Title
The Total Synthesis of Galbulimima Alkaloid (+/-) G. B. 13 and the Development of an Anomalous Heck Reaction

Author
Larson, Kimberly Katherine

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The Total Synthesis of *Galbulimima* Alkaloid (±)-G. B. 13
and
The Development of an Anomalous Heck Reaction

by

Kimberly Katherine Larson

A dissertation submitted in partial satisfaction of the

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Committee in charge:

Professor Richmond Sarpong, Chair
Professor Jonathan A. Ellman
Professor Joseph L. Napoli

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Abstract

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Professor Richmond Sarpong, Chair

This dissertation describes our strategy for the total synthesis of *Galbulimima* alkaloid (±)-G. B. 13. First, an overview of the isolation and structural classification of the twenty-eight alkaloids in the *Galbulimima* family is presented. Proposals for the biosyntheses of these natural products as well as the determination of their absolute stereochemical relationships are discussed. Additionally, the biological and medicinal properties of himbacine, another *Galbulimima* alkaloid, are presented. The four total syntheses of alkaloid G. B. 13 that have been completed by research groups other than our own are briefly examined.

Our own total synthesis of (±)-G. B. 13 was accomplished in eighteen linear steps from commercially available starting materials. A detailed account of our synthetic endeavors, which include the rational development of both an allylic alcohol transposition under modified Parikh-Doering conditions and an unprecedented rhodium(I)-catalyzed addition of an aryl boronic ester into an unactivated ketone carbonyl, is described. The completion of this synthesis demonstrates the synthetic utility of a pyridine moiety as a piperidine surrogate.

The last section of this dissertation conveys our work developing a novel palladium(0)-mediated transformation that provides stereochemically-defined enals, enones, and dienones through the union of aryl and vinyl halides with divinyl and enyne carbinol coupling partners. This reaction is believed to proceed through a cyclopropanol intermediate and to involve a novel skeletal reorganization. Experimental observations in support of our proposed mechanism, as well as a complete substrate scope, are presented.

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Acknowledgments

I am forever grateful to Richmond Sarpong for starting up a research group at Berkeley the same year that I began graduate school. It is very satisfying to be able to look back at my graduate school career at the end of five years and know undoubtedly that I chose the right research group. Richmond gave me such excellent chemistry to work on and never ceased to provide new ideas for my projects. He was also incredibly morally supportive during those long periods when it seemed like the chemistry was never going to pan out. Working for Richmond was a truly great experience because he took a vested interest not only in the success of his students' projects but also in our personal development into highly skilled scientists, and he genuinely cared about us as people.

Being Richmond's very first graduate student meant that I had no older group members to learn from, but, because of this, I was encouraged to seek out wisdom from graduate students in other groups. Ming Chen Hammond was certainly the most influential of these older students. She and I shared a lab for my first nine months, as she was the last graduate student of Prof. Paul Bartlett, whose space on the eighth floor of Latimer the Sarpong group was moving into. Ming was invaluable to me my first summer and went out of her way to help me adjust to graduate school. I was so fortunate to have her as a mentor, and my graduate school career really came full circle when she accepted an Assistant Professor position at Berkeley and returned a few months before I left. My first year was also enriched by lunches in the Bertozzi group room with Margot Paulick and Danielle Dube as well as hallway dodgeball with Jen Prescher and other Bertozzi group members during those late nights on the eighth floor. Then there were a number of older students in the Toste and Trauner groups (Ben Sherry, Josh Kennedy-Smith, and Chris Beaudry, just to name a few) to whom I could always go for synthesis advice.

I consider myself incredibly fortunate to have had three amazing grad students join the Sarpong group with me in the fall of 2004 – Eric Bunnelle, Andrew Marcus, and Eric Simmons. The four of us were major proponents of having fun while working hard (though I claim no participation in the "let's quench a large jar full of sodium chunks outside on the balcony during a rain storm" stunt which may or may not have taken place). I cannot imagine going through graduate school without having these three to bounce ideas off of and to bond with both in lab and out, and they will remain among my dearest friends.

And then there were my labmates. Maina Ndungu, the crazy, goat-slaughtering Kenyan, started as a post-doc in my lab a month after I got to Berkeley and manned the desk next to mine for my first three years. He had an uncanny ability to make me smile even when I was feeling down and said so many ridiculous things that I had to start keeping a list. From telling our other labmates to "beware the wrath of a crazy white woman," (i.e., me) and showing up to work with two un-matching shoes on his feet to calling me in the mornings to make sure I didn't oversleep and bringing me bananas because I was always jealous of his mid-morning snacks, Maina was truly a one-of-a-kind labmate.

Simmons occupied the hood next to mine for our first year. The nights ran late and the music came loud. Those were the days of "pop rock y reggaetón," TLC lane competitions, and knowing every ad on Live 105. My second year, Simmons was replaced by Scott West in my lab, and Jesse Cortez and Jess Wood soon followed. Having such bright people around me to casually discuss chemistry with, in conjunction with their great senses of humor, made for a really great working environment, and my insanity level during my later years would have been much higher had I not had them.

The Sarpong group was full of characters who challenged each other intellectually, provided moral support when it was needed, and loved to make each other laugh. Other influential members during my time in the group included “Bad Ass” Bhanu Prasad, who coined the term Boom-Boom room, Freddie Bowie, who spent just a couple of months in the group our first summer before moving on, apparently because he was intimidated by Richmond’s ability to out-dress him, Brian “Püj” Pujanauski, who liked to weird me out with his unnatural scalp movements, Cameron “the Dragon” Smith, Tony “Draw benzene!” Yao, and Laura Miller and Sarah House who were always there to lend an ear or helping hand.

I also want to thank Theresa Liang, a Berkeley undergrad who worked with me on the G. B. 13 project in its early states and who kept us guessing by alternating between wearing flip-flops and fuzzy boots in lab, depending on the current state of the harsh Californian climate.

Herman van Halbeek, Rudi Nunlist, and Chris Canlas, the NMR guys, did a phenomenal job at keeping the NMR facility running smoothly. Herman was incredibly patient and taught me how to run numerous NMR experiments, and Rudi was able to fix any problem an instrument or computer was having in thirty seconds or less. Jim Breen, our glass blower, saved me many times by helping to keep my FVP glassware in good working condition.

All of the research groups at Berkeley (including the Bergman, Bertozzi, Ellman, Francis, Toste, Trauner, and Vollhardt groups) were incredibly generous in letting me use their chemicals and equipment. I want to especially express my extreme gratitude to the Ellman group, for without the use of their glovebox, I would not have been able to work out the rhodium chemistry that secured a path to G. B. 13 so efficiently.

Finally, I want to thank all of my friends at Berkeley (especially Melissa Beenen Herbage and Melanie Chiu), as well as my older friends from home, and of course my family, for always believing in me and providing me with unconditional support.

Chapter One

Galbulimima Alkaloid G. B. 13

1.1 Introduction

Galbulimima alkaloid G. B. 13 (**1.1**, see Figure 1.1) is one of twenty-eight structurally related alkaloids that have been isolated from the tree *Galbulimima belgraveana*. This chapter details the origin and classification of this family of compounds as well as possible biogenetic links between the three major classes of Galbulimima alkaloids. In addition, recently disclosed information regarding the absolute stereochemistry of these compounds, the medicinal properties of himbacine (**1.2**), the most thoroughly examined family member, and the four prior total syntheses of G. B. 13 are all discussed. Our own total synthesis of G. B. 13 is examined in Chapter Two.

1.2 Isolation and Classification

The Himantandraceae family of trees is found throughout the rainforest areas of Queensland (Australia), Papua New Guinea, and the Moluccan Islands of Indonesia.[1] The Himantandraceae family is a relic family consisting of a sole genus, *Galbulimima*, though there has been some debate concerning the naming of the members of this family and the genus has also been called *Himantandra* in years past.[2] In addition, while the genus was originally segregated into four species, *baccata, belgraveana, nitida,* and *parvifolia*, more recently van Royan has concluded that due to the high degree of morphological variation within the genus, only a single species should be recognized – *Galbulimima belgraveana*.[3]

In the 1950s and 1960s twenty-eight alkaloids were isolated from the bark of the trees *Galbulimima belgraveana* by E. Ritchie, W. C. Taylor, and coworkers in the regions of North Queensland and Papua New Guinea.[1,2] When the first set of alkaloids were isolated, the genus name was thought to be *Himantandra*. Thus, the compounds were granted names beginning with "him." Due to the large number of compounds isolated in a second round, subsequent alkaloids were named numerically and designated with the initials "G. B."

The twenty-eight *Galbulimima* alkaloids may be divided into three structurally distinct classes of molecules and one miscellaneous class of compounds whose structures have not been elucidated. The first class, as exemplified by himbacine (**1.2**, Figure 1.1), consists of tetracyclic lactones. The second class, which includes himandrine (**1.3**), is a group of highly oxygenated hexacyclic ester alkaloids. Finally, the third class is a group of two pentacyclic (e.g., G. B. 13, **1.1**) and one hexacyclic (i.e., himgaline, **1.4**) alkaloids that are characterized by their low oxygen content.

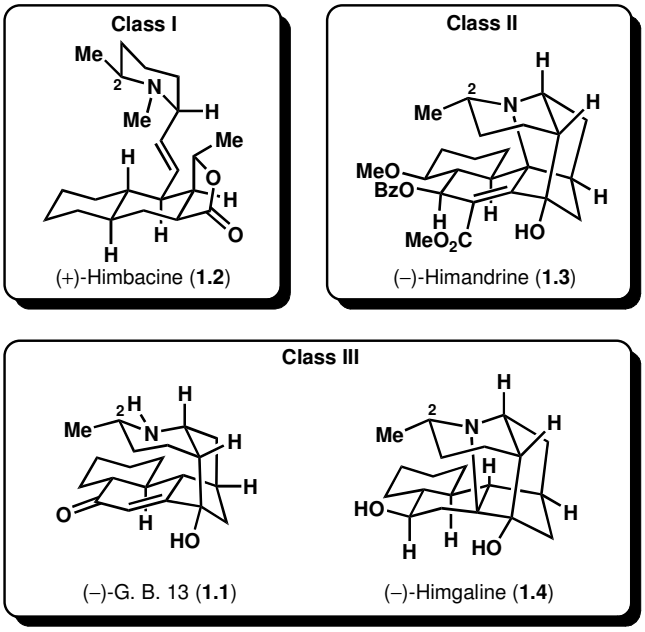


Figure 1.1 Selected *Galbulimima* alkaloids.

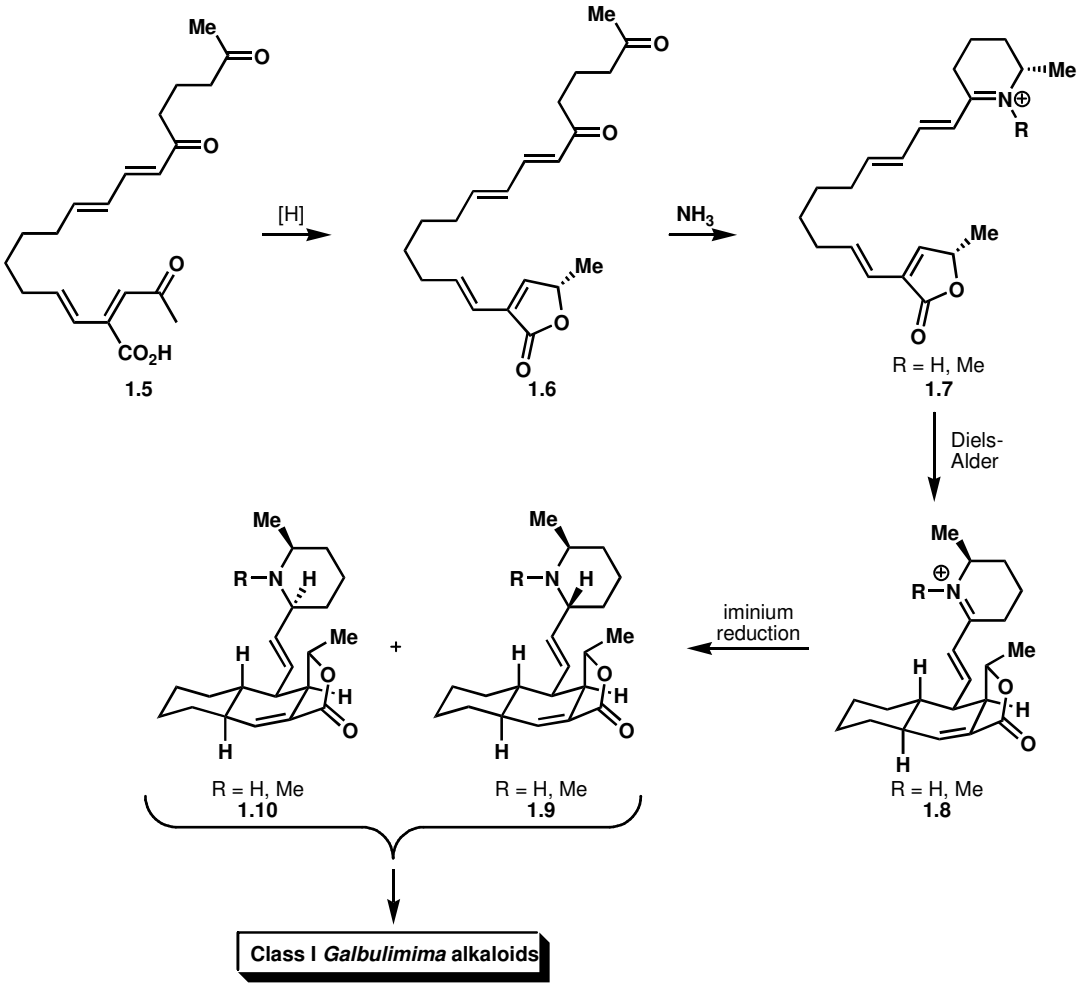
In the course of elucidating the structure of G. B. 13, Ritchie, Taylor, and coworkers found that the natural product undergoes a conjugate addition of its secondary piperidine nitrogen into the β-carbon of the enone moiety upon treatment with trifluoroacetic acid.[4] They found that this process was reversible upon basification. Other structural studies revealed that G. B. 13 could be obtained by oxidation of himgaline (**1.4**) with nitric acid.

1.3 Biosynthetic Proposals

In Mander, Ritchie, and Taylor's initial series of isolation and structure determination papers, they proposed that the three classes of *Galbulimima* alkaloids could all be biosynthetically derived from nine acetate units, one pyruvate, and ammonia.[5] Baldwin and coworkers, who completed biomimetic syntheses of himbacine (**1.2**),[6] himbeline, and himandravine[7] (Class I *Galbulimima* alkaloids) proposed biosynthetic routes to both the Class I alkaloids and Class II/III alkaloids. Both routes start from ketide **1.5** (Schemes 1.1 and 1.2), which may be derived from the same nine acetates and one pyruvate as proposed by Mander et al., through standard polyketide biosynthesis.

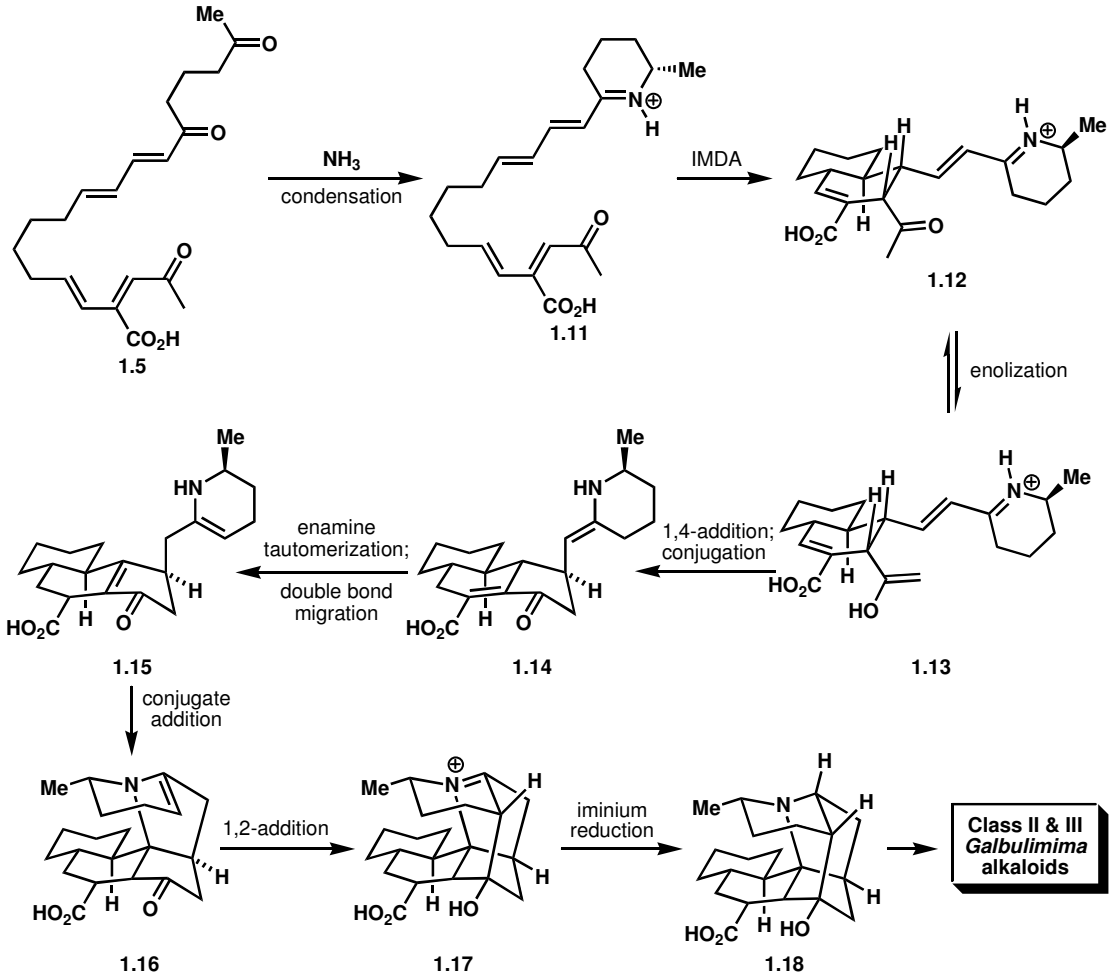
For the Class I alkaloids, Baldwin proposed that reductive lactonisation of **1.5** would lead to butenolide **1.6**, which could undergo a reductive condensation with ammonia to form iminium ion **1.7** (Scheme 1.1). Intramolecular Diels-Alder cycloaddition of this activated system via an *endo* transition state would provide **1.8**. Reduction of this iminium ion from the β-face would provide **1.9**, en route to natural products himbacine (**1.2**), himgravine, and himbeline; reduction from the α-face would provide **1.10** en route to natural product himandravine.

Scheme 1.1 Baldwin's postulated biogenesis of Class I *Galbulimima* alkaloids.



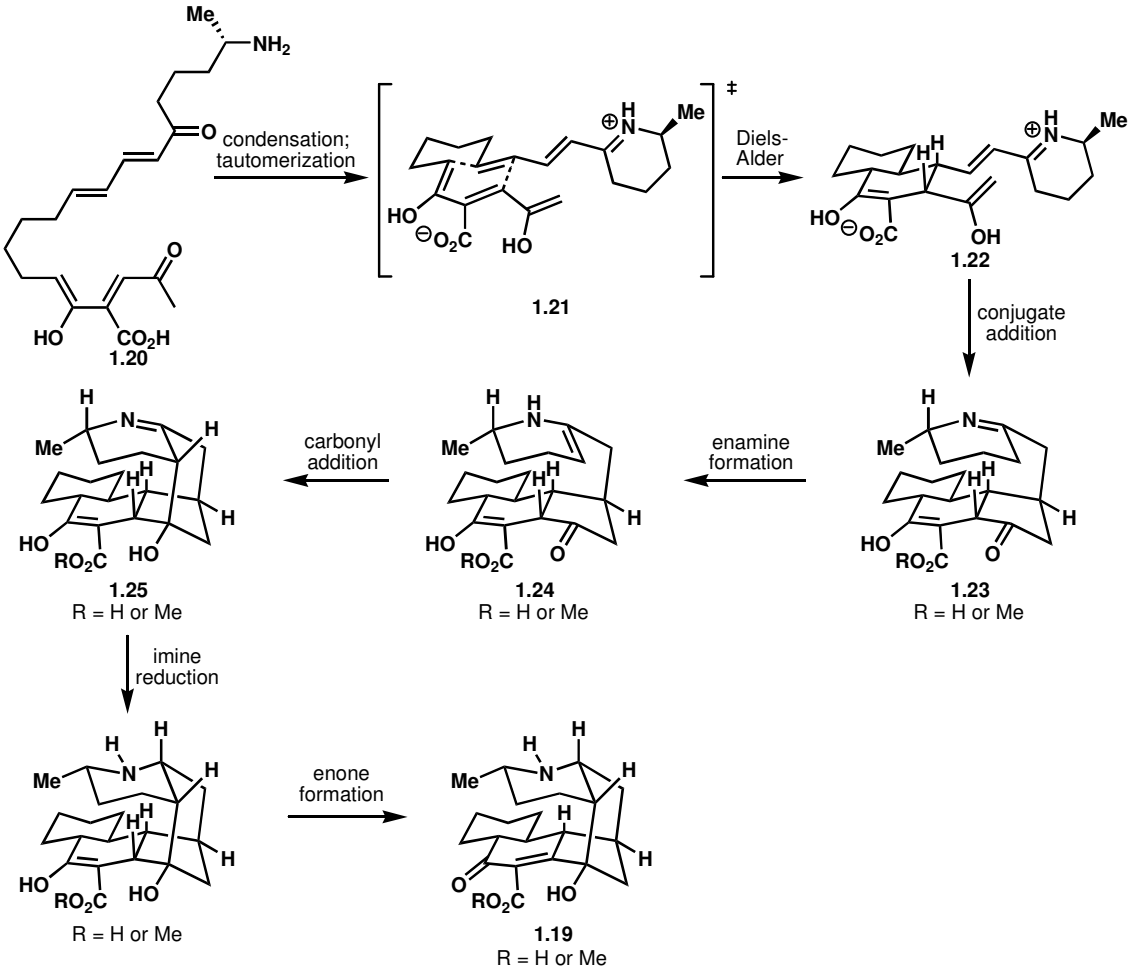
Biosynthetic intermediate **1.5** may also lead to *Galbulimima* Class II and III alkaloids as proposed by Baldwin (Scheme 1.2). Intramolecular Diels-Alder of iminium substrate **1.11** would provide **1.12**, the enol tautomer of which (**1.13**) can undergo a conjugate addition into the *α,β*-unsaturated iminium ion to give **1.14** after migration of the double bond into conjugation. Further double bond migration and enamine tautomerization leads to **1.15**. Intramolecular conjugate addition of the nitrogen would then provide pentacyclic structure **1.16**. 1,2-Addition of the enamine into the carbonyl would give iminium ion **1.17**, which, upon reduction, provides hexacyclic amine **1.18**. Baldwin postulates that **1.18** may be an intermediate in the biosynthesis of Class II and III alkaloids.

Scheme 1.2 Baldwin's postulated biogenesis of Class II/III *Galbulimima* alkaloids.



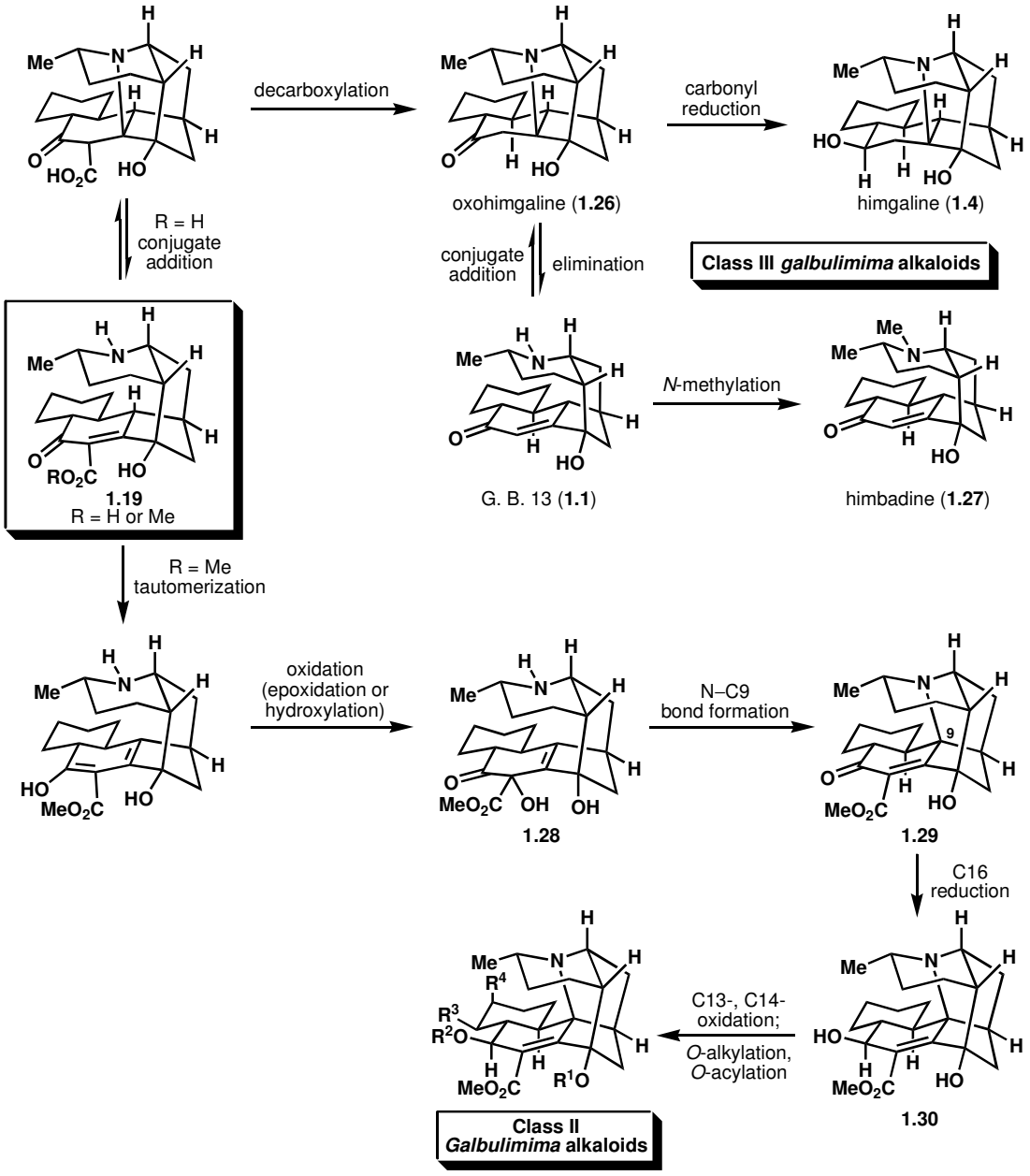
An independent biosynthetic hypothesis has been reported by Movassaghi[8] that accounts for the formation of Class II and Class III *Galbulimima* alkaloids from a common intermediate. Movassaghi postulates that the shared precursor (**1.19**) to the natural products may be derived from **1.20** (Scheme 1.3). Condensation and tautomerization of **1.20** provides an intermediate poised to undergo an intramolecular Diels-Alder reaction via transition state **1.21** to give tricycle **1.22**. Conjugate addition of this enol into the unsaturated iminium ion would give tetracycle **1.23**. Tautomerization to the enamine (**1.24**) followed by addition into the ketone carbonyl would provide **1.25**. Reduction of this imine followed by oxidation to the enone would yield common biosynthetic intermediate **1.19**.

Scheme 1.3 Movassaghi's proposed biosynthesis of common intermediate **1.19**.



Precursor **1.19** serves as a branching point for the Class II and Class III *Galbulimima* alkaloids (Scheme 1.4). Nitrogen conjugate addition followed by decarboxylation leads to the formation of 16-oxo-himgaline (**1.26**), which in turn can lead to Class III compounds himgaline (**1.4**) by carbonyl reduction, G. B. 13 (**1.1**) by elimination, and himbadine (**1.27**) by *N*-methylation of G. B. 13. Alternatively, tautomerization of intermediate **1.19** followed by oxidation would provide **1.28**. Allylic substitution by the piperidine nitrogen would form the N-C9 bond present in the Class II alkaloids (See 1.29). Reduction of the carbonyl would give **1.30** which may be elaborated to yield various highly oxygenated hexacyclic *Galbulimima* alkaloids.

Scheme 1.4 Movassaghi's proposed biosynthesis of Class II and III alkaloids.



1.4 Absolute Stereochemistry Resolution

The absolute stereochemistry of himbacine (**1.2**) was determined in 1962 by X-ray crystallographic analysis.[9] Since then, the absolute stereochemistry of himbacine's decalin ring system and also of its C-2 piperidine methyl group has been shown to be conserved among other Class I *Galbulimima* alkaloids.[10] On the basis of the structural similarities of the carbon skeletons of the Class I and the Class II/Class III *Galbulimima* alkaloids, some had believed that the absolute stereochemistry of the decalin systems would be the same.[11] However, as a consequence of matching the decalin absolute stereochemistry of the Class I alkaloids with the

Class II and III alkaloids, the absolute stereochemistry of the C-2 methyl on the piperidine ring would necessarily be opposite. In other words, since the C-2 stereochemistry was known to be *S* in the Class I alkaloids, it would have to be *R* in the Class II and III alkaloids if the decalin absolute stereochemistry was to be consistent.

In 2006, X-ray crystal structures by Mander and coworkers of Class II and Class III alkaloids determined that, contrary to previous notions, the absolute stereochemistry at C-2 of the methyl piperidine ring was conserved across all three *Galbulimima* alkaloid classes and hence that of the decalin system was not.[11] Just prior to this report, Movassaghi and coworkers confirmed the 2*S* stereochemistry of naturally occurring (−)-G. B. 13 by total synthesis.[8]

1.5 Synthetic Interest in the *Galbulimima* Alkaloids

1.5.1 General interest and biological relevance

Himbacine (**1.2**) has received considerable interest as a synthetic target due to its potent biological activity. Originally shown to possess antispasmodic activity,[12] it has garnered much attention due to the discovery that it acts as a potent antagonist for M2/M4 muscarinic receptors (K_d value of 3 nm for blocking the cardiac receptor) with high selectivity over M1/M3/M5 sites (as large as 86-fold selectivity for the M2 receptor versus the M3 receptor).[13-15] Because blockage of presynaptic inhibitory muscarinic receptors (the putative M2 or M4 receptors) may increase acetylcholine levels in the brain, agents that serve as M2 or M4 antagonists have the potential to be used to treat neurodegenerative disorders that are characterized by the degeneration of cholinergic neurons.[16] Thus, himbacine and derivatives have been targeted as potential Alzheimer's drugs.[17-19]

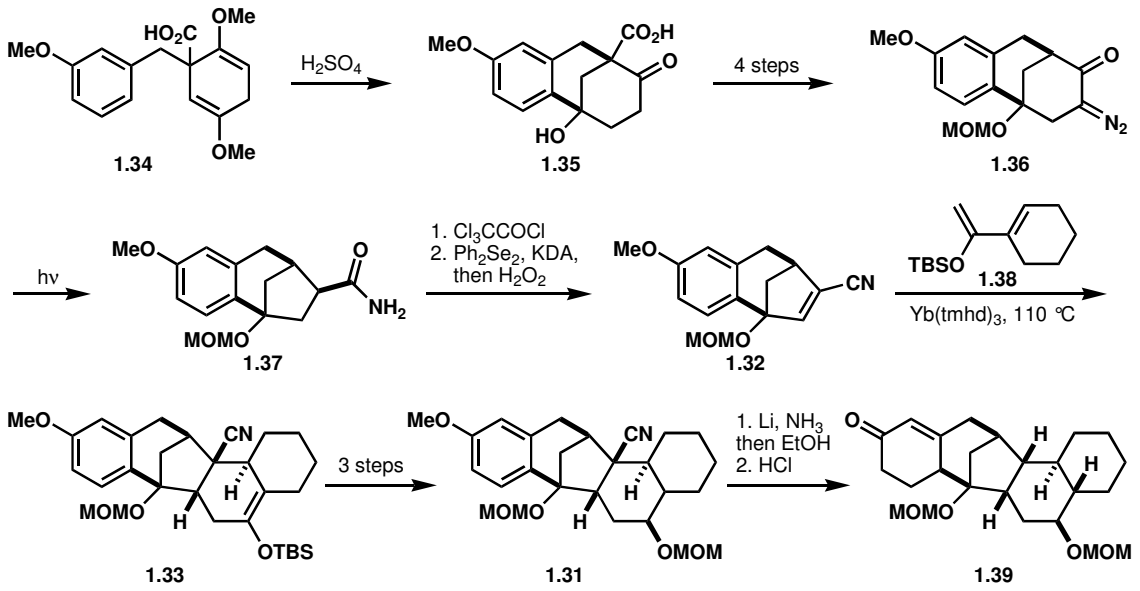
In addition to the muscarinic antagonist activity of himbacine, researchers found that certain derivatives of himbacine, in which its piperidine moiety has been replaced with a less basic pyridine structure, possess antithrombic effects through their antagonism of thrombin receptor (PAR-1).[20,21] One such himbacine-related compound has reached clinical trials for the treatment of acute coronary syndrome.[22]

Because of this biological activity, a number of syntheses of himbacine and related compounds have been reported.[6,7,23-30] The first total synthesis of a Class II or III *Galbulimima* alkaloid was not reported until 38 years after its isolation. Mander, who was a member of the original *Galbulimima* alkaloids isolation team, and McLachlan reported the first synthesis of (±)-G. B. 13 in 2003.[31] Four more syntheses of G. B. 13 soon followed. In 2006 Movassaghi, Hunt, and Tjandra completed the first synthesis of (+)- and (−)-G. B. 13.[8] Later that year, a team from Schering-Plough led by Chackalamannil completed the first enantioselective synthesis of (−)-G. B. 13 and showed that it could be transformed into (−)-himgaline.[32] Evans and Adams also completed (+)-G. B. 13 and (+)-himgaline in 2007,[33] and our group reported the synthesis of (±)-G. B. 13 in 2009.[34] The first total synthesis of a Class II *Galbulimima* alkaloid, (−)-himandrine, was reported in 2009 by Movassaghi, Tjandra, and Qi.[35] The first four syntheses of G. B. 13 will be discussed in the following sections. The synthesis by our group will be detailed in Chapter Two.

1.5.2 Mander and McLachlan's synthesis of (±)-G. B. 13

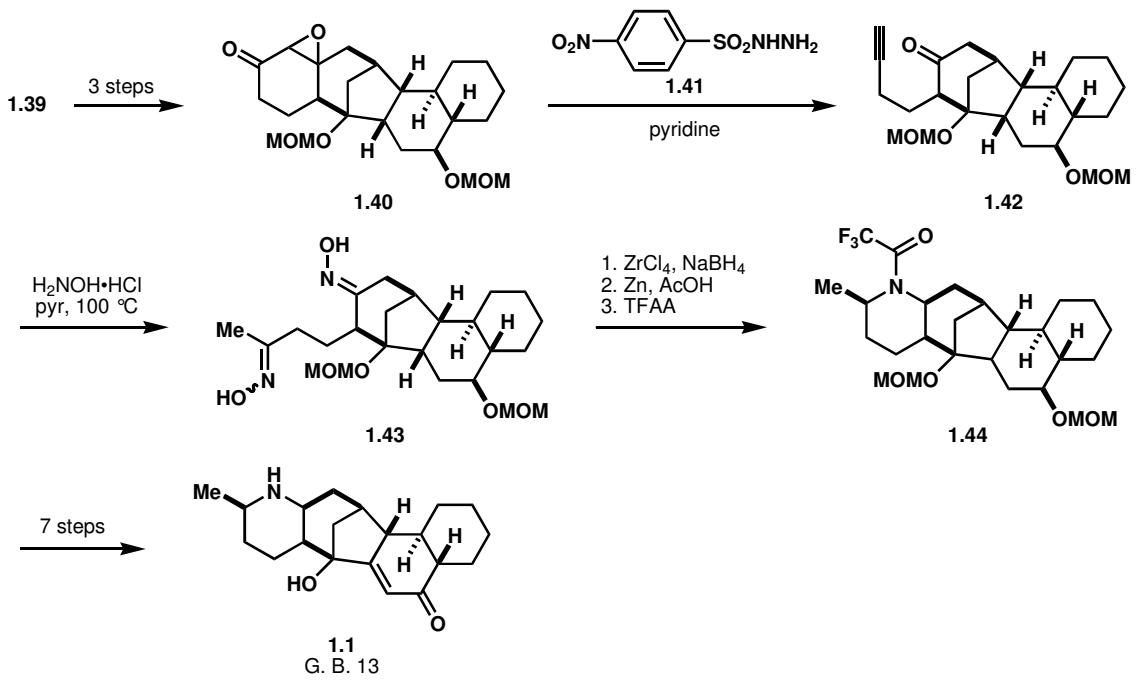
Mander's synthesis of G. B. 13 is characterized by the use of a benzenoid synthon, i.e., **1.31** (Scheme 1.5) to construct a complex molecule and also by the use of a removable nitrile functional group to activate and control the regiochemistry of a Diels-Alder reaction (see **1.32** to **1.33**). The synthesis begins with an acid-catalyzed cyclizaiton of **1.34**[36] to give ketone **1.35**. Decarboxylation, MOM-ether protection, and diazo formation via the two step Regitz procedure[37] (EtOCHO, NaH; *p*-$NO_2C_6H_4SO_2N_3$, Et_3N) gave Wolff rearrangement substrate **1.36**. Subjection of this α-diazo ketone to photolysis conditions then provided amide **1.37**, which could be dehydrated using trichloroacetyl chloride; the resulting nitrile was then oxidized to the corresponding α,β-unsaturated nitrile **1.32**. *Endo* Diels-Alder cycloaddition with diene **1.38** yielded pentacycle **1.33**. After functional group manipulation, **1.31** was subjected to dissolving metal Li/NH_3 conditions to remove the cyano group, and the subsequent addition of EtOH achieved a Birch reduction of the aromatic ring. The resultant methyl enol ether was transformed to enone **1.39** by exposure to HCl in MeOH.

Scheme 1.5 Mander's installation of the carbons of G. B. 13.



Enone **1.39** was converted to epoxide **1.40** (Scheme 1.6), which underwent Eschenmoser fragmentation upon treatment with *p*-nitrobenzenesulfonylhydrazide (**1.41**) when it was used in place of toluenesulfonylhydrazide. Alkyne **1.42** was converted to bis-oxime **1.43** to provide a substrate amenable to reductive cyclization upon treatment with zirconium tetrachloride and sodium borohydride. The resulting *N*-hydroxy piperidine, possessing the requisite all *cis* ring stereochemistry, was reduced, and the piperidine nitrogen was trifluoracetylated, giving **1.44**. Protecting group manipulation and Saegusa-Ito oxidation led ultimately to G. B. 13 (**1.1**) in 29 steps from advanced intermediate **1.34**.

Scheme 1.6 Mander's completion of (±)-G. B. 13.

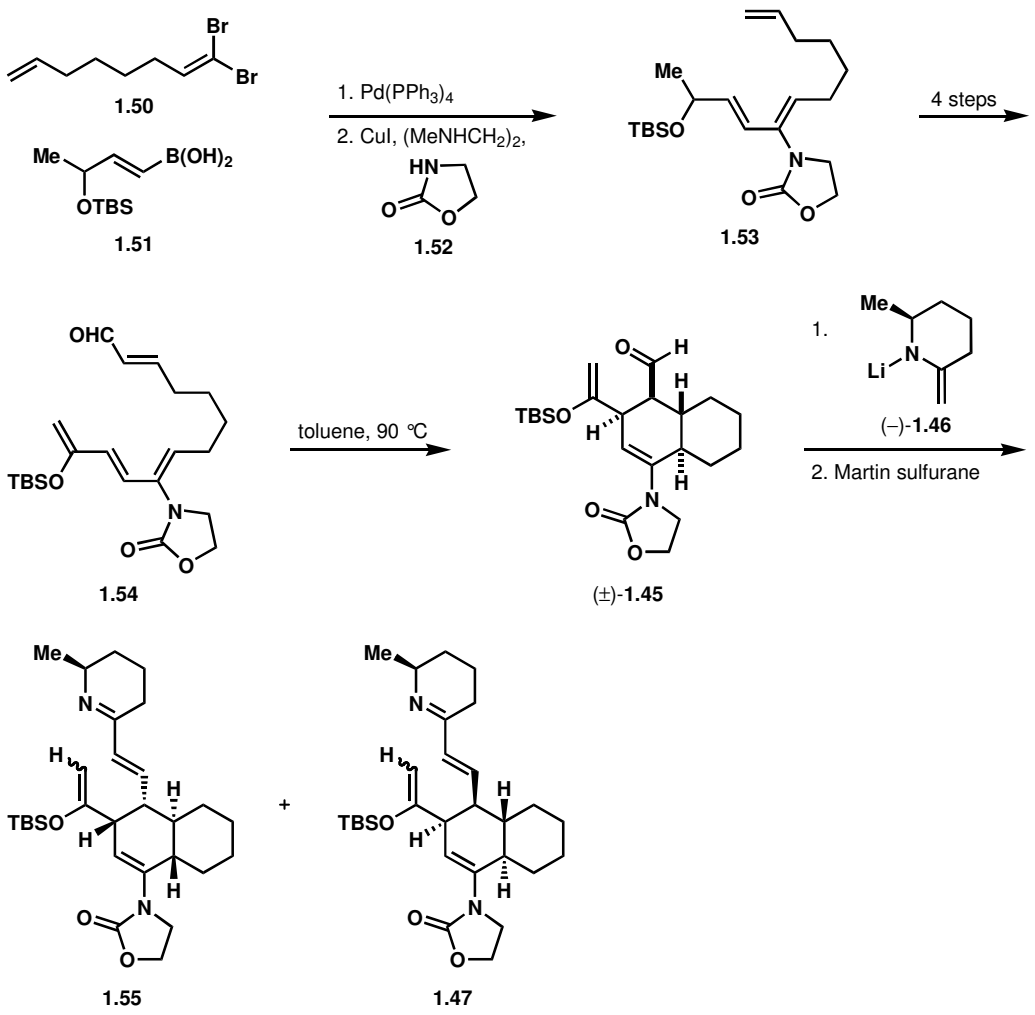


1.5.3 Movassaghi, Hunt, and Tjandra's synthesis of (+)- and (−)-G. B. 13

The Movassaghi group carried out efficient syntheses of (+)- and (−)-G. B. 13 by coupling racemic aldehyde **1.45** with enantioenriched (+)- or (−)-lithiated enamine **1.46** and later separating the resultant diastereomers (see Scheme 1.7). Their synthesis showcases a 5-*exo*-trig radical cyclization (see **1.47** to **1.48**, Scheme 1.8) and an enamine carbonyl addition (see **1.48** to **1.49**, Scheme 1.8), inspired by their biomimetic proposal (see Scheme 1.3), to form the pentacyclic framework of the natural product.

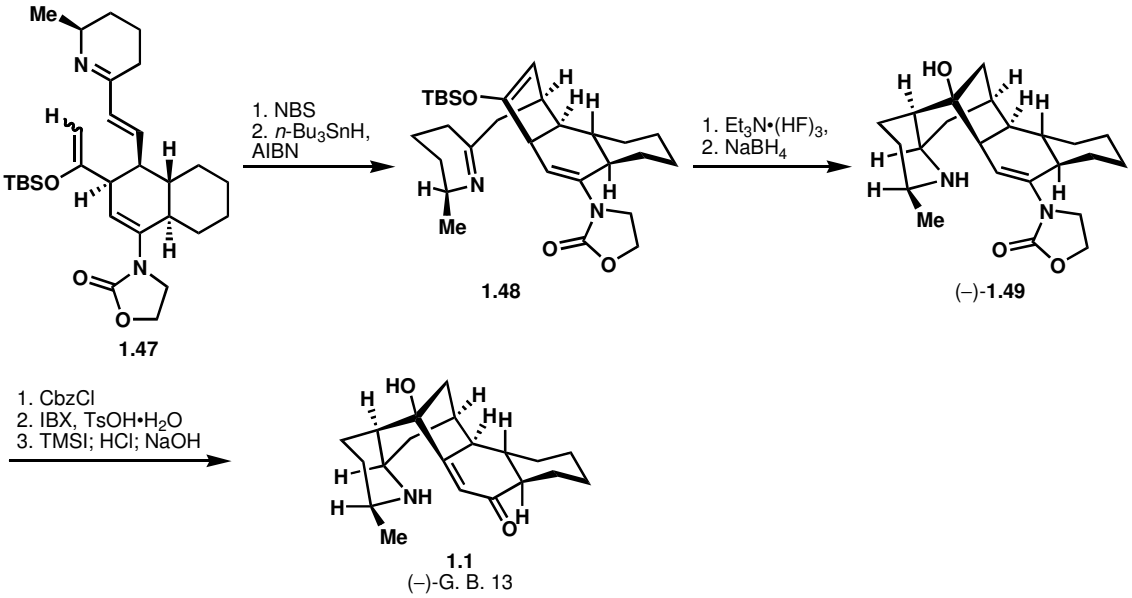
Suzuki cross-coupling of dibromide **1.50** and vinyl boronic acid **1.51** followed by copper(I)-catalyzed coupling of oxazolidin-2-one (**1.52**) gave triene **1.53**. Silyl enol ether formation and olefin cross-metathesis with acrolein provided Diels-Alder substrate **1.54**, which afforded *trans*-decalin system **1.45** upon heating. Coupling of this racemic intermediate with lithio-anion **1.46**, which is derived from the corresponding enantioenriched iminium chloride, produced diastereomeric alcohols that were dehydrated to give **1.55** and **1.47**.

Scheme 1.7 Movassaghi's approach to (+)- and (−)-G. B. 13.



Conversion of silyl enol ether **1.47** (inseparable diastereomer not shown) to the corresponding vinyl bromide followed by subjection to radical conditions gave annulated product **1.48** via a 5-*exo*-trig cyclization. Exposure of **1.48** to $Et_3N•(HF)_3$ cleaved the silyl enol ether and led to enamine addition into the resultant carbonyl group. Reduction of the imine thus formed provided pentacyclic core **1.49**. Oxidation to the requisite enone was accomplished by subjection of vinyl carbamate **1.49** to IBX and *p*-TsOH•H_2O after *N*-Cbz protection. Removal of the Cbz group with TMSI then yielded (−)-G. B. 13 (**1.1**).

Scheme 1.8 Movassaghi's G. B. 13 synthesis endgame.

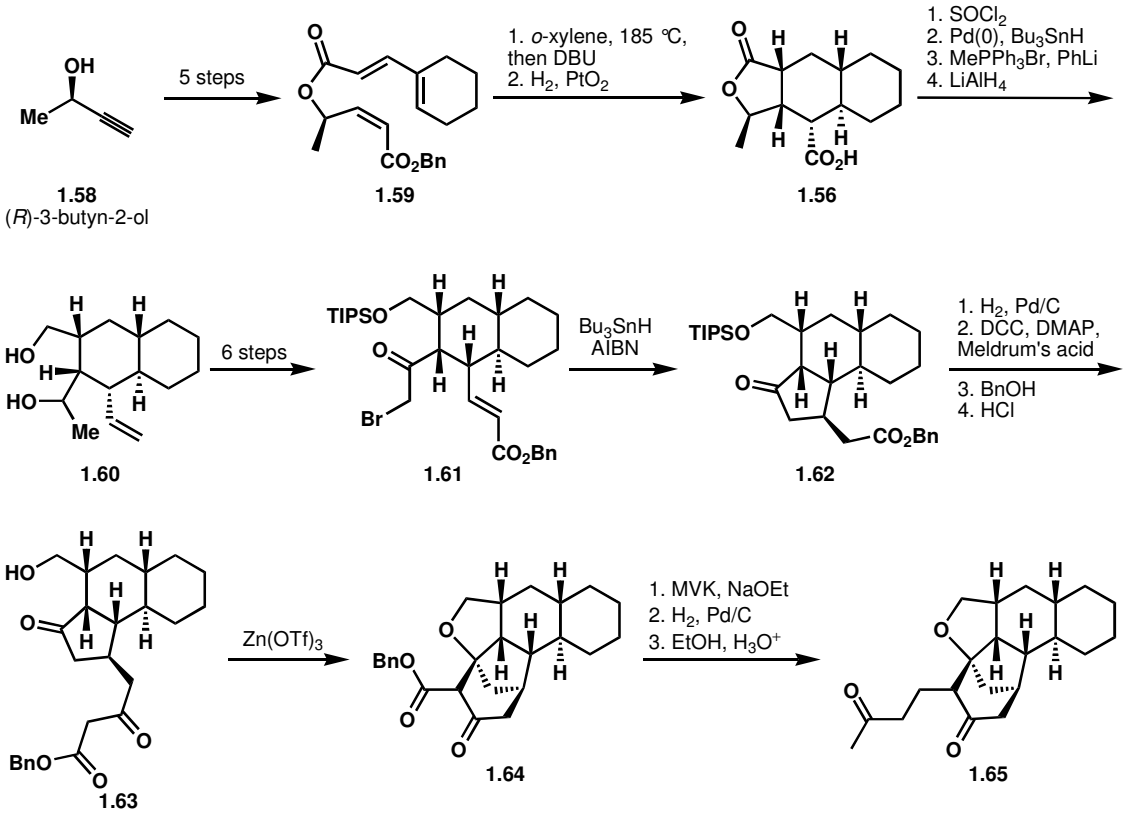


1.5.4 Chackalamannil, et al.'s synthesis of (−)-himgaline

Chackalamannil's group prepared (−)-himgaline (**1.4**) through the intermediacy of G. B. 13. Their route utilizes tricyclic lactone **1.56** (Scheme 1.9), which is an intermediate used in their synthesis of a himbacine-derived PAR-1 antagonist.[20] In their synthesis, G. B. 13 is unraveled from **1.57** (see Scheme 1.11) through a tandem decarboxylative intramolecular *N*-conjugate addition/*β*-elimination.

Tricyclic lactone **1.56** was prepared in enantionenriched form from (*R*)-3-butyn-2-ol (**1.58**) through a diastereoselective intramolecular Diels-Alder cycloaddition of **1.59** (Scheme 1.9). Reductive cleavage of the lactone ring provided *trans*-decalin compound **1.60**, which could be elaborated to *α*-bromo ketone **1.61**. Diastereoselective radical cyclization, presumably controlled by the thermodynamically preferred conformation of the *trans*-double bond, provided tricycle **1.62**. *β*-Keto ester formation gave **1.63**, which underwent a Lewis-acid catalyzed cyclization, thought to proceed through an oxocarbenium ion that is formed upon addition of the primary hydroxyl group into the ketone carbonyl and then trapped by the *β*-keto ester, to provide ether **1.64**. Installation of the necessary carbons for the piperidine ring by conjugate addition into methyl vinyl ketone then gave diketone **1.65**.

Scheme 1.9 Chackalamannil's elaboration of himbacine-related lactone **1.56**.



1.58 (*R*)-3-butyn-2-ol

1.59

1.56

1.60

1.61

1.62

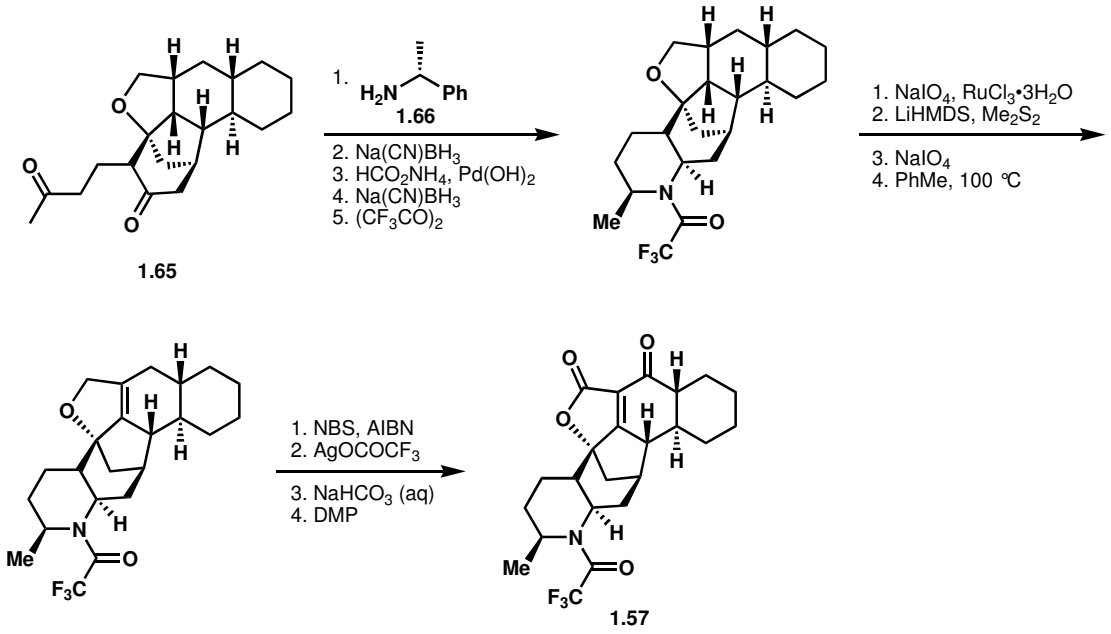
1.63

1.64

1.65

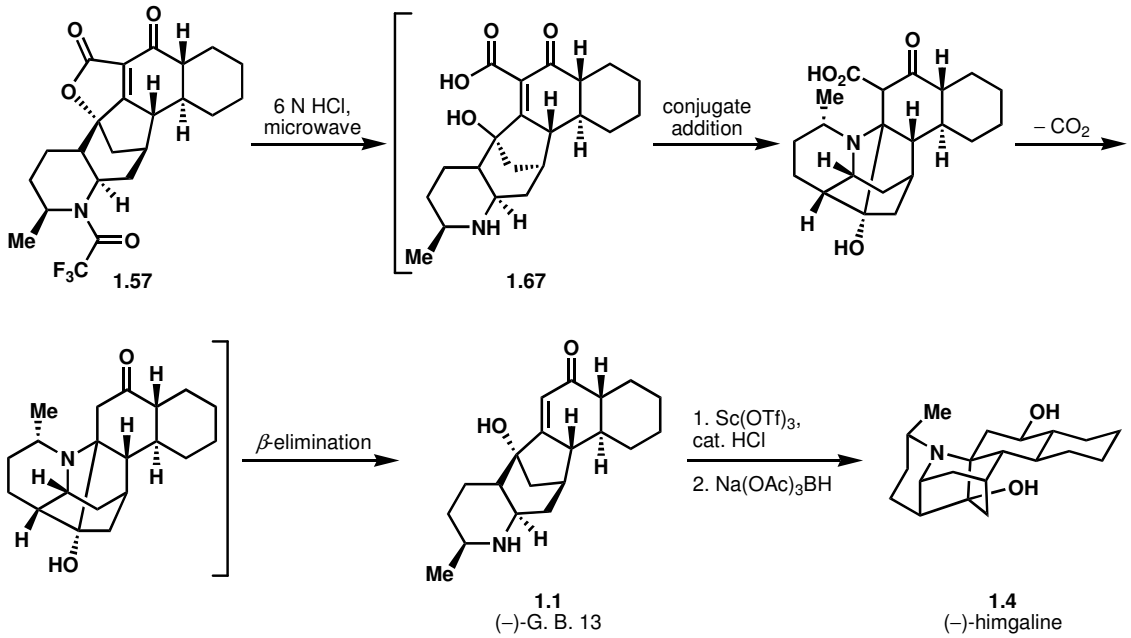
The piperidine ring was constructed through consecutive reductive aminations of (*R*)-α-methylbenzylamine (**1.66**, Scheme 1.10) with the diketone (**1.65**). The ring system could then be oxidized to key substrate **1.57** through an eight-step sequence.

Scheme 1.10 Chackalamannil's assembly of the G. B. 13 skeleton.



The final cascade to G. B. 13 was realized by the subjection of **1.57** to 6 N HCl under microwave irradiation (see Scheme 1.11). Initial hydrolysis of the butenolide gave carboxylic acid **1.67**. *N*-conjugate addition followed by decarboxylation and then *β*-elimination of the nitrogen provided (–)-G. B. 13 (**1.1**). *N*-Conjugate addition of G. B. 13 was initiated under acidic conditions, and diastereoselective reduction of the ketone carbonyl using $Na(OAc)_3BH$ afforded (–)-himgaline (**1.4**). Importantly, the use of $NaBH_4$ in this reduction gave exclusively the undesired diastereomer possessing an axial hydroxyl group. Using $Na(OAc)_3BH$ allowed for internal hydride delivery through ligand exchange of the reagent with the resident hydroxyl group in the substrate.

Scheme 1.11 Chackalamannil's synthesis of (−)-G. B. 13 and (−)-himgaline.

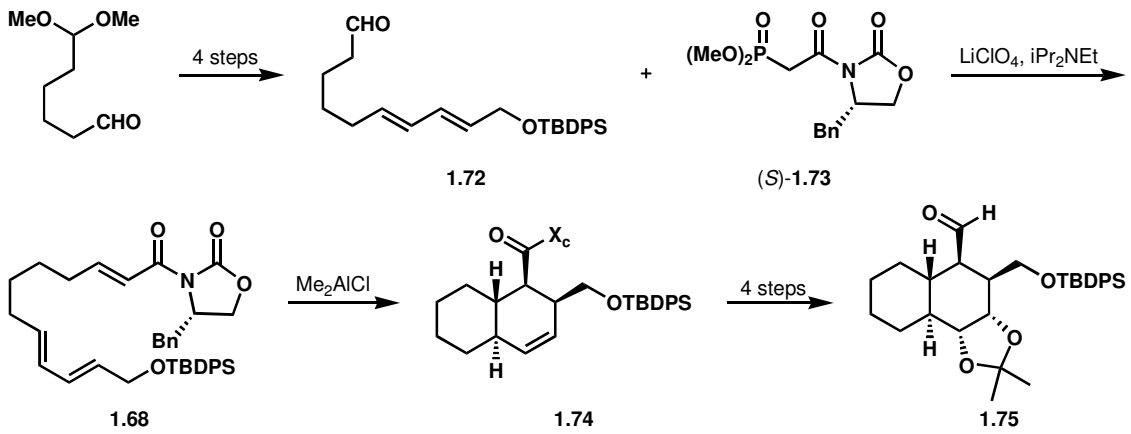


1.5.5 Evans and Adams' synthesis of (+)-himgaline

Evans and Adams carried out an enantioselective synthesis of the antipode of natural G. B. 13 and showed that it could be converted to (+)-himgaline in one pot. Inspired by the postulated polyketide-derived biosynthetic pathway of the *Galbulimima* alkaloids, the group prepared the decalin portion of G. B. 13 through an intramolecular Diels-Alder reaction of a linear precursor (i.e., **1.68**, Scheme 1.12). The five-membered ring was constructed through a Michael addition of a β-keto ester into an α,β-unsaturated ketone (see **69** to **70**, Scheme 1.13), and the piperidine ring was incorporated through the enamine addition of the tautomer of a cyclic imine (see **71**, Scheme 1.14) intramolecularly into a ketone carbonyl, akin to the transformation utilized in Movassaghi's synthesis.

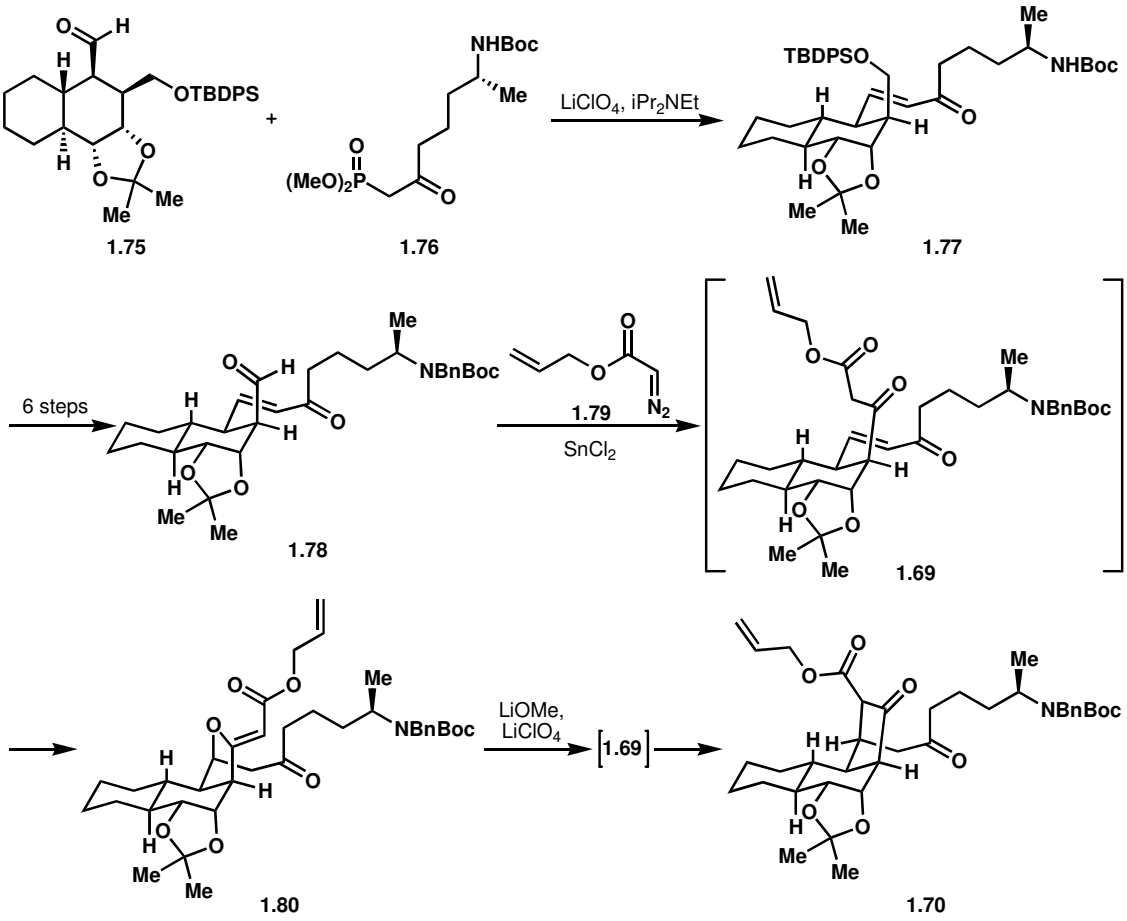
Horner-Wadsworth-Emmons (HWE) reaction of aldehyde **1.72** and phosphonate **1.73** provided enantiomerically enriched triene **1.68**, which underwent a Diels-Alder reaction upon exposure to Me_2AlCl (Scheme 1.12). Adduct **1.74** was elaborated to aldehyde **1.75** in four steps.

Scheme 1.12 Evans' enantioselective synthesis of a *trans*-decalin intermediate.



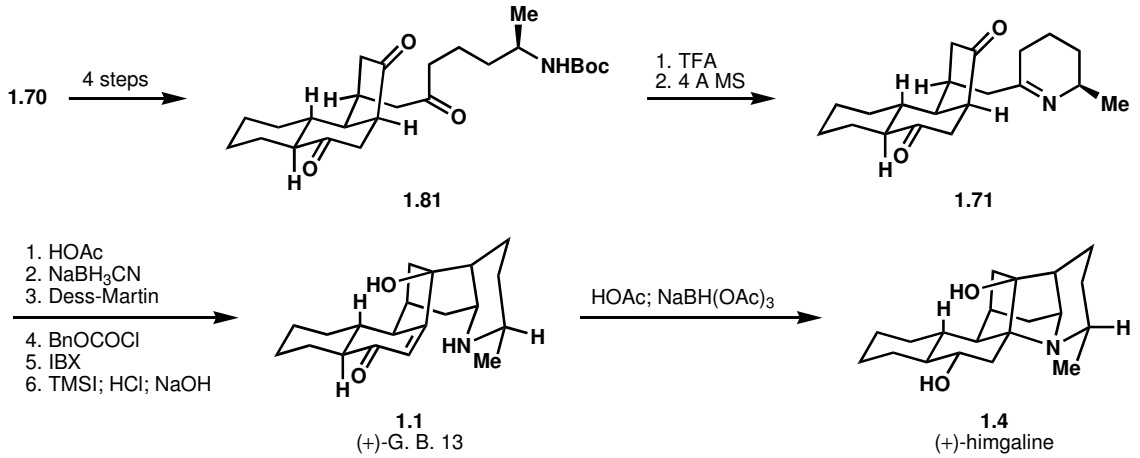
HWE olefination of enantiomerically enriched coupling partners **1.75** and **1.76** gave enone **1.77**, which was converted to aldehyde **1.78** in six steps (Scheme 1.13). Roskamp reaction[38] of this compound with allyldiazoacetate (**1.79**) provided β-keto ester **1.69**, which spontaneously underwent *O*-conjugate addition to give enol ester **1.80**. Under conditions known to form chelates of β-keto ester anions[39] ($LiOMe/LiClO_4$), β-keto ester **1.69** was revealed and Michael addition was accomplished to provide annulated product **1.70**.

Scheme 1.13 Evans' synthesis of the tricyclic core of himgaline.



Decarboxylation, *N*-debenzylation, and transformation of the acetonide group to ketone **1.81** provided a substrate that, after acid-catalyzed amine deprotection, underwent condensation to form cyclic imine **1.71** (Scheme 1.14). Aldol addition of the enamine tautomer of **1.71** and reduction of the resultant iminium ion yielded the requisite pentacyclic framework, and the enone functionality was subsequently installed to provide (+)-G. B. 13 (**1.1**). The treatment of (+)-G. B. 13 with acetic acid followed by the addition of $NaBH(OAc)_3$ then gave (+)-himgaline (**1.4**).

Scheme 1.14 Evans' completion of (+)-himgaline.



