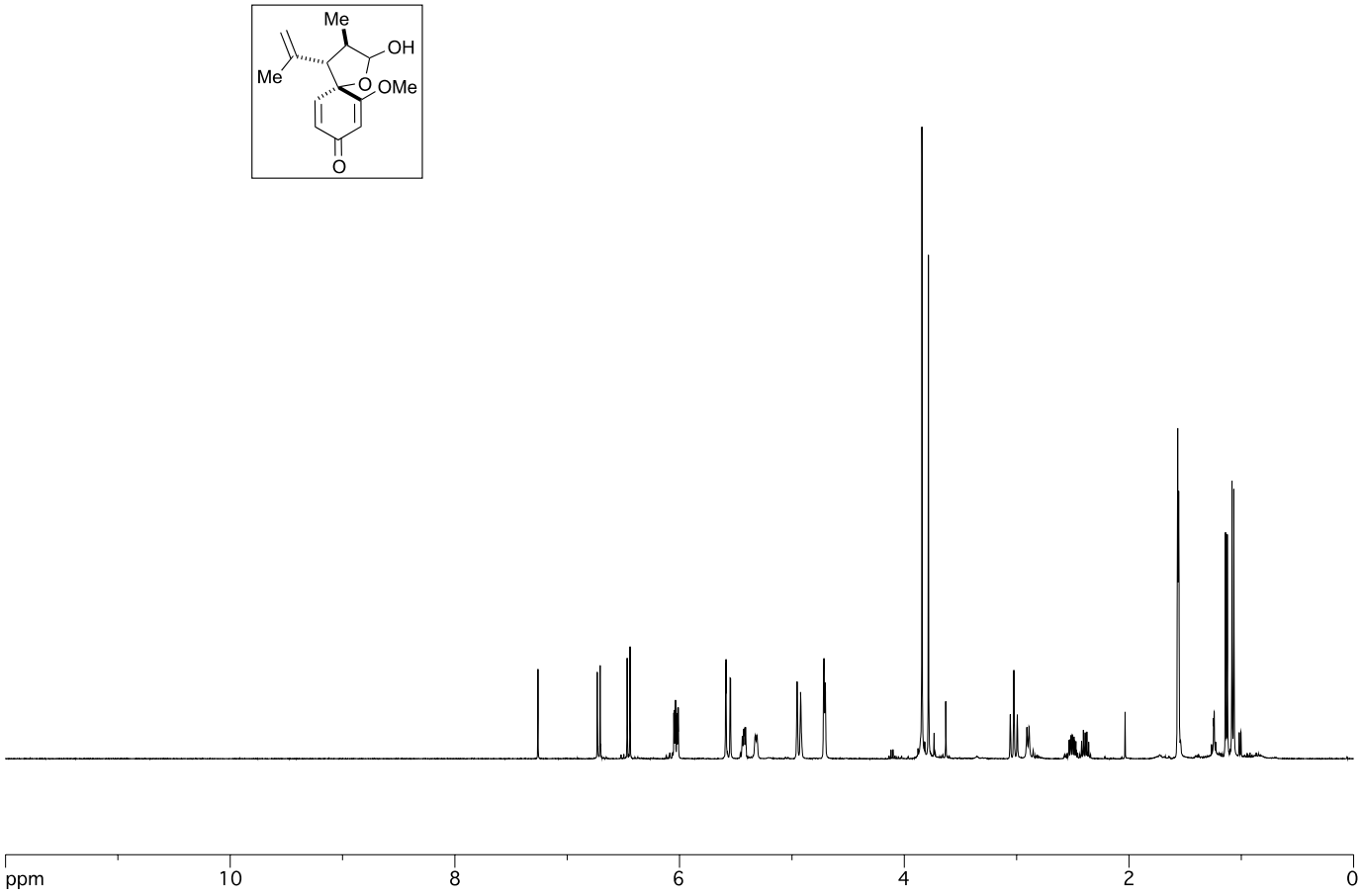


Figure A.1.66 ^{1}H-NMR (400 MHz; $CDCl_3$) of Compound **162**

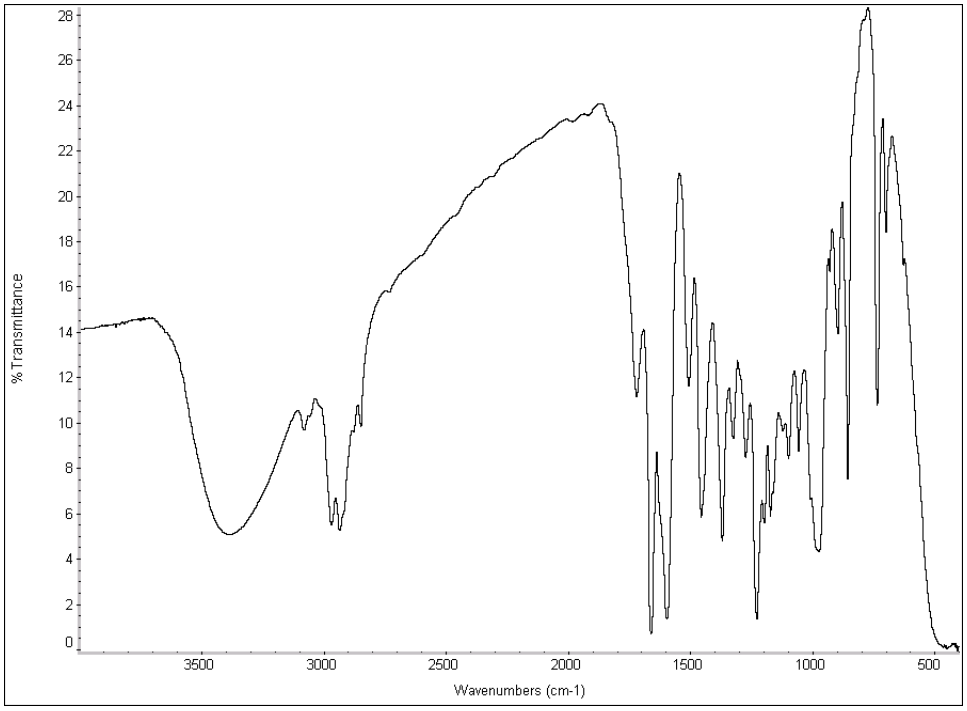


Figure A.1.67 FTIR (thin film/NaCl) of Compound **162**

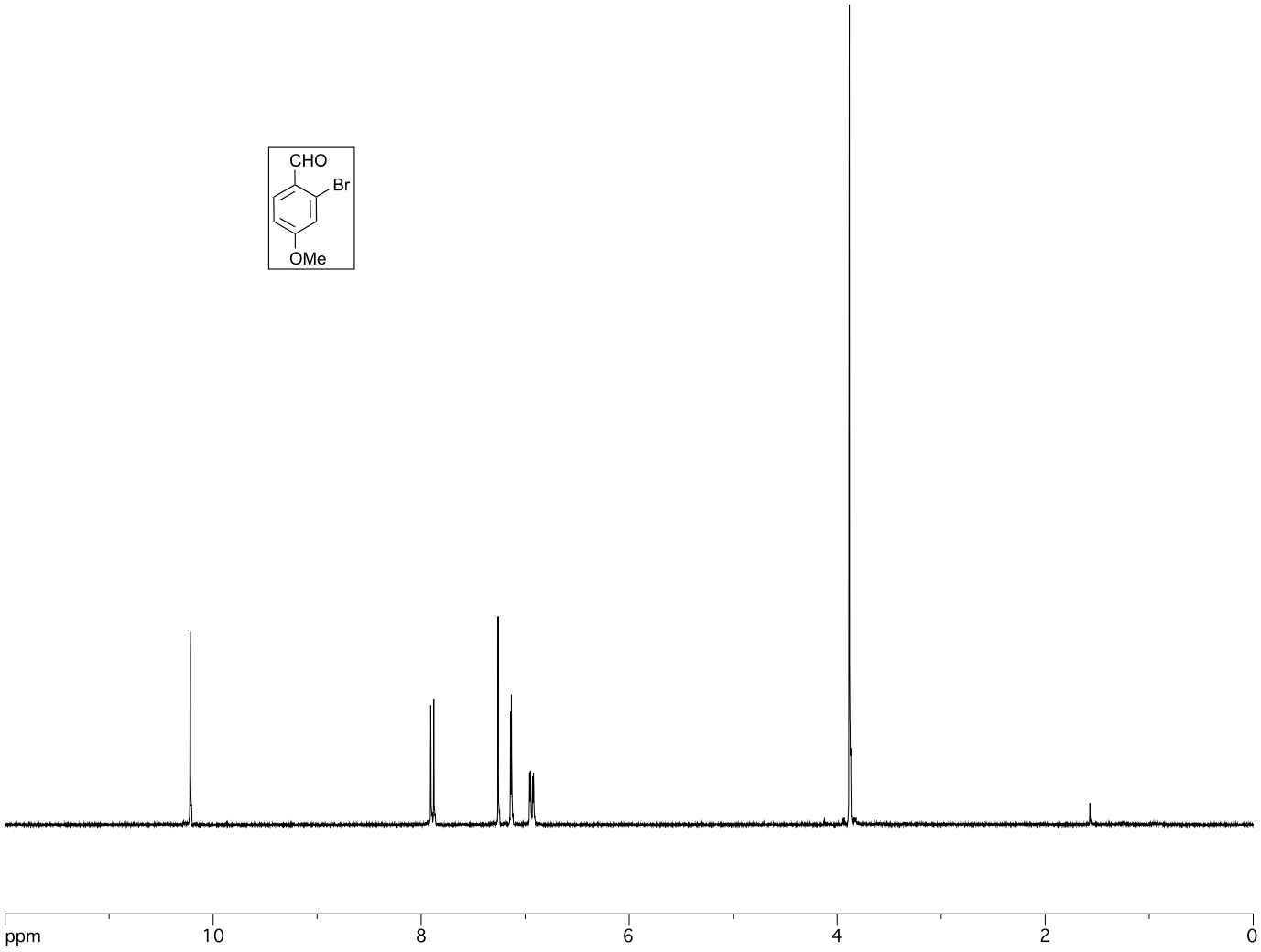


Figure A.1.68 ^{1}H-NMR (300 MHz; $CDCl_3$) of Compound **173**

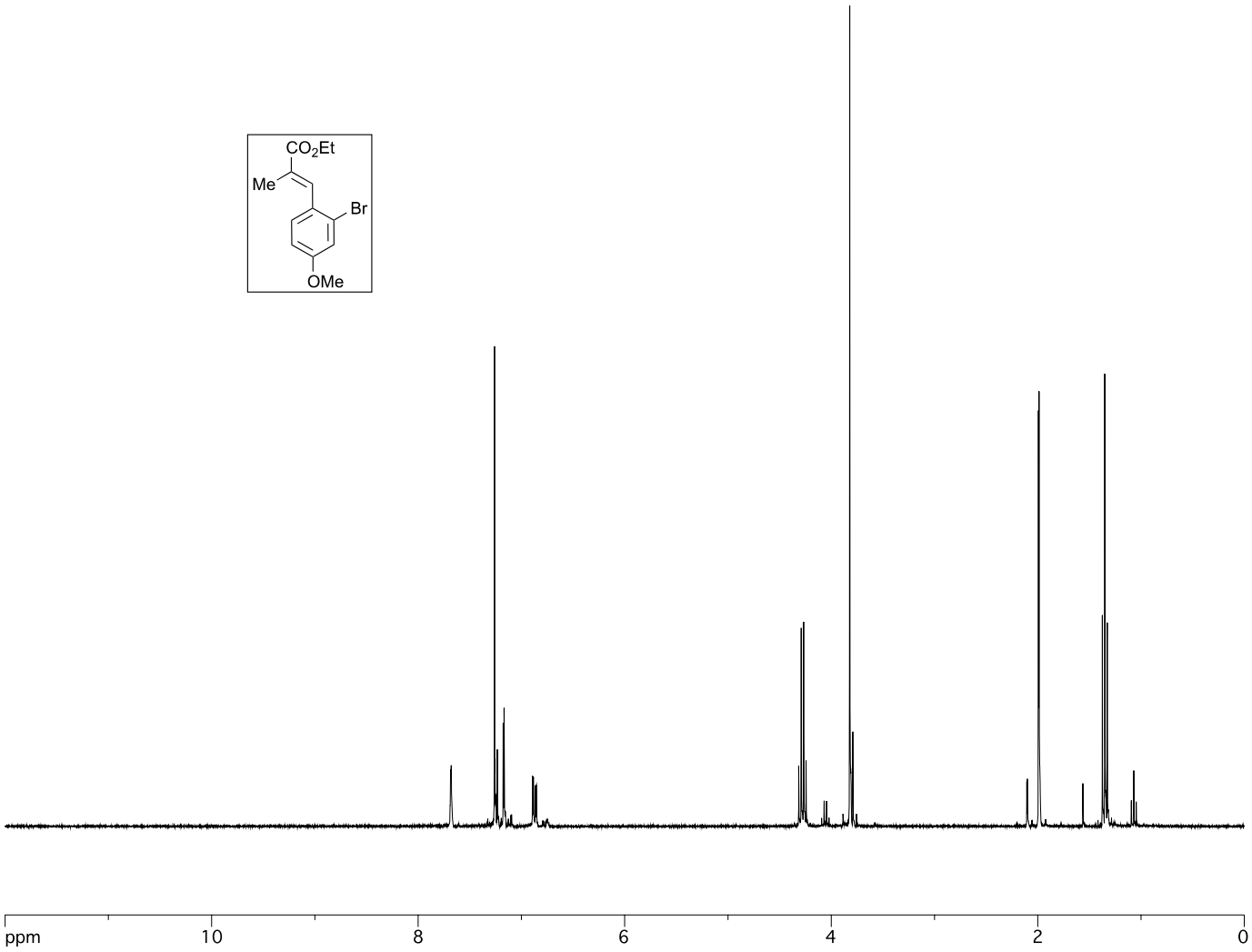


Figure A.1.69 ^{1}H-NMR (300 MHz; $CDCl_3$) of Compound **174**

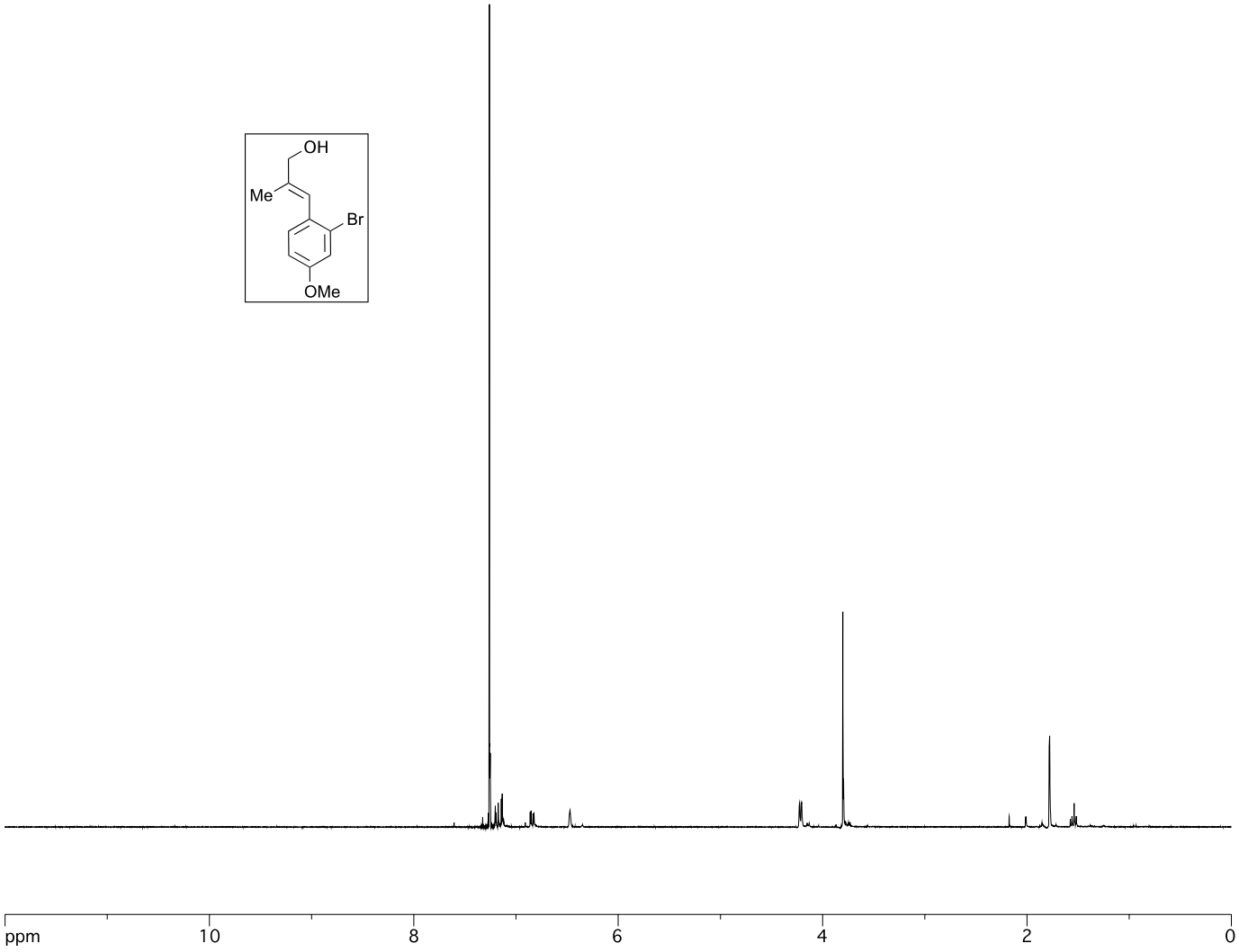


Figure A.1.70 ^{1}H-NMR (300 MHz; $CDCl_3$) of Compound **175**

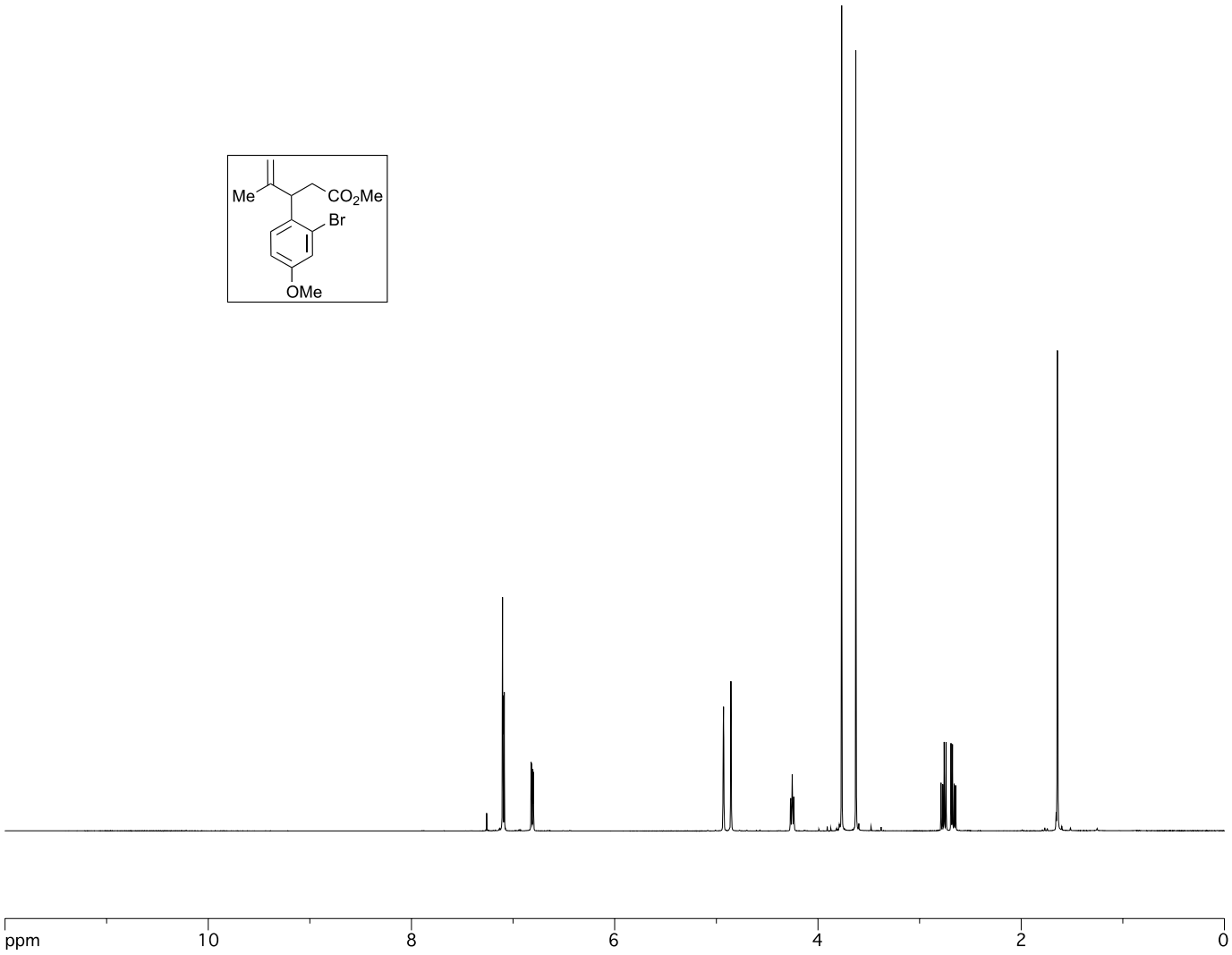


Figure A.1.71 ^{1}H-NMR (500 MHz; $CDCl_3$) of Compound **176**

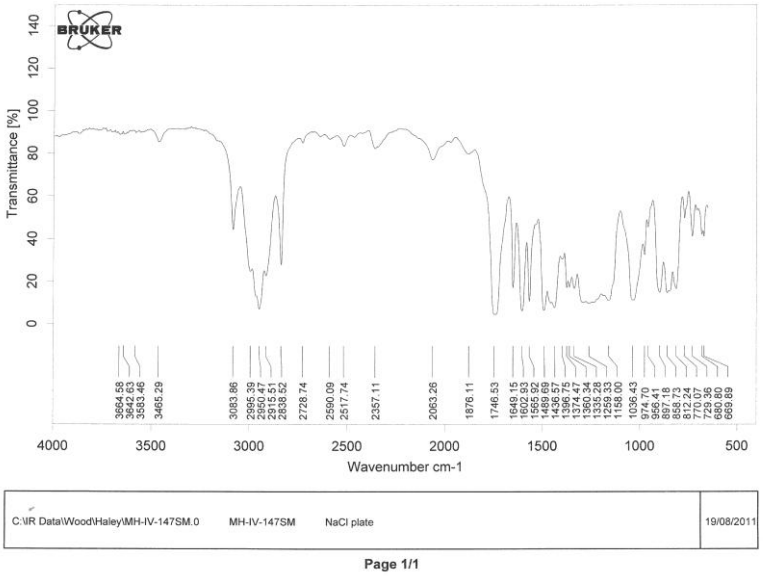


Figure A.1.72 FTIR (thin film/NaCl) Spectrum of Compound **176**

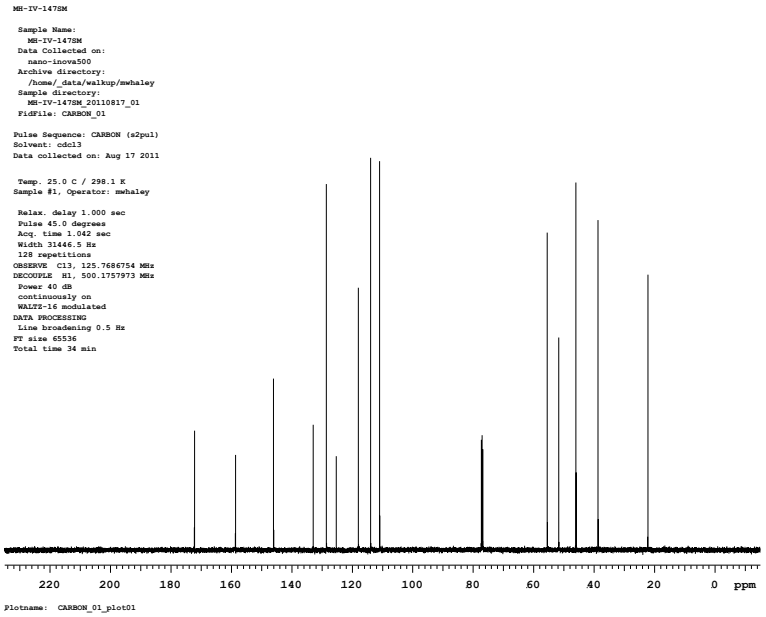


Figure A.1.73 ^{13}C-NMR (126 MHz, $CDCl_3$) of Compound **176**

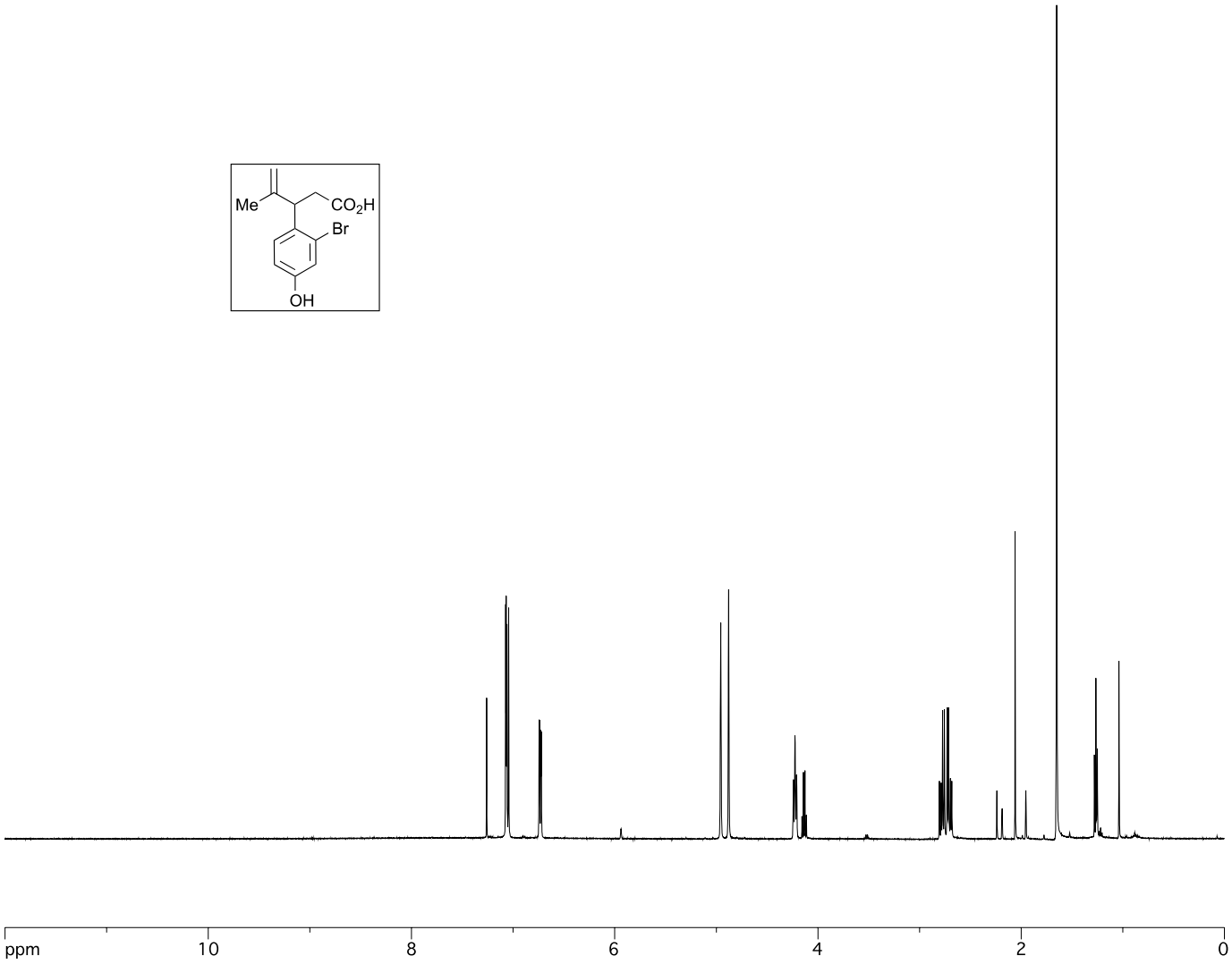


Figure A.1.74 ^{1}H-NMR (500 MHz; $CDCl_3$) of Compound **177**

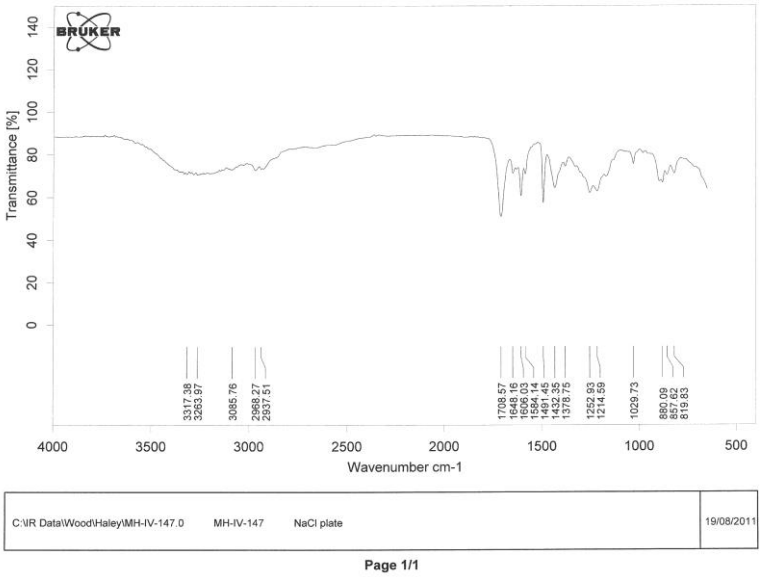


Figure A.1.75 FTIR (thin film/NaCl) Spectrum of Compound **177**

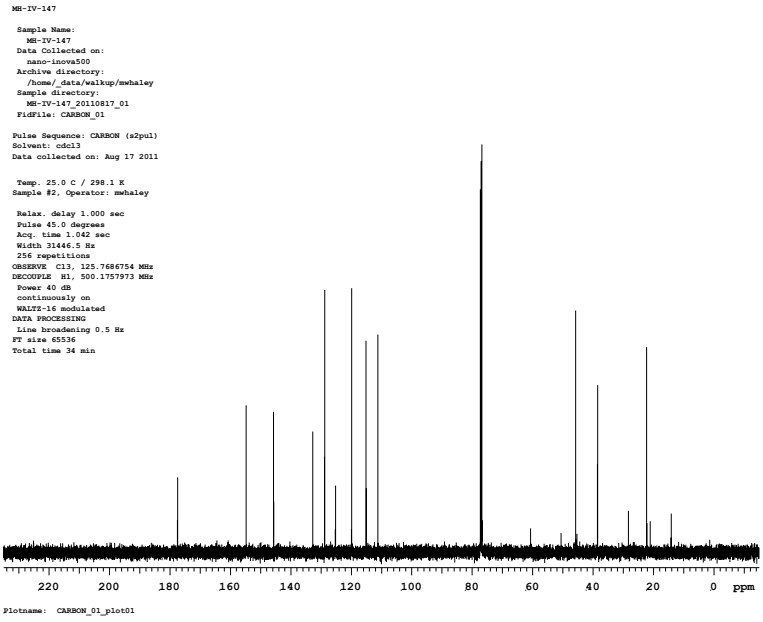


Figure A.1.76 ^{13}C-NMR (126 MHz, $CDCl_3$) of Compound **177**

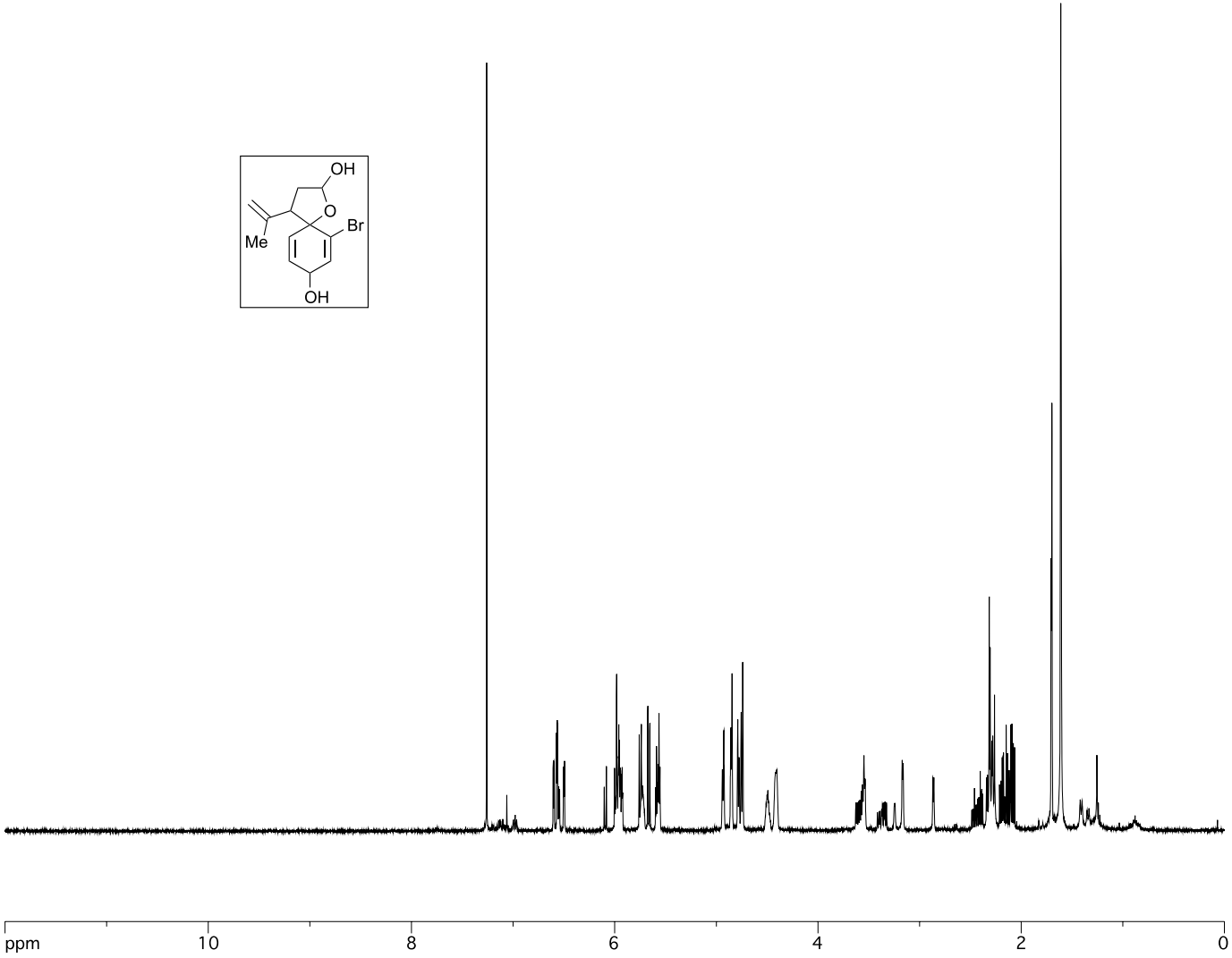


Figure A.1.77 ^{1}H-NMR (500 MHz; $CDCl_3$) of Compound **179**

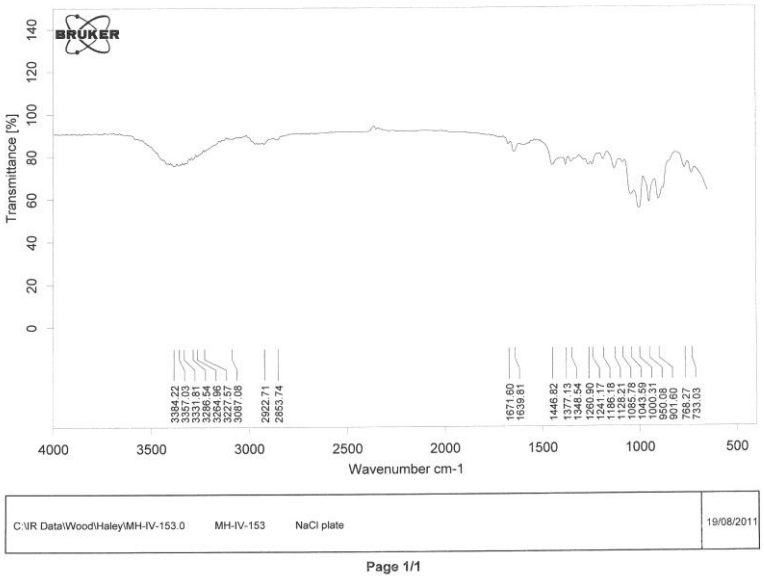


Figure A.1.78 FTIR (thin film/NaCl) Spectrum of Compound **179**

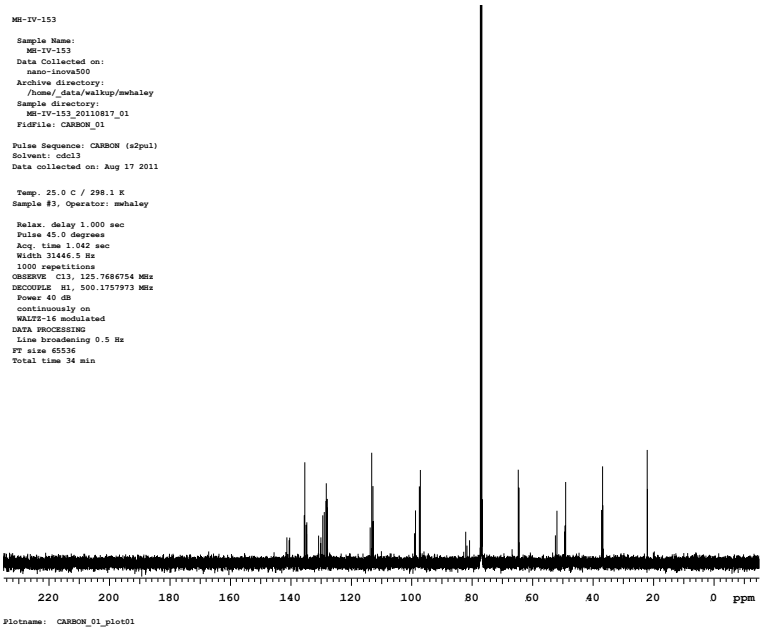


Figure A.1.79 ^{13}C-NMR (126 MHz, $CDCl_3$) of Compound **179**

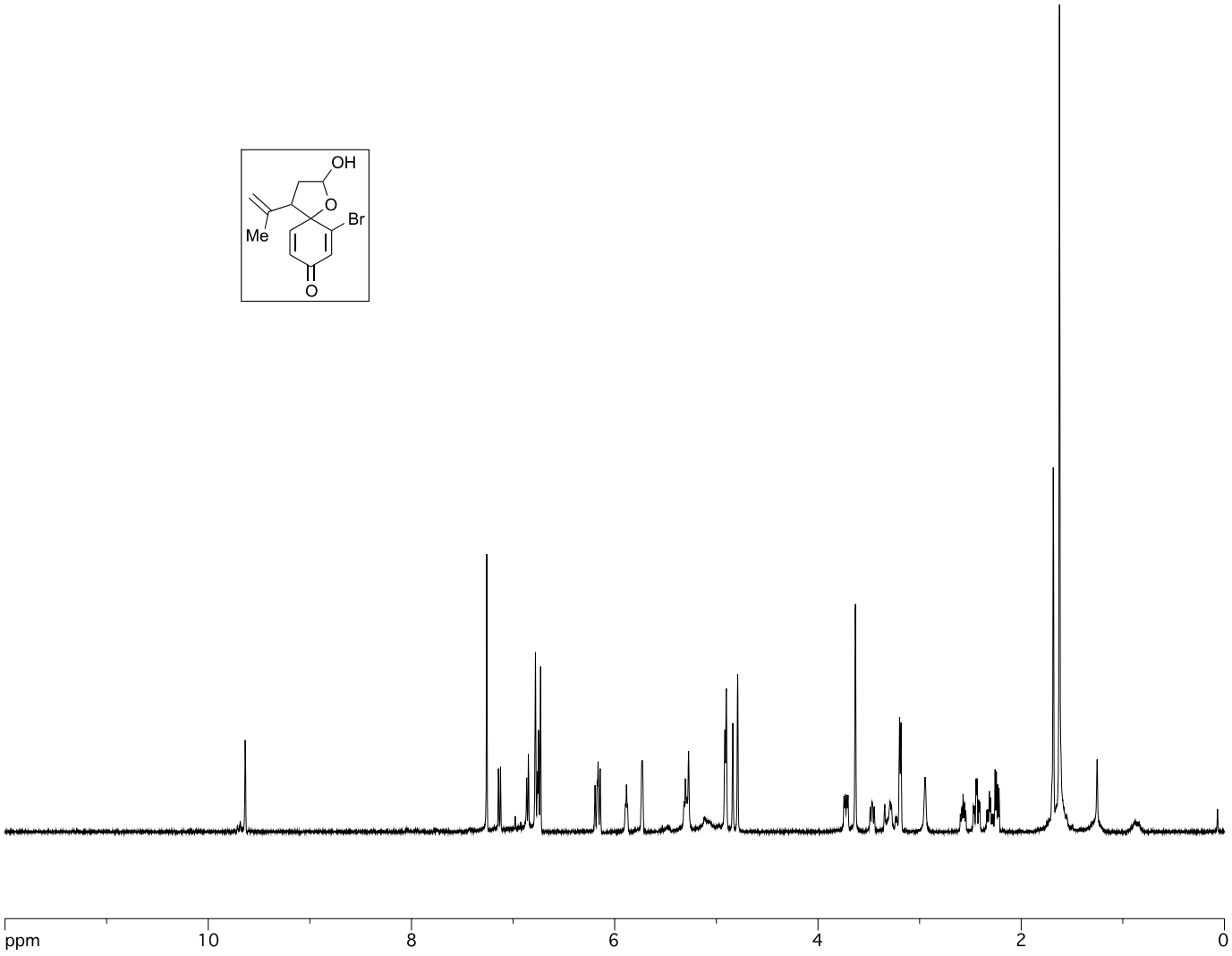


Figure A.1.80 ^{1}H-NMR (500 MHz; $CDCl_3$) of Compound **180**

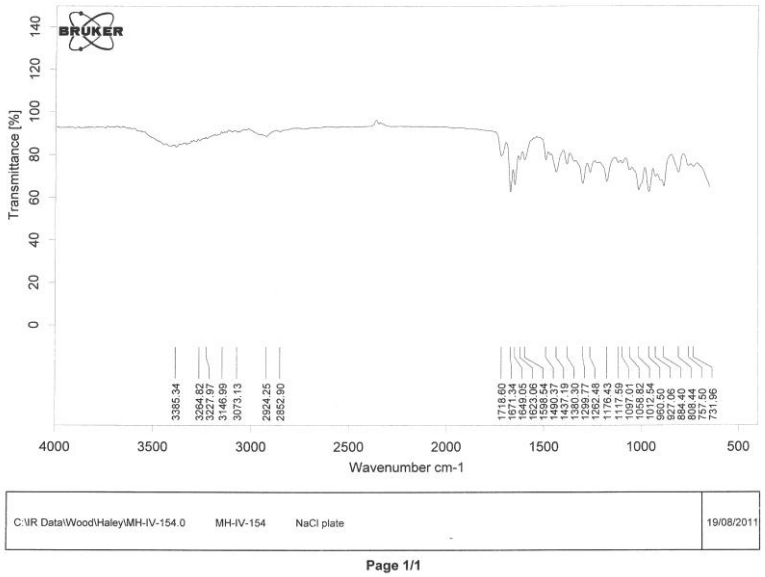


