**Title**
Synthesis of Lycodine-Type Lycopodium Alkaloids Using C-H Functionalization Tactics



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# Synthesis of Lycodine-Type *Lycopodium* Alkaloids Using C-H Functionalization Tactics

by

James Neel Newton

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Professor F. Dean Toste
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**Abstract**

Synthesis of Lycodine-Type *Lycopodium* Alkaloids Using C-H Functionalization Tactics

By

James Neel Newton

Doctor of Philosophy in Chemistry

University of California, Berkeley

Professor Richmond Sarpong, Chair

This dissertation describes our syntheses of several lycodine-type *Lycopodium* alkaloids by the late-stage C-H functionalization of lycodine derivatives. Lycodine-type alkaloids are well-known for their neurological activity. For example, huperzine A is a potent acetylcholinesterase inhibitor and the complanadine family of molecules has been shown to induce the secretion of Nerve Growth Factor. Due to these properties, lycodine-type alkaloids serve as interesting lead compounds for the development of new therapies for neurodegenerative disorders, such as Alzheimer's disease. Unsurprisingly, these molecules have attracted the attention of the synthetic community. Chapter 1 reviews syntheses of lycodine-type *Lycopodium* alkaloids with particular emphasis on the syntheses of biologically active congeners. Chapter 2 describes our synthesis of complanadine B, an unsymmetrical dimer of lycodine, using two approaches. In the first, the requisite skeletal oxygenation was installed early in the synthetic sequence. Our second approach utilized a blocking group strategy to enable the late-stage oxygenation of the complanadine skeleton by preventing oxygenation at undesired sites. Chapter 3 describes our efforts toward the synthesis of the casuarinine family of *Lycopodium* alkaloids by the late-stage C-H functionalization of lycodine derivatives. Using this strategy, we have been able to complete the synthesis of casuarinine D and have made significant progress toward the synthesis of casuarinine H, which we believe can serve as an intermediate in the synthesis of several other lycodine-type alkaloids.

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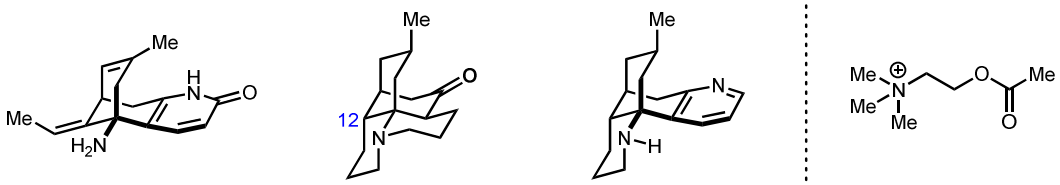
**Chapter Three: Synthesis of the Casuarinine Family of *Lycopodium* Alkaloids by the Late-Stage C-H Functionalization of Lycodine Derivatives**

## Chapter 1. Synthesis of Biologically Active Lycodine-Type *Lycopodium* Alkaloids

### 1.1 Introduction

For centuries, plants in the *Lycopodium* genus, commonly known as club mosses, have been revered for their medicinal properties by several cultures around the world. *Qian Ceng Ta*, a traditional Chinese folk medicine prepared from *Huperzia serrata* (Thunb.) Trev., has been employed in the treatment of contusions, schizophrenia, and myasthenia gravis (muscle weakness) among other conditions.[1] Celtic and Native American tribes also utilized preparations of *L. clavatum* as an ingredient in remedies for numerous other maladies.[2] More recently, the discovery of the potent acetylcholinesterase inhibition properties of huperzine A (**1.1**, Figure 1.1) and related alkaloids have spurred a resurgence in research centered on *Lycopodium* alkaloids, where the isolation of new alkaloids as well as the total synthesis of the more prominent molecules in the family have been a particular focus.

**Figure 1.1** Selected *Lycopodium* Alkaloids.

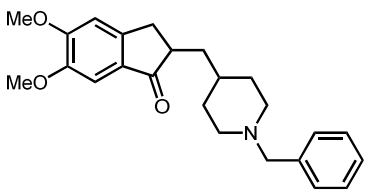



(-)-huperzine A (**1.1**) (-)-lycopodine (**1.2**) (-)-lycodine (**1.3**) Acetylcholine (**1.4**)

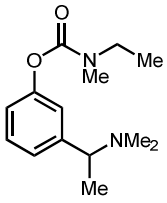
Modern interest in *Lycopodium* alkaloids began with Bödeker's isolation of the first *Lycopodium* alkaloid, lycopodine (**1.2**), in 1881.[3] Despite this early accomplishment, the structure of lycopodine was not elucidated until 1960 by MacLean.[4] In 1967, Wiesner completed the first synthesis of the lycopodine skeleton in the form of 12-*epi*-lycopodine.[5] One year later, the first total syntheses of lycopodine were reported nearly simultaneously by Stork[6] and Ayer[7]. These initial syntheses have served as a foundation for subsequent work in the field and are described in more detail in Section 1.3.

A resurgence in interest in the *Lycopodium* alkaloids occurred in the 1980s after Giacobini and coworkers reported that huperzine A (**1.1**), a lycodine-type *Lycopodium* alkaloid, was an extremely potent acetylcholine esterase (AChE) inhibitor.[8] Acetylcholine esterase inhibition is an exciting biological property because molecules that exhibit this property have been shown to treat the symptoms of Alzheimer's disease. In fact, several acetylcholine esterase inhibitors, including donepezil (**1.5**, Figure 1.2), rivastigmine (**1.6**), and galantamine (**1.7**), are currently prescribed to ameliorate the symptoms of Alzheimer's disease.[1] The discovery of these properties spurred several total syntheses of **1.1**, the first racemic synthesis of which was reported by Kozikowski in 1989.[9] Due to the elegance of Kozikowski's strategy, several investigators have pursued similar approaches that feature tactical enhancements and methods for the introduction of asymmetry. A more important contribution by Kozikowski and coworkers was their systematic study of the structural features of **1.1** that confer function. These features were identified by studying the biological activity of a series of synthetic analogues.[10] Kozikowski's synthetic program serves as a sterling example of how total synthesis can fuel biological discovery.

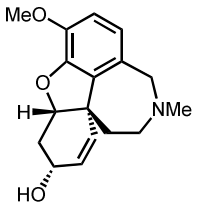
**Figure 1.2** Approved Drugs for the Treatment of Alzheimer's Disease.



donepezil (**1.5**)



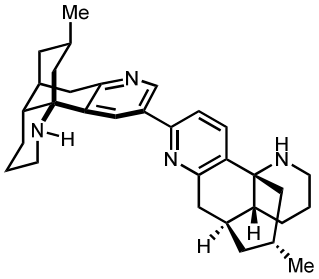
rivastigmine (**1.6**)



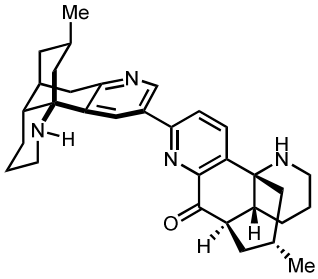
galantamine (**1.7**)

As studies have demonstrated the limited success of AChE inhibitor therapy in the treatment of Alzheimer's disease,[11] the impetus for studying *Lycopodium* alkaloids had diminished until recent discoveries reinvigorated the research community. In 2000, Kobayashi isolated complanadine A (**1.8**, Figure 1.3), the first dimeric lycodine-type *Lycopodium* alkaloid.[12] This unsymmetrical dimer of lycodine (**1.3**) induces the secretion of neurotrophic factors from human astrocytoma cells and enhances gene expression of Nerve Growth Factor (NGF).[13,14] Administration of NGF to Alzheimer's patients has been shown to improve their cognitive performance.[15] However, challenges remain with delivering NGF to the brain. Small molecules that can induce production of NGF *in vivo* possess significant therapeutic potential. Subsequently, complanadine B (**1.9**),[16] D (**1.10**),[17] and E (**1.11**)[18] have been isolated and shown to exhibit similar biological properties. Therefore, this family of molecules could serve as interesting lead molecules for the development of new treatments for neurodegenerative diseases.

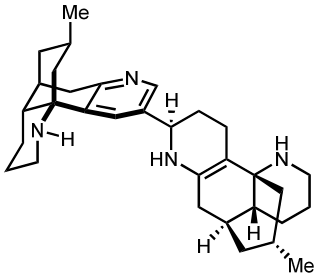
**Figure 1.3** The Complanadine Family.



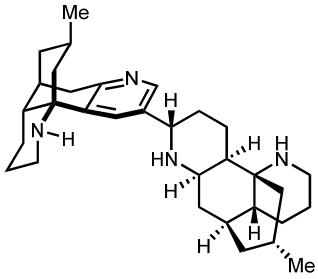
complanadine A (**1.8**)



complanadine B (**1.9**)



complanadine D (**1.10**)



complanadine E (**1.11**)

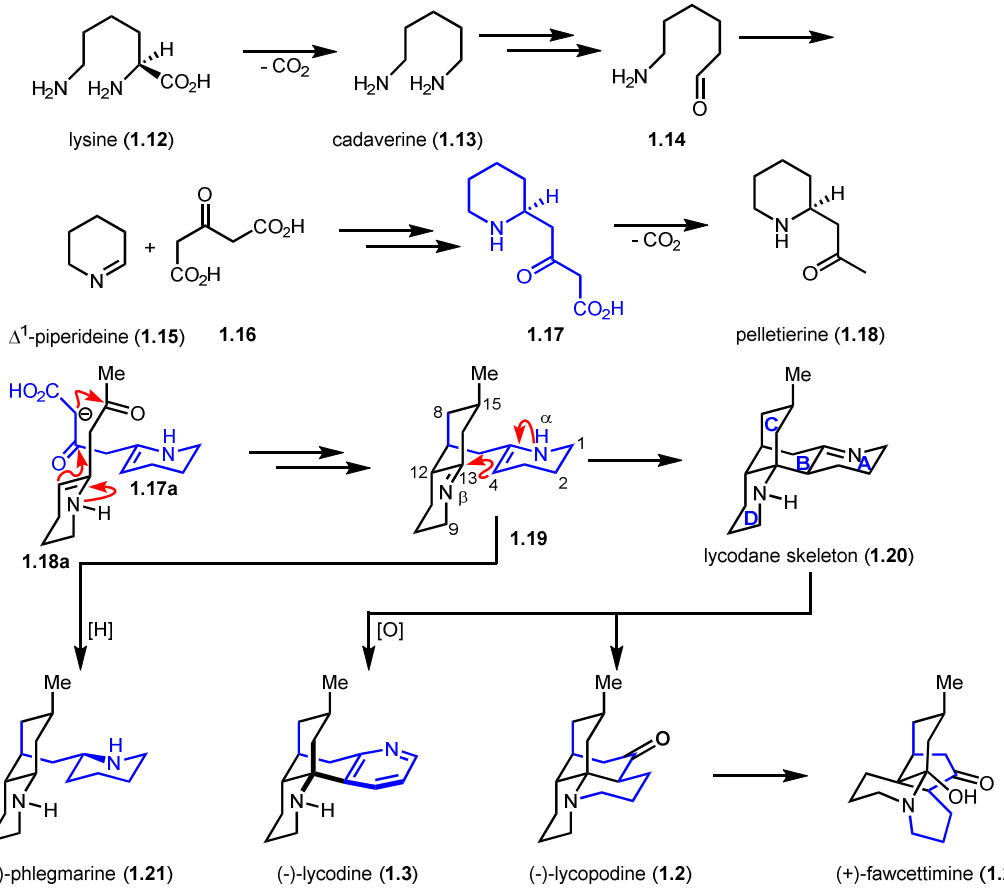
Due in part to their important biological activity, several syntheses of lycodine-type *Lycopodium* alkaloids have been reported. A study of these approaches reveals that a limited number of strategies have been employed in the synthesis of these molecules but a diverse array of tactics have been used to execute these strategies. A thorough understanding of these tactics and strategies could enable the development of more efficient syntheses of molecules in this family, which could in turn support further

biological investigation. In this chapter, the syntheses of lycodine-type *Lycopodium* alkaloids are reviewed with particular emphasis on approaches to the biologically active members of the family, huperzine A (**1.1**) and the complanadines.

## 1.2 Biosynthesis of *Lycopodium Alkaloids*

*Lycopodium* alkaloids are typically divided into four classes based on their hypothesized biosynthetic origin using a classification system first developed by Ayer.[19] Three of these classes are named after the representative molecules lycodine (**1.3**), lycopodine (**1.2**), and fawcettimine (**1.22**), which are all believed to be derived from a common intermediate **1.20** (Scheme 1.1). Oxidation of the A ring of **1.20** to the pyridine or pyridone leads to molecules in the lycodine-type. Scission of the C-1-$N_\alpha$ bond followed by bond formation between C-1 and $N_\beta$ affords **1.2**. Fawcettimine (**1.22**) in turn is derived from **1.2** by a migration of C-4 from C-13 to C-12. An additional Miscellaneous class, represented by phlegmarine (**1.21**), contains molecules that are derived from other biogenic pathways.

**Scheme 1.1** Proposed Biosynthesis of the *Lycopodium* alkaloids.



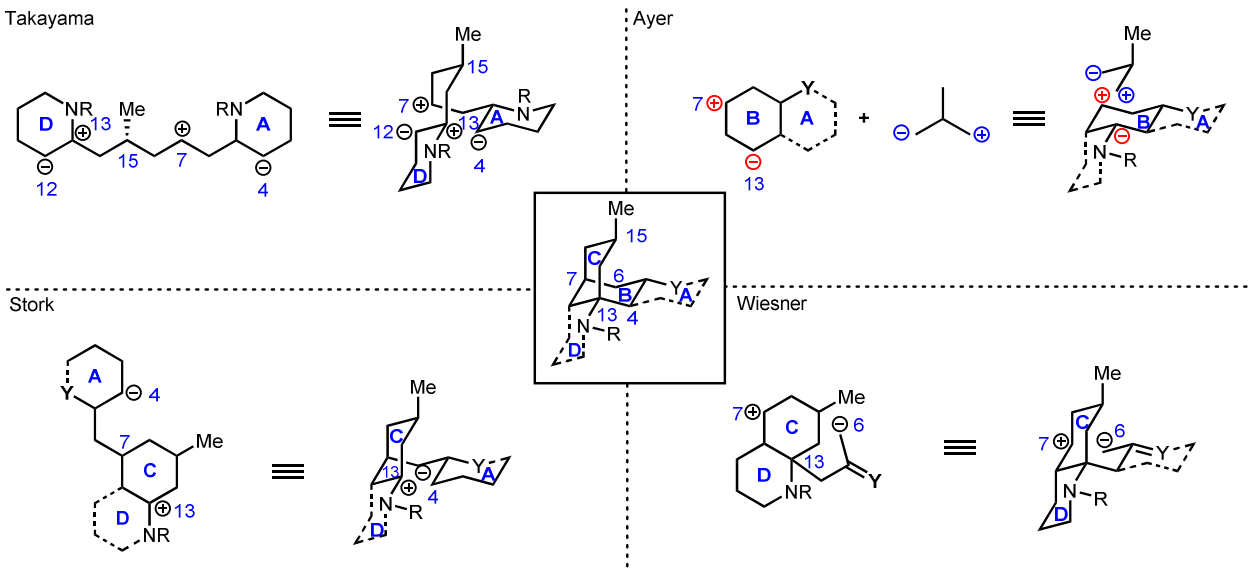

The elucidation of the biosynthetic pathway of these alkaloids has been hampered by the challenges associated with the cultivation of *Lycopodium* species.[1] In fact, cultivation only recently became possible.[20] What is known about the biosynthesis of these molecules has been determined through a series of studies carried out by Spenser and coworkers where radiolabeled precursors were fed to *Lycopodium* species in their natural habit.[21] Through these studies, it was determined that the carbon atoms

of *Lycopodium* alkaloids ultimately arise from two equivalents of lysine (**1.12**) and an equivalent of acetone dicarboxylic acid (**1.16**). Lysine first undergoes decarboxylation to afford cadaverine (**1.13**), which in turn is converted into $\Delta^1$-piperideine (**1.15**). Addition of **1.16** followed by decarboxylation results in piperidine **1.17**. A subsequent decarboxylation affords pelletierine (**1.18**). The phlegmarine skeleton (**1.19**) arises from the cyclization of partially dehydrogenated derivatives of **1.17** and **1.18** (**1.17a** and **1.18a**, respectively). Bond formation between C-4 and C-13 in turn forges **1.20**.

### 1.3 Strategies for the Synthesis of Lycodine-type Lycopodium Alkaloids

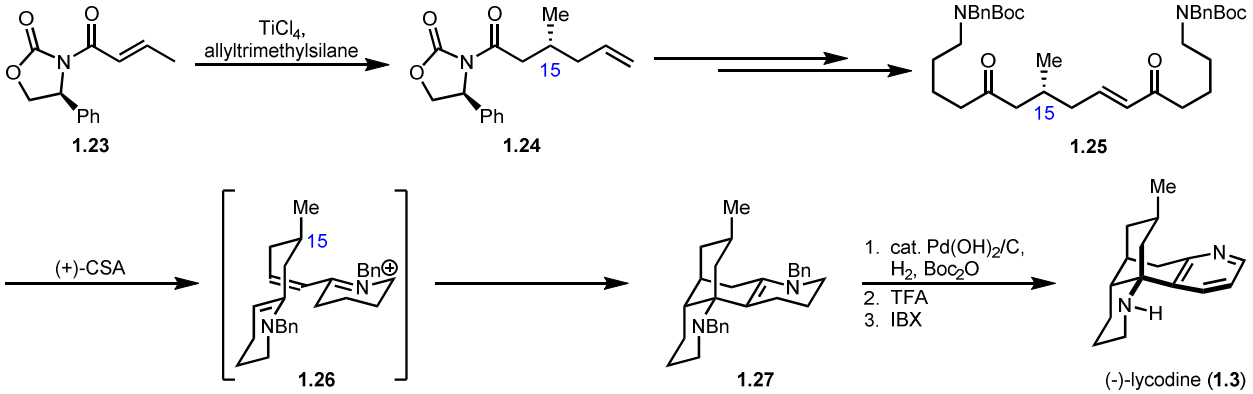
There are two central challenges associated with the synthesis of *Lycopodium* alkaloids. The first is the construction of the *cis*-decahydroquinoline system (comprising the B and D rings). The other is controlling the stereochemistry of the methyl group attached to C-15. Surprisingly, only three distinct strategies have been employed to accomplish these goals in the context of lycodine-type *Lycopodium* alkaloid synthesis. Takayama recently reported a biogenetically inspired synthesis of (-)-**1.3** that features a cascade cyclization reaction similar to the proposed biosynthetic pathway of the lycodane skeleton (Figure 1.4).[22] The two other strategies originate from the seminal syntheses of **1.2** by Ayer and Stork. The Ayer-type strategy employs a four carbon fragment to complete the construction of the C ring. Stork-type strategies utilize partially saturated quinoline derivatives, which become the C and D rings, with latent nucleophiles affixed to C-7. Intramolecular addition of the nucleophile to C-13 forges the B ring and completes the lycodane skeleton. The Ayer and Stork strategies are still the predominant method for the preparation of *Lycopodium* alkaloids of all classes over 40 years after their initial publication, which is a testament to these original synthetic designs. Wiesner reported a strategy similar to Stork's for the synthesis of 12-*epi*-**1.2** a year before Stork's report. By preparing a quinoline derivative with a latent nucleophile affixed to C-13, the B ring was closed by addition of the nucleophile to C-7. Therefore, Wiesner and Stork both closed the B ring by the addition of a 3 carbon fragment to the C-7 and C-13 positions of the quionline derivative, but in reverse order. To our knowledge, no other total syntheses employ a Wiesner-type strategy have been reported. It is instructive to examine the Takayama, Ayer, and Stork syntheses to gain an appreciation for the advantages and challenges presented by each strategy.

**Figure 1.4** Strategies for the Synthesis of Lycodine-Type *Lycopodium* Alkaloids.




Takayama employed a diastereoselective Sakurai allylation of crotonamide **1.23** to set the stereochemistry of C-15 and to provide alkene **1.24** (Scheme 1.2). The early establishment of the stereochemistry at this position is essential to their strategy as it dictates the diastereoselectivity of their critical cyclization cascade sequence later in the synthesis. Several steps were required to prepare diamine **1.25** from **1.24**. Treatment of **1.25** with (+)-CSA resulted in the cleavage of the Boc groups, imine formation, and concomitant cyclization to form tetracycle **1.27**. This type of cyclization reaction closely mimics the proposed biosynthetic pathway for the *Lycopodium* alkaloids, except the bond between C-8 and C-15 was formed before the cyclization reaction in Takayama's example. Cleavage of the benzyl protecting groups and oxidation of the A ring with IBX completes the synthesis of (-)-**1.3**.

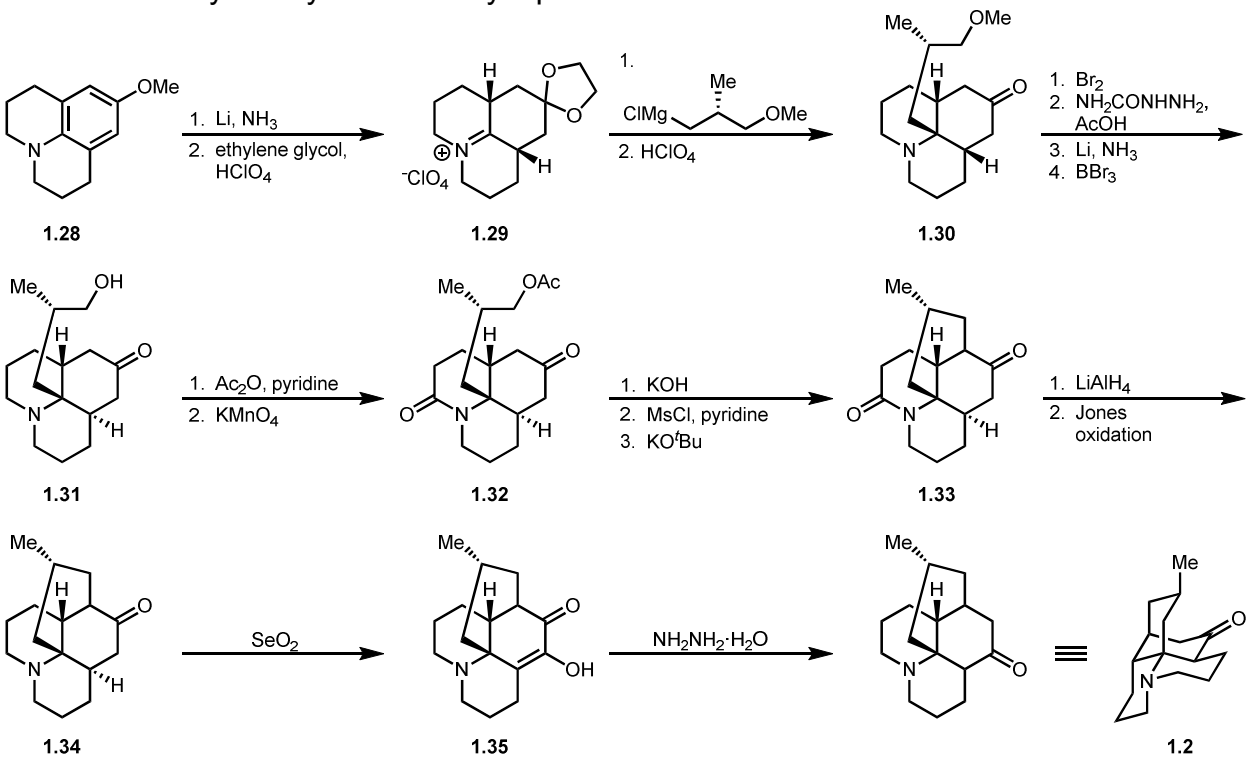
**Scheme 1.2** Takayama's Biomimetic Approach to (-)-Lycodine.




Ayer's strategy for the synthesis of **1.2** focused on the preparation of the *cis*,*trans*-hexahydrojulolidine core, which would become the A,B, and D rings of the final molecule (Scheme 1.3).[7] The C ring was constructed by appending a four carbon fragment to this core. Several syntheses of **1.1** have adopted this strategy for the construction of the C ring. Ayer's synthesis commenced with a Birch reduction of 9-methoxyjulolidine (**1.28**). The crude reaction mixture was treated with perchloric acid in ethylene glycol to provide immonium salt **1.29**. The four carbon fragment that would comprise the majority of the C ring was added in the form of a Grignard reagent

prepared from 1-chloro-2-methyl-3-methoxypropane. Hydrolysis of the ketal afforded *cis*,*cis*-hexahydrojulolidine **1.30**. Several steps were required to epimerize **1.30** to prepare the *cis*,*trans*-hexahydrojulolidine core. α-Bromination of the ketone, elimination of HBr, Birch reduction of the resulting enone, and cleavage of the methyl ether provided *cis*,*trans*-hexahydrojulolidine **1.31**. In an effort to close the C ring, **1.31** was tosylated, which resulted in a spontaneous, undesired alkylation of the tertiary amine. Subsequent Ayer-type syntheses have installed the amino group at a late stage to avoid these types of deleterious side reactions. To circumvent this undesired reactivity, the amino group was oxidized to the amide to reduce the nucleophilicity of the nitrogen atom. Protection of **1.31** as the acetate and oxidation with $KMnO_4$ provided lactam **1.32**. Cleavage of the acetyl group, mesylation of the resulting alcohol, and treatment with $KO^tBu$, resulted in successful α-alkylation of the keto group to afford tetracycle **1.33**. The reduction of the lactam was accomplished with $LiAlH_4$, and oxidation of the resulting alcohol with Jones' reagent provided access to ketone **1.34**. In order to complete the synthesis, the keto group was transposed to the adjacent carbon atom. This was accomplished by a two-step procedure. Riley oxidation of **1.34** provided diosphenol **1.35**, and Wolff-Kischner reduction of **1.35** afforded **1.2**.

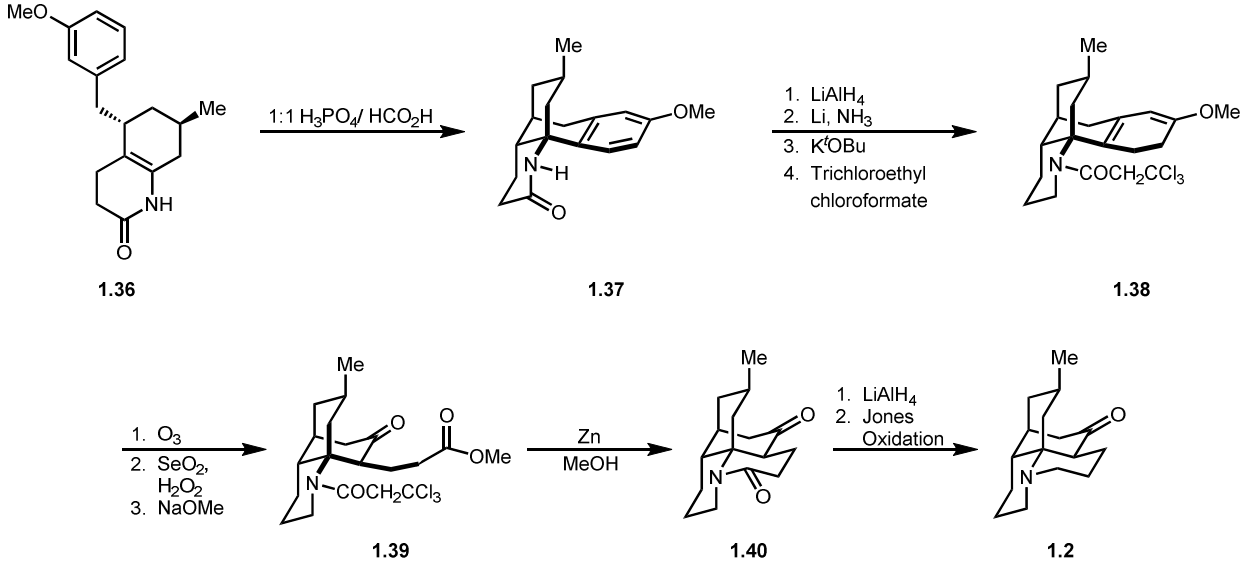
**Scheme 1.3** Ayer's Synthesis of Lycopodine.




Stork and coworkers prepared quinoline derivative **1.36** as their key intermediate for the synthesis of **1.2** (Scheme 1.4).[6] Treatment of **1.36** with acid catalyzed an intramolecular cyclization between an iminium ion and the pendant arene to forge the B ring and provide access to tetracyle **1.37**. The arene also served as a masked A ring, as all of the remaining carbon atoms that would eventually constitute the A ring were contained in the arene. Reduction of the amide, Birch reduction of the anisole ring, double bond isomerization, and protection of the amine provided diene **1.38**. Ozonolysis, Baeyer-Villiger oxidation of the resulting aldehyde, and cleavage of the

resulting formate ester afforded keto ester **1.39**. Cleavage of the trichloroethyl carbamate unveiled the secondary amine which underwent intramolecular condensation with the methyl ester to close the A ring and provide access to lactam **1.40**. Finally, global reduction followed by oxidation of the resulting alcohol completed the synthesis **1.2**.

**Scheme 1.4** Stork's Synthesis of Lycopodine.



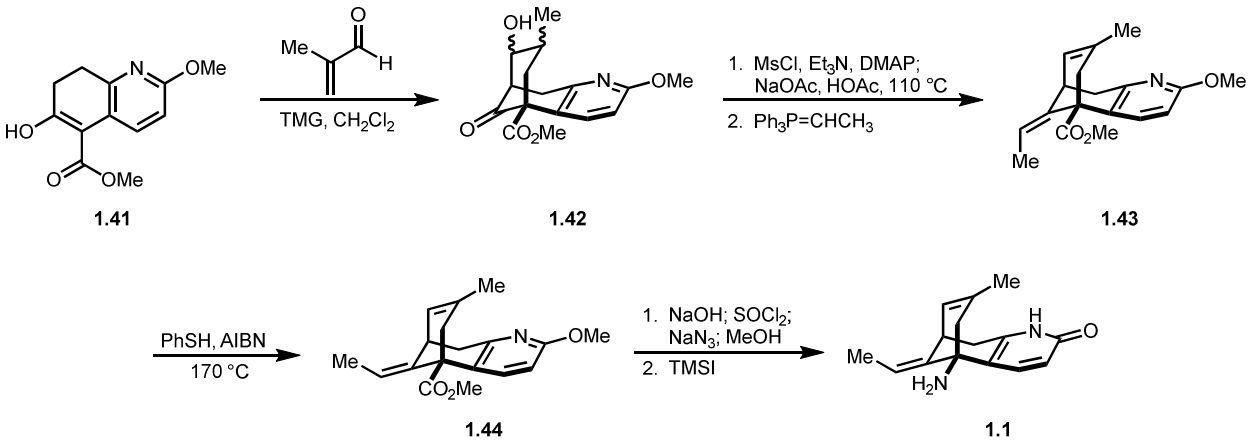

**1.36** **1.37** **1.38** **1.39** **1.40** **1.2**

## 1.4 Synthesis of Huperzine A Utilizing an Ayer-type Strategy

Due to its potent biological activity, myriad approaches to the synthesis of huperzine A (**1.1**) have been reported. Some interesting structural features of **1.1** include the double bond between C-8 and C-15, and the ethylidene group bound to C-12. Due to its lack of a D ring, many investigators have adopted an Ayer-type strategy for the synthesis of the molecule by adding four carbon fragments to quinoline derivatives, which become the A and B rings, to complete the C ring. Kozikowski was the first to complete a synthesis of **1.1** in 1989.[23] Due to its elegance, several groups have pursued syntheses of **1.1** that adopt the Kozikowski strategy.

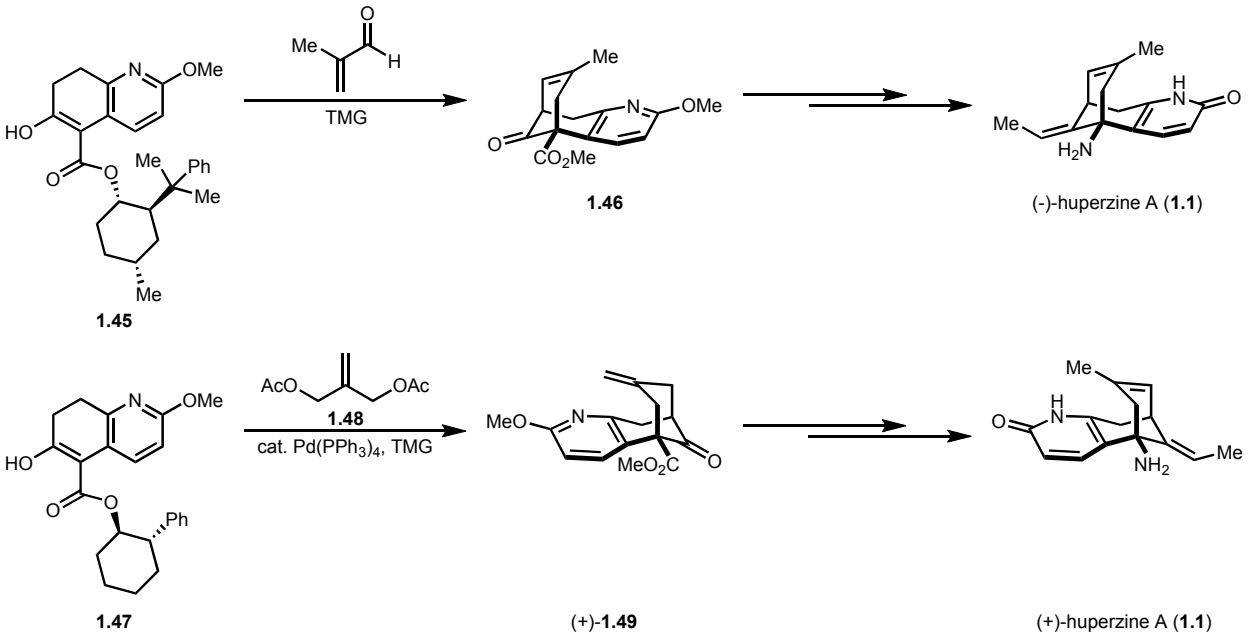
Kozikowski utilized an Ayer-type strategy for the synthesis of (±)-**1.1**. A tandem Micheal addition/aldol reaction between methacrolein and dihydroquinoline derivative **1.41** builds the C ring in a single step to afford alcohol **1.42** as an inconsequential mixture of diastereomers. Mesylation of **1.42** and subsequent elimination furnished the double bond between C-8 and C-15. A Wittig reaction with ethylidenetriphenylphosphorane provided olefin **1.43** as a mixture favoring the undesired *Z* isomer. Double bond isomerization was accomplished by treating **1.43** with thiophenol and AIBN to afford ester **1.45** as a mixture favoring the desired *E* isomer (9:1). Hydrolysis of the ester, Curtius rearrangement, and treatment with TMSI, which effected the demethylation of the methoxypyridine moiety and cleavage of the carbamoyl group provided **1.1**. Ji and coworkers reported an almost identical synthesis less than a month later.[24]

**Scheme 1.5** Kozikowski's Synthesis of Huperzine A.

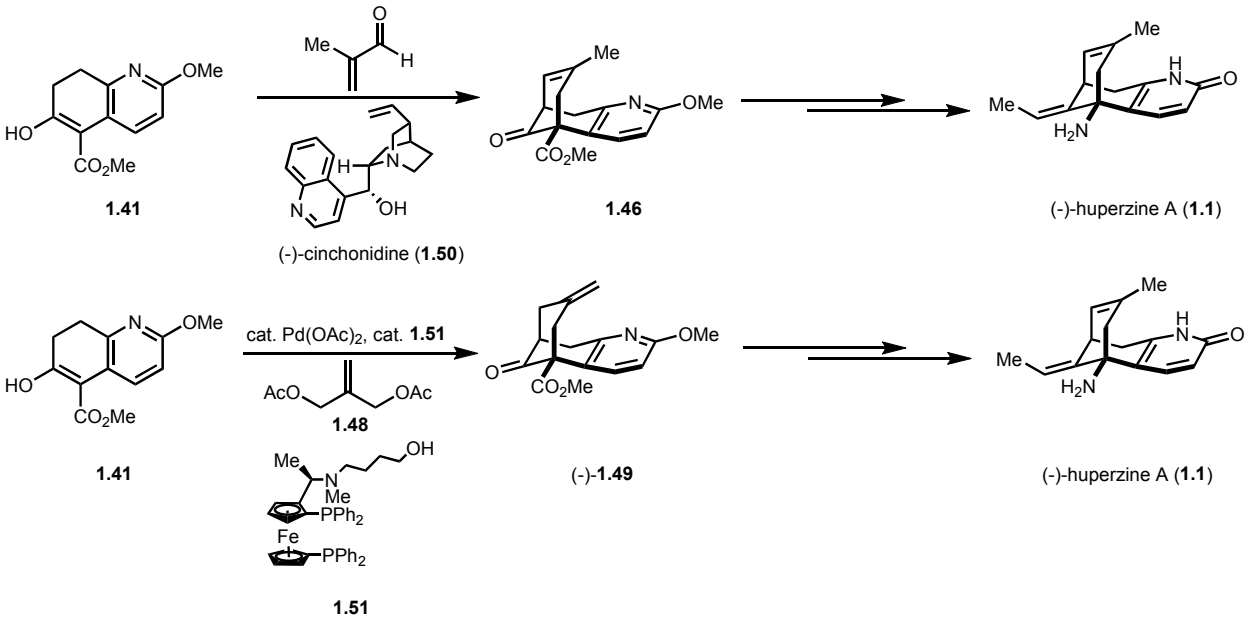



Several investigators have reported asymmetric synthesis of **1.1** based on Kozikowski's original route. Two years after the completion of their racemic synthesis, Kozikowski reported the synthesis of (-)-**1.1**, the biologically active enantiomer.[25] (-)-8-phenylmenthol was employed as a chiral auxiliary to control the diasteroselectivity of the Michael addition/aldol reaction. Ester **1.45** was subjected to the Michael addition/aldol reaction conditions. Mesylation of the resulting alcohol and elimination of MsOH afforded tricycle **1.46**, which was isolated as a mixture of diastereomers (9:1) favoring the desired stereoisomer. Terashima reported that the diasteroselectivity of the Michael addition/aldol reaction could be controlled by the addition of the *Cinchona* alkaloid (-)-cinchonidine (**1.50**).[26] Treatment of dihydroquinoline **1.41** with methacrolein and 1 equivalent of **1.50** at -10 °C, mesylation of the intermediate alcohol, and elimination of MsOH provided olefin (+)-**1.49** in 43% yield and 64% ee. After recrystallization, this intermediate was obtained in a highly enantioenriched form (>99% ee).

**Scheme 1.6** Kozikowski Inspired Asymmetric Syntheses of Huperzine A.





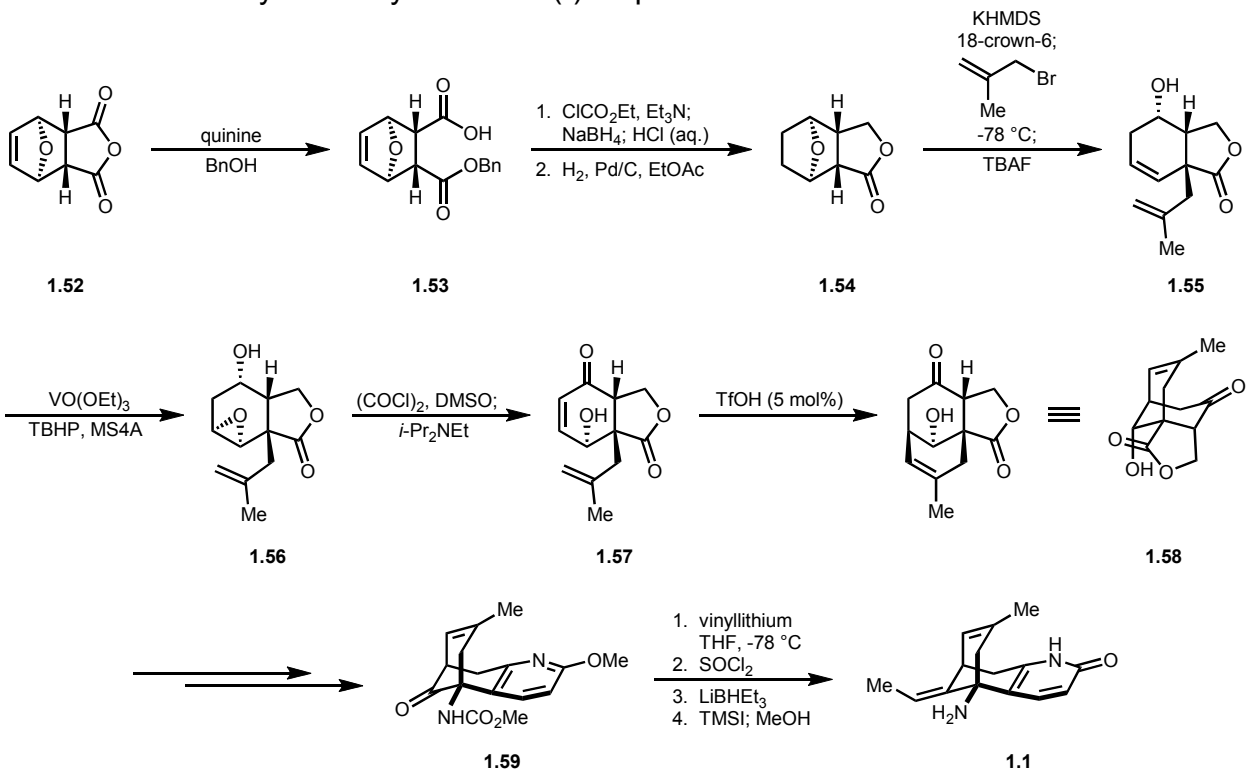




The Terashima group also developed a diastereoselective palladium-cataylzed bicycloannulation to synthesize (-)-**1.1**. Treatment of dihydroquinoline **1.41** with diacetate **1.48**, catalytic $Pd(OAc)_2$, and catalytic chiral ferrocenylphoshine ligand **1.51**, afforded olefin **1.46** in 92% yield and 64% ee.[27] Bai and coworkers also studied the use of other chiral ligands in this palladium-cataylzed bicycloannulation, but were not able to identify conditions that improved upon Terashima's initial report.[28] In a merging of tactics utilized by Kozikowski and Terashima, Langlois reported that a palladium-catalyzed bicycloannulation could be effected in a diastereoselective fashion on dihydroquinoline **1.47**, which contains a (1R,2S)-2-phenylcyclohexanol moiety that

serves as a chiral auxiliary.[29] Treatment of **1.47** with **1.48**, $Pd(PPh_3)_4$ (5 mol%), and TMG affords olefin (-)-**1.49** in 75% yield in 92% de. Langlois was able to use this route to complete a formal synthesis of (+)-**1.1**.[30] Other investigators have developed unique Ayer-type strategies for the synthesis of (-)-**1.1**.

Fukuyama prepared (-)-**1.1** by the desymmetrization of meso anhydride **1.52**.[31] Using a procedure developed by Bolm,[32] **1.52** was desymmetrized in the presence of quinine and BnOH. Selective reduction of the resulting carboxylic acid was accomplished via mixed anhydride **1.53**. Finally, hydrogenation resulted in lactone **1.54**. Alkylation with methallyl bromide, the four carbon building block that would eventually constitute the C ring, afforded olefin **1.55**. A directed, stereoselective epoxidation of **1.56** was effected with catalytic $VO(OEt)_3$. Swern oxidation cleaved the resulting epoxide to provide enone **1.57**. The C ring was closed via a cation-olefin cyclization to furnish ketone **1.58**. Several steps were then required to elaborate **1.58** to methoxypyridine **1.59**. Olefination of the keto group was accomplished using a unique procedure. Addition of vinyllithium to **1.59** afforded the allyl alcohol as an inconsequential mixture of diastereomers. Deoxygenation was accomplished using a two-step procedure. Treatment of the alcohol intermediates with thionyl chloride furnished an allyl chloride, which was subsequently reduced with $LiBHEt_3$ to provide the *E* isomer of the olefin as the sole product. Subjecting this olefin to TMSI afforded (-)-**1.1**.

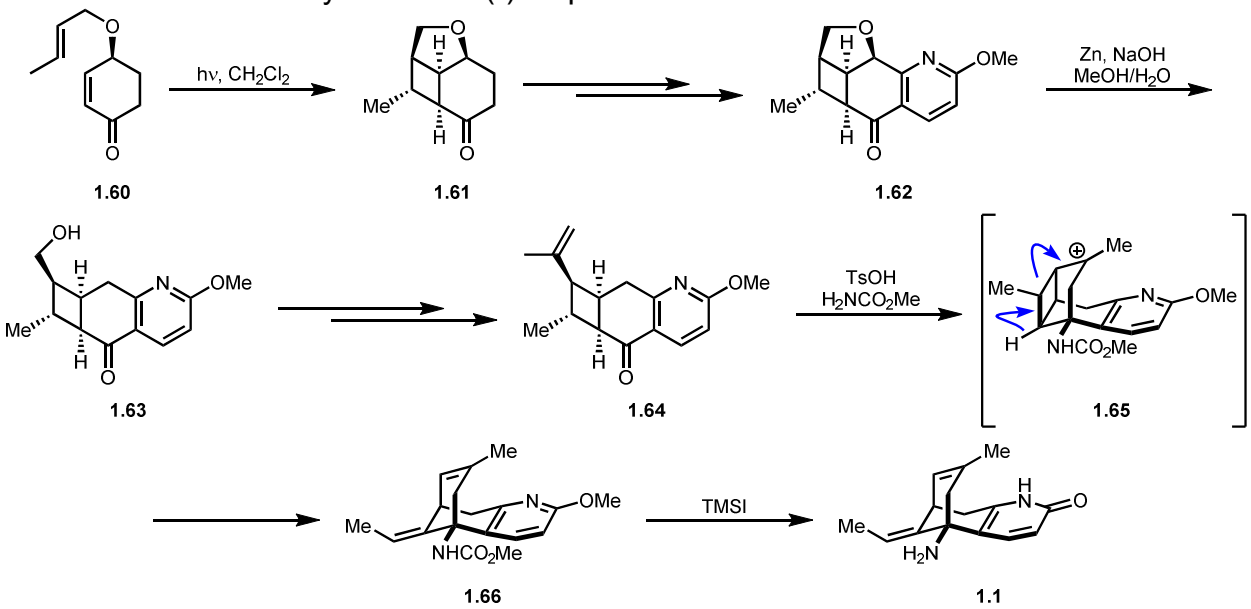
**Scheme 1.7** Fukuyama's Synthesis of (-)-Huperzine A.




Finally, White and coworkers were able to complete a formal synthesis of (-)-**1.1** by employing a tandem intramolecular aza-Prins cyclization/cyclobutane fragmentation.[33] Readily accessible diene **1.60** was irradiated with UV light to effect a [2+2] photocycloaddition. Several steps were then required to elaborate photoadduct **1.61** to methoxypyridine **1.62**. A Zn-mediated reductive cleavage of the pseudobenzylic

ether afforded alcohol **1.63**. Several more steps were then required to access alkene **1.64**, the key substrate for the tandem aza-Prins cyclization/cyclobutane fragmentation. White was able to intercept an intermediate in Kozikowski's synthesis of **1.1** by treating **1.64** with anhydrous TsOH and methyl carbamate to provide carbamate **1.66**, which presumably arises from cyclobutane intermediate **1.65**.

**Scheme 1.8** White's Synthesis of (-)-Huperzine A.



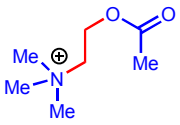

## 1.5 Synthesis Driven Study of the Biological Activity of Huperzine A and its Derivatives

Kozikowski's synthesis of huperzine A was an important contribution that enabled a thorough study of the structural aspects of **1.1** that impart function. Through modification of their synthetic route, Kozikowski and coworkers were able to access several analogues of **1.1** and study their biological activity. Through these studies, several important structural motifs were identified.

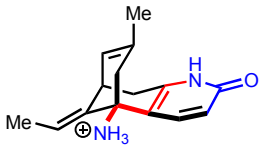
Huperzine A shares several structural features with acetylcholine (**1.4**, Figure 1.5A). For example, **1.1** contains an amino group, which under physiological pH is likely protonated. This ammonium cation serves to mimic the trimethylammonium group in **1.4**. The amide contained in the pyridone moiety is in the same configuration as the ester group in **1.4**. The most notable difference in structure is the length of the carbon chain that links these functional groups together. Acetylcholine (**1.4**) has a two carbon chain while **1.1** has a three carbon chain.

