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Total Synthesis of (±) and (+)-Lyconadin A
and
Mechanistic Studies of Oxidative C-N Bond Formation

By

Scott P. West

A dissertation submitted in partial satisfaction of the

requirements for the degree of

Doctor of Philosophy

in

Chemistry

in the

Graduate Division

of the

University of California, Berkeley

Committee in Charge:

Professor Richmond Sarpong, Chair
Professor Jonathan A. Ellman
Professor Isao Kubo

Spring 2010

Abstract

Total Synthesis of (±) and (+)-Lyconadin A
and
Mechanistic Studies of Oxidative C-N Bond Formation

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Scott P. West

Doctor of Philosophy in Chemistry

University of California, Berkeley

Professor Richmond Sarpong, Chair

An overview of the *Lycopodium* alkaloids is presented covering their isolation, structural classification and biosynthesis. The isolation, biological activity and biosynthesis of the miscellaneous group of the *Lycopodium* alkaloids are discussed in detail. Synthetic studies on the miscellaneous *Lycopodium* alkaloids are summarized and an overview of a previous total synthesis of (+)-lyconadin A and an approach to lyconadin A is presented.

The development of a unified strategy to access several miscellaneous *Lycopodium* alkaloids has been achieved. Utilizing this approach, the racemic and enantioselective syntheses of lyconadin A were achieved in 17 steps. Key strategic bond formations in the synthesis include olefin cross-metathesis, intramolecular Heck reaction, Curtius rearrangement, and intramolecular reductive amination. The lyconadin pentacycle was assembled by an unprecedented oxidative C-N bond-forming reaction from a dianion intermediate. The enantioselective route utilizes a Corey-Bakshi-Shibata reduction and a diastereoselective hydrogenation to set three key stereocenters.

An overview of oxidative bond-forming reactions from dianion intermediates is presented. The mechanism of the oxidative C-N bond formation was examined. NMR studies and DFT calculations were conducted to investigate the structure of the dianion intermediate. Several oxidants were found to promote C-N bond formation by oxidation of the dianion intermediate. The reactivity studies revealed that the C-N bond formation may proceed by polar or SET mechanisms and that the mechanistic pathway is dependent on the type of oxidant utilized.

To Sarah,
For all of her support.

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Laura Miller, my fellow classmate, accompanied me on countless Strada runs to decompress from lab. Our daily strada runs made each day of graduate school a little bit easier. It was great to have a friend like Laura in lab that I could always turn to for support, to vent and to talk with about anything on my mind. During the many high and low points during the 5 years of graduate school that Laura and I have shared, I was always glad to have her as a supportive friend and labmate.

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Sarah C. Bell has been my partner through the many years of graduate school. Her unconditional support has made my time in graduate school so much better. She has always been there to talk about chemistry and lab or to go on adventures to take a break from lab. I am grateful to have a supportive partner in Sarah that has helped me make it through graduate school and more importantly, to have a great time going through it.

Finally, I want to thank all of my friends and family for their support.

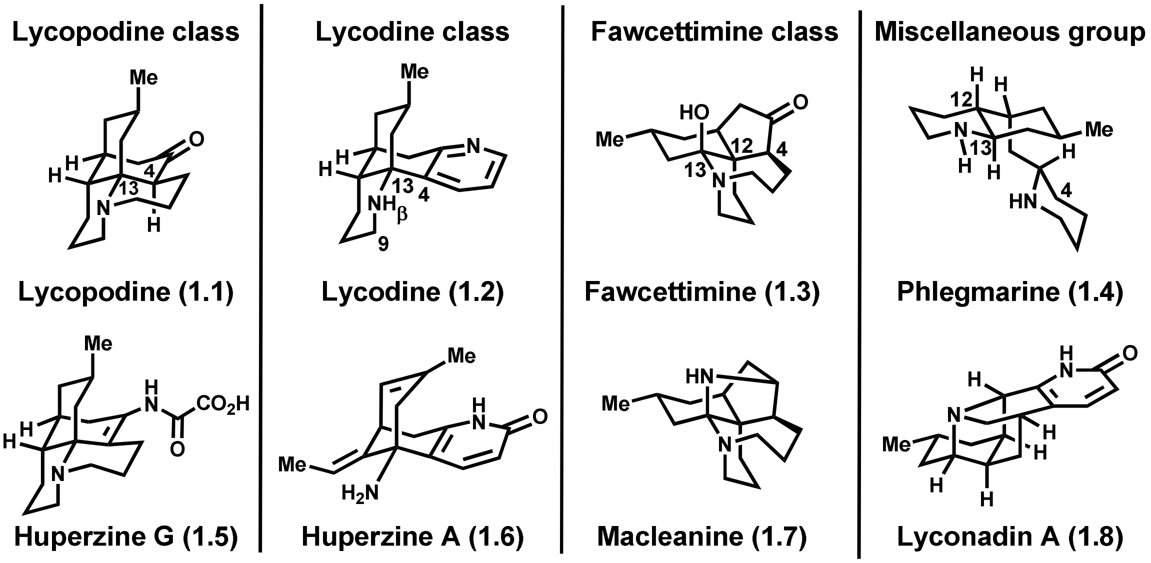
Chapter 1. Total Synthesis of (±) and (+)-Lyconadin A

1.1 *Lycopodium* Alkaloids Background

The *Lycopodium* alkaloids are a group of over 250 natural products that possess diverse architectures and interesting bioactivity ranging from neurotrophic activity to anticancer properties. Initial investigations of *Lycopodium* alkaloids began in the 19th century with the isolation of lycopodine (**1.1**, Figure 1.1) by Bödeker in 1881.[1] The isolation of thirty-five alkaloids from *Lycopodium* club mosses by Manske and Marion in the late 1940s initiated extensive investigations to determine the structures of these *Lycopodium* alkaloids.[2] Following the isolation work by Manske and Marion, several Canadian research groups, including the groups of Ayer, Burnell, MacLean, and Wiesner, pioneered the isolation, structural elucidation, and biogenesis of numerous other *Lycopodium* alkaloids.[3] The complex structures of the *Lycopodium* alkaloids have inspired a plethora of synthetic endeavors.[2,4,5] In the late 1980s, the discovery that several *Lycopodium* alkaloids were potent inhibitors of acetylcholinesterase stimulated further research in this area. [6-9] Due to the unique architectures and interesting biological activity of this family of alkaloids, the isolation, structure elucidation, and synthesis of *Lycopodium* alkaloids have continued to attract extensive interest from the scientific community.

The *Lycopodium* alkaloids are divided into four structural classes: lycopodine, lycodine, fawcettimine, and the miscellaneous group (Figure 1.1).[2] The lycopodine family is characterized by a tetracyclic core composed of four connected 6-membered rings (e.g., lycopodine (**1.1**)) and is the largest class comprising seventy-nine alkaloids. Members of the lycodine family (e.g., lycodine (**1.2**)) contain a tetracyclic core possessing an annulated pyridine or pyridone moiety. Several notable members of the lycodine family, including huperzines A (**1.6**), C, and D, are the products of cleavage of the βN-C9 bond of the lycodine tetracycle. The fawcettimine group (see **1.3** and **1.7**) is classified by a tetracyclic ring system composed of two 6-membered rings, a 5-membered ring and a 7-membered ring. The remainder of the *Lycopodium* alkaloids belong to the miscellaneous group which does not possess unifying structural elements, but instead contains a multitude of different structural motifs. Members of the miscellaneous group are connected via the proposed biogenesis of its members from a common tricyclic intermediate, phlegmarine (**1.4**). Recently, phlegmarine (**1.4**) has been proposed to be a key intermediate in the biosynthesis of the tetracyclic cores of the three other classes via formation of the C4-C12 or C4-C13 bond. Members of the miscellaneous group are distinct from the other three structural classes since they do not possess the C4-C12 or C4-C13 bond.

Figure 1.1. Selected Congeners of the *Lycopodium* Alkaloid Family


Lycopodine class | **Lycodine class** | **Fawcettimine class** | **Miscellaneous group**

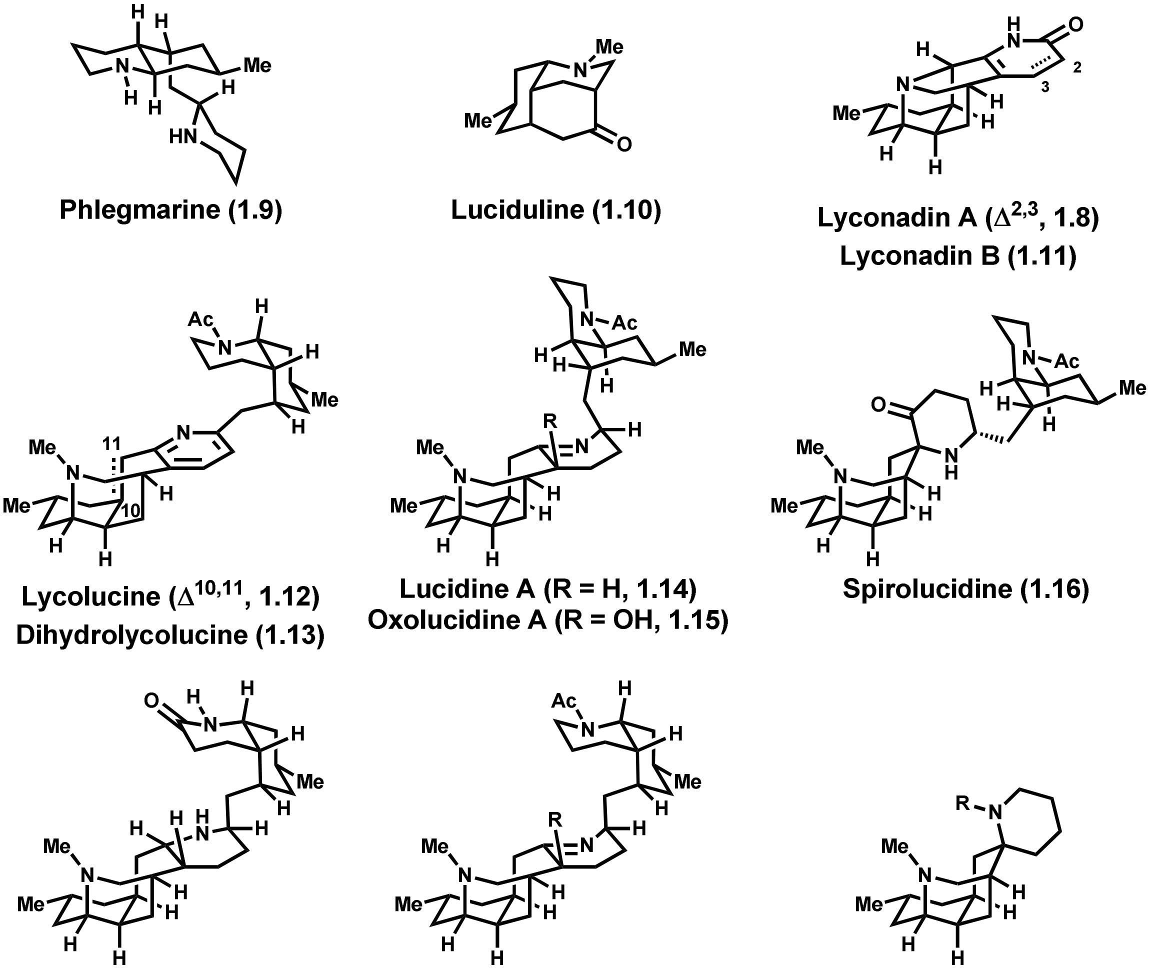
Lycopodine (1.1) | **Lycodine (1.2)** | **Fawcettimine (1.3)** | **Phlegmarine (1.4)**

Huperzine G (1.5) | **Huperzine A (1.6)** | **Macleanine (1.7)** | **Lyconadin A (1.8)**

1.2 Isolation of Miscellaneous Lycopodium Alkaloids

The miscellaneous group of *Lycopodium* alkaloids comprises sixty of the 250 *Lycopodium* alkaloids. Due to the unique architectures and interesting biological activity of its members, the miscellaneous group continues to attract interest as evidenced by the isolation and structure elucidation of twenty congeners of the family since 2004.[5] The first examples of alkaloids belonging to the miscellaneous group were isolated from the club moss *Lycopodium lucidulum* by Ayer and co-workers in 1963.[10] Five years after its initial isolation, luciduline (**1.10**, Figure 1.2) was the first miscellaneous group alkaloid to have its structure determined.[11] In addition to luciduline (**1.10**), several alkaloids possessing a $C_{27}N_3$ architecture were isolated from *Lycopodium lucidulum*. Of these alkaloids, the structures of lucidine B (**1.18**), oxolucidine B (**1.19**), lycolucine (**1.12**) and dihydrolycolucine (**1.13**) were the first to be elucidated in 1979.[12] Next, the unique structure of spirolucidine (**1.16**) was determined by X-ray crystallographic analysis of a reduced derivative in 1984. The structure of the remaining alkaloids with $C_{27}N_3$ scaffolds from *L. lucidulum*, lucidine A (**1.14**) and oxolucidine A (**1.15**), were reported in 2000.[13] Huperzine V (**1.17**), an additional member possessing a $C_{27}N_3$ architecture, was isolated from *Huperzia serrata* in 2004.[14] The structural diversity of the miscellaneous group continued to increase with the isolation of the unique pentacyclic alkaloids lyconadins A (**1.8**) and B (**1.11**) from *Lycopodium complanatum* in 2001[15] and 2006,[16] respectively. In addition to lyconadins A and B, lycopladines A-H were recently isolated from *Lycopodium complanatum*.[16-20] Spirocyclic alkaloids nankakurines A (**1.20**) and B (**1.21**), which possess a similar tetracyclic core to spirolucidine, were isolated from *Lycopodium hamiltonii* in 2004 and 2006, respectively.[21,22]

Figure 1.2. Selected Miscellaneous *Lycopodium* Alkaloids


Phlegmarine (1.9)
Luciduline (1.10)
Lyconadin A ($\Delta^{2,3}$, 1.8)
Lyconadin B (1.11)
Lycolucine ($\Delta^{10,11}$, 1.12)
Dihydrolycolucine (1.13)
Lucidine A (R = H, 1.14)
Oxolucidine A (R = OH, 1.15)
Spirolucidine (1.16)
Huperzine V (1.17)
Lucidine B (R = H, 1.18)
Oxolucidine B (R = OH, 1.19)
Nankakurine A (R = H, 1.20)
Nankakurine B (R = Me, 1.21)

1.3 Biological Activity of *Lycopodium* Alkaloids

The most prominent biological activity attributed to *Lycopodium* alkaloid congeners is the potent and selective inhibition of acetylcholinesterase exhibited by members of the lycodine class, specifically huperzine A (**1.6**). Inhibition of acetylcholinesterase has been shown to improve the symptoms of patients with Alzheimer's disease and result in the enhancement of learning and memory. Several drugs that are approved for the treatment of Alzheimer's disease in the US, such as Aricept and Exelon, are acetylcholinesterase inhibitors.[3] The discovery that huperzine A is a potent, selective, and reversible acetylcholinesterase inhibitor has led to numerous studies on its biological activity as well as the activity of synthetic analogs.[23] Huperzine A is currently approved for the treatment of Alzheimer's disease in China and is marketed in the US as a dietary supplement that enhances learning and memory.

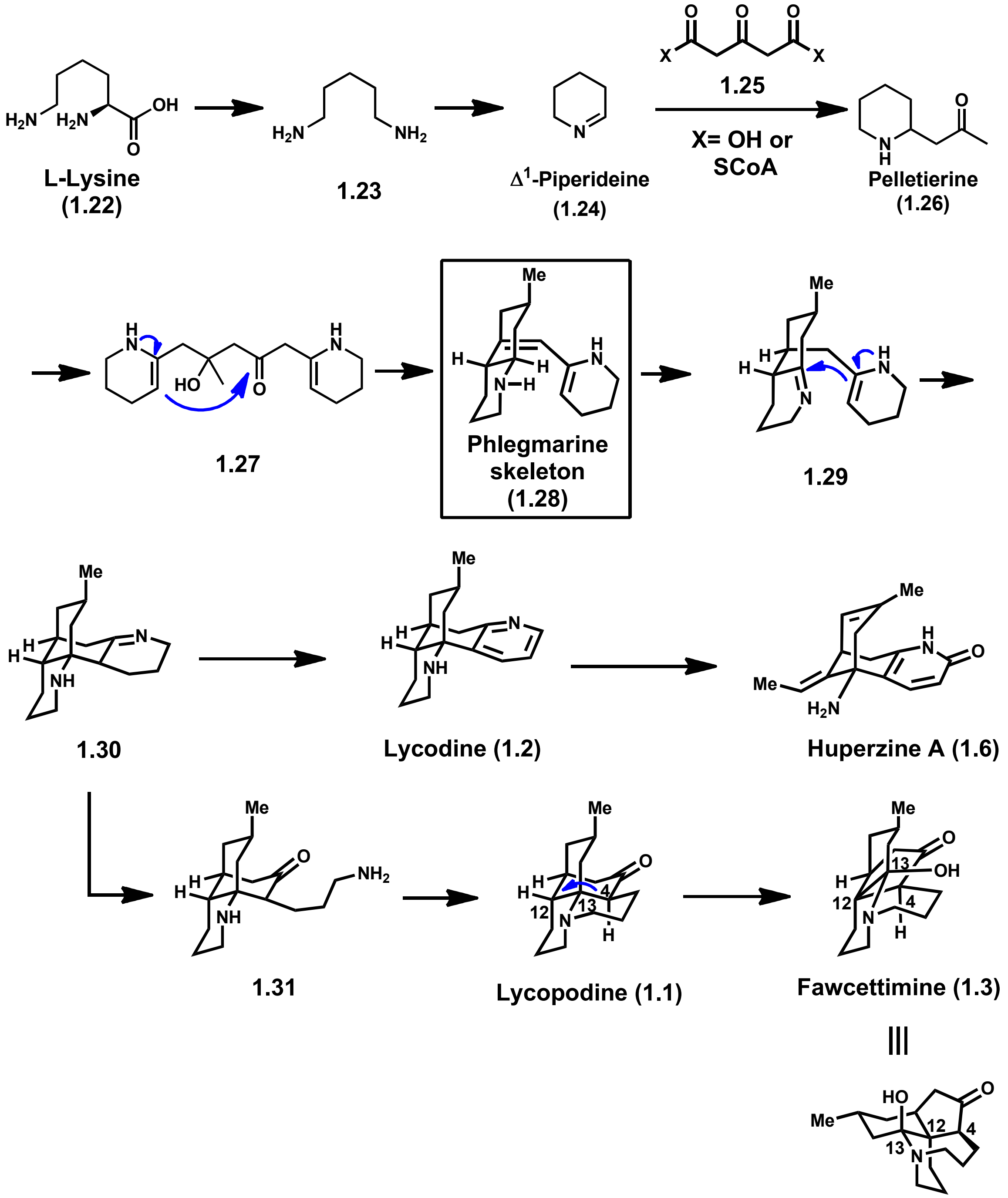
In addition to acetylcholinesterase inhibition, numerous *Lycopodium* alkaloids have been shown to be modest cytotoxic agents against several cancer cell lines and have also exhibited neurotrophic activity. Lyconadin A (**1.8**) displayed cytotoxicity against murine lymphoma L1210 cells (IC_{50} = 0.46 μg/mL) and against human epidermoid carcinoma KB cells (IC_{50} = 1.7 μg/mL).[15] Additionally, lyconadins A (**1.8**) and B (**1.11**) were shown to increase the nerve growth factor (NGF) mRNA expression in 1321N1 human astrocytoma cells,[16] which could result in enhanced NGF biosynthesis and promotion of the growth of neural networks. Compounds that amplify the growth of neural networks have potential utility in the treatment of several neurodegenerative diseases including Alzheimer's and Parkinson's disease. Despite the interesting biological activity of lyconadins A and B, extensive investigation of the pharmacological properties of the majority of miscellaneous *Lycopodium* alkaloids has not been undertaken.

1.4 Biosynthesis of Lycopodium Alkaloids

The unique structures and biological activity of the *Lycopodium* alkaloids have sparked interest in their biogenesis. Despite this interest, only a few studies have been performed to elucidate their biosynthesis due to the difficulty in cultivating *Lycopodium* club mosses.[5] Even the growth of plant tissue culture of *Lycopodium* club mosses has been difficult to achieve.[24]

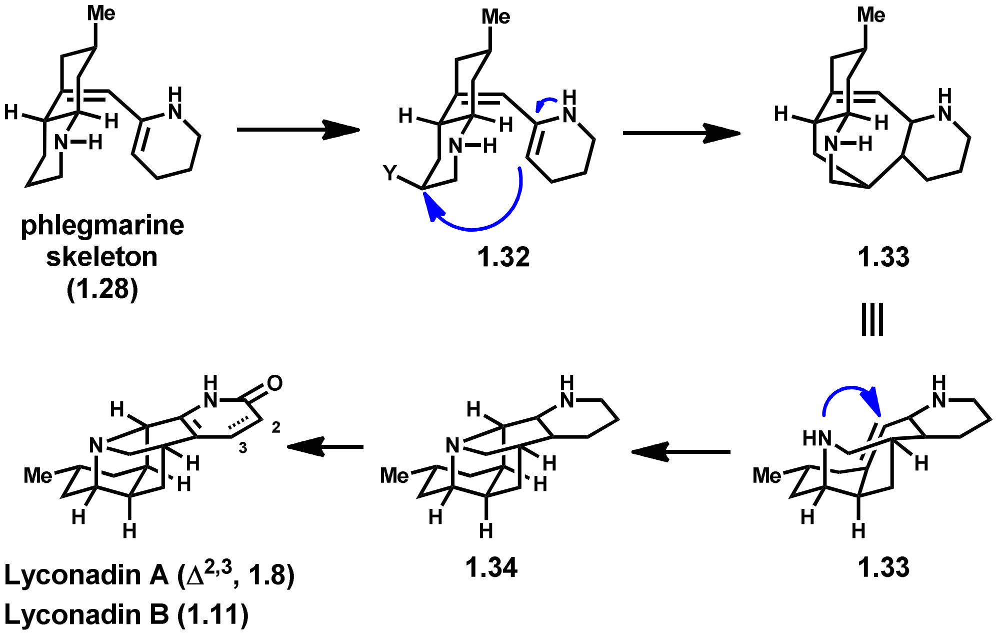
Through extensive feeding studies of *Lycopodium* species in their natural habitat by Spenser and co-workers, the entry point for the biosynthesis of *Lycopodium* alkaloids was determined to be L-lysine (**1.22**, Scheme 1.1).[25-27] Decarboxylation of lysine (**1.22**) provides symmetrical diamine **1.23** which undergoes oxidation followed by condensation to afford Δ^1-piperideine (**1.24**). Union of acetone dicarboxylic acid or its bis-coenzyme A ester (**1.25**) with imine **1.24** and subsequent decarboxylation furnishes pelletierine (**1.26**), a key intermediate in the biosynthesis of all *Lycopodium* alkaloids.[28] Intermolecular aldol addition between two equivalents of pelletierine (**1.26**) provides enamine **1.27** which cyclizes to form the phlegmarine skeleton (**1.28**). Recent evidence suggests that phlegmarine (**1.4**) or a closely related derivative (**1.28**) is a central intermediate and the key point of divergence for the different structural classes of *Lycopodium* alkaloids.[29] Oxidation of **1.28** to imine **1.29** followed by intramolecular cyclization provides tetracyclic amine **1.30**. Oxidation of **1.30** to a pyridine moiety provides lycodine (**1.2**) which can undergo further oxidation and cleavage of the piperidine ring to furnish huperzine A (**1.6**). Alternatively, hydrolysis of imine **1.30** can provide diamine **1.31**, which can undergo cyclization to afford lycopodine (**1.1**). Subsequent skeletal rearrangement of lycopodine via migration of the C4-C12 bond to form the C4-C13 bond provides access to fawcettimine (**1.3**).

Scheme 1.1. Biosynthesis of Lycodine, Lycopodine and Fawcettimine Classes

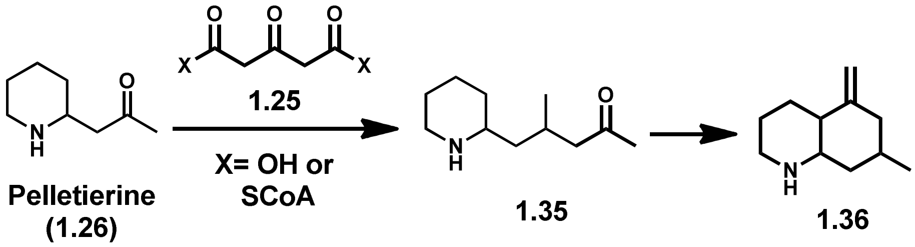

L-Lysine
(1.22)
1.23
Δ1-Piperideine
(1.24)
1.25
X= OH or SCoA
Pelletierine
(1.26)
1.27
Phlegmarine skeleton
(1.28)
1.29
1.30
Lycodine (1.2)
Huperzine A (1.6)
1.31
Lycopodine (1.1)
Fawcettimine (1.3)

The biosynthesis of the miscellaneous group diverges from the other classes by functionalization of the piperidine ring of amine **1.28** to provide tricycle **1.32** (Scheme 1.2). Attack of the enamine moiety of **1.32** to displace nucleofuge Y can furnish tetracycle **1.33**, a key biosynthetic intermediate for several miscellaneous *Lycopodium* alkaloids. Intramolecular hydroamination of olefin **1.33** affords the pentacyclic core of the lyconadins (**1.34**), which can undergo oxidation to provide lyconadins A (**1.8**) and B (**1.11**). Several members of the miscellaneous group possess an additional bicyclic moiety that can arise biosynthetically from pelletierine (**1.26**, Scheme 1.3). Addition of acetonedicarboxylic acid or its bis-CoA ester (**1.25**) to pelletierine (**1.26**) provides access to ketone **1.35**. Cyclization of **1.35** furnishes bicyclic amine **1.36**. Coupling tetracycle **1.33** with bicycle **1.36** affords lycolucine (**1.12**, Scheme 1.4), which upon reduction gives dihydrolycolucine (**1.13**). Additionally, the union of tetracycle **1.33** with alkene **1.36** furnishes lucidine A (**1.14**), which undergoes oxidation to give oxolucidine A (**1.15**). The biosynthesis of amine **1.36** can provide two diastereomers of the bicycle as evidenced by the diastereomeric bicyclic moieties incorporated in dihydrolycolucine (**1.13**) and lucidine A (**1.14**). Ring-contractive rearrangement of the α-hydroxyimine moiety of **1.15** forms the spirocenter and completes construction of spirolucidine (**1.16**). Oxidation of tetracycle **1.33** to α-hydroxyimine **1.37** followed by a similar rearrangement constructs the spirocyclic core of the nankakurines (**1.38**). Reduction of ketone **1.38** provides nankakurine A (**1.20**), which upon methylation affords nankakurine B (**1.21**).

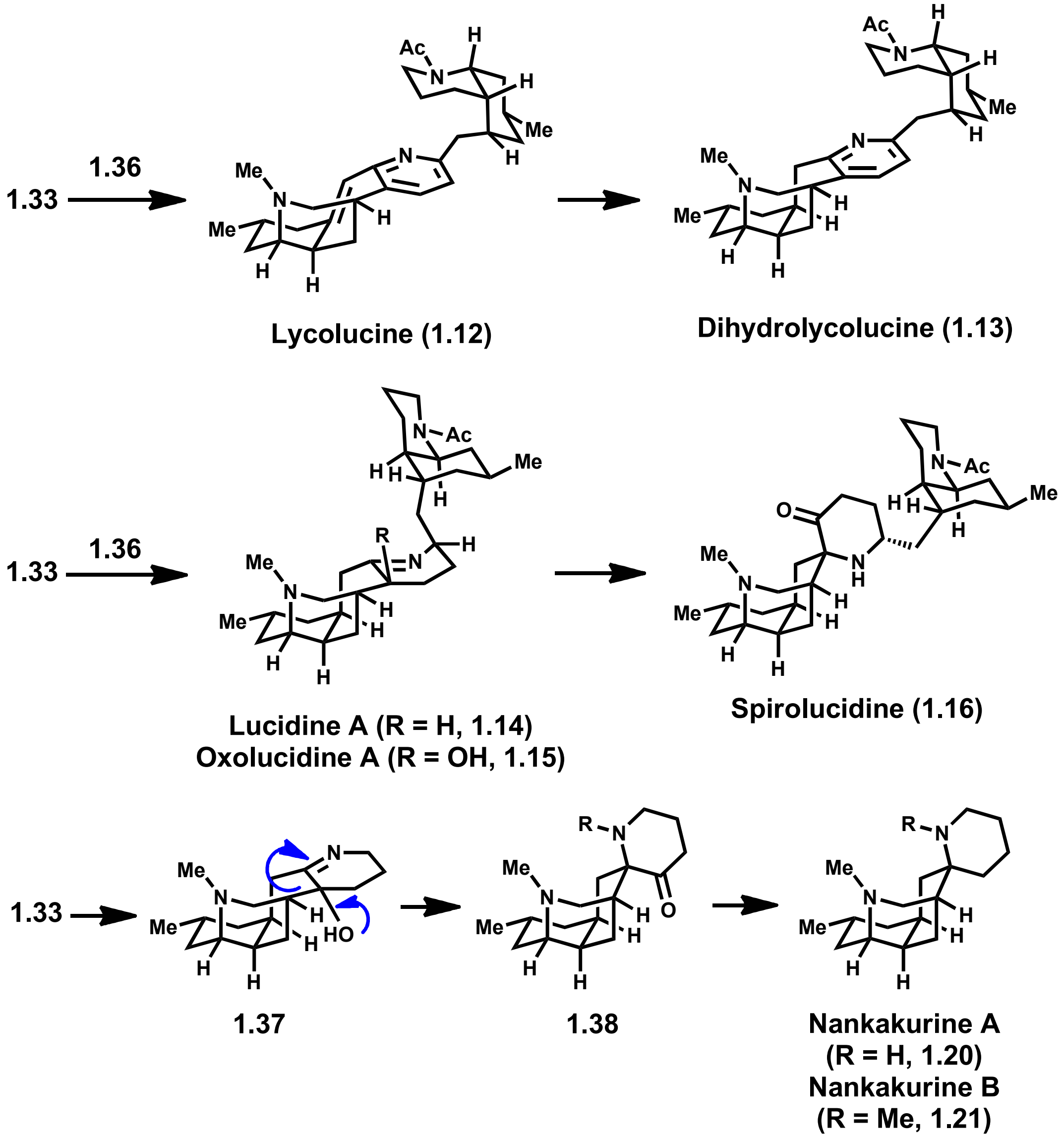
Scheme 1.2. Biosynthesis of Lyconadins A and B


Me
H
H
N–H
phlegmarine skeleton (1.28)
Me
H
H
N–H
Y
1.32
Me
H
H
N–H
1.33
H
N
O
H
N
Me
H
H
2
3
Lyconadin A (Δ^{2,3}, 1.8)
Lyconadin B (1.11)
H
N
H
N
Me
H
H
H
1.34
H
N
HN
Me
H
H
H
1.33

Scheme 1.3. Biosynthesis of Bicycle **1.36**


O
N
H
Pelletierine (1.26)
O O O
X X
1.25
X= OH or SCoA
O
N
H
1.35
N
H
1.36

Scheme 1.4. Biosynthesis of Several Miscellaneous *Lycopodium* Alkaloids


1.33
1.36
Lycolucine (1.12)
Dihydrolycolucine (1.13)
1.33
1.36
Lucidine A (R = H, 1.14)
Oxolucidine A (R = OH, 1.15)
Spirolucidine (1.16)
1.33
1.37
1.38
Nankakurine A
(R = H, 1.20)
Nankakurine B
(R = Me, 1.21)

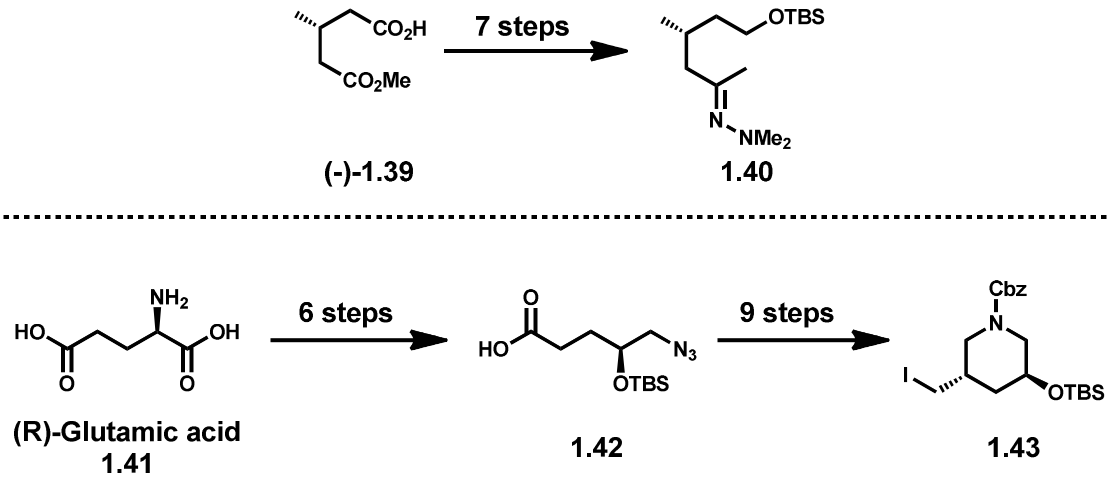
1.5 Previous Synthetic Approaches to Miscellaneous Lycopodium Alkaloids

The biological activity and complex structures of the *Lycopodium* alkaloids have attracted extensive synthetic interest over the years. Recently, the diverse architectures of the miscellaneous group of *Lycopodium* alkaloids have provided inspiration for numerous synthetic endeavors. The first total syntheses of nankakurines A (**1.20**) and B (**1.21**) were achieved by Overman and co-workers by employing an intramolecular dipolar cycloaddition and aza-Prins cyclization.[30] Additionally, Waters and Cheng reported concise syntheses of nankakurines A (**1.20**) and B (**1.21**) via the *Lycopodium* alkaloid luciduline (**1.10**),[31] which had previously been synthesized by Evans and Scott.[32] Approaches to spirolucidine (**1.16**) and dihydrolycolucine (**1.13**) have been presented by Comins and co-workers.[33-35] To date, the total synthesis of any *Lycopodium* alkaloid possessing a $C_{27}N_3$ architecture, (i.e., lucidines A/B (**1.14**, **1.18**) or spirolucidine (**1.16**)) has not been achieved. The unique pentacyclic core of lyconadins A (**1.8**) and B (**1.11**) has sparked interest in their synthesis from our research group in addition to many others. Smith and Beshore reported the first total synthesis of (+)-lyconadin A (**1.8**) and (-)-lyconadin B (**1.11**) in 2007.[36,37] In addition, synthetic approaches to the lyconadins were reported by the groups of Castle[38] and Hsung.[39]

1.5.1 Smith and Beshore's Synthesis of Lyconadins A and B

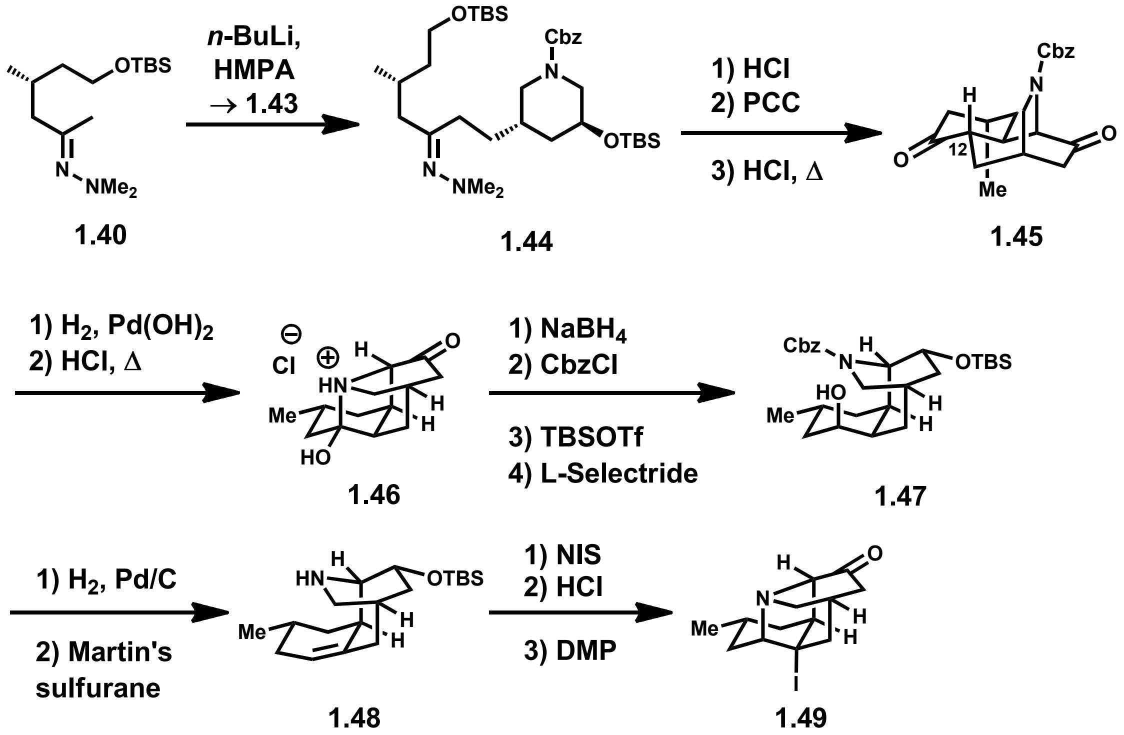
In 2007, Smith and Beshore reported the first total synthesis of lyconadins A (**1.8**) and B (**1.11**). Their synthetic effort commenced with the synthesis of two fragments, **1.40** and **1.43** (Scheme 1.5). Elaboration of (-)-methyl-(*R*)-3-methylglutarate (**1.39**) by a seven step sequence provided hydrazone **1.40**. (*R*)-glutamic acid (**1.41**) was transformed to known acid **1.42**[40] via a six step route. Formation of *trans*-substituted piperidine **1.43** from **1.42** was achieved by a sequence that employed an Evans aldol reaction to furnish the desired *trans* stereochemistry and a reduction-cyclization cascade to provide the piperidine ring.

Scheme 1.5. Smith and Beshore's synthesis of hydrazone **1.40** and piperidine **1.43**



Alkylation of the anion of hydrazone **1.40** with iodide **1.43** afforded piperidine **1.44** (Scheme 1.6). Cleavage of both silyl ethers of **1.44** followed by oxidation with PCC provided the substrate for an acid-catalyzed aldol condensation/conjugate addition cascade, which furnished tricyclic diketone **1.45**. Tricycle **1.45** possesses the incorrect stereochemistry at C12 and prevents the proximal orientation necessary for formation of the key C13-N bond of tetracycle **1.49**. Cleavage of the Cbz group and epimerization under acidic conditions with concomitant hemiaminal formation furnished tetracycle **1.46** bearing the desired stereochemistry at C12. Due to the difficulties encountered in the reduction of hemiaminal **1.46**, an alternate method of forming the tetracycle was explored. Hemiaminal hydrochloride salt **1.46** was elaborated to alcohol **1.47** via a four step sequence. Deprotection of the secondary amine of **1.47** and subsequent dehydration promoted by Martin's sulfurane ($Ph_2S(OCPh(CF_3)_2)_2$)[41] afforded key tricyclic alkene **1.48**. Aminoiodination of **1.48** proceeded smoothly to provide the key tetracyclic core, which was elaborated to ketone **1.49**.

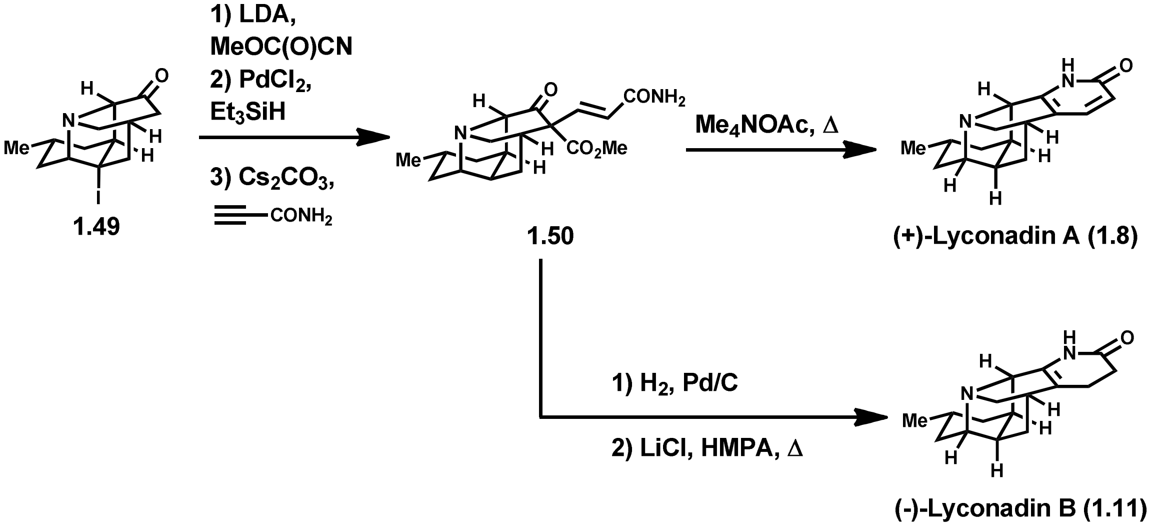
Scheme 1.6. Synthesis of Lyconadin Tetracycle



OTBS
N
NMe2
1.40
n-BuLi,
HMPA
→ 1.43
OTBS
Cbz
N
OTBS
N
NMe2
1.44
1) HCl
2) PCC
3) HCl, Δ
Cbz
N
H
O
12
O
Me
1.45
1) H2, Pd(OH)2
2) HCl, Δ
Cl
HN
H
O
Me
H
H
HO
1.46
1) NaBH4
2) CbzCl
3) TBSOTf
4) L-Selectride
Cbz
N
H
OTBS
HO
Me
H
H
1.47
1) H2, Pd/C
2) Martin's sulfurane
HN
H
OTBS
Me
H
H
1.48
1) NIS
2) HCl
3) DMP
H
O
N
Me
H
H
I
1.49

Formation of the β-keto ester from **1.49** utilizing Mander's reagent[42] (MeOC(O)CN) followed by reduction of the carbon-iodine bond with $PdCl_2$ and Et_3SiH afforded the desired tetracycle (Scheme 1.7). Conjugate addition of the resultant ketoester to propiolamide furnished amide **1.50**. Treatment of **1.50** with Me_4NOAc triggered an annulation cascade involving decarboxylation, olefin isomerization and condensation to provide (+)-lyconadin A (**1.8**). Alternatively, reduction of unsaturated amide **1.50** and subsequent treatment with LiCl promoted cyclization to generate (-)-lyconadin B (**1.11**). Overall, the syntheses of (+)-lyconadin A (**1.8**) and (-)-lyconadin B (**1.11**) were achieved in 28 and 29 steps, respectively, from acid **1.42** and (-)-methyl-(*R*)-3-methylglutarate (**1.39**).

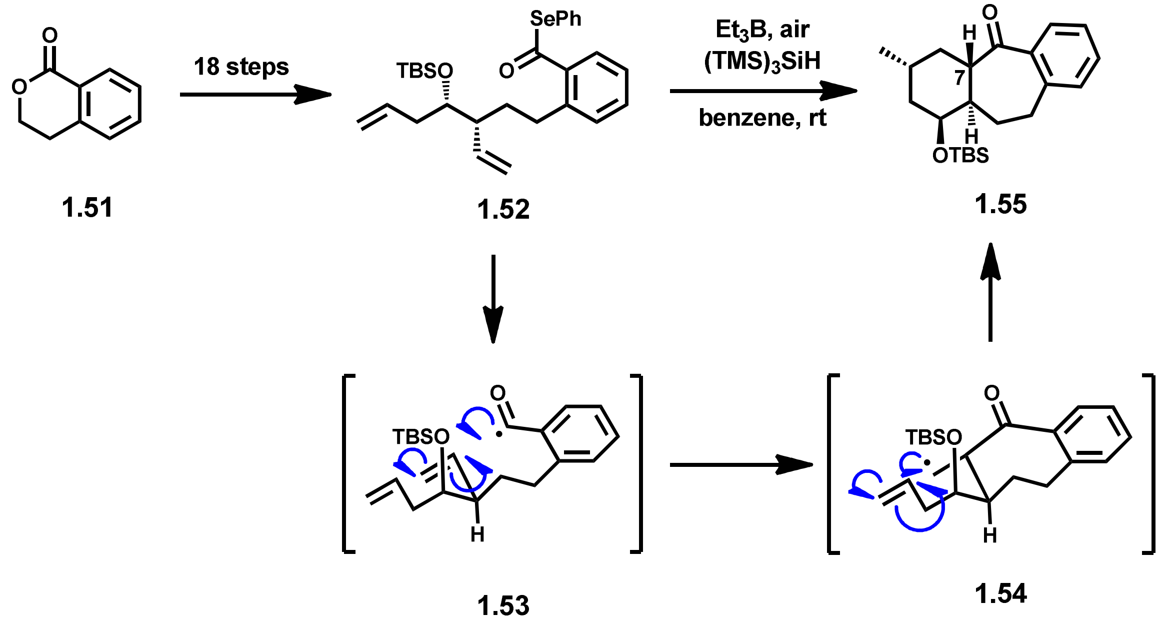
Scheme 1.7. Completion of (+)-Lyconadin A and (-)-Lyconadin B



1.5.2 Castle's Approach to the Lyconadins

In 2006, Castle and co-workers reported a radical cascade cyclization approach to form the [6-7-6] tricycle which is embedded in the lyconadin core.[38] 1-Isochromanone (**1.51**) was elaborated over an extensive 18 step sequence to provide selenoester **1.52** (Scheme 1.8). Radical initiation utilizing Et$_3$B and air[43] followed by homolytic cleavage of the selenoester provided acyl radical **1.53**. Subsequent cyclization of acyl radical **1.53** onto the proximal alkene gave primary radical **1.54**. Attack of radical **1.54** on the pendant alkene formed another primary radical, which upon hydrogen atom abstraction from (TMS)$_3$SiH afforded tricycle **1.55** as a single diastereomer. Although the cyclization cascade proceeded with excellent diastereoselectivity, the stereocenter generated at C7 in tricycle **1.55** is epimeric with respect to the [6-7-6] tricycle present in lyconadin A. Importantly, model tricycle **1.55** bears a substituted benzene ring which does not address the installation of the α-pyridone moiety necessary for the synthesis of the lyconadins.

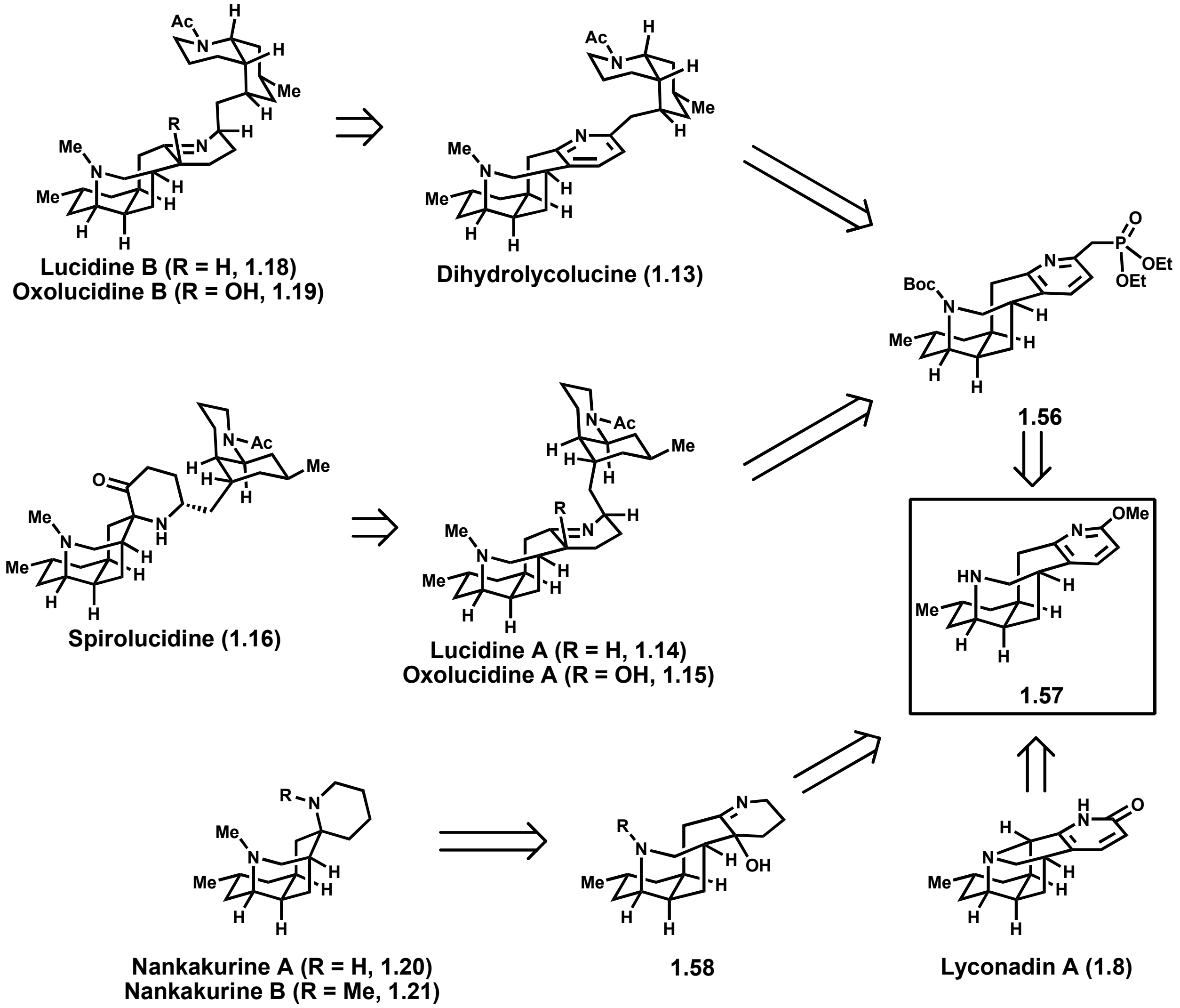
Scheme 1.8. Castle's Radical Cyclization Approach


18 steps
TBSO
SePh
O
Et3B, air
(TMS)3SiH
benzene, rt
H
7
OTBS
1.51
1.52
1.55
1.53
1.54

1.6 Unified Approach to Miscellaneous *Lycopodium* Alkaloids

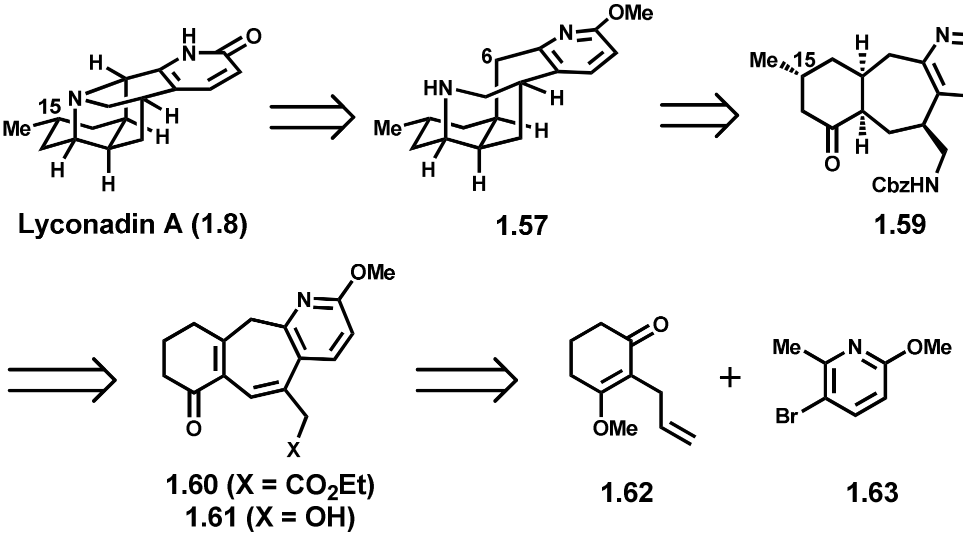
Inspired by the common structural elements and biosynthetic connections among a subset of the miscellaneous *Lycopodium* alkaloids, we envisioned the development of a unified approach to synthesize several of these natural products. The central element of this strategy was the concise synthesis of tetracyclic amine **1.57**, which could be transformed into multiple *Lycopodium* alkaloids (Scheme 1.9). Oxolucidine B (**1.19**) could be obtained via the oxidation of lucidine B (**1.18**), which can be accessed by the reduction of the pyridine moiety of dihydrolycolucine (**1.13**). Construction of dihydrolycolucine (**1.13**) could be achieved by a Horner-Wadsworth-Emmons coupling involving phosphonate **1.56**. Additionally, spirolucidine (**1.16**) could arise from an α-hydroxy imine rearrangement of oxolucidine A (**1.15**), which can be produced by oxidation of lucidine A (**1.14**). Analogously to dihydrolycolucine, lucidine A (**1.14**) may be synthesized from phosphonate **1.56** via a Horner-Wadsworth-Emmons reaction. Formation of phosphonate **1.56** may be achieved from tetracycle **1.57**. Nankakurines A and B (**1.20** and **1.21**) could be constructed via an α-hydroxy imine rearrangement of tetracycle **1.58**, which could be derived from amine **1.57**. Lyconadin A (**1.8**) could also be accessed from key tetracyclic amine **1.57** via oxidative C-N bond formation.

Scheme 1.9. Retrosynthesis of Several Miscellaneous *Lycopodium* Alkaloids


Lucidine B (R = H, 1.18)
Oxolucidine B (R = OH, 1.19)
Dihydrolycolucine (1.13)
1.56
Spirolucidine (1.16)
Lucidine A (R = H, 1.14)
Oxolucidine A (R = OH, 1.15)
1.57
Nankakurine A (R = H, 1.20)
Nankakurine B (R = Me, 1.21)
1.58
Lyconadin A (1.8)

The initial target of our unified strategy was lyconadin A (**1.8**). Retrosynthetically (Scheme 1.10), we anticipated that late-stage C6-N bond formation to construct the lyconadin pentacycle could be achieved from tetracycle **1.57**. Secondary amine **1.57** could be accessed from cycloheptane **1.59** via an intramolecular reductive amination process. Tricycle **1.59** could derive from cycloheptadiene **1.60** or **1.61**, which could in turn arise from the union of vinylogous ester **1.62** and bromomethoxypicoline **1.63**.

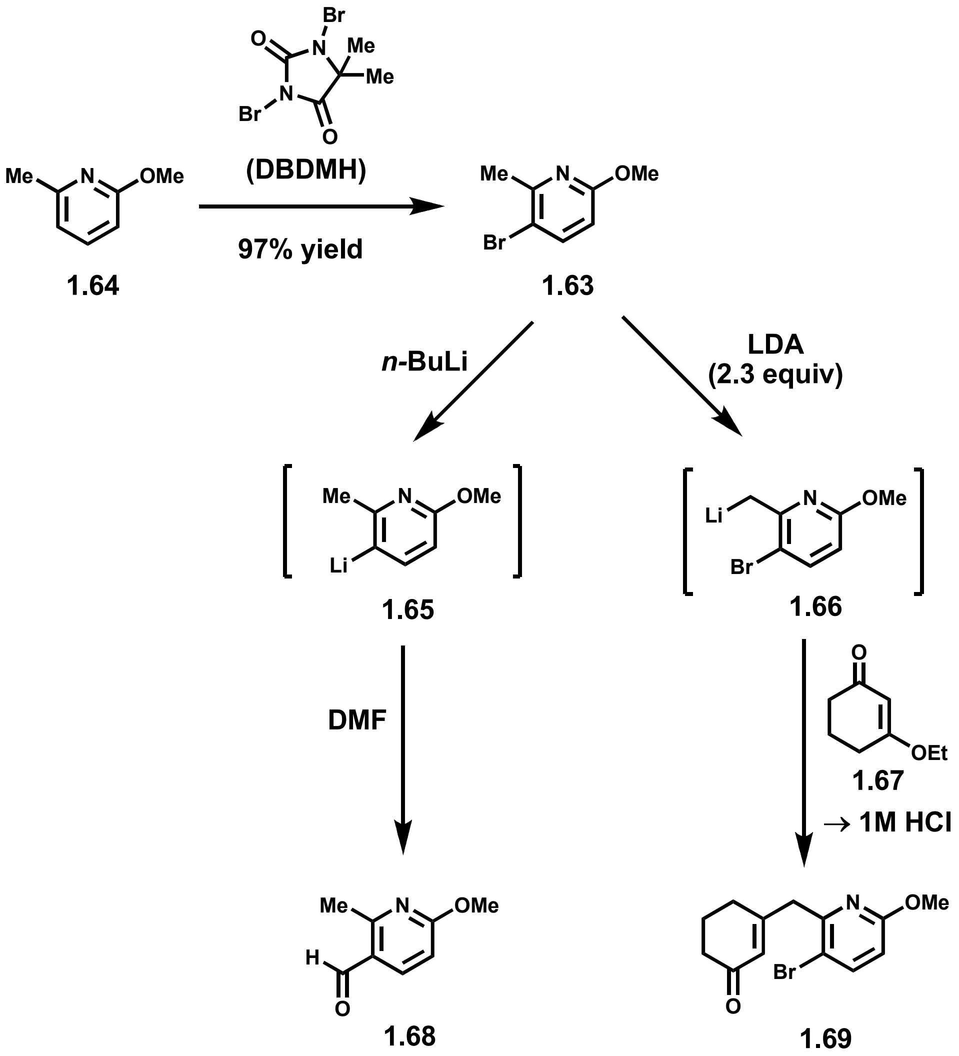
Scheme 1.10. Retrosynthesis of Lyconadin A



1.7 Synthesis of Cycloheptadiene Intermediates

Our synthetic efforts began with the investigation of the union of picoline **1.63** and vinylogous ester **1.62**. Synthesis of bromomethoxypicoline **1.63** (Scheme 1.11) was accomplished by bromination of 2-methoxy-6-methylpyridine (**1.64**) with 1,3-dibromo-5,5-dimethylhydantion (DBDMH).[44] Langlois and co-workers investigated the reactivity of pyridine **1.63** during their synthetic studies toward huperzine A (**1.6**).[45] They found that treatment of **1.63** with excess LDA (2.3 equiv) effected deprotonation at the pseudo-benzylic ("picolinic") position and the resultant anion (**1.66**) reacted with vinylogous ester **1.67**, which following treatment with dilute acid provided enone **1.69**. Alternatively, treatment of **1.63** with *n*-BuLi results in lithium-halogen exchange to provide 3-lithiated pyridine **1.65**, which upon reaction with DMF gave formylpyridine **1.68**. Our synthetic plan utilizes the reactivity of picoline **1.63** to construct two key bonds of the central 7-membered ring of cycloheptadiene **1.60**. Synthesis of the vinylogous ester coupling partner **1.62**[46] (Scheme 1.12) was achieved by allylation of 1,3-cyclohexanedione (**1.70**) followed by reaction with trimethylorthoformate to form **1.62**.

Scheme 1.11. Synthesis and Reactivity of Pyridine **1.63**


(DBDMH)
97% yield
1.64
1.63
n-BuLi
LDA
(2.3 equiv)
1.65
1.66
DMF
1.67
→ 1M HCl
1.68
1.69

Scheme 1.12. Synthesis of Vinylogous Ester **1.62**

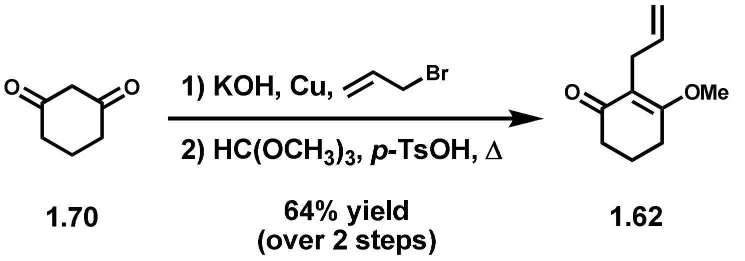
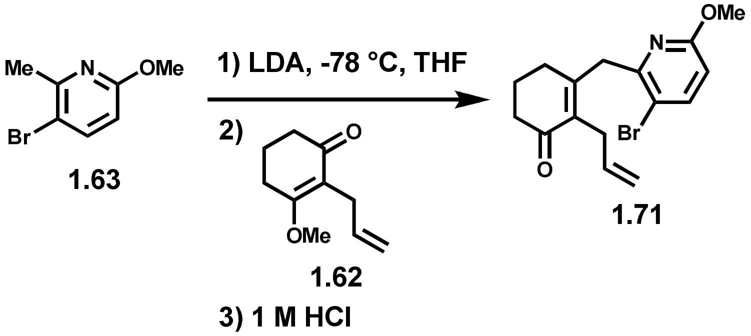

1) KOH, Cu,
2) HC(OCH3)3, p-TsOH, Δ
64% yield
(over 2 steps)
1.70
1.62

Table 1.1. Synthesis of Enone **1.71**

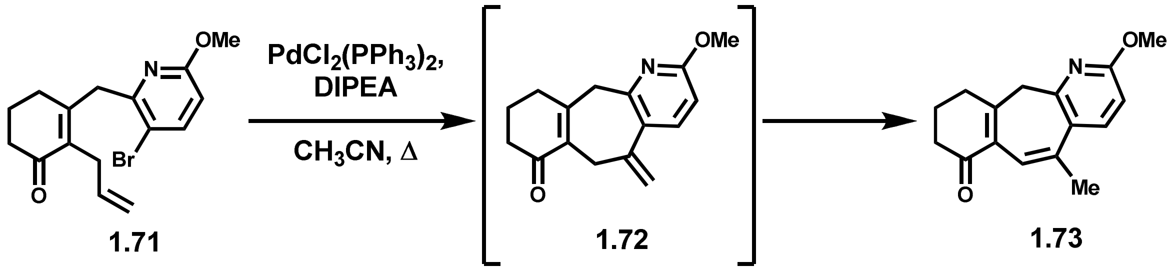


entry	picoline 1.63 (equiv)	ester 1.62 (equiv)	LDA (equiv)	yield
1	1	2.3	2.3	38%
2	1.5	1	3.45	6%
3	1	1	2.3	32%
4	1	1	1.5	54%
5	1	1.5	1.5	64%

Following the procedure for the synthesis of enone **1.69** described by Langlois and co-workers,[44] picoline **1.63** was treated with 2.3 equivalents of LDA to generate the picolinic anion (**1.66**), which was subsequently reacted with 2.3 equivalents of vinylogous ester **1.62** and then subjected to 1 M HCl to furnish enone **1.71** in 38% yield (entry 1, Table 1.1). Increasing the amount of picoline anion (entry 2) or decreasing the equivalents of vinylogous ester (entry 3) did not improve the yield. However, a smaller excess of LDA (1.5 equiv, entry 4) could be used to effectively generate the picolinic anion and provided enone **1.71** in 54% yield. In addition to using 1.5 equivalents of LDA, employing an excess of vinylogous ester **1.62** (1.5 equiv) improved the yield of enone **1.71** to 64% yield (entry 5) and proved to be the optimal conditions for the union of **1.62** and **1.63**.

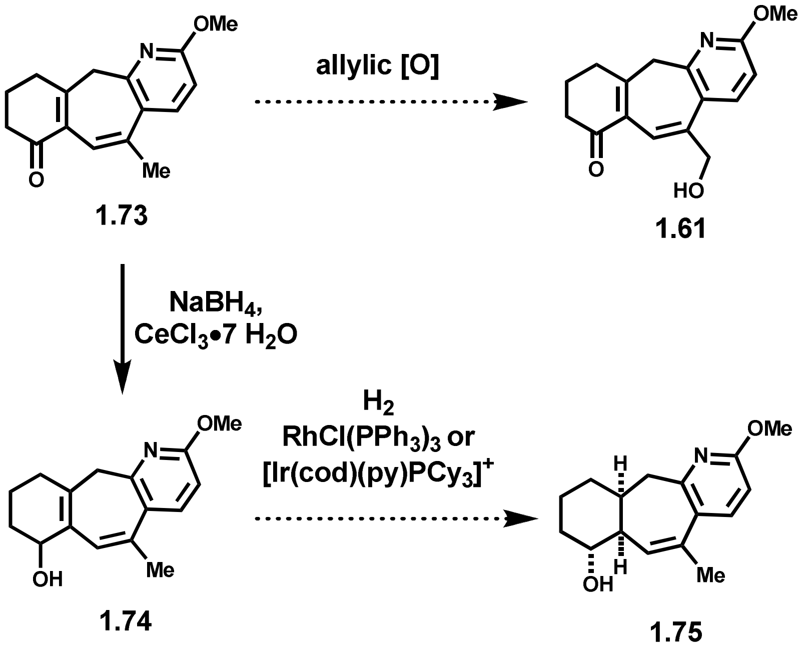
Our initial attempts to synthesize cycloheptadiene **1.72** focused on the intramolecular Heck reaction of olefin **1.71**. Exposure of **1.71** to $PdCl_2(PPh_3)_2$ unexpectedly provided tricycle **1.73** in a modest 44% yield (Scheme 1.13). Under the reaction conditions, the intramolecular Heck reaction occurs to initially form tricycle **1.72**, which undergoes isomerization to afford cross-conjugated enone **1.73**. Screening a variety of Pd sources, bases, ligands and solvents did not lead to any improvement in the efficiency of the cycloheptadiene formation.

Scheme 1.13. Initial Intramolecular Heck Approach



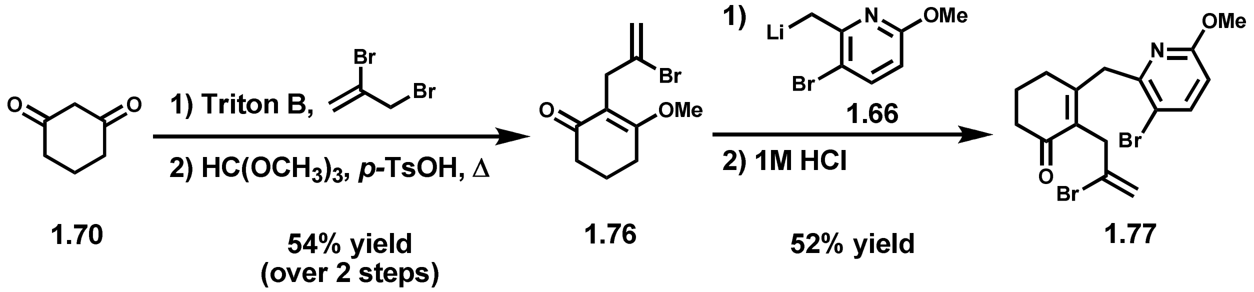
Due to the isomerization to cross-conjugated cycloheptadiene **1.73**, the conversion to **1.61** from **1.73** requires allylic oxidation of the methyl group (Scheme 1.14). Under a variety of conditions utilizing selenium dioxide to promote allylic oxidation, only decomposition of diene **1.73** was observed. Allylic oxidation using excess chromium trioxide and 3,5-dimethylpyrazole[47] resulted in oxidation of diene **1.73** to multiple products. Alternatively, initial Luche reduction of enone **1.73** provided alcohol **1.74**, which could be utilized to direct the selective reduction of the tetrasubstituted alkene. However, allylic alcohol **1.74** proved unreactive under directed hydrogenation conditions with Crabtree's or Wilkinson's catalyst.[48]

Scheme 1.14. Functionalization of Cycloheptadiene **1.73**



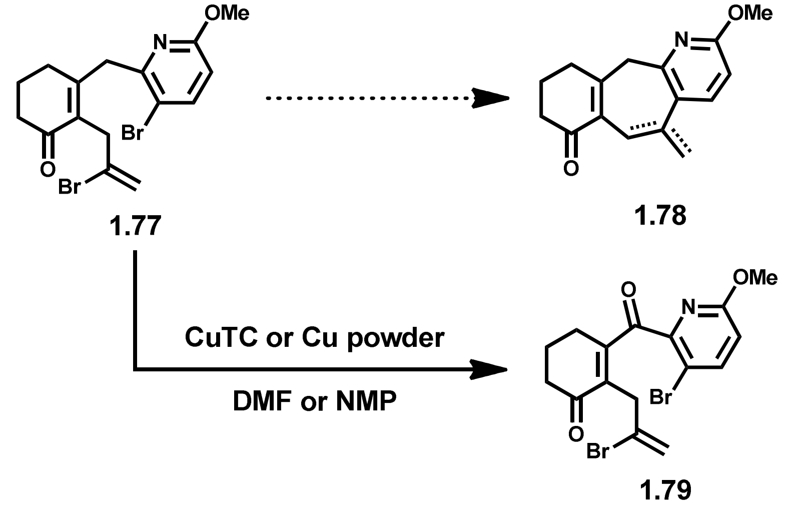
Due to the poor yield of the intramolecular Heck reaction and the difficulty associated with selectively functionalizing tricycle **1.73**, other approaches to form the cycloheptadiene bearing an exo-methylene were explored. To investigate the use of a Stille-Kelly coupling or intramolecular Suzuki coupling to form the 7-membered ring, dibromoenone **1.77** was synthesized from 1,3-cyclohexanedione (**1.70**) and picoline **1.63** (Scheme 1.15). Alkylation of **1.70** with 2,3-dibromopropene followed by reaction with trimethyl orthoformate provided vinylogous ester **1.76**. Addition of picolinic anion **1.66** to **1.76** and subsequent acid hydrolysis provided dibromoenone **1.77**.

Scheme 1.15. Synthesis of Dibromide **1.77**


1) Triton B,
Br
Br
2) HC(OCH3)3, p-TsOH, Δ
54% yield
(over 2 steps)
1.70
1.76
OMe
1)
Li
N
OMe
Br
1.66
2) 1M HCl
52% yield
1.77
OMe
N
Br
O
Br

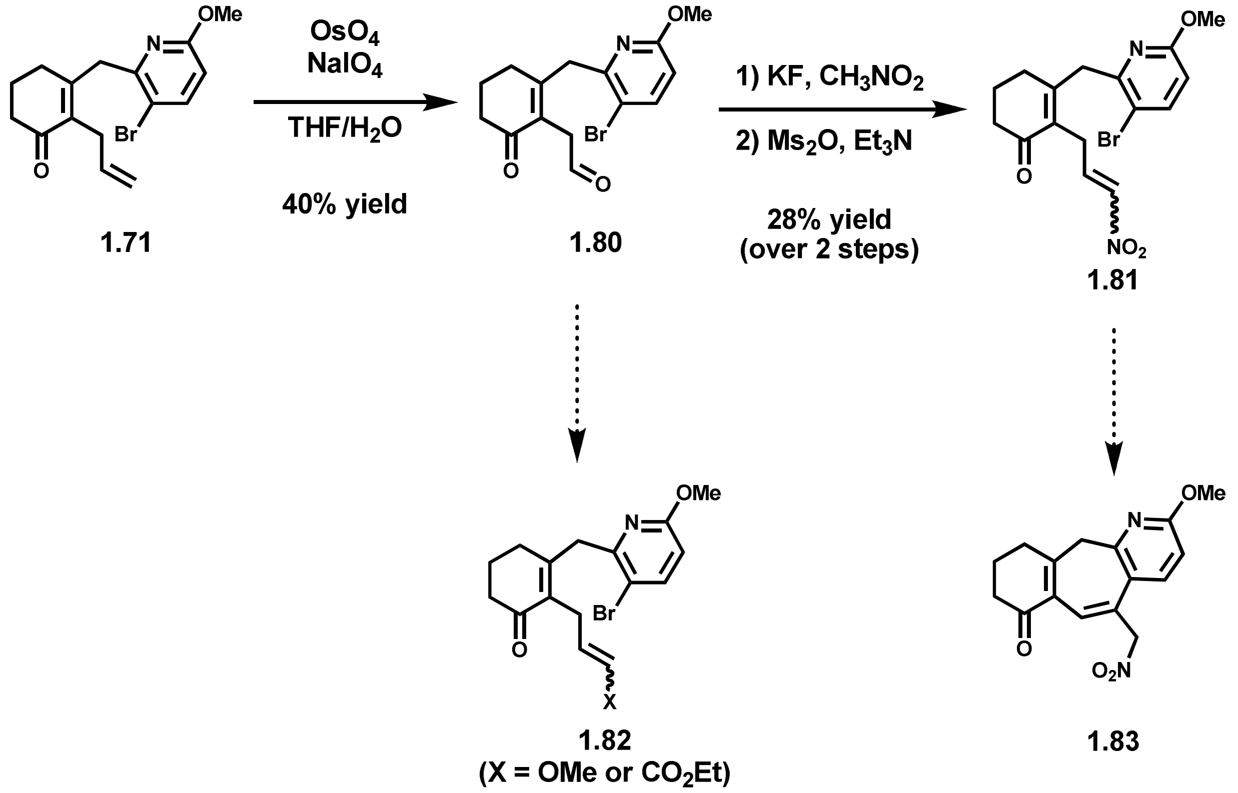
Treatment of dibromide **1.77** with $Pd(PPh_3)_4$ and $(Bu_3Sn)_2$ to effect a Stille-Kelly coupling[49,50] resulted in decomposition of the starting material. Alternatively, *in situ* formation of the boronic ester of **1.77** followed by intramolecular Suzuki coupling was attempted utilizing $Pd(dppf)Cl_2$ and $(Bpin)_2$ and also resulted in decomposition of **1.77**. Attempts utilizing other precedented conditions for Stille-Kelly or intramolecular Suzuki coupling did not result in productive formation of the desired tricycle **1.78**. Other reductive coupling conditions (Pd/C, In, LiCl[51] or $Pd(OAc)_2/Bu_4NBr/IPA/DMF$[52]) were attempted, but similarly failed to provide the desired cycloheptadiene. Next, our attention shifted to utilizing copper to promote an Ullman coupling of dibromoenone **1.77** to form the key bond (Scheme 1.16). Reaction of dibromide **1.77** with excess copper(I) thiophenecarboxylate (CuTC)[53] in NMP or DMF at 80 °C resulted in oxidation of the picolinic position to provide ketone **1.79** in low yield. Additionally, treatment of **1.77** with copper powder in DMF also provided ketone **1.79** in low yield. The ketone oxygen in **1.79** presumably arises from adventitious oxygen dissolved in DMF or NMP.

Scheme 1.16. Alternative Cyclization Approach


OMe
N
Br
O
Br
1.77
OMe
N
O
1.78
CuTC or Cu powder
DMF or NMP
O
OMe
N
Br
O
Br
1.79

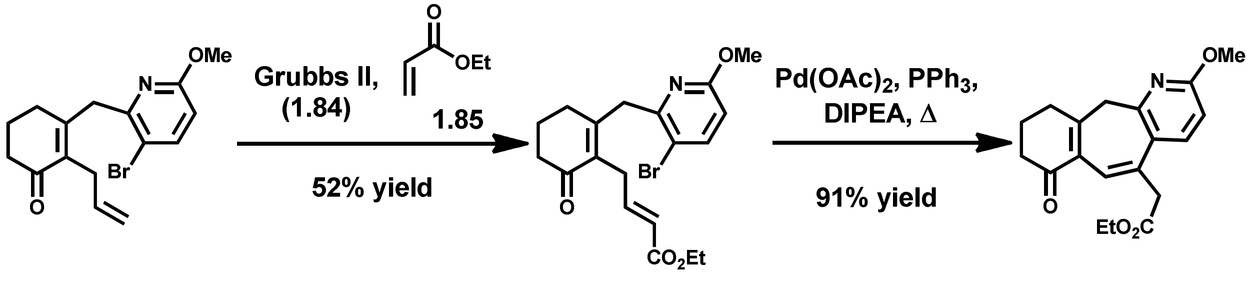
Considering the difficulty in functionalizing cycloheptadiene **1.73** and forming the 7-membered ring bearing an exo-methylene (**1.72**), functionalizing the exocyclic position prior to formation of the 7-membered ring proved necessary. Oxidative cleavage of the allyl group of **1.71** to obtain aldehyde **1.80** could provide a pathway to functionalize the exocyclic position of the tricycle in a variety of ways. Reaction of alkene **1.71** with OsO_4 and $NaIO_4$ resulted in formation of aldehyde **1.80** in low yield (Scheme 1.17). A variety of oxidative cleavage conditions were attempted but did not lead to any improvement in the yield of **1.80**. Under Wittig and Horner-Wadsworth-Emmons olefination conditions, only decomposition of aldehyde **1.80** was observed. Henry reaction of **1.80** with KF and CH_3NO_2[54] followed by elimination with Ms_2O furnished nitroalkene **1.81** in low yield. Subsequent attempted intramolecular Heck reactions of **1.83** resulted in decomposition of the nitroalkene.

Scheme 1.17. Henry and Wittig Approaches



Due to the challenges in functionalizing aldehyde **1.80**, direct conversion of the pendant allyl group of **1.71** to the α,β-unsaturated ester directly via olefin cross-metathesis was investigated (Scheme 1.18). Reaction of alkene **1.71** with excess ethyl acrylate (**1.85**) and Grubbs second generation catalyst (**1.84**, Figure 1.3) produced desired enoate **1.86** in moderate yield. Gratifyingly, subjection of **1.86** to intramolecular Heck conditions furnished cycloheptadiene **1.60** in excellent yield.

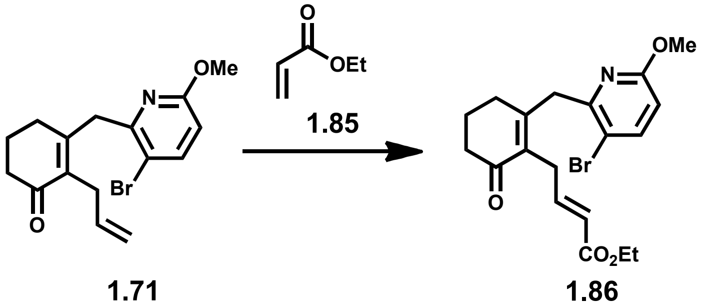
Scheme 1.18. Cross-Metathesis Route



1.71 **1.86** **1.60**

Considering the success of the intramolecular Heck reaction to afford key intermediate **1.60**, optimization of the cross-metathesis reaction[55] was undertaken to improve the efficiency of the synthetic route to cycloheptadiene **1.60** (Table 1.2). Changing the reaction solvent from dichloromethane to benzene (entries 1-2) improved the yield of enoate **1.86**. Under the initial cross-metathesis conditions, formation of the dimer of **1.71** was a significant competing reaction pathway. Increasing the equivalents of ethyl acrylate, decreasing the catalyst loading and increasing the temperature dampened the formation of the dimer and resulted in increased yields of enoate **1.86** (entries 3-5). Importantly, the concentration of alkene **1.71** proved vital to the efficient transformation to the enoate. At a concentration of 0.1 M, the reaction proceeds to completion in 48 h and dimer formation is minimized. Switching to the more active Grubbs-Hoveyda II catalyst (**1.87**, Figure 1.3), cross-metathesis proceeded at room temperature to furnish enoate **1.86** in 88% yield. Grubbs-Hoveyda II (o-tolyl) catalyst (**1.88**) required elevated temperatures and larger excesses of ethyl acrylate to provide **1.86** in comparable yield. Fast-initiating catalysts, Grubbs II-bromopyridine catalyst (**1.89**) and Grubbs II-pyridine catalyst (**1.90**), afforded enoate **1.86** in 48% and 51%, respectively. The optimized conditions with Grubbs-Hoveyda II catalyst (**1.87,** entry 6) achieved excellent yields of **1.86** on multigram scale.

Table 1.2. Cross-metathesis Optimization

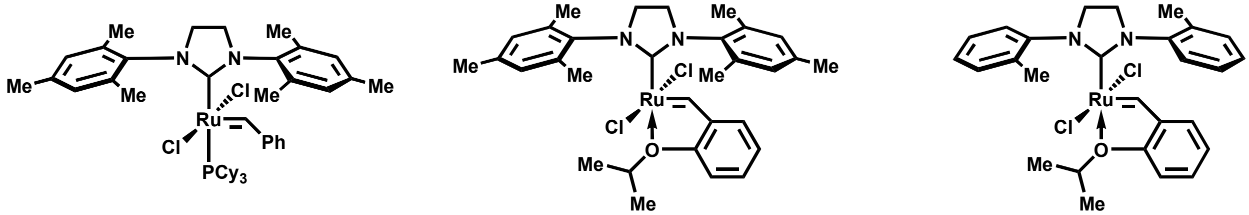


1.71

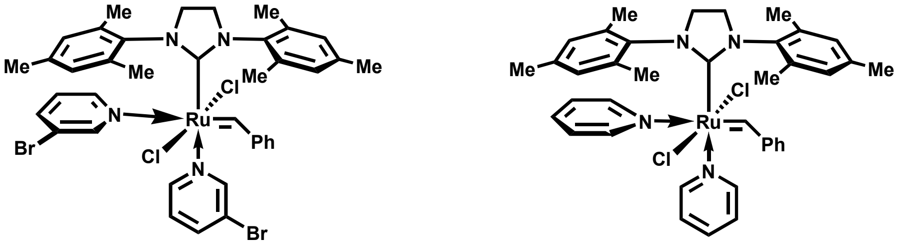
1.86

entry	catalyst	catalyst loading (mol%)	ethyl acrylate (equiv)	temperature (°C)	solvent	molarity of 1.71 (M)	yield
1	Grubbs II (1.84)	10	3	23	CH_2Cl_2	0.2	52%
2	Grubbs II (1.84)	10	3	23	PhH	0.2	63%
3	Grubbs II (1.84)	5	5	60	PhH	0.2	62%
4	Grubbs II (1.84)	5	5	60	PhH	0.04	48%
5	Grubbs II (1.84)	3	5	60	PhH	0.1	79%
6	Grubbs-Hoveyda II (1.87)	3	5	23	PhH	0.1	88%
7	Grubbs-Hoveyda II (1.87)	3	10	23	PhH	0.1	84%
8	Grubbs-Hoveyda II (o-tolyl) (1.88)	3	10	40	CH_2Cl_2	0.1	83%
9	Grubbs-Hoveyda II (o-tolyl) (1.88)	3	10	60	PhH	0.1	87%
10	Grubbs II-bromopyridine (1.89)	3	10	23	PhH	0.1	48%
11	Grubbs II-pyridine (1.90)	3	10	23	PhH	0.1	51%

Figure 1.3 Cross-Metathesis Catalysts



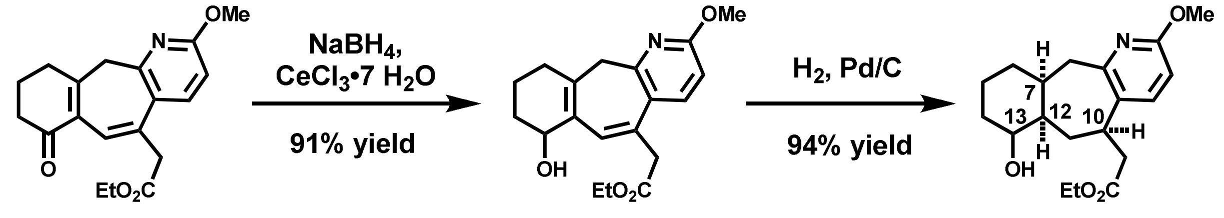
Grubbs II (1.84) **Grubbs-Hoveyda II (1.87)** **Grubbs-Hoveyda II (o-tolyl) (1.88)**



Grubbs II-bromopyridine (1.89) **Grubbs II-pyridine (1.90)**

With an efficient route to cycloheptadiene **1.60** defined, elaboration of the tricycle to install the requisite stereochemistry at C7, C10, C12 was the next synthetic challenge. Luche reduction of enone **1.60** (Scheme 1.19) proceeded smoothly to furnish **1.91** in 91% yield. Hydrogenation of allylic alcohol **1.91** provided cycloheptane **1.92** with good diastereoselectivity. Hydrogenation of both alkenes presumably occurs from the same face to place the three hydrogens at the newly-created stereocenters *syn* to each other. The stereochemistry of the hydrogen at C13 was presumed to be set *syn* relative to the hydrogens introduced in the hydrogenation. The C13 stereocenter will be ablated later in the synthesis; therefore the C13 hydroxyl group's stereochemistry is not vital to its utility as a synthetic intermediate.

Scheme 1.19. Reduction of Cycloheptadiene **1.60**

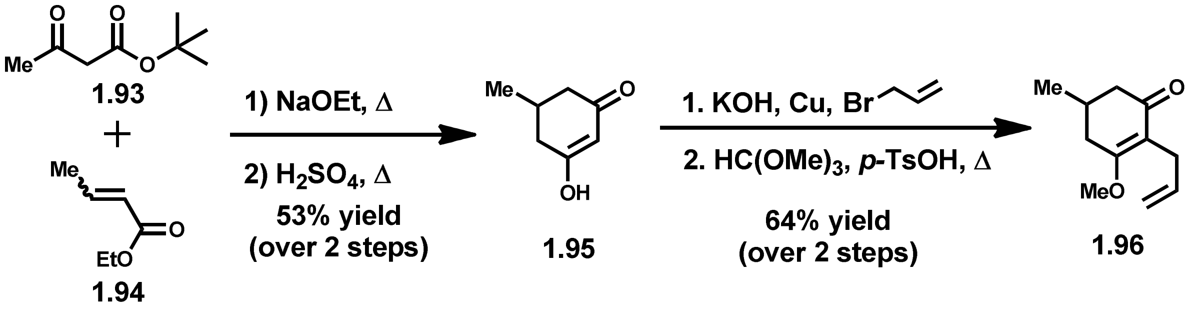


1.60 **1.91** **1.92**

1.8 Second Generation Cycloheptadiene Route

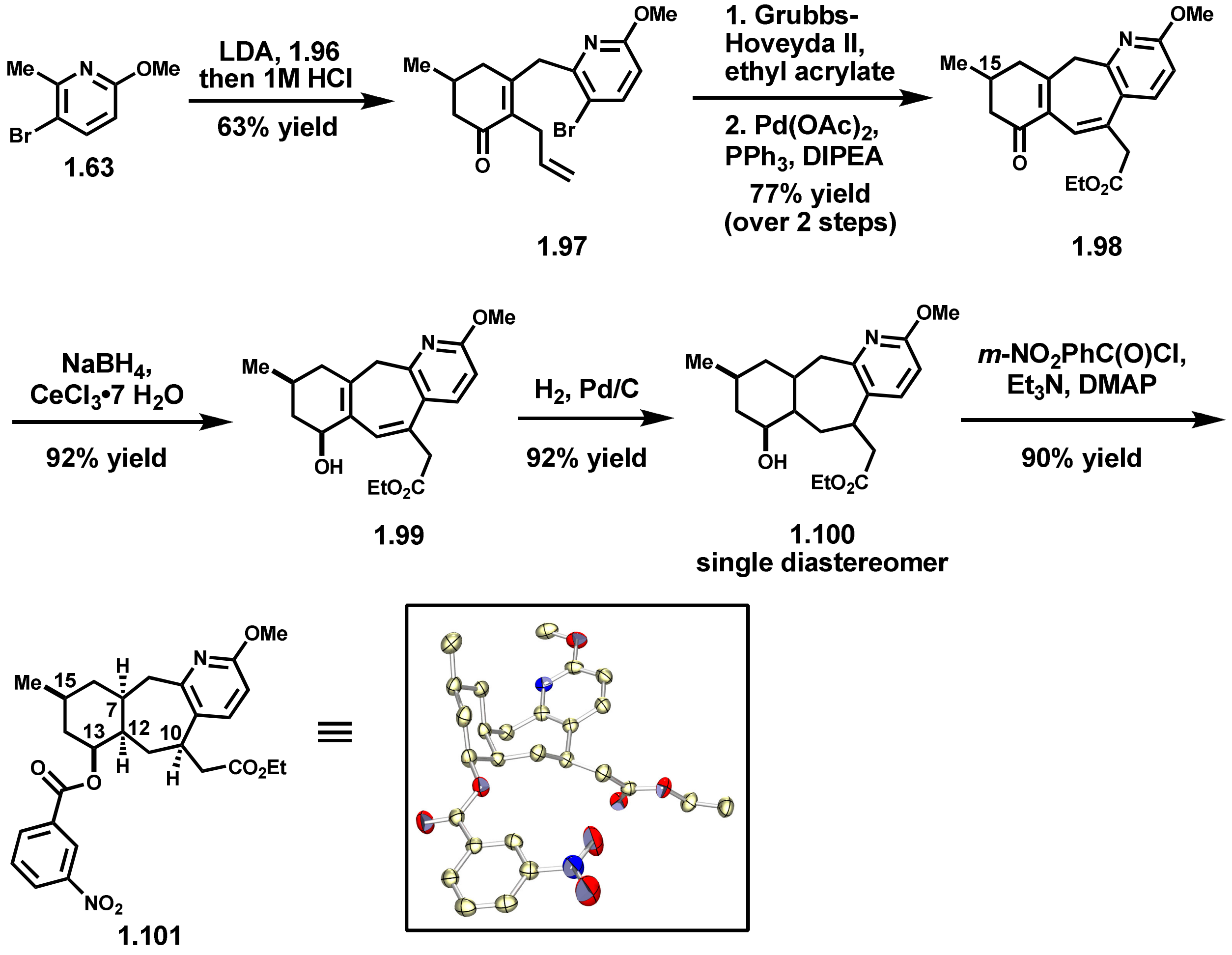
Considering the observed high diastereoselectivity for the hydrogenation of cycloheptadiene **1.91**, synthesis of cycloheptadiene **1.98** bearing a methyl group at C15 was pursued. This synthetic plan would rely on utilizing the C15 stereocenter to govern the diastereoselectivity of the reduction of the carbonyl and diene moieties of **1.98**. Synthesis of **1.98** began with formation of 5-methyl-1,3-cyclohexanedione (**1.95,** Scheme 1.20) from *tert*-butyl acetoacetate and ethyl crotonate via initial Michael addition followed by Claisen reaction and subsequent decarboxylation to furnish **1.95**.[56] Allylation of **1.95** followed by treatment with trimethyl orthoformate afforded vinylogous ester **1.96** in 64% yield.

Scheme 1.20. Synthesis of Vinylogous Ester **1.96**



Addition of the picolinic anion of **1.63** to vinylogous ester **1.96** and subsequent acid treatment provided enone **1.97** in 63% yield (Scheme 1.21). Cross-metathesis of **1.97** with ethyl acrylate followed by intramolecular Heck reaction afforded cycloheptadiene **1.98**. Luche reduction of enone **1.98** proceeds diastereoselectively (>14:1 dr) with hydride delivery occurring from the α-face, opposite the methyl group, to give allylic alcohol **1.99** in 92% yield. Cycloheptadiene **1.99** was subjected to hydrogenation over Pd/C, which resulted in the formation of a single diastereomer of cycloheptane **1.100**. Alcohol **1.100** was treated with *m*-nitrobenzoyl chloride to give *m*-nitrobenzoate **1.101**, which provided X-ray quality crystals. X-ray crystallographic analysis of **1.101** revealed that reduction of the diene installed the hydrogens at C7, C10, and C12 *syn* to each other, but *anti* relative to the methyl group at C15, which is opposite to the relative stereochemistry necessary to access the natural product.

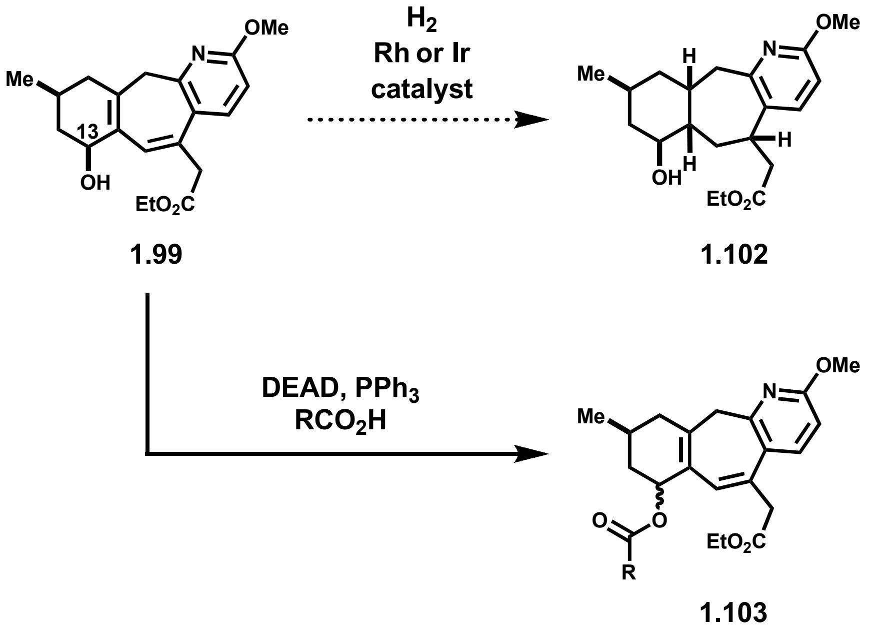
Scheme 1.21. Synthesis of Cycloheptane **1.100**


1.63
LDA, 1.96 then 1M HCl
63% yield
1.97
1. Grubbs-Hoveyda II, ethyl acrylate
2. Pd(OAc)2, PPh3, DIPEA
77% yield (over 2 steps)
1.98
NaBH4, CeCl3•7 H2O
92% yield
1.99
H2, Pd/C
92% yield
1.100
single diastereomer
m-NO2PhC(O)Cl, Et3N, DMAP
90% yield
1.101
≡

In an attempt to reverse the diastereoselectivity of the hydrogenation of diene **1.99**, directed hydrogenation[48] utilizing homogeneous rhodium and iridium catalysts was investigated (Scheme 1.22). Treatment of **1.99** with Crabtree's[57] ([Ir(cod)(py)PCy_3]PF_6), Wilkinson's (RhCl(PPh_3)$_3$), or Brown's[58] ([Rh(nbd)dppe]BF_4) catalysts at low (1 atm, balloon) or high (1000 psi) hydrogen pressure did not promote the diastereoselective reduction of the diene. Formation of the alkoxide of **1.99** with NaH prior to treatment with Crabtree's or Brown's catalyst and hydrogen did not result in reduction of the diene. Molecular modeling reveals that the C13 hydroxyl group of **1.99** preferentially resides in a pseudoequatorial orientation and could prevent productive metal-hydride orientation. Additionally, coordination of the methoxypyridine moiety of **1.99** to the metal center could lead to reduced catalyst activity.

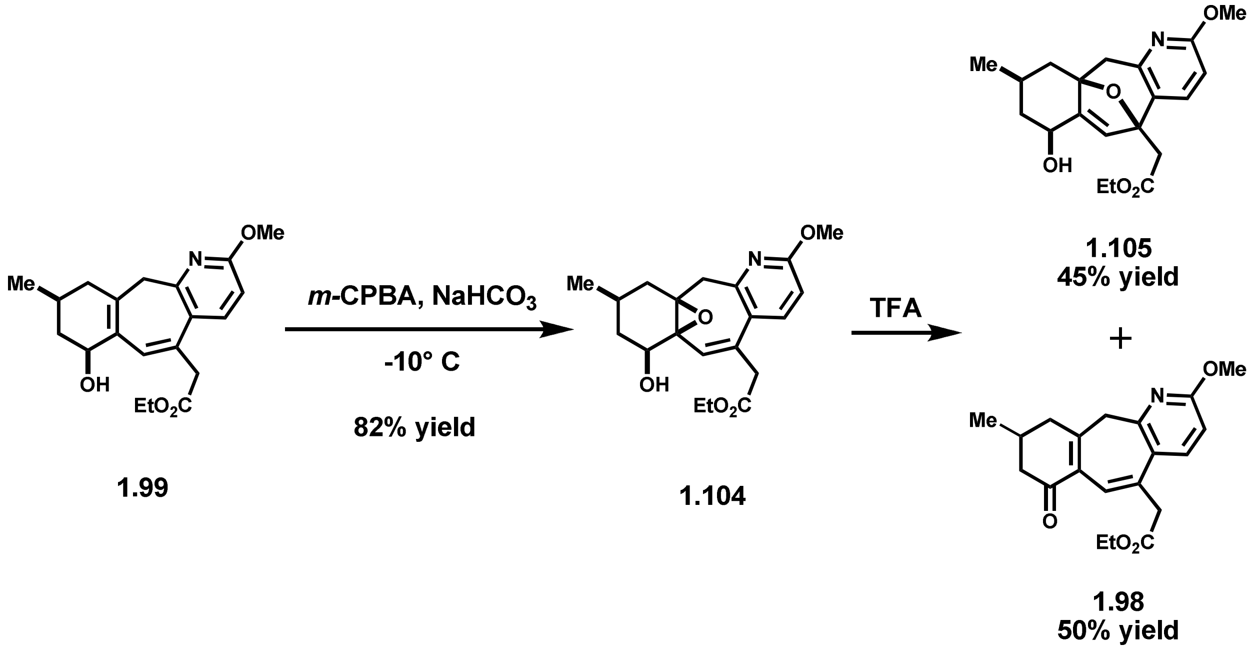
Inversion of the alcohol stereocenter at C13 in alcohol **1.99** and functionalization with a sterically demanding group could promote hydrogenation with the desired diastereoselectivity. To obtain the *anti* diastereomer of alcohol **1.99**, large reducing agents such as L-selectride were utilized, but resulted in poor diastereoselectivity (3:2 *anti*:*syn*). Mitsunobu reaction of allylic alcohol **1.99** with *p*-nitrobenzoic acid or chloroacetic acid resulted in the formation of ester **1.103**, but with low diastereoselectivity (2.5:1 *anti*:*syn*). Competing ionization to form the allylic cation followed by attack of the nucleophile on the planar cation could be the cause of the poor diastereoselectivity observed. Due to the difficulty in obtaining the *anti* diastereomer of **1.99** selectively, investigation of the subsequent hydrogenation was not pursued.

Scheme 1.22. Directed Hydrogenation and Mitsunobu Routes



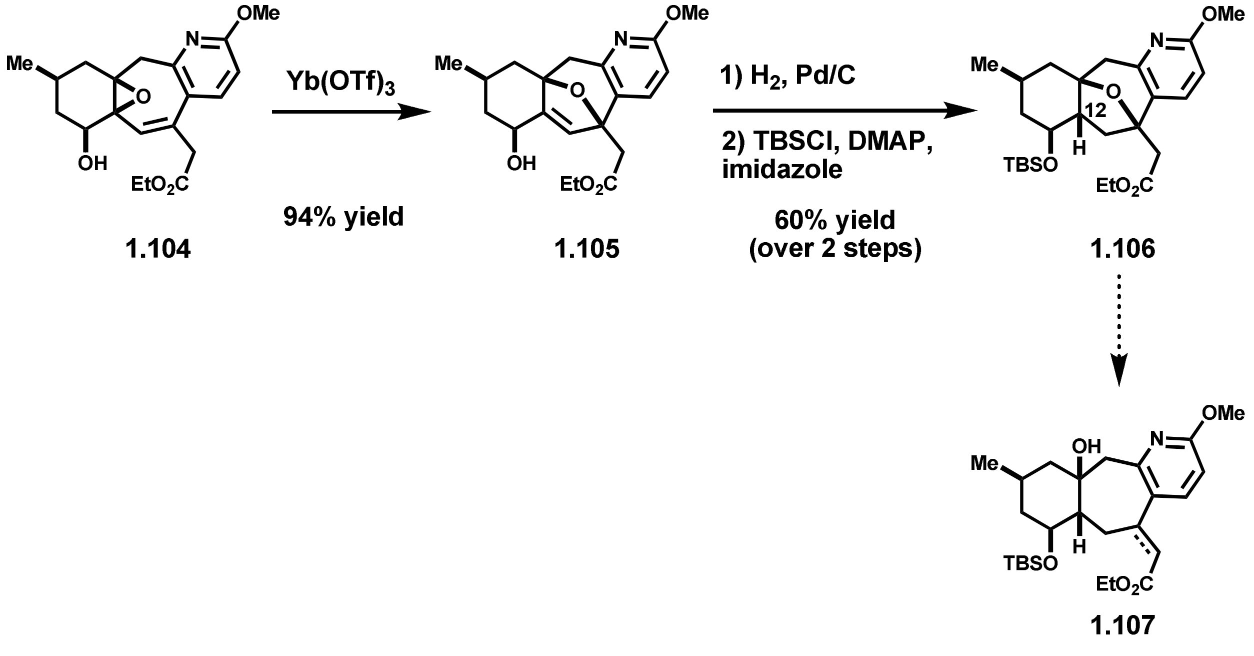
Turning to other substrate-directed transformations, investigation of the hydroxyl group of **1.99** as a directing group for epoxidation was pursued (Scheme 1.23). Diastereoselective formation of epoxide **1.104** could change the concavity of the tricycle and enable reduction to set the stereocenters of the cycloheptane ring *syn* to the methyl group. Additionally, the epoxide intermediate could enable functionalization of the picolinic position, which could be utilized in the late-stage C-N bond formation to provide the lyconadin pentacycle (**1.57**) or in the formation of the tetracyclic core of lycolucine (**1.12**). Treatment of alcohol **1.99** with *m*-CPBA at 0 °C led to the formation of epoxide **1.104** with modest diastereoselectivity (4:1 dr, Scheme 1.23). Lowering the reaction temperature to -10 °C increased the diastereoselectivity of the epoxidation to >20:1 in favor of the *syn* diastereomer. Inspired by the endgame of our group's salviasperanol total synthesis,[59] isomerization of vinyl epoxide **1.104** to dihydrofuran **1.105** and subsequent reduction could appropriately install the C12 stereocenter. Treatment of epoxide **1.104** with trifluoroacetic acid provided dihydrofuran **1.105** in low yield. In addition to dihydrofuran **1.105**, cycloheptadiene **1.98** is generated from epoxide **1.104** by a competing acid-catalyzed pathway involving a 1,2 hydride shift followed by elimination of the resultant tertiary alcohol. Alternatively, addition of Yb(OTf)$_3$, a Lewis acid catalyst, to vinyl epoxide **1.104** efficiently afforded dihydrofuran **1.105** (Scheme 1.24). Hydrogenation of **1.105** proceeded diastereoselectively from the β-face, *syn* to the ether bridge, and subsequent protection of the tetrahydrofuran intermediate with TBSCl provided TBS ether **1.106** in 60% yield. Base-induced fragmentation of tetrahydrofuran **1.106** was investigated with a variety of bases including LDA, NaHMDS, and DBU. None of the basic conditions resulted in productive fragmentation of the tetrahydrofuran ring. Alternatively, reductive cleavage of the THF ring was attempted with SmI$_2$, but only resulted in cleavage of the methyl ether of **1.106**. Complexation of the THF oxygen with Lewis acids in the presence of DIPEA similarly failed to promote fragmentation of the THF ring.

Scheme 1.23. Rearrangement of Epoxide **1.104**



OMe
Me
N
OH
EtO2C
1.99
m-CPBA, NaHCO3
-10° C
82% yield
O
1.104
TFA
1.105
45% yield
+
O
1.98
50% yield

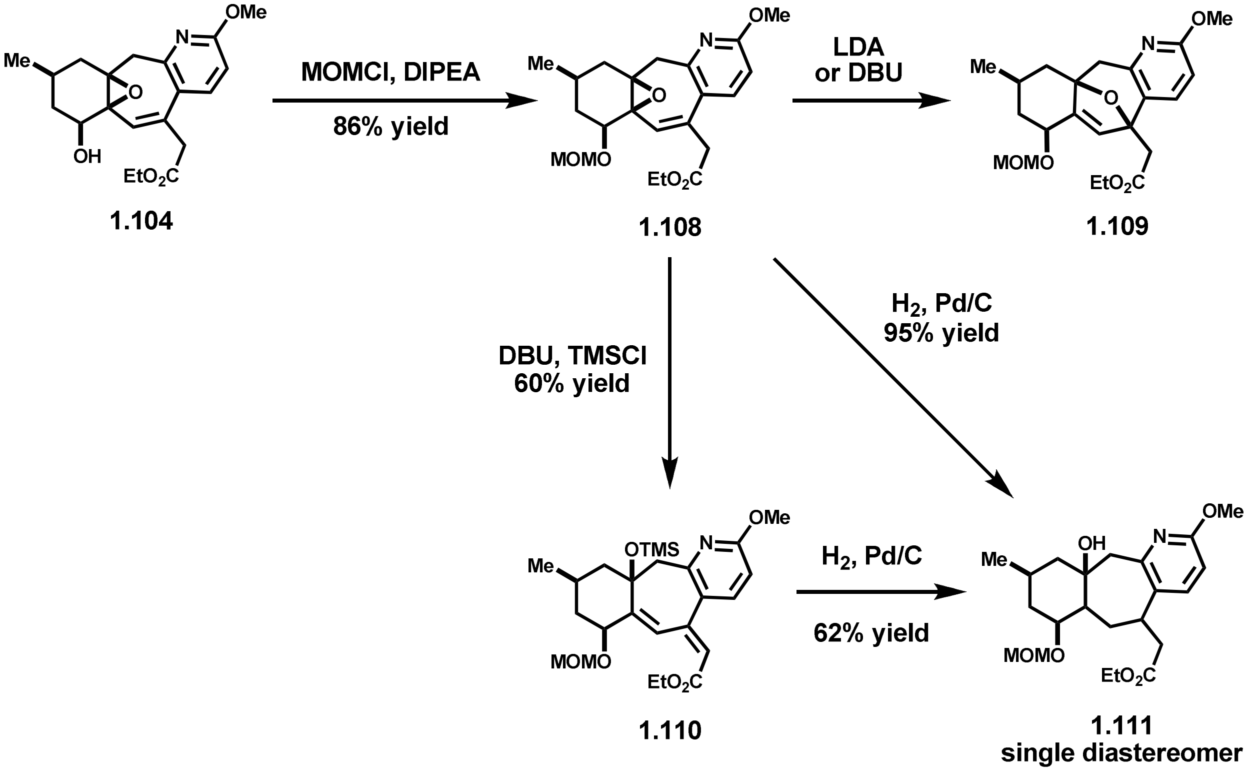
Scheme 1.24. Synthesis of Tetrahydrofuran **1.106**



OMe
Me
N
O
OH
EtO2C
1.104
Yb(OTf)3
94% yield
1.105
1) H2, Pd/C
2) TBSCl, DMAP, imidazole
60% yield
(over 2 steps)
12
H
TBSO
1.106
1.107

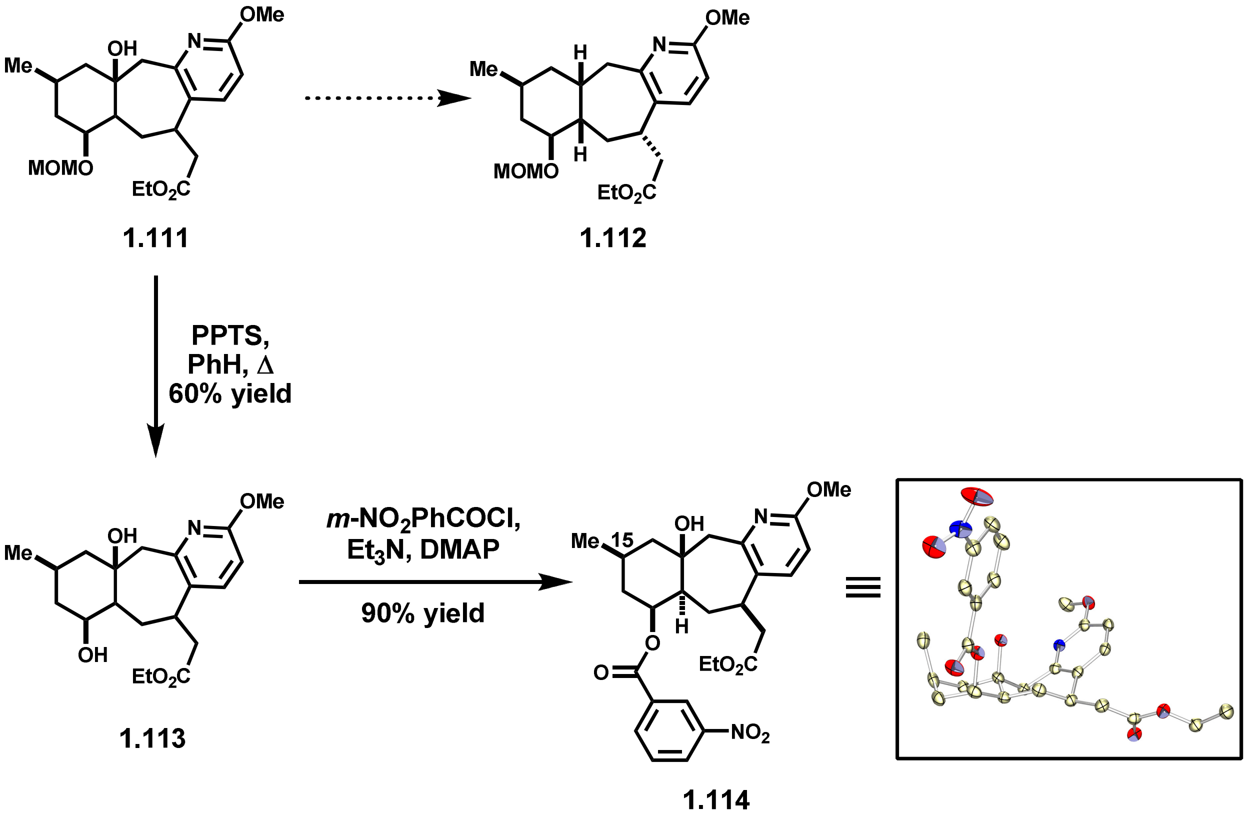
After the difficulty in cleaving the THF ring and functionalizing tricycle **1.106**, fragmentation of vinyl epoxide **1.104** and subsequent reduction of the resultant tricycle was investigated (Scheme 1.25). Alcohol **1.104** was protected as the methoxymethyl ether and subjected to a variety of conditions to open the vinyl epoxide. Treatment of epoxide **1.108** with bases such as LDA or DBU induced fragmentation of the epoxide to the tertiary alkoxide followed by oxy-Michael addition to the newly-formed enoate to generate dihydrofuran **1.109**. Subjecting epoxide **1.108** to TMSCl in addition to DBU enabled epoxide rupture to the tertiary alkoxide which reacted with TMSCl to provide diene **1.110** in 60% yield. Hydrogenation of diene **1.110** over Pd/C proceeded with concomitant cleavage of the silyl ether to provide tertiary alcohol **1.111** as a single diastereomer in 62% yield. On the basis of simple molecular modeling, the concave structure of diene **1.110** appeared similar to dihydrofuran **1.105**. Therefore, similar reduction of diene **1.110** from the β-face, *syn* to the methyl and tertiary hydroxyl groups was expected. Additionally, hydrogenation of vinyl epoxide **1.108** effected reduction of the alkene and opening of the epoxide to afford tertiary alcohol **1.111**. The hydrogenation of vinyl epoxide **1.108** more efficiently provided the same diastereomer of alcohol **1.111** as the 2 step fragmentation/reduction sequence.