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Chapter Two

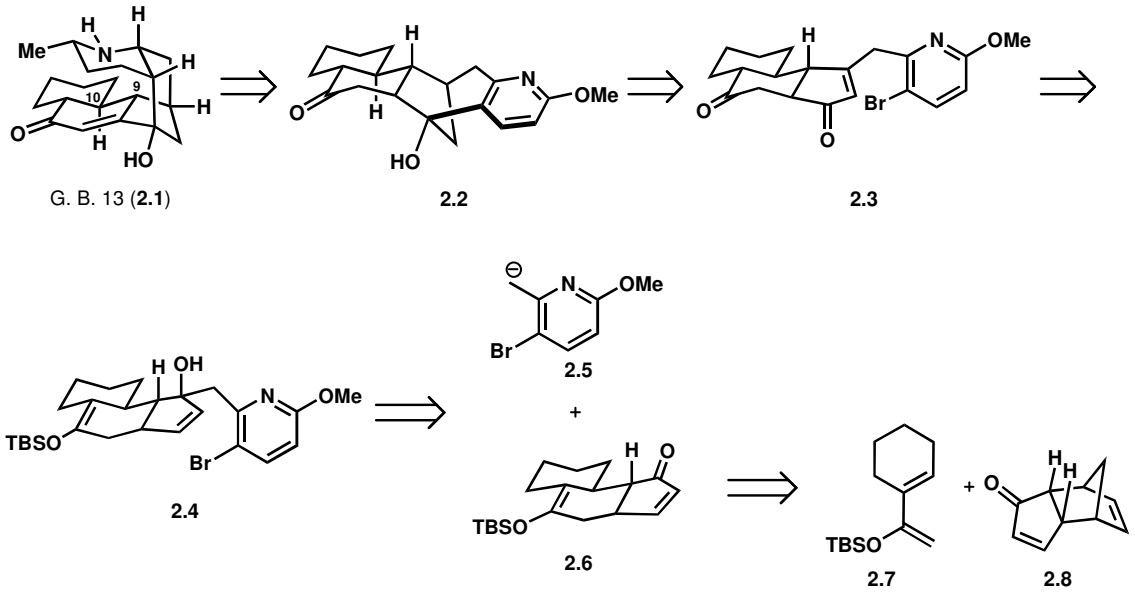
Total Synthesis of Alkaloid (±)-G. B. 13

2.1 Introduction

G. B. 13 (**2.1**) is one of 28 alkaloids isolated from the tree species *Galbulimima belgraveana*, as discussed in Chapter 1. We became interested in synthesizing this molecule because of its potential biological activity, as evidenced by the muscarinic antagonist activity of its family member himbacine (see Chapter 1), and also because of its beautiful architectural structure and the synthetic challenge of constructing this molecule in a highly concise manner.

In our approach to G. B. 13 (see Scheme 2.1), we recognized that carrying its nitrogen heterocycle through the synthesis masked as a synthetically practical pyridine moiety could greatly simplify its synthesis. Hence, we expected that late-stage intermediate **2.2** could be reduced to the corresponding piperidine compound with the concomitant introduction of three stereocenters. The pentacyclic structure of **2.2** may be formed through a metal-mediated 1,2-addition of the aryl bromide of **2.3** into its cylclopentenone carbonyl group. We envisioned the carbonyl of **2.3** being installed through an allylic transposition of tertiary allylic alcohol **2.4**. This alcohol, in turn, could arise from the 1,2-addition of a "picolinic" anion (**2.5**) into enone **2.6**. We anticipated forming the six-membered B ring of tricycle **2.6** through a Diels-Alder reaction between silyloxy diene **2.7** and enone **2.8**. Because **2.8** is known in enantiopure form,[1] this route to G. B. 13 could be readily rendered enantioselective.

Scheme 2.1 Retrosynthetic approach to (±)-G. B. 13.

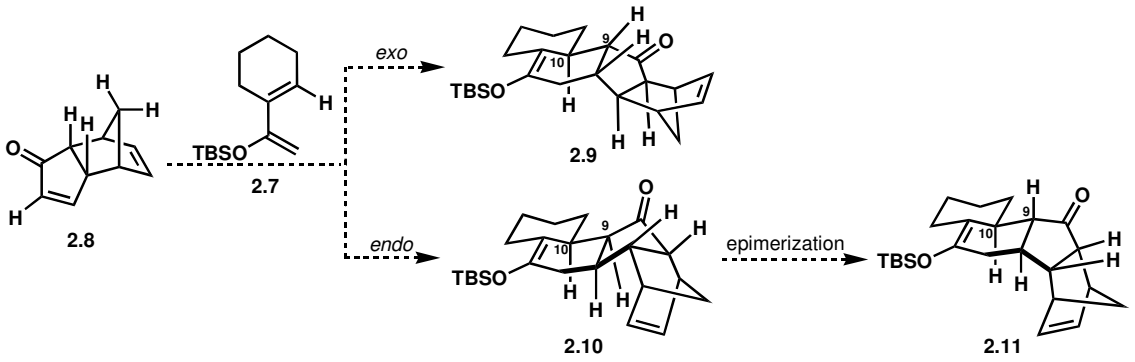


2.2 Construction of the Tricyclic Core of G. B. 13

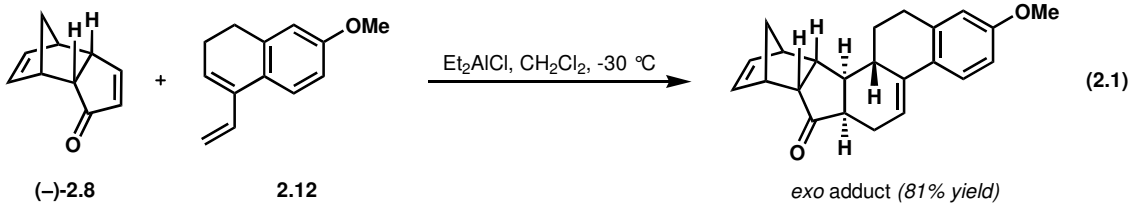
The stereochemical outcome of the proposed cycloaddition between enone **2.8** and diene **2.7** was critical because of the obligatory *anti*-relationship between the hydrogens at C-9 and C-

10 in G. B. 13 (see **2.1**, Scheme 2.1). We reasoned that the steric clash between the bridging methylene group of the tricycle (**2.8**, see Scheme 2.2) and the TBS-diene (**2.7**) may disfavor an *endo*-transition state and give the *exo*-product (**2.9**) with the desired anti-stereochemistry. Alternatively, if *endo*-approach was in fact possible, we anticipated that the hydrogen at C-9 in the resulting adduct (**2.10**) could be epimerized to give the more thermodynamically favorable isomer (**2.11**), which would possess the requisite *anti*-stereochemistry.

Scheme 2.2 *Endo* and *exo*-Diels-Alder reaction possibilities.



In a related study in the synthesis of (+)-estrone, Takano and coworkers have demonstrated that the Diels-Alder cycloaddition between the enone we intended to utilize, **2.8**, and diene **2.12** (see eq 2.1) proceeds through an *exo* transition state.[2] This example suggests that there is a steric clash between the diene and dienophile which disfavors an *endo* transition state.



A later study by Corey, et al., though, suggests that the diene partner in the Takano example likely plays a role in the steric clash that leads to the *exo* Diels-Alder preference.[3] Corey and coworkers found that allowing 2-methyl-2-cyclohexenone to react with either bicyclic diene **2.13** (eq 2.2) or monocyclic diene **2.14** (eq 2.3) in the presence of a Lewis acid leads to either *exo* adduct **2.15** or *endo* adduct **2.16**, respectively. Utilizing molecular mechanics (MM2) calculations, the Corey group discovered that the aromatic ring in the dihydronaphthalene-derived diene **2.13** leads to a steric repulsion that twists the diene out of planarity (see Figure 2.1) and also causes repulsive interactions between the arene moiety and a methylene unit on the dienophile. Both of these effects, which are absent in the case of monocyclic diene **2.14**, lead to a preference for an *exo* transition state for bicyclic diene **2.13**.

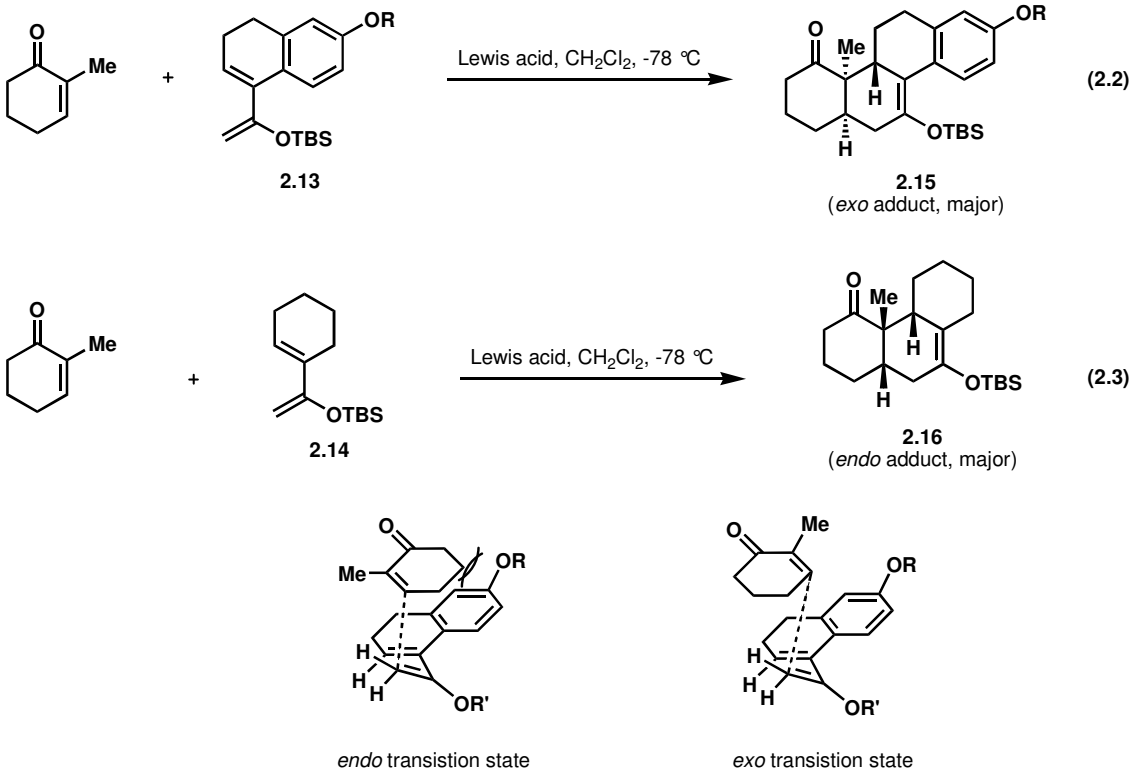
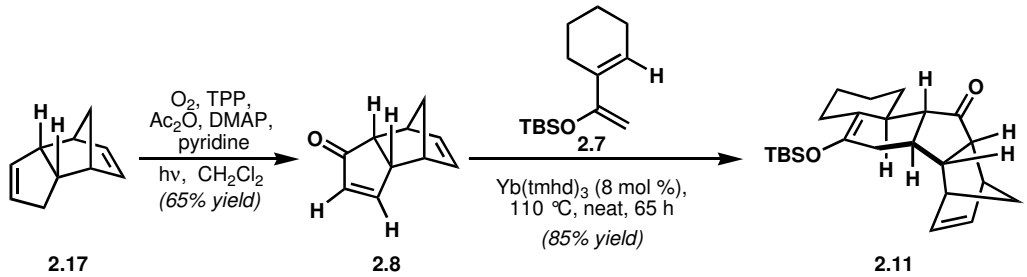


Figure 2.1 *Endo* and *exo* transition state models.[3]

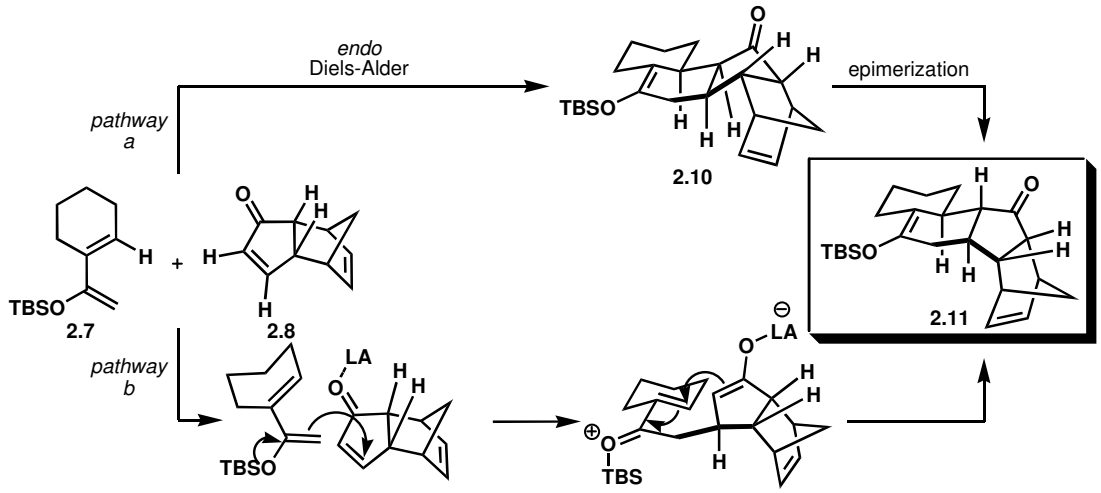
The known enone for our desired Diels-Alder reaction (**2.8**)[4] was prepared in racemic form through the Mihelich-Eickhoff oxygenation[5] of cyclopentadiene dimer (**2.17**) using tetraphenylporphin as a photochemical sensitizer (Scheme 2.3). The diene partner (**2.7**) was synthesized according to the procedure of Ohkata, et al.[6] Subjecting this pair to a catalytic amount of the Lewis acid $Yb(tmhd)_3$[7] at 110 °C under neat conditions provided Diels-Alder adduct **2.11** in 85% yield.

Scheme 2.3 Synthesis of Diels-Alder adduct.

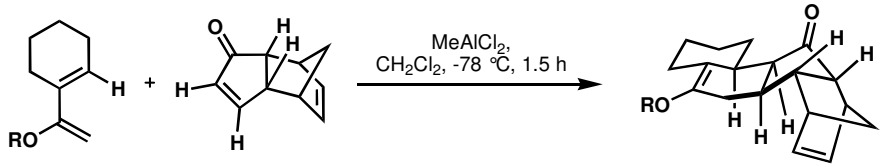


Presumably, this reaction proceeds through an *endo*-selective cycloaddition followed by in situ epimerization (Scheme 2.4, pathway a) to give the necessary *anti*-stereochemical relationship between the hydrogens at C-9 and C-10 in **2.11**. An alternative stepwise mechanism (pathway b), commencing with a Mukaiyama-type Michael addition, is also a possibility.

Scheme 2.4 Possible cycloaddition mechanisms.

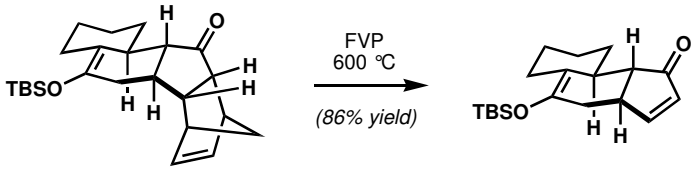


In addition, *endo*-adduct **2.10a** has been isolated using low temperature, Lewis-acid promoted conditions (eq 2.4). Trace amounts of *endo*-adduct **2.10** have been detected by ^{1}H NMR in the crude reaction mixture of the Yb(III)-catalyzed reaction. The $MeAlCl_2$-promoted reaction, which was studied in detail using the TES- (**2.7a**) rather than TBS- (**2.7b**) silyl enol ether, was found to require an excess of the Lewis acid relative to the enone. While 1.4 equiv of $MeAlCl_2$ provided **2.10a** in 95% yield, 1.0 equiv of the Lewis acid gave a mixture of products, with the *endo*-adduct **2.10a** predominating, and use of a catalytic amount (10 mol %) led to only 7% conversion of enone **2.8**.



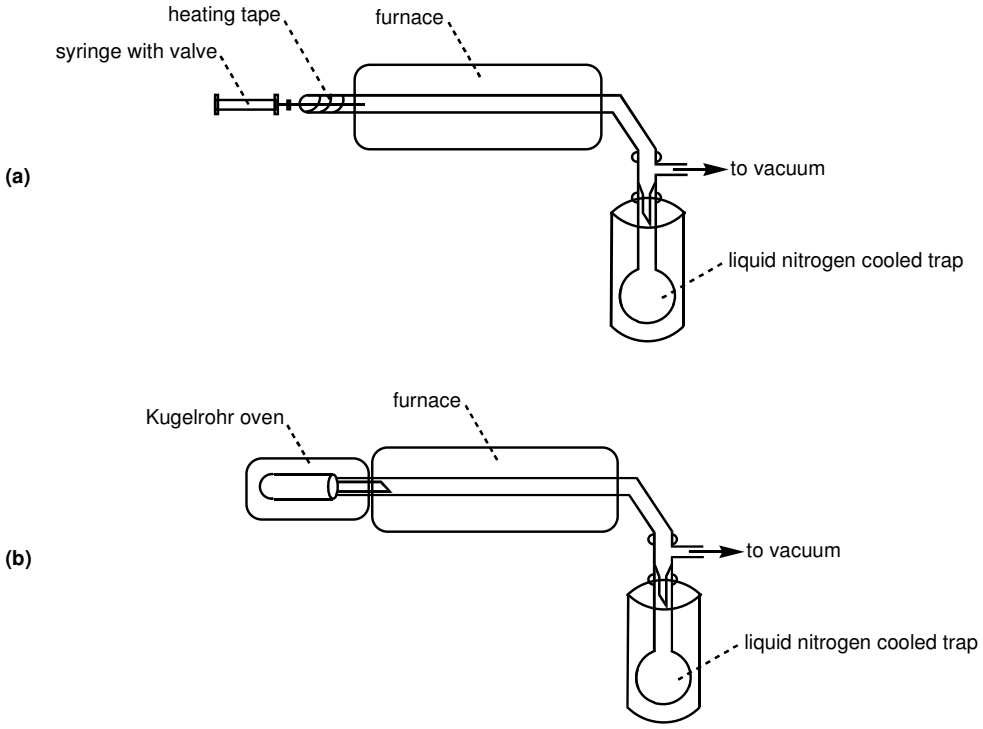
(2.4)

With cyclcoadduct **2.11** in hand, we were ready to perform a retro Diels-Alder reaction to reveal the double bond of the tricyclic enone core of G. B. 13 (see **2.18**, eq 2.5). Attempts to perform the cycloreversion under solution-phase thermal conditions (e.g., 200 – 220 °C in 1,2-dichlorobenzene) required extended reaction times (> 4 days) and proved to be irreproducible. Microwave experiments were similarly impractical, necessitating greater than 6 hours at 250 °C in 1,2-dichlorobenzene to reach over 80% conversion, which was not conducive to scale-up. Retro Diels-Alder reactions that liberate cyclopentadiene have also been performed under Lewis-acid catalysis[8,9] using $MeAlCl_2$, but we anticipated that the temperatures required for this transformation (ca. 55 °C) would be intolerable to the silyl enol ether functionality of both starting compound **2.11** and product **2.18** (see eq 2.5).



2.11 2.18 (2.5)

We found the most efficient method for performing the desired cycloreversion to be the use of flash vacuum pyrolysis (FVP). Reactions run under these gas-phase conditions benefit from low contact times (0.1-1 sec under moderate vacuum of 0.01-1 mmHg)[10] and are in essence devoid of intermolecular interactions as well as oxygen.[11] Tricycle **2.18** could be routinely obtained in good yield by FVP (eq 2.5) on multigram scale through the slow injection of adduct **2.11** as a 1 M solution in benzene to the entrance side of a tube furnace at 600 °C under vacuum (see Figure 2.2a). Other methods of introducing adduct **2.11** to the furnace were investigated, including vaporization by sublimation/distillation from a melt either by heating the substrate neat in a Kugelrohr oven (Figure 2.2b) or by volatilizing it at elevated temperature using a nitrogen bleed (Figure 2.2c). However, these modes proved to be inefficient for large scale reactions because the relatively low melting point of the substrate (i.e., **2.11**) precluded its facile sublimation at the experimental pressure and led to molten material that readily underwent decomposition to involatile polymers that entrapped the substrate. Attempts to volatilize the substrate after adsorbing it onto powdered glass, thereby increasing its surface area, and then heating it in a Kugelrohr oven were also met with limited success.



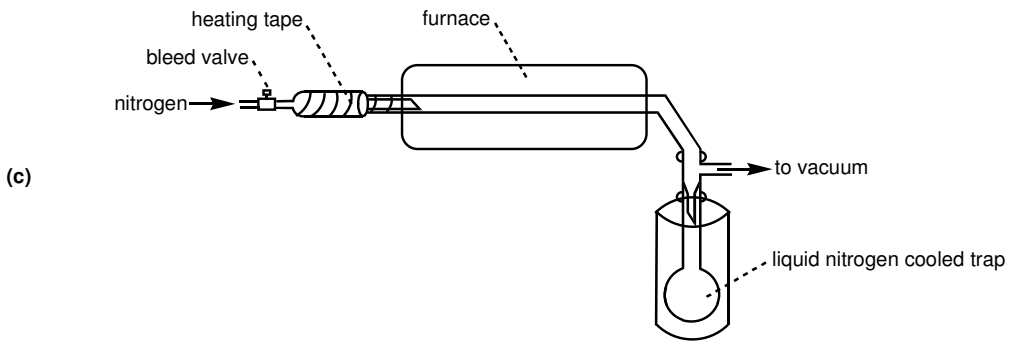
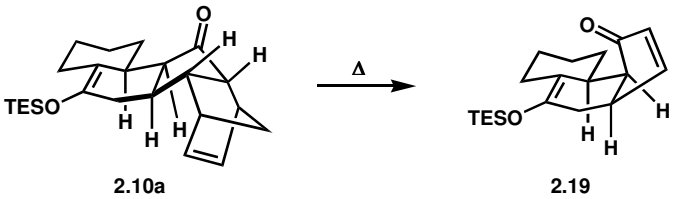


Figure 2.2 FVP experimental setup.

At 600 °C, of the two cyclohexene rings in adduct **2.11**, only the bridged ring system undergoes the retro Diels-Alder. When *endo*-Diels-Alder adduct **2.10a** (see eq 2.6) is subjected to FVP conditions at 600 °C, however, cycloreversion of both cyclohexene rings is observed to some extent. The undesired reaction can be avoided by lowering the furnace temperature to 450 °C. In addition, the transformation of *endo* Diels-Alder adduct **2.10a** to tricycle **2.19** even proceeds in solution phase at 180 °C (in 1,2-dichlorobenzene) within 3 h.

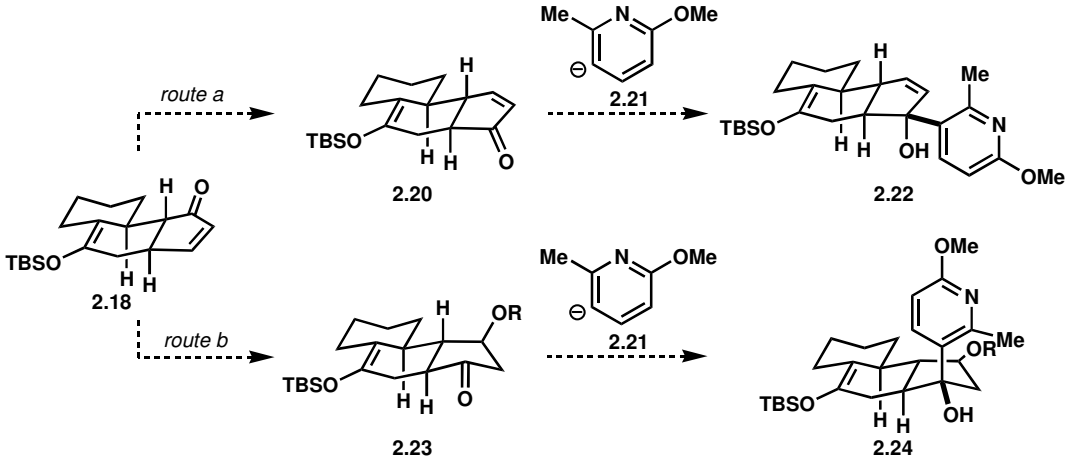


2.10a 2.19 (2.6)

2.3 Strategies Toward Achieving *β*-Oxygenation of the Tricyclic Core

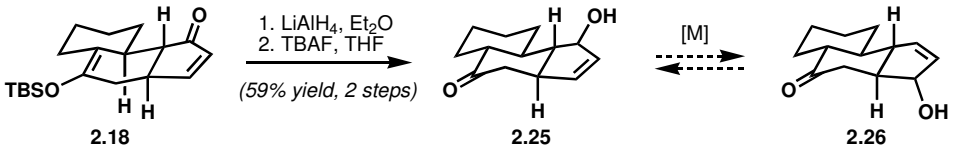
En route to G. B. 13, oxygenation at the *β*-position of the enone in tricycle **2.18** (see Scheme 2.5) is required. Two possible routes for achieving this oxygenation and then installing the pyridine are outlined in Scheme 2.5. Route *a* involves the allylic transposition of some derivative of enone **2.18** which would lead to enone **2.20**, followed by a 1,2-addition of pyridinyl anion **2.21** to give **2.22**. In route *b*, the double bond of enone **2.18** or a derivative would be oxygenated to give 1,3-dioxygenated species **2.23**. Addition of pyridinyl anion **2.21** into the ketone carbonyl would then provide **2.24**.

Scheme 2.5 Possible routes to β-oxygenation.



The first metal catalysts developed for the transposition of allylic alcohols (e.g., **2.25** to **2.26**, Scheme 2.6) were trialkyl vanadates, $VO(OR)_3$, which require temperatures of greater than 150 °C.[12] Other vanadium,[13] tungsten,[14] molybdenum,[13,15] and rhenium[16] metal-oxo complexes have also been developed for the catalysis of allylic alcohol isomerizations. The accepted mechanism for most of these catalysts involves a cyclic transition state comprised of the allylic alcohol and metal-oxo unit.[12] Because this is a reversible process, the product distribution ultimately depends on the thermodynamic stabilities of the two isomers. Osborn's rhenium complexes $ReO_3(OSiR_3)$ (R = Me, Ph)[16] are regarded as the most efficient catalysts for allylic alcohol isomerizations,[17] facilitating isomer equilibration in under ten minutes at room temperature.

Scheme 2.6 Possible transposition of secondary allylic alcohol.



Tricycle **2.18** was reduced to the corresponding allylic alcohol with $LiAlH_4$ and the silyl enol ether was cleaved to give **2.25**. Subjection of this compound to $ReO_3(OSiPh_3)$,[18] however, failed to provide any useful amount of the transposed allylic alcohol. Subjecting the corresponding silyl enol ether (see **2.27**, Table 2.1) to $(Ph_3SiO)_2VO_2{\bullet}^nBu_4N$ at 70 °C for 12 h returned only starting material.

We also sought to access epoxy ketone **2.28** in order to perform a Wharton transposition to arrive at transposed allylic alcohol **2.29** (Scheme 2.7). Attempts to epoxidize **2.18** or corresponding alcohol **2.27**, however, were unsuccessful (see Table 2.1).[19]

Scheme 2.7 Potential Wharton transposition approach.

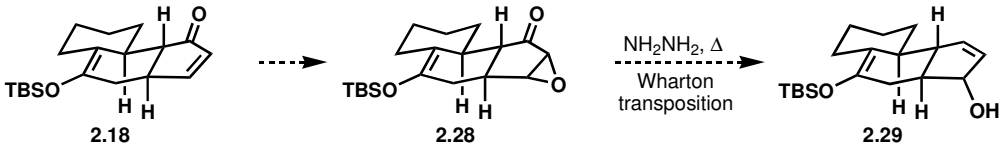
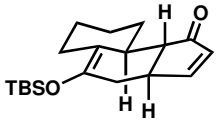
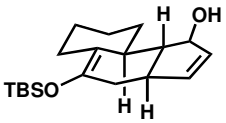
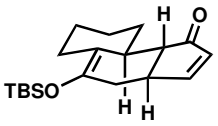
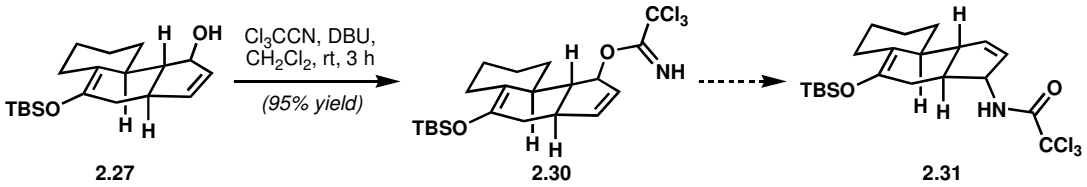


Table 2.1 Epoxidation attempts.

Entry	Substrate	Conditions	Results
1	 2.18	HOOH, NaOH, EtOH, 40 °C, 2d	no reaction
2		HOOH, $MgAl(OH)CO_3$, 40 °C, 2 d	no reaction
3		TBHP, $VO(acac)_2$, benzene, RT, 10 h	no reaction
4	 2.27	TBHP, $VO(acac)_2$, CH_2Cl_2, 45 °C, 15 h	multiple products
5		*m*-CPBA, CH_2Cl_2, rt, 2 d	multiple products
6		TBHP, $Ti(O^iPr)_4$, CH_2Cl_2, 12 h	 2.18

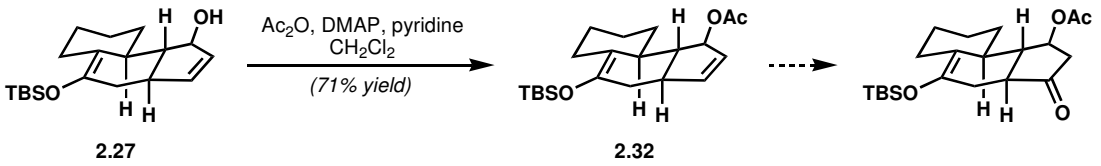
The Overman rearrangement is another allylic transposition protocol that converts allylic trichloroacetimidates to allylic trichloroacetamides (see **2.30** to **2.31**, Scheme 2.8). We prepared substrate **2.30**[20] with the intention of performing this rearrangement to give **2.31** and then converting the allylic nitrogen to an oxygen at a later stage. The desired transformation failed, however, upon subjection of **2.30** to temperatures of up to 140 °C.

Scheme 2.8 Possible Overman rearrangement approach.



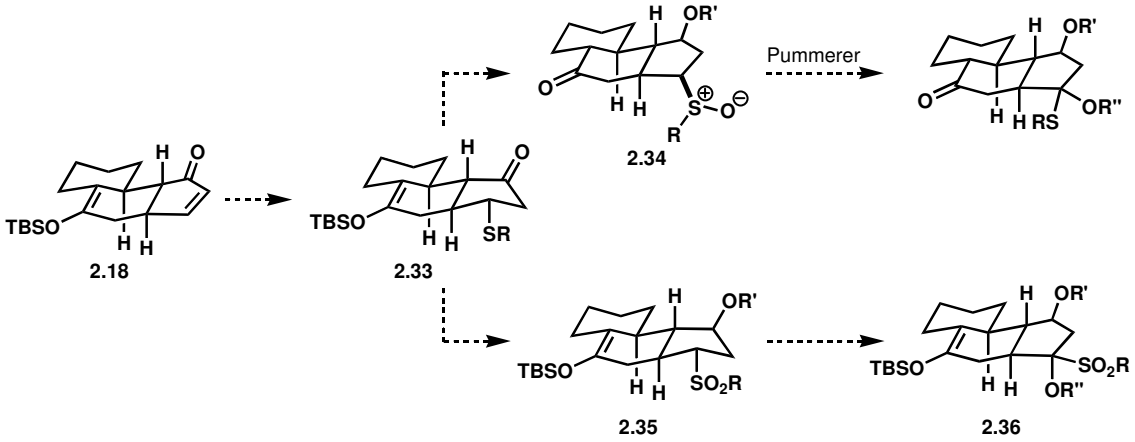
Besides using the already installed oxygen of tricyclic enone **2.18** to direct an allylic transposition (Scheme 2.5, route *a*), we also investigated utilizing the enone double bond to introduce the necessary oxygen (Scheme 2.5, route *b*). Oxidation of the double bond was attempted using Wacker conditions ($PdCl_2$, CuCl, O_2, H_2O, DMF, 60 °C) on allylic acetate **2.32** (Scheme 2.9), though the regiochemical outcome of the potential oxidation was unclear. However, only starting material was recovered.

Scheme 2.9 Possible Wacker approach.



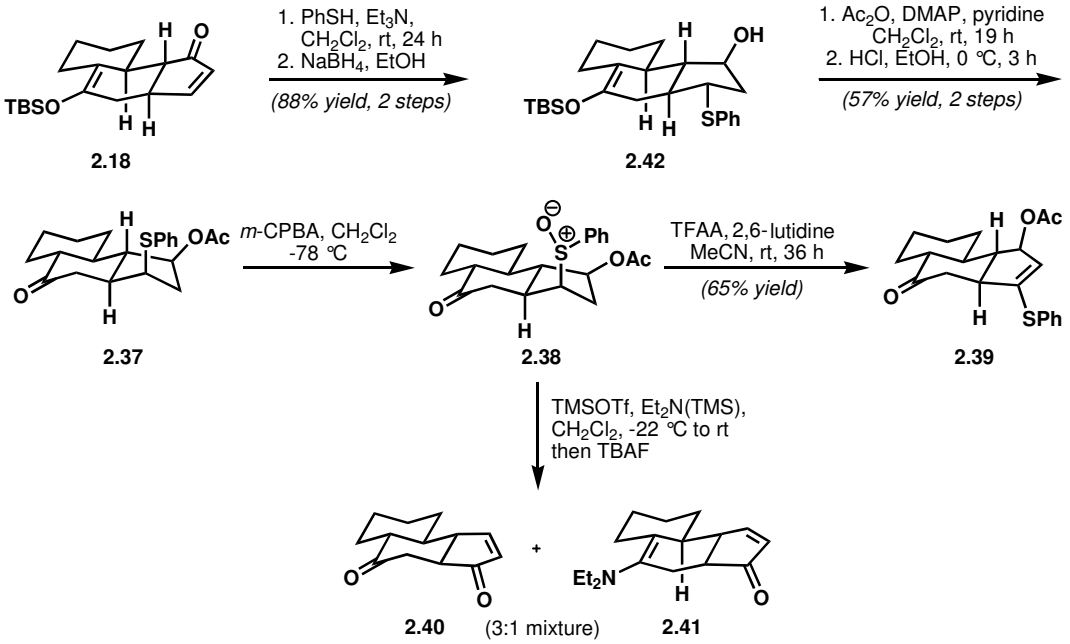
We next considered performing a conjugate addition on tricycle **2.18** with a functional handle that would allow the introduction of an oxygen alpha to it. Thus, we looked first to thiol 1,4-additions. Oxidation of the resulting sulfide (see **2.33**, Scheme 2.10) to the corresponding sulfoxide (**2.34**) would provide a substrate for a Pummerer rearrangement.[21] Alternatively, oxidation of the sulfide to the corresponding sulfone (**2.35**) would provide a substrate that could undergo alpha-deprotonation followed by electrophilic oxygen trapping to give **2.36**.

Scheme 2.10 Thiol conjugate approaches.



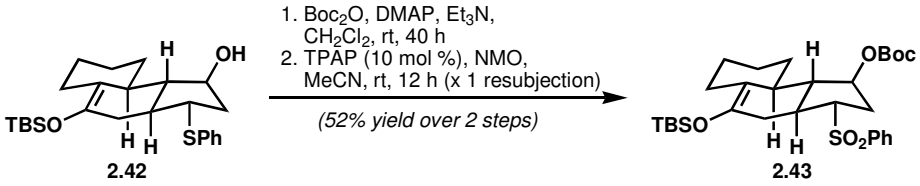
In preparation for conducting Pummerer chemistry, conjugate addition of thiophenol into enone **2.18** proceeded in good yield (Scheme 2.11). Reduction of the ketone carbonyl, protection of the resulting hydroxyl group as an acetate, and desilylation provided phenyl sulfide **2.37** in 50% yield over four steps. Oxidation with *m*-CPBA at low temperature gave sulfoxide **2.38**. Treatment of this compound with trifluoroacetic anhydride, however, gave vinyl sulfide **2.39** instead of the desired oxygenated Pummerer product. Using an alternative set of conditions (TMSOTf and $Et_2N(TMS)$ as a mild base),[22] small amounts of two compounds, presumed to be enones **2.40** and **2.41**, were obtained.

Scheme 2.11 Pummerer approach.



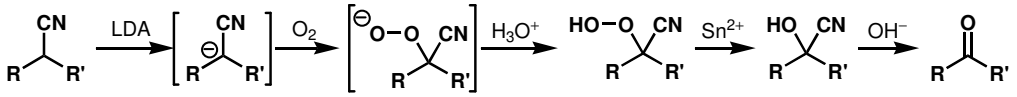
We next prepared sulfone **2.43** (Scheme 2.12) on the Boc-protected alcohol using catalytic tetrapropylammonium perruthenate (TPAP) and an excess of *N*-methylmorpholine *N*-oxide (NMO).[23] Attempting to deprotonate the sulfone (**2.43**) using a variety of bases (LDA, NaHMDS,[24] iPr$_2$NMgBr) and trap the resultant anion with an electrophilic oxygen source (TMSOOTMS,[25,26] Davis' oxaziridine,[24,27] O_2, or oxodiperoxymolebdenum(pyridine)hexamethylphosphosphoramide (MoOPH)) resulted in only epimerization alpha to the sulfonyl group. Though we found that alkylation alpha to the sulfone of **2.43** occurs readily using allyl bromide as the electrophile, oxygenation was never accomplished.

Scheme 2.12 Sulfone synthesis.



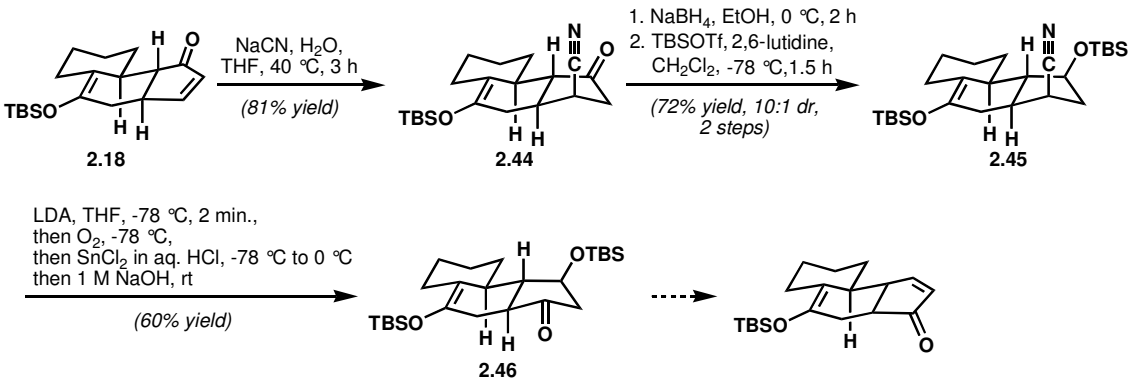
Another method that we investigated for installing oxygenation at the beta-position of enone **2.18** was to introduce a nitrile group at that position and then use its electron-withdrawing character to deprotonate alpha to it and trap with an electrophilic oxygen source. Watt and coworkers have developed an efficient method for the oxidative decyanation of secondary nitriles using molecular oxygen as the oxygen source and $SnCl_2$ to reduce the intermediate α-hydroperoxynitrile (see Scheme 2.13).[28,29] Importantly, secondary dialkyl nitriles are competent substrates for this protocol.

Scheme 2.13 Watt et al. oxidative decyanation protocol.



Our substrate for the oxidative decyanation reaction was prepared as outlined in Scheme 2.14. Conjugate addition of cyanide using NaCN proceeded readily to give β-cyano ketone **2.44**, the structure and relative stereochemistry of which was determined by X-ray analysis (see Figure 2.3B). Ketone reduction and silyl ether protection of the resulting hydroxyl group provided **2.45**. Deprotonation with LDA followed by anion trapping with dry O_2, peroxide reduction with acidic $SnCl_2$, and base-promoted elimination of the cyanohydrin provided ketone **2.46** in 60% yield. Base-induced elimination provided mixtures of enone products, and attempts to epimerize to a single diastereomer were unsuccessful.

Scheme 2.14 Nitrile α-oxygenation.



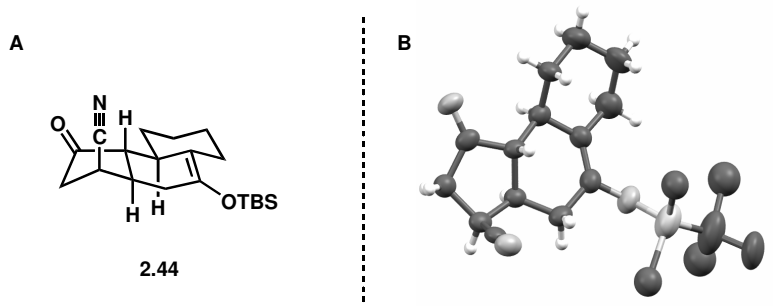


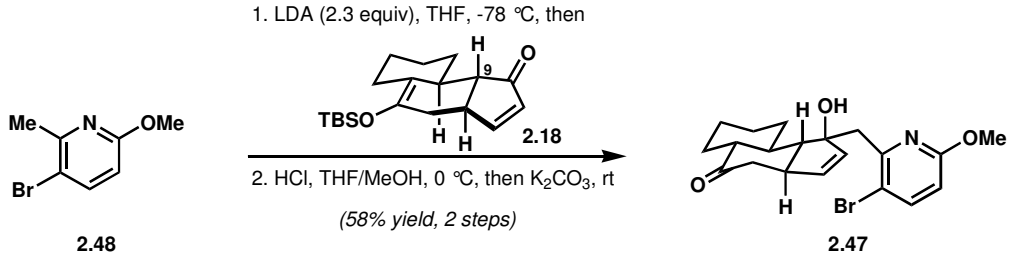
Figure 2.3 a) Enantiomeric portrayal of **2.44**. b) ORTEP representation of **2.44** (portrayed as its enantiomer; disorder and hydrogens about TBS group removed for clarity).

2.4 Achieving an Allylic Transposition of the Methylenylpyridinyl Alcohol

Performing the necessary alcohol transposition on a tertiary allylic alcohol as opposed to a secondary alcohol benefits from both the inherent thermodynamic preference for the trisubstituted double bond and also the opportunity to oxidatively trap the secondary alcohol. The prototypical method for performing an oxidative tertiary allylic alcohol transposition is the Dauben

reaction.[30] Tertiary allylic alcohol substrate **2.47** was prepared by the lateral deprotonation of picoline **2.48**[31] at its pseudobenzylic position, followed by the anion's 1,2-addition[32] into tricyclic enone **2.18** (Scheme 2.15). This addition proceeded with good diastereocontrol, presumably directed away from the proximal axial hydrogen at C-9. Acid-catalyzed hydrolysis of the silyl enol ether provided tertiary alcohol **2.47** and its cis-decalin epimer in approximately 10:1 dr. Addition of K_2CO_3 to the reaction mixture following hydrolysis generated methoxide which facilitated epimerization to the trans-decalin diastereomer in approximately 95:5 dr. Notably, a much lower dr (~4.5:1) was observed when the desilylation was performed using TBAF. The constitution and stereochemistry of ketone **2.47** was confirmed by X-ray analysis (see Figure 2.4).

Scheme 2.15 Synthesis of tertiary allylic alcohol.



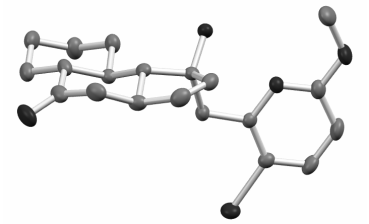
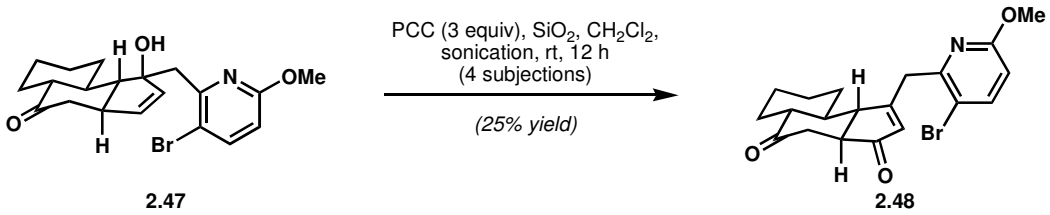


Figure 2.4 ORTEP representation of **2.47** (hydrogens omitted for clarity).

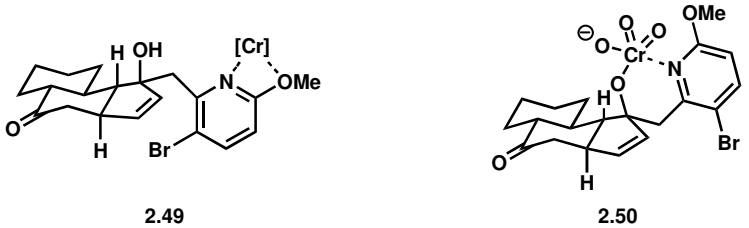
After careful optimization of Dauben's PCC (pyridinium chlorochromate)[33] conditions (see eq 2.7) a 25% yield of transposed enone **2.48** was obtained. Although this reaction does not proceed at all using 2 equivalents of PCC, even at temperatures up to 80 °C, increasing the amount of reagent to 3 equivalents allows the oxidative transposition to take place. However, the reaction stalls before reaching completion, and three additional subjections to three equivalents of PCC are required before complete consumption of the starting material is obtained. At the end of this sequence, only 47% of the mass, including a 25% yield of the desired product, was recovered.



(2.7)

A 1:1 weight mixture of PCC and silica gel in addition to sonication of the reaction were necessary for the optimized reaction conditions.[34] Adsorbents and supports, including alumina,[35] Celite,[36] clays,[37] molecular sieves,[38] and silica gel,[39] have been used in oxochromium-amine oxidations to mitigate the deleterious effects of the chromium(IV) byproducts of these reactions. These reduced chromium species are known to cause polymerization of the nitrogen heterocycles in the active reagent, thus taking portions of the chromium reagent out of commission. The resulting black, polymeric tars may entrain the starting material and oxidized products. These effects are especially harmful to oxidation yields when the rate of polymerization exceeds that of oxidation. Luzzio and coworkers have found that the use of sonication in PCC/SiO_2-enabled oxidations increases both the rate and yield of these reactions.[34] They attribute these improvements to the ultrasound activation of the silica gel, which increases its affinity for the chromium byproducts, thus minimizing the amount of unadsorbed chromium(IV) that can potentially entrain substrate and product, and also to the sonication-induced solubility increase of PCC in methylene chloride, which facilitates the formation of the chromate ester and also its oxidative decomposition, hence increasing the overall rate of the reaction.

There are a number of factors that likely contribute to the poor performance of PCC in our desired transformation (i.e., **2.47** to **2.48**). First, the pyridine moiety in substrate **2.47** may be one source of the low yields. The chromium(VI) reagent may be forming an unproductive complex with the pyridine-containing substrate or product, thus effectively constraining this material. Ligand exchange of pyridinyl substrates with oxochromium-amine reagents has been observed previously.[40] Our pyridine-containing substrate or product also may be interacting with the reduced chromium(IV) byproducts. As has already been discussed, chromium(IV) is known to polymerize nitrogen-containing heterocycles. Additionally, in their study of sulfur-containing tertiary allylic alcohols, Luzzio and coworkers have reported drastically reduced yields for substrates of oxochromium(VI)-amine oxidative transpositions that possess basic lone-pair containing heteroatoms, specifically, dithiane moieties.[41] They attribute these low yields to the two-point binding opportunities of the reduced chromium(IV) species with the dithianes. Importantly, the isolated yields of the dithiane substrates increase with increasing steric congestion alpha to the dithiane group, and, additionally, Luzzio et al. found that related systems possessing sulfide functional groups in place of dithianes did not suffer from diminished yields. It is conceivable that our 2-methoxypyridine substrate is similarly capable of two-point binding with either the chromium(VI) or (IV) in the reaction mixture, contributing to the low observed product return (see **2.49**, Figure 2.5). An over-stabilizing coordination of the pyridine nitrogen to the tertiary chromate ester (see **2.50**) would also effectively remove substrate from the reaction mixture. The negative effects of all of these factors will be augmented if the rate of the desired oxidative transposition is slow relative to the rate of any irreversible or thermodynamically favored side-reactions.

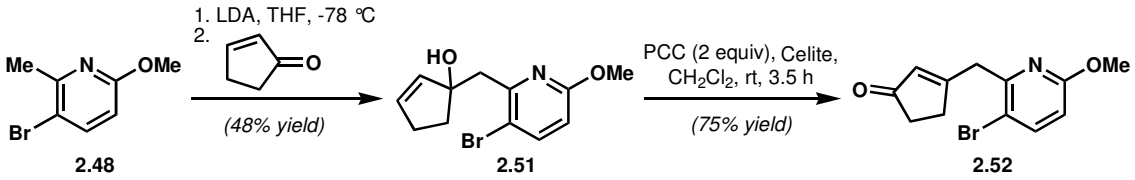


2.49 2.50

Figure 2.5 Postulated unproductive chromium complexes.

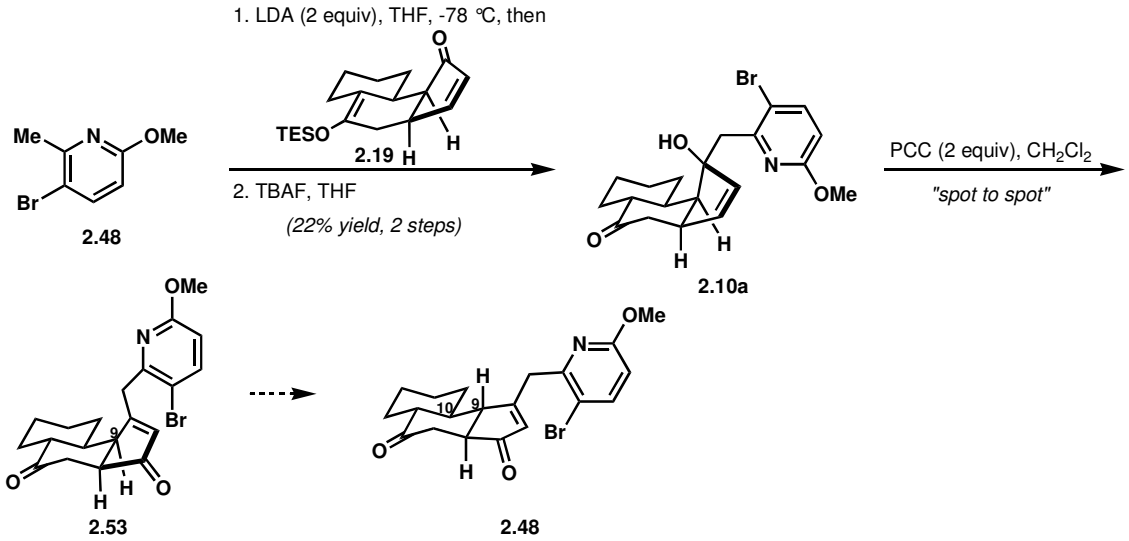
We prepared model system **2.51** (Scheme 2.16) in an attempt to better understand this reaction. This substrate, which possesses a monocyclic cyclopentene core, underwent the Dauben oxidation with only two equivalents of PCC to give **2.52** in 75% yield.

Scheme 2.16 Dauben oxidation of model system.



Moreover, substrate **2.19** (Scheme 2.17), derived from *endo* Diels-Alder adduct **2.10a** (see eq 2.4), also readily underwent the transformation to provide **2.53**. The success of the Dauben oxidation on this substrate that is closely related to **2.47** (which also possesses a tricyclic core) indicates that there are very subtle structural features that must impede the reaction's success on alcohol **2.47** (eq 2.7). While we now had access to transposed enone **2.53**, which could potentially be epimerized at C-9 to obtain the required *trans* relative stereochemistry between C-9 and C-10, the 1,2-addition of the picoline anion of **2.48** into enone **2.19** proceeded in a low 32% yield, even after attempted optimization, rendering this route untenable.

Scheme 2.17 Dauben transposition of *endo*-Diels-Alder derived substrate.



We explored the possibility of using a 2,6-lutidine-derived substrate for the Dauben reaction. The lithiated anion of 2,6-lutidine did add into enone **2.19** in good yield (65%), but subjecting the substrate following TBAF deprotection (**2.54**) to PCC returned only starting material (Scheme 2.18). It is likely that the increased basicity of the methyl-substituted pyridine rings relative to the methoxy-variant (see Figure 2.6) leads to increased unproductive interactions with the chromium species.

Scheme 2.18 Unsuccessful Dauben substrate.

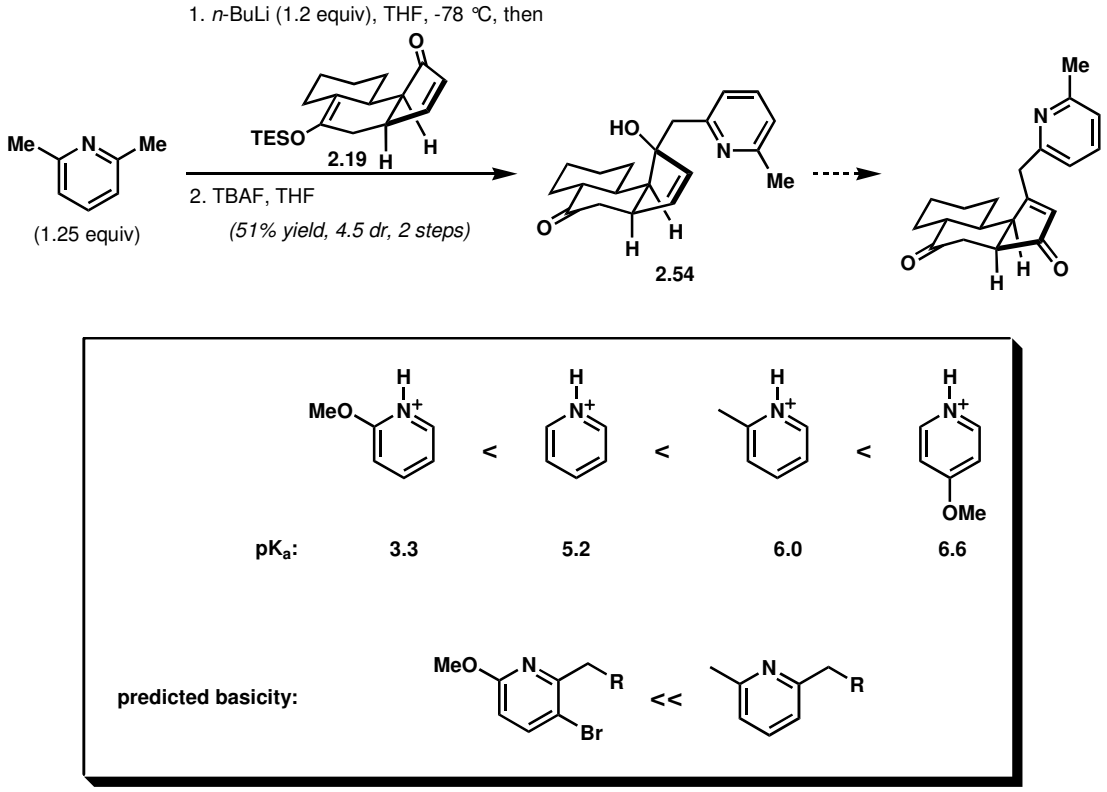
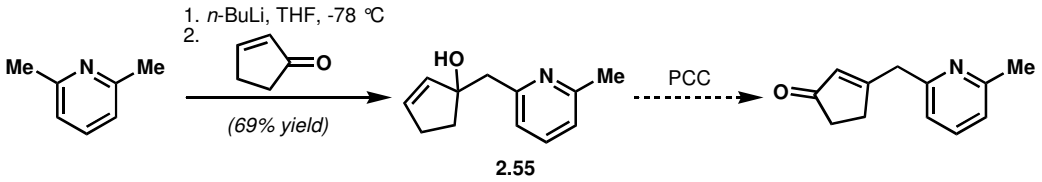


Figure 2.6 pK_a's of protonated pyridines[42] and predicted basicities of substrates.

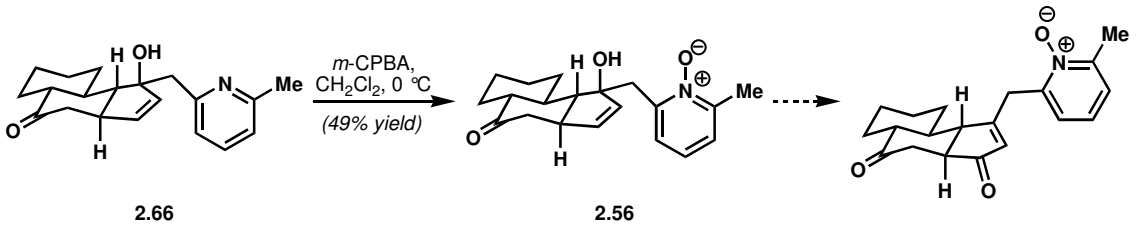
We observed a similar effect with our model system: whereas the 3-bromo-6-methoxypyridinyl substrate was a competent PCC substrate (see **2.51** to **2.52**, Scheme 2.16), the corresponding 2-methylpyridinyl compound **2.55** (Scheme 2.19) did not undergo the Dauben transformation. Interestingly, in addition to isolating starting material **2.55** upon purification of the crude reaction mixture, another compound was isolated which possessed the characteristic NMR peaks of the substrate but was insoluble in chloroform and benzene, unlike the substrate itself. We believe that this compound, which is soluble in methanol, is a chromium complex of the substrate, possibly via ligand exchange with the PCC pyridine, analogous to that observed by Luzzio.[40]

Scheme 2.19 Attempted Dauben oxidation of 2,6-lutidine-derived allylic alcohol.

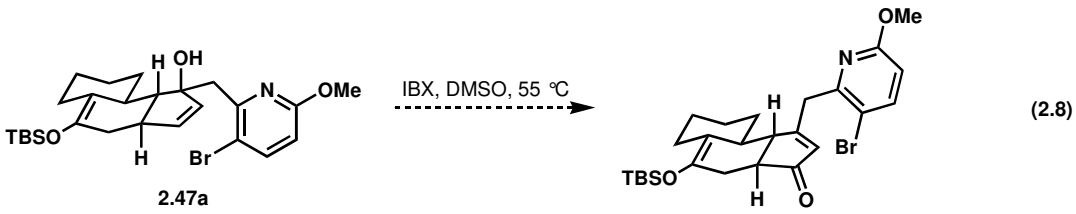


We prepared N-oxide substrate **2.56** in order to probe the role of the basic pyridine nitrogen functionality in the Dauben oxidation (Scheme 2.20). This compound, also, failed to undergo the oxidative transposition.

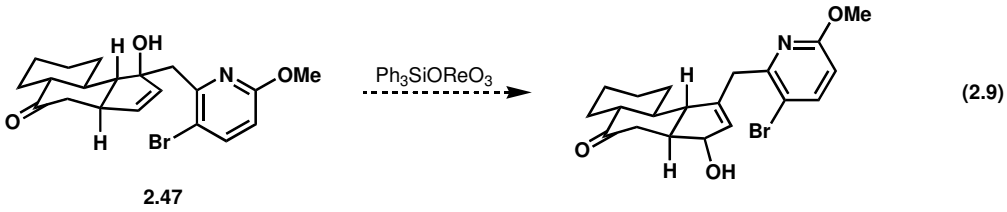
Scheme 2.20 Dauben attempt on N-oxide substrate.



IBX (1-hydroxy-1,2-benziodoxal-3(*1H*)-one-1-oxide) has been shown by Iwabuchi and coworkers to be another general reagent for the oxidative transposition of 5- and 6-membered cyclic tertiary allylic alcohols.[43] Employing these conditions on alcohol **2.47a** (eq 2.8), however, led only to desilylated starting material.

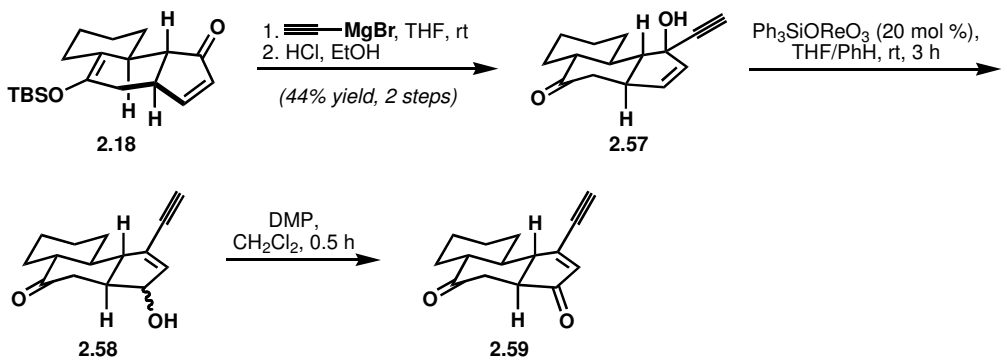


Subjection of alcohol **2.47** to Osborn's $Ph_3SiOReO_3$ catalyst[16] (eq 2.9) in various solvents (Et_2O, CH_2Cl_2, CH_2Cl_2/THF, and PhH/THF) also proved ineffective, giving multiple products but none of the transposed alcohol.



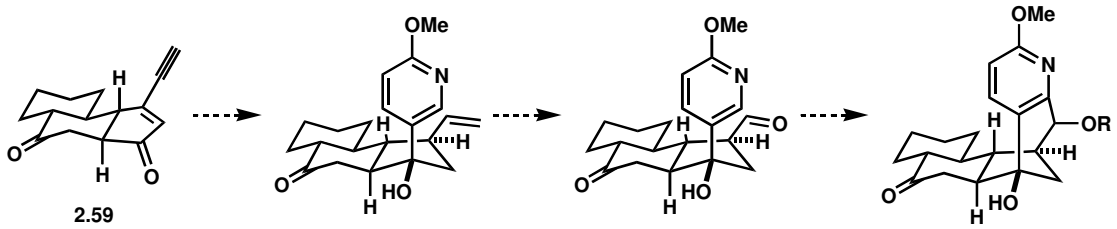
Rearrangement using Osborn's catalyst was effected on tertiary ethynyl alcohol **2.54** (Scheme 2.21), which was derived from the 1,2-addition of ethynyl Grignard into enone **2.18**. The allylic transposition product mixture appeared to contain two diastereomeric products (**2.58**), which upon subjection to Dess-Martin reagent gave a single product, presumably enone **2.59**.

Scheme 2.21 Rhenium-catalyzed transposition of ethynyl tertiary allylic alcohol.



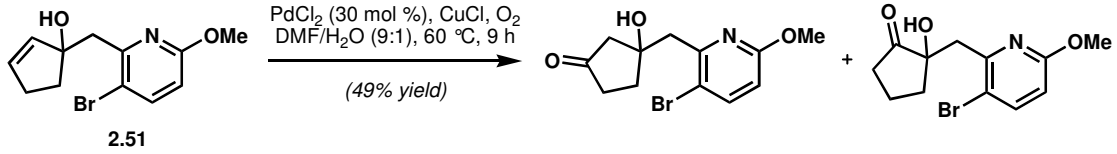
Enone **2.59** could potentially be elaborated to an intermediate en route to the synthesis of G. B. 13 (see Scheme 2.22), but this route was not explored. Notably, attempted Dauben oxidation of tertiary alcohol **2.57** (Scheme 2.21), which lacks the pyridine functionality, failed using 2 equivalents of PCC and provided mainly starting material.

Scheme 2.22 Potential synthetic route employing β-ethynyl enone **2.59**.



We next considered methods to hydrate the cyclopentenol double bond to install the necessary oxygenation. We could later deoxygenate the tertiary hydroxyl group to set the appropriate stereochemistry and oxidation level at C-8 (see **2.60**, Scheme 2.24). Subjecting model system **2.51** to Wacker conditions led to a 5:3 mixture of two chromatographically inseparable products (Scheme 2.23). Two carbonyl peaks were observed in the ^{13}C NMR, suggesting that the Wacker oxidation proceeds on this system but with poor regiocontrol.

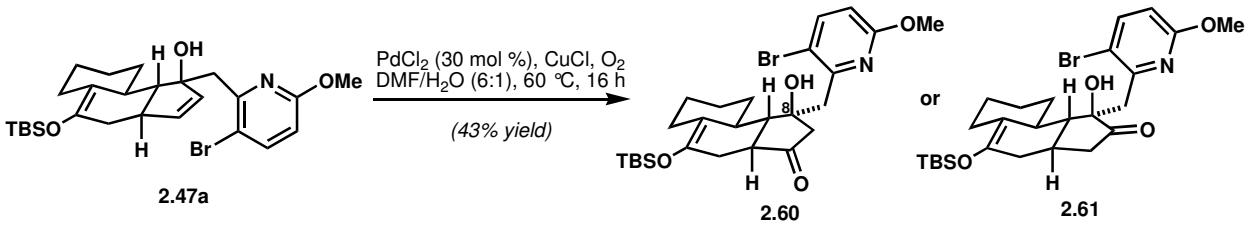
Scheme 2.23 Wacker oxidation of model system.



Subjecting our actual system, tertiary allylic alcohol **2.47a**, to Wacker conditions (Scheme 2.24) provided one major product, spectroscopically consistent with the desired ketone **2.60**, in a modest 43% yield. Attempts to optimize the reaction by varying solvent (DMF, DMA, NMP, MeOH, EtOH), oxidant (O_2, TBHP, benzoquinone), catalyst ($PdCl_2$, $PdCl_2(PhCN)_2$,

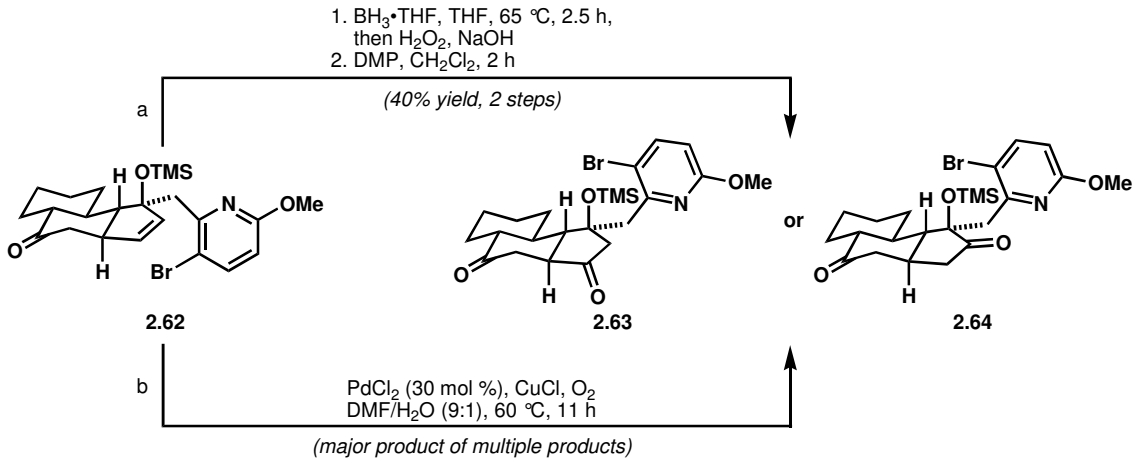
$PdCl_2(MeCN)_2$), temperature (45 – 80 °C), and/or additive (LiCl, Et_4NCl), were unsuccessful. The regiochemistry of the product (i.e., **2.60** vs. **2.61**) was not conclusively determined.

Scheme 2.24 Wacker oxidation on tertiary allylic alcohol.



