TOTAL SYNTHESIS OF HALICLONACYCLAMINE C

By

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To my mother and father, for always supporting my goals

and

my lovely fiancée, Leila Deravi, for her infinite love and support

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CHAPTER I

3-ALKYLPIPERIDINES: ISOLATION, BIOSYNTHESIS, & SYNTHESES

Introduction to Marine Secondary Metabolites

Marine organisms produce a fascinating array of structurally novel secondary metabolites.[1] These compounds are presumed to have no direct relationship to the organism's normal function, although many scientists believe these metabolites may play a significant role in the life of the producing species, despite lack of any evidence related to actual function.[2] An important source of marine secondary metabolites are sponges. Sponges are aquatic animals that occur in all oceans and have a wide distribution from tropical to temperate to arctic regions. They occasionally develop symbiotic relationship with both algae and bacteria, and quite often contain many complex chemicals that have potential medicinal value. Because of their prevalence, ease of collection, and ability to produce a variety of natural product structural classes, sponges have become one of the dominant sources of biologically active marine natural products.[2]

One important class of secondary metabolites isolated from marine sponges is the alkaloid group, one of the largest classes of natural products. There is some variation in the definition of alkaloids; however, they are generally known to be plant-derived compounds that are physiologically active, contain at least one basic nitrogen in a heterocyclic ring, have complex structure, and are often of limited distribution in natural sources.[3] There has been a great deal of biological, chemical, and pharmacological interest in naturally occurring alkaloids worldwide. This diverse group of secondary

metabolites has been classified into smaller sub-groups based upon their biogenetic origin.[3] One unique group of alkaloids is believed to share a common biogenetic pathway starting from various bis-pyridine macrocycles.[4,6] Many of these alkaloids possess significant biological activity including antimicrobial, antiviral, cytotoxic, and protein kinase inhibition.[4] These alkaloids have been isolated from marine invertebrates, particularly from sponges and tunicate, and a majority are composed of 3-alkylpyridines or reduced 3-alkylpiperidine units.[4] Furthermore, these alkaloids can be categorized by increasing molecular complexity with incorporation of tricyclic, tetracyclic, and pentacyclic motifs among other relatives[4]. Collectively this group of natural products is referred to as 3-alkylpiperidine alkaloids with representative examples shown in Figure 1.

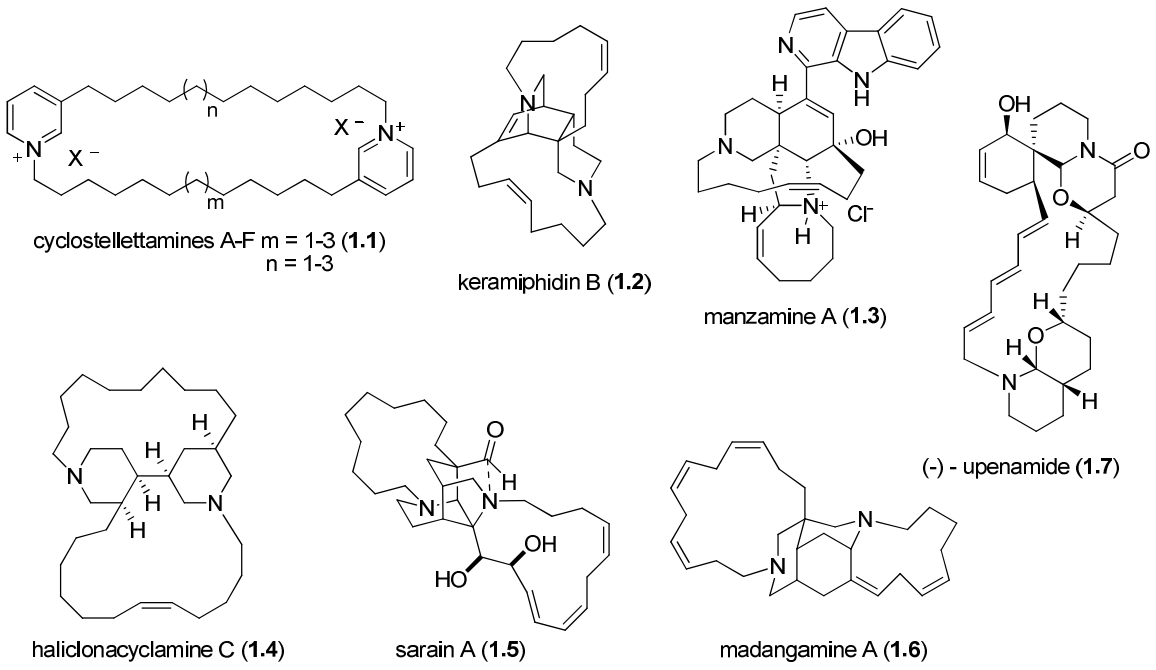
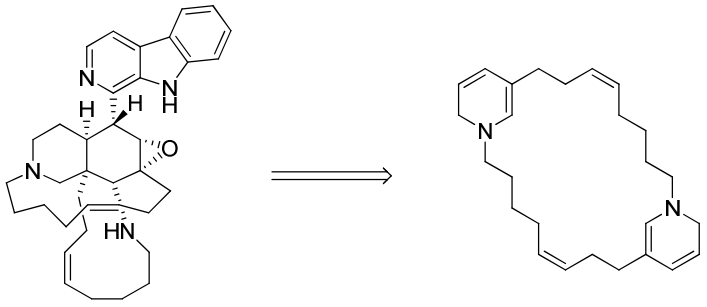


Figure 1. Representatives of 3-Alkylpiperidine Marine Alkaloids.

Proposed Biosynthetic Pathways

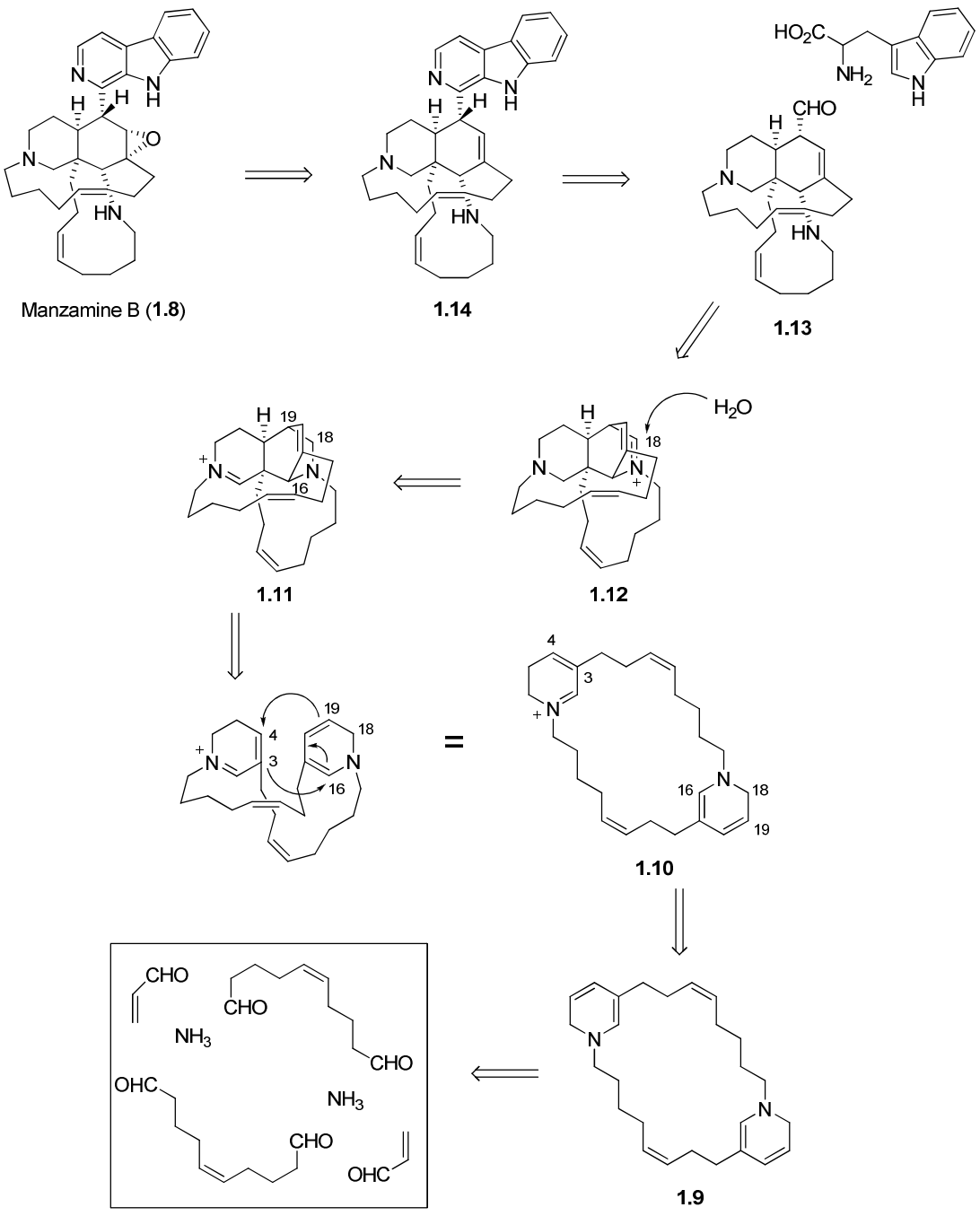
Manzamine A (**1.3**) and B (**1.8**)

In 1986 Higa and co-workers isolated the structurally unprecedented cytotoxic alkaloid manzamine A (**1.3**), as a hydrochloride salt, from the marine sponge *Haliclona sp*. while searching for bioactive natural products in the Okinawan waters off the coast of Japan.[5] This complicated pentacyclic alkaloid consisting of 5-, two 6-, 8-, and 13-membered rings, apart from the β-carboline substituent, elicited the statement, "… its provenance is problematical as there appears to be no obvious biogenic path."[5] This prompted Baldwin and Whitehead to propose a bis-dihydropyridine macrocycle (**1.9**) as a biosynthetic precursor to manzamines A (**1.3**) and B (**1.8**) (Scheme 1).[6,7] Their insightful proposal not only revealed a "hidden symmetry" not previously recognized in the complex manzamine alkaloids, but provided a key to defining biosynthetic pathways to a number of structurally diverse alkaloids (Figure 1).[6] The following discussion will focus on Baldwin and Whitehead's hypothesis, with experimental evidence to follow.



manzamine B (**1.8**) **1.9**

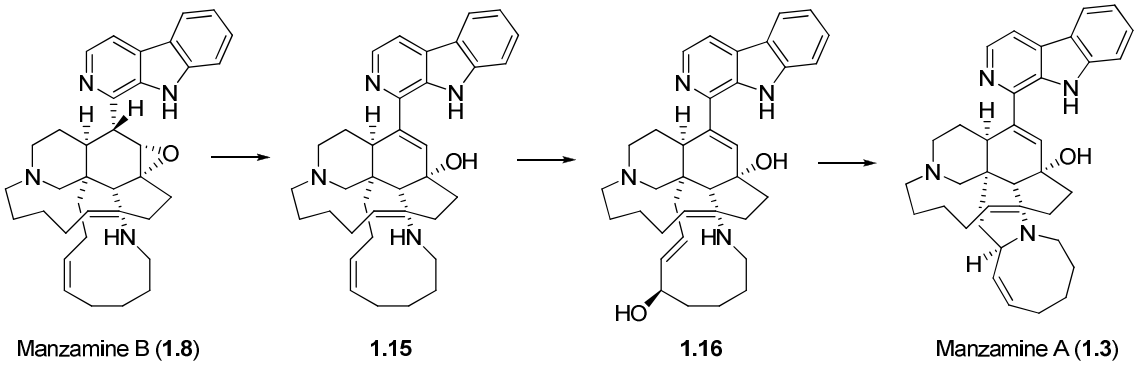
Scheme 1. *Bis*-dihydropyridine Precursor (**1.9**) to Manzamine B (**1.8**).



Scheme 2. Baldwin's Proposed Biosynthesis of Manzamine B (**1.8**).

The biosynthesis of manzamine B (**1.8**) is proposed to start from the condensation/reduction of two equivalents of acrolein with two dialdehyde units and two

equivalents of ammonia.[6] After protonation of one of the dihyropyridine units (**1.10**), an intramolecular Diels-Alder cycloaddition proceeds to pentacyclic iminium salt **1.11** with the relative stereochemistry and connectivity from the expected endo cycloaddition. Redox exchange between the two piperidine rings leads to a new imimium salt **1.12**. Hydrolytic ring cleavage then leads to aldehyde **1.13**, which condensation with β-carboline provides **1.14**. Selective oxidation of **1.14** at the trisubstituted olefin yields manzamine B (**1.8**). Manzamine B (**1.8**) is proposed to be converted to manzamine A (**1.3**) by an isomerization and allylic oxidation leading to ring closure and formation of the 8-membered ring (Scheme 3).[6]

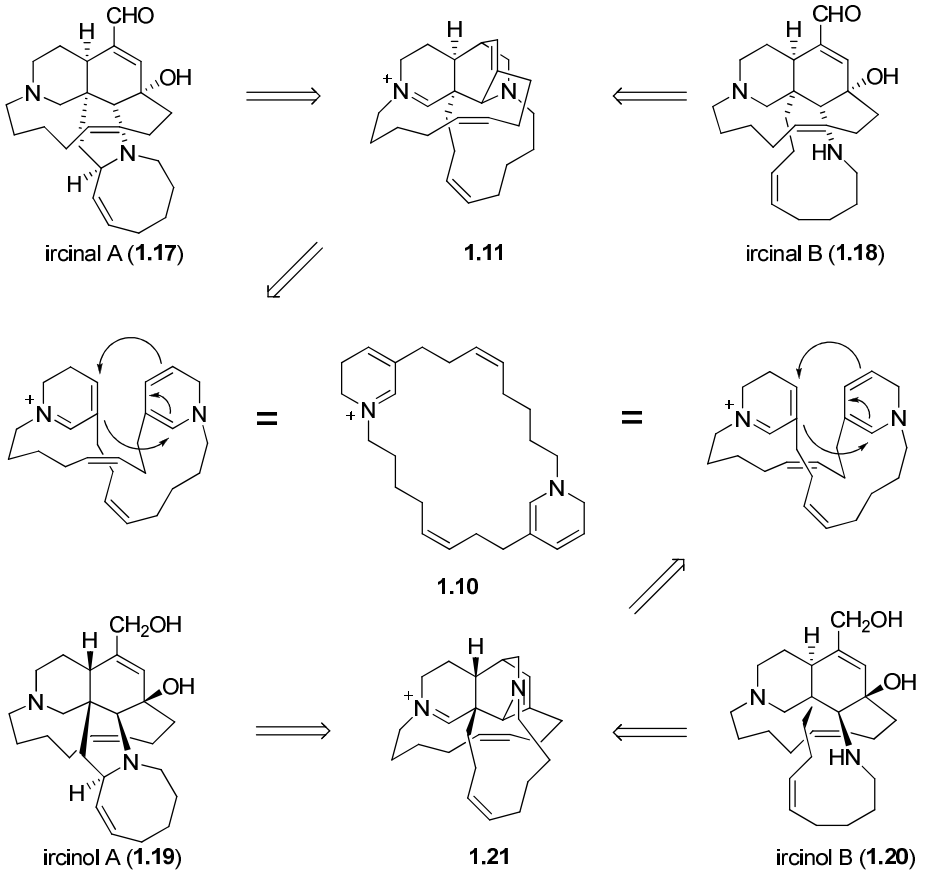


Scheme 3. Baldwin's Proposed Biosynthesis of Manzamine A (**1.3**).

Ircinal A (**1.17**) and B (**1.18**) / Ircinol A (**1.19**) and B (**1.20**)

Two additional alkaloids isolated from Okinawan waters in 1992 by Kobayashi and co-workers are ircinal A (**1.17**) and B (**1.18**).[8] Interestingly, the structures of ircinal A and B are very similar to the tetracyclic aldehyde (**1.13**) proposed earlier by Baldwin. Ircinal A was indeed converted to manzamine A through a Pictet-Spengler cyclization

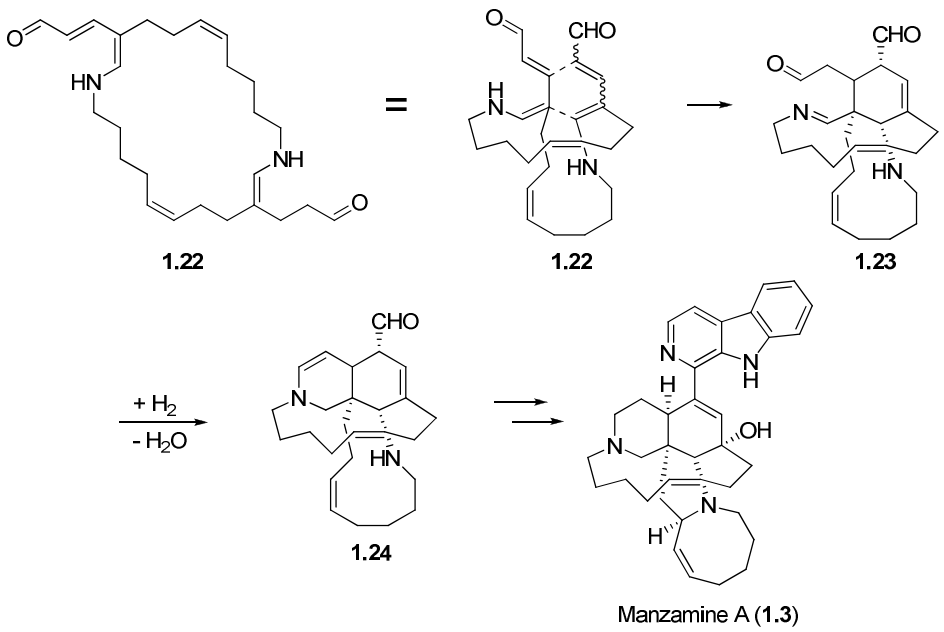
with tryptamine by Kobayashi.[8] These two cytotoxic alkaloids were the first supportive evidence for the Baldwin proposal.[6,8] Ircinol A (**1.19**) and B (**1.20**) were actually found to be antipodal to ircinal A (**1.17**) and B (**1.18**).[9] This poses some interesting questions about the nature of the [4+2] cycloaddition reaction and subsequent transformations presented in Baldwin's biosynthetic hypothesis. Potentially, the cycloaddition leads to a racemic cycloadduct (**1.21**) that undergoes an enzyme-mediated kinetic resolution to provide ircinol A/B and ircinal A/B (Scheme 4).[9]



Scheme 4. Biosynthetic Rational of Ircinols A/B (**1.19/1.20**) / Ircinals A/B (**1.17/1.18**).

Marazano's Modification of Baldwin's Proposal

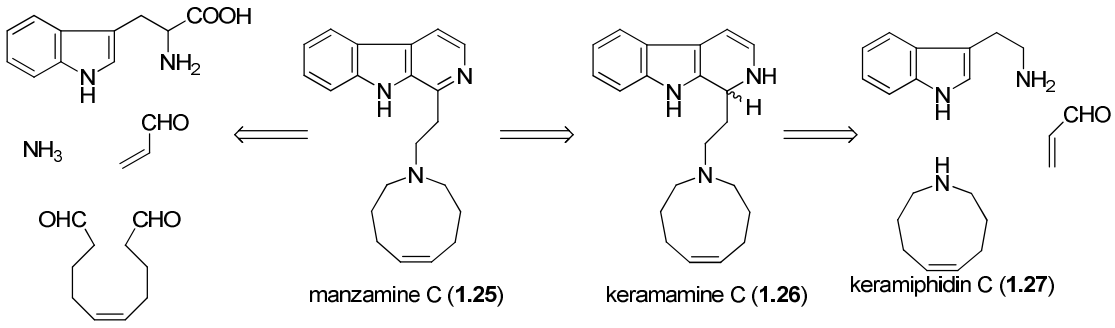
Marazano and co-workers have proposed an alternative to the Baldwin and Whitehead manzamine biosynthetic proposal.[10] They believe that intermediates that are more flexible than bis-dihydropyridine macrocycle (**1.9**) are the biogenetic precursors to manzamine and related alkaloids. Their hypothesis suggests 5-amino-2,4-pentadienal derivatives lead to the production of pyridinium salts (c.f. **1.1**). In this way they propose to arrive at key macrocycle **1.22** by substituting malondialdehyde for acrolein in the condensation step with ammonia and an appropriate dialdehyde. This pathway would then lead to a direct cyclization of **1.22** to give **1.23** followed by reduction and cyclization of the imine functionality to produce enamine **1.24** (Scheme 5).[10]



Scheme 5. Marazano's Modification of Baldwin's Approach.

Proposed Biosynthesis of Related Alkaloids

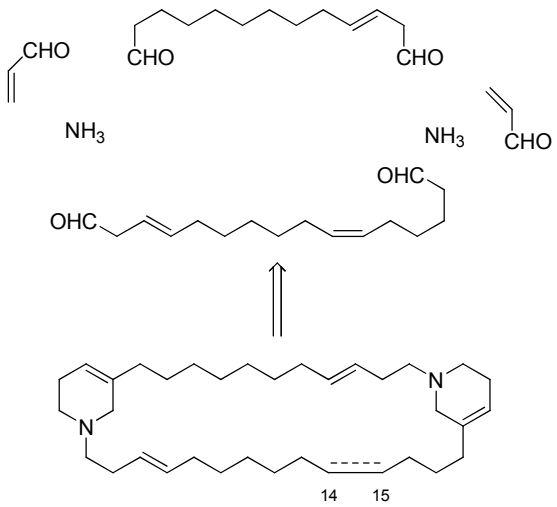
The original proposal put forth by Baldwin and Whitehead has lead to biosynthetic proposals accounting for many related 3-alkylpiperidines. Manzamine C (**1.25**)[7], keramamine C (**1.26**), and keramiphidin C (**1.27**)[11] could also be products of a condensation between a dialdehyde, acrolein, and ammonia. This was indeed proposed by Baldwin and Whitehead for manzamine C (Scheme 6).[6] After the isolation of keramiphidin C (**1.27**) and keramamine C (**1.26**) by Kobayashi and co-workers, they produced a modified biosynthetic approach as well. Kobayashi proposes a coupling of a dialdehyde unit with ammonia to construct keramiphidin C (**1.27**). After condensation with acrolein, a Pictet-Spengler type cyclization with tryptamine, keramiphidin C (**1.27**) can account for the biosynthesis keramamine C (**1.26**).[11] Further oxidation of **1.26** leads to manzamine C (**1.25**). Notably, the Kobayashi group isolated tryptamine from the same sponge that produced keramiphidin C (**1.25**) and keramamine C (**1.26**).[11]



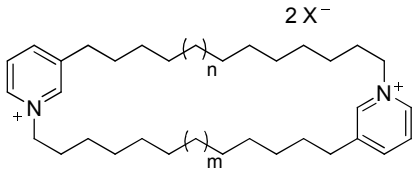
Scheme 6. Proposal of Keramamine C, Keramiphidin C, and Manzamine C (**1.25-1.27**).

Most natural products derived from 3-alkylpyridines do not have an obvious relationship to the manzamines at first glance. However, the haliclamines[12] and the

cyclostellettamines A-F[13] not only have a clear relationship, but represent the building blocks of this sub-group of natural products according to the Baldwin hypothesis. By varying the chain length in the dialdehydes that are reductively coupled with two units of acrolein and two equivalents of ammonia, followed by partial reduction of the dihydropyridine moieties leads to haliclamine B (**1.28**). Further reduction of the *cis* double bond produces haliclamine A (**1.29**). Then an oxidation of the dihydropyridine units would yield the cyclostellettamines A-F (**1.30-1.35**). Additionaly, Berlinck and co-workers have isolated cyclostellettamines G-I, K, and L.[14]



haliclamine A (**1.28**)
haliclamine B; Δ= 14,15 (**1.29**)



cyclostellettamine A (m = 1, n =1) (**1.30**)
cyclostellettamine B (m = 1, n =2) (**1.31**)
cyclostellettamine C (m = 2, n =2) (**1.32**)
cyclostellettamine D (m = 1, n =3) (**1.33**)
cyclostellettamine E (m = 2, n =3) (**1.34**)
cyclostellettamine F (m = 3, n =3) (**1.35**)

Scheme 7. Haliclamines (**1.28** and **1.29**) and Cyclostellettamines (**1.30-1.35**).

Keramaphidin B (**1.36**)[15], ingenamines[16,17], inagamines[16,17], and the xestocyclamines[18,19] are another class of pentacyclic 3-alkylpiperidines that have a close resemblance to the proposed Diels-Alder cycloadduct of Baldwin (Figure 2). Likewise, these compounds would arrive from an intramolecular cycloaddition reaction of a reduced bis-dihydropyridine macrocycle with varying alkyl chain lengths and degrees of unsaturation. Keramaphidin B (**1.36**)[15] is structurally identical to the reduced form of the proposed cycloadduct (**1.11**) in the Baldwin hypothesis. In fact, this class of alkaloids was anticipated by Baldwin and Whitehead in their proposal.[6] Crews and co-workers found that xestocyclamine A and B[19] were inhibitors of protein kinase C.

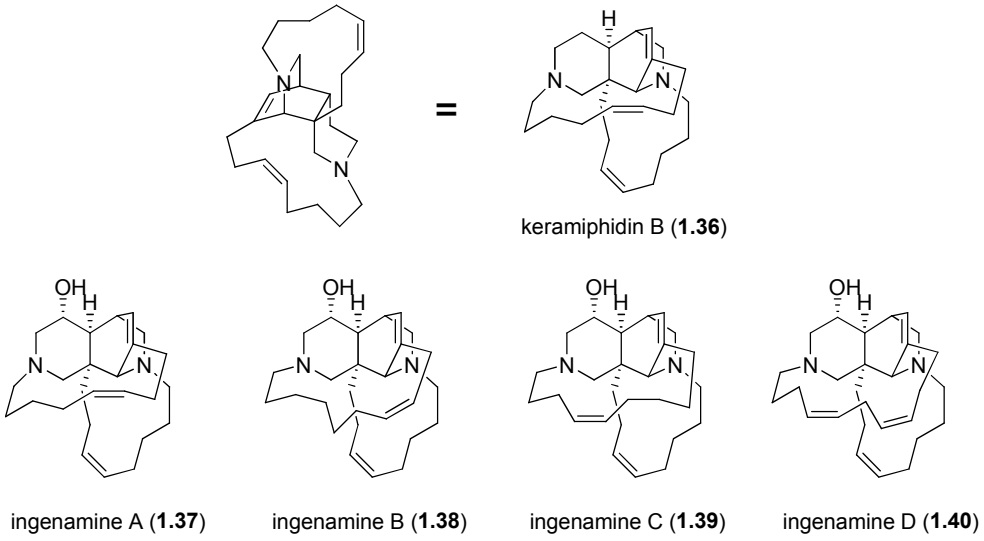
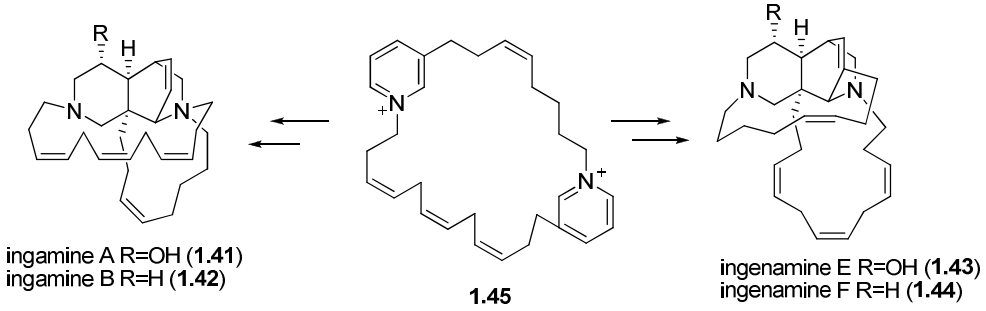


Figure 2. Keramaphidin B (**1.36**) and Ingenamines A-D (**1.37 – 1.40**).

Closer examination of the ingamines[20] and ingenamines[17] reveals some ambiguities in the nature of the proposed Diels-Alder cycloaddition. Ingamine A (**1.41**) and B (**1.42**)[20] and ingenamine E (**1.43**)[17] and F (**1.44**)[17] appear to arise from the same

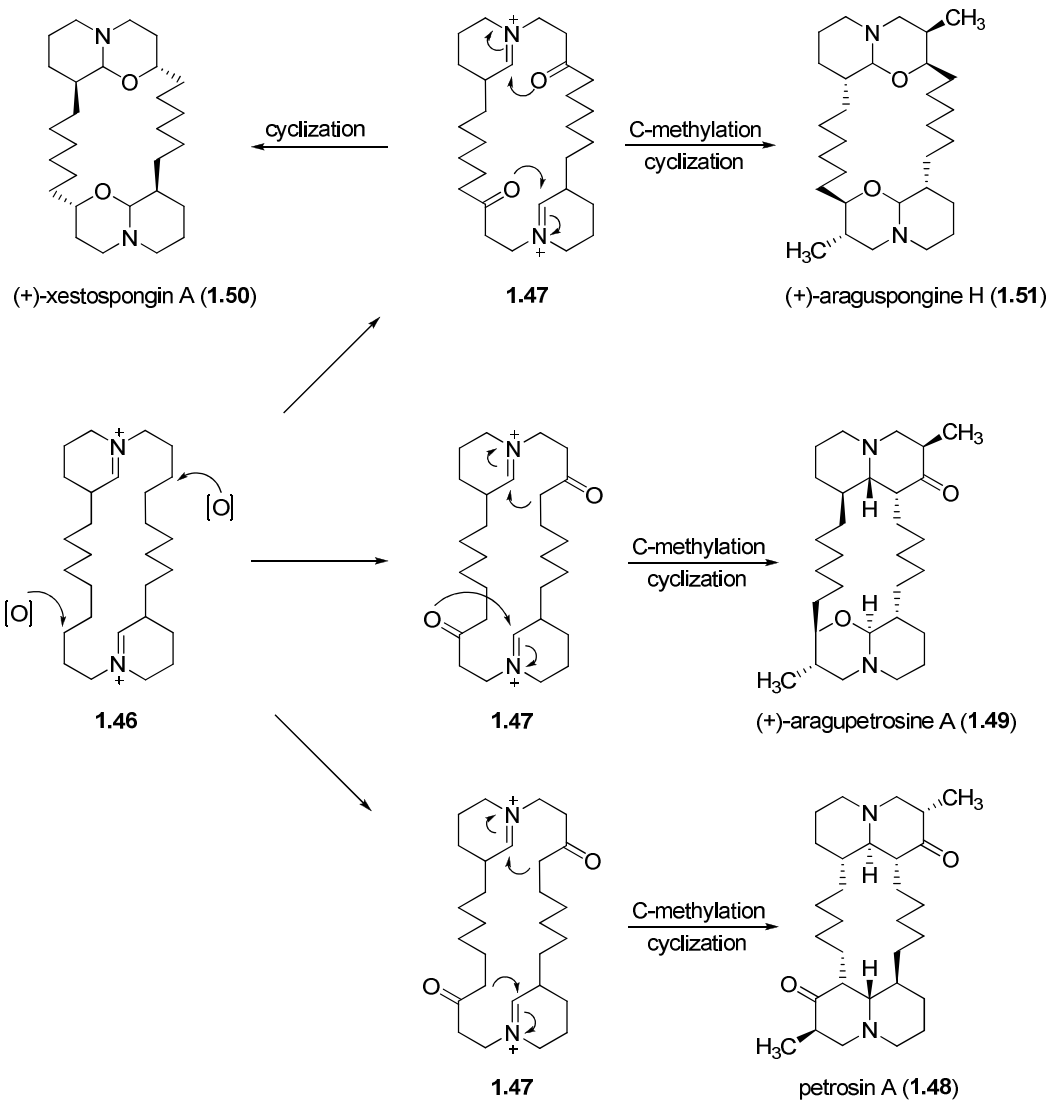
bis-dihydropyridine macrocycle (**1.45**). Ingamine A (**1.41**) and B (**1.42**)[20] are formed by a reduced ring B acting as the diene and a reduced ring A as the dienophile in the cycloaddition. However, ingenamine E (**1.43**) and F (**1.44**)[17] are formed by ring A acting as the diene and ring B as the dienophile (Scheme 8). This observation, along with the ircinals and ircinols rationale (Scheme 4), suggest multiple products can be formed. The ingenamines have been found to be antipodal to manzamine A (**1.3**) and B (**1.8**).



Scheme 8. Cycloaddition of the Ingamines (**1.41, 1.42**) and Ingenamines (**1.43, 1.44**).

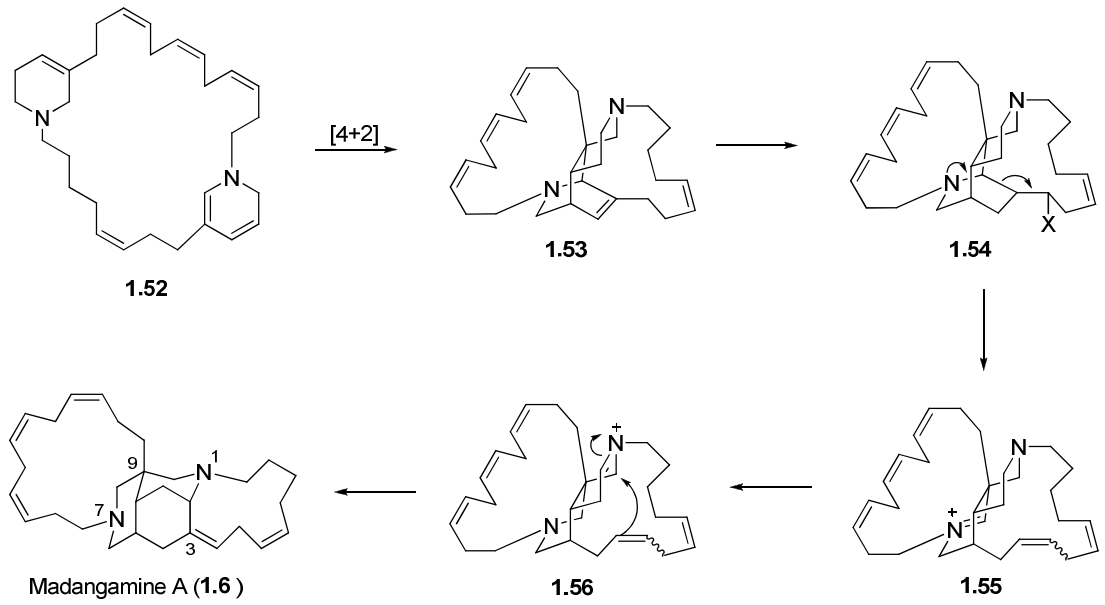
The petrosins[21], aragupetrosines[22], araguspongines[23-25], and xestospongins[24,26,27] are another class of 3-alkylpiperidines that derive from oxidation of the alkyl portion of a hypothetical bis-dihydropyridine macrocycle. Beginning from common precursor iminium salt (**1.46**), oxidation of both alkyl chains leads to diketone (**1.47**) (Scheme 9). Petrosin A (**1.48**)[20] is then produced by rotation of the alkyl chains, followed by two Mannich cyclizations, and methylation. Methylation and Mannich cyclizations with both oxygen and carbon acting as the nucleophile lead to aragupetrosine A (**1.49**).[22] Rotation of the alkyl chains of **1.46**, followed by nucleophilic attack by oxygen yields (+)-

xestospongin A (**1.50**).[25] Cyclization and methylation would produce (+)-araguspongine H (**1.51**) (Scheme 9).[22]



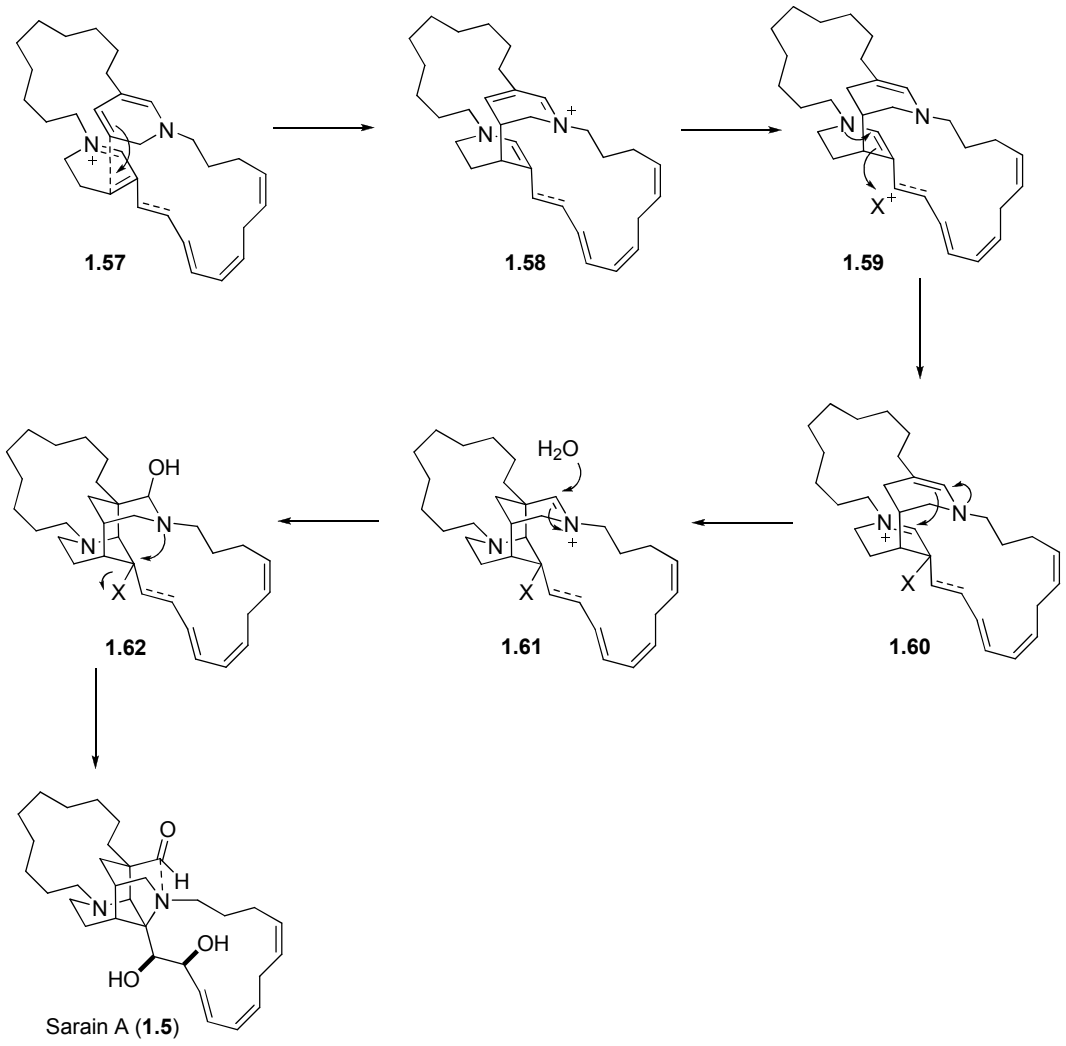
Scheme 9. Hypothetical Biosynthesis of Petrosin A (**1.48**), (+)-Araguspetrosine A (**1.49**), (+)-Araguspongine H (**1.51**), and (+)-Xestospongin A (**1.50**).

The madangamines[28,29] are pentacyclic alkaloids presumably derived from bis-dihydropyridine macrocycles similar to those in the ingenamine biosynthesis. The proposed biosynthesis for madangamine A is shown below (Scheme 10). Cycloaddition of ingenamine like precursor **1.52** yields diamine **1.53**. Allylic activation, followed by fragmentation provides tetracyclic iminium intermediate **1.55**. Redox exchange and Mannich like trapping of the iminium salt, followed by oxidation provides madangamine A (**1.6**).[27] All the madangamines have identical N-1 to C-3 bridges, but vary in unsaturation within the N-7 to C-9 bridge. Kong and Anderson have suggested that the enzyme(s) catalyzing this rearrangement may have a specific requirement for a particular functionality and chain length.[28]



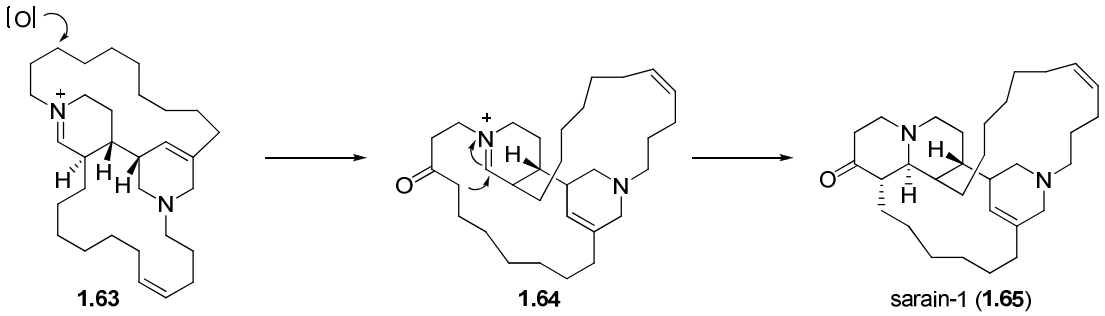
Scheme 10. Hypothetical Biosynthesis of Madangamine A (**1.6**).

Another class of structurally impressive pentacyclic alkaloids is the sarains.[30-32] Cimino and co-workers were able to produce a crystal of an acetate derivative of sarain A (**1.5**) suitable for X-ray analysis to unambiguously assign its structure. The biosynthesis begins with formation of a 3, 4-linked bis-macrocycle (**1.58**), reduction of iminium salt and olefin activation of **1.59**, followed by Mannich-like reaction gives **1.61**. Hydrolysis, followed by nucleophilic attack by the nitrogen and dihydroxylation yields sarain A (**1.5**).



Scheme 11. Hypothetical Biosynthesis of Sarain A (**1.5**).

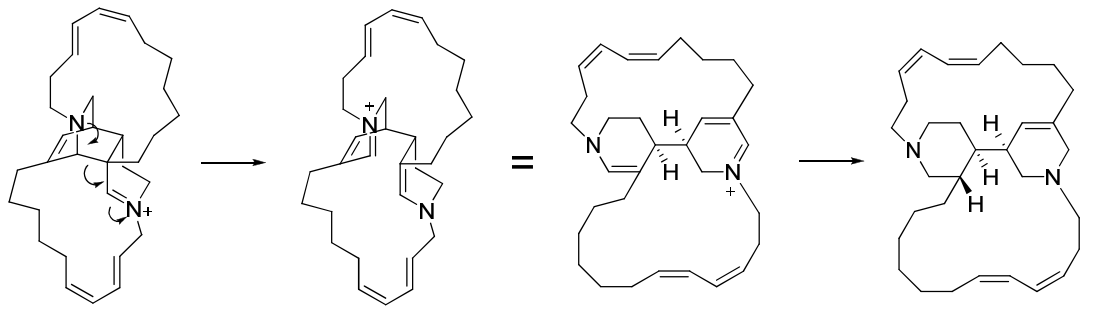
Sarain -1[30] is another pentacyclic alkaloid which presumably arises from a 3, 4-linked *bis*-piperidine precursor. Starting from the iminium salt of the 3, 4-linked bis-piperidine (**1.63**), oxidation at the γ-position of the macrocycle leads to ketone (**1.64**). Intramolecular Mannich cyclization of ketone **1.64** yields sarain-1 (**1.65**).[31]



Scheme 12. Hypothetical Biosynthesis of Sarain-1 (**1.65**).

A majority of natural products derived from 3-alkylpyridines comprise the pentacyclic alkaloids described above. Another growing class of biologically active compounds derived from 3-alkylpyridines is the tetracyclic alkaloids, which features a 3,4-linked bis-piperidine core attached to two macrocycles.[33-37] In 1994 Crews and co-workers isolated halicyclamine A(**1.68**)[33] from the marine sponge *Haliclona* sp which has recently been evaluated as a lead for the discovery of new anti-tuberculosis agents.[38] The hypothetical biosynthesis of halicyclamine A (**1.68**) is outlined in Scheme 13. Fragmentation of the keramaphindin and ingenamine-like precursor leads to iminium salt **1.67**. Reduction of the iminium species and the enamine produces halicyclamine A (**1.68**). It is easy to see how these tetracyclic compounds are related to their pentacyclic

relatives. Iminium salt **1.67** is almost identical to intermediate **1.58** in the propsed biosynthesis of sarain A (**1.5**).



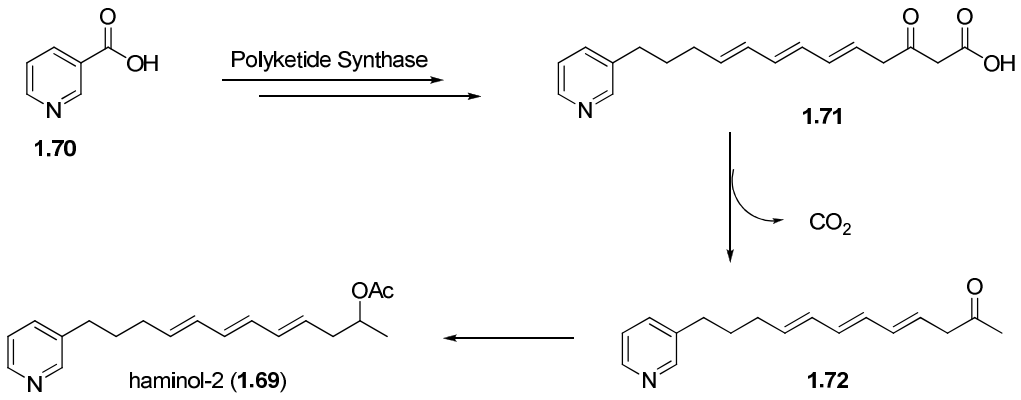
Scheme 13. Hypothetical Biosynthesis of Halicyclamine A (**1.68**).

In Vivo Evidence for Biosynthetic Proposals

The natural products discussed above in the proposed biosynthetic pathways section are clearly related based on a common biosynthetic precursor, the 3-alkylpyridine moiety. Although the number of natural products isolated within this class of alkaloids supports the logical hypothesis by Baldwin and Whitehead, there has been no *in vivo* evidence in support of their proposal to date. Therefore, a key issue that has to be address is the origin of the 3-alklypyridines. Baldwin and Whitehead have proposed a condensation of a C-3 (acrolein) and a C-10 (an unsaturated dialdehyde) with an equivalent of ammonia. Marazano has altered this proposal using malonaldehyde in place of acrolein.

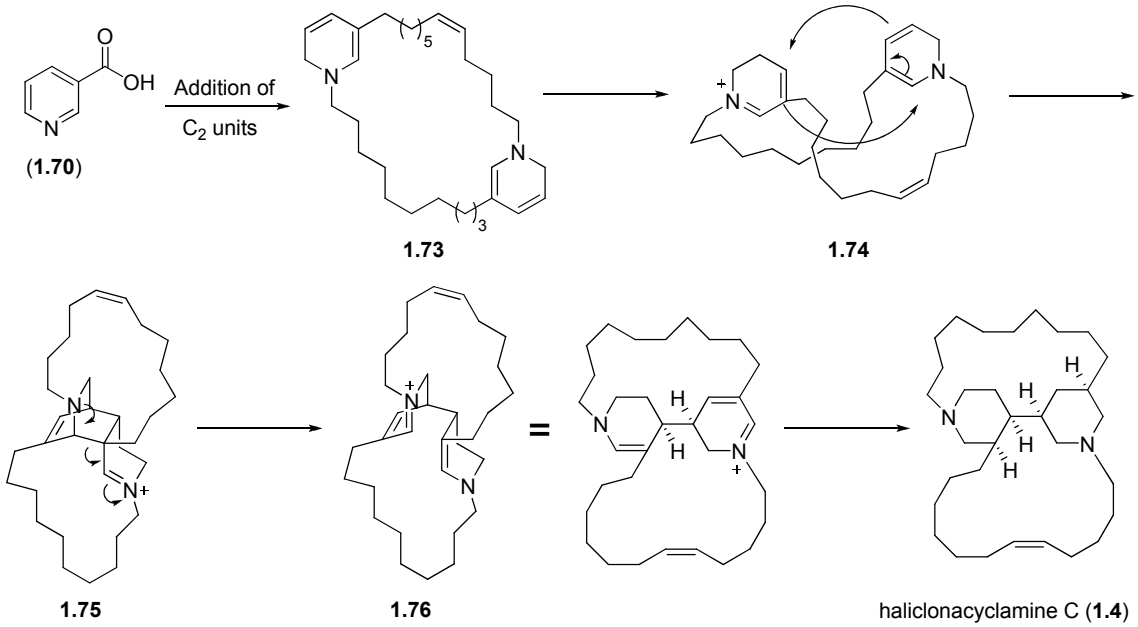
In 2003 Fontana and co-workers described the only *in vivo* evidence to date concerning the origin of 3-alkylpyridines.[39,40] By conducting feeding studies, they have

been able to elucidate a polyketide biosynthetic pathway leading to haminol-2 (**1.69**). Haminol -2 (**1.69**) is a 3-alkylpyridine alkaloid isolated from the Meditteranean mollusc *Haminoea orbigny*ana. Fontana and co-workers were able to feed the mollusc *Haminoea orbigny*ana with radio-labelled [2-^{14}C]-acetic acid and nicotinic acid-carboxy-^{14}C. After injection of the labeled precursors they detected significant levels of radioactivity in the isolated haminol-2 (**1.69**). They also administered to the mollusc d_4-nicotinic acid ethyl ester or [1-^{13}C] acetic acid. After multiple feeding experiments, they proved the origin of haminol-2 (**1.69**) via a polyketide synthase (PKS) using nicotinic acid (**1.70**) as a starter unit and six molecules of acetate as extender units. Loss of the terminal carbon of the PKS-emerging chain (**1.71**), presumably due to a post-PKS decarboxylation, provides the skeleton (**1.72**) of haminol-2 (**1.69**) (Scheme 14).[39] This discovery proves that haminols are produced in the mollusc *Haminoea orbignyana* by a PKS (polyketide synthase) pathway.[40]



Scheme 14. Proposed Biosynthesis of Haminol-2 (**1.69**).

Fontana's experiments rule out other hypotheses about the origin of 3-alkylpyridines. This experimental work does not however, discount the subsequent biosynthetic steps in which complex natural products arise from 3-alkylpyridines. Recognizing that a nicotinic acid moiety serves as the biosynthetic precursor a biosynthesis of haliclonacyclamine C (**1.4**)[36] is shown below (Scheme 15). Starting form nicotinic acid (**1.70**), the *bis*-dihyropyridine intermediate (**1.73**) would now arrive by acetate or malonate acting as extender intermediates, followed by a decarboxylation step. Once the key intermediate is formed, the Diels-Alder cyclization leads to **1.75** which after fragmentation and reduction yields haliclonacyclamine C (**1.4**).

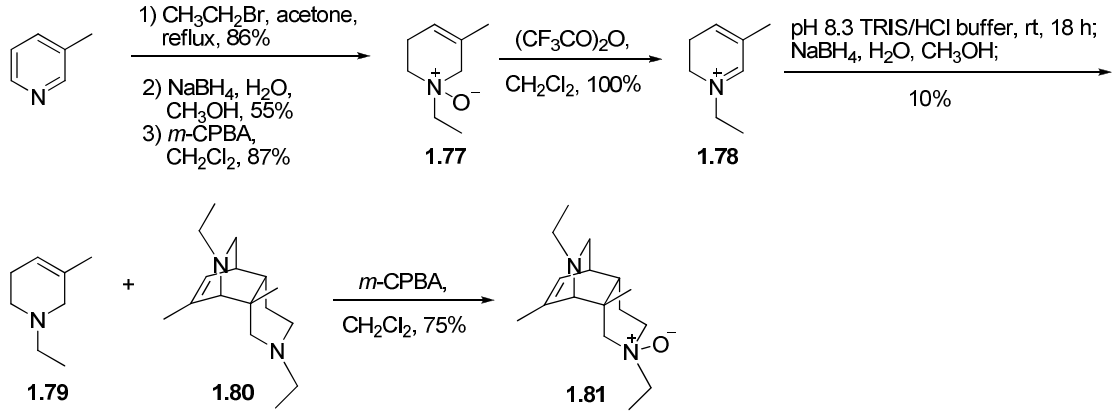


Scheme 15. Proposed Biosynthesis of Haliclonacyclamine C (**1.4**).

Biomimetic Approaches

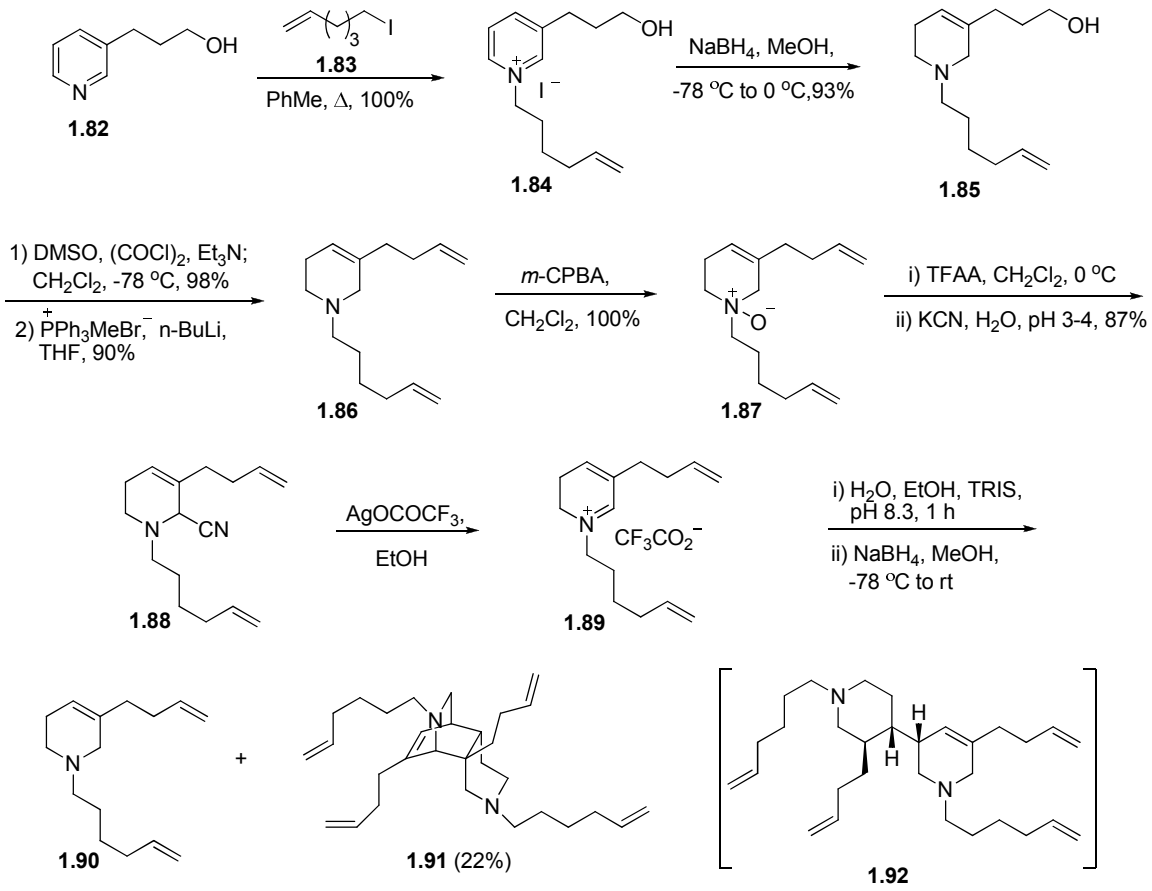
Baldwin's Biomimetic Studies

One area of interest to Baldwin and co-workers is applying their proposed biosynthesis to a biomimetic approach towards various 3-alkylpiperidines. Their initial work involved a model study on the proposed [4+2] cyclization to obtain the core of keramiphidin B (**1.36**).[41,42] They began the study by treating 3-methylpyridine with bromoethane in acetone, followed by sodium borohydride reduction, and oxidation with *m*-CPBA provided *N*-oxide **1.77** (Scheme 16). Reaction of **1.77** with trifluoroacetic anhydride gave dihyropyridinium salt **1.78**. Treatment of **1.78** with TRIS/HCl buffer (pH 8.3), followed by sodium borohydride reduction produced tetrahydropyridine **1.79**, as well as a minor amount of the desired tricycle **1.80** (10% yield from **1.78**). Oxidation with *m*-CPBA provided *N*-oxide **1.81**. (Scheme 16).[41,42]



Scheme 16. Baldwin's Biomimetic Model Study.

Baldwin's next report involved the installation of the necessary alkyl chains with terminal olefins to obtain a more functionalized core of keramaphidin B (**1.36**) which would allow for further progress toward keramaphidin.[41-43] Their synthesis started with reaction of 6-iodohex-1-ene with 3-pyridinepropanol (**1.82**) to give pyridinium salt **1.84** (Scheme 17). Sodium borohydride reduction followed by oxidation and subsequent Wittig olefination gave tetrahydropyridine **1.86**. Formation of the *N*-oxide using *m*-CPBA, followed by treatment with trifluoroacetic anhydride and *in situ* trapping of the iminium ion provided **1.88**.

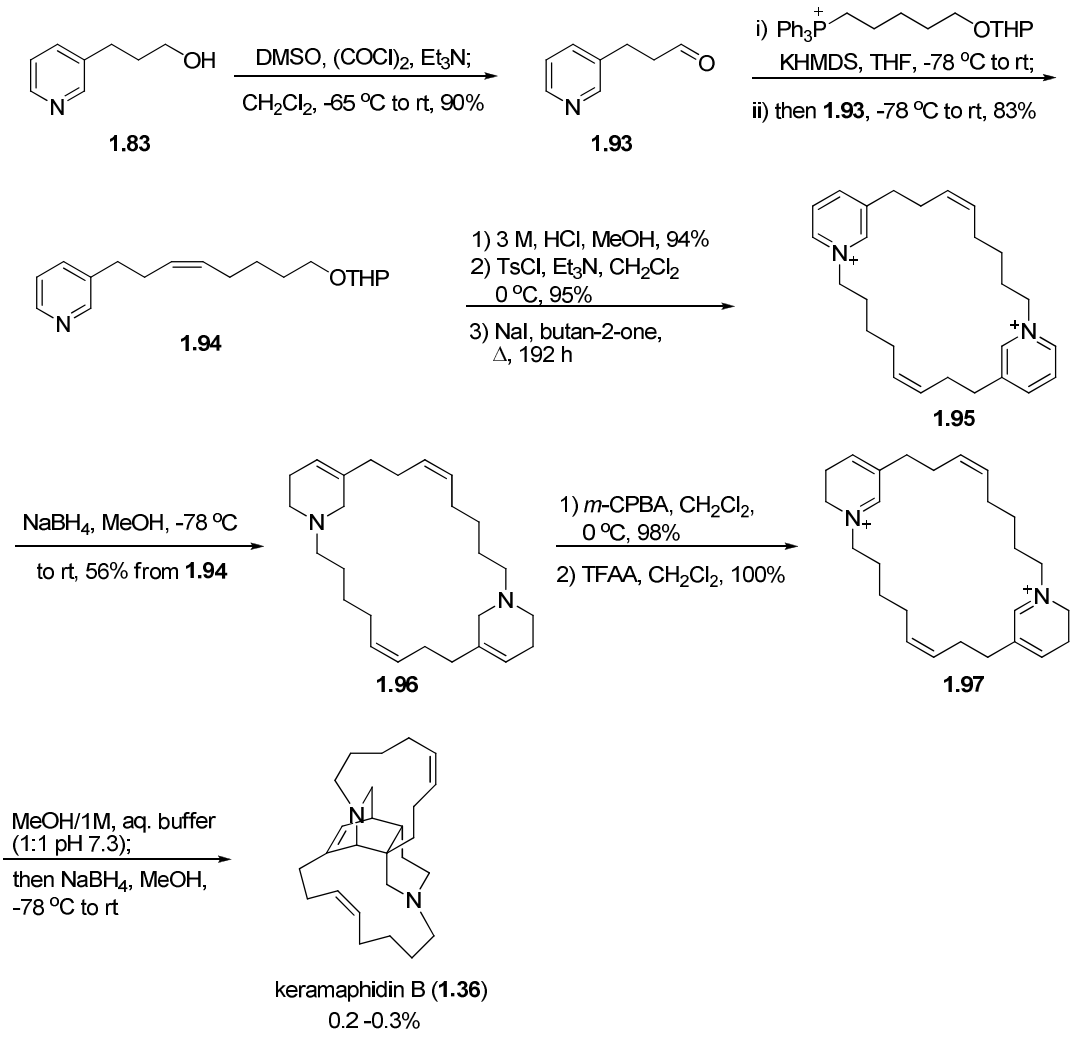


Scheme 17. Baldwin's Approach to the Tricyclic Core of Keramaphidin B (**1.36**).

Conversion of **1.88** to the dihydropyridinium salt **1.89** was accomplished by addition of $AgOCOCF_3$. The Diels-Alder cycloaddition of dihydropyridinium salt **1.89** was achieved by using a buffered (pH 8.3) solution of 1:1 ethanol/water at 23 °C for one hour. The crude product was then treated with sodium borohydride to afford tetrahydropyridine **1.90** as the major product and the desired tricycle **1.91** in 22% yield. In addition, when tricycle **1.91** was treated with sodium borohydride at 23 °C "small quantities" of a structure tentatively assigned (**1.92**) resembling the 3,4-linked bis-piperidine core common to of halicyclamine A (**1.68**) was formed (Scheme 17).[43,44]

Armed with the evidence that the [4+2] cycloaddition reaction was indeed feasible, Baldwin and co-workers continued their study toward a biomimetic synthesis of keramaphidin B (**1.36**).[44,45] One unanswered question that still remained was could the [4+2] cycloaddition be performed in a transannular fashion?[45] To investigate this problem Baldwin and co-workers first oxidized 3-pyridinepropanol (**1.83**) under Swern conditions to aldehyde **1.93**. Wittig olefination of **1.93** afforded 3-alkylpyridine **1.94** (Scheme 18). After removal of the THP protecting group, the Oxford group found dimerization was optimal using an iodide leaving group. Thus, the alcohol was converted to the iodide by treatment with triphenylphospine, iodine, and imidazaole. Unfortunately, they found that the yield was inconsistent (56-90%) and upon concentration the product underwent polymerization. Later it was determined conversion of the alcohol to the corresponding tosylate provided a product that underwent decomposition after extended storage. The iodide could now be generated in situ by utilizing a Finkelstein/dimerization/macrocyclization reaction by slow addition of the derived

tosylate to a refluxing solution of sodium iodide in butan-2-one to yield *bis*-pyridinium macrocycle **1.95**.

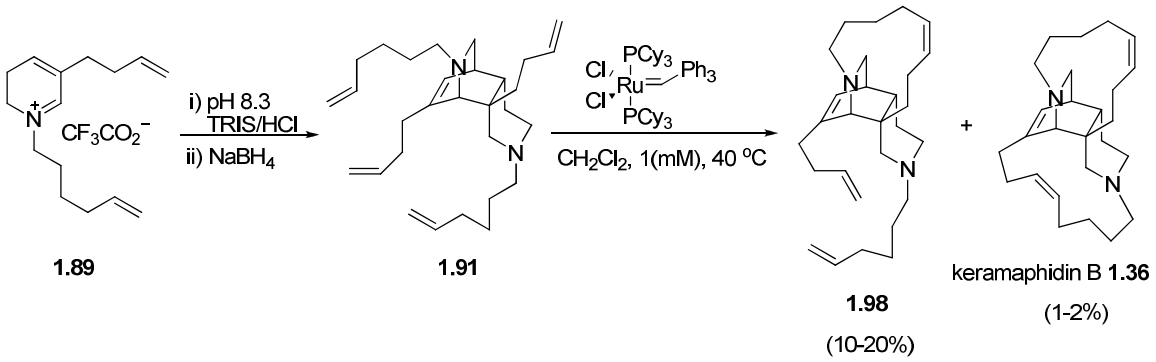


Scheme 18. Biomimetic Synthesis of Keramaphidin B (**1.36**).

Sodium borohydride reduction of *bis*-pyridinium salt **1.95** provided *bis*-tetrahydropyridine **1.96**. Treatment of **1.96** with two equivalents of *m*-CPBA followed by trifluoroacetic anhydride afforded the hypothetical manzamine biosynthetic precursor

1.97. Extensive studies on the transannular Diels-Alder reaction of **1.97** to form keramaphidin B (**1.36**) were then conducted. Baldwin found that using a 1 M aqueous solution of 1:1 TRIS/HCl (pH 7.3) and methanol, followed by reduction with sodium borohydride provide a *very* minor amount of keramaphidin B (**1.36**) that was detected after tedious HPLC purification. The major product of the attempted [4+2] cycloaddition was reduced bis-tetrahydropyridine **1.96** (Scheme 18).[45]

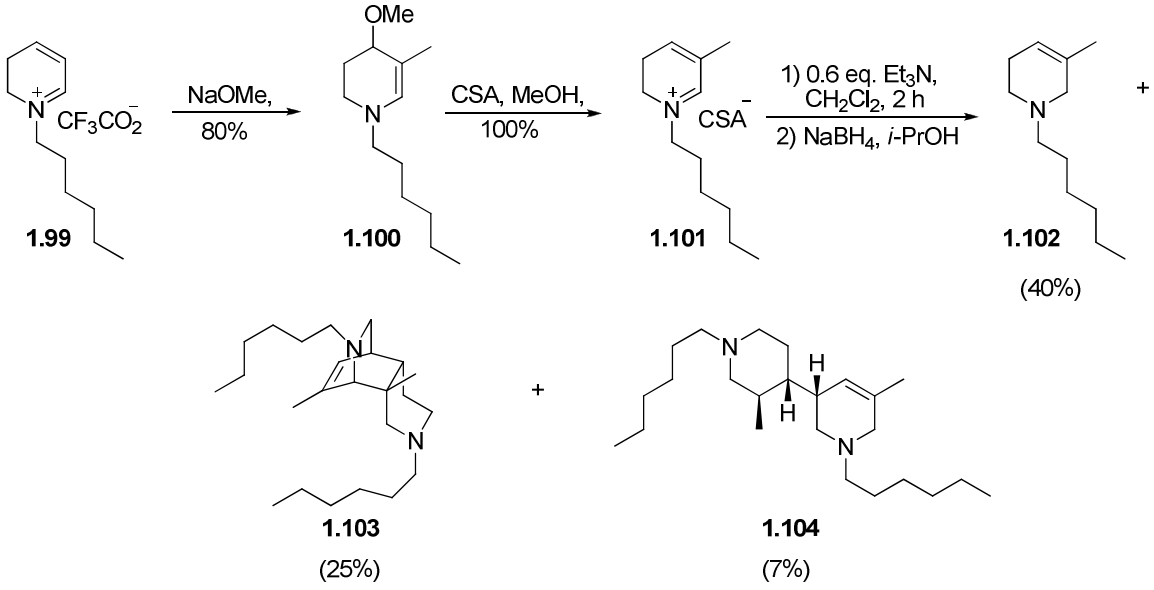
Due to the biomimetic synthesis of keramaphidin B (**1.36**) resulting in such a low yield, Baldwin and co-workers turned their attention to a semi-biomimetic approach.[45] Having optimized the biomimetic synthesis of the keramaphidin core (**1.91**) to 22% overall yield, they investigated a ring closing metathesis using both the Schrock molybdenum catalyst and Grubbs first generation ruthenium catalyst. The Grubbs catalyst was found to give the best result providing mono-cyclized product **1.98** and keramaphidin B (**1.36**) in 1-2% yield (Scheme 19).[45]



Scheme 19. Semi-biomimetic Synthesis of Keramaphidin B (**1.36**).

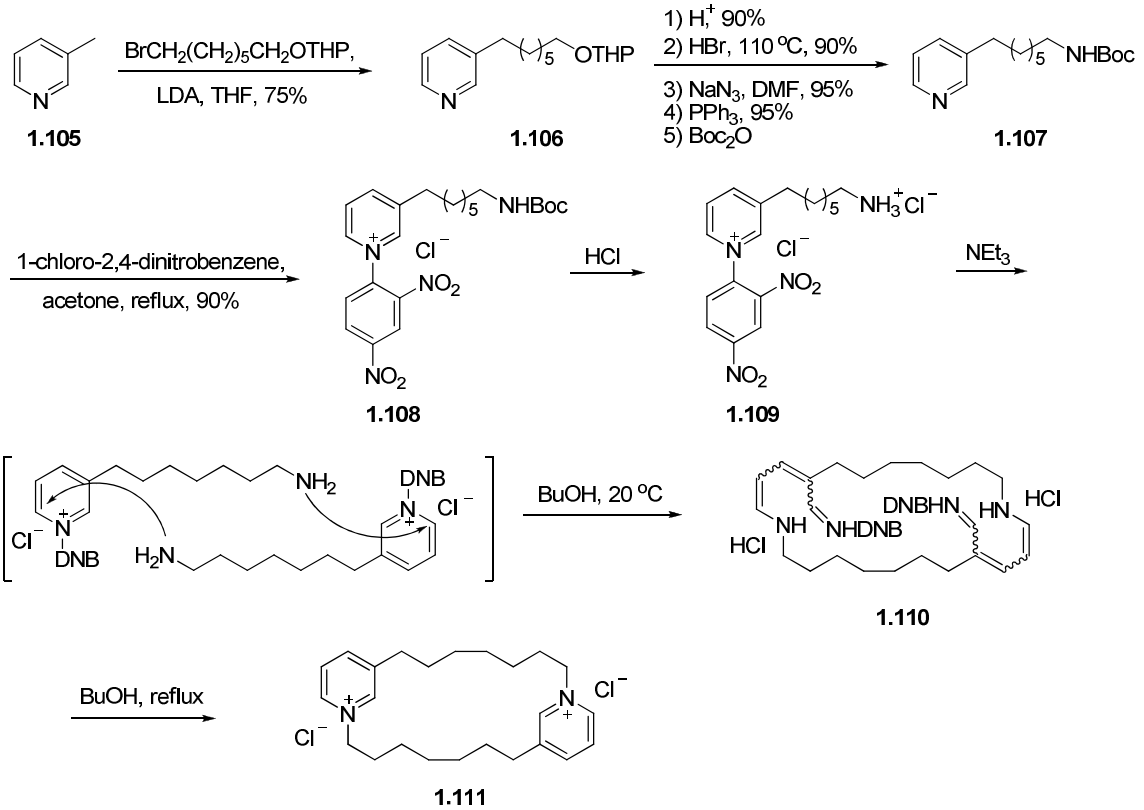
Marazano's Biomimetic Studies

The initial biomimetic experiments carried out by Marazano and co-workers are quite similar to the Baldwin approach.[46,47] Marazano's synthesis begins by treating dihydropyridinium salt **1.99** with NaOMe to afford tetrahydropyridine **1.100** (Scheme 20). Reaction with camphorsulfonic acid provided dihydropyridinium salt **1.101**. Treatment of salt **1.101** with 0.6 equivalents of triethylamine in dichloromethane, followed by sodium borohydride reduction in isopropanol gave **1.102** in 40% yield, along with the tricycle core of keramaphindin (**1.103**) and the halicyclamine-type compound (**1.104**) in 25% and 7% yields, respectively.[46,47]



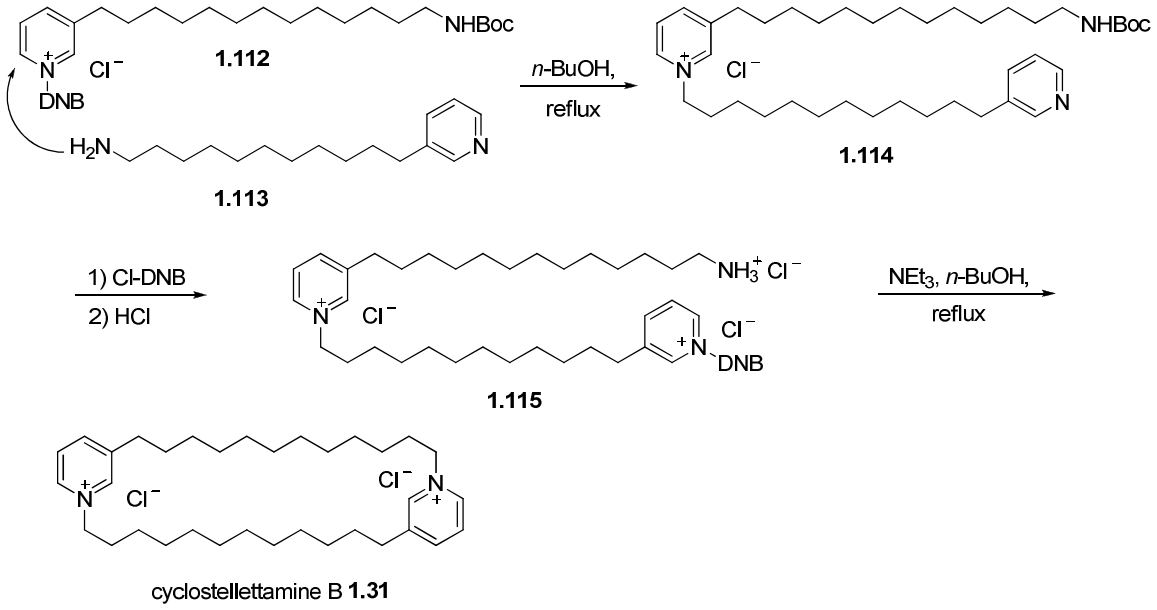
Scheme 20. Marazano's Approach to the Tricyclic Core of Keramaphidin B (**1.36**).