Figure A.1.81 FTIR (thin film/NaCl) Spectrum of Compound **180**

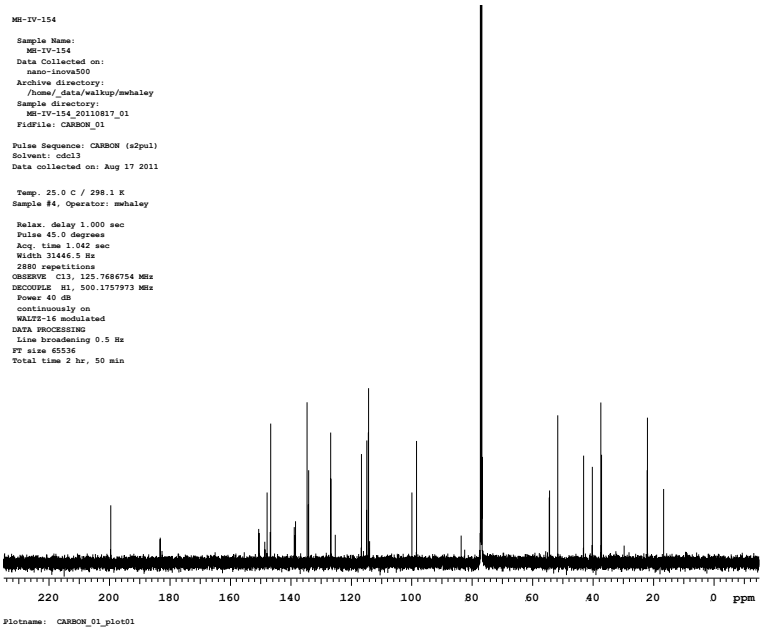


Figure A.1.82 ^{13}C-NMR (126 MHz, $CDCl_3$) of Compound **180**

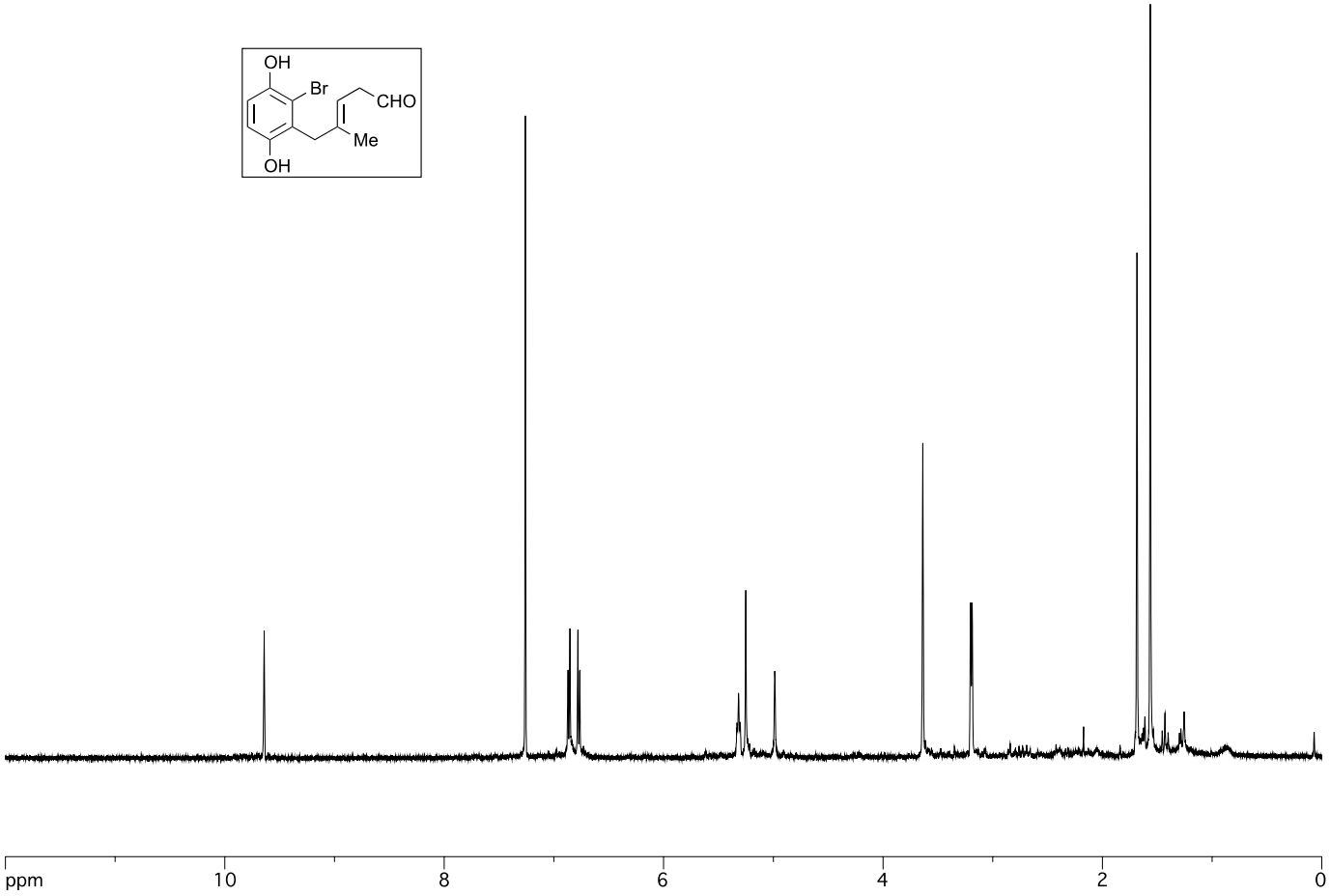


Figure A.1.83 ^{1}H-NMR (500 MHz; $CDCl_3$) of Compound **183**

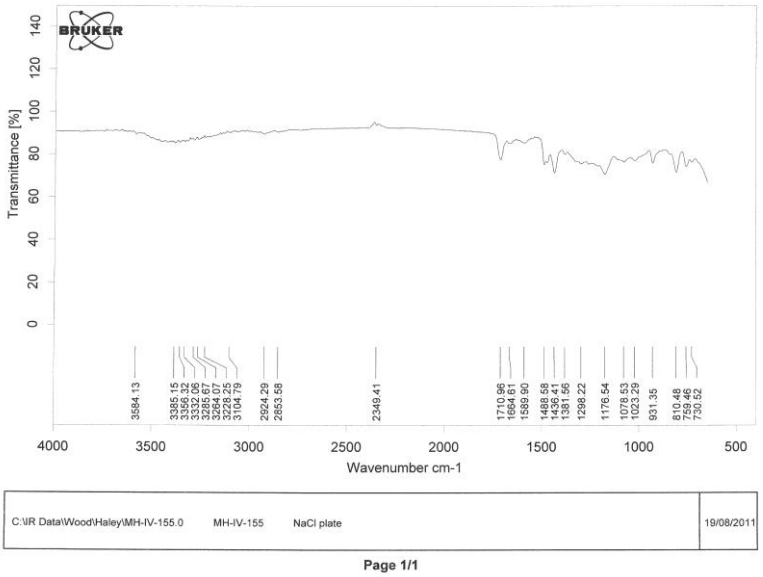


Figure A.1.84 FTIR (thin film/NaCl) Spectrum of Compound **183**

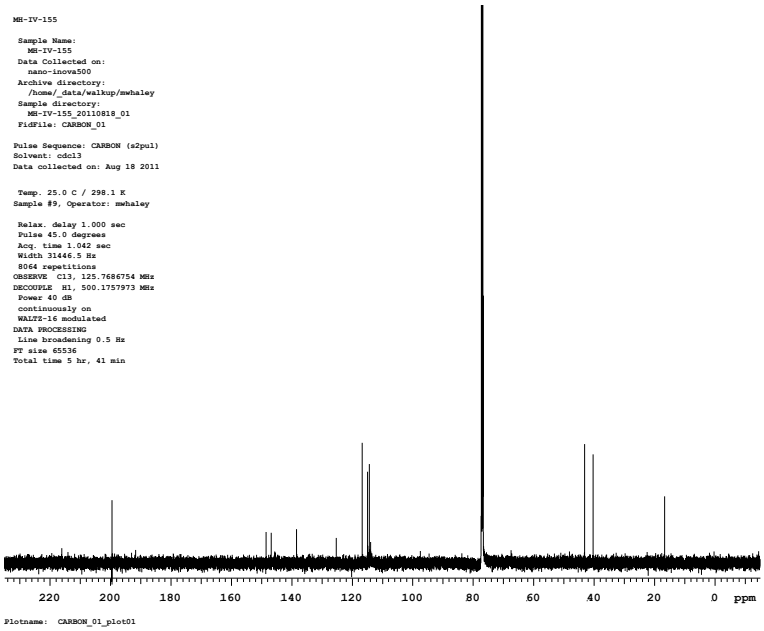


Figure A.1.85 ^{13}C-NMR (126 MHz, $CDCl_3$) of Compound **183**

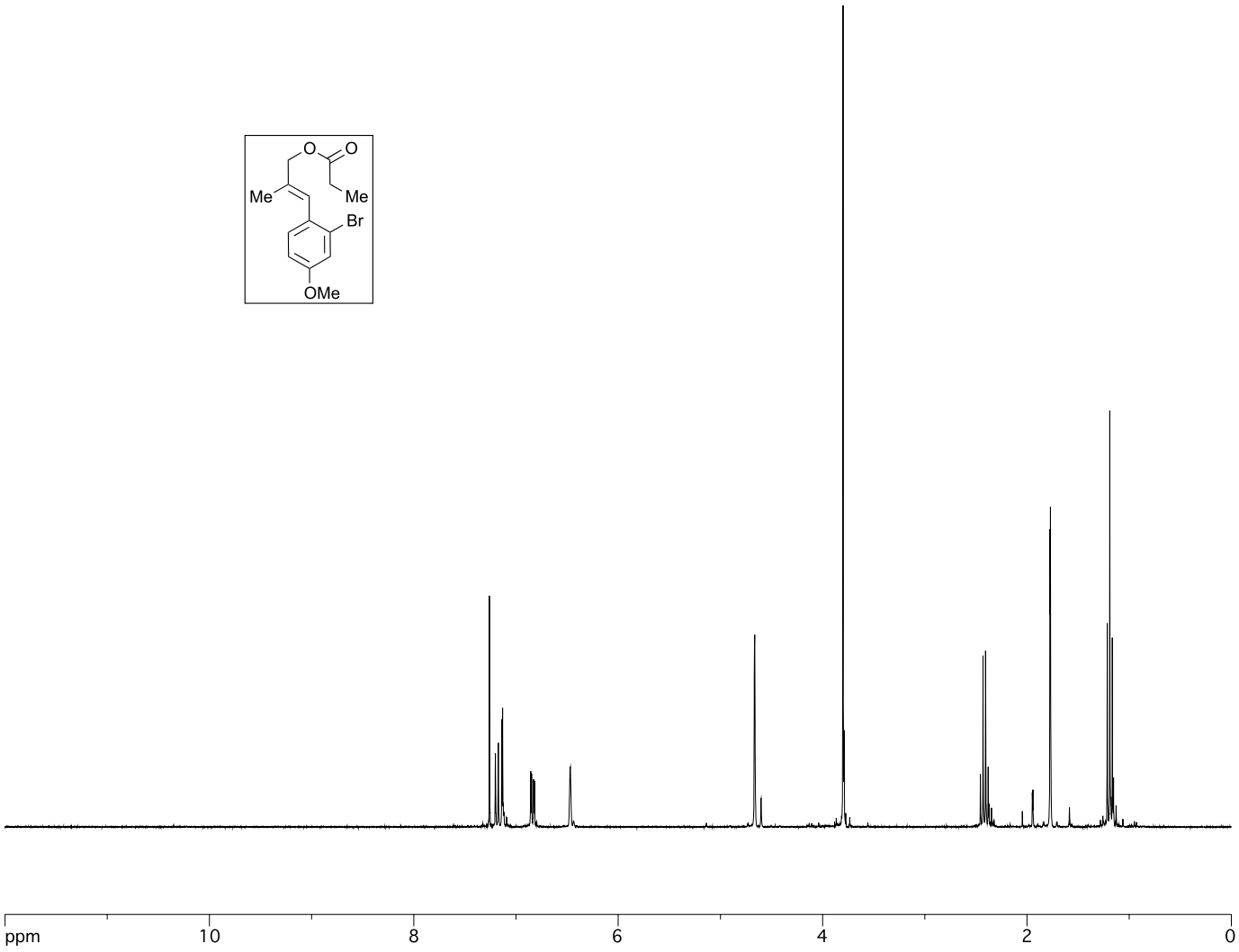


Figure A.1.86 ^{1}H-NMR (300 MHz; $CDCl_3$) of Compound **189**

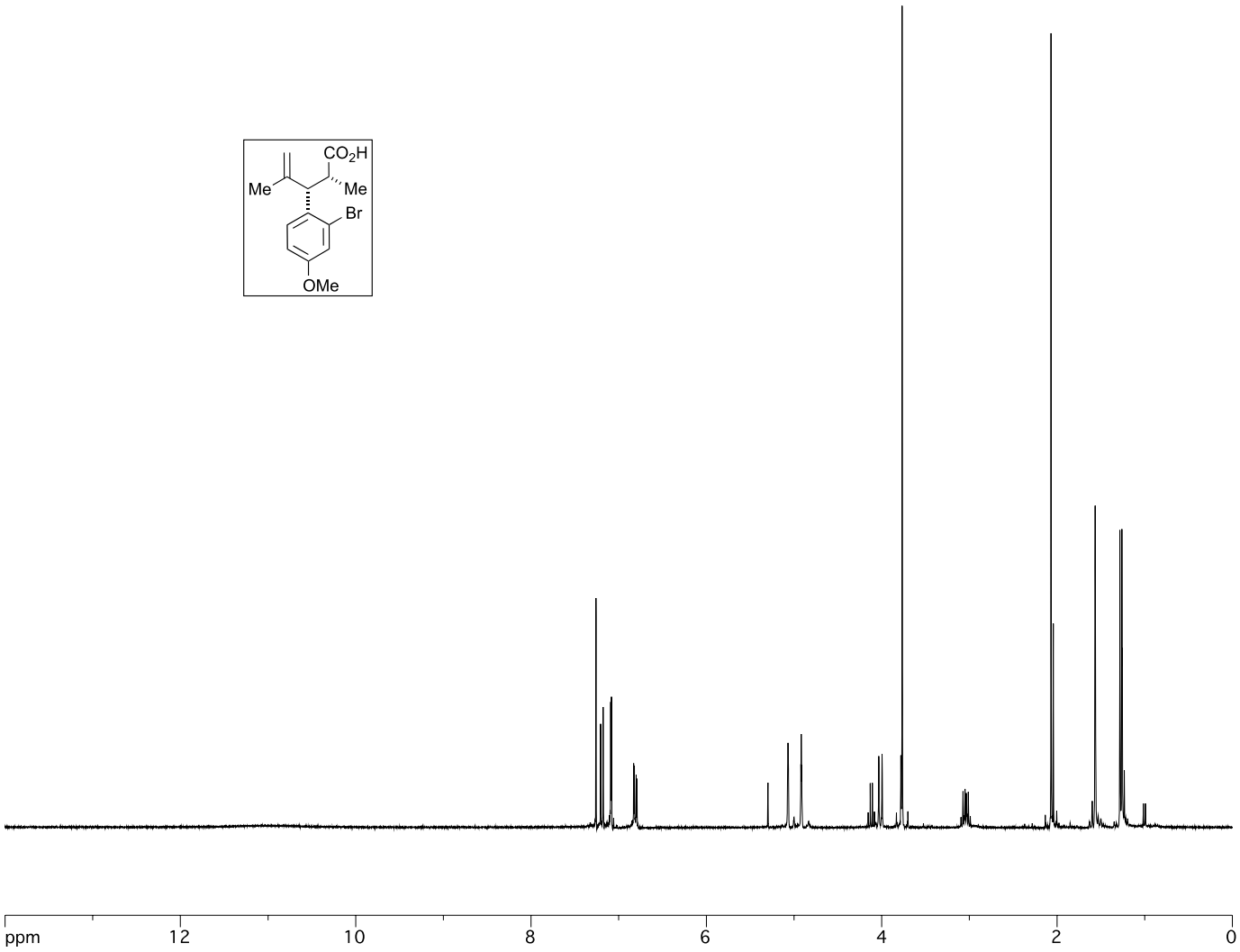


Figure A.1.87 ^{1}H-NMR (300 MHz; $CDCl_3$) of Compound **190**

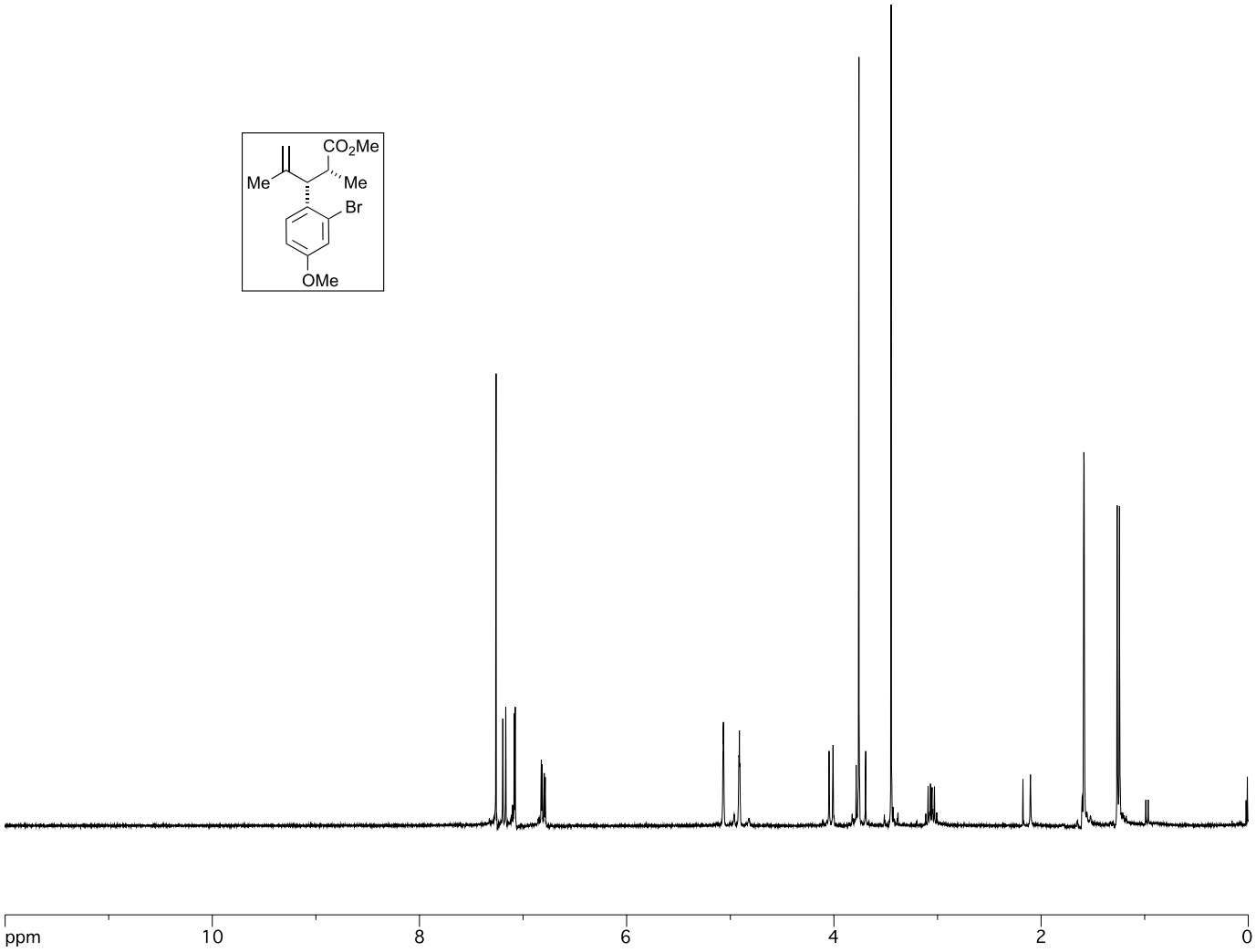


Figure A.1.88 ^{1}H-NMR (300 MHz; $CDCl_3$) of Compound **188**

Appendix 2

Spectra Relevant to Chapter 3

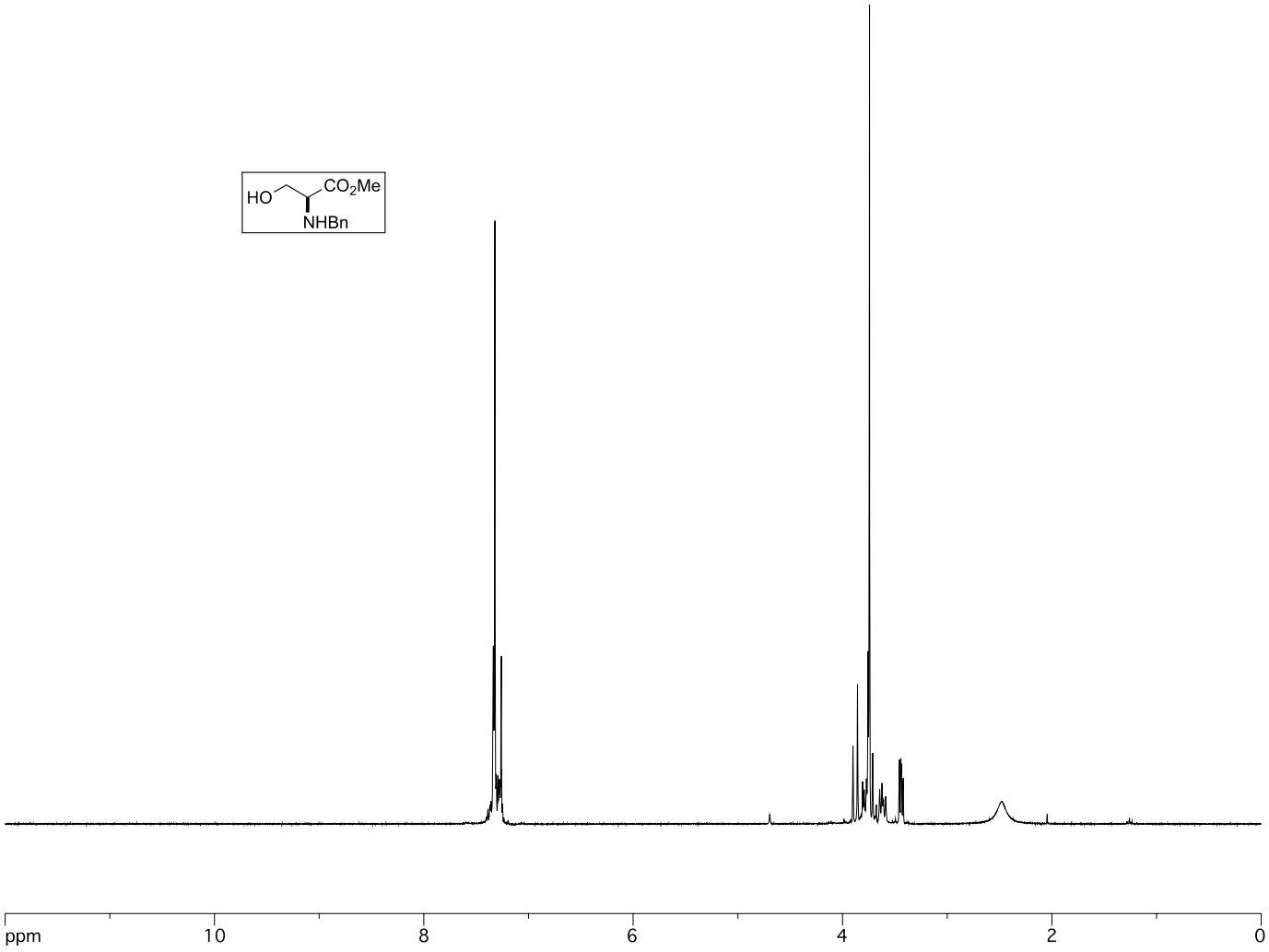


Figure A.2.1 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **237**

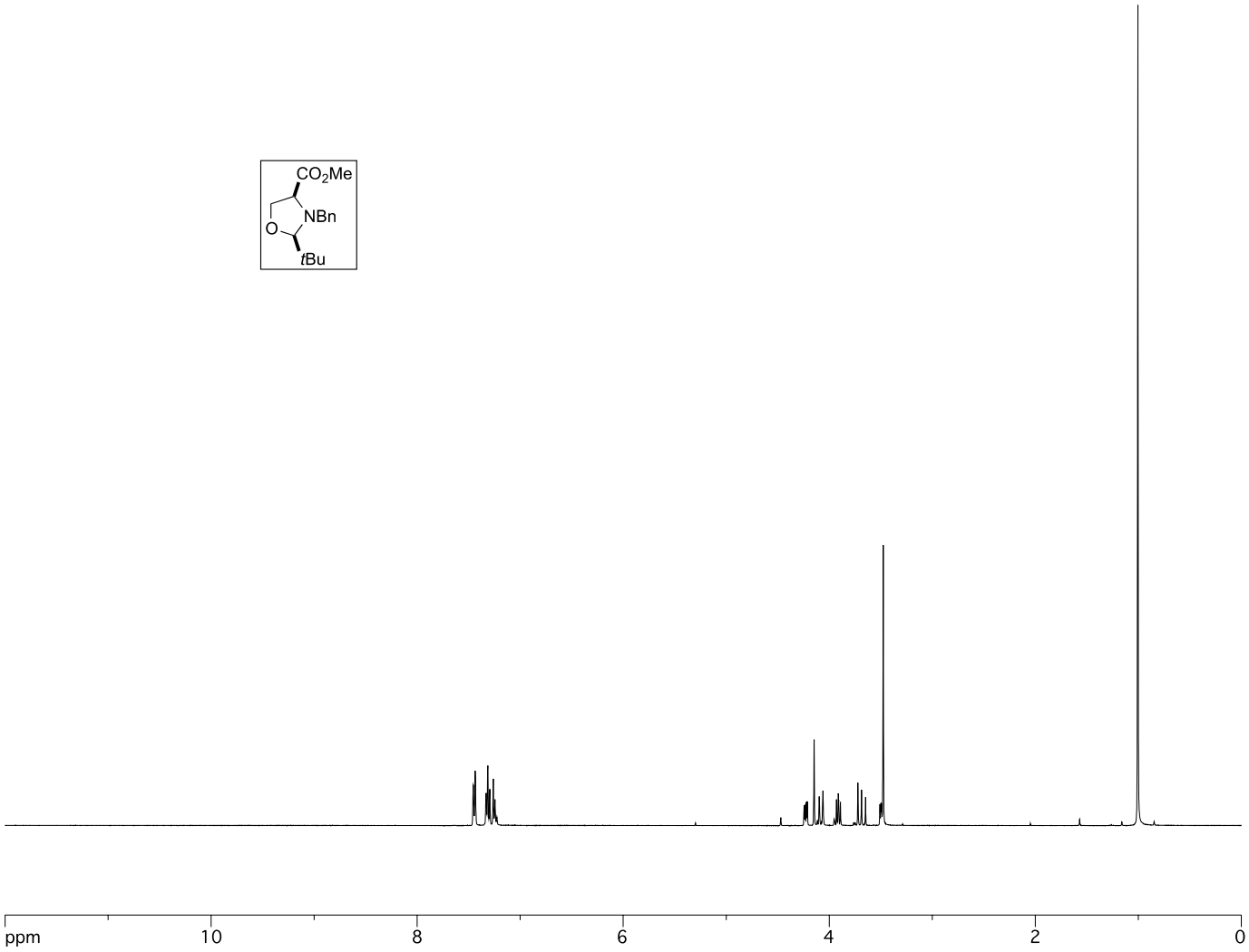


Figure A.2.2 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **238**

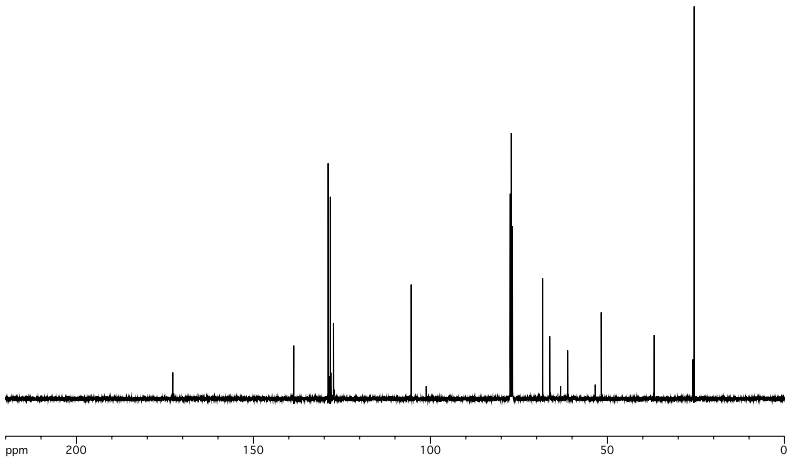


Figure A.2.3 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **238**

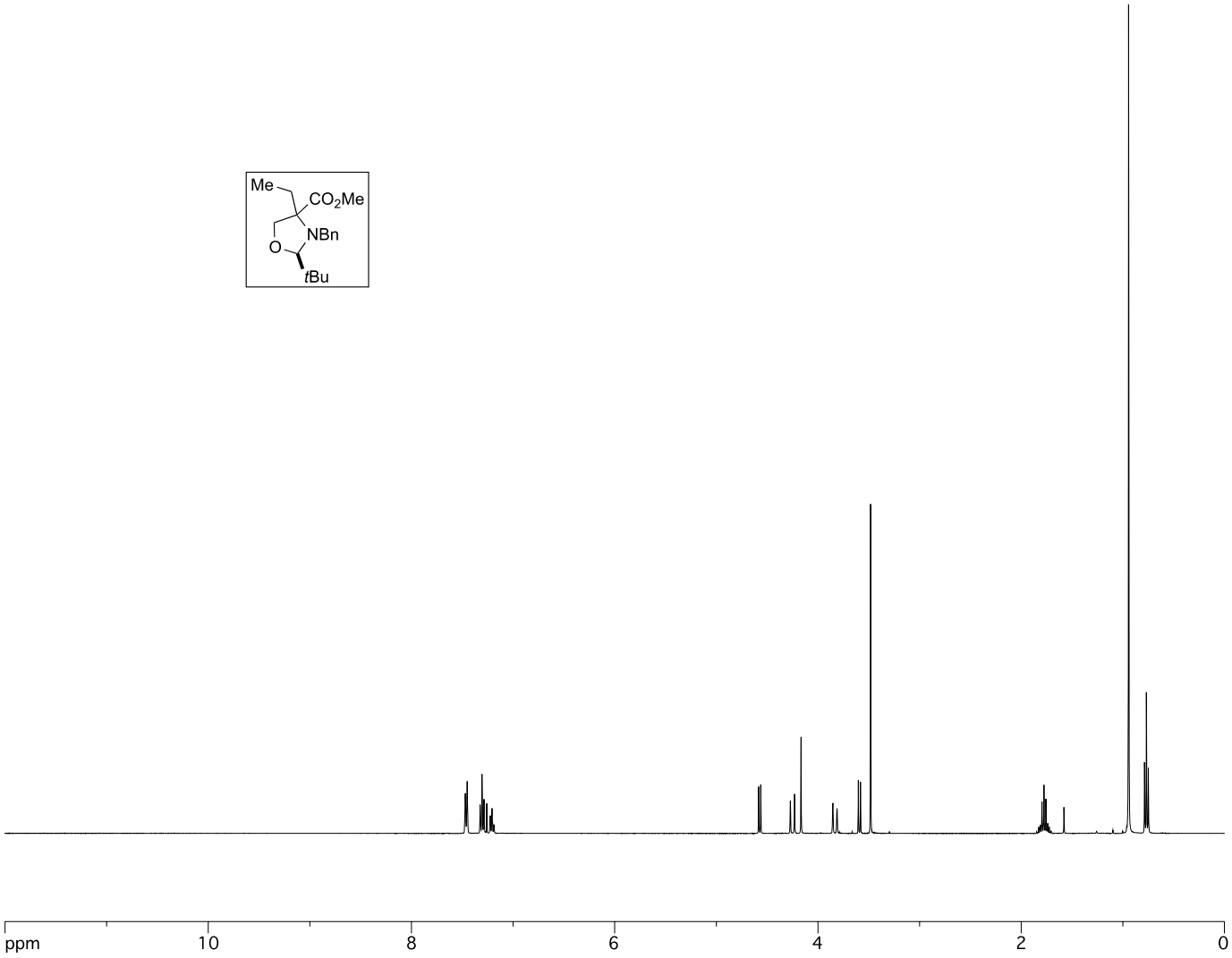


Figure A.2.4 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **244a**

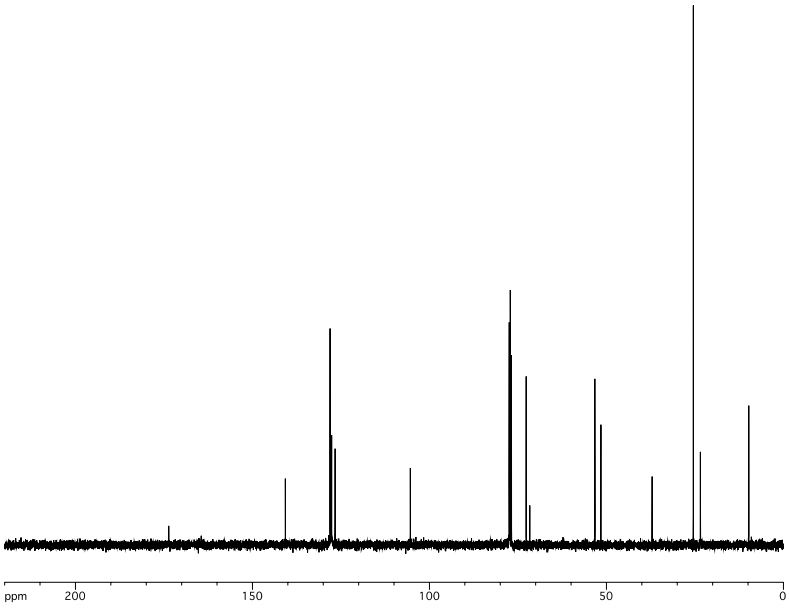


Figure A.2.5 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **244a**

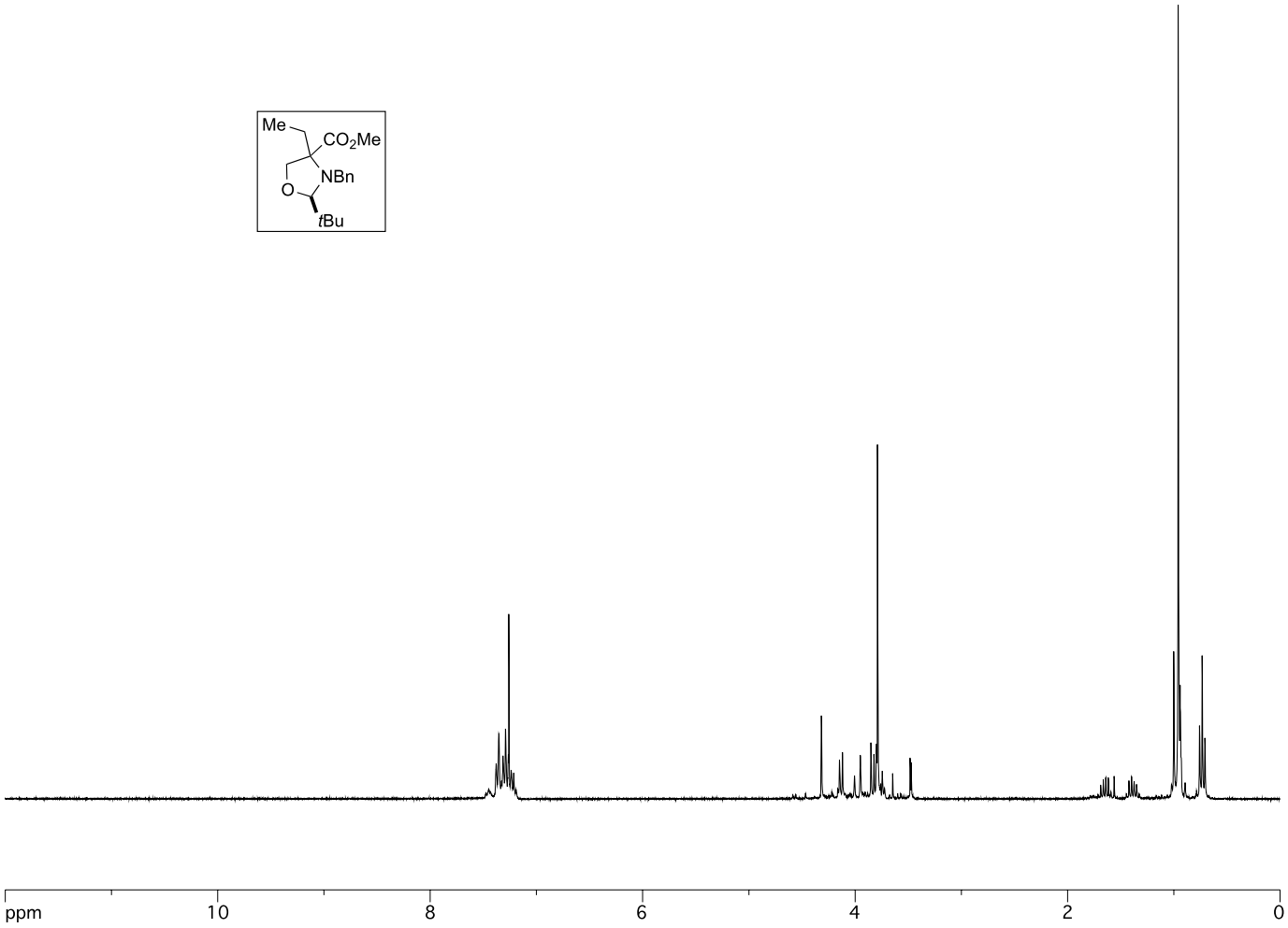


Figure A.2.6 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **244b**

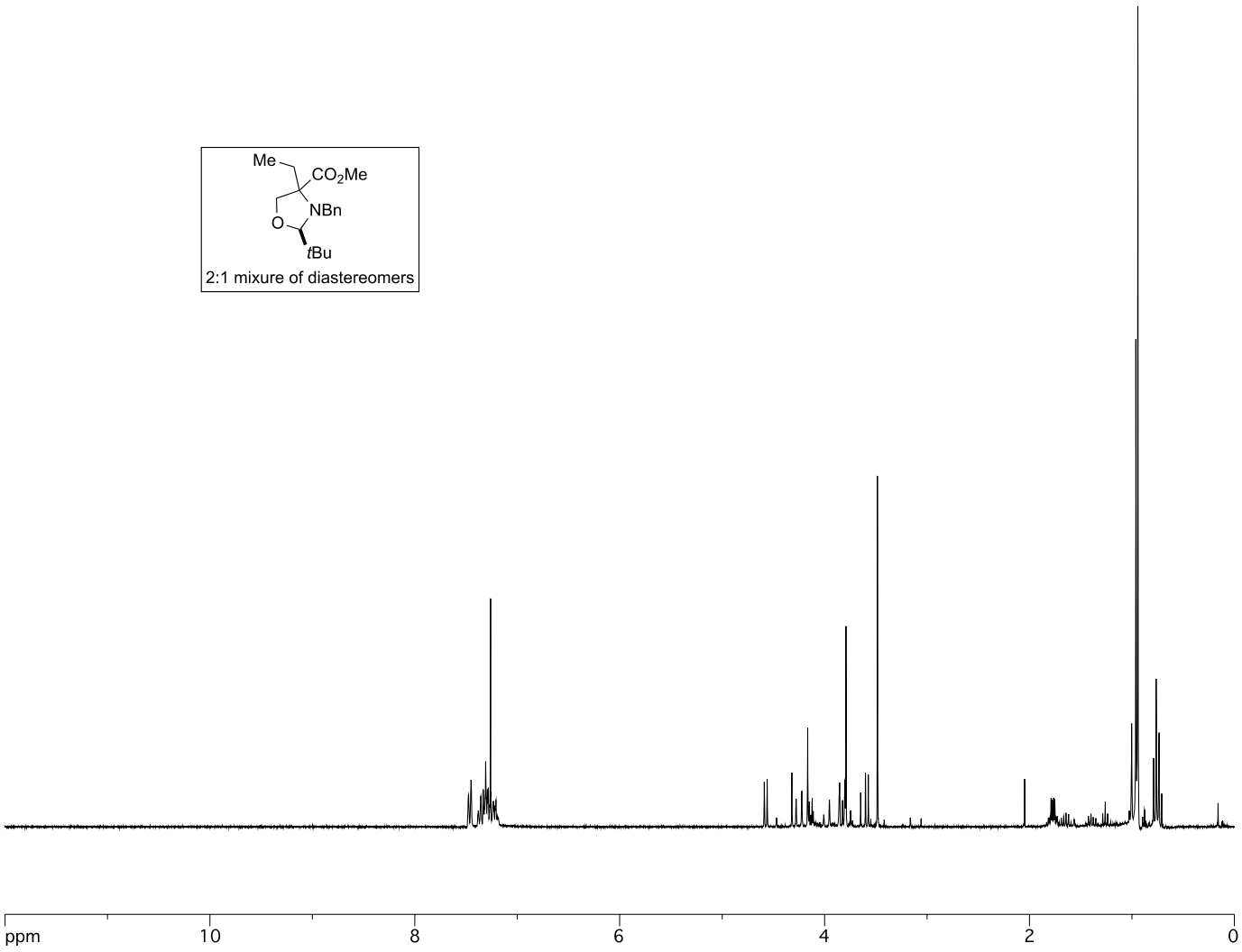


Figure A.2.7 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **244** (2:1 a/b mixture)