Scheme 1.25. Synthesis of Tertiary Alcohol **1.111**



Elaboration of alcohol **1.111** to key tricyclic intermediate **1.112** by deoxygenation or elimination and reduction was investigated (Scheme 1.26). Formation of the xanthate of tertiary alcohol **1.111** under multiple conditions (NaH, CS_2, MeI; NaH, PhOC(S)Cl; or Et_3N, PhOC(S)Cl) were unsuccessful and resulted in recovery of starting material. Formation of the trifluoroacetate of alcohol **1.111** could be achieved, but subsequent attempts to effect deoxygenation with diphenylsilane and *tert*-butyl peroxide[60] led to decomposition. Attempted elimination of alcohol **1.111** under a variety of conditions (TFAA, Ms_2O, $POCl_3$, $SOCl_2$, Martin's sulfurane,[41] or Burgess reagent) led to complex mixtures of products and decomposition of the starting material. Cleavage of the methoxymethyl ether of **1.111** with PPTS followed by transformation of alcohol **1.113** to *m*-nitrobenzoate **1.114** enabled crystallization of tricycle **1.114**. X-ray crystallographic analysis of **1.114** revealed that reduction of the diene and vinyl epoxide proceeds from the α-face to place the newly-introduced hydrogens *anti* relative to the methyl and hydroxyl groups. Alcohol **1.111** obtained from reduction of vinyl epoxide **1.108** or diene **1.110** does not provide the correct relative stereochemistry at C15 necessary to achieve the synthesis of the lyconadins.

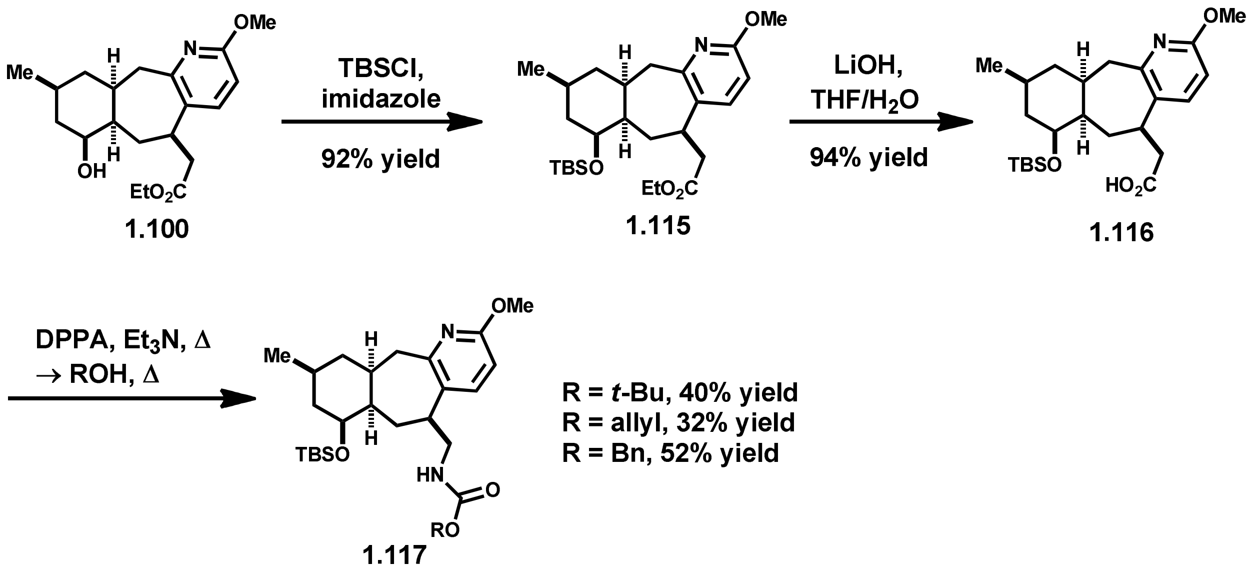
Scheme 1.26. Synthesis of *m*-Nitrobenzoate **1.114**



1.9 Model Tetracycle Synthesis

Despite the incorrect relative stereochemistry of cycloheptane **1.100**, it served as a valuable model system to investigate the synthesis of the key tetracyclic amine **1.123** (Scheme 1.27). Application of the Curtius rearrangement was examined to install the amino nitrogen of key tricyclic aminoketone **1.122**. Saponification of ester **1.100** bearing a free hydroxyl proved challenging and dictated protection of the hydroxyl group prior to acid formation. Protection of alcohol **1.100** as the silyl ether and subsequent hydrolysis of ester **1.115** proceeded without event to provide acid **1.116**. Treatment of acid **1.116** with triethylamine and diphenylphosphoryl azide (DPPA)[61] effected formation of the intermediate isocyanate which was trapped *in situ* by addition of an alcohol to form carbamate **1.117**. Allyl alcohol and *tert*-butanol provided allyl and *tert*-butyl carbamates of **1.117** in 32% and 40% yields, respectively. Addition of benzyl alcohol afforded the Cbz-protected amine of **1.117** in 52% yield. In addition to formation of carbamate **1.117**, extensive desilylation of both acid **1.116** and carbamate **1.117** was observed.

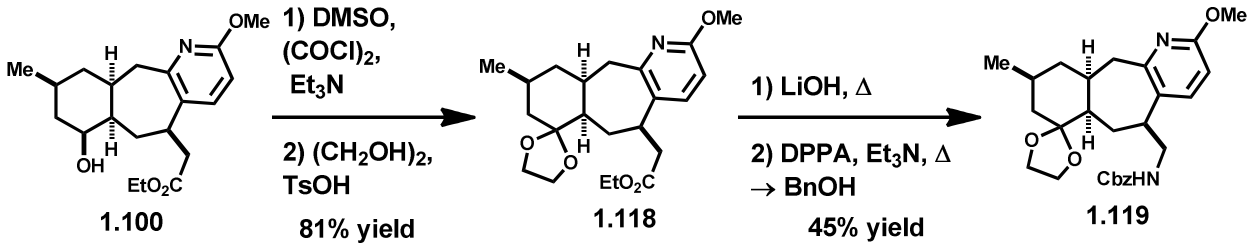
Scheme 1.27. Curtius Rearrangement Optimization



R = *t*-Bu, 40% yield
R = allyl, 32% yield
R = Bn, 52% yield

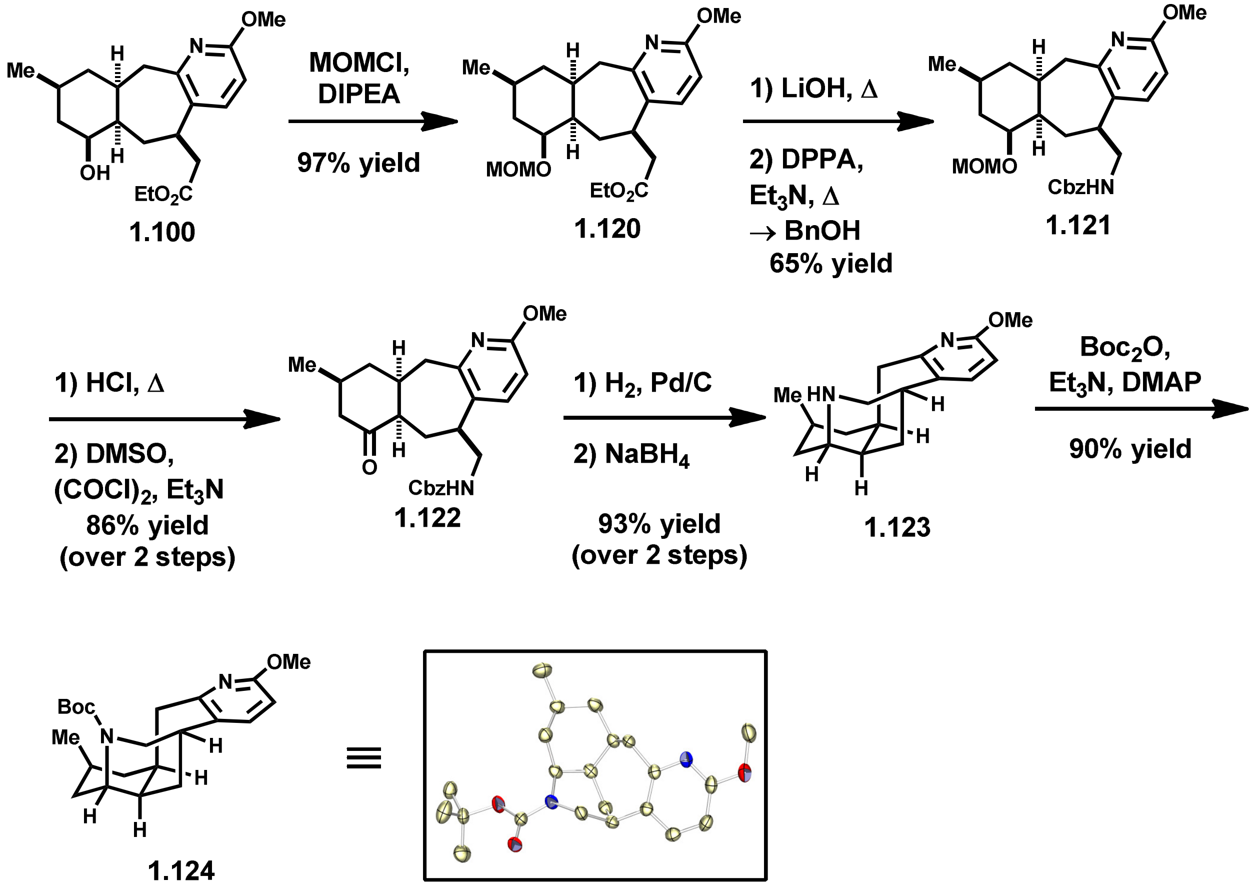
To circumvent desilylation of the hydroxyl group, oxidation of alcohol **1.100** and subsequent protection as the ketal group was pursued (Scheme 1.28). Ketal protection would enable retention of the ketone oxidation level necessary for the reductive amination sequence to form the tetracyclic core and reduce the number of redox steps in the synthetic sequence. Swern oxidation of alcohol **1.100** followed by treatment with ethylene glycol and tosic acid furnished ketal **1.118** in 81% yield. Saponification of ester **1.118** and subsequent Curtius rearrangement provided Cbz-protected amine **1.119** in low yield.

Scheme 1.28. Synthesis of protected aminoketone **1.119**



Due to the instability of ketal and silyl protecting groups to the reaction conditions for the Curtius rearrangement, a more robust protecting group for the hydroxyl group, methoxymethyl ether (MOM), was examined (Scheme 1.29). Protection of the hydroxyl group with methoxymethyl chloride (MOMCl) provided MOM ether **1.120** in 97% yield. Saponification of ester **1.120** followed by Curtius rearrangement afforded Cbz-protected amine **1.121** in an improved 65% yield over the two steps. Cleavage of the methoxymethyl ether and Swern oxidation of the resultant alcohol furnished ketone **1.122**. Hydrogenolysis of benzyl carbamate **1.122** over Pd/C proceeded to provide a mixture of the intermediate hemiaminal and tetracyclic amine **1.123**. Initial hydrogenolysis attempts in methanol unexpectedly afforded significant amounts of the N-methylated analog of amine **1.123**. Changing the reaction solvent to ethyl acetate obviated the formation of the N-methylated amine. Prolonged reaction times (24-48 h) for the hydrogenolysis in ethyl acetate would frequently accomplish the reductive amination to give exclusively tetracyclic amine **1.123**. If a mixture of the intermediate hemiaminal and tetracyclic amine **1.123** was obtained from the hydrogenolysis, the mixture was subjected to reduction with $NaBH_4$ to provide tetracyclic amine **1.123**. Both reductive amination procedures furnished amine **1.123** in excellent yield. Treatment of **1.123** with Boc_2O and Et_3N afforded Boc-protected tetracycle **1.124**, which provided X-ray quality crystals. X-ray crystallographic analysis of **1.124** confirmed the connectivity and relative stereochemistry of tetracycle **1.123**.

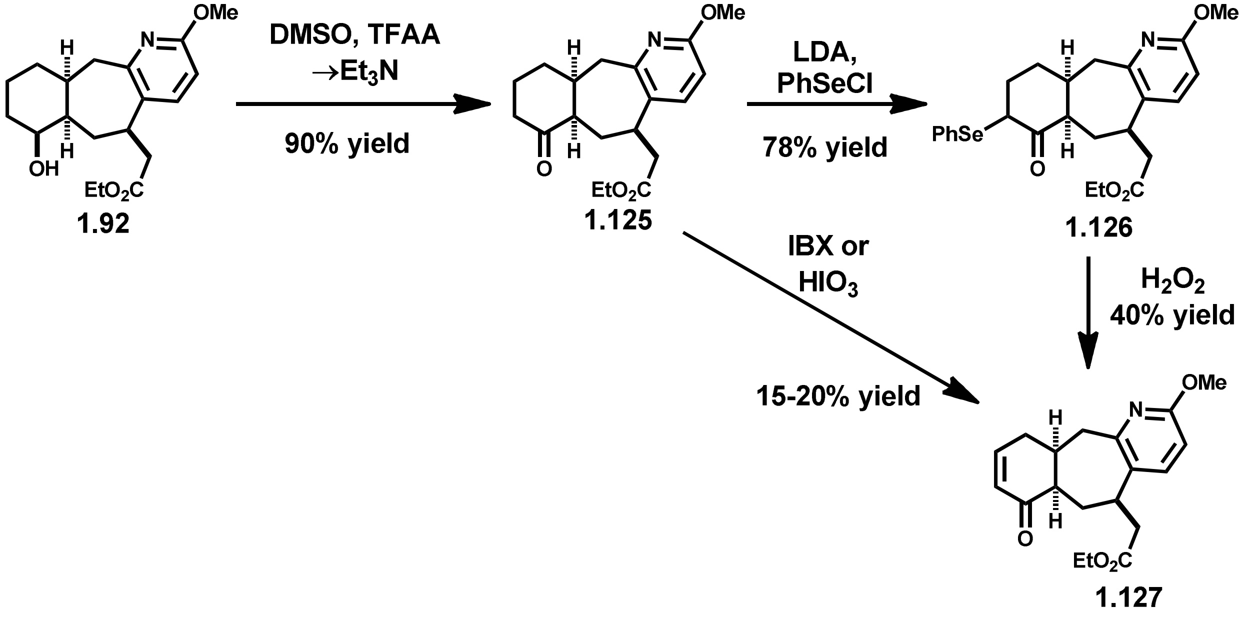
Scheme 1.29. Synthesis of Tetracycle **1.123**


OMe
Me
H
N
OH
H
EtO2C
1.100
MOMCl,
DIPEA
97% yield
MOMO
1.120
1) LiOH, Δ
2) DPPA,
Et3N, Δ
→ BnOH
65% yield
CbzHN
1.121
1) HCl, Δ
2) DMSO,
(COCl)2, Et3N
86% yield
(over 2 steps)
O
1.122
1) H2, Pd/C
2) NaBH4
93% yield
(over 2 steps)
Me HN
1.123
Boc2O,
Et3N, DMAP
90% yield
Boc
Me
1.124
≡

1.10 Tetracycle Synthesis

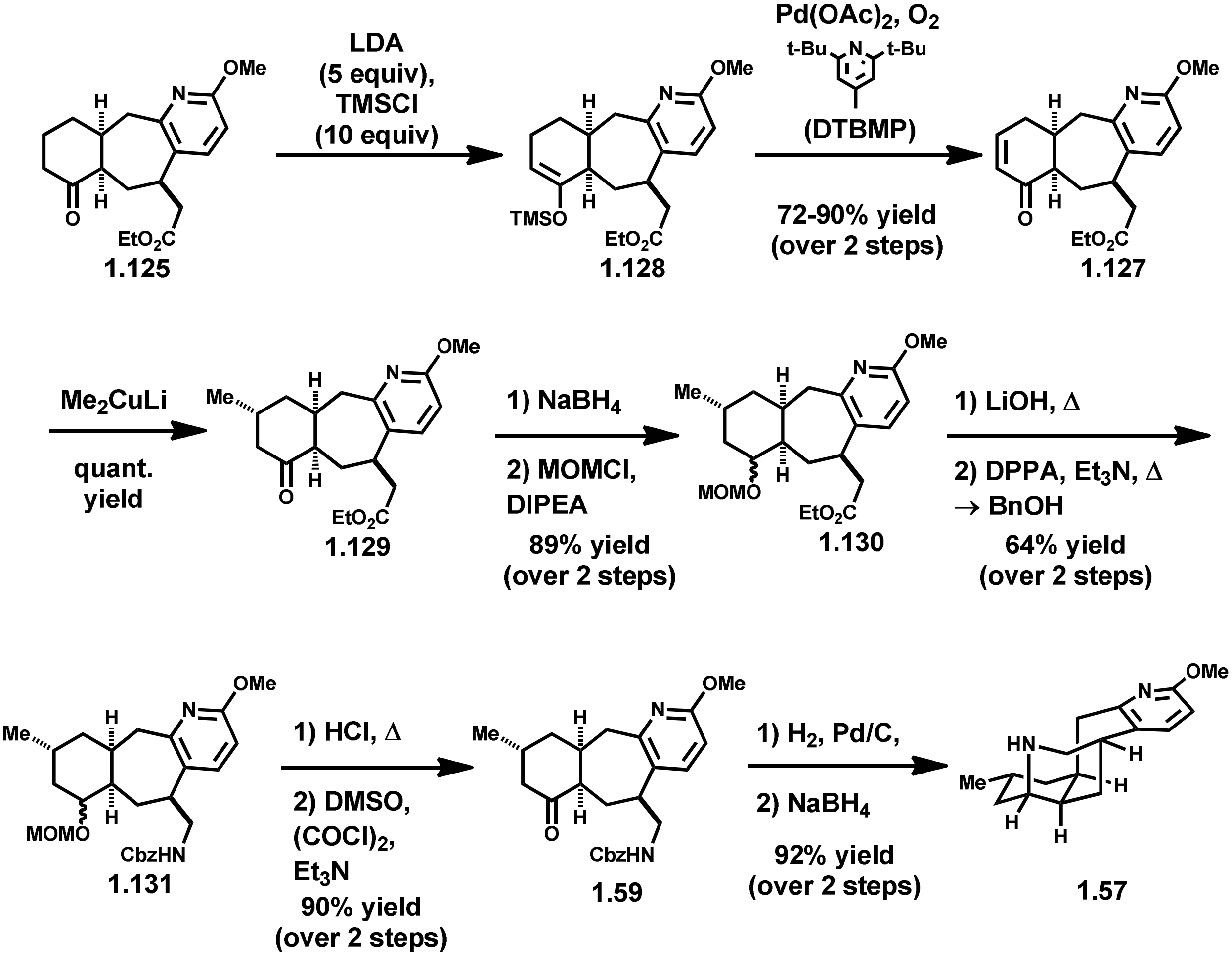
Due to the difficulty in obtaining the correct diastereomer of tricycle **1.100** from cycloheptadiene **1.99**, installation of the C15 methyl group at a later stage in the synthesis proved necessary. After diastereoselective installation of the three stereocenters on the central cycloheptane via hydrogenation, tricycle **1.92** adopts a concave structure that would favor the addition of nucleophiles from the α-face. Simple molecular modeling of enone **1.127** indicated that the concave nature of the tricycle is maintained and supported the prediction that conjugate addition of the Gilman reagent would proceed from the convex face to afford the desired stereochemistry at C15. To test this hypothesis, oxidation of tricyclic alcohol **1.92** to enone **1.127** was investigated. Swern oxidation of **1.92** provided ketone **1.125** in 90% yield (Scheme 1.30). Treatment of **1.125** with LDA and PhSeCl afforded α-selenoketone **1.126** in good yield, but subsequent oxidation with hydrogen peroxide gave enone **1.127** in only 40% yield. Direct oxidation of **1.125** to enone **1.127** with hypervalent iodine reagents such as IBX[62] or iodic acid fared poorly.

Scheme 1.30. Oxidation to Enone **1.127**



Initial formation of silyl enol ether **1.128** proved challenging, but using large excesses of LDA and TMSCl[63] resulted in efficient formation of silyl enol ether **1.128** (Scheme 1.31). Saegusa-Ito oxidation[64] of **1.128** with stoichiometric $Pd(OAc)_2$ and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) furnished the desired enone (**1.127**) in 90% yield. Catalytic loadings of 25 and 50 mol% of palladium(II) acetate provided enone **1.127** in 38% and 72% yield, respectively. For scale-up of the Saegusa-Ito oxidation, 50 mol% of $Pd(OAc)_2$ was used. Conjugate addition of the Gilman reagent to **1.127** proceeded diastereoselectively from the convex face to afford tricyclic ketone **1.129** bearing the desired stereochemistry at C15. Reduction of **1.129** formed an inconsequential mixture of diastereomeric alcohols (1:1 dr), which was treated with MOMCl to provide protected alcohol **1.130**. Saponification of **1.130** followed by Curtius rearrangement gave Cbz-protected amine **1.131**. Cleavage of the MOM ether of **1.131** followed by Swern oxidation provided protected aminoketone **1.59** in excellent yield. Hydrogenolysis of the benzyl carbamate of **1.59** and concomitant reductive amination efficiently afforded tetracyclic amine **1.57**.

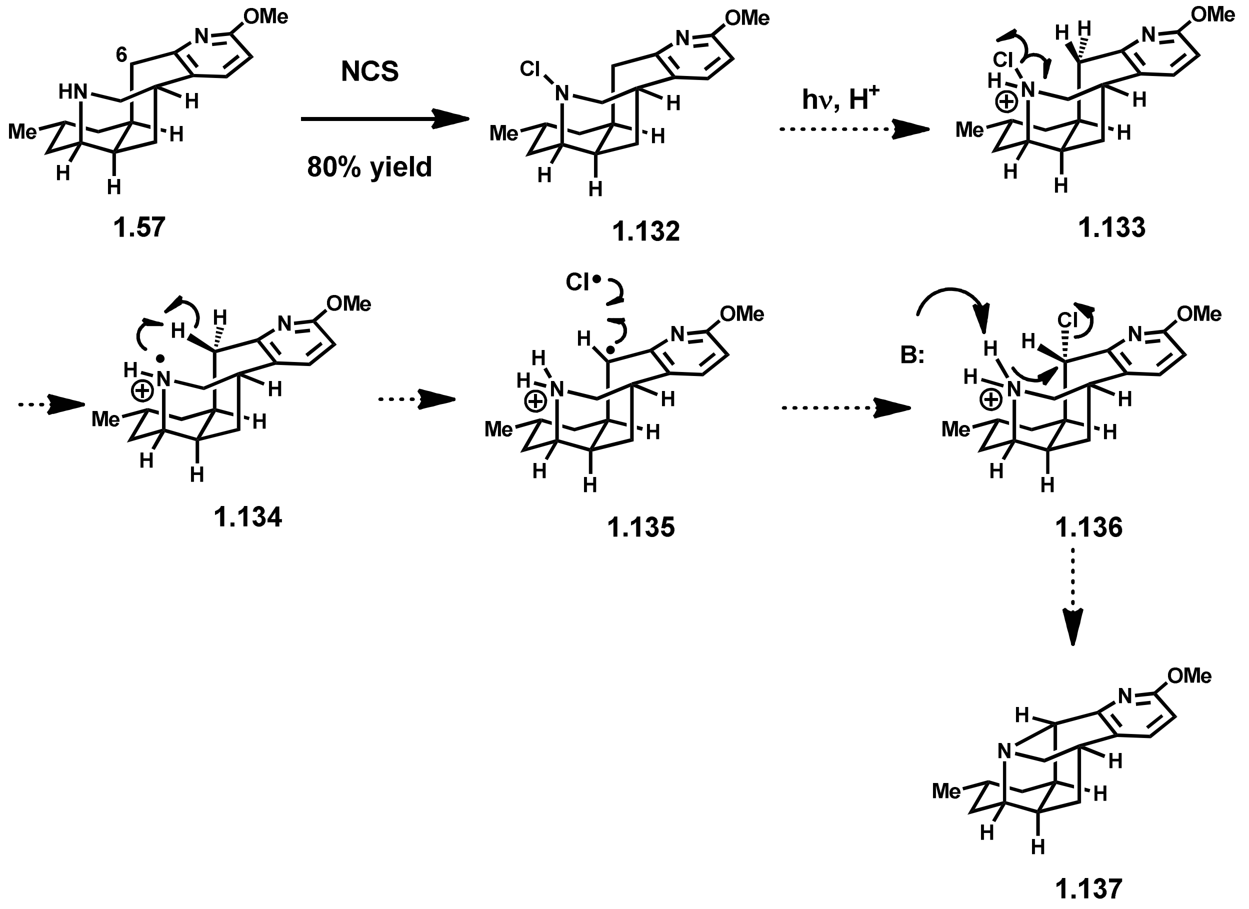
Scheme 1.31. Tetracycle Synthesis


1.125
LDA (5 equiv), TMSCl (10 equiv)
1.128
Pd(OAc)$_2$, O$_2$
(DTBMP)
72-90% yield (over 2 steps)
1.127
Me$_2$CuLi
quant. yield
1.129
1) NaBH$_4$
2) MOMCl, DIPEA
89% yield (over 2 steps)
1.130
1) LiOH, Δ
2) DPPA, Et$_3$N, Δ → BnOH
64% yield (over 2 steps)
1.131
1) HCl, Δ
2) DMSO, (COCl)$_2$, Et$_3$N
90% yield (over 2 steps)
1.59
1) H$_2$, Pd/C,
2) NaBH$_4$
92% yield (over 2 steps)
1.57

1.11 Completion of Lyconadin A

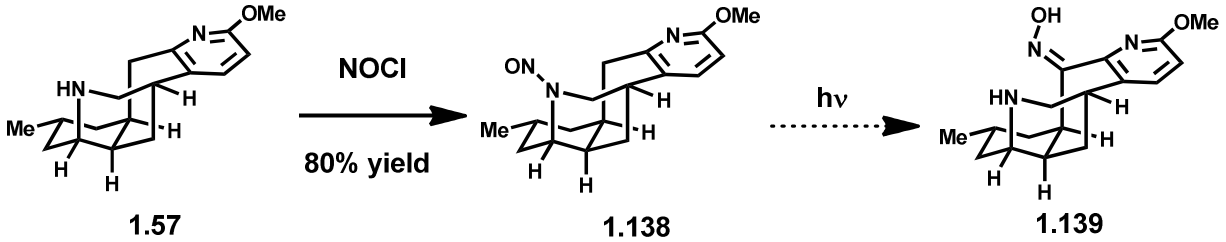
After developing a concise synthetic route to key tetracyclic intermediate **1.57**, investigation of its conversion to the initial *Lycopodium* alkaloid target, lyconadin A (**1.8**), was pursued. The final synthetic challenge was the formation of the key C6-N bond to forge the lyconadin pentacycle from amine **1.57**. The first approach to forming **1.137** was inspired by Shibanuma's examples[65] of constructing caged alkaloids utilizing the Hofmann-Löffler-Freytag (HLF) reaction.[66,67] Formation of HLF substrate **1.132** (Scheme 1.32) was achieved by treatment of amine **1.57** with N-chlorosuccinimide. Photolysis of chloroamine **1.132** should initiate homolysis of the N-Cl bond of ammonium **1.133**, followed by 1,5-hydrogen atom abstraction by amidyl radical **1.134** to form secondary radical **1.135**. Picolinic radical **1.135** can recombine with the chlorine radical to form chloride **1.136**. Subsequent displacement under the reaction conditions or upon treatment with base should effect formation of pentacycle **1.137**. Under a variety of conditions (TFA, Et_3N, H_2SO_4) with precedent to promote the HLF reaction, photolysis of **1.132** led to a complex mixture of products. Under several conditions, cleavage of the N-Cl bond of **1.132** to provide amine **1.57** and elimination of HCl to give imine byproducts were observed.

Scheme 1.32. Proposed HLF Mechanism



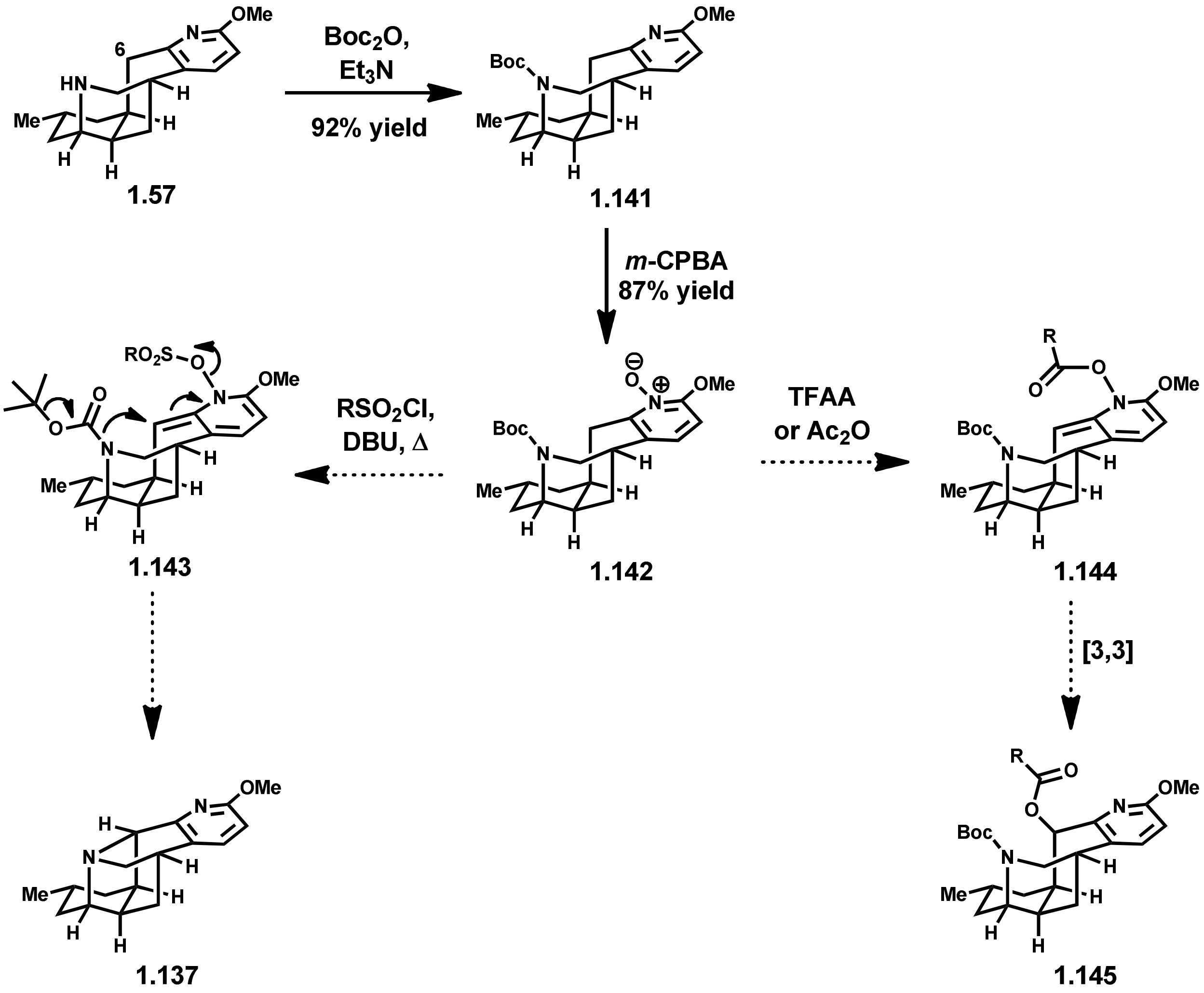
Alternatively, N-nitrosoamine **1.138** was synthesized by nitrosylation of amine **1.57** with NOCl to investigate a variant of the Barton nitrite ester oxidation (Scheme 1.33).[66] Photolysis of **1.138** could lead to homolysis of the N-N bond and 1,5-hydrogen atom abstraction similar to the HLF reaction followed by recombination with nitrosyl radical and tautomerization to provide oxime **1.139**. Installation of the oxime functionality at C6 in **1.139** would enable multiple approaches to form pentacycle **1.137**. Irradiation of N-nitrosoamine **1.138** resulted in the nonspecific decomposition of the substrate.

Scheme 1.33. Photolysis of N-Nitrosoamine



Additionally, in an attempt to form pentacycle **1.137** or functionalize the picolinic position of **1.57**, the reactivity of pyridine N-oxide **1.142** was explored (Scheme 1.34). Boc-protection of **1.57** and subsequent treatment with *m*-CPBA generated pyridine N-oxide **1.142** in good yield. To directly effect the C-N bond formation, pyridine N-oxide **1.142** could be activated by sulfonation that could enable more facile isomerization to enamine **1.143**. Thermal cleavage of the Boc group of **1.143** and intramolecular addition to the alkene with ejection of the sulfate could afford pentacycle **1.137**. Treatment of pyridine-N-oxide **1.142** with DBU and TsCl or MsCl followed by heating at elevated temperatures did not promote the desired reactivity, but instead resulted in decomposition of **1.142**. Next, the Boekelheide variant[68] of the Polonovski rearrangement[69] of N-oxide **1.142** was investigated to functionalize the picolinic position. Reaction of pyridine N-oxide **1.142** with TFAA or Ac_2O could acylate **1.142** and induce isomerization to enamine **1.144**. Subsequent [3,3] sigmatropic rearrangement of **1.144** could furnish tetracycle **1.145** bearing functionality at C6, which could be utilized for formation of pentacycle **1.137**. Upon treatment of **1.142** with TFAA or Ac_2O and heating at elevated temperatures, non-specific decomposition of the substrate was observed.

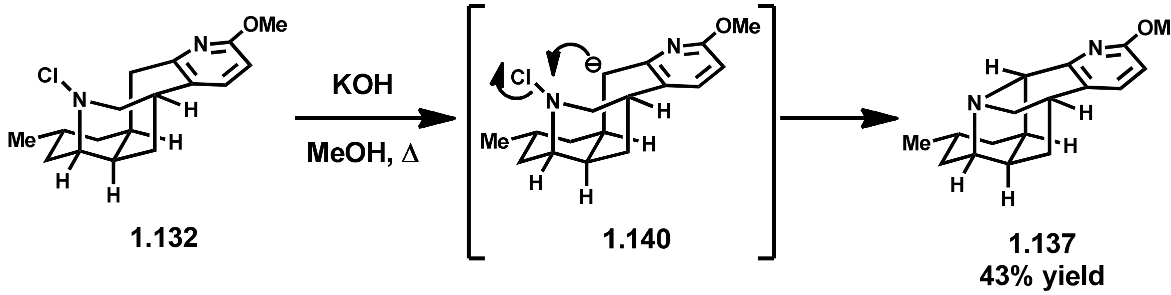
Scheme 1.34. Alternative C-N Bond Formation Strategies



1.57
Boc2O, Et3N
92% yield
1.141
m-CPBA
87% yield
1.142
RSO2Cl, DBU, Δ
1.143
TFAA or Ac2O
1.144
[3,3]
1.137
1.145

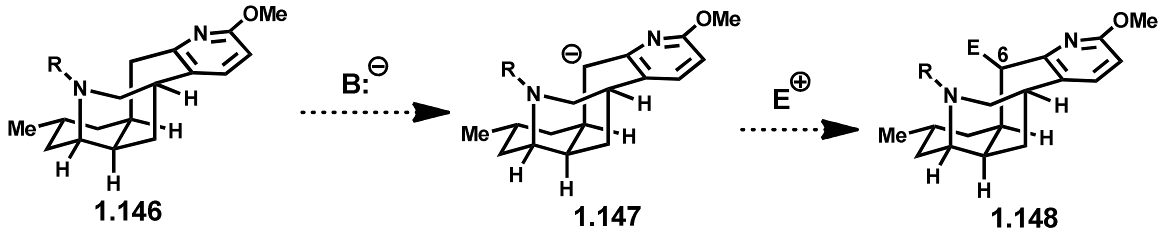
Alternatively, inspired by the key C-N bond formation in Rabe's synthesis of quinine[70] recently revisited by Williams,[71] lateral deprotonation of **1.132** followed by intramolecular nucleophilic attack on the chloroamine nitrogen with loss of chloride could provide the desired pentacycle **1.137** (Scheme 1.35). However, attempted deprotonation of **1.132** with a variety of bases (LDA, LiTMP, NaHMDS, NaH, $NaNH_2$, KO*t*-Bu) led to complex mixtures of products. Treatment of chloroamine **1.132** with KOH in refluxing methanol effected the desired transformation to afford pentacycle **1.137**, albeit in low yield.

Scheme 1.35. Pentacycle Synthesis

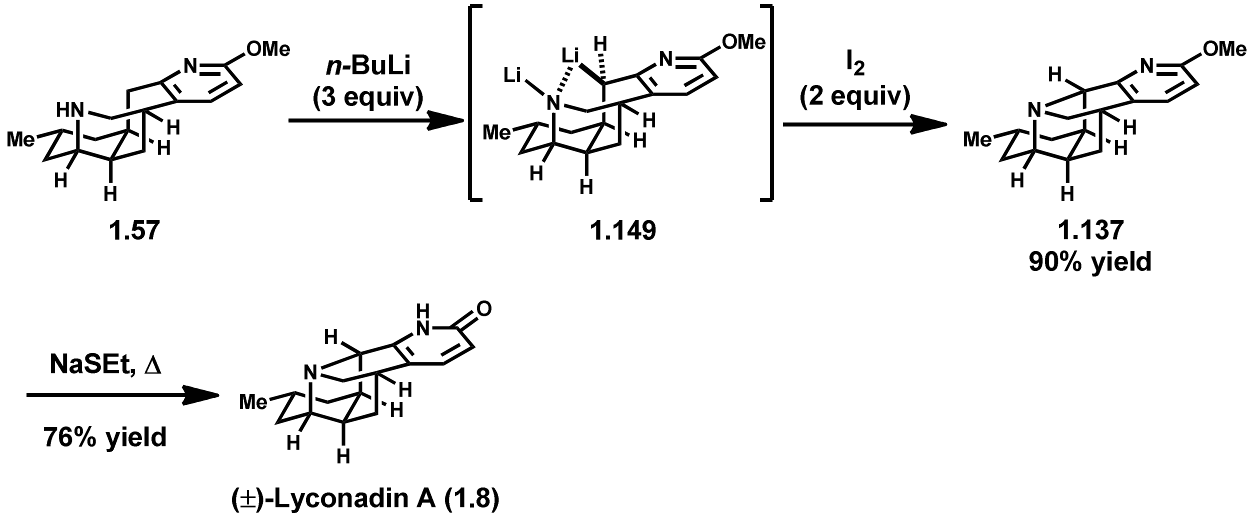


Attempting to utilize the acidity of the picolinic position, deprotonation of protected amine **1.146** could afford anion **1.147** which could be treated with an electrophile to provide a functional handle at C6 (see **1.148**) to enable subsequent formation of the pentacycle (Scheme 1.36). Attempts to deprotonate the picolinic position of protected amine **1.146** (R= allyl, Boc, or Cbz) with a variety of strong bases (*n*-BuLi, LDA, or LiTMP) was not effective and led exclusively to recovery of starting material. However, reaction of secondary amine **1.57** with an excess of *n*-BuLi (3 equiv) efficiently generated dianion **1.149** (Scheme 1.37). Addition of metal salts such as $Pd(OAc)_2$, $FeCl_3$, $Cu(OAc)_2$, and $Cu(OTf)_2$ to dianion **1.149** did not promote formation of pentacycle **1.137**. Addition of I_2 (2 equiv) to dianion **1.149** forged the pentacycle in 90% yield. Cleavage of the methyl ether of **1.137** with NaSEt furnished lyconadin A (**1.8**) in 76% yield.[72]

Scheme 1.36. Deprotonation and Functionalization at C6



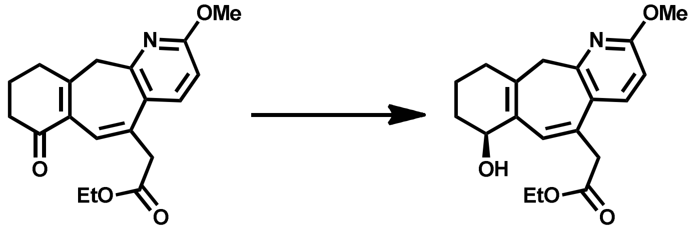
Scheme 1.37. Completion of (±)-Lyconadin A Synthesis



1.12 Enantioselective Synthesis of Lyconadin A

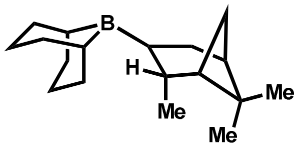
After the completion of the racemic synthesis of (±)-lyconadin A (**1.8**), the enantioselective reduction of enone **1.60** was investigated to provide a synthetic route to enantioenriched tetracycle **1.57** and (+)-lyconadin A (**1.8**). A stereodefined hydroxyl group at C13 in **1.91** should be able to govern the installation of the three stereocenters generated in the diastereoselective hydrogenation. Subsequent Swern oxidation would complete the sequence to afford ketone **1.125** in high enantiomeric purity. Chiral reducing agents derived from α-pinene (Table 1.3, entries 1-3), *S*-Alpine-Borane® (**1.150**) and (+)-B-chlorodiisopinocampheylborane (**1.151**, (+)-DIP-Cl), were screened for the enantioselective reduction of ketone **1.60**. Reduction with *S*-Alpine-Borane® provided a complex mixture of products (entry 1), however, (+)-DIP-Cl provided allylic alcohol **1.91** in 40% yield and -59% *ee* (entry 2). Prolonged reaction of **1.60** with (+)-DIP-Cl (entry 3) afforded modest asymmetric induction to give alcohol **1.91** with -65% *ee*. Although not a synthetically viable enantiomeric ratio, the results of (+)-DIP-Cl reduction demonstrated that differentiation of the enantiotopic faces of enone **1.60** could be achieved. Utilizing (*R*)-CBS-Me catalyst (**1.152**)[73-75] with borane-tetrahydrofuran complex as the stoichiometric reductant (entries 4-5), only modest conversion of **1.60** to alcohol **1.91** was achieved. Employing catecholborane as the stoichiometric reductant with (*R*)-CBS catalyst **1.152** in CH_2Cl_2 (entry 6) provided the desired alcohol in modest yield and good enantioselectivity. Examining other solvents (entries 7-8) revealed that CBS reduction of enone **1.60** in toluene (entry 8) proceeded with excellent enantioselectivity and afforded alcohol **1.91** in 85% yield.

Table 1.3. Enantioselective Reduction Optimization

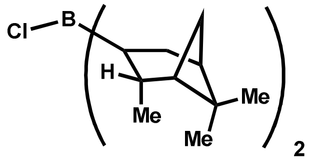


1.60 **1.91**

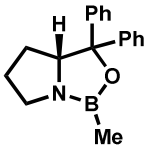
entry	catalyst/reagent	temperature (°C)	solvent	time (h)	result	*ee*
1	(*S*)-Alpine Borane	0 to rt	THF	72	multiple products	-
2	(+)-DIP-Cl	0 to rt	THF	48	40%	-59%
3	(+)-DIP-Cl	0	THF	48	63%	-65%
4	(*R*)-CBS-Me/BH_3•THF	0 to rt	THF	24	4:1 (sm:pdt)	-
5	(*R*)-CBS-Me/BH_3•THF	-78	PhMe	8	1:1 (sm:pdt)	-
6	(*R*)-CBS-Me/ catecholborane	-78	CH_2Cl_2	8	63%	83%
7	(*R*)-CBS-Me/ catecholborane	-78	THF	8	1:1 (sm:pdt)	-
8	(*R*)-CBS-Me/ catecholborane	-78	PhMe	5	85%	98%



(S)-Alpine Borane (1.150)



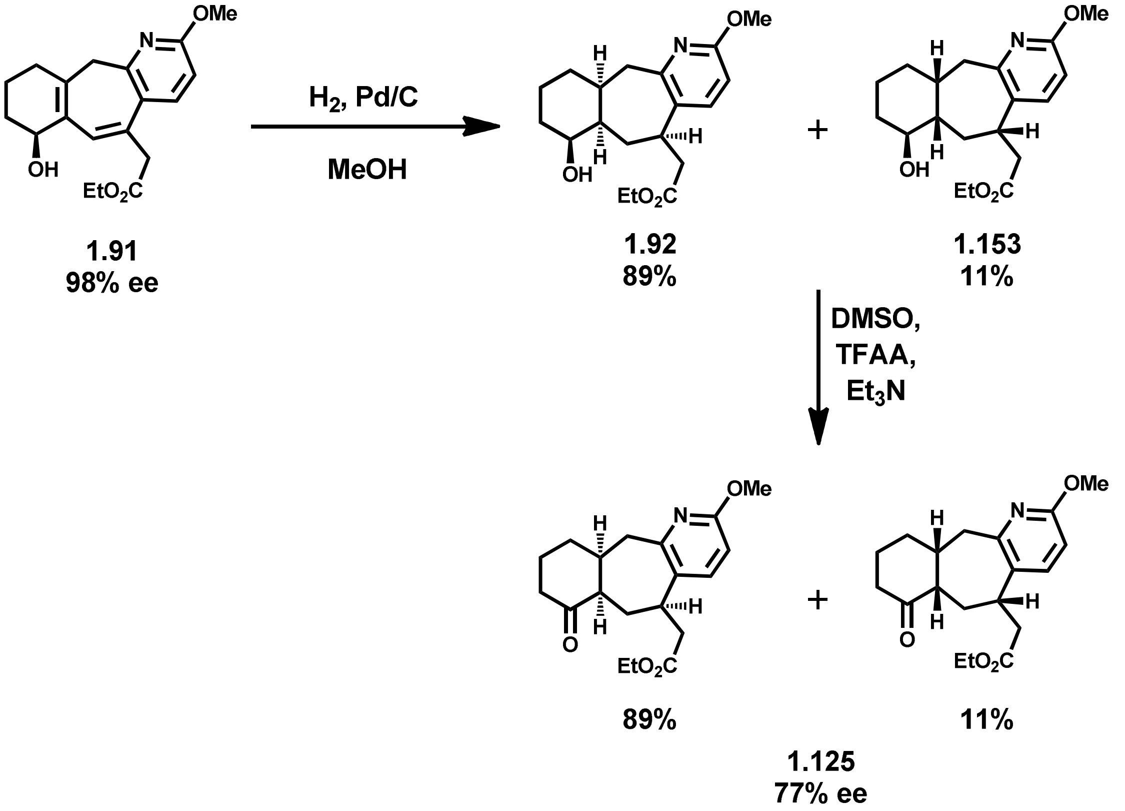
(+)-DIP-Cl (1.151)



(R)-CBS-Me (1.152)

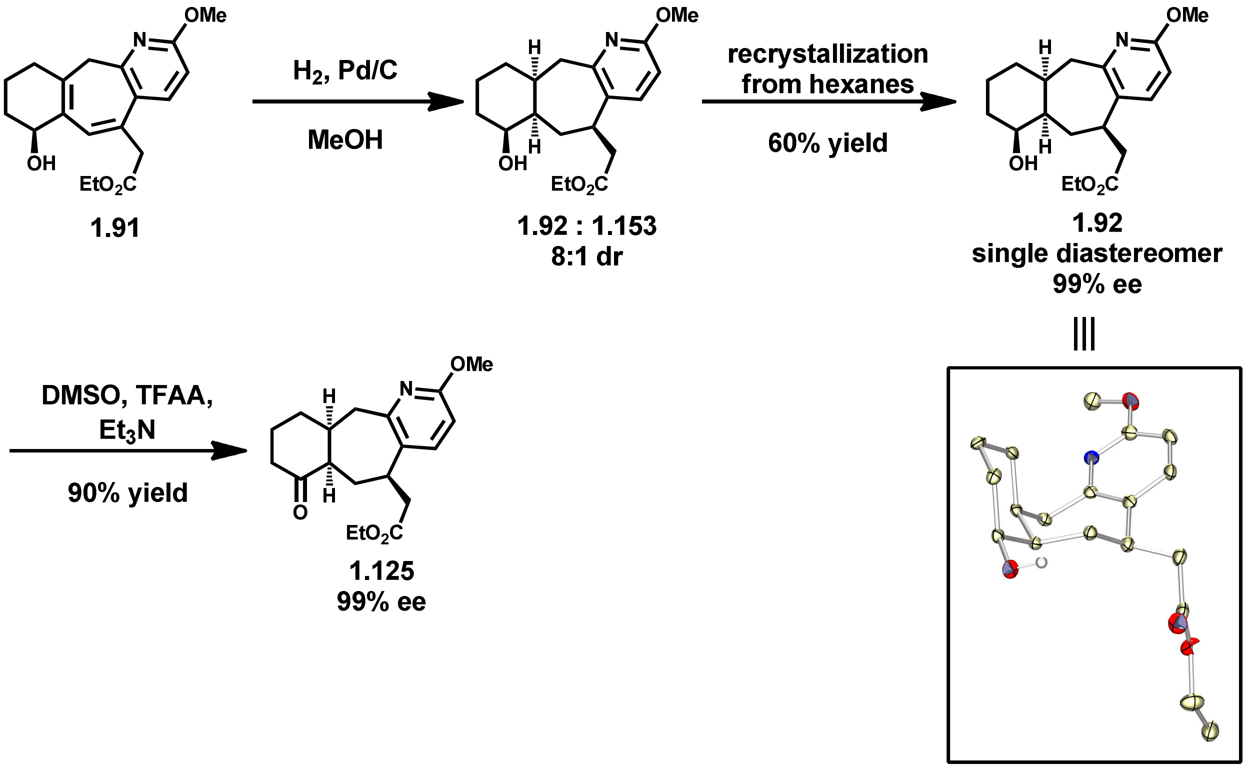
Hydrogenation of enantioenriched alcohol **1.91** and subsequent Swern oxidation provided tricyclic ketone **1.125** in an eroded 77% *ee* (Scheme 1.38). Thorough analysis of the HPLC data revealed that hydrogenation of alcohol **1.91** proceeds with only modest diastereoselectively to provide alcohols **1.92** and **1.153** in an 89:11 ratio. Swern oxidation of the diastereomeric alcohols **1.92** and **1.153** affords enantiomers of ketone **1.125** and results in the decrease in the observed enantiomeric excess. Since diastereomeric alcohols **1.92** and **1.153** were not separable by column chromatography, improving the diastereoselectivity of hydrogenation was necessary to achieve the synthesis of ketone **1.125** in high *ee*. A screen of heterogeneous hydrogenation catalysts (Pt/C, Rh/C, PtO_2) and solvents (MeOH, EtOH, EtOAc, THF) for the formation of cycloheptane **1.92** showed that the best diastereoselectivity was achieved under the original conditions, which utilized Pd/C in MeOH. Protection of alcohol **1.91** with a sterically large group (TBS or TBDPS) and hydrogenation of the protected alcohol provided the cycloheptane in a similar diastereomeric ratio.

Scheme 1.38. Oxidation of Diastereomeric Alcohols



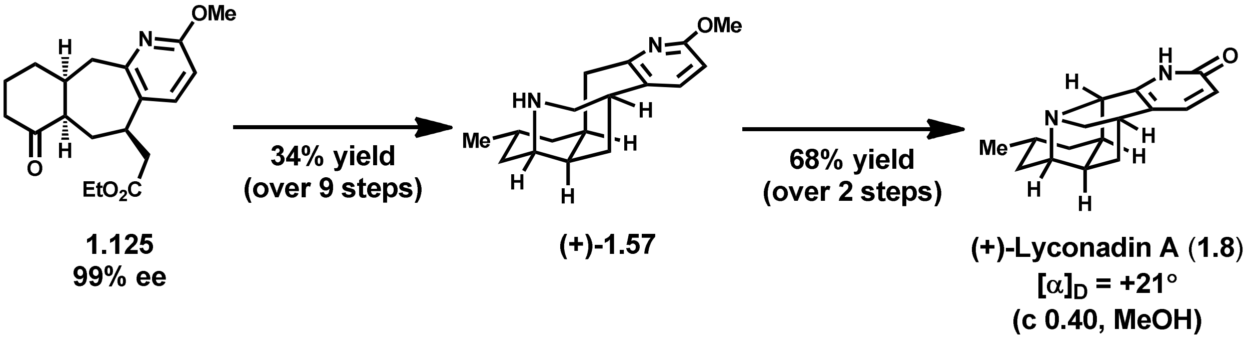
Recrystallization of the diastereomeric mixture of alcohols afforded tricyclic alcohol **1.92** in 60% yield as a single diastereomer with 99% *ee* (Scheme 1.39). The absolute and relative stereochemistry of **1.92** was confirmed by X-ray crystallographic analysis.[76,77] Swern oxidation of **1.92** proceeded without event to provide ketone **1.125**. The synthesis of (+)-lyconadin A (**1.8**, Scheme 1.40) was achieved from **1.125** in a sequence analogous to that described in Schemes 1.31 and 1.37.[78] Spectral data for synthetic (+)-lyconadin A (**1.8**) were in agreement with spectroscopic (^{1}H, ^{13}C, IR, MS) and chiroptical data obtained for natural (+)-lyconadin A[15] and synthetic (+)-lyconadin A prepared by Smith and Beshore.[36,37]

Scheme 1.39. Synthesis of Enantioenriched Ketone **1.125**



OMe
N
OH
EtO2C
1.91
H2, Pd/C
MeOH
H
1.92 : 1.153
8:1 dr
recrystallization from hexanes
60% yield
1.92
single diastereomer
99% ee
DMSO, TFAA, Et3N
90% yield
O
1.125
99% ee

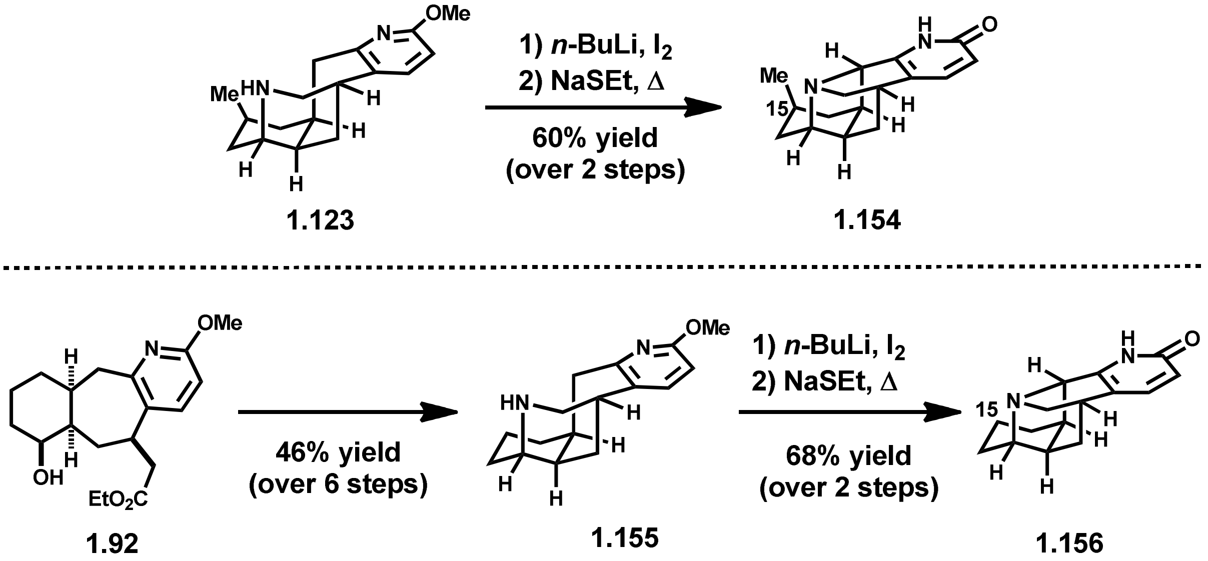
Scheme 1.40. Completion of (+)-Lyconadin A



OMe
N
H
O
EtO2C
1.125
99% ee
34% yield (over 9 steps)
HN
Me
(+)-1.57
68% yield (over 2 steps)
O
(+)-Lyconadin A (1.8)
[α]D = +21°
(c 0.40, MeOH)

In addition to synthesizing lyconadin A, analogs of lyconadin A that differ at C15 (**1.154** and **1.156**, Scheme 1.41) were prepared. Oxidative C-N bond formation of epimeric tetracycle **1.123** followed by cleavage of the methyl ether with NaSEt provided C15-*epi*-lyconadin A (**1.154**) in 60% yield. Alcohol **1.92** was advanced to tetracycle **1.155** via a sequence analogous to the conversion of **1.100** to **1.123** in 46% yield over 6 steps. Tetracycle **1.155** was subjected to *n*-BuLi and I_2 to provide the pentacyclic core, which was subsequently deprotected to afford C15-nor-Me-lyconadin A (**1.156**). Lyconadin A (**1.8**) and analogs **1.154** and **1.156** will be evaluated in a comprehensive screen for neurotrophic activity, which will hopefully lead to a further elucidation of the biological activity of these compounds.

Scheme 1.41. Synthesis of Lyconadin Analogs


OMe
MeHN
H
H
H
H
1) n-BuLi, I_2
2) NaSEt, Δ
60% yield
(over 2 steps)
H
O
H
Me
N
15
H
H
H
H
1.123
1.154
OMe
H
H
OH
EtO_2C
46% yield
(over 6 steps)
OMe
HN
H
H
H
H
1) n-BuLi, I_2
2) NaSEt, Δ
68% yield
(over 2 steps)
H
O
H
15
N
H
H
H
H
1.92
1.155
1.156

1.13 Conclusion

The enantioselective total synthesis of (+)-lyconadin A (**1.8**) has been achieved in 17 steps and 6% overall yield. Key cycloheptadiene **1.60** was assembled by a sequence of three consecutive C-C bond formations, which includes an olefin cross-metathesis and intramolecular Heck reaction. The synthetic route to enantioenriched cycloheptane **1.92** employs a CBS reduction and diastereoselective hydrogenation to set three key stereocenters in a single operation. The development of an oxidative C-N bond-forming reaction to efficiently construct the pentacyclic core of the lyconadins proved to be a vital component of our strategy. This unified approach lays the foundation for the enantioselective total synthesis of several miscellaneous *Lycopodium* alkaloids including dihydrolycolucine, lucidine A, and the nankakurines.

1.14 Experimental Contributions

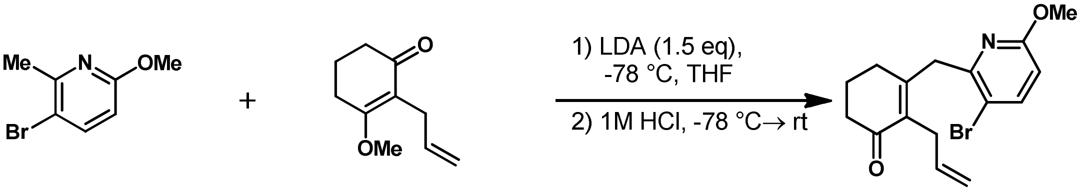
Dr. Alakesh Bisai, a postdoctoral researcher in our group, made significant contributions to the development of the lyconadin synthesis presented in this chapter. Dr. Bisai designed and conducted the experiments that resulted in the synthesis of the model tetracycle (Schemes 1.27-1.29), and the synthesis of the lyconadin tetracycle (Schemes 1.30 and 1.31). Dr. Bisai designed and conducted the initial studies to form the lyconadin pentacycle and also completed the racemic total synthesis of (±)-lyconadin A (Schemes 1.32-1.36). Andrew D. Lim, an undergraduate in our group, synthesized material that was used to pursue the enantioselective synthesis of (+)-lyconadin A. Raja R. Narayan, an undergraduate in our group, synthesized material in support of Dr. Bisai's synthetic efforts and completed the synthesis of C15-epi-lyconadin A. The remainder of the work presented in this chapter was designed and conducted by Scott P. West including the synthesis of the cycloheptadiene intermediates, investigation of the epoxide intermediates, and the enantioselective total synthesis of (+)-lyconadin A.

1.15 Experimental Methods

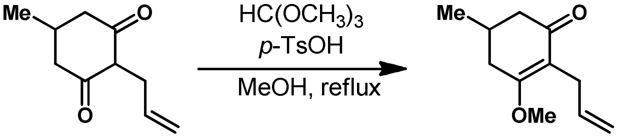
Materials and Methods

Unless otherwise stated, reactions were performed in oven-dried glassware fitted with rubber septa under a nitrogen atmosphere and were stirred with Teflon-coated magnetic stirring bars. Liquid reagents and solvents were transferred via syringe using standard Schlenk techniques. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled over sodium/benzophenone ketyl. Dichloromethane (CH_2Cl_2), toluene, and benzene were distilled over calcium hydride. Acetonitrile was distilled over potassium carbonate. N,N-Diisopropylethylamine (DIPEA) was distilled over calcium hydride prior to use. All other solvents and reagents were used as received unless otherwise noted. Reaction temperatures above 23 °C refer to oil bath temperature, which was controlled by an OptiCHEM temperature modulator. Thin layer chromatography was performed using SiliCycle silica gel 60 F-254 precoated plates (0.25 mm) and visualized by UV irradiation and anisaldehyde stain. SiliCycle Silica-P silica gel (particle size 40-63 μm) was used for flash chromatography. Melting points were recorded on a Laboratory Devices Mel-Temp 3.0 and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on Bruker AVB-400, DRX-500, AV-500 and AV-600 MHz spectrometers with ^{13}C operating frequencies of 100, 125, 125 and 150 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal ($\delta = 7.26$ for ^1H NMR and $\delta = 77.0$ for ^{13}C NMR). Data for ^1H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants, number of hydrogens). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). IR spectra were recorded on a Nicolet MAGNA-IR 850 spectrometer and are reported in frequency of absorption (cm^{-1}). Only selected IR absorbencies are reported. High resolution mass spectral data were obtained from the Mass Spectral Facility at the University of California, Berkeley. Enantiomeric excesses (*ee*'s) were determined on a Shimadzu VP Series Chiral HPLC. A Perkin-Elmer 241 polarimeter with a sodium lamp was used to determine specific rotations and concentrations are reported in g/dL.

Experimental Procedures

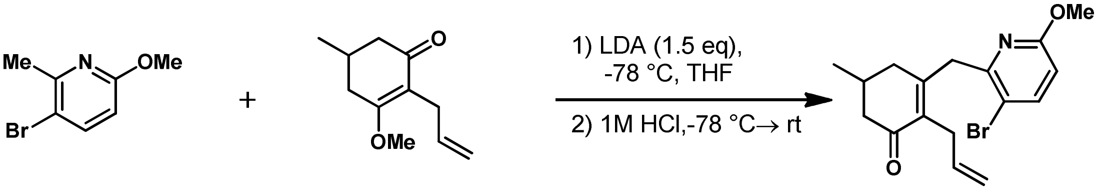


Enone (1.71): To a stirred solution of diispropylamine (4.20 mL, 29.7 mmol) in THF (100 mL) at -78 °C was added *n*-butyllithium (2.5 M in hexanes, 11.9 mL, 29.7 mmol) dropwise over 5 min. After 30 min, a solution of picoline **1.63**[44] (4.00 g, 17.8 mmol) in THF (40 mL) at -78 °C was added by cannula over 5 minutes. After stirring for 40 min at -78 °C, a solution of vinylogous ester **1.62**[46] (4.93 g, 29.7 mmol) in THF (40 mL) at -78 °C was added by cannula over 5 minutes. After stirring for 3.5 h at -78 °C, the reaction mixture was quenched by the addition of 1N HCl (40 mL) at -78 °C. The reaction mixture was stirred for 3 h while it was allowed to warm to room temperature and then neutralized by the addition of saturated $NaHCO_3$ (75 mL). The resulting mixture was extracted with EtOAc (4 x 80 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash chromatography (8:1 hexanes/EtOAc) to give 3.80 g (64% yield) of **1.71** as a yellow viscous oil. **R$_f$** 0.68 (8:1 hexanes/EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.7 Hz, 1H), 6.52 (d, *J* = 7.2 Hz, 1H), 5.76 (tdd, *J* = 16.2, 10.1, 6.1 Hz, 1H), 4.96 (qd, *J* = 17.2, 1.8 Hz, 1H), 4.90 (qd, *J* = 10.1, 1.6 Hz, 1H), 3.83 (s, 2H), 3.82 (s, 3H), 3.16 (d, *J* = 6.1 Hz, 2H), 2.46-2.35 (m, 4H), 1.95 (td, *J* = 12.4, 6.2 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.85, 162.66, 157.12, 153.96, 142.60, 136.03, 134.76, 114.73, 112.29, 110.84, 53.84, 41.62, 38.17, 31.58, 29.67, 22.65; **IR** (film) υ_{max} 3072, 2946, 2360, 2332, 1668, 1576, 1415 cm^{-1}; **HRMS** (FAB) m/z 336.0602 [$(M+H)^+$; calculated for $[C_{16}H_{19}NO_2Br]^+$: 336.0599].

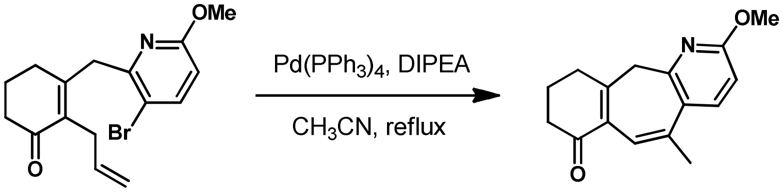


Vinylogous Ester (1.96): A two-necked round-bottom flask fitted with a reflux condenser was charged with 2-allyl-5-methyl-1,3-cyclohexanedione[79] (7.38 g, 44.4 mmol) and MeOH (150 mL). Trimethyl orthoformate (14.6 mL, 133 mmol) and *p*-toluenesulfonic acid monohydrate (845 mg, 4.44 mmol) were added and the reaction mixture was heated at reflux for 36 h. The reaction mixture was allowed to cool to rt and the solvent was removed under vacuum. The crude residue was dissolved in EtOAc (200 mL) and washed with saturated aq. $NaHCO_3$ (4 X 100 mL), water (1 X 100 mL), and saturated aq. NaCl (1 X 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum to provide 6.94 g of **1.96** (87% yield) as a yellow viscous oil. This material was used in the next step without purification. **R$_f$** 0.54 (4:1 hexanes/EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.75 (m, 1H), 4.94 (qd, *J* = 17.2, 2.0 Hz, 1H), 4.82 (qd, *J* = 10.0, 1.6 Hz, 1H), 3.77 (s, 3H), 2.96 (d, *J* = 6.0 Hz, 2H), 2.67-2.61 (m, 1H), 2.41-2.34 (m, 1H), 2.19-2.09 (m, 2H), 2.03-1.96 (m, 1H), 1.05 (d, *J* = 6.0 Hz, 3H); **^{13}C**

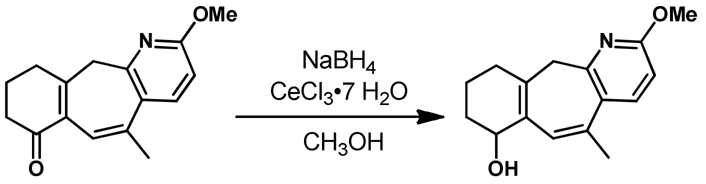
NMR (100 MHz, $CDCl_3$) δ 197.72, 171.91, 136.50, 116.77, 113.83, 55.27, 44.67, 33.06, 28.51, 26.26, 21.26; **IR** (film) υ_{max} 2957, 2360, 1734, 1609, 1458, 1378, 1235, 1081, 910 cm^{-1}; **HRMS** (EI+) m/z 180.1154 [(M^+); calculated for $[C_{11}H_{16}O_2]^+$: 180.1150].



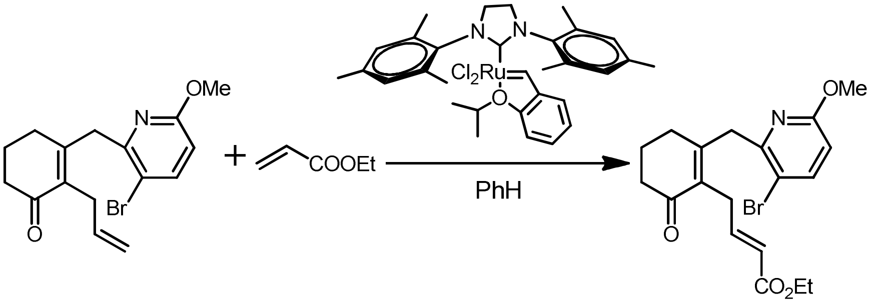
Enone (1.97): The title compound was obtained according to the procedure described for **1.71**, as a clear yellow viscous oil (65% yield). $\mathbf{R_f}$ 0.72 (8:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.5 Hz, 1H), 6.52 (d, *J* = 8.5 Hz, 1H), 5.81-5.72 (m, 1H), 4.97 (dd, *J* = 17.0, 2.0 Hz, 1H), 4.90 (dd, *J* = 12.0, 2.0 Hz, 1H), 3.95-3.77 (m, 2H), 3.85 (s, 3H), 3.16 (m, 2H), 2.52 (m, 1H), 2.39 (m, 1H), 2.16 (m, 1H), 2.08 (m, 2H), 1.00 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 198.93, 162.75, 156.07, 153.68, 142.38, 135.77, 134.15, 114.49, 112.07, 110.62, 53.59, 46.02, 41.29, 39.60, 29.69, 29.35, 21.20; **IR** (film) υ_{max} 2950, 1667, 1636, 1576, 1460, 1415, 1371, 1328, 1288, 1014, 909, 822 cm^{-1}; **HRMS** (EI+) m/z 349.0669 [(M^+); calculated for $[C_{17}H_{20}BrNO_2]^+$: 349.0739].



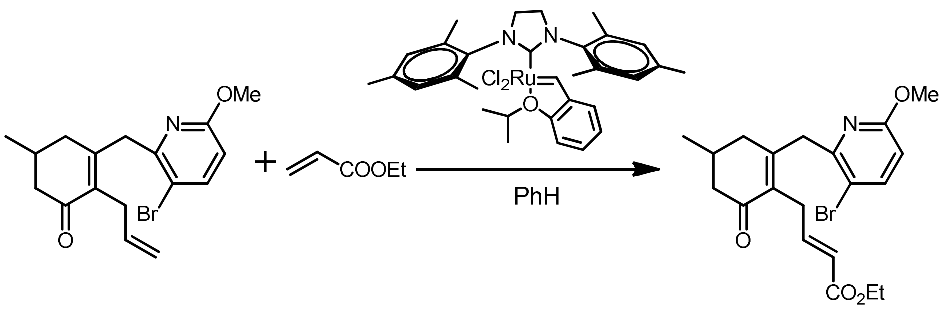
Cycloheptadiene (1.73): To a Schlenk flask containing $Pd(PPh_3)_4$ (35 mg, 0.030 mmol) was added **1.71** (100 mg, 0.30 mmol) in acetonitrile (6 mL) and diisopropylethylamine (160 μL, 0.90 mmol). The reaction mixture was degassed by bubbling nitrogen through the mixture for 10 minutes. The flask was then sealed and heated at reflux for 7 h. The reaction mixture was allowed to cool to room temperature and filtered through Celite. The solids were washed with EtOAc (3 x 20 mL), and the combined organic layers were concentrated under vacuum. The crude product was purified by flash chromatography (8:1 hexanes/EtOAc) to give 34 mg (44%) of **1.61** as a pale yellow solid. **^{1}H NMR** (400 MHz) 7.67 (d, 1H, *J* = 8.6 Hz), 6.97 (s, 1H), 6.68 (d, 1H, *J* = 8.6 Hz), 3.95 (s, 3 H), 3.22 (s, 2 H), 2.72 (t, 2H, *J* = 6.0 Hz), 2.44-2.37 (m, 2H), 2.34 (s, 3H), 1.92 (m, 2H); **^{13}C NMR** (100 MHz) δ 198.2, 164.0, 152.1, 149.1, 136.7, 136.4, 131.1, 125.9, 122.1, 108.2, 53.6, 43.9, 37.4, 31.9, 23.9, 22.0; **IR** (film) υ_{max} 2944, 2359, 1670, 1583, 1480, 1318 cm^{-1}; MS (EI): m/z 255(M^+), 240, 226, 212, 198, 184; **HRMS** (EI) calculated for $[C_{16}H_{17}NO_2]^+$: m/z 255.1264, found 255.1259; mp 112 °C.



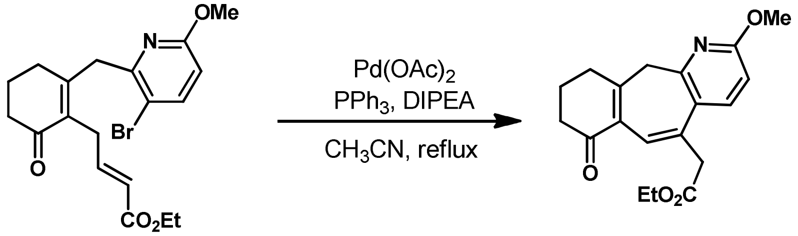
Alcohol (1.74): To a stirred solution of **1.73** (40 mg, 0.15 mmol) in CH_3OH (5 mL) was added $CeCl_3$•7 H_2O (170 mg, 0.47 mmol). The reaction mixture was cooled to 0 ºC, stirred for 30 min and then $NaBH_4$ (7.0 mg, 0.18 mmol) was added. After stirring for 2 h at 0 ºC, the reaction mixture was quenched by the addition of 1M NaOH (15 mL). The resulting mixture was extracted with EtOAc (4 x 25 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash chromatography (4:1 hexanes/EtOAc) to give 23 mg (58%) of **1.74** as a clear oil. **^{1}H NMR** (400 MHz) δ 7.65 (d, 1H, *J* = 8.6 Hz), 6.63 (d, 1H, *J* = 8.6 Hz), 6.43 (s, 1H), 4.21 (br s, 1H), 3.93 (s, 3H), 3.92 (br s, 1H), 3.16 (d, 1H, *J* = 11.9 Hz), 2.84 (d, 1H, *J* = 11.8 Hz), 2.36 (s, 2H), 2.30 (s, 3H), 1.66 (m, 4H); **^{13}C NMR** (100 MHz) 163.8, 151.1, 136.4, 135.5, 134.0, 130.7, 128.0, 125.6, 107.2, 68.1, 53.4, 43.0, 31.3, 31.2, 23.7, 17.7; **IR** (film) υ_{max} 2924, 2854, 1462, 1437, 1119, 721 cm^{-1}; MS (EI) m/z 257 (M^+), 228, 201, 186; **HRMS** (EI) calculated for $[C_{16}H_{19}NO_2]^+$: m/z 257.1416, found 257.1422.



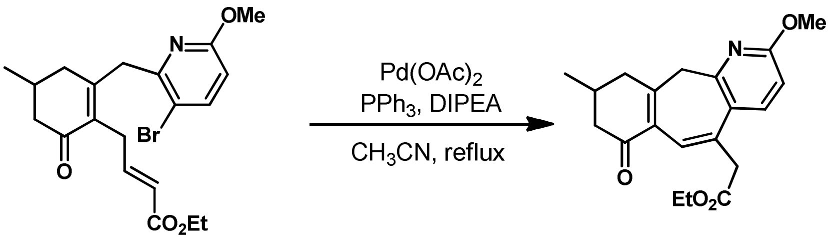
Enoate (1.86): To a solution of enone **1.71** (5.62 g, 16.7 mmol) in benzene (170 mL) was added ethyl acrylate (9.06 mL, 83.6 mmol). The reaction mixture was degassed by bubbling nitrogen through it for 5 minutes. To this reaction mixture, Grubbs-Hoveyda Second Generation catalyst (**1.84,** 207 mg, 0.33 mmol) was added. The reaction mixture was stirred at rt until TLC showed complete consumption of starting material (48 h). The solvent was removed under vacuum and the crude product was purified by flash chromatography (4:1 hexanes/EtOAc) to afford 6.73 g (88% yield) of **1.86** as a yellow viscous oil. **R_f** 0.34 (6:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.7 Hz, 1H), 6.87 (td, *J* = 15.6, 6.3 Hz, 1H), 6.51 (d, *J* = 8.7 Hz, 1H), 5.71 (td, *J* = 15.6, 1.7 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 3.80 (s, 2H), 3.32 (d, *J* = 5.9 Hz, 2H), 2.48-2.38 (m, 4H), 2.02-1.93 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 198.18, 166.50, 162.53, 158.30, 153.21, 146.21, 142.44, 133.02, 121.30, 112.03, 110.87, 60.09, 53.64, 41.55, 37.75, 31.49, 28.01, 22.29, 14.22; **IR** (film) υ_{max} 2979, 2947, 2360, 1717, 1666, 1577, 1462, 1415, 1328, 1288, 1266, 1161, 1036, 975, 824 cm^{-1}; **HRMS** (EI+) m/z 407.0733 [(M^+); calculated for $[C_{19}H_{22}BrNO_4]^+$: 407.0681].



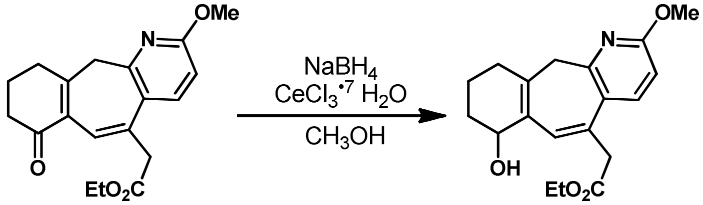
Enoate (1.157): The title compound was obtained, according to the procedure described for **1.71**, as a yellow viscous oil (80% yield). **R$_f$** 0.42 (6:1 hexanes/EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.7 Hz, 1H), 6.83 (td, *J* = 15.6, 6.2 Hz, 1H), 6.47 (d, *J* = 8.6 Hz, 1H), 5.67 (td, *J* = 15.6, 1.7 Hz, 1H), 4.07 (q, *J* = 7.1, Hz, 2H), 3.77 (s, 3H), 3.73 (m, 2H), 3.33-3.23 (m, 2H), 2.51-2.38 (m, 2H), 2.17-1.99 (m, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), 0.97 (d, *J* = 6.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.36, 166.40, 162.48, 157.44, 153.12, 146.16, 142.41, 132.62, 121.25, 112.00, 110.85, 60.01, 53.59, 45.79, 41.41, 39.70, 29.61, 27.92, 21.17, 14.18; **IR** (film) υ_{max} 2952, 2823, 1717, 1669, 1609, 1576, 1492, 1415, 1371, 1321, 1207, 1176, 1016 cm^{-1}; **HRMS** (FAB) m/z 424.0959 [(M+2H)$^+$; calculated for $[C_{20}H_{26}BrNO_4]^+$: 424.0960].



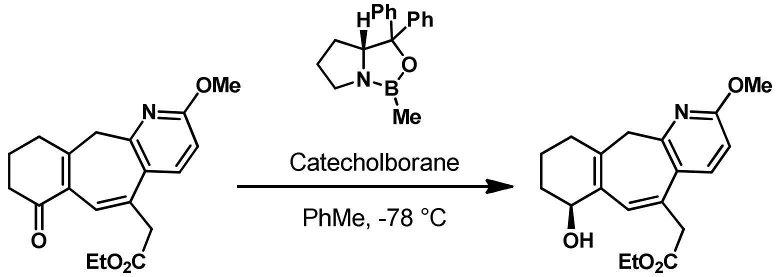
Tricyclic Cycloheptadiene (1.60): An oven-dried Schlenk flask was charged with enoate **1.86** (7.16 g, 17.5 mmol) and acetonitrile (175 mL). To this reaction mixture was added N,N-diisopropylethylamine (DIPEA) (9.2 mL, 52.6 mmol) followed by triphenylphosphine (1.84 g, 7.02 mmol) and $Pd(OAc)_2$ (788 mg, 3.51 mmol). The flask was then sealed and heated at 85 °C for 12 h. The reaction mixture was allowed to cool to rt and filtered through Celite. The solids were washed with EtOAc (3 x 60 mL), and the combined organic layers were concentrated under vacuum. The crude product was purified by flash chromatography (4:1 hexanes/EtOAc) to give 5.23 g (91% yield) of **1.60** as a pale yellow oil. **R$_f$** 0.40 (6:1 hexanes/EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.6 Hz, 1H), 7.04 (s, 1H), 6.66 (d, *J* = 8.6 Hz, 1H), 4.03 (q, *J* = 7.1 Hz, 2H), 3.93 (s, 3H), 3.71 (s, 2H), 3.27 (s, 2H), 2.72 (t, *J* = 5.8, Hz, 1H), 2.44-2.35 (m, 2H), 1.93 (dd, *J* = 12.48, 6.1 Hz, 2H), 1.13 (t, *J* = 7.1, Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.90, 171.26, 164.26, 154.34, 149.99, 136.29, 133.80, 130.69, 125.29, 124.38, 108.38, 60.83, 53.62, 43.82, 43.20, 37.36, 32.02, 21.93, 14.08; **IR** (film) υ_{max} 2951, 2868, 1735, 1672, 1585, 1482, 1391, 1319, 1272, 1187, 1032 cm^{-1}; **HRMS** (EI+) m/z 327.1470 [(M$^+$); calculated for $[C_{19}H_{21}NO_4]^+$: 327.1470].



Tricyclic cycloheptadiene (1.98): The title compound was obtained, according to the procedure described for **1.60**, as a yellow solid (88 % yield). **R$_f$** 0.44 (6:1 hexanes/EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.6 Hz, 1H), 7.02 (s, 1H), 6.66 (d, *J* = 8.6 Hz, 1H), 4.03 (q, *J* = 7.1 Hz, 2H), 3.94 (s, 3H), 3.78 (d, *J* = 16.2 Hz, 1H), 3.64 (d, *J* = 16.2 Hz, 1H), 3.41 (d, *J* = 11.5 Hz, 1H), 3.15 (d, *J* = 11.3 Hz, 1H), 2.72 (dd, *J* = 18.9, 2.8 Hz, 1H), 2.45 (m, 2H), 2.11 (q, *J* = 12.3 Hz, 2H), 1.13 (t, *J* = 7.1 Hz, 3H), 1.03 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.07, 171.21, 164.15, 153.81, 149.97, 136.26, 133.75, 130.27, 125.14, 124.34, 108.27, 60.78, 53.61, 45.46, 43.72, 43.14, 40.39, 29.41, 21.02, 14.03; **IR** (film) υ_{max} 2954, 2360, 1733, 1671, 1604, 1585, 1482, 1392, 1319, 1272, 1163, 1033, 832 cm^{-1}; **HRMS** (EI+) m/z 341.1626 [(M$^+$); calculated for $[C_{20}H_{23}NO_4]^+$: 341.1627]; **MP** 104-105 °C.

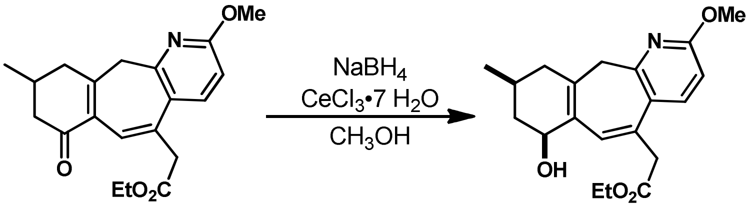


Tricyclic alcohol (1.91): In a round-bottom flask, tricyclic cycloheptadiene **1.60** (2.40 g, 7.33 mmol) was dissolved in MeOH (73 mL). To this solution was added $CeCl_3$•$7H_2O$ (5.50 g, 14.66 mmol). The reaction mixture was stirred at rt for 15 min and then was cooled to 0 °C. $NaBH_4$ (555 mg, 14.66 mmol) was added to the reaction mixture in three portions (3 X 185 mg) over 15 mins. The reaction mixture was slowly allowed to warm to rt while stirring was continued. After completion of the reaction (TLC, 5 h), it was quenched with saturated aq. NH_4Cl (10 mL) and aq. $NaHCO_3$ (10 mL). After stirring vigorously for 30 mins, the solvent was removed under reduced pressure. Water (50 mL) was added to the crude reaction mixture and it was extracted with EtOAc (3 X 70 mL). The combined organic extracts were washed with saturated aq. NaCl (70 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by flash chromatography (2:1 hexanes/EtOAc) to provide 2.20 g (91% yield) of **1.91** as a light yellow viscous oil. **R$_f$** 0.40 (2:1 hexanes/EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.5 Hz, 1H), 6.59 (d, *J* = 9.0 Hz, 1H), 6.52 (br, s, 1H), 4.21 (br, s, 1H), 4.02 (q, *J* = 7.0 Hz, 2H), 3.90 (s, 3H), 3.72 (d, *J* = 15.8 Hz, 1H), 3.54 (d, *J* = 15.8 Hz, 1H), 3.17 (d, *J* = 11.5 Hz, 1H), 2.89 (d, *J* = 11.0 Hz, 1H), 2.35 (br, s, 2H), 1.74-1.59 (m, 5H), 1.12 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.54, 163.90, 151.70, 136.08, 136.03, 132.61, 131.13, 130.31, 124.06, 107.36, 67.81, 60.74, 53.43, 43.08, 42.87, 31.33, 31.27, 17.69, 14.01; **IR** (film) υ_{max} 3414, 2939, 1731, 1584, 1555, 1480, 1430, 1394, 1316, 1273, 1161, 1029, 994 830 cm^{-1}; **HRMS** (EI+) m/z 329.1622 [(M$^+$); calculated for $[C_{19}H_{23}NO_4]^+$: 329.1627].

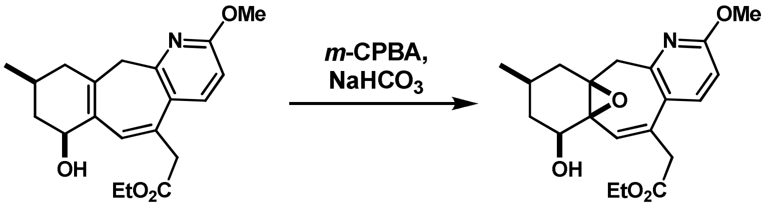


Tricyclic alcohol (1.91): To a solution of tricyclic enone **1.60** (3.52 g, 10.8 mmol) in toluene (85 mL) was added R-CBS-Me catalyst **1.152** (1M in toluene, 4.30 mL, 4.30 mmol) and the solution was cooled to -78 ºC. A solution of catecholborane (3.44 mL, 32.3 mmol) in toluene (20 mL) was added dropwise over 30 minutes. After stirring for 6 hours at -78 ºC, water (40 mL) was added and the reaction was allowed to warm to rt. The reaction mixture was poured on water (150 mL) and extracted with Et_2O (3 x 125 mL). The combined organic layers were washed with 1N NaOH (2 x 100 mL), saturated NaCl (100 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by flash chromatography (4:1 hexanes/EtOAc) to provide 3.00 g (85% yield) of **1.91** as a clear oil. Enantiomeric excess was determined by HPLC analysis (Chiralpak AD-H column, 92:8 hexanes/ethanol, 1 mL/min) t_r 9.8 min(minor), 13.5 min (major): 98% *ee*.

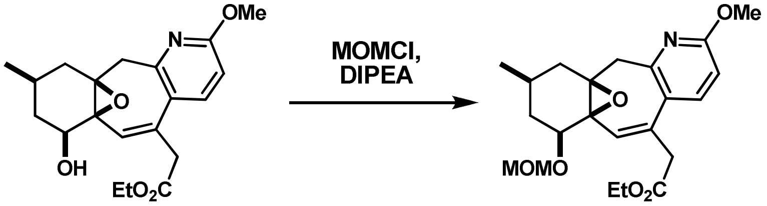
See previous procedure for full characterization data.



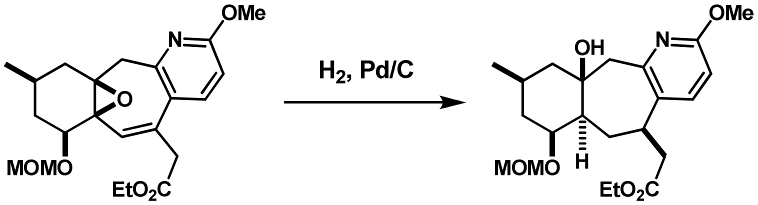
Tricyclic allylic alcohol (1.99): The title compound was obtained according to the procedure described for racemic **1.91** as a light yellow viscous oil (92% yield) and as a single diastereomer. **R$_f$** 0.66 (2:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.6 Hz, 1H), 6.74 (s, 1H), 6.60 (d, *J* = 8.6 Hz, 1H), 4.29 (br, s, 1H), 4.03 (q, *J* = 7.1 Hz, 2H), 3.92 (s, 3H), 3.64 (br, s, 2H), 3.10 (d, *J* = 11.6 Hz, 1H), 3.01 (br, 1H), 2.35 (dd, *J* = 18.2, 4.5 Hz, 1H), 2.07 (dd, *J* = 17.9, 10.6 Hz, 1H), 2.02 (ddd, *J* = 10.0, 8.3, 5.9 Hz, 1H), 1.72 (br, s, 2H), 1.13 (t, *J* = 7.1 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 171.64, 163.78, 152.09, 135.98, 131.99, 131.45, 129.21, 129.16, 124.10, 107.28, 69.65, 60.73, 53.44, 43.17, 42.78, 41.57, 40.30, 27.98, 21.59, 14.02; **IR** (film) υ_{max} 3417, 2949, 2773, 2820, 1732, 1585, 1480, 1396, 1316, 1274, 1159, 1021, 982, 830 cm^{-1}; **HRMS** (EI+) m/z 343.1778 [(M^+); calculated for $[C_{20}H_{25}NO_4]^+$: 343.1783].



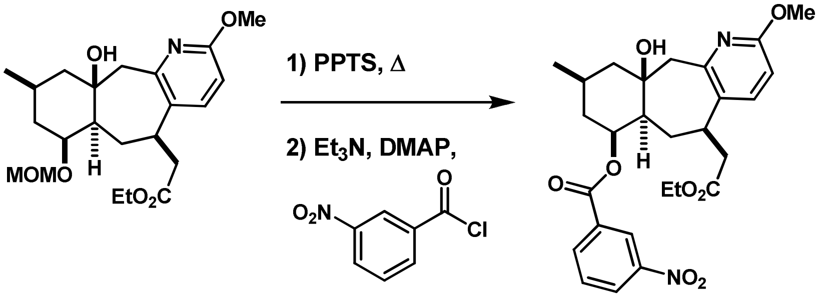
Epoxide (1.104): To a solution of alcohol **1.99** (3.06 g, 8.91 mmol) and $NaHCO_3$ (1.50 g, 17.82 mmol) in CH_2Cl_2 (45 mL) at -10 °C was added *meta*-chloroperoxybenzoic acid (*m*-CPBA (~75%), 3.08 g, 13.37 mmol) in portions over 30 minutes. After stirring the reaction mixture at -10 °C for 5h, the reaxtion mixture was poured on saturated $NaHSO_3$ (200 mL) and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with saturated $NaHSO_3$ (2 x 50 mL), saturated $NaHCO_3$ (2 x 50 mL) and saturated NaCl (50 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by flash chromatography (4:1 hexanes/EtOAc to 2:1 hexanes/EtOAc) to provide 2.62 g (82% yield) of epoxide **1.104** as a clear oil. **R$_f$** 0.45 (1:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.5 Hz, 1H), 6.62 (d, *J* = 8.5 Hz, 1H), 6.47 (br s, 1H), 4.03-3.94 (m, 2H), 3.92 (s, 3H), 3.66 (br s, 1H), 3.55 (d, *J* = 16.1 Hz, 1H), 3.43-3.30 (m, 1H), 3.17 (d, *J* = 12.3 Hz, 1H), 2.92 (d, *J* = 12.0 Hz, 1H), 2.06-1.99 (m, 2H), 1.62-1.50 (m, 2H), 1.07 (t, *J* = 7.1 Hz, 1H), 0.81 (d, *J* = 6.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.67, 162.30, 154.62, 137.09, 132.70, 128.37, 125.32, 107.93, 72.23, 63.79, 60.75, 53.51, 45.45, 43.24, 36.84, 35.74, 27.74, 21.27, 13.95.



MOM ether (1.108): To a solution of epoxide **1.104** (2.45 g, 6.82 mmol) in CH_2Cl_2 (70 mL) at 0 °C was added N,N-diisopropylethylamine (DIPEA, 2.38 mL, 13.6 mmol) and chloromethyl methyl ether (MOMCl, 5M in MeOAc, 2.73 mL, 13.6 mmol). The reaction was allowed to warm to rt and stirred for 12 h. The reaction mixture was poured on water (200 mL) and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water (100 mL) and saturated NaCl (100 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by flash chromatography (4:1 hexanes/EtOAc to 2:1 hexanes/EtOAc) to provide 2.37 g (86% yield) of MOM ether **1.108** as a white solid. **R$_f$** 0.60 (2:1 hexanes/EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.5 Hz, 1H), 6.62 (d, *J* = 8.5 Hz, 1H), 6.41 (br s, 1H), 4.73 (d, *J* = 6.9 Hz, 1H), 4.65 (d, *J* = 6.9 Hz, 1H), 4.05-3.96 (m, 2H), 3.92 (s, 3H), 3.65 (br s, 1H), 3.51 (d, *J* = 15.9 Hz, 1H), 3.38 (s, 3H), 3.35-3.27 (m, 1H), 3.13 (d, *J* = 12.4 Hz, 1H), 2.89 (d, *J* = 12.3 Hz, 1H), 2.02 (dd, *J* = 15.2, 6.0 Hz, 1H), 1.64-1.48 (m, 2H), 1.23 (q, *J* = 12.1 Hz, 1H), 1.09 (t, *J* = 7.1 Hz, 3H), 0.81 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.57, 162.26, 154.87, 137.21, 132.23, 128.60, 125.45, 107.96, 95.47, 77.41, 62.27, 60.75, 55.51, 53.47, 45.61, 43.26, 35.50, 33.26, 27.57, 21.39, 13.98.

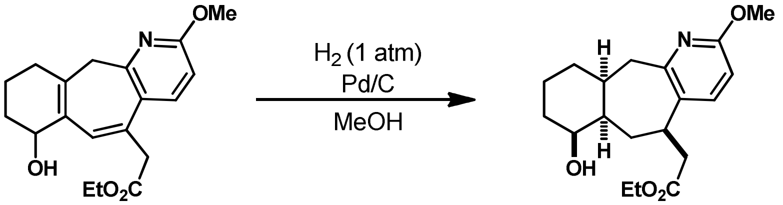


Alcohol (1.111): Epoxide **1.108** (200 mg, 0.58 mmol) was dissolved in MeOH (20 mL) and sparged under a nitrogen atmosphere for 5 minutes. 10% Pd on activated carbon (20 mg) was added and the flask was evacuated and backfilled with hydrogen 3 times. The reaction mixture was placed under a hydrogen atmosphere (1 atm. balloon) and stirred at rt for 18 h until TLC indicated complete consumption of the starting material and finally sparged with nitrogen for 5 minutes. The reaction mixture was filtered through a pad of celite and washed with MeOH (3 X 15 mL). The filtrate was concentrated under vacuum to provide 194 mg (95 % yield) of alcohol **1.111**. **R$_f$** 0.65 (1:1 hexanes/EtOAc); **^{1}H NMR** (600 MHz, CDCl$_3$) δ 7.27 (d, *J* = 8.7 Hz, 1H), 6.54-6.51 (d, *J* = 8.7 Hz, 1H), 4.69-4.66 (d, *J* = 6.9 Hz, 1H), 4.45 (d, *J* = 6.9 Hz, 1H), 4.21-4.13 (m, 2H), 3.92 (s, 3H), 3.90-3.87 (m, 2H), 3.59 (br s, 1H), 3.40-3.33 (m, 1H), 3.31 (s, 3H), 3.15-3.11 (m, 1H), 3.06 (d, *J* = 14.0 Hz, 1H), 2.84 (dd, *J* = 15.6, 5.9 Hz, 1H), 2.70-2.64 (m, 1H), 2.16-2.08 (m, 1H), 2.03-1.84 (m, 4H), 1.80 (dd, *J* = 14.2, 6.6 Hz, 1H), 1.72-1.65 (m, 2H), 1.46 (d, *J* = 13.4 Hz, 1H), 1.26 (m, 6H); **^{13}C NMR** (125 MHz, CDCl$_3$) δ 172.47, 161.62, 156.02, 134.01, 130.31, 107.12, 94.54, 79.03, 71.64, 60.56, 55.97, 53.33, 51.36, 50.42, 45.34, 39.39, 36.84, 34.63, 33.67, 26.46, 22.93, 14.21; **HRMS** (ESI) m/z 408.2391 [(M+H)$^+$; calculated for [$C_{22}H_{34}NO_6$]$^+$: 408.2381].

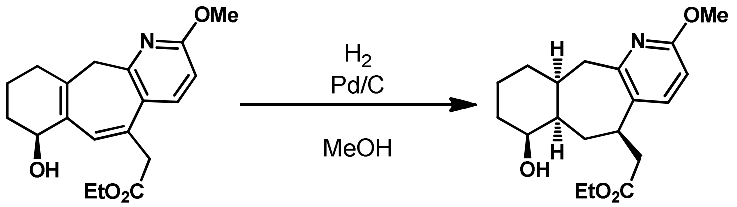


***m*-Nitrobenzoate (1.114)**: To a solution of alcohol **1.111** (20 mg, 0.05 mmol) in benzene (2 mL) was added pyridinium *p*-toluenesulfonate (38 mg, 0.15 mmol). The reaction vial was sealed and heated at 80 °C for 18 hours. The reaction was allowed to cooled to rt, poured on saturated NaHCO$_3$ (10 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 5 mL) and the combined organic layers were dried over MgSO$_4$ and concentrated under vacuum. The crude product was purified by flash chromatography (4:1 hexanes/EtOAc to 2:1 hexanes/EtOAc) to give 11 mg (60% yield) of diol **1.113**.

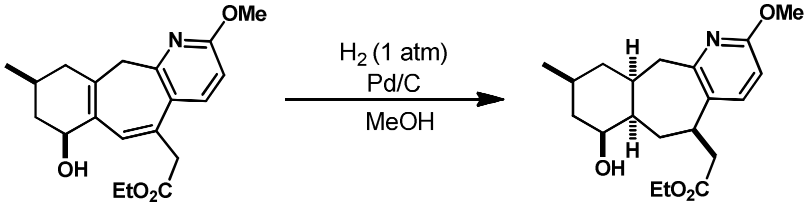
To a solution of diol **1.113** (11 mg, 0.03 mmol) in CH$_2$Cl$_2$ (1.5 mL) was added triethylamine (25 μL, 0.18 mmol), *m*-nitrobenzoyl chloride (17 mg, 0.09 mmol), and 4-dimethylaminopyridine (DMAP, 2 mg, 0.015 mmol). The reaction was stirred for 18 hours at room temperature. The reaction mixture was diluted with CH$_2$Cl$_2$ (8 mL) and then was poured on saturated NaHCO$_3$ (10 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 5 mL) and the combined organic layers were washed with saturated NaHCO$_3$ (5 mL), dried over MgSO$_4$, and concentrated under vacuum. The crude product was purified by flash chromatography (8:1 hexanes/EtOAc to 4:1 hexanes/EtOAc) to afford 13.5 mg (90% yield) of *m*-nitrobenzoate **1.114**. Vapor diffusion crystallization from CH_2Cl_2 and pentane provided X-ray quality crystals of **1.114**. **R$_f$** 0.80 (1:1 hexanes/EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.85-8.80 (m, 1H), 8.35 (ddd, *J* = 8.2, 2.3, 1.0 Hz, 1H), 8.26-8.23 (m, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.28-7.26 (m, 1H), 6.56 (d, *J* = 8.4 Hz, 1H), 5.37 (m, 1H), 4.21-4.11 (m, 2H), 3.93 (s, 3H), 3.42-3.36 (m, 1H), 3.30 (d, *J* = 14.1 Hz, 1H), 3.05 (d, *J* = 14.1 Hz, 1H), 2.81 (dd, *J* = 15.9, 6.0 Hz, 1H), 2.62 (dd, *J* = 15.9, 9.2 Hz, 1H), 2.20-2.14 (m, 1H), 2.12 (td, *J* = 12.0, 2.8 Hz, 1H), 2.02-1.98 (m, 2H), 1.93 (d, *J* = 4.4 Hz, 2H), 1.73-1.65 (m, 1H), 1.64-1.57 (m, 1H), 1.55-1.47 (m, 2H), 1.29 (d, *J* = 7.59 Hz, 3H), 1.26 (t, *J* = 7.12 Hz, 3H), 0.87 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 172.25, 164.19, 161.99, 154.96, 148.36, 135.16, 134.28, 132.25, 131.01, 129.65, 127.20, 124.85, 107.59, 76.62, 70.71, 60.75, 53.49, 52.68, 50.66, 45.25, 39.07, 37.00, 35.13, 34.08, 31.58, 26.32, 22.30, 14.23; **IR** (film) υ_{max} 3435, 2936, 2360, 1720, 1616, 1533, 1351, 1288, 721 cm^{-1}; **HRMS** (ESI) m/z 513.2239 [$(M+H)^+$; calculated for $[C_{27}H_{33}N_2O_8]^+$: 513.2231].



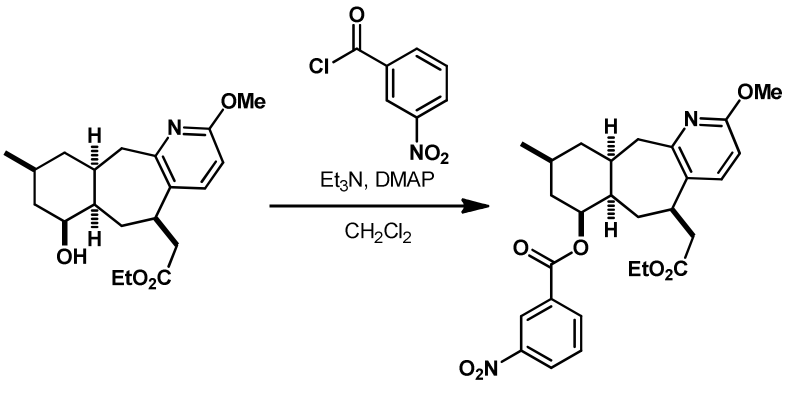
Cycloheptane (1.92): In a round-bottom flask, tricyclic allylic alcohol **1.91** (0.75 g, 2.28 mmol) was dissolved in MeOH (38 mL) and sparged under a nitrogen atmosphere for 5 minutes. 10% Pd on activated carbon (262 mg) was added and the mixture was sparged under a hydrogen atmosphere for 1 minute. The reaction mixture was placed under a hydrogen atmosphere (1 atm. balloon) and stirred at rt for 12 h until TLC indicated complete consumption of the starting material and finally sparged with nitrogen for 5 minutes. The reaction mixture was filtered through a pad of celite and washed with MeOH (3 X 5 mL). The filtrate was concentrated under vacuum to provide tricyclic hydroxyl-ester **1.92** as the major diastereomer (8:1 dr) in 94% yield (712 mg) as a colorless viscous oil which was directly used in the next step without purification. **R$_f$** 0.38 (2:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.4 Hz, 1H), 6.50 (d, *J* = 8.4 Hz, 1H), 4.14 (m, 2H), 3.87 (s, 3H), 3.73 (m, 1H), 3.31 (q, *J* = 8.0 Hz, 1H), 3.24 (d, *J* = 13.4 Hz, 1H), 2.92 (dd, *J* = 13.6, 6.7 Hz, 1H), 2.79 (dd, *J* = 15.6, 6.8 Hz, 1H), 2.66 (dd, *J* = 15.6, 8.6 Hz, 1H), 2.28 (br, 1H), 2.12 (br, 1H), 1.88 (m, 2H), 1.63-1.53 (m, 2H), 1.31-1.27 (m, 3H),, 1.24 (t, *J* = 7.1 Hz, 3H), 1.20 (m, 1H), 0.61-0.50 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.42, 161.32, 156.97, 134.98, 131.29, 106.36, 73.13, 60.56, 53.59, 50.50, 47.92, 42.10, 39.68, 36.14, 35.86, 29.11, 26.78, 24.77, 24.08, 14.18; **IR** (film) υ_{max} 3403, 2934, 2861, 2359, 1733, 1594, 1475, 1425, 1299, 1159, 1034, 990, 821 cm^{-1}; **HRMS** (FAB) m/z 334.2017 [$(M+H)^+$; calculated for $[C_{19}H_{28}NO_4]^+$: 334.2018].



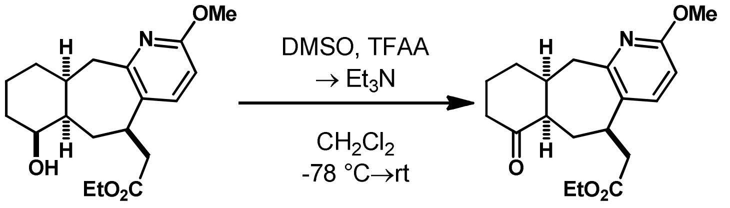
Cycloheptane (1.92): In a round-bottom flask, tricyclic alcohol **1.91** (3.00 g, 9.06 mmol) was dissolved in MeOH (180 mL) and sparged under a nitrogen atmosphere for 5 minutes. 10% Pd on activated carbon (500 mg) was added and the mixture was sparged under a hydrogen atmosphere for 1 minute. The reaction mixture was placed under a hydrogen atmosphere (1 atm. balloon) and stirred rapidly at rt for 24 h until TLC indicated complete consumption of the starting material. The reaction mixture was filtered through a pad of celite and the solids washed with MeOH (2 x 100 mL). The filtrate was concentrated under vacuum to provide a colorless oil. The crude product was purifed by flash chromatography (2:1 hexanes/EtOAc) to provide 2.85 g of **1.92** (major diastereomer, 8:1 dr) as a white solid. Recrystallization of the mixture from hexanes (350 mL) provided 1.80 g (60% yield) of **1.92** as thin white needles. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.5.4 Hz, 1H), 6.50 (d, *J* = 8.5 Hz, 1H), 4.14 (m, 2H), 3.87 (s, 3H), 3.73 (m, 1H), 3.31 (q, *J* = 8.0 Hz, 1H), 3.24 (d, *J* = 13.5 Hz, 1H), 2.92 (dd, *J* = 14.0, 7.0 Hz, 1H), 2.79 (dd, *J* = 15.5, 6.5 Hz, 1H), 2.66 (dd, *J* = 15.5, 8.5 Hz, 1H), 2.28 (br d, *J* = 8.0 Hz, 1H), 1.88 (m, 2H), 1.63-1.53 (m, 2H), 1.31-1.27 (m, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.20 (m, 1H), 0.61-0.50 (m, 1H); **MP** 105-106 °C; Enantiomeric excess was determined by HPLC analysis (Chiralpak AD-H column, 92:8 hexanes/ethanol, 1 mL/min) t_r 10.3 min (major), 16.9 min (minor): 99% *ee*. See previous procedure for full characterization data.