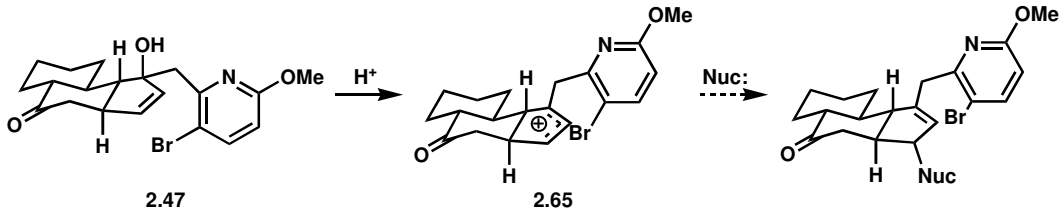
Using TMS-protected tertiary allylic alcohol **2.62** (Scheme 2.25, *vide infra* for its preparation), we were successful in performing a hydroboration oxidation sequence (route a) by conducting the hydroboration at elevated temperature (65 °C). Though the regiochemistry of the product following Dess-Martin oxidation to the corresponding ketone (i.e., **2.63 or 2.64)** was not conclusively determined, the same compound was obtained as the most predominant component in the mixture of products following Wacker oxidation of olefin **2.62** (route b).

Scheme 2.25 Hydration of TMS-protected tertiary allylic ether.



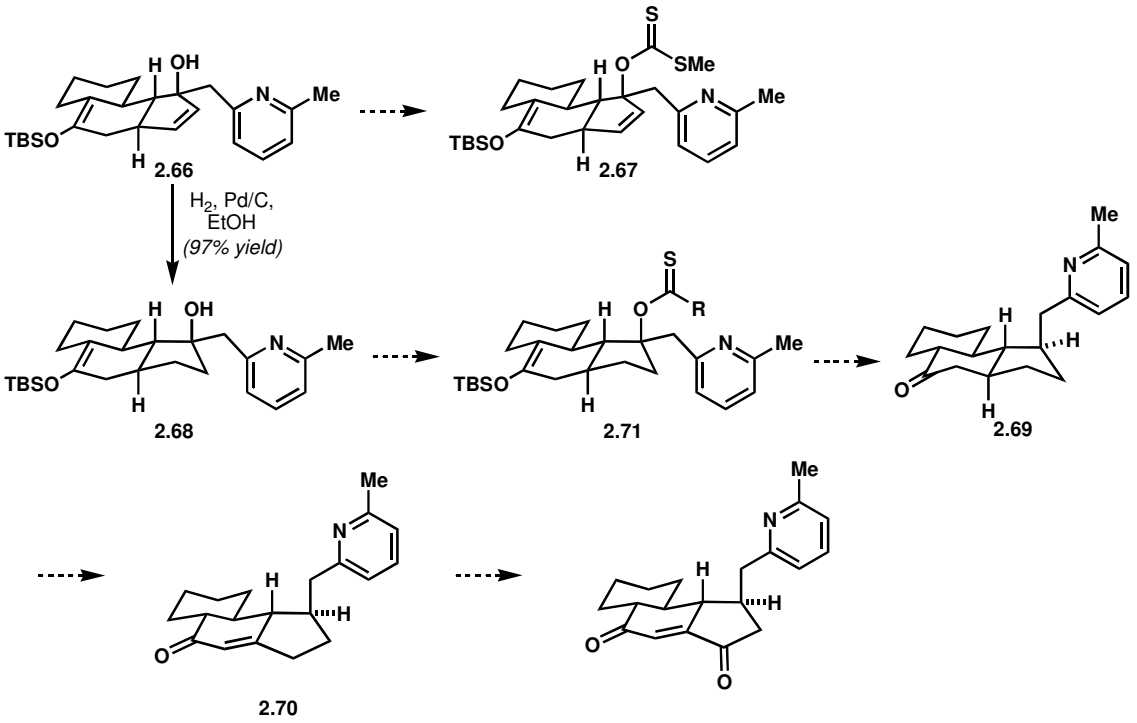
From tertiary allylic alcohol **2.47**, we anticipated that if we could access allylic cation **2.65** by acid-promoted elimination (Scheme 2.26), we might be able to intercept the cation with a nucleophile at the kinetically favored, less-substituted position to provide the necessary functionalization. In practice, we found that acids such as trifluoroacetic acid (TFA) and toluenesulfonic acid (TsOH) were effective at promoting elimination whereas hydrochloric acid and acetic acid were not, but we were unsuccessful in our attempts to trap the cation with a variety of nucleophiles (CF_3CO_2H, Bu_4NI, Bu_4NBr, $Me_3SiOSiMe_3$, MeOH, and H_2O). Only dehydration products were observed.

Scheme 2.26 Attempted nucleophilic trapping of allylic cation.



We considered removing the tertiary hydroxyl group of **2.66** (Scheme 2.27) through a Barton-McCombie deoxygenation[44] to investigate its effect on our inability to efficiently functionalize the cyclopentene double bond. We hoped that upon forming a radical at the tertiary carbon, kinetic hydrogen atom abstraction would take place on the alpha-face of the molecule to properly set the stereochemistry at that center. The hydroxyl group, however, proved unresponsive to attempts to functionalize it as a xanthate (i.e., **2.66** to **2.67**, Scheme 2.27). Another potential route is outlined in Scheme 2.27. Hydrogenating the cyclopentene double bond to give **2.68**, followed by xanthate formation, deoxygenation with hydrogen abstraction from the alpha-face, and finally ketone deprotection, would lead to **2.69**. Oxidation of the ketone to the corresponding enone to give **2.70** would then put us in a position to perform an allylic oxidation to bring in the requisite oxygenation on the five-membered ring. Attempts to form a xanthate or thiocarbonate of **2.68** (**2.71**, R = SMe, OPh, respectively) were unsuccessful.

Scheme 2.27 Attempted preparation of xanthate derivatives.

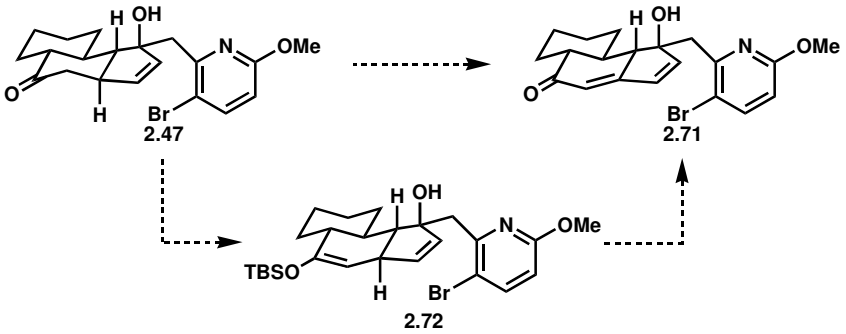


The tertiary hydroxyl group of bromomethoxy pyridine **2.47** and methyl pyridine **2.66** eluded functionalization under a variety of conditions. Electrophiles including TMSCl, tri-

chloroacetonitrile, CS_2, acetyl chloride, phenyl chlorothionoformate/DMAP, Ac_2O/DMAP, TFAA, and MeI used in combination with bases such as *n*-BuLi, LDA, KHMDS, NaH, KH, DBU, pyridine, and Ag_2CO_3 all failed to derivatize the hydroxyl group. Our first successful functionalization, in fact, took place inadvertently.

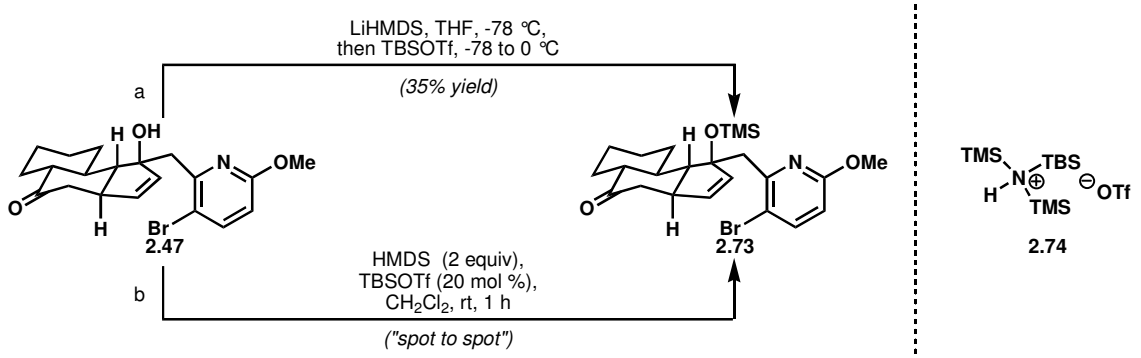
In an effort to study the potential chemistry of an altered tricyclic framework, we sought to oxidize the ketone **2.47** to the corresponding less-substituted enone, **2.71** (Scheme 2.28). Hypervalent iodine sources (IBX[45] or HIO_3[46]) failed to effect the desired oxidation directly from **2.47**. Thus, we decided to attempt a Saegusa-Ito oxidation on silyl enol ether **2.72**.

Scheme 2.28 Attempted oxidation of ketone to enone.



To make silyl enol ether **2.72**, we chose to use the bulky base LiHMDS, in order to favor kinetic deprotonation, with TBSOTf as the silylating reagent (see Scheme 2.29, pathway a). Upon workup, instead of isolating TBS silyl enol ether **2.72**, however, we isolated TMS ether **2.73** in 35% yield. Presumably, this product arises through silyl transfer from **2.74**, which may be generated through the reaction of hexamethyldisilazane (HMDS) and TBSOTf. HMDS is, in fact, a common silylating reagent when used in the presence of a catalyst,[47] and we found that subjecting alcohol **2.47** to HMDS in the presence of catalytic TBSOTf at room temperature (Scheme 2.29, pathway b) provided clean conversion to the corresponding TMS silyl ether within one hour. The facile manner in which the trimethylsilyl group is transferred to the tertiary hydroxyl group under these conditions is attributed to the high electrophilicity of the active silylating agent **2.74**.

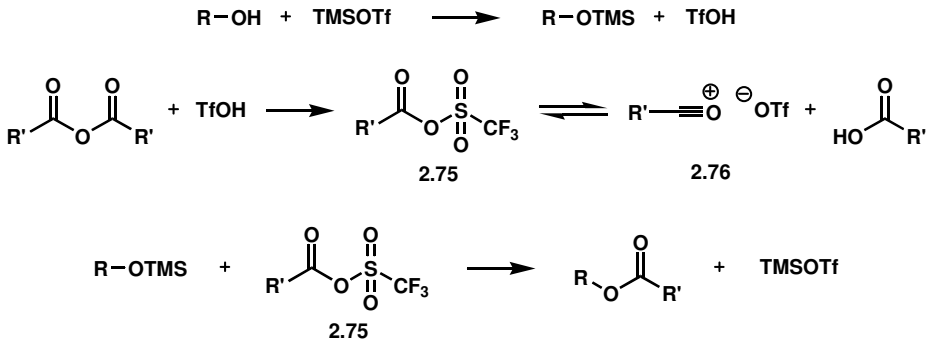
Scheme 2.29 Synthesis of TMS-protected tertiary alcohol.



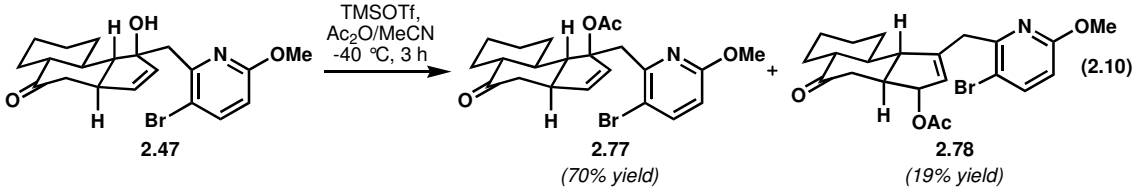
With an understanding of the type of electrophile effective for functionalizing tertiary allylic alcohol **2.47**, we were now in a position to try new methods of derivatizing the hydroxyl group in preparation for the desired transposition. Seeking to use conditions with highly electrophilic agents, we turned to Procopiou[48] and Yamamoto's[49] TMSOTf- and $Sc(OTf)_3$-catalyzed acetylation protocols.

Tertiary alcohol **2.47** had proven completely inert to typical acetic anhydride/DMAP acetylation conditions. Procopiou and Yamamoto have independently developed methods which use acid anhydrides and a Lewis acid catalyst that allow for the ready acylation of even tertiary alcohols. The active acylating species in the proposed mechanism of Procopiou and coworkers' TMSOTf-catalyzed acylation procedure is mixed anhydride **2.75**, which may exists as acylium ion **2.76** (Scheme 2.30).

Scheme 2.30 Procopiou's proposed TMSOTf-catalyzed acylation mechanism.

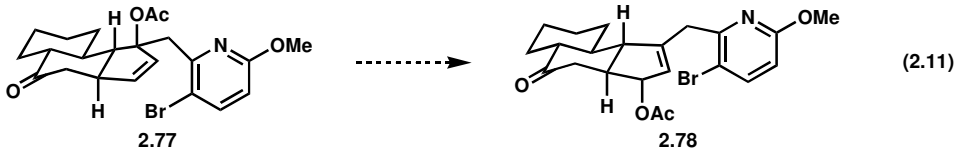


Upon subjecting alcohol **2.47** to TMSOTf in acetic anhydride and acetonitrile at -40 °C, we obtained a 70% yield of the acetylated tertiary alcohol **2.77** along with 19% of the rearranged secondary acetate **2.78**. Increasing the temperature or reaction time in attempts to access more of transposed alcohol **2.78** led only to significant amounts of elimination products and a severely diminished yield of combined tertiary and secondary acetates.

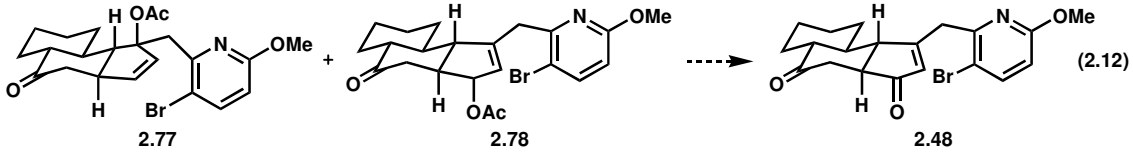


$Sc(OTf)_3$ also proved to be effective in catalyzing the acetylation, and comparable yields of mixtures of tertiary acetate **2.77** and secondary acetate **2.78** were again obtained, though the relative amount of rearranged acetate was higher here (up to 30 – 45%). This reaction proceeded at room temperature typically in 12 – 24 hours. Again, attempts to favor the allylic rearrangement to provide synthetically useful amounts of transposed acetate **2.78** were unsuccessful. Lewis acids including BF_3•OEt_2, $SnCl_4$, and $Sn(OTf)_2$ also provided acetylated products, though with no synthetic improvement. The formal allylic transposition likely takes place through an ionization mechanism, and the formation of elimination products severely competes with recombination of the allylic cation with the ionized acetate.

We subjected tertiary allylic acetate **2.77** to π-Lewis acids such as $PdCl_2(MeCN)_2$ and $PtCl_2$ at elevated temperatures, but these failed to effect the transposition of **2.77** to **2.78** (eq 2.11). Heating the mixture of acetates under Kornblum conditions with DMSO and base was unsuccessful in providing any of the transposed enone (**2.48**, eq 2.12), and attempting to perform a Ganem-type oxidation[50,51] by treating tertiary acetate **2.77** with *N*-methylmorpholine *N*-oxide (NMO) did not give any of the desired enone (**2.48**).



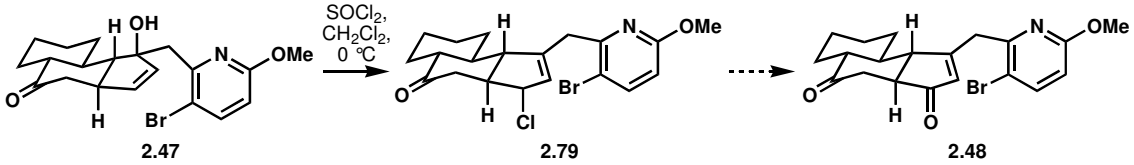
(2.11)



(2.12)

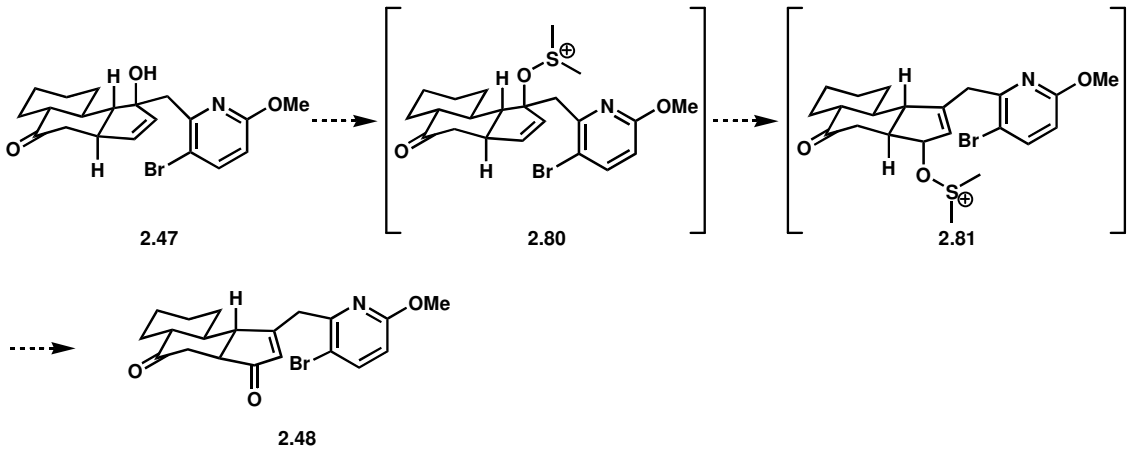
We were also able to prepare secondary allylic chloride **2.79** by treating alcohol **2.47** with thionyl chloride, but this product proved to be unstable and readily decomposed upon subjection to DMSO and $NaHCO_3$ in an attempt to conduct a Kornblum oxidation (see Scheme 2.31).

Scheme 2.31 Synthesis of allylic chloride and attempted Kornblum oxidation.



We considered subjecting alcohol **2.47** to Swern conditions in the presence of excess DMSO to determine if a molecule of DMSO might engage the activated tertiary hydroxyl group (i.e., **2.80** to **2.81**, Scheme 2.32) in a formal S_N2'-type fashion to effect the transposition. Addition of Et_3N could then lead to the decomposition of **2.81** to transposed enone **2.48**. Upon subjection of alcohol **2.47** to Swern conditions, however, a mixture of starting material and allylic chloride **2.79** were obtained as the major products.

Scheme 2.32 Potential activated DMSO-mediated oxidative allylic rearrangement.



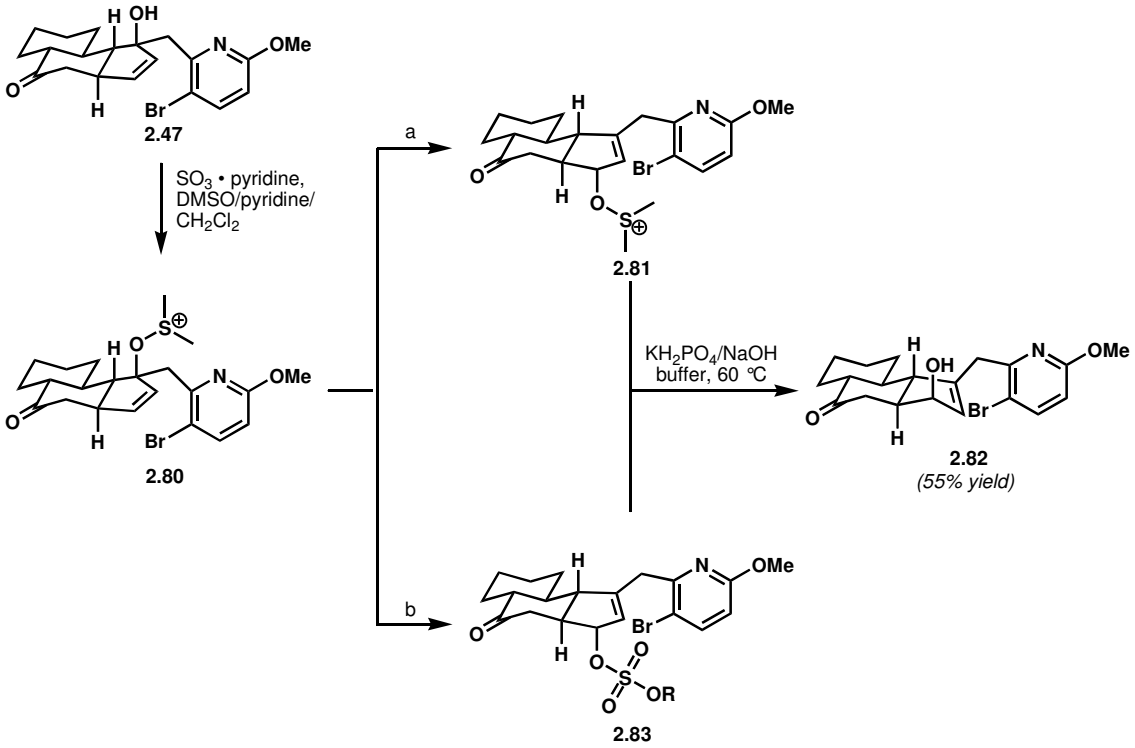
With the knowledge that in order to achieve the type of activated DMSO transformation described in Scheme 2.32 we would need conditions free of chloride ions, we next considered utilizing the Parikh-Doering modification[52] of the Swern reaction. Thus, we exposed tertiary alcohol **2.47** to the activated DMSO species generated according to the Parikh-Doering protocol by treating DMSO with SO_3•pyridine. In our initial attempt, contrary to the standard Parikh-Doering procedure, we waited to add Et_3N until TLC analysis indicated the complete consumption of starting alcohol. After adding Et_3N, however, we did not observe any of transposed enone **2.48**, but we did obtain a 16% yield of transposed alcohol **2.82**. The rest of the crude mass was comprised of elimination products.

Hydrolysis of SO_3•pyridine leads to significant amounts of H_2SO_4•pyridine and H_2SO_4•(pyridine)$_2$ in the commercial reagent, the former of which is relatively acidic and leads to undesired side reactions. Chen and coworkers at Pfizer have reported that adding additional pyridine to reagent grade SO_3•pyridine in DMSO will convert the acidic H_2SO_4•pyridine 1:1 salt to the inactive H_2SO_4•(pyridine)$_2$ 1:2 salt, thereby greatly diminishing acid-related side reactions.[53] We indeed found that by adding excess pyridine to SO_3•pyridine in DMSO prior to its exposure to alcohol **2.47** we could significantly reduce the proportion of elimination products in our reaction.

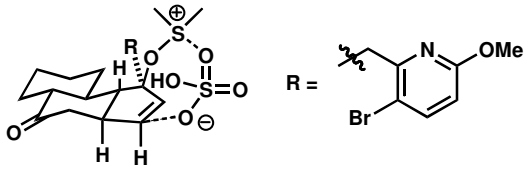
All attempts to directly access the transposed enone by quenching the presumed alkoxysulfonium intermediate (**2.80**, see Scheme 2.33) with bases such as Et_3N, *i*Pr_2EtN, DBU, $NaHCO_3$, NaOAc, NaOMe, or KO*t*-Bu, were unsuccessful. In addition, the salt formed upon recombination of the allylic cation with an oxygen species (e.g., DMSO, see **2.81**, Scheme 2.33) proved relatively resistant to hydrolysis to the corresponding alcohol **2.82**, which severely compromised yields of this desired product. Treatment of this salt with H_2O, MeOH, Et_2NH, *N*-hydroxysuccinimide, or NaSPh at room temperature gave only minimal conversion from the salt to the alcohol after extended reaction times. Quenching the reaction with either dilute aqueous

HCl or NaOH did effect the hydrolysis to the alcohol, but this was accompanied by significant amounts of byproducts and decomposition. Eventually we found that vigorously stirring the reaction mixture with a pH 7 KH_2PO_4/NaOH/EDTA aqueous buffer solution was the most efficient means for hydrolyzing the salt to the corresponding alcohol. On reaction scales greater than 30 mg, elevated temperatures (60 °C for 3 h) were required for the hydrolysis. Under these conditions, we could obtain a 55% yield of **2.82** on a 200 mg scale. The stereochemistry of the hydroxyl group was confirmed by X-ray analysis of a later intermediate (vide infra).

Scheme 2.33 Allylic alcohol transposition using modified Parikh-Doering conditions.



The exact nature of the intermediate salt formed is not known. We expect that initially, tertiary alkoxysulfonium intermediate **2.80** is formed, according to the accepted mechanism for activated DMSO reactions. At this point, **2.80** either ionizes to the allylic cation, which is intercepted at the less substituted position by an oxygen nucleophile or else undergoes an S_N2' with such a nucleophile. On the basis of the observation that the remainder of the mass balance of the 55% yield of transposed alcohol that is obtained may be attributed to elimination products, it is likely that an ionic pathway is predominant. Our initial proposal was that DMSO itself would act as the nucleophile (pathway a) to give alkoxysulfonium intermediate **2.81**. DMSO is known to trap carbocations to form alkoxysulfonium species, and the stability of this type of intermediate towards hydrolysis varies widely based on the substrate.[54] It is also possible that instead of nucleophilic DMSO, it is a sulfate species that attacks (pathway b), which would lead to intermediate **2.83**. In this case, an ion pair such as **2.84** (Figure 2.7) may be involved.



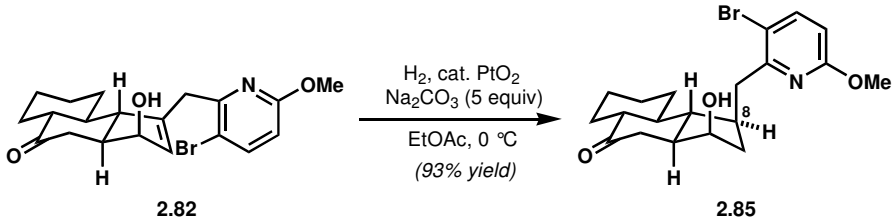
2.84

Figure 2.7 Alkoxysulfonium ion pair.

Though the actual identity of the transposed salt has not been investigated, there are a few ways we might go about studying it if its isolation is not possible. First, if the reaction were run in the presence of excess SO_3•pyridine, such that all of the DMSO had reacted with it to form the activated sulfonium salt, and the reaction still proceeded, this would be an indication that the sulfate ion was indeed a competent nucleophile (pathway b). Though, this would only hold true if the generation of the activated sulfonium salt is an irreversible or thermodynamically preferred process. Alternatively, if pathway a is viable, we may be able to observe alkoxysulfonium intermediates **2.80** or **2.81** by ^{1}H NMR if the reaction is run using CD_2Cl_2 and pyridine-d_5 or by ^{2}H NMR if DMSO-d_6 is used.

2.5 Hydrogenation of the Transposed Allylic Alcohol

With the allylic alcohol transposition achieved, we now needed to diastereoselectively reduce the cyclopentene double bond to set the appropriate stereochemistry at C-8. Substrate **2.82** (see eq 2.14) bears several functional groups that are susceptible to hydrogenation conditions. In addition to the desired reduction of the double bond, the aryl bromide and allylic alcohol are prone to hydrogenolysis and the carbonyl also may get reduced. Thus, the hydrogenation conditions needed to be carefully selected.

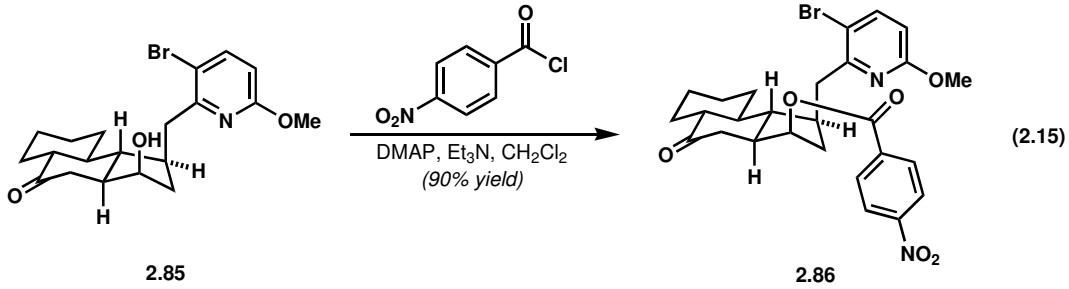


2.82 2.85

(2.14)

Pd/C proved to be a very unselective hydrogenation catalyst and provided a mixture of reduced products including large amounts of hydrogenolyzed desbromo compound. The aryl bromide could be preserved by switching from palladium to platinum catalysts such as Pt/C and PtO_2; however, hydrogenolysis of the allylic alcohol was still a significant issue. We found that the combination of Adams' catalyst (PtO_2) and Na_2CO_3 under a hydrogen atmosphere in EtOAc selectively reduced the double bond to give **2.85** in 93% yield. The hydrogenation took place with good diastereocontrol (95:5 dr) when performed at 0 °C. Reduction of the ketone carbonyl under these conditions was only observed if the reaction time was extended beyond that needed to reduce the double bond.

Conversion of **2.85** to its *para*-nitrobenzoate ester (**2.86** eq 2.8) provided X-ray quality crystals which allowed for the confirmation that the hydrogenation took place as required on the alpha face of the molecule, correctly setting the C-8 stereocenter (see Figure 2.8).



2.85 2.86 (2.15)

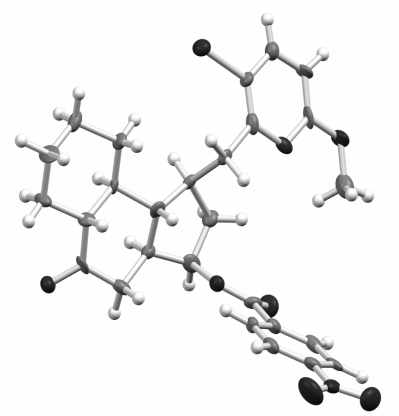
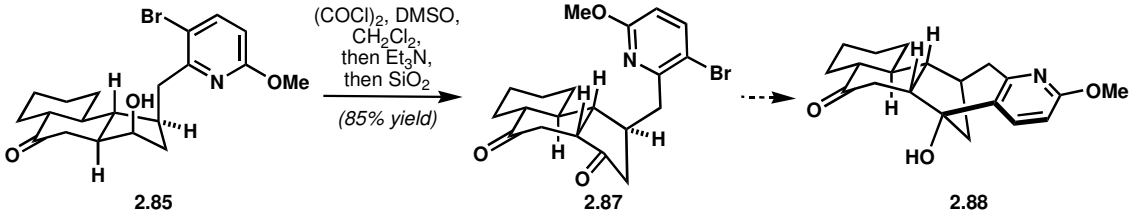


Figure 2.8 ORTEP representation of nitrobenzoate **2.86**.

2.6 Strategies Toward the 1,2-Carbonyl Addition of a Pyridinyl Bromide

Oxidation of alcohol **2.85** to ketone **2.87** in preparation for the 1,2-addition of the pyridinyl bromide into the carbonyl was accomplished using standard Swern conditions[55] followed by epimerization to the thermodynamically favored cis [6-5] ring fusion (Scheme 2.34).

Scheme 2.34 Preparation for pentacyclic formation.



2.85 2.87 2.88

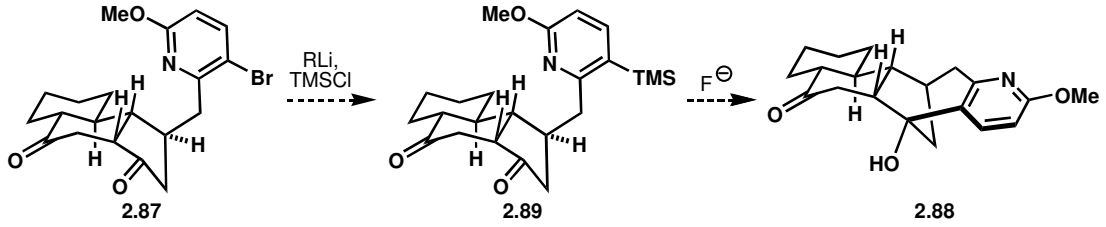
The formation of pentacycle **2.88** from aryl bromide **2.87** presents the challenge of generating a nucleophilic aryl species at the 3-position of the pyridine ring in the presence of a ketone with alpha-protons. Thus, typical methods of halogen/metal exchange for the generation of aryl anions would likely prove difficult to use on the given system.

One of the most direct method for achieving halogen/metal exchange is the use of organolithium reagents to generate lithium anions. Halogen/lithium exchange takes place at temperatures of -78 °C or below using reagents such as *n*-BuLi and *t*-BuLi. However, these reagents readily alkylate ketones at these temperatures as well. In addition, if we were in fact able to selectively generate the desired aryl lithium species on our substrate by halogen/lithium exchange without the organolithium reagent adding into the ketone, the high basicity of the lithium anion may preferentially deprotonate alpha to the carbonyl of **2.87** rather than adding into it. Direct deprotonation of non-activated pyridine rings using alkyllithium reagents is not favorable at low temperature and thus did not pose a significant threat to our low temperature attempts.

We decided to begin our halogen/lithium exchange studies using *t*-BuLi because of its steric encumbrance, which we hoped would favor halogen exchange over alkylation or deprotonation. Upon subjecting aryl bromide **2.87** to two equivalents of *t*-BuLi, we obtained a mixture of three major products, all of which had been alkylated either once or twice by the butyl anion and all of which were debrominated. It is likely that the rate of butyl alkylation was at least competitive with that of the halogen/lithium exchange since the second equivalent of *t*-BuLi otherwise would have been consumed by the *t*-BuBr that was generated.

Treatment of **2.87** with *n*-BuLi or PhLi returned mainly starting material in addition to minor byproducts, indicating that deprotonation by the reagent alpha to the carbonyls was predominating and forming unproductive enolates of the starting material. We reasoned that if we could first deprotonate the carbonyls and then generate and trap the aryl anion with a trimethylsilyl group, we may be able to utilize the resulting substrate **2.89** (see Scheme 2.35). Treatment of trimethylsilyl derivative **2.89** with a fluoride source should selectively generate an anion at the 3-position of the pyridine that may be able to add into the carbonyl. Although an attempt to generate TMS-pyridine **2.89** by treating bromide **2.87** with two equivalents of mesityl lithium followed by one equivalent of *n*-BuLi[56] did provide some of the desbromo starting material, the aryl anion intermediate failed to trap the trimethylsilyl group.

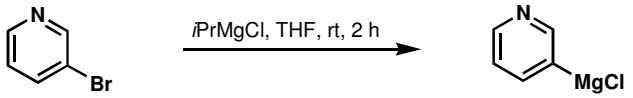
Scheme 2.35 Aryltrimethylsilyl approach to pentacyle.



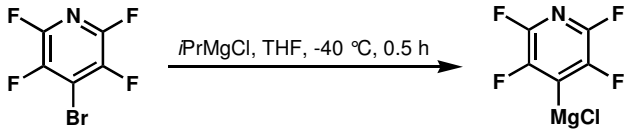
2.87 2.89 2.88

We turned next to halogen/magnesium exchange. We expected that the substantially diminished basicity of organomagnesium reagents compared to organolithium reagents would favor addition of a pyridinyl Grignard into the proximal carbonyl over alpha deprotonation of that carbonyl. However, formation of the pyridinyl Grignard was the first obstacle. The use of *i*PrMgCl and *i*PrMgCl•LiCl[57] to effect halogen/magnesium exchange on pyridinyl halides has been studied by the groups of Quéguiner[58-60] and Knochel.[58,61,62] Because it does not possess electron-withdrawing substituents, 3-bromopyridine requires ambient temperature for bromo/magnesium exchange to take place using *i*PrMgCl (eq 2.16).[59] Introducing electron-withdrawing substituents on the pyridine ring (eqs 2.17 and 2.18) enables the exchange to take place at lower temperature (-30 to -40 °C).[61,62] Yet, the product distribution observed in eq 2.18

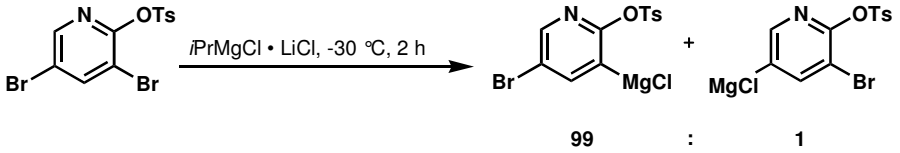
emphasizes the importance of the inductive effects of the electron-withdrawing substituents on the rate of the magnesium exchange. The bromide ortho to the tosylate undergoes exchange at a rate two orders of magnitude higher than the bromide para to the tosyl group. At the temperature required to induce bromide/magnesium exchange on our substrate (**2.87**) or on an accessible, more electronically favorable derivative, the *i*PrMgCl reagent would presumably not be compatible with the ketone carbonyl of the substrate.



(2.16)



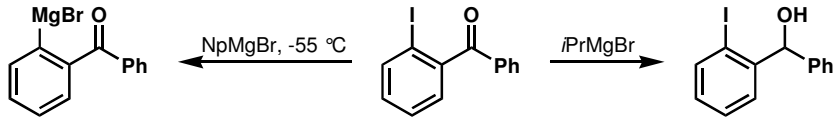
(2.17)



(2.18)

Knochel has attempted to address the issue of preparing aryl and heteroaryl magnesium compounds bearing keto groups.[63] Whereas iodophenyl ketone **2.90** (Scheme 2.36) undergoes reduction via hydride transfer when treated with *i*PrMgBr, the ketone carbonyl is tolerant of the reagent *neo*-pentylmagnesium bromide and undergoes magnesium exchange at -55 °C. This technology, documented only for *electron-deficient* phenyl, furan, and thiophenyl *iodides*, is still not general enough to be applied to our system.

Scheme 2.36 Compatibility of keto groups with NpMgBr and *i*PrMgBr.



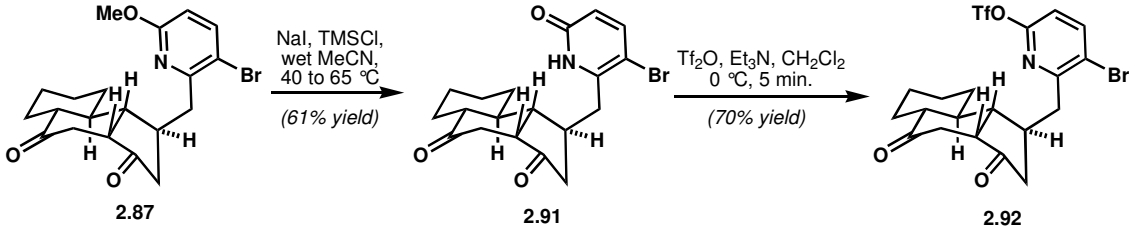
2.90

Because of the functional group incompatibility of our substrate with *i*PrMgCl-type reagents, we decided to attempt direct Grignard formation using magnesium metal. Subjecting pyridinyl bromide **2.87** to magnesium, which had been activated by stirring under an inert atmosphere, with either Br_2, LiCl, or LiCl and catalytic diisobutylaluminum hydride (DIBALH) in THF at reflux returned only starting material. Knochel has reported that the use of LiCl facilitates the synthesis of aryl magnesium and zinc reagents by helping to solubilize the organomagnesium reagent as it forms, thus revealing a clean metal surface, activating the aryl ring to promote electron transfer, and stabilizing charge separation which aids in the metal insertion.[64] DIBALH has been shown to effectively activate magnesium by reacting with water, alcohols, and peroxides and activating the metal surface.[65]

In order to use the most active magnesium source possible, we next turned to Rieke magnesium, a highly reactive magnesium powder generated by the alkali-metal reduction of $MgCl_2$.[66,67] Exposure of **2.87** to Rieke magnesium in THF under an argon atmosphere at up to 70 °C led to no reaction. Increasing the temperature to 80 °C in a sealed tube, however, yielded a product with the bromide intact, but which had incorporated a butyl ether. Presumably, the Rieke magnesium inserted into the THF, and this species interacted with the substrate. Oxidative addition of Rieke magnesium into THF has been observed previously.[68]

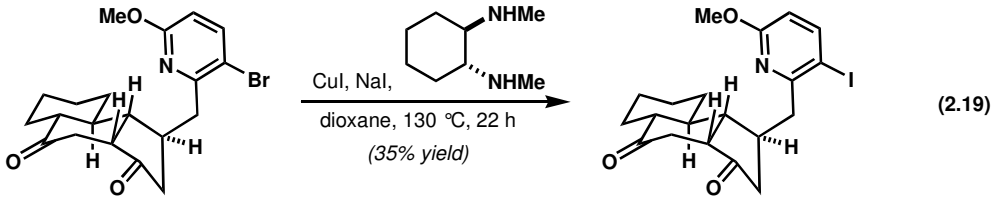
We thought that we might be able to facilitate Grignard formation by derivatizing the pyridine on our substrate. Hence, we converted the methoxy group of **2.87** at the 2-position of the pyridine ring to an electron-withdrawing triflate group as shown in Scheme 2.37. The methyl ether was cleaved using NaI/TMSCl to expose the pyridone **2.91** in 61% yield, and subsequent triflation then provided triflate **2.92**. However, exposure of **2.92** to Rieke magnesium at 70 °C led to the recovery of starting material.

Scheme 2.37 Preparation of a pyridinyl triflate.



2.87 **2.91** **2.92**

Because aryl iodides undergo magnesium insertion more readily than aryl bromides, we sought to make the iodinated version of **2.87**. To this end, we used Buchwald's aromatic Finkelstein protocol.[69] This copper-catalyzed reaction is an equilibrium reaction that is dependent on the solubility differences of the sodium salts. We were able to obtain up to a 10:1 mixture of aryl iodide (**2.93**) to aryl bromide (**2.87**) compounds using this method (eq 2.19). Subjection of pyridinyl iodide **2.93** to Rieke magnesium in refluxing THF, though, failed to generate the desired Grignard.

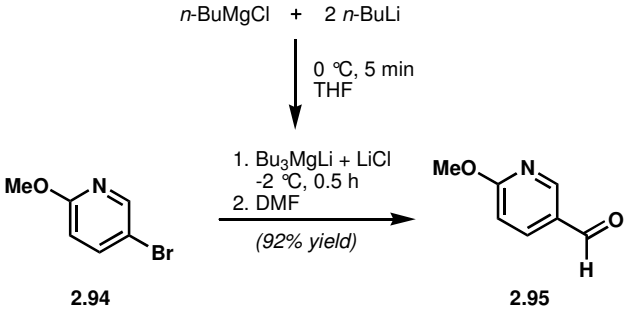


2.87 **2.93**
10:1 iodide/bromide

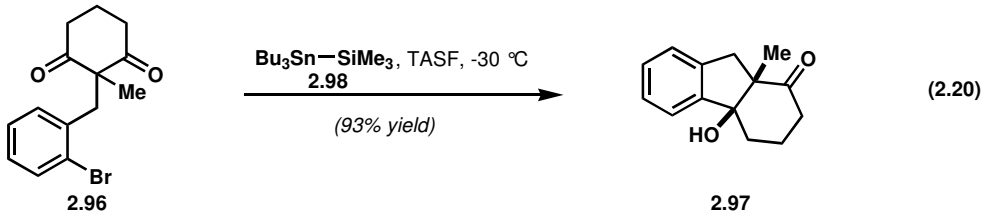
(2.19)

Oshima and coworkers have developed a halogen/magnesium exchange reaction that is not limited to electron-deficient aryl halides.[70,71] Using R_3MgLi reagents electron-rich aryl iodides and bromides, including 5-bromo-2-methoxy pyridine **2.94** (Scheme 2.38), can be readily converted to their corresponding magnesium-ate complexes and then trapped with electrophiles (see **2.95**). However, the R groups of the R_3MgLi magnesium-ate complexes are nucleophilic, and even though esters and nitriles are compatible with this methodology, Oshima et al. have not reported ketone-containing substrates.

Scheme 2.38 Magnesium-ate complexes.



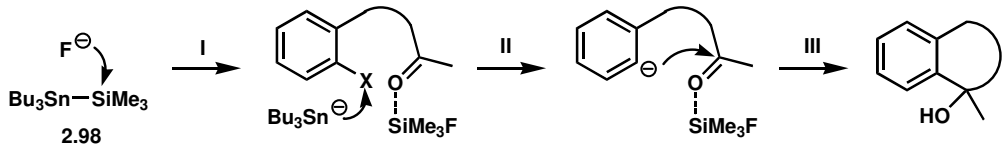
Given the difficulties of performing a halogen/metal exchange in the presence of a keto-carbonyl, a protocol that was developed by Mori and Shibasaki[72-74] that uses a stannyl anion to generate aryl and vinyl anions, which may then react intramolecularly with carbonyls (e.g., **2.96** to **2.97**, eq 2.20), seemed promising.



(2.20)

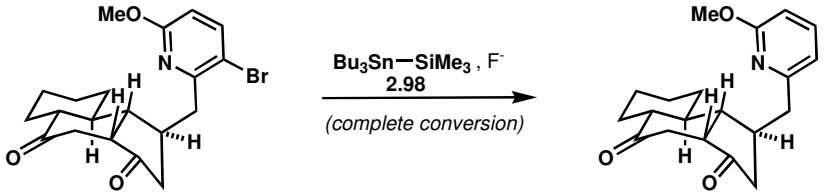
This methodology utilizes the bismetallic reagent $Bu_3SnSiMe_3$ (**2.98**) in combination with a fluoride source to produce Bu_3Sn^- (see I, Scheme 2.39). This stannyl anion then nucleophilically attacks the aryl halide to generate an aryl anion (see II). The carbonyl, presumably activated by the Me_3SiF is attacked by the aryl anion to form the cyclized product (see III).[72] Importantly, the carbonyl group is tolerant of the stannyl anion and reacts preferentially with the generated aryl anion.

Scheme 2.39 Cyclization via stannyl anion mechanism.



Mori, Shibasaki, and coworkers have shown that this process may be applied to both aryl and vinyl iodides as well as aryl bromides. The reacting carbonyl partner may be a ketone, ester, or aldehyde. While many of their substrates possess acidic protons alpha to their carbonyl groups, they report only examples in which five-membered rings are formed, and five-membered cyclizations should be kinetically more favorable than the six-membered ring bicycle formation that is desired in our case. Mori and Shibasaki's group also commonly observed conjugate addition of Bu_3Sn^- into α,β-unsaturated carbonyl groups but never any 1,2-addition. They did report seeing dehalogenation products with some substrates, and they generally attributed this to trace amounts of water in solvent (e.g., DMF) or reagent (e.g., TBAF).

We found that by subjecting substrate **2.87** to Bu_3Sn-$SiMe_3$ in the presence of a fluoride source, we were routinely able to obtain the desbromo compound **2.99**. This represented the first time that we were able to cleanly generate the aryl anion; however, the anion failed to add into the carbonyl as desired. Use of solvents free of trace amounts of water was found to be essential for generating a persistent aryl anion. We found that the temperature at which the anion formed was highly dependent on both fluoride source and solvent. Using CsF in NMP (Acros <50 ppm H_2O), the halogen/metal exchange takes place readily at room temperature, while in THF it does not begin until around 40 °C, and in toluene, temperatures of 80 °C or above are required. The reagent Bu_4N^+ $Ph_3SiF_2^-$ is much more active, facilitating Bu_3Sn^- formation at -78 °C in THF.



2.87 2.99 (2.21)

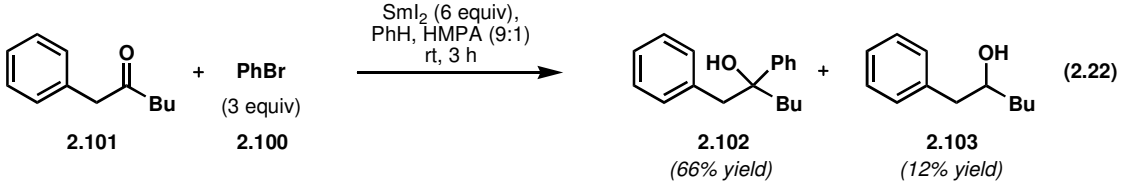
Table 2.2 Attempted stannyl anion-mediated cyclization D_2O-quenching studies.

Entry	Conditions	Results
1	**2.98**, CsF, THF, 50 °C, 3 h then D_2O quench	66% aryl deuteration of **2.99**
2	**2.98**, CsF, THF, 70 °C, 3 h then D_2O quench	minimal aryl deuteration of **2.99**
3	**2.98**, CsF, $CeCl_3$, THF, 50 °C, 3 h then D_2O quench	starting material **2.87** recovered
4	**2.98**, CsF, $MgCl_2$, THF, 60 °C, 3 h then D_2O quench	starting material **2.87** recovered
5	**2.98**, CsF, NMP, rt, 1 h then D_2O quench	deuteration of **2.99** at two separate sites α to a carbonyl (41% and 44%)
6	**2.98**, Bu_4N^+ $Ph_3SiF_2^-$, THF, -78 °C, 45 min. then D_2O quench	64% aryl deuteration and 30% α to carbonyl deuteration of **2.99**
7	**2.98**, Bu_4N^+ $Ph_3SiF_2^-$, THF, rt, 1 h, then D_2O quench	deuteration of **2.99** exclusively α to carbonyl

Table 2.2 show the results observed upon quenching the stannyl anion reaction with D_2O. Using CsF as the fluoride source, the aryl anion persists in the reaction mixture at 50 °C, as evidenced by a 66% deuterium incorporation on the aryl ring upon the addition of D_2O (entry 1). However, increasing the temperature to 70 °C in an attempt to facilitate cyclization led to only protonation of the aryl anion (entry 2). Use of Lewis acids such as $CeCl_3$ or $MgCl_2$ in the reaction mixture inhibited anion generation, leading to the recovery of starting material (entries 3 and 4). In NMP, using CsF, the aryl anion did not persist very long in the presence of the acidic α-protons and deuterium incorporation was observed exclusively at two separate sites α to a carbonyl (entry 5). Using the fluoride source Bu_4N^+ $Ph_3SiF_2^-$, the aryl anion persisted long enough for 64% of it to be trapped by D_2O at -78 °C (entry 6) though at room temperature, deuterium was observed only α to a carbonyl (entry 7).

Tani and coworkers have reported a SmI_2-mediated intermolecular reaction of aryl halides (e.g., **100**, eq 22) with ketones (e.g., **101**).[75] This reaction must be conducted in benzene/HMPA rather than THF as aryl radicals are known to abstract a hydrogen atom from THF faster than they will react with ketones.[76] The researchers found that using bromobenzene

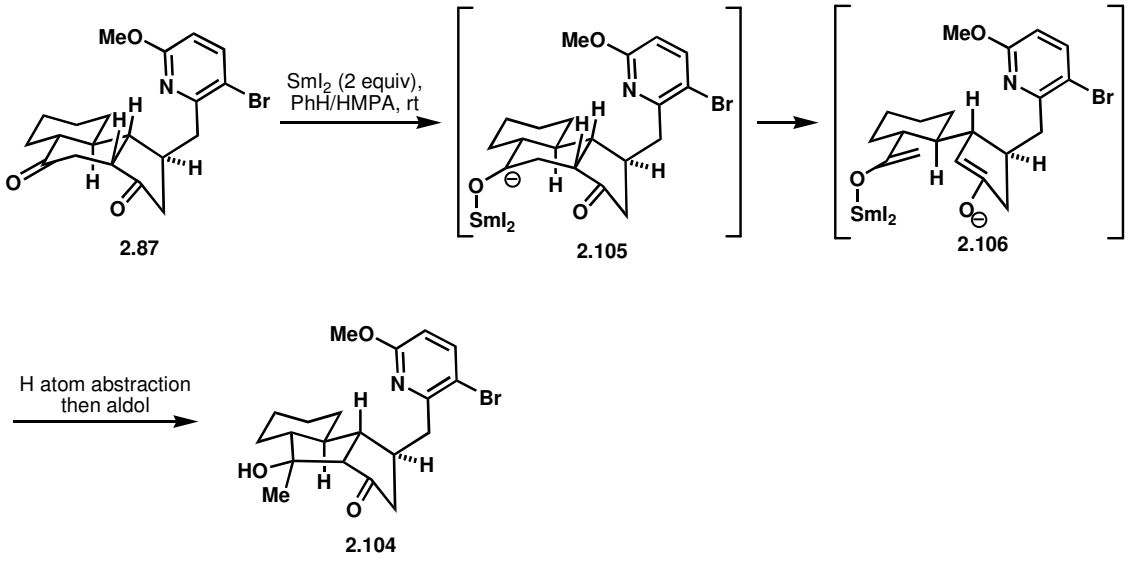
(**2.100**) as the aryl halide provided a 66% yield of tertiary alcohol **2.102** in addition to 12% of the reduced product **2.103**. Iodobenzene provided a higher yield of alcohol **2.102** (74%) without the formation of the reduced byproduct (**2.103**).



(2.22)

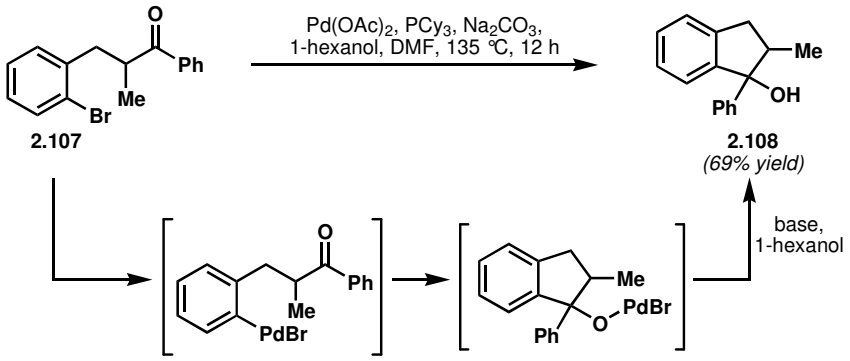
Upon subjecting substrate **2.87** (Scheme 2.40) to 2 equivalents of samarium(II) iodide, we saw no aryl/carbonyl coupling product, but instead observed the production of two isomeric ring contracted products, likely diastereomers of **2.104**. The formation of these two compounds indicates that one of the carbonyl groups is reduced faster than the pyridinyl bromide. A possible mechanism, which proceeds through the fragmentation of organo-samarium species **2.105**, followed by hydrogen abstraction and intramolecular aldol addition of **2.106** to give **2.104** is outlined in Scheme 2.40.

Scheme 2.40 SmI_2-mediated ring contraction.

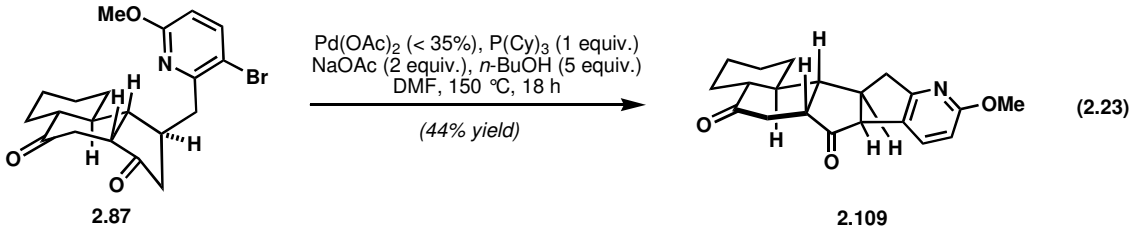


Yamamoto and coworkers have shown that intramolecular cyclizations of aryl halides into ketone carbonyls can be effected under Pd(0) catalysis, using $Pd(OAc)_2$ in conjunction with an aliphatic phosphine ligand, base, and aliphatic alcohol (e.g., **2.107** to **2.108**, Scheme 2.41).[77] Both 5- and 6-membered ring products are prepared in this report, though the six-membered ring forming reactions take place in somewhat diminished yields. All of Yamamoto's substrates have at least one substituent α to the ketone on the internal position, and the reaction generally proceeds in higher yield with increasing steric demand. The only byproducts reported were dehalogenated starting ketone.

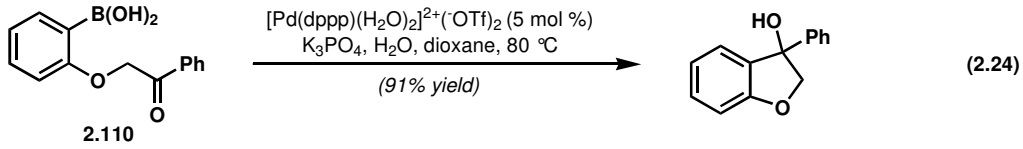
Scheme 2.41 Yamamoto's palladium-catalyzed addition of aryl halides to ketones.



When we subjected pyridinyl bromide **2.87** to the Yamamoto conditions, we observed none of the desired cyclization product but instead a 44% yield of α-arylation product **2.109** (see eq 2.23).

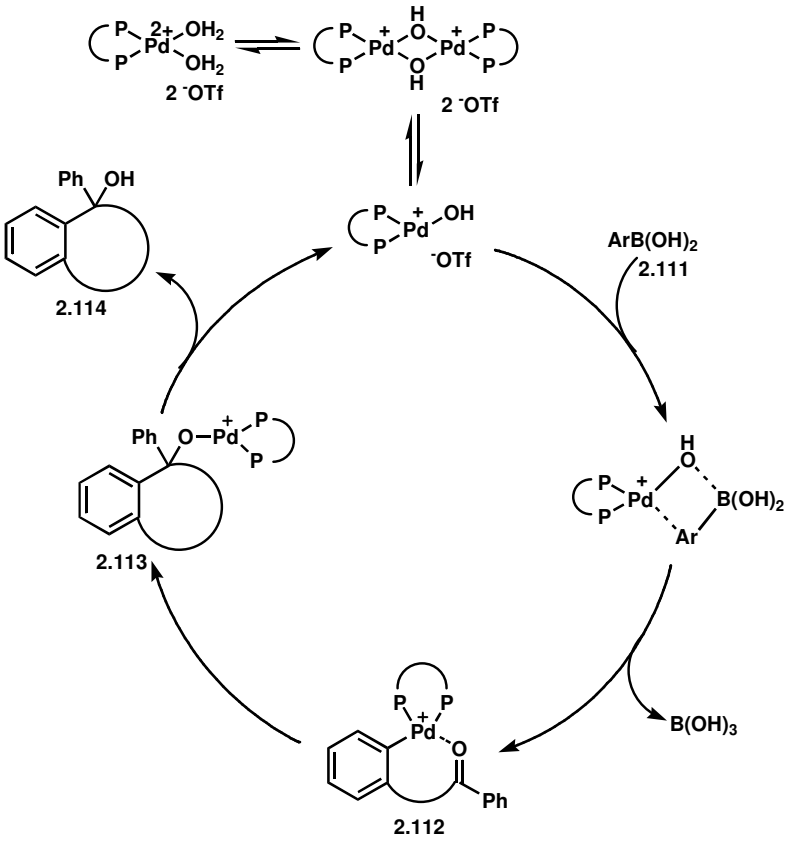


Liu and Lu have developed a method for the addition of aryl boronic acids intramolecularly into ketone carbonyls (see eq 2.24).[78,79] Their protocol utilizes cationic Pd(II) to effect this transformation because it offers certain advantages over neutral Pd(II), including its vacant coordination site and stronger Lewis acidity. The group did find, though, that Pd(II) could also be used in select phenyl boronic acid substrates that possess a neighboring oxygen on the aryl ring (e.g., **2.110**).



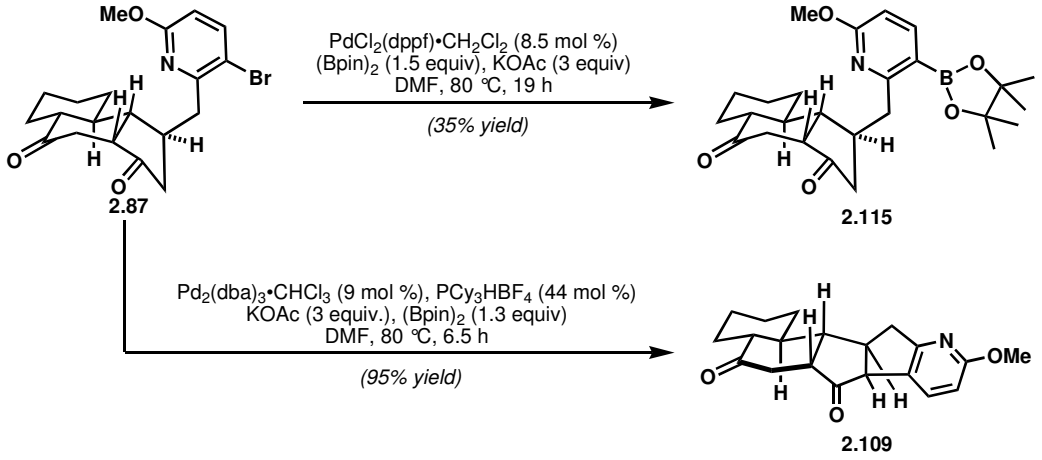
The catalytic cycle for the cationic Pd(II)-cyclization is delineated in Scheme 2.42. The aryl group of **2.111** is transmetalated to palladium source **2.112** aided by the both the cationic nature of the palladium and the metal's hydroxo ligand.[80] Following transmetallation, the Lewis acidic palladium center in **2.112** may activate the carbonyl through its open coordination site, leading to the 1,2 addition that gives **2.113**. Hydrolysis then provides tertiary alcohol **2.114** and regenerates the hydroxo palladium species.

Scheme 2.42 Proposed catalytic cycle for Liu and Lu's $[Pd(II)]^+$-catalyzed cyclization.



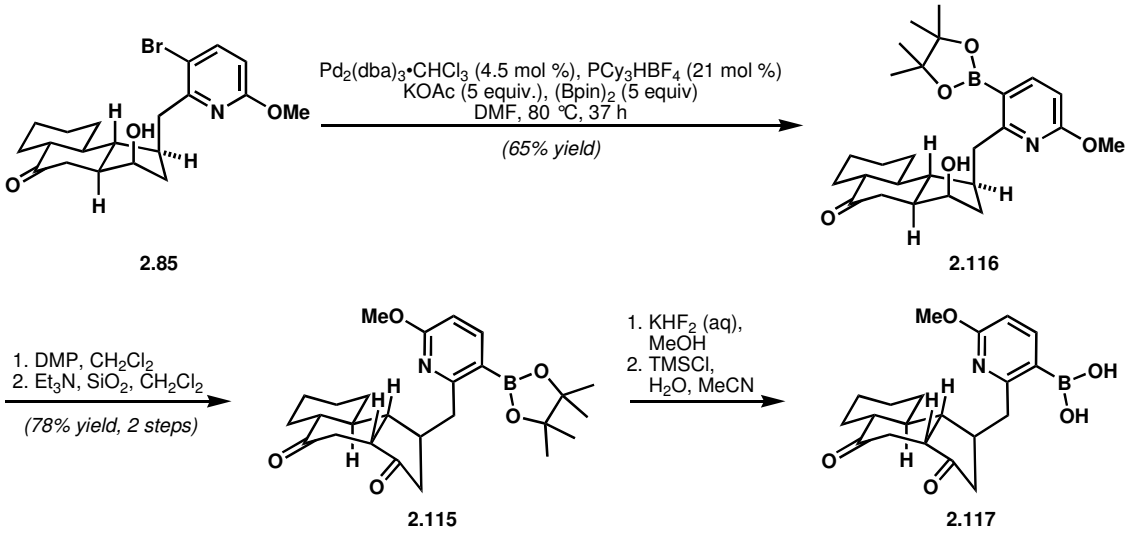
To prepare the aryl boronic acid necessary to attempt Lu's cationic palladium method, we first subjected ketone **2.87** to Miyaura borylation conditions ($PdCl_2(dppf)•CH_2Cl_2$, $(Bpin)_2$, KOAc, see Scheme 2.43)[81] in DMF rather than DMSO (which yielded a sluggish reaction). A low yield (35%) of boronic ester **2.115** was obtained, however, so modified Miyaura conditions[82] using $Pd(dba)_3/PCy_3$ that had been developed for aryl chloride and electron-rich aryl bromide and triflate substrates were employed using the relatively air stable catalyst system $Pd_2(dba)_3/PCy_3HBF_4$ (Scheme 2.43). These conditions, however, gave the undesired α-arylation product **2.109** in excellent yield.

Scheme 2.43 Utilization of Miyaura borylation conditions.



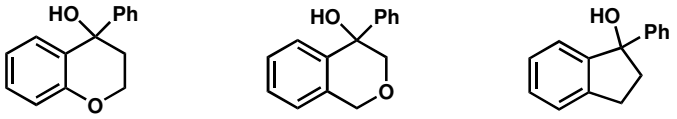
We were able to circumvent these issues associated with borylation by performing the cross coupling on alcohol substrate **2.85** (Scheme 2.44) and obtained the desired pinacol boronate ester **2.116** in 65% yield. Commonly, presumed ligand exchange on the boron of the secondary hydroxyl group of **2.116** for one of the pinacol hydroxyl groups was observed, yet this compound reverted to the pinacol borate upon exposure to silica column chromatography. Dess-Martin oxidation of alcohol **2.116** was followed by epimerization at the [6,5] ring fusion to the thermodynamically favored diastereomer **2.115**. The boronic acid, needed as prescribed by Lu's cationic palladium protocol, could be generated in a two step sequence by treatment of pinacol boronate ester **2.115** with KHF_2 to convert the substrate to the corresponding potassium aryl trifluoroborate and then exposure of this salt to $TMSCl/H_2O$ to hydrolyze it to the boronic acid (**2.117**).

Scheme 2.44 Synthesis of boronic acid substrate.



Upon subjecting pyridinyl boronic acid **2.117** to $[Pd(dppp)(H_2O)_2]^{2+}(^{-}OTf)_2$[83,84] according to the procedure of Lu, no 1,2-addition was observed and instead the deborylated compound

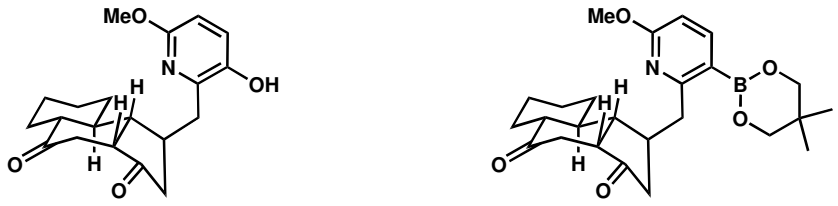
was recovered as the major product. Our substrate is not a trivial one for this chemistry. The reports by Lu and Liu detailing the scope of their cationic palladium intramolecular ketone addition include only two examples of six-membered ring formation (**2.118** and **2.119**, Figure 2.9), and both of the substrates for these cyclization products possess a neighboring oxygen that can coordinate to the palladium and direct the 1,2-addition by disfavoring protonolysis. The group also reports only one successful cyclization product (**2.120**) that lacks an ether-linked ketone carbonyl, and it is a kinetically favorable five-membered ring that is formed in this case.



2.118 *(88% yield)* **2.119** *(82% yield)* **2.120** *(83% yield)*

Figure 2.9 Products of Lu's cationic palladium cyclization.