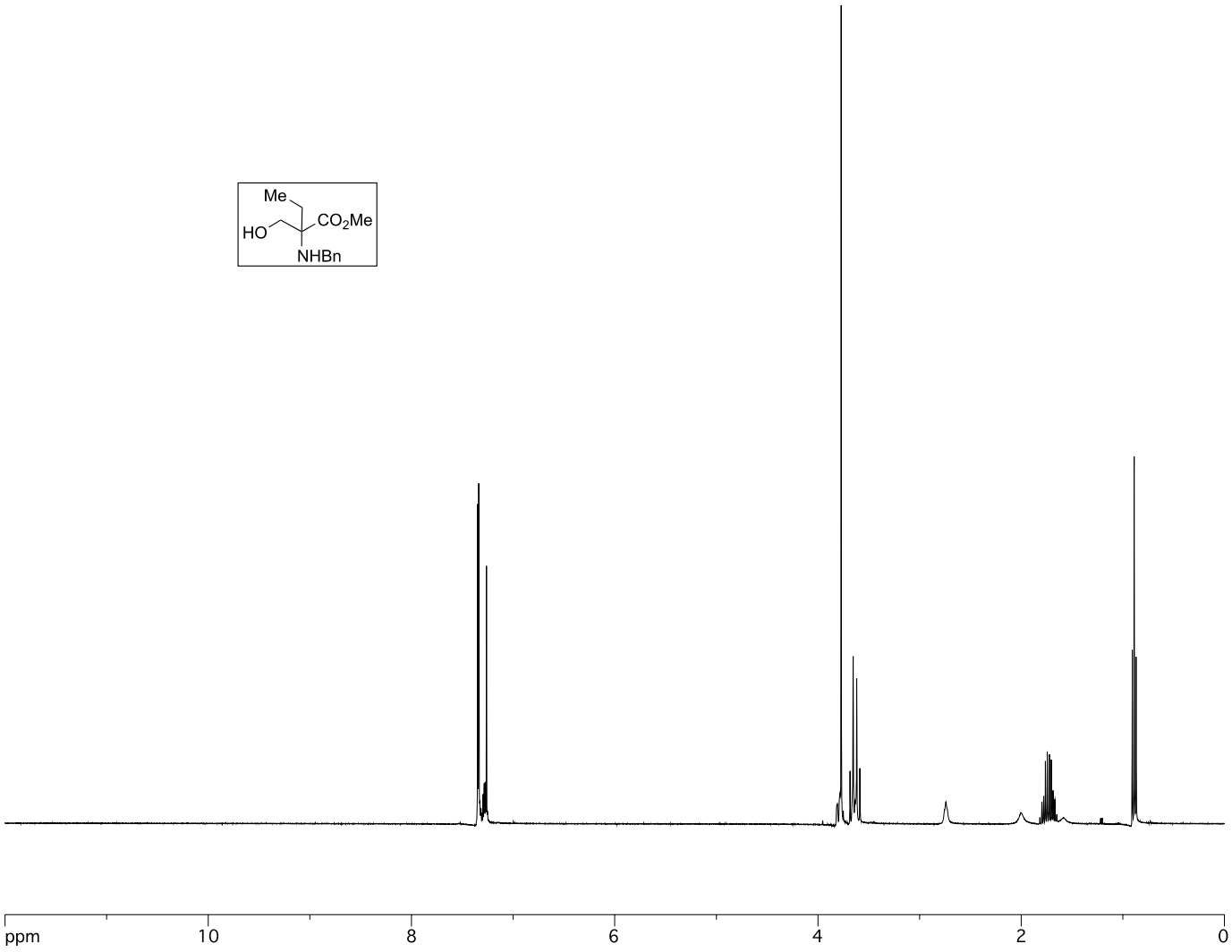


Figure A.2.8 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **245**

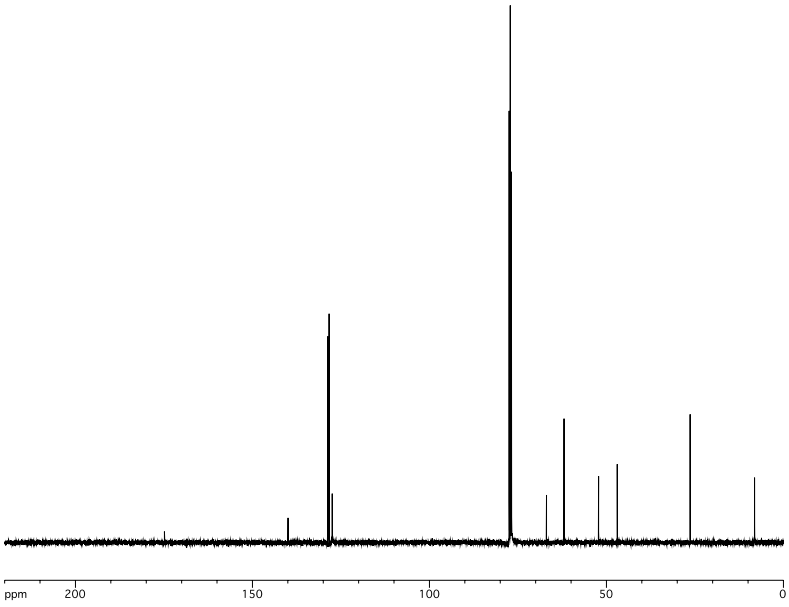


Figure A.2.9 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **245**

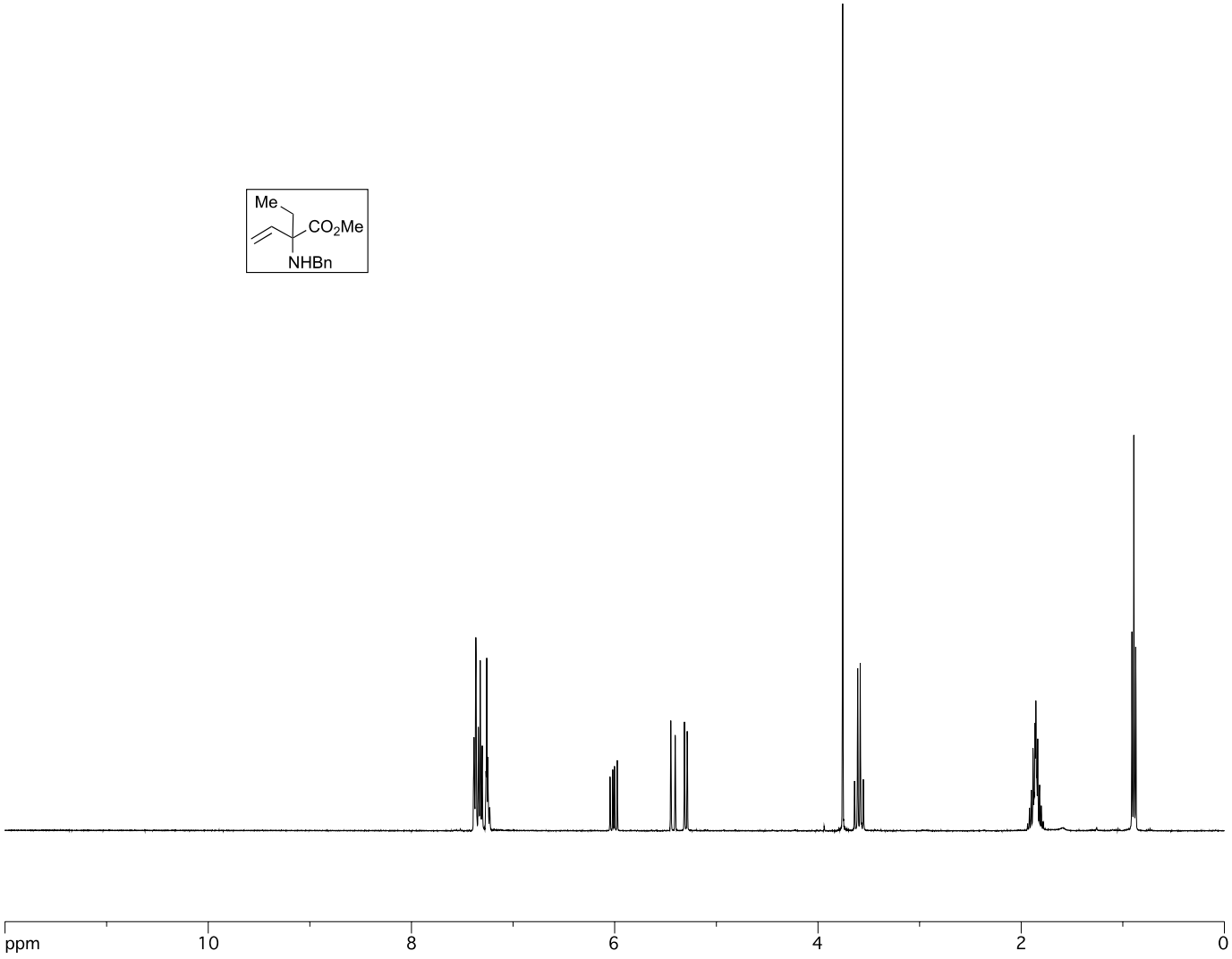


Figure A.2.10 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **247**

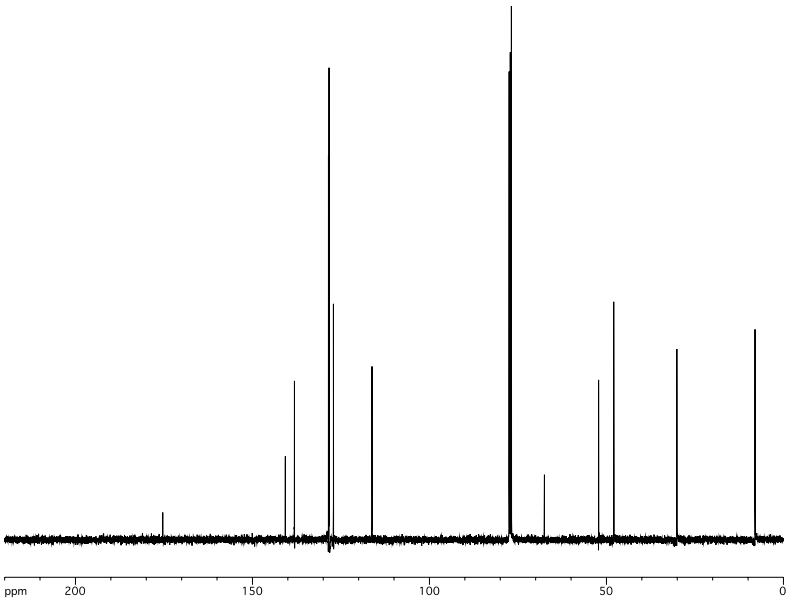


Figure A.2.11 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **247**

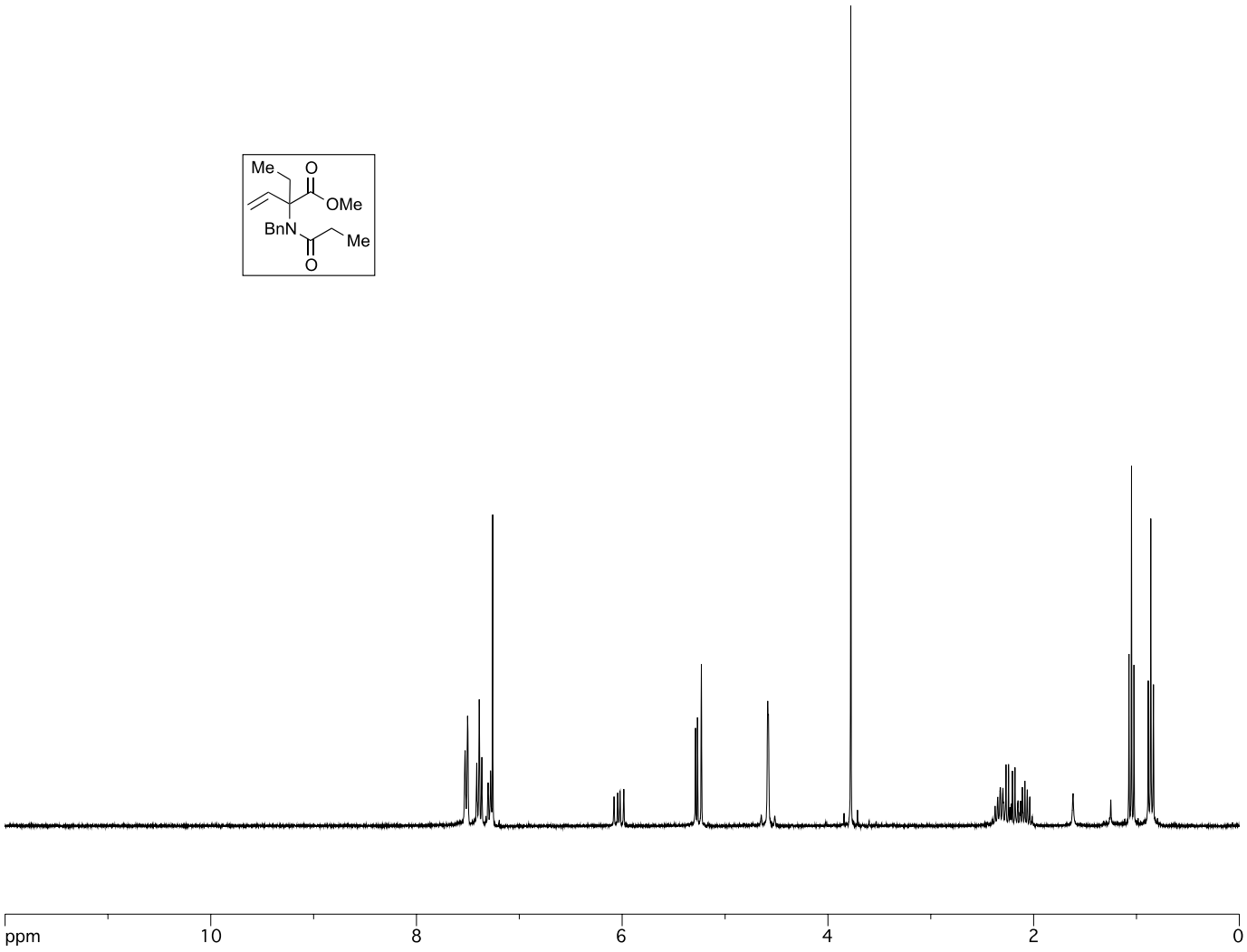


Figure A.2.12 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **248**

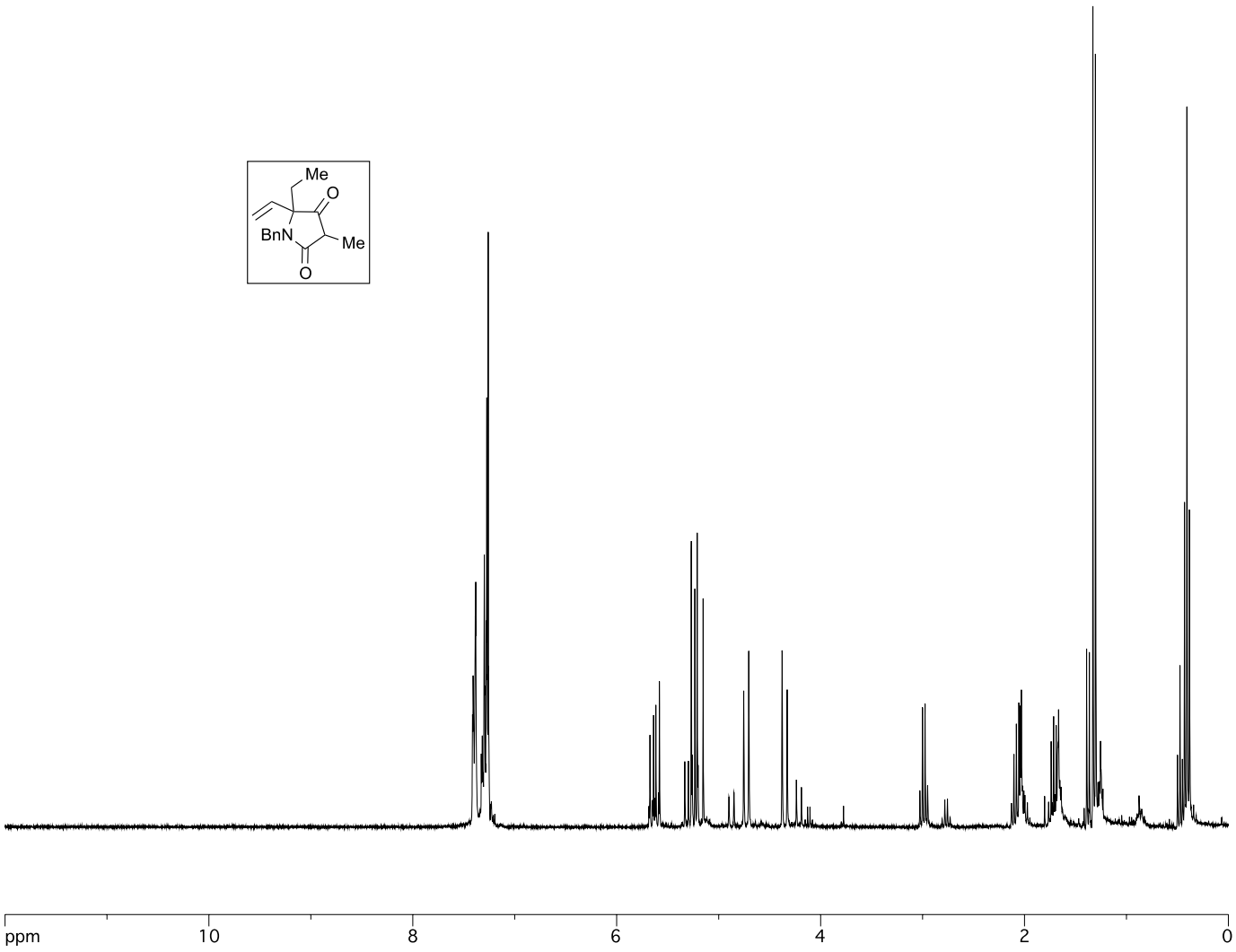


Figure A.2.13 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **249**

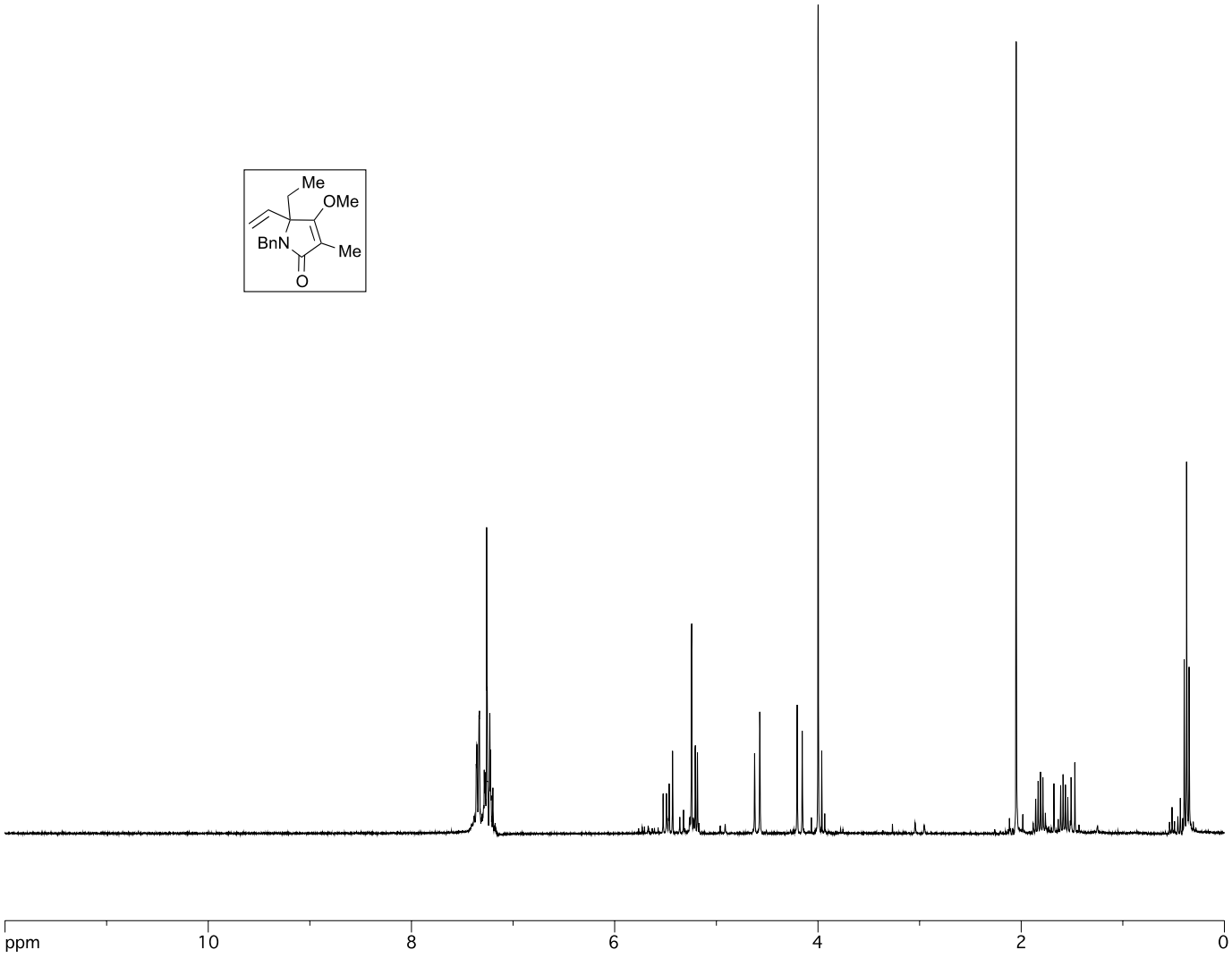


Figure A.2.14 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **250**

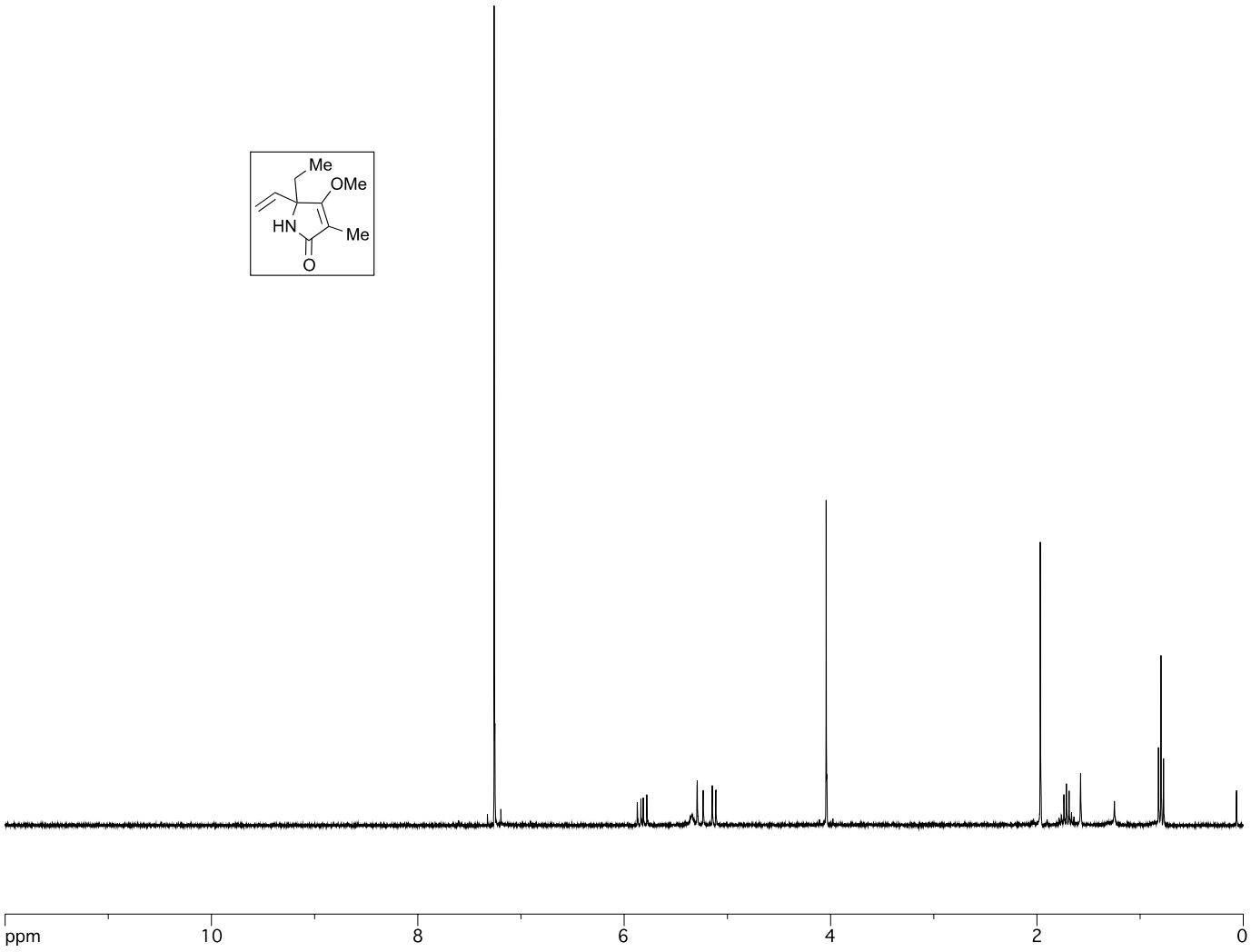


Figure A.2.15 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **251**

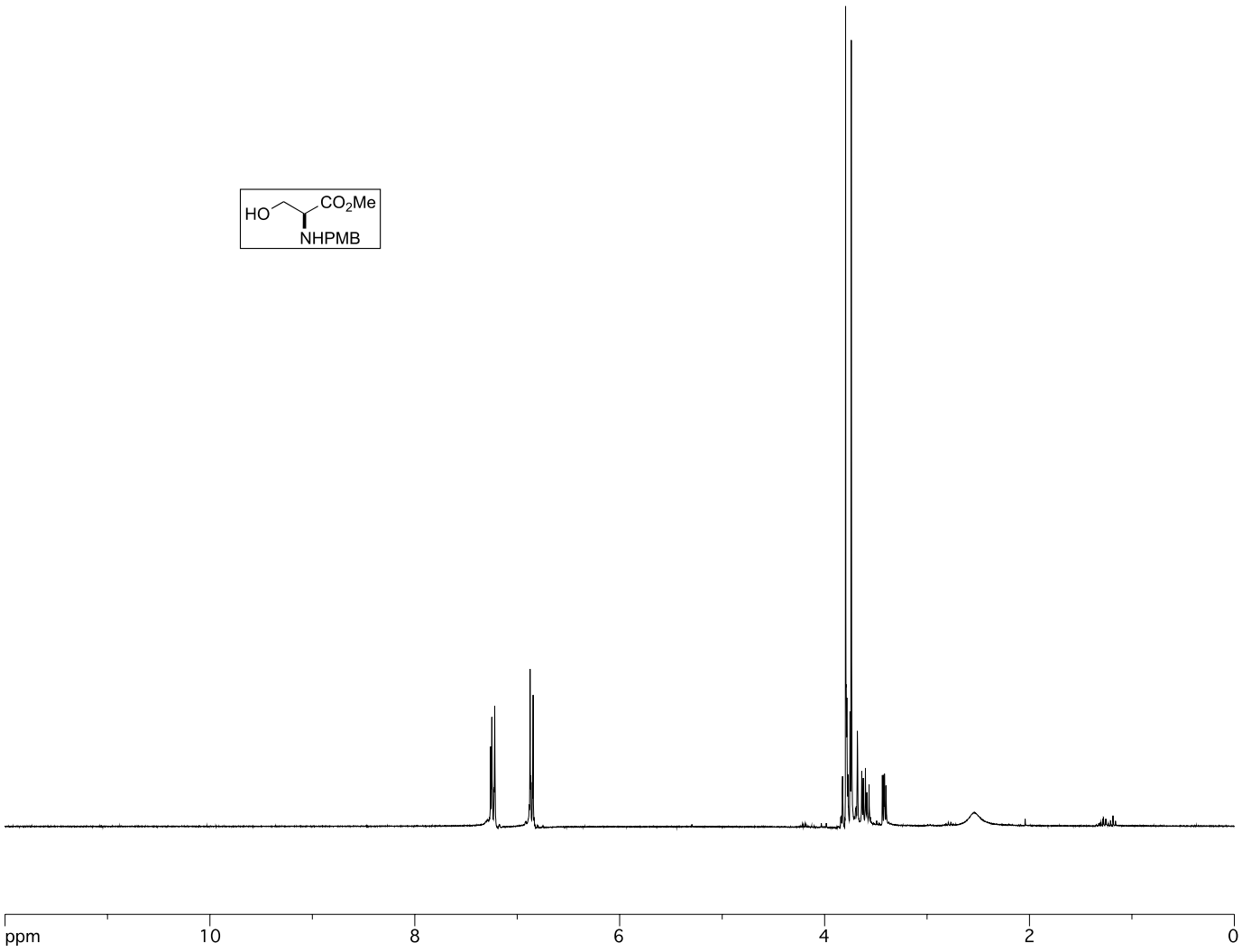


Figure A.2.16 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **253**

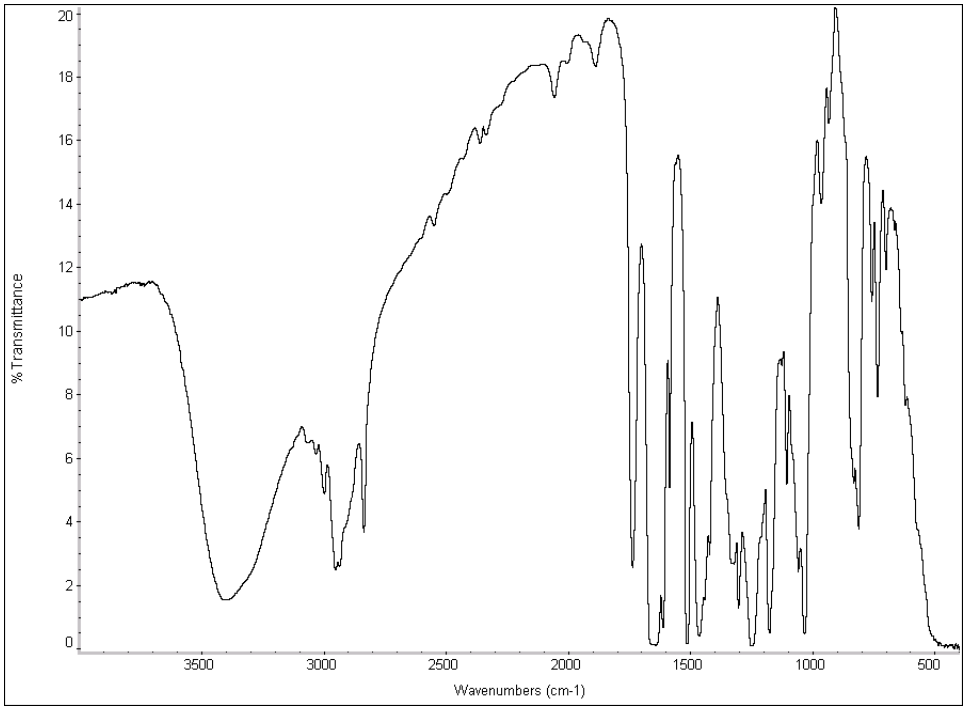


Figure A.2.17 FTIR (thin film/NaCl) of Compound **253**

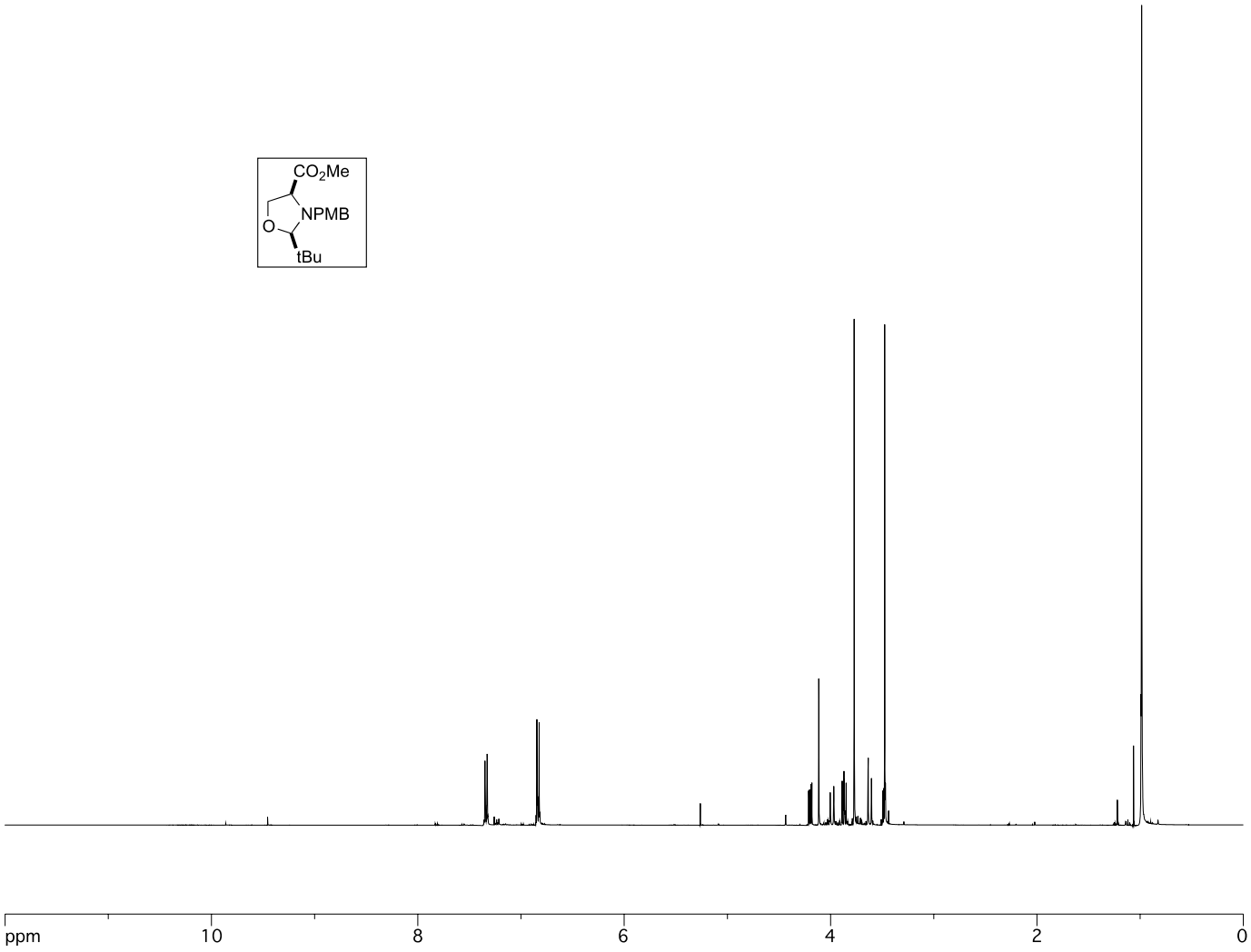


Figure A.2.18 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **254**

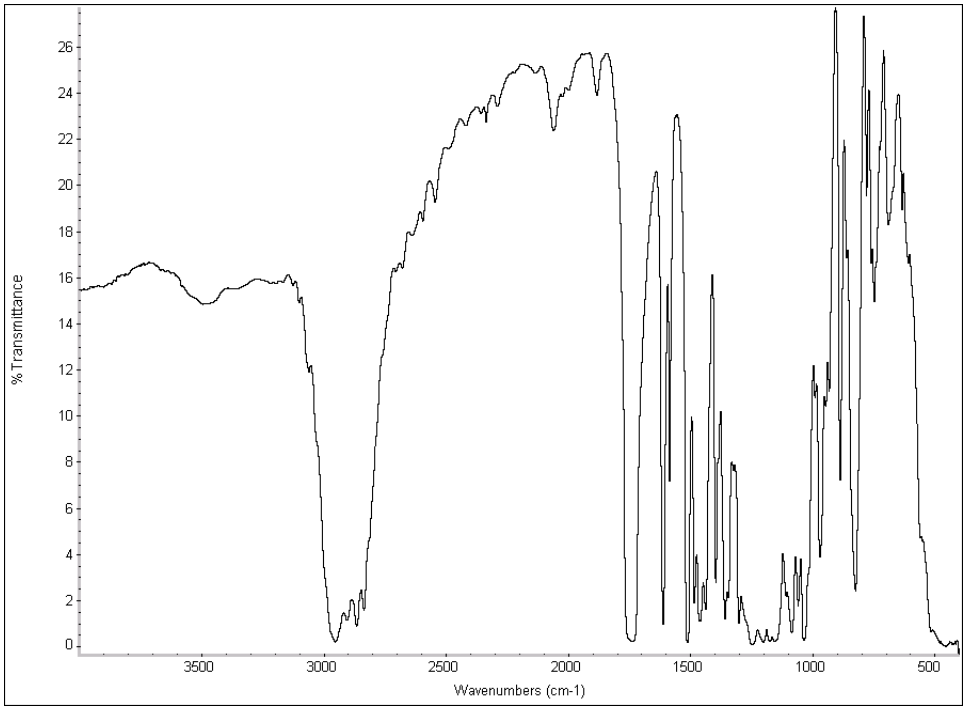


Figure A.2.19 FTIR (thin film/NaCl) of Compound **254**

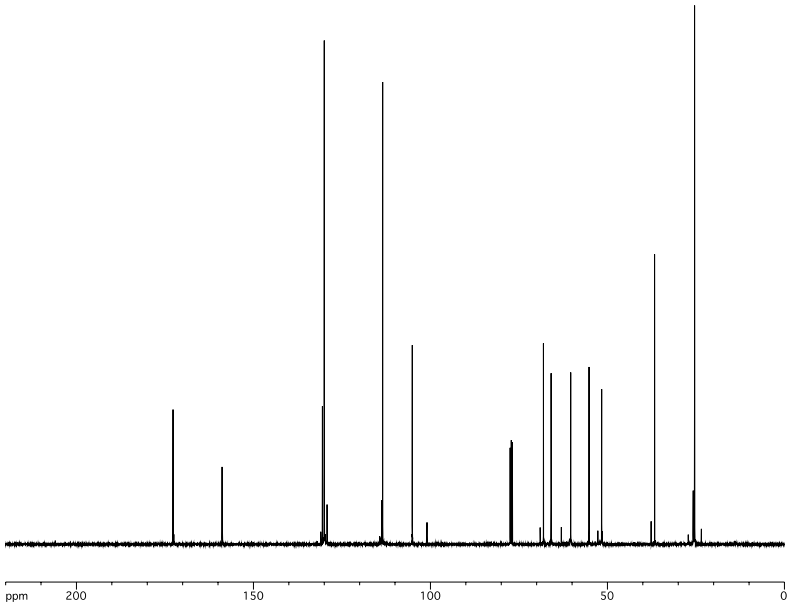


Figure A.2.20 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **254**

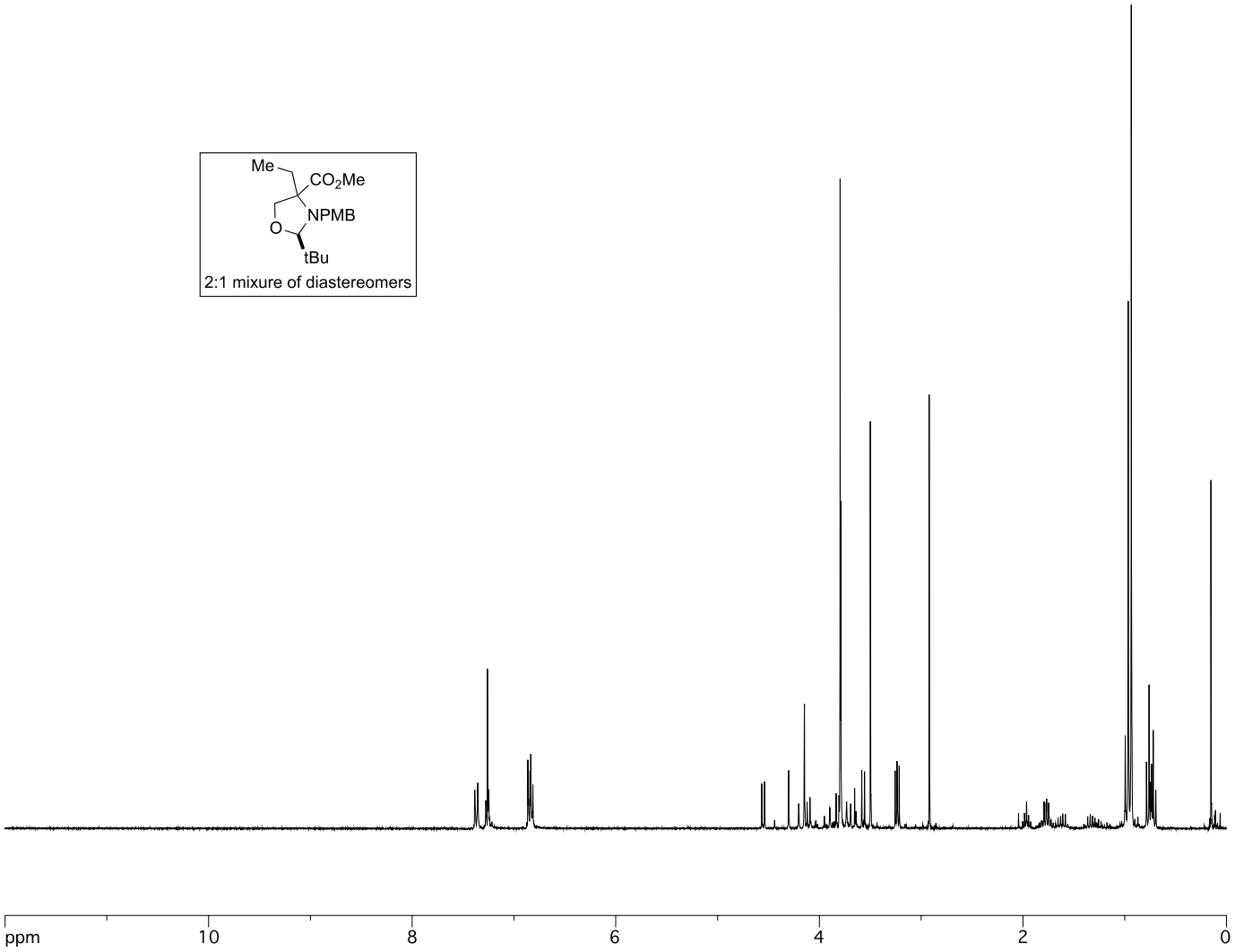


Figure A.2.21 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **256**

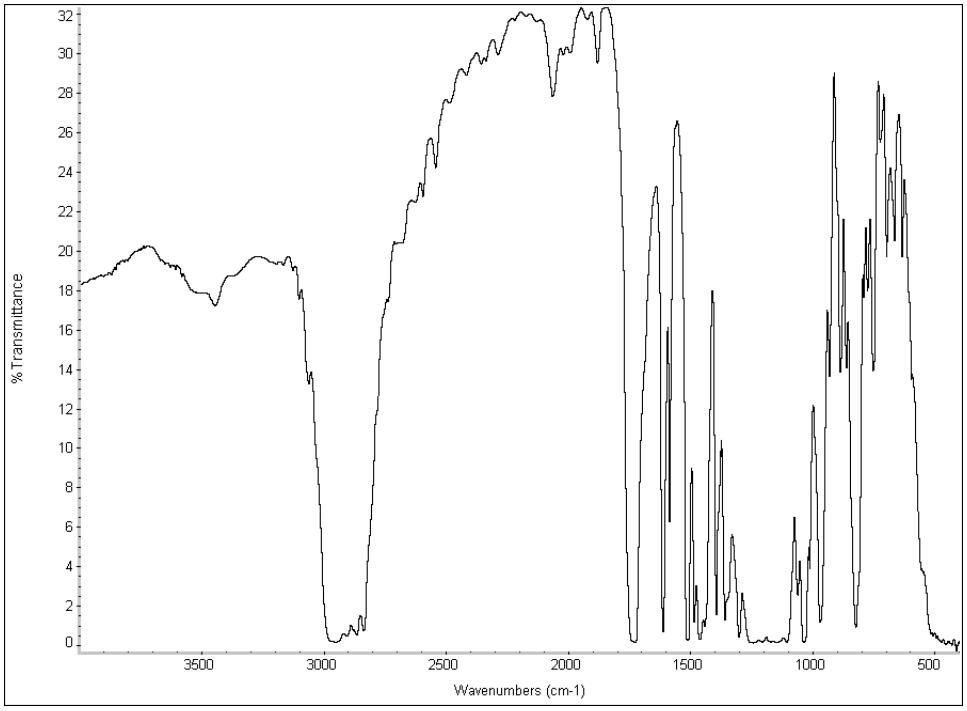


Figure A.2.22 FTIR (thin film/NaCl) of Compound **256**

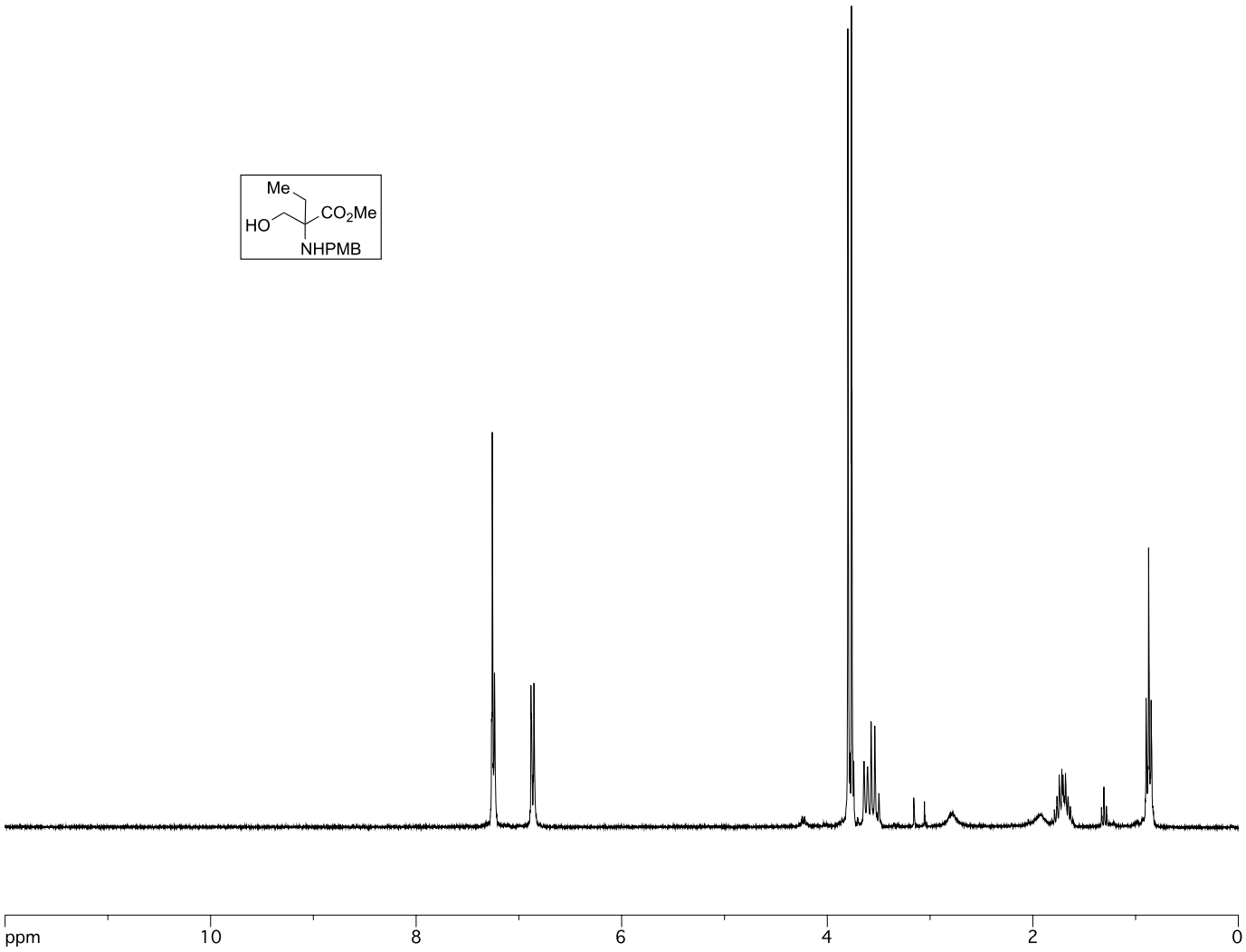


Figure A.2.23 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **257**

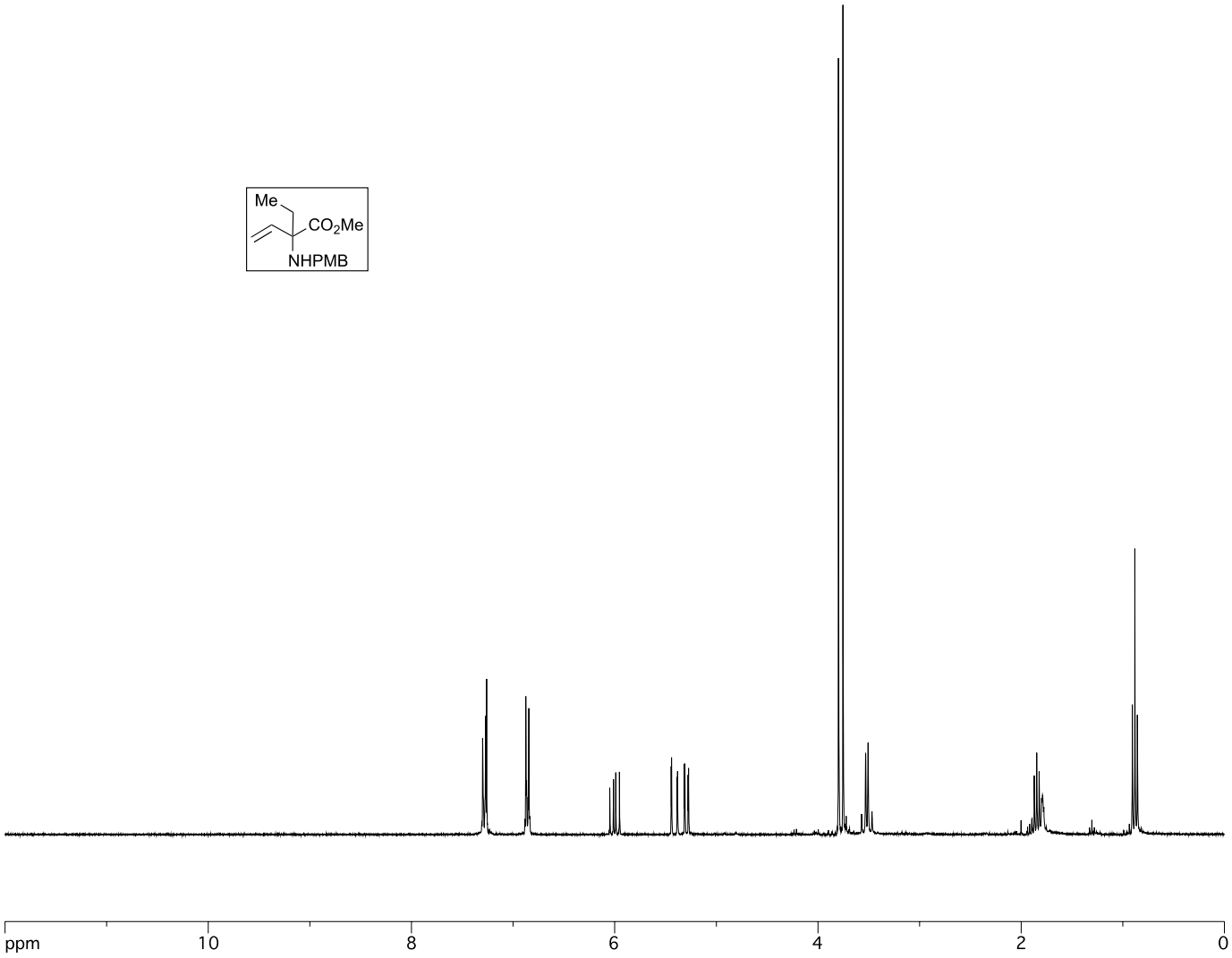


Figure A.2.24 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **259**

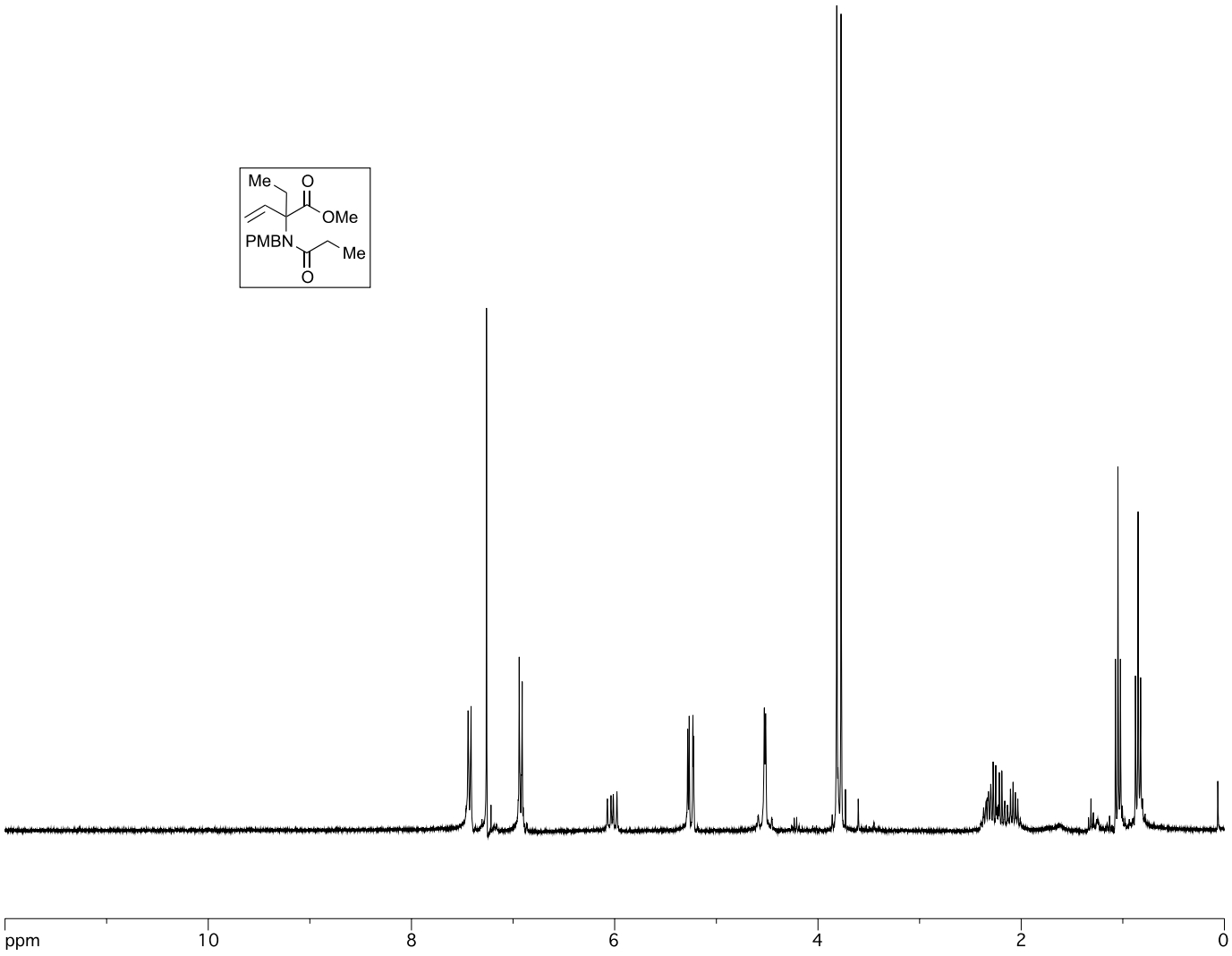


Figure A.2.25 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **260**

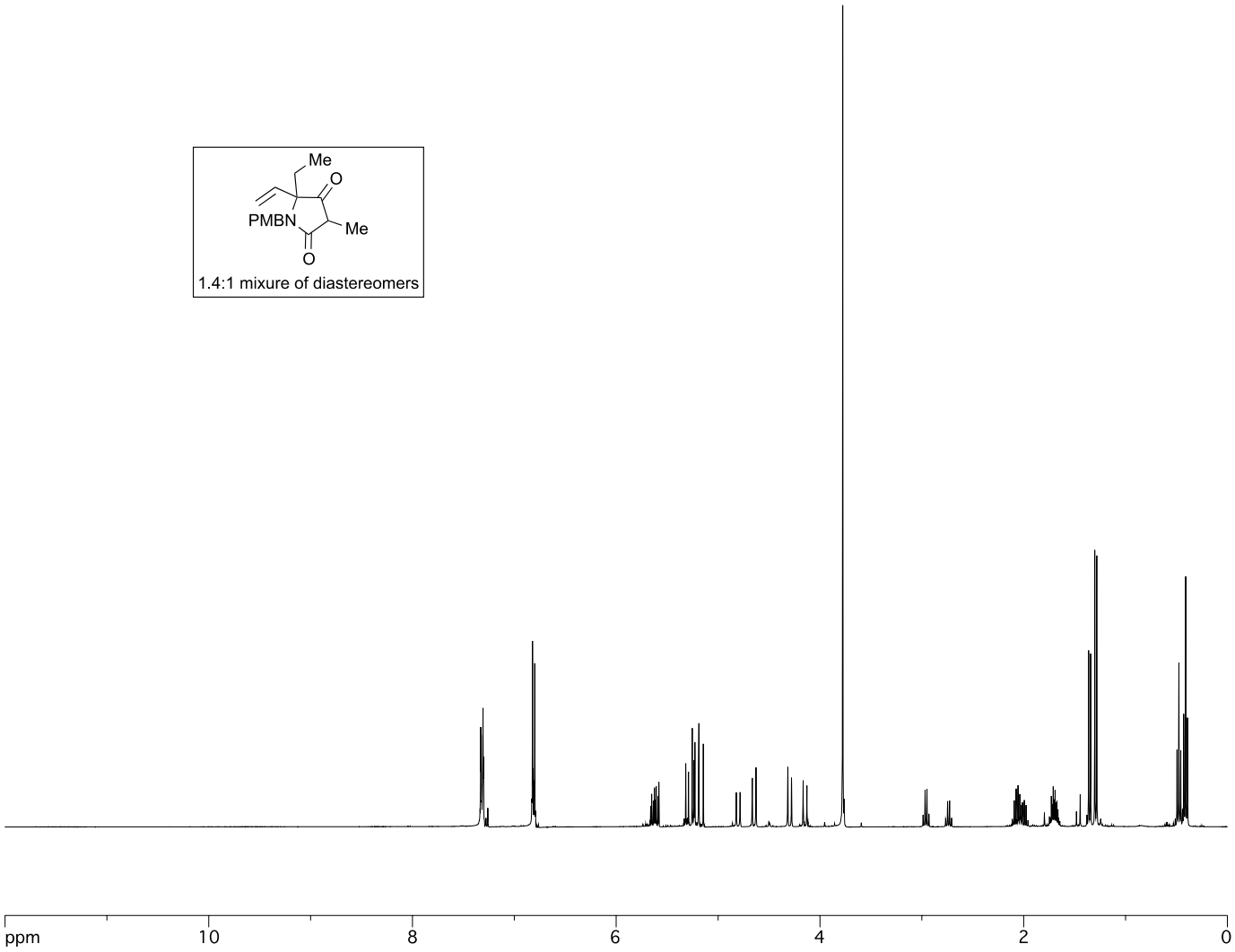


Figure A.2.26 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **261**

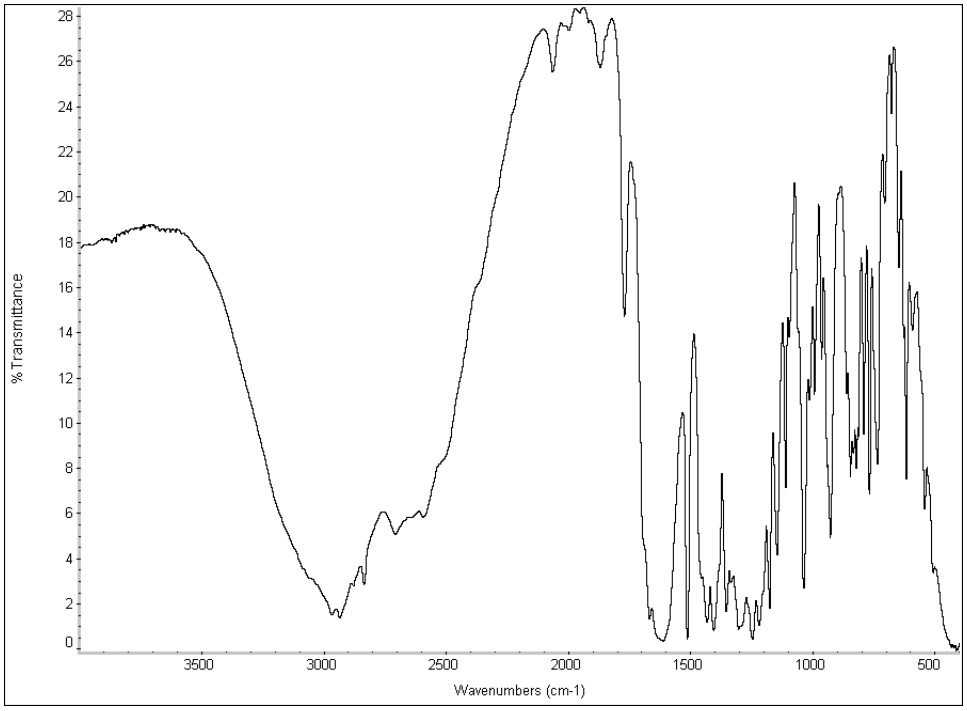


Figure A.2.27 FTIR (thin film/NaCl) of Compound **261**

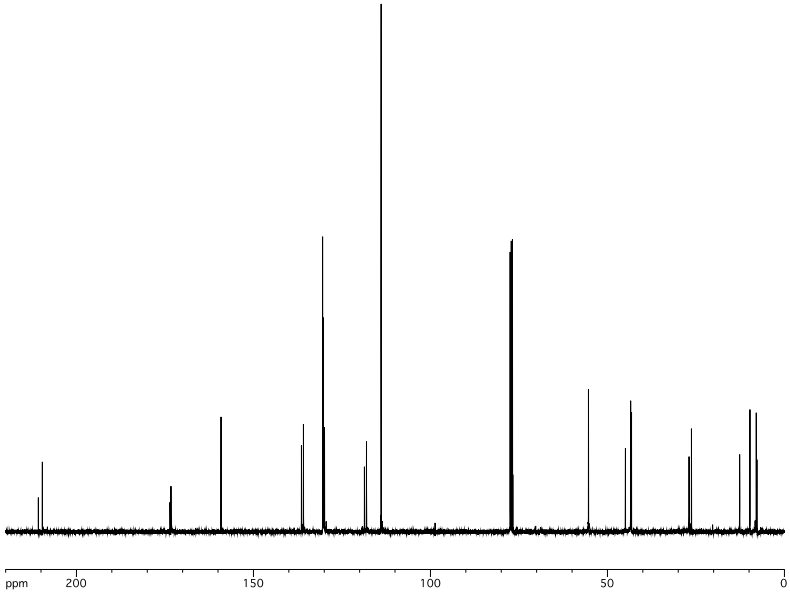


Figure A.2.28 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **261**

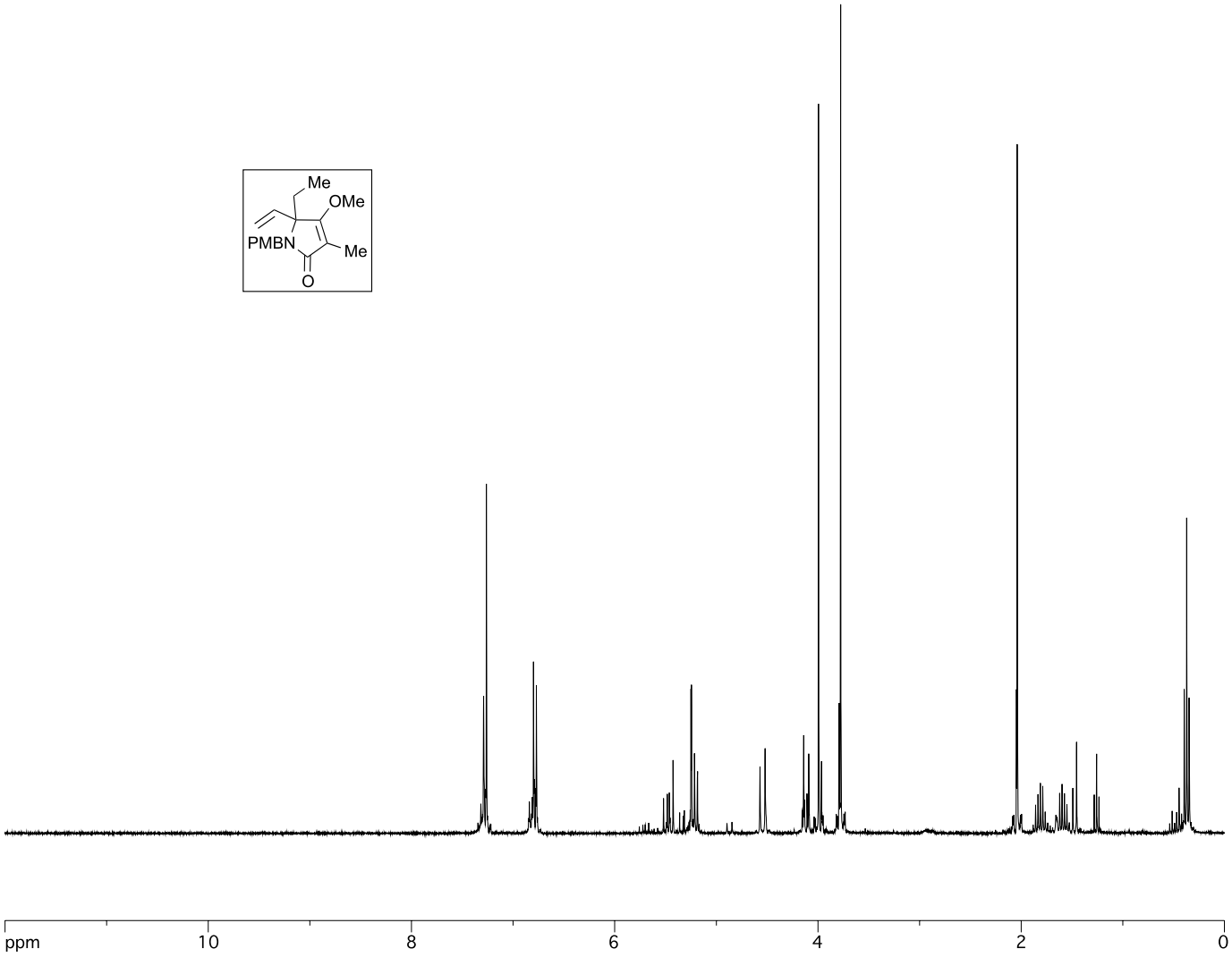


Figure A.2.29 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **262**

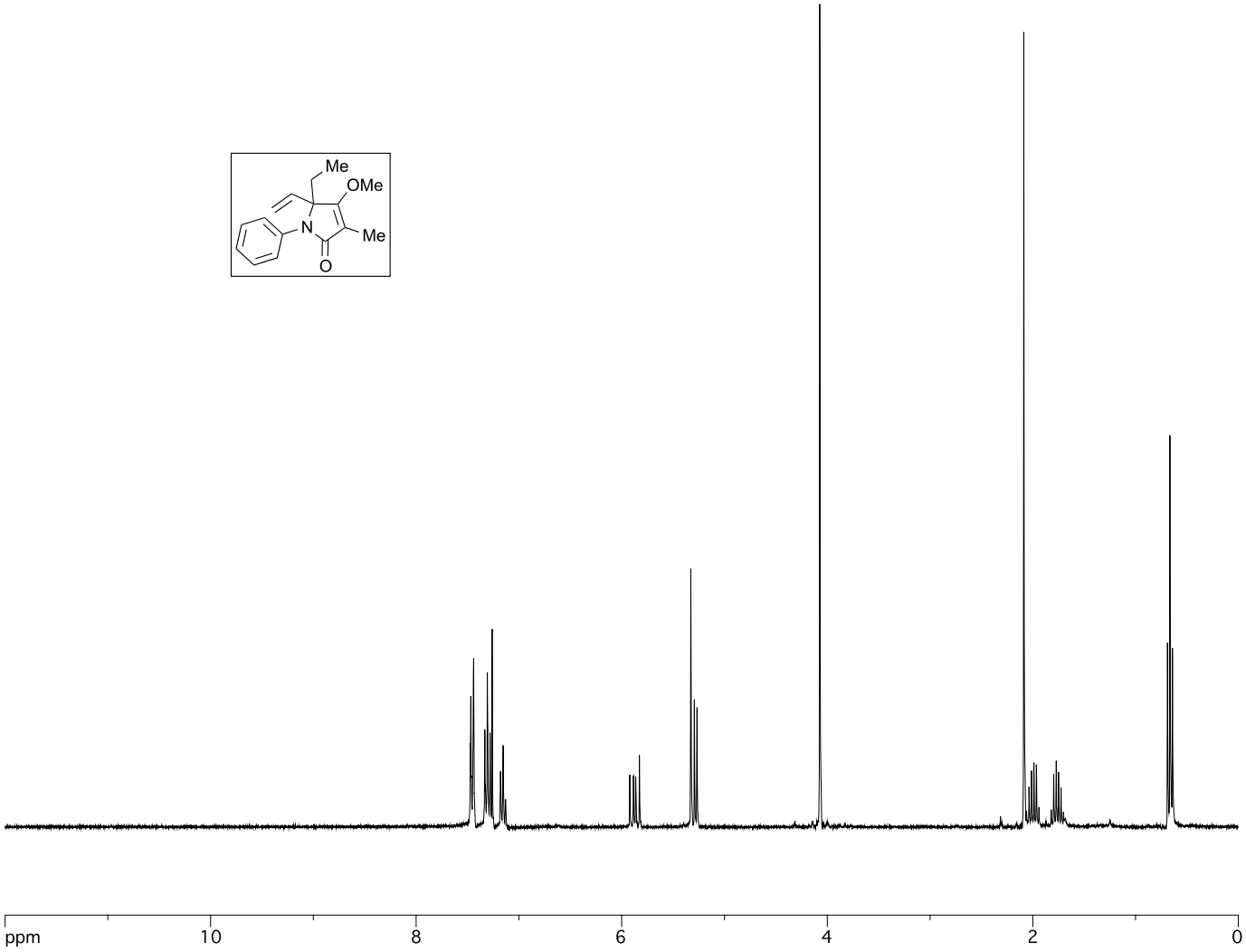


Figure A.2.30 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **272**

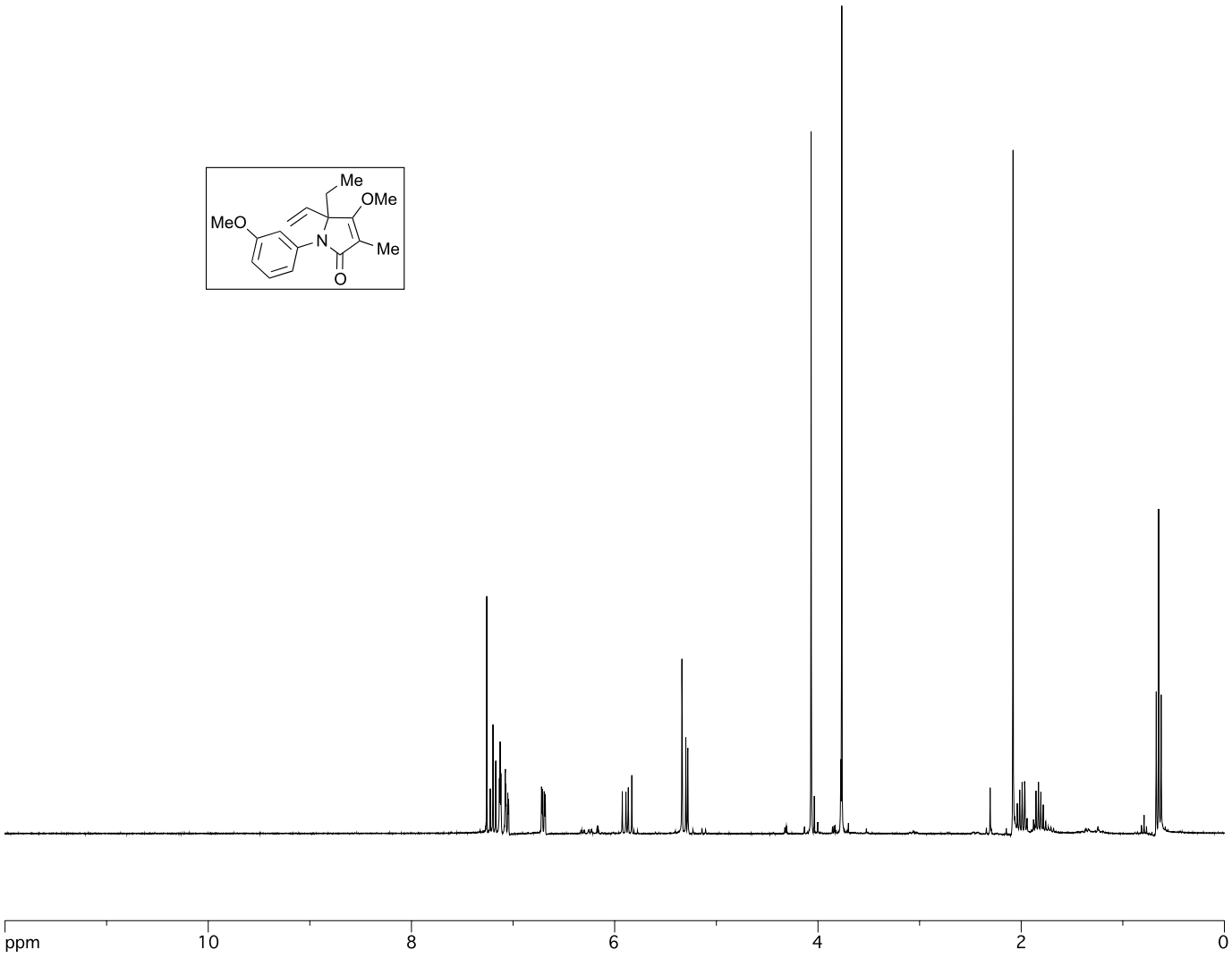


Figure A.2.31 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **274**