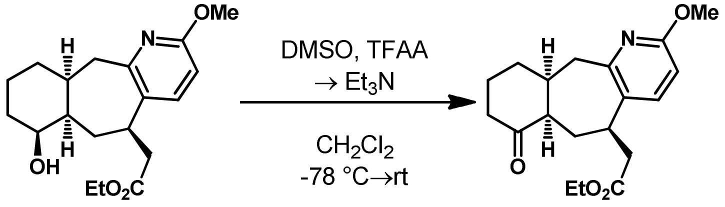
Tricyclic hydroxyl-ester (1.100): The title compound was obtained according to the procedure described for racemic **1.92** as a white solid (92% yield) and as a single diastereomer. **R_f** 0.66 (2:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 1H), 6.50 (d, *J* = 8.4 Hz, 1H), 4.11 (m, 2H), 3.86 (s, 3H), 3.74 (td, *J* = 11.8, 4.4 Hz, 1H), 3.32-3.19 (m, 2H), 2.91 (m, 1H), 2.77 (dd, *J* = 15.6, 6.9 Hz, 1H), 2.64 (dd, *J* = 15.7, 8.5 Hz, 1H), 2.23 (m, 1H), 1.95-1.86 (m, 1H), 1.83 (d, *J* = 13.6 Hz, 1H), 1.53 (d, *J* = 12.3 Hz, 1H), 1.49-1.39 (m, 1H), 1.28 (d, *J* = 13.6 Hz, 1H), 1.22 (t, *J* = 7.0 Hz, 3H), 1.04-0.77 (m, 1H), 0.93 (m, 1H), 0.78 (d, *J* = 6.5 Hz, 3H), 0.27 (q, *J* = 12.5 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.61, 161.58, 157.12, 134.66, 131.10, 106.64, 72.86, 60.61, 53.42, 50.59, 42.84, 39.80, 37.96, 36.56, 35.42, 33.66, 31.05, 26.80, 22.01, 14.23; **IR** (film) υ_{max} 3421, 2924, 2868, 2360, 1733, 1594, 1476, 1425, 1279, 1160, 1040, 823 cm^{-1}; **HRMS** (FAB) m/z 348.2165 $[(M+H)^+$; calculated for $[C_{20}H_{29}NO_4]^+$: 348.2161]; **MP** 96-97 °C.



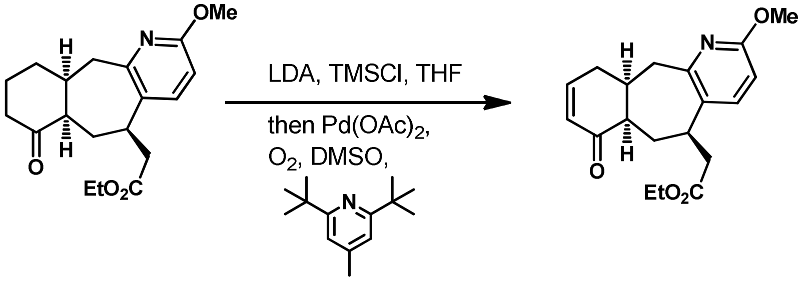
Tricyclic benzoate-ester (1.101): In a round-bottom flask, tricyclic hydroxyl-ester **1.100** (75 mg, 0.23 mmol) was dissolved in CH_2Cl_2 (2.0 mL). To this solution was added triethylamine (96 μL, 0.69 mmol) and DMAP (2.4 mg, 0.023 mmol) at rt. The reaction mixture was cooled to 0 °C and *m*-nitrobenzoyl chloride (63 mg, 0.34 mmol) in CH_2Cl_2 (0.3 mL) was added dropwise. The reaction mixture was allowed to warm to rt and stirred an additional 4 h. At the completion of the reaction as determined by TLC, the solvent was removed under vacuum. The crude product was purified by flash chromatography (4:1 hexanes/EtOAc) to provide 99 mg (90% yield) of **1.101** as a light yellow solid, which provided crystals suitable for X-ray crystallography. **R$_f$** 0.62 (4:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.42 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.36 (d, *J* = 7.72 Hz, 1H), 7.66 (t, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 6.54 (d, *J* = 8.4 Hz, 1H), 5.15 (td, *J* = 9.2, 4.4 Hz, 1H), 3.98 (m, 2H), 3.90 (s, 3H), 3.31 (dd, *J* = 14.9, 9.6 Hz, 2H), 2.97 (dd, *J* = 13.8, 6.6 Hz, 1H), 2.80 (dd, *J* = 15.6, 6.1 Hz, 1H), 2.66 (dd, *J* = 15.5, 9.3 Hz, 1H), 2.56 (d, *J* = 10.8 Hz, 1H), 2.10 (br, s, 1H), 1.85 (d, *J* = 13.2 Hz, 1H), 1.76 (d, *J* = 12.0 Hz, 1H), 1.63 (m, 1H), 1.48 (dt, *J* = 12.8, 10.79 Hz, 1H), 1.40 (d, *J* = 13.7 Hz, 1H), 1.21 (m, 1H), 1.13 (t, *J* = 7.1 Hz, 3H), 0.87 (d, *J* = 6.5 Hz, 3H), 0.42 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.13, 163.92, 161.96, 148.30, 135.23, 132.24, 129.54, 127.25, 124.42, 106.90, 60.43, 53.38, 42.12, 42.08, 39.88, 35.96, 35.14, 34.65, 33.38, 30.97, 21.85, 14.08; **IR** (film) υ_{max} 2950, 2869, 1725, 1594, 1534, 1476, 1376, 1350, 1294, 1265, 1134, 971, 824, 720 cm^{-1}; **HRMS** (FAB) m/z 497.2286 $[(M+H)^+$; calculated for $[C_{27}H_{32}N_2O_7]^+$: 497.2288]; **MP** 149-150 °C.



Ketoester (1.125): A flame-dried round-bottom flask was charged with DMSO (1.53 mL, 21.6 mmol), CH_2Cl_2 (30 mL) and cooled to -78 °C. In a separate flask, trifluoroacetic anhydride (1.50 mL, 10.8 mmol) was dissolved in CH_2Cl_2 (5 mL). The trifluoroacetic anhydride solution was added dropwise to the DMSO/CH_2Cl_2 solution at -78 °C *via* syringe over 5 mins. After stirring for 30 mins at -78 °C, cycloheptane **1.92** (1.80 g, 5.40 mmol) in CH_2Cl_2 (20 mL) was added dropwise over 10 mins and stirred at -78 °C for an additional 2.5 h. Triethylamine (6.02 mL, 43.2 mmol) was added dropwise and then the reaction mixture was allowed to slowly warm to rt. After stirring at rt for 3 h, the reaction mixture was diluted with CH_2Cl_2 (50 mL), poured into a separatory funnel and washed with water (80 mL) . The aqueous layer was extracted with CH_2Cl_2 (2 X 50 mL). The combined organic extracts were washed with water (2 x 50 mL), saturated NaCl (50 mL), dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash chromatography (4:1 hexanes/EtOAc) to afford 1.62 g (90% yield) of **1.125** as a yellow gel. **R_f** 0.42 (4:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.5 Hz, 1H), 6.51 (d, *J* = 8.4 Hz, 1H), 4.10 (m, 2H), 3.86 (s, 3H), 3.41 (m, 1H), 3.20 (d, *J* = 13.4 Hz, 1H), 2.94 (dd, *J* = 13.9, 7.0 Hz, 1H), 2.73 (dd, *J* = 15.5, 6.9 Hz, 2H), 2.60 (dd, *J* = 15.5, 8.3 Hz, 1H), 2.23-2.16 (m, 3H), 1.92 (m, 1H), 1.73-1.51 (m, 4H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.12 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 213.28, 171.72, 161.83, 156.15, 135.15, 129.93, 107.15, 60.63, 60.31, 53.31, 41.35, 39.53, 38.23, 36.96, 36.27, 32.07, 25.79, 25.04, 14.14; **IR** (film) υ_{max} 2937, 2865, 2386, 1732, 1707, 1596, 1477, 1301, 1185, 1158, 1031, 824 cm^{-1}.



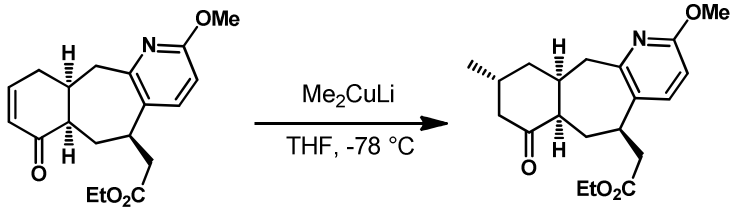
Ketoester (1.125): Enantioenriched **1.125** was obtained according to the procedure described for racemic **1.125.** Enantiomeric excess was determined by HPLC analysis (Chiralpak AS-H column, 90:10 hexanes/ethanol, 1 mL/min) t_r 10.1 min (major), 21.0 min (minor): 99% *ee*.
See previous procedure for full characterization data.



Tricyclic enone (1.127): To a stirred solution of diisopropylamine (5.32 mL, 37.7 mmol) in THF (20 mL) at -78 °C was added *n*-butyllithium (2.5 M in hexanes, 14.5 mL, 36.2 mmol) dropwise over 5 min. After stirring at -78 °C for 30 mins, TMSCl (9.16 mL, 72.4 mmol) was introduced dropwise to the reaction mixture. After 10 min, ketoester **1.125** (2.40 g, 7.24 mmol) in THF (30 mL) was added to the reaction mixture at -78 °C. After stirring for 30 min, the reaction mixture was quenched with triethylamine (20 mL) at -78 °C followed by saturated aq. $NaHCO_3$ (50 mL). The reaction mixture was allowed to warm to rt, diluted with water (60 mL) and extracted with

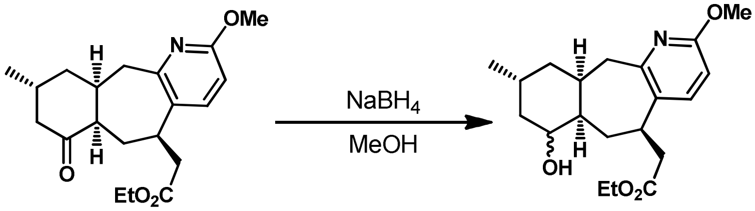
Et_2O (3 X 50 mL). The combined organic extracts were dried over K_2CO_3 and concentrated under vacuum to give an oil. The crude product was used without further purification.

The crude silyl enol ether of **1.125** was dissolved in DMSO (60 mL), treated with 2,6-di-*tert*-butyl-4-methylpyridine (2.08 g, 10.1 mmol) and $Pd(OAc)_2$ (813 mg, 3.62 mmol) and placed under an atmosphere of oxygen (1 atm. balloon). The dark suspension was stirred at rt for 16 h (until TLC indicated complete consumption of starting material) and diluted with Et_2O (50 mL) and H_2O (50 mL). The aqueous layer was extracted with Et_2O (2 X 50 mL), and the combined organic layers were washed with saturated NaCl (50 mL), dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash chromatography (4:1 hexane/EtOAc) to provide the desired tricyclic enone **1.127** (1.71 g) in 72% yield as a yellow solid. $\mathbf{R_f}$ 0.32 (4:1 hexanes/EtOAc);); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.5 Hz, 1H), 6.86 (m, 1H), 6.54 (d, *J* = 8.5 Hz, 1H), 5.91 (d, *J* = 9.0 Hz, 1H), 4.14 (m, 2H), 3.89 (s, 3H), 3.43 (t, *J* = 8.0 Hz, 1H), 3.32 (m, 1H), 3.02 (m, 1H), 2.85-2.79 (m, 2H), 2.68-2.59 (m, 2H), 2.21 (m, 1H), 1.70-1.61 (m, 2H), 1.42 (m, 1H), 1.24 (t, *J* = 7.0 Hz, 3H); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ 201.92, 171.75, 161.79, 156.20, 150.86, 134.58, 130.56, 128.27, 107.17, 60.72, 54.21, 53.41, 41.03, 39.20, 36.09, 33.21, 32.78, 26.76, 14.16; **IR** (film) υ_{max} 2927, 1722, 1636, 1595, 1461, 1435, 1461, 1326, 1040, 919, 734 cm^{-1}; **HRMS** (FAB) m/z 330.1712 $[(M+H)^+$; calculated for $[C_{19}H_{24}NO_4]^+$: 330.1705]; **MP** 118-119 °C.

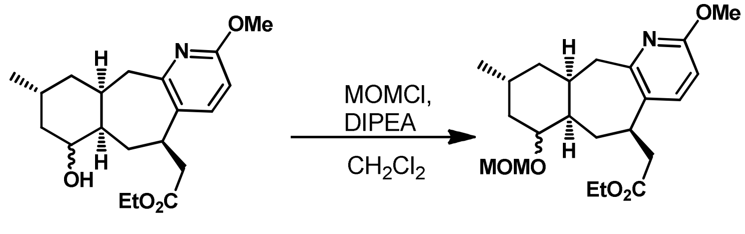


Tricyclic ketone (1.129): To a suspension of CuI (2.95 g, 15.5 mmol) in THF (30 mL) at 0 °C was added MeLi (1.6M in Et_2O, 19.4 mL, 31.0 mmol) and the reaction mixture turned a yellow color. After stirring the reaction mixture for 30 min at 0 °C followed by an additional 15 min at rt, the solution became colorless. The reaction mixture was cooled to -78 °C and stirred for 10 min. A solution of tricylic enone **1.127** (1.70 g, 5.16 mmol) in THF (30 mL) was introduced dropwise to the reaction mixture over a period of 30 min at -78 °C and stirred at -78 °C for an additional 3 h (TLC showed complete consumption of the starting material). The reaction was quenched at -78 °C by addition of saturated aq. NH_4Cl (40 mL), removed from the ice bath and allowed to warm to rt. The reaction mixture was diluted with water (40 mL) and extracted with Et_2O (3 X 40 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum to afford **1.129** (1.78 g) in quantitative yield as a yellow gel. Without further purification, this material was taken on to the next step. ^{1}H-NMR and ^{13}C-NMR spectral data of crude product are reported below. $\mathbf{R_f}$ 0.45 (4:1 hexanes/EtOAc); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.4 Hz, 1H), 6.47 (d, *J* = 8.4 Hz, 1H), 4.07 (q, *J* = 6.8 Hz, 2H), 3.83 (s, 3H), 3.37 (dq, *J* = 8.0, 3.9 Hz, 1H), 3.09 (br, 1H), 2.84 (dd, *J* = 14.1, 7.6 Hz, 1H), 2.63 (m, 3H), 2.49 (br, s, 1H), 2.35 (dd, *J* = 14.2, 5.5 Hz, 1H), 2.24 (dt, *J* = 11.5, 5.6 Hz, 1H), 1.89 (dd, *J* = 14.2, 6.0 Hz, 2H), 1.67 (d, *J* = 13.4 Hz, 1H), 1.52-1.46 (m, 1H), 1.17 (t, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H); ^{13}**C NMR** (125 MHz, $CDCl_3$) δ 212.68, 171.91, 161.82, 156.10, 137.12, 129.75, 107.26, 60.48, 53.25, 52.96, 45.81, 46.08, 41.16, 39.52, 36.23, 31.14, 30.30, 29.18, 20.42, 14.13;

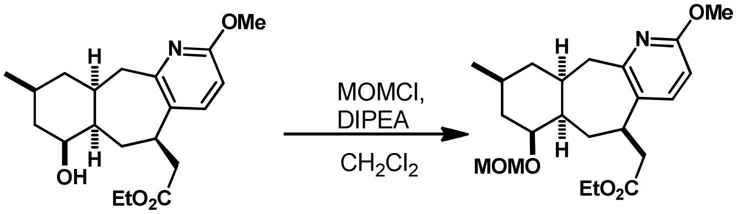
IR (film) υ_{max} 2954, 2360, 1733, 1707, 1595, 1477, 1302, 1036, 824 cm^{-1}; **HRMS** (FAB) m/z 346.2018 [(M+H)$^+$; calculated for [$C_{20}H_{28}NO_4$]$^+$: 346.2018].



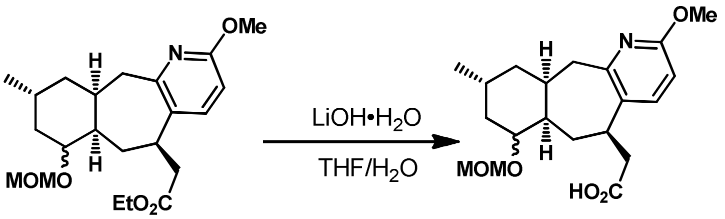
Tricyclic hydroxy-ester (1.158): Tricyclic ketone **1.129** (1.78 g, 5.16 mmol) was dissolved in MeOH (50 mL) and cooled to 0 °C. To this solution $NaBH_4$ (196 mg, 5.16 mmol) was added portionwise over a period of 15 min and stirred at 0 °C for an additional 30 min. The reaction mixture was quenched with saturated aq. NH_4Cl (10 mL) and the solvents were removed under reduced pressure. Water (25 mL) was added to the crude mixture which was extracted with EtOAc (3 X 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum to afford two diastereomers (ca. 1:1) of **1.158** (1.79 g) in quantitative yield as a colorless gel. Without further purification, this material was taken on to the next step. ^{1}H-NMR and ^{13}C-NMR spectral data of the crude product are reported below. **R$_f$** 0.54 and 0.50 for two diastereomers (2:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$, spectrum is of a 1:1 mixture of diastereomers) δ 7.27 (d, *J* = 8.6 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 1H), 6.47 (d, *J* = 8.4 Hz, 1H), 6.44 (d, *J* = 8.4 Hz, 1H), 4.10 (m, 4H), 3.97-3.89 (m, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.75 (br, s, 1H), 3.33 (dq, *J* = 7.3, 2.1 Hz, 1H), 3.25 (m, 2H), 3.10 (br, 1H), 2.83 (dd, *J* = 13.7, 6.7 Hz, 1H), 2.77-2.72 (m, 3H), 2.62 (dd, *J* = 15.7, 8.6 Hz, 1H), 2.40-2.21 (m, 5H), 1.93 (br, 2H), 1.82-1.71 (m, 6H), 1.37-1.34 (m, 2H), 1.26 (dd, *J* = 17.7, 7.1 Hz, 1H), 1.19 (q, *J* = 7.3 Hz, 6H), 1.14 (dd, *J* = 13.5, 6.0 Hz, 1H), 1.07 (br, d, *J* = 13.3 Hz, 1H), 0.94 (d, *J* = 7.0 Hz, 6H), 0.82 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$, spectrum is of a 1:1 mixture of diastereomers) δ 172.76, 172.50, 161.53, 161.47, 157.99, 157.08, 134.16, 134.02, 131.02, 130.25, 106.56, 106.46, 68.44, 60.56, 60.42, 53.30, 53.28, 53.24, 48.12, 47.18, 42.48, 41.52, 41.51, 39.76, 39.71, 36.18, 36.13, 34.64, 30.87, 30.48, 30.47, 30.45, 30.07, 27.47, 26.03, 26.02, 22.17, 19.31, 14.15, 14.14; **IR** (film) υ_{max} 3423, 2921, 2360, 2346, 1733, 1594, 1476, 1424, 1299, 1188, 1038, 822 cm^{-1}; **HRMS** (FAB) m/z 348.2178 [(M+H)$^+$; calculated for [$C_{20}H_{30}NO_4$]$^+$: 348.2175].



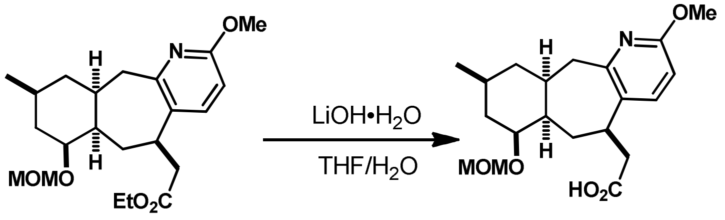
MOM-protected hydroxy-ester (1.130): The diastereomeric mixture (ca. 1:1) of tricyclic hydroxy-ester **1.158** (1.79 g, 5.16 mmol) was dissolved in CH_2Cl_2 (52 mL). To this solution at 0 °C was added N,N-diisopropylethylamine (DIPEA, 5.36 mL, 31.0 mmol) and chloromethyl methyl ether[80] (MOMCl, 6M in MeOAc, 2.58 mL, 15.48 mmol). The reaction mixture was allowed to warm to rt and stirred for 8 h. At the completion of the reaction (as indicated by TLC), water (80 mL) was added to the reaction mixture which was transferred to a separatory funnel. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 X 40 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum to afford 1.98 g of two diastereomers (ca. 1:1) of **1.130** (98% yield) as a light yellow gel. Without further purification, this material was taken on to the next step. An analytical sample was obtained by flash chromatography (8:1 hexane/EtOAc) to afford a colorless gel. **R_f** 0.40 and 0.39 for two diastereomers (8:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$, spectrum is of a 1:1 mixture of diastereomers) δ 7.24 (t, *J* = 9.0, Hz, 2H), 6.47 (t, *J* = 8.6 Hz, 2H), 4.67 (m, 2H), 4.58 (m, 2H), 4.10 (m, 4H), 3.85 (s, 3H), 3.84 (s, 3H), 3.83-3.75 (m, 2H), 3.45 (br, 1H), 3.35 (m, 1H), 3.34 (s, 6H), 3.31-3.22 (m, 2H), 2.98 (br, s, 2H), 2.84 (dd, *J* = 13.7, 6.7 Hz, 1H), 2.77 (dt, *J* = 15.6, 6.9 Hz, 2H), 2.61 (td, *J* = 15.7, 8.8 Hz, 2H), 2.46 (br, s, 1H), 2.34 (br, 1H), 2.10 (m, 1H), 2.01 (m, 2H), 1.76-1.60 (m, 5H), 1.48-1.25 (m, 4H), 1.21 (t, *J* = 7.0 Hz, 6H), 1.18-1.04 (m, 2H), 1.00 (d, *J* = 6.3 Hz, 3H), 0.97 (d, *J* = 7.3 Hz, 3H), 0.91 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$, spectrum is of a 1:1 mixture of diastereomers) δ 172.32, 172.30, 161.47, 161.39, 157.74, 157.02, 140.08, 131.03, 130.15, 106.55, 106.51, 94.82, 94.32,77.98, 73.56, 60.41, 60.39, 55.32, 55.23, 53.21, 53.18, 46.44, 45.64, 42.52, 41.88, 39.90, 39.74, 36.19, 36.08, 33.84, 32.62, 30.62, 29.94, 27.38, 26.61, 21.64, 19.25, 14.16; **IR** (film) υ_{max} 2929, 1735, 1595, 1477, 1299, 1150, 1102, 1010, 915, 825 cm^{-1}; **HRMS** (FAB) m/z 392.2444 $[(M+H)^+$; calculated for $[C_{22}H_{34}NO_5]^+$: 392.2437].



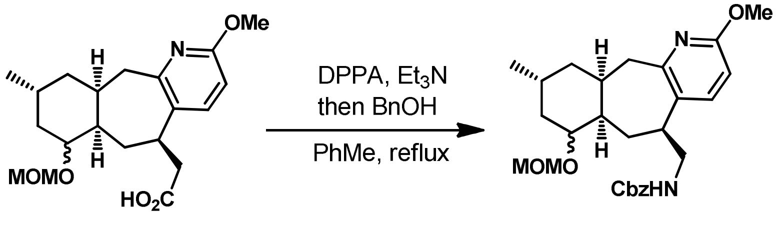
MOM-protected hydroxy-ester (1.120): The title compound was obtained according to the procedure described for **1.130**. The crude material was purified by flash chromatography on silica gel (8:1 hexane/EtOAc) to afford **1.120** as a colorless viscous oil (97% yield). **R_f** 0.79 (4:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 1H), 6.50 (d, *J* = 8.4 Hz, 1H), 4.67 (d, *J* = 6.7 Hz, 1H), 4.63 (d, *J* = 6.7 Hz, 1H), 4.12 (q, *J* = 7.1, Hz, 2H), 3.9 (s, 3H), 3.63 (td, *J* = 12.0, 4.4 Hz, 1H), 3.36 (s, 3H), 3.37-3.22 (m, 2H), 2.90 (dd, *J* = 13.7, 6.7 Hz, 1H), 2.77 (dd, *J* = 15.5, 6.7 Hz, 1H), 2.63 (dd, *J* = 15.5, 8.7 Hz, 1H), 2.33 (d, *J* = 8.8 Hz, 1H), 1.90 (m, 1H), 1.80 (br, d, *J* = 13.7 Hz, 1H), 1.58 (br, d, *J* = 12.38 Hz, 1H), 1.46-1.44 (m, 1H), 1.29 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.92 (q, *J* = 12.2 Hz, 1H), 0.80 (d, *J* = 6.5 Hz, 3H), 0.31 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 172.37, 161.49, 156.85, 131.09, 106.39, 94.31, 77.52, 60.47, 60.36, 55.27, 53.35, 42.41, 39.81, 36.28, 35.74, 35.32, 33.98, 31.13, 27.88, 22.02, 14.21; **IR** (film) υ_{max} 2948, 2882, 1735, 1594, 1476, 1425, 1302, 1149, 1104, 1012, 915, 823 cm^{-1}; **HRMS** (FAB) m/z 392.2441 $[(M+H)^+$; calculated for $[C_{22}H_{34}NO_5]^+$: 392.2437].



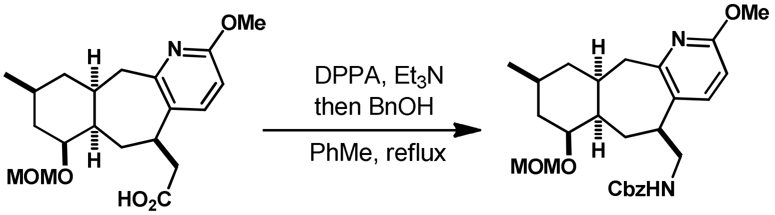
MOM-protected hydroxy-acid (1.159): To a solution of MOM-protected hydroxy-ester **1.130** (1.00 g, 2.55 mmol) in THF (25 mL) and H_2O (12.5 mL) was added LiOH•H_2O (858 mg, 20.4 mmol). The reaction mixture was heated at reflux for 12 h. The reaction mixture was allowed to cool to rt and the THF layer was separated. The aqueous layer was acidified with 6N HCl at 0 °C to pH = 2.0 and extracted with CH_2Cl_2 (2 X 25 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum to afford a diastereomeric mixture (ca. 1:1) of **1.159** (860 mg, 93% yield) as a colorless gel. Without further purification, this material was carried on to the next step. **R$_f$** 0.10 for two diastereomers (2:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$, spectrum is of a 1:1 mixture of diastereomers) δ 10.32 (br, 2H), 7.28 (br, s, 2H), 6.50 (br, s, 2H), 4.70 (br, s, 2H), 4.61 (br, s, 2H), 3.87 (s, 6H), 3.77 (br, s, 2H), 3.47 (br, s, 2H), 3.37 (s, 3H), 3.36 (s, 3H), 3.35-3.19 (m, 2H), 3.11-2.63 (m, 6H), 2.57-2.30 (m, 2H), 2.26-1.90 (m, 5H), 1.88-1.55 (m, 4H), 1.48-1.29 (m, 3H), 1.28-1.09 (m, 4H), 1.02 (d, *J* = 5.60 Hz, 3H), 0.98 (d, *J* = 5.60 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$, spectrum is of a 1:1 mixture of diastereomers) δ 161.60, 161.59, 157.88, 157.16, 140.72, 134.28, 130.87, 130.02, 106.48, 94.89, 94.83, 94.37, 94.33, 78.12, 73.83, 67.91, 55.39, 55.26, 53.44, 53.40, 42.51, 42.48, 41.84, 41.76, 36.15, 36.08, 34.52, 34.21, 32.64, 30.61, 30.59, 29.94, 29.68, 27.40, 26.64, 26.62, 25.58, 21.75, 21.71, 19.29; **IR** (film) υ_{max} 3405, 2928, 1709, 1644, 1594, 1476, 1299, 1278, 1149, 1039, 915, 820 cm^{-1}; **HRMS** (FAB) m/z 364.2116 [(M+H)$^+$; calculated for $[C_{20}H_{30}NO_5]^+$: 364.2111].



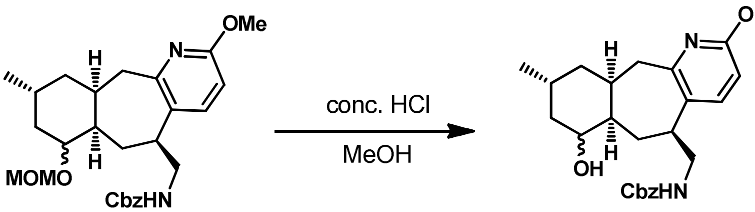
MOM-protected hydroxy-acid (1.162): The title compound was obtained according to the procedure described for **1.159** as a colorless viscous oil (94% yield). **R$_f$** 0.15 (2:1 hexanes/EtOAc); **IR** (film) υ_{max} 3404, 2926, 2898, 2360, 1723, 1635, 1460, 1326, 1304, 1199, 1040, 921, 829 cm^{-1}; **HRMS** (FAB) m/z 364.2116 [(M+H)$^+$; calculated for $[C_{20}H_{30}NO_5]^+$: 364.2111].



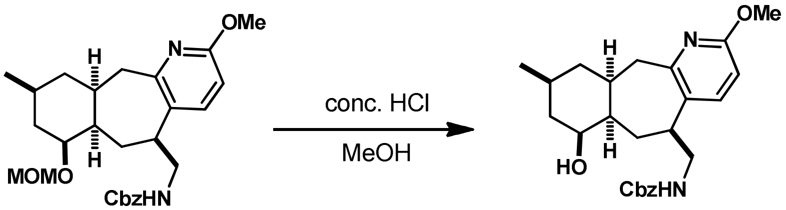
Cbz-protected amine (1.131): A flame-dried two-necked round-bottom flask fitted with a reflux condenser was charged with MOM-protected hydroxy-acid **1.159** (860 mg, 2.36 mmol) and toluene (24 mL). To this solution was added diphenyl phosphoryl azide (DPPA, 1.53 mL, 7.09 mmol) followed by triethylamine (1.65 mL, 11.8 mmol) at rt and then the reaction mixture was heated at reflux for 1 h. The reaction mixture was cooled to rt and benzyl alcohol (490 µL, 4.73 mmol) was added. The reaction mixture was heated at reflux with vigorous stirring for 18 h. After allowing the reaction to cool to rt, the solvent was removed under reduced pressure and the residue purified by flash chromatography (4:1 hexanes/EtOAc) to provide 760 mg of a diastereomeric mixture (ca. 1:1) of **1.131** (69% yield) as a yellow oil. **R$_f$** 0.39 and 0.36 for the two diastereomers (4:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$, spectrum is of a 1:1 mixture of diastereomers, major rotamer) δ 7.34 (m, 10H), 7.27 (m, 2H), 6.51 (m, 2H), 5.09 (br, s, 4H), 4.91 (br, s, 1H, NH), 4.83 (br, s, 1H, NH), 4.72 (d, *J* = 6.8 Hz, 1H), 4.62 (m, 3H), 3.88 (s, 6H), 3.84-3.76 (m, 1H), 3.71-3.41 (m, 4H), 3.31 (s, 3H), 3.35 (s, 3H), 3.11 (m, 1H), 2.97 (m, 1H), 2.89 (m, 1H), 2.84 (m, 1H), 2.41 (br, 1H), 2.24 (br, 2H), 2.13 (br, 1H), 2.00 (m, 2H), 1.86 (m, 2H), 1.74-1.62 (m, 4H), 1.44 (m, 3H), 1.32-1.22 (m, 4H), 1.12 (m, 2H), 1.00 (d, *J* = 7.3 Hz, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$, spectrum is of a 1:1 mixture of diastereomers, major rotamer) δ 161.69, 161.67, 161.53, 158.35, 158.22, 156.28, 136.41, 128.50, 128.45, 128.13, 128.08, 128.6, 128.04, 128.02, 107.02, 106.86, 94.98, 94.88, 78.09, 74.35, 66.73, 55.48, 55.35, 53.33, 53.29, 44.85, 44.80, 44.78, 44.76, 42.35, 32.73, 30.24, 29.68, 27.38, 26.84, 26.56, 19.24; **IR** (film) υ_{max} 3346, 2926, 1720, 1594, 1530, 1476, 1300, 1256, 1144, 1039, 915, 737 cm^{-1}; **HRMS** (FAB) m/z 469.2695 $[(M+H)^+$; calculated for $[C_{27}H_{37}N_2O_5]^+$: 469.2702].



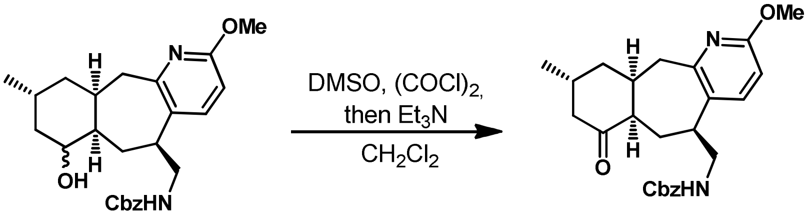
Cbz-protected amine (1.121): The title compound was obtained according to the procedure described for **1.131**. The crude material was purified by flash chromatography on silica gel (4:1 hexane/EtOAc) to afford **1.121** as a yellow viscous oil (69% yield). **R$_f$** 0.44 (4:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$, major rotamer) δ 7.30 (m, 6H), 6.53 (d, *J* = 8.4 Hz, 1H), 5.16-5.04 (m, 2H), 4.82 (s, 1H, NH), 4.65 (br, s, 2H), 3.89 (s, 3H), 3.66-3.54 (m, 2H), 3.54-3.44 (m, 1H), 3.35 (s, 3H), 3.12 (br, d, *J* = 13.5 Hz, 1H), 2.96-2.78 (m, 2H), 2.22 (br, 1H), 1.90 (br, m, 2H), 1.61 (br, d, *J* = 11.4 Hz, 2H), 1.45 (br, 1H), 1.28 (m, 1H), 0.94 (m, 1H), 0.82 (d, *J* = 6.5 Hz, 3H), 0.35 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$, major rotamer) δ 161.69, 156.28, 136.41, 129.83, 128.51, 128.49, 128.14, 120.12, 106.76, 94.90, 78.25, 66.74, 55.33, 53.38, 44.81, 44.77, 42.20, 42.15, 40.24, 40.22, 40.12, 35.77, 35.50, 31.04, 22.01; **IR** (film) υ_{max} 3424, 2948, 1701, 1647, 1594, 1475, 1254, 1143, 1040, 968, 736 cm^{-1}; **HRMS** (FAB) m/z 469.2695 $[(M+H)^+$; calculated for $[C_{27}H_{37}N_2O_5]^+$: 469.2702].



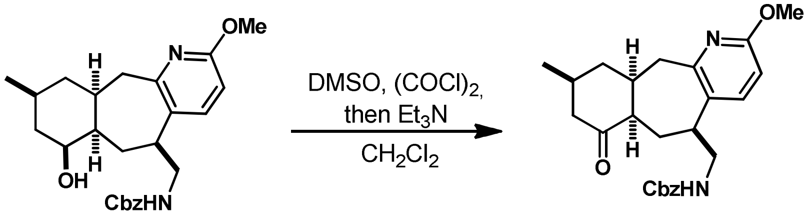
Alcohol (1.160): A round-bottom flask fitted with a reflux condenser was charged with MOM-protected alcohol **1.131** (760 mg, 1.62 mmol) in MeOH (20 mL). To this solution was added conc. HCl (760 µL) and the resultant reaction mixture was heated at reflux for 6 h. The reaction mixture was allowed to cool to rt and the solvent was removed under reduced pressure. The residue was neutralized with saturated aq. $NaHCO_3$ (25 mL) which was extracted with EtOAc (3 X 25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum to afford a diastereomeric mixture (ca. 1:1) of **1.160** (688 mg, >99% yield) as a light yellow oil. Without further purification, this material was taken on to the next step. An analytical sample was obtained by flash chromatography (1:2 hexane/EtOAc) to afford a colorless gel. **R_f** 0.38 & 0.36 for two diastereomers (1:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$, spectrum consists of a 1:1 mixture of diastereomers, major rotamer) δ 7.34-7.27 (m, 10H), 7.26 (m, 2H), 6.51 (d, *J* = 8.3 Hz, 1H), 6.48 (d, *J* = 8.3 Hz, 1H), 5.09 (m, 4H), 4.92 (t, *J* = 5.4 Hz, 1H), 4.00-3.92 (m, 1H), 3.88 (s, 6H), 3.68-3.55 (m, 2H), 3.54-3.37 (m, 2H), 3.29-3.02 (m, 3H), 3.01-2.77 (m, 4H), 2.64 (br, 1H), 2.63 (d, *J* = 9.3 Hz, 1H), 2.31-2.06 (m, 3H), 2.04-1.90 (m, 1H), 1.87 (br, d, *J* = 13.6 Hz, 2H), 1.80-1.67 (m, 3H), 1.63-1.56 (2H), 1.44-1.35 (m, 2H), 1.35-1.27 (m, 2H), 1.27-1.16 (m, 1H), 1.12 (dd, *J* = 12.0, 4.5 Hz, 2H), 0.99 (d, *J* = 7.4 Hz, 3H), 0.97 (d, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$, spectrum consists of a 1:1 mixture of diastereomers, major rotamer) δ 161.74, 161.69, 158.25, 157.30, 156.56, 156.38, 136.64, 136.42, 128.75, 128.74, 128.50, 128.45, 128.13, 128.11, 128.02, 128.00, 127.95, 127.93, 107.00, 106.83, 68.62, 66.84, 66.76, 66.57, 53.41, 53.34, 47.17, 45.58, 44.84, 44.80, 42.30, 41.42, 35.07, 30.82, 30.30, 29.68, 27.50, 26.92, 26.84, 23.89, 23.88, 22.22, 19.28, 19.25; **IR** (film) υ_{max} 3423, 2924, 1697, 1595, 1540, 1475, 1268, 1140, 1036, 822, 736 cm^{-1}; **HRMS** (FAB) m/z 425.2449 [$(M+H)^+$; calculated for $[C_{25}H_{33}N_2O_4]^+$: 425.2440].



Alcohol (1.162): The title compound was obtained according to the procedure described for **1.160**. Without further purification, this material was carried on to the next step. An analytical sample was obtained by flash chromatography (1:1 hexane/EtOAc) to afford a colorless gel. **R_f** 0.38 and 0.36 for two diastereomers (1:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$, major rotamer) δ 7.39-7.29 (m, 4H), 7.26 (m, 1H), 7.18 (m, 1H), 6.53 (d, *J* = 8.3 Hz, 1H), 5.17-5.03 (m, 2H), 4.90 (t, *J* = 5.1 Hz, 1H, NH), 3.89 (s, 3H), 3.75 (td, *J* = 11.3, 4.3 Hz, 1H), 3.64 (m, 1H), 3.52 (m, 1H), 3.12 (br, d, *J* = 13.3 Hz, 1H), 2.98-2.78 (m, 2H), 2.13 (br, d, *J* = 9.6 Hz, 1H), 1.90 (br, d, *J* = 13.0 Hz, 2H), 1.59 (m, 1H), 1.49-1.40 (m, 1H), 1.31 (br, d, *J* = 13.5 Hz, 1H), 1.18 (m, 1H), 0.98-0.85 (m, 1H), 0.81 (d, *J* = 6.5 Hz, 3H), 0.32 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$, major rotamer) δ 161.69, 157.19, 156.36, 150.70, 136.41, 129.73, 128.51, 128.12, 125.14, 120.32, 120.28, 106.73, 72.89, 66.76, 53.41, 53.39, 44.85, 44.84, 42.14, 40.15, 38.27, 35.51, 33.91, 30.96, 21.95; **IR** (film) υ_{max} 3415, 2948, 2868, 1699, 1594, 1540, 1475, 1272, 1029, 936, 824 cm^{-1}; **HRMS** (EI) m/z 424.2371 $[(M)^+$; calculated for $[C_{25}H_{32}N_2O_4]^+$: 424.2362].

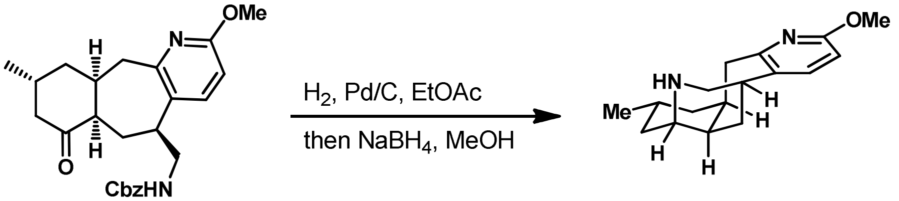


Amino ketone (1.59): A flame-dried round-bottom flask was charged with DMSO (74 μL, 1.05 mmol), CH_2Cl_2 (2 mL) and cooled to -78 °C. To this solution, oxalyl chloride (45 μL, 0.52 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise *via* syringe over 2 min. After stirring for 20 min at -78 °C, alcohol **1.160** (89 mg, 0.21 mmol) in CH_2Cl_2 (2 mL) was added dropwise to the reaction mixture over 2 min and stirred at -78 °C for 2.5 h. Triethylamine (5.02 mL, 36.0 mmol) was added to the reaction mixture dropwise and it was slowly allowed to warm to rt. After stirring at rt for 2.5 h (TLC showed complete consumption of starting material), the reaction mixture was poured into a separatory funnel and washed with water (1 X 8 mL) . The aqueous layer was extracted with CH_2Cl_2 (2 X 8 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash chromatography (2:1 hexanes/EtOAc) to afford 79 mg (90% yield) of **1.59** as a light yellow foam. **R_f** 0.48 (2:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$, major rotamer) δ 7.36 (br, 2H), 7.33 (br, 3H), 7.32 (d, *J* = 8.2 Hz, 1H), 6.52 (d, *J* = 8.3 Hz, 1H), 5.10 (m, 2H), 3.88 (s, 3H), 3.46 (m, 1H), 3.25 (m, 1H), 3.02 (m, 1H), 2.87 (br, s, 2H), 2.66 (br, s, 1H), 2.44 (dd, *J* = 14.4, 5.0 Hz, 2H), 2.23 (br, 1H), 1.98 (dd, *J* = 14.2, 8.7 Hz, 1H), 1.80-1.63 (m, 2H), 1.62-1.50 (br, 1H), 1.27 (m, 1H), 1.00 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$, major rotamer) δ 213.68, 162.07, 156.74, 156.42, 136.57, 128.47, 128.41, 128.11, 128.09, 128.05, 107.54, 66.61, 53.43, 53.37, 44.16, 41.68, 41.64, 41.12, 29.30, 29.01, 21.20, 21.16; **IR** (film) υ_{max} 3347, 2952, 2862, 1708, 1595, 1535, 1476, 1256, 1024, 824, 736 cm^{-1}; **HRMS** (FAB) m/z 423.2287 $[(M+H)^+$; calculated for $[C_{25}H_{31}N_2O_4]^+$: 423.2284].



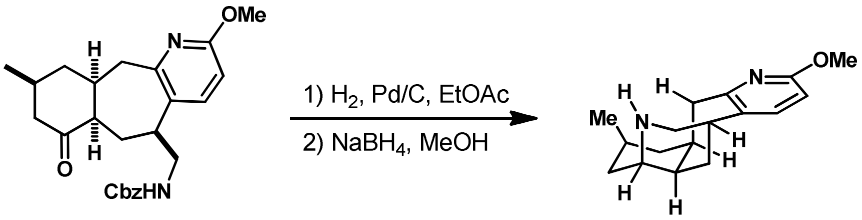
Amino ketone (1.122): The title compound was obtained according to the procedure described for **1.59**. The crude material was purified by flash chromatography (2:1 hexane/EtOAc) to afford **1.122** as a light yellow foam (86% yield). **R_f** 0.46 (2:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz,

$CDCl_3$, major rotamer) δ 7.31 (m, 5H), 7.26 (m, 1H), 6.53 (d, *J* = 8.3 Hz, 1H), 5.16 (br, s, 1H, NH), 5.12-5.01 (m, 2H), 3.87 (s, 3H), 3.52 (m, 1H), 3.42 (td, *J* = 13.3, 6.7, 6.7 Hz, 1H), 3.07 (br, d, *J* = 13.4 Hz, 1H), 2.98 (m, 1H), 2.89 (dd, *J* = 13.7, 7.4 Hz, 1H), 2.59 (br, d, *J* = 8.4 Hz, 1H), 2.14 (br, d, *J* = 12.5 Hz, 2H), 1.89 (t, *J* = 13.5 Hz, 1H), 1.76 (m, 3H), 1.56 (m, 1H), 0.90 (d, *J* = 6.3 Hz, 3H), 0.80 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$, major rotamer) δ 213.51, 161.95, 156.45, 156.21, 136.36, 129.78, 128.49, 128.13, 128.02, 120.08, 107.30, 66.75, 53.38, 53.34, 46.49, 44.48, 41.00, 40.11, 36.02, 34.22, 32.90, 29.33, 22.22; **IR** (film) υ_{max} 3338, 2952, 2844, 1708, 1595, 1537, 1476, 1305, 1256, 1042, 824, 736 cm^{-1}; **HRMS** (FAB) m/z 423.2280 $[(M+H)^+$; calculated for $[C_{25}H_{31}N_2O_4]^+$: 423.2284].

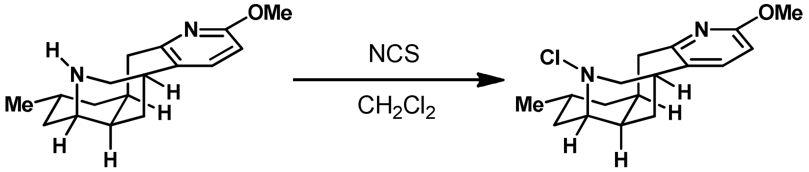


Tetracyclic amine (1.57): Amino ketone **1.59** (79 mg, 0.19 mmol) was dissolved in EtOAc (8 mL) and sparged with nitrogen for 5 min. 10% Pd on activated carbon (24 mg) was added and the mixture was sparged with hydrogen and placed under a hydrogen atmosphere (1 atm. balloon). The reaction mixture was stirred at rt for 24 h then sparged with nitrogen. The reaction mixture was filtered through a pad of celite, washed with EtOAc (15 mL), and concentrated under vacuum. Complete conversion to tetracycle **1.57** was often achieved under these hydrogenation conditions.

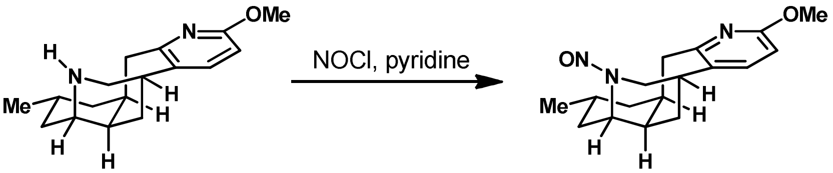
If conversion to tetracycle **1.57** was not complete after hydrogenation conditions based on NMR, the residue was dissolved in MeOH (10 mL), cooled to 0 °C and $NaBH_4$ (21 mg, 0.55 mmol) was added. After stirring for 2 h, saturated aq. NH_4Cl (2 mL) was added to the reaction mixture then the solvent was removed under vacuum. 1N NaOH (5 mL) was added to the crude residue which was extracted with CH_2Cl_2 (3 X 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum to provide 47 mg (92% yield) of tetracyclic amine **1.57** as a white solid. This material was used without further purification in the next step. ^{1}H-NMR and ^{13}C-NMR spectral data of the crude product (>95 % pure) are reported here. **R_f** 0.30 (5 % MeOH in CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.0 Hz, 1H), 6.42 (d, *J* = 8.0 Hz, 1H), 4.63 (m, 1H), 3.89 (s, 3H), 3.24-3.17 (m, 2H), 3.03 (br, s, 1H), 2.78 (dd, *J* = 15.5, 4.5 Hz, 1H), 2.66 (br, 1H), 2.13-2.01 (m, 3H), 1.85 (dd, *J* = 13.5, 1.5 Hz, 1H), 1.80 (br, 1H), 1.72 (m, 1H), 1.68 (m, 1H), 1.37-1.23 (m, 2H), 0.88 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 161.29, 158.89, 141.20, 134.33, 106.17, 57.13, 54.25, 53.10, 46.31, 43.11, 42.40, 38.82, 37.49, 35.16, 34.39, 22.74, 21.55; **IR** (film) υ_{max} 3409, 2911, 2886, 1594, 1576, 1475, 1425, 1308, 1257, 1035, 820 cm^{-1}; **HRMS** (ESI) m/z 272.1884 $[(M)^+$; calculated for $[C_{17}H_{24}N_2O]^+$: 272.1886]; **MP** 74-75 °C.



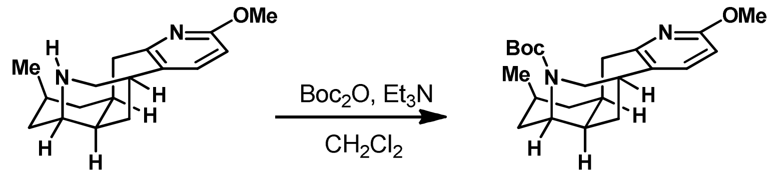
Tetracyclic amine (1.123): The title compound was obtained according to the procedure described for **1.57** in 93% yield as a white solid. This material was used without further purification in the next step. ^{1}H-NMR and ^{13}C-NMR spectral data of the product (>95 % pure) are reported here. **R$_f$** 0.26 (5 % MeOH in CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.3 Hz, 1H), 6.51 (d, *J* = 8.3 Hz, 1H), 3.89 (s, 3H), 3.49 (dd, *J* = 15.6, 8.9 Hz, 1H), 3.24 (dd, *J* = 15.6, 4.8 Hz, 1H), 3.12 (m, 1H), 3.09-3.02 (m, 2H), 2.80 (br, s, 1H), 2.27 (dd, *J* = 16.1, 8.9 Hz, 1H), 2.16-2.02 (m, 1H), 2.00-1.90 (m, 2H), 1.86-1.66 (m, 2H), 1.23 (m, 2H), 1.11-1.01 (m, 1H), 0.94 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 161.16, 157.67, 141.43, 131.28, 107.23, 55.38, 55.12, 53.19, 46.57, 38.77, 38.64, 37.30, 35.73, 32.29, 32.14, 26.30, 23.70; **IR** (film) υ_{max} 2918, 2885, 1595, 1475, 1424, 1305, 1247, 1036, 820 cm^{-1}; **MS** (FAB) m/z 273 $[(M+H)^+$ for $[C_{17}H_{24}N_2O]^+]$; **MP** 86-87 °C.



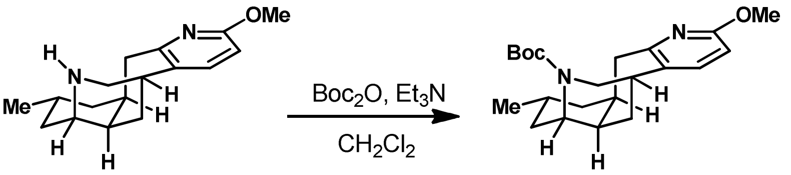
***N*-Chloro tetracyclic amine (1.132):** A round-bottom flask was charged with tetracyclic amine **1.57** (42.8 mg, 0.157 mmol) in CH_2Cl_2 (3.2 mL) and cooled to 0 °C. To this solution was added *N*-chlorosuccinimide (NCS, 41.9 mg, 0.314 mmol). The reaction mixture was allowed to warm to rt and stirred for 6 h. The solvent was removed under vacuum and the resultant residue was purified by flash chromatography (5% Et_2O in CH_2Cl_2) to afford 39.0 mg (80% yield) of **1.132** as a white solid. **R$_f$** 0.82 (8:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.2 Hz, 1H), 6.44 (d, *J* = 8.2 Hz, 1H), 4.38 (m, 1H), 3.89 (s, 3H), 3.71 (d, *J* = 10.7 Hz, 1H), 3.37 (dd, *J* = 10.7, 4.8 Hz, 1H), 3.00 (d, *J* = 2.6 Hz, 1H), 2.92 (t, *J* = 4.7 Hz, 1H), 2.79 (dd, *J* = 15.3, 3.6 Hz, 1H), 2.55-2.45 (m, 1H), 2.17 (br, s, 1H), 2.10-2.02 (m, 3H), 1.76 (dd, *J* = 13.5, 1.4 Hz, 2H), 1.29 (dt, *J* = 12.6, 4.3 Hz, 1H), 1.12 (ddd, *J* = 14.4, 12.6, 3.5 Hz, 1H), 0.92 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 161.64, 158.61, 140.97, 132.36, 106.49, 70.99, 70.51, 53.17, 45.86, 43.29, 42.96, 42.17, 39.87, 34.76, 34.40, 22.43, 21.23; **IR** (film) υ_{max} 2948, 2917, 2889, 1597, 1574, 1476, 1425, 1309, 1253, 1036, 822 cm^{-1}; **HRMS** (ESI) m/z 307.1581 $[(M+H)^+$; calculated for $[C_{17}H_{24}ClN_2O]^+$: 307.1577]]; **MP** 114-115 °C.



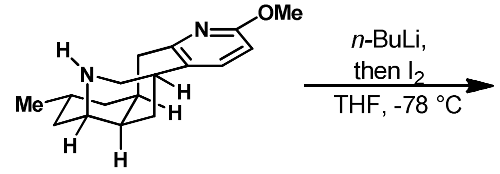
***N*-Nitroso tetracyclic amine (1.138):** A round-bottom flask was charged with tetracyclic amine **1.57** (8 mg, 0.029 mmol) and pyridine (0.98 mL) and cooled to 0 °C. Into this solution was bubbled freshly prepared NOCl[81] for 10 min. The reaction mixture was a deep yellow color after 2 h and was allowed to warm to rt and stirred for an additional 4 h. The solvent was removed under vacuum and water (10 mL) was added which was extracted with CH_2Cl_2 (2 X 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum to provide *N*-Nitroso tetracyclic amine **1.138** (8.7 mg) in 98% yield as a yellow gel. ^{1}H-NMR and ^{13}C-NMR spectral data of the crude product (>95 % pure) are reported here. **R$_f$** 0.71 (8:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.2 Hz, 1H), 6.42 (d, *J* = 8.2 Hz, 1H), 5.20 (d, *J* = 14.8 Hz, 1H), 4.11 (s, 1H), 3.84 (s, 3H), 3.36-3.25 (m, 1H), 3.05 (m, 1H), 3.03-2.96 (m, 2H), 2.84 (dd, *J* = 14.8, 6.5 Hz, 1H), 2.68 (dd, *J* = 16.1, 3.3 Hz, 1H), 2.28-2.09 (m, 3H), 1.98 (d, *J* = 12.9 Hz, 1H), 1.83 (d, *J* = 12.9 Hz, 1H), 1.55-1.38 (m, 2H), 0.96 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 161.72, 156.75, 140.81, 132.22, 106.97, 60.94, 53.36, 44.36, 42.86, 42.63, 38.63, 37.82, 36.16, 34.42, 33.69, 22.41, 21.45; **IR** (film) υ_{max} 3427, 2921, 2894, 1598, 1477, 1423, 1310, 1255, 1201, 1032, 826 cm^{-1}; **HRMS** (FAB) m/z 302.1869 [(M+H)$^+$; calculated for $[C_{17}H_{24}N_3O_2]^+$: 302.1869].



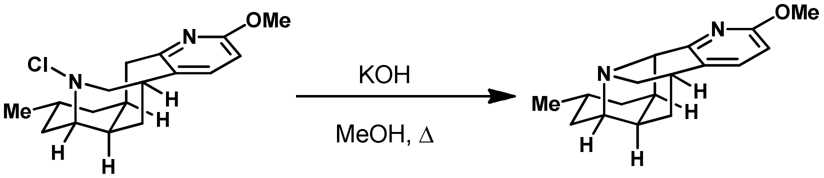
Boc-protected tetracyclic amine (1.124): A round-bottom flask was charged with tetracyclic amine **1.123** (116 mg, 0.426 mmol) and triethylamine (178 μL, 1.28 mmol) in CH_2Cl_2 (8.5 mL) and cooled to 0 °C. To this solution was added di-*tert*-butyldicarbonate ($(Boc)_2O$, 147 μL, 0.639 mmol). The reaction mixture was allowed to warm to rt and stirred for 7 h. The solvent was removed under vacuum and the crude residue was purified by flash chromatography (8:1 hexanes/EtOAc) to afford 143 mg (90% yield) of **1.124** as a white solid, which provided crystals suitable for X-ray crystallography. **R$_f$** 0.58 (8:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.1 Hz, 1H), 6.45 (d, *J* = 8.1 Hz, 1H), 4.34 (m, 2H), 3.88 (s, 3H), 3.58 (t, *J* = 14.9 Hz, 1H), 3.17 (m, 2H), 2.91 (dd, *J* = 15.9, 3.6 Hz, 1H), 2.37 (br, s, 1H), 2.22 (td, *J* = 14.2, 8.8 Hz, 1H), 2.10 (ddd, *J* = 13.2, 8.5, 3.9 Hz, 1H), 1.97 (ddd, *J* = 13.0, 7.6, 5.0 Hz, 1H), 1.86 (m, 1H), 1.72-1.57 (m, 1H), 1.53 (m, 2H), 1.48 (s, 9H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.98 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 161.66, 156.60, 155.58, 140.06, 132.74, 106.97, 79.32, 53.27, 51.87, 49.12, 40.81, 39.32, 35.77, 34.32, 32.68, 31.34, 29.41, 28.52, 25.66, 23.46; **IR** (film) υ_{max} 2923, 2855, 2360, 2324, 1690, 1595, 1476, 1420, 1305, 1261, 1162, 1048, 824 cm^{-1}; **HRMS** (FAB) m/z 373.2491 [(M+H)$^+$; calculated for $[C_{22}H_{33}N_2O_3]^+$: 373.2491]; **MP** 99-100 °C.



Boc protected tetracyclic amine (1.141): The title compound was obtained according to the procedure described for **1.124**. The crude material was purified by flash chromatography (8:1 hexane/EtOAc) to afford **1.141** as a colorless oil (92% yield). **R$_f$** 0.60 (2:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 10.0 Hz, 1H), 6.44 (d, *J* = 10.0 Hz, 1H), 4.25 (br, 1H), 3.87 (s, 3H), 3.76 (m, 1H), 3.53 (br, 1H), 3.20 (dd, *J* = 17.0, 6.0 Hz, 1H), 2.82-2.77 (m, 3 H), 2.16-2.02 (m, 3H), 1.89-1.68 (m, 3H), 1.32 (s, 9H), 1.26 (m, 1H), 1.14 (m, 1H), 0.92 (d, *J* = 8.0 Hz, 3H); **^{13}C NMR** (100 MHz) δ 161.45, 157.68, 154.98, 141.31, 132.37, 106.77, 79.37, 57.67, 53.19, 51.91, 43.85, 42.75, 39.73, 39.19, 38.99, 35.26, 35.20, 28.49, 23.11, 22.67; **IR** (film) υ_{max} 2923, 2855, 2359, 1690, 1595, 1476, 1420, 1364, 1306, 1260, 1162, 1048, 824 cm^{-1}; **HRMS** (ESI) m/z 373.2487 [(M+H)$^+$; calculated for $[C_{22}H_{33}N_2O_3]^+$: 373.2491].

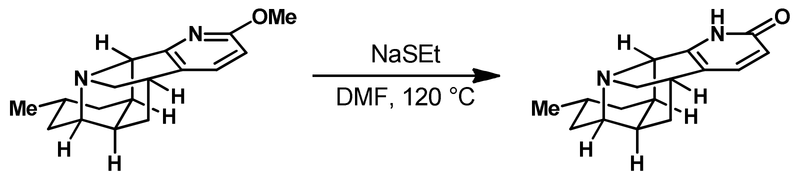


Methyl ether protected Lyconadin A (1.137): To a solution of **1.57** (22 mg, 0.081 mmol) in THF (4 mL) at -78 °C was added *n*-butyllithium (2.5M in hexanes, 96 μL, 0.24 mmol) over 2 min. After stirring the resulting bright orange solution for 30 min at -78 °C, iodine (40 mg, 0.16 mmol) was added in one portion. The reaction mixture was stirred at -78 °C for 2 h and then slowly allowed to warm to 0 °C (ca. 2 h). The color changed from bright orange to reddish amber during this time. The reaction mixture was quenched by sequential slow addition of saturated aq. NH_4Cl (1 mL), saturated aq. $NaHSO_3$ (1 mL) and 1N NaOH (10 mL), and extracted with CH_2Cl_2 (3 X 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum to afford a yellow oil which was purified by flash chromatography (10 % MeOH in CH_2Cl_2) to afford 19.8 mg (90% yield) of **1.137** as a yellow oil. **R$_f$** 0.38 (10 % MeOH in CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.0 Hz, 1H), 6.44 (d, *J* = 8.0 Hz, 1H), 4.20 (s, 1H), 3.90 (s, 3H), 3.39 (dd, *J* = 13.0, 3.0 Hz, 1H), 3.26 (br, s, 1H), 2.85 (d, *J* = 13.0 Hz, 1H), 2.65 (br, 1H), 2.13-2.08 (m, 1H), 2.00-1.95 (m, 3H), 1.91 (m, 1H), 1.81 (br, 1H), 1.68 (d, *J* = 13.5 Hz, 1H), 1.24 (m, 1H), 1.03 (m, 1H), 0.92 (m, 1H), 0.90 (d, *J* = 6.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 162.67, 159.82, 134.83, 133.33, 106.17, 77.31, 68.58, 61.04, 53.53, 49.19, 46.33, 40.76, 39.82, 34.33, 33.72, 25.04, 21.85; **IR** (film) υ_{max} 3408, 2922, 2825, 1601, 1476, 1422, 1310, 1270, 1111, 1033, 824 cm^{-1}; **HRMS** (FAB) m/z 271.1805 [(M+H)$^+$; calculated for $[C_{17}H_{23}N_2O]^+$: 271.1810].

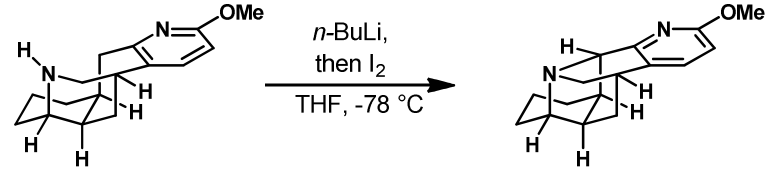


Methyl ether protected Lyconadin A (1.137): To a solution of **1.132** (9 mg, 0.033 mmol) in MeOH (1.5 mL) was added KOH (0.65 mmol, 37 mg). The reaction was heated at reflux for 2 h.

The reaction was allowed to cool to rt and then concentrated under vacuum. The crude residue was dissolved in CH_2Cl_2 (5 mL) and H_2O (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (9:1 CH_2Cl_2/MeOH) to provide 3.8 mg (43% yield) of **1.137** as a clear oil. See previous procedure for full characterization of **1.137**.

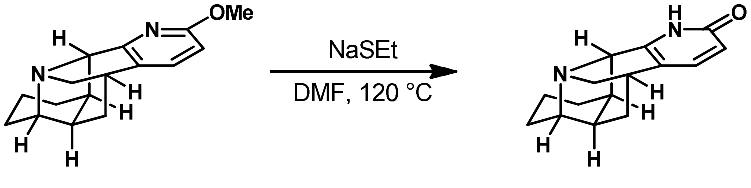


Lyconadin A (1.8): An oven-dried Schlenk tube was charged with pentacyclic methyl ether protected lyconadin A **1.137** (9.4 mg, 0.035 mmol) in DMF (400 µL) and cooled to 0 °C. To this reaction mixture was added EtSH (55 µL, 0.70 mmol) followed by 14 mg (0.35 mmol) of NaH (60 % dispersion on mineral oil). The Schlenk tube was then sealed and heated at 120 °C for 5 h. The reaction mixture was allowed to cool to rt, water (2 mL) was added and the mixture was extracted with CH_2Cl_2 (3 X 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum to afford 6.8 mg of **1.8** (76% yield) as a yellow gel. **R$_f$** 0.15 (20 % MeOH in CH_2Cl_2); **^{1}H NMR** (500 MHz, MeOD) δ 7.44 (d, *J* = 8.9 Hz, 1H), 6.38 (d, *J* = 8.9 Hz, 1H), 4.32 (s, 1H), 3.67 (s, 1H), 3.64 (dd, *J* = 12.3, 3.0 Hz, 1H), 2.96 (d, *J* = 12.3 Hz, 1H), 2.89 (m, 1H), 2.30 (br, d, *J* = 3.6 Hz, 1H), 2.17 (dd, *J* = 5.7, 3.9 Hz, 1H), 2.15 (dd, *J* = 5.4, 3.9 Hz, 1H), 2.11 (br, s, 1H), 1.95 (dd, *J* = 12.1, 4.8 Hz, 1H), 1.86 (m, 1H), 1.77 (d, *J* = 13.8 Hz, 1H), 1.23 (t, *J* = 13.2 Hz, 1H), 1.08 (t, *J* = 12.4 Hz, 1H), 0.97 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (125 MHz, MeOD) δ 165.34, 148.26, 141.54, 126.22, 116.77, 73.66, 65.08, 61.19, 50.15, 48.16, 40.08, 39.64, 33.81, 33.51, 26.11, 21.91; **IR** (film) υ_{max} 3396, 2923, 2824, 1656, 1609, 1557, 1456, 1418, 1193, 948, 834, 702 cm^{-1}; **HRMS** (FAB) m/z 257.1651 $[(M+H)]^+$ calculated for $[C_{16}H_{21}N_2O]^+$: 257.1654]; $[\alpha]_D$ = + 21 ° (*c* 0.40, MeOH). (natural: $[\alpha]_D$ = + 14 ° (*c* 0.35, MeOH)^7; synthetic: $[\alpha]_D$ = + 33 ° (*c* 0.13, MeOH)^8)

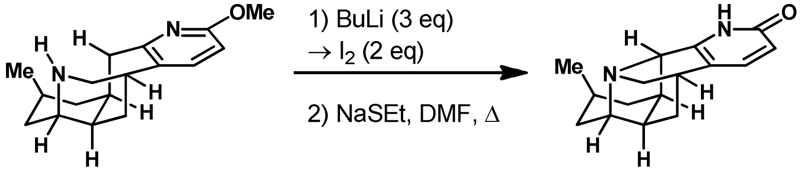


Tertiary Amine (1.161): To a solution of **1.155** (15 mg, 0.058 mmol) in THF (3 mL) at -78 °C was added *n*-butyllithium (2.5M in hexanes, 46 µL, 0.116 mmol) over 2 min. After stirring the resulting bright orange solution for 30 min at -78 °C, iodine (15 mg, 0.058 mmol) was added in one portion. The reaction mixture was stirred at -78 °C for 2 h and then slowly allowed to warm to 0 °C (ca. 2 h). The reaction mixture was quenched by sequential slow addition of saturated aq. NH_4Cl (1 mL), saturated aq. $NaHSO_3$ (1 mL) and 1N NaOH (5 mL), and extracted with CH_2Cl_2 (3 X 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum to afford a yellow oil which was purified by flash chromatography (10 % MeOH in CH_2Cl_2) to afford **1.161** (13.4 mg) in 90% yield as a yellow oil. **R$_f$** 0.32 (10 % MeOH in CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.1 Hz, 1H), 6.46 (d, = 8.14 Hz, 1H), 4.25

(br s, 1H), 3.91 (s, 3H), 3.42 (dd, *J* = 13, 3.5 Hz, 1H), 3.31 (br s, 1H), 2.90-2.84 (m, 1H), 2.73-2.68 (m, 1H), 2.13-2.05 (m, 2H), 2.05-1.96 (m, 1H), 1.92-1.87 (m, 1H), 1.87-1.73 (m, 2H), 1.72-1.66 (m, 1H), 1.62-1.48 (m, 1H), 1.47-1.38 (m, 1H), 1.34-1.26 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 162.67, 159.72, 134.84, 133.39, 106.04, 71.16, 68.07, 61.04, 53.55, 49.13, 46.53, 34.63, 33.74, 31.70, 30.77, 18.25; **IR** (film) υ_{max} 2931, 2856, 1709, 1600, 1477, 1423, 1310, 1264, 1179, 1030, 780 cm^{-1}; **HRMS** (ESI) m/z 257.1652 [(M+H)$^+$; calculated for $[C_{16}H_{21}N_2O]^+$: 257.1648].

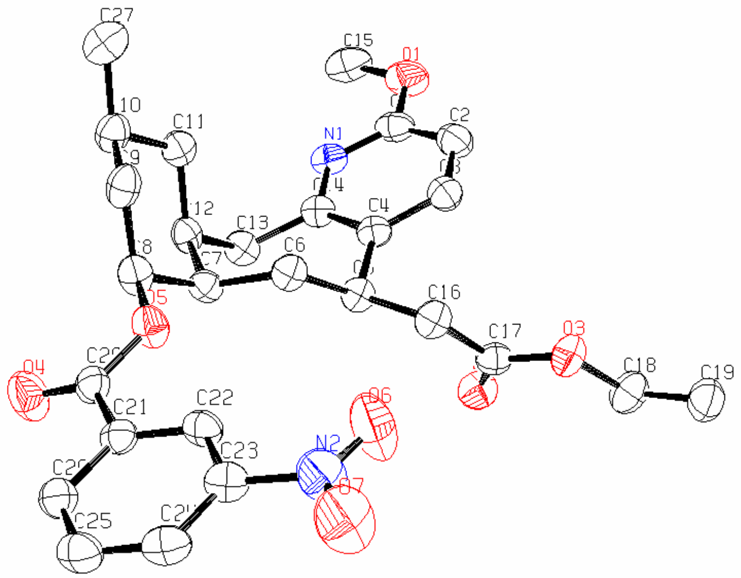


C15-nor-Me-lyconadin A (1.156): The title compound was obtained according to the procedure described for **1.8** in 72% yield as a yellow oil. **R_f** 0.20 (20 % MeOH in CH_2Cl_2); **^{1}H NMR** (600 MHz, CD_3OD) δ 7.37 (d, *J* = 8.9 Hz, 1H), 6.30 (d, *J* = 8.9 Hz, 1H), 4.11 (br s, 1H), 3.47 (dd, *J* = 12.5, 3.3 Hz, 1H), 3.45-3.42 (m, 1H), 3.27 (m, 1H), 2.82-2.79 (m, 1H), 2.76-2.72 (m, 1H), 2.21-2.18 (m, 1H), 2.08 (ddd, *J* = 13.7, 5.7, 3.9 Hz, 1H), 2.03-1.99 (m, 1H), 1.95-1.89 (m, 1H), 1.83-1.74 (m, 1H), 1.69-1.64 (m, 1H), 1.64-1.53 (m, 1H), 1.49 (ddt, *J* = 13.4, 6.6, 2.0 Hz, 1H), 1.38 (m, 1H); **^{13}C NMR** (150 MHz, CD_3OD) δ 165.42, 141.75, 126.33, 121.19, 116.61, 72.79, 63.87, 61.54, 50.56, 48.28, 34.50, 33.77, 31.59, 31.37, 19.05; **IR** (film) υ_{max} 2926, 2851, 1654, 1616, 1559, 1458, 1418, 796, 705 cm^{-1}; **HRMS** (EI) m/z 242.1409 [(M)$^+$; calculated for $[C_{15}H_{18}N_2O]^+$: 242.1409].



C15-epi-lyconadin A (1.154): The title compound was obtained according to the procedures described for the conversion of **1.57** to **1.8** in 60% yield over the 2 steps as a yellow oil. **R_f** 0.1 (20 % MeOH in CH_2Cl_2); **^{1}H NMR** (600 MHz, CD_3OD) δ 7.43 (d, *J* = 8.9 Hz, 1H), 6.36 (d, *J* = 8.9 Hz, 1H), 4.20 (s, 1H), 3.83 (d, *J* = 8.7 Hz, 1H), 3.65-3.59 (m, 1H), 2.93-2.87 (m, 2H), 2.50-2.46 (m, 1H), 2.32-2.24 (m, 1H), 2.21 (d, *J* = 7.4 Hz, 1H), 2.14-2.05 (m, 2H), 1.75 (d, *J* = 13.9 Hz, 1H), 1.69-1.60 (m, 1H), 1.39-1.29 (m, 2H), 0.93 (d, *J* = 6.68 Hz, 3H); **^{13}C NMR** (150 MHz, CD_3OD) δ 163.83, 147.23, 140.43, 123.60, 115.18, 70.07, 67.66, 59.07, 48.44, 40.25, 38.64, 36.54, 32.27, 30.93, 20.49, 20.40; **IR** (film) υ_{max} 2926, 1658, 1608, 1456, 1191, 1102, 1031, 959, 834, 732, cm^{-1}; **HRMS** (EI) m/z 257.1641 [(M+H)$^+$; calculated for $[C_{16}H_{21}N_2O]^+$: 257.1648].

X-Ray Crystallography Data for tricylic benzoate ester 1.101


C27
C15
O1
C11
C2
N1
C4
C12
C13
C7
C6
C16
O5
C17
O3
C18
C19
O4
C21
C22
O6
C23
N2
O7
C25

Crystal data and Structure Refinement for tricyclic benzoate ester 1.101

A. Crystal Data

Empirical Formula	$C_{27}N_2O_7H_{32}$
Formula Weight	496.56
Crystal Color, Habit	colorless, blocky
Crystal Dimensions	0.45 X 0.35 X 0.00 mm
Crystal System	triclinic
Lattice Type	Primitive
Lattice Parameters	a = 10.5537(8)Å
	b = 10.9345(7) Å
	c = 11.9132(8) Å
	α = 69.127(1)°
	β = 83.691(1)°
	γ = 77.491(1)°
	V = 1253.3(2) $Å^3$
Space Group	P -1 (#2)
Z value	2
D_{calc}	1.316 g/cm^3
F_{000}	528.00
$\mu(MoK\alpha)$	0.95 cm^{-1}

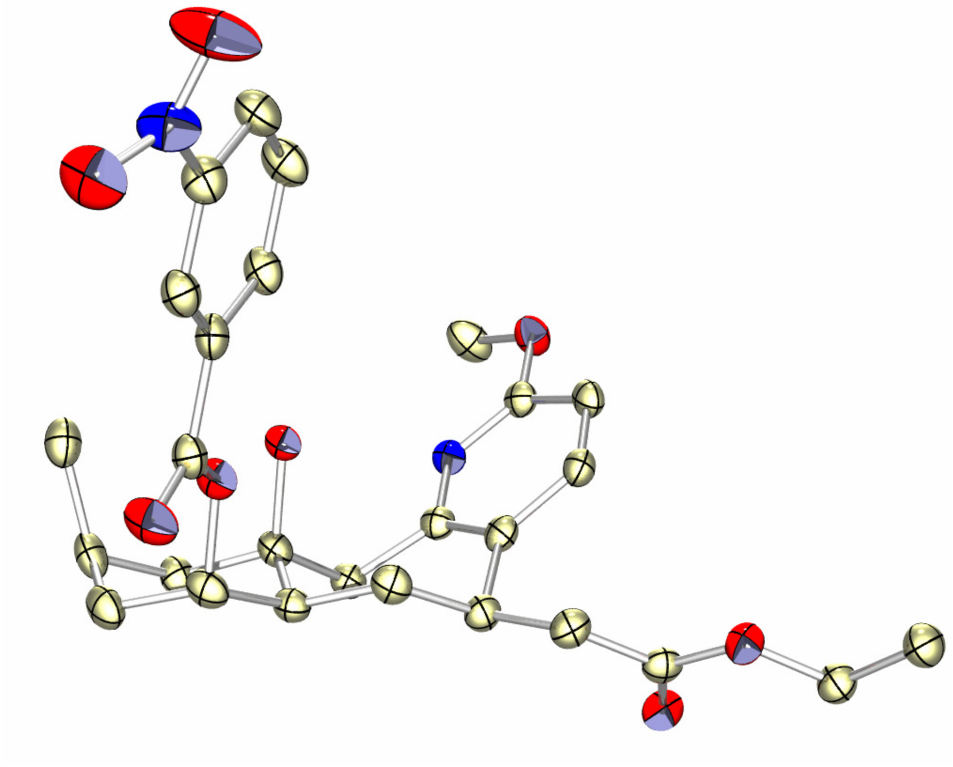
B. Intensity Measurements

Diffractometer	Bruker SMART CCD
Radiation	$MoK\alpha$ (λ = 0.71069 Å)
	graphite monochromated
Detector Position	60.00 mm
Exposure Time	10.0 seconds per frame.
Scan Type	ω (0.3 degrees per frame)
$2\theta_{max}$	52.8°
No. of Reflections Measured	Total: 9728
	Unique: 3369 (R_{int} = 0.012)
Corrections	Lorentz-polarization
	Absorption (Tmax = 1.00
	Tmin =0.91)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR97)
Refinement	Full-matrix least-squares
Function Minimized	Σ w (|Fo| - |Fc|)^2
Least Squares Weights	$1/\sigma^2(Fo) = 4Fo^2/\sigma^2(Fo^2)$
p-factor	0.0500
Anomalous Dispersion	All non-hydrogen atoms
No. Observations ($I>3.00\sigma(I)$)	3442
No. Variables	325
Reflection/Parameter Ratio	10.59
Residuals: R; Rw; Rall	0.039 ; 0.055; 0.055
Goodness of Fit Indicator	1.73
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.20 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.16 $e^-/Å^3$

X-Ray Crystallography Data for m-Nitrobenzoate 1.114



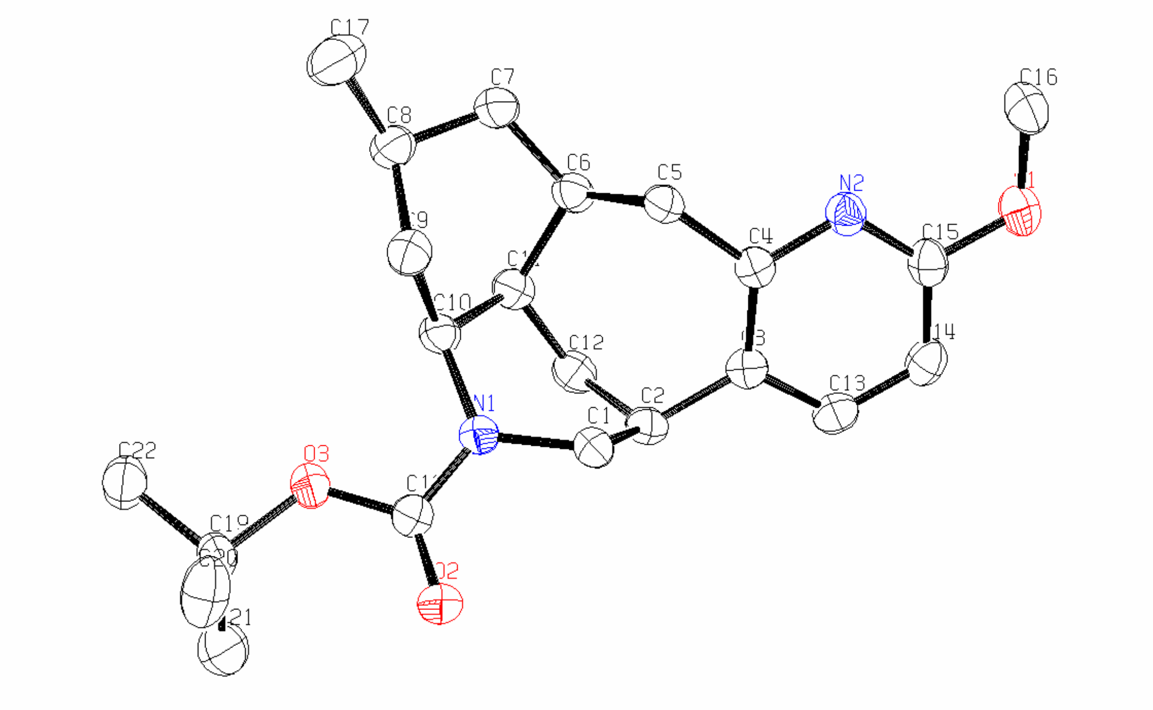
Crystal data and Structure Refinement for tricyclic alcohol 1.114

A colorless needle 0.12 x 0.10 x 0.06 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of 1.0°. Data collection was 99.7% complete to 67.00° in θ. A total of 19373 reflections were collected covering the indices, $-12<=h<=12$, $-35<=k<=35$, $-9<=l<=9$. 4367 reflections were found to be symmetry independent, with an R_{int} of 0.0246. Indexing and unit cell refinement indicated a C-centered, monoclinic lattice. The space group was found to be Cc (No. 9). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SIR-97) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-97). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-97.

Table 1. Crystal data and structure refinement for **1.114**.

X-ray ID	sarpong11	
Sample/notebook ID	SW-VI-112B	
Empirical formula	C27 H32 N2 O8	
Formula weight	512.55	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	Cc	
Unit cell dimensions	a = 10.2059(4) Å	α= 90°.
	b = 29.7555(12) Å	β= 93.801(3)°.
	c = 8.2858(4) Å	γ = 90°.
Volume	2510.71(19) Å^3	
Z	4	
Density (calculated)	1.356 Mg/m^3	
Absorption coefficient	0.833 mm^{-1}	
F(000)	1088	
Crystal size	0.12 x 0.10 x 0.06 mm^3	
Crystal color/habit	colorless needle	
Theta range for data collection	2.97 to 68.14°.	
Index ranges	-12<=h<=12, -35<=k<=35, -9<=l<=9	
Reflections collected	19373	
Independent reflections	4367 [R(int) = 0.0246]	
Completeness to theta = 67.00°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9517 and 0.9067	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4367 / 2 / 338	
Goodness-of-fit on F^2	1.060	
Final R indices [I>2sigma(I)]	R1 = 0.0296, wR2 = 0.0674	
R indices (all data)	R1 = 0.0332, wR2 = 0.0697	
Absolute structure parameter	0.01(13)	
Largest diff. peak and hole	0.184 and -0.154 e.Å^{-3}	

X-Ray Crystallography Data for Boc-protected tetracyclic amine 1.124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C7
C8
C6
C5
N2
C16
C9
C4
C15
C10
C12
C3
C14
C13
N1
C2
C1
C22
O3
C19
C20
O2
C21

Crystal data and Structure Refinement for Boc-protected tetracyclic amine 1.124

A. Crystal Data

Empirical Formula	$C_{22}N_2O_3H_{32}$
Formula Weight	372.51
Crystal Color, Habit	colorless, tabular
Crystal Dimensions	0.15 X 0.15 X 0.24 mm
Crystal System	monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 11.129(1)Å b = 14.816(2) Å c = 13.034(1) Å β = 107.184(2)^{o} V = 2053.3(4) Å^3
Space Group	$P2_1/c$ (#14)
Z value	4
D_{calc}	1.205 g/cm^3
F_{000}	808.00
μ(MoKα)	0.80 cm^{-1}

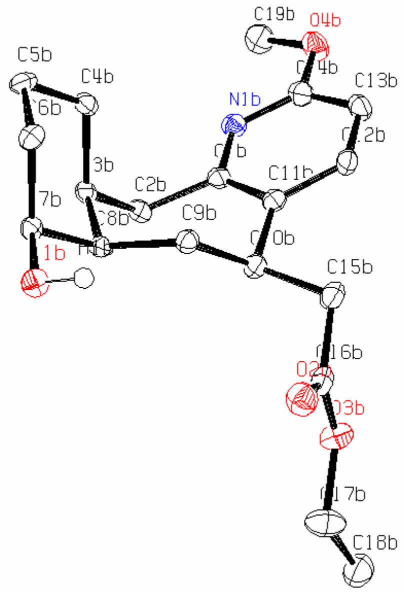
B. Intensity Measurements

Diffractometer	Bruker APEX CCD
Radiation	MoKα (λ = 0.71069 Å) graphite monochromated
Detector Position	60.00 mm
Exposure Time	20.0 seconds per frame.
Scan Type	ω (0.3 degrees per frame)
$2\theta_{max}$	52.8^{o}
No. of Reflections Measured	Total: 11559 Unique: 4454 (R_{int} = 0.027)
Corrections	Lorentz-polarization Absorption (Tmax = 1.00 Tmin = 0.84)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR97)
Refinement	Full-matrix least-squares
Function Minimized	Σ w (|Fo| - |Fc|)^2
Least Squares Weights	$1/\sigma^2(Fo) = 4Fo^2/\sigma^2(Fo^2)$
p-factor	0.0300
Anomalous Dispersion	All non-hydrogen atoms
No. Observations ($I>3.00\sigma(I)$)	2931
No. Variables	244
Reflection/Parameter Ratio	12.01
Residuals: R; Rw; Rall	0.040 ; 0.049; 0.061
Goodness of Fit Indicator	1.82
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.19 $e^-/\text{Å}^3$
Minimum peak in Final Diff. Map	-0.17 $e^-/\text{Å}^3$

X-Ray Crystallography Data for tricyclic alcohol 1.92


C19b
O4b
C5b
C4b
N1b
C 4b
C13b
6b
C b
C 2b
3b
C11b
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7b
C8b
C9b
1b
C 0b
C15b
C16b
O2
O3b
C17b
C18b

Crystal data and Structure Refinement for tricyclic alcohol 1.92

A colorless needle 0.20 x 0.05 x 0.02 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 20 seconds per frame using a scan width of 1.0°. Data collection was 99.9% complete to 67.00° in θ. A total of 22748 reflections were collected covering the indices, $-6<=h<=6$, $-37<=k<=37$, $-12<=l<=12$. 6151 reflections were found to be symmetry independent, with an R_{int} of 0.0511. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P2(1) (No. 4). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SIR-2004) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-97). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-97. Absolute stereochemistry was unambiguously determined at C3A, C3B, C7A, and C7B to be *S* and at C8A, C8B, C10A, and C10B to be *R*.

Empirical formula	C19 H27 N O4	
Formula weight	333.42	
Temperature	100(2) K	
Wavelength	1.54178 Å (CuKα)	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 5.1506(5) Å	α= 90°.
	b = 30.990(3) Å	β= 90.789(7)°.
	c = 10.7824(11) Å	γ = 90°.
Volume	1720.9(3) Å^3	
Z	4	
Density (calculated)	1.287 Mg/m^3	
Absorption coefficient	0.724 mm^{-1}	
F(000)	720	
Crystal size	0.20 x 0.05 x 0.02 mm^3	
Crystal color/habit	colorless needle	
Theta range for data collection	2.85 to 68.46°.	
Index ranges	-6<=h<=6, -37<=k<=37, -12<=l<=12	
Reflections collected	22748	
Independent reflections	6151 [R(int) = 0.0511]	
Completeness to theta = 67.00°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9857 and 0.8687	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6151 / 1 / 439	
Goodness-of-fit on F^2	1.040	
Final R indices [I>2sigma(I)]	R1 = 0.0414, wR2 = 0.0969	
R indices (all data)	R1 = 0.0490, wR2 = 0.1007	
Absolute structure parameter	0.03(16)	
Largest diff. peak and hole	0.322 and -0.301 e.Å^{-3}	

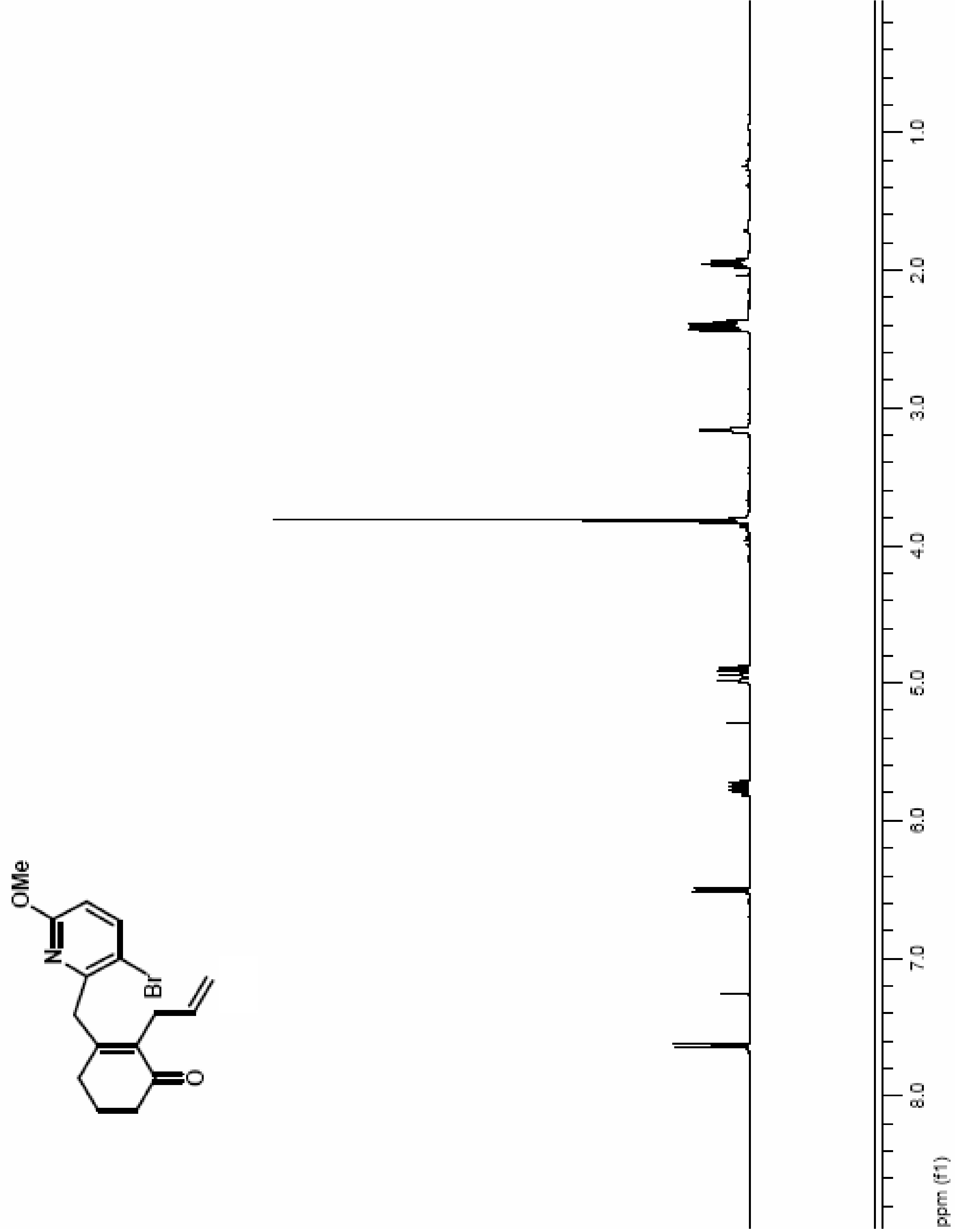
1.16 References

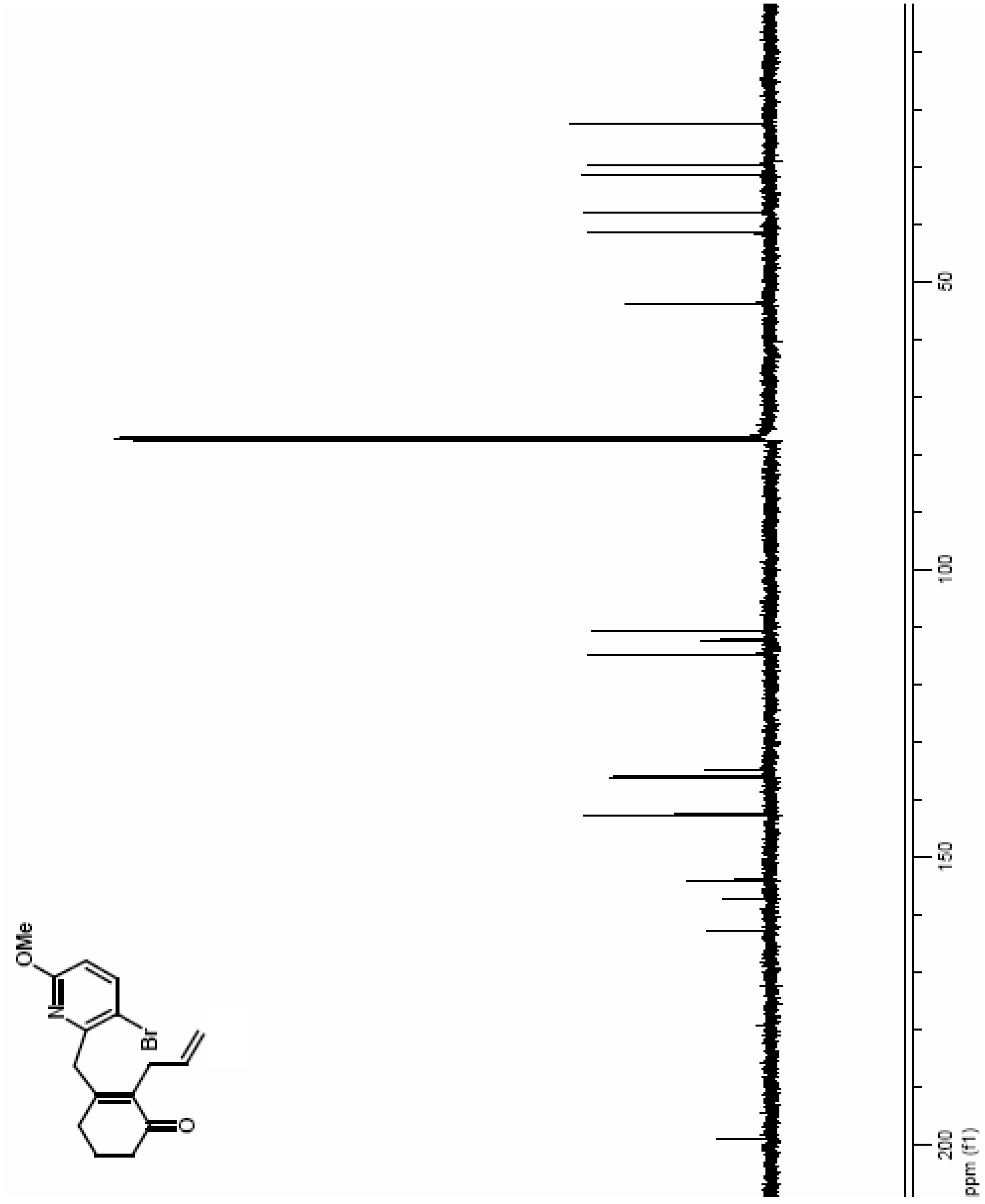
(1) Bödeker, K. *Ann. Chem.* **1881**, *208*, 363.
(2) Ayer, W. A.; Trifonov, L. S. *Alkaloids (Academic Press)* **1994**, *45*, 233.
(3) Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004**, *21*, 752.
(4) Kobayashi, J. I.; Morita, H. *Alkaloids (Academic Press)* **2005**, *61*, 1.
(5) Hirasawa, Y.; Kobayashi, J.; Morita, H. *Heterocycles* **2009**, *77*, 679.
(6) Liu, J. S.; Zhu, Y. L.; Yu, C. M.; Zhou, Y. Z.; Han, Y. Y.; Wu, F. W.; Qi, B. F. *Can. J. Chem.* **1986**, *64*, 837.
(7) Tang, X. C.; Han, Y. F.; Chen, X. P.; Zhu, X. D. *Acta Pharmacol. Sin.* **1986**, *7*, 507.
(8) Wang, Y. E.; Yue, D. X.; Tang, X. C. *Acta Pharmacol. Sin.* **1986**, *7*, 110.
(9) Tang, X. C.; Desarno, P.; Sugaya, K.; Giacobini, E. *J. Neurosci. Res.* **1989**, *24*, 276.
(10) Ayer, W. A.; Berezows, J.; Law, D. A. *Can. J. Chem.* **1963**, *41*, 649.
(11) Ayer, W. A.; Masaki, N.; Nkunika, D. S. *Can. J. Chem.* **1968**, *46*, 3631.
(12) Ayer, W. A.; Browne, L. M.; Nakahara, Y.; Tori, M.; Delbaere, L. T. J. *Can. J. Chem.* **1979**, *57*, 1105.
(13) Tori, M.; Shimoji, T.; Shimura, E.; Takaoka, S.; Nakashima, K.; Sono, M.; Ayer, W. A. *Phytochemistry* **2000**, *53*, 503.
(14) Liu, H. Q.; Tan, C. H.; Jiang, S. H.; Zhu, D. Y. *Chin. Chem. Lett.* **2004**, *15*, 303.
(15) Kobayashi, J.; Hirasawa, Y.; Yoshida, N.; Morita, H. *J. Org. Chem.* **2001**, *66*, 5901.
(16) Ishiuchi, K. I.; Kubota, T.; Hoshino, T.; Obara, Y.; Nakahata, N.; Kobayashi, J. I. *Bioorg. Med. Chem.* **2006**, *14*, 5995.
(17) Ishiuchi, K.; Kubota, T.; Morita, H.; Kobayashi, J. *Tetrahedron Lett.* **2006**, *47*, 3287.
(18) Kubota, T.; Yahata, H.; Ishiuchi, K.; Obara, Y.; Nakahata, N.; Kobayashia, J. *Heterocycles* **2007**, *74*, 843.
(19) Ishiuchi, K.; Kubota, T.; Hayashi, S.; Shibata, T.; Kobayashi, J. *Tetrahedron Lett.* **2009**, *50*, 6534.
(20) Ishiuchi, K.; Kubota, T.; Hayashi, S.; Shibata, T.; Kobayashi, J. *Tetrahedron Lett.* **2009**, *50*, 4221.
(21) Hirasawa, Y.; Morita, H.; Kobayashi, J. *Org. Lett.* **2004**, *6*, 3389.
(22) Hirasawa, Y.; Kobayashi, J.; Obara, Y.; Nakahata, N.; Kawahara, N.; Goda, Y.; Morita, H. *Heterocycles* **2006**, *68*, 2357.
(23) Ma, X. Q.; Tan, C. H.; Zhu, D. Y.; Gang, D. R.; Xiao, P. G. *Journal Of Ethnopharmacology* **2007**, *113*, 15.
(24) Ma, X. Q.; Gang, D. R. *Phytochemistry* **2008**, *69*, 2022.
(25) Gupta, R. N.; Castillo, M.; Maclean, D. B.; Spenser, I. D.; Wrobel, J. T. *J. Am. Chem. Soc.* **1968**, *90*, 1360.
(26) Castillo, M.; Gupta, R. N.; Ho, Y. K.; MacLean, D. B.; Spenser, I. D. *Can. J. Chem.* **1970**, *48*, 2911.
(27) Castillo, M.; Gupta, R. N.; MacLean, D. B.; Spenser, I. D. *Can. J. Chem.* **1970**, *48*, 1893.
(28) Hemscheidt, T.; Spenser, I. D. *J. Am. Chem. Soc.* **1996**, *118*, 1799.
(29) Hemscheidt, T. *Top. Curr. Chem.* **2000**, *209*, 175.
(30) Nilsson, B. L.; Overman, L. E.; Read de Alaniz, J.; Rohde, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 11297.
(31) Cheng, X. Y.; Waters, S. P. *Org. Lett.* **2010**, *12*, 205.
(32) Scott, W. L.; Evans, D. A. *J. Am. Chem. Soc.* **1972**, *94*, 4779.

(33) Comins, D. L.; Williams, A. L. *Org. Lett.* **2001**, *3*, 3217.
(34) Comins, D. L.; Brooks, C. A. *Abstracts of Papers,* 220th American Chemical Society National Meeting, Washington, DC, August 2000; ORGN 415.
(35) Cash, B.; Wagner, F.; Prevost, N.; Comins, D. *Abstracts of Papers,* 59th Southeast Regional Meeting of the American Chemical Society, Greenville, SC, October 2007; GEN 562.
(36) Beshore, D. C.; Smith, A. B., III *J. Am. Chem. Soc.* **2007**, *129*, 4148.
(37) Beshore, D. C.; Smith, A. B., III *J. Am. Chem. Soc.* **2008**, *130*, 13778.
(38) Grant, S. W.; Zhu, K.; Zhang, Y.; Castle, S. L. *Org. Lett.* **2006**, *8*, 1867.
(39) Tracey, M. R.; Hsung, R. *Abstracts Of Papers*, 226th National Meeting of the American Chemical Society, New York, September 2003; ORGN 721.
(40) Kottirsch, G.; Metternich, R. Patent, E. EP 0 560 730 B1, 1996
(41) Arhart, R. J.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5003.
(42) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.
(43) Evans, P. A.; Manangan, T.; Rheingold, A. L. *J. Am. Chem. Soc.* **2000**, *122*, 11009.
(44) Gray, M. A.; Konopski, L.; Langlois, Y. *Synth. Commun.* **1994**, *24*, 1367.
(45) Haudrechy, A.; Chassaing, C.; Riche, C.; Langlois, Y. *Tetrahedron* **2000**, *56*, 3181.
(46) Patterson, J. W. *Tetrahedron* **1993**, *49*, 4789.
(47) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057.
(48) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.
(49) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163.
(50) Mori, M.; Kaneta, N.; Shibasaki, M. *J. Org. Chem.* **1991**, *56*, 3486.
(51) Lee, P. H.; Seomoon, D.; Lee, K. *Org. Lett.* **2005**, *7*, 343.
(52) Penalva, V.; Hassan, J.; Lavenot, L.; Gozzi, C.; Lemaire, M. *Tetrahedron Lett.* **1998**, *39*, 2559.
(53) Zhang, S. J.; Zhang, D. W.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 2312.
(54) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915.
(55) Schrodi, Y.; Pederson, R. L. *Aldrichimica Acta* **2007**, *40*, 45.
(56) Friary, R. J.; Gilligan, J. M.; Szajewsk, R.; Falci, K. J.; Franck, R. W. *J. Org. Chem.* **1973**, *38*, 3487.
(57) Nell, P. G. *Synlett* **2001**, 160.
(58) Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866.
(59) Simmons, E. M.; Sarpong, R. *Org. Lett.* **2006**, *8*, 2883.
(60) Jang, D. O.; Kim, J. G.; Cho, D. H.; Chung, C. M. *Tetrahedron Lett.* **2001**, *42*, 1073.
(61) Shioiri, T.; Yamada, S.; Ninomiya, K. *J. Am. Chem. Soc.* **1972**, *94*, 6203.
(62) Nicolaou, K. C.; Zhong, Y. L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596.
(63) Stoltz, B. M.; Kano, T.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 9044.
(64) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
(65) Shibanuma, Y.; Okamoto, T. *Chem. Pharm. Bull.* **1985**, *33*, 3187.
(66) Majetich, G. *Tetrahedron* **1995**, *51*, 7095.
(67) Wolff, M. E. *Chem. Rev.* **1963**, *63*, 55.
(68) Cohen, T.; Deets, G. L. *J. Am. Chem. Soc.* **1972**, *94*, 932.
(69) Grierson, D. *Org. React. (N.Y.)* **1990**, *39*, 85.
(70) Rabe, P.; Kindler, K. *Ber. Dtsch. Chem. Ges.* **1918**, *51*, 466.
(71) Smith, A. C.; Williams, R. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 1736.
(72) Bisai, A.; West, S. P.; Sarpong, R. *J. Am. Chem. Soc.* **2008**, *130*, 7222.

(73) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.
(74) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.
(75) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611.
(76) Flack, H. D. *Acta Crystallographica Section A* **1983**, *39*, 876.
(77) Bernardinelli, G.; Flack, H. D. *Acta Crystallographica Section A* **1985**, *41*, 500.
(78) West, S. P.; Bisai, A.; Lim, A. D.; Narayan, R. R.; Sarpong, R. *J. Am. Chem. Soc.* **2009**, *131*, 11187.
(79) Sonn, A. *Chem. Ber.* **1932**, *65*, 1865.
(80) Berliner, M. A.; Belecki, K. *J. Org. Chem.* **2005**, *70*, 9618.
(81) Konoike, T.; Takahashi, K.; Araki, Y.; Horibe, I. *J. Org. Chem.* **1997**, *62*, 960.

