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Andrew C. Flick

Utilization of a Michael Addition-Dipolar Cycloaddition Cascade Involving 2,3-*bis*(Phenylsulfonyl)butadiene for Alkaloid Synthesis

By

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An Abstract of

A dissertation submitted to the Faculty of the Graduate School of Arts and Sciences of Emory University in partial fulfillment of the requirements for the degree of Doctor of Philosophy

Department of Chemistry

2008

Abstract

The azaspirocyclic nucleus is a structural motif found in a wide variety of medicinally relevant natural products. A unique and operationally-simple approach to the construction of this structural subunit was developed and makes use of readily available oxime substrates and a disubstituted diene. The reaction platform represents facile entry into complex azacyclic structures, permitting rapid generation of a variety of 2,2-disubstituted piperidine derivatives.

Approaches to several natural product alkaloid targets are presented utilizing the tandem Michael Addition-Dipolar Cycloaddition Cascade. The key element of each synthesis consisted of a conjugate addition of an oxime to one of the termini of 2,3-*bis*(phenylsulfonyl)butadiene, followed by a proton transfer to give a nitrone intermediate. This nitrone immediately cyclizes across the tethered π-bond providing unique azaoxabicyclo[2.2.1]heptanes with diastereospecificity. The *N-O* bond in these systems was readily cleaved under reductive conditions to furnish functionalizable 4-piperidone subunits. Depending on the nature of the starting oxime, 4-piperidone core structures were generated which allowed for the total syntheses of (±)-cylindricine C, (±)-7,8-*epi*-perhydrohistrionicotoxin, and (±)-yohimbenone. Formal syntheses of (±)-desamyl-perhydrohistrionicotoxin and (±)-emetine were reached through this reaction manifold, as well as an approach to halichlorine. The method's tractability is underscored by its versatility, operational ease, and its ability to employ readily available oxime inputs. A previously unreported ring-oxidation mechanism involving *N*-alkyl-4-piperidones is also described, as well as a novel [4+2]-cycloaddition involving an oxofuran derivative.

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many years of abbreviated holidays and abridged phone calls, as have my siblings. I am thankful and proud to be related to Mr. & Mrs. Matt and Kate Flick and to Mr. and Mrs. Josh & Betsy Jones. Aunt Marilyn, Uncle Tim, Aunt Lisa, Uncle Dennis, Uncle Mark, Aunt Linda, Uncle Steve, Aunt Jean, Dr. Margaret "Aunt Peggy" Dolan, John, Christy & Rich, Jeff, Tim, Ryan, Amy, Ashley… thank you for everything!

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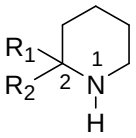
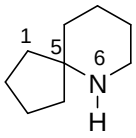
I. INTRODUCTION

Among the enormous number of biologically relevant alkaloids, the 2,2-disubstituted piperidine nucleus has emerged as one of the more widely studied molecular substructures.[1] Along with the related 1-azaspiro[5.5]undecane and 6-azaspiro[4.5]decane systems, these heterocycles represent architectures found in many important nitrogen-containing natural product classes, including the histrionicotoxin[2] and erythrina[3] families.

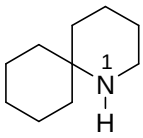
Figure 1: 2,2,-Disubstituted Piperidine and Related Azaspirocycles



2,2-disubstituted piperidine



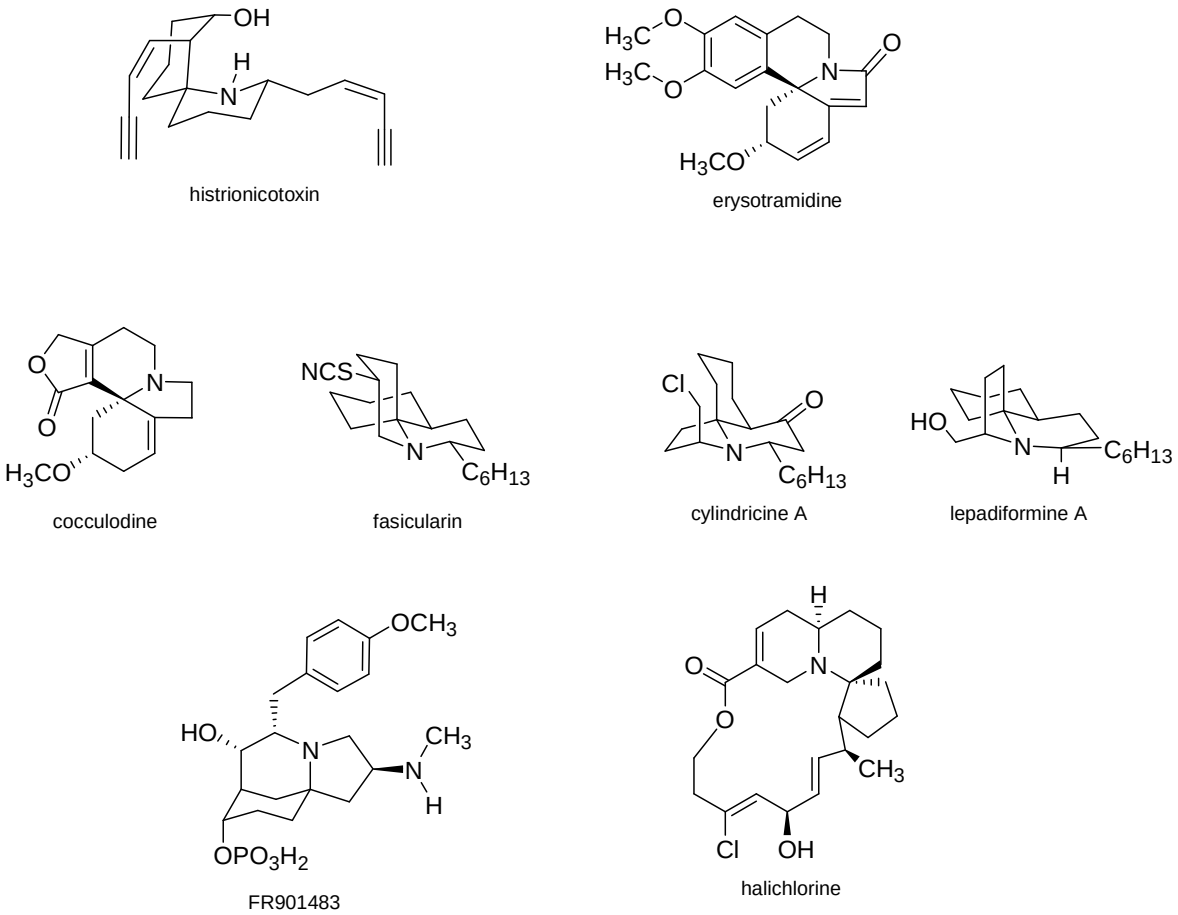
6-Aza-spiro[4.5]decane



1-Aza-spiro[5.5]undecane

In addition to the yohimbenone[4] and emetine[5] families of alkaloids, a number of more recently discovered natural alkaloids have been reported bearing piperidine ring systems, such as FR901483,[6] the pinnaic acids,[7] and halichlorine.[7] This skeleton is also found within several recently isolated tricyclic marine natural products.[8] Over the years, this important heterocyclic subunit has received considerable attention from the synthetic and medicinal communities due to its promising therapeutic potential and the challenge to its construction. The development of methods which establish a highly congested tertiary carbon center adjacent to a nitrogen atom within a piperidine ring is of considerable importance to the field of medicinal chemistry. A premium is placed on methods to prepare these ring systems in a stereocontrolled manner as well as those which further functionalize the core piperidine unit.

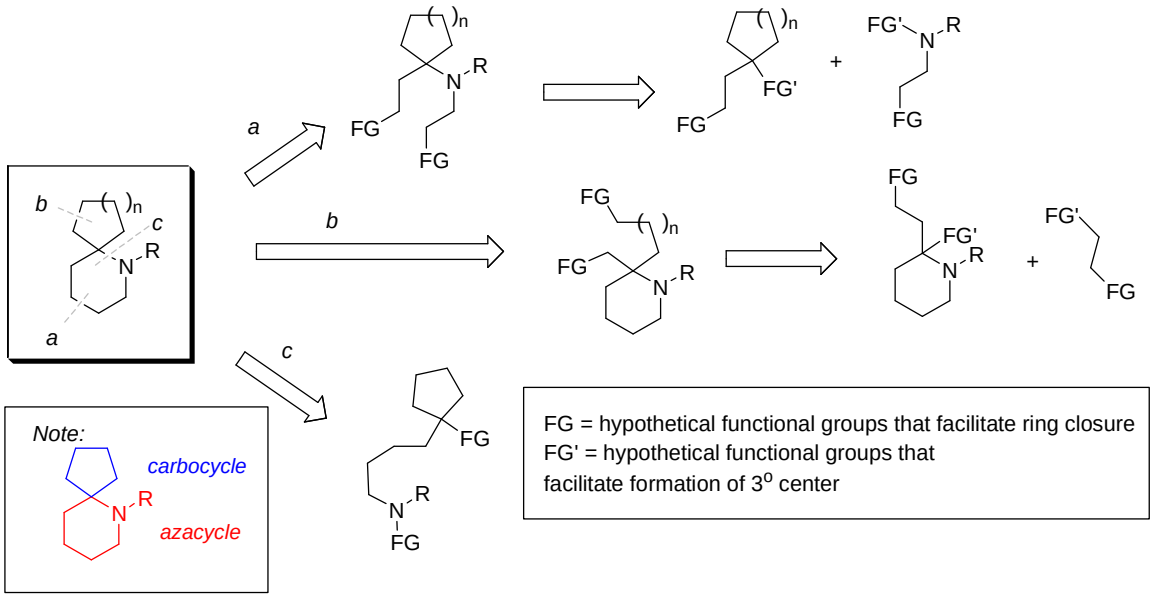
Figure 2: Representative 2,2,-Disubstituted and Azaspirocyclic Alkaloid Natural Products.



Consequentially, a number of synthetic methods have been developed for the construction of disubstituted piperidine and azaspirocyclic ring systems within the context of total synthesis of the molecular targets depicted in Figure 2.[9,10] Generally, two central challenges are considered for the assembly of 2,2-disubstituted or azaspirocyclic frameworks: (1) construction of a tertiary carbon center bearing a nitrogen atom which will ultimately become the azaspirocyclic center; and (2) construction of the carbocyclic ring (or rings) peripheral to the

nitrogen-containing ring. In a recent review, Dake summarized the typical strategies to prepare azaspirocyclic systems, and this is outlined in Figure 3.[9]

Figure 3: Typical Strategies for 2,2-Disubstituted Piperidine and Azaspirocyclic Alkaloid Assembly.

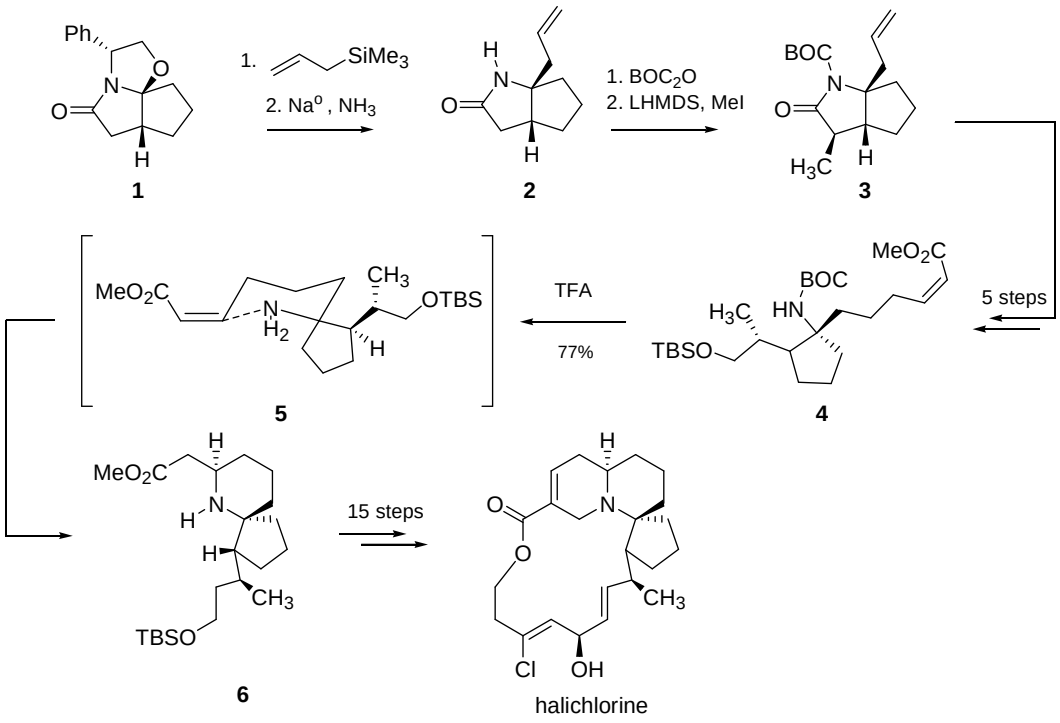


To meet these challenges, three general synthetic approaches have evolved and are defined in Figure 3. The first strategy involves the construction of the tertiary carbon center and the azacycle is formed in two separate events (path *a*). This strategy relies on a preestablished carbocycle and a separate ring closure step which ultimately forms the azacycle. The second strategy relies on the formation of a 2,2-disubstituted piperidone at an early stage of the synthesis, followed by carbocycle formation by linkage of the 2,2-disubstitution pattern (path *b*). Arguably the most efficient strategy is the third approach (path *c*) which combines both the generation of the tertiary center and the formation of the spirocyclic ring system within the same reaction.

In the forward sense, several methods to prepare 2,2-disubstituted piperidine systems have been reported, typically with application to total synthesis of azaspirocycle-containing natural products, including the class of tricyclic marine alkaloids.[8] The most common preparative methods can be classified into the following categories based on the key synthetic step: (1) the use of an iminium ion;[11] (2) [4+2]-cycloadditions;[12] (3) 1,3-dipolar cycloadditions;[13] (4) intramolecular conjugate additions;[14] and (5) rearrangements.[15] Aside from these commonly used methods, an array of unique and imaginative approaches to the 2,2-disubstituted piperidine core have also been reported which typically involve dearomatization protocols,[16] radical cyclizations,[17] and metal catalysis.[18] A brief overview of the key methods used for the construction of selected piperidine-containing alkaloid targets is listed in Figure 2 and is described below.

One of the most frequently reported strategies for azaspirocycle construction involves nucleophilic attack onto an iminium species. Within this context, excellent stereocontrol can often be achieved when the iminium precursor contains a preexisting chiral center. Toward this end, Danishefsky utilized the readily available Meyers lactam (**1**, Scheme 1)[19,20] to influence attack of an allyl silane onto the preferred α-face of the iminium ion species generated from **1**, delivering the bicyclic amide **2** as a single diasteromeric product.[21] Stereoselective methylation subsequently occurred from the convex face of the protected lactam to deliver carbamate **3**. Several steps ensued to convert **3** to the protected amine **4** which then underwent a Michael addition upon acid-mediated deprotection. The selectivity of this reaction arises from the propensity of the primary amine to adopt the conformation shown in intermediate **5**. Azaspirocycle **6** was then transformed to halichlorine in fifteen further synthetic operations.

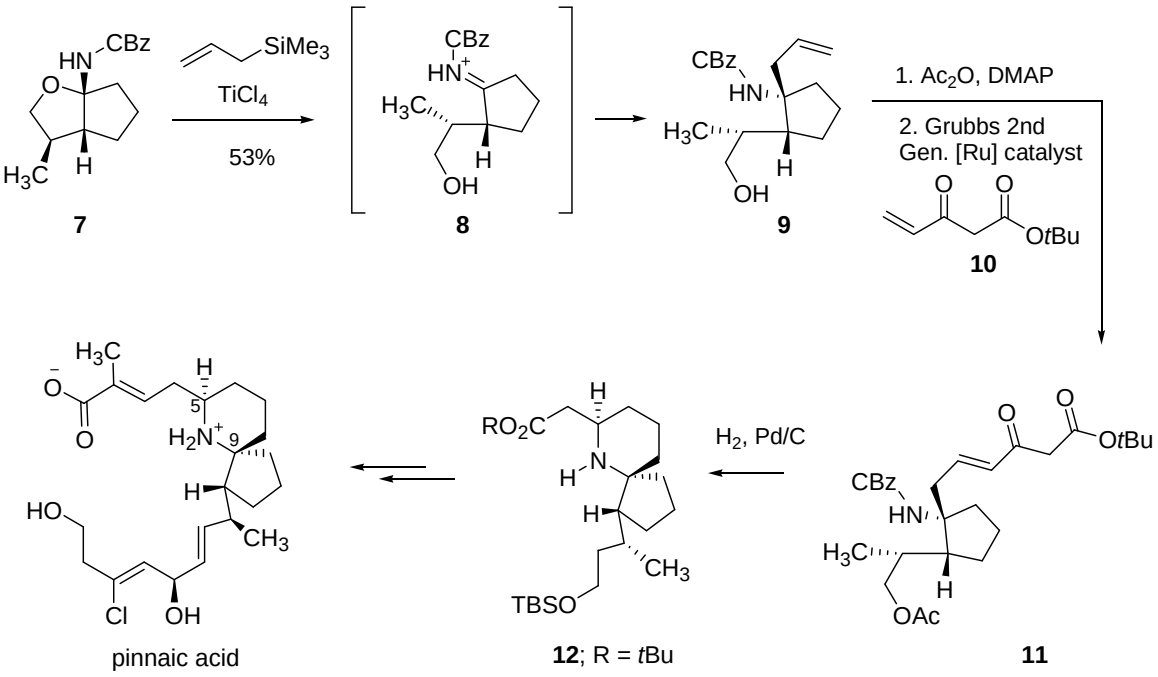
Scheme 1. Danishefsky's Iminium Ion-Conjugate Addition Approach to Halichlorine.[21]



Similar to Danishefsky's approach, Heathcock also employed an allyl silane attack onto the *cis*-fused bicyclic hemiaminal **7** *en route* to a racemic synthesis of halichlorine and pinnaic acid (Scheme 2).[22] The stereochemical outcome of the conversion of **7** to **9** arises from allyl silane attack from the least hindered face of acyl iminiuim intermediate **8**, which sets the encumbent pinnaic acid configuration at C-9. Alkene **9** was then elaborated into ketoester **11** through the use of a bimolecular cross metathesis reaction involving Grubbs' second generation ruthenium catalyst with Nazarov ester **10**,[23] which produced **11** exclusively as the *E*-isomer. Hydrogenation/hydrogenolysis of enone **11** produced piperidine **12** as a single diastereomer whose geometry corresponded to the desired C-5 configuration of pinnaic acid—an anticipated result based on earlier work by Arimoto and coworkers.[24] Through separate synthetic sequences,

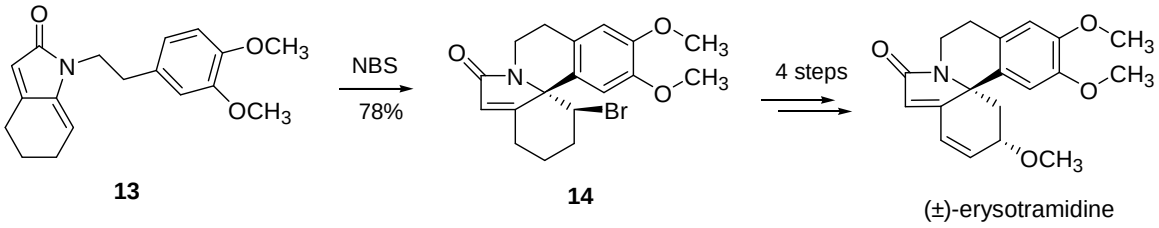
Heathcock and coworkers impressively constructed pinnaic acid, halichlorine, and tauropinnaic acid each from azaspirocycle **12**.

Scheme 2. Heathcock's Iminium Ion-Reductive Amination Approach to Halichlorine and Pinnaic Acid.[22]



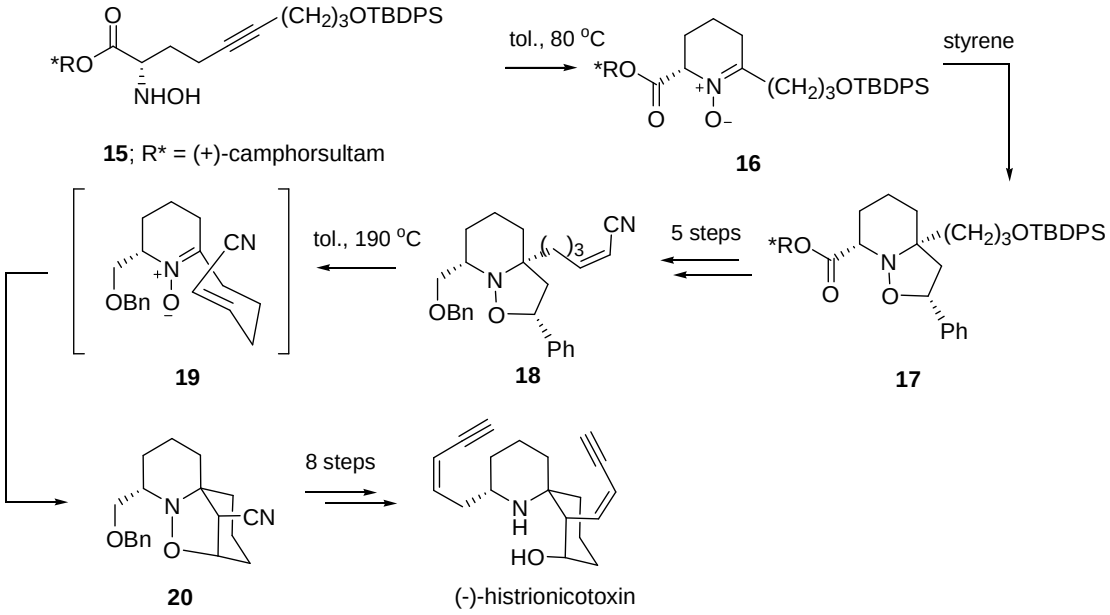
As an additional contribution to iminium ion chemistry, Padwa and coworkers have reported on the NBS-promoted intramolecular electrophilic aromatic substitution reaction of a hexahydroindolinone derivative which was then used to assemble the tetracyclic core of the erythrinane skeleton (Scheme 3).[25] The resulting cyclization product **14** was efficiently transformed into (±)-erysotramidine in four synthetic steps—one of which involved an unusual bromine elimination-isomerization sequence.

Scheme 3. Padwa's Electrophilic-Induced Cyclization Approach to Erysotramidine.[25]



A number of authors who have attempted the use of a [3+2]-dipolar cycloaddition approach toward a synthesis of histrionicotoxin have encountered regioselectivity issues resulting from undesired cycloaddition products.[26] Scheme 4 summarizes a creative solution to this problem as described by Holmes.[27] In an enantioselective fashion, Holmes generated cyclic nitrone **16** which was then treated with styrene to give isoxazolidine **17**, which effectively served as a

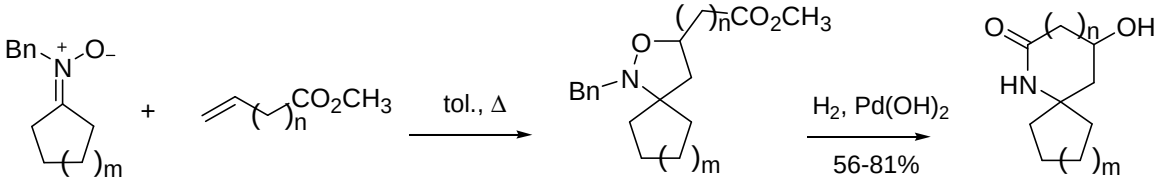
Scheme 4. Holmes' [3+2] Cycloaddition Approach to Histrionicotoxin.[27]



nitrone protecting group. The terminal silyl ether was then converted to the *E*-vinyl nitrile **18** through a five-step sequence. Heating a sample of **18** resulted in the extrusion of a molecule of styrene which unmasked the latent nitrone *via* a retro [3+2]-cycloaddition. The dipole then underwent cyclization across the tethered vinyl nitrile group to furnish the tricyclic isoxazolidine **20**. The use of an α,β-unsaturated nitrile was found to be critical to the regiocontrol of this reaction. Rupture of the *N-O* bond followed by two separate side chain elaboration sequences furnished (-)-histrionicotoxin.

In the late 1980s, Funk and coworkers described a practical and efficient route to azaspirocycle formation (Scheme 5),[28] which was later adapted by the Snider group in their synthesis of (-)-FR901483.[29] Condensation of *N*-benzyl hydroxylamine with the appropriate ketone produced a nitrone (*e.g.* **21**) which reacted intermolecularly with an alkenyl ester. Reduction of the resulting isoxazolidine (**22**) resulted in cleavage of the *N-O* bond, which also triggered an intramolecular lactamization, giving rise to spirocycles such as amidoalcohol **23**.

Scheme 5. Funk's Cycloaddition-Reduction Protocol for Azaspirocyclic Synthesis.[28]

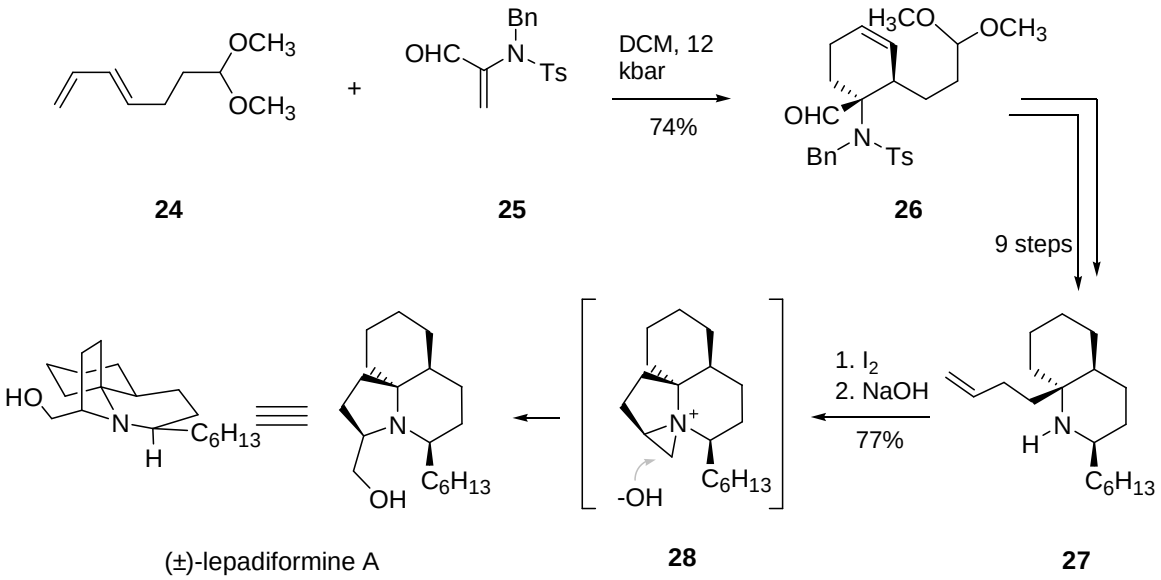


21 **22** **23**

It should be noted that the *N*-benzyl protecting group was also removed during this reduction step (**22** to **23**), allowing three separate functional group transformations to be performed within a single operation.

Funk has also described an additional synthetic approach to azaspirocyclic systems whose utility has been demonstrated by a synthesis of both lepadiformine A and fasicularin (Scheme 6).[30] Diene **24** was heated under high pressure in the presence of enamine **25** to furnish cyclohexene **26**, which exhibited the requisite C-5 and C-10 geometry of lepadiformine and fasicularin. A nine step synthetic sequence was subsequently employed to secure octahydroquinoline **27** which was then subjected to an iodoamination protocol to produce (±)-lepadiformine A directly. The authors attribute the establishment of

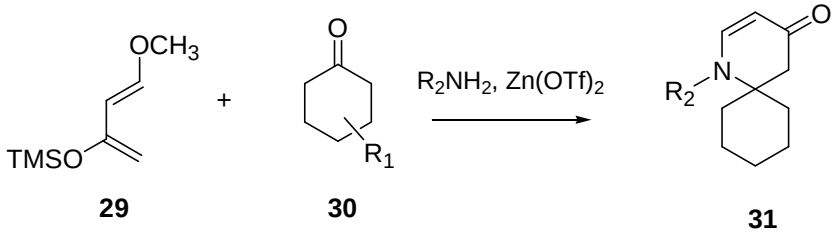
Scheme 6. Funk's [4+2]-Cycloaddition-iodoamination Approach to Lepadiformine A.[30]



the C-13 hydroxymethylene functionality to an aziridinium intermediate (**28**) formed during the iodoamination step. The steric bulk of the lepadiformine ring system directed hydroxyl attack to the least hindered position of the aziridinium ring.

During the late 1990's, Oh and coworkers reported a straightforward method for azaspirocyclic synthesis which could also be applied to the synthesis of monocyclic 2,2-disubstituted 4-piperidones as described in Scheme 7.[31] Condensation of a primary amine with a cyclic ketone (*e.g.* **30**) generated an imine *in situ* which then underwent a [4+2]-cycloaddition reaction with Danishefsky's diene (**29**) to produce a spirocyclic vinylogous amide (*e.g.* **31**). Oh's three-component, one-pot reaction produced several 4-piperidone spirocycles, whose carbocyclic ring size varied as a function of the starting cyclic ketone **30**. The efficiency of this process depended on the nature of the nitrogen substituent (R_2). Sterically bulkier substituents were found to be detrimental to the process.

Scheme 7. Oh's Hetero Diels-Alder Cycloaddition Protocol for *N*-alkyl-1-aza-spiro[5.5]undec-2-en-4-one Synthesis.[31]

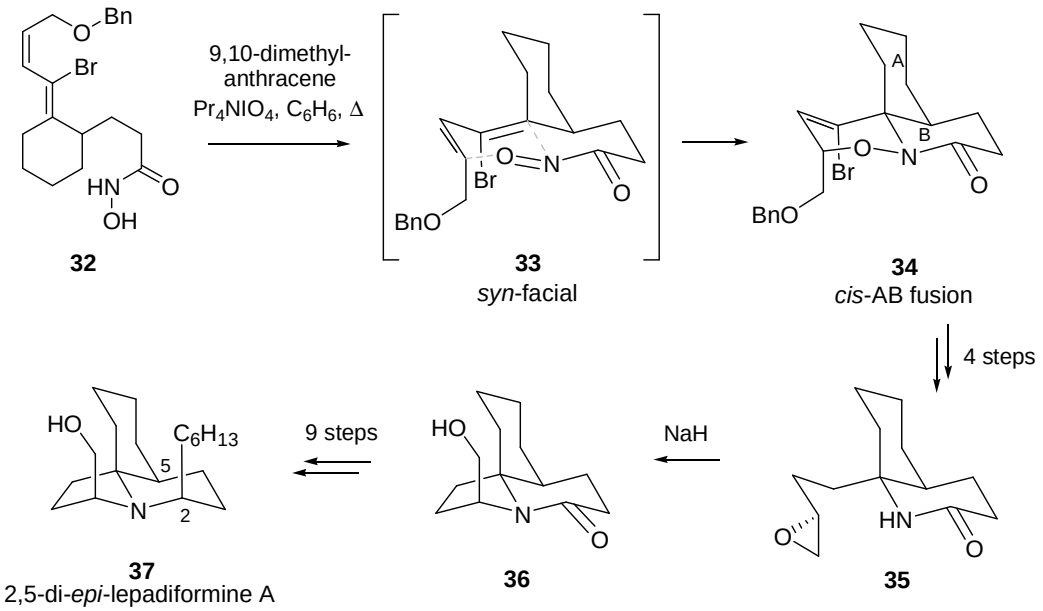


29 **30** **31**

One of the more interesting approaches toward azaspirocyclic synthesis involves Kibayashi's acyl nitroso [4+2]-cycloaddition approach to lepadiformine A

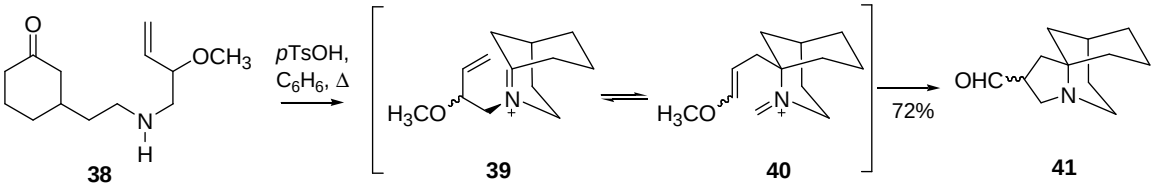
and fasicularin.[32] In early attempts to construct the putative structure of lepadiformine, Kibayashi converted hydroxamic acid **32** (Scheme 8) to the acyl nitroso species **33** under refluxing benzene conditions. This resulted in the formation of the *cis*-AB ring fused system **34** as the major product. The [4+2]-cycloaddition product was thought to arise from the *syn*-facial transition state intermediate **33** which minimized allylic-1,3 strain between the bromine atom and the tether bearing the acyl nitroso functionality. The tricyclic oxazinane **34** was efficiently converted to epoxide **35**, which was subsequently treated with sodium hydride to secure the tricyclic amide **36**. Further functional group manipulation converted amidoalcohol **36** to the tricyclic amine **37**. However, this compound exhibited spectroscopic data in stark contrast to that of the naturally isolated material. Amine **37** was later determined to be epimeric to lepadiformine A at the C-5 and C-2 centers. Through Kibayashi's and other synthetic efforts, the structure of lepadiformine A has been unequivocally established.[8]

Scheme 8. Kibayashi's Acyl Nitroso [4+2] Entry to Lepadiformine A.[32]



In a fascinating approach to the core structure of FR901483, Brummond and coworkers described an aza-Cope-Mannich cascade sequence which resulted in the formation of tricyclic amine **41** (Scheme 9).[33] In five tractable steps from cyclohexenone, aminoketone **38** was prepared and subjected to *p*-toluenesulfonic acid in refluxing benzene which induced a cascade sequence. The secondary amine in **38** condensed intramolecularly with the proximal ketone to form the transient iminium intermediate **39** which then equilibrated to iminium ion **40** through a 3,3-sigmatropic rearrangement. The vinyl ether functionality within **40** then attacked the iminium species to form the fused pyrrolidine **41**. Interestingly, this approach corresponds to the first example of an aza-Cope-Mannich sequence which incorporated a bridgehead iminium species.[34]

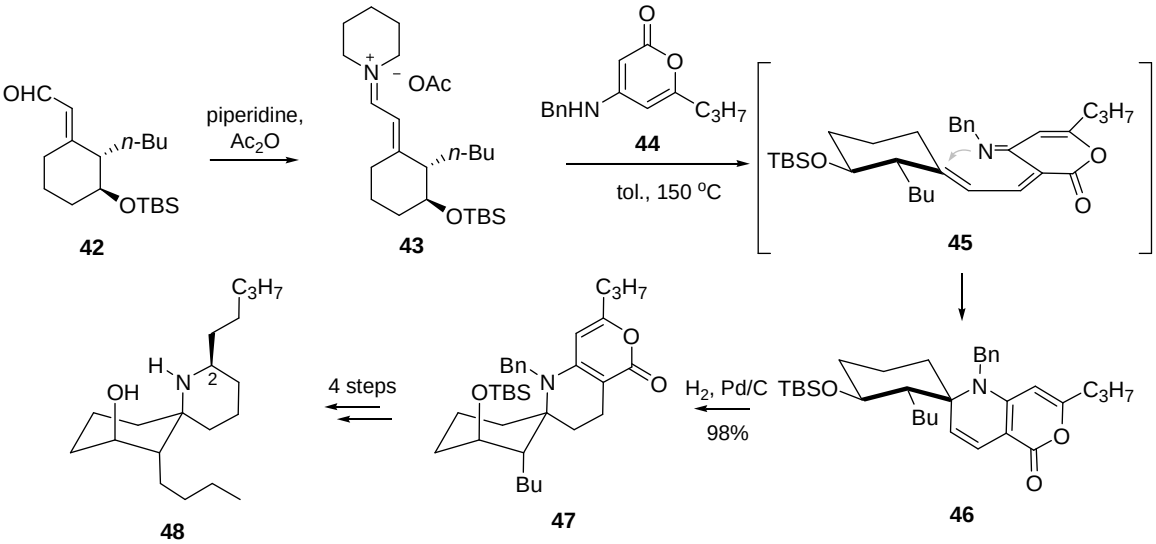
Scheme 9. Brummond's aza-Cope-Mannich Cyclization Approach to the Core Structure of FR901483.[33]



In the late 1990's, Hsung established a versatile method to synthesize dihydropyridines from the condensation of vinylogous amides and α,β-unsaturated imines.[35] This reaction sequence corresponds to a formal [3+3] annulation, which was utilized in a novel approach to azaspirocyclic natural product synthesis.[36] In their approach to perhydrohistrionicotoxin, Hsung and coworkers described a Knoevenagel condensation of vinylogous amide **44** with iminium salt **43** that led to a 6π–electrocyclic ring closure of the resulting 1-

azatriene intermediate (**45**)—essentially a formal [3+3]-annulation. An interesting feature of the reaction sequence shown in Scheme 10 is that the nitrogen atom within intermediate **45** prefers an equatorial approach to the carbocycle during the ring closure step, which ultimately results in azacycle **46**. Also interesting is that the reduction of **46** also promoted conformational inversion of the carbocycle, thereby placing the *N*-benzyl and silyl ether functionality in a 1,3-diaxial position about the cyclohexane ring system within **47**. Another unique aspect of this synthesis was that the reduction of **47** set three contiguous stereogenic centers of the perhydrohistrionicotoxin frame, ultimately delivering 2-*epi*-perhydrohistrionicotoxin (**48**) as the end product.

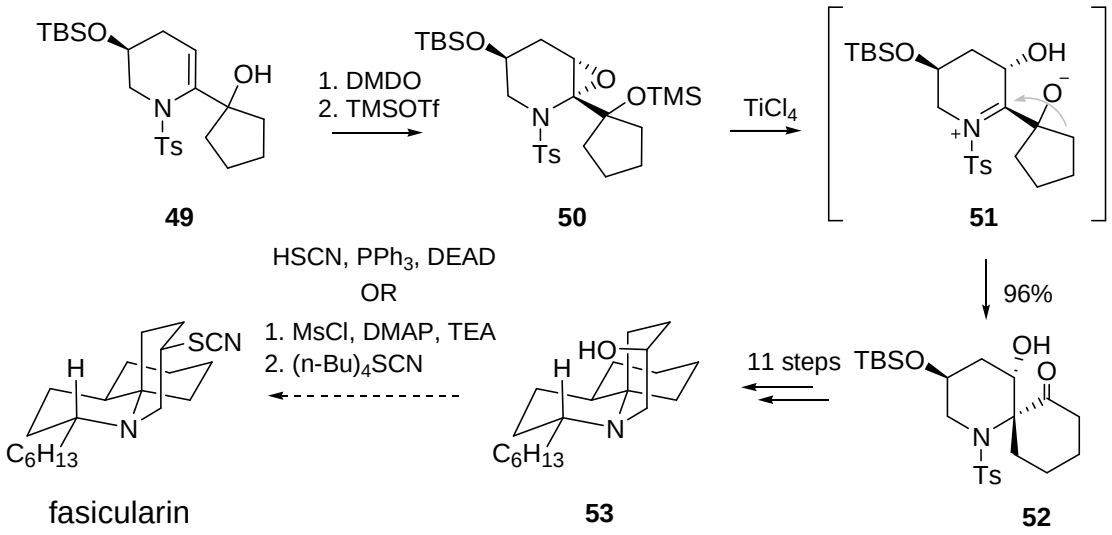
Scheme 10. Hsung's [3+3] Annulation Approach Toward Perhydrohistrionicotoxin.[36]



The Dake group has developed an innovative reaction platform to produce azaspirocyclic architectures involving a semi-pinacol rearrangement. A recent report from this group divulged the application of this methodology toward an

enantioselective synthesis of fasicularin, which is summarized in Scheme 11.[37] Starting from tetrahydropyridine **49**—which was constructed in five high-yielding steps from *l*-glutamic acid—the enamine was epoxidized using dimethyldioxirane (DMDO). Due to the chiral nature of **49**, the electrophilic source of oxygen approached the π-system from the face opposite the bulky silyl ether. A subsequent silylation produced disilane **50**. Treatment of epoxide **50** with titanium tetrachloride facilitated smooth ring expansion giving **52** as a single enantiomer in impressive yield. The authors report that the trimethylsilyl group in this case is required for clean conversion of **50** to **52**, which proceeds through the intermediacy of **51**. Eleven steps were then required to synthesize **53** from **52**. Procedures reported by Funk[38] or Kibayashi[39] for the conversion of **53** to fasicularin proceeded poorly, giving mediocre yields of mixtures of products. In

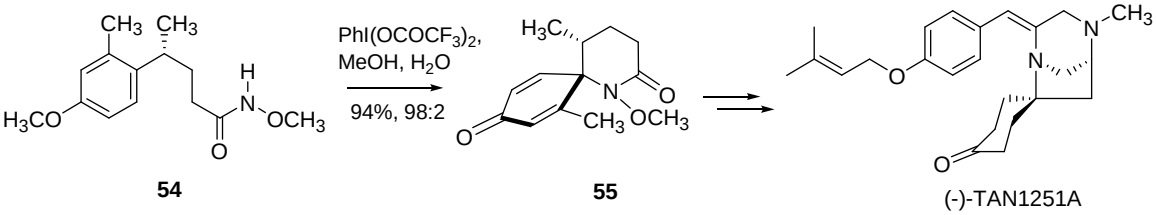
Scheme 11. Dake's Semi-Pinacol Entry to A Formal Synthesis of Fasicularin.[37]



Dake's case, no characterizable fasicularin was obtained from attempts to repeat the Funk or Kibayashi methods, thereby limiting the authors to an enantioselective formal synthesis. These observations underscore the difficulties associated with late-stage tricycle manipulation for natural products of this class.

A well-established reaction that has been used for this class of alkaloids involves the interaction between silver salts and *N*-chloro-*N*-methoxyamides to generate an intermediary aziridinium ion. When treated with the appropriate nucleophile, these systems undergo nucleophilic attack.[40] In the case of Wardrop, the use of hypervalent iodine led to a facile approach to an azaspirocyclic synthesis (Scheme 12) while avoiding the need to produce *N*-halogenated intermediates.[41] Thus, when treated with phenyliodine*bis*(trifluoroacetate), systems such as **54** readily undergo nucleophilic attack by pendant electron-rich arenes to give *N*-methoxyspirolactams (*e.g.* **55**), often with high levels of selectivity. These reactions have proven to be quite general, and have been applied toward the synthesis of the piperazine alkaloid (-)-TAN1251A and desmethylamino FR901483.