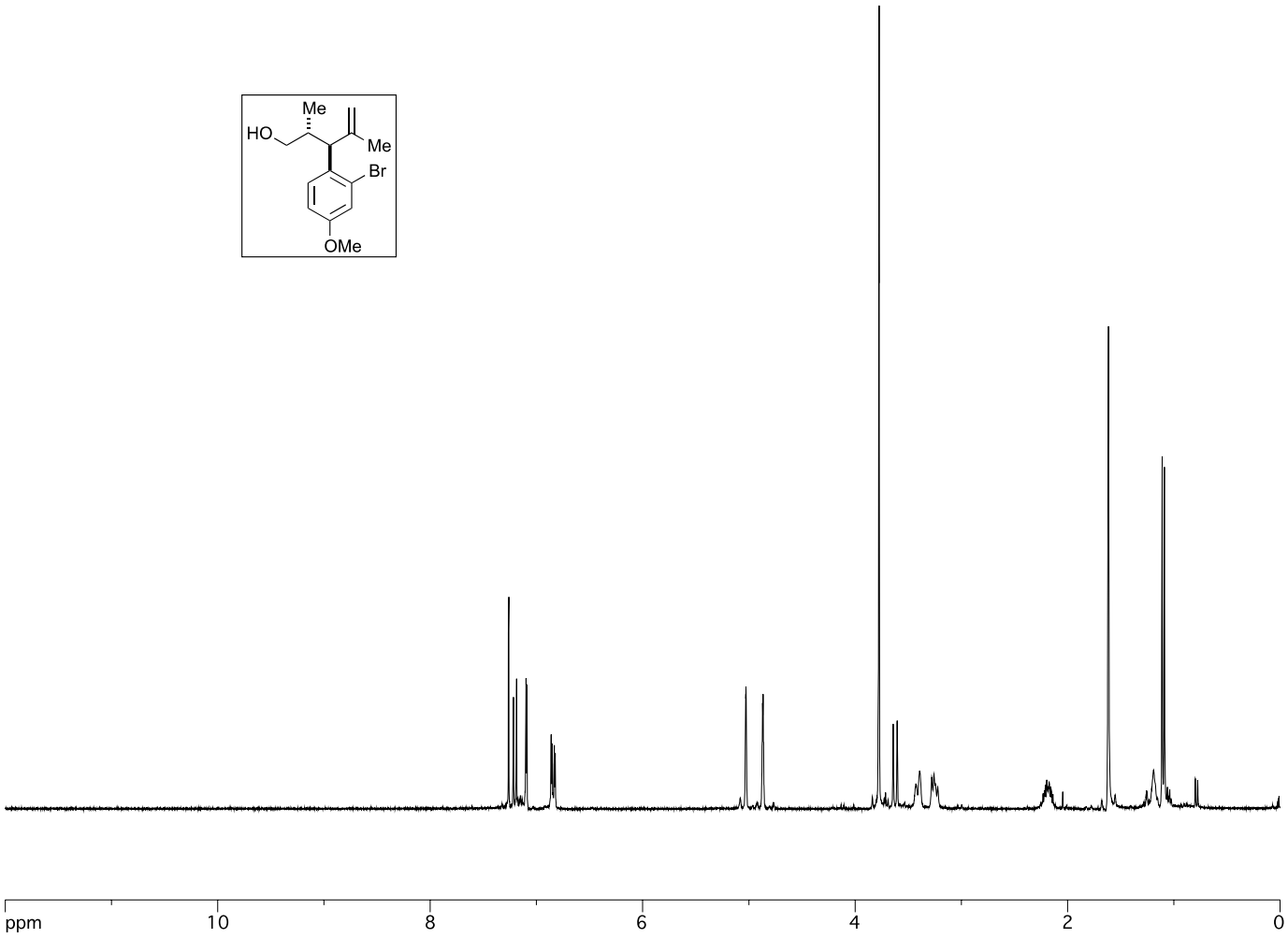


Figure A.2.32 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **318**

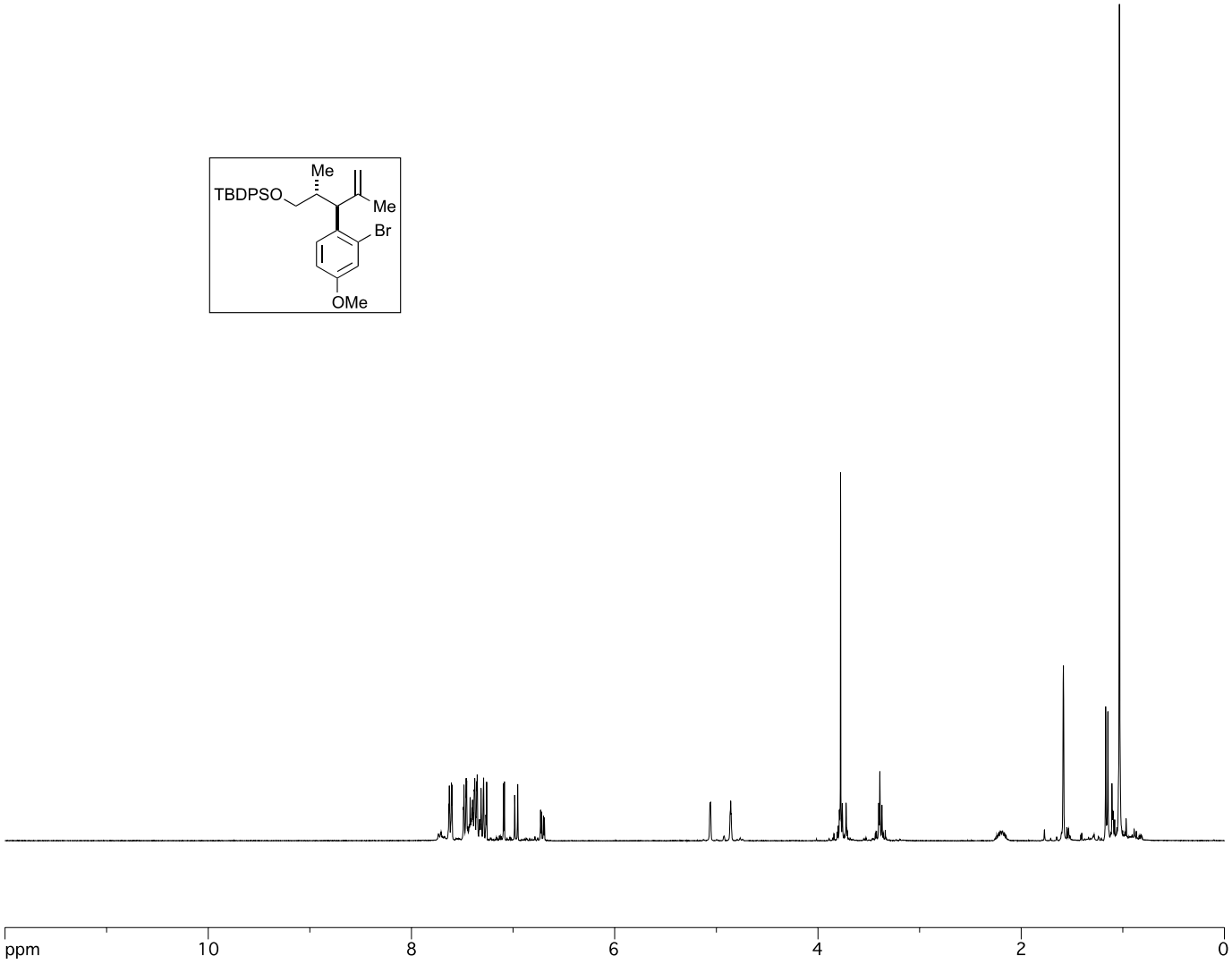


Figure A.2.33 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **277**

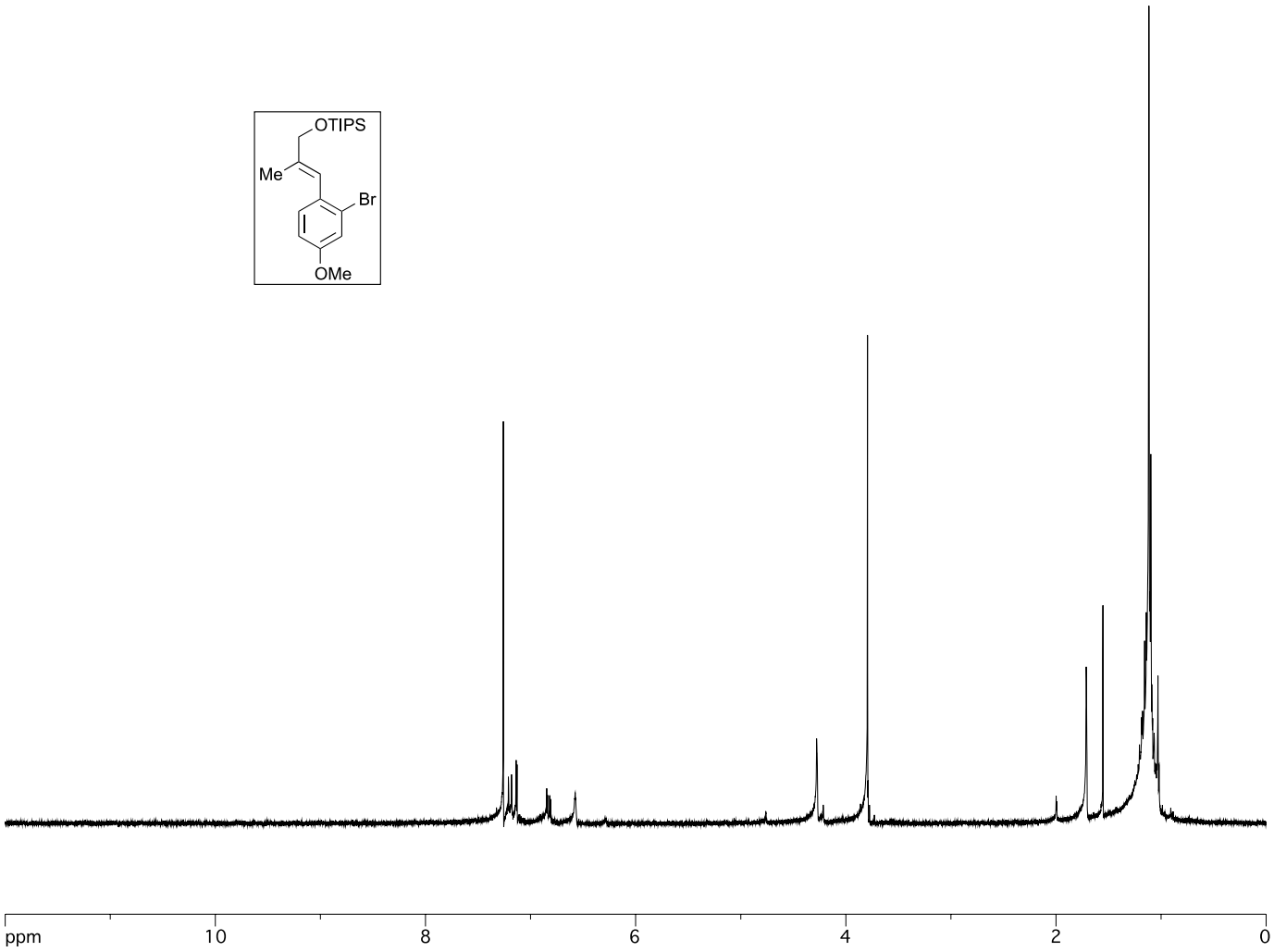


Figure A.2.34 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **279**

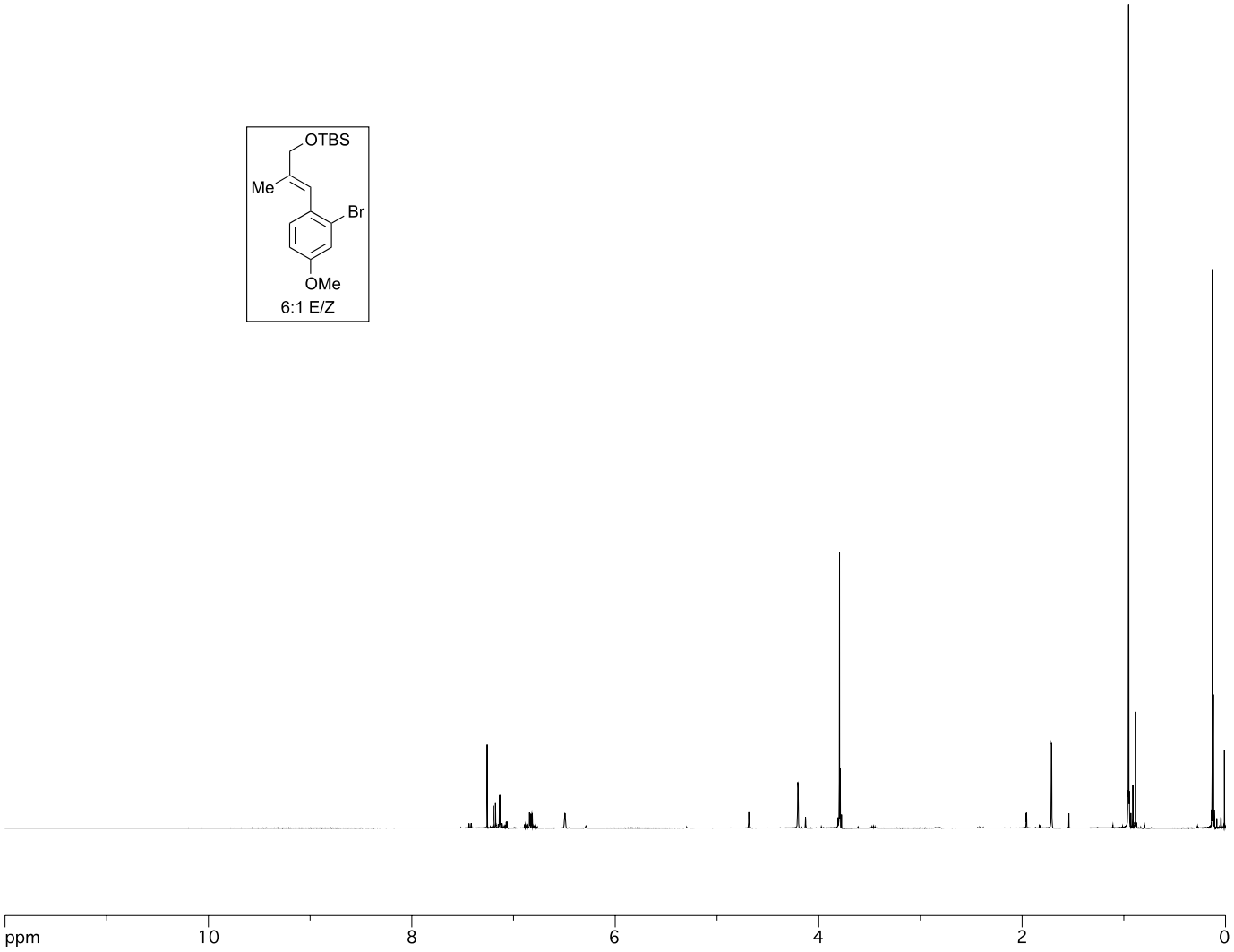


Figure A.2.35 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **294**

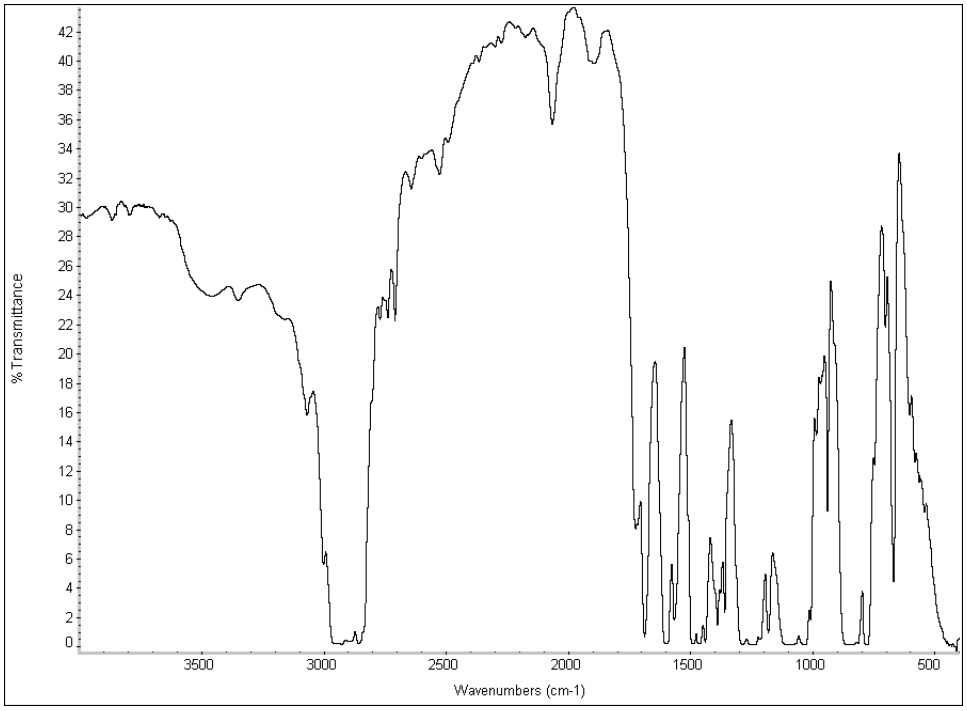


Figure A.2.36 FTIR (thin film/NaCl) of Compound **294**

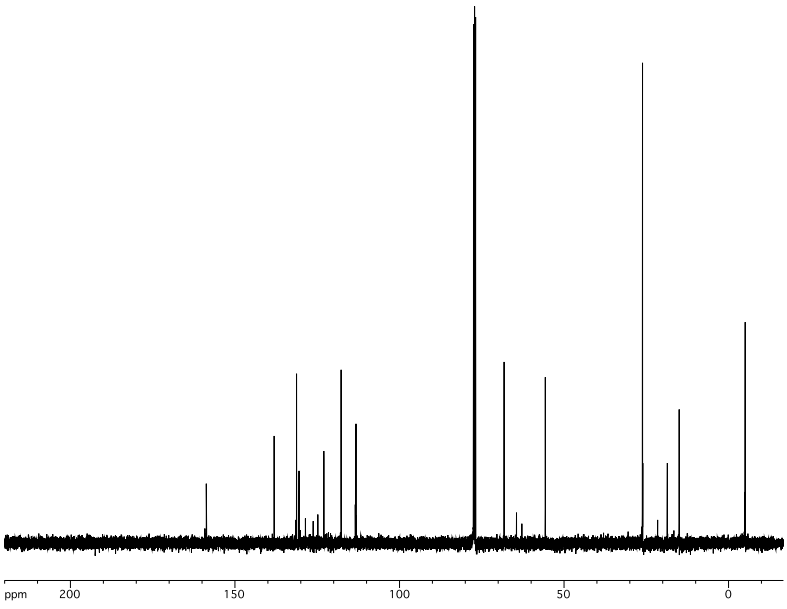


Figure A.2.37 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **294**

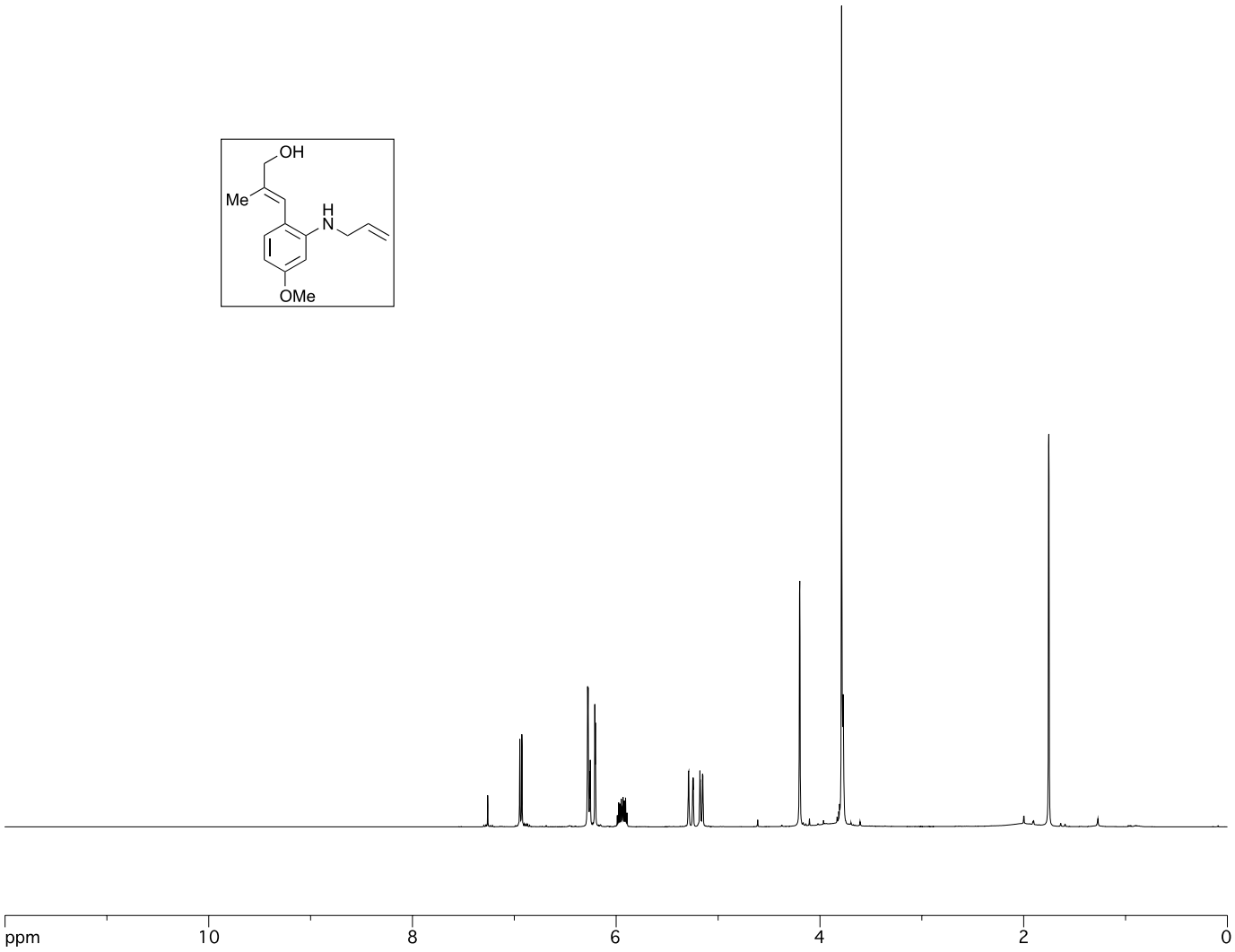


Figure A.2.38 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **296**

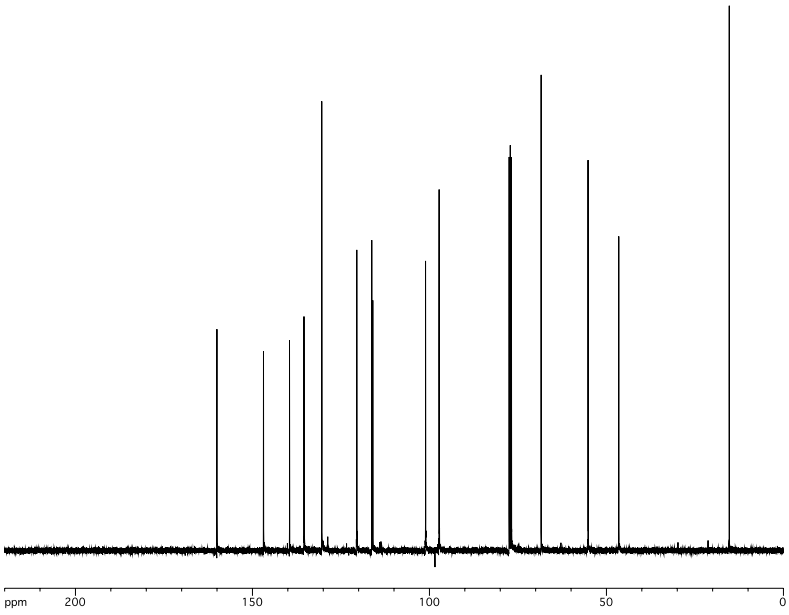


Figure A.2.39 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **296**

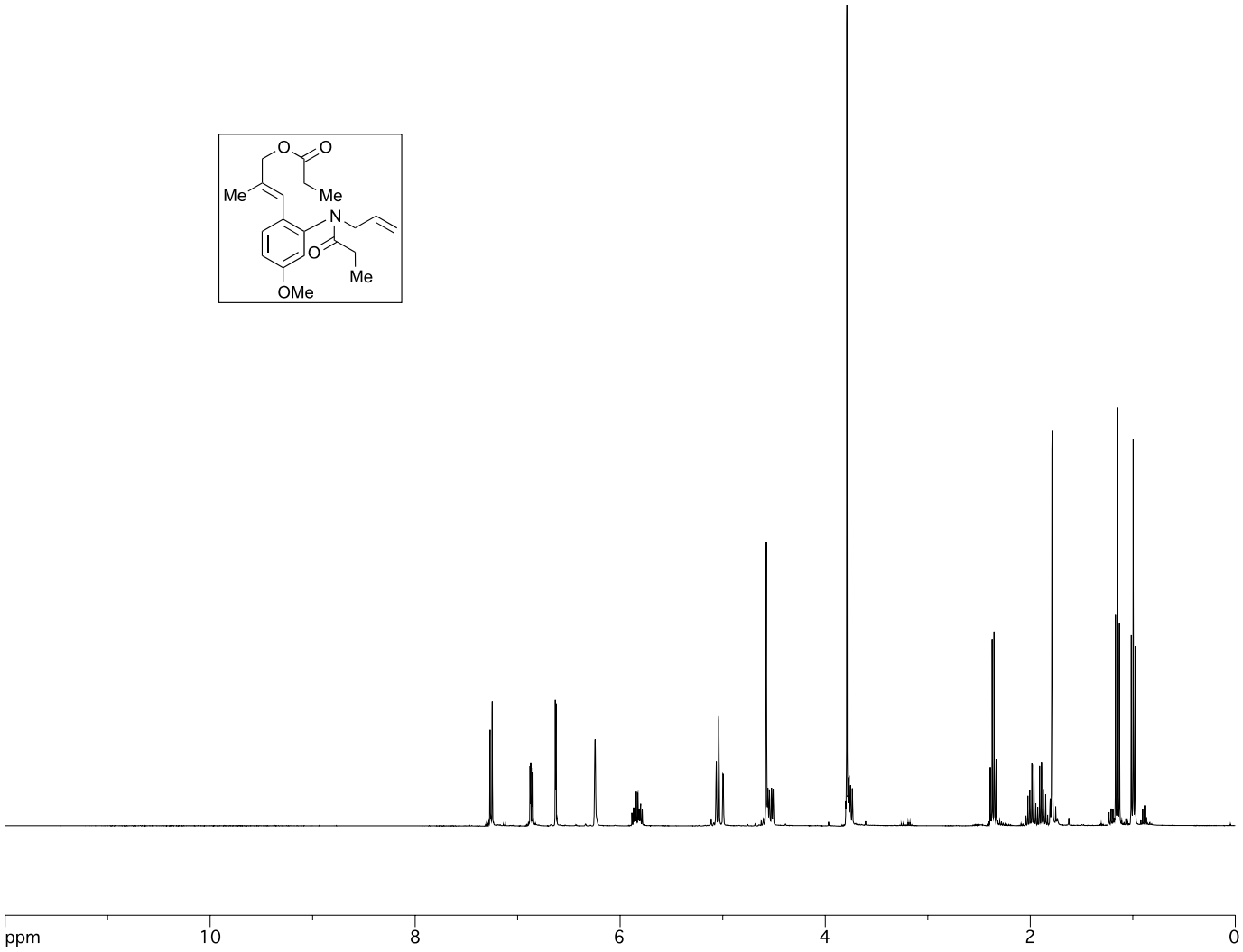


Figure A.2.40 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **297**

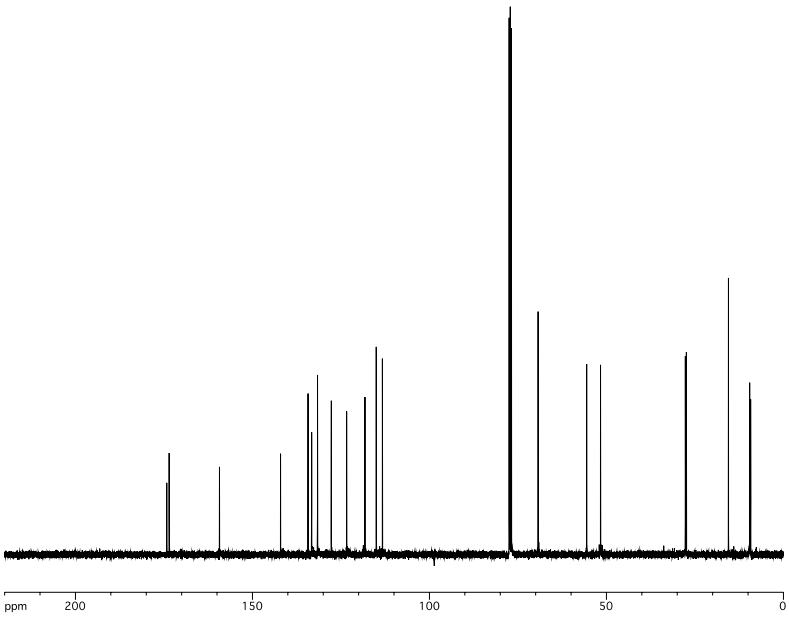


Figure A.2.41 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **297**

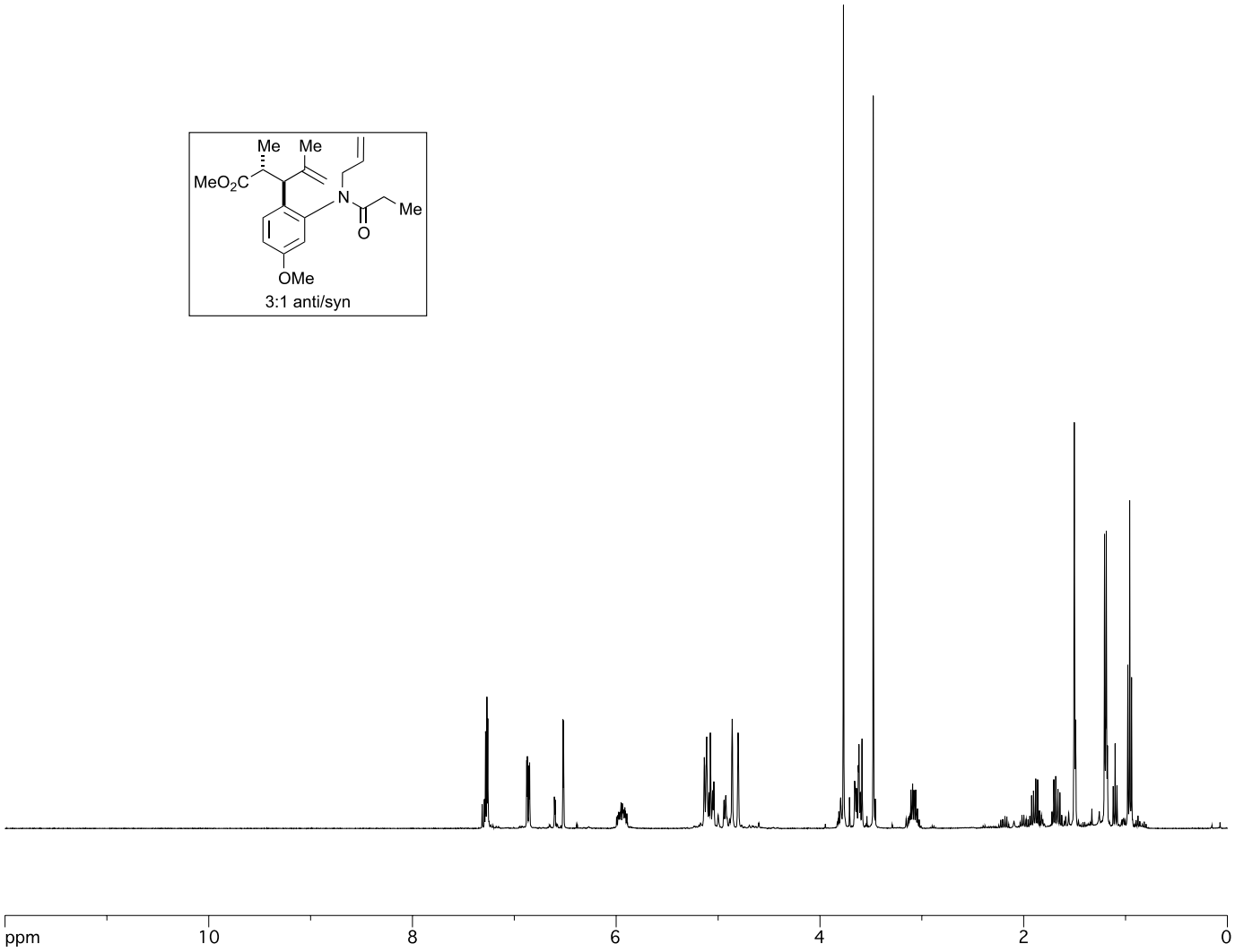


Figure A.2.42 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **298**

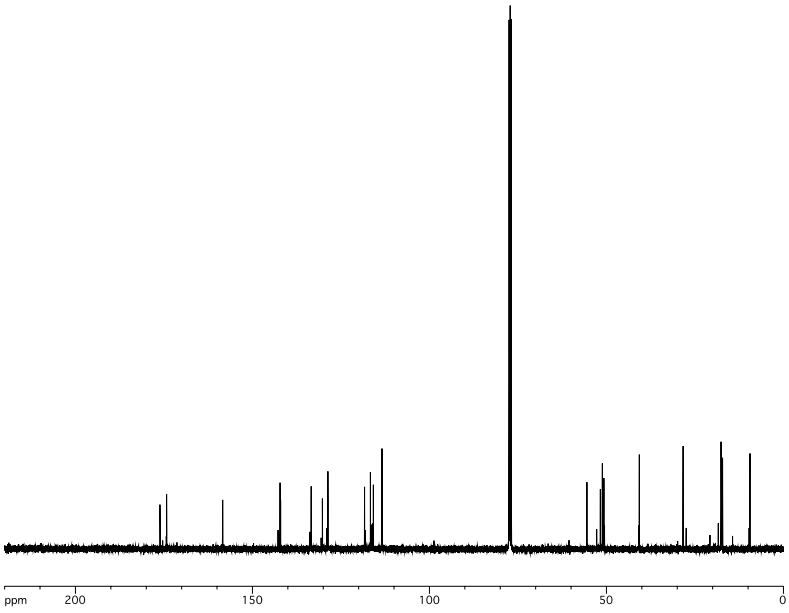


Figure A.2.43 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **298**

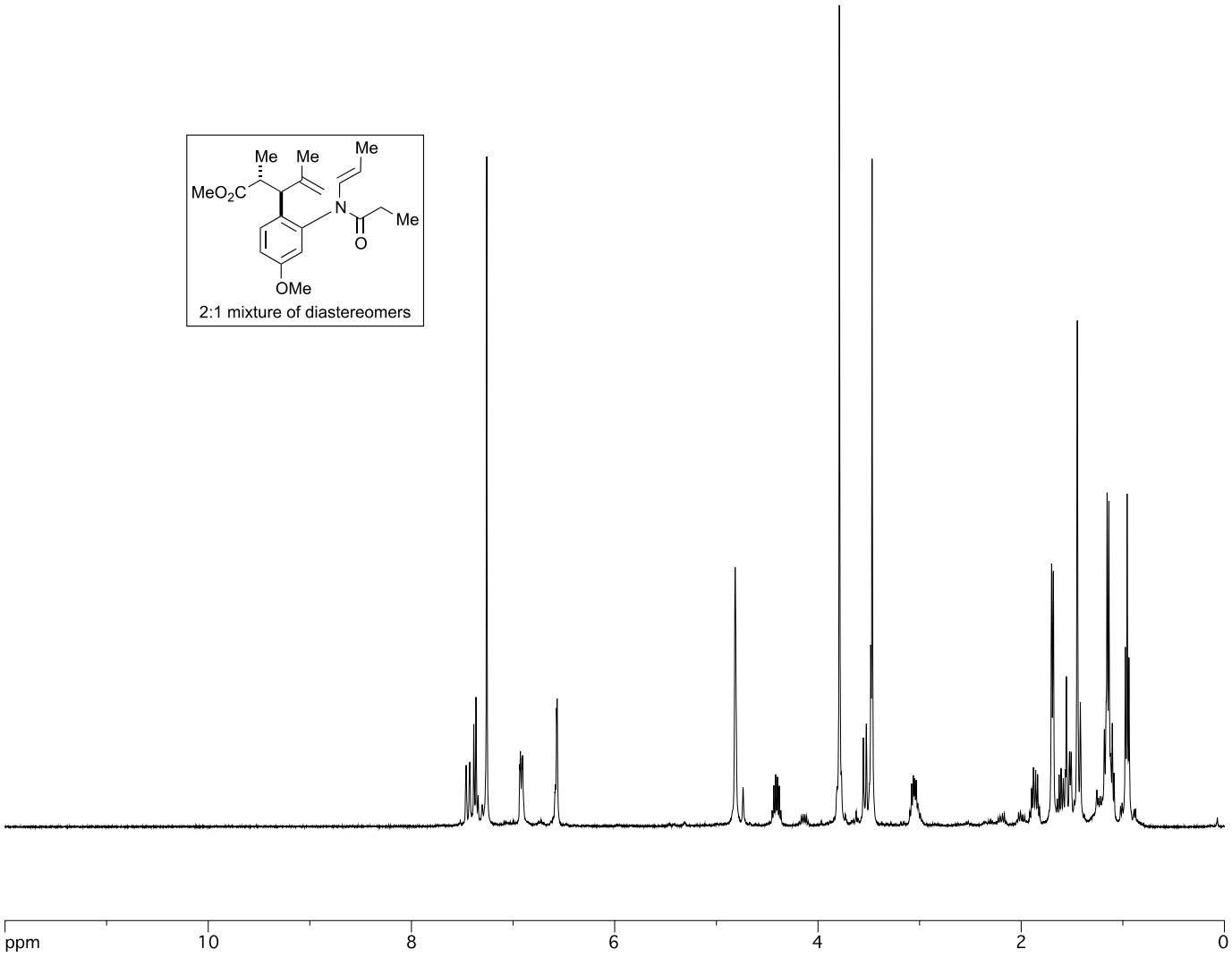


Figure A.2.44 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **308**

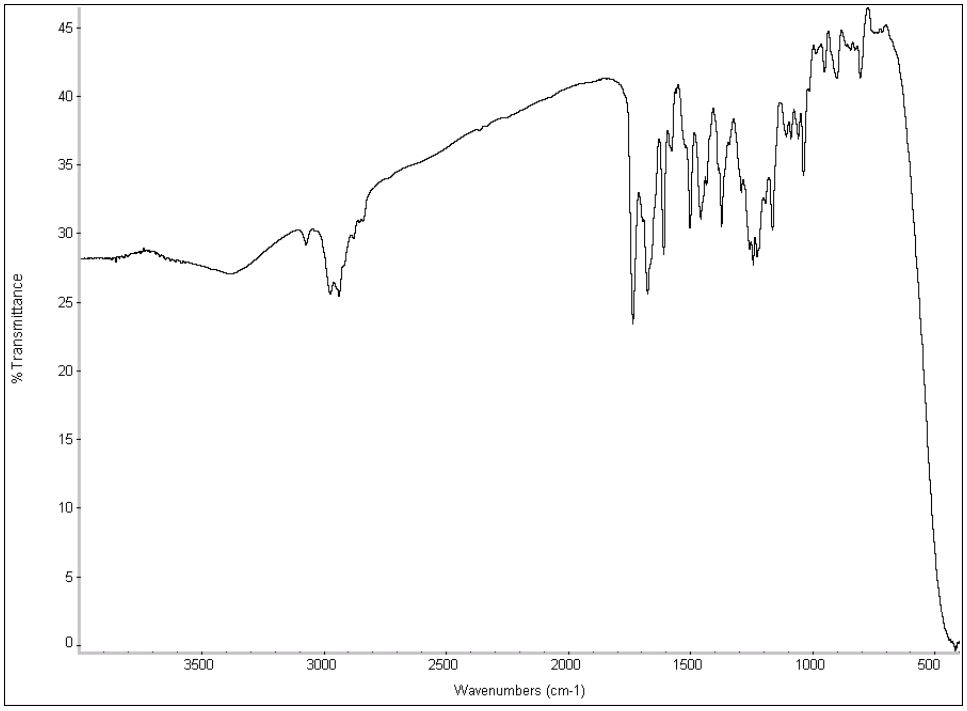


Figure A.2.45 FTIR (thin film/NaCl) of Compound **308**

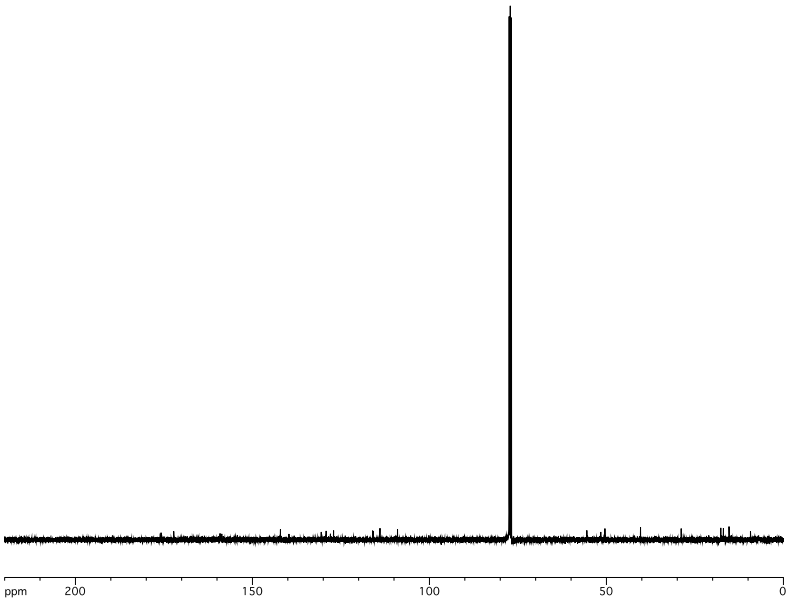


Figure A.2.46 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **308**

Appendix 3

Spectra Relevant to Chapter 4

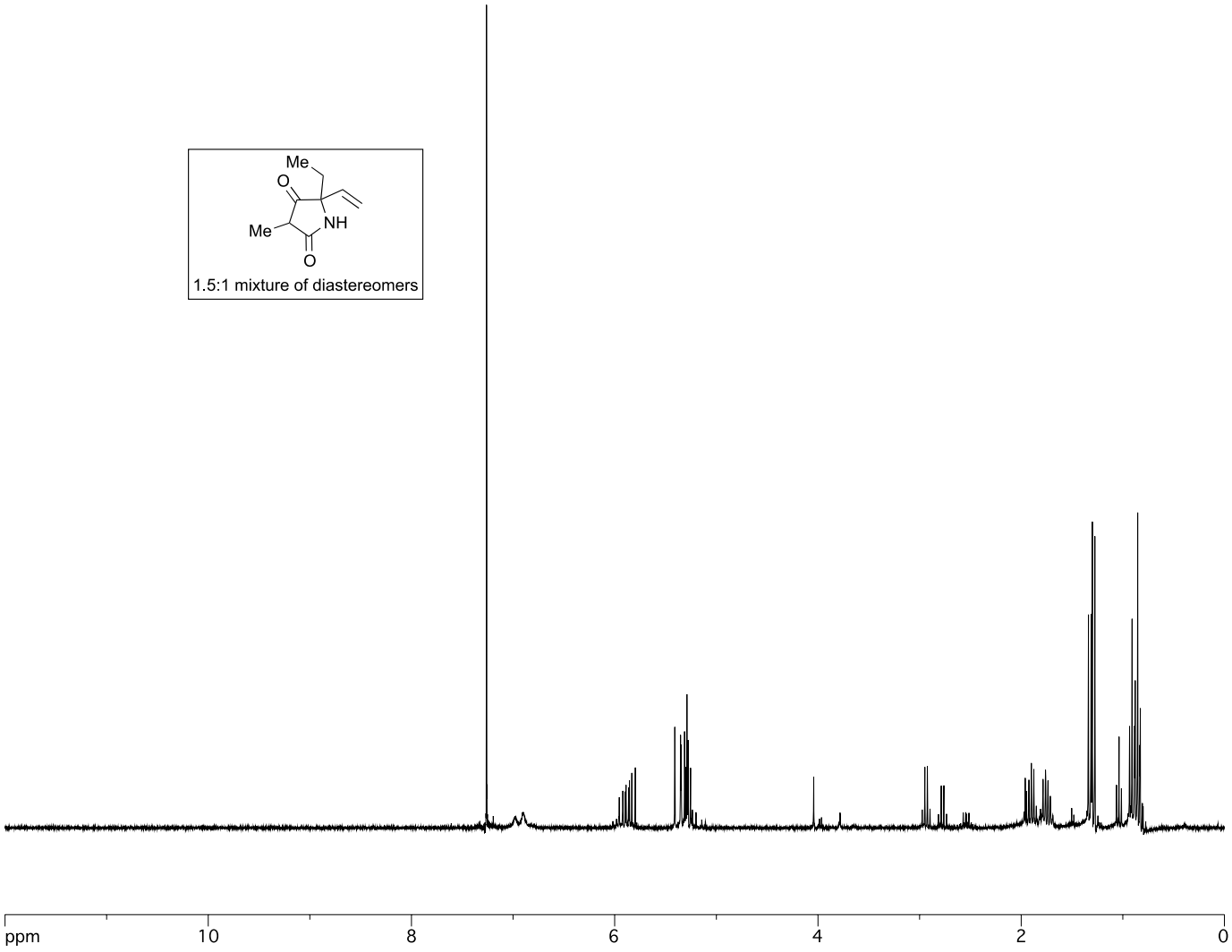


Figure A.3.1 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **337**

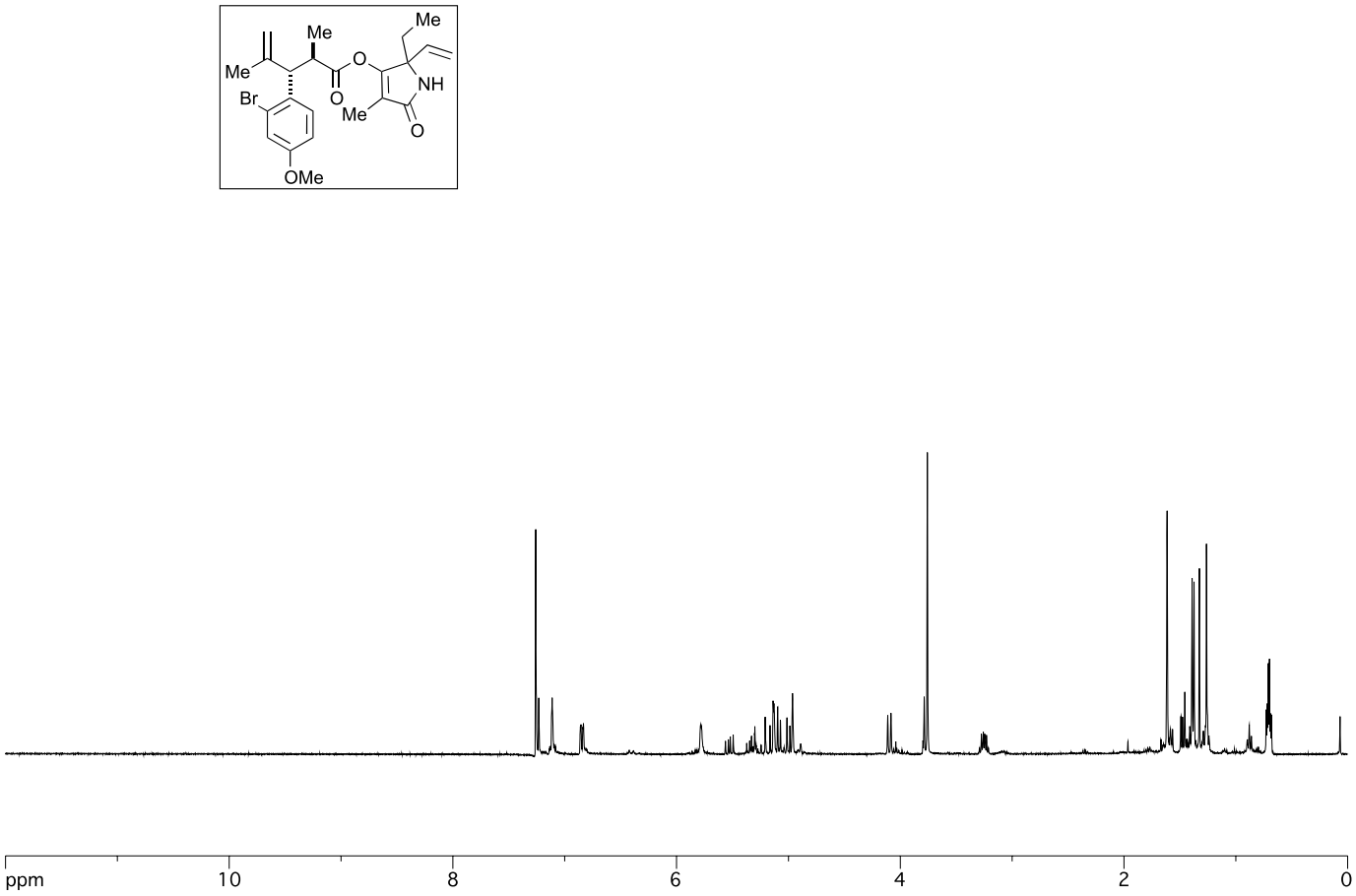


Figure A.3.2 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **338**

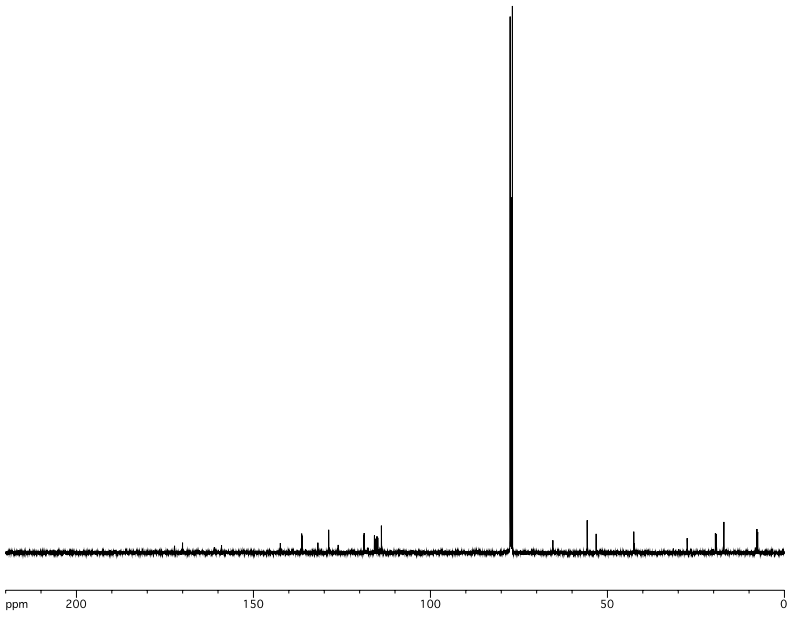


Figure A.3.3 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **338**

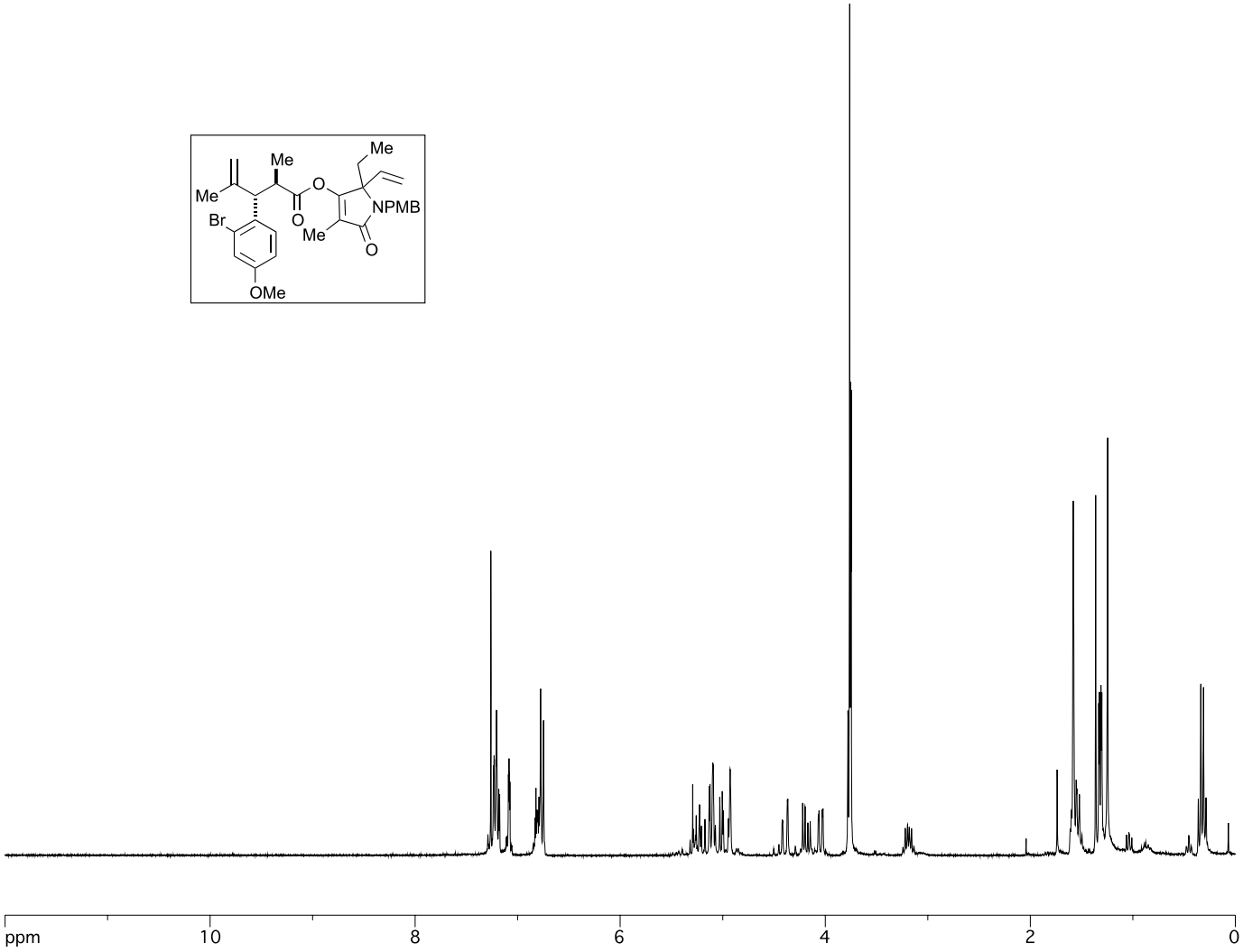


Figure A.3.4 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **339**

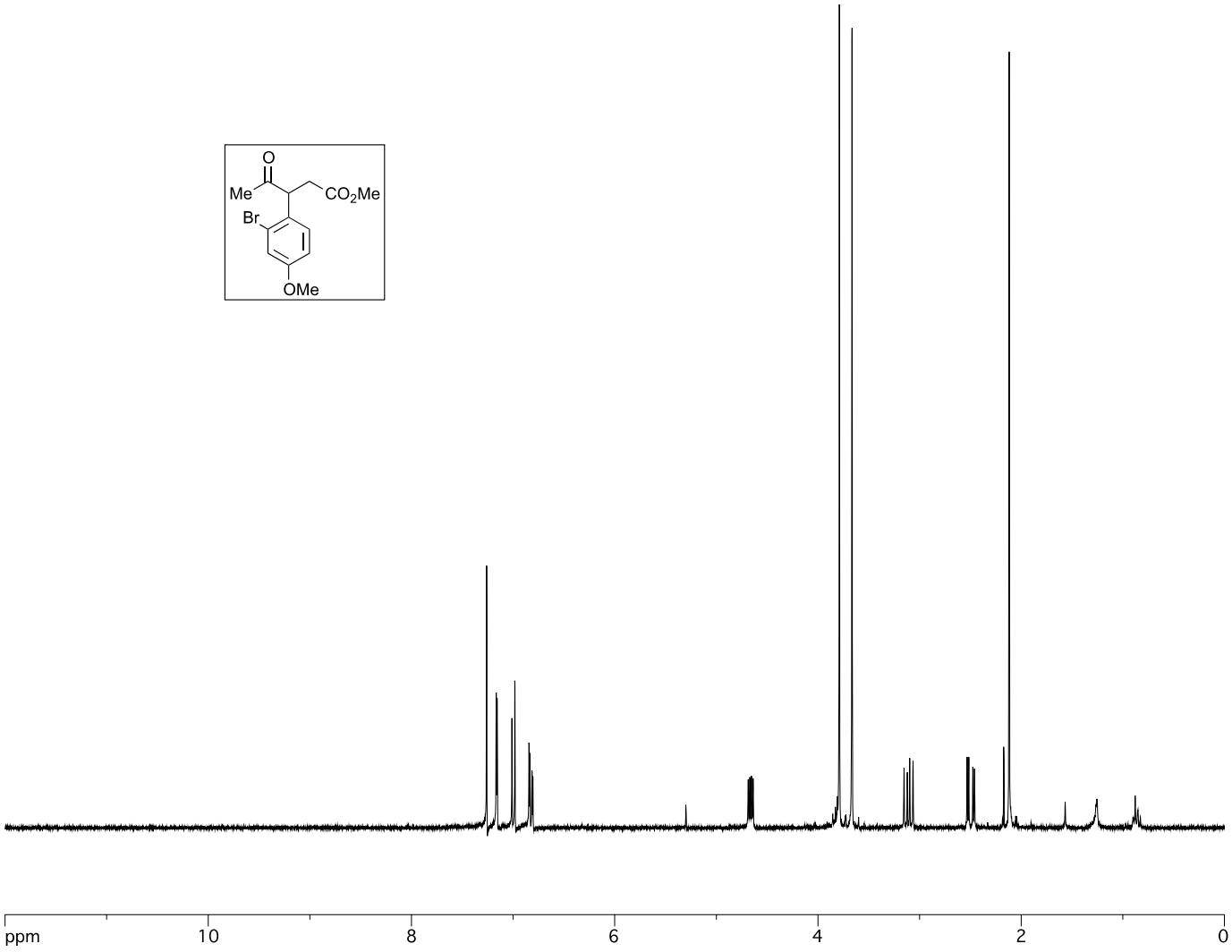


Figure A.3.5 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **350**

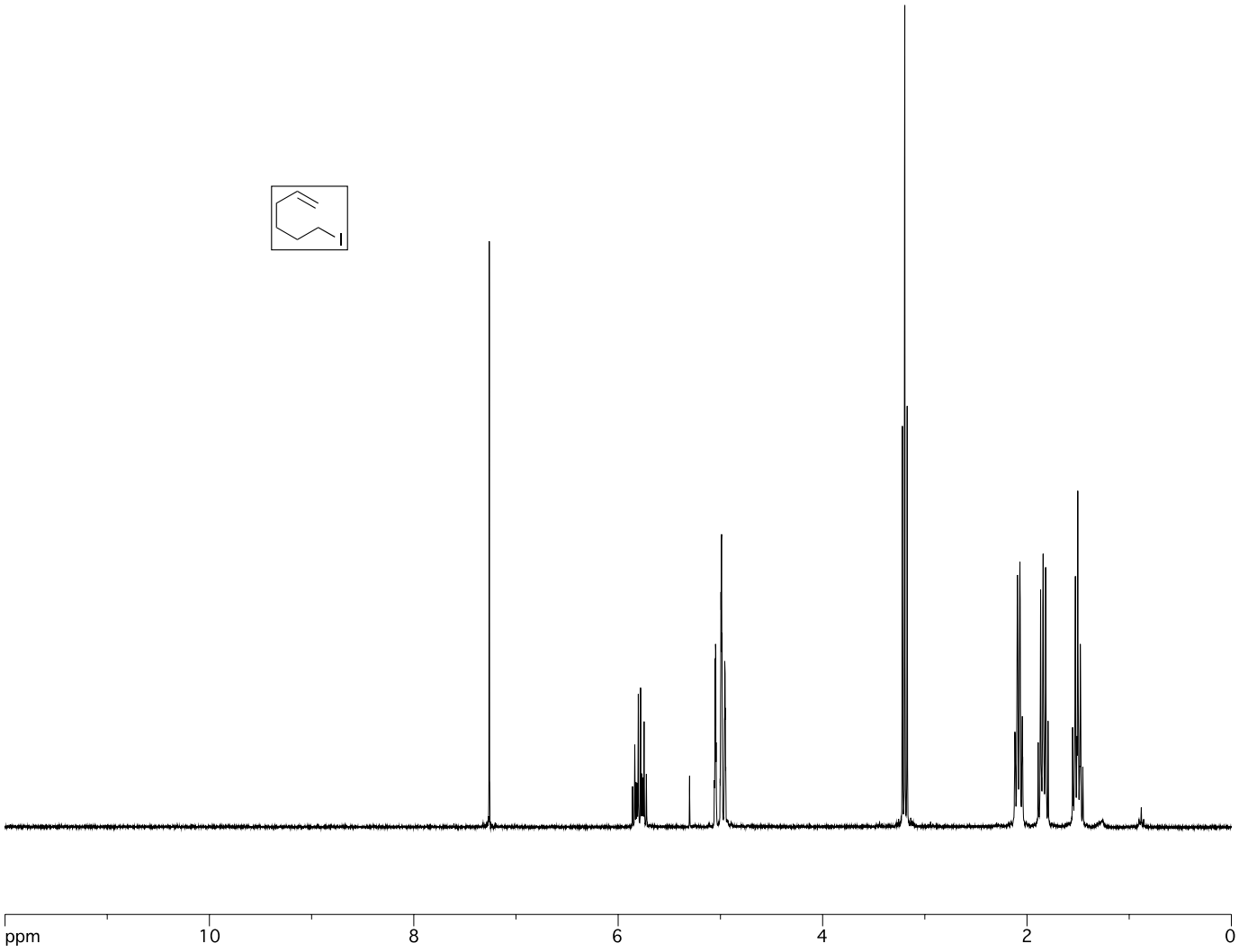


Figure A.3.6 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **389**

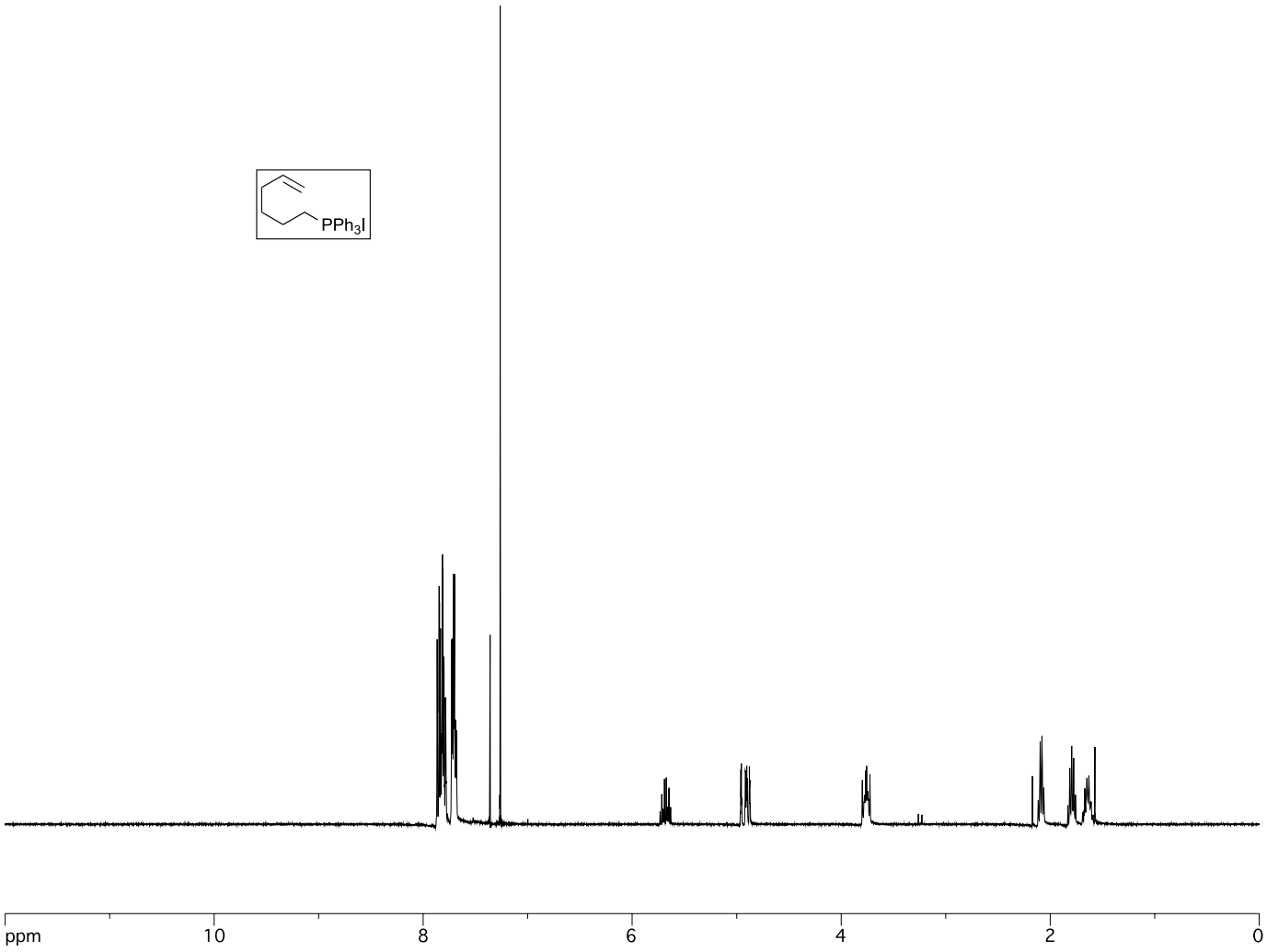


Figure A.3.7 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **390**

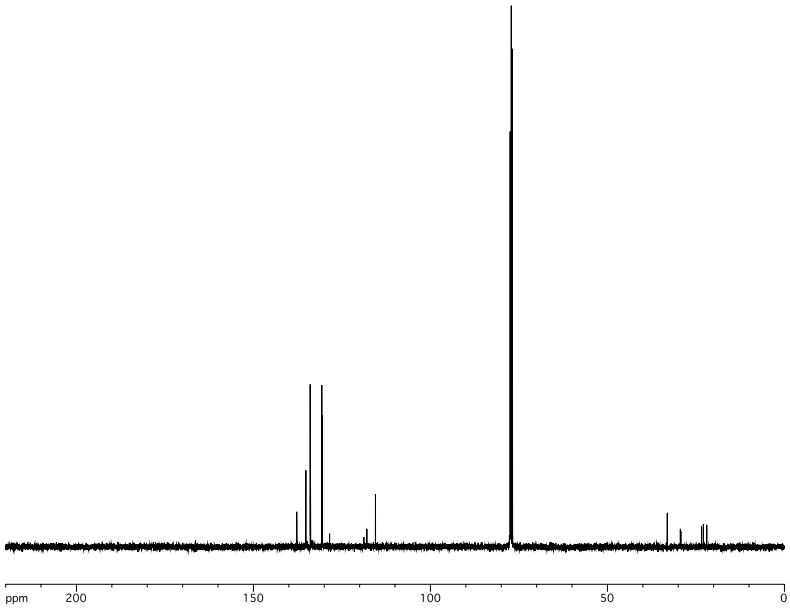


Figure A.3.8 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **390**

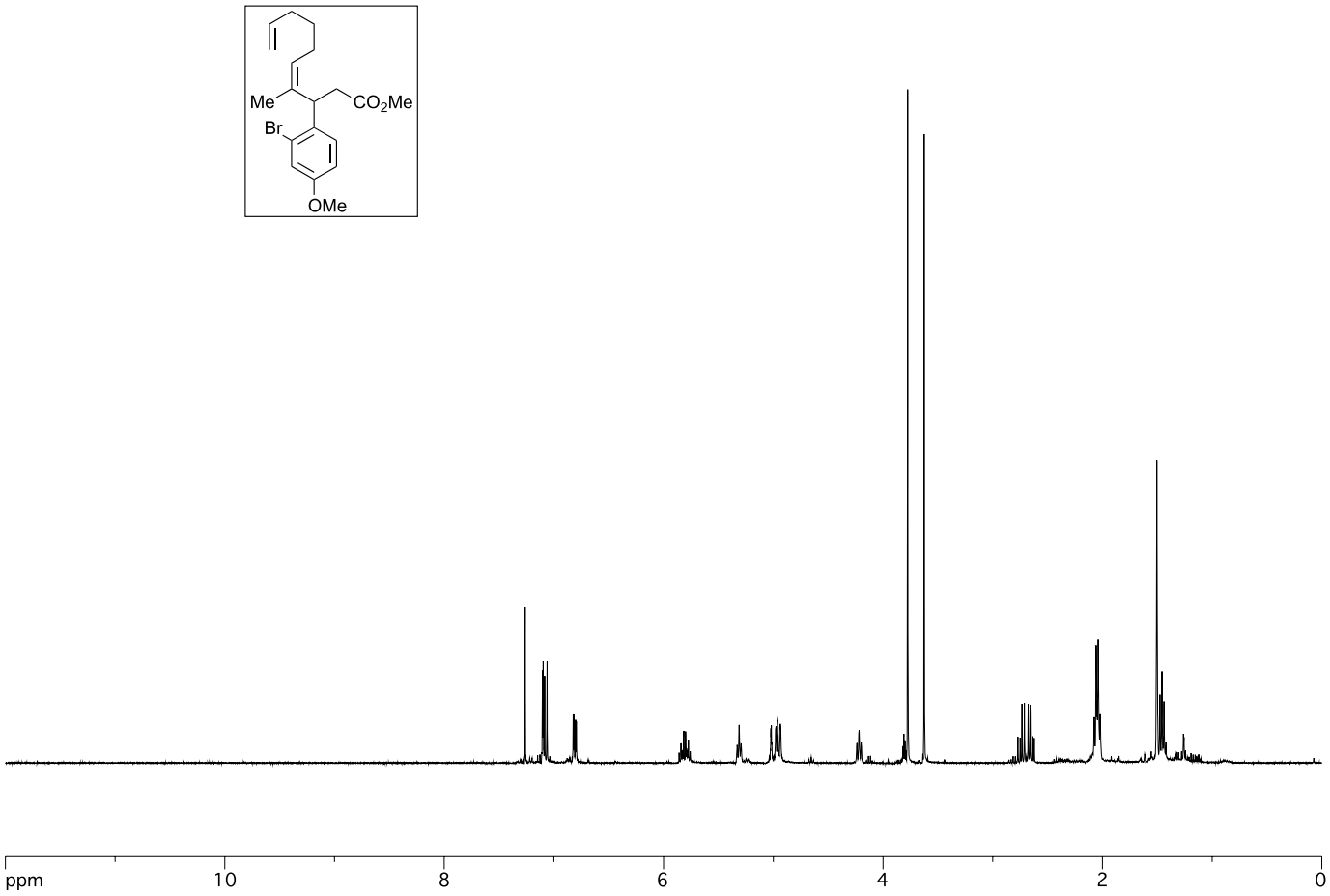