Appendix 1: Spectra Relevant to Chapter 1

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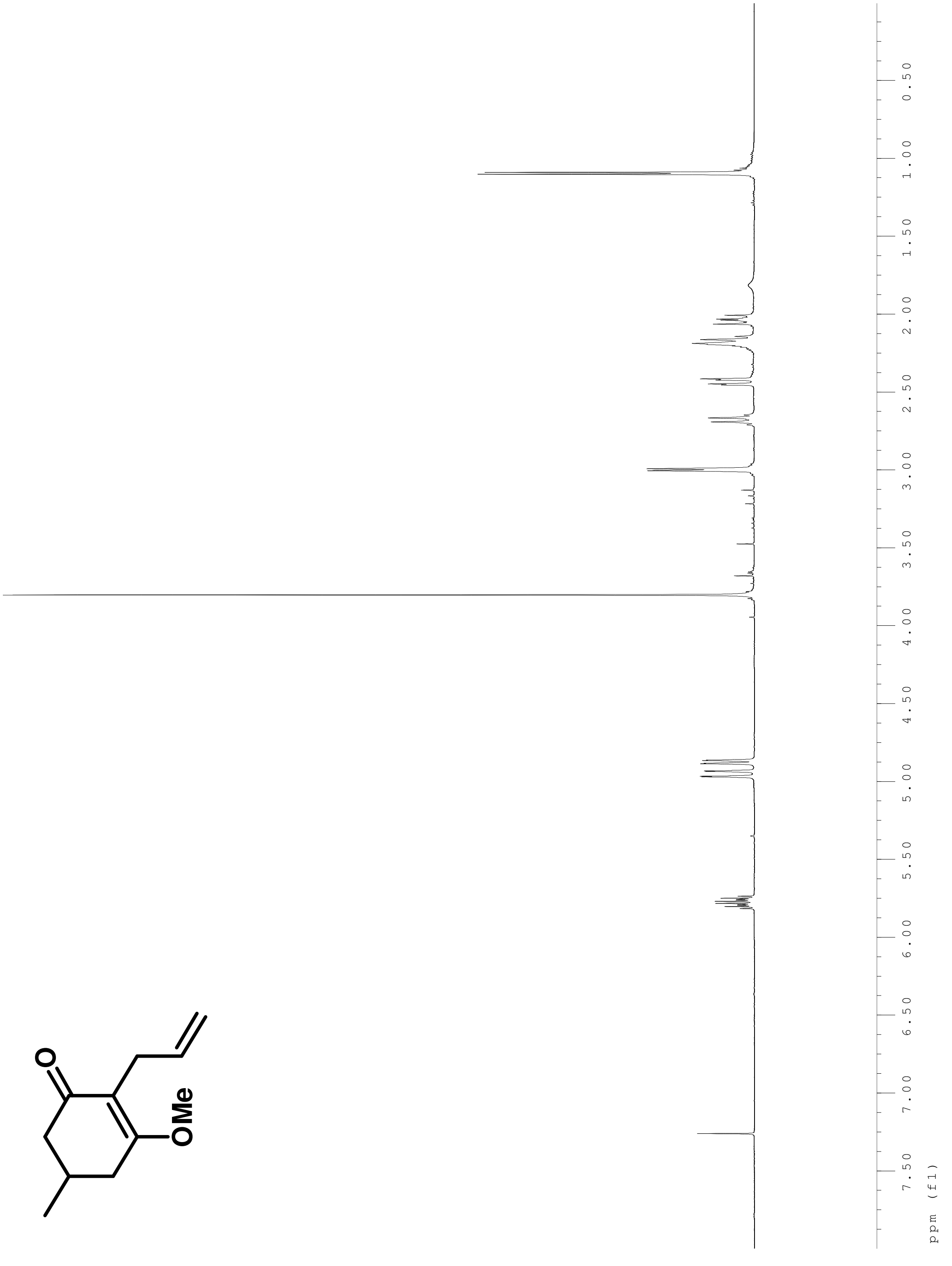
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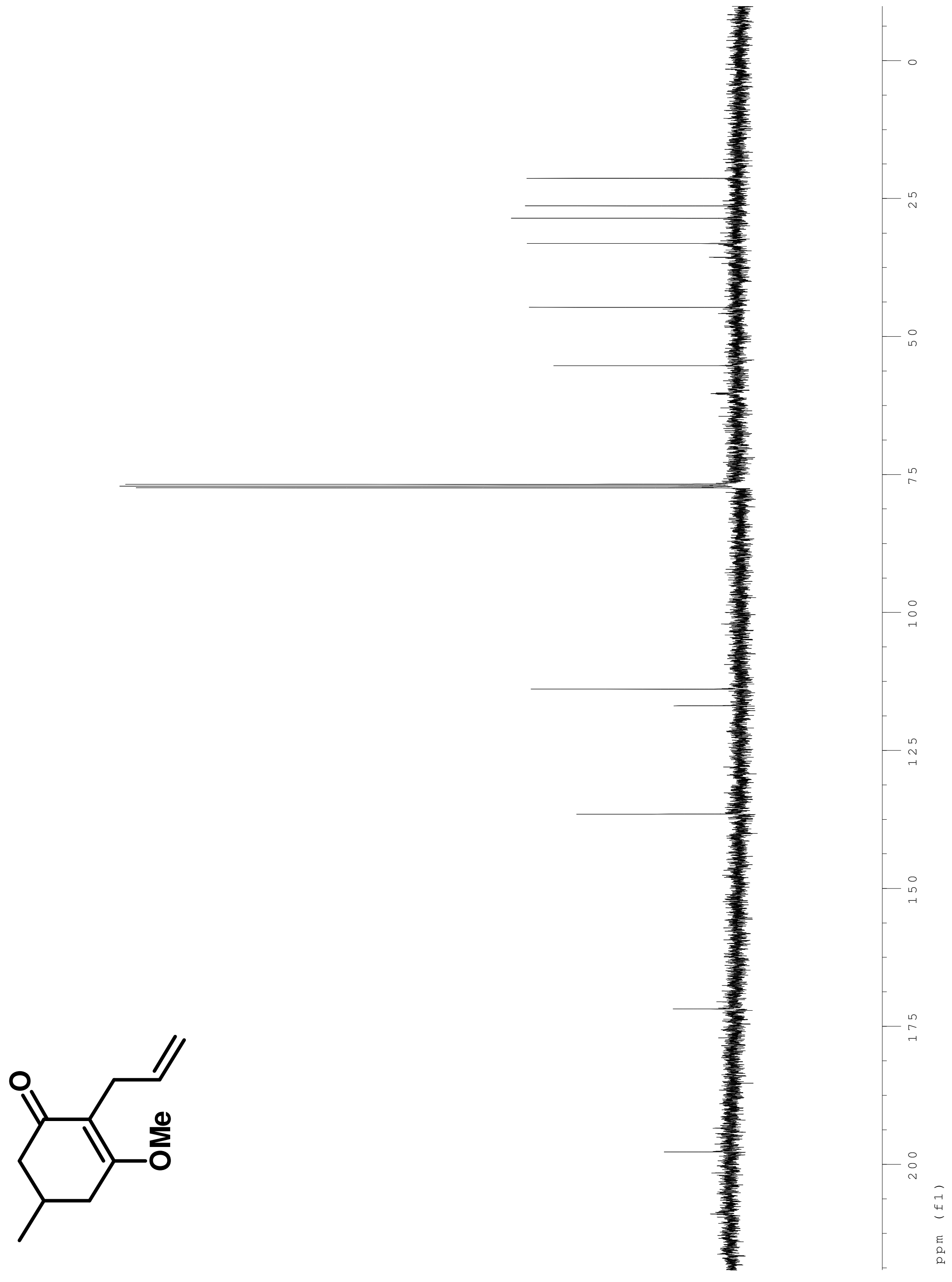
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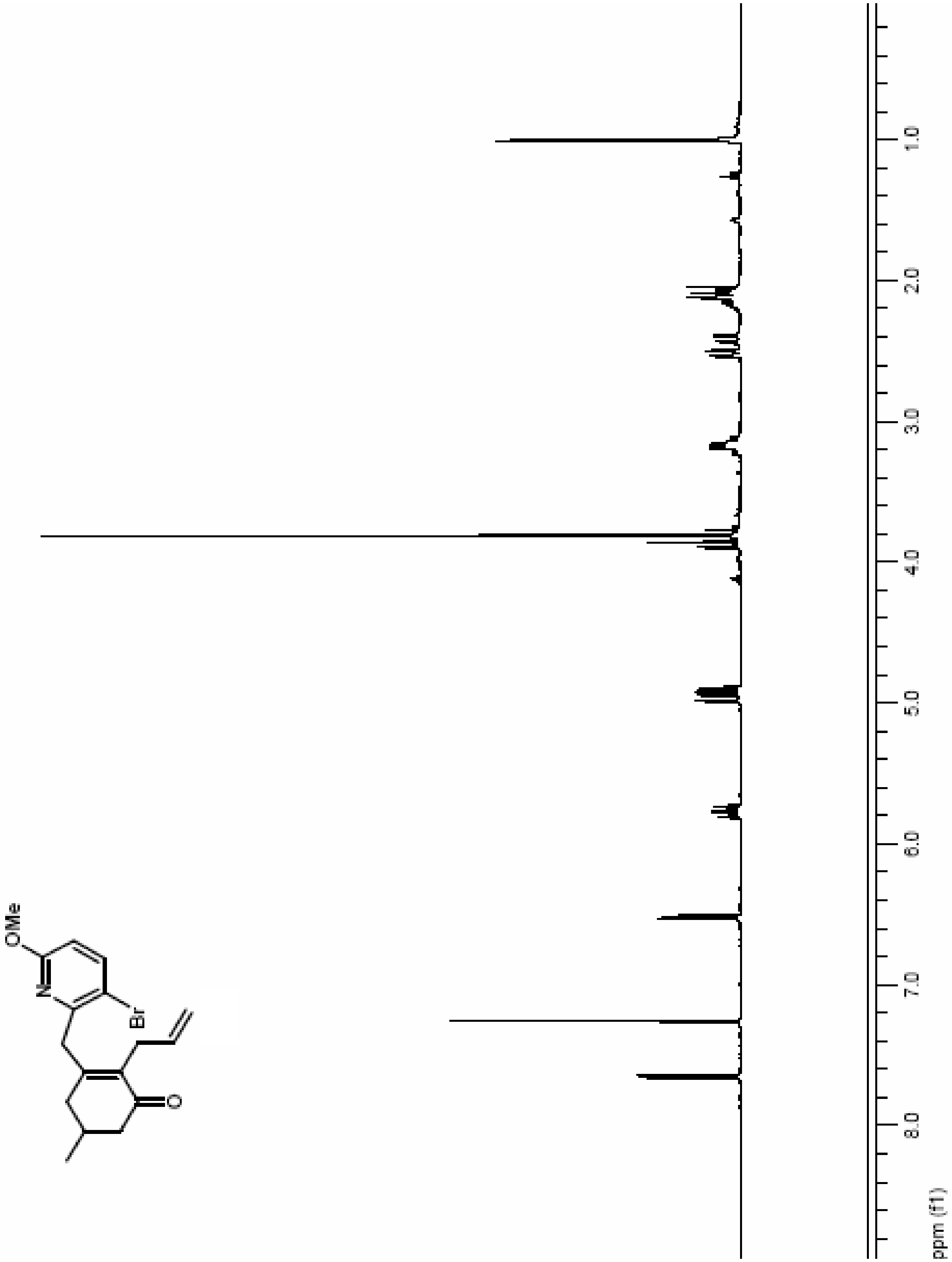

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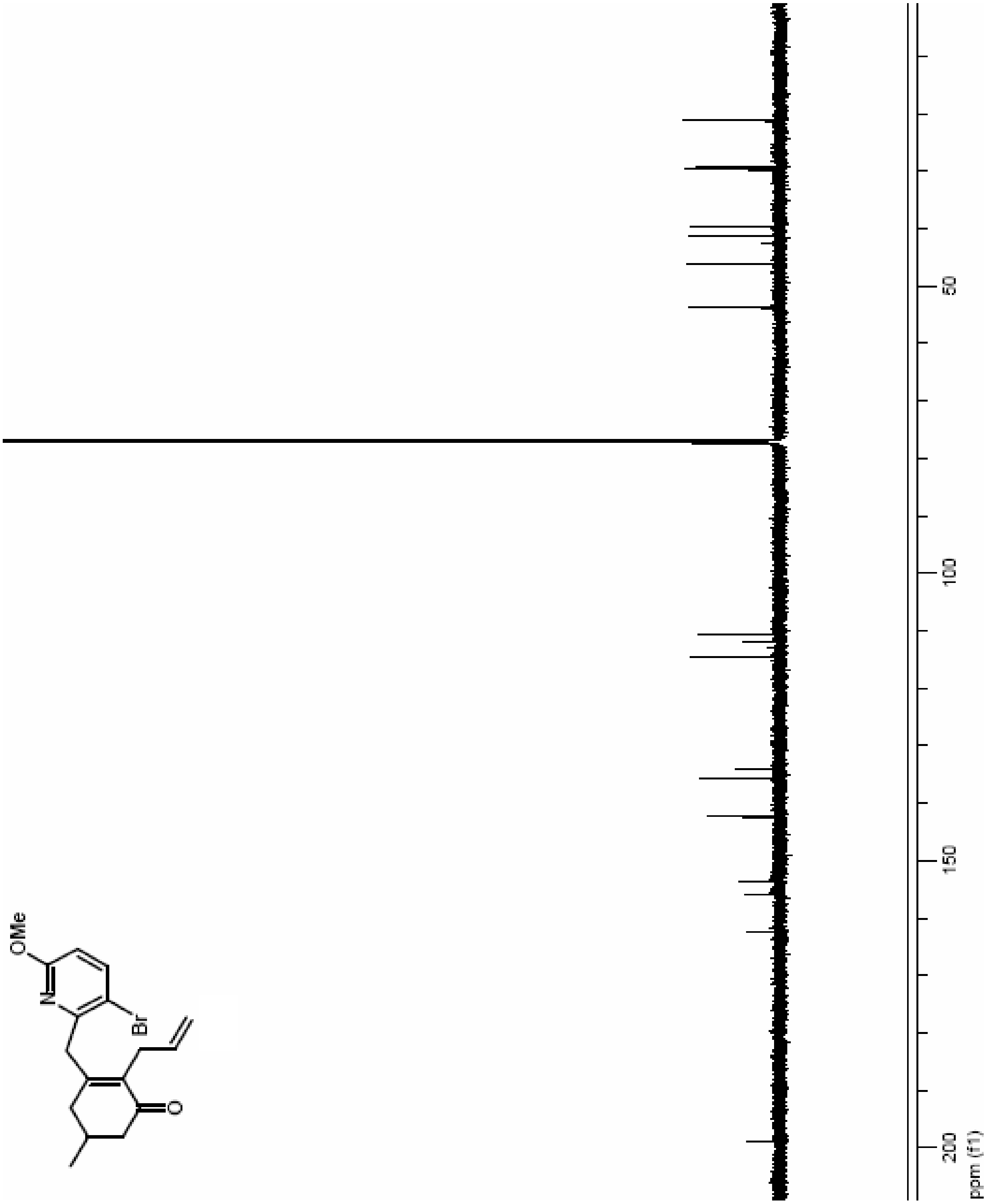
ppm (f1)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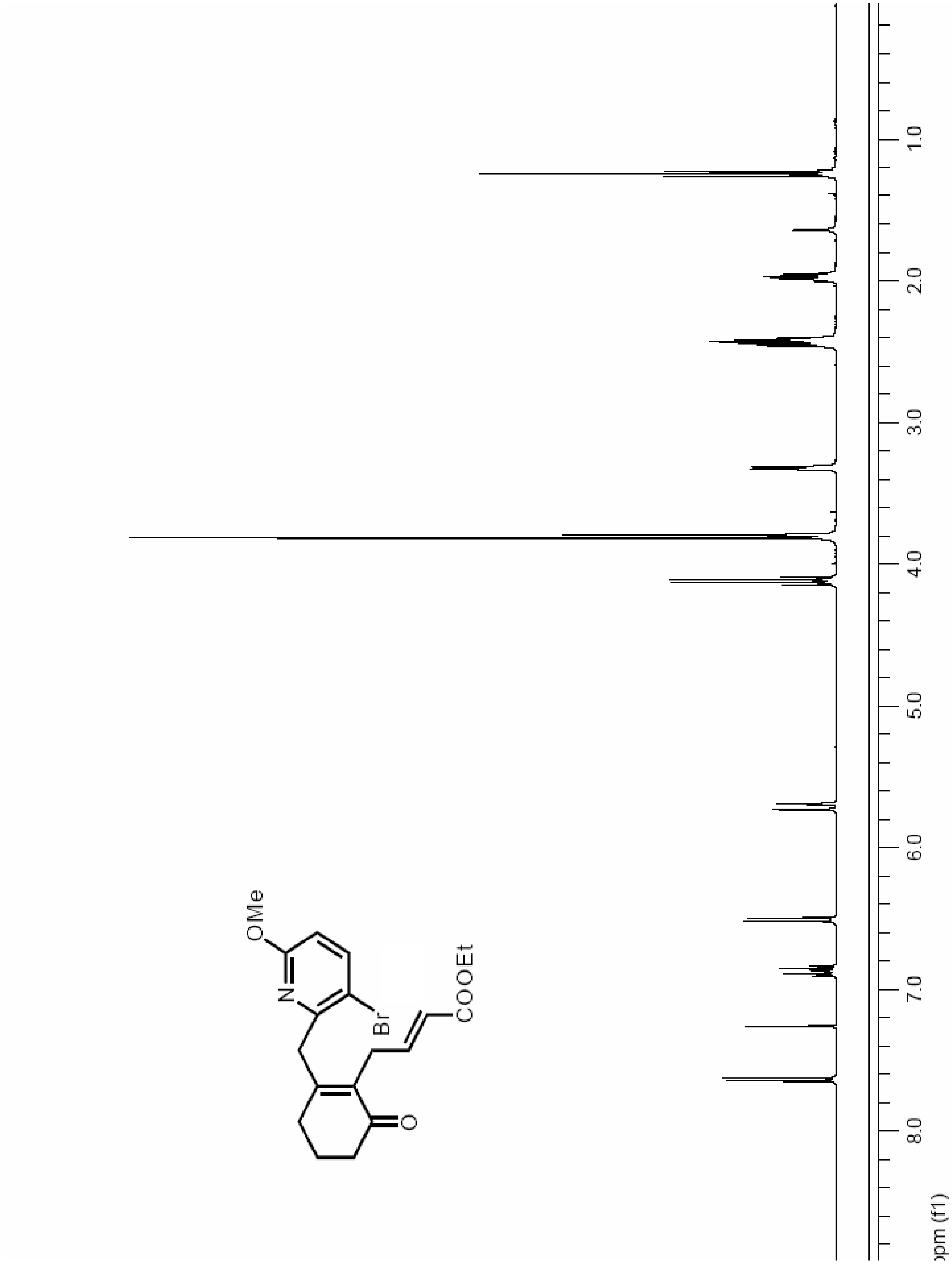
ppm (f1)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3.0
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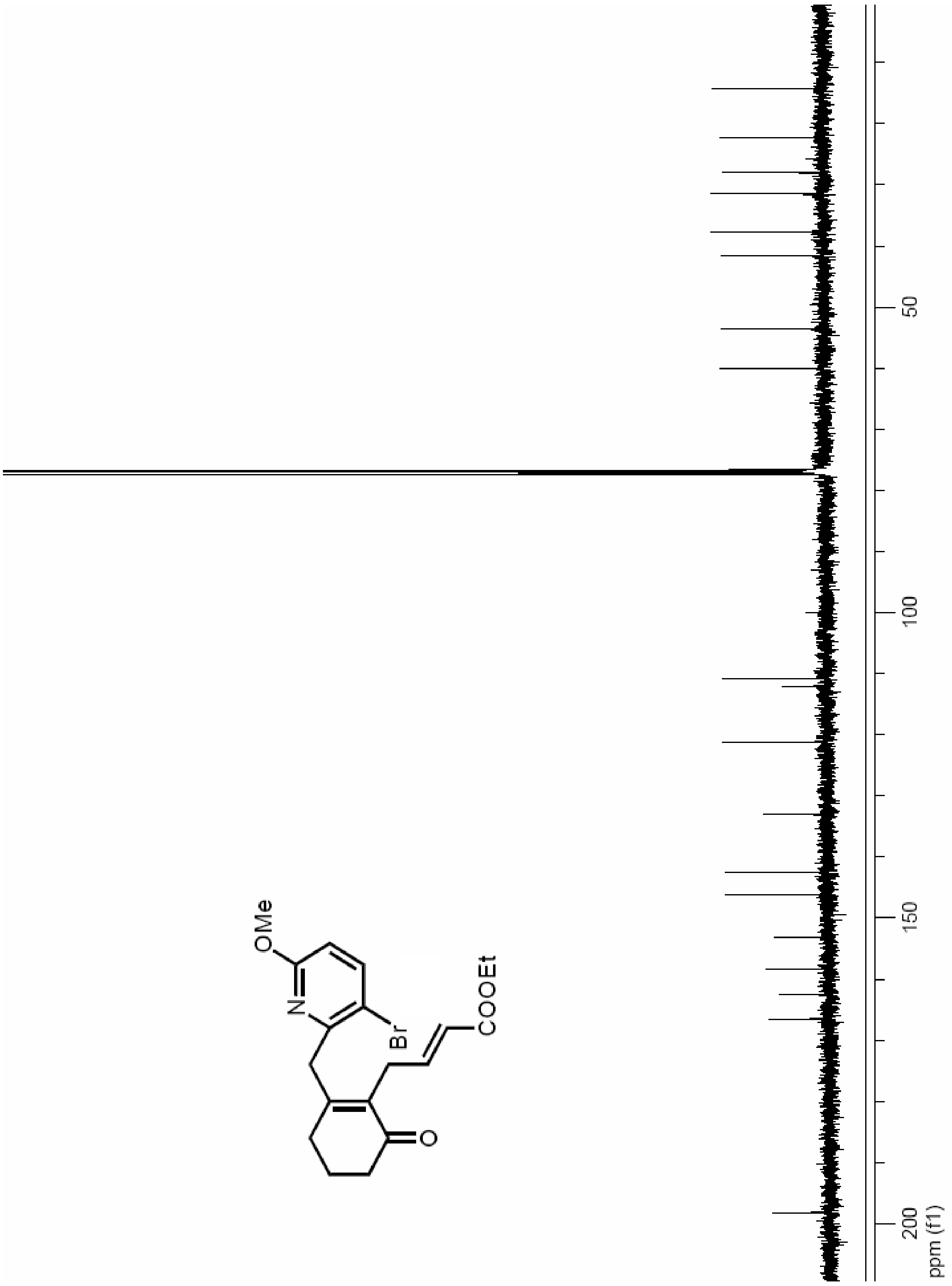
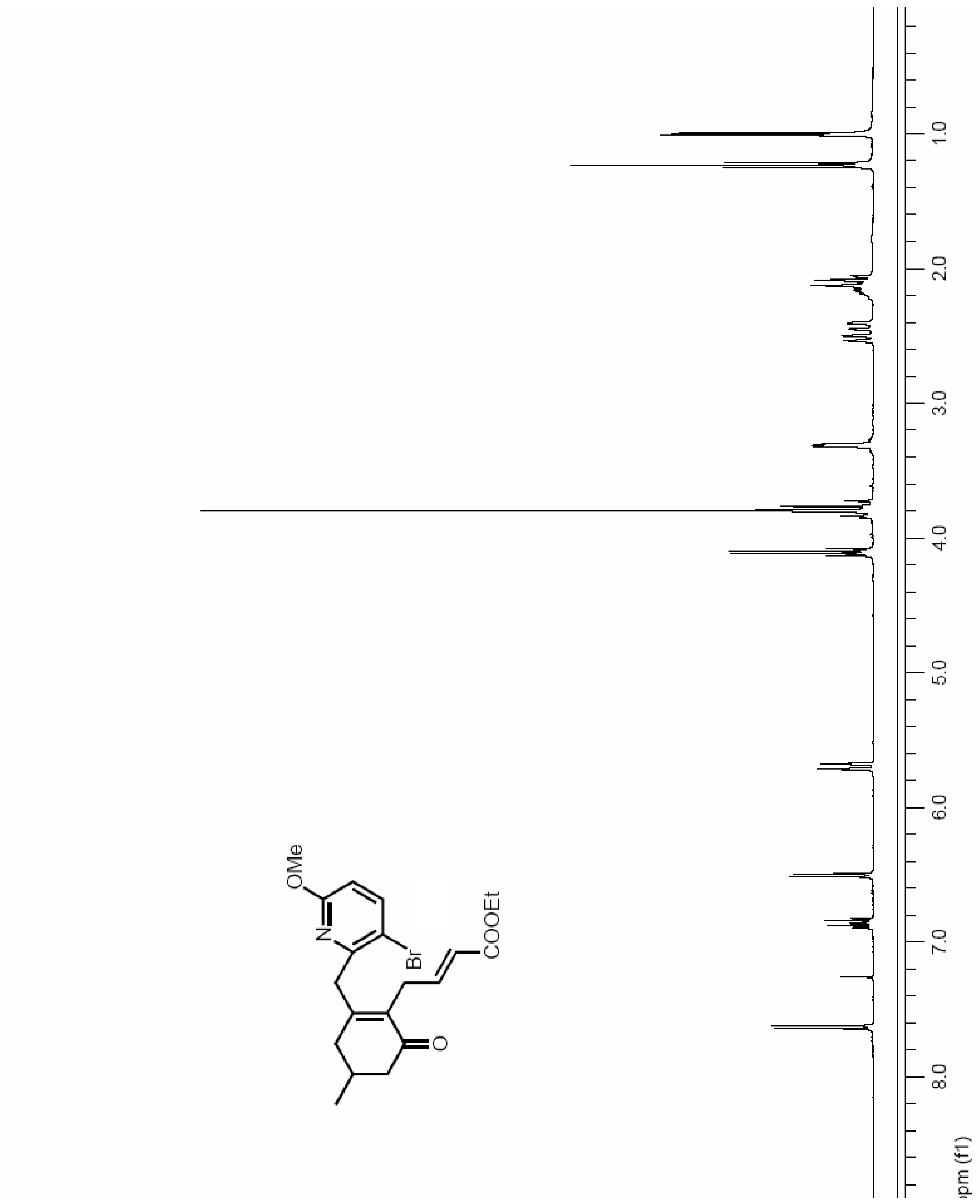
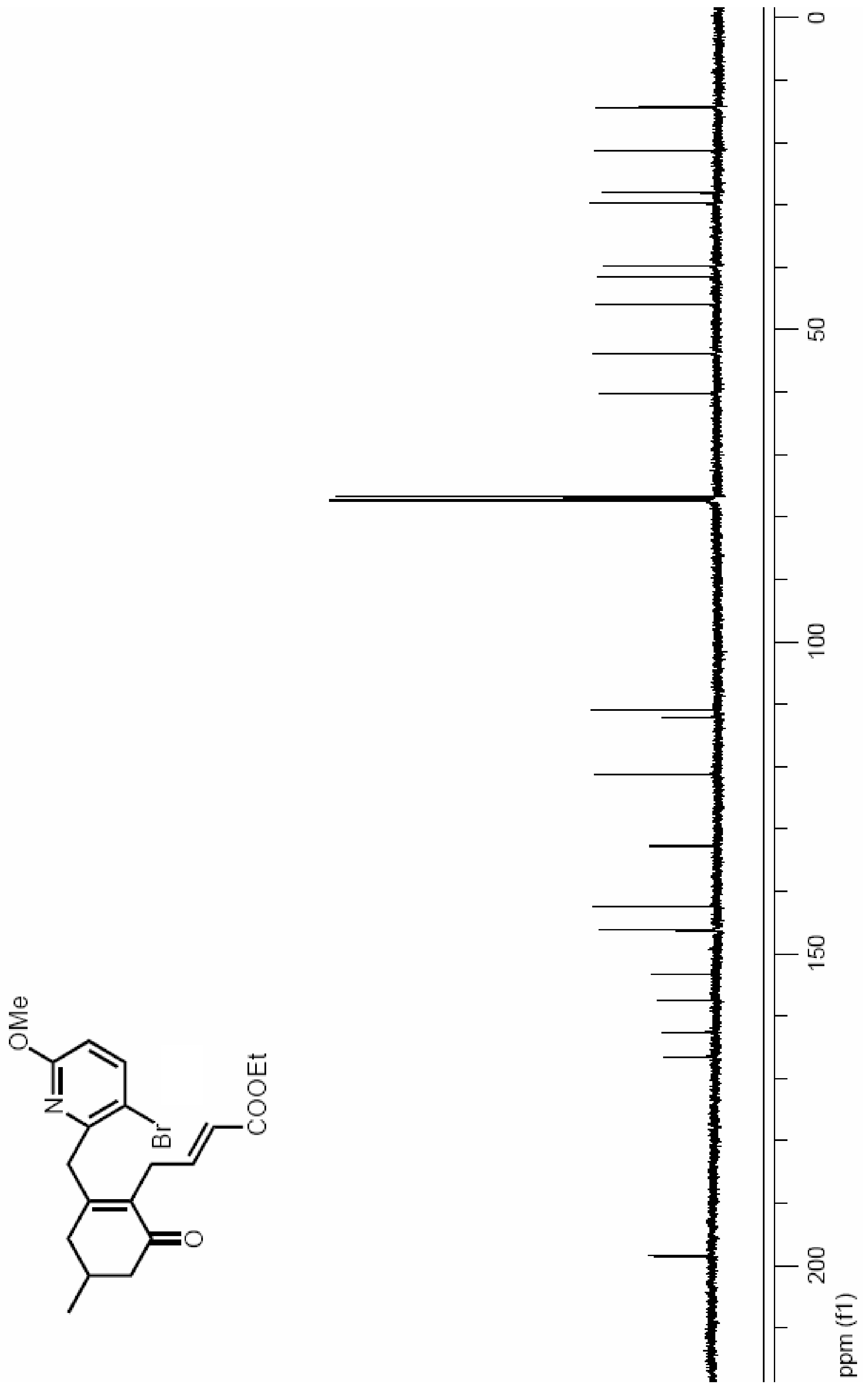
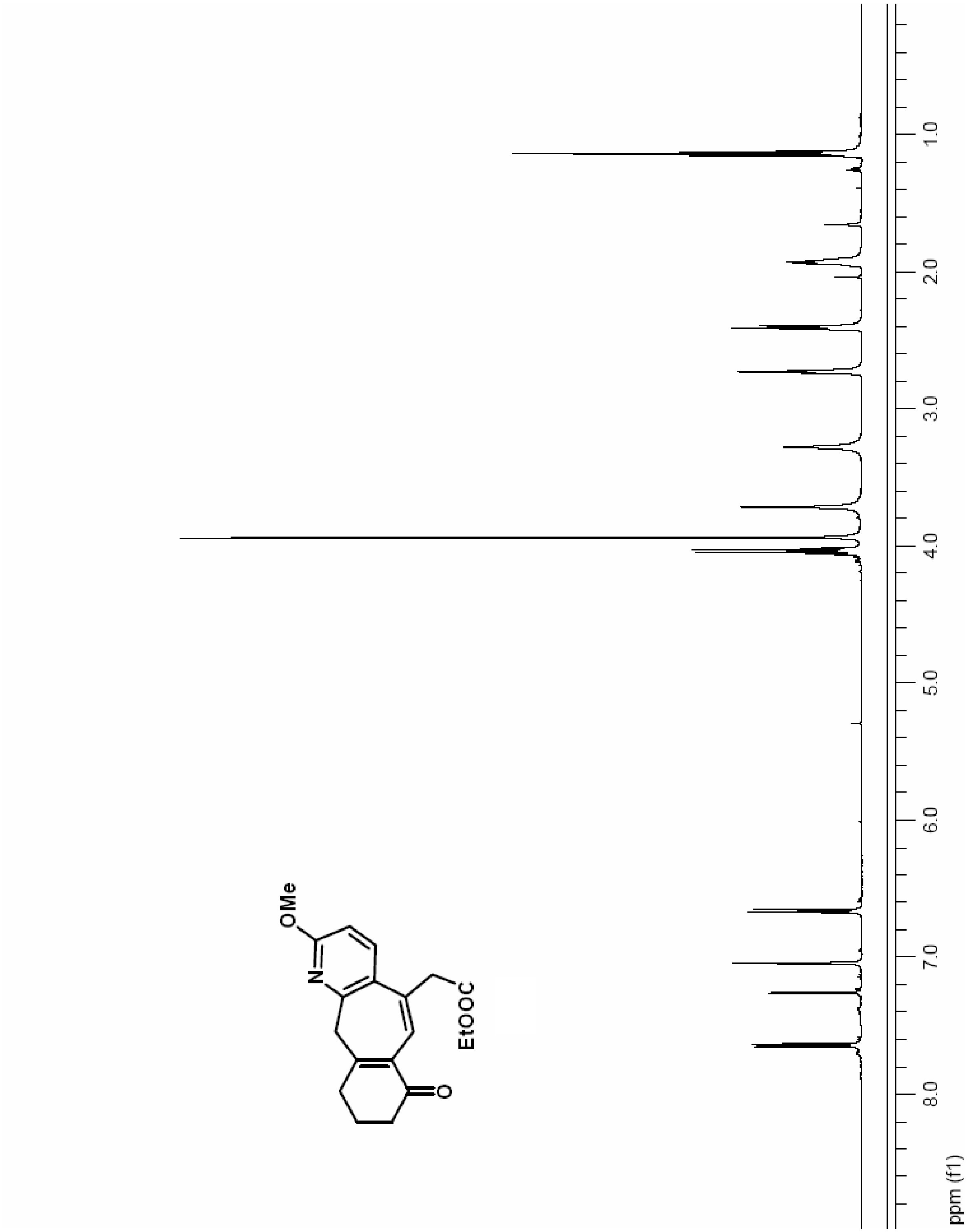
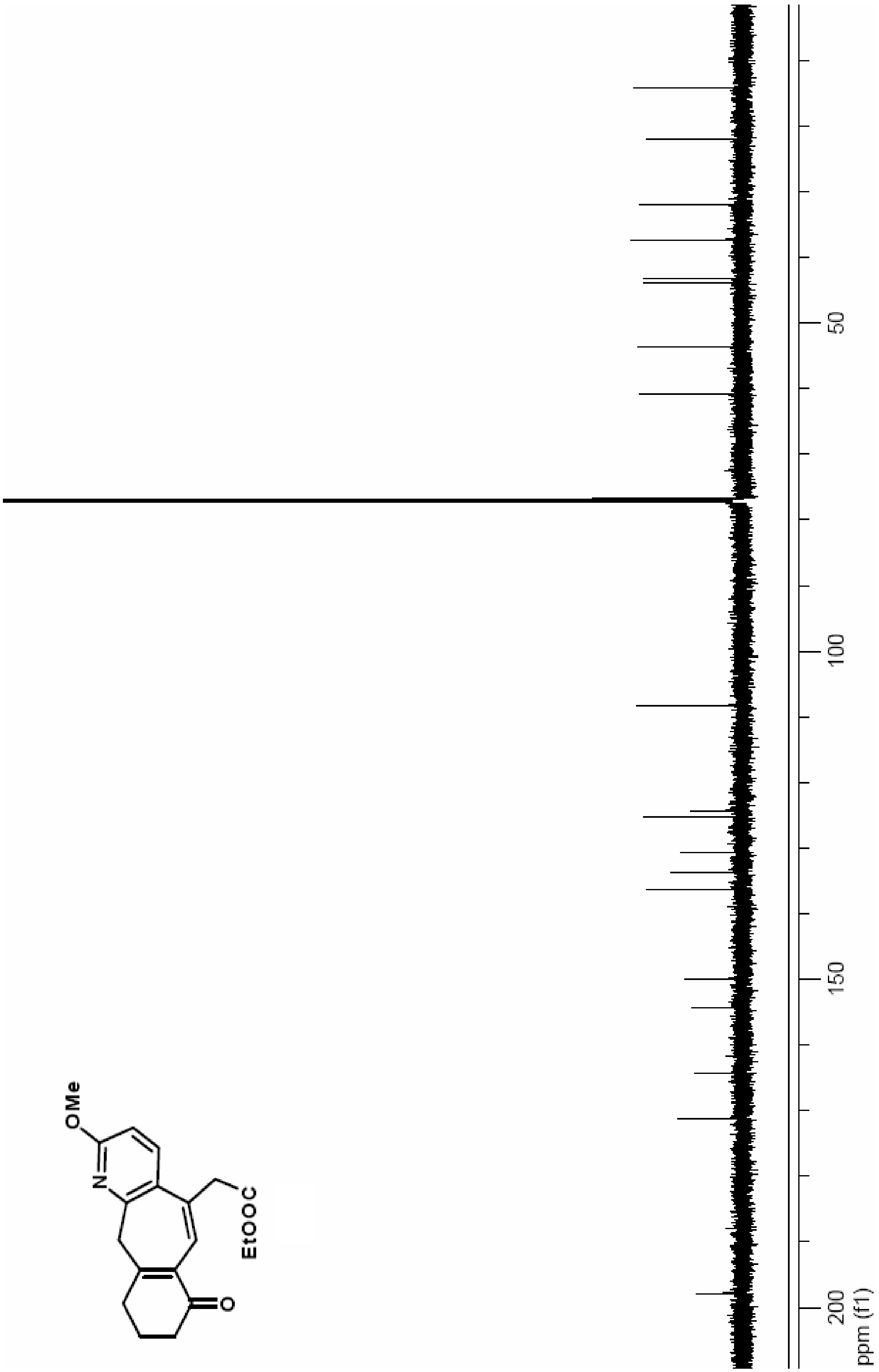
6.0
7.0
8.0
ppm (f1)

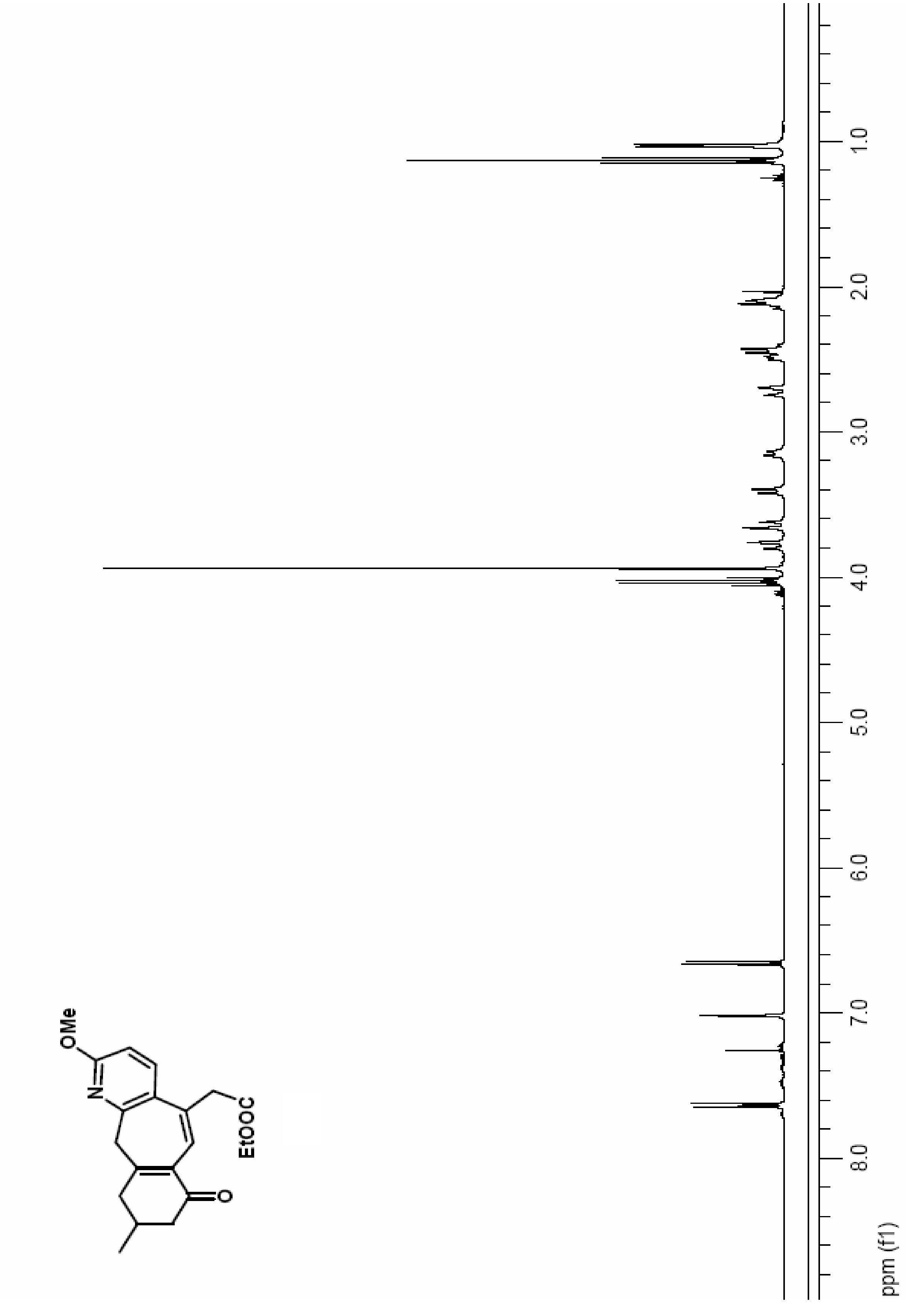

OMe
N
Br
COOEt
O
50
100
150
200
ppm (f1)

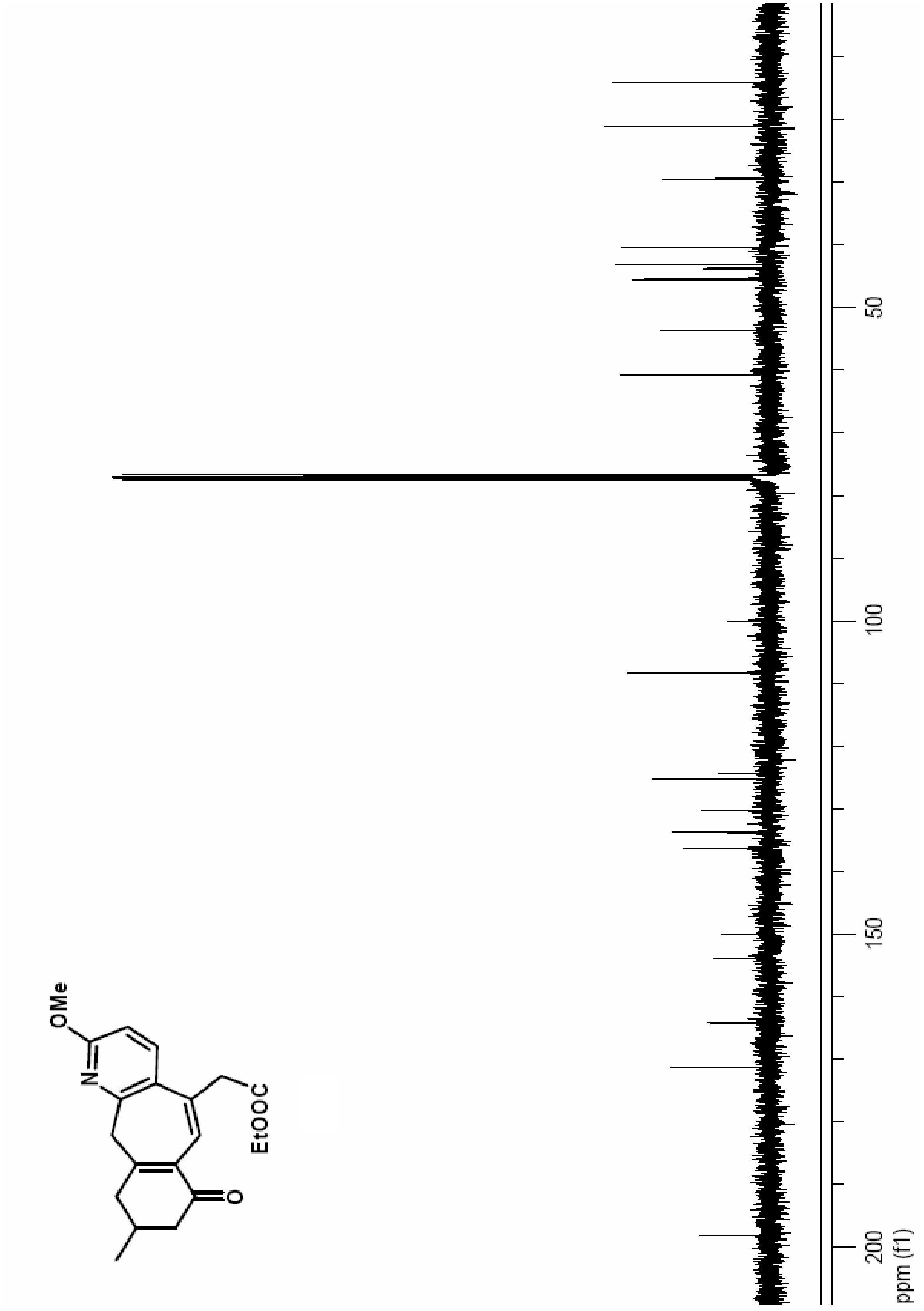

OMe
N
Br
COOEt
O
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (f1)

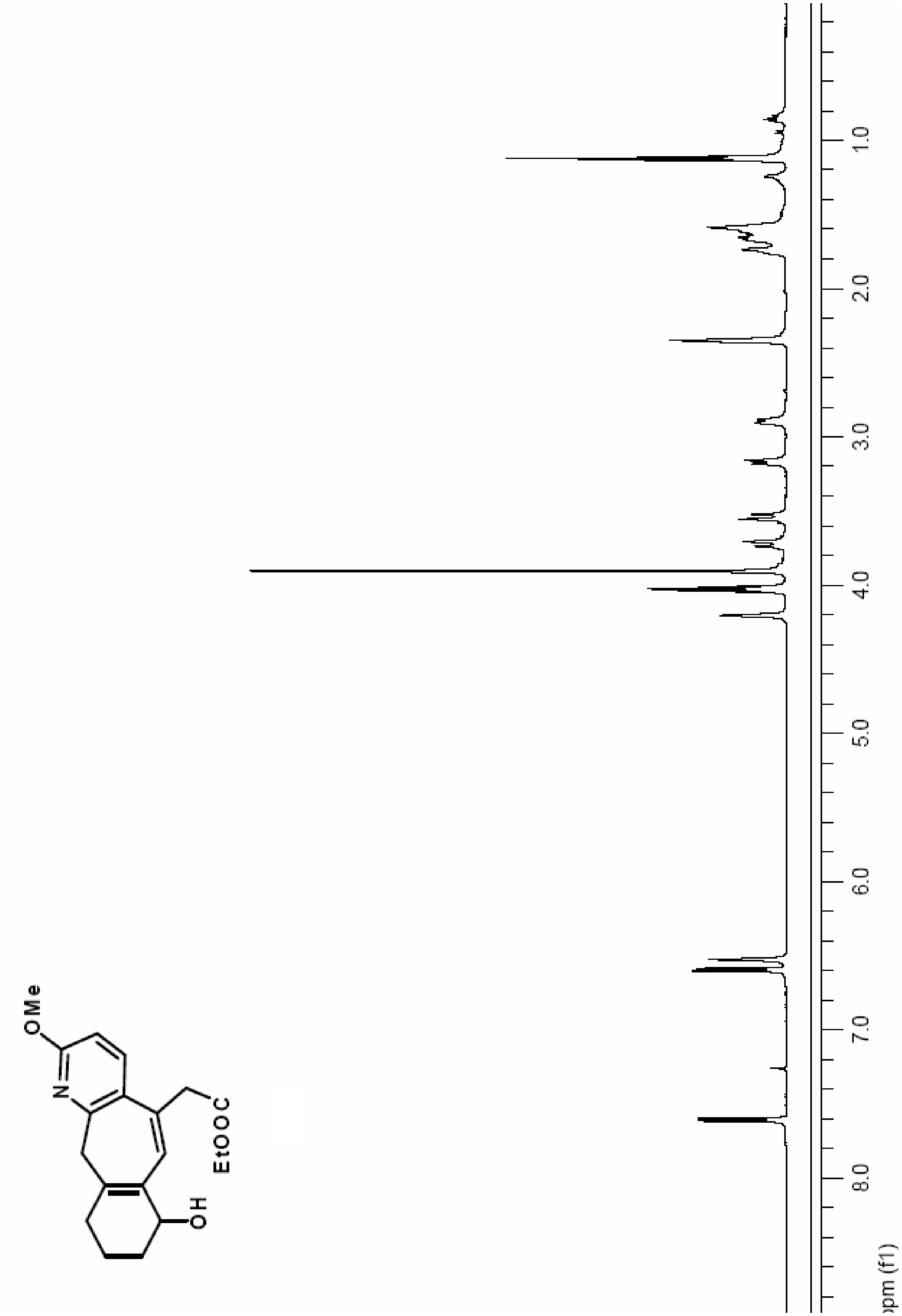

OMe
N
Br
COOEt
O
0
50
100
150
200
ppm (f1)

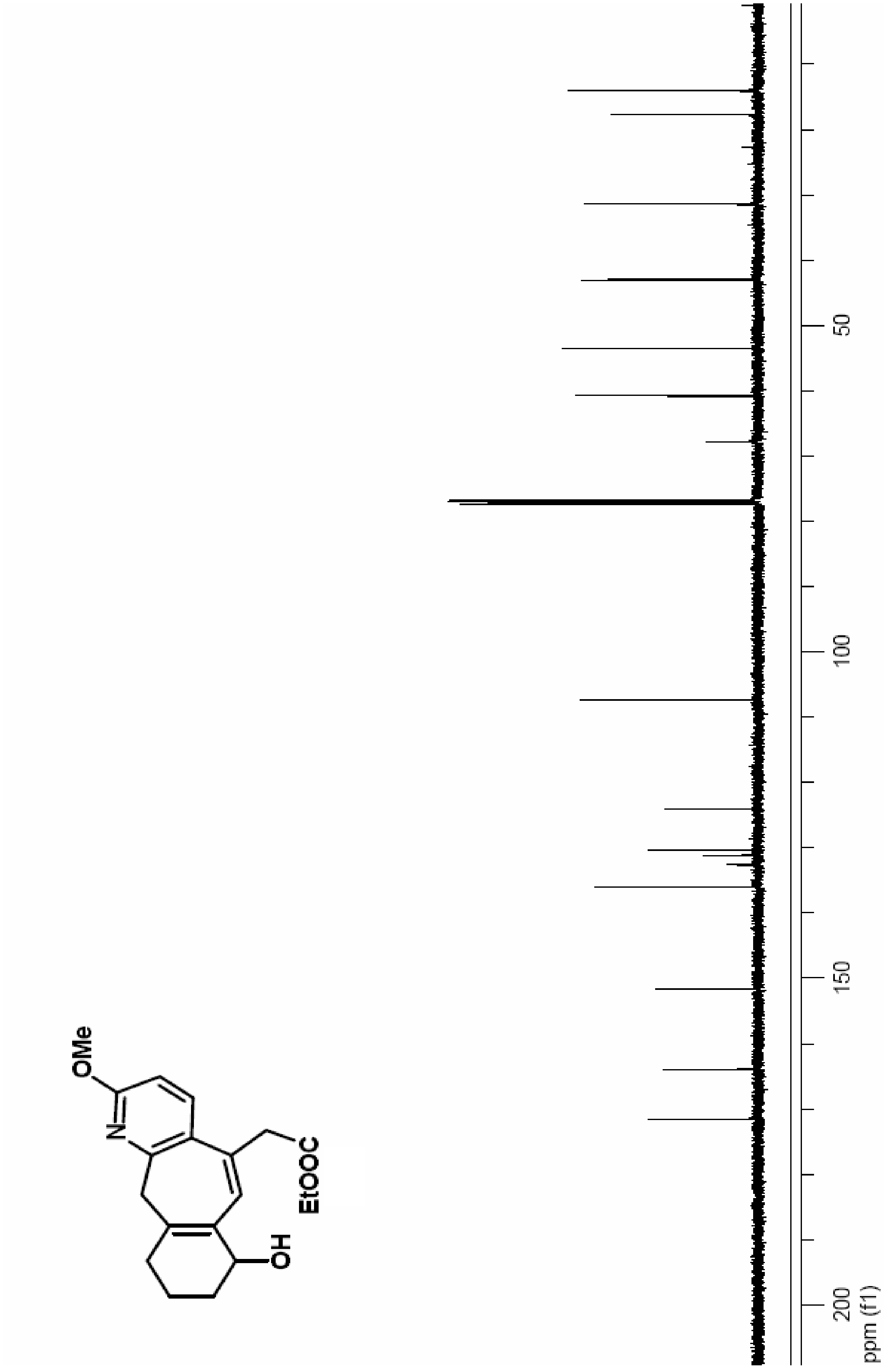

OMe
N
EtOOC
O
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (f1)


OMe
N
EtOOC
O
50
100
150
200
ppm (f1)

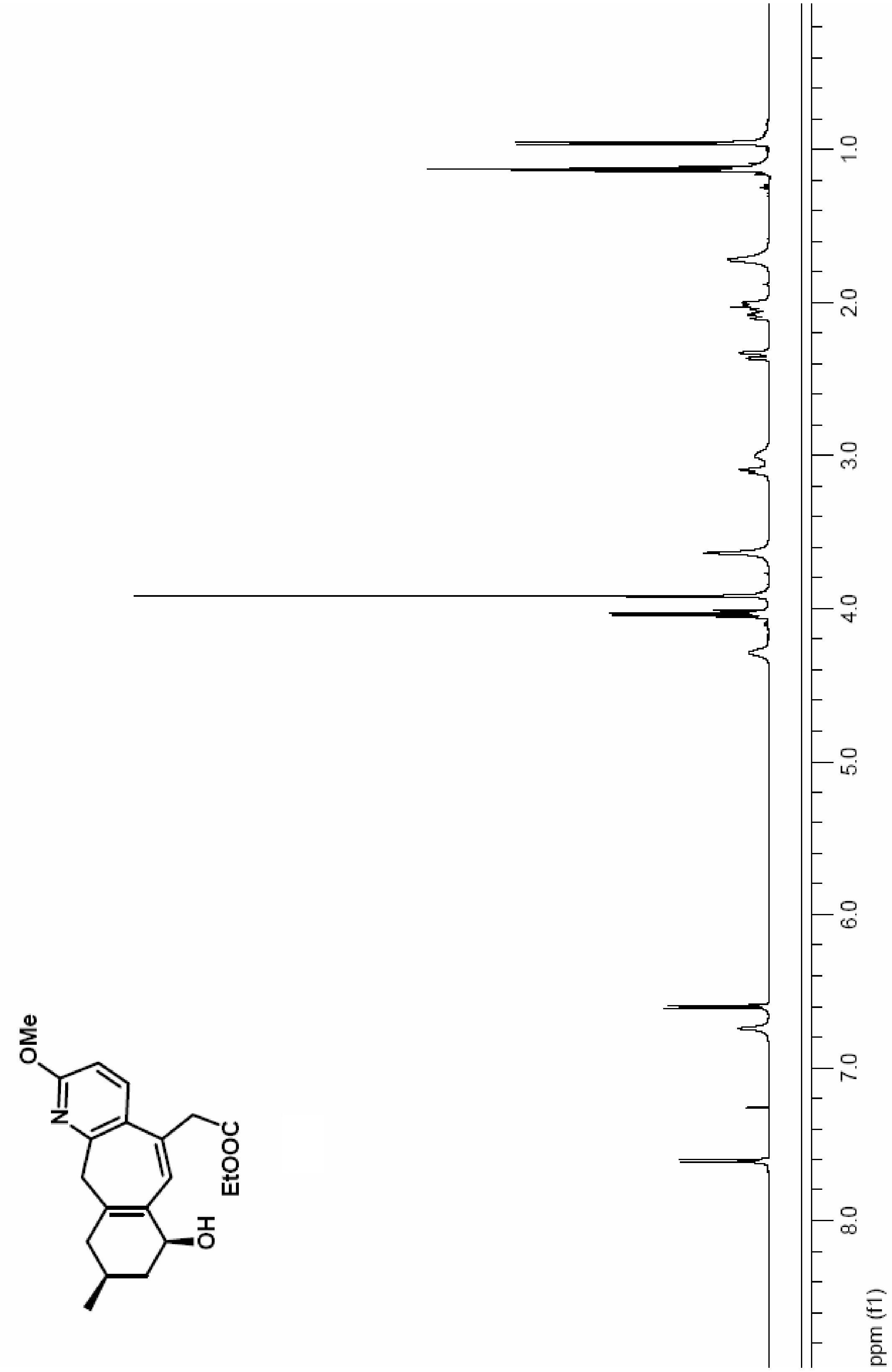

OMe
N
EtOOC
O
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (f1)


OMe
N
EtOOC
O
50
100
150
200
ppm (f1)

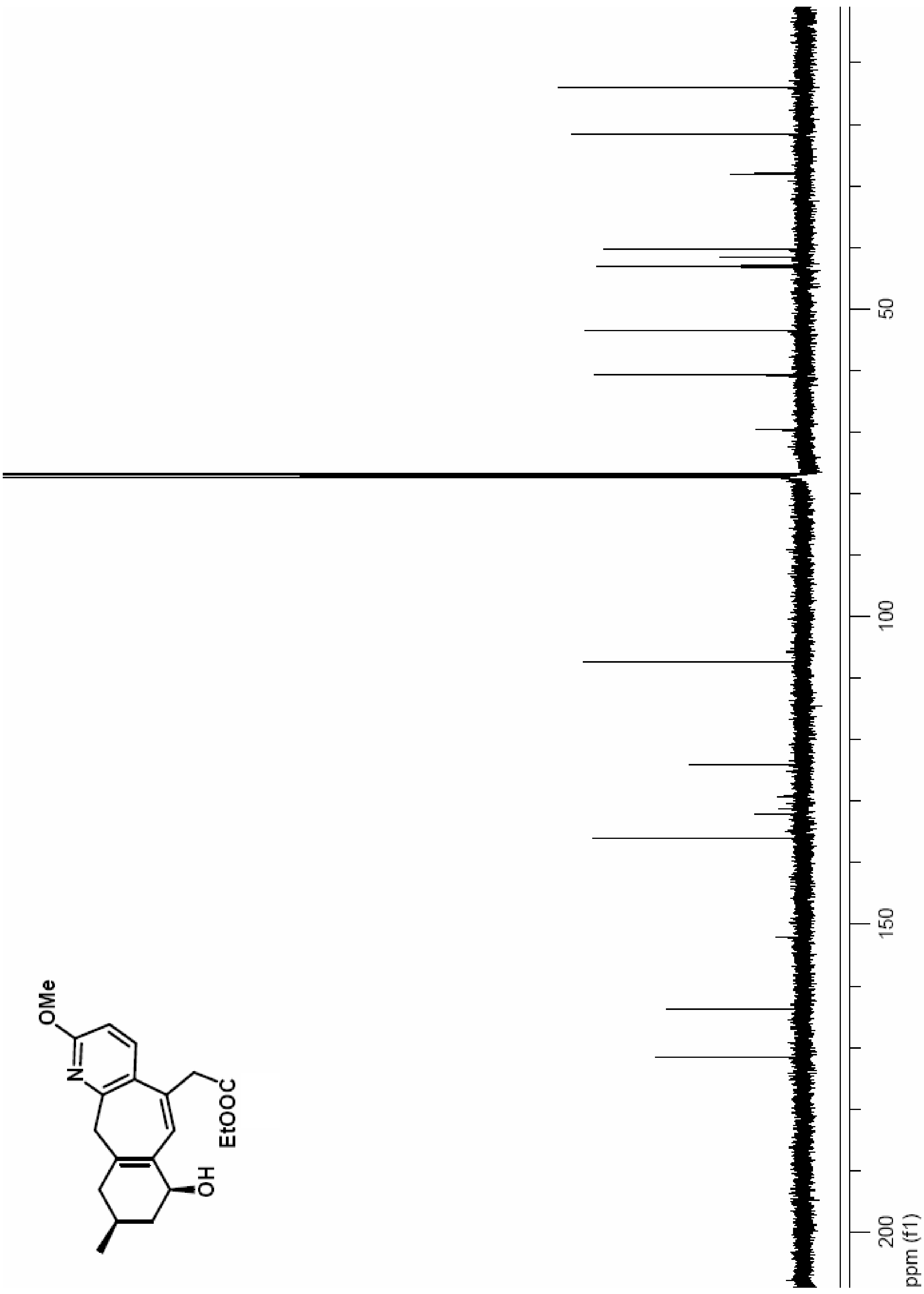

OMe
N
OH
EtOOC
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (f1)

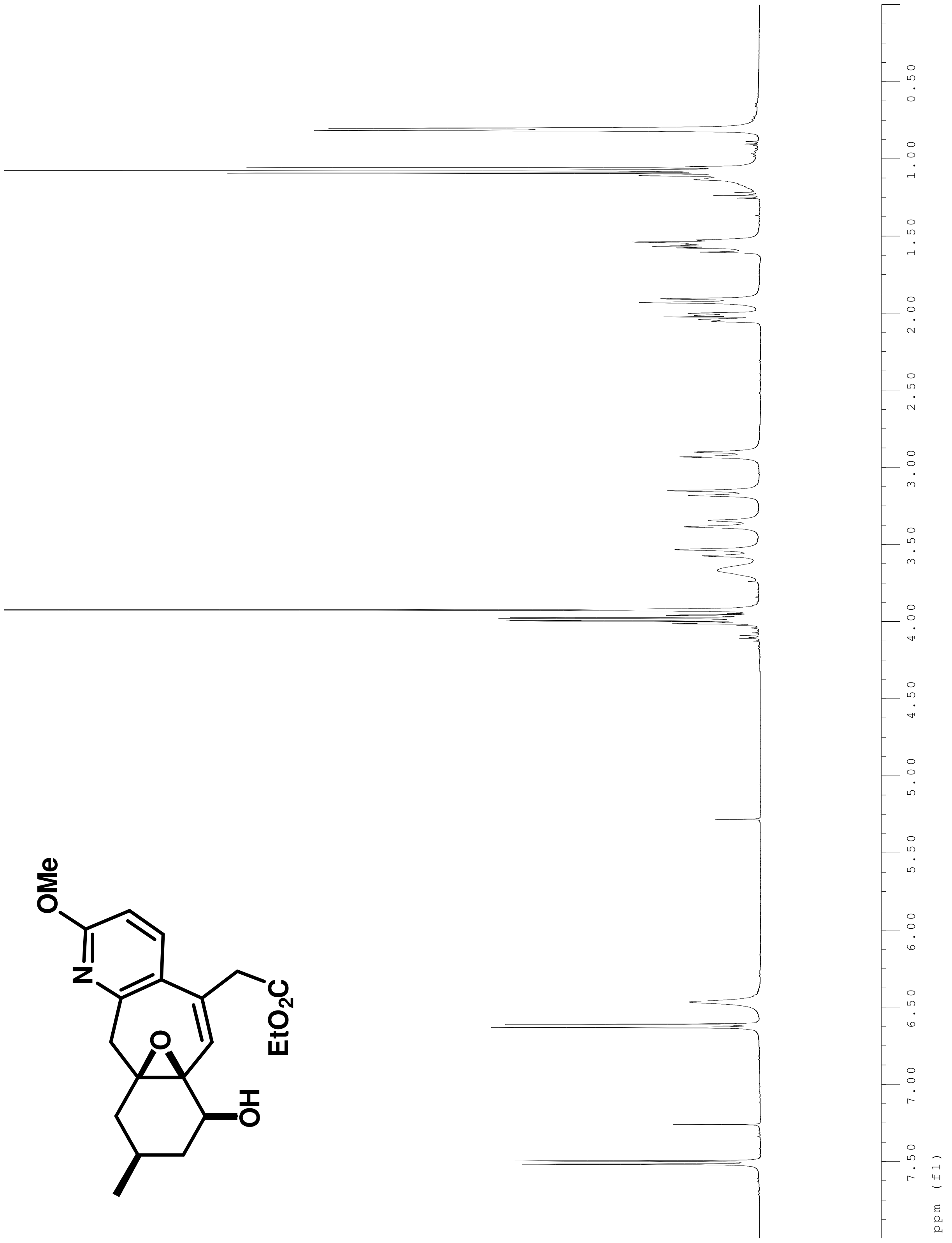


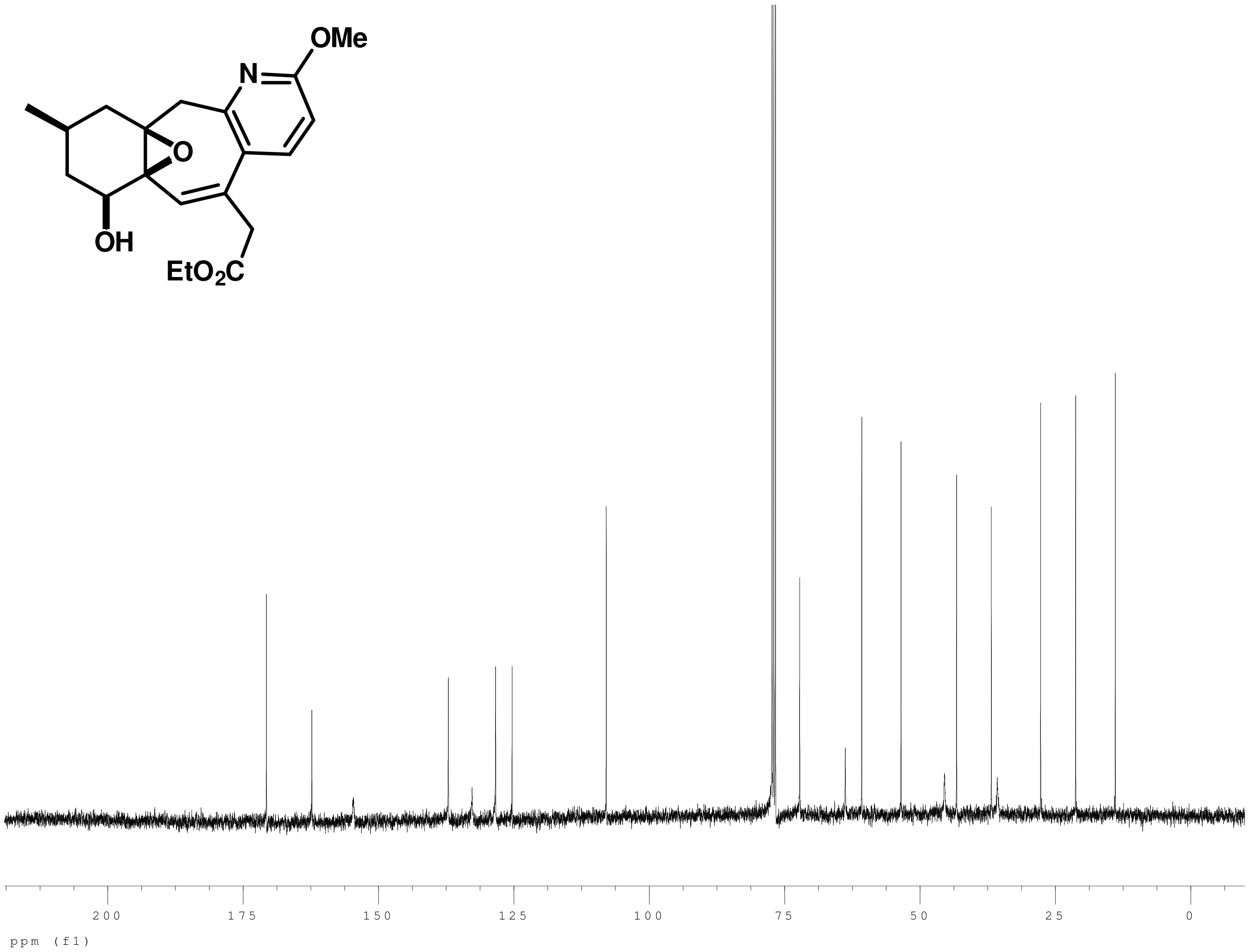
OMe
N
EtOOC
OH
50
100
150
200
ppm (f1)

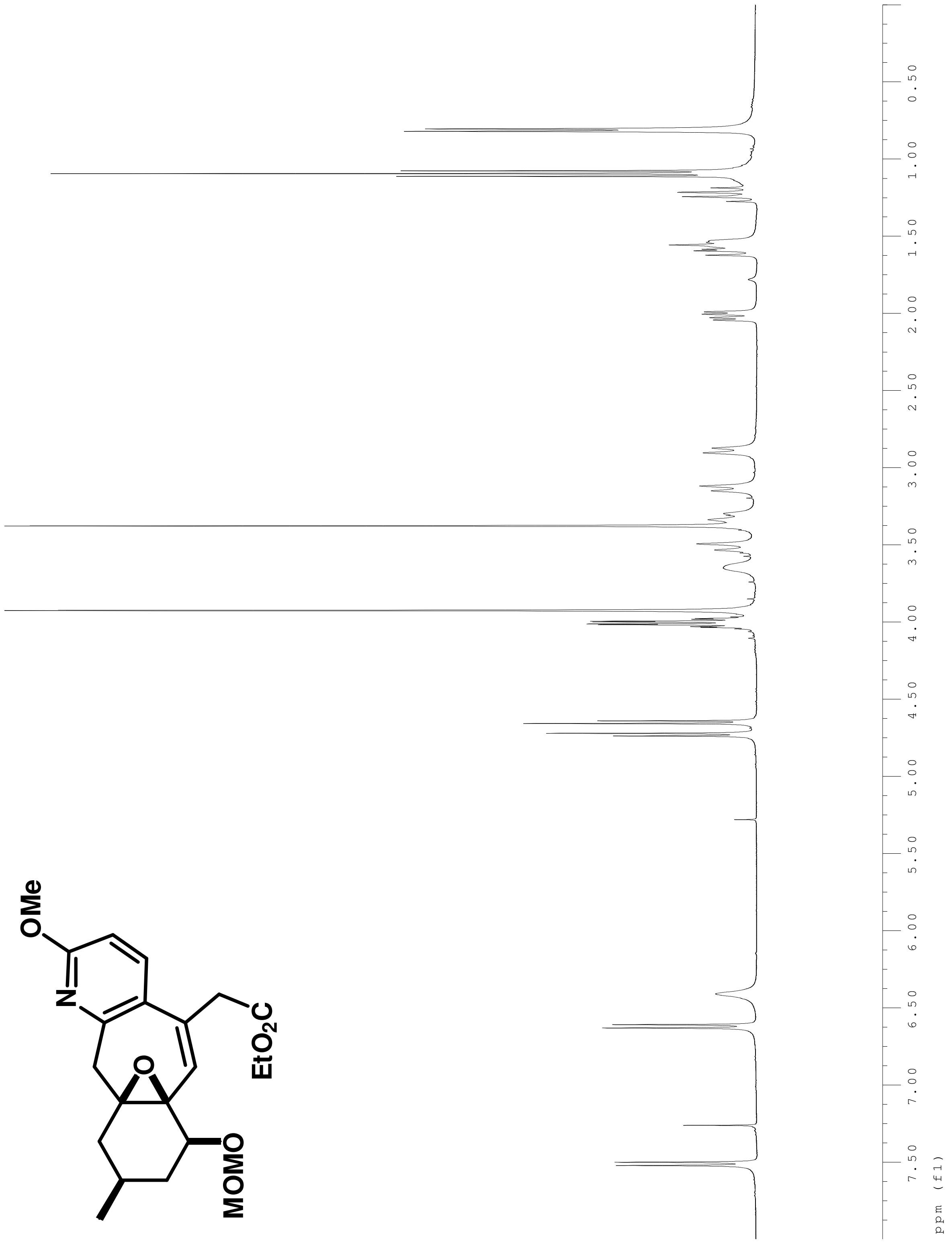


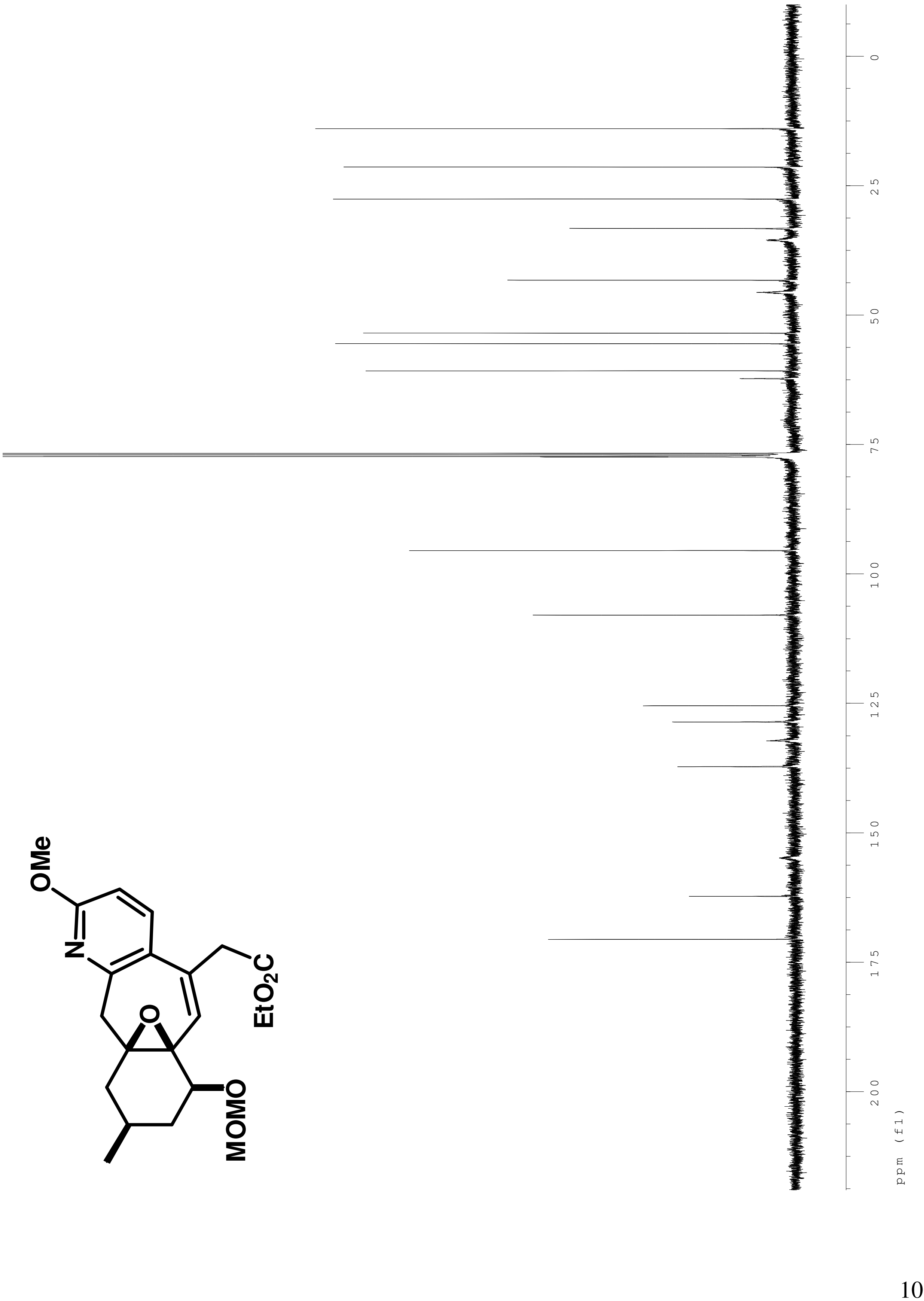
OMe
N
EtOOC
OH
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (f1)

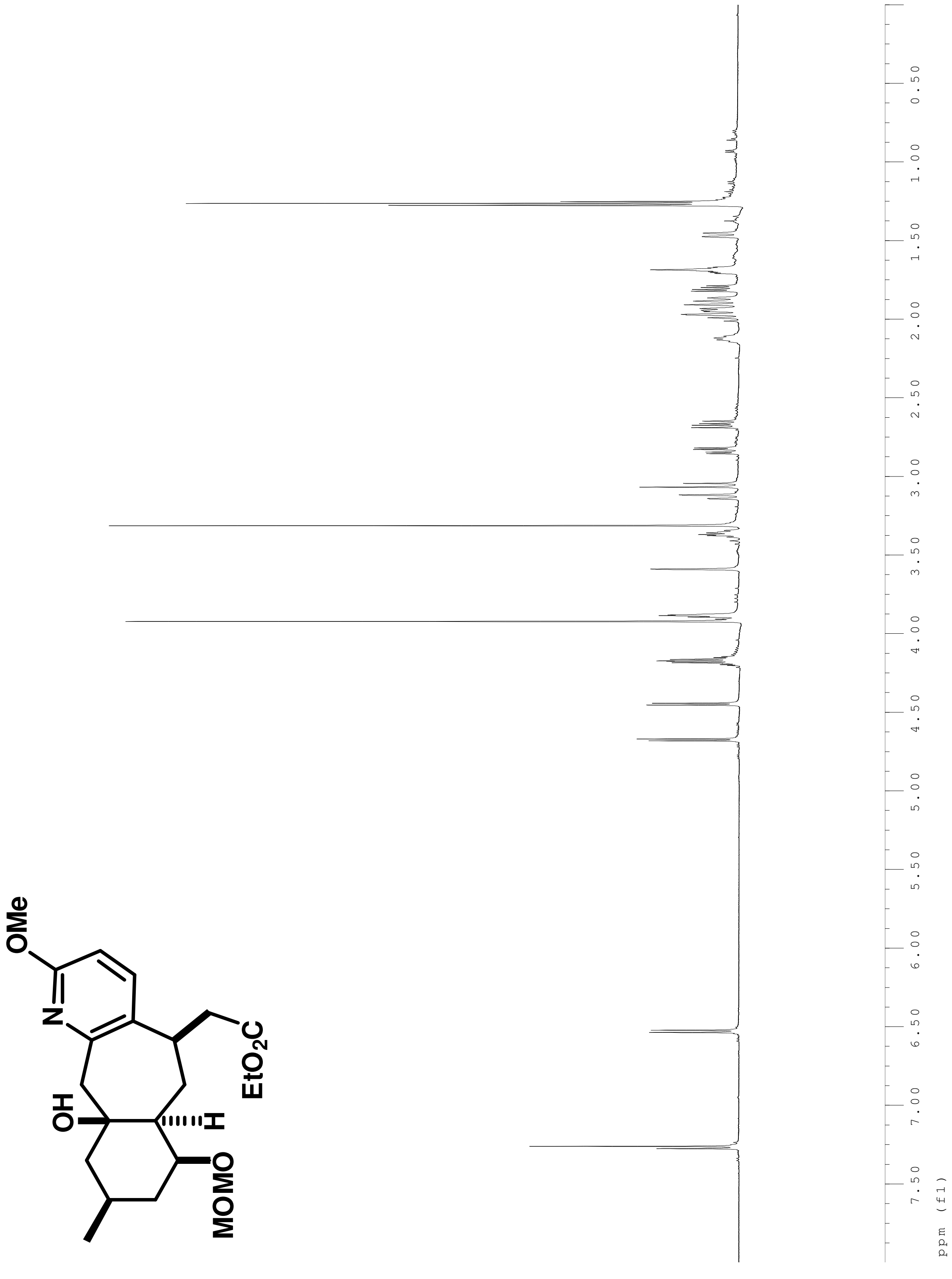

OMe
N
OH
EtOOC
50
100
150
200
ppm (f1)

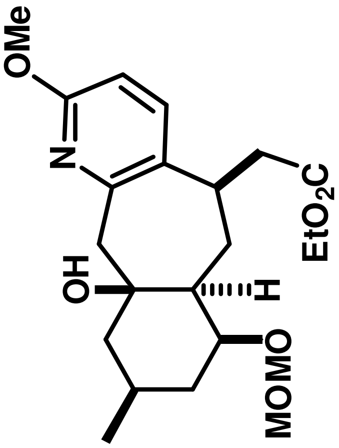

OMe
N
O
OH
EtO2C
0.50
1.00
1.50
2.00
2.50
3.00
3.50
4.00
4.50
5.00
5.50
6.00
6.50
7.00
7.50
ppm (f1)

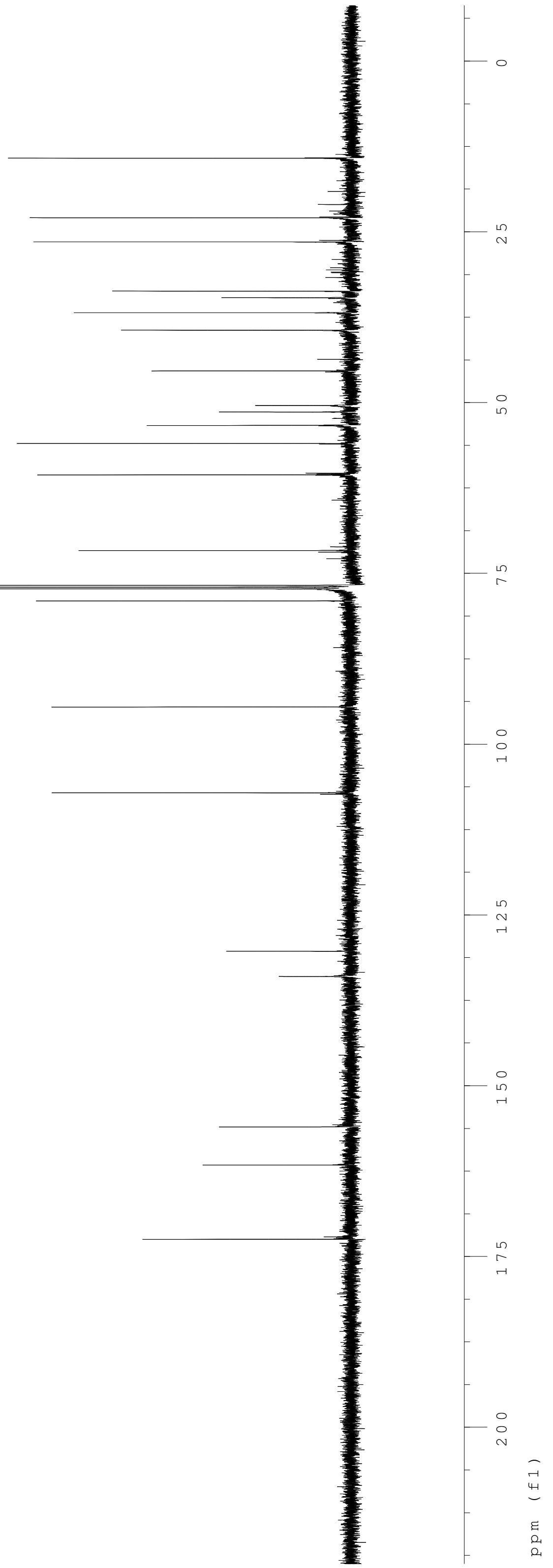

OMe
N
O
OH
EtO_2C
200
175
150
125
100
75
50
25
0
ppm (f1)

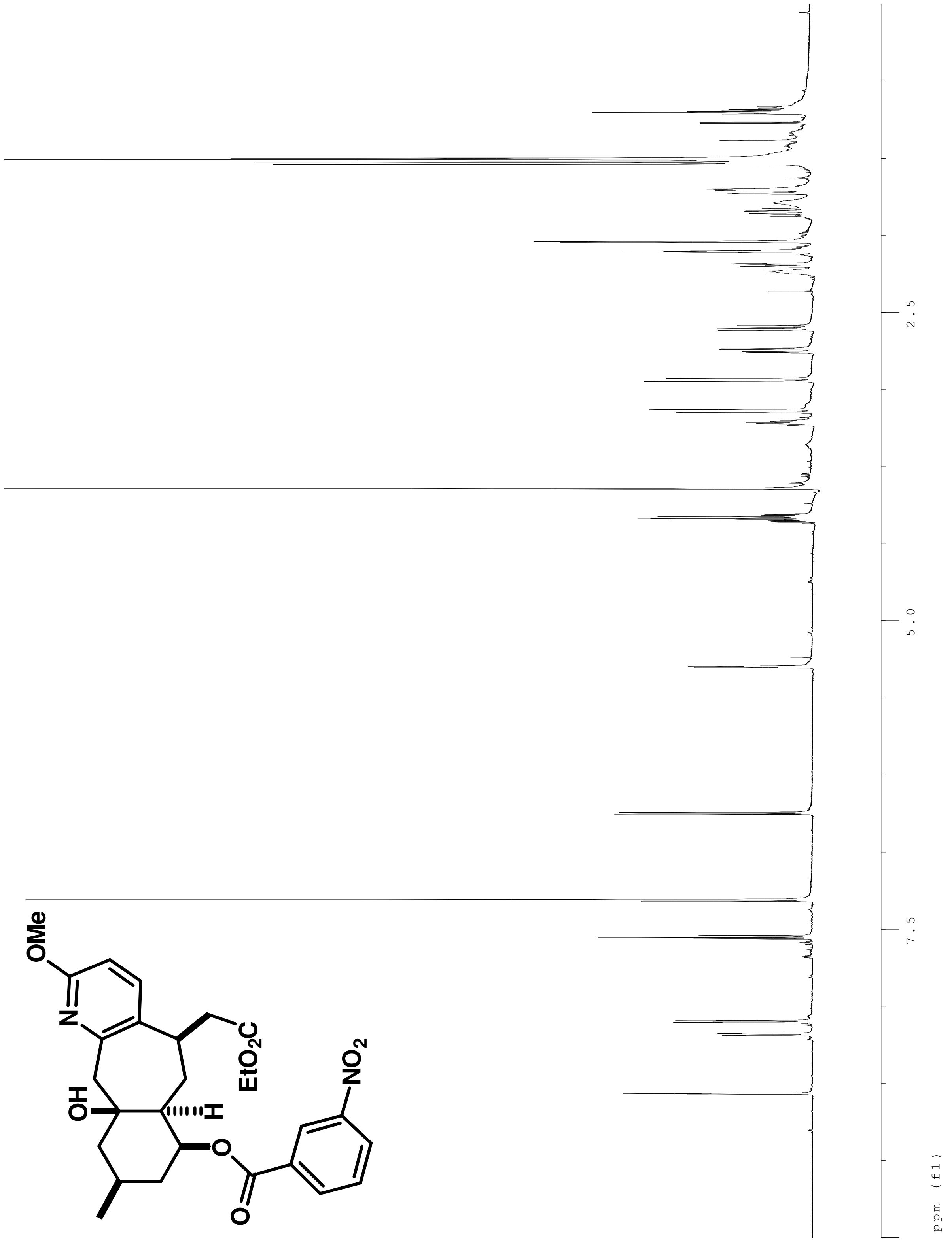

OMe
N
O
EtO$_2$C
MOMO
0.50
1.00
1.50
2.00
2.50
3.00
3.50
4.00
4.50
5.00
5.50
6.00
6.50
7.00
7.50
ppm (f1)

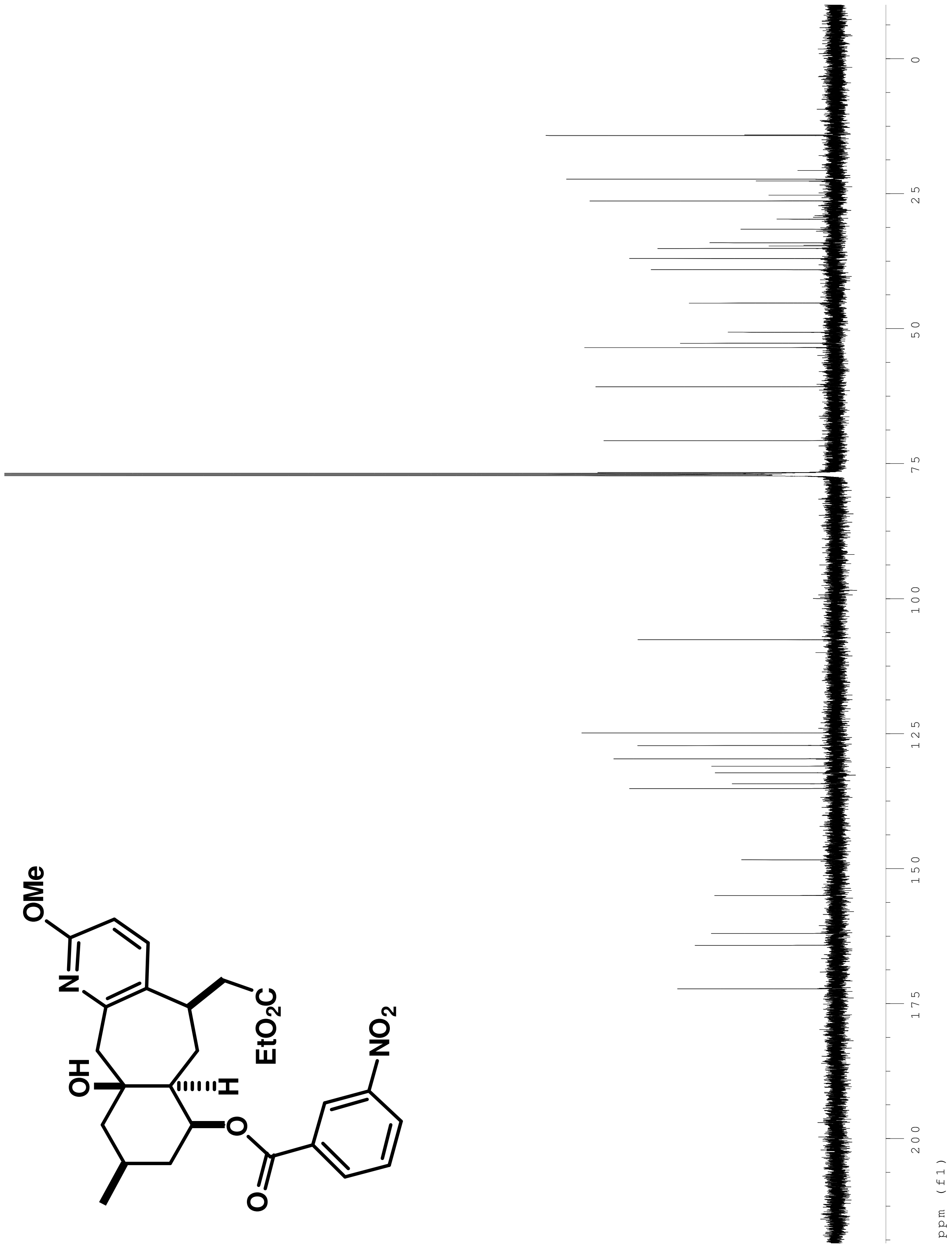

OMe
N
O
EtO$_2$C
MOMO
0
25
50
75
100
125
150
175
200
ppm (f1)

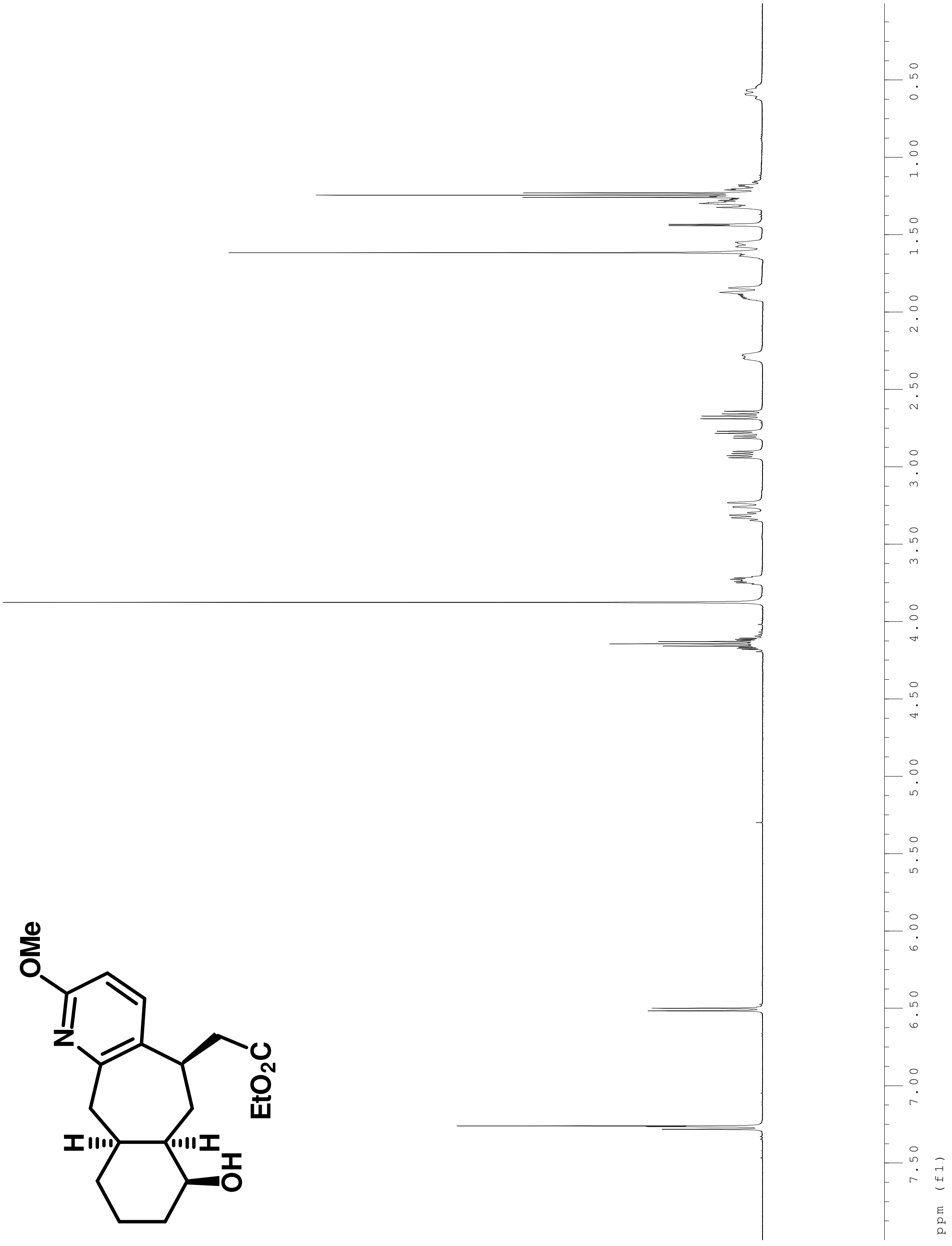

OMe
N
OH
H
MOMO
EtO$_2$C
0.50
1.00
1.50
2.00
2.50
3.00
3.50
4.00
4.50
5.00
5.50
6.00
6.50
7.00
7.50
ppm (f1)

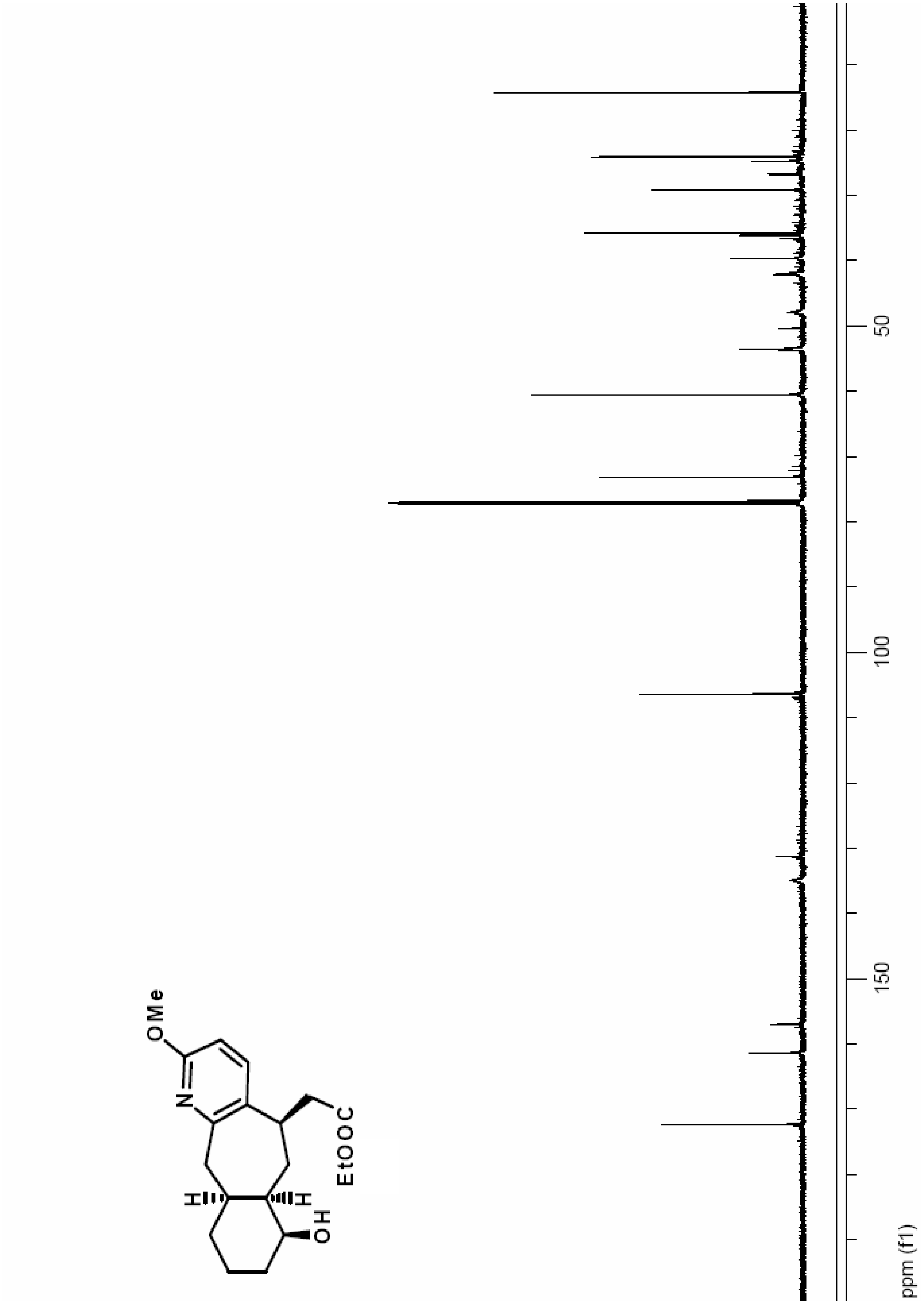

OMe
N
OH
H
MOMO
EtO2C

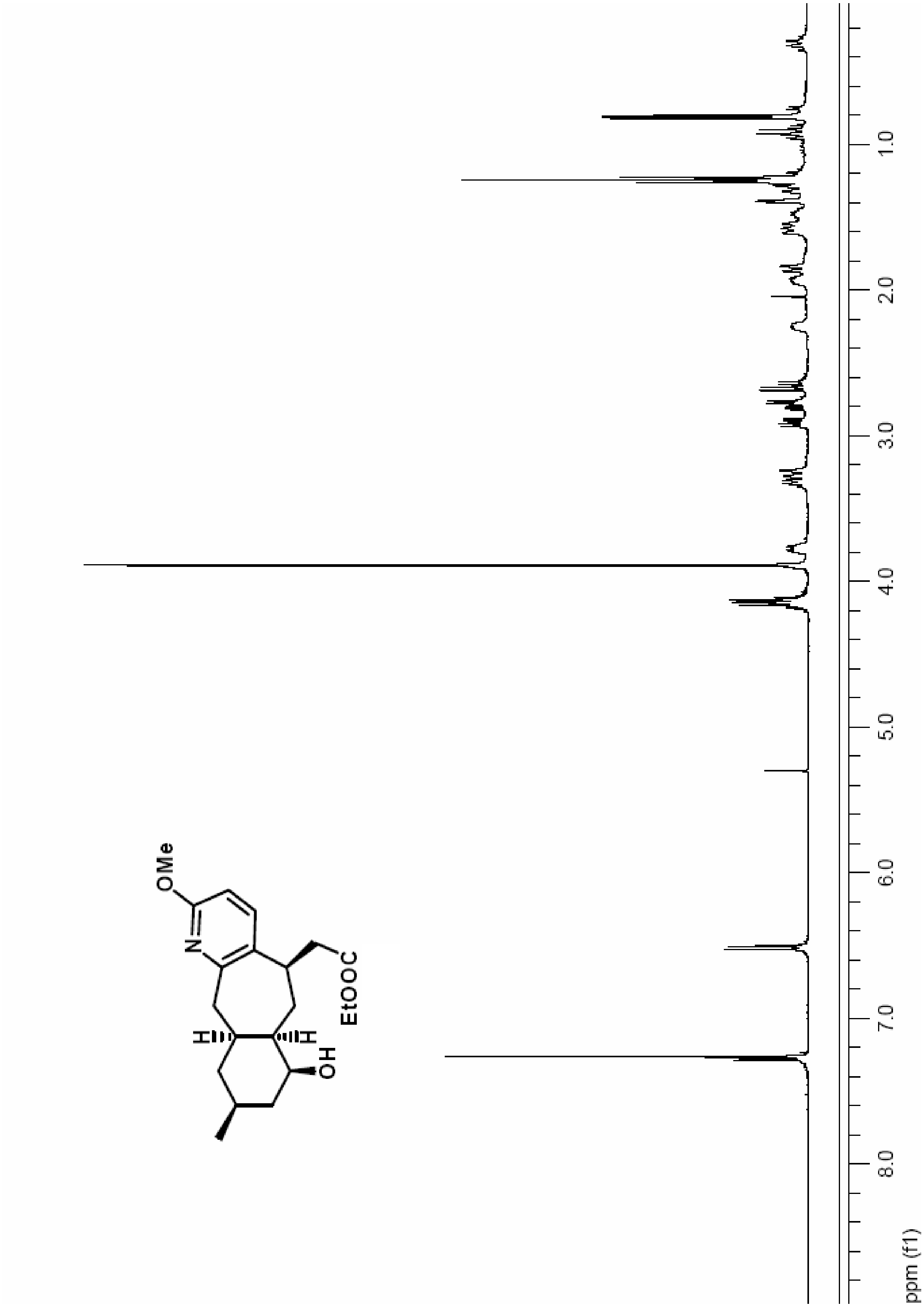

0
25
50
75
100
125
150
175
200
ppm (f1)

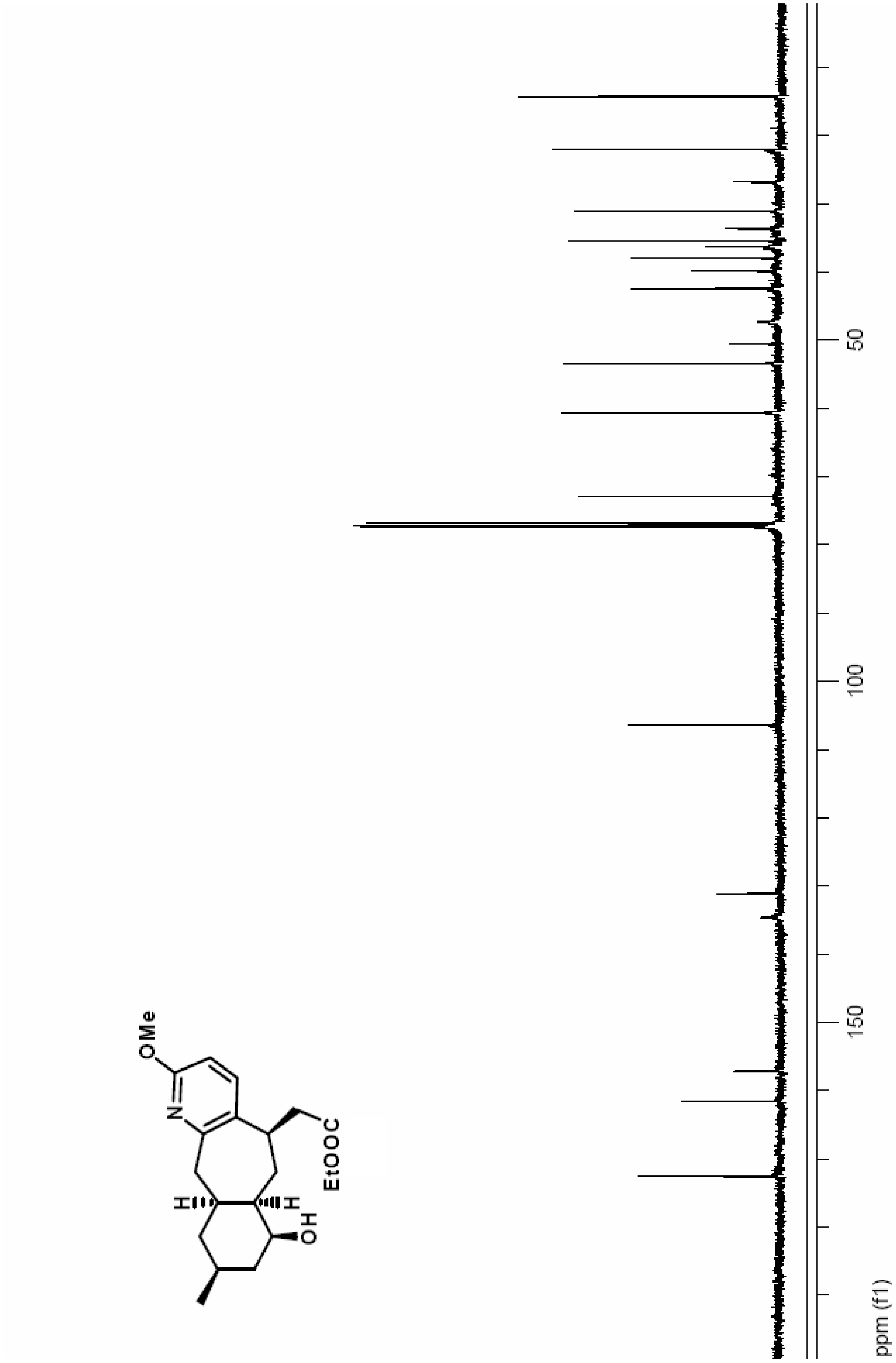

OMe
N
OH
H
EtO$_2$C
NO$_2$
O
O
O
7.5
5.0
2.5
ppm (f1)

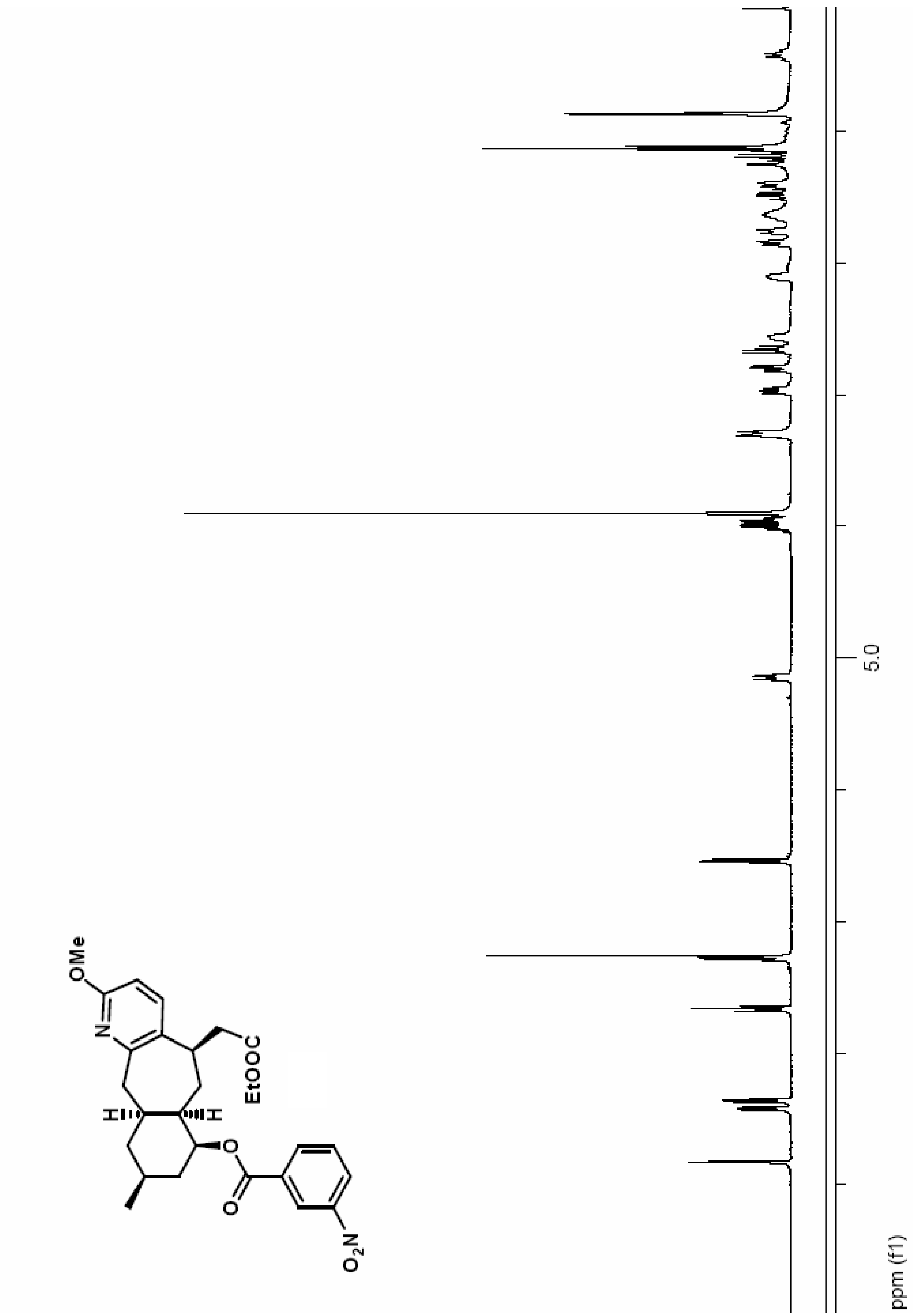

OMe
N
OH
H
EtO2C
O
O
NO2
0
25
50
75
100
125
150
175
200
ppm (f1)

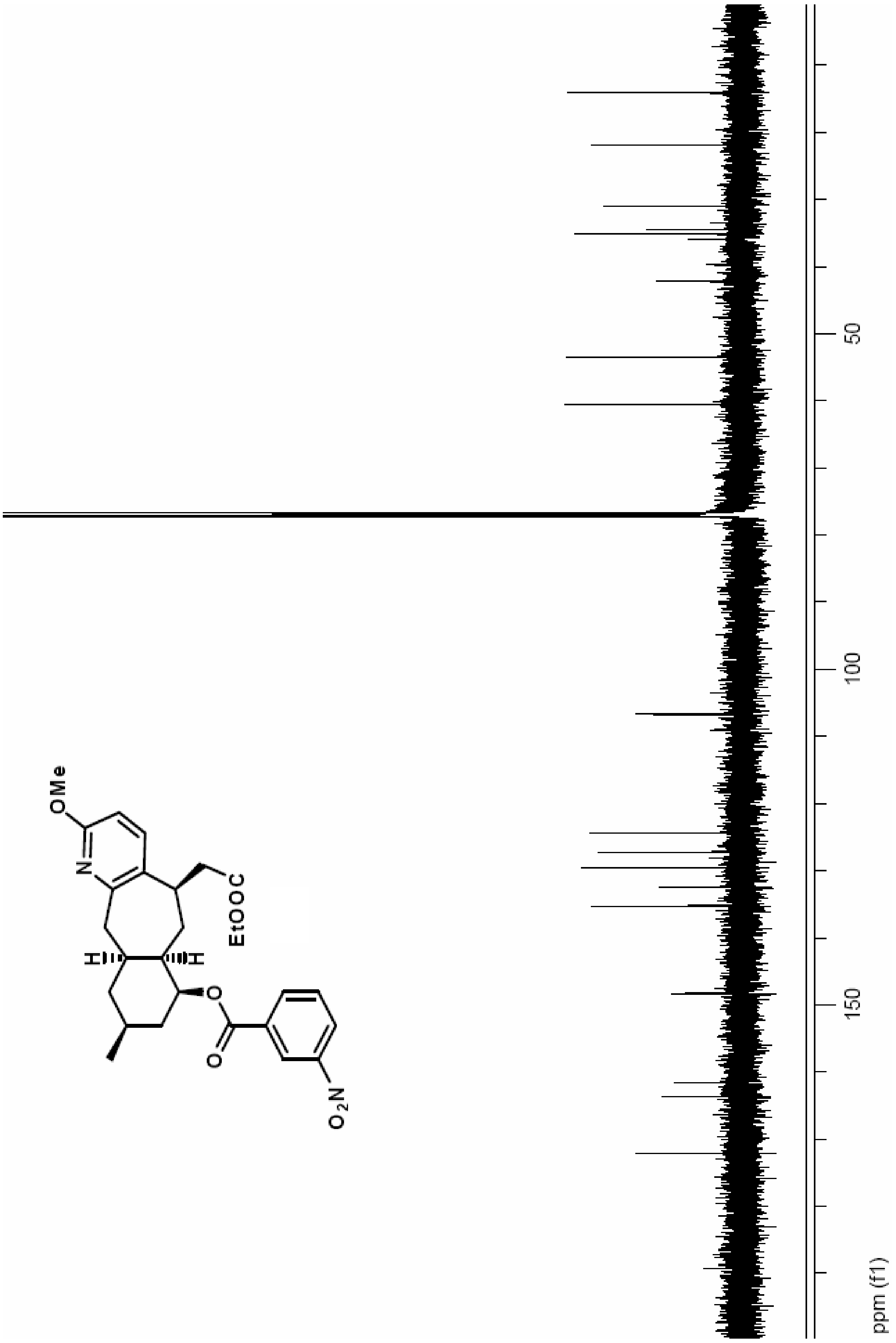

OMe
N
H
H
OH
EtO2C
0.50
1.00
1.50
2.00
2.50
3.00
3.50
4.00
4.50
5.00
5.50
6.00
6.50
7.00
7.50
ppm (f1)