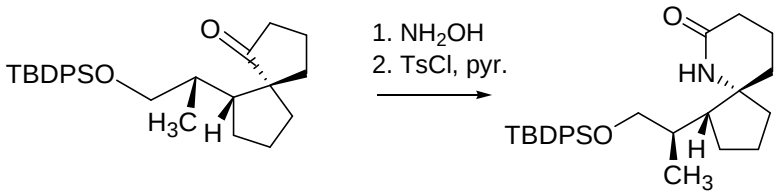
Scheme 12. Wardrop's Dearomatization Protocol for Spirolactam Synthesis.[41]



54 **55** (-)-TAN1251A

When the starting substrate contains limited functional groups, well-established interconversion methods can be applied to generate complex molecular structures. Pilli has demonstrated this concept through a creative use of a Beckmann rearrangement (Scheme 13).[42] Effectively inserting a nitrogen atom between a preexisting spirocyclic center and an adjacent carbonyl group, Pilli was able to convert spiroketone **56** to azaspirocycle **57** through transformation of the starting ketone to an oxime, followed by treatment with tosyl chloride and base.[43]

Scheme 13. Beckmann Rearrangement Entry to Azaspirocycles.[43]

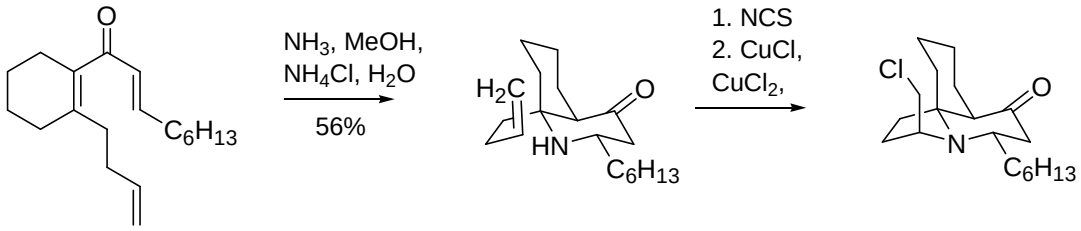


56 **57**

Michael addition of an amine to an appropriately substituted α,β-unsaturated ketone can produce the requisite tertiary carbon center for 2,2-disubstituted piperidines and higher-order heterocycles. This strategy has been cleverly applied by several groups toward the synthesis of the cylindricine family of alkaloids, as exemplified by Snider's approach to cylindricine A (Scheme 14).[44] Dienone **58** was prepared and was subjected to reaction with ammonia which gave a mixture of 4-piperidone products. By controlling the pH of the reaction mixture, the desired *cis*-octahydroquinolone **59** was obtained as the major product—these results were consistent with the previous observations of Korshevets.[45] The *cis*-ring fusion configuration of azadecalone **59**, which could be separated from the mixture of octahydroquinolone products, bears the

characteristic AB-azadecalone ring geometry within the cylindricine family of alkaloids. The *N*-chloroamine variant of **59** was treated with cuprous chloride to secure the pyrrolo B-ring of the tricycle along with concomitant chloromethylene formation. (±)-Cylindricine A was obtained as the major product from this sequence.

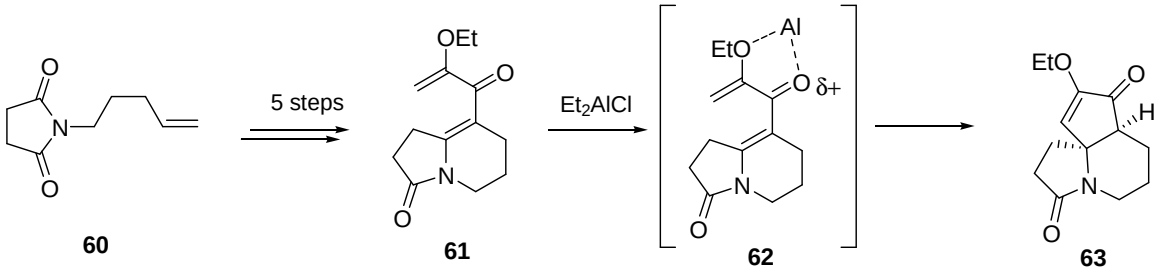
Scheme 14. Snider's Double Michael Addition Approach to Cylindricine A.[44]



58 **59** cylindricine A

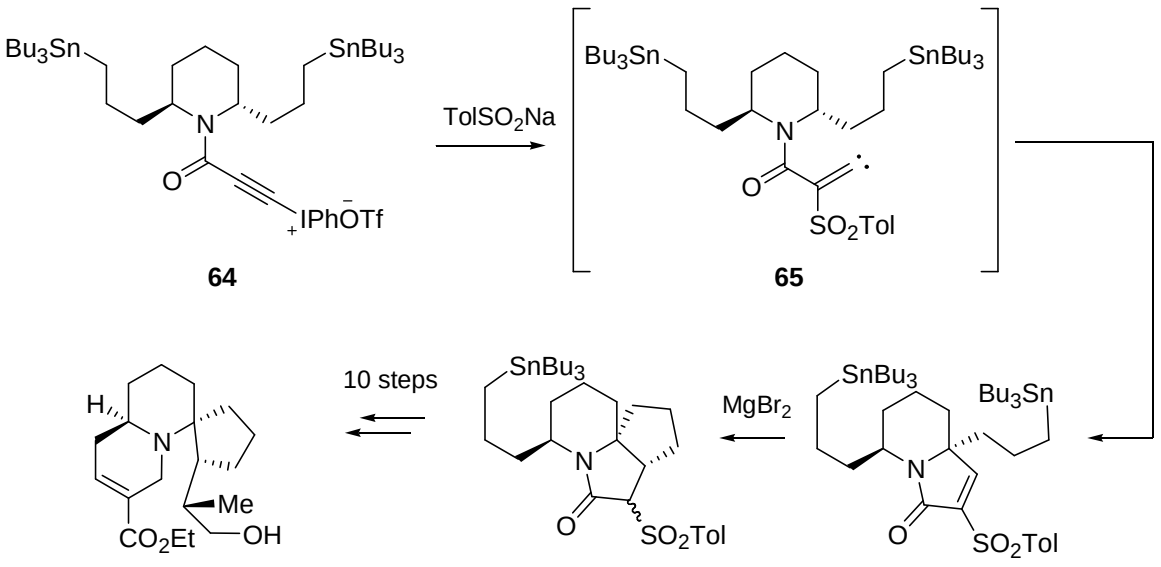
Another dienone was ingeniously used for the construction of 2,2-disubstituted piperidones. In 2000, Cha devised a route to analogs of cephalotaxine[46] through the implementation of a Nazarov reaction as summarized in Scheme 15.[47] A five step sequence starting from the easily available succinimide **60** was used to prepare the dienone **61**. This compound was subsequently treated with an aluminum Lewis acid which initiated a 4π–electrocyclic ring closure step. This was followed by subsequent reprotonation to furnish azaspiropiperidine **63**.[48] The authors report that the vinyl ethoxy group within the Nazarov substrate **61** is critical to the success of the reaction. This observation can be attributed to the aluminum species requiring bidentate coordination to facilitate the formation of the oxyallyl cation under mild conditions. Interestingly, attempts to use enantioselective Lewis acids designed to control 4π conrotational direction failed to give any of the desired product.[49]

Scheme 15. Cha's Nazarov Approach to Azaspirocyclic Synthesis.[47]



Another clever entry to heterocycles of this type was demonstrated by Feldman in an approach to the core piperidinyl subunit of halichlorine (Scheme 16).[50] Alkynyliodonium salt **64** (prepared in six steps from pyridine) produced alkylidenecarbene **65** upon treatment with sodium *p*-toluenesulfinate. This reactive intermediate underwent a 1,5-C-H insertion reaction to set the pivotal quaternary center within the halichlorine alkaloid frame. The authors report that

Scheme 16. Feldman's C-H Insertion Entry to Halichlorine Alkaloid Core.[50]

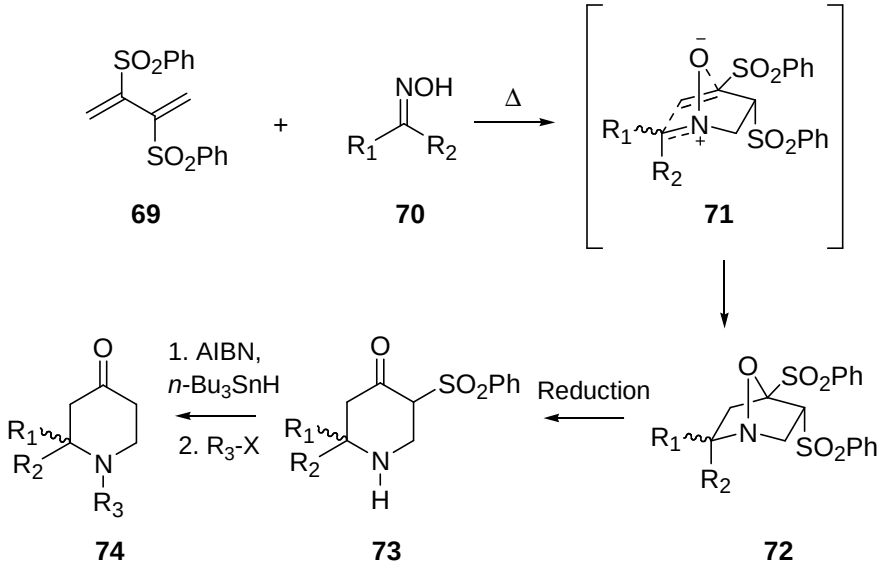


the carbene insertion reaction proceeds quite well on gram-scale, which currently stands as an excellent advance for the scope of C-H insertion methodology.[51] The proximity of the enone portion of lactam **66** to the 2,2-disubstituted center within the piperidine ring permitted differentiation of the propylstannane side chains. The alkyl-tin group stemming from the tetrasubstituted carbon on the piperidine ring underwent nucleophilic addition to the juxtaposed α,β-unsaturated enone to afford tricyclic amide **67**. Ten steps were then required to convert amide **67** to the tricyclic amine **68**.

In the late 1960's, Ochiai reported the first reaction of an oxime with a Michael acceptor olefin to form a nitrone. Once formed, the nitrone was observed to undergo both inter- and intramolecular cycloaddition.[52] Shortly thereafter, Grigg and coworkers nicely exploited this methodology for the synthesis of various nitrogen-containing heterocycles.[53] Taking a cue from the findings of Grigg, Norman and Padwa extended this technology to 2,3-bis(phenylsulfonyl)butadiene (**69**, Scheme 17).[54,55] Conjugated dienes with electron withdrawing substituents within the diene unit have long attracted considerable interest.[56] Owing to the significantly lowered LUMO energy level of the sulfonated π-system, sulfone-substituted dienes have been extensively used for inverse electron demand Diels-Alder reactions because of the amplified reactivity of the diene and added regiocontrol of the cycloaddition.[57] In spite of its simplicity and ease of preparation, 2,3-*bis*(phenylsulfonyl)butadiene (**69**, Scheme 17) has seen limited use in organic synthesis.[58] Although *bis*-sulfone **69** reacts poorly as a [4+2]-dienyl substrate in Diels-Alder reactions (the prohibitively high energetic barrier of rotation about the C2-C3 bond prevents the diene from adopting the *S-cis* conformation required for [4+2]-cycloaddition), the Padwa group demonstrated the versatility of **69** as an excellent Michael acceptor.[59] In seminal publications, the Padwa group reported the reaction of aldehyde and

ketone oximes with diene **69** and observed the successful production of interesting cycloadducts of type **72**. The mechanism by which **72** is formed is of considerable interest. The oxime undergoes conjugate addition to one of the termini of dienyl sulfone **69** followed by a proton transfer step to generate a transient nitrone (*i.e.* **71**) which immediately participates in a regiospecific dipolar cycloaddition.[54]

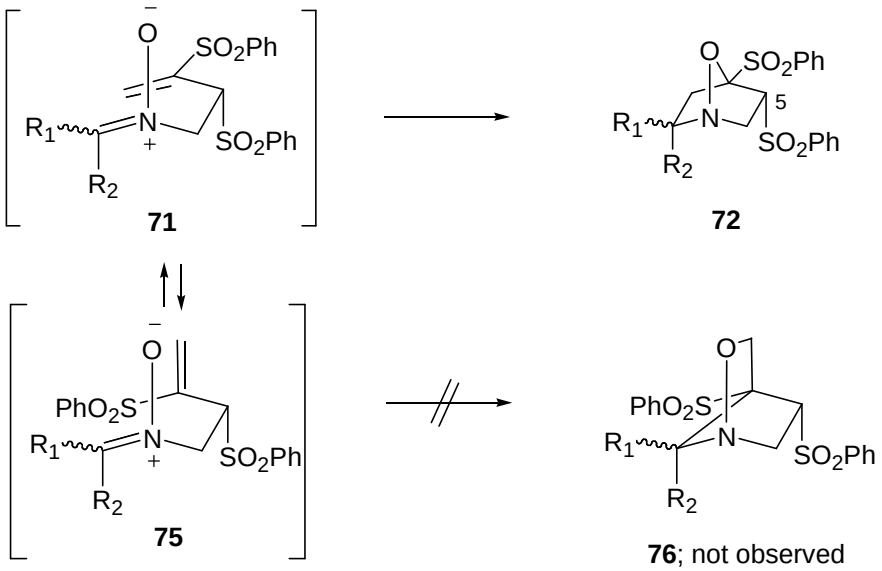
Scheme 17. Padwa's synthesis of Michael Addition-Dipolar Cycloaddition Approach to 4-piperidone Synthesis.[54]



The regiospecificity arises from two possible transition states **71** and **75** (Scheme 18) corresponding to two possible cycloadducts **72** and **76**. Molecular modeling calculations (MM2) were performed to determine the relative energies of possible regioisomeric cycloadducts. These studies revealed that the the lower energy product **72** relative to that of **76** mimicked the energetic values of the transition state nitrones **71** and **75**. The cycloaddition product of the nitrone

conformer **75** would generate a markedly different cycloadduct (*cf.* **76**)—which has not been observed in any case. Another intriguing phenomenon regarding these cycloadducts (*i.e.* **72**) is that the steric interaction of the vicinal diphenylsulfonyl groups is clearly responsible for the sulfonyl group orientation at the C-5 position of the ring system. Thus, the phenylsulfonyl group resides exclusively in a pseudoaxial orientation about the ring system. This observation can be best rationalized by the two phenylsulfonyl groups avoiding eclipsing interactions within the transition state, forcing the phenylsulfonyl group at C-5 within **72** to adopt a pseudoaxial orientation relative to the bicyclic system.

Scheme 18. Possible Dipolar Cycloaddition Regiochemical Outcomes.



Padwa and Norman also reported that treatment of the resulting oxazabicycles (*e.g.* **72**) with a variety of reducing agents facilitated smooth reduction of the *N-O* bond to provide piperidones (*e.g.* **73**, Scheme 17) in 67-95% yield.[54c] The residual phenylsulfonyl group in these structures could be

removed by treatment with excess AIBN and tributyltin hydride in excellent yield,[60] and the piperidone nitrogen could be derivatized through the use of a wide selection of electrophiles (R_3-X). The overall sequence outlined in Scheme 17 represents a tractable, high-yielding method for the synthesis of a variety of 2,2-disubstituted piperidones (**74**). Although this reaction platform was reasonably well studied, it had not been applied to any natural product synthesis and we felt that the method would warrant facile synthesis of several of the alkaloid targets depicted in Figure 2.

With this in mind, the above methodology was extended to some of the aforementioned azaspirocyclic alkaloid targets thereby demonstrating the utility of this reaction manifold. We therefore set out to apply this methodology to the synthesis of several natural alkaloids such as the tricyclic marine natural products, the perhydrohistrionicotoxin family, the pinnaic acid/halichlorine framework, and the yohimbane/emetine alkaloid skeletons. The following sections of this thesis describe the details of the synthetic efforts directed toward these molecular targets.

II. RESULTS AND DISCUSSION

Chapter 1. Part 1. Application to the Total Synthesis of (±)-Cylindricine C.

Introduction

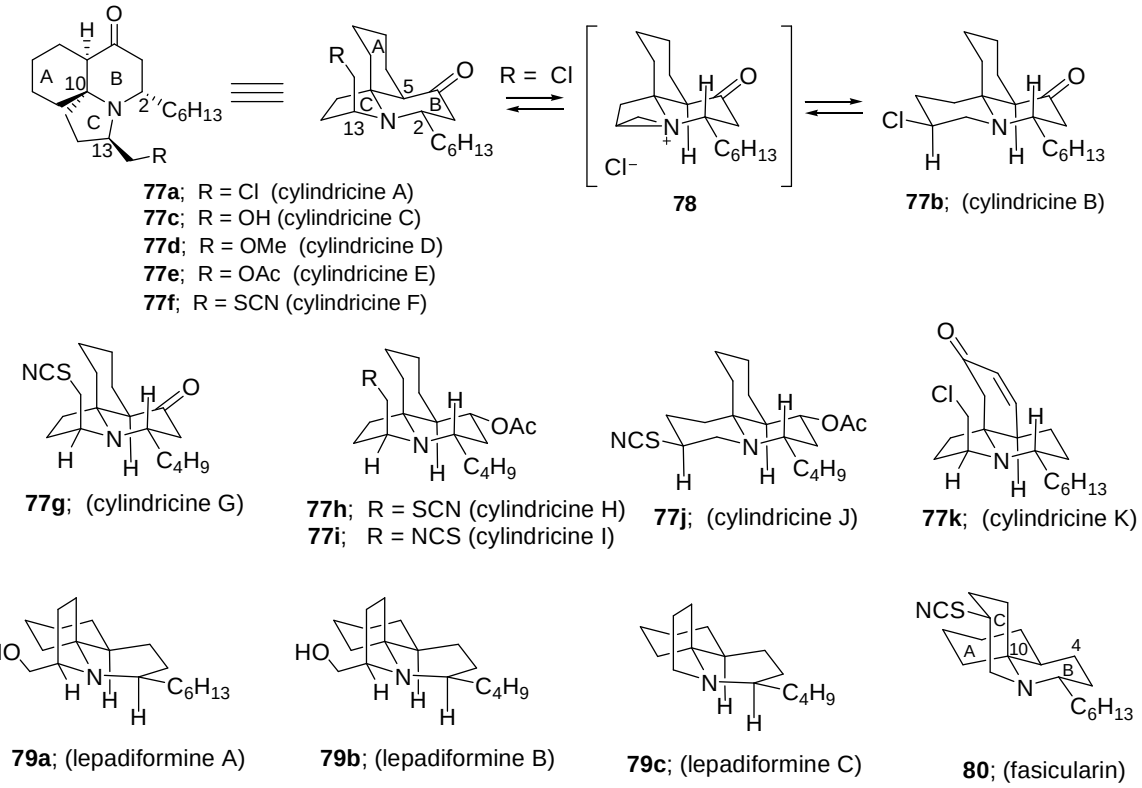
In the early 1990s, a novel family of 2,2-disubstituted piperidine-containing alkaloids were extracted from the marine invertebrate *C. cylindrica* off the eastern Tasmanian coast.[61] This series of pyrrolo[2,1-*j*]quinolines (**77a**, **77c**-**k**, Figure 4) along with a C-ring expanded pyrido[2,1-*j*]quinoline tricyclic species (**77b**), were identified as the cylindricines. In 1994, Biard described the isolation of a novel, related tricyclic marine alkaloid, named lepadiformine A (**79a**),[62] which was obtained from *C. lepadiformis* in the Mediterranean Sea. Twelve years later, lepadiformine A was also extracted from *C. moluccensis* in the Arabian Sea,[62] along with two other related compounds that were identified as lepadiformines B and C.[63] In 1997, yet another related tricyclic alkaloid, fasicularin (**80**), was isolated from *N*. *fasicularis* off the coast of Micronesia by researchers at SmithKline Beecham.[64]

Each of these marine natural products (**77**-**80**) can be classified into two main groups according to their AB-ring fusion geometry: the cylindricine class being the *cis*-fused and the lepadiformine-fasicularin class being *trans*-fused. Further structural examination of the cylindricines A-G (**77a**-**g**) reveals four centers of asymmetry, three of which reside on the piperidinyl B-ring. Each of these metabolites contains either a *n*-butyl or *n*-hexyl side chain at C-2. A variety of functional group substitution patterns occupy the C-14 position, perhaps most extraordinary being the isothiocyanate functionality appended to **77g**. In solution, a 3:2 equilibrium mixture exists between the free bases **77a** and **77b**.[61a] Molecular mechanics calculations, NMR data, and X-ray crystal structures suggest that these alkaloids prefer to exist in the conformation shown in Figure 4.[61c]

This class of tricyclic marine alkaloids demonstrate intriguing biological activity, presumably due to their propensity to form aziridinium intermediates (*e.g.*

78).[65] Lepadiformine A (**79a**) was shown to have both *in vivo* and *in vitro* cardiovascular potency as well as antiarrhythmic properties.[62,63] Fasicularin (**80**) exhibits selective activity against a DNA repair-deficient yeast strain and is cytotoxic to Vero cells.[64]

Figure 4. Tricyclic Marine Alkaloid Natural Products.



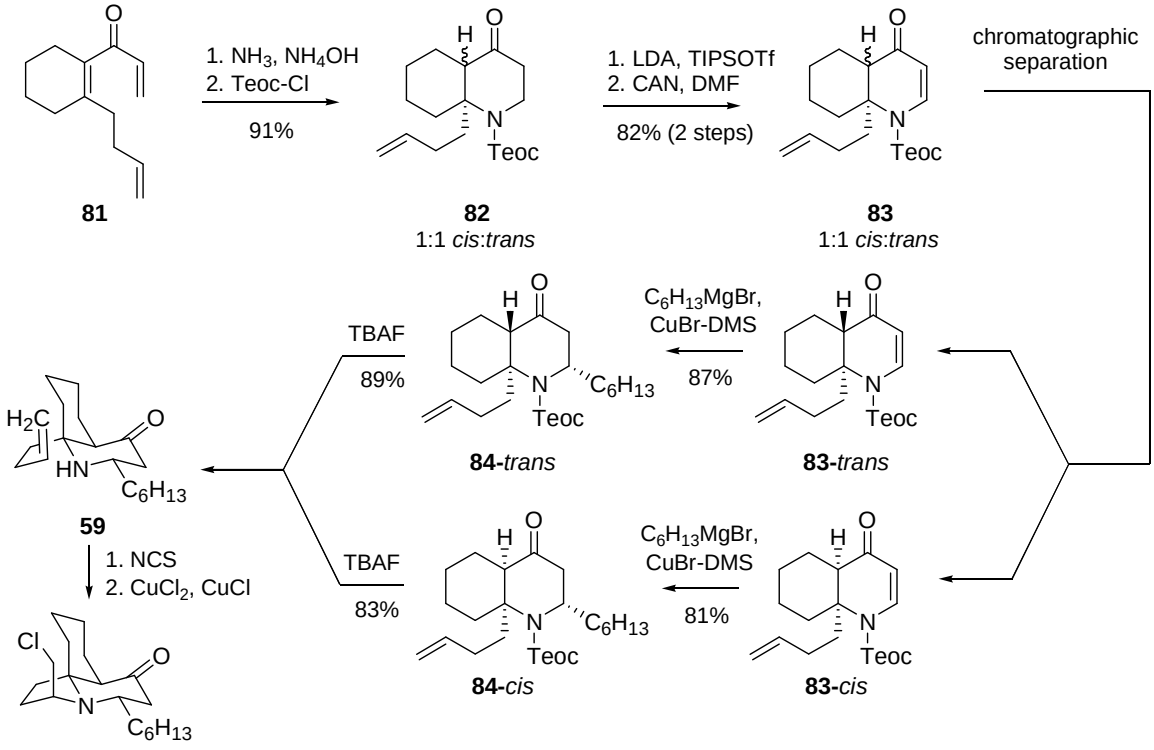
Other than displaying potency against a brine shrimp assay, few studies have been conducted to reveal the therapeutic potential of the cylindricines (**77a**-**k**).[61] However, their limited natural abundance and challenging azacyclic core requires efficient methods to construct these natural products in order to more fully probe their biological importance.

Toward this end, a substantial amount of synthetic effort has been devoted to the cylindricine family in recent years, resulting in numerous

imaginative approaches to their assembly. Generally, the key synthetic feature of each route has revolved around establishment of the sterically congested C-10 center. The most frequently-implemented synthetic approach to this problem has been the use of a double Michael addition of an amine. In addition to Snider (Scheme 14),[66] Molander,[67] Trost,[68] and Heathcock[69] have each employed this approach in separate cylindricine total synthesis efforts. In fact, Heathcock's first generation synthesis of cylindricines A and B is essentially identical to that of Snider's. Heathcock also reported a second-generation synthesis of cylindricines A and B and this is depicted in Scheme 19.[69] Since the stereoselectivity of the double Michael addition was low, this provided the incentive to develop a more efficient second generation strategy. In practice, heating dienone **81** with ammonia/ammonium hydroxide in refluxing ethanol resulted in the double Michael addition to afford the desired AB-ring system in excellent yield. The nitrogen atom was then protected as the 2-trimethylsilanylethoxy carbamate (Teoc), giving **82** as a 1:1 mixture of *cis* and *trans* azadecalins. The mixture of ketones **82** were then converted to their α,β-unsaturated counterparts, which could be separated by chromatography to give **83**-*trans* and **83**-*cis.* These vinylogous amides were each individually alkylated to install the *n*-hexyl side chain at the incumbent C-2 position of the cylindricine system.[70] The cuprate addition was highly stereoselective, preferring axial attack on **83**-*trans* to provide the corresponding **84**-*trans* ketone. Interestingly, axial cuprate approach was also preferred in the case of **83**-*cis*, giving **84**-*cis* in good yield. Carbamate **84**-*cis* was then treated with TBAF to remove the Teoc protecting group affording alkene **59** as the *cis*-fused azadecalin. Similarly, when carbamate **84**-*trans* was treated with TBAF, the Teoc group was removed with concomitant epimerization of the α-keto C-5 center to furnish alkene **59** as the *cis*-fused azadecalin. Alkene

59 was then subjected to Snider's conditions for C-ring closure to give cylindricine A,[66a] which exists as a 3:2 mixture of cylindricines A and B in C_6D_6.[61]

Scheme 19. Heathcock's Double Michael Addition Route to Cylindricine A.[69]

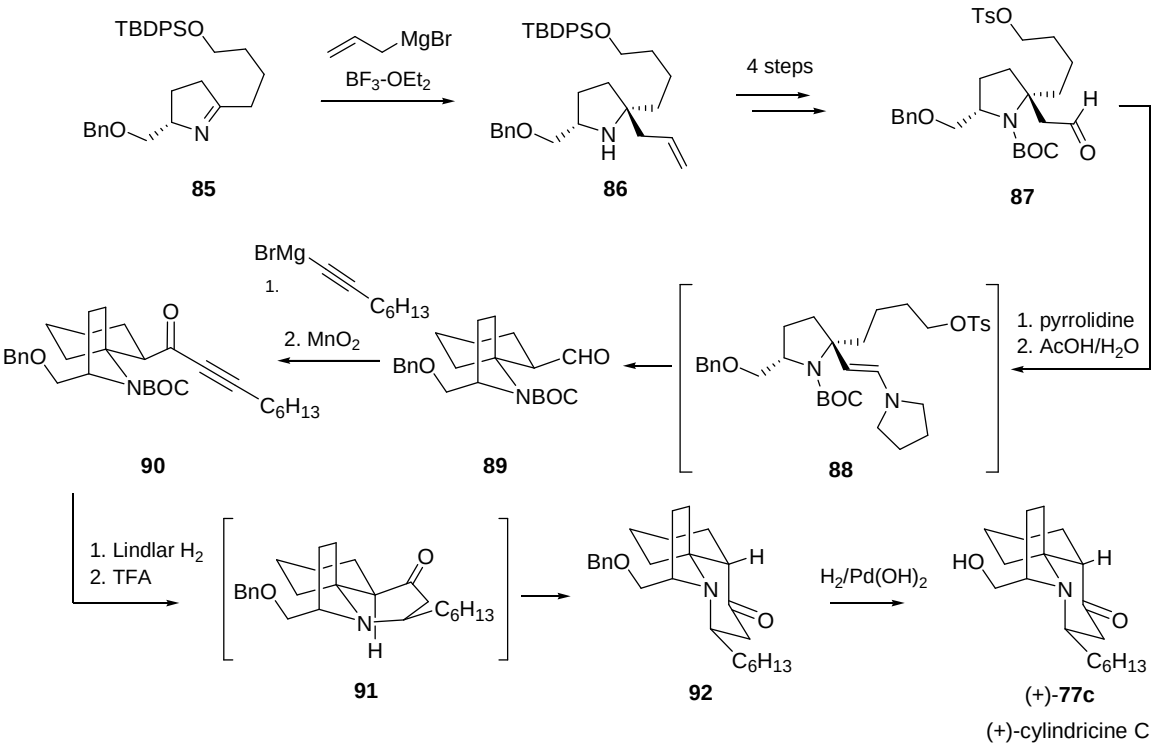


77a; (±)-cylindricine A

The Kibayashi group has reported two different enantioselective syntheses of (+)-cylindricine C. The first was published in 2004, and involves the sequence outlined in Scheme 20.[71] Imine **85**, which originates from (*S*)-pyroglutamic acid, was treated with propylene Grignard to produce alkene **86**. Four steps were then used to furnish aldehyde **87**. At this stage, a number of attempts were made to cyclize the enolate of aldehyde **87**. However, aldehyde **87** was found to undergo a retro-Michael reaction under strongly basic conditions. Alternatively, it was found that condensation of this aldehyde with pyrrolidine led to enamine **88** attack on the pendant tosylate to secure the AC-

azaspirocycle **89**, which was obtained as a single enantiomer. Aldehyde **89** was then reacted with an alkynyl Grignard and subsequently oxidized to yield ketone **90**. This compound was hydrogenated with Lindlar's catalyst and then subjected to TFA-promoted BOC-removal, which afforded the cylindricine tricycle **92**. The authors report that this cyclization proceeds through the intermediacy of the *trans*-fused tricycle **91**, but this intermediate was not isolated. Epimerization at the α-keto C-5 position of **91** led to the observed *cis*-1-azadecalin product **92**, which upon reductive debenzylation, yielded (+)-cylindricine C (**77c**).

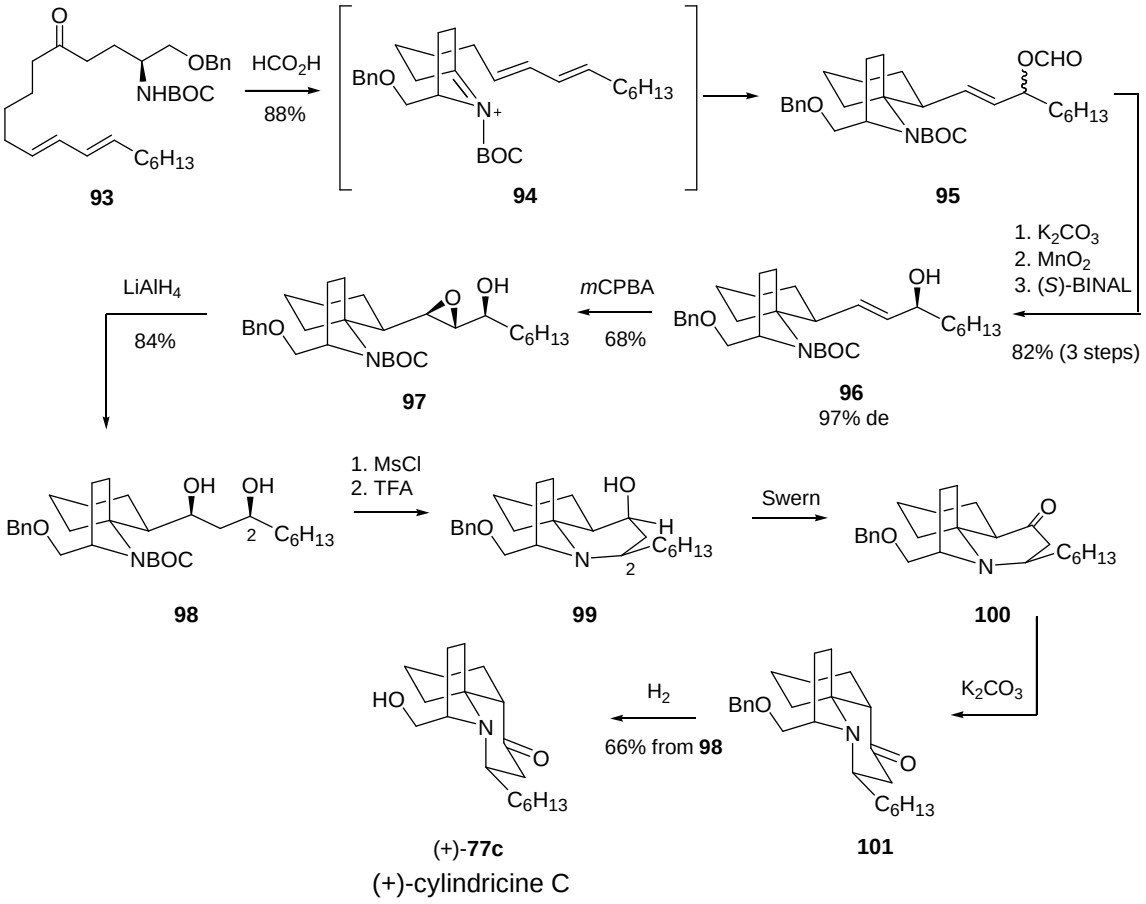
Scheme 20. Kibayashi's Synthesis of (+)-Cylindricine C.[72]



In 2005, Kibayashi reported a second enantioselective synthesis of (+)-cylindricine C utilitzing a pivotal *N*-acyl iminium ion cyclization (Scheme 21).[72] This approach began with enantiopure ketone **93**, which also came from (*S*)-

pyroglutamic acid. Exposure of **93** to formic acid first generated iminium ion **94** which cyclized stereoselectively via a chairlike transition state to afford spirocycle **95** in excellent yield. This key intermediate **95** was also used for an enantioselective synthesis of both (-)-fasicularin and (-)-lepadiformine A.[73] The mixture of formate esters **95** were saponified, oxidized, and then reduced with (*S*)-BINAL-H to produce **96** in 97% de. Hydroxyl-directed epoxidation of **96** with *m*CPBA returned a 4.9:1 mixture of epoxides. The major epoxide **97** was isolated in 68% yield. This system then underwent hydride-mediated ring opening with lithium alumninum hydride to produce diol **98**. It was possible to selectively form

Scheme 21. Kibayashi's Second Synthesis of (+)-Cylindricine C.[73]

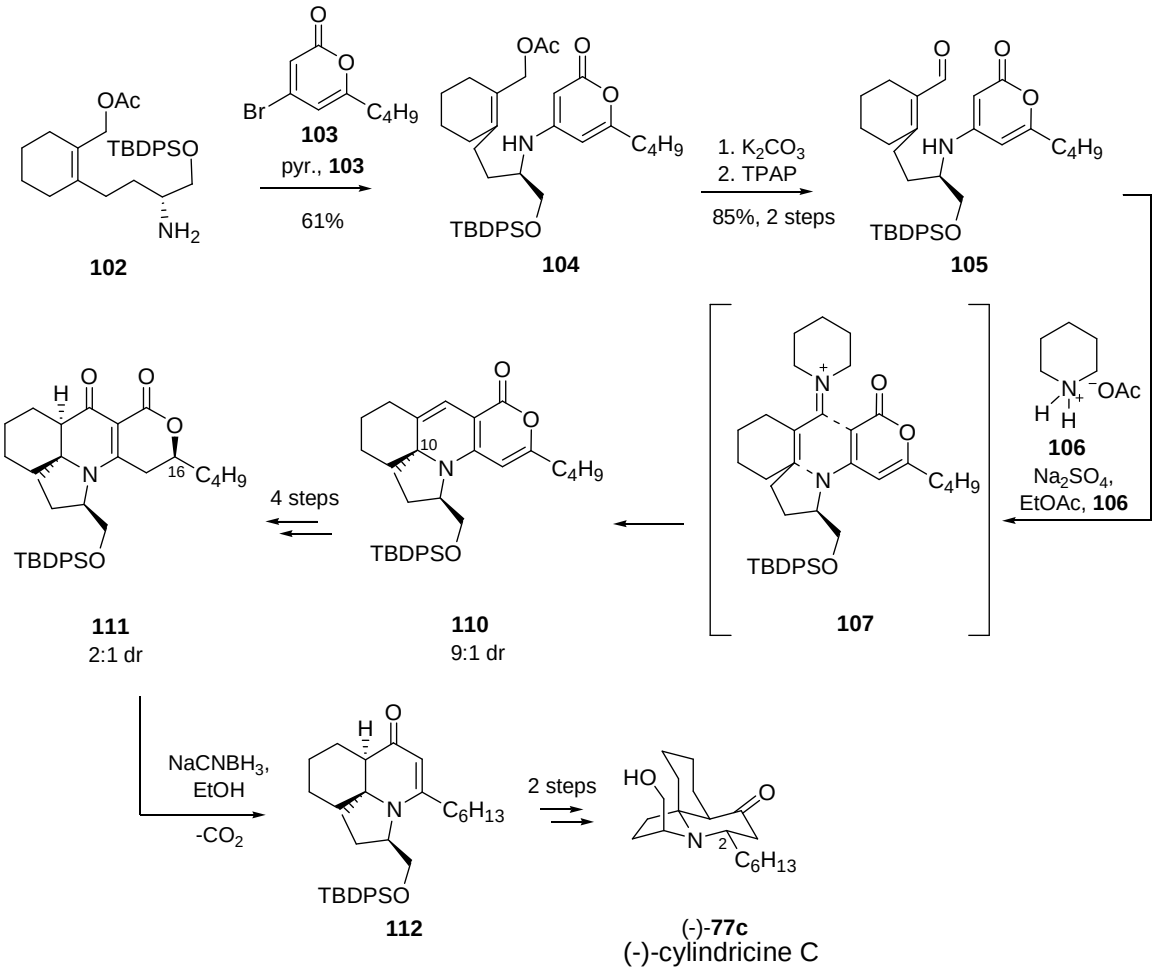


the mesylate at the less hindered alcohol at the C-2 position of this system. Upon *N*-BOC deprotection, the liberated amine attacked the tethered mesylate group to produce alcohol **99**. Swern oxidation of this alcohol led to the *trans*-fused AB-azadecalone system **100**. Molecular mechanics calculations indicated that the *cis*-fused AB azadecalone system **101** is more stable than its *trans*-fused diastereomer **100** by 5.5 kcal/mol. In the event, azadecalone **100** was treated with K_2CO_3 which resulted in complete epimerization to the energetically more favored *cis*-fused cylindricine array **101**. Debenzylation of **101** provided enantiopure (+)-cylindricine C.

In 2004, Hsung described an enantioselective synthesis of (+)-cylindricine C utilitzing a pivotal *N*-acyl iminium ion cyclization which is extremely similar to the Kibayashi sequence detailed in Scheme 21.[74] In a separate approach, Hsung developed a unique synthesis of this alkaloid target which made use of a [3+3]-annulation platform (Scheme 22).[75] Amine **102**, which was available in 11 steps from *l*-serine, was coupled with bromo-2-pyrone **103** to produce vinylogous amide **104**. This compound's acetate group was removed and the resulting alcohol was oxidized to give aldehyde **105**. The key step in this synthesis was the intramolecular cycloaddition of aldehyde **105**, which could be triggered by heating the system in the presence of catalytic piperidinium acetate. The sequence involves the formation of iminium intermediate **107** which then ultimately delivered **110** as a 9:1 mixture of diastereomers at C-10. Four subsequent steps converted the major diastereomer of **110** to ketoester **111** which exists as a 2:1 diastereomeric mixture at C-16. In the presence of sodium cyanoborohydride, ester **111** experienced an unusual chemoselective hydride attack at C-16 of the incumbent cylindricine side chain. In an SN_2 fashion, hydride displacement of the lactone followed by decarboxylation furnished enone **112** as the sole product. Enone **112** was then converted to (-)-cylindricine C via a

two-step protocol. It is notable that (-)-2-*epi*-cylindricine C ((-)-2-*epi*-**77c**) was also obtained from enone **112** using a separate set of conditions.