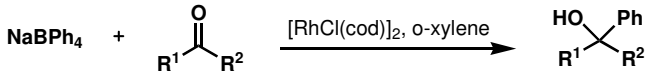
With facile access to pinacol boronic ester **2.115**, we also considered subjecting it to trifluoroacetic acid (TFA), similar to work done by Schaus.[85] It was anticipated that the trifluoroacetate ion would displace one of the pinacol hydroxyl ligands on the boron to generate a more electron deficient borate that could activate the carbonyl and deliver the aryl group to it. However, treatment of **2.115** with TFA only oxidized the substrate to the corresponding hydroxyl pyridine **2.121**, presumably due to the presence of trace oxygen. Use of neopentyl glycolato borate **2.122** (prepared analogously to pinacolato borate **2.115**) similarly led to only hydroxyl pyridine **2.121**. Furthermore, the glycolato borate substrate was unstable to silica gel chromatography. Hydroxy pyridine **2.121** was also obtained upon treatment of aryl boronic ester/alcohol **2.116** with IBX.



2.121 **2.122**

2.7 Achieving the 1,2-Carbonyl Addition of a Pyridinyl Boronic Ester

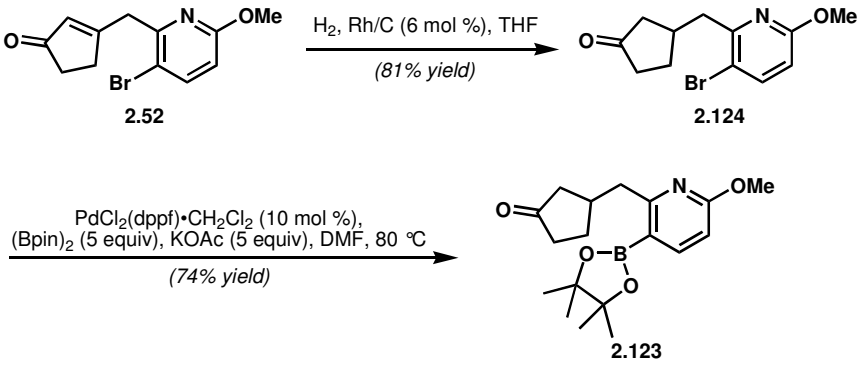
Because of our unsuccessful attempts to use cationic palladium to catalyze the desired intramolecular aryl boron addition to the ketone, we began to consider the possibility of using rhodium(I) to effect this transformation. Aryl rhodium(I) species are typically more nucleophilic than are aryl palladium species, which are more commonly utilized in electrophilic reactions. However, though aryl boron compounds have been used in rhodium-catalyzed reactions to effect additions into aldehydes and aldimines[86] and, more recently, activated ketones,[87-90] there were previously no reports of the addition of an aryl boronic acid, ester, or trifluoroborate into an unactivated ketone. An isolated example which uses sodium tetraphenylborate to effect a rhodium-catalyzed phenylation of unactivated ketones has been reported by Miura (see eq 25).[91]



(2.25)

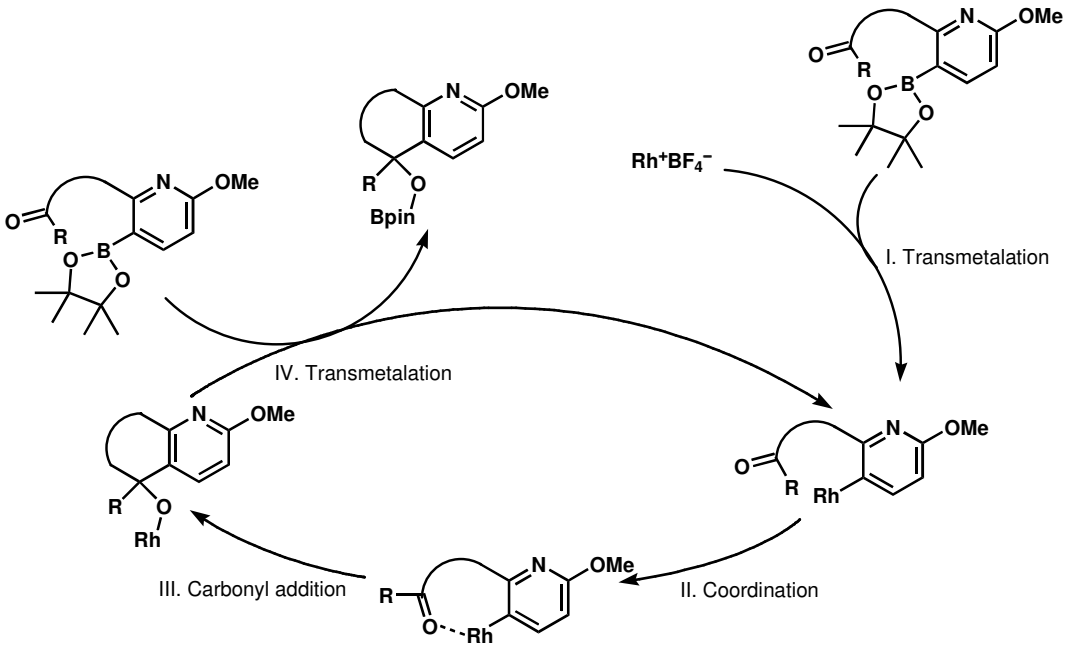
To investigate the feasibility of performing a rhodium(I)-catalyzed arylation of a pyridinyl boron species into a ketone carbonyl, we prepared model system **2.123** (Scheme 2.45). The double bond of enone **2.52** could be selectively hydrogenated using Rh/C in good yield. Miyaura borylation of aryl bromide **2.124** using $PdCl_2$(dppf) as catalyst then provided pinacol boronate **2.123**.

Scheme 2.45 Preparation of boronic ester model substrate.



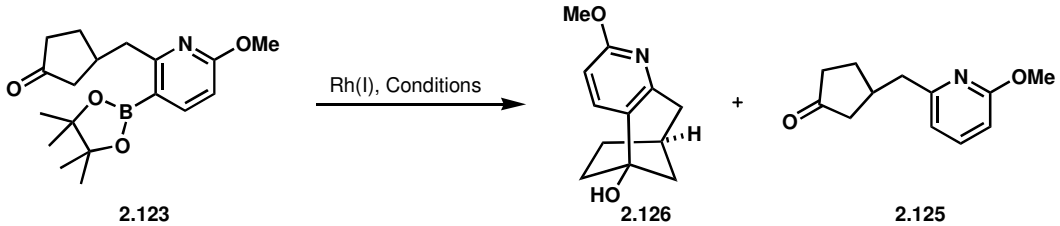
We began our rhodium(I)-catalyzed cyclization studies using $[Rh(cod)(OH)]_2$ with dppbenz in DMF/H_2O (entry 1, Table 2.3) but obtained predominately deborylated starting material **2.125**. Thus, we decided to switch to the more active catalyst $[Rh(cod)(MeCN)_2]^+BF_4^-$, whose cationic nature may help facilitate transmetalation of the aryl boronic ester to the rhodium (see I, Scheme 2.46).

Scheme 2.46 Plausible mechanism for rhodium(I)-catalyzed ketone hydroarylation.



We found that $[Rh(cod)(MeCN)_2]^+BF_4^-$ was indeed able to effect the desired 1,2-ketone addition to give model tricycle **2.126** (see Table 2.3). A solvent and temperature screen revealed that highly coordinating solvents seemed to impede the performance of the catalyst. Use of DMF provided no product formation (entry 8), and dioxane proved to be a very inefficient solvent (entries 6 – 7). While THF and toluene allowed the reaction to proceed sluggishly at 80 °C (entries 3 – 5 and 9 – 10), THF appeared to destroy the activity of the catalyst at 100 °C (entry 11). Our optimal conditions (toluene at 100 °C, entry 12) provided a better than 4:1 ratio of tricycle **2.126** to deborylated starting material **2.125**.

Table 2.3 Rhodium-catalyzed cyclization model system studies.

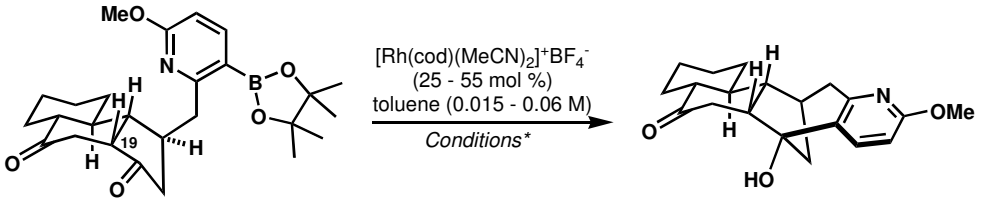


2.123 2.126 2.125

Entry	Catalyst (loading)	Solvent	Temperature	Time	Ratio 2.123 : 2.126 : 2.125
1	$[Rh(cod)(OH)]_2$ (15 mol %), dppbenz (15 mol %) with K_3PO_4	DMF/H_2O (5:1)	100 °C	6 h	0 : 5 : 95
2	$[Rh(cod)(MeCN)_2]^+ BF_4^-$ (~15 mol %)	THF	60 °C	22 h	88 : 8 : 4
3	$[Rh(cod)(MeCN)_2]^+ BF_4^-$ (~15 mol %)	THF	80 °C	22 h	60 : 22 : 19
4	$[Rh(cod)(MeCN)_2]^+ BF_4^-$ (16 mol %)	toluene	80 °C	22 h	83 : 14 : 3
5	$[Rh(cod)(MeCN)_2]^+ BF_4^-$ (16 mol %)	toluene	80 °C	91 h	25 : 57 : 17
6	$[Rh(cod)(MeCN)_2]^+ BF_4^-$ (13 mol %)	dioxane	80 °C	22 h	82 : 11 : 7
7	$[Rh(cod)(MeCN)_2]^+ BF_4^-$ (13 mol %)	dioxane	80 °C	91 h	56 : 18 : 26
8	$[Rh(cod)(MeCN)_2]^+ BF_4^-$ (9 mol %)	DMF	80 °C	22 h	89 : 0 : 11
9	$[Rh(cod)(MeCN)_2]^+ BF_4^-$ (49 mol %)	THF	80 °C	16 h	50 : 42 : 8
10	$[Rh(cod)(MeCN)_2]^+ BF_4^-$ (49 mol %)	THF	80 °C	44 h	32 : 56 : 11
11	$[Rh(cod)(MeCN)_2]^+ BF_4^-$ (25-30 mol %)	THF	100 °C	25 h	100 : 0 : 0
12	*$[Rh(cod)(MeCN)_2]^+ BF_4^-$ (~15 mol %)*	*toluene*	*100 °C*	*24 h*	*0 : 82 : 18*

Upon subjecting our actual system, **2.115**, to the conditions found to be optimal for our model system at 100 °C, we observed no reaction. By increasing the reaction temperature to 120 °C, though, we did observe formation of our desired pentacycle **2.127**; however, significant amounts of protodeborylation thwarted the reaction yield (Table 2.4, entry 2). Diluting the reaction mixture to 0.008 M in toluene did decrease the amount of protodeborylation (entry 3). Adding H_2O to the reaction mixture also increased the relative ratio of pentacycle **2.127** to deborylated starting material (entry 4). Additionally, in the absence of water, the reaction did not reach complete conversion within 24 hours whereas in the presence of water, all of the starting material was consumed in less than 9 hours. The key finding was that the addition of 2 equivalents of triethylamine to the reaction mixture both greatly reduced the reaction time (to less than 2 h at 120 °C, entry 5) and effectively suppressed protodeborylation to provide the 1,2-addition product in a 10:1 ratio with the deborylated starting material. Furthermore, the reaction proceeded at temperatures as low as 60 °C (entry 8).

Table 2.4 Rhodium-catalyzed pentacycle formation.

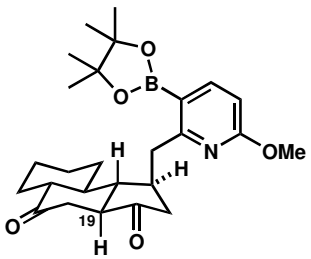


2.115 **2.127**

Entry	*Conditions	Time to complete conversion	2.127:deborylated SM	Yield
1	110 °C	No reaction	N/A	N/A
2	120 °C	> 24 h	2:1 to 3:2	N/A
3	120 °C and 0.008 M toluene	> 24 h	~5:1	~60%
4	120 °C and 50 equiv H_2O	< 9 h	~5:1	~45%
5	120 °C and 2 equiv Et_3N	< 2 h	>10:1	N/A
6	100 °C and 2 equiv Et_3N	< 4.5 h	>10:1	N/A
7	80 °C and 2 equiv Et_3N	~90% conversion at 3 h	>10:1	N/A
8	60 °C and 2 equiv Et_3N	~90% conversion at 18 h	>10:1	N/A

We were able to obtain a 77% yield of pentacycle **2.127** using 25 mol % $[Rh(cod)(MeCN)_2]^+BF_4^-$ and 2 equivalents of triethylamine at 80 °C in toluene. The catalyst loading could be lowered to at least 8 mol % rhodium to still obtain a 71% yield of the desired product. Beneficial effects of triethylamine in rhodium(I)-catalyzed reactions have been observed before.[92-96] Generally, these reaction-temperature lowering and rate increasing effects are attributed to triethylamine's ability to facilitate the boron/rhodium transmetalation step, and Corey has proposed that the Et_3N displaces a ligand on the rhodium center (e.g., OH) to form a more electrophilic rhodium complex.[95] Batey has postulated that the addition of Et_3N prevents protonation of the aryl-Rh(I) intermediate by buffering the reaction mixture.[93]

Performing the rhodium-catalyzed arylation on the trans [6-5] ring fusion substrate (**2.128**) provided an inconsequential mixture of cis and trans cyclized products (~3:2), since the stereochemistry at C-19 would be ablated later in the synthesis. Attempts to epimerize trans substrate **2.128** at C-19 to its cis isomer in situ prior to the rhodium addition by stirring the reaction mixture at 40 °C under the rhodium/Et_3N conditions and then heating to 80 °C did not fully epimerize the substrate, and inconsequentially diastereomeric mixtures of products were still obtained.



2.128

Interestingly, we found that heating the cis substrate (**2.115**) with $[Rh(cod)(MeCN)_2]^+BF_4^-$ in toluene in a sealed vessel at elevated temperatures of 130 – 140 °C led to the unique formation of methyl ether/pyridone **2.129** (Figure 2.10A) as a byproduct of the reaction. The formation of this compound may arise, nominally, from a process as depicted in Figure 2.10B in which the pyridine nitrogen is activated by the boron, which leads to a methyl transfer from the pyridinyl ether oxygen to the tertiary boronic ester oxygen.

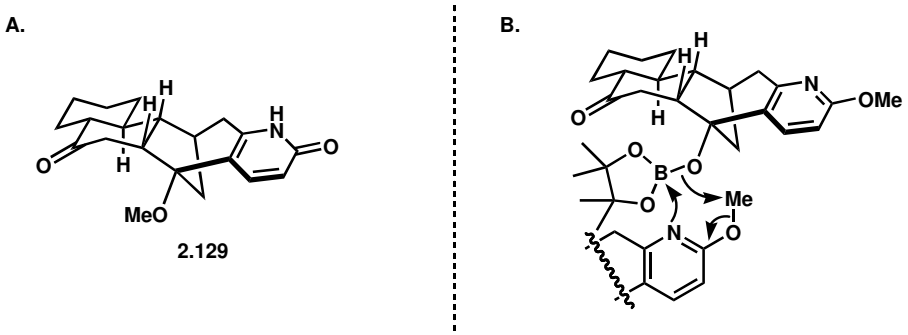
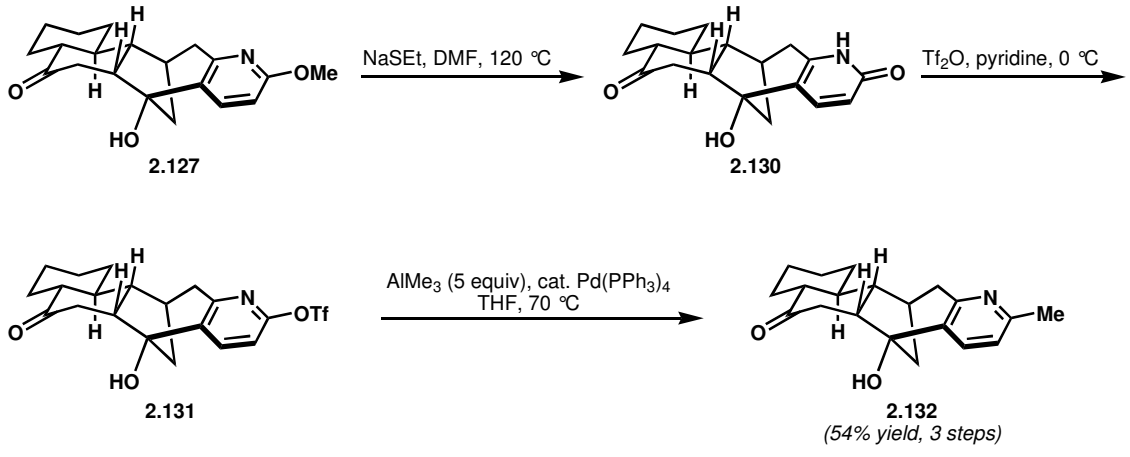


Figure 2.10 Methyl transfer product (A) and possible pathway (B).

2.8 Completion of the Synthesis of G. B. 13

Having secured a route to pentacycle **2.127**, we now needed to install the methyl group on the pyridine ring. Treatment of methoxy pyridine **2.127** with sodium ethane thiolate at 120 °C cleaved the methyl ether to give pyridone **2.130** (Scheme 2.47). Selective triflation of the pyridone in the presence of both the enolizable ketone carbonyl and the hydroxyl group provided triflate **2.131**. Finally, methyl cross-coupling using $AlMe_3$ and catalytic $Pd(PPh_3)_4$ according to Hirota's protocol,[97] which is notably tolerant of the ketone carbonyl, provided **2.132**, which comprises the complete scaffold of G. B. 13.

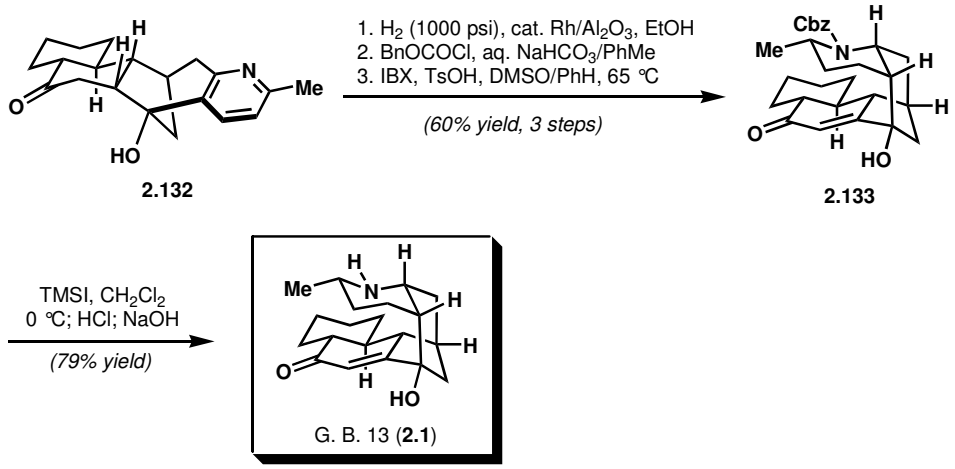
Scheme 2.47 Installation of pyridinyl methyl group.



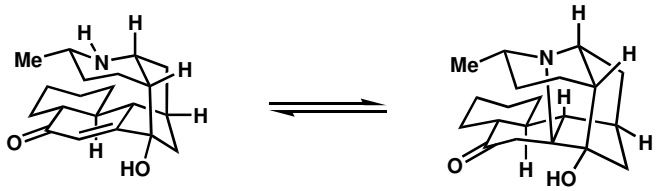
To reveal the latent piperidine moiety present in G. B. 13, we needed to execute a hydrogenation of the pyridine ring of **2.132**. Though under PtO_2/AcOH hydrogenation conditions at

1000 psi we observed solely reduction of the carbonyl group and no aromatic ring hydrogenation, use of rhodium on alumina in ethanol at 1000 psi did provide the corresponding piperidine compound (Scheme 2.48). This reduction proceeded from the desired *exo* face of the molecule with good diastereocontrol (~8:1 dr) and was accompanied by an inconsequential partial reduction of the ketone group, from both faces of the molecule, in accordance with the observations of Evans.[98] Following selective Cbz protection of the piperidine nitrogen in the presence of the hydroxyl group using basic, biphasic conditions, treatment of the secondary alcohol/ketone mixture with excess IBX[45,99] afforded the corresponding enone **2.133**. Removal of the Cbz group using previously established conditions[99] then yielded alkaloid G. B. 13 (**1**).[100]

Scheme 2.48 Pyridine hydrogenation and completion of G. B. 13.



In the final Cbz cleavage step (i.e., **2.133** to **2.1**, Scheme 2.48), treatment of the crude product with dilute HCl to remove superfluous trimethylsilyl groups presumably leads to the conjugate addition of the piperidine nitrogen into the enone moiety to give 16-oxo-himgaline (**2.134**, eq 2.26), which may be reverted to G. B. 13 (**2.1**) by subsequent treatment with dilute aqueous base. Interestingly, we found that G. B. 13 exists as a 5:2 mixture with 16-oxo-himgaline in C_6D_6, but we observed no significant amount of this *N*-conjugate addition constitutional isomer when the compound was analyzed in $CDCl_3$. Subjecting the apparent 5:2 mixture of compounds to aqueous base with and without an organic cosolvent, followed by ^1H NMR analysis in C_6D_6, revealed an unchanged 5:2 product distribution. These results suggest a solvent dependent equilibration of G. B. 13 and 16-oxo-himgaline.



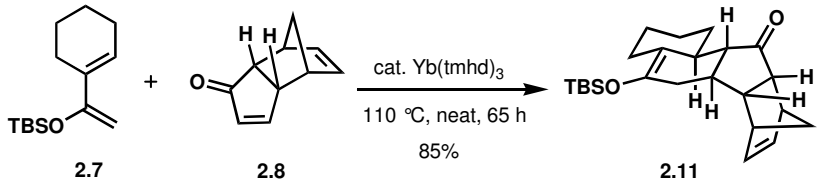
(2.26)

2.9 Conclusion

We have completed a concise total synthesis of (±)-G. B. 13 in 17 total steps from diene **2.7** and dienone **2.8**. The synthesis highlights the synthetic utility of a pyridine moiety as a piperidine surrogate. Key to the synthesis was a 1,3-allylic alcohol transposition under modified Parikh-Doering conditions. We also developed an unprecedented Rh(I)-catalyzed ketone hydroarylation reaction that enabled formation of the pentacycle of G. B. 13. Because our only chiral building block, dienone **2.8**, is known in enantioenriched form, our synthesis should be readily rendered enantioselective.

2.10 Experimental Methods

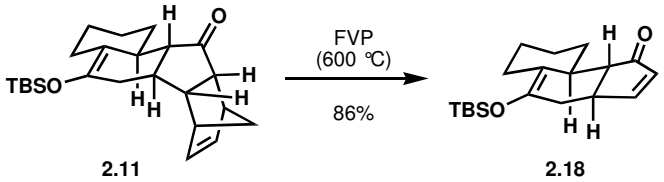
Unless stated otherwise, reactions were performed in flame-dried glassware sealed with rubber septa under a nitrogen atmosphere and were stirred with Teflon-coated magnetic stir bars. Liquid reagents and solvents were transferred via syringe using standard Schlenk techniques. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled over sodium/benzophenone ketyl. Dichloromethane (CH_2Cl_2), toluene, methanol (MeOH), and benzene were distilled over calcium hydride. Potassium acetate (KOAc) was dried at 130 °C under vacuum overnight prior to use. All other solvents and reagents were used as received unless otherwise noted. Reaction temperatures above 23 °C refer to oil bath or heating block temperatures, which were controlled by an IKAmag® temperature modulator. Thin layer chromatography was performed using SiliCycle silica gel 60 F-254 precoated plates (0.25 mm) and visualized by UV irradiation and anisaldehyde stain or CAM stain. Sorbent silica gel (particle size 40-63 μm) was used for flash chromatography. ^{1}H NMR were recorded on a Bruker AV-600 (at 600 MHz) spectrometer, and ^{13}C NMR were recorded on a Bruker AV-600 spectrometer (at 150 MHz). ^{19}F NMR were recorded on a Bruker AVQ-400 spectrometer (at 376 MHz). ^{1}H and ^{13}C chemical shifts (δ) are reported relative to the residual solvent signal, $CHCl_3$ (δ = 7.26 for ^{1}H NMR and δ = 77.16 for ^{13}C NMR) or C_6H_6 (δ 7.16 for ^{1}H and δ 128.06 for ^{13}C). ^{19}F chemical shifts are reported relative to $CFCl_3$ at 0 ppm. Data for ^{1}H NMR are reported as follows: chemical shift (multiplicity, coupling constants where applicable, number of hydrogens). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), ddd (doublet of doublet of doublet), m (multiplet), br (broad). IR spectra were recorded on a Nicolet MAGNA-IR 850 spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectral data were obtained from the University of California, Berkeley Mass Spectral Facility.



2.7 2.8 2.11

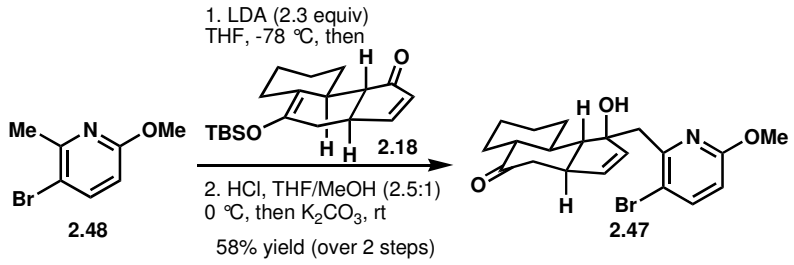
Diels-Alder Adduct 2.11. Diene **2.7**[101] (8.21 g, 34.3 mmol, 1 equiv), enone **2.8**[102] (5.01 g, 34.3 mmol, 1 equiv), and tris(2,2,6,6-tetramethyl-3,5-heptanedionato)-ytterbium (III) ($Yb(tmhd)_3$) (1.24 g, 1.72 mmol, 5 mol %) were placed in a 50 mL Schlenk flask. The flask was evacuated and backfilled with nitrogen, sealed with a Teflon screw cap, and the reaction mixture was then stirred at 110 °C in an oil bath for 65 h. The crude reaction mixture was loaded on to a silica

column and purified by flash chromatography (hexanes to 29:1 hexanes/EtOAc) to give **2.11** (11.2 g, 85%) as a slightly yellow oil. $\mathbf{R_f}$ 0.59 (2:1 hexanes/EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.20 (dd, *J* = 5.5, 2.8 MHz, 1H), 5.97 (dd, *J* = 5.5, 3.0 MHz, 1H), 3.09-3.03 (m, 2H), 2.97-2.94 (br, 1H), 2.86-2.80 (m, 1H), 2.66-2.61 (m, 1H), 2.32-2.26 (m, 2H), 2.21-2.13 (m, 1H), 2.05-1.99 (m, 1H), 1.96-1.90 (m, 1H), 1.71-1.63 (m, 3H), 1.50-1.42 (m, 2H), 1.37-1.24 (m, 2H), 1.12-1.03 (m, 1H), 0.95 (s, 9H), 0.71-0.62 (m, 1H), 0.13 (s, 3H), 0.11 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 214.4, 140.9, 137.1, 135.7, 119.2, 60.0, 55.3, 52.9, 45.4, 44.5, 42.9, 39.4, 38.2, 36.0, 33.8, 26.7, 26.3, 26.0, 25.8, 18.3, -3.6, -4.1; **IR** (film) 2954, 2928, 2855, 1738, 1252, 1198, 836 cm^{-1}; **HRMS** (ESI$^+$) calc'd for $[C_{24}H_{37}O_2Si]^+$ $(M+H)^+$: *m/z* 385.2557, found 385.2548.



2.11 2.18

Enone 2.18. Diels-Alder adduct **2.11** (4.02 g, 10.5 mmol) in benzene (10.5 mL, 1.0 M) was injected into a quartz tube (~2 cm in diameter) inside a tube furnace (12 in) at 600 °C under vacuum (~0.02 torr) (see Figure S1). The solution was injected into the system through a 20-guage needle from a gas-tight syringe (fitted with a valve) in small aliquots (~0.3 mL every 30-45 s). The product was collected in a liquid nitrogen-cooled trap. The crude product was purified via flash chromatography (29:1 hexanes/EtOAc) to give **2.18** (2.85 g, 86% yield) as a colorless oily solid. $\mathbf{R_f}$ 0.59 (2:1 hexanes/EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.46 (d, *J* = 5.8 Hz, 1H), 6.09 (dd, *J* = 5.8, 2.5 Hz), 2.95-2.89 (m, 1H), 2.74-2.65 (m, 2H), 2.38-2.24 (m, 3H), 1.83 (dd, *J* = 10.5, 6.5 Hz, 1H), 1.78-1.72 (m, 2H), 1.61-1.53 (m, 1H), 1.40-1.32 (m, 1H), 1.20-1.11 (m, 1H), 0.96 (s, 9H), 0.93-0.85 (m, 1H), 0.14-0.13 (m, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 207.9, 159.8, 141.5, 134.5, 121.5, 57.3, 42.9, 36.9, 35.6, 33.5, 26.6, 26.5, 26.0, 25.6, 18.4, -3.6, -4.0; **IR** (film) 2928, 2855, 1716, 1256, 1191, 1152, 839, 778cm^{-1}; HRMS (ESI$^+$) calc'd for $[C_{19}H_{31}O_2Si]^+$ $(M+H)^+$: *m/z* 319.2088, found 319.2083.

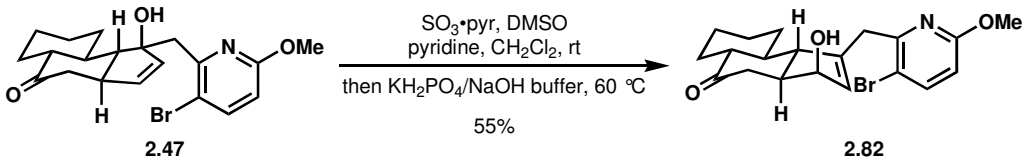


2.48 2.47

Tertiary allylic alcohol 2.47. Lithium diisopropyl amide was generated by the addition of n-BuLi (10.7 mL of a 2.5 M soln. in hexanes, 27 mmol, 2.3 equiv) to a solution of diisopropyl amine (3.9 mL, 28 mmol, 2.4 equiv) in 50 mL of THF at -78 °C. The solution of LDA was stirred for 1 h at this temperature. Picoline **2.48**[31] (2.34 g, 11.6 mmol, 1 equiv) in THF (30 mL) at -78 °C was then added to the LDA solution via cannula. The resulting apple-red solution was stirred 30 min at -78 °C. At this time, enone **2.18** (3.87 g, 12.1 mmol, 1.04 equiv) in THF (30 mL) at -78 °C was transferred to the reaction flask via cannula, and the color of the solution turned to orange. After stirring for 25 min, the reaction mixture was quenched at -78 °C with

saturated aqueous NH_4Cl (50 mL) and then allowed to come to rt. The mixture was extracted with Et_2O (2 x 200 mL), and the organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The majority of impurities in the crude product could be removed by flash chromatography (29:1 hexanes/EtOAc). This material was of suitable purity and taken on to the next step. **R_f** 0.60 (2:1 hexanes/EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.7 Hz, 1H), 6.56 (d, *J* = 8.7 Hz, 1H), 5.78 (s, 1H), 5.76 (d, *J* = 5.7 Hz, 1H), 5.60 (dd, *J* = 5.7, 2.5 Hz, 1H), 3.91 (s, 3H), 3.21 (d, *J* = 15.1 Hz, 1H), 2.99-2.94 (m, 2H), 2.48-2.41 (m, 1H), 2.33-2.24 (m, 3H), 2.15-2.08 (m, 1H), 1.76-1.70 (m, 2H), 1.65-1.55 (m, 2H), 1.34-1.24 (m, 1H), 1.23-1.13 (m, 1H), 1.09-1.00 (m, 1H), 0.96 (s, 9H), 0.13 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 162.2, 155.1, 143.3, 141.7, 139.5, 133.7, 120.4, 112.9, 110.9, 84.5, 60.0, 54.0, 43.4, 38.3, 37.3, 36.5, 34.0, 26.7, 26.5, 26.0, 18.4, -3.6, -4.0; **IR** (film) 3425, 2928, 2854, 1579, 1463, 1293, 854, 839 cm^{-1}; **HRMS** (ESI^+) calc'd for $[C_{26}H_{39}O_3NBrSi]^+$ $(M+H)^+$: *m/z* 520.1877, found 520.1885.

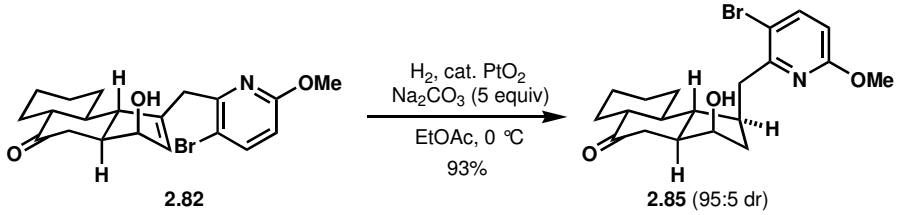
12 N HCl (0.06 mL, 0.72 mmol) was added to the chromatographed silyl enol ether in THF (25 mL) and MeOH (10 mL) at 0 °C, and the reaction mixture was stirred at this temperature for 2 h. K_2CO_3 (2 g, 14.5 mmol) was then added (to epimerize to the trans-decalin isomer), and the reaction mixture was allowed to come to rt and was stirred for 1 h before a second portion of K_2CO_3 (1.3 g, 9.4 mmol) was added. After an additional 2.5 h of stirring, the solution was diluted sequentially with Et_2O (100 mL) and saturated aqueous NH_4Cl (75 mL). The layers were separated and the aqueous layer was extracted with additional Et_2O (2 x 100 mL). The combined organic layers were then washed with H_2O (2 x 100 mL) and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (using a gradient of 5:1 to 4:1 hexanes/EtOAc) to give tertiary allylic alcohol **2.47** as a slightly yellow oily solid (2.72 g, 58% yield over two steps, >95:5 trans/cis decalin isomers). **R_f** 0.32 (2:1 hexanes/EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.7 Hz, 1H), 6.56 (d, *J* = 8.7 Hz), 5.79 (s, 1H), 5.72 (d, *J* = 5.8 Hz, 1H), 5.62 (dd, *J* = 5.8, 2.6 Hz, 1H), 3.91 (s, 3H), 3.23 (d, *J* = 15.1 Hz, 1H), 2.95 (d, *J* = 15.1 Hz, 1H), 2.68 (dd, *J* = 12.6, 3.5 Hz, 1H), 2.60-2.53 (m, 1H), 2.43-2.36 (m, 1H), 2.33-2.27 (m, 1H), 2.09-1.97 (m, 3H), 1.86-1.81 (m, 1H), 1.78-1.70 (m, 2H), 1.35-1.16 (m, 4H); **^{13}C NMR** (150 MHz, CDCl3) δ 210.7, 162.2, 154.5, 143.3, 140.3, 132.9, 112.8, 111.1, 83.8, 61.6, 55.8, 54.0, 47.1, 46.4, 42.8, 37.3, 32.2, 25.8, 25.7, 25.5; **IR** (film) 3408, 2928, 2852, 1709, 1580, 1463, 1413, 1294 cm^{-1}; **HRMS** (ESI^+) calc'd for $[C_{20}H_{25}O_3NBr]^+$ $(M+H)^+$: *m/z* 406.1012, found 406.1007.



2.47 **2.82**

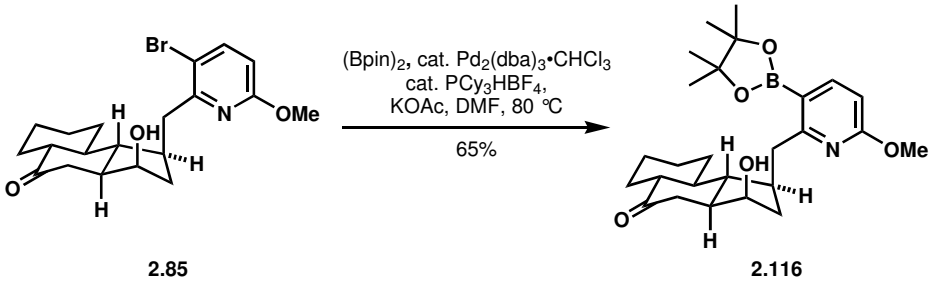
Secondary allylic alcohol 2.82. Pyridine (1.2 mL, 15 mmol, 30 equiv) was added to SO_3•pyridine (396 mg, 2.49 mmol, 5 equiv) in DMSO (1.8 mL, 25 mmol, 50 equiv) at rt, and the solution was stirred for 15 min.[53] Tertiary allylic alcohol **2.47** (202 mg, 0.497 mmol, 1 equiv) in CH_2Cl_2 (5 mL) was then added, and the reaction mixture was stirred at rt for 6 h. At this time, 5 mL of Fisher® pH 7.00 KH_2PO_4-NaOH buffer solution concentrate was added, and the biphasic mixture was stirred vigorously at 60 °C for 3.5 h. The reaction mixture was then allowed to cool to rt, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered through a fritted fun-

nel, and concentrated under reduced pressure. The crude product was purified by flash chromatography (using a gradient of 4:1 to 1:1 hexanes/EtOAc) to afford 111 mg (55% yield) of secondary allylic alcohol **2.82** as a colorless oil. $\mathbf{R_f}$ 0.13 (2:1 hex/EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.6 Hz, 1H), 6.53 (d, *J* = 8.6 Hz, 1H), 5.41-5.38 (m, 1H), 4.33-4.30 (m, 1H), 3.88 (s, 3H), 3.79 (d, *J* = 16.9 Hz, 1H), 3.74 (d, *J* = 16.8 Hz, 1H), 2.91-2.85 (m, 1H), 2.76-2.70 (m, 1H), 2.52 (dd, *J* = 13.4, 3.4 Hz, 1H), 2.24-2.18 (m, 1H), 2.09-1.99 (m, 2H), 1.98-1.92 (m, 1H), 1.83-1.78 (m, 1H), 1.72-1.67 (m, 1H), 1.66-1.58 (m, 1H), 1.29-1.11 (m, 5H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 211.6, 162.8, 154.9, 150.4, 142.7, 131.4, 112.2, 110.4, 73.9, 55.8, 53.9, 52.4, 51.7, 46.6, 42.6, 40.2, 32.6, 25.8, 25.7, 25.6; **IR** (film) 3400, 2924, 2855, 1705, 1575, 1460, 1416 cm^{-1}; **HRMS** (ESI$^+$) calc'd for $[C_{20}H_{25}O_3NBr]^+$ $(M+H)^+$: *m/z* 406.1012, found 406.1024.



2.82 **2.85** (95:5 dr)

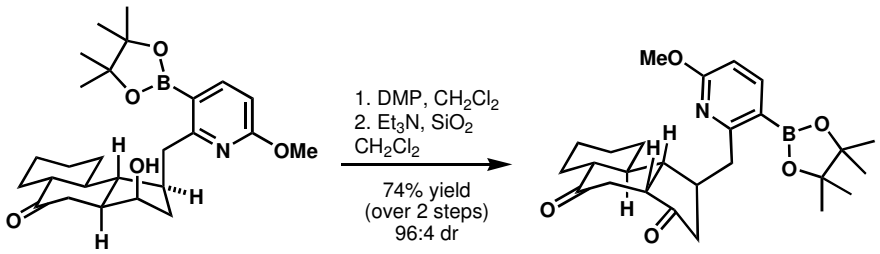
Secondary alcohol 2.85. Na_2CO_3 (227 mg, 2.14 mmol, 5 equiv) and PtO_2 (9.5 mg, 0.042 mmol, 10 mol %) were added to a solution of **2.82** (174 mg, 0.428, 1 equiv) in EtOAc (3.6 mL, 0.12 M) at 0 °C. The flask was evacuated and backfilled with H_2 (x 3), and the mixture (held at a temperature between 0 and 8 °C) was stirred under a balloon of H_2 for 5 h. The reaction mixture was then filtered through a plug of silica, which was rinsed with additional EtOAc. The filtrate was then concentrated under reduced pressure to provide 162 mg (93%) of **2.85** as a colorless oily solid (95:5 diastereomeric ratio). This product was > 95% pure and used in the ensuing reaction without further purification. $\mathbf{R_f}$ 0.17 (2:1 hexanes/EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) (major diastereomer) δ 7.64 (d, *J* = 8.6 Hz, 1H), 6.48 (d, *J* = 8.6 Hz, 1H), 4.08-4.03 (m, 1H), 3.90 (s, 3H), 3.27 (dd, *J* = 15.0, 3.2 Hz, 1H), 2.94 (dd, *J* = 15.0, 10.9 Hz, 1H), 2.67-2.60 (m, 1H), 2.51-2.46 (m, 1H), 2.46-2.37 (m, 1H), 2.26-2.21 (m, 1H), 2.20-2.13 (m, 1H), 2.04-1.94 (m, 3H), 1.84-1.74 (m, 2H), 1.73-1.57 (m, 3H), 1.45-1.35 (m, 1H), 1.33-1.15 (m, 4H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 212.9, 162.5, 156.6, 142.4, 112.2, 109.4, 73.5, 54.2, 53.8, 52.0, 50.8, 48.1, 44.4, 42.9, 42.0, 38.7, 32.8, 25.9, 25.6, 25.4. **IR** (film) 3446, 2929, 2854, 1702, 1574, 1459, 1417, 1293 cm^{-1}; **HRMS** (ESI$^+$) calc'd for $[C_{20}H_{27}O_3NBr]^+$ $(M+H)^+$: *m/z* 408.1169, found 408.1177.



2.85 **2.116**

Boronic ester 2.116. DMF (3 mL) was added to $Pd_2(dba)_3$•$CHCl_3$ (37 mg, 0.036 mmol, 4.5 mol %) and PCy_3HBF_4 (62 mg, 0.18 mmol, 21 mol %) in a 25 mL Schlenk flask under N_2. The solution was stirred at rt for 10 min. Bis(pinacolato)diboron (1.01 g, 3.98 mmol, 5 equiv), KOAc (391 mg, 3.98 mmol, 5 equiv), and a solution aryl bromide **2.85** (325 mg, 0.796 mmol, 1 equiv)

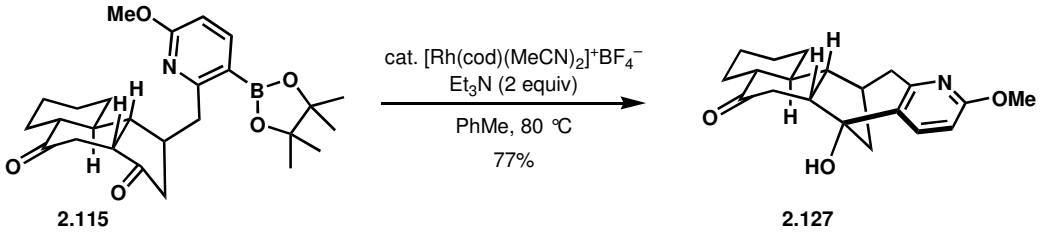
in DMF (5 mL) were added sequentially to the reaction mixture. The Schlenk flask was evacuated and backfilled with N_2, and the reaction mixture was stirred at 80 °C for 37 h. At this time, the reaction mixture was allowed to cool to rt and then diluted with H_2O (25 mL) and Et_2O (25 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 25 mL). The combined ethereal layers were washed with 15% aqueous NH_4OH (2 x 25 mL) and H_2O (2 x 25 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude reaction mixture was purified by flash chromatography (3:1 hexanes/EtOAc). The chromatographed product was then washed with 15% aqueous NH_4OH and H_2O (to remove co-eluting pinacol boronic acid) and dried over anhydrous $MgSO_4$ to give **2.116** (236 mg, 65% yield) as a colorless oil. $\mathbf{R_f}$ 0.19; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.3 Hz, 1H), 6.54 (d, *J* = 8.3 Hz, 1H), 4.01-3.97 (m, 1H), 3.93 (s, 3H), 3.23 (dd, *J* = 13.1, 4.1 Hz, 1H), 3.12-3.06 (m, 1H), 2.71-2.65 (m, 1H), 2.50 (dd, *J* = 13.2, 3.6 Hz, 1H), 2.41 (d, *J* = 3.7 Hz, 1H), 2.38-2.30 (m, 2H), 2.04-1.91 (m, 3H), 1.89-1.76 (m, 3H), 1.66-1.59 (m, 2H), 1.45-1.37 (m, 1H), 1.35 (s, 12H), 1.27-1.18 (m, 4H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 213.2, 166.4, 165.3, 146.8, 107.0, 84.2, 73.7, 54.6, 53.5, 52.6, 51.6, 48.1, 45.3, 43.2, 40.1, 39.8, 32.7, 26.1, 25.6, 25.6, 25.2, 24.7; **IR** (film) 3502, 2977, 2929, 2855, 1705, 1587, 1345, 1301; **HRMS** (ESI$^+$) calc'd for $[C_{26}H_{39}O_5NB]^+$ $(M+H)^+$: *m/z* 456.2916, found 456.2919.



2.116 2.115

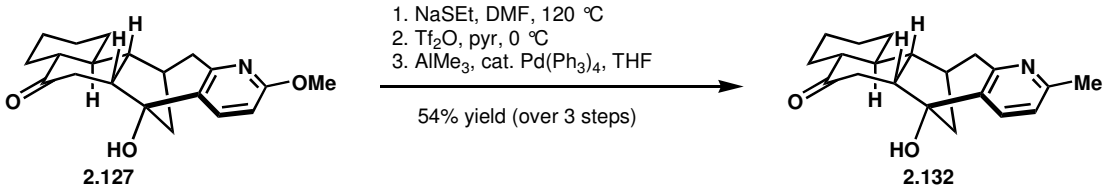
Dione 2.115. $NaHCO_3$ (77 mg, 0.92 mmol, 2.5 equiv) and Dess-Martin periodinane (DMP) (391 mg, 0.92 mmol, 2.5 equiv) were added to a solution of alcohol **2.116** (168 mg, 0.369 mmol, 1 equiv) in CH_2Cl_2 (3.7 mL, 0.1 M). The reaction mixture was stirred at rt for 11 h. Saturated aqueous $NaHCO_3$ (25 mL) and saturated aqueous $Na_2S_2O_5$ (25 mL) were then added, and the resulting heterogeneous mixture was stirred until the layers became colorless. Et_2O (20 mL) was then added and the layers were separated. The aqueous layer was then extracted with additional Et_2O (2 x 20 mL). The combined organic layers were washed sequentially with saturated aqueous $NaHCO_3$ (2 x 20 mL), H_2O (20 mL), and brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (4:1 hexanes EtOAc) to provide 141 mg (84% yield) of the trans [6-5] ring-fused ketone as a colorless oily solid. $\mathbf{R_f}$ 0.47 (2:1 hexanes/EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.3 Hz, 1H), 6.55 (d, *J* = 8.3 Hz, 1H), 3.92 (s, 3H), 3.86 (dd, *J* = 12.9, 3.8 Hz, 1H), 2.83 (dd, *J* = 12.9, 10.8 Hz, 1H), 2.77-2.72 (m, 1H), 2.67-2.62 (m, 1H), 2.60-2.52 (m, 1H), 2.37-2.20 (m, 4H), 2.08-2.04 (m, 1H), 2.03-1.96 (m, 1H), 1.86-1.82 (m, 2H), 1.81-1.75 (m, 1H), 1.66-1.59 (m, 1H). 1.38-1.29 (m, 13H), 1.28-2.21 (m, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 214.7, 210.1, 165.4, 165.0, 147.0, 107.5, 83.8, 55.7, 54.4, 53.5, 52.4, 48.8, 44.7, 43.2, 41.1, 39.8, 32.4, 26.0, 25.7, 25.3, 25.1, 25.0; **IR** (film) 2978, 2928, 2848, 1743, 1710, 1588, 1346, 1297 cm^{-1}; **HRMS** (ESI$^+$) calc'd for $[C_{26}H_{37}O_5NB]^+$ $(M+H)^+$: *m/z* 454.2759, found 454.2768.

Triethylamine (0.060 mL, 0.43 mmol, 1.5 equiv) and SiO_2 (131 mg) were added to the trans [6-5] ring-fused ketone (131 mg, 0.289 mmol, 1 equiv) in CH_2Cl_2 (2.9 mL, 0.1 M). The heterogeneous mixture was stirred at rt for 4 h at which time it was filtered through cotton wool with a short pad of silica. The silica was rinsed with additional CH_2Cl_2 and the filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (using a gradient of 6:1 to 4:1 hexanes/EtOAc) to give 122 mg (93% yield) of a colorless oily solid. $\mathbf{R_f}$ 0.43 (2:1 hexanes/EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.3 Hz, 1H), 6.56 (d, *J* = 8.3 Hz, 1H), 3.92 (s, 3H), 3.26 (dd, *J* = 12.6, 8.0 Hz, 1H), 3.16-3.11 (m, 1H), 3.01 (dd, *J* = 12.6, 8.3 Hz, 1H), 2.86-2.80 (m, 2H), 2.45-2.40 (m, 1H), 2.27-2.24 (m, 2H), 2.09-2.03 (m, 2H), 1.92-1.85 (m, 2H), 1.81-1.65 (m, 2H), 1.29 (s, 12H), 1.16-1.03 (m, 4H), 0.86-0.78 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 217.2, 210.2, 165.2, 165.1, 146.7, 107.7, 83.9, 53.4, 52.4, 48.0, 46.0, 43.4, 41.9, 40.0, 36.9, 35.9, 32.3, 25.6, 25.4, 25.2, 25.1, 24.9; **IR** (film) 2977, 2930, 2855, 1742, 1713, 1589, 1341, 1305; **HRMS** (ESI^+) calc'd for $[C_{26}H_{37}O_5NB]^+$ $(M+H)^+$: *m/z* 454.2759, found 454.2772.



Tertiary alcohol 2.127. *25 mol % Catalyst loading procedure:* In a glovebox, a solution of ketone **2.115** (19 mg, 0.042 mmol, 1 equiv) in toluene (0.5 mL, 0.09 M) was added to a vial containing $[Rh(cod)(MeCN)]^+BF_4^-$ (4.1 mg, 0.011 mmol, 25 mol %), and a stir bar. Et_3N (12 μL, 0.084 mmol, 2 equiv) was then added to the vial. The vial was sealed with a Teflon cap, brought outside of the glovebox, and heated in a metal heating block (tall enough to cover ~ 90% of the vial) at 80 °C for 6.5 h. The reaction mixture was then diluted with EtOAc (15 mL) and H_2O (8 mL). The layers were separated and the aqueous layer was extracted with EtOAc (10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (using a gradient of 5:1 to 4:1 hexanes/EtOAc) to give **2.127** as a yellow oil (0.032 mmol, based on ^{1}H NMR integration using 1,2-dichloroethane as an internal standard, 77% yield), contaminated with pinacol boronic acid. This material was used without further purification in the subsequent reaction. *8 mol % Catalyst loading procedure:* In a glovebox, a solution of ketone **2.115** (22 mg, 0.049 mmol, 1 equiv) in toluene (0.49 mL, 1.0 M) was added to a vial containing $[Rh(cod)(MeCN)]^+BF_4^-$ (1.5 mg, 0.0039 mmol, 8 mol %), and a stir bar. Et_3N (14 μL, 0.098 mmol, 2 equiv) was then added to the vial. The vial was sealed with a Teflon cap, brought outside of the glovebox, and heated in a metal heating block (tall enough to cover ~ 90% of the vial) at 80 °C for 18 h. The reaction mixture was then diluted with EtOAc (15 mL) and H_2O (8 mL). The layers were separated and the aqueous layer was extracted with EtOAc (10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (5:1 hexanes/EtOAc) to give **2.127** as a yellow oil (0.035 mmol, based on ^{1}H NMR integration using 1,2-dichloroethane as an internal standard, 71% yield), contaminated with pinacol boronic acid. This material was used without further purification in the subsequent reaction. The majority of the contaminating pinacol boronic acid could be

removed to provide an analytically pure sample as follows: The chromatographed material was dissolved in Et_2O (8 mL) and washed with 15% aqueous NH_4OH (5 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (8 mL). The combined organic layers were then washed with 15% aqueous NH_4OH (2 x 5 mL) and brine (5 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give pure **2.127**. $\mathbf{R_f}$ 0.20 (2:1 hexanes/EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.5 Hz, 1H), 6.57 (d, *J* = 8.5 Hz, 1H), 3.89 (s, 3H), 3.14 (dd, *J* = 17.5, 4.2 Hz, 1H), 2.73 (d, *J* = 17.5 Hz, 1H), 2.50-2.45 (m, 1H), 2.41-2.35 (m, 2H), 2.34-2.21 (m, 3H), 2.12-2.07 (m, 1H), 1.84-1.72 (m, 4H), 1.72-1.67 (m, 1H), 1.62-1.56 (m, 1H), 1.47-1.39 (m, 1H), 1.26-1.15 (m, 2H), 1.09-0.92 (m, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 214.3, 163.3, 152.0, 134.8, 133.9, 108.2, 79.2, 53.6, 51.1, 49.1, 47.3, 42.9, 41.4, 38.4, 37.9, 36.7, 33.1, 27.5, 26.0, 25.9; **IR** (film) 3446, 2925, 2854, 1706, 1474, 1307; **HRMS** (ESI^+) calc'd for $[C_{20}H_{26}O_3N]^+$ $(M+H)^+$: *m/z* 328.1907, found 328.1902.



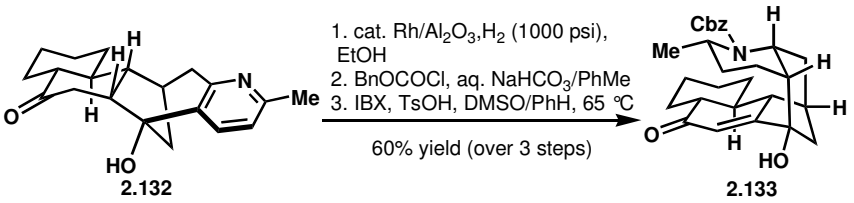
2.127 2.132

Methylpyridinyl ketone 2.132. EtSH (74 μL, 1.0 mmol, 20 equiv) was added to a suspension of NaH (20 mg of a 60% NaH dispersion in mineral oil, 0.50 mmol, 10 equiv) in DMF (0.2 mL) under N_2 in a Schlenk tube. 2-Methoxypyridinyl ketone **2.127** (0.05 mmol, 1 equiv) in DMF (0.5 mL) was then added. The Schlenk tube was quickly evacuated and backfilled with N_2 then sealed, and the reaction mixture was stirred at 120 °C for 15 h. The reaction mixture was allowed to cool to rt and then quenched with H_2O (0.06 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 12 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure via rotary evaporation and then on a high vacuum line (flask at 30 °C). The crude pyridone (containing a trace amount of DMF) was used in the subsequent step.

The pyridone was dissolved in pyridine (0.35 mL) and cooled to 0 °C. Trifluoromethanesulfonic anhydride (20 μL, 0.12 mmol, 2.4 equiv) was then added, and the reaction mixture was stirred at 0 °C for 35 min. The reaction mixture was quenched at 0 °C with saturated aqueous $NaHCO_3$ (2 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (using a gradient of 4:1 to 3:1 hexanes/EtOAc) to give 16.9 mg of the pyridinyl triflate (76% yield over two steps) as a colorless oil. $\mathbf{R_f}$ 0.19 (2:1 hexanes/EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.3 Hz, 1H), 6.99 (d, *J* = 8.3 Hz, 1H), 3.20 (dd, *J* = 18.2, 4.2 Hz, 1H), 2.85 (d, *J* = 18.2 Hz, 1H), 2.51-2.43 (m, 2H), 2.42-2.30 (m, 3H), 2.27-2.21 (m, 1H), 2.17-2.12 (br, 1H), 2.11-2.06 (m, 1H), 1.85-1.75 (m, 3H), 1.74-1.69 (m, 1H), 1.64-1.57 (m, 1H), 1.49-1.42 (m, 1H), 1.27-1.14 (m, 2H), 1.09-0.95 (m, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 213.8, 155.1, 154.6, 143.1, 136.3, 118.8 (q, *J* = 320 Hz), 112.7, 79.2, 51.0, 49.0, 47.1, 42.5, 41.2, 38.1, 37.2, 36.3, 33.0, 27.4, 25.9, 25.8; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -72.3; **IR** (film) 3442, 2927, 2856, 1701, 1419, 1219, 1137 cm^{-1}; **HRMS** (ESI^+) calc'd for $[C_{20}H_{23}O_5NF_3S]^+$ $(M+H)^+$: *m/z* 446.1244, found 446.1238.

$Pd(PPh_3)_4$ (0.6 mg, 0.0005 mmol, 5 mol %) in THF (0.1 mL) was added to a solution of the pyridinyl triflate described above (4.8 mg, 0.011 mmol, 1 equiv) in THF (0.3 mL) in a Schlenk

tube under N_2. Trimethyl aluminum (20 μL of a 2.0 M solution in toluene, 0.04 mmol, 4 equiv) was then added to this solution. The Schlenk tube was evacuated and backfilled with N_2, sealed, and heated in an oil bath at 80 °C for 12.5 h. The reaction mixture was then allowed to cool to rt; MeOH (0.05 mL) was added and stirring was continued for another 5 min. $NaHCO_3$ (75 mg) and anhydrous $MgSO_4$ (300 mg) were added, and the mixture was diluted with CH_2Cl_2 (5 mL) and then stirred for 10 min. This mixture was filtered through Celite, which was rinsed with additional CH_2Cl_2 (10 mL). The filtrate was concentrated under reduced pressure to give the crude product, which was purified by flash chromatography (using a gradient from 0.5% MeOH in CH_2Cl_2 to 4% MeOH in CH_2Cl_2). 2-Methylpyridinyl ketone **2.132** (2.4 mg, 71% yield) was thus obtained as a yellow oil. $\mathbf{R_f}$ 0.3 (10% MeOH in CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 3.21 (dd, *J* = 17.5, 4.2 Hz, 1H), 2.83 (d, *J* = 17.5 Hz, 1H), 2.51-2.46 (m, 4H), 2.43-2.36 (m, 2H), 2.33-2.27 (m, 2H), 2.26-2.21 (m, 1H), 2.12-2.07 (m, 1H), 1.94-1.90 (br, 1H), 1.84-1.74 (m, 3H), 1.72-1.67 (m, 1H), 1.61-1.55 (m, 1H), 1.48-1.40 (m, 1H), 1.24-1.14 (m, 2H), 1.09-1.01 (m, 1H), 1.00-0.92 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 214.2, 157.1, 154.0, 139.2, 131.1, 121.2, 79.3, 51.1, 49.0, 47.2, 43.1, 41.4, 38.3, 37.7, 36.7, 33.0, 27.5, 26.0, 25.8, 24.3; **IR** (film) 3368, 2924, 2853, 1709, 1461, 1101 cm^{-1}; **HRMS** (ESI$^+$) calc'd for $[C_{20}H_{26}O_2N]^+$ $(M+H)^+$: *m/z* 312.1958, found 312.1953.

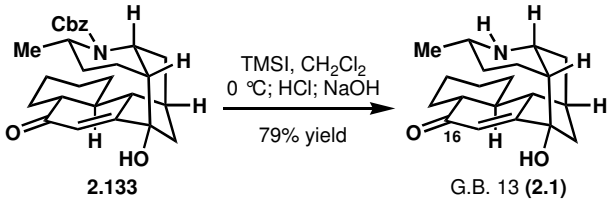


N-Cbz-G. B. 13 (2.133). 5% Rh on alumina (10 mg, 0.005 mmol, 25 mol %) was added to a solution of methylpyridinyl ketone **2.132** (6.1 mg, 0.020 mmol, 1 equiv) in absolute EtOH (0.3 mL) in a 4 mL vial. The reaction vessel was placed inside a Parr bomb, which was pressurized to 1000 psi with H_2. The reaction mixture was stirred at this pressure for 19.5 h. At this time, the Parr bomb was vented. The mixture was filtered through Celite, which was rinsed with CH_2Cl_2 (5 mL), and then concentrated under reduced pressure to give the corresponding piperidine as a mixture of ketone and alcohol products. The crude mixture was used immediately without purification.

To the piperidine mixture described above was added toluene (0.25 mL), saturated aqueous $NaHCO_3$ (0.25 mL), and benzylchloroformate (9.1 μL, 0.064 mmol, 3 equiv). The reaction mixture was stirred at rt for 2.5 h at which time it was diluted with CH_2Cl_2 (7 mL) and H_2O (2 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 7 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (eluting with 2:1 hexanes/EtOAc to CH_2Cl_2 to 9:1 CH_2Cl_2/MeOH). The fractions containing Cbz-protected piperidine ketone and alcohol products were combined, concentrated under reduced pressure, and used in the next step.

p-Toluenesulfonic acid monohydrate (15 mg, 0.079 mmol, 4 equiv) and IBX (84 mg, 0.30 mmol, 15 equiv) were added to a solution of the Cbz-protected piperidine mixture described above in DMSO (0.20 mL) and benzene (0.15 mL). The mixture was stirred at 65 °C for 18.5 h and then diluted with EtOAc (8 mL) and saturated aqueous $NaHCO_3$ (5 mL). The layers were separated and the aqueous layer was extracted with additional EtOAc (2 x 8 mL). The combined organic layers were then washed sequentially with saturated aqueous $NaHCO_3$ (2 x 5 mL), H_2O (5 mL),

and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (eluting with a gradient of 4:1 to 2:1 hexanes/EtOAc) to give 5.3 mg (60% yield over three steps) of N-Cbz-G. B. 13 (**2.133**) as a colorless oil. $\mathbf{R_f}$ 0.45 (1:2 hexanes/EtOAc); **^{1}H NMR** (600 MHz, C_6D_6) δ 7.32-7.28 (m, 2H), 7.17-7.13 (m, 2H), 7.09-7.05 (m, 1H), 5.96 (d, *J* = 2.0 Hz, 1H), 5.21 (s, 2H), 4.71-4.62 (m, 1H), 4.45-4.35 (m, 1H), 2.64-2.50 (m, 2H), 1.95-1.88 (m, 1H), 1.72-1.62 (m, 4H), 1.53-1.42 (m, 3H), 1.34-1.22 (m, 3H), 1.18-1.12 (m, 1H), 1.12-0.84 (m, 9H), 0.84-0.79 (m, 1H), 0.63-0.54 (m, 1H); **^{13}C NMR** (150 MHz, C_6D_6) δ 198.7, 172.2, 155.5, 137.8, 119.0, 80.8, 67.2, 56.4, 52.3, 47.10, 47.05, 45.9, 45.0, 35.8, 35.5, 31.4, 30.0, 29.9, 26.6, 26.2, 25.6, 20.0, 19.0; **IR** (film) 3423, 2931, 2852, 1687, 1665, 1414, 1317 cm^{-1}; **HRMS** (ESI$^+$) calc'd for $[C_{28}H_{36}O_4N]^+$ $(M+H)^+$: *m/z* 450.2639, found 450.2640.



G. B. 13 (2.1). The procedure of Movassaghi, et al.,[99] was followed. Trimethylsilyliodide (1 drop every 25 min for 125 min, ~ 0.06 mL total) was added to a solution of **2.133** (5.3 mg, 0.012 mmol) in CH_2Cl_2 (1 mL) at 0 °C. After 125 min, TLC analysis indicated the complete consumption of starting material, and 1.5 mL 1 N HCl was added at 0 °C. The reaction mixture was allowed to stir with warming to rt and then was further diluted with 1 N HCl (3.5 mL) and hexanes (10 mL). The layers were separated and the organic phase was extracted with additional 1 N HCl (2 x 5 mL). The combined aqueous layers were washed sequentially with hexanes (2 x 10 mL), CH_2Cl_2 (5 mL), and hexanes (10 mL) and then brought to pH 13 with 15% aqueous NaOH (4.5 mL). The basic, aqueous solution was stirred at rt for 1.25 h and then extracted with CH_2Cl_2 (5 x 15 mL). The combined CH_2Cl_2 layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 2.9 mg (79% yield) of a ~ 1:2 mixture of G. B. 13 (**2.1**) and its N-conjugate addition product, 16-oxo-himgaline (**2.134**), in C_6D_6. Stirring this mixture in 15% aqueous NaOH for an additional two hours followed by extraction into CH_2Cl_2 then provided a ~ 5:2 mixture of G. B. 13 and 16-oxo-himgaline (in C_6D_6), consistent with the observations of Evans.[98] Impurities from solvents could be removed by flash chromatography (eluting with a gradient of 0.1% Et_3N in CH_2Cl_2 to 1% Et_3N in CH_2Cl_2). **^{1}H NMR** (600 MHz, C_6D_6) G. B. 13: δ 6.06 (d, *J* = 2.0 Hz, 1H), 3.31-3.27 (m, 1H), 2.91-2.88 (m, 1H), 2.71-2.65 (m, 1H), 2.60-2.54 (m, 1H), 2.20-2.13 (m, 1H), 1.93-1.89 (m, 1H), 1.85-1.82 (m, 1H), 1.82-1.47 (m, 6H), 1.44-1.40 (ddd, *J* = 10.7, 5.6, 1.9 Hz, 1H), 1.28-0.90 (m, 9H), 0.83-0.74 (m, 1H), 0.76 (d, *J* = 6.1 Hz, 3H); **^{13}C NMR** (150 MHz, C_6D_6) G. B. 13: δ 199.1, 178.6, 118.9, 79.4, 55.1, 53.0, 52.8, 50.9, 47.9, 47.3, 46.4, 40.7, 32.8, 31.6, 30.3, 27.0, 26.4, 25.8, 24.7, 23.3; **IR** (film) 3391, 2927, 2853, 1706, 1647, 1447, 1317, 1147 cm^{-1}; **HRMS** (ESI$^+$) calc'd for $[C_{20}H_{30}O_2N]^+$ $(M+H)^+$: *m/z* 316.2271, found 316.2273.

2.11 References and Notes

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(101) Diene **2.7** was prepared from 1-acetylcyclohexene and TBSCl, according to the procedure of Ohkata et al.: Ohkata, K.; Lee, Y. G.; Utsumi, Y.; Ishimaru, K.; Akiba, K. *J. Org. Chem.* **1991**, *56*, 5052-5059.
(102) Enone **2.8** was prepared via the Mihelich-Eickhoff photooxygenation of cyclopentadiene dimer, according to the procedure of Borsato et al.: Borsato, G.; De Lucchi, O.; Fabris, F.; Lucchini, V.; Frascella, P.; Zambon, A. *Tetrahedron Lett.* **2003**, *44*, 3517-3520. Purification was achieved by flash chromatography eluting with a gradient of hexanes to 29:1 hexanes/EtOAc.