**Figure 1.5** Biological Study Huperzine A and Analogues.

**A.** Structural Similarities between Acetylcholine and Huperzine A

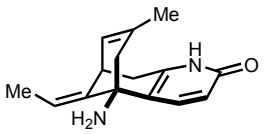


**1.4**

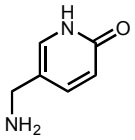


**1.67**

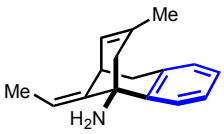
**B.** $IC_{50}$ (M) Values for Inhibition of AChE from Rate Hippocampal Crude Homogenate by Racemic Huperzine A and Analogues



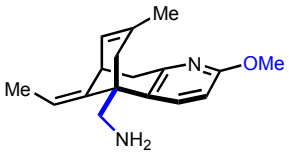
**1.1**
$3 \times 10^{-7}$
$K_I$ (M) = $2.4 \times 10^{-8}$ for FBS AChE



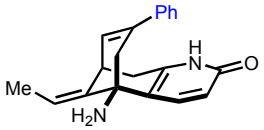
**1.68**
$3 \times 10^{-3}$



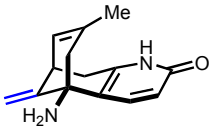
**1.69**
$> 10^{-4}$



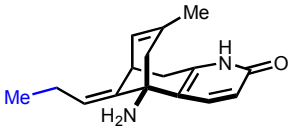
**1.70**
no activity



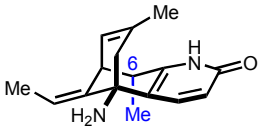
**1.71**
$8 \times 10^{-4}$



**1.72**
$5 \times 10^{-6}$



**1.73**
$2 \times 10^{-5}$



**1.74**
$K_I$ (M) = $3 \times 10^{-9}$ for FBS AChE

These structural similarities led Kozikowski to propose that the active pharmacophore of **1.1** is this amino pyridone motif. [34] Kozikowski tested the biological activity of amino pyridone **1.68** (Figure 1.5B) and found that while it had activity, it was significantly less active than **1.1**, demonstrating that other structural aspects of **1.1** are also important for its activity. Not surprisingly, analogues that lack the pyridone moiety have little to no activity (see **1.69** and **1.70**). Substitution of the methyl group at C-15 with a phenyl group (see **1.71**) is also less active than **1.1**, which suggests that the methyl group might sit in a small pocket in the enzyme. The addition of a methylene group between the amino group and the core of the molecule also results in significant loss of activity. Truncation or homologation of the ethylidene group is also not tolerated (see **1.72** and **1.73**). In fact, the only position that was found to be amenable to modification was C-6. Excitingly, analogue **1.74**, which has an axially disposed methyl group at C-6, was found to be 8-fold more potent than **1.1**.[35]

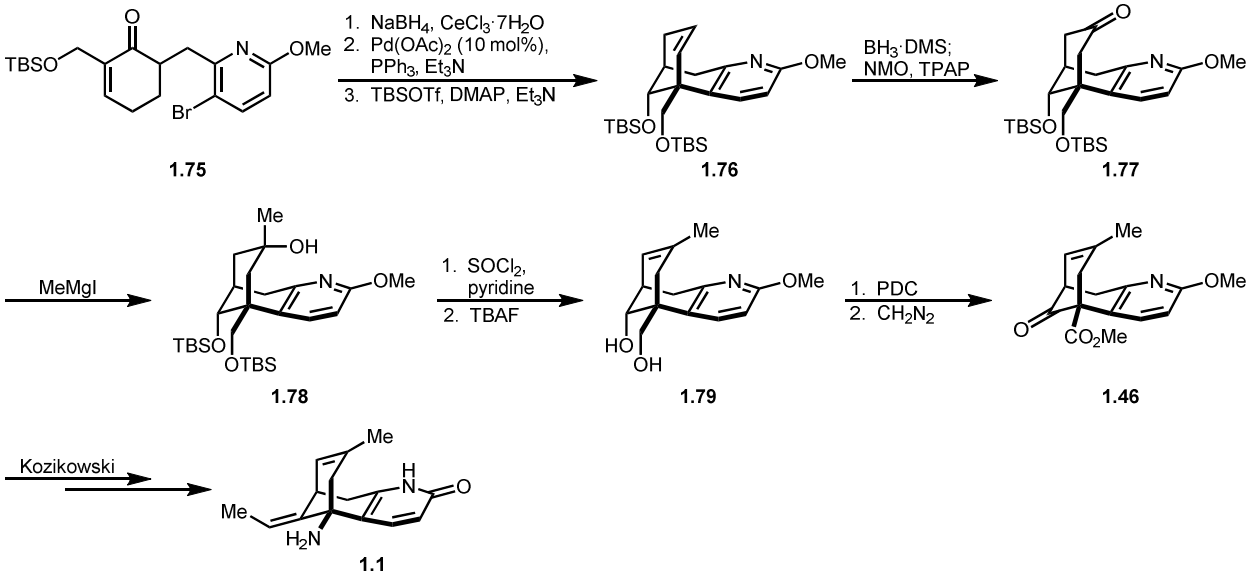
The synthesis of **1.1** also enabled Sussman and coworkers to obtain a crystal structure of a huperzine A–acetylcholinesterase complex.[36] Several interesting insights were gleaned from these studies. Perhaps the most surprising finding is that **1.1** sits in a conformation nearly orthogonal to that of acetylcholine in the active site of acetylcholine esterase, despite their structural similarities. The pyridone oxygen participates in the molecule's only strong hydrogen bond to the protein, which is bound to a tyrosine residue. Cation-π interactions between the ammonium group of **1.1** and aromatic residues (tyrosine and phenylalanine) provide additional stability. Finally, the methyl group on the ethylidene moiety participates in an unusual C-H-O hydrogen bond. This interaction explains the modest drop in activity of analogues where the ethylidene chain has been modified (see **1.72** and **1.73**).

## 1.6 Synthesis of Huperzine A Utilizing a Stork-type Strategy

Several investigators have also utilized a Stork-type strategy for the synthesis of **1.1**. Because **1.1** doesn't contain a piperidine ring (D ring), these syntheses have not utilized quinoline derivatives as their starting materials, as in other Stork-type syntheses of *Lycopodium* alkaloids with intact D rings. However, these approaches still utilize the intramolecular addition of a heteroaryl nucleophile, which becomes the A ring, to an electrophile on the C ring to complete the B ring, the hallmark of a Stork-type strategy. Several of these reports utilize a Heck reaction between a pyridine (pseudo)halide and a cyclohexene ring to complete the tricyclic skeleton of **1.1**.

One such synthesis was reported by Mann and coworkers (Scheme 1.9).[37] Starting from enone **1.75**, Mann was able to effect a Luche reduction. The alcohol product was then subjected to Heck conditions to close the B ring. Protection of the free hydroxyl group with TBSOTf afforded tricycle **1.76**. Several steps were then required to install the methyl group at C-15. First, **1.76** was subjected to a hydroboration/oxidation sequence to provide access to ketone **1.77**. Addition of MeMgI to **1.78**, elimination of the resulting hydroxyl group with $SOCl_2$/pyridine, and cleavage of the TBS groups afforded diol **1.79**. Kozikowski's synthesis was intercepted after oxidation of **1.79** with PDC and methylation of the resulting acid with diazomethane to afford **1.46**.

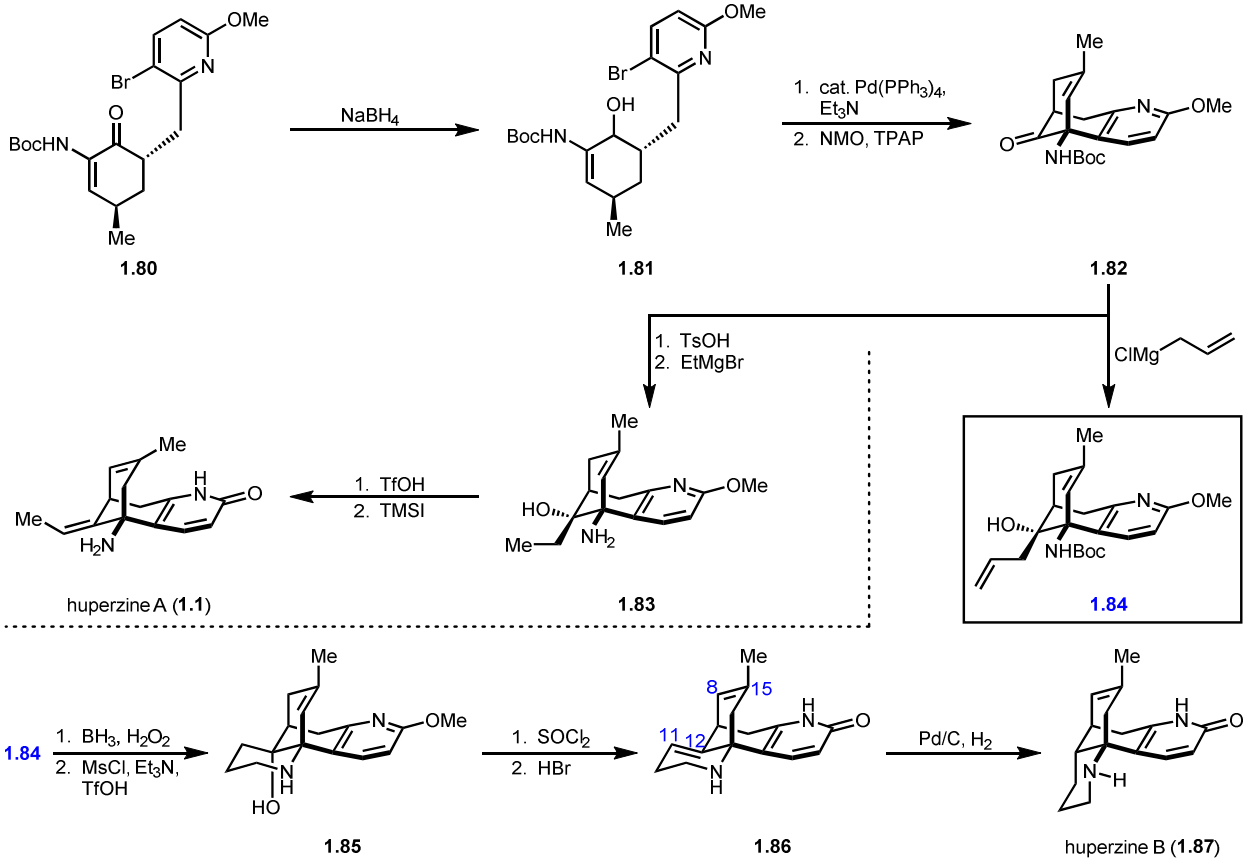
**Scheme 1.9** Mann's Synthesis of Huperzine A.




Lin and coworkers also employed a Heck reaction as a key step in their synthesis of **1.1** (Scheme 1.10).[38] Because the Mann synthesis required several steps to introduce the methyl group at C-15, cyclohexene derivative **1.80**, which has a methyl group at the desired location, was employed to avoid the challenges associated with late-stage incorporation. Reduction of **1.80** with $NaBH_4$ provided alcohol **1.81** as a mixture of diastereomers. Treatment of **1.81** with catalytic $Pd(PPh_3)_4$ effected a Heck reaction. Ley oxidation of the resulting alcohol affords ketone **1.82**. Attempts to install the ethylidene group using a Wittig reaction, Julia olefination, and Takai olefination were met with limited success. Instead, an addition-elimination procedure was employed. Treatment of **1.82** with TsOH cleaved the Boc group. Addition of EtMgBr to the keto group afforded alcohol **1.83**. Dehydration of **1.83** was accomplished by the action of

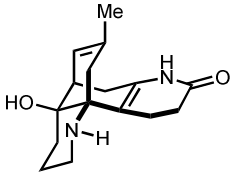
TfOH. Finally, TMSI was used to effect demethylation of the methoxypyridine moiety and isomerization of the exocyclic double bond to provide **1.1**.

**Scheme 1.10** Lin's Synthesis of Huperzine A and B.




Lin and coworkers were also able to prepare huperzine B (**1.87**) from ketone **1.82**. Addition of allylmagnesium chloride to **1.82** afforded alcohol **1.84**. Hydroboration and oxidation furnished the primary alcohol. Mesylation of this alcohol resulted in spontaneous closure of the D ring to provide tetracycle **1.85**. Elimination of the hydroxyl group was achieved by action of $SOCl_2$ and pyridine. Treatment of the resulting olefin with HBr effected demethylation of the hydroxypyridine moiety and migration of the double bond in the C ring to furnish pyridone **1.86**. Finally, treatment with Pd/C effected a chemoselective hydrogenation of $\Delta^{11(12)}$ over $\Delta^{8(15)}$ to afford **1.87**. This strategy of building the D ring from tricyclic intermediate **1.82** to achieve the synthesis of **1.87** is interesting from the perspective that it runs counter to the proposed biosynthesis of these molecules. **1.1** is believed to be prepared from the degradation of the D ring of **1.87**. Lin and coworkers also accomplished the synthesis of huperzine U (**1.88**, Figure 1.6) using a similar route.

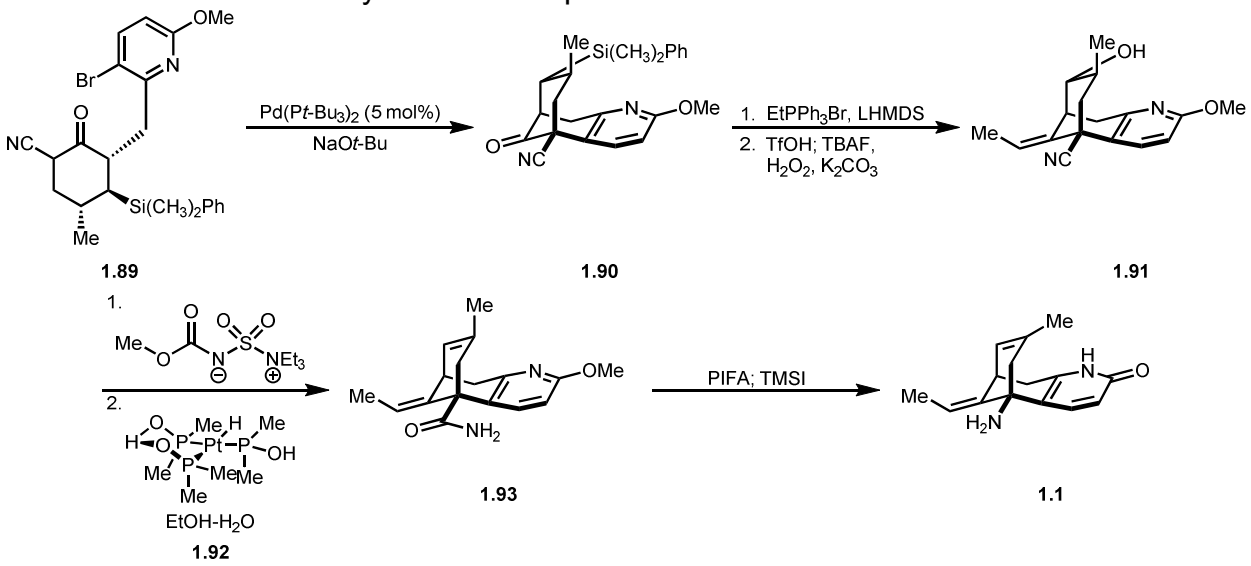
**Figure 1.6** Huperzine U.




**1.88**

Herzon and coworkers have developed a Stork-type approach for the synthesis of **1.1** that employs a heteroarylation methodology developed by Hartwig[39] close the B ring (Scheme 1.11).[40] Cyclohexanone **1.89** was treated with catalytic Pd(P*t*-Bu$_3$)$_2$ and NaO*t*-Bu to effect an intramolecular heteroarylation to provide ketone **1.90**. Olefination of **1.90** with ethyltriphenylphosphonium ylide, protection of the pyridine moiety as the triflate salt, and oxidative desilylation affords alcohol **1.91**. Elimination of the hydroxyl group was accomplished by the action of the Burgess reagent and hydration of the cyano group with the Parkins-Ghaffar catalyst (**1.92**),[41] which provides access to amide **1.93**. Treatment of **1.93** with PIFA effected a Hoffman rearrangement. Global deprotection was accomplished by the action of TMSI to provide **1.1**.

**Scheme 1.11** Herzon's Synthesis of Huperzine A.



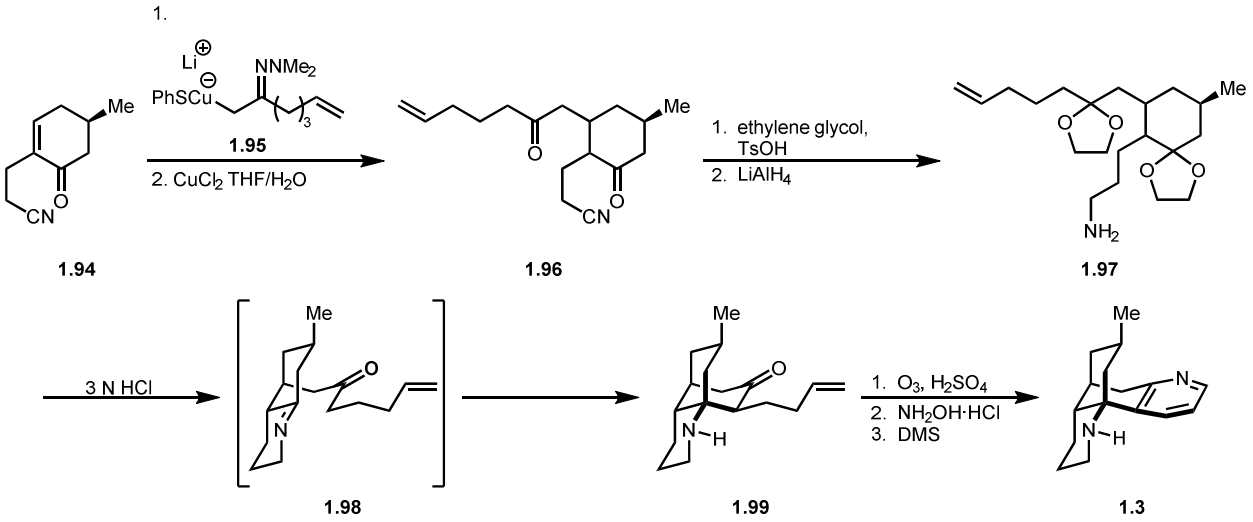

**1.89** **1.90** **1.91** **1.92** **1.93** **1.1**

## 1.7 Synthesis of Lycodine Utilizing a Stork-type Strategy

Several Stork-type strategies have been developed for tetracyclic *Lycopodium* alkaloids such as lycodine (**1.3**). Lycodine is not known to possess any biological activity of consequence. However, the complanadines, which are unsymmetrical dimers of **1.3**, induce the secretion of NGF and consequently may be useful tools for the study and treatment of neurodegenerative diseases. While the syntheses of the complanadines are covered in detail in Section 1.8, many approaches to these molecules are rooted in classical syntheses of **1.3**. Therefore, it is important to highlight some of this work.

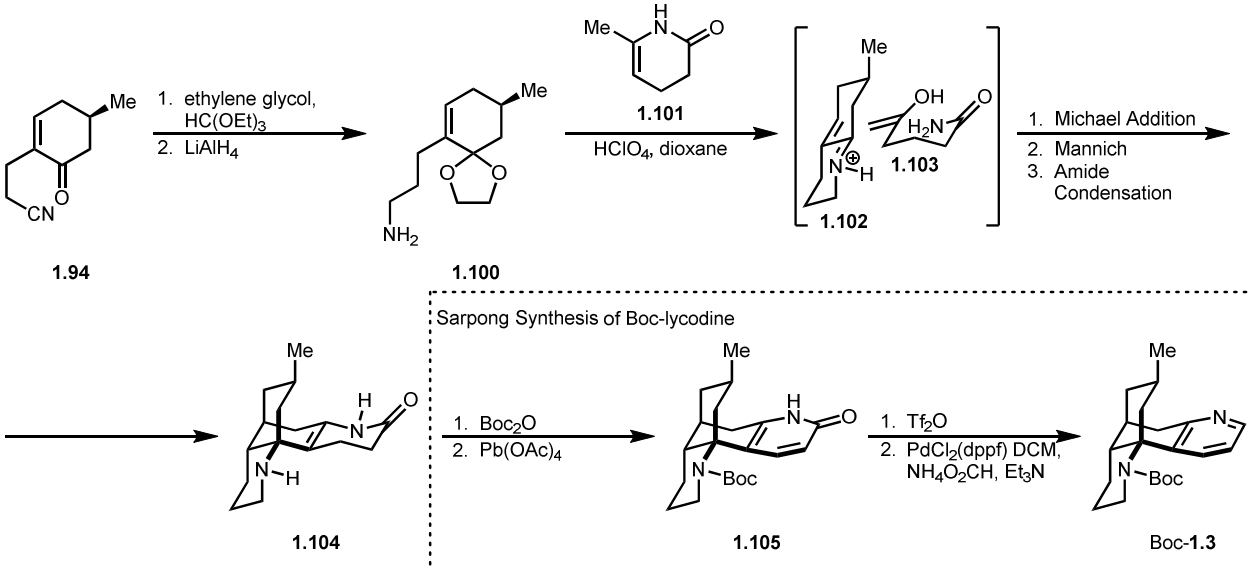
Heathcock and coworkers developed an elegant synthesis of (±)-**1.3** based on their synthesis of (±)-**1.2** published a year earlier (Scheme 1.12).[42,43] Cuprate reagent **1.95** was added to cyanoenone **1.94** to afford ketone **1.96**. Protection of the keto groups and reduction of the cyano group afforded amine **1.97**. Treatment of **1.97** with acid cleaved the ketal groups and effected an intramolecular condensation between the amino group and the keto group to prepare the Stork-type intermediate **1.98**. A Mannich cyclization forged the bond between C-4 and C-13, furnishing tricycle **1.99**. Ozonolysis of the alkene, condensation of hydroxylamine with the resulting ketone, and dehydration of the resulting tetracyclic compound afforded **1.3**.

**Scheme 1.12** Heathcock's Synthesis of Lycodine.




Schumann further streamlined Heathcock's approach by developing an impressive procedure to construct the entire lycodane skeleton from an intermolecular cyclization between amine **1.100** and enamide **1.103**.[44] Heathcock's cyanoenone **1.94** was protected as the ketal and reduced with $LiAlH_4$ to afford amine **1.100**. Treatment of **1.100** with enamide **1.101** under acidic conditions provides desmethyl-α-obscurine (**1.104**). This reaction presumably proceeds through a Micheal addition/Mannich cyclization/amide condensation sequence between 2,3,4,6,7,8-hexahydroquinoline **1.102** and enol **1.103**, the hydrolysis product of enamide **1.102**. Protonation of the enamine and intramolecular Mannich cyclization forges the B ring of the lycodane skeleton. By preparing enantiopure cyanoenone **1.94**, Sarpong and coworkers have utilized Schumann's procedure to achieve an enantiospecific synthesis of Boc-**1.3**.

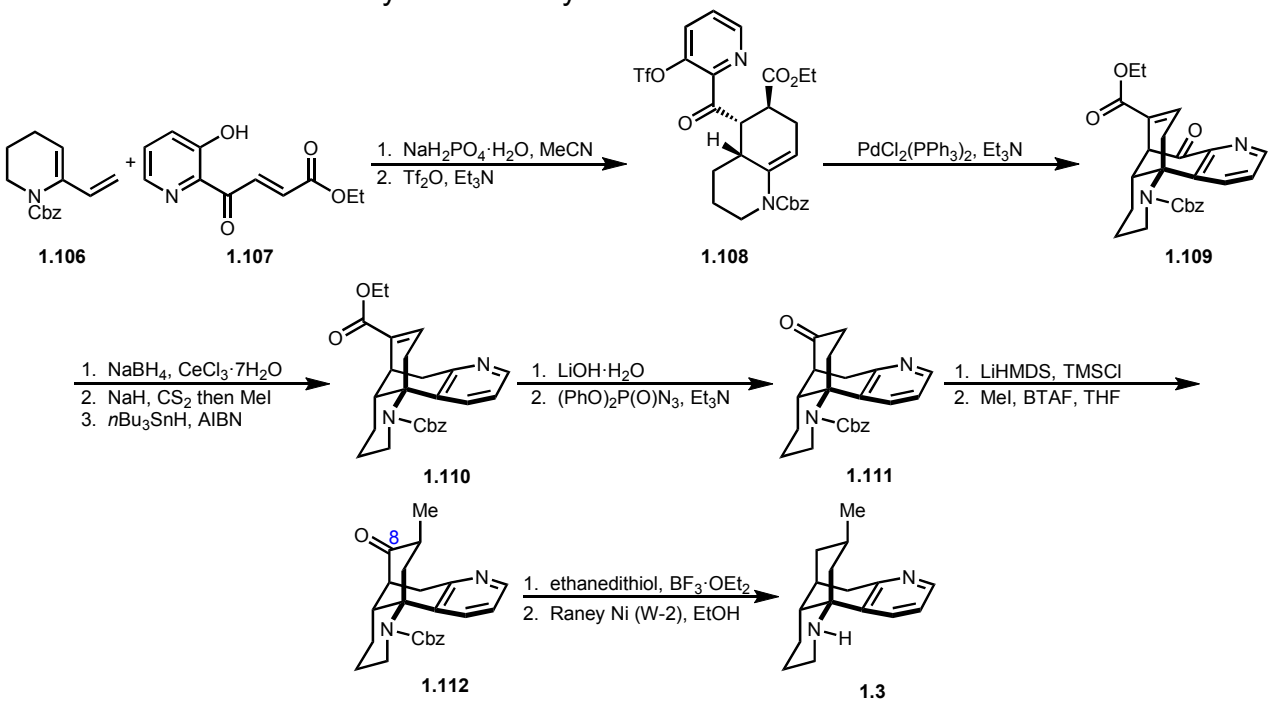
**Scheme 1.13** Schumann's Synthesis of Desmethyl-α-Obscurine.




Tsukano and coworkers also utilized a Stork-type strategy in a recent synthesis of **1.3** (Scheme 1.14).[45] Octahydroquinoline **1.108** was prepared via a Diels-Alder reaction between diene **1.106** and dienophile **1.107**, which bore a pyridine moiety that would become the A ring of the molecule. A Heck reaction closed the B ring and concomitant migration of the resulting double bond furnished enone **1.109**.

Chemoselective reduction of the keto group at C-6 and Barton-McCombie deoxygenation of the resulting alcohol provided access to ester **1.110**. Hydrolysis of the ester of **1.110**, Curtius rearrangement, and hydrolysis of the resulting isocyanate afforded ketone **1.111**. Preparation of the trimethylsilyl enol ether and alkylation with iodomethane provided Cbz-8-ketolycodine. Dithiane formation and Raney Ni reduction afforded **1.3**.

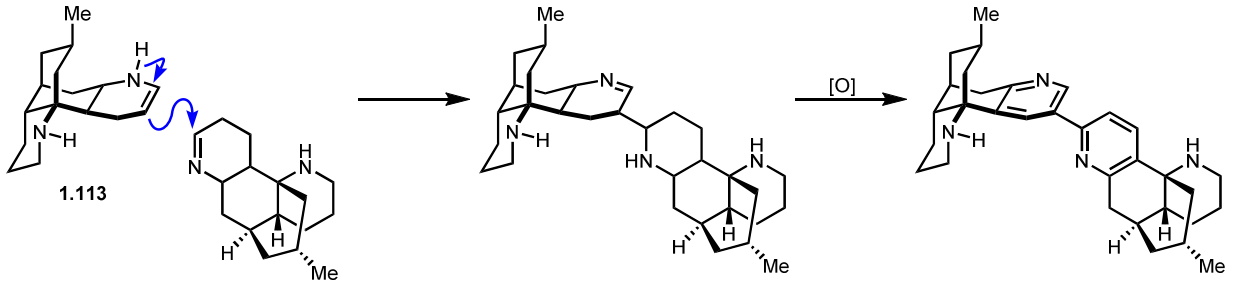
**Scheme 1.14** Tsukano's Synthesis of Lycodine.



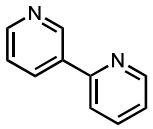

## 1.8 Synthesis of the Complanadine A and B Utilizing a Stork-type Strategy

Several syntheses of **1.3** have been modified to enable the synthesis of members of the complanadine family. These molecules are unsymmetrical dimers of **1.3** where C-1 of a lycodine moiety is joined to C-2 of another lycodine unit. Kobayashi proposed that **1.3** might arise from the self-condensation of two unsaturated lycodane derivatives (see **1.113** and **1.114**)[13] in analogy to the established biosynthesis of α,β-dipyridyl (**1.116**), [46] which shares an unsymmetrical bipyridine core (Scheme 1.15). Building this unsymmetrical bipyridine core is the key synthetic challenge for the preparation of these molecules. To date, three groups have reported syntheses of molecules in the complanadine family. Each of these approaches have utilized Stork-type strategies to construct lycodine derivatives to serve as building blocks for the preparation of these molecules.

**Scheme 1.115** Proposed Biosynthesis of Complanadine A.



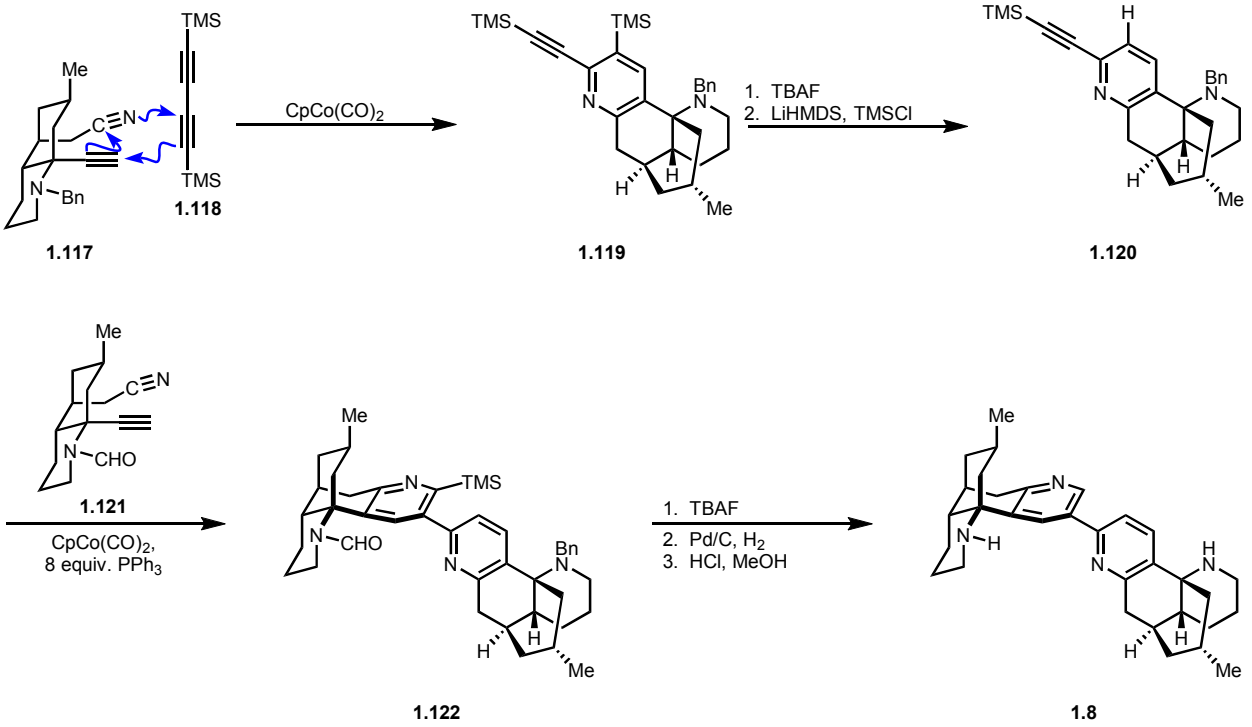

**1.113** **1.114** **1.115** **1.8**




**1.116**

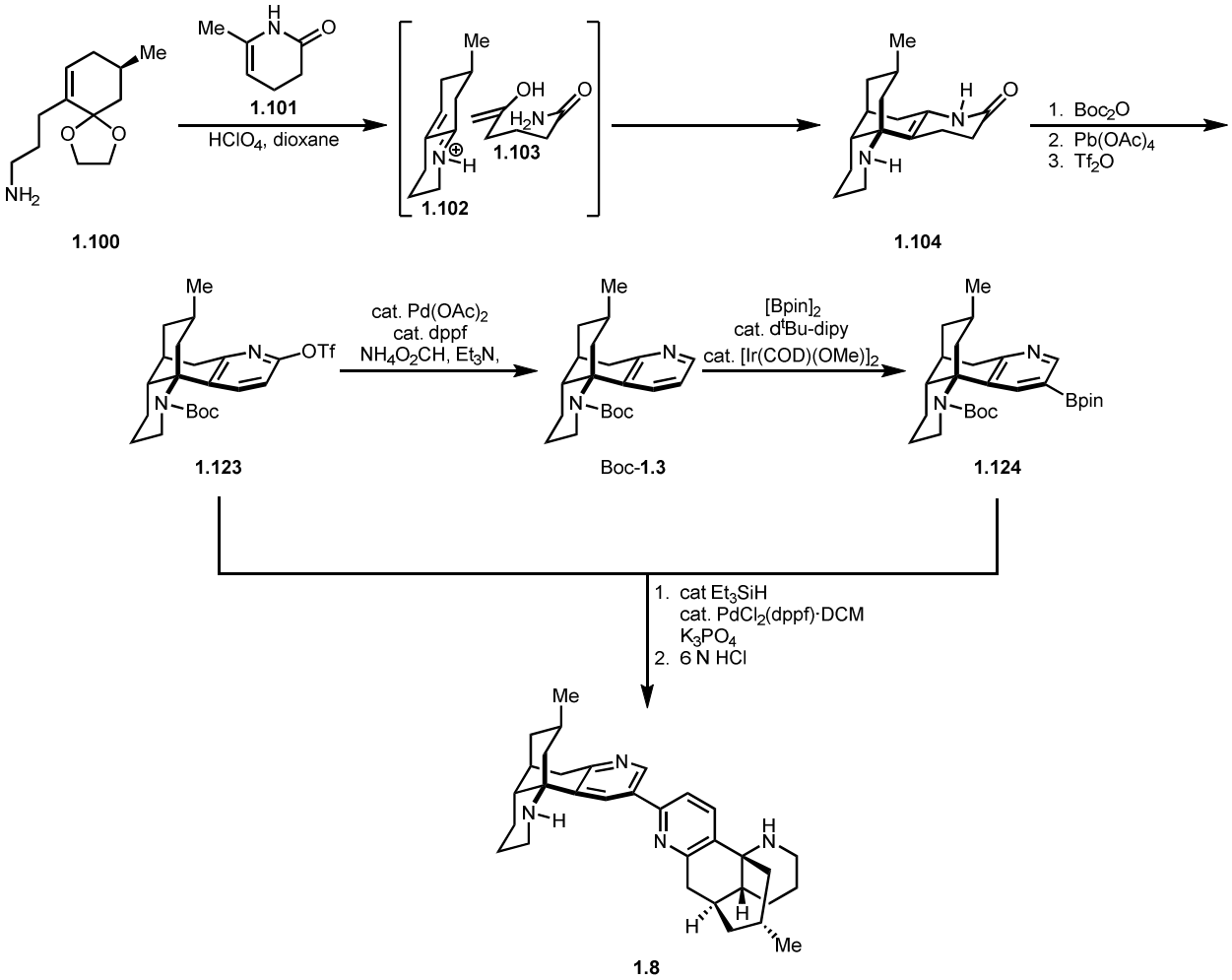
The Siegel group reported the synthesis of complanadine A in 2010 using a heavily modified Stork-type strategy (Scheme 1.16).[47] Decahydroquinoline **1.117** and bis(trimethylsilyl)butadiyne (**1.118**) underwent a [2+2+2] cycloaddition mediated by $CpCo(CO)_2$ to close the A and B rings simultaneously and provide pyridine **1.119** as the major regioisomer (25:1). Global desilylation followed by silylation of the terminal alkyne afforded alkyne **1.120**. A second [2+2+2] Co(I)-mediated cycloaddition between **1.120** and decahydroquinoline **1.121** afforded a mixture of bipyridine compounds favoring the desired regioisomer, **1.122** (3:1). The addition of $PPh_3$ was found to have a profound influence on the regioselectivity of the reaction, as the reaction run in the absence of $PPh_3$ resulted in a mixture of bipyridine compounds favoring the undesired symmetrical dimer (1:3.3). The reaction was also sensitive to the nature of the nitrogen protecting group. Related compound **1.117** did not react with **1.120** under a variety of conditions that were screened. Desilylation, hydrogenolysis of the benzyl group, and cleavage of the formyl group afforded **1.8**.

**Scheme 1.16** Siegel's Synthesis of Complanadine A.



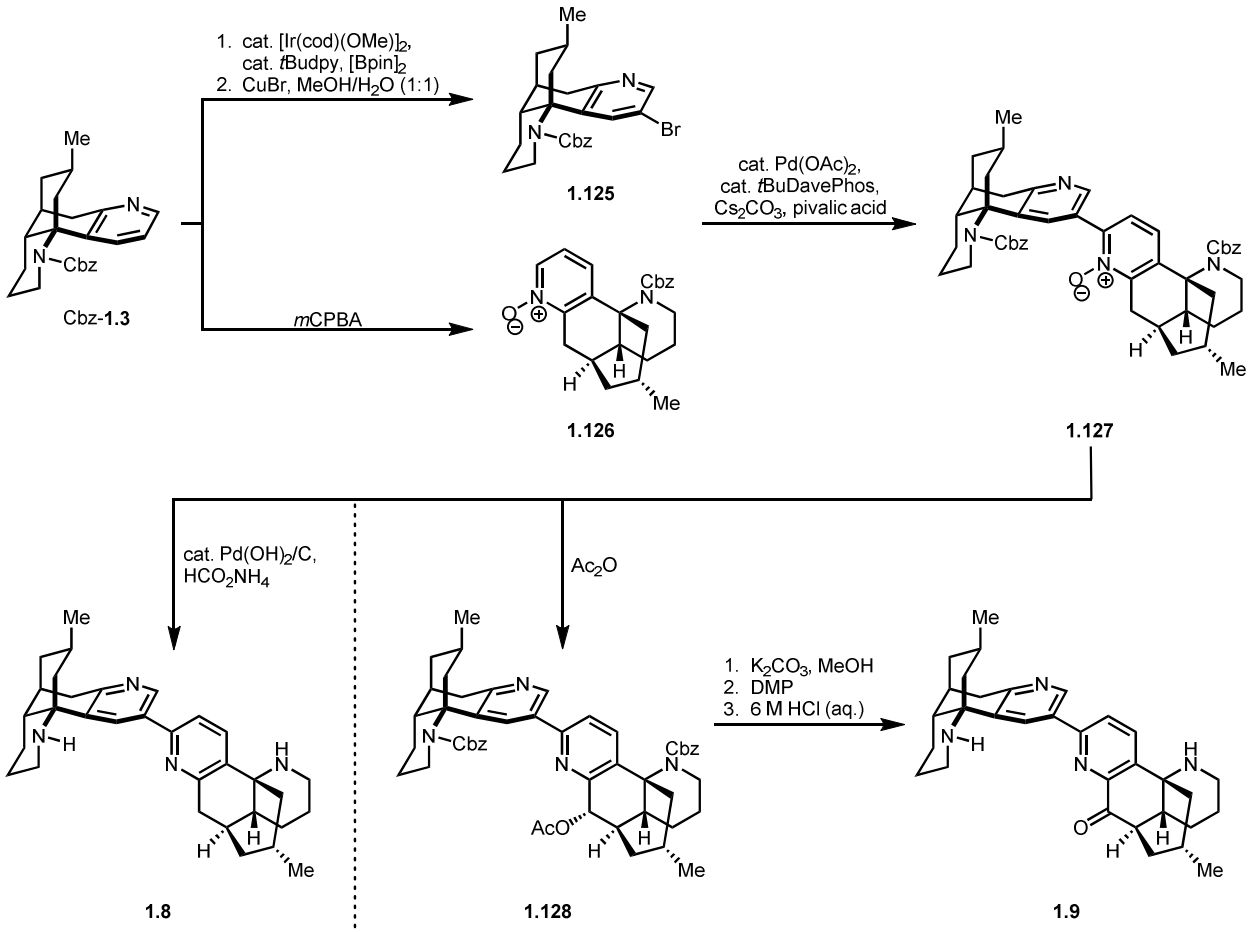

Sarpong and coworkers effected a Suzuki cross-coupling reaction to forge the central C1-C2' bond of **1.8** (Scheme 1.18).[48] Triflate **1.123** was accessed by an enantiospecific version of a route developed by Schumann for the synthesis of α-obscurine discussed in Section 1.7 (see Scheme 1.13). Hydrogenolysis of **1.123** afforded Boc-lycodine (Boc-**1.3**). An Ir-catalyzed C-H borylation method developed by Hartwig[49] was employed to prepare boronic ester **1.124** as the sole regioisomer. Suzuki cross-coupling of **1.123** and **1.124** and cleavage of the Boc group provided access to **1.8**. Using a similar route, complanadine B (**1.9**) was also prepared. This work is discussed in detail in Chapter 2.

**Scheme 1.17** Sarpong Synthesis of Complanadine A.




Finally, the Tsukano group has developed a similar approach for the synthesis of **1.8** and **1.9** where the central C1-C2' bond was forged by a direct-arylation method developed by the Fagnou group (Scheme 1.18).[50] The required substrates were accessed from Cbz-lycodine (Cbz-**1.3**), which they accessed using their reported route to lycodine (see Scheme 1.14). Treatment of Cbz-**1.3** with *m*CPBA afforded *N*-oxide **1.126**. Bromopyridine **1.125** was prepared from Cbz-**1.3** utilizing an Ir-catalyzed borylation/halogenation sequence developed by the Hartwig group.[51] Coupling of **1.125** and **1.126** was accomplished upon treatement with catalytic $Pd(OAc)_2$/*t*-BuDavePhos to afford Cbz-complanadine A *N*-oxide (**1.127**). Subjecting **1.127** to hydrogenolysis conditions cleaved the CBz groups and reduced the *N*-oxide to afford **1.8**. Alternatively, treatment of **1.127** with $Ac_2O$ effected a Boekelheide rearrangement to provide access to acetate **1.128**. After cleavage of the acetyl group, oxidation of the resulting alcohol, and cleavage of the CBz groups, **1.9** was obtained.

**Scheme 1.18** Tsukano's Synthesis of Complanadine A and B.




## 1.9 Biological Activity of the Complanadines

Much of what is known about the biological activity of the complanadines was discovered by Kobayashi and coworkers, who first isolated the molecules. Complanadine A (**1.8**) was found to be cytotoxic to murine leukemia L1210 cells ($IC_{50}$ = 5.6 μg/mL).[12] Later, it was reported that **1.11** was cytotoxic to the same cell line ($IC_{50}$ = 7 μg/mL) and exhibited antimicrobial activity against *Cryptococcus neoformans* and *Aspergillus niger* (MIC = 0.26 and 4.16 μg/mL, respectively). More importantly, **1.8**, **1.9**, **1.10**, and **1.11** have all demonstrated the ability to enhance NGF expression by 3.9-, 2.3-, 2.4-, and 2.8-fold respectively as determined by a quantitative RT-real time PCR method.[18] Complanadine A (**1.8**) was isolated in sufficient quantity to evaluate its ability to induce the secretion of neurotrophic factors in a phenotypic assay. Rat pheochromocytoma (PC-12) cells incubated with the culture medium of human astrocytoma cells, a glial cell line, treated with **1.8** differentiated into neurons, which implies that **1.8** induced the secretion of neurotrophic factors.[13] Due to the low natural abundance of these compounds, further biological studies will need to be supported by synthetic efforts.

The Siegel group has initiated studies **1.8**'s mode of action, using material they prepared with their synthetic route.[52] In a screen of 165 G protein-coupled receptors (GPCRs), it was found that **1.8** was a selective agonist for Mas-related GPCR X2 (MrgprX2) with an $EC_{50}$ = 5.5 μM. Other agonists of MrgprX2 function as inhibitors of persistent pain in animal models, which opens new avenues of investigation for the

therapeutic uses of **1.8**.[53] Siegel and coworkers also investigated the activity of (-)-**1.3**, toward MrgprX2 and found the molecule to be inactive. This finding implies that the dimeric structure of **1.8** is crucial for its activity. The synthetic routes of Siegel, Tsukano, and Sarpong should enable the preparation of analogues of **1.8** to further investigate the structure-activity relationships of the molecule.

## 1.10 Conclusion

Lycodine-type *Lycopodium* alkaloids have very important neurological activities that have drawn interest from the research community as potential lead compounds for the treatment of neurodegenerative disorders such as Alzheimer's and Parkinson's disease. The synthesis of the potent acetylcholine esterase inhibitor **1.1** by Kozikowski and coworkers enabled an extensive investigation into the molecule's structural features that confer activity and identified modifications that improved the potency of the molecule. Although recent studies have demonstrated that the inhibition of ACh is not an effective strategy for the treatment of Alzheimer's disease, the example set by Kozikowski provides a blueprint for how to use synthetic chemistry as a tool to make impactful biological discoveries. With the recent discovery that the complanadines are capable of inducing the secretion of NGF, a new opportunity for chemists to make important contributions toward the treatment of neurodegenerative diseases has presented itself. The recent completion of the first total syntheses of members of the complanadine family should serve as a foundation for future investigation into the activity of these molecules.

## 1.11 References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## Chapter 2

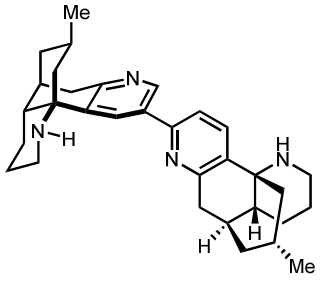
Synthesis of Complanadine B

*A portion of this work has already been published:* Newton, J. N.; Fischer, D. F.; Sarpong, R. *Angew. Chem. Int. Ed.* **2013**, *52*, 1726.

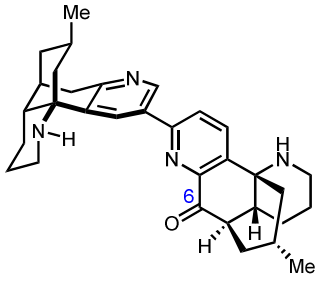
### 2.1 Introduction

As discussed in Chapter 1, the complanadine family of *Lycopodium* alkaloids is composed of several related unsymmetrical lycodine (**1.3**) dimers (Figure 2.1). These molecules have interesting biological activity that could form the basis for new treatments of neurodegenerative disorders such as Alzheimer's disease. With this impetus, our group developed a synthesis of complanadine A (**1.8**, see Section 1.8), the most active of these molecules.[1] Upon the completion of this project, we sought to pursue the synthesis of other members of the complanadine family using our initial work as a foundation. While these congeners exhibit lower biological activity, the synthesis of these molecules and their derivatives could enable us to explore structure-activity relationships, which could drive the design of more active compounds. They also present an interesting synthetic challenge. In each of these molecules, only one of the two lycodine moieties has been functionalized: C-6 has been oxygenated in **1.9** and the A ring has been partially or fully hydrogenated in **1.10** and **1.11**, respectively. Therefore, we envisioned that all of these molecules could be prepared from **1.8** using late-stage, chemoselective functionalizations.

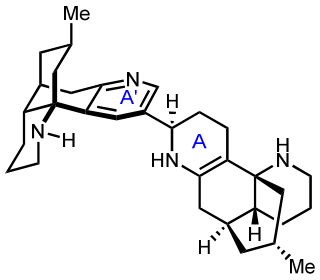
**Figure 2.1** The Complanadine Family.