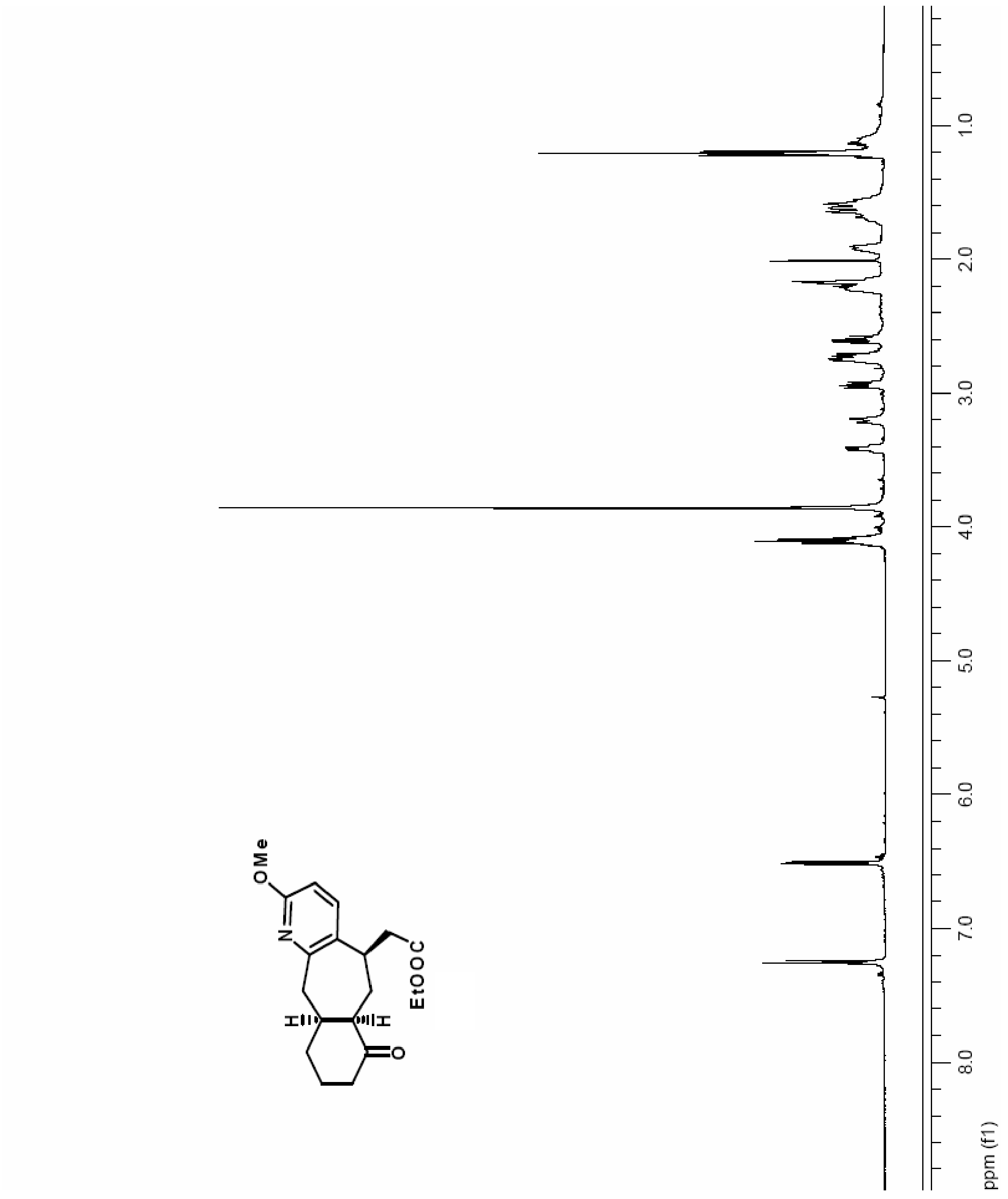

OMe
N
H
H
OH
EtOOC
ppm (f1)
150
100
50

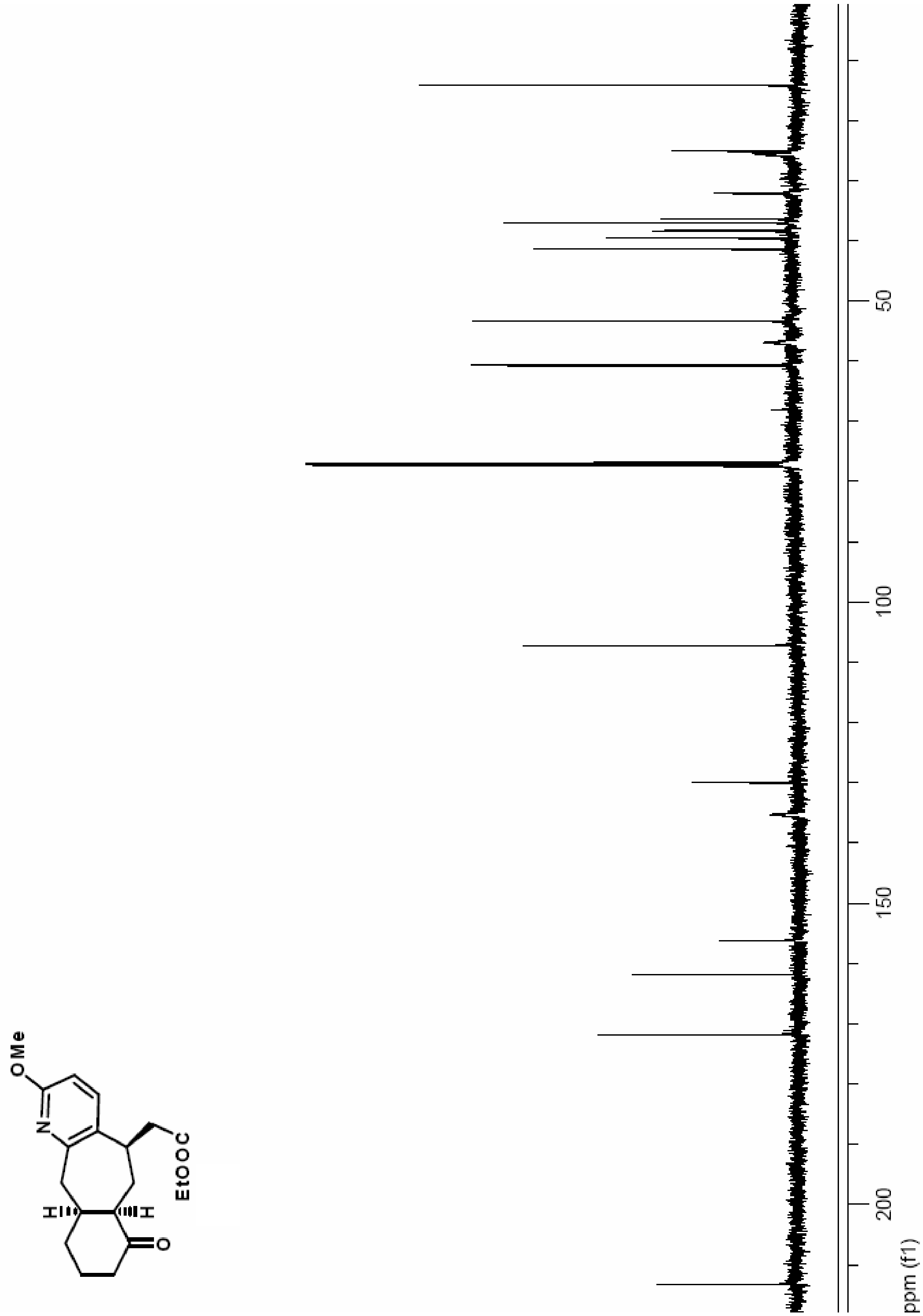

OMe
N
EtOOC
OH
H
H
ppm (f1)
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0

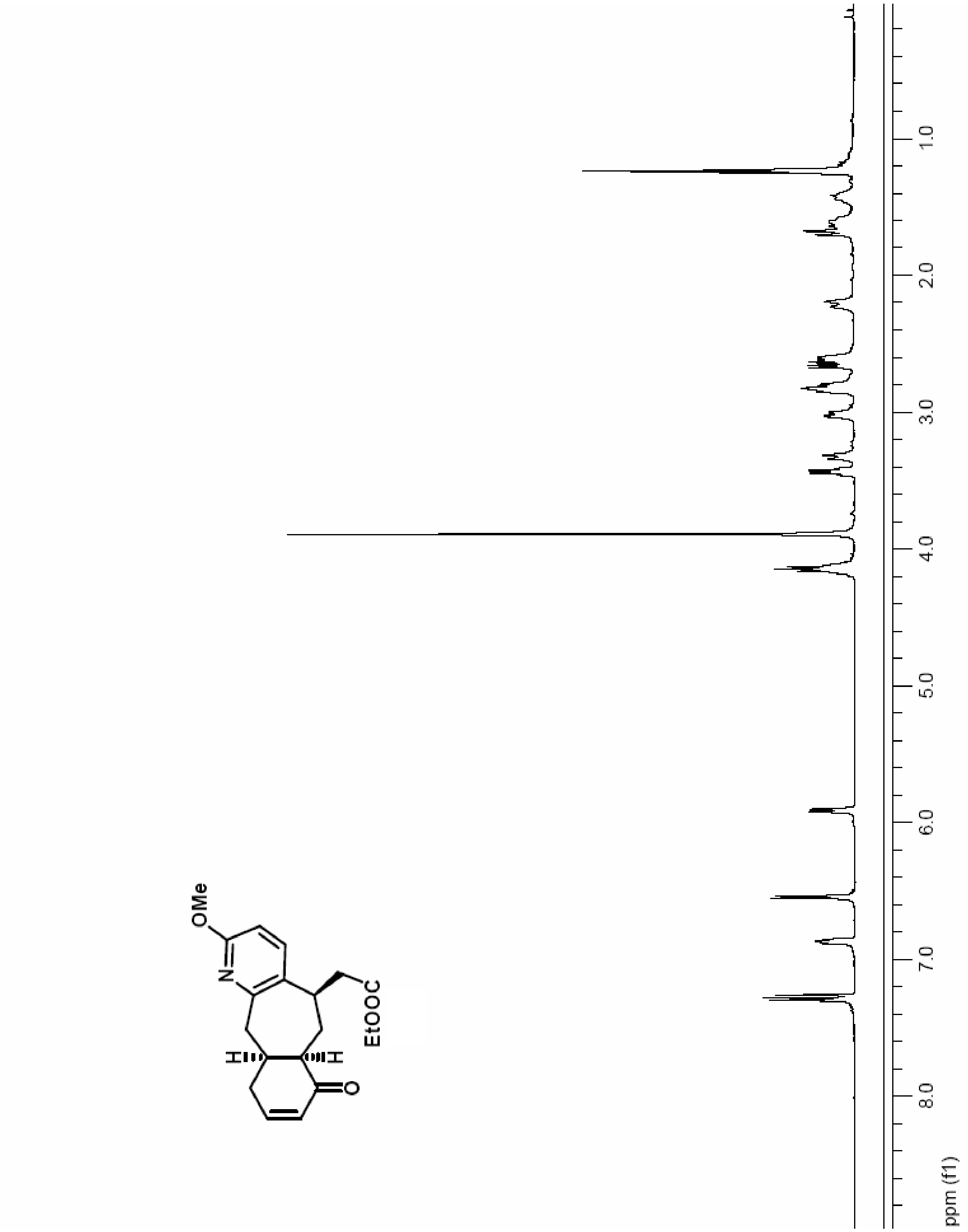

OMe
N
H
H
OH
EtOOC
ppm (f1)
150
100
50

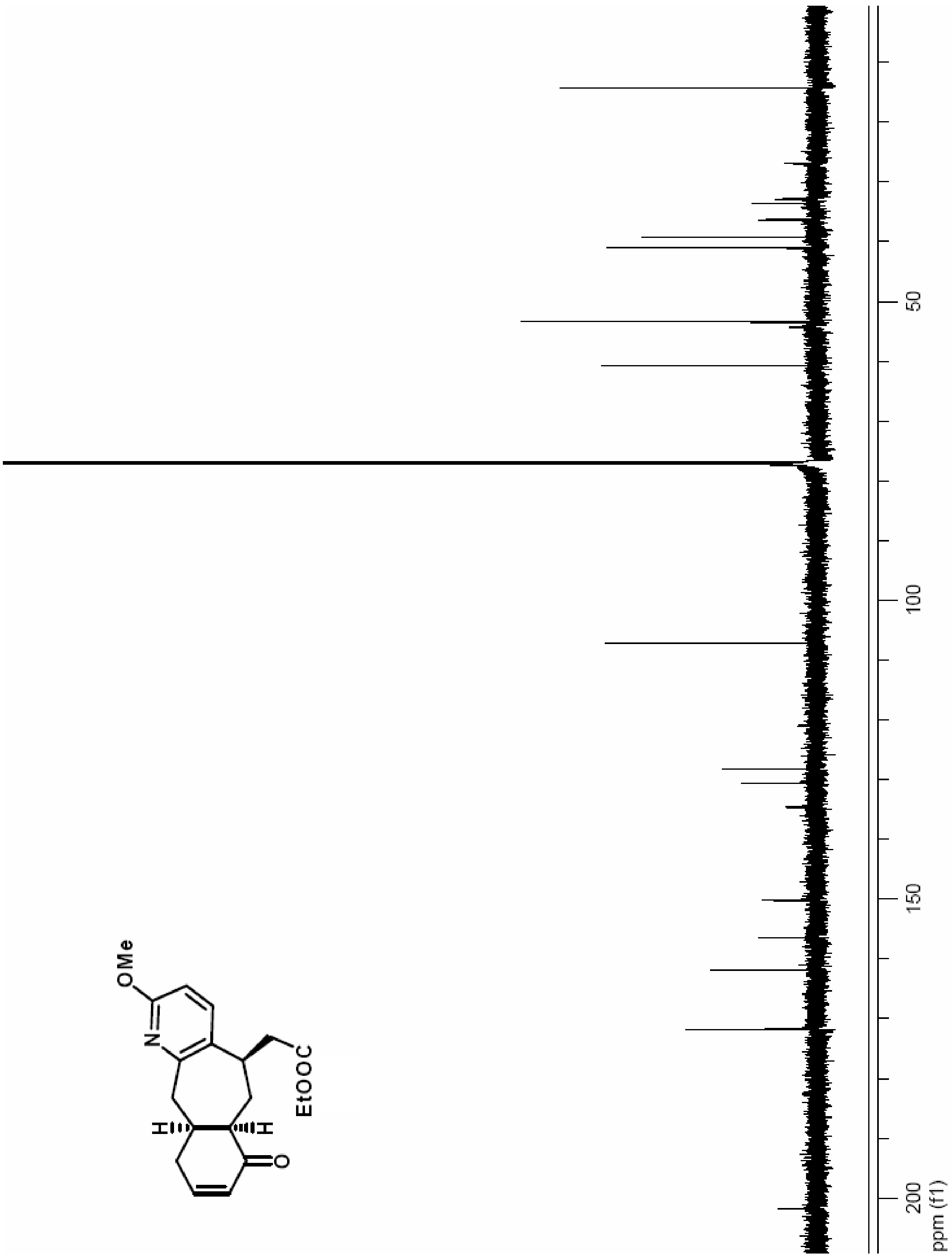

OMe
N
EtOOC
H
H
O
O
O$_2$N
5.0
ppm (f1)

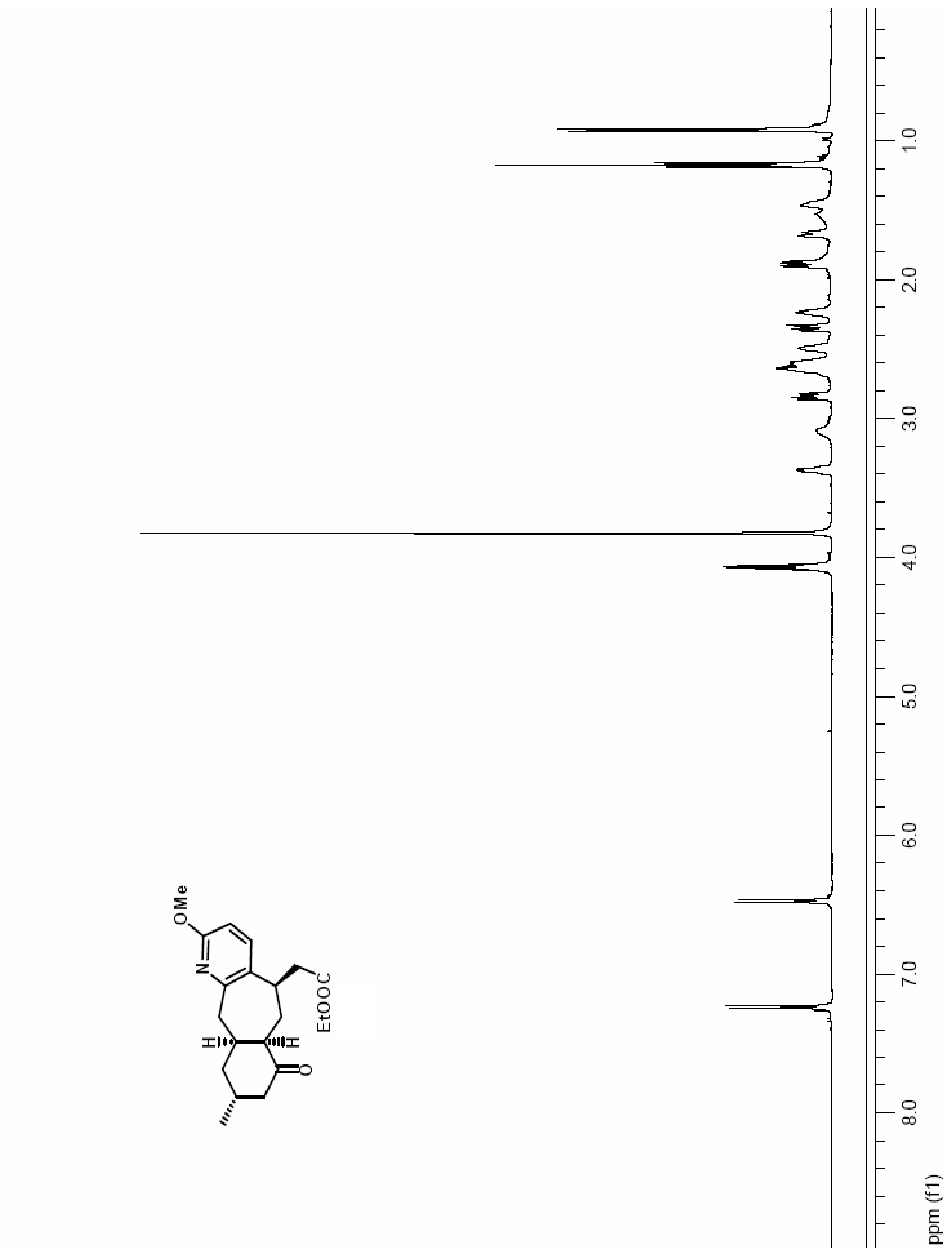

OMe
N
EtOOC
H
H
O
O
O_2N
50
100
150
ppm (f1)

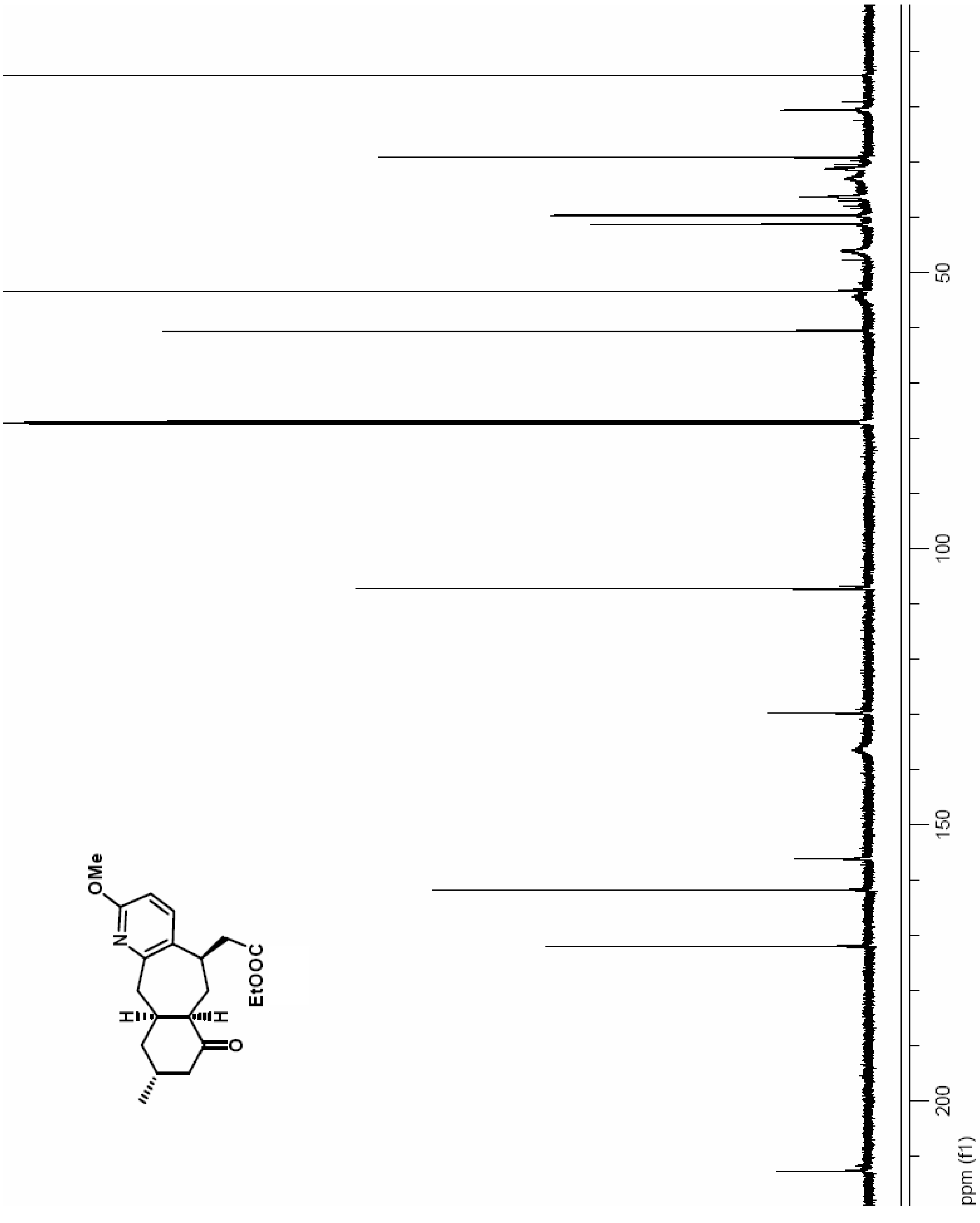

OMe
N
H
H
O
EtOOC
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (f1)


OMe
N
H
H
O
EtOOC
50
100
150
200
ppm (f1)

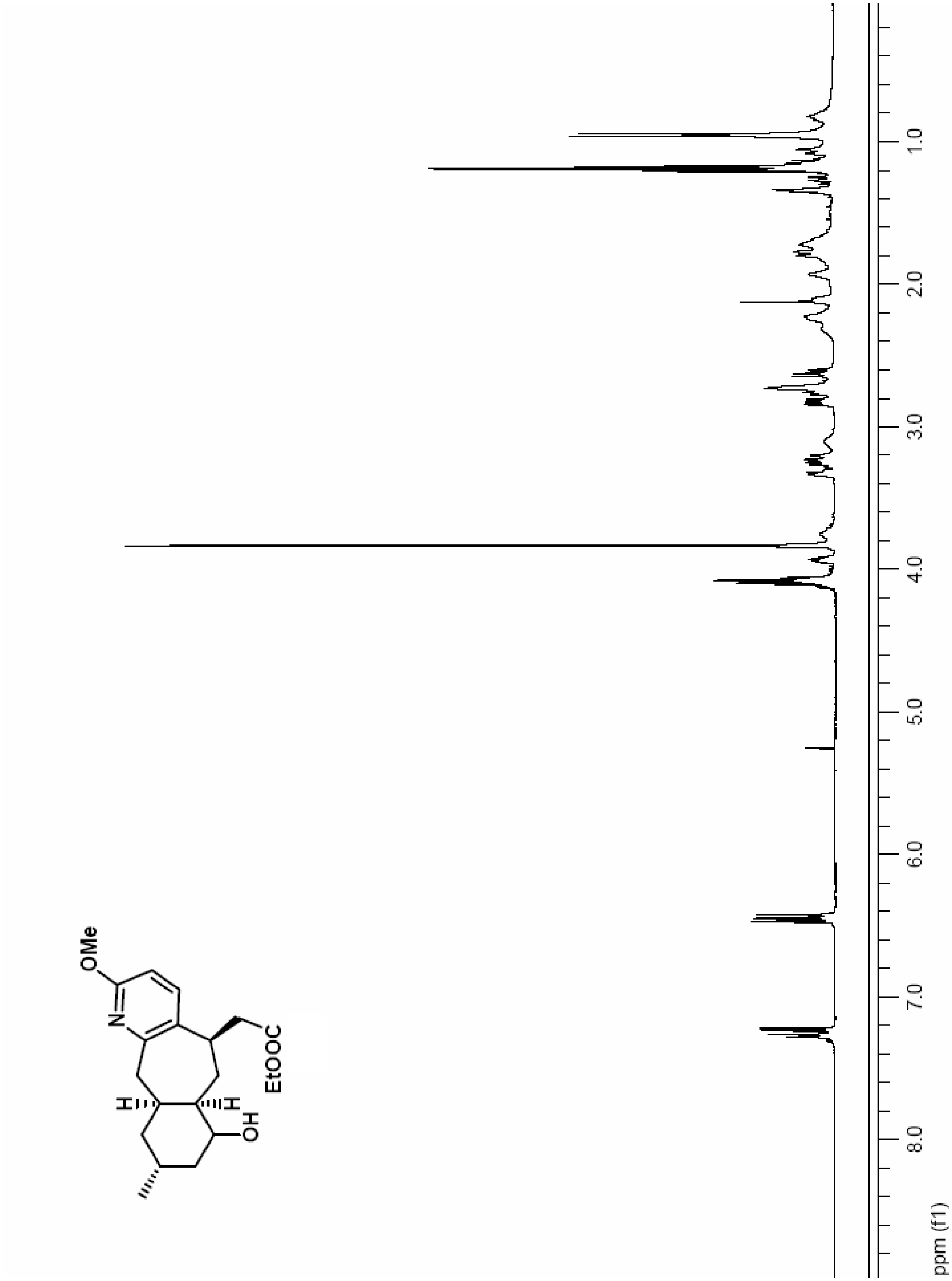

OMe
N
EtOOC
H
H
O
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (f1)

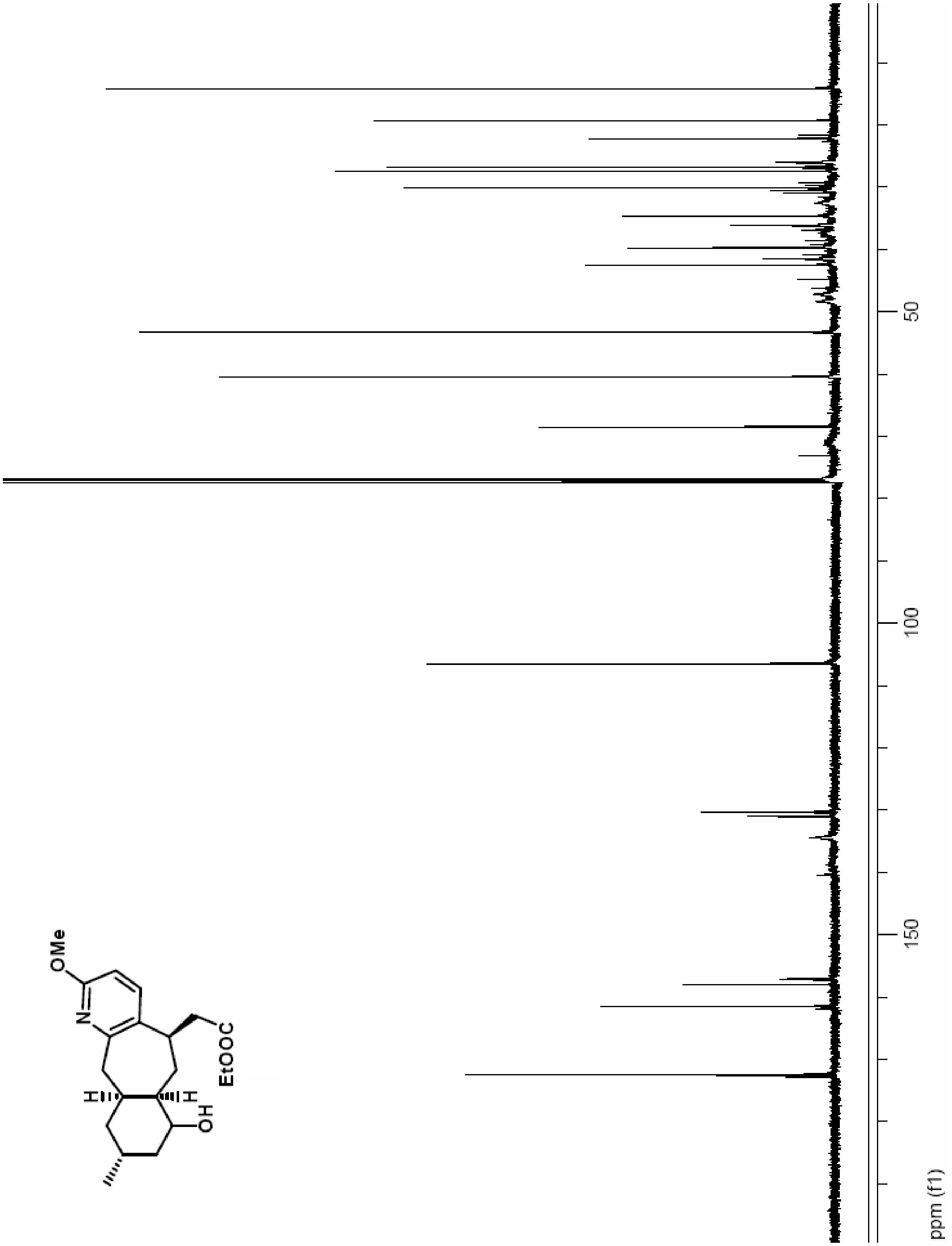

OMe
N
H
H
O
EtOOC
50
100
150
200
ppm (f1)

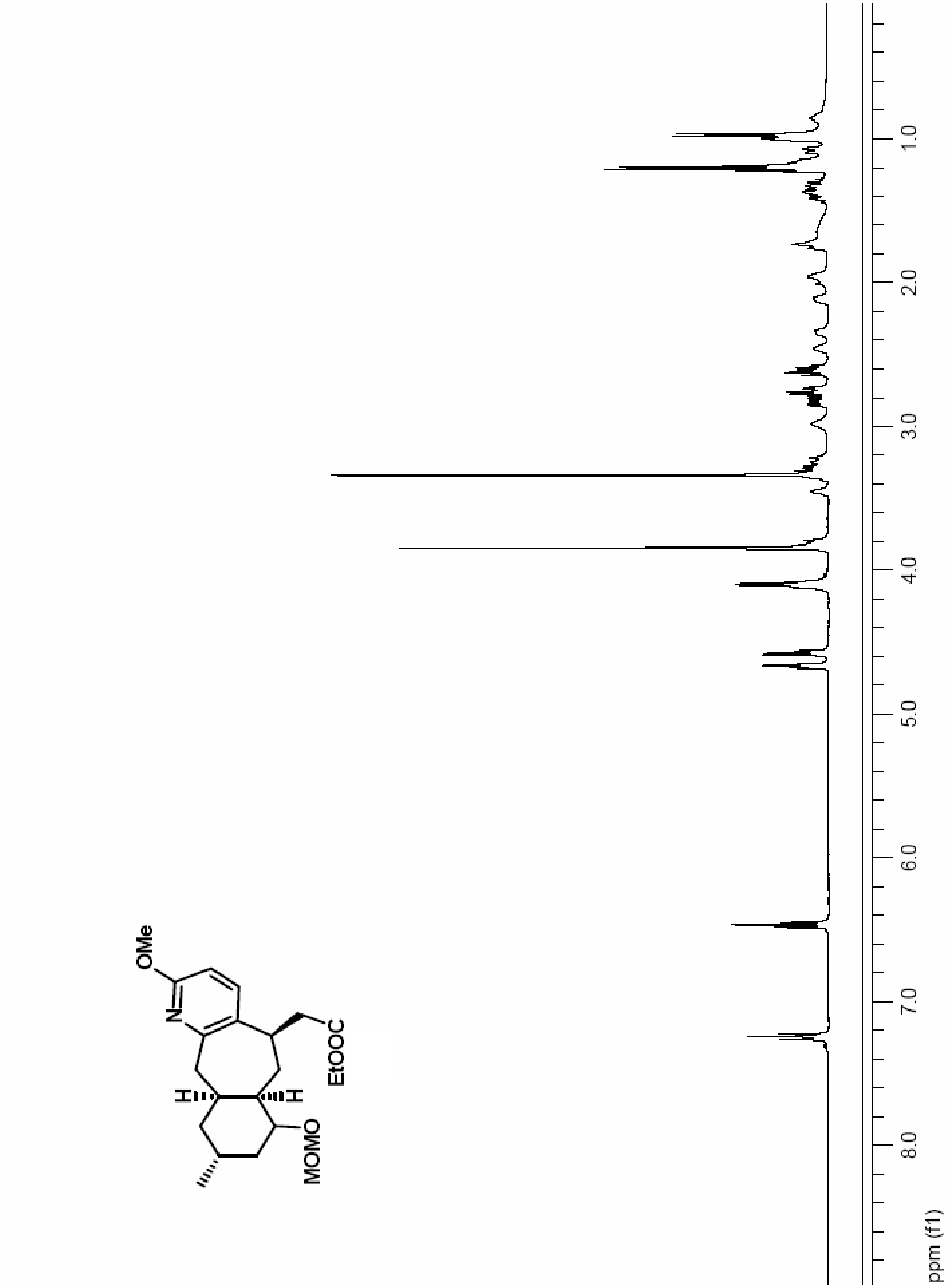

OMe
N
H
H
O
EtOOC
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (f1)

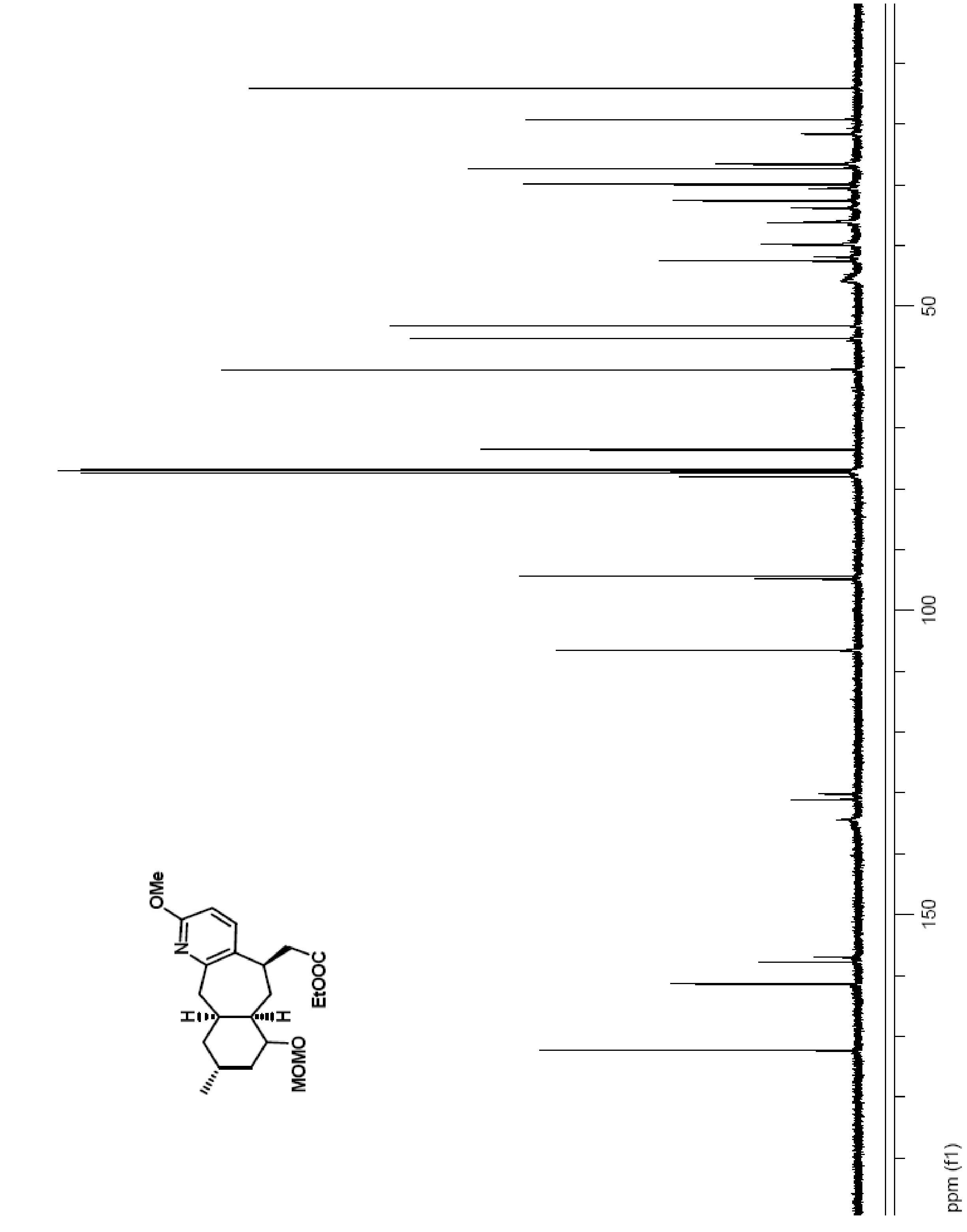


OMe
N
H
H
O
EtOOC
50
100
150
200
ppm (f1)

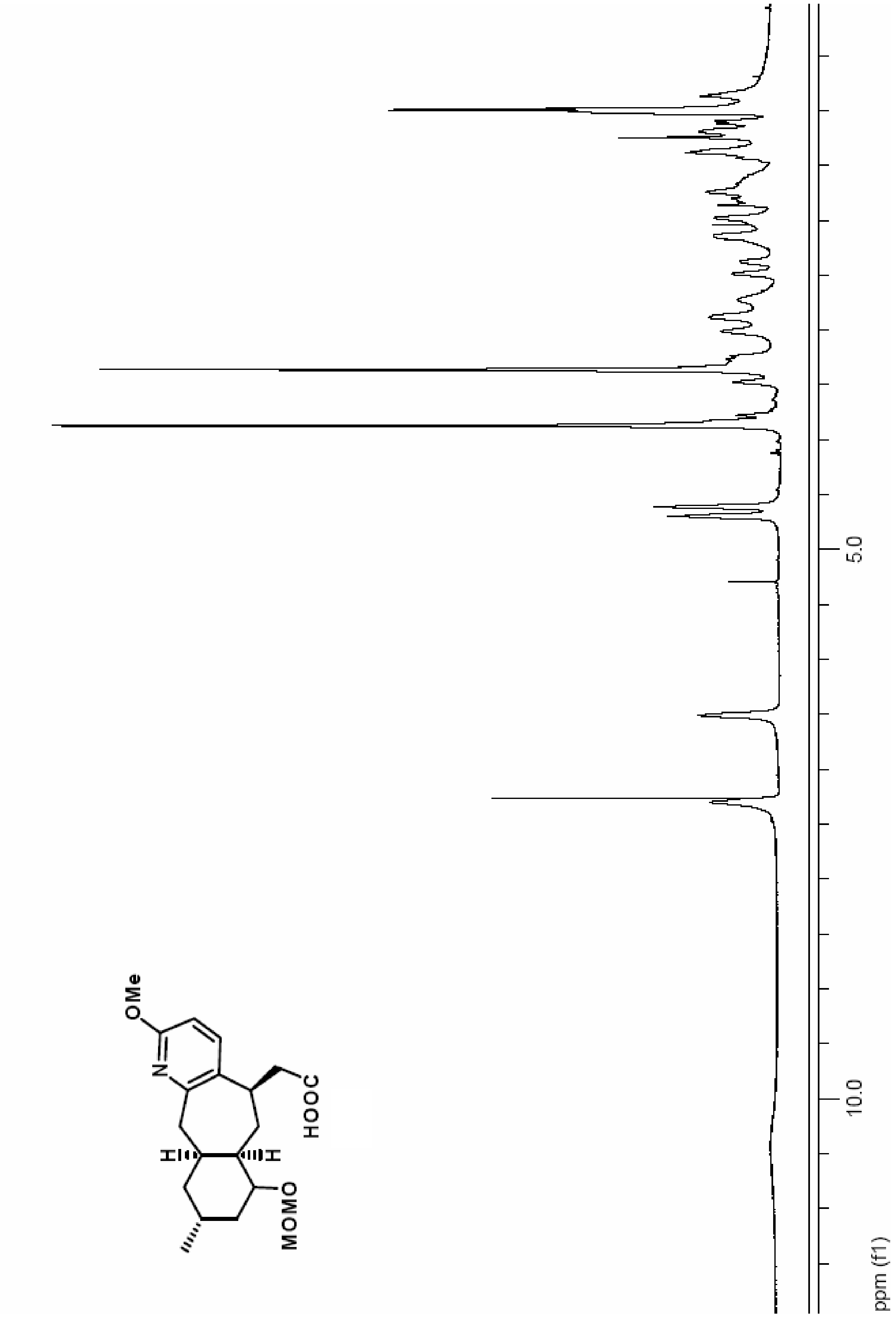

OMe
N
H
H
OH
EtOOC
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (f1)


OMe
N
EtOOC
OH
H
H
50
100
150
ppm (f1)


OMe
N
H
H
MOMO
EtOOC
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (f1)



OMe
N
H
H
MOMO
EtOOC
50
100
150
ppm (f1)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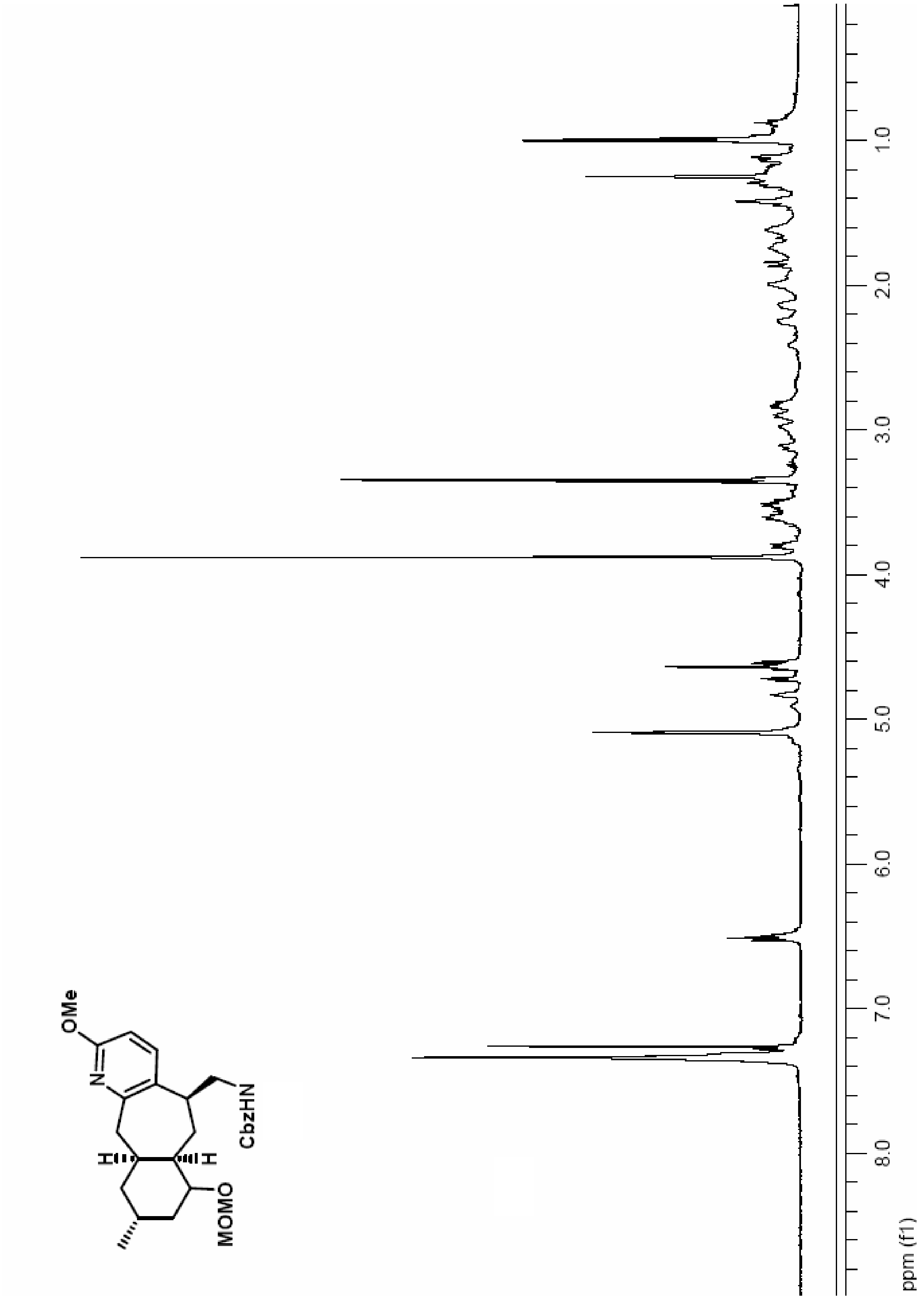
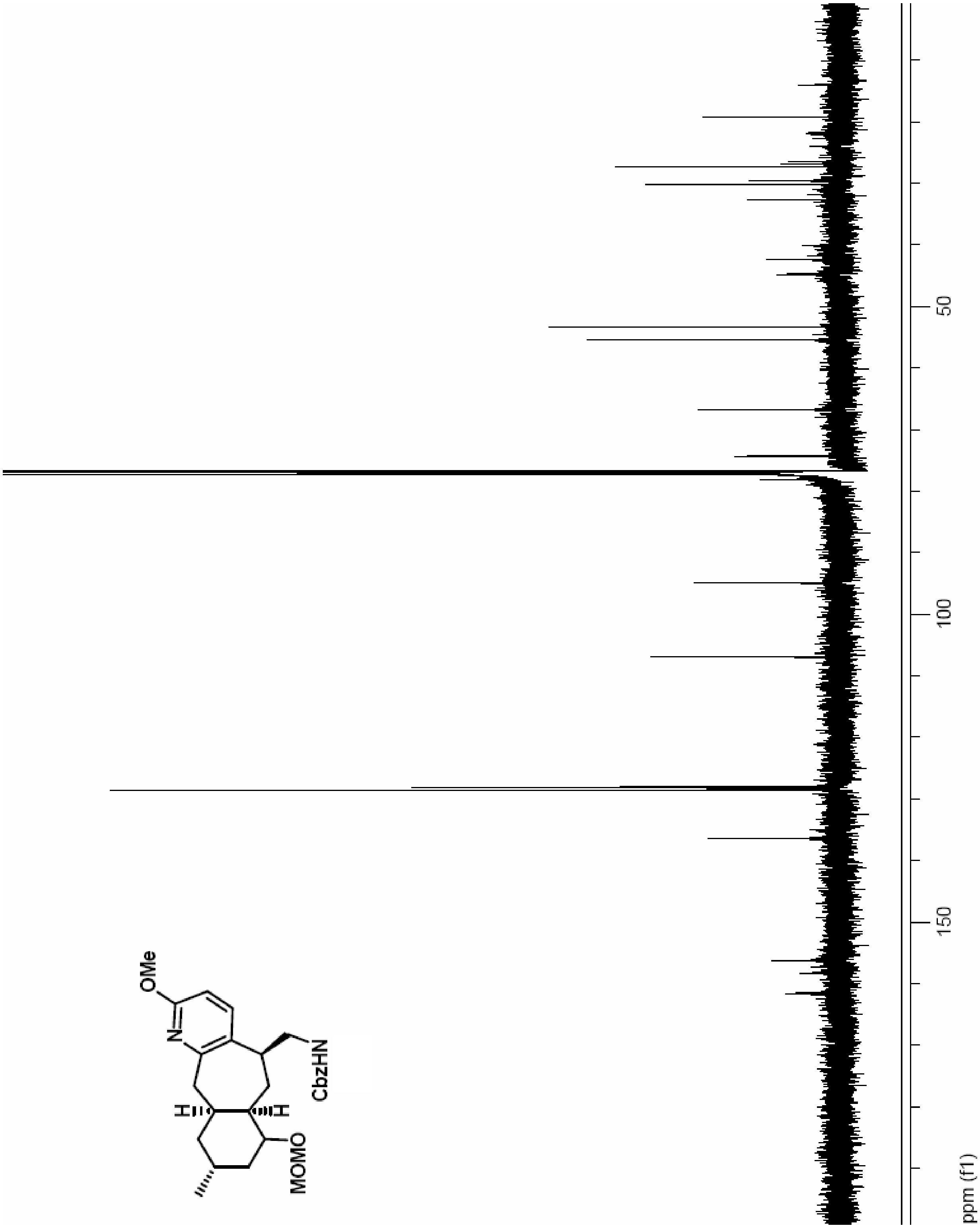
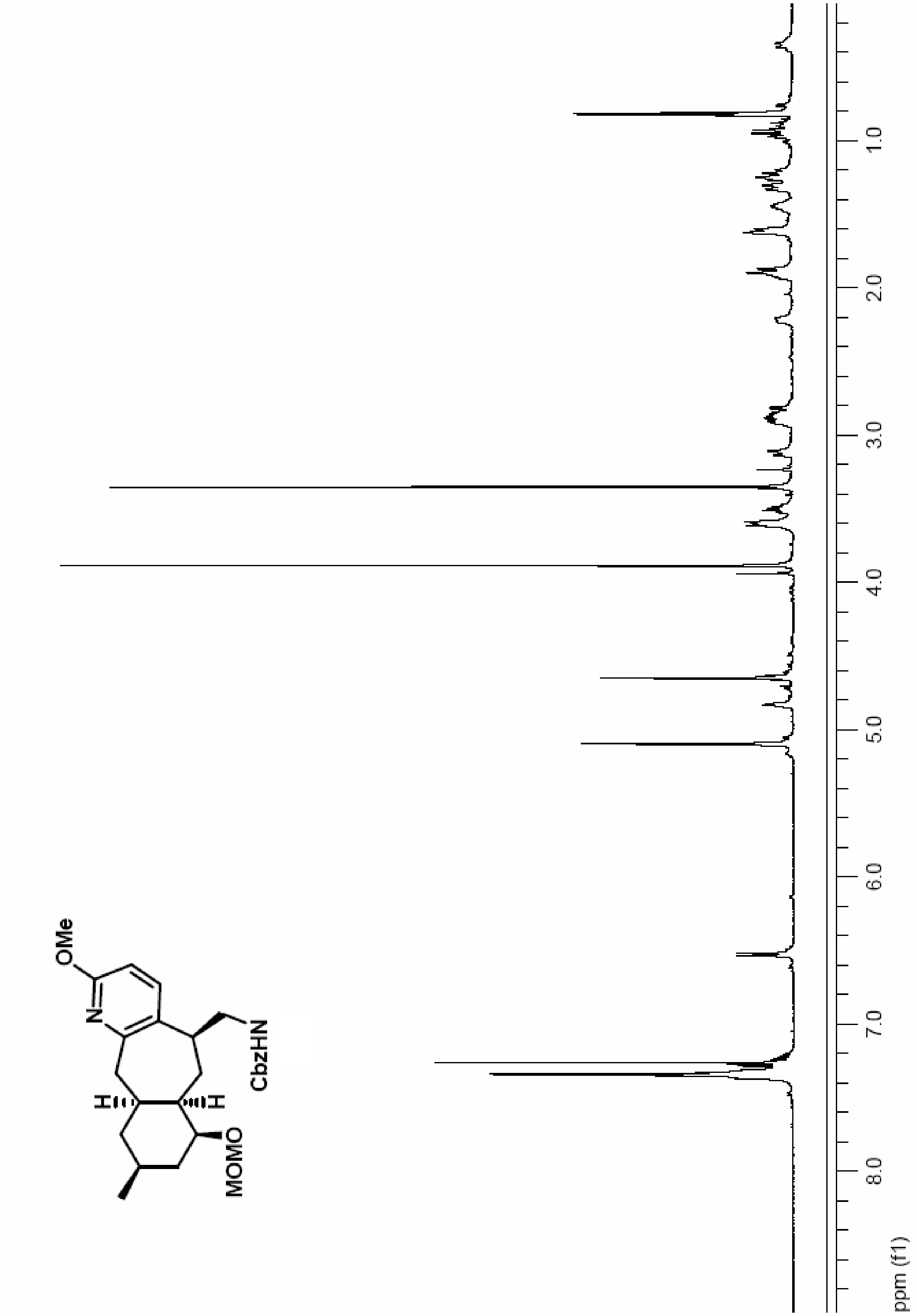
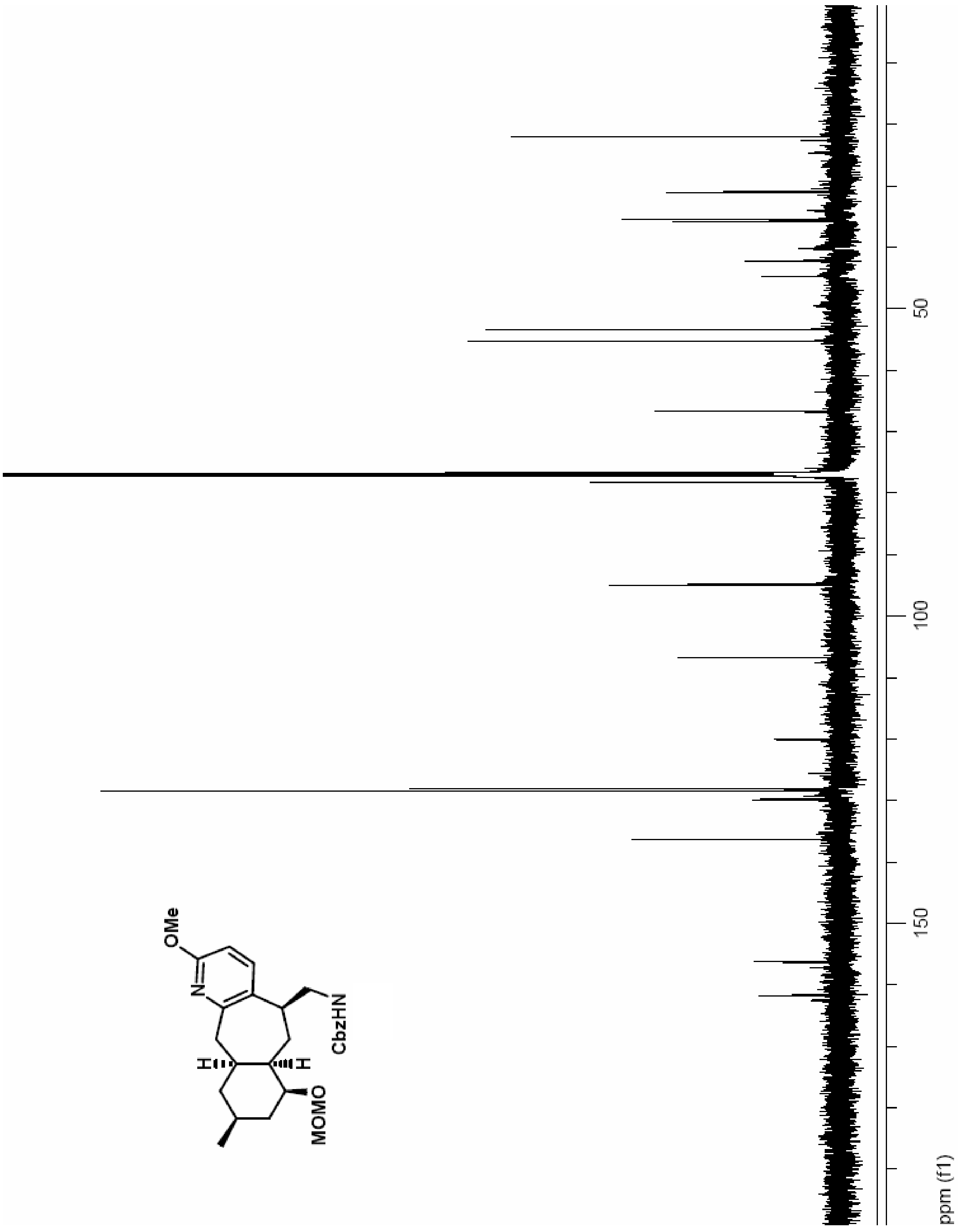
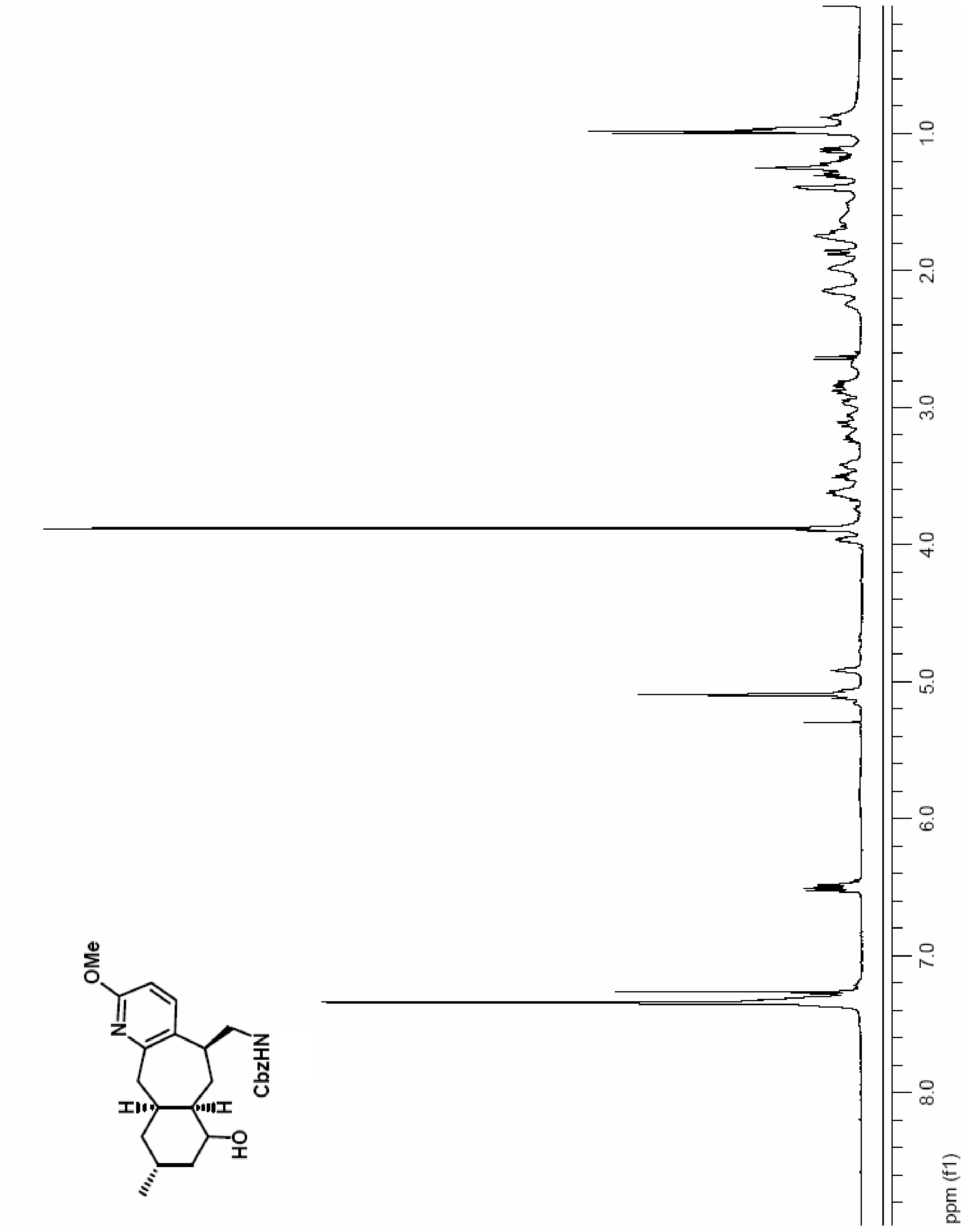
H
H
MOMO
HOOC
5.0
10.0
ppm (f1)

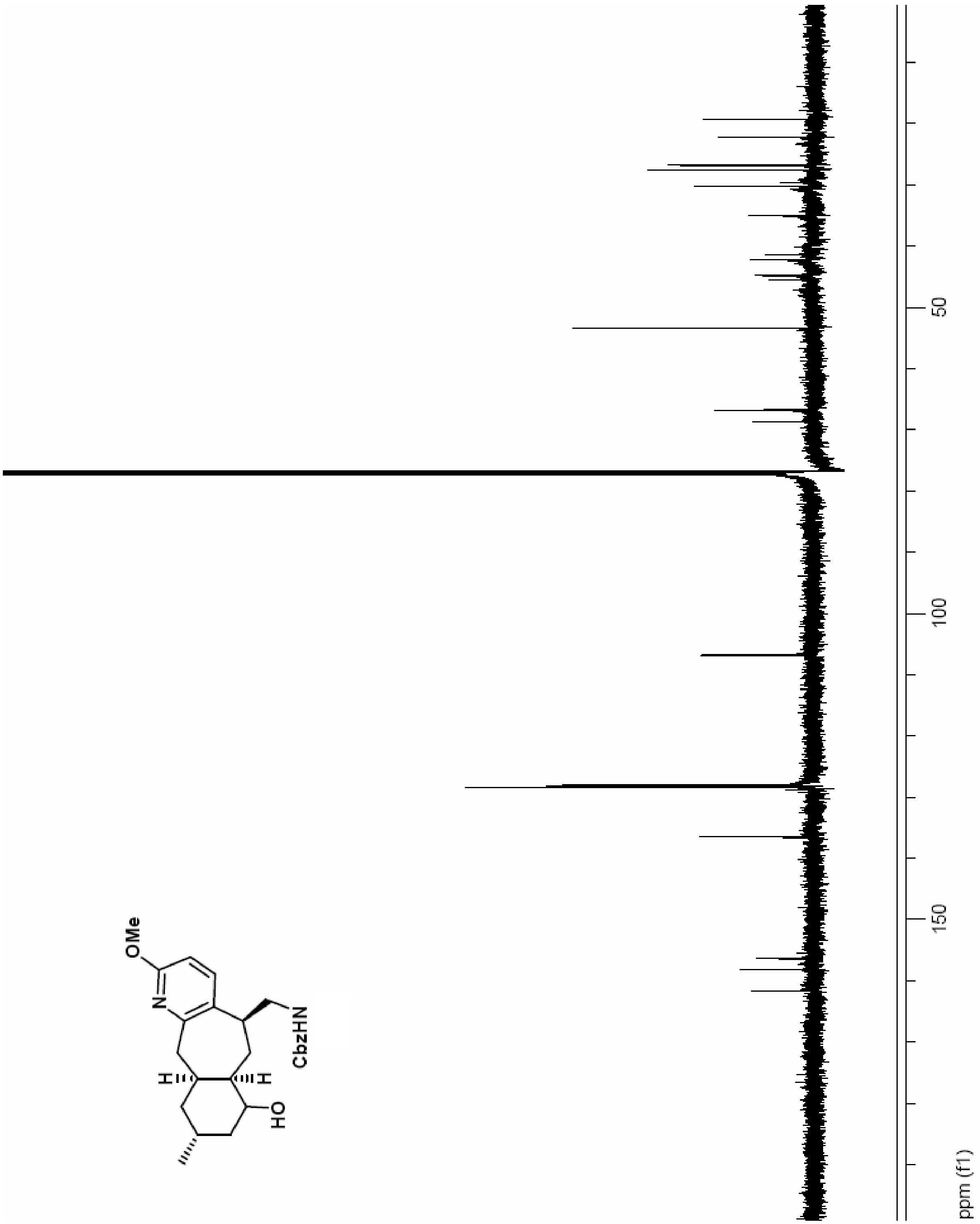

OMe
N
H
H
CbzHN
MOMO
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (f1)


OMe
N
H
H
MOMO
CbzHN
50
100
150
ppm (f1)


OMe
N
H
H
MOMO
CbzHN
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (f1)


OMe
N
H
H
MOMO
CbzHN
ppm (f1)
150
100
50


OMe
N
H
H
HO
CbzHN
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (f1)


OMe
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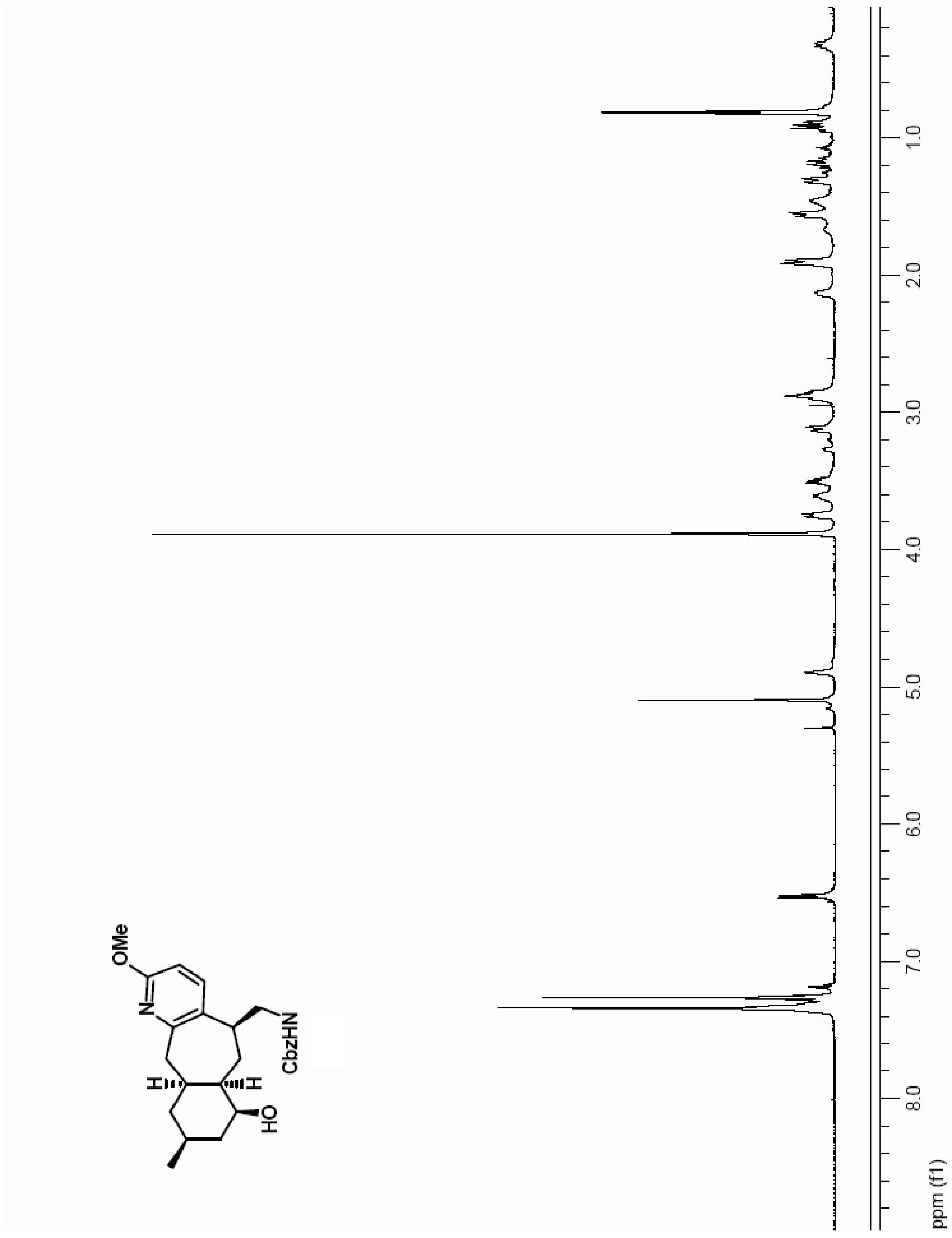
H
H
HO
CbzHN
50
100
150
ppm (f1)


OMe
N
H
H
HO
CbzHN
8.0
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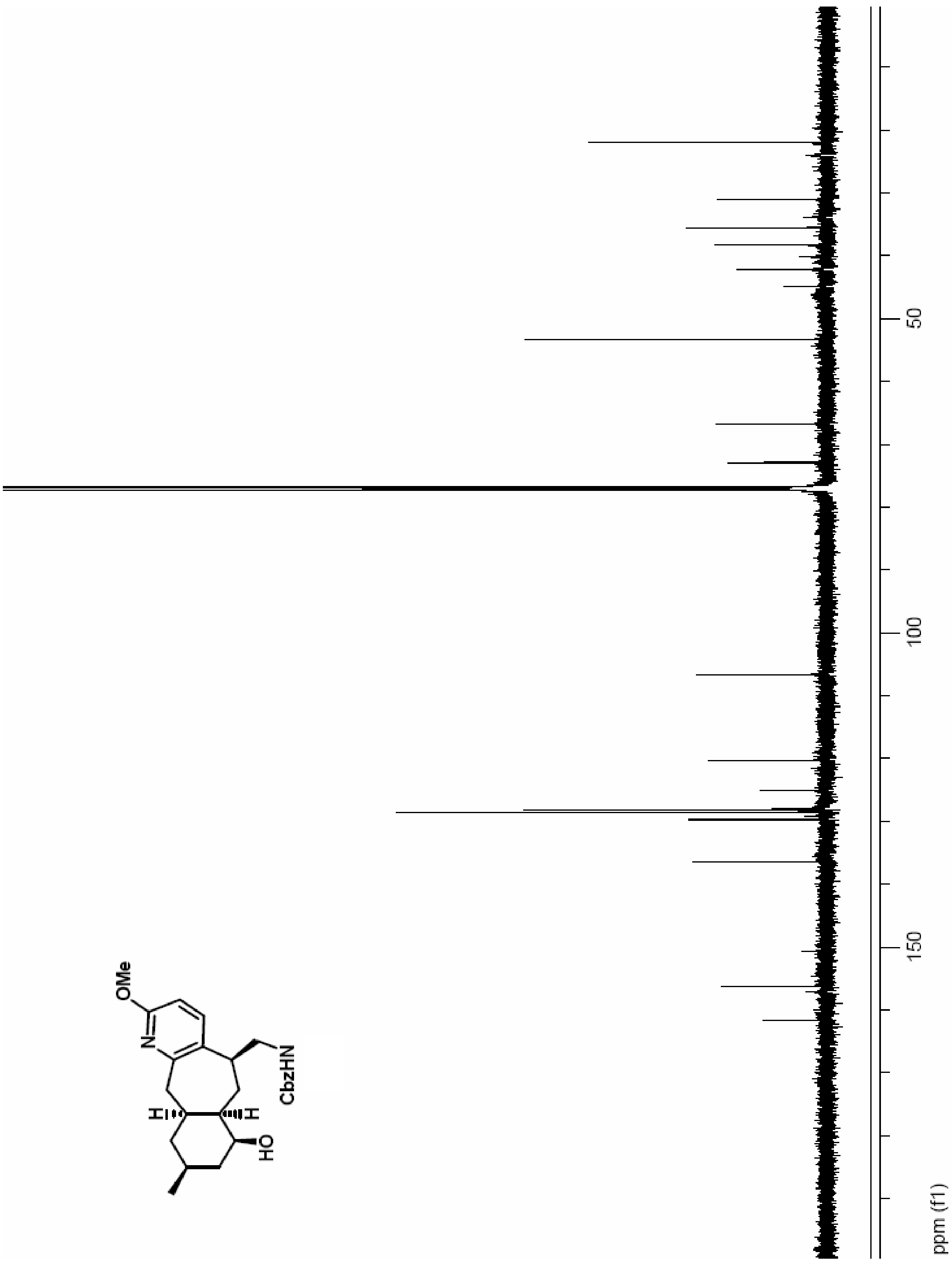
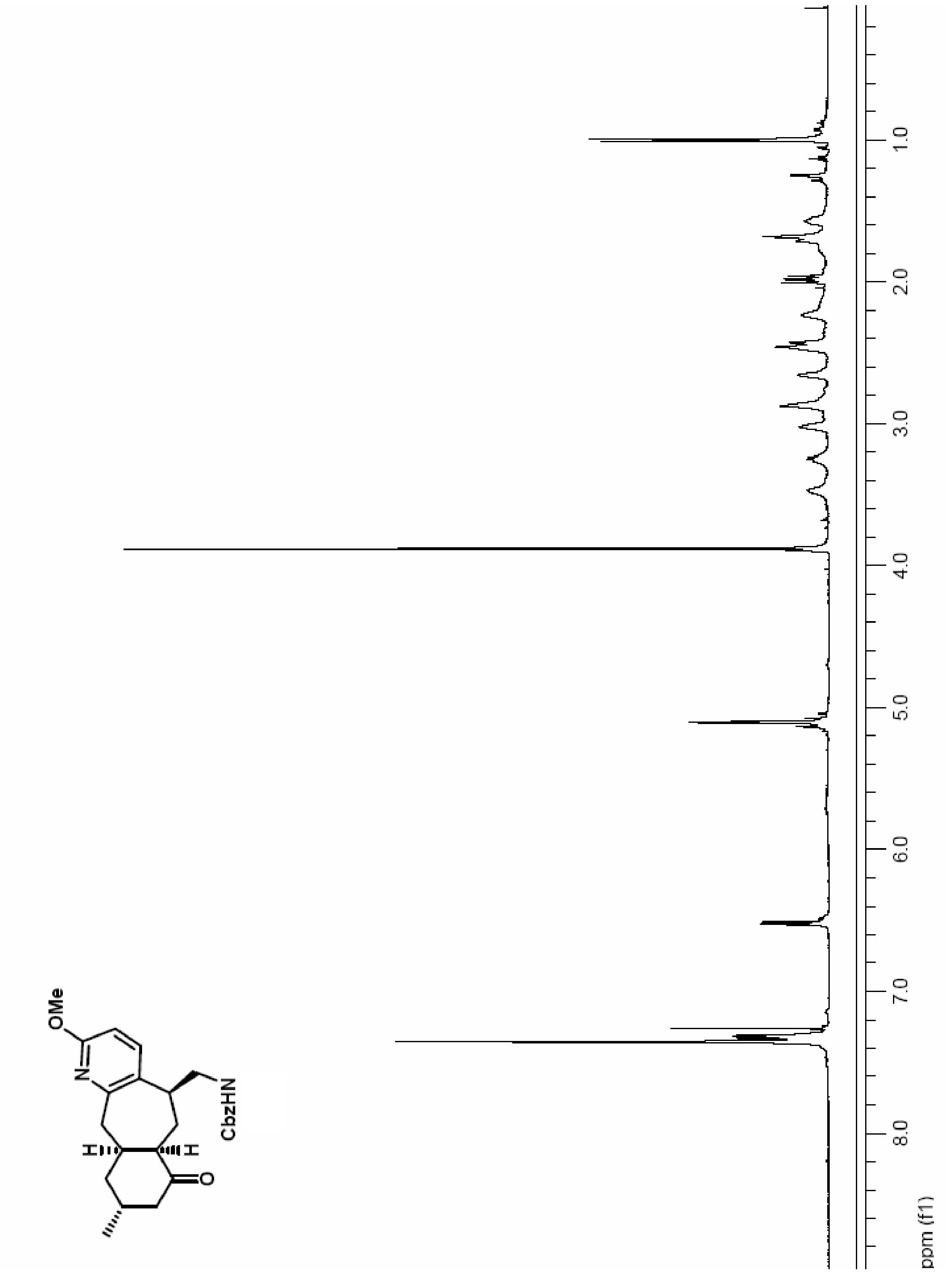
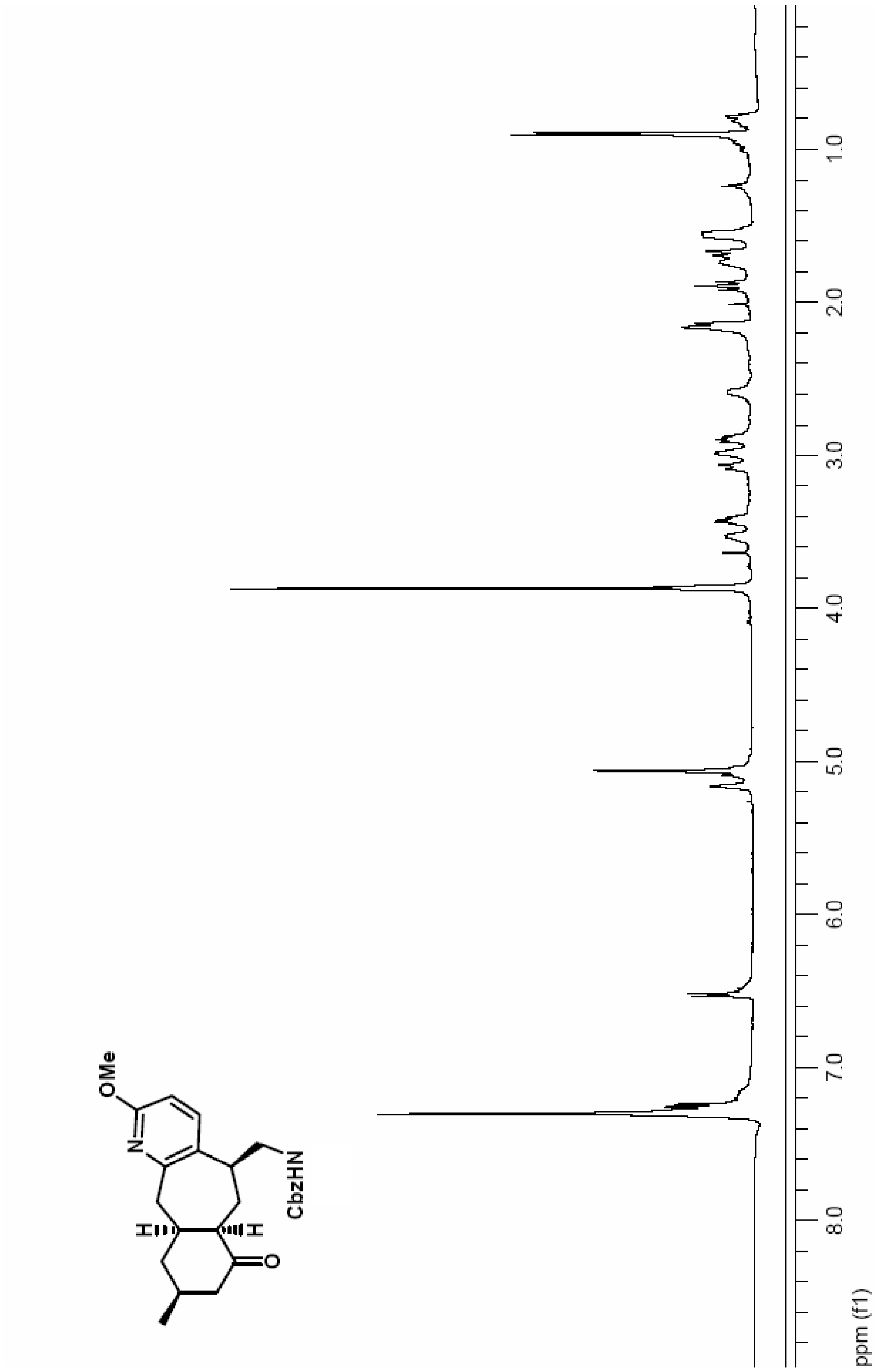
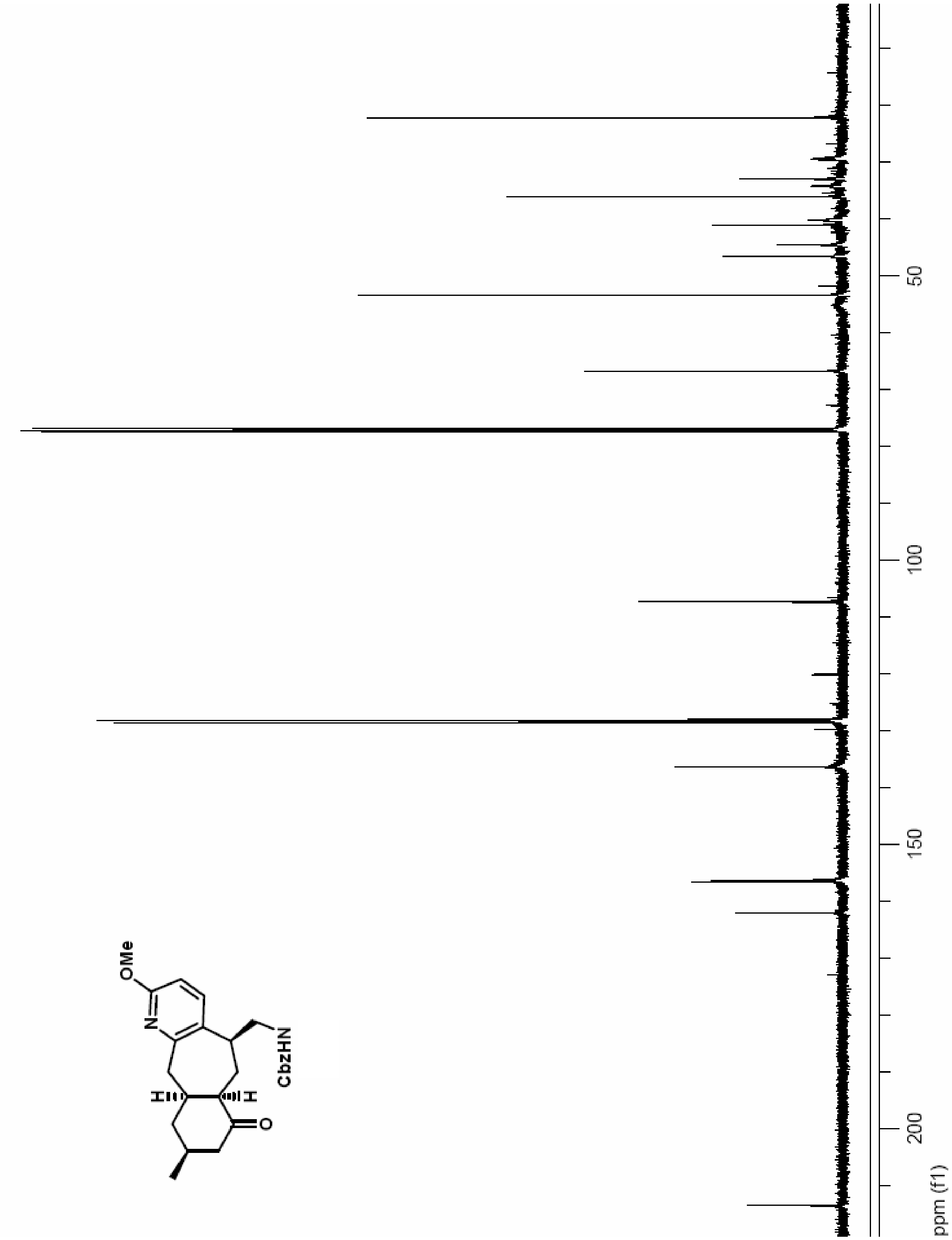
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)


OMe
N
CbzHN
H
H
HO
50
100
150
ppm (f1)


OMe
N
CbzHN
H
H
O
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (f1)


OMe
N
H
H
O
CbzHN
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)


OMe
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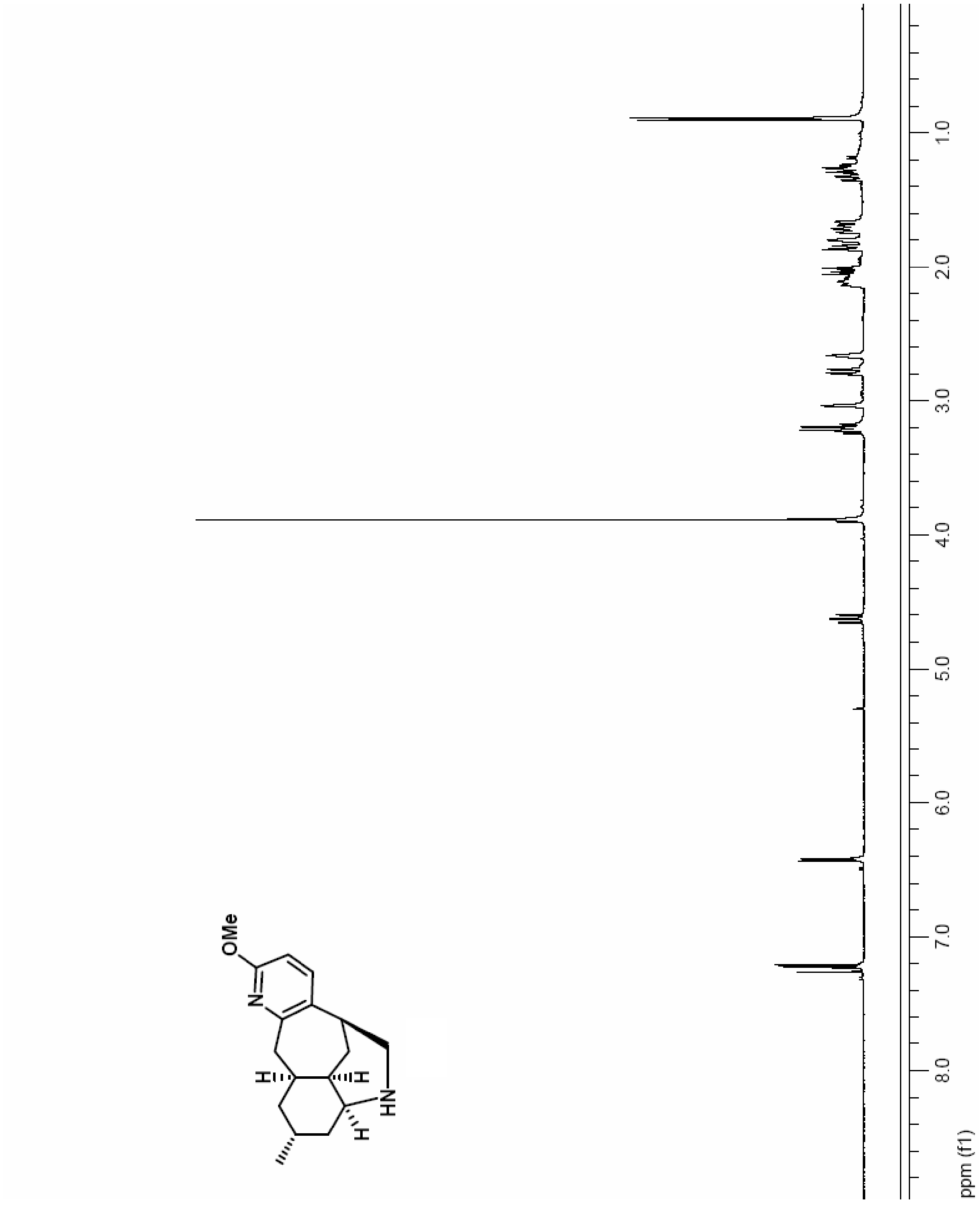
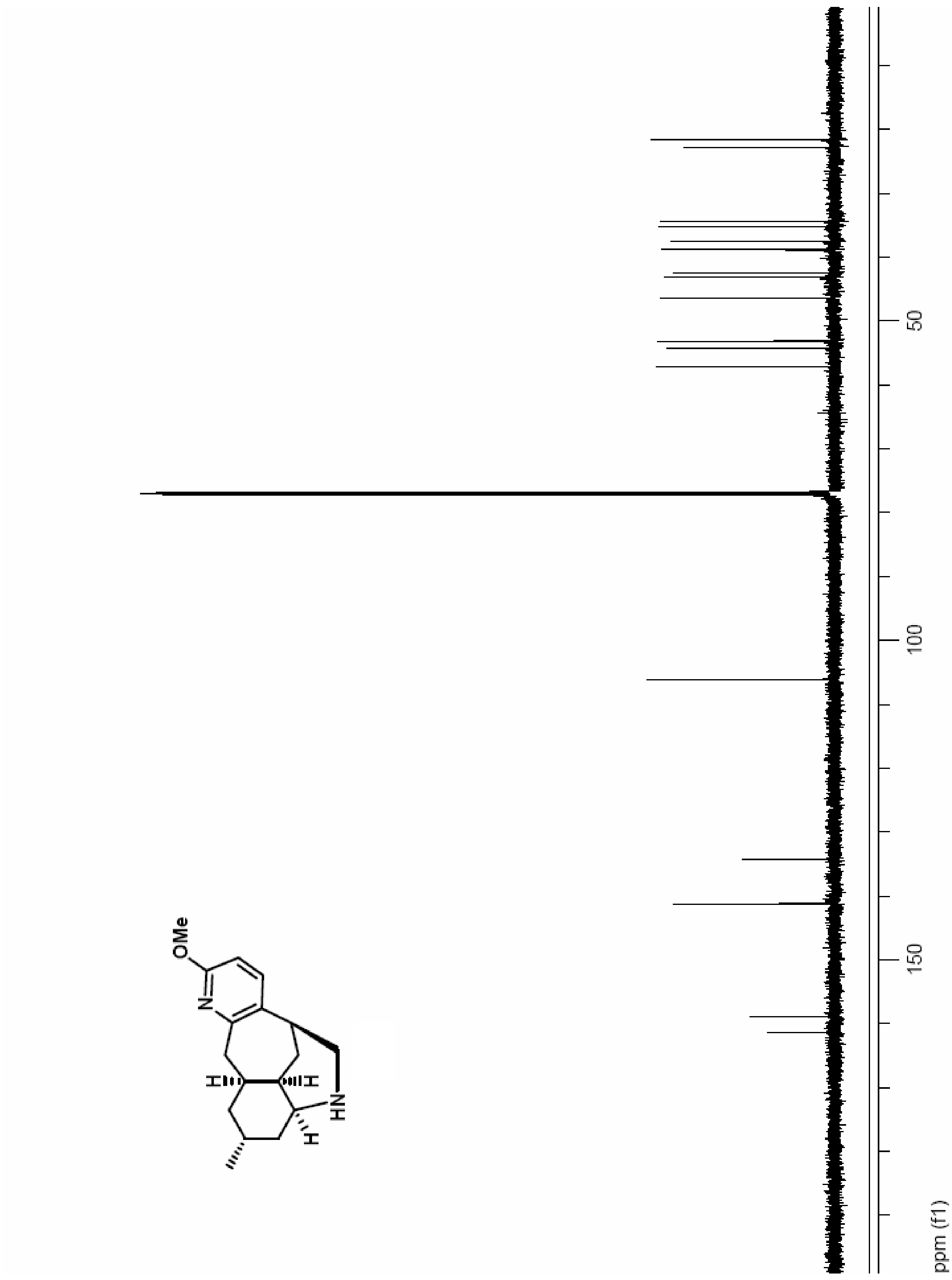
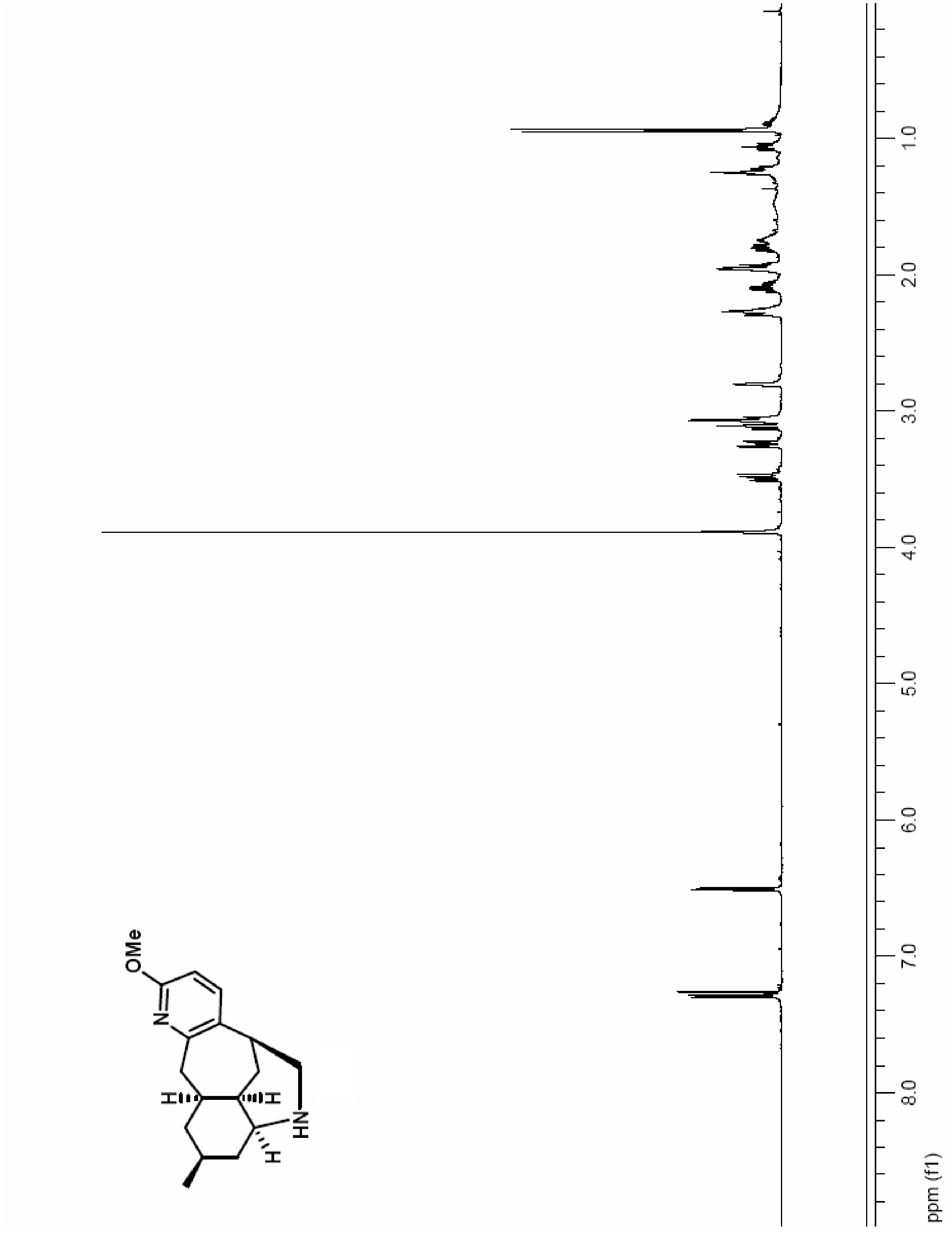
H
H
O
CbzHN
50
100
150
200
ppm (f1)


OMe
N
H
H
HN
H
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (f1)


OMe
N
H
H
H
HN
50
100
150
ppm (f1)