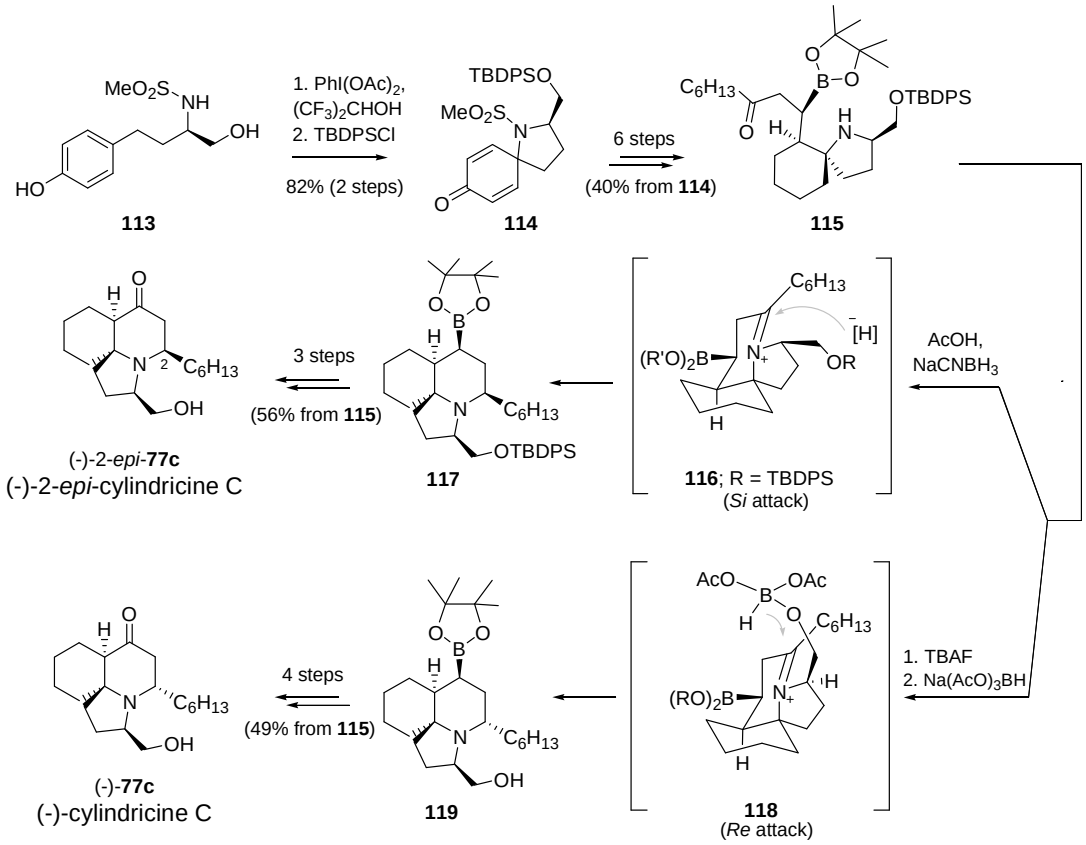
Scheme 22. Hsung's [3+3] Annulation Approach to (-)-Cylindricine C.[75]



Ciufolini also utilized a novel approach to enantioselectively produce both (-)-cylindricine C (-)-**77c** and its unnatural relative (-)-2-*epi*-cylindricine C ((-)-2-*epi*-**77c**) as outlined in Scheme 23.[76] The key precursor **113** (available in four steps from (*R*)-homotyrosine) was oxidized with iodosobenzene diacetate which triggered an oxidative azaspirocyclization. Subsequent alcohol protection

afforded dienone **114**. Six steps were used to convert this structure into boronic ester **115** which could be obtained as a single stereoisomer. Separate reaction sequences were employed to furnish the target material. In the first sequence, sodium cyanoborohydride reduction of **115** proceeded by hydride attack of iminium intermediate **116** from the least hindered *si* face to afford tricycle **117**. Conversion of the resulting boronate **117** to the unnatural alkaloid (-)-2-*epi*-cylindricine C was achieved in three subsequent steps. A second sequence was also devised to construct the natural product from the late-stage aminoketone **115**. In this sequence, the silyl ether within **115** was first removed to provide the

Scheme 23. Ciufolini's Oxidative Spirocyclization Approach to (-)-Cylindricine C and (-)-2-epi-cylindricine C.[76]

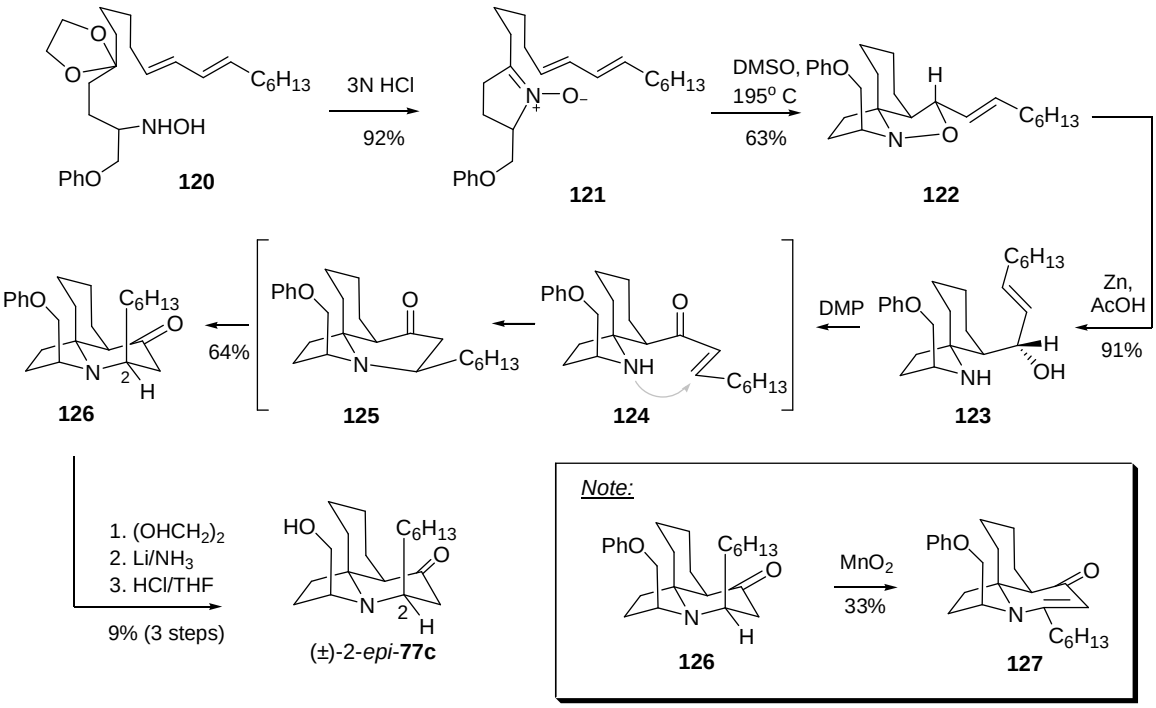


corresponding alcohol. Using a procedure previously described by Evans,[77] this alcohol underwent a hydroxyl-directed reductive amination (*cf*. **118**) to afford tricycle **119**. Four steps were then used to convert **119** to (-)-cylindricine C ((-)-**77c**).

The Weinreb group has devoted a significant amount of attention to the synthesis of the natural products listed in Figure 4. In an effort to confirm the structure of lepadiformine A, Weinreb incorporated a key nitrone dipolar cycloaddition reaction for the synthesis of this alkaloid.[78] This venture also led to a racemic synthesis of (±)-2-*epi*-cylindricine C ((±)-2-*epi*-**77**), as described in Scheme 24. The synthesis commenced by subjecting hydroxylaminoketal **120** (available in nine steps from acetone oxime) to aqueous HCl. These conditions led to the formation of the isolable nitrone **121**, which upon thermolysis produced cycloadduct **122**. Reductive scission of the isoxazolidine *N*-*O* bond led to aminoalcohol **123**. Dess-Martin oxidation gave rise to tricyclic amine **126** in 64% yield via an *in situ* cyclization of amino enone **124**. Conjugate addition of the amino group to the enone functionality in **124** initially occurred through a transition state leading to the boat B-ring **125**. This system then underwent a ring flip to produce the observed all-chair product **126**. Ketone **126** was protected as the corresponding acetal prior to Birch reduction of the phenyl ether functionality and subsequent acetal removal. The outcome of this sequence provided (±)-2-*epi*-cylindricine C ((±)-2-*epi*-**77c**). It is of particular importance to our research interests (*vide inra*) that Weinreb attempted to epimerize **126** at C-2 through the intermediacy of vinylogous amide **127**. Although the authors reported unsuccessful reduction of enone **127** to the naturally occurring cylindricine geometry at C-2, the low yield of the ring oxidation provided an insufficient amount material to fully explore this conversion. Clearly, the low yield of

compound **127** underscores the need for a synthetic method capable of reliably introducing an α,β-unsaturated carbonyl within an *N*-alkyl-4-piperidone frame.

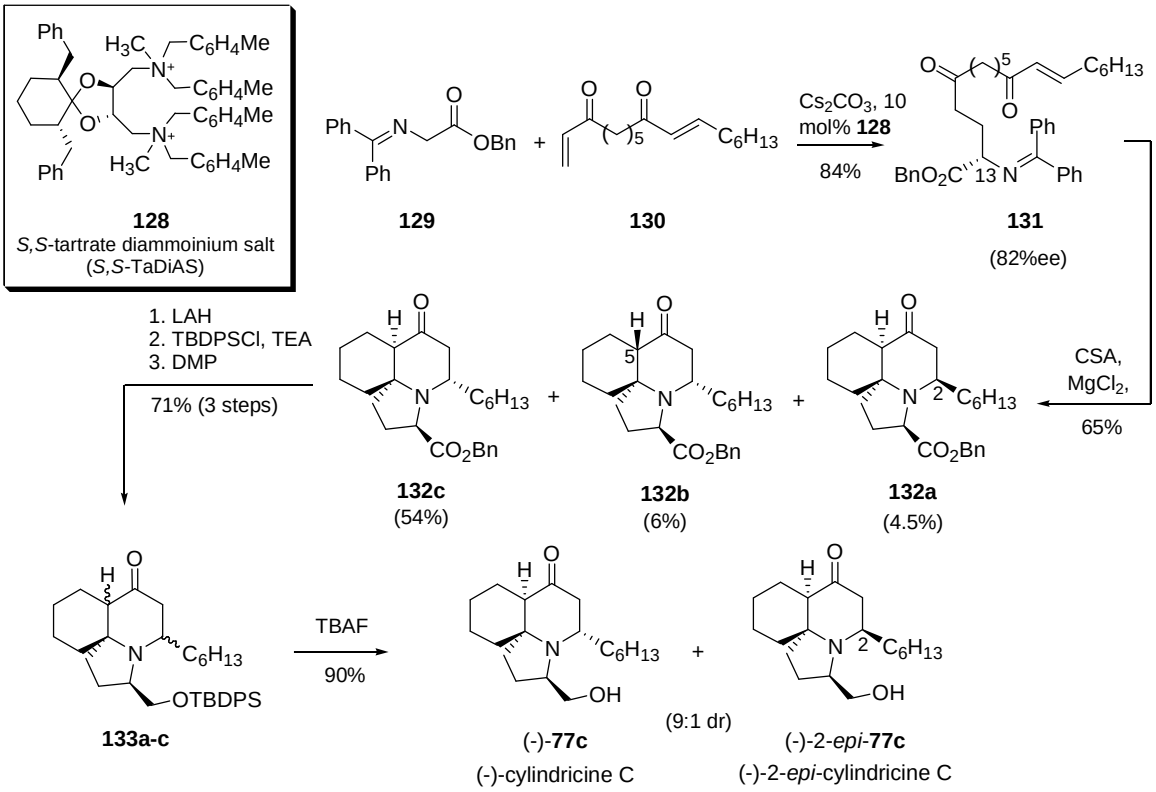
Scheme 24. Weinreb's Synthesis of (±)-2-epi-Cylindricine C.[78]



An impressive biomimetic total synthesis involving enantioselective organocatalysis has been reported by Shibasaki.[79] Recently, this research group has developed a two-center organocatalyst (**128**, TaDiAS; tartrate-derived diammonium salt) that efficiently catalyzes phase-transfer alkylation,[80] Michael reactions,[80] and Mannich-type reactions of a glycine-derived Schiff base.[81] Through implementation of this technology, the Shibasaki group was able to execute a short, enantioselective route to (-)-**77c**.[81] Extensive research was first conducted to optimize the regio- and enantioselective Michael addition of achiral iminoester **129** to the less substituted enone of the *bis*-α,β-unsaturated ketone

130. These conditions involved using the 2,6-disubstituted cyclohexane catalyst (*S,S*)-TaDiAS (**128**). Exposure of iminoester **129** to enone **130** in the presence of a catalytic amount of **128** gave rise to Michael adduct **131** in 84% yield and 82% ee. Treating iminoketone **131** with camphorsulfonic acid and magnesium chloride triggered a cascade reaction which returned a mixture of three diastereomeric tricycles **132a**-**c**.[82] Intriguingly, the major product from this reaction (**132c**) possessed the requisite configuration at all four cylindricine stereogenic centers. The two minor products were determined to be epimeric to the natural product geometry at C-2 (**132a**) and C-5 (**132b**), respectively. The three-component mixture of esters was subjected to excess LAH, followed by protection of the

Scheme 25. Shibasaki's Organocatalysis Approach to (-)-Cylindricine C and (-)-2-epi-Cylindricine C.[81]

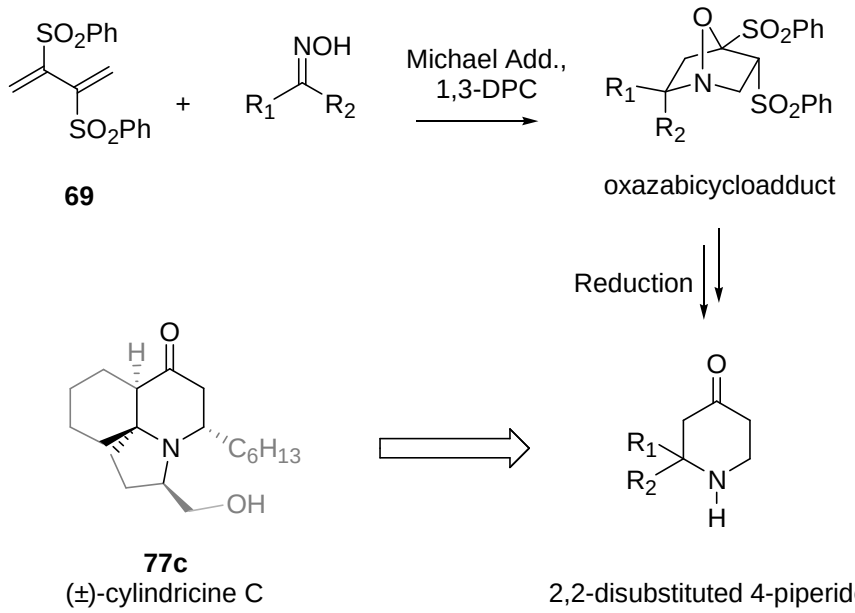


resulting primary alcohols. Subsequent re-oxidation gave the mixture of cylindricine silyl ethers **133a**-**c**. Taking cue from previous authors who have exploited a base-induced AB-ring fusion epimerization, Shibasaki treated **133a**-**c** with TBAF. These conditions removed the silyl functionality and facilitated concomitant epimerization of the C-5 center. This gave rise to (-)-**77c** and (-)-2-*epi*-**77c**, which were obtained in a 9:1 ratio in favor of the natural product (-)-cylindricine C.

In addition to these total synthesis efforts (*vide supra*), other approaches to the cylindricine framework which did not result in the synthesis of the naturally occurring alkaloid have also been reported.[83,84]

Against this backdrop, the Padwa group has a well-documented interest in dipolar cycloaddition methodology and its application to alkaloid natural product synthesis. The use of an intramolecular nitrone dipolar cycloaddition has been recognized to be of considerable synthetic utility.[85] These cycloadditions often produce heterocycles with a high degree of stereoselectivity, which are controlled by steric constraints present within the starting substrate.[86] This chemistry also benefits from the ready access to nitrone starting materials, allowing simple substrates to be transformed into complex heterocycles through a tractable reaction platform. Our laboratory had previously described the generation of nitrones from the condensation of 2,3-*bis*(phenylsulfonyl)-1,3-butadiene (**69**)[87] with oximes as a method for 4-piperidone synthesis (Scheme 26).[88] When treated with diene **69**, oximes undergo a Michael addition and a subsequent dipolar cycloaddition to give diastereospecific oxazabicycloadducts. The bridging *N-O* bond within these bicycloadducts can be reductively cleaved to produce 2,2-disubstituted 4-piperidones in excellent yield.

Scheme 26. Padwa's Entry to 2,2-Disubstituted 4-Piperidone Synthesis.[88]

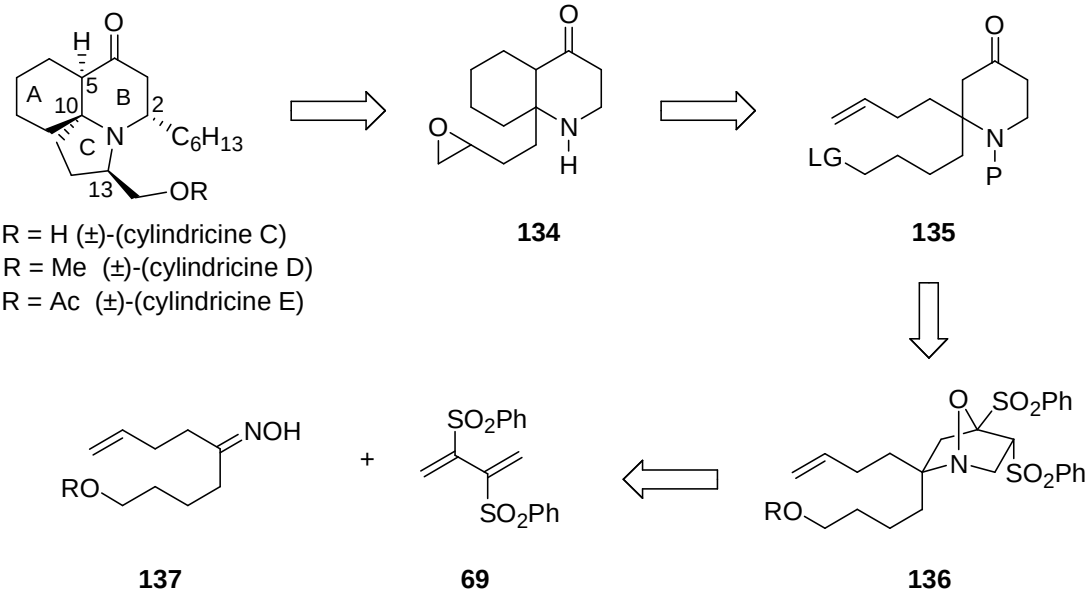


Recognizing the 4-piperidone subunit within the cylindricine architecture, it was reasoned that an appropriately substituted oxime could be subject to the above reaction platform thereby providing entry to this alkaloid class. A synthesis of (±)-cylindricine C involving the above sequence would therefore highlight the versatility of this reaction manifold. This unique approach would also be complementary to those already in existence while offering potential advantages over previous routes. The following section of this thesis details how the intended application was pursued.[89]

Results and Discussion

A unique synthetic strategy directed toward the cylindricine alkaloids involves taking advantage of the tandem addition-cycloaddition-reduction sequence as had been outlined in earlier reports from this laboratory (Scheme 17).[54] A retrosynthetic analysis of (±)-cylindricine C (**77c**) is shown in Scheme 27. A strategic advantage offered by this synthetic approach is the construction of the congested cylindricine C-10 center at an early synthetic stage. It was envisaged that enolate displacement of a tethered leaving group would convert a 2,2-disubstituted piperidone (**135**) into a decalone resembling **134**. Upon securing the AB-azadecalone ring system (**134**), the *cis*-fused AB ring juncture could be accessed through a precedented α-keto epimerization.[65,66,68,69,72,75,78,81] Precedent also exists for the stereocontrolled installation of the *n*-hexyl side chain at C-2 from an azadecalone resembling **134**.[69] Should the intramolecular epoxide ring-opening of **134** not provide the desired stereochemistry at C-13, subjecting the corresponding terminal alkene to conditions described by Snider

Scheme 27. Key disconnections for the synthesis of (±)-cylindricines.



77c; R = H (±)-(cylindricine C)
77d; R = Me (±)-(cylindricine D)
77e; R = Ac (±)-(cylindricine E)

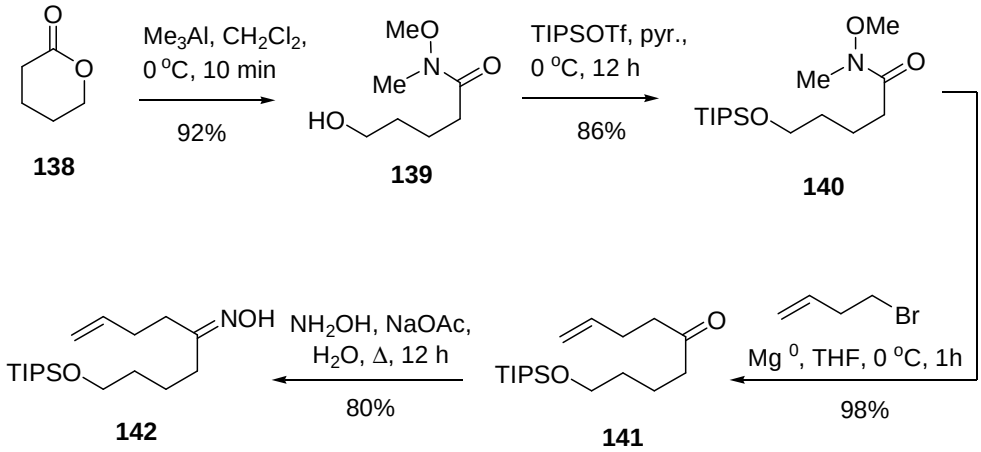
134 **135**

137 **69** **136**

would permit entry to this class through cylindricines D or E.[66] To probe the likelihood of success of this approach, an oxime bearing two distinguishable tethers (**137**) was assembled.

First Generation Cylindricine Approach. Construction of the key oxime proceeded as shown in Scheme 28. Treating redistilled δ-valerolactone (**138**) with trimethylaluminum and *N,O*-dimethylhydroxylamine hydrochloride installed the Weinreb amide, giving alcohol **139** in 92% yield. The terminal hydroxyl group in **139** was then silylated with TIPS triflate. Selection of triisopropylsilyl etherification was critical, as this functionality was envisioned to be able to survive strongly acidic, thermolytic, nucleophilic, and reductive conditions prior to its deprotection. Weinreb amide **140** was then treated with an excess of 3-butenylmagnesium bromide in THF to provide ketone **141**. It should be noted that this Grignard reagent originated from 3-butenyl bromide, which was carefully prepared on gram-scale using a modified procedure originally described by Kraus.[90] The resulting ketone **141** was then converted to the desired oxime **142** through condensation with aqueous hydroxylamine hydrochloride. This four-step

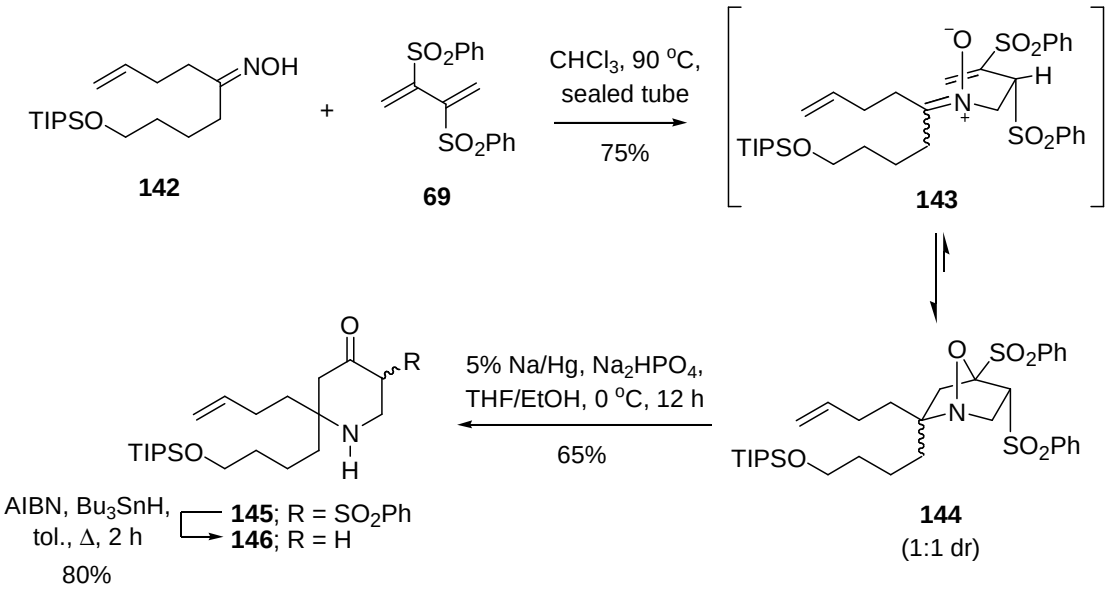
Scheme 28. Preparation of oxime 142.



sequence (**138→142**) proceeded in 62% overall yield from δ-valerolactone and could be used to produce gram-scale quantities of oxime **142** without the use of chromatographic purification.

The stage was then set for the key-step piperidone-forming sequence which proceeded as shown in Scheme 29. Exposure of oxime **142** to dienyl sulfone **69** in chloroform heated at 90 ^{o}C in a sealed tube returned cycloadduct **144** as an equal mixture of diastereomers in 75% yield. It should also be noted that this key cycloadduct can be reequilibrated with nitrone **143** in $CDCl_3$ (this equilibrium lies in favor of the cycloadduct and typically ranges from 6:1 to 15:1 depending on concentration). Cycloadduct **144** was cleanly reduced with sodium-mercury amalgam to give α-keto sulfonyl piperidone **145** in 65% yield. Oxime **142** and ketone **141** (Scheme 28) were also recovered from this reaction as side products. Employing a procedure originally described by

Scheme 29. Michael Addition-Cycloaddition-Reduction Sequence.



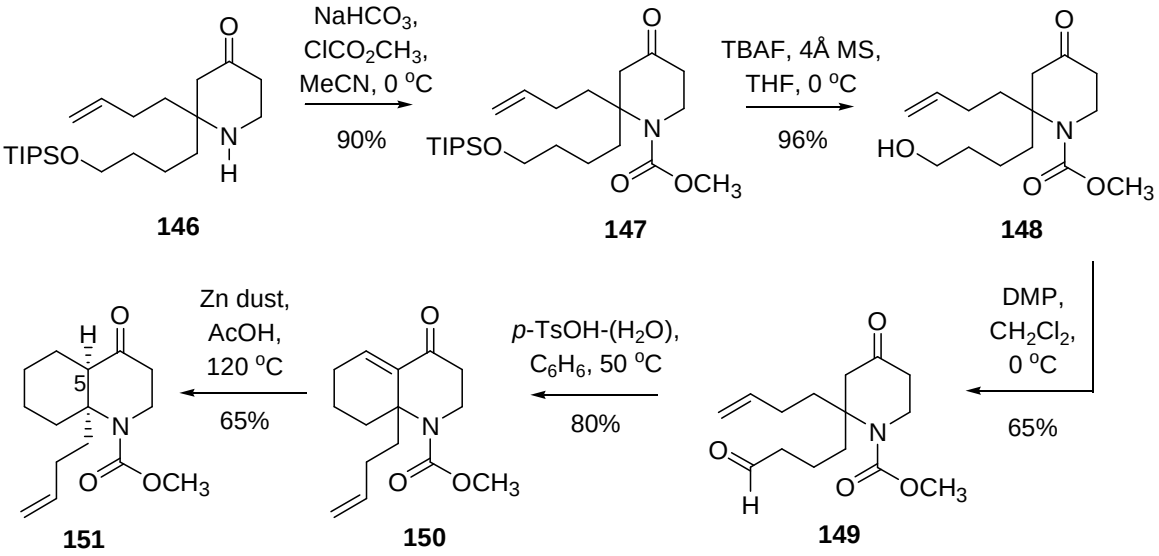
Smith,[91] tin-mediated phenylsulfonyl removal converted **145** to branched piperidone **146** in good yield.

At this stage, we were encouraged by our synthetic sequence which produced gram-scale quantities of the desired 4-piperidone **146**. To avoid potential difficulties with the A-ring cyclization step, *N*-protection of piperidone **146** was required at this stage of the synthesis. Therefore, protection of the nitrogen atom of **146** as a 2-trimethylsilanylethoxy (Teoc) carbamate was undertaken. Selection of this protecting group was based on earlier work by Heathcock.[69] Also, in the event we encountered difficulties with late-stage functionalization, we could potentially intercept a Heathcock intermediate *en route* to the natural target.[69] During our initial attempts at protection, however, piperidone **146** failed to react with Teoc-Cl and other Teoc-containing mixed anhydrides. It was subsequently discovered that various other acylating or alkylating reagents (benzaldehyde/$NaCNBH_3$, CBzCl, BOC_2O, *etc*.) also failed to give any *N*-substituted products when reacted with **146**. Heathcock had reported similar issues, which is likely due to the steric bulk of the side chains anchored to the tetrasubstituted piperidone center within **146**.[69]

After extensive research, conditions were developed to convert **146** to the corresponding methyl carbamate **147** (Scheme 30). With this compound in hand, an A-ring closure strategy was pursued. It was postulated that an intramolecular aldol condensation-dehydration protocol would furnish the desired AB-azadecalone system. Therefore, carbamate **147** was treated with TBAF, resulting in the clean removal of the TIPS group in excellent yield. The resulting alcohol (**148**) was then oxidizied using Dess-Martin periodinane to give aldehyde **149**, setting the stage for the critical ring-forming step. When subjected to weakly acidic conditions, aldehyde **149** underwent smooth condensation and immediate dehydration to provide enone **150**. Selective reduction of the resulting α,β-

unsaturated ketone **150** was carried out by heating this system in the presence of zinc dust and acetic acid. Interestingly, the reduction gave rise to the *cis*-fused decahydroquinoline **151** as the exclusive product, which exactly matched the previously reported spectral data for this compound.[69] In contrast to Heathcock, who generated this same azadecalone **151** as a 1:1 mixture of diastereomers at the cylindricine C-5 center, our reduction protocol proceeded stereospecifically. This *cis*-fusion selectivity can be attributed to the reprotonation step which occurs from the least hindered face of the bicyclic array under thermodynamic zinc reduction conditions.[92]

Scheme 30. Synthesis of the AB-azadecalone ring system.

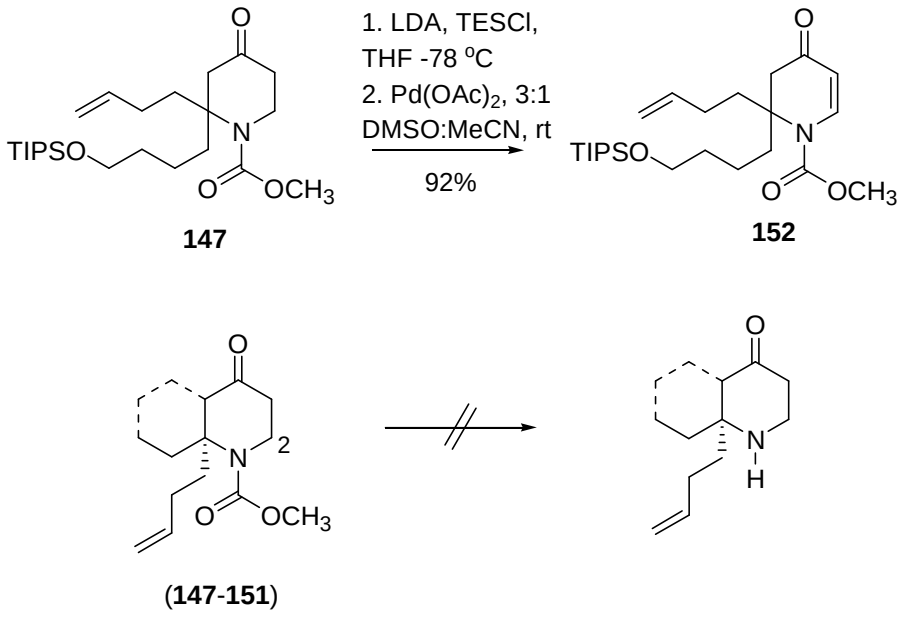


After developing a facile conversion of piperidone **146** to the *cis*-fused cylindricine AB-ring construct **151**, significant difficulty was encountered deprotecting the methyl carbamate group from this late-stage intermediate. Also, this methyl carbamate functionality was unable to be removed from any earlier intermediates (**147**-**150**). Under a variety of conditions—including forcing acid,

base, and thermolysis—these methyl carbamates (**147**-**151**) were recovered unchanged or led to various decomposition products. Substitution of the nitrogen atom within **146** was also attempted with other protecting groups that would allow more facile deprotection at later stages. Unfortunately, methyl chloroformate was the only reagent capable of reacting with **146** in any appreciable yield. These protection/deprotection difficulties are consistent with the earlier observations by Heathcock.[69] The results further support the concept that the nitrogen atom embedded within the 2,2-disubstituted piperidone system is significantly crowded by the adjacent groups.

However, it should be noted that we were able to functionalize the piperidone systems for C-2 side chain installation. Through use of a Saegusa oxidation,[93] ketone **147** was converted to the corresponding vinylogous amide **152** (Scheme 31) in excellent yield. However, it was assumed that earlier

Scheme 31. Saegusa Oxidation of Piperidone 147.



147 **152**

(**147**-**151**)

deprotection difficulties with sterically-encumbered carbamates (**147**-**151**) would only be compounded by incorporating an additional alkyl group at C-2. Therefore, installation of the *n*-hexyl side chain was not attempted on any of the members of this series.

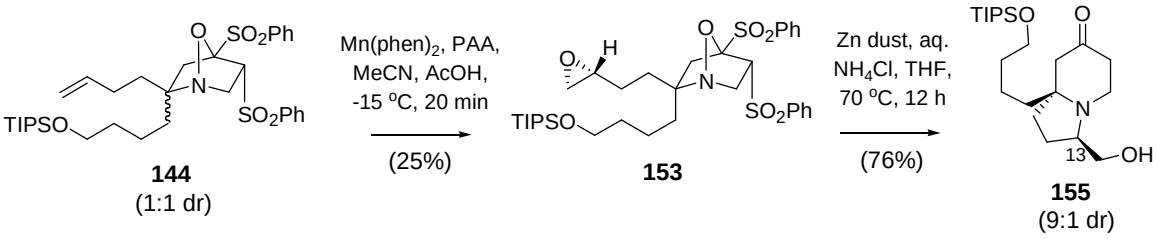
Despite establishing a tractable route to the *cis*-fused AB-azadecalone **151**, the difficulties surrounding *N*-protection/deprotection of this hindered amine prevented synthetic entry to the cylindricines by this route.[69] This development prompted us to seek an alternative paradigm to alleviate *N*-substitution issues.

Epoxidation-Reduction Sequence. Since the difficulty of protecting the nitrogen atom was the central issue with the aforementioned first-generation approach, means to circumvent this problem were considered. It was reasoned that an intramolecular ring opening reaction might enhance reactivity by bringing the electrophilic species closer to the nitrogen atom. The presence of an epoxide ring could conceivably solve the *N*-protection issues while simultaneously establishing the requisite cylindricine hydroxymethylene functionality at C-13. Several reports in the literature describe where an amino nitrogen atom exhibits exceptional nucleophilicity under reducing conditions, especially when the electrophile is tethered.[94] Since the first generation synthetic route featured a reduction step, equipping a reduction substrate with an epoxide would provide a good chance to assemble the core ring skeleton. We therefore pursued this design, and set out to convert cycloadduct alkene **144** to the corresponding epoxide.

It was soon discovered that cycloadduct alkene **144** was not reactive toward the conventional means of direct epoxidation. Hydrogen peroxide, *m*-CPBA, Shi's procedure, *t*-butyl peroxide, vanadium oxidants, trifluoroperacetic acid, as well as several other methods all failed to produce any characterizable

epoxide. This difficulty was not unexpected since the terminal alkene **144** is relatively unreactive and competes with the *N-O* cycloadduct for electrophilic sources of oxygen.[95] However, using a modified procedure recently described by Stack,[96] the desired epoxide **153** was generated cleanly, but only in 25% yield (Scheme 32). Intriguingly, the zinc reduction of the manganese-derived epoxide produced a 9:1 mixture of 7-indolizidones **155**. The major diastereomeric product of this reaction corresponded to the requisite cylindricine geometry at C-13 (later determined by total synthesis).

Scheme 32. Epoxidation-Reduction Sequence.

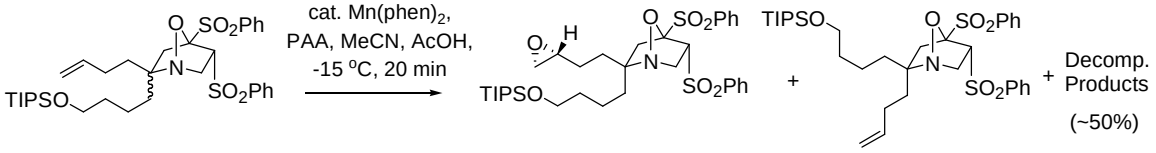


The mechanistic details of this sequence are of some interest, since the stereochemical outcome of **155** is derived from the epoxidation of **144**. We hypothesized that the epoxidation reaction (**144→153**) proceeds with high *exo*-selectivity and that the manganese catalyst probably coordinates with the *N-O* functionality to direct the alkene facial selectivity of the epoxidation reaction. Therefore, a series of experiments were conducted to explore these speculations.

A control experiment which involved subjecting alkene **144** to the Stack conditions *without* any manganese catalyst returned starting material. This suggested that manganese was clearly responsible for the observed epoxidation reactivity. Secondly, an experiment was conducted where alkene **144** (1:1 dr)

was subjected to the Stack conditions using a stoichiometric amount of manganese catalyst. This reaction gave little epoxide **153**, but did provide strong evidence for manganese complexation with the *N*-*O* cycloadduct as determined by ^{1}H-NMR. Thirdly, alkene **144** (1:1 dr) was treated with dimethyldioxirane (DMDO), which produced the desired epoxide **153**, but only in 10% yield. However, the subsequent reduction of the DMDO-generated epoxide produced an approximately 3:2 mixture of indolizidones **155** (in favor of the desired C-13 geometry of the cylindricines). It should be noted that the yield of indolizidone **155** generated from the DMDO-derived epoxide was similar to the yield obtained in the manganese-derived epoxide reduction (~76%). A fourth experiment where **144** (1:1 dr) was subjected to iodohydrination conditions returned *endo*-**144** as evidenced by examining the crude reaction mixture by ^{1}H-NMR spectroscopy. This result suggests that *exo*-**144** had selectively reacted to produce aqueous-soluble products, and that *endo*-*exo* selectivity likely takes place for the alkene epoxidation as well. Lastly, the desired epoxide **153**, which was produced from **144** (1:1 dr) using the modified Stack epoxidation conditions, was accompanied

Scheme 33. Products Recovered from the Modified Stack Epoxidation[96] of Alkenes 144.



144
(1:1 mixture of *endo* and *exo*)

153
(25%)

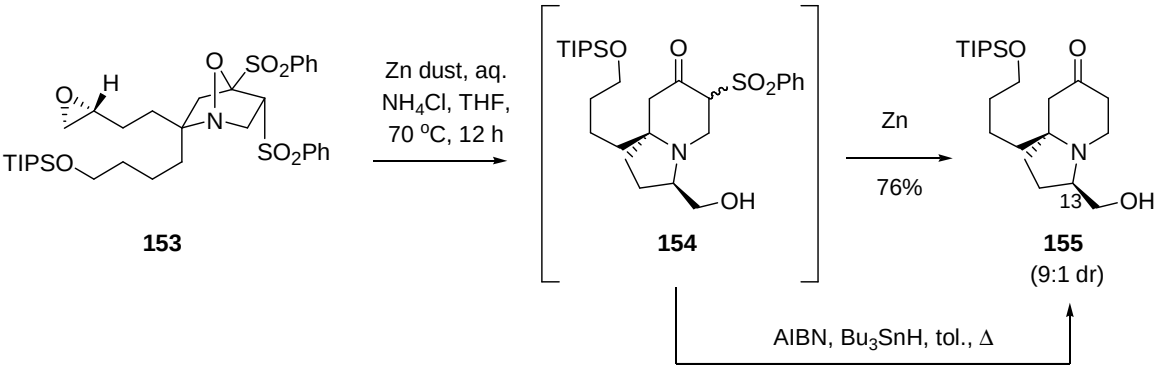
endo-**144**
(~25%)

by two major byproducts. Approximately 25% of the mass recovery from this reaction corresponded to the *endo*-alkene (*endo*-**144**) while the remaining 50% mass recovery were *N*-*O* oxidative decomposition products (Scheme 33).

From this series of experiments and observations, we assume that the manganese-catalyzed epoxidation of **144** (1:1 dr) is responsible for the selectivity of the subsequent reduction product. This critical reaction involves: (1) selective *exo*-epoxidation of the mixture of alkenes **144**; and (2) epoxide formation proceeding via manganese coordination to the *N*-*O* functionality within the cycloadduct alkene. The low yield of this reaction can be attributed to facial-selective delivery of electrophilic oxygen to the *exo*-alkene. It was reasoned that facile gram-scale production of the key cycloadduct alkene **144** would offset the poor yield of the epoxidation, thereby providing enough late-stage material to reach the target natural alkaloid. From this point forward in this thesis, the major epoxide diastereomer—which corresponds to the major indolizidone product **155**—will be referred to as epoxide **153**.

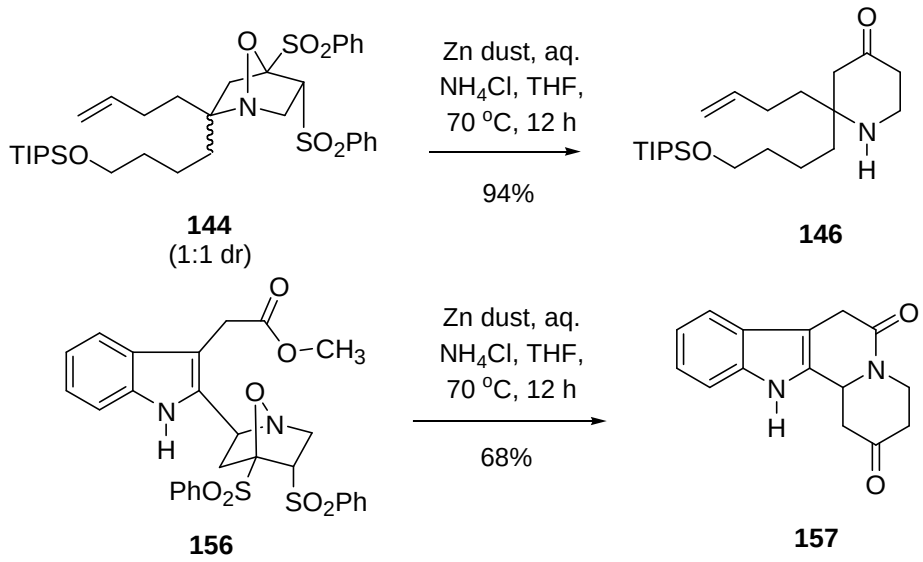
In addition to the unusual stereoselective epoxidation, the details of the reduction sequence are also of some interest. Monitoring the reduction (**153**→**155**, Scheme 34) by crude ^{1}H-NMR spectroscopy shows the progressive disappearance of epoxide **153**, accompanied by emergence of the major diastereomer of **155**. This observation strongly suggests a S_{N2} epoxide-ring opening, ruling out any *in situ* epimerization during the reduction step. This result also substantiates our hypothesis that the stereoselectivity of indolizidone **155** is ultimately derived from the stereoselective epoxidation of **153**. It should be noted that α-ketosulfone **154** was also observed as a side product during the zinc reduction step. Although minor amounts (<20%) of this impurity co-eluted with the major diastereomer of **155** during purification, sulfone **154** could be cleanly converted to **155** upon further reductive desulfonylation (Scheme 34).

Scheme 34. Residual α-keto Phenylsulfonyl Reduction.