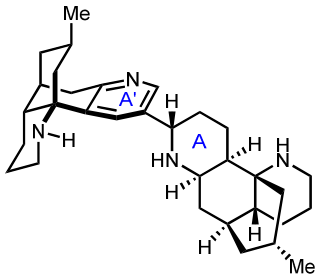

complanadine A (**1.8**)




complanadine B (**1.9**)




complanadine D (**1.10**)

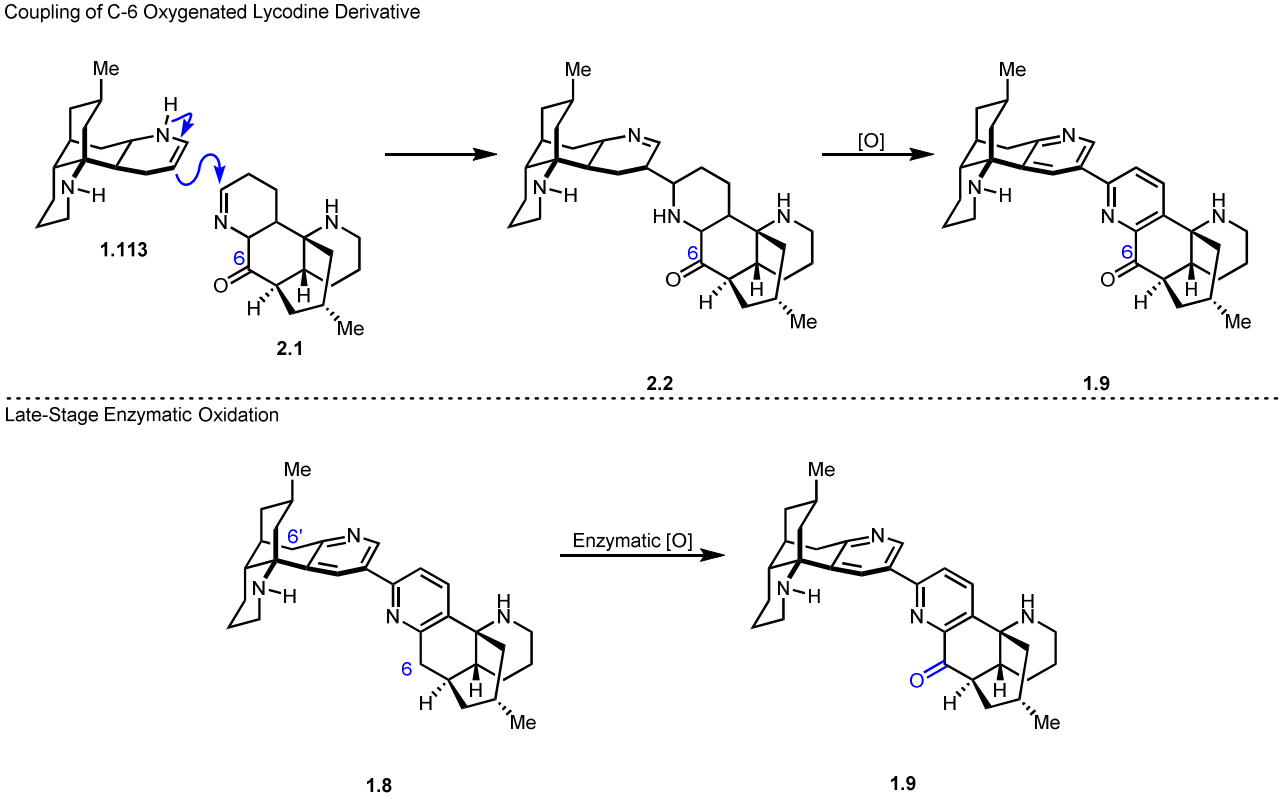



complanadine E (**1.11**)

As discussed in Section 1.8, the complanadine core most likely arises from the coupling of two partially dehydrogenated lycodane derivatives, such as imine **2.1** and enamine **1.113** (Scheme 2.1). This hypothesis was inspired by the established biosynthesis of other alkaloids containing a 2,3'-bipyridine core.[2] Further

dehydrogenation of the A and A' rings would then furnish **1.8**. In contrast to our synthetic plan (vide infra), it is possible that **1.10** and **1.11** are actually the biosynthetic intermediates of **1.8**. At the outset of our studies, the biosynthetic origin of **1.9** was unclear. We envisioned that C-6 oxygenation could arise from two distinct pathways. (1) The coupling of a C-6-oxygenated lycodane derivative with a non-oxygenated derivative could furnish an appropriately functionalized skeleton, or (2) oxygenation could occur at a late-stage (after dimerization), perhaps mediated by a P-450 enzyme.[3]

**Scheme 2.1** Possible Biosyntheses of Complanadine B.



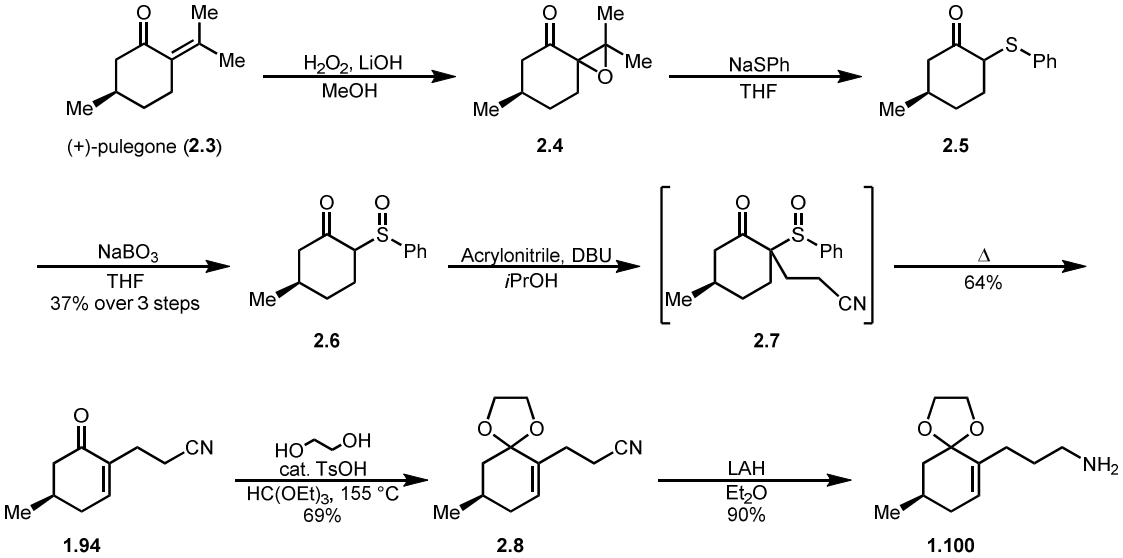

Due to our interest in pursuing the synthesis of complanadine alkaloids through late-stage functionalizations of **1.8**, we were initially more intrigued by the latter hypothesis. While the selectivity of such an oxidation in a biological system would certainly be influenced by the constraints of an enzyme pocket, the innate selectivity of an oxidation of **1.8** was unclear to us upon cursory analysis. We envisioned that the two pseudo-benzylic positions (C6 and C6') would both be susceptible to oxidation. This question would serve as our entry point into our program directed at the synthesis of functionalized complanadine congeners as we sought to effect a selective oxidation of **1.8** in an attempt to access **1.9**.

## 2.2 Attempted Synthesis of Complanadine B via Direct Oxygenation of Complanadine A

To study the selective oxygenation of **1.8**, we prepared the natural product using the route developed previously in our group.[1] Our synthesis of **1.8** from amine **1.100** was described in Section 1.8. The synthesis of **1.100** began from the commercially available chiral molecule (+)-pulegone (**2.3**, Scheme 2.2). Weitz-Scheffer epoxidation of

**2.3** afforded epoxide **2.4**.[4] Addition of NaSPh to **2.4** and concomitant extrusion of acetone provided thioether **2.5**. Oxidation of the resulting thioether with $NaBO_3$ gave access to sulfoxide **2.6**. Alkylation of **2.6** with acrylonitrile under basic conditions and elimination of sulfenic acid from the resulting nitrile provided cyclohexenone **1.94**. To prepare **1.100** from **1.94**, protection of the carbonyl group as the ketal was required. Then, the cyano group was reduced to amine **1.100**. However, ketalization of **1.94** proved to be challenging. We initially employed 1,2-bis(trimethylsiloxy)ethane and catalytic TMSOTf, conditions developed by Noyori and coworkers,[5] in an attempt to prepare ketal **2.8**. Under these conditions, ketalization of **1.94** was sluggish and did not reach completion, necessitating separation of **2.8** from **1.94**. We found that **2.8** hydrolyzed on silica gel, so the recovery of product from this process was low (40%). Subsequently, we have found that treatment of **1.94** with ethylene glycol and catalytic *p*-toluenesulfonic acid in triethyl orthoformate held at reflux resulted in complete consumption of **1.94**, which obviated the need for purification and enabled higher recovery of **2.8** (69%). Reduction of **2.8** with $LiAlH_4$ afforded amine **1.100**.

**Scheme 2.2** Synthesis of Amine **1.100**.

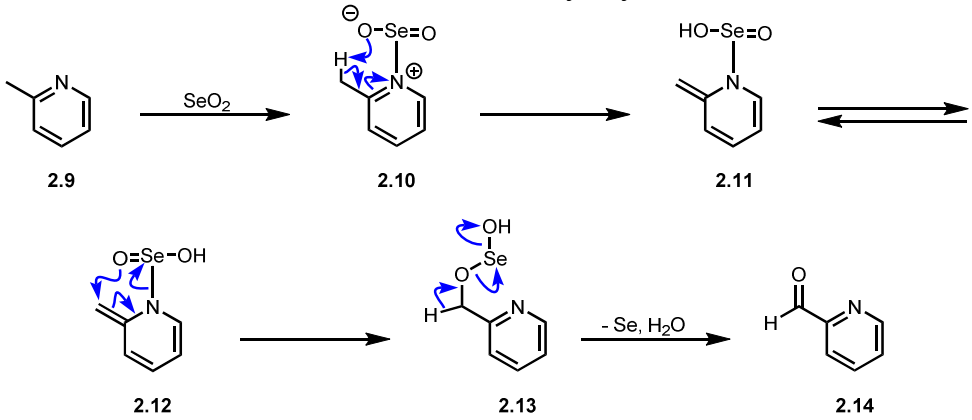



With access to **1.8** from **1.100**, we were able to begin our oxidation studies. We envisioned that **1.9** could be prepared from **1.8** through the oxidation of C-6, a pseudo-benzylic position. The challenge would be achieving selectivity for C-6 over C-6', which is also a pseudo-benzylic position. A survey of the literature reveals a dearth of methods for the oxidation of the pseudo-benzylic positions of alkyl pyridines. $SeO_2$ is the most commonly employed oxidant for this type of transformation.[6] Strong oxidants such as $KMnO_4$[7] and Jones's reagent[8] have also been applied with some success. Recently, catalytic copper and iron salts were reported to oxidize the pseudo-benzylic positions of benzylpyridine derivatives under aerobic conditions.[9] However, this reactivity did not extend to alkyl pyridines.

Due to the mild nature of the $SeO_2$ conditions, we were interested in employing these conditions for the oxidation of Boc-**1.8**. To our knowledge, the mechanism for the oxidation of alkyl-*N*-heterocycles has not been extensively studied, but it is believed to proceed through the coordination of $SeO_2$ to the nitrogen atom in analogy to the mechanism proposed for the oxidation of carbonyl compounds (Scheme 2.3).[10]

Deprotonation of the pseudo-benzylic position would result in enamine **2.11**, which could then undergo a [2,3]-Wittig rearrangement to afford **2.13**. Liberation of Se and $H_2O$ provides oxygenated product **2.14**.

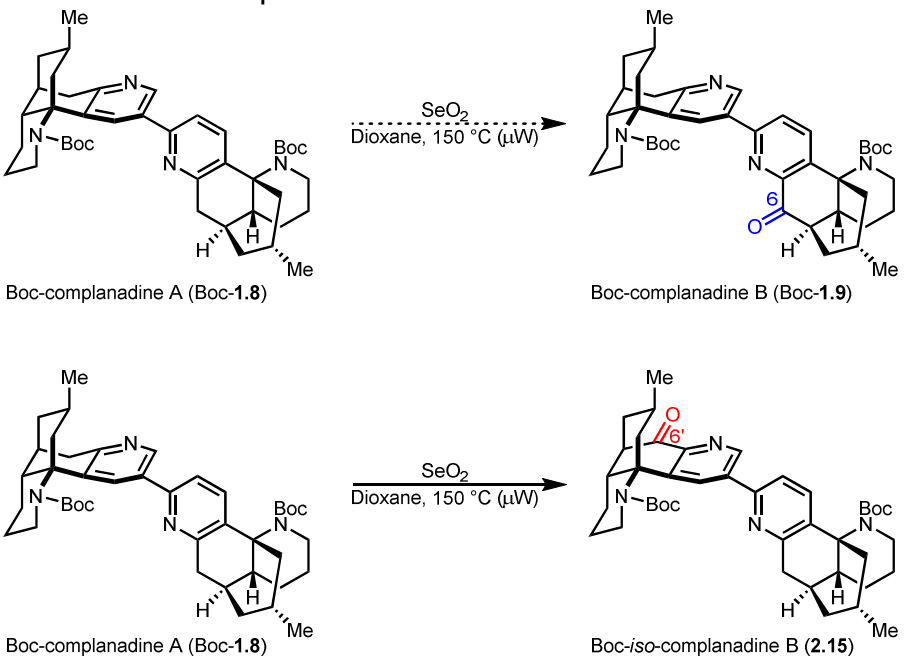
**Scheme 2**.3 Mechanism of $SeO_2$ Oxidation of Alkyl-Pyridines.




**2.9** **2.10** **2.11** **2.12** **2.13** **2.14**

With these considerations in mind, we were cognizant that achieving the desired site-selectivity would be challenging. In order for oxygenation to occur at C-6, $SeO_2$ would have to coordinate to the more sterically hindered pyridine nitrogen. Therefore, it seemed likely that C-6' oxygenation would be favored. However, we were surprised that the treatment of Boc-**1.8** with $SeO_2$ afforded Boc-iso-complanadine B (**2.15**, Scheme 2.4) as the only product. Because Boc-**1.9** was not observed, even in trace amounts, it is apparent that this reaction is highly sensitive to the steric environment around the pyridine nitrogen atom.

**Scheme 2.4** Oxidation of Complanadine A with $SeO_2$.



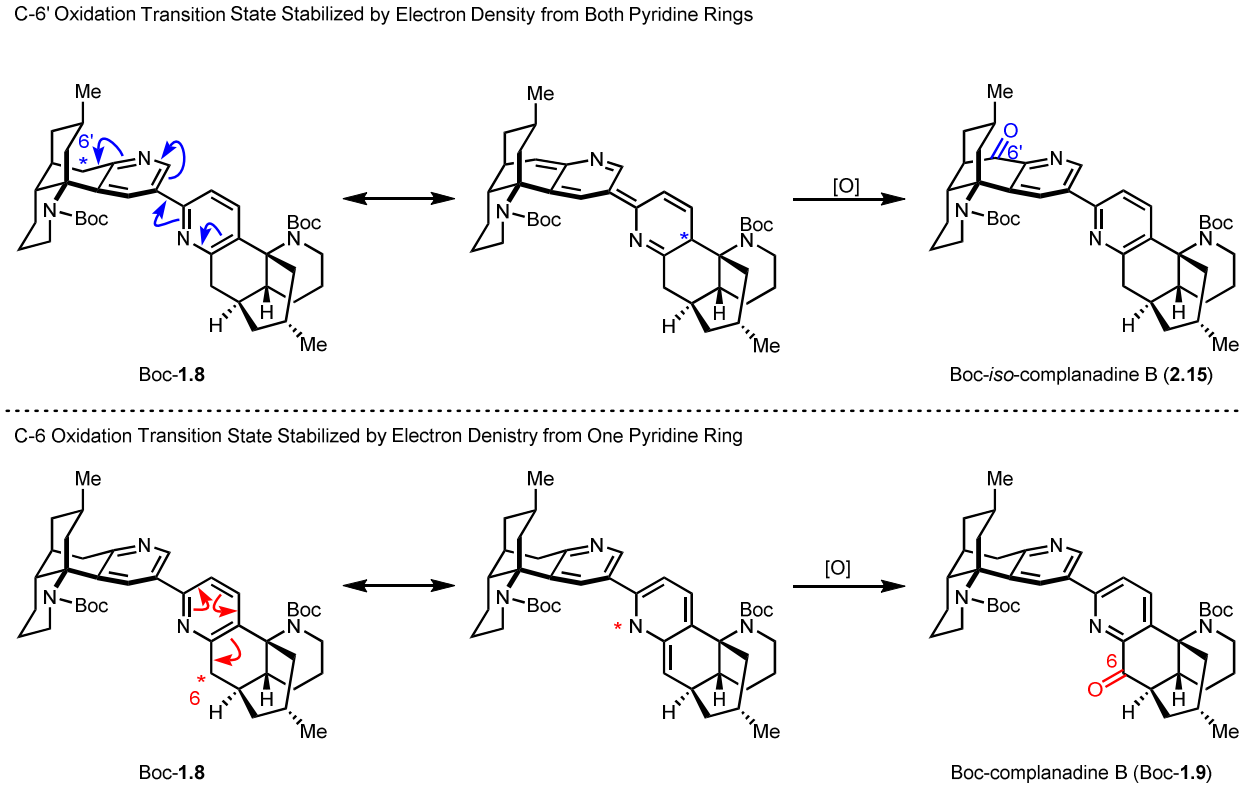

Boc-complanadine A (Boc-**1.8**) Boc-complanadine B (Boc-**1.9**)

Boc-complanadine A (Boc-**1.8**) Boc-*iso*-complanadine B (**2.15**)

There may also be an electronic component to the observed selectivity. Due to the unsymmetrical configuration of the 2,3'-bipyridine core, C-6 and C-6' receive unequal electron density from the heteroaromatic system. This phenomenon can be illustrated through the use of resonance structures (Scheme 2.5). C-6' is positioned

*para* to the second pyridine ring in the bipyridine core. Therefore, electron density from this ring can participate in the stabilization of partial positive or radicaloid character that develops at C-6' during the oxidation. In contrast, the C-6 position is *meta* to the second pyridine ring, so donation of electron density from this ring to this position is expected to be minimal. This electronic stabilization argument assumes that the pyridine rings can adopt a coplanar conformation.

**Scheme 2.5** Electronic Stabilization of Oxidation Transition States.



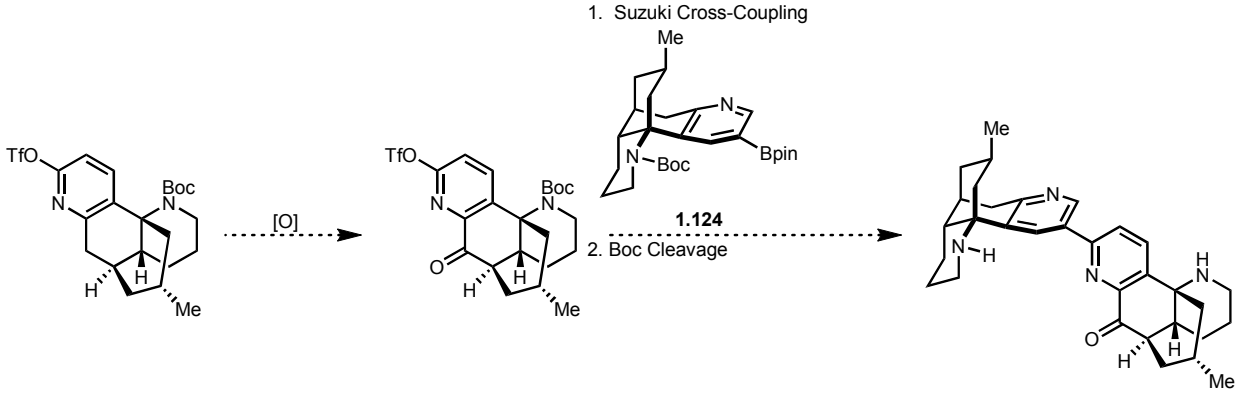

Combined, these factors suggested that our strategy for the synthesis of **1.9** by the direct oxygenation of Boc-**1.8** was not viable due to the unfavorable, inherent reactivity of the substrate. While **1.9** might still be synthesized using a late-stage enzymatic oxidation of **1.8** where the constraints of the enzyme pocket could override the innate reactivity of the substrate, the overwhelming selectivity for C-6' over C-6 may also suggest that the keto group in **1.9** is installed before the dimerization of the lycodine precursors in the biosynthetic process. Taking inspiration from this alternative, we developed a strategy for the synthesis of **1.9** from an oxygenated lycodine derivative.

### 2.3 Synthesis of Complanadine B from an Oxygenated Lycodine Derivative

We envisioned that we could rapidly prepare an oxygenated lycodine derivative that could be applied to the synthesis of **1.9** from lycodine derivatives prepared previously in our synthesis of **1.8**. For example, pseudo-benzylic oxidation of triflate **1.123** would provide ketone **2.16**, which could be directly employed in a Suzuki cross-coupling reaction with boronic ester **1.124** to provide **1.9** after cleavage of the Boc

groups (Scheme 2.6). Due to the appealing nature of this route, we were interested in developing a protocol for the oxidation of **1.123**.

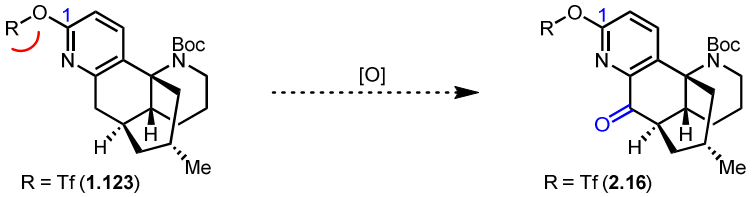
**Scheme 2.6** Proposed Synthesis of Complanadine B from an Oxygenated Lycodine Derivative.




**1.123** **2.16** complanadine B (**1.9**)

The oxidation of **1.123** proved challenging (Scheme 2.7). Treatment of **1.123** with $SeO_2$ returned starting material. As we have already seen, these oxidations are sensitive to the steric environment around the pyridine nitrogen atom, which must coordinate to $SeO_2$ to initiate the reaction. Therefore, it is likely that substitution α to the nitrogen (i.e., at C-1) blocks coordination, which prevents oxygenation. The triflate group is also highly electron withdrawing, so the pyridine nitrogen is expected to be less nucleophilic due to inductive deactivation. Because a limited number of oxidants have been applied to the pseudo-benzylic oxidation of pyridines, we also screened several oxidants including PDC,[11] *o*-iodoxybenzoic acid (IBX),[12] ceric ammonium nitrate (CAN), $Mn(OAc)_3$/*t*-butylhydroperoxide (TBHP), and DDQ in an effort to effect the desired transformation. These reagents led to the non-specific decomposition of the substrate or returned starting material. A similar screen of oxidants on Boc-β-obscurine (**1.105**) also failed to provide C-6-oxygenated products.

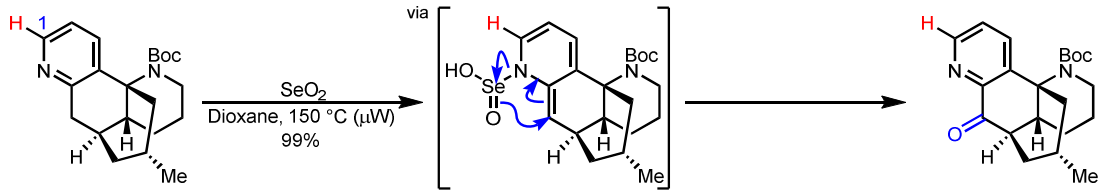
**Scheme 2.7** Attempted Oxidation of C-1 Functionalized Lycodine Derivatives.




Oxidants screened: $SeO_2$, PDC, IBX, CAN, $Mn(OAc)_3$/TBHP, DDQ

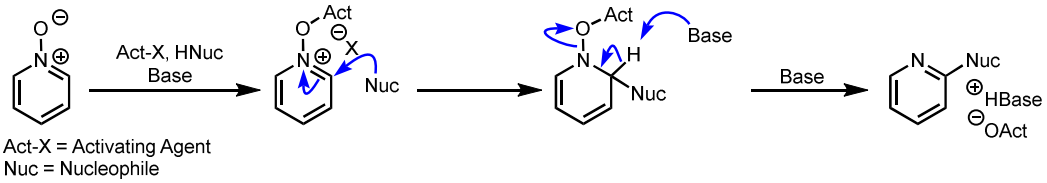
To circumvent this challenge, we studied the oxygenation of Boc-lycodine (Boc-**1.3**), which is unfunctionalized at C-1. We were cognizant that while this substrate might be more susceptible to oxygenation, it lacked a functional handle that could be employed in our key Suzuki reaction. Therefore, the substrate would have to be further functionalized if oxygenation was successful. Treatment of Boc-**1.3** with $SeO_2$ afforded Boc-ketolycodine (**2.19**) in near quantitative yield. This result combined with our inability to oxygenate C-1 substituted lycodine derivatives is another dramatic example of the sensitivity of the $SeO_2$ oxidation reaction to the steric environment of the substrate.

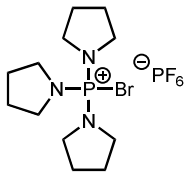
**Scheme 2.8** Oxidation of Boc-Lycodine (Boc-**1.3**).




With oxygenation incorporated at C-6, we were faced with the task of functionalizing C-1 of **2.19**. We envisioned that halogenation of C-1 would afford a C-6 oxygenated substrate that could serve as a Suzuki cross-coupling partner. The most common way to halogenate the position α to the nitrogen in a pyridine ring is through a Reissert-Henze functionalization (Scheme 2.9).[13,14] Using this approach, the pyridine is oxidized to the pyridine *N*-oxide. The *N*-oxide is then treated with an electrophilic activating agent, which functionalizes the oxygen atom of the *N*-oxide and activates the α position toward nucleophilic addition. Addition of a nucleophile to the α position quenches the iminium ion and elimination of the oxygenated activating agent reestablishes aromaticity and affords the functionalized product. Several activating groups have been reported. Classically, $POCl_3$ has been employed to effect the α-chlorination of pyridines.[15] Baran has shown that the treatment of heterocyclic *N*-oxides with $Ts_2O$ and tetrabuytylammonium bromide (TBABr) affords α-brominated products.[16] Londregan extended the scope of this type of functionalization by employing PyBroP (**2.20**) as an activating agent, which enabled the addition of a variety of nucleophiles including amines and phenols.[17]

**Scheme 2.9** Mechanism of the Reissert-Henze Functionalization.

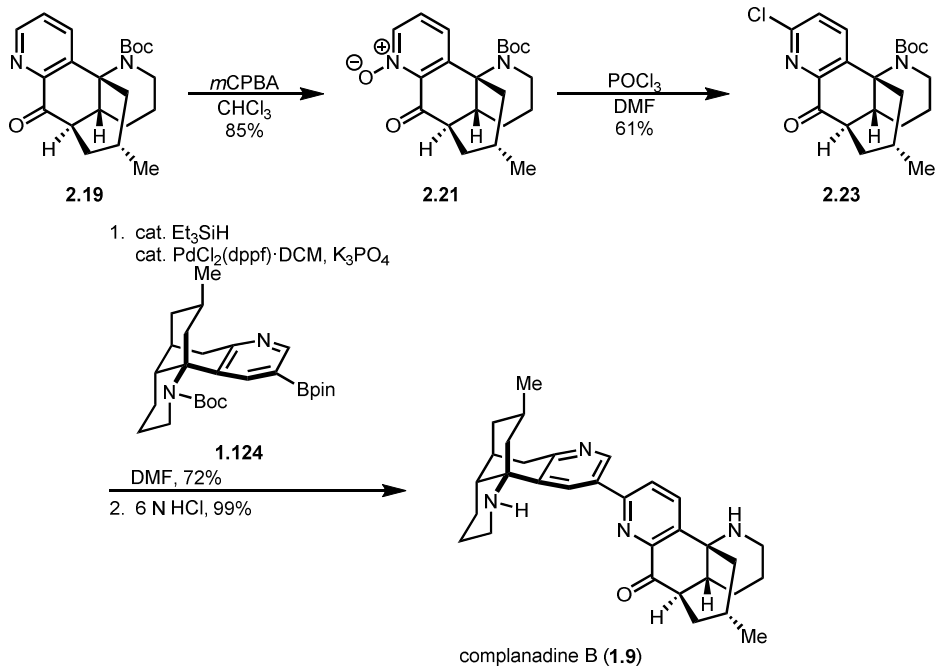



PyBroP (**2.20**)

This functionalization approach was successful when applied to the synthesis of our targeted lycodine derivative (Scheme 2.10). Treatment of **2.19** with *m*CPBA afforded *N*-oxide **2.21**. Chlorination was effected by treatment of **2.21** with $POCl_3$ to provide chloride **2.23**. With **2.23** in hand, we were able to forge the bond between the two lycodine fragments by effecting a Suzuki cross-coupling reaction with **1.124**. Cleavage of the Boc groups completed our synthesis of **1.9**.

**Scheme 2.10** First Generation Synthesis of Complanadine B.

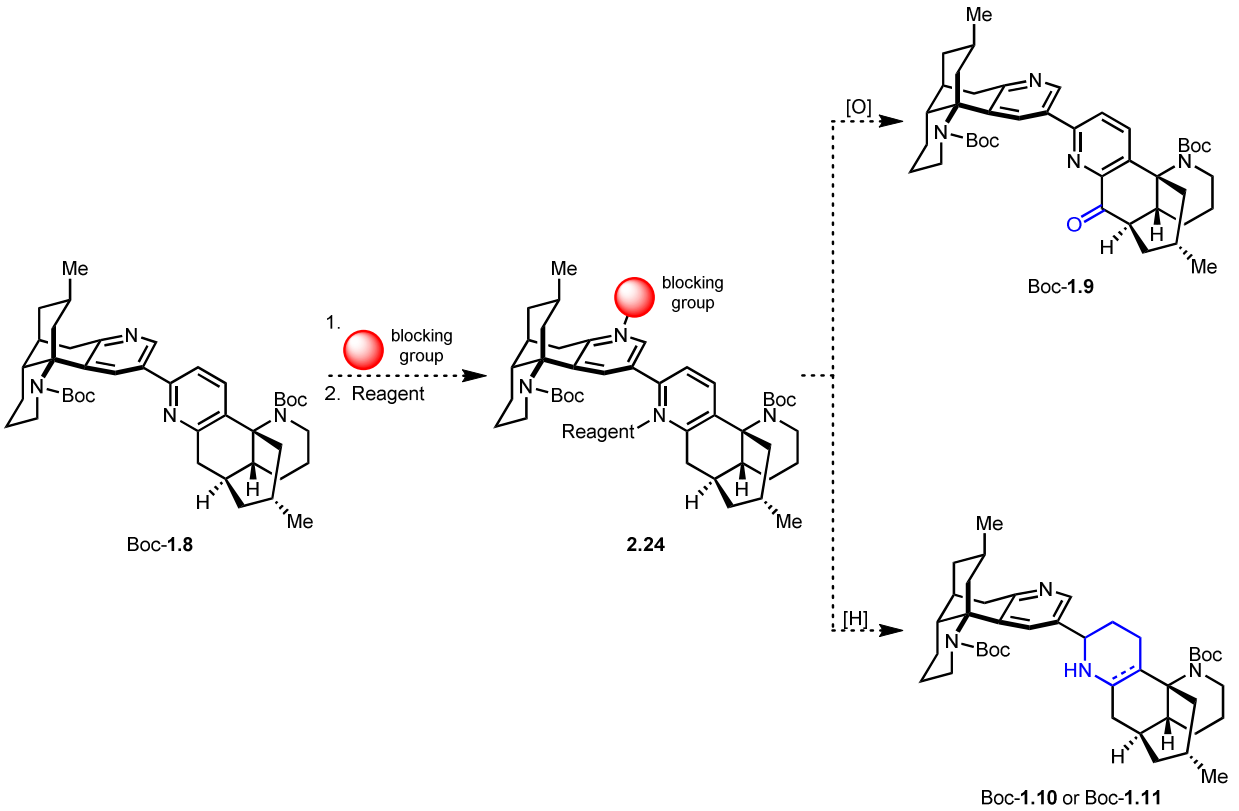



While we were able of prepare **1.9** from an oxygenated lycodine derivative, this route was not as efficient as we had originally anticipated due to the challenges associated with effecting C-6 oxygenation of C-1 substituted lycodine derivatives. We still believed that a synthesis of **1.9** by the late-stage functionalization of Boc-**1.8** would be more direct if the innate reactivity of Boc-**1.8** could be overcome. Further, we envisioned that a late-stage functionalization strategy could be generalized to provide access to **1.10** and **1.11** as well. With these opportunities in mind, we sought to develop an approach that would enable the late-stage functionalization of Boc-**1.8** at inherently less reactive sites.

## 2.4 Synthesis of Complanadine B via Late-Stage Oxygenation of a Complanadine A Derivative Facilitated by a Blocking Group Strategy

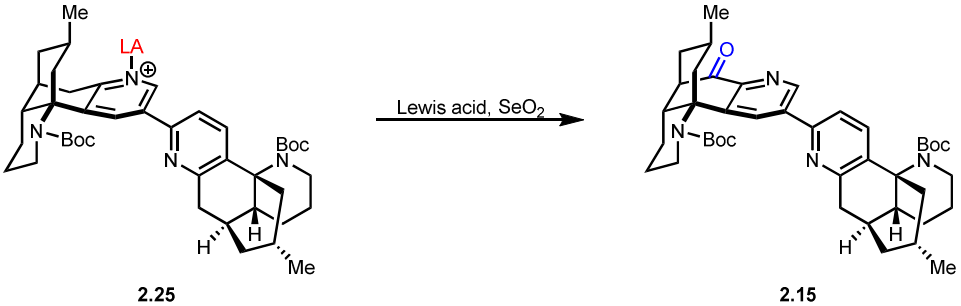
When considering this challenge, we were cognizant that the selectivity of the $SeO_2$ oxygenation of Boc-**1.8** was determined by the accessibility of the two pyridine nitrogen atoms. The $SeO_2$ coordinates to the less hindered pyridine nitrogen, resulting in C-6' oxygenation. We envisioned that the addition of a sacrificial electrophile might serve to block this pathway, as the electrophile would preferentially bind to the more nucleophilic nitrogen atom leaving the other available for functionalization (Scheme 2.11). Such a blocking group strategy could be applied to the synthesis of **1.10** and **1.11** as well, due to the fact that several methods for the reduction of pyridine rings also are initiated by the coordination of reagents to the pyridine. For example, the reduction of pyridines with $SmI_2$[18] and a rhodium-catalyzed hydroboration of pyridines developed by Ohmura and Suginome for the synthesis of 1,2-dihydropyridines both proceed by the aforementioned mechanism.[19] By blocking the more nucleophilic pyridine nitrogen in Boc-**1.8**, the desired pyridine ring could be hydrogenated. In order to implement this strategy, we first had to identify an appropriate blocking group.

**Scheme 2.11** Blocking Group Strategy for the Synthesis of the Complanadines.




Our initial efforts focused on employing Lewis acids as blocking groups for the synthesis of **1.9** (Scheme 2.12). We envisioned that a Lewis acid would preferentially coordinate to the most accessible pyridine nitrogen atom leaving the desired pyridine nitrogen available to coordinate to $SeO_2$ in order to initiate the oxygenation of C-6. This approach would directly provide Boc-**1.9** after decomplexation of the Lewis acid. Unfortunately, treatment of Boc-**1.8** with $SeO_2$ and a variety of Lewis acid additives (e.g., $BF_3{\cdot}Et_2O$ and $Ag_2CO_3$) afforded only **2.15**. Therefore, these additives were apparently not effective blocking groups. At the elevated temperature of the $SeO_2$ oxidation (60 °C), it is likely that the binding of the Lewis acids to the pyridine nitrogen is reversible. Without a robust blocking group, the $SeO_2$ would still capable be of engaging the least hindered pyridine nitrogen, resulting in C-6' oxygenation.

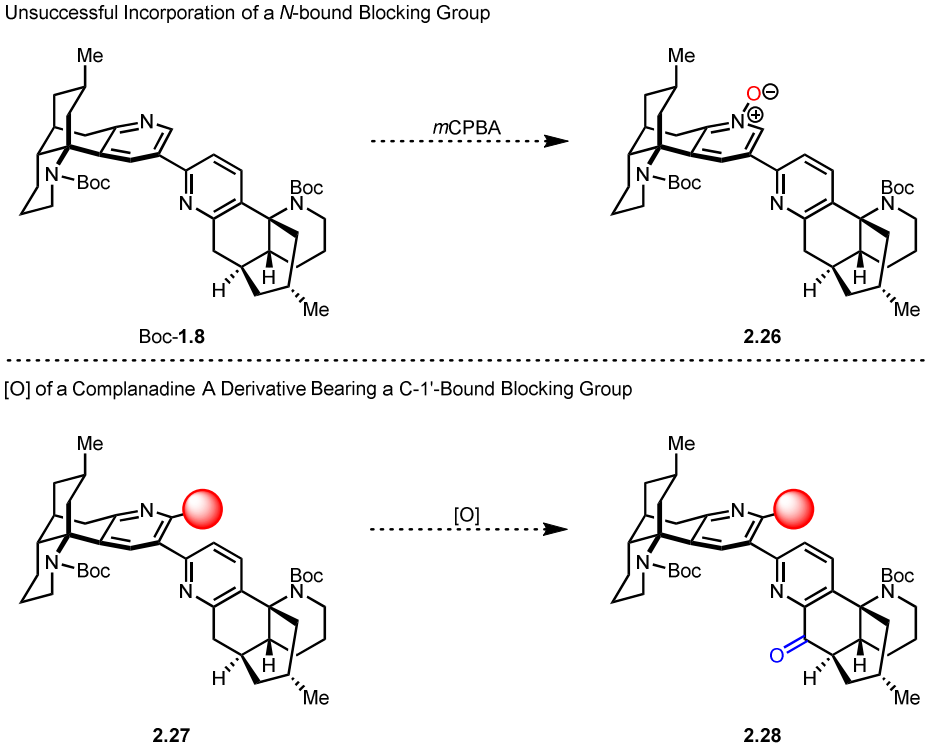
**Scheme 2.12** Oxygenation of Complanadine A with Lewis Acid Additives.




The presumed instability of these Lewis acid complexes led us to pursue more stable blocking groups, specifically covalently bound blocking groups. We briefly pursued the synthesis of derivatives with *N*-bound blocking groups (Scheme 2.13). For

example, we attempted to prepare *N*-oxide **2.26** by the treatment of Boc-**1.8** with *m*CPBA, but this protocol returned starting material even at elevated temperatures (60 °C). As we continued to refine our strategy, we drew inspiration from the challenges we faced effecting C-6 oxygenation on lycodine derivatives bearing C-1 substituents (see Scheme 2.7). We envisioned that a **1.8** derivative bearing a C-1' blocking group would be recalcitrant to oxygenation at C-6', due to the blocking group's ability to block the coordination of $SeO_2$ to the proximal nitrogen atom. To maximize the chances of success for this approach, we realized that the blocking group would have to fulfill several criteria. The blocking group would have to be (1) large in order to block the coordination of $SeO_2$ to the nitrogen atom, (2) inductively withdrawing to further reduce the nucleophilicity of the pyridine nitrogen, and (3) removable, so that **1.9** could be readily prepared from the substrate in the event of successful oxygenation.

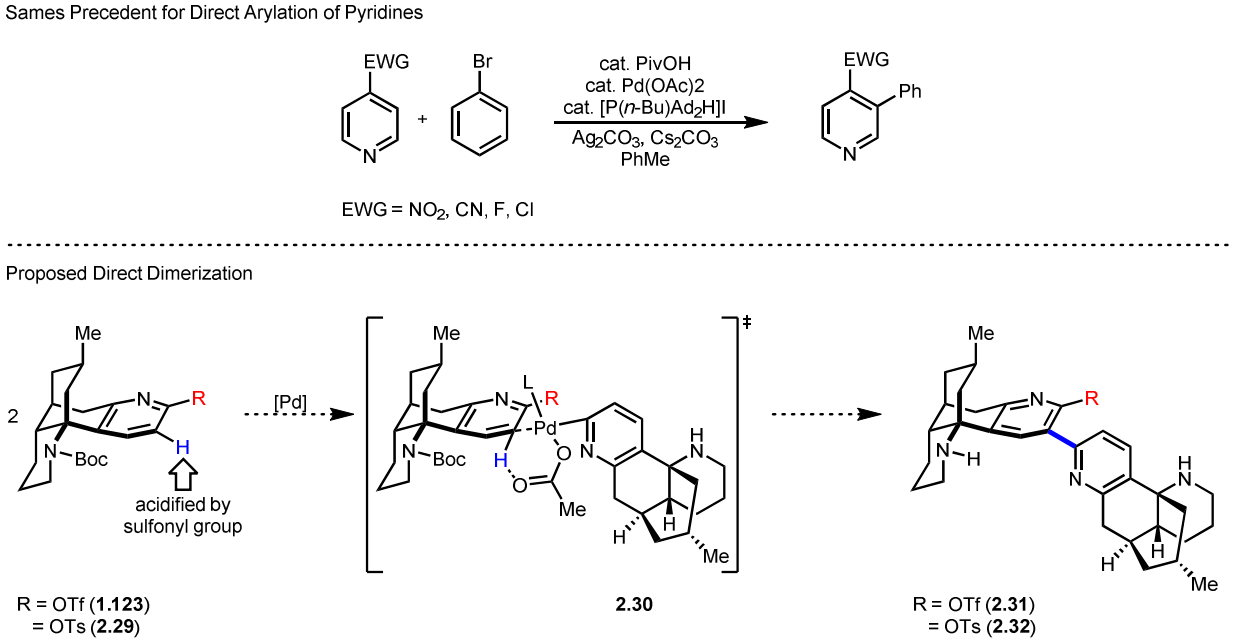
**Scheme 2.13** Complanadine A Derivatives with Covalently Bound Blocking Groups.




When approaching the synthesis of the target complanadine A derivative, we were inspired by a method developed by the Sames group that enabled the direct arylation of pyridines (Scheme 2.14).[20] The authors demonstrated that pyridines could be arylated at positions *ortho* to electron withdrawing groups using palladium catalysts. Further, halides survived the reaction conditions and were sufficiently electron withdrawing to direct functionalization. From these results, we reasoned that we may be able to effect a direct dimerization of triflate **1.123** to afford **2.31**. We envisioned that an oxidative addition of a Pd-complex to the C-OTf bond would afford palladated lycodine derivative **2.30**. This complex could then participate in the direct arylation of another molecule of **1.123** at C-2, which would be acidified by the electron withdrawing nature of the triflate group, to afford **2.31**. The triflate group fulfills all of the criteria that we set forward for an ideal blocking group, making **2.31** an enticing target. Unfortunately, we found that **1.123** readily hydrolyzed under the reaction conditions to afford pyridone

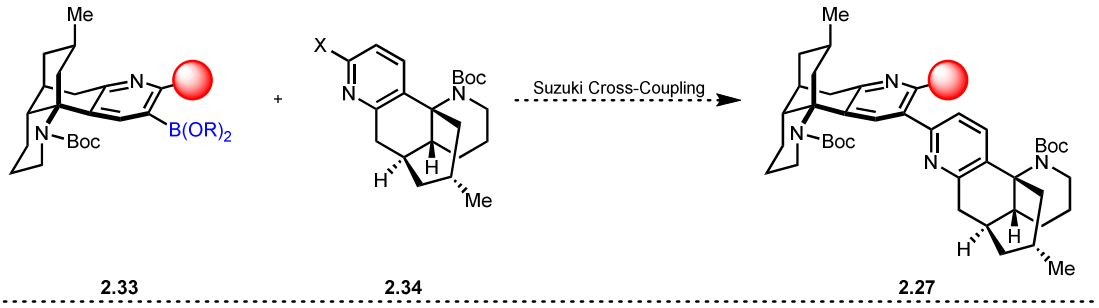
**1.105**. Tosylate **2.29** was resistant to hydrolysis, but was not susceptible to direct arylation. Due to these unpromising results, we adopted a more conservative approach for the synthesis of **2.27**.

**Scheme 2.14** Attempted Direct Dimerization of **1.123**.

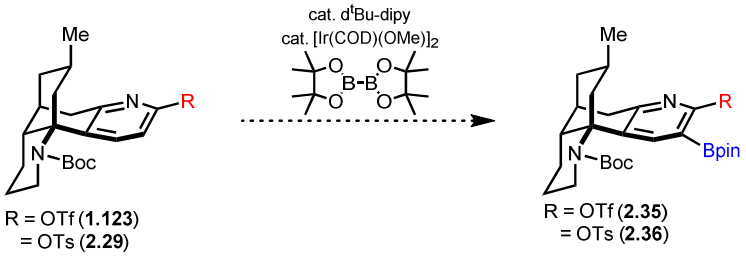



We envisioned that **2.27** could be synthesized using a Suzuki cross-coupling reaction (Scheme 2.15). This approach would necessitate the synthesis of a lycodine derivative bearing a blocking group at C-1 and a boronic acid/ester at C-2. Due to our success borylating the C-2 position of Boc-lycodine (Boc-**1.3**) using Hartwig's Ir-catalyzed C-H borylation method,[21] we sought to apply this method to the synthesis of C-1 substituted lycodine derivatives. We found that these conditions were ineffectual when applied to triflate **1.123** and tosylate **2.29**. Hartwig has shown that this method is sensitive to the steric environment of the substrate, so it is possible that the substituents at C-1 block borylation at C-2.[22]

**Scheme 2.15** Cross-coupling Approach for the Preparation of **2.27**.

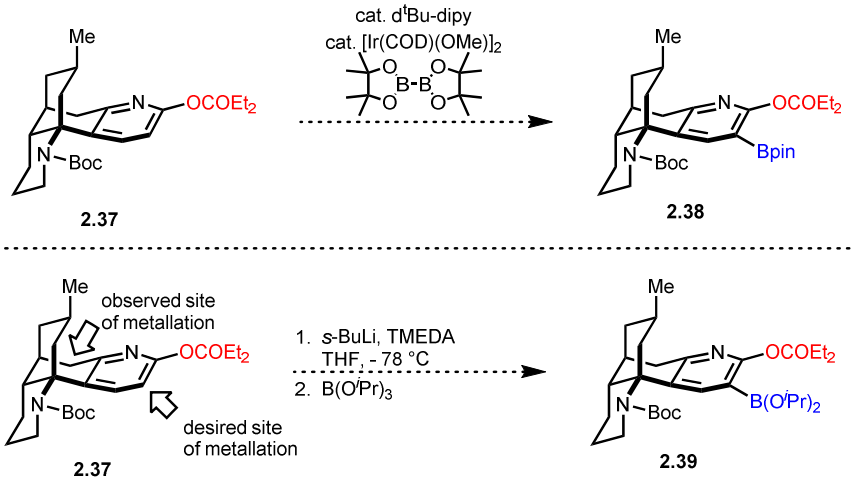



Attempted Borylation of Sulfonate Derivatives of Lycodine




We also investigated several tactics to achieve the borylation of carbamate **XX** (Scheme 2.16). We anticipated that carbamates could be effective blocking groups because they are bulky and mildly inductively withdrawing. Also, Garg[23] and Chatani[24] has shown that the hydrogenolysis of aryl carbamates can be achieved using nickel catalysts. We began by subjecting **2.37** to the Hartwig borylation conditions, but starting material was recovered as in the case of the sulfonate derivatives. As an alternative, we investigated a protocol developed by the Snieckus group for the *ortho* metalation of *O*-pyridyl carbamates.[25] We envisioned that *ortho*-metalation of **2.37** followed by a borate quench could be used to prepare **2.39**. However, treatment of **2.37** with *sec*-butyl lithium led to deprotonation at C-6, an acidic pseudo-benzylic position. Deuterium quenching studies demonstrated that the addition of multiple equivalents of base did not result in *ortho*-metalation of the substrate.

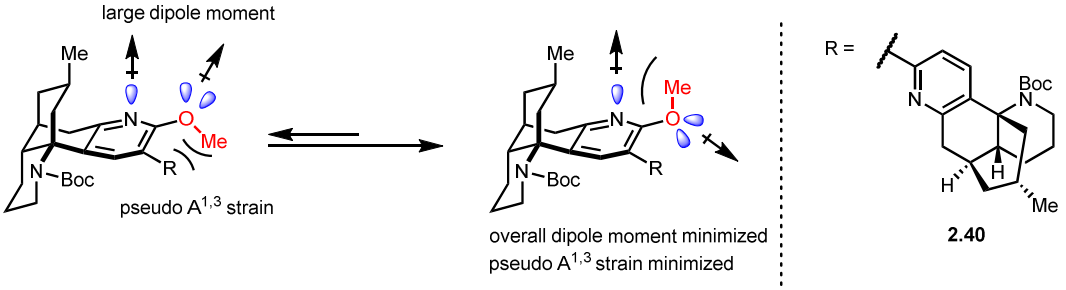
**Scheme 2.16** Attempted Borylation of Carbamate **2.37**.