OMe
N
H
H
H
HN
1.0
2.0
3.0
4.0
5.0
6.0
7.0
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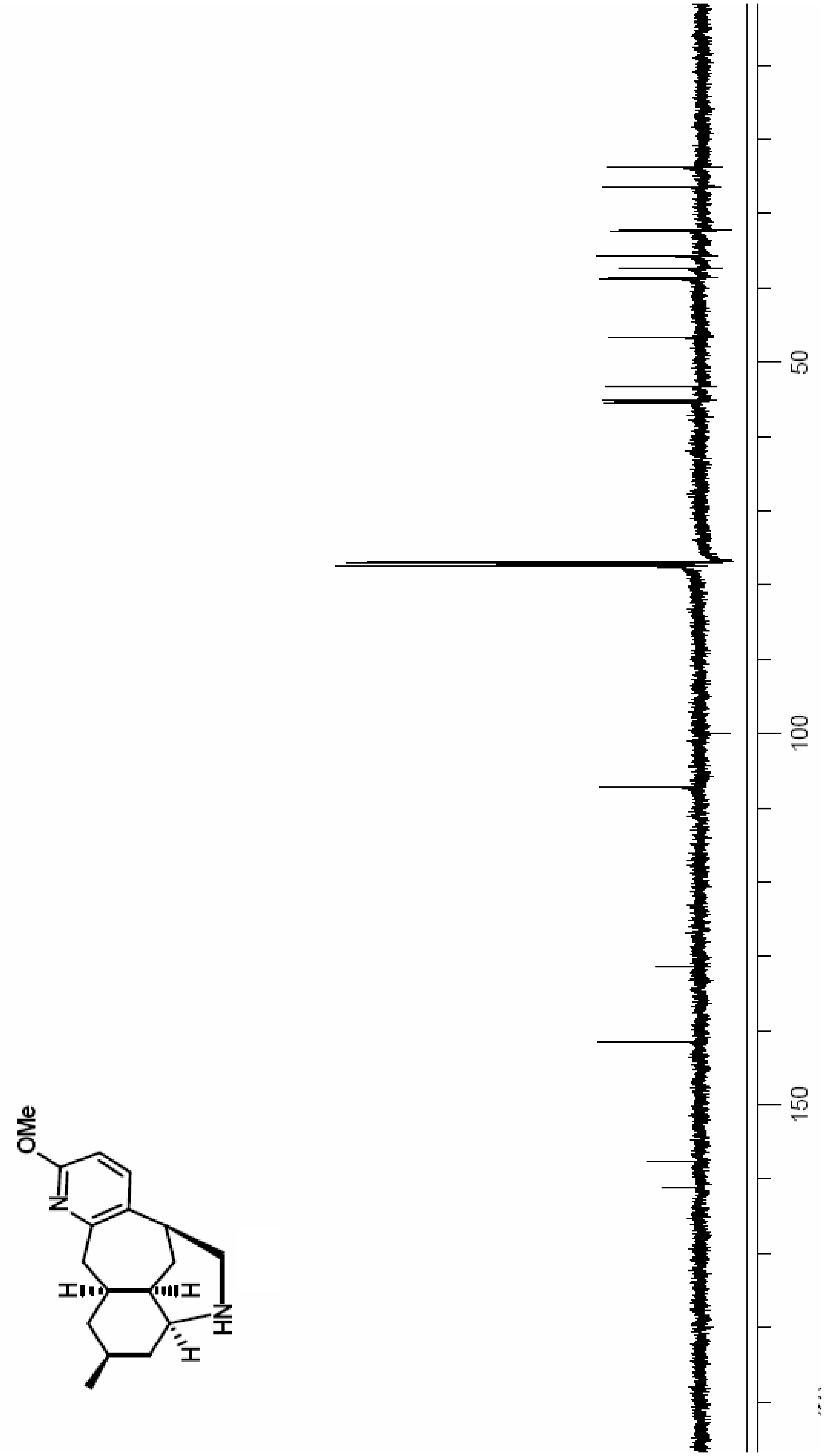
ppm (f1)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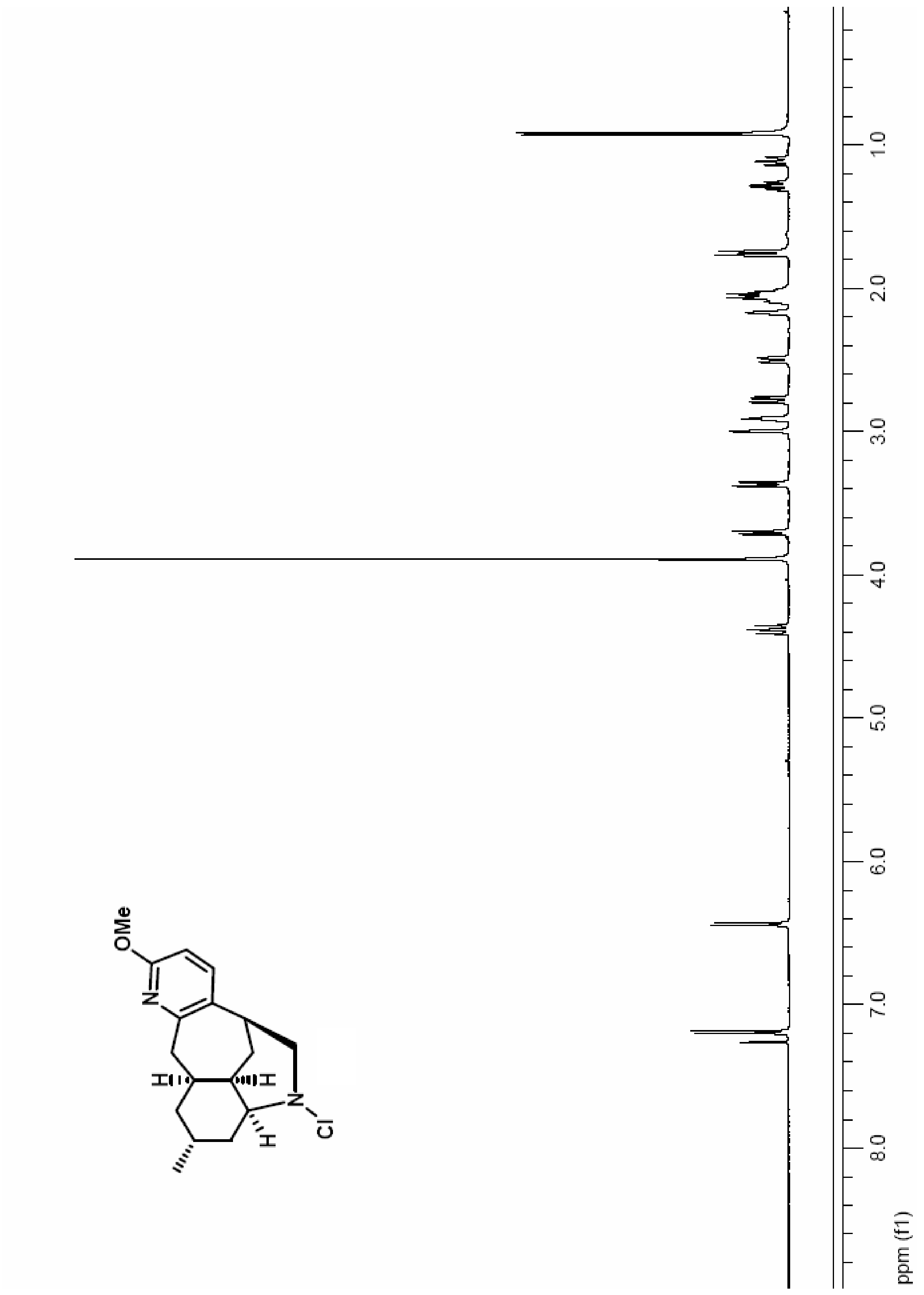
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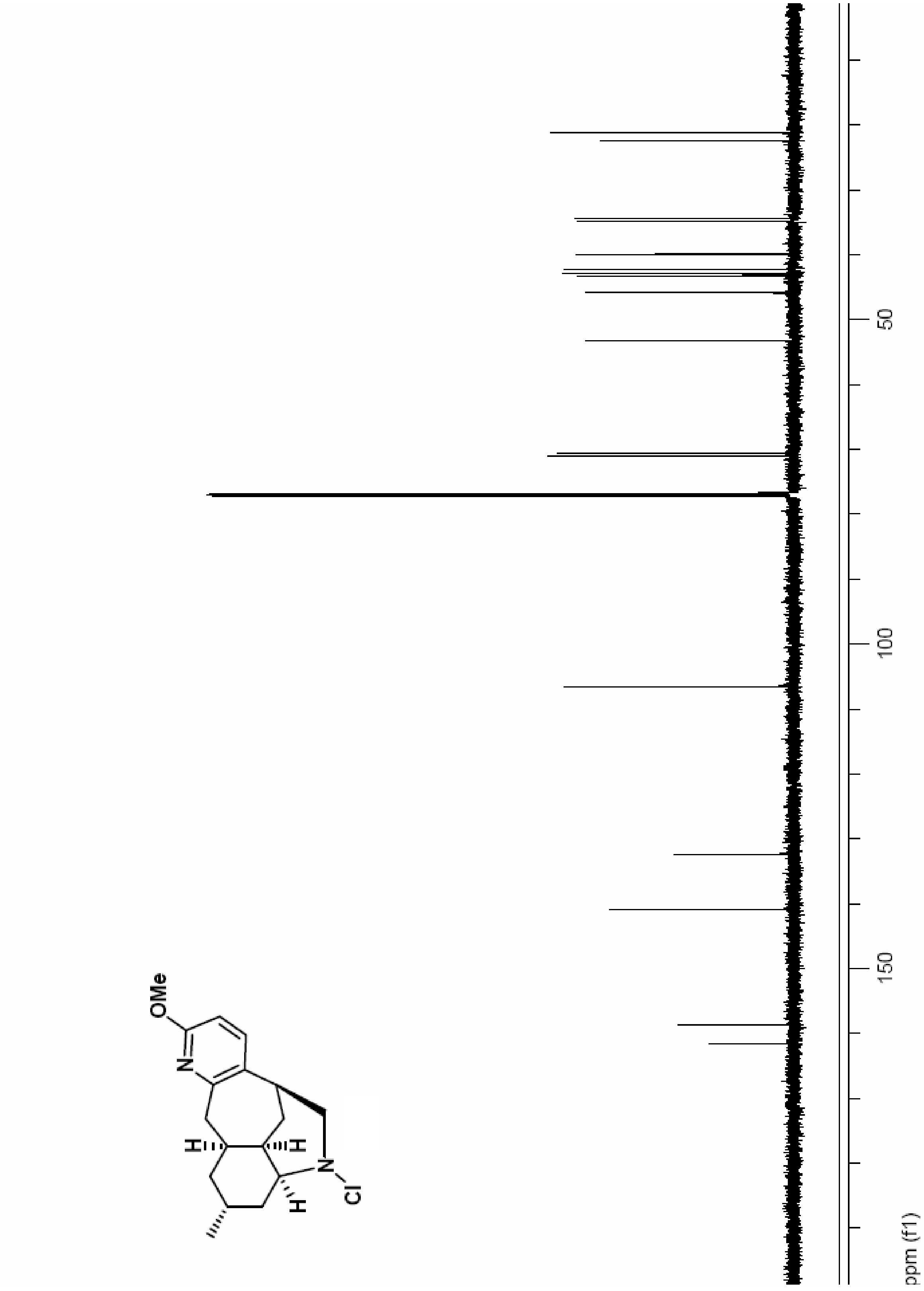
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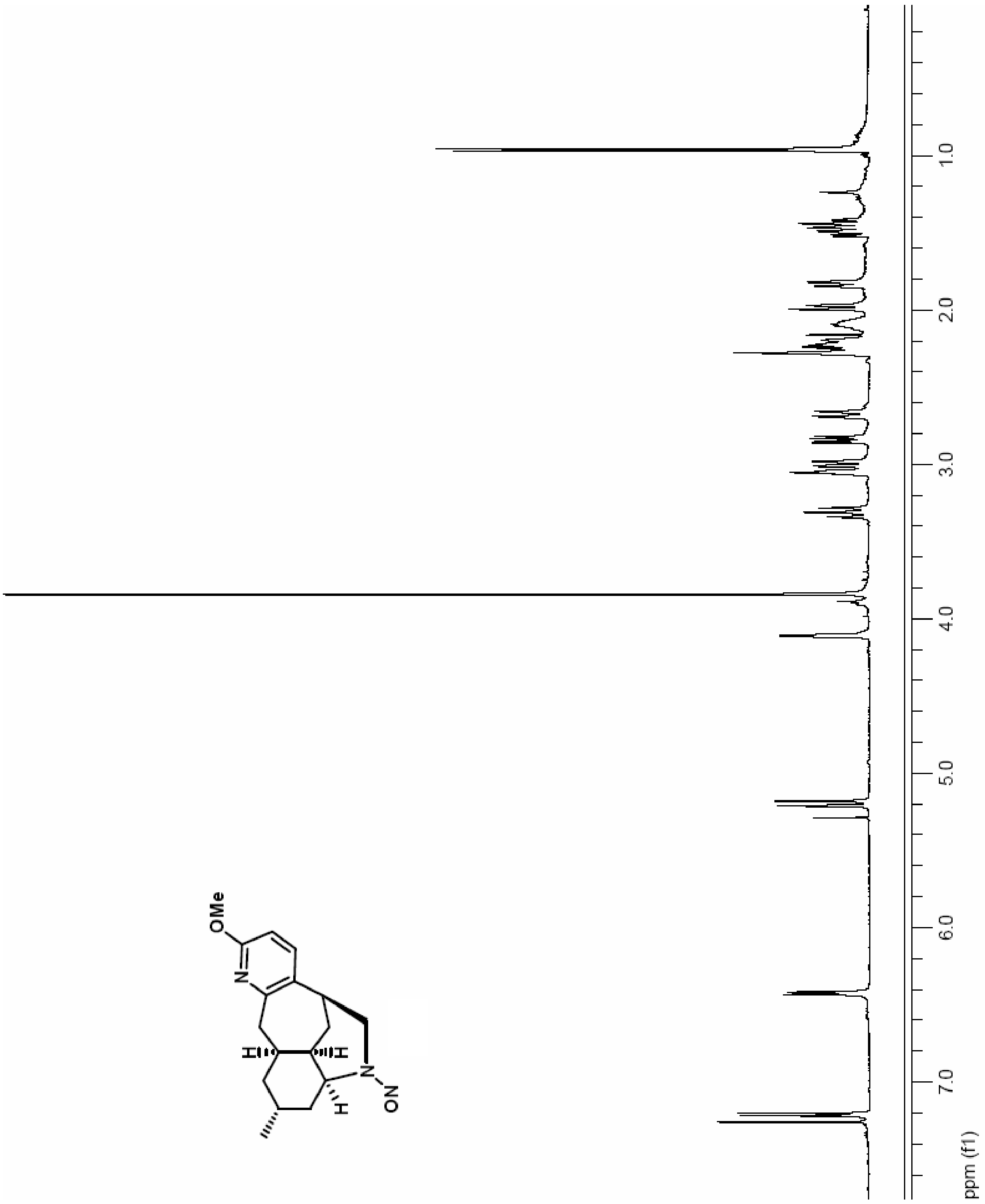
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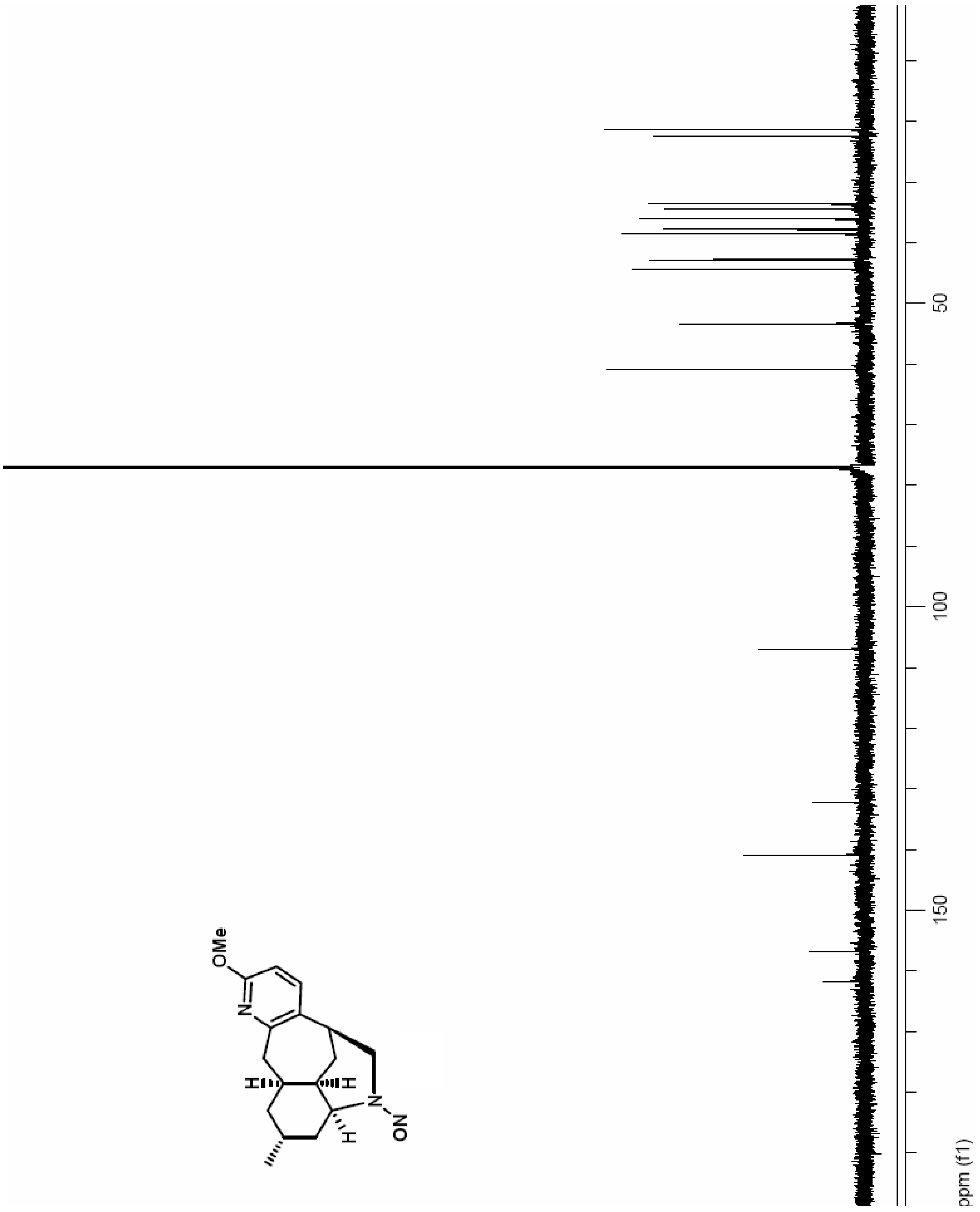
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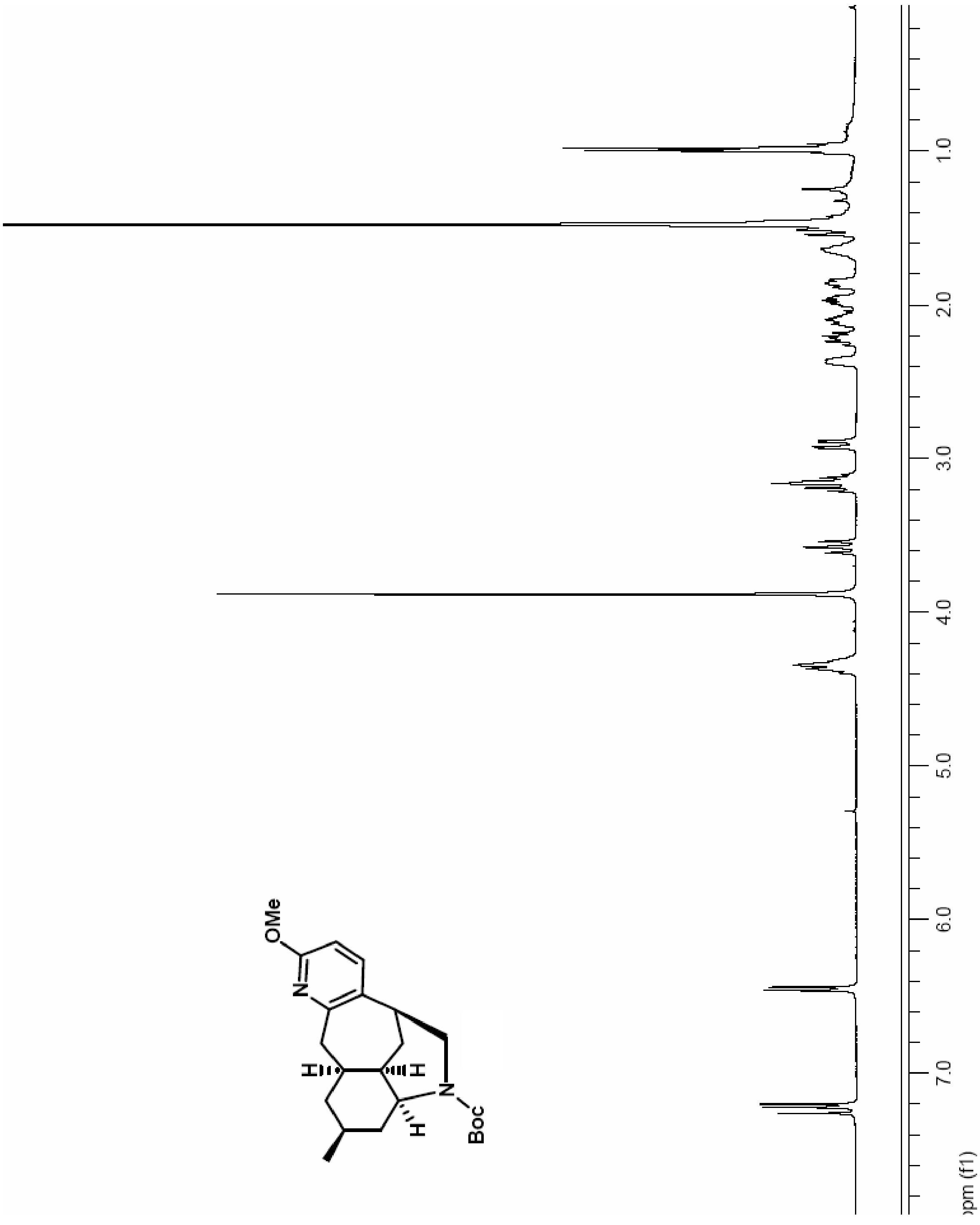
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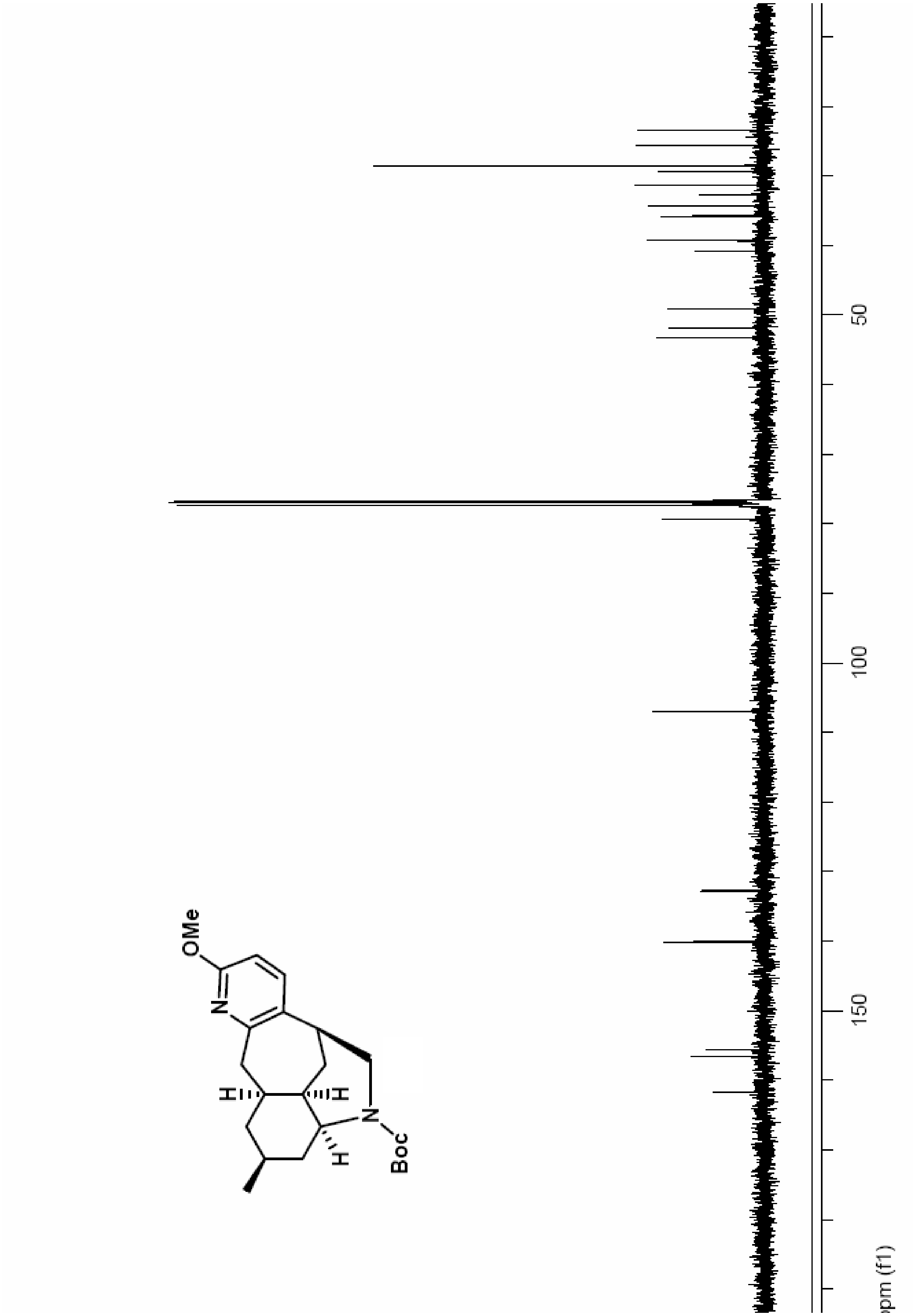
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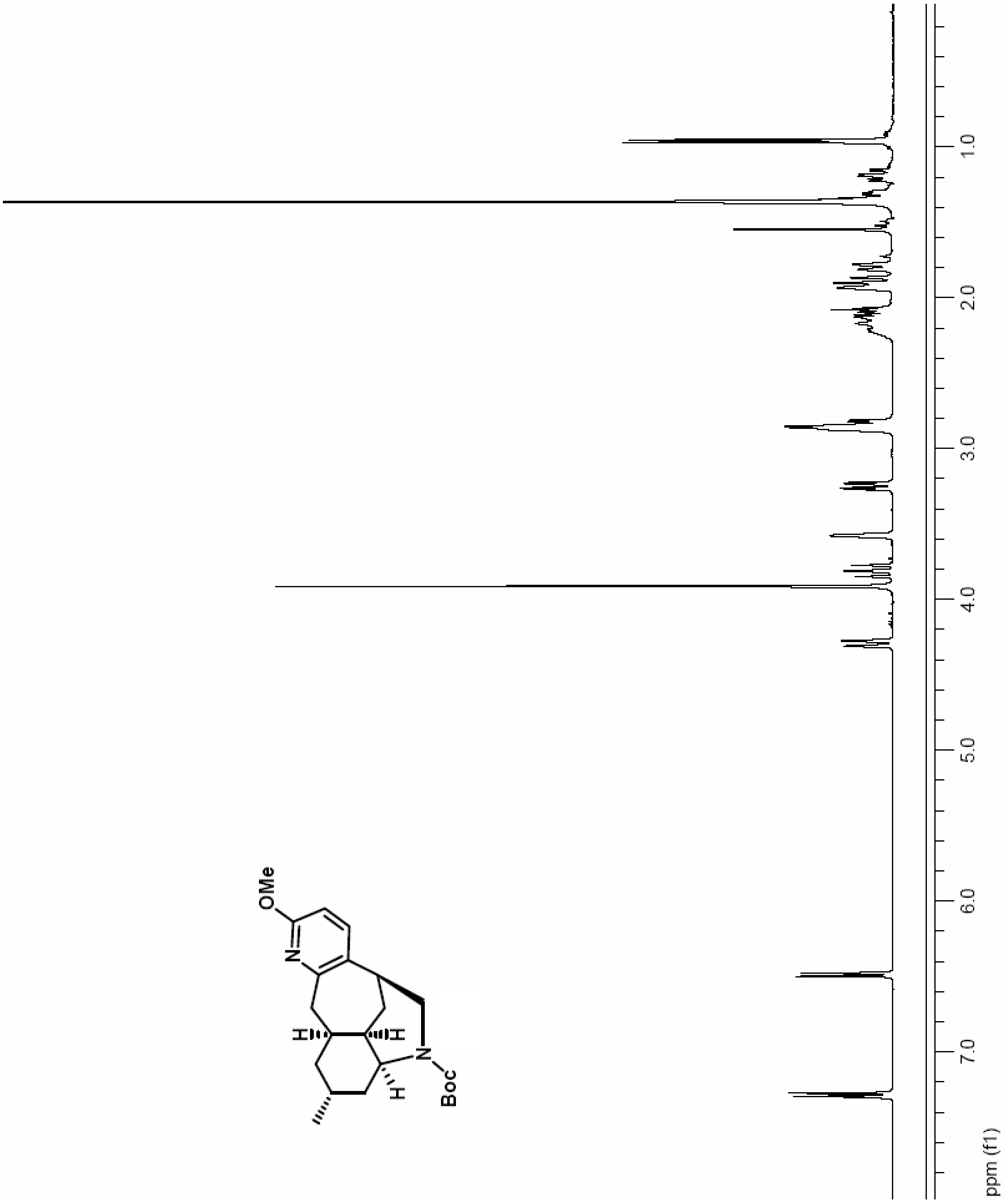
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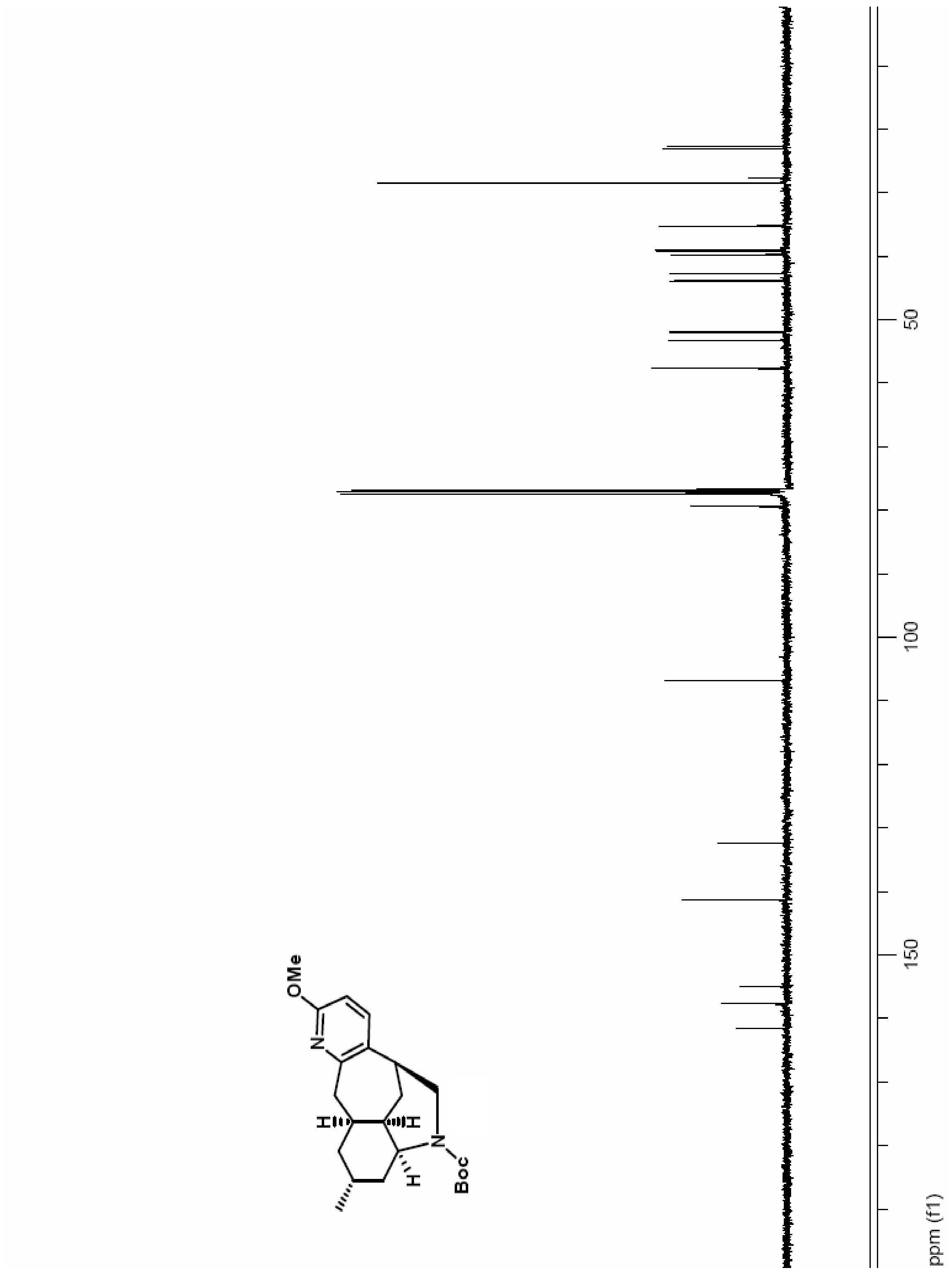
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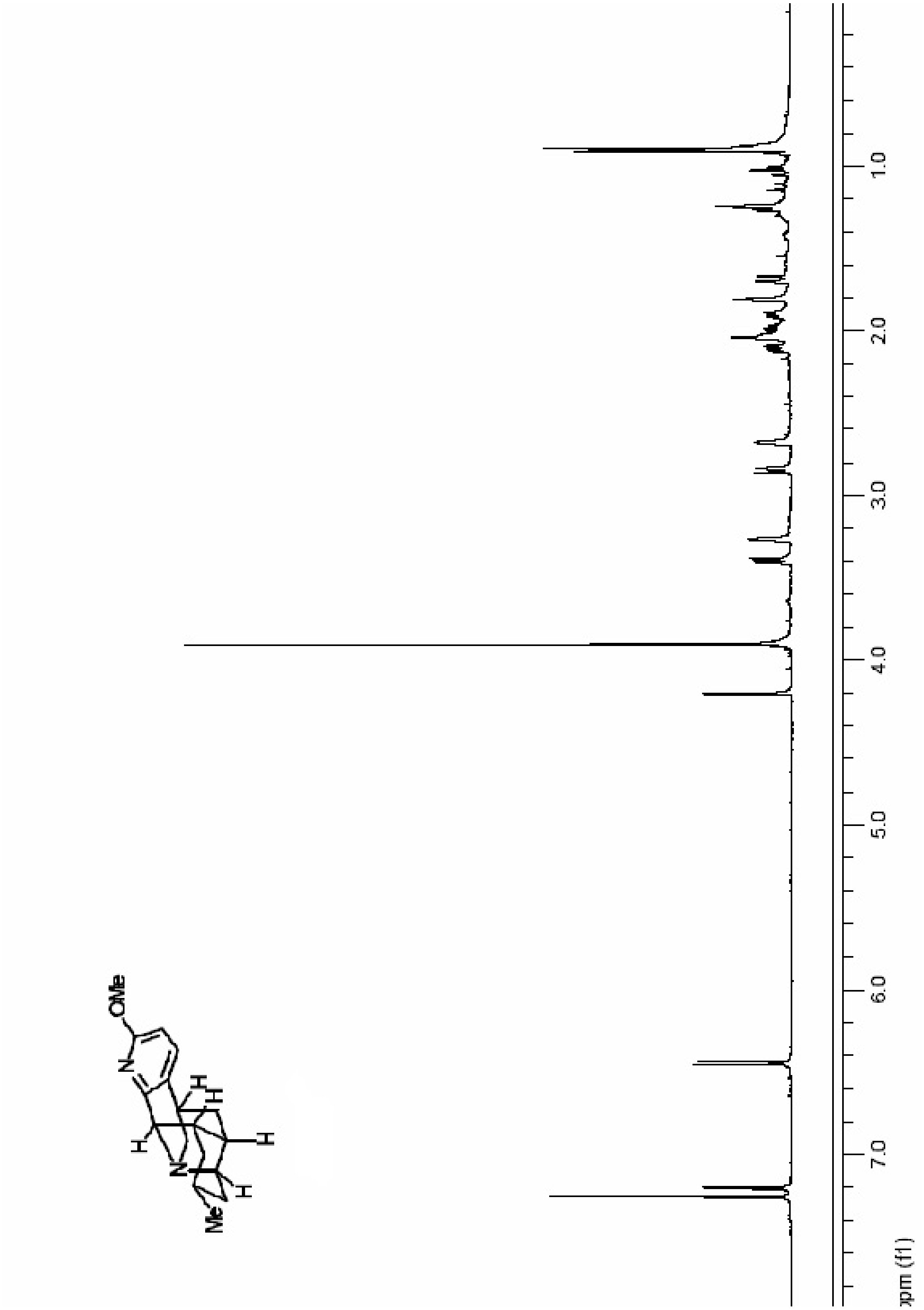
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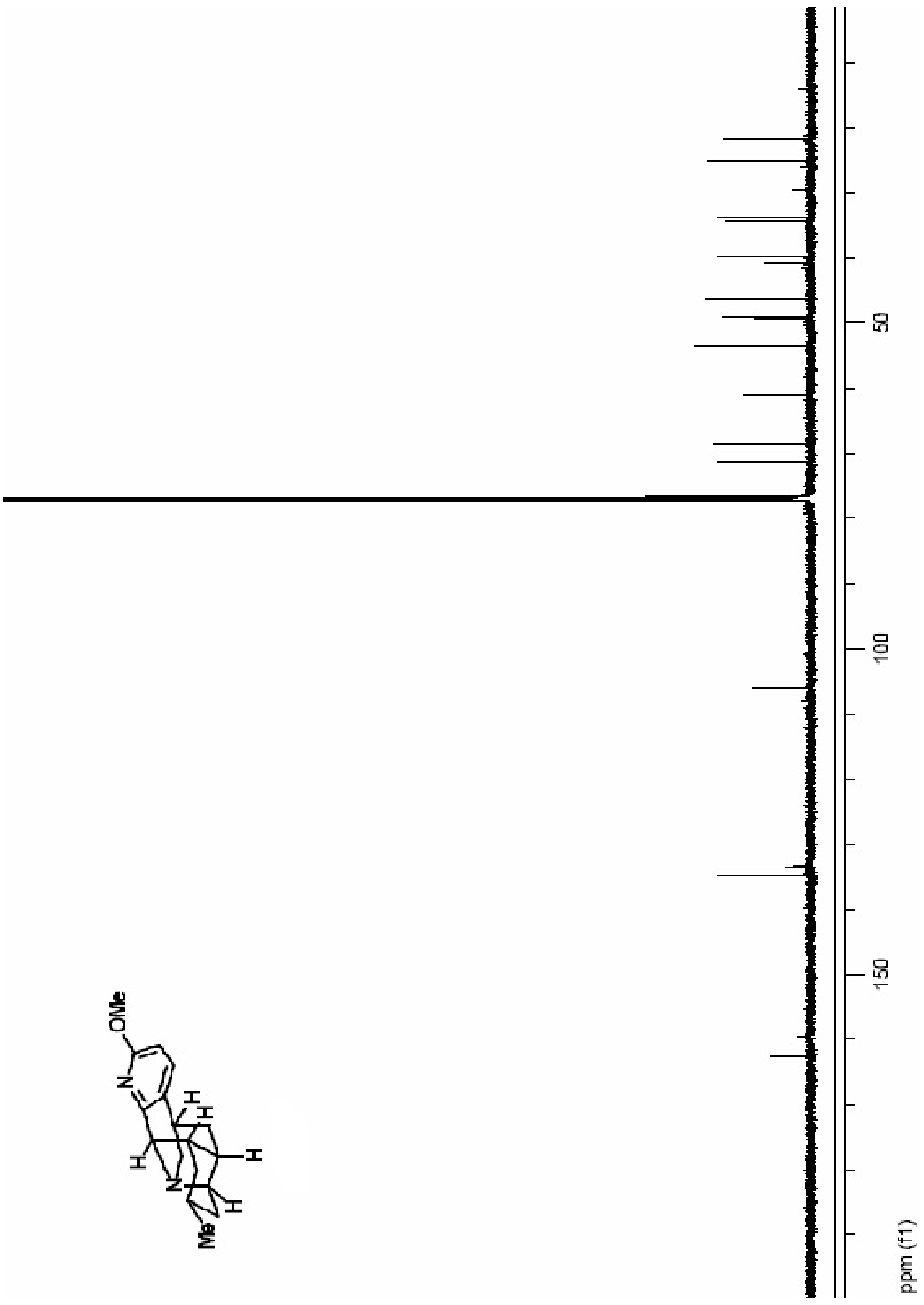
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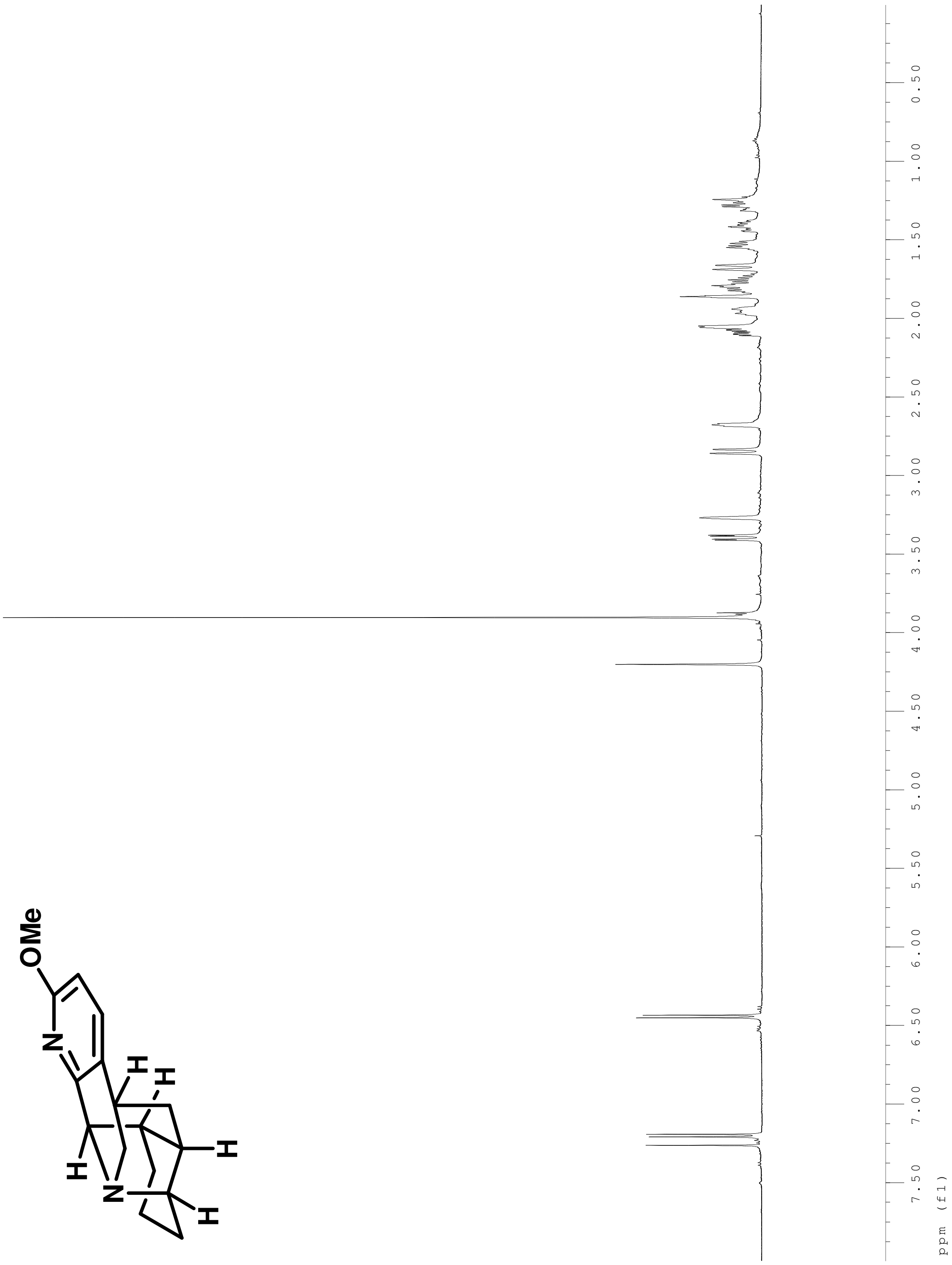
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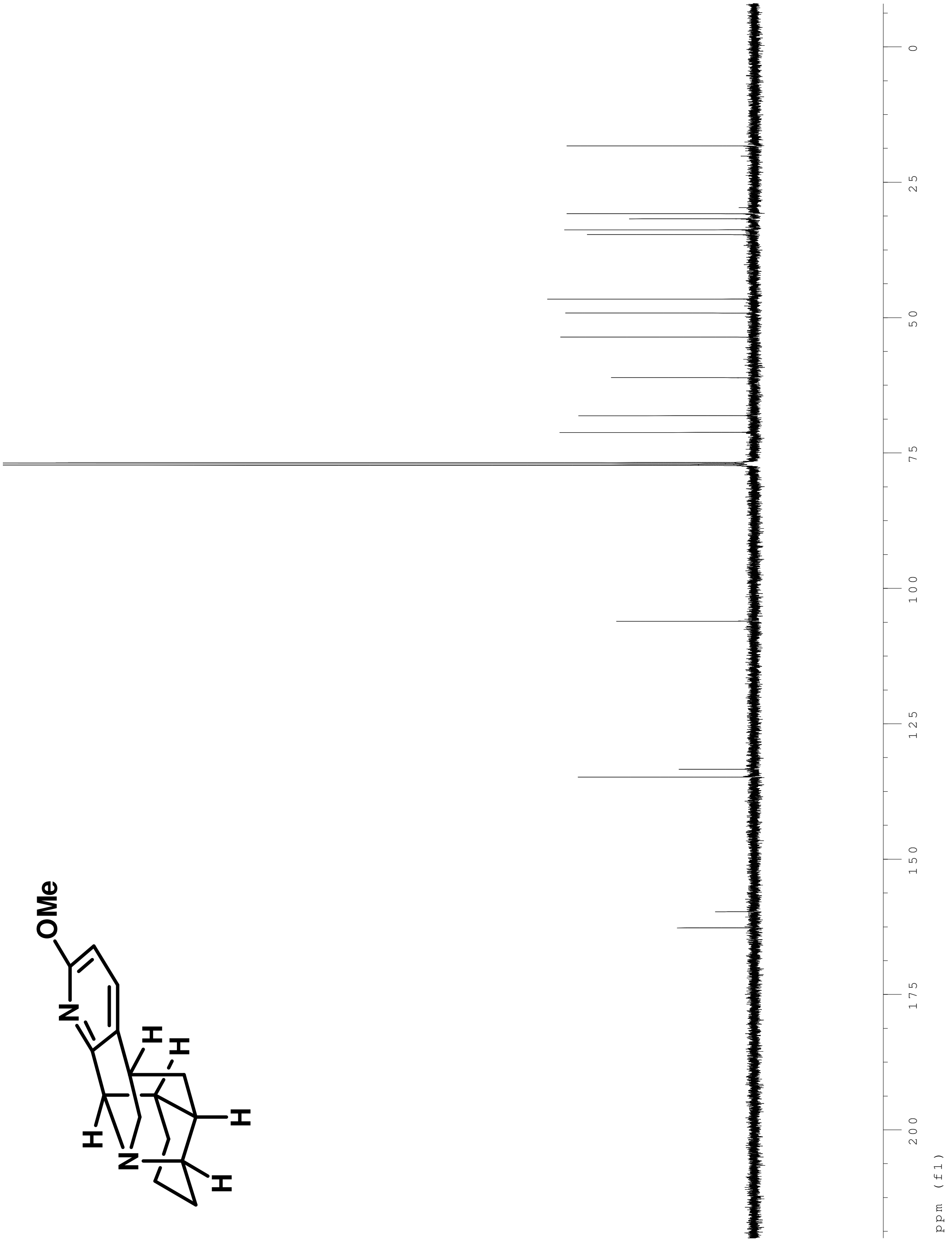
ppm (f1)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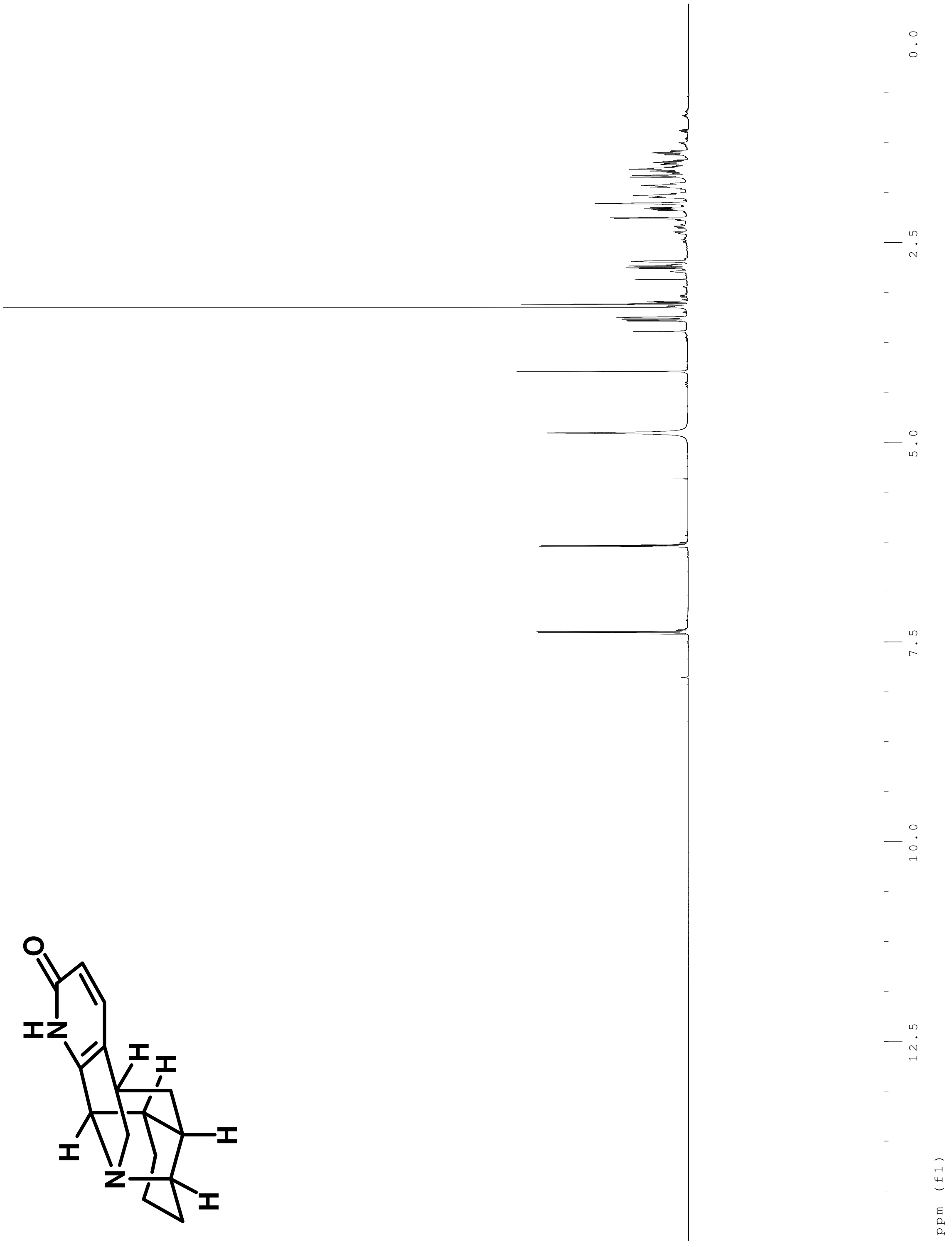
ppm (f1)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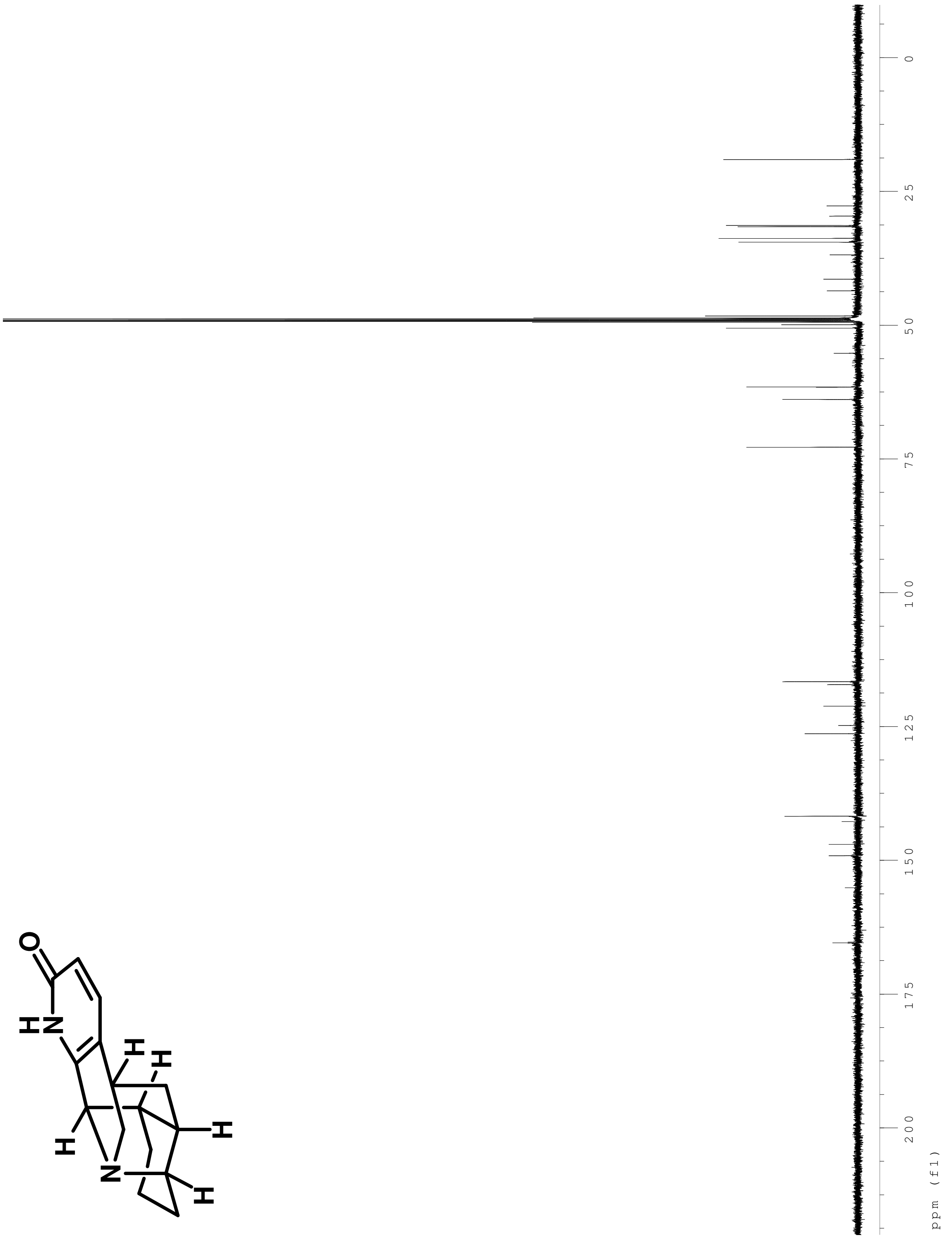
H
H
H
N
H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125
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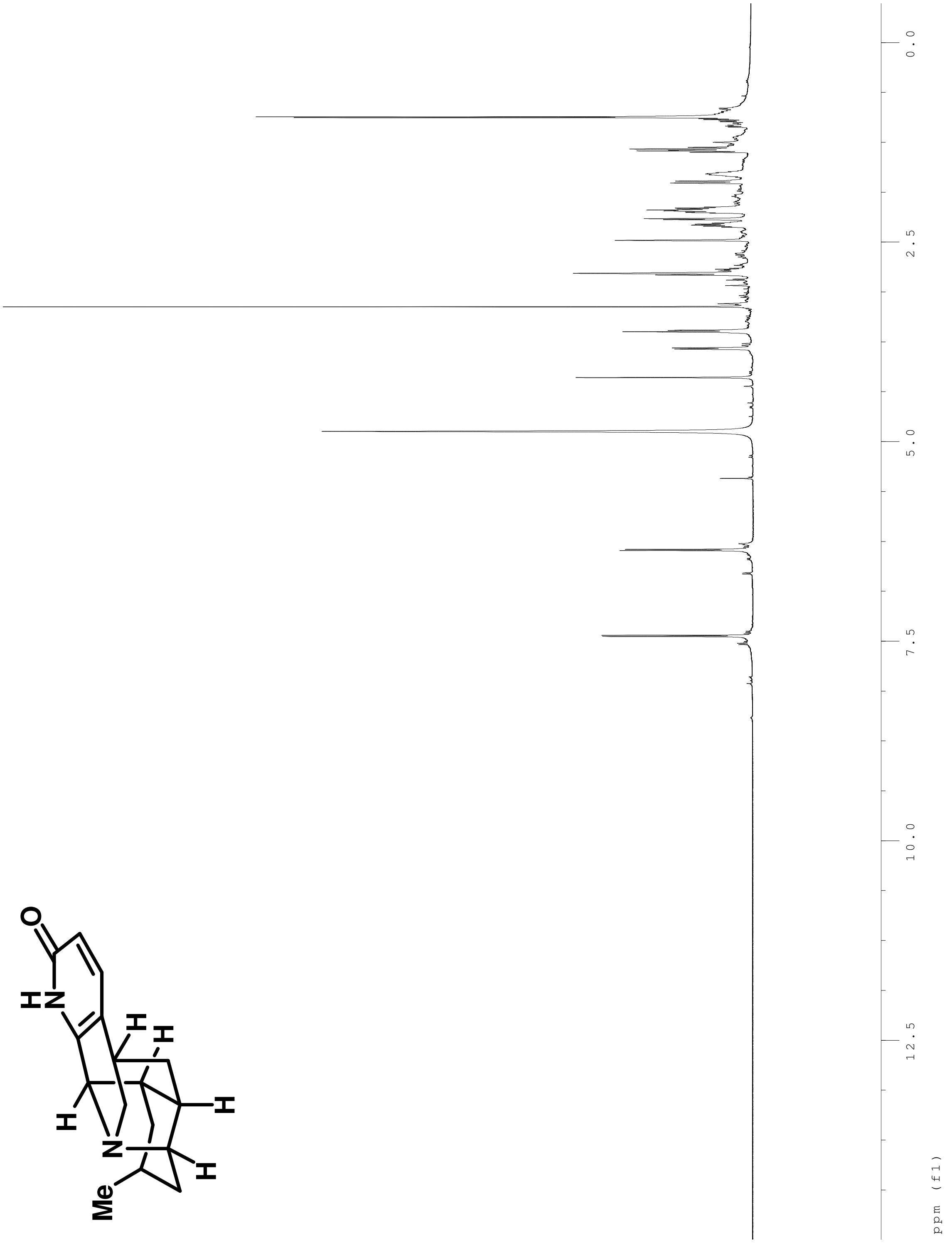
ppm (f1)
O
HN
H
N



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ppm (f1)
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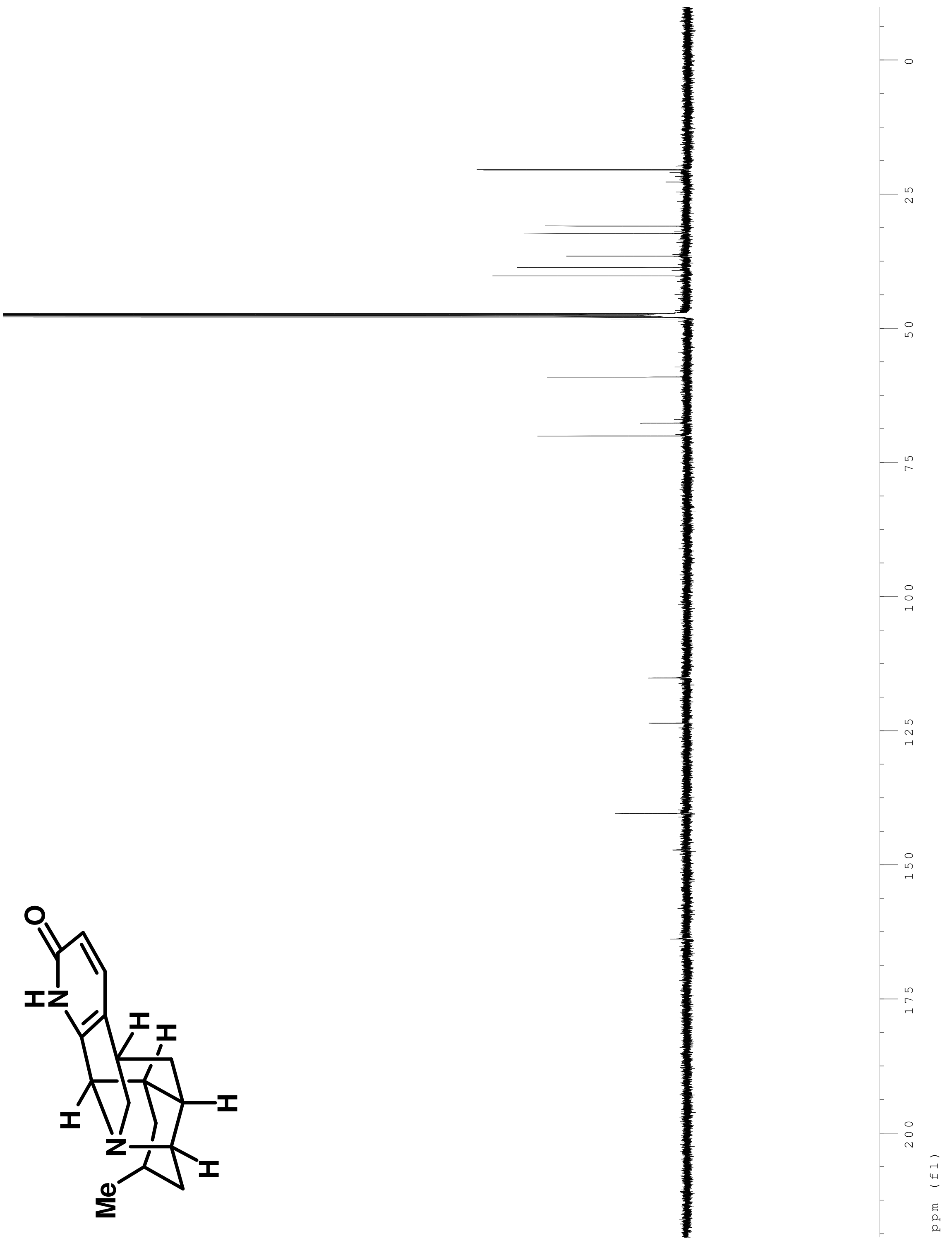
H
H
N
Me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H
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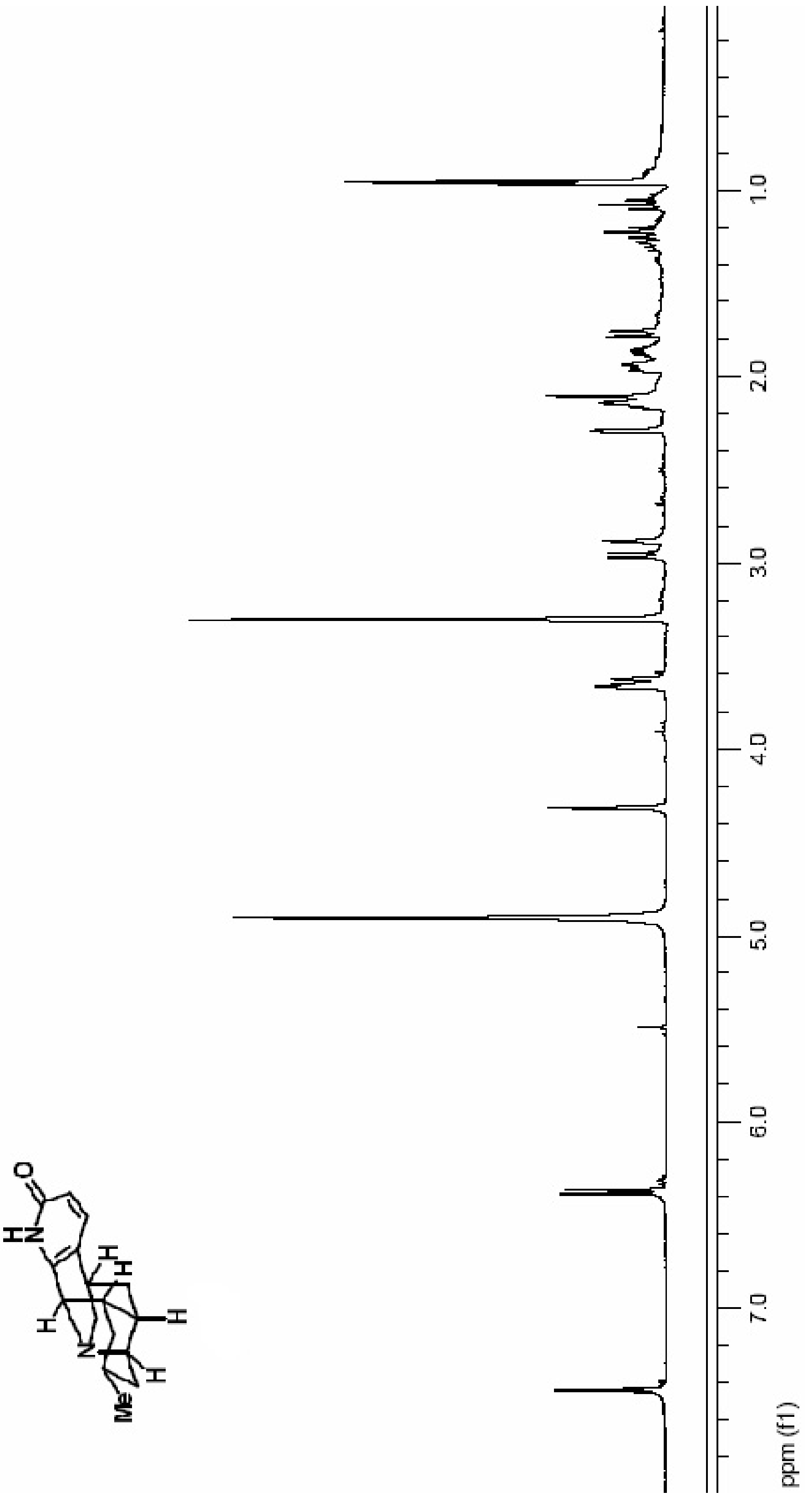
N
Me



O
H
N
H
H
H
H
N
H
Me
1.0
2.0
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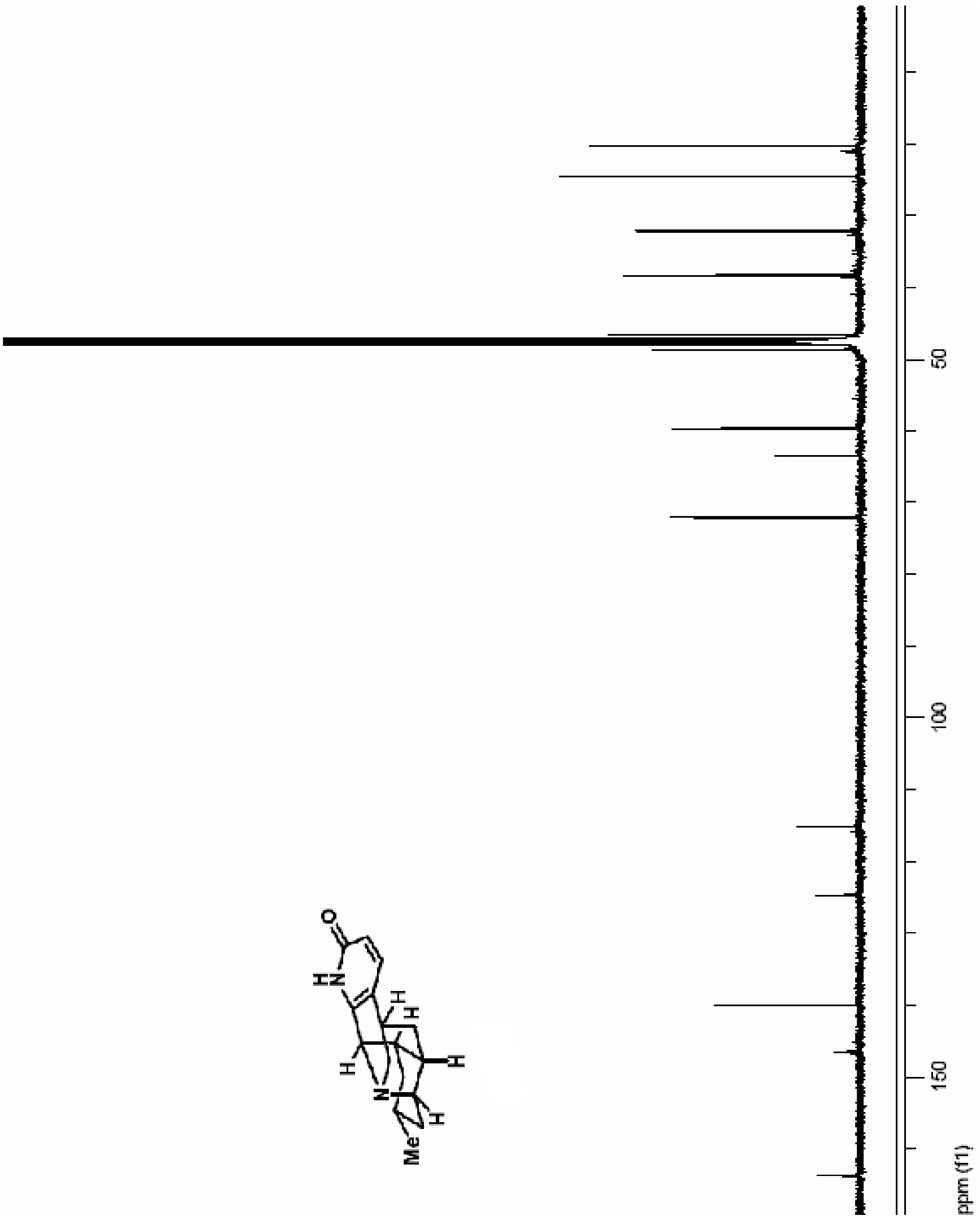
6.0
7.0
ppm (f1)


50
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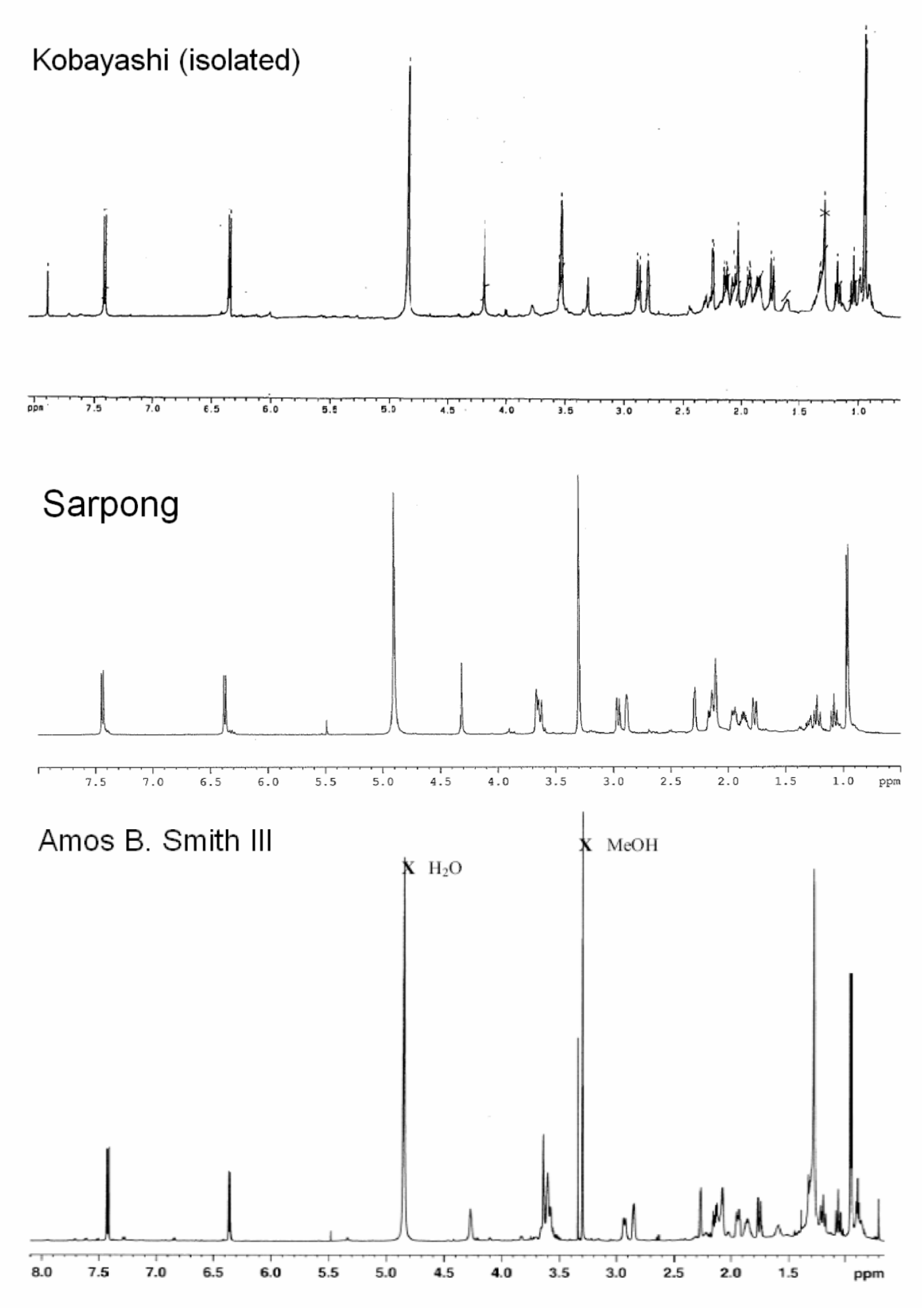
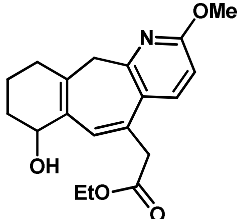
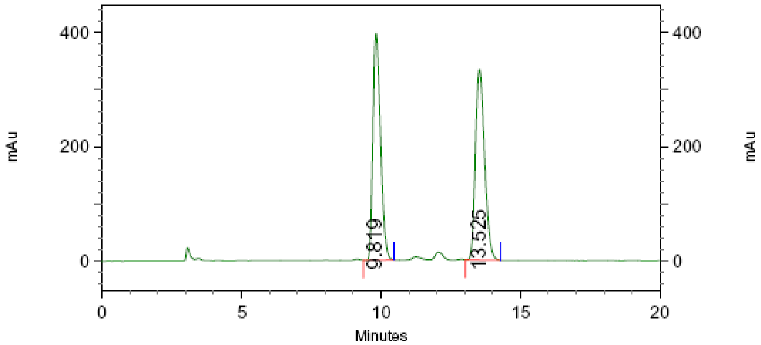
150
ppm (f1)
O
N
H
Me

Comparison of ^{1}H NMR Spectra of Lyconadin A:



HPLC trace of racemic alcohol **1.91**
(Chiralpak AD-H column, 92:8 hexanes/ethanol, 1 mL/min)





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                            13.525       7610260              50.383
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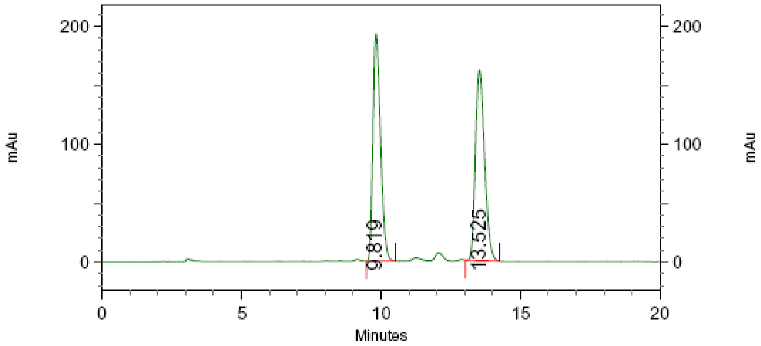

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3: 270 nm, 4 nm Results
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                            13.525       3668583              50.149
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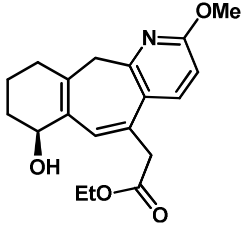
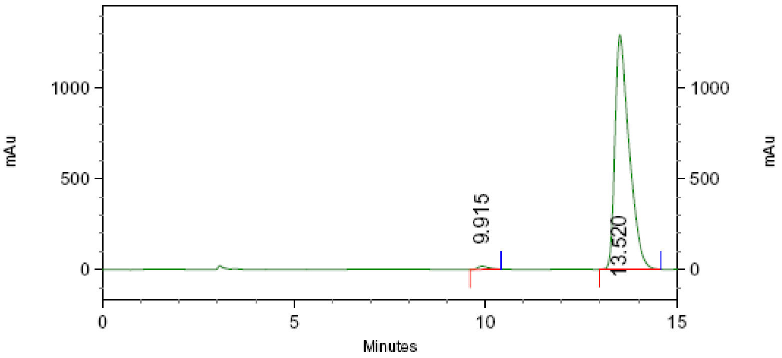
HPLC trace of enantioenriched alcohol **1.91**
(Chiralpak AD-H column, 92:8 hexanes/ethanol, 1 mL/min)





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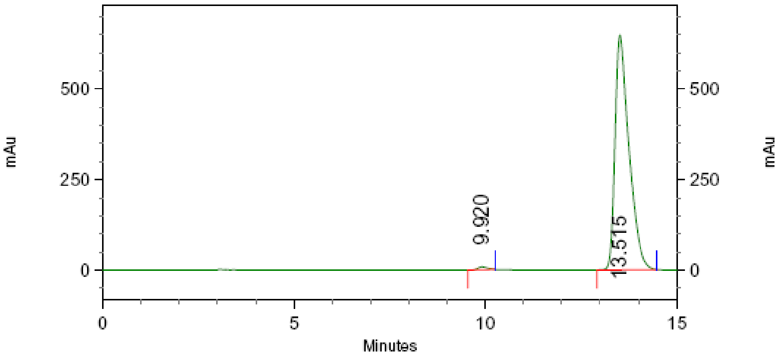

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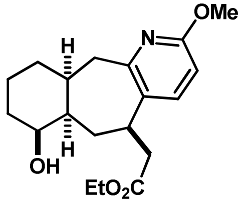
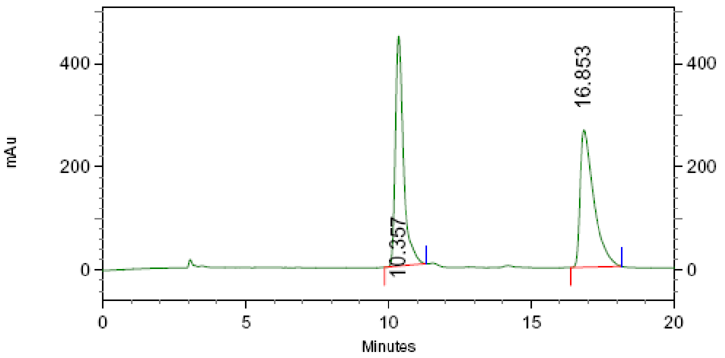
HPLC trace of racemic cycloheptane **1.92**
(Chiralpak AD-H column, 92:8 hexanes/ethanol, 1 mL/min)





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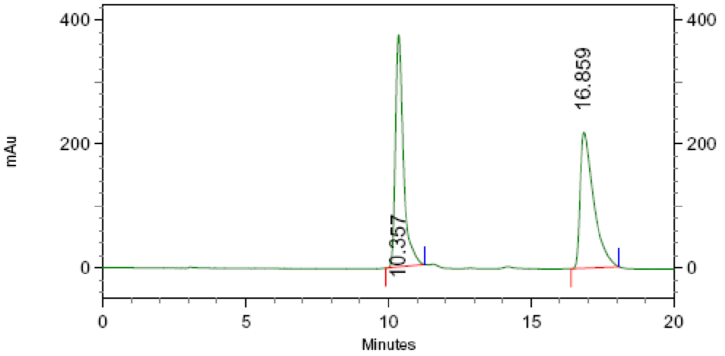
16.853	8865536	50.561



3: 270 nm, 4 nm Results

Retention Time	Area	Area Percent
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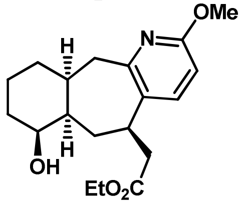
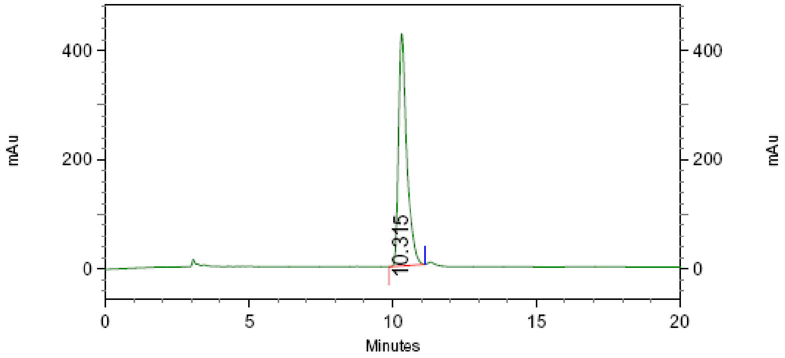
16.859	7211522	50.098

HPLC trace of enantioenriched cycloheptane **1.92**
(Chiralpak AD-H column, 92:8 hexanes/ethanol, 1 mL/min)





1: 230 nm, 4 nm Results

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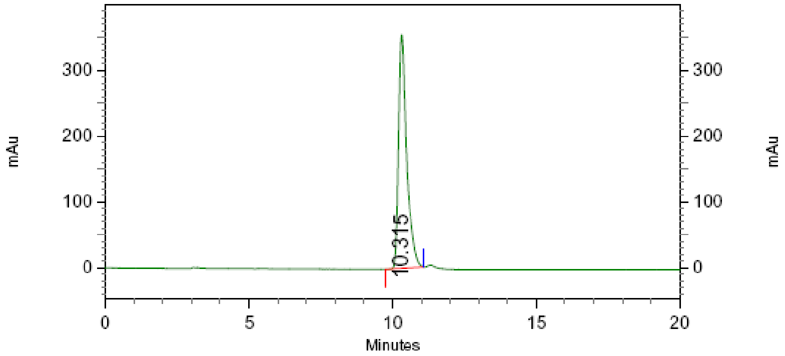

3: 270 nm, 4 nm Results

Retention Time	Area	Area Percent
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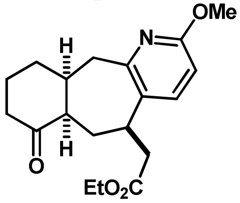
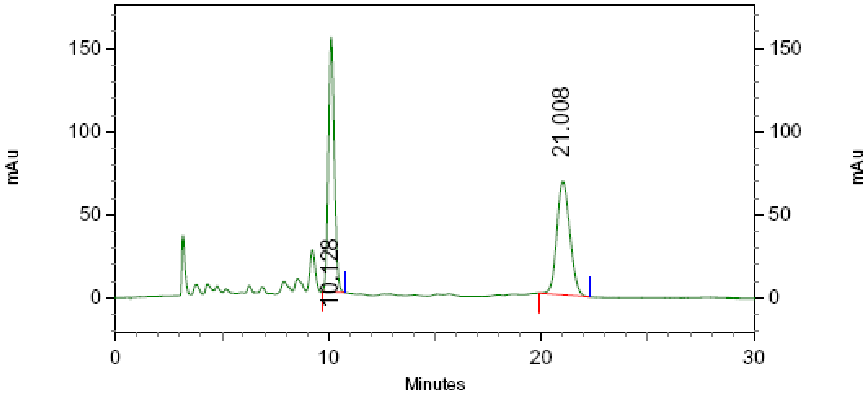
HPLC trace of racemic ketone **1.125**
(Chiralpak AS-H column, 90:10 hexanes/ethanol, 1 mL/min)





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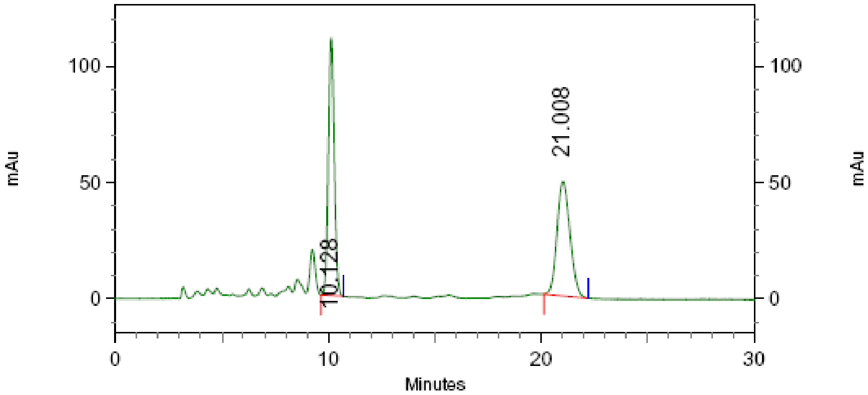

3: 270 nm, 4 nm Results

Retention Time	Area	Area Percent
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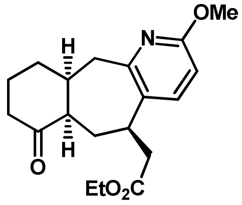
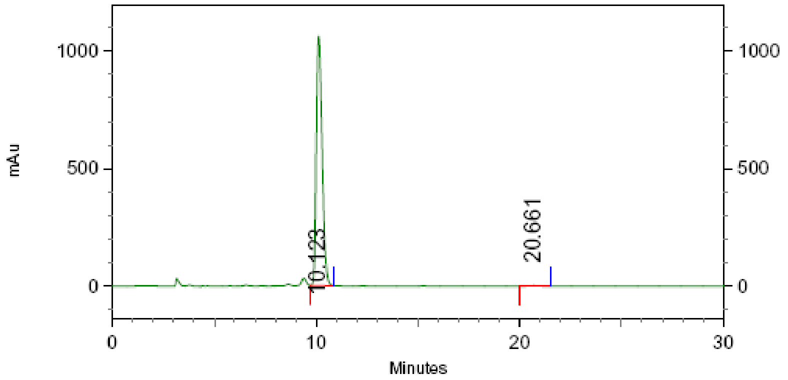
21.008	2086275	49.531

HPLC trace of enantioenriched ketone **1.125**
(Chiralpak AS-H column, 90:10 hexanes/ethanol, 1 mL/min)





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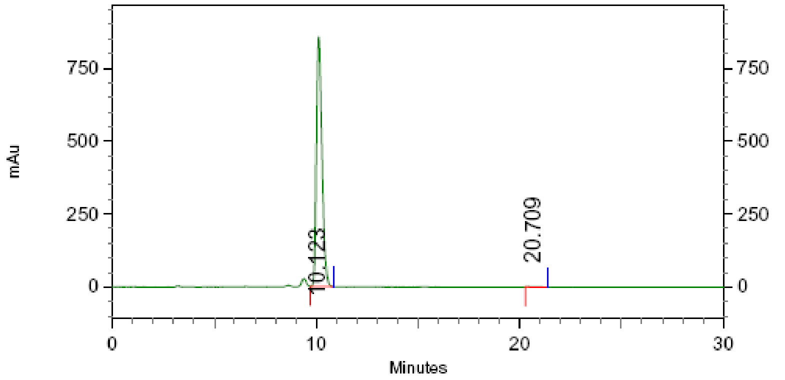

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3: 270 nm, 4 nm Results
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                       20.709           35135                 0.212
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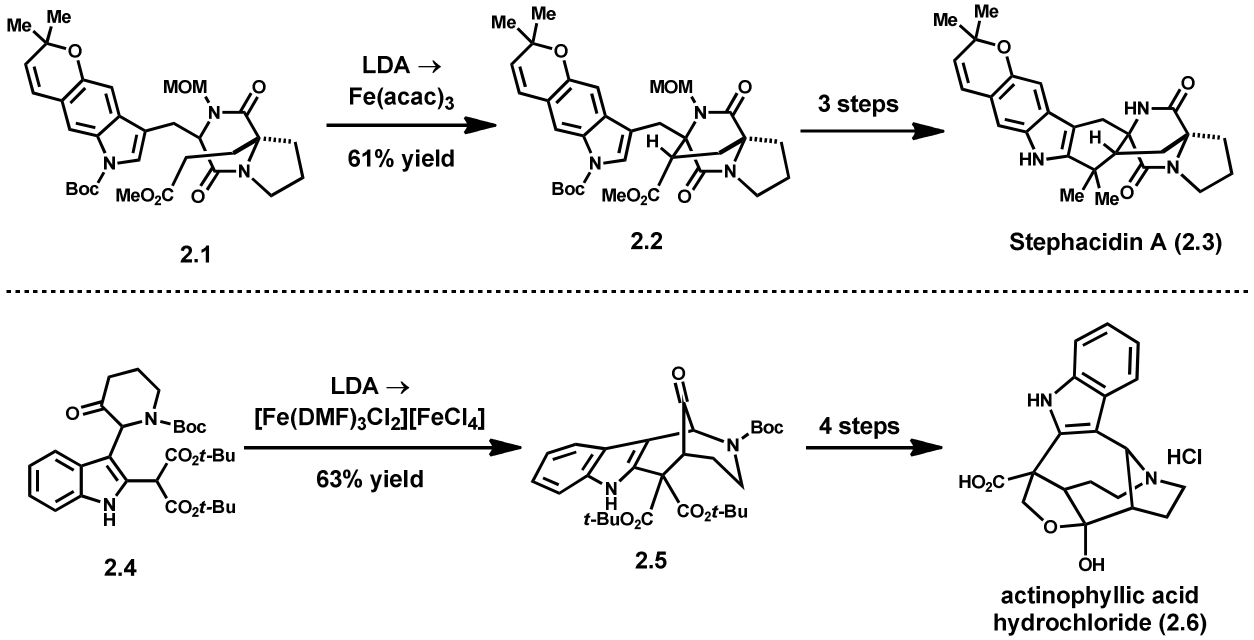
Chapter 2. Mechanistic Studies of Oxidative C-N Bond Formation

2.1 Introduction

An umpolung transformation is characterized by the inversion in the reactivity of an atom from donor to acceptor or from acceptor to donor. The union of two electrophilic positions or two nucleophilic positions to form a bond are examples of umpolung reactions. The Stetter reaction[1,2] and the use of anions of dithianes as acyl anion surrogates are both examples of umpolung tactics that utilize the inversion of the reactivity of an electrophilic center to form a reactive nucleophile. The oxidative coupling of enolates is an umpolung reaction that utilizes a reversal in reactivity of the nucleophilic carbon of an enolate to form an electrophilic carbon and achieve the formation of a C-C bond. Umpolung reactions have proven to be powerful simplifying transformations that have enabled new efficient strategies for the synthesis of complex molecules.

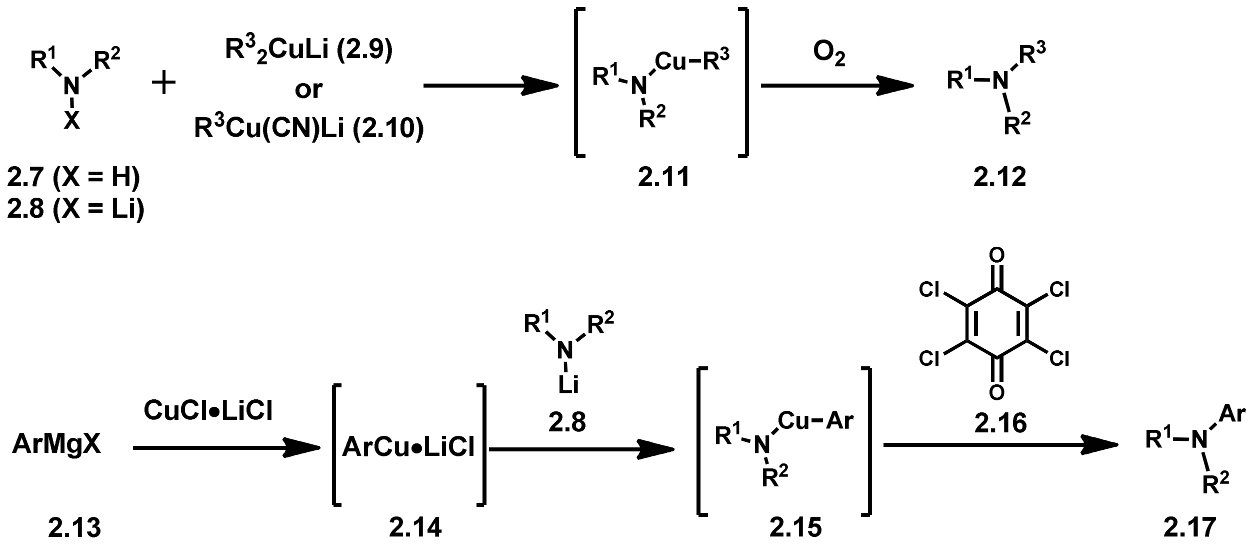
Enolate coupling is an example of an umpolung transformation that employs the combination of two anions to form a carbon-carbon bond via an oxidative process. Since the discovery of the oxidative dimerization of enolates in 1935,[3] extensive research has been conducted on the intermolecular and intramolecular oxidative coupling of enolates utilizing a wide variety of oxidants.[4-6] Recently, Baran and co-workers have extended the scope of the intermolecular heterocoupling of enolates and have also developed the oxidative coupling of enolates with indole and pyrrole anions.[7] Intramolecular oxidative coupling of dienolates have been utilized to form three-, four-, five-, and six-membered rings in simple systems.[8-11] Only a few examples of the oxidative coupling of a dianion have appeared in synthetic studies of complex molecules. The limited number of examples may arise from the harsh conditions often necessary to generate the requisite dianion intermediate and the required chemoselectivity of the oxidant. One or both of these requirements often proves incompatible with polyfunctional substrates. Recently, the syntheses of avrainvillamide and the stephacidins (e.g., **2.3,** Scheme 2.1) by Baran and co-workers were achieved employing an intramolecular oxidative coupling of amide and ester enolates generated from **2.1** to afford key intermediate **2.2**.[12] Additionally, Overman and co-workers utilized the oxidation of a dienolate intermediate arising from **2.4** to synthesize bridged ketone **2.5**, an important intermediate in their synthesis of actinophyllic acid (**2.6**).[13,14]

Scheme 2.1. Examples of dianion coupling in total synthesis



Although numerous examples of the intramolecular oxidative coupling of dianion intermediates to form C-C bonds have been reported, employing C,N-dianions to form carbon-nitrogen bonds has not been extensively studied.[15] The majority of examples of oxidative C-N bond formation are intermolecular and utilize amidocuprate intermediates. The first example of this transformation (Scheme 2.2) involved the treatment of primary and secondary amines with dialkylcuprate **2.9** to form amidocuprate intermediate **2.11** which upon exposure to oxygen underwent oxidation to the alkylated amine product **2.12**.[16] Additionally, addition of lithium amide **2.8** to cyanocuprate **2.10** resulted in the formation of amidocuprate **2.11**, which was then exposed to oxygen to promote the oxidative formation of the C-N bond of the amine product **2.12**.[17] Grignard reagents (**2.13**) have also been utilized to form arylcopper species **2.14**, which upon addition of lithium amide **2.8** form an amidocuprate intermediate (**2.15**) that is subsequently oxidized by chloranil (**2.16**) to mediate formation of the C-N bond.[18] Although these methods provide an alternative amine synthesis via the intermolecular oxidative coupling of a carbanion and an amide, their application to an intramolecular substrate had not been reported prior to our work.

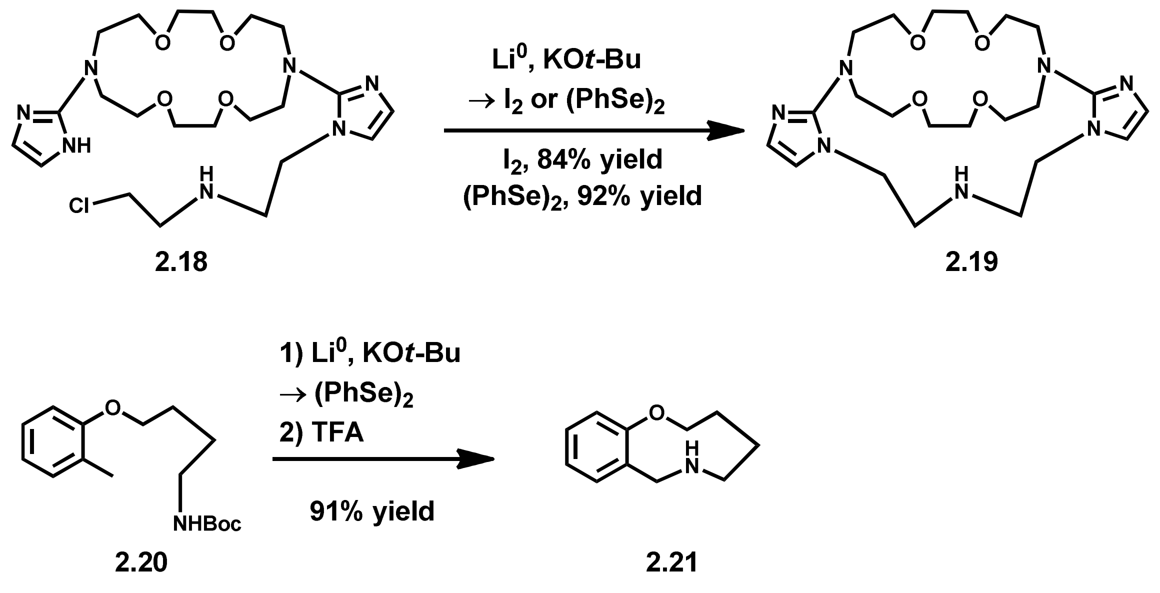
Scheme 2.2. Intermolecular Oxidative C-N Bond Formation Examples



2.7 (X = H)
2.8 (X = Li)
R^3_2CuLi (2.9) or $R^3Cu(CN)Li$ (2.10)
O_2
2.11
2.12
ArMgX
CuCl•LiCl
ArCu•LiCl
2.8
2.16
2.13
2.14
2.15
2.17

After the publication of our mechanistic studies, Verkman and co-workers reported the oxidation of an internally chelated dianion generated from chloride **2.18** (Scheme 2.3) to form a key C-N bond in the synthesis of macrocycle **2.19**. Both I_2 and $(PhSe)_2$ were found to effectively promote this oxidative transformation. Additionally, this approach was applied successfully to the synthesis of 6- to 15-membered cyclic amino ethers (e.g., **2.20** → **2.21**).[19]

Scheme 2.3. Intramolecular Oxidative C-N Bond Formation Examples



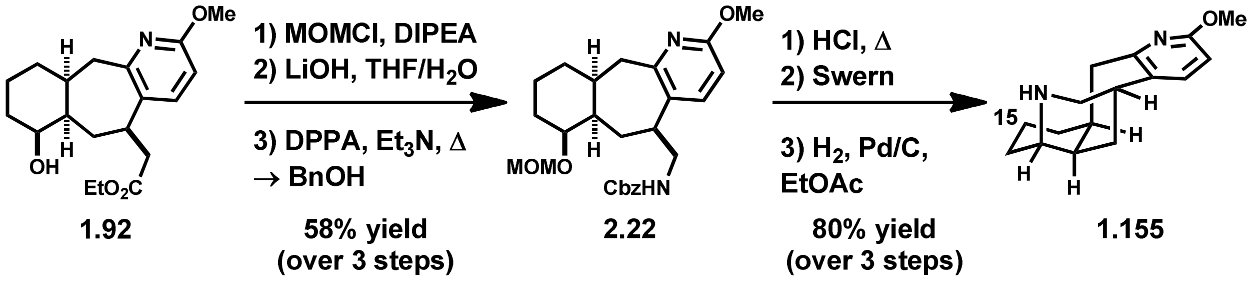
Li^0, KO*t*-Bu → I_2 or $(PhSe)_2$
I_2, 84% yield
$(PhSe)_2$, 92% yield
2.18
2.19
1) Li^0, KO*t*-Bu → $(PhSe)_2$
2) TFA
91% yield
2.20
2.21

2.2 Proposed Mechanism of Oxidative C-N Bond Formation

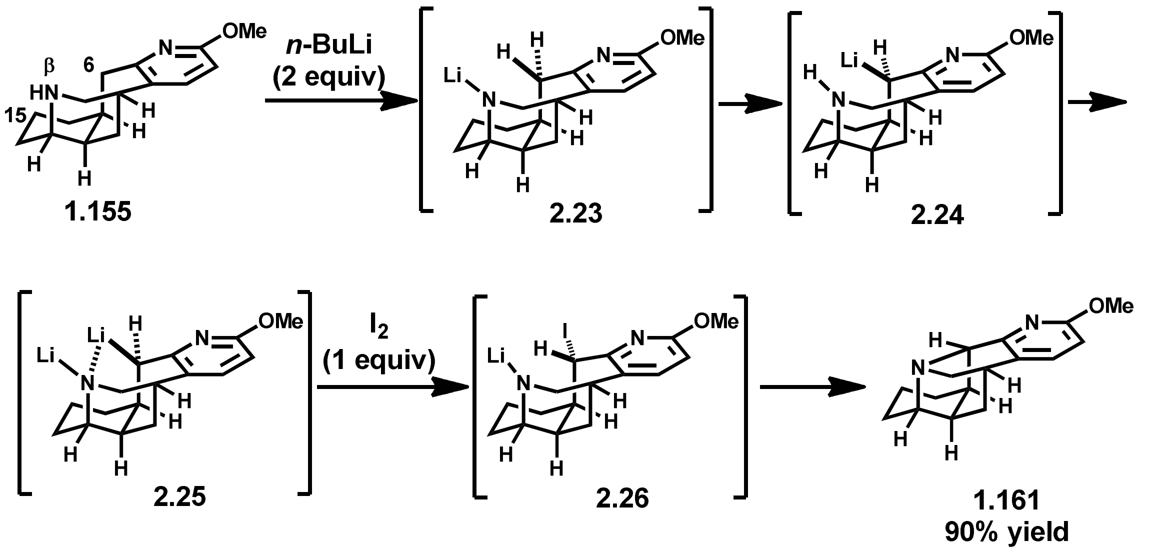
In our synthesis of lyconadin A, direct formation of the C-N bond from a dianion intermediate to afford the pentacyclic core was an effective simplifying transform. Oxidation of a C,N-dianion to form a carbon-nitrogen bond is a transformation that we envisioned could be utilized to form a variety of alkaloid ring systems. Prior to exploring the scope of this oxidative C-N bond formation, examination of the structure and reactivity of the dianion intermediate was conducted. Deuterium quenching experiments, NMR studies, DFT calculations and reactivity studies with different oxidants and electrophiles were performed to gain a better understanding of the mechanism of the C-N bond-forming reaction.

Mechanistic studies of the C-N bond formation were conducted utilizing tetracyclic amine **1.155**, which does not possess a methyl group at C15. Model tetracycle **1.155** can be synthesized from cycloheptane **1.92** in six steps and 46% overall yield (Scheme 2.4). Treatment of **1.155** with two equivalents of *n*-butyllithium at -78 °C results in the formation of dianion **2.25** (Scheme 2.5). Upon addition of one equivalent of iodine to **2.25**, initial reaction may occur at C6 to generate iodide **2.26** which is rapidly converted to pentacycle **1.161**.

Scheme 2.4. Synthesis of Model Tetracycle


OMe
H
N
H
OH
EtO2C
1.92
1) MOMCl, DIPEA
2) LiOH, THF/H2O
3) DPPA, Et3N, Δ
→ BnOH
58% yield
(over 3 steps)
MOMO
CbzHN
2.22
1) HCl, Δ
2) Swern
3) H2, Pd/C,
EtOAc
80% yield
(over 3 steps)
HN
15
1.155

Scheme 2.5. Proposed Mechanism of C-N Bond Formation

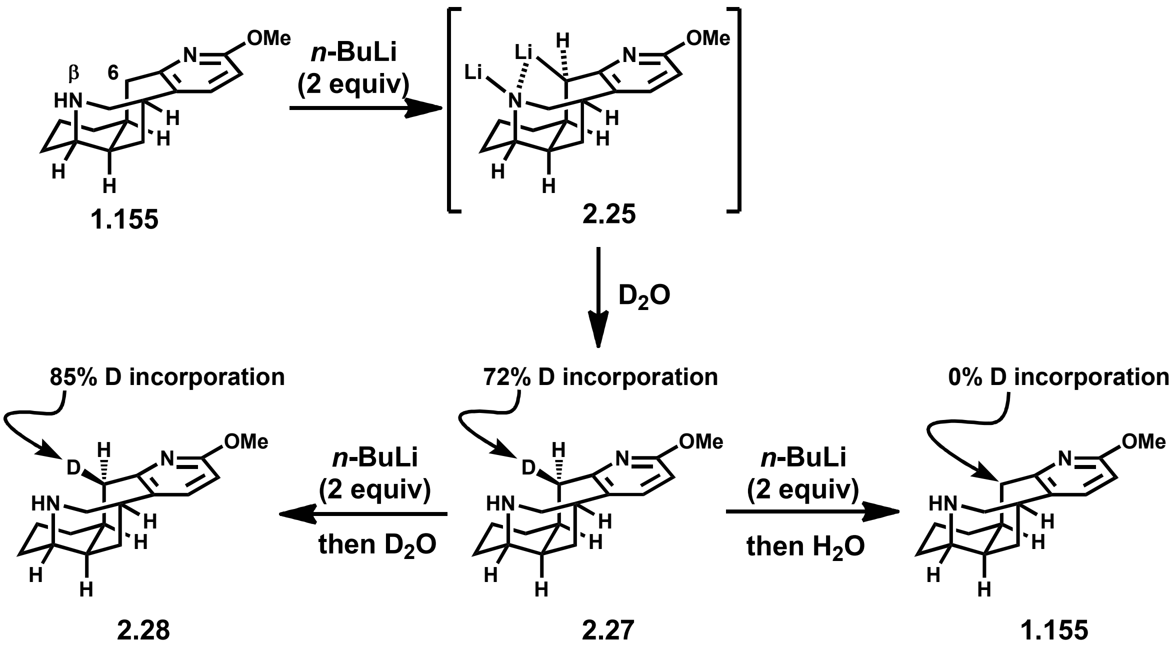

β
6
HN
15
OMe
N
H
1.155
n-BuLi
(2 equiv)
Li
2.23
2.24
2.25
I2
(1 equiv)
I
2.26
1.161
90% yield

Although the picolinic methylene position is relatively acidic (pKa ≈ 34 in THF),[20] the deprotonation of the secondary amine of **1.155** appears vital to successful formation of the carbanion at C6. Initial deprotonation of tetracycle **1.155** (Scheme 2.5) provides lithium amide **2.23**, which could serve as an intramolecular base to promote lateral deprotonation of the C6 picolinic position to form carbanion **2.24**. Subsequent reaction with a second equivalent of *n*-BuLi would afford dianion **2.25**. Additionally, the C6-bound lithium of **2.25** could form an internal chelate with the β-nitrogen lone pair, which would stabilize the dianion intermediate. The importance of the free secondary amine moiety in **1.155** is supported by the observation that protection (Boc, allyl, Cbz) of the amine nitrogen of **1.155** followed by attempted lateral deprotonation at C6 and trapping with different electrophiles (D_2O and I_2) only resulted in the recovery of starting material. These experiments indicate that formation of the carbanion at C6 was not achieved for these protected tetracyclic amine substrates.

Reaction of dianion **2.25** (Scheme 2.5) with iodine may proceed with inversion of stereochemistry at C6 due to the steric bulk and soft nature of iodine to provide *exo*-iodide **2.26**. Subsequent intramolecular nucleophilic attack of the lithium amide of **2.26** to displace the C6-*exo* iodide furnishes pentacycle **1.161**. In contrast, reaction of dianion **2.25** with a sterically small, hard electrophile such as D_2O should result in retention of stereochemistry, placing deuterium in the C6 endo position due to the configurational stability of **2.25**. Generation of dianion **2.25** and treatment with D_2O (Scheme 2.6) resulted in exclusive *endo*-deuteration to provide tetracycle **2.27** (72% D). Previous examples of the stereodivergence of sterically encumbered lithium anions based on the electrophile have been reported by Applequist and Glaze [21,22] and are consistent with our results. Additionally, studies on the conducted tour mechanism of epimerization of heteroatom stabilized carbanions provides support for the reaction of halogen electrophiles to occur with inversion of stereochemistry.[23,24] In these examples, two pathways are proposed to rationalize the stereochemical inversion of the carbanion. A concerted mechanism which involves the interaction of the electrophile with the minor lobe of the sp^3 carbanion orbital could be operative and result in stereochemical inversion. For dianion **2.25**, interaction of the electrophile with the major lobe of the carbanion orbital would involve severe steric clash and therefore the interaction with the carbanion would likely occur with the minor lobe from the more sterically accessible *exo* face. Alternatively, a single-electron transfer (SET) pathway could proceed by one electron oxidation of dianion **2.25** to a radical followed by inversion and subsequent recombination to provide the product with the electrophile in the *exo* position. In the SET mechanism, the recombination would occur on the *exo* face due to the steric considerations in the approach of the electrophile. In both of these mechanisms, sterically bulky electrophiles should result in stereochemical inversion, which is in agreement with our results.

To further examine the stereoselectivity of the deprotonation of amine **1.155**, deuterated amine **2.27** (72% D) was treated with two equivalents of *n*-BuLi and quenched by the addition of D_2O to provide tetracycle **2.28** (85% D) possessing increased deuterium incorporation (Scheme 2.6). Formation of the dianion from amine **2.27** and treatment with H_2O afforded amine **1.155** with no deuterium incorporation. These studies illustrate that the C6 *endo* proton is deprotonated stereoselectively to generate dianion **2.25** and subsequent quenching with H_2O or D_2O occurs with retention of stereochemistry to place H/D at the C6 *endo* position.

Scheme 2.6. Deuteration Experiments


β
6
HN
N
OMe
H
H
H
H
1.155
n-BuLi
(2 equiv)
Li
Li
H
N
N
OMe
2.25
D₂O
85% D incorporation
D
2.28
n-BuLi
(2 equiv)
then D₂O
72% D incorporation
2.27
n-BuLi
(2 equiv)
then H₂O
0% D incorporation
1.155

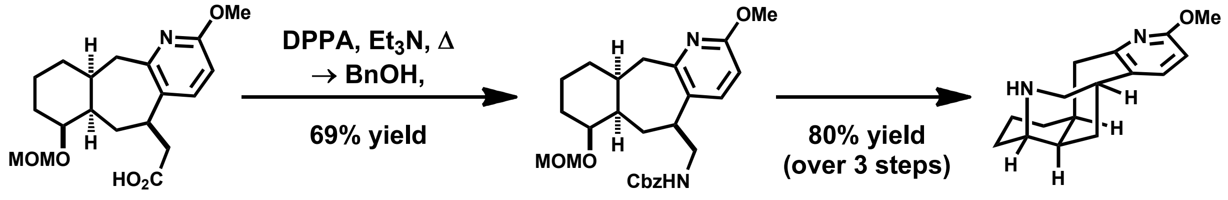
2.3 NMR Studies of Dianion

To gain further insight into the structure of dianion **2.25**, NMR studies of the dianion intermediate were conducted in collaboration with the Collum group at Cornell University. In addition to examining tetracycle **1.155**, NMR studies utilizing ^{15}N-labeled amine **2.31** would enable direct observation of Li-N coupling, which could provide support for the proposed internal chelation of dianion **2.25**. Investigation of the dianions generated from amine **1.155** and labeled amine **2.31** should enable elucidation of the structure of the key dianion intermediate.

In our original synthesis of amine **1.155** (Scheme 2.7), installation of the β-N was achieved by a Curtius rearrangement utilizing diphenylphosphoryl azide (DPPA). Since ^{15}N-labeled azide sources are prohibitively expensive or unavailable, redesigning the synthesis to enable installation of the β-N from a commercially available ^{15}N precursor was necessary. Formation of a primary amide from acid **2.29** using labeled ammonium chloride or labeled ammonium hydroxide followed by Hofmann rearrangement could provide ^{15}N-labeled Cbz-amine **2.31**, which could be advanced to ^{15}N-labeled tetracycle **2.31** by the established route for the conversion of **2.22** to **1.155**.

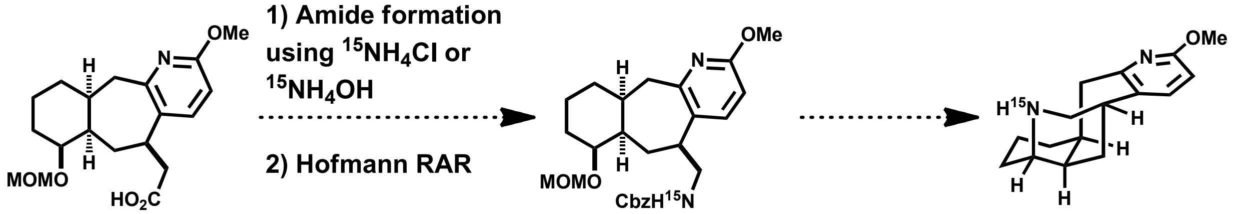
Scheme 2.7. Proposed Synthesis of ^{15}N-labeled Tetracycle

Original Tetracycle Synthesis



2.29 2.22 1.155

Proposed ^{15}N Labeled Tetracycle Synthesis



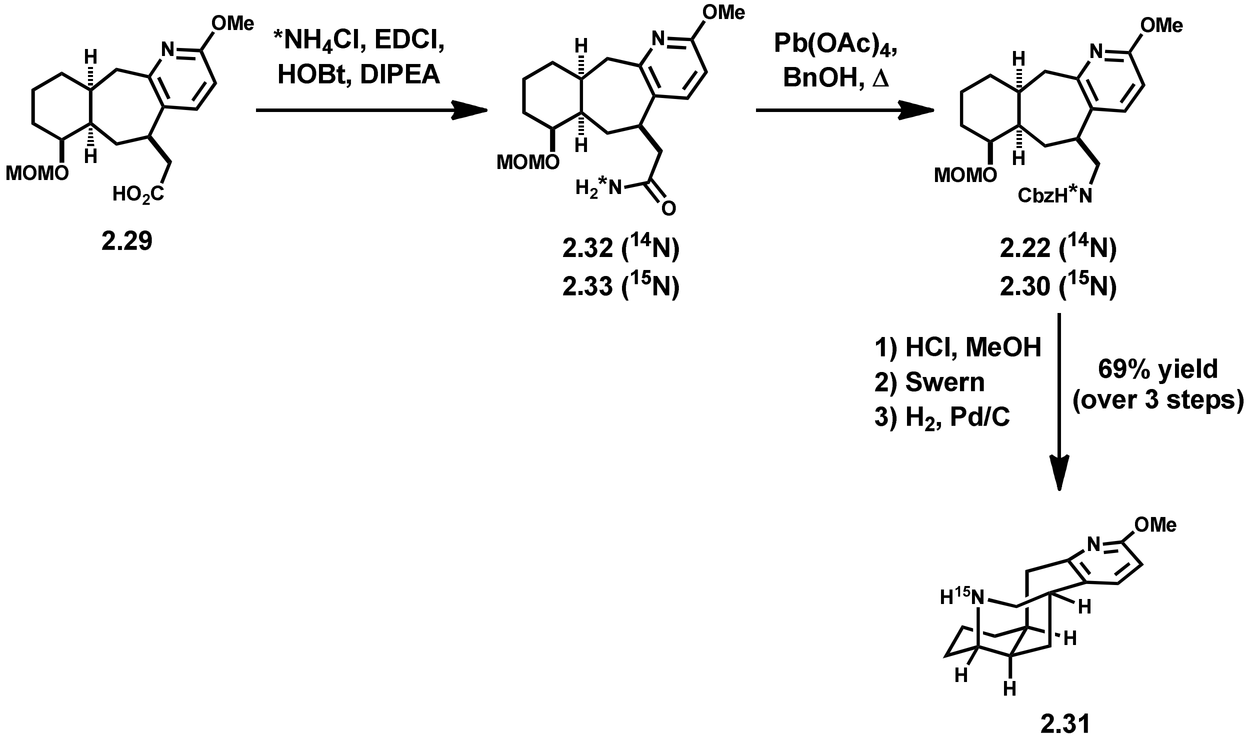
2.29 2.30 2.31

Treatment of acid **2.29** with oxalyl chloride and catalytic DMF provided the intermediate acid chloride, which upon treatment with an aqueous solution of NH_3 generated from NH_4Cl and NaOH provided primary amide **2.32** in 35% yield. Reaction of the acid chloride of **2.29** with excess ammonium hydroxide provided amide **2.32** in 70% yield. Alternatively, treatment of acid **2.29** with EDCI and HOBt to activate the acid moiety as well as DIPEA and NH_4Cl to generate NH_3 *in situ* resulted in the formation of amide **2.32** in excellent yield (Scheme 2.8).[25] In addition to furnishing amide **2.32** in high yield, the EDCI-mediated amide formation utilized only 2 equivalents of NH_4Cl, which was amenable to larger scales using $^{15}NH_4Cl$.

Initial attempts to promote a Hofmann rearrangement of amide **2.32** using standard conditions (NaOMe, Br_2, Δ or DBU, NBS, Δ[26]) resulted in complex mixtures possessing only trace amounts of the desired product. Oxidants such as hypervalent iodine reagents[27] and lead(IV) tetraacetate[28] effectively mediate the Hofmann rearrangement, which can be performed in the presence of a variety of alcohols to directly provide carbamate products. Inspired by this precedent, amide **2.32** was subjected to $PhI(OAc)_2$ in the presence of benzyl alcohol, which provided Cbz-amine **2.22** in 30% yield. Alternatively, amide **2.32** was treated with $Pb(OAc)_4$ and benzyl alcohol to afford Hofmann rearrangement product **2.22** in a modest 42% yield.

With an alternate route to Cbz-amine **2.22** developed, the synthesis of ^{15}N-tetracycle **2.31** commenced by treatment of acid **2.29** with $^{15}NH_4Cl$, EDCI, HOBt, and DIPEA to efficiently furnish amide **2.33** in 91% yield. Subjecting amide **2.33** to $Pb(OAc)_4$ and benzyl alcohol promoted Hofmann rearrangement to afford Cbz-amine **2.30** in 46% yield. Cleavage of the methoxymethyl ether of **2.30** followed by Swern oxidation yielded an intermediate ketone which was subjected to H_2 and Pd/C to effect hydrogenolysis of the Cbz group and reductive amination to provide ^{15}N-tetracyclic amine **2.31**.

Scheme 2.8. ^{15}N-Labeled Tetracycle Synthesis

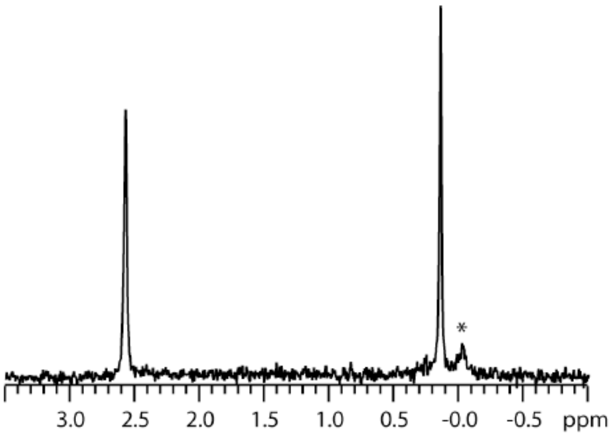


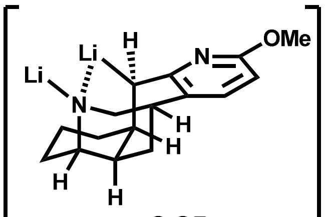
Tetracycle **1.155** was treated with 2 equivalents of ^{6}Li-butyllithium to form dianion intermediate **2.25**, which was examined by NMR spectroscopy. The ^{6}Li NMR of **2.25** (Figure 2.1) contains two singlets in a 1:1 ratio, indicating a single dianionic species with two distinct coordinated lithium ions present in solution. ^{13}C NMR of dianion **2.25** was conducted to determine ^{6}Li-^{13}C coordination, but the signal for the picolinic carbon did not exhibit distinct coupling. Rapid exchange of the lithium bound to the picolinic carbanion could be responsible for the absence of ^{6}Li-^{13}C coupling in the ^{13}C NMR spectrum of **2.25**. Fast lithium exchange has been reported in previous studies of benzylic carbanions and results in no observed ^{6}Li-^{13}C coupling,[29] which is consistent with our results.

Similarly, ^{15}N-labeled tetracycle **2.31** was subjected to ^{6}Li-butyllithium to afford dianion **2.34** which was studied spectroscopically. The ^{6}Li NMR spectrum of **2.34** (Figure 2.2) displays two doublets in a 1:1 ratio. The observed ^{6}Li-^{15}N coupling for both lithium resonances exhibited in this spectrum is due to both lithium ions of **2.34** being coordinated to the ^{15}N-labeled nitrogen. Consistent with the ^{6}Li NMR spectrum, ^{15}N NMR spectrum (Figure 1.2) of dianion **2.34** shows a single quintet resonance due to coupling to both lithium ions. Due to the absence of ^{6}Li-^{13}C coupling, lithium coordination to the carbanionic position could not be determined from the ^{13}C NMR spectrum. Proposed structure **2.25** (Figure 2.1) for the dianion intermediate possessing a single bridging lithium ion is consistent with the NMR data. Additionally, proposed structure **2.35** (Figure 2.3) with two bridging lithium ions is also in agreement with the NMR data.