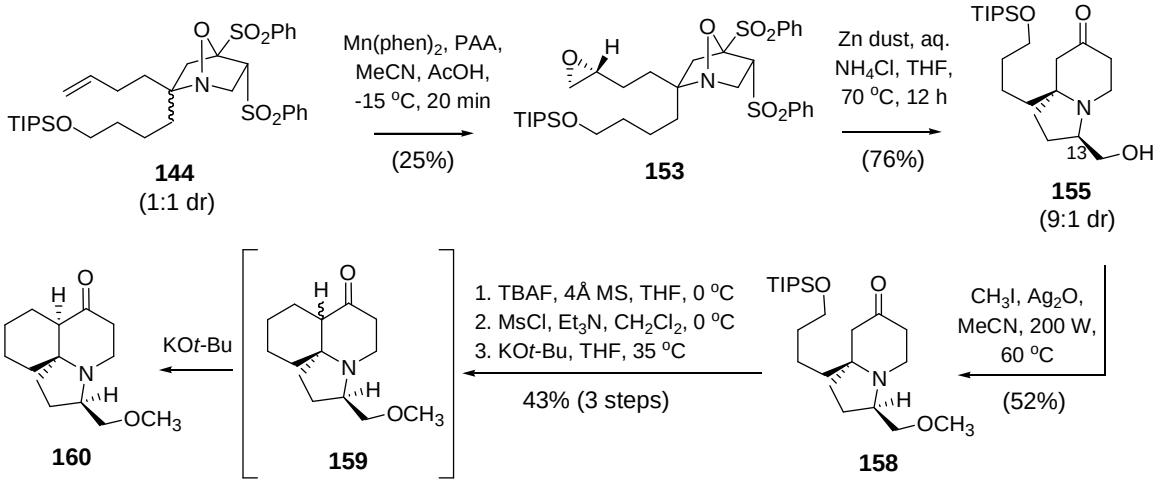
It is also notable that the mild, aqueous zinc reduction conditions[97] represents a general method for a one-pot reduction of *N-O* cycloadducts to give fully desulfonated 4-piperidones. For example, when subjected to these zinc conditions, oxazabicycloadducts **144** and **156** (Scheme 35, *vide infra*) were fully reduced to the corresponding desulfonated piperidone systems **146** and **157**.

Scheme 35. Additional Examples of Zinc-mediated Reductive N-O Cleavage Accompanied by α-Keto Desulfonylation.



Second Generation Cylindricine Approach. It was our belief that selectivity of the epoxidation-reduction sequence (Scheme 32) could be further utilized for a synthesis of a cylindricine alkaloid. An ethereal functionality corresponds to the C-14 substitution pattern of cylindricine D (**77d**). Therefore, we converted alcohol **155** (Scheme 36) to the corresponding methyl ether **158** through the use of a microwave-assisted etherification procedure which proceeded in modest yield. We were also to remove the minor C-13 diastereomeric methoxy ether at this stage. Silane **158** was then deprotected upon treatment with TBAF and the resulting alcohol was converted the corresponding mesylate. Following in close analogy to the procedure described by Spencer,[98] the crude mesylate was subjected to base-induced intramolecular alkylation. The exclusive product obtained from this reaction corresponded to the *cis*-fused cylindricine tricycle **160**. The intramolecular cyclization probably proceeds through initial generation of a mixture of diastereomers at C-5 (**159**). By design, a twofold stoichiometric

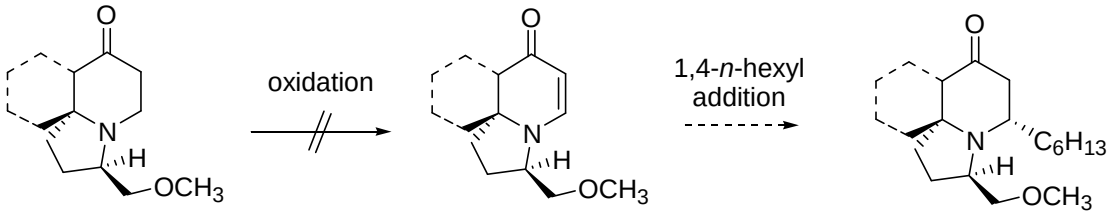
Scheme 36. Second-Generaton Reduction and A-Ring Cyclization Sequence.



amount of base was used during the mesylate displacement step and thus facilitated *in situ* epimerization at C-5 to the more stable *cis*-fused cylindricine tricycle **160**.[65,66,68,69,72,75,78,81]

Generation of an α,β-unsaturated carbonyl unit within either tricycle **160** or indolizidone **158** (Scheme 37), followed by addition of the appropriate *n*-hexyl cuprate would provide the necessary functionality. However, we encountered significant difficulty in generating the vinylogous amide functionality within either tricyclic amine **160** or the progenitor indolizidone **158**. A variety of standard methods such as IBX, CAN, and $PhSeCl/NaIO_4$ were explored but failed to produce any synthetically useful amounts of the requisite enaminoketone.

Scheme 37. Strategy for n-hexyl Side Chain Installation.

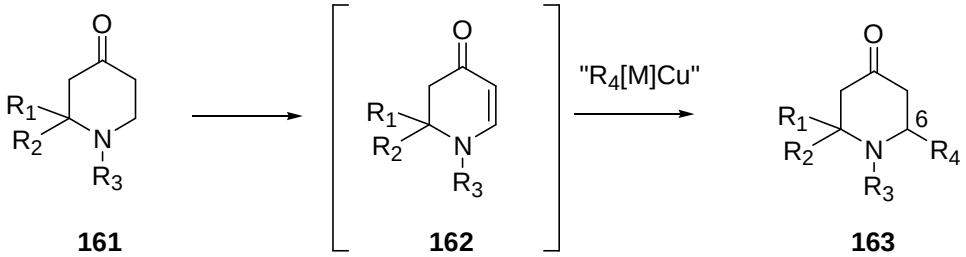


158-**160** enaminoketone

Although the sequence outlined in Scheme 36 allowed for efficient entry into the cylindricine tricyclic skeleton **160**, our inability to introduce the required unsaturation (Scheme 37) impeded the total synthesis effort. Thus it was necessary to develop a method to reliably introduce an α,β-unsaturation within these cylindricine systems. This particular oxidation was also critical to the success of 4-piperidone functionalization methodology for the community at large.

Studies Dealing With the Oxidation of* N-*Alkyl-4-piperidones. In order to convincingly demonstrate the utility of the *bis*-sulfone methodology toward the synthesis of cylindricine alkaloids, substitution of the piperidone framework at all positions is required. Toward this end, alkyl incorporation at C-6 (R_4, Scheme 38) was envisaged to arise from a conjugate alkylmetal addition onto a vinylogous amide intermediate **162**. Unfortunately, literature-reported examples of ring-oxidation of 4-piperidones (*e. g.* **161→162**) are relatively few in number.[99] From the infrequent examples reported, it was realized that *N*-alkyl-4-piperidone ring oxidations (**161→162**, R_3 = alkyl; Scheme 38) generally proceed under completely different conditions than that used for the *N*-acyl counterparts (R_3 = acyl).[100]

Scheme 38. Strategy for Piperidone C-6 Substitution.



161 **162** **163**

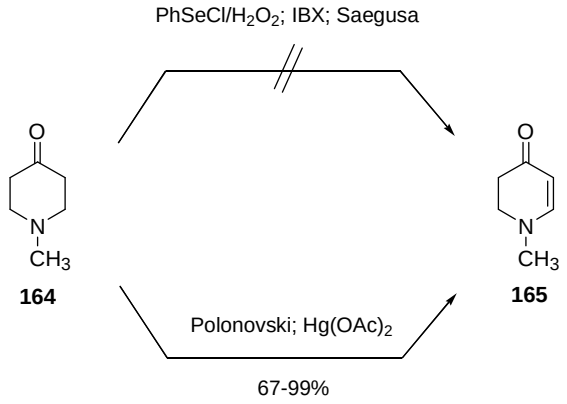
R_1= alkyl
R_2= H, alkyl

The reported oxidation of *N*-acylated 4-piperidones are typically effected by using $PhSeCl/H_2O_2$, Saegusa, or IBX methods ("carbonyl-directed" dehydrative protocols).[99] In contrast, the reported oxidation of *N*-alkylated 4-piperidones almost always involve the use of a Polonovski reaction ("nitrogen-directed" oxidation).[100] Moreover, the successful oxidations that involve the *N*-alkyl variety generally give meager yields of the desired vinylogous amide (Scheme 24).[78] Since the synthetic targets in mind arising from the *bis*-sulfone

reaction platform would ultimately depend on the introduction of an unsaturation onto *N*-alkyl-4-piperidone framework, a reliable, high-yielding means to effect this transformation would most likely require the use of the Polonovski reaction.

Since we were also curious about this *N*-alkyl/*N*-acyl reactivity difference, we set out to show that nitrogen substitution plays a key role in the oxidative pathway pathway of 4-piperidones. A control study was first initiated where *N*-methyl-4-piperidone (**164**, Scheme 39) was subjected to various oxidation methods in order to explore the reaction details. Analogous to the observations with the cylindricine synthons **158** and **160**, it was not possible to generate any characterizable enone was generated when piperidone **164** (Scheme 39) was treated with the "carbonyl-directed" oxidation methods mentioned previously (*i. e.* $PhSeCl/H_2O_2$; Saegusa; IBX). By contrast, the conversion of **164** to **165** proceeded in good yields (67%) when the Stuetz and Stadler Polonovski

Scheme 39. Oxidation Study Involving N-methyl-4-piperidone 164.



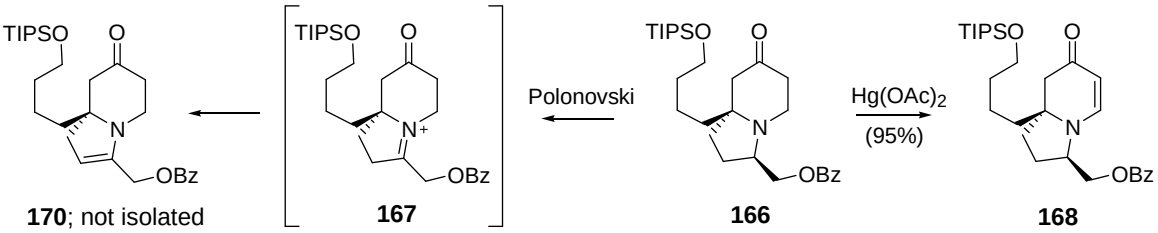
procedure was used.[100d] Enhanced yields of **165** (93%) were obtained when *N*-methyl-4-piperidone was converted to its corresponding silyl enol ether prior to

exposure to the Polonovski-Potier oxidation conditions. These results were consistent with Husson's observations.[100e]

Under Polonovski and Polonovski-Potier conditions, amines generally form the corresponding *N*-oxides which are readily *O*-acylated and then undergo α-proton elimination giving rise to products derived from an iminium ion.[100d,e] The regioselectivity of iminium ion formation is dictated by the proton oriented in a 180^{o} dihedral angle relative to the acylated *N*-oxide.[101] Treatment with a mild base removes the β-proton and ultimately leads to the formation of the enaminoketone (*i. e.* **165**).

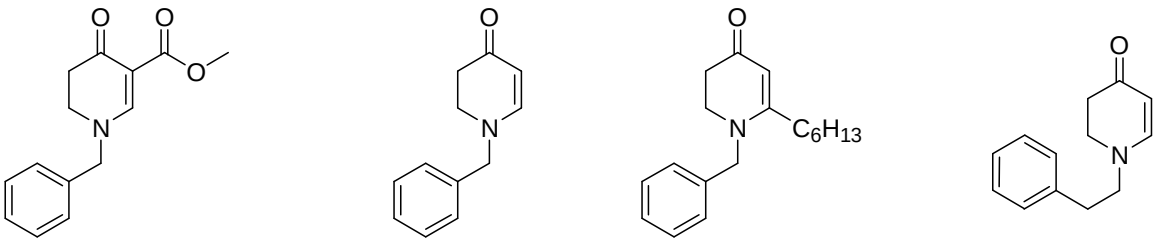
Unfortunately, and in contrast to the model study, subjection of the cylindricine intermediate **166** (Scheme 40) to the Polonovski[100d] and Husson[100e] method failed to produce any detectable quantity of enone **168**. Converting **166** to the corresponding triethylsilyl enol ether prior to the Polonovski conditions only returned complex mixtures of products. Adjusting temperature, solvent, and acylating reagents also failed to produce the desired enone **168**. The only discernable product obtained from any of the Polonovski reactions appeared to be enamine **170** as was suggested by an examination of the crude ^{1}H-NMR spectra taken. The chances of a successful mercuric acetate oxidation of **166** to enone **168** seemed doubtful since examples of mercuric acetate oxidations are rare in the literature,[100a,f-h] and there is also the problem of the toxicity of the mercury by-products involved. Some prior mechanistic studies of mercuric acetate oxidation suggest that the oxidation pathway proceeds by a similar Polonovski reaction pathway.[102] Against this background, we were delighted to discover that heating a sample of indolizidone **166** in the presence of stoichiometric amount of mercuric acetate and EDTA in aqueous ethanol quantitatively produced the desired vinylogous amide **168** (Scheme 40).

Scheme 40. Ring Oxidations of 7-indolizidone 166.



The success of the mercuric acetate oxidation of **166** to **168** prompted us to determine if mercuric acetate could be used to oxidize other *N*-alkyl-4-piperidones. Each of the enones (**175**-**178**) shown in Scheme 41 was generated in good to excellent yield from the fully saturated 4-piperidone precursor by subjecting it to the mercuric acetate oxidation conditions.[100g] Interestingly, in substrates where regioisomeric formation is possible (**175**, **177**, and **178**), the thermodynamically-favored enone was formed as the major product in each

Scheme 41. Examples of Ring-oxidized 4-Piperidone Products Formed by Mercuric Acetate.



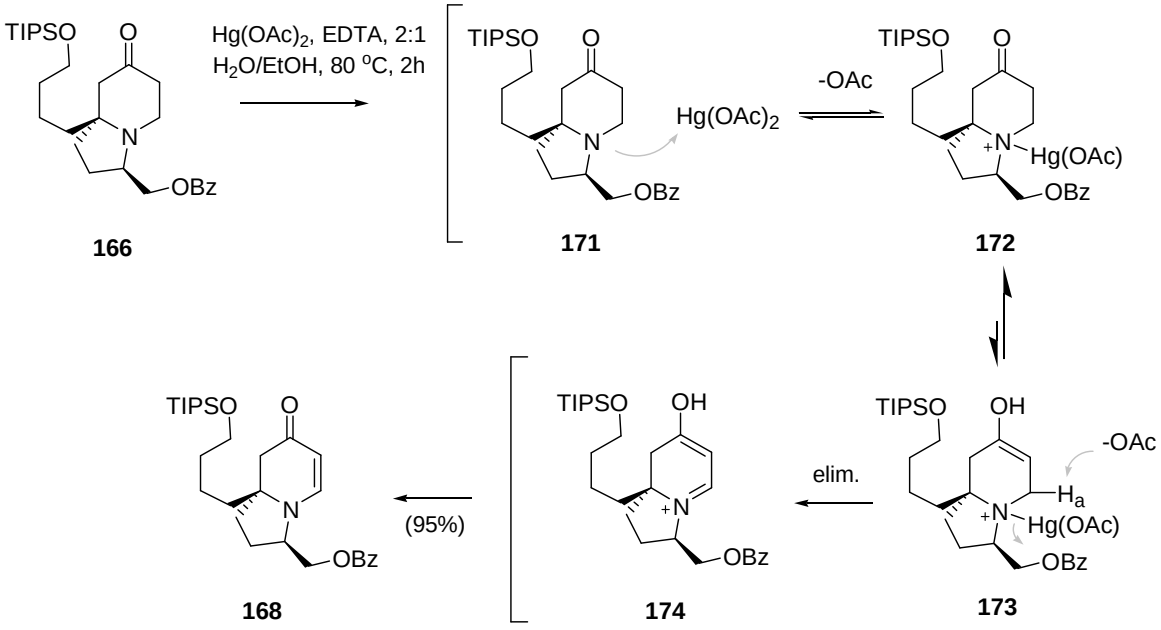
175 (95%) **176** (95%) **177** (71%) **178** (95%)

case. It should be noted that while vinylogous amides **175** and **178** were formed regiospecifically, **177** was obtained as a 7:2 mixture containing the minor

regioisomeric enone. Also, no overoxidized products were observed in any of the cases studied.

We suggest that the mercuric acetate oxidation reaction proceeds by the pathway outlined in Scheme 42. The reaction is initiated by tertiary amine attack on mercuric acetate to form the ammonium-mercurate intermediate **172**. Unlike the Polonovski-derived *N*-oxides, the ammonium-mercurate intermediate species **172** is relatively more stable, thereby permitting tautomerization of this ketone to the enol form **173**. The enol tautomer has an allylic proton (H_a) that is positioned next to a quarternary nitrogen atom. Acetate anion acting as the base then

Scheme 42. Proposed Mechanism of Mercury Acetate Oxidation of 4-piperidones.

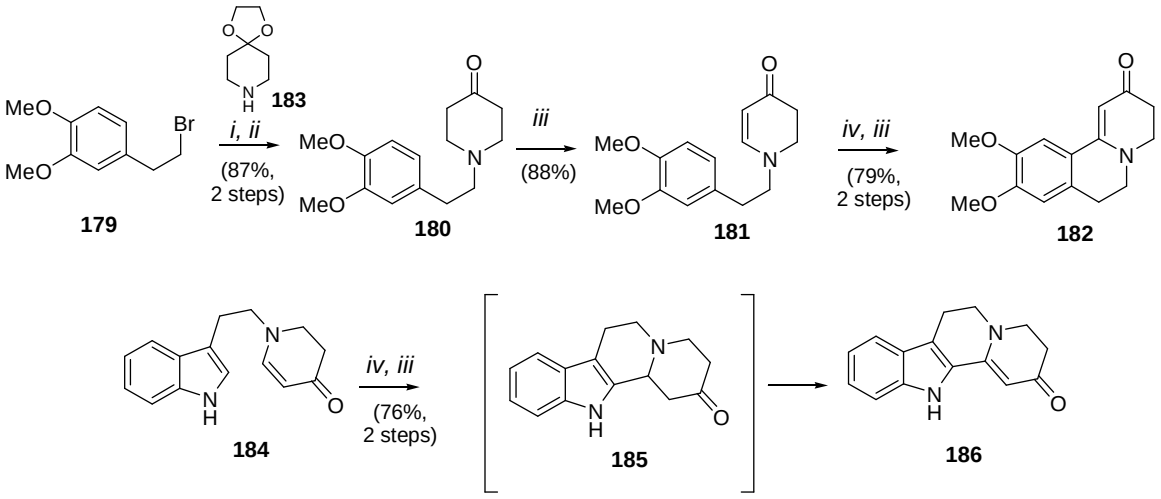


removes this acidic proton, resulting in the ejection of mercury and producing the betaine-like intermediate **174**. To dissipate the charge, deprotonation of the enol

occurs to give rise to enone **168**. Regioselectivity of enone formation can be attributed to the selective removal of the most acidic allylic proton (H_a) and this corresponds to the more substituted enol tautomer. In the case of the cylindricine intermediate **173** (Scheme 42), tautomerization can only result in deprotonation of one possible set of allylic protons (H_a), thereby accounting for the regiospecific formation of **168**. It should be noted that mercury metal (Hg^0) is recovered from the reaction, and that the reaction works without the aid of EDTA (which is used to reduce emulsions upon workup).

This study was expanded to include a series of higher-order heterocyclic systems. Using simple alkylation chemistry with piperidine **183**, piperidone **180** (Scheme 43) was efficiently constructed. Treatment of this system with the mercuric acetate oxidation conditions produced enone **181**, in excellent yield. Subsequent exposure of **181** to acidic conditions with heating facilitated nucleophilic aromatic ring closure. Further oxidation of the resulting cyclized

Scheme 43. Mercuric Acetate-Promoted Entry into the Yohimbenone and Emetine Skeletons.



Conditions: *i*) **183**, K_2CO_3, 1:1 DMF:H_2O, rt, 24 h; *ii*) 2N HCl in AcOH, 90 ^oC, 3 h; *iii*) $Hg(OAc)_2$, EDTA, 2:1 H_2O:EtOH, 80 ^oC, 1.5 h *iv*) 10% H_2SO_4, 90 ^oC, 12 h.

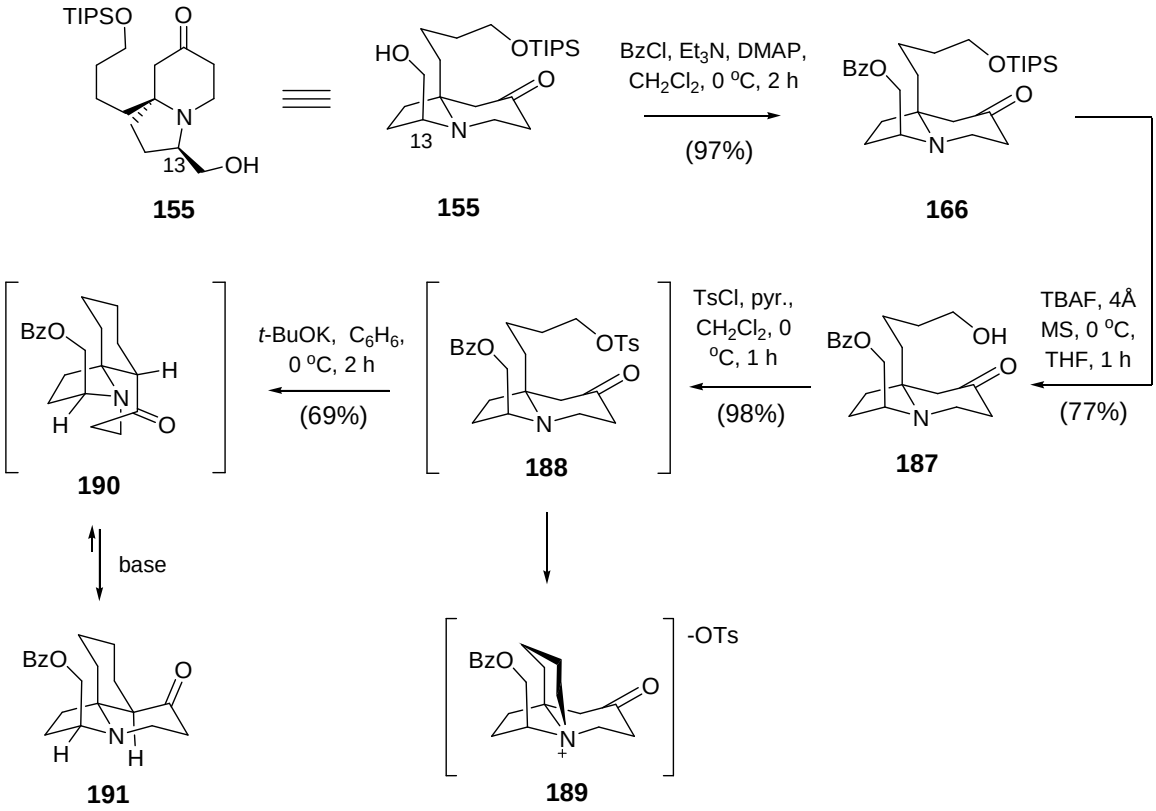
product gave vinylogous amide **182** as the exclusive products. Once again, the thermodynamically-favored enaminoketone was formed in good to excellent with no indication of any regioisomeric dehydration products as evidenced by an examination of the crude residue by ^{1}H-NMR spectroscopy. An analagous sequence was also executed with indoles **184**-**186**. For both the indole and 3,4-dimethoxyphenethyl systems, these tractable routes outlined in Scheme 43 required only a single chromatographic purification (**181** and **186**) for each system. This short protocol represents a rapid and operationally simple entry into the emetine[103] and yohimbenone[104] alkaloid classes.

These findings demonstrate that $Hg(OAc)_2$ is an excellent reagent for ring oxidation of *N*-alkyl-4-piperidones. This reagent's reactivity profile complements the Polonovski-Potier reaction manifold, permitting the functionalization of 4-piperidones regioselectively for further substrate elaboration.

Final Approach to (±)-Cylindricine C. Having established a reliable method for generating an unsaturation within *N*-alkyl-4-piperidones, functionalizing late-stage indolizidone **155** toward the target natural alkaloid was undertaken. Strategically, securing the cylindricine tricyclic topography prior to C-2 *n*-hexyl installation would be more likely to influence a pseudoequatorial approach of the *n*-hexyl cuprate and thus provide the natural product stereochemistry at this position. Consequently, the A-ring cyclization sequence was carried out by first protecting the hydroxyl group within **155** instead of subjecting it to etherification (Scheme 44), since the the silver-promoted etherification step (**155**→**158**, Scheme 36) was rather low-yielding. Benzoylation of the hydroxyl group seemed to be a good choice, despite the need for an additional deprotection step prior to arrival at the target natural alkaloid. The chromophore-containing benzoyl group corresponds to an excellent choice for spectroscopic identification purposes,

giving a unique ^{1}H-NMR signature which allowed for reaction products to be readily identified. Thus, benzoylation of **155** (Scheme 44) proceeded in excellent yield (97%). The minor C-13 diastereomeric benzoyl ester **166** could be cleanly removed at this stage by column chromatography. Fluoride deprotection of the TIPS group also proceeded smoothly to provide alcohol **187**. It was reasoned that tosylate activation of the terminal alcohol would render the system to be more workable than the earlier attempts using a mesylate group. The bulkier tosyl sulfonate **188** was less likely to react intramolecularly with the nearby tertiary amine (*i. e.* **189**). In earlier attempts, the mesylate was especially prone to this competitive reaction pathway. In practice, the conversion of **187** to the

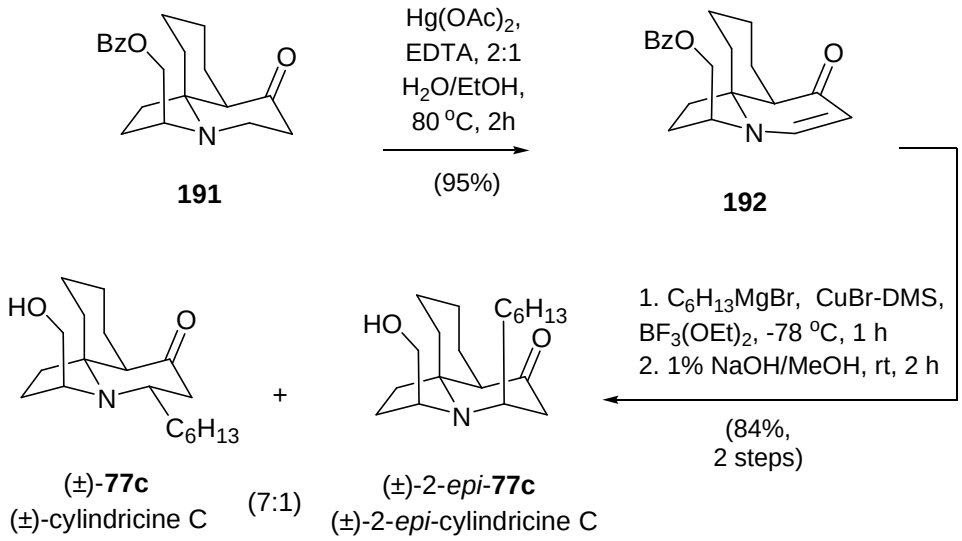
Scheme 44. Tosylate-mediated A-Ring Cyclization Sequence.



corresponding tosylate **188** proceeded smoothly and the desired product was found to be quite stable. In fact, tosylate **188** even withstood chromatographic purification unlike the previous mesylate. However, if **188** was left in solution for too long a period of time, decomposition was observed within a few hours at 25 ^{o}C. Interestingly, this decomposition pathway had been described earlier and exploited by Kutney.[105] For our purposes, the conversion of **188** to **191** required a prompt reaction with base. Excess base was also used to facilitate *in situ* epimerization of the AB-ring juncture. Thus, exposure of tosylate **188** to *t*-butoxide in chilled benzene furnished the desired cylindricine tricyclic array **191** as a single diastereomer in 69% yield. This three-step sequence (**187→191**) proceeded in noticeably improved yields over the first-and second-generation A-ring cyclizations.

By close analogy to the earlier studies with mercuric acetate, the oxidation

Scheme 45. Oxidation of Tricycle (191) Toward Completion of (±)-Cylindricine C.



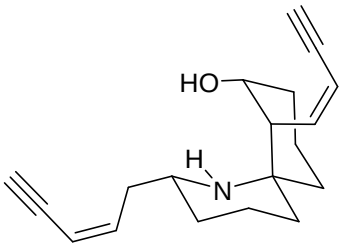
of the cylindricine azacycle **191** proceeded in excellent yield to produce vinylogous amide **192** (Scheme 45). As anticipated, *n*-hexyl cuprate attack prefers to approach from the least-hindered pseudoequatorial face of tricycle **192** to give a 7:1 mixture of cylindricine benzoyl esters in favor of the natural cylindricine geometry at C-2. The mixture of benzoyl esters was saponified to produce the natural product (±)-**77c** as well as its unnatural epimer (±)-2-*epi*-**77c** directly. The natural product was purified, isolated, and fully characterized. This sample of synthetic (±)-cylindricine C exhibited characterization data completely identical to that of the natural product.[61]

In summary, a novel synthetic approach to the marine alkaloid (±)-cylindricine C ((±)-**77c**) was developed. The key element of the synthesis consists of a Michael addition/dipolar cycloaddition cascade of 2,3-*bis*(phenylsulfonyl)-1,3-butadiene (**69**) and oxime **142**. Although reduction of the resulting cycloadduct proceeded smoothly, protection issues associated with a sterically crowded 2,2-dialkylpiperidone nitrogen atom prohibited entry to this alkaloid class. By using a stereoselective reductive-cyclization cascade, the resulting BC-ring skeleton was converted into cylindricine C by a base-induced cyclization to construct the tricyclic core, followed by an oxidation-conjugate addition of the *n*-hexyl side chain. The oxidation protocol, which was critical to the total synthesis effort, was found to reliably produce the thermodynamically favored unsaturation within the *N*-alkyl-4-piperidone framework. The use of mercuric acetate for this oxidation can be of significant value to the synthetic community, and is currently unreported. Further studies toward the synthesis of related natural product targets using the methodology outlined in this thesis currently underway in our laboratories.

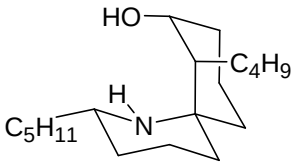
Part 2. Application of the Method toward Perhydrohistrionicotoxin (PHTx).

In 1971, Witkop described 16 azaspirocyclic alkaloids recovered from the skin extracts of the neotropical frog *Dendrobates histrionicus*.[106] Since their discovery, these alkaloids have emerged as important neurophysiological compounds owing to their unusual effects as selective noncompetitive inhibitors of the neuromuscular, ganglionic, and central neuronal nicotinic acetylcholine receptors.[107] The alkaloids of this family share a unique azaspiro[5.5]undecane core structure, and vary only in the length and degree of saturation present in the two side chains, with the exception of the three deoxygenated members.[108] The unique neurophysiological properties of the histrionicotoxin group, coupled with their intriguing structure, have prompted a large number of synthetic approaches towards the core spiropiperidine ring system. This has resulted in a number of

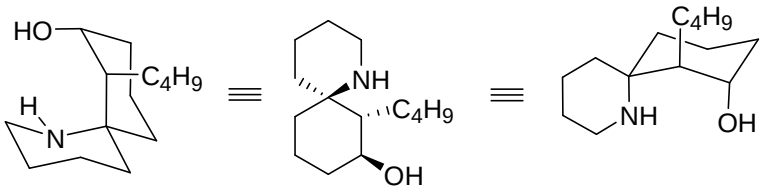
Figure 5. Representative Azaspiro[5.5]undecane Alkaloids.



108; histrionicotoxin (HTx)



193; perhydrohistrionicotoxin (PHTx)

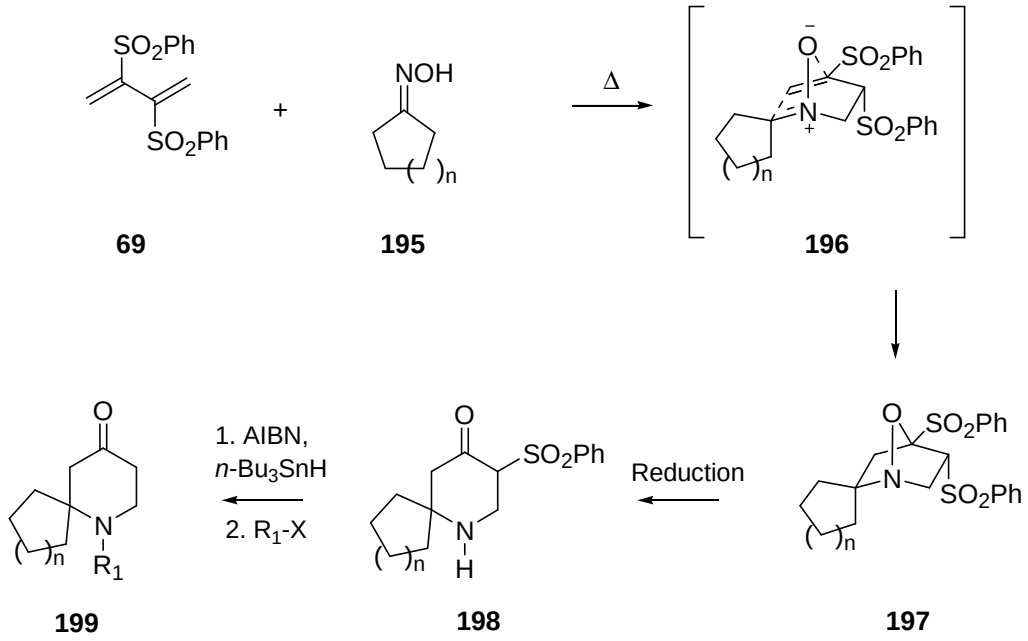


194; desamyl-perhydrohistrionicotoxin (desamyl-PHTx)

imaginative total synthetic efforts to the parent alkaloid histrionicotoxin (**108**; HTx, Figure 5) and its derivatives.[109] Several of the earlier approaches to this alkaloid family have already been discussed in the Introduction section of this thesis. A significant portion of the synthetic effort toward alkaloids of this class has been directed to some of the the unnatural analogues of perhydrohistrionicotoxin (**193**; PHTx) as well as desamyl-perhydrohistrionicotoxin (**194**; desamyl-PHTx).[110] Interestingly, both **193** and **194** exhibit comparable biological activity to the parent natural products, yet possess simplified structures.

Recognizing the need for synthetic methods capable of producing azacyclic congeners of this class of alkaloids, the tandem Michael addition-cycloaddition cascade involving 2,3-*bis*(phenylsulfonyl)butadiene (**69**)[55] presents a reaction platform capable of producing the functionalized azaspiro[5.5]undecane scaffold (Scheme 46). Previous studies have established that the subjection of oximes to dienyl sulfone **69** leads to cycloadducts of type **197** through the intermediacy of a transient nitrone (*i.e.* **196**).[54] Indeed, we have found that treatment of bicyclic **197** with a variety of reducing agents facilitates smooth reduction of the *N*-*O* bond to give piperidones (*i. e.* **198**) in good to excellent yield. The residual phenylsulfonyl group in these structures can be removed by treatment with tributyltin hydride, and the piperidonyl nitrogen can be further derivatized through the use of a wide selection of electrophiles (R_1, Scheme 46). The sequence outlined in Scheme 46 represents a high yielding method for the synthesis of a variety of polysubstituted piperidones (*i.e.* **199**). For ketone-derived oximes resembling **195**, this methodology provides facile access to functionalized 2-azaspirocycles with a high degree of functional group compatibility.

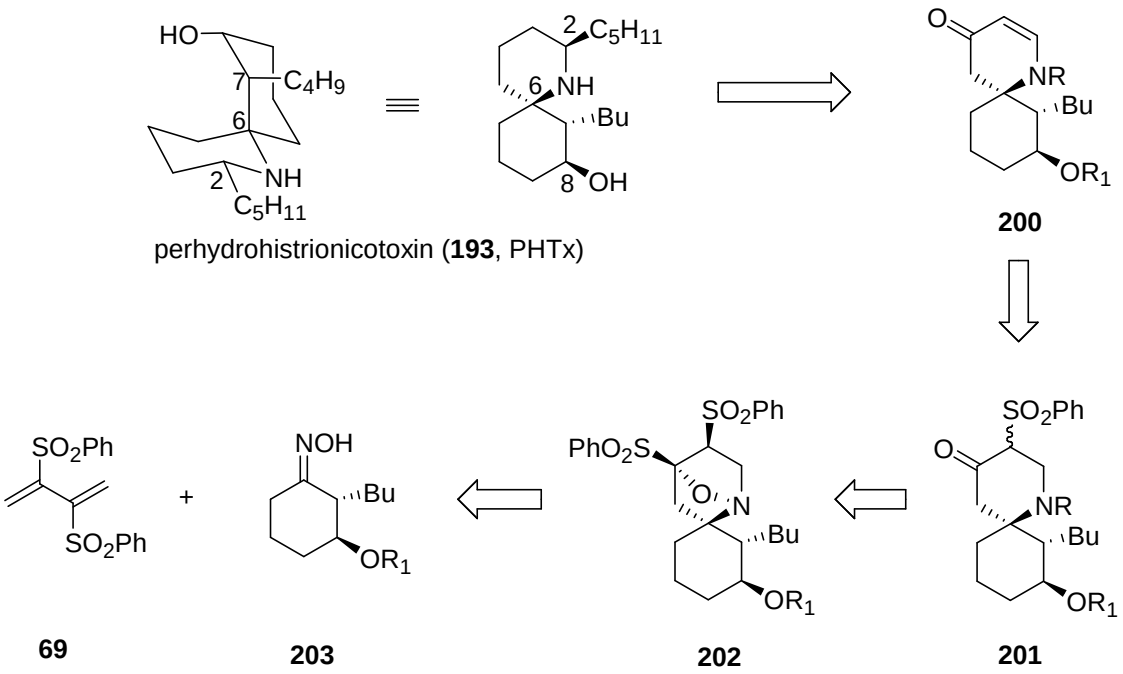
Scheme 46. Michael Addition-Dipolar Cycloaddition Approach to the Azaspiro[5.5]undecane Ring System.[54]



The alkaloids represented in Figure 5 contain the key azaspiro[5.5]undecane ring system. Therefore, the synthesis of various members of this alkaloid class would further highlight the utility of the tandem Michael addition-cycloaddition manifold outlined in Scheme 46. We envisioned the synthesis of **193** (PHTx, Scheme 47) arising from a stereoselective 1,4-alkylmetal addition to the vinylogous amide **200**. The *n*-pentyl group would predictively approach from the least-hindered face of the π-array within this system to give the natural product geometry at C-2. Piperidone **200** could be obtained from α-keto sulfonyl piperidone **201**, which corresponds to the reduction product of cycloadduct **202**. This bridged isoxazoline **202** would effectively come about from the condensation of oxime **203** and *bis*-sulfone **69**. In the retrosynthetic sense, an oxime equipped with a pre-existing functionality (**203**, Scheme 47) might also influence the diastereoselectivity of the cycloaddition. In

the event that the undesired stereochemistry resulted from the cycloaddition, the stereorelationship present in oxime **203** could be reversed at an earlier stage of the synthesis. Guided by this synthetic strategy, the synthesis of an oxime bearing the requisite stereorelationship at the incumbent C-7 and C-8 histrionicotoxin carbon centers was undertaken.

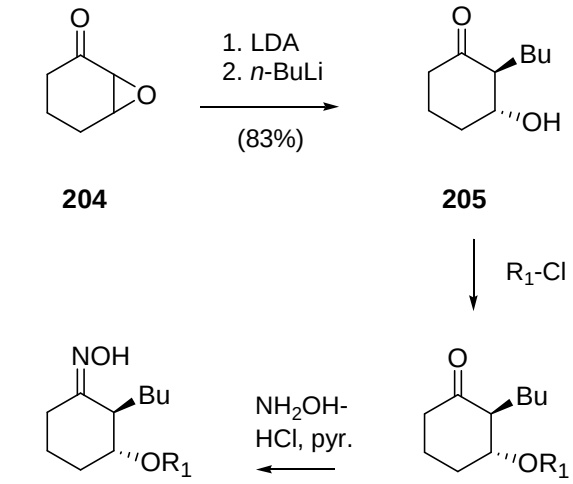
Scheme 47. Retrosynthetic Dissection of Perhydrohistrionicotoxin.



Earlier studies by Wender suggested that a facile, stereocontrolled entry to the starting oxime could be achieved by means of an epoxide ring opening involving ketone **204** (Scheme 48).[111] Therefore, the initial stereochemistry was established using a directed addition of *n*-butyllithium to the known epoxide **204**[112] producing ketoalcohol **205** possessing the relative stereochemistry shown in Scheme 48. At this point, alcohol **205** was protected with a TBS group. This protective functionality was chosen on the basis of its ability to tolerate the

thermal, reductive, and oxidative conditions necessary to furnish the intended late-stage azaspirocycle.[113] However, we were also aware of earlier 4-piperidone *N*-protection/deprotection issues which were dependent on the degree of steric crowding about the nitrogen atom, as well as literature examples of such difficulties.[69] To preemptively counteract such possible problems, a supplementary ketone (**207**) was also prepared using the less-bulky methoxylmethyl (MOM) ether as a latent alcohol functionality. Ketones **206** and **207** were each treated with hydroxylamine hydrochloride to furnish oximes **208** and **209** in good yields.

Scheme 48. Assembly of Oximes 208 and 209.



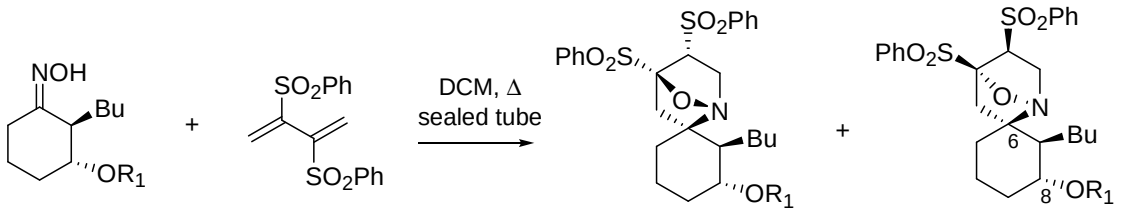
208; R_1 = TBS (94%)
209; R_1 = MOM (96%)

206; R_1 = TBS (73%)
207; R_1 = MOM (93%)

After extensive experimentation, optimized conditions to facilitate the Michael addition-cycloaddition cascade sequence were realized and this involved using a refluxing solution of dichloromethane in a sealed tube. The silylated cycloadducts **210** and **211** (Scheme 49) were produced as a 3:2-mixture of

diasteromers in 52% overall yield. The relative configuration of the diastereomeric products were confirmed by x-ray crystallographic data. Despite the low yields of the tandem Michael addition step, the reaction proceeded with high stereocontrol generating the desired azaspirocyclic geometry at the histrionicotoxin C-6 center. This selectivity can be attributed to the Michael acceptor diene (**69**) approaching the oxime from a trajectory which avoids steric interaction with the proximal *n*-butyl group.

Scheme 49. Stereoselective Tandem Michael Addition-Cycloadditions of Oximes 208 and 209.



208; R_1 = TBS
209; R_1 = MOM

69

210; R_1 = TBS (31%)
212; R_1 = MOM (34%)

211; R_1 = TBS (21%)
213; R_1 = MOM (34%)

X-ray crystal structure data of cycloadducts **210** (Figure 6) and **211** (Figure 7) revealed that we had generated the opposite relative stereochemistry at both the incipient C-7 and C-8 histrionicotoxin centers (Figure 6). This problem had also been previously encountered by Godleski.[114] To counteract this difficulty, a *bis*-epimerization sequence was devised by Godleski which allowed him to achieve the correct stereochemistry about these vicinal carbon centers. For our purposes, the Godleski sequence was envisaged to be utilized at a later synthetic stage.