Figure A.3.9 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **352**

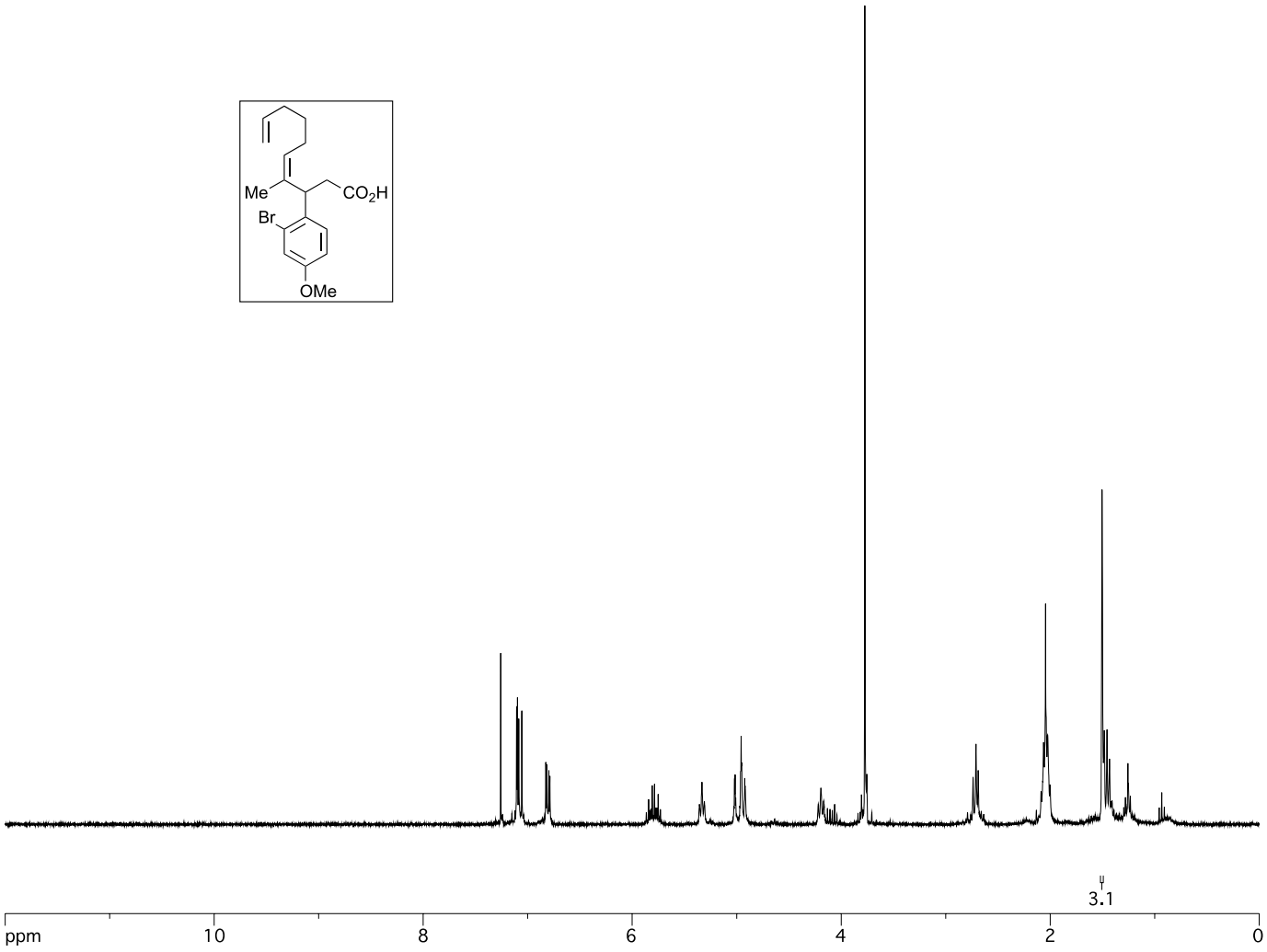


Figure A.3.10 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **353**

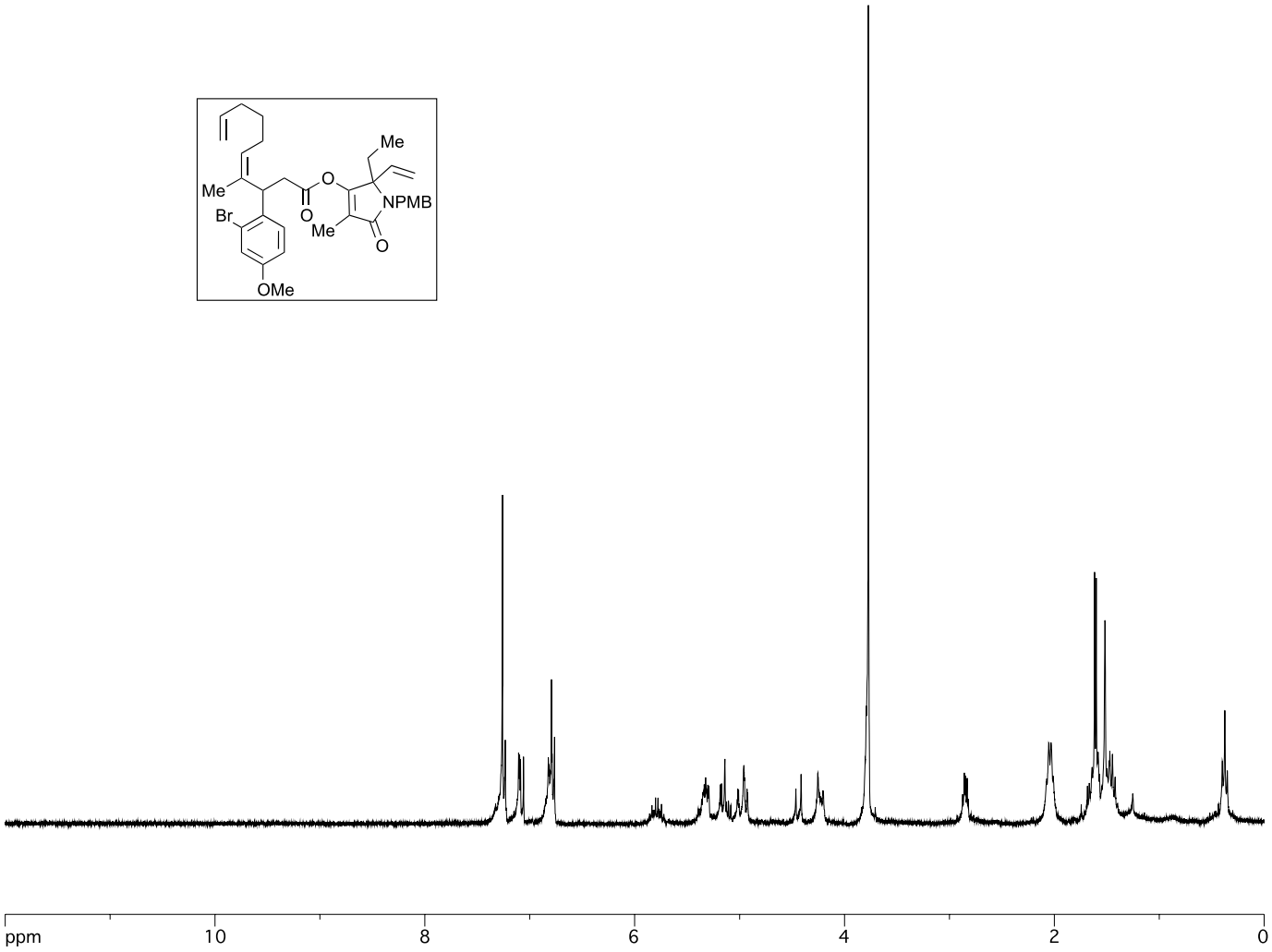


Figure A.3.11 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **354**

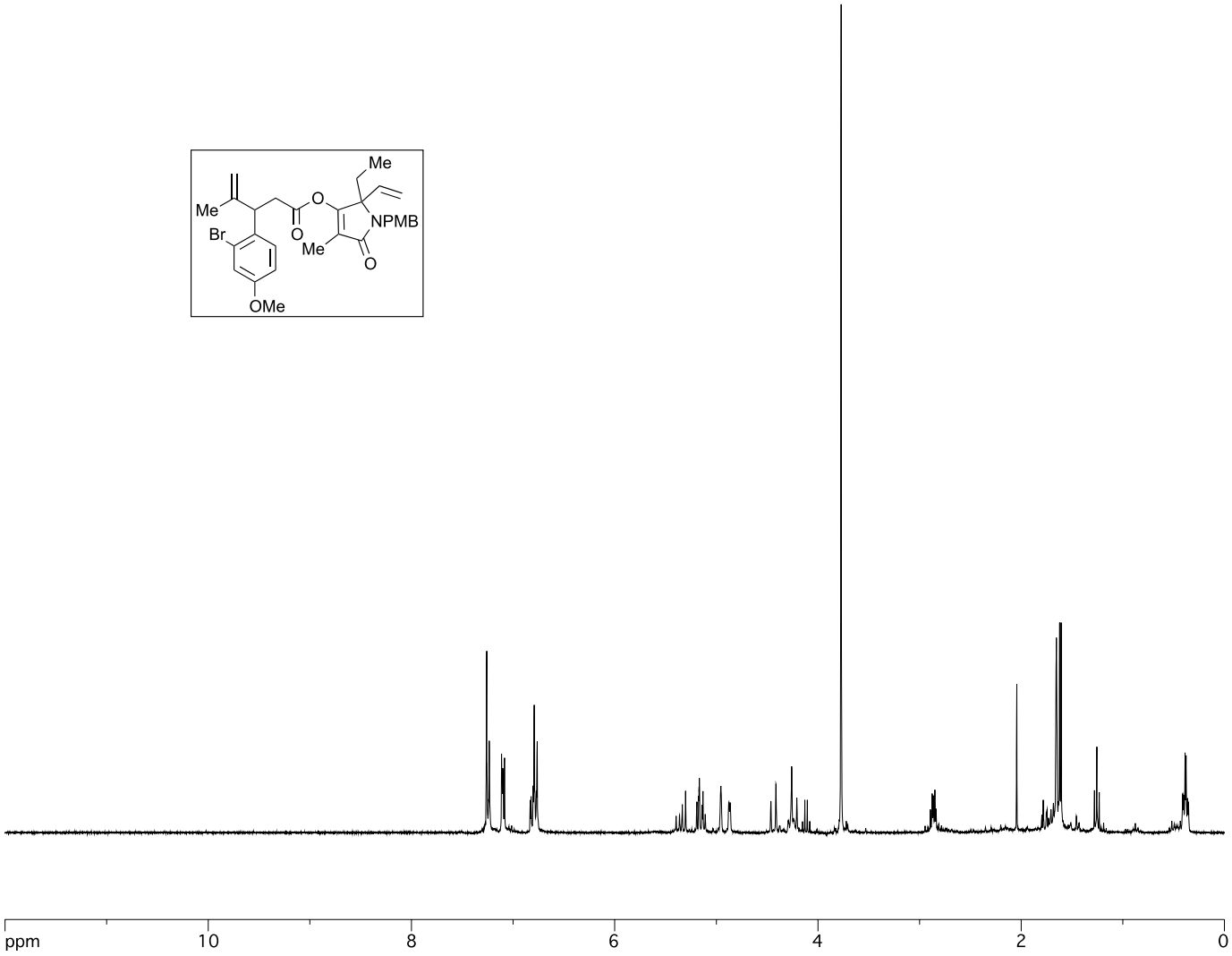


Figure A.3.12 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **355**

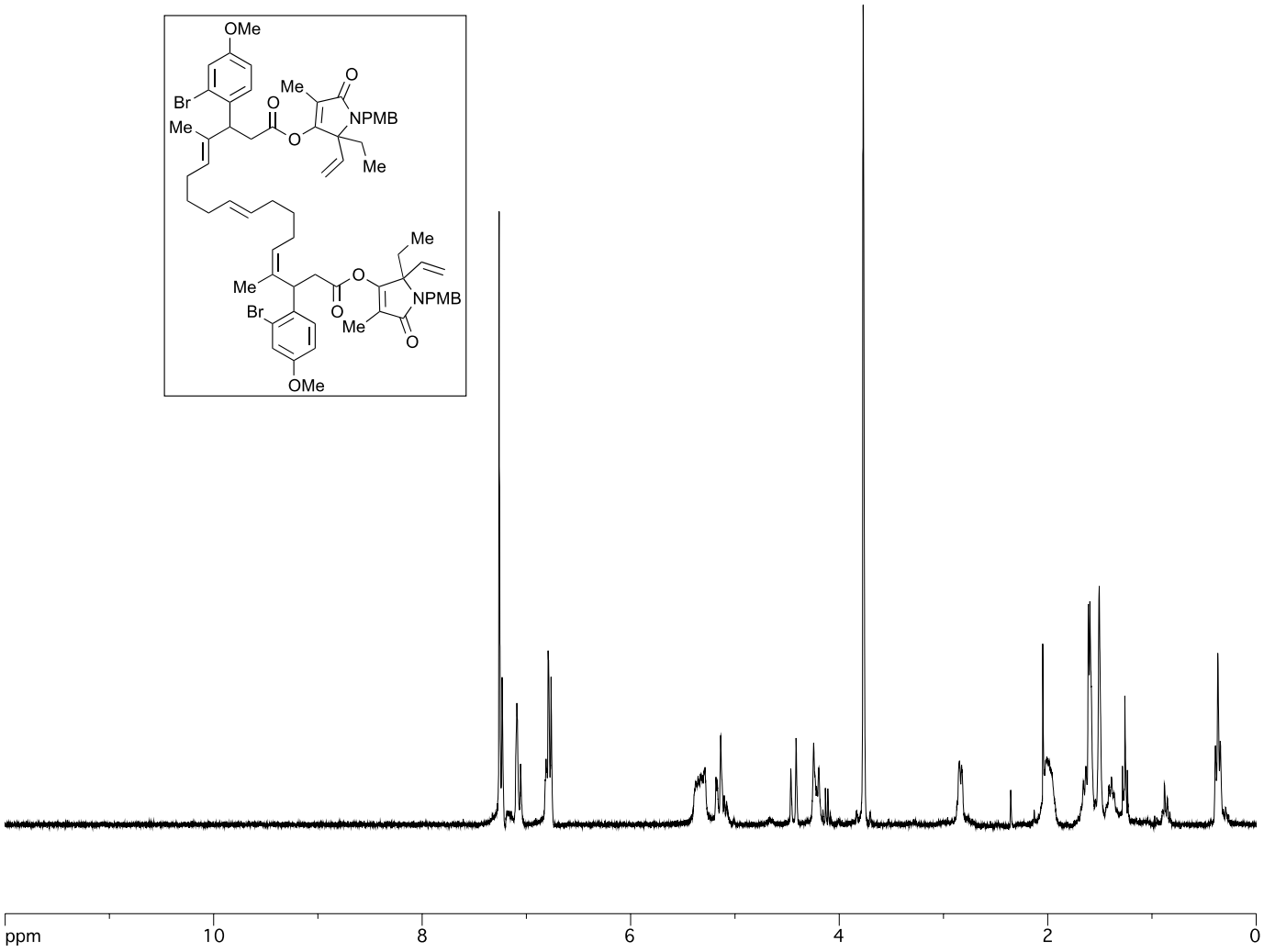


Figure A.3.13 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **356**

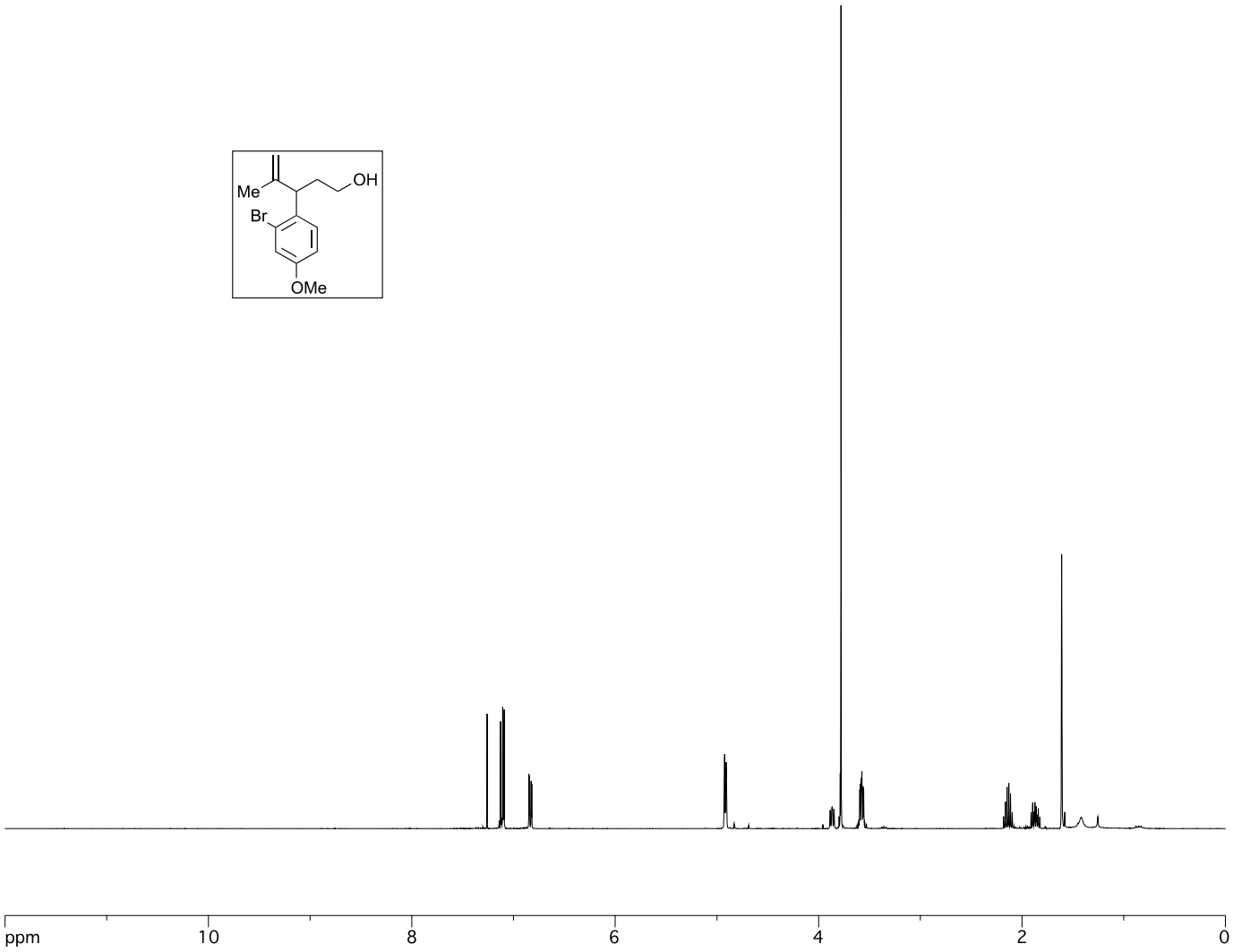


Figure A.3.14 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **366**

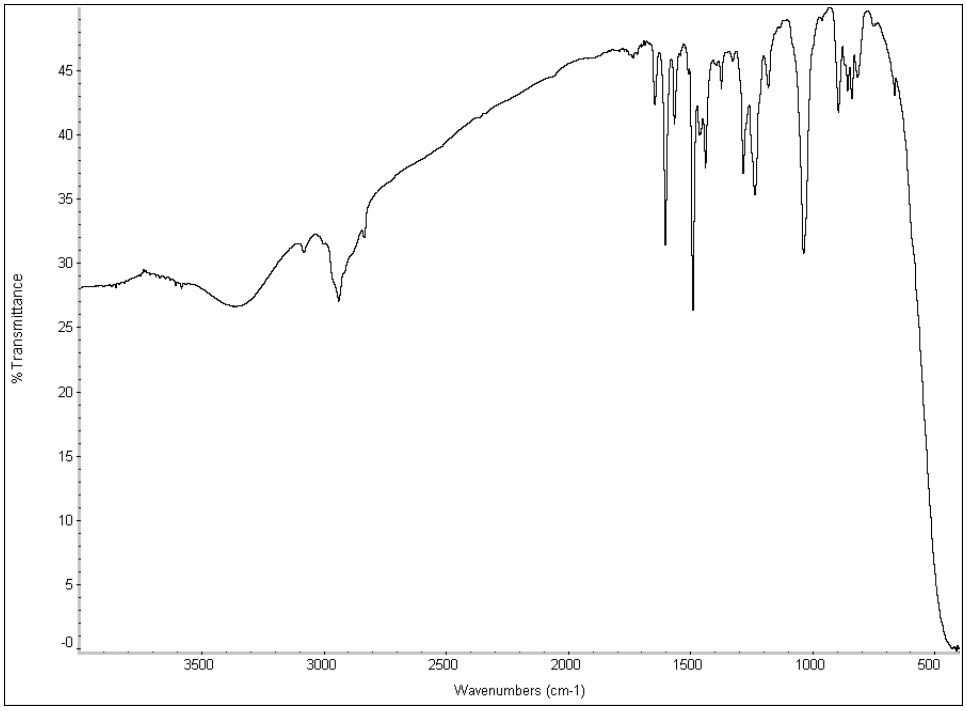


Figure A.3.15 FTIR (thin film/NaCl) of Compound **366**

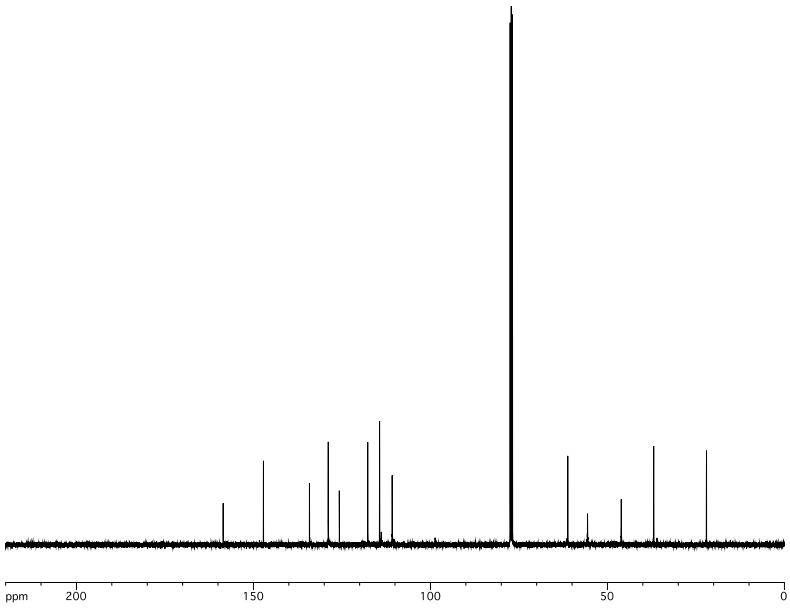


Figure A.3.16 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **366**

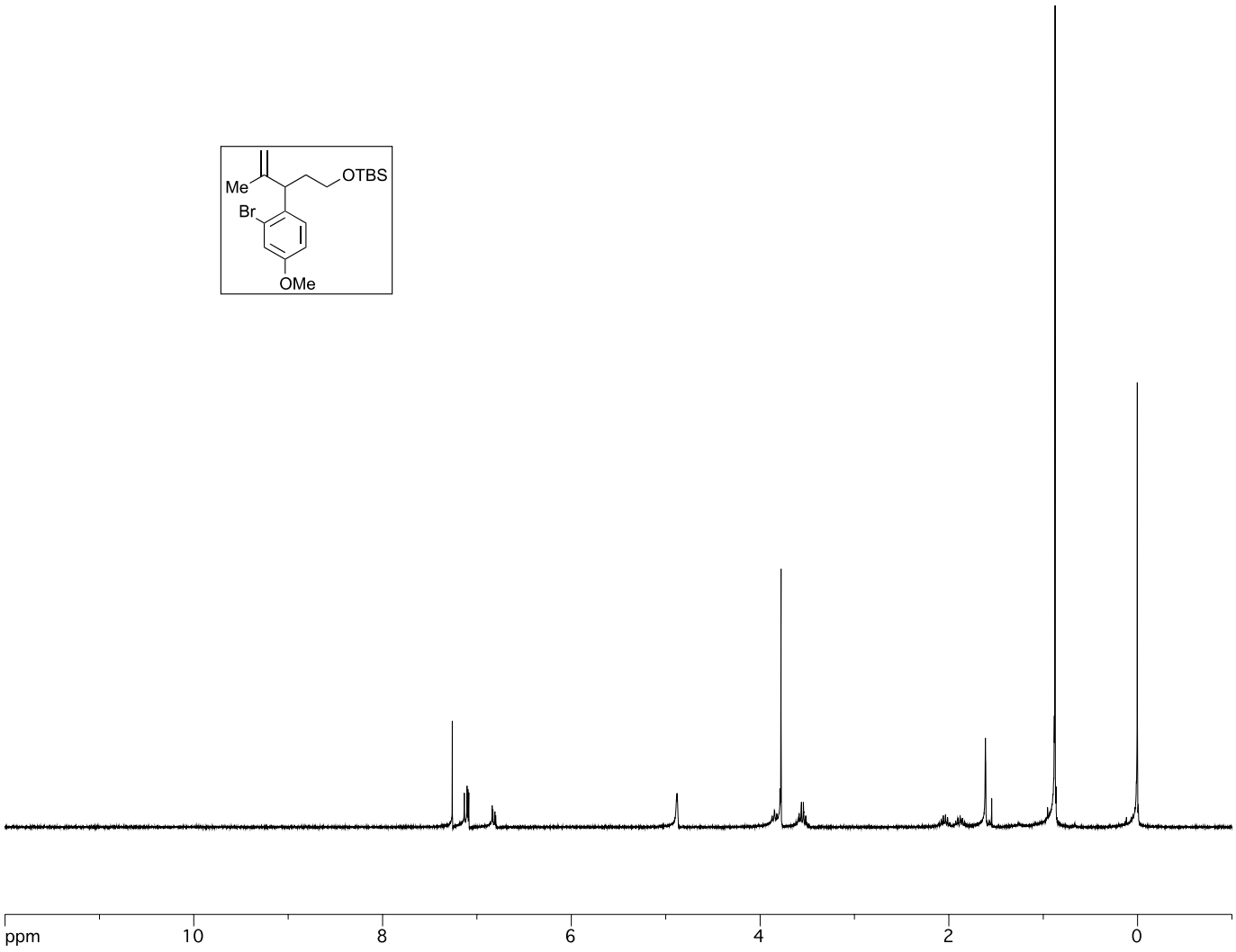


Figure A.3.17 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **367**

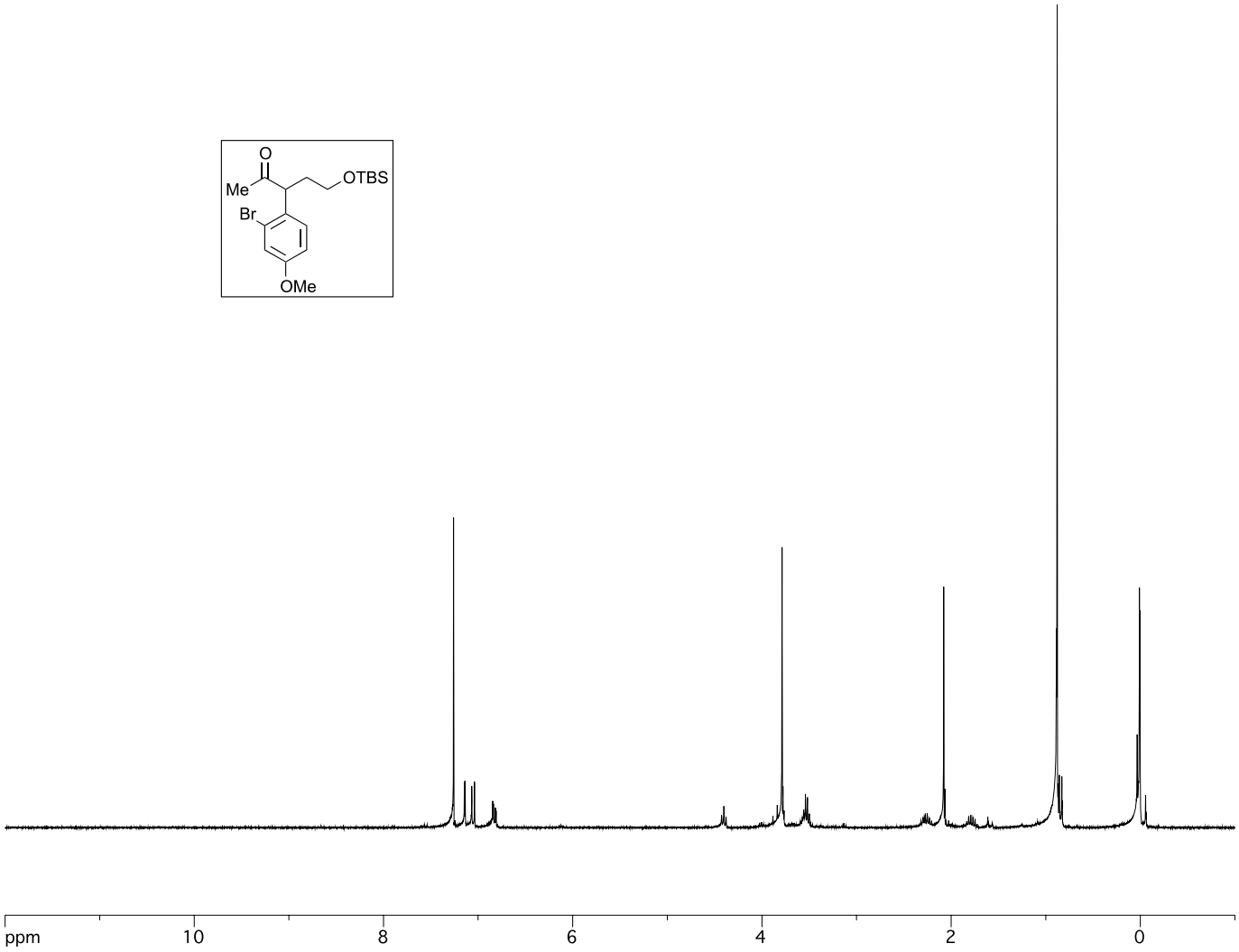


Figure A.3.18 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **368**

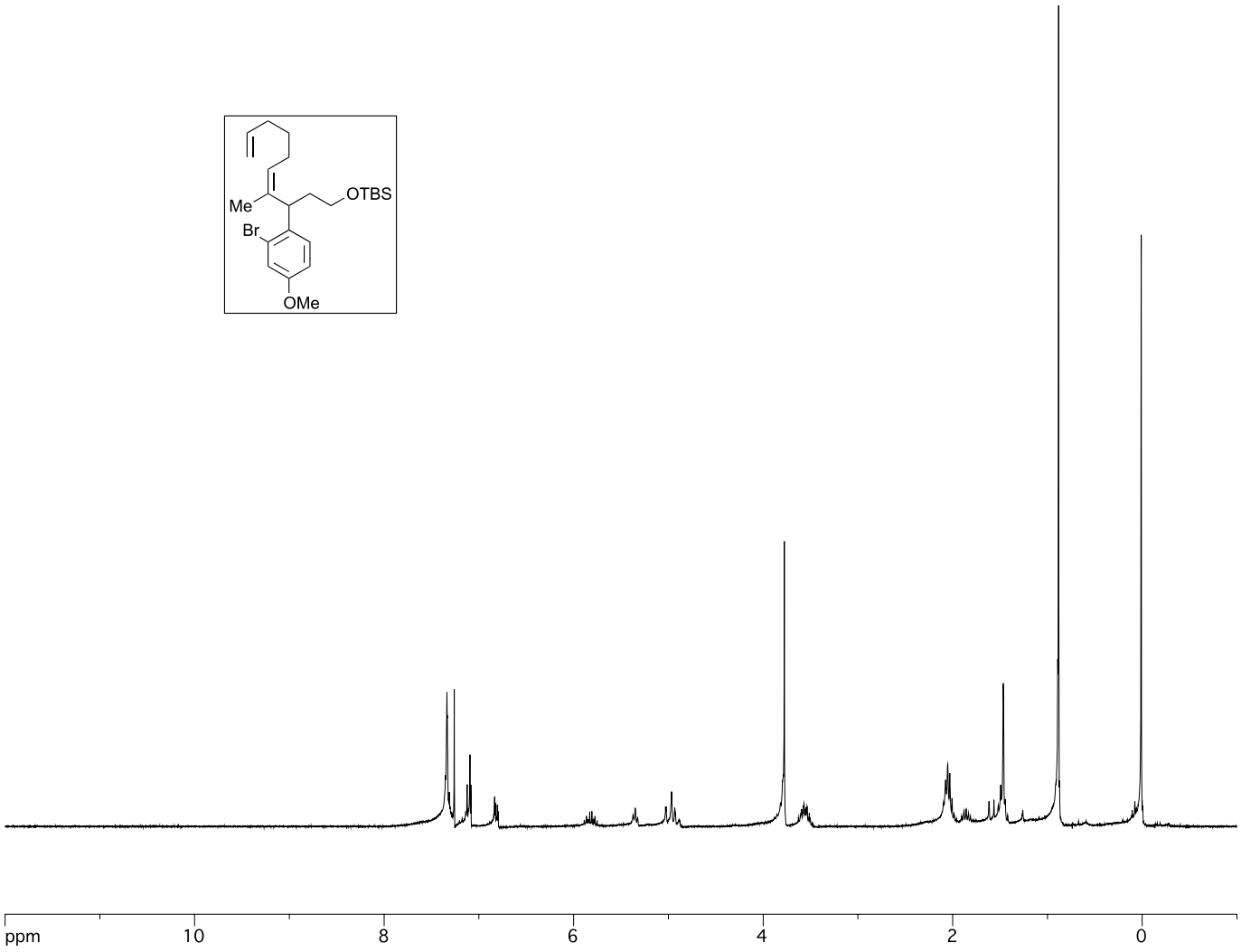


Figure A.3.19 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **369**

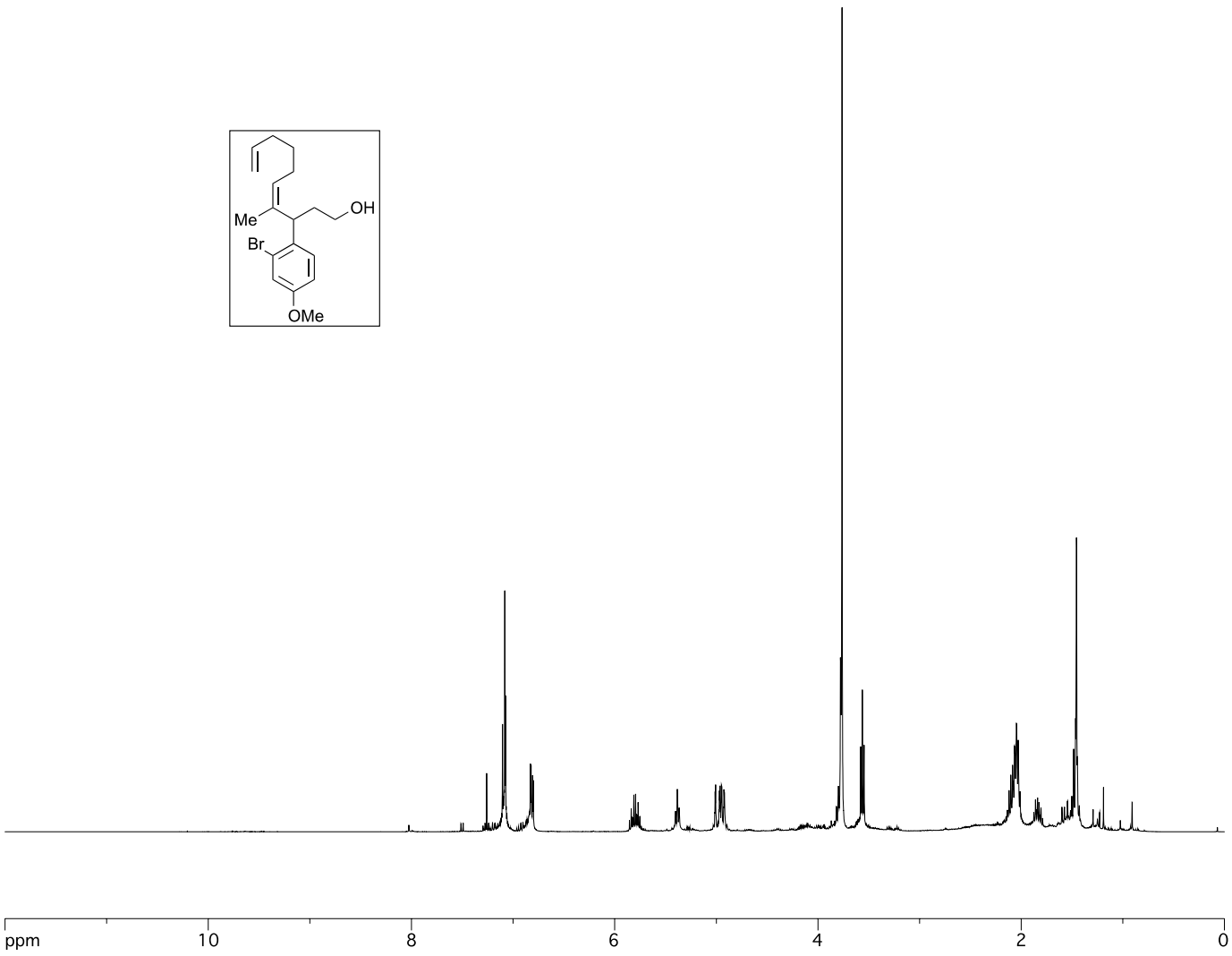


Figure A.3.20 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **365**

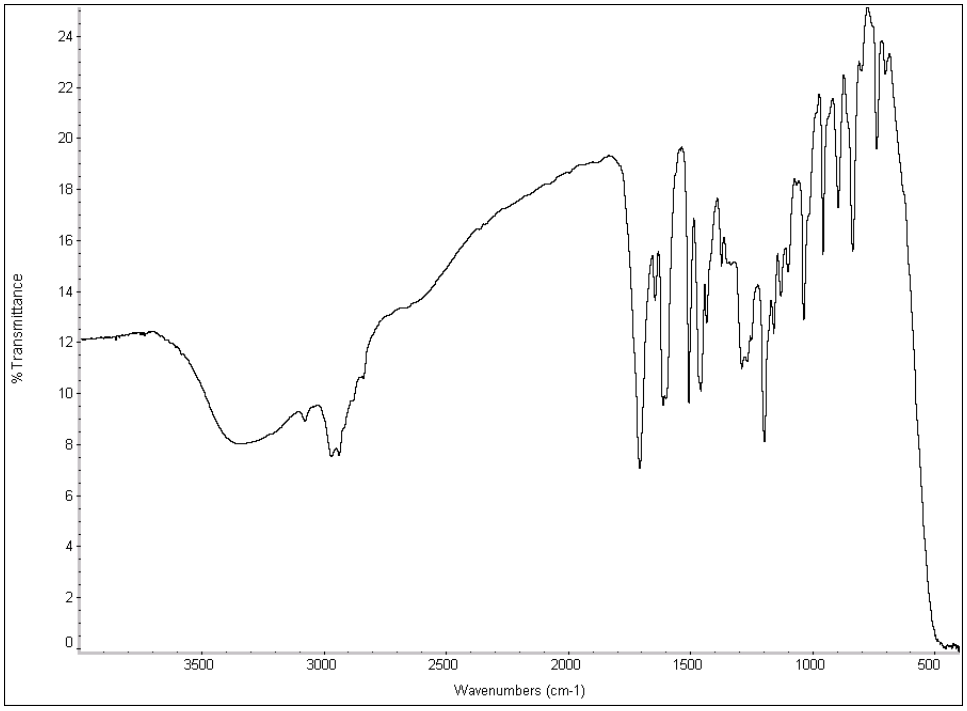


Figure A.3.21 FTIR (thin film/NaCl) of Compound **365**

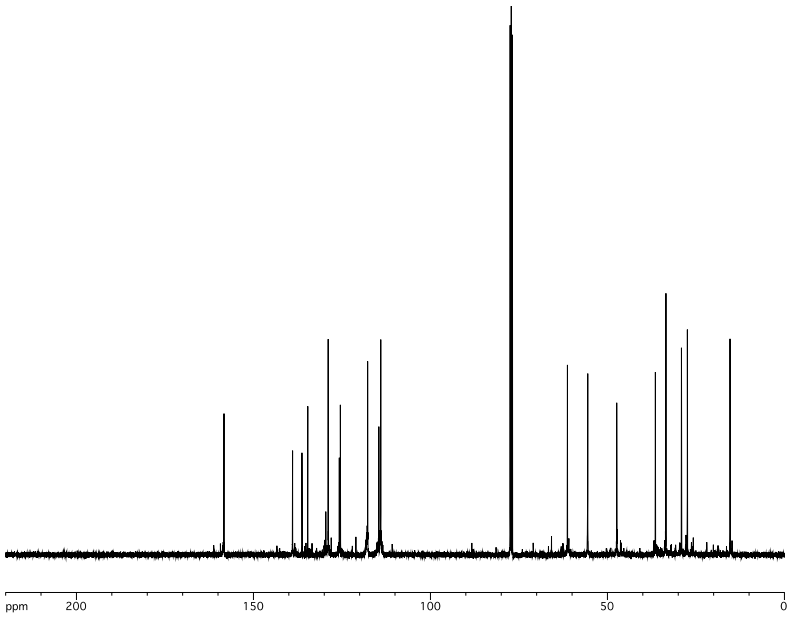


Figure A.3.22 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **365**

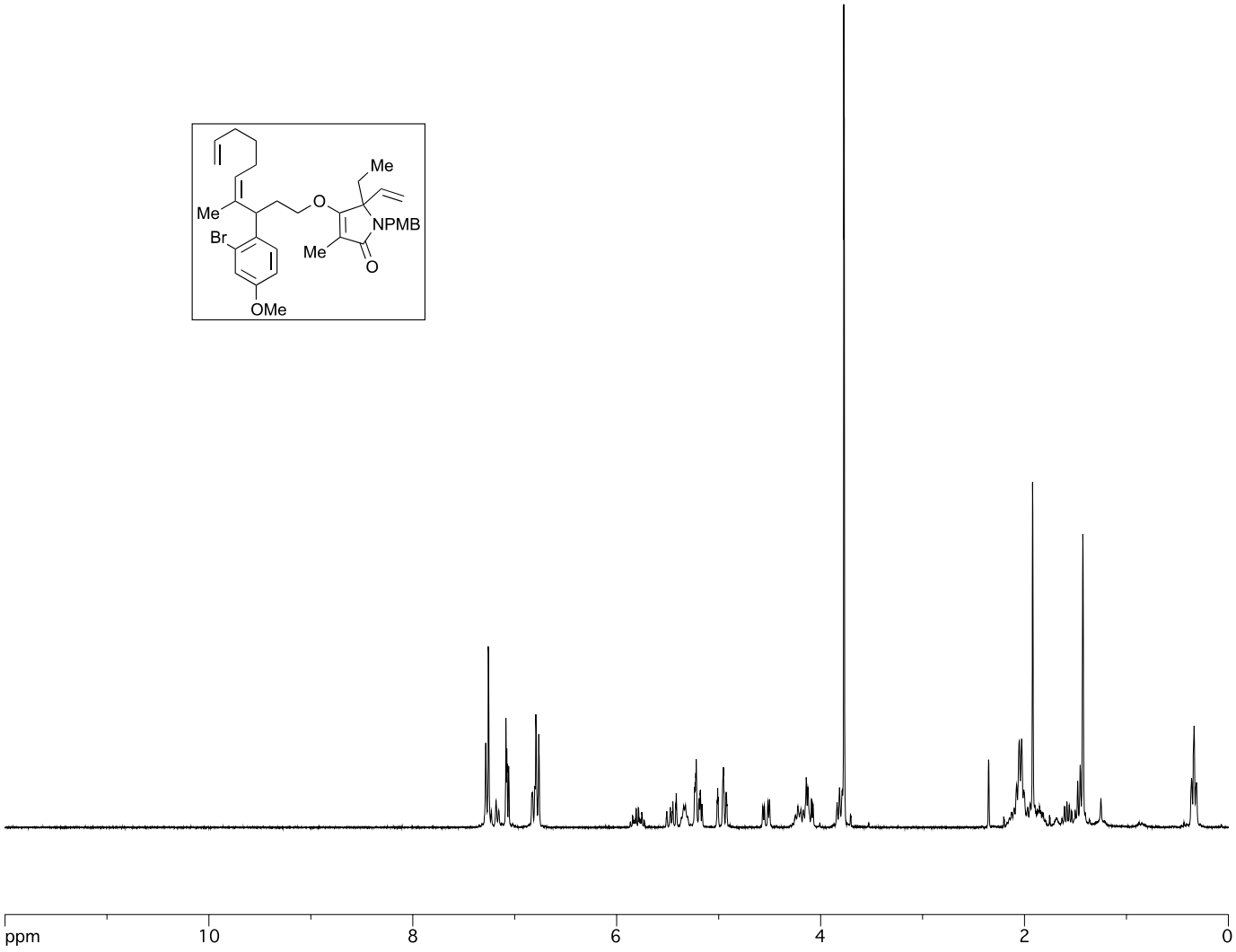


Figure A.3.23 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **364**

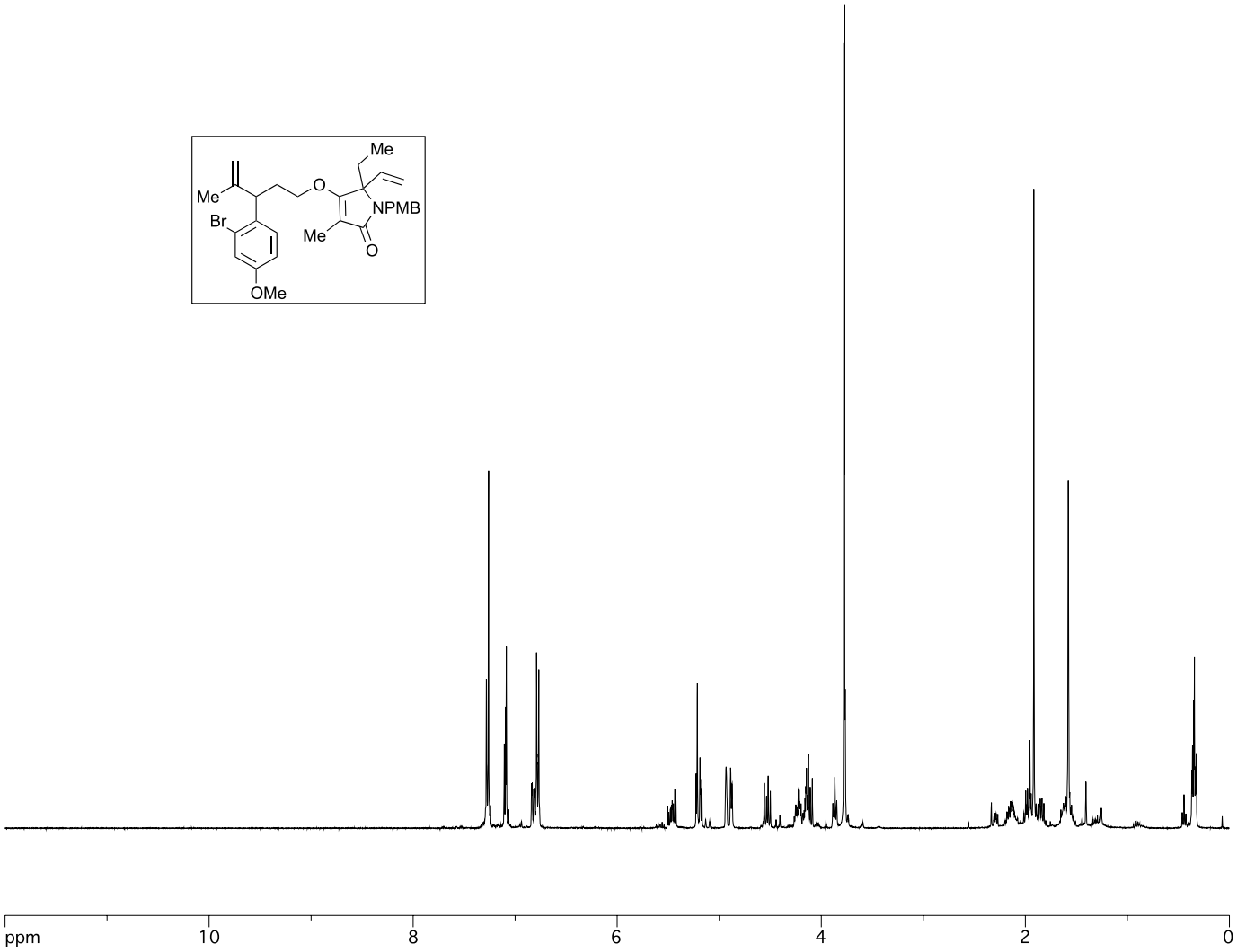


Figure A.3.24 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **370**

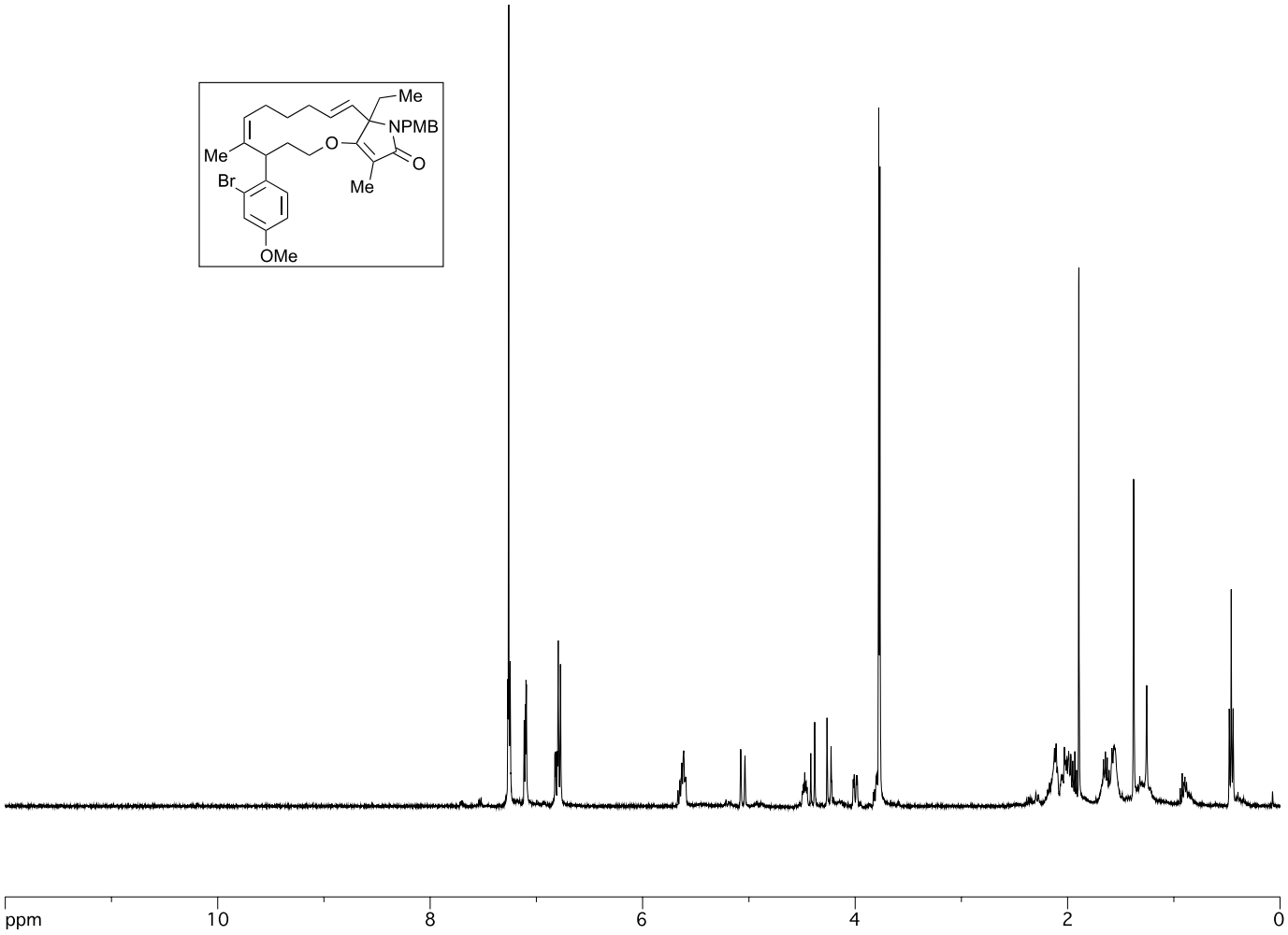


Figure A.3.25 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **371**

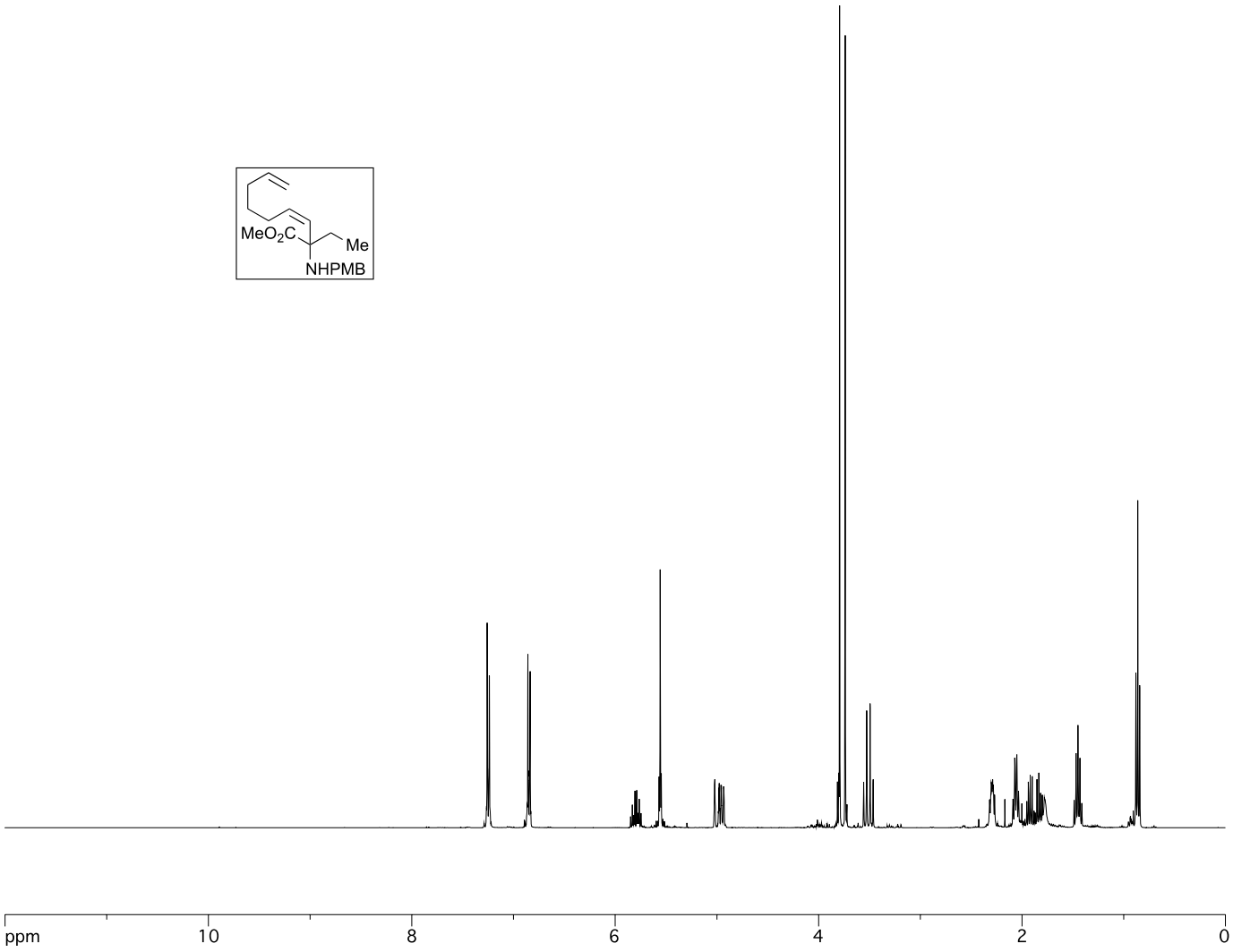


Figure A.3.26 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **380**

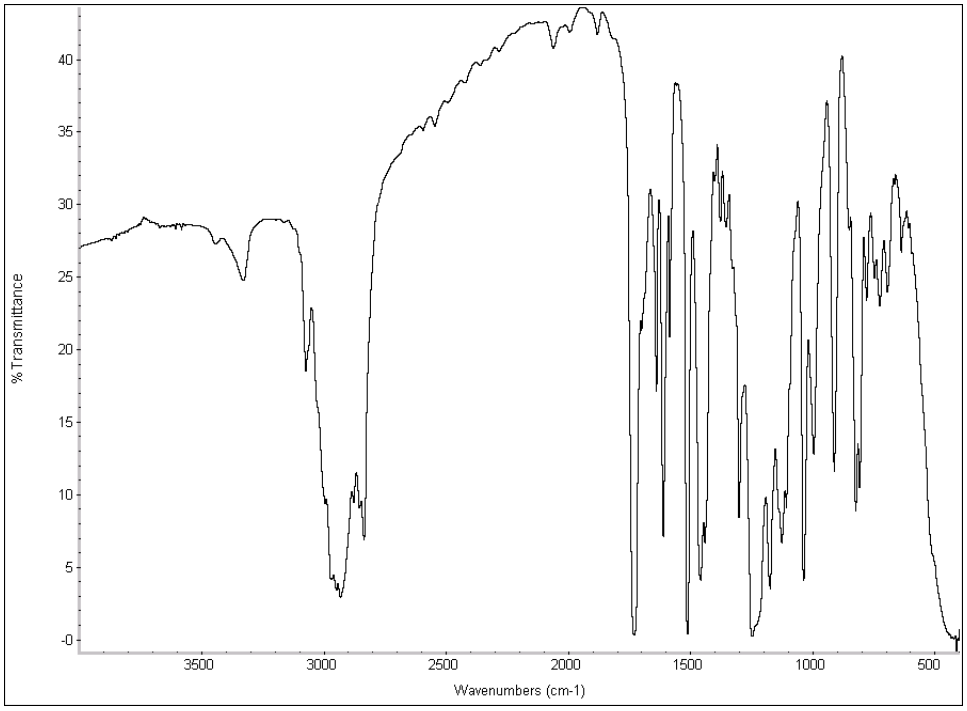


Figure A.3.27 FTIR (thin film/NaCl) of Compound **380**

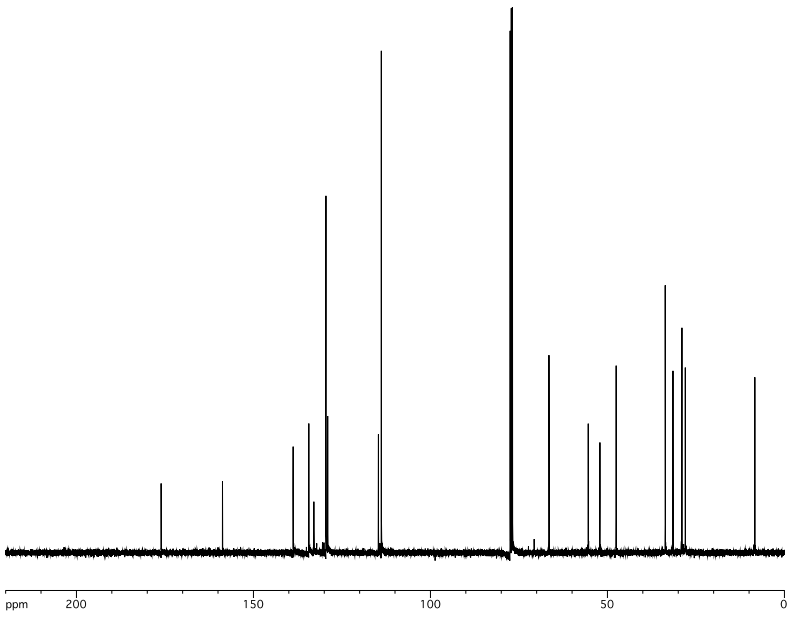


Figure A.3.28 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **380**

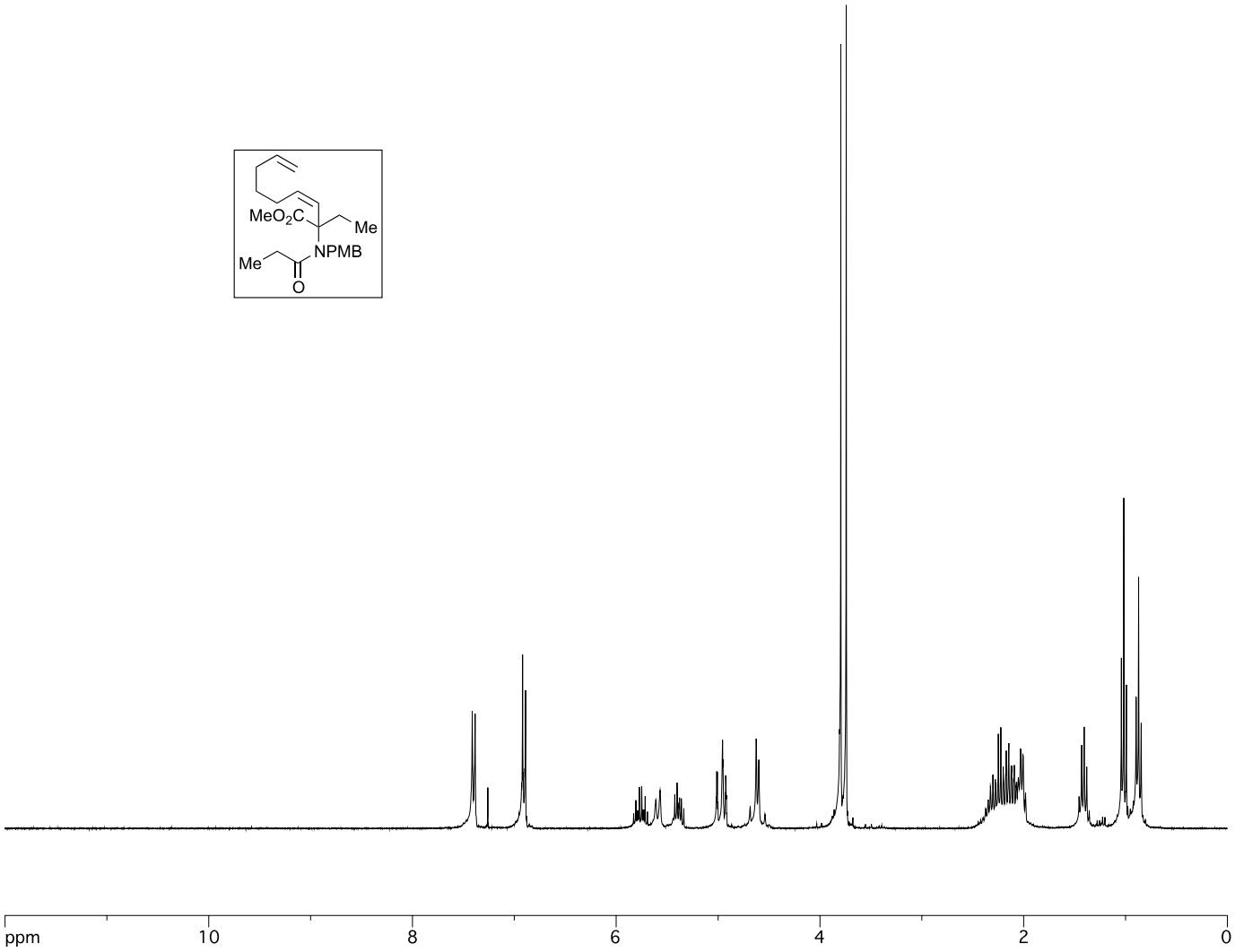


Figure A.3.29 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **381**

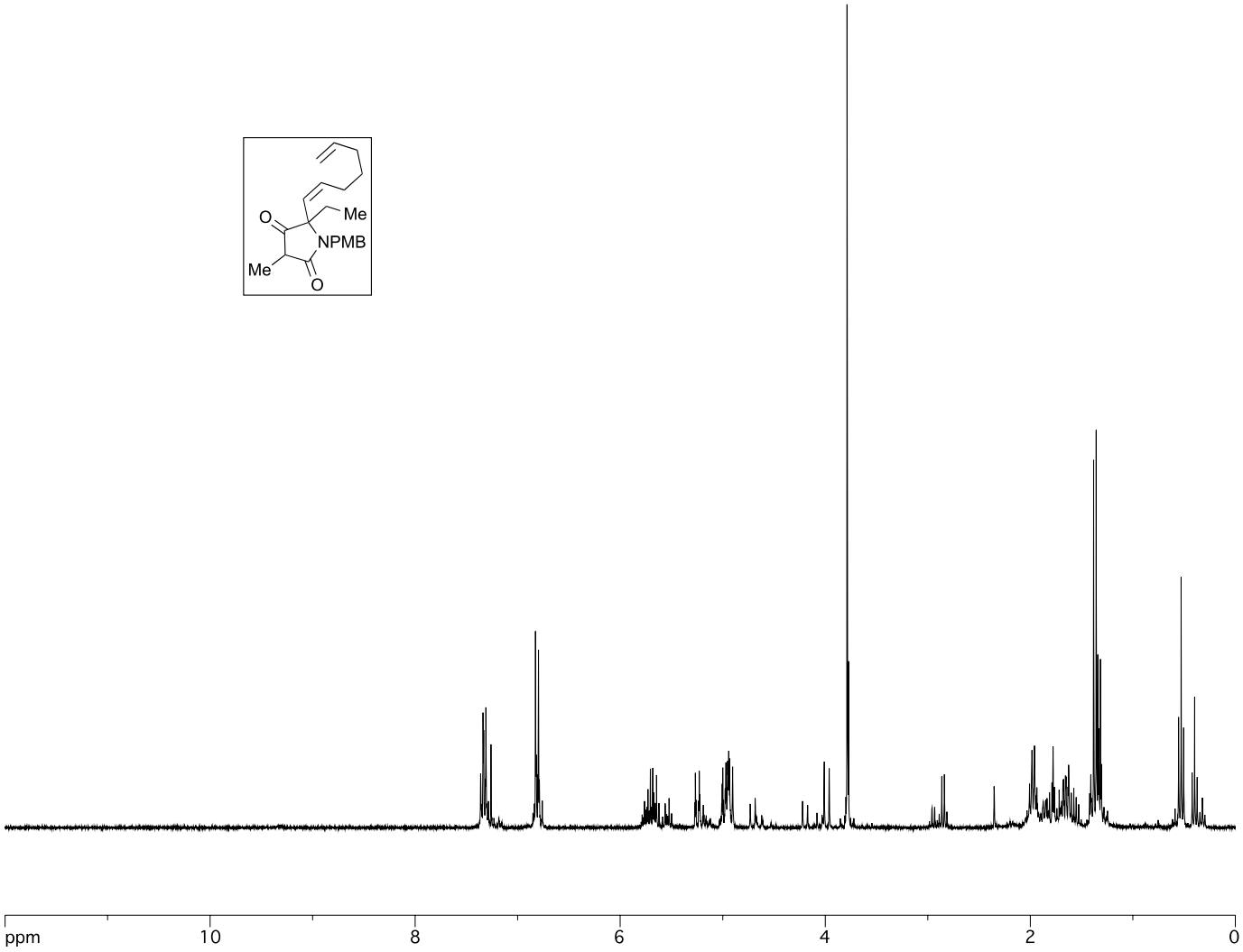


Figure A.3.30 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound 379

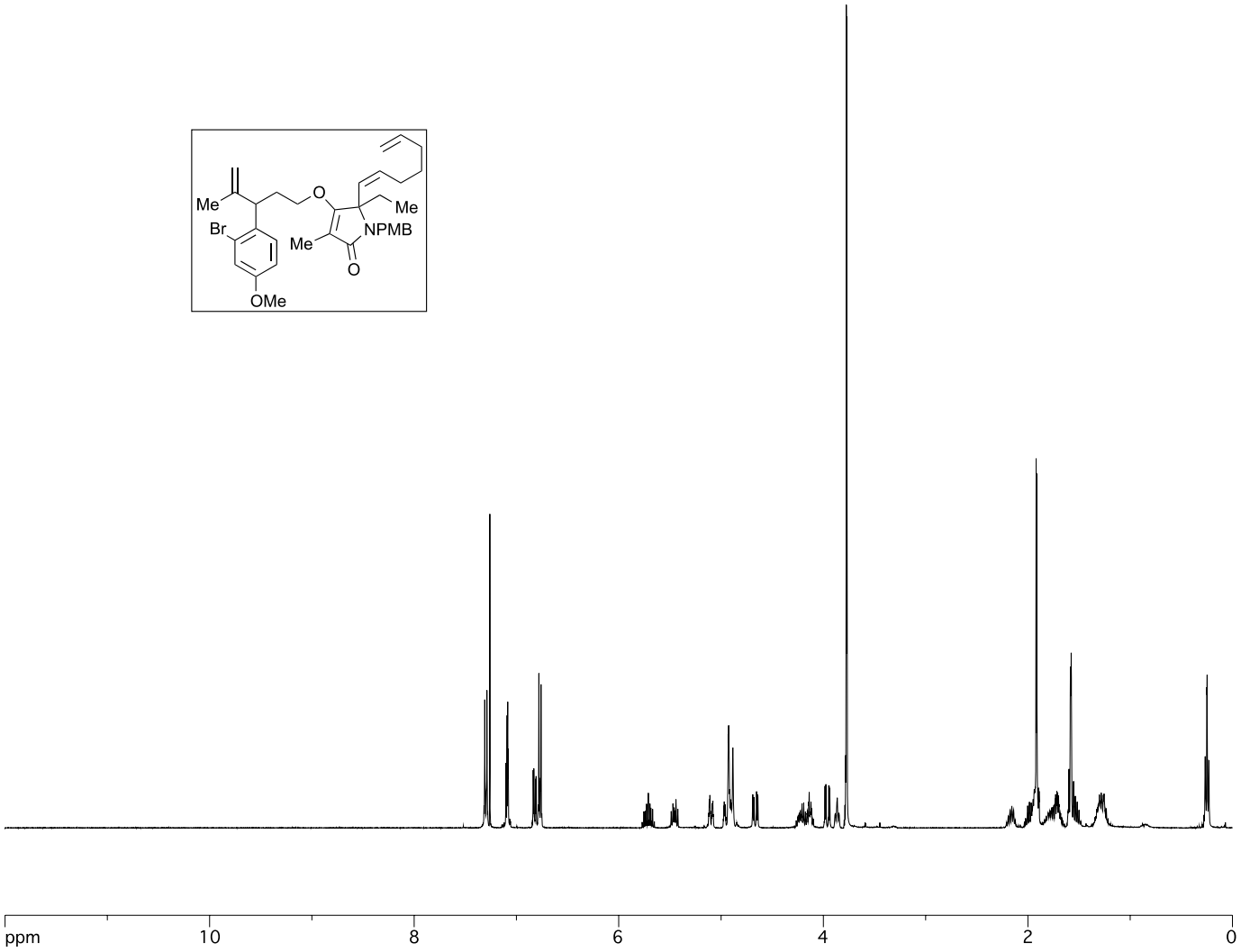


Figure A.3.31 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **378**

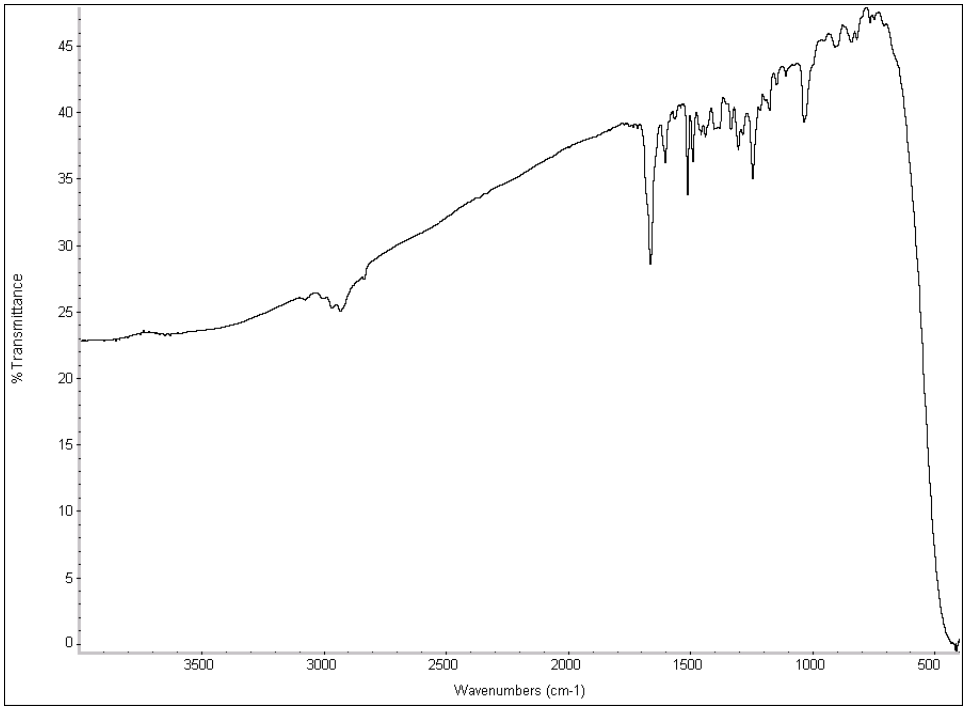


Figure A.3.32 FTIR (thin film/NaCl) of Compound **378**