Figure 2.1. NMR Spectra of Dianion **2.25**

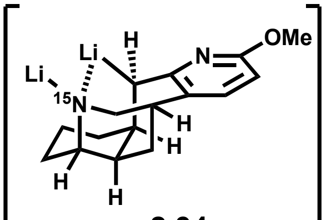
^{6}Li NMR of 2.25
*** indicates artifact of [^{6}Li]*n*-BuLi**




Li
Li
H
N
OMe
H
H
H
H

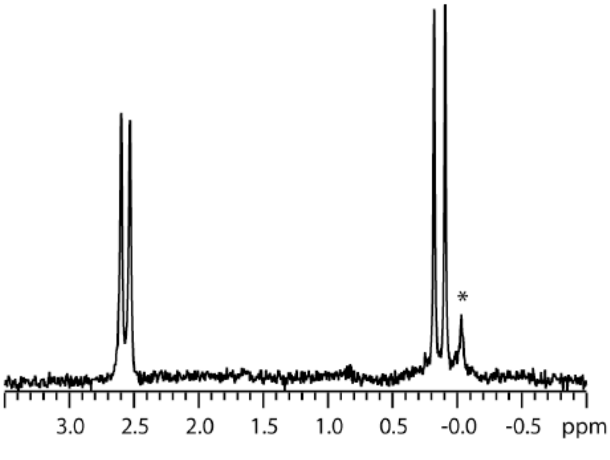
2.25

Figure 2.2. NMR Spectra of Dianion **2.34**

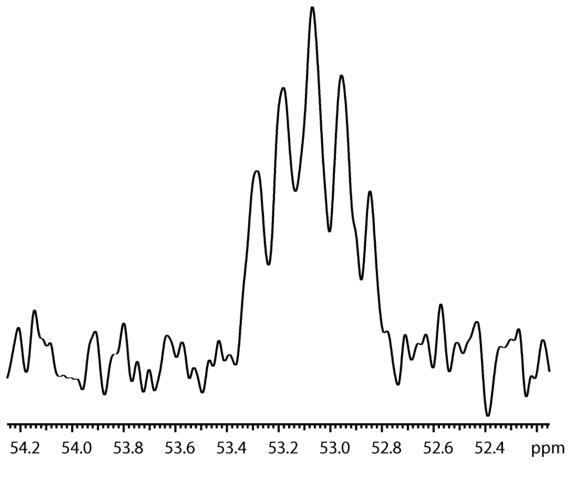

Li
Li
15N
H
N
OMe
H
H
H
H

2.34

^{6}Li NMR of 2.34
*** indicates artifact of [^{6}Li]*n*-BuLi**



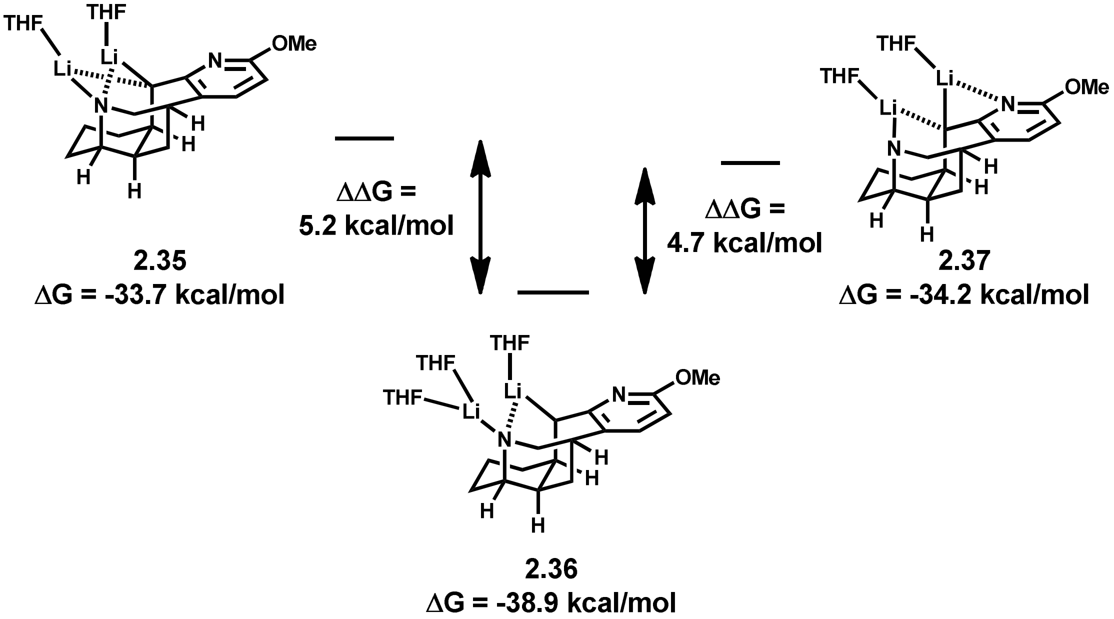
^{15}N NMR of 2.34



2.4 DFT Calculations of Proposed Dianion Structures

To provide further insight regarding the structure of the dianion intermediate, DFT calculations were conducted by the Collum group at Cornell University to analyze proposed structures **2.35**, **2.36** and **2.37** (Figure 2.3). The relative energies of the solvent-coordinated dianion structures were calculated. The unsolvated structure of **2.25** including three unbound THF molecules was set as the zero point for these calculations. Mono-bridging lithium species **2.36** possessing three coordinated THF molecules was calculated to have a free energy of -38.9 kcal/mol. Alternatively, the free energies of structures **2.35** and **2.37**, which both contain two bridging lithium ions, were determined to be -33.7 and -34.2 kcal/mol, respectively. Overall, dianion structure **2.36** with a single bridging lithium is lower in energy than structures **2.35** and **2.37** by 5.2 and 4.7 kcal/mol, respectively. The data from the DFT calculations and the NMR studies indicate that the structure of the dianion is best represented by structure **2.36**.

Figure 2.3. Energy Diagram of Proposed Dianion Structures

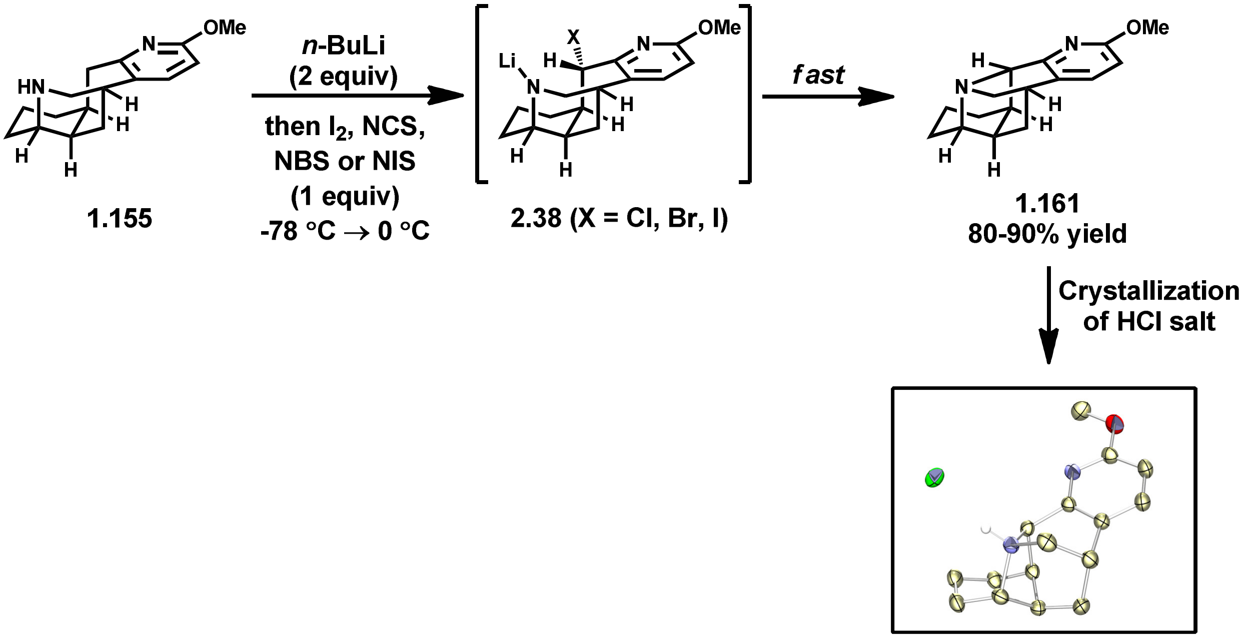


Note: Calculated energies of structures **2.35** and **2.37** include an unbound THF.

2.5 Dianion Reactivity Studies

During the initial attempts to promote oxidative C-N bond formation in our lyconadin synthesis, iodine was found to be an effective oxidant, whereas transition metal salts such as $Pd(OAc)_2$, $Cu(OTf)_2$ and $FeCl_3$ did not result in formation of the desired pentacycle. Screening other halogen electrophiles (NCS, NBS, and NIS) revealed that all of them efficiently provided pentacycle **1.161** in excellent yield (Scheme 2.9). Mechanistically, treatment of dianion **2.25** with halogen electrophiles may proceed by reaction at C6 with inversion to provide halide **2.38**, which rapidly forms the C6-βN bond via intramolecular displacement of the halide to furnish pentacycle **1.161**. X-ray analysis of crystals of the HCl salt of amine **1.161** (**2.39**) provided unambiguous support for the structure of **1.161**. To confirm the C6 stereochemistry after reaction with a halogen electrophile, quenching of the reaction and attempted isolation of the corresponding amine of **2.38** was pursued. Addition of the halogen electrophile to the dianion at -78 °C, followed by quenching the reaction at -78 °C after short reaction times provided exclusively the pentacyclic amine product **1.161** in high yield. This result indicates that the oxidative C-N bond formation is facile and rapid at -78 °C.

Scheme 2.9. Screen of Halogen Electrophiles



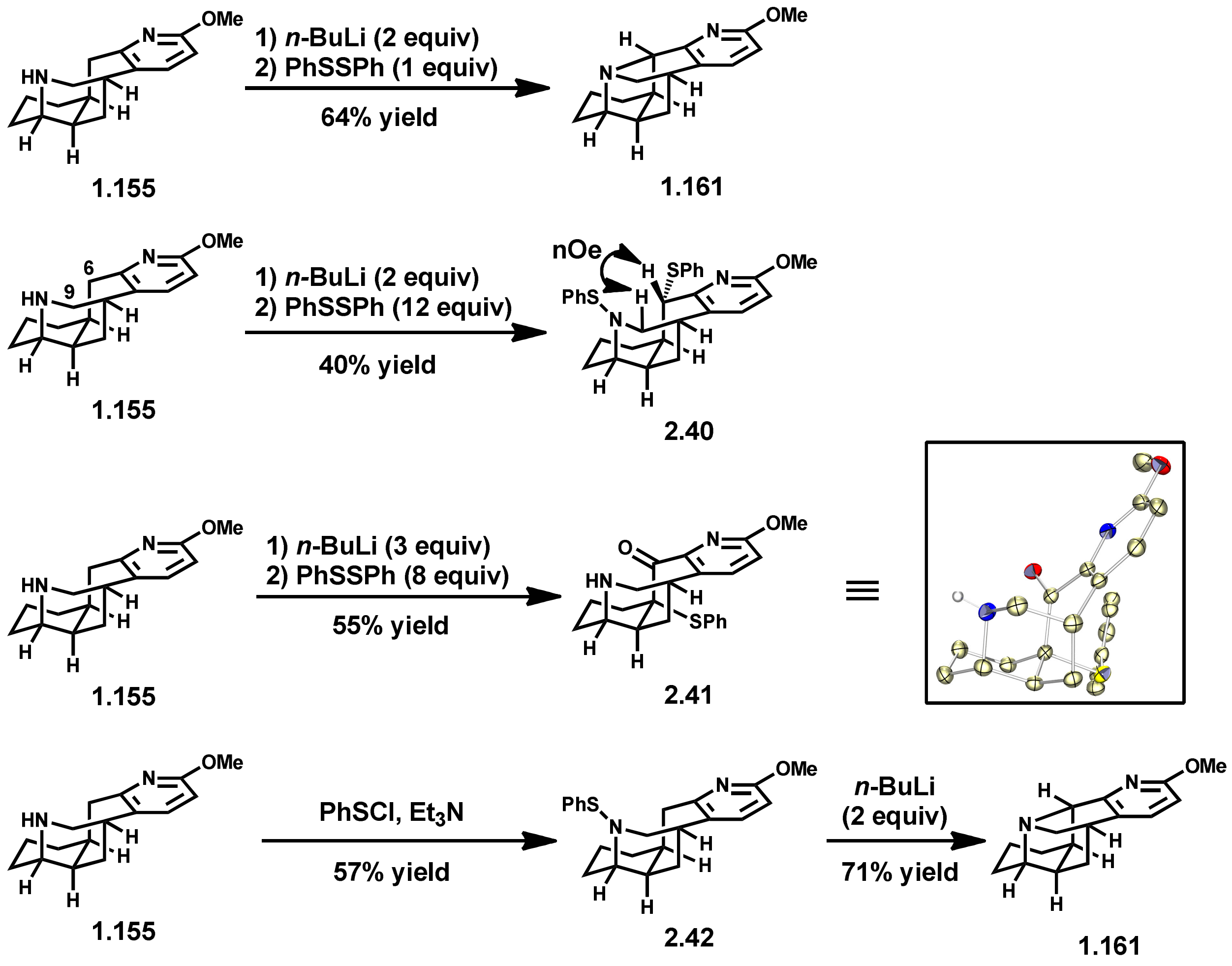
After the unsuccessful attempts to quench and isolate an intermediate possessing a halide at C6 to confirm the stereochemical outcome, additional electrophiles were screened that would hopefully lead to a more persistent and isolable intermediate bearing a substituent at C6. Treatment of dianion **2.25** with trimethylsilyl chloride (TMSCl) or trimethylstannyl chloride resulted in complex mixtures of products. Generation of the dianion of **1.155** followed by addition of excess phenylselenyl chloride or diphenyldiselenide afforded products bearing a phenylseleno group at C6; however these compounds were unstable under a variety of purification conditions. Addition of one equivalent of diphenyl disulfide to dianion **2.25** afforded pentacyclic amine **1.161** in 64% yield (Scheme 2.10). Treatment of dianion **2.25** with a large excess of diphenyl disulfide furnished bis-sulfide **2.40** in 40% yield and likely proceeds with inversion of the carbanion to place the thiophenoxy group in the C6 *exo* position. NOESY experiments with bis-sulfide **2.40** revealed a nOe interaction between the hydrogen atom at C6 and the axial hydrogen atom at C9 in **2.40**, which indicates that the thiophenoxy substituent at C6 occupies the *exo* position and the hydrogen atom is in the *endo* position.

Generation of the dianion from **1.155** with three equivalents of *n*-BuLi followed by treatment with excess diphenyl disulfide unexpectedly afforded ketosulfide **2.41** after aqueous workup. Recrystallization of **2.41** and subsequent X-ray crystallographic analysis confirmed its structure. Formation of ketone **2.41** could proceed by the mechanism outlined in Scheme 2.11.

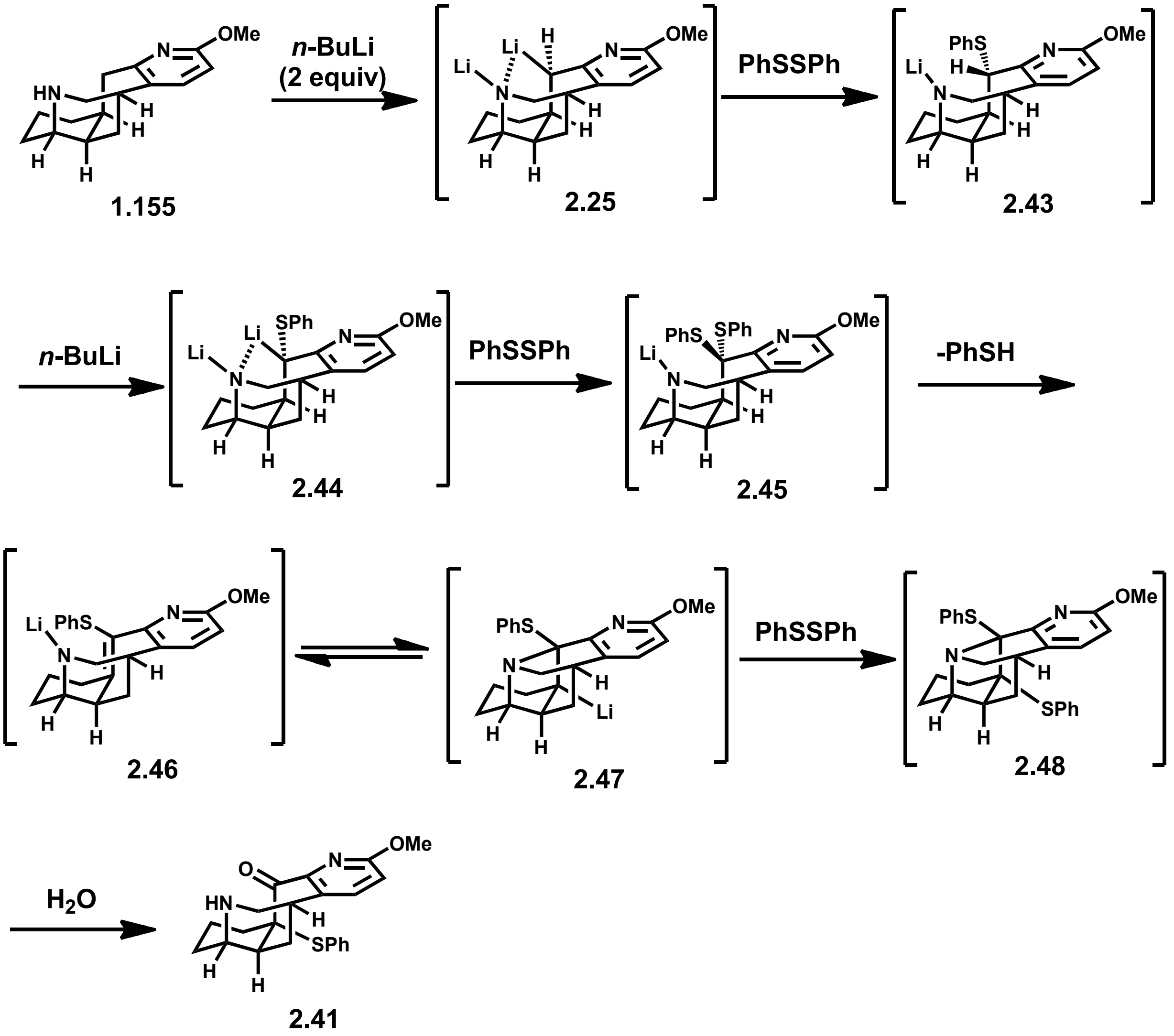
Generation of dianion **2.25** from **1.155** followed by reaction with diphenyl disulfide could provide sulfide **2.43**. Subsequent deprotonation of **2.43** at C6 could generate dianion **2.44**, which could react with diphenyl disulfide to furnish disulfide **2.45**. Loss of thiophenol from **2.45** could give thioenolether **2.46**, which could be in equilibrium with carbanion **2.47**. Reaction of **2.47** with diphenyl disulfide could then provide hemithioaminal **2.48**, which upon aqueous workup could hydrolyze to afford ketosulfide **2.41**.

To gain further insight into the mechanism of C-N bond formation utilizing PhSSPh, N-sulfide **2.42** (Scheme 2.10) was prepared from amine **1.155** by treatment with PhSCl. Treatment of **2.42** with 2 equivalents of *n*-BuLi afforded pentacycle **1.161** in 71% yield. On the basis of these results, formation of the pentacycle with PhSSPh could occur by formation of the N-sulfide followed by nucleophilic attack of the carbanion on nitrogen to form the C-N bond with the displacement of thiophenoxide. Formation of the C-N bond by this pathway is supported by an earlier observation that the N-chloroamine derivative of **1.155** is converted to pentacycle **1.161** upon treatment with KOH in refluxing methanol. To determine which position (C6 or N) of dianion **2.25** reacts with PhSSPh initially, **2.25** was treated with diphenyl disulfide for 1 h at -78 °C and provided sulfide **2.49** as the major product (Scheme 2.11) along with bissulfide **2.40** (**2.49** : **2.40**, 5:3). Sulfide **2.49** was unstable to column chromatography, so the mixture of **2.40** and **2.49** was treated with Boc$_2$O to afford bis-sulfide **2.40** and sulfide **2.50** in 25% and 35% yield, respectively. The formation of sulfide **2.49** provides support that initial reaction of the electrophile occurs at the carbanionic position of dianion **2.25**. In contrast, earlier experiments revealed that formation of pentacycle **1.161** could be achieved from N-sulfide **2.42**. Overall, these experiments have demonstrated that multiple reaction pathways are viable for the reaction of dianion **2.25** with diphenyl disulfide to provide pentacycle **1.161**.

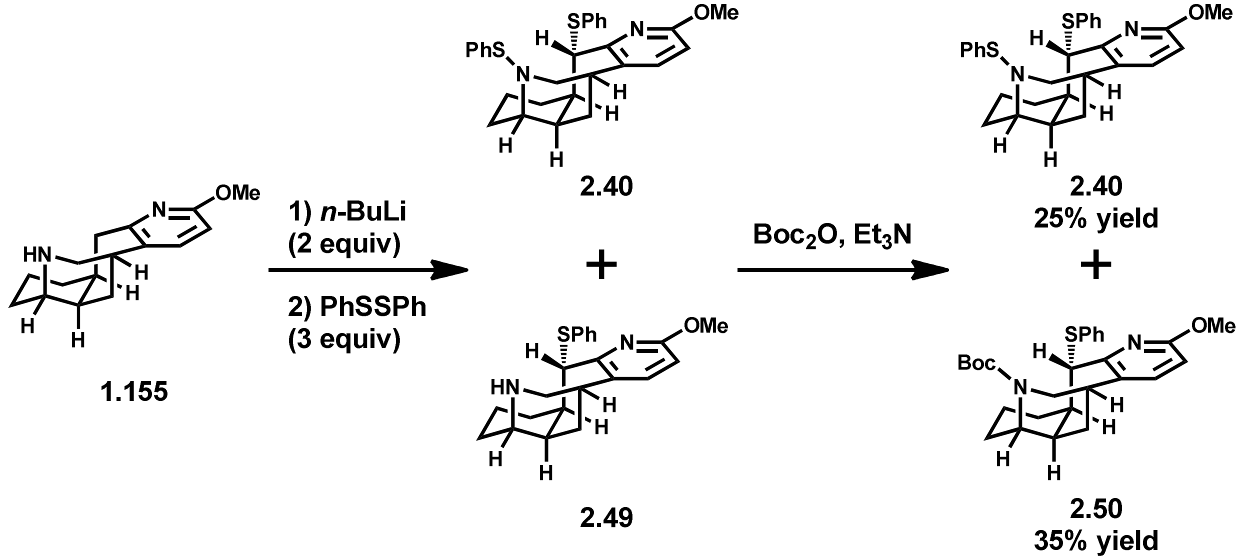
Scheme 2.10. Sulfur Electrophiles


1.155
1) n-BuLi (2 equiv)
2) PhSSPh (1 equiv)
64% yield
1.161
6
9
1) n-BuLi (2 equiv)
2) PhSSPh (12 equiv)
40% yield
nOe
PhS
SPh
2.40
1) n-BuLi (3 equiv)
2) PhSSPh (8 equiv)
55% yield
2.41
≡
PhSCl, Et3N
57% yield
2.42
n-BuLi
(2 equiv)
71% yield
OMe
HN
N
H

Scheme 2.11. Proposed Mechanism for Ketosulfide Formation

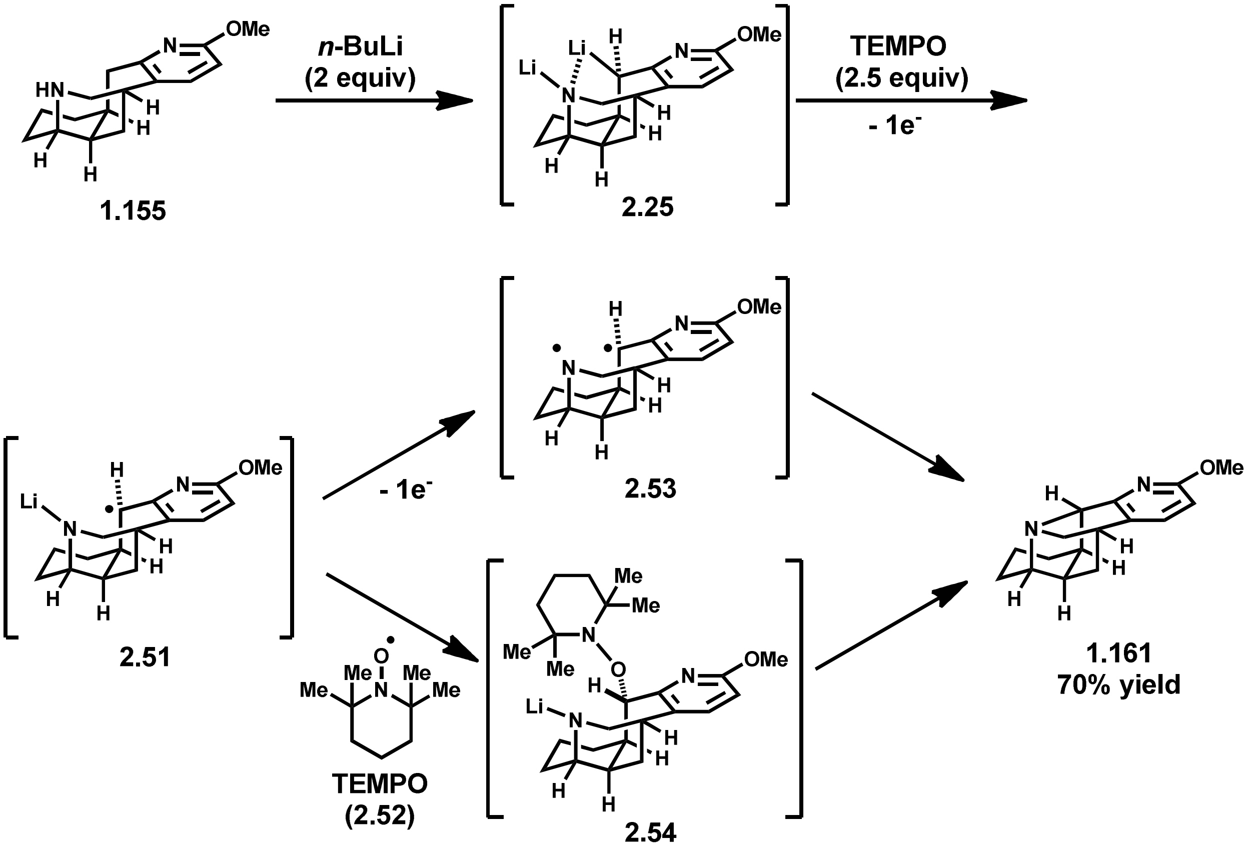

OMe
HN
H
H
H
H
1.155
n-BuLi
(2 equiv)
Li
Li
H
N
OMe
2.25
PhSSPh
PhS
H
Li
N
OMe
2.43
n-BuLi
Li
Li
SPh
N
OMe
2.44
PhSSPh
PhS
SPh
Li
N
OMe
2.45
-PhSH
Li
PhS
N
OMe
2.46
PhS
N
OMe
Li
2.47
PhSSPh
PhS
N
OMe
SPh
2.48
H2O
O
HN
OMe
SPh
2.41

Scheme 2.12. Synthesis of Sulfides



In addition to halogen electrophiles and diphenyl disulfide, phenyliodine(III) diacetate (PIDA) promotes the formation of pentacycle **1.161** from dianion **2.25** in 65% yield. Although experimental evidence from reactivity studies with PhSSPh provides support for polar mechanistic pathways for the transformation of tetracycle **1.155** to tertiary amine **1.161**, a single-electron transfer (SET) mechanistic pathway can not be excluded. For halogen electrophiles (NCS, NBS, NIS, I_2) and hypervalent iodine (PIDA), both polar and radical mechanisms could be operative during the formation of pentacycle **1.161**. SET reactions of metalated organic compounds are well-documented and are often dependent on the nature of the electrophile.[30,31] To test the viability of SET processes, amine **1.155** was treated with 2 equivalents of *n*-BuLi to generate dianion **2.25**, which upon treatment with 2.5 equivalents of 2,2,6,6-tetramethylpiperidine-N-oxyl (TEMPO, **2.52**) furnished pentacyclic amine **1.161** in 70% yield (Scheme 2.13). Mechanistically, single electron oxidation of dianion **2.25** mediated by TEMPO could provide radical anion **2.51**. Subsequent oxidation of radical anion **2.51** to diradical **2.53** followed by recombination could afford pentacycle **1.161**. Alternatively, radical combination of TEMPO (**2.52**) and radical anion **2.51** could furnish TEMPO adduct **2.54**. Intramolecular displacement by the lithium amide of **2.54** could give pentacycle **1.161**. The oxidation of dianion **2.25** to tertiary amine **1.161** facilitated by TEMPO provides support that the mechanism of the oxidative C-N bond formation could proceed by a SET pathway.

Scheme 2.13. Proposed Mechanism for TEMPO Oxidation



2.6 Conclusion

NMR experiments and DFT calculations were employed to investigate the structure of dianion intermediate **2.25** and these studies indicate that the structure of the dianion is best represented by internally-chelated dianion **2.36**, which possesses three coordinated THF molecules. Consistent with the NMR studies and DFT calculations, deuterium quenching studies provide support that the stereodefined carbanion of **2.25** resides in the C6 *endo* position. Several oxidants including PhSSPh, I_2, PIDA and TEMPO were found to promote C-N bond formation by oxidation of dianion **2.25** to furnish pentacycle **1.161**. The diverse nature of the reagents capable of mediating this oxidation provides support that the C-N bond formation may proceed by polar or SET mechanisms and that the mechanistic pathway is dependent on the type of oxidant utilized. Electrophilic reagents such as PhSSPh were found to react initially at C6 of dianion **2.25** and to proceed with stereochemical inversion to place the electrophile in the C6 *exo* position. The application of intramolecular oxidative C-N bond formation in other systems is currently being examined.

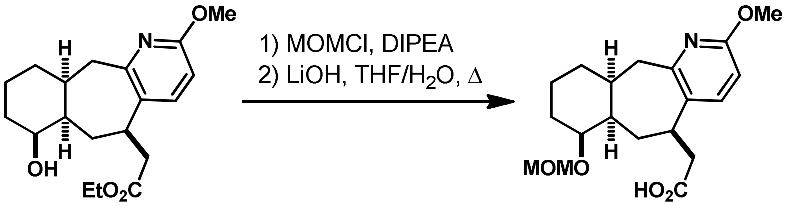
2.7 Experimental Contributions

Jocelyn M. Gruver under the direction of Professor David B. Collum at Cornell University conducted the NMR experiments on the dianion intermediates (Figures 2.1 and 2.2). Jocelyn M. Gruver performed the DFT calculations on the proposed dianion structures (Figure 2.3). Andrew D. Lim synthesized intermediates that were used to prepare the model tetracycle for the mechanistic studies. The remainder of the work in this chapter was conducted by Scott P. West.

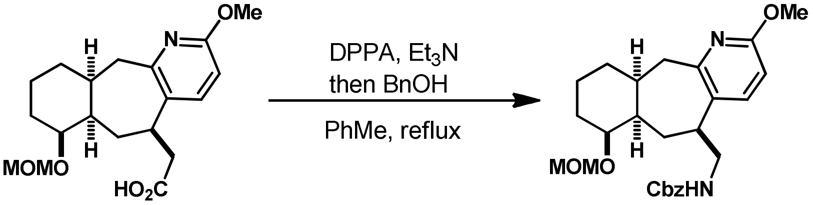
2.8 Experimental Methods

Materials and Methods

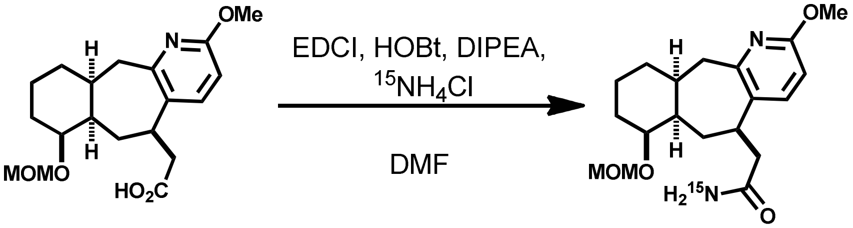
Unless otherwise stated, reactions were performed in oven-dried glassware fitted with rubber septa under a nitrogen atmosphere and were stirred with Teflon-coated magnetic stirring bars. Liquid reagents and solvents were transferred via syringe using standard Schlenk techniques. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled over sodium/benzophenone ketyl. Dichloromethane (CH_2Cl_2), toluene, and benzene were distilled over calcium hydride. Acetonitrile was distilled over potassium carbonate. N,N-Diisopropylethylamine (DIPEA) was distilled over calcium hydride prior to use. All other solvents and reagents were used as received unless otherwise noted. Reaction temperatures above 23 °C refer to oil bath temperature, which was controlled by an OptiCHEM temperature modulator. Thin layer chromatography was performed using SiliCycle silica gel 60 F-254 precoated plates (0.25 mm) and visualized by UV irradiation and anisaldehyde stain. SiliCycle Silica-P silica gel (particle size 40-63 μm) was used for flash chromatography. Melting points were recorded on a Laboratory Devices Mel-Temp 3.0 and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on Bruker AVB-400, DRX-500, AV-500 and AV-600 MHz spectrometers with ^{13}C operating frequencies of 100, 125, 125 and 150 MHz, respectively. ^{15}N NMR spectra were recorded on Bruker AVB-400 with ^{15}N operating frequency of 40 MHz. Chemical shifts (δ) are reported in ppm. ^{15}N NMR spectra are calibrated relative to $^{15}NH_4Cl$ in D_2O at $\delta = 20.0$ ppm. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal ($\delta = 7.26$ for ^1H NMR and $\delta = 77.0$ for ^{13}C NMR). Data for ^1H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants, number of hydrogens). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). IR spectra were recorded on a Nicolet MAGNA-IR 850 spectrometer and are reported in frequency of absorption (cm^{-1}). Only selected IR absorbencies are reported. High resolution mass spectral data were obtained from the Mass Spectral Facility at the University of California, Berkeley.



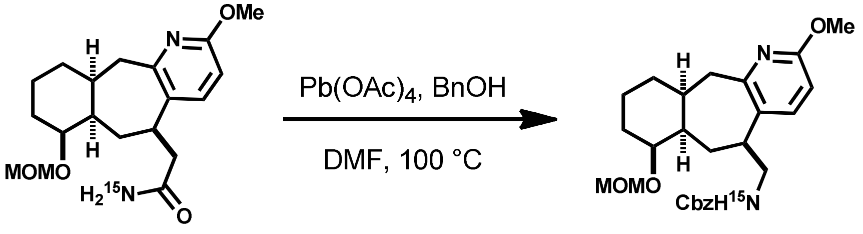
Acid (2.29): The title compound was prepared according to the procedures described for the conversion of alcohol **1.158** to acid **1.159** in 86% yield over 2 steps to give a pale yellow foam. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.4 Hz, 1H), 6.50 (d, *J* = 8.4 Hz, 1H), 4.68 (d, *J* = 6.7 Hz, 1H), 4.61 (d, *J* = 6.7 Hz, 1H), 3.85 (s, 3H), 3.60-3.55 (m, 1H), 3.39-3.35 (m, 1H), 3.34 (s, 3H), 3.32-3.25 (m, 1H), 3.21 (d, *J* = 14.2 Hz, 1H), 2.91 (dd, *J* = 13.5, 6.5 Hz, 1H), 2.82 (dd, *J* = 16.0, 6.6 Hz, 1H), 2.69 (dd, *J* = 16.04, 8.5 Hz, 1H), 2.40-2.34 (m, 1H), 1.88-1.80 (m, 2H), 1.65-1.53 (m, 2H), 1.37-1.14 (m, 4H), 0.64-0.49 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 177.59, 161.58, 157.09, 134.41, 130.97, 106.37, 94.27, 78.15, 55.18, 53.41, 45.57, 42.34, 39.44, 35.96, 35.87, 27.51, 27.00, 24.93, 24.19; **HRMS** (ESI) m/z 350.1970 [$(M+H)^+$; calculated for $[C_{19}H_{28}NO_5]^+$: 350.1962].



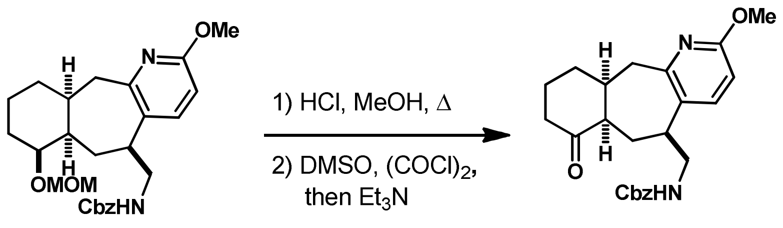
Cbz-protected amine (2.22): The title compound was prepared according to the procedures described for the preparation of Cbz-protected amine **1.131** in 66% yield to give a colorless oil. **R$_f$** 0.50 (1:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$, major rotamer) δ 7.37-7.21 (m, 6H), 6.50 (d, J = 8.37 Hz, 1H), 5.11-5.04 (m, 2H), 4.99-4.93 (m, 1H), 4.67-4.61 (m, 2H), 3.86 (s, 3H), 3.65-3.43 (m, 3H), 3.39-3.29 (m, 3H), 3.13-2.98 (m, 1H), 2.96-2.78 (m, 2H), 2.32-2.15 (m, 1H), 1.92-1.80 (m, 1H), 1.67-1.51 (m, 2H), 1.40-1.14 (m, 5H), 0.68-0.53 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$, major rotamer) δ 161.56, 156.33, 156.25, 136.37, 128.42, 128.40, 128.02, 128.01, 127.97, 106.70, 94.75, 78.58, 66.04, 55.22, 53.24, 44.68, 42.28, 42.15, 36.00, 31.14, 26.99, 25.64, 24.07, 20.49; **IR** (film) υ_{max} 3336, 2937, 2146, 1701, 1594, 1533, 1474, 1299, 1254, 1032, 915, 823 cm^{-1}; **HRMS** (ESI) m/z 455.2538 [$(M+H)^+$; calculated for $[C_{26}H_{35}N_2O_5]^+$: 455.2540].



Amide (2.33): To a solution of acid **2.29** (500 mg, 1.43 mmol) in N,N-dimethylformamide (DMF, 14 mL) was added ^{15}N-labeled ammonium chloride ($^{15}NH_4Cl$, 156 mg, 2.86 mmol), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI, 412 mg, 2.15 mmol), and 1-hydroxybenzotriazole (HOBt, 291 mg, 2.15 mmol) followed by N,N-diisopropylethylamine (DIPEA, 0.996 mL, 5.72 mmol). The reaction mixture was stirred at rt for 12 h. The reaction mixture was diluted with CH_2Cl_2/Et_2O (1:3, 50 mL) and poured on H_2O (50 mL). The aqueous layer was extracted with CH_2Cl_2/Et_2O (1:3, 25 mL). The combined organic layers were washed with water (3 x 25 mL), saturated NH_4Cl (2 x 25 mL), saturated NaCl (25 mL), dried over $MgSO_4$ and concentrated under vacuum to afford amide **2.33** (456 mg) in 91% yield. This material was >95% pure and was taken on to the next step without purification. **R$_f$** 0.10 (9:1 $CH_2Cl_2/MeOH$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.26 (d, J = 8.4 Hz, 1H), 6.50 (d, J = 8.4 Hz, 1H), 5.72 (d, $J(^{15}N,H)$ = 88.4 Hz, 1H), 5.61 (d, $J(^{15}N,H)$ = 88.6 Hz, 1H), 4.68 (d, J = 6.7 Hz, 1H), 4.62 (d, J = 6.70 Hz, 1H), 3.87 (s, 3H), 3.61-3.55 (m, 1H), 3.37 (s, 3H), 3.35-3.29 (m, 1H), 3.25-3.19 (m, 1H), 2.90 (dd, J = 13.7, 7.0 Hz, 1H), 2.69 (dd, J = 14.8, 6.2 Hz, 1H), 2.52 (dd, J = 14.8, 8.8 Hz, 1H), 2.40-2.32 (m, 1H), 1.92-1.81 (m, 2H), 1.67-1.54 (m, 2H), 1.35-1.18 (m, 4H), 0.66-0.54 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.76 (d, $J(C,^{15}N)$ = 13.8 Hz), 161.56, 157.03, 134.73, 131.05, 106.53, 94.42, 78.07, 55.33, 53.34, 45.18, 42.54, 41.08, 36.30, 35.89, 27.13, 25.11, 24.22, **^{15}N NMR** (40 MHz, $CDCl_3$) δ 105.5; **IR** (film) υ_{max} 2929, 1735, 1595, 1477, 1299, 1150, 1102, 1010, 915, 825 cm^{-1}; **HRMS** (ESI) m/z 350.2104 [(M+H)$^+$; calculated for [$C_{19}H_{29}{}^{15}NNO_4$]$^+$: 350.2092].

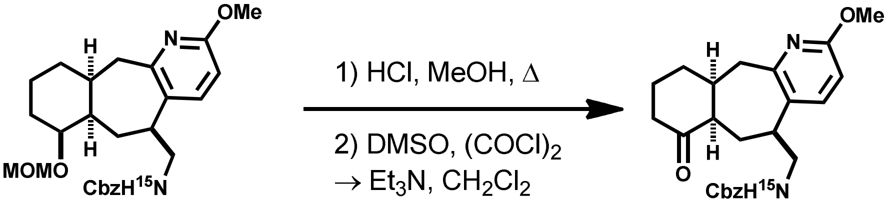


Cbz-amine (2.30): To a solution of amide **2.33** (320 mg, 0.92 mmol) in N,N-dimethylformamide (DMF, 14 mL) was added lead (IV) tetraacetate (2.45 g, 5.5 mmol) and benzyl alcohol (574 µL, 5.5 mmol). The reaction vial was sealed and heated at 100 ºC for 48 h. The reaction was allowed to cool to rt, poured on saturated $NaHCO_3$ (30 mL), and extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with saturated $NaHCO_3$ (25 mL), water (2 x 25 mL), and saturated NaCl (25 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by flash chromatography (8:1 hexanes/EtOAc to 4:1 hexanes/EtOAc) to provide Cbz-amine **2.30** (193 mg) in 46% yield. **R_f** 0.35 (2:1 hexanes/EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.37-7.21 (m, 6H), 6.50 (d, *J* = 8.4 Hz, 1H), 5.11-5.04 (m, 2H), 4.95-4.77 (dt, *J*(^{15}N,H) = 90.8 Hz, *J*(H,H) = 5.6 Hz, 1H), 4.67-4.61 (m, 2H), 3.86 (s, 3H), 3.65-3.43 (m, 3H), 3.39-3.29 (m, 3H), 3.13-2.98 (m, 1H), 2.96-2.78 (m, 2H), 2.32-2.15 (m, 1H), 1.92-1.80 (m, 1H), 1.67-1.51 (m, 2H), 1.40-1.14 (m, 5H), 0.68-0.53 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 161.71, 157.23, 156.30 (d, *J*(C,^{15}N) = 26.9 Hz), 136.46, 129.30, 128.49, 128.10, 128.09, 128.06, 106.84, 94.88, 78.69, 66.72, 55.30, 53.30, 44.75 (d, *J*(C,^{15}N) = 12.0 Hz), 42.37, 40.22, 34.63, 27.09, 24.75, 24.14, 23.51; **^{15}N NMR** (40 MHz, $CDCl_3$) δ 80.9; **IR** (film) υ_{max} 3336, 2937, 2146, 1701, 1594, 1533, 1474, 1299, 1254, 1032, 915, 823 cm^{-1}; **HRMS** (ESI) m/z 456.2530 [(M+H)$^+$; calculated for [$C_{26}H_{35}{}^{15}NNO_5$]$^+$: 456.2511].

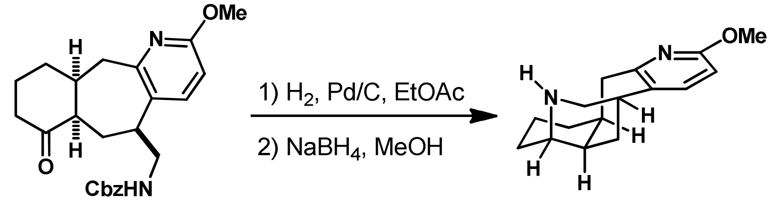


Amino ketone (2.55): The title compound was prepared according to the procedures described for the conversion of Cbz-protected amine **1.131** to amino ketone **1.59** in 86% yield over the two steps to give a yellow oil. **R_f** 0.70 (1:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$, major rotamer) δ 7.38-7.25 (m, 6H), 6.53 (d, *J* = 8.3 Hz, 1H), 5.08 (br s, 2H), 3.88 (s, 3H), 3.61-3.28 (m, 2H), 3.11-2.96 (m, 2H), 2.96-2.87 (m, 1H), 2.73-2.58 (m, 1H), 2.33-2.15 (m, 3H), 2.00-1.87 (m, 1H), 1.76-1.54 (m, 4H), 1.26-1.12 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$, major rotamer) δ

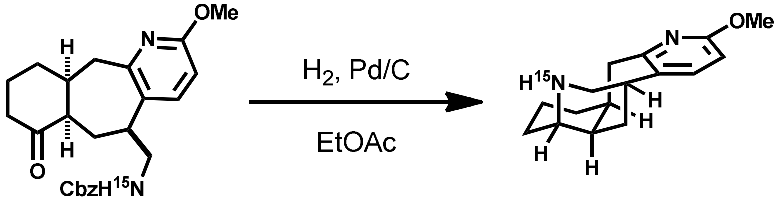
213.68, 161.97, 156.39, 156.21, 140.50, 136.35, 128.45, 128.08, 128.03, 127.92, 107.37, 66.72, 53.36, 52.74, 44.33, 41.22, 38.63, 37.26, 34.05, 28.70, 25.80, 24.63; **IR** (film) υ$_{max}$ 3335, 2937, 1709, 1595, 1477, 1301, 1255, 1032, 734, 698 cm^{-1}; **HRMS** (ESI) m/z 409.2123 [(M+H)$^+$; calculated for [$C_{24}H_{29}N_2O_4$]$^+$: 409.2122].


OMe
N
H
H
MOMO
CbzH¹⁵N
1) HCl, MeOH, Δ
2) DMSO, (COCl)2
→ Et3N, CH2Cl2
OMe
N
H
H
O
CbzH¹⁵N

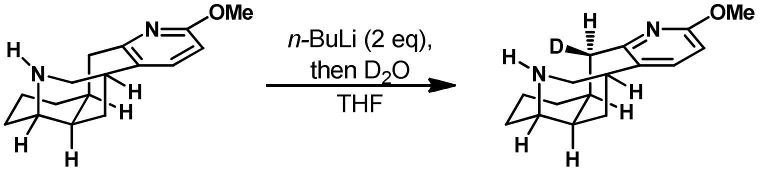
Ketone (2.56): The title compound was obtained according to the procedure described for the conversion of **1.131** to **1.59** in 76% yield. **R$_f$** 0.70 (1:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$, major rotamer) δ 7.38-7.25 (m, 6H), 6.53 (d, *J* = 8.3 Hz, 1H), 5.08 (br s, 2H), 3.88 (s, 3H), 3.61-3.28 (m, 2H), 3.11-2.96 (m, 2H), 2.96-2.87 (m, 1H), 2.73-2.58 (m, 1H), 2.33-2.15 (m, 3H), 2.00-1.87 (m, 1H), 1.76-1.54 (m, 4H), 1.26-1.12 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$, major rotamer) δ 213.53, 161.97, 156.46, 156.28, 140.44, 136.40, 128.42, 128.04, 128.01, 127.99, 107.37, 66.69, 53.28, 52.72, 44.36 (d, *J*(C,^{15}N) = 10.7 Hz), 41.22, 38.66, 37.27, 30.56, 28.92, 24.59, 19.03; **^{15}N NMR** (40 MHz, $CDCl_3$) δ 80.4; **IR** (film) υ$_{max}$ 3335, 2937, 1709, 1595, 1477, 1301, 1255, 1032, 734, 698 cm^{-1}; **HRMS** (ESI) m/z 410.2102 [(M+H)$^+$; calculated for [$C_{24}H_{29}{}^{15}NNO_4$]$^+$: 410.2092].


OMe
N
H
H
O
CbzHN
1) H2, Pd/C, EtOAc
2) NaBH4, MeOH
OMe
N
H
N
H
H
H
H

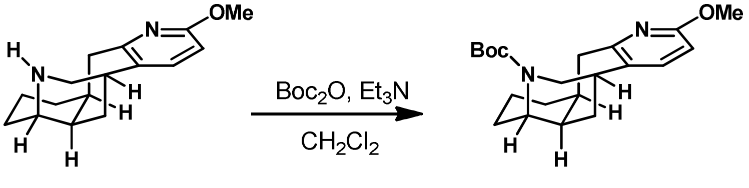
Tetracyclic amine (1.155): The title compound was obtained according to the procedure described for **1.57** in 90% yield as a colorless gel. This material was used without further purification in the next step. **R$_f$** 0.15 (10% MeOH in CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.1 Hz, 1H), 6.43 (d, *J* = 8.1 Hz, 1H), 4.66 (m, 1H), 3.89 (s, 3H), 3.27-3.15 (m, 2H), 3.02 (br s, 1H), 2.74 (dd, *J* =15.5, 4.5 Hz, 1H), 2.66 (m, 1H), 2.13-2.06 (m, 1H), 2.00 (m, 1H), 1.95-1.79 (m, 2H), 1.79-1.54 (m, 4H), 1.43-1.33 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 161.65, 157.45, 141.20, 132.27, 106.94, 70.48, 55.19, 53.16, 44.32, 36.83, 36.28, 34.14, 33.35, 33.06, 31.08, 15.59; **IR** (film) υ$_{max}$ 2928, 2865, 1596, 1478, 1425, 1307, 1283, 1034, cm^{-1}; **HRMS** (ESI) m/z 259.1808 [(M+H)$^+$; calculated for [$C_{16}H_{23}N_2O$]$^+$: 259.1805].


OMe
N
H
H
O
CbzH¹⁵N
H2, Pd/C
EtOAc
OMe
N
H¹⁵N
H
H
H
H

Tetracyclic amine (2.31): The title compound was obtained according to the procedure described for **1.57** in 91% yield as a colorless gel. This material was used without further purification in the next step. **R$_f$** 0.15 (10% MeOH in CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.1 Hz, 1H), 6.43 (d, *J* = 8.1 Hz, 1H), 4.66 (m, 1H), 3.89 (s, 3H), 3.27-3.15 (m, 2H), 3.02 (br s, 1H), 2.74 (dd, *J* =15.5, 4.5 Hz, 1H), 2.66 (m, 1H), 2.13-2.06 (m, 1H), 2.00 (m, 1H), 1.95-1.79 (m, 3H), 1.79-1.54 (m, 4H), 1.43-1.33 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 161.36, 158.96, 141.21, 134.32, 106.19, 56.50 (d, *J*(C,^{15}N) = 3.0 Hz), 54.25(d, *J*(C,^{15}N) = 3.3 Hz), 53.12, 45.54 (d, *J*(C,^{15}N) = 2.2 Hz), 38.84, 37.73, 35.58, 34.12, 33.75, 33.37, 16.01; **^{15}N NMR** (40 MHz, $CDCl_3$) δ 48.1; **IR** (film) υ_{max} 2928, 2865, 1596, 1478, 1425, 1307, 1283, 1034, cm^{-1}; **HRMS** (ESI) m/z 260.1774 [(M+H)$^+$; calculated for $[C_{16}H_{23}{}^{15}NNO]^+$: 260.1775].

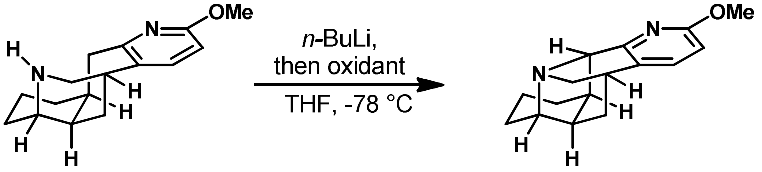


Deuterated amine (2.27): To a solution of **1.155** (5.0 mg, 0.019 mmol) in THF (1 mL) at -78 °C was added *n*-butyllithium (2.5M in hexanes, 15 μL, 0.038 mmol). After stirring the resulting bright orange solution for 30 min at -78 °C, D_2O (30 μL, 1.7 mmol) was added in one portion. The reaction mixture was allowed to warm to rt over 1 h. The reaction mixture was added to 1N NaOH (5 mL) and extracted with CH_2Cl_2 (3 X 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum to provide **2.27** (5 mg, 72% D incorporation) in quantitative yield as a colorless oil. **R$_f$** 0.15 (10% MeOH in CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.1 Hz, 1H), 6.43 (d, *J* = 8.1 Hz, 1H), 4.66 (m, 0.28 H), 3.89 (s, 3H), 3.27-3.15 (m, 2H), 3.02 (br s, 1H), 2.72 (m, 1H), 2.66 (m, 1H), 2.13-2.06 (m, 1H), 2.00 (m, 1H), 1.95-1.79 (m, 2H), 1.79-1.54 (m, 4H), 1.43-1.33 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 161.35, 158.94, 141.22, 134.38, 106.20, 56.52, 54.30, 53.15, 45.23(t), 38.87, 37.74, 35.60, 34.13, 33.68, 33.39, 16.03; **IR** (film) υ_{max} 2926, 1594, 1476, 1424, 1246, 1100, 1036, 821, 664 cm^{-1}; **HRMS** (EI) m/z 259.1799 [(M+H)$^+$; calculated for $[C_{16}H_{21}DN_2O]^+$: 259.1795]. This procedure was used for the conversion of **2.27** → **2.28** (D_2O quench) and **2.27** → **1.155** (H_2O quench).

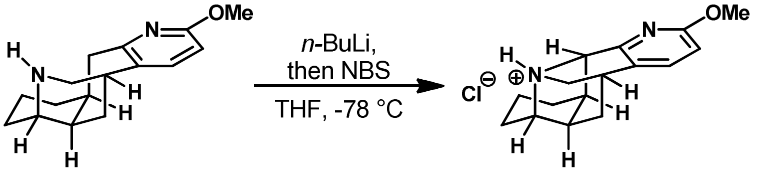


Boc-protected tetracyclic amine (2.57): The title compound was obtained according to the procedure described for **1.124** to provide **2.57** as a colorless oil in 90% yield. **R$_f$** 0.55 (2:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, C_6D_6) δ 6.79 (d, *J* = 8.2 Hz, 1H), 6.46 (d, *J* = 8.2 Hz, 1H), 4.26-4.22 (m, 1H), 3.96 (dd, *J* = 16.1, 13.8 Hz, 1H), 3.82 (s, 3H), 3.22-3.17 (m, 1H), 3.07 (dd, *J* = 16.4, 4.3 Hz, 1H), 3.04-2.96 (m, 1H), 2.93 (dd, *J* = 13.5, 4.6 Hz, 1H), 2.36-2.32 (m, 1H), 2.30-2.21 (m, 1H), 1.91-1.84 (m, 1H), 1.63-1.56 (m, 2H), 1.54-1.48 (m, 1H), 1.48-1.39 (m, 3H), 1.38-1.29 (m, 1H), 1.25 (s, 9H); **^{13}C NMR** (125 MHz) δ 161.53, 157.55, 153.66, 141.08, 131.84, 107.28, 78.35, 56.90, 52.52, 52.04, 43.47, 39.19, 38.71, 35.33, 34.51, 33.36, 30.26, 28.02, 18.13. NOESY, COSY, and HMBC data for **2.57** is included with ^{1}H and ^{13}C.

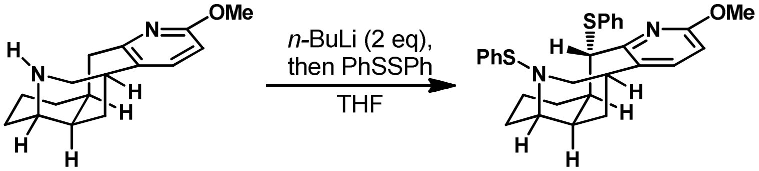
General Procedure for C-N bond formation using the following oxidants: iodine, N-chlorosuccinimide (NCS), N-bromosuccinimide (NBS), N-iodosuccinimide (NIS), and (diacetoxyiodo)benzene.



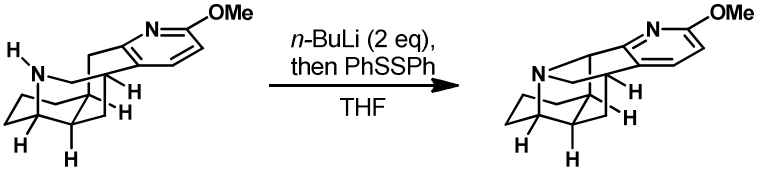
Tertiary Amine (1.161): To a solution of **1.155** (1 equiv) in THF (0.02M) at -78 ºC was added *n*-butyllithium (2.5M in hexanes, 2 equiv) over 2 min. After stirring the resulting bright orange solution for 30 min at -78 ºC, the oxidant (1 equiv) was added in one portion. The reaction mixture was stirred at -78 ºC for 2 h and then slowly allowed to warm to 0 ºC (ca. 2 h). The reaction mixture was quenched by sequential slow addition of saturated aq. NH_4Cl (1 mL), saturated aq. $NaHSO_3$ (1 mL) and 1N NaOH (5 mL), and extracted with CH_2Cl_2 (3 X 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum to afford a yellow oil which was purified by flash chromatography (10 % MeOH in CH_2Cl_2) to afford **1.161** as a yellow oil. The results for the different oxidants are I_2 (90% yield), NCS (80% yield), NBS (86% yield), NIS (90% yield) and (diacetoxyiodo)benzene (65% yield). **R_f** 0.32 (10 % MeOH in CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.1 Hz, 1H), 6.46 (d, = 8.14 Hz, 1H), 4.25 (br s, 1H), 3.91 (s, 3H), 3.42 (dd, *J* = 13, 3.5 Hz, 1H), 3.31 (br s, 1H), 2.90-2.84 (m, 1H), 2.73-2.68 (m, 1H), 2.13-2.05 (m, 2H), 2.05-1.96 (m, 1H), 1.92-1.87 (m, 1H), 1.87-1.73 (m, 2H), 1.72-1.66 (m, 1H), 1.62-1.48 (m, 1H), 1.47-1.38 (m, 1H), 1.34-1.26 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 162.67, 159.72, 134.84, 133.39, 106.04, 71.16, 68.07, 61.04, 53.55, 49.13, 46.53, 34.63, 33.74, 31.70, 30.77, 18.25; **IR** (film) υ_{max} 2931, 2856, 1709, 1600, 1477, 1423, 1310, 1264, 1179, 1030, 780 cm^{-1}; **HRMS** (ESI) m/z 257.1652 [$(M+H)^+$; calculated for $[C_{16}H_{21}N_2O]^+$: 257.1648].



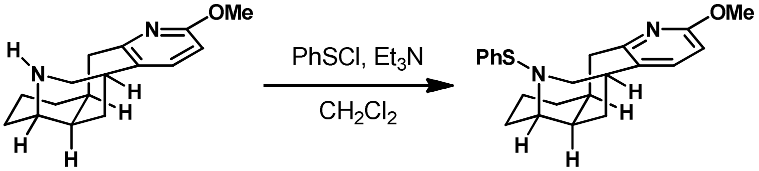
Tertiary amine salt (2.39): To a solution of **1.155** (10 mg, 0.039 mmol) in THF (2 mL) at -78 ºC was added *n*-BuLi (2.5M in hexanes, 62 μL, 0.156 mmol) over 2 min. After stirring at -78 ºC for 30 min (bright orange reaction mixture), solid *N*-bromosuccinimide (NBS, 56 mg, 0.312 mmol) was added in one portion. The reaction mixture was stirred at -78 ºC for 2 h and then slowly allowed to warm to 0 ºC (2 h). During this time, the color of the reaction mixture changed from bright orange to amber. The reaction mixture was quenched by sequential slow addition of saturated aq. NH_4Cl (1 mL), saturated aq. $NaHSO_3$ (2 mL) and 1N NaOH (10 mL), and extracted with CH_2Cl_2 (3 X 5 mL). The combined organic extracts were dried over $MgSO_4$, concentrated under vacuum and purified by flash chromatography ($CH_2Cl_2 \rightarrow$ 9:1 CH_2Cl_2/MeOH $\rightarrow$ 4:1 CH_2Cl_2/MeOH $\rightarrow$ 1:1 CH_2Cl_2/MeOH) to provide 7.0 mg (61% yield) of **2.39** as a yellow solid. Recrystallization of **2.39** from CH_2Cl_2/pentane provided crystals suitable for X-ray analysis. **R_f** 0.10 (10 % MeOH in CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.0 Hz, 1H), 6.59 (d, *J* = 8.0 Hz, 1H), 4.95 (s, 1H), 3.95 (s, 1H), 3.91 (s, 3H), 3.79 (dd, *J* = 12.5, 3.5 Hz 1H), 3.30 (d, *J* = 12 Hz 1H), 3.14 (br s, 1H), 2.86-2.75 (m, 1H), 2.37 (m, 1H), 2.30 (s, 1H), 2.26-2.18 (m, 1H), 2.15-1.96 (m, 2H), 1.95-1.89 (m, 1H), 1.83-1.75 (m, 1H), 1.70-1.59 (m, 1H), 1.50 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.71, 152.53, 135.63, 129.67, 109.84, 73.68, 67.76, 58.59, 53.89, 47.24, 46.95, 32.83, 32.10, 29.73, 27.53, 17.06; **IR** (film) υ_{max} 3420, 2928, 2856, 1647, 1608, 1482, 1425, 1318, 1030, 831 cm^{-1}; **HRMS** (ESI) m/z 257.1654 $[(M)^+$; calculated for $[C_{16}H_{21}N_2O]^+$: 257.1648]; **MP** 193-194 °C.



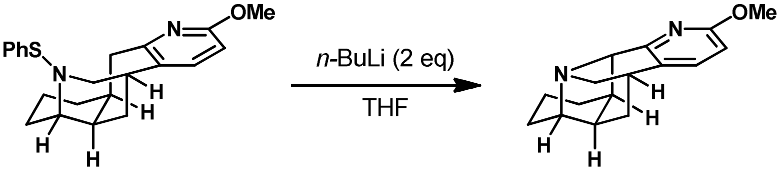
Bissulfide (2.40): To a solution of **1.155** (10 mg, 0.039 mmol) in THF (2 mL) at -78 °C was added *n*-BuLi (0.3M in hexanes/diethyl ether, 260 µL, 0.078 mmol) over 2 min. After stirring at -78 °C for 30 min (bright orange reaction mixture), diphenyl disulfide (102 mg, .47 mmol) in THF (0.5 mL) was added over 1 min. The reaction mixture was stirred at -78 °C for 2 h and then slowly allowed to warm to 0 °C (3 h). During this time, the color of the reaction mixture changed from bright orange to yellow. The reaction mixture was quenched by sequential slow addition of saturated aq. NH_4Cl (2 mL) and water (3 mL). The reaction mixture was poured on 1N NaOH (8 mL) and extracted with CH_2Cl_2 (3 X 5 mL). The combined organic extracts were dried over $MgSO_4$, concentrated under vacuum and purified by flash chromatography (hexanes $\rightarrow$ 50:1 hexanes/EtOAc $\rightarrow$ 20/1 hexanes/EtOAc $\rightarrow$ CH_2Cl_2 $\rightarrow$ 10% MeOH/CH_2Cl_2) to provide 7.2 mg (40% yield) of bissulfide **2.40** as a clear oil and 2.2 mg (22% yield) of tertiary amine **1.161** as a yellow oil. **R_f** 0.52 (8:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $(CD_3)_2CO$) δ 7.50 (d, *J* = 8.3 Hz, 1H), 7.39-7.37 (m, 2H), 7.32-7.24 (m, 7H), 7.14-7.10 (m, 1H), 6.54 (d, *J* = 8.2 Hz, 1H), 5.60 (d, *J* = 7.6 Hz, 1H), 3.64 (s, 3H), 3.61-3.59 (m, 1H), 3.38 (dd, *J* = 12.0, 4.2 Hz, 1H), 3.06 (br s, 1H), 3.02 (m, 1H), 2.89-2.81 (m, 1H), 2.49-2.47 (m, 1H), 2.43 (m, 1H), 2.37-2.30 (m, 2H), 1.96-1.90 (m, 1H), 1.67-1.51 (m, 2H), 1.46-1.37 (m, 2H); **^{13}C NMR** (125 MHz, $(CD_3)_2CO$) δ 161.80, 156.64, 143.05, 140.34, 137.09, 132.57, 131.03, 129.98, 129.68, 129.46, 128.45, 126.17, 109.35, 66.57, 62.54, 60.32, 53.27, 41.87, 41.56, 39.00, 34.11, 31.11, 28.75, 17.76; **IR** (film) υ_{max} 2924, 2854, 2359, 1732, 1597, 1477, 1438, 1272, 1026, 737 cm^{-1}; **HRMS** (ESI) m/z 475.1875 $[(M+H)^+$; calculated for $[C_{28}H_{31}N_2OS_2]^+$: 475.1872]. 2D NOESY data was used to determine relative stereochemistry. NOESY, COSY, and HMQC data for **2.40** is included with ^{1}H and ^{13}C.



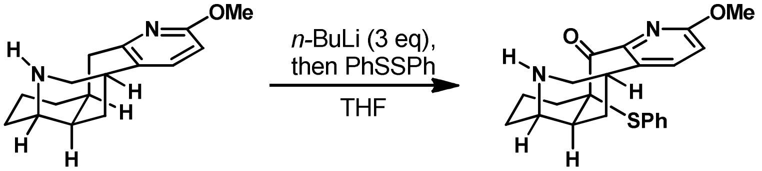
Tertiary amine (1.161): To a solution of **1.155** (10 mg, 0.039 mmol) in THF (2 mL) at -78 ºC was added *n*-BuLi (2.5 M in hexanes, 32 μL, 0.078 mmol) over 2 min. After stirring at -78 ºC for 30 min (bright orange reaction mixture), diphenyl disulfide (9 mg, 0.039 mmol) is added in one portion. The reaction mixture was stirred at -78 ºC for 2 h and then slowly allowed to warm to 0 ºC (3 h). During this time, the color of the reaction mixture changed from bright orange to yellow. The reaction mixture was quenched by sequential slow addition of saturated aq. NH_4Cl (2 mL) and water (2 mL). The reaction mixture was poured on 1M NaOH (5 mL) and extracted with CH_2Cl_2 (3 X 5 mL). The combined organic extracts were dried over $MgSO_4$, concentrated under vacuum and purified by flash chromatography (CH_2Cl_2 → 5% MeOH/CH_2Cl_2→ 10% MeOH/CH_2Cl_2) to provide 6.4 mg (64% yield) of tertiary amine **1.161** as a yellow oil.



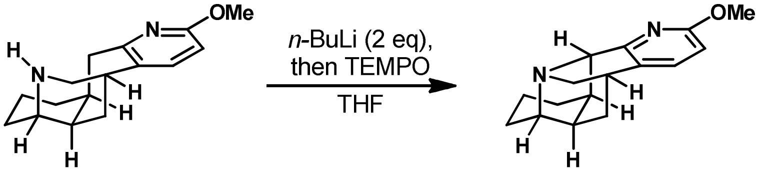
Aminosulfide (2.42): To a solution of amine **1.155** (10 mg, 0.038 mmol) and triethylamine (54 μL, 0.38 mmol) in CH_2Cl_2 (1 mL) is added PhSCl[6] (0.95 M soln in CH_2Cl_2, 0.20 mL, 0.19 mmol) over 2 min. Reaction is allowed to stir for 12 h and then poured on water (5 mL) and extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were dried over $MgSO_4$, concentrated under vacuum and purified by flash chromatography (hexanes → 50:1 hexanes/EtOAc → 20/1 hexanes/EtOAc) to give 8.0 mg (57% yield) of aminosulfide **2.42** as a light red oil. **R$_f$** 0.62 (8:1 hexanes/EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.37 (m, 2H), 7.32-7.28 (m, 2H), 7.27-7.24 (m, 1H) 7.20 (d, *J* = 8.2 Hz, 1H), 6.44 (d, *J* = 8.1 Hz, 1H), 4.50-4.43 (m, 1H), 3.91 (s, 3H), 3.54 (td, *J* = 11.8, 1.7 Hz, 1H), 3.28 (dd, *J* = 11.9, 4.7 Hz, 1H), 2.98 (m, 2H), 2.75 (t, *J* = 5.0 Hz, 1H), 2.69 (dd, *J* = 15.3, 3.9 Hz, 1H), 2.13-2.06 (m, 1H), 2.06-2.02 (m, 1H), 1.90 (td, *J* = 13.4, 5.7 Hz, 1H), 1.82-1.74 (m, 1H), 1.68 (td, *J* = 13.5, 4.2 Hz, 1H), 1.50 (td, *J* = 9.1, 4.2 Hz, 1H), 1.43 (m, 1H), 1.28 (m, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 161.56, 158.83, 141.08, 135.71, 133.53, 131.37, 128.51, 127.64, 106.35, 64.59, 61.25, 53.20, 44.63, 41.23, 39.54, 35.22, 34.45, 34.37, 30.43, 15.97; **IR** (film) υ_{max} 2928, 1597, 1477, 1425, 1302, 1265, 1035, 822, 749, 692 cm^{-1}; **HRMS** (ESI) m/z 367.1838 [(M+H)$^+$; calculated for $[C_{22}H_{27}N_2OS]^+$: 367.1839].



Tertiary amine (1.161): To a solution of aminosulfide **2.42** (4.0 mg, 0.011 mmol) in THF (1 mL) at -78 °C was added *n*-BuLi (0.2 M in hexanes/diethyl ether, 110 µL, 0.022 mmol) over 2 min. After stirring for 1.5 h at -78 °C, the reaction was slowly allowed to warm to 0 °C (1.5 h). Water (3 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were dried over $MgSO_4$, concentrated under vacuum and purified by flash chromatography (50:1 hexanes/EtOAc → 20/1 hexanes/EtOAc → CH_2Cl_2 → 10% MeOH/CH_2Cl_2)) to give 2.0 mg (71% yield) of tertiary amine **1.161** as a yellow oil.

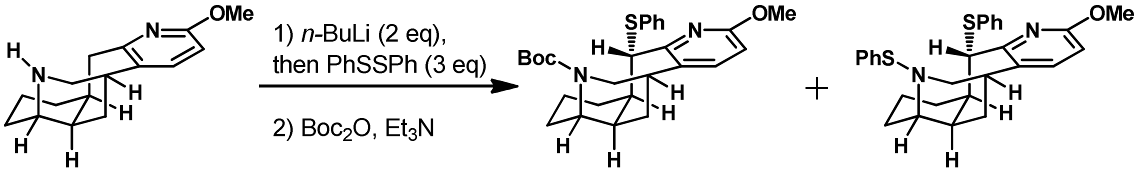


Ketosulfide (2.41): To a solution of **1.155** (15 mg, 0.058 mmol) in THF (2.5 mL) at -78 °C was added *n*-BuLi (2.5 M in hexanes, 70 µL, 0.174 mmol) over 2 min. After stirring at -78 °C for 30 min (bright orange reaction mixture), diphenyl disulfide (101 mg, .46 mmol) in THF (0.5 mL) was added over 1 min. The reaction mixture was stirred at -78 °C for 2 h and then slowly allowed to warm to 0 °C (2 h). During this time, the color of the reaction mixture changed from bright orange to yellow. The reaction mixture was quenched by sequential slow addition of saturated aq. NH_4Cl (2 mL) and water (3 mL). The reaction mixture was poured on 1M NaOH (8 mL) and extracted with CH_2Cl_2 (2 X 8 mL). The combined organic extracts were dried over $MgSO_4$, concentrated under vacuum and purified by flash chromatography (50:1 hexanes/EtOAc → 20:1 hexanes/EtOAc →2:1 hexanes/EtOAc → 1:1 hexanes/EtOAc) to provide 11.5 mg (55% yield) of **2.41** as a yellow solid. **R$_f$** 0.38 (1:1 hexanes/EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.61-7.55 (m, 2H), 7.40 (d, *J* = 8.3 Hz, 1H), 7.36-7.32 (m, 1H), 7.28 (m, 2H), 6.77 (d, *J* = 8.2 Hz, 1H), 4.09 (s, 3H), 3.12 (dd, *J* = 11.3, 3.9 Hz, 1H), 2.93-2.87 (m, 2H), 2.87-2.83 (m, 1H), 2.68-2.62 (m, 1H), 2.32-2.29 (m, 1H), 2.13-2.08 (m, 1H), 2.02-1.95 (m, 2H), 1.80-1.72 (m, 1H), 1.72-1.66 (m, 1H), 1.50-1.43 (m, 1H), 1.40 (dt, *J* = 13.0, 4.1 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 188.70, 162.27, 152.83, 140.56, 137.26, 130.23, 129.20, 128.46, 123.14, 112.59, 61.39, 58.77, 53.26, 52.92, 46.23, 36.69, 36.2, 32.46, 30.93, 19.18; **IR** (film) υ_{max} 2926, 2240, 1673, 1599, 1477, 1321, 1267, 1017, 837, 730 cm^{-1}; **HRMS** (ESI) m/z 381.1639 [(M+H)$^+$; calculated for [$C_{22}H_{25}N_2O_2S$]$^+$: 381.1637]; **MP** 152-154 °C.



Tertiary amine (1.161): To a solution of **1.155** (10 mg, 0.039 mmol) in THF (2 mL) at -78 °C was added *n*-BuLi (0.3M in hexanes/diethyl ether, 260 µL, 0.078 mmol) over 2 min. After stirring at -78 °C for 30 min (bright orange reaction mixture), 2,2,6,6-Tetramethyl-1-

piperidinyloxy (TEMPO, 15 mg, 0.098 mmol) in THF (0.2 mL) is added in one portion and the reaction mixture turned red. The reaction mixture was stirred at -78 °C for 2 h and then slowly allowed to warm to rt and stir overnight (14 h). During this time, the color of the reaction mixture changed from red to yellow. The reaction mixture was quenched by sequential addition of saturated aq. NH_4Cl (2 mL) and water (2 mL). The reaction mixture was poured on 1M NaOH (5 mL) and extracted with CH_2Cl_2 (3 X 5 mL). The combined organic extracts were dried over $MgSO_4$, concentrated under vacuum and purified by flash chromatography (CH_2Cl_2 → 5% MeOH/CH_2Cl_2→ 10% MeOH/CH_2Cl_2) to provide 7.0 mg (70% yield) of tertiary amine **1.161** as a yellow oil.



Boc-sulfide (2.50): To a solution of **1.155** (10 mg, 0.039 mmol) in THF (2 mL) at -78 °C was added *n*-BuLi (0.3M in hexanes/diethyl ether, 260 µL, 0.078 mmol) over 2 min. After stirring at -78 °C for 30 min (bright orange reaction mixture), diphenyl disulfide (26 mg, 0.117 mmol) in THF (0.25 mL) was added over 1 min. The reaction mixture was stirred at -78 °C for 2 h. During this time, the color of the reaction mixture changed from bright orange to yellow. The reaction mixture was quenched at -78 °C by sequential slow addition of saturated aq. NH_4Cl (2 mL) and water (3 mL). The reaction mixture was poured on 1N NaOH (8 mL) and extracted with CH_2Cl_2 (3 X 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum.

The crude residue was dissolved in CH_2Cl_2 (1 mL), and triethylamine (54 µL, 0.39 mmol) and di-tert-butyl dicarbonate (44 µL, 0.19 mmol) were added. The reaction was allowed to stir at rt for 16 h. The reaction was diluted with CH_2Cl_2 (5 mL) and poured on water (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude residue was purified by flash chromatography (hexanes → 50:1 hexanes/EtOAc → 20:1 hexanes/EtOAc→ 8:1 hexanes/EtOAc) to provide 6.5 mg (35% yield) of boc-sulfide **2.50** as a clear oil and 4.6 mg (25% yield) of bissulfide **2.40** as a clear oil. **R_f** 0.4 (8:1 hexanes/EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.56-7.53 (m, 2H), 7.28 (d, *J* = 8.3 Hz, 1H), 7.27-7.24 (m, 2H), 7.21-7.17 (m, 1H), 6.53 (d, *J* = 8.3 Hz, 1H), 4.70 (d, *J* = 5.2 Hz, 1H), 3.97-3.91 (m, 1H), 3.90-3.86 (m, 1H), 3.69 (s, 3H), 3.42 (dd, *J* = 14.1, 5.6 Hz, 1H), 3.26-3.20 (m, 1H), 2.70-2.66 (m, 1H), 2.66-2.60 (m, 1H), 2.54-2.49 (m, 1H), 2.32-2.25 (m, 1H), 1.90 (ddd, *J* = 14.4, 6.5, 4.1 Hz, 1H), 1.73-1.64 (m, 2H), 1.55-1.50 (m, 3H), 1.38 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 161.03, 155.14, 154.81, 141.78, 138.01, 131.12, 130.16, 128.63, 126.40, 109.00, 79.35, 61.82, 54.03, 53.08, 48.51, 38.86, 36.45, 32.73, 30.01, 28.42, 26.96, 26.37, 16.98 ; **HRMS** (ESI) m/z 467.2369 [$(M+H)^+$; calculated for $[C_{27}H_{35}N_2O_3S]^+$: 467.2363].

Materials and Methods for ^{6}Li NMR experiments

Reagents and Solvents.

[^{6}Li]*n*-BuLi was prepared and recrystallized in *n*-pentane as described previously.[32,33] An aliquot was removed and the pentane was evaporated and replaced with freshly distilled cyclopentane. *n*-BuLi was then titrated using diphenylacetic acid to determine a precise molarity. THF-d_8 was distilled from a solution containing sodium benzophenone ketyl. Cyclopentane was distilled from blue solutions containing sodium benzophenone ketyl with approximately 1% tetraglyme to dissolve the ketyl. Air- and moisture-sensitive materials were manipulated under argon using standard glove box, vacuum line, and syringe techniques.

Sample Preparation.

A stock solution of **2.31** was prepared at room temperature. After flame drying the NMR tube under vacuum and flushing with argon, the tube was placed in a -78 °C dry ice/acetone bath. The appropriate amount of the amine and THF-d_8 was added via syringe, followed by dropwise addition *n*-BuLi. All samples had a total volume of 0.60 mL. The tube was sealed under partial vacuum and immediately vortexed for approximately 5 seconds before being replaced into a -78 °C bath. The samples were stored in a -94 °C freezer.

Spectroscopic Analysis.

NMR spectra were recorded at -90 °C or -100 °C on a 500 or 600 MHz spectrometer with a delay between scans set to >5 x T1 to ensure accurate integrations. ^{6}Li chemical shifts are reported relative to a 0.30 M ^{6}LiCl/MeOH standard and ^{15}N chemical shifts are reported relative to a [^{15}N]DMEA standard.

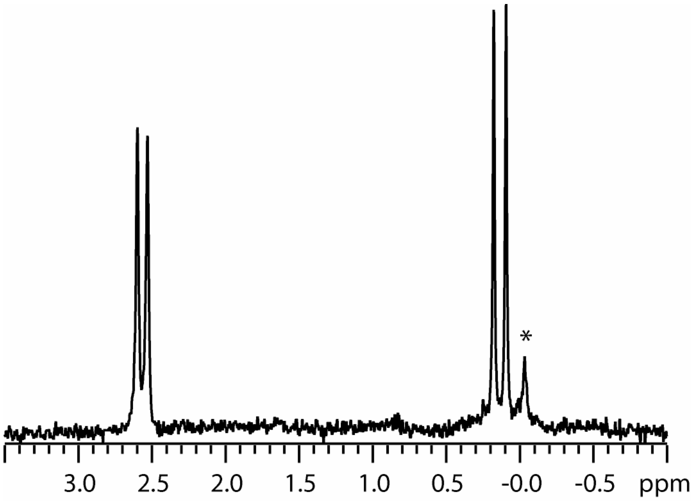


Figure 2.4. ^{6}Li NMR spectrum of 0.05 M [^{15}N]**2.31** and 2 equiv [^{6}Li]*n*-BuLi in THF-d_8 at -90 °C. * denotes an artifact of [^{6}Li]*n*-BuLi.

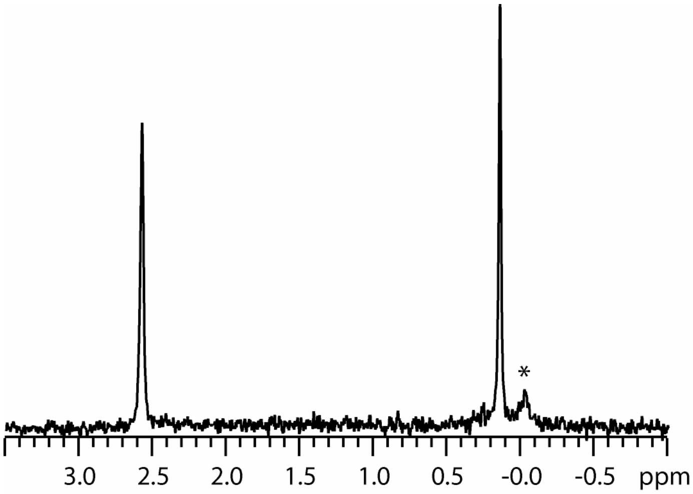


Figure 2.5. {^{15}N}^{6}Li NMR spectrum of 0.05 M [^{15}N]**2.31** and 2 equiv [^{6}Li]*n*-BuLi in THF-d_8 at -90 °C. * denotes an artifact of [^{6}Li]*n*-BuLi.

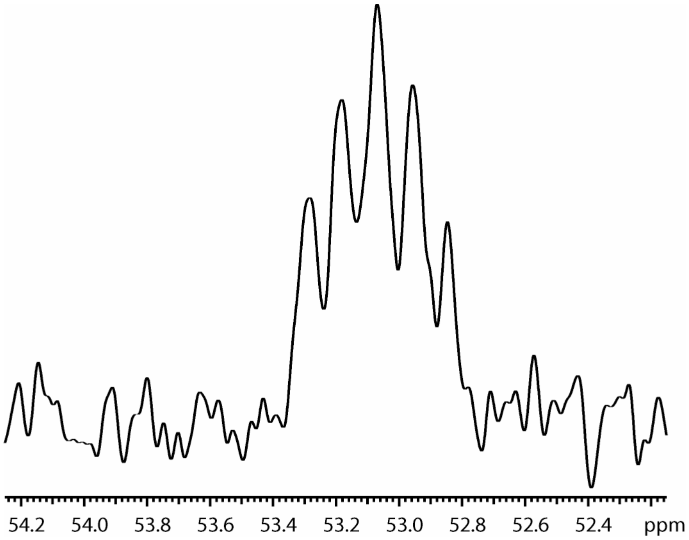


Figure 2.6. ^{15}N NMR spectrum of 0.05 M [^{15}N]**2.31** and 2 equiv [^{6}Li]*n*-BuLi in THF-d_8 at -90 °C.

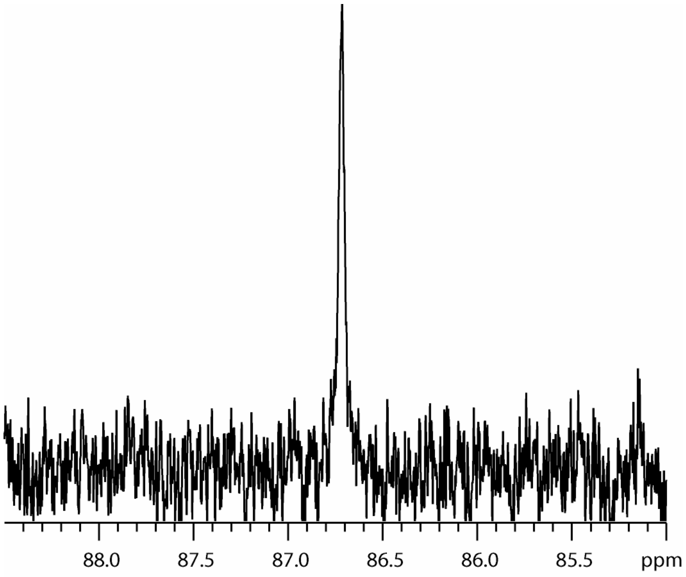
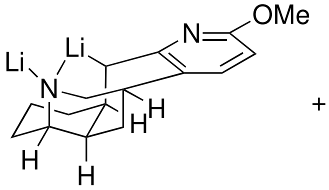
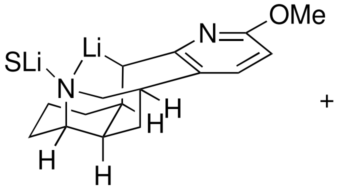
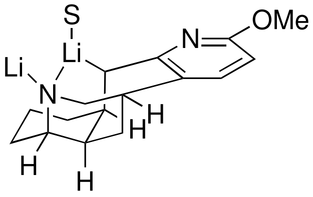
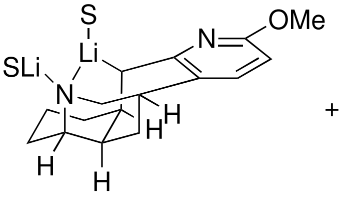
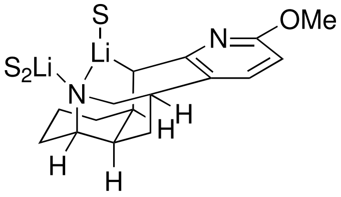
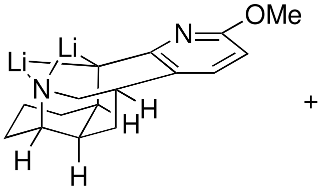
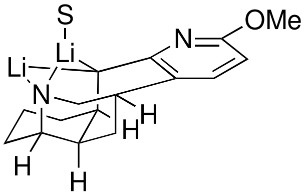
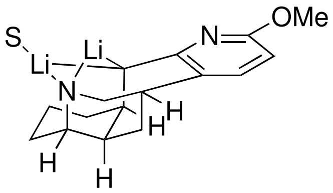
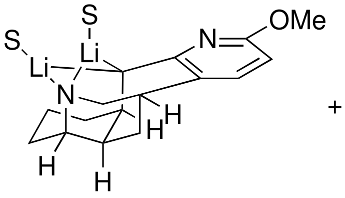
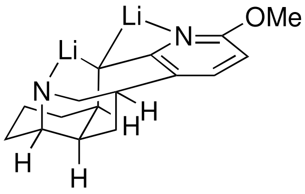
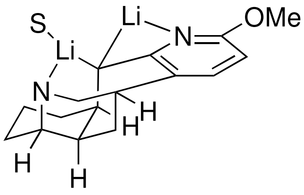


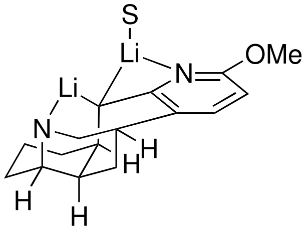
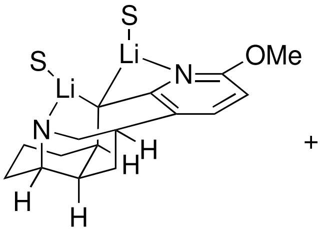
Figure 2.7. ^{13}C NMR spectrum of 0.025 M **1.155** and 2 equiv [^{6}Li]*n*-BuLi in THF-d_8 at -100 °C expanded around benzylic carbon resonance. 2-D NMR techniques (COSY, HMBC, and HSQC) were used to identify the chemical shift of the benzylic carbon.

DFT Calculations Data

Table 1.1. Relative free energies (Δ*G*, kcal/mol) of various forms of **2.25** at -78 °C calculated using B3LYP level of theory with 6-31G(d) basis set

Structure (S=THF)	**Free Energy (Δ*G*, kcal/mol)**
 + 3S	0.0
 + 2S	-19.9
 + 2S	-19.5
 + S	-32.0
	-38.9 (see Fig. 2.8)

 + 3S	+4.2
 + 2S	-13.7
 + 2S	-13.8
 + S	-33.7 (see Fig. 2.8)
 + 3S	-3.2
 + 2S	-20.1

 + 2S	-21.7
 + S	-34.2 (see Fig. 2.8)

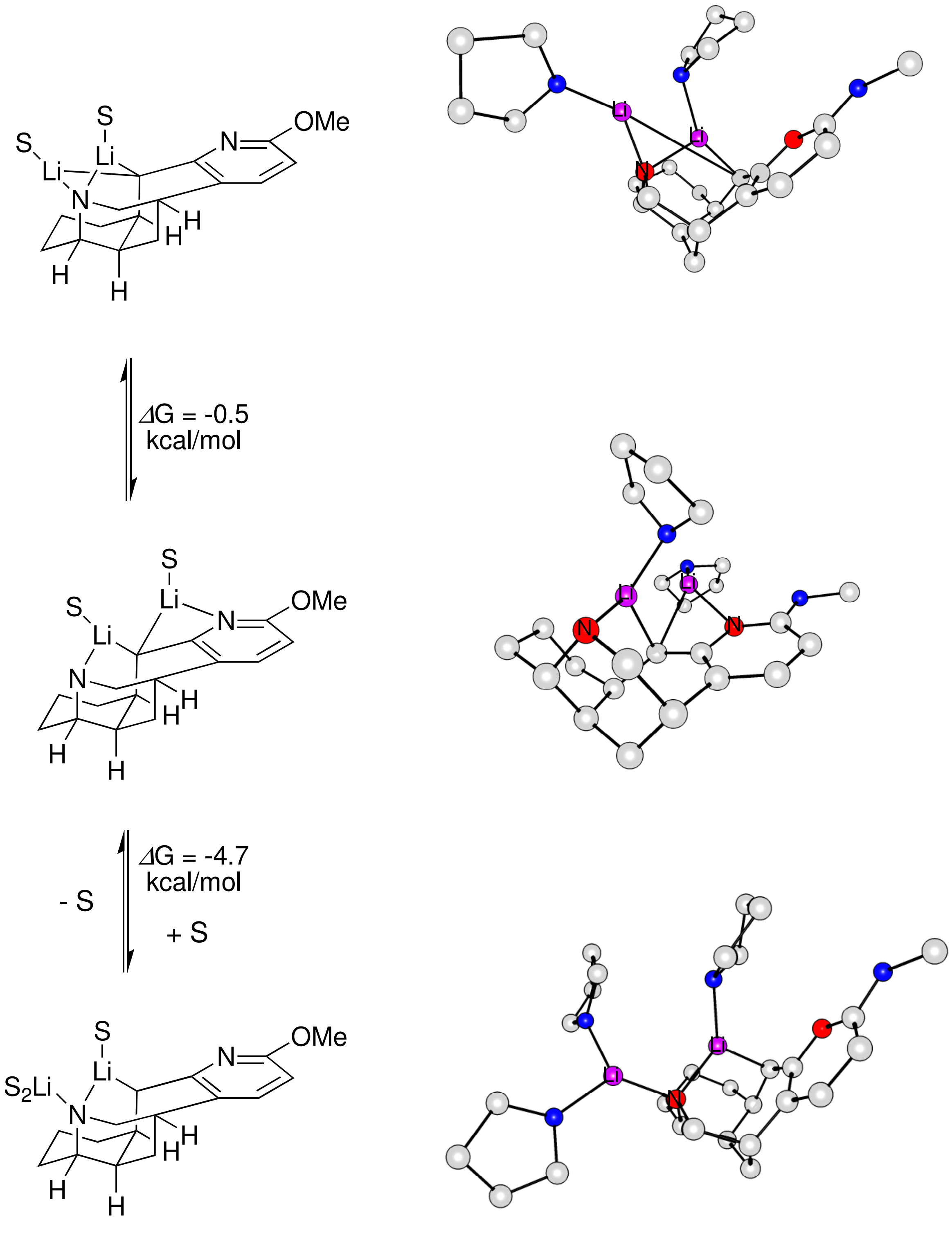
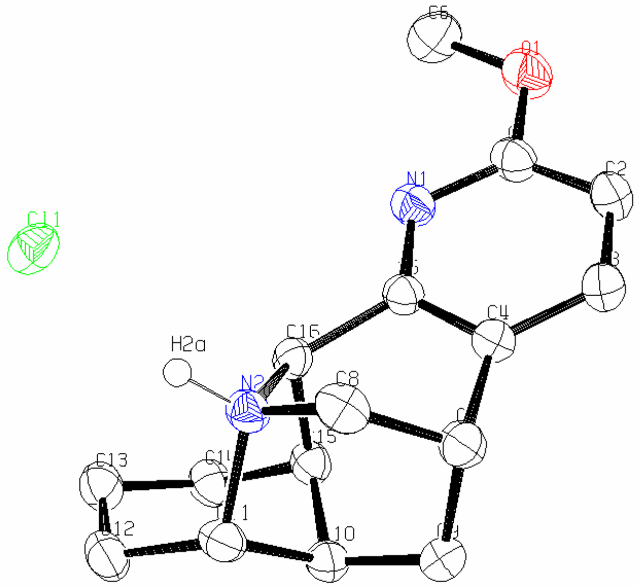

S
S
Li
Li
N
N
OMe
H
H
H
H
ΔG = -0.5
kcal/mol
S
S
Li
Li
N
N
OMe
H
H
H
H
- S
ΔG = -4.7
kcal/mol
+ S
S
S_2Li
Li
N
N
OMe
H
H
H
H
Li
Li
N
Li
Li
N
N
Li
Li
N

Figure 2.8. The relative energies of the three most stable solvates of the three prominent structural forms of **2.25**.

X-Ray Crystallography Data for pentacyclic amine salt 2.39

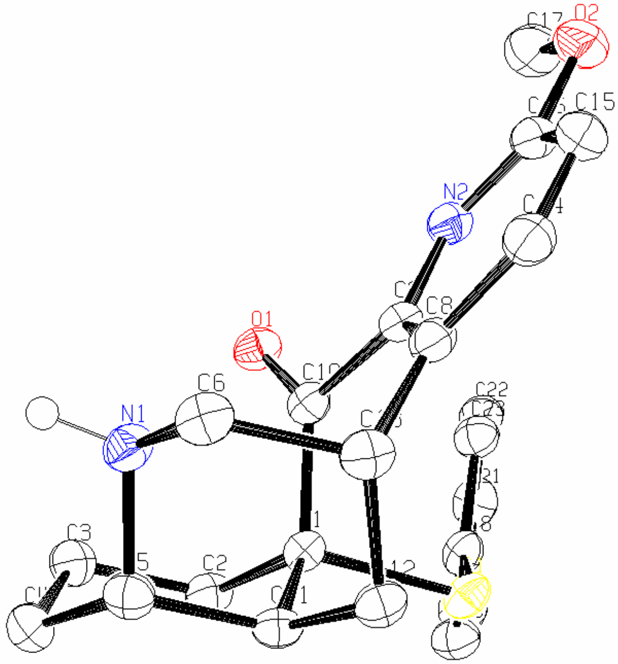

C6
O1
C2
N1
Cl1
C4
C16
H2a
N2
C8
C15
C13
C12
C10

Crystal data and Structure Refinement for pentacyclic amine salt 2.39

A colorless block 0.20 x 0.15 x 0.10 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 139(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 10 seconds per frame using a scan width of 0.3°. Data collection was 99.5% complete to 25.00° in θ. A total of 8916 reflections were collected covering the indices, $-9<=h<=9$, $-10<=k<=11$, $-17<=l<=18$. 3587 reflections were found to be symmetry independent, with an R_{int} of 0.0196. Indexing and unit cell refinement indicated a primitive, triclinic lattice. The space group was found to be P-1 (No. 2). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SIR-2004) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-97). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-97.

Empirical formula	C16 H21 Cl N2 O	
Formula weight	292.80	
Temperature	139(2) K	
Wavelength	0.71073 Å (MoKα)	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.3398(7) Å	α= 84.584(2)°.
	b = 8.3066(8) Å	β= 75.864(2)°.
	c = 13.8028(13) Å	γ = 68.311(2)°.
Volume	758.28(13) $Å^3$	
Z	2	
Density (calculated)	1.282 Mg/m^3	
Absorption coefficient	0.250 mm^{-1}	
F(000)	312	
Crystal size	0.20 x 0.15 x 0.10 mm^3	
Crystal color/habit	colorless block	
Theta range for data collection	1.52 to 28.34°.	
Index ranges	-9<=h<=9, -10<=k<=11, -17<=l<=18	
Reflections collected	8916	
Independent reflections	3587 [R(int) = 0.0196]	
Completeness to theta = 25.00°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9755 and 0.9518	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3587 / 0 / 182	
Goodness-of-fit on F^2	1.028	
Final R indices [I>2sigma(I)]	R1 = 0.0444, wR2 = 0.1087	
R indices (all data)	R1 = 0.0581, wR2 = 0.1193	
Largest diff. peak and hole	0.414 and -0.241 e.$Å^{-3}$	

X-Ray Crystallography Data for Ketosulfide 2.41


C17
O2
C15
N2
O1
C8
C6
N1
C22
C3
C2

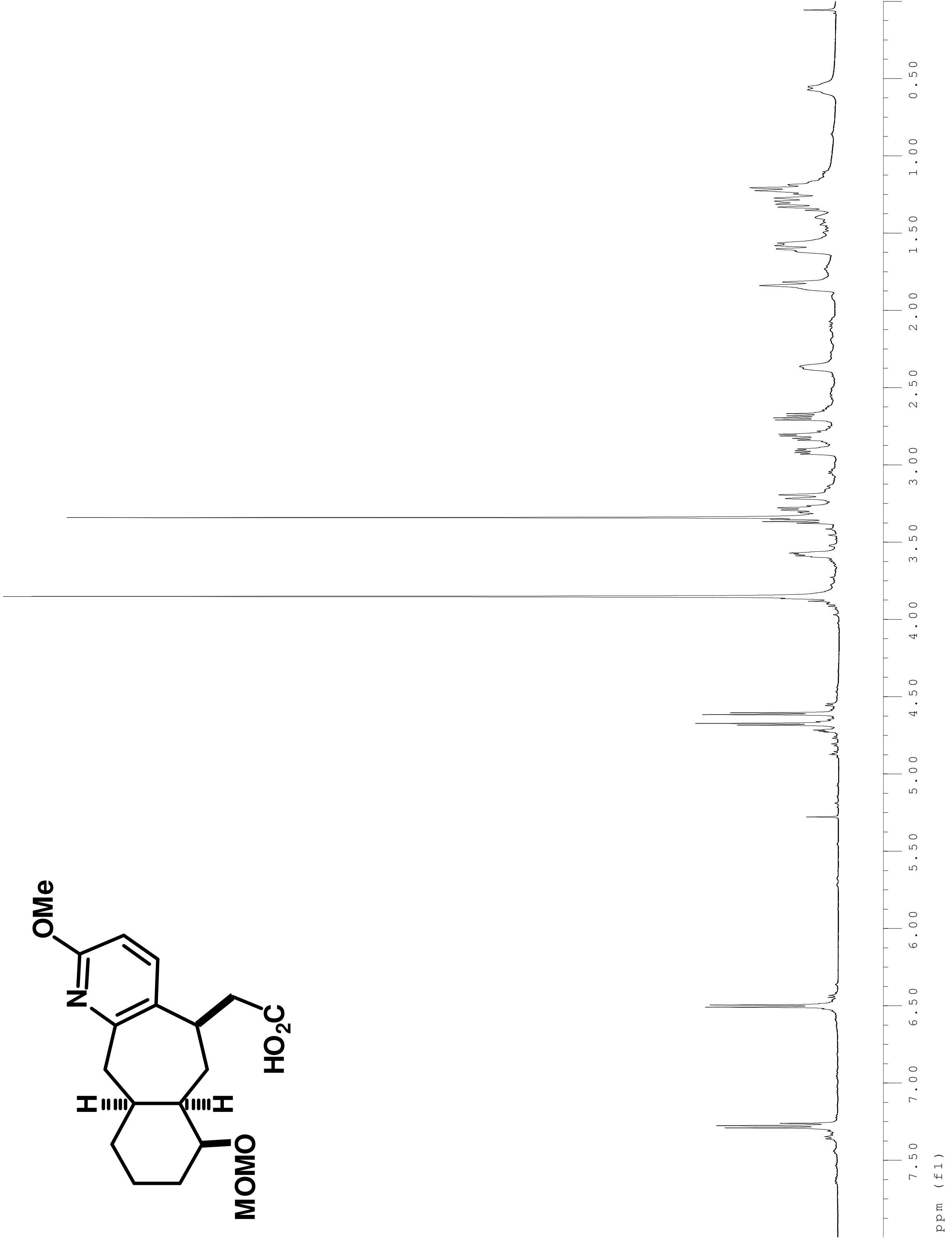
Crystal data and Structure Refinement for ketone 2.41

A colorless needle 0.08 x 0.06 x 0.06 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of 1.0°. Data collection was 97.8% complete to 67.00° in θ. A total of 13774 reflections were collected covering the indices, $-9<=h<=9$, $-13<=k<=13$, $-13<=l<=10$. 3271 reflections were found to be symmetry independent, with an R_{int} of 0.0193. Indexing and unit cell refinement indicated a primitive, triclinic lattice. The space group was found to be P-1 (No. 2). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SIR-2004) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-97). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-97.