Marazano's next approach focused on a semi-biomimetic entry to the bis-dihydropyridine precursor.[10] The synthesis began with lithiation of 3-picoline (**1.105**), followed by quenching with the alkyl bromide to yield pyridine **1.106** (Scheme 21). Removal of the protecting group followed by reactions with hydrobromic acid and sodium azide provided an intermediate azide, which was treated with triphenylphosphine to produce amine **1.107**. After Boc protection of the amine (**1.108**), the pyridine moiety was reacted with 1-chloro-2,4-dinitrobenzene to afford salt **1.109** in quantitative yield. The Boc protecting group was then removed with HCl and treatment with triethylamine was presumed to provide dimeric species **1.110** Refluxing salt **1.110** resulted in the formation of the symmetric bis-pyridinium dimer **1.111** in 43% yield (Scheme 21).[10]



Scheme 21. Marazano's Synthesis of the Bis-pyridinium Intermediate.

With a biomimetic approach to the key bis-pyridinium intermediate complete, Marazano was able to apply this chemistry to a synthesis of cyclostellettamine B (**1.31**) (Scheme 22).[10] They extended the alkyl chains by altering the reactions above with 3-picoline (**1.105**) to obtain a protected (**1.112**) and unprotected amine (**1.113**). Exposure of a mixture of **1.112** and **1.113** to refluxing *n*-BuOH afforded (**1.114**). Treatment of **1.114** and 1-chloro-2,4-dinitrobenzene with HCl afforded salt **1.115**. They subjected salt **1.115** to triethylamine in refluxing *n*-BuOH to provide cyclostellattamine B (**1.31**) in 20-25% overall yield from 3-picoline (**1.105**) (Scheme 22).[10] Marazano was also able to arrive at haliclamine A (**1.28**) in a similar fashion.[48]



Scheme 22. Marazano's Synthesis of Cyclostellettamine B (**1.31**).

CHAPTER II

SYNTHETIC APPROACHES AND TOTAL SYNTHESES OF 3-ALKYLPIPERIDINE ALKALOIDS

Introduction

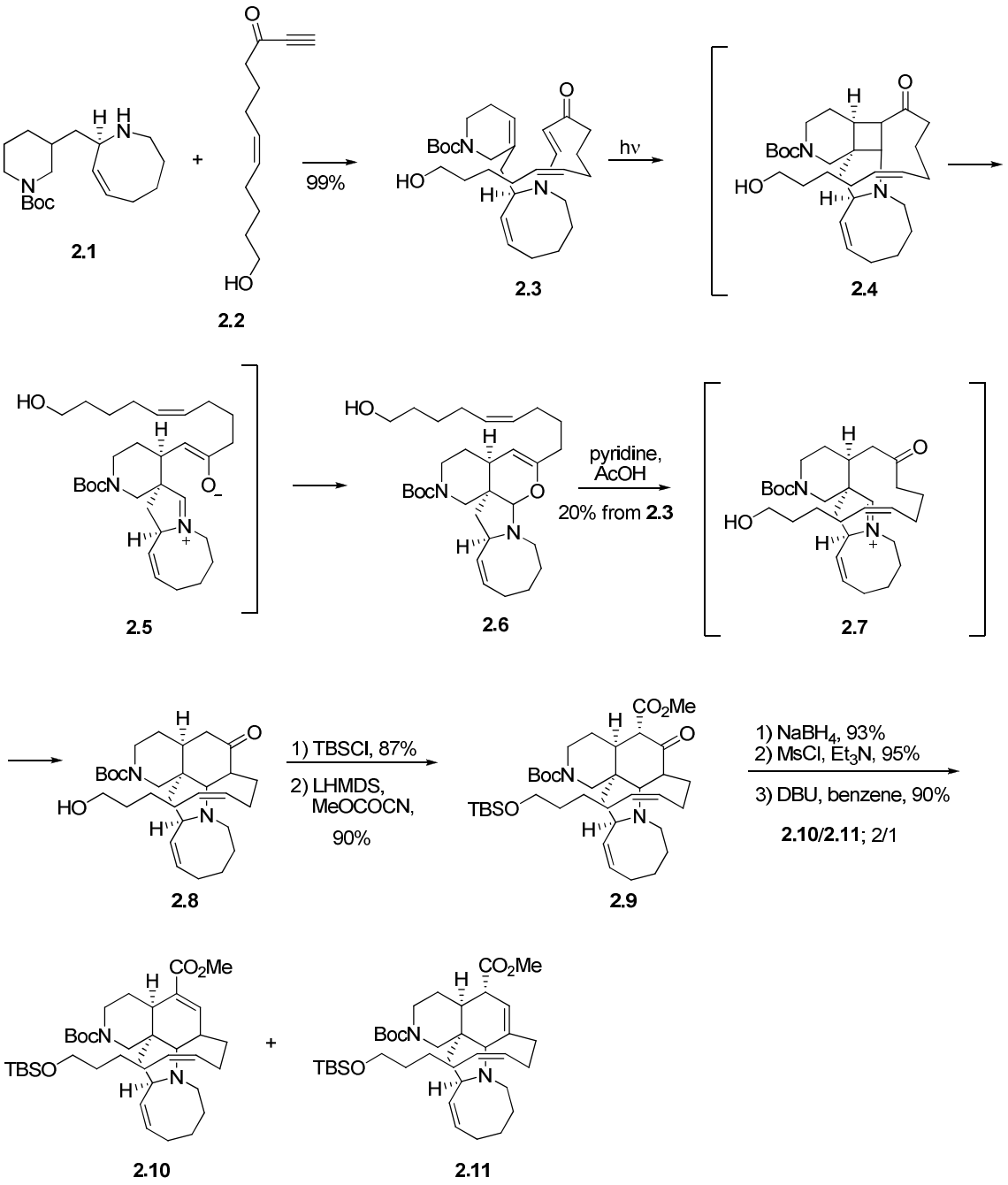
The number of natural products isolated containing 3-alkylpiperidines continues to grow. The unique structures of these alkaloids along with the biological activity have stimulated a considerable amount of interest in the total synthesis of many of these compounds. A number of elegant synthetic approaches have been developed by multiple investigators in order to develop new synthetic strategies and gain entry into this class of alkaloids. Target structures have ranged from some of the simpler tricyclic bis-pyridine macrocycles to more complex structures such as the sarains and madangamines, culminating in a number of impressive synthetic routes. This section will attempt to highlight some of the synthetic strategies toward the more complex 3-alkylpiperidines, beginning with the manzamine alkaloid, manzamine A (**1.3**).

Synthetic Approaches Toward Manzamine A

Winkler Total Synthesis of Manzamine A (**1.3**)

The total synthesis of manzamine A (**1.3**), along with ircinol A (**1.19**) and ircinal A (**1.17**), was accomplished by Winkler and co-workers in 1998.[49,50] Their synthesis

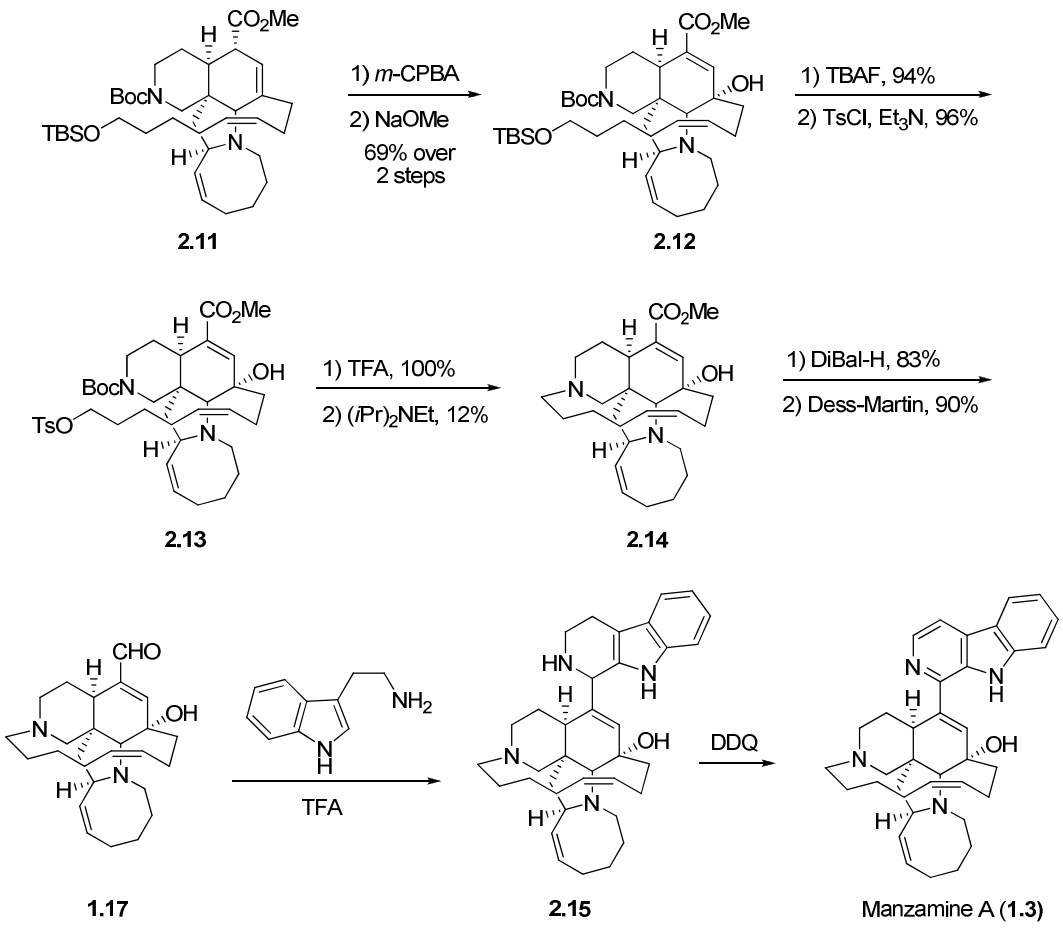
involves a Pictet-Spengler reaction to convert ircinal A (**1.17**) to manzamine A (**1.3**). The synthesis of ircinal A (**1.17**) is described below.



Scheme 23. Winkler's Approach to Manzamine A (**1.3**).

The key reaction leading to the framework of the manzamine alkaloids was a tandem [2+2] photocycloaddition, retro Mannich, followed by a Mannich cyclization (Scheme 23). The key photochemical substrate is prepared starting with Michael addition of amine **2.1** to alkynone **2.2** (Scheme 23) .[49,50] The [2+2] cycloadduct was not isolated but underwent a retro Mannich reaction and cyclization to provide aminal **2.6**. Enol ether **2.6** was isomerized to tetracycle **2.8** by treatment of aminal **2.6** with pyridinium acetate providing a 20% overall yield of **2.6** from **2.3**. The primary alcohol was then protected as a TBS ether, followed by formation of β-keto ester **2.9** using Mander's reagent. Ketone reduction followed by dehydration afforded a mixture of unsaturated esters **2.10** and **2.11**.[49,50] Completion of tetracycle **2.11** (Scheme 23) set the stage for completion of ircinol A (**1.19**) and ircinal A (**1.17**), with only macrocyclization through N-alkylation remaining to afford the complex pentacyclic motif of manzamine natural products.

Macrocyclization of **2.11** required selective alkene epoxidation (*m*-CPBA) followed by based promoted (NaOMe) isomerization to allylic alcohol **2.12**.[50] The assigned stereochemistry of the newly formed secondary hydroxyl group was supported by hydrogen bonding observed between the hydroxyl hydrogen of **2.12** and the azocine nitrogen by ^{1}H-NMR. The silicon protecting group was removed by treatment with TBAF, and the corresponding alcohol was converted to the tosylate by reaction with tosyl chloride and triethylamine.[50]



Scheme 24. Completion of Manzamine A (**1.3**) by Winkler.

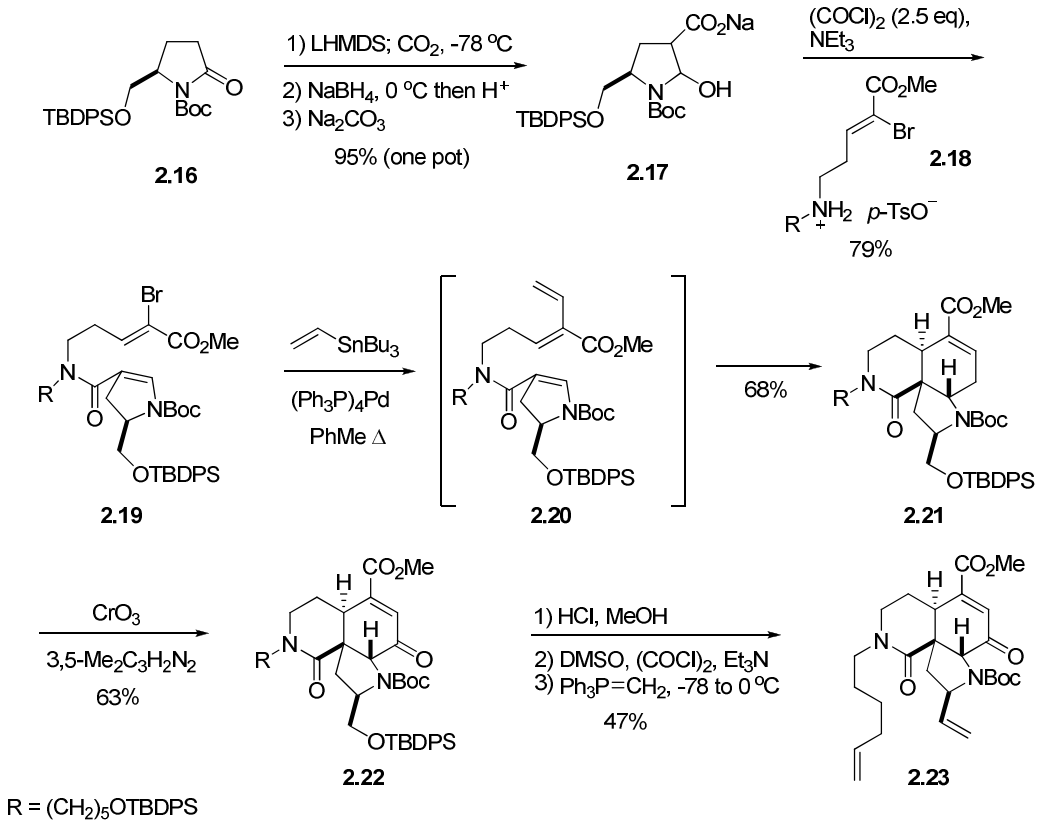
Deprotection of carbamate **2.13** was accomplished using trifluoroacetic acid. Exposure of the derived secondary amine to Hunig's base under high dilution conditions led to the formation of the 13-membered macrocycle in a modest 12% yield (Scheme 24).[50] The yield was later improved by using an alkyne in place of the isolated *cis*-alkene. Lindlar semi-hydrogenation then afforded **2.14**.[50] Reaction of enolate **2.14** with DIBAL-H completed ircinol A (**1.19**) and oxidation of **1.19** produced ircinal A (**1.17**). Finally, manzamine A (**1.3**) was obtained by reaction of ircinal (**1.17**) and tryptamine,

followed by oxidation with DDQ (Scheme 24).[8] This completed the first total synthesis of manzamine in 33 overall steps (31 steps longest linear sequence).[50]

Martin Total Synthesis of Manzamine A (**1.3**)

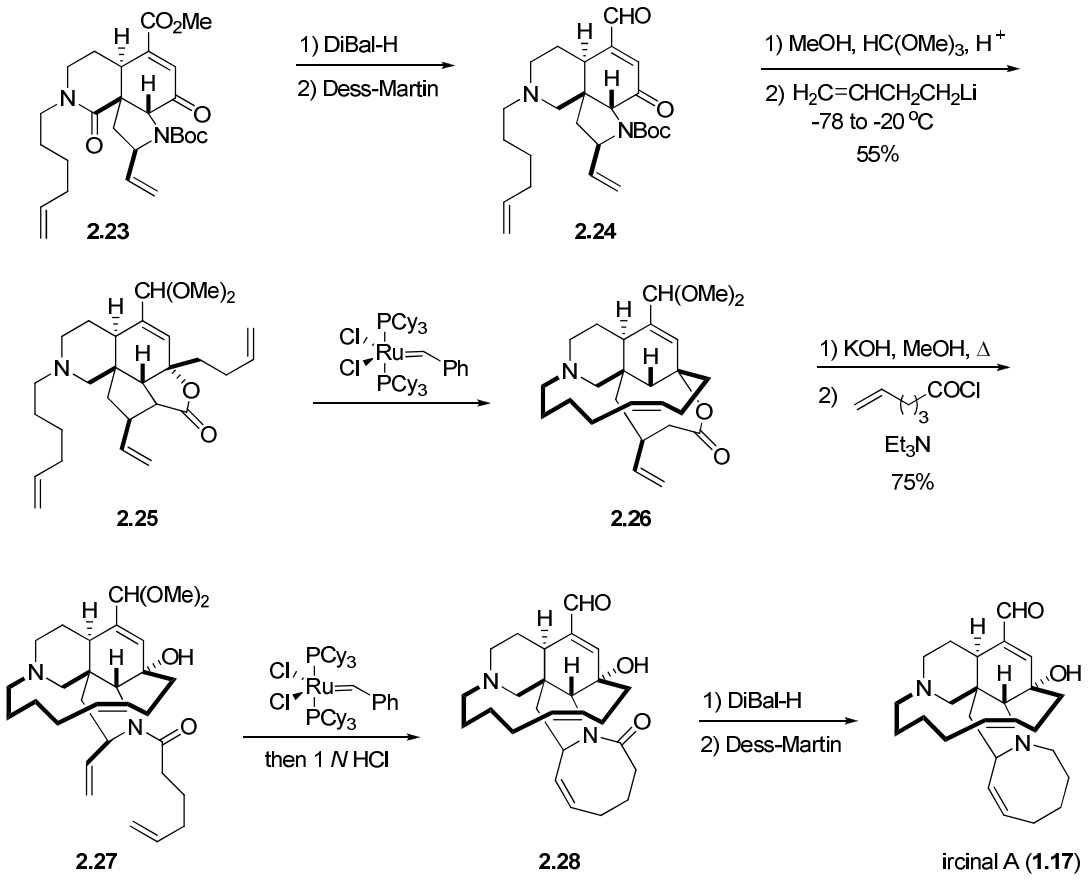
In 1999 Martin and co-workers completed the total synthesis of manzamine A (**1.3**).[51,52] Their route also utilizes a Pictet-Spengler cyclization to convert ircinal A (**1.17**) to manzamine A (**1.3**). One of the major differences between the Winkler and Martin routes is Martin's use of the ring closing metathesis reaction in two key ring forming reactions. First, he employs the RCM reaction to close the 13-membered macrocycle, and later the 8-membered ring. The Martin group also makes use of a Diels-Alder cyclization to form the tricyclic core of manzamine A (**1.3**).

The Martin synthesis begins with a "one pot" conversion of imide **2.16** to "dieneophilic precursor" **2.17** by carboxylation and reduction (Scheme 25). [51,52] Reaction of **2.17** with oxalyl chloride followed by addition of ammonium tosylate **2.18** produced amide **2.19**. The tricycle (**2.21**) was then generated by a sequential Stille cross-coupling and spontaneous Diels-Alder reaction to give **2.21** in 68% yield. The stereocenter in **2.19** nicely defines the absolute and relative stereochemistry in the tricyclic unit of ircinal A (**1.17**). Oxidation of the allylic methylene group was achieved by treatment with CrO_3 and 3,5-dimethylpyrazole to produce tricyclic subunit **2.22** in good yield. Removal of the silyl protecting groups was accomplished by reaction with hydrochloric acid in methanol. The resulting diol was oxidized to the dialdehyde under Swern conditions, and then converted to the bis alkene by a double Wittig reaction.[51,52]



Scheme 25. Martin's Approach to Manzamine A (**1.3**).

With the tricyclic core complete, reduction of the ester and ketone carbonyls was accomplished with excess DIBAL-H and the resulting allylic alcohols were oxidized with Dess-Martin Periodinane to provide keto-aldehyde **2.24**. Protection of aldehyde **2.24** as a dimethyl acetal, followed by a 1,2-addition of 4-butenyllithium provided the ring closing metathesis substrate **2.25**. Treatment of **2.25** with Grubbs' first generation catalyst furnished **2.26** as a 8:1 (*Z*:*E*) mixture of geometrical isomers in 67% yield.[51,52] Notably, the tertiary amine did not require protonation prior to exposure to the ruthenium catalyst. Hydrolytic cleavage and *N*-acylation provided diene **2.27** which was characterized by X-ray crystallography.[51,52]



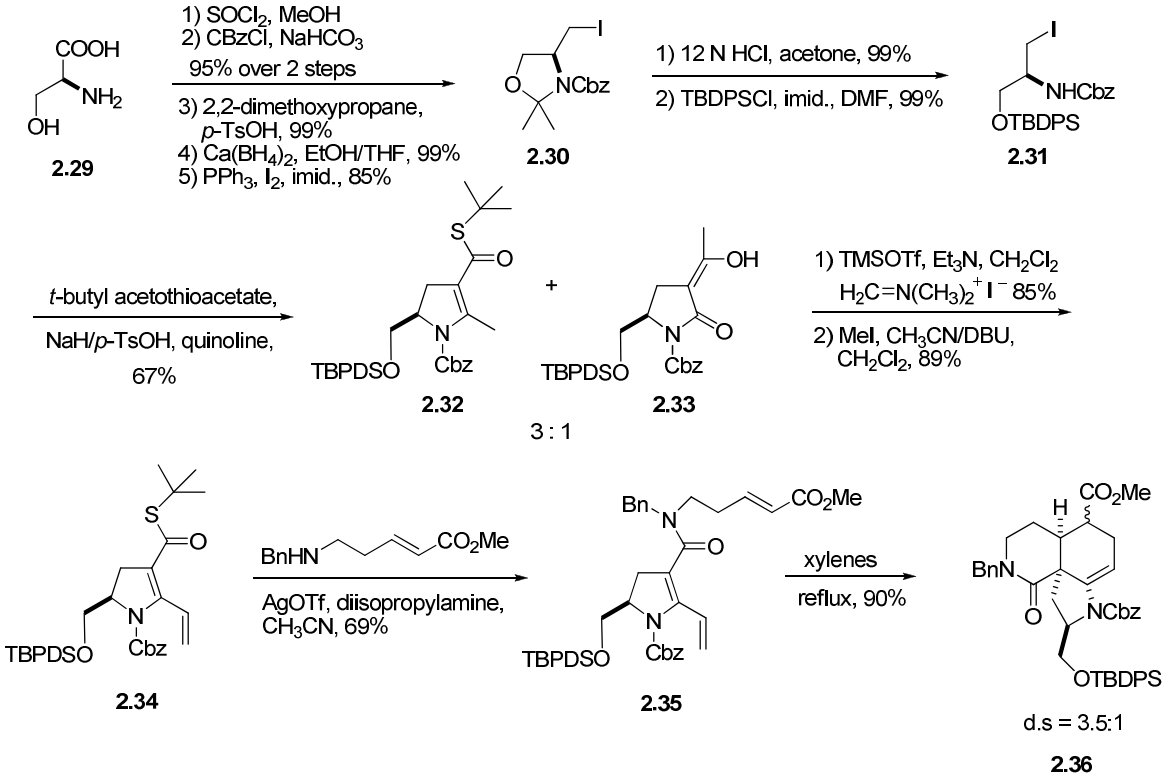
Scheme 26. Martin Total Synthesis of Manzamine A (**1.3**).

Although the ring closing metathesis of the 13-membered ring proceeded in good yield and stereoselectivity, the 8-membered ring proved difficult.[51,52] Difficulty in the latter closure might be due to either the allylic nature of the olefin, or conformational restraint within the molecule. Nonetheless, the closure was accomplished in 26% yield "under the best conditions." Reduction of **2.28** with DIBAL-H yielded ircinol A (**1.19**) and oxidation with Dess-Martin Periodinane provided ircinal A (**1.17**). Ircinal A (**1.17**) was then converted to manzamine A using Kobayashi's protocol.[8,51,52]

Pandit's Approach to Manzamine A (**1.3**)

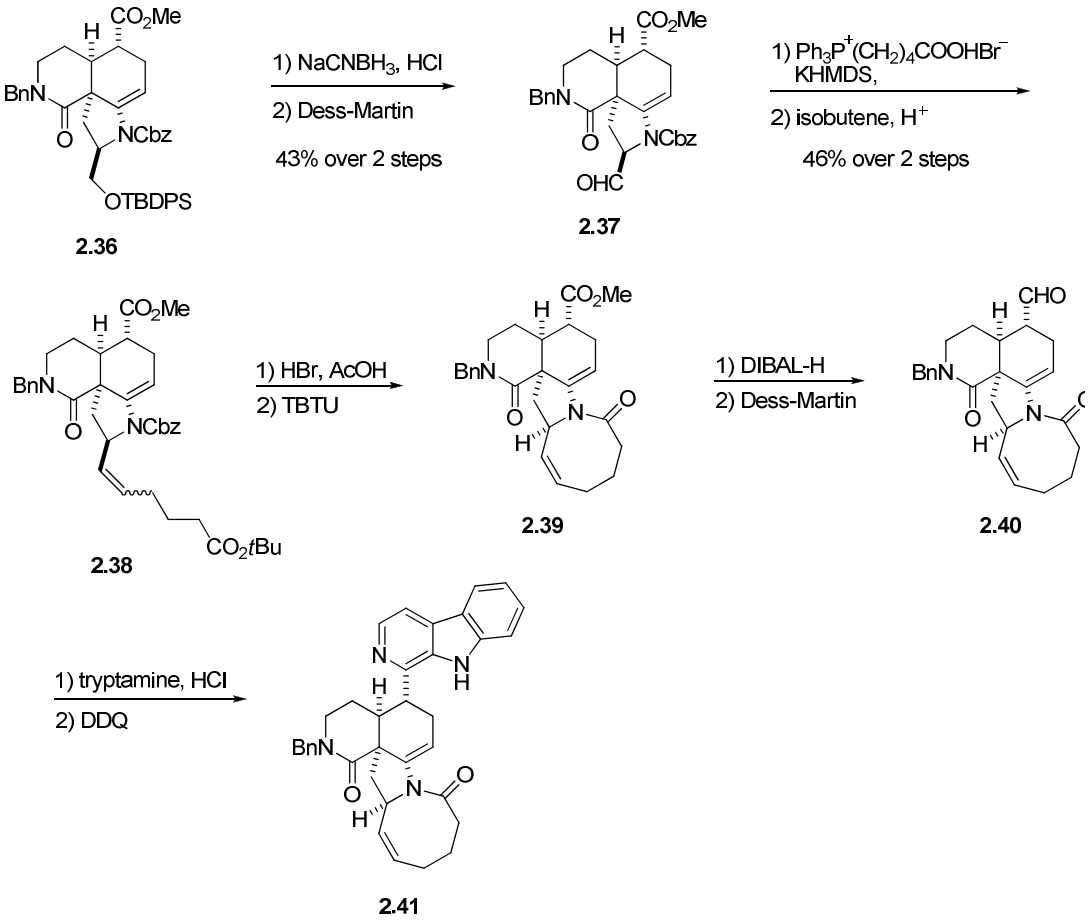
Pandit and co-workers published a series papers detailing the formation of the tricyclic core of manzamine A starting from inexpensive L-serine.[53-58] By utilizing an intramolecular Diels-Alder strategy they were able to not only form the tricycle, but set three chiral centers in a single step (Scheme 27).[6] They constructed the unsaturated 13-membered ring using a ring closing metathesis reaction.[9-11] They were also able to install the 8-membered ring by a lactamization and introduced the β-carboline unit using the Pictet-Spengler reaction similar to the Winkler and Martin approaches.[7,8]

The Pandit synthesis began with L-Serine (**2.29**), which was transformed to iodide **2.30** in five steps. Conversion to **2.31** was achieved by protecting group manipulation and treatment with *t*-butyl acetothioacetate and sodium hydride followed by dehydration to provide thioester **2.32** and the 1,3-diketone (**2.33**) in a 3:1 ratio. Installation of the diene moiety for the cycloaddition was accomplished by conversion of **2.32** to an O-silyketene acetal which upon reaction with Eschenmoser salt yielded an intermediate terminal amine. Formation of the quaternary ammonium salt and subsequent treatment with DBU completed diene **2.34**. The cyclization precursor was attained in 69% yield by reaction of the benzyl protected secondary amine and thioester **2.34** in the presence of silver triflate. Enantiopure diene **2.35** was then heated at reflux in xylenes to provide the desired tricycle **2.36** in 90% combined yield as a 3.5:1 ratio of diastereomers[6-8] (Scheme 27).



Scheme 27. Pandit's Assembly of the Tricyclic Core.

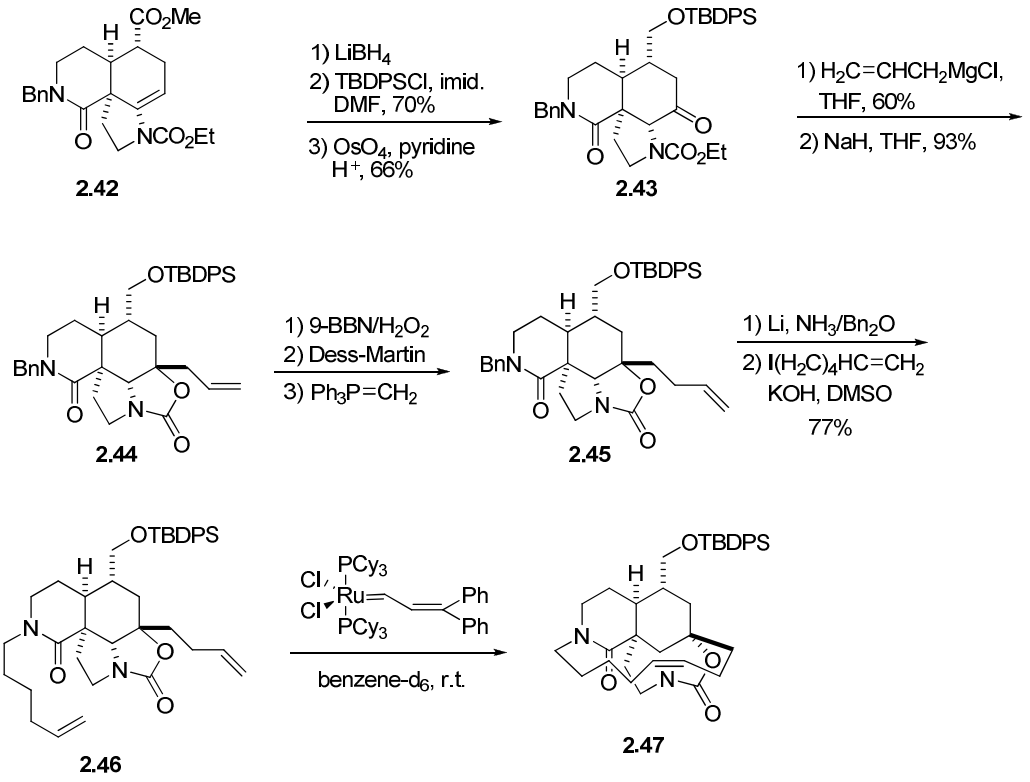
Tricycle **2.36** was further manipulated to install the 8-membered ring common to the manzamine alkaloids (Scheme 28). Thus, conversion of tricycle **2.36** to aldehyde **2.37** set the stage for olefination using a Wittig to arrive at alkene ester **2.38**. With the ester in hand, the t-butyl group was removed under acidic conditions to an amino-acid that was cyclized to azocine **2.39**. Reduction of the ester moiety with diisobutylaluminum hydride and oxidation to the aldehyde prepared the Pictet-Spengler precursor **2.40**. Pictet-Spengler reaction with tryptamine and aldehyde **2.40** followed by aromatization provided **2.41** with the 8-membered ring and β-carboline moieties in place (Scheme 28).[9]



Scheme 28. Pandit's Synthesis of an Advanced Manzamine A Intermediate.

Pandit and co-workers were the first to accomplish the synthesis of the difficult 13-membered ring employing a ring closing metathesis in a manner similar to the Martin approach. Ene carbamate **2.42**, lacking the protected hydroxylmethyl group (compound **2.36**), was treated with osmium tetroxide followed by acid catalyzed dehydration to afford ketone **2.43**. One of the terminal olefins required for the ring closing metathesis reaction was installed utilizing an allyl Grignard addition. Hydroboration of the resulting terminal olefin followed by Dess-Martin oxidation and subsequent Wittig reaction with methylenetriphenylphosphorane afforded the newly formed terminal olefin **2.45**.

Removal of the benzyl protecting group and alkylation with 1-iodo-5-hexene delivered the ring closing metathesis precursor **2.46**. In the presence of the ruthenium catalyst afforded the desired 13-membered macrocycle as a single isomer in 30% yield (Scheme 29).[9,10]

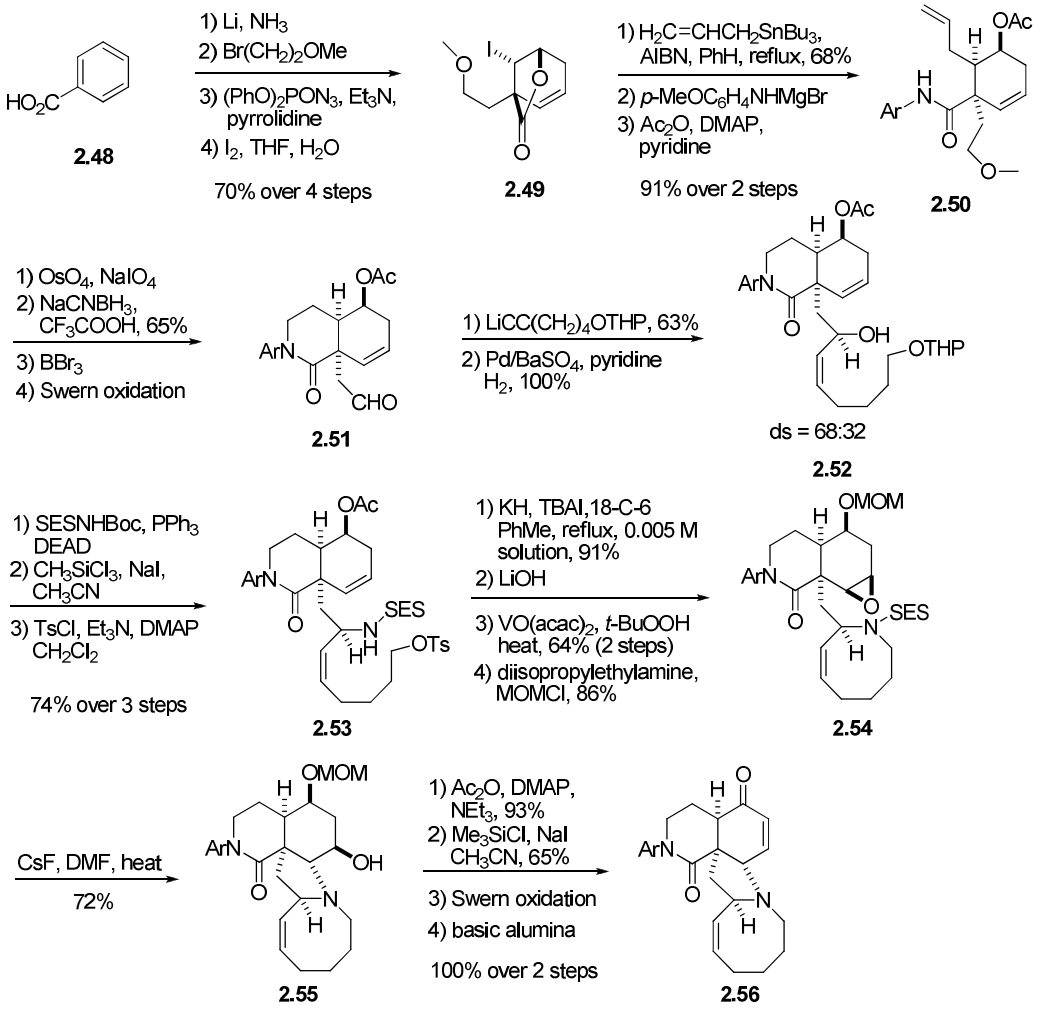


Scheme 29. Pandit's Approach to the 13-membered Marcocycle of Manzamine A (**1.3**).

Hart's Approach to Manzamine A (**1.3**)

A racemic route to manzamine A (**1.3**) developed by Hart and co-workers utilizes an *N*-alkylation to form the 8-membered ring, followed by an amine opening of an epoxide (Scheme 30).[59,60] Starting with benzoic acid the Hart group produced

iodolactone **2.49** in 70% yield over 4 steps. Radical mediated allylation with allyltributylstannane followed by ring opening of the lactone with an arylamine installed the requisite nitrogen (**2.50**).



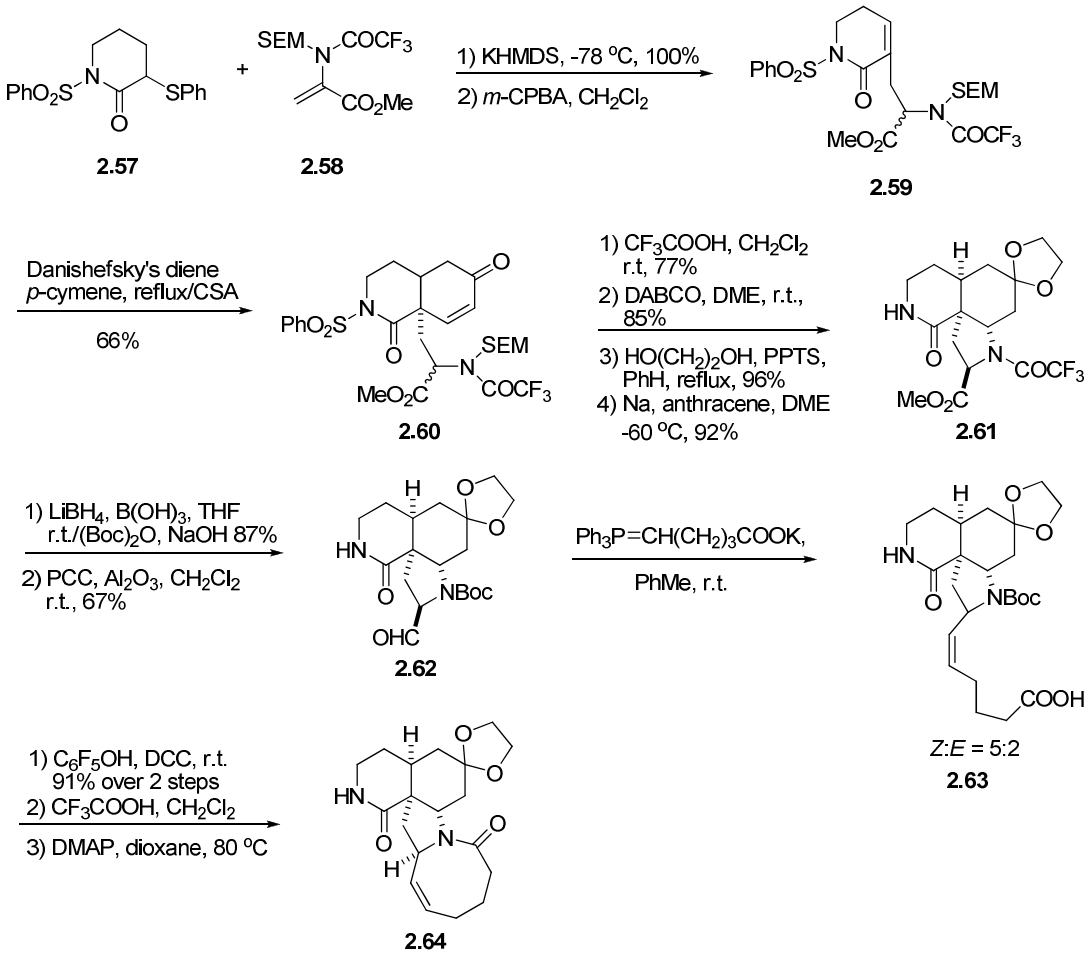
Scheme 30. Hart's Approach to Manzamine A (**1.3**).

Oxidative cleavage of the terminal olefin and intramolecular reductive amination afforded **2.51**. Addition of the lithium acetylide followed by Lindlar reduction resulted in a separable mixture of diastereomeric alcohols (**2.52**). Conversion of **2.52** to **2.53**

proceeded with retention of configuration via a double inversion process involving neighboring group participation. The 8-membered azocine ring was produced by treatment of **2.53** with potassium hydride under high dilution conditions. Reaction with lithium hydroxide resulted in deacetylation and facial selective epoxidation of the homoallylic alcohol using $VO(acac)_2$/*t*-BuOOH provided **2.54**. Deprotection of the sulfonamide with cesium fluoride promoted amine opening of the epoxide to produce the tetracyclic core of manzamine A (**2.55**). Further manipulation yielded enone **2.56**.[59,60]

Nakagawa's Approach to Manzamine A (**1.3**)

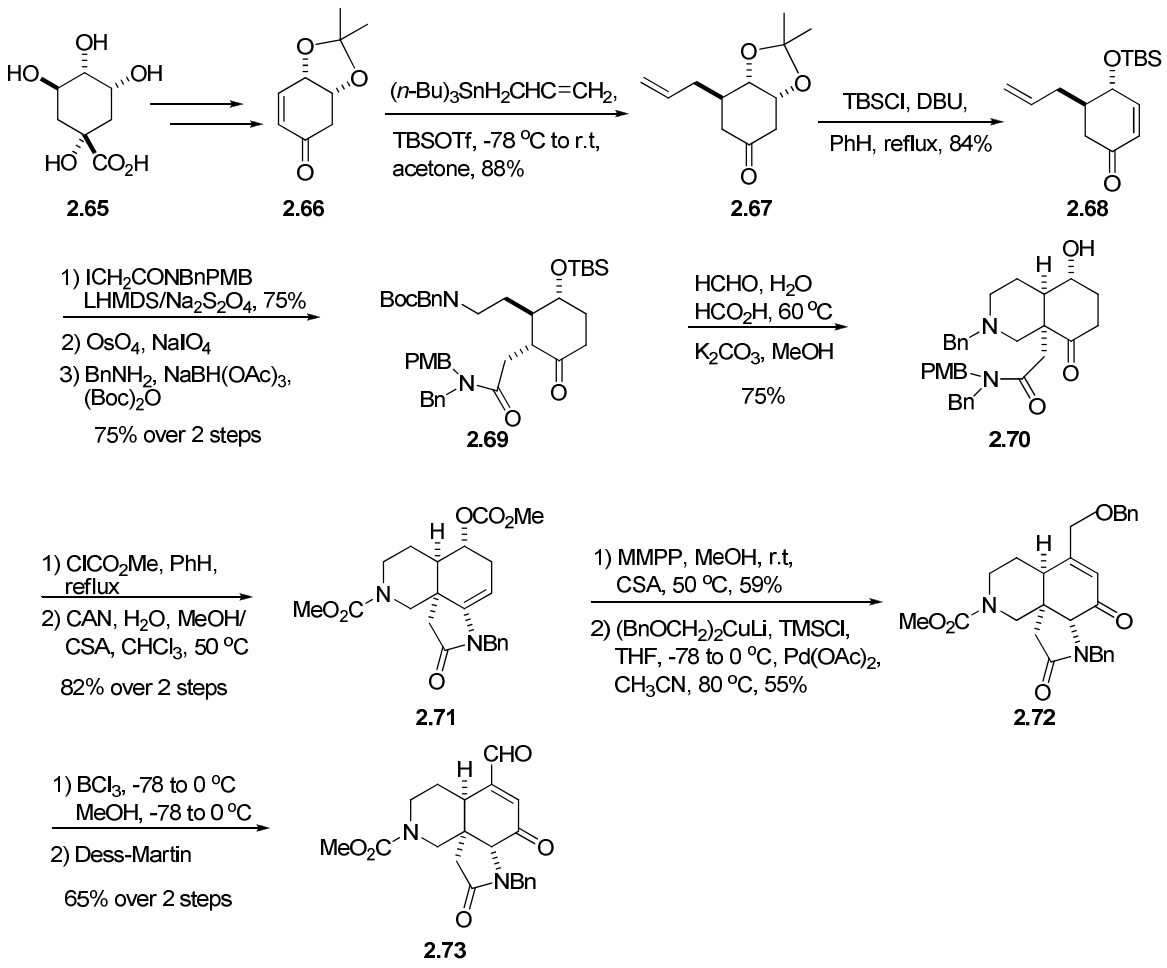
Nakagawa and co-workers reported the synthesis of the tetracyclic core of manzamine A in 1992. Their route to the tricyclic core involves an intermolecular Diels-Alder reaction between a racemic dihydropyridinone and Danishefsky's diene, followed by an intramolecular 1,4-addition of an amine to an α,β-unsaturated ketone (Scheme 31).[61-63] The tetracyclic ring system was completed by lactamization to afford azocine **2.64**.[64-66] Michael addition of the anion derived from **2.57** to amido acrylate **2.58** followed sulfoxide elimination provided dienophile **2.59**. Diels-Alder reaction of **2.59** with Danishefsky's diene to afforded the *cis*-fused isoquinoline **2.60** as a 1:1 mixture of diastereomers. Removal of the SEM group followed by exposure of the trifluoroacetamide to DABCO afforded tricycle **2.61**. Standard deprotections and functional group manipulations provided **2.63** as a 5:2 mixture of *Z* and *E* olefins. Trifluoroacetic acid removal of the carbamate provided the substrate needed for lactamization and azocine formation.



Scheme 31. Nakagawa's Route to the Tetracyclic Core of Manzamine A (**1.3**).

Overman's Synthesis of the Tricyclic Core

Starting with (-)-quinic acid Overman and co-workers examined an enantioselective approach toward manzamine A (**1.3**).[67] In four steps (-)-quinic acid was converted to enone **2.66** which was treated with an allylstannane in the presence of TBSOTf to stereoselectively deliver ketone **2.67**. Reaction with TBSCl and DBU resulted in formation of enone **2.68** (Scheme 32).



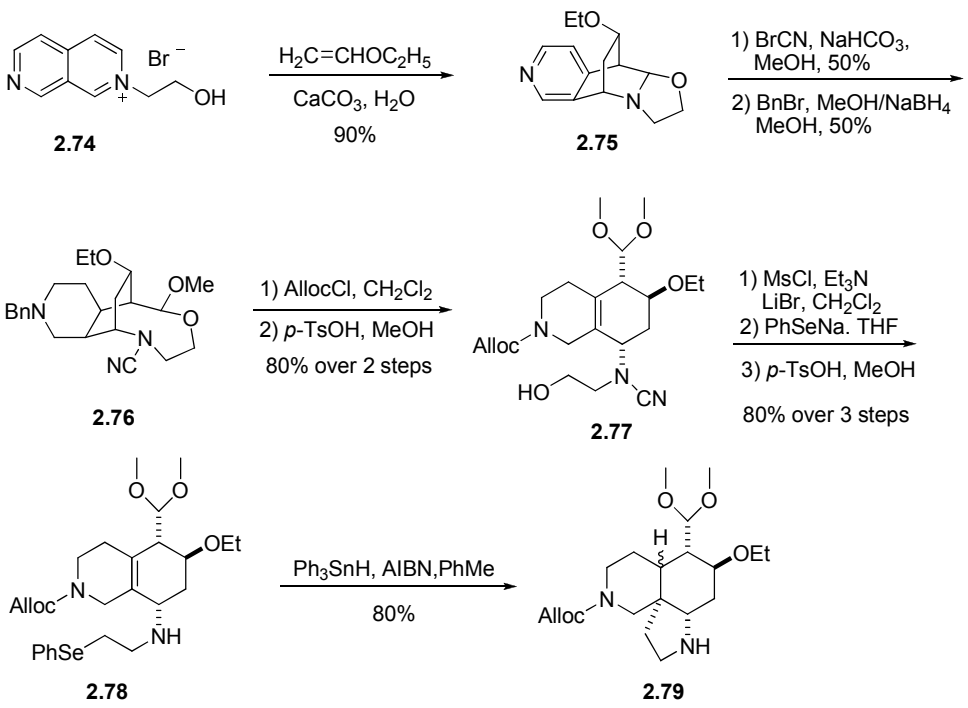
Scheme 32. Overman's Appraoch to the Tricyclic Core of Manzamine A(**1.3**).

The isoquinoline ring construction began with alkylation of enone **2.68** with an *N,N*-disubstituted iodoacteamide and subsequent reduction of the enone to give an α-substituted ketone. The protected amine was introduced by oxidative cleavage of the terminal olefin under Lemieux conditions, followed by reductive amination with benzylamine and *in situ* Boc-protection to afford **2.69**. A key Mannich cyclization was accomplished by reaction of **2.69** with aqueous formaldehyde in formic acid. Protection

group removal and dehydration using camphor sulfonic acid resulted in formation of tricycle **2.71**. Epoxidation and acid catalyzed rearrangement followed by β-elimination gave an enone that upon 1,4-addition with benzyloxymethyl homocuprate in the presence of TMSCl yielded enone **2.72**. Cleavage of the benzyl ether and subsequent Dess-Martin oxidation provided desired enal **2.73**.[67]

Langolis' Synthesis of the Tricyclic Core

The Langlois approach to manzamine A (**1.3**) involved a Bradsher intermolecular [4+2]-cycloaddition of a pyridinium salt with an ethyl vinyl ether and a radical cyclization to enable construction of the tricyclic core.[68-70] Thus, cycloaddition of quaternary salt **2.74** and ethyl vinyl ether in water led to compound **2.75** which underwent ring expansion with cyanogen bromide. Reduction of the pyridine moiety with sodium borohydride and *in situ* benzyl protection produced acetal **2.76**. Protecting group manipulation and methanolysis of the acetal furnished alcohol **2.77**. The alcohol was then converted to the mesylate and displacement with the sodium salt of phenyl selenide gave selenide **2.78**. Treatment of selenide **2.78** with triphenylstannane and AIBN produced the desired tricyclic core along with the undesired diastereomer in a 1:1 ratio (Scheme 33).[68-70]



Scheme 33. Langlois' Approach to the Tricyclic Core of Manzamine A(**1.3**).

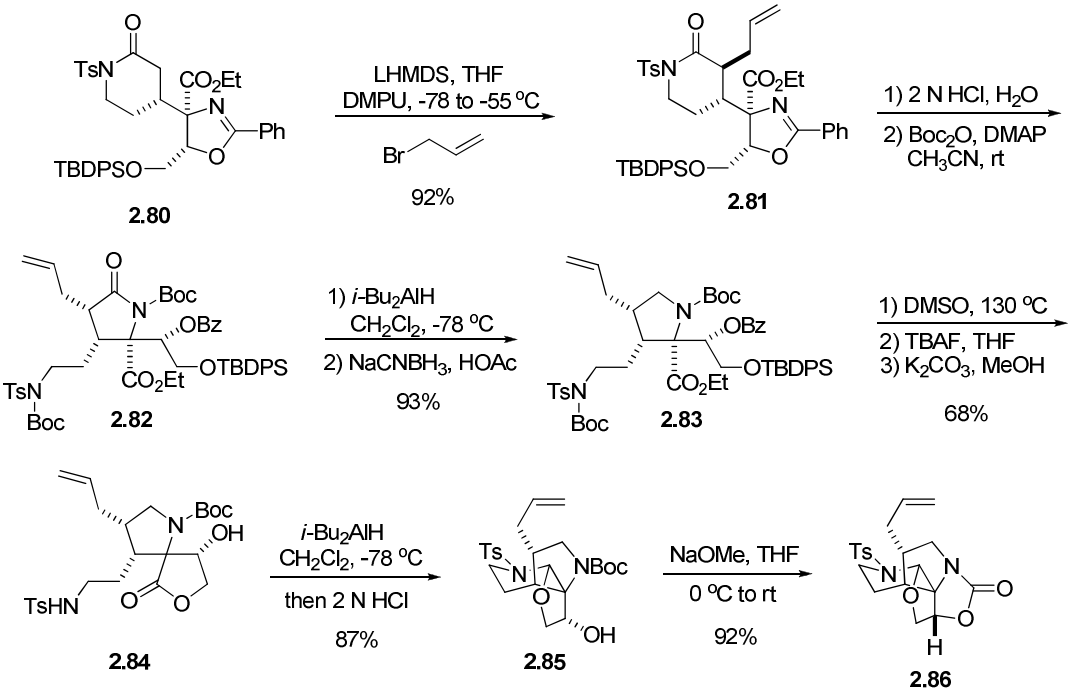
Among all 3-alkylpiperidine the synthesis of manzamines has undoubtedly been studied more than any other group of alkaloids isolated from this family of natural products. With the total synthesis of manzamine C by Hino[65,71] and Gerlach,[72] the approaches to manzamine A by Yamamura,[73-78] Clark,[79,80] Simpkins,[81,82] Leonard,[83,84] Markó,[85,86] as well as the total syntheses and approaches outlined above, the manzamines have clearly been the target of choice among the synthetic community. However, sarain A (**1.5**) is another structurally intriguing pentacyclic natural product presumably biosynthesized from 3-alkylpyridines that has also caught the attention of synthetic investigators. The major challenges associated with constructing sarain A (**1.5**) include stereocontrol of the seven stereogenic centers and formation of the tightly fused tricyclic core annulated to two large ring systems. The zwitterionic tertiary amine-aldehyde

interaction is another unique feature that must be taken into account. Despite these signifigant challenges a number of routes have been developed including the only total synthesis reported by Overman and co-workers.

Synthetic Approaches Toward Sarain A

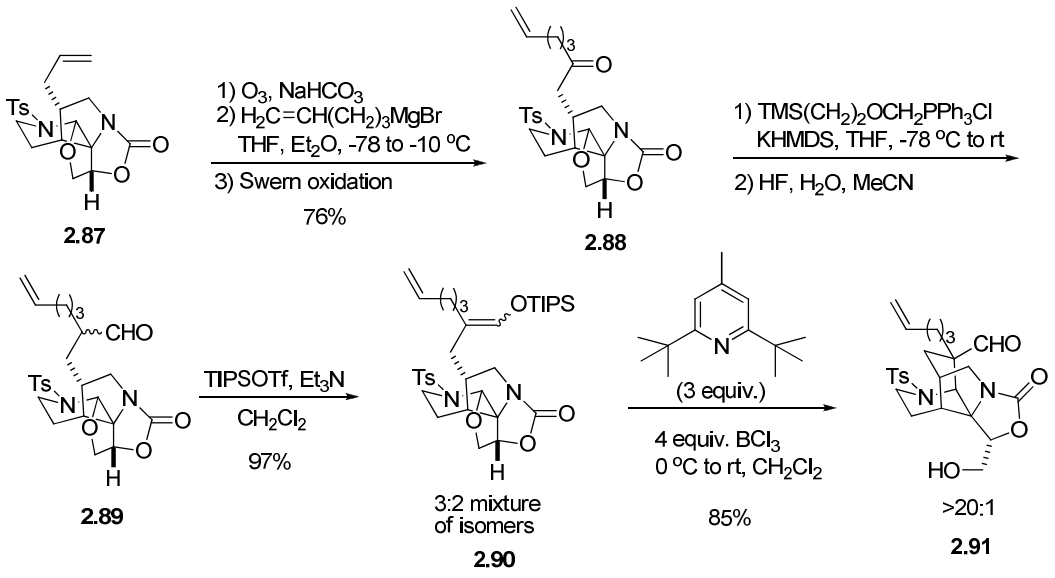
Overman Total Synthesis of Sarain A (**1.5**)

The Overman synthesis of sarain A (**1.5**) began with a seven step sequence from (-)-diethyl D-tartrate to provide lactam **2.80** (Scheme 34).[87-89] Alkylation of lactam **2.80** with allyl bromide provided **2.81** which on treatment with acid led to oxazoline ring cleavage, followed by translactamazation, and protection to provide pyrrolidinone **2.82**.



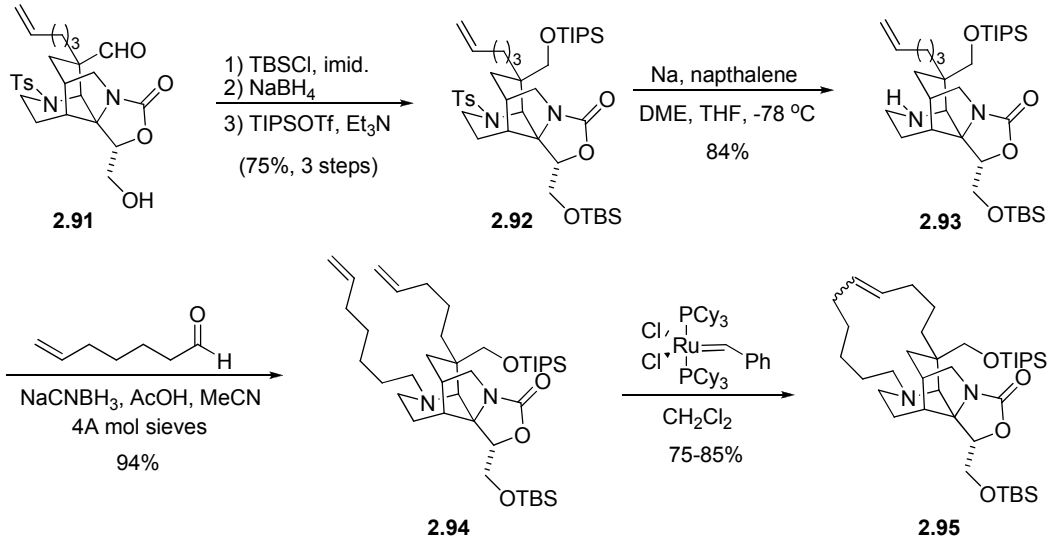
Scheme 34. Overman's Synthesis of Tetracycle **2.86**.

A two step reduction of the lactam afforded **2.83** and mono-Boc deprotection, desilyation, and spirolactone formation furnished intermediate **2.84**. Tetracycle **2.86** was acquired in two steps from **2.84** by DIBAL-H reduction of the lactone followed by reaction of β-amino alcohol **2.85** with sodium methoxide. An ozonolysis/Grignard addition/oxidation sequence delivered ketone **2.88** in a 76% yield. One carbon homologation of **2.88** by way of a Wittig reaction provided aldehyde **2.89** upon hydrolysis. Aldehyde **2.89** was converted to TIPS enol ether **2.90** as an inconsequential 3:2 mixture of stereoisomers. It was found that treatment of **2.90** with BCl_3 at 0 °C and slowly warming to room temperature led to aldehyde **2.91** in 20:1 diastereoselectivity (Scheme 35).[87-89]



Scheme 35. Overman's Enoxysilane-*N*-Sulfonyliminium Ion Cyclization.

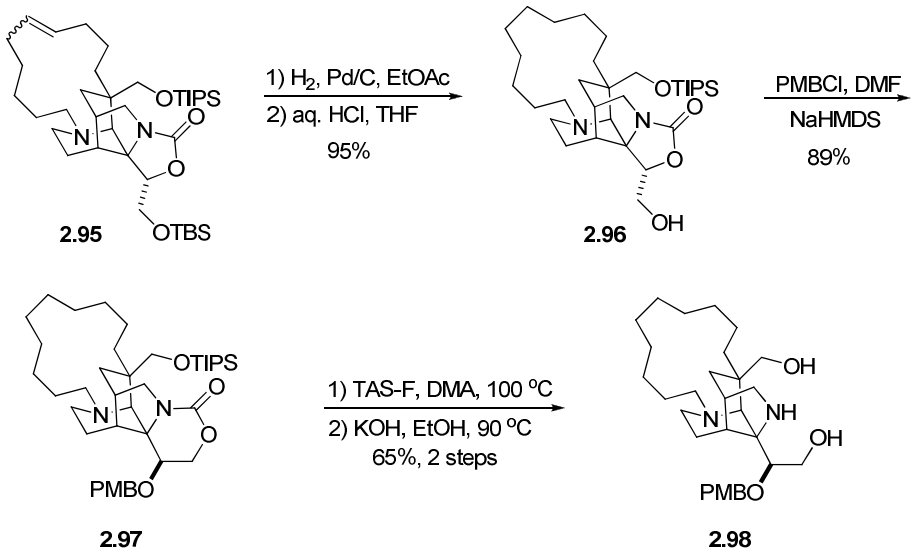
Having a high-yielding route to the diazatricycloundecane core established, Overman and co-workers began to focus their attention on elaboration to a ring-closing metathesis precursor (Scheme 36). Thus, TBS-protection of the primary alcohol followed by reduction and subsequent TIPS-protection afforded **2.92**. Removal of the tosyl protecting group and reductive amination with 6-hepten-1-al provided ring-closing metathesis precursor **2.94**. Under optimal conditions, the Western macrocycle was formed without need for protonation of the tertiary amine using Grubbs' first generation catalyst to furnish an inconsequential mixture of geometrical isomers, macrocycles **2.95**.[88,89]



Scheme 36. Overman's Closure of the Western Ring of Sarain A (**1.5**).

Hydrogenation of **2.95** with Pd/C completed installation of the saturated macrocycle and exposure to hydrochloric acid yielded alcohol **2.96**. Treatment of alcohol **2.96** with para-methoxybenzyl chloride and NaHMDS led to the rearrangement of the

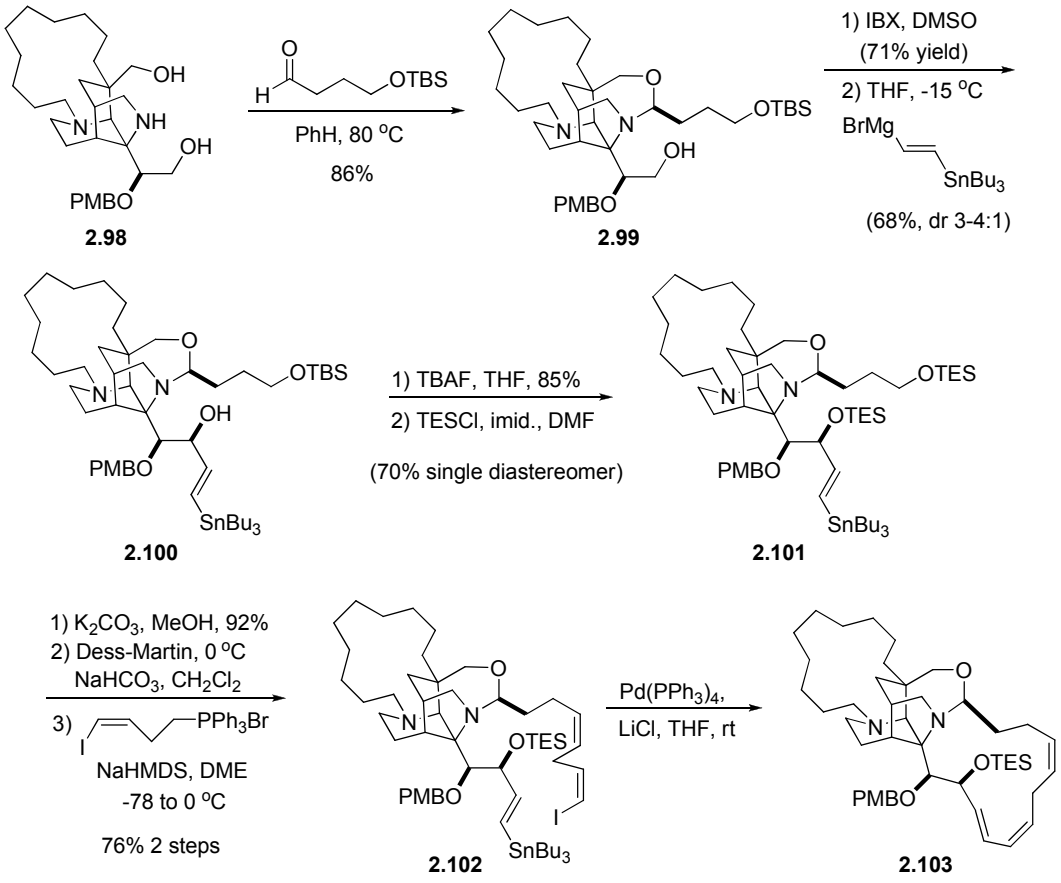
oxzaolidine to the 5-hydroxy-[1,3]oxizinan-2-one with protection of the secondary hydroxyl to afford PMB ether **2.97**. After considerable experimentation it was found that removal of the TIPS protecting group could be accomplished with tris(dimethylamino)sulfonium difluorotrimethylsilicate in dimethylacetamide. The tetrahydroooxazine fragment was cleaved with potassium hydroxide in ethanol to provide diamine diol **2.98**.[88,89]



Scheme 37. Overman's Elaboration in Route to Sarain A (**1.5**).

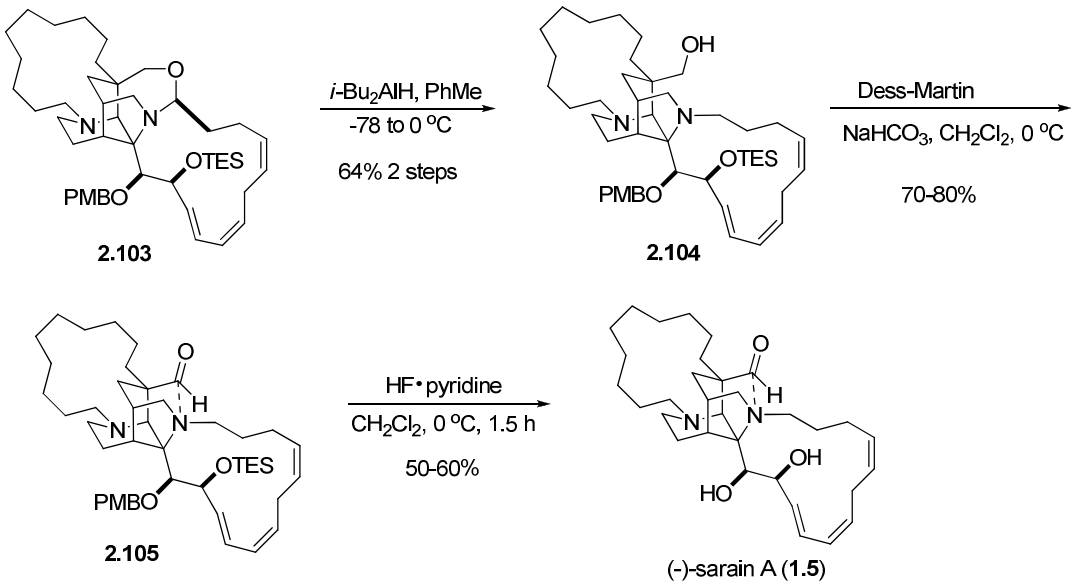
With the diamine diol **2.98** in hand attention was turned toward construction of the Eastern half of sarain A. To begin this process diamine **2.98** was condensed with the protected butanal to provide oxazocane **2.99**. IBX oxidation followed by a Grignard addition accomplished installation of the requisite vinyl stannane (**2.100)** with 3-4:1 diastereoselectivity. Removal of the TBS protecting group and subsequent protection of

the diol with TES groups was found to be necessary due to the inability to selectively oxidize the primary alcohol. This proved to be advantageous, as the separation of diastereomers became possible at this point. Selective cleavage of the primary TES protective group followed by Dess-Martin oxidation, allowed for reaction with a phosphonium ylide that delivered the key Stille coupling substrate in 76% over two steps. Treatment of coupling precursor **2.102** with $Pd(PPh_3)_4$ and excess LiCl in THF completed closure of the 14-membered triene ring product **2.103**.[88,89]



Scheme 38. Closure of the 14-Membered Ring of Sarain A (**1.5**).

Reduction of the *N,O*-acetal with DIBAL-H delivered the full skeleton of sarain A (**1.5**), pentacyclic alcohol **2.104**. To complete the synthesis of Sarain A (**1.5**) oxidation of a sterically encumbered, neopentylic alcohol and deprotection of two different protecting groups lied ahead. The resulting oxidation would yield an extremely advanced synthetic intermediate that would result in a zwitterionic product (due to the close proximity to the tertiary amine) that would be difficult to handle in the laboratory. The unique nature of this substrate is a prime example of the difficulty encountered when executing a synthesis of any of the complex 3-alkylpiperidine natural products. With predicted difficulty of handling the product, and the inherent difficult with oxidations in the presence of tertiary amines, several mild oxidants were examined. Ultimately, Dess-Martin periodinane buffered with sodium bicarbonate proved to be the most effective to provide crude aldehyde **2.105**, which was directly used in the next step without further purification.[88,89]

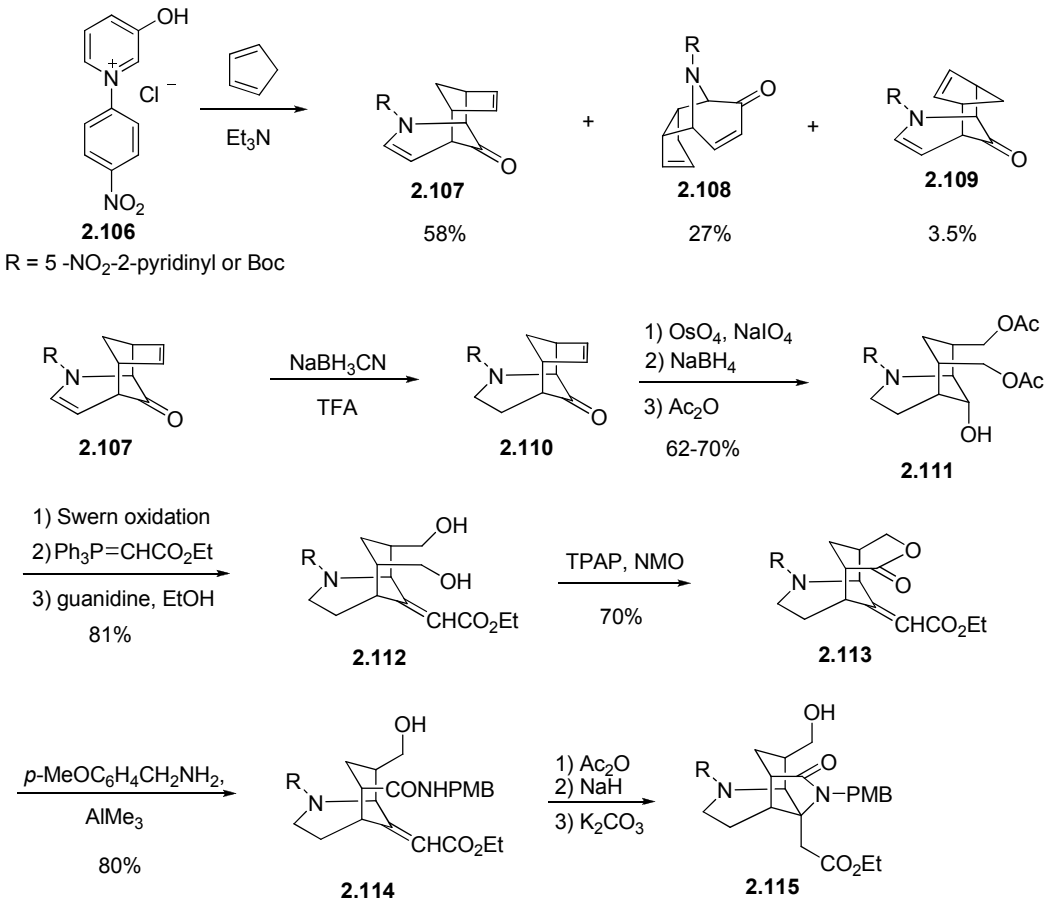


Scheme 39. Completion of Sarain A (**1.5**) by Overman.