Due to challenges we faced attempting to borylate sulfonate and carbamate derivatives of lycodine, we sought other blocking groups to pursue. We were intrigued by a report by the Corey group that demonstrated that 2-methoxypyridines preferentially adopt a conformation where the methyl group lies in plane with the nitrogen atom lone

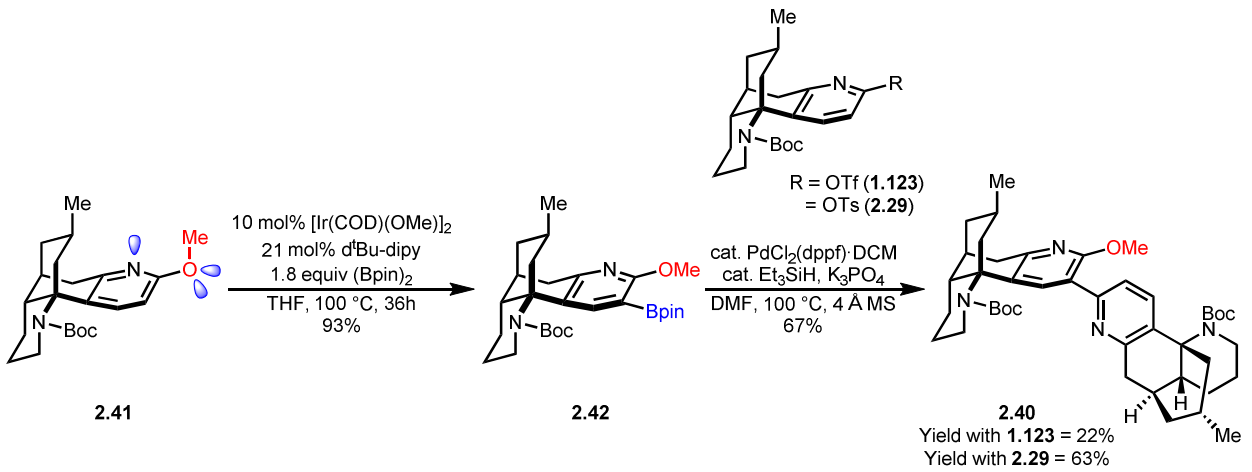
pair (Scheme 2.17).[26] This conformation is energetically favorable because it results in the minimization of the overall dipole moment of the molecule due to the opposition of the dipole moment generated by the pyridine ring and the dipole moments generated by the lone pairs on the oxygen atom. Also, pseudo $A^{1,3}$ strain between the methoxy group and the *ortho* substituent is also minimized in this conformation. Finally, the oxygen lone pair is able to interact with the low-lying C-N σ* orbital, which further stabilizes this conformation. We envisioned that if Boc-methoxycomplanadine A (**2.40**) adopted a similar conformation, coordination of $SeO_2$ to the nitrogen atom α to the methoxy group would be blocked, which would in turn enable functionalization at C-6. We anticipated that this derivative would be more amenable to borylation using the Hartwig conditions, due to the fact that the methyl group prefers to reside away from the site of functionalization.

**Scheme 2.17** Conformations of 2-Methoxypyridines.




In fact, this was the case. Treatment of **2.41** with the Hartwig borylation conditions afforded boronic ester **2.42** in low yield (15%, Scheme 2.18). Nevertheless, this result was exciting, as it was the first time we had achieved the synthesis of a boronic ester derivative that bore a blocking group. We were able to rapidly optimize this reaction by increasing the catalyst loading, equivalents of $(Bpin)_2$, reaction temperature, and reaction time. The fully opitimized conditions provided **2.42** in 93% yield. With **2.42** in hand, we desired to effect a Suzuki cross-coupling. Subjecting **2.42** and **1.123** to Suzuki cross-coupling conditions afforded Boc-methoxycomplanadine A (**2.40**), albeit in low yield (22%). The major side products in this reaction were Boc-methoxylycodine (**2.41**), which likely arose from the protodeborylation of **2.42**, and pyridone **1.105**, the hydroylsis product of **1.123**. Recalling our discovery that tosylate **2.29** was less susceptible to hydrolysis than **1.123** in our direct arylation studies, we employed **2.29** in the cross-coupling instead. This reaction provided **2.40** in 67% yield.

**Scheme 2.18** Synthesis of Boc-Methoxycomplanadine A (**2.40**).

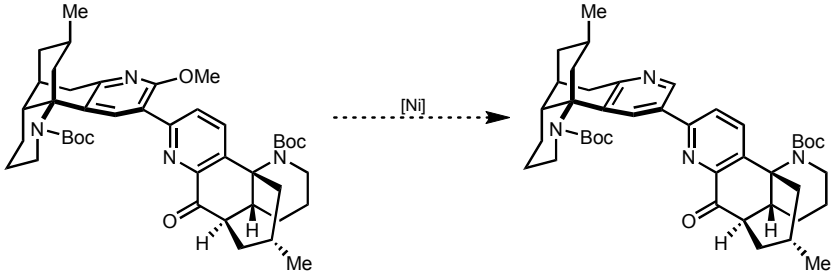



Having achieved the synthesis of a complandine A derivative bearing a blocking group in the C-1' position, we were now ready to test the viability of our blocking group strategy when applied toward the synthesis of **2.9**. Gratifyingly, treatment of **2.40** with $SeO_2$ afforded Boc-methoxycomplanadine B (**2.43**) in 63% yield. C-6' oxygenated products were not observed, illustrating the effectiveness of this strategy. With **2.43** in hand, we envisioned that a direct demethoxylation of this compound would afford Boc-**1.9**.

**Scheme 2.19** Oxidation of Boc-Methoxycomplanadine A (**2.40**).

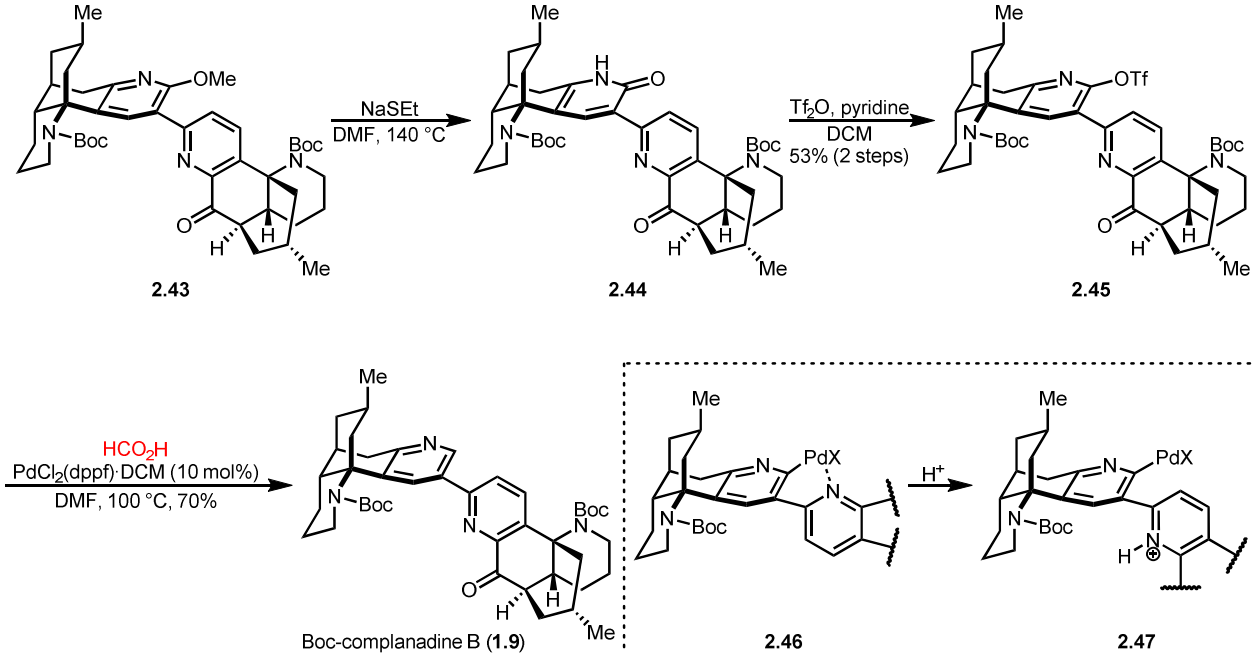

Several groups have reported methods for the demethoxylation of methyl aryl ethers. For example, Martin and coworkers have developed nickel catalysts for the demethoxylation of aryl methoxy groups *ortho* to directing groups.[27] Recently, Hartwig has reported conditions that enable the hydrogenolysis of methoxy groups in the absence of directing groups.[28] In the context of strong bond activation in pyridine systems, Chatani has developed a nickel-catalyzed amination reaction for *N*-heteroaryl methyl ethers.[29] The functionalization of 2-methoxypyidine was conspicuously missing from Chatani's report. In fact, a survey of the literature revealed only one example of the activation of the $C_{sp^2}$-O bond in a 2-methoxypridine. Dankwardt demonstrated that 2-methoxypyridine could be employed in a Kumada coupling with aryl Grignard reagents.[30] Undaunted by this lack of precedent, we subjected **2.43** to the hydrogenolysis conditions developed by Martin and by Hartwig. Unfortunately, starting material was recovered in both cases. We speculate that the activation of 2-methoxypyridine systems is challenging due to the molecule's ability to bind to the nickel center in a bidentate fashion to form stable complexes. In the future, we are interested in trying to repurpose the Dankwardt conditions for the hydrogenolysis of 2-methoxypyridines in an attempt to address this challenge.

**Scheme 2.20** Attempted Demethoxylation of **2.43**.




Due to our inability to effect a direct demethoxylation, we pursued a mutli-step approach for the removal of the methoxy group. Treatment of **2.43** with NaSEt afforded pyridone **2.44**. Addition of $Tf_2O$ to **2.44** afforded triflate **2.45**. With **2.45** in hand, we expected that hydrogenolysis of the triflate would provide access to Boc-**1.9**. However, we found that when **2.45** was subjected to hydrogenolysis conditions that employed neutral hydride sources (e.g., EtSiH and $NH_4HCO_2$) only the starting material was recovered. We postulated that the palladium complex formed after oxidative addition to the C-OTf bond might be stabilized by the second pyridine moiety in the core of the molecule. Reductive elimination from such a complex might be slow, which may limit catalyst turnover. To disfavor the formation of this complex, hydrogenolysis was attempted under acidic conditions. We envisioned that the pyridine ring would be protonated, preventing its coordination to the metal complex. Gratifyingly, treatment of **2.45** with hydrogenolysis conditions that employed formic acid as the hydride source afforded Boc-**1.9** in 70% yield. The synthesis of Boc-**1.9** through this approach demonstrates that our blocking group strategy formally enables the selective, late-stage functionalization of Boc-**1.8** at sites that are inherently poorly reactive.

**Scheme 2.21** Completion of the Synthesis of Complanadine B using Our Blocking Group Strategy.



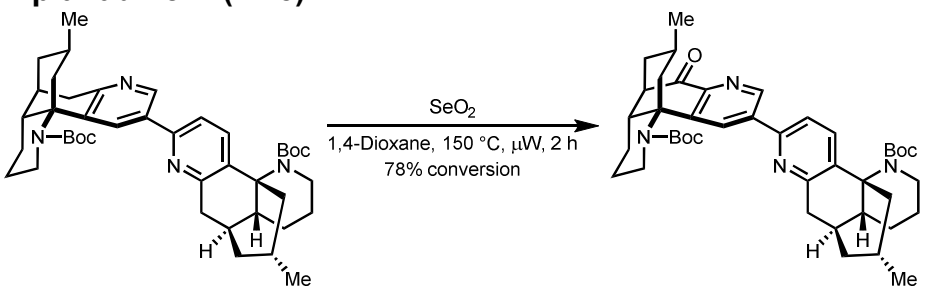
## 2.5 Conclusion

We have achieved the synthesis of **1.9** through two separate approaches. In the first, we prepared an oxygenated lycodine derivative that was employed in a Suzuki cross-coupling to directly provide **1.9**. In the second, we employed a blocking group strategy to enable the late-stage oxygenation of C-6 of a complandine A derivative. This approach was necessitated by the innate reactivity of Boc-**1.8**, which exclusively underwent oxygenation at C-6'. Therefore, we found that this blocking group strategy was an effective method to overcome the inherent reactivity of Boc-**1.8**. In the future, we plan to apply this blocking group strategy to the synthesis of other members of the complanadine family including **1.10** and **1.11**.

## 2.6 Experimental Section

Unless stated otherwise, reactions were performed in oven-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), toluene, and ether (Et2O) were dried by passage over a column of activated alumina; dichloromethane was distilled over calcium hydride. Anhydrous chloroform was obtained in a Sure/Seal bottle from Aldrich. All other solvents and reagents were used as received unless otherwise noted. Thin layer chromatography was performed using SiliCycle silica gel 60 F-254 precoated plates (0.25 mm) and visualized by UV irradiation and anisaldehyde, CAM, potassium permanganate, or iodine stain. Sorbent silica gel (particle size 40-63 μm) was used for flash chromatography. NMR experiments were performed on Bruker spectrometers operating at 300, 400, 500 or 600 MHz for 1H and 75, 100, 125, or 150 MHz for 13C experiments. 1H and 13C chemical shifts (δ) are reported relative to the residual solvent signal. Data 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), dt (doublet of triplet), p (pentet), hept (heptet), m (multiplet), bs (broad singlet). Only select 1H and 13C spectra are reported. IR spectra were recorded on a Nicolet MAGNA-IR 850 spectrometer as thin films on NaCl plates and are reported in frequency of absorption ($cm^{-1}$). Only selected IR absorbencies are reported. Low and high-resolution mass spectral data were obtained from the University of California, Berkeley Mass Spectral Facility, on a VG 70-Se Micromass spectrometer for FAB, and a VG Prospec Micromass spectrometer for EI. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

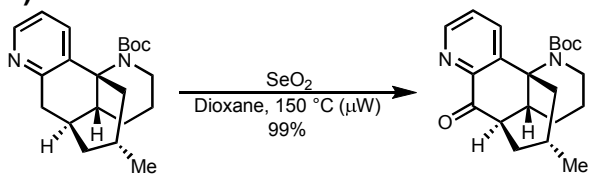
### Boc-*iso*-complanadine B (2.15)




Boc-**1.8** **2.15**

To a 0.5 mL microwave vial equipped with a stir bar was added $SeO_2$ (3.6 mg, 33 μmol). The vial was then sealed with a septum and evacuated/backfilled with $N_2$ (3 X). A solution of Boc-complanadine A (Boc-**1.8**, 8.9 mg, 13 μmol) in anhydrous 1,4-dioxane (0.2 mL) was added to the vial via a syringe and the reaction mixture was heated to 150 °C and stirred in a microwave reactor for 2 h. After 2 h, the reaction mixture was filtered over sand and the solvent was removed under reduced pressure to yield Boc-*iso*-complanadine B (**2.15**, 78% conversion as determined by NMR) An analytically pure sample was obtained by silica gel chromatography (20% $Et_2O$ in hexanes to 100% $Et_2O$). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 9.29 (s, 1H), 8.47 (s, 1H), 7.69 (s, 2H), 4.20 (dd, *J* = 29.7, 13.1 Hz, 2H), 3.27 (dd, *J* = 18.9, 7.2 Hz, 1H), 3.17 (d, *J* = 13.2 Hz, 1H), 2.89 (s, 1H), 2.85 – 2.74 (m, 2H), 2.54 (t, *J* = 12.3 Hz, 1H), 2.46 (t, *J* = 12.9 Hz, 1H), 2.20 (s, 3H), 2.01 (t, *J* = 12.6 Hz, 3H), 1.90 (t, *J* = 12.7 Hz, 3H), 1.75 (s, 5H), 1.69 – 1.43 (m, 18H), 1.43 – 1.22 (m, 5H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.87 (d, *J* = 6.3 Hz, 3H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 199.1, 159.0, 156.4, 156.2, 151.0, 148.4, 147.7, 141.8, 139.2, 136.3, 135.0, 133.7, 119.5, 80.5, 79.9, 64.0, 63.8, 56.0, 51.9, 48.4, 47.2, 45.8, 44.3, 44.2, 43.6, 43.0, 37.8, 35.3, 34.4, 28.7, 28.6, 28.6, 28.0, 27.8, 27.2, 26.7, 25.7, 25.2, 22.4, 22.1. **HRMS (ESI)** calcd for $C_{42}H_{57}N_4O_5^+$ $(M+H)^+$: m/z 697.4323, found 697.4331.

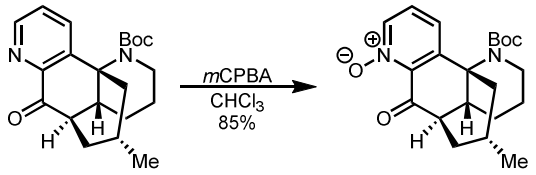
**Boc-ketolycodine (2.19)**




Boc-**1.3** **2.19**

A 30 mL microwave vial equipped with a stir bar was charged with $SeO_2$ (2.06 g, 18.6 mmol, 2.5 equiv), sealed, and evacuated/backfilled with $N_2$ (3 X). A solution of Boc-lycodine (Boc-**1.3**, 2.54 g, 7.42 mmol, 1 equiv) in anhydrous 1,4-Dioxane (20 mL) was introduced to the vial via a septum. The vial was heated in a microwave reactor with stirring at 150 °C for 2 h. After cooling the reaction mixture to room temperature, the resulting orange solution was washed with 10% aqueous $NH_4OH$ (50 mL). Then, the aqueous phase was extracted with DCM (3 X). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield Boc-ketolycodine (**2.19**, 2.63 g, 7.38 mmol, 99%) as a brown solid, which was used in the next step without further purification. An analytically pure sample was obtained by silica gel chromatography (100% $Et_2O$). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.74 – 8.70 (dd, *J* = 4.5, 1.6 Hz, 1H), 7.78 – 7.74 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.53 – 7.49 (dd, *J* = 8.0, 4.5 Hz, 1H), 4.14 – 4.08 (d, *J* = 15.0 Hz, 1H), 2.98 – 2.89 (d, *J* = 12.3 Hz, 1H), 2.84 – 2.79 (bs, 1H), 2.42 – 2.34 (t, *J* = 13.1 Hz, 1H), 2.18 – 2.10 (d, *J* = 12.9 Hz, 1H), 2.02 – 1.88 (m, 2H), 1.72 – 1.15 (s, 15H + $H_2O$), 0.88 – 0.81 (d, *J* = 6.4 Hz, 3H). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 199.1, 155.9, 149.3, 148.8, 141.8, 135.7, 128.5, 80.3, 63.6, 51.8, 46.9, 45.7, 44.0, 37.7, 28.5, 27.9, 27.1, 25.1, 22.1. **IR** (film): v = 2927, 2857, 2342, 1700, 1455, 1365, 1293, 1270, 1156 $cm^{-1}$. **HRMS (ESI)** calcd for $C_{21}H_{29}N_2O_3^+$ $(M+H)^+$: m/z 357.2173, found 357.2178.

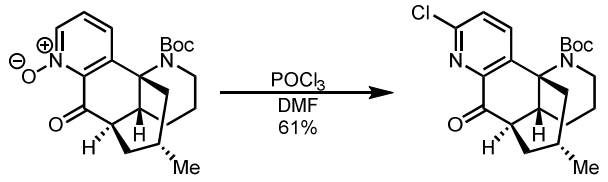
**Boc-ketolycodine *N*-oxide (2.21)**




**2.19** **2.21**

A solution of Boc-ketolycodine (**2.19**, 2.56 g, 7.18 mmol) and *m*CPBA (2.48 g, 10.8 mmol) in $CHCl_3$ (65 mL) was stirred at room temperature for 4 h. The resulting yellow solution was washed with 1 M aqueous NaOH (30 mL), and the aqueous layer was extracted with DCM (3 X). The combined organic layers were dried over $MgSO_4$, filtered, and solvent removal under reduced pressure afforded Boc-ketolycodine *N*-oxide (**2.21**, 2.28 g, 6.12 mmol, 85%) as a yellow solid, which was used in the next step without further purification. An analytically pure sample was obtained by silica gel chromatography (100% $Et_2O$ to 20% MeOH in $Et_2O$). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.23 – 8.19 (d, *J* = 6.5 Hz, 1H), 7.39 – 7.33 (t, *J* = 7.2 Hz, 1H), 7.25 – 7.21 (d, *J* = 8.0 Hz, 1H), 4.19 – 4.10 (m, 1H), 3.01 – 2.94 (d, *J* = 14.2 Hz, 1H), 2.80 – 2.74 (s, 1H), 2.45 – 2.36 (t, *J* = 12.7 Hz, 1H), 2.11 – 2.02 (m, 1H), 2.01 – 1.92 (t, *J* = 12.5 Hz, 2H), 1.77 – 1.15 (s, 15H + $H_2O$), 0.93 – 0.86 (d, *J* = 5.4 Hz, 3H). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 191.4, 155.6, 147.1, 141.3, 141.1, 128.5, 122.3, 80.5, 64.1, 53.1, 46.0, 45.9, 44.3, 37.0, 28.5, 27.8, 27.0, 24.8, 22.0. **IR (film):** ν = 2927, 2869, 2857, 2361, 2238, 1693, 1365, 1269, 1149 $cm^{-1}$. **HRMS (ESI)** calcd for $C_{21}H_{29}N_2O_4^+$ $(M+H)^+$: m/z 373.2122, found 373.2131.

**Boc-chloroketolycodine (2.23)**



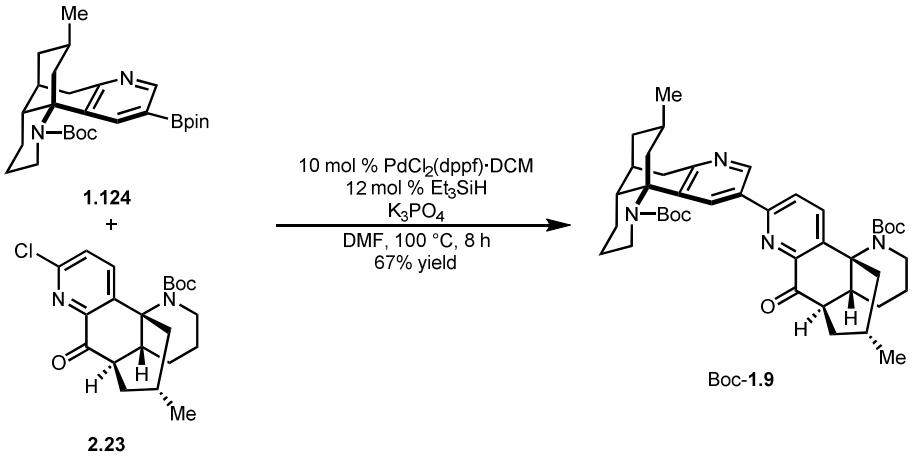

**2.21** **2.23**

A solution of Boc-ketolycodine *N*-oxide (**2.21**, 95 mg, 0.26 mmol) in DMF (4 mL) was cooled to 0 °C. $POCl_3$ (95 µL, 1.0 mmol) was added dropwise at 0 °C to the resulting solution. Then, the solution was stirred for 4 h at 0 °C, at which time the reaction mixture was quenched with 1 M aqueous NaOH (2 mL). The resulting mixture was extracted with DCM (3 X). The combined organic phases were dried with $MgSO_4$ and filtered. The solvent was removed under reduced pressure, and the crude product was purified by silica gel chromatography (50% pentane in $Et_2O$) to yield Boc-chloroketolycodine (**2.23**, 66 mg, 0.17 mmol, 66%) as a clear oil. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 1H), 7.54 (d, *J* = 8.3 Hz, 1H), 4.12 (d, *J* = 13.7 Hz, 1H), 2.95 (dd, *J* = 13.4, 3.3 Hz, 1H), 2.82 (s, 1H), 2.44 – 2.33 (m, 1H), 2.19 – 2.08 (m, 1H), 1.98 (t, *J* = 12.8 Hz, 1H), 1.92 (d, *J* = 13.2 Hz, 1H), 1.67 (bs, 2H), 1.59 (dt, *J* = 13.0, 3.8 Hz, 1H), 1.51 (s, 9H), 1.43 (dd, *J* = 13.3, 4.7 Hz, 1H), 1.32 – 1.15 (m, 2H), 0.88 (d, *J* = 6.3 Hz, 3H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 199.1, 159.0, 156.4, 156.2, 151.0, 148.4, 147.7, 141.8, 139.2, 136.3, 135.0, 133.7, 119.5, 80.5, 79.9, 64.0, 63.8, 56.0, 51.9, 48.4, 47.2, 45.8, 44.3, 44.2, 43.6, 43.0, 37.8, 35.3, 34.4, 28.7, 28.6, 28.6, 28.0, 27.8, 27.2, 26.7, 25.7, 25.2, 22.4, 22.1. **IR** (film): ν = 3392, 3071, 2928, 2858, 2360, 2240, 1702,

1576, 1550, 1507, 1456, 1433, 1389, 1365, 1318, 1271, 1253, 1216, 1156, 1146, 1115, 1082, 976, 941, 912, 853, 839, 732 $cm^{-1}$. **HRMS (ESI)** calcd for $C_{21}H_{28}ClN_2O_3^+$ $(M+H)^+$: m/z 391.1783, found 391.1784.

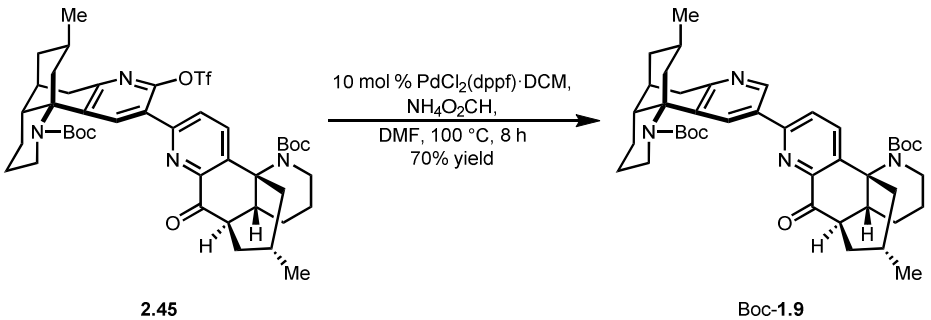
**Boc-complanadine B (**Boc-**1.9)**

*Method 1*




$PdCl_2$(dppf)·DCM (16 mg, 19 µmol, 12.5 mol%), $K_3PO_4$ (116 mg, 0.55 mmol), were added to a flame-dried Schlenk tube equipped with a stir bar. The flask was fitted with a Teflon screw-cap and septum and evacuated/backfilled with $N_2$. A solution of **2.23** (73 mg, 0.16 mmol) and **1.124** (67 mg, 0.17 mmol) in anhydrous DMF (1.0 mL) was added to the vessel via the septum. Then, a solution of $Et_3SiH$ (6.2 µL, 39 µmol, 25 mol %) in anhydrous DMF (0.5 mL) was added to the vessel via the septum. The tube was sealed, and the reaction mixture was heated to 80 °C and stirred for 8 h. After the resulting solution was cooled to room temperature, the solvent was removed under reduced pressure, and the product was purified by silica gel chromatography (100% $Et_2O$) to yield Boc-complanadine B (Boc-**1.9**, 78 mg, 0.11 mmol, 72%) as a white foam.

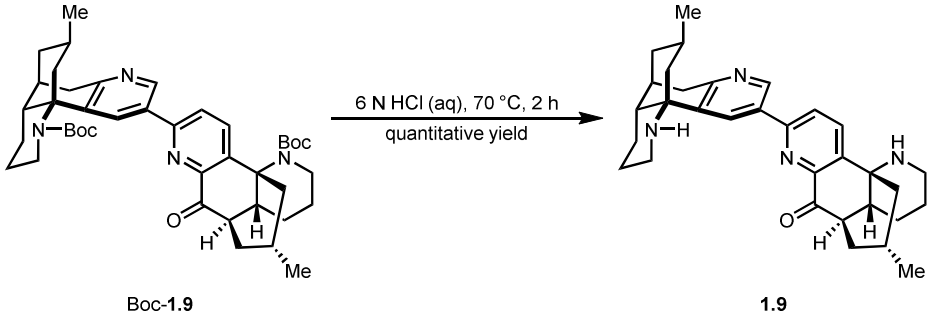
*Method 2*




A 4 mL microwave vial was charged with $PdCl_2$(dppf)·DCM (4.8 mg, 5.9 µmol, 10 mol %), sealed, and evacuated/backfilled with $N_2$ (3 X) . A solution of triflate **2.45** (50. mg, 59 µmol) in DMF (0.5 mL) was added to the vial via the septum. Then, formic acid (22 µL, 0.59 mmol) and $Et_3N$ (41 µL, 0.30 mmol) were added to the vial and the reaction mixture was heated to 100 °C and stirred for 8 h. After cooling to room temperature, the

solvent was removed under reduced pressure and the crude mixture was purified by silica gel chromatography to afford Boc-complanadine B (Boc-**1.9**, 31 mg, 44 µmol, 76%) as a white foam. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.98 (d, *J* = 2.2 Hz, 1H), 8.09 (d, *J* = 2.2 Hz, 1H), 7.91 – 7.78 (m, 2H), 4.14 (d, *J* = 13.6 Hz, 2H), 3.25 (dd, *J* = 19.2, 7.4 Hz, 1H), 2.97 (dd, *J* = 13.5, 2.9 Hz, 2H), 2.91 – 2.80 (m, 2H), 2.74 (d, *J* = 19.1 Hz, 1H), 2.51 – 2.39 (m, 2H), 2.19 – 2.13 (m, 2H), 2.01 (t, *J* = 12.7 Hz, 2H), 1.95 – 1.77 (m, 5H), 1.71 (t, *J* = 12.7 Hz, 2H), 1.64 – 1.46 (m, 25H), 1.46 – 1.14 (m, 11H), 0.84 (dd, *J* = 17.0, 6.3 Hz, 6H). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 198.5, 159.0, 156.6, 155.9, 155.1, 148.9, 146.2, 140.6, 136.7, 135.7, 132.9, 125.7, 80.3, 80.2, 67.9, 64.0, 63.6, 52.0, 48.4, 46.9, 45.7, 44.2, 44.1, 43.6, 42.9, 37.7, 35.0, 34.3, 28.5, 28.5, 27.9, 27.7, 27.2, 26.6, 25.6, 25.6, 25.1, 22.3, 22.1. **IR** (film): v = 2926, 1703, 1693, 1678, 1587, 1435, 1366, 1270, 1253, 1213, 1157, 1116, 1080, 971, 940, 735 $cm^{-1}$. **HRMS (ESI)** calcd for $C_{42}H_{57}N_4O_5^+$ $(M+H)^+$: m/z 697.4323, found 697.4326.

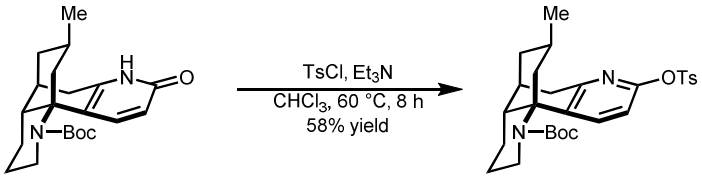
**Complanadine B (1.9)**




Boc-**1.9** **1.9**

A solution of Boc-complanadine B (Boc-**1.9**, 40. mg, 57 µmol) in 6 N aqueous HCl (1 mL) was stirred at 70 °C for 2 h. Then, $K_2CO_3$ was added to the solution until it remained basic. The mixture was extracted with DCM (3 X), and the combined organic phases were dried with $MgSO_4$ and filtered. Finally, the solvent was removed under reduced pressure to yield complanadine B (**1.9**) as a white foam.
**$^1$H NMR** (500 MHz, $CD_3OD$) δ 9.05 (s, 1H), 8.80 (s, 1H), 8.32 – 8.22 (m, 1H), 3.21 (dd, *J* = 19.2, 7.1 Hz, 1H), 2.88 – 2.70 (m, 4H), 2.48 (q, *J* = 11.5 Hz, 2H), 2.17 (s, 1H), 2.04 (d, *J* = 12.1 Hz, 1H), 1.93 (d, *J* = 13.6 Hz, 1H), 1.80 (d, *J* = 16.0 Hz, 2H)1.72 – 1.08 (m, 19H), 0.86 (d, *J* = 6.1 Hz, 3H), 0.81 (d, *J* = 5.4 Hz, 3H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 202.5, 160.9, 154.9, 150.5, 146.1, 143.6, 138.3, 133.8, 133.8, 126.6, 58.3, 58.3, 52.7, 51.4, 48.0, 44.6, 44.1, 42.1, 42.0, 39.7, 35.7, 34.7, 27.6, 27.3, 27.1, 27.1, 27.0, 22.3, 22.1. **IR** (film): v = 3398, 2922, 2852, 2360, 1697, 1586, 1438, 1145, 735 $cm^{-1}$. **HRMS (ESI)** calcd for $C_{32}H_{41}N_4O^+$ $(M+H)^+$: m/z 497.3275, found 497.3284.

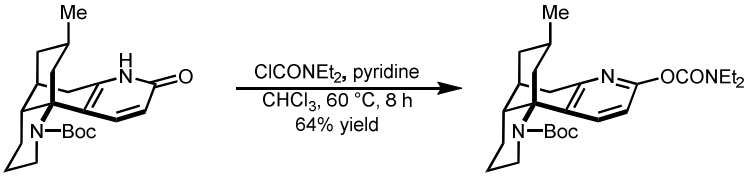
**Tosylate 2.29**




**1.105** **2.29**

Pyridone **1.105** (1.70 g, 4.74 mmol) and 4-toluenesulfonyl chloride (TsCl, 1.36 g, 7.13 mmol) were added to a 100 mL round-bottom flask equipped with a stir bar. The flask was fitted with a septum and evacuated/backfilled with $N_2$ (3 X). Then $CHCl_3$ (50 mL) and $Et_3N$ (1.32 mL, 9.48 mmol) were added to the vessel via the septum. The reaction mixture was stirred at 60 °C for 8 h, at which time, the solvent was removed under reduced pressure, and the crude product was purified by silica gel chromatography (10% EtOAc in hexanes to 20% EtOAc in hexanes) to yield **2.29** (1.52 g, 4.24 mmol, 62%) as a white foam. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.2 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.27 (d, *J* = 7.9 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 1H), 4.03 (d, *J* = 13.2 Hz, 1H), 2.95 (dd, *J* = 19.3, 7.3 Hz, 1H), 2.67 (dd, *J* = 13.4, 2.4 Hz, 2H), 2.43 (s, 1H), 2.38 (s, 3H), 2.31 – 2.21 (m, 2H), 2.01 (d, *J* = 3.5 Hz, 1H), 1.73 (t, *J* = 12.5 Hz, 1H), 1.59 (d, *J* = 12.3 Hz, 1H), 1.44 (s, 15H), 1.29 – 0.94 (m, 2H), 0.76 (d, *J* = 6.4 Hz, 3H). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 157.1, 155.9, 154.6, 145.1, 138.1, 134.5, 133.7, 129.4, 128.7, 113.2, 79.7, 63.4, 47.9, 44.0, 43.4, 42.7, 34.5, 34.0, 28.5, 27.4, 26.4, 25.5, 22.3, 21.6. **IR** (film): v = 2926, 2360, 2252, 1697, 1577, 1451, 1367, 1279, 1253, 1174, 1093, 1076, 968, 932, 914, 810, 733 cm$^{-1}$. **HRMS (ESI)** calcd for $C_{28}H_{37}N_2O_5S^+$ $(M+H)^+$: m/z 513.2418, found 513.2416.

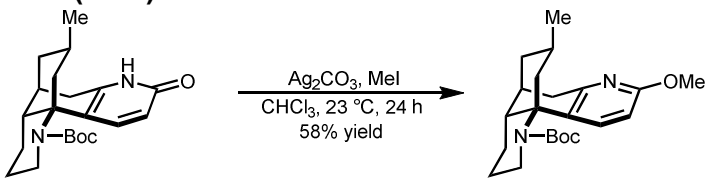
**Carbamate 2.37**




**1.105** **2.37**

Pyridone **1.105** (102 mg, 0.285 mmol) was to round-bottom flask equipped with a stir bar. The flask was fitted with a septum and evacuated/backfilled with $N_2$ (3 X). Then $CHCl_3$ (3 mL), pyridine (230 µL, 2.85 mmol), diethylcarbamoyl chloride (108 µL, 0.852 mmol) were added to the vessel via the septum. The reaction mixture was stirred at 60 °C for 8 h, at which time, the solvent was removed under reduced pressure, and the crude product was purified by silica gel chromatography ($Et_2O$) to yield **2.37** (83.7 mg, 0.183 mmol, 64%) as a white foam. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.3 Hz, 1H), 6.92 (d, *J* = 8.3 Hz, 1H), 4.08 (d, *J* = 15.2 Hz, 1H), 3.47 (q, *J* = 6.7 Hz, 2H), 3.38 (q, *J* = 7.0 Hz, 2H), 3.15 (dd, *J* = 19.0, 7.3 Hz, 1H), 2.73 (d, *J* = 15.0 Hz, 1H), 2.62 (d, *J* = 19.0 Hz, 1H), 2.41 (t, *J* = 11.7 Hz, 1H), 2.13 – 2.06 (m, 1H), 1.80 (t, *J* = 12.4 Hz, 2H), 1.68 (d, *J* = 12.1 Hz, 1H), 1.59 – 1.44 (m, 11H), 1.37 – 1.16 (m, 10H), 0.81 (d, *J* = 6.2 Hz, 3H).

**Boc-methoxylycodine (2.41)**

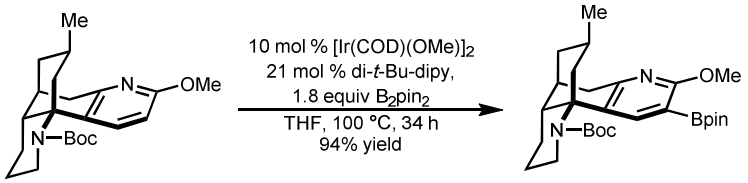



**1.105** **2.41**

To a solution of pyridone **1.105** (1.02 g, 2.86 mmol) in $CHCl_3$ (20 mL) was added $Ag_2CO_3$ (1.02 g, 3.71 mmol) and methyl iodide (MeI, 1.78 mL, 28.6 mmol). The solution

was stirred at room temperature for 24 h in the dark. Then, the solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography (10% EtOAc in hexanes) to provide Boc-methoxylycodine (**2.41**, 614 mg, 1.65 mmol, 58%) as a yellow oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.5 Hz, 1H), 6.49 (d, *J* = 8.5 Hz, 1H), 4.01 (d, *J* = 13.2 Hz, 1H), 3.81 (s, 3H), 3.00 (dd, *J* = 18.9, 7.3 Hz, 1H), 2.66 (d, *J* = 12.6 Hz, 2H), 2.45 (d, *J* = 19.1 Hz, 1H), 2.34 (t, *J* = 13.0 Hz, 1H), 1.99 (s, 1H), 1.74 – 1.68 (t, *J* = 11.6 Hz, 2H), 1.61 (d, *J* = 11.8 Hz, 1H), 1.43 (s, 11H), 1.29 – 1.13 (m, 3H), 0.76 (d, *J* = 5.8 Hz, 3H). **$^{13}$C NMR** (150 MHz, $CDCl_3$) δ 162.0, 156.0, 154.9, 136.6, 127.4, 108.7, 79.3, 63.5, 53.1, 48.1, 43.8, 43.7, 43.0, 35.0, 34.3, 28.5, 28.5, 27.5, 26.5, 25.7, 22.3. **IR** (film): v = 2924, 2361, 1699, 1676, 1596, 1577, 1476, 1421, 1389, 1365, 1260, 1154, 1074, 1033, 962 $cm^{-1}$. **HRMS (ESI)** calcd for $C_{22}H_{33}N_2O_3^+$ $(M+H)^+$: m/z 373.2486, found 373.2485.

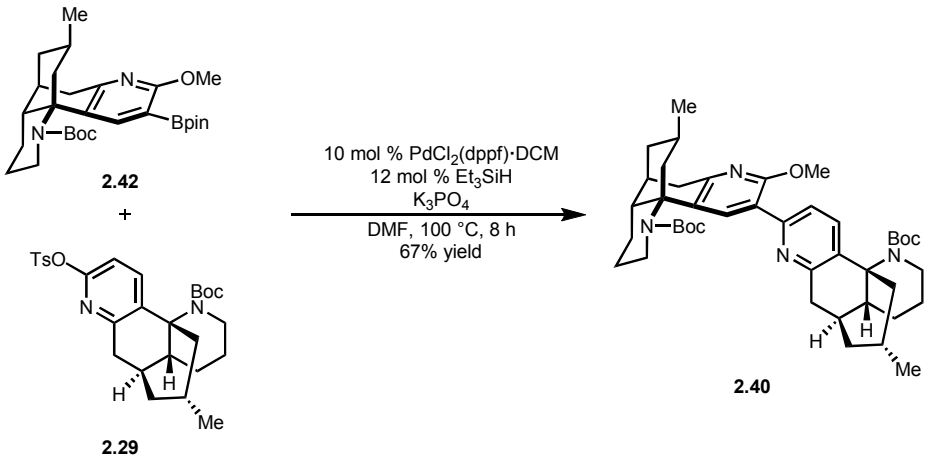
**Boronic Ester 2.42**




**2.41** **2.42**

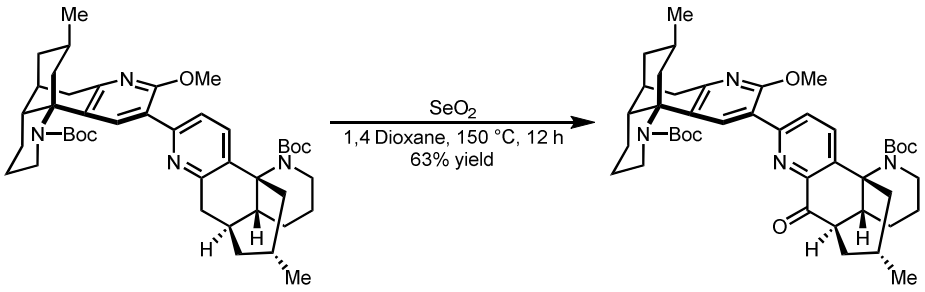
Boc-methoxylycodine (**2.41)**, 860. mg, 2.31 mmol), $[Ir(COD)(OMe)]_2$ (153 mg, 0.231 mmol), 4,4′-Di-*tert*-butyl-2,2′-dipyridyl (di-*t*-Bu-dipy, 130. mg, 0.485 mmol), and Bis(pinacolato)diboron ($B_2pin_2$, 1.06 g, 4.16 mmol) were added to a Schlenk flask. The flask was fitted with a Teflon screw-cap and a septum and was evacuated/backfilled with $N_2$ (3 X). THF (23 mL) was added via the septum. The vessel was sealed and the reaction mixture was heated to 100 °C and stirred for 36 h. After cooling to room temperature, the solvent was removed under reduced pressure, and the crude mixture was heated under vacuum for 2 h at 100 °C to remove various byproducts. The resultant residue was loaded onto a basic alumina column (Fisher Scientific, Brockman activity I, 60-365 mesh), where it was washed with a solution of 20% EtOAc in hexanes (3 X 75 mL) to remove excess $B_2pin_2$ and unreacted **2.41**. Then the product was eluted from the column (20% MeOH in $Et_2O$). After the solvent was removed under reduced pressure, boronic ester (**2.42**, 1.08 g, 2.17 mmol, 94%) was obtained as a red oil. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 4.11 (d, *J* = 12.4 Hz, 1H), 3.92 (s, 3H), 3.06 (dd, *J* = 19.2, 7.4 Hz, 1H), 2.88 (d, *J* = 11.2 Hz, 1H), 2.51 (d, *J* = 19.2 Hz, 1H), 2.44 (td, *J* = 13.7, 12.3, 2.7 Hz, 1H), 2.10 – 2.04 (m, 2H), 1.77 (d, *J* = 12.4 Hz, 1H), 1.68 (d, *J* = 11.6 Hz, 2H), 1.52 (s, 9H), 1.35 – 1.17 (m, 16H), 0.83 (d, *J* = 6.0 Hz, 3H). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 165.3, 158.2, 156.6, 144.7, 126.8, 83.5, 79.6, 63.5, 53.6, 48.1, 43.9, 43.0, 35.2, 34.4, 28.6, 27.6, 26.5, 25.7, 24.8, 24.8, 24.5, 22.3. **IR** (film): v = 2976, 2926, 2869, 2357, 2250, 1701, 1596, 1563, 1459, 1395, 1356, 1320, 1301, 1275, 1213, 1144, 1067, 1049, 1036, 984, 961, 918, 858, 834, 820, 780, 733, 703 $cm^{-1}$. **HRMS (ESI)** calcd for $C_{28}H_{43}BN_2O_5^+$ $(M+H)^+$: m/z 499.3338, found 499.3341.

**Boc-methoxycomplanadine A (2.40)**




$PdCl_2$(dppf)·DCM (177 mg, 0.217 mmol, 10 mol %), 4 Å molecular sieves (1.10 g), and freshly flame-dried $K_3PO_4$ (1.38 g, 6.50 mmol) were added to a flame-dried Schlenk flask equipped with a stir bar. The flask was fitted with a Teflon screw-cap and septum and was evacuated/backfilled with $N_2$ (3 X). Then, a solution of $Et_3SiH$ (42 µL, 0.26 mmol, 12 mol %) in anhydrous DMF (11 mL) was added to the vessel via a syringe. The flask was sealed, and the reaction mixture heated to 100 °C and stirred for 30 min in order to pre-form the active Pd(0) catalyst. We found that this procedure was necessary to obtain high yields. Then, the flask was cooled to room temperature and a solution of **2.29** (1.08 g, 2.17 mmol) and **2.42** (1.11 g, 2.17 mmol) in anhydrous DMF (11 mL) was added to the reaction vessel via the septum. The reaction mixture was heated to 100 °C and stirred an additional 8 h. Finally, the solvent was removed under reduced pressure, and the crude product was purified by silica gel chromatography (20% EtOAc in hexanes) to yield Boc-methoxycomplanadine A (**2.40**, 1.03 g, 1.44 mmol, 67%) as a white foam. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.51 (d, *J* = 8.1 Hz, 1H), 4.15 (td, *J* = 15.9, 2.4 Hz, 2H), 3.99 (s, 3H), 3.17 (dd, *J* = 18.7, 7.2 Hz, 1H), 3.11 (dd, *J* = 19.0, 7.4 Hz, 1H), 2.92 (d, *J* = 14.8 Hz, 1H), 2.74 (dd, *J* = 13.0, 2.0 Hz, 1H), 2.70 (d, *J* = 18.7 Hz, 1H), 2.58 (d, *J* = 19.0 Hz, 1H), 2.55 – 2.46 (m, 2H), 2.11 (d, *J* = 3.4 Hz, 1H), 1.87 – 1.78 (m, 3H), 1.77 – 1.66 (m, 4H), 1.55 (s, 14H), 1.52 (s, 11H), 1.45 – 1.29 (m, 6H), 1.25 (s, 1H), 0.84 (d, *J* = 5.5 Hz, 3H), 0.81 (d, *J* = 6.2 Hz, 3H). **$^{13}$C NMR** (150 MHz, $CDCl_3$) δ 159.1, 157.5, 156.7, 156.2, 155.1, 151.9, 137.7, 133.8, 133.6, 128.1, 122.5, 121.3, 79.7, 79.6, 64.0, 63.7, 53.3, 48.5, 48.3, 44.1, 44.0, 43.8, 43.7, 43.1, 43.0, 35.2, 34.9, 34.5, 34.5, 28.7, 28.6, 27.7, 27.7, 26.6, 26.6, 25.7, 22.4, 22.3. **IR** (film): v = 2925, 2250, 1701, 1572, 1458, 1429, 1366, 1277, 1259, 1157, 1115, 1075, 1036, 983, 937, 843, 816, 733 $cm^{-1}$. **HRMS (ESI)** calcd for $C_{43}H_{63}N_4O_5^+$ $(M+H)^+$: m/z 713.4636, found 713.4625.