Figure 6. ORTEP Representation of 210.

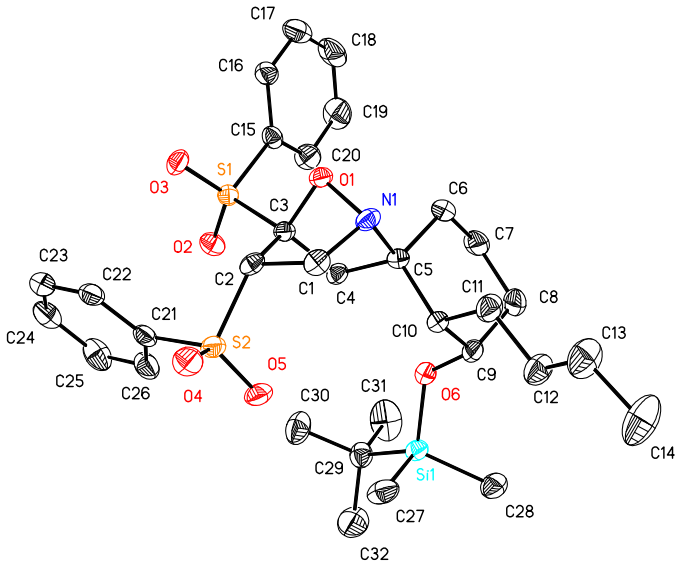
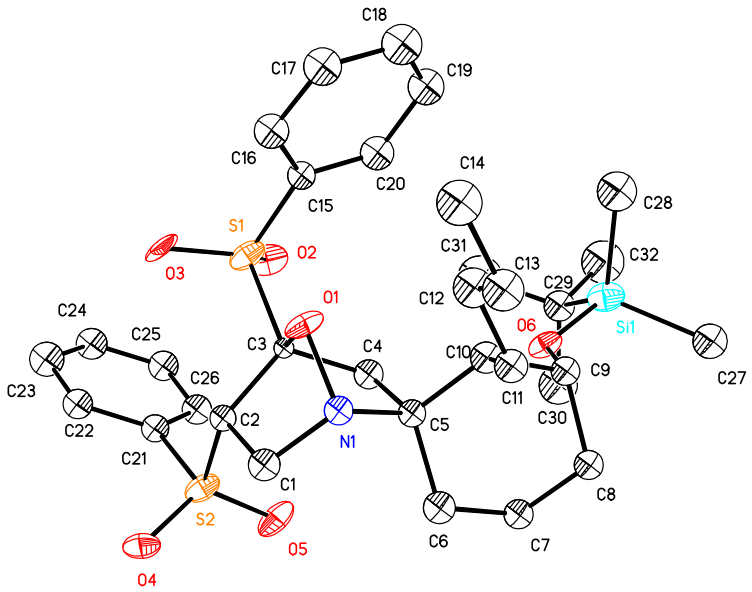
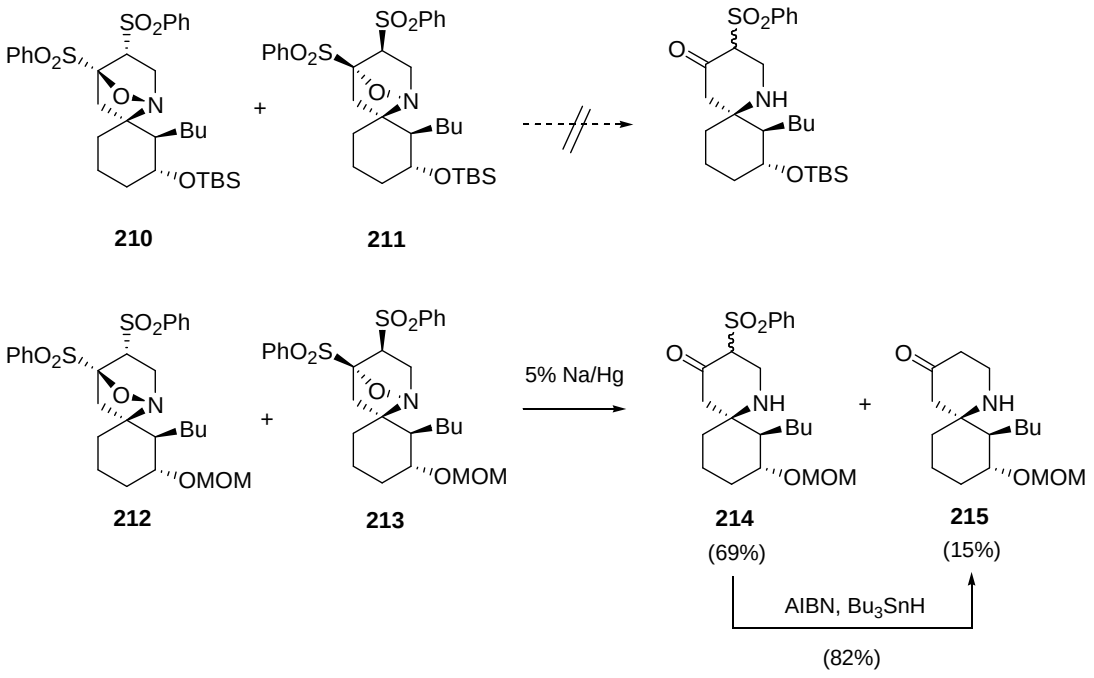


Figure 7. ORTEP Representation of 211.



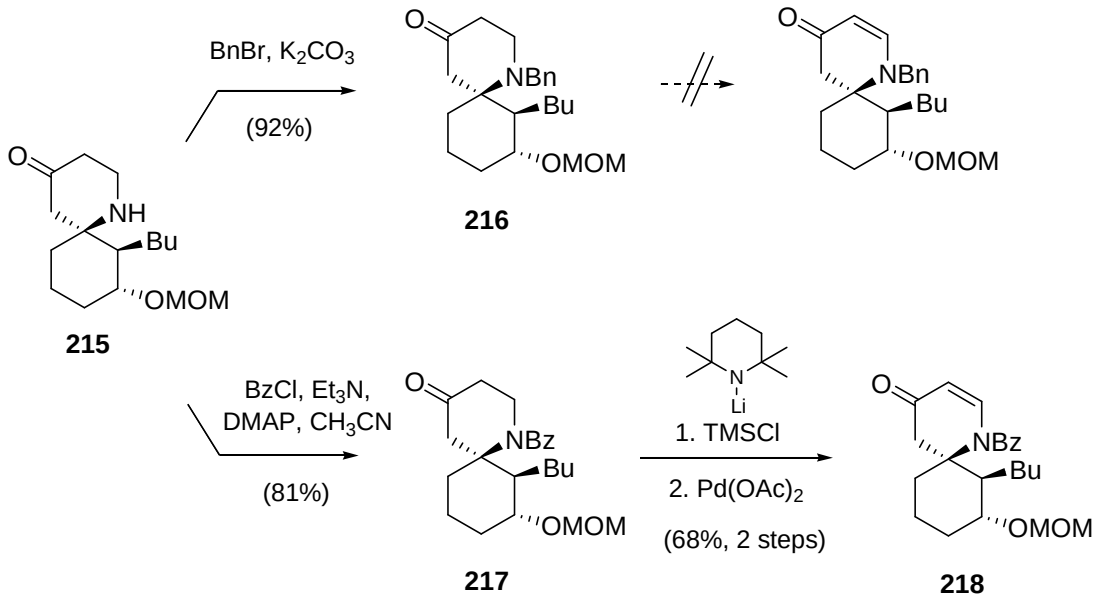
Each of the silylated cycloadducts produced in Scheme 50 (**210**,**211**) differ only in terms of the oxo bridge stereochemistry, and which were envisioned to be destroyed during the reductive cleavage step. Therefore, separation of the mixture was deemed to be unnecessary. Unfortunately, all of our attempts at reductive *N*-*O* cleavage of the mixture of **210** and **211** (Scheme 50) were unsuccessful, leading only to recovered starting material or decomposition products. The steric bulk of these densely functionalized azaspirocycles is likely responsible for the lack of desired reactivity. By contrast, *N*-*O* bond reduction of the less-hindered MOM-protected cycloadducts **212** and **213** proceeded smoothly. Thus, the reduction of these azaoxabicycles proceeded smoothly using 5% sodium-mercury amalgam in THF and returned piperidone **214** in 69% yield, along with some the over-reduced product **215**. Further desulfonation of **214** provided the key azaspiropiperidone **215** in high yield.

Scheme 50. Reduction of Bicycloadducts 210-213.



With **215** in hand, *n*-pentyl installation at the C-2 position was pursued. The functionalization of this 4-piperidone system necessitated the generation of an α,β-keto unsaturation within this ring system. However, when the piperidone nitrogen atom was benzylated (**216**, Scheme 51), the requisite enone was not formed using standard oxidation conditions. To circumvent this problem, protection of the nitrogen as the benzoyl amide **217** allowed for easy oxidation by means of a Saegusa protocol.[115] This difference in observed reactivity is presumably related to the availability of the lone pair of electrons on the amine nitrogen which interferes with the oxidative reaction pathways designed to bring about the unsaturation.[116] Mercuric acetate was not attempted for this system.

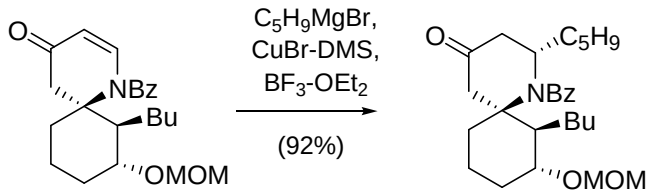
Scheme 51. Azaspirocycle N-alkyl/N-acyl Ring Oxidation Dichotomy.



Introduction of the final stereocenter was accomplished by treating vinylogous amide **218** with pentylmagnesium bromide, copper bromide-dimethylsulfide complex, and boron trifluoride diethyletherate. This reaction

provided piperidone **219** (Scheme 52) as a single diastereomeric product in excellent yield. The stereochemical nature of the C-2 carbon center could not be easily determined through conventional NMR spectroscopic techniques. Therefore, it was necessary that ketone **219**, which existed as an oil, be derivatized as a crystalline solid.

Scheme 52. Stereospecific C-2 Side Chain Installation.

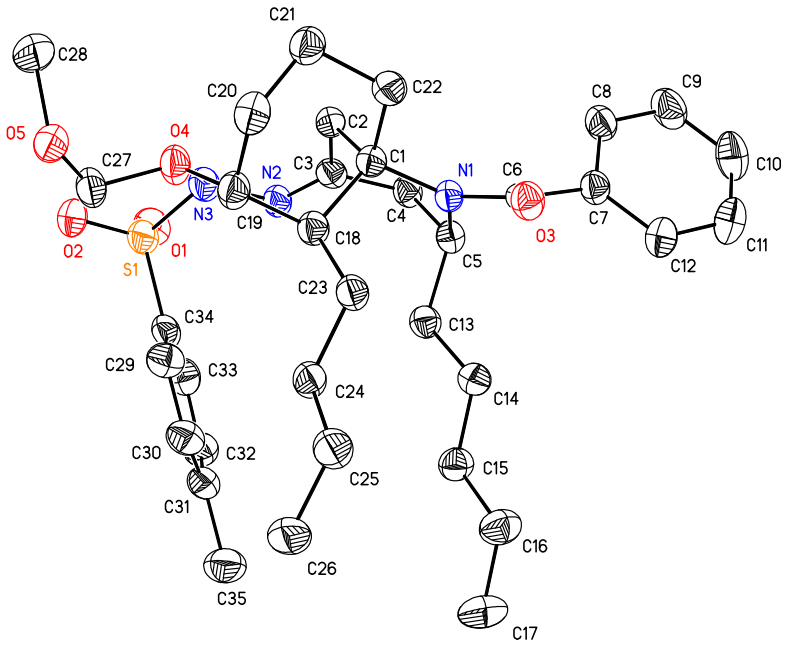


218 **219**

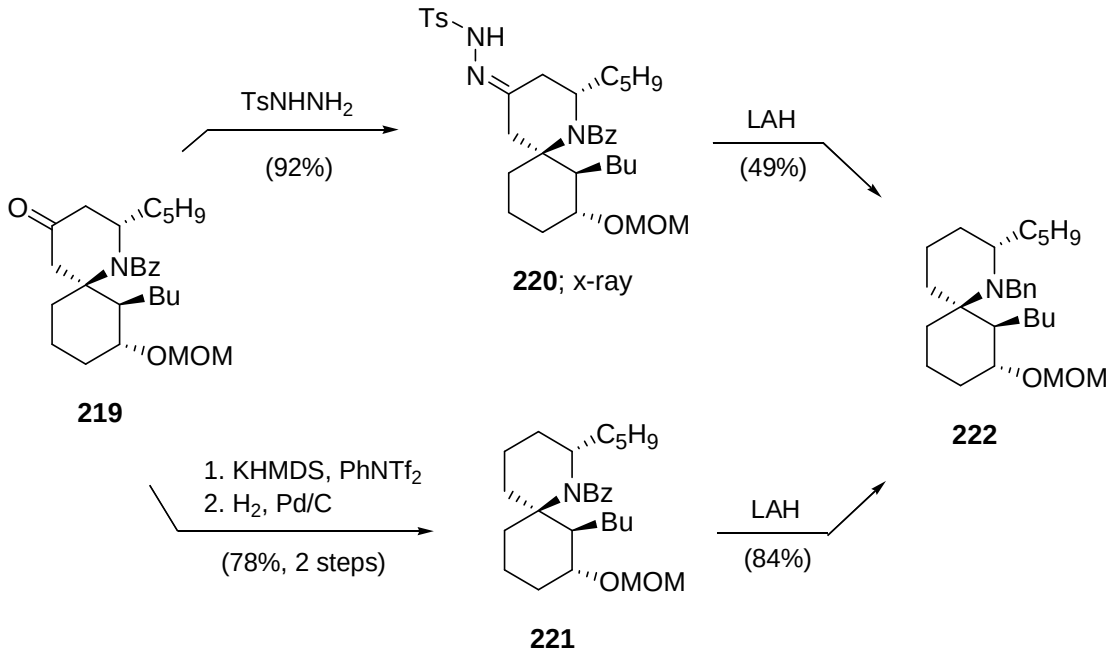
In addition to crystal structure generation, reduction of the ketone functionality at C-4 within **219** was also necessary at this stage of the synthesis. Both issues were addressed through the sequence of reactions described in Scheme 53. Condensation of ketone **219** with tosyl hydrazine led to the corresponding hydrazone **220**, which existed a crystalline solid capable of X-ray examination.

Regarding the cuprate addition step, the resulting ORTEP representation of hydrazone **220** (Figure 8) confirmed that the nucleophilic 1,4-addition had resulted in the formation of the axial side chain stereochemistry at C-2. As evidenced by the results of the pentyl group installation, the steric constraints of the enone **218** (Scheme 52) dictated a single trajectory for *n*-pentyl addition step onto the π-array.

Figure 8. ORTEP drawing of Hydrazone 220.



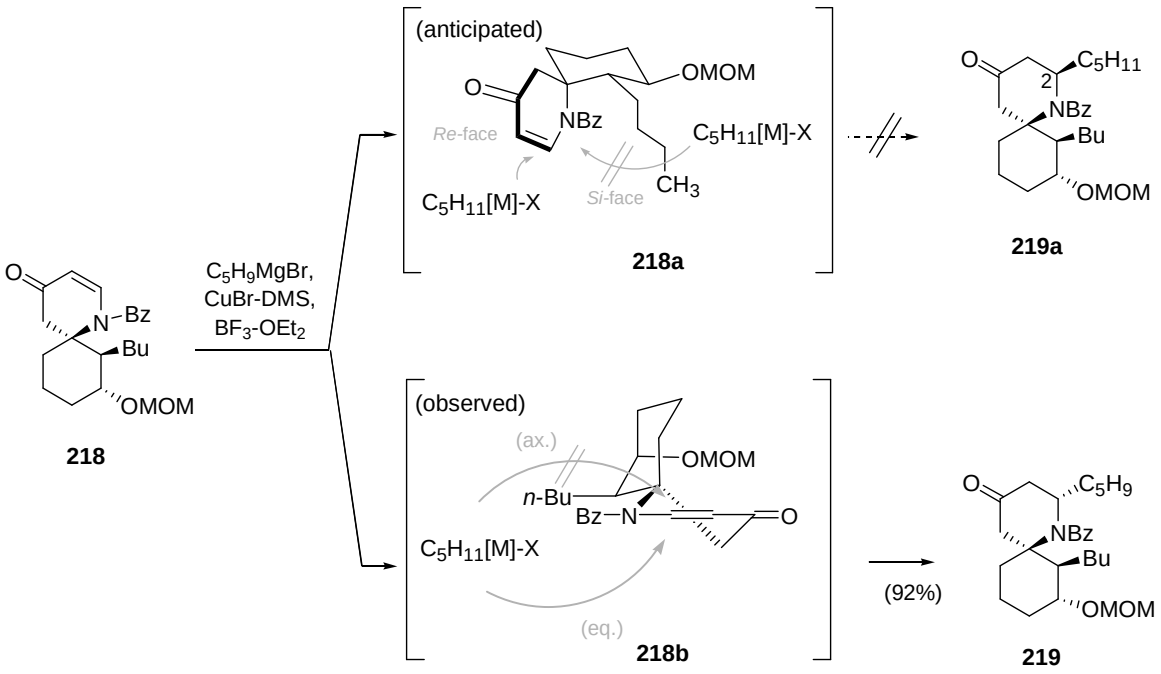
Scheme 53. C-4 Carbonyl Reduction Paradigm.



Subjecting hydrazone **220** to LAH (Scheme 53) converted the carbonyl functionality at C-4 to a methylene group with concomitant reduction of the benzyl amide, resulting in the isolation of *N*-benzyl spirocycle **222**. However, in order to have ample quantities of late stage azacycle for the final Godleski epimerization step, yields obtained with this sequence required optimization. Toward this end, trapping the enolate formed from ketone **219** with Comins' reagent (*N*-phenyltriflamide)[117] followed by hydrogenation resulted in smooth reduction of the carbonyl functionally at C-4 and gave amide **221**. This amide could be easily converted to the corresponding amine **222** via treatment with LAH.

It was originally assumed that approach of the cuprate would occur from the least hindered pseudoequatorial *Re*-face of the π-array (**218a**, Scheme 54). We thought that this supposed trajectory would minimize cuprate interaction with

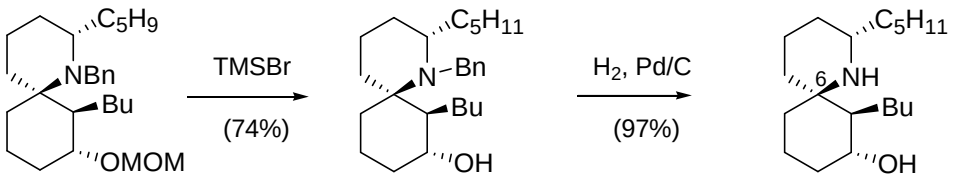
Scheme 54. Rationale for Stereospecific 1,4-Addition to 218.



the butyl group at C-7 and deliver the anticipated C-2 adduct **219a**. Rather, the observed C-2 product (**219**) suggests that the π-array of **218** exists in the conformation as drawn (**218b**) in Scheme 54. Steric repulsion between the butyl group at C-7 and the *N*-benzyl amide—which is involved in extended conjugation with the vinylogous amide functionality and is therefore rigidly planar—forces the π-array to be more prone to attack from a pseudoequatorial approach. The incoming cuprate reagent prefers to minimize interaction with the carbocyclic group which directs nucleophilic attack to the *Si*-face of **218b**. Related stereochemical results have been reported by the Comins group.[118]

The pentyl group geometry at C-2 (Scheme 55) therefore represented an opportunity to construct 6-epi-PHTx (6-epi-**193**). Towards this end, compound **222** was deprotected using trimethylsilylbromide and this was followed by palladium-catalyzed hydrogenolysis to furnish 6-epi-PHTx (6-epi-**193**) in good yield.[119]

Scheme 55. Synthesis of 6-*epi*-PHTx.



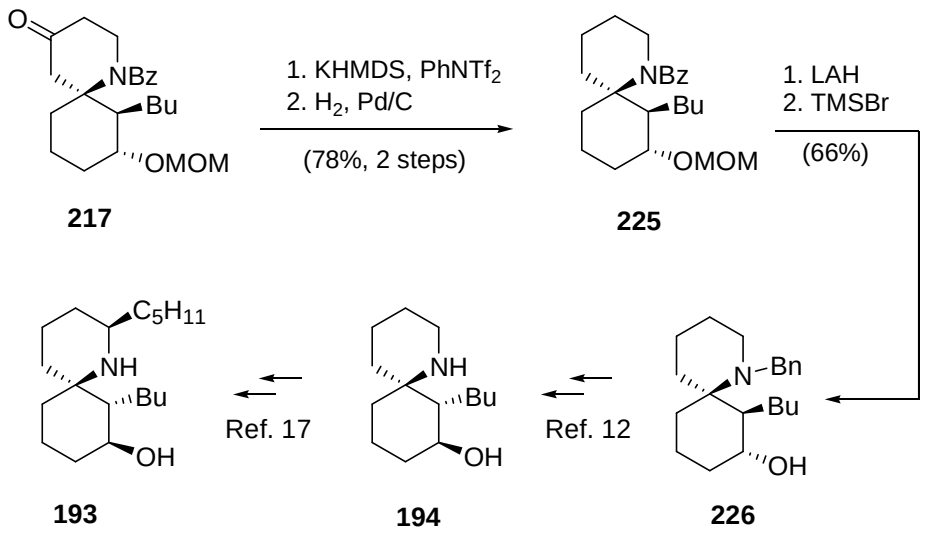
222 **223** 6-*epi*-**193**

6-*epi*-perhydrohistrionicotoxin

The interception of the Godleski intermediate **226** (Scheme 56) from ketone **217** represents a formal synthesis of (±)-desamyl-PHTx (**194**).[114] Sequential decarbonylation, MOM-removal, and oxidation state adjustment of the *N*-protecting group within piperidone **217** was required. Toward this end,

conversion of ketone **217** to the corresponding enol triflate prior to hydrogenation produced benzamide **225** in 78% yield for the two-step sequence. LAH reduction followed by MOM deprotection furnished alcohol **226**, thereby intercepting the Godleski route towards (±)-desamyl-PHTx (**194**).[114] Intermediate **226** also represents an indirect formal synthesis of (±)-PHTx (**193**) since this compound had been earlier synthesized from (±)-desamyl-PHTx (**194**) by Corey and co-workers.[120]

Scheme 56. Formal Synthesis of (±)-Desamyl-PHTx.



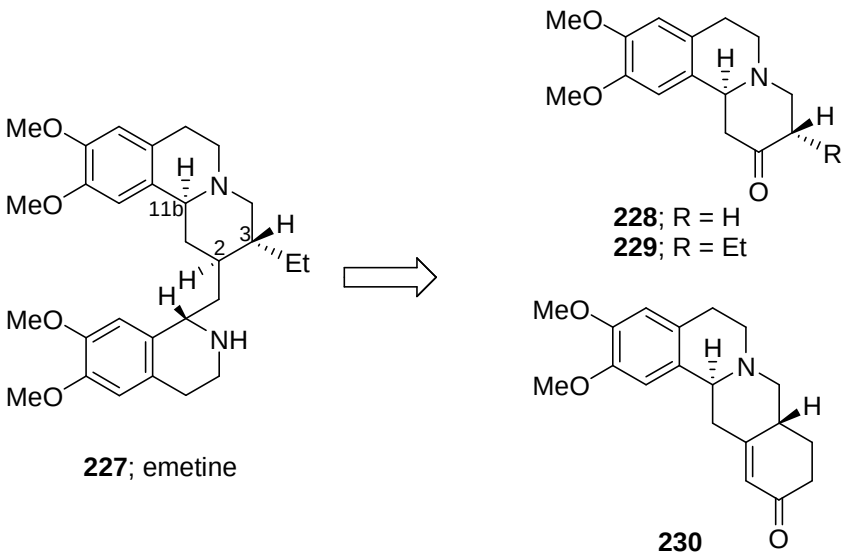
In conclusion, a highly diastereoselective annulation methodology for entry into the azaspiro[5.5]undecane ring system has been demonstrated through a total synthesis of (±)-6-epi-perhydrohistrionicotoxin ((±)-6-epi-**193**) and a formal synthesis of (±)-desamyl-PHTx ((±)-**194**). The key features of the synthetic route involve: (1) a stereoselective tandem Michael addition-cycloaddition cascade which leads to the highly congested C-6 azaspirocyclic center; and (2) a stereospecific cuprate attack onto a vinylogous amide functionality which

establishes the configuration of the C-2 *n*-pentyl side chain. Application of this methodology towards other azapolycycles is currently underway in the Padwa laboratory and will be reported in due course.

Part 3. Application of the Method to a Formal Synthesis of (±)-Emetine.

The roots of *C. ipecacuanha* have been used for centuries as an emetic, and were subsequently found to show antiamoebic activity.[121] The principal substance found in the root, to which it owes its pharmacological importance, is emetine (**227**, Figure 9). More than a dozen syntheses of emetine have been described to date,[122] and these approaches showcase many elegant and important transformations. Several common synthetic intermediates that have been used for the preparation of emetine and for other related ipecac alkaloids are the benzo[*a*]quinolizidines **228**-**230**. Ketone **229** is a key intermediate in which two of the four stereocenters (*cf*. C-11b, C-3) of emetine are contained. The configurations about these centers in the naturally-occuring benzo[*a*]quinolizidine ring system correspond to the most sterically demanding group at each center being positioned equatorially. A construction of any of the ketones **228**-**230** constitute a synthesis of emetine in the formal sense.[123] Piperidone **229** is the most commonly used intermediate amongst the formal synthetic approaches reported to date. One of the more creative entries to

Figure 9. Common Synthetic Intermediates in the Preparation of Emetine (227).



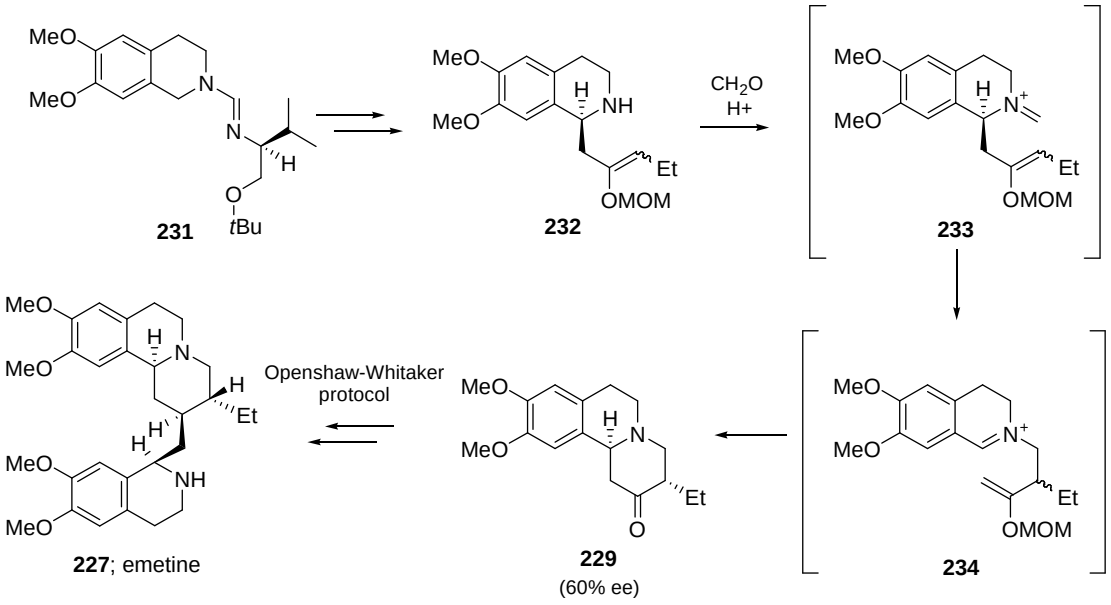
227; emetine

228; R = H
229; R = Et

230

intermediate **229** was described by Meyers in the early 1990s (Scheme 57).[124] Beginning with this laboratory's characteristic formamidine chiral auxiliary **231**, isoquinoline **232** was constructed in the asymmetric sense. Condensation of this amine with formaldehyde in the presence of acid triggered an aza-Cope-Mannich cyclization sequence which resulted in the formation of intermediate **229** which had been previously used for a synthesis of emetine (**227**).[125] Although the stereoselectivity of this transformation was rather low (60% ee), gram-scale material was synthesized through this very tractable synthetic route.

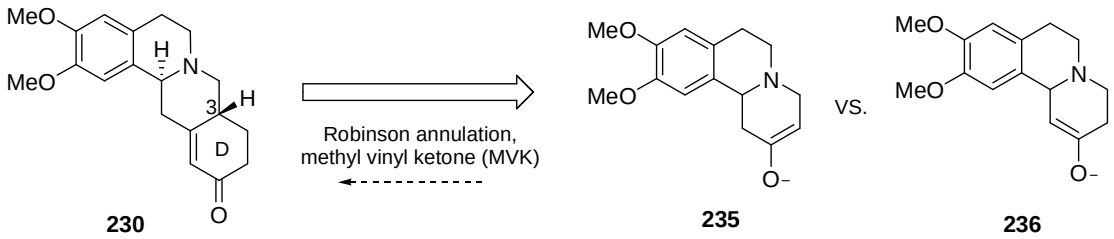
Scheme 57. Meyers' Approach to Emetine Intermediate 229.



One of the more significant synthetic challenges for the construction of ketone **230** (Scheme 58) is the regioselective Robinson annulation at the C-3 position of the benzoquinolizidine precursor (**235** or **236**). Efficient D-ring elaboration requires preferential enolate formation at the incipient C-3 emetine

carbon center (*e. g.* **235**) to avoid undesired alkylation products arising from the undesired enolate (**236**).

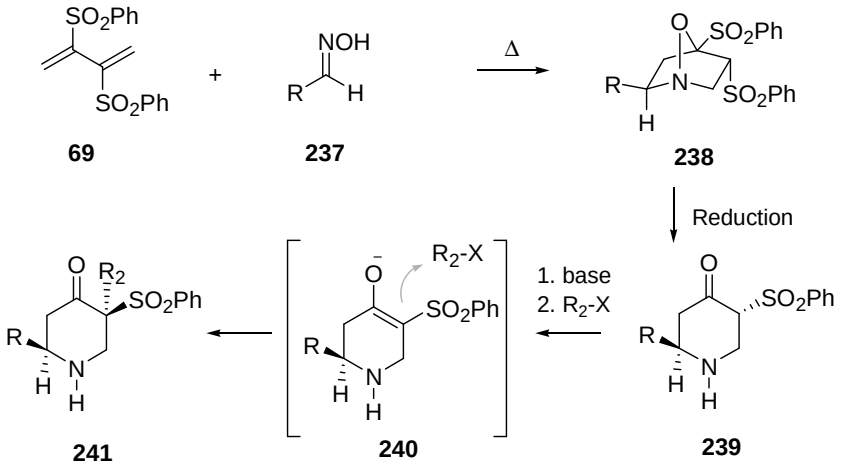
Scheme 58. Robinson Annulation Approach to Emetine Intermediate 230.



230 **235** **236**

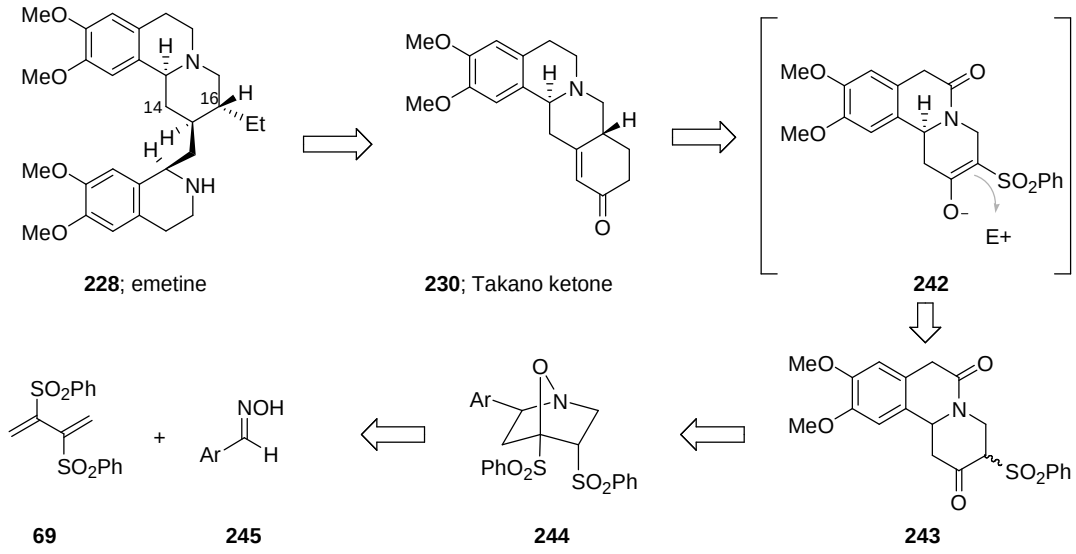
Toward this end, a benzoquinolizidine possessing a α-phenylsulfonyl group should allow for selective enolate generation at the C-3 position. In earlier parts of this thesis, a description of the synthetic utility of the tandem Michael addition-cycloaddition reaction platform was outlined. This involved the use of 2,3-*bis*(phenylsulfonyl)-1,3-butadiene (**69**, Scheme 59)[55] for the synthesis of the functionalized 4-piperidone scaffold **241**.[54] With the earlier results as a background, we became interested in making use of the α-keto phenylsulfonyl functionality for a synthetic entry to emetine. Oxazabicycle **238**, which is formed from the condensation of **69** with the appropriate aldehyde oxime (**237**), should be easily converted to ketosulfone **239**. Further reaction with an electrophile would be expected to provide the desired α-keto alkylation product **241**. The highly enolizable α-ketosulfonyl carbon center would also allow the benzoquinolizidine system to adopt the thermodynamically most favored stereochemical configuration.

Scheme 59. Tandem Addition Approach to α-Phenylsulfonyl 4-piperidones.[54]



In the retrosynthetic sense (Scheme 60), synthesis of the Takano ketone[126] (**230**) by a Robinson annulation of α- ketosulfone **243** would constitute a formal synthesis of emetine (**228**). Piperidone **243** would be the reduction product derived from cycloadduct **244**, thus reducing the task to construction of

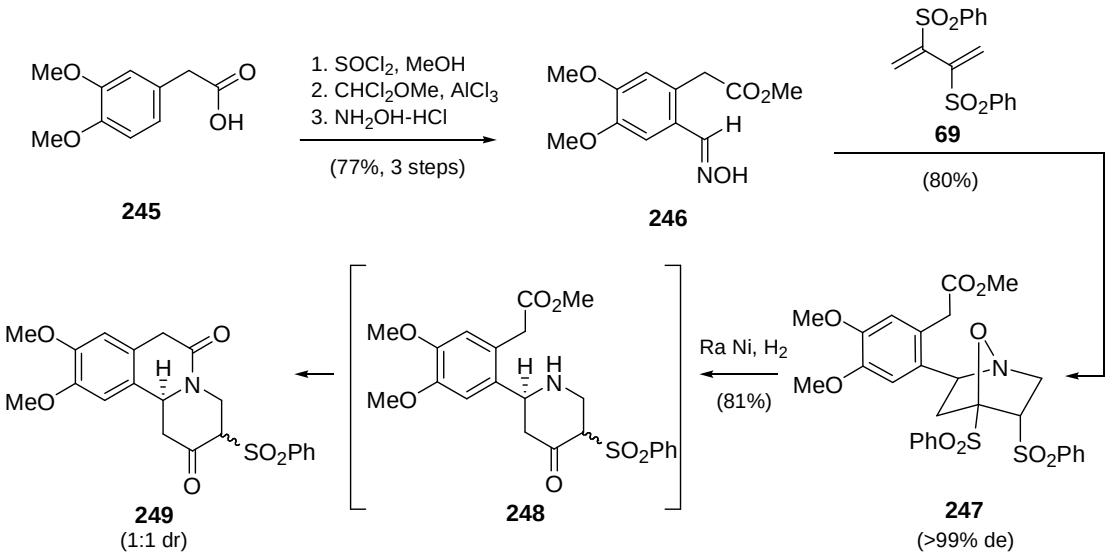
Scheme 60. Retrosynthetic Approach to (±)-Emetine.



the key oxime precursor **245**. The advantage of this approach is that the expected regiospecific alkylation involving ketosulfone **243** should arise with minimal dependence on protecting group chemistry. An oxime resembling **245** was then constructed to test the viability of this plan.

Commercially available 2-(3,4-dimethoxy-phenyl)acetic acid (**245**, Scheme 60) was esterified prior to formylation (Scheme 61).[127] The resulting aldehyde was then condensed with hydroxylamine hydrochloride to provide **246** in 77% yield over 3 steps. The stage was now set for the key Michael addition-cycloaddition cascade sequence. Heating a sample of oxime **246** in the presence of diene **69** cleanly afforded cycloadduct **247** in 80% yield. Analogous to the previous observations for aldehyde oximes,[88] the aryl group prefers to adopt an *exo*-orientation relative to the newly formed cycloadduct in the transition state, resulting in excellent selectivity for the diastereoselective formation of **247**. After several attempts to optimize *N-O* reduction conditions to cleave **247**, it was found that subjection of this cycloadduct to Raney nickel under an atmosphere of

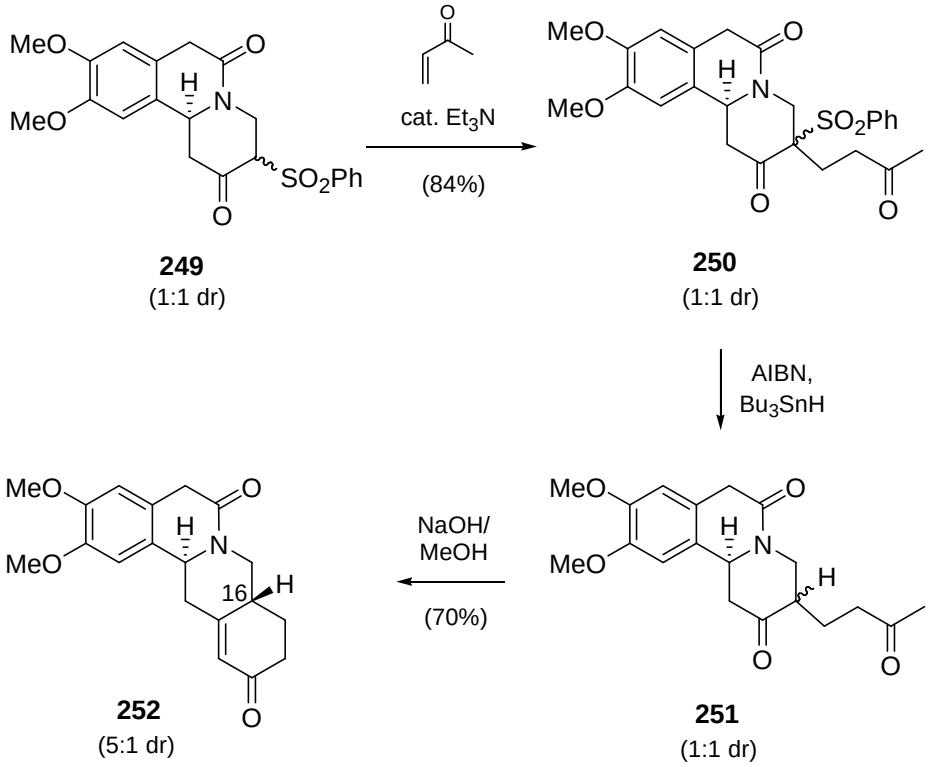
Scheme 61. Synthesis of Emetine Isoquinoline Scaffold 246.



hydrogen ultimately provided a 1:1 mixture of amides **249** in 81% yield. This reduction presumably proceeds through intermediacy of **248**, although this transient intermediate could not be detected as it cyclized very rapidly.

Having benzoquinolizine **249** in hand, the key Robinson annulation step was then implemented (Scheme 62).[128] Conjugate addition of **249** to methyl vinyl ketone (MVK) in the presence of catalytic triethylamine gave an equal distribution of the two possible diastereomeric ketones (**250**) in 84% yield.[129] Although no diastereoselectivity was observed during this alkylation step, the 1:1-mixture of diastereomers was carried forward in the synthetic sequence. Single electron reduction of the phenylsulfonyl group within **250** was expected to facilitate reprotonation from the less hindered face of the heterocyclic array to

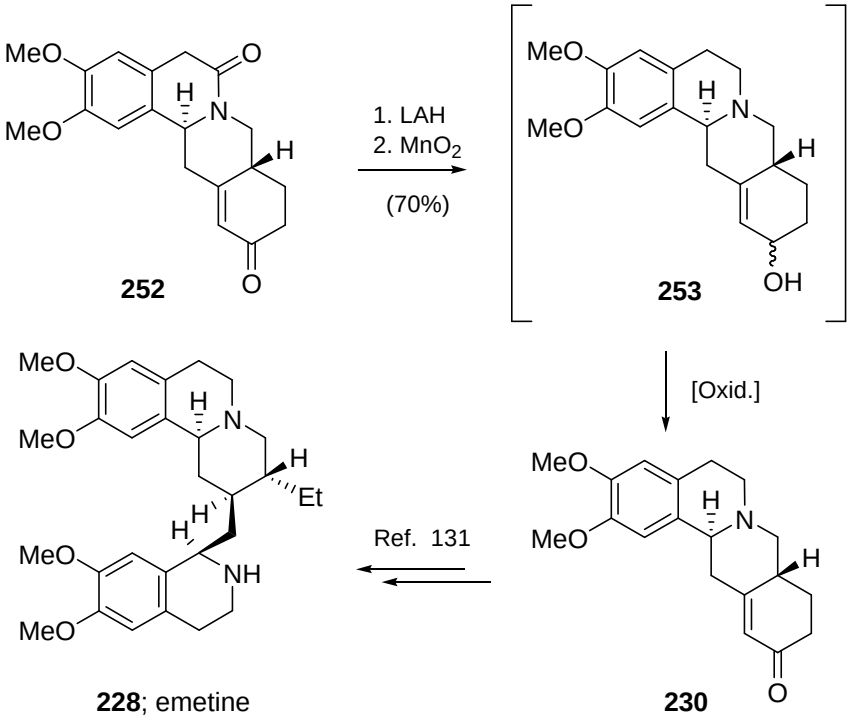
Scheme 62. Robinson Annulation of Isoquinoline 246.



furnish the desired C-3 configuration. In the event, phenylsulfonyl reduction according to the procedure of Smith[91] gave rise to **251** as a 1:1-mixture of diastereomeric amides. Although no selectivity was observed in the generation of **251**, the subsequent Robinson annulation step (**251→252**) gave rise to a 5:1 mixture of diastereomers at this stereocenter within enone **252**. The major stereoisomer was isolated and taken forward to be used for the final reduction of the amide carbonyl group toward the target enone **230**.