With the aldehyde now in place only one major problem remained, deprotection to provide sarain A (**1.5**). Thus, an authentic sample of sarain A (**1.5**), provided by Cimino, was treated with iodotrimethylsilane for 15 minutes to probe the stability of the skipped triene moiety. The skipped triene was found to stable and aldehyde **2.105** was treated with iodotrimethylsilane but found to only produce a mixture of complex products. Ultimately, treatment with HF•pyridine at 0 °C in dichloromethane for 1.5 hours led to the clean formation of sarain A (**1.5**) (Scheme 39).[88,89]

Cha's Approach to Sarain A (**1.5**)

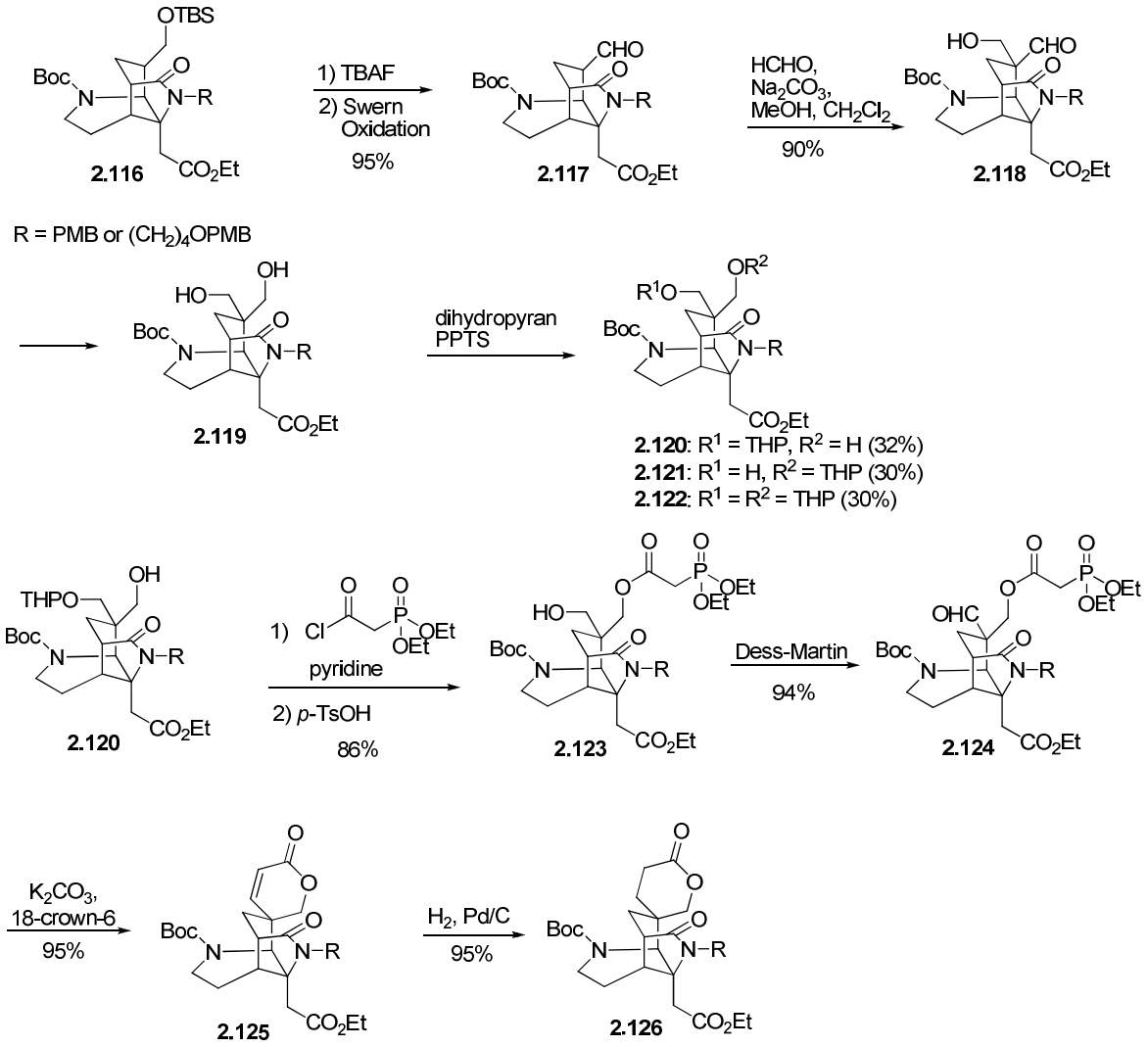
In 1999 Cha and co-workers published a route to the tricyclic core of the sarains using Katritzky's cycloaddition with 3-oxidopyridinium betaines.[90] Thus, exposure of 3-oxidopyridinium betaines **2.106** to cyclopentadiene in the presence of triethylamine led to the formation of three cycloaddition products (Scheme 40). Enamine **2.107** was reduced with $NaBH_3CN$ to tricycle **2.110**. Oxidative cleavage, reduction, and acetylation provided diacetate **2.111**. The α,β-unsaturated ester (**2.112**) was obtained through Swern oxidation, subsequent Wittig olefination, and deacetylation. TPAP oxidation provided lactone **2.113** as a single regioisomer. To begin the assembly of the pyyrolidine ring the lactone (**2.113**) was converted to *N*-*p*-methoxybenzyl amide **2.114**, which was converted to tricycle **2.115** by treatment with sodium hydride.[90]



Scheme 40. Cha's Formation of the Tricyclic Core.

Using the same synthetic sequence described above (Scheme 40) a modified substrate (**2.116**) was aimed at the formation of the Western macrocycle of sarain A (**1.5**).[91] Deprotection and Swern oxidation provided aldehyde **2.117** which was treated with an excess of aqueous formaldehyde in the presence of sodium carbonate produced diol **2.119**, presumably through a Tishchenko reaction and subsequent hydrolysis of the resulting formate. Formation of a tetrahydropyran protecting group produced an almost equal mixture of three products. Treatment of **2.120** with diethylphosphonoacetyl chloride in the presence of pyridine, followed by removal of the THP-protective group

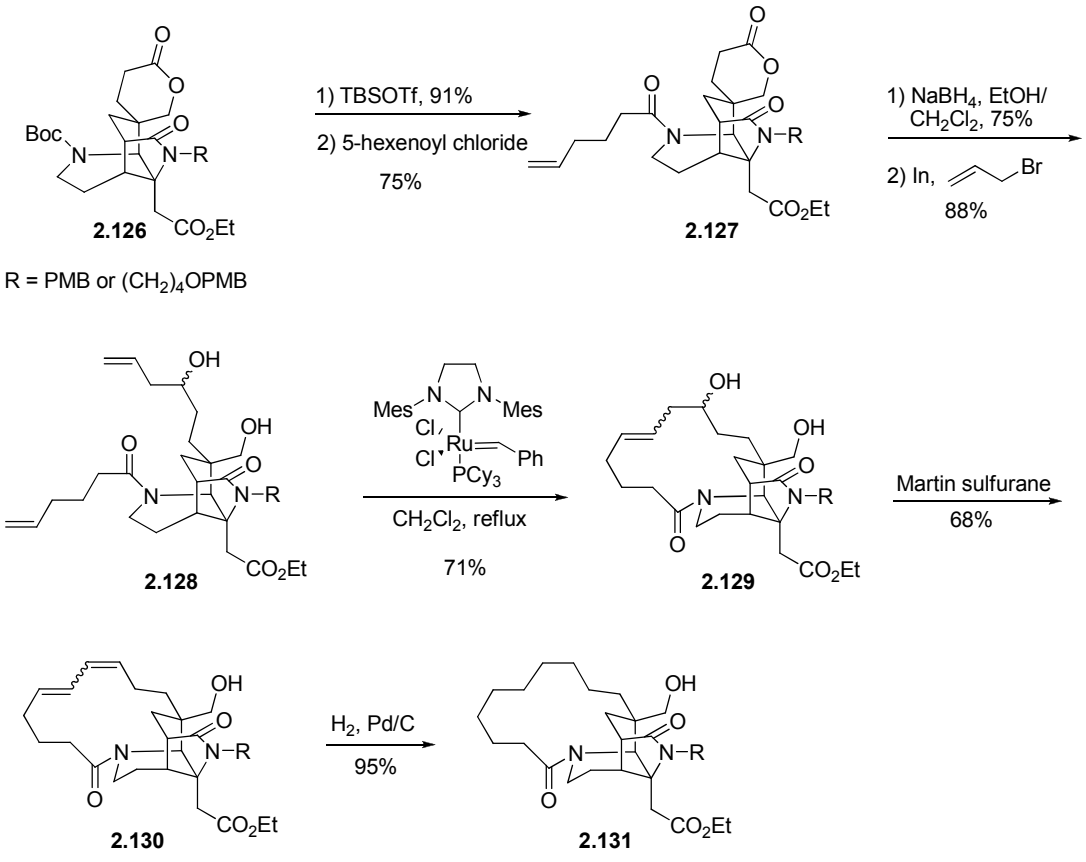
provided alcohol **2.123**. Dess-Martin oxidation and intramolecular Wittig olefination provide α,β-unsaturated lactone **2.125**, which was converted to lactone **2.126** by reaction with Pd/C in a hydrogen atmosphere (Scheme 41).[91]



Scheme 41. Cha's Route to the Western Macrocycle of Sarain A (**1.5**).

To begin building the necessary substrate for formation of the 13-membered ring by ring-closing metathesis compound **2.126** was treated with TBSOTf and acylated with

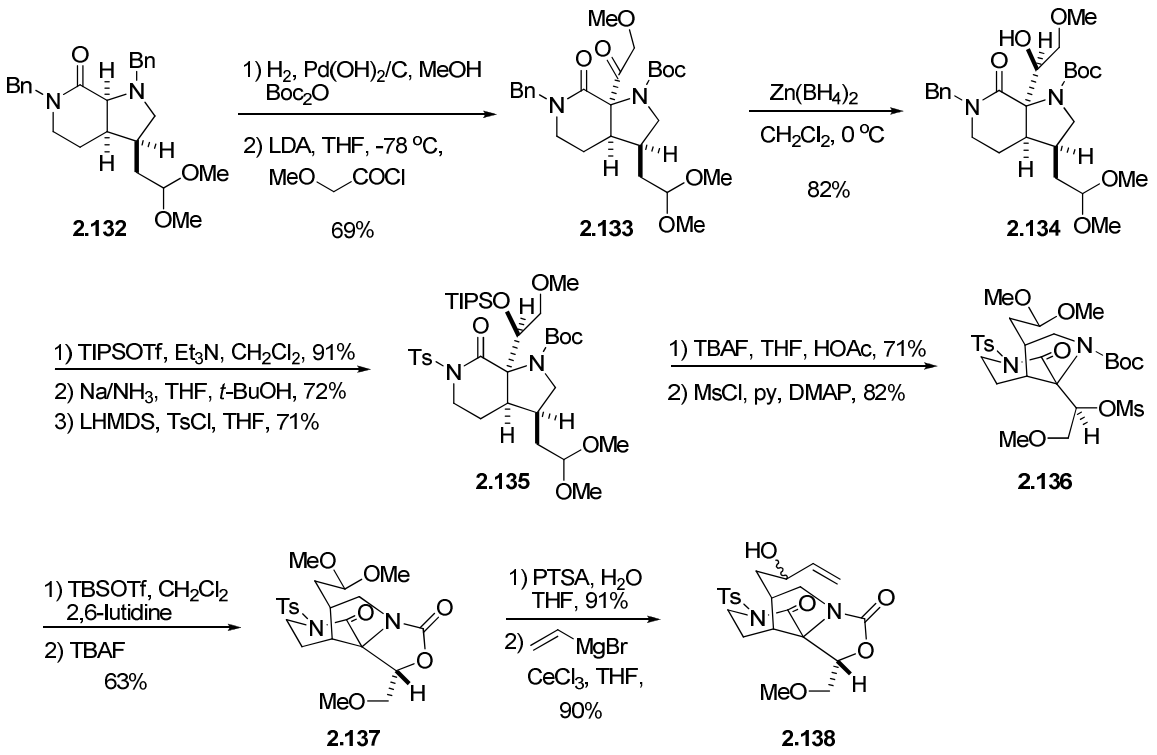
5-hexenoyl chloride in 75% yield. Sodium borohydride reduction of the lactone, followed by indium-mediated allylation resulted in ring-closing metathesis precursor **2.128**. Formation of the 13-membered ring was accomplished using Grubbs' second generation catalyst followed by dehydration with Martin sulfurane and hydrogenation afforded the saturated 13-membered macrocycle of sarain A (**1.5**), compound **2.131**.[91]



Scheme 42. Cha's Formation of the Western Macrocycle of Sarain A (**1.5**).

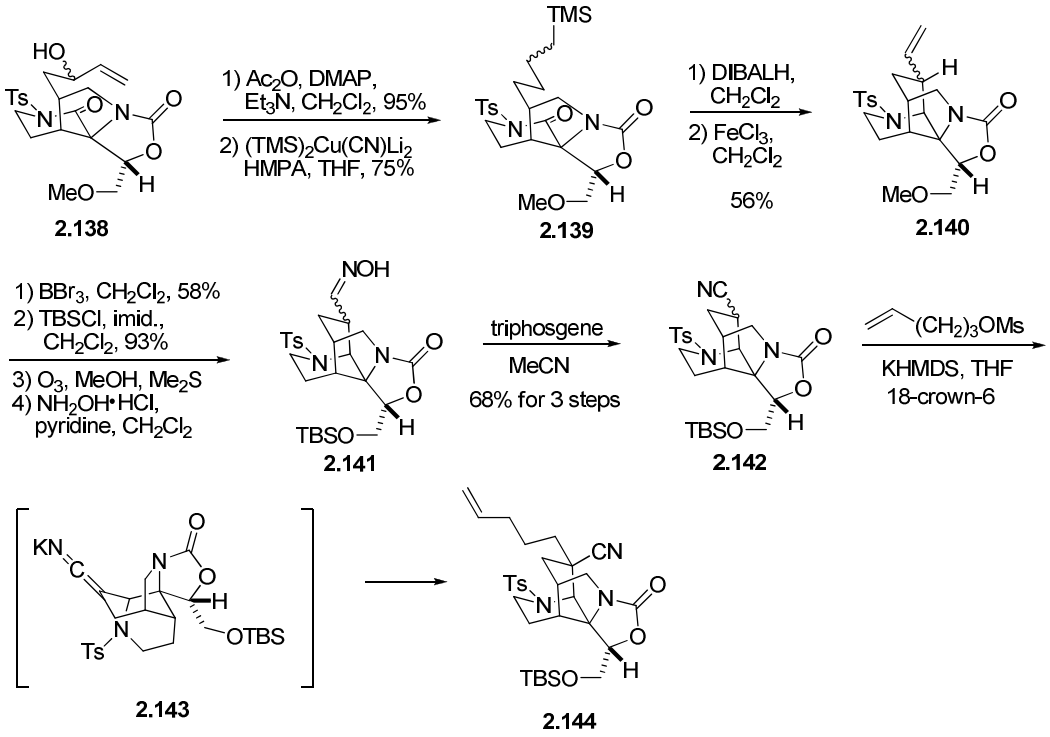
Weinreb's Approach to Sarain A (**1.5**)

The Weinreb approach to Sarain A (**1.5**) begins with *N*-benzyllactam **2.132**, prepared via a 1,3-dipolar azomethine ylide/olefin intramolecular cycloaddition (Scheme 43).[92-94] Hydrogenolysis of the benzyl protected amine and subsequent protection as the carbamate, followed by alkylation afforded β-ketolactam **2.133**. Treament of **2.133** with zinc borohydride provided alcohol **2.134** as a single stereoisomer. Protecting group manipulation led to *N*-tosyllactam **2.135**. Removal of the silyl protecting group and conversion to the mesylate promoted cyclization via the Ohfune protocol provided cyclic carbamate **2.137**. Acetal **2.137** was then hydrolyzed to the aldehyde which underwent Grignard addition to yield allylic alcohol **2.138** as a mixture of stereoisomers.



Scheme 43. Weinreb's Synthesis of the Cyclic Core of Sarain A (**1.5**).

Allylic alcohol **2.138** was acetylated subjected to the Fleming silyl cuprate reagent to provide allylsilane **2.139** as a mixture of geometrical isomers. The *N*-tosyllactam moiety was reduced with DIBALH and the resulting aminal underwent ferric chloride catalyzed allylsilane/*N*-sulfonyliminium ion cyclization to afford the sarain core **2.140** as a 2.1:1 mixture of epimers (Scheme 44). Protecting group manipulation, oxidative cleavage, and condensation with the hydroxyl amine provided oxime **2.141**. Arrival at anion **2.143**, produced from nitrile **2.142** and deprotonation with KHMDS, underwent stereoselective alkylation with the mesylate of 4-pentenol from the less hindered equatorial face to afford olefin **2.144**.[92-94]



Scheme 44. Weinreb's Access to the Tricyclic Core of Sarain A (**1.5**).

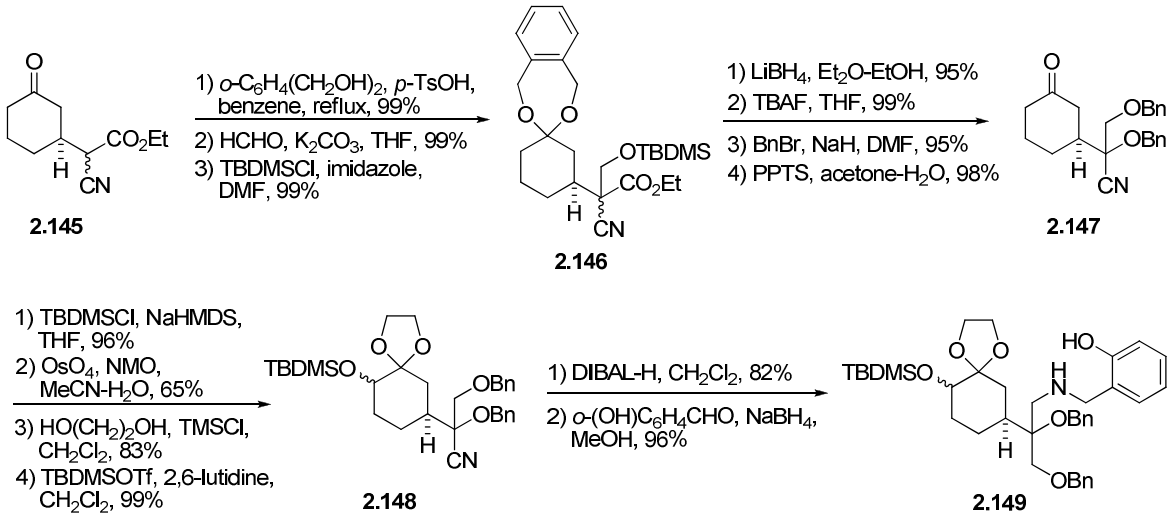
Aside from the synthetic work on sarain A (**1.5**) described above, significant progress has been made by the Heathcock[95,96] and Marazano[97] groups. Madangamine A (**1.6**) is yet another pentacyclic alkaloid that has attracted attention in the field of synthetic organic chemistry. Isolated from the sponge *Xestospongia ingens* in 1994, it was shown to be cytotoxic against several tumor cell lines. Structurally, the natural product is composed of a diamond lattice core and two macrocycles. Yamazaki[98,99] and co-workers as well as the Weinreb[100] group have reported approaches to this unprecedented alkaloid.

Synthetic Approaches Toward Madangamine A

Yamazaki's Approach to Madangamine A (**1.6**)

Yamazaki and co-workers were able to obtain the 11-membered ring of the madangamines using an intramolecular reductive amination and *N, O*-acetalization protocol.[98,99] The synthesis commenced with protection of the keto group with 1,2 bis(hydroxymethyl)benzene to yield the seven membered ring acetal.

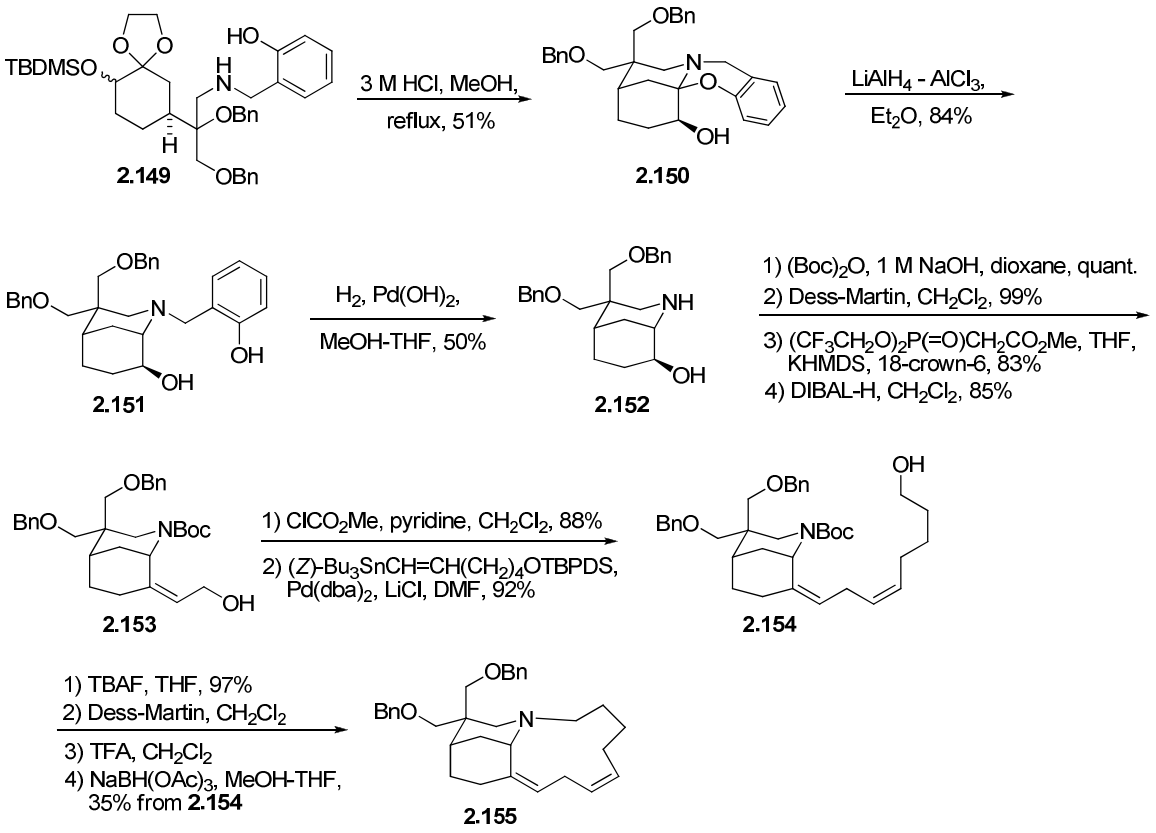
Hydroxymethylation with potassium carbonate and protection with TBDMSCl provided ester **2.146**. Reduction of the ester with lithium borohydride and protecting group manipulation led to cyclohexanone **2.147**. A modified Rubottom oxidation followed by treatment with ethylene glycol, trimethylsiylchloride, and TBDMSOTf in the presence of 2,6-lutidine gave **2.148** as a 3:1 mixture of diastereomers. The nitrile was then reduced with DIBAL-H and the resulting primary amine was converted to amine **2.149** via reductive amination with salicylaldehyde (Scheme 45).[98,99]



Scheme 45. Yamazaki's Route Toward Madangamine A (**1.6**).

Ketal **2.149** was treated with hydrochloric acid in refluxing methanol to provide *N,O*-acetal **2.150** as a single diastereomer (Scheme 46). Some of the uncyclized product was produced as well and was converted to **2.150** under the same conditions. The 2-aza-bicyclo[3.3.1]nonane derivative was obtained by reductive cleavage of the *N,O*-acetal with alane. Cleavage of the (2-hydroxyphenyl)methyl group was accomplished by hydrogenation with palladium hydroxide providing bicycle **2.152**. The secondary amine was then protected as a carbamate, followed by oxidation of the alcohol with Dess-Martin. The resulting ketone was converted to the (*Z*)-exo-olefin as inseparable geometrical mixture (11:1) by employing Still's *Z*-selective Horner-Emmons olefination using KHMDS as a base. Reduction of the corresponding ester with DIBAL-H provided the separable (*Z*)-allylic alcohol **2.153**. Methoxycarbonylation set the stage for a Stille coupling with the allylic acetate and the vinyl stannane to afford skipped diene **2.154** as a single stereoisomer. After removal of the TBDPS group with TBAF, the 11-membered

ring was constructed by oxidation with Dess-Martin followed by deprotection of the Boc group and intramolecular reductive amination provided tricyclic product **2.155** (Scheme 46).[98,99]

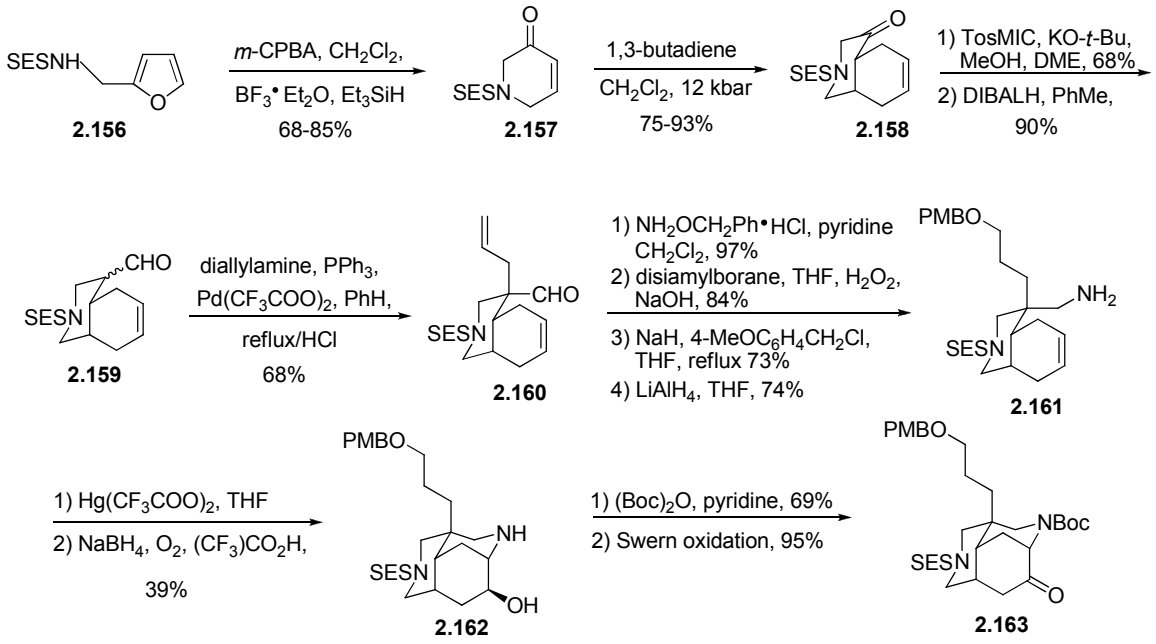


Scheme 46. Synthesis of the 11-Membered Ring.

Weinreb's Approach to the Tricyclic Core of Madangamine A (**1.6**).

The Weinreb approach began with ring expansion of a SES-protected furfurylamine (**2.156**) to a hemiaminal by exposure to *m*-chloroperbenzoic acid and *in situ* reaction with triethylsilane/BF_3•Et_2O to yield enone **2.157** (Scheme 47).[100] High pressure cycloaddition with 1,3-butadiene afforded the *cis*-decaline system **2.158**.

Homologation to aldehyde **2.159** followed by palladium catalyzed aza-Claisen rearrangement of the corresponding diallyl enamine gave aldehyde **2.160**. *O*-Benzyloxime formation, followed by hydroboration, protection of the resulting alcohol as the PMB ether and subsequent reduction afforded amine **2.161**. Electrophilic cyclization mediated by mercury (II), followed by oxidative cleavage of the organomercury intermediate furnished tricycle **2.162**. Protection of the secondary amine as a Boc carbamate and Swern oxidation to the ketone provided **2.163** ready for further manipulation to madangamine A (**1.6**).[100] Significant progress toward Madangamine A has also been made by Bonjoch[101] and Marazano[102] as well.



Scheme 47. Weinreb's Synthesis of the Tricyclic Core of Madangamine A (**1.6**).

CHAPTER III

TETRACYCLIC 3-ALKYLPIPERIDINE ALKALOIDS: ISOLATION, STRUCTURE ELUCIDATION, AND BIOACTIVITY

Introduction

The pentacyclic alkaloids containing 3-alkylpiperidine motifs have attracted a great deal of attention from the synthetic community.[50,52,88] However, very little progress has been reported on the intermediate class of tetracyclic alkylpiperidines featuring a 3,4-linked bis-piperidine core.[46,103,104] These tetracyclic natural products are presumed to be derived via a Diels-Alder cycloaddition as described in Chapter I.[6] The structural variations within this sub-group primarily occur in the relative stereochemistry of the 3,4-linked bis-piperidine core and the degree and location of unsaturation in the two appending macrocycles.[33-37,105,106]

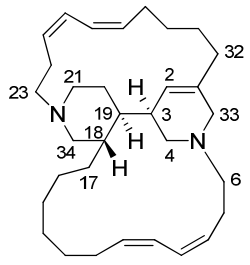
Due to subtle variations in their complex framework, the structure elucidation of many tetracyclic alkaloids has been extremely challenging. Rigorous NMR studies using in depth experiments were required for structural assignment of this group of alkylpiperidines. The ^{1}H-NMR spectra of these compounds are difficult to extract information from due to significant signal overlap in the δ 0.9-2.0 region, making determination of structure and relative stereochemistry difficult. Impurities leading to broad ^{1}H-NMR resonances have also contributed to difficulty in structural assignment, which are replaced by sharp, but severely overlapping signals upon purification. Despite the challenges encountered during structure elucidation of tetracyclic 3-alkylpiperidines,

Crews, Garson, Berlinck, Kashman, and co-workers have isolated and determined structure for over sixteen tetracyclic alkaloids.[33-37,105,106] This chapter will examine structural differences and the assignment of relatively stereochemistry among this sub-group of 3-alkylpiperidine alkaloids.

Halicyclamines

Halicyclamine A (**1.68**)

In 1994 Crews and co-workers began investigation on a crude extract from a massive, olive green, tubular sponge, *Haliclona* sp., collected from Biak, Indonesia.[33] Interest in purification and structure elucidation was stimulated by observed inhibition activity against the enzyme target inosine monophosphate dehyrogenase. Extensive purification led to the identification of halicyclamine A, a tetracyclic alkaloid possessing 5 olefins (Figure 3).[33]



halicyclamine A (**1.68**)

Figure 3. Proposed Structure of Halicyclamine A (**1.68**).

Connectivity of halicyclamine A (**1.68**) was assigned using 2D-NMR techniques including HMBC, ^{1}H-^{1}H COSY, HMQC-TOCSY correlations, as well as analysis of MS fragmentation patterns. The relative orientation between H18 and H19 was assigned using 2D NMR *J*-resolved data. A coupling constant of 0 Hz between H2 and H3 indicated H3 was axial and the *syn* relationship between H3 and H19 was assigned based on the presumed Diels-Alder cyclization in the hypothetical biosynthesis. Furthermore, a coupling constant of 7.5 Hz between H34 and H18 oriented H18 in an axial position and a coupling constant between H18 and H19 of 8.0 Hz suggested H18 and H19 to occupy in a diaxial relationship. Molecular modeling using the MMX forcefield in PCMOD 4.0 supported the observed coupling constants with calculated $J_{34\text{-}18}$ = 8.0 Hz and $J_{18\text{-}19}$ = 5.7 Hz. Alternative modeled isomers were shown to have different predicted coupling constants.[33]

Halicyclamine B (**3.1**)

Two years after the isolation and structure elucidation of halicyclamine A (**1.68**) the Crews group isolated a second tetracyclic alkaloid from *Xestospongia* sp. assigned halicyclamine B (**3.1**) (Figure 4).[34] Analysis of high resolution mass spectra and ^{13}C NMR data suggested the molecular formula $C_{26}H_{42}N_2$ and seven degrees of unsaturation, three of which were double bonds. A combination of HMBC and ^{1}H-^{1}H COSY correlations led to the proposed tetracyclic alkaloid incorporating a 3,4-linked bis-piperidine core. However, difficulties were encountered while trying to join fragments assigned by NMR experiments to the bis-piperidine core due to severe overlap of aliphatic resonances.[34] Fortunately, crystals formed during the slow evaporation of a

methanol solution containing halicyclamine B (**3.1**), which were then subjected to single-crystal X-ray analysis leading to the assigned structure.[34] Halicyclamine B (**3.1**) was shown to have weak but selective antimicrobial activity as it showed growth inhibition of 20% and 50% at 200 µg/disk against *E. coli* and *B. subtilis*.[34]

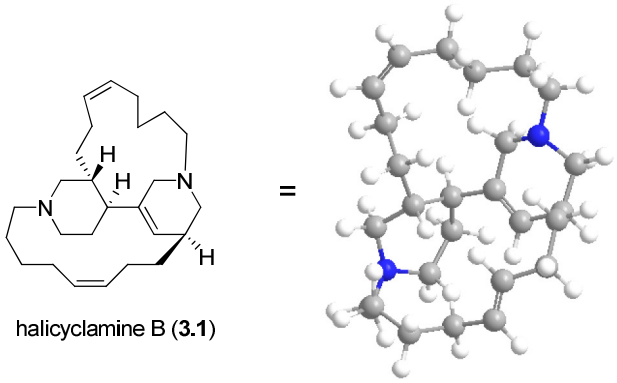


Figure 4. Halicyclamine B (**3.1**).

Haliclonacyclamines

Haliclonacyclamine A (**3.2**)

In 1996 the Garson group (University of Queensland) isolated two new tetracyclic alkaloids from the extracts of the olive-brown finger sponge *Haliclona* sp. found at Heron Island, Great Barrier Reef.[35] The first of the two metabolites was haliclonacyclamine A (**3.2**), which displaced an IC_{50} value of 0.8 ug/mL in a P_{388} assay. Garson determined the molecular formula of haliclonacyclamine A (**3.2**) to be $C_{32}H_{56}N_2$, indicating the presence of two olefins, and a tetracyclic core. Further structural features were established by interpretation of HMQC, HMBC, DFQCOSY, and HOHAHA NMR data. Once structural connectivity was established the four allylic carbons were examined and found

to possess a chemical shift below 30 ppm, consistent with a *cis* geometry at both isolated carbon-carbon double bonds.[35] Treatment of haliclonacyclamine A (**3.2**) with Pd/C under an atmosphere of hydrogen (60 psi) provided tetrahydrohaliclonacyclamine A (**3.3**, Figure 5).

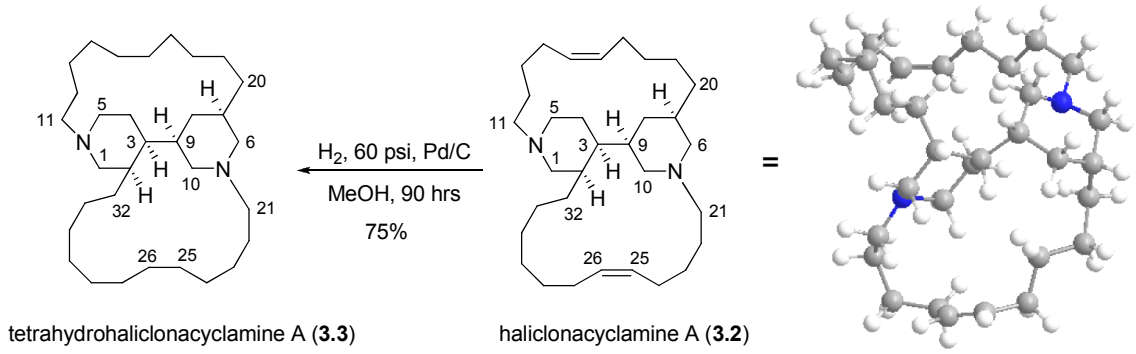


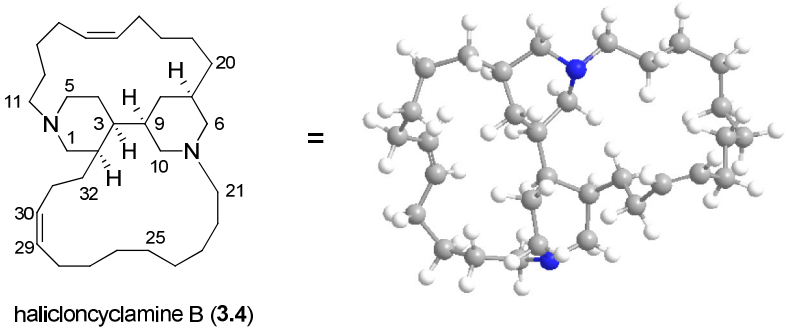
Figure 5. Haliclonacyclamine A (**3.2**) and Tetrahydrohaliclonacyclamine A (**3.3**).

Unfortunately, due to the highly congested methylene region the relative stereochemistry of the bis-piperidine core could only be partially deduced by analysis of 2D NOESY data. The Garson group determined that H7 and H9 possessed a *cis* relationship, but were unable to assign relative stereochemistry of the second piperidine ring. Alternate solvents and higher field strength of (750 MHz) did not improve resolution. Using an ethyl acetate/hexane/triethylamine solvent system they were able to produce X-ray quality crystals of haliclonacyclamine A (**3.2**). X-ray analysis confirmed structural assignments and relative stereochemistry as shown in Figure 5. Recently, Garson and co-workers reported on the absolute configuration (as shown in Figure 5) of haliclonacyclamine A (**3.2**) by using X-ray crystallographic analysis.[35] Notably, the

structural assignments of haliclonacyclamine A (**3.2**) based on a single-crystal x-ray analysis allows confident structural assignment of tetrahydrohaliclonacyclamine A (**3.3**).

Haliclonacyclamine B (**3.4**)

An isomer of haliclonacyclamine A (**3.2**) was isolated by the Garson group and assigned haliclonacyclamine B (**3.4**, Figure 6).[35] This secondary metabolite showed potent cytotoxicity with an IC_{50} value of 0.6 ug/mL in a P_{388} assay. A combination of HSQC, HMBC, DQFCOSY, and HOHAHA experiments led to an initial structural assignment of haliclonacyclamine B.[35] The assigned structure was supported by hydrogenation of haliclonacyclamine B (**3.4**) to afford (+) tetrahydrohaliclonacyclamine A (**3.3**).[36] This result indicates haliclonacyclamines A and B share identical bis-piperidine stereochemistry and absolute stereochemistry.[35] Crystals were obtained of haliclonacyclamine B (**3.4**), but yielded an incomplete analysis due to disorder in the crystal lattice.[35]



halicloncyclamine B (**3.4**)

Figure 6. Originally Proposed Structure of Haliclonacyclaime B (**3.4**).

Haliclonacyclamine C (**1.4**)

In 1998 Garson and co-workers published a correction of the original haliclonacyclamine B (**3.4**) structural assignments.[36] The minor correction relocated the *cis* carbon-carbon double bond from the C30-C29 to C28-C27 position. The structural correction was based on resolved X-ray data. In the same publication a third haliclonacyclamine was described from the olive-brown finger sponge *Haliclona* sp. and named haliclonacyclamine C (**1.4**). Haliclonacyclamine C (**1.4**) was reported to be cytotoxic in a P_{388} assay, have antibacterial activity towards *Bacillus subtilis*, and strong antifungal activity toward *Candida albicans* and *Trichophyton mentagrophytes*.[36]

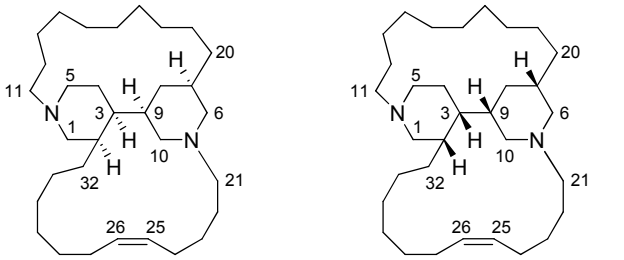


Figure 7. Structure of Haliclonacyclamine C (**1.4**).

Haliclonacyclamine C (**1.4**) could be considered a dihydro analogue of haliclonacyclamine A (**3.2**). Indeed, hydrogenation of haliclonacyclamine C (**1.4**) provided tetrahydrohaliclonacyclamine A (**3.3**) with an optical rotation ($[\alpha]_D$ +12.7°) of the same sign and similar magnitude as the hydrogenated products obtained from haliclonacyclamines A (**3.2**) and B (**3.4**), +23.9° and +24.9° respectively.[36] This

observation indicates that all three haliclonacyclamines isolated thus far have identical stereochemistry in the 3,4-linked bis-piperdine core. We suggest this configuration to be described as *cis-syn-cis*.

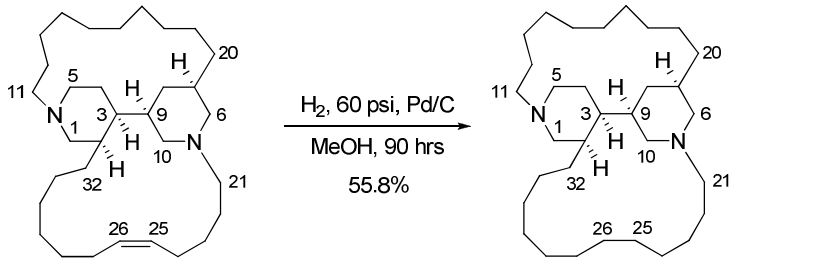
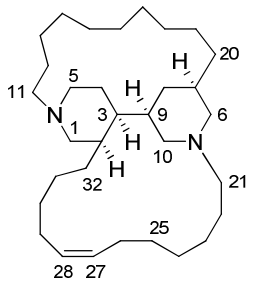


Figure 8. Hydrogenation Product of Haliclonacyclamine C (**1.4**).

The structural assignment for haliclonacyclamine C (**1.4**) followed a similar line of NMR analysis as reported for haliclonacyclamine A (**3.2**) and haliclonacyclamine B (**3.4**). First a series of HSQC, HMBC, DQFCOSY, and TOCSY experiments provided basic structural connectivity.[36] The assigned *cis* olefin was based on ^{13}C NMR analysis of chemical shift. A NOESY experiment showed a correlation between H7 and H9, which was consistent with the assigned stereochemistry for haliclonacyclamines A (**3.2**) and B (**3.4**). Unfortunately, no concrete conclusions could be made concerning the stereochemistry between H3 and H9 from NOESY data, however convergence to the dihydro product proved that haliclonacyclamine C (**1.4**) possesses the same relative ring stereochemistry as haliclonacyclamine A (**3.2**) and B (**3.4**).[36]

Haliclonacyclamine D (**3.5**)

Haliclonacyclamine D (**3.5**, Figure 9), was later identified by the Garson group and found to have a molecular formula of $C_{32}H_{58}N_2$ by high resolution mass spectrometry, which combined with the ^{13}C NMR data indicated only one double bond present within the tetracyclic system.[36] Structural assignments for the bis-piperdine core and the two appending macrocycles were made through extensive HSQC, HMBC, DQFCOSY, and TOCSY experiments. This NMR data also suggested that haliclonacyclamine D (**3.5**) had a structure that was similar to haliclonacyclamine B (**3.3**) except the olefin located at C15-C16. There was insufficient material to compare relative stereochemistry to haliclonacyclamines A-C by hydrogenation and convergence to (tetrahydrohaliclonacyclamine A (**3.4**)). However, NOESY data suggested that the stereochemistry at C7 and C9 was identical to haliclonacyclamines A-C. No biological studies were conducted on haliclonacyclamine D (**3.5**) due to lack of material.[36]

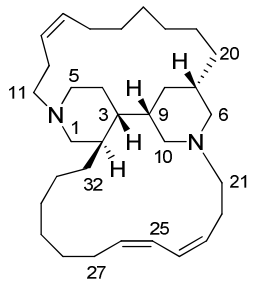


halicloncyclamine D (**3.5**)

Figure 9. Proposed Structure of Haliclonacyclamine D (**3.5**).

Haliclonacyclamine E (**3.6**)

In 2000 the Berlinck group isolated four new tetracyclic alklaoids from the extracts of a marine sponge belonging to the order Haplosclerida, *Arenosclera brasiliensis*, collected off the southeastern coast of Brazil.[37] The first of these new isolates was assigned haliclonacyclamine E (**3.6**, Figure 10). High resolution mass spectrometry provided the molecular formula $C_{32}H_{55}N_2$, and the ^{13}C NMR indicated six sp^2 hybridized carbons corresponding to three double bonds within the tetracyclic framework. Structural arrangement of haliclonacyclamine E (**3.6**) was made through a series of HSQC, ^1H-^1H COSY, HSQC-TOCSY, and HMBC experiments. However, the Berlinck group was unable to produced crystals suitable for single crystal X-ray analysis of any isolated natural products, including haliclonacyclamine E (**3.6**). This forced them to rely solely on dipolar couplings from NOESY and ROESY data for assignment of relative stereochemistry.[37]



halicloncyclamine E (**3.6**)

Figure 10. Proposed Structure of Haliclonacyclamine E (**3.6**).

Throughout their structural analysis the Berlinck group noticed several spectral discrepancies for haliclonacyclamine E (**3.6**) in comparison to data for

haliclonacyclamines A-D. Spectral differences resided in the bis-piperidine core.[37] First, the chemical shifts around the core were different. For example, C2 (δ 31.6) in haliclonacyclamine E (**3.6**) was shielded by 10 ppm compared to haliclonacyclamines A-D (δ between 40.0 and 41.1), C2 (Δδ of +5 ppm in **3.6**), C4 (Δδ of -3 ppm in **3.6**), C5 (Δδ of +4 ppm in **3.6**), and C8 (Δδ of -8 ppm in **3.6**). This difference in spectral data suggested a different relative core stereochemistry for haliclonacyclamine E (**3.6**). Differences in bis-piperidine stereochemistry was further supported by NOESY and ROESY data. For example, H8b (in this chapter a and b will denote downfield and upfield resonances respectively of a germinal pair) was a well-defined quartet (12 Hz) having the same coupling constant as H7, H8a, and H9. Thus, H8b and H7 must be axial-axial, as well as H8b and H9. This supported the C7 and C9 relative stereochemistry was identical to haliclonacyclamines A-D.[37]

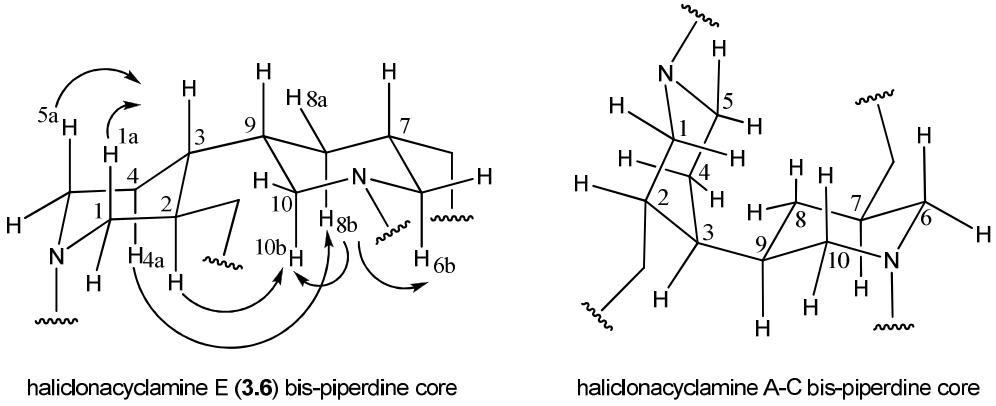
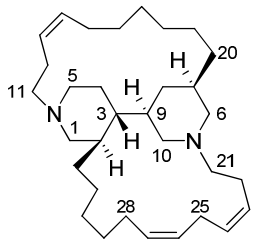


Figure 11. NOESY Correlations for Haliclonacyclamine E (**3.6**).

The NOESY spectra also showed clear dipolar couplings between H8b, H6b, and H10b indicating are all axial and on the same face of the piperidine ring (Figure 11).[37] A dipolar coupling observed between H2 and H10b indicated that the C2/C3 relative stereochemistry was opposite of that observed in the haliclonacyclamines A-D. Other dipolar couplings placed H2, H4a, H6b, H8b, and H10b in an axial orientation and on the same face of the bis-piperidine system. Dipolar couplings observed between H1a and H3, as well as H5a and H3, indicated that H1a, H3, and H5a were all axial.[37]

Haliclonacyclamine F (**3.7**)

In 2007 Berlinck isolated haliclonacyclamine F (**3.7**) from a Brazilan marine sponge *Pachychalina alcaloidifera*.[106] The cytotoxicity of haliclonacyclamine F (**3.7**) was evaluated against several cell lines showing activities of 4.5µg/mL for SF 295 (human CNS), 1.0 µg/mL for MDA-MB435 (human breast), 8.6 µg/mL for HCT8 (colon), and 2.2 µg/mL for HL60 (leukemia) cancer cell lines using the MTT method.[106]



halicloncyclamine F (**3.7**)

Figure 12. Proposed Structure of Haliclonacyclamine F (**3.7**).

The tetracyclic nature of haliclonacyclamine F (**3.6**) was established through ^{13}C-NMR and high resolution mass spectrometry indicating a molecular formula of $C_{32}H_{55}N_2$. Structural assignments were made by interpretation of COSY, HMBC, and HSQC-TOCSY data. A NOESY spectrum was used to establish relative stereochemistry of the bis-piperidine core (Figure 13).[106] There were dipolar couplings between H2 and H4b, H2 and H9, H6b and H10b, and between H8b and H10b. This indicated that the relative stereochemistry of H3 and H2 was the same as haliclonacyclamine E (**3.6**). Comparison of the ^{13}C-NMR chemical shifts of C1 to C5 was in agreement with this conclusion. Unfortunately, the relative stereochemistry of the eastern ring could not be completely established since NOE dipolar couplings were not observed for H7. Since the chemical shifts of C6 to C10 are almost identical to arenosclerin C (**3.10**, arenosclerin section), the relative stereochemistry was proposed as shown in Figures 12 and 13.[106] Notably, the proposed relative stereochemistry between H3 and H9 is in contrast to the stereochemical outcome of the Diels-Alder cyclization proposed by Baldwin and Whitehead (Schemes 2 and 13).[6]

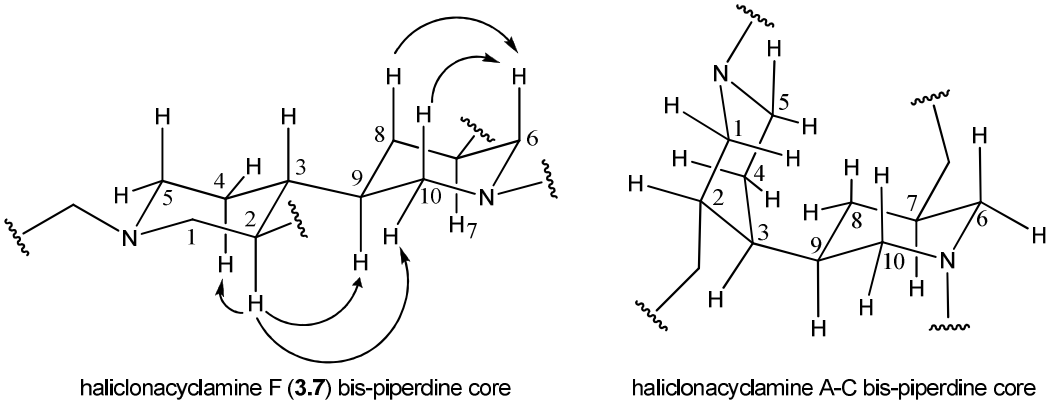
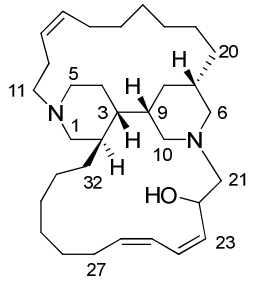


Figure 13. NOESY Correlations for Haliclonacyclamine F (**3.7**)

Arenosclerins

Arenosclerin A (**3.8**)

In addition to haliclonacyclamine E (**3.7**), Berlinck and co-workers isolated three other tetracyclic alkaloids in 2000, arenosclerins A-C (**3.8** – **3.10**).[37] The arenosclerins were the first examples of hydroxylated haliclonacyclamine/halicyclamine type alkaloids. The tetracyclic nature and the presence of three double bonds were established by analysis of ^{13}C-NMR and high resolution mass spectrometry data indicating the molecular formula $C_{32}H_{55}N_2O$ of an optically active glassy solid, arenosclerin A (**3.8**, Figure 14).[37] Structural assignments of arenosclerin A (**3.8**) were made by interpretation of COSY, HMBC, and HSQC-TOCSY data.



arenosclerin A (**3.8**)

Figure 14. Proposed Structure of Arenosclerin A (**3.8**).

Assignment of relative stereochemistry for arenosclerin A (**3.8**) was identical to haliclonacyclamine E (**3.6**).[37] This comparison was based primarily on ^{13}C chemical shifts of the bis-piperidine ring system. Analysis of the ^{1}H-NMR spectrum futher supported a core structure identical to haliclonacyclamine E (**3.6**). The ^{1}H-NMR

spectrum of haliclonacyclamine E (**3.6**) presented a well-defined quartet (12 Hz) at δ 0.85 assigned to H8b. In the ^{1}H-NMR spectrum of arenosclerin A (**3.8**) an identical quartet (12 Hz) was located at δ 0.83. There were also dipolar couplings observed between H8b and H2, and H6b, H10b, and H18b (Figure 15). Furthermore, NOEs were observed between H2 and H10b, and H2 and H8b. This indicated that the C-2 stereochemistry was opposite to the haliclonacyclamines A-D (**3.2-3.4, 1.4**). Furthermore, dipolar couplings were observed between H4a and H10b indicating H2, H4a, H8b, and H10b were all located on the same face of the bis-piperidine system.[37]

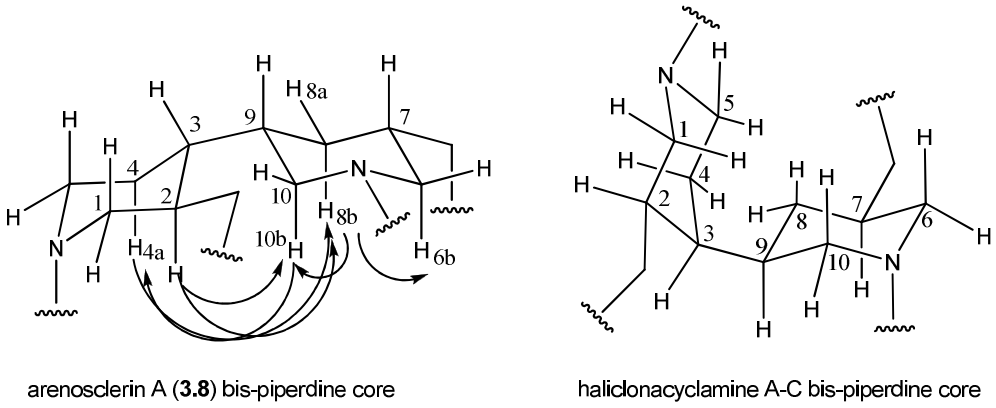
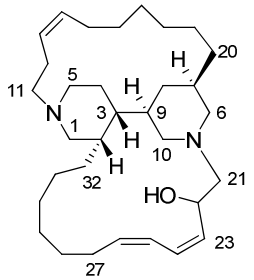


Figure 15. NOESY Correlations for Arenosclerin A (**3.8**).

Arenosclerin B (**3.9**)

The second hydroxylated tetracyclic alkaloid isolated from the sponge belonging to the order Haplosclerida, *Arenosclera brasiliensis*, was the optically active arenosclerin B (**3.9**).[37] It presented the same molecular formula, $C_{32}H_{55}N_2O$, and same number of olefins as arenosclerin A (**3.8**). Thus, it was assumed that the new alkaloid had the same

basic structure as arenosclerin A (**3.8**), but differed in relative stereochemistry. This assumption was confirmed by COSY, HMBC, and HSQC-TOCSY spectral analysis, which showed that arenosclerin B (**3.9**) had identical connectivity as arenosclerin A (**3.8**). Dipolar couplings between H12 and H15, between H22 and H25, and between H24 and H27a observed in the NOESY and ROESY spectra supported the same *cis* geometry for the three double bonds as in arenosclerin A (**3.8**).[37]



arenosclerin B (**3.9**)

Figure 16. Proposed Structure of Arenosclerin B (**3.9**).

The assignment of relative stereochemistry of the bis-piperidine core was based on analysis of the ^{1}H-NMR, NOESY, and ROESY data (Figure 17).[37] The first evidence of different stereochemistry of arenosclerin B (**3.9**) relative to arenosclerin A (**3.8**) and the haliclonacyclamines was the chemical shift of the H8b quartet (12 Hz). For haliclonacyclamine E (**3.6**) and arenosclerin A (**3.8**) the chemical shift of the H8b quartet was δ 0.85 and 0.83 respectively. However for arenosclerin B (**3.9**) H8b had a chemical shift of δ 0.58, which was indicative of a strong steric compression on H8b.[37] There were dipolar couplings observed between H5 and H3 and between H3 and H1a, indicative of

an axial orientation in a chair conformation. An NOE between H1b and H4b confirmed the assumption. Furthermore, dipolar couplings between H2 and H10a and between H3 and H10a placed H2 and H3 on the same face of the ring. Dipolar couplings between H10b and H8b, between H8b and H20a, and between H20a, H6, and H10b suggested a chair conformation and that H8b, H10b, and one of the H6 protons were all axial.[37]

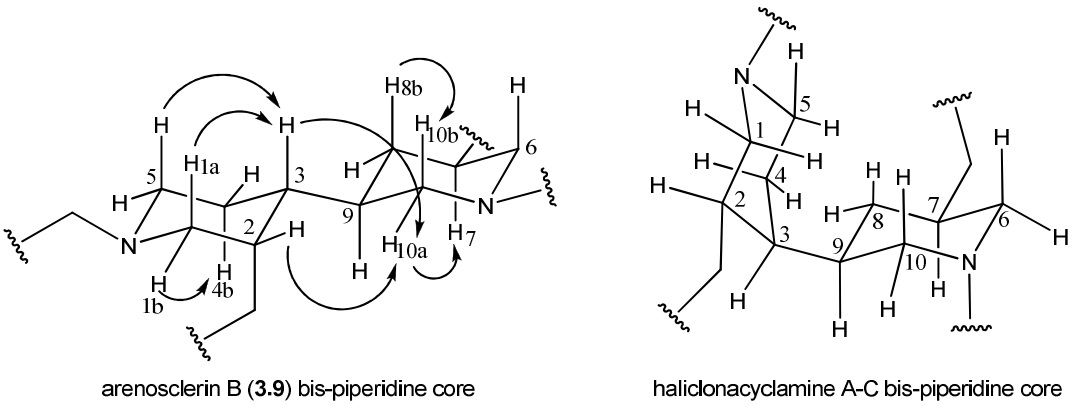


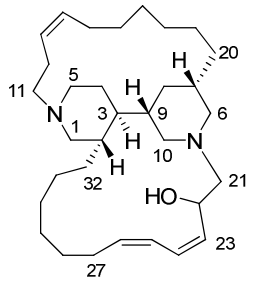
Figure 17. NOESY Correlations for Arenosclerin B (**3.9**).

An interesting long range dipolar coupling was observed between H3 and one of the H6 hydrogens. This assignment was rationalized by magnetization transfer either through H8b or through H10b.[37] Magnetization transfer (or saturation transfer) arises from a relay mechanism in which the population changes on hydrogen B (A, B, and C will be used for three generic hydrogens on a system), brought about by the initial NOE between hydrogen A and hydrogen B, and subsequently alters the population of spin C when this also shares a dipolar coupling with B.[107] However, this is typically slow to develop and long presaturation periods are needed for magnetization transfer to occur.

This is usually done by conducting a separate experiment where the long presaturation periods are employed and is typically used to study the proximity of a smaller molecule to a larger one. Nevertheless, this observation for arenosclerin B (**3.9**) suggested that H3, H8b, H10b, and one of the hydrogens of H6 were all on the same face of the molecule, justifying the shielding effect on H8b.[37] Further dipolar coupling between H7 and H10a was observed indicating that H7 and H9 were on the same face of the molecule. As in the proposed structure for haliclonacyclamine F (**3.7**) the relative stereochemistry joining the two piperidine rings is *anti*, where as the predicted stereochemistry of these tetracycles from the proposed Diels-Alder cyclization is *syn*.[37]

Arenosclerin C (**3.10**)

The third hyroxylated alkaloid isolated from *Arenosclera brasiliensis*, arenosclerin C (**3.10**, Figure 18), presented a molecular formula $C_{32}H_{55}N_2O$ and the same number of olefins as arenosclerins A and B (**3.8**, **3.9**).[37] The connectivity and carbon-carbon double bond geometry was shown to be identical by analysis of COSY, HMBC, and HSQC data.



arenosclerin C (**3.10**)

Figure 18. Proposed Structure of Arenosclerin C (**3.10**).

The relative stereochemistry of the bis-piperidine system was established by NOESY and ROESY spectra.[37] Observed dipolar couplings suggested a different relative stereochemistry than the two previously isolated arenosclerins.[37] A dipolar coupling between H3 and H10b and between H2 and H10a indicated that H3 and H2 were on opposite faces of the ring. Furthermore, the lack of dipolar couplings between H5 and H3 and between H1 and H3 suggested that the C3 relative configuration had changed.

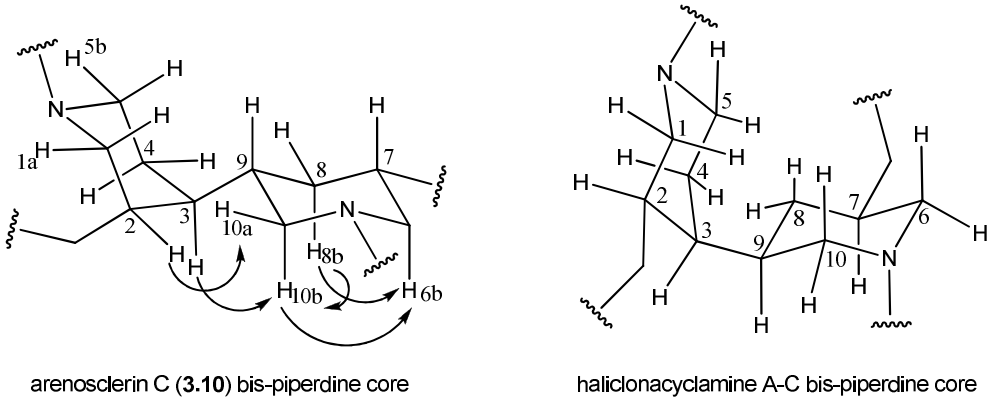
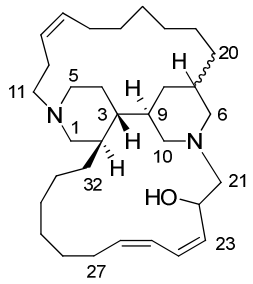


Figure 19. NOESY Correlations for Arenosclerin C (**3.10**).

Arenosclerin D (**3.11**)

In addition to arenosclerins A-C isolated from *Arenosclera brasiliensis* in 2000 by Berlinck, a new arenoseclerin was isolated from the Brazilian marine sponge *Pachychalina alcaloidifera* in 2007, arenosclerin D (**3.11**, Figure 20).[106] The Berlinck group quickly observed a close relationship of the new isolate with arenosclerins A-C, evident by a molecular formula of $C_{32}H_{55}N_2O$ and the presence of three double bonds. This initial observation confirmed by analysis of ^{1}H and ^{13}C NMR data. Analysis of COSY, HMBC, and HSQC-TOCSY spectra secured structural assignments for

arenosclerin D (**3.11**). Minor differences in the chemical shifts for H2, H7, H9, C20, and C3 suggested a different relative stereochemistry of the bis-piperidine core than arenosclerins A-C.[106]



arenosclerin D (**3.11**)

Figure 20. Tentative Structure of Arenosclerin D (**3.11**).

The relative stereochemistry for arenosclerin D (**3.11**) proved to be difficult to determine.[106] Based on the chemical shift and coupling constants of H8b (δ 0.91, dd, 7 and 11 Hz) it was deduced that this proton was in a pseudoaxial orientation. The H8a proton (δ 2.31) showed a geminal coupling constant of 11 Hz, thus the 7 Hz coupling of H8b had to be either with H7 or H9. This corresponded to either H7 or H9 in a pseudoaxial position relative to H8b. Further NOEs were observed between H8b and H5b, between H5b and H3, between H2 and H10b, and between H-10a and the methylene at C32. There were no dipolar couplings observed at all for H7, thus a tentatively proposed structure of the bis-piperidine core that can accommodate theses couplings is shown Figure 21.[106]

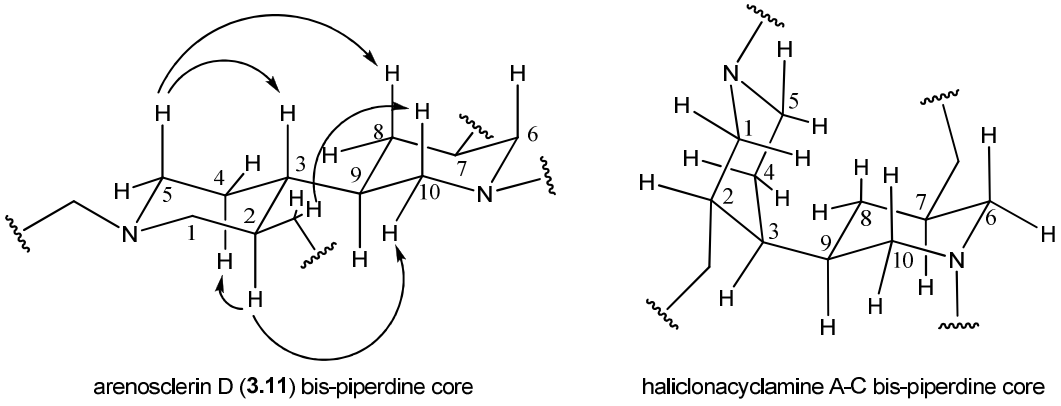


Figure 21. NOESY Correlations for Arenosclerin D (**3.11**).

Arenosclerin E (**3.12**)

In addition to arenosclerin D (**3.11**) another tetracyclic alkaloid with a molecular formula $C_{32}H_{55}N_2O$, three double bonds, and an allylic hydroxyl group was isolated, arenosclerin E (**3.12**, Figure 22).[106] COSY, HMBC, and HSQC-TOCSY spectra were anlayzed in order to make structural assignments.

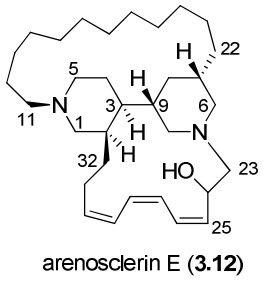


Figure 22. Proposed Structure of Arenosclerin E (**3.12**).

Their analysis yielded the first haliclonacyclamine/arenosclerin alkaloid to have a completely saturated macrocycle with a 12-carbon chain length connecting Nα to C7. Moreover, the macrocycle connecting Nβ to C2 was on 10 carbons in length and possessed an unprecedented three *cis* alkenes.[106] In all other haliclonacyclamines and arenosclerins the chain lengths are reversed, with the Nα to C7 connection being 10 carbons and the Nβ to C2 having 12 carbons.

As in the other tetracyclic alkaloids isolated by Berlinck and co-workers, the bis-piperdine relative stereochemistry was established by ROESY and NOESY correlations.[106] There were dipolar couplings between H1, H3 and H5b, placing these hydrogens in an axial orientation. NOEs were also observed between H4b and H9, between H9 and H7, between H7 and H10a, between H6b and H10b, and between H10b and H8b, indicating a conformation where H9, H7, H6b, H8b. and H10b are all axially oriented. Further, dipolar couplings between H2 and H10a, as well as between H32b and H9 indicated the relative configuration at C2 as shown in Figure 23.[106]

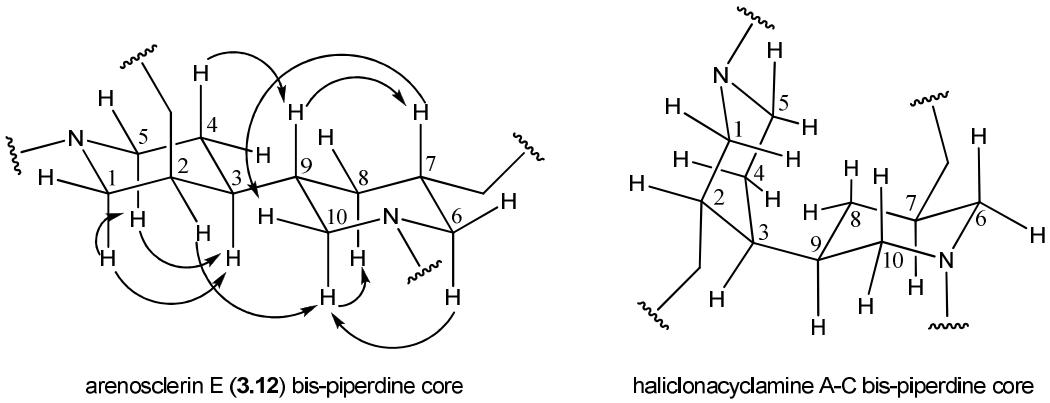


Figure 23. NOESY Correlations for Arenosclerin E (**3.12**).

Halichondramine

A new tetracyclic bis-piperidine alkaloid was isolated in 2002 from the extracts of a marine sponge belonging to the order *Halichondria* sp., in the Dahlak archipelago (the Red Sea, Eritrea), by a group from Israel.[105] Kashman and co-workers used the electron ionization mass spectrometry and ^{13}C NMR experiments to determine that halchondramine (**3.13**, Figure 24) was a diamine tetracyclic alkaloid possessing two olefins. The ^{1}H-NMR was extremely congested and made interpretation of data difficult however, a combined analysis of COSY, HMQC, HMBC, and HMQC-TOCSY spectra provided structural connectivity.[105]

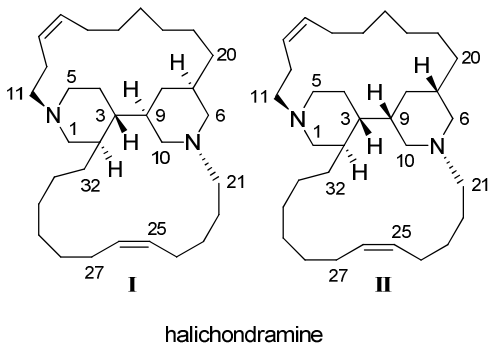


Figure 24. Two Possible Structures of Halichondramine (**3.13**).

The relative stereochemistry of halichondramine (**3.13**) was unclear.[105] Assignments were made from the multiplicity, coupling constants, and interpretation of the NOESY spectrum. The distinctive H8b quartet presented a 12.7 Hz coupling constant, due to coupling with H8a, H9, and H7. It was thus inferred that H8b, H9, and

H7 were all axial. H6b and H10b had coupling constants of 12.7 and 12.9 respectively, and were axial as well.[105] NOESY correlations between H8b and both H10b and H6b suggested the relative stereochemistry of C7 and C9 as shown in Figure 25. The H1b proton is a triplet having a coupling constant of 13 Hz due to coupling to H1a and H2, thus H1b and H2 are axial. Further NOEs between H5b and H1b, between H2 and H1a, and between H3 and both H1b and H5b provided the relative stereochemistry of C2 and C3.[105]

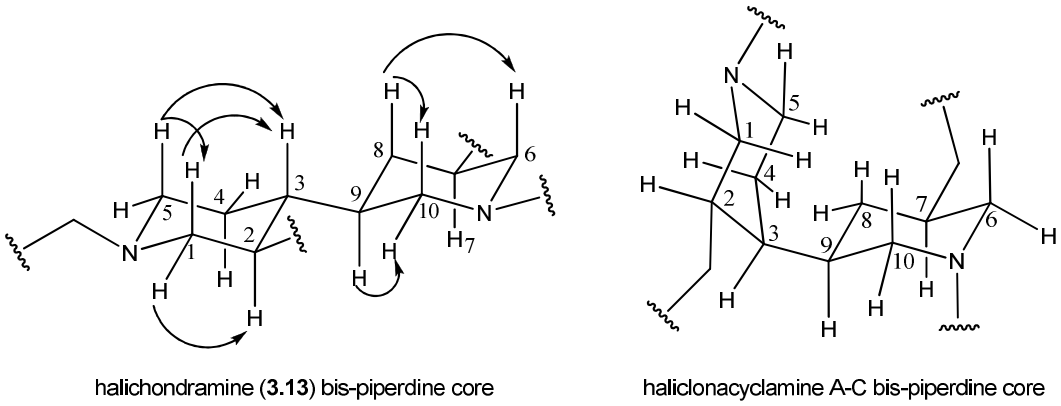


Figure 25. NOESY Correlations for Halichondramine (**3.13**).

The stereochemistry could be established for each ring based on the correlations above, but the relative stereochemistry could not be determine due to overlapping in the ^{1}H-NMR spectrum.[105] Although two possible structures of halichondramine have been proposed that could conform to the stereochemical analysis above, the absence of a COSY correlation between H3 and H9, and that H9 is a triplet (J = 13.7 Hz) indicated the relative stereochemistry in structure I (Figure 24) was more accurate. However, on the

basis of the proposed Diels-Alder cycloaddition by Baldwin and Whitehead, Kashman and co-workers prefer structure II over I (Figure 24).[105]

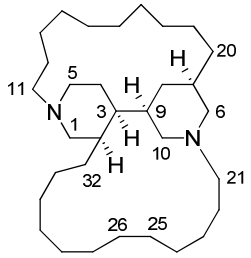
CHAPTER IV

TOTAL SYNTHESIS OF TETRAHYDROHALICLONACYCLAMINE A AND HALICLONACYCLAMINE C

Introduction

The tetracyclic alkaloids that are presumed to arrive biosynthetically from an intramolecular cycloaddition of a *bis*-dihydropyridine macrocycle (**1.9**) represent a unique class of 3-alkylpiperidines that have been the subject of modest synthetic exploration.[46,103,104] Many of these natural products not only have a distinctive architecture, but have also shown good biological activity. For example, in a P_{388} assay haliclonacyclamine C displayed an IC_{50} value of 0.7 μg/mL, displays antibacterial activity against *Bacillus subtilus*, and strong antifungal properties against *Candida Albicans* and *Trichophyton mentagrophytes*.[36]

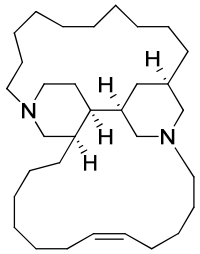
Although the exquisite biosynthetic proposal put forth by Baldwin and Whitehead suggested a biomimetic approach to the tetracyclic alkaloids, we decided to gain access to the tetracyclic alkaloids using a classical synthetic approach.[6,44] We specifically chose to first examine the synthesis of tetrahydrohaliclonacyclamine A (**3.3**) obtained from the palladium catalyzed hydrogenation of natural haliclonacyclamines A-C, as described by Garson and co-workers (Figure 26).[36]



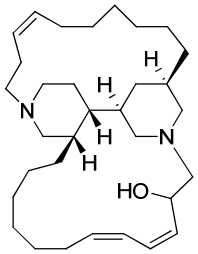
tetrahydrohaliclonacyclamine A (**3.3**)

Figure 26. Hydrogenation Product of Haliclonacyclamines A-C.