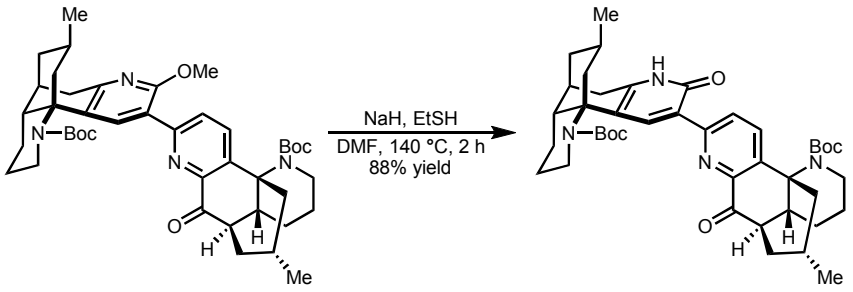
**Boc-methoxycomplanadine B (2.43)**




**2.40** **2.43**

To an oven-dried Schlenk flask was added Boc-methoxycomplanadine A (**2.40**, 1.03 g, 1.44 mmol) and $SeO_2$ (401 mg, 3.61 mmol). The flask was equipped with an oven-dried stir bar, fitted with a septum and a Teflon screw-cap, evacuated/backfilled with $N_2$ (3 X). Anhydrous 1,4-Dioxane (14 mL) was introduced to the reaction vessel via the septum. Then, the flask was sealed, and the reaction mixture was heated to 150 °C and stirred for 12 h. After cooling the reaction mixture to room temperature, the resulting solution was filtered over sand and the solvent removed under reduced pressure. The product was purified by silica gel chromatography (20% EtOAc in hexanes) to yield Boc-methoxycomplanadine B (**2.43**, 662 mg, 0.911 mmol, 63%) as a white foam. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.3 Hz, 1H), 7.98 (s, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 4.22 (t, *J* = 14.9 Hz, 2H), 4.01 (s, 3H), 3.15 (dd, *J* = 19.1, 7.4 Hz, 1H), 3.02 – 2.94 (m, 2H), 2.84 (s, 1H), 2.65 (d, *J* = 14.9 Hz, 1H), 2.60 – 2.49 (m, 2H), 2.18 – 2.12 (m, 2H), 2.04 (t, *J* = 12.8 Hz, 1H), 1.91 (d, *J* = 13.0 Hz, 1H), 1.85 (d, *J* = 12.0 Hz, 1H), 1.73 (t, *J* = 15.4 Hz, 4H), 1.57 (s, 22H), 1.51 – 1.32 (m, 3H), 1.28 (s, 4H), 0.91 – 0.85 (m, 6H). **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 198.3, 158.9, 157.0, 156.2, 156.0, 154.6, 148.7, 140.0, 138.6, 135.3, 129.5, 128.6, 121.0, 80.5, 80.3, 63.8, 63.7, 53.8, 53.5, 52.0, 48.3, 47.0, 45.9, 44.1, 43.9, 43.9, 43.0, 37.8, 35.0, 34.5, 31.0, 29.3, 28.6, 28.5, 27.9, 27.8, 27.2, 26.7, 25.8, 25.2, 22.3, 22.2. **IR** (film): v = 2926, 2248, 1701, 1586, 1570, 1459, 1421, 1366, 1297, 1269, 1255, 1213, 1157, 1117, 1076, 1035, 976, 915, 853, 773, 732, 646 $cm^{-1}$. **HRMS (ESI)** calcd for $C_{43}H_{59}N_4O_6^+$ $(M+H)^+$: m/z 727.4429, found 727.4425.

**Pyridone 2.44**

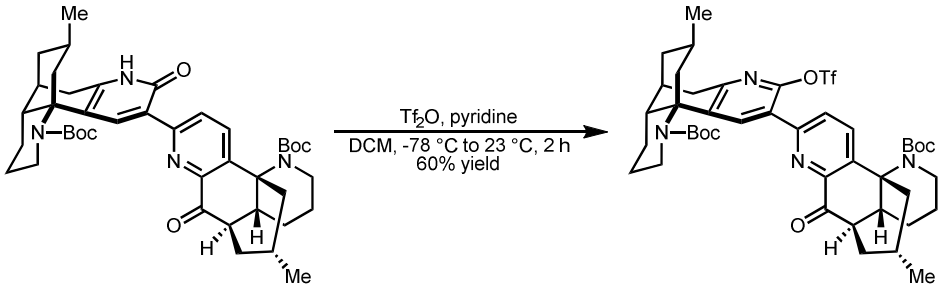



**2.43** **2.44**

Ethanethiol (407 µL, 5.50 mmol) was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 110. mg, 2.75 mmol) in anhydrous DMF (2.8 mL) at room temperature in an open reaction vessel. The mixture was allowed to stir for 10 min. Then, Boc-methoxycomplanadine B (**2.43**, 200. mg, 0.275 mmol) was added in one portion. The reaction vessel was sealed and heated to 150 °C and stirred for 12 h. After the solution was cooled to room temperature, the solvent was removed under

reduced pressure. The resultant residue was dissolved in saturated aqueous $NH_4Cl$ (10 mL) and shaken vigorously until the bright yellow color dissipated. The aqueous solution was then extracted with DCM (3 X). The combined organic fractions were collected and dried with $MgSO_4$ and filtered over sand. Then the solvent was removed under reduced pressure. The product was purified using silica gel chromatography (100% $Et_2O$ to 20% MeOH in $Et_2O$) to yield pyridone **2.44** (173 mg, 0.243 mmol, 88%) as a white foam. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 12.59 (s, 1H), 8.51 (s, 1H), 8.18 (s, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 4.23 (d, *J* = 14.1 Hz, 1H), 4.18 (d, *J* = 13.2 Hz, 1H), 3.07 (dd, *J* = 18.4, 6.9 Hz, 1H), 2.96 (dd, *J* = 30.8, 11.2 Hz, 2H), 2.82 (s, 1H), 2.62 – 2.45 (m, 3H), 2.21 – 2.13 (m, 2H), 2.04 (t, *J* = 12.7 Hz, 1H), 1.89 (d, *J* = 13.3 Hz, 1H), 1.83 (d, *J* = 12.3 Hz, 1H), 1.72 (t, *J* = 10.2 Hz, 4H), 1.65 – 1.47 (m, 23H), 1.46 – 1.19 (m, 8H), 0.89 (d, *J* = 6.4 Hz, 3H), 0.86 (d, *J* = 6.2 Hz, 3H). **IR** (film): v = 2926, 2870, 2246, 1701, 1647, 1587, 1561, 1477, 1456, 1390, 1366, 1316, 1271, 1253, 1158, 1145, 1117, 1079, 916, 855, 732 $cm^{-1}$. **HRMS (ESI)** calcd for $C_{42}H_{57}N_4O_6^+$ $(M+H)^+$: m/z 713.4273, found 713.4262.

**Triflate 2.45**




**2.44** **2.45**

A flame-dried 4 mL vial fitted with a septum was evacuated/backfilled with $N_2$ (3 X). A solution of pyridone **2.44** (153 mg, 2.15 mmol) in DCM (0.3 mL) and pyridine were (174 µL, 2.15 mmol) added to the vial via a syringe. The reaction mixture was cooled to -78 °C and $Tf_2O$ (54 µL, 0.32 mmol) was added dropwise. After stirring for 10 min at -78 °C, the solution was removed from the -78 °C bath and allowed to warm to room temperature over 2 h. The solvent was removed under reduced pressure, and the crude mixture was purified by silica gel chromatography (20% EtOAc in hexanes) to yield triflate **2.45** (109. mg, 0.30 mmol, 60%) as a clear oil. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.87 (q, *J* = 8.3 Hz, 2H), 4.19 (t, *J* = 15.1 Hz, 2H), 3.19 (dd, *J* = 19.7, 7.4 Hz, 1H), 2.96 (d, *J* = 13.0 Hz, 2H), 2.85 (s, 1H), 2.70 (d, *J* = 19.7 Hz, 1H), 2.49 (dtd, *J* = 14.1, 11.7, 10.6, 3.5 Hz, 2H), 2.16 (s, 2H), 2.06 (t, *J* = 12.7 Hz, 1H), 1.89 (t, *J* = 10.8 Hz, 2H), 1.83 – 1.68 (m, 4H), 1.65 – 1.41 (m, 23H), 1.41 – 1.15 (m, 6H), 0.89 (d, *J* = 6.4 Hz, 3H), 0.86 (d, *J* = 6.2 Hz, 3H). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 198.0, 158.3, 156.7, 151.6, 150.7, 149.1, 141.4, 140.6, 136.9, 136.6, 128.7, 124.2, 80.6, 80.4, 63.6, 51.9, 48.0, 46.8, 45.7, 44.1, 43.6, 42.6, 37.7, 34.4, 34.0, 28.5, 28.3, 27.8, 27.6, 27.2, 26.5, 25.4, 25.1, 22.1, 22.1. **IR** (film): v = 2928, 2860, 2359, 2250, 1701, 1609, 1587, 1561, 1456, 1423, 1367, 1270, 1251, 1213, 1159, 1080, 1033, 1001, 984, 940, 912, 867, 825, 767, 733, 647, 605 $cm^{-1}$. **HRMS (ESI)** calcd for $C_{43}H_{56}F_3N_4O_8S^+$ $(M+H)^+$: m/z 845.3765, found 845.3758.

## 2.7 References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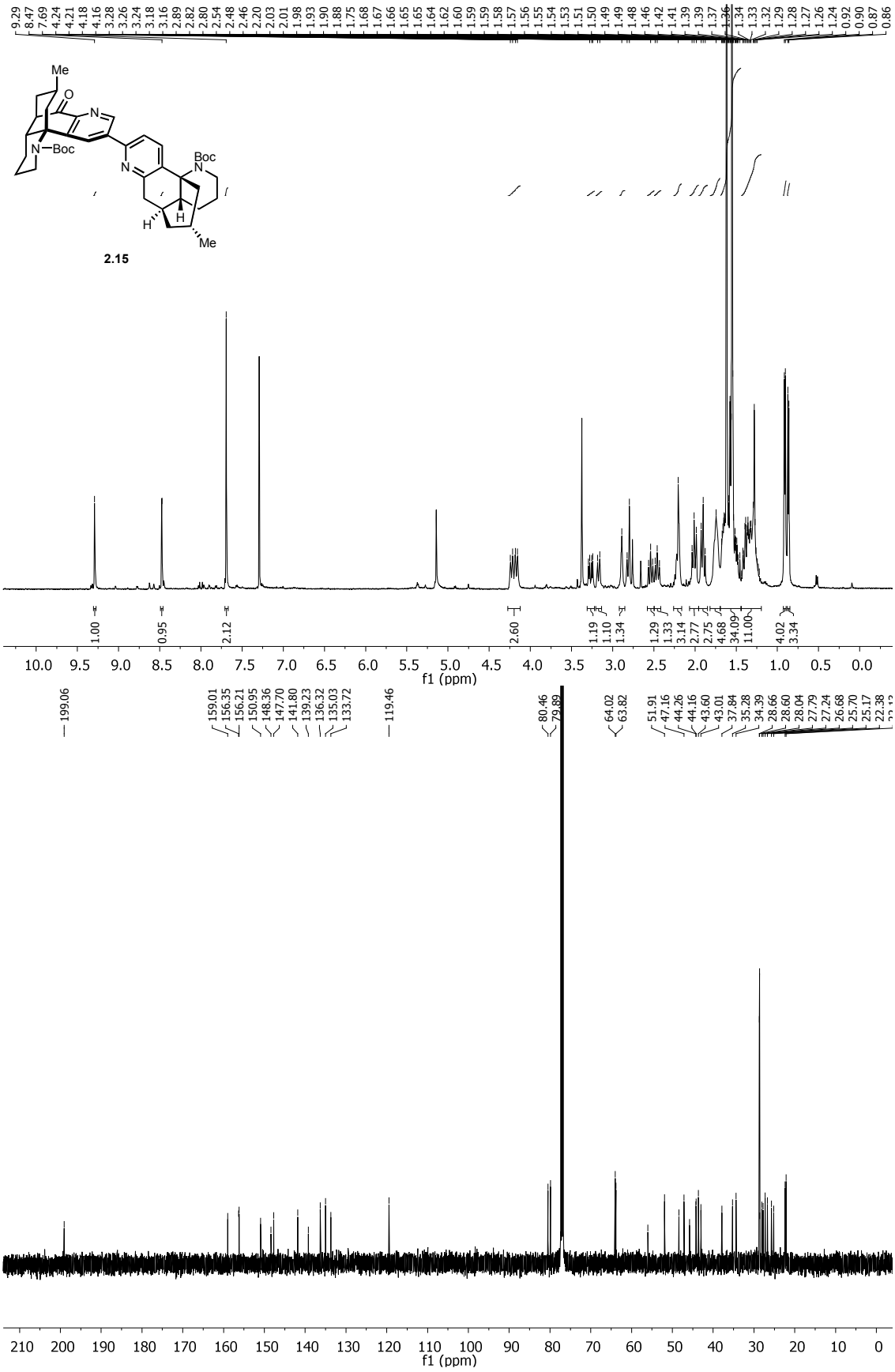
# APPENDIX ONE

## Spectra Relevant to Chapter 2:

Synthesis of Complanadine B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H
H
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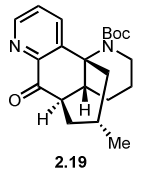
f1 (ppm)


Boc
N
N
O
H
H
Me

**2.19**


8.72
8.72
8.71
8.71
7.77
7.77
7.75
7.75
7.53
7.52
7.51
7.50
4.13
4.09
2.96
2.93
2.81
2.38
2.15
2.12
2.01
1.98
1.95
1.66
1.50
1.22
0.88
0.84
0.97
0.92
0.96
1.02
1.03
1.01
1.06
1.15
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1.05
11.20
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3.00
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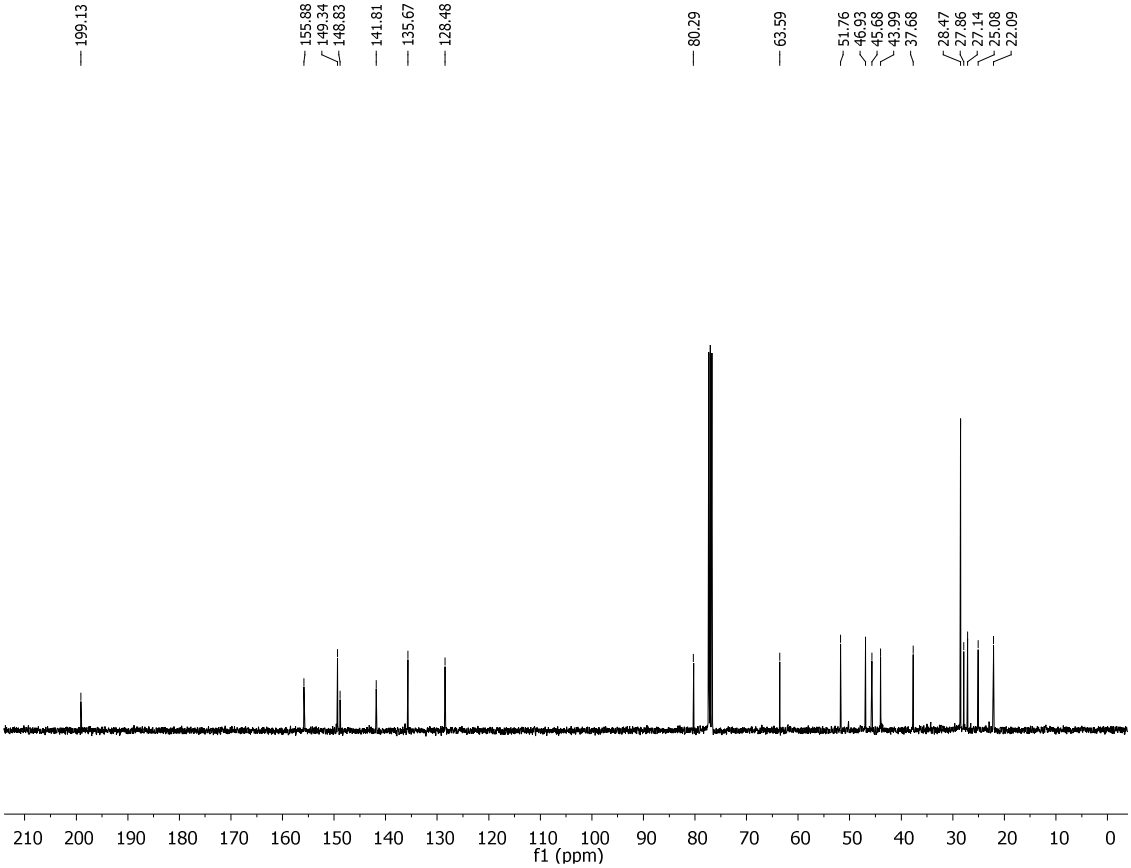
f1 (ppm)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43.99
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28.47
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27.14
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22.09
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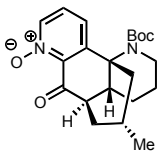
f1 (ppm)


Boc
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O
N
O
H
H
Me

**2.21**


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2.41
2.37
2.09
2.06
2.04
2.00
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1.94
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0.96
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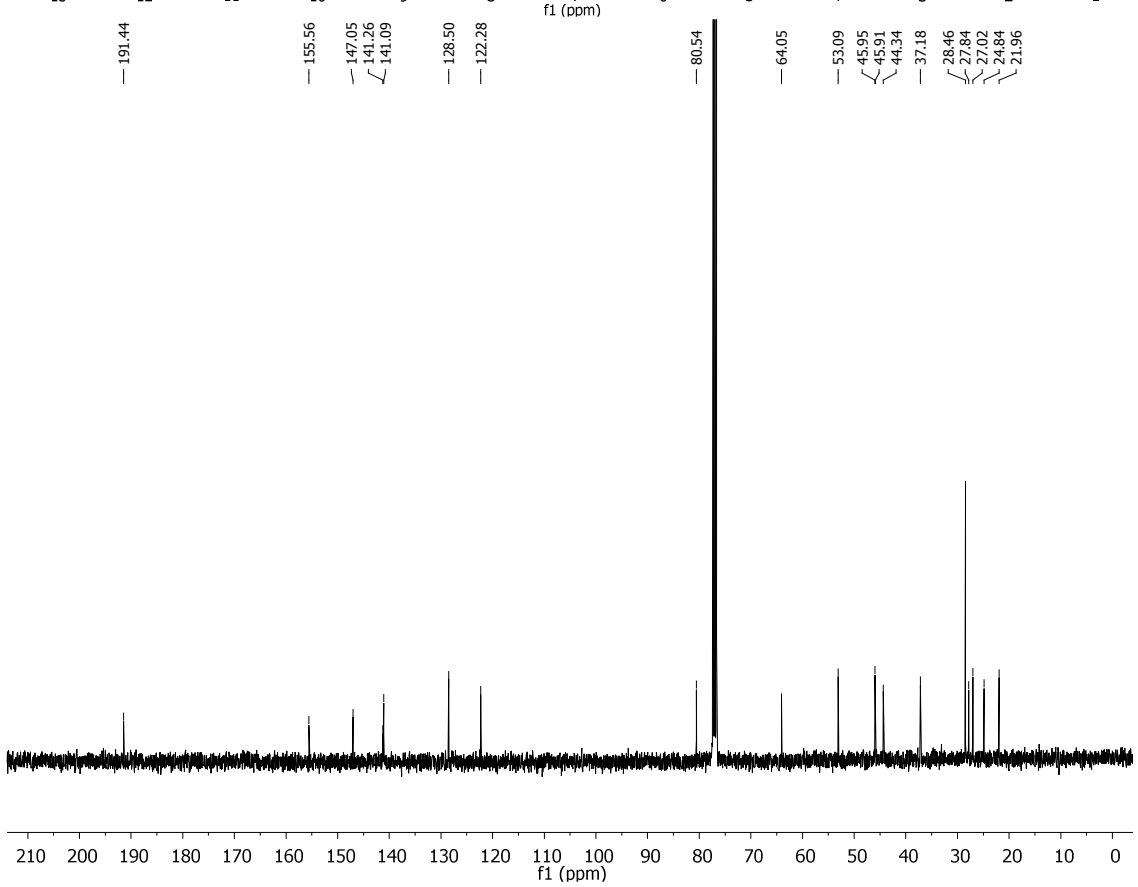
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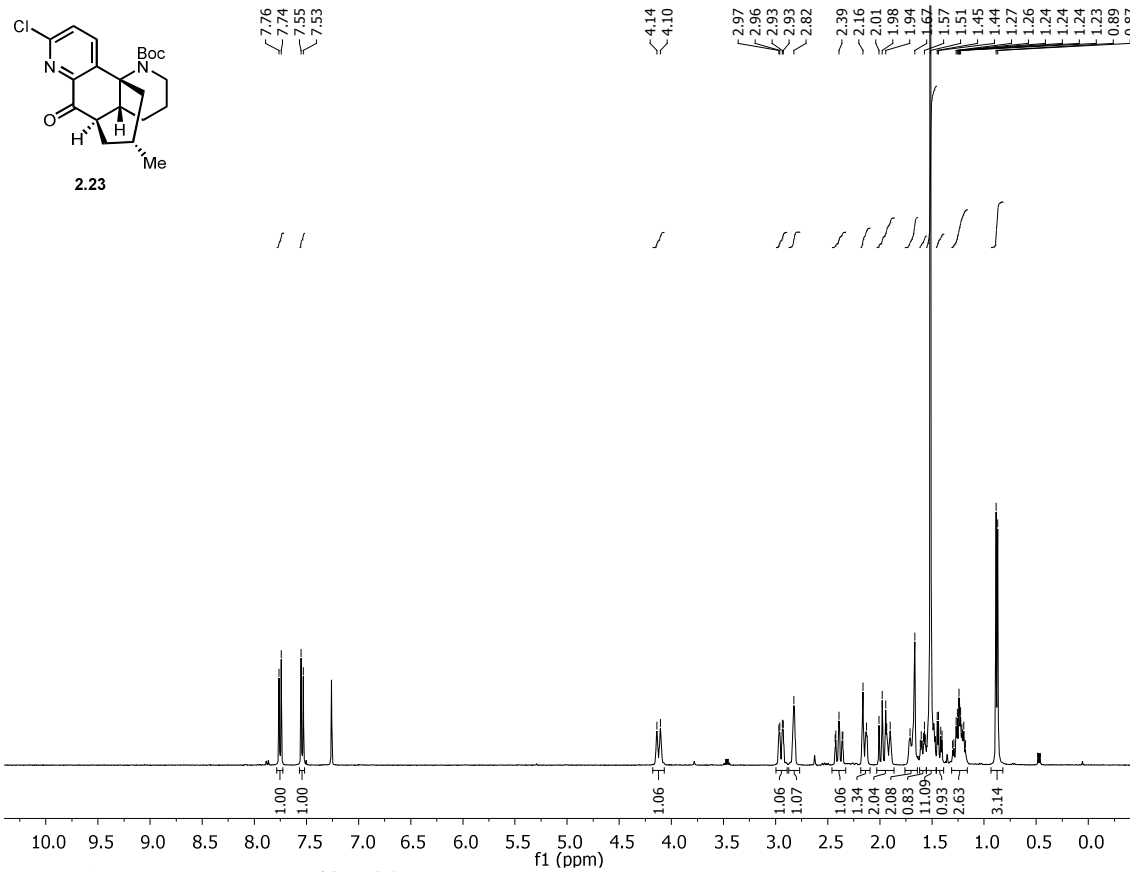
f1 (ppm)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1.51
1.45
1.44
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1.26
1.24
1.24
1.24
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1.00
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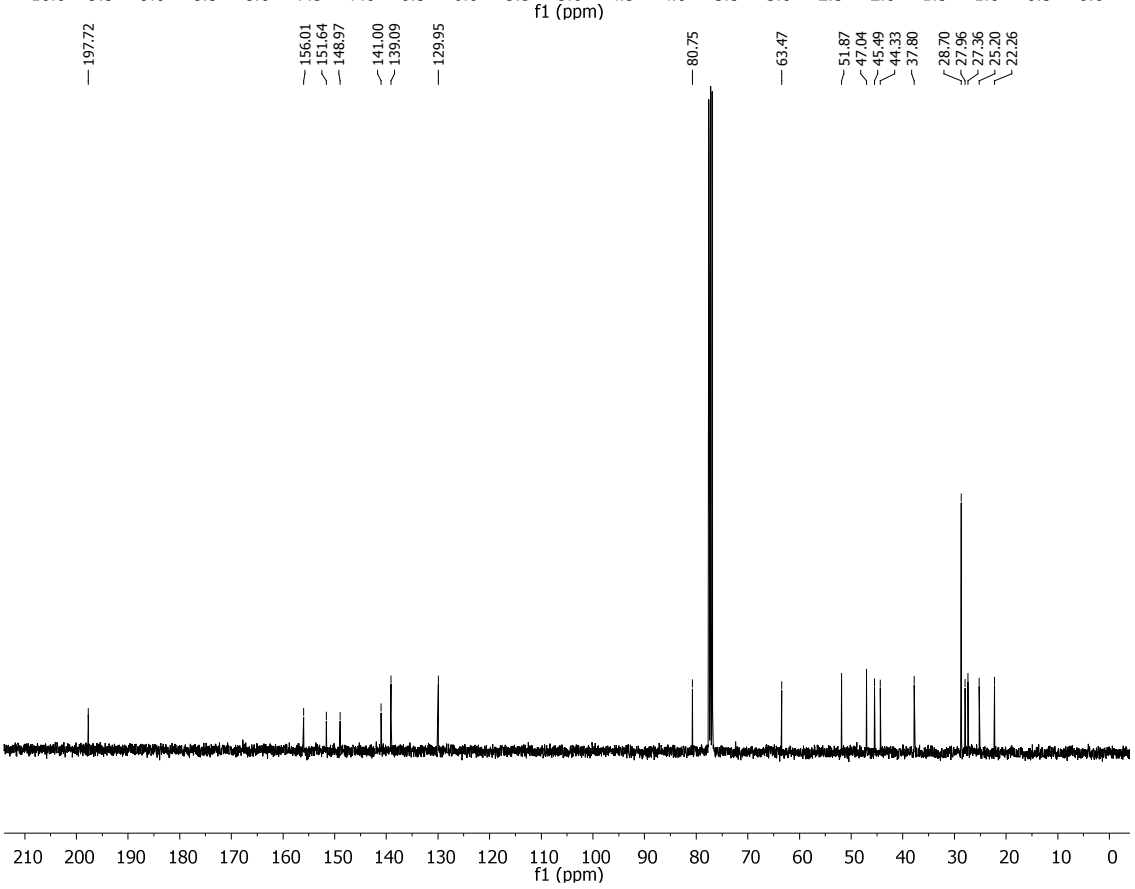
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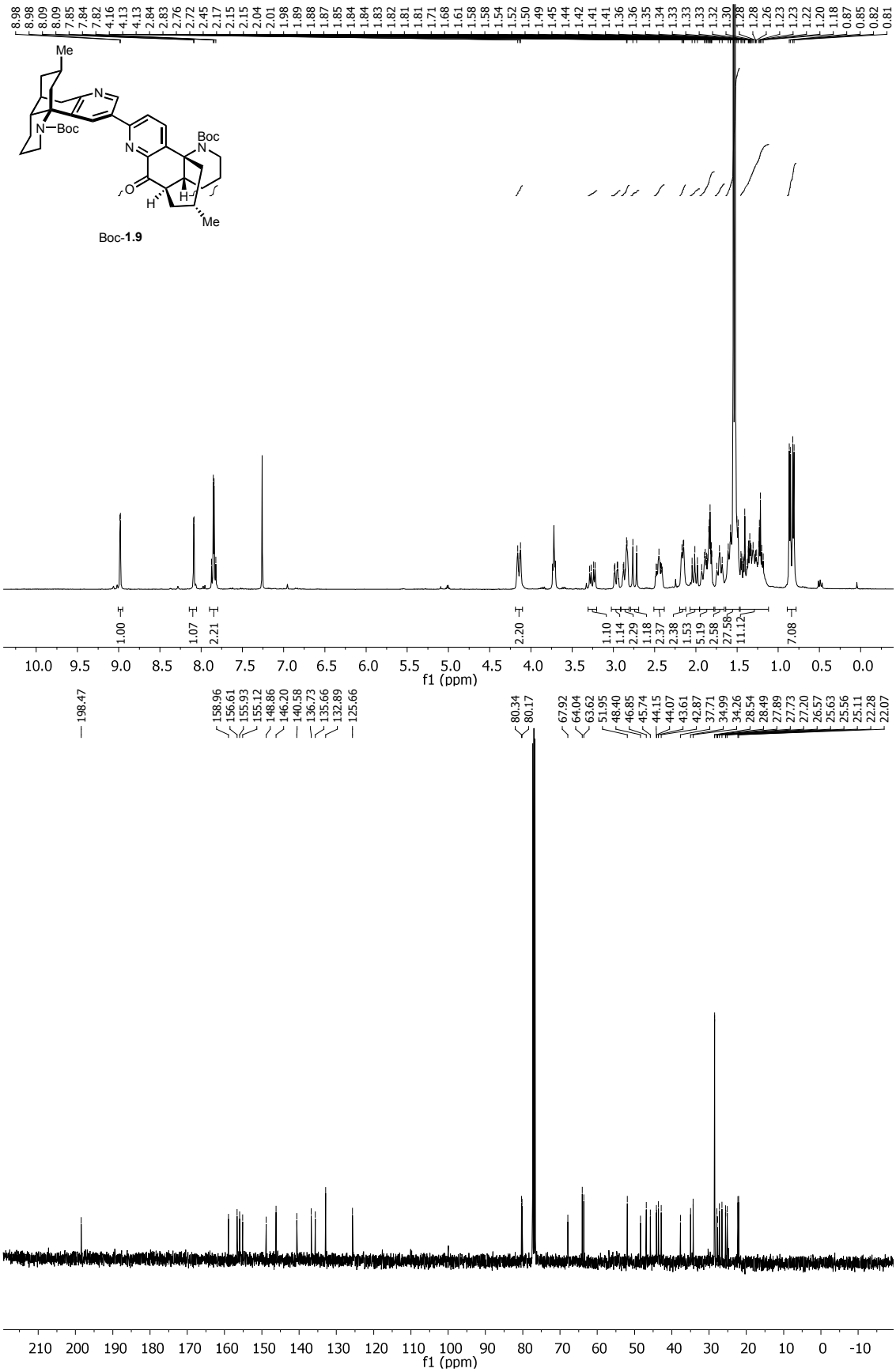
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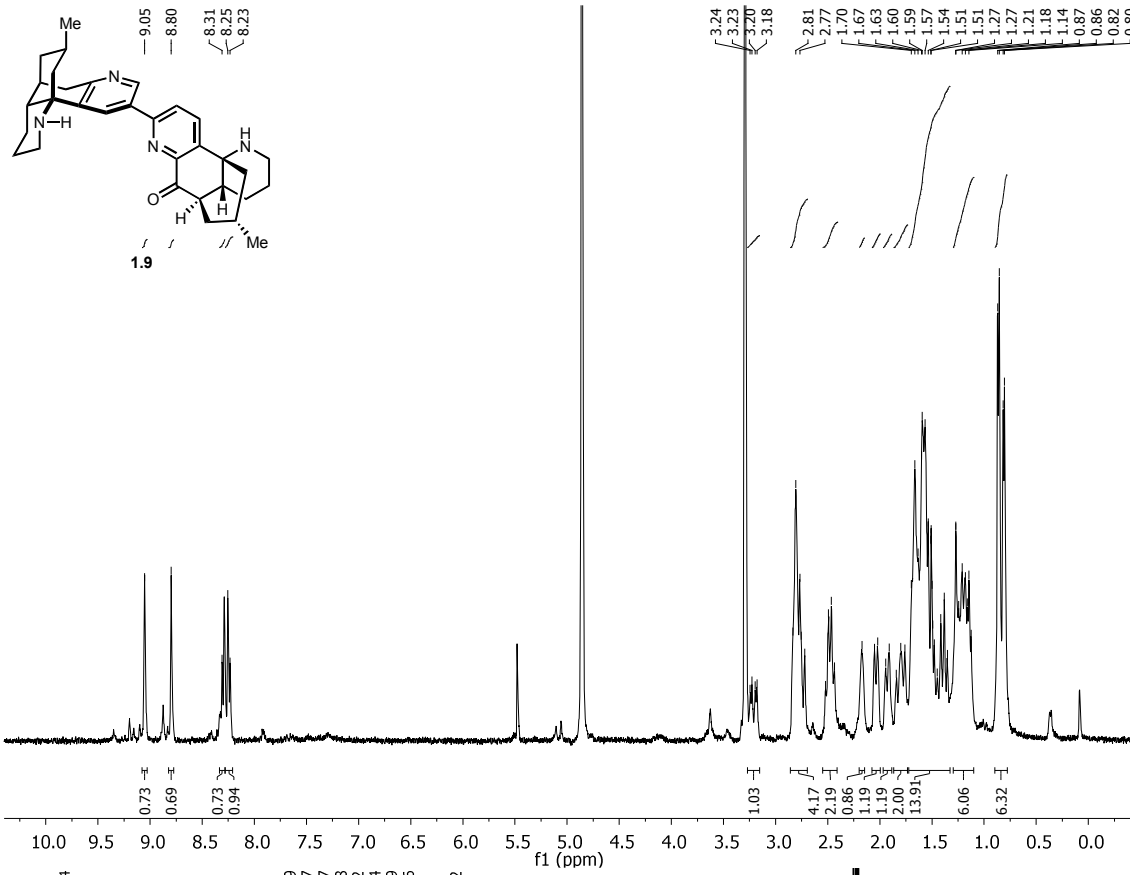
f1 (ppm)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1.19
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13.91
6.06
6.32
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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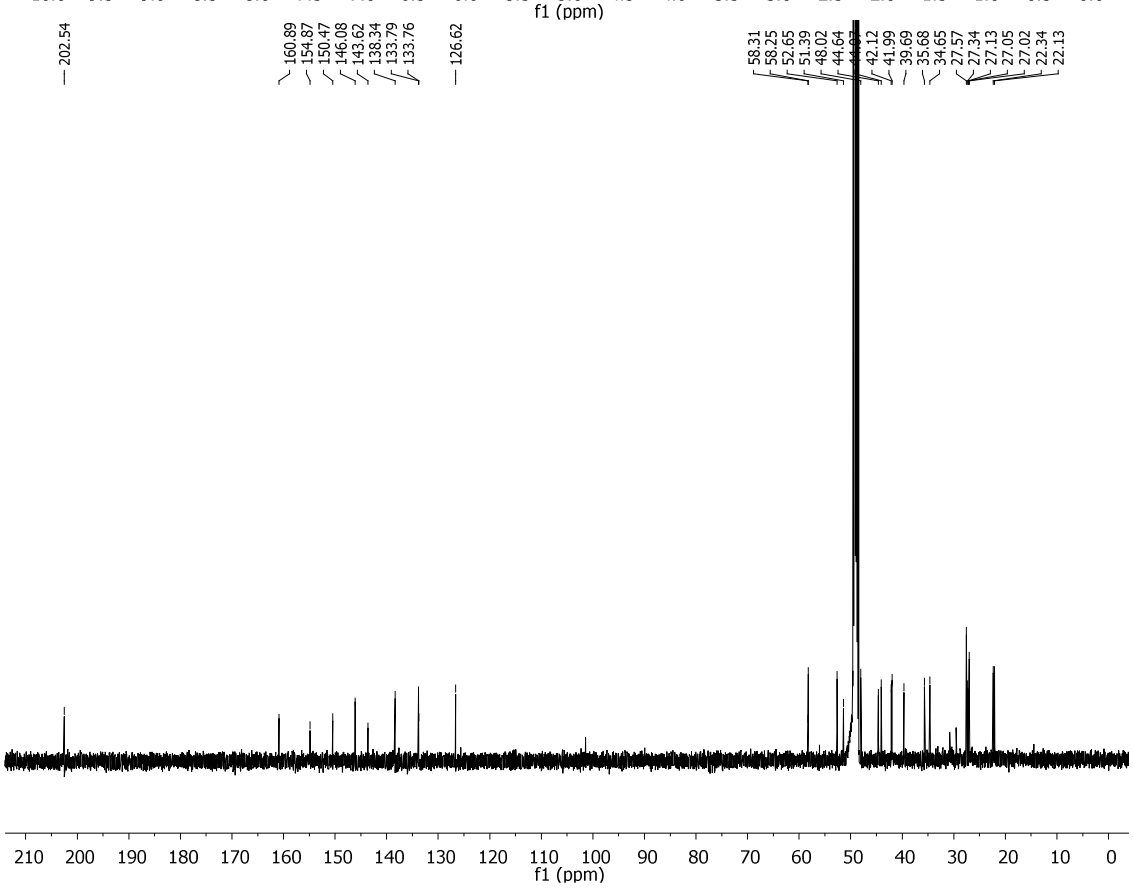
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34.65
27.57
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27.02
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22.13
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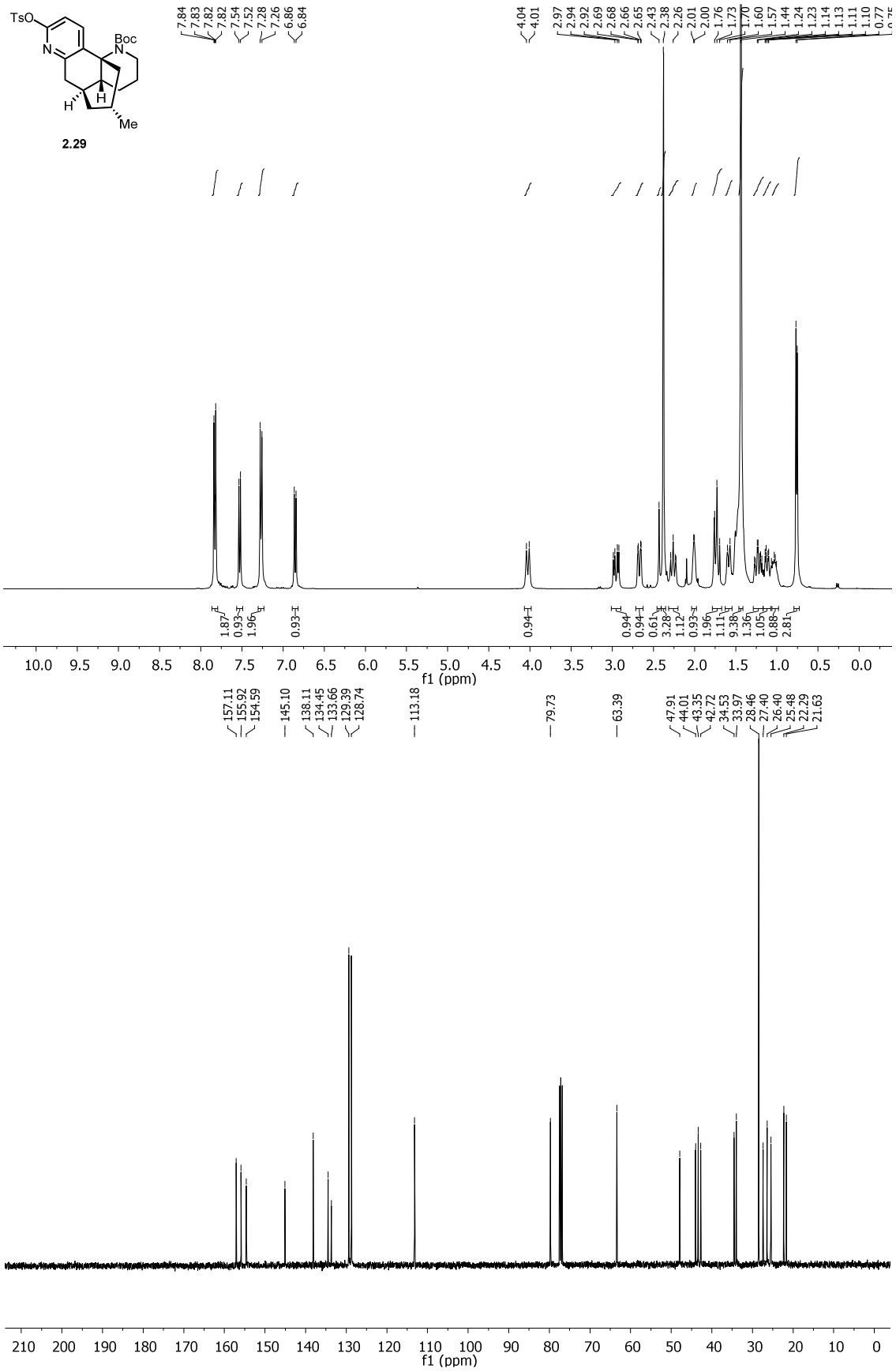
f1 (ppm)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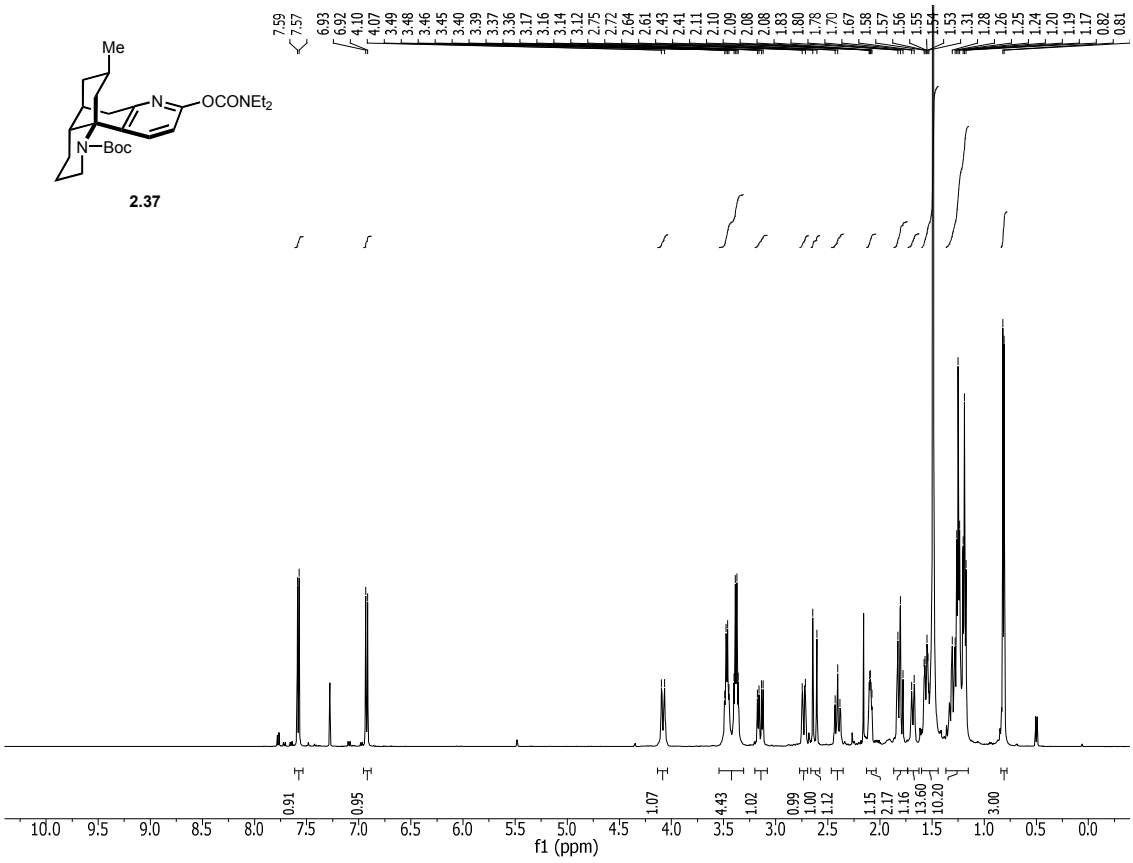
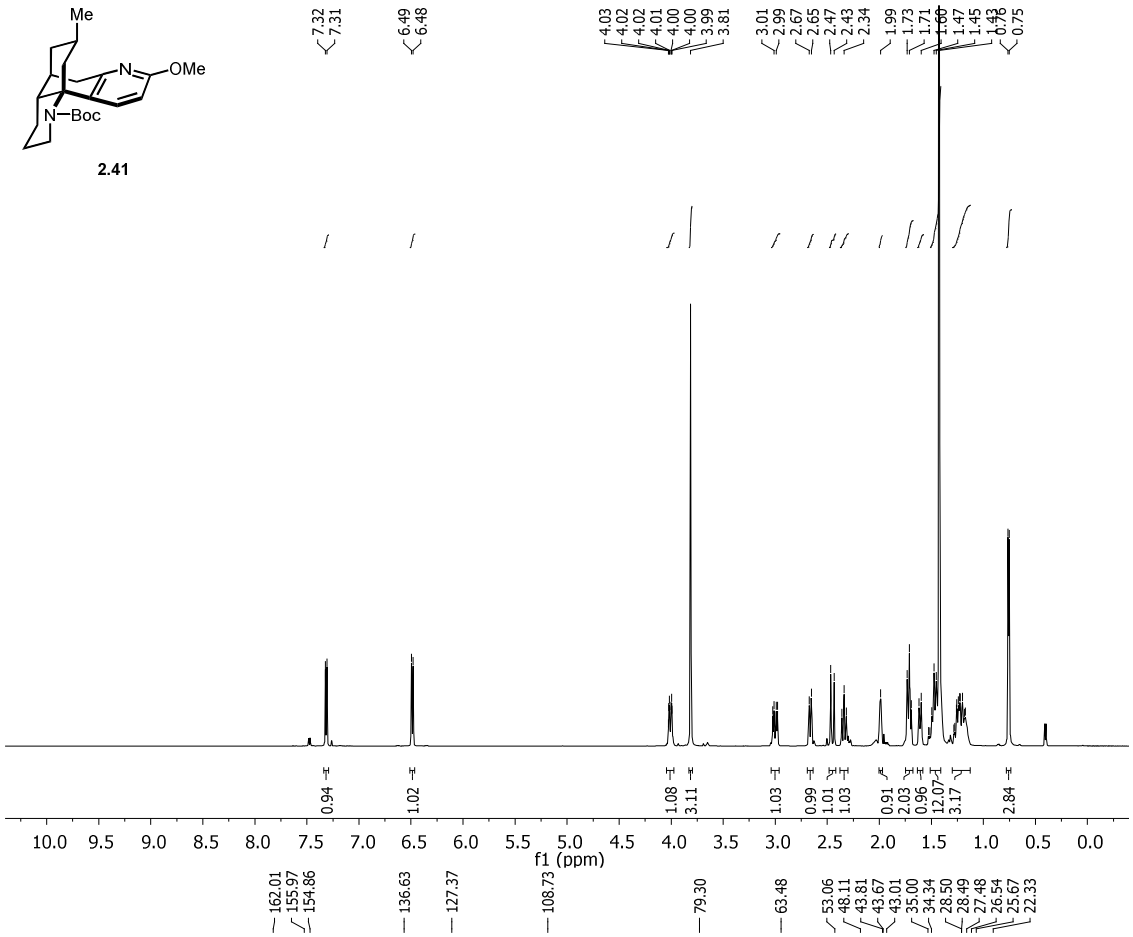
f1 (ppm)


Me
N
OCONEt2
N
Boc
2.37
f1 (ppm)