APPENDIX ONE

Spectra Relevant to Chapter Two:

Total Synthesis of Alkaloid (±)-G. B. 13

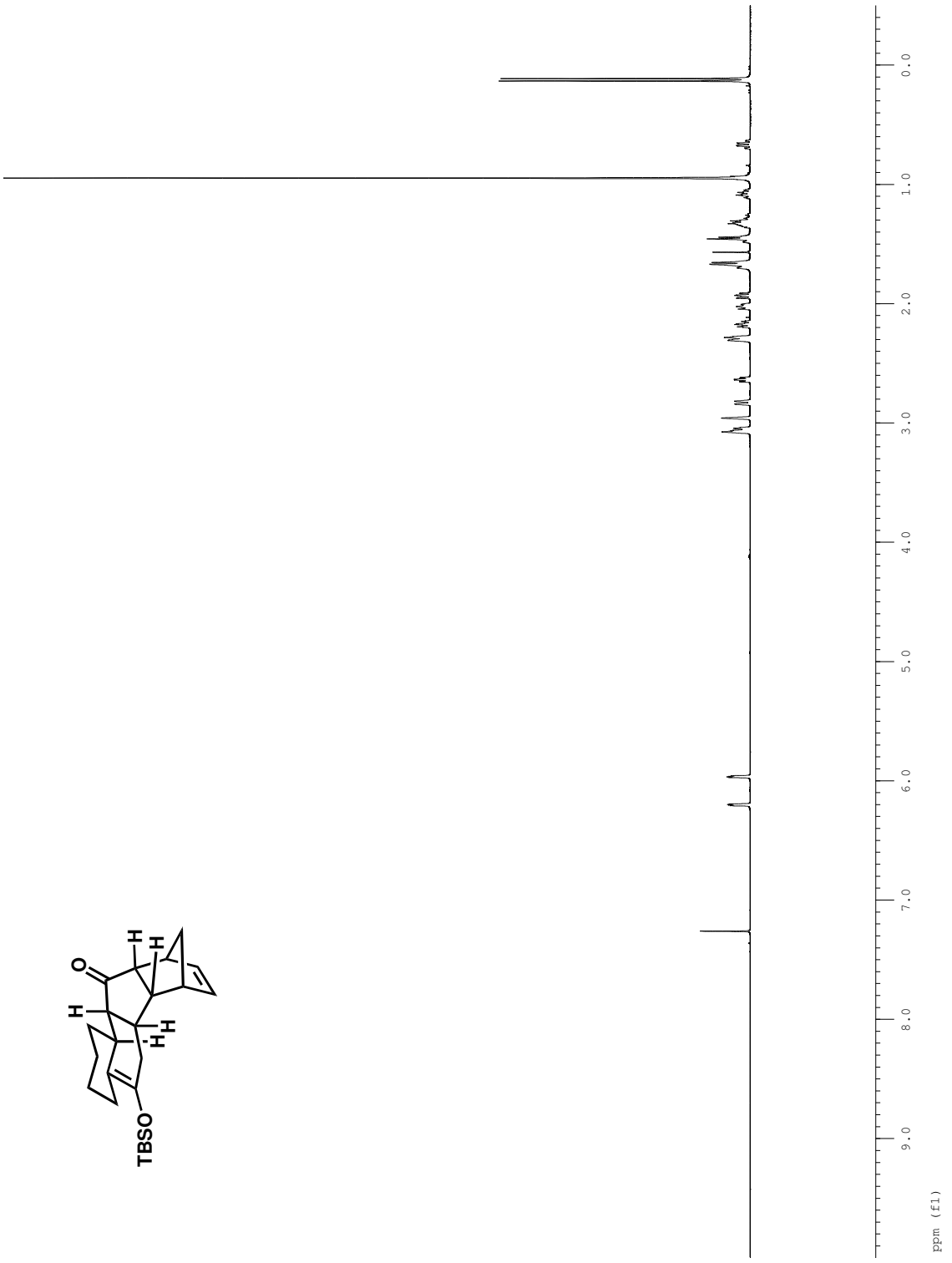


Figure A1.1 ^{1}H NMR (600 MHz, $CDCl_3$) of compound **2.11**.

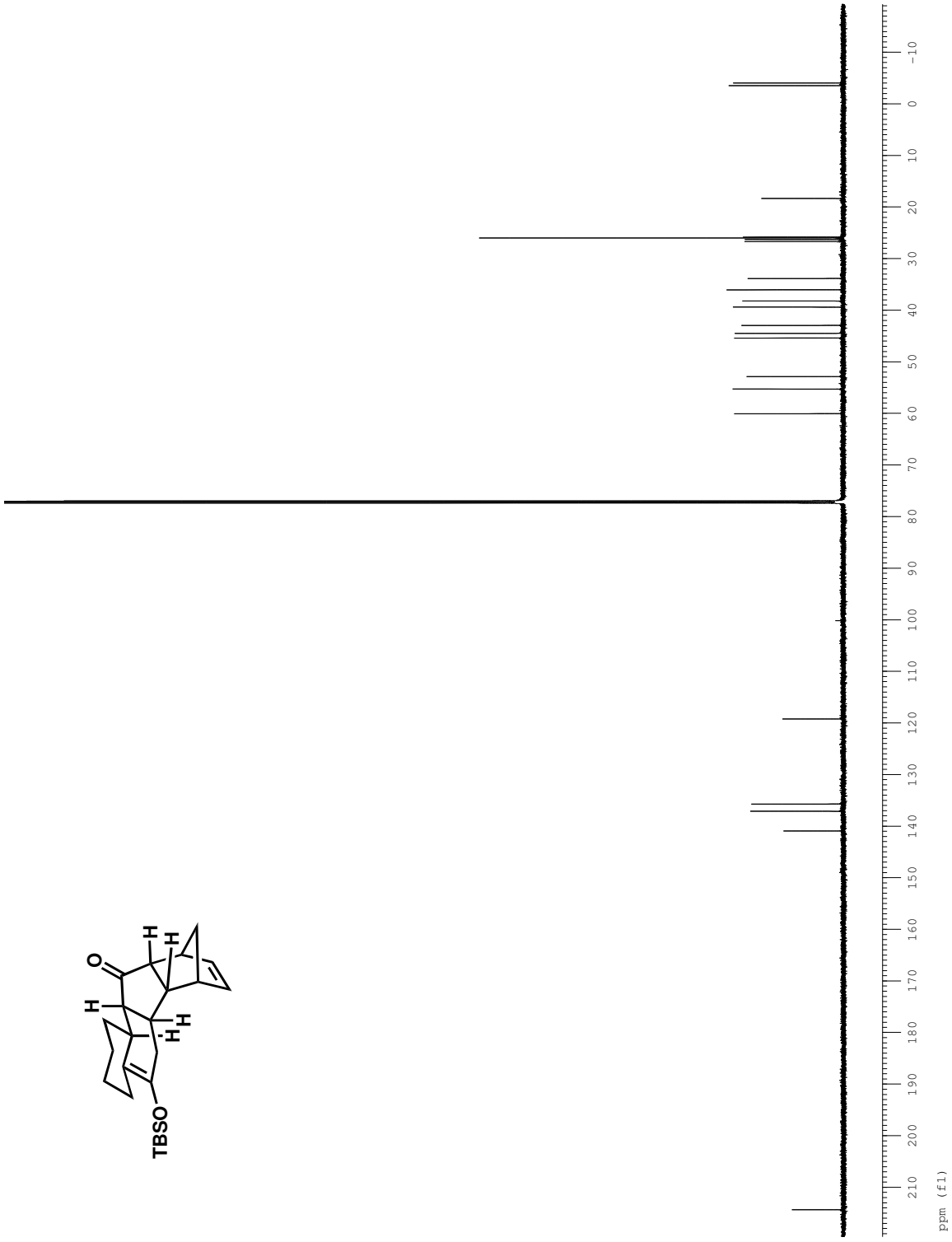


Figure A1.2 ^{13}C NMR (150 MHz, $CDCl_3$) of compound **2.11**.

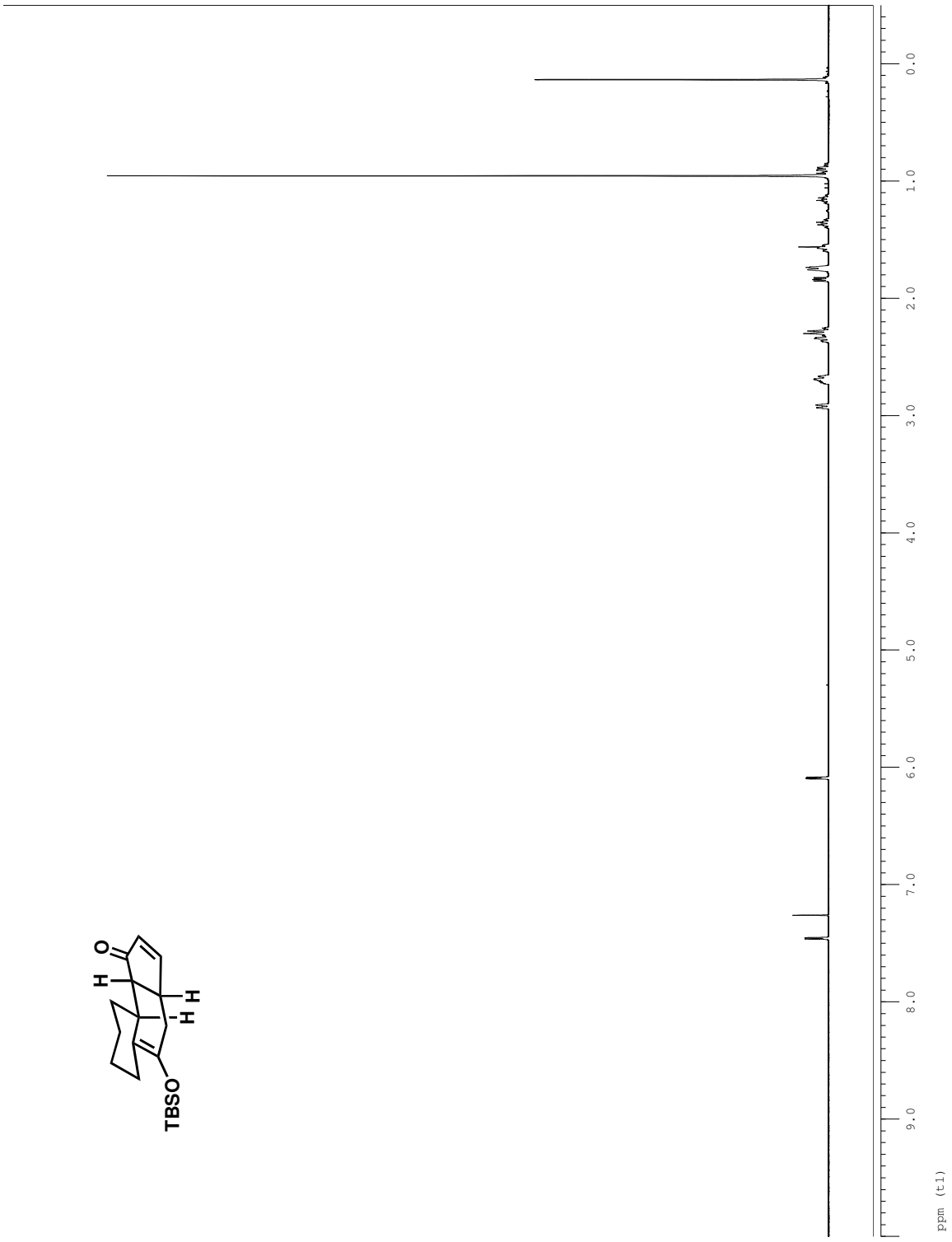


Figure A1.3 ^{1}H NMR (600 MHz, $CDCl_3$) of compound **2.18**.

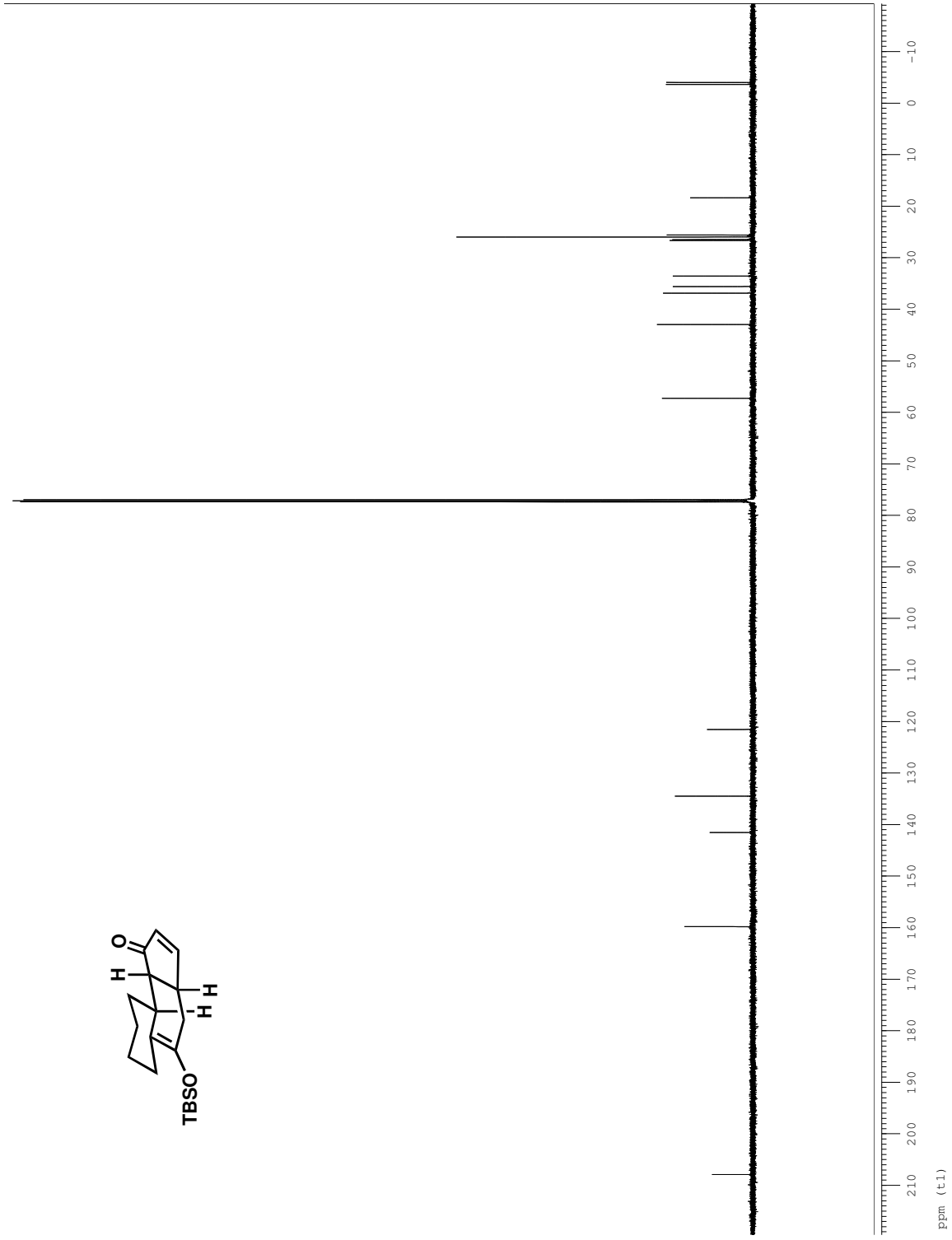


Figure A1.4 ^{13}C NMR (150 MHz, $CDCl_3$) of compound **2.18**.

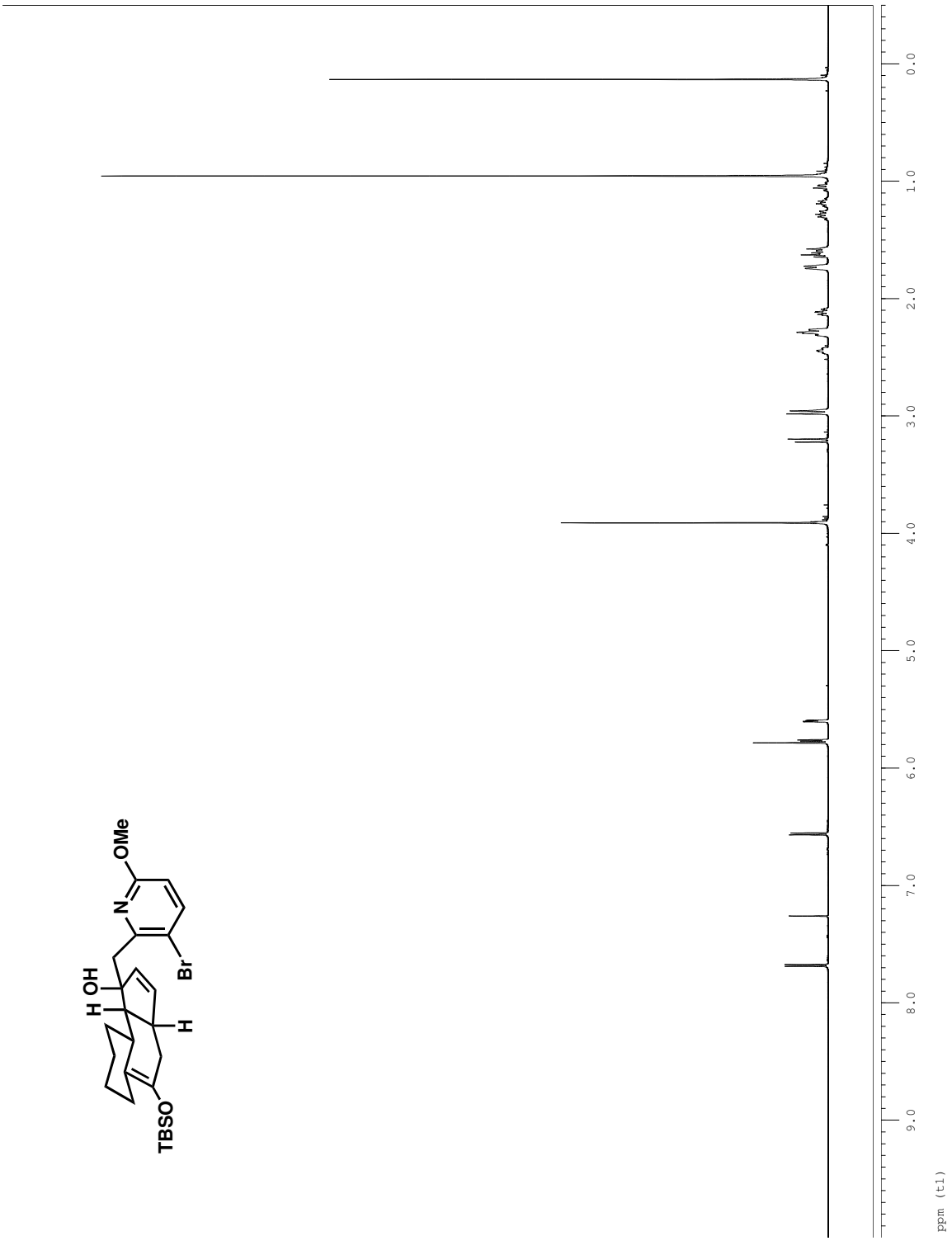


Figure A1.5 ^{1}H NMR (600 MHz, $CDCl_3$) of compound **2.47a**.

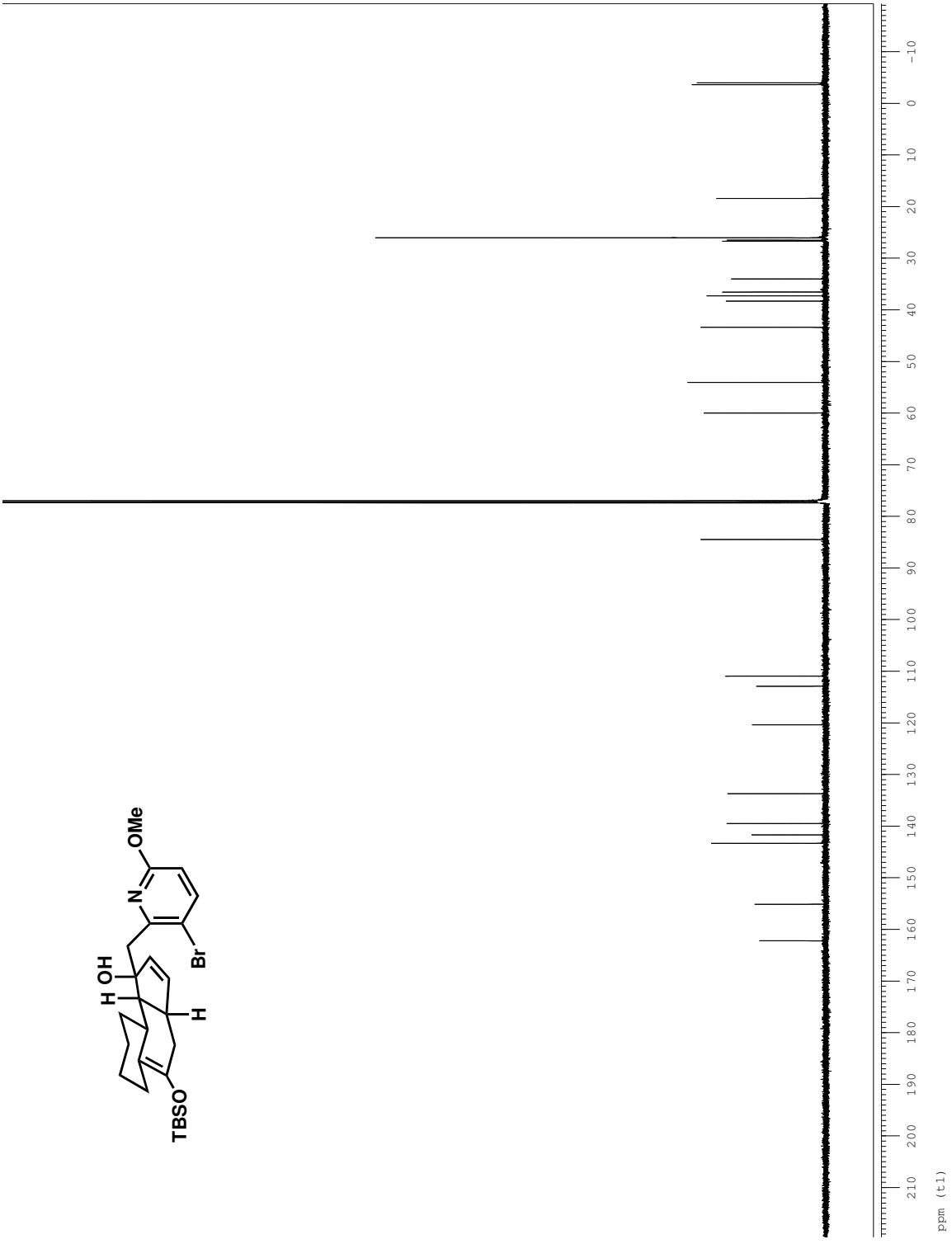


Figure A1.6 ^{13}C NMR (150 MHz, $CDCl_3$) of compound **2.47a**.

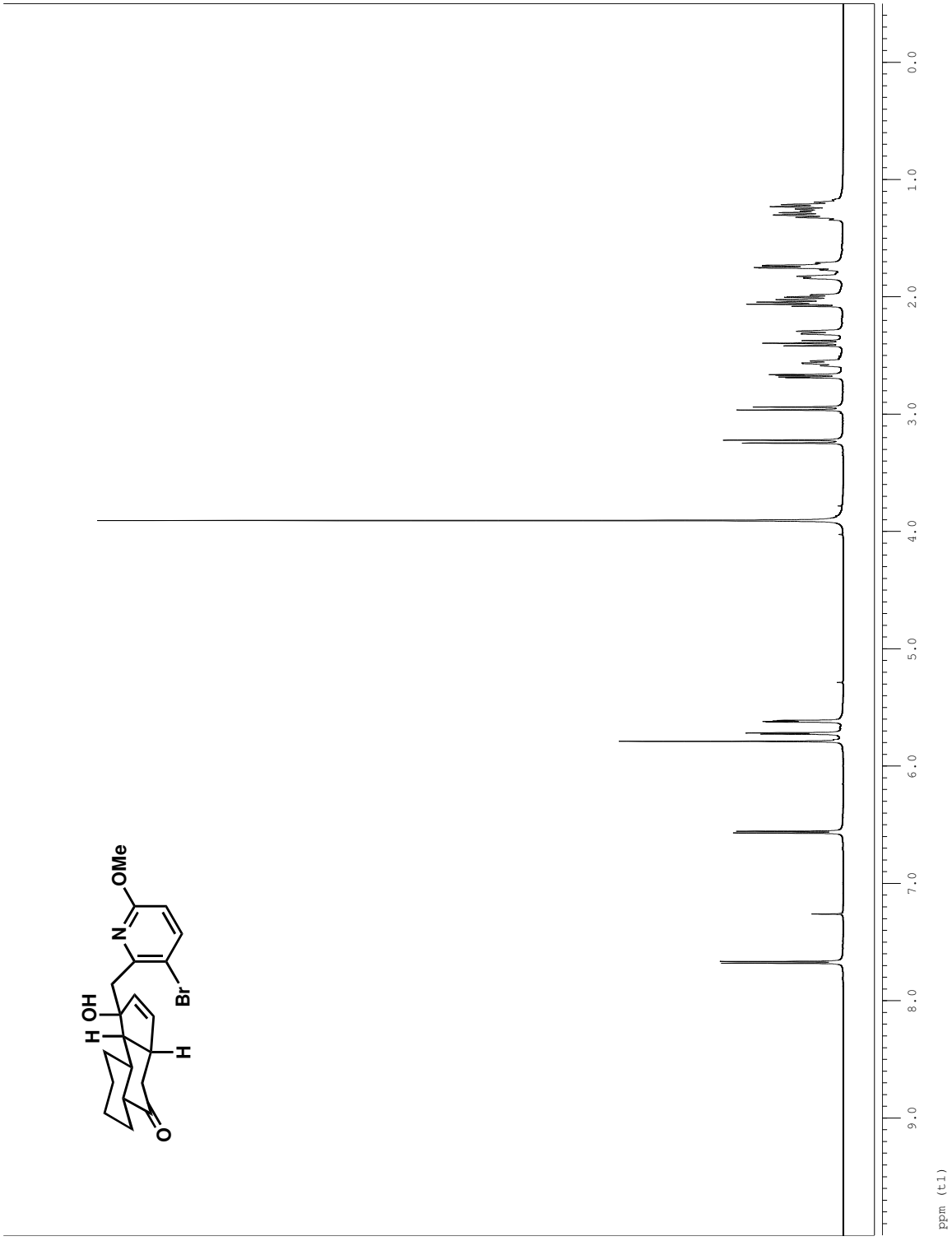


Figure A1.7 ^{1}H NMR (600 MHz, $CDCl_3$) of compound **2.47**.

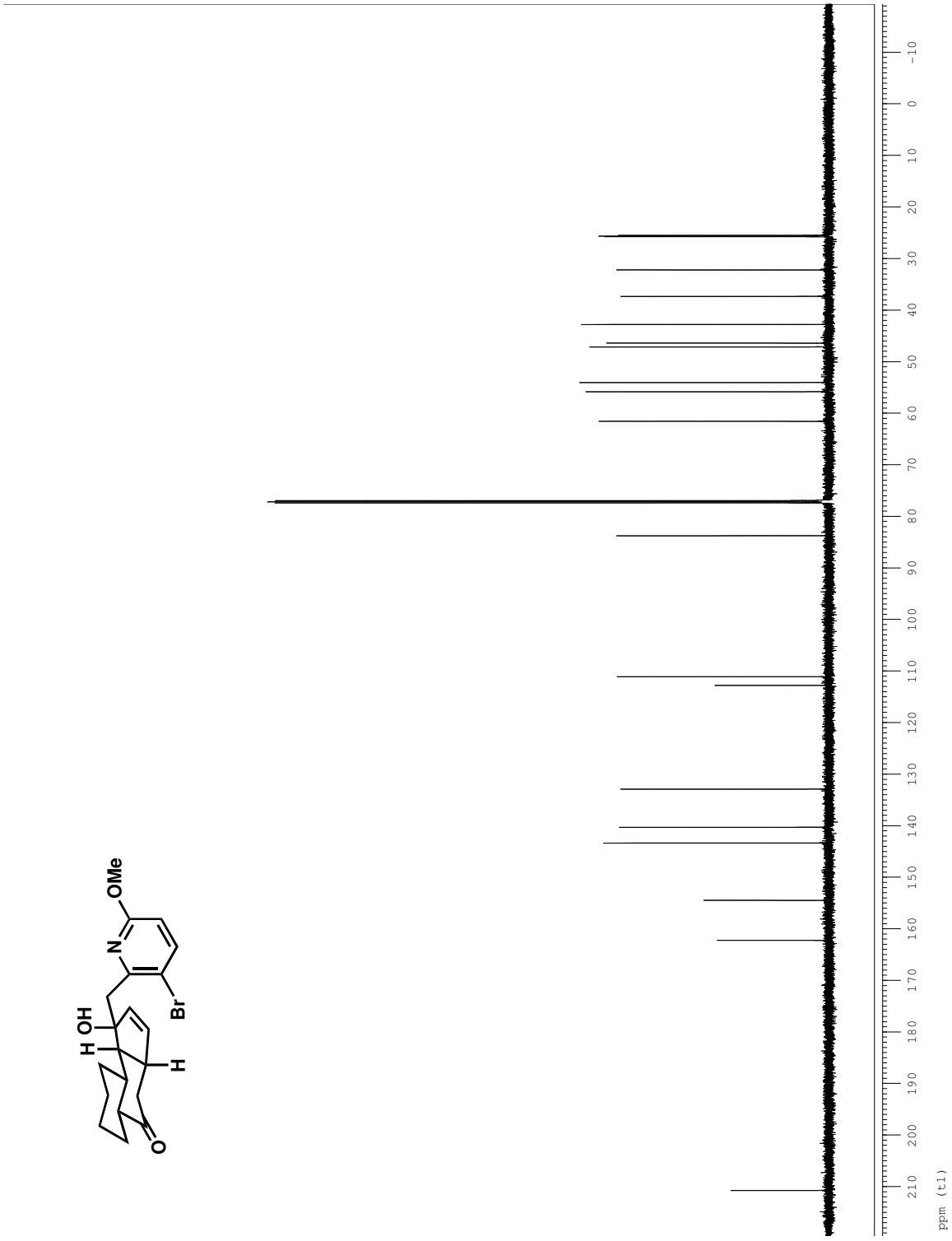


Figure A1.8 ^{13}C NMR (150 MHz, $CDCl_3$) of compound **2.47**.

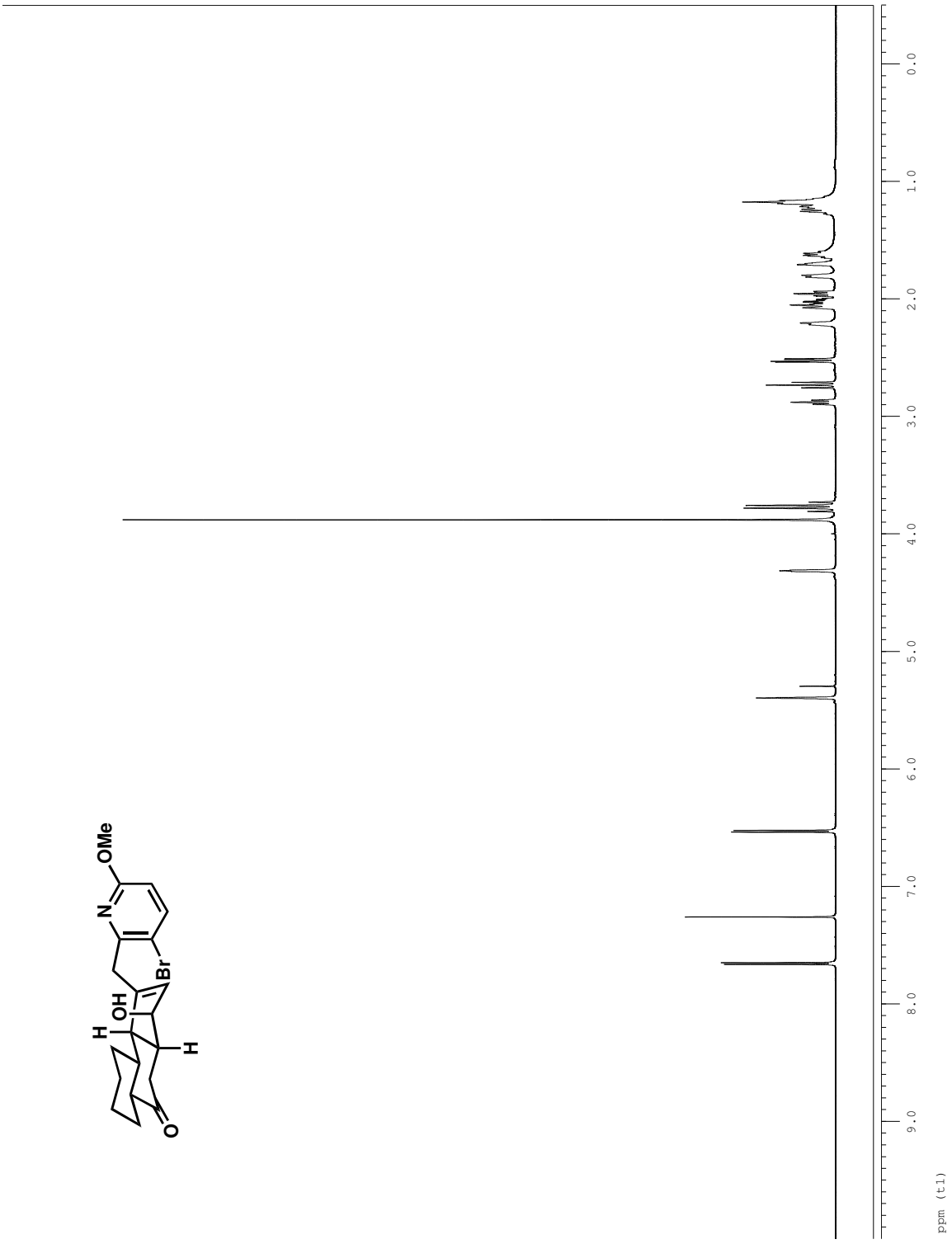


Figure A1.9 ^{1}H NMR (600 MHz, $CDCl_3$) of compound **2.82**.

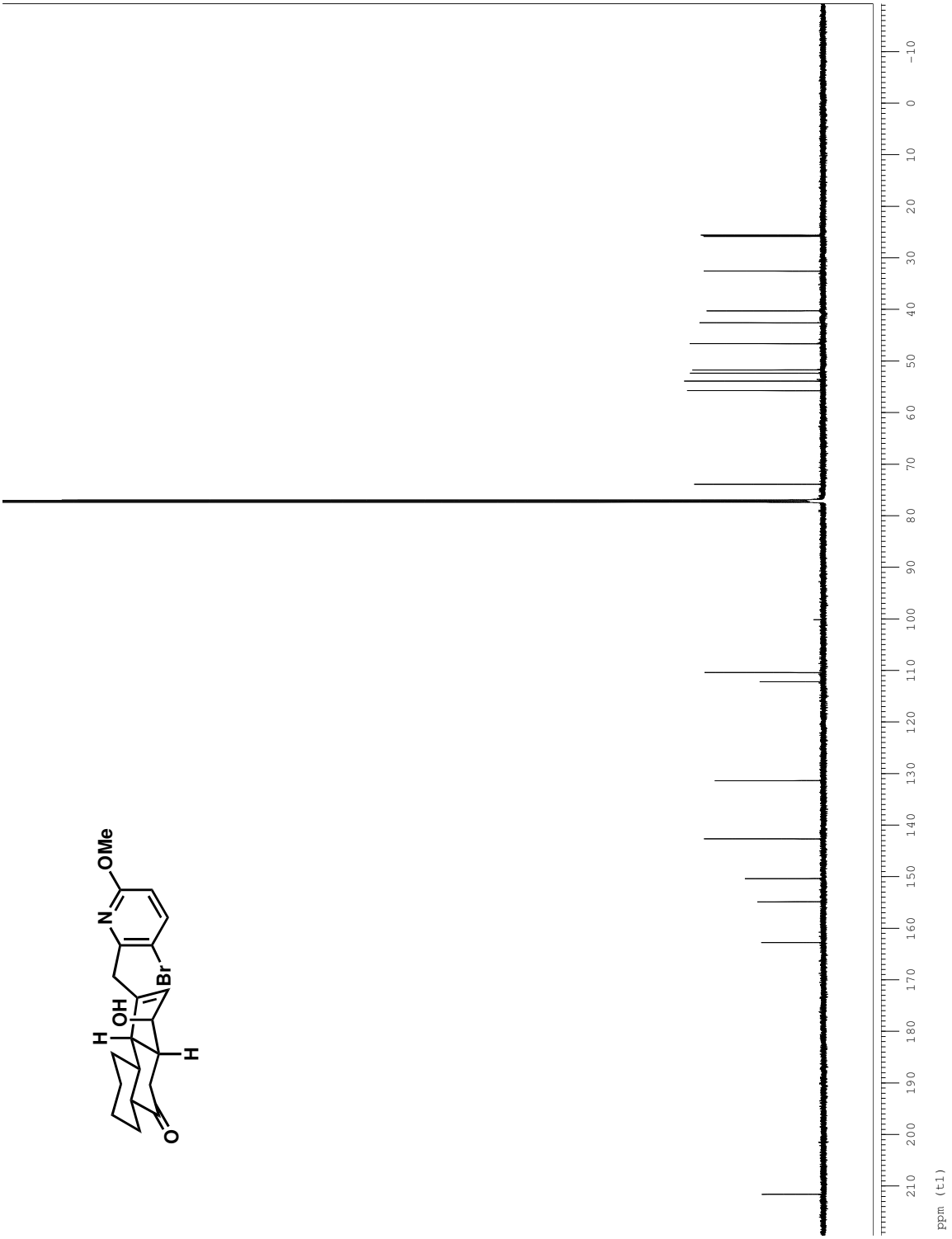


Figure A1.10 ^{13}C NMR (150 MHz, $CDCl_3$) of compound **2.82**.

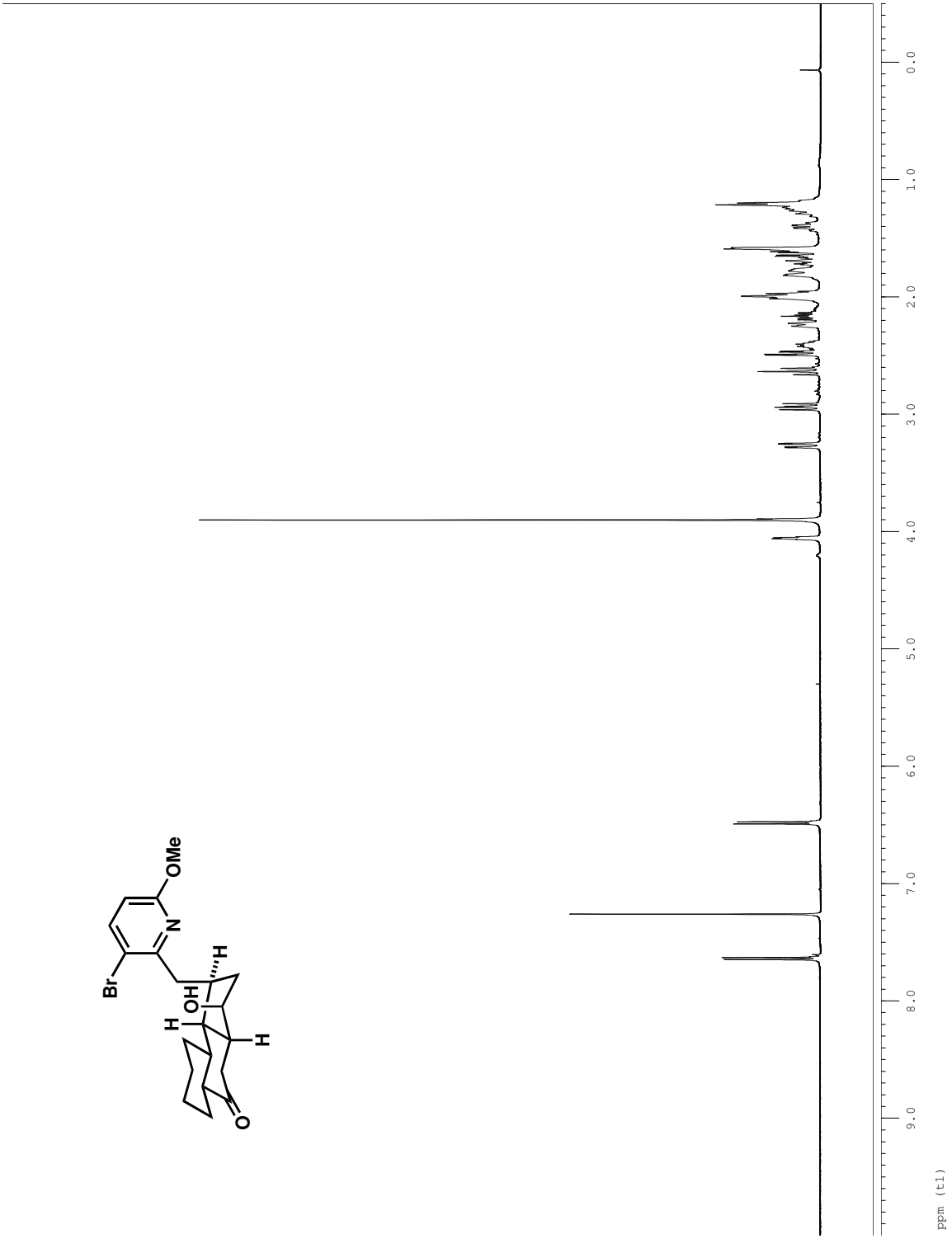


Figure A1.11 ^{1}H NMR (600 MHz, $CDCl_3$) of compound **2.85**.

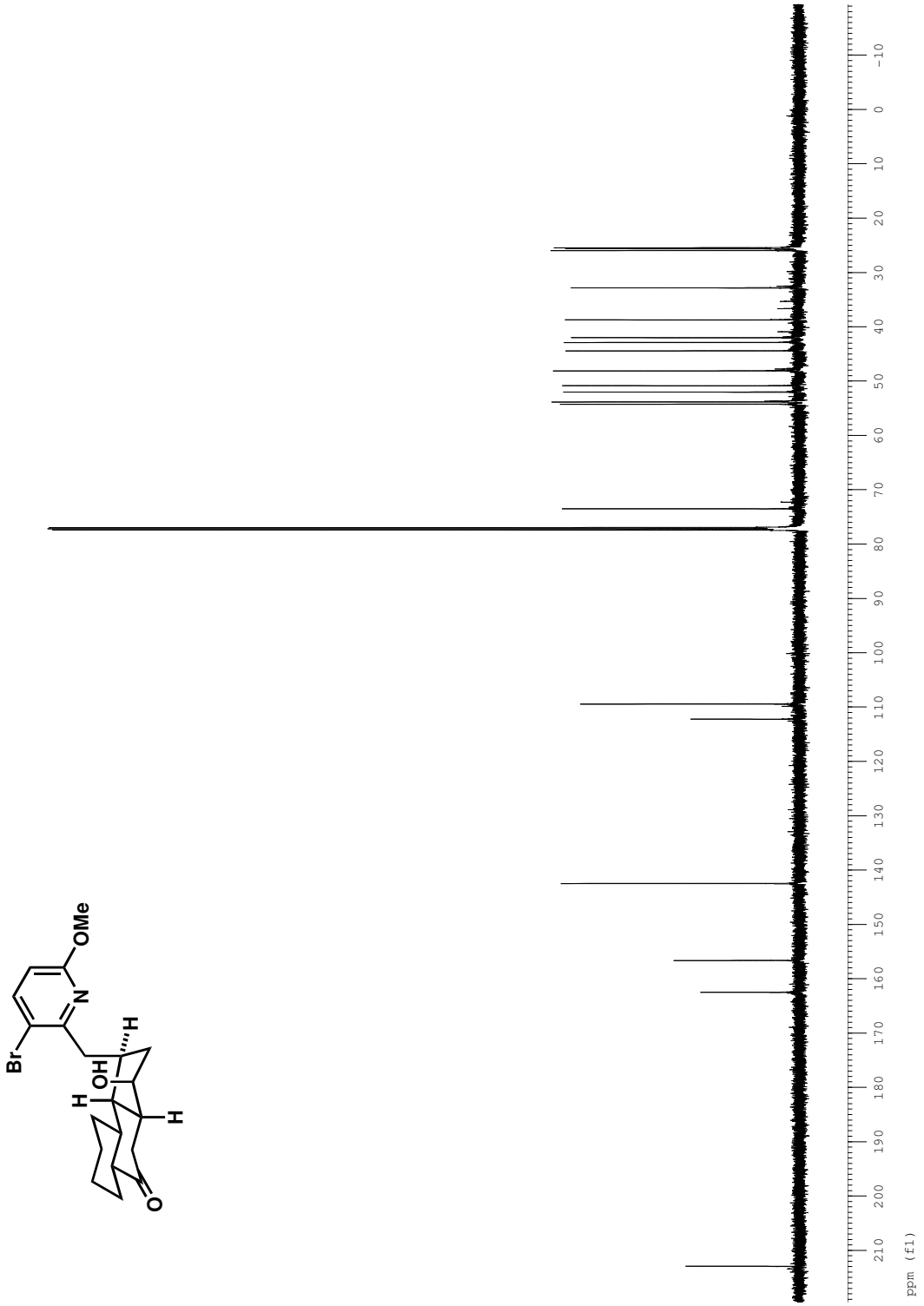


Figure A1.12 ^{13}C NMR (150 MHz, $CDCl_3$) of compound **2.85**.

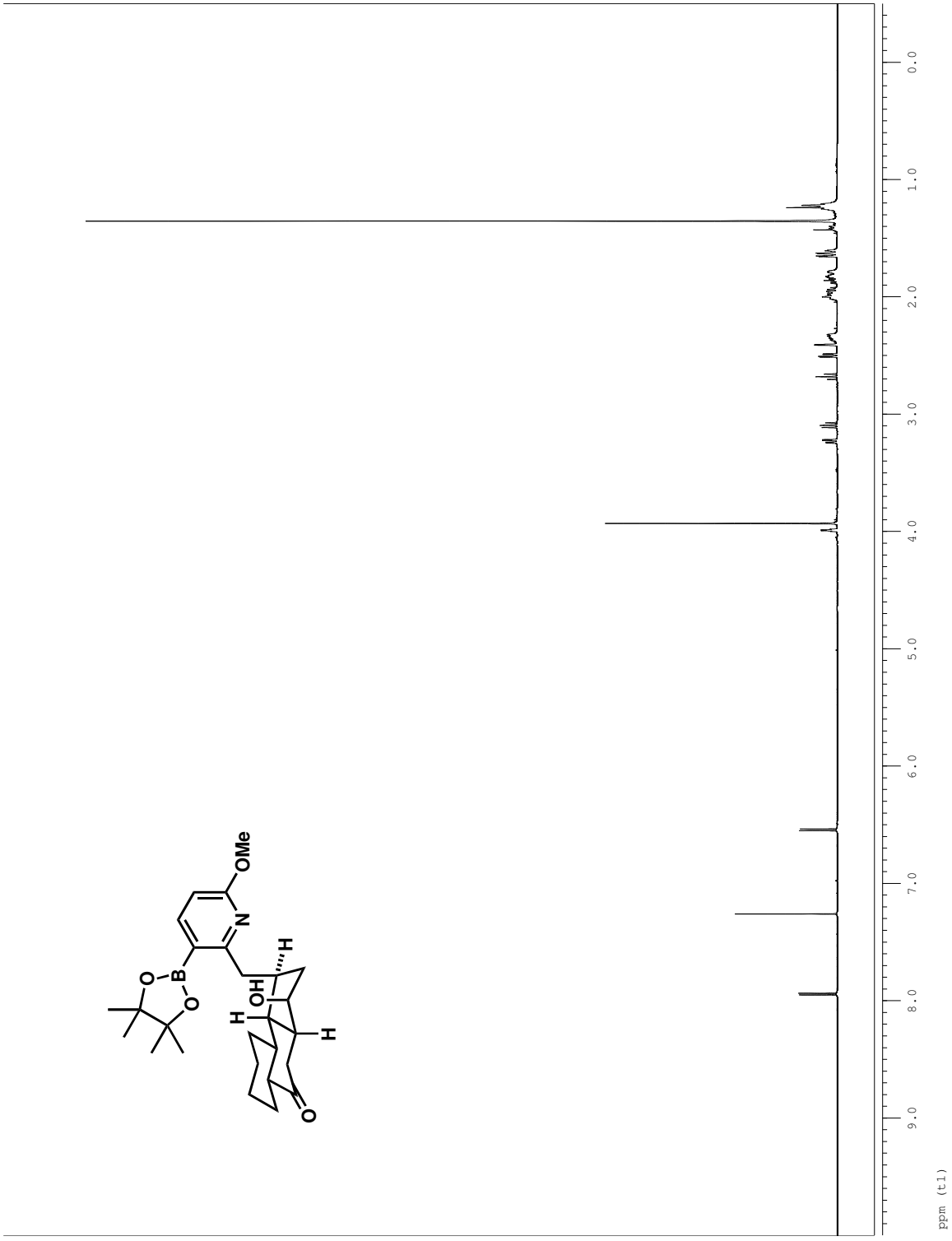


Figure A1.13 ^{1}H NMR (600 MHz, $CDCl_3$) of compound **2.116**.

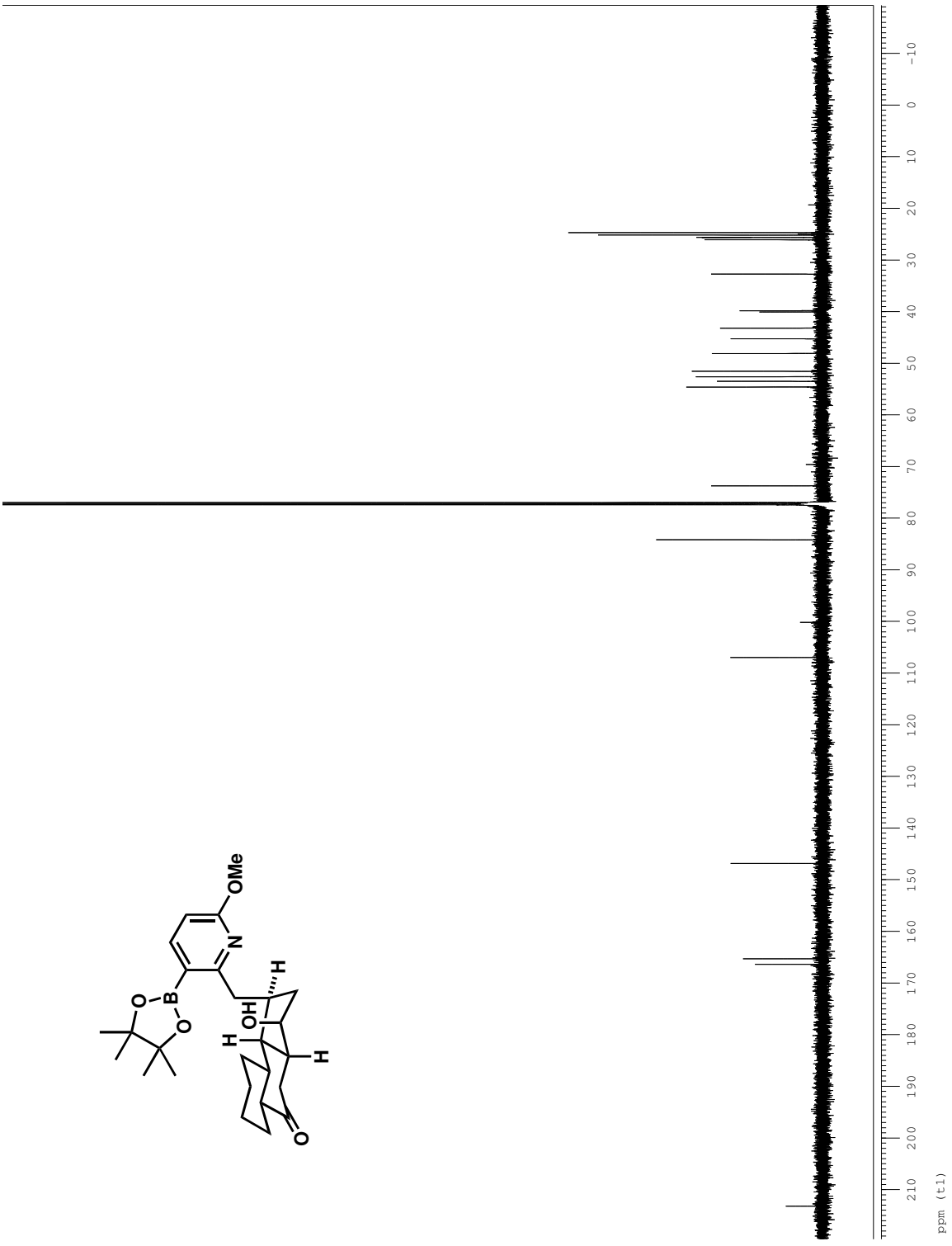


Figure A1.14 ^{13}C NMR (150 MHz, $CDCl_3$) of compound **2.116**.

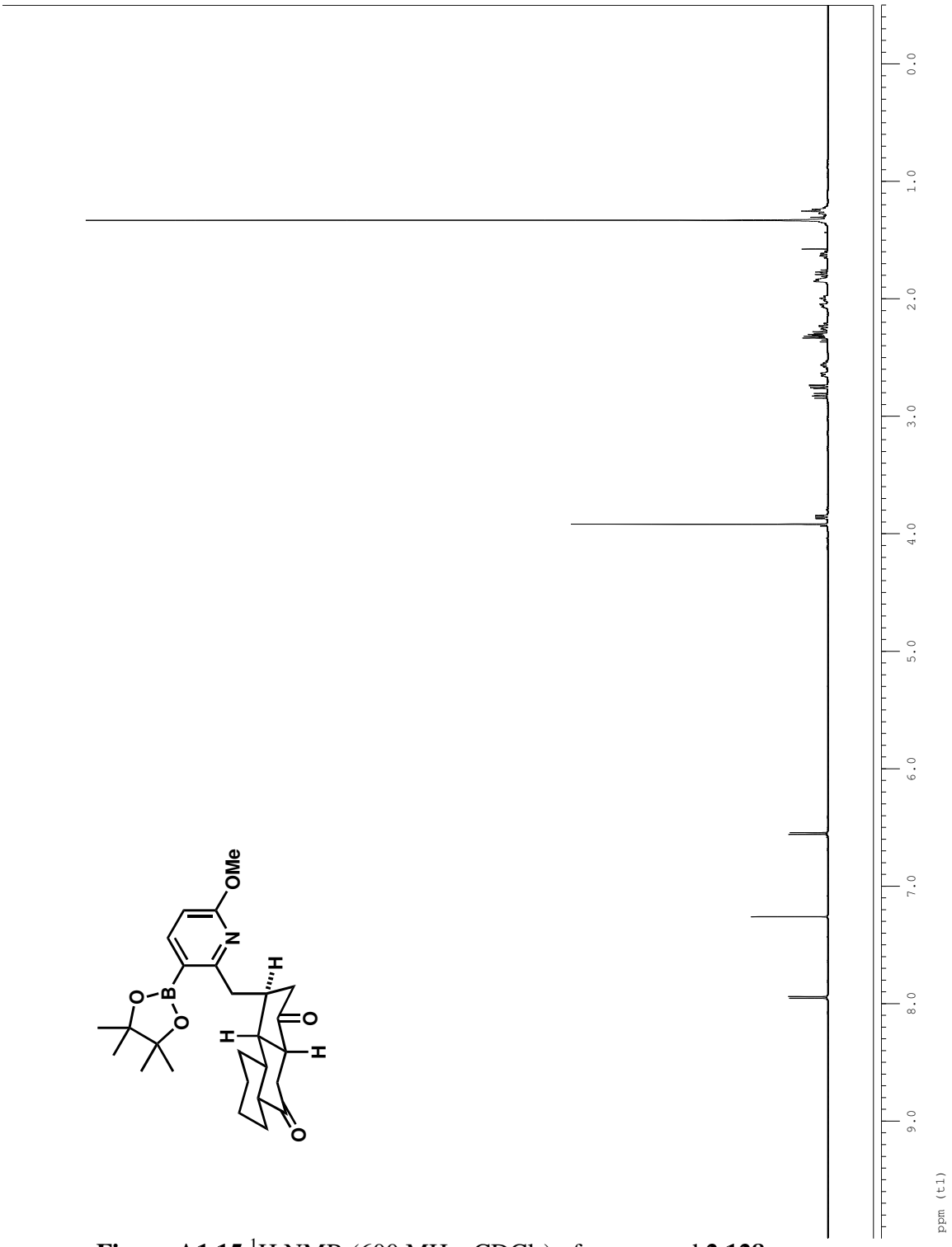


Figure A1.15 ^{1}H NMR (600 MHz, $CDCl_3$) of compound **2.128**.

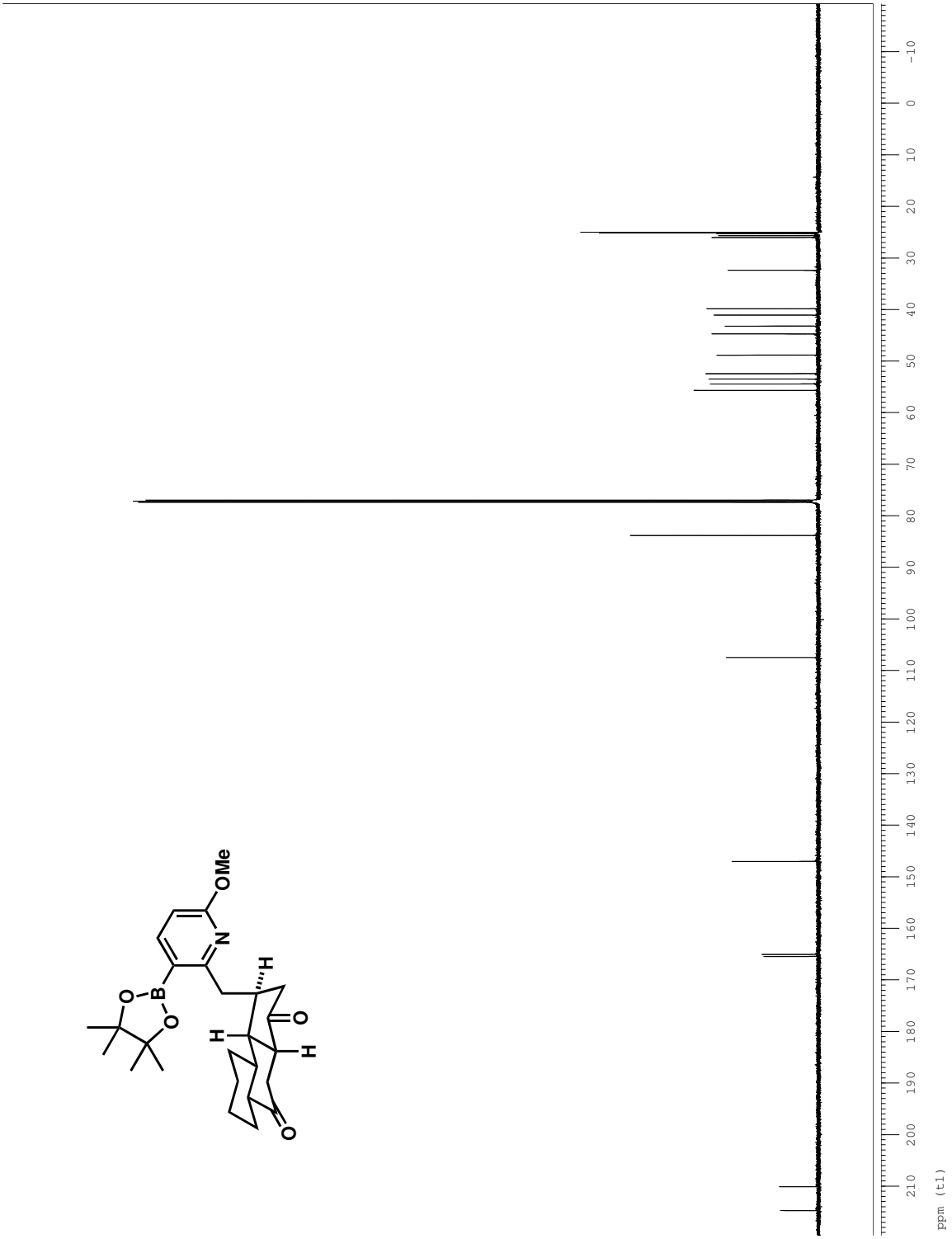


Figure A1.16 ^{13}C NMR (150 MHz, $CDCl_3$) of compound **2.128**.

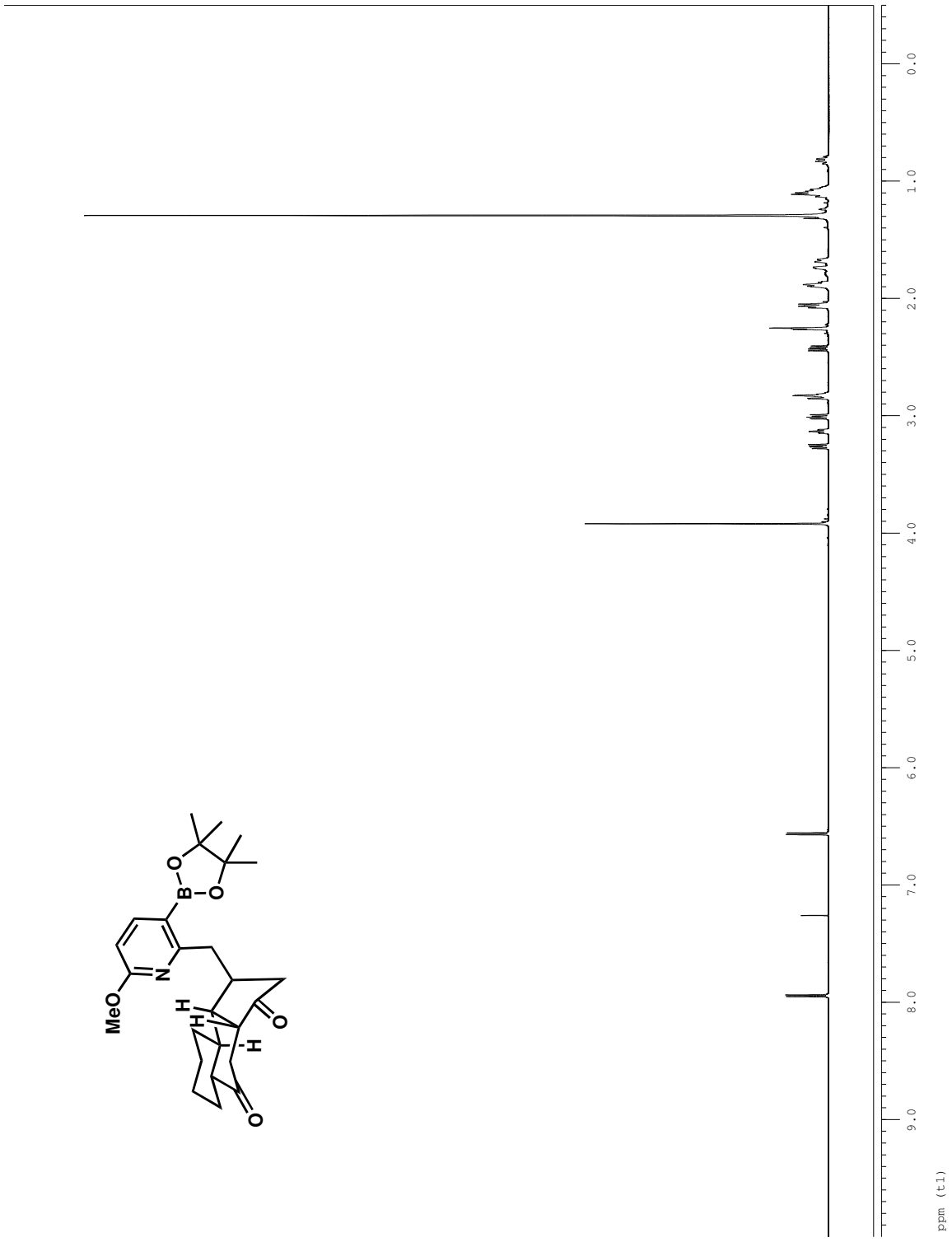


Figure A1.17 ^{1}H NMR (600 MHz, $CDCl_3$) of compound **2.115**.

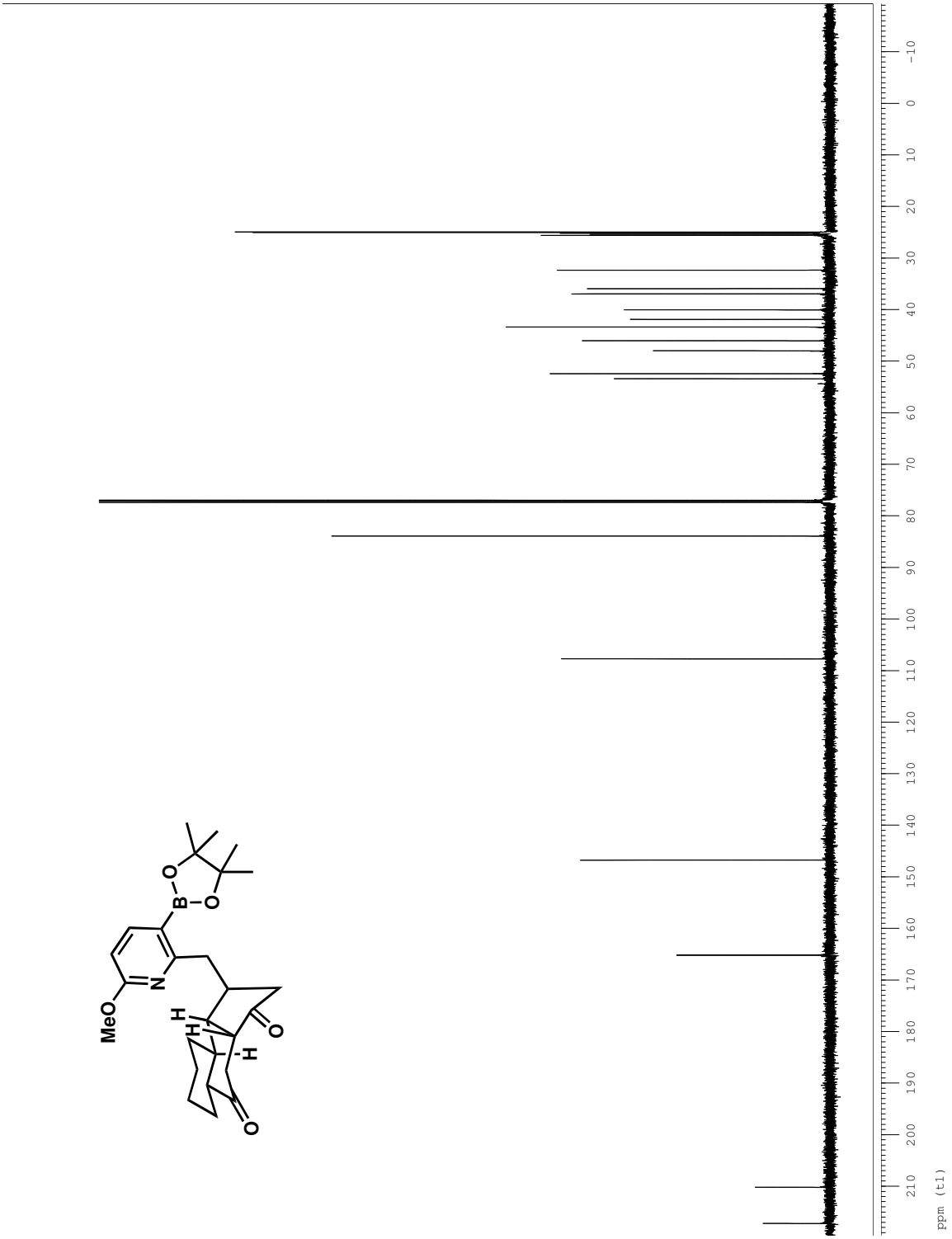


Figure A1.18 ^{13}C NMR (150 MHz, $CDCl_3$) of compound **2.115**.