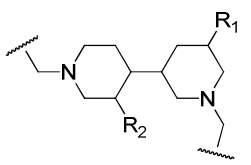
As discussed in Chapter III, one of the primary structural features that all tetracyclic 3-alkylpiperidines alkaloids have in common is a 3,4-linked bis-piperidine core (Figure 27). We expected the introduction of the four stereocenters incorporated within the 3,4-linked bis-piperidine core to be a major hurdle in our attempt to access the tetracyclic alkylpiperidine alkaloids. Tetrahydrohaliclonacyclamine A (**3.3**) was selected as the initial target in order to direct focus primarily toward the incorporation of these four stereocenters common to biosynthetically related tetracyclic 3-alkylpiperidine alkaloids, with the synthesis of haliclonacyclamine C (**1.4**) being our ultimate goal.[36]



halicloncyclamine C (**1.4**)
cis-syn-cis relative configuration



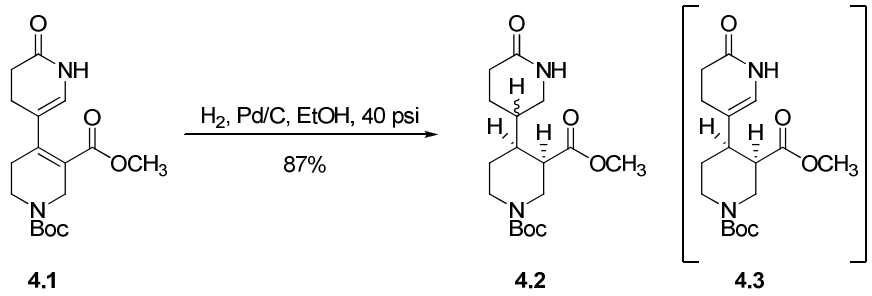
arenosclerin B (**3.9**)
cis-anti-cis relative configuaration



3, 4'-linked bis-piperidine core

Figure 27. Examples of Differing Stereochemistry for Tetracyclic Alkaloids.

We anticipated the common *cis-syn-cis* relative stereochemistry pattern of haliclonacyclamines A-C could be obtained through stereoselective hydrogenation of the 3,4-linked bis-piperidine core (c.f.**4.1**). Preliminary results were obtained by our group using a heterogeneous catalyst system as illustrated in Scheme 48.[108] Thus, treatment of diene **4.1** with Pd/C in ethanol under hydrogen at 40 psi in a Parr shaker produced hydrogenation products **4.2** and **4.3**.

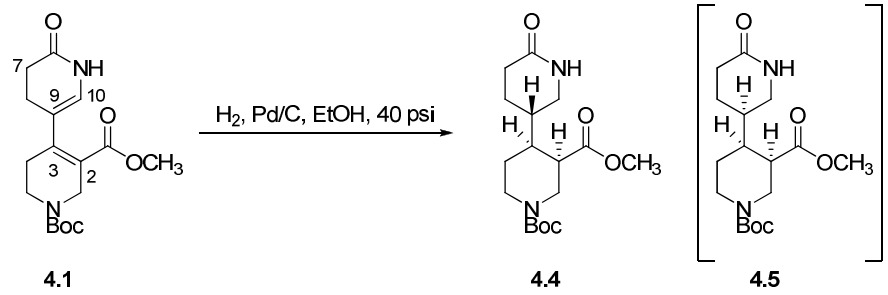


Scheme 48. Preliminary Hydrogenation Results of the Bis-piperidine Core.

Interestingly, when bis-piperidine **4.2** was analyzed by Gas Chromatography (GC), only one product was detected. Initial ^{1}H-NMR experiments at 500 MHz were not well resolved due to rotamers and little information could be obtained concerning the number of isomers formed.[108] However, when a variable temperature NMR was conducted at 75 °C in $(CD_3)_2SO$ the spectrum showed a single diastereomer. The unreacted enamide product (**4.3**) was also isolated, which indicated that the tetrasubstituted olefin was more easily reduced than the enamide olefin (Scheme 48).[108]

Conformational analysis was then carried out on partially reduced enamide **4.3** using molecular modeling in macromodel (MMFF94 force field, water GB/SA model).[108]

The molecular modeling clearly showed that the methyl ester moiety blocks one face of the northern ring of **4.1**. Hydrogenation would therefore take place on the opposite face of this ring to yielding the undesried *cis-anti-cis* isomer. Using this molecular modeling analysis, it was assumed that the hydrogenation of diene **4.1** leads to the formation of diastereomer **4.4** and not the desired diastereomer **4.5** as illustrated in Scheme 49.[108] Unfortunately, attempts to crystallize hydrogenation product **4.2** were unsuccessful in order to confirm this hypothesis.[108]

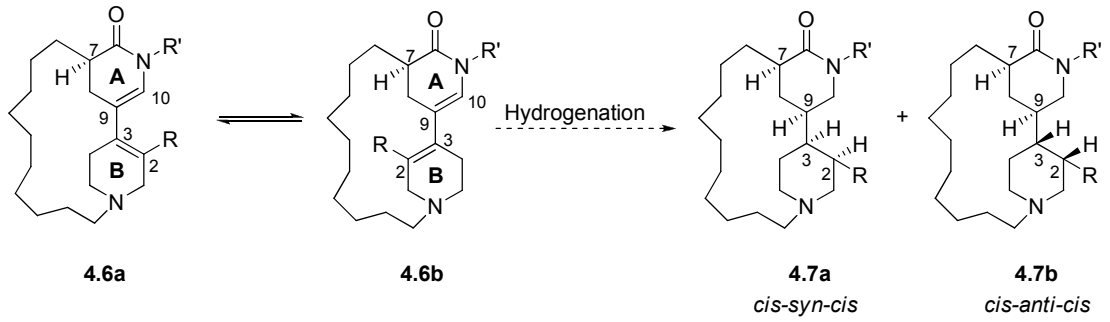


Scheme 49. Predicted Hydrogenation Product of Diene **4.1**.

Armed with the initial results above, we chose to develop a synthetic strategy toward tetrahydrohaliclonacyclamine A (**3.3**) and haliclonacyclamine C (**1.4**) that would support peripheral hydrogenation of the C9-C10 alkene by incorporation of the macrocycle, in order to obtain the desired *cis* relationship between the C7 and C9 stereocenters. This concept of peripheral stereocontrol was first introduced by Still in the context of periplanone B by accessing one face of a carbonyl, with the other side being hindered by a medium ring.[109] Vedejs further elaborated on peripheral control as a means of stereoselective reaction by using the directing properties of an allylic methyl

substituent in 8-15 membered rings to provide a single epoxide.[110,111] Schreiber later applied this strategy to epoxidize macrocycles containing 1,5-dienes using conformer control.[112] Other work using a peripheral control approach in the context of epoxidation been carried out by Mulzer and Weiler as well.[113,114]

We were interested in extending this type of approach to the hydrogenation of a substrate similar to diene **4.2**, with the western macrocycle already in place to dictate facial preference and provide the correct relative stereochemistry between C7 and C9 (Scheme 50). While this tactic provided confidence in potentially securing a *cis* relationship between C7 and C9, we were unsure of the diastereofacial selectivity of the hydrogenation of the C2-C3 olefin. Hydrogenation of bis-piperidine **4.6** might be problematic as ring B incorporates a stereochemically dynamic nitrogen atom. This could potentially result in the production of two diastereomers, which we have denoted as our desired *cis-syn-cis* isomer and the *cis-anti-cis* isomer as shown in Scheme 50.



Scheme 50. Hydrogenation Strategy Toward Tetrahydrohaliclonacyclamine A (**3.3**).

Conformational analysis was carried out on **4.6** by evaluating a series of stochastic conformational settings (MMFF94 force field). Two representative low energy

conformations are shown in Figure 28. Based on the molecular modeling, the macrocycle present in conformation A clearly blocks one face of the bis-piperidine system, and hydrogenation would therefore take place on the opposite face of this ring to produce the desired *cis-syn-cis* relative stereochemistry. However, conformation B represents a system similar to diene **4.6b**, which upon hydrogenation would lead to the undesired *cis-anti-cis* relative stereochemistry. This simple model supports our strategy represented in Scheme 50.

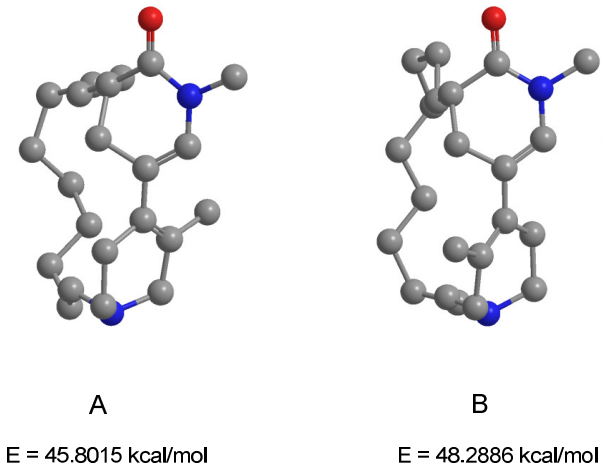
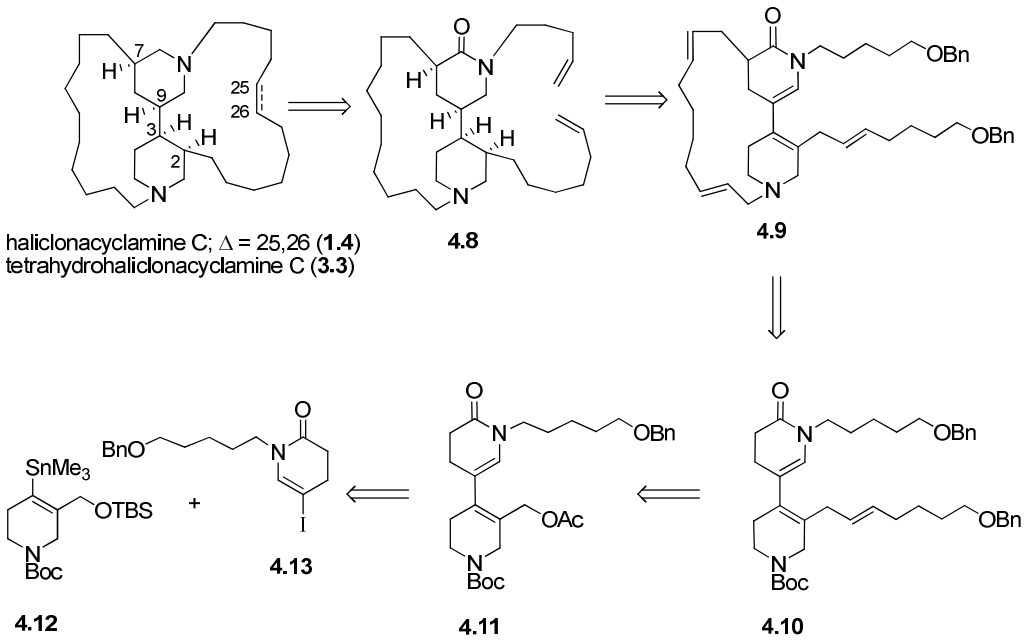


Figure 28. Conformation Analysis of **4.6** using a MMFF94 Force Fiels.

An N-Alkylation Route to Tetrahydrohaliclonacyclamine A

With a proposal to access the correct relative stereochemistry incorporated within the core, we needed to devise a route to install the western macrocycle represented in diene **4.6a**, as well as the unsaturated eastern macrocycle with the correct *cis* geometry as required for haliclonacyclamine C (**1.4**). An initial retrosynthetic analysis, outlined in Scheme 51, requires lactam reduction and a key ring-closing metathesis (RCM) of the

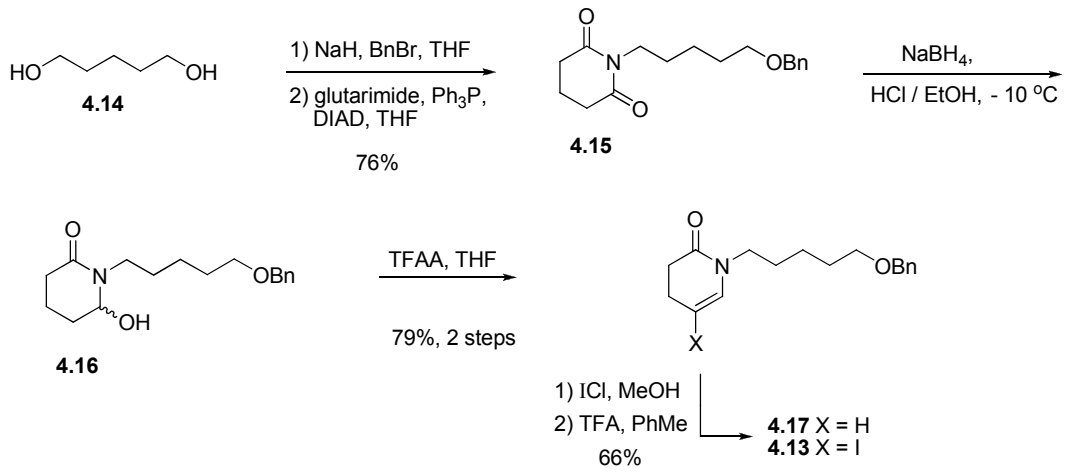
advanced intermediate **4.8**.[115,116] It was envisioned that the terminal diene **4.8** would be obtained from **4.9** via peripheral hydrogenation, oxidation to the dialdehyde, followed by olefination. Diene **4.9** would be obtained via alkylation of an amide enolate, and N-alkylation[50] of **4.10** to construct what would eventually become the saturated macrocycle of haliclonacyclamine C (**1.4**). Alkene **4.10** would be synthesized through cross-coupling of allylic acetate **4.11** and the appropriate vinyl stannane. Finally, the 3,4'-linked bis-piperidine core would be prepared by a Stille cross-coupling reaction of the independently prepared vinyl tin **4.12** and vinyl iodide **4.13**.



Scheme 51. Initial Retrosynthetic Analysis of Haliclonacyclamine C (**1.4**).

At the outset of the project, the goal was to first produce the bis-piperidine core by utilizing a carbon-carbon bond forming cross-coupling reaction. We began by

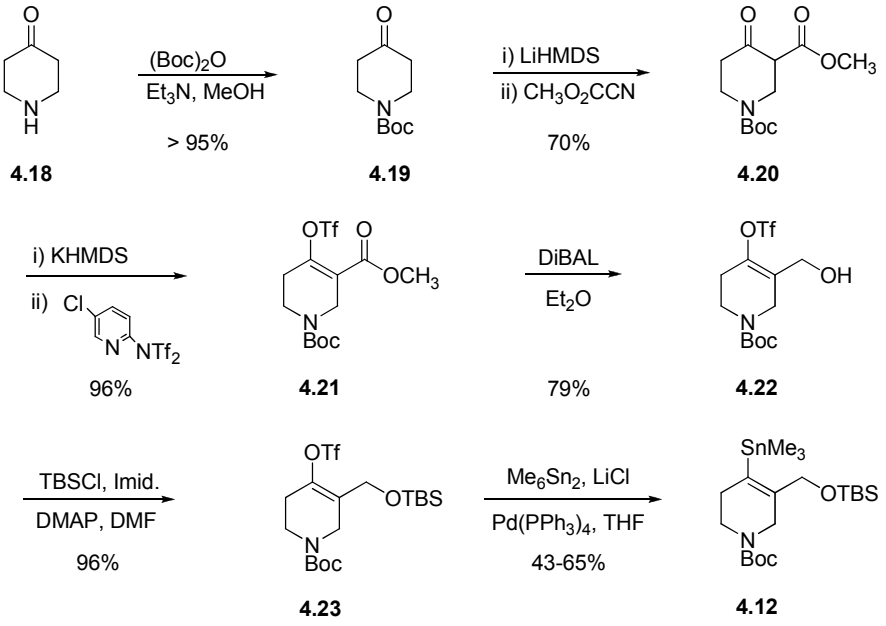
preparing 3-iodoenamide **4.13** from glutarimide and as illustrated in Scheme 52. Iodoenamide **4.13** would serve as one of two piperidine units to produce the C3-C9 bond.



Scheme 52. Preparation of Vinyl Iodide **4.13**.

The reaction sequence was initiated with a Mitsunobu[117] reaction between glutarimide and mono benzylated 1,5-pentanediol to yield imide **4.15** (Scheme 52). Sodium borohydride reduction followed by treatment with trifluoroacetic anhydride yielded enamine **4.17** in 79% overall yield.[118] This transformation was originally carried out with boron trifluoride etherate (30-40%), but trifluoroacetic anhydride gave improved yields and shorter reaction times. Enamine **4.17** was then treated with iodine monochloride in methanol resulting a regioselective iodo methoxylation to afford an intermediate δ-methoxylactam that was immediately subjected to a catalytic amount of trifluoroacetic acid in refluxing toluene for 15 minutes to furnish iodoenamide **7** in 66% yield from **4.13**.[119]

With a successful route toward iodoenamide **4.13** complete attention turned to the construction of the cross-coupling counterpart **4.12**. This synthesis of **4.12** started with *t*-butyl carbamate protection of commercially available 4-piperidone (**4.18**) to give carbamate **4.19**, which was treated with lithium hexamethyldisilazide followed by a methyl cyanoformate quench to generate β-keto ester **4.20** (Scheme 53).[120,121]

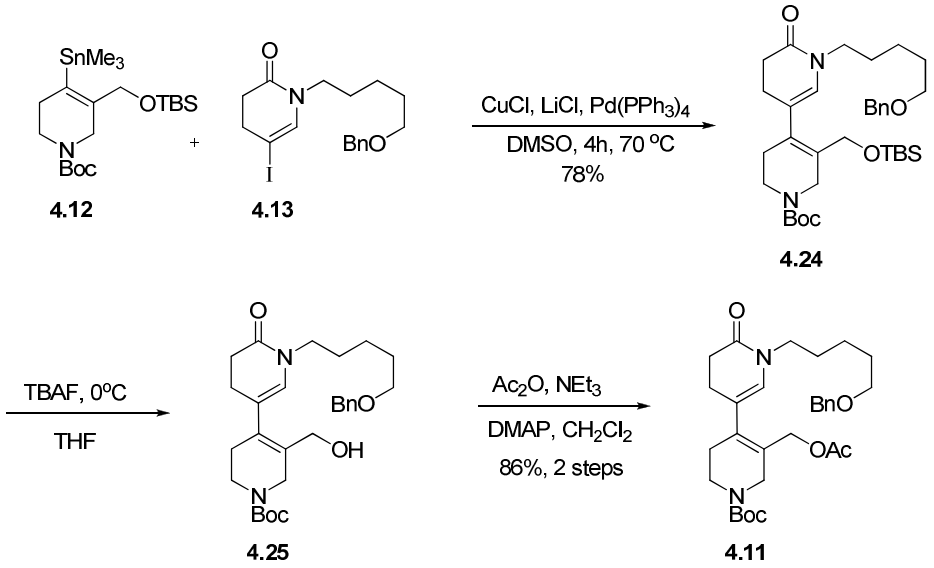


Scheme 53. Preparation of Vinyl Stannane **4.12**.

The β-keto ester was then converted to vinyl triflate **4.21** by treatment with potassium hexamethyldisilazide followed by the addition of Comins' reagent.[122] Reduction of **4.21** with diisobutylaluminium hydride afforded allylic alcohol **4.22**, which was immediately converted to the silyl ether (**4.23**) without further purification in

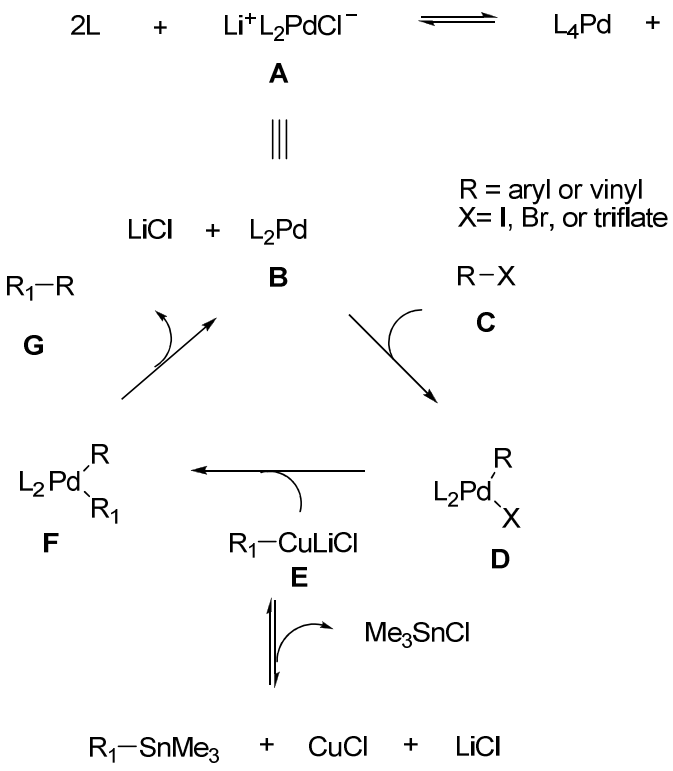
preparation of the Stille coupling.[123,124] Vinyl triflate **4.23** was treated with hexamethyldistannane to yield desired vinyl stannane **4.12**.[24]

The stage was now set for a cross-coupling between vinyl stannane **4.12** and iodoenamide **4.13**. Optimal conditions for the cross-coupling employed cuprous chloride as an accelerant to provided bis-piperidine **4.24** in 78% yield.[125,126] To this end, Corey-Liebskind conditions (copper chloride, lithium chloride, and tetrakis(triphenylphosphine) palladium(0) in dimethyl sulfoxide) and heating for 4 hours gave diene **20** in 50-60% yield. It was later found that shorter reaction times between 2 and 4 hours gave yields greater than 70%. However, reaction times longer than 4 hours led to slow decomposition of the desired product. Exchange of the TBS ether (**4.24**) for allylic acetate **4.11** set the stage for a second cross-coupling reaction. (Scheme 54).



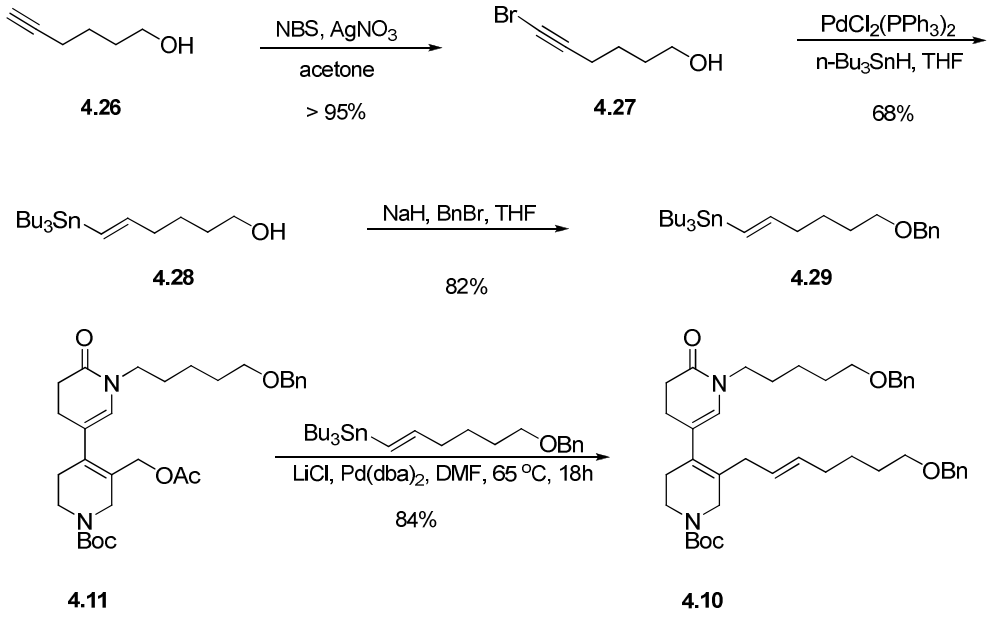
Scheme 54. Completion of the Bis-piperidine Core.

The proposed mechanism for the general cuprous chloride accerlated Stille coupling is represented in Scheme 55.[125] Thus, a 18-electron palladium(0) species (**B**) is generated, which then reacts with an organic electrophile (**C**) through oxidative addition to form the 16-electron palladium(II) intermediate **D**. The cuprous chloride serves to convert the vinylstannane to a more reactive vinylcopper species (**E**) in order to accelerate transmetalation. Intermediate **D** then reacts with vinylcopper species **E** to form a key palladium(II) intermediate **F**. The desired coupling product **G** is then produced by reductive elimination, which regenerates active catalyst **B**.



Scheme 55. Mechanism of the Cuprous Chloride Accelerated Stille Coupling.

We next wanted required a cross-coupling partner for allylic acetate **4.11**. Due to our success with the vinyl stannane for the synthesis of the bis-piperidine core, we began preparation of another vinyl stannane species for the allylic acetate cross-coupling. Thus, commercially available 5-hexyn-1-ol (**4.26**) was treated with *N*-bromosuccinimide and silver nitrate in acetone to give alkynyl bromide **4.27** in 95% yield, followed by hydrostannylation to yield vinyl stannane **4.28** (Scheme 56).[127-129]

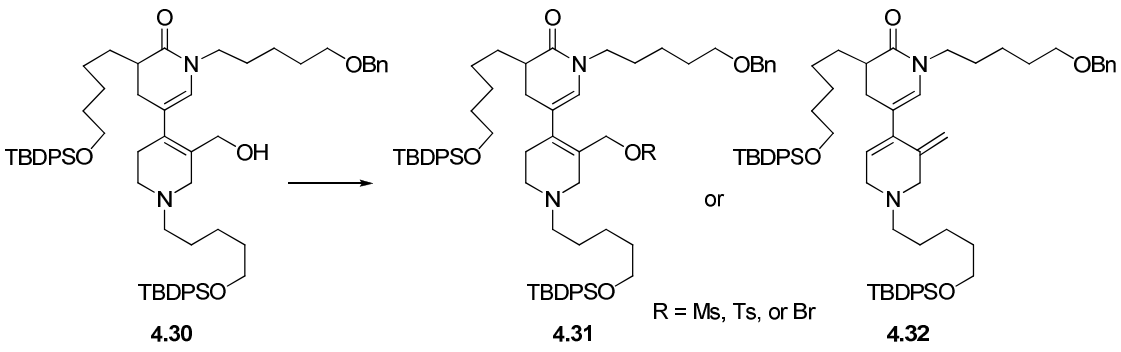


Scheme 56. Further Elaboration to Tetrahydroaliclonacyclamine A (**3.3**).

Next, the primary alcohol of **4.28** was benzyl protected to afford vinyl stannane **4.29.** It is noteworthy that by protecting the alcohol last and quenching the benzyl protection reaction with sodium bicarbonate a minimal amount of stannane protolysis product was observed.[130] With vinyl stannane **4.29** in hand, the Stille cross-coupling was

attempted with allylic acetate **4.11**. Using conditions developed by Stille and Hegedus,[131] allylic acetate **4.11** and vinyl stannane **4.29** were dissolved in dimethylformamide, treated with lithium chloride, bis(dibenzylideneacetone) palladium(0), and heated to 70 ^{o}C for 18 hours providing advanced precursor **4.10** (Scheme 56).

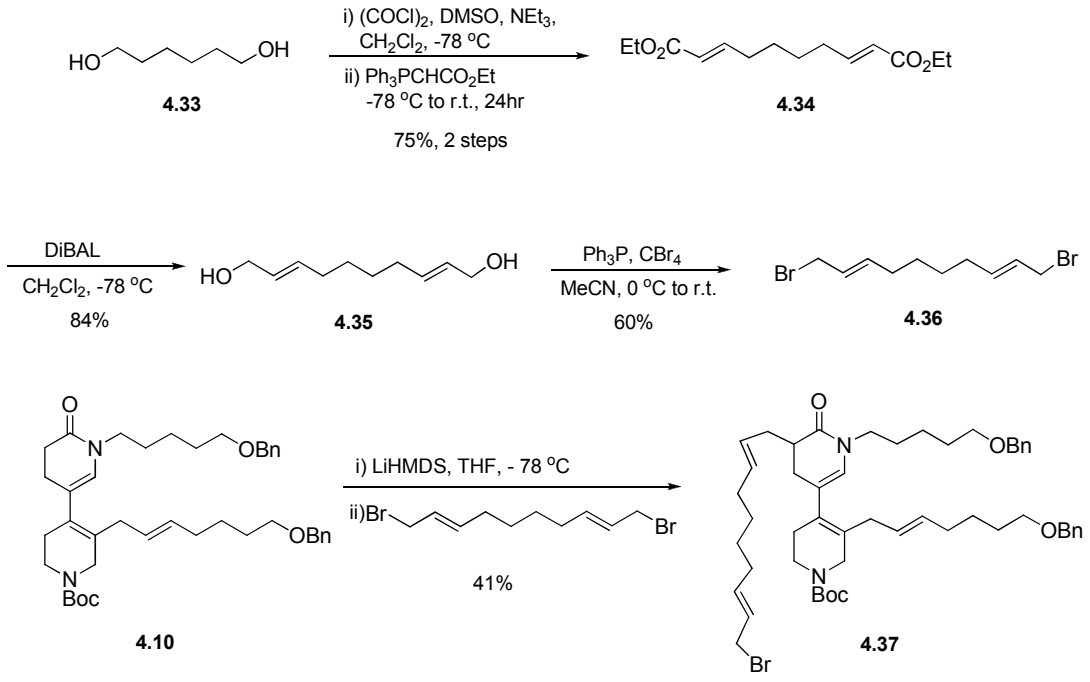
Interestingly, in the course of examining a protected route to the western macrocycle of tetrahydrohaliclonacyclamine A (**3.3**), we also examined a displacement method in place of an allylic acetate Stille coupling (Table 1). This would potentially provide us with the desired product (**4.10**) without having to use expensive palladium catalysts or vinyl stannanes. Unfortunately, all attempts to install a proper leaving group in preparation for the substitution led to an undesired elimination product **4.32**.



Experiment #	Conditions	Results
1	TsCl, pyridine, CH_2Cl_2, 0^{o}C	Elimination
2	MsCl, NEt_3, CH_2Cl_2, 0^{o}C	Elimination
3	TsCl, NEt_3, DMAP, CH_2Cl_2, 0^{o}C	Elimination
4	MsCl, NEt_3, CH_2Cl_2, -78^{o}C	Elimination
5	PPh_3, CBr_4, CH_2Cl_2, 0^{o}C	Elimination

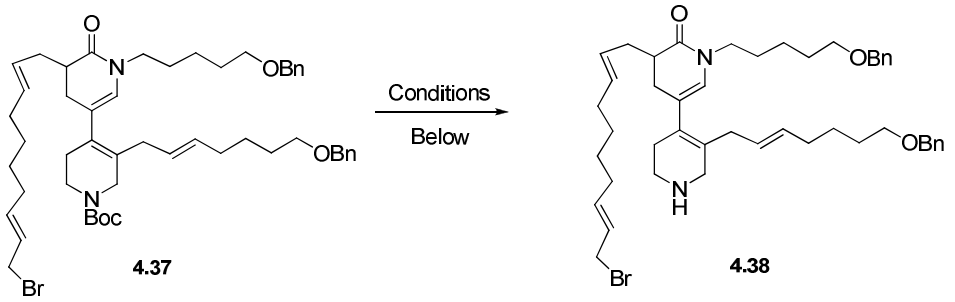
Table 1. Undesired Elimination to Triene **4.32**.

We quickly turned our attention back to the formation of the eastern macrocycle of tetrahydrohaliclonacyclamine A (**3.3**). Beginning with 1,6-hexanediol a one pot double oxidation, double Wittig[132] was performed using Swern[133] conditions, followed by the addition of (carboethoxymethylene)triphenylphosphorane to give the diester **4.34** in 75% yield (Scheme 57).[134] The diester was reduced to diol **4.35** by treatment with diisobutylaluminum hydride, followed by conversion to dibromide **4.36** using triphenylphosphine and carbon tetrabromide. Having dibromide **4.36** in hand, we submitted lactam **4.10** to a solution of lithium hexamethyldisilazide in tetrahydrofuran at -78 ^{o}C. The enolate was then added to a stirring solution of dibromide **4.36** in tetrahydrofuran at -78 ^{o}C to provide alkylation product **4.37** in an unoptimized yield of 41%.



Scheme 57. Macrocyclization Precusor **4.37**.

We were now in position to attempt the first macrocyclic closure. To prepare for macrocyclization through N-alkylation,[50] we needed to remove the carbamate protecting group on **4.37**. Unfortunately, all efforts to remove the Boc protecting group resulted in decomposition of starting material as illustrated in Table 2.[135] We attempted to use the crude material from one of the deprotection reactions in the N-alkylation step without any further purification (although no product could be isolated). Ring closure under basic conditions (*N,N*-diisopropylethylamine) yielded unpromising results.



Experiment #	Conditions	Results
1	TFA, CH_2Cl_2, 0°C	Decomposition
2	HCl ,EtOH, 0°C to r.t.	Decomposition
3	TFA, EtOH, 0°C	Decomposition
4	PhOH, TMSCl, CH_2Cl_2, r.t.	Decomposition
5	$AlCl_3$, CH_2Cl_2, 0°C	Decomposition
6	TBSOTf, 2,6-lutidine, CH_2Cl_2, r.t	Decomposition

Table 2. Attempted Carbamate Deprotection.

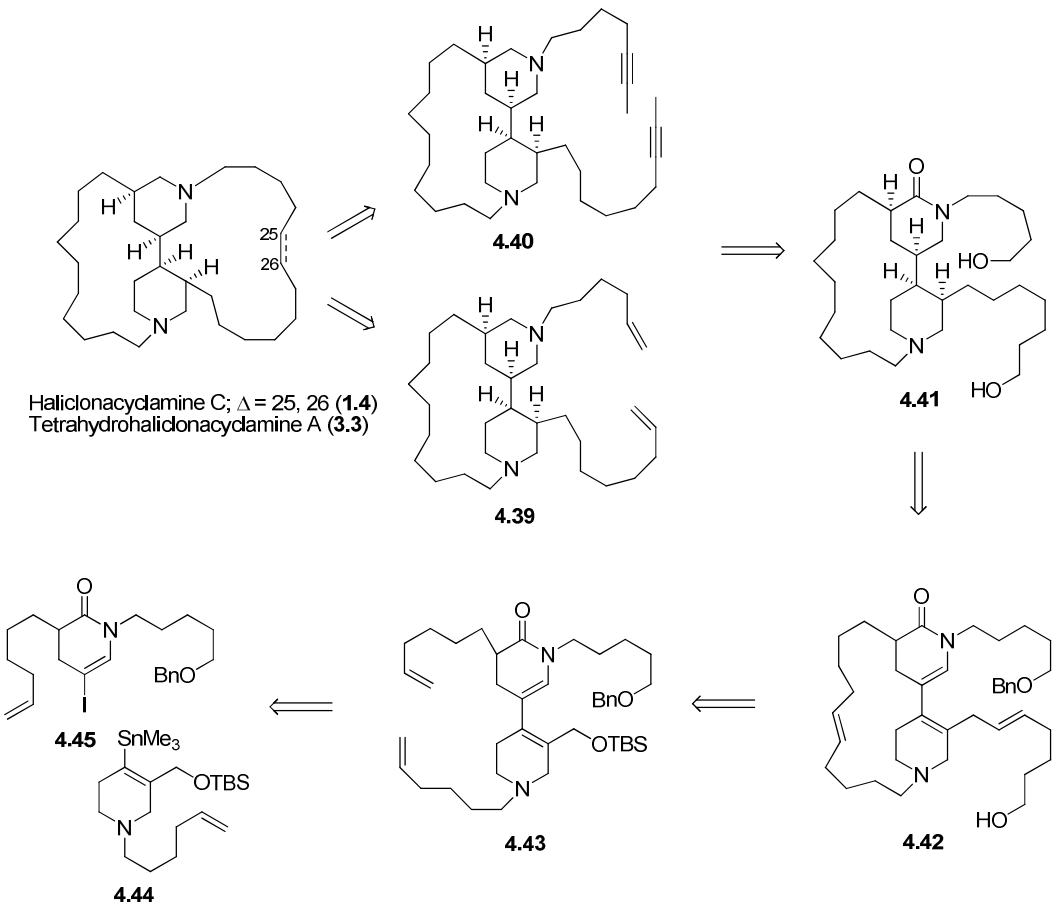
At this point in our synthetic endeavor we had exhausted all of our material to produce **4.37** and were now at crossroads in the synthesis. It was necessary to

contemplate a synthetic appraoch that would allow for reproducible closure of the western macrocycle in good yield and set the stage for the key hydrogenation of the core. We could produce more of our alkylation precursor **4.37** and further examine deprotection conditions, or alter the current route to a more feasible approach. Since we had been unable to successfully remove the carbamate protecting to even attempt macrocyclic ring closure by N-alkylation, we choose to modify our strategy.

A Ring Closing Metathesis Approach to Tetrahydrohaliclonacyclamine A

Although we were unable to form the western macrocycle in the previous route, we decided to employ the two Stille[125,131] cross-couplings and create an altered route to arrive at tetrahydrohaliclonacyclamine A (**3.3**). The new strategy involved the installation of two terminal olefins early in the synthesis and closure of the ring by a metathesis reaction[115,116,136] in place of the failed N-alkylation. Our original retrosynthesis had already outlined a ring closing metathesis approach for the closure of the eastern unsaturated macrocycle of haliclonacyclamine C (**1.4**) Thus, this new approach would not only solve the problem of closing the eastern ring, but provide information on the ring-closing metathesis catalysts, as we had considered the incompatibility of tertiary amines in this context.[137]

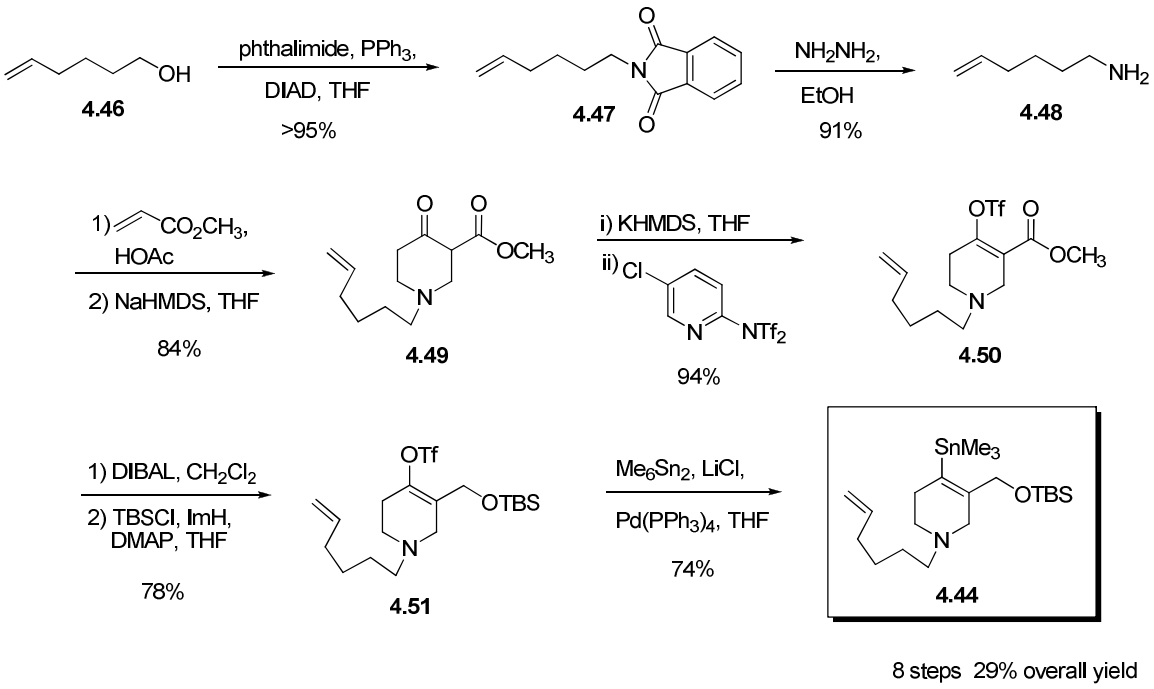
Having established a route to the bis-piperdine core we had two major uncertainties to consider; the diastereoselectivity of the hydrogenation and the *E*/*Z* ratio obtained from a ring-closing alkene metathesis to provide the unsaturated macrocycle. For the latter, we had considered using an alkyne metathesis/Lindlar semi-reduction approach.[138] A complete retrosynthetic analysis is shown in Scheme 58.



Scheme 58. Revised Retrosynthetic Analysis of Haliclonacyclamine C (**1.4**).

A ring closing (alkene or alkyne) metathesis of the advanced intermediate **4.39** or **4.40** would provide tetrahydrohaliclonacyclamine A (**3.3**) and haliclonacyclamine C (**1.4**). It was envisioned that terminal diene **4.39**, or terminal diyne **4.40**, would be obtained from **4.41** via oxidation to the dialdehyde, followed by either olefination or alkynlation, and lactam reduction. Diol **4.41** was thought to arrive from peripheral hydrogenation as previously discussed. Tetraene **4.42** would be obtained via a ring-closing metathesis reaction and cross-coupling of **4.43**. Finally, the bis-piperidine core would be prepared by a similar carbon-carbon bond forming cross coupling reaction using Corey-Liebskind conditions, with an alkylated vinyl tin **4.44** and vinyl iodide **4.45**.

Our new synthesis began with an eight step preparation of vinyl stannane **4.44** from commercially available 5-hexen-1-ol (Scheme 59). This would serve as the first of two piperidine units used to construct the bis-piperidine core in preparation for closure of the western macrocycle by ring closing metathesis. The reaction sequence started with Mitsunobu[117] condensation of phthalimide with 5-hexen-1-ol to provide imide **4.47**. Treatment of imide **4.47** with hydrazine resulted in primary amine **4.48** in good yield.[139] β-keto ester **4.49** was prepared in two steps by a double Michael addition followed by a Dieckmann cyclization.[140-142]

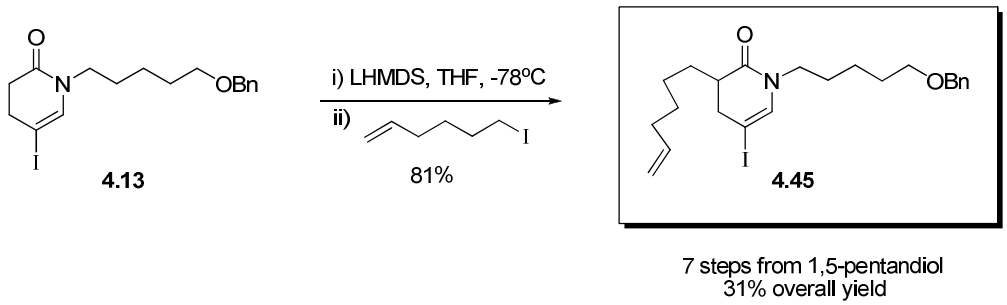


Scheme 59. Preparation of Alkylated Vinyl Stannane **4.44**.

With the requisite terminal alkene now in place for the ring-closing metathesis reaction we followed our previous route (Scheme 53) to complete the synthesis of vinyl

stannane **4.44**. Thus, β-keto ester **4.49** was converted to the intermediate enol triflate **4.50** that was subsequently reduced to an allylic alcohol.[122] Silylation of the allylic alcohol paved the way for Stille coupling with hexamethyldistannane to provide vinyl stannane **4.44**.[124]

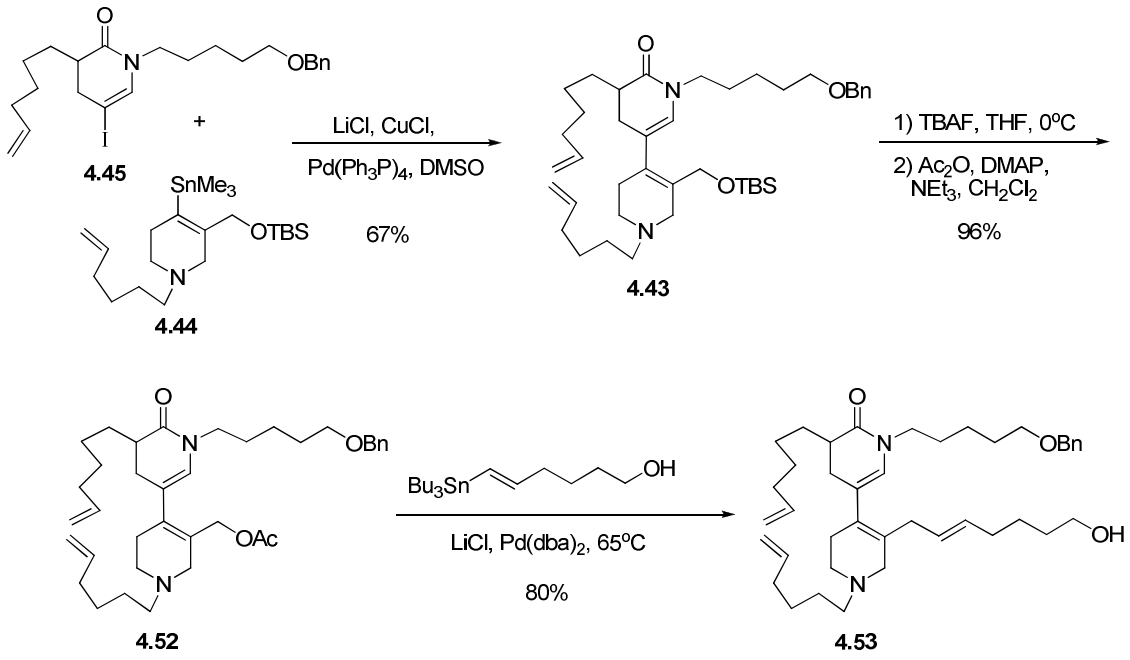
We next had to prepare the proper counterpart for the cross-coupling with vinyl stannane **4.44**, which would then set the stage for a ring closing metathesis reaction. This was accomplished by deprotonation of the previously prepared iodoenamide **4.13** (Scheme 52) with lithium hexamethyldisilazide in tetrahydrofuran at -78 °C followed by the addition of 6-iodo-1-hexene[143] to yield iodoenamide **4.45** (Scheme 60). This completed the second of our requisite two piperidine units, in 31% overall yield from 1,5-pentandiol (**4.4**, Scheme 52), used to construct the bis-piperidine core in preparation for closure of the western macrocycle by ring-closing metathesis.



Scheme 60. Preparation of Alkylated Vinyl Iodide **4.45**.

By employing the cuprous(I) chloride accelerated Stille cross coupling previously described the assembly of bis piperidine **4.43** was complete (Scheme 61). Removal of the silyl protecting group and treatment with acetic anhydride provided allyic acetate **4.52**

in excellent yield. We then utilized a second Stille coupling with unprotected (E)-6-(tributylstannyl)hex-5-1-ol[144] to provide ring closing metathesis substrate **4.53**.



Scheme 61. Stille Cross Couplings.

Closure of Western Macrocycle

With all carbons now in place we began to investigate the first of two ring-closing metathesis reactions. The ruthenium carbene complexes originally developed by Grubbs are known to be far superior to the molybdenum systems developed by Schrock in terms of handling and reactivity for metathesis of alkenes.[137] The Grubbs' catalysts are robust enough that they can be weighed in air and still provide active catalyst solutions, which is inconceivable with all other structurally defined molybdenum catalysts and precatalysts known to date (Figure 29).[115,137]

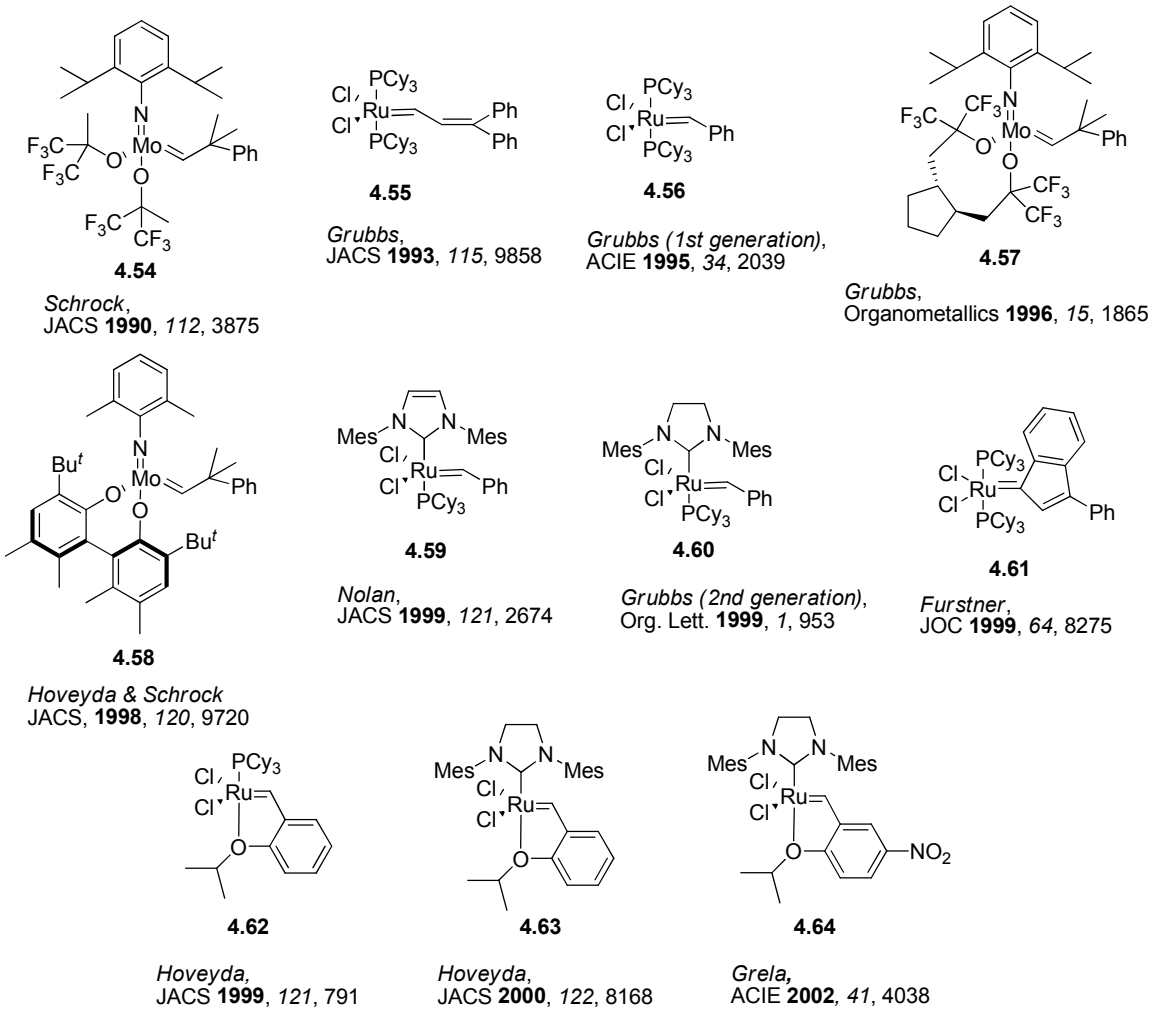
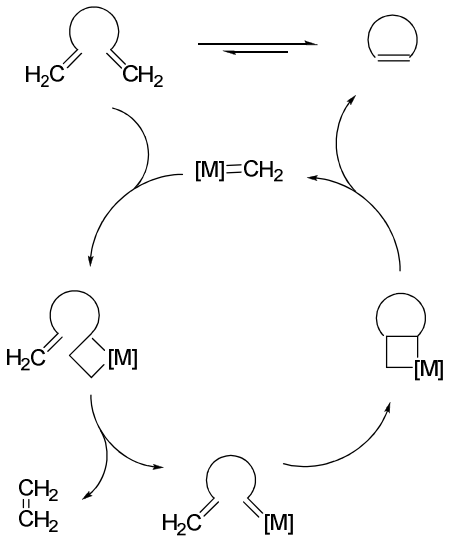


Figure 29. Alkene Ring-Closing Metathesis Catalysts.

Moreover, the molybdenum systems are known to react with acids, alcohols, and aldehydes, where the ruthenium complexes are stable to these functional groups.[137,145] However, the commonly used first and second generation ruthenium carbene systems[146,147] are not always an effective catalyst with substrates incorporating sulfides or amines. Conversion to the corresponding ammonium salts is sometimes necessary in the

latter case for metathesis to occur.[137] We had anticipated that this could be a problem for our system due to the tertiary amine present in the bis-piperidine core.

Although we wanted to effect a ring-closing metathesis for our substrate (**4.53**), alkene metathesis can occur in three types of related reactions: 1) ring opening metathesis polymerization (ROMP); 2) acyclic cross metathesis, which can result in polymers (ADMET); 3) ring-closing metathesis.[115] It is generally accepted that the mechanism for acyclic and cyclic metathesis occurs through a series of a ruthenium carbene complexes and metacyclobutanes.[136] A basic catalytic cycle for a ring-closing metathesis is shown in Scheme 62.[136]



Scheme 62. General Mechanism for Ring-Closing Alkene Metathesis.

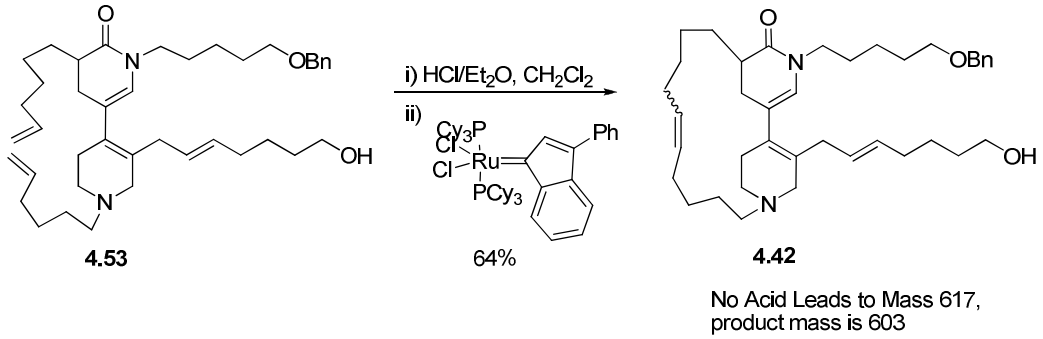
There are three main factors that govern the success of a ring-closing metathesis reaction. The forward progress of a ring-closing metathesis reaction is entropically driven because ring-closing metathesis cuts one substrate molecule into two products.

Typically the two products are ethylene gas and the desired cycloalkene. The sensitivity of the catalyst to the substitution pattern of the olefin, as this constitutes a kinetic obstacle. Also, there is usually competition between competing ring-closing and acyclic diene metathesis polymerization (ADMET), which can be somewhat controlled by dilution and preexisting conformational constraints in the substrate.[136] The potential formation of dimers is a typical problem with the closure of large macrocycles and was a concern we would take into consideration.

We decided to first attempt the closure of diene **4.53** as the free amine to form the western 17-membered macrocycle of tetrahydrohaliclonacyclamine A (**3.3**). While amines are typically not compatible with the ruthenium catalyst systems, there was literature precedent for ring closure of large macrocycles in the presence of amines using ruthenium catalysts specifically in the context of 3-alkylpiperdine natural product synthesis, as discussed in chapter II.[51,88] Thus, we submitted diene **4.53** to both Grubbs' first and second generation catalysts (**4.56** and **4.60**) in refluxing toluene and dichloromethane. Unfortunately, our desired product was not formed. We noticed that consumption of starting material had occurred. Analyzing the crude reaction mixture by LC/MS (Agilent Technologies 6130 Quadrupole instrument) provided a consistent mass of 617, with the molecular weight of our desired product being 603. Although we were unable to provide a structure for the unidentified substance corresponding to a mass of 617, we believe our starting material possessing the tertiary amine interacted in an unfavorable way with the ruthenium catalyst and shut down the catalytic cycle.[137]

The next step was to attempt the closure using the quaternary ammonium salt of diene **4.53**. To our delight, product was obtained using both Grubbs' first generation

catalyst (**4.56**) and Fürstner's ruthenium indenylidene catalyst[148] (**4.61**) in refluxing dichloromethane (Scheme 63). Although we could obtain product with both catalysts in good yield, we choose to use Fürstner's ruthenium indenylidene catalyst (**4.61**) to provide tricycle **4.42** as almost exclusively the *trans* isomer (> 90%) due to cost and ease of handing in air.



Scheme 63. Closure of the Eastern Macrocycle.

Removal of Ruthenium By-Products

It was now time to test the peripheral hydrogenation in order to set correct relative incorporated within the bis-piperidine core. We wanted examined a stepwise approach by removing the benzyl protecting group and reducing the olefins residing in the alkyl chains of tetraene **4.42**, to later focus on hydrogenation of the core. Although we had obtained the hydrogenation precursor **4.42**, there was concern regarding the purity of our metathesis product. Due to the polar nature of tricycle **4.42**, we obtained a product that was contaminated with a substantial amount of residual ruthenium left over from the

reaction, despite examing multiple purification methods. This problem has been address by various research groups and some solutions are represented in Figure 30 below.

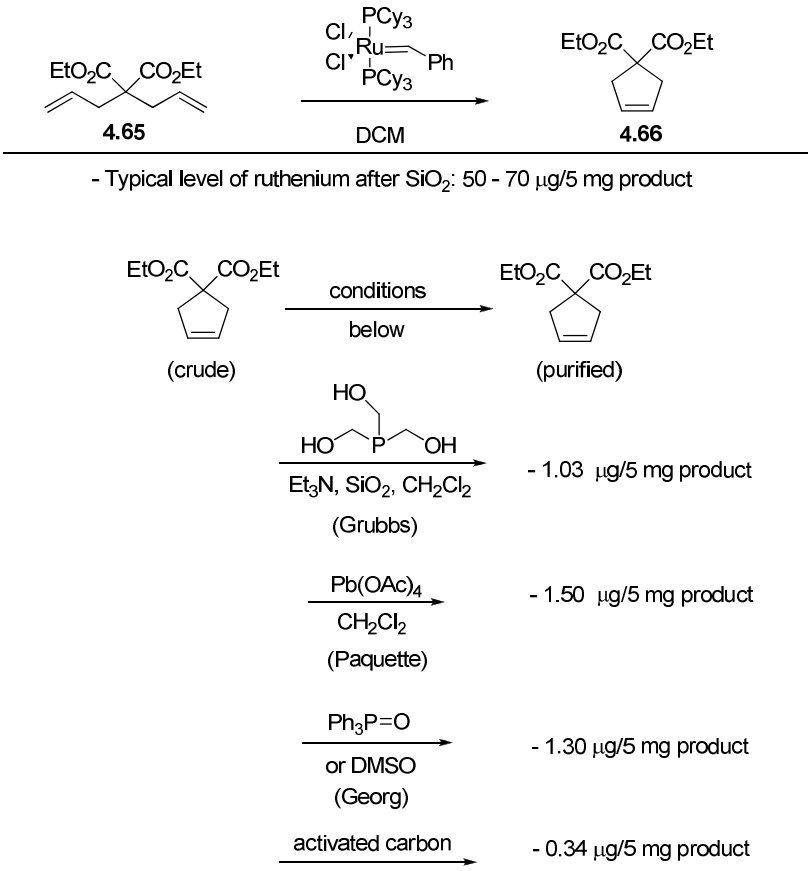


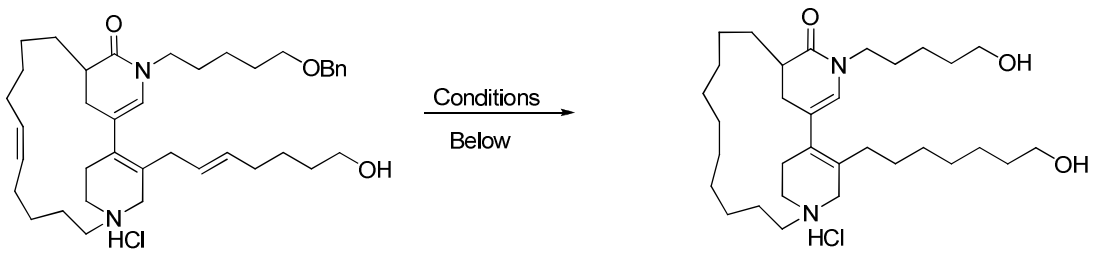
Figure 30. Methods for Ruthenium Removal.

While all are viable methods, we were discouraged by both the methods developed by Grubbs and Paquette.[149,150] The Grubbs method involved using tris(hydroxymethyl)phosphine to react with residual ruthenium by-products that would later be removed during aqueous work-up. However, tris(hydroxymethyl)phosphine is an extremely expensive reagent and we sought other means to remedy this problem. We

were also unenthusiastic about the Paquette method due to the harsh reaction conditions involved and potential exchange of ruthenium impurities for lead impurities. Attempts using the method developed by Georg involving polymer-bound triphenylphosphine oxide unfortunately did not provide a product that was much cleaner than we had originally isolated.[151] Removal with activated carbon leads to the same unfavorable result.[152] The problem was finally resolved by use of Varian strong cation exchange chromatography.[153] Using our ruthenium contaminated crude reaction mixture we were able to wash out ruthenium by-products using methanol as the eluent, and then releasing our desired tricycle from the acidic stationary phase using a 2N solution of ammonia in methanol to provide tricycle **4.42** with significantly less ruthenium contamination.[153]

Hydrogenation of the Bis-piperidine Core

With pure tricycle **4.42** in hand, we were ready to investigate hydrogenation of the core. We wanted to first examine a stepwise approach by removing the benzyl protecting group and reducing the olefins residing in the alkyl chains in order to focus on hydrogenation of the core, as mentioned above. The analysis began by a preliminary examination of the reactivity of hydrogenation catalysts with our substrate. We initially conducted these reactions on the free tertiary amines, but realized this provided inconsistent results.[154] Thus, we choose to carry out the hydrogenation on an ammonium salt, which provided reproducible results. Our preliminary results are represented in Table 3.



4.42 **4.67**

RXN #	Catalyst	Solvent	Temp.	Time	Result
1	$Pd(OH)_2$	EtOAc	r.t.	24 h	mixture of core hydrogenation
2	$Pd(OH)_2$	EtOAc	50°C	24 h	complex mixture of products
3	$Pd(OH)_2$	EtOH	r.t.	24 h	mixture of core hydrogenation
4	$Pd(OH)_2$	EtOH	50°C	24 h	complete hydrogenation(including core)
5	$RhCl(PPh_3)_3$	EtOAc	r.t	24 h	only S.M. present
6	$RhCl(PPh_3)_3$	EtOH	r.t.	24 h	S.M. plus one alkene hydrogenated
7	Pt/C	EtOH	r.t.	24 h	mixture of core hydrogenation
8	Pd/C	EtOAc	r.t.	24 h	complete mixture of products
9	Pd/C	EtOH	r.t.	72 h	decomposition
10	$Pd(OH)_2$	EtOH	r.t.	72 h	mostly complete hydrogenation

Table 3. Preliminary Hydrogenation Results.

We choose to examine multiple hydrogenation conditions at one atmosphere pressure to obtain a general knowledge concerning the reactivity of tetraene **4.42** using mostly heterogeneous hydrogenation as well as Wilkinson's catalyst.[155] All results were analyzed by LC/MS in order to indicate the degree of hydrogenation that had taken place. Most catalysts were found to yield inseparable mixtures of hydrogenation products (Figure 31).

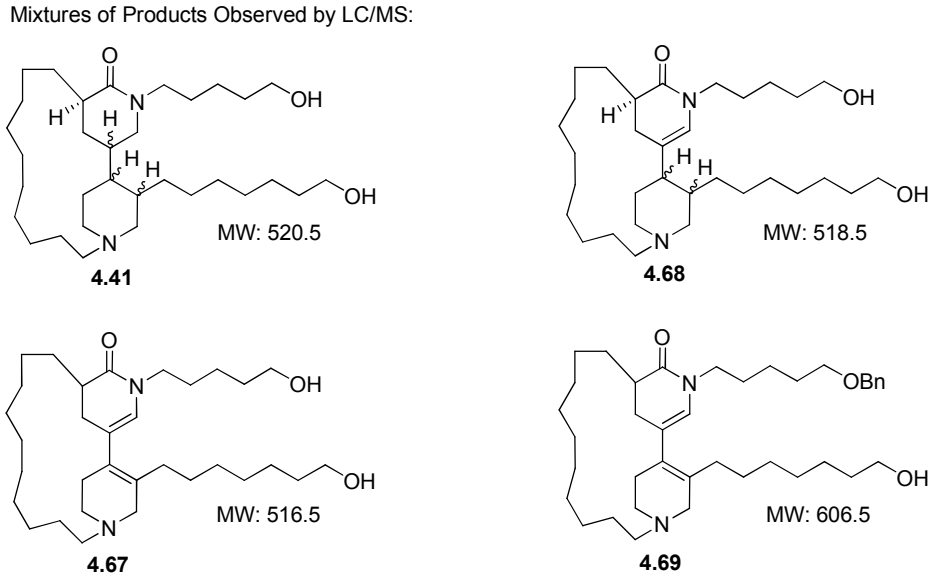
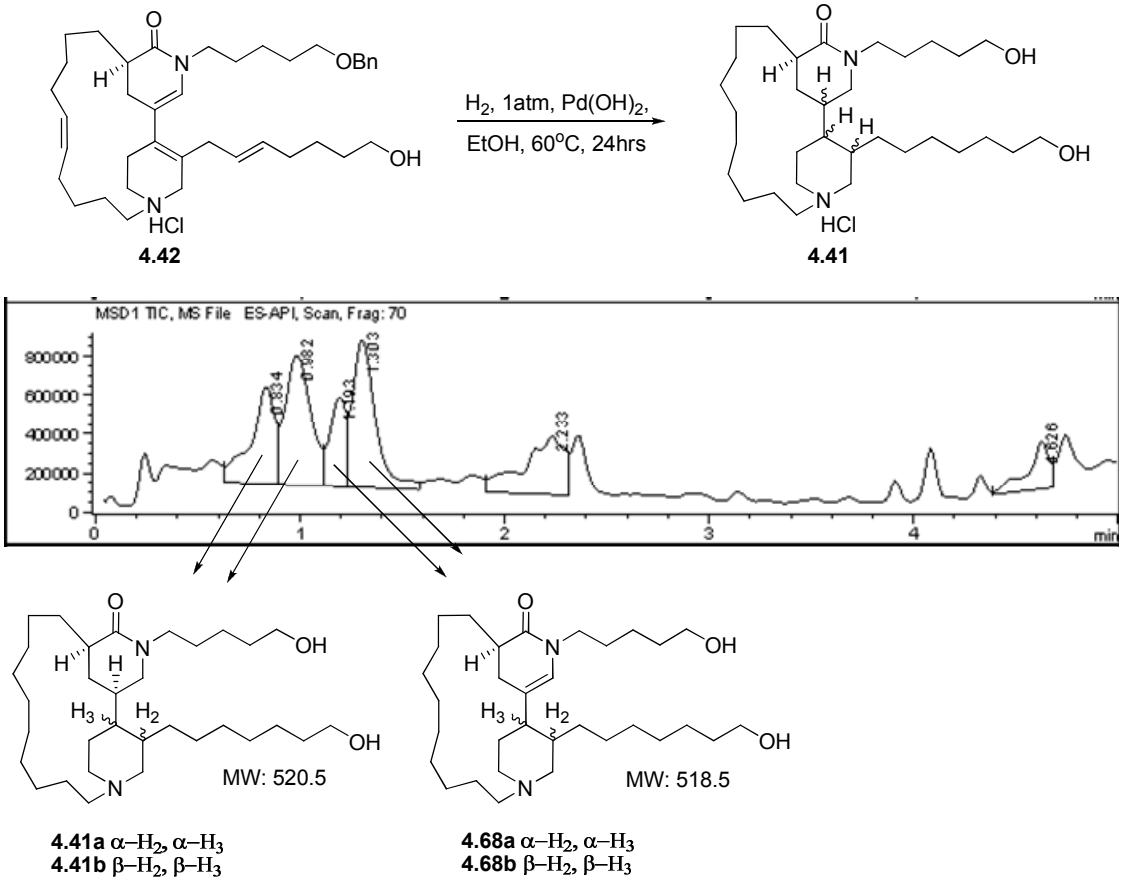


Figure 31. Products Observed During Hydrogenation Catalyst Analysis.

The homogenous system was found to be very slow to react (ethanol and ethyl acetate as solvent) resulting in mostly starting material and very little reduction of one alkene. The heterogeneous catalysts were found to be much more effective in terms of reactivity. Palladium on carbon (ethanol and ethyl acetate) provided a mixture of products and eventually decomposed when exposed to prolonged reaction times. Platinum on carbon (ethanol) resulted in good reactivity, but again yielded mixtures of hydrogenation products without approaching completion. Palladium hydroxide on carbon (Pearlman's catalyst)[156] afforded the best reactivity providing complete hydrogenation when using ethanol as a solvent. However, using any of the catalysts above, we could not consistently obtain complete hydrogenation or selective

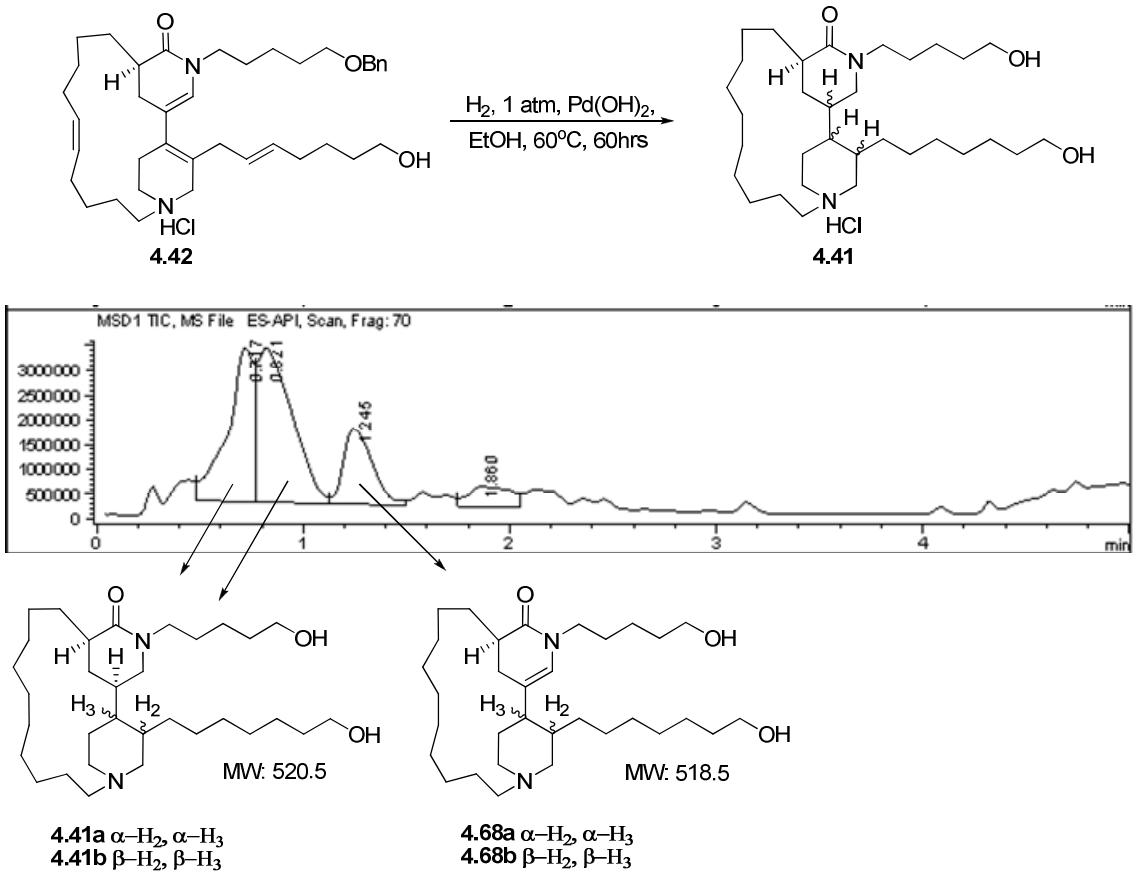
hydrogenation of the benzyl group and the olefins residing in the alkyl chains in order to focus on hydrogenation of the core.

Due to the inability to effect a stepwise reduction of tetraene **4.42**, we began to examine more rigorous reaction conditions. Thus, tetraene **4.42** was treated with Pearlman's catalyst under an atmosphere of hydrogen in ethanol at 60 °C for 24 hours. LC/MS analysis indicated that 4 major products formed which we tentatively assigned as the two diastereomers of compounds **4.41** and **4.68** as illustrated in Scheme 64.