Me
N
OMe
N—Boc
2.41
7.32
7.31
6.49
6.48
4.03
4.02
4.02
4.01
4.00
4.00
3.99
3.81
3.01
2.99
2.67
2.65
2.47
2.43
2.34
1.99
1.73
1.71
1.66
1.47
1.45
1.43
0.76
0.75
0.94
1.02
1.08
3.11
1.03
0.99
1.01
1.03
0.91
2.03
0.96
12.07
3.17
2.84
f1 (ppm)
162.01
155.97
154.86
136.63
127.37
108.73
79.30
63.48
53.06
48.11
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35.00
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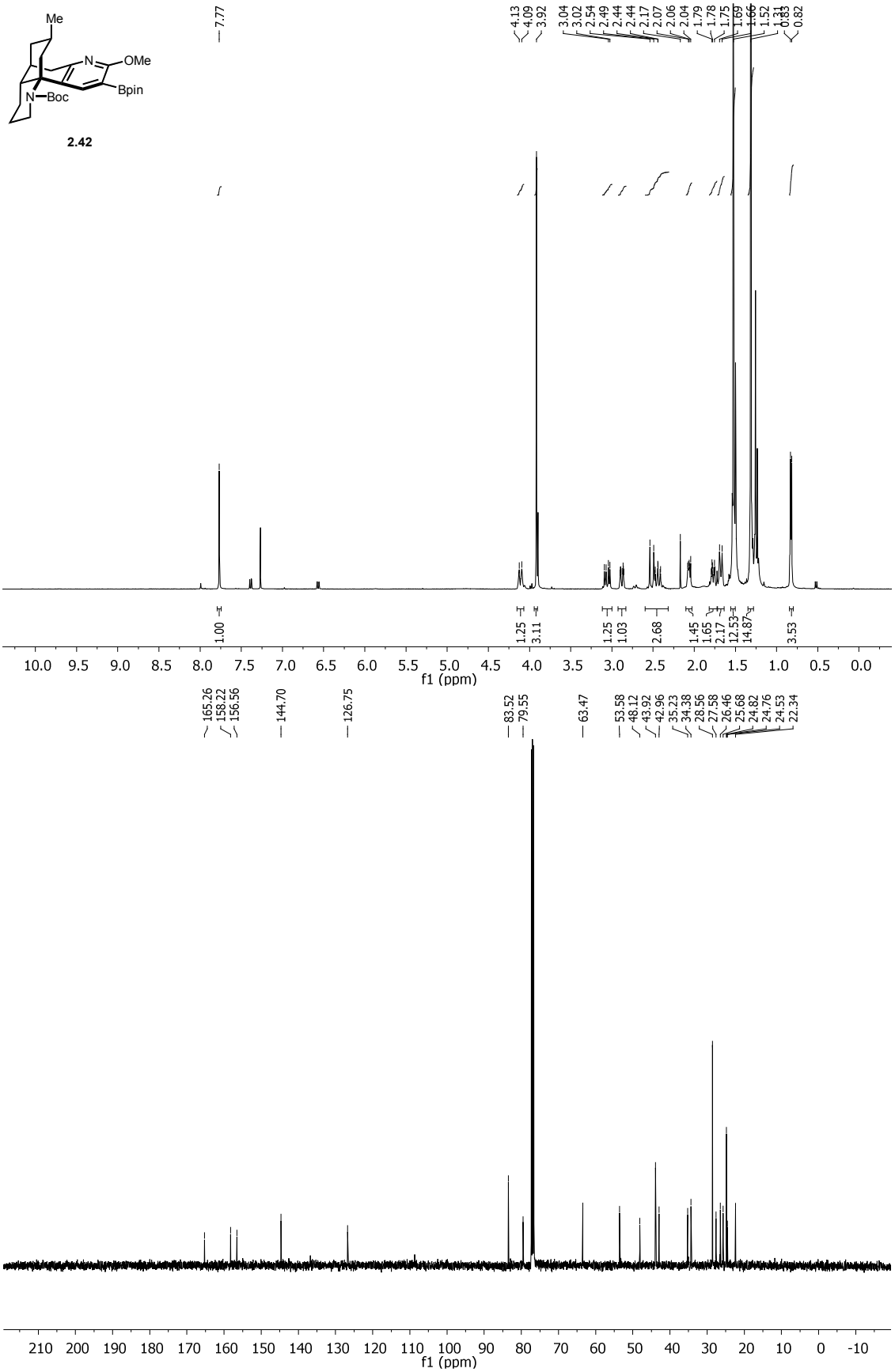
26.54
25.67
22.33
f1 (ppm)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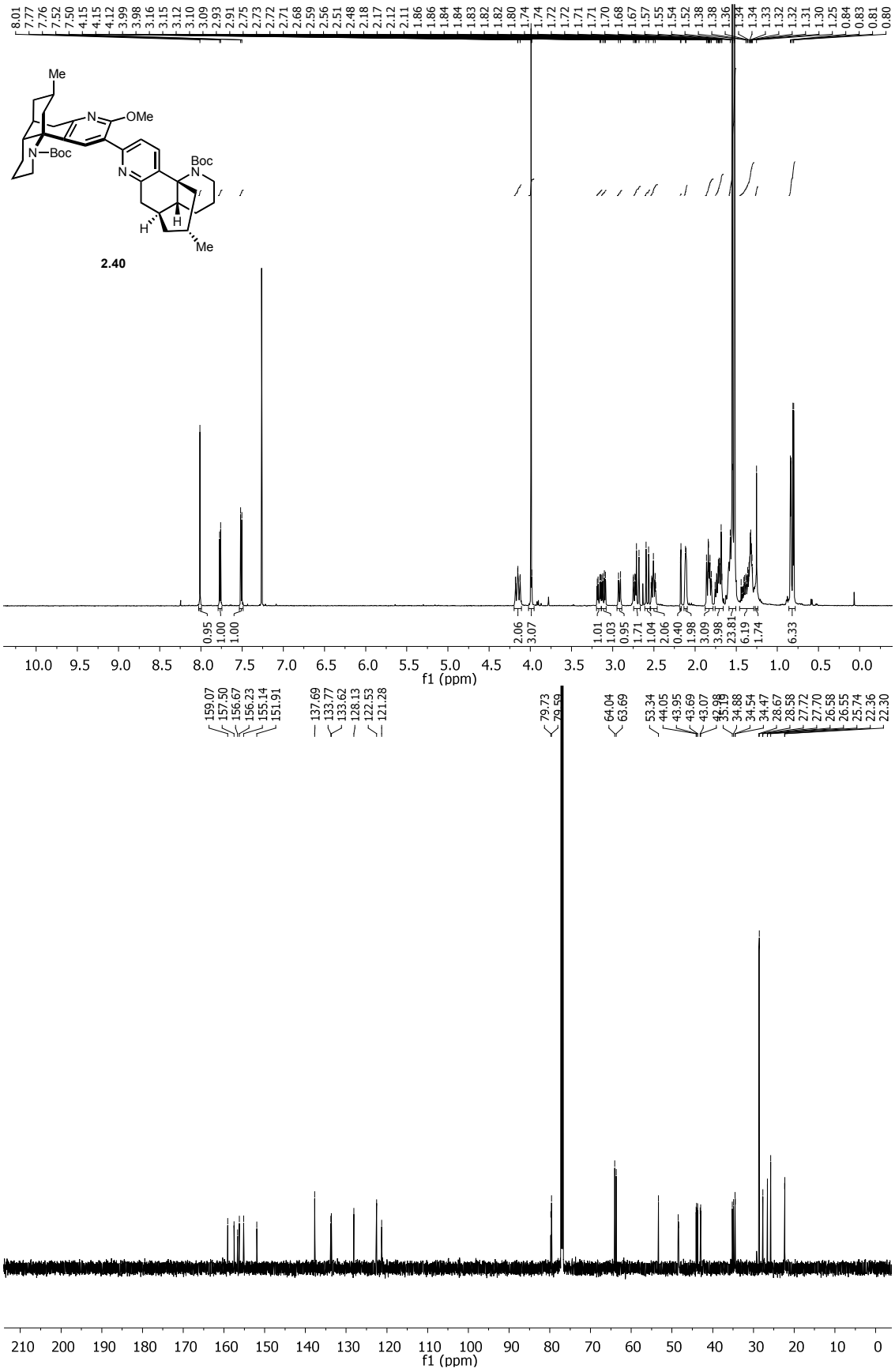
N
OMe
Bpin
N
Boc
2.42
f1 (ppm)
f1 (ppm)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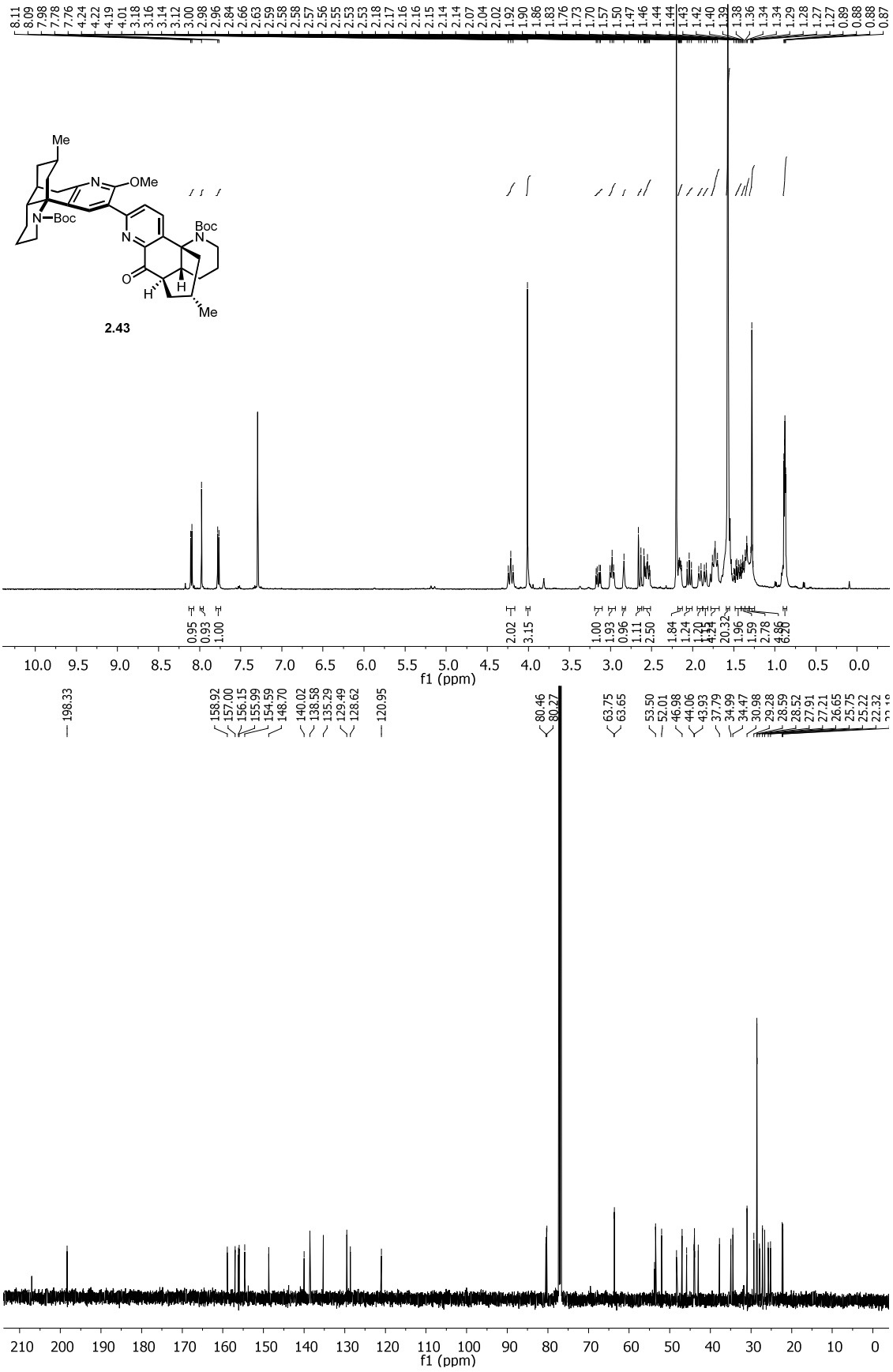
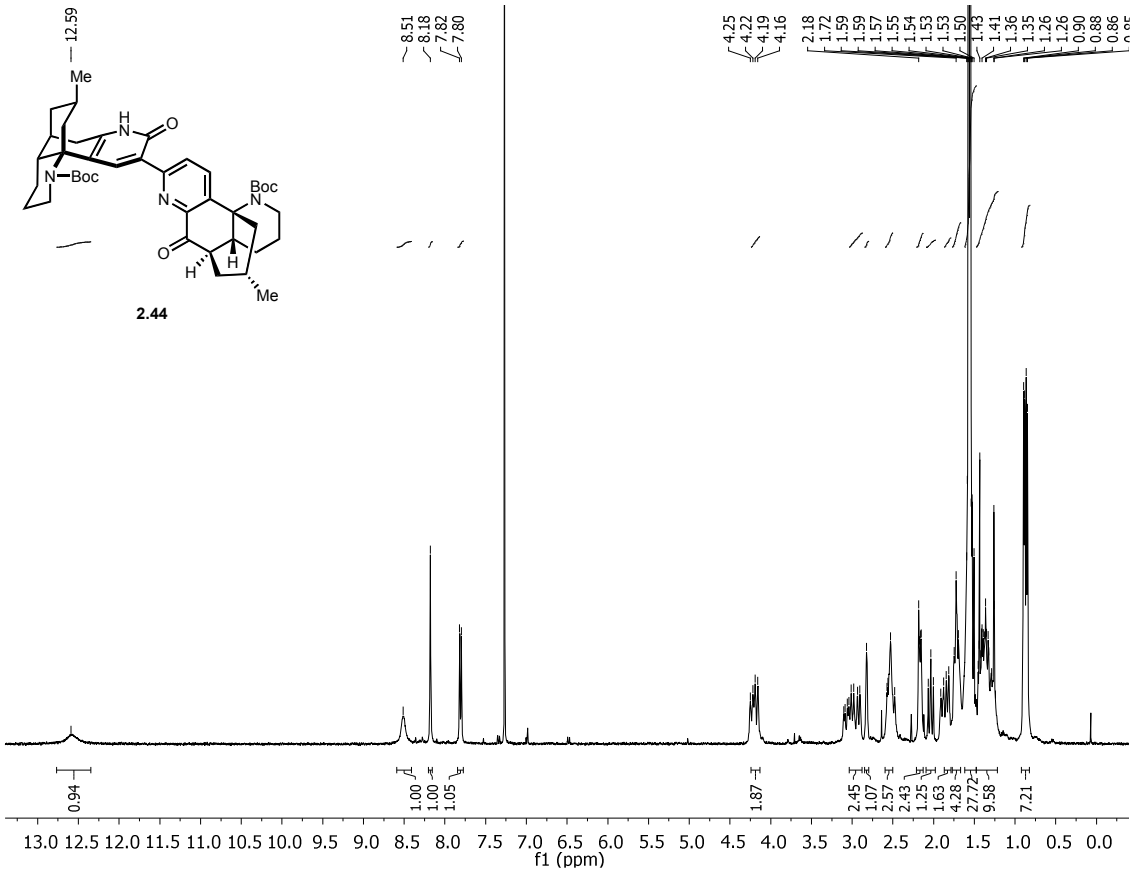
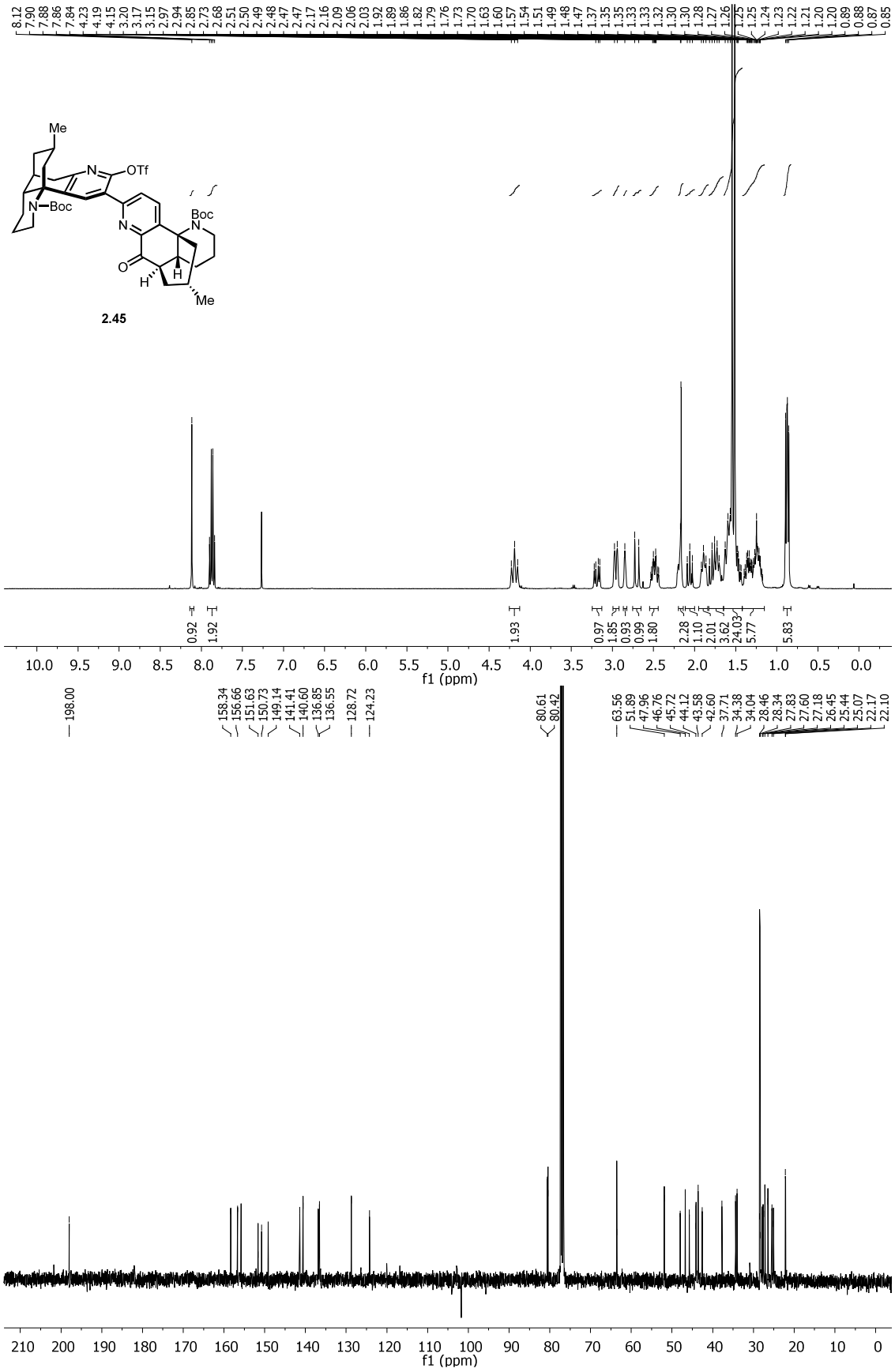
N
OMe
N—Boc
Boc
N
N
H
H
Me
2.40
f1 (ppm)
f1 (ppm)


Me
OMe
N
N–Boc
N
Boc
N
O
H
H
Me
2.43
f1 (ppm)
f1 (ppm)


12.59
Me
H
N
O
N
Boc
N
Boc
O
H
H
Me
2.44
8.51
8.18
7.82
7.80
4.25
4.22
4.19
4.16
2.18
1.72
1.59
1.59
1.57
1.55
1.54
1.53
1.53
1.50
1.43
1.41
1.36
1.35
1.26
1.26
0.90
0.88
0.86
0.94
1.00
1.00
1.05
1.87
2.45
1.07
2.57
2.43
1.25
1.63
4.28
27.72
9.58
7.21
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


Me
OTf
N
N–Boc
N
Boc
N
O
H
H
Me
2.45
f1 (ppm)
f1 (ppm)

## Chapter 3

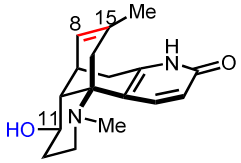
Synthesis of the Casuarinine Family of *Lycopodium* Alkaloids by the Late-Stage C-H Functionalization of Lycodine Derivatives

*A portion of this work was carried out in collaboration with Frederick M. Tomlin*

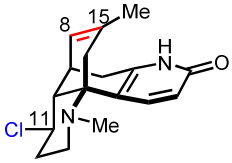
### 3.1 Introduction

In 2013, several new oxygenated alkaloids were isolated from *Lycopodiastrum casuarinoides* (Figure 3.1).[1] Like other lycodine-type natural products, some exhibited modest biological activity. For example, casuarinine C (**3.2**) and I (**3.5**) were shown to inhibit acetylcholine esterase ($IC_{50}$ = 20.9 and 12.1 μM, respectively), which is perhaps unsurprising due to their structural similarity to huperzine A (**1.1**). Casuarinine H (**3.4**) was shown to protect neurons from oxidative stress.

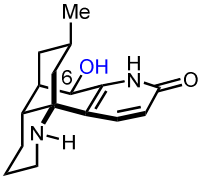
**Figure 3.1** Selected Lycodine-type Alkaloids Isolated from *Lycopodiastrum casuarinoides*.



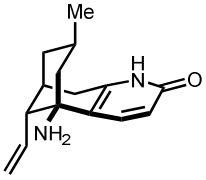

casuarinine A (**3.1**)



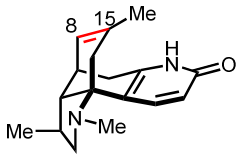

casuarinine C (**3.2**)



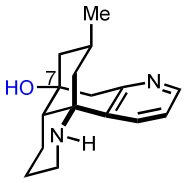

casuarinine D (**3.3**)



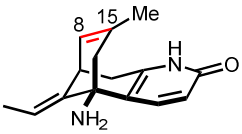

casuarinine H (**3.4**)



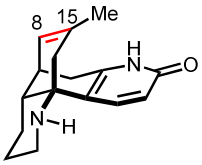

casuarinine **I** (**3.5**)




casuarinine J (**3.6**)




huperzine A (**1.1**)

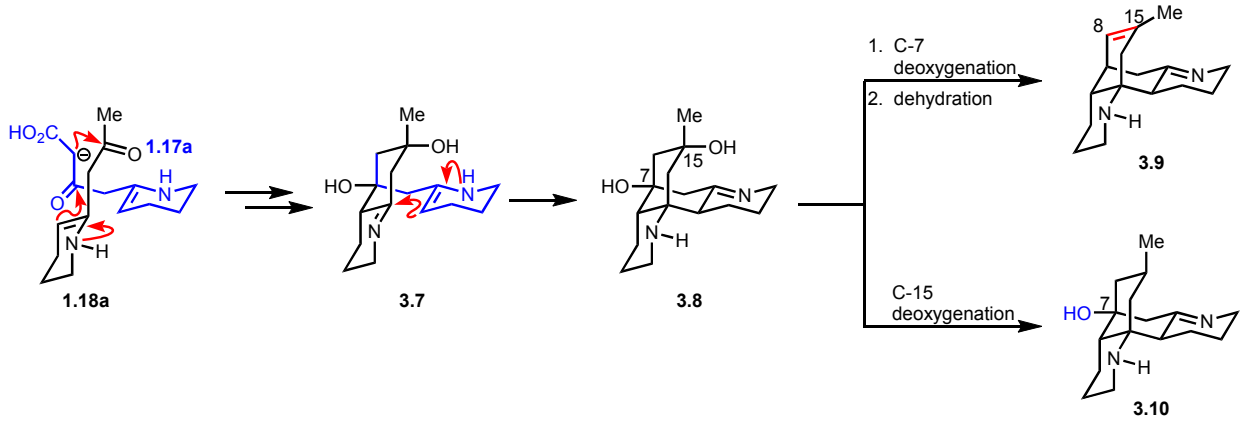



huperzine B (**1.87**)

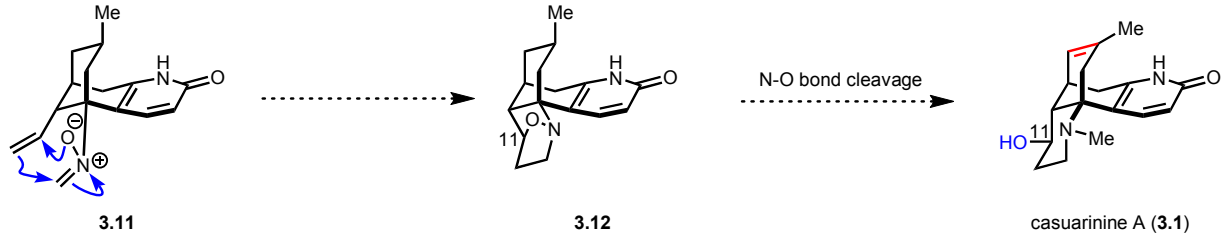
The site-diversity of functionalization in this family of secondary metabolites is remarkable. Several molecules contain double bonds between C-8 and C-15 (e.g., **3.1** and **3.2**), and functionalization at C-6 (see **3.3**), C-7 (see **3.6**), and C-11 (see **3.1** and **3.2**) is also observed. The standard hypothesis for the biosynthesis of lycodine derivatives accounts for oxygenation at C-7 and C-15, which arises from the addition of **1.17a** to**1.18a** (Scheme 3.1A, see Section 1.2 for a more detailed discussion of the biosynthesis of *Lycopodium* alkaloids). Dehydration of a C-15-hydroxylated intermediate could furnish the double bond between C-8 and C-15. We propose that functionalization at C-11 might originate from an intramolecular [3+2] cycloaddition between a nitrone and a terminal vinyl group (see Scheme 3.1B). This proposal is related to Hu's hypothesis for the genesis of **3.5**.[1] Hydroxylation at C-6 might be installed by a P-450 enzyme at a late stage.[2]

**Scheme 3.1** Biogenesis of Oxygenated Lycodine-type Alkaloids.

Biogenesis of C-7 and C-15 Functionalization




Biogenesis of C-11 Functionalization



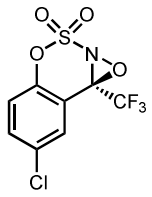

These functionalized molecules present an interesting synthetic challenge, as efforts toward lycodine-type alkaloids to date have focused on the simplest of the family members. One strategy to achieve the synthesis of these more complex derivatives is to employ starting materials with functional handles at the desired locations, which could ultimately be converted into the desired group at an appropriate stage in the synthesis. For example, the Herzon group incorporated a silyl group into cyclohexanone **1.89** (see Scheme 1.11) to serve as a surrogate for the double bond between C-8 and C-15 in the initial phase of their synthesis of **1.1**.[3] However, this strategy becomes cumbersome when it is expanded to encompass the synthesis of several natural products. Each target would require a uniquely functionalized intermediate. Alternatively, a common intermediate with functional handles at each of the desired positions could be employed, but it is anticipated that such a densely functionalized intermediate would be difficult to synthesize. Recent advances in the field of C-H functionalization may obviate the need for these pre-functionalized substrates.

Several reagents have been developed for the oxidation of C-H bonds. Dioxiranes,[4] oxaziridines,[5,6] and $RuO_4$[7,8] are all capable of oxidizing saturated hydrocarbons. Groves has also developed metalloporphine catalysts capable of oxidizing C-H bonds.[9,10] A survey of these studies reveals that site-selective oxidations are often achieved on simple substrates. In general, sites α to electron-rich groups, such as heteroatoms and cyclopropyl groups, are oxidized preferentially. Tertiary positions are also activated toward oxidation. Oxidation of secondary positions occurs under some circumstances and generally provides ketone products. Oxidation of methyl groups is rarely observed. The sterics and electronics of the substrate play a role in determining site-selectivity. The most sterically accessible tertiary positions often

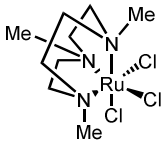
undergo oxidation preferentially. Also, hydroxylation typically occurs distal to electron-withdrawing groups.

Unfortunately, these harsh oxidants are not compatible with a wide range of functional groups necessitating the development of more selective reagents. Du Bois has developed a milder C-H hydroxylation procedure employing catalytic oxaziridine **3.13** with a number of terminal oxidants (Figure 3.2)[11,12] Du Bois has also developed ruthenium catalyzed oxidations that employ Lewis basic ligands such as pyridine and 1,4,7-trimethyl-1,4,7-triazacyclononane (see $RuCl_3$ complex **3.14**) to improve functional group tolerance.[13,14] Finally, White has employed Fe(*S*,*S*-PDP) (**3.15**) for the oxidation of tertiary[15] and secondary[16] positions. The latter catalyst is a remarkably selective oxidant for C-H positions, even when applied to complex natural product substrates. Further, White has shown that oxidation can be directed by carboxylic acid groups.[17]

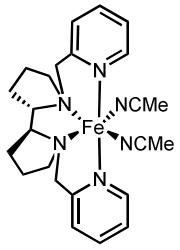
**Figure 3.2** Aliphatic C-H Bond Oxidants.




**3.13**



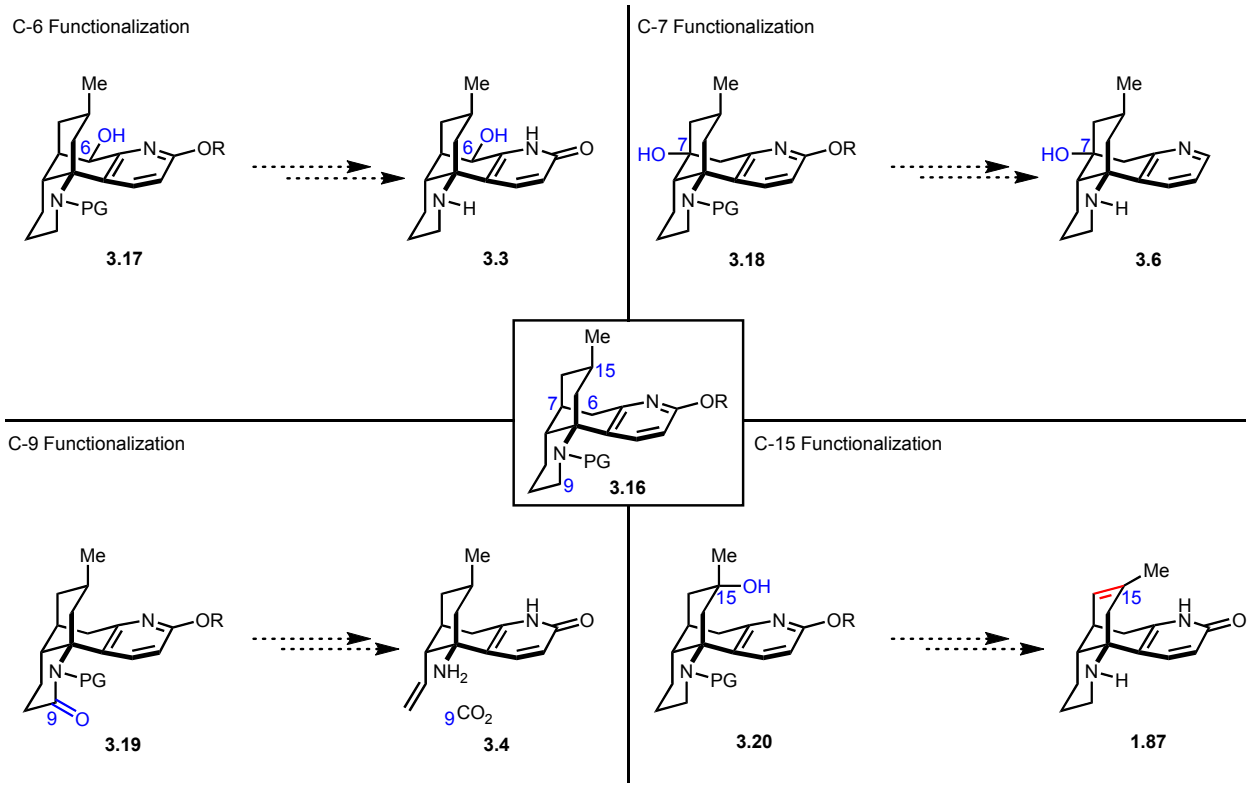

[($Me_3$tacn)$RuCl_3$] (**3.14**)




Fe(*S*,*S*-PDP) (**3.15**)

In light of these advancements, we are interested in developing a divergent strategy for the synthesis of oxygenated lycodine-type *Lycopodium* alkaloids from lycodine or a lycodine derivative using C-H functionalization tactics (Scheme 3.2). Several positions on the lycodine skeleton are activated toward C-H functionalization. For example, C-9 is α to a heteroatom, so it is anticipated to be the most activated position toward C-H functionalization. Oxidation at this position introduces a functional handle that can be used to cleave the D ring and enables the syntheses of molecules such as **3.4** and **1.1**. Our efforts toward this goal are detailed in Section 3.3. C-7, C-12, and C-15 are all tertiary positions, which should be activated toward C-H functionalization as well. Oxygenation at C-7 and C-12 could provide access to **3.6** and huperzine U (**1.88**), respectively. Through the studies detailed in Chapter 2, we have already developed strategies to install a keto group at the C-6 position of lycodine derivatives. We anticipated that the reduction of this ketone would afford derivatives that could be advanced to casuarinine D (**3.4**), which has an equatorially disposed hydroxyl at C-6. Therefore, **3.4** was the first molecule in this family that we targeted.

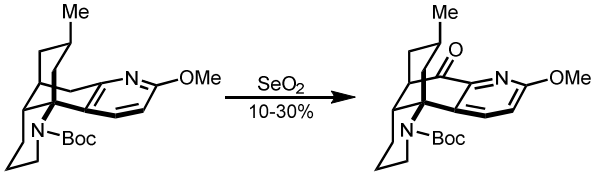
**Scheme 3.2** Divergent Strategy for the Synthesis of Lycodine-type *Lycopodium* Alkaloids.




## 3.2 Synthesis of Casuarinine D

We decided to pursue the synthesis of **3.3** from Boc-methoxylycodine (**2.41**). An advantage to this approach is that the methoxypyridine moiety of **2.41** serves as a masked pyridone that can be unveiled at a late stage, circumventing many of the challenges associated with processing pyridone derivatives, such as their acidity and high polarity. However, we recognized that this strategy would present an inherent challenge. Based on our previous experience preparing C-6-oxygenated lycodine derivatives in our synthesis of complanadine B (**1.9** see Scheme 2.7; Chapter 2), we found that C-1-substituted lycodine derivatives are recalcitrant to direct oxygenation at C-6. For example, treatment of **2.41** with $SeO_2$ at 150 °C for 12 hours afforded ketone **3.21** in unreproducible and low yield (Scheme 3.3). This result was not surprising given that we successfully employed a methoxy group to block the C-6 oxygenation of complanadine derivative **2.40** in our second generation synthesis of **1.8** (see Section 2.X). With these considerations in mind, we sought to develop a multi-step procedure for the C-6 oxygenation of **2.41**.

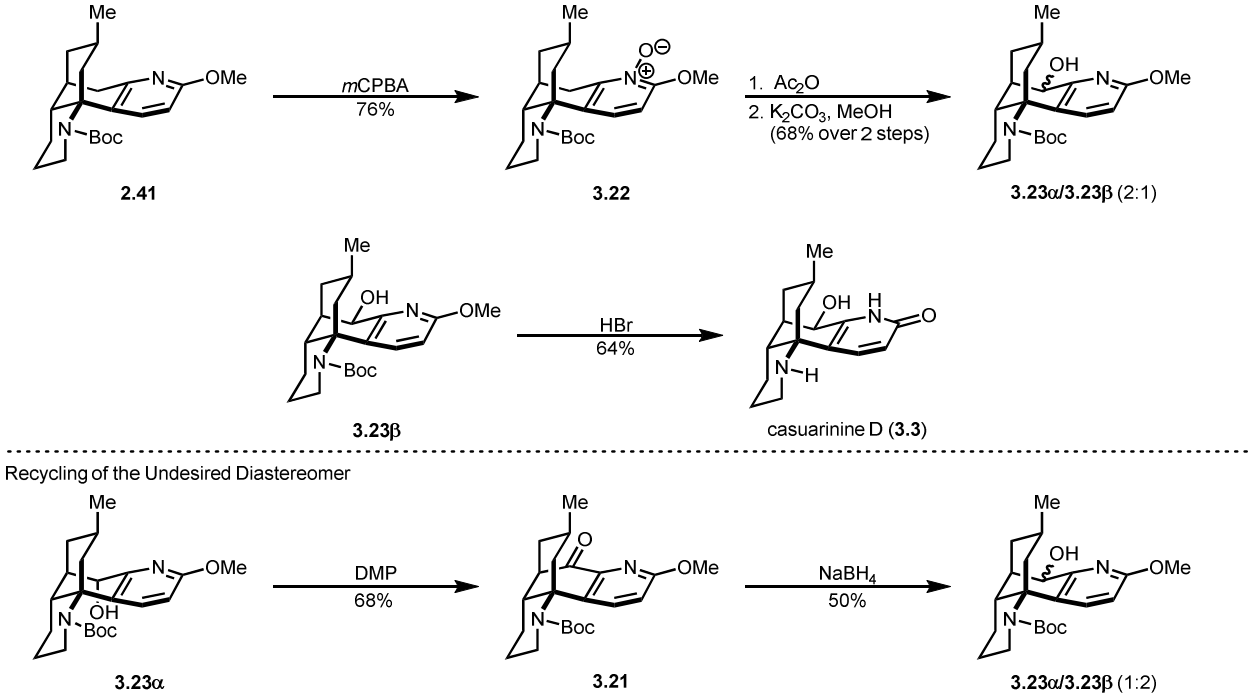
**Scheme 3.3** Attempted Oxygenation of Boc-methoxylycodine (**2.41**).




We realized that a Boekelheide rearrangement might be useful in the preparation of C-6 oxygenated lycodine derivatives. To pursue this tactic, we prepared *N*-oxide **3.22** by treating **2.41** with *m*CPBA (Scheme 3.4). Gratifyingly, we were then able to

effect a Boekelheide rearrangement upon treatment of **3.22** with $Ac_2O$. Cleavage of the acetyl groups with $K_2CO_3$ in MeOH provided a mixture of diastereomeric alcohol products favoring the undesired diastereomer (**3.23α, 3.23α**/**3.23β** 2:1). These products were separable by silica gel chromatography. Despite the unfavorable diastereoselectivity of this reaction, we were able to achieve the synthesis of **3.3** by treatment of **3.23β** with HBr. To improve the overall yield of this route, we developed a two-step protocol to epimerize **3.23α** to **3.23β**, the synthetically useful epimer. Treatment of **3.23α** with DMP afforded ketone **3.21**. Reduction of **3.21** with $NaBH_4$ afforded a mixture of diastereomeric alcohol products favoring **3.23β** (**3.23α**/**3.23β**, 1:2). Through the use of this procedure, the unfavorable diastereoselectivity of the Boekelheide rearrangement is mollified to some extent.

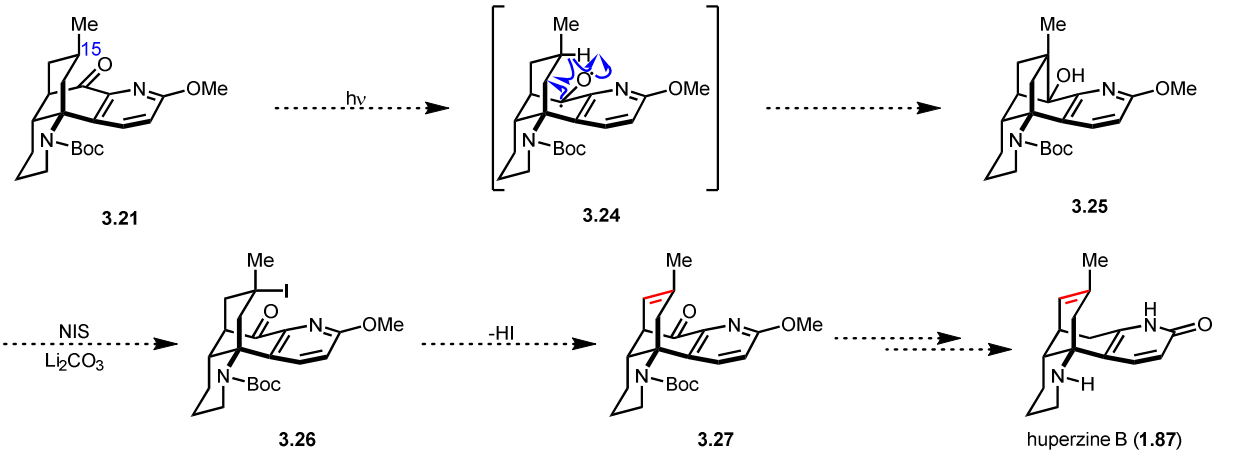
**Scheme 3.4** Synthesis of Casuarinine D.



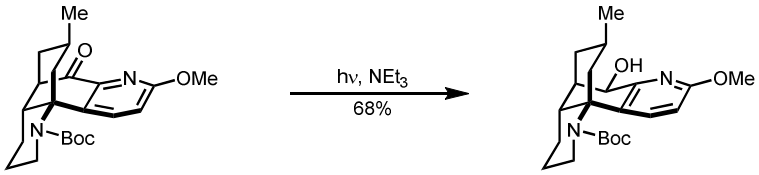

We also discovered a diastereoselective photoreduction of **3.21** in the course of investigating a potential strategy for the functionalization of C-15 (Scheme 3.5). Our original goal was to effect a Norrish-Yang reaction on **3.21** by irradiating the substrate with UV light.[18] The resulting diradical could then abstract a hydrogen atom from the promixal C-15 position to afford cyclobutanol **3.25**. Following precedent established by the Baran group in their synthesis of ouabagenin,[19] oxidative ring opening would then provide iodide **3.26**. We envisioned that a double bond between C-8 and C-15 could be installed by elimination of HI from **3.26**. Instead, we found that irradiation of **3.21** with UV light afforded **3.23β** as a single diastereomer, albeit in 21% yield. The addition of $NEt_3$ as a sacrificial hydrogen atom donor dramatically improved the efficiency of this transformation to 68%. Due to the surprising efficiency and diastereoselectivity of this reaction, future efforts will focus on developing a more efficient synthesis of **3.21** to further streamline the preparation of **3.3**.

**Scheme 3.5** Photoreduction of **3.21**.

Attempted C-15 Functionalization



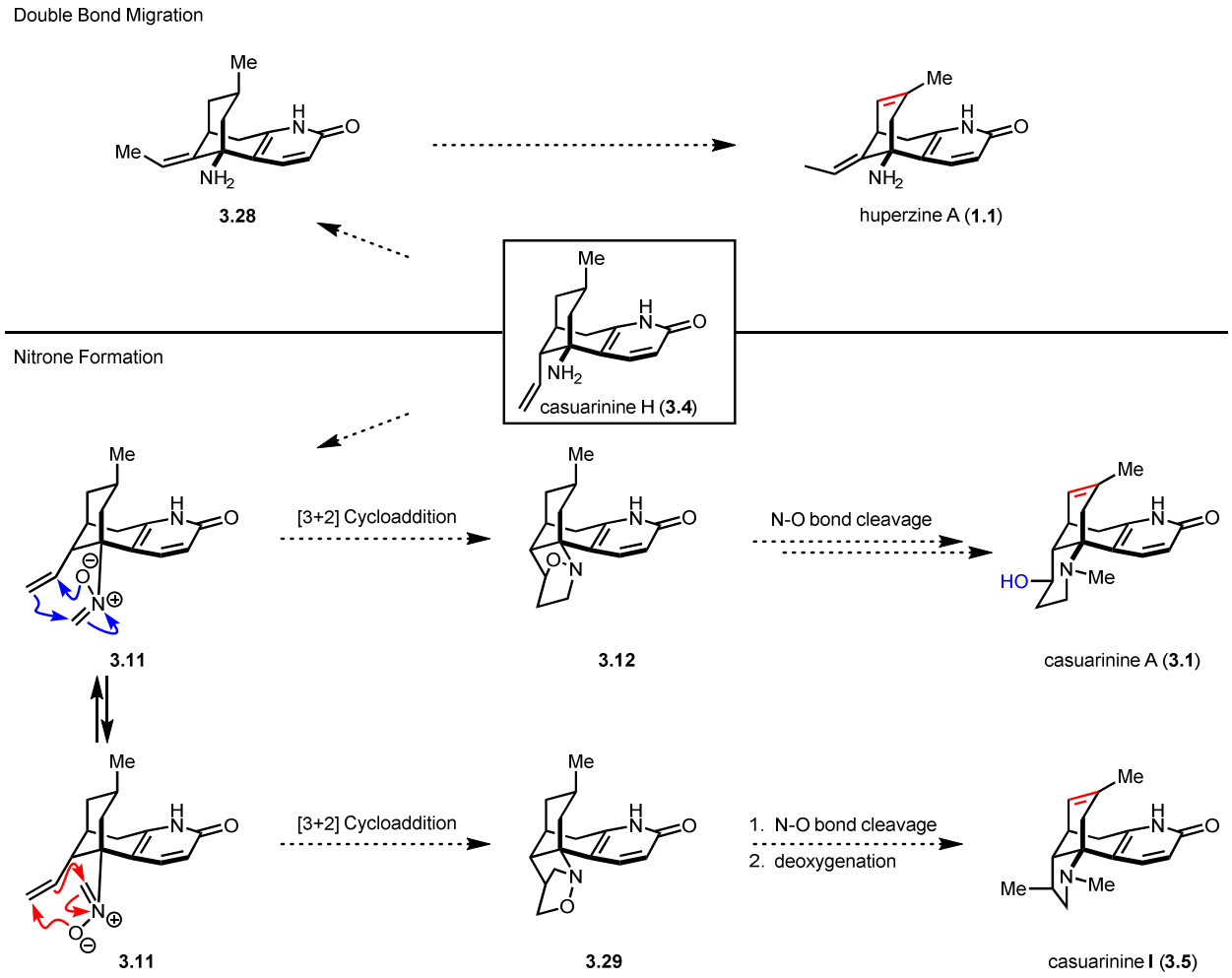

Optimized Photoreduction of **XX**




## 3.3 Progress Toward the Synthesis of Casuarinine H

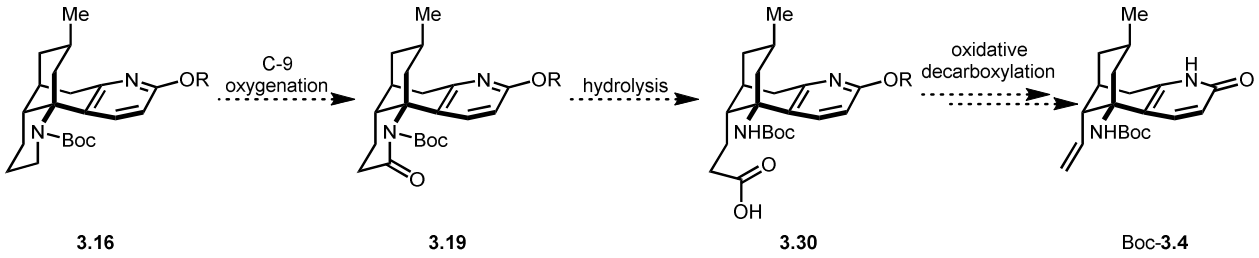
Upon completing our synthesis of **3.3**, we turned our efforts toward casuarinine H (**3.4**). The preparation of **3.4** is an essential milestone in our program directed at the synthesis of a number of lycodine-type *Lycopodium* alkaloids. We envision that **3.4** can serve as an intermediate in the synthesis of several natural products. Therefore, **3.4** serves as an important strategic pivot in our synthetic plan. For example, isomerization of the terminal double bond to the interior position could enable the synthesis of **1.1** (Scheme 3.6). Preparation of nitrone **3.11** from **3.4** could enable the preparation of both **3.1** and **3.5** from the two regioisomers of a [3+2] cycloaddition between the nitrone and the terminal vinyl group. Cleavage of the N-O bonds of the resulting cycloadducts should provide intermediates that can be advanced to the natural products. As mentioned in Section 3.1, this sequence mimics Hu's proposal for the biosynthesis of **3.5**, so the pursuit of this route would enable us to test the viability of this hypothesis.[1]

**Scheme 3.6** Casuarinine H as a Strategic Pivot.




In order to prepare **3.4**, we wished to effect an oxidation of C-9 using C-H functionalization chemistry to prepare amide **3.16** (Scheme 3.7). Amide **3.16** would then be hydrolyzed to acid **3.30**. Finally, an oxidative decarboxylation could be used to install the vinyl group. There is already precedent for the oxidation of C-9 using strong oxidants. In fact, Ayer employed $KMnO_4$ to oxidize C-9 of an intermediate in his seminal synthesis of lycopodine (**1.2**) to prepare amide **1.32** (see Scheme 1.3).[20] We were drawn to a report by Sheehan and coworkers that established that cyclic amines could be oxidized to lactams using $RuO_4$.[21] As discussed in Section 3.1, $RuO_4$ is also capable of oxidizing tertiary C-H bonds.[22] In order to achieve the synthesis of natural products downstream from **3.4** in our synthetic plan, both of these transformations will be required. We anticipate that hydroxylation at C-15 would enable us to install the double bond between C-8 and C-15. Due to its highly reactive nature, we envisioned that oxidation of a lycodine derivative with $RuO_4$ could install the desired functionalities at both C-9 and C-15 under appropriate reaction conditions.