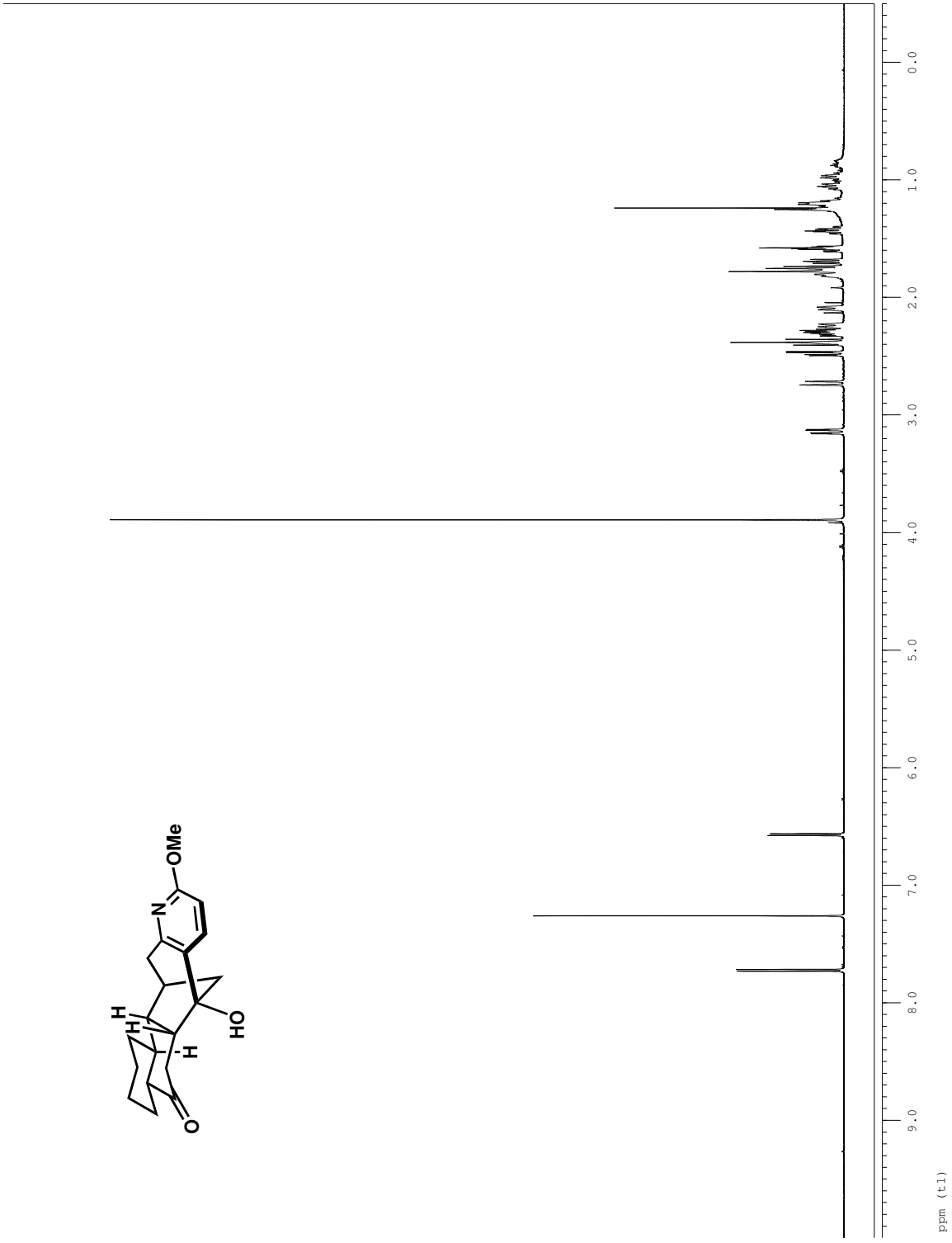


Figure A1.19 ^{1}H NMR (600 MHz, $CDCl_3$) of compound **2.127**.

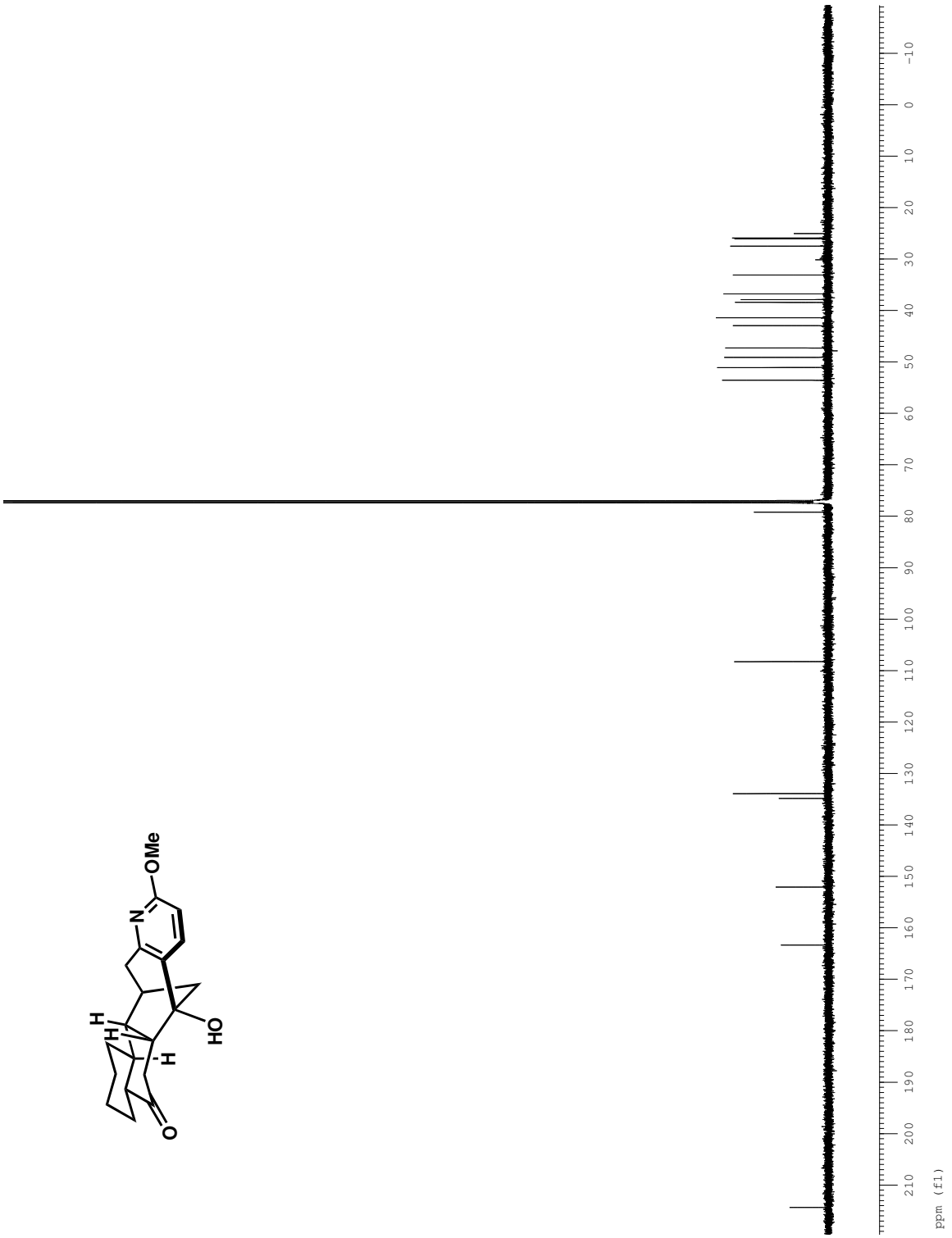


Figure A1.20 ^{13}C NMR (150 MHz, $CDCl_3$) of compound **2.127**.

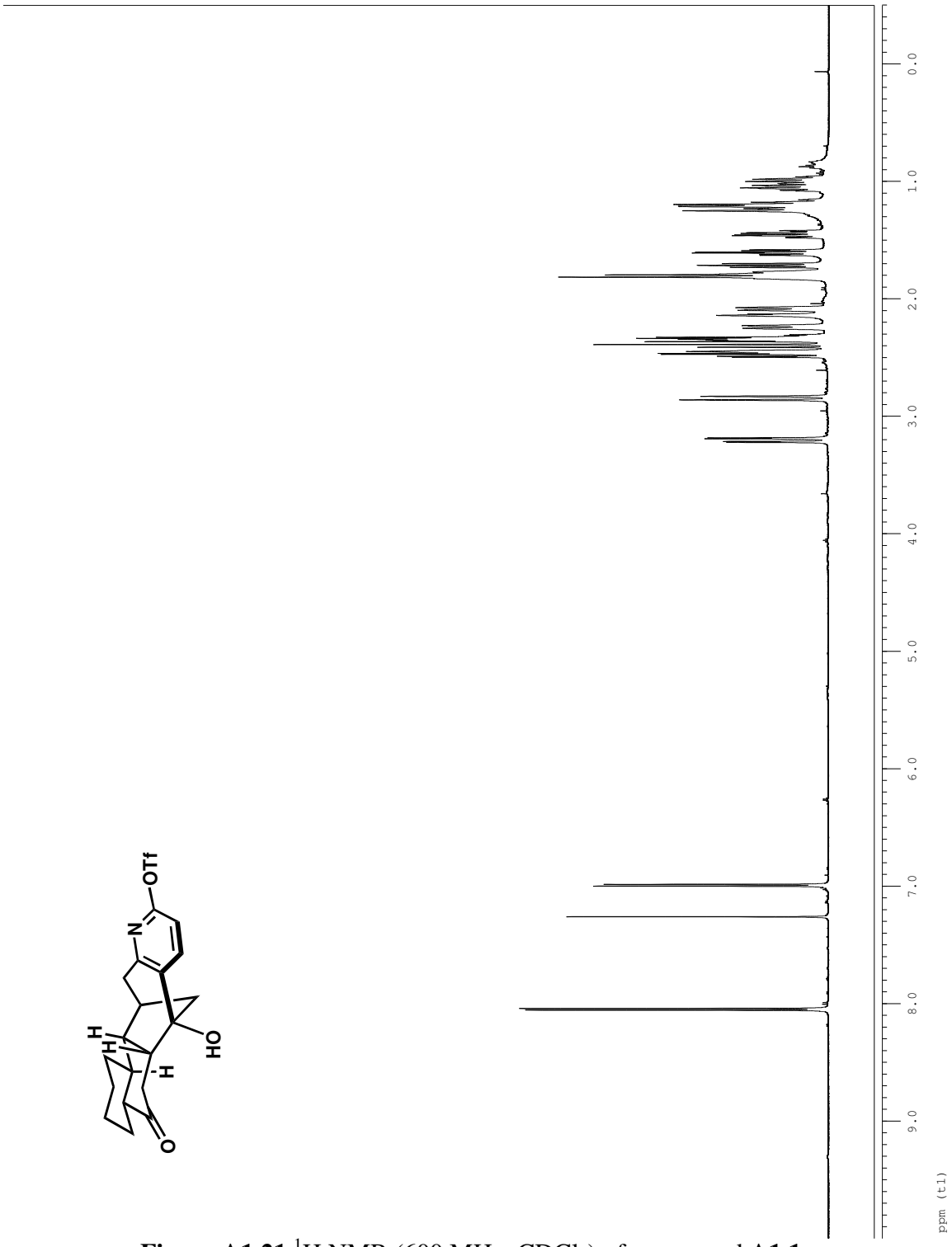


Figure A1.21 ^{1}H NMR (600 MHz, $CDCl_3$) of compound **A1.1**.

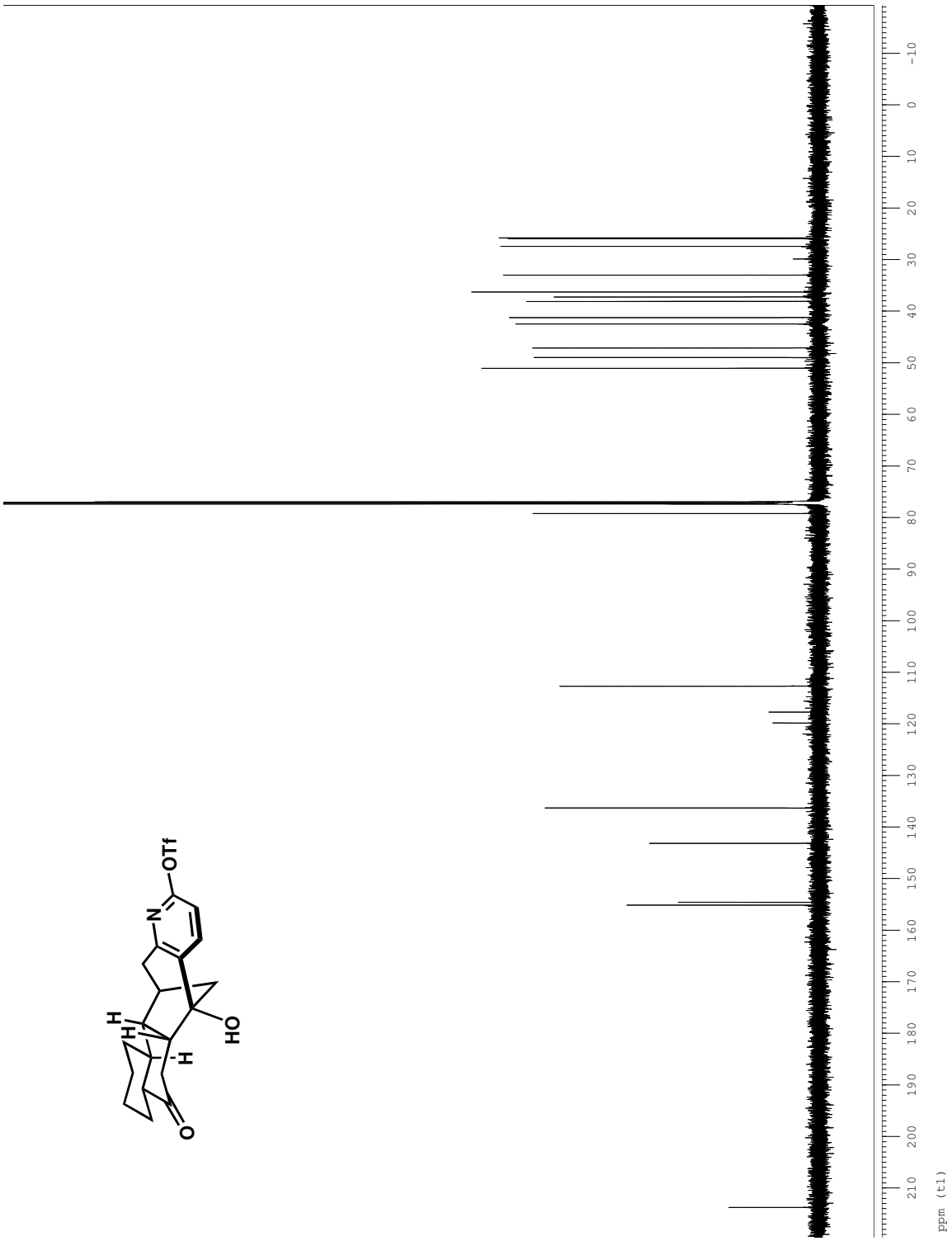


Figure A1.22 ^{13}C NMR (150 MHz, $CDCl_3$) of compound **A1.1**.

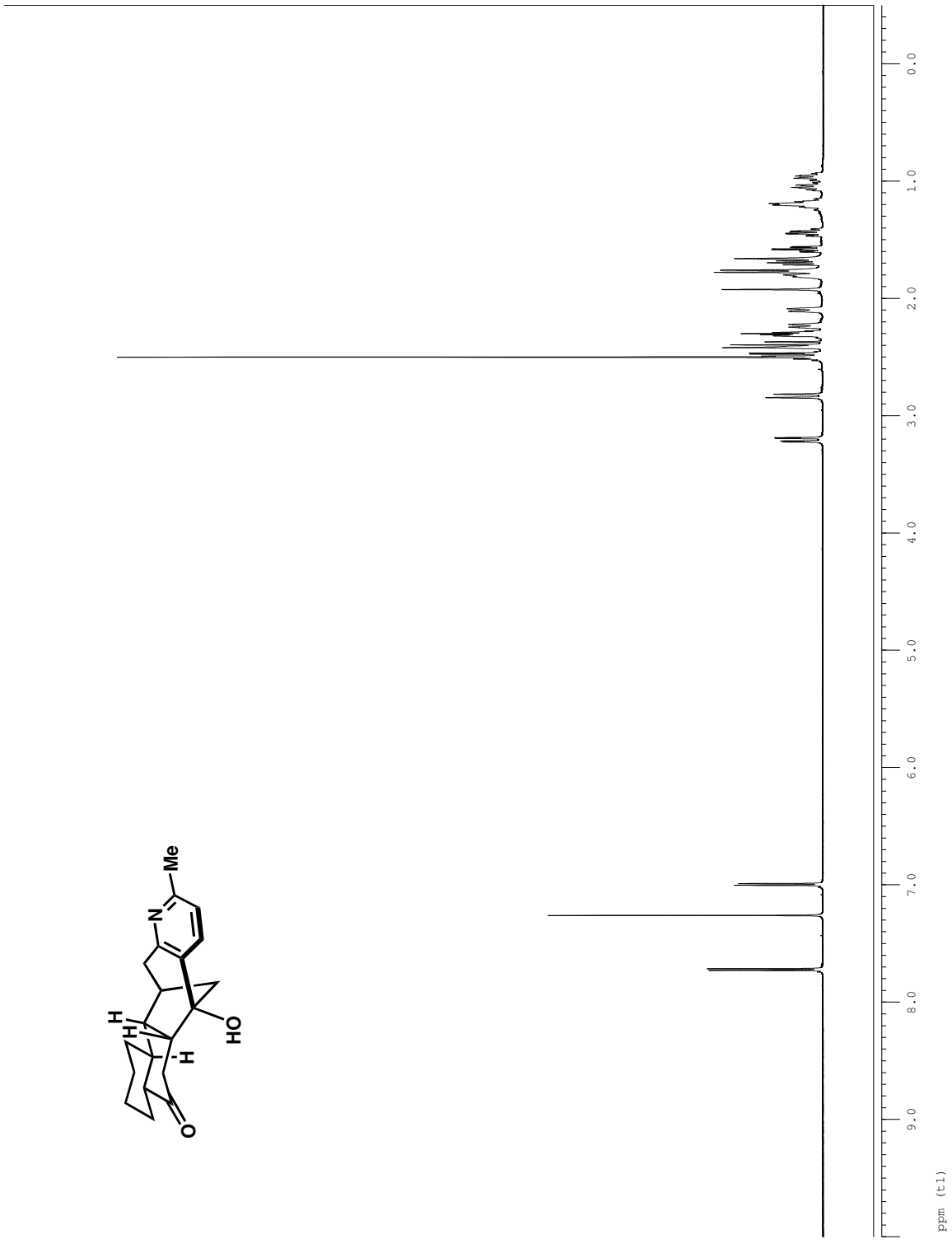


Figure A1.23 ^{1}H NMR (600 MHz, $CDCl_3$) of compound **2.132**.

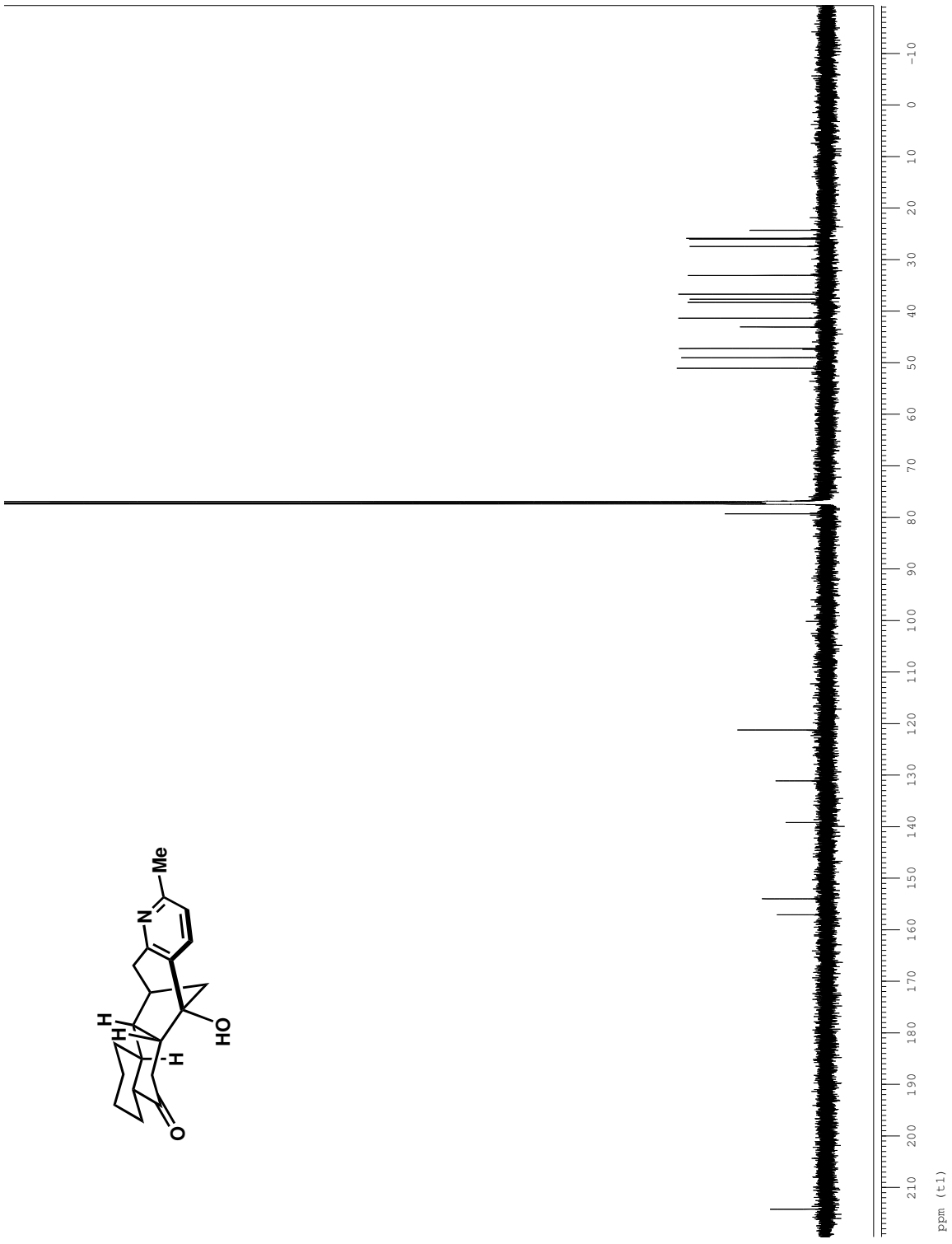


Figure A1.24 ^{13}C NMR (150 MHz, $CDCl_3$) of compound **2.132**.

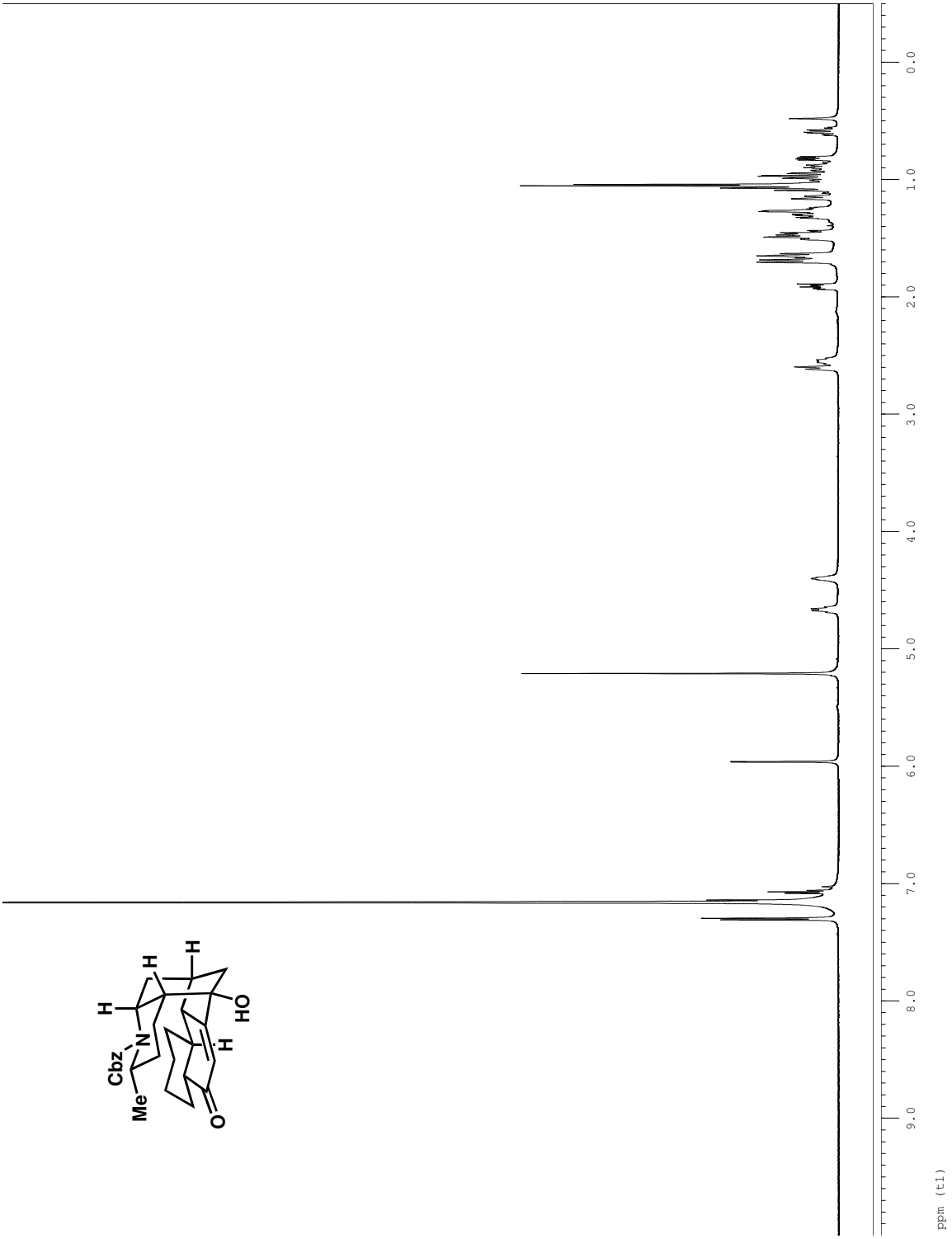


Figure A1.25 ^{1}H NMR (600 MHz, C_6D_6) of compound **2.133**.

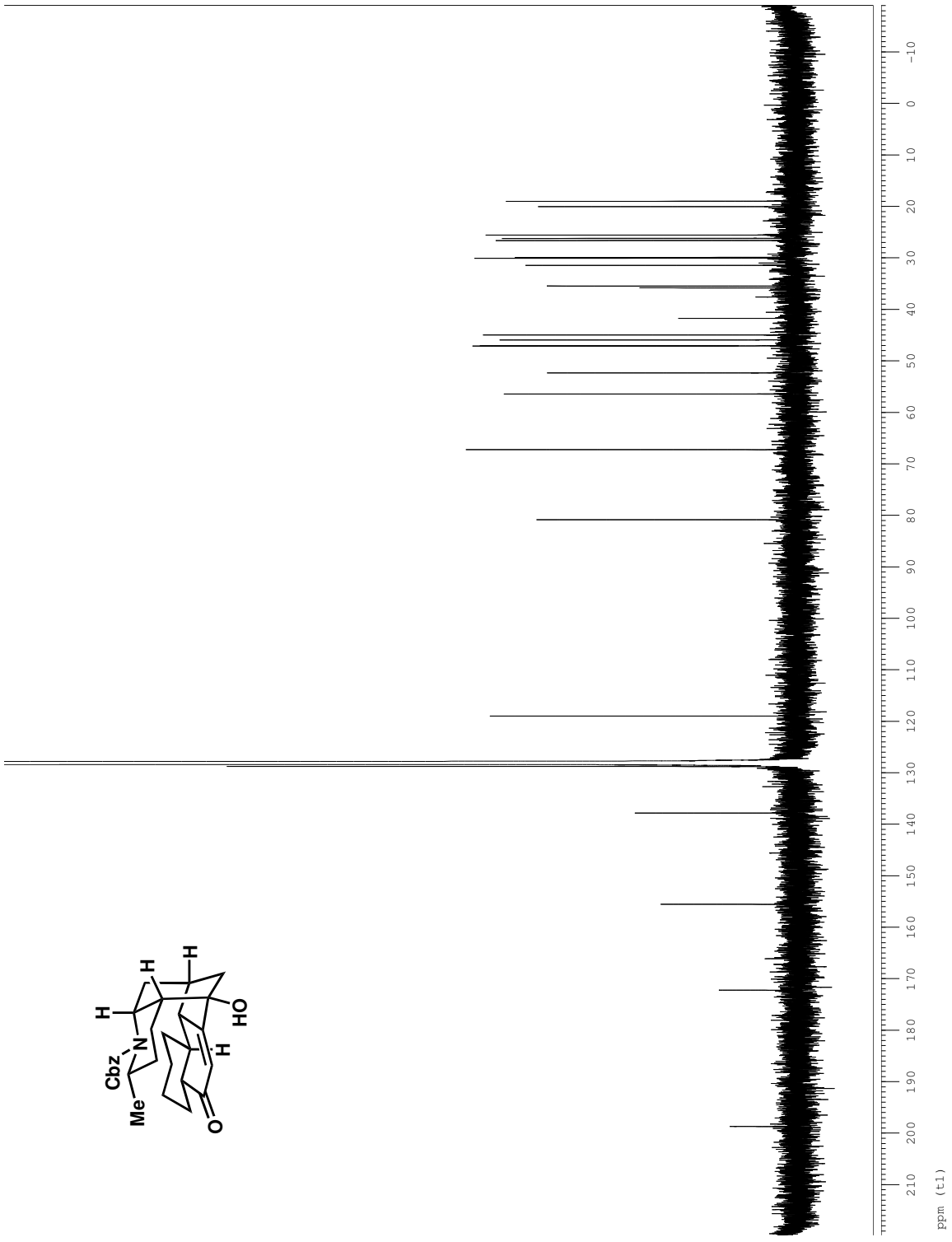


Figure A1.26 ^{13}C NMR (150 MHz, C_6D_6) of compound **2.133**.

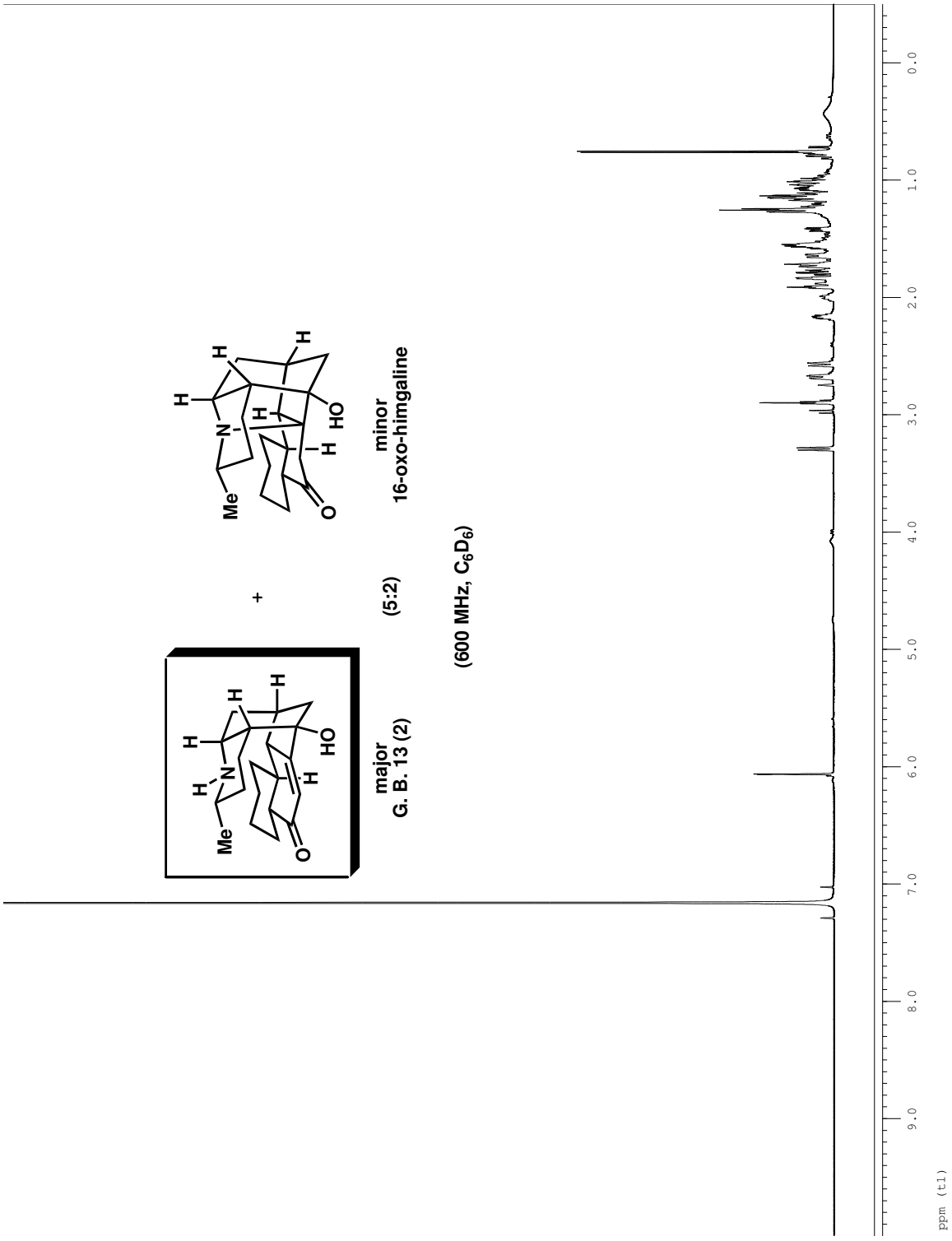


Figure A1.27 ^{1}H NMR (600 MHz, C_6D_6) of compounds **2.1** and **2.134**.

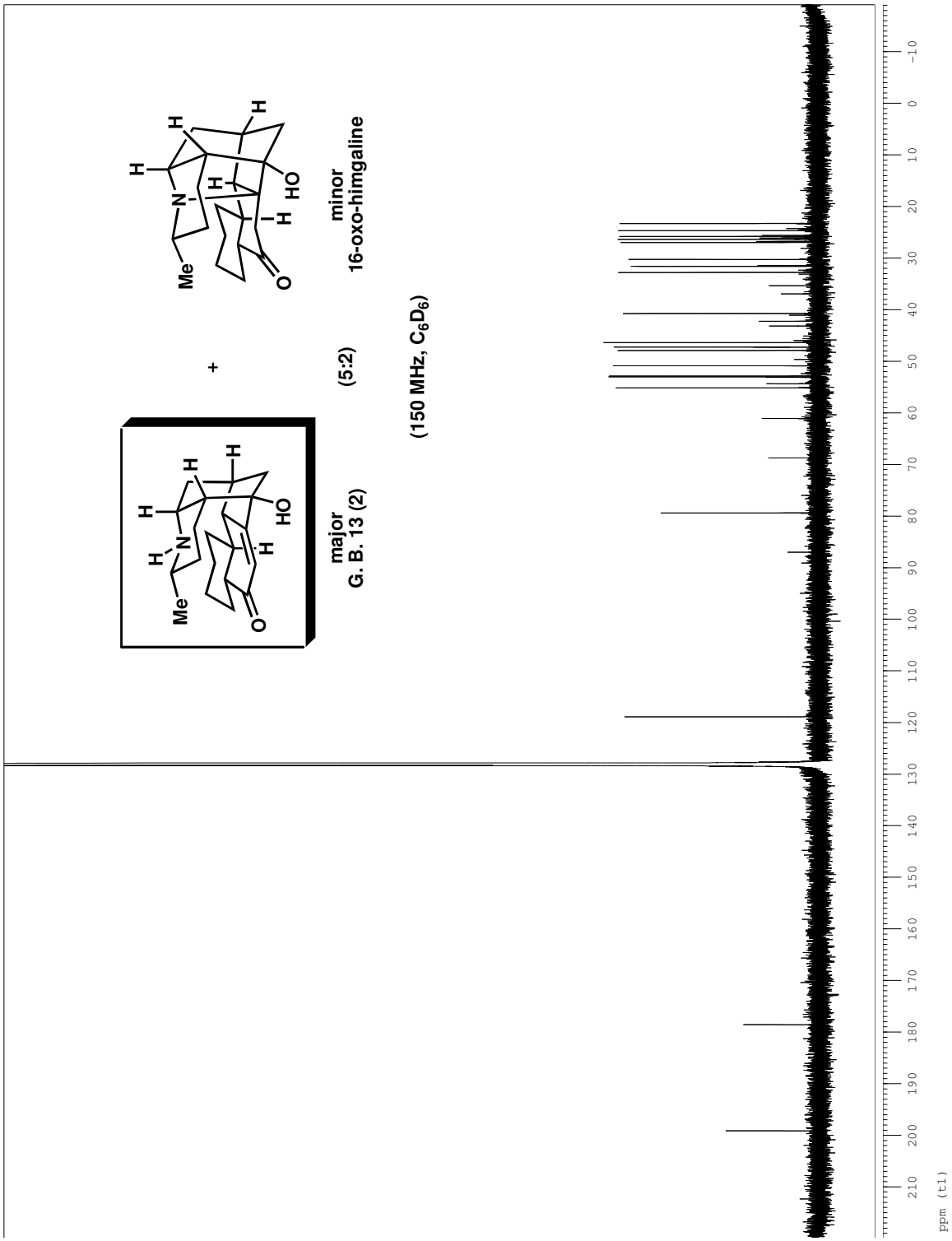


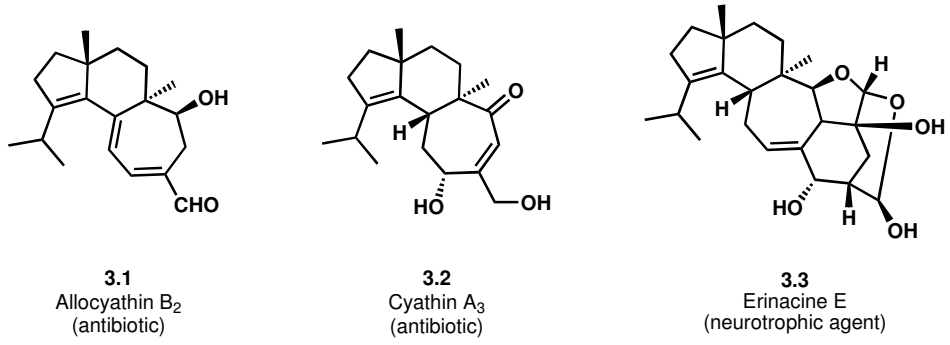
Figure A1.28 ^{13}C NMR (150 MHz, C_6D_6) of compounds **2.1** and **2.134**.

Chapter Three

Development of an Anomalous Heck Reaction

3.1 Introduction

The high degree of architectural complexity associated with natural products deems them excellent targets for total synthesis driven by the prospect of developing new chemical methods. Despite the abundance of natural products possessing seven-membered rings, general methods for the synthesis of this ring size remain limited. To this end, we identified the cyathane family of seven-membered ring containing natural products (Figure 3.1) whose common [5-6-7] tricyclic core could be accessed through a novel process. In the cyathane family, allocyathin B_2 (**3.1**) and cyathin A_3 (**3.2**), first isolated from the fungus *Cyathus helenai* Brodie, possess antibiotic activity,[1] while erinacine E (**3.3**), which was isolated from the mycelia of *Hericium erinaceum*, is a neurotrophic agent.[2]



3.1
Allocyathin B_2
(antibiotic)

3.2
Cyathin A_3
(antibiotic)

3.3
Erinacine E
(neurotrophic agent)

Figure 3.1 Selected cyathane diterpenoid natural products.

We envisioned forming the seven-membered ring of the cyathane core (**3.4**, Figure 3.2) through a double-Heck cyclization reaction between a vicinally-substituted "dihalide" (**3.5**) and a divinyl carbinol (e.g., **3.6**). "Dihalide" **3.5** could ultimately be derived from the Hajos-Parrish ketone (**3.7**).

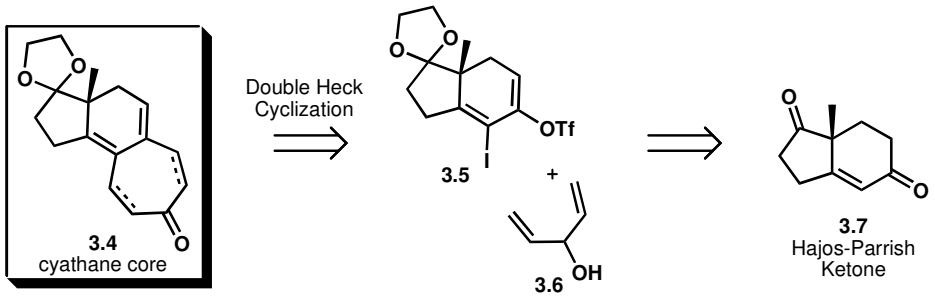
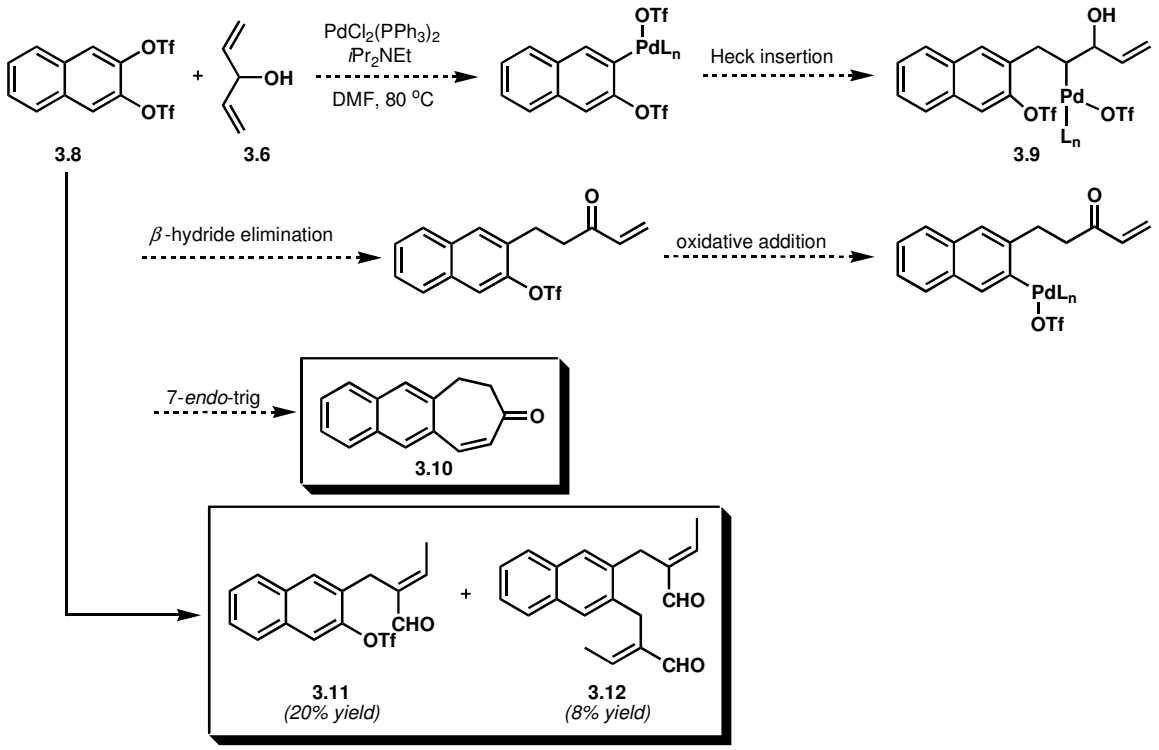


Figure 3.2 Retrosynthesis of cyathane core via double Heck cyclization.

In order to determine the viability of using a double Heck cyclization approach to synthesize seven-membered rings, we prepared bis-triflate **3.8** (Scheme 3.1) as a model system

and subjected it to standard Heck conditions using divinyl carbinol **3.6** as the coupling partner. We expected that after initial oxidative addition and migratory insertion, intermediate **3.9** would undergo β-hydride elimination to regenerate Pd(0). At this point, the palladium could oxidatively add into the other carbon-triflate bond and insert across the pendant olefin, hopefully in a 7-*endo*-trig manner, to give annulated product **3.10**. In actuality, a complex mixture of products resulted, which, interestingly, included enal **3.11** and bis-enal **3.12** in addition to trace amounts of a seven-membered ring-containing product. The two unexpected products exhibit a skeletal reorganization of the incorporated divinyl carbinol. The non-intuitive nature of this rearrangement, in addition to the potential ability to access highly-substituted double bonds of defined geometry, encouraged us to conduct a more in-depth study of this reaction.

Scheme 3.1 Double Heck approach to seven-membered rings.



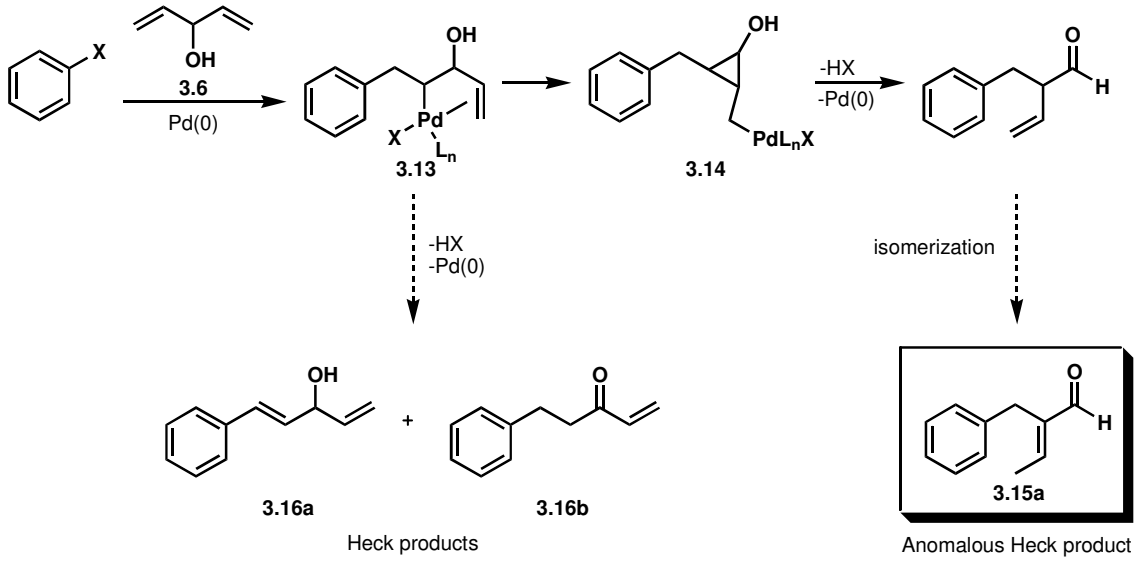
3.2 Reaction Optimization

In the pursuit of developing a broadly applicable method, we looked at the reaction of a variety of simple aryl halides and triflates with divinyl carbinol **3.6** but found that standard Heck products were formed preferentially over products arising from the novel skeletal reorganization pathway. A close examination of the literature revealed that a single, isolated example of this transformation had been reported by Gribble[3] in a study of the synthesis of 3-vinyl and 3-alkynyl indoles using the Stille-Ortar variant[4,5] of the Heck reaction. However, in our hands, we obtained the rearranged product of 3-indolyl triflate with divinyl carbinol **3.6** in only 35% yield using Gribble's reported conditions (see Table 3.1, entry 6).

On the basis of careful consideration of the observed products, we proposed a mechanism (see Scheme 3.2) for this anomalous Heck reaction in which the *in situ* generated Pd(0) catalyst

does not dissociate from the substrate following the first Heck coupling, but instead associates with the second double bond of the divinyl carbinol to give complex **3.13**. At this stage, migratory insertion of the second double bond across the C–Pd bond forms a strained cyclopropanol intermediate (**3.14**), which can then open and tautomerize to give *α*,*β*-unsaturated aldehyde **3.15a**. Alternatively, *β*-hydride elimination from intermediate **3.13** would lead to the formation of standard Heck products **3.16a** and/or **3.16b**.

Scheme 3.2 Formation of standard and anomalous Heck products from complex **3.13**



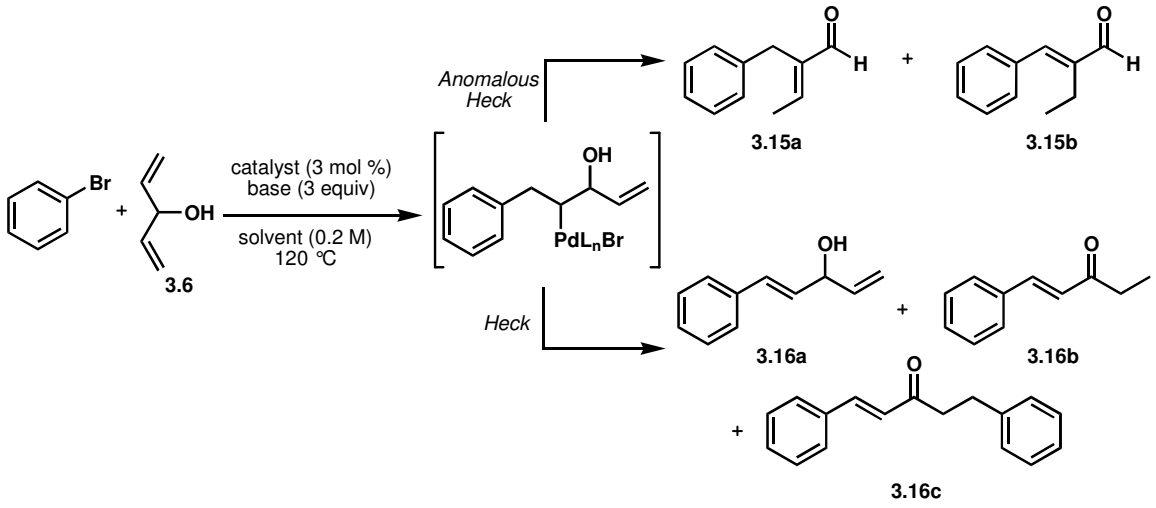
The ability to suppress *β*-hydride elimination following the first Heck coupling is critical for the initiation of the second migratory insertion step which leads to the cyclopropanol intermediate (**3.14**, Scheme 3.2). Thus, fully exploiting this anomalous Heck behavior necessitates establishing conditions that disfavor *β*-hydride elimination. Recent studies of coupling reactions that circumvent *β*-hydride elimination (e.g. sp^3-sp^3 couplings) have shown the importance of catalyst, ligand, and additives in minimizing this type of unwanted side-reaction.[6] Our studies of this anomalous Heck reaction therefore commenced with the development of conditions that would sufficiently stabilize the metal toward *β*-hydride elimination and promote the first Heck intermediate **3.13** to undergo a second migratory insertion to form the key cyclopropanol intermediate **3.14**.

We decided to investigate the transformation using commercially available bromobenzene and divinylcarbinol **3.6** as model substrates under the previously described conditions (Table 1, entry 1). At 120 ºC, we observed the major products to be those derived from a standard Heck pathway (**3.16a-c**) along with significantly lesser amounts of the anomalous Heck products (**3.15a,b**). Under these conditions, the standard Heck products were favored in a greater than 9 to 1 ratio.

We examined the effects of solvent, base, catalyst, and additives on the product ratio in order to determine conditions that disfavor *β*-hydride elimination and hence promote the formation of the desired anomalous Heck product.[7] Changing the base to TMEDA (entry 2) gave no reaction and complete recovery of starting material, pointing to the likely importance of the base in initial reduction of the precatalyst to Pd(0). Subsequent studies supported this

hypothesis; addition of small quantities of Hünig's base (1:5 *i*Pr_2NEt/TMEDA) promotes the reaction, though an improvement in the ratio of **3.15** to **3.16** is not observed.

Table 3.1 Reaction condition screen for anomalous Heck reaction.



Entry	Catalyst	Additive	Base	Solvent	Time (h)	Product ratio (3.15:3.16)[b]
1	$PdCl_2(PPh_3)_2$	-	*i*Pr_2NEt	DMF	10	<1:9
2	$PdCl_2(PPh_3)_2$	-	TMEDA	DMF	18	no reaction
3	Pd(P*t*-$Bu_3)_2$	-	Cy_2NMe	THF	4	1:9
4	$PdCl_2(PPh_3)_2$	Bu_4NCl	*i*Pr_2NEt	DMF	5	3:4
5	$PdCl_2(PPh_3)_2$	LiBr	*i*Pr_2NEt	DMF	4	5:6
6	$PdCl_2(PPh_3)_2$	Et_4NCl	*i*Pr_2NEt	DMF	5	3:2
7	$PdCl_2(PPh_3)_2$	Et_4NCl	*i*Pr_2NEt	NMP	8	5:2
8	$PdCl_2(PPh_3)_2$	Et_4NCl	*i*Pr_2NEt	DMA	5	10:3

[a] All reactions were run with 3 mol % catalyst loading, 1 equiv of additive, and 3 equiv of base as a 0.2 M solution at 120 °C for 5 h.
[b] Product ratios were determined using integration of ^{1}H NMR resonances.

We hypothesized that increasing the electron density at the metal center would disfavor *β*-hydride elimination, presumably by impeding the agostic interaction required for this process to occur. Pd[P(*t*-$Bu)_3]_2$ has recently been shown to be an effective catalyst for sp^3-sp^3 couplings,[8] which must inherently confront the issue of *β*-hydride elimination as an unwanted side reaction since the alkyl species coordinated to the metal will, by the nature of the reaction, possess *β*-hydrogens. The bulky, electron-rich phosphine ligands of this complex may contribute to its efficacy as a catalyst for alkyl-alkyl couplings. However, when this complex was employed in our system, little improvement over the original conditions was observed (entry 3).

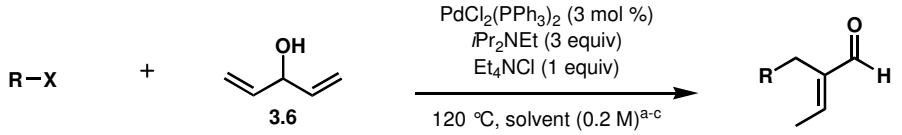
At this stage we looked to using salts as additives (entries 4-6), which are known to stabilize reactive, low-valent palladium species.[9] The salt's anion may coordinate the metal center, thus occupying a coordination site such that *β*-hydride elimination is less favored. Salt additives may also enhance reactivity by increasing the dielectric constant of the solvent. Of the salts investigated, Et_4NCl proved most beneficial, and DMA was subsequently determined to be

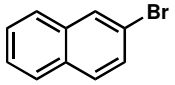
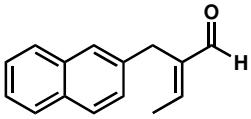
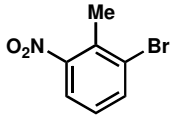
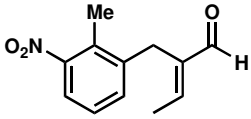
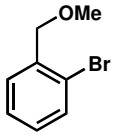
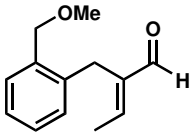
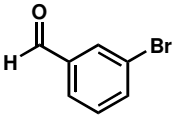
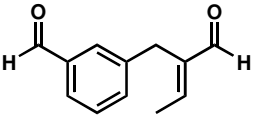
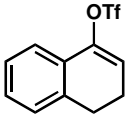
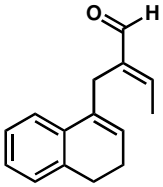
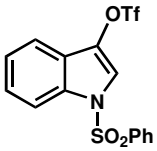
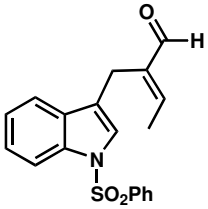
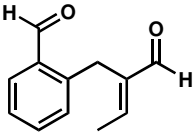
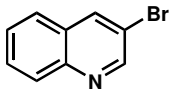
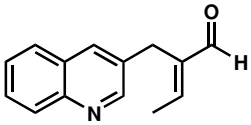
the most favorable solvent. With these optimized conditions, the anomalous Heck products were favored over the standard Heck products by a ratio of 10 to 3 (entry 8).

3.3 Scope of the Anomalous Heck Reaction

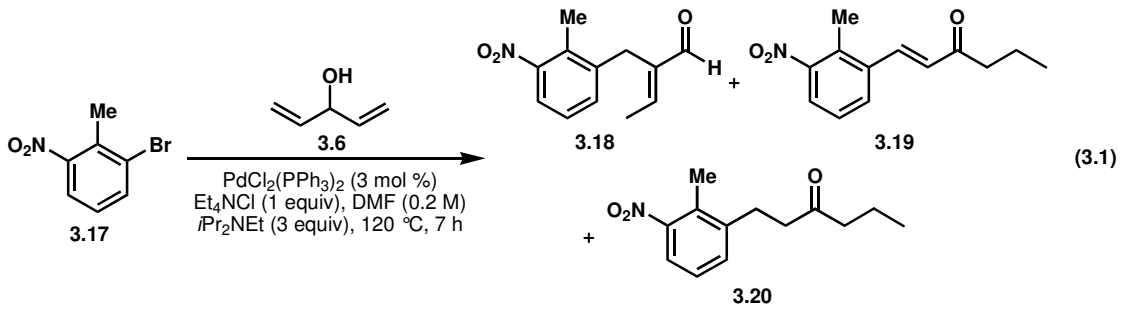
In order to investigate the scope of the reaction, a variety of aryl, heteroaryl, and vinyl halides and triflates were subjected to the reaction conditions using commercially available 1,4-pentadien-3-ol (**3.6**) as the divinyl carbinol component (Table 3.2). Using this secondary alcohol, the anomalous Heck rearrangement affords an α,β-unsaturated aldehyde as the final product. Isolated yields for these products are noticeably modest. Though the α,β-unsaturated aldehydes produced are inherently unstable, an additional problem thwarting good yields is the highly competitive standard Heck reaction. For example, with the substrate 2-bromo-6-nitrotoluene **3.17** (eq 3.1), both the desired anomalous Heck product **3.18** and two products resulting from the standard Heck reaction (the expected enone **3.19** and an *in situ* reduced ketone **3.20**) were observed in a ratio of 9:5:6, respectively.[10]

Table 3.2 Scope of the "halide" substrate using a secondary divinyl carbinol.



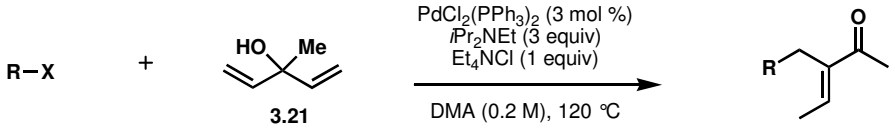
Entry	Substrate	Product	Time	Yield
1[a]			8 h	31%
2[a]	 **3.17**	 **3.18**	7 h	9%
3[b]			6.5 h	32%
4[a]			4 h	60%
5[b]			8 h	29%
6[c]			19 h	35%
7[a]			4 h	15%
8[b]			4 h	45%

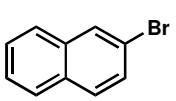
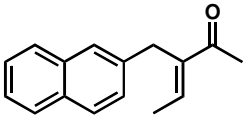
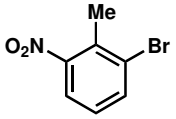
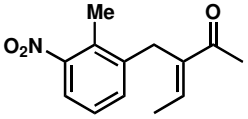
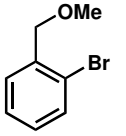
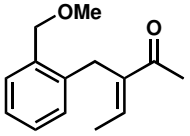
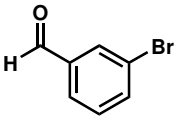
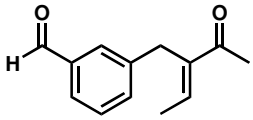
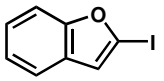
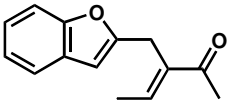
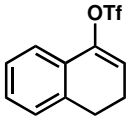
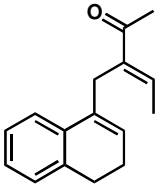
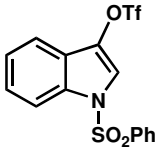
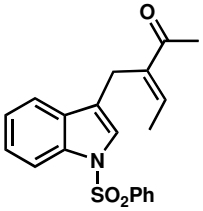
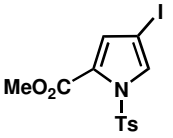
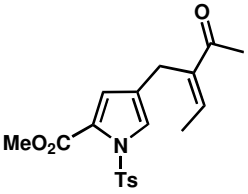
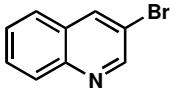
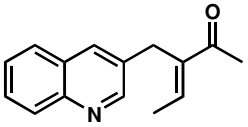
[a]Reaction was run in DMF. [b]Reaction was run in NMP. [c]Reaction was run in DMF at 80 °C with no Et_4NCl.



We also investigated the competency of using a tertiary alcohol (i.e., **3.21**, Table 3.3) as the divinyl carbinol coupling partner with various halide and triflate substrates under our optimized conditions. Gratifyingly, the use of tertiary divinyl carbinol **3.21** provided the desired anomalous Heck product enones[11] in good isolated yields (up to 83%) for a range of substituted aryl halides (entries 1-4), heteroaryl halides and triflates (entries 5, 7-9), and vinyl triflates (entry 6).

Table 3.3 Scope of the "halide" substrate using a tertiary divinyl carbinol.

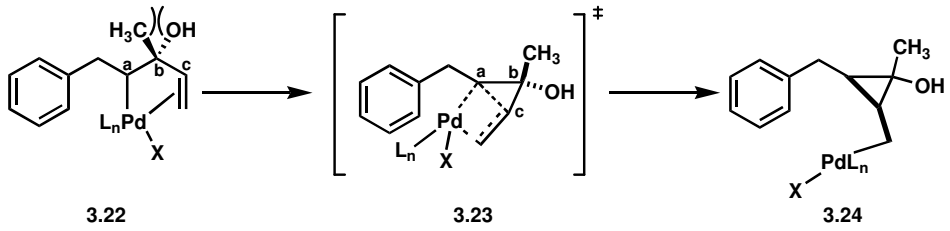


Entry	Substrate	Product	Time	Yield
1			8 h	83%
2[a]			8 h	65%
3			24 h	71%
4			26 h	70%
5			6.5 h	74%
6[b]			6 h	60%
7			9 h	71%
8			6 h	52%
9			14 h	77%

[a]Reaction was run using 6 mol % catalyst loading. [b]Product is a 3:1 mixture of trans and cis isomers. Major product is shown.

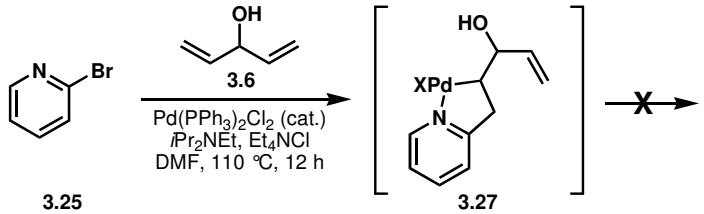
Though the α,β-unsaturated aldehydes generated from the *secondary* carbinol suffered from poor stability, an additional problem that thwarted good yields of the desired product was the highly competitive standard Heck reaction. On the other hand, using the tertiary alcohol, a virtually complete preference for the anomalous Heck mechanism was observed. A plausible explanation for the enhanced production of anomalous Heck product in the *tertiary* carbinol case is the Thorpe-Ingold effect.[12] The additional strain imparted on the system by replacing the hydrogen geminal to the alcohol with a methyl group in the tertiary alcohol case will cause the C_a-C_b-C_c bond angle (see **3.22**, Scheme 3.3) to decrease in order to accommodate the added electron density at C_b. This smaller bond angle more closely resembles that of the transition state **3.23** associated with the formation of the strained cyclopropanol σ-palladium complex **3.24**. Thus, the overall $\Delta E^{\ddagger}$ for the migratory insertion step in the tertiary alcohol case is expected to be less than that for the secondary alcohol. Another argument[13] that accounts for the Thorpe-Ingold effect is that there will be a higher population of conformers with the palladium proximal to the pendant vinyl group in the tertiary alcohol case (see **3.22**) since the secondary divinyl carbinol-derived intermediate has more energetically favorable conformations where the vinyl group is distal from the metal center. An additional factor contributing to the decreased propensity for β-hydride elimination in the tertiary alcohol systems (i.e., **3.22**) is the absence of a β' hydrogen (i.e., at C_b).

Scheme 3.3 Thorpe-Ingold effect of tertiary carbinols.

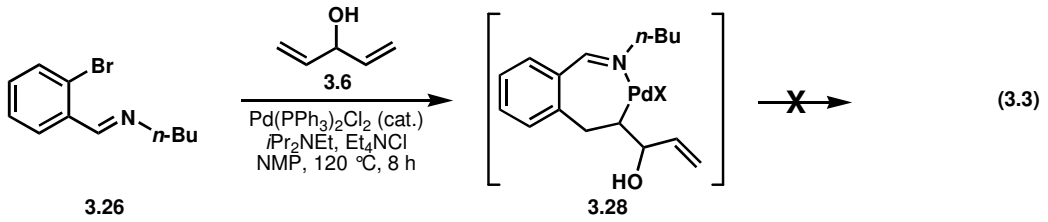


3.22 3.23 3.24

Certain substrates were completely incompatible with the reaction conditions. Both 2-bromopyridine **3.25** and ortho-bromophenyl imine **3.26** gave complete recovery of starting material (eqs 3.2 and 3.3). The inability of these compounds to progress through the catalytic cycle may be attributed to the Lewis basicity of the nitrogen atoms. The pyridine and imine nitrogens may chelate the palladium following the first Heck insertion, leading to over-stabilized organo-palladium intermediates **3.27** and **3.28** and essentially arresting the catalytic cycle.