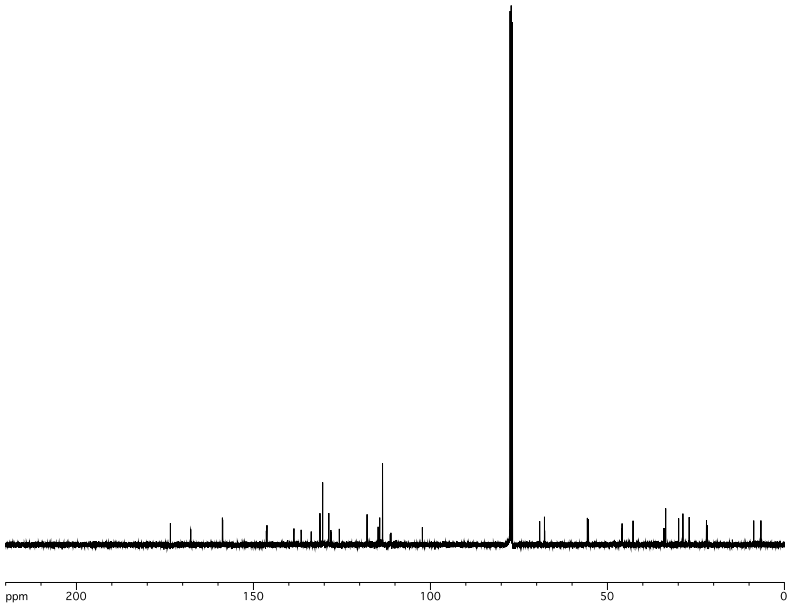


Figure A.3.33 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **378**

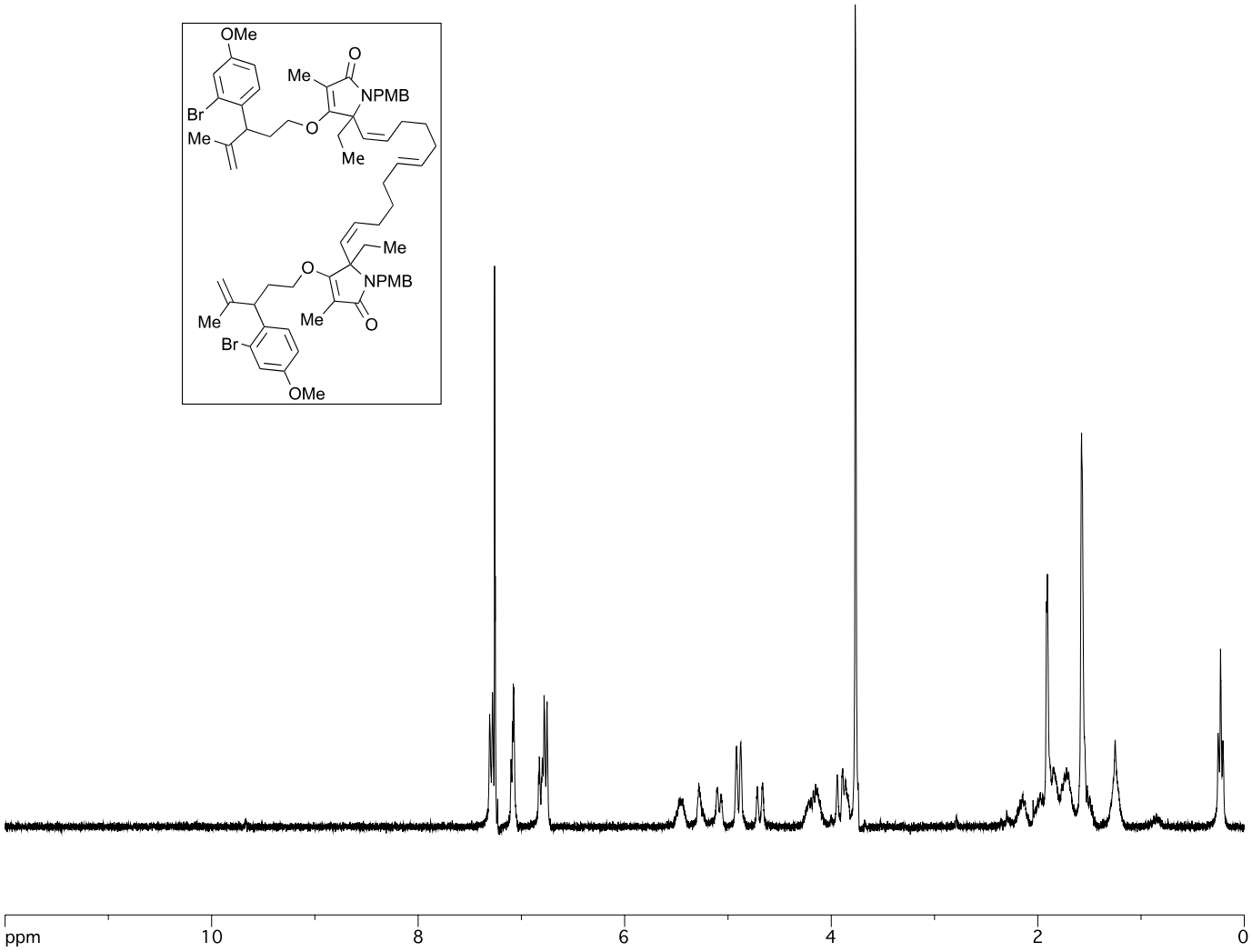


Figure A.3.34 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **382**

Appendix 4

Spectra Relevant to Chapter 5

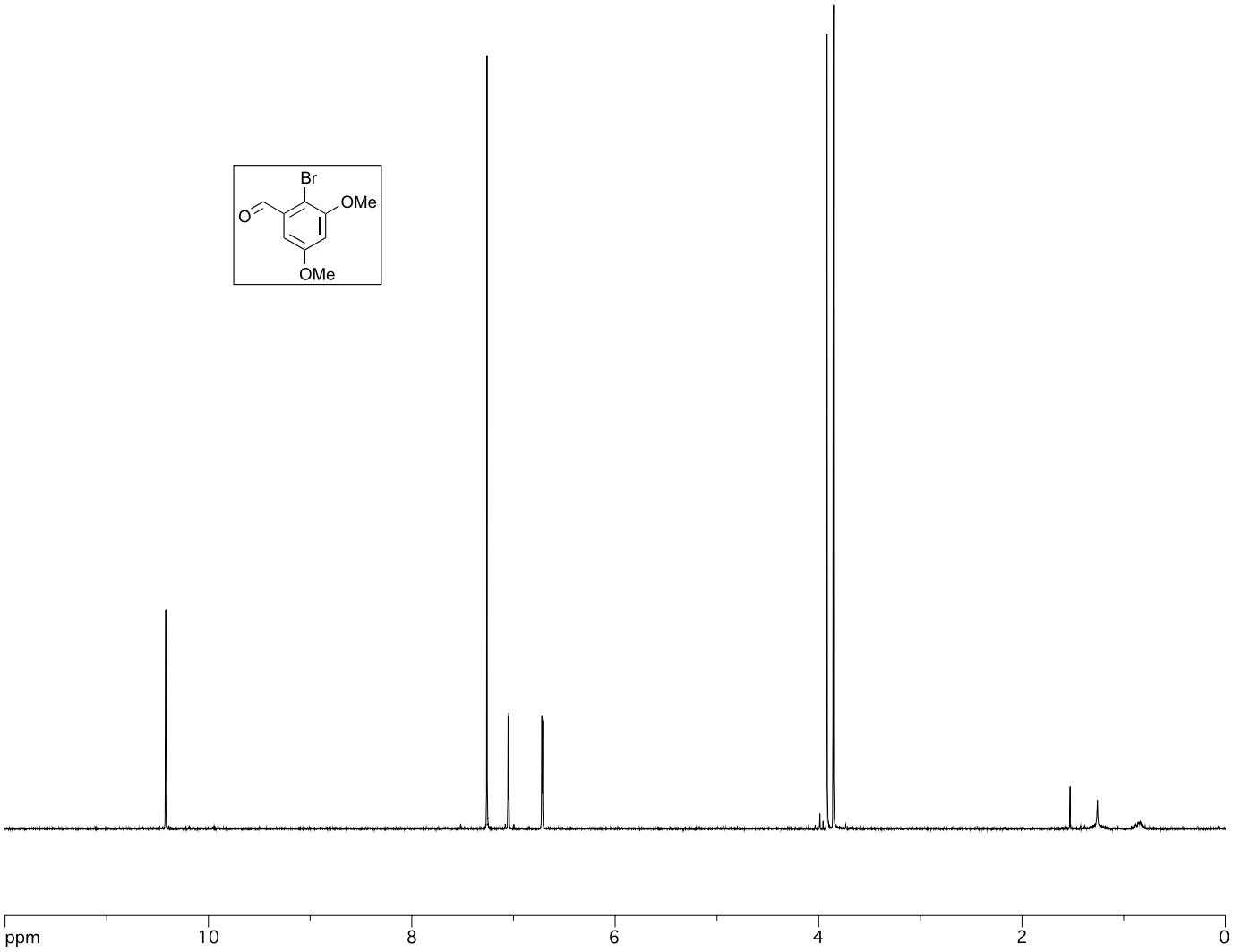


Figure A.4.1 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **406**

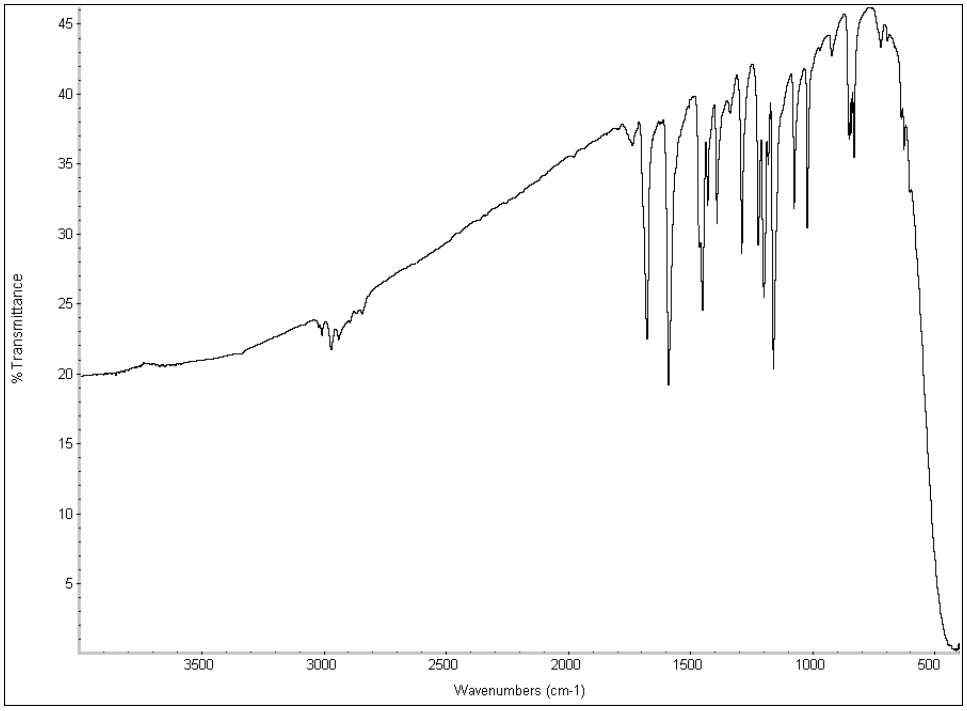


Figure A.4.2 FTIR (thin film/NaCl) of Compound **406**

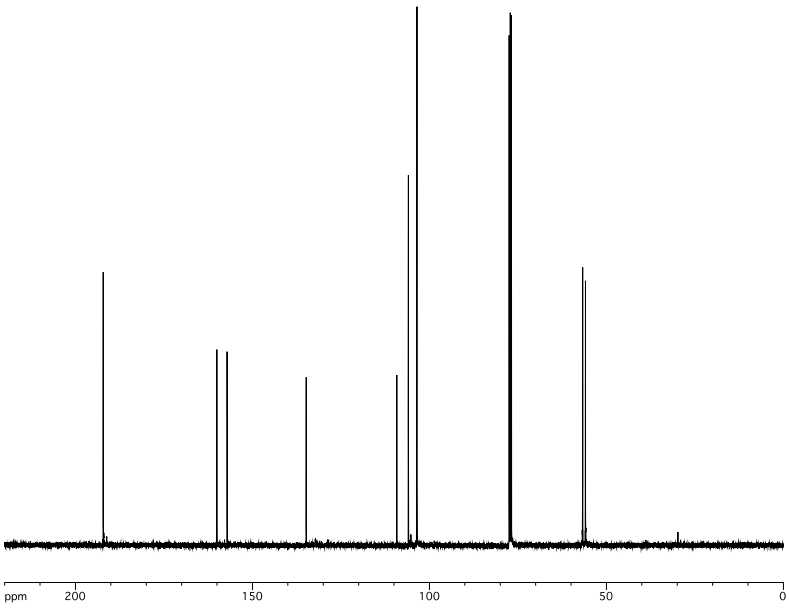


Figure A.4.3 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **406**

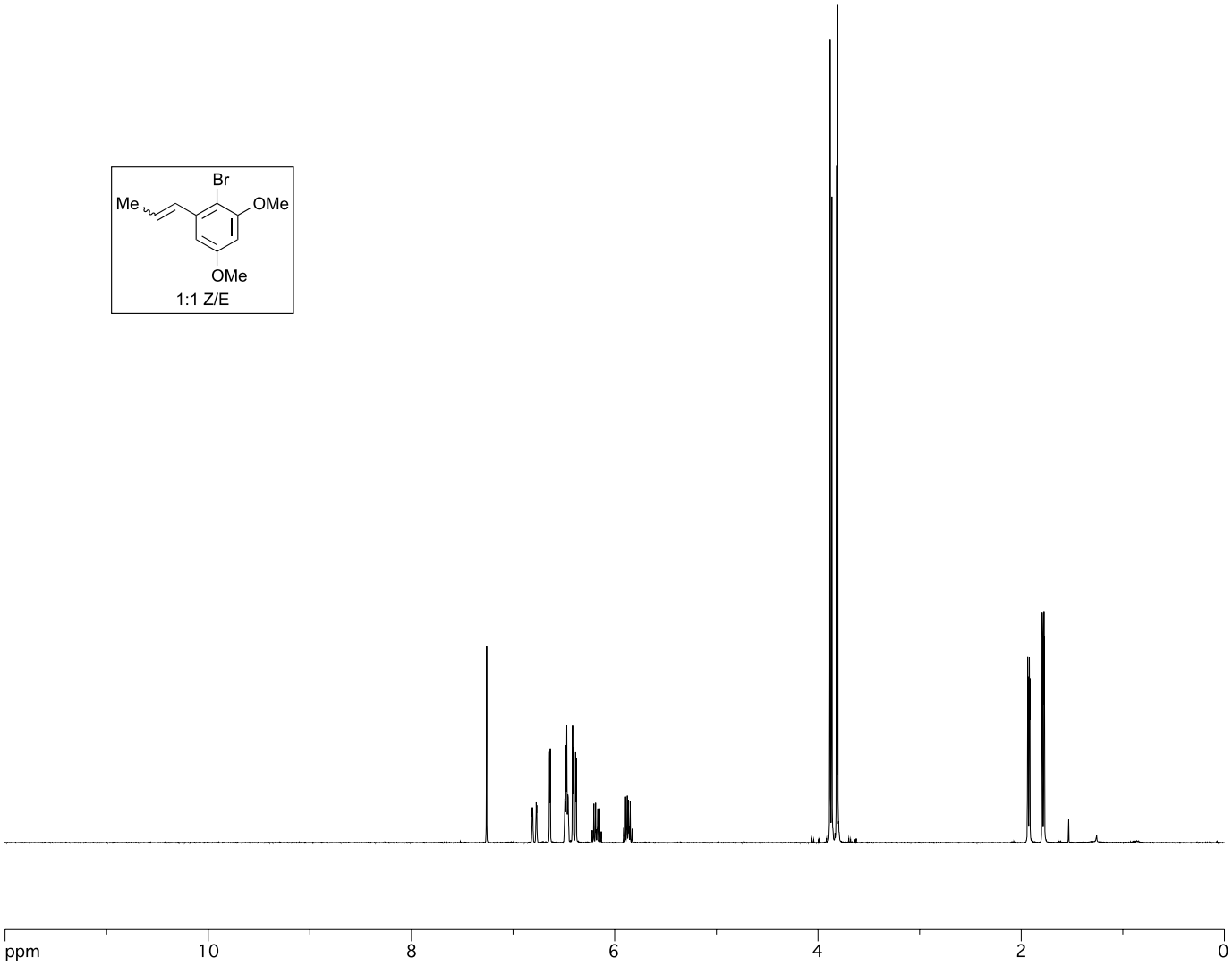


Figure A.4.4 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **407**

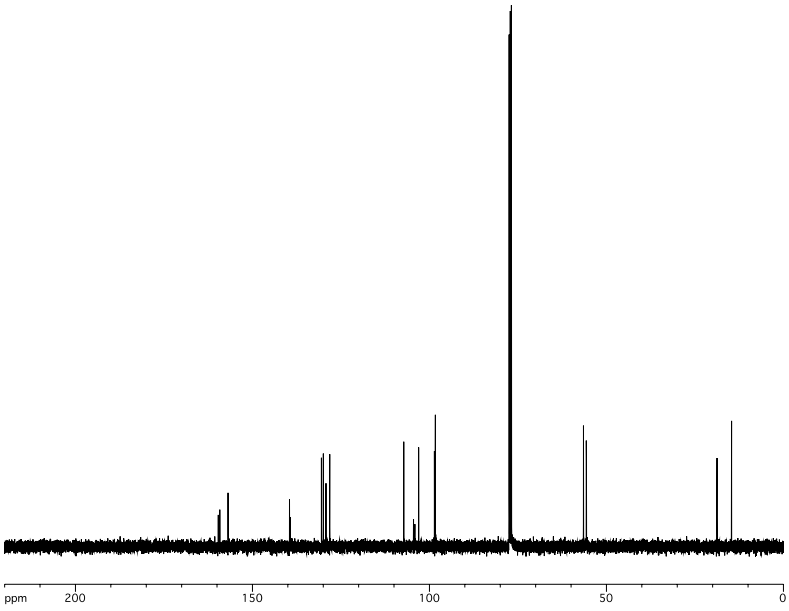


Figure A.4.5 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **407**

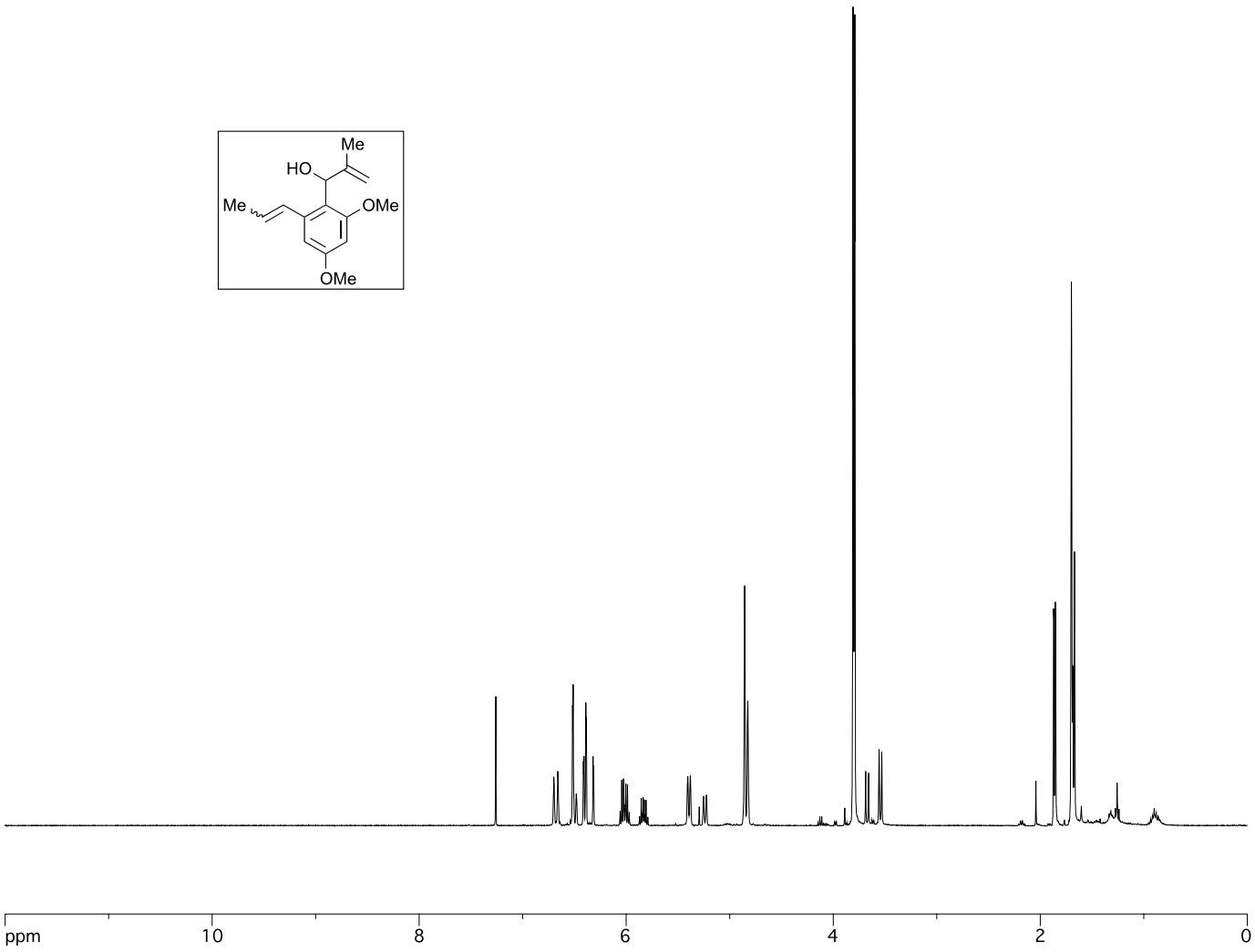


Figure A.4.6 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **409**

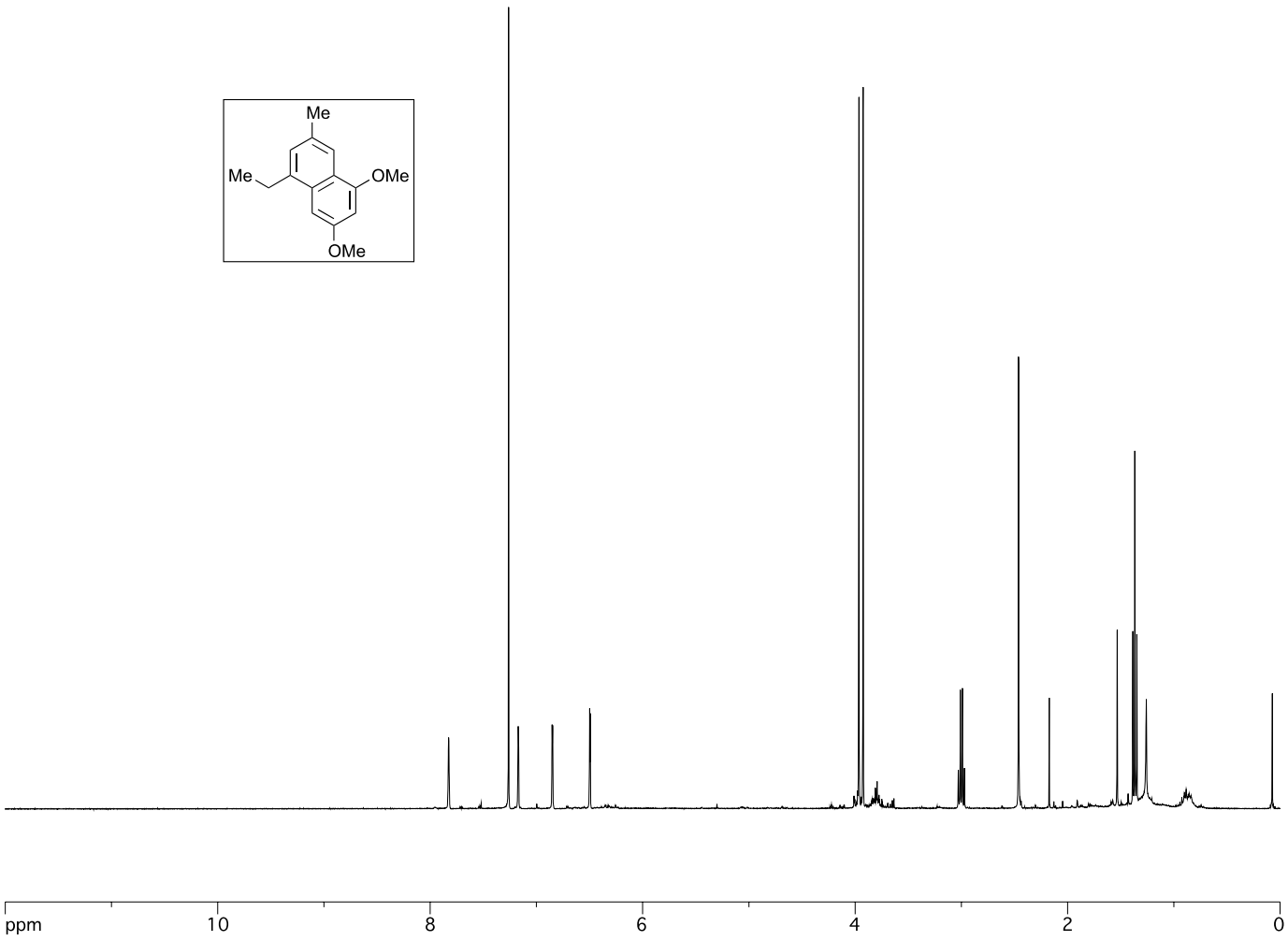


Figure A.4.7 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **413**

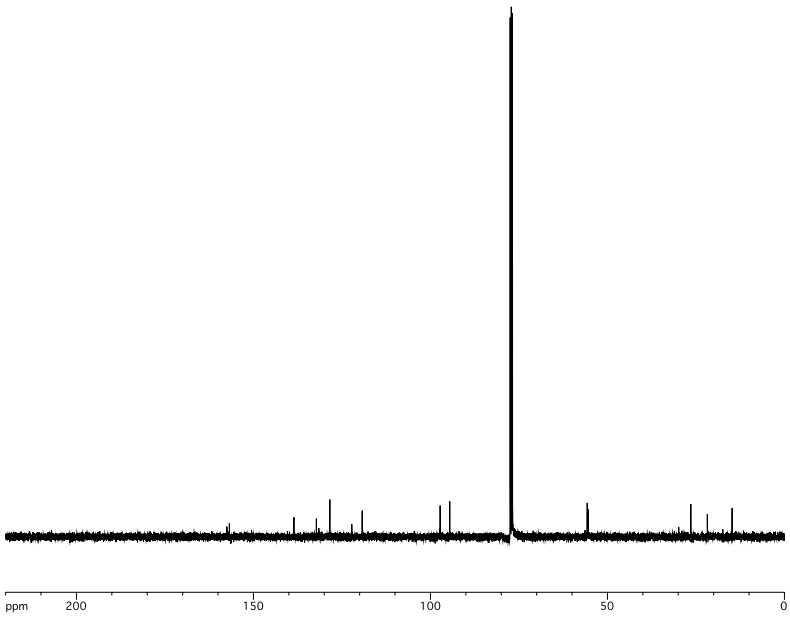


Figure A.4.8 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **413**

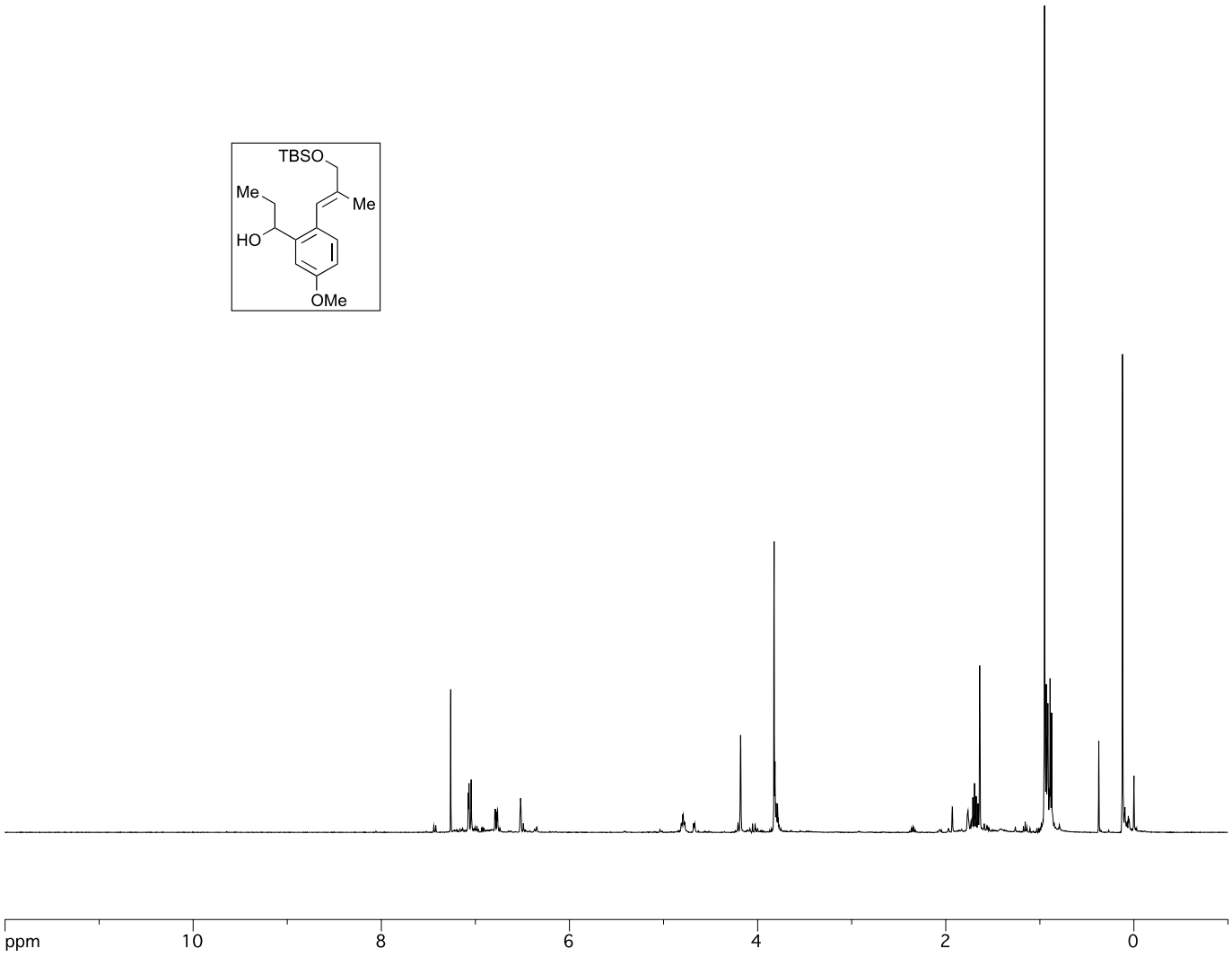


Figure A.4.9 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **420**

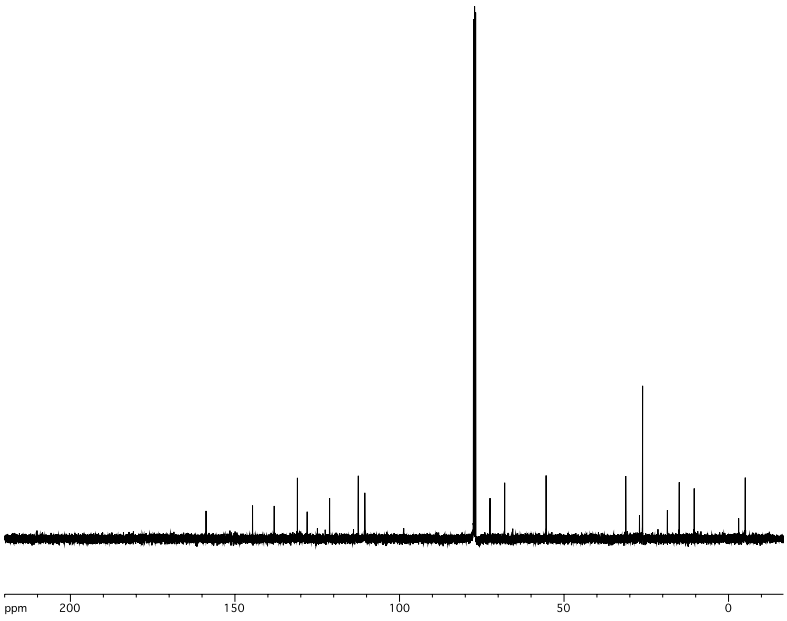


Figure A.4.10 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **420**

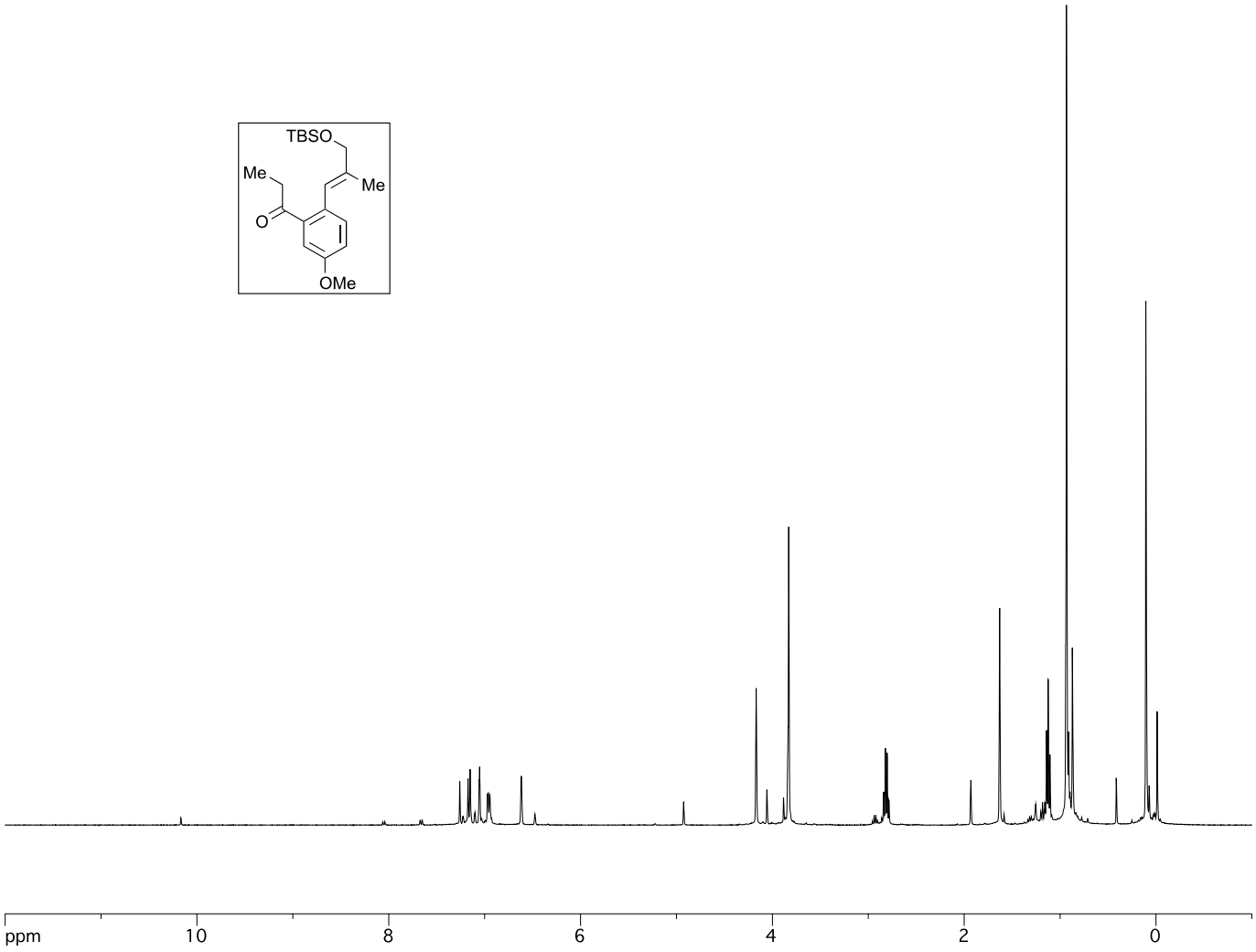


Figure A.4.11 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **421**

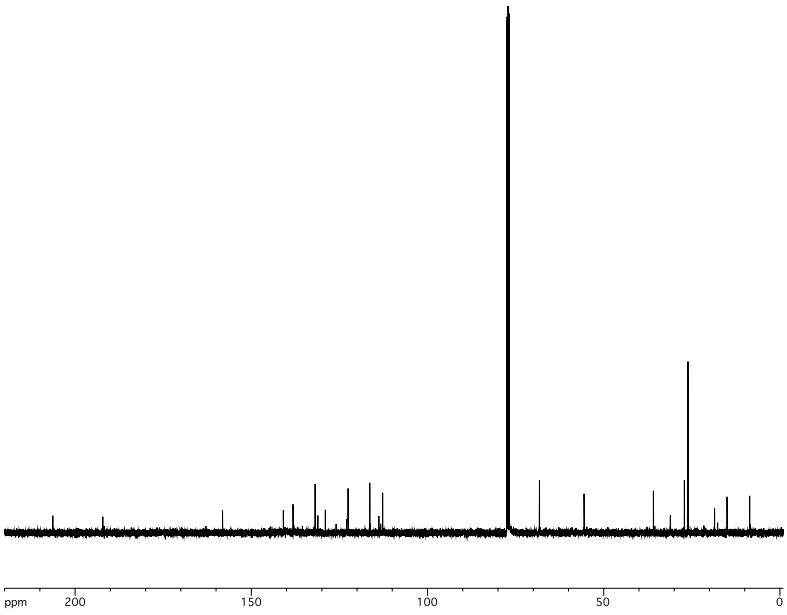


Figure A.4.12 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **421**

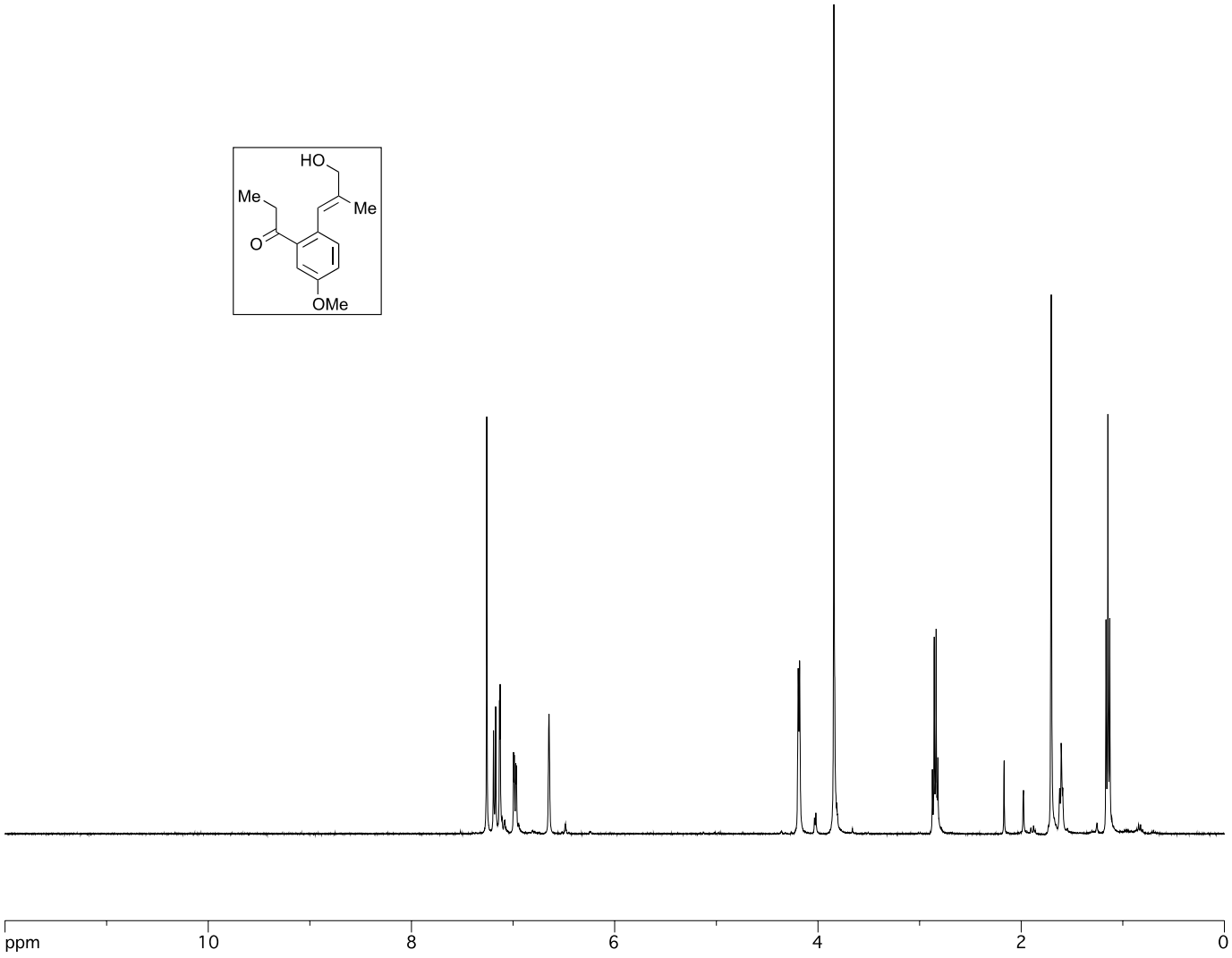


Figure A.4.13 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **422**

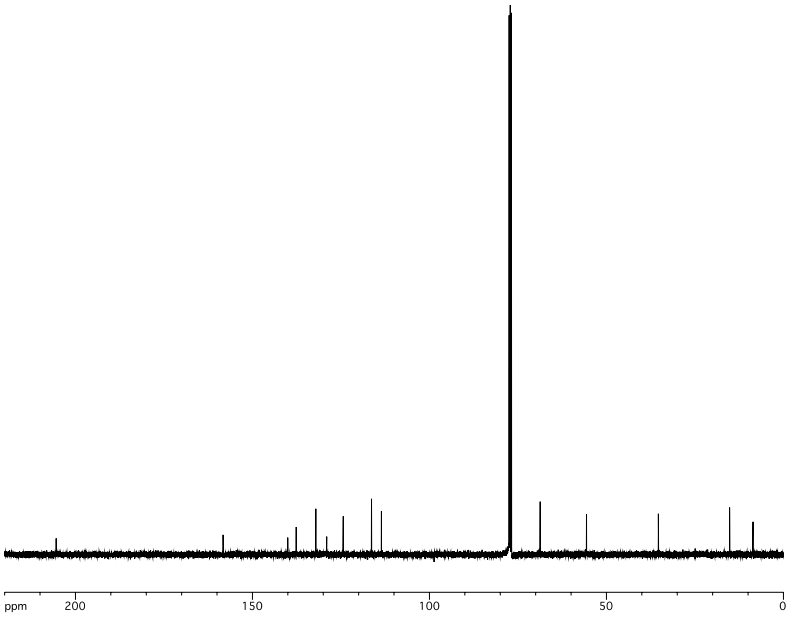


Figure A.4.14 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **422**

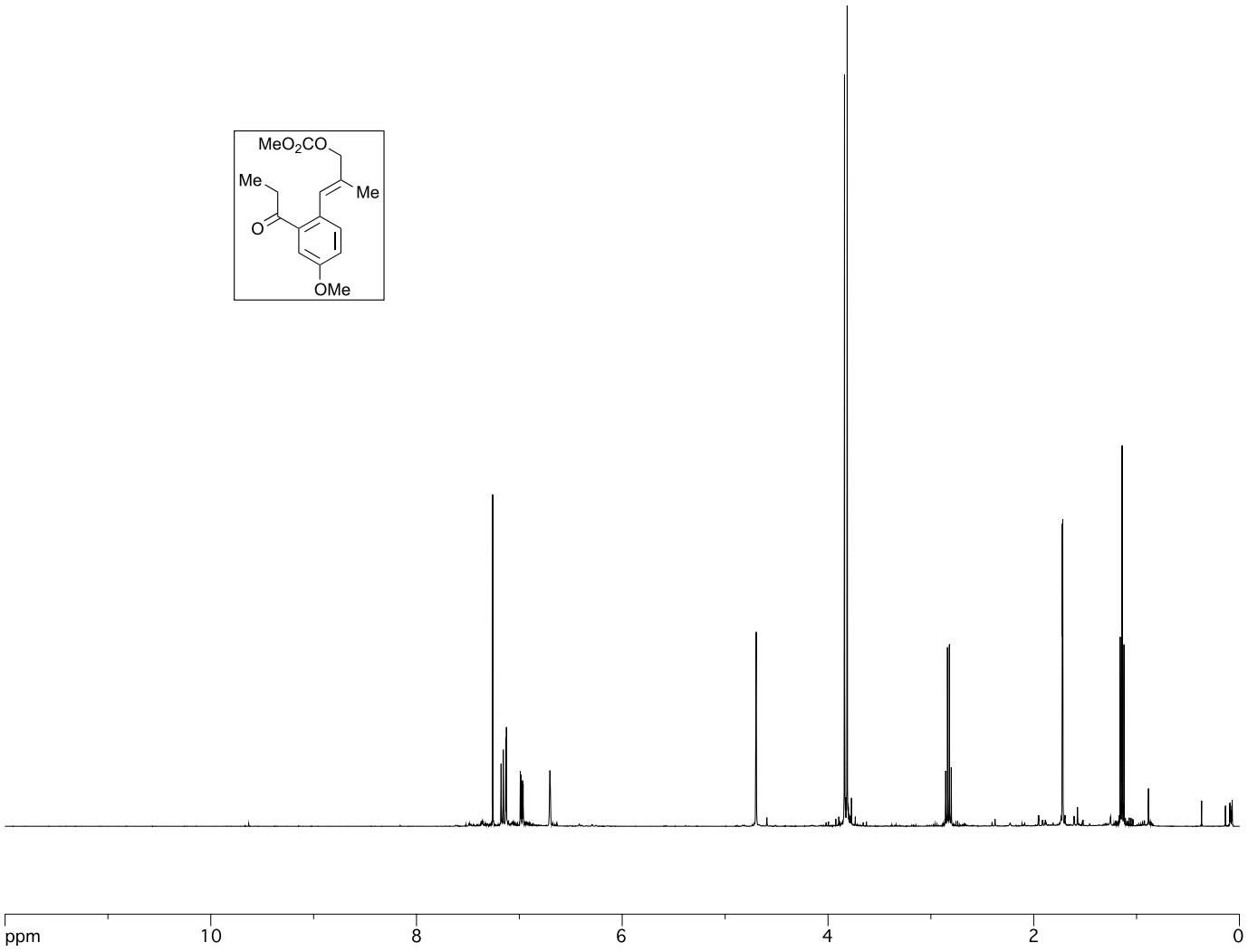


Figure A.4.15 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **423**

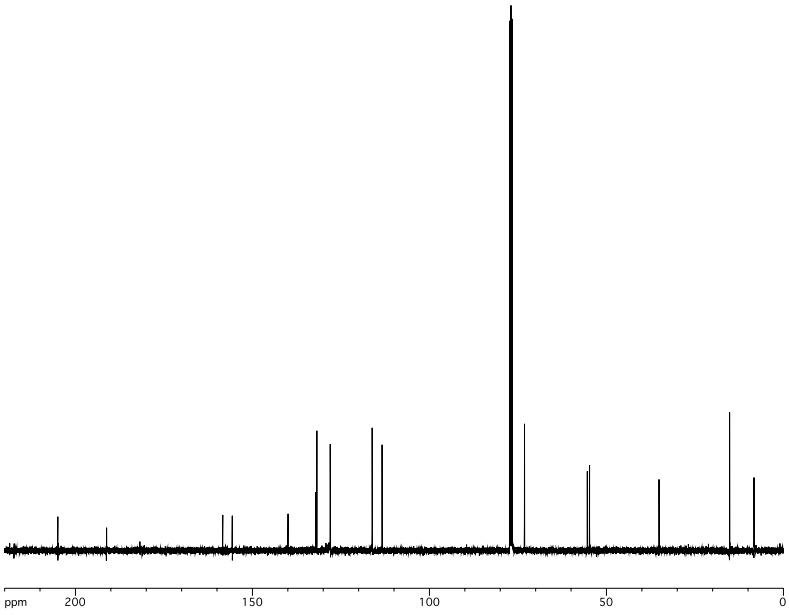


Figure A.4.16 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **423**

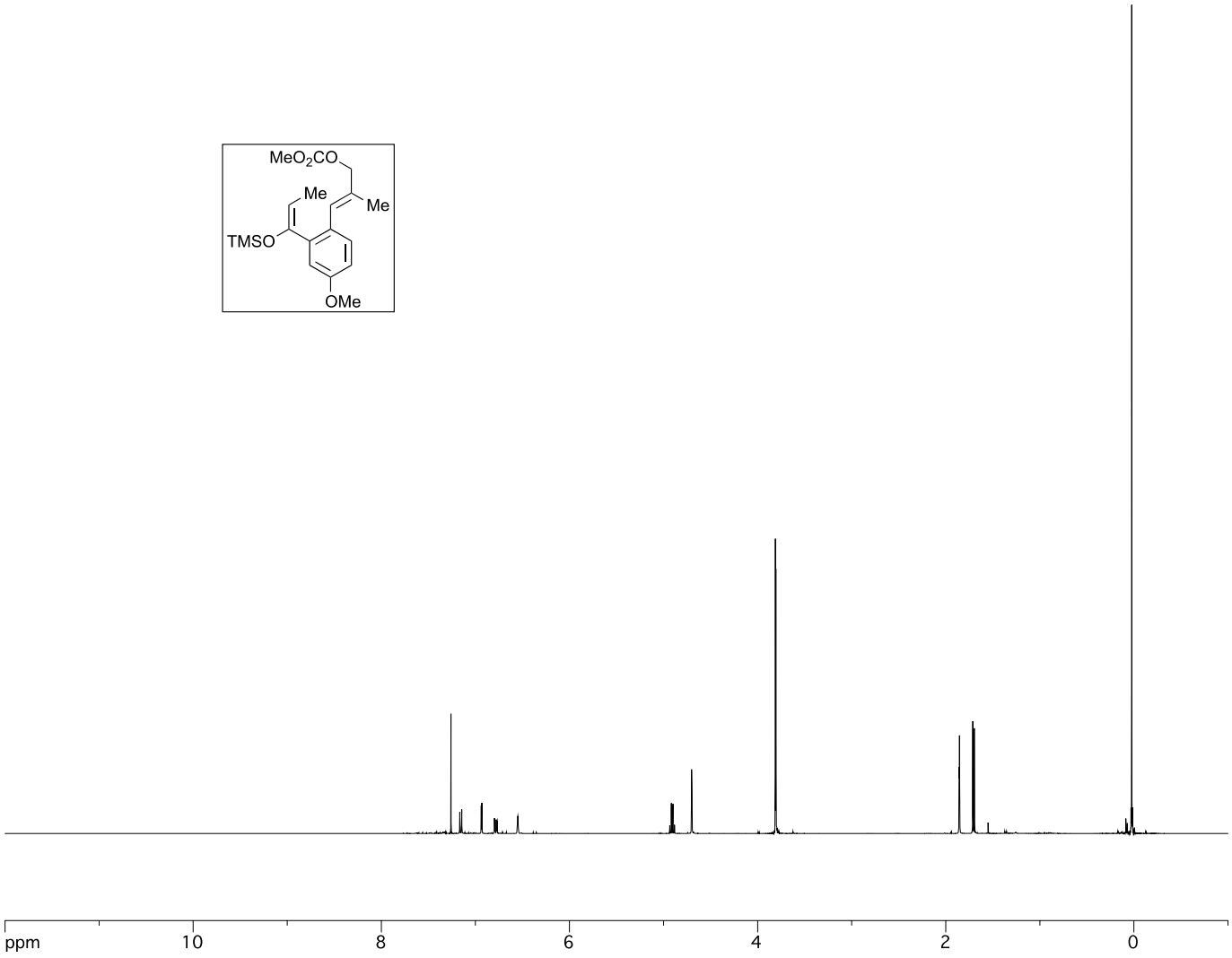


Figure A.4.17 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **424**

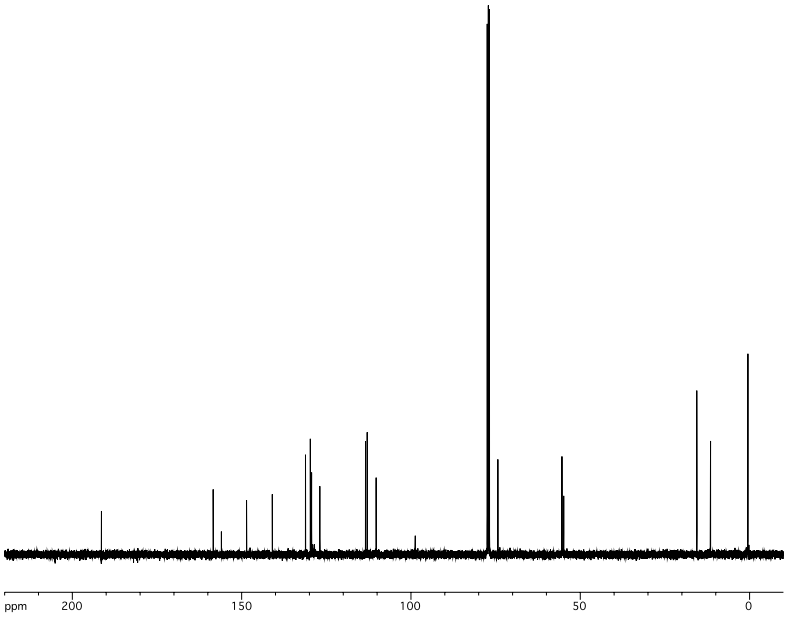


Figure A.4.18 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **424**

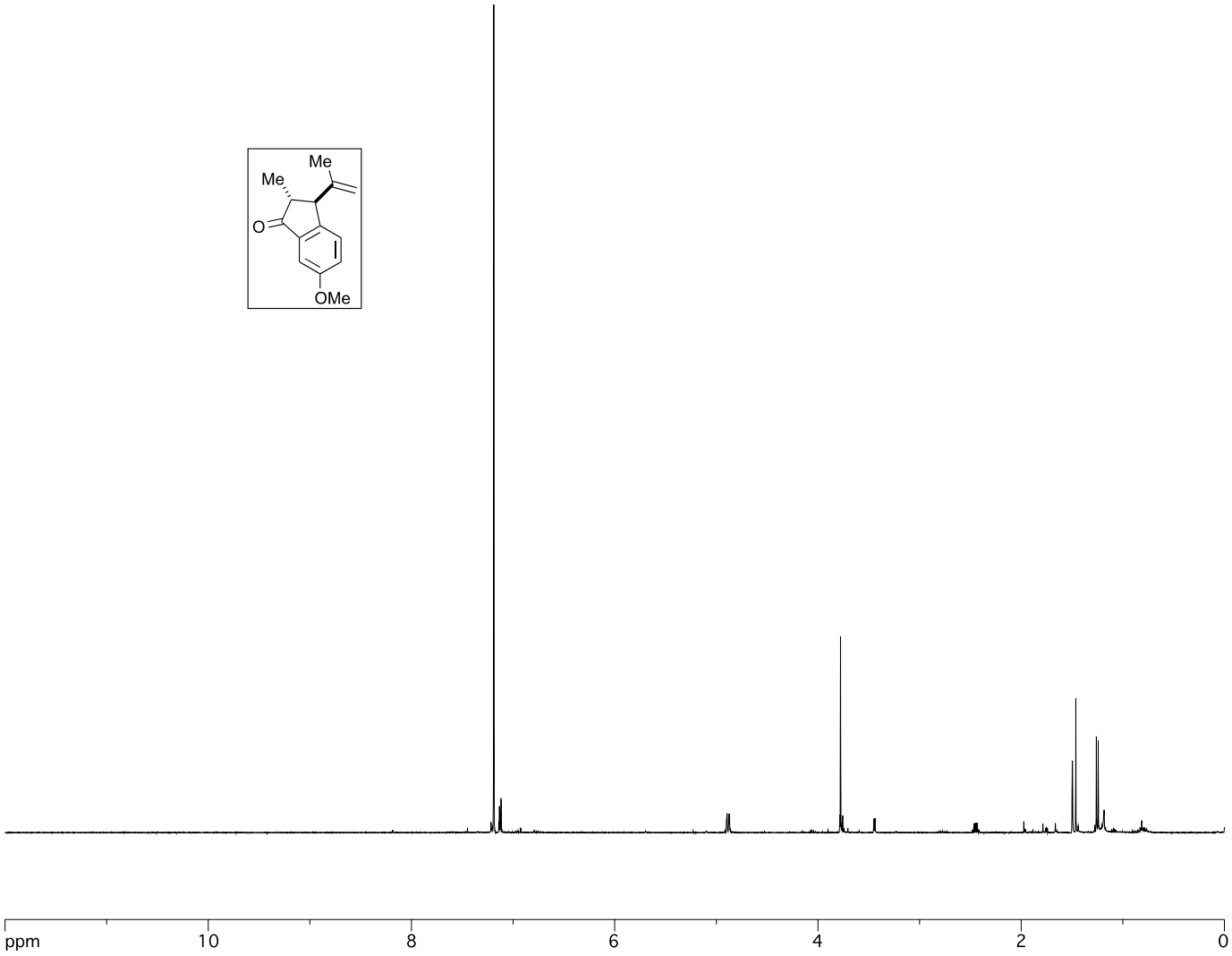


Figure A.4.19 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **427**

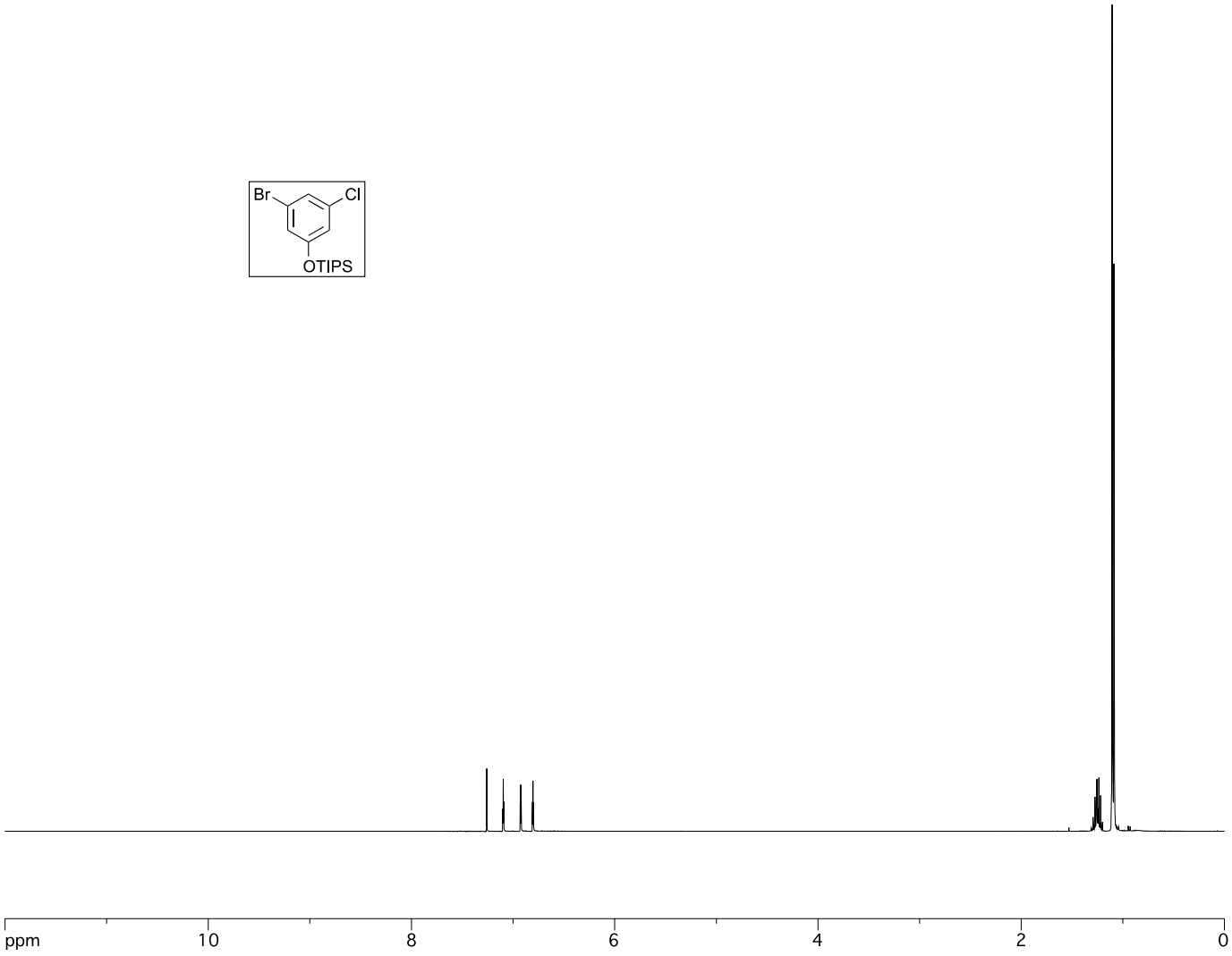


Figure A.4.20 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **432**

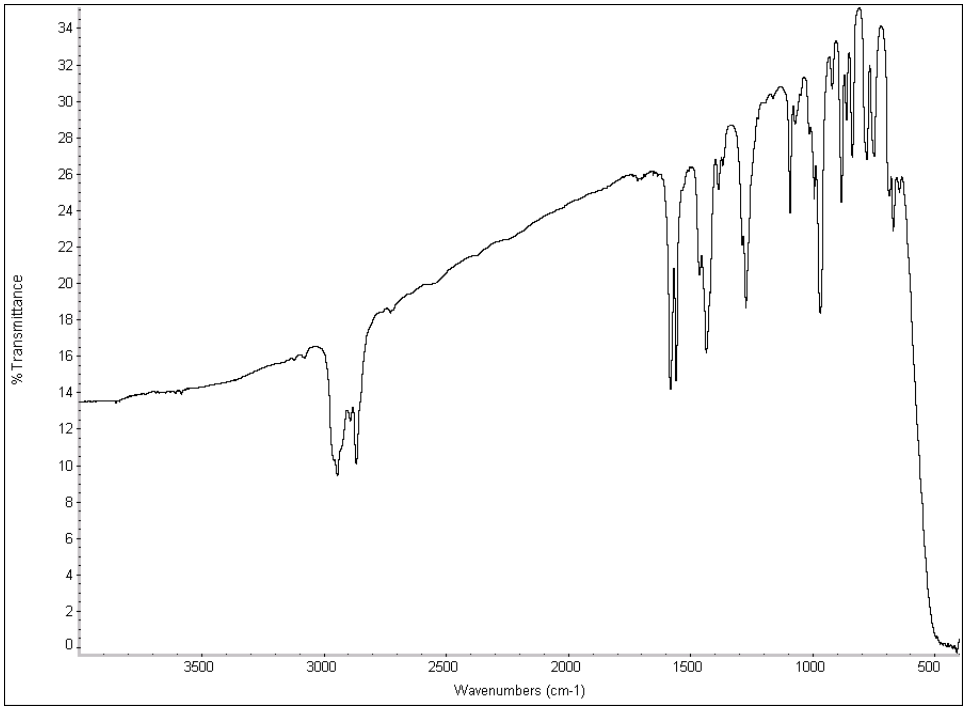


Figure A.4.21 FTIR (thin film/NaCl) of Compound **432**

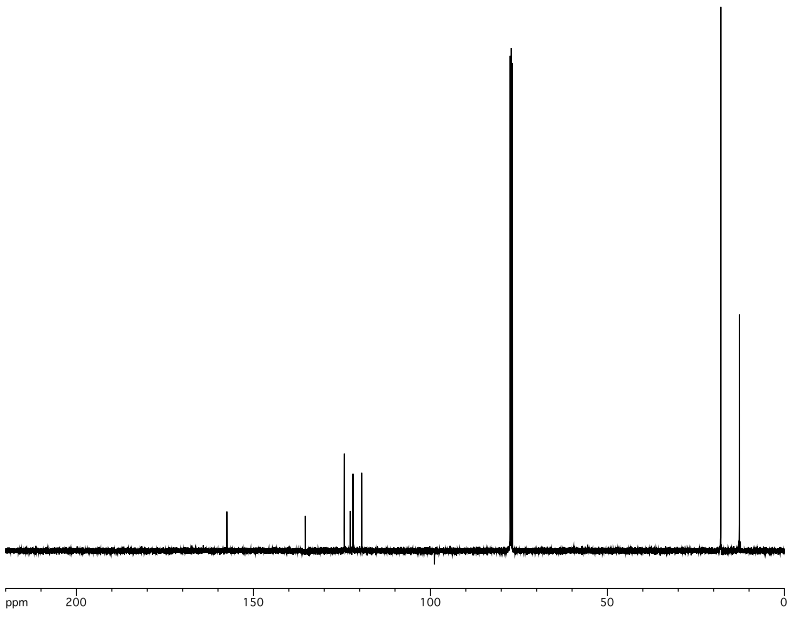