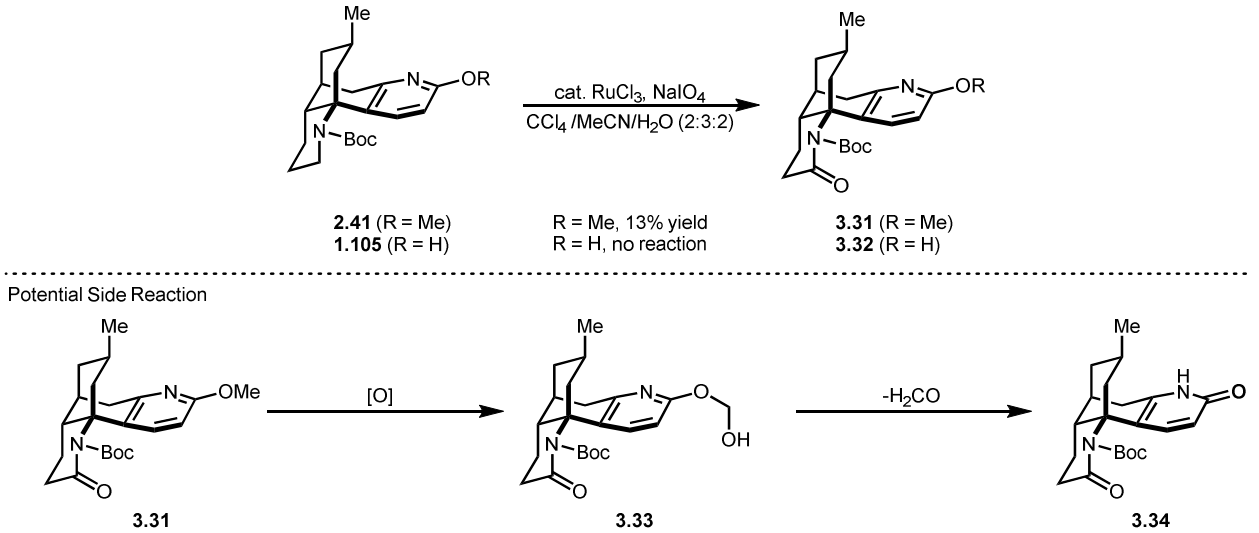
**Scheme 3.7** Proposed Synthesis of Casuarinine H from a Lycodine Derivative.




**3.16** **3.19** **3.30** Boc-**3.4**

With this potential set of site-selective C-H functionalizations in mind, we first investigated the $RuO_4$ oxidation of Boc-methoxylycodine (**2.41**, Scheme 3.8). Treatment of **2.41** with conditions developed by Sharpless for the *in situ* generation of $RuO_4$ afforded amide **3.31** in low yield (13%). Under these conditions substantial decomposition of the substrate was observed. One deleterious pathway may be the oxidation of the methoxy group, which would yield acetal **3.33**. **3.33** can readily lose formaldehyde to afford pyridone **3.34**. Although **3.34** was never isolated, a mass peak that corresponds to this product was observed after LCMS analysis of the crude reaction mixture. In retrospect, this reactivity is unsurprising due to the fact that the methyl group is α to an oxygen atom and therefore is activated toward oxidation. Attempted oxygenation of Boc-β-obscurine (**1.105**), which contains an unprotected pyridone moiety, returned starting material. These results demonstrate the need for suitably protected derivatives moving forward.

**Scheme 3.8** $RuO_4$ Oxidation of Lycodine Derivatives.

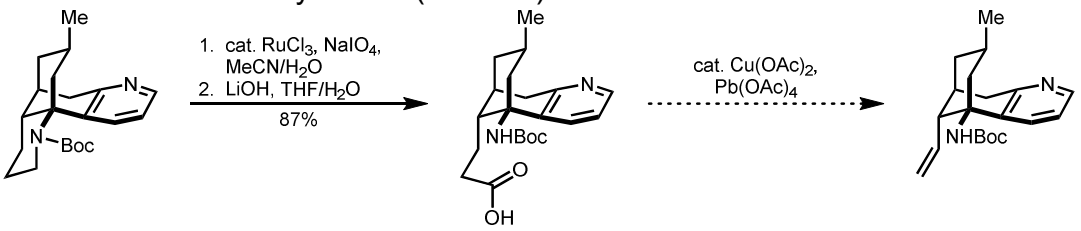



**3.31** **3.33** **3.34**

In an effort to circumvent these particular challenges, we studied the $RuO_4$ oxidation of Boc-lycodine (Boc-**1.3**, Scheme 3.9). We were cognizant that Boc-**1.3** was not an ideal substrate for the synthesis of **3.4**, as it lacked functionality at C-1 to install the pyridone oxygen atom of the final product. However, we envisioned that Boc-**1.3** would serve as a good model substrate for the development of downstream chemistry. Gratifyingly, treatment of Boc-**1.3** with the Sharpless conditions provided a mixture of the desired amide, which partially hydrolyzed to acid **3.35**, under the reaction conditions. Therefore, the crude reaction mixture was treated with LiOH in THF/$H_2O$ to afford **3.35** in 87% yield over the two steps. With **3.35** in hand, we briefly investigated the use of oxidative decarboxylation procedures to install the vinyl group found in **3.36**

on this model system. Kochi and coworkers have shown that the treatment of aliphatic carboxylic acids with $Pb(OAc)_4$ and catalytic $Cu(OAc)_2$ affords dehomologated olefins.[23] Unfortunately, these conditions returned starting material when applied to **3.35**. Although this initial attempt to effect an oxidative decarboxylation on a lycodine derivative was unsuccessful, we were pleased with our ability to access **3.35** using our C-H functionalization strategy. Encouraged by our success on our model substrate, we sought to identify a substrate that could be directly applied to the synthesis of **3.4**.

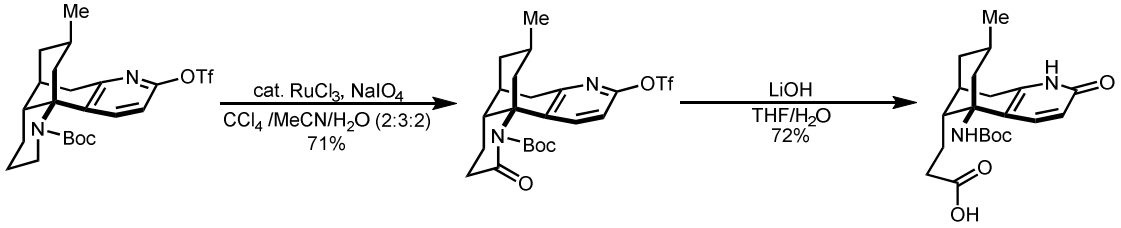
**Scheme 3.9** $RuO_4$ of Boc-lycodine (Boc-**1.3**).




Boc-**1.3** **3.35** **3.36**

We anticipated that triflate **1.123** would be recalcitrant toward undesired oxidation pathways, due to the triflate group's lack of C-H bonds. Hydrolysis of the trifyl group at an appropriate stage in the synthesis would furnish the pyridone moiety of **3.4**. Our rationale was validated when the treatment of **1.123** with $RuO_4$ afforded amide **3.37** in 64% yield (Scheme 3.10). Subjecting **3.37** to LiOH in $THF/H_2O$ resulted in the hydrolysis of the amide and trifyl groups to provide acid **3.38**. Our preparation of this substrate was quite exciting as the successful oxidative decarboxylation of **3.38** would afford Boc-**3.4** in a single synthetic operation.

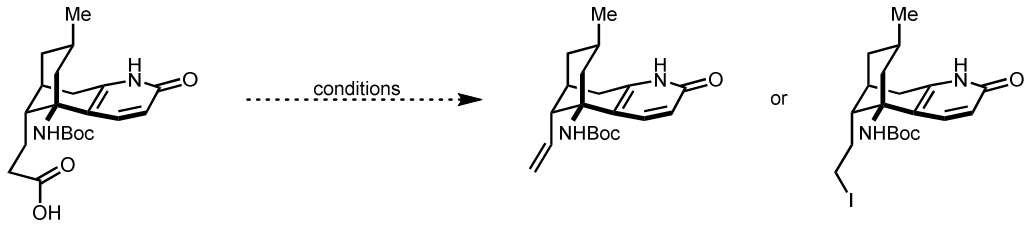
**Scheme 3.10** $RuO_4$ of Triflate **1.123**.




**1.123** **3.37** **3.38**

Unfortunately, we have been unable to effect the desired transformation to date. Kochi conditions were ineffectual (Scheme 3.11).[23] The Suarez modification of this procedure, which employs phenyliodonium diacetate (PIDA) as an oxidant instead of $Pb(OAc)_4$,[24] also returned starting material. A decarboxylative iodination procedure developed by Barton[25] resulted in the non-specific decomposition of our substrate. Despite these results, we are optimistic that we will be able to prepare Boc-**3.4** directly from **3.38** using other oxidative decarboxylative methods. A number of Lewis basic sites in **3.36** and **3.38** may hamper methods that employ metal salts, like the Kochi and Suarez methods. Therefore, metal-free oxidative decarboxylation methods, such as the one reported by Gandelman,[26] might be more appropriate for these types of substrates.

**Scheme 3.11** Attempted Oxidative Decarboxylation of **3.38**.




**3.38** Boc-**3.4** **3.39**

## 3.4 Conclusion

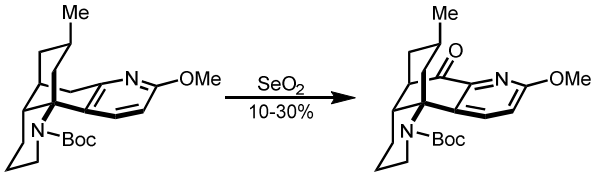
We have achieved two milestones in our program directed toward the synthesis of oxygenated lycodine-type alkaloids via the late-stage functionalization of lycodine derivatives. The synthesis of casuarinine D (**3.3**) was achieved after late-stage C-6-oxygenation of Boc-methoxylycodine (**2.41**). Functionalization of the C-9 position of **1.123** facilitated the cleavage of the D ring of the lycodane skeleton. We are optimistic that this route will enable us to achieve the synthesis of casuarinine H (**3.4**), which in turn will enable us to pursue the synthesis of several other lycodine-type alkaloids, such as **3.1**, **3.5**, and **1.1**. Beyond these lines of investigation, we believe that our late-stage functionalization could be more widely applied to the synthesis of several other oxygenated lycodine-type alkaloids. This will be the focus of future research endeavors in this area.

## 3.5 Experimental Section

Unless stated otherwise, reactions were performed in oven-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), toluene, and ether (Et2O) were dried by passage over a column of activated alumina; dichloromethane was distilled over calcium hydride. Anhydrous chloroform was obtained in a Sure/Seal bottle from Aldrich. All other solvents and reagents were used as received unless otherwise noted. Thin layer chromatography was performed using SiliCycle silica gel 60 F-254 precoated plates (0.25 mm) and visualized by UV irradiation and anisaldehyde, CAM, potassium permanganate, or iodine stain. Sorbent silica gel (particle size 40-63 μm) was used for flash chromatography. NMR experiments were performed on Bruker spectrometers operating at 300, 400, 500 or 600 MHz for 1H and 75, 100, 125, or 150 MHz for 13C experiments. 1H and 13C chemical shifts (δ) are reported relative to the residual solvent signal. Data 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), dt (doublet of triplet), p (pentet), hept (heptet), m (multiplet), bs (broad singlet). Only select 1H and 13C spectra are reported. IR spectra were recorded on a Nicolet MAGNA-IR 850 spectrometer as thin films on NaCl plates and are reported in frequency of absorption ($cm^{-1}$). Only selected IR absorbencies are reported. Low and high-resolution mass spectral data were obtained from the University of California, Berkeley Mass Spectral Facility, on a VG 70-Se Micromass spectrometer for FAB, and a VG Prospec Micromass spectrometer for EI. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

### Ketone 3.21

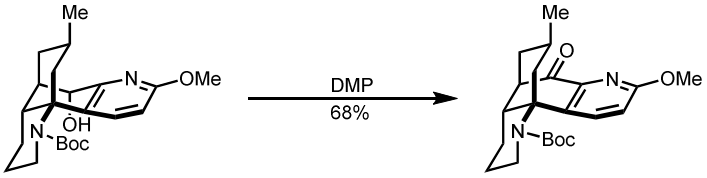
*Method 1*




**2.41** **3.21**

A 0.5 mL microwave vial was charged with $SeO_2$ (7.4 mg, 67 µmol). The vial was sealed with a septum cap and purged with nitrogen. A solution of **2.41** (10.0 mg, 26.8 µmol) in dioxane (0.31 mL) was introduced with a syringe via the septum. The reaction mixture was stirred in the microwave at 150 ˚C for 24 h. After cooling the reaction mixture to 23 ˚C, the solvent was removed under reduced pressure and the remaining black residue was purified by silica gel chromatography (20% EtOAc in hexanes), affording **3.21** (2.1 mg, 5.4 µmol, 20% yield) as a clear oil.

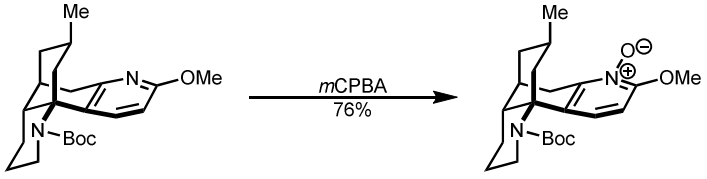
*Method 2*




**3.23α** **3.21**

To a solution of **3.23α** (10.0 mg, 25.7 µmol) in DCM (1 mL) was added $NaHCO_3$ (ca. 20 mg, 9 equiv) and DMP (13.1 mg, 30.9 µmol). The solution was stirred at 23 ˚C for 1 h. Then, water (2 mL) was added and the aqueous phase was extracted with DCM (3X). The combined organic phases were dried over $Na_2SO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (33% EtOAc in hexanes) to provide **3.21** (8.1 mg, 21 µmol, 82% yield) as a white foam. Characterization Data for **3.21**. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.3 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 1H), 4.11 (dt, *J* = 14.2, 3.2 Hz, 1H), 4.05 (s, 3H), 2.91 (dd, *J* = 13.6, 4.0 Hz, 1H), 2.77 (s, 1H), 2.42 (dt, *J* = 13.3, 2.2 Hz, 1H), 2.12 (dq, *J* = 12.9, 2.0 Hz, 1H), 1.94 (t, *J* = 12.5 Hz, 1H), 1.90 (d, *J* = 12.7 Hz, 1H), 1.66 (d, *J* = 13.2 Hz, 1H), 1.61 (s, 1H), 1.57 (dt, *J* = 13.0, 4.1 Hz, 1H), 1.52 (s, 9H), 1.48 (s, 1H), 1.41 (dt, *J* = 13.2, 4.8 Hz, 1H), 1.27 (m, 2H), 0.87 (d, *J* = 6.2 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 198.8, 163.1, 155.8, 146.1, 138.1, 135.5, 117.9, 80.1, 63.4, 53.7, 51.9, 47.2, 45.3, 44.0, 37.6, 28.5, 27.8, 27.1, 25.1, 22.0. **IR** (film): v = 2927, 2359, 1698, 1598, 1478, 1422, 1365, 1333, 1145, 1080, 1023. **HRMS (ESI)** calcd for $[C_{22}H_{30}N_2O_4Na]^+$ $(M+H)^+$: *m/z* 409.2098, found 409.2096.

***N*-oxide 3.22**

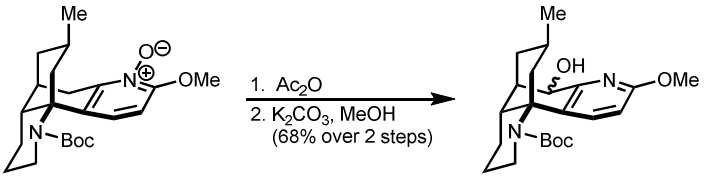



**2.41** **3.22**

Boc-methoxylycodine (**2.41**) (195 mg, 0.524 mmol) was dissolved in anhydrous DCM (6 mL) in a screw-cap vial (20 mL). *m*CPBA (226 mg, 1.31 mmol) was added in one portion. The reaction mixture was sparged with nitrogen, and the vial was fitted with a teflon-coated cap. The reaction mixture was stirred at 60 ˚C for 4 h, at which time another portion of *m*CPBA (90.3 mg, 0.523 mmol) was added. The resulting mixture was stirred for an additional 10 h at 60 ˚C. After cooling to room temperature, the solution was washed with sat. $NaHCO_3$ (aq.) until the aqueous phase remained basic (pH ≥ 10). The phases were separated and the aqueous phase was extracted with DCM (3 X). The combined organic phases were dried over $Na_2SO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (33% EtOAc in hexanes, then flushed with 5% MeOH in DCM) to provide **3.22** (151 mg, 0.387 mmol, 74% yield) as a yellow foam. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.7 Hz, 1H), 6.77 (d, *J* = 8.7 Hz, 1H), 4.06 (q, *J* = 7.2 Hz, 1H), 4.05 (d, *J* = 12.5 Hz, 1H), 4.00 (s, 3H), 3.00 (dd, *J* = 20.2, 7.4 Hz, 1H), 2.82 (d, *J* = 20.4 Hz, 1H), 2.77 (dd, *J* =13.5, 2.3 Hz, 1H), 2.31 (t, *J* = 12.1 Hz, 1H), 2.16 (m, 1H), 1.98 (s, 1H), 1.76 (dt, *J* = 12.4, 2.6 Hz, 1H), 1.72 (t, *J* = 12.6 Hz, 1H), 1.63 (d, *J* = 12.9 Hz, 1H), 1.50 (m, 2H), 1.44 (s, 9H), 1.20 (m, 5H), 0.77 (d, *J* = 6.3 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) 157.0, 156.0, 150.0, 130.7, 124.3, 104.9, 79.9, 63.1, 60.4, 57.1, 47.8, 44.2, 43.1, 42.4, 33.3, 28.7, 28.5, 27.3, 26.3, 25.4, 22.1, 14.2. **IR** (film): v = 3390, 2927, 2868, 2360, 2342, 2212, 1694, 1604, 1574, 1504, 1456, 1419, 1367, 1305, 1267, 1213, 1156, 1080, 921, 730. **HRMS (ESI)** calcd for $[C_{22}H_{33}N_2O_4]^+$ $(M+H)^+$: *m/z* 389.2435, found 389.2433.

**Alcohol 3.23**

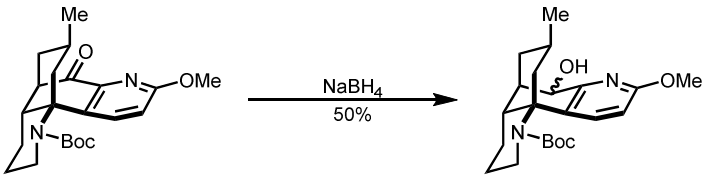
*Method 1*




**3.22** **3.23α/3.23β** (2:1)

*N*-oxide **3.22** (151 mg, 0.387 mmol) was dissolved in anhydrous DCM (7 mL) in a screw-cap vial (20 mL). $Et_3N$ (0.27 mL, 1.9 mmol) and acetic anhydride (0.18 mL, 1.9 mmol) were added, the vial was fitted with a telfon-coated cap, and the mixture was stirred at 52 ˚C for 17 h. After cooling to room temperature, the solvent was removed under reduced pressure, and the remaining yellow oil was dissolved in MeOH (7 mL). $K_2CO_3$ (200. mg, 1.45 mmol) was added in one portion, and the solution was stirred at 60 ˚C for 6 h. The solution was diluted with $H_2O$ (15 mL), and the aqueous phase was extracted with DCM (3X). The organic phases were combined, dried over $Na_2SO_4$, and concentrated under reduced pressure. The remaining white foam was purified using an automated column chromatography apparatus (silica gel column, 15 to 25% ethyl acetate in hexanes, linear gradient over 24 min) to provide **3.23** as a mixture of diastereomers (**3.23α**/**3.23β** 2:1, 93.3 mg, 0.263 mmol, 68% yield).

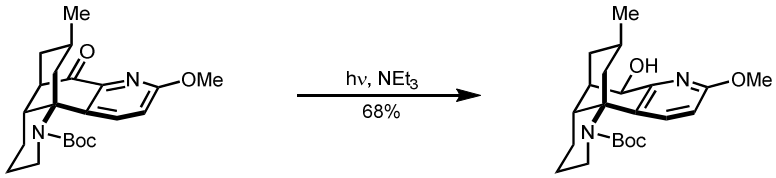
*Method 2*




**3.21** **3.23α/3.23β** (1:2)

In a 4 mL screw-cap vial, $NaBH_4$ (0.9 mg, 23 μmol, 1.1 equiv) was added in one portion to **3.21** (7.9 mg, 20 μmol) dissolved in MeOH (0.5 mL). The solution was stirred at 50 ˚C for 2 h. After cooling to 23 ˚C, DCM and sat. $NaHCO_3$ (aq) were added, and following phase separation, the aqueous phase was washed with DCM (3X). The combined organic phases were dried over $Na_2SO_4$, filtered, and the solvent was removed under reduced pressure. The remaining clear oil was purified by flash chromatography (33% EtOAc in hexanes) to provide **3.23** as a mixture of diastereomers (**3.23α**/**3.23β** 1:2, 4.0 mg, 10 μmol, 50% yield).

*Method 3*




**3.21** **3.23β**

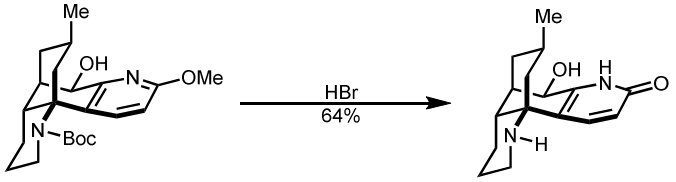
Ketone **3.21** (3.2 mg, 8.3 μmol) was dissolved in $C_6D_6$ (1 mL), and the resulting solution was pipetted into a borosilicate NMR tube. The tube was sealed with a rubber septum, placed in a pyrex filter, and irradiated with a medium-pressure Hg lamp (cooled by water) in a photobox for 13 h. The solvent was removed and the remaining yellow residue was purified using flash chromatography (20% EtOAc in hexanes), providing **3.23β** (2.2 mg, 5.7 μmol, 68% yield) as a clear oil.

Characterization for **3.23α**: **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.6 Hz, 1H), 6.69 (d, *J* = 8.3 Hz, 1H), 4.26 (s, 1H), 4.06 (dq, *J* = 13.8, 1.8 Hz, 1H), 3.93 (s, 3H), 2.90 (m, 2H), 2.36 (m, 1H), 2.24 (q, *J* = 3.1 Hz, 1H), 1.80 (dq, *J* = 12.5, 1.7 Hz, 1H), 1.74 (dt, *J* = 13.0, 4.2 Hz, 1H), 1.67 (m, 2H), 1.50 (s, 9H), 1.46 (m, 2H), 1.28 (dt, *J* = 12.8, 4.2 Hz, 1H), 1.06 (bs, 1H), 0.84 (d, *J* = 6.1 Hz, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 162.9, 156.2, 155.3, 137.5, 126.2, 111.2, 79.6, 72.2, 63.9, 53.4, 46.8, 44.1, 43.1, 40.7, 40.6, 28.5, 27.6, 27.0, 25.8, 22.3. **IR** (film): v = 3479, 2926, 2868, 2250, 1698, 1600, 1576, 1479, 1457, 1425, 1365, 1321, 1264, 1219, 1146, 1077, 1059, 1036. **HRMS (ESI)** calcd for $[C_{22}H_{33}N_2O_4]^+$ $(M+H)^+$: *m/z* 389.2435, found 389.2432.

Characterization for **3.23β**: **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.9 Hz, 1H), 6.71 (d, *J* = 7.8 Hz, 1H), 4.81 (d, *J* = 6.4 Hz, 1H), 4.17 (dq, *J* = 13.6, 2.1 Hz, 1H), 3.98 (s, 3H), 3.73 (s, 1H), 2.73 (d, *J* = 11.8 Hz, 1H), 2.46 (m, 2H), 2.26 (dt, *J* = 11.8, 1.9 Hz, 1H), 2.04 (dt, *J* = 12.7, 3.6 Hz, 1H), 1.83 (dd, *J* = 13.0, 11.4 Hz, 1H), 1.70 (d, *J* = 12.7 Hz, 1H), 1.66 (s, 1H), 1.58 (m, 2H), 1.54 (s, 9H), 1.46 (s, 1H), 1.30 (bs, 1H), 1.11 (bs, 1H), 0.92 (s, 1H), 0.86 (d, *J* = 6.0 Hz, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 162.7, 156.1, 154.9, 137.0, 126.7, 110.8, 79.7, 77.4, 77.2, 77.0, 76.7, 68.3, 63.9, 53.5, 48.3, 45.9, 44.2, 39.5, 34.9, 31.6, 28.6, 27.5, 26.6, 25.9, 22.7, 22.4, 14.2. **IR** (film): v = 3520, 2945, 2360,

2250, 1698, 1598, 1578, 1478, 1424, 1366, 1313, 1263, 1147, 1082, 1059, 1034. **HRMS (ESI)** calcd for $[C_{22}H_{33}N_2O_4]^+$ $(M+H)^+$: *m/z* 389.2435, found 389.2430.

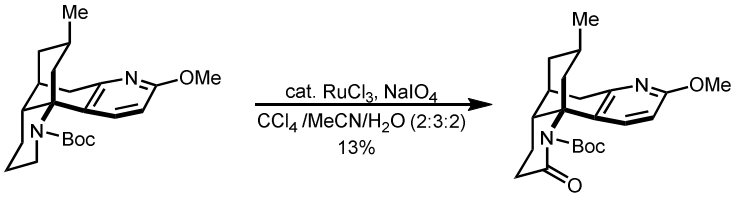
**Casuarinine D (3.3)**




**3.23β** casuarinine D (**3.3**)

In a screw-cap vial (4 mL), HBr (0.11 mL, 48% in $H_2O$) was added to a solution **3.23β** (12.2 mg, 31.4 µmol, 1 equiv) in distilled $H_2O$ (0.89 mL). The vial was sealed with a teflon cap and stirred at 105 ˚C for 10 h. After cooling to room temperature, the solution was diluted with DCM (1 mL) and quenched with sat. $NaHCO_3$ (aq) until the solution remained basic. The aqueous layer was extracted with DCM (3X), and the combined organic phases were dried over $Na_2SO_4$. The solvent was removed under reduced pressure to afford **3.3** (5.6 mg, 20 µmol, 65% yield) as a white gum. **$^1$H NMR** (600 MHz, $CD_3OD$) δ 7.65 (d, *J* = 9.8 Hz, 1H), 6.49 (d, *J* = 9.2 Hz, 1H), 4.72 (d, *J* = 6.4 Hz, 1H), 2.75 (d, *J* = 12.8 Hz, 1H), 2.43 (t, *J* = 11.9 Hz, 1H), 2.19 (d, *J* = 13.3 Hz, 1H), 2.15 (s, 1H), 1.79 (d, *J* = 12.8 Hz, 1H), 1.58 (m, 3H), 1.44 (d, *J* = 11.9 Hz, 1H), 1.32 (m, 3H), 1.22 (t, *J* = 11.9 Hz, 1H), 1.07 (dt, *J* = 13.2, 3.4 Hz, 1H), 0.83 (d, *J* = 6.4 Hz, 3H). **$^{13}$C NMR** (151 MHz, MeOD) δ 163.6, 145.3, 139.6, 118.4, 118.0, 65.3, 55.2, 48.6, 45.5, 40.8, 40.0, 34.8, 26.1, 25.3, 25.2, 20.7. **IR** (film): v = 3271, 2924, 1652, 1601, 1553, 1456, 838, 736. **HRMS (ESI)** calcd for $[C_{16}H_{23}N_2O_2]^+$ $(M+H)^+$: *m/z* 275.1754, found 275.1753. **[α]$_D^{20}$** -49 (*c* 0.12, MeOH).

**Amide 3.31**

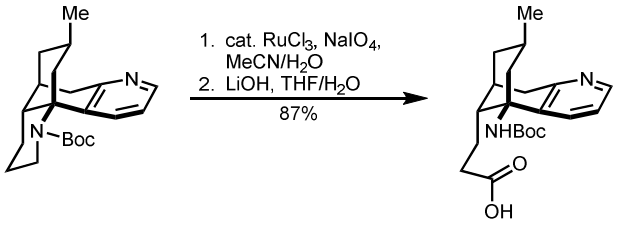



**2.41** **3.31**

In a 4 mL screw-cap vial, $RuCl_3$ (0.8 mg, 4 µmol, 0.1 equiv) was added to a solution of **2.41** (13.9 mg, 37.3 µmol, 1 equiv) in a ternary solvent system (0.14 mL $CCl_4$, 0.14 mL $CH_3CN$, and 0.21 mL $H_2O$). $NaIO_4$ (31.9 mg, 149 µmol, 4.00 equiv) was added to the opaque solution in one portion, and the reaction mixture was stirred at room temperature for 4 h. The mixture was quenched with sat. $NaHCO_3$ (aq) and the aqueous phase was extracted with DCM (3X). The organic phases were combined, dried over $Na_2SO_4$, and concentrated under reduced pressure. The remaining black residue was purified by silica gel chromatography (33% EtOAc in hexanes -> 100% EtOAc) to afford **3.31** (1.8 mg, 4.7 µmol) as a clear oil in 13% yield. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.7 Hz, 1H), 6.58 (d, *J* = 8.7 Hz, 1H), 3.89 (s, 3H), 3.08 (dd, *J* = 19.2, 7.5 Hz, 1H), 2.63 (d, *J* = 19.1 Hz, 1H), 2.46 (dt, *J* = 17.8, 8.7 Hz, 1H), 2.29 (m, 1H), 2.18 (ddd, *J* = 17.5, 8.1, 3.8 Hz, 1H), 2.05 (m, 2H), 1.81 (d, *J* = 9.1 Hz, 1H), 1.77 (m, 1H), 1.57 (s, 9H), 1.37 (m, 3H), 1.25 (bs, 1H), 0.86 (d, *J* = 5.1 Hz, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ

171.5, 162.5, 154.1, 153.8, 139.0, 127.8, 108.5, 99.9, 84.1, 62.8, 53.3, 44.9, 42.8, 41.6, 34.7, 32.7, 30.9, 27.6, 24.8, 22.1, 21.6. **IR** (film): v = 2925, 1738, 1678, 1595, 1479, 1250, 1154, 1031, 851, 732, 682. **HRMS (ESI)** calcd for $[C_{22}H_{31}N_2O_4]^+$ $(M+H)^+$: *m/z* 387.2278, found 387.2275. **$[\alpha]_D^{20}$** +72 (*c* 0.13, $CH_2Cl_2$).

**Acid 3.35**

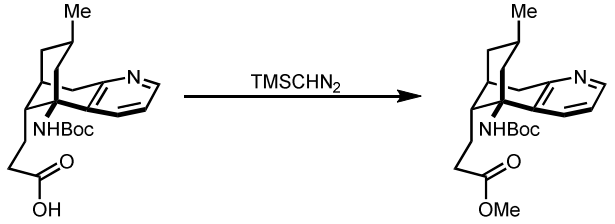



Boc-**1.3** **3.35**

$RuCl_3$ (9.6 mg, 46 µmol) and Boc-**1.3** (159 mg, 0.464 mmol) were dissolved in a solution of $H_2O$/MeCN (1:1, 5 mL) in a screw-cap vial (20 mL). $NaIO_4$ (397 mg, 1.86 mmol) was added and the reaction mixture was stirred at room temperature for 4 h. Saturated $Na_2CO_3$ (aq.) was added and the resulting mixture was extracted with DCM (3 X). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure.

The crude reaction mixture was dissolved in a solution of THF/$H_2O$ (1:1, 1 mL) in a 4 mL vial. $LiOH{\cdot}H_2O$ (193 mg, 4.60 mmol) was added, the vial was capped, and the reaction mixture was stirred for 8 h at 60 °C. After cooling to room temperature, a solution of 10% AcOH in $H_2O$ was added until the mixture remained acidic. The resulting solution was extracted with EtOAc (3 X). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure to yield **3.36** as a brown foam (151.7 mg, 0.4051 mmol, 87%).

The compound was characterized as methyl ester **3.40**, which was prepared by the dropwise addition of $TMSCHN_2$ (100. µL, 2.0 M in hexanes, 0.20 mmol) to a solution of **3.36** (22.6 mg, 60.4 µmol) in MeOH (0.6 mL) at room temperature. The reaction mixture was stirred for 10 min at room temperature and then quenched with formic acid (10% in $H_2O$). Saturated $Na_2CO_3$ (aq) was added until the solution remained basic. The aqueous phase was then extracted with DCM (3 X). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude reaction mixture was purified by silica gel chromatography (EtOAc) to afford **3.40** as a yellow oil.

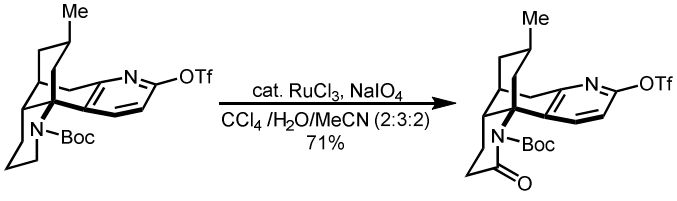



**3.35** **3.40**

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.44 (d, *J* = 4.6 Hz, 1H), 7.82 (d, *J* = 7.0 Hz, 1H), 7.28 – 7.22 (m, 1H), 5.00 (s, 1H), 3.67 (s, 3H), 3.27 (dd, *J* = 19.2, 6.7 Hz, 1H), 2.83 (d, *J* = 19.4 Hz, 1H), 2.55 – 2.23 (m, 4H), 1.79 (d, *J* = 13.1 Hz, 1H), 1.69 (d, *J* = 11.3 Hz, 1H), 1.57 – 1.08 (m, 13H), 0.82 (d, *J* = 6.3 Hz, 3H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 173.88, 156.51, 154.85, 146.02, 136.44, 134.30, 122.05, 79.76, 59.06, 51.68, 47.34, 42.46, 41.35, 33.27, 31.88, 30.30, 28.40, 26.16, 23.28, 21.71. **IR (film)** v = 3364.93 (broad), 2950.94, 2916.31, 1718.79, 1490.04, 1454.54, 1437.29, 1389.05, 1365.81, 1245.78, 1162.18,

1090.59, 1059.55, 1026.65, 919.36, 874.94, 855.86, 804.82, 732.70. **HRMS (ESI)** calcd for $[C_{22}H_{33}N_2O_4]^+$ $(M+H)^+$: *m/z* 389.2435 found 389.2426

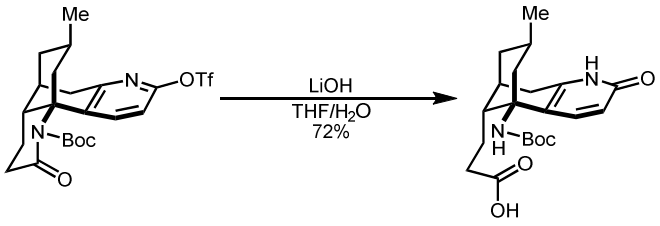
**Amide 3.37**




**1.123** **3.37**

$RuCl_3$ (11 mg, 53 µmol) and triflate **1.123** (261 mg, 0.532 mmol) were dissolved in a solution of $CCl_4/H_2O$/MeCN (0.750 mL $CCl_4$, 1.125 mL $H_2O$, 0.750 mL MeCN) in a screw-cap vial (20 mL). $NaIO_4$ (455 mg, 2.13 mmol) was added and the reaction mixture was stirred at room temperature for 4 h. Saturated $Na_2CO_3$ (aq.) was added and the resulting mixture was extracted with DCM (3 X). The combined organic fractions were dried with $MgSO_4$ and concentrated under reduce pressure. The crude reaction mixture was purified by silica gel chromatography (25% EtOAc in hexanes) to provide **3.37** as a white foam (191 mg, 0.379 mmol, 71%). **$^1$H NMR** (600 MHz, $CDCl_3$) δ 8.67 (d, *J* = 8.5 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 3.14 (dd, *J* = 19.6, 7.5 Hz, 1H), 2.76 (d, *J* = 19.6 Hz, 1H), 2.59-2.47 (m, 1H), 2.38-2.30 (m, 1H), 2.24 (ddd, *J* = 18.0, 7.7, 2.9 Hz, 1H), 2.11 (dt, *J* = 12.3, 4.4 Hz, 1H), 2.06 (dd, *J* = 11.9, 2.7 Hz, 2H), 1.85 (d, *J* = 13.1 Hz, 1H), 1.82-1.75 (m, 1H), 1.56 (s, 9H), 1.53 – 1.36 (m, 3H), 1.35 – 1.24 (m, 1H), 0.88 (d, *J* = 6.3 Hz, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 170.97 , 156.66 , 154.06 , 141.95 , 136.42 , 118.56 (q, *J* = 320.4 Hz), 112.62 , 84.64 , 62.77 , 44.66 , 42.41 , 41.40 , 34.43 , 32.39 , 30.99 , 27.56 , 24.62 , 22.31 , 21.49. **IR (film)** v = 3082.03, 2928.09, 1737.73, 1676.68, 1597.25, 1571.54, 1448.23, 1417.25, 1368.74, 1343.90, 1290.80, 1250.60, 1209.16, 1170.58, 1139.01, 931.93, 918.54, 881.20, 847.21, 600.03. **HRMS (ESI)** calcd for $[C_{22}H_{38}F_3N_2O_6S]^+$ $(M+H)^+$: *m/z* 505.1615 found 505.1613

**Acid 3.38**




**3.37** **3.38**

Amide **3.37** (106 mg, 0.210 mmol) was dissolved in a solution of THF/$H_2O$ (1:1, 2 mL) in a vial (4 mL). LiOH·$H_2O$ (88 mg, 2.10 mmol) was added, the vial was capped, and the reaction mixture was stirred for 8 h at 60 °C. After cooling to room temperature, a solution of 10% AcOH in $H_2O$ was added until the mixture remained acidic. The resulting solution was extracted with DCM (3 X). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure to yield **3.38** as a white foam (58.5 mg, 0.150 mmol, 72%). **$^1$H NMR** (600 MHz, $CD_3OD$) δ 7.63 (d, *J* = 9.4 Hz, 1H), 6.50 (d, *J* = 9.4 Hz, 1H), 2.99 (dd, *J* = 19.3, 7.1 Hz, 1H), 2.48 – 2.07 (m, 6H), 1.94 – 1.83 (m, 1H), 1.75 (d, *J* = 8.7 Hz, 1H), 1.59 – 1.51 (m, 2H), 1.50 – 1.21 (m, 14H), 0.85

(d, *J* = 5.3 Hz, 3H). **$^{13}$C NMR** (126 MHz, $CD_3OD$) δ 165.23, 157.13, 145.09, 142.00, 119.42, 119.40, 117.67, 58.61, 43.52, 34.33, 31.70, 30.77, 29.54, 28.80, 27.32, 25.09, 25.05, 22.12, 21.96. **IR (film)** v = 2952.42 (broad), 2922.94, 1705.41, 1652.49, 1614.69, 1555.01, 1491.46, 1456.10, 1366.66, 1246.67, 1163.91, 912.33, 835.41, 731.02. **HRMS (ESI)** calcd for $[C_{21}H_{31}N_2O_5]^+$ $(M+H)^+$: *m/z* 391.2227 found 391.2223.

### 3.6 References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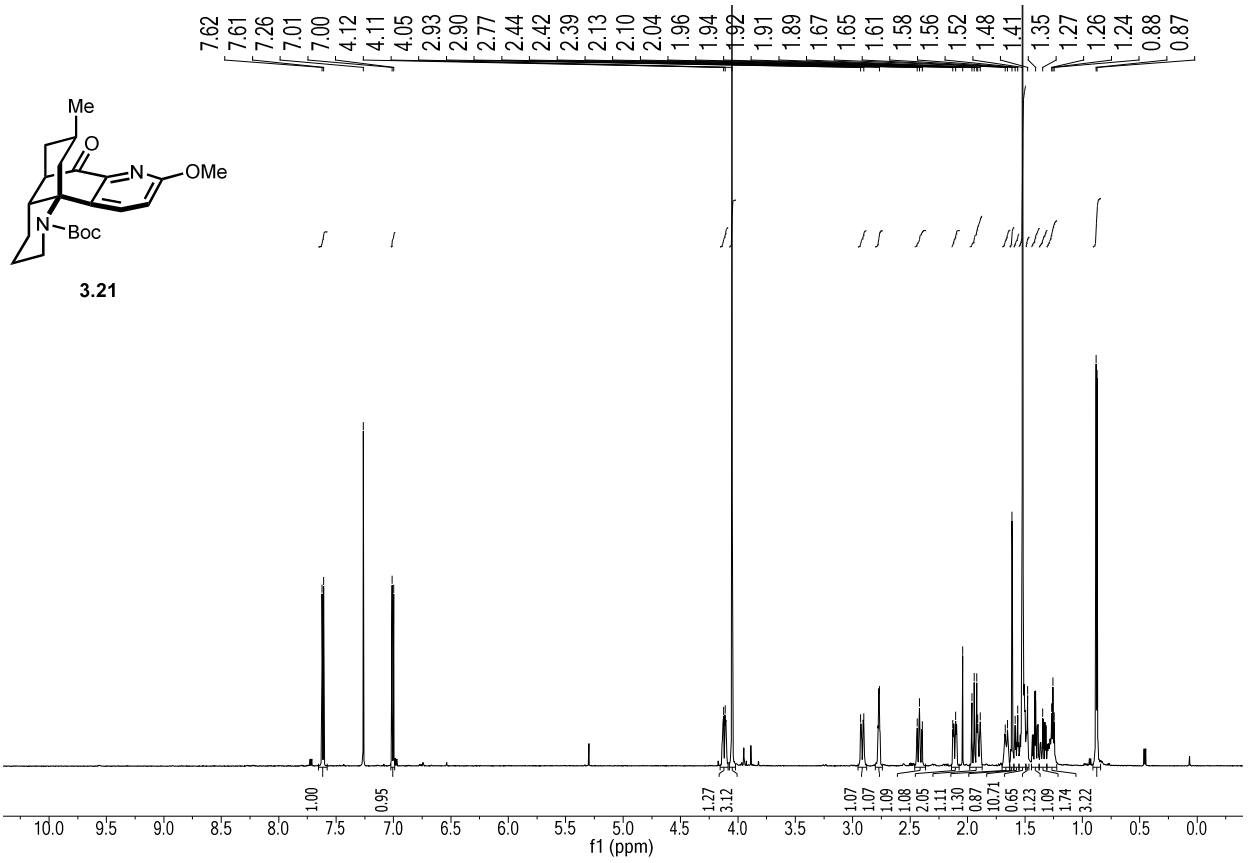
# APPENDIX TWO