Some difficulties were initially encountered with the selective removal of the amide functionality within **252** (Scheme 63). However, treatment with excess LAH effected the desired amide carbonyl reduction, which also gave some of the overreduced alcohol (**253**) in the crude product mixture.[130] A subsequent manganese oxidation of the crude reduction mixture cleanly provided the known enone **230** which corresponds to the same advanced intermediate that the

Scheme 63. Formal Synthesis of (±)-Emetine.



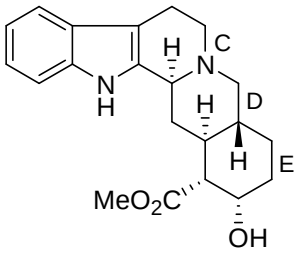
Takano group employed for a synthesis of emetine.[126]

In summary, a formal synthesis of emetine by intercepting the Takano enone **230** is described. The synthetic sequence features the utilization of a tandem Michael addition-cycloaddition cascade using 2,3-*bis*(phenylsulfonyl)-1,3-butadiene (**69**) *en route* to an α-phenylsulfonyl substituted ketone capable of regiospecifically introducing the final target functionality. A late-stage *in situ* epimerization furnished the relative geometry of the emetine alkaloid skeleton at C-3. Further studies toward related alkaloid targets were then carried out.

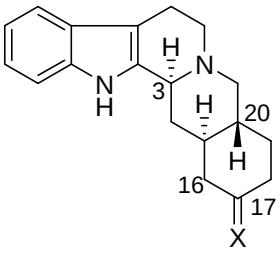
Part 4. Application of the Method to the Synthesis of (±)-Yohimbenone.

Because of their clinical importance as anti-hyertensives, the alkaloids isolated from the West-African evergreen *Pausinystalia yohimbe* have emerged as important pharmacological agents (Figure 10).[131] These complex and architecturally interesting systems have been the subject of a vast number of chemical degradation and synthetic studies. Members of this class of alkaloids possess a pentacyclic ring system bearing various functional groups within the D and E rings. An earlier report by Martin details the historical synthetic efforts dedicated to this class of alkaloids.[132] The basic strategies employed by Martin[15] and Wender[133] to this alkaloid frame involved coupling of a preconstructed DE ring to tryptophyl bromide with all or some of the prerequisite stereocenters in place.

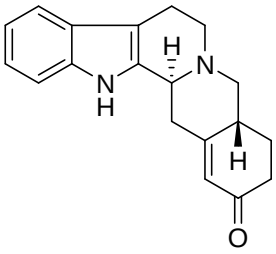
Figure 10. Yohimbenoid Indole Alkaloids.



254; yohimbine



255; X = O; yohimbone
256; X = H_2; yohimbane

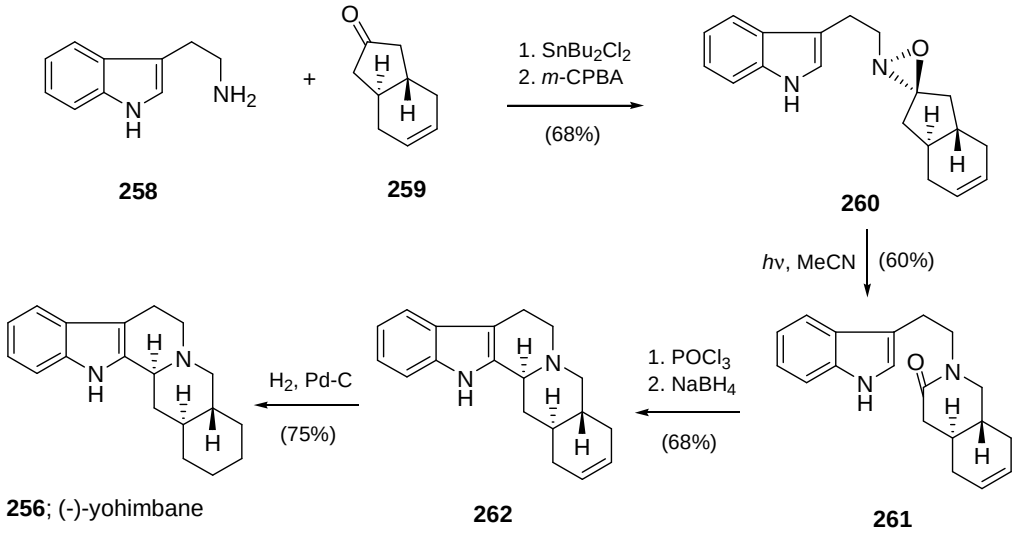


257; yohimbenone

One of the more creative constructions of this alkaloid frame was reported in 1994 by Aube (Scheme 64).[134] In this particular approach, the asymmetrically constructed bicyclic ketone **259** was condensed with tryptamine (**258**) and the resulting imine was subsequently oxidized with *m*CPBA to produce oxaziridine **260**. This strained ring construct underwent ring expansion upon photolysis to produce bicyclic lactam **261** in good yield. A stereoselective Bischler-Napieralski

reaction was then employed to secure the carbon framework of the yohimbane precursor **262**.[135,136] The remaining alkene unsaturation was then subjected to hydrogenation to furnish (-)-yohimbane ((-)-**256**).

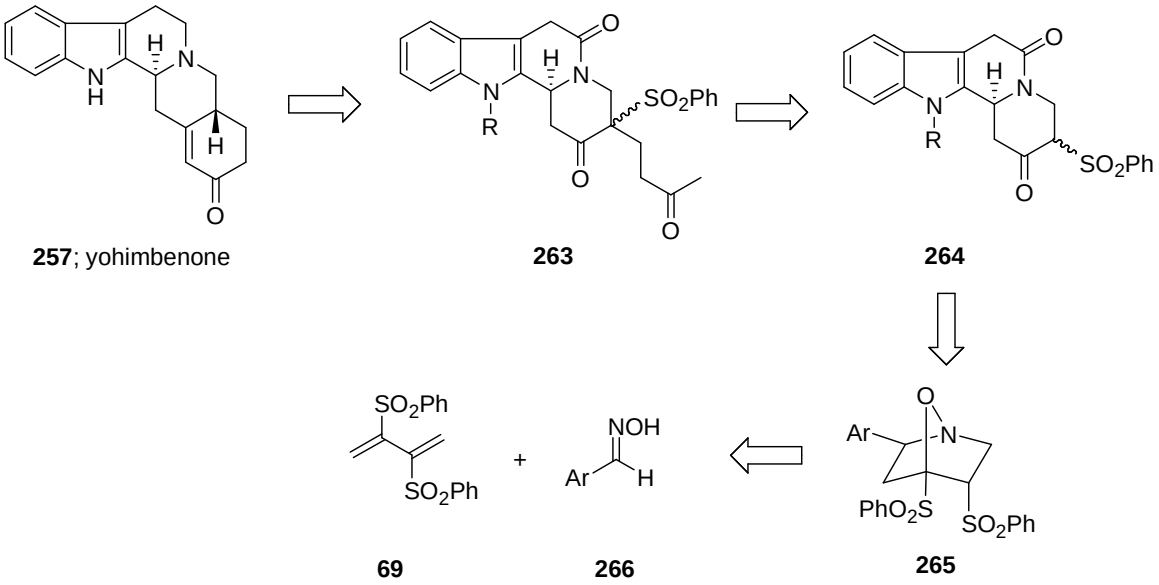
Scheme 64. Aube's Approach to (-)-Yohimbane.



In addition to the previous examples outlined in this thesis, the tandem Michael addition-cycloaddition reaction cascade also presents a potential entry to this class of indole alkaloids.[54] Similar in application to the emetine approach described earlier, an α-keto phenylsulfonyl piperidone (*i. e.* **264**) was the initial target for a synthetic entry to the yohimbenone skeleton. Alkylation of this intermediate with methyl vinyl ketone (MVK) followed by a subsequent Robinson annulation would deliver the BCD-yohimbenone ring system in an efficient manner. Reduction of the phenylsulfonyl group and protecting group modification would then be required to furnish the natural product. Epimerization of the proton at C-20 within this alkaloid system would be facilitated by the neighboring ketone functionality contained within the piperidone **264**. This would permit the ring

system to adopt the thermodynamically more stable conformation relative to the C-3 configuration as had been previously described within the context of the emetine synthesis.

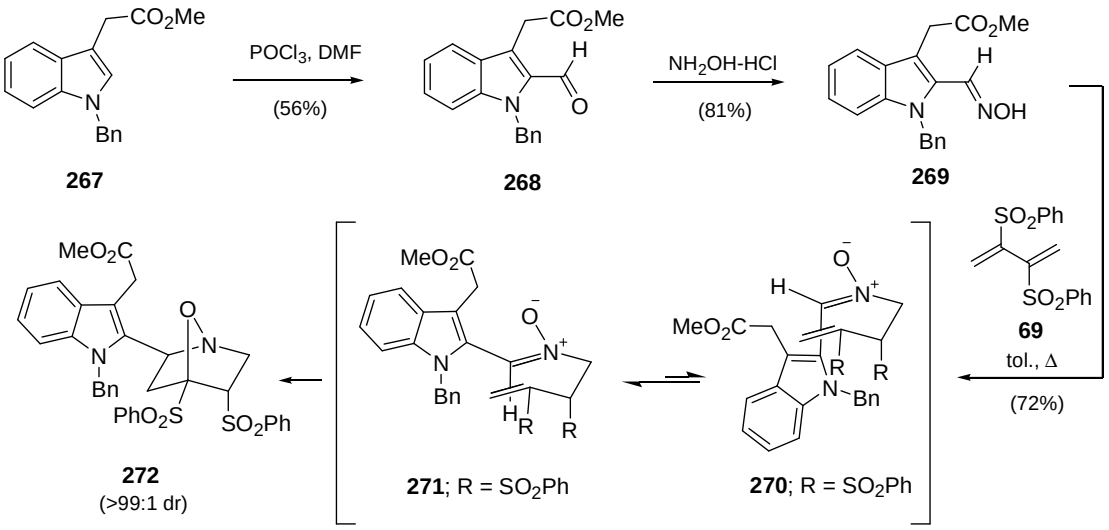
Scheme 65. Retrosynthetic Approach to (±)-Yohimbenone.



We envisioned that a yohimbenone synthesis would require minimal modification of the earlier emetine route. Commencing with the known indole **267** (Scheme 66),[171] carbonylation at the 2-position proceeded through the use of DMF and phosphorous oxychloride. The resultant aldehyde **268** was treated with hydroxylamine HCl to provide the key oxime **269**, which was at this point ready to be used for the critical Michael addition-cycloaddition sequence. Subjection of **269** to *bis*-sulfone **69** in refluxing toluene produced cycloadduct **272**. The excellent diastereoselectivity of this reaction can be attributed to the conformation of the nitrone intermediate in the transition state. Steric interactions between the indole moiety and the proximal phenylsulfonyl groups within **270**

prevent the formation of the *endo*-cycloaddition product. Instead, nitrone **270** equilibrates to the more stable intermediate **271**, positioning the bulky aryl group away from the nearby phenylsulfonyl groups. The product of this cyclization ultimately gave azaoxabicycle **272**, with no detectable amount of any other diastereomeric cycloadduct.

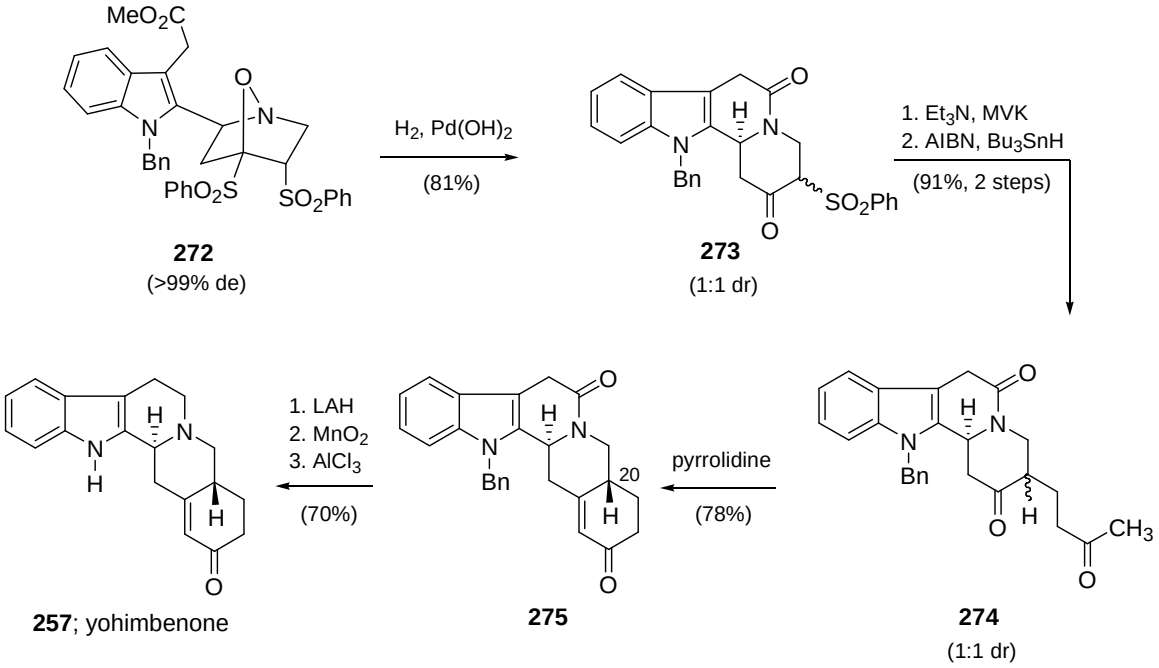
Scheme 66. Synthesis of *N-O*-Cycloadduct 272.



Carrying **272** forward, the smooth reduction of this cycloadduct was accompanied by simultaneous intramolecular amidation using palladium-catalyzed hydrogenolysis (Scheme 67). The resultant carboline, **273**, was obtained as a 1:1-mixture of diastereomers at the α-ketophenylsulfonyl position of the piperidone ring. Carboline **273** was alkylated by treating it with methyl vinyl ketone and catalytic triethylamine and the resulting product was immediately subjected to tin reduction of the sulfonyl moiety to produce the pendant ketone **274** in excellent yield. The diastereomeric mixture present in **274** was subjected to the pyrrolidine-mediated Robinson annulation. The resulting product **275**

possessed the requisite relative geometry of the ABCD ring construct of yohimbenone. As a consequence of the mild pyrrolidine cyclization conditions used to produce **275**, epimerization at the critical C-20 carbon center was observed during this D-ring formation step. Removal of the amide functionality within **275** by LAH reduction produced (±)-yohimibenone (**257**), whose spectroscopic properties exactly matched those reported for the natural product.[137]

Scheme 67. Total Synthesis of (±)-Yohimbenone 230.



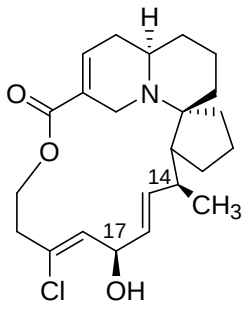
In summary, a concise method has been developed for the synthesis of yohimbenone. The key steps used correspond to: (1) a Michael addition-cycloaddition cascade to generate the arylated *N*-*O*-bicycloadduct **254** and (2) chemoselective Michael addition of methyl vinyl ketone to the privileged α-

phenylsulfonyl piperidone **255**. Application of this methodology toward other alkaloid targets is currently under further study in our laboratories.

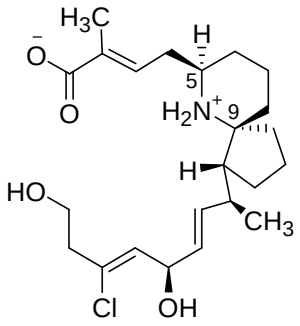
Part 5. Use of the Cascade Method for an Approach to Halichlorine and Pinnaic Acid.

In 1996, Uemura and co-workers reported the isolation and structural characterization of two novel alkaloids. Pinnaic acid (**277**, Figure 11) which was isolated from the Japanese bivalve *Pinna muricata*, was found to be a remarkably potent and specific inhibitor of cytosolic phospholipase A_2 (*c*PLA_2) which plays a key role in regulating inflammation.[138] Halichlorine (**276**), which was isolated from the marine sponge *Halichondria okadai*, was shown to inhibit the expression of vascular cell adhesion molecule-1 (VCAM-1).[139] Consequentially, **276** has potential as a treatment against arteriosclerosis, asthma, and cancer.[140]

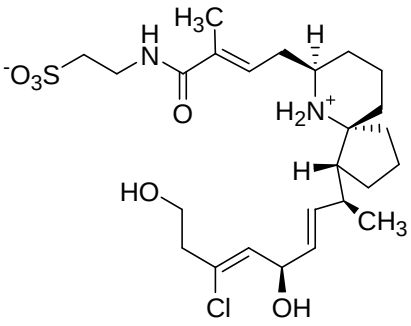
Figure 11. Azaspiro[4.5]decane-containing Natural Products.



276; halichlorine



277; pinnaic acid



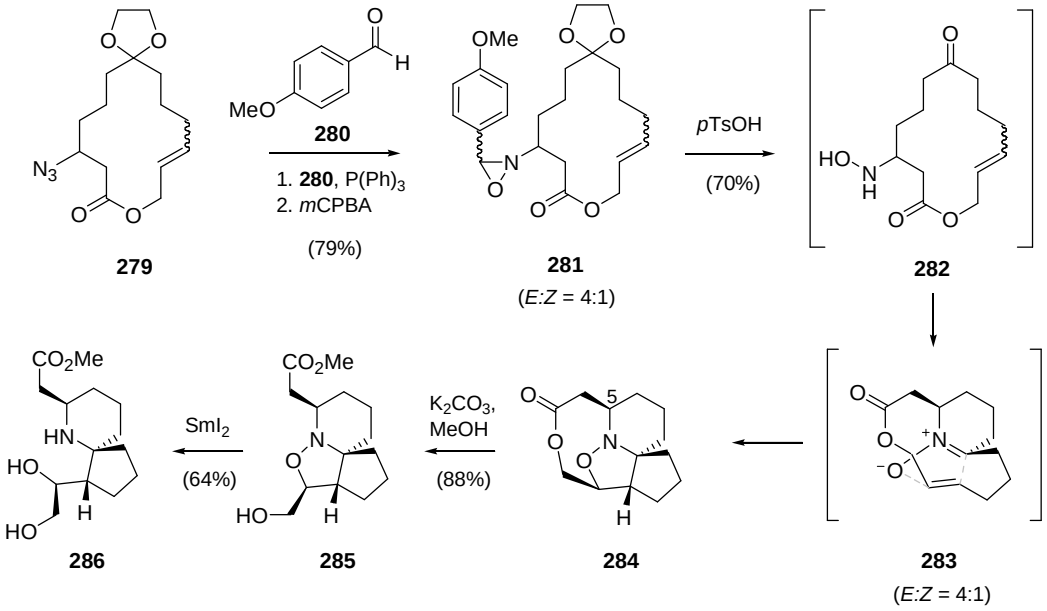
278; tauropinnaic acid

As evident from examination of their structures, pinnaic acid, halichlorine, and tauropinnaic acid (**278**) uniformly possess the azaspiro[4.5]decane ring system. Interestingly, carboxylate **277** and its naturally-occurring relative tauropinnaic acid (**278**) exist as zwitterions. Because of their intriguing structures and biological activities, these alkaloids have attracted considerable attention from the synthetic community. Although a large number of groups have published syntheses for assembling the azaspirobicyclic and azaspirotricyclic cores (many of which have already been outlined in the Introduction section of this thesis),[141]

only two total syntheses of **276**[142,6d] and three total syntheses of **277**[143] have been reported.

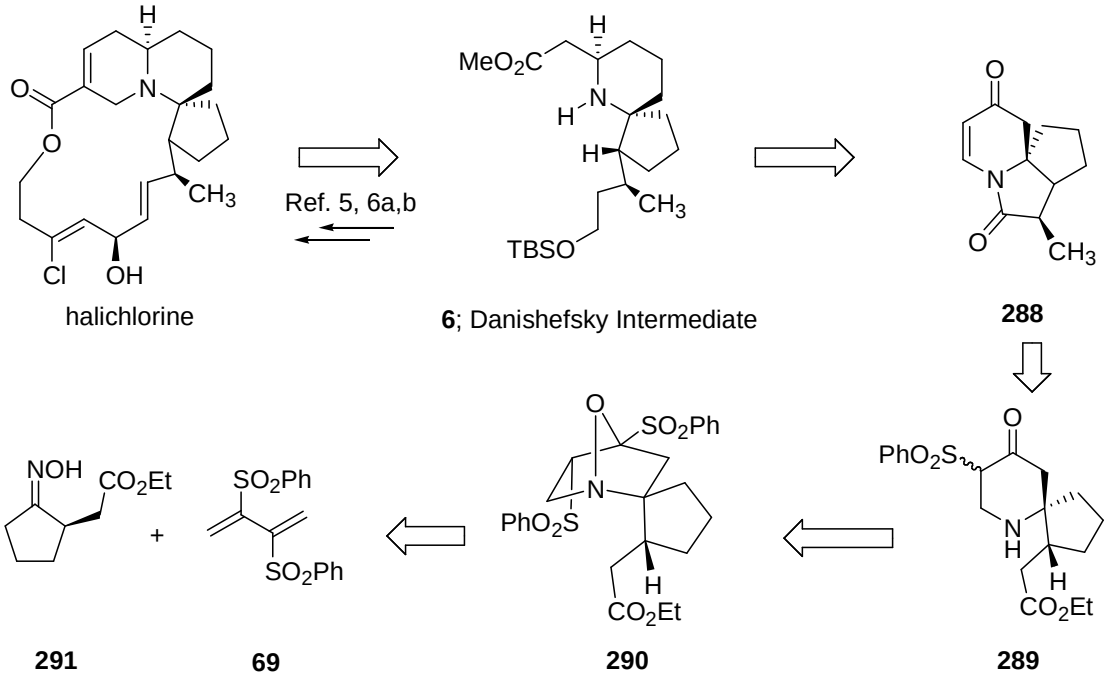
Among the recent contributions, the approach developed by White is noteworthy (Scheme 68).[144] Azide **279** was converted to oxaziridine **281** prior to treatment with tosic acid. The resulting hydroxylamine intermediate **282** underwent condensation intramolecularly with the proximal ketone functionality to produce nitrone **283**. This transient intermediate then cyclized intramolecularly, generating azapolycycle **284**. This complex isoxazolidine structure was subsequently saponified and reduced to furnish azaspirocycle **286**. White's approach is unique because it represents the first reported example of a transannular version of a nitrone adding across a π bond in which both the dipole and the olefin are contained within the same ring. Consequently, a high degree of stereocontrol was observed.

Scheme 68. White's Approach to the Azaspiro[4.5]decane Core of Halichlorine.[144]



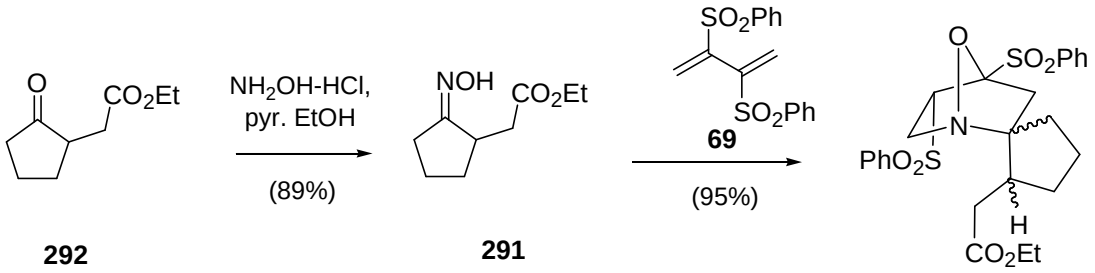
The natural alkaloids **276**-**278** correspond to molecular targets for which we believed the tandem Michael addition-cycloaddition cascade could be used for their synthesis. To simplify the task, interception of the late-stage intermediate **6** (Scheme 69) reported by Danishefsky would represent a formal synthetic entry into this class of natural alkaloids.[5,6a,b] The general reaction platform by which azaspirocycles (*i. e.* **289**) can arise from the subjection of oximes to dienyl sulfone **69** has been described earlier in this thesis. Given that the *N*-*O* cycloadducts (*i. e.* **290**) can be formed diastereospecifically, a high degree of stereocontrol is incorporated in this approach toward halichlorine. Also, a facile asymmetric synthesis of this target could come about from this reaction platform if the starting oxime **291** possessed preexisting chirality.

Scheme 69. Retrosynthetic Approach to Halichlorine.



In order to probe the likelihood of success of an eventual synthesis of halichlorine, oxime **291** was prepared from the corresponding ketone **292** (Scheme 70).[145] Subjecting oxime **291** to dienyl sulfone **69** in refluxing toluene gave rise to a diastereomeric mixture of cycloadducts **290** in excellent yield.

Scheme 70. Generation of a Mixture of Spirocyclic Cycloadducts 290.

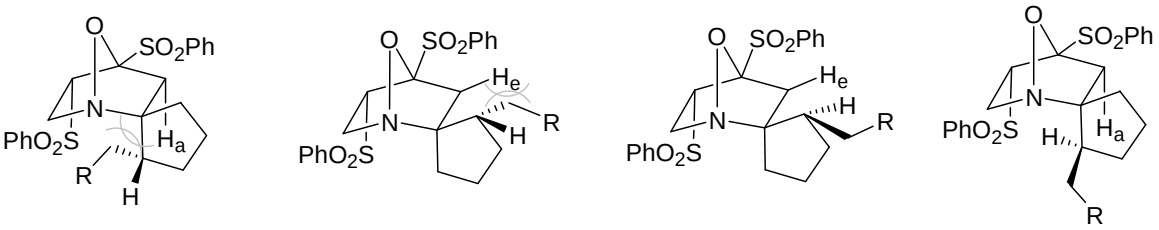


292 **291** **290**

Although four possible diastereomers are possible from the reaction of **69** and racemic **292**, only two products were observed. A rationale for the observed selectivity for this cycloaddition is depicted in Scheme 71. Steric repulsion between the methylene ester group and the adjacent axial cycloadduct proton (H_a) prevents the formation of the densely crowded system present in **290A**. Similarly, **290B** is not formed due to the unfavorable interaction of the *exo*-methylene proton (H_e) with the methylene carboxylate group. Cycloaddition products are obtained when the methylene ester is positioned away from the cycloadduct system (**290**-*major* and **290**-*minor*). Of these two possibilities, having the methylene ester group positioned *exo*- to the cycloadduct ring system (**290**-*major*) is slightly favored over the corresponding *endo*-cogener (**290**-*minor*). The ratio of **290**-*major* to **290**-*minor* was found to be 1.3:1, and the major diastereomer could be separated completely from the minor product by column

chromatograpy. The diastereomeric cycloadducts **290**-*major* and **290**-*minor* could be distinguished by the ^{1}H-NMR chemical shift of the methylene ester protons. In the case of **290**-*minor* are significantly more deshielded by the axial phenylsulfonyl group.

Scheme 71. Rationale for Stereoselective Formation of 290.



290A; R = CO_2Et
not observed

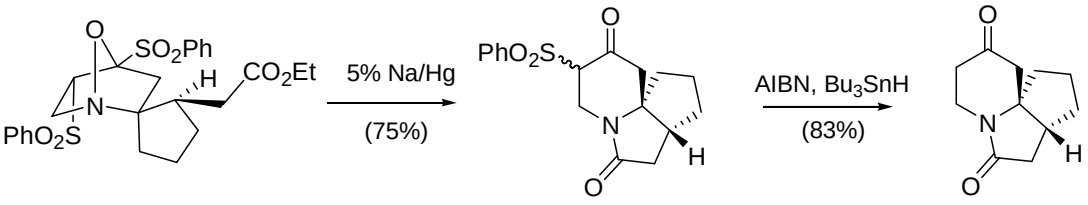
290B
not observed

290-*major*
(54%)

290-*minor*
(41%)

The major diastereomer (**290**-*major*) was then reduced with sodium amalgam to give the expected sulfonyl substituted ketone **293** (Scheme 72). The sulfonyl functionality was further removed through the use of AIBN and tributyltin hydride, providing the tricyclic amide **294** in good yield and possessing the relative configuration required for the halichlorine framework.

Scheme 72. Reduction and Desulfonation of Cycloadduct 290-*major*.



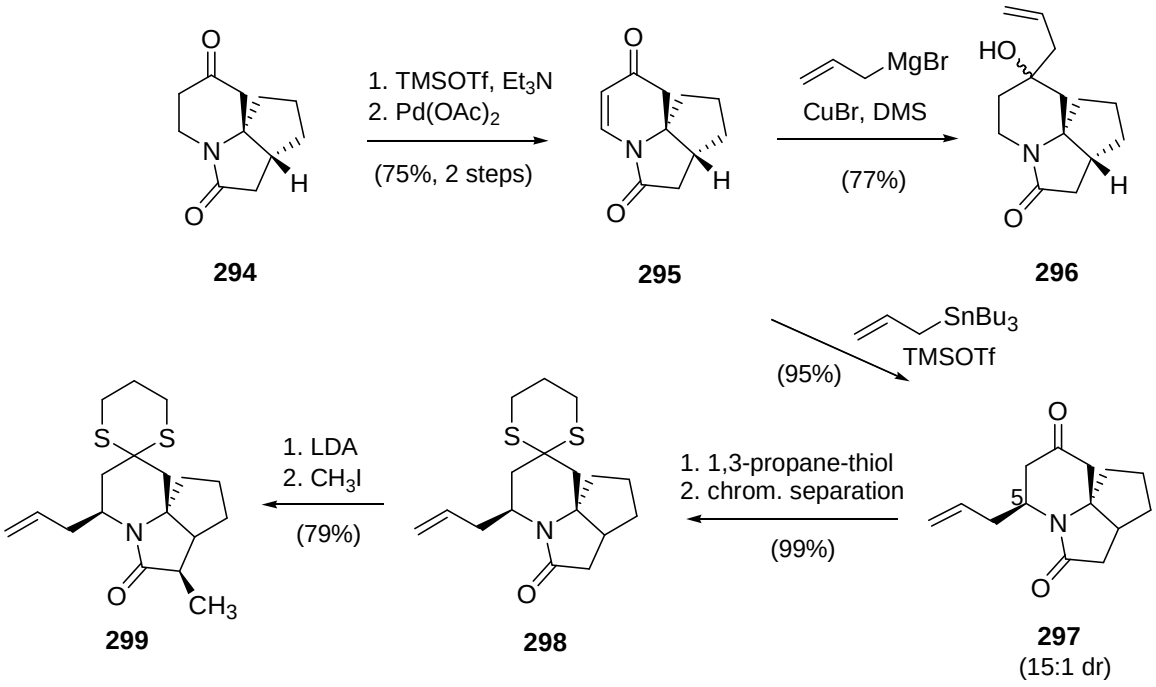
290-*major*

293

294

Similar to previous alkylations used with related 4-piperidone systems, it was envisioned that stereoselective cuprate addition would occur from the least-hindered face of the vinylogous amide **295**. Through the use of a Saegusa oxidation, piperidone **294** was converted to the requisite vinylogous amide **295** (Scheme 73) in excellent yield. Quite unexpectedly, the cuprate coupling of **295** with allylmagnesium bromide gave the unexpected 1,2-addition product in 77% yield.

Scheme 73. Functionalizing the C-5 and C-14 Halichlorine Positions.



However, treating **295** with allyl stannane and TMSOTf delivered the desired 1,4-alkylation product as a 15:1-mixture of diastereomers at C-5 (which were separated after conversion to the dithiane **298**). The diastereoselectivity of this alkylation can be attributed to stannyl approach from the convex face of the tricyclic system to give the desired stereogenicity at the incumbent C-5 center.

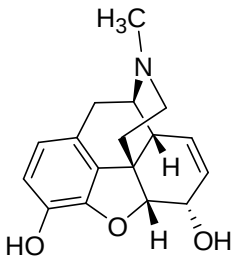
After generation of the enolate of **298** using LDA, methyl iodide approached the system from the least-hindered convex face to furnish the α-methyl amide **231** as a single diastereomer, corresponding to the halichlorine geometry at C-14. Unfortunately, our attempts to hydrolyze dithiane **299** failed and we abandoned further work with this system.[146]

In summary, an efficient and stereocontrolled approach to the halichlorine core has been developed and is based on a tandem Michael addition-cycloaddition cascade involving sulfonyl diene **69**. Stereocontrolled alkylations were utilized to set the configuration at the C-5 and C-14 halichlorine centers. Simple functional group manipulation should allow the late-stage amide **299** to be converted into the Danishefsky amine (**6**), but the inability to cleanly hydrolyze the dithiane prevented us from achieving this goal.

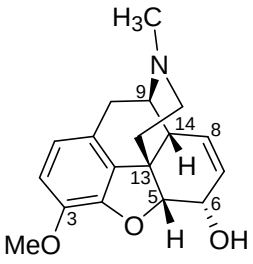
Chapter 2. Studies Directed Toward an Oxofuran Diels-Alder Approach to the Morphine Skeleton.

The powerfully euphoric opium alkaloids occupy a prominent place in modern medicine. Opiates are used extensively as analgesics and are abused in equal measure as illicit narcotics. The study of morphine and its congeners (Figure 12) by organic and medicinal chemists has been ongoing for centuries. Despite an enormous number of synthetic approaches to this alkaloid frame,[147] scale production of morphine and its congeners relies on extraction from natural sources. A demand for a practical synthesis of this alkaloid class has accelerated in recent years due to the uncertain political climate of nations which primarily supply the natural product host organism. Also, modern studies dealing with this class of alkaloids have focused on developing a large-scale synthetic route which gives consideration to environmental factors within its design. The impetus towards synthesis which this scenario provides has been noted earlier by Hudlicky[148] and White[149] among others.

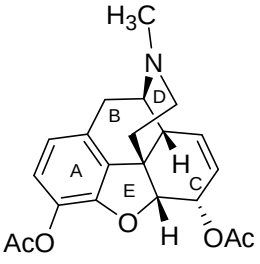
Figure 12. Opium Alkaloids.



300
(+/-)- morphine



301
(+/-)- codeine

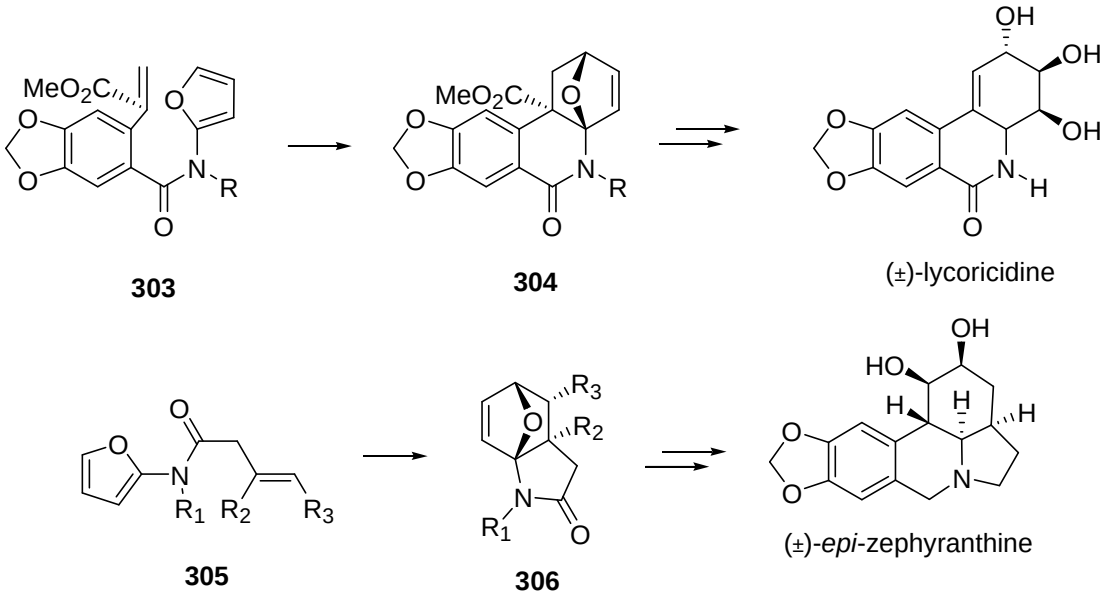


302
(+/-)- heroin

In an effort to design such a synthesis which meets these criteria, it was believed that an entry to this class of alkaloids could be efficiently achieved by using a Diels-Alder cycloaddition of an oxysubstituted furan. Inspired by previous examples of the intramolecular Diels-Alder reaction of imidofurans (IMDAF) for

natural product synthesis (Scheme 74),[150] we became curious about the analogous use of the related oxofuran for heterocyclic synthesis.

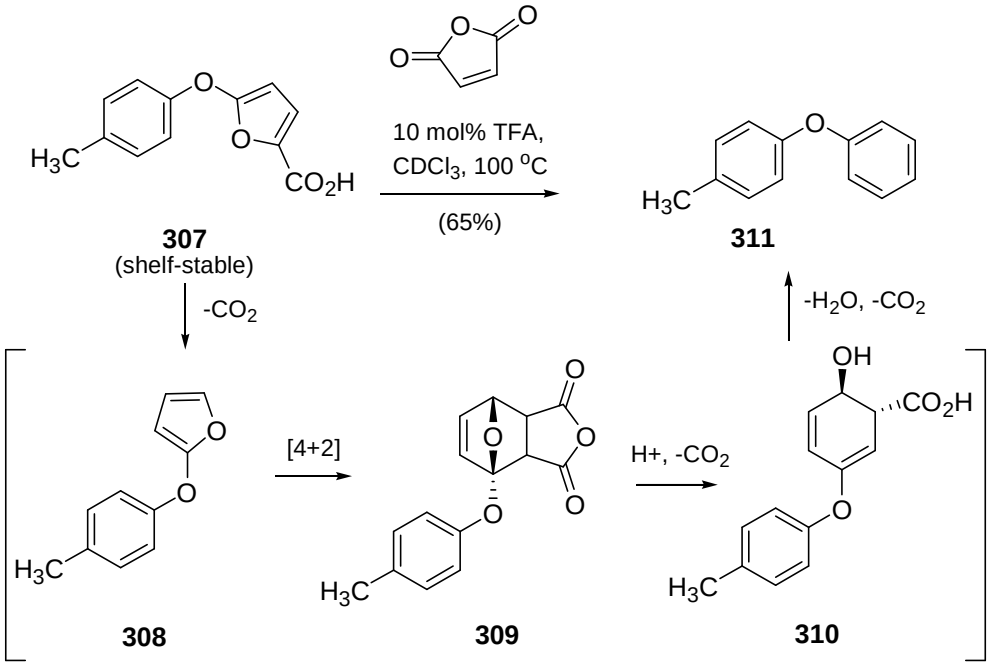
Scheme 74. Examples of IMDAF Reactions Used for Natural Product Synthesis.



In the late 1950s, Manly and Amstutz described the synthesis of 2-aryloxy-substituted furans, compounds which readily decomposed upon exposure to air and water.[151] However, when the 2-oxofuran was substituted with an electron withdrawing group at the 5-position, the 2-aryloxyfuran exhibited markedly improved stability. Unfortunately, the stability of these 5-carboxylate-2-aryloxyfurans rendered them unreactive toward dienophiles. In the late 1980s, Cella devised a creative solution to this reactivity dichotomy.[152] Converting a 2-aryloxy-5-carboxylate furan ester to the corresponding carboxylic acid allowed the 2-aryloxyfuran to be stored indefinitely (Scheme 75). Cella also discovered that heating a sample of 5-cresoxy-furan-2-carboxylic acid (**307**) in the presence

of maleic anhydride triggered an intermolecular Diels-Alder cycloaddition followed by a spontaneous hydrolysis-decarboxylation cascade to give diaryl ether **311**. Although compound **311** is an unlikely structural progenitor to be used in a synthesis of morphine, the mechanism by which the product is formed (**308**-**310**) is of considerable interest in the context of a Diels-Alder cycloaddition of 2-aryloxyfurans.

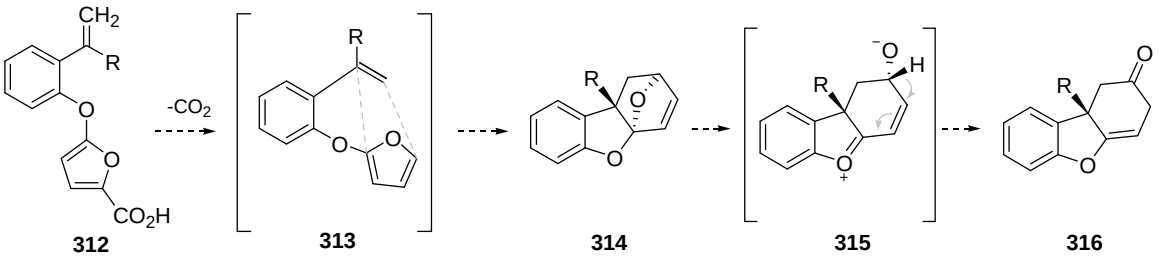
Scheme 75. Cella's [4+2]-Cycloaddition Protocol for Diaryl Ether Synthesis.



We hypothesized that if an R group was positioned within the dienophile such that it could block the aromatization pathway, and if the cycloaddition took place intramolecularly, the resulting oxobicycloadduct **314** (Scheme 76) could be realized. If the oxobridge were to be subsequently ruptured by participation of the benzofuranyl lone pair, cleavage of the ring and a hydride shift might lead to dihydrodibenzofuran **316**. The resulting ring system **316** would represent the

AEC-ring construct of morphine. Since precedent exists for similar reaction pathways which involve nitrogen,[153] the synthesis of a furanyl ether resembling **312** was undertaken.

Scheme 76. Proposed Synthesis of Dihydrodibenzofurans.