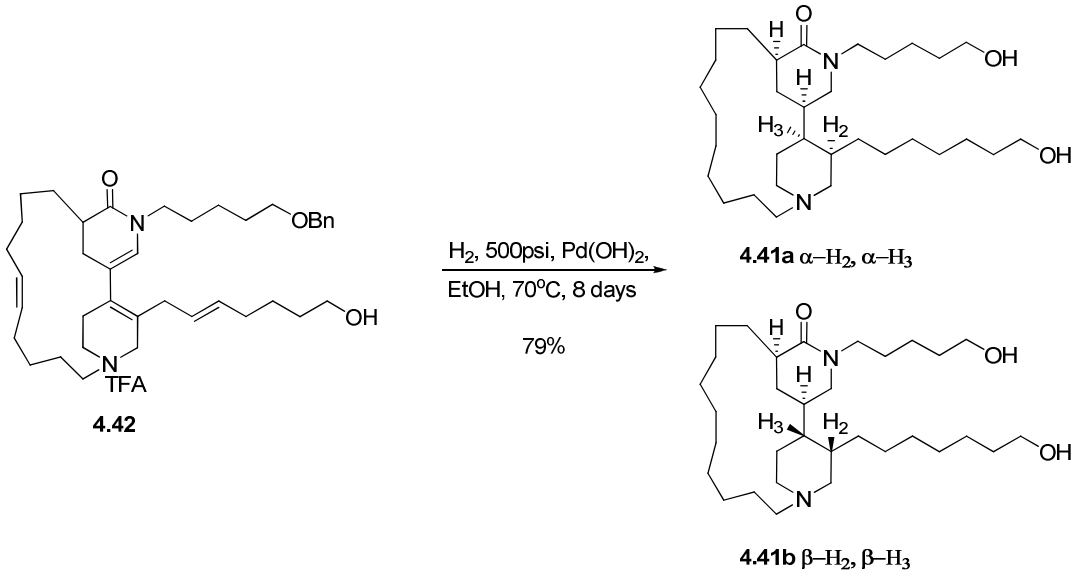
Scheme 64. LC/MS Analysis of Initial Exhaustive Hydrogenation Attempt.

With this encouraging result in hand, we wanted to investigate Pearlman's catalyst further. At this point, we were unsure of relative stereochemistry and could not separate the products from the small scale test reaction described in Scheme 63. However, this result looked to be consistent with our initial peripheral hydrogenation analysis of tetraene **4.42**. We decided to increase reaction time in hope of producing only complete hydrogenation products **4.41**. Treatment of tetraene **4.42** with Pearlman's catalyst under an atmosphere of hydrogen in ethanol at 60 °C for 60 hours provided almost complete hydrogenation shown in Scheme 65 below.



Scheme 65. LC/MS Analysis of Exhaustive Hydrogenation Attempt.

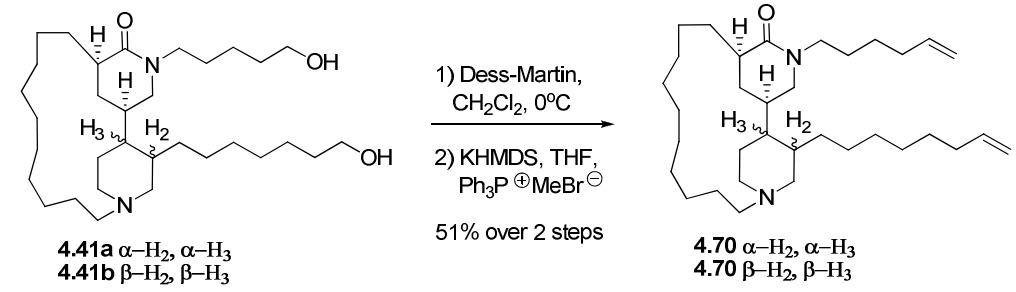
Optimal conditions for the reduction of **4.42** provided a ca. 1:1 mix of products tentatively assigned **4.41a** and **4.41b**. A Parr hydrogenator mini bench top reactor (model 4560) was then used to ensure exhaustive hydrogenation. Thus, the TFA salt of tetraene **4.42** was dissolved ethanol, transferred to the Parr reactor and treated with Pearlman's catalyst. The mixture was placed under a hydrogen atmosphere at 500 psi and heated to 70 °C. The progress of the reaction was monitored by LC/MS, and after 3 days the reaction was incomplete with compound **4.68** still remaining. After much experimentation we found that 500 psi at 70 °C for 8 days lead to complete hydrogenation of the bis-piperdine core in 79% yielding an inseparable mixture of two isomers in a ratio of 1.3:1. We tentatively assigned the relative stereochemistry of the two inseparable isomers based upon our analysis as shown in Scheme 66.



Scheme 66. Tentatively Assigned Hydrogenation Products **4.41**.

Completion of Tetrahydrohaliclonacyclamine A (**3.3**)

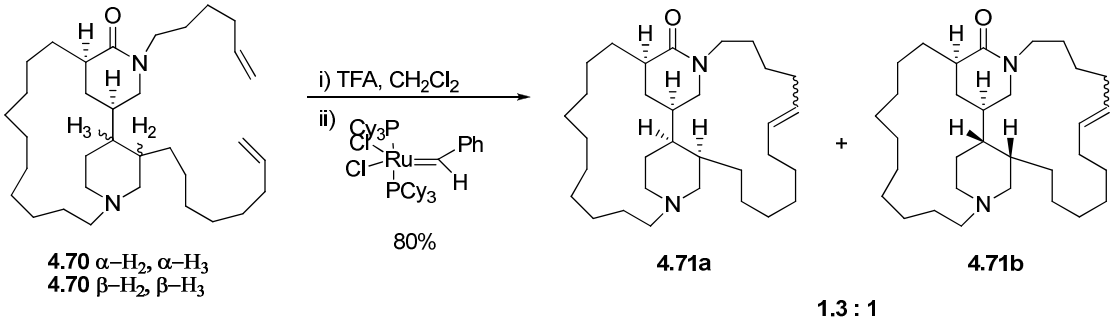
The synthesis of **4.41** represented the completion of three of the four rings. We now turned our attention to the formation of the remaining macrocycle of haliclonacyclamines A-C. Surprisingly, the oxidation of diols **4.41** to the corresponding bis-aldehydes proved to be difficult. It is known that the oxidation of alcohols in the presence of tertiary amines is not always a trivial proces.[89] Attempts using Swern,[133] Ley-Griffith,[157] and chromium based oxidants proved unproductive. However, treatment with Dess-Martin periodinane[158] provided a crude oxidation product that could be taken directly to the next step following careful reaction work-up. This bis-aldehyde proved to be unstable to purification using flash chromatography. Conversion to diene **4.70** was accomplished using 10 equivalents of methylenetriphenylphosphorane in a 51% over all yield for the two-step process (Scheme 67).



Scheme 67. Conversion to the Ring-Closing Metathesis Precursor.

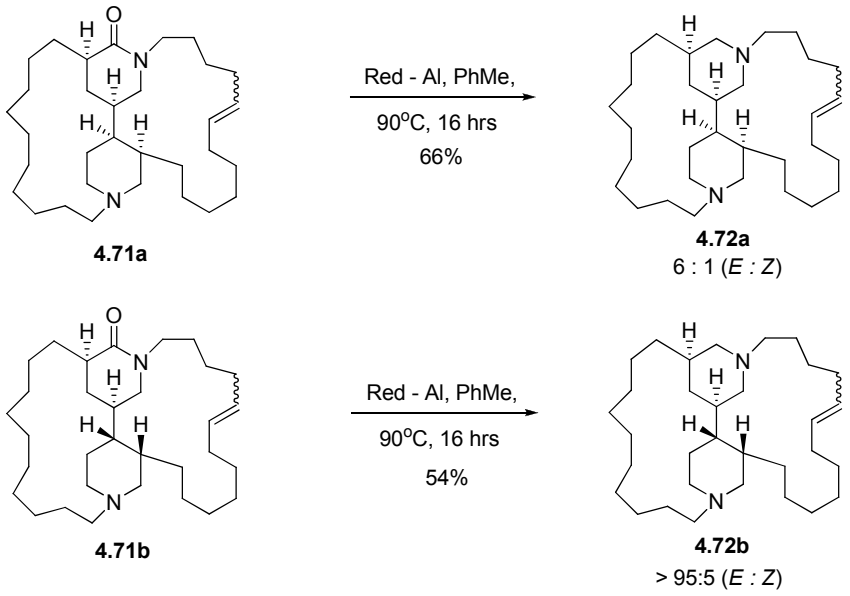
Once we developed a route to dienes **4.70** we were now prepared to examine closure of the 17-membered ring and completed the tetracyclic framework of the

haliclonacyclamines. We anticipated that the two isomers would be separable by chromatography upon formation of the tetracycle. Indeed, the ring system was fashioned upon treatment of the TFA salt of dienes **4.70** with Grubbs' first generation catalyst (**4.56**) to afford isomers **4.71a** and **4.71b** in a combined yield of 80% (Scheme 68), separated by flash chromatography (3:6.5:0.25 hexanes/ethyl acetate/triethylamine).



Scheme 68. Formation of the Tetracyclic Framework.

Lactams **4.71a** and **4.71b** were then reduced with Red-Al to provided diamines **4.72a** and **4.72b**. At this point we were able to determine both possessed an undesired *trans* double bond [6:1 (**4.72a**) and > 95:5 (**4.72b**)] by ^{13}C-NMR analysis (Scheme 69). Interestingly, the ^{13}C-NMR values of the **4.72a**, (6:1 *E*/*Z* ratio) corresponding to the *cis* geometry were found to be in agreement with the assigned values for natural haliclonacyclamine C (**1.4**).[36] The reported ^{13}C-NMR values in the olefin region for natural haliclonacyclamine C (**1.4**) were δ 130.0 and 131.2, which were in exact agreement with the minor amount of the *cis* isomer, diamine **4.72a**, obtained by ring-closing metathesis (Figure 33).[36]



Scheme 69. Attempted Formation of Haliclonacyclamine C (**1.4**) by RCM.

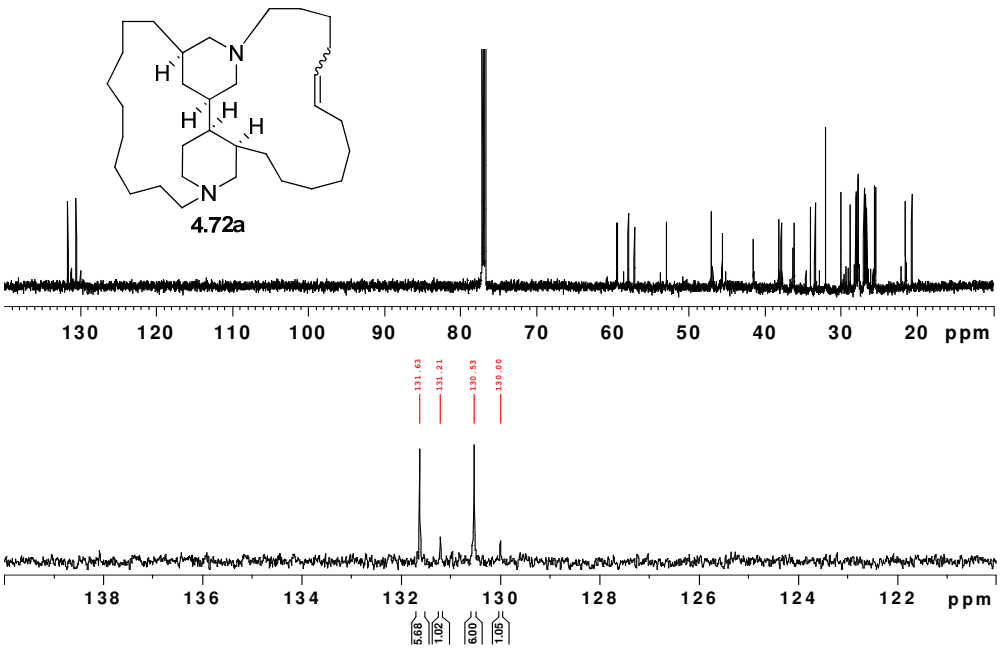
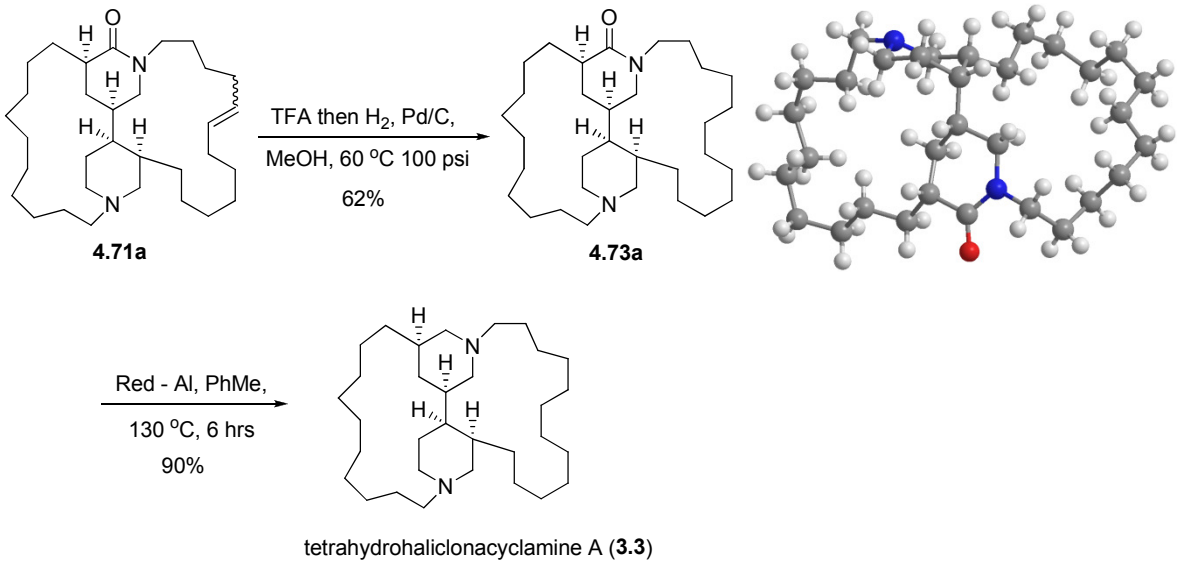


Figure 32. ^{13}C-NMR Analysis of **4.72a.**

Although we had obtained the undesired *trans* isomer (**4.71a**) as the major product, we were encouraged by the ^{13}C-NMR values corresponding to the minor *cis* isomer as it indicated the relative stereochemistry was in alignment with haliclonacyclamine C (**1.4**). This initial observation was validated upon conversion of metathesis product **4.71a** to tetrahydrohaliclonacyclamine A (**3.3**). Thus, metathesis product **4.71a** was treated with Pd/C and stirred vigorously in an atmosphere of hydrogen at 100 psi to provide lactam **4.73a**. Crystals were formed from pure **4.73a** using an ethyl acetate/ hexane/triethylamine solvent system. Single crystal x-ray analysis confirmed the desired *cis-syn-cis* stereochemistry. Lactam **4.73a** was then reduced with Red-Al to afford tetrahydrohaliclonacyclamine A (**3.3**, Scheme 70).



Scheme 70. Crystal Structure and Formation of Haliclonacyclamine C (**1.4**).

Mary Garson (University of Queensland) was kind enough to provided us with a small sample of natural haliclonacyclamine A (**3.2**) and tetrahydrohaliclonacyclamine A

(**3.3**). We were now in a position to compare synthetic tetrahydrohaliclonacyclamine A (**3.3**) to semi-synthetic tetrahydrohaliclonacyclamine A (**3.3**) obtained from Garson. To our surprise the two samples did not match by ^{1}H-NMR or ^{13}C-NMR. We suspected that semi-synthetic tetrahydrohaliclonacyclamine A (**3.3**) was possibly contaminated with acid or palladium, thus altering the spectral properties. Our suspicions were proven to be correct. Their spectral properties agreed upon purification using a strong cation exchange column (Figure 33).

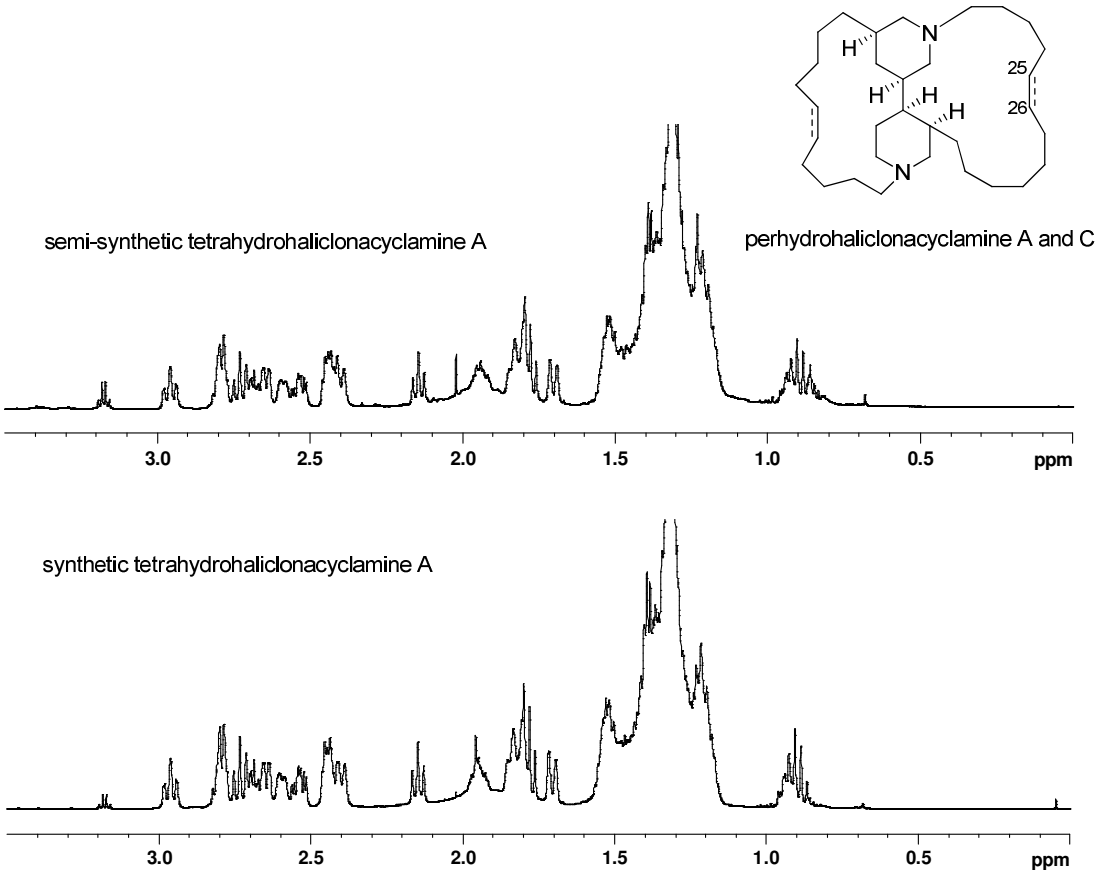
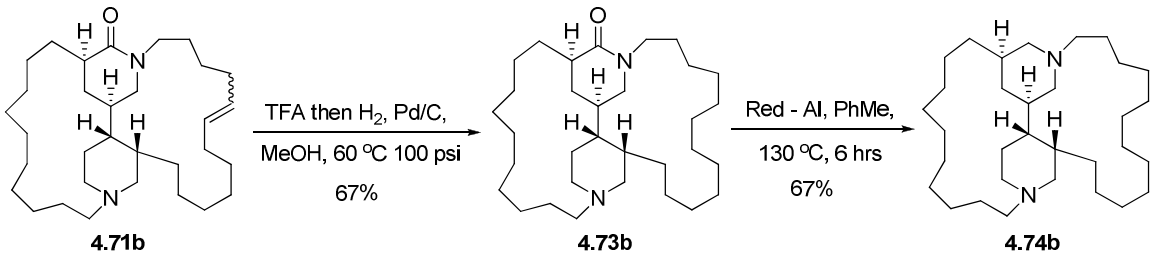


Figure 33. ^{1}H-NMR Comparison of Synthetic and Semi-Synthetic Samples.

The *cis-anti-cis* isomer, **4.71b**, was converted to the dihydroanalogue using the same protocol for tetrahydrohaliclonacyclamine A (**3.3**). Metathesis product **4.71b** was treated with Pd/C and stirred vigorously in an atmosphere of hydrogen at 100 psi to provide lactam **4.73b**. The lactam was then reduced with Red-Al to afford diamine **4.74b** (Scheme 71). The assignment of relative stereochemistry for the undesired *cis-anti-cis* isomer **4.74b** is outlined in Chapter V.



Scheme 71. Reduction of the *Cis-Anti-Cis* Isomer **4.74b**.

Total Synthesis of Haliclonacyclamine C (**1.4**)

The unambiguous assignment of relative stereochemistry for the two diastereomers, obtained from the hydrogenation of tetraene **4.42** (Scheme 66), enabled the completion of tetrahydrohaliclonacyclamine A (**3.3**). However, the total synthesis of haliclonacyclamine C (**1.4**) had not yet been reached. The major problem with the current synthesis was one we had anticipated, unfavorable geometrical outcome of the olefin ring-closing metathesis reaction. To produce the *cis* double bond present in haliclonacyclamine C (**1.4**) we wanted to explore a ring-closing alkyne metathesis followed by semi-hydrogenation strategy first introduced by Fürstner.[138]

We were aware that this was an ambitious endeavor as few examples of this approach applied in the context of total synthesis have been reported.[139,148,159-170] One major issue that has likely contributed to little published work in the area of alkyne metathesis is preparation and use of catalysts and precatalysts, which typically requires rigorous exclusion of moisture and air in order to preserve activity. Furthermore, basic amines were known to be incompatible with the most common and readily accessible alkyne metathesis catalyst, Schrock's tungsten neopentylidyne (**4.75**), due to the Lewis acidic tungsten center (Figure 34).[138,171-174] Mindful of these issues, we were aware of other tungsten and molybdenum catalysts and precatalysts that might possibly be compatible with amines, as well as exploring the reactivity of amines protected as ammonium salts.

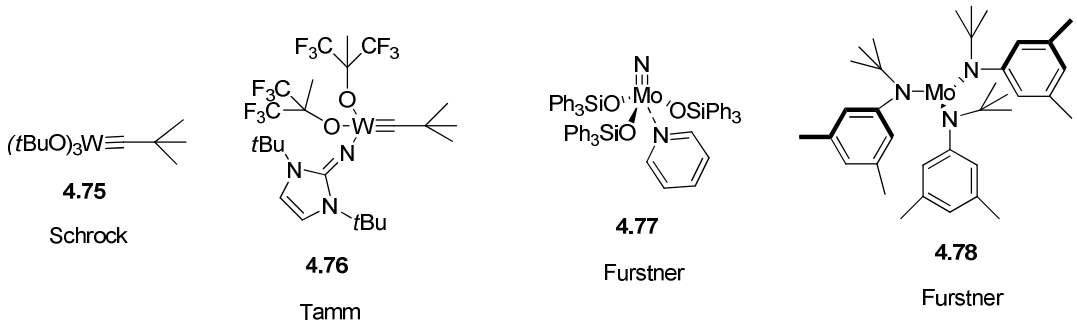
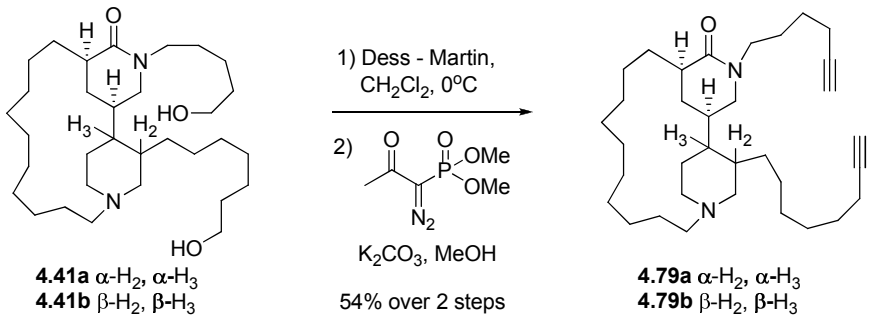


Figure 34. Representative Alkyne Metathesis Catalysts.

The synthesis of the ring-closing alkyne metathesis precursor **4.40** required conversion of diols **4.41a** and **4.41b** to the bis-aldehyde, then to a diyne, followed by bis methylation of the terminal alkynes. To this end, diols **4.41a** and **4.41b** were treated with Dess-Martin[158] to provided the crude bis-aldehyde that was immediately subjected to an

excess of the Bestmann-Ohira[175,176] reagent to afford diynes **4.79a** and **4.79b** (Scheme 72).

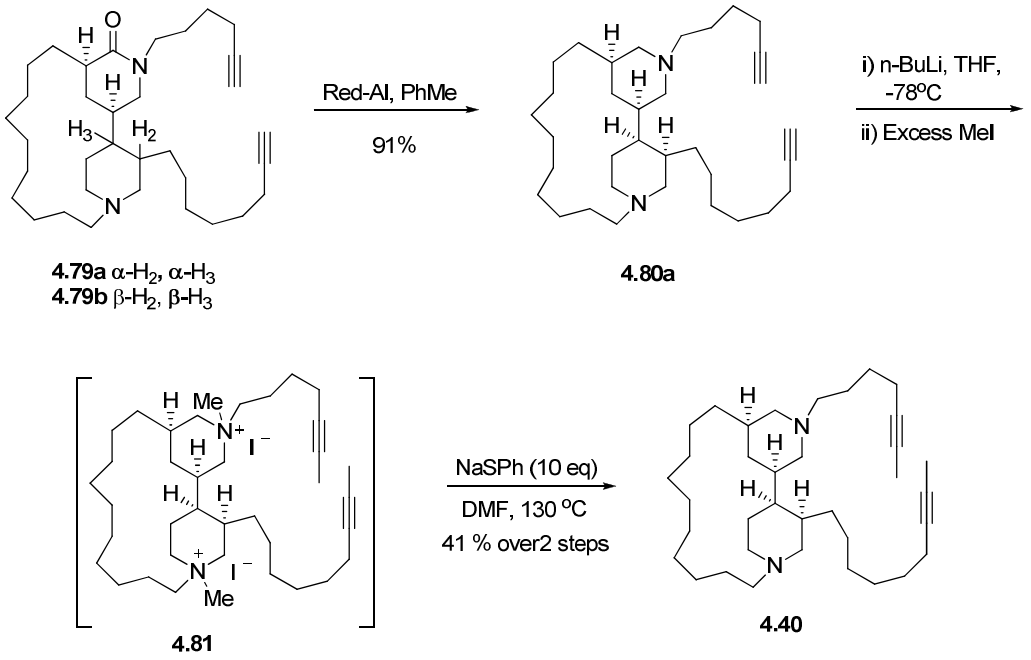


Scheme 72. Conversion to Diynes **4.79a** and **4.79b**.

With a reliable route to diynes **4.79a** and **4.79b**, attention was focused on preparation of the ring-closing alkyne metathesis precursor. Fortunately, lactam reduction with Red-Al provided diamines **4.80a** (51%) and **4.80b** (39%) that separated by flash chromatography (3:6.5:0.5 hexane/ethyl acetate/ triethylamine). Bis-methylation of terminal alkyne **4.80a** proved to be more difficult than anticipated. Despite our best efforts, bis-methylation of terminal alkyne was invariably accompanied by *N*-methylation yielding quaternary ammonium salt **4.81**. After extensive experimentation, the diamine ring-closing alkyne metathesis precursor **4.40** was generated following a two step procedure.

Unable to achieve selective bis-methylation of the terminal alkynes we proceeded with complete methylation to quaternary ammonium salt **4.80** by treatment with *n*-butyllithium and an excess of methyl iodide, following a methanol quench and concentration, the crude product was taken immediately to the next step. Selective *N*-

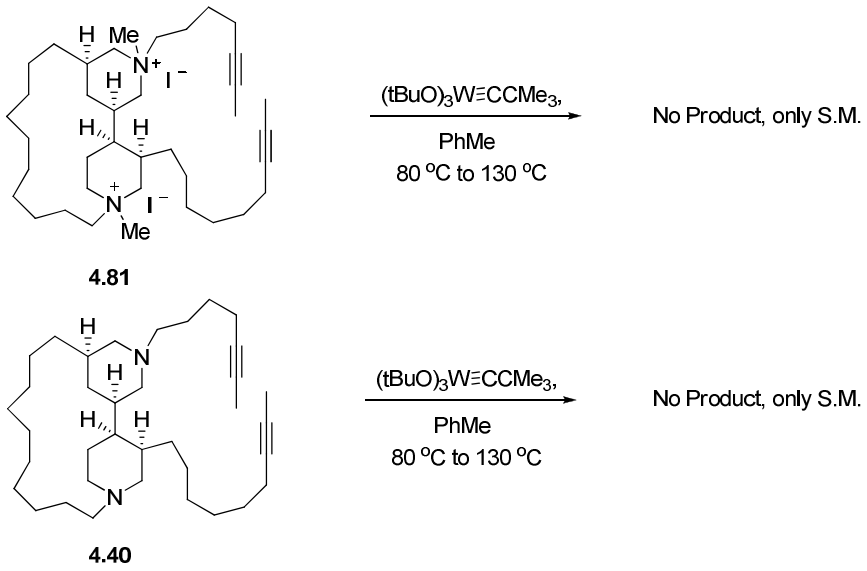
demethylation of the crude mixture was realized upon treatment of ammonium salt **4.80** with an excess of sodium thiophenoxide in dimethylformamide at 130 °C to provide diamine **4.40** in 41% yield for the two step procedure (Scheme 73).[177]



Scheme 73. Preparation of Ring-Closing Alkyne Metathesis Precursor (**4.40**).

The production of methylated diyne **4.40** had now put us in position to begin studying the ring-closing alkyne metathesis of a complex diamine intermediate. Schrock's tungsten neopentylidyne catalyst (**4.75**) was a logical first choice as it is the most commonly used and currently the only alkyne metathesis catalyst commercially available. Although we were aware the catalytic activity of tungsten neopentylidyne catalyst **4.75** would likely be inhibited by the free amine of **4.40**, a solution of diyne **4.40** and tungsten catalyst **4.75** in toluene was heated to 80 °C for 6 hours and eventually

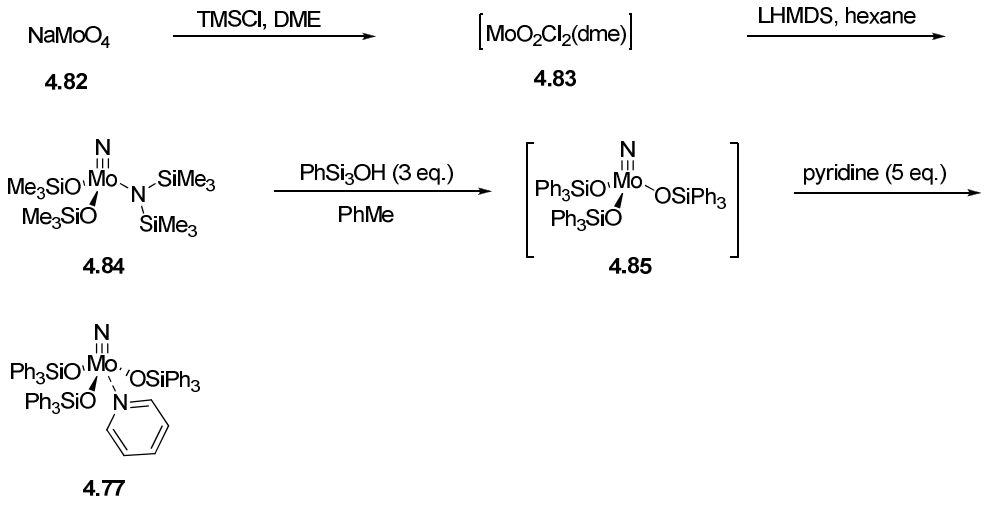
heated to reflux (Scheme 74). No product was detected by thin-layer chromatography or LC/MS analysis, with only starting material remaining. We submitted both quaternary ammonium salt **4.81** and a salt generated by treatment of diamine **4.40** with TFA to the same reaction conditions only to recover unreacted starting material.



Scheme 74. Attempted Ring-Closing Alkyne Metathesis.

The unfavorable results with Schrock's tungsten neopentylidyne catalyst (**4.75**) led us to examine a different catalyst system. We were particularly interested in a recent publication by Fürstner and co-workers describing practical and tolerant molybdenum nitride systems.[172] The preparation of the two catalysts, as described by literature procedure, is outlined in scheme 75.[172] Notably, the Fürstner group found molybdenum nitride species **4.84** to be completely inactive as a catalyst for metathesis. After examination of additives they found that triphenylsilanol and precatalyst **4.84** led to the *in*

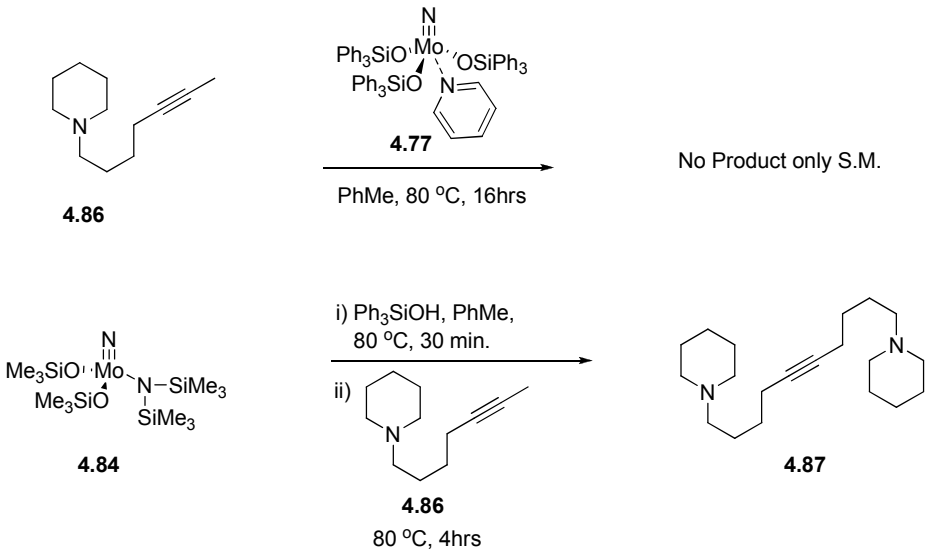
situ formation of active species **4.85** which is structurally undefined. However, NMR evidence suggested the $-(NSiMe_3)_2$ unit is protonated by triphenolsilanol and following substiution gives **4.85**. Treatment of complex **4.85** with pyridine did lead to a complex that not only could be crystallized for structure determination, but also retained similar activity to complex **4.85** while being robust enough to quickly be weighed in air with high catalysts loadings.[172] This concept is impossible with all other catalysts systems to date.



Scheme 75. Preparation of Molybdenum Nitride Systems as Described by Fürstner.

Of particular interest to our studies was Furstner's successful alkyne cross metathesis of a basic pyridine derivative.[172] This result suggested that species **4.77** might tolerate tertiary amines as well. We decided to construct a very simple model system to test our hypothesis. An alkylation of piperidine provided us with amine **4.86**, an easily accessible system to attempt alkyne cross metathesis with both complexes **4.85** and **4.77**.

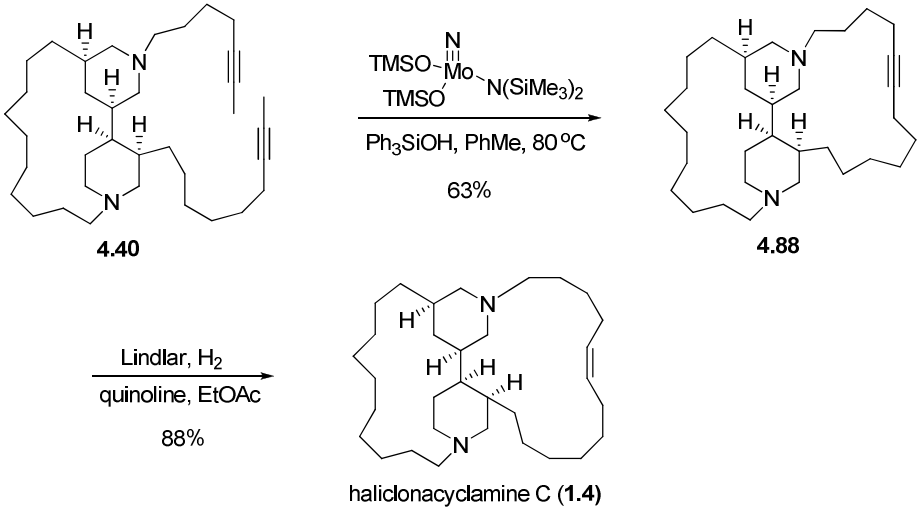
Although this provided no information on a successful ring-closing alkyne metathesis, it provided knowledge about the catalytic activity of these species in the presence of basic amines. Thus, treatment of amine **4.86** with molybdenum nitride species **4.77** in toluene at 80 °C provided no product and only starting material. However, attempts with the *in situ* formation of catalyst **4.85** with tertiary amine **4.86** under the same conditions led to successful construction of cross metathesis product **4.87** (Scheme 76). This result was somewhat surprising due to the success with a pyridine system by Fürstner and co-workers using pyridine coordinated catalyst **4.77**, not *in situ* prepared catalyst **4.85**.



Scheme 76. Catalyst Compatibility Accessment.

With a catalyst system proven to be active in the presence of a tertiary amine, we immediately turned our attention back to the ring-closing alkyne metathesis of diamine **4.40**. To this end, precatalyst **4.84** was treated with 3 equivalents of triphenolsilanol in

toluene over 4Å molecular sieves and heated to 80 °C for 30 minutes. Notably, the formation of active system **4.85** can be qualitatively determined by observation of solution color change from bright yellow, to light orange, and finally turning a pale yellow. Diamine **4.40** was then added to the catalyst solution at room temperature and the resulting solution was heated to 80 °C. To our delight, all starting material had been consumed after 2 hours and product was detected by LC/MS. Further analytical data on the pure product confirmed the successful construction of cycloalkyne **4.88** (Scheme 77). This establishes the first ring-closing alkyne metathesis of a substrate containing basic amine functionality to date. Subsequent Lindlar reduction of cycloalkyne **4.88** provided synthetic haliclonacyclamine C (**1.4**) identical to the natural product in all respects except for optical rotation.



Scheme 77. Completion of Haliclonacyclamine C (**1.4**).

Bioactivity of Tetrahydrohaliclonacyclamine A

Haliclonacyclamines A-C have been reported to display cytotoxic, antibiotic, and antifungal activity. Haliclonacyclamine C (**1.4**) specifically has an IC_{50} value of 0.7 µg/mL in a P_{388} assay, displays antibacterial activity against *Bacillus subtilus*, and strong antifungal properties against *Candida Albicans* and *Trichophyton mentagrophytes*.[36] Berlinck and co-workers have also shown that some arenosclerins have bioactivity as well.[106] With the synthesis of tetrahydrohaliclonacyclamine A (**3.3**) and haliclonacyclamine C (**1.4**) complete, we wanted to further investigate the potential biological activity of tetrahydrohaliclonacyclamine A (**3.3**).

Our evaluation began by submitting the bis-TFA salt of tetrahydrohaliclonacyclamine A (**3.3**) to MSD Pharma Services for a primary biochemical analysis. A panel of ion channel and GPCR receptors were used for evaluation in a radioligand single-point (10 µM) biochemical assay to obtain information on the primary biochemical activity. Responses of greater than 50% inhibition or stimulation are listed in Table 4 below.

Primary Biochemical Assay	Species Source	Concentration	% Inihibition
Adenosine A_3	Human recombinant CHO cells	10 µM	77
Adrenergic α_{1A}	Wister Rat submaxillary	10 µM	98
Adrenergic α_{1B}	Wistar Rat liver	10 µM	100
Adrenergic α_{1D}	Human recombinant HEK-293 cells	10 µM	89
Adrenergic α_{2A}	Human recombinant insect Sf9 cells	10 µM	99
Adrenergic β_1	Human recombinant CHO-K1 cells	10 µM	54

Transporter, Norepineephrine (NET)	Human recombinant MDCK cells	10 µM	70
Calcium Channel L-Type, Benzothiazepine	Wistar Rat brain	10 µM	81
Dopamine D_{25}	Human recombinant CHO cells	10 µM	52
Dopamine D_3	Human recombinant CHO cells	10 µM	97
Transporter, Dopamine (DAT)	Human recombinant CHO-K1 cells	10 µM	86
Histamine H_1	Human recombinant CHO-K1 cells	10 µM	63
Histamine H_2	Human recombinant CHO-K1 cells	10 µM	73
Muscarinic M_1	Human recombinant CHO cells	10 µM	82
Neuropeptide Y Y_1	Human SK-N-MC cells	10 µM	64
Opiate κ (OP2, KOP)	Human recombinant HEK-293 cells	10 µM	83
Opiate µ (OP3, MOP)	Human recombinant CHO-K1 cells	10 µM	92
Potassium Channel hERG	Human recombinant HEK-293 cells	10 µM	98
Serotonin (5-Hydroxy-tryptamine) 5-HT_{1A}	Human recombinant CHO-K1 cells	10 µM	100
Sodium Channel, Site 2	Wister Rat brain	10 µM	111

Table 4. Summary of Signifigant Biochemical Assay Results.

Tetrahydrohaliclonacyclamine A (**3.3**) was found to inhibit endogenous ligand binding of a number of receptors including opiate k (83%), muscarinic M1 (82%), potassium hERG channel (98%), as well as other receptor assays at a concentration of 10 µM as shown in Table 4. Although tetrahydrohaliclonacyclamine A (**3.3**) possessed signifigant bioactivity, it was not found to be receptor selective. These preliminary results provided us with a solid inital analysis, but provided no information about functional activity (i.e. agonist or antagonist effect).

We were particularly interested in further examinination of the agonist and antagonist affects of tetrahydrohaliclonacyclamine A (**3.3**) with muscarinic receptors. This was based on two factors. The first being that macrocyclic bis-pyridinium marcocycles cyclostellettamines A-F (**1.30-1.35**) have been found to block the binding of [^{3}H]-methyl quinuclidinyl benzilate to the muscarinic subtypes M_1 (rat brain), M_2 (rat heart), and M_3 (rat salivary gland).[178] It is proposed that the positively charged pyridinium moieties of the cyclostellettamines participate in binding to TM III Asp residue in the ligand-binding domain of the muscarinic receptors.[178] The second factor was the availability to evaluate tetrahydrohaliclonacyclamine A (**3.3**) and congeners with muscarinic receptors within Vanderbilt University.

In a collaboration with Craig Lindsley's group, Meredith Notezel led an investigatation examining the functional activity on hM1 mAChR with tetrahydrohaliclonacyclamine A (**3.3**), the *cis-anti-cis* isomer (**4.74b**), and 2 other analogues with the lactam carbonyl in place as depicted in Figure 35. We wanted to evaluate the lactam systems as this significantly reduces the basicity of one nitrogen within the tetracycle system. Unfortunately, the lactam systems and the *cis-anti-cis* diamine were modestly active and not fully functional antagonist against hM1. However, tetrahydrohaliclonacyclamine A (**3.3**) (Vanderbilt University ID: 110N) was shown to be a fully functional antagonist against hM1 as illustrated in Figure 35. Analysis of haliclonacyclamine C (**1.4**) bioactivity has currently not been evaluated.

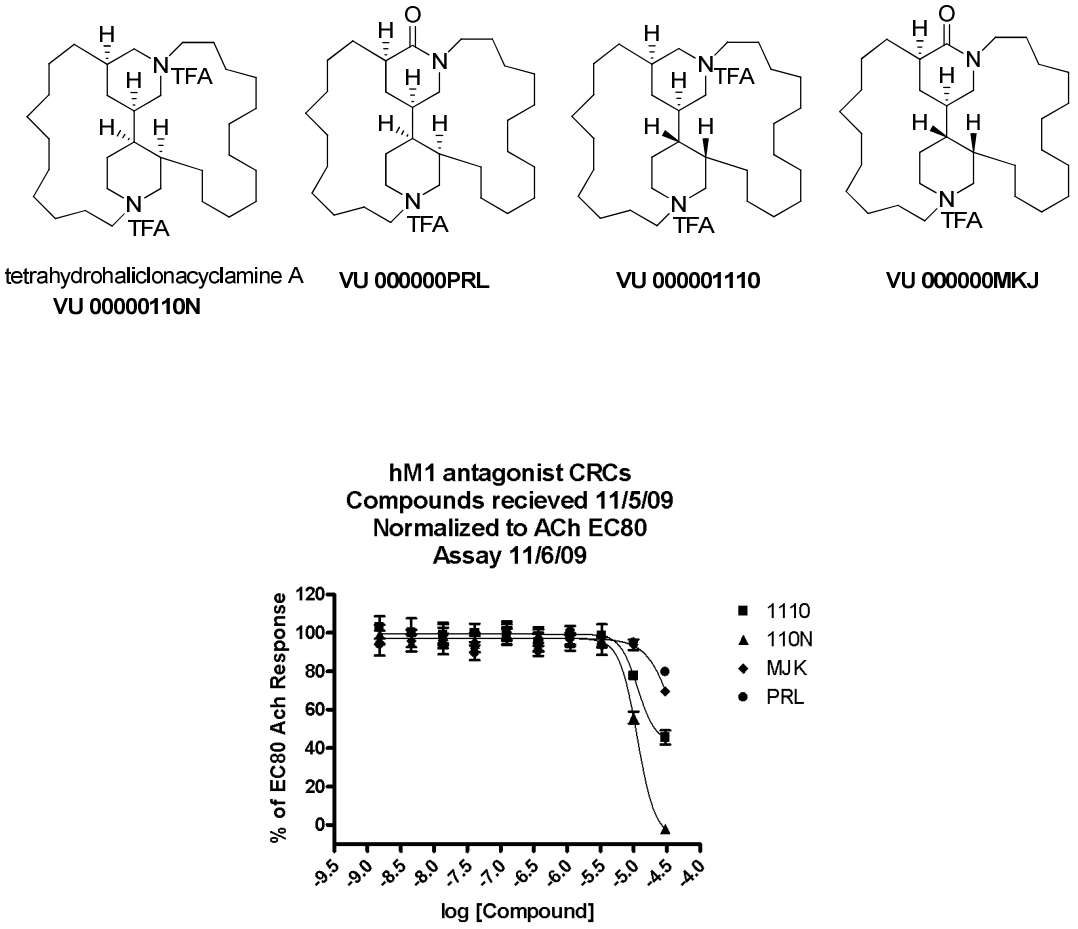


Figure 35. In Vitro Screening of Tetrahyrdohaliclonacyclamine A (**3.3**).

In summary, we have completed the synthesis of tetrahydrohaliclonacyclamine A (**3.3**) in 19 steps and haliclonacyclamine C (**1.4**) in 21 steps by utilizing the Stille cross coupling and ring closing metathesis protocols. We were also able to achieve semi-stereoselective hydrogenation of the bis-piperidine core, common to the haliclonacyclamines and related tetracyclic alkaloids, as well as a ring-closing alkyne metathesis of a complex diamine alkaloid.

CHAPTER V

EXPERIMENTAL SECTION

General Procedure

All non-aqueous reactions were performed in flame-dried or oven dried round-bottomed flasks under an atmosphere of argon. Where necessary (so noted) solutions were deoxygenated by alternate freeze (liquid nitrogen)/evacuation/argon-flush/thaw cycles (FPT, three iterations) or degassed by purging with argon for several minutes. Stainless steel syringes or cannulae were used to transfer air- and moisture-sensitive liquids. Reaction temperatures were controlled using a thermocouple thermometer and analog hotplate stirrer. Reactions were conducted at room temperature (rt, approximately 23 °C) unless otherwise noted. Flash column chromatography was conducted as described Still et. al. using silica gel 230-400 mesh.[179] Where necessary, silica gel was neutralized by treatment of the silica gel prior to chromatography with the eluent containing 1% triethylamine. Were indicated ammonium salts were converted to free-amines using Strong Cation Exchange (SCX) cartridges purchased from Varian. Analytical thin-layer chromatography (TLC) was performed on E. Merck silica gel 60 F254 plates and visualized using UV, ceric ammonium molybdate, potassium permanganate, and anisaldehyde stains. Yields were reported as isolated, spectroscopically pure compounds.

Materials

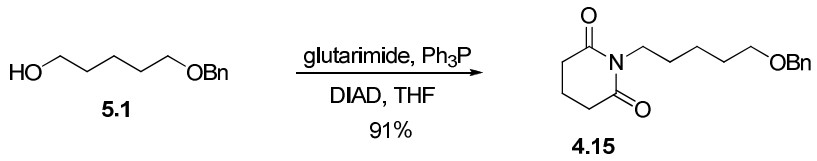
Solvents were obtained from either a MBraun MB-SPS solvent system or freshly distilled (tetrahydrofuran was distilled from sodium-benzophenone; toluene was distilled from calcium hydride and used immediately; dimethyl sulfoxide was distilled from calcium hydride and stored over 4Å molecular sieves). Commercial reagents were used as received with the following exceptions: *N,N*-bis(trifluoromethylsulfonyl)-5-chloro-2-pyridylamine was prepared according to literature procedure.[122] The molarity of *n*-butyllithium solutions was determined by titration using diphenylacetic acid as an indicator (average of three determinations).

Instrumentation

Reverse phase HPLC was conducted on a Varian ProStar HPLC system using a Phenomenex Luna 5u C18(2) 100A Axia 50 x 30.00 mm column. All reverse phase fractions were concentrated using a Genevac EZ-2 plus. Hydrogenation was conducted using a Parr hydrogenator mini bench top reactor (model 4560). Infrared spectra were obtained as thin films on NaCl plates using a Thermo Electron IR100 series instrument and are reported in terms of frequency of absorption (cm^{-1}). ^{1}H NMR spectra were recorded on Bruker 300, 400, 500, or 600 MHz spectrometers and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad, app = apparent), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on Bruker 75, 100, 125, or 150 MHz spectrometers and are reported relative to deuterated solvent signals. LC/MS was conducted and recorded on an

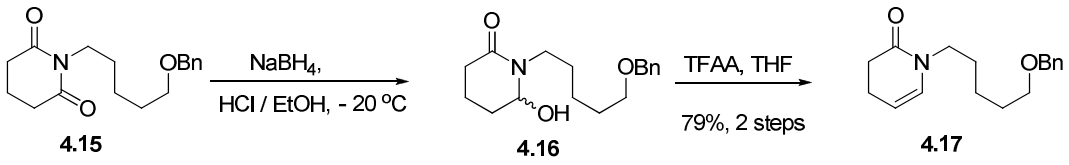
Agilent Technologies 6130 Quadrupole instrument. High-resolution mass spectra were obtained from the Department of Chemistry and Biochemistry, University of Notre Dame using either a JEOL AX505HA or JEOL LMS-GCmate mass spectrometer or from Vanderbilt Institute of Chemical Biology Drug Discovery Program laboratory using a Waters Acquity UPLC and Micromass Q-Tof Ultima API. The structure of lactam 26 was obtained by Dr. Joseph Reibenspies at the X-ray diffraction facility of Department of Chemistry, Texas A&M University.

Compound Preparation



1-(5-(benzyloxy)pentyl)piperidine-2,6-dione (4.15) To a solution of glutarimide (840 mg, 4.33 mmol), triphenylphosphine (1.23 g, 4.70 mmol), and 5-benyzyloxypentanol (**5.1**)[180] at 0 °C in tetrahydrofuran (23 mL) was added diisopropylazodicarboxylate (0.93 mL, 4.70 mmol) dropwise. The solution was allowed to warm to room temperature and stirring continued for 24 h. The reaction mixture was concentrated and the residue triturated with a 1:1 ratio of hexanes/diethyl ether. The newly formed solid was removed by filtration and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (eluent: 2:1 hexanes/ethyl acetate) to yield 1-(5-(benzyloxy)pentyl)piperidine-2,6-dione **4.15** (863 mg, 91%) as a pale yellow oil: IR (neat) 2936, 2861, 1690, 1354 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.32-7.30 (m, 5H),

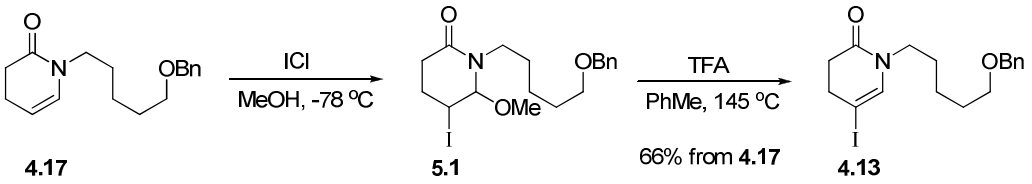
4.47 (s, 2H), 3.73 (t, *J* = 8.0 Hz, 2H), 3.43 (t, *J* = 8.0 Hz, 2H), 2.62 (t, *J* = 8.0 Hz, 4H), 1.89 (m, 2H), 1.65 (m, 2H), 1.51 (m, 2H), 1.39 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.1, 138.3, 128.1, 127.2, 127.2, 127.1, 72.4, 69.8, 39.1, 32.5, 29.0, 27.5, 23.2, 16.8. HRMS calculated for $C_{17}H_{23}NO_3$ $(M + H)^+$ *m/z*: 290.1756, measured: 290.1749.



1-(5-(benzyloxy)pentyl)-3,4-dihydropyridin-2(1*H*)-one (4.17) A solution of imide **4.15** (16.0 g, 55.4 mmol) in ethanol (500 mL) was cooled to -20 °C. Sodium borohydride (16.8 g, 443.2 mmol) was added and the mixture was stirred for 5 h at -20 °C. During this 5 h period 2 N HCl/ethanol (12.0 mL/h) was added dropwise via syringe pump. The reaction was quenched with cold water (500 mL). The aqueous phase was extracted with chloroform (4 x 300 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to yield alcohol **4.16** as a colorless oil used without further purification.

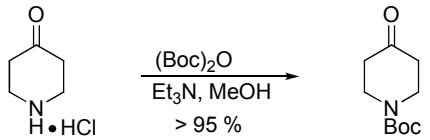
To a solution of alcohol **4.16** (16.1 g, 55.4 mmol) in tetrahydrofuran (500 mL) was added trifluoroacetic anhydride (8.46 mL, 60.9 mmol). The solution was stirred for 30 min at room temperature and quenched with saturated aqueous sodium bicarbonate (500 mL) and extracted with ethyl acetate (3 x 300 mL), the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column

chromatography on silica gel (eluent: 2:1 hexanes/ethyl acetate) to yield 1-(5-(benzyloxy)pentyl)-3,4-dihydropyridin-2(1*H*)-one **4.17** (12.0 g, 79% over two steps) as a yellow oil: IR (neat) 2963, 2858, 1676, 1386 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.33-7.30 (m, 5H), 5.97 (d, *J* = 8.0 Hz, 1H), 5.09 (dt, *J* = 7.7, 4.4 1H), 4.47 (s, 2H), 3.44 (m, 4H) 2.49 (t, *J* = 7.8 Hz, 2H), 2.28 (m, 2H), 1.65 (m, 4H), 1.39, (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.0, 138.5, 129.8, 128.2, 127.4, 127.3, 105.7, 72.7, 70.0, 45.8, 31.3, 29.3, 28.3, 23.2, 20.2. HRMS calculated for $C_{17}H_{23}NO_2$ $(M + H)^+$ *m/z*: 274.1807, measured: 274.1809.



1-(5-(benzyloxy)pentyl)-5-iodo-3,4-dihydropyridin-2(1*H*)-one (4.13). To a solution of enamine **4.17** (200 mg, 1.07 mmol) in methanol (10 mL) at -78 °C was added a 1.0 M solution of iodine monochloride (1.60 mL, 1.60 mmol) in dichloromethane (10 mL). The mixture was allowed to stir at -78 °C for 1 h. The solution was allowed to warm to room temperature and methanol was removed *in vacuo*. The residue was diluted with dichloromethane (10 mL) and aqueous sodium sulfite was slowly added until the deep red solution became clear. The mixture was diluted with water (5 mL). The aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to give iodoaminal **5.1** (360 mg as a crude weight). The product was immediately used in the next step without further purification.

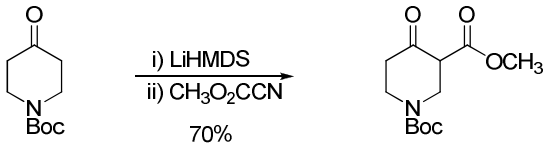
To a solution of the iodo aminal (**5.1**, 369 mg 1.07 mmol) in toluene (10 mL) was added a catalytic amount of trifluoroacetic acid (10 μL). The flask was immersed into an oil bath at 145 °C and allowed to reflux for 15 min at which time the mixture turned a dark red color. The solution was cooled to room temperature and then to 0 °C. Triethylamine (1.00 mL) was introduced to the solution. The solvent was removed *in vacuo* and the residue purified by flash column chromatography (eluent: 4:1 hexane/ethyl acetate) to afford 213 mg (66% over two steps) of 1-(5-(benzyloxy)pentyl)-5-iodo-3,4-dihydropyridin-2(1*H*)-one **4.13** as a light brown oil: IR (neat) 2933, 2857, 1671 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300MHz) δ 7.23 – 7.21 (m, 5H), 6.39 (s, 1H), 4.64 (s, 2H), 3.42 (m, 4H), 2.66 (t, *J* = 7.4 Hz, 2H), 2.54 (t, *J* = 7.1 Hz, 2H) 1.61 (m, 4H), 1.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.3, 138.5, 135.4, 128.3, 127.6, 127.5, 72.6, 70.0, 68.6, 46.2, 33.4, 32.6, 29.3, 28.5, 23.3. HRMS calculated for $C_{17}H_{22}INO_2$ $(M + H)^+$ *m/z*: 400.0774, measured: 400.0787.



4.18 **4.19**

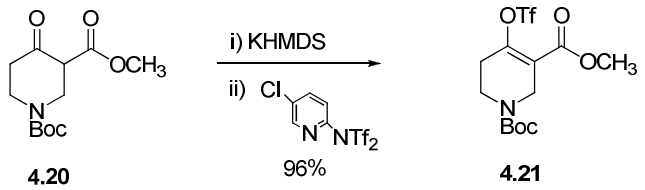
***tert*-butyl 4-oxocyclohexanecarboxylate (4.19).** To a stirred solution of triethylamine (4.52 mL, 32.5 mmol) in methanol (25 mL) was added 4-piperidone monohydrate hydrochloride **4.18** (1.00 g, 6.49 mmol) and di-*tert*-butyl dicarbonate (4.48 mL, 19.5 mmol). The reaction mixture was heated at 45 ^{o}C for 1.5 h, the solvent was evaporated in vacuo. 2 N HCl (10 mL) and ethyl acetate (20 mL) were added. The two phases were

seperated and the aqueous phase was extracted with ethyl acetate (EtOAc) (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel eluting with 3:1 (hexanes/ethyl acetate) to yield *tert*-butyl 4-oxocyclohexanecarboxylate **4.19** (1.29 g, 95%) as a white solid. Spectral data correlated with the reported values.[120]

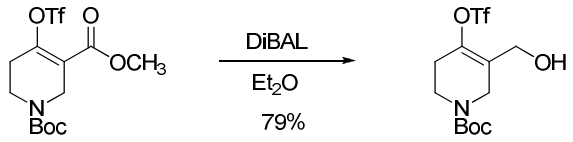


4.19 **4.20**

1-*tert*-butyl 3-methyl 4-oxocyclohexane-1,3-dicarboxylate (4.20). To a stirred solution of carbamate **4.19** (4.10 g, 20.60 mmol) in tetrahydrofuran at -78 ^oC, LiHMDS (26.87 mL of 1.0 M solution in tetrahydofuran, 26.78 mmol) was added dropwise. The mixture was stirred at -78 ^oC for 1 h. Methyl cyanoformate (2.62 mL, 26.78 mmol) was added and the resulting solution was stirred for an additional hour then quenched with H_2O. The mixture was washed with water (100 mL). The aqueous phase extracted with EtOAc (3 x 50 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel eluting with 8:1 (hexanes/ethyl acetate) to yield 1-*tert*-butyl 3-methyl 4-oxocyclohexane-1,3-dicarboxylate **4.20** (4.11 g, 74%) as a yellow oil. Spectral data correlated with the reported values.[121]

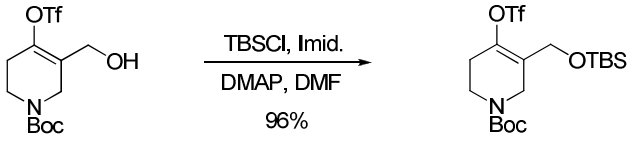


1-*tert*-butyl 3-methyl 4-(trifluoromethylsulfonyloxy)cyclohex-3-ene-1,3 dicarboxylate (4.21). To a solution of β-keto ester **4.20** (2.64 g, 10.27 mmol) KHMDS (24.65 mL of a 0.5 M solution in toluene, 12.32 mmol) was added dropwise at -78 ^{o}C. The reaction mixture was warmed to -20 ^{o}C during the course of 2 h, then cooled down to -78 ^{o}C. Then 2 – [*N*, *N* – bis (trifluromethylsulfonyl) amino] – 5 chloropyridine (4.81 g, 12.32 mmol) was added in tetrahydrofuran via cannula. The reaction was warmed to room temperature and proceeded for 24 h. The solution was concentrated and purified by flash column chromatography on silica gel eluting with 10:1 (hexanes/ethyl acetate 1% triethylamine) to yield 1-*tert*-butyl 3-methyl 4-(trifluoromethylsulfonyloxy) cyclohex-3-ene-1,3-dicarboxylate **4.21** (3.84 g, 96%) as a yellow oil. IR (neat) 2976, 1706, 1424, 1245, 1209 cm-1; 1H-NMR (500 MHz, CDCl3) δ 4.27 (s, 2H), 3.83 (s, 3H), 3.62 (t, J = 5.5 Hz, 2H), 2.51 (m, 2H), 1.48 (s, 9H); 13C-NMR (125MHz, CDCl3) δ 162.8, 153.9, 122.0, 119.5, 116.9, 114.4, 81.0, 52.3, 43.0, 39.3, 28.8, 28.3; HRMS (ESI) calculated for $C_{13}H_{19}O_7F_3NS$ (M+H)+ *m/z*: 390.0834, measured 390.0804.



4.21 4.22

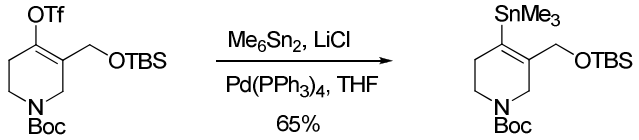
Allylic Alcohol (4.22). To a solution of vinyl triflate **4.21** (3.84 g, 9.87 mmol) in diethyl ether (150 mL) at 0 ^{o}C was added DIBAL (5.28 mL in ether, 29.61 mmol). The reaction was stirred for 30 minutes then quenched with 1 N HCl. The solution was washed with 1 N HCl. The aqueous phase was extracted with ethyl acetate (3 x 80 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel eluting with 3:1 (hexanes/ethyl acetate 1% triethylamine) to yield allylic alcohol **4.22** (2.92g, 79%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.26 (s, 2H), 4.12 (s, 2H), 3.61 (t, *J* = 5.8 Hz, 2H), 2.43 (m, 2H), 1.46 (s, 9H).



4.22 4.23

Vinyl Triflate (4.23). To a solution of allylic alcohol **4.22** (2.23 g, 6.18 mmol) in DMF at 0 ^{o}C was added Imidazole (2.10 g, 30.90 mmol) followed by TBSCl, (4.67 g, 30.90 mmol) then DMAP (151 mg, 1.24 mmol). The reaction mixture was allowed to warm to room temperature and stir for 19 h. The solution was washed with water and the aqueous phase was extracted with ethyl acetate (3 x 90 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column

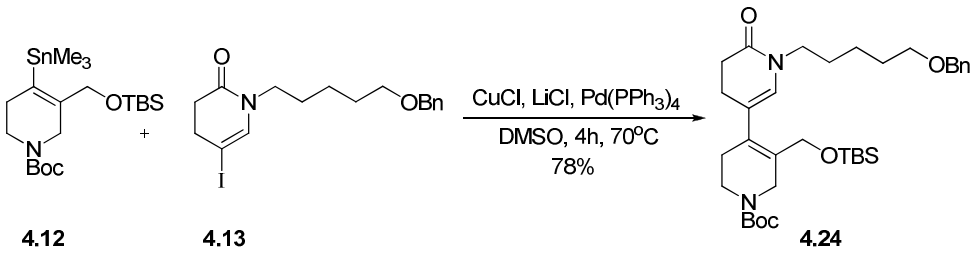
chromatography on silica gel eluting with 50:1 (hexanes/ethyl acetate 1% triethylamine) to yield vinyl triflate **4.23** (2.82 g, 96%) as a colorless oil . IR (neat) 2927, 2856, 1699, 1418, 1365, 1249, 1162; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.32 (s, 2H), 4.08 (br s, 2H), 3.59 (t, *J* = 6.0 Hz, 2H), 2.44 (m, 2H), 1.45 (s, 9H), 0.88 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.3, 140.2, 128.6, 119.8 (q, *J* = 310), 80.2, 58.4, 43.3, 41.1, 39.9, 28.1, 25.6, 18.0, -4.3; HRMS (ESI) m/z 482.1788 [(M + Li)$^{+}$ calculated for $C_{18}H_{32}F_3NO_6SSiLi$: 482.1832.



4.23 **4.12**

Vinyl Stannane (4.12). To a solution of vinyl triflate **4.23** (1.5 g, 3.15 mmol) in tetrahydrofuran was added hexamethylditin (1.96 mL, 9.45 mmol) dropwise followed addition of LiCl (794 mg, 18.90 mmol), and tetrakis(triphenylphosphine)palladium(0) (726 mg, 0.63 mmol). The resulting solution was degassed (3x) by the freeze-pump-thaw method. The mixture was then placed in an oil bath preheated to 80 ^{o}C and allowed to stir for 20 h monitoring by thin layer chromatography 10:1 (hexane/ethyl acetate). The solution was quenched and washed with sodium bicarbonate. The aqueous phase was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel eluting with 100:1 (hexanes/ethyl acetate 1% triethylamine) to yield vinyl stannane **4.12** (1.00 g, 65%) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 300

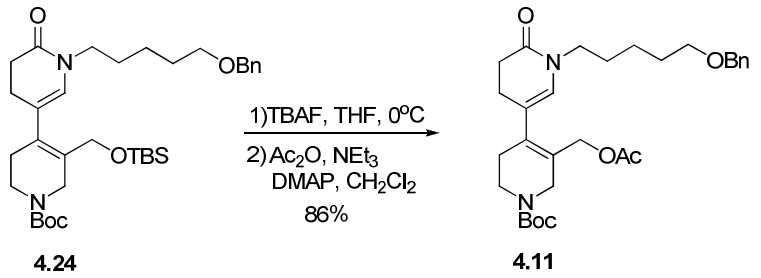
MHz) δ 4.03 (s, 2H), 3.96 (br s, 2H), 3.40 (t, *J* = 6.4 Hz, 2H), 2.24 (m, 2H), 1.44 (s, 9H), 0.89 (s, 9H), 0.15 (s, 9H), 0.06 (s, 6H).



4.12 **4.13** **4.24**

Bis-piperidine (4.24). To a flame dried flask/condenser was added vinyl tin **4.12** (1.70 g, 3.46 mmol) and vinyl iodide **4.13** (1.38 g, 3.46 mmol) in dimethyl sulfoxide, followed by addition of copper chloride (1.71 g, 17.30 mmol), lithium chloride (874 mg, 20.80 mmol), and tetrakis (triphenylphosphine)palladium(0) (400 mg, 0.35 mmol). The solution was stirred, then degassed (3x) freeze–pump–thaw. The reaction mixture was placed into an oil bath preheated to 70 ^{o}C, stirred for 4 h cooled to room temperature and quenched with saturated $NaHCO_3$. The resulting solution was filtered over Celite. The filtrate was washed with H_2O (100 mL), extracted with ethyl acetate (3 x 75 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel eluting with 3:1 (hexanes/ethyl acetate) to yield bis-piperidine **4.24** (1.62 g, 78%) as a yellow oil. IR (neat) 2983, 2811, 1731, 1669, 1366, 1248, 1165, 698; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.29 - 7.25 (m, 5H), 5.96 (s, 1H), 4.46 (br s, 2H), 4.15 (br s, 2H), 3.97 (br s, 2H), 3.44 (m, 6H), 2.49 (t, *J* = 7.2 Hz, 2H), 2.27 (t, *J* = 7.1 Hz, 2H), 2.13 (br s, 2H), 1.61 (m, 4H), 1.45 (s, 9H), 1.35 (m, 2H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 168.2, 154.4, 138.2, 131.1, 127.9, 127.3,

127.1, 117.2, 79.3, 72.5, 69.8, 62.5, 45.8, 44.5, 39.7, 31.0, 29.1, 28.2, 28.1, 27.8, 25.6, -5.54; HRMS (ESI) m/z 605.3872 [(M + Li)$^+$ calculated for $C_{34}H_{54}N_2O_5SiLi$: 605.3962.

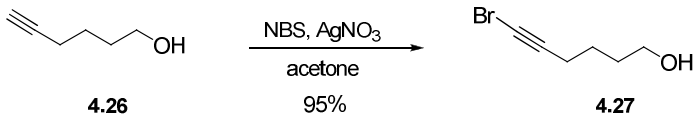


4.24 4.11

Allylic Acetate (4.11). To a stirred solution of diene **4.24** (1.62 g, 2.70 mmol) in tetrahydrofuran (45 mL) at 0 ^oC was added a 1.0 M solution of tertbutylammonium fluoride in tetrahydrofuran (5.40 ml, 5.40 mmol). The mixture was stirred at 0 ^oC for 40 minutes. The reaction was quenched and washed with water. The aqueous phase was extracted with ethyl acetate (3 x 50 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated. The residue was taken directly to the next step without any further purification.

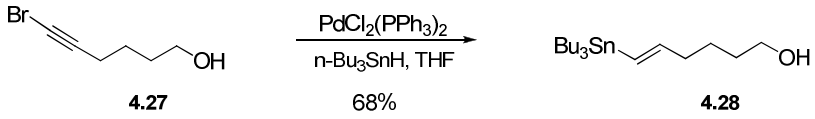
To a stirred solution of alcohol **4.25** (1.30 g, 2.69 mmol) in dichloromethane (25 mL) were added 4-dimethylaminopyridine (26.0 mg, 0.22 mmol), triethylamine (1.31 mL, 9.42 mmol), and acetic anhydride (0.52 mL, 5.38 mmol). The mixture was stirred at room temperature for 45 minutes then quenched with water. The solution was washed with water (100 mL), extracted with ethyl acetate (3 x 50 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel eluting with 1:1 (hexanes/ethyl acetate) to yield allylic acetate **4.11** (1.25 g, 86%) as a dark yellow gum. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.28 - 7.25 (m, 5H), 5.96 (s,

1H), 4.46 (br s, 2H), 4.15 (br s, 2H), 3.97 (br s, 2H), 3.44 (m, 6 H), 2.49 (t, J = 7.6 Hz, 2H), 2.27 (t, J = 7.4 Hz, 2H), 2.13 (br s, 2H), 1.91 (s, 3H), 1.61 (m, 4H), 1.45 (s, 9H), 1.35 (m, 2H).