## Spectra Relevant to Chapter Three:

Synthesis of the Casuarinine Family of *Lycopodium* Alkaloids by the Late-Stage C-H Functionalization of Lycodine Derivatives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7.61
7.26
7.01
7.00
4.12
4.11
4.05
2.93
2.90
2.77
2.44
2.42
2.39
2.13
2.10
2.04
1.96
1.94
1.92
1.91
1.89
1.67
1.65
1.61
1.58
1.56
1.52
1.48
1.41
1.35
1.27
1.26
1.24
0.88
0.87
Me
O
N
OMe
N
Boc
3.21
1.00
0.95
1.27
3.12
1.07
1.07
1.09
1.08
2.05
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1.23
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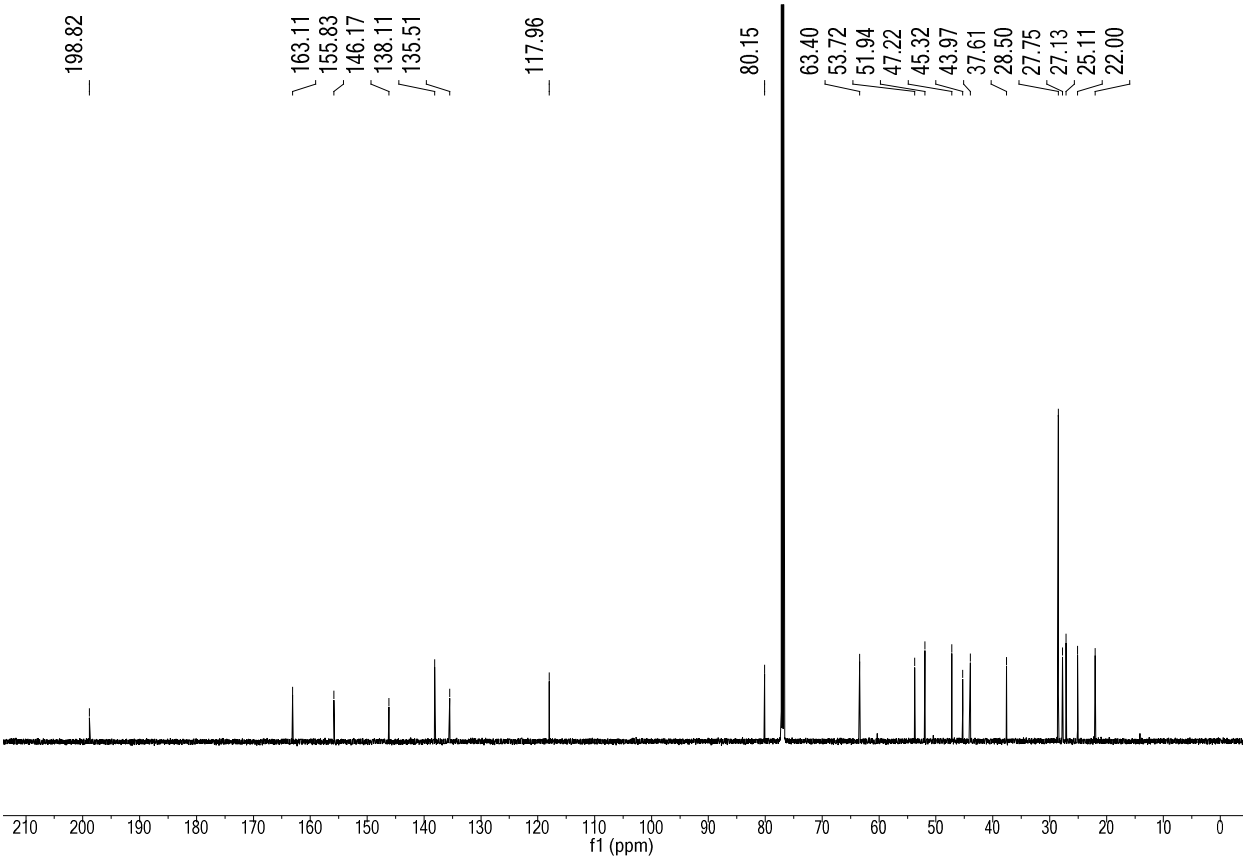
1.74
3.22
f1 (ppm)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27.13
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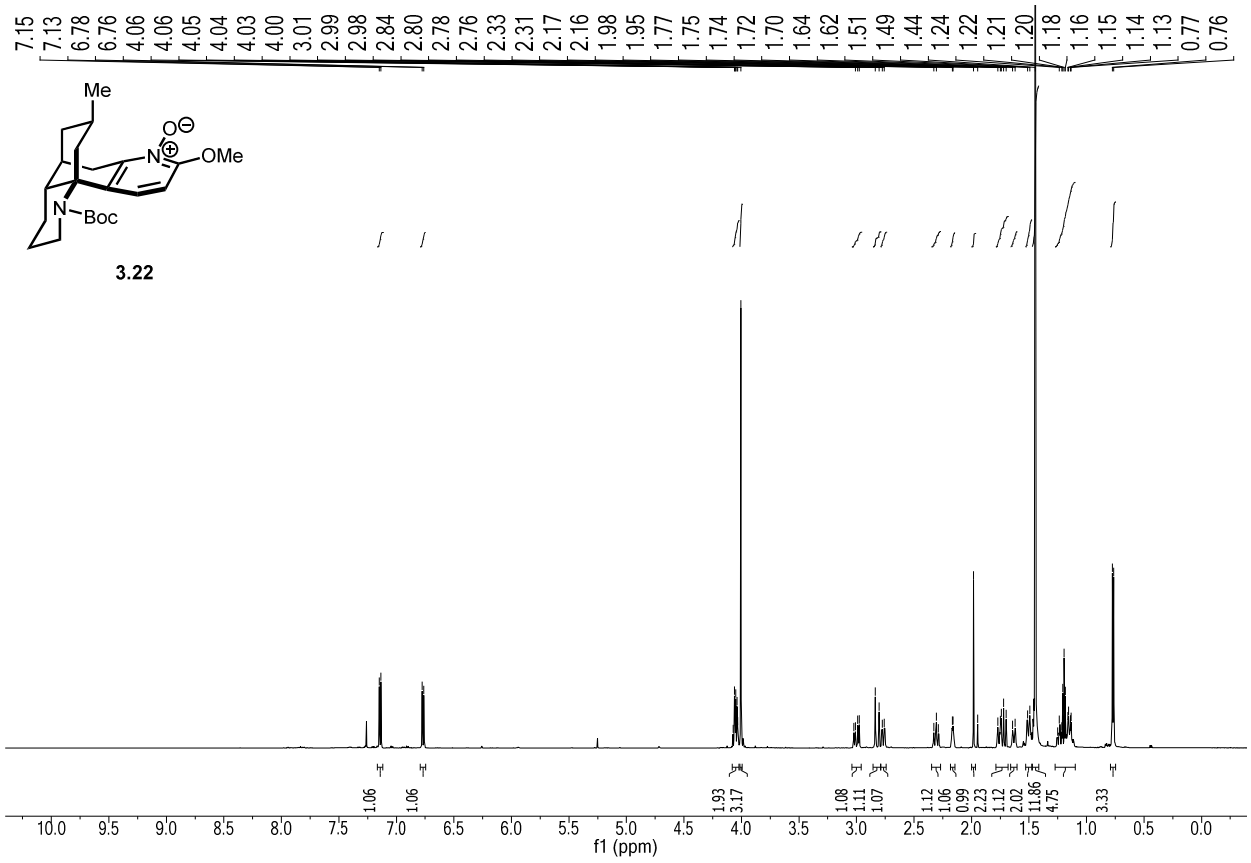
22.00
f1 (ppm)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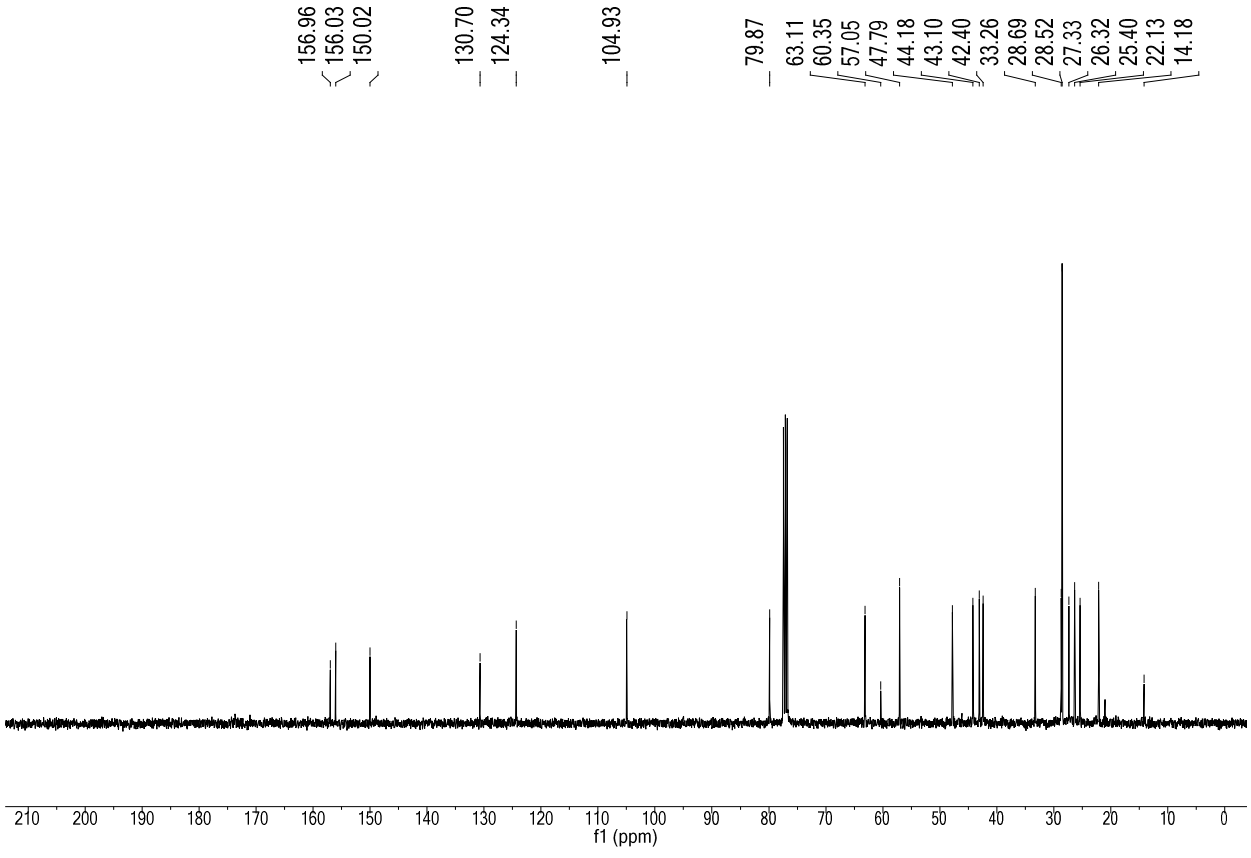
Me
OMe
N
Boc
3.22
1.06 1.06 1.93 3.17 1.08 1.11 1.07 1.12 1.06 0.99 2.23 1.12 2.02 11.86 4.75 3.33
f1 (ppm)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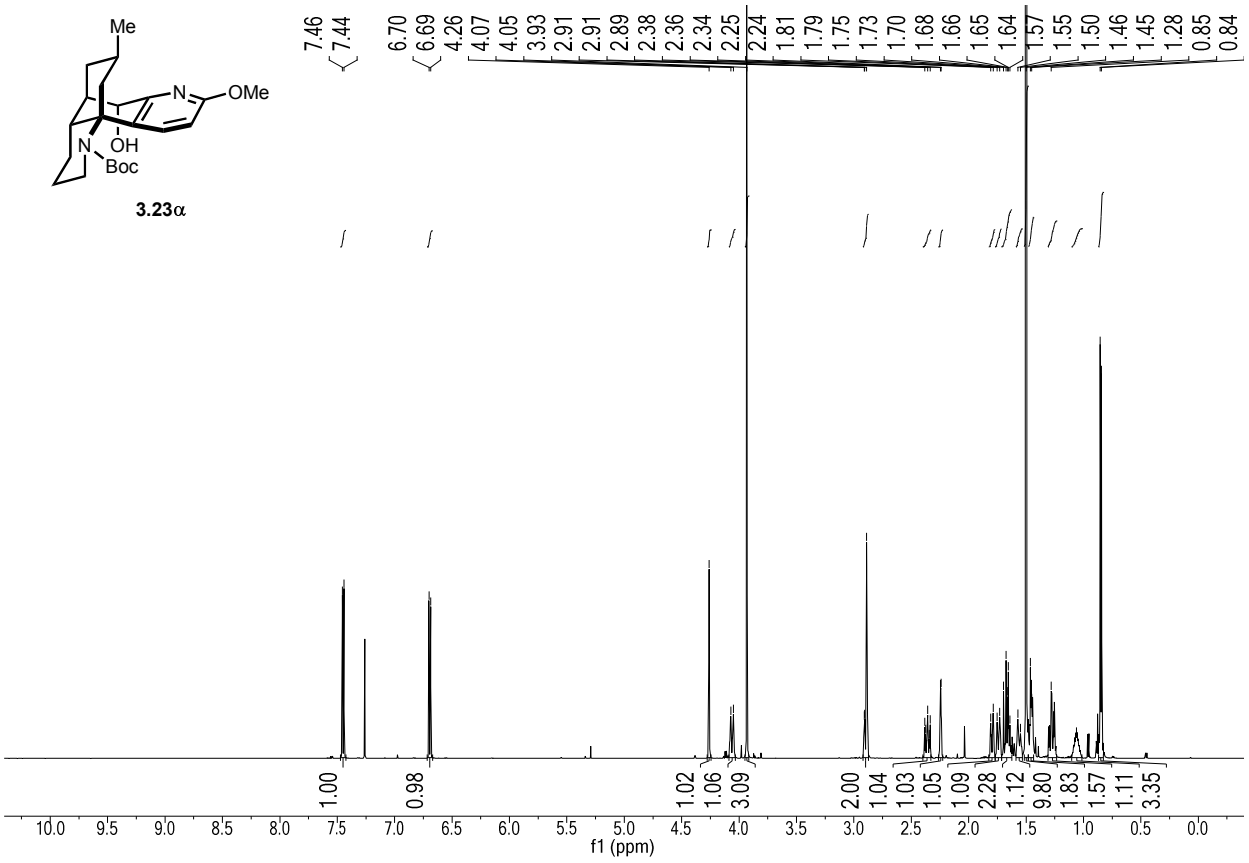
f1 (ppm)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Boc
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6.69
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4.07
4.05
3.93
2.91
2.91
2.89
2.38
2.36
2.34
2.25
2.24
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1.79
1.75
1.73
1.70
1.68
1.66
1.65
1.64
1.57
1.55
1.50
1.46
1.45
1.28
0.85
0.84
1.00
0.98
1.02
1.06
3.09
2.00
1.04
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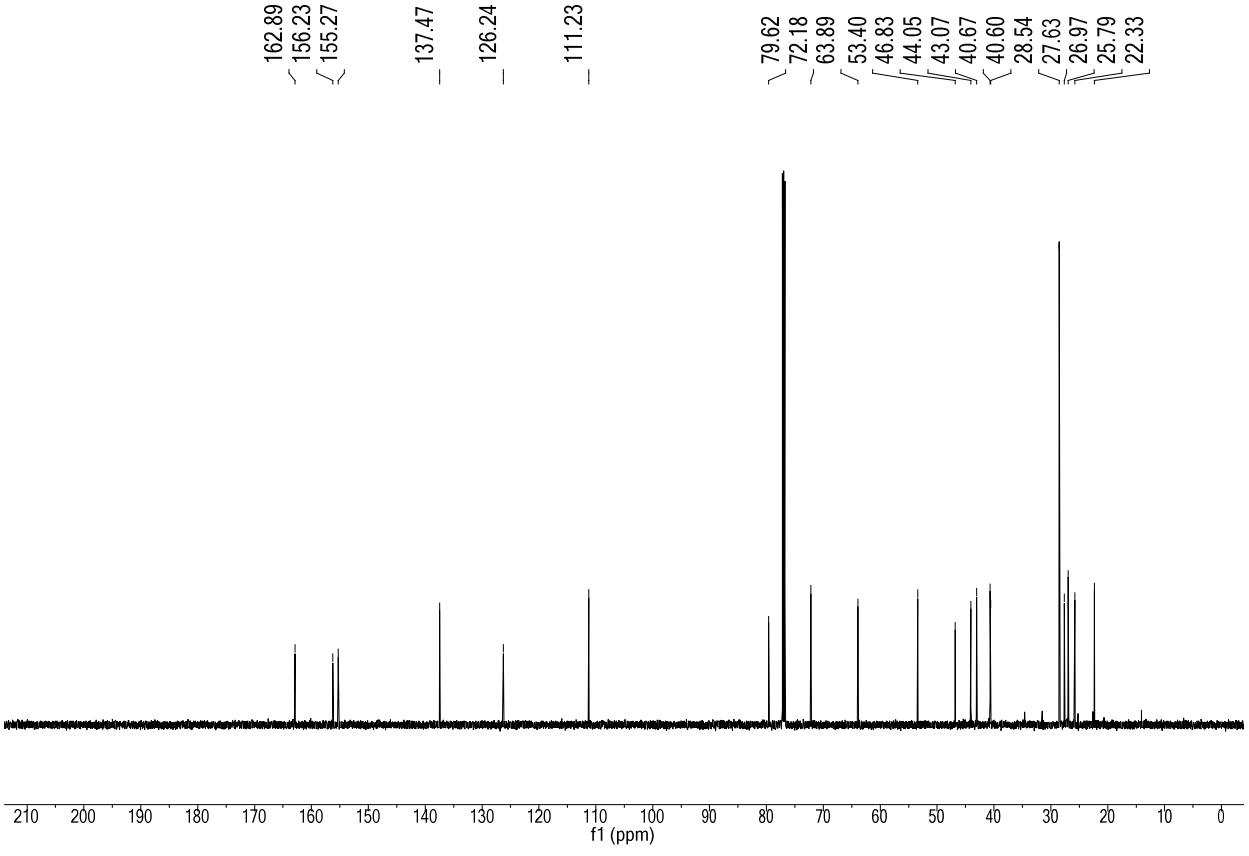
f1 (ppm)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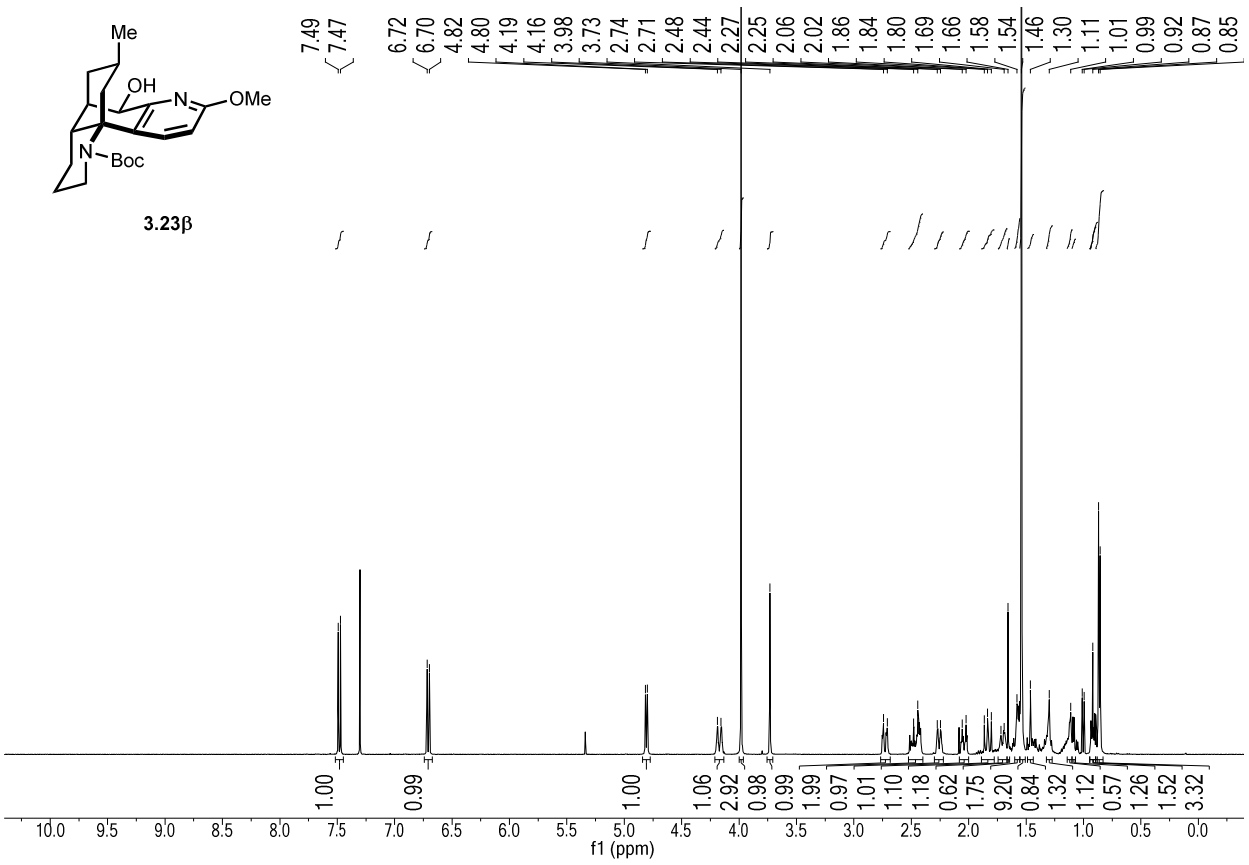
22.33
f1 (ppm)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2.48
2.44
2.27
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0.85
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2.92
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0.97
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1.18
0.62
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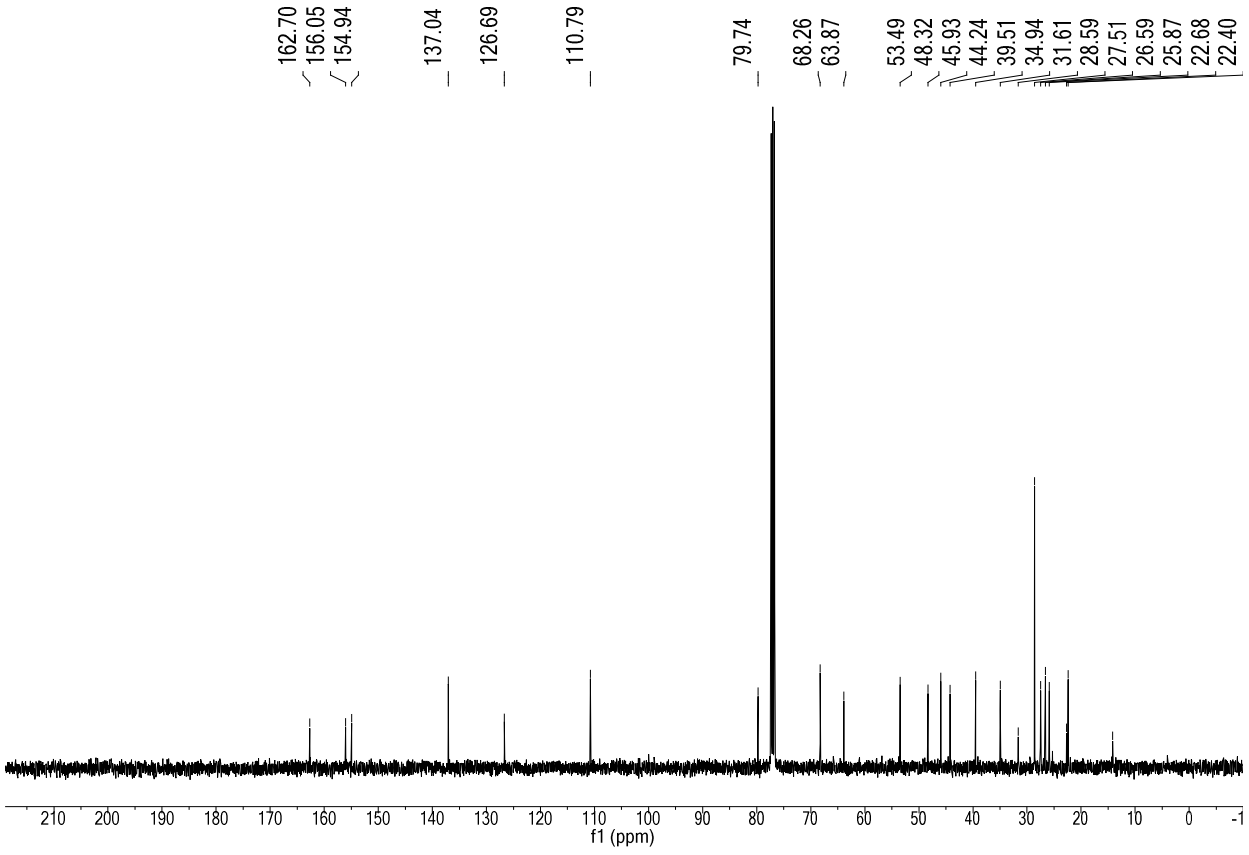
f1 (ppm)

**3.23β**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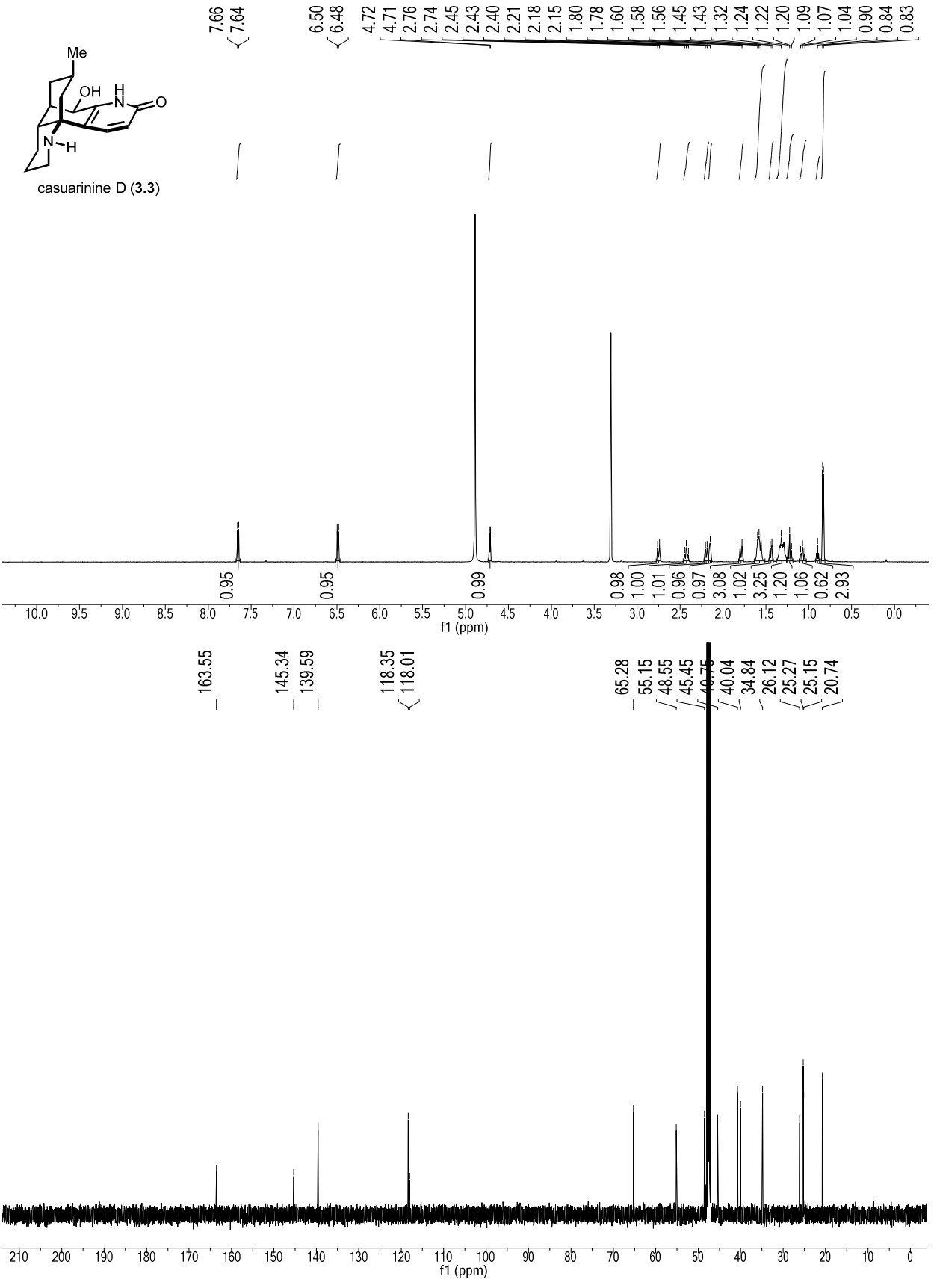
f1 (ppm)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O
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H
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0.95
0.99
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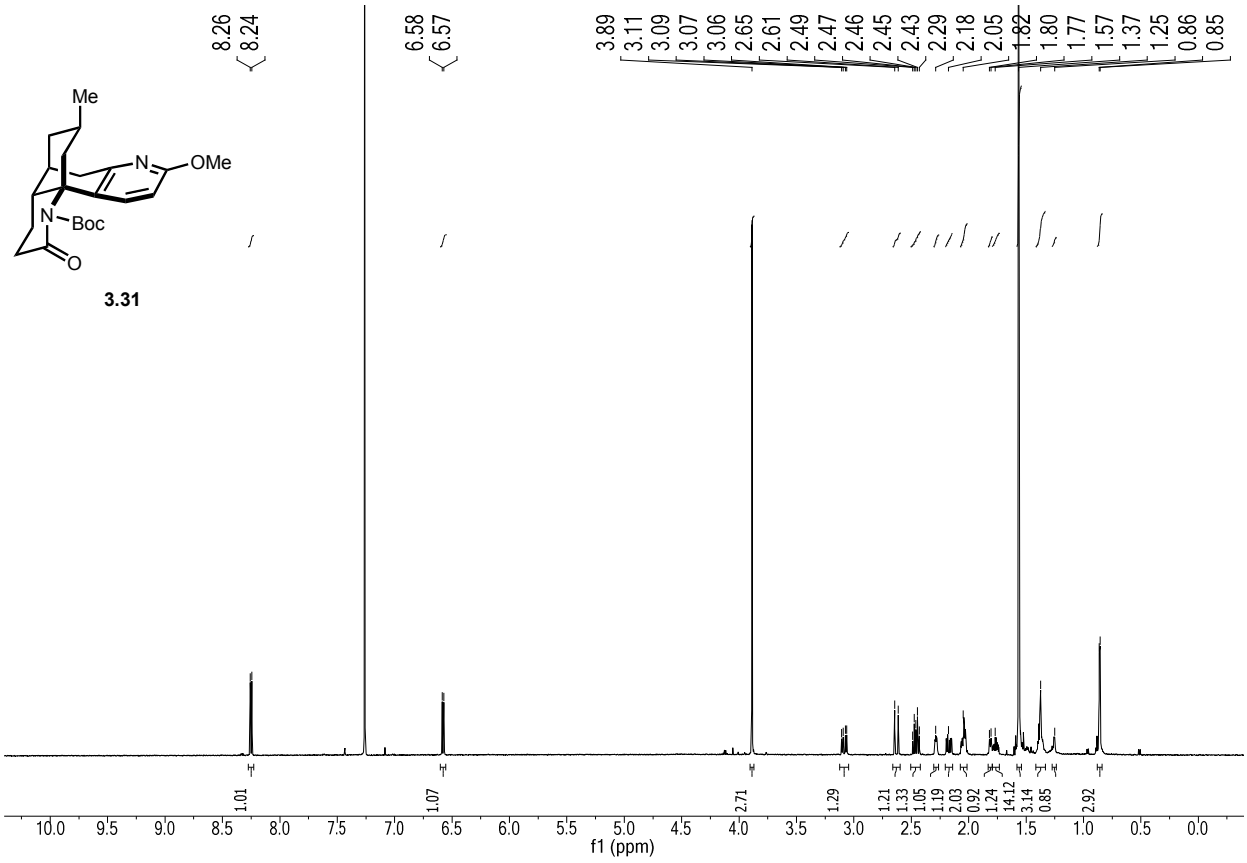
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2.46
2.45
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2.29
2.18
2.05
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1.77
1.57
1.37
1.25
0.86
0.85
Me
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OMe
N
Boc
O
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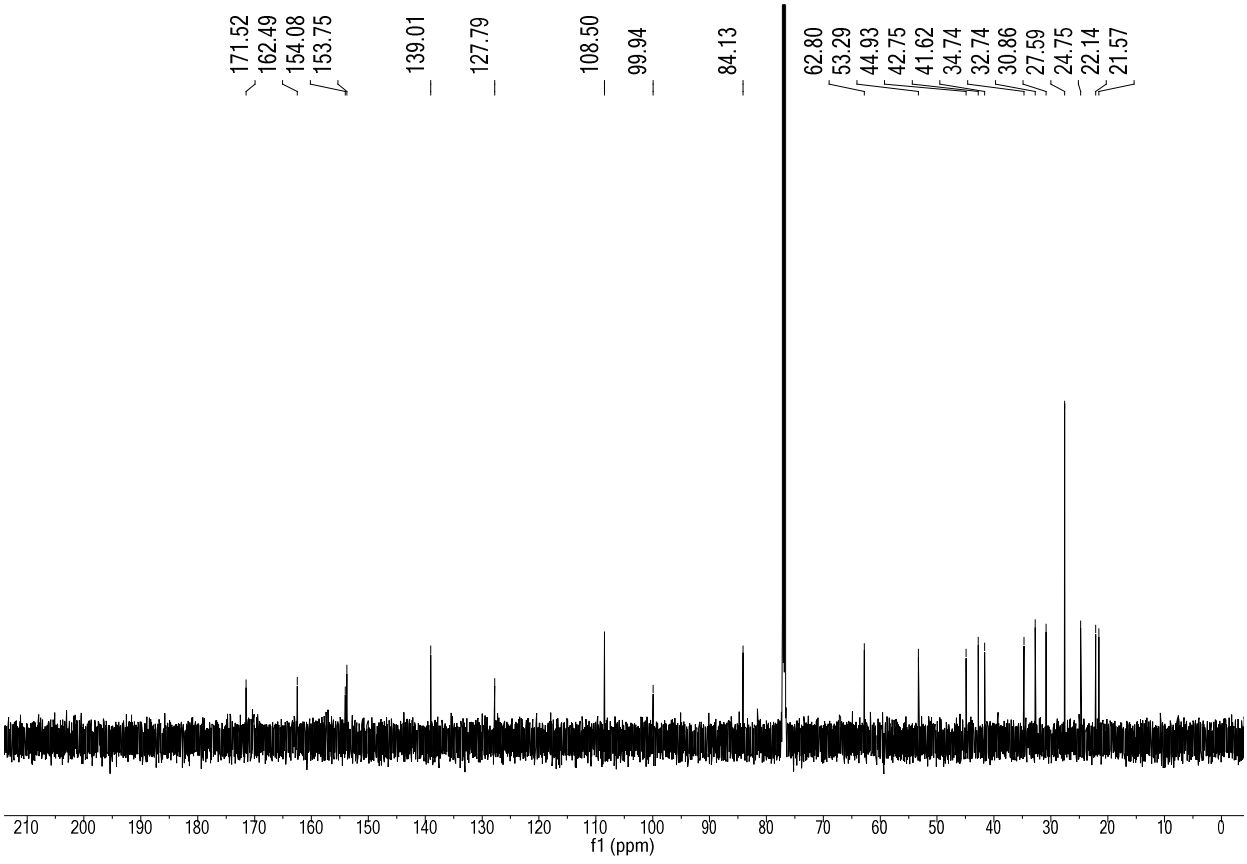
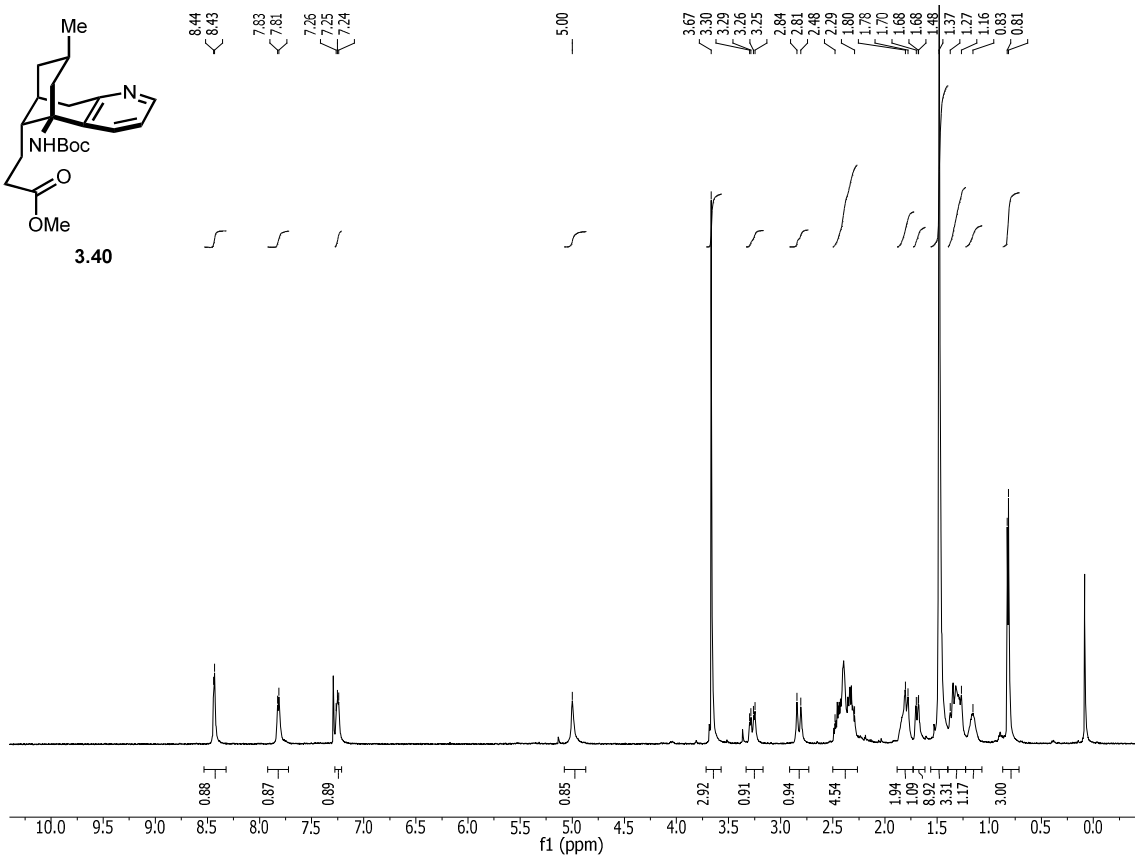
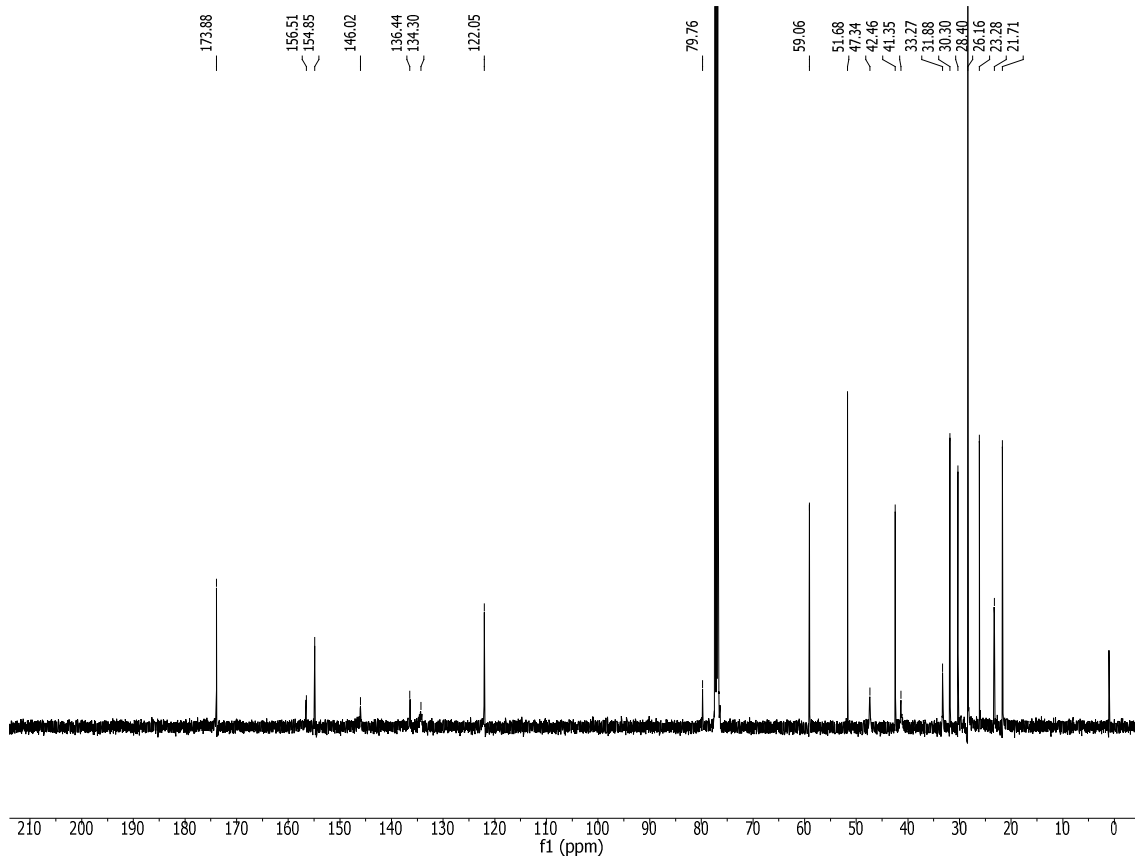
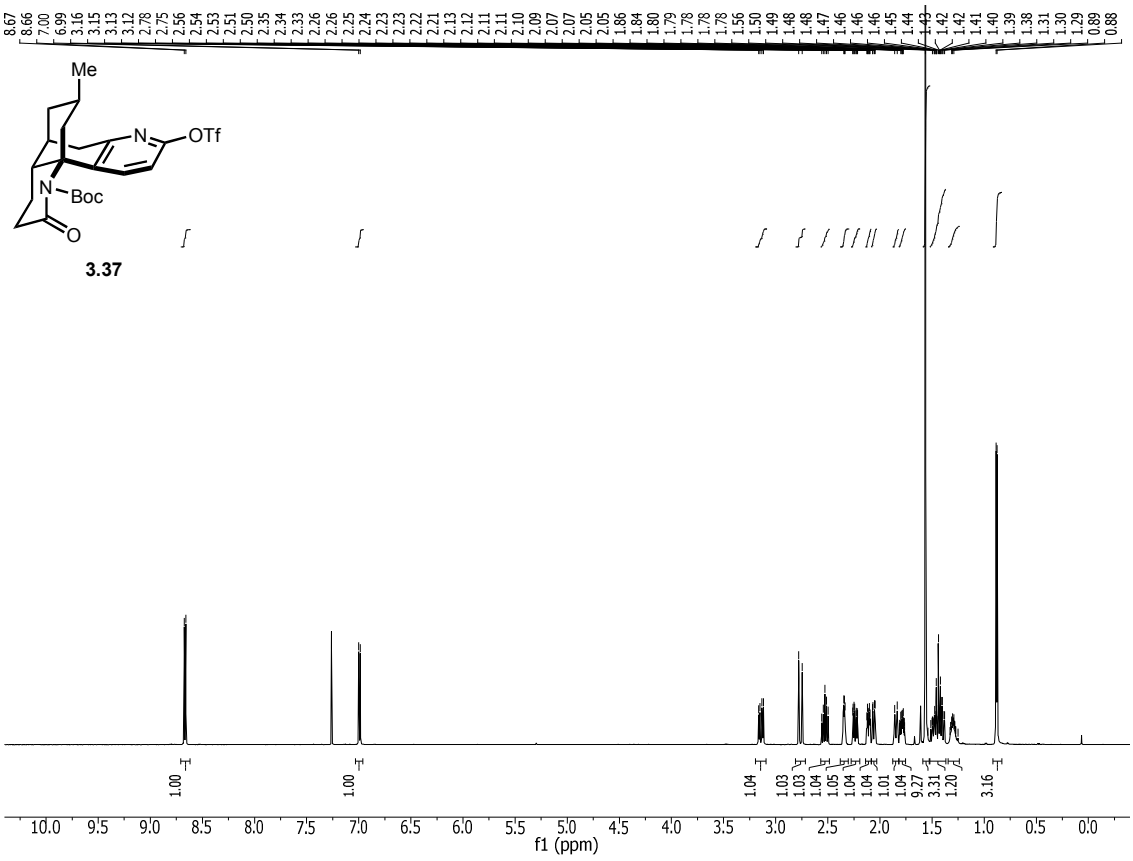
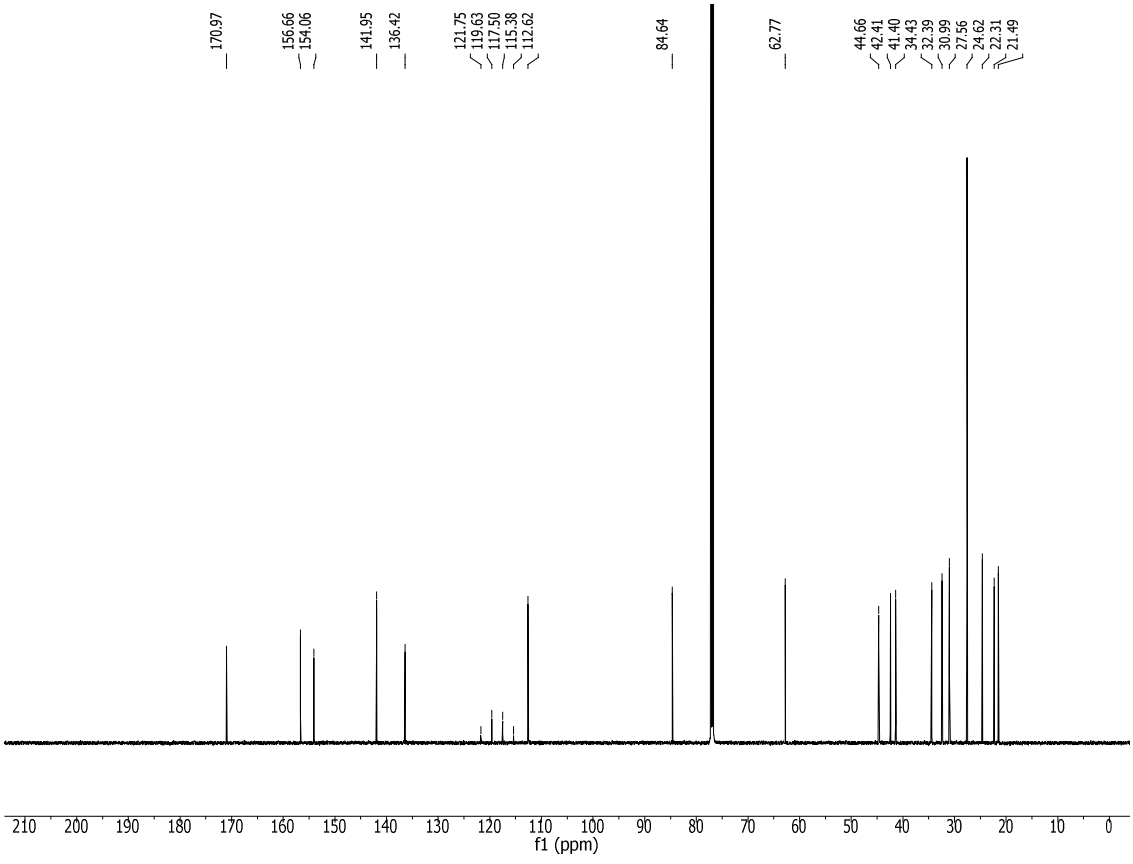
1.01
1.07
2.71
1.29
1.21
1.33
1.05
1.19
2.03
0.92
1.24
14.12
3.14
0.85
2.92
f1 (ppm)

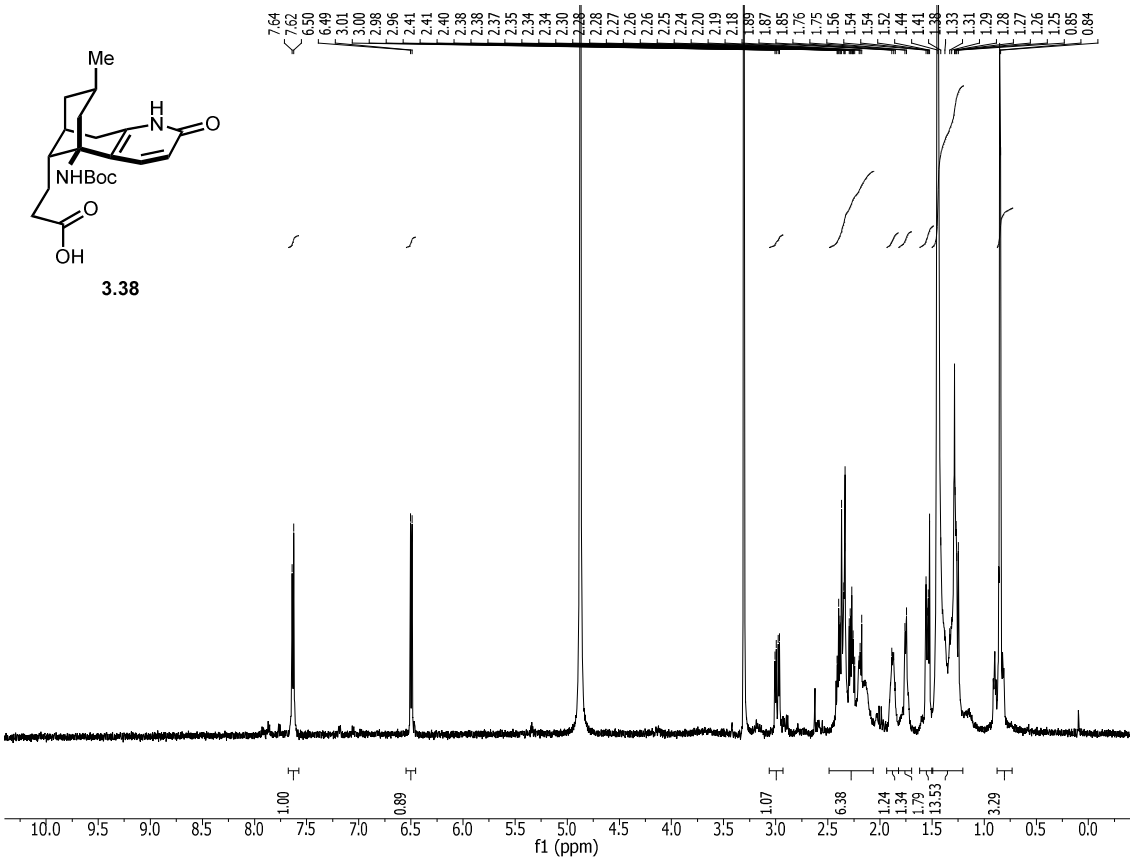

171.52
162.49
154.08
153.75
139.01
127.79
108.50
99.94
84.13
62.80
53.29
44.93
42.75
41.62
34.74
32.74
30.86
27.59
24.75
22.14
21.57
f1 (ppm)

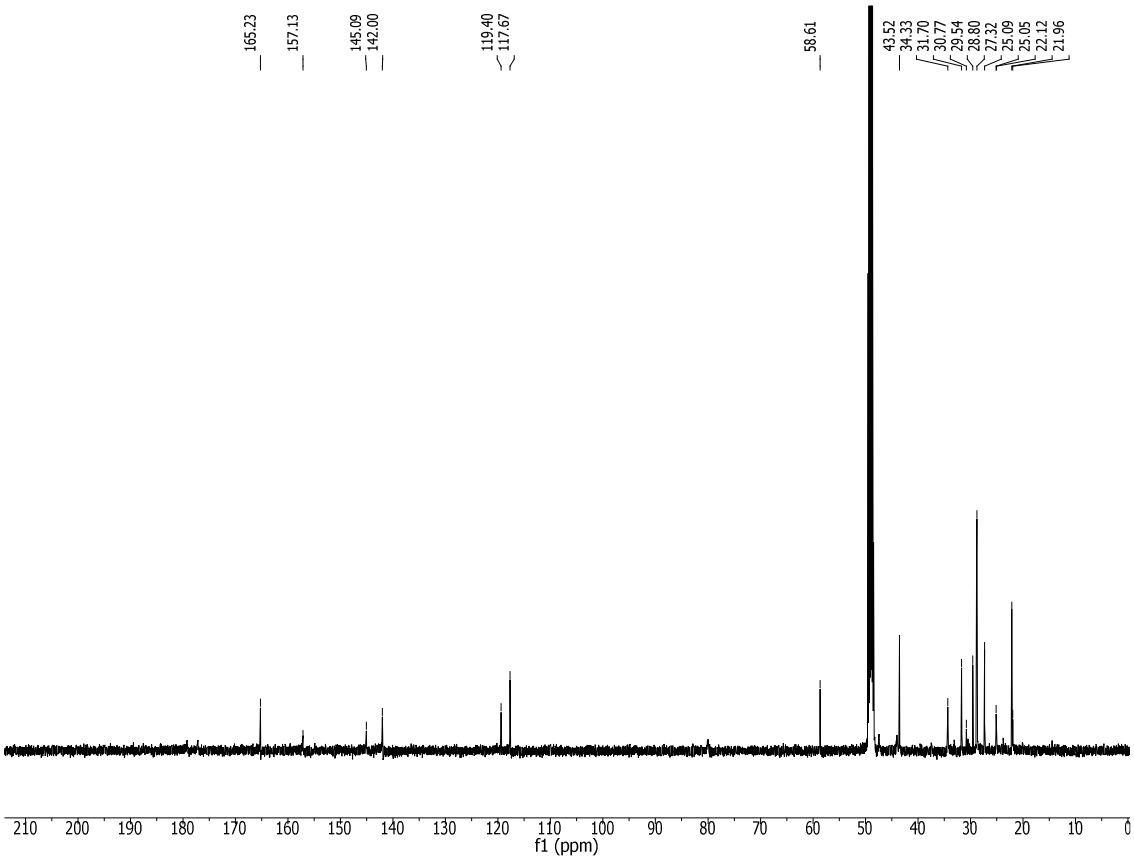

Me
N
NHBoc
O
OMe
3.40
f1 (ppm)


f1 (ppm)


Me
N
OTf
N
Boc
O
3.37
f1 (ppm)


f1 (ppm)


Me
H
N
O
NHBoc
O
OH
3.38
f1 (ppm)


f1 (ppm)