Figure A.4.22 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **432**

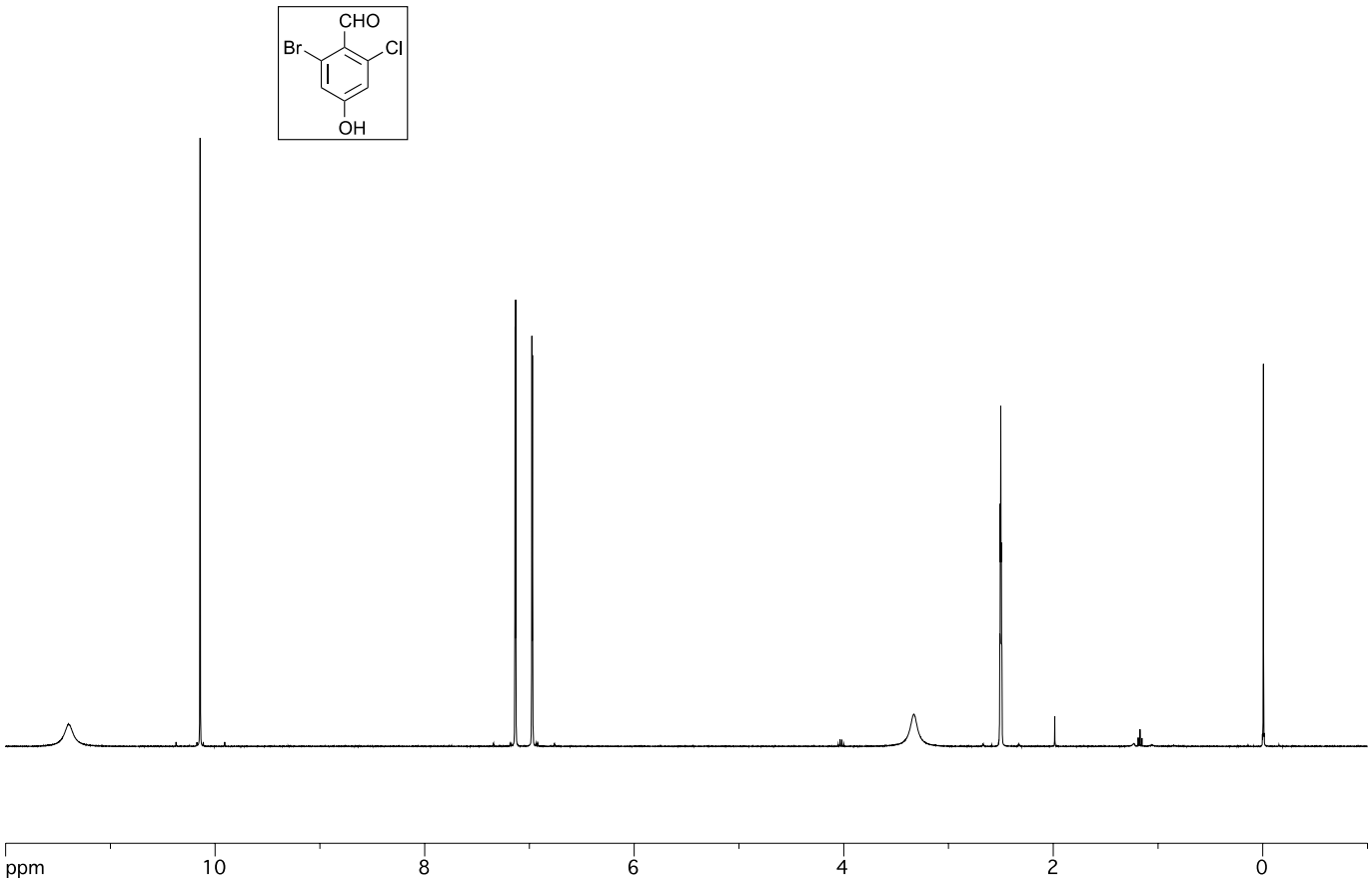


Figure A.4.23 ^{1}H NMR (400 MHz, DMSO-d_6) of Compound **433**

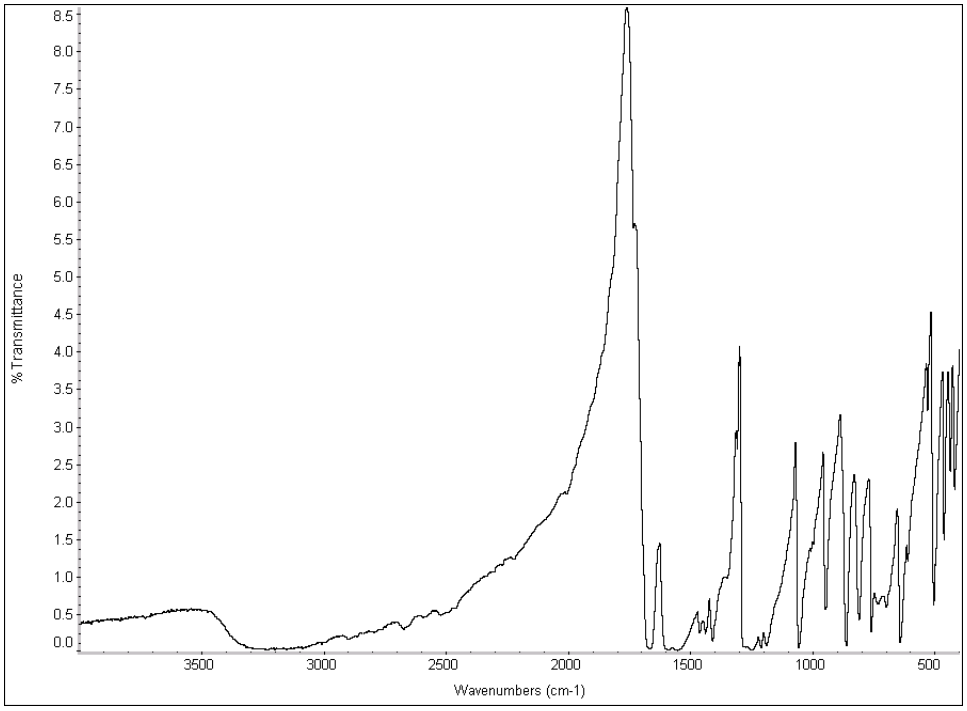


Figure A.4.24 FTIR (KBr pellet) of Compound **433**

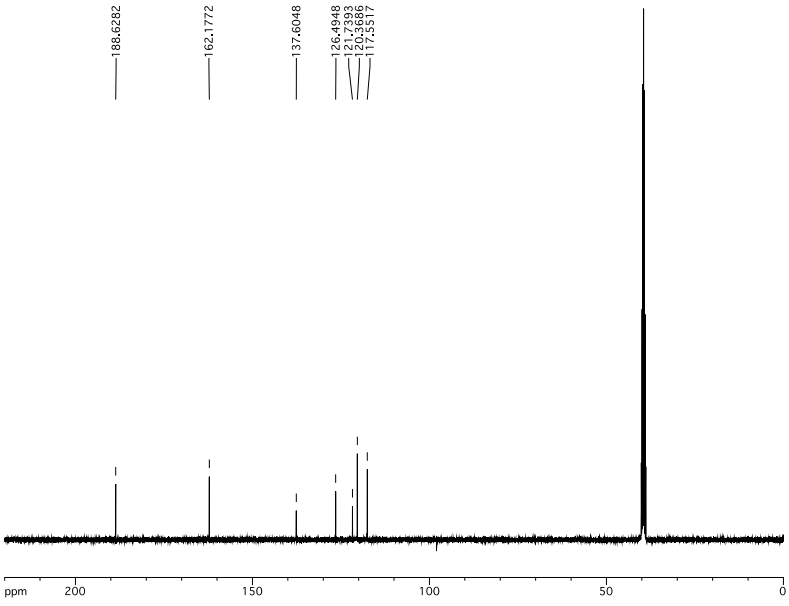


Figure A.4.25 ^{13}C NMR (101 MHz, DMSO-d_6) of Compound **433**

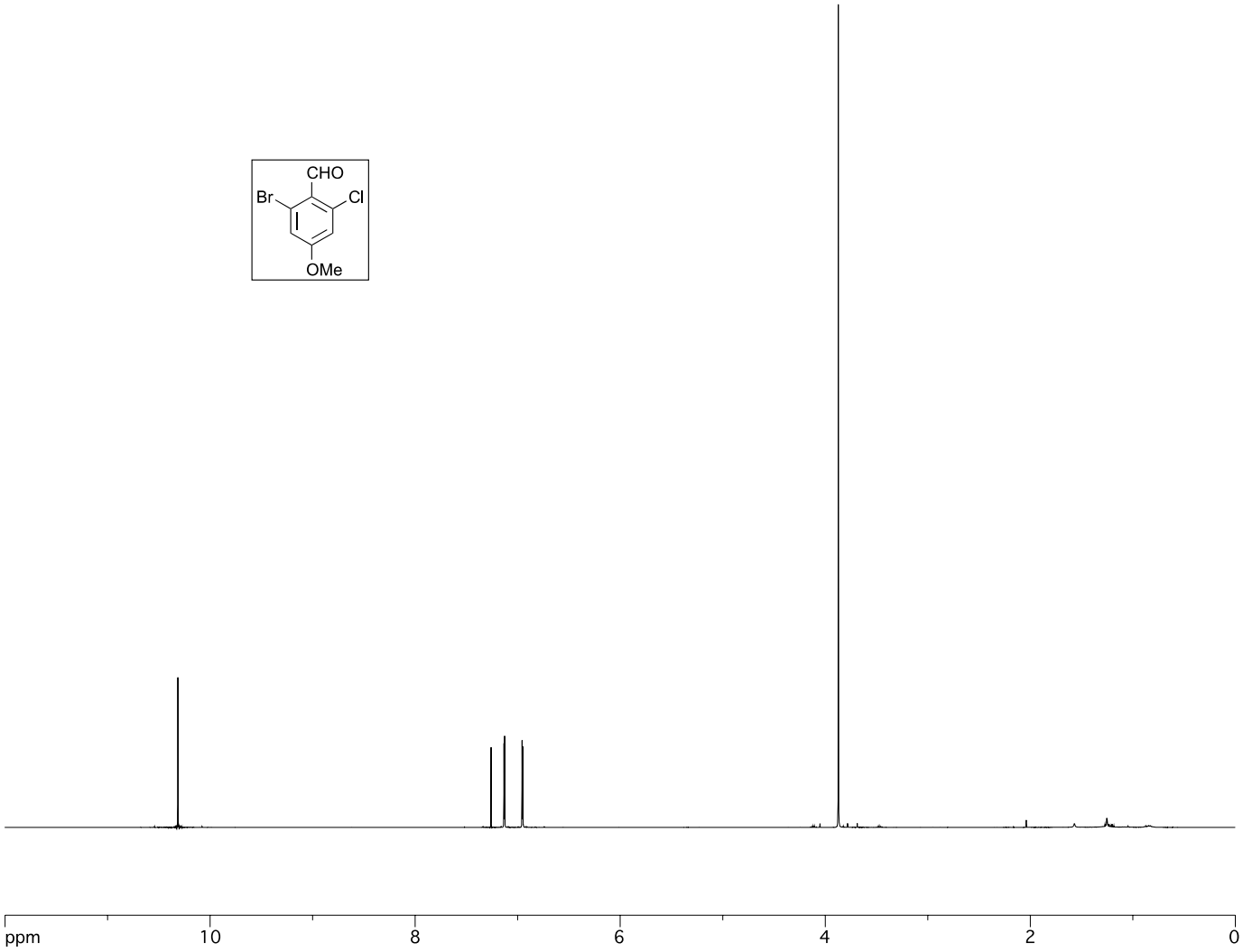


Figure A.4.26 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **434**

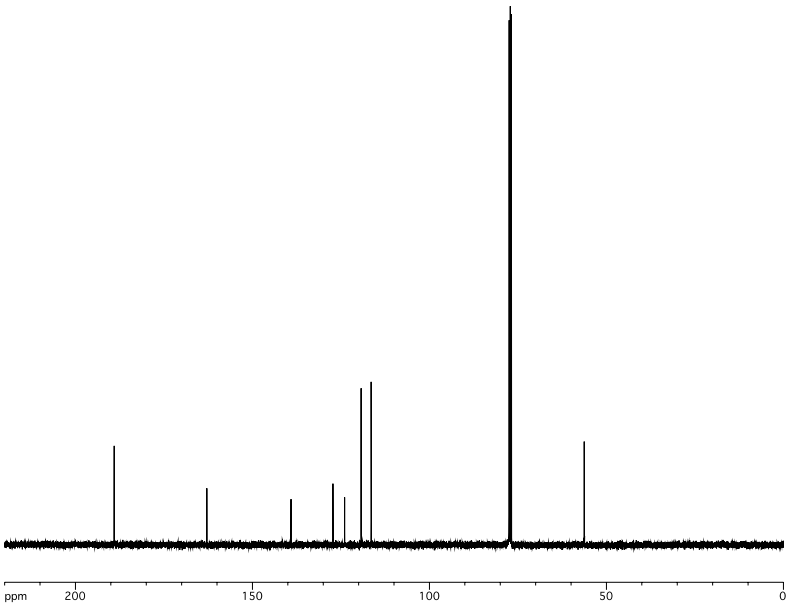


Figure A.4.27 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **434**

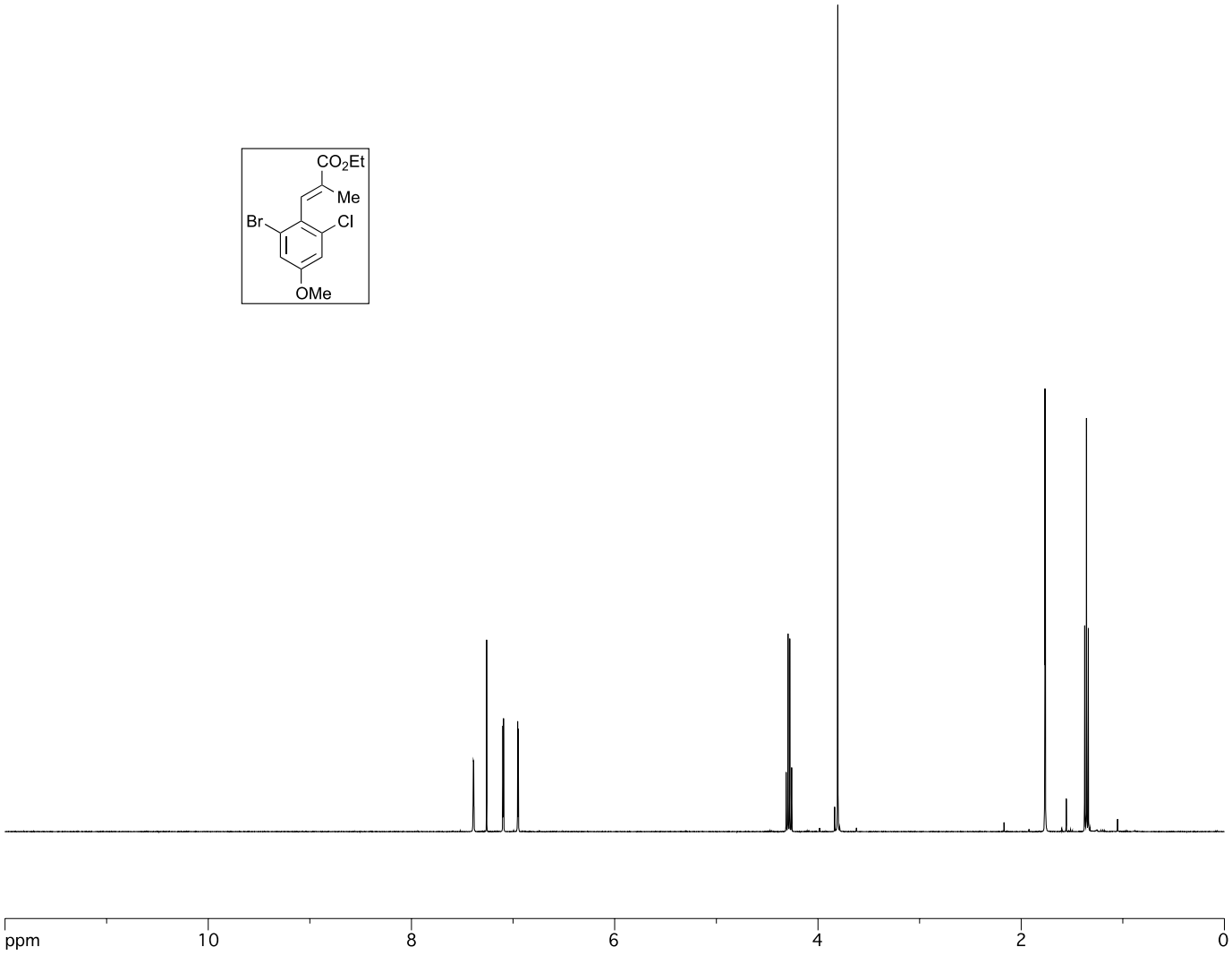


Figure A.4.28 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **435**

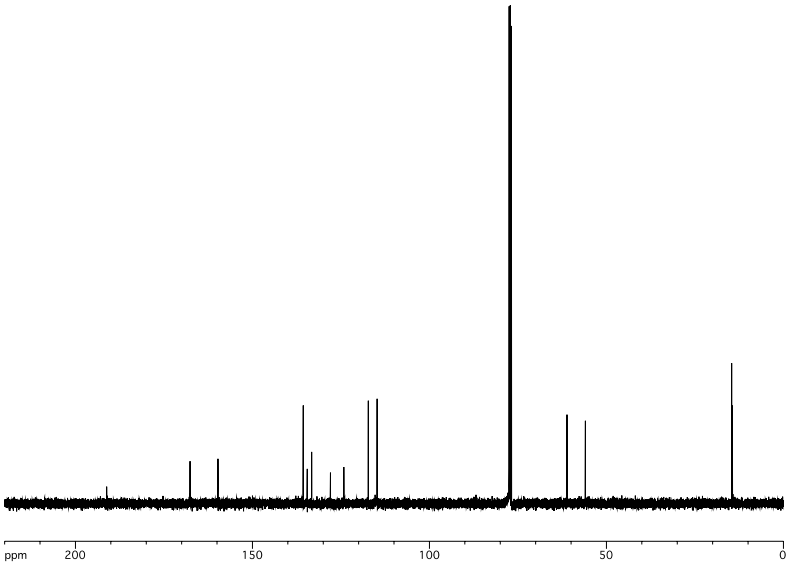


Figure A.4.29 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **435**

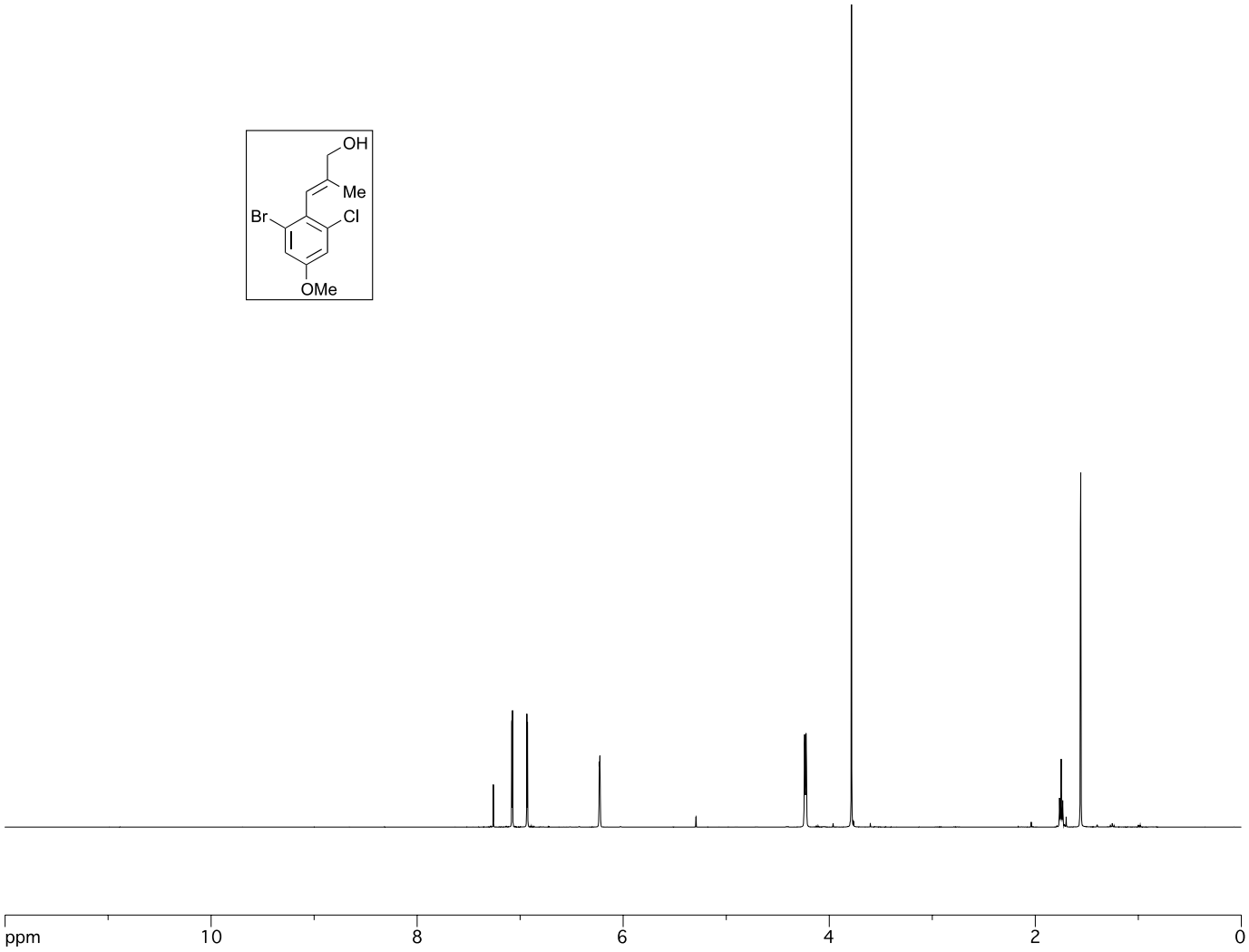


Figure A.4.30 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **436**

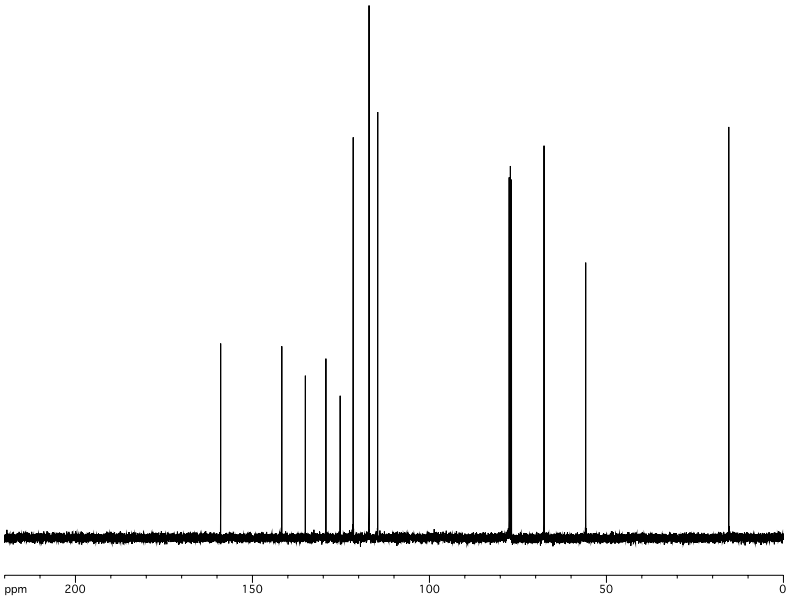


Figure A.4.31 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **436**

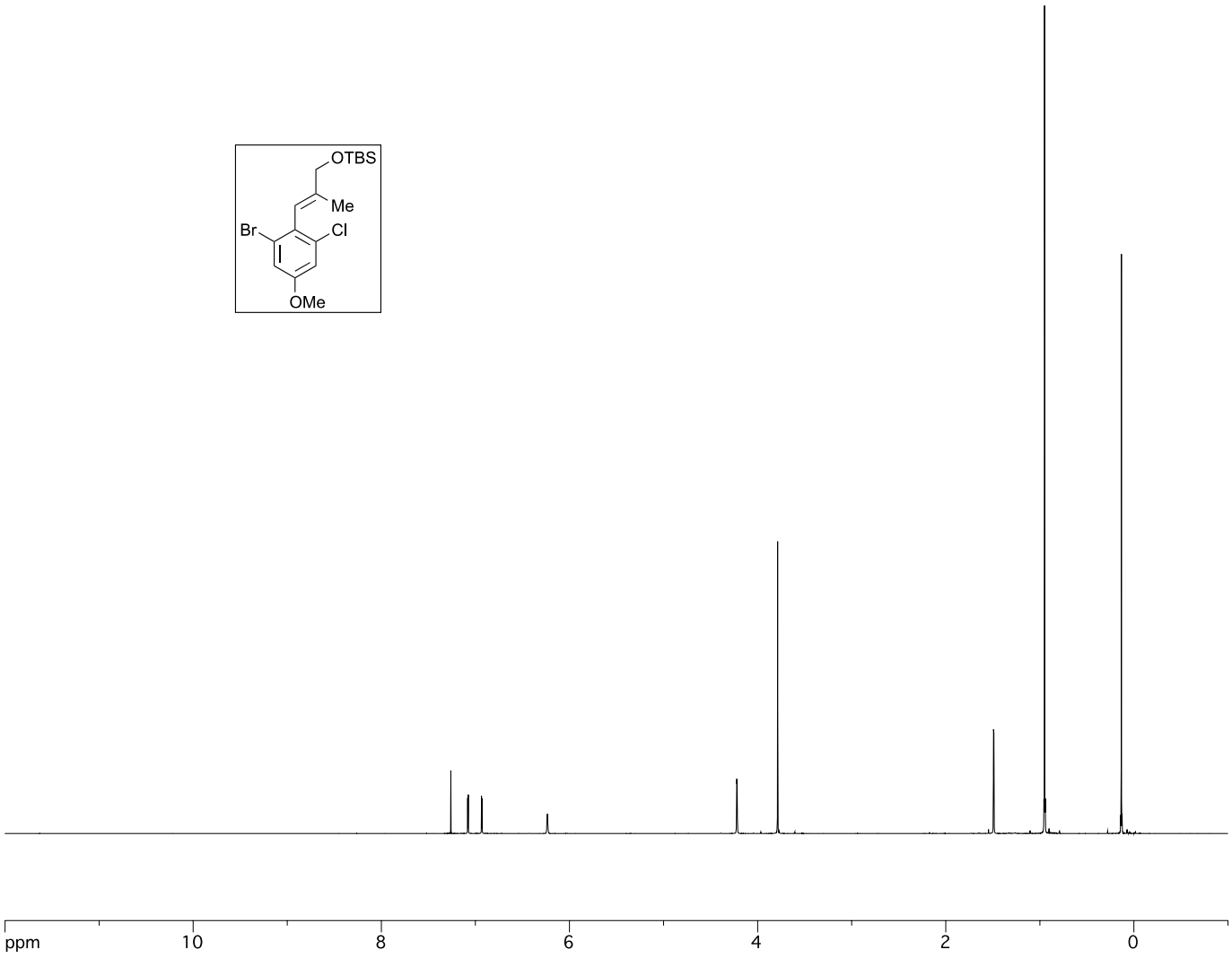


Figure A.4.32 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **437**

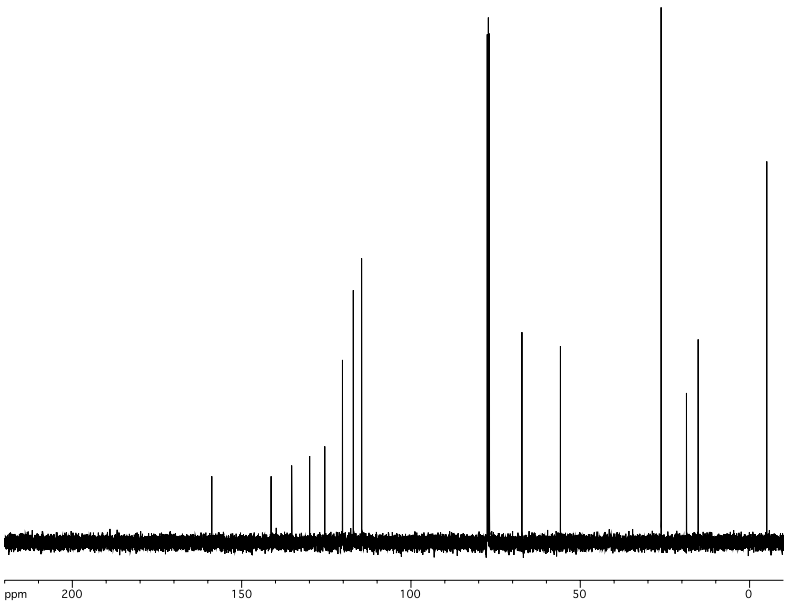


Figure A.4.33 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **437**

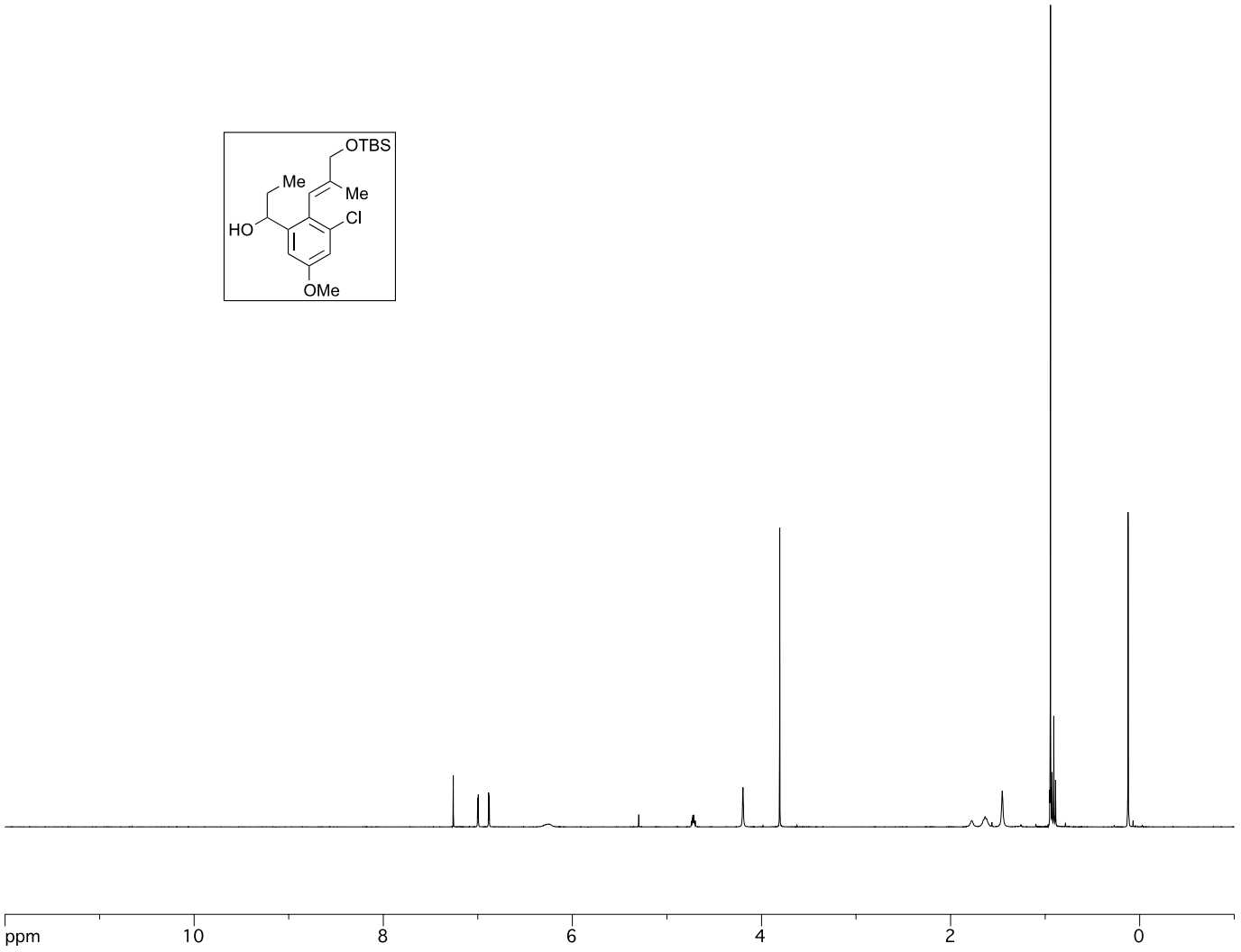


Figure A.4.34 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **438**

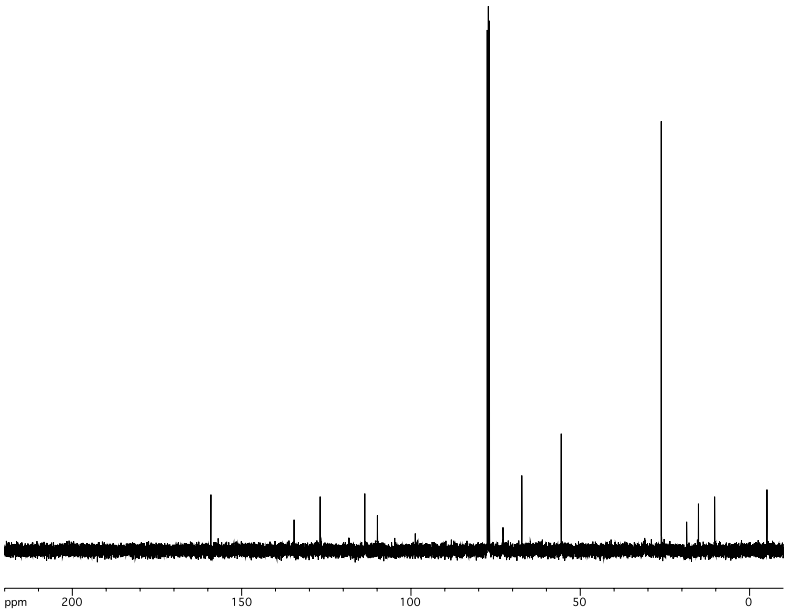


Figure A.4.35 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **438**

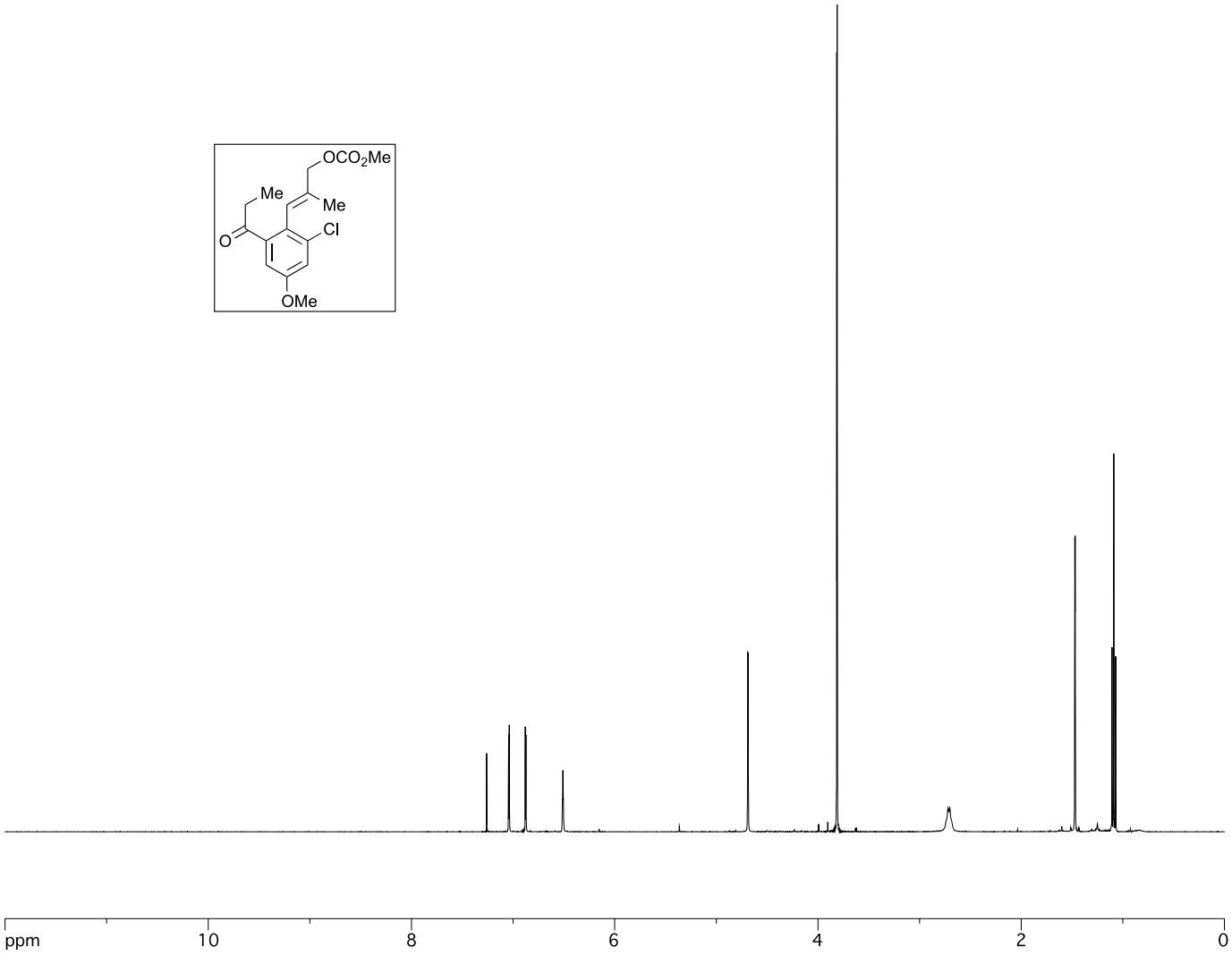


Figure A.4.36 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **441**

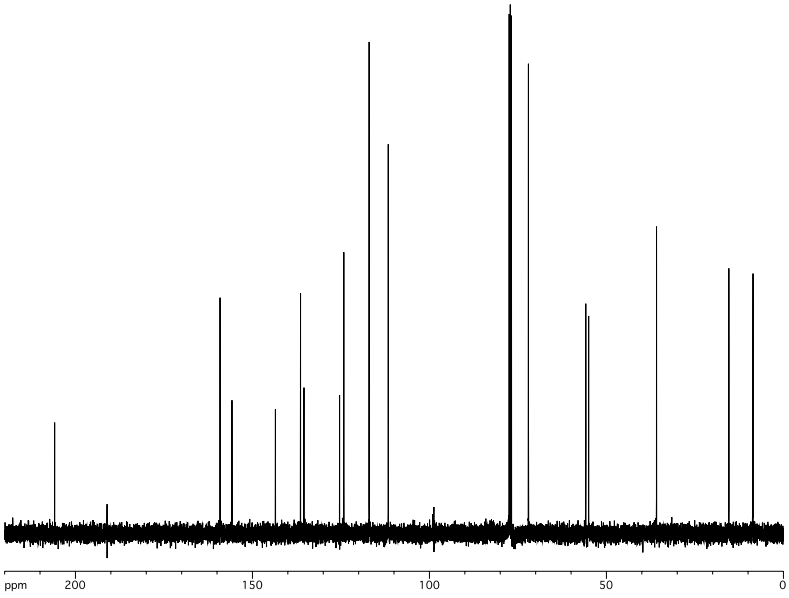


Figure A.4.37 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **441**

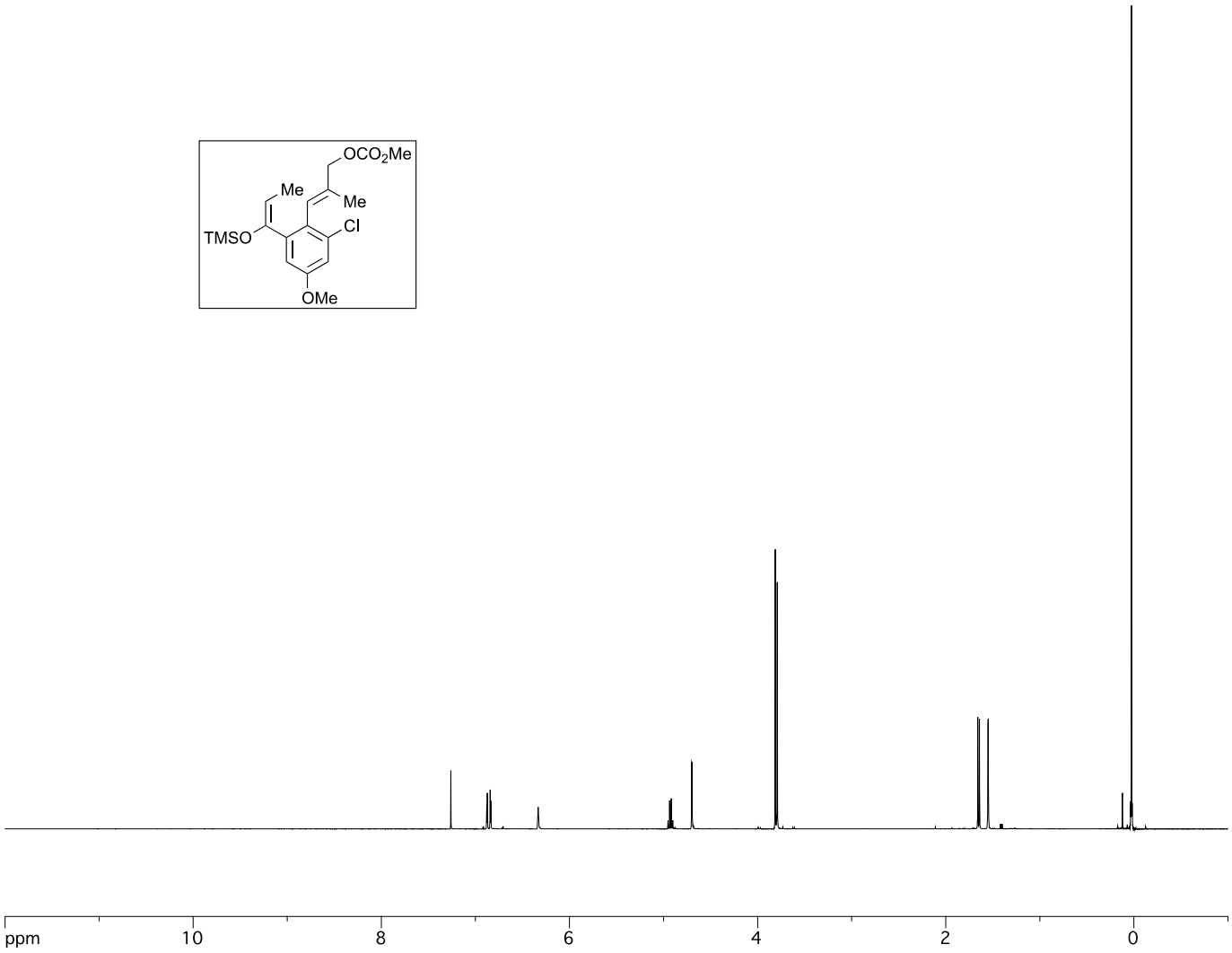


Figure A.4.38 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **442**

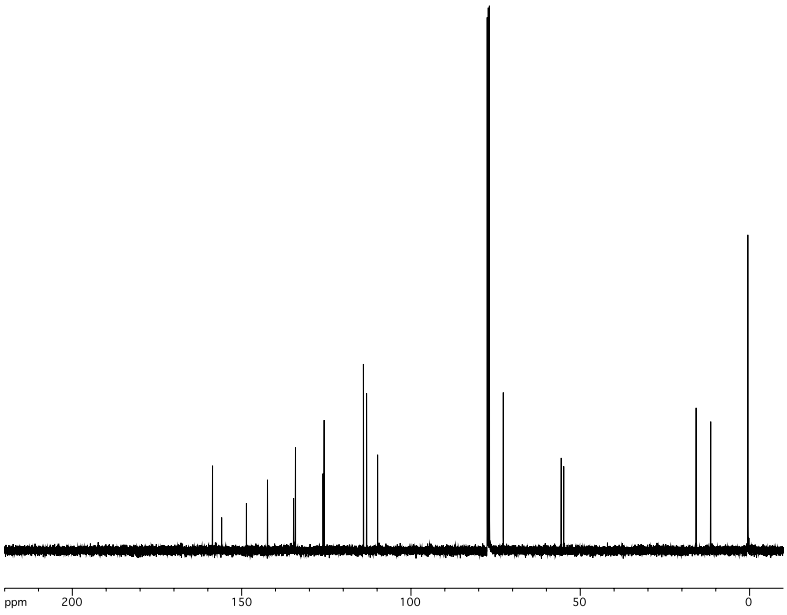


Figure A.4.39 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **442**

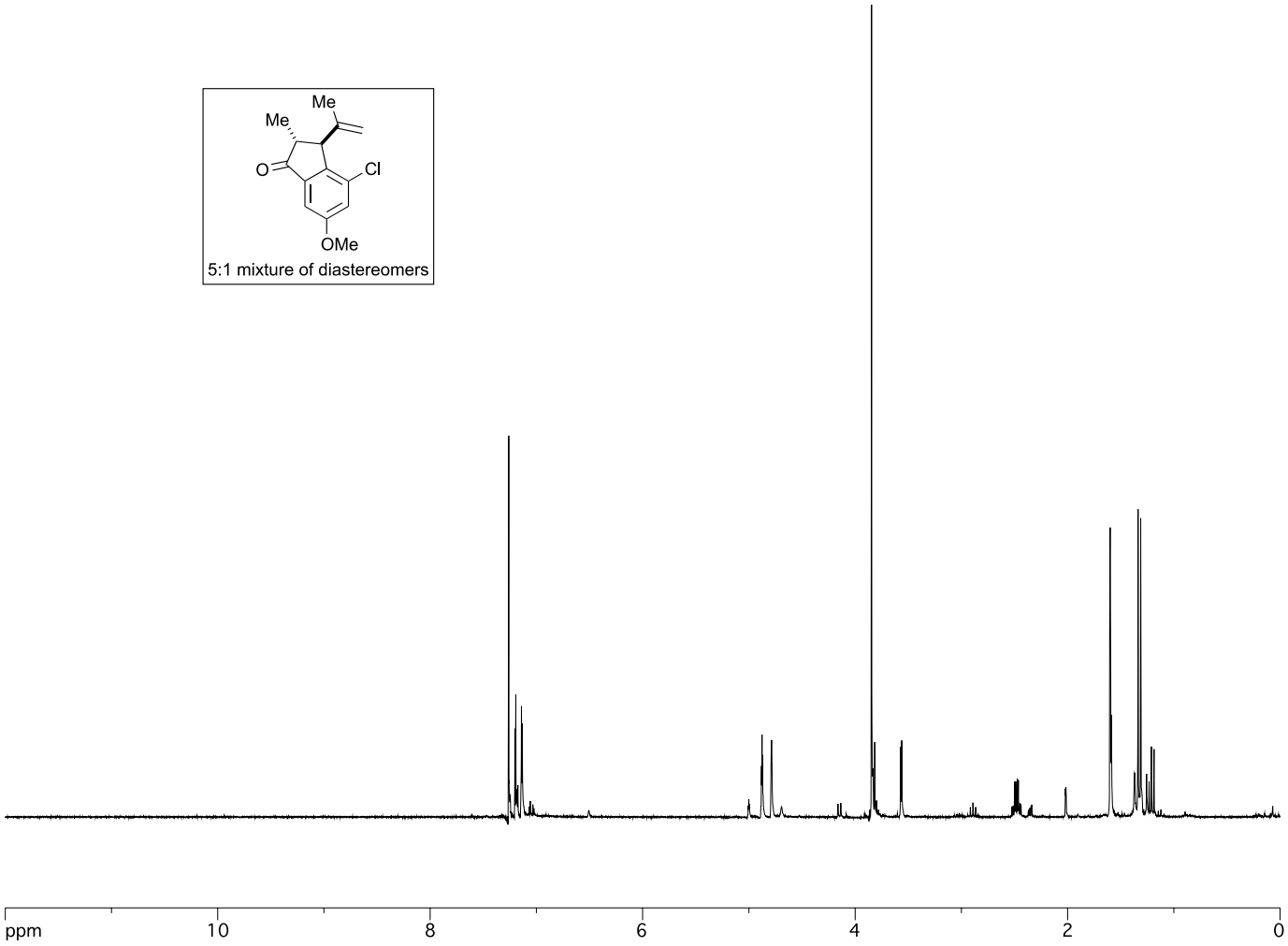


Figure A.4.40 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **443**

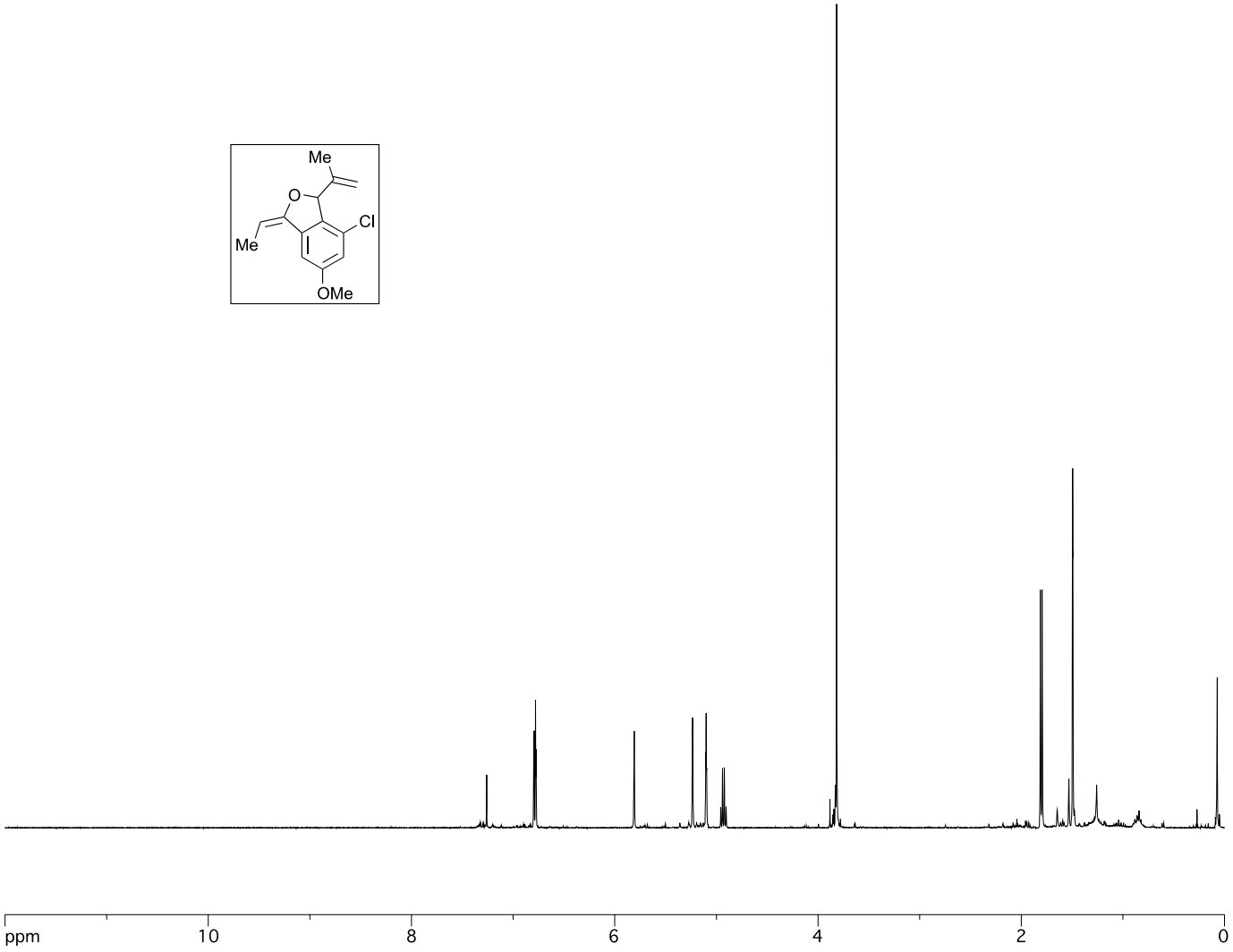


Figure A.4.41 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **444**

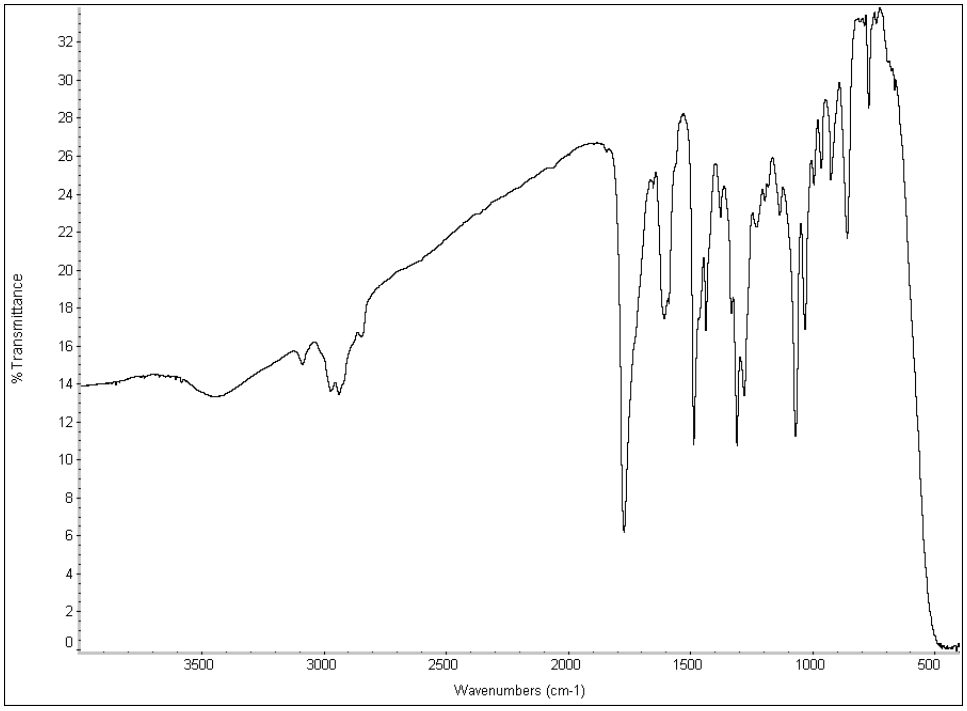


Figure A.4.42 FTIR (thin film/NaCl) of Compound **444**

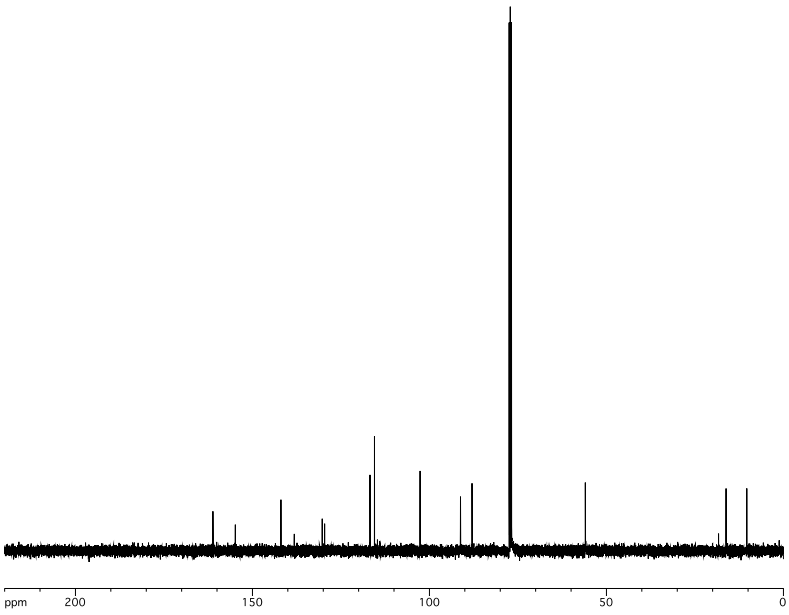


Figure A.4.43 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **444**

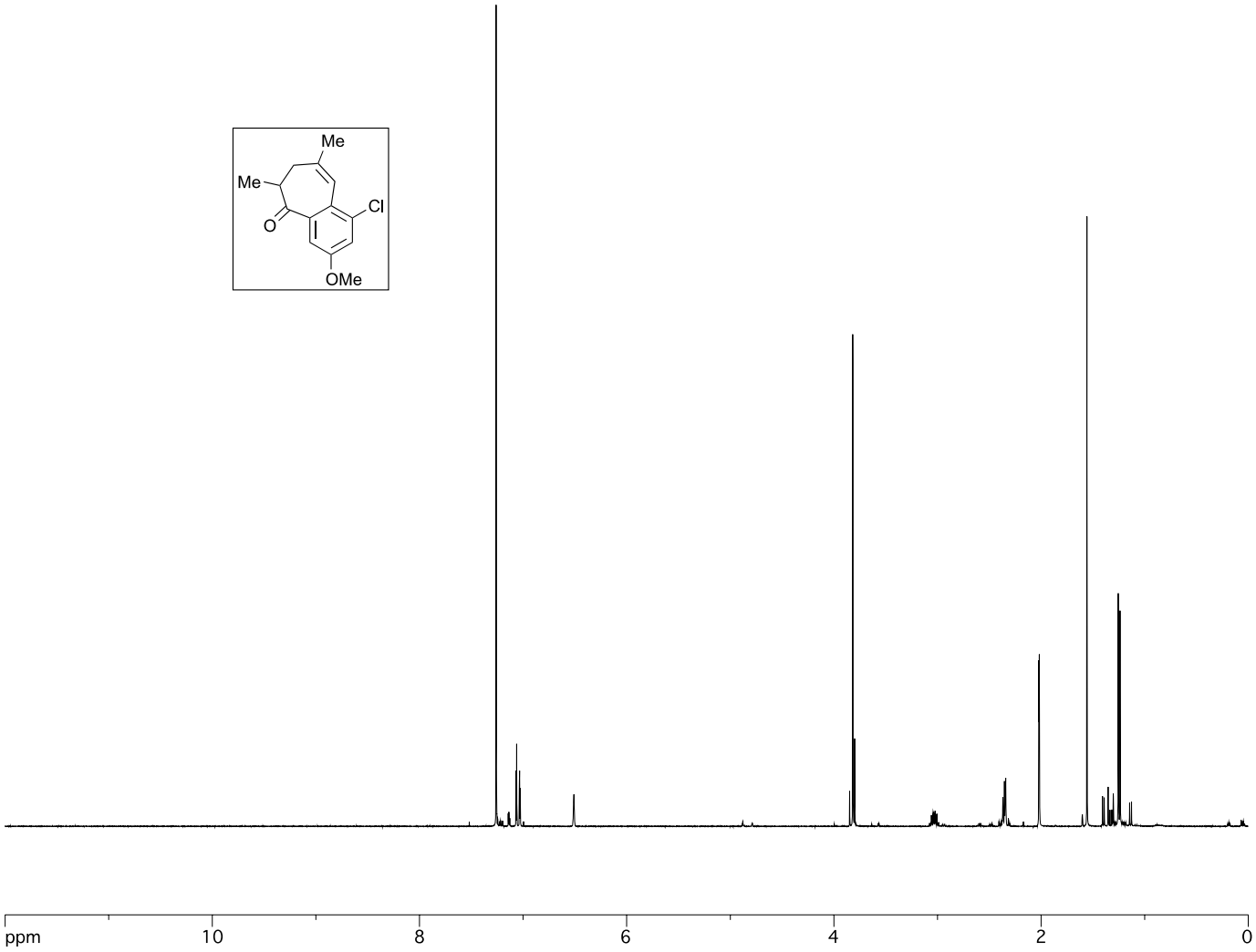


Figure A.4.44 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **445**

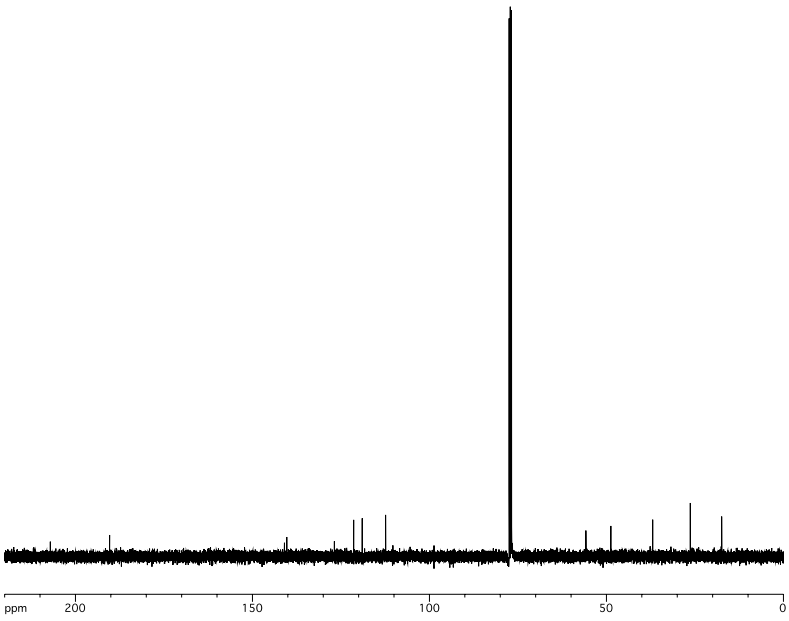


Figure A.4.45 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **445**

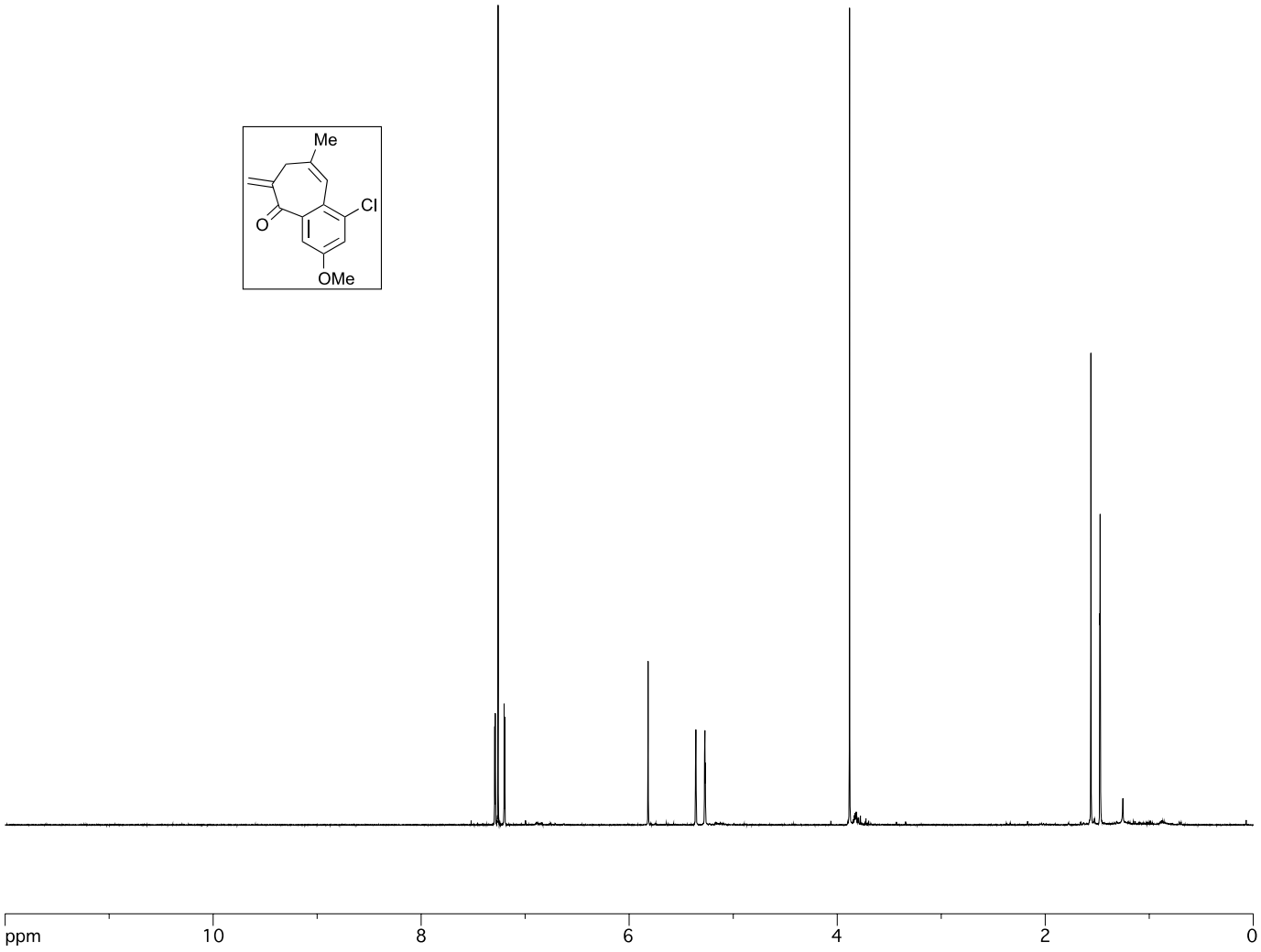