4.26 **4.27**

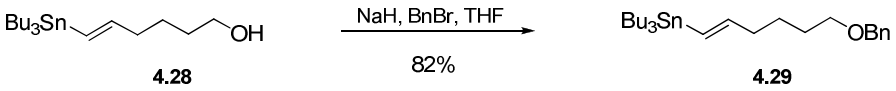
6-bromohex-5-yn-1-ol (4.27). To a solution of 5-Hexyn-1-ol (**4.26**, 526 mg, 5.37 mmol) in acetone (22.0 mL) was *N*-bromosuccinimde (1.43 g, 8.06 mmol) and silver nitrate (274 mg, 1.61 mmol). The mixture was allowed to stir for 30 minutes, and then concentrated. The residue was purified by flash column chromatography on silica gel eluting with 4:1 (hexanes/ethyl acetate) to yield 6-bromohex-5-yn-1-ol **4.27** (920 mg, 95%) as a pale yellow oil. Spectral data correlated to reported values.[181]



4.27 **4.28**

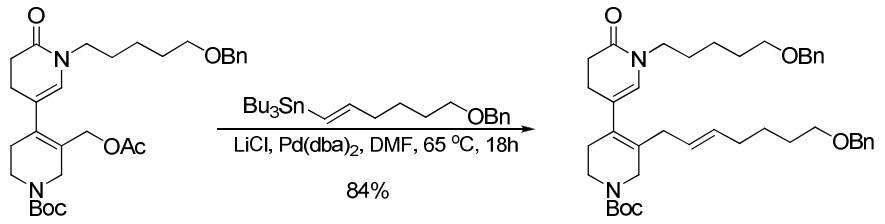
(E)-6-(tributylstannyl)hex-5-en-1-ol (4.28). To a solution of alkynyl bromide **4.27** (670 mg, 3.78 mmol) in tetrahydrofuran (15 mL) was added bis(triphenylphosphine)palladium(II) chloride (53.0 mg, 0.08 mmol) followed by the slow addition of tributyltin hydride (1.32 mL, 4.91 mmol). The yellow solution turned to a dark orange color after approximately 10 minutes, and after the addition of another equivalent of tributyltin hydride the mixture turned to a dark brownish-red color. The

mixture was concentrated and the residue was purified by flash column chromatography on silica gel eluting with 10:1 (hexanes/ethyl acetate) to yield (E)-6-(tributylstannyl)hex-5-en-1-ol **4.28** (999 mg, 68%) as a colorless oil. Spectral data correlated to reported values.[144]



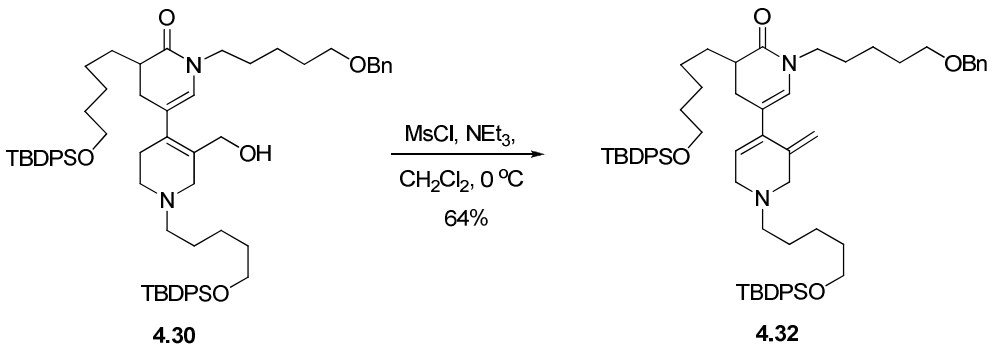
4.28 4.29

(E)-(6-(benzyloxy)hex-1-enyl)tributylstannane (4.29). To a solution of vinyl tin **4.28** (1.00 g, 2.57 mmol) in tetrahydrofuran (20 mL) at 0 ^{o}C was added sodium hydride (514 mg, 12.85 mmol, in two portions over 10 minutes). Then benzyl bromide (0.76 mL, 6.43 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stir for 27 h. The solution was cooled to 0 ^{o}C and quenched with saturated sodium bicarbonate. The aqueous phase was extracted with ethyl acetate. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel eluting with 4:1 (hexanes: ethyl acetate, 1% triethylamine) to yield (E)-(6-(benzyloxy)hex-1-enyl)tributylstannane **4.29** (1.00 g mg, 82%) as a pale yellow oil. Spectral data correlated to reported values.[182]



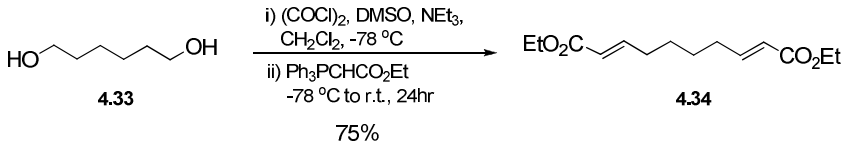
4.11 **4.10**

Triene (4.10). To a solution of allylic acetate **4.11** (18.0 mg, 0.034 mmol) and vinyl tin **4.29** (49.0 mg, 0.103 mmol) in dimethylformamide (0.6 mL) was added bis (dibenzylidieneacetone) palladium(0) (4.0 mg, 0.007 mmol) and lithium chloride (7.0 mg, 0.170 mmol). The mixture was immediately degassed 3x (freeze-pump-thaw). The solution was allowed to warm back to room temperature after the final degassing, placed into a preheated oil bath a 65 ^{o}C, and stirred for 18 h. The mixture was then quenched with saturated sodium bicarbonate. The solution was washed with water (15 mL). The aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel eluting with 2:1 (hexanes/ethyl acetate) to yield triene **4.10** (18.4 mg, 84%) as a yellow gum. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.35 - 7.25 (m, 10H), 5.85 (s, 1H), 5.39 (m, 1H), 5.33 (m, 1H), 4.47 (s, 2H), 4.46 (s, 2H), 3.80 (br s, 2H), 3.43 (m, 8H), 2.75 (d, *J* = 5.3 Hz, 2H), 2.49 (t, *J* = 7.6 Hz, 2H), 2.27 (t, *J* = 7.3 Hz, 2H), 2.11 (m, 2H), 1.99 (m, 2H), 1.61 (m, 10H), 1.52 (s, 9H). ^{13}C NMR ($CDCl_3$, 100MHz) δ 168.4, 154.5, 138.4 (2C), 131.1, 128.3 (5C), 127.6 (5C), 127.5 (3C), 126.5, 118.4, 79.7, 72.8, 72.9, 70.1, 70.2, 65.8, 40.7, 35.2, 32.4, 31.5, 30.3, 29.6, 29.4, 29.3, 28.5, 26.1, 24.0, 23.4; HRMS (ESI) m/z 663.4197 [(M + Li)$^{+}$ calculated for $C_{41}H_{56}N_2O_5Li$: 663.4349.

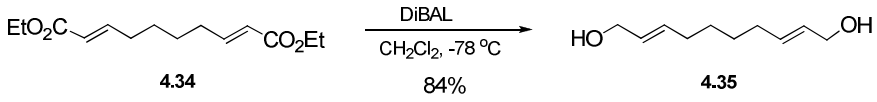


4.30 **4.32**

Representative Procedure for Elimination Product (4.32). To a solution of allylic alcohol **4.30** (18.0 mg, 0.0174 mmol) in dichloromethane at -78 °C was added triethylamine (3.4 µL, 0.0224 mmol). Methanesulfonyl chloride (1.8 µL, 0.0226 mmol) was added and the solution was slowly warmed to room temperature. The reaction mixture was monitored by thin layer chromatography every 15 minutes to monitor for any products forming other than elimination product **4.32**. The reaction was quenched with water (3 mL) and extracted with ethyl acetate (3 x 5 mL), the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (eluent: 2:1 hexanes/ethyl acetate) to yield elimination product **4.32** (11.3 mg, 0.0111 mmol) in a 64% yield. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.65 (m, 8H), 7.39-7.30 (m, 17H), 6.01 (s, 1H), 5.63 (br s, 1H), 4.95 (d, J = 9.3 Hz, 1H), 4.46 (s, 2H), 3.62 (m, 4H), 3.43 (app t, J = 6.3 Hz, 4H), 3.12 (m, 4H), 2.43-3.36 (m, 4H), 2.17 (m, 1H), 1.58-1.35 (m, 18H), 1.02 (s, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.5, 138.6, 136.4, 135.6, 134.1, 134.1, 129.5, 129.5, 128.3, 127.6, 127.5, 127.3, 125.2, 117.7, 111.4, 72.9, 70.2, 63.9, 63.8, 57.9, 57.8, 46.3, 40.6, 32.5, 29.9, 29.8, 29.5, 28.5, 26.9, 25.9, 23.8, 23.4. LC/MS m/z 1016.500 [$(M + H)^+$ calculated for $C_{65}H_{87}N_2O_4Si_2$: 1016.560.

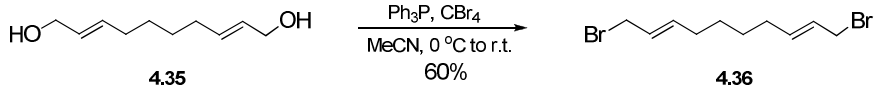


(2*E*, 8*E*)-diethyl deca-2,8-dienedioate (4.34). To a solution of oxalyl chloride (1.82 mL, 21.2 mmol) in dichloromethane (80 mL) at -78 °C was added dimethyl sulfoxide (3.61 mL, 42.4 mmol) dropwise. After 10 minutes, a solution of 1,6 hexanediol (**4.33**, 1.00 g, 8.47 mmol) in dichloromethane (10 mL) was added to the reaction mixture. The solution was allowed to stir for 30 minutes, treated with triethylamine (11.8 mL, 84.7 mmol) and allowed to warm to 0 °C. (Carbethoxymethylene) triphenylphosphorane (14.8 g, 42.4 mmol) was then added to the mixture as a solid and the resulting solution was allowed to warm to room temperature and stir overnight. The reaction was quenched and washed with H_2O. The aqueous phase was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel eluting with 12:1 (hexanes/ethyl acetate) to yield (2E, 8E)-diethyl deca-2,8-dienedioate **4.34** (1.61 g, 75%) as a yellow oil. Spectral data correlated to reported values.[183]



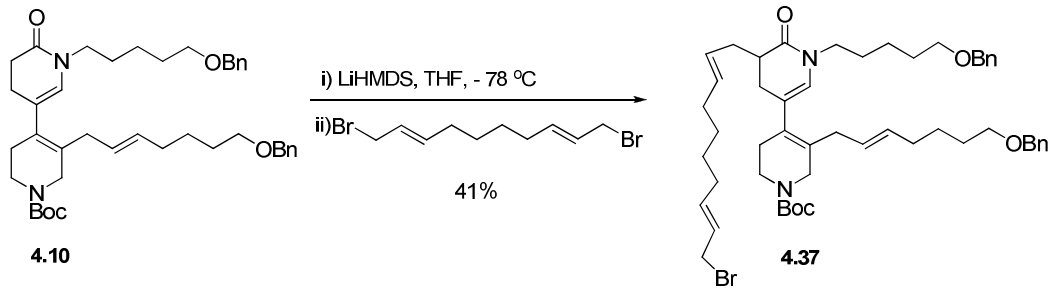
(2*E*, 8*E*)-deca-2,8-diene-1,10-diol (4.35). To a solution of diisobutyl- aluminum hydride (12.4 mL, 69.7 mmol) in dichloromethane (100 mL) at -78 °C was added the bis allylic

ester **4.34** (2.95 g, 11.6 mmol) in dichloromethane (10 mL) dropwise. The mixture was allowed to stir at -78 ^{o}C for 1 h. The reaction was poured into 50 mL of Rochelle's salt and allowed to stir for 30 minutes. The mixture was extracted with ethyl acetate (3 x 50 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel eluting with 1:1 (hexanes/ethyl acetate) to yield (2E, 8E)-deca-2,8-diene-1,10-diol **4.35** (1.65 g, 84%) as a colorless oil. Spectral data correlated to reported values.[184]

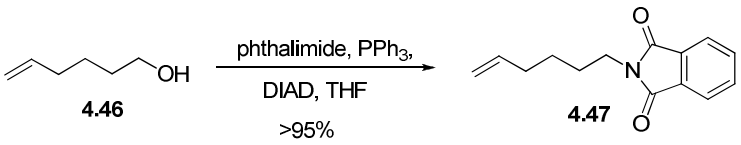


4.35 **4.36**

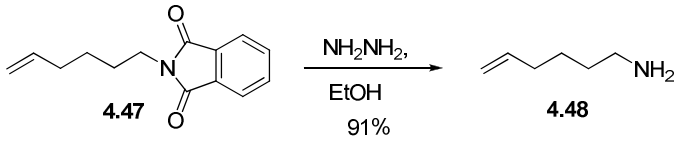
(2*E*, 8*E*)-1,10-dibromodeca-2,8-diene (4.36). To a solution of diol **4.35** (20.0 mg, 0.12 mmol) in acetonitrile (1.50 mL) was added triphenylphosphine (108 mg, 0.41 mmol), followed by carbon tetrabromide (137 mg, 0.41 mmol). The solution was allowed to stir for 17 h. The mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with 20:1 (hexanes/ethyl acetate) to yield (2E, 8E)-1,10-dibromodeca-2,8-diene **4.36** (21 mg, 60%) as a pale yellow oil. Spectral data correlated to reported values.[185]



Alkylated Bis-Piperidine (4.37). To a solution of amide **4.10** (43.0 mg, 0.065 mmol) in tetrahydrofuran (0.50 mL) at -78 °C was added LiHMDS (91 μL, 0.091 mmol) dropwise. The mixture was stirred for 1.5 h at -78 °C. In a separate flask the bis allylic bromide (29.0 mg, 0.098 mmol) in tetrahydrofuran (0.20 mL) was cooled to -78 °C. The enolate solution was added to the allylic bromide via cannula. The resulting solution was stirred for 1 h at -78 °C. The reaction was quenched with aqueous sodium bicarbonate. The mixture was washed with aqueous sodium bicarbonate. The aqueous phase extracted with ethyl acetate (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel eluting with 5:1 to 4:1 (hexanes/ethyl acetate) to yield alkylated bis-piperidine **4.37** (23.3 mg, 41%) as a yellow gum. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.35 - 7.25 (m, 10H), 5.84 (s, 1H), 5.71 (m, 2H), 5.39 (m, 4H), 4.46 (s, 4H), 3.93 (d, J = 8.0 Hz, 2H), 3.80 (br s, 2H), 3.43 (m, 8H), 2.77 (d, J = 4.0 Hz, 2H), 2.51 – 2.42 (m, 2H), 2.12 – 2.10 (m, 3H), 2.02 – 1.98 (m, 6H), 1.60 (m, 4H), 1.58 (m, 4H), 1.45 (s, 9H), 1.34 (m, 8H).

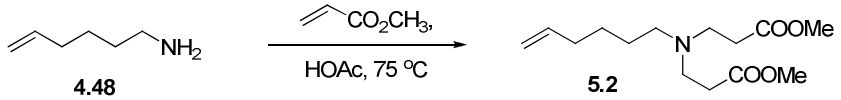


2-(hex-5-enyl)isoindoline-1,3-dione (4.47) To a solution of 5-hexen-1-ol (**4.46**, 5.21 g, 52.1 mmol), triphenylphosphine (15.3 g, 67.7 mmol), phthalimide (7.73 g, 52.6 mmol) at 0 °C in tetrahydrofuran (23.0 mL) was added diiospropylazodicarboxylate (13.3 mL, 67.7 mmol) dropwise. The solution was allowed to warm to room temperature and stirred for 24 h. The reaction mixture was concentrated and the residue triturated with diethyl ether/hexanes (1:1). The combined extracts were concentrated and the residue purified by flash column chromatography on silica gel (eluent: 2:1 hexanes/ethyl acetate) to yield 2-(hex-5-enyl)isoindoline-1,3-dione **4.47** (11.3 g, 95%) as a pale yellow oil. Spectral data correlated with the reported values.[186]

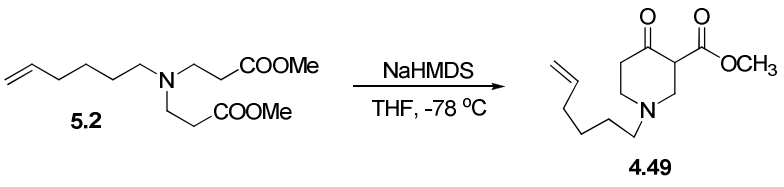


5-Amino-1-hexene (4.48). To a solution of imide **4.47** (10.9 g, 47.4 mmol) in 95% ethanol (150 mL) was added hydrazine hydrate (6.91 mL, 142.1 mmol) dropwise. The solution was heated to reflux for 1 h. The reaction mixture was cooled to room temperature and the resulting white precipitate removed by filtration and washed with ethanol (100 mL). The filtrate was treated with 12 M hydrochloric acid (10 mL) and concentrated *in vacuo*. The residue was diluted with water (100 mL) and the pH adjusted to 10 by the dropwise addition of 1 M NaOH. The alkaline solution was extracted with

diethyl ether (4 x 50 mL), the combined organic extracts dried over $MgSO_4$, filtered, and concentrated *in vacuo* at 0 °C. The residue was distilled (bp 90-110 °C, 760 mm) to yield hex-5-en-1-amine **4.48** (4.38 g, 93%) as a colorless oil. Spectral data correlated with the reported values.[187]

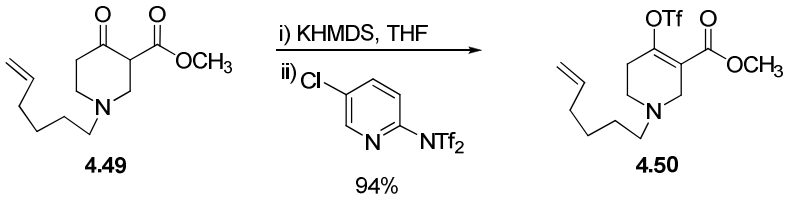


Amine 5.2. To a mixture of amine **4.48** (200 mg, 2.02 mmol) and methyl acrylate (0.64 mL, 7.07 mmol) was added 1 drop of acetic acid. The mixture was heated to 75 °C for 24 h. The excess methyl acrylate was removed *in vacuo* and the crude amine (**5.2**) taken to the next step without further purification. Isolated as a light yellow oil: IR (neat) 2949, 1737, 1437 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 5.77 (ddt, *J* = 6.7, 10.2, 16.9 Hz, 1H), 5.00 (m, 2H), 3.65 (s, 6H), 2.74 (t, *J* = 7.3 Hz, 2H), 2.42 (t, *J* = 7.3 Hz, 2H), 2.39 (t, *J* = 7.5 Hz, 2H), 2.04 (m, 2H), 1.33 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.0, 138.7, 114.4, 53.4, 51.5, 49.1, 33.5, 32.3, 26.5, 26.3. HRMS calculated for $C_{14}H_{26}NO_4$ $(M + H)^+$ *m/z*: 272.1862, measured: 272.1852.



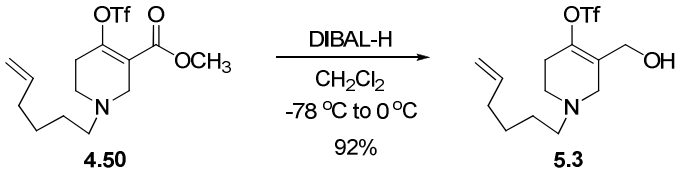
Methyl 1-(hex-5-enyl)-4-oxopiperidine-3-carboxylate (4.49) To a solution of amine **5.2** (100 mg, 0.37 mmol) in tetrahydrofuran (3 mL) at -78 °C was added sodium

bis(trimethylsilyl)amide dropwise (0.55 mL, 0.55 mmol, of a 1.0 M solution in tetrahydrofuran). The resulting solution was stirred for 1.5 h at -78 °C, and then quenched with saturated sodium bicarbonate (10 mL). The aqueous phase was extracted with ethyl acetate (3 x10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel (eluent: 3.5:1 hexanes/ethyl acetate) to yield β-keto ester **4.49** (74 mg, 84%) as a pale yellow oil: IR (neat) 2937, 2807, 1665, 1625, 1443 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.77 (ddt, *J* = 6.7, 10.2, 16.9 Hz, 1H), 5.02 (m, 2H), 3.73 (s, 3H), 3.10 (s, 2H), 2.58, (t, *J* = 5.9 Hz, 2H), 2.43, (m, 4H), 2.15, (s, 1H), 2.04, (m, 4H), 1.53-1.39, (m, 4H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 204.1, 171.4, 170.4, 169.3, 138.7, 114.5, 96.7, 57.8, 56.8, 56.4, 55.1, 53.4, 52.2, 51.4, 49.8, 49.3, 40.7, 36.6, 33.5, 29.4, 26.8, 26.7, 26.5. HRMS calculated for $C_{13}H_{21}NO_3$ $(M + H)^+$ *m/z*: 240.1600, measured: 240.1592.



Methyl 1-(hex-5-enyl)-4-(trifluoromethylsulfonyloxy)-1,2,5,6-tetrahydropyridine-3-carboxylate 4.50. A solution of β-keto ester **4.49** (4.45 g, 19.87 mmol) in tetrahydrofuran (150 mL) at -78 °C was treated with potassium bis(trimethylsiyl) amide (47.7 mL, 23.85 mmol, of a 0.5 M solution in toluene) dropwise. The solution was warmed to -20 °C over 2 h. The mixture was then cooled back to -78 °C and *N,N*-bis(trifluoromethylsulfonyl)-5-chloro-2-pyridylamine (9.37 g, 23.85 mmol) in

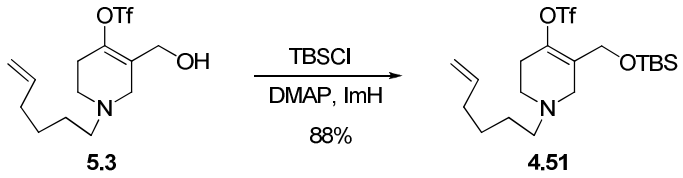
tetrahydrofuran (20 mL) was added dropwise via cannula. The resulting solution was slowly warmed to room temperature and stirring continued overnight. The solution was quenched with saturated sodium bicarbonate. The aqueous phase was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel (eluent: 4:1 hexanes/ethyl acetate) to yield triflate **4.50** (6.92 g, 94%) as a pale yellow oil: IR (neat) 2932, 1723, 1424 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.77 (ddt, J = 6.7, 10.3, 16.9 Hz, 1H), 5.02 (m, 2H), 3.79 (s, 1H), 3.36, (s, 2H) 2.71, (t, J = 5.6 Hz, 2H), 2.52 (m, 4H), 2.05, (m, 2H) 1.53-1.40, (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.1, 150.8, 138.3, 124.0, 120.2 (q, J = 282 Hz), 114.6, 56.5, 52.1, 51.5, 48.8, 33.3, 28.7, 26.3, 26.1. HRMS calculated for $C_{13}H_{20}F_3NO_5S$ $(M + H)^+$ *m/z*: 372.1093, measured: 372.1080.



4.50 **5.3**

Allylic alcohol 5.3. A solution of diisobutylaluminum hydride (28.2 mL, 158.1 mmol diluted in 50 mL of CH_2Cl_2) was added to a solution of ester **4.50** (19.5 g, 52.7 mmol) in CH_2Cl_2 (600 mL) at -50 °C via cannula. The mixture was stirred for 2 h and allowed to warm to 0 °C. The solution was quenched by slow addition of a saturated aqueous solution of potassium sodium tartrate (50 mL). The resulting mixture was vigorously stirred for 1 h. The aqueous phase was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to yield a residue that was taken directly to the next step without further purification. Isolated as

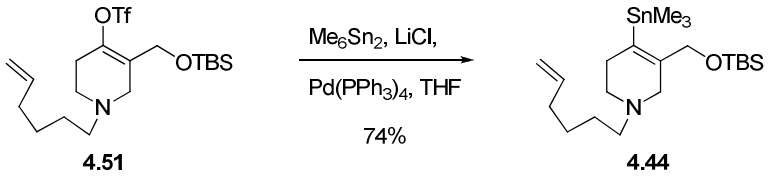
light yellow oil: IR (neat) 3430, 1415, 1209, 1140 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.77 (ddt, *J* = 6.8, 10.3, 17.1 Hz, 1H), 5.02 (m, 2H), 4.19 (s, 1H), 3.21, (s, 2H), 2.67 (t, *J* = 5.7 Hz, 2H), 2.45 (m, 4H), 2.05 (m, 2H) 1.55-1.40 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.6, 138.5, 128.5, 119.6 (q, *J* = 319 Hz), 114.6, 57.6, 57.1, 52.5, 49.6, 33.5, 27.8, 26.6, 26.3. HRMS calculated for $C_{13}H_{20}F_3NO_4S$ $(M + H)^+$ *m/z*: 344.1143, measured: 344.1131.



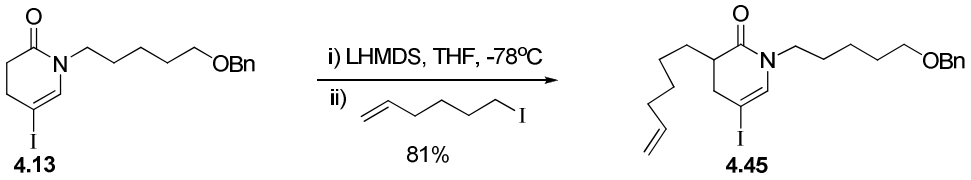
5.3 **4.51**

Silyl Ether 4.51. To a solution of 4-(dimethylamino)pyridine (406 mg, 3.34 mmol), imidazole (2.27 g, 33.4 mmol), and alcohol **5.3** (5.72 g, 16.7 mmol) in tetrahydrofuran (150 mL) at 0 °C was added tert-butylchlorodimethylsilane (5.04 g, 33.4 mmol). The resulting solution was slowly warmed to room temperature and stirring continued for 22 h. The mixture was quenched with brine (100 mL) and the aqueous phase extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to yield a residue that was purified by column chromatography on silica gel (gradient elution: 100:1 to 10:1 hexanes/ethyl acetate, 1% triethylamine) yield silyl ether **4.51** (6.74 g, 88%) as a pale yellow oil: IR (neat) 3075, 2857, 1640 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.78 (ddt, *J* = 7.0, 9.8, 16.9 Hz), 5.00 (m, 2H), 4.02 (s, 2H), 3.00, (s, 2H), 2.46 (t, *J* = 6.0 Hz), 2.33 (m, 4H), 2.04 (m, 2H), 1.53 (m, 2H), 1.39 (m, 2H), 1.23 (m, 2H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.6, 138.5, 128.3, 119.6 (q, *J* = 318 Hz), 114.6, 58.5, 56.9, 52.3, 49.9, 33.65, 27.9, 26.7, 26.6,

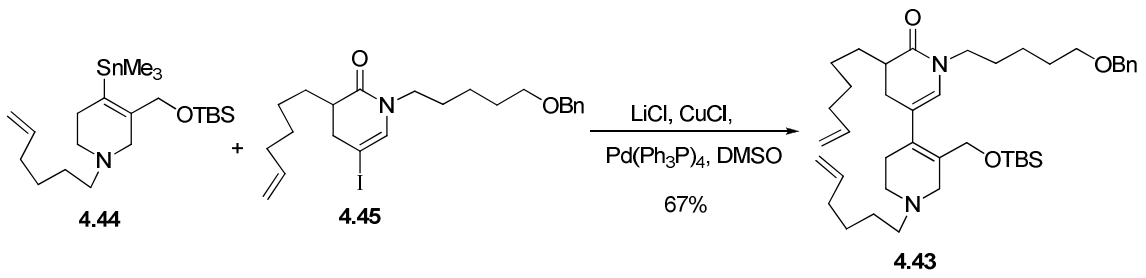
25.7, 18.2, -5.6. HRMS calculated for $C_{19}H_{34}F_3NO_4Si$ $(M + H)^+$ *m/z*: 458.2008, measured: 458.1999.



Vinyl stannane 4.44. Silyl ether **4.51** (5.00 g, 10.9 mmol) was dissolved in tetrahydrofuran (100 mL) then treated with hexamethyldistannane (4.65 g, 14.2 mmol), lithium chloride (2.29 g, 54.7 mmol), and tetrakis(triphenylphosphine)palladium (1.26 g, 1.09 mmol). The resulting mixture was degassed 3 times (freeze-pump-thaw) and warmed to room temperature. Once the mixture had reached room temperature, it was placed into an oil bath pre-heated to 80 °C and kept at reflux for 24 h (until the yellow solution turned black). The solution was quenched with saturated aqueous sodium bicarbonate then filtered over celite. The filtrate was extracted with with ethyl actetate (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to yield a residue that was purified by column chromatography on silica gel (eluent: 300:10:0.05 hexane/ethyl acetate/triethylamine) to yield vinyl stannane **4.44** (3.87 g, 75%) as a yellow oil. IR (neat) 2933, 1416, 1250, 1210 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.77 (ddt, *J* = 6.6, 10.2, 16.8 Hz), 5.01 (m, 2H), 4.28 (s, 2H), 3.16, (s, 2H), 2.68 (t, *J* = 5.5 Hz), 2.45 (m, 4H), 2.04 (m, 2H), 1.52-1.40 (m, 4H), 0.87 (s, 9H), 0.122 (s, 6H), 0.42 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.7, 138.6, 133.7, 114.4, 68.04, 58.6, 55.3, 50.6, 33.6, 32.7, 26.9, 26.5, 25.9, 18.3, -5.3, -8.7. HRMS calculated for $C_{21}H_{44}NOSiSn$ $(M + H)^+$ *m/z*: 474.2214, measured: 474.2206.

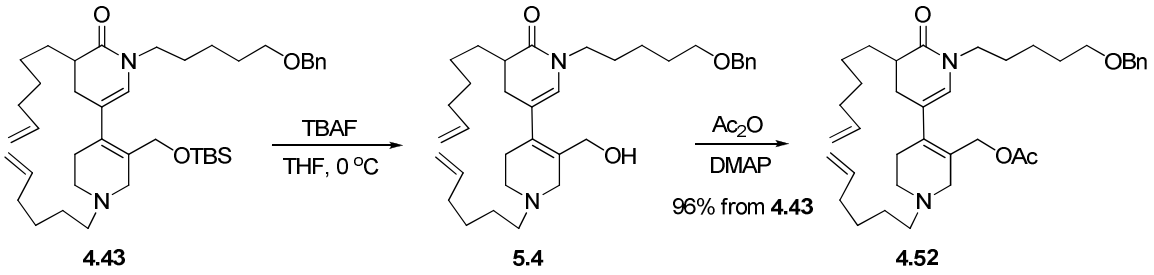


Vinyl Iodide 4.45. Lithium bis(trimethylsilyl)amide (5.75 mL of a 1.0 M solution in tetrahydrofuran) was added to vinyl iodide **4.13** (2.00 g, 5.01 mmol) in tetrahydrofuran (42 mL) at -78 °C. The solution was strirred for 2 h and allowed to warm to 0 °C. The resulting enolate solution was cooled to -78 °C and treated with alkyl iodide 6-iodo-1-hexene (1.26 g, 6.01 mmol).[143] The resulting solution was allowed to warm to 0 °C over 1 h. The reaction was quenched with water and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to yield a residue that was purified by column chromatography on silica gel (gradient eluent: 12:1 to 8:1 hexane/ethyl acetate) to yield vinyl iodide **4.45** (2.03 g, 84%) as a yellow oil: IR (neat) 2931, 2858, 1671 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300MHz) δ 7.31 – 7.23 (m, 5H), 6.36 (s, 1H), 7.0 (ddt, *J* = 7.0, 11.4, 18.4 Hz, 1H), 5.00 (m, 2H), 4.47 (s, 2H), 3.43 (m, 4H), 2.71 (m, 4H), 2.47 (m, 2H), 2.02 (m, 2H), 1.86 (m, 2H), 1.61-1.49 (m, 4H), 1.41-1.31 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.8, 138.5, 138.4, 134.9, 128.2, 127.4, 127.3, 114.4, 72.7, 69.8, 67.4, 46.2, 41.9, 38.4, 33.4, 29.6, 29.2, 28.6, 28.4, 26.2, 23.1. HRMS calculated for $C_{23}H_{32}INO_2Na$ $(M + Na)^+$ *m/z*: 504.1376, measured: 540.1374.



Bis-piperidine 4.43. A solution of vinyl stannane **4.44** (2.47 g, 5.23 mmol) and vinyl iodide **4.45** (2.05 g, 4.26 mmol) in dimethyl sulfoxide (38 mL) was treated with copper chloride (2.26 g, 22.8 mmol), lithium chloride (1.15 g, 27.3 mmol, flame dried under argon), and tetrakis(triphenylphosphine)palladium (526 mg, 0.46 mmol) at room temperature. The mixture was immediately degassed (3x) under high vacuum with an argon purge. The mixture was then warmed to room temperature and stirred for 2 h, followed by heating to 60 °C for 14 h. The black mixture was quenched with brine, and the resulting solution was filtered over celite. The filtrate was washed with brine (100 mL) and 5% ammounium hydroxide (5 mL), extracted with ethyl acetate (4 x 50 mL), and the combined organic extracts were washed again with brine (25 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (gradient elution: 2:1 to 1:1 to 1:1:0.01 hexanes:ethyl acetate:triethylamine) to yield bis-piperidine **4.43** (1.90 g, 67%) as a yellow oil: IR (neat) 2930, 2855, 1670, 1403 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400MHz) δ 7.32 - 7.26 (m, 5H), 5.91 (s, 1H), 5.79 (m, 2H), 4.94 (m, 4H), 4.47 (s, 2H), 4.13 (s, 2H), 3.43 (m, 4H), 3.04 (m, 2H), 2.54 (m, 2H), 2.40 – 2.36, (m, 2H), 2.20 (m, 2H), 2.10 – 2.02 (m, 5H), 1.82, (m, 2H), 1.62 – 1.50 (m, 6H), 1.43 – 1.31 (m, 8H), 0.88 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1, 138.8, 138.6, 138.5, 131.0, 130.3, 128.3, 127.5,

127.4, 126.8, 116.7, 114.4, 114.3, 72.8, 70.1, 62.5, 58.4, 54.8, 50.2, 46.2, 40.4, 33.6, 33.5, 29.8, 29.3, 29.1, 28.9, 28.8, 28.5, 26.8, 26.6, 26.5, 25.8, 23.3, 18.2, -5.8 HRMS calculated for $C_{41}H_{67}N_2O_3Si$ $(M + H)^+$ *m/z*: 663.4954, measured: 663.4921.

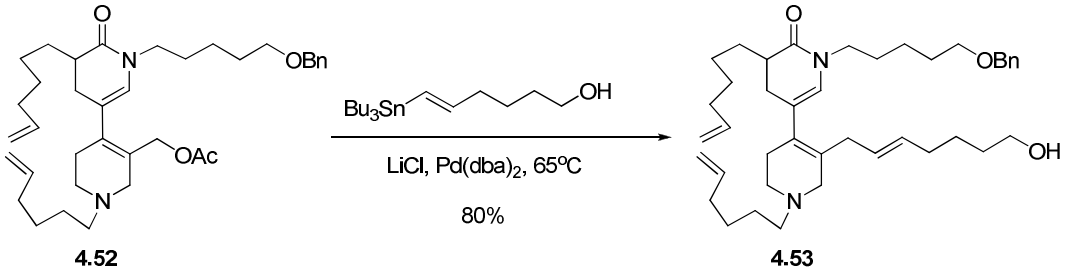


4.43 **5.4** **4.52**

Allylic acetate 18. Tetrabutylammonium fluoride (1.0 mL of a 1.0 M solution in tetahydrofuran) was added dropwise to a solution of silyl ether **4.43** (329.0 mg, 0.496 mmol) in THF (8 mL) at 0 °C. The solution was stirred for 1 h at 0 °C, and then quenched with water (5 mL). The aqueous layer was extracted with ethyl acetate (4 x 10 mL), dried over $MgSO_4$, filtered, and concentrated. The crude alcohol (**5.4**) was taken directly to the next step without further purification.

To a solution of crude alcohol **5.4** (272.0 mg, 0.496 mmol) in dichloromethane (6 mL) at room temperature was added acetic anhydride (85 μL, 0.893 mmol), 4–(dimethylamino)pyridine (48 mg, 0.397), and triethylamine (0.21 mL, 1.49 mmol). The resulting solution was allowed to stir for 1 h, and then quenched with brine (10 mL). The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (gradient elution: 1:1 to 1:1:0.01 hexanes:ethyl acetate:triethylamine) to yield allylic acetate **4.53** (280 mg, 96% from **4.43**) as a yellow oil. IR (neat) 2930, 1738, 1668 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500MHz) δ 7.30 -

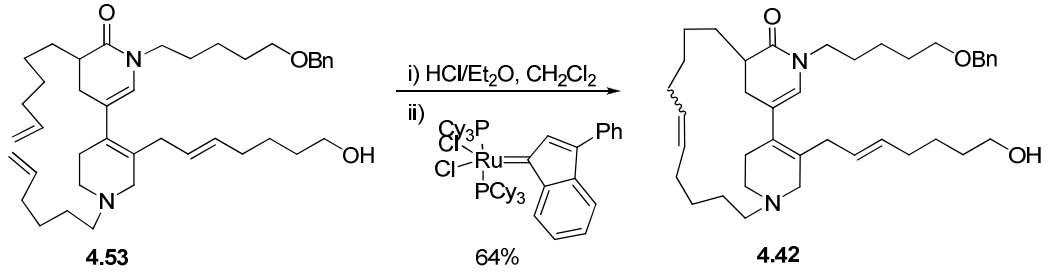
7.25 (m, 5H), 5.87 (s, 1H), 5.76 (m, 2H), 4.93 (m, 4H), 4.58 (m, 2H), 4.45 (s, 2H), 3.43 – 3.35 (m, 4H), 3.06 (m, 2H), 2.61 (m, 2H), 2.45, (t, J = 7.6 Hz, 2H), 2.35 (m, 2H), 2.25 (m, 2H), 2.06 – 2.01, (m, 8H), 1.59 – 1.50 (m, 6H), 1.38 – 1.32 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.0, 170.8, 138.8, 138.5 (2C), 135.6, 128.2, 127.5, 127.4, 127.2, 125.0, 115.9, 114.6, 114.3, 72.7, 70.0, 63.7, 57.7, 54.3, 49.4, 46.3, 40.3, 33.5 (2C), 29.7, 29.3, 28.8, 28.7 (2C), 28.4, 26.7, 26.4, 25.9, 23.3, 20.9. HRMS calculated for $C_{37}H_{55}N_2O_4$ $(M + H)^+$ *m/z*: 591.4162, measured: 591.4161.



4.52 **4.53**

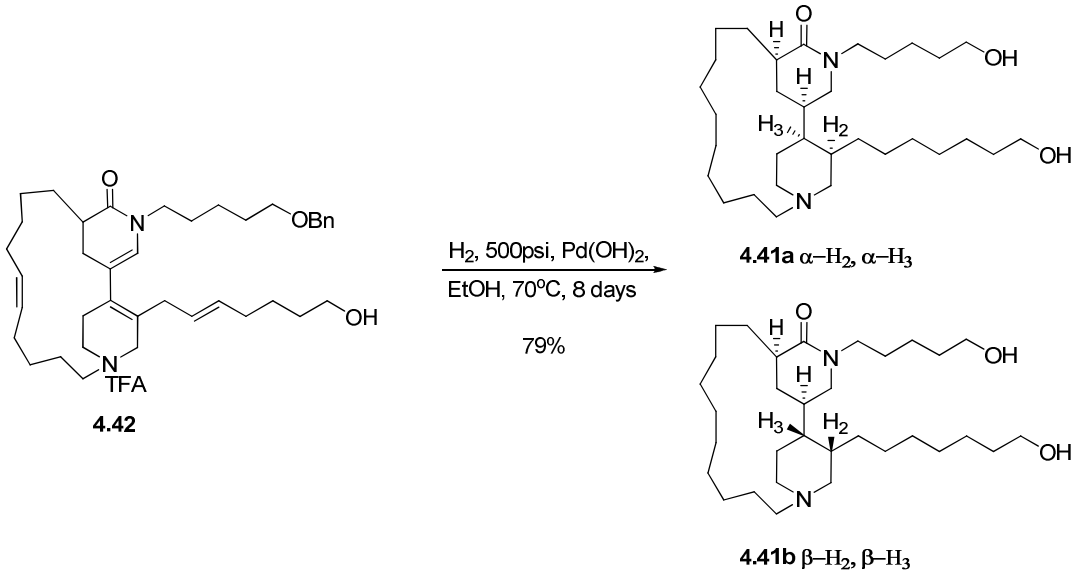
Tetraene 4.53. To a solution of alyllic acetate **4.52** (2.50 g, 4.23 mmol) in dimethylformamide (35 mL) at room temperature was added (*E*)-6-(tributylstannyl)hex-5-en-1-ol[144] (2.47 g, 6.34 mmol), lithium chloride (888 mg, 21.2 mmol), and bis(dibenzylidieneacetone)palladium (245 mg, 0.42 mmol). The mixture was heated to 65 °C and stirred for 22 h total with 0.01 equivalents of bis(dibenzylidieneacetone)palladium (24.5 mg, 0.04 mmol) added after 14 h. The reaction was filtered thru Celite and the filtrate was washed with brine (20 mL). The aqueous layer was extracted with ethyl acetate (3 x 40 mL) and the combined organic extracts were washed with brine (2 x 20 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel

(gradient elution with 2:1 to 1:1:0.01 hexanes:ethyl acetate:triethylamine) to yield tetraene **4.53** (2.13 g, 80%) as a yellow oil. IR (neat) 3625, 2928, 2856, 1666, 1404 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300MHz) δ 7.30 - 7.24 (m, 5H), 5.85 (s, 1H), 5.78 (m, 2H), 5.00 – 4.92 (m, 4H), 4.46 (s, 2H), 3.57 (m, 2H), 3.43 – 3.32 (m, 4H), 2.88 (m, 2H), 2.73 (m, 2H), 2.52, (m, 2H), 2.39 – 2.35 (m, 3H), 2.18 (m, 2H), 2.18, (m, 2H), 2.07 – 2.02 (m, 6H), 1.62 – 1.50 (m, 10H), 1.41 – 1.33 (m, 12)H; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.1, 138.8, 138.6, 138.5, 134.4, 129.3, 129.0, 128.5, 128.3, 127.6, 127.5, 125.8, 117.6, 114.4, 114.3, 72.8, 70.1, 62.5, 58.3, 56.0, 50.4, 46.2, 40.5, 35.5, 33.5, 33.5, 32.2, 29.8, 29.6, 29.4, 29.2, 28.8, 28.5, 27.8, 26.9, 26.8, 26.5, 25.6, 23.3, 17.5, 13.5. HRMS calculated for $C_{41}H_{63}N_2O_3$ $(M + H)^+$ *m/z*: 631.4839, measured: 631.4850.



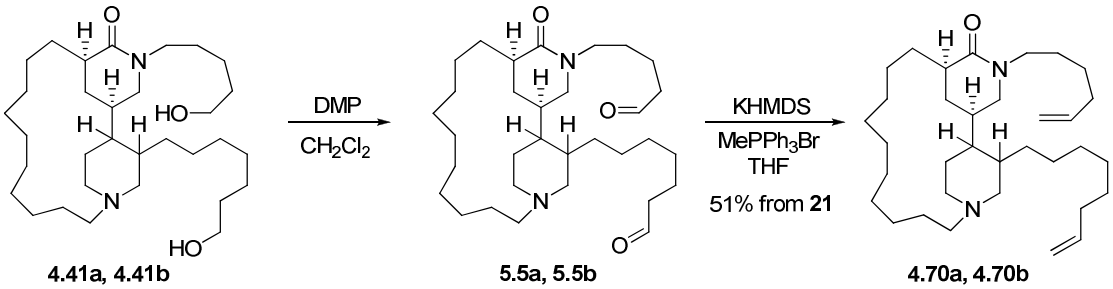
Tricycle 4.42. A hydrochloric acid (5 mL of 2 M solution in ether) was added to a solution of tetraene **4.53** (220 mg, 0.35 mmol) in dichloromethane (5 mL), and the resulting solution was stirred for 30 min at ambient temperature. The solution was then concentrated and dried *in vacuo*. The viscous, bright yellow hydrochloride salt was dissolved in dichloromethane (1 L) and Bis(tricyclohexylphosphine)-3-phenyl-1H-inden-1-ylidene ruthenium(II) dichloride (32 mg, 0.035 mmol) was quickly added in one portion. The solution was brought to reflux for 2 h, at which point an additional (32 mg,

10 mol%) of the catalyst was added. The solution was maintatained at reflux for an additional 20 h, cooled to room temperature and concentrated. The resulting residue was dissolved in methanol and passed through a Varian SCX ion exchange column to remove ruthenium byproducts, followed by eluting tricycle **4.42** with 2N ammonia in methanol to release the free amine. Additionally, the residue was purified by Biotage (KP-C18-HS) reverse phase chromatography eluting with H_2O (0.1% TFA) / Acetonitile (20 % to 60% acetonitrile over 10 column volumes). The aqueous fractions were concentrated by Genevac and the resulting material analyzed by LC/MS to yield 134 mg, 64% of tricycle **4.42**. The material was typically kept as the trifluoroacetic acid salt for use in the next step. The salt was converted to the free amine passage through a Varian SCX ion exchange column for calculation of yield and analytical data. IR (neat) 3530, 2932, 2846, 1666 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400MHz) δ 7.30 - 7.24 (m, 5H), 5.87 (s, 1H), 5.44 – 5.30 (m, 4H), 4.46 (s, 2H), 3.62 – 3.57 (m, 2H), 3.44 (app. t, *J* = 6.4 Hz, 2H), 3.32 (m, 2H), 3.06 (m, 2H), 2.73 (m, 2H), 2.60 (m, 2H), 2.50, (m, 1H), 2.37 (m, 2H), 2.07 – 2.02 (m, 6H), 1.61 – 1.52 (m, 10H), 1.42 – 1.35 (m, 7H), 1.23 (m, 6H), 0.88 – 0.83 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.2, 133.1, 132.7, 132.0, 131.9, 130.8, 130.7, 130.6 (2C), 128.7, 128.2, 128.0, 127.9, 73.3, 70.5, 62.8, 51.8, 46.4, 41.1, 36.2, 32.8, 32.7, 31.9, 31.8, 31.0, 30.1 (2C), 29.8, 28.9 (2C), 27.6, 27.5, 26.2, 26.1 (2C), 25.1, 23.8. HRMS calculated for $C_{39}H_{59}N_2O_3$ $(M + H)^+$ *m/z*: 603.4526, measured: 603.4528.



Diols 4.41. The trifluoroacetic acid salt of tetraene **4.42** (340.0 mg, 0.56 mmol, free amine weight) was dissolved in ethanol (30 mL), treated with palladium hydroxide (79.0 mg, 0.11 mmol), and transferred to a Parr hydrogenator. Once the vessel was tightly secured, the solution was purged with hydrogen, evacuated, and back-filled a total of five times. The pressure was set to 500 psi and the mixture was heated to 70 °C with vigorous stirring. The progress of the reaction mixture was monitored by LC/MS. After 8 days the reaction was filtered thru Celite and concentrated. The resulting residue was purified by reverse phase HPLC chromatography eluting with H_2O (0.1% TFA) / Acetonitile (12% to 40% acetonitrile) to afford a non-separable mixture of **4.41a** and **4.41b**. Fractions were analyzed using LC/MS and concentrated by Genevac. The products were converted to their free amines by passing through a Varian SCX ion exchange column by eluting first with methanol then 2N ammonia in methanol to release 230.1 mg [79% yield of **4.41a** and **4.41b** (1.3:1 determined by ^{13}C NMR), characterized as a mixture]: IR (neat) 3400, 2920, 1622, 1494, 1461 cm^{-1} ; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.61 (app. t, *J*

= 6.4 Hz, 4H), 3.37 – 3.27 (m, 2H), 3.23 – 3.17 (m, 1H), 3.03 (m, 1H), 2.85 – 2.77 (m, 3H), 2.65 – 2.53 (m, 5H), 2.26 (m, 1H), 2.11 (m, 2H), 1.93 – 1.86 (m, 3H), 1.67 (m, 1H), 1.63 – 1.55 (9H), 1.38 – 1.26 (28H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.1, 171.9 (2 diasteromers); 62.6 (2C); 62.3, 56.9, 56.8, 54.5, 53.9, 52.9, 52.2, 47.2, 47.0, 46.0, 42.0, 41.6, 41.0, 40.1, 39.9, 36.0, 34.7, 34.6, 33.7, 33.3, 32.9, 32.6, 32.5, 32.2, 31.4, 30.9, 30.6, 29.7, 29.3 (2C), 28.1, 27.9, 27.5, 27.4, 27.2, 27.1 (2C), 26.9 (2C), 26.6, 26.5, 26.3, 26.1, 25.9, 25.7 (2C), 25.3, 22.8, 21.8, 21.6. HRMS calculated for $C_{32}H_{61}N_2O_3$ $(M + H)^+$ *m/z*: 521.4682, measured: 521.4682.

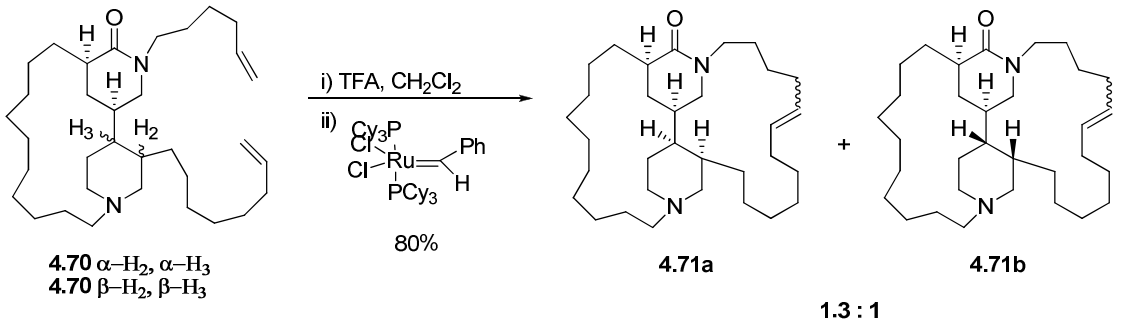


4.41a, 4.41b **5.5a, 5.5b** **4.70a, 4.70b**

Dienes 4.70. To a solution of diols **4.41** (170.0 mg, 0.327 mmol) in dichloromethane (8 mL) at 0 °C was added freshly prepared Dess Martin periodinane[158] (277.0 mg, 0.654 mmol). The resulting mixture was stirred at 0 °C for 30 minutes, then additional Dess Martin periodinane (277 mg, 0.654 mmol) was added. The mixture was slowly warmed to room temperature and stirred for 1 h. The light yellow solution was then cooled to 0 °C and quenched with water (2 mL), saturated aqueous sodium bicarbonate (2 mL), and saturated aqueous $NaHSO_3$ (2 mL). The mixture was stirred for 5 min at 0 °C, allowed to warm to room temperature and stirring continued for 30 min. The solution was then extracted with dichloromethane (4 x 10 mL). The combined organic extracts were dried

over $MgSO_4$, filtered, and concentrated. The crude bis-aldehydes **5.5** was used immediately in the next step without further purification.

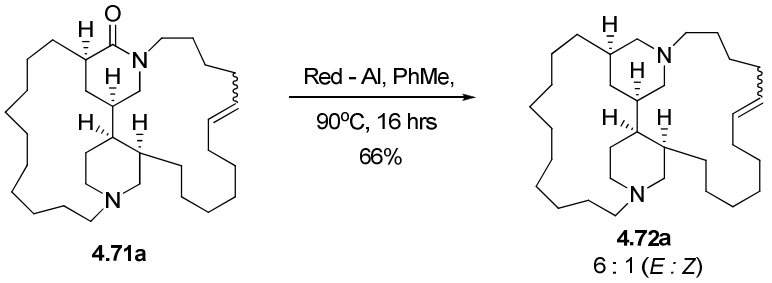
A solution of methyl triphenylphosphonium bromide (1.17 g, 3.27 mmol) in tetrahydrofuran (8.0 mL) was cooled to 0 °C and potassium bis(trimethylsilyl)amide (3.90 mL of a 0.5 M solution in toluene) was added dropwise. The yellow mixture was allowed to warm to room temperature and stirred for 1 h. The mixture was cooled to 0 °C and bis-aldehydes **5.5** in tetrahydrofuran (1.5 mL) added dropwise. The resulting mixture was stirred for 20 min, and then quenched with water (10 mL). The aqueous layer was extracted with ethyl acetate (4 x 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (gradient elution 2:2:0.25 hexanes:ethyl acetate:methanol to 3:6.5:0.5 hexanes:ethyl acetate:triethylamine) to yield dienes **4.70** (85.0 mg, 51%) as a yellow oil. Characterized as a mixture of 2 diastereomers: IR (neat) 3076, 2918, 2236, 1643, 1490 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400MHz) δ 5.81 – 5.71 (m, 2H), 5.00 – 4.90 (m, 4H), 3.32 – 3.14 (m, 4H), 2.99, (m, 1H), 2.76 – 2.67 (m, 3H), 2.57 (m, 2H), 2.52 – 2.50 (m, 2H), 2.23, (m, 2H), 2.08 – 1.99 (m, 6H), 1.85 (m, 3H), 1.62 (m, 1H), 1.51 – 1.48 (m, 6H), 1.37 – 1.28 (m, 30H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.0, 171.7, 139.0, 138.5, 114.6, 114.2, 60.3, 57.2, 57.1, 55.9, 54.6, 54.2, 54.0, 53.7, 53.6, 53.4, 53.1, 52.4, 49.1, 47.4, 47.1, 47.0, 46.0, 43.3, 42.0, 41.7, 41.4, 41.3, 40.2, 40.1, 39.4, 38.5, 36.4, 34.9, 34.1, 33.9, 33.7, 33.4, 32.9, 32.7, 31.8, 31.6, 31.0, 30.6, 30.4, 29.8, 29.6, 29.0, 28.9, 28.3, 28.0, 27.7, 27.5, 27.4, 27.3, 27.2, 27.1, 27.0, 26.9, 26.7, 26.5, 26.4 (2C), 26.1, 26 (2C), 25.3, 22.1, 21.9. HRMS calculated for $C_{34}H_{61}N_2O$ $(M + H)^+$ *m/z*: 513.4784, measured: 513.4784.



Alkenes 4.71a and 4.71b. To a solution of dienes **4.70a/4.70b** (20.0 mg, 0.039 mmol, free amine weight) in dichloromethane (2.0 mL) was added trifluoroacetic acid (2 drops). The solution was stirred for 30 minutes and concentrated. The residue was then dissolved in dichloromethane (250 mL) and Bis(tricyclohexylphosphine)benzylidine ruthenium(IV) chloride (3.3 mg, 0.004 mmol) was added. The solution was refluxed for 2 h, cooled to room temperature and treated with additional catalyst (3.3 mg, 0.004 mmol). This solution was heated at reflux for 16 h and concentrated. The resulting residue was purified by a SCX ion exchange column24; eluting with methanol, then 2N ammonia in methanol. This residue was further purified by reverse phase HPLC chromatography eluting with H_2O (0.1% TFA) / Acetonitile (30 % to 60% acetonitrile). The resulting fractions were concentrated by Genevac. The purified TFA salt was converted to the free amine by running the residue through an SCX ion exchange column. The fractions were concentrated and the 2 pure diastereomers were separated by flash column chromatography on silica gel (eluent 3:6.5:0.25 hexanes:ethyl acetate:triethylamine) to yield 5.6 mg of **4.71b** and 9.5 mg of **4.71a** (80 % combined yield).

4.71a: light yellow oil: IR (neat) 2925, 2853, 1639 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 600MHz) δ 5.31 – 5.23 (m, 2H), 4.34 (m, 1H), 3.53 (app t, *J* = 12.0 Hz, 1H), 2.99 (m, 1H), 2.87 (app. t, *J* = 10.8 Hz, 1H), 2.73 (m, 1H), 2.71 – 2.58 (m, 4H), 2.37 (m, 1H), 2.25 (m, 1H), 2.07 – 1.95 (m, 7H), 1.69 (m, 1H), 1.71 (m, 2H), 1.54 (m, 4H), 1.42 – 1.24 (m, 29H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 171.8, 131.0, 130.8, 57.0, 54.7, 52.3, 47.7, 46.3, 42.7, 42.0, 41.4, 36.0, 35.2, 34.2, 33.1, 32.4, 31.6, 31.3, 29.6, 28.4, 28.2, 27.4, 27.3, 27.2, 27.1, 27.1, 26.8, 26.5, 26.3, 26.2, 25.6, 21.6. HRMS calculated for $C_{32}H_{57}N_2O$ $(M + H)^+$ *m/z*: 485.4471, measured: 485.4471.

4.71b: light yellow oil: IR (neat) 2923, 2851, 1644 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600MHz) δ 5.31 – 5.25 (m, 2H), 4.14 (m, 1H), 3.18, (m, 1H), 2.99 (app. t, *J* = 11.4 Hz, 1H) 2.77 (m, 1H), 2.68 (m, 3H), 2.55 (m, 1H), 2.37 (app t, *J* = 11.4 Hz, 1H), 2.29 (m, 2H), 2.17 (m, 1H), 2.05 – 1.97 (m, 5H), 1.84 (m, 3H), 1.51 (m, 3H), 1.33 – 1.29 (m, 32H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 171.7, 131.1, 130.1, 56.7, 55.3, 52.4, 47.4, 47.1, 41.0, 40.8, 32.3, 32.3, 31.7, 31.6, 31.4, 30.5, 29.7, 29.3, 28.3, 28.0, 27.6, 27.4, 27.3, 27.2, 27.2, 27.0, 26.9, 26.8, 26.5, 26.4, 26.0. HRMS calculated for $C_{32}H_{57}N_2O$ $(M + H)^+$ *m/z*: 485.4471, measured: 485.4469.

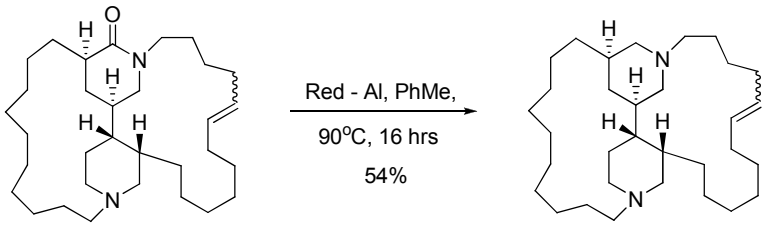


4.71a

4.72a
6 : 1 (*E* : *Z*)

Alkene 4.72a. A solution of lactam **4.71a** (7.0 mg, 0.014 mmol) in toluene (1.5 mL) was cooled to 0 °C and sodium bis(2 – methoxyethoxy)aluminuim hydride (43.0 μL, 0.14 mmol of a 65 % wt. solution in toluene) was added dropwise. The solution was then placed into a pre-heated oil bath at 90 °C and stirred for 16 h. The resulting solution was cooled to 0 °C and slowly quenched with a saturated aqueous solution of potassium sodium tartrate (1.5 mL) and stirred for 5 minutes. The mixture was then diluted with ethyl acetate, warmed to room temperature, and stirred for 30 minutes. The aqueous layer was extracted with ethyl acetate (4 x 5 mL) and the combined extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (eluent 3:6.5:0.5 hexanes:ethyl acetate:triethylamine) to yield alkenes (**4.72a**) as a inseparable mixture of *E*:*Z* (6:1) isomers (4.5 mg, 66 %). IR (neat) 2923, 2853 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 600MHz) δ 2.95 (app t, *J* = 11.2 Hz, 1H), 2.78 (m, 1H), 2.70 – 2.66 (m, 2H), 2.62 – 2.56 (m, 4H), 2.45 – 2.43 (m, 1H), 2.38 (m, 1H), 2.33 (app t, *J* = 11.5 Hz, 1H), 2.16 – 2.09 (2H), 1.95 – 1.83 (m, 4H), 1.81 – 1.73 (m, 2H), 1.69 (m, 1H), 1.54 – 1.51 (m, 4H), 1.44 – 1.15 (m, 32H), 0.92 (m, 1H), 0.85 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 131.6, 130.5, 59.5, 59.4, 58.0, 57.2, 53.0, 47.1, 45.7, 41.6, 38.3, 37.9, 36.4, 36.2, 34.0, 33.5, 32.1, 30.0, 28.8, 28.1, 28.0, 27.9, 27.7, 27.0, 26.9, 26.8,

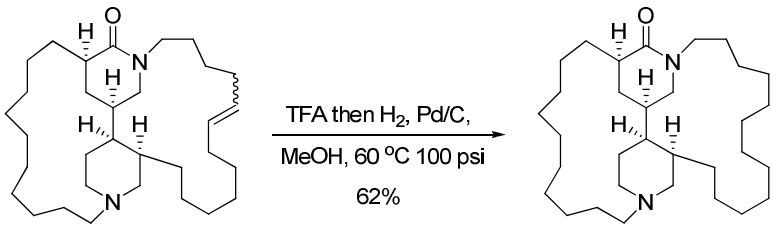
26.7, 26.6, 25.7, 25.4, 21.5 (2C). HRMS calculated for $C_{32}H_{59}N_2$ $(M + H)^+$ *m/z*: 471.4678, measured: 471.4678.



4.71b **4.72b**
> 95:5 (*E* : *Z*)

Alkene 4.72b. A solution of lactam **4.71b** (5.6 mg, 0.011 mmol) in toluene (1.5 mL) was cooled to 0 °C and sodium bis(2 – methoxyethoxy)aluminuim hydride (34.0 μL, 0.11 mmol of a 65 % wt. solution in toluene) was added dropwise. The solution was then placed into a pre-heated oil bath at 90 °C and stirred for 16 h. The resulting solution was cooled to 0 °C and slowly quenched with a saturated aqueous solution of potassium sodium tartrate (1.5 mL) and stirred for 5 minutes. The mixture was then diluted with ethyl acetate, warmed to room temperature, and stirred for 30 minutes. The aqueous layer was extracted with ethyl acetate (4 x 5 mL) and the combined extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (eluent 3:6.5:0.25 hexanes:ethyl acetate:triethylamine) to yield alkene (**4.72b)** as a light yellow oil (2.9 mg, 54 %). IR (neat) 2923, 2853 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 600MHz) δ 5.25 (m, 2H), 3.11 (m, 1H), 2.87 (m, 1H), 2.69 (m, 1H), 2.57 (m, 3H), 2.48 (m, 1H), 2.41 – 2.36 (m, 2H), 2.09 (m, 2H), 1.99 – 1.96 (m, 4H), 1.81 (m, 1H), 1.70 -1.55 (m, 8H), 1.37 – 1.23 (m, 30H), 0.88 (m, 1H), 0.45 (m, 1H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 131.6, 130.4, 63.9, 61.3, 59.4, 56.6, 51.0, 47.9, 42.6, 36,0,

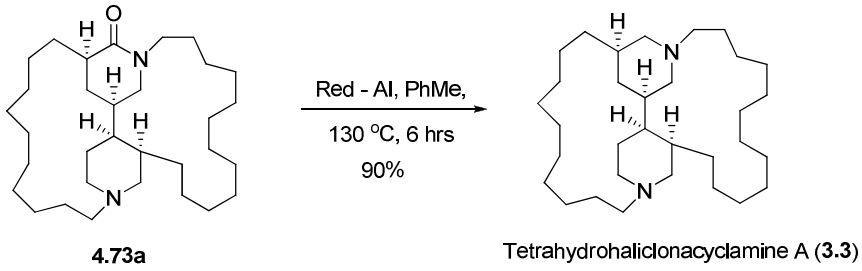
34.6, 34.1, 33.3, 33.1, 32.9, 32.0, 31.8, 30.2, 30.0, 28.8 (2C), 28.1 (2C), 27.8, 27.6, 27.2, 27.1 (2C), 26.9, 26.5, 24.8, 21.7. HRMS calculated for $C_{32}H_{59}N_2$ $(M + H)^+$ *m/z*: 471.4678, measured: 471.4676.



4.71a 4.73a

Lactam 4.73a. The trifluoroacetic acid salt of lactam **4.71a** (28.5 mg, 0.059 mmol, free amine weight) was dissolved in ethanol (20 mL), treated with palladium hydroxide (8.5 mg, 0.012 mmol), and transferred to a Parr Hydrogenator. Once the vessel was tightly secured, the solution was purged with hydrogen, evacuated, and back-filled a total of five times. The pressure was set to 100 psi and the mixture was heated to 70 °C with vigorous stirring. The progress of the reaction mixture was monitored by LC/MS. After 40 h the mixture was filtered thru Celite and concentrated. The resulting residue was carefully purified by reverse phase HPLC chromatography eluting with water (0.1% TFA) / Acetonitile (35 % to 60% acetonitrile). Fractions were analyzed using LC/MS and concentrated by Genevac. The resulting residue was further purified and converted to the free amines by passing through a Varian SCX ion exchange column by eluting first with methanol then 2N ammonia in methanol. The resulting residue was subjected to flash column chromatography on silica gel (eluent 3:6.5:0.25 hexane:ethyl actetate:triethylamine) to yield lactam **4.73a** (17.6 mg, 62%) as a clear oil. Crystals were

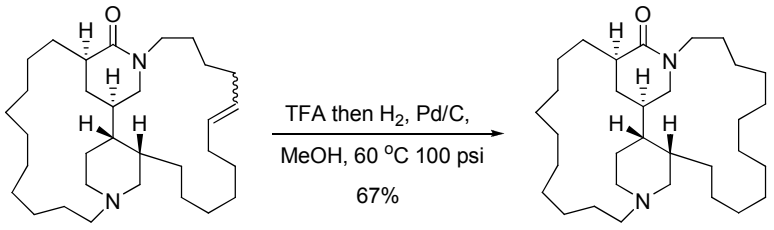
obtain of **4.73a** using hexane:ethyl actetate:triethylamine (3:6.5:0.25) white crystalline solid (crystallized from 6.5:3:0.25 EtOAc/hexanes/triethylamine) m.p. 134-135 °C. IR (neat) 2923, 2856, 1632, 1456 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600MHz) δ 4.26 (m, 1H), 3.53 (app. t, *J* = 11.9 Hz, 1H), 3.27 (m, 1H), 3.05 (m, 1H), 2.89 (app. t, *J* = 11.3 Hz, 1H), 2.78 – 2.59 (m, 6H), 2.41 (m, 2H), 2.27 (m, 2H), 2.08 (m, 2H), 2.00 – 1.99 (m, 2H), 1.74 – 1.69 (m, 2H), 1.55 – 1.27 (m, 36H), 0.87 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 171.8, 56.8, 55.5, 52.1, 48.2, 46.1, 42.5, 41.8, 41.2, 35.8, 35.3, 33.9, 33.3, 31.1, 28.8, 27.7 (2C), 27.3, 27.2, 27.2, 27.0 (2C), 26.9, 26.8, 26.6 (2C), 26.5, 26.2, 26.1, 25.5, 25.4, 21.5. HRMS calculated for $C_{32}H_{59}N_2O$ $(M + H)^+$ *m/z*: 487.4627, measured: 487.4624.



4.73a Tetrahydrohaliclonacyclamine A (**3.3**)

Tetrahydrohaliclonacyclamine A (3.3). A solution of lactam **4.73a** (20.0 mg, 0.041 mmol) in toluene (4 mL) was cooled to 0 °C and sodium bis(2 – methoxyethoxy)aluminuim hydride (130 μL, 0.410 mmol of a 65 % wt. solution in toluene) was added dropwise. The solution was then placed into a pre-heated oil bath at 130 °C and stirred for 6 h. The resulting solution was cooled to 0 °C and slowly quenched with a saturated aqueous solution of potassium sodium tartrate (4 mL) and stirred for 5 minutes. The mixture was then diluted with ethyl acetate, warmed to room temperature, and stirred for 30 minutes. The aqueous layer was extracted with ethyl

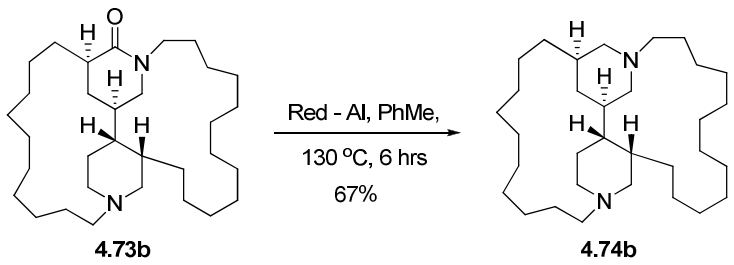
acetate (4 x 10 mL) and the combined extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by passing through a Varian SCX ion exchange column by eluting first with methanol then 2N ammonia in methanol. After concentration, the residue was subjected to flash column chromatography on silica gel eluting with 3:6.5:0.5 (hexanes:ethyl acetate:triethylamine) to yield tetrahydrohaliclonacyclamine A (**3.3**) (15.8 mg, 90 %). ^{1}H-NMR ($CDCl_3$, 600MHz) δ 2.96 (app. t, *J* = 11.1 Hz, 1H), 2.80 – 2.79 (m, 2H), 2.75 – 2.64 (m, 3H), 2.59 (m, 1H), 2.55 – 2.51 (m, 1H), 2.46 – 2.39 (m, 3H), 2.15 (app. t, *J* = 11.2 Hz, 1H), 1.95 (m, 1H), 1.85 – 1.76 (m, 4H), 1.72 – 1.69 (m, 2H), 1.53 – 1.50 (m, 5H), 1.39 – 1.20 (m, 34H), 0.92 – 0.88 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 60.7, 60.3, 58.4, 57.1, 53.2, 47.0, 45.5, 41.4, 38.3, 37.8, 36.4, 35.6, 34.1, 33.5, 29.3, 27.9, 27.8 (2C), 27.7, 27.6, 27.2, 27.1, 26.8 (2C), 26.5, 26.3, 26.1, 25.7 (2C), 25.6, 22.0, 21.5. HRMS calculated for $C_{32}H_{61}N_2$ $(M + H)^+$ *m/z*: 473.4835, measured: 473.4833.



4.71b **4.73b**

Lactam 4.73b. The trifluoroacetic acid salt of lactam **4.71b** (20.9 mg, 0.041 mmol, free amine weight) was dissolved in ethanol (20 mL), treated with palladium hydroxide (6.2 mg, 0.009 mmol), and transferred to a Parr Hydrogenator. Once the vessel was tightly secured, the solution was purged with hydrogen, evacuated, and back-filled a total of five

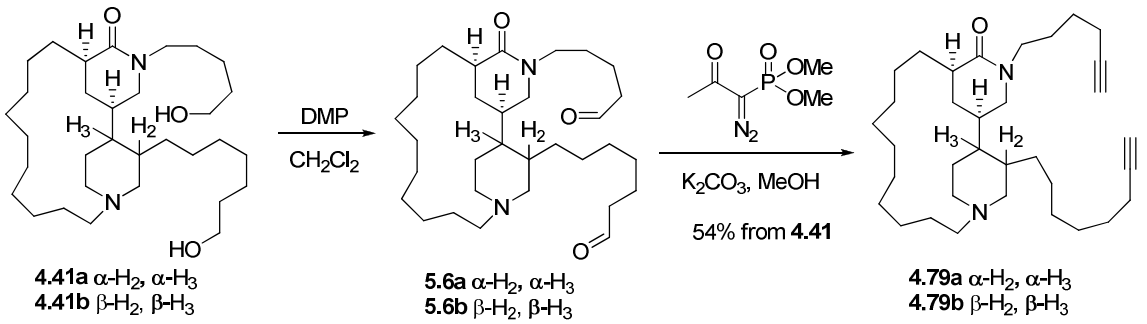
times. The pressure was set to 100 psi and the mixture was heated to 70 °C with vigorous stirring. The progress of the reaction mixture was monitored by LC/MS. After 40 h the mixture was filtered thru Celite and concentrated. The resulting residue was carefully purifed by reverse phase HPLC chromatography eluting with water (0.1% TFA) / Acetonitile (35 % to 60% acetonitrile). Fractions were analyzed using LC/MS and concentrated by Genevac. The resulting residue was further purified and converted to the free amines by passing through a Varian SCX ion exchange column by eluting first with methanol then 2N ammonia in methanol. The resulting residue was subjected to flash column chromatography on silica gel (eluent 3:6.5:0.25 hexane:ethyl actetate:triethylamine) to yield lactam **4.73b** (14.1 mg, 67%) as a clear oil. IR (neat) 2924, 2856, 1643, 1460 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600MHz) δ 4.12 (m, 1H), 3.16 (m, 1H), 3.06 (app. t, *J* = 11.7 Hz, 1H), 2.64 (m, 1H), 2.69-2.65 (m, 3H), 2.51 (m, 1H), 2.46-2.39 (m, 2H), 2.27 (m, 2H), 2.16 (m, 1H), 2.04 (m, 2H), 1.83 (m, 2H), 1.56-1.52 (m, 4H), 1.34-1.25 (m, 36H), 0.86 (m, 1H) ; ^{13}C NMR ($CDCl_3$, 150 MHz) δ 171.9, 56.9, 55.1, 53.0, 47.4, 47.0, 41.3, 40.8, 34.5, 32.9, 32.1, 31.3, 30.6, 28.5, 27.8, 27.7, 27.6, 27.2 (2C), 27.1 (2C), 27.0 (2C), 26.8, 26.7, 26.4 (2C), 26.3 (2C), 25.8, 25.2, 21.6. HRMS calculated for $C_{32}H_{59}N_2O$ $(M + H)^+$ *m/z*: 487.4627, measured: 487.4627.



4.73b **4.74b**

Diamine 4.74b (*cis-anti-cis* isomer). A solution of lactam **4.73b** (8.0 mg, 0.016 mmol) in toluene (2 mL) was cooled to 0 °C and sodium bis(2 – methoxyethoxy)aluminuim hydride (49 μL, 0.16 mmol of a 65 % wt. solution in toluene) was added dropwise. The solution was then placed into a pre-heated oil bath at 95 °C and stirred for 15 h. The resulting solution was cooled to 0 °C and slowly quenched with a saturated aqueous solution of potassium sodium tartrate (4 mL) and stirred for 5 minutes. The mixture was then diluted with ethyl acetate, warmed to room temperature, and stirred for 30 minutes. The aqueous layer was extracted with ethyl acetate (4 x 10 mL) and the combined extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by passing through a Varian SCX ion exchange column by eluting first with methanol then 2N ammonia in methanol. Flash column chromatography on silica gel eluting with 3:6.5:0.3 (hexanes:ethyl acetate:triethylamine) to yield cis-anti-cis product (**4.74b**) (5.1 mg, 67 %). ^{1}H-NMR ($CDCl_3$, 600MHz) δ 2.97 (app. d, *J* = 10.9 Hz, 1H), 2.85 (m, 1H), 2.69 (app. d, *J* = 9.6 Hz, 1H), 2.62 (m, 1H), 2.58 (m, 1H), 2.56 (m, 1H), 2.45-2.43 (m, 2H), 2.39 (m, 2H), 2.10 (app. d, *J* = 12.2 Hz, 1H), 2.04 (m, 1H), 1.84 (m, 1H), 1.74 (m, 1H), 1.72 (m, 1H), 1.63 (m, 1H), 1.62 (m, 1H), 1.59 (m, 1H), 1.51 (m, 1H), 1.45 (m, 1H), 1.43 (m, 1H), 1.36-1.24 (m, 38H), 0.52 (m, q, *J* = 10.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 63.1, 61.4, 58.8, 56.8, 52.2, 47.9, 42.1, 35.5, 35.3, 35.1, 33.6, 33.2, 32.1, 29.3,

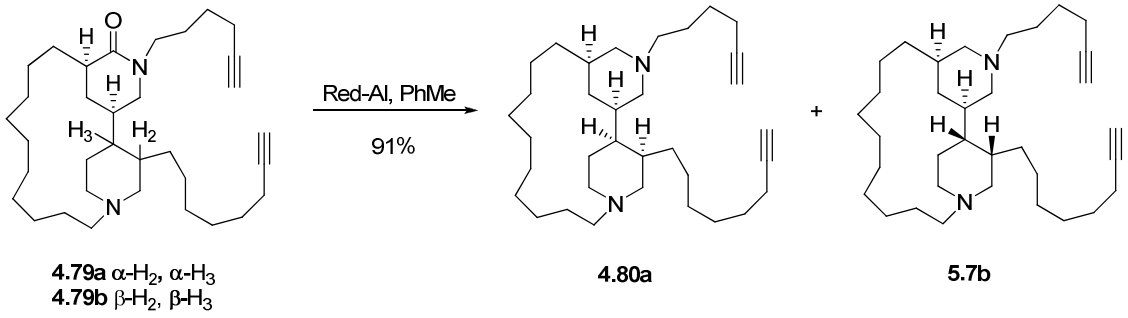
28.4, 28.3, 28.1, 27.8, 27.7, 27.6, 27.5, 27.3, 27.0 (3C), 26.8 (2C), 26.7, 26.5, 26.0, 24.9, 21.7 . HRMS calculated for $C_{32}H_{61}N_2$ $(M + H)^+$ *m/z*: 473.4835, measured: 473.4835.