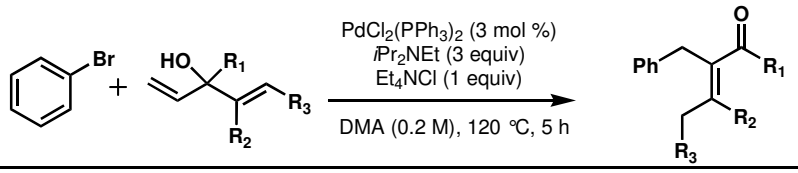


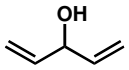
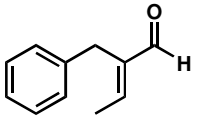
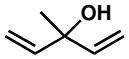
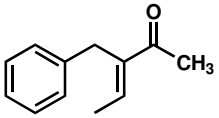
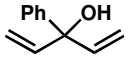
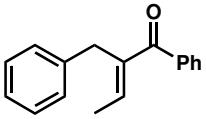
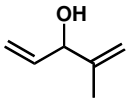
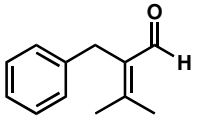
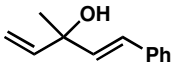
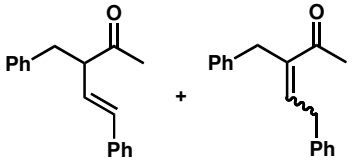
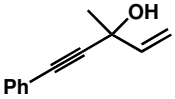
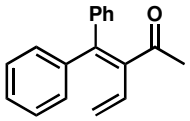
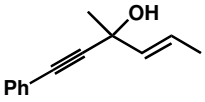
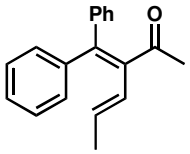
3.25 3.27 (3.2)



We also investigated the effect of substituents on the carbinol component (Table 3.4).[14] Using our optimized conditions, we examined the abilities of a number of divinyl and enyne carbinols, to give a variety of enals, enones, and dienones upon skeletal rearrangement by the anomalous Heck reaction. Substitution at R_1 is well tolerated and leads to good yields of the desired product (entries 2 and 3). In contrast, substitution at R_2 leads to diminished yields of the anomalous Heck product (entry 4), accompanied by a significant amount of the standard Heck product. While substitution at R_3 completely favors the standard Heck products, substitution at both R_1 and R_3 provides moderate yields of the desired anomalous Heck products (entry 5). Additionally, enyne carbinol substrates (entries 6 and 7) react chemoselectively and lead to good yields of dienone products.

Table 3.4 Scope of the carbinol component.

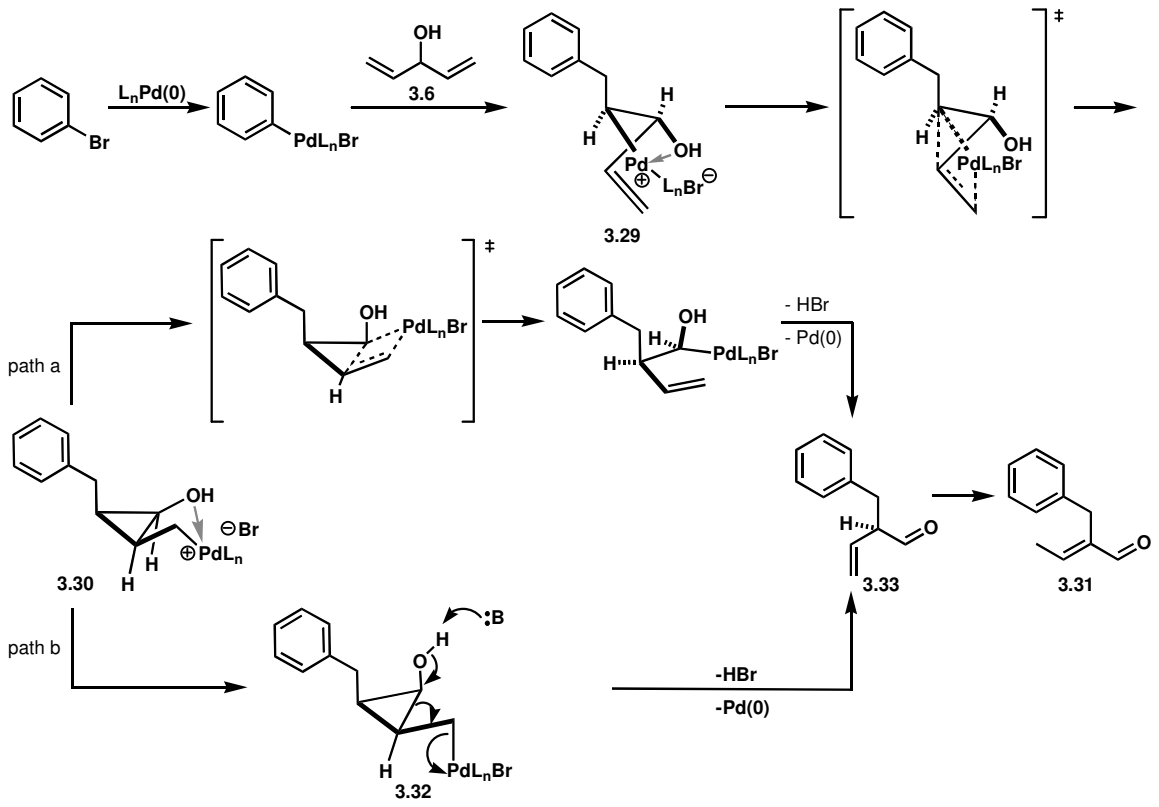


Entry	Divinyl carbinol	Product	Yield
1			43%
2			60%
3			69%
4			18%
5			50%
6			69%
7			65%

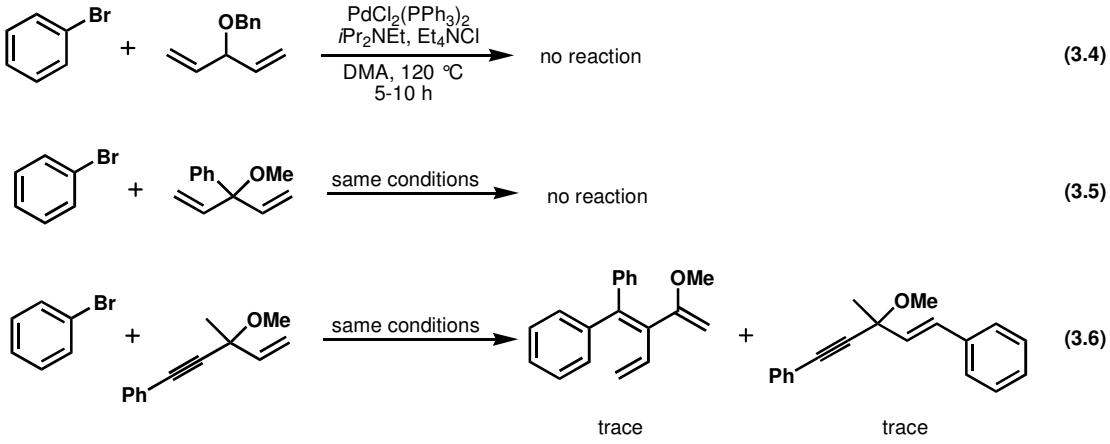
3.4 Mechanistic Analysis of the Anomalous Heck Reaction

In our proposed mechanism for the observed reaction[15] (Scheme 3.4), σ-palladium complex **3.29**, formed following the initial migratory insertion step, is stabilized toward β-hydride elimination, likely through coordination to its free hydroxyl and/or pendant olefin. This allows for insertion of the second double bond to give a strained cyclopropanol intermediate (**3.30**). At this point, the palladium can undergo a decarbopalladative rearrangement (path a), followed by β-hydride elimination and tautomerization to give **3.31**. Alternatively, in path b, proton abstraction from the hydroxyl group of **3.32**, followed by fragmentation of the cyclopropranol ring and loss of Pd(0) may afford **3.33**, which isomerizes under the reaction conditions to **3.31**.

Scheme 3.4 Proposed mechanism of the anomalous Heck reaction

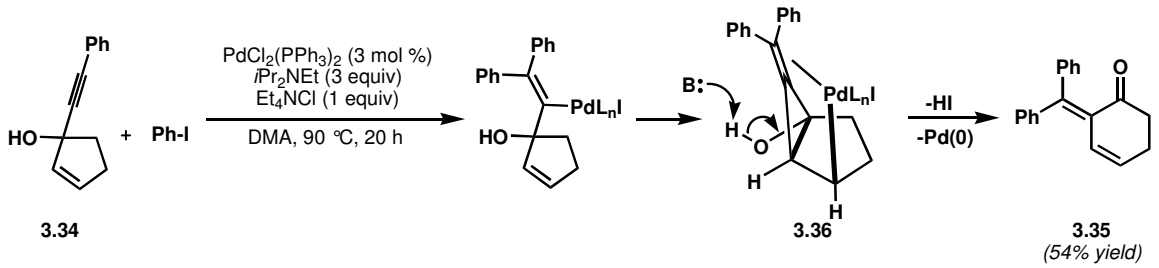


Importantly, we found that a free hydroxyl group on both the divinyl and enyne carbinol substrates was critical to the success of the reaction (see eqs 3.4 – 3.6), presumably due to a key precoordination of the hydroxyl group to the palladium center that promotes the initial migratory insertion. This is consistent with the observations of Ortar[16] and Oestereich[17]. It is also likely that coordination of the hydroxyl group with σ-palladium intermediate **3.29** (Scheme 3.4) helps stabilize the intermediate towards β-hydride elimination[18] thus enabling formation of cyclopropanol intermediate **3.30**.



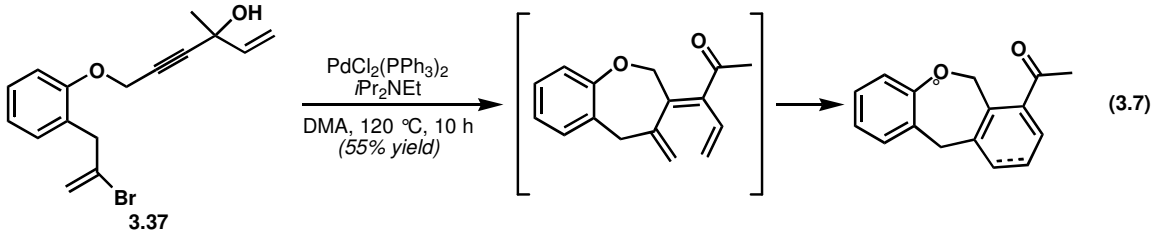
We gained further insight into the anomalous Heck transformation by investigating the reaction course of cyclic enyne carbinol **3.34** (Scheme 3.5) when subjected to the anomalous Heck conditions.[19] The reaction did proceed through the anomalous Heck pathway to give the ring-expanded product **3.35**. Significantly, the success of this reaction indicates that β-hydride elimination is sufficiently suppressed in cyclopropanol intermediate **3.36** without the aid of the hydroxyl group. Also, it lends support to the ring fragmentation mechanism shown in path b of Scheme 3.4 since the coplanar arrangement between the breaking C–C bond and the C–Pd bond necessary for a ring expansion through a decarbopalladative rearrangement (path a) to take place cannot be achieved.

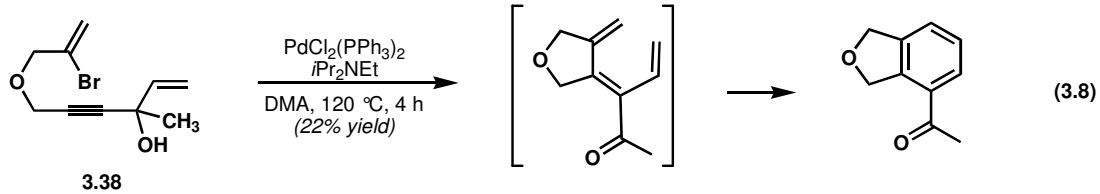
Scheme 3.5 Ring expansion of a cyclic substrate.



3.5 Applications of the Anomalous Heck Reaction

Having demonstrated the ability of both divinyl and enyne carbinols to undergo this Pd-catalyzed skeletal rearrangement, we saw the potential to use the anomalous Heck reaction to efficiently build complex systems from easily accessible starting materials. To this end, we prepared vinyl bromides **3.37** and **3.38** that are tethered to enyne carbinol moieties (eqs 3.7 and 3.8). Subjecting these compounds to our standard conditions enabled us to effect a tandem intramolecular anomalous Heck/6-π electrocyclization to yield annulated products. Some degree of oxidation of the diene products to the corresponding aromatic compounds was observed in both cases.





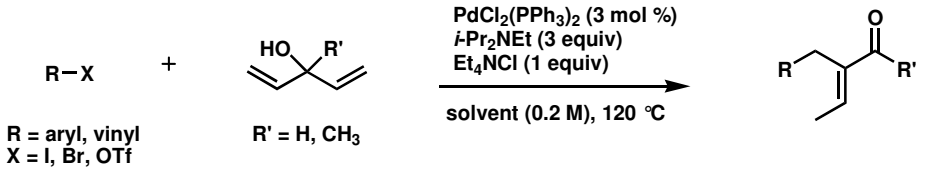
3.6 Conclusion

We have demonstrated that the Pd-catalyzed skeletal rearrangement observed upon coupling aromatic, heteroaromatic, and vinyl halides and triflates with divinyl and enyne carbinols grants access to a series of enals, enones, and dienones. Additionally, we have provided evidence that this anomalous Heck reaction may be utilized to construct substituted fused ring systems through an intramolecular anomalous Heck reaction and ensuing electrocyclization. Our mechanistic proposal, which is consistent with experimental observations, suggests that suppression of β-hydride elimination, as well as the presence of a hydroxyl group on the divinyl or enyne carbinol, is key to facilitating this transformation.

3.7 Experimental Methods

Unless stated otherwise, reactions were performed in flame-dried glassware, sealed with rubber septa under an atmosphere of nitrogen, using dry, deoxygenated solvents. Reaction temperatures were controlled by an IKAmag® temperature modulator. Thin layer chromatography was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV and anisaldehyde stain. Fisher silica gel 240-400 mesh (particle size 0.032 – 0.063 mm) was used for flash chromatography. ^{1}H and ^{13}C NMR were recorded on a Bruker DRX500 (at 500 MHz and 125 MHz, respectively). Chemical shifts (δ ppm) are reported relative to $CHCl_3$ (δ = 7.26 for ^{1}H NMR and δ = 77.2 for ^{13}C NMR). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity, (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, dq = doublet of quartet, m = multiplet, br = broad signal), coupling constant (Hz), and integration. IR spectra were recorded on a Nicolet MAGNA-IR 850 spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectral data were obtained from the University of California, Berkeley Mass Spectral Facility.

General procedure for anomalous Heck coupling:



A solution of the halide/triflate (0.95 mmol, 1 equiv), the divinyl carbinol (1.90 mmol, 2 equiv), and Hünig's base (2.85 mmol, 3 equiv) in solvent (5 mL, 0.2 M) was added via syringe to a Schlenk vessel containing $PdCl_2(PPh_3)_2$ (0.028 mmol, 3 mol %) and tetraethylammonium chloride (0.95 mmol, 1 equiv). The vessel was evacuated and backfilled with nitrogen three times and then placed in an oil bath preheated to 120 °C. The solution was held at this temperature for 4 – 26 h depending on substrate (see Tables 2 and 3). After cooling to room temperature, the mixture was diluted with diethyl ether (20 mL) and poured into 1% HCl (20 mL). The aqueous layer was extracted three times with diethyl ether (15 mL). The combined ether layers were then washed with H_2O (15 mL) and brine (15 mL), dried over Mg_2SO_4, and concentrated *in vacuo*.

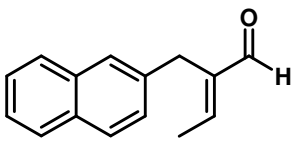


Table 3.2, Entry 1. The reaction was run in DMF at 120 °C for 8 h. The crude product was purified by flash chromatography (9:1 hexanes/EtOAc) to afford 62 mg of a yellow oil in 31% yield. R_F 0.62 (4:1 toluene/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.79-7.77 (m, 1H), 7.75-7.73 (m, 2H), 7.58 (s, 1H), 7.45-7.39 (m, 2H), 7.31 (dd, *J* = 8.5, 1.7 Hz, 1H), 6.79 (q, *J* = 7.1 Hz, 1H), 3.80 (s, 2H), 2.07 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 194.7, 151.5, 143.6, 136.7, 133.6, 132.2, 128.2, 127.7, 127.6, 127.2, 126.5, 126.1, 125.5, 29.6, 15.5; IR (film) 3054, 2925, 2815, 2713, 1679, 1601, 1365, 748 cm^{-1}; LRMS (EI$^+$) for $[C_{15}H_{14}O]^+$: *m/z* 210; HRMS (EI$^+$) calc'd for $[C_{15}H_{14}O]^+$: *m/z* 210.1045, found 210.1048.

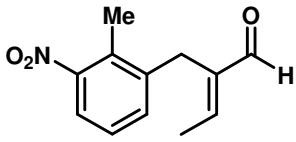


Table 3.2, Entry 2. The reaction was run in DMF at 120 °C for 7 h. The crude product was purified by flash chromatography (using a gradient from 9:1 to 4:1 hexanes/EtOAc) to afford 19 mg of a yellow oil in 9% yield. R_F 0.27 (2:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.50 (s, 1H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.20-7.17 (m, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 6.92 (q, *J* = 7.1 Hz, 1H), 3.64 (s, 2H), 2.44 (s, 3H), 1.96 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 194.1, 152.4, 151.6, 142.0, 139.5, 131.3, 130.5, 126.3, 122.0, 27.3, 15.4, 15.1; IR (film) 2928, 2824, 2721, 1684, 1645, 1525, 1354, 737 cm^{-1}; LRMS (EI$^+$) for $[C_{12}H_{13}NO_3]^+$: *m/z* 219; HRMS (EI$^+$) calc'd for $[C_{12}H_{13}NO_3]^+$: *m/z* 219.0895, found 219.0893.

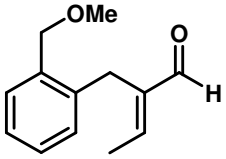


Table 3.2, Entry 3. The reaction was run in NMP at 120 °C for 6.5 h. The crude product was purified by flash chromatography (9:1 hexanes/EtOAc) to afford 62 mg of a yellow liquid in 32% yield. R_F 0.25 (4:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.50 (s, 1H), 7.32-7.31 (m, 1H), 7.18-7.16 (m, 2H), 6.93-6.92 (m, 1H), 6.85 (q, *J* = 7.1 Hz, 1H), 4.57 (s, 2H), 3.69 (s, 2H), 3.41 (s, 3H), 1.97 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 199.6, 151.9, 143.2, 137.3, 136.0, 129.3, 128.1, 127.7, 126.2, 73.2, 58.3, 25.7, 15.4; IR (film) 2925, 2821, 2719, 1684, 1643, 1381, 1184, 1090, 750 cm^{-1}; LRMS (FAB$^+$) for $[C_{13}H_{17}O_2]^+$: *m/z* 205; HRMS (FAB$^+$) calc'd for $[C_{13}H_{17}O_2]^+$: *m/z* 205.1229, found 205.1225.

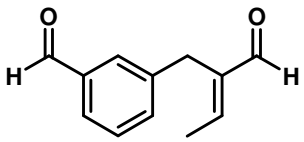


Table 3.2, Entry 4. The reaction was run in DMF at 120 °C for 4 h. The crude product was purified by flash chromatography (run on a gradient from 5:1 to 2:1 pentane/Et_2O) to afford 107 mg of a yellow liquid in 60% yield. R_F 0.28 (2:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.96 (s, 1H), 9.47 (s, 1H), 7.69 (d, *J* = 7.3 Hz, 1H), 7.65 (s, 1H), 7.47-7.41 (m, 2H), 6.80 (q, *J* = 7.1 Hz, 1H), 3.71 (s, 2H), 2.06 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 194.4, 192.5, 151.6, 142.9, 140.3, 136.8, 134.8, 129.3, 129.3, 128.1, 29.3, 15.5; IR (film) 2926, 2819, 2729, 1684, 1643, 1586, 1238, 691 cm^{-1}; LRMS (EI$^+$) for $[C_{12}H_{12}O_2]^+$: *m/z* 188; HRMS (EI$^+$) calc'd for $[C_{12}H_{12}O_2]^+$: *m/z* 188.0837, found 188.0837.

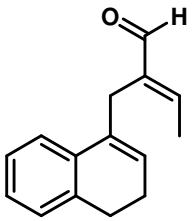


Table 3.2, Entry 5. The reaction was run in NMP at 120 °C for 8 h. The crude product was purified by flash chromatography (run on a gradient from 9:1 to 4:1hexanes/EtOAc) to afford 58 mg of a yellow oil in 29% yield. R_F 0.44 (2:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.48 (s, 1H), 7.31 (d, *J* = 7.5

Hz, 1H), 7.22-7.19 (m, 1H), 7.17-7.12 (m, 2H), 6.83 (q, *J* = 7.0 Hz, 1H), 5.58-5.57 (m, 1H), 3.41 (s, 2H), 2.73-2.70 (m, 2H), 2.23-2.19 (m, 2H), 1.97 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 194.6, 152.6, 142.3, 136.8, 135.2, 132.3, 127.6, 127.0, 126.5, 124.6, 122.7, 28.3, 26.3, 23.3, 15.4; IR (film) 2932, 2883, 2830, 2711, 1684, 1643, 1487, 759 cm^{-1}; LRMS (EI$^+$) for $[C_{15}H_{16}O]^+$: *m/z* 212; HRMS (EI$^+$) calc'd for $[C_{15}H_{16}O]^+$: *m/z* 212.1201, found 212.1197.

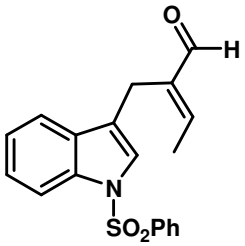


Table 3.2, Entry 6. The reaction was run in DMF at 80 °C for 8 h with no Et_4NCl. The crude product was purified by flash chromatography (run on a gradient from 9:1 to 4:1hexanes/EtOAc) to afford 113 mg of a yellow oil in 35% yield. R_F 0.31 (2:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.95 (d, *J* = 8.3 Hz, 1H), 7.81-7.79 (m, 2H), 7.52-7.49 (m, 2H), 7.42-7.39 (m, 2H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.25-7.22 (m, 1H), 7.18 (s, 1H), 6.79 (q, *J* = 7.1 Hz, 1H), 3.63 (s, 2H), 1.99 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 194.2, 152.0, 141.9, 138.2, 135.5, 133.8, 130.7, 129.3, 126.8, 125.0, 123.5, 123.4, 120.4, 119.8, 113.9, 19.2, 15.4; IR (film) 3065, 2919, 2821, 2719, 1684, 1646, 1363, 1173 cm^{-1}; LRMS (EI$^+$) for $[C_{19}H_{17}NO_3S]^+$: *m/z* 339; HRMS (EI$^+$) calc'd for $[C_{19}H_{17}NO_3S]^+$: *m/z* 339.0929, found 339.0928.

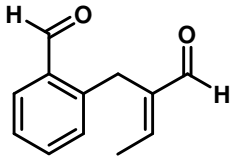


Table 3.2, Entry 7. The reaction was run in DMF at 120 °C for 4 h. The crude product was purified by flash chromatography (run on a gradient from 9:1 to 2:1hexanes/EtOAc) to afford 27 mg of a yellow oil in 15% yield. R_F 0.45 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.30 (s, 1H), 9.49 (s, 1H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.46-7.42 (m, 1H), 7.38-7.34 (m, 1H), 7.07 (m, 1H), 7.07 (d, *J* = 7.7 Hz, 1H), 6.86 (q, *J* = 7.1 Hz, 1H), 4.12 (s, 2H), 1.95 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 194.4, 193.1, 152.3, 142.6, 140.8, 133.9, 133.8, 133.1, 129.1, 126.7, 25.9, 15.3; IR (film) 2831, 2732, 1684, 1645, 1599, 1204, 756 cm^{-1}; LRMS (EI$^+$) for $[C_{12}H_{12}O_2]^+$: *m/z* 188; HRMS (EI$^+$) calc'd for $[C_{12}H_{12}O_2]^+$: *m/z* 188.0837, found 188.0836.

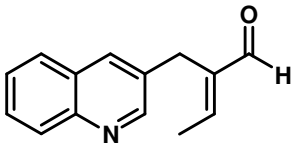


Table 3.2, Entry 8. The reaction was run in NMP at 120 °C for 4 h. The crude product was purified by flash chromatography (1:2 hexanes/EtOAc) to afford 90 mg of a yellow oil in 45% yield. R_F 0.34 (1:2 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.49 (s, 1H), 8.78 (s, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.88 (s, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.66-7.63 (m, 1H), 7.52-7.49 (m, 1H), 6.81 (q, *J* = 7.1 Hz, 1H), 3.80 (s, 2H), 2.09 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 194.3, 151.7, 151.5, 147.0, 142.7, 134.5, 131.9, 129.2, 129.0, 128.2, 127.6, 126.8, 27.1, 15.5; IR (film) 2980, 2821, 2718, 1682, 1644, 1496, 788, 754 cm^{-1}; LRMS (EI$^+$) for $[C_{14}H_{13}NO]^+$: *m/z* 211; HRMS (EI$^+$) calc'd for $[C_{14}H_{13}NO]^+$: *m/z* 211.0997, found 211.0995.

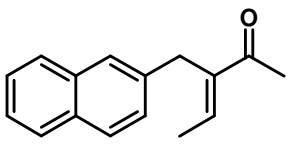


Table 3.3, Entry 1. The reaction was run in DMA at 120 °C for 8 h. The crude product was purified by flash chromatography (using a gradient from 9:1 to 4:1 hexanes/EtOAc) to afford 177 mg of a yellow oil in 83% yield. R_F 0.47 (2:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78-7.72 (m, 3H), 7.56 (s, 1H), 7.44- 7.38 (m, 2H), 7.31 (d, *J* = 8.5 Hz, 1H), 6.97 (q, *J* = 7.0 Hz, 1H), 3.86 (s, 2H), 2.34 (s, 3H), 1.98 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 199.01, 142.1, 140.4, 137.5, 133.7, 132.1, 128.1, 127.7, 127.6,

127.4, 126.4, 126.0, 125.3, 31.0, 25.9, 15.4; IR (film) 3053, 3015, 1665, 1637, 1387, 1277, 816, 758 cm^{-1}; LRMS (EI^+) for $[C_{16}H_{16}O]^+$: *m/z* 224; HRMS (EI^+) calc'd for $[C_{16}H_{16}O]^+$: *m/z* 224.1201, found 224.1203.

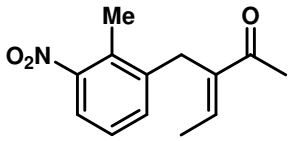


Table 3.3, Entry 2. The reaction was run in DMA for 8 h at 120 °C using 6 mol % catalyst because the longer reaction time needed for completion of the reaction using 3 mol % catalyst led to reduction of the nitro group to the corresponding amine. The crude product was purified by flash chromatography (using a gradient from 9:1 to 4:1 hexanes/EtOAc) to afford 144 mg of a yellow oil in 65% yield. R_F 0.34 (2:1 hexanes/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.0 Hz, 1H), 7.16 (t, *J* = 7.9, 1H), 7.09-7.06 (m, 2H), 3.67 (s, 2H), 2.46 (s, 3H), 2.37 (s, 3H), 1.87 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 198.7, 151.6, 141.6, 140.8, 140.5, 130.8, 130.4, 126.2, 121.8, 28.6, 25.7, 15.4, 15.0; IR (film) 3048, 1667, 1643, 1525, 1387, 1351, 1282, 734 cm^{-1}; LRMS (EI^+) for $[C_{13}H_{15}NO_3]^+$: *m/z* 233; HRMS (EI^+) calc'd for $[C_{13}H_{15}NO_3]^+$: *m/z* 233.1052, found 233.1053.

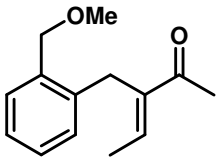


Table 3.3, Entry 3. The reaction was run in DMA at 120 °C for 24 h. The crude product was purified by flash chromatography (using a gradient from 9:1 to 4:1 hexanes/EtOAc) to afford 147 mg of a yellow oil in 71% yield. R_F 0.40 (2:1 hexanes/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 7.32-7.30 (m, 1H), 7.18-7.14 (m, 2H), 7.00 (q, *J* = 7.0 Hz, 1H), 6.91-6.89 (m, 1H), 4.59 (s, 2H), 3.72 (s, 2H), 3.41 (s, 3H), 2.33 (s, 3H), 1.88 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 199.1, 141.6, 140.6, 138.2, 135.9, 129.1, 128.0, 127.2, 125.9, 73.2, 58.2, 27.0, 25.9, 15.2; IR (film) 2983, 1667, 1455, 1387, 1088, 760 cm^{-1}; LRMS (FAB^+) for $[C_{14}H_{19}O_2]^+$: *m/z* 219; HRMS (FAB^+) calc'd for $[C_{14}H_{19}O_2]^+$: *m/z* 219.1385, found 219.1388.

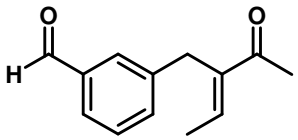


Table 3.3, Entry 4. The reaction was run in DMA at 120 °C for 26 h. The crude product was purified by flash chromatography (using a gradient from 9:1 to 4:1 hexanes/EtOAc) to afford 134 mg of a yellow oil in 70% yield. R_F 0.33 (2:1 hexanes/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 9.96 (s, 1H), 7.67 (d, *J* = 7.3 Hz, 1H), 7.63 (s, 1H), 7.46-7.39 (m, 2H), 6.97 (q, *J* = 7.0 Hz, 1H), 3.75 (s, 2H), 2.33 (s, 3H), 1.97 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 198.9, 192.7, 141.6, 141.2, 140.9, 136.7, 134.9, 129.3, 129.2, 127.8, 30.6, 25.7, 15.5; IR (film) 3056, 3007, 2839, 2731, 1697, 1665, 1602, 688 cm^{-1}; LRMS (EI^+) for $[C_{13}H_{14}O_2]^+$: *m/z* 202; HRMS (EI^+) calc'd for $[C_{13}H_{14}O_2]^+$: *m/z* 202.0994, found 202.0990.

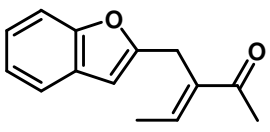


Table 3.3, Entry 5. The reaction was run in DMA at 120 °C for 6.5 h. The crude product was purified by flash chromatography (using a gradient from 9:1 to 4:1 hexanes/EtOAc) to afford 151 mg of a yellow oil in 74% yield. R_F 0.47 (2:1 hexanes/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.21-7.14 (m, 2H), 6.98 (q, *J* = 7.0 Hz, 1H), 6.32 (d, *J* = 0.9 Hz, 1H), 3.84 (s, 2H), 2.35 (s, 3H), 2.02 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 198.2, 156.7, 154.8, 141.6, 138.8, 129.0, 123.3, 122.5, 120.4, 110.9, 102.7, 25.6, 24.4, 15.3; IR (film) 3056, 1668, 1643, 1455, 1254, 751 cm^{-1}; LRMS (EI^+) for $[C_{14}H_{14}O_2]^+$: *m/z* 214; HRMS (EI^+) calc'd for $[C_{14}H_{14}O_2]^+$: *m/z* 214.0994, found 214.0989.

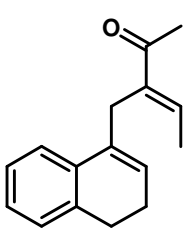


Table 3.3, Entry 6. The reaction was run in DMA at 120 °C for 6 h. The product was obtained in 60% yield as a 3:1 mixture of the trans and cis isomers, respectively, determined using integration of ^{1}H NMR resonances and confirmed by NOESY. The two isomers were separated by flash chromatography (using a gradient from 9:1 to 2:1 hexanes/EtOAc), though the minor isomer could not be obtained free from the major isomer. The major trans isomer was obtained as a gold-colored oil. R_F 0.52 (2:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.6 Hz, 1H), 7.24-7.21 (m, 1H), 7.16-7.14 (m, 2H), 7.00 (q, *J* = 7.0 Hz, 1H), 5.54-5.52 (m, 1H), 3.45 (d, *J* = 1.8 Hz, 2H), 2.72 (t, *J* = 8.0 Hz, 2H), 2.36 (s, 3H), 2.23-2.19 (m, 2H), 1.85 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 199.1, 140.9, 140.6, 136.7, 135.5, 132.8, 127.5, 126.8, 126.4, 123.8, 122.5, 28.3, 27.6, 25.9, 23.2, 15.1; IR (film) 3056, 2932, 1668, 1429, 1211, 753 cm^{-1}; LRMS (EI$^+$) for $[C_{16}H_{18}O]^+$: *m/z* 226; HRMS (EI$^+$) calc'd for $[C_{16}H_{18}O]^+$: *m/z* 226.1358, found 226.1359.

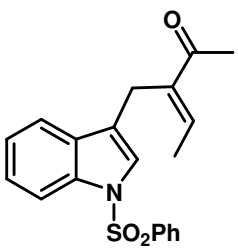


Table 3.3, Entry 7. The reaction was run in DMA at 120 °C for 9 h. The crude product was purified by flash chromatography (using a gradient from 9:1 to 2:1 hexanes/EtOAc) to afford 238 mg of a yellow oil in 71% yield. R_F 0.30 (2:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.2 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.53-7.48 (m, 2H), 7.41-7.38 (m, 2H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.13 (s, 1H), 6.95 (q, *J* = 7.0 Hz, 1H), 3.68 (s, 2H), 2.35 (s, 3H), 1.89 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 198.6, 140.8, 140.5, 138.2, 135.5, 133.8, 131.0, 129.3, 126.7, 124.9, 123.4, 123.3, 121.4, 119.8, 113.8, 25.7, 20.6, 15.3; IR (film) 3064, 1665, 1448, 1364, 1175, 1120, 748, 724 cm^{-1}; LRMS (EI$^+$) for $[C_{20}H_{19}NO_3S]^+$: *m/z* 353; HRMS (EI$^+$) calc'd for $[C_{20}H_{19}NO_3S]^+$: *m/z* 353.1086, found 353.1081.

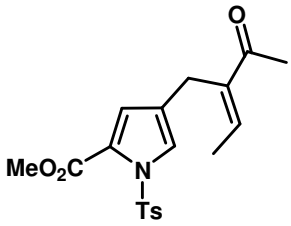


Table 3.3, Entry 8. The reaction was run in DMA at 120 °C for 6 h. The crude product was purified by flash chromatography (using a gradient from 9:1 to 2:1 hexanes/EtOAc) to afford 185 mg of a yellow oil in 52% yield. R_F 0.63 (1:2 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.0 Hz, 2H), 7.41 (s, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 6.88 (q, *J* = 7.0 Hz, 1H), 6.84 (d, *J* = 2.1 Hz, 1H), 3.68 (s, 3H), 3.45 (s, 2H), 2.41 (s, 3H), 2.33 (s, 3H), 1.94 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 198.7, 159.3, 144.9, 141.3, 140.4, 136.1, 129.5, 128.2, 126.5, 124.6, 124.2, 123.7, 51.8, 25.6, 22.0, 21.8, 15.2; IR (film) 3134, 1731, 1665, 1229, 1190, 1177, 1094, 671 cm^{-1}; LRMS (EI$^+$) for $[C_{19}H_{21}NO_5S]^+$: *m/z* 375; HRMS (EI$^+$) calc'd for $[C_{19}H_{21}NO_5S]^+$: *m/z* 375.1140, found 375.1139.

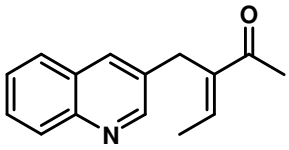
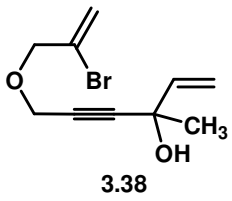


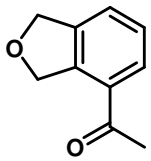
Table 3.3, Entry 9. The reaction was run in DMA at 120 °C for 14 h. The crude product was purified by flash chromatography (using a gradient from 2:1 to 1:2 hexanes/EtOAc) to afford 165 mg of a yellow oil in 77% yield. R_F 0.31 (1:2 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (d, *J* = 2.1 Hz, 1H), 8.31 (d, *J* = 8.5 Hz, 1H), 8.15 (s, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.77-7.74 (m, 1H), 7.63-7.60 (m, 1H), 7.02 (q, *J* = 7.0 Hz, 1H), 3.87 (s, 2H), 2.33 (s, 3H), 2.04 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 198.7, 151.5, 146.5, 141.1, 140.9, 134.7, 132.9, 128.9, 128.8, 128.2, 127.5, 126.7, 28.3, 25.6, 15.5; IR (film) 1666,

1641, 1495, 1423, 1387, 1279, 789, 756 cm^{-1}; LRMS (EI^+) for $[C_{15}H_{15}NO]^+$: *m/z* 225; HRMS (EI^+) calc'd for $[C_{15}H_{15}NO]^+$: *m/z* 225.1154, found 225.1154.



3.38

Carbinol 3.38. 1-[2-Bromo-2-propen-1-yloxy]-prop-2-yne[20] (175 mg, 1.00 mmol) was dissolved in diethyl ether (1 mL) and cooled to -78 ºC. *n*-Butyl lithium (0.44 mL, 2.5 M soln. in hexanes) was slowly added and the solution allowed to stir with warming to 0 ºC over 25 min and then cooled again to -78 ºC. Methyl vinyl ketone (97 µL, 1.2 mmol) was added slowly at -78 ºC and the reaction was allowed to warm to room temperature and stir for 1.5 h. The reaction was quenched by the addition of saturated ammonium chloride. The aqueous layer was extracted with ethyl acetate (2 x 20 mL), and the combined organic layers were dried over Mg_2SO_4. Purification by flash chromatography (run on a gradient from 9:1 to 4:1 hexanes/EtOAc) afforded a clear liquid (138 mg, 56% yield). R_F 0.49 (2:1 hexanes/EtOAc). ^1H NMR (500 MHz, $CDCl_3$) δ 6.00-5.94 (m, 2H), 5.66-5.65 (m, 1H), 5.50 (dd, *J* = 17.0 Hz, 0.6 Hz, 1H), 5.14 (dd, *J* = 10.3 Hz, 0.7 Hz, 1H), 4.27 (s, 2H), 4.20 (s, 2H), 1.57 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ141.8, 128.6, 118.8, 114.0, 89.0, 80.0, 73.5, 68.4, 57.5, 30.1; IR (film) 3405, 2978, 2848, 1631, 1358, 1086, 924 cm^{-1}; LRMS (FAB^+) calc'd for $[C_{10}H_{13}BrO_2Li]^+$: *m/z* 251.026, found 251. This compound was not amenable to HRMS.



3-acetyl-dihydro-isobenzofuran. A solution of enyne **3.38** (126 mg, 0.514 mmol) and Hünig's base (0.26 mL, 1.5 mmol) in DMA (5 mL) was added via syringe to a Schlenk vessel containing $PdCl_2(PPh_3)_2$ (11 mg, 3 mol%) and tetraethylammonium chloride (34 mg, 0.21 mmol). The vessel was evacuated and backfilled with nitrogen three times and then placed in an oil bath preheated to 120 ºC. The solution was held at this temperature for 4 h. After cooling to room temperature, the mixture was diluted with diethyl ether (15 mL) and poured into water (15 mL). The aqueous layer was extracted three times with diethyl ether (10 mL). The combined ether layers were then washed with H_2O (10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography (run on a gradient from 9:1 to 4:1 hexanes/EtOAc) afforded a pale yellow oil (18 mg, 22% yield). R_F 0.48 (2:1 hexanes/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.4 Hz, 1H), 7.45-7.39 (m, 2H), 5.40 (s, 2H), 5.11 (s, 2H), 2.61 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 198.5, 141.2, 141.0, 131.8, 128.7, 127.9, 125.6, 75.5, 72.6, 27.2; IR (film) 2905, 2864, 1673, 1359, 1273, 1131, 899, 784 cm^{-1}**;** LRMS (EI^+) for $[C_{10}H_{10}O_2]^+$: *m/z* 162; HRMS (EI^+) calc'd for $[C_{10}H_{10}O_2]^+$: *m/z* 162.0681, found 162.0683.

3.8 References and Notes

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(7) Optimization studies were carried out in our lab by Dr. J. Maina Ndungu.
(8) Hills, I. D.; Netherton, M. R.; Fu, G. C. *Angew. Chem. Int. Ed.* **2003**, *42*, 5749-5752.
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(10) Product ratios were determined using integration of ^{1}H NMR resonances.
(11) The *trans* stereochemistry of both the α,β-unsaturated aldehydes and ketones is supported by NOE analysis (see Appendix Two).
(12) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080-1106.
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(14) Studies of the carbinol component were conducted in our lab by Dr. J. M. Ndungu.
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(19) Study performed in our lab by Dr. J. Maina Ndungu.
(20) Prepared according to the procedure of Parsons, et al.: Parsons, P. J.; Willis, P.; Eyley, S. C. *Tetrahedron* **1992**, *48*, 9461-9472.

APPENDIX TWO

Spectra Relevant to Chapter Three:

Development of an Anomalous Heck Reaction

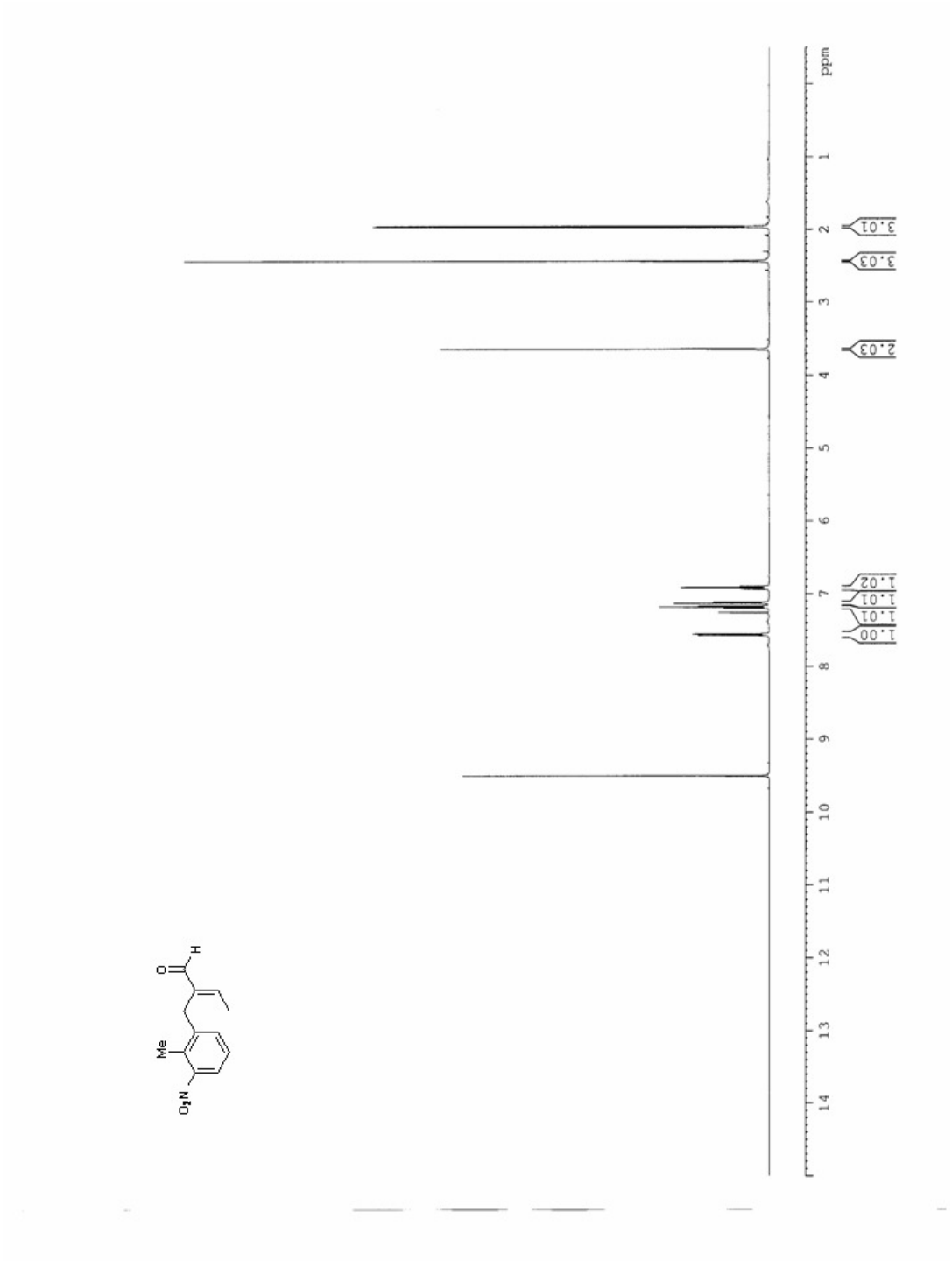

Figure A2.1 ^{1}H NMR (500 MHz, $CDCl_3$) of Table 3.2, Entry 2.

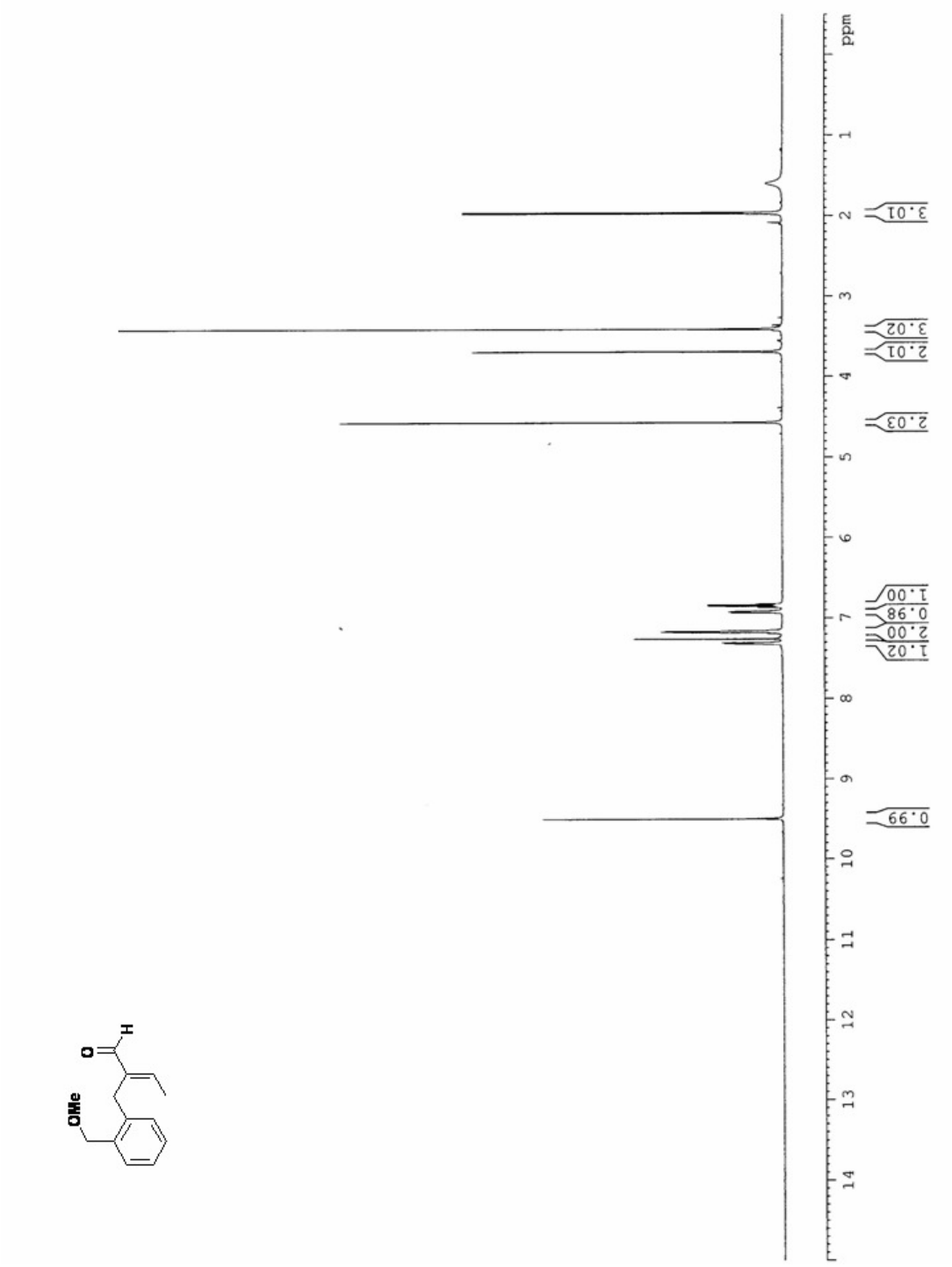

Figure A2.2 ^{1}H NMR (500 MHz, $CDCl_3$) of Table 3.2, Entry 3.

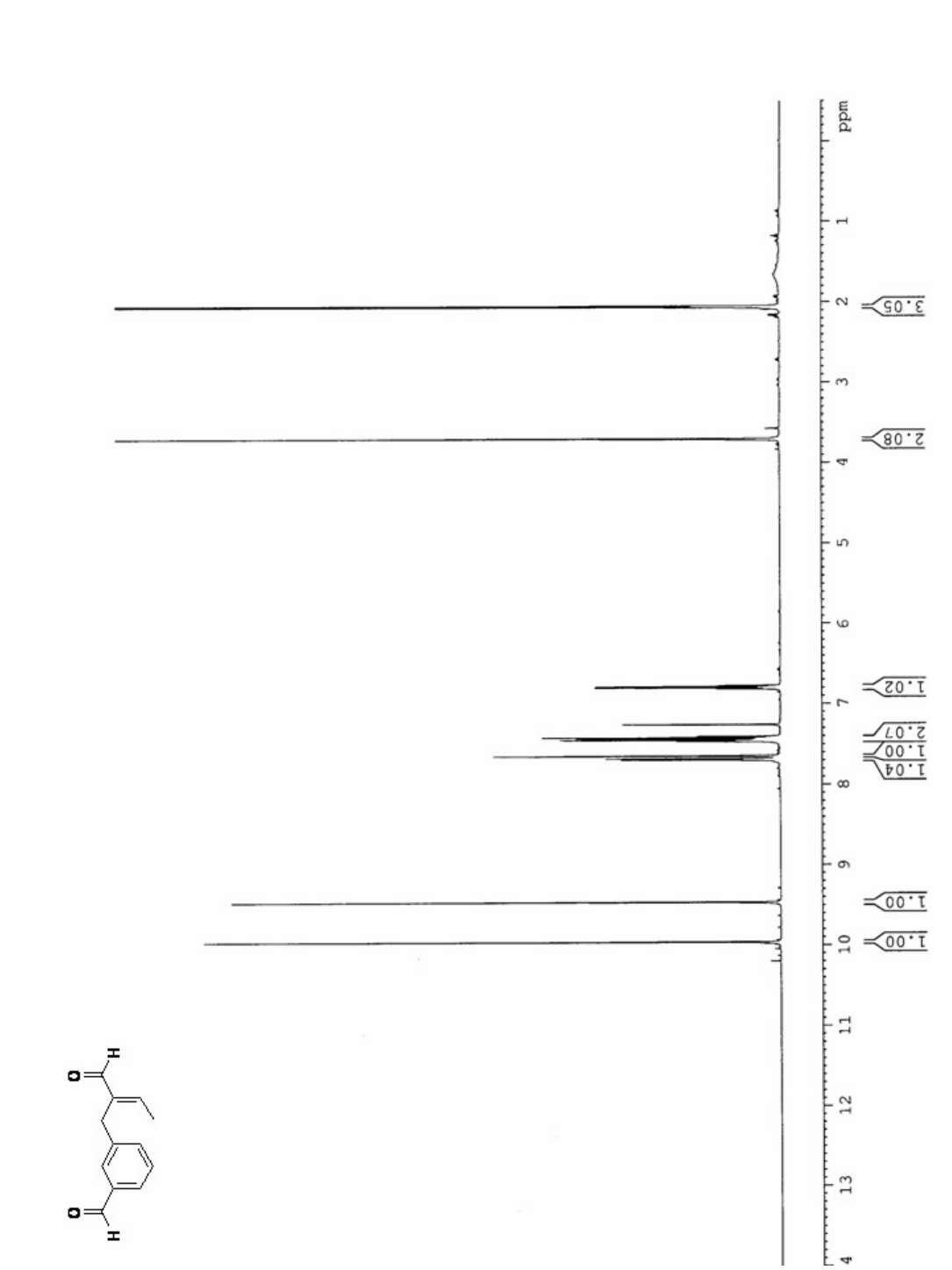

Figure A2.3 ^{1}H NMR (500 MHz, $CDCl_3$) of Table 3.2, Entry 4.

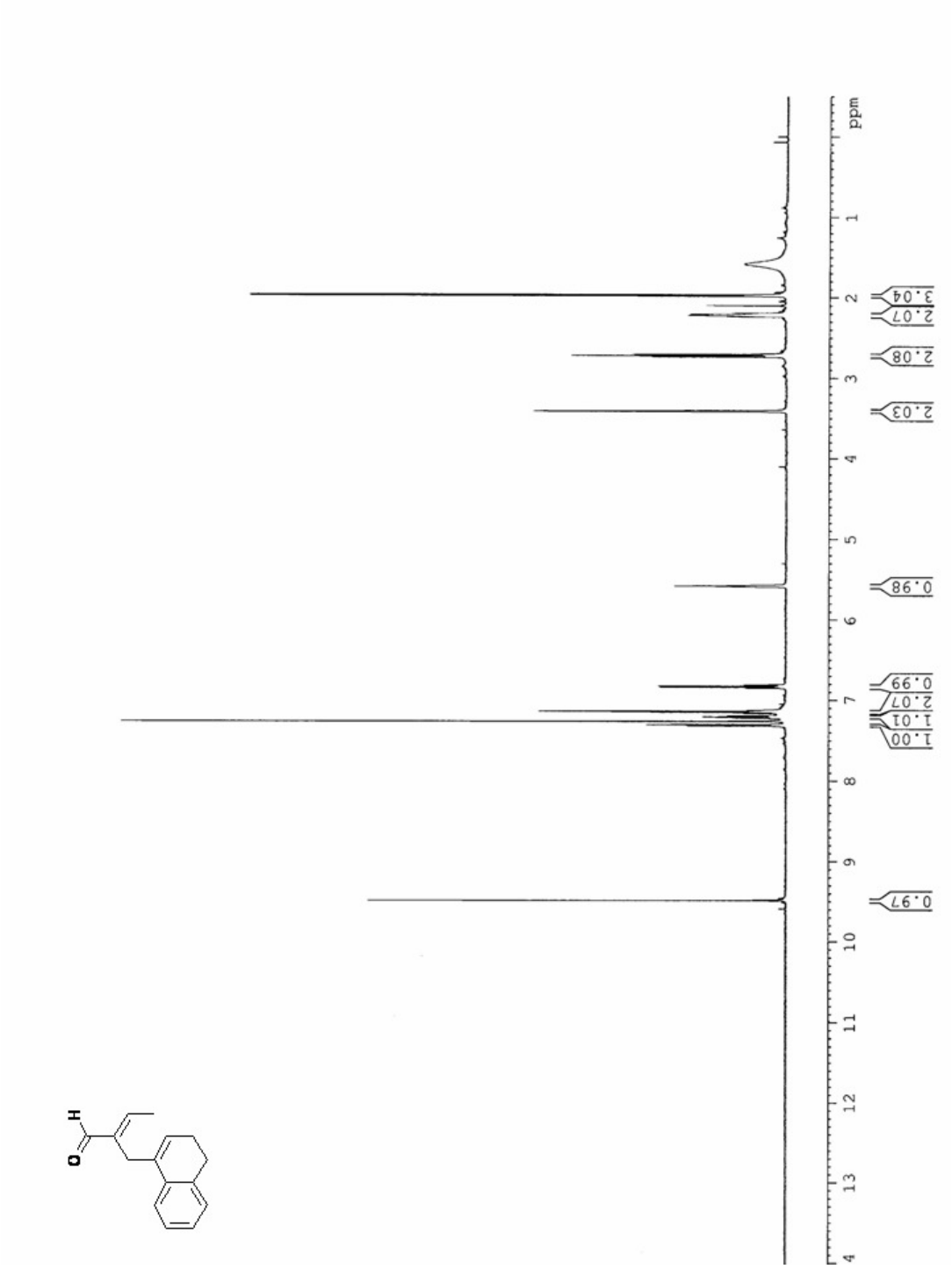

Figure A2.4 ^{1}H NMR (500 MHz, $CDCl_3$) of Table 3.2, Entry 5.

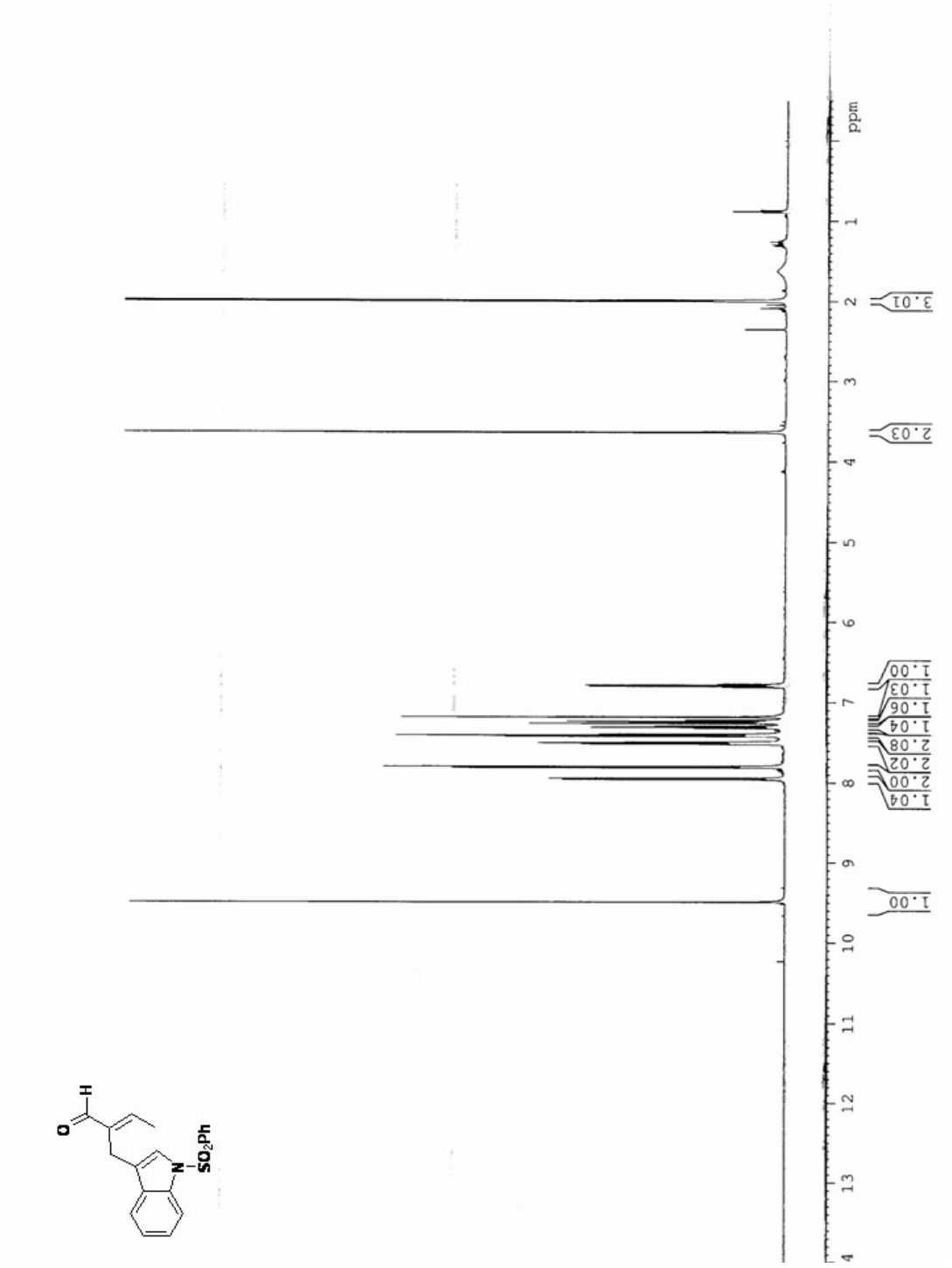

Figure A2.5 ^{1}H NMR (500 MHz, $CDCl_3$) of Table 3.2, Entry 6.

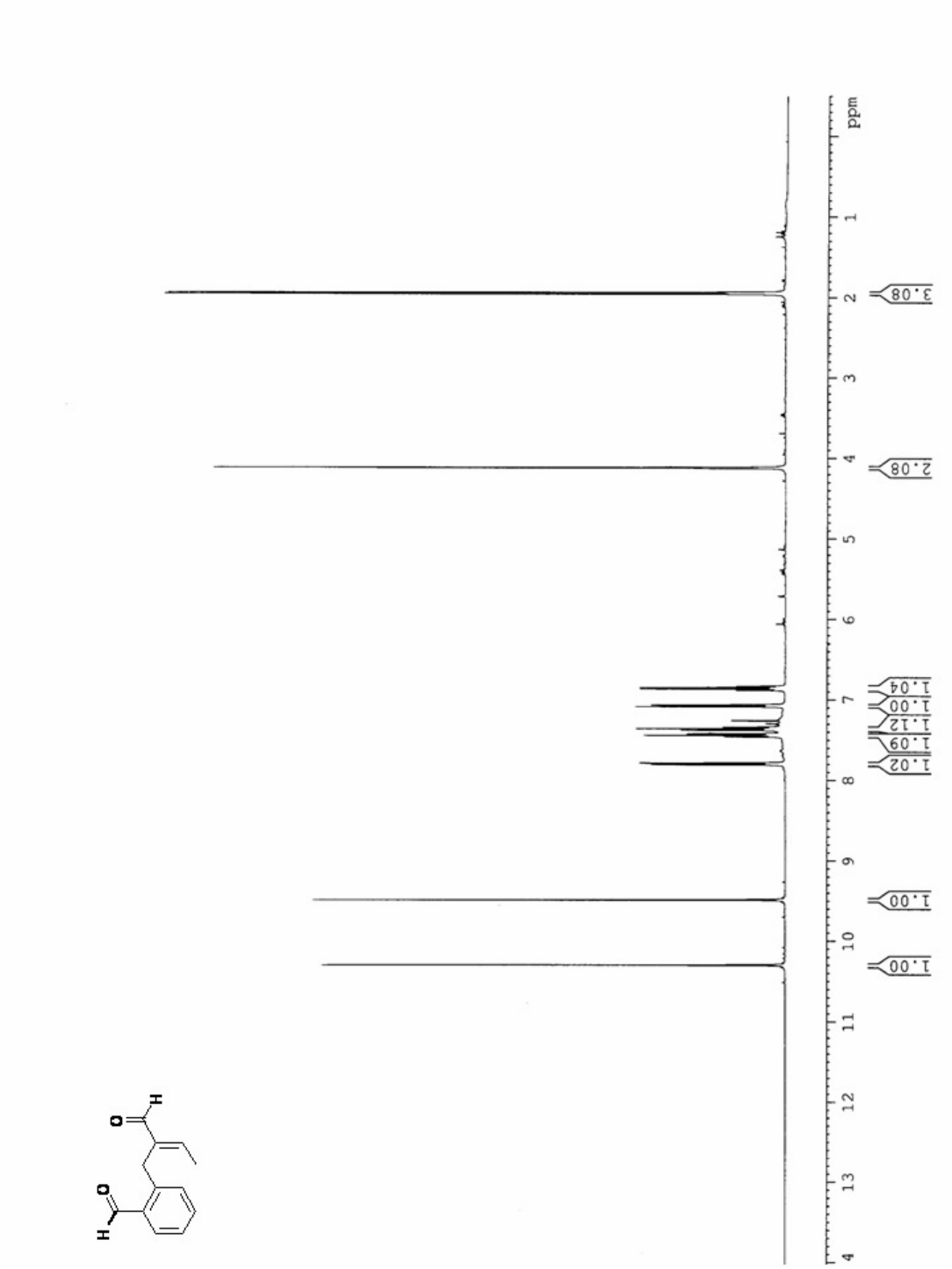

Figure A2.6 ^{1}H NMR (500 MHz, $CDCl_3$) of Table 3.2, Entry 7.

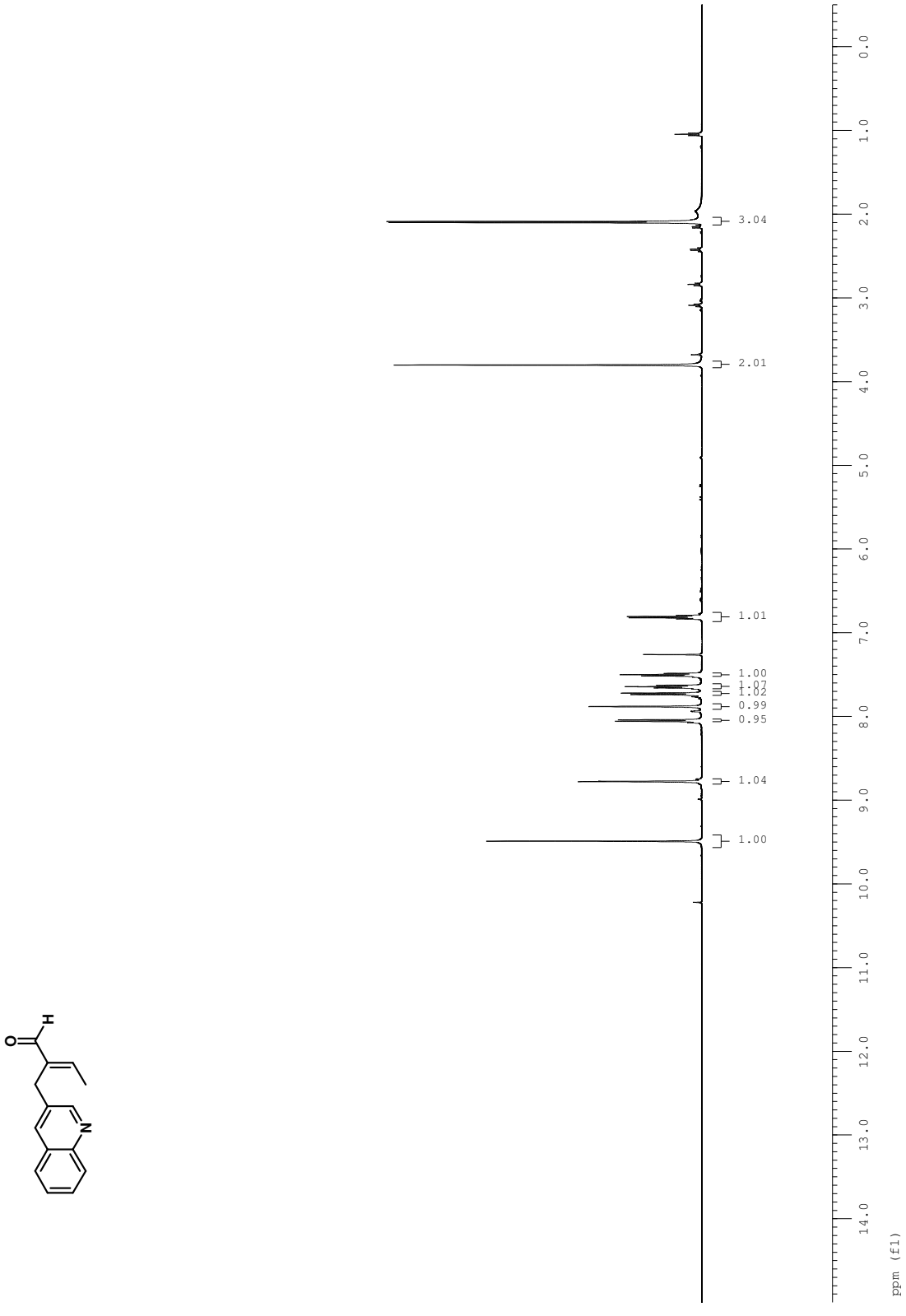

Figure A2.7 ^{1}H NMR (500 MHz, $CDCl_3$) of Table 3.2, Entry 8.