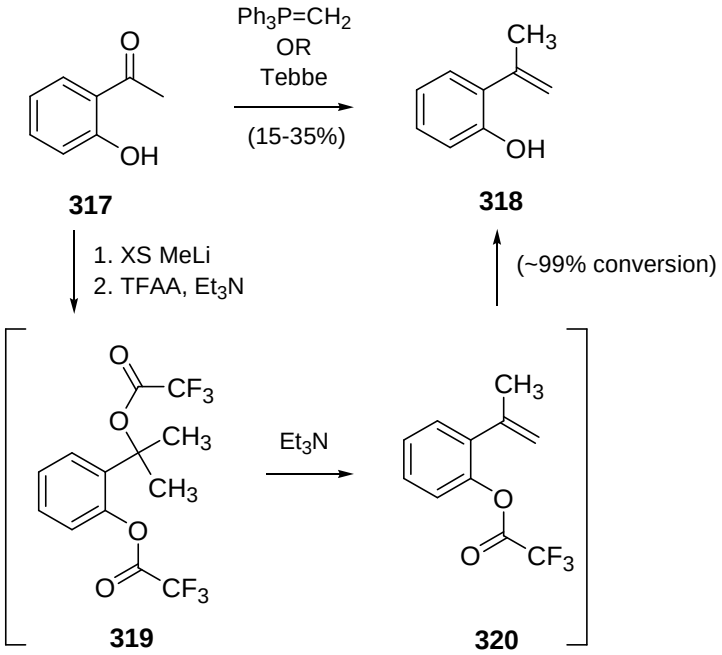


312 **313** **314** **315** **316**

It was envisioned that the simplest and quickest way to test this hypothesis would be to generate a phenol which had a tethered π bond capable of participating in a [4+2]-cycloaddition reaction. Coupling of this phenol with 5-bromo-2-methyl furoate using either Manly-Amstutz conditions or cross-coupling chemistry would then deliver the required Diels-Alder precursor. Salicylic-derived 2-isopropenyl-phenol **318** was selected as the initial target material for the phenolic coupling partner. The conversion of the salicylic ketone **317** to styrene **318** was expected to proceed smoothly from known Wittig or Tebbe procedures (Scheme 77).[154] Unfortunately, these protocols gave mediocre yields and the starting material was difficult to separate from the desired product by both chromatographic or distillation methods. Instead, a novel synthesis was developed which was capable of producing the target styrene in excellent yield on gram-scale quantities. Treating ketone **317** with an excess of methyllithium followed by acylation with trifluoroacetic anhydride under basic conditions initially led to the *bis*-acylated intermediate **319**. This compound underwent elimination *in*

situ and upon aqueous workup gave near quantitative amounts of the desired phenol **318**. The conditions used to convert ketone **317** to styrene **318** could possibly be extended to the synthesis of analogous aniline derivatives.

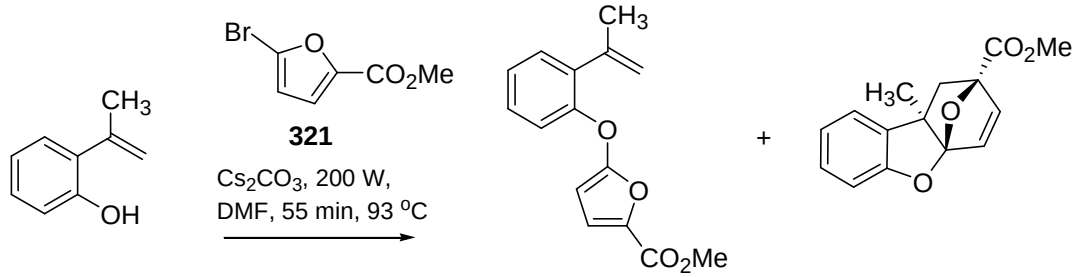
Scheme 77. Synthesis of Phenolic Coupling Partner 318.



Although the coupling of phenol **318** and bromofuroate **321** proceeded poorly under standard addition-elimination conditions, the conversion was markedly enhanced under microwave irradiation. Optimized reaction conditions generated a 3:2-mixture of the intended coupling product **322** along with the unexpected cycloaddition product **323** (Scheme 78). The energetics of a [4+2]-cycloaddition involving **322** would initially appear unfavorable due to the poorly activated styrenyl π bond and the significantly lowered LUMO energy of the esterified furan. However, cycloadduct **323** was the major product obtained from this reaction together with minor amounts of **322** as determined by ^{1}H-NMR

examination of the crude reaction mixture. Although **322** and **323** could be cleanly separated by chromatography, the stability of both systems was quite limited. Decomposition was observed within a few hours—findings which are consistent with the reports of Cella.[155]

Scheme 78. Generation of Ethereal Styrene 322 and Cycloadduct 323.



318 **322** (30%) **323** (45%)

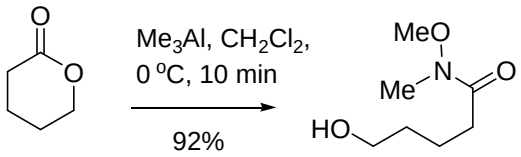
To our knowledge, the formation of **323** represents the first example of a [4+2]-cycloaddition involving a 2,5-disubstituted furoate ester.[156] Although this cycloadduct exhibits limited stability, its synthetic utility has not yet been realized and requires further study. Moreover, bromocarboxylate **321** may not be the best choice for this particular coupling reaction. Since the seminal reports of Diels-Alder cycloadditions involving 2-aryloxyfurans were divulged, cross-coupling technology has advanced significantly. Therefore, mild conditions likely exist to facilitate aryloxy-bromo exchange at the 2-position of furan though the use of a metal-catalyzed transformation, and this is the direction that further study needs to take.

In conclusion, the AEC-ring construct of morphine has been approached using a novel, one-pot intramolecular [4+2]-cycloaddition involving a 2,5-disubstituted aryloxyfuran. The cycloaddition occurs during a microwave-assisted

nucleophilic aromatic substitution reaction involving 5-bromo-2-furoate methyl ester. The phenolic coupling partner 2-isopropenyl-phenol was synthesized on gram-scale through an *in situ* protection-elimination-deprotection sequence. Further studies dealing with these findings are currently underway in our laboratories.

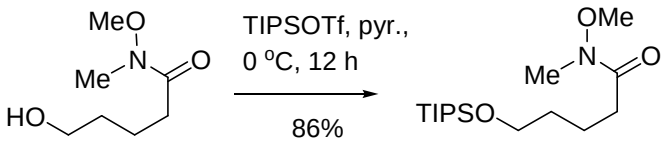
III. EXPERIMENTAL SECTION

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. Unless otherwise noted, all reactions were performed in flame-dried glassware under an atmosphere of dry nitrogen. Solutions were evaporated under reduced pressure with a rotary evaporator and the residue was chromatographed on a silica gel column using an ethyl acetate-hexane mixture eluent unless specified otherwise.



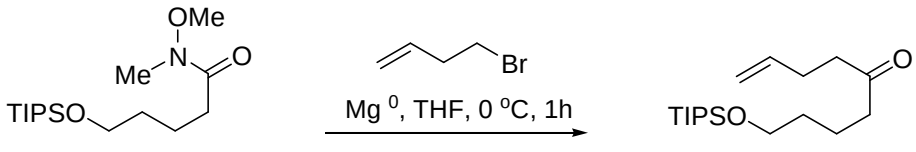
138 **139**

5-Hydroxy-pentanoic acid methoxy-methyl-amide (139). To a stirred solution containing 2.2 g (22.5 mmol) of *N,O*-dimethylhydroxylamine hydrochloride in dry CH_2Cl_2 (5 mL) at 0 ^oC was added dropwise 11.2 mL (22.5 mmol, 2.0 M in hexane) of $AlMe_3$. The mixture was stirred for 20 min at 0 ^oC and 1.4 mL (1.5 mmol) of δ-valerolactone (**138**) was added dropwise. After stirring at 0 ^oC for 20 min, the mixture was diluted with 25 mL of $CHCl_3$ and then 3 mL of a 0.1 N HCl solution was added dropwise at 0 ^oC. The mixture was stirred for 1 h, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give 2.2 g (92%) of the titled amide **139** acid as a white solid; mp 61-63 ^oC; IR (CH_2Cl_2) 3440, 1640, 1072, and 1003 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 1.60 (m, 2H), 1.72 (m, 2H), 2.46 (brs, 2H), 3.17 (s, 3H), 3.63 (t, 2H, *J* = 6.6 Hz) and 3.67 (s, 3H), 4.01 (br s, 1H). The spectral data of this compound is identical to that reported in the literature.[157]



139 **140**

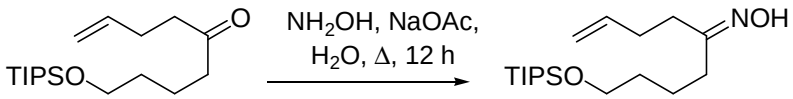
5-Triisopropylsilanyloxy-pentanoic acid methoxy-methyl-amide (140). To a stirred solution containing 0.9 g (5.5 mmol) of alcohol **139** and 1.4 mL (12 mmol) of 2,6-lutidine in 10 mL of dry CH_2Cl_2 at 0 ºC was added 1.7 mL (6 mmol) of triisopropylsilyl trifluoromethanesulfonate. The mixture was allowed to warm to rt, stirred for 24 h, and was then quenched with 1 mL of a 0.05 N HCl solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10% EtOAc in hexane) to give 1.5 g (86%) of 5-triisopropylsilanyloxy-*N,O*-dimethylpentanohydroxamic acid (**140**) as a pale oil; IR (neat) 1674, 1463, 1415, 1383, 1105, 999, 883 and 681 cm^{-1}; ^{1}H-NMR(400 MHz, $CDCl_3$) δ 1.03-1.06 (m, 21H), 1.58 (m, 2H), 1.70 (m, 2H), 2.44 (brs, 2H), 3.16 (s, 3H), 3.66 (s, 3H) and 3.69 (t, 2H, *J* = 8.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 12.2, 17.8, 18.2, 21.4, 31.9, 32.9, 61.4, 63.3 and 97.9; HRMS Calcd for $C_{16}H_{35}NO_3Si$: 318.2459. Found 318.2460.



140 **141**

9-Triisopropylsilanyloxy-non-1-en-5-one (141). To a solution containing 3.4 g (10.6 mmol) of the above hydroxamic acid (**140**) in 10 mL of THF at 0 ºC

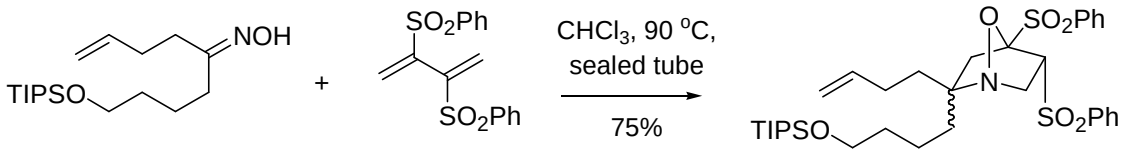
was added dropwise 20 mL (20.2 mmol, 1.0 M in THF) of a solution of 3-butenylmagnesium bromide. The mixture was stirred for 1 h at 0 ºC and was allowed to warm to rt and was stirred for an additional 1 h. At the end of this time the solution was quenched with 3 mL of a 0.1N HCl solution and was diluted with ether. The organic layer was separated and the aqueous layer was further extracted with ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography (10% EtOAc in hexane) to give 3.3 g (98%) of ketone **141** as a yellow oil; IR (neat) 1716, 1674, 1463, 1105, 996, 882 and 680 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.02-1.20 (m, 21H), 1.49-1.54 (m, 2H), 1.62-1.67 (m, 2H), 2.29 (dd, 2H, *J* = 13.8 and 6.6 Hz), 2.42 (t, 2H, *J* = 7.2 Hz), 2.47 (t, 2H, *J* = 7.2 Hz), 3.66 (t, 2H, *J* = 6.3 Hz), 4.94 (d, 1H, *J* = 10.2 Hz), 4.99 (d, 1H, *J* = 17.1 Hz) and 5.77-5.85 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 12.2, 18.2, 20.6, 28.0, 32.6, 41.9, 42.9, 63.3, 115.4, 137.4 and 210.5; HRMS Calcd for $C_{18}H_{36}O_2Si$: 313.2557. Found 313.2559.



141 **142**

9-Triisopropylsilanyloxy-non-1-en-5-one oxime (142). To a stirred solution containing 1.0 g (1.5 mmol) of hydroxylamine hydrochloride and 2.4 g (3.0 mmol) of sodium acetate in 50 mL of water was added the above ketone **141** (1.0 g, 5 mmol). The mixture was heated at reflux for 8 h, cooled to rt and extracted with CH_2Cl_2. The organic extracts were washed with a saturated solution of $NaHCO_3$, brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography (10% EtOAc in hexane) to give 0.9 g (80%) of oxime **142** as a yellow oil which consisted of a

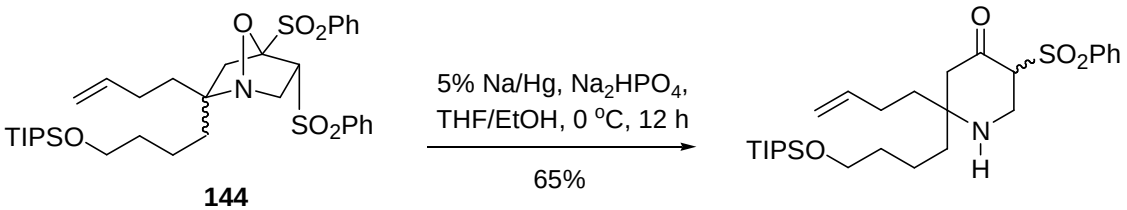
1:1-mixture of the *syn* and *anti* diastereomers; IR (neat) 3201, 1642, 1461, 1106, 996 and 680 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.98-1.15 (m, 21H), 1.55-1.59 (m, 4H), 2.20 (t, 1H, *J* = 7.4 Hz), 2.25-2.30 (m, 3H), 2.36 (t, 1H, *J* = 7.7 Hz), 2.42 (t, 1H, *J* = 7.7 Hz), 3.64-3.69 (m, 2H), 4.97-5.04 (m, 2H), 5.79-5.84 (m, 1H) and 8.87 (brs, 1H); ^{13}C-NMR(100 MHz, $CDCl_3$) δ 12.2, 18.2, 22.2, 27.1, 30.5, 32.7, 33.2, 34.3, 63.1, 115.2, 137.7, and 161.2; HRMS Calcd for $C_{18}H_{37}NO_2Si$: 328.2663. Found: 328.2667.



142 **69** **144** (1:1 dr)

2-(3-Butenyl)-2-(4-triisopropylsilanyloxybutyl)-4,5-*bis*(phenylsulfonyl)-7-oxa-1-aza-bicyclo[2.2.1]heptane (144). A solution containing 2.5 g (7.2 mmol) of 2,3-*bis*(phenylsulfonyl)-1,3-butadiene (**69**)[55] and 1.5 g (6 mmol) of oxime **142** in 100 mL of $CHCl_3$ was added to a sealed tube equipped with a stirbar. The tube was sealed, placed in a sandbath, and heated to 90 °C for 12 h. The mixture was cooled and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (15% EtOAc in hexane) to give 3.5 g (75%) of an unseparable 1:1-diastereomeric mixture of cycloadduct **144** as a yellow oil: IR (neat) 2942, 1447, 1153, 720, 686 and 614 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.92-1.10 (m, 42H), 1.80-1.95 (m, 14H), 2.99 (d, 2H, *J* = 12.8 Hz), 3.50-3.55 (m, 1H), 3.63 (t, 4H, *J* = 12.4 Hz), 3.68-3.73 (m, 1H), 3.95 (dd, 2H, *J* = 12.8 and 5.6 Hz), 4.32 (ddd, 2H, *J* = 10.8, 5.2 and 2.2 Hz), 4.80 (d, 2H, *J* = 10 Hz), 5.02 (d, 2H, *J* = 16.4 Hz), 5.50-5.55 (m, 1H), 5.79-5.84 (m, 1H), 7.50 (t, 4H, *J* = 7.6 Hz), 7.78-7.60 (m, 12H) and 7.97 (d, 4H, *J* = 7.6 Hz); ^{13}C-NMR(100 MHz, $CDCl_3$)

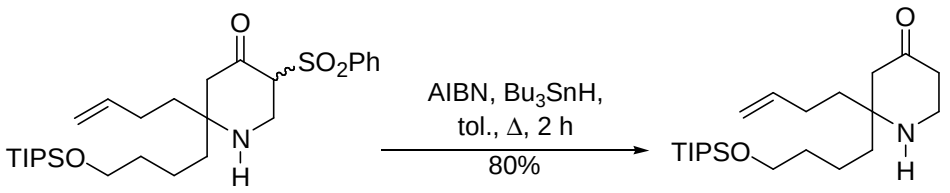
δ 12.2, 18.2, 20.0, 21.2, 27.8, 29.1, 30.4, 30.9, 33.4, 33.5, 37.2, 37.8, 53.3, 62.9, 63.2, 66.7, 75.0, 114.6, 115.5, 129.1, 129.5, 130.5, 134.5, 134.7, 134.9, 137.7, 138.1 and 139.4; Anal. Calcd. for $C_{34}H_{51}NO_7S_2Si$: C, 61.69; H, 7.77; N, 2.12; S, 9.69. Found: C, 61.89; H, 7.51; N, 2.21; S, 9.54.



144
(1:1 dr)

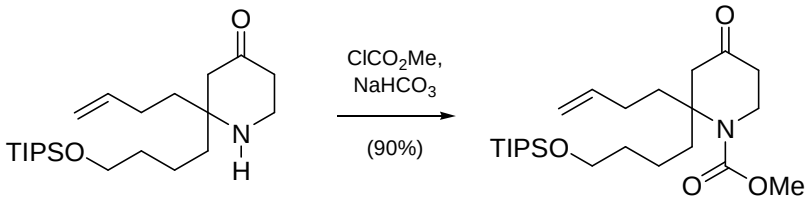
145

2-(3-Butenyl)-2-(4-triisopropylsilanyloxybutyl)-5-phenylsulfonyl-4-piperidone (145). A solution containing 2.0 g (3 mmol) of the mixture of cycloadducts **144** and 2.1 g (15.2 mmol) of sodium phosphate dibasic in a 2:1-THF/EtOH mixture (21 mL total volume) at 0 °C was charged with 3.5 g (7.6 mmol) of 5% Na(Hg) in two portions. The mixture was stirred at this temperature for 5 h and was then filtered through a pad of Celite. The solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (15% EtOAc in hexane) to give 1.0 g (65%) of a 1:1-diastereomeric mixture of piperidone **145** as a pale yellow oil; IR (neat) 1711, 1642, 1463, 1104, 883, and 629 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.98-1.12 (m, 21H), 1.30-1.62 (m, 8H), 1.95-2.03 (m, 3H), 2.43 (d, 1H, *J* = 13.6 Hz), 2.77 (dd, 1H, *J* = 13.6 and 2.8 Hz), 3.30-3.35 (m, 1H), 3.65-3.67 (m, 2H), 3.71 (t, 1H, *J* = 6 Hz), 3.85 (dd, 1H, *J* = 4 and 1.3 Hz), 3.89 (dd, 1H, *J* = 4 and 1.6 Hz), 4.95-5.10 (m, 2H), 5.85-5.95 (m, 1H), 7.57 (t, 2H, *J* = 7.6 Hz), 7.60-7.68 (t, 1H, *J* = 7.2 Hz) and 7.84 (d, 2H, *J* = 7.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 7.8, 13.9, 14.9, 22.9, 29.1, 30.2, 34.7, 35.0, 37.7, 48.1, 58.7, 68.1, 110.8, 124.3, 125.3, 130.2, 133.7, 133.9, and 196.0; HRMS Calcd for $C_{23}H_{47}NO_4SSi$: 522.3060. Found: 522.3064.



145 **146**

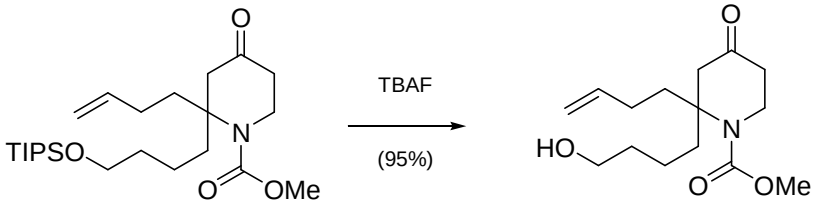
2-(3-Butenyl)-2-(4-triisopropylsilanyloxybutyl)-4-piperidone (146). To a solution containing 1.0 g (1.9 mmol) of piperidone **145** and 2.1 mL (7.7 mmol) of tri-*n*-butyltin hydride in 50 mL of dry toluene at reflux was added 0.2 g (1.3 mmol) of AIBN followed by the addition of a further 0.1 g (0.8 mmol) of AIBN after 5 min. After heating at reflux for 2 h, the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel chromatography (75% EtOAc in hexane) to give 0.5 g (80%) of piperidone **146** as a pale yellow oil; IR (neat) 3101, 1709, 1640, 1381, 1070, 883, and 658 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.91 (t, 3H, *J* = 6.4 Hz), 0.94-1.07 (m, 21H), 1.22-1.63 (m, 6H), 1.96-2.00 (m, 2H), 2.24 (s, 2H), 2.31 (t, 2H, *J* = 6 Hz), 3.10 (t, 2H, *J* = 6 Hz), 3.65 (t, 2H, *J* = 6.4 Hz), 4.92 (brd, 1H, *J* = 10 Hz), 4.99 (brd, 1H, *J* = 16.8 Hz) and 5.75-5.80 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 12.2, 18.2, 19.3, 27.5, 33.5, 35.9, 36.8, 40.8, 42.6, 52.9, 59.2, 63.1, 114.9, 138.4 and 210.2; HRMS Calcd for [$C_{22}H_{43}NO_2Si+H^+$]: 382.3132. Found: 382.3133.



146 **147**

2-(3-Butenyl)-2-(4-triisopropylsilanyloxybutyl)-4-piperidone-1-carboxylic Acid Methyl Ester (147). To a solution containing 0.3 g (0.8 mmol) of piperidone **146** and 0.1 g (1.6 mmol) of $NaHCO_3$ in CH_3CN (8 mL) at 0 ^{o}C was added methyl chloroformate (0.09 mL, 1.2 mmol). The mixture was allowed to warm to rt and

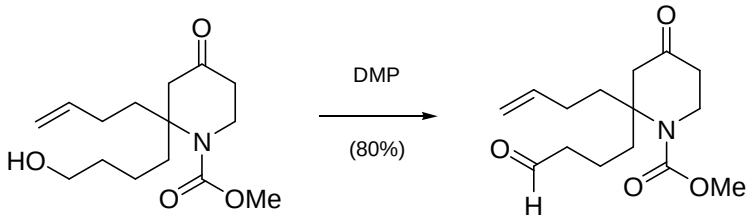
was stirred overnight. To this mixture was added a saturated aqueous ammonium chloride solution (10 mL) and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to flash silica gel column chromatography (15% EtOAc in hexane) to give 0.3 g (90%) of the titled carbamate **147** as a colorless oil; IR (neat) 1727, 1697, 1381, 1102, 883, and 658 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.98-1.08 (m, 21H), 1.25-1.29 (m, 2H), 1.45-1.72 (m, 4H), 1.96 (dd, 2H, *J* = 16 and 7 Hz), 2.10-2.16 (m, 2H), 2.43 (t, 2H, *J* = 6 Hz), 2.59 (d, 1H, *J* = 15.6), 2.64 (d, 1H, *J* = 15.6 Hz), 3.64 (t, 2H, *J* = 6.4 Hz), 3.68 (s, 3H), 3.87-3.91 (m, 2H), 4.92 (brd, 1H, *J* = 10 Hz), 4.98 (brd, 1H, *J* = 17.2 Hz) and 5.70-5.75 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 12.2, 18.2, 20.4, 28.5, 33.4, 38.9, 39.5, 39.7, 41.3, 48.7, 52.6, 61.4, 63.3, 115.1, 138.1, 155.7 and 210.2; HRMS Calcd for [$C_{24}H_{45}NO_4Si$ + H^+]: 440.3190. Found: 440.3188.



147 **148**

2-(3-Butenyl)-2-(4-hydroxybutyl)-4-piperidone-1-carboxylic Acid Methyl Ester (148). To a solution containing 0.1 g (0.3 mmol) of carbamate **147** in 5 mL of dry THF at 0 ^oC was added 2 g of 4Å molecular sieves and 0.3 mL, (0.3 mmol, 1.0 M in THF) of tetrabutylammonium fluoride. The mixture was allowed to warm to room temperature and was stirred for 4 h and then filtered through a pad of Celite. The solution was diluted with water (10 mL) and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered

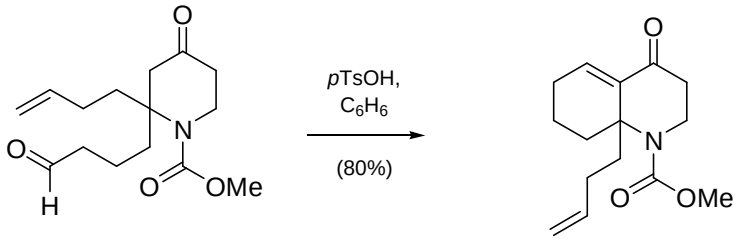
and concentrated under reduced pressure. The residue was subjected to flash silica gel column chromatography (60% EtOAc in hexane) to give 0.08 g (95%) of the titled alcohol **148** as a colorless oil; IR (neat) 1727, 1692, 1384, 1229, 998, 914 and 772 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.25-1.30 (m, 2H), 1.55-1.59 (m, 4H), 1.96-2.00 (m, 2H), 2.13-2.17 (m, 3H), 2.44 (t, 2H, *J* = 6.4 Hz), 2.60 (d, 1H, *J* = 15.6 Hz), 2.65 (d, 1H, *J* = 15.6 Hz), 3.62 (t, 2H, *J* = 6.8 Hz), 3.69 (s, 3H), 3.85-3.91 (m, 2H), 4.93 (brd, 1H, *J* = 10.4 Hz), 4.95-4.97 (m, 1H) and 5.72-5.75 (m, 1H); ^{13}C- NMR(100 MHz, $CDCl_3$) δ 20.1, 28.5, 32.7, 38.8, 39.1, 39.6, 41.4, 48.6, 53.0, 61.4, 62.5, 115.2, 138.0, 155.8 and 210.1; HRMS Calcd for [$C_{15}H_{25}NO_4$+H^+]: 284.1856. Found: 284.1856.



148 **149**

2-(3-Butenyl)-2-(4-oxobutyl)-4-piperidone-1-carboxylic Acid Methyl Ester (149). To a solution containing alcohol **148** (0.05 g, 0.2 mmol) in dry CH_2Cl_2 (2 mL) at 0 ^{o}C was added Dess Martin periodinane (0.09 g, 0.2 mmol) in one portion. The mixture was allowed to warm to room temperature and was stirred overnight. After this time, the solution was diluted with ether (10 mL) and washed with a saturated solution of sodium bisulfite and sodium bicarbonate. The aqueous layer was extracted with ether and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (40% EtOAc in hexane) to give 0.04 g (80%) of the titled aldehyde **149** as a colorless oil; IR (neat) 2954, 1724, 1693, 1382, 1089, and 772 cm^{-1}; ^{1}H-NMR

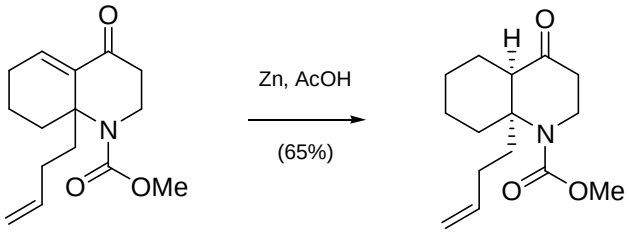
(400 MHz, $CDCl_3$) δ 1.49-1.73 (m, 4H), 1.97 (dd, 2H, *J* = 16.0 and 6.8 Hz), 2.15 (m, 2H), 2.44 (m, 4H), 2.65 (s, 2H), 3.69 (s, 3H), 3.90 (dt, 2H, *J* = 6.2 and 2.0 Hz), 4.93 (d, 1H, *J* = 10.4 Hz), 4.97-5.01 (m, 1H), 5.70-5.74 (m, 1H) and 9.73 (br s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 16.6, 28.5, 38.6, 38.9, 39.6, 41.4, 43.9, 48.5, 52.7, 61.3, 115.3, 137.8, 155.7, 201.9 and 209.8; HRMS Calcd for [$C_{15}H_{23}NO_4$+ H^+]: 282.1701. Found: 282.1699.



149 **150**

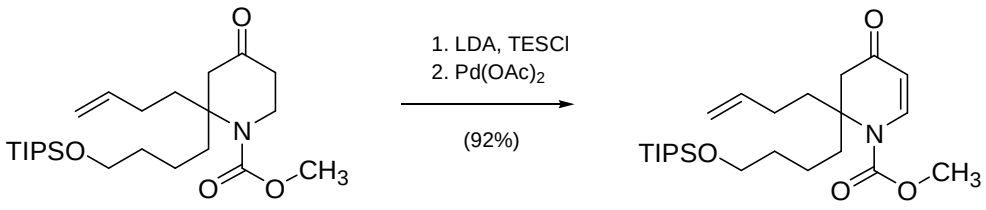
8*a*-(3-Butenyl)-3,4,6,7,8*a*-hexahydro-2*H*-quinolin-4-one-1-carboxylic Acid Methyl Ester (150). To a solution containing 0.05 g (0.2 mmol) of aldehyde **149** in 2 mL of anhydrous benzene was added 0.03 g (0.2 mmol) of *p*-toluensulfonic acid monohydrate and the mixture was stirred at 50 ^{o}C for 8 h. The solution was allowed to cool to room temperature and was quenched with 15 mL of a saturated $NaHCO_3$ solution**.** The layers were separated and the aqueous phase was extracted with ether and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20% EtOAc in hexane) to give 0.04 g (80%) of the titled enone **150** as a colorless oil; IR (neat) 1694, 1623, 1386, 1252, 1093, and 771 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.61-1.82 (m, 5H), 1.95-1.99 (m, 1H), 2.26-2.30 (m, 2H), 2.36 (t, 1H, *J* = 2.4 Hz), 2.41 (t, 1H, *J* = 2.4 Hz), 2.58-2.62 (m, 2H), 3.11 (dt, 1H, *J* = 13.2 and 2.4 Hz), 3.70 (s, 3H), 4.35 (d, 1H, *J* = 13.2 Hz), 4.90 (d, 1H, *J* = 10.4 Hz), 4.95 (d, 1H, *J* = 17.2 Hz), 5.68-5.72 (m, 1H) and 6.62 (t, 1H, *J* = 4.0 Hz); ^{13}C-NMR (100

MHz, $CDCl_3$) δ 18.2, 24.8, 28.9, 31.1, 38.9, 39.8, 39.9, 52.6, 60.4, 115.1, 138.2, 138.4, 141.6, 157.9 and 193.2; HRMS Calcd for [$C_{15}H_{21}NO_3$+ H^+]: 264.1594. Found: 264.1595.



150 **151**

***cis*-8*a*-(3-Butenyl)octahydro-4-quinolin-4-one-1-carboxylic Acid Methyl Ester (151)**. To a solution containing 0.05 g (0.2 mmol) of enone **150** in 4 mL of acetic acid was added 0.2 g of zinc dust and the mixture was stirred at 120 ^oC overnight. Water (20 mL) was added and the mixture was extracted with CH_2Cl_2. The extracts were washed with water, an aqueous solution of $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 0.03 g (65%) of the *cis*-fused decalone **151** as a colorless oil: IR (CH_2Cl_2) 2940, 2864, 1714, 1686, 1448, and 883 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ1.38-1.57 (m, 6H), 2.00-2.04 (m, 3H), 2.10-2.16 (m, 1H), 2.33-2.36 (m, 1H), 2.43-2.45 (m, 2H), 2.56-2.60 (m, 1H), 2.89 (b rs, 1H), 3.48 (dt, 1H, *J* = 13.6 Hz), 3.70 (s, 3H), 4.40 (ddd, 1H, *J* = 14.2, 5.2, and 3.6 Hz), 4.96 (d, 1H, *J* = 10.4 Hz), 5.04 (d, 1H, *J* = 17.2 Hz) and 5.79-5.83 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 22.1, 22.2, 28.1, 30.0, 33.0, 35.7, 39.7, 40.8, 49.9, 52.5, 61.6, 115.1, 138.3, and 210.8. The spectral data for this compound is identical to that reported in the literature.[158]

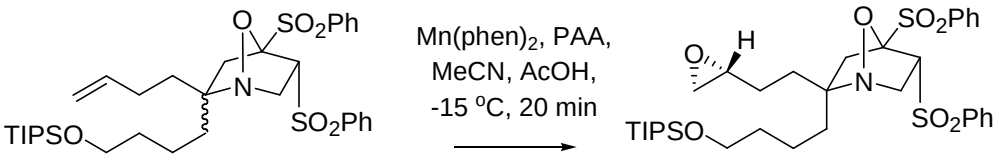


147 **152**

2-But-3-enyl-4-oxo-2-(4-triisopropylsilanyloxy-butyl)-3,4-dihydro-2H-pyridine-1-carboxylic acid methyl ester (152). To a round bottom flask charged with 0.19 g (0.44 mmol) of the starting piperidone **147** in 5.0 mL of dry THF at -70 ^{o}C was slowly added 1.4 mL (0.63 mmol) of a 0.45 M solution of LDA in THF. The solution was allowed to stir for 15 min. To this mixture was added 77 μL (0.45 mmol) of chlorotriethylsilane and the solution was warmed to 0 ^{o}C and stirred for an additional 15 min. The reaction mixture was then transferred to a separatory funnel and was partitioned between water and ethyl ether. The organic layer was washed twice with water, once with brine, dried over Na_2SO_4 and concentrated under reduced pressure to provide the crude silyl enol ether as a yellow oil. This crude material was immediately taken up in 4.0 mL of DMSO/acetonitrile (3:1).

To this solution was added 0.10 g (0.45 mmol) of $Pd(OAc)_2$ and the mixture was allowed to stir at rt for 18 h. The mixture was then filtered through a pad of Celite and the filtrates were partitioned between ethyl ether and water. The organic layer was washed twice with water, once with brine, dried over Na_2SO_4 and then concentrated under reduced pressure. Purification of the residue by silica gel column chromatography provided 0.17 g (92%) of the titled vinylogous amide **152** as a yellow oil: IR (CH_2Cl_2) 2944, 1737, 1675, 1610, and 679 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 0.93-1.07 (m, 21H), 1.24-1.66 (m, 6H), 1.96-2.06 (m, 2H), 2.22-2.34 (m, 2H), 2.56 (d, 1H, *J* = 16.4 Hz), 2.62 (d, 1H, *J* = 16.4 Hz), 3.65 (t, 2H, *J* = 6.2), 3.82 (s, 3H), 5.02-4.93 (m, 2H), 5.25 (d, 1H, *J* =

8.6 Hz), 5.68-5.78 (m, 1H), and 7.81 (d, 1H, *J* = 7.81 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 12.1, 18.2, 20.6, 28.4, 33.4, 37.3, 38.1, 45.5, 54.0, 63.1, 65.1, 106.0, 115.3, 137. 7, 145.2, 153. 5, and 193.8; HRMS Calcd for [$C_{24}H_{43}NO_4Si+H^+$]: 438.2995. Found 438.2959.

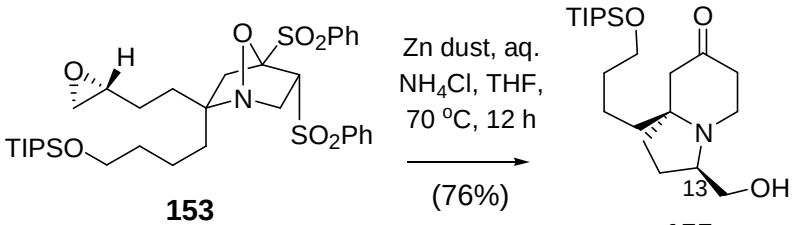


144
(1:1 dr)

153

4,5-*bis*-Benzenesulfonyl-2-(2-oxiranyl-ethyl)-2-(4-triisopropylsilanyloxy-butyl)-7-oxa-1-aza-bicyclo[2.2.1]heptane (153). To a round bottom flask charged with 11.0 g (16.6 mmol) of the above alkene **144** in 80 mL of MeCN/AcOH (97:3) at -15 ºC was slowly added 16.6 mL (0.4 mmol) of a 2.5 M solution of manganese phenanthroline[159] in CH_3CN/AcOH (97:3). To this mixture was added 5.9 mL (24.9 mmol) of a 32% wt solution of aqueous peracetic acid (PAA) over the course of 20 min. The solution was allowed to stir for 10 min while being warmed to 0 ºC. The reaction mixture was then transferred to a separatory funnel and was partitioned between aqueous $NaHCO_3$ and ethyl acetate. The organic layer was washed twice with water, once with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography provided the 3.0 g (25%) of the titled epoxide **153** as a mixture of diastereomers as a yellow oil: IR (CH_2Cl_2) 2943, 2865, 1329, 1153, 1100, and 603 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.03-1.06 (m, 21H), 1.20-1.30 (m, 4H), 1.46-1.56 (m, 3H), 1.89 (dq, 1H, *J* = 6.3 and 2.2 Hz), 2.00-2.05 (m, 2H), 2.51 (q, 1H, *J* = 2.4 Hz), 2.78 (dd, 1H, *J* = 5.2 and 3.6 Hz), 2.92-2.97 (m, 1H), 3.10 (d, 1H, *J* = 12.8 Hz), 3.52-3.55 (m, 2H), 3.61-3.69 (m, 2H), 3.97 (dt, 1H, *J* = 12.4 and 4.7 Hz), 4.29-4.37 (m, 1H), 7.52 (t, 2H, *J* = 7.6 Hz), 7.61-7.79 (m, 6H),

and 7.97-8.00 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 7.8, 13.9, 15.3, 22.4, 23.4, 24.0, 29.0, 34.3, 42.7, 47.8, 49.0, 58.8, 62.3, 70.3, 99.9, 124.6, 124.7, 125.1, 125.2, 126.1, 130.1, 130.4, 130.6, and 135.0; HRMS Calcd for [$C_{34}H_{51}NO_7S_2Si$ + H^+]: 678.2949. Found: 678.2940.

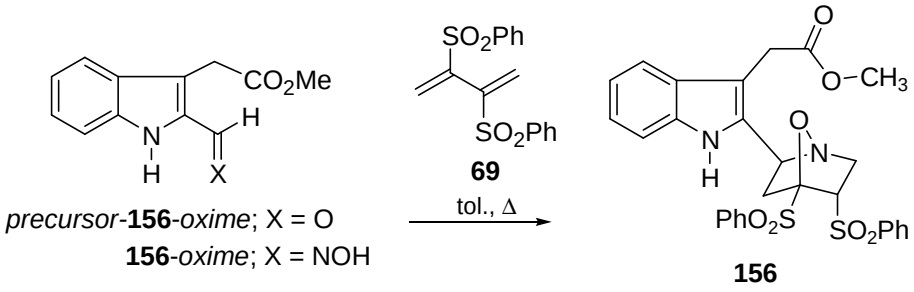


153 **155** (9:1 dr)

3-Hydroxymethyl-8*a*-(4-triisopropylsilanyloxy-butyl)-hexahydro-indolizin-7-one (155). To a round bottom flask charged with 2.4 g (3.5 mmol) of epoxide **153** in 220 mL of a saturated NH_4Cl/H_2O/THF (1:1:1) solution was added 11.6 g (177 mmol) of zinc dust. The reaction mixture was stirred vigorously and was heated to 70 ºC for 12 h, cooled to rt and filtered through a pad of celite. The filtered solid was washed with an aqueous $NaHCO_3$ solution, and the filtrate was collected and extracted with ether. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography provided 1.07 g (68%) of the major diastereomer of **155** as a yellow oil: IR (CH_2Cl_2) 3454, 2940, 2864, 1701, 1459 and 1104 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 1.03-1.05 (m, 21H), 1.34-1.39 (m, 4H), 1.49-1.52 (m, 4H), 1.83-1.91 (m, 2H), 2.04-2.08 (m, 2H), 2.20 (dd, 1H, *J* = 13.6 and 1.8 Hz), 2.34 (d, 1H, *J* = 13.6 Hz), 2.52 (ddd, 1H, *J* = 13.7, 12.6, and 6.6 Hz), 3.07 (dt, 1H, *J* = 12.0 and 3.5 Hz), 3.21 (ddd, 1H, *J* = 14.4, 6.6, and 1.8 Hz), 3.34 (br d, 1H, *J* = 9.1 Hz), 3.44 (dd, 1H, *J* = 10.8 and 1.8 Hz) and 3.64-3.69 (m, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 7.8, 13.9, 15.9, 20.4, 29.1, 31.2, 31.9, 33.1,

38.4, 43.5, 55.7, 58.2, 58.9, 64.8, and 205.8; HRMS Calcd for [$C_{22}H_{43}NO_3Si+H^+$]: 398.3046. Found: 398.3045.

The minor diastereomer of **155** (9%) was separated from the major diastereomer and showed characteristic ^{1}H-NMR peaks at δ 1.03-1.05 (m, 21H), 1.34-1.39 (m, 4H), 1.49-1.52 (m, 2H), 1.83-1.91 (m, 2H), 2.04-2.08 (m, 1H), 2.20-2.30 (m, 2H), 2.45-2.58 (m, 2H), 2.62 (t, 1H, *J* = 9.6 Hz), 2.67 (dd, 1H, *J* = 13.6 and 2.1 Hz), 2.83 (dt, 1H, *J* = 9.6 and 3.6 Hz) , 2.88-2.96 (m, 1H), 3.05-3.10 (m, 1H), 3.43-3.46 (m, 1H), and 3.64-3.69 (m, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 7.8, 12.2, 18.2, 21.4, 26.4, 27.5, 33.8, 34.6, 40.3, 52.1, 59.6, 61.5, 63.1, 66.4, and 210.3.

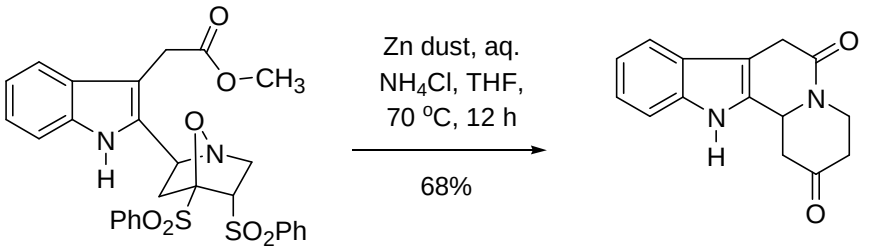


precursor-**156**-*oxime*; X = O
156-*oxime*; X = NOH

156

[2-(4,5-Bis-benzenesulfonyl-7-oxa-1-aza-bicyclo[2.2.1]hept-2-yl)-1H-indol-3-yl]-acetic acid methyl ester (156). To a solution of 1.0 g (4.6 mmol) of (2-formyl-1H-indol-3-yl)-acetic acid methyl ester (*precursor*-**156**-*oxime*)[160] in 23 mL of EtOH was added 0.9 g (13.8 mmol) of hydroxylamine hydrochloride and 0.7 g (9.2 mmol) of pyridine. The solution was stirred at rt for 24 h, then concentrated in vacuo. The residue was purified by silica gel chromatography to provide 0.6 g (56%) of the intermediate oxime (**156**-*oxime*) as a yellow oil: IR (neat) 3340, 2254, 1720, 1439, 1221, and 966 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.84 (s, 2H), 7.05-7.19 (m, 2H), 7.64 (d, 2H, *J* = 8.8 Hz), 7.75 (br s, 1H), and 8.70 (br s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 30.1, 52.5, 111.3, 112.8, 119.7, 120.5, 124.8, 127.9, 128.1, 136.5, 141.1, and 171.7.