Diynes 4.79. To a solution of diols **4.41** (65.0 mg, 0.125 mmol) in dichloromethane (3 mL) at 0 °C was added freshly prepared Dess Martin periodinane[158] (106.0 mg, 0.250 mmol). The resulting mixture was stirred at 0 °C for 45 minutes, and then additional Dess Martin periodinane (106.0 mg, 0.250 mmol) was added. The mixture was slowly warmed to room temperature and stirred for 1.15 h. The light yellow solution was then cooled to 0 °C and quenched with water (2 mL), saturated aqueous sodium bicarbonate (2 mL), and saturated aqueous sodium metabisulfite (2 mL). The mixture was stirred for 5 min at 0 °C, allowed to warm to room temperature and stirring continued for 15 min. The solution was then extracted with dichloromethane (4 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The crude bis-aldehydes **5.6** was used immediately in the next step without further purification.

To a solution of crude bis-aldehydes **5.6** (64.5 mg, 0.125 mmol) in methanol (3 mL) was added potassium carbonate (260.0 mg, 1.88 mmol) followed by dropwise addition of dimethyl-1-diazo-2-oxopropylphosphonate[175,176] (192 mg, 1.00 mmol in 0.5 mL of methanol). The resulting mixture was stirred for 16 h and then concentrated. The residue

was diluted with ethyl acetate (5 mL) and water (5 mL). The aqueous layer was extracted with ethyl acetate (4 x 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel eluting with 3:6.5:0.25 (hexanes:ethyl acetate:triethylamine) to yield diynes **4.79** (34.0 mg, 54% over 2 steps) as a yellow oil. Characterized as a mixture of 2 diastereomers: IR (neat) 2926, 2857, 1639, 1456 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600MHz) δ 3.30 – 3.15 (m, 4H), 2.74 (app. t, J = 6.6 Hz, 2H), 2.71 (m, 1H), 2.59 (m, 2H), 2.52 – 2.48 (m, 2H), 2.19 (m, 3H), 2.15 (m, 4H), 1.90 (m, 4H), 1.64 – 1.59 (m, 3H), 1.49 – 1.46 (m, 6H), 1.36 – 1.27 (m, 25); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 172.1, 171.8, 84.6, 84.1, 68.5, 68.1, 57.0, 56.9, 54.5, 53.9, 52.9, 52.2, 47.2, 46.6, 46.5, 45.9, 42.0, 41.7, 41.2, 40.0, 36.4, 34.8, 33.9, 33.4, 32.8, 32.7, 31.5, 31.0, 30.5, 29.2 (2C), 28.6, 28.4, 28.2, 28.0, 27.6, 27.5, 27.3, 27.2, 27.1, 26.9 (2C), 26.7, 26.6, 26.4, 26.1, 26.0, 25.6, 25.3, 22.0, 21.7, 18.3, 18.1. HRMS calculated for $C_{34}H_{57}N_2O$ $(M + H)^+$ *m/z*: 509.4471, measured: 509.4471.



4.79a α-H_2, α-H_3
4.79b β-H_2, β-H_3

4.80a

5.7b

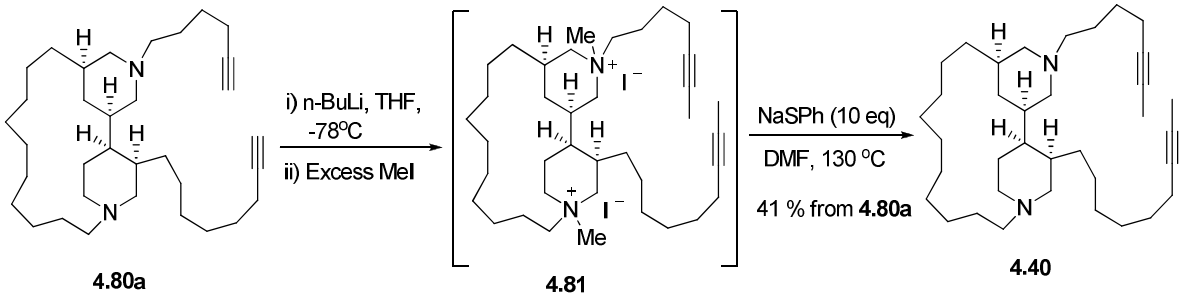
Diyne 4.80a and 5.7b. A solution of diynes **4.79** (45.0 mg, 0.088 mmol) in toluene (2 mL) was cooled to 0 °C and sodium bis(2 – methoxyethoxy)aluminuim hydride (270 µL, 0.880 mmol of a 65 % wt. solution in toluene) was added dropwise. The solution was

then placed into a pre-heated oil bath at 130 °C and stirred for 6 h. The resulting solution was cooled to 0 °C and slowly quenched with a saturated aqueous solution of potassium sodium tartrate (4 mL) and stirred for 5 minutes. The mixture was then diluted with ethyl acetate, warmed to room temperature, and stirred for 30 minutes. The aqueous layer was extracted with ethyl acetate (4 x 5 mL) and the combined extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (gradient elution 3:6.5:0.2 to 3.6.5:0.5 hexanes:ethyl acetate:triethylamine) to yield diynes **5.7b** (17.0 mg, 39%) and **4.80a** (22.0 mg, 51%) in a 90% overall yield.

Diyne **4.80a**: IR (neat) 2927, 2857, 1460 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600MHz) δ 2.88 (app. t, *J* = 11.9 Hz, 2H), 2.82 (m, 2H), 2.77 (m, 1H), 2.68 (m, 1H), 2.62 (app. t, *J* = 11.6 Hz, 1H), 2.54 (app. t, *J* = 11.3Hz, 2H), 2.30 – 2.24 (m, 3H), 2.17 (dddd, *J* = 16.5, 7.0, 7.0, 2.6 Hz, 4H), 1.91 (app. q, *J* = 2.9 Hz, 2H), 1.79 – 1.73 (m, 4H), 1.62 – 1.56 (m, 4H), 1.50 – 1.48 (m, 7H), 1.38 – 1.22 (m, 24H), 1.03 (m, 1H), 0.85 (m, 1H), 0.70 (app. q, *J* = 11.9 Hz, 1H) ; ^{13}C NMR ($CDCl_3$, 150 MHz) δ 84.7, 84.4, 68.4, 68.1, 62.2, 61.3, 58.5, 56.7, 52.2, 45.9, 41.8, 41.1, 37.0, 36.4, 36.1, 33.9, 33.5, 33.4, 29.2, 28.7, 28.4, 28.3, 28.2, 28.0, 27.4 (2C), 27.2, 26.7, 26.6, 26.1, 25.3, 22.0, 18.4 (2C). HRMS calculated for $C_{34}H_{59}N_2$ $(M + H)^+$ *m/z*: 495.4678, measured: 495.4674.

Diyne **5.7b**: IR (neat) 2924, 2855, 1460 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600MHz) δ 2.79 – 2.71 (m, 4H), 2.67 (app. d, *J* = 10.1 Hz, 1H), 2.58 (m, 1H), 2.50 (m, 2H), 2.27 (app. t, *J* = 7.6 Hz, 1H), 2.14 (dddd, *J* = 19.8, 7.1, 7.1, 2.6 Hz, 4H), 2.03 (app. d, *J* = 12.1 Hz, 1H), 1.91

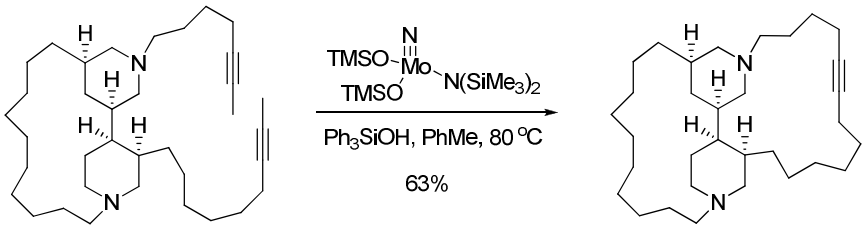
(app. q, J = 2.5 Hz, 2H), 1.81 (app. d, J = 12.2 Hz, 3H), 1.71 (m, 2H), 1.58 (m, 3H), 1.51 – 1.48 (m, 9H), 1.36 – 1.25 (m, 20H), 0.99 (m, 1H), 0.85 – 0.79 (m, 3H), 0.68 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 84.7, 84.3, 68.4, 68.1, 61.4, 61.1, 59.2, 58.5, 56.9, 52.7, 47.7, 40.6, 37.3, 36.0, 35.7, 34.8, 33.5, 31.6, 29.7, 29.3, 28.7, 28.5, 28.2, 27.6, 27.4, 27.3, 27.1, 26.6 (2C), 26.0, 24.6, 22.0, 18.4 (2C). HRMS calculated for $C_{34}H_{59}N_2$ $(M + H)^+$ *m/z*: 495.4678, measured: 495.4677.



4.80a **4.81** **4.40**

Methylated Diyne 4.40. A solution of diyne **4.80a** (32.0 mg, 0.065 mmol) over 4Å molecular sieves in tetrahydrofuran (2 mL) was cooled to -78 °C and *n*-butyllithium (236 μL, 0.517 mmol of a 2.19 M solution in hexanes) was added dropwise. The resulting solution was allowed to slowly warm to room temperature over the course of 1 h. The solution was cooled back to -78 °C and methyl iodide (60.0 μL, 0.971 mmol) was added dropwise. The -78 °C bath was immediately removed after the addition and the solution was stirred for 1 h at room temperature. The progress of the reaction was monitored by LC/MS analysis. After completion, the mixture was quenched by the addition of methanol (3 mL) and concentrated. The crude ammonium salt **4.81** was used immediately in the next step without further purification.

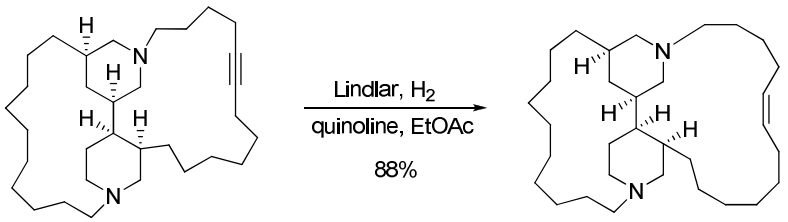
To a solution of crude ammonium salt **4.81** (34.8 mg, 0.065 mmol) in dimethylformamide (1.0 mL) at room temperature was added the sodium salt of benzenethiol (86 mg, 0.65 mmol). The resulting mixture was placed into a pre-heated oil bath set to 130 °C and stirred for 1.5 h. The solution was then cooled to room temperature and quenched with water (10 mL). Sodium hydroxide (2.0 mL of a 1 M aqueous solution) was added and aqueous layer was extracted with ethyl acetate (4 x 15 mL). The combined organic extracts were washed with water (2 x 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The resulting residue was carefully purifed by reverse phase HPLC chromatography eluting with water (0.1% TFA) / Acetonitile (18 % to 55% acetonitrile). Fractions were analyzed using LC/MS and concentrated by Genevac. The resulting residue was further purified and converted to the free amine by passing through a Varian SCX ion exchange column by eluting first with methanol then 2N ammonia in methanol. The resulting residue was subjected to flash column chromatography on silica gel (eluent 3:6.5:0.5 hexane:ethyl actetate:triethylamine) to yield methylated diyne **4.40** (13.7 mg, 41% over 2 steps) as a pale yellow oil. IR (neat) 2933, 2856, 1442 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600MHz) δ 2.85 (app. t, *J* = 11.8 Hz, 1H), 2.79 (m, 1H), 2.76 (m, 1H), 2.65 (m, 1H), 2.59 (app. t, *J* = 11.5 Hz, 1H), 2.48 (m, 2H), 2.29 – 2.24 (m, 3H), 2.11 – 2.08 (m, 4H), 1.75 – 1.73 (m, 7H), 1.62 (m, 2H), 1.55 (m, 3H), 1.48 – 1.41 (m, 8H), 1.34 – 1.25 (m, 26H), 1.03 (m, 1H), 0.68 (app. q, *J* = 11.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 79.3, 79.0, 75.6, 75.3, 62.3, 61.4, 58.6, 56.9, 52.4, 45.9, 42.1, 41.0, 37.3, 36.4, 36.1, 34.1, 33.6, 33.4, 29.3, 29.0, 28.9, 28.4, 28.2, 28.1, 27.5, 27.4, 27.3, 27.1, 26.6, 26.3, 25.2, 22.2, 18.7 (2C), 3.4 (2C). HRMS calculated for $C_{36}H_{63}N_2$ $(M + H)^+$ *m/z*: 523.4991, measured: 523.4988.



4.40 **4.88**

Cycloalkyne 4.88. Triphenylsilanol (3.5 mg, 0.0121 mmol) was added to a two neck 15 mL flask charged with 4Å molecular sieves and fit with a condenser. Toluene (1 mL) was added and $[(Me_3SiO)_2((Me_3Si)_2N)Mo{\equiv}N]$[172] (2.0 mg, 0.004 mmol in 0.5 mL of toluene) was introduced dropwise. The resulting solution was heated to 80 °C for 30 minutes changing from a yellow solution to a light orange, and finally pale yellow. The newly formed complex was cooled to room temperature and methylated diyne **4.40** (4.3 mg, 0.008 mmol in 5 mL of toluene) was added to the catalyst solution. The solution was heated to 130 °C for 2 h, then cooled to room temperature and filtered through a pad of silica. The filtrate was concentrated and the resulting residue was carefully purified by reverse phase HPLC chromatography eluting with water (0.1% TFA) / Acetonitile (15 % to 50% acetonitrile). Fractions were analyzed using LC/MS and concentrated by Genevac. The resulting residue was converted to the free amine by passing through a Varian SCX ion exchange column by eluting first with methanol then 2N ammonia in methanol. After concentrating, the residue was subjected to flash column chromatography on silica gel (eluent 3:6.5:1.0 hexane:ethyl actetate:triethylamine) to yield cycloalkyne **4.88** (2.4 mg, 63%) as a light yellow oil. IR (neat) 2933, 2854, 1442, 1123 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600MHz) δ 3.30 – 3.15 (m, 4H), 2.74 (app. t, J = 6.6 Hz, 2H), 2.71 (m, 1H), 2.59 (m, 2H), 2.52 – 2.48 (m, 2H), 2.19 (m, 3H), 2.15 (m, 4H), 1.90

(m, 4H), 1.64 – 1.59 (m, 3H), 1.49 – 1.46 (m, 6H), 1.36 – 1.27 (m, 25); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 80.8, 79.9, 59.7, 59.5, 58.0, 57.1, 53.1, 47.2, 45.8, 41.6, 38.3, 37.9, 35.7, 34.1, 33.3, 29.7, 29.5, 28.7, 28.2, 28.1, 28.0, 27.7, 27.0, 26.7, 26.5, 25.3, 25.6, 25.4, 21.6, 21.5, 18.6, 18.2. HRMS calculated for $C_{32}H_{57}N_2$ $(M + H)^+$ *m/z*: 469.4522, measured: 469.4514.



4.88 haliclonacyclamine C (**1.4**)

Haliclonacyclamine C (1.4). To a solution of cycloalkyne **4.88** (2.4 mg, 0.005 mmol) and quinoline (10.0 μL, 0.080 mmol) in ethyl acetate (2 mL) was added 10 mg of Lindlar's catalyst ($Pd/CaCO_3$, poisoned with Pb by the supplier). The mixture was placed under H_2 (1 atm) and degassed/purged with H_2 a total of five times. The resulting mixture was vigorously stirred for 2.5 h at room temperature, then filtered through a Millipore syringe filter (0.2 μm, 13 mm) and concentrated. The resulting residue was subjected to flash column chromatography on silica gel (eluent 3:6.5:0.75 hexane:ethyl actetate:triethylamine) to yield haliclonacyclamine C (**1.4**) (2.1 mg, 88%) as a colorless gum. ^{1}H-NMR ($CDCl_3$, 600MHz) δ 5.27 (m, 2H), 2.97 (app. t, *J* = 11.5 Hz, 1H), 2.82 (m, 2H), 2.73 (m, 2H), 2.65 (m, 3H), 2.47 – 2.36 (m, 3H), 2.17 – 2.12 (m, 3H), 1.99 – 1.79 (m, 6H), 1.73 (m, 1H), 1.63 – 1.54 (m, 4H), 1.43 – 1.24 (m, 28H), 1.12 (app. t, *J* = 13.1 Hz, 1H), 0.94 – 0.85 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 131.2, 130.0, 60.6,

59.4, 58.5, 56.9, 53.5, 46.9, 45.0, 41.0, 38.0, 37.6, 36.1, 34.3, 34.0, 32.7, 29.3, 29.1, 28.3, 27.9, 27.7 (2C), 27.5, 27.0, 26.8, 26.7, 26.2, 26.1, 25.8, 25.4, 22.1, 21.3. HRMS calculated for $C_{32}H_{59}N_2$ $(M + H)^+$ *m/z*: 471.4678, measured: 471.4679.

Compound Analysis and Comparison

Table 5. Comparison of synthetic and semi-synthetic[a] tetrahydrohaliclonacyclamine A (**3.3**).

Carbon Signal (Ordered from downfield to upfield)	Published Data[36]	Semisynthetic from HalA[a,36]	Semisynthetic Passed thru SCX Column	Synthetic Passed thru SCX Column
1	59.5	59.4	60.7	60.7
2	59.2	59.0	60.3	60.3
3	57.7	57.7	58.4	58.4
4	55.8	55.8	57.0	57.1
5	53.4	51.9	53.1	53.2
6	52.0	46.8	47.0	47.0
7	46.7	43.8	45.4	45.5
8	44.0	39.3	41.4	41.4
9	39.5	37.3	38.2	38.3
10	37.4	36.7	37.7	37.8
11	36.9	34.1	36.3	36.4
12	34.3	33.9	35.6	35.6
13	34.1	33.8	34.0	34.1
14	33.8	32.9	33.5	33.5
15	32.9	29.1	29.3	29.3
16	29.2	27.7	27.9	27.9
17	27.8	27.4	27.8	27.8
18	27.5	27.4	27.7	27.8
19	27.5	27.4	27.7	27.7
20	27.3	27.3	27.6	27.6
21	27.1	27.0	27.2	27.2
22	26.8	26.8	27.0	27.1
23	26.7	26.6	26.8	26.8
24	26.6	26.6	26.8	26.8
25	26.1	26.0	26.4	26.5
26	26.0	26.0	26.2	26.3
27	25.6	25.5	26.1	26.1
28	25.5	25.5	25.7	25.7
29	25.3	25.2	25.7	25.7
30	23.4	23.3	25.5	25.6
31	21.5	21.4	21.9	22.0
32	20.9	20.9	21.4	21.5

[a]Prepared by Garson and co-workers by hydrogenation of haliclonacyclamine A according to literature procedure.[36]

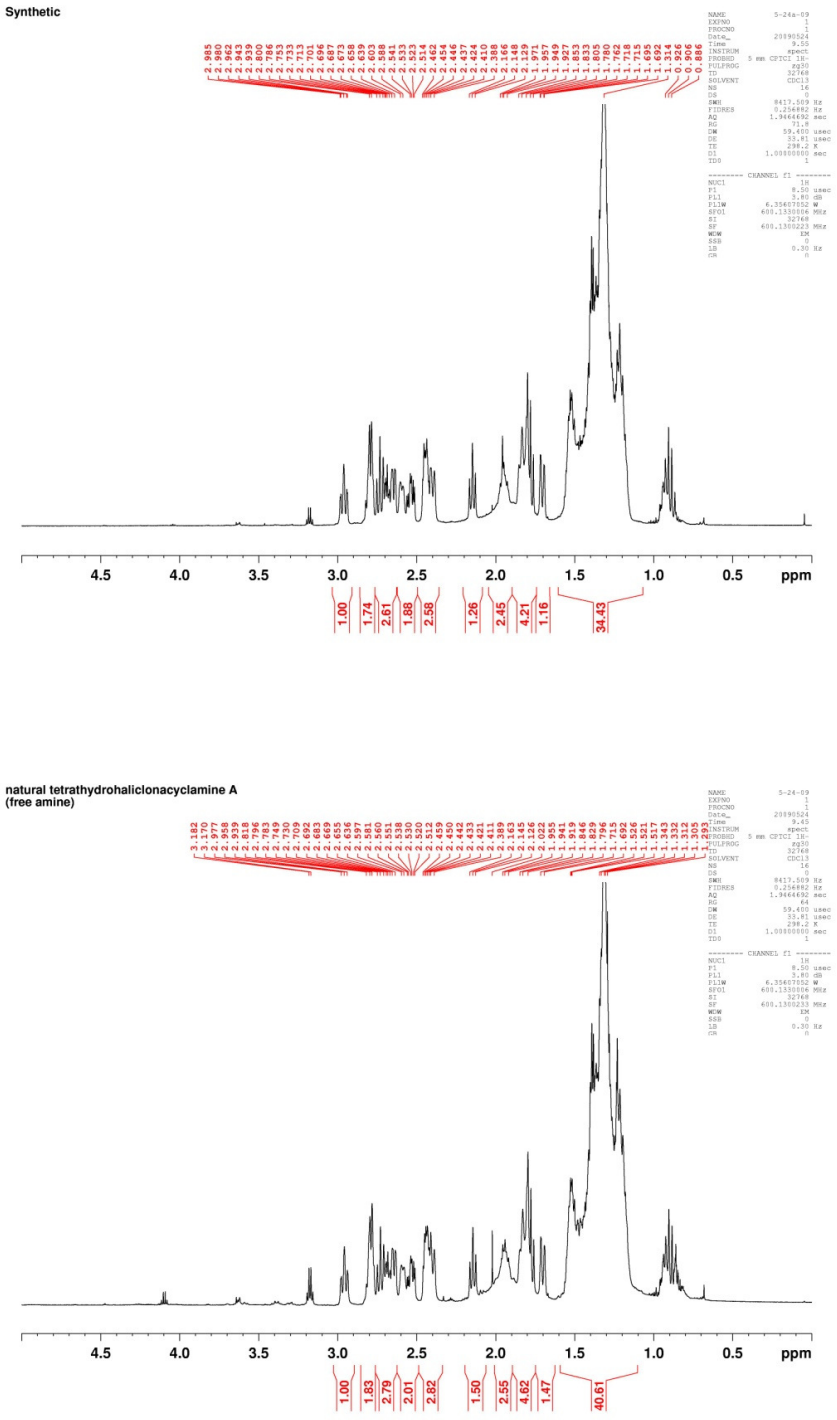
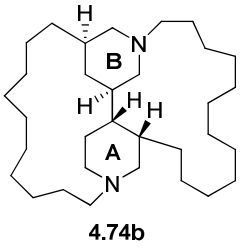


Figure 36. Comparison of ^{1}H NMR spectrum of synthetic and semisynthetic tetrahydrohaliclonacyclamine A (**3.3**) (from hydrogenation of haliclonacyclamine A).

Table 6. ^{1}H and ^{13}C Data for Compound **4.74b** (*cis-anti-cis* isomer).

Position	$^{1}H^{a,c}$	$^{13}C^{a,c}$	DQFCOSY[a,b,d]	HMBC[a,b]
1	2.97, 1.45	61.4	H2, *H3*	H5b, H3, H2, H11ab
2	1.72	33.6	H1a, H3, *H1b*	H1b, H3
3	1.43	35.5	H2, *H5a, H4a*	H1b, H5b, H4a
4	1.84, 1.62	28.3	H5a	H1b, H5b
5	2.69, 1.59	63.1	H4b, *H3*	H1b, H11b, H3
6	2.62, 2.56	47.9	H7, *H8b, H21*	H21b, H10ab, H7
7	1.63	35.1	H8a, H6ab	H8a
8	2.10, 0.52	35.3	H9, H7, *H6*	H10ab, H7
9	1.74	42.1	H8a, H10ab	H10ab, H8b
10	2.45, 2.43	52.2	H9	H21b, H6ab,
11	2.39, 2.04	58.8	H1ab, *H5b, H1b*	-
21	2.85, 2.58	56.8	-	-

[a]All 2D data obtained by 600 MHz NMR; solution in $CDCl_3$ referenced to 7.25 and 77.0 ppm.
[b]a and b denote upfield and downfield resonances respectively of a germinal pair.
[c]Proton and carbon correlations obtained by HSQC and further confirmed by DQFCOSY.
[d]TOCSY correlations in italics.



4.74b

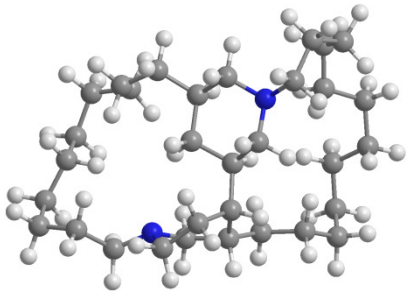


Figure 37. Representation of Lowest Energy Conformation of **4.74b**.

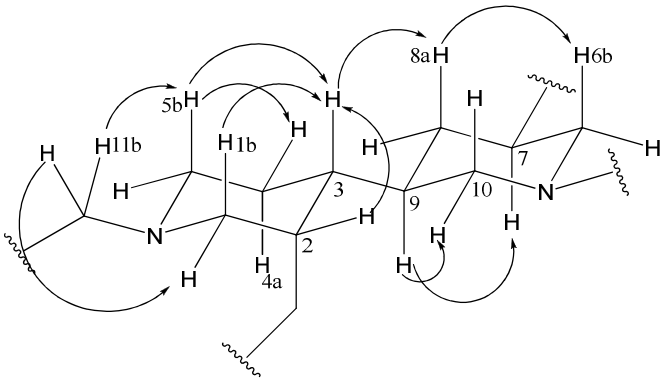


Figure 38. NOESY Correlations for **4.74b**.

Table 7. NOESY Correlations for Compound **4.74b**.

Position	^{1}H	^{13}C	NOESY
1	2.97, 1.45	61.4	H3, H11a
2	1.72	33.6	H3, H1b(w)
3	1.43	35.5	H1b, H2, H5b, H4b(w)
4	1.84, 1.62	28.3	H3, H5b
5	2.69, 1.59	63.1	H11b, H4b
6	2.62, 2.56	47.9	H8b
7	1.63	35.1	H9
8	2.10, 0.52	35.3	H6b, H3(w)
9	1.74	42.1	H7, H10a
10	2.45, 2.43	52.2	H9, H21b(w)
11	2.39, 2.04	58.8	H5b, H1a(w)
21	2.85, 2.58	56.8	H10(w)

The carbon resonances were matched to their respective protons by HSQC, and the germinal proton pairings crosschecked by DQFCOSY. The ^{1}H NMR spectrum was extremely congested, with the region from δ 3.00 – 2.00 ppm having the most resolved resonances, although some resonances had significant overlap. The carbons at δ 63.1, 61.4, 58.8, 56.8, 52.2, and 47.9 were assigned to be adjacent to nitrogen atoms, and the four methine protons at δ 1.74, 1.72, 1.63, and 1.43 were used for initial correlations.

The resonance at δ 61.4 (C-1) showed an HMBC link to H5b, H3, H2, and H11ab. The resonance at δ 63.1 (C-5) showed an HMBC link to H1b, H11b, and H3. The resonance at 47.9 (C-6) showed an HMBC link to H21b, H10ab, and H7. The resonance at 52.2 (C-10) showed an HMBC to link H21b and H6ab. These initial assignments enabled grouping of the six atoms adjacent to the nitrogen; 63.1 (C-1), 61.4 (C-5) and 58.8 (C-11) were on one ring while 56.8 (C-21), 52.2 (C-10), and 47.9 (C-6) were on the other ring. DQFCOSY correlations enabled further placing. There were DQFCOSY correlations from H-2 to H1a and H3, H-1 to H-2, and H-3 to H-2 which indicated all of the resonances were located on ring A. The DQFCOSY correlation between H-3 and H-2, along with the lack of any DQFCOSY correlation between H-3 and H-9 indicated H-3 and H-2 were on ring A. Other DQFCOSY correlations of H-4 to H5a, and H5 to H4b helped in beginning to put together ring A. TOCSY correlations of H-1 to H-3, H-2 to H-1b, H-3 to H5a and H4a, and H-5 to H-3 along with the DQFCOSY correlations above finalized the assignment of ring A. The assignments of ring B were made in a similar manner. Key DQFCOSY assignments were H-7 to H8 and H6ab, as well as, H-8 to H7 and H-9. H-9 also had a DQFCOSYcorrelation to H-10. A 2-D NOESY experiment confirmed that C-7 and C-9 were on the same face of the molecule. Furthermore, the signal of H8a is a well defined quartet, presenting the same 12-Hz coupling constant as H-7, H-8b, and H-9 (although H-7 and H-9 are highly congested regions and the coupling constants are not easily defined). This analysis indicates the relative stereochemistry between H8a and H7 must be axial-axial, as well as between H-8a and H-9 indicating the C-7 and C-9 stereochemistry. There were no NOESY correlation between C-9 and C-3, however there was a correlation between H-2 and H-3 indicating they were on the same

face of the molecule but opposite to H-9 and H-7. Due to crystal structure of isomer **4.73a** and the NOESY correlations above the relative stereochemistry is as shown in Figure 38.

Table 8. Comparison of natural and synthetic haliclonacyclamine C (**1.4**).

Carbon Signal (Ordered from downfield to upfield)	Published Data[36]	Synthetic
1	131.2	131.2
2	130.0	130.0
3	60.5	60.6
4	59.4	59.4
5	58.4	58.5
6	56.8	56.9
7	53.4	53.5
8	46.7	46.9
9	45.0	45.0
10	41.1	40.0
11	38.0	38.0
12	37.6	37.6
13	36.2	36.1
14	34.9	34.3
15	34.1	34.0
16	32.7	32.7
17	29.3	29.3
18	29.1	29.1
19	28.3	28.3
20	27.9	27.9
21	27.8	27.7
22	27.7	27.7
23	27.5	27.5
24	27.0	27.0
25	26.9	26.8
26	26.7	26.7
27	26.3	26.2
28	26.1	26.1
29	25.8	25.8
30	25.5	25.4
31	22.1	22.1
32	21.3	21.3

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APPENDIX A

SPECTRA RELEVANT TO HALICLONACYCLAMINE C

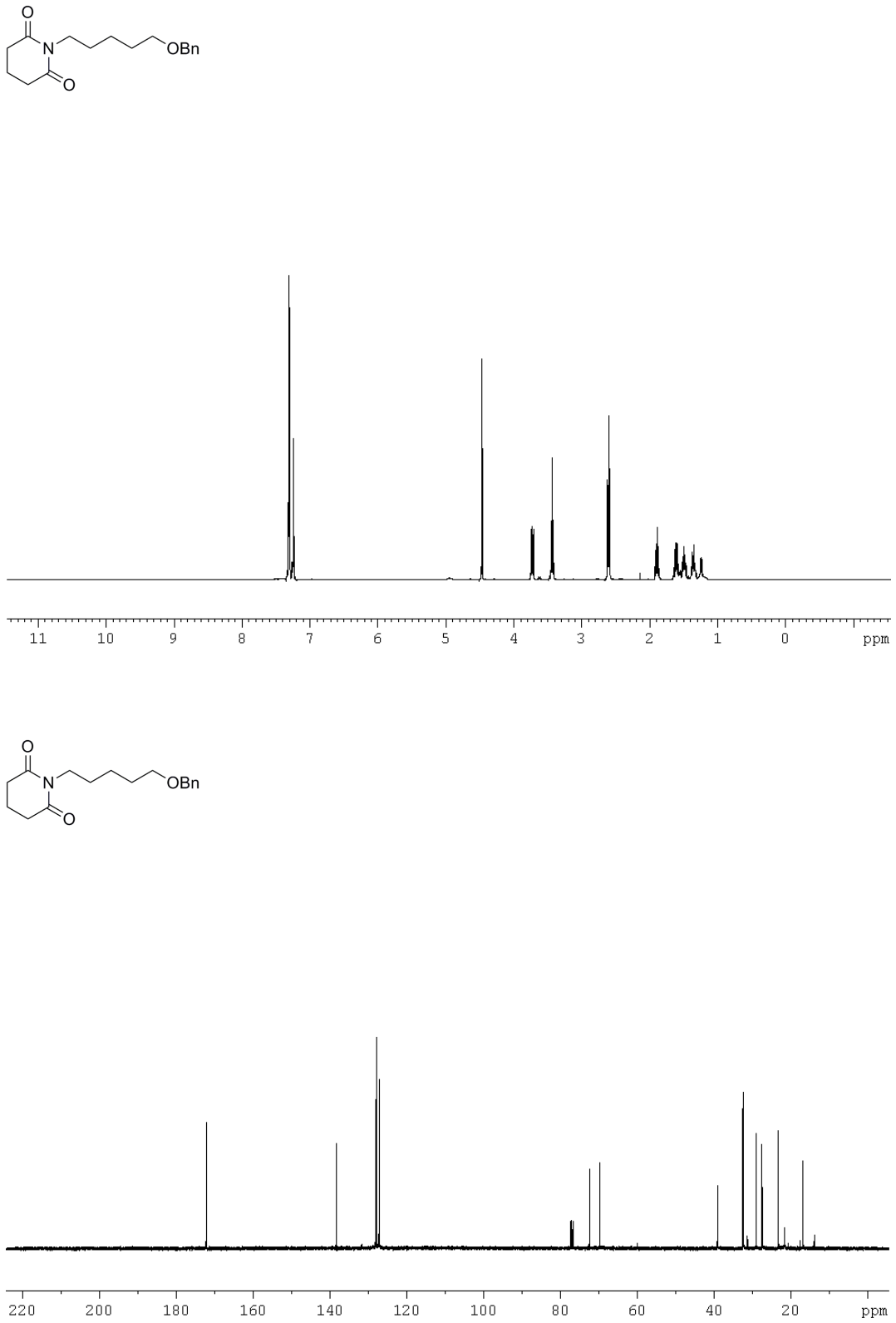

Figure A1. 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **4.15** in $CDCl_3$

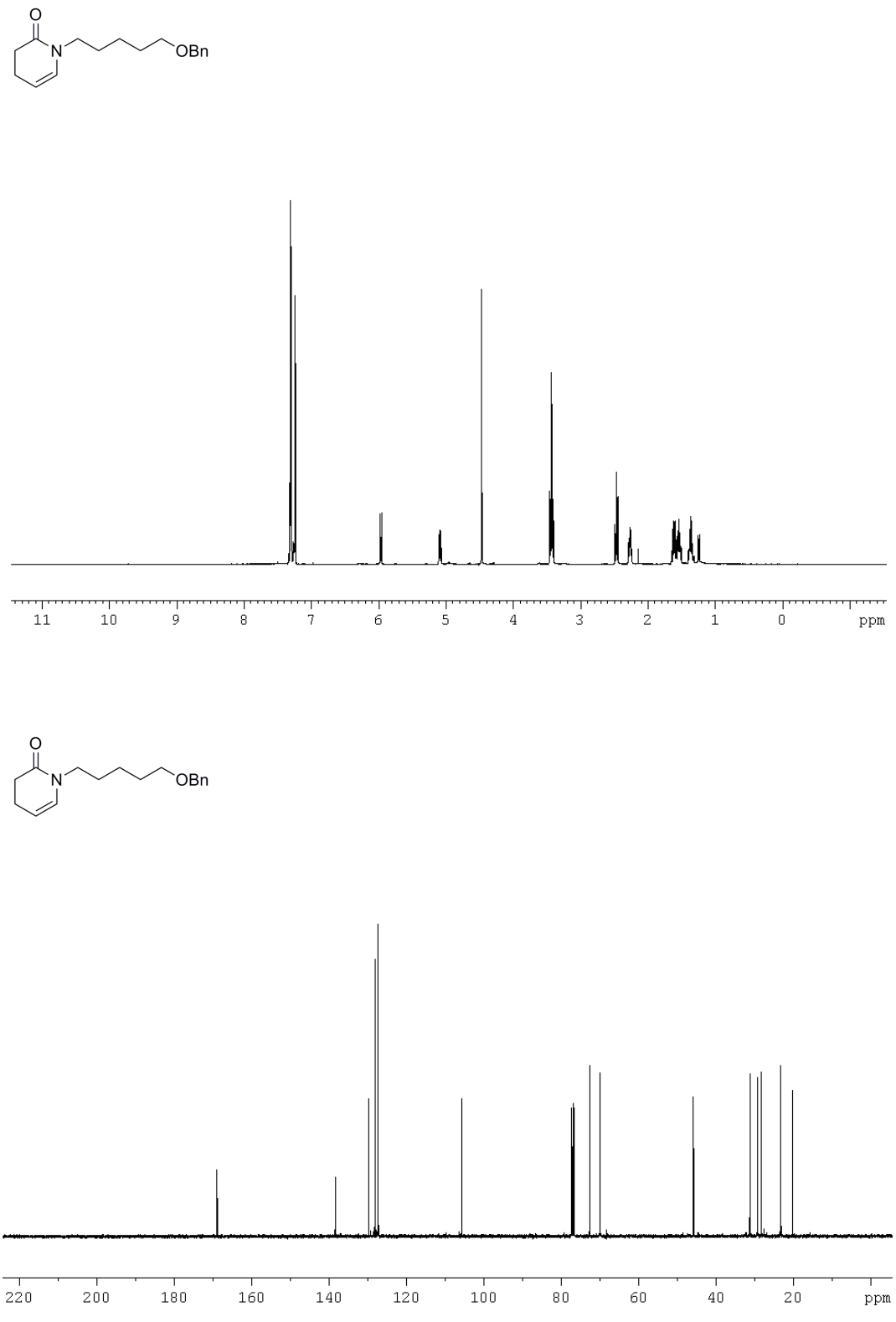

Figure A2. 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **4.17** in $CDCl_3$

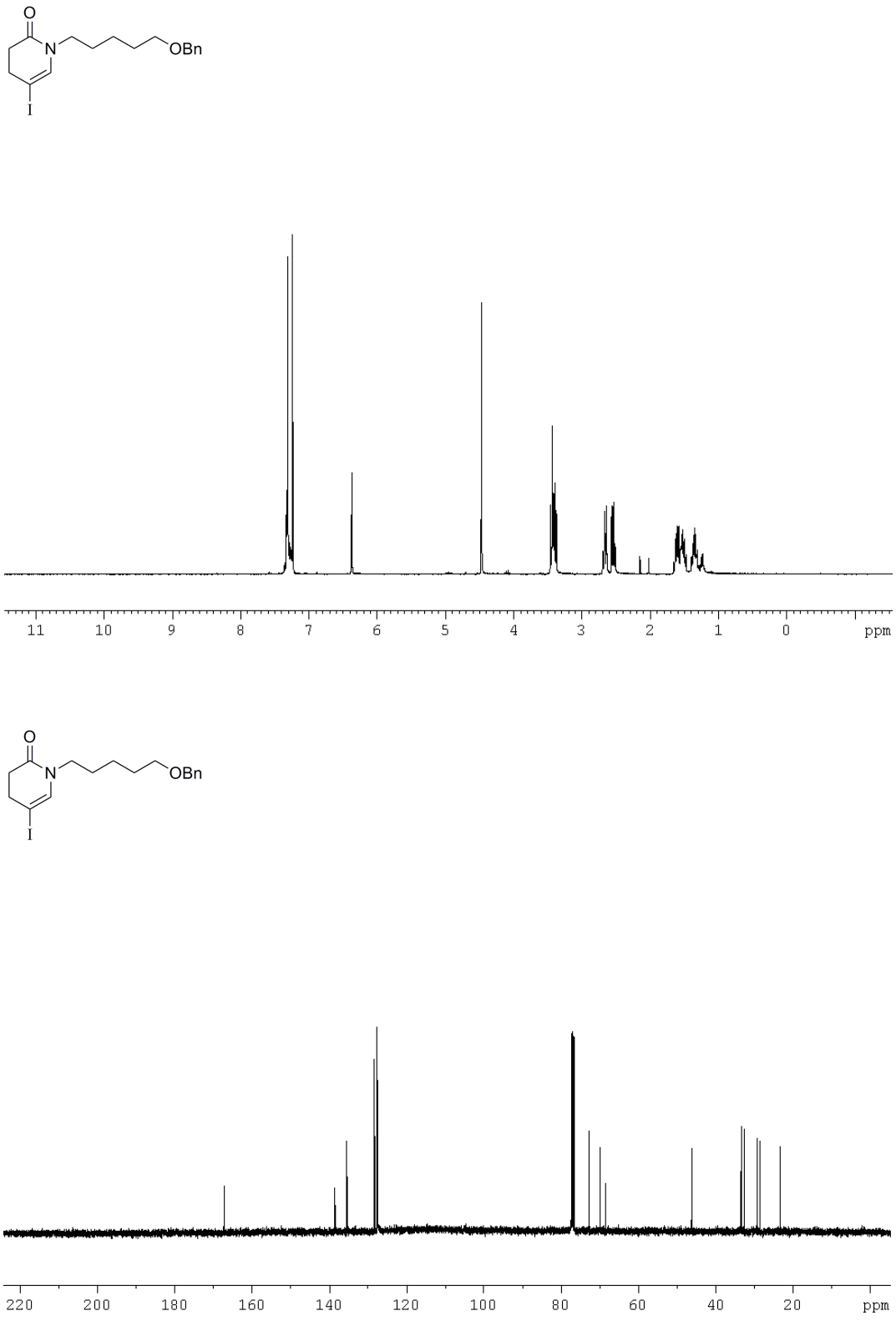

Figure A3. 300 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **4.13** in $CDCl_3$

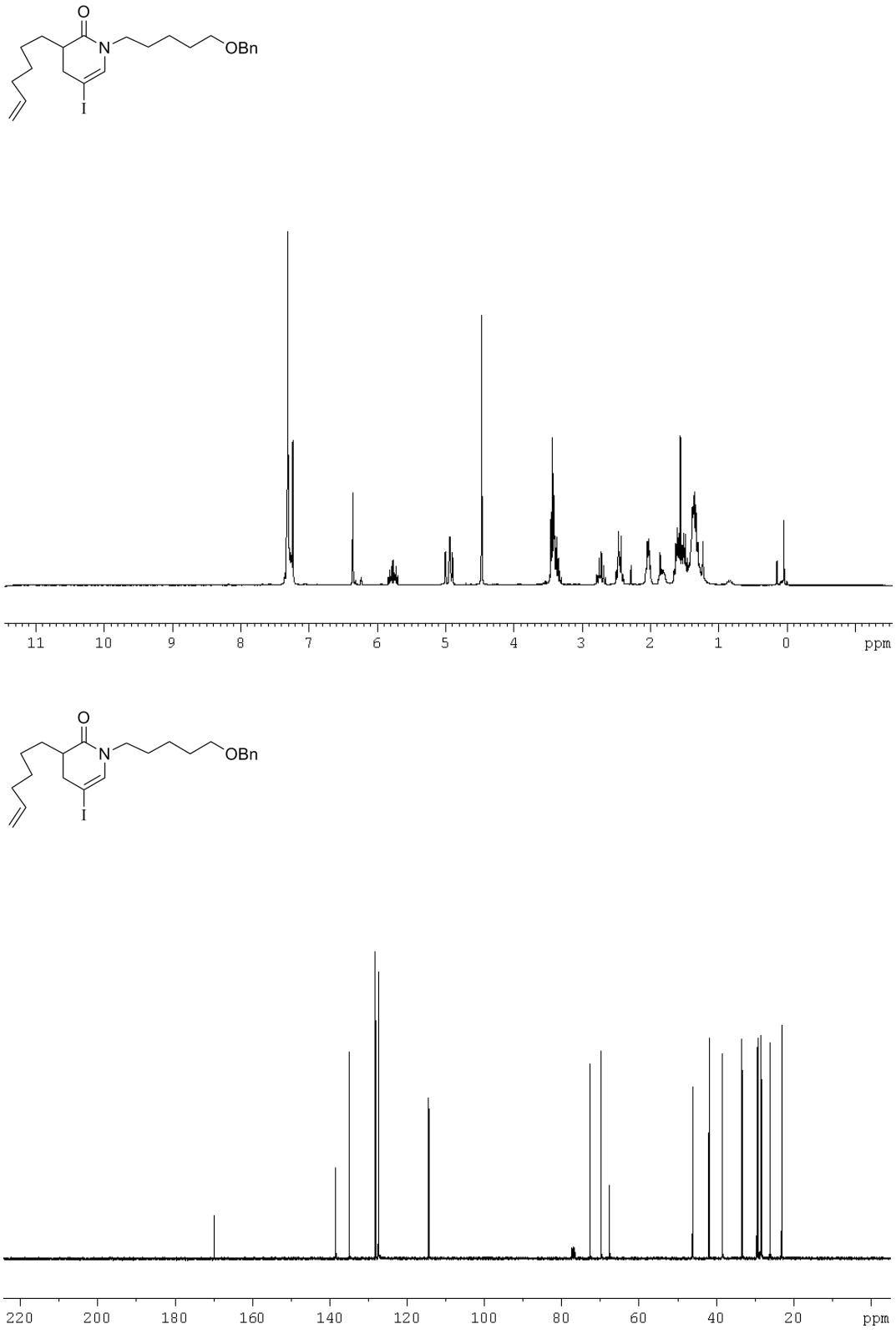

Figure A4. 300 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **4.45** in $CDCl_3$

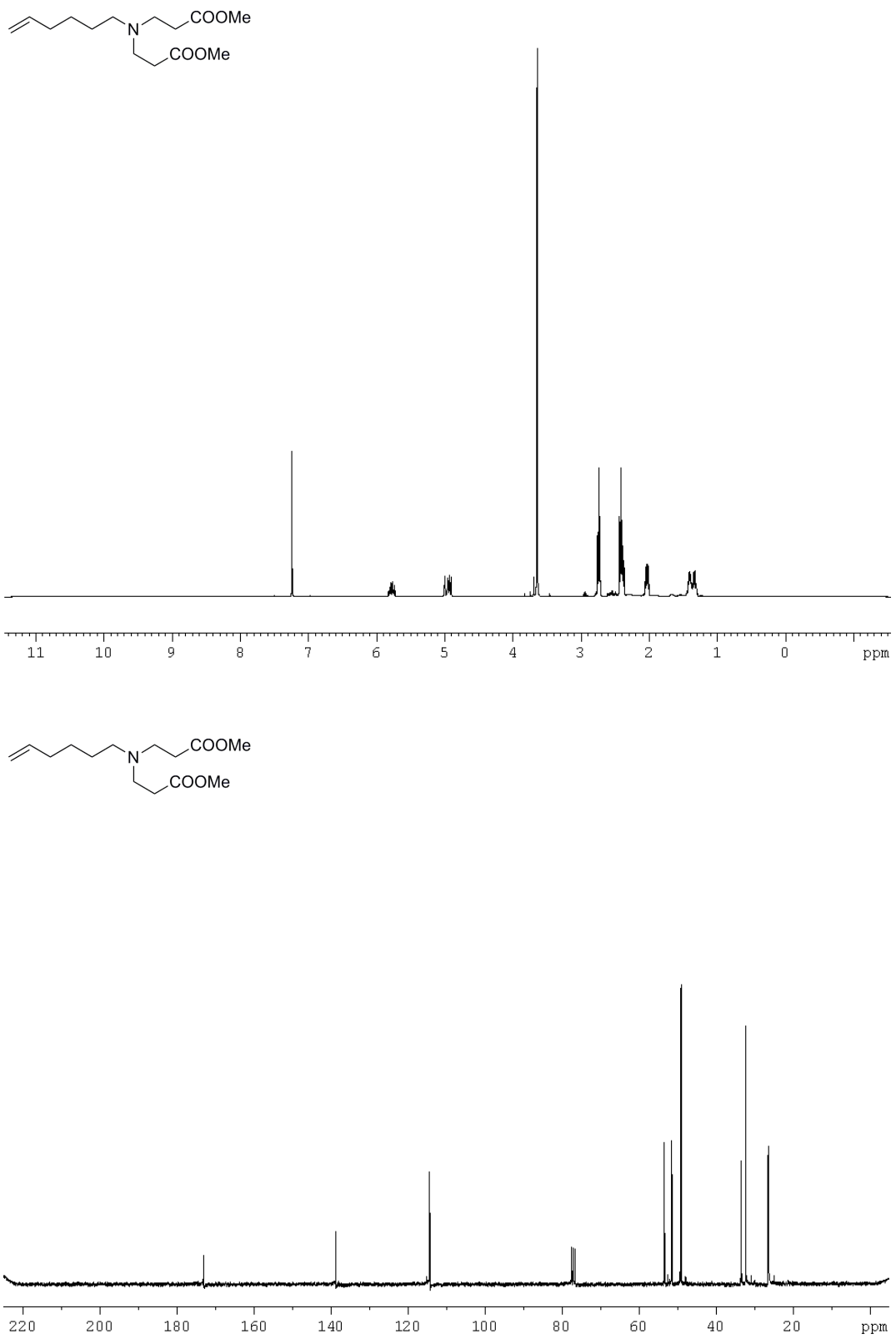

Figure A5. 400 MHz ^{1}H-NMR 75 MHz ^{13}C-NMR spectrum of **5.2** in $CDCl_3$

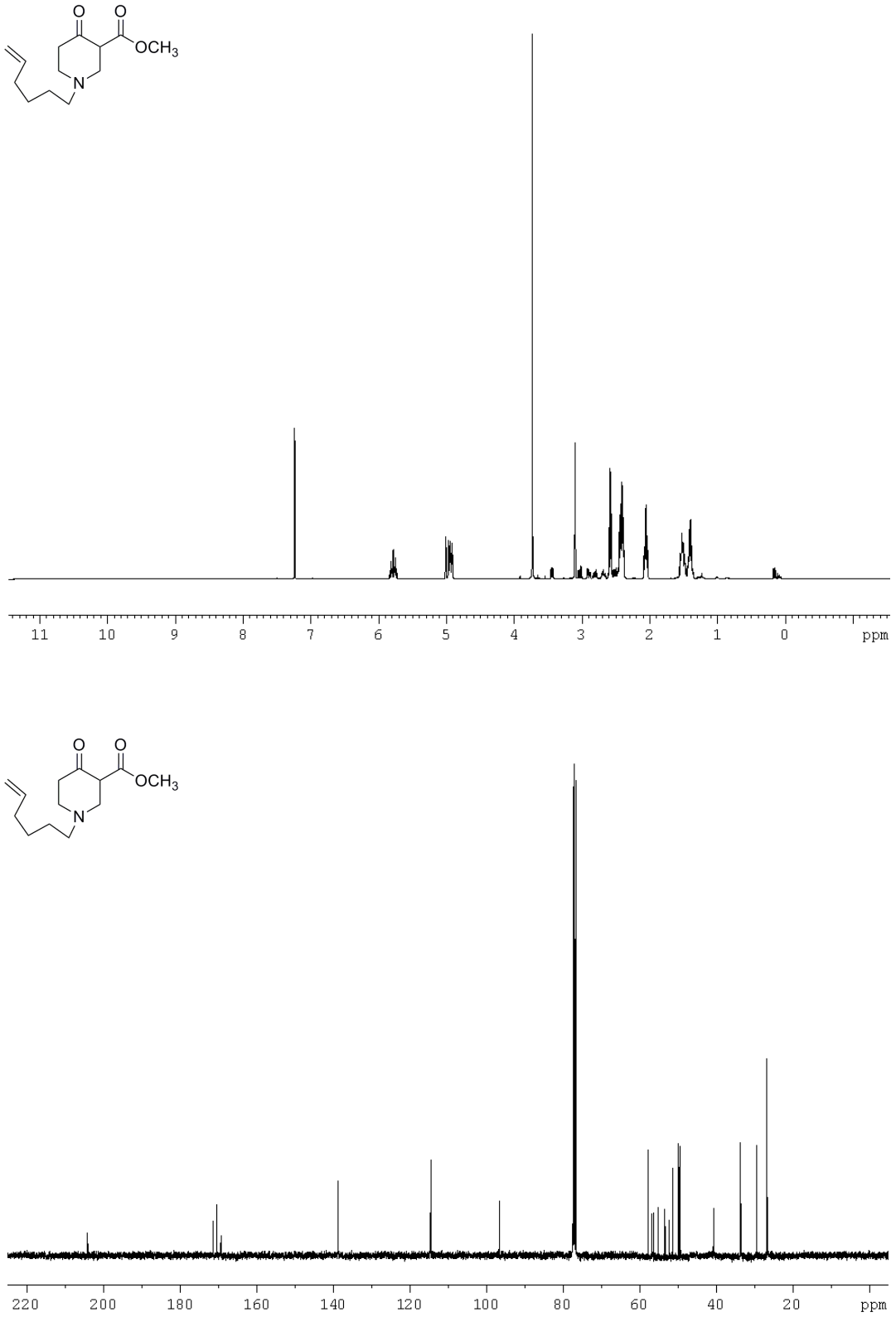

Figure A6. 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **4.49** in $CDCl_3$

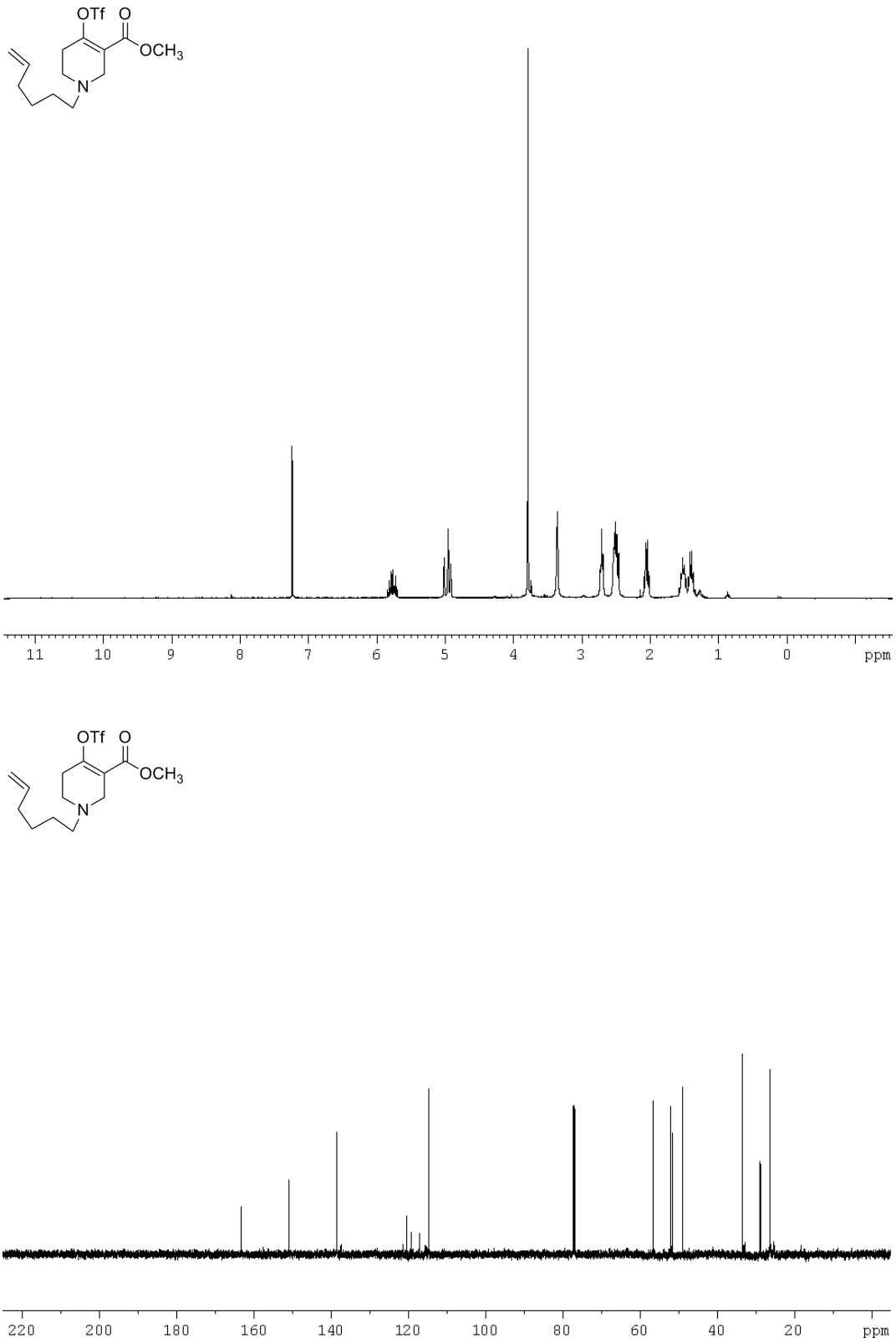

Figure A7. 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **4.50** in $CDCl_3$

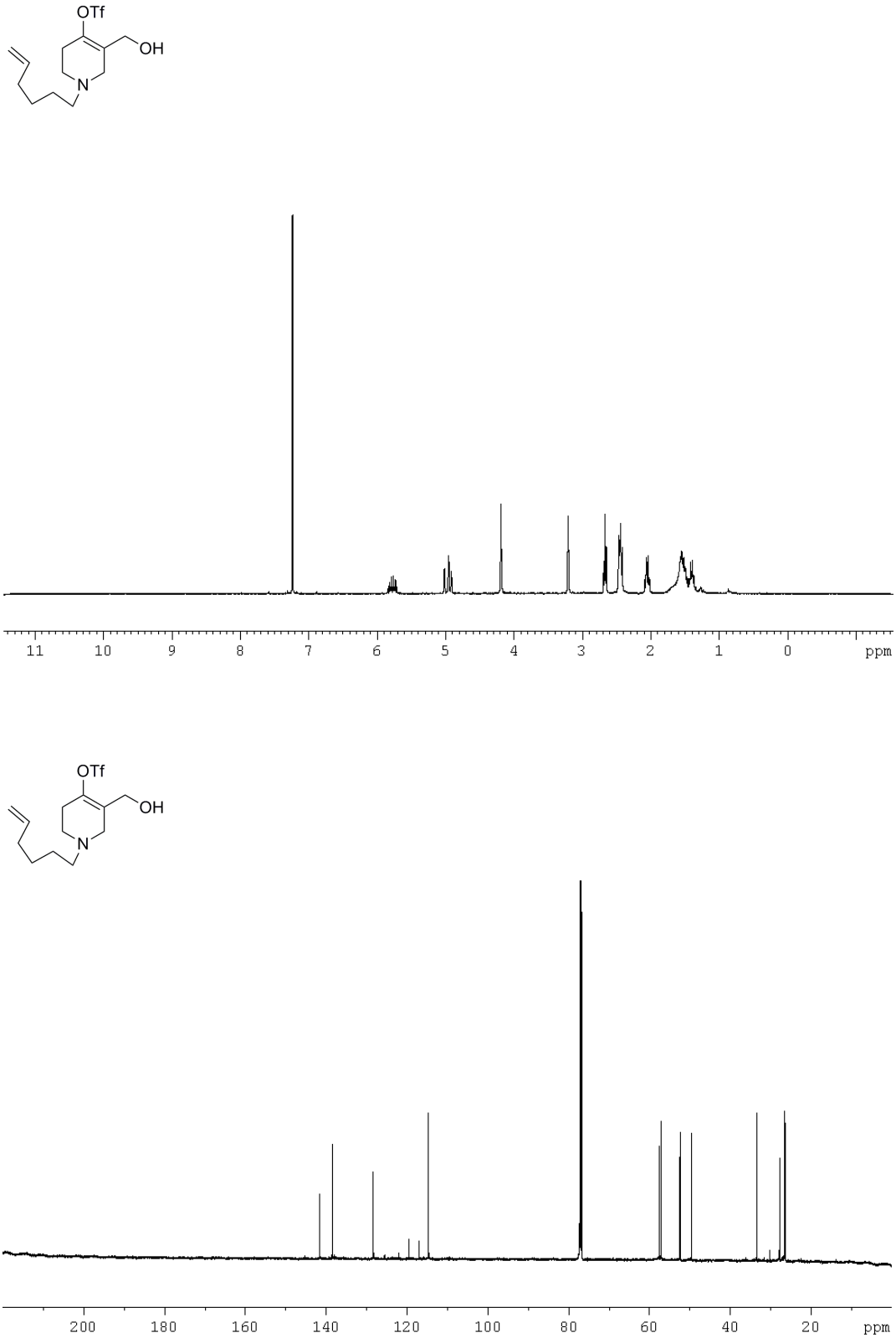

Figure A8. 300 MHz ^{1}H-NMR and 75 MHz ^{13}C-NMR spectrum of **5.3** in $CDCl_3$

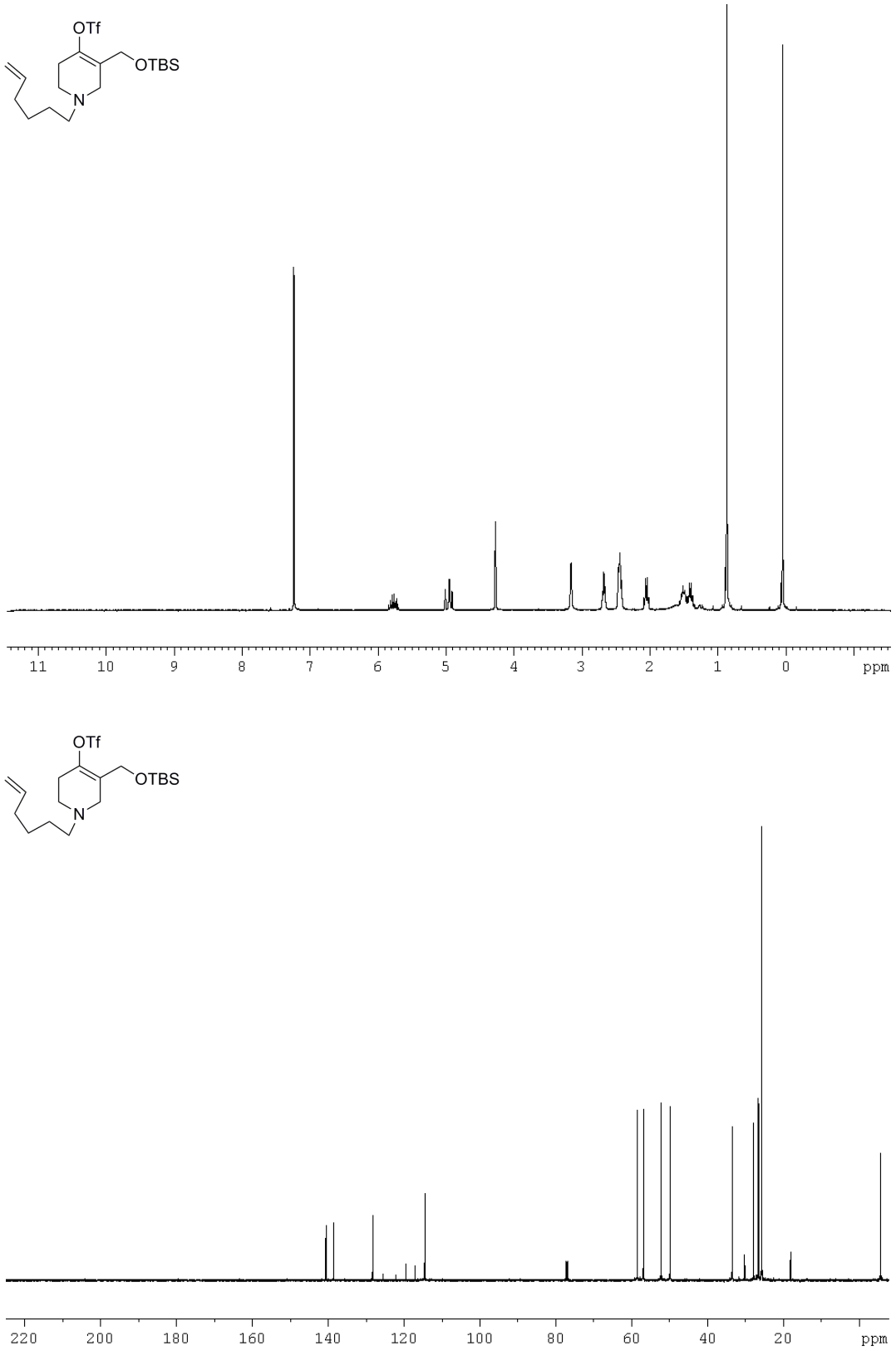

Figure A9. 300 MHz ^{1}H-NMR and 125 MHz ^{13}C-NMR spectrum of **4.51** in $CDCl_3$

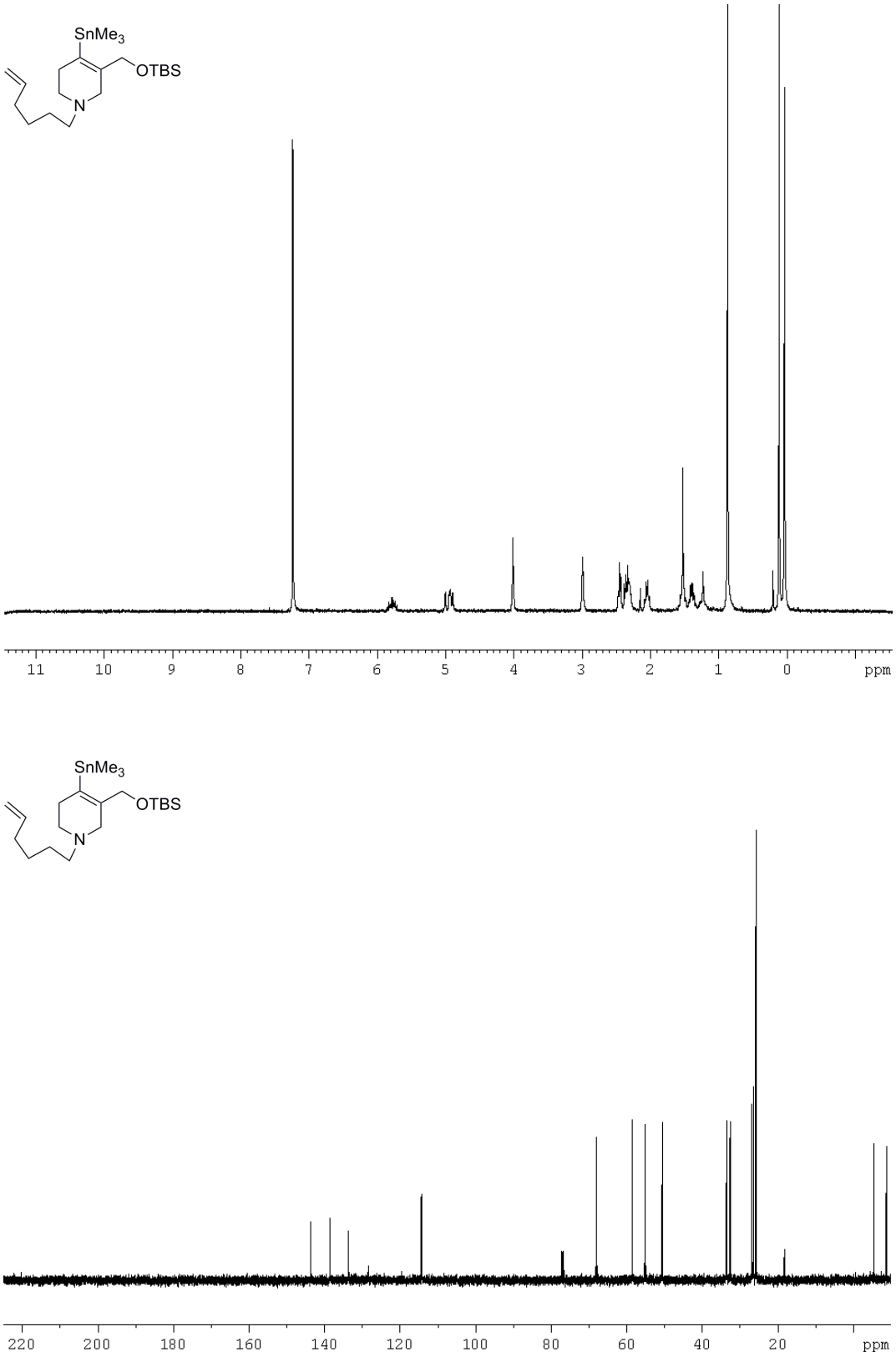

Figure A10. 300 MHz ^{1}H-NMR and 125 MHz ^{13}C-NMR spectrum of **4.44** in $CDCl_3$

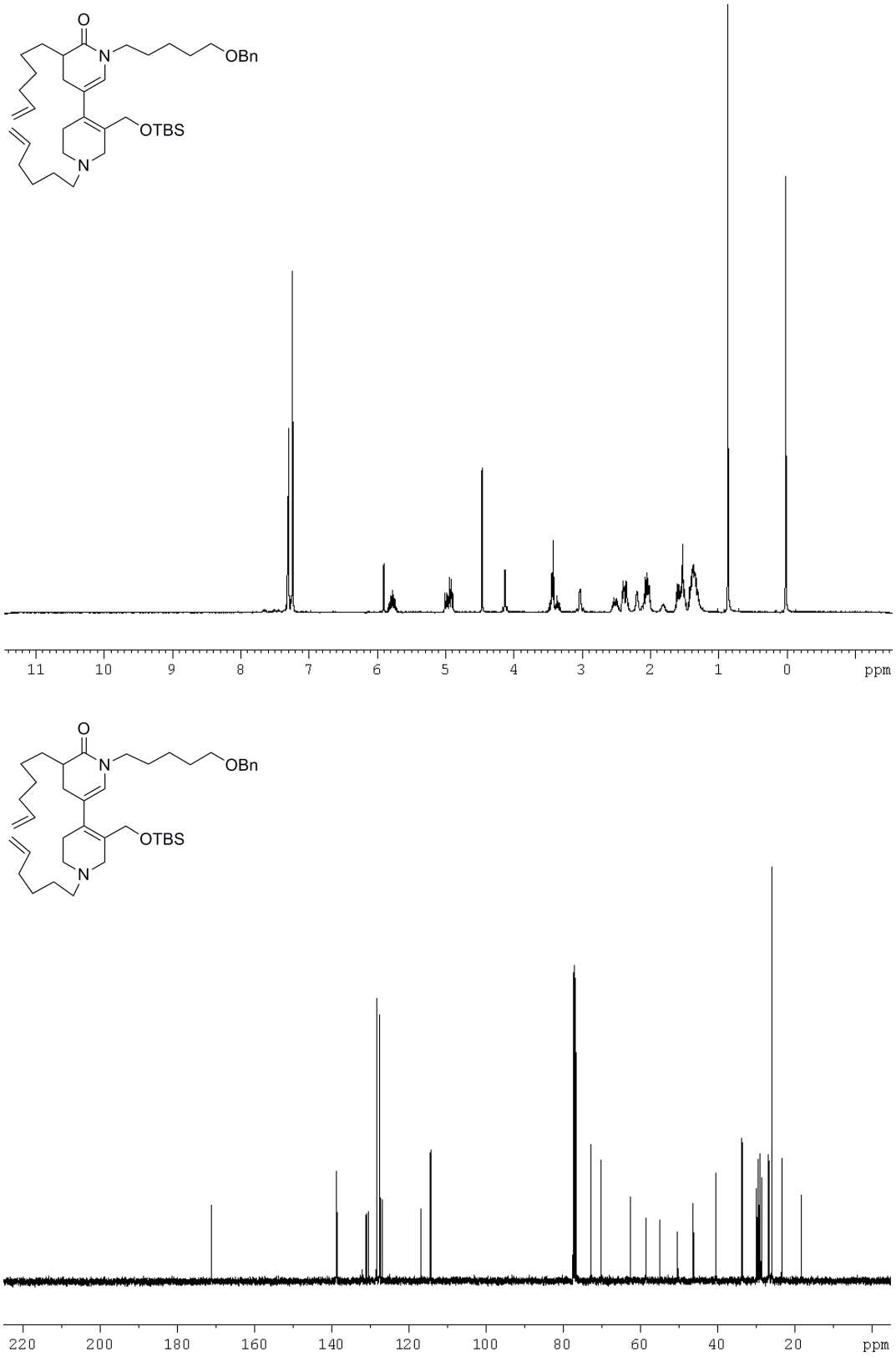

Figure A11. 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **4.43** in $CDCl_3$