Empirical formula	C22 H24 N2 O2 S	
Formula weight	380.49	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.6286(7) Å	α= 107.145(5)°.
	b = 11.1810(12) Å	β= 95.759(5)°.
	c = 12.0135(13) Å	γ = 105.904(4)°.
Volume	923.21(16) Å^{3}	
Z	2	
Density (calculated)	1.369 Mg/m^{3}	
Absorption coefficient	1.715 mm^{-1}	
F(000)	404	
Crystal size	0.08 x 0.06 x 0.06 mm^{3}	
Crystal color/habit	colorless needle	
Theta range for data collection	3.93 to 68.25°.	
Index ranges	-9<=h<=9, -13<=k<=13, -13<=l<=10	
Reflections collected	13774	
Independent reflections	3271 [R(int) = 0.0193]	
Completeness to theta = 67.00°	97.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9041 and 0.8750	
Refinement method	Full-matrix least-squares on F^{2}	
Data / restraints / parameters	3271 / 0 / 248	
Goodness-of-fit on F^{2}	1.034	
Final R indices [I>2sigma(I)]	R1 = 0.0381, wR2 = 0.1016	
R indices (all data)	R1 = 0.0386, wR2 = 0.1021	
Largest diff. peak and hole	0.532 and -0.295 e.Å^{-3}	

2.9 References

(1) Johnson, J. S. *Angew. Chem. Int. Ed.* **2004**, *43*, 1326.
(2) Stetter, H.; Kuhlmann, H. *Org. React.* **1991**, *40*, 407.
(3) Ivanoff, D.; Spassoff, A. *Bull. Soc. Chim. Fr.* **1935**, *2*, 76–78.
(4) Csaky, A. G.; Plumet, J. *Chem. Soc. Rev.* **2001**, *30*, 313.
(5) Baran, P. S.; Ambhaikar, N. B.; Guerrero, C. A.; Hafensteiner, B. D.; Lin, D. W.; Richter, J. M. *Arkivoc* **2006**, 310.
(6) Richter, J. M.; Whitefield, B. W.; Maimone, T. J.; Lin, D. W.; Castroviejo, M. P.; Baran, P. S. *J. Am. Chem. Soc.* **2007**, *129*, 12857.
(7) DeMartino, M. P.; Chen, K.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 11546.
(8) Babler, J. H.; Sarussi, S. J. *J. Org. Chem.* **1987**, *52*, 3462.
(9) Chung, S. K.; Dunn, L. B., Jr. *J. Org. Chem.* **1983**, *48*, 1125.
(10) Kobayashi, Y.; Taguchi, T.; Morikawa, T.; Tokuno, E.; Sekiguchi, S. *Chem. Pharm. Bull.* **1980**, *28*, 262.
(11) Ito, Y.; Konoike, T.; Harada, T.; Saegusa, T. *J. Am. Chem. Soc.* **1977**, *99*, 1487.
(12) Baran, P. S.; Hafensteiner, B. D.; Ambhaikar, N. B.; Guerrero, C. A.; Gallagher, J. D. *J. Am. Chem. Soc.* **2006**, *128*, 8678.
(13) Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 7568.
(14) Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 4894.
(15) Thompson, C. M. *Dianion Chemistry in Organic Synthesis*, 1994.
(16) Yamamoto, H.; Maruoka, K. *J. Org. Chem.* **1980**, *45*, 2739.
(17) Alberti, A.; Cane, F.; Dembech, P.; Lazzari, D.; Ricci, A.; Seconi, G. *J. Org. Chem.* **1996**, *61*, 1677.
(18) del Amo, V.; Dubbaka, S. R.; Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 7838.
(19) Carpenter, R. D.; Verkman, A. S. *Org. Lett.* **2010**, *12*, 1160.
(20) Fraser, R. R.; Mansour, T. S.; Savard, S. *J. Org. Chem.* **1985**, *50*, 3232.
(21) Applequist, D. E.; Chmurny, G. N. *J. Am. Chem. Soc.* **1967**, *89*, 875.
(22) Glaze, W. H.; Selman, C. M.; Ball, A. L., Jr.; Bray, L. E. *J. Org. Chem.* **1969**, *34*, 641.
(23) Cram, D. J.; Gosser, L. *J. Am. Chem. Soc.* **1964**, *86*, 2950.
(24) Gawley, R. E.; Zhang, Q. *J. Org. Chem.* **1995**, *60*, 5763.
(25) Kalgutkar Amit, S.; Crews Brenda, C.; Saleh, S.; Prudhomme, D.; Marnett Lawrence, J. *Bioorg. Med. Chem.* **2005**, *13*, 6810.
(26) Huang, X.; Seid, M.; Keillor, J. W. *J. Org. Chem.* **1997**, *62*, 7495.
(27) Lopez-Garcia, M.; Alfonso, I.; Gotor, V. *J. Org. Chem.* **2003**, *68*, 648.
(28) Evans, D. A.; Scheidt, K. A.; Downey, C. W. *Org. Lett.* **2001**, *3*, 3009.
(29) Fraenkel, G.; Martin, K. *J. Am. Chem. Soc.* **1995**, *117*, 10336.
(30) Meyers, A. I.; Edwards, P. D.; Rieker, W. F.; Bailey, T. R. *J. Am. Chem. Soc.* **1984**, *106*, 3270.
(31) Maji, M. S.; Pfeifer, T.; Studer, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9547.
(32) Hoffmann, D.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 5810.
(33) Kottke, T.; Stalke, D. *Angew. Chem. Int. Ed.* **1993**, *32*, 580.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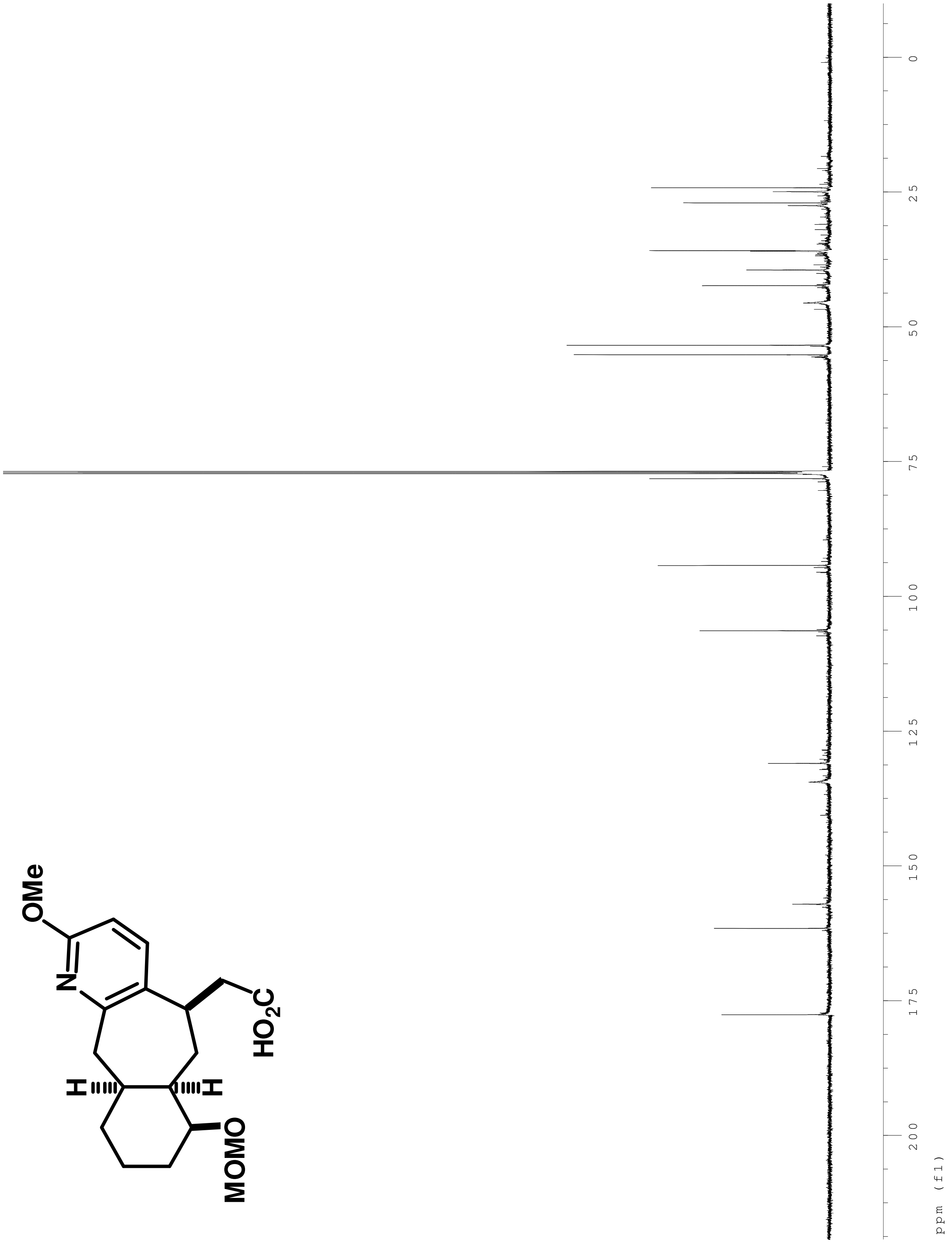
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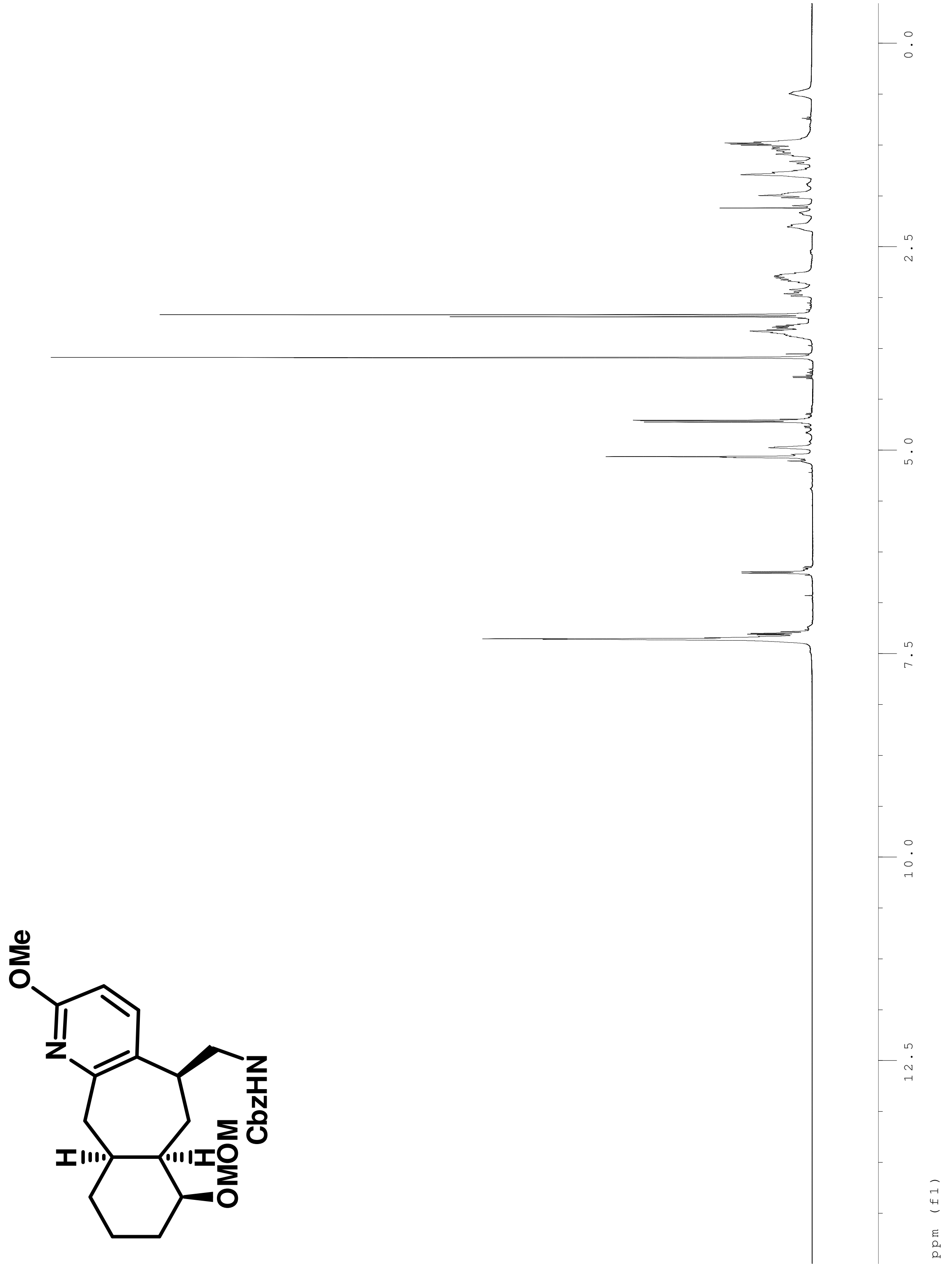

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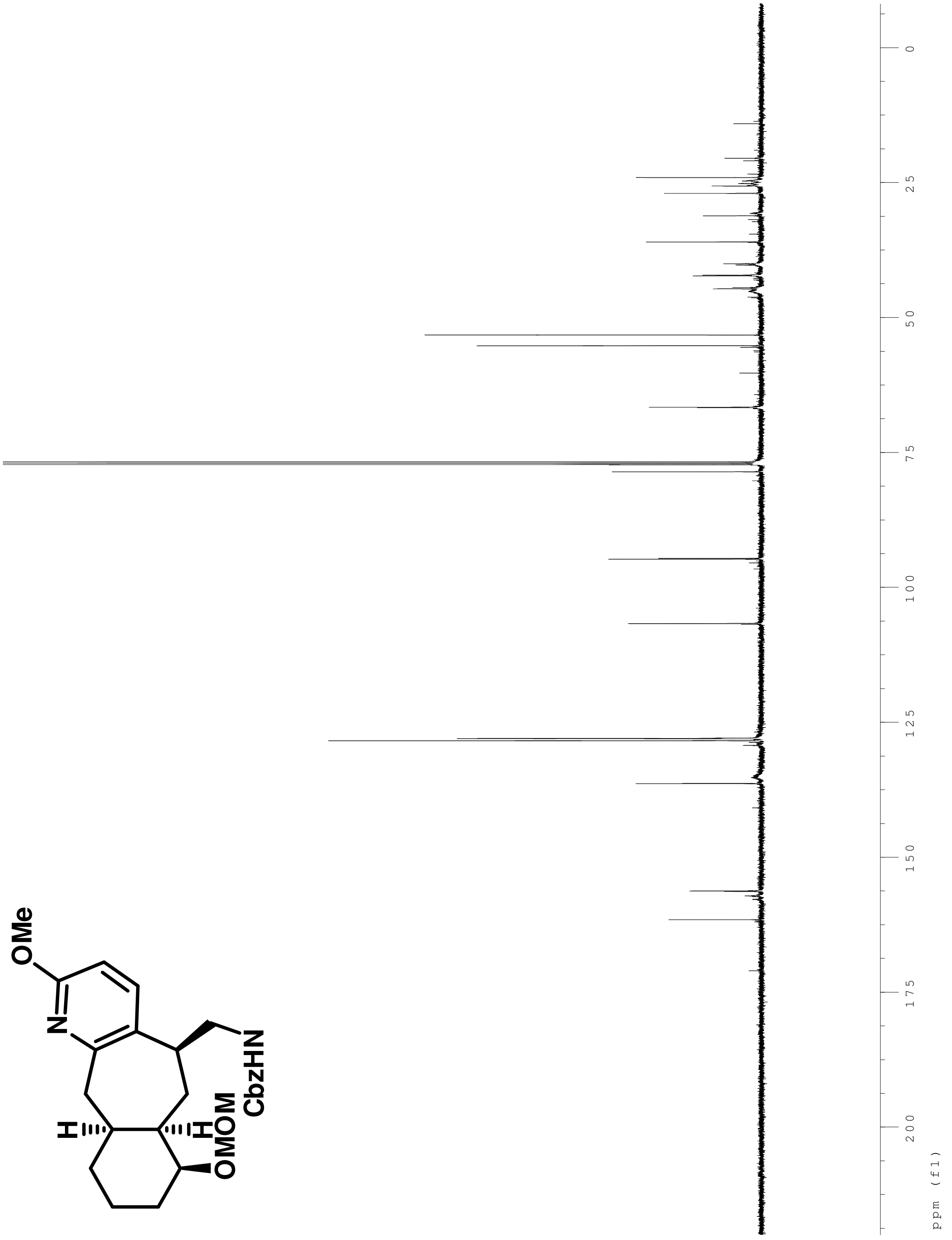
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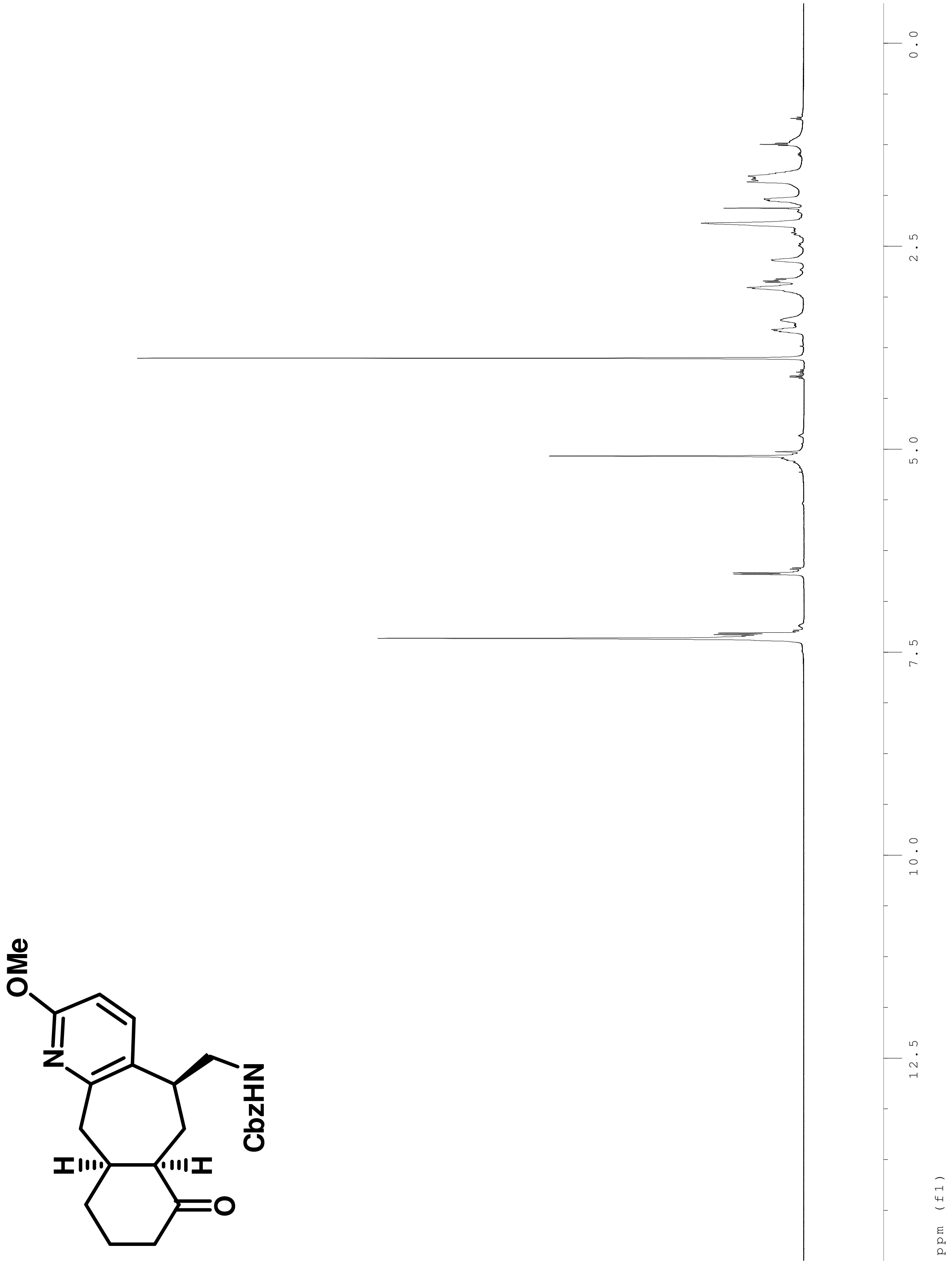
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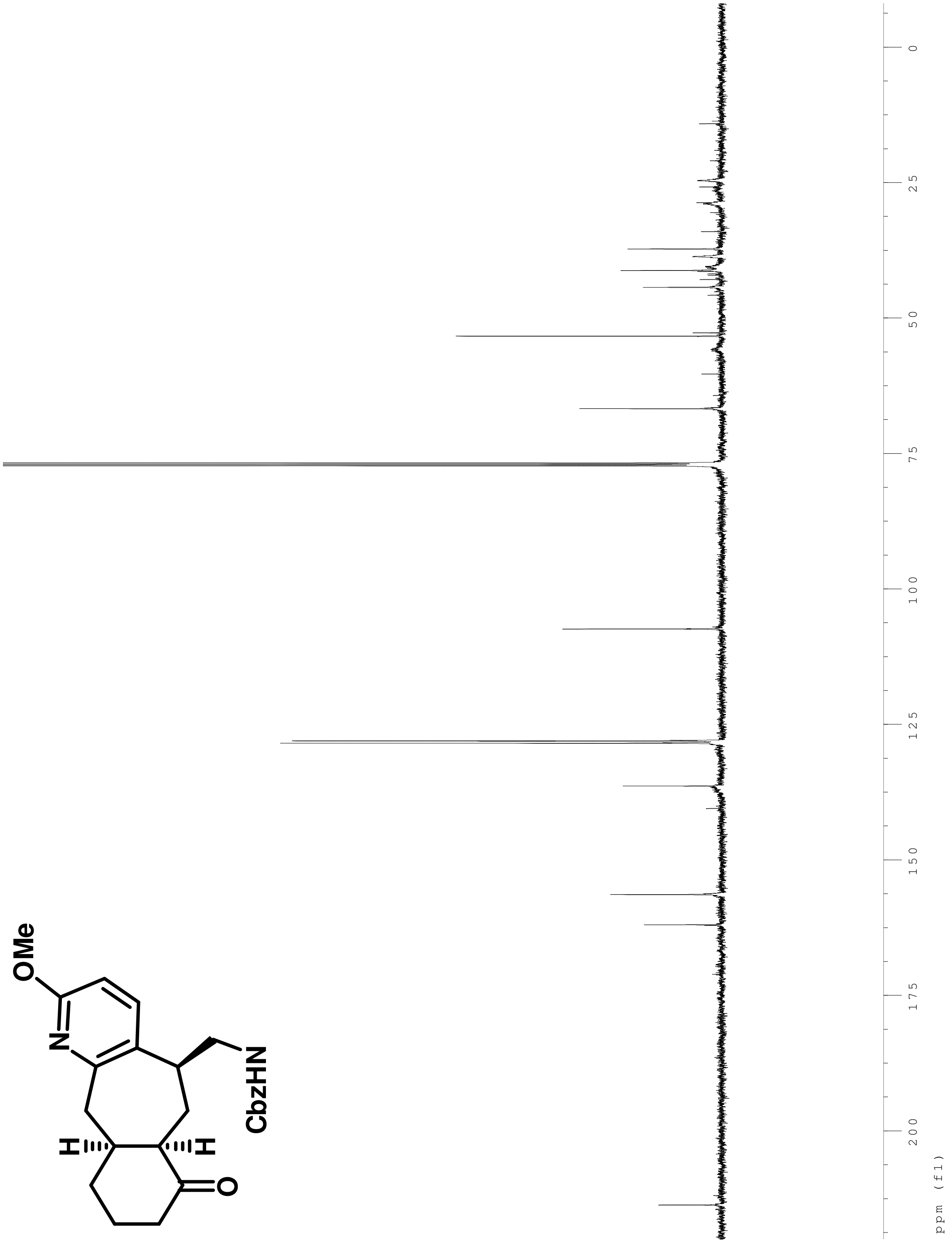
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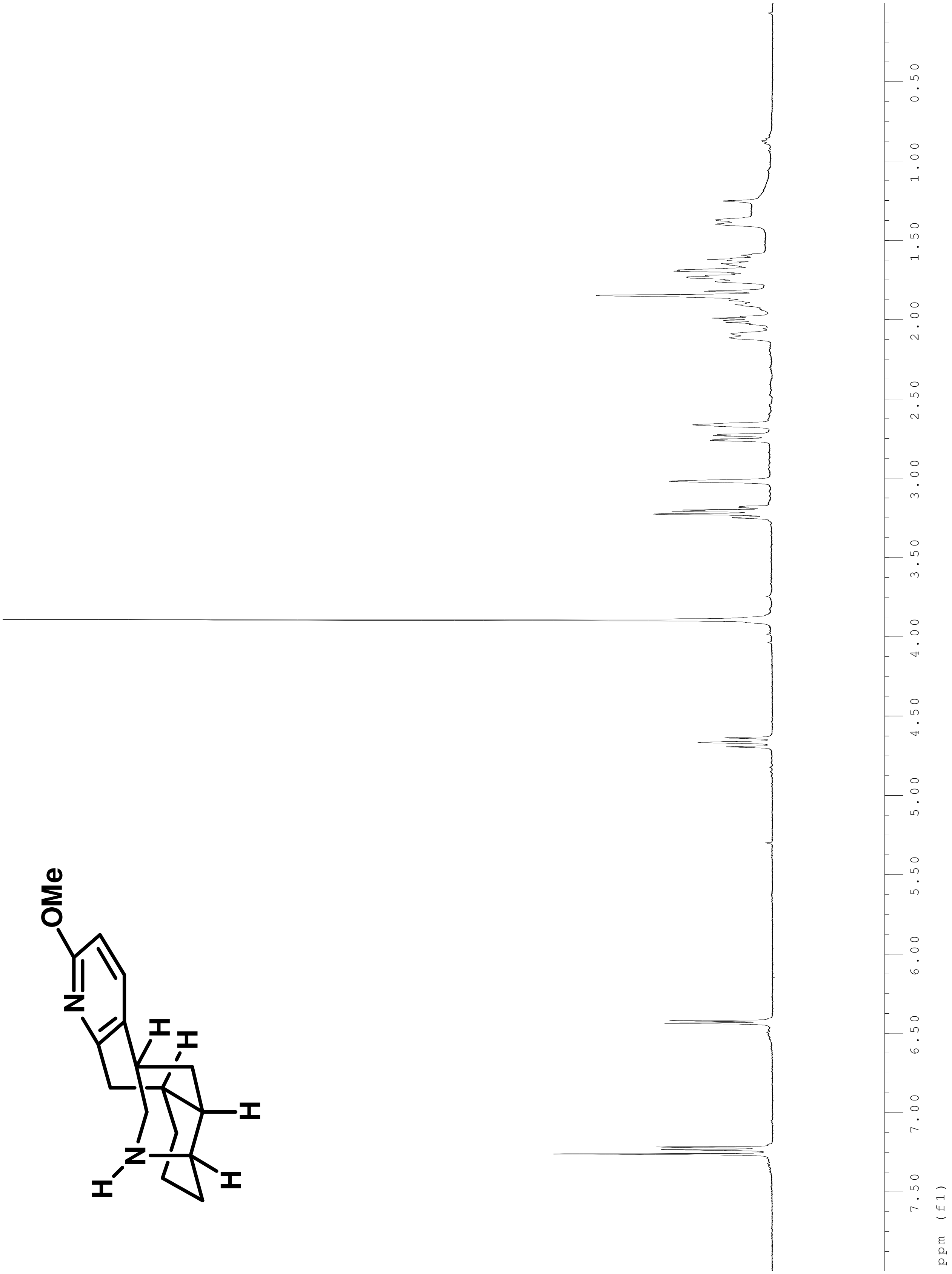
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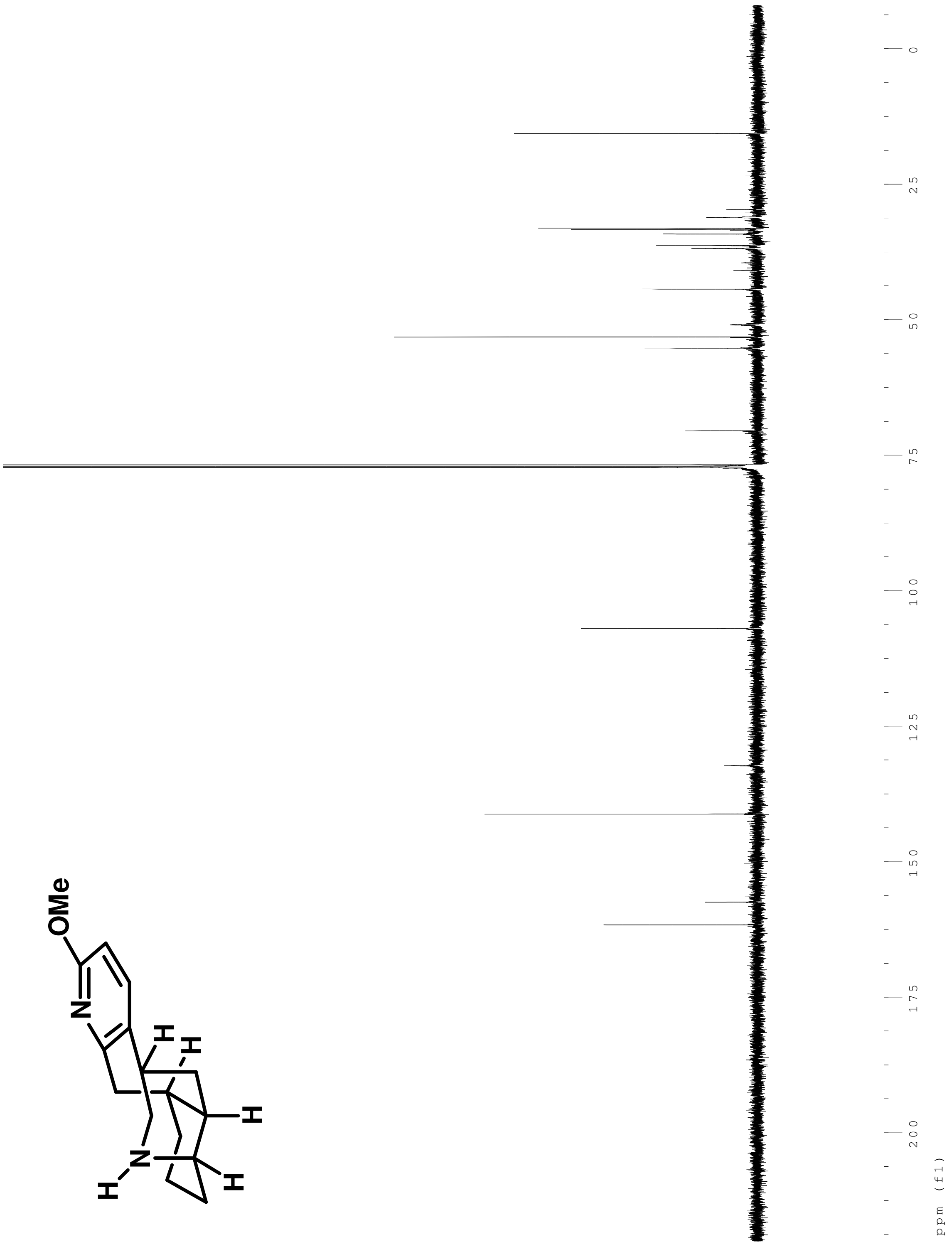
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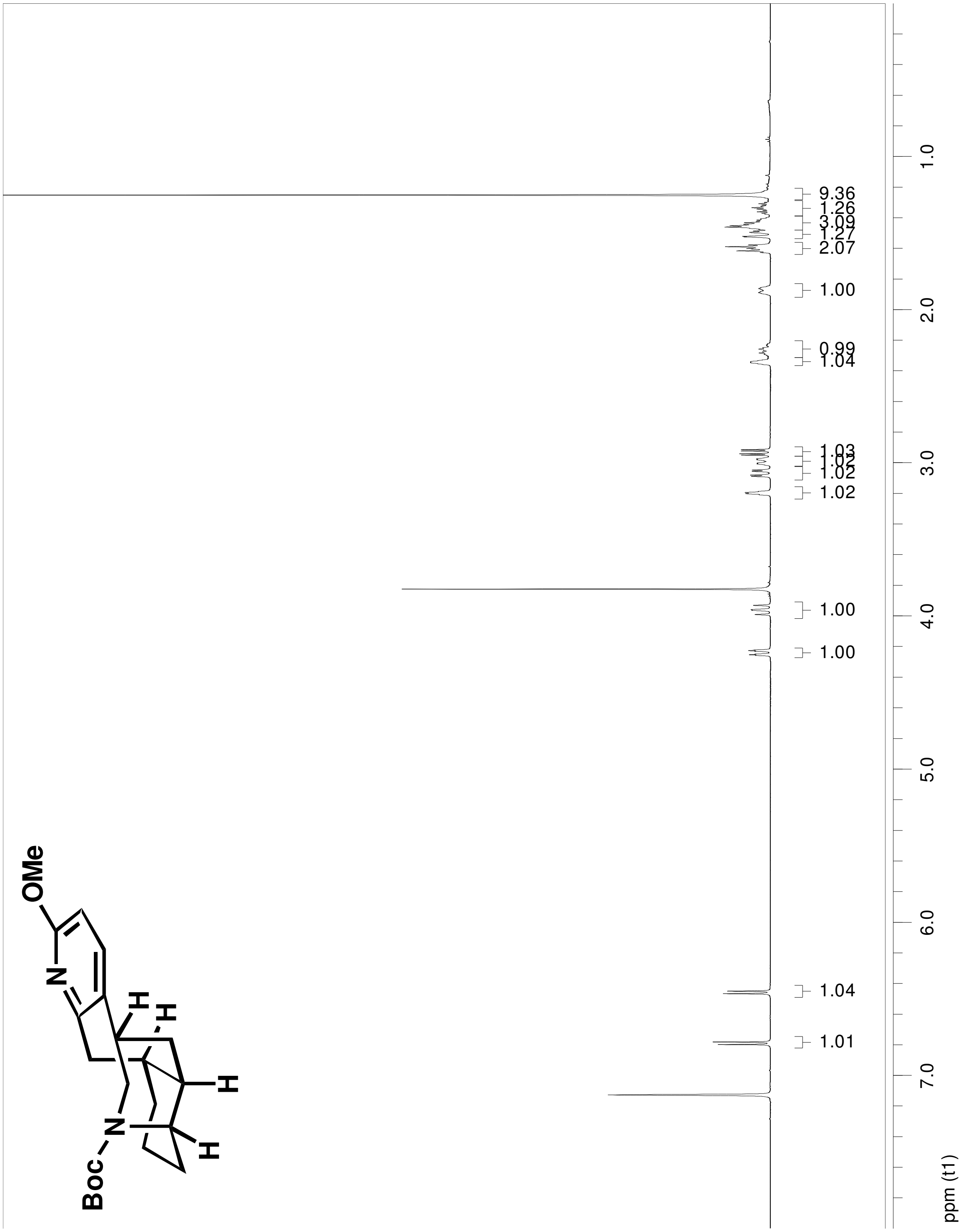

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N
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2.07
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1.04
1.03
1.02
1.02
1.02
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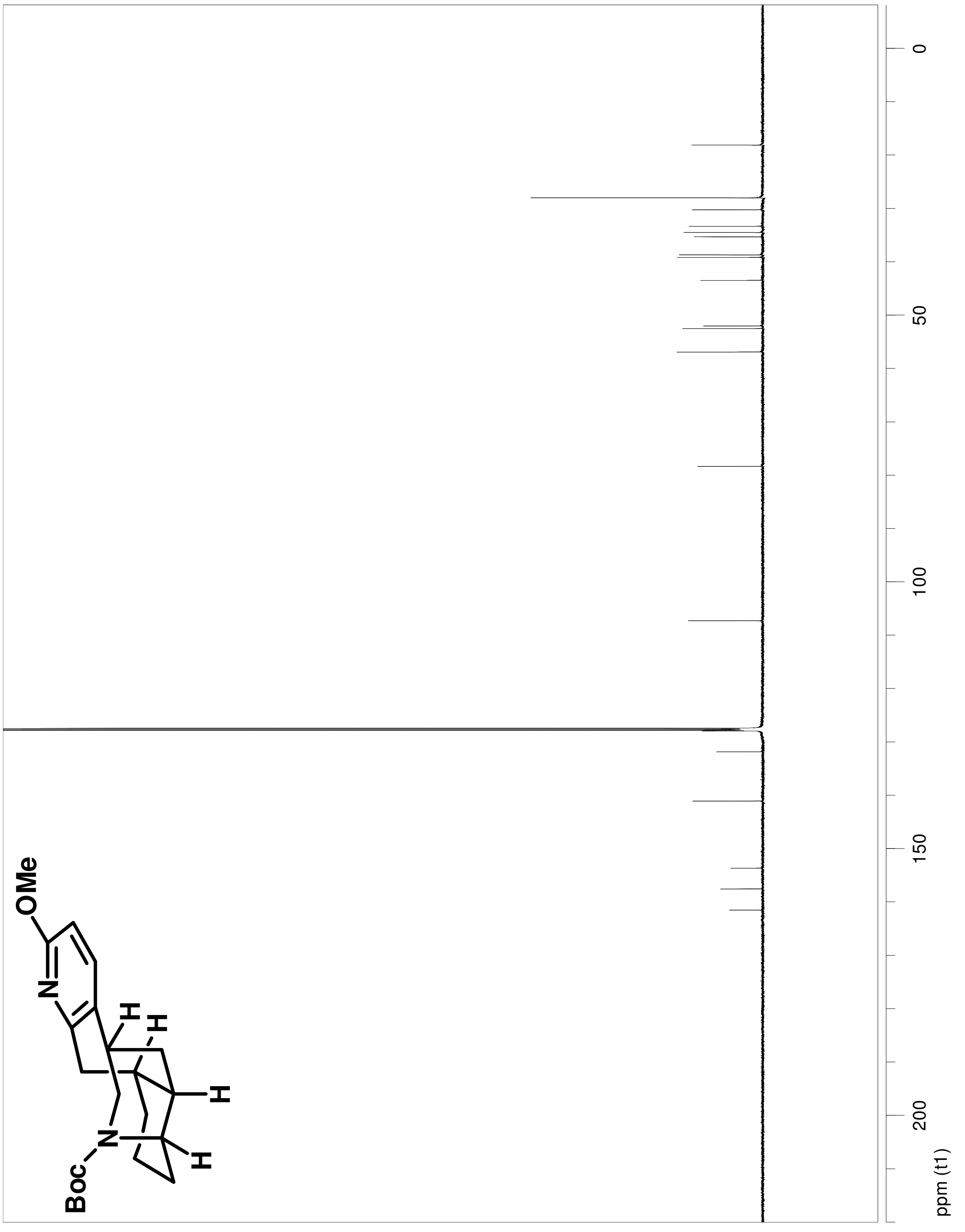
ppm (t1)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ppm (t1)

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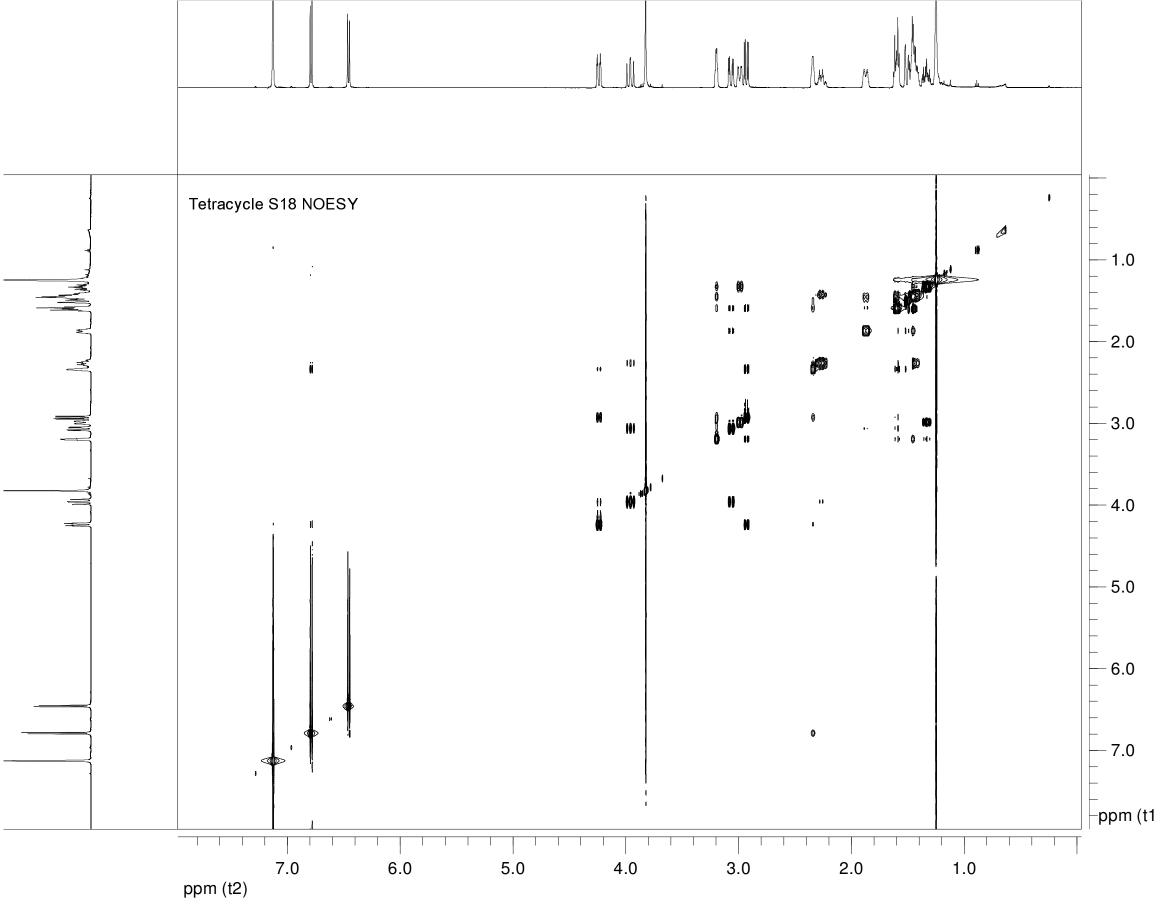

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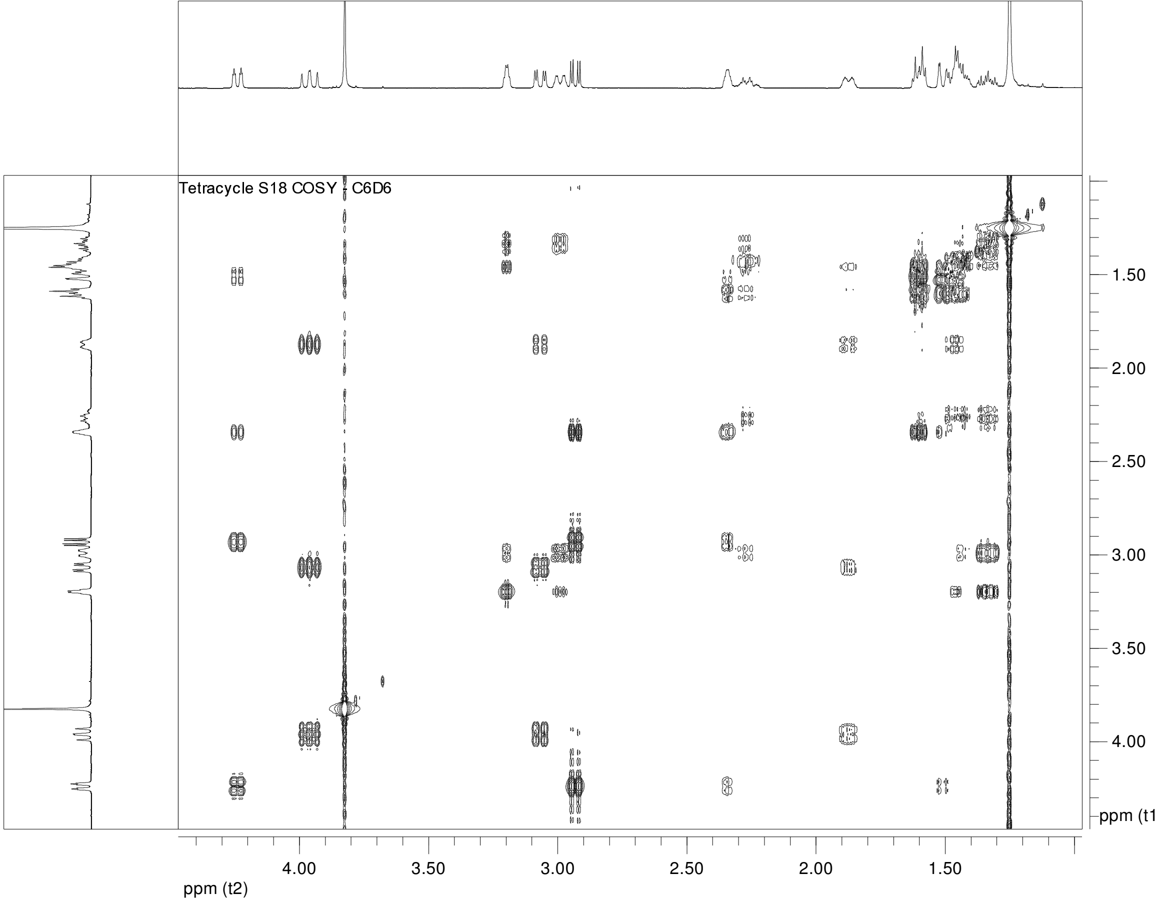
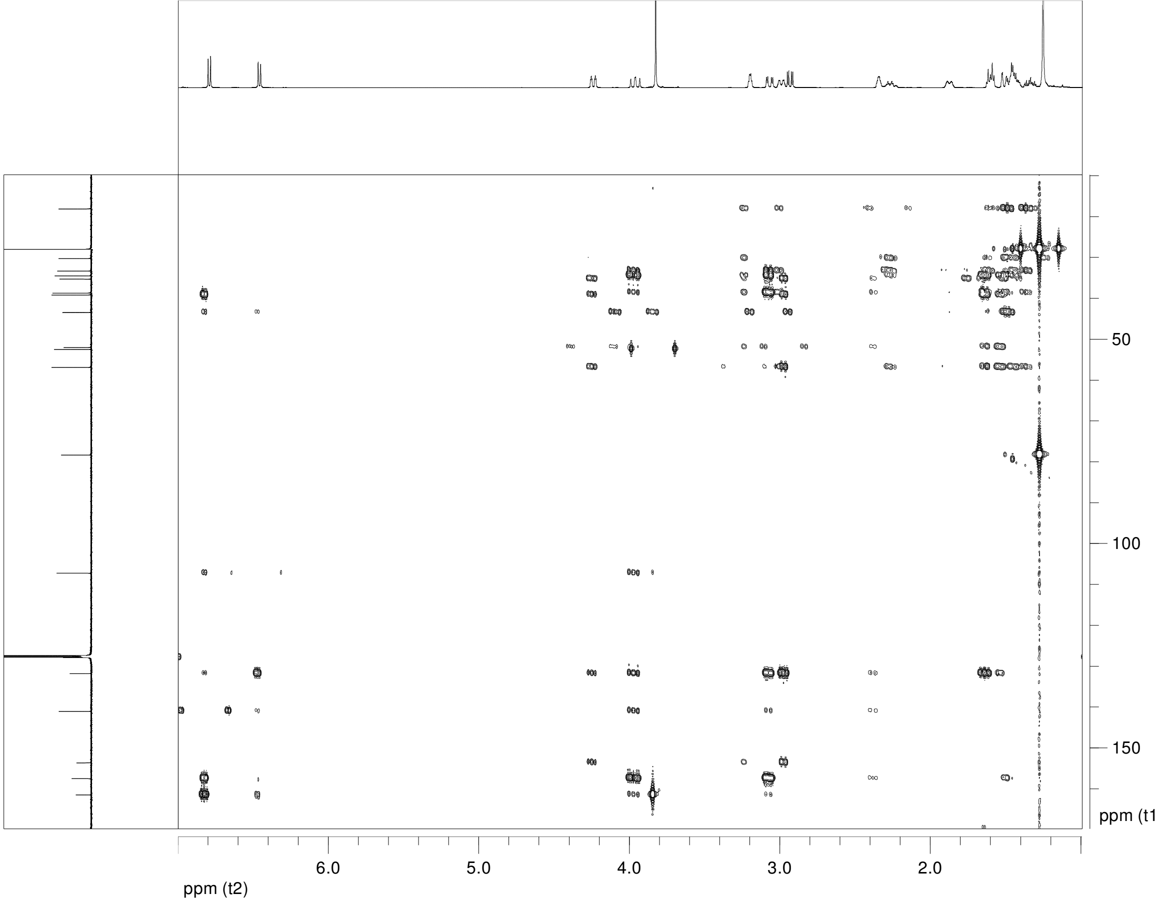
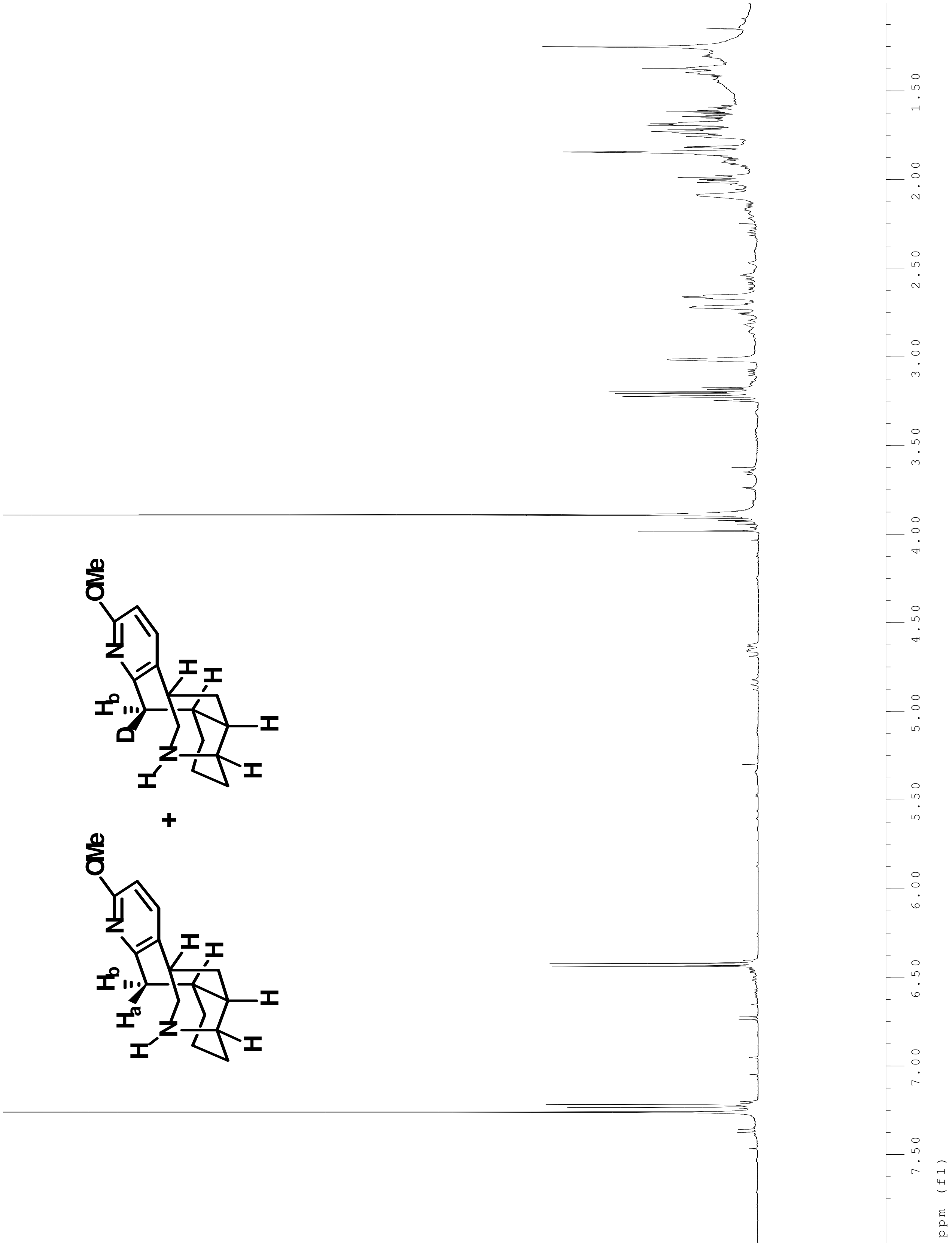


HMBC of Tetracycle **2.57**





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H
H
H
Hb
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4.00
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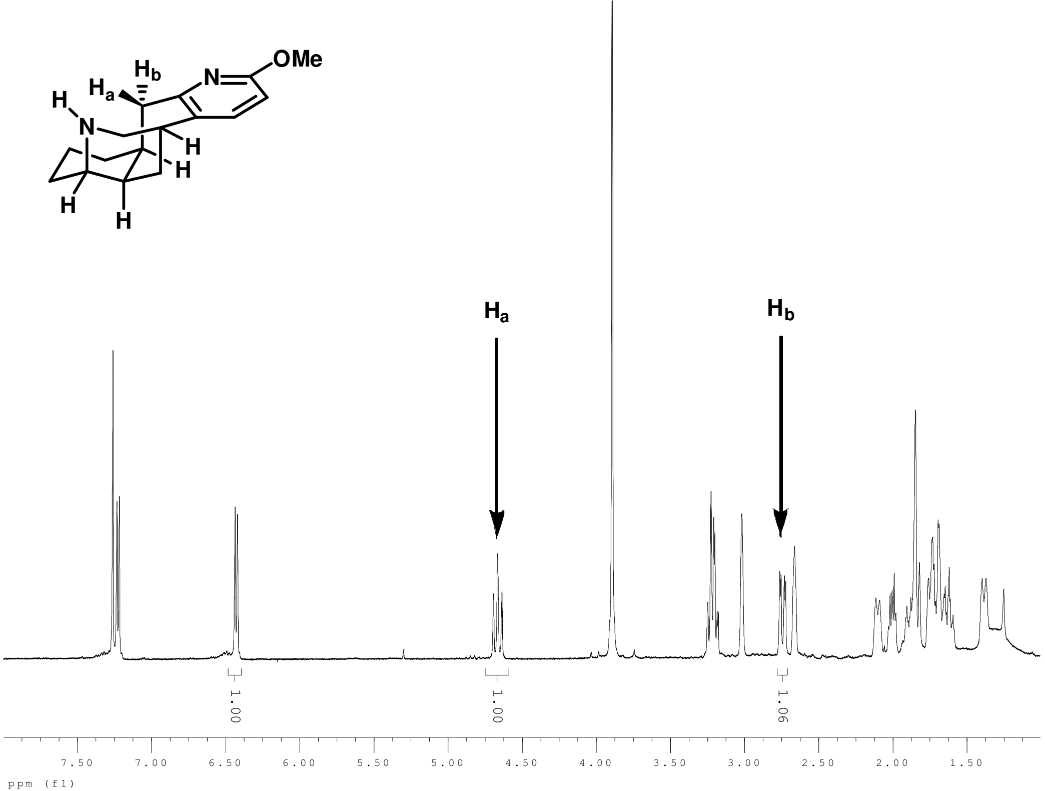
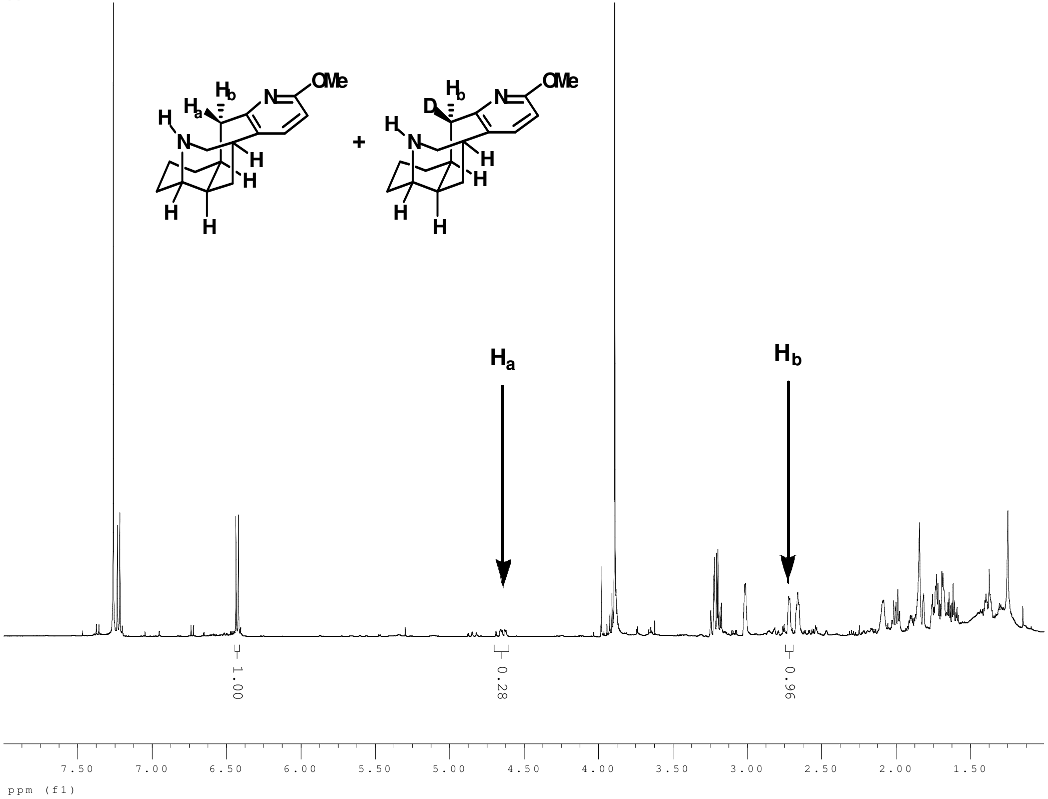
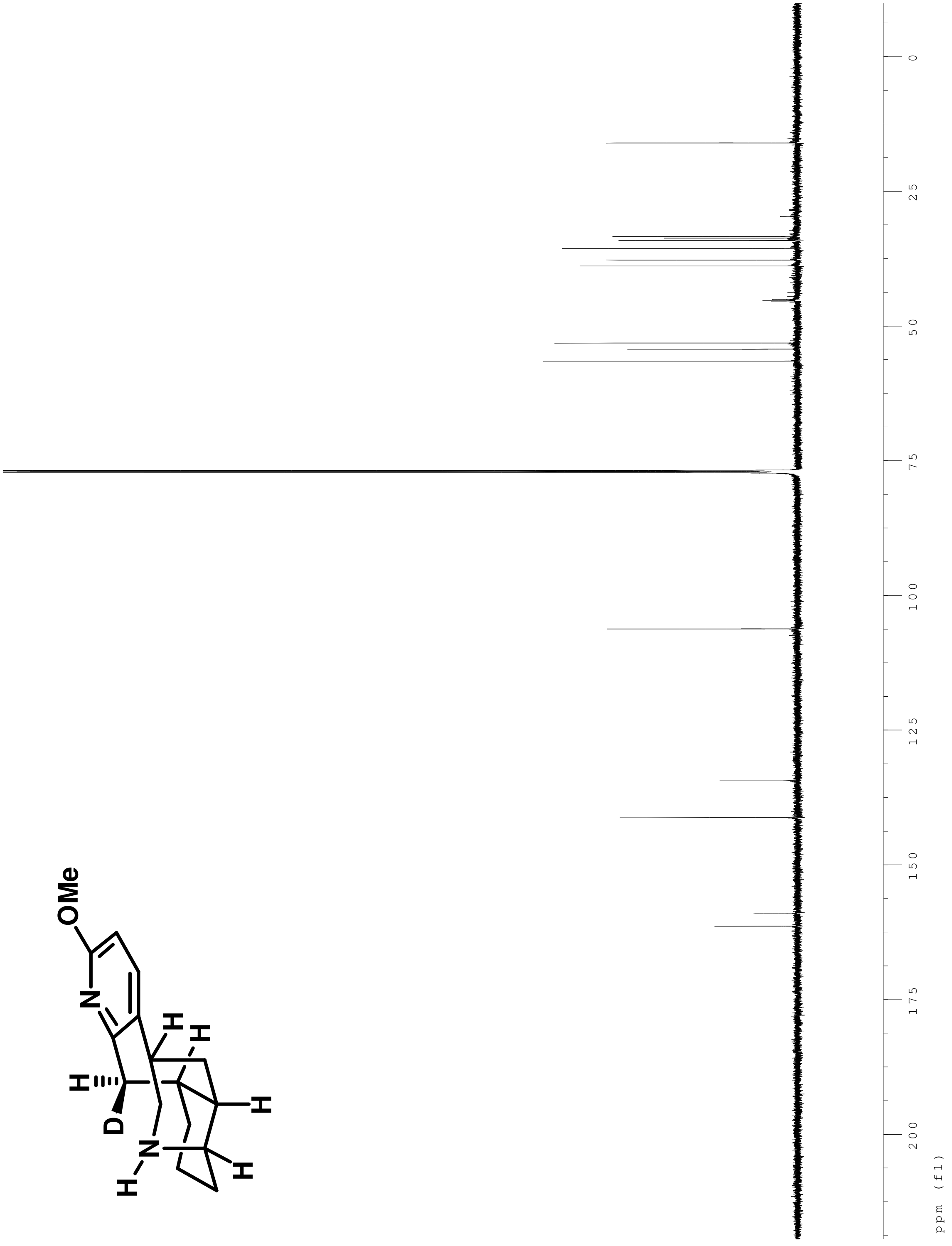
ppm (f1)

Comparison of Amine **1.155** and Amine-*d* **2.27**



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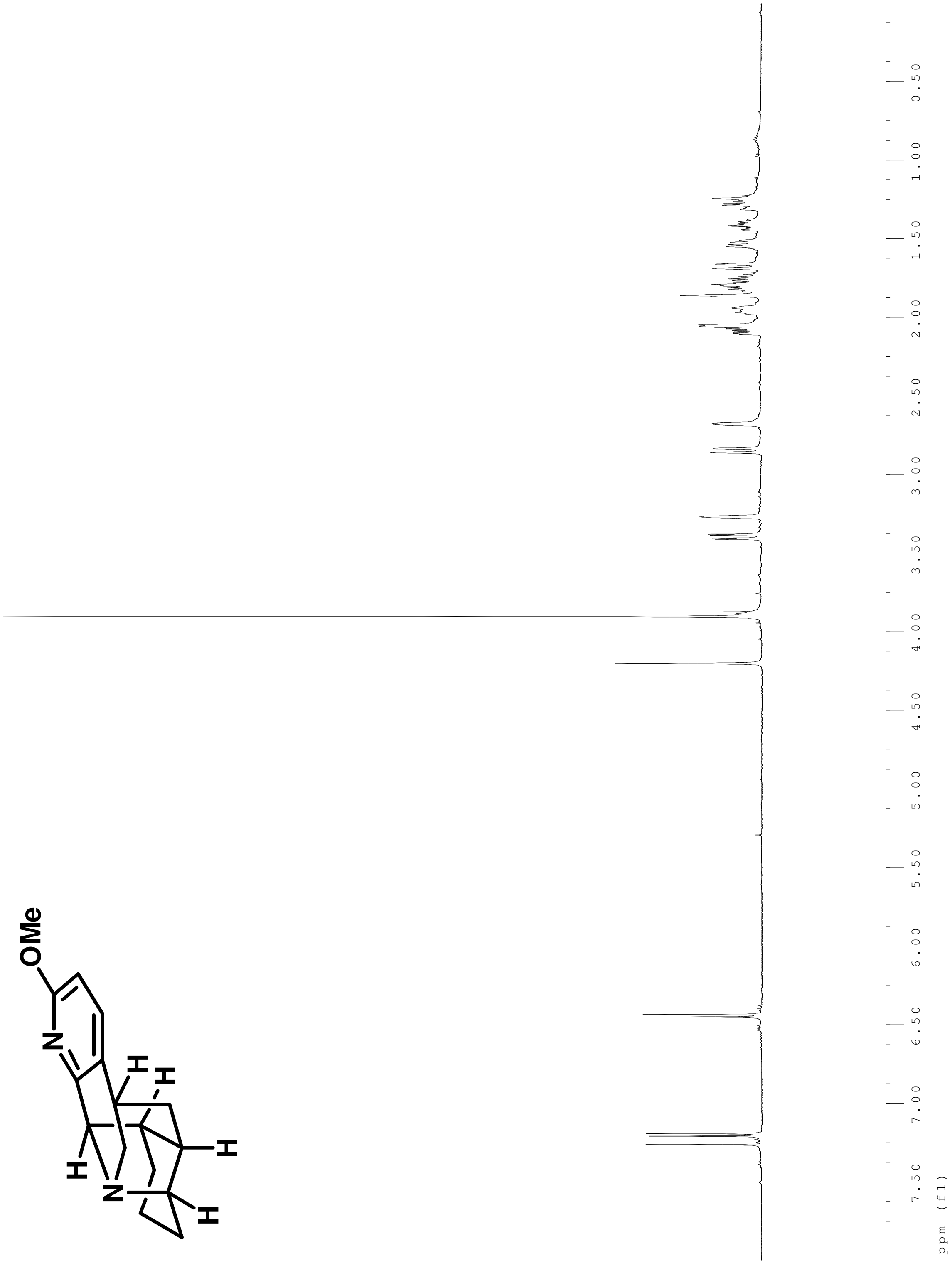
ppm (f1)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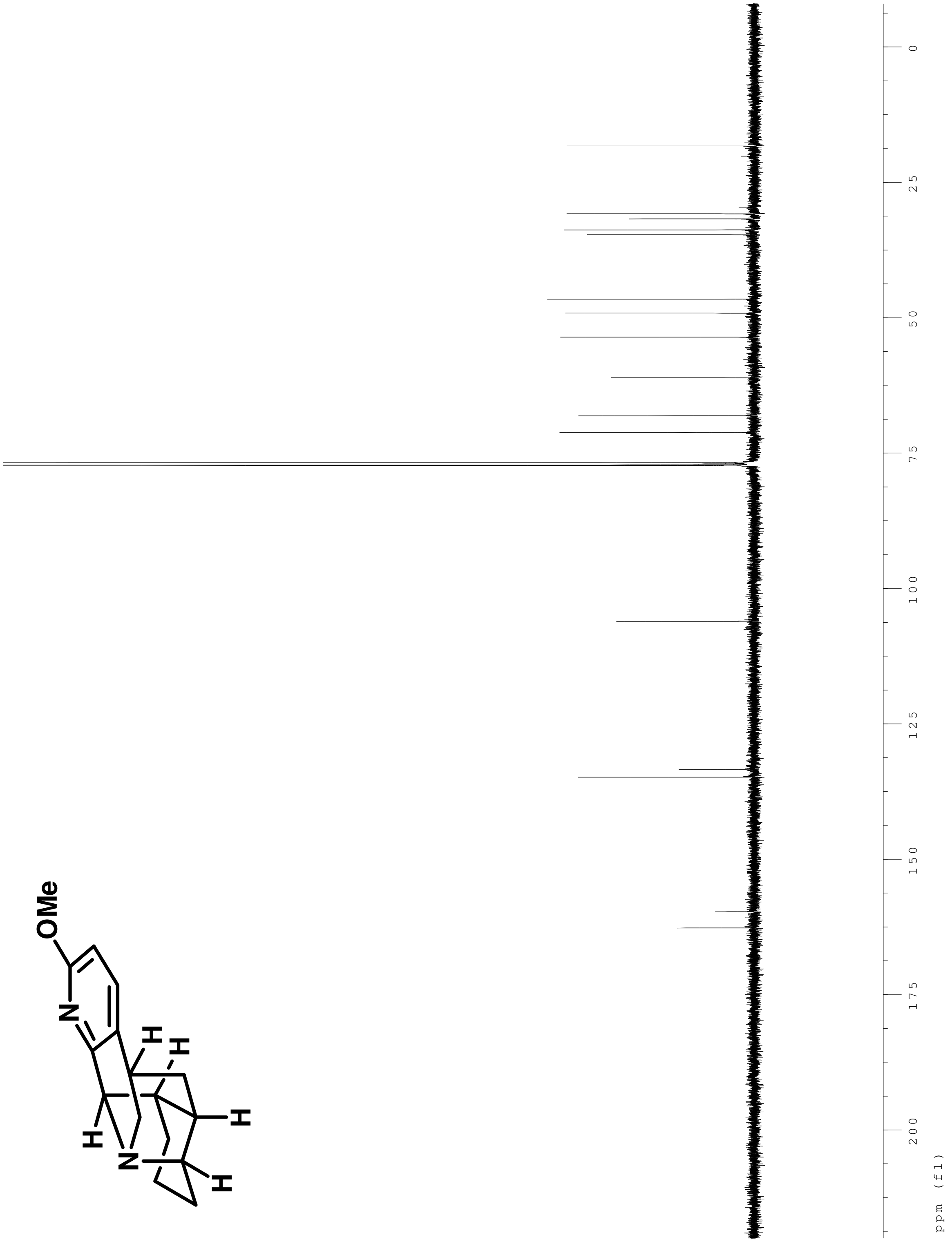
ppm (f1)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H
H
H
H
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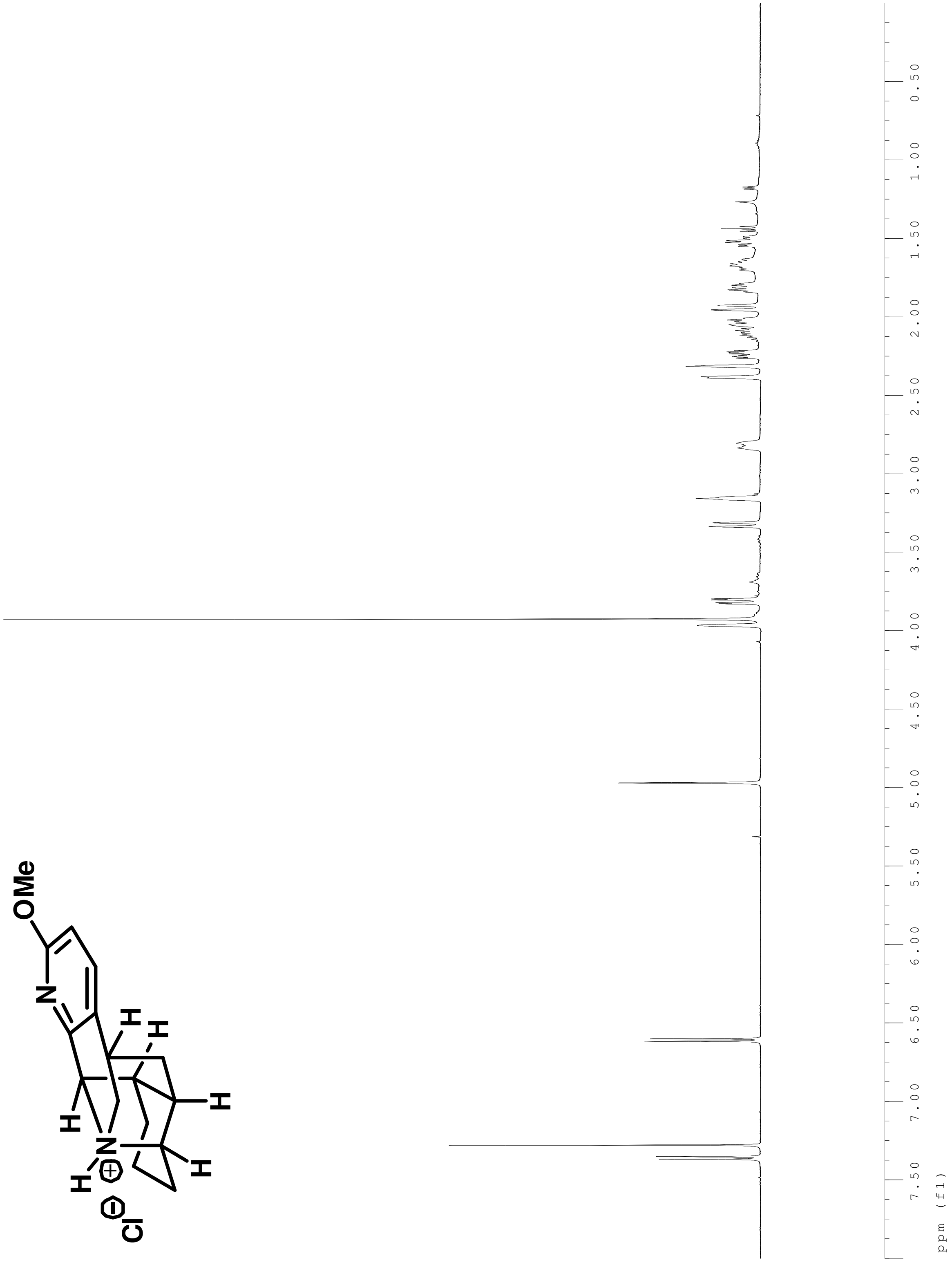
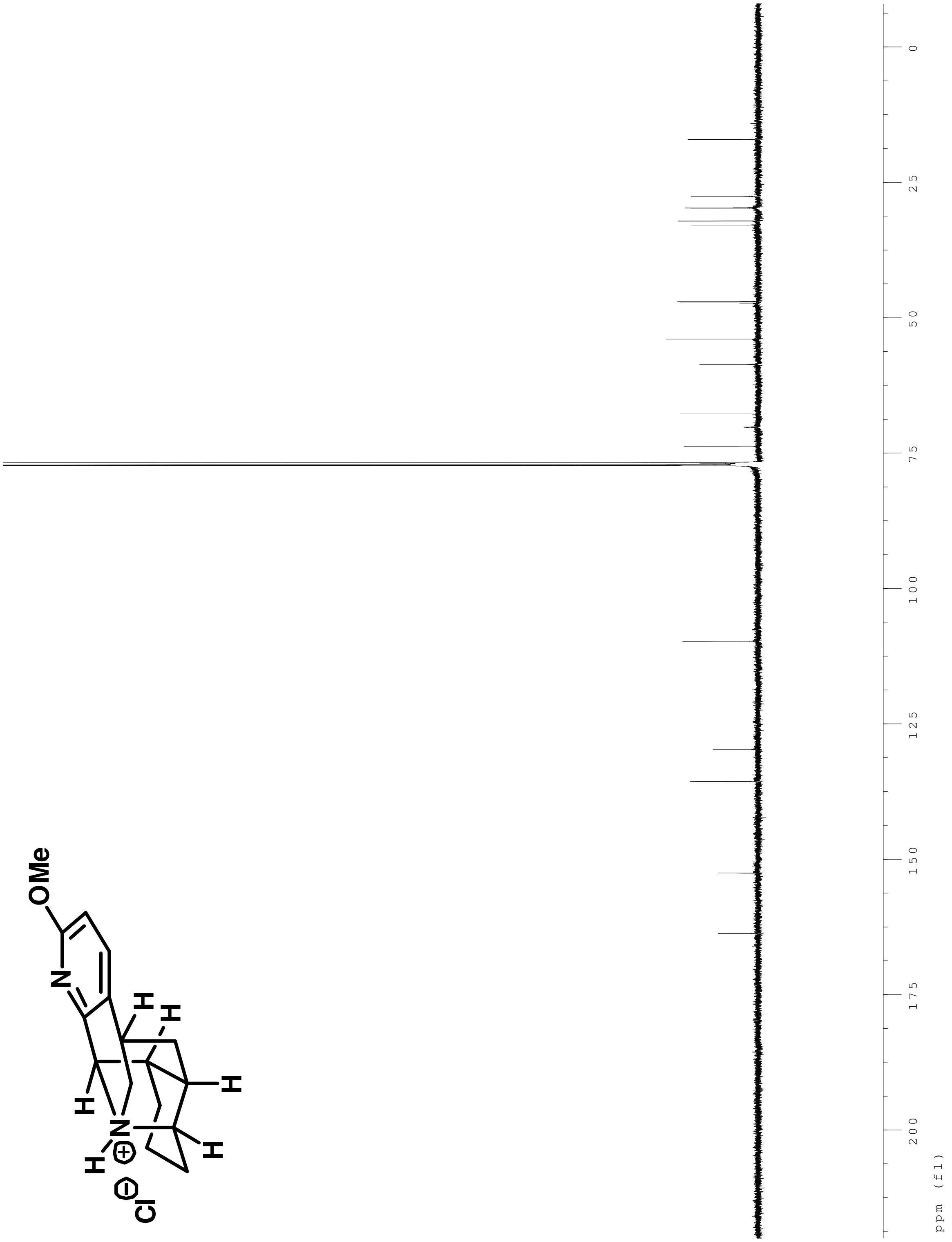
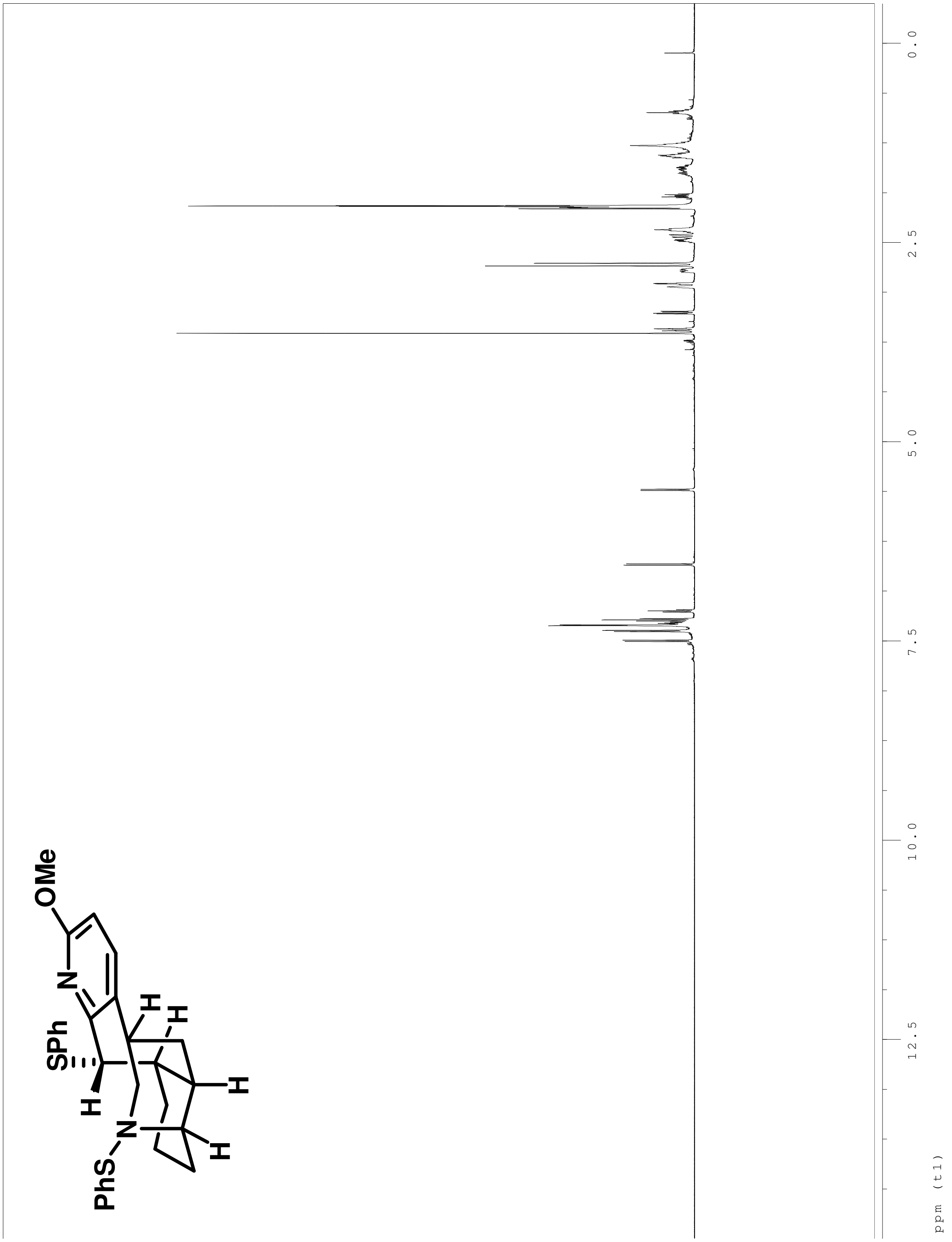
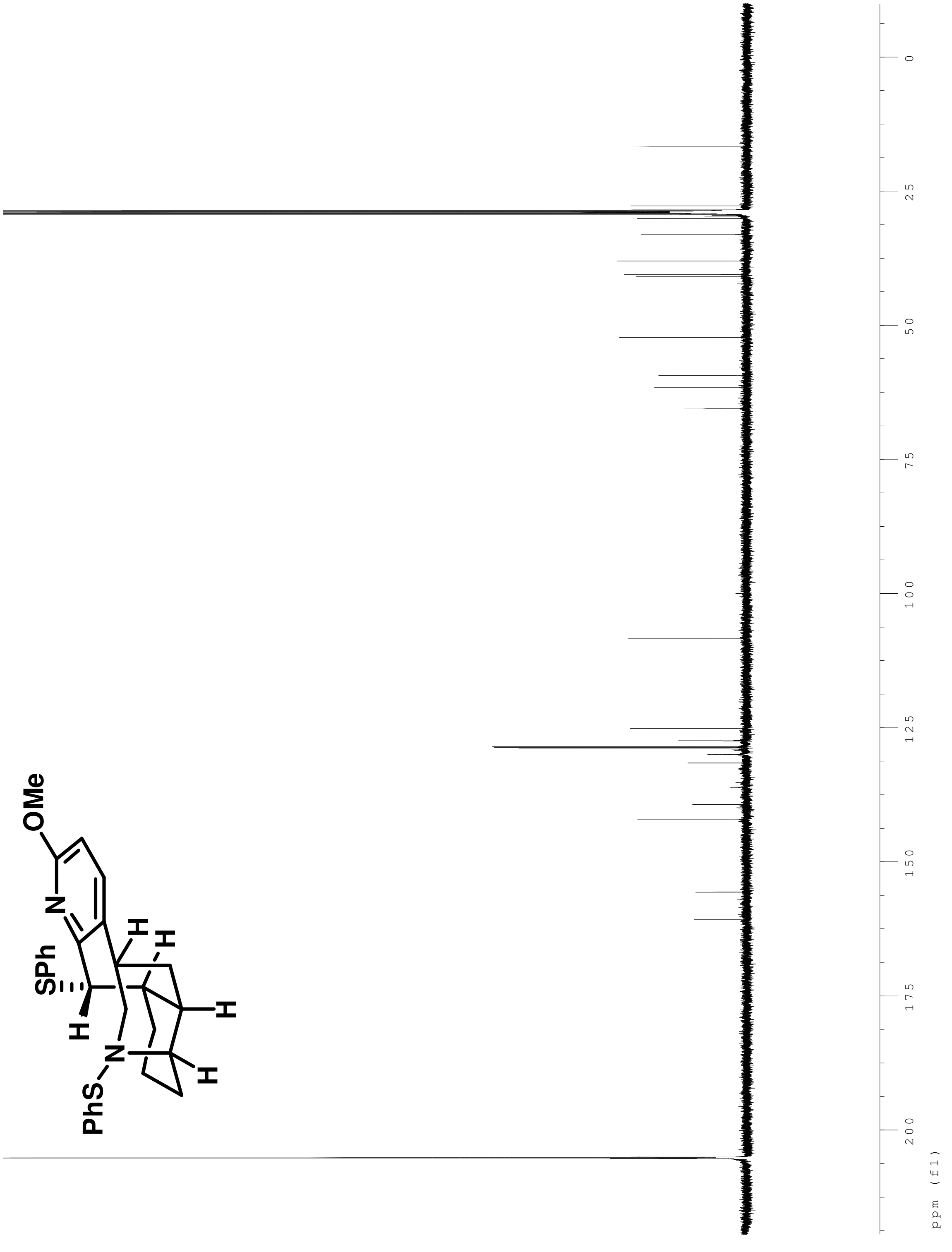
175
200
ppm (f1)


OMe
N
H
H
H
H
H
N
⊕
⊖
Cl
0.50
1.00
1.50
2.00
2.50
3.00
3.50
4.00
4.50
5.00
5.50
6.00
6.50
7.00
7.50
ppm (f1)

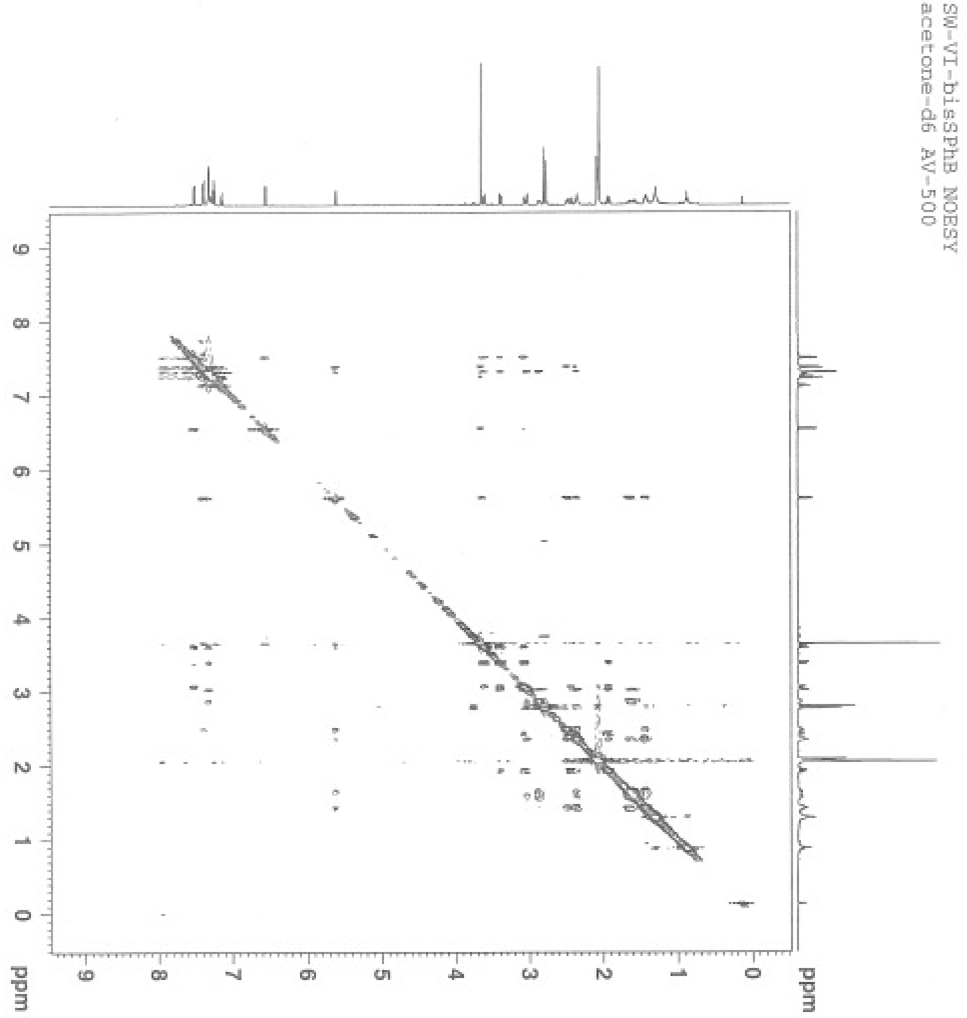


OMe
N
H
H
H
H
H
N
H
Cl
0
25
50
75
100
125
150
175
200
ppm (f1)

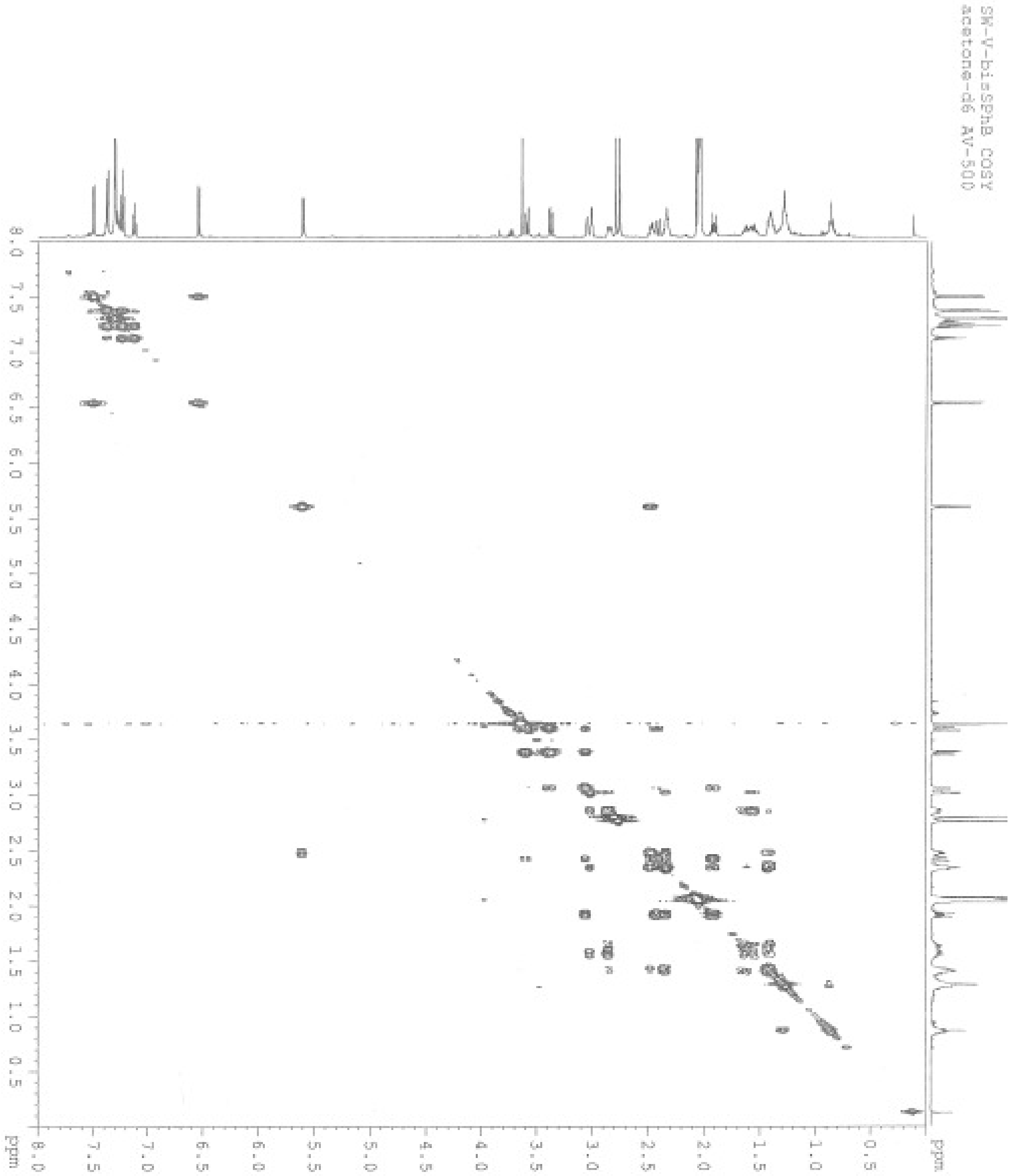

OMe
N
SPh
H
H
H
H
H
PhS
N
0.0
2.5
5.0
7.5
10.0
12.5
ppm (t1)


OMe
N
SPh
H
H
H
H
H
PhS
N
0
25
50
75
100
125
150
175
200
ppm (f1)

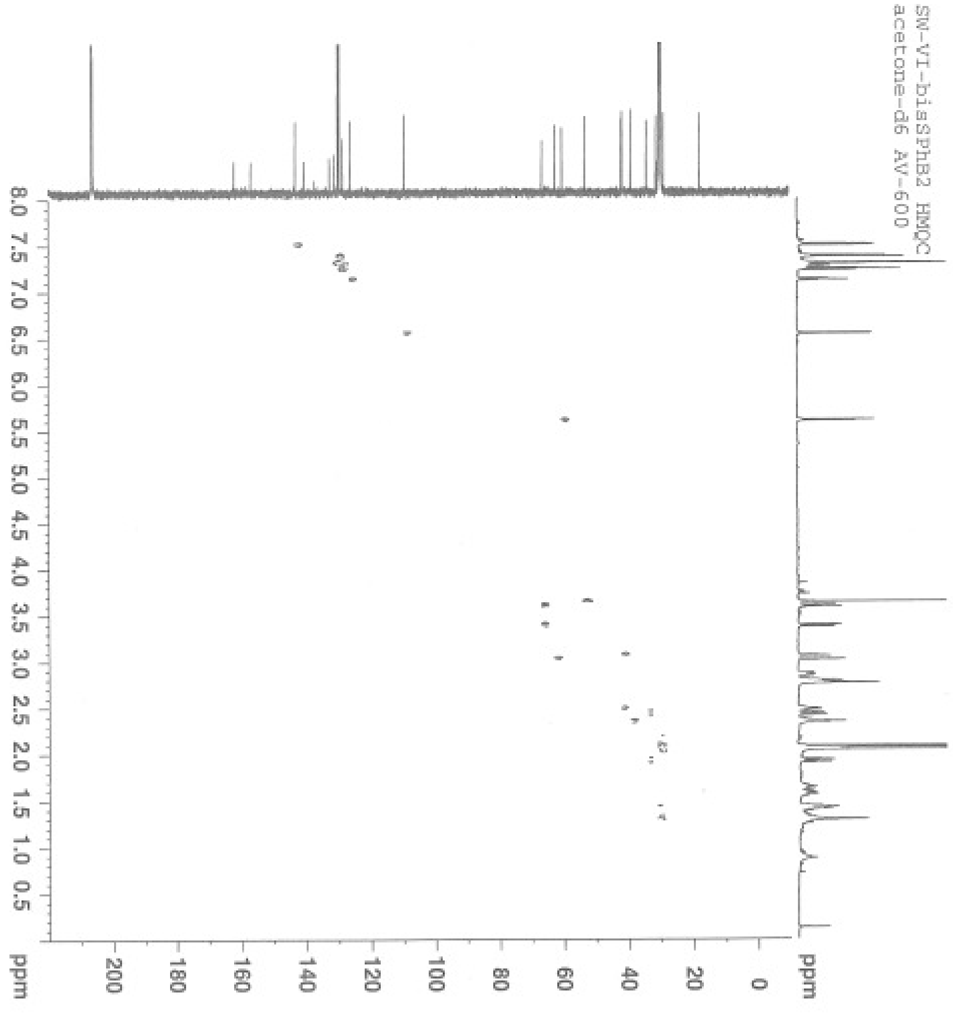
NOESY of Bissulfide **2.40**

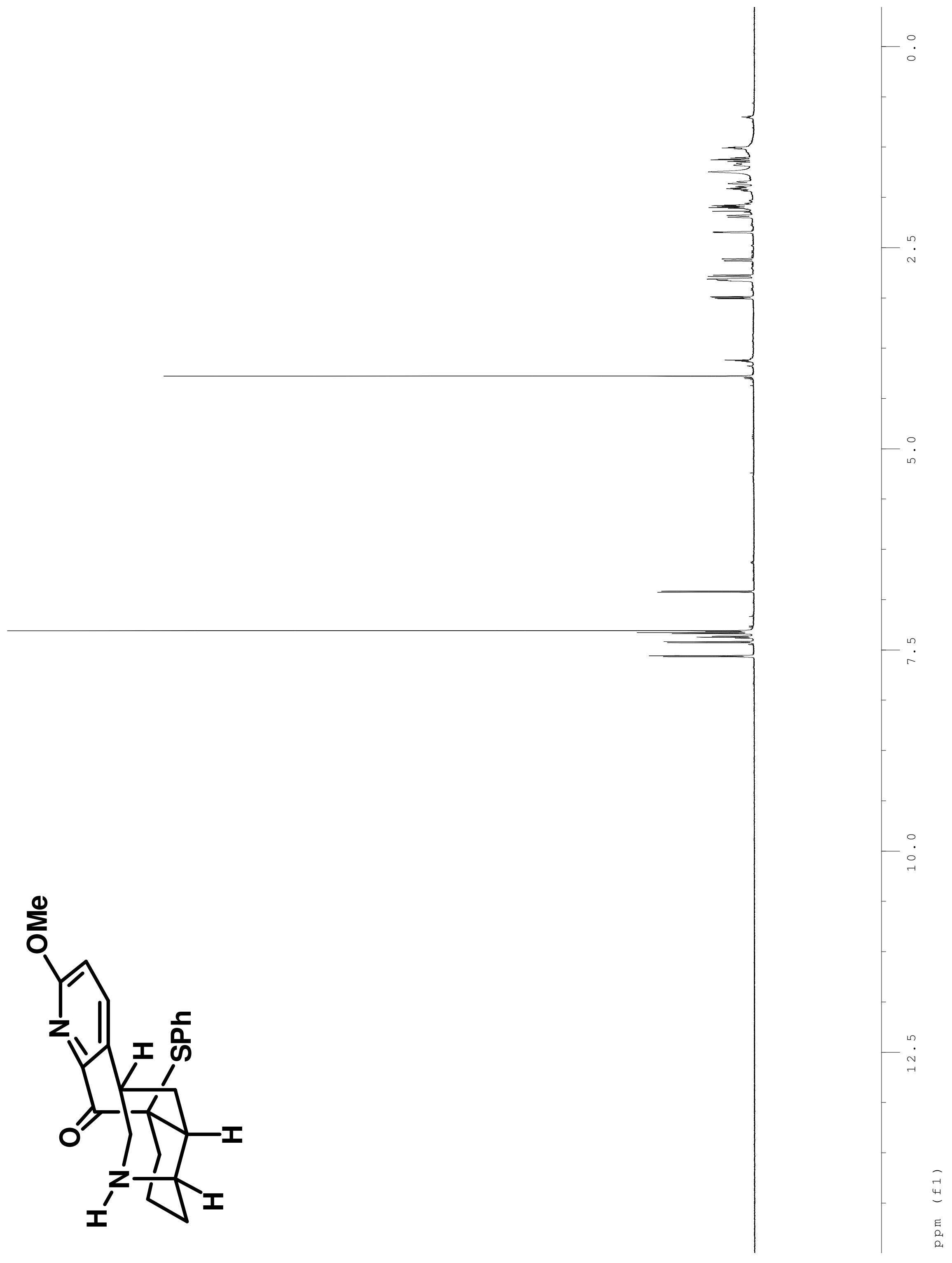


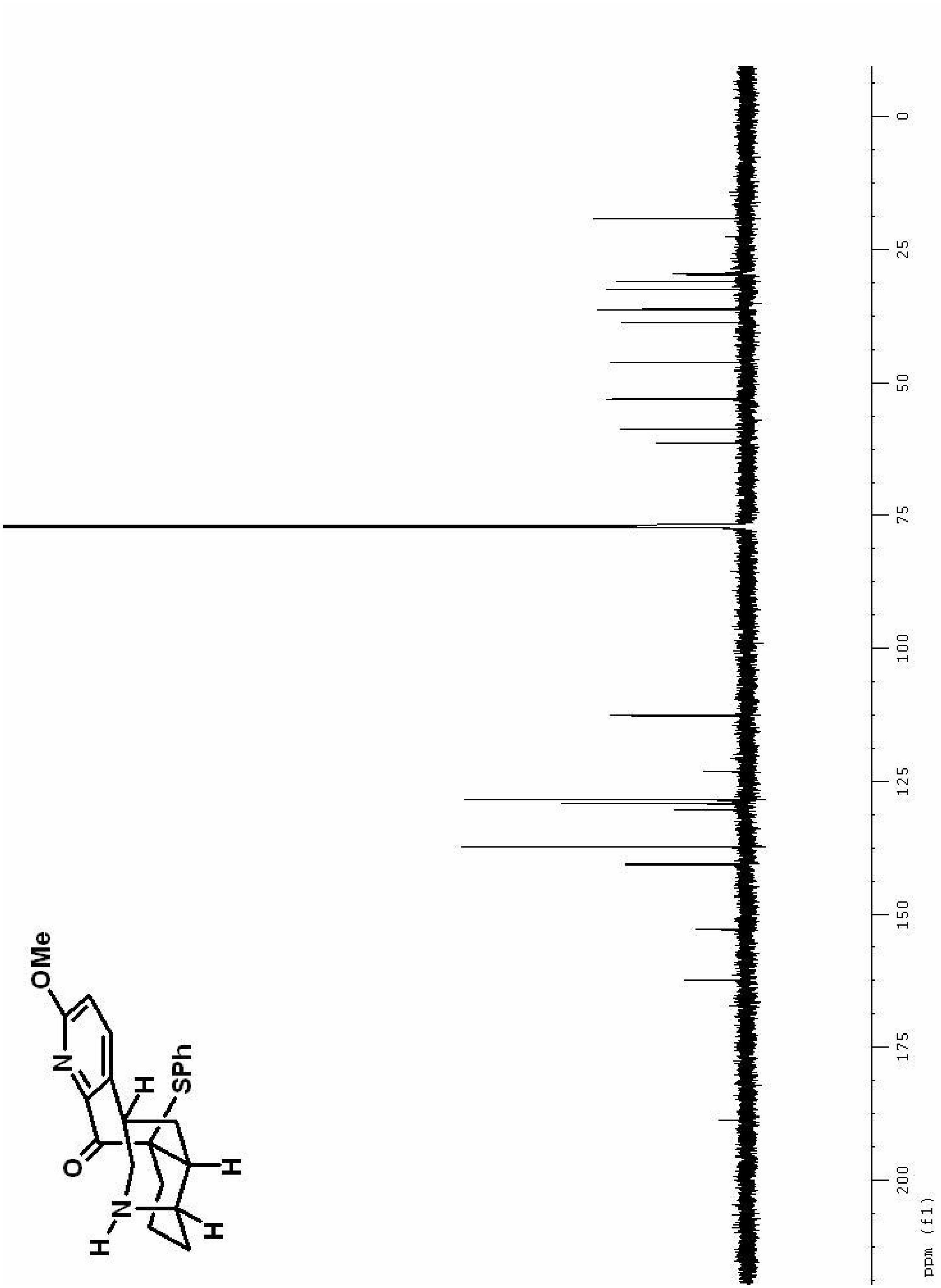
COSY of Bissulfide **2.40**



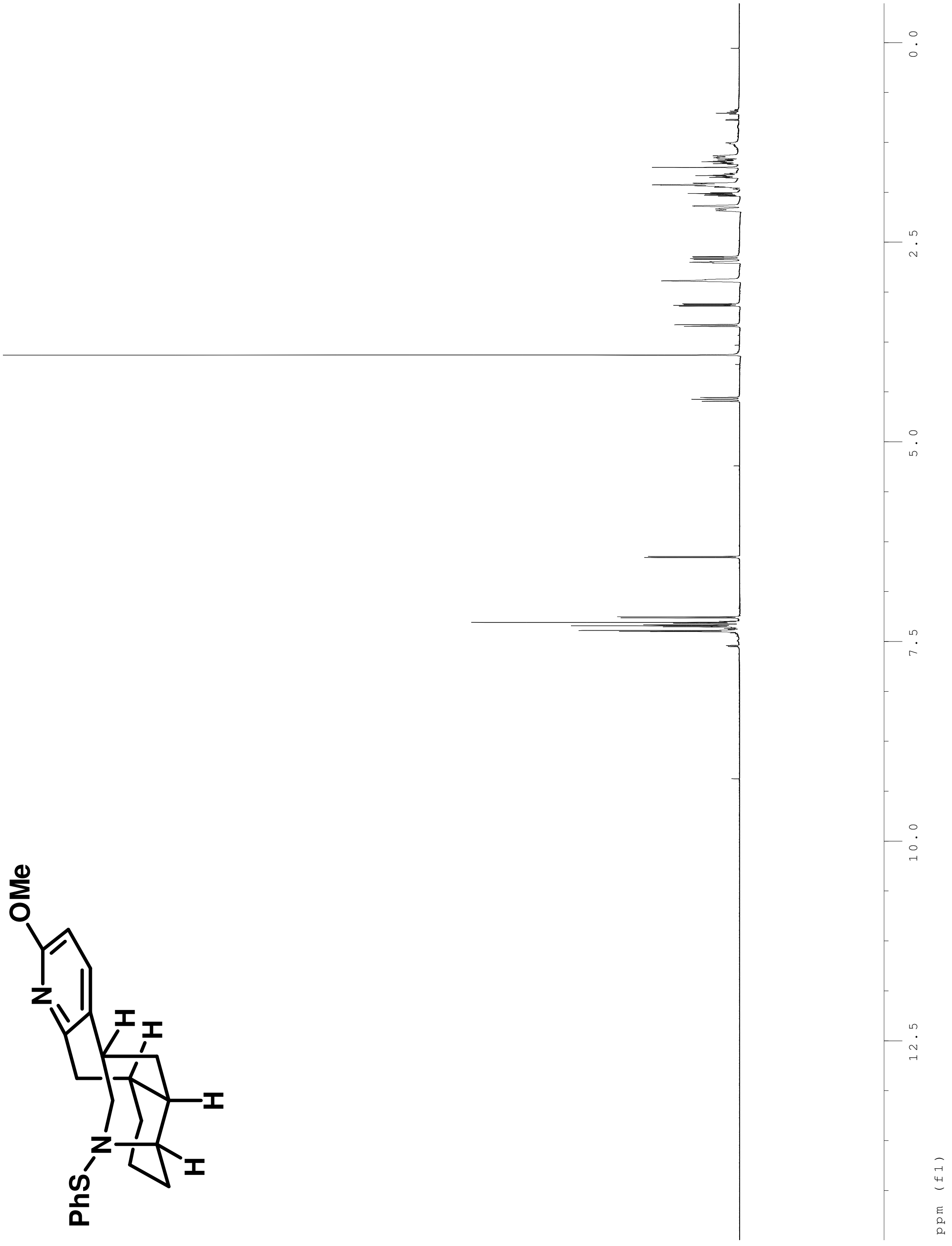
HMQC of Bissulfide **2.40**

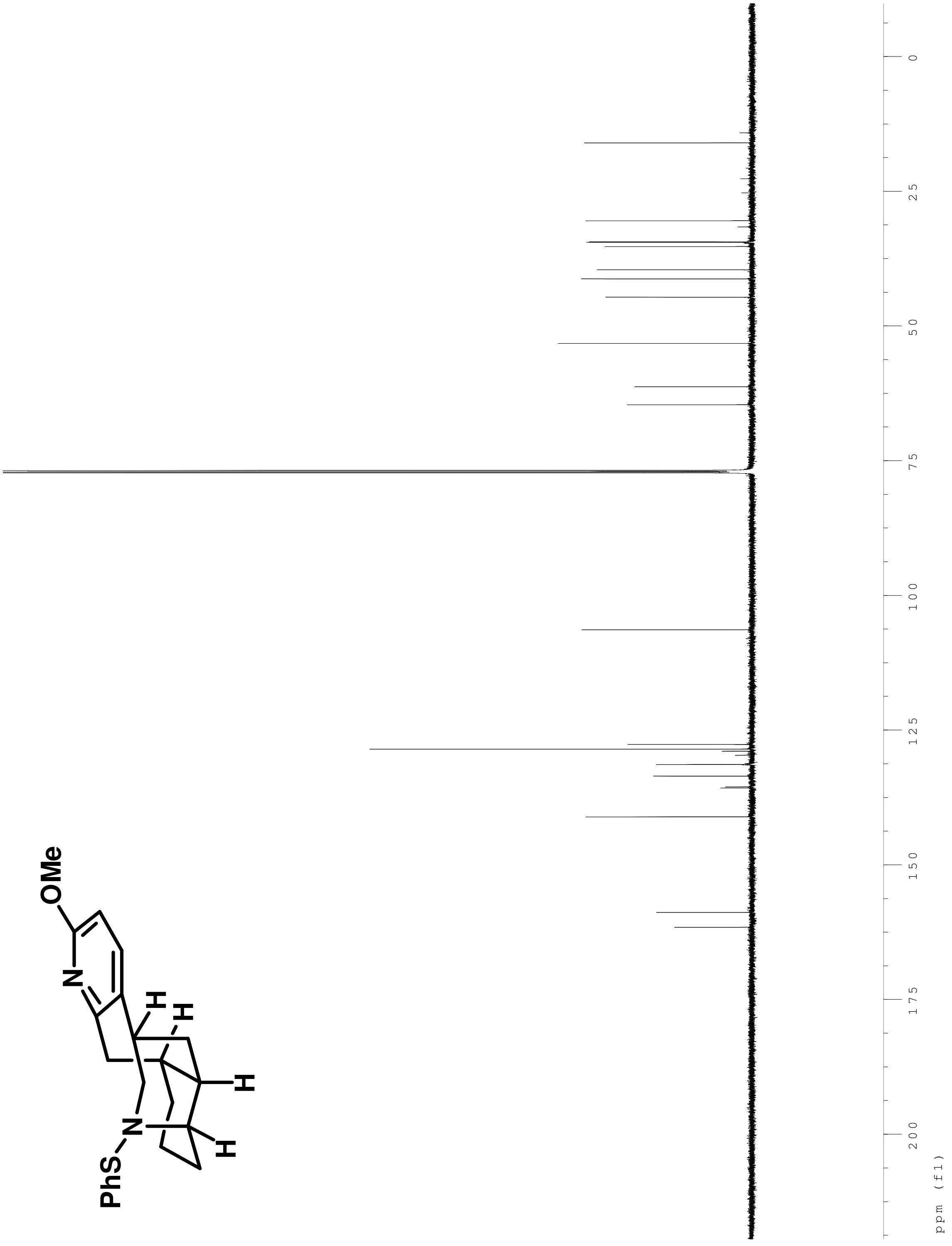


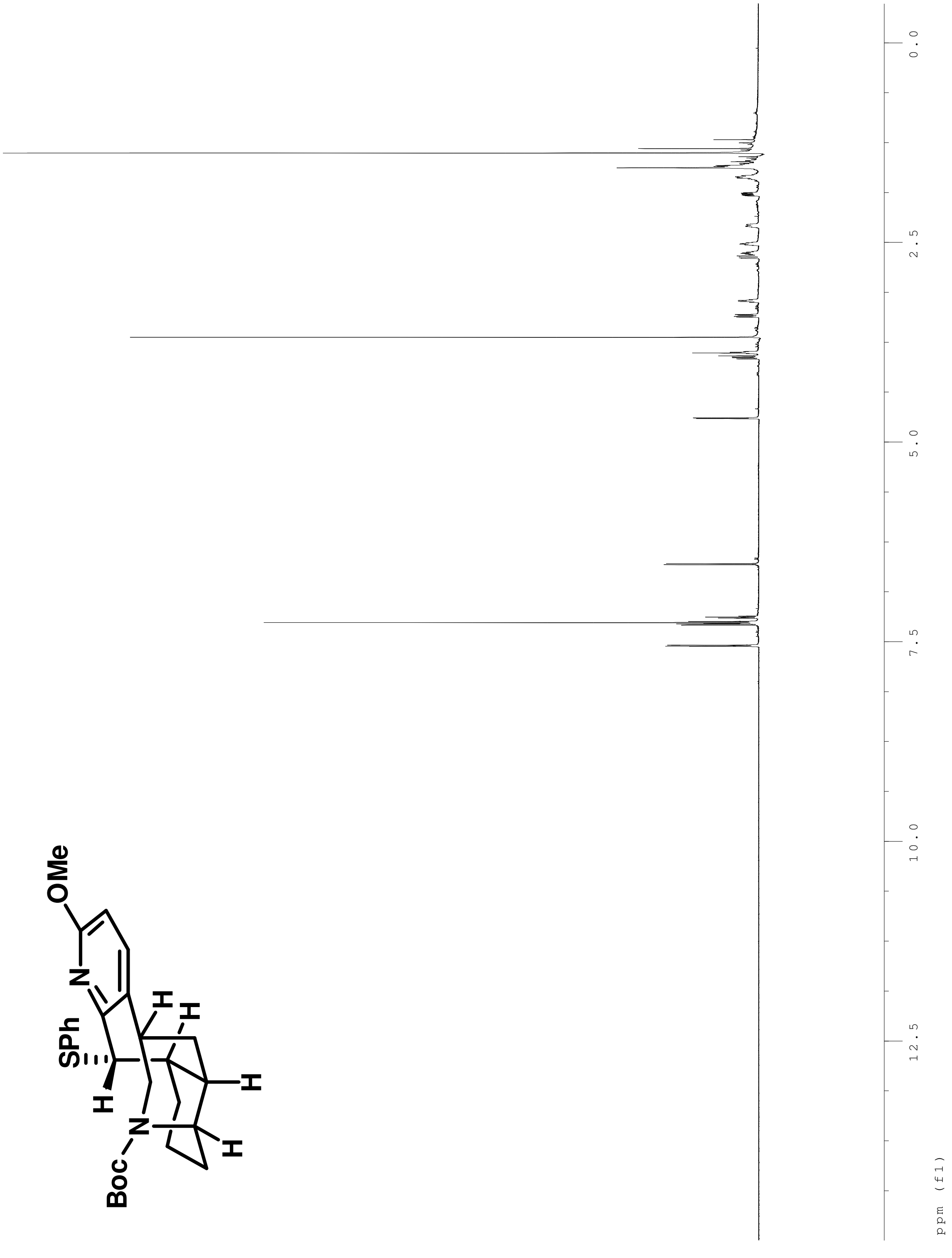

OMe
N
SPh
H
O
H
N
H
H
0.0
2.5
5.0
7.5
10.0
12.5
ppm (f1)

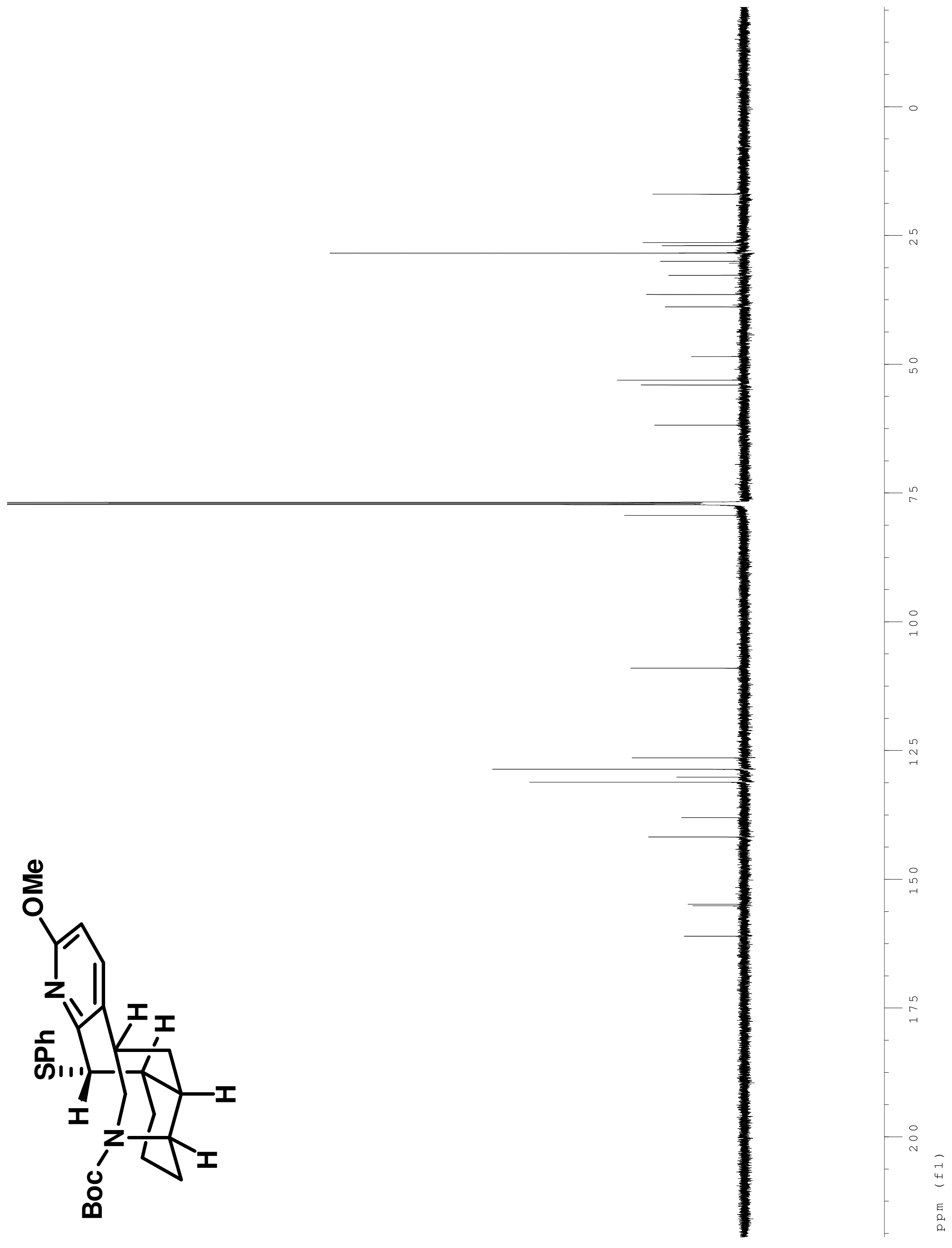


q


OMe
N
H
H
H
H
N
PhS
0.0
2.5
5.0
7.5
10.0
12.5
ppm (f1)


OMe
N
H
H
H
H
PhS
N
0
25
50
75
100
125
150
175
200
ppm (f1)


OMe
N
SPh
H
H
H
H
H
N
Boc
0.0
2.5
5.0
7.5
10.0
12.5
ppm (f1)


OMe
N
SPh
H
Boc
N
H
H
H
H
0
25
50
75
100
125
150
175
200
ppm (f1)