Figure A.4.46 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **446**

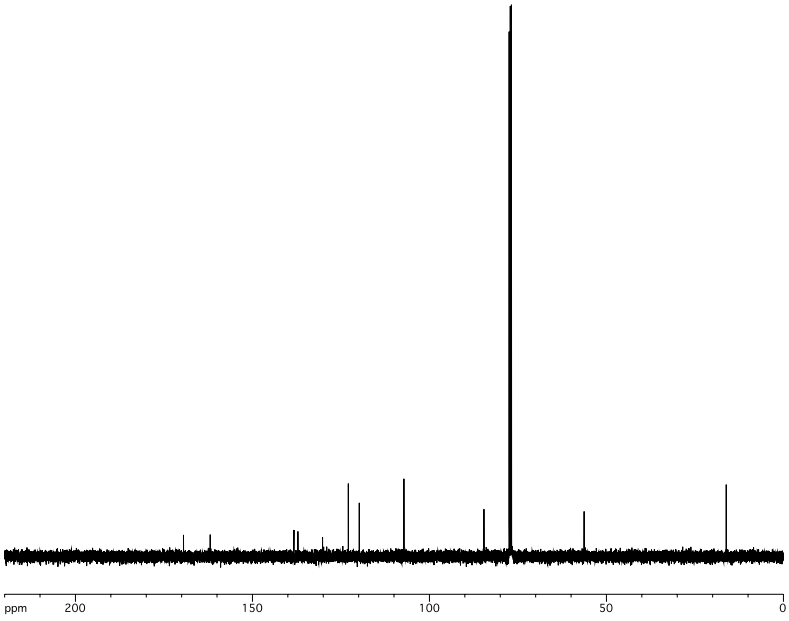


Figure A.4.47 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **446**

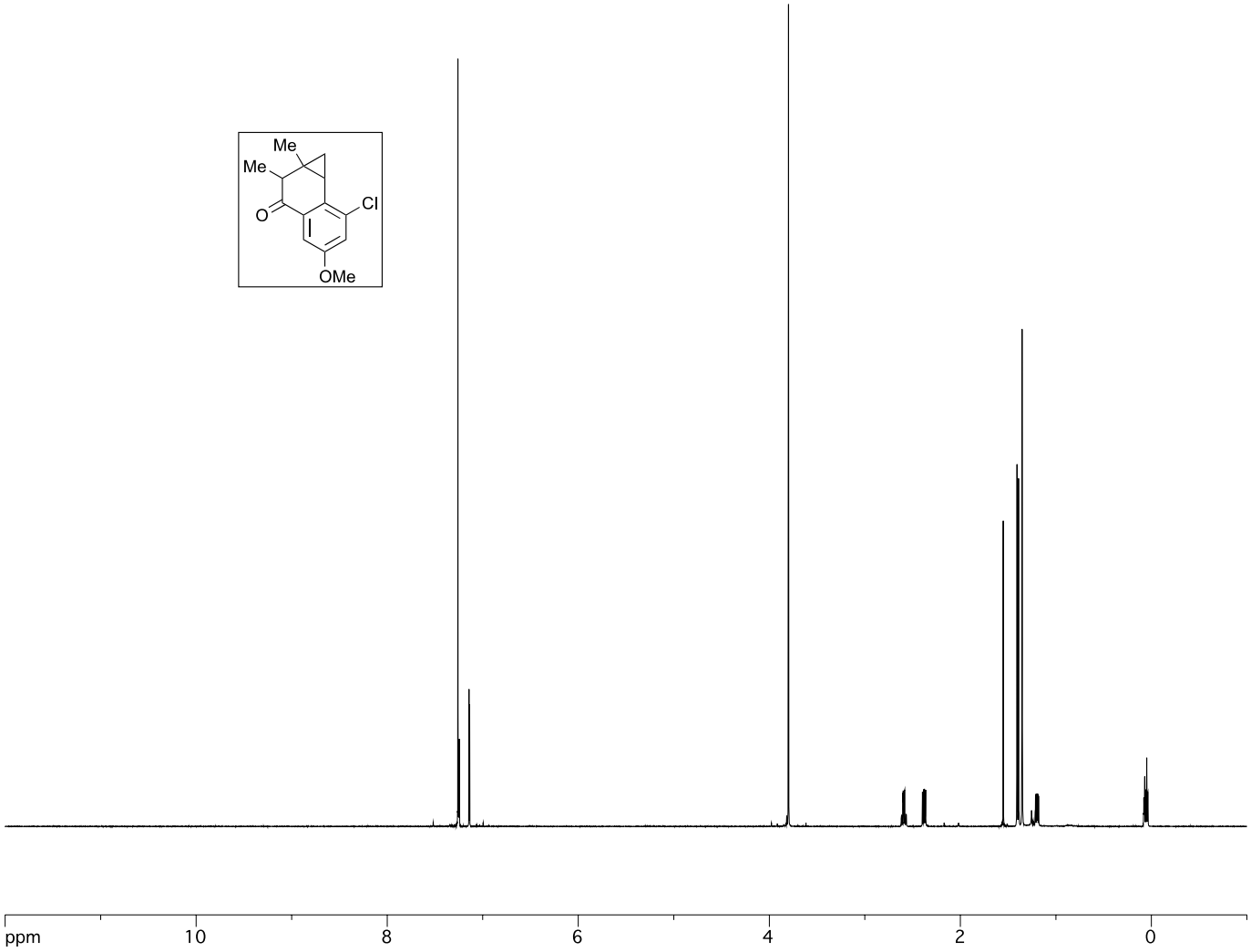


Figure A.4.48 ^{1}H NMR (400 MHz, $CDCl_3$) of Compound **447**

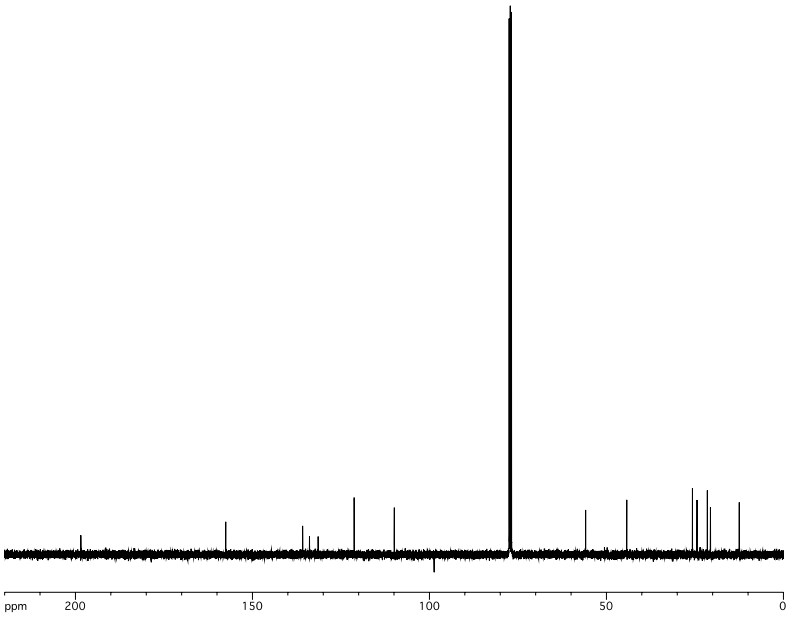


Figure A.4.49 ^{13}C NMR (101 MHz, $CDCl_3$) of Compound **447**

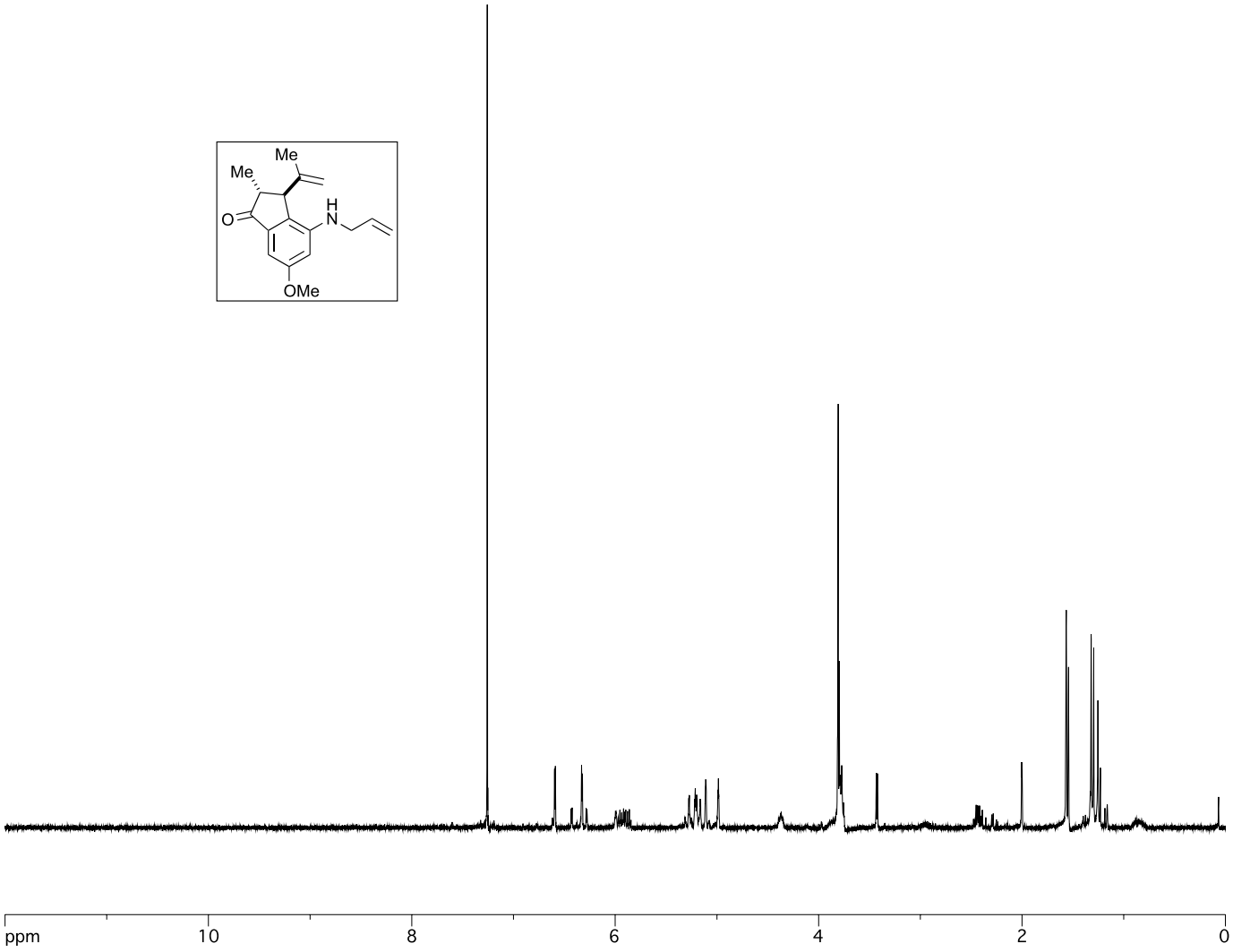


Figure A.4.50 ^{1}H NMR (300 MHz, $CDCl_3$) of Compound **448**

Appendix 5

Notebook Cross Reference

Chapter 2

Chapter 4

Chapter 5

LIST OF ABBREVIATIONS

Å	angstrom
Ac	acetate
AcOH	acetic acid
app	apparent
Ar	aryl
Bn	benzyl
br	broad
Bz	benzoyl
C	carbon
C_6H_6	benzene
cat.	catalytic
CH_2Cl_2	dichloromethane
CH_3CN	acetonitrile
CuI	copper(I) iodide
d	doublet
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
dddd	doublet of doublet of doublet of doublets
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
dt	doublet of triplet
ent	enantiomer
ESI–APCI	electrospray ionization – atmospheric pressure chemical ionization
Et	ethyl
Et_3N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
g	gram
h	hour(s)
H	hydrogen
H_2O	water
H_2SO_4	sulfuric acid
$Hg(OAc)_2$	mercury(II) acetate
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons
Hz	hertz

hν	light
Im	imidazole
i-Pr$_2$NEt	N,N-Diisopropylethylamine, Hünig's Base
IR	infrared
J	coupling constant
K_2CO_3	potassium carbonate
kg	kilogram
KHMDS	potassium bis(trimethylsilyl)amide
KOt-Bu	potassium tert-butoxide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
m	multiplet (NMR), mid (IR)
Me	methyl
Me_2SO_4	dimethylsulfate
MeOH	methanol
mg	milligram
min	minute(s)
mL	milliliter
mmol	millimole
mol sieves	molecular sieves
mol	mole(s)
$NaBH_4$	sodium borohydride
NaH	sodium hydride
$NaHCO_3$	sodium bicarbonate
NaHMDS	sodium bis(trimethylsilyl)amide
NaI	sodium iodide
n-BuLi	*n*-butyllithium
NH_4Cl	ammonium chloride
nm	nanometer
NMR	nuclear magnetic resonance
O_3	ozone
ºC	degrees Celsius
$Pd(OAc)_2$	palladium(II) acetate
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
PG	protecting group
Ph	phenyl
PMB	paramethoxybenzyl
ppm	parts per million
p-TSA	*p*-toluenesulfonic acid
Py	pyridine
q	quartet
quint.	quintuplet
RCM	ring closing metathesis
R_f	retention factor
rt	room temperature

s	singlet (NMR), strong (IR)
$SOCl_2$	thionyl chloride
t	triplet
TBAF	tetrabutylammonium fluoride
TBDPS	tert-butyldiphenylsilyl
TBS	tert-butyldimethylsilyl
t-Bu	tert-butyl
t-BuLi	tert-butyllithium
tert	tertiary
Tf_2O	triflic anhydride
TFA	trifluoroacetate, trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
$TMSCHN_2$	trimethylsilyldiazomethane
TOF LCMS	time of flight liquid chromatography mass spectrometry
w	weak
δ	chemical shift
Δ	heat