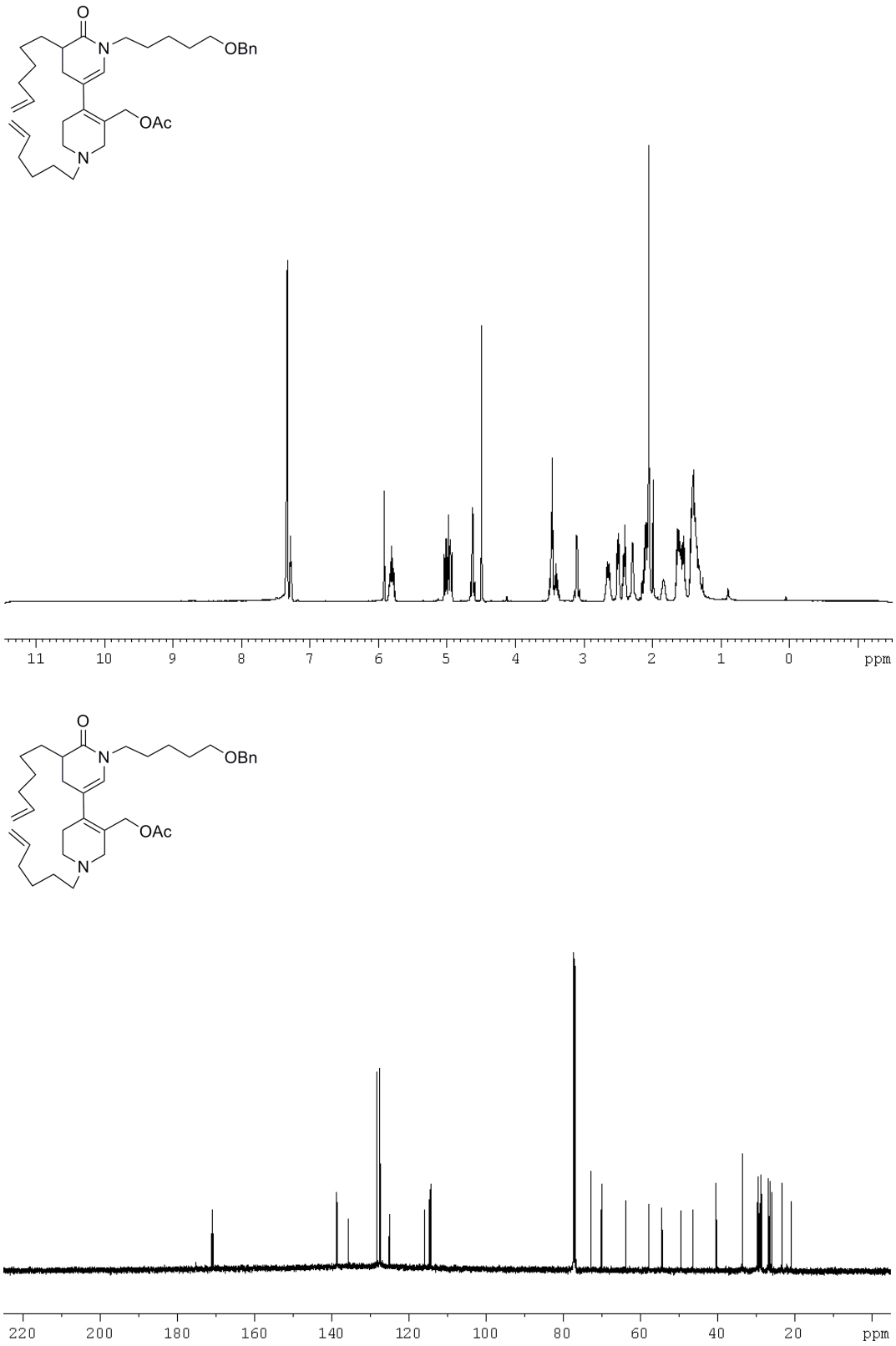

Figure A12. 500 MHz ^{1}H-NMR and 125 MHz ^{13}C-NMR spectrum of **4.52** in $CDCl_3$

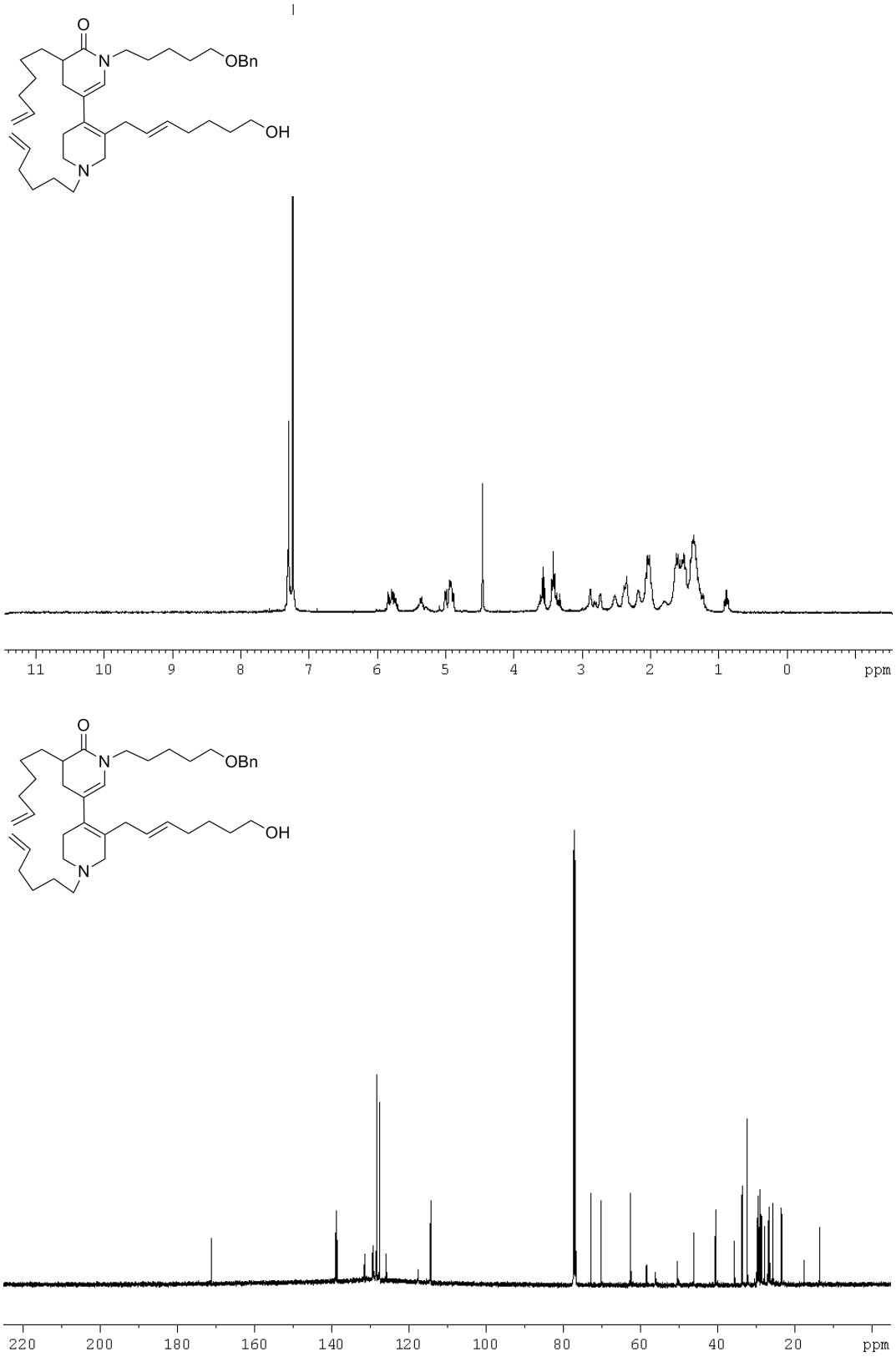

Figure A13. 300 MHz ^{1}H-NMR and 125 MHz ^{13}C-NMR spectrum of **4.53** in $CDCl_3$

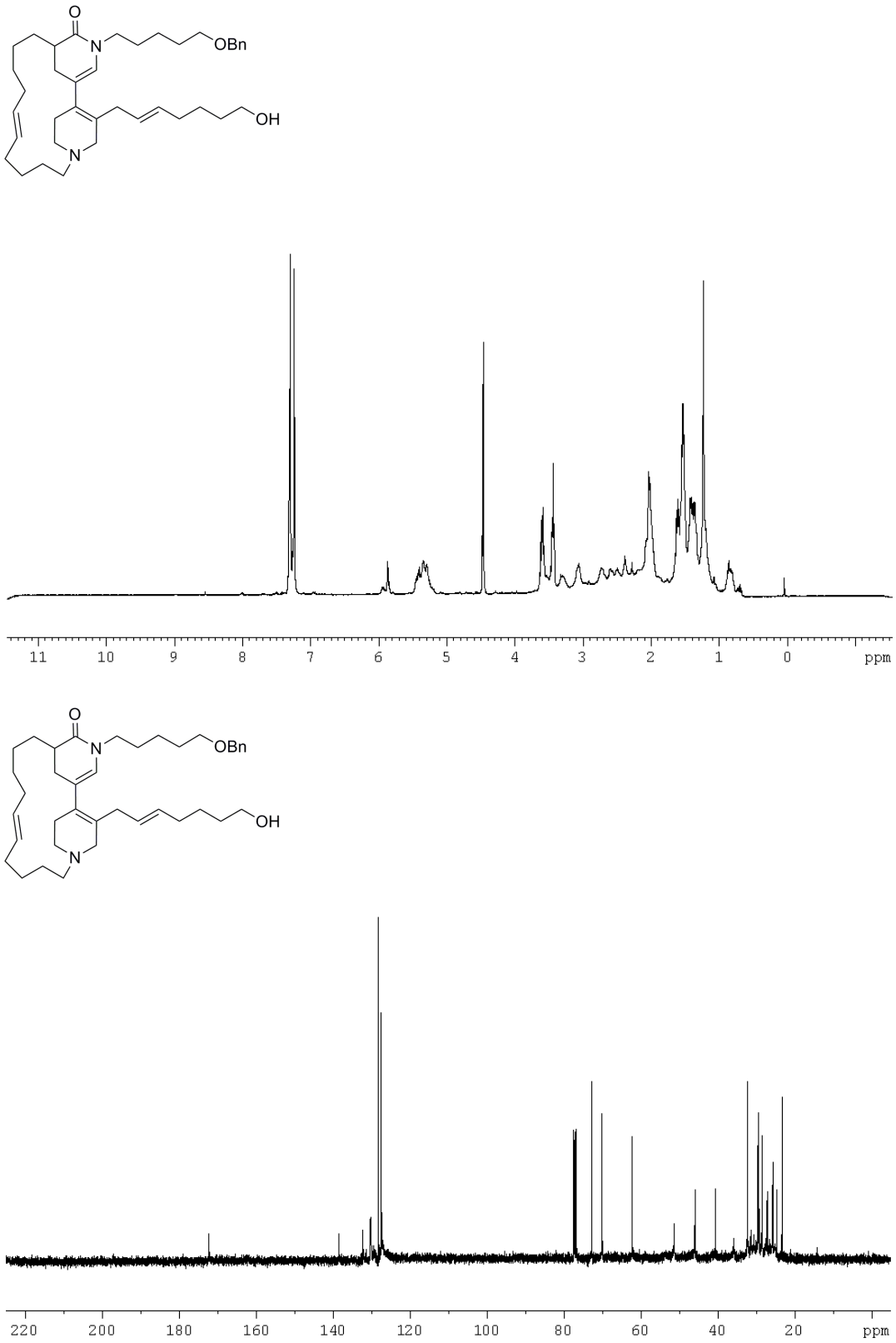

Figure A14. 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **4.42** in $CDCl_3$

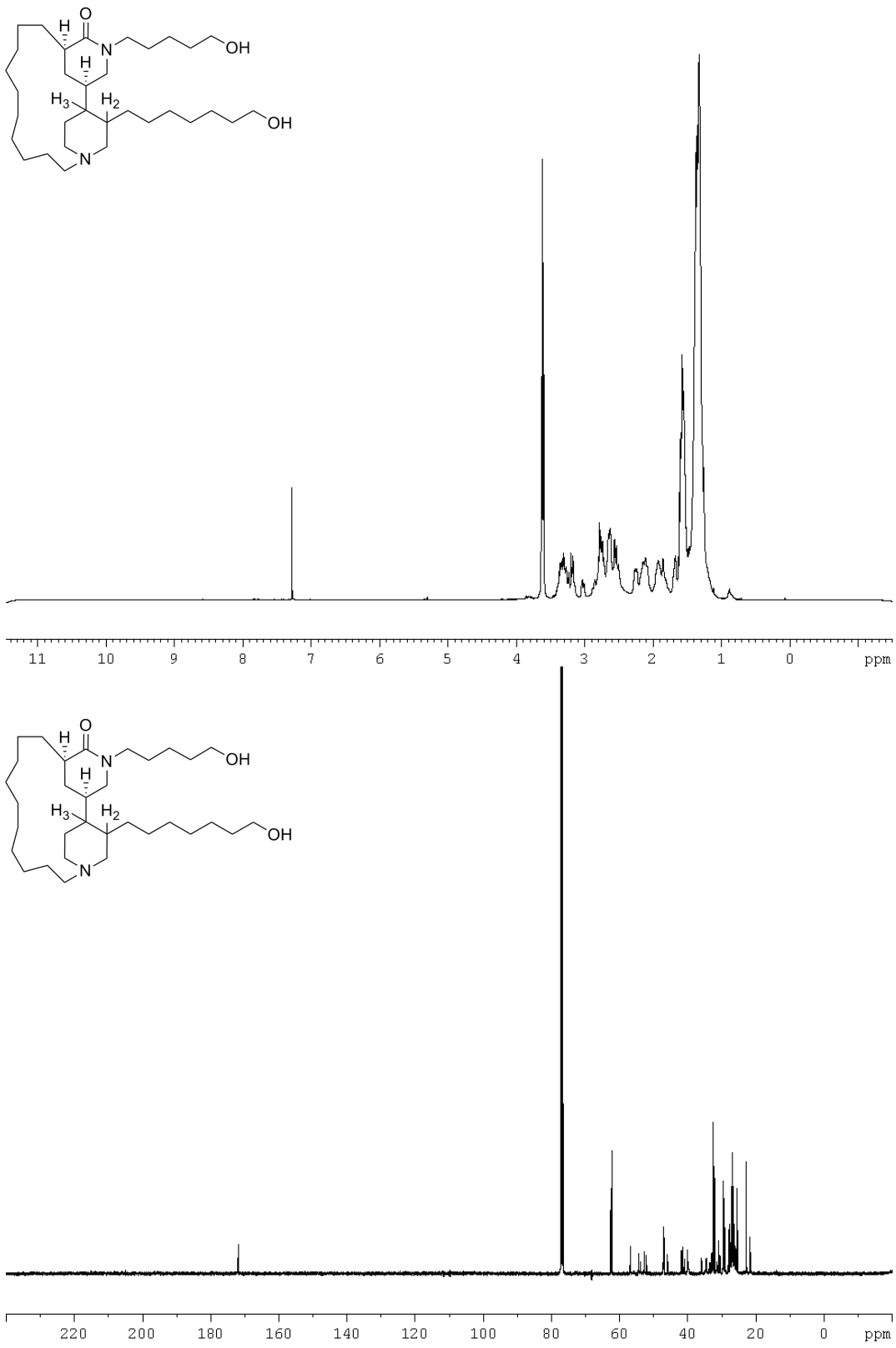

Figure A15. 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR spectrum of **4.41a/b** in $CDCl_3$

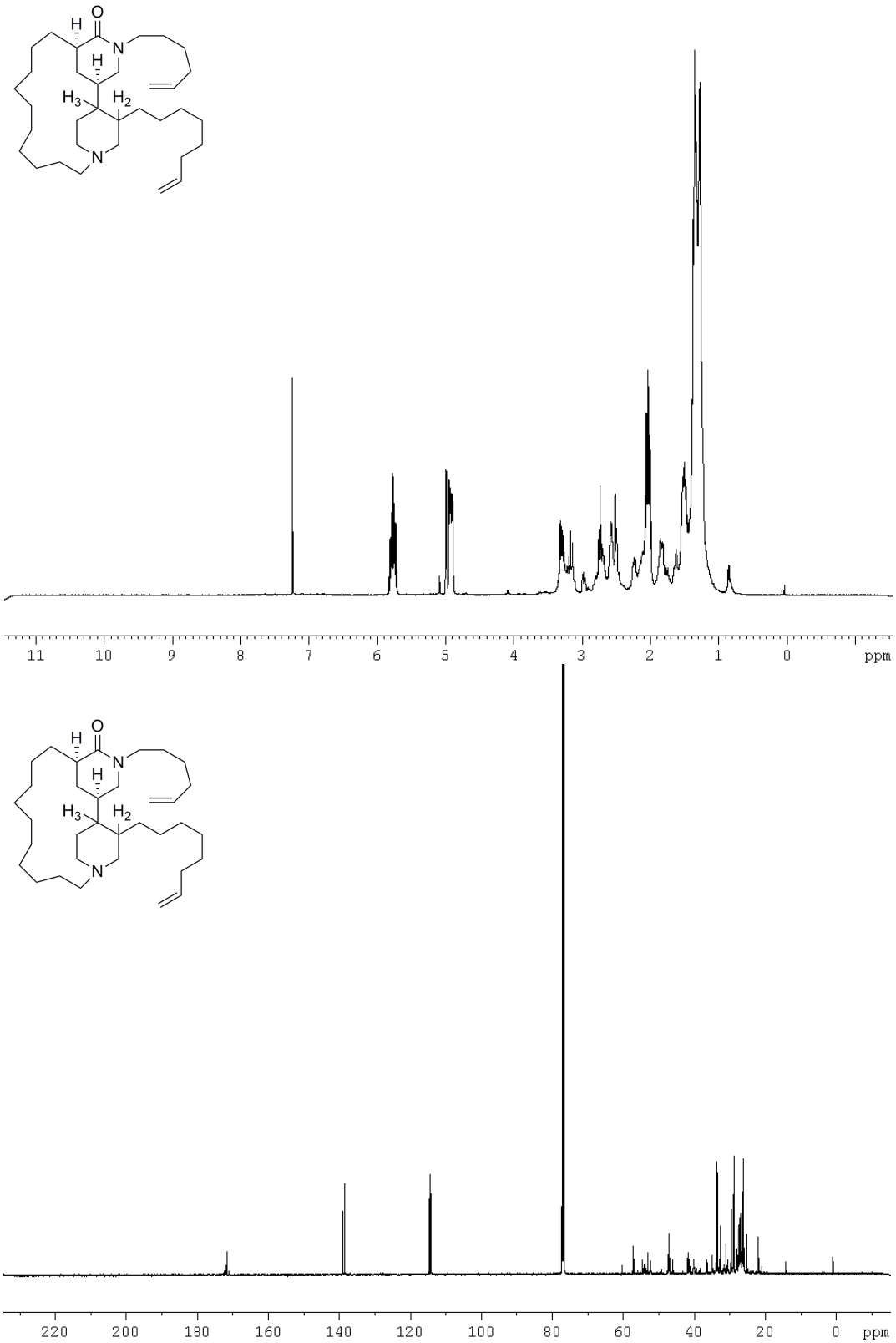

Figure A16. 400 MHz ^{1}H-NMR and 125 MHz ^{13}C-NMR spectrum of **4.70a/b** in $CDCl_3$

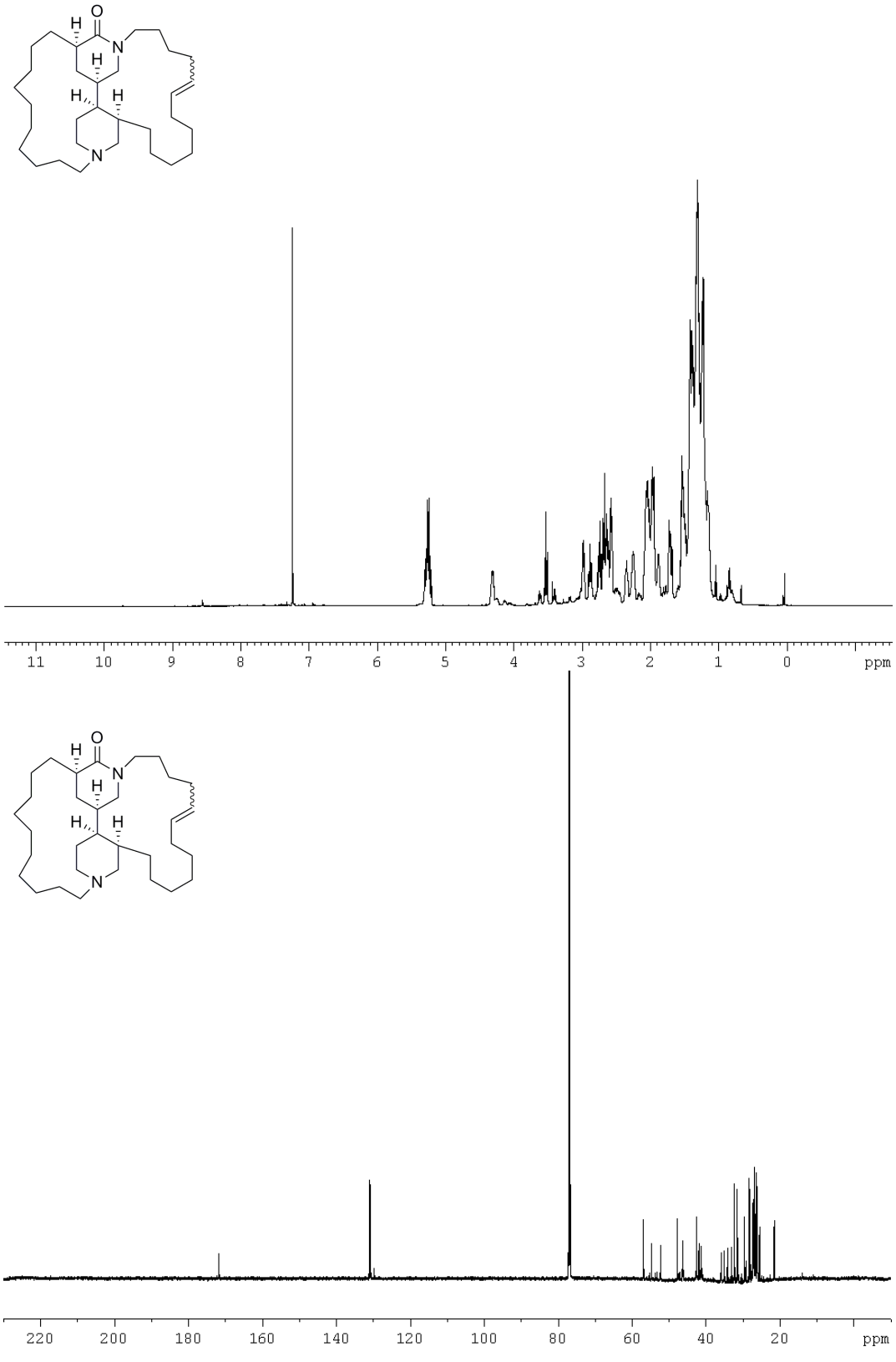

Figure A17. 600 MHz ^{1}H-NMR and 150 MHz ^{13}C-NMR spectrum of **4.71a** in $CDCl_3$

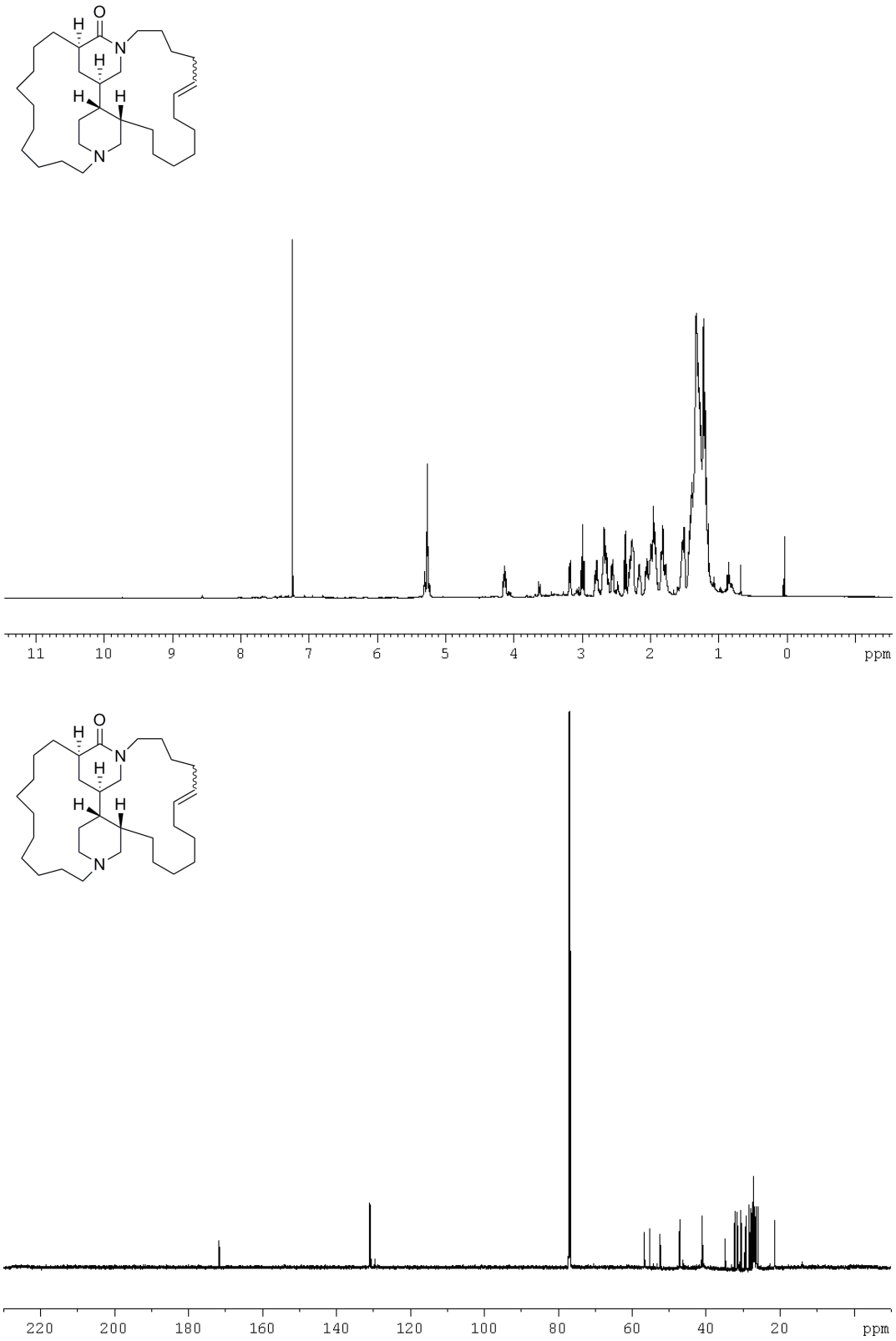

Figure A18. 600 MHz ^{1}H-NMR and 150 MHz ^{13}C-NMR spectrum of **4.71b** in $CDCl_3$

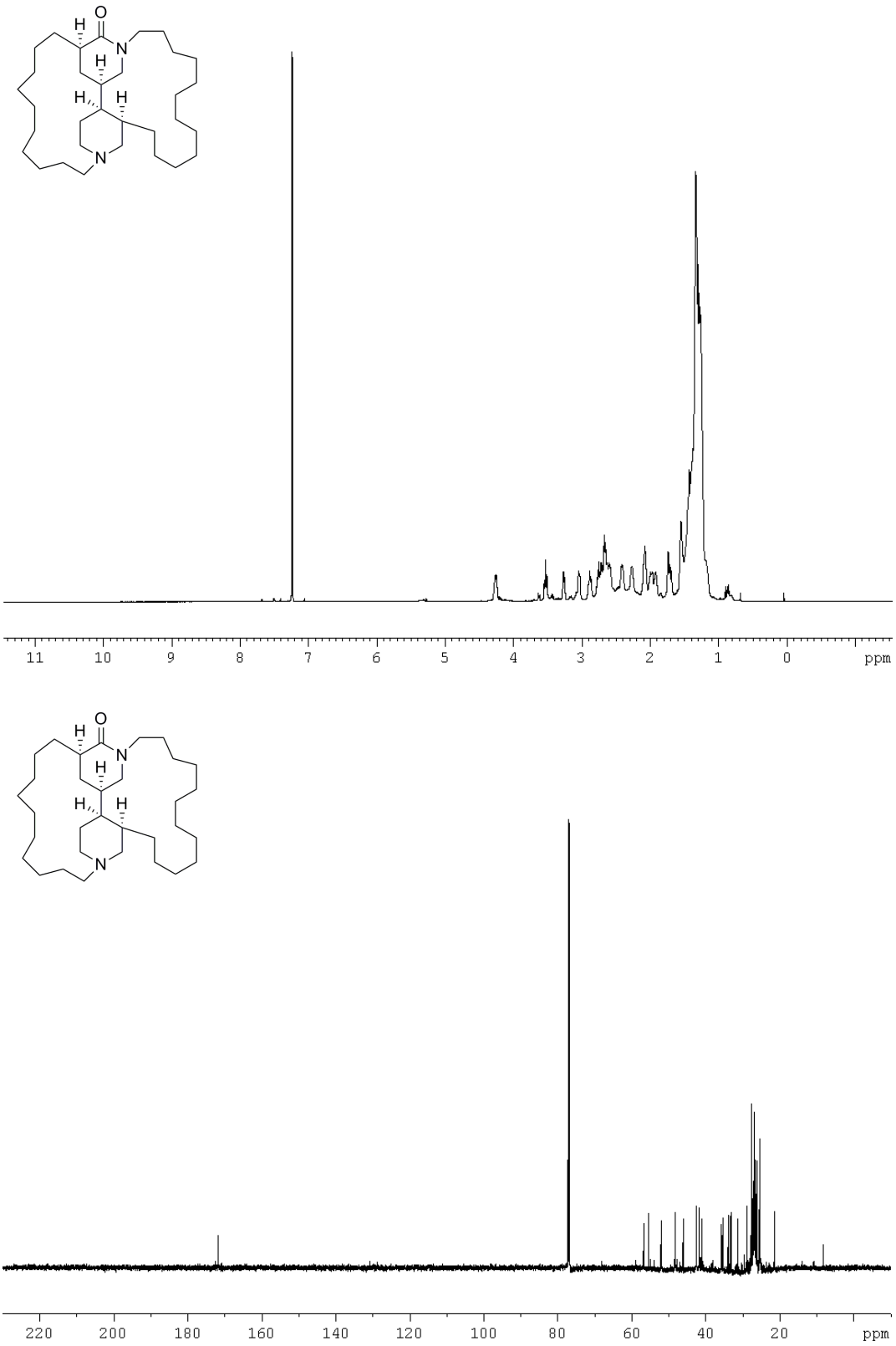

Figure A19. 600 MHz ^{1}H-NMR and 150 MHz ^{13}C-NMR spectrum of **4.73a** in $CDCl_3$

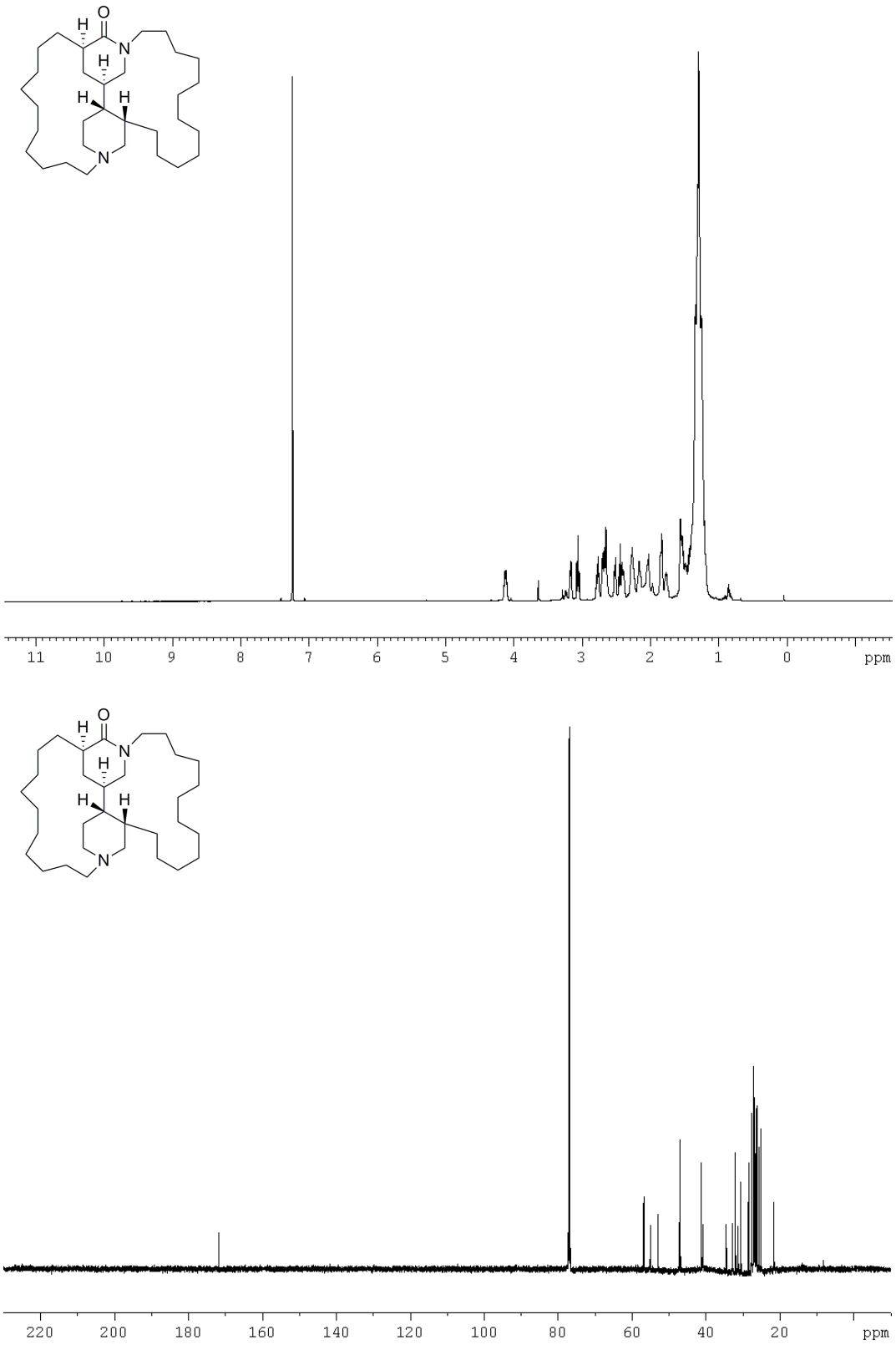

Figure A20. 600 MHz ^{1}H-NMR and 150 MHz ^{13}C-NMR spectrum of **4.73b** in $CDCl_3$

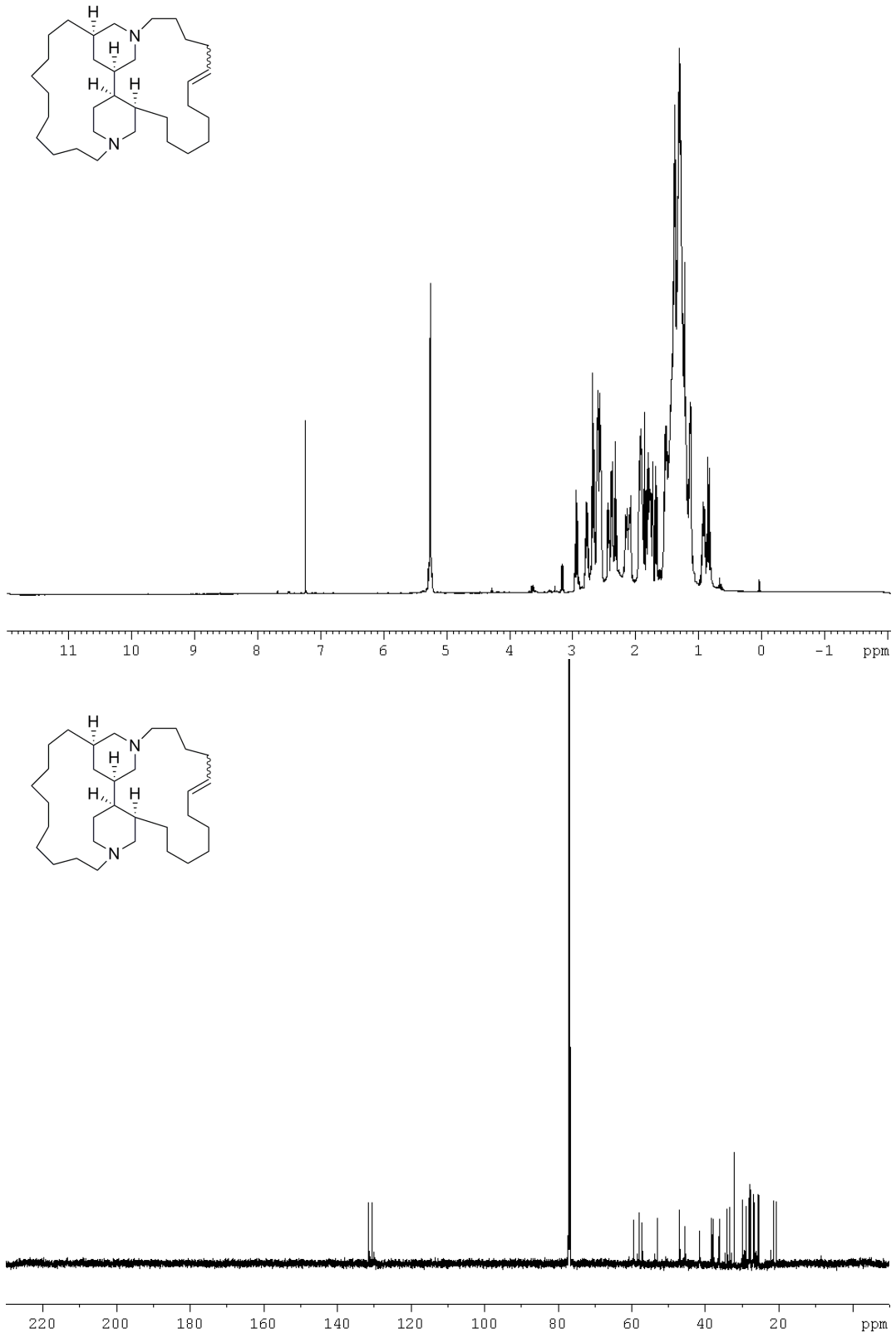

Figure A21. 600 MHz ^{1}H-NMR and 150 MHz ^{13}C-NMR spectrum of **4.73a** in $CDCl_3$

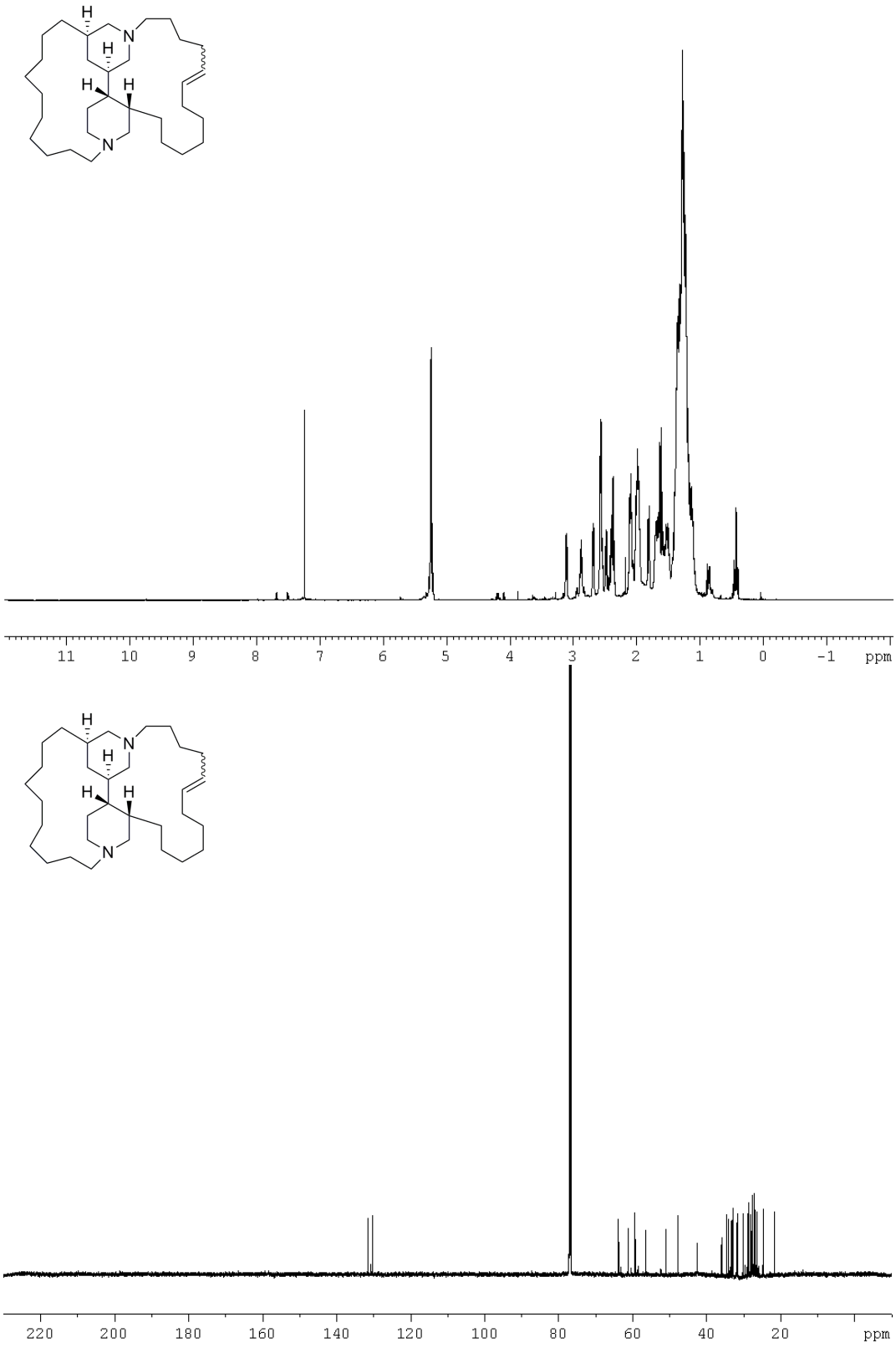

Figure A22. 600 MHz ^{1}H-NMR and 150 MHz ^{13}C-NMR spectrum of **4.72b** in $CDCl_3$

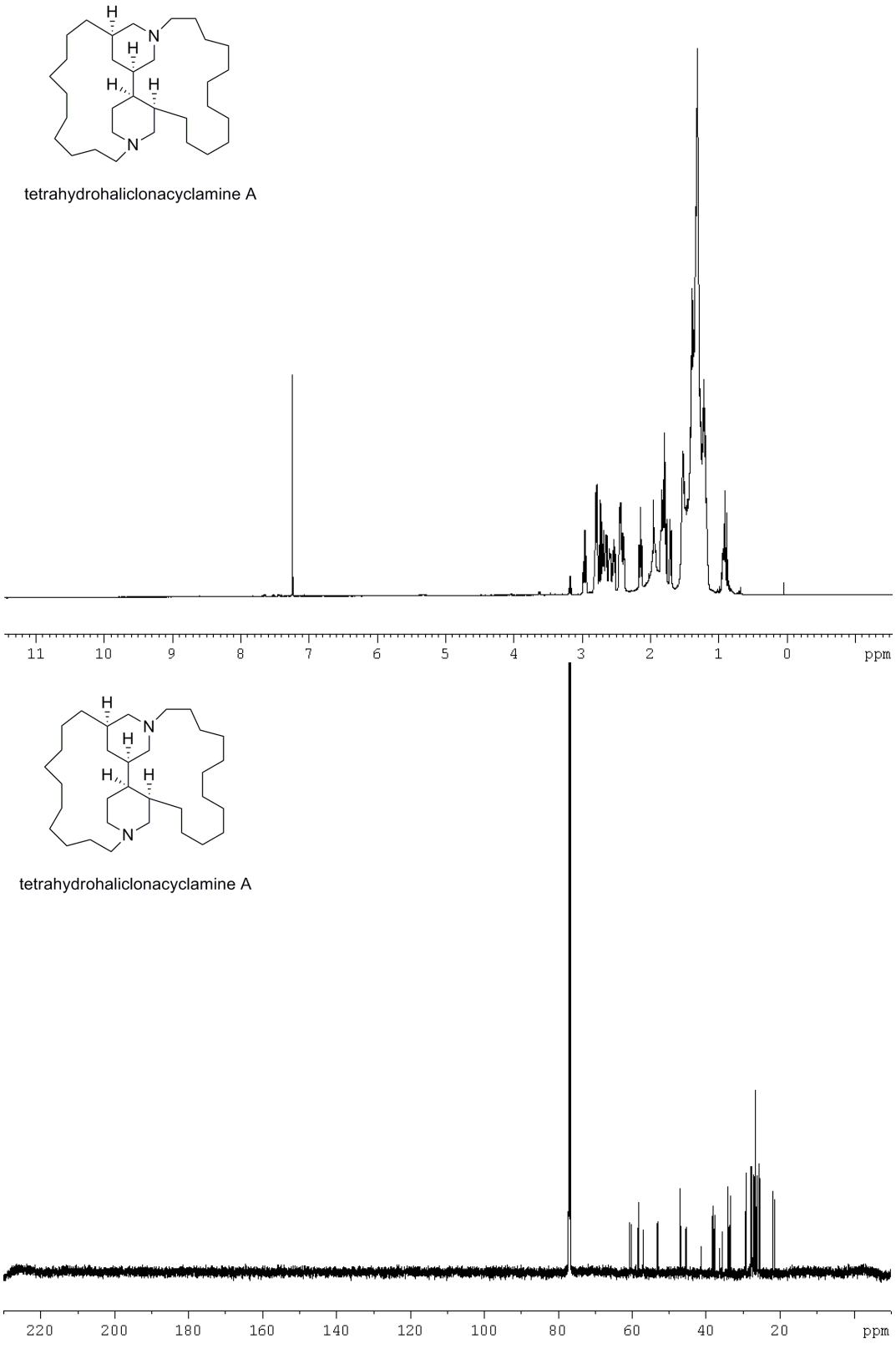

Figure A23. 600 MHz ^{1}H-NMR and 150 MHz ^{13}C-NMR spectrum of **3.3** in $CDCl_3$

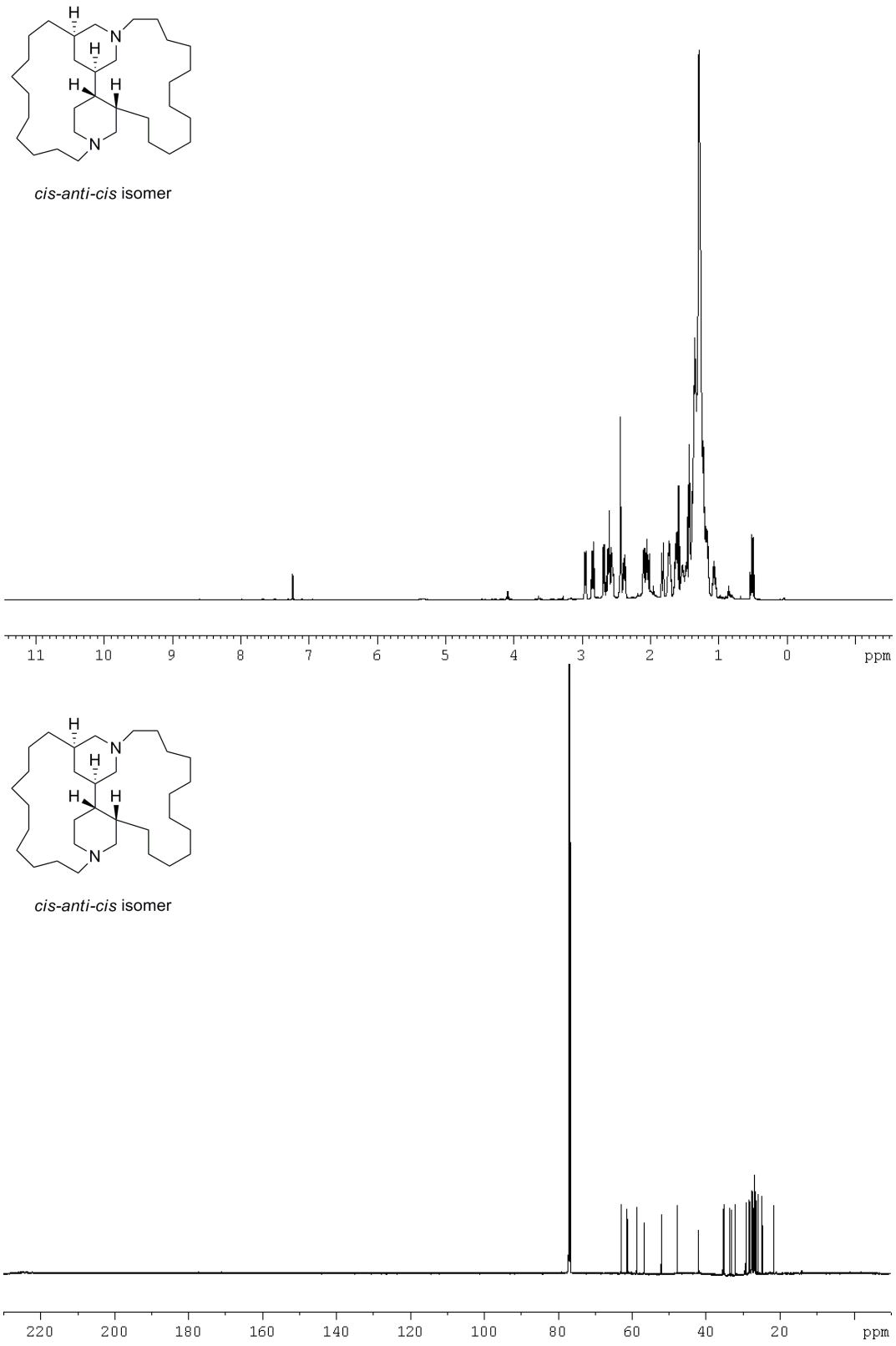

Figure A24. 600 MHz ^{1}H-NMR and 150 MHz ^{13}C-NMR spectrum of **4.74b** in $CDCl_3$

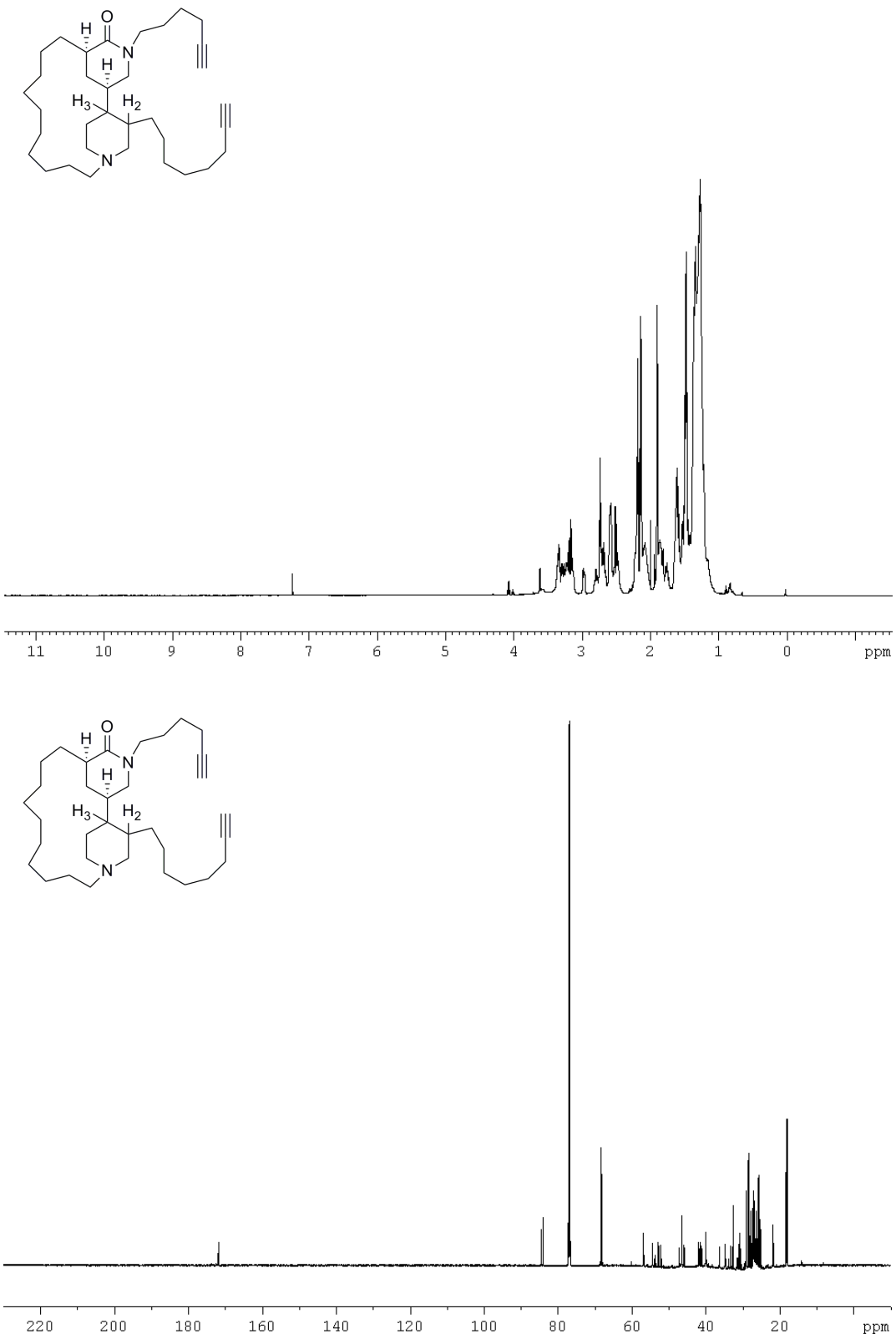

Figure A25. 600 MHz ^{1}H-NMR and 150 MHz ^{13}C-NMR spectrum of **4.79a/b** in $CDCl_3$

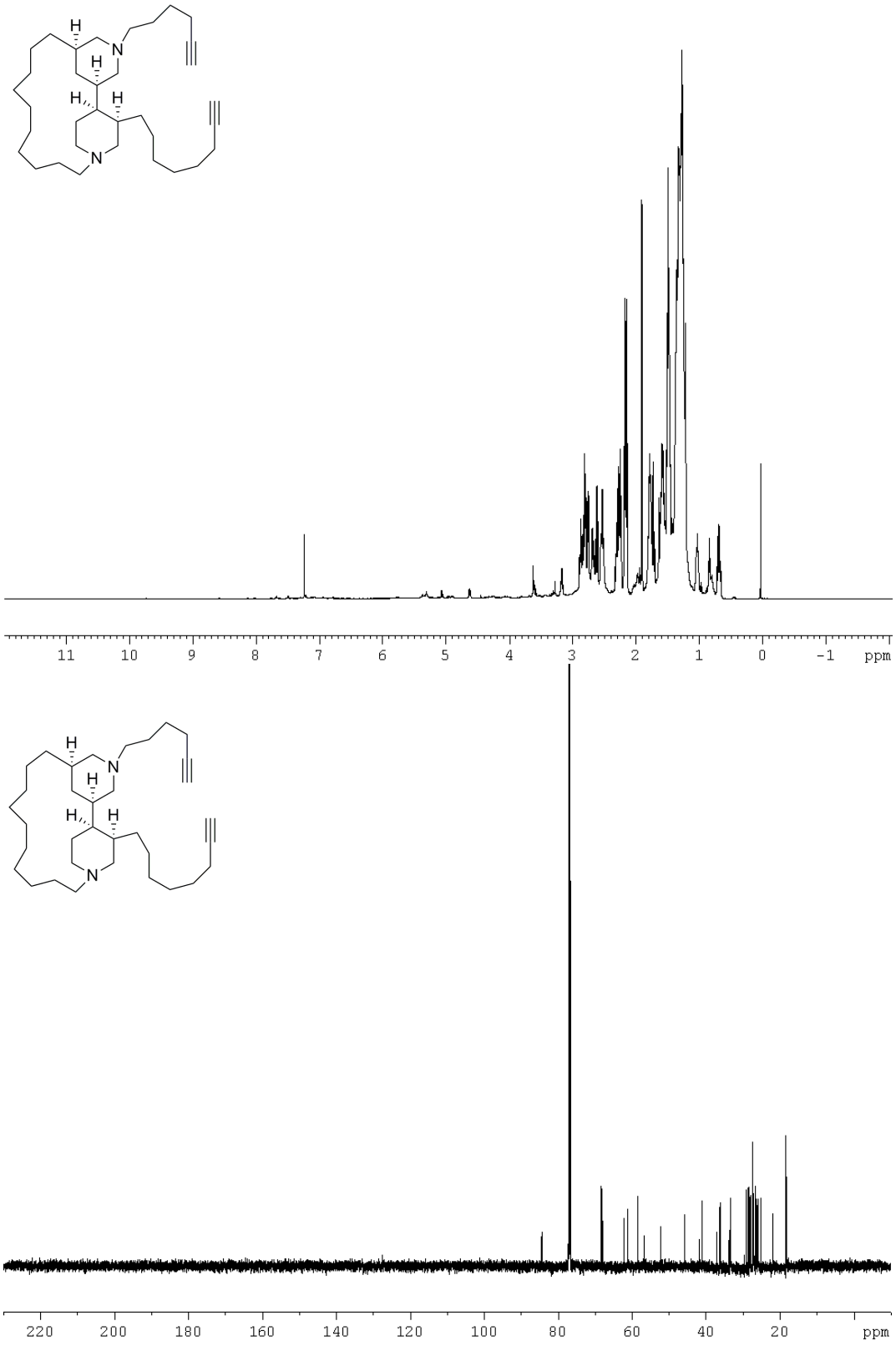

Figure A26. 600 MHz ^{1}H-NMR and 150 MHz ^{13}C-NMR spectrum of **4.80a** in $CDCl_3$

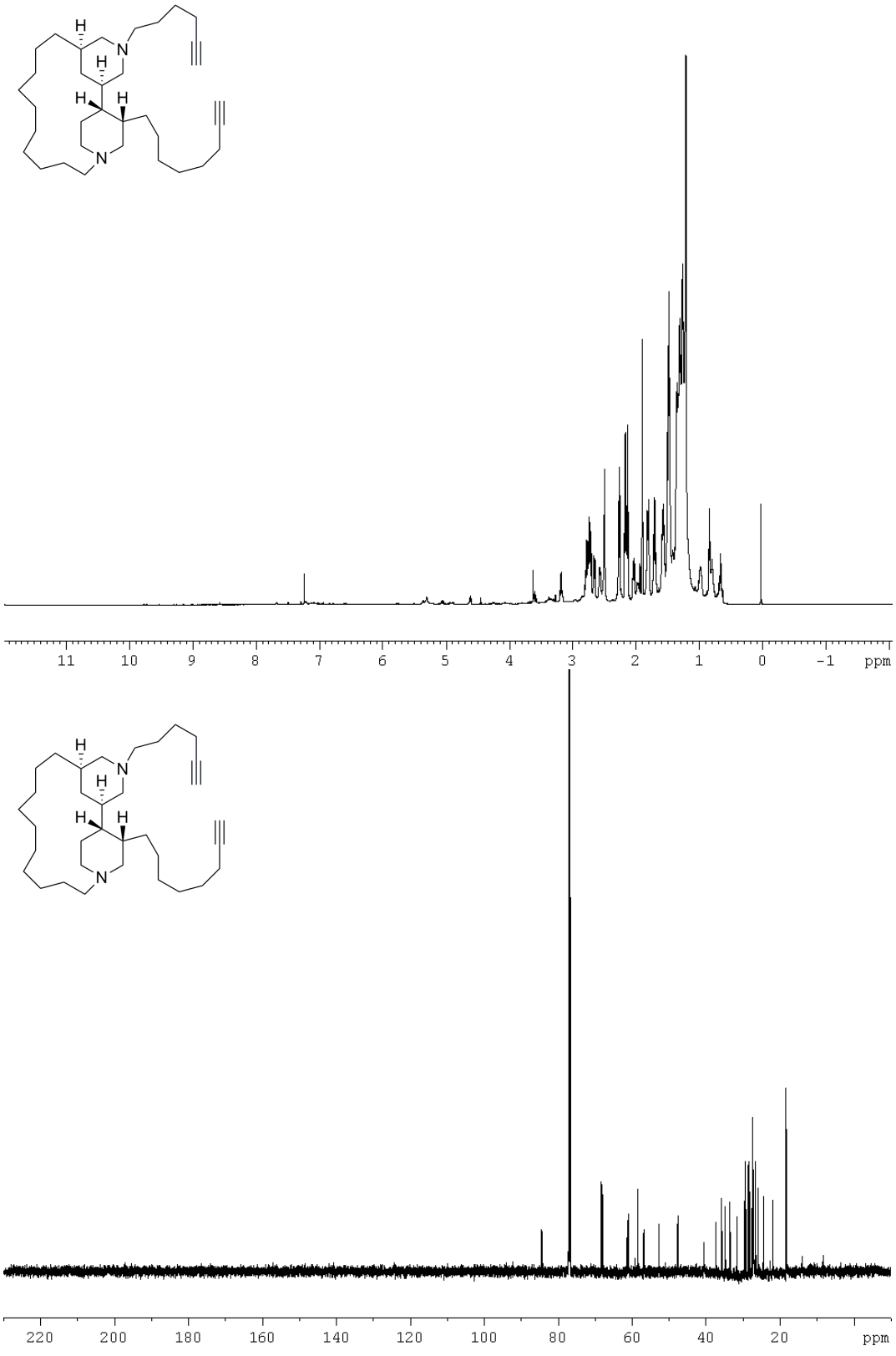

Figure A27. 600 MHz ^{1}H-NMR and 150 MHz ^{13}C-NMR spectrum of **5.7b** in $CDCl_3$

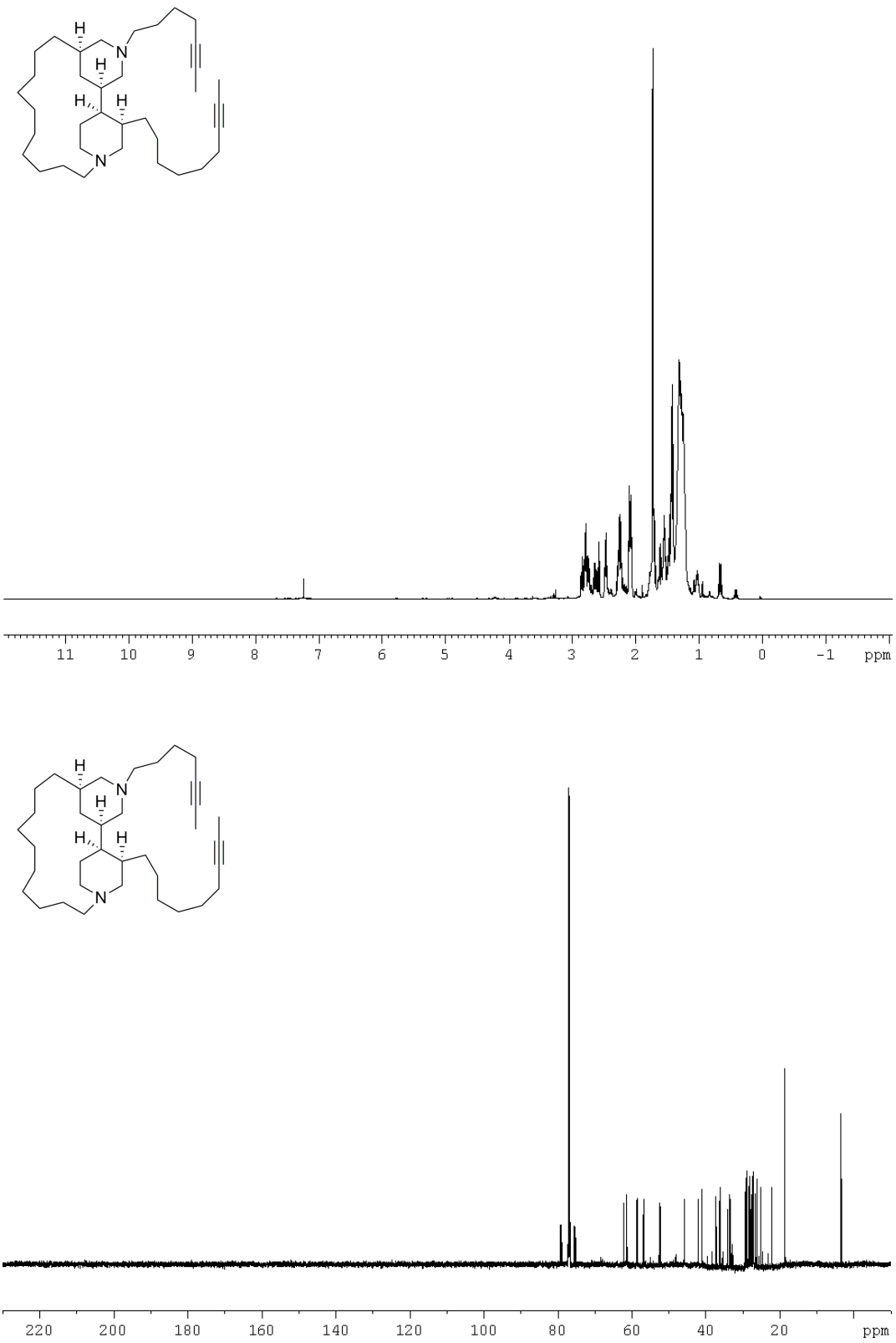

Figure A28. 600 MHz ^{1}H-NMR and 150 MHz ^{13}C-NMR spectrum of **4.40** in $CDCl_3$

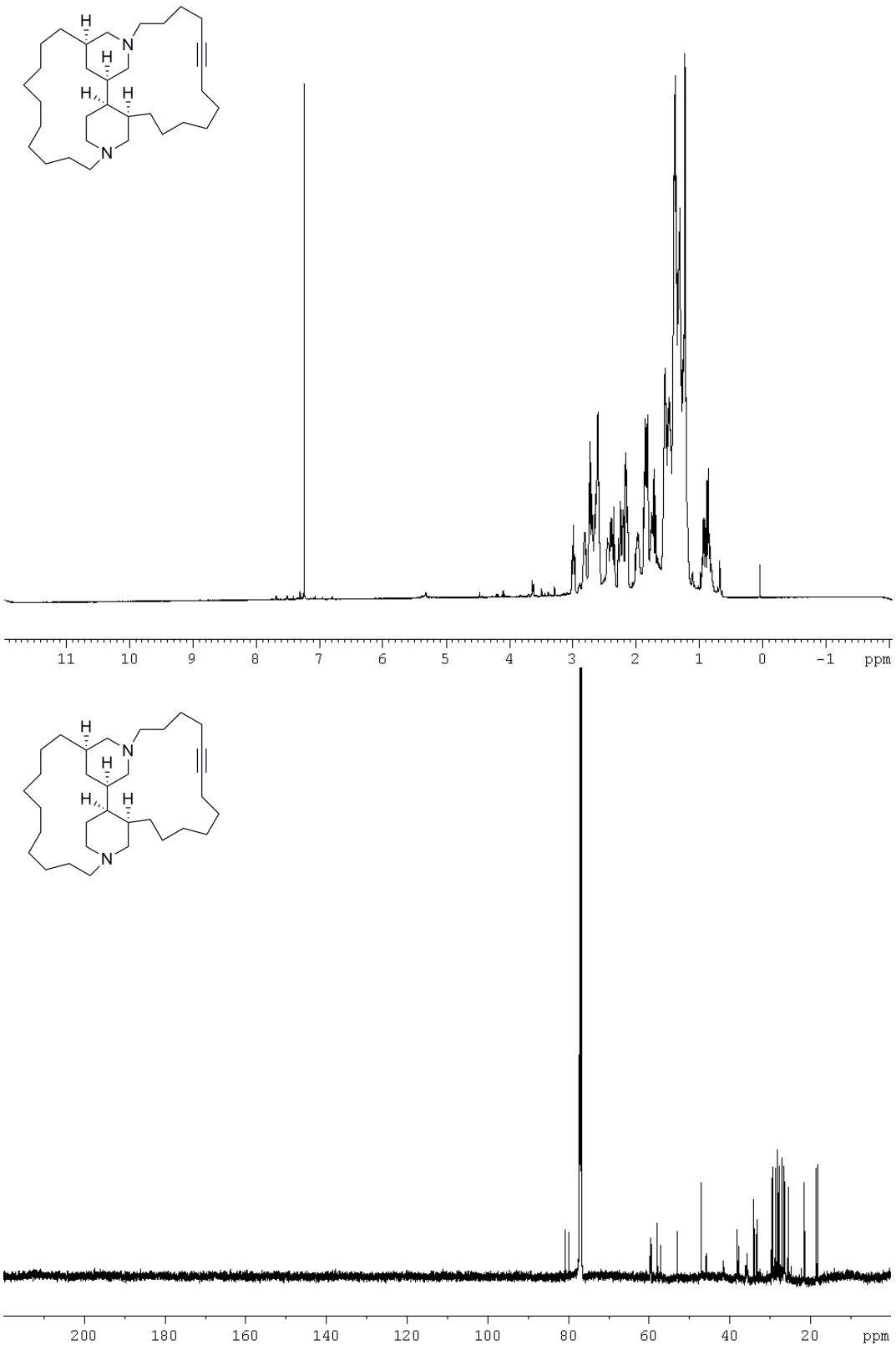

Figure A29. 600 MHz ^{1}H-NMR and 150 MHz ^{13}C-NMR spectrum of **4.88** in $CDCl_3$

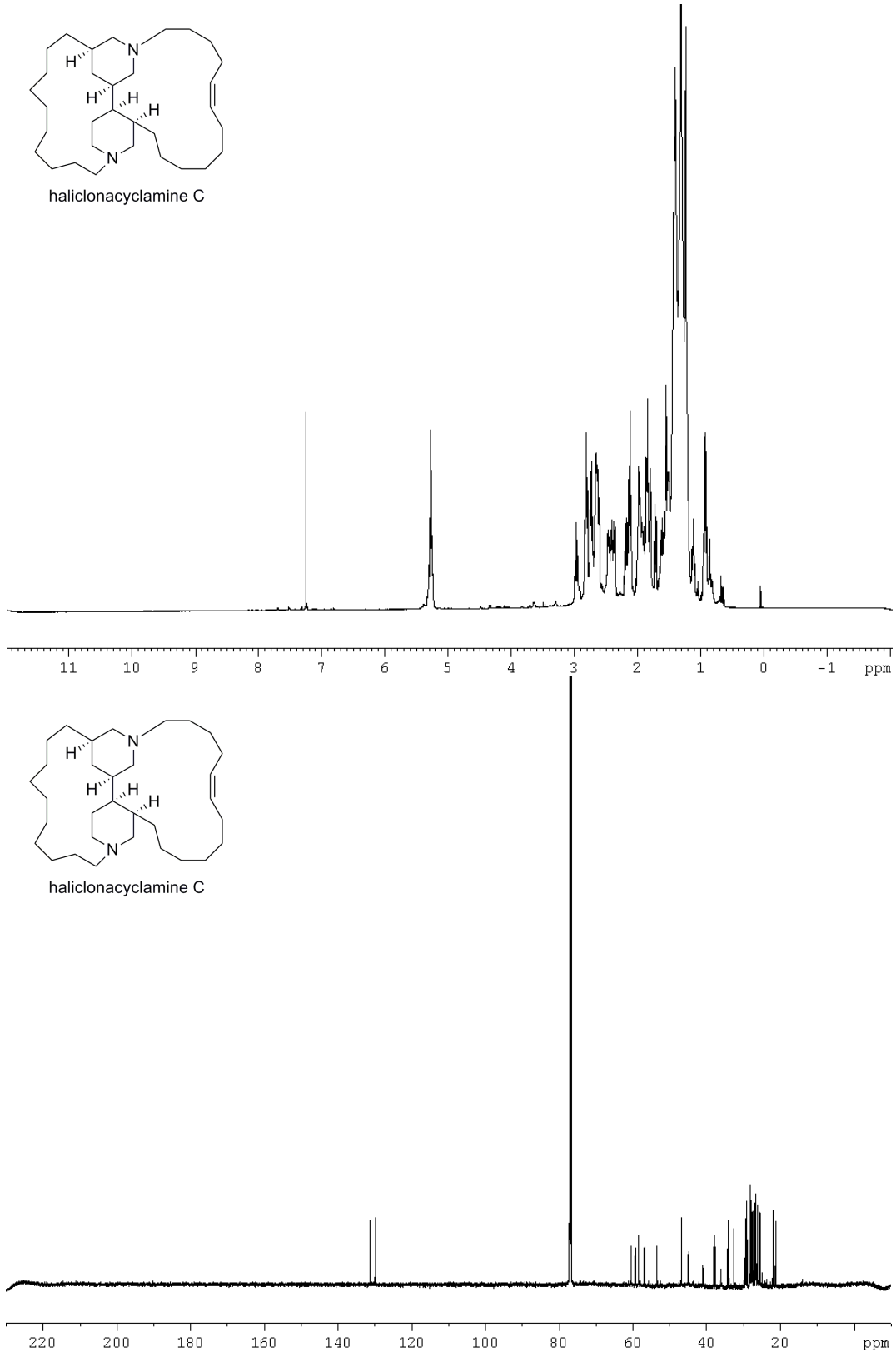

Figure A30. 600 MHz ^{1}H-NMR and 150 MHz ^{13}C-NMR spectrum of **1.4** in $CDCl_3$