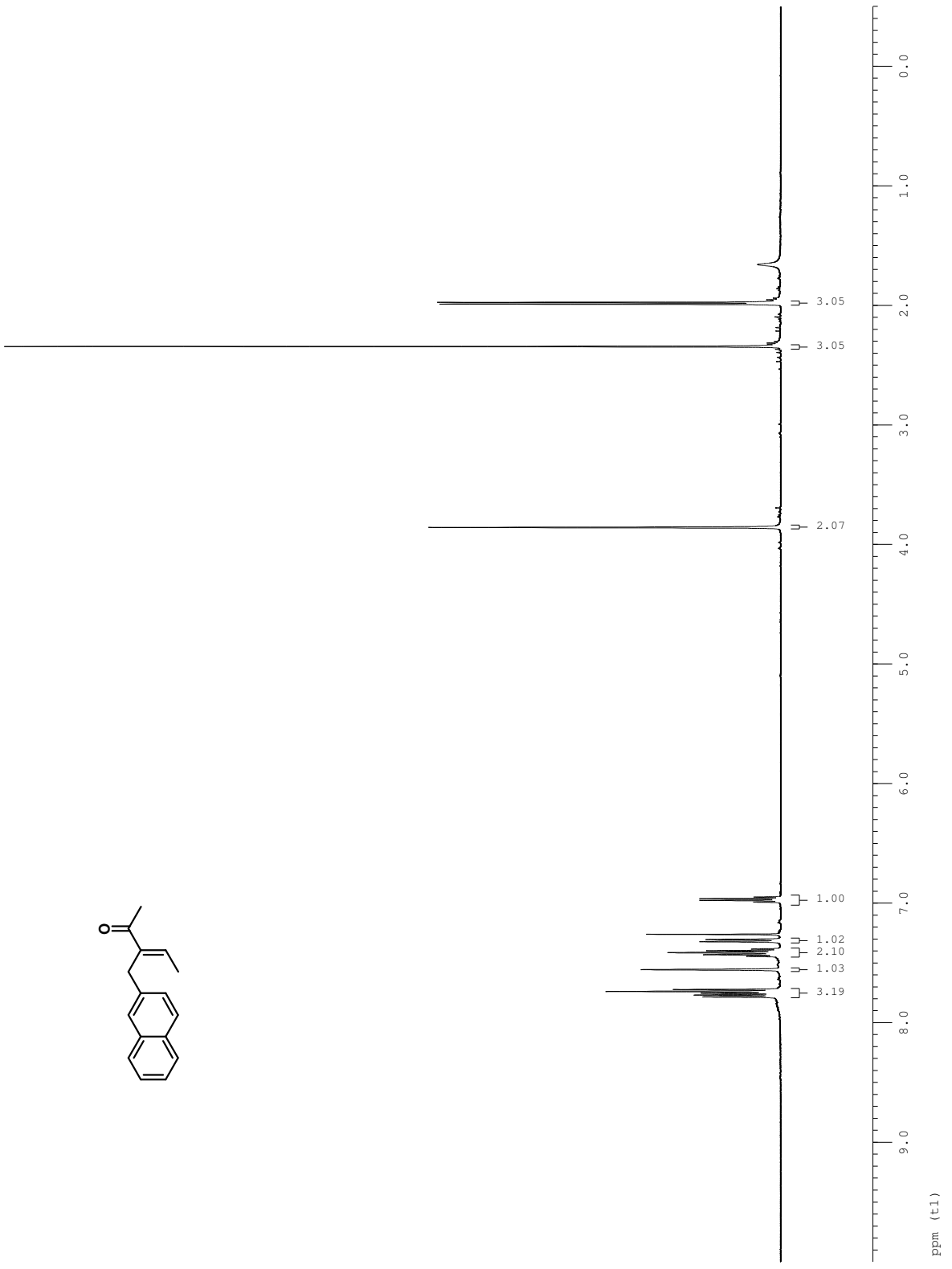

Figure A2.8 ^{1}H NMR (500 MHz, $CDCl_3$) of Table 3.3, Entry 1.

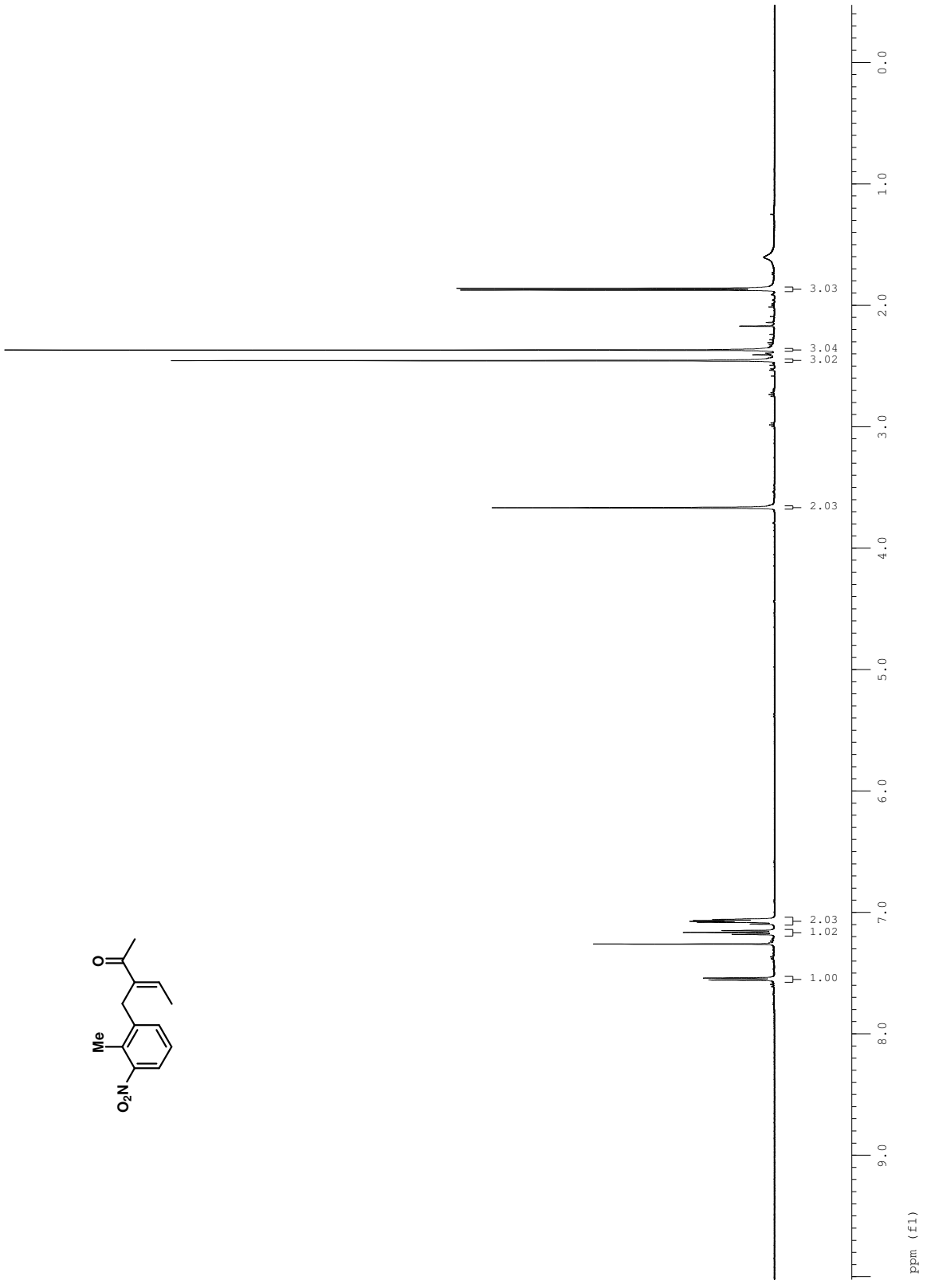

Figure A2.9 ^{1}H NMR (500 MHz, $CDCl_3$) of Table 3.3, Entry 2.

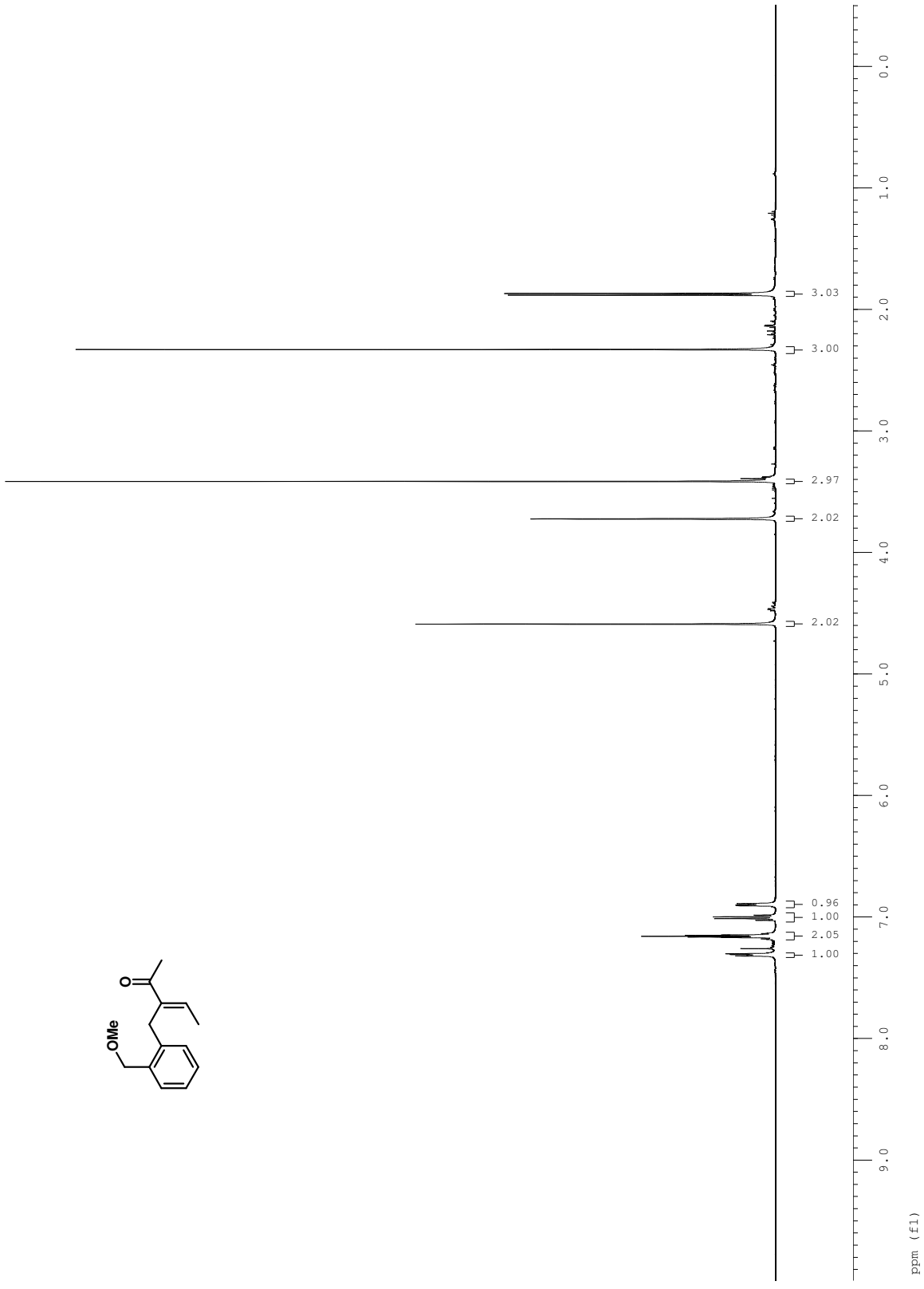

Figure A2.10 ^{1}H NMR (500 MHz, $CDCl_3$) of Table 3.3, Entry 3.

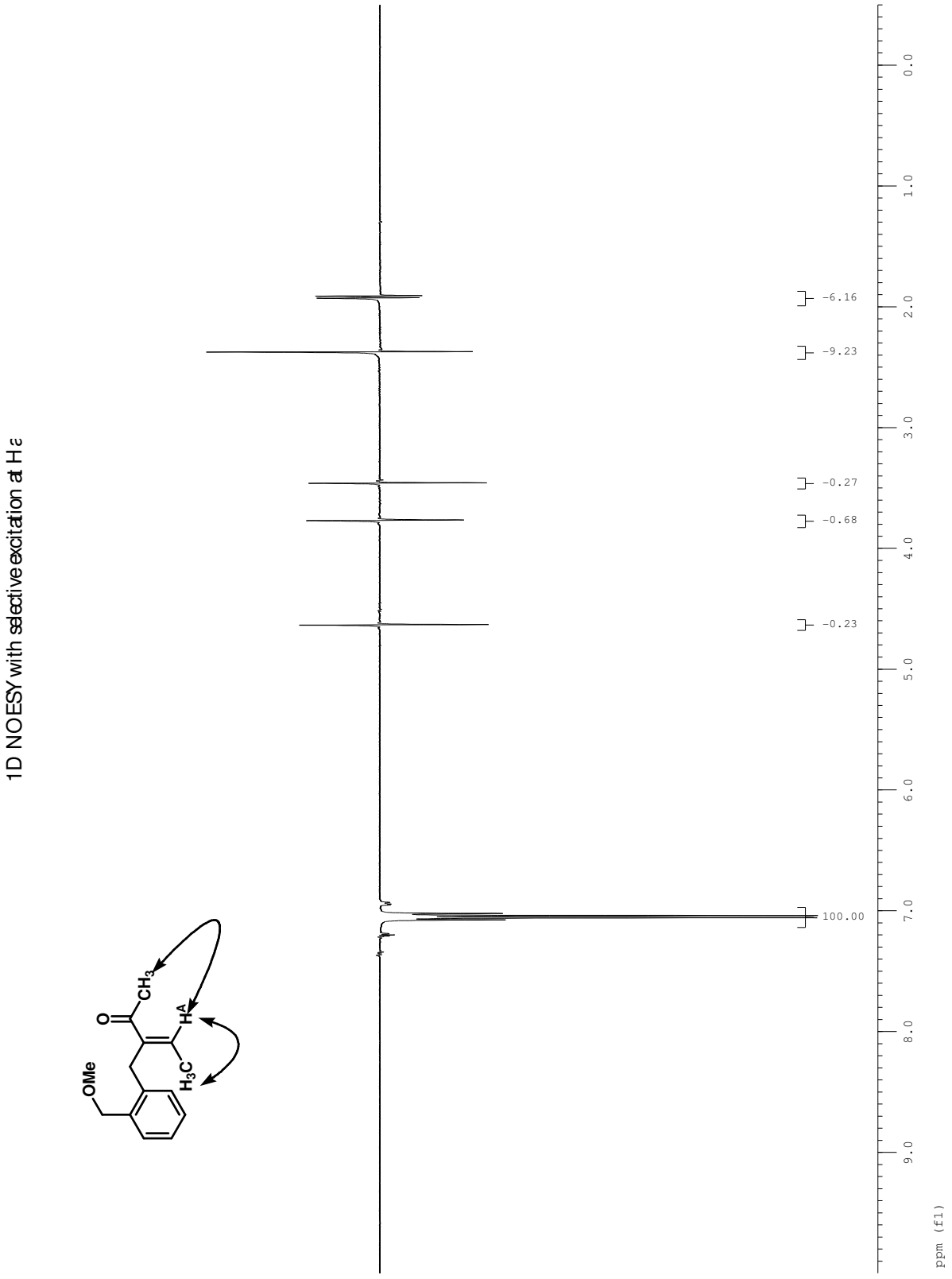

Figure A2.11 1D NOESY NMR with selective excitation at H^A (400 MHz, $CDCl_3$) of Table 3.3, Entry 3.

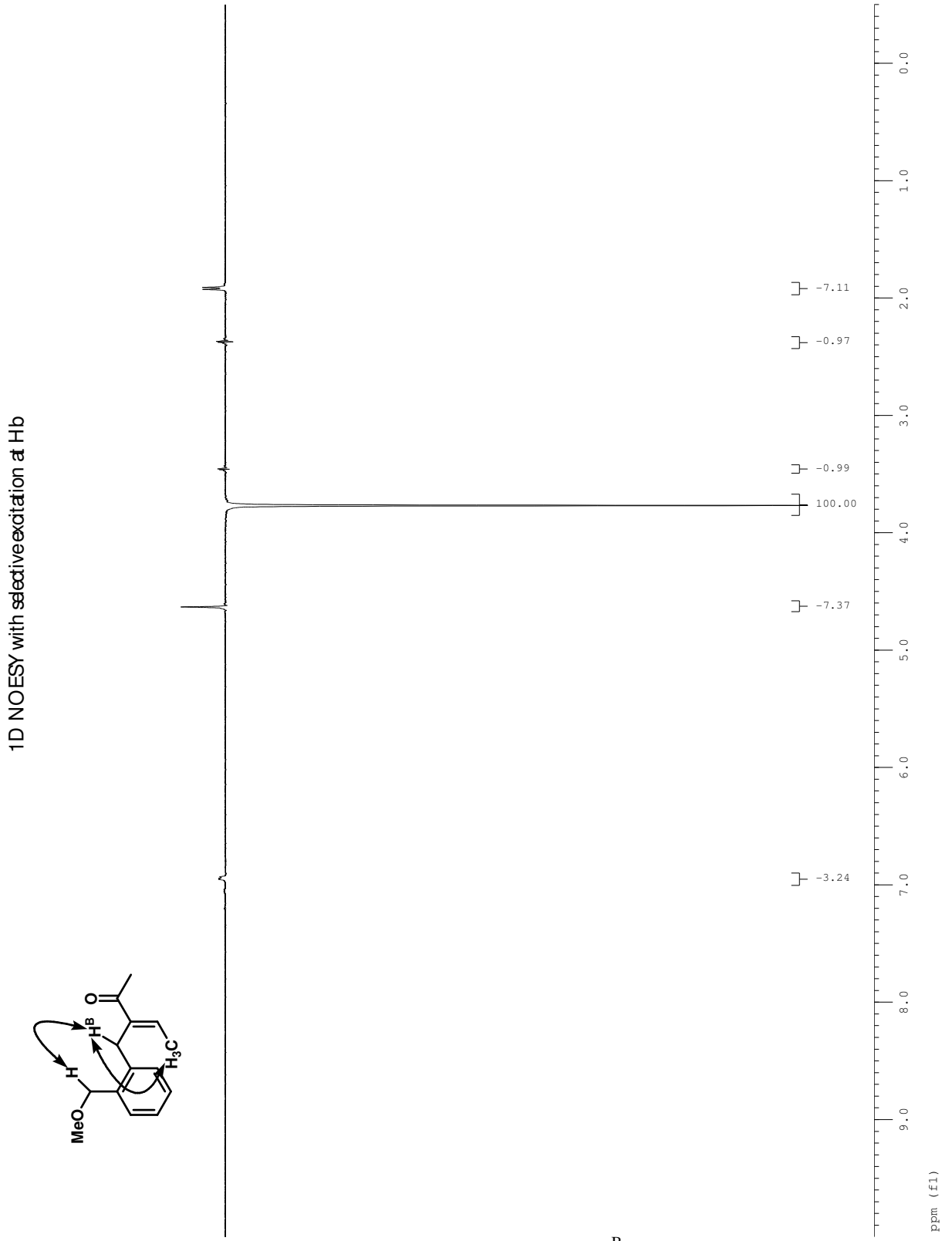

Figure A2.12 1D NOESY NMR with selective excitation at H^B (400 MHz, $CDCl_3$) of Table 3.3, Entry 3.

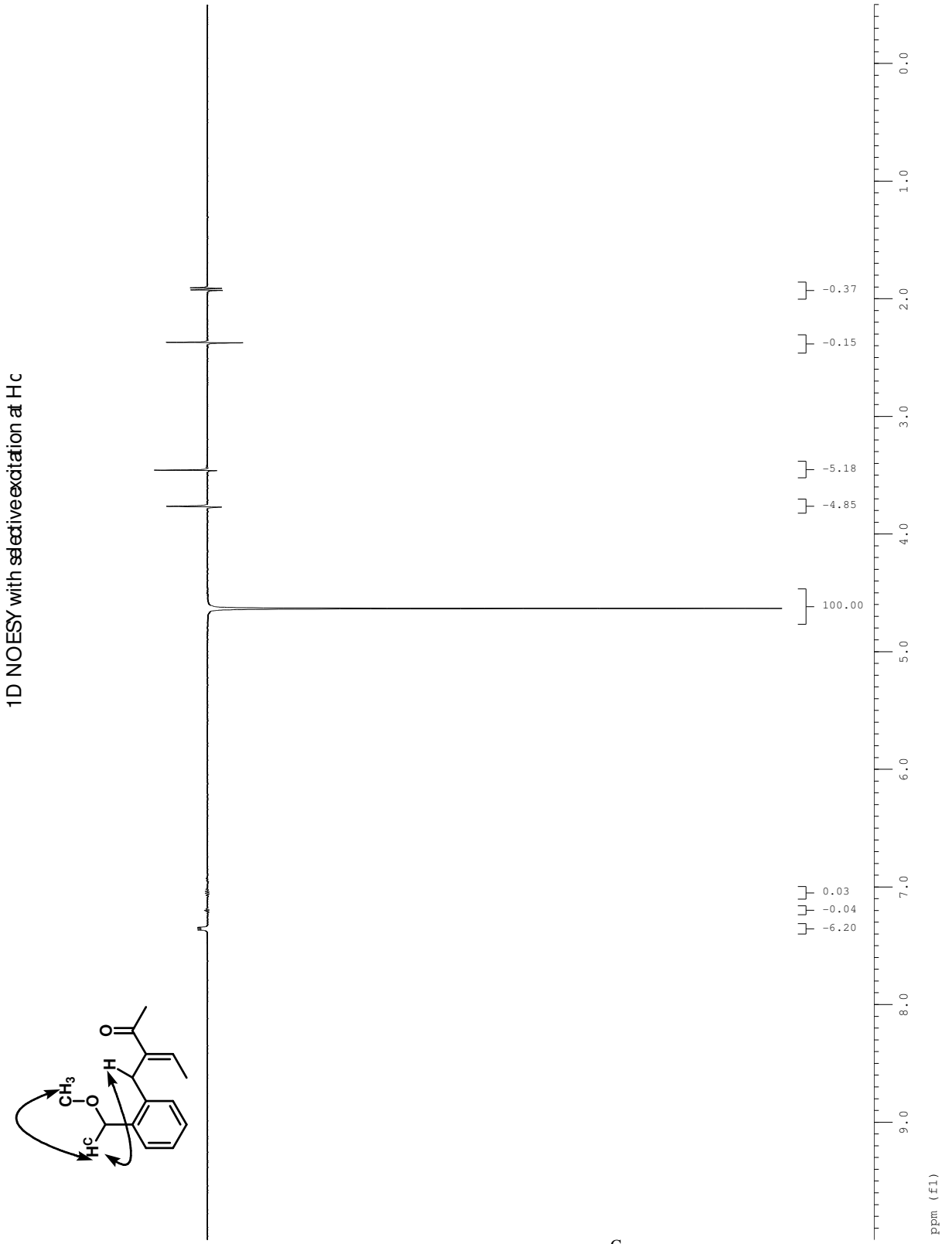

Figure A2.13 1D NOESY NMR with selective excitation at H^C (400 MHz, $CDCl_3$) of Table 3.3, Entry 3.

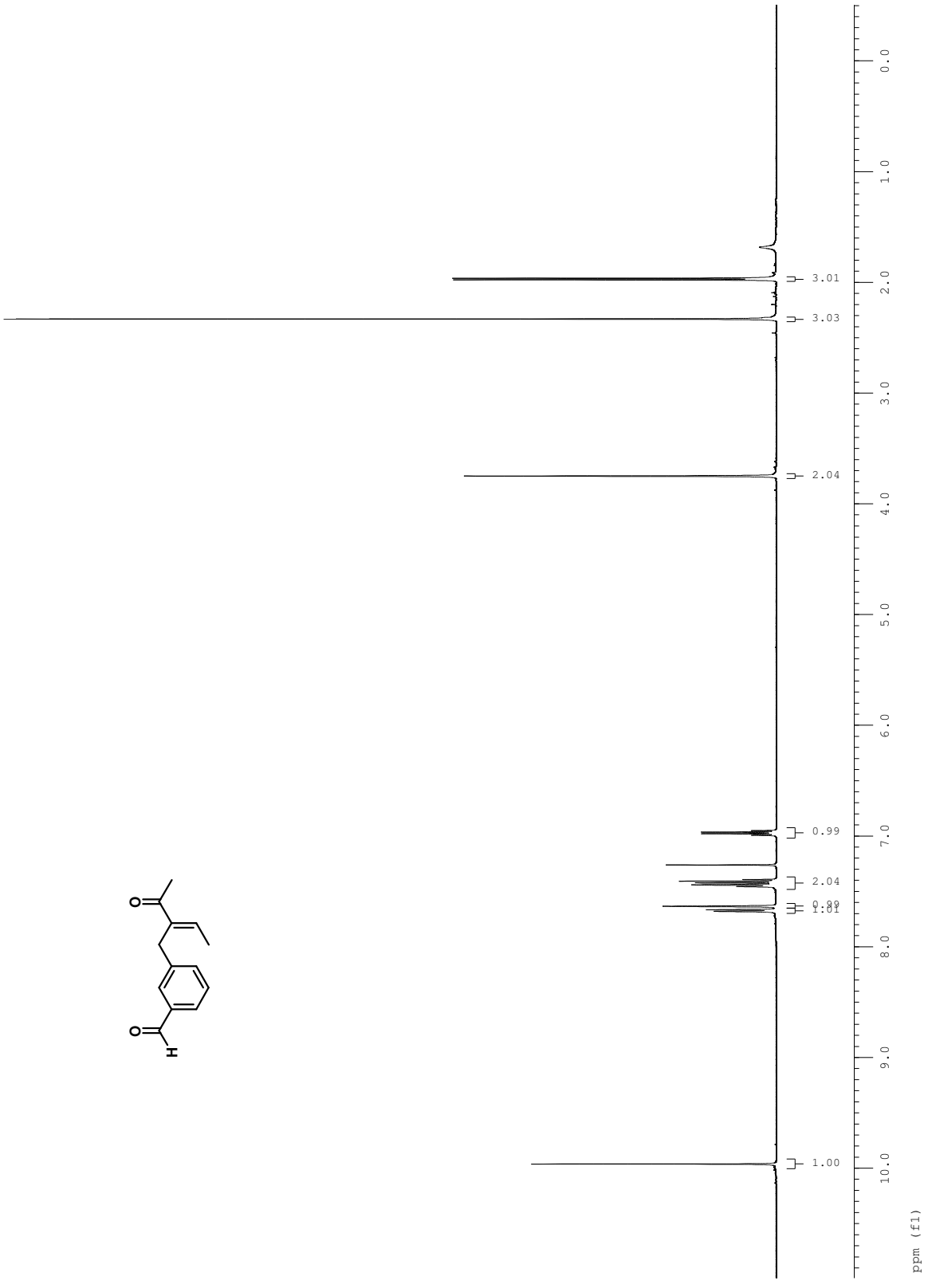

Figure A2.14 ^{1}H NMR (500 MHz, $CDCl_3$) of Table 3.3, Entry 4.

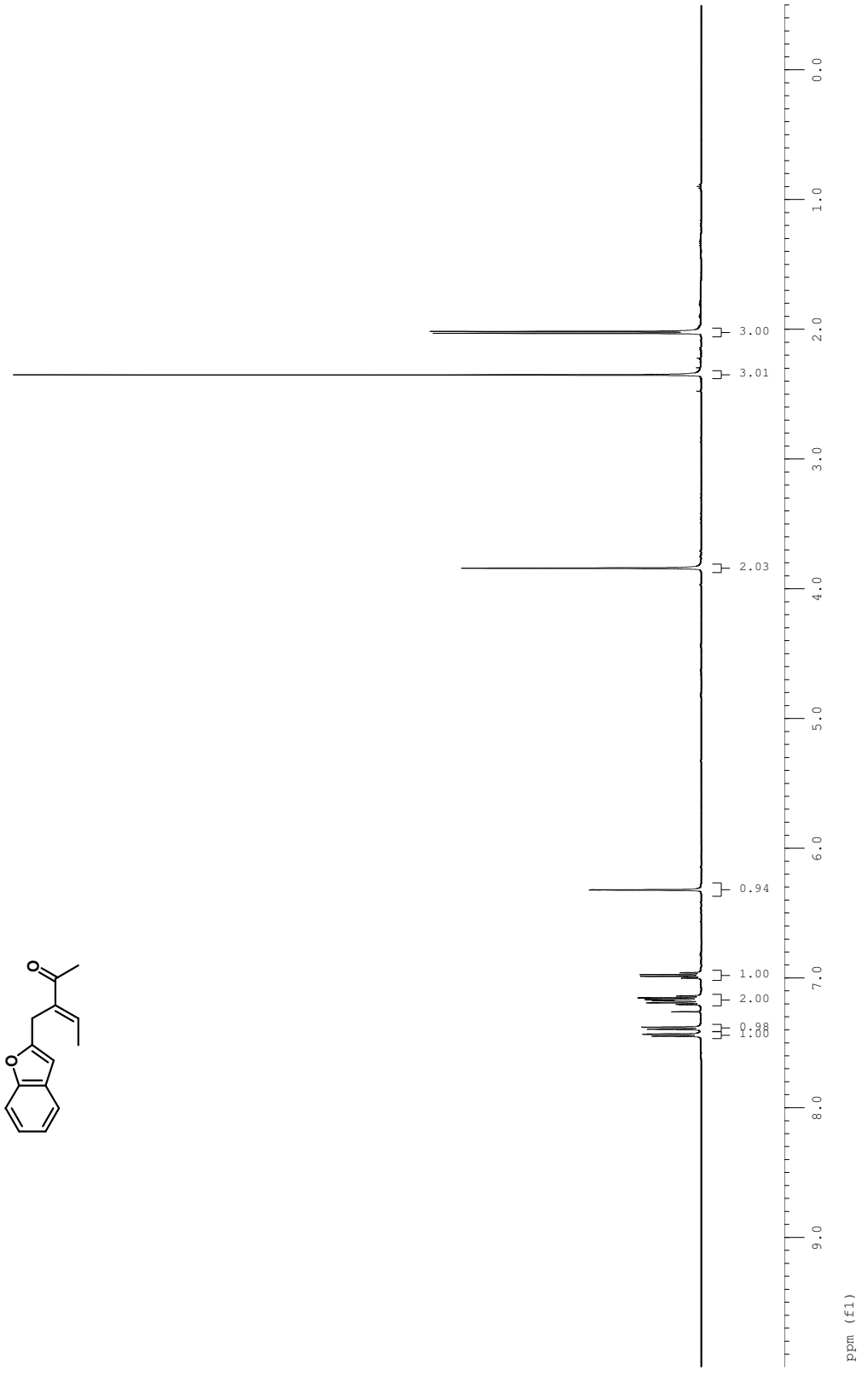

Figure A2.15 ^{1}H NMR (500 MHz, $CDCl_3$) of Table 3.3, Entry 5.

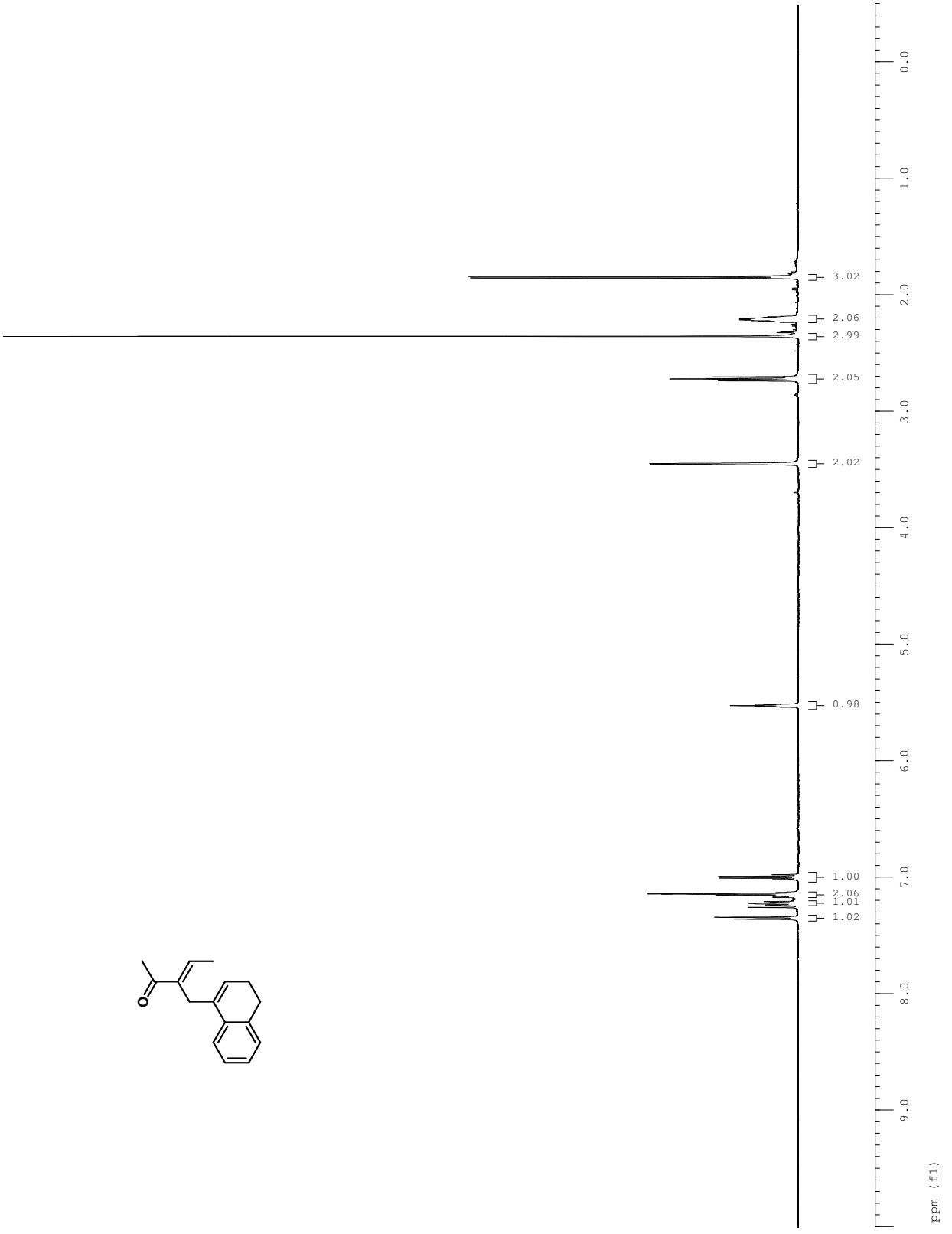

Figure A2.16 ^{1}H NMR (500 MHz, $CDCl_3$) of Table 3.3, Entry 6.

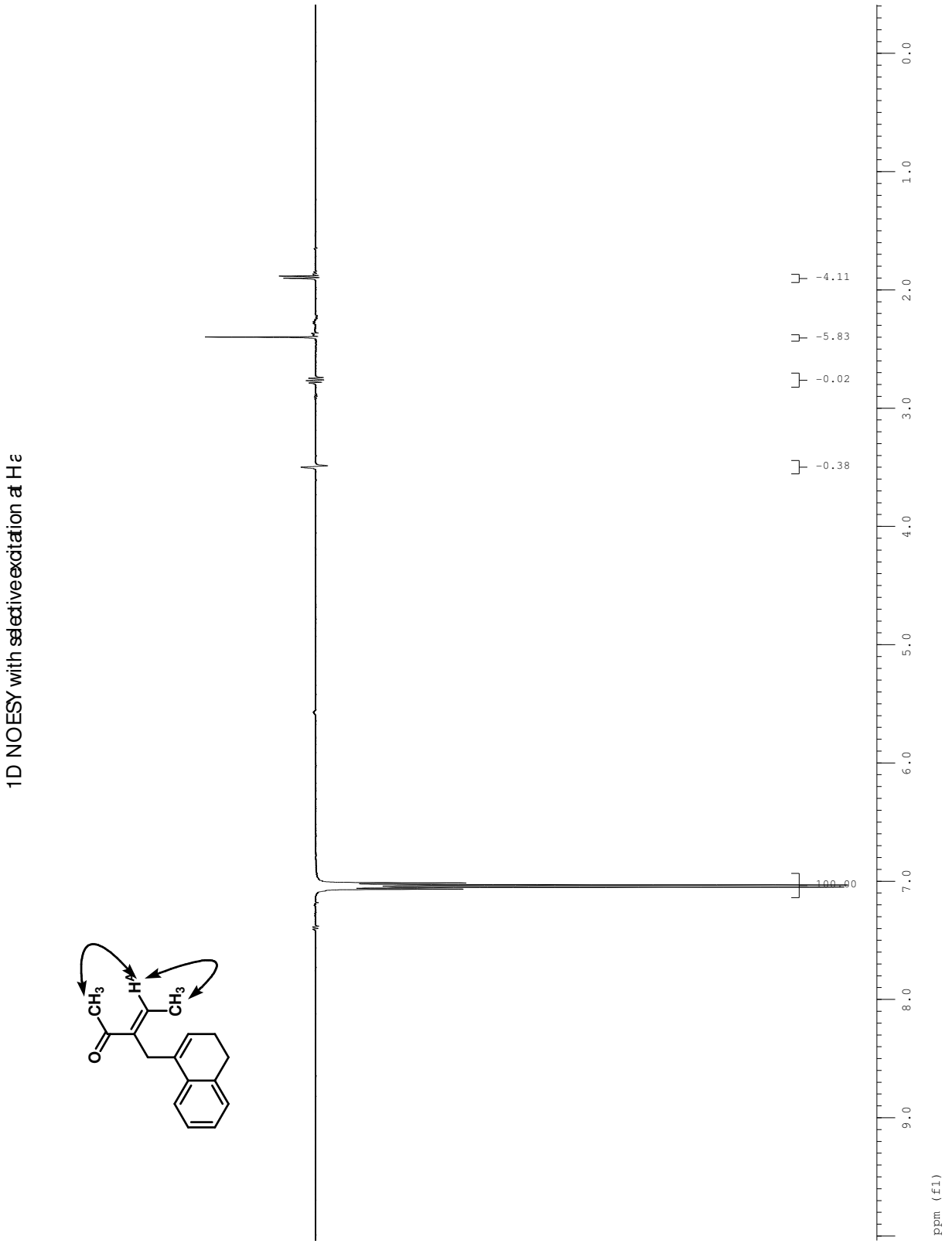

Figure A2.17 1D NOESY NMR with selective excitation at H^A (400 MHz, $CDCl_3$) of Table 3.3, Entry 6.

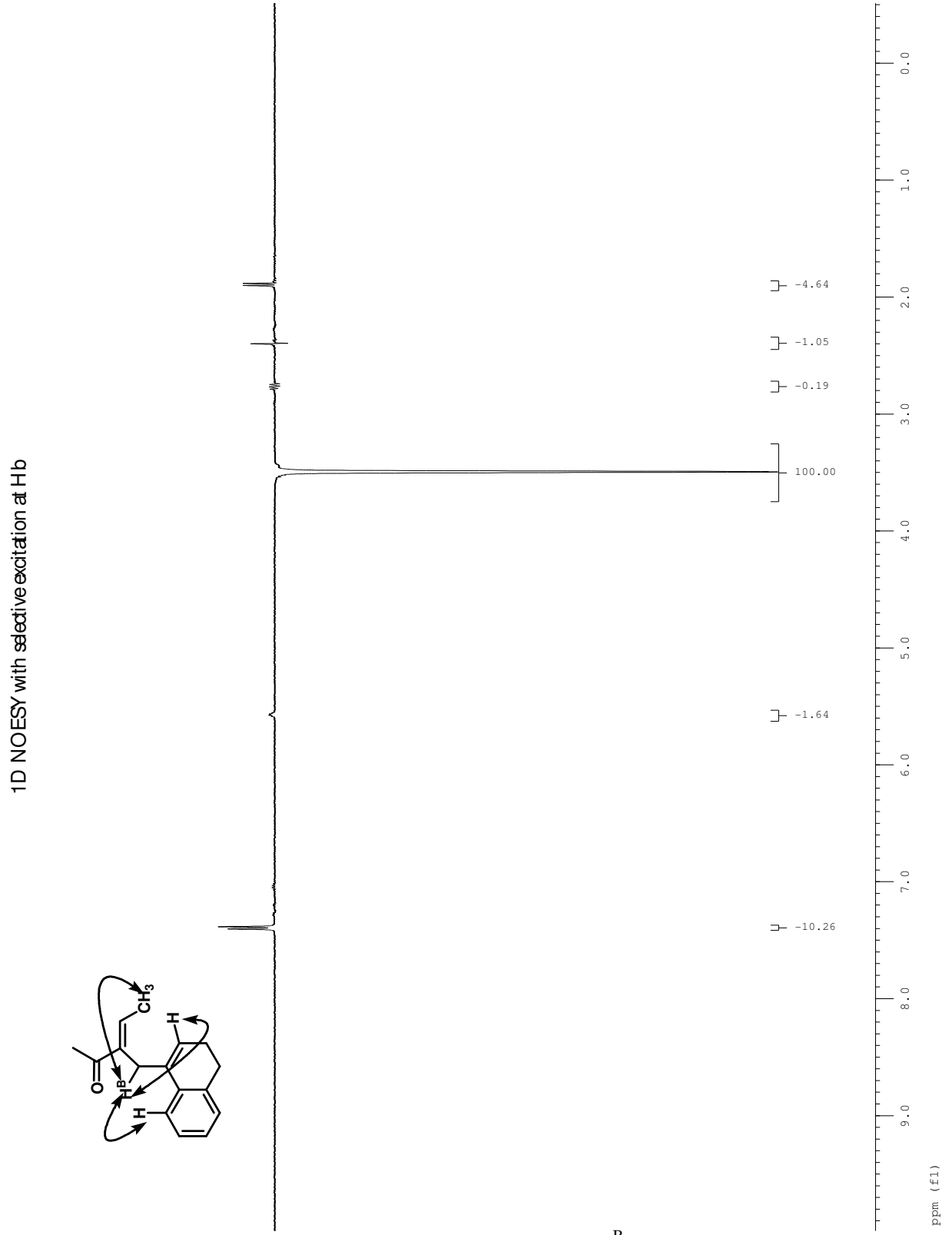

Figure A2.18 1D NOESY NMR with selective excitation at H^B (400 MHz, $CDCl_3$) of Table 3.3, Entry 6.

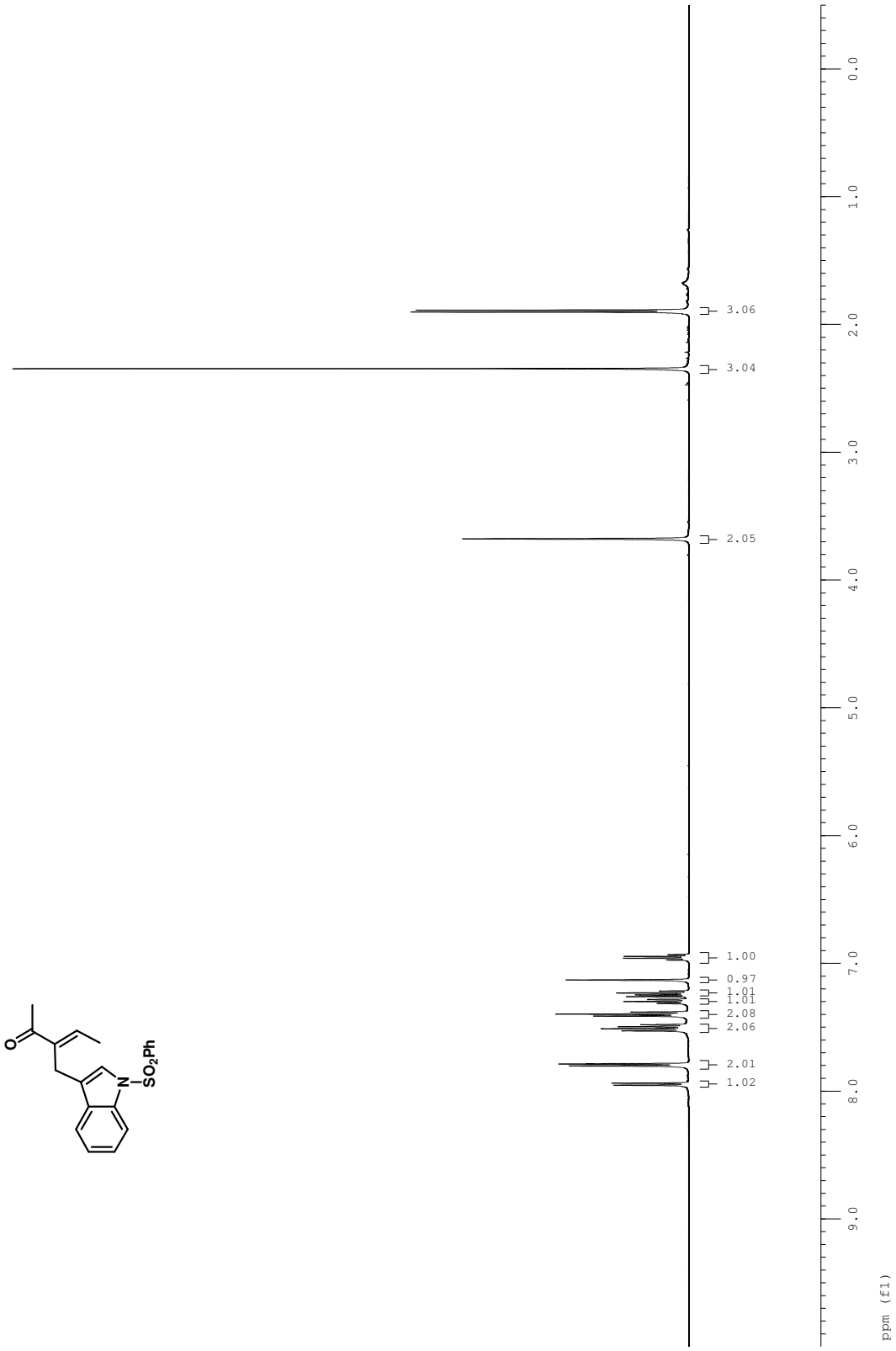

Figure A2.19 ^{1}H NMR (500 MHz, $CDCl_3$) of Table 3.3, Entry 7.

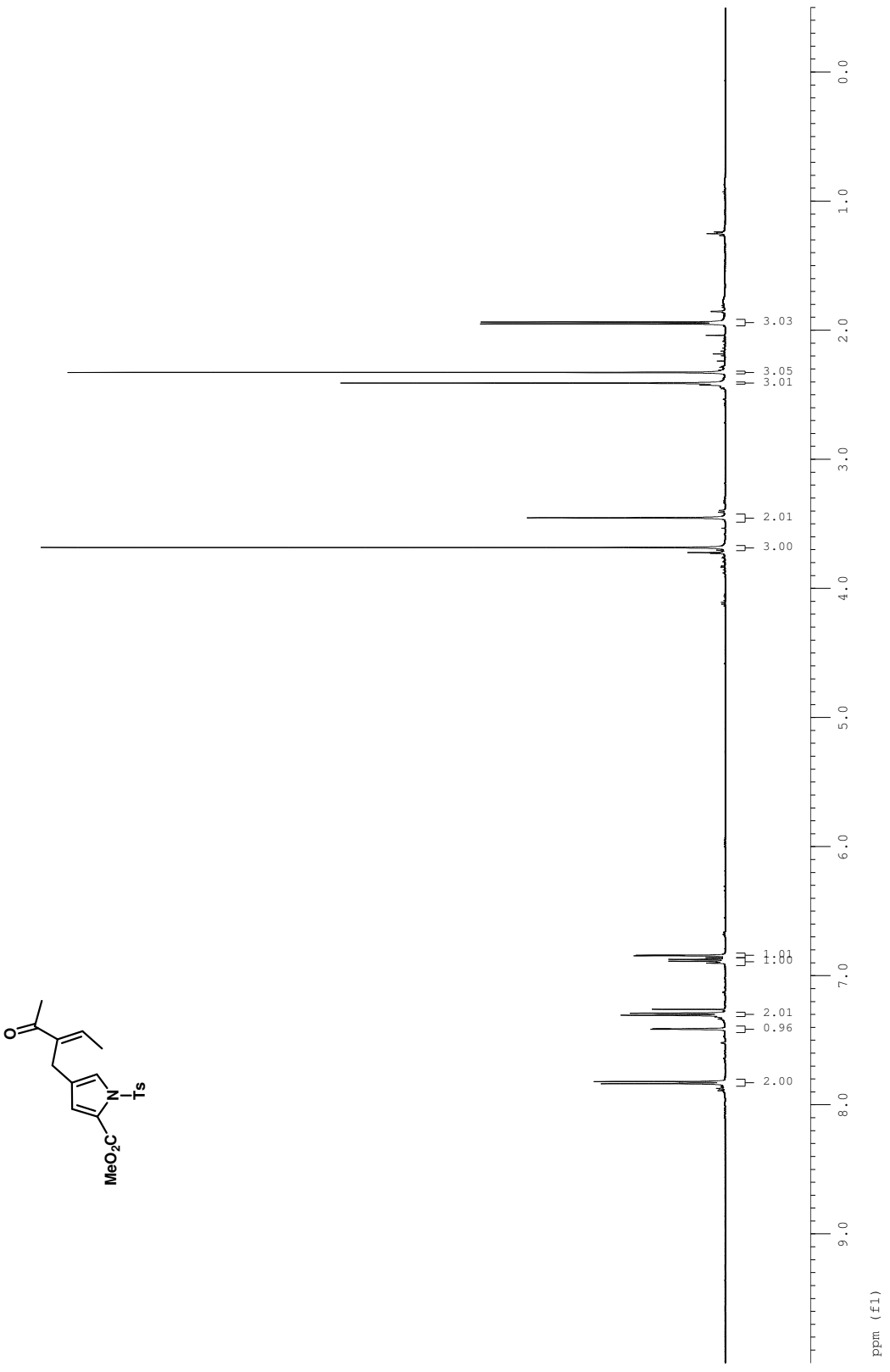

Figure A2.20 ^{1}H NMR (500 MHz, $CDCl_3$) of Table 3.3, Entry 8.

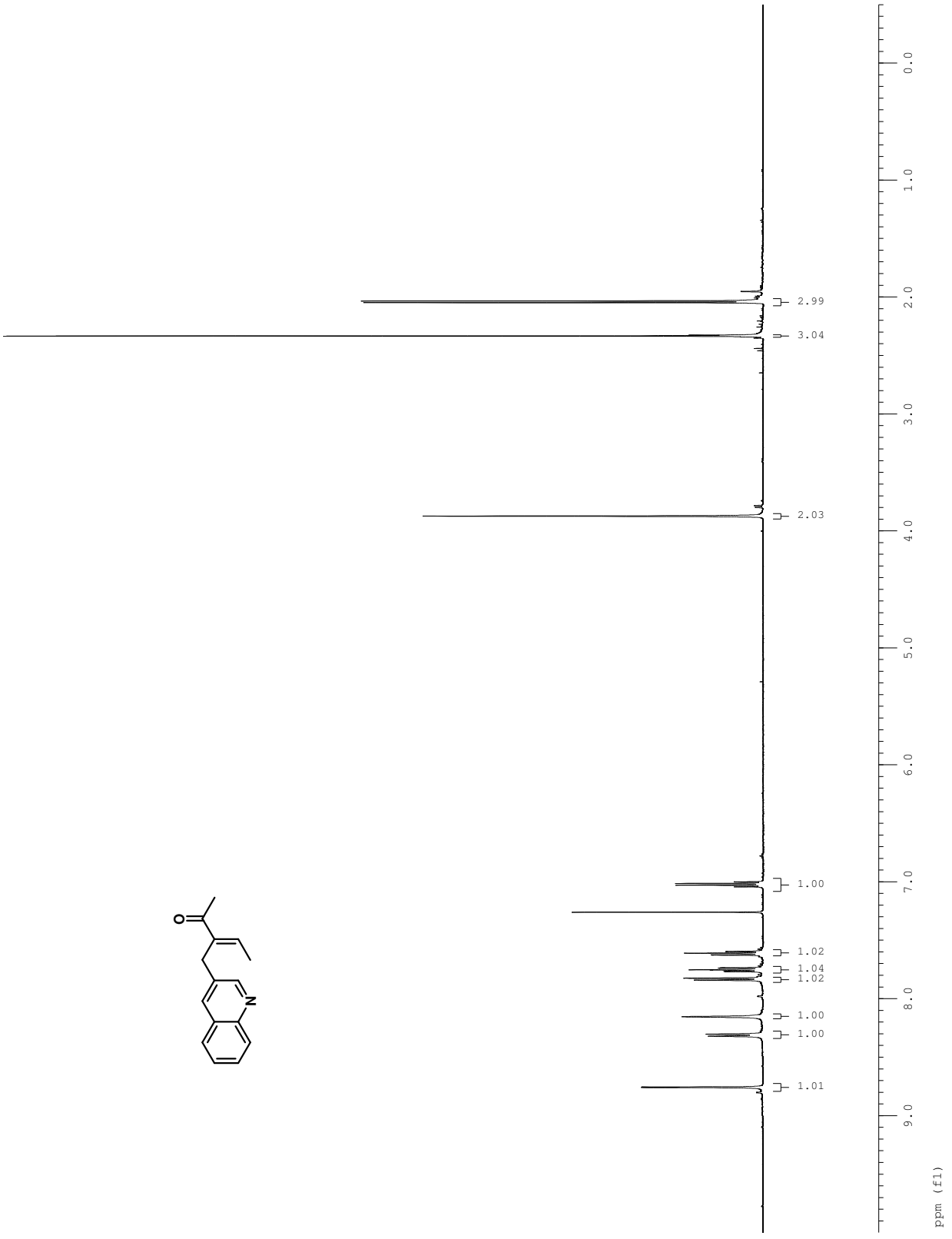

Figure A2.21 ^{1}H NMR (500 MHz, $CDCl_3$) of Table 3.3, Entry 9.

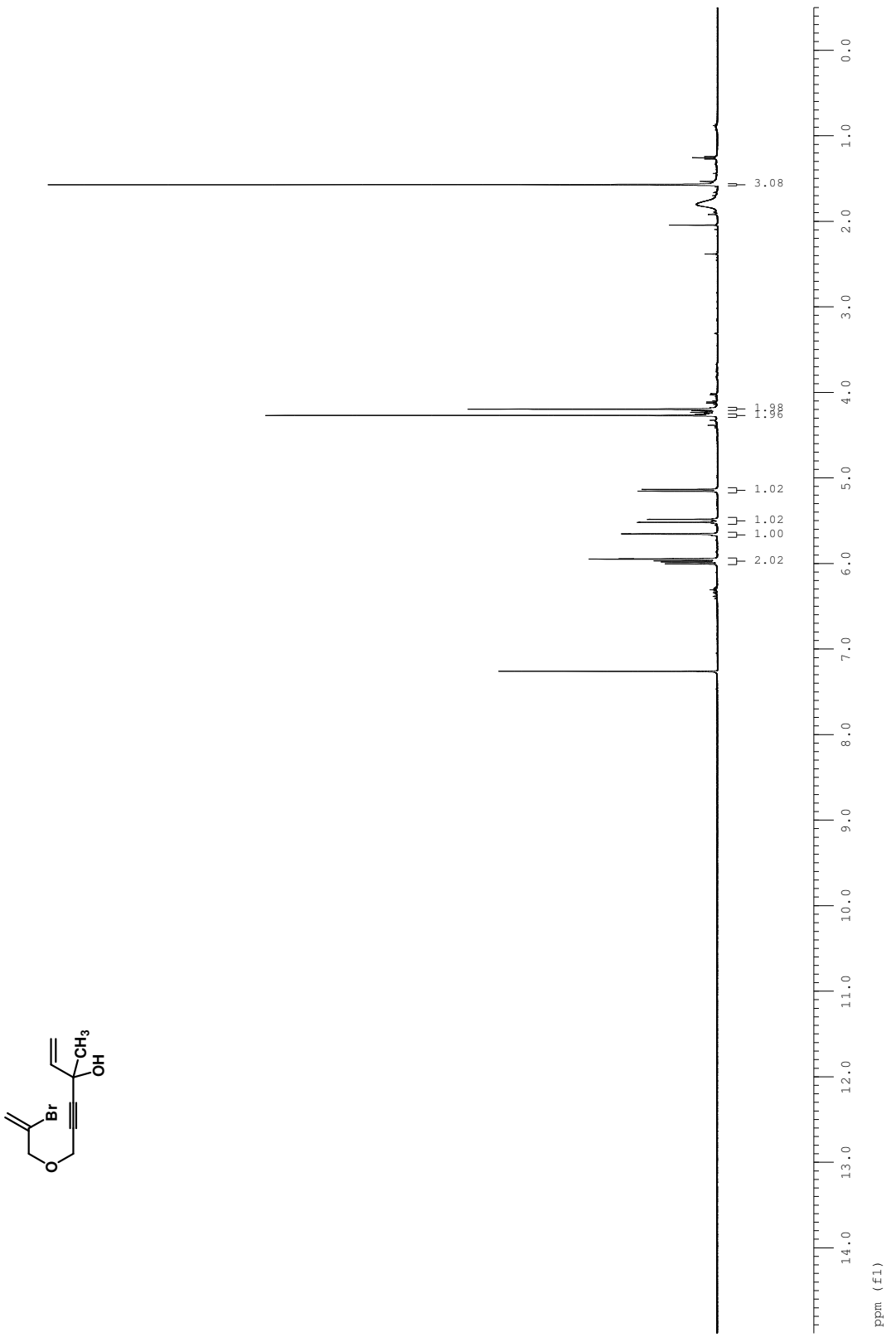

Figure A2.22 ^{1}H NMR (500 MHz, $CDCl_3$) of Compound **3.38**.

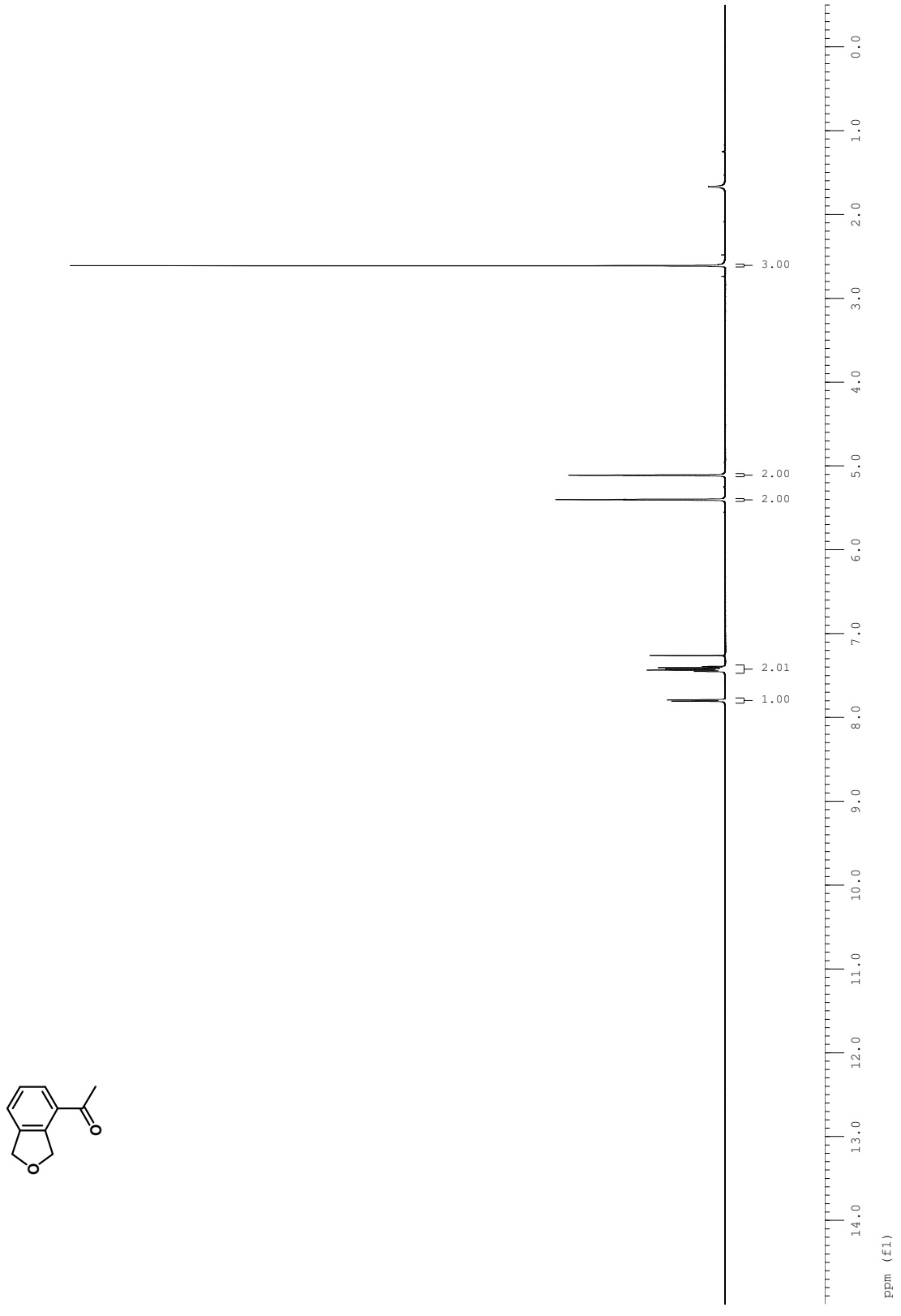

Figure A2.23 ^{1}H NMR (500 MHz, $CDCl_3$) of 3-acetyl-dihydro-isobenzofuran.

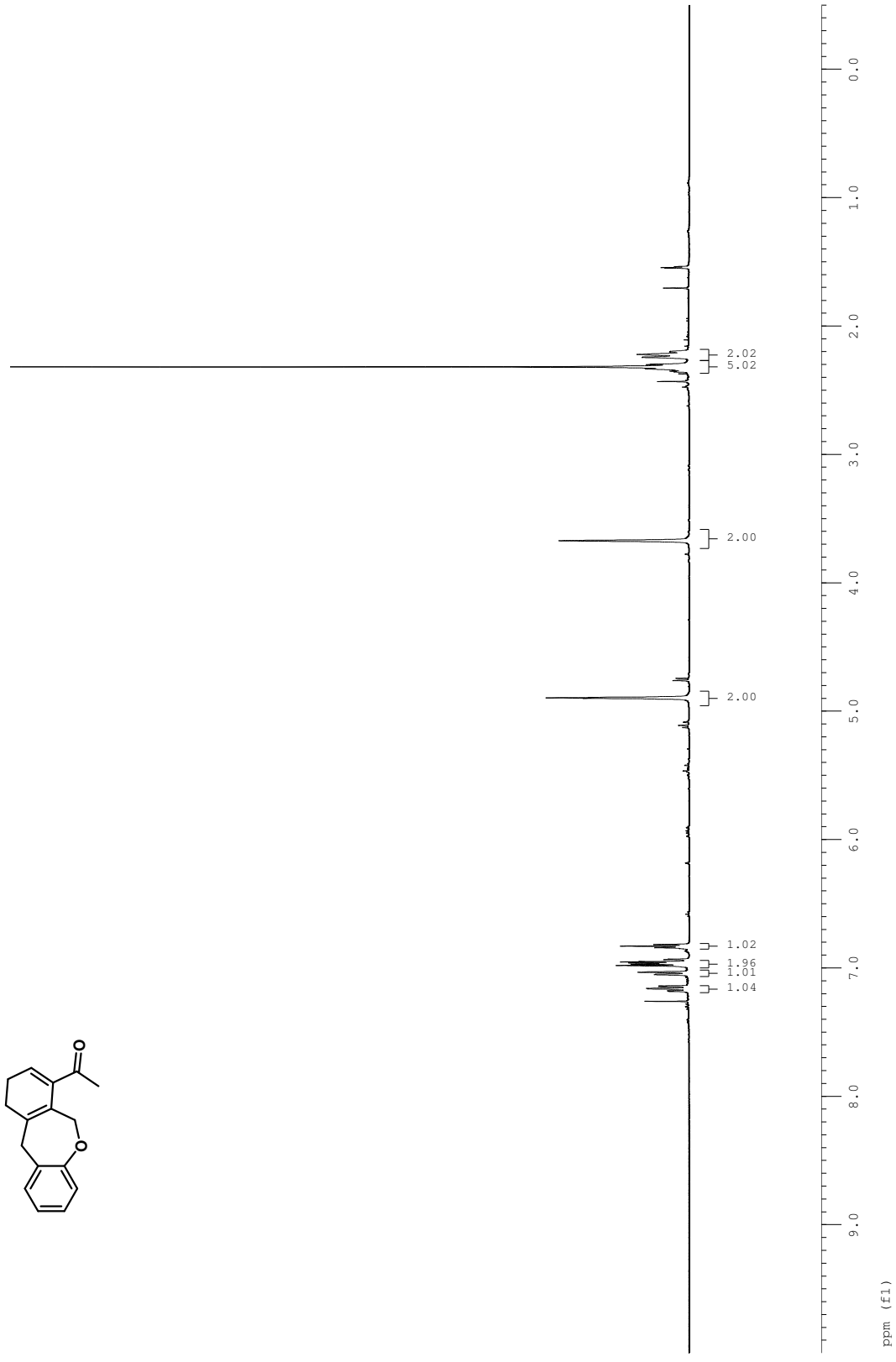

Figure A2.24 ^{1}H NMR (500 MHz, $CDCl_3$) of unaromatized product of eq 3.7.