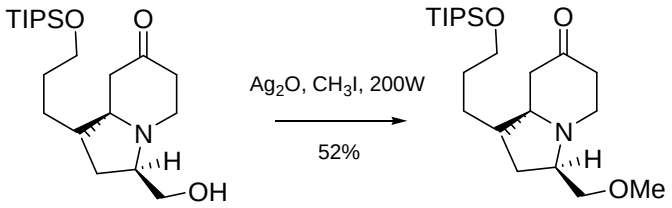
To a sealed tube charged with 0.6 g (2.5 mmol) of the above oxime (**156**-*oxime*) in 20 mL of toluene was added 1.0 g (2.8 mmol) of 2,3-*bis*(phenylsulfonyl)butadiene (**69**).[55] The vessel was sealed and heated to 125 ^{o}C for 12 h. The reaction was then cooled and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography to give 0.7 g (49%) of the titled cycloadduct **156** as a pale yellow oil: IR (neat): 3448, 2954, 2255, 1737, 1449, and 1086 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 2.25-2.30 (m, 1H), 3.71 (s, 3H), 3.79-3.87 (m, 6H), 4.52-4.59 (m, 1H), 4.76 (dd, 1H, *J* = 16.6 and 6.6 Hz), 6.93 (d, 1H, *J* = 10.8 Hz), 7.07-7.94 (m, 12 H), and 8.04 (d, 1H, *J* = 10.8 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 30.0, 37.9, 52.4, 60.4, 66.3, 102.9, 105.2, 110.8, 118.9, 120.0, 122.8, 128.9, 130.5, 135.0, 135.3, 135.5, 138.7, and 171.9.



156 **157**

1,3,4,7,12,12b-Hexahydro-indolo[2,3-a]quinolizine-2,6-dione (157). To a round bottom flask charged with 100 mg (0.17 mmol) of cycloadduct **156** in 4 mL of a saturated NH_4Cl/H_2O/THF (1:1:1) solution was added 577 mg (8.82 mmol) of zinc dust. The reaction mixture was stirred vigorously and was heated to 70 ºC for 12 h, cooled to rt and filtered through a pad of celite. The filtered solid was washed with an aqueous $NaHCO_3$ solution, and the filtrate was collected and extracted with ether. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography provided 31 mg (68%) of carboline **157** as a yellow oil: IR (CH_2Cl_2): 3402, 3055, 2926, 1714, 1616, and 1264 cm^{-1}; ^{1}H-NMR

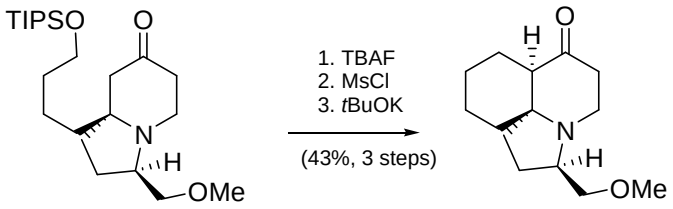
($CDCl_3$, 400 MHz) δ 2.56-2.70 (m, 3H), 2.91 (m, 1H), 3.04 (dt, 1H, *J* = 4.0 and 12.8 Hz), 3.84 (d, 2H, *J* = 2.8 Hz), 5.00 (dd, 1H, *J* = 3.2 and 12.0 Hz), 5.24-5.29 (m, 1H), 7.17 (t, 1H, *J* = 8.0 Hz), 7.26 (t, 1H, *J* = 8.0 Hz), 7.38 (d, 1H, *J* = 8.0 Hz), 7.51 (d, 1H, *J* = 8.0 Hz), and 7.91 (br s, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 29.4, 29.9, 41.3, 41.9, 49.6, 96.3, 111.4, 118.9, 123.5, 126.0, 132.9, 137.0, 177.0, and 202.8. HRMS Calcd for [$C_{15}H_{14}N_2O_2$+ H^+]: 255.1135. Found: 255.1128.



155 **158**

3-Methoxymethyl-8a-(4-triisopropylsilanyloxy-butyl)-hexahydro-indolizin-7-one (158). To a microwave vessel equipped with a magnetic stirbar and charged with 0.08 g (0.20 mmol) of alcohol **155** in 0.40 mL of acetonitrile was added 0.09 g (0.40 mmol) of Ag_2O and 0.25 mL (4.02 mmol) of methyl iodide. The vessel was flushed with argon, sealed, and heated to 60 ^oC in a microwave reactor for 50 min at 200 W. The reaction mixture was then filtered through a celite pad, concentrated under reduced pressure, and purified using silica gel chromatography to give 0.04 g (52%) of the titled ether **158** as a yellow oil: IR (CH_2Cl_2) 2926, 1703, 1438, 1116, and 908 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 1.04-1.05 (m, 21H), 1.25-1.51 (m, 7H), 1.57-1.60 (m, 2H), 1.85 (dt, 1H, *J* = 12.6 and 3.5 Hz), 2.00-2.06 (m, 2H), 2.16 (dd, 1H, *J* = 13.6 and 1.8 Hz), 2.31 (d, 1H, *J* = 13.6 Hz), 2.55 (ddd, 1H, *J* = 13.7, 12.6, and 6.6 Hz), 3.08 (dt, 1H, *J* = 12.0 and 3.5 Hz), 3.28 (dd, 1H, *J* = 8.4 and 6.0), 3.32-3.46 (m, 5H), and 3.62-3.70 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 12.2, 18.2, 20.4, 25.6, 33.6, 35.0, 36.7, 37.6, 44.6,

47.8, 58.9, 59.4, 63.4, 69.5, 78.1, and 211.1; HRMS Calcd for [$C_{23}H_{45}NO_3Si+H^+$]: 412.3202. Found: 412.3216.



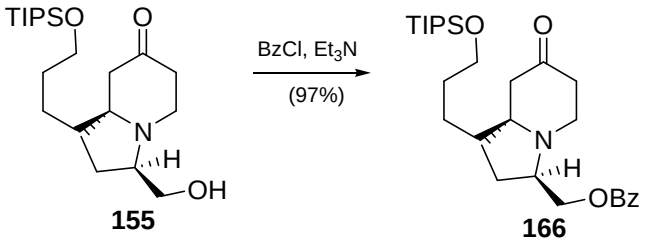
158 **160**

3-Methoxymethyl-octahydro-pyrrolo[2,1-j]quinolin-7-one (160) To a roundbottom flask charged with 70 mg (0.18 mmol) of the starting silyl ether **158** was added 4Å molecular sieves and 3 mL of dry THF. The reaction vessel was then purged with nitrogen and chilled to 0 ^oC. To this stirring mixture was added dropwise 0.19 mL (0.19 mmol) of a 1.0 M solution of TBAF in THF over the course of 10 min. The reaction mixture was then warmed to rt and allowed to stir for 1 h, filtered through a pad of Celite, and rinsed with ethyl ether. The filtrate was then partitioned between ether and an aqueous sodium bicarbonate solution, the organic layer was collected, washed with brine, dried with Na_2SO_4, then concentrated under reduced pressure. The crude residue was purified by flash silica chromatography to give a yellow oil which was dissolved in 1 mL of CH_2Cl_2 and immediately subjected to the next step.

To a roundbottom flask charged with the above residue that was dissolved in 1 mL of CH_2Cl_2 was added 30 μL (0.39 mmol) of mesyl chloride and the mixture was chilled to 0 ^oC. To this stirring solution was added dropwise 0.11 mL (0.78 mmol) of triethylamine over the course of 5 min. The solution was then warmed to rt and allowed to stir for 1 h, then partitioned between CH_2Cl_2 and aqueous sodium bicarbonate. The organic layer was collected, washed with

water and brine, dried over Na_2SO_4, and concentrated to give a yellow residue which was immediately dissolved in 3 mL of DMF and subjected to the next step.

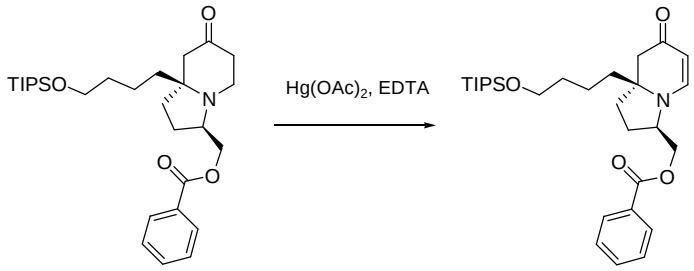
To a roundbottom flask charged with the above mesylate solution chilled to 0 ^oC was added 0.20 mL (0.20 mmol) of 1.0 M potassium *t*-butoxide solution in THF. The reaction was allowed to stir at 35 ^oC over the course of 2 h. The reaction was then partitioned between ethyl acetate and water. The organic layer was collected, washed with water twice, then brine, then dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography to give 17 mg (43% for 3 steps) of the titled tricyclic amine **160** which was isolated as a single diastereomer as a pale yellow oil: IR (CH_2Cl_2) 1716, 1663, 1358, 1114, and 747 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.93-0.98 (m, 1H), 1.01-1.04 (m, 1H), 1.23-1.75 (m, 8H), 2.05-2.10 (m, 2H), 2.22 (dd, 1H, *J* = 13.2 and 1.8 Hz), 2.39 (br d, 1H, *J* = 3.6 Hz), 2.58 (ddd, 1H, *J* = 13.7, 12.6, and 6.6 Hz), 2.88-3.04 (m, 1H), 3.25 (t, 1H, *J* = 13.8 Hz), and 3.30-3.43 (m, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 15.3, 16.2, 18.0, 19.4, 28.9, 29.8, 30.8, 38.0, 44.1, 52.8, 52.9, 63.2, 71.5, and 210.4; HRMS Calcd for [$C_{14}H_{23}NO_2$+ H^+]: 238.1802. Found: 238.1800.



155 **166**

Benzoic Acid 7-Oxo-8*a*-(4-triisopropylsilanyloxy-butyl)-octahydro-indolizin-3-yl Methyl Ester (166). To a round bottom flask charged with 1.0 g (2.4 mmol) of the starting alcohol **155** in 24.4 mL of CH_2Cl_2 was added 0.7 mL (4.9 mmol) of triethylamine, 0.4 mL (2.9 mmol) of benzoyl chloride, and a catalytic amount of DMAP, sequentially. The reaction mixture was stirred at rt for 2 h, and was then

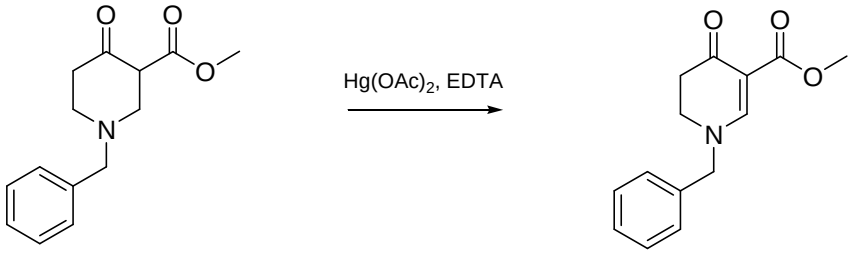
partitioned between CH_2Cl_2 and aqueous $NaHCO_3$. The organic layer was extracted with ether, washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography provided 1.2 g (97%) of the titled ester **166** as a yellow oil: IR (CH_2Cl_2) 2942, 2856, 1722, 1269, 1108, and 712 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.03-1.06 (m, 21H), 1.25-1.35 (m, 3H), 1.41-1.55 (m, 4H), 1.76-1.83 (m, 1H), 1.90-1.98 (m, 1H), 2.04-2.10 (m, 1H), 2.12-2.18 (m, 1H), 2.19 (dd, 1H, *J* = 13.6 and 2.1 Hz), 2.33 (d, 1H, *J* = 13.6 Hz), 2.51-2.60 (m, 1H), 3.07-3.15 (m, 1H), 3.41 (ddd, 1H, *J* = 14.4, 6.4 and 1.9 Hz), 3.52-3.56 (m, 1H), 3.59 (t, 2H, *J* = 6.8 Hz), 4.24-4.33 (m, 2H), 7.44 (t, 2H, *J* = 7.6 Hz), 7.56 (t, 1H, *J* = 7.4 Hz) and 8.03 (dd, 2H, *J* = 7.4 and 1.4 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 12.2, 18.2, 20.1, 25.5, 33.5, 34.9, 36.7, 37.3, 44.3, 48.2, 58.5, 63.3, 68.1, 69.2, 128.6, 129.8, 133.2, 166.8, and 210.7; HRMS Calcd for [$C_{29}H_{47}NO_4Si + H^+$]: 502.3347. Found: 502.3342.



166 **168**

Benzoic acid 7-oxo-8a-(4-triisopropylsilanyloxy-butyl)-1,2,3,7,8,8a-hexahydro-indolizin-3-ylmethyl ester (168). To a RB flask charged with 40 mg (0.08 mmol) of the starting benzoic ester **166** dissolved in 2 mL of 1:1 EtOH/H_2O was added 38 mg (0.12 mmol) of $Hg(OAc)_2$ and 44 mg (0.12 mmol) of EDTA. The mixture was then heated to 80 ^oC for 2 h, then cooled to rt and filtered through a pad of Celite. The filtrates were then partitioned between CH_2Cl_2 and aq. NH_4Cl. The organics were extracted, washed with water, brine, then dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to

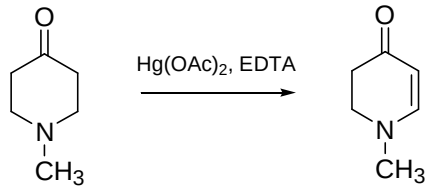
give was prepared to give 38 mg (95%) of the titled enone **168** as a yellow oil: IR (CH_2Cl_2) 2349, 1854, 1717, 1585, and 976 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 1.02-1.05 (m, 21H), 1.18-1.28 (m, 4H), 1.71-1.79 (m, 2H), 1.92-2.02 (m, 2H), 2.17-2.27 (m, 2H), 2.48-2.57 (m, 2H) 3.57-3.67 (m, 2H), 4.05-4.07 (m, 1H), 4.32 (dd, 1H, *J* = 5.8 and 11.6 Hz), 4.60 (dd, 1H, *J* = 4.0 and 12.0 Hz), 4.96 (d, 1H, *J* = 7.2 Hz), 7.28 (d, 1H, *J* = 7.2 Hz), 7.47 (t, 2H, *J* = 7.6 Hz), 7.60 (t, 1H, *J* = 7.6 Hz), and 8.03 (d, 2H, *J* = 7.6 Hz); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 12.1, 18.2, 20.9, 27.1, 29.9, 33.5, 34.2, 36.5, 45.6, 59.7, 63.1, 66.1, 97.3, 128.8, 129.6, 129.8, 133.7, 148.2, 166.3, and 191.6; HRMS Calcd. for [$C_{29}H_{45}NO_4Si$+H+]: 500.3189. Found: 500.3190.



precursor **175** **175**

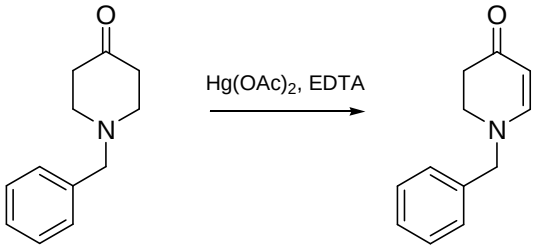
General Procedure for the dehydration of N-alkyl-4-piperidones using $Hg(OAc)_2$: 1-Benzyl-4-oxo-1,4,5,6-tetrahydro-pyridine-3-carboxylic acid methyl ester (175): To a RB flask charged with 250 mg (88 mmol) of 1-benzyl-4-oxo-3-piperidinecarboxylate was added 30 mL of a solution of H_2O/EtOH (2:1) , 295 mg (92 mmol) of $Hg(OAc)_2$, and 344 mg (92 mmol) of EDTA sequentially. The mixture was then heated to 80 ^oC for 2 h, then cooled to rt and filtered through a pad of Celite. The filtrates were then partitioned between CH_2Cl_2 and aq. NH_4Cl. The organics were extracted, washed with water, brine, then dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give 191 mg (88%) of the titled vinylogous amide **175** as a colorless oil which

required no further purification: : IR (CH_2Cl_2): 1719, 1658, 1601, 1436, 1337, 1155, and 1054 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 2.56 (t, 2H, *J* = 8.1 Hz), 3.52 (t, 2H, *J* = 7.2 Hz), 3.84 (s, 3H), 4.62 (s, 2H), 7.34 (t, 2H, *J* = 6.6 Hz), 7.43-7.48 (m, 3H), 8.41 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 36.1, 46.3, 51.7, 61.3, 100.5, 128.0, 129.2, 129.5, 134.2, 160.0, 166.4, and 186.6; HRMS Calcd. for [$C_{14}H_{15}NO_3$+ H+]: 246.1052. Found: 246.1125.



precursor **165** **165**

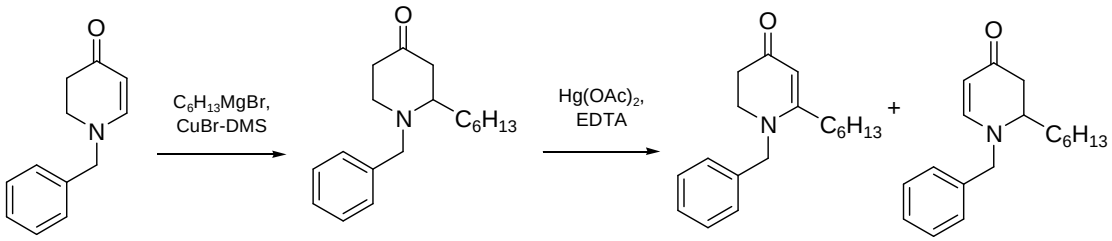
1-Methyl-2,3-dihydro-1H-pyridin-4-one (165) was prepared using the general mercuric acetate conditions in 95% yield as a pale yellow oil; IR (CH_2Cl_2) 2854, 1707, 1631, 1581, and 1269 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.49 (t, 2H, *J* = 8.2 Hz), 3.02 (s, 3H), 3.41 (t, 2H, *J* = 8.2 Hz), 4.94 (d, 1H, *J* = 7.2 Hz), and 6.94 (d, 1H, *J* = 7.2 Hz). The spectral data was identical to the values reported in the literature.[161]



precursor **176** **176**

1-Benzyl-2,3-dihydro-1H-pyridin-4-one (176) was prepared using the general mercuric acetate conditions in 90% yield as a yellow oil; IR (CH_2Cl_2) 2923, 1716, 1634, 1584, and 1180 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.45 (t, 2H, *J* = 8.0 Hz), 3.38 (t, 2H, *J* = 8.0 Hz), 4.36, (s, 2H), 4.99 (d, 1H, *J* = 7.6 Hz), 7.14 (d, 1H, *J* =

7.6 Hz), 7.24-7.26 (m, 2H), and 7.32-7.42 (m, 3H). The spectral data was identical to the values reported in the literature.[162]



176 **176a** **177** (71%) **177**-*minor* (20%)

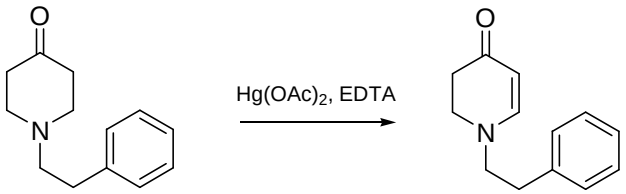
1-Benzyl-6-hexyl-2,3-dihydro-1H-pyridin-4-one (177). To an oven-dried RB flask charged with 15 mg (0.08 mmol) of 1-benzyl-2,3-dihydro-1H-pyridin-4-one (**176**) was added 59 mg (0.28 mmol) of dry copper (I) bromide-dimethylsulfide complex and the atmosphere was flushed with argon. To this mixture was added 0.9 mL of redistilled THF and the solution was cooled to -78 ^oC. To this stirring solution was added 40 μL (0.32 mmol) of redistilled BF_3-OEt_2 and the mixture was allowed to stir at -78 ^oC for 15 minutes. To this mixture was dropwise added 144 μL (0.28 mmol) of a 2.0 M solution of *n*-hexylmagnesium bromide in THF and the reaction was allowed to stir for 15 minutes, then warmed to 0 ^oC and stirred for an additional 15 minutes, before being warmed to rt. The reaction mixture was then transferred to a separatory funnel and partitioned between ether and water. The organics were extracted, washed twice with water, then brine, then dried using $MgSO_4$, filtered, and concentrated. The crude residue was purified using flash silica chromatography to give 20 mg (91%) of 1-benzyl-2-hexyl-piperidin-4-one (**176a**) as a pale yellow oil: IR (CH_2Cl_2) 2934, 1721, and 1104 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 0.88 (t, 3H, *J* = 6.9 Hz), 1.26-1.48 (m, 8H), 1.59-1.66 (m, 2H), 2.31-2.34 (m, 2H), 2.39-2.43 (m, 1H), 2.57 (dd, 1H, *J* = 5.1 and 14.1 Hz), 2.69-2.73 (m, 1H), 2.95-2.99 (m, 1H), 3.01-3.06 (m, 1H), 3.64

(d, 1H, *J* = 13.5 Hz), 3.90 (d, 1H, *J* = 13.5 Hz), 7.27 (t, 1H, *J* = 7.8 Hz), 7.33 (t, 2H, *J* = 7.8 Hz), and 7.38 (d, 2H, *J* = 7.8 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.3, 22.8, 25.8, 29.5, 31.3, 31.9, 39.7, 44.9, 48.2, 56.2, 60.9, 127.3, 128.6, 128.8, 139.4, and 210.4.

To a RB flask charged with 20 mg (0.07 mmol) of the above starting piperidone **176a** was added 2.4 mL of water/ethanol (2:1) at rt. To this solution was added 30 mg (0.09 mmol) of mercuric acetate and 35 mg (0.09 mmol) of EDTA. The mixture was heated to 80 ^{o}C for 2h, then cooled to rt. The mixture was then transferred to a separatory funnel and partitioned between CH_2Cl_2 and aqueous NH_4Cl. The organics were extracted, washed with aqueous $NaHCO_3$, water, brine, dried using $MgSO_4$, filtered, and then concentrated under reduced pressure. The crude material was then purified by silica gel chromatography to produce 14 mg (71%) of the titled vinylogous amide **177** as a colorless oil: IR (CH_2Cl_2) 2955, 2359, 1639, 1544, and 1458 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, 3H, *J* = 6.9 Hz), 1.04-1.06 (m, 2H), 1.25-1.65 (m, 8H), 2.30 (t, 2H, *J* = 7.8 Hz), 2.40 (t, 2H, *J* = 7.7 Hz), 3.45 (t, 2H, *J* = 7.7 Hz), 4.51 (s, 2H), 5.07 (s, 1H), 7.20 (d, 2H, *J* = 6.9 Hz), and 7.32-7.41 (m, 3H); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 14.2, 18.2, 22.6, 28.4, 29.9, 33.8, 35.8, 49.1, 54.1, 99.1, 126.7, 128.1, 129.2, 169.3, and 194.7. HRMS Calcd. for [$C_{18}H_{25}NO$+ H+]: 272.2005. Found: 272.2008.

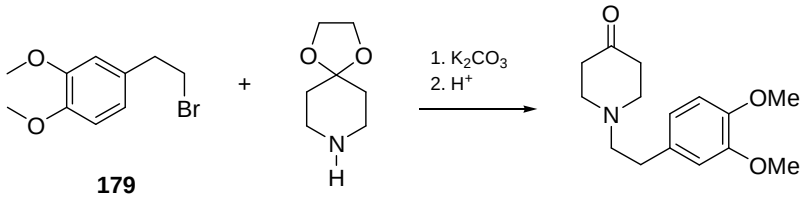
The minor regioisomer was fully separated from the major regioisomer. Silica gel purification gave 4 mg (20%) of 1-benzyl-2-hexyl-2,3-dihydro-1H-pyridin-4-one (**177**-*minor*) as a yellow oil which exhibited the following characteristic spectroscopic data: IR (CH_2Cl_2) 1633, 1579, 1269, 1211, and 1111 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.82-0.90 (m, 3H), 1.04-1.30 (m, 8H), 2.31 (d, 1H, *J* = 12.9 Hz), 2.42-2.48 (m, 1H), 2.70 (dd, 1H, *J* = 16.7 and 6.2 Hz), 3.41-3.46 (m, 1H), 4.32-4.45 (m, 2H) , 4.94 (d, *J* = 7.1 Hz, 1H), 7.05 (d, *J* = 7.1, 1H),

and 7.20-7.42 (m, 5H). HRMS Calcd. for [$C_{18}H_{25}NO$+ H+]: 272.2007. Found: 272.2009.



precursor **178** **178**

1-Phenethyl-2,3-dihydro-1H-pyridin-4-one (178) was prepared using the general mercuric acetate conditions in 92% yield as a yellow oil; IR (CH_2Cl_2) 3060, 1713, 1628, 1585, and 1180 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.43 (t, 2H, *J* = 7.9 Hz), 2.88 (t, 2H, *J* = 7.9 Hz), 3.41-3.48 (m, 4H), 4.85 (d, 1H, *J* = 7.5 Hz), 6.81 (d, 1H, *J* = 7.5 Hz), 7.16-7.19 (m, 2H), and 7.23-7.35 (m, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 35.7, 47.4, 57.9, 98.7, 128.2, 128.7, 130.0, 138.0, 154.4, and 191.6; HRMS Calcd. for [$C_{13}H_{15}NO+H^+$]: 202.1225. Found: 202.1226.

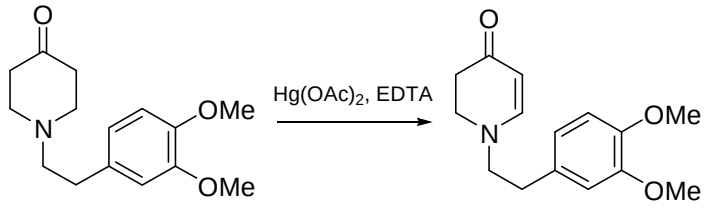


179 **183** **180**

1-[2-(3,4-Dimethoxy-phenyl)-ethyl]-piperidin-4-one (180). To a solution containing 1.00 g (6.98 mmol) of 4-(2-bromo-ethyl)-1,2-dimethoxy-benzene (**179**)[163] in 28 mL of a MeCN/water (6:1) at rt was slowly added 2.41 g (17.5 mmol) of K_2CO_3 and 1.45 mL (6.63 mmol) of 1,4-dioxa-8-aza-spiro[4.5]decane (**183**)[164] sequentially. The reaction mixture was then transferred to a separatory funnel and partitioned between aqueous $NaHCO_3$ and ethyl acetate. The organic layer was washed twice with water, once with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash

silica chromatography to give 1.94 g (90%) of the intermediate acetal[165] as a yellow oil which was immediately dissolved in 79 mL of 2N HCl in AcOH and subjected to the following reaction conditions.

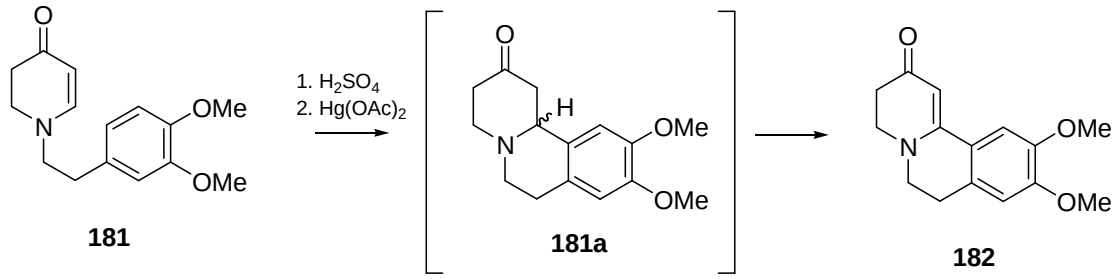
A solution of the above acetal in 2N HCl in AcOH was heated to 90 ^{o}C for 16 h. The reaction mixture was then cooled to RT, brought to pH 8.0 with dilute NaOH, and extracted twice with toluene. The combined organics were washed with water, brine, then dried with $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash chromatography to give 1.10 g (66%) of the titled piperidone **180** as a colorless oil: IR (CH_2Cl_2) 2926, 2359, 1710, 1515, and 1148 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.48 (t, 4H, *J* = 6.2 Hz), 2.68-2.74 (m, 2H), 2.78-2.82 (m, 2H), 2.83 (t, 4H, *J* = 6.2 Hz), 3.86 (s, 3H), 3.88 (s, 3H), 6.75 (dd, 2H, *J* = 2.0 and 8.0 Hz), and 6.81 (d, 1H, *J* = 8.0 Hz).



180 **181**

1-[2-(3,4-Dimethoxy-phenyl)-ethyl]-2,3-dihydro-1H-pyridin-4-one (181) was prepared using the general mercuric acetate conditions in 81% as a yellow oil: IR (CH_2Cl_2) 2940, 2360, 1841, 1634, 1585, and 731 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 2.42 (t, 2H, *J* = 7.4 Hz), 2.81 (t, 2H, *J* = 7.4 Hz), 3.40-3.46 (m, 4H), 3.85 (s, 6H), 4.84 (d, 1H, *J* = 7.5 Hz), 6.66 (d, 1H, *J* = 2.0 Hz), 6.69 (dd, 1H, *J* = 8.1 and 2.1Hz), 6.79 (d, 1H, *J* = 7.5 Hz), and 6.81-6.84 (m, 1H); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 30.1, 35.4, 36.0, 47.6, 56.2, 56.3, 58.3, 98.1, 111.8, 112.2, 118.5,

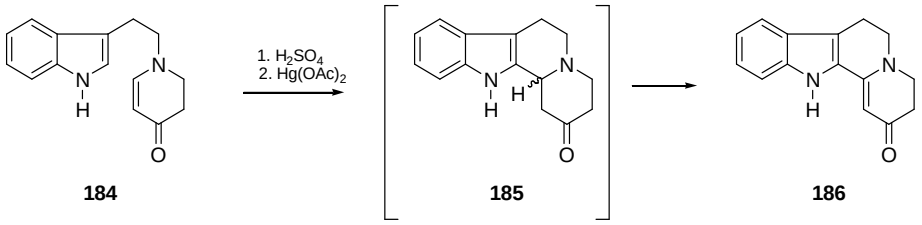
121.3, 130.4, 154.4, and 191.7; HRMS Calcd. for [$C_{15}H_{19}NO_3$+H+]: 262.1436. Found: 262.1437.



9,10-Dimethoxy-3,4,6,7-tetrahydro-pyrido[2,1-a]isoquinolin-2-one (182) To a RB flask charged with 11 mg (0.04 mmol) of 1-[2-(3,4-dimethoxy-phenyl)-ethyl]-2,3-dihydro-1H-pyridin-4-one (**181**) was added 3 mL of 10% H_2SO_4 and the mixture was heated to 90 ^oC for 12 h. The reaction mixture was then cooled to RT, brought to pH 8.0 with dilute NaOH, and extracted twice with CH_2Cl_2. The combined organics were washed with water, brine, then dried with $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash silica chromatography to give 10 mg (91%) of the intermediate quinolinone **181a** as a pale yellow oil which was immediately subjected to the following reaction conditions.

To a RB flask charged with the intermediate quinolinone **181a** was added in 6.7 mL of water/ethanol (2:1), 12 mg (0.04 mmol) of mercuric acetate, and 15 mg (0.04 mmol) of EDTA sequentially. The mixture was heated to 80 ^oC for 2 h, then cooled to rt and partitioned between aqueous NH_4Cl and CH_2Cl_2. The organics were extracted, washed with aqueous $NaHCO_3$, water, brine, dried using $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash silica chromatography to give 6 mg (59%) of the titled vinylogous amide **182** as a colorless oil: IR (CH_2Cl_2) 2091, 1644, and 1293 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.58 (t, 2H, *J* = 7.6 Hz), 2.80 (t, 2H, *J* = 7.6 Hz), 2.95 (t, 2H, *J* = 6.2 Hz), 3.39 (t,

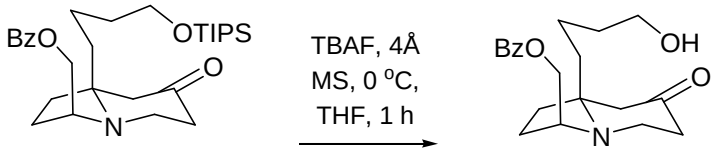
1H, *J* = 6.2 Hz), 3.62 (t, 1H, *J* = 7.6 Hz), 3.87 (s, 3H), 3.92 (s, 3H), 5.69 (s, 1H), 6.66 (s, 1H), and 7.16 (s, 1H). The spectral data was identical to the values reported in the literature.[166]



3,4,7,12-Tetrahydro-6H-indolo[2,3-a]quinolizin-2-one (186). To a solution of 45 mg (0.18 mmol) of 1-[2-(1H-indol-3-yl)-ethyl]-2,3-dihydro-1H-pyridin-4-one[167] (**184**) in 3 mL of 20% H_2SO_4 was added 1 mL of water and the mixture was heated to 90 ^oC for 12 h. The reaction mixture was then cooled to RT, brought to pH 8.0 with dilute NaOH, and extracted twice with CH_2Cl_2. The combined organics were washed with water, brine, then dried with $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash silica chromatography to give 45 mg (90%) of intermediate **185** as a pale yellow oil which was immediately dissolved in 6.7 mL of water/ethanol (2:1) and subjected to the following reaction conditions.

To a solution of the above intermediate **185** in 6.7 mL of water/ethanol (2:1) was sequentially added 54 mg (0.18 mmol) of mercuric acetate and 65 mg (0.18 mmol) of EDTA. The mixture was heated to 80 ^oC for 2 h, then cooled to rt and partitioned between aqueous NH_4Cl and CH_2Cl_2. The organics were extracted, washed with aqueous $NaHCO_3$, water, brine, dried using $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash silica chromatography to give 32 mg (71%) of the titled vinylogous amide **186** as a pale yellow oil: IR (CH_2Cl_2) 3403, 2839, 1708, and 1105 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.66 (t, 2H, *J* = 7.5 Hz), 3.12 (t, 2H, *J* = 6.8 Hz), 3.47 (t, 2H, *J* = 6.8 Hz),

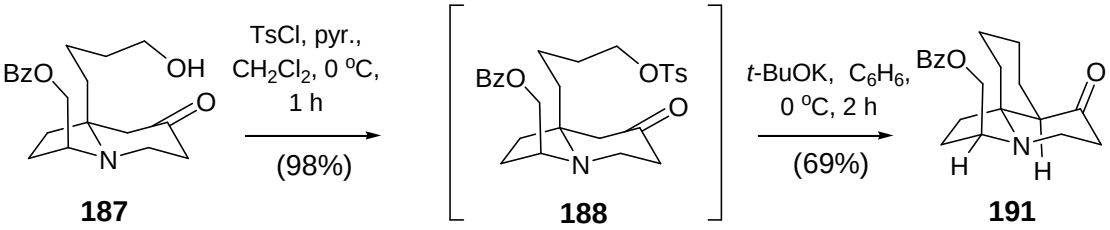
3.59 (t, 2H, *J* = 7.5 Hz), 5.60 (s, 1H), 7.13-7.33 (m, 2H), 7.46 (d, 1H, *J* = 8.0 Hz), 7.56 (d, 1H, *J* = 8.0 Hz), and 8.90 (br s, 1H). The spectral data was identical to the values reported in the literature.[167]



166 **187**

Benzoic acid 8a-(4-hydroxy-butyl)-7-oxo-octahydro-indolizin-3-ylmethyl ester (187). An oven-dried round bottom flask was charged with 0.96 g (1.92 mmol) of the starting silyl ether **166**, 4Å molecular sieves and 19 mL of anhydrous THF and was cooled to 0 ºC under an argon atmosphere. To this mixture was added 2.3 mL (2.3 mmol) of a 1.0 M solution of TBAF in THF over the course of 30 min. The solution was allowed to stir for an additional 1.5 h while being warmed to rt. The reaction mixture was filtered through a pad of celite and the collected solid was rinsed with ether. The filtrate was then partitioned between ether and aqueous $NaHCO_3$ and the organic layer was extracted, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography provided 0.51 g (77%) of alcohol **187** which was isolated as a colorless oil: IR (CH_2Cl_2) 3361, 2918, 1717, 1271, 1146 and 713 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.22-1.29 (m, 5H), 1.38-1.54 (m, 4H), 1.78-1.83 (m, 2H), 1.89-1.96 (m, 1H), 2.04-2.06 (m, 1H), 2.10-2.14 (m, 1H), 2.16 (d, 1H, *J* = 7.6 Hz), 2.32 (d, 1H, *J* = 9.2 Hz), 2.50-2.57 (m, 1H), 3.05-3.12 (m, 1H), 3.39 (ddd, 1H, *J* = 9.4, 4.2, and 0.8 Hz), 3.49-3.54 (m, 1H), 4.23 (dd, 1H, *J* = 7.4 and 3.0 Hz), 4.35 (dd, 1H, *J* = 7.4 and 3.8 Hz), 7.4 (t, 2H, *J* = 7.6 Hz), 7.55 (dt, 1H, *J* = 7.4 and 0.4 Hz) and 8.01 (dd, 2H, *J* = 7.4 and 1.4 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 20.7, 26.0, 33.8, 35.6, 37.4, 37.8,

45.0, 48.9, 59.3, 63.5, 68.5, 69.9, 129.3, 130.4, 131.1, 133.9, 167.4, and 211.5; HRMS Calcd for [$C_{20}H_{27}NO_4$+ H^+]: 346.2009. Found: 346.2007.

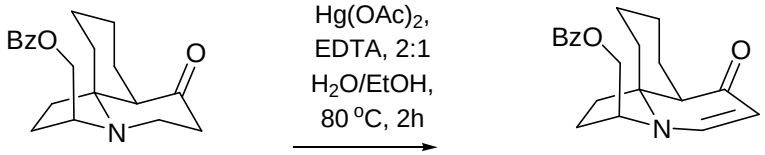


187 **188** **191**

Benzoic acid 7-oxo-decahydro-pyrrolo[2,1-j]quinolin-3-ylmethyl ester (191). To a round bottom flask charged with 42 mg (0.12 mmol) of alcohol **187** was added 1.2 mL of CH_2Cl_2 and 0.025 mL (0.27 mmol) of pyridine, sequentially. The mixture was cooled to 0 °C prior to the addition of 49 mg (0.26 mmol) of tosyl chloride. The solution was allowed to stir for 1 h while being warmed to rt. The reaction mixture was then partitioned between CH_2Cl_2 and aqueous $NaHCO_3$. The organic layer was extracted, washed with water, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash silica chromatography to give 60 mg (98%) of the unstable tosylate **188** as a yellow oil which was dissolved in 4 mL of dry benzene and immediately subjected to next step.

An oven-dried round bottom flask equipped with a stirbar and 4 Å molecular sieves was sealed and degassed with argon. To this flask was added 2 mL of dry benzene and 0.25 mL (0.25 mmol) of a 1.0 M solution of potassium *t*-butoxide in THF. The mixture was cooled to 0 °C and 4 mL (0.12 mmol) of a 0.03 M solution of tosylate **188** in benzene was added dropwise over the course of 30 min. After stirring for an additional 30 min, the reaction mixture was warmed to rt and stirred for an additional 1h and then filtered through a pad of celite. The filtrate was concentrated under reduced pressure and then partitioned between ethyl acetate and aqueous $NaHCO_3$. The organic layer was extracted with ether

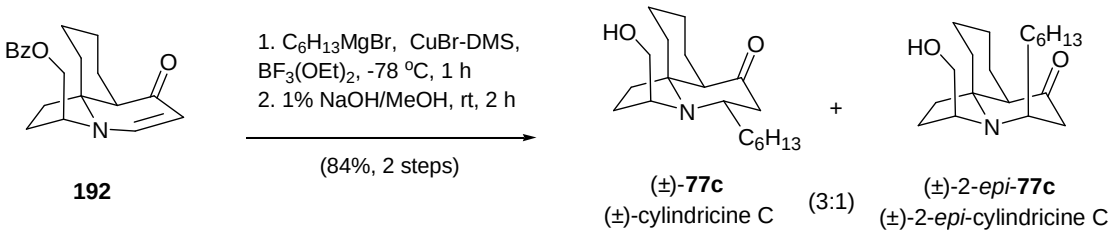
and washed with brine, dried over Na_2SO_4, then concentrated under reduced pressure. Purification of the residue by silica gel chromatography provided 27 mg (69%) of the titled compound **191** as a yellow oil: IR (CH_2Cl_2) 2923, 1717, 1459, 1271, and 1104 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 1.25-1.51 (m, 6H), 1.67 (d, 1H, *J* = 10.4 Hz), 1.74-1.84 (m, 2H), 2.07-2.10 (m, 1H), 2.14-2.18 (m, 2H), 2.23-2.26 (m, 1H), 2.40 (d, 1H, *J* = 4.2 Hz), 2.59 (ddd, 1H, *J* = 13.5, 12.0, and 5.4 Hz), 3.30 (ddd, 1H, *J* = 14.4, 11.7, and 3.5 Hz) 3.38 (ddd, 1H, *J* = 14.4, 6.3, and 3.3 Hz), 3.60 (dt, 1H, *J* = 9.6 and 3.6 Hz), 4.29 (dd, 1H, *J* = 11.4 and 6.0 Hz), 4.30 (dd, 1H, *J* = 11.4 and 5.9 Hz), 7.46 (t, 2H, *J* = 7.6 Hz), 7.57 (dt, 1H, *J* = 7.4 and 1.2 Hz) and 8.03 (dd, 2H, *J* = 7.4 and 1.4 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 21.8, 22.8, 24.5, 25.6, 35.5, 36.5, 37.5, 44.4, 50.9, 59.0, 68.5, 69.4, 128.6, 129.7, 130.4, 133.2, 166.8, and 211.1; HRMS Calcd for [$C_{20}H_{25}NO_3$ + H^+]: 328.1907. Found: 328.1901.



191 **192**

Benzoic Acid 7-Oxo-2,3,7,7*a*,8,9,10,11-octahydro-1*H*-pyrrolo[2,1-*j*]quinolin-3-yl Methyl Ester (192). To a round bottom flask charged with 4.8 mg (14.4 μmol) of the octahydroquinolone **191** dissolved in 1.0 mL of a 2:1-EtOH/water mixture at rt was added 5.8 mg (15.5 μmol) of EDTA and 4.9 mg (15.5 μmol) of mercuric acetate. The mixture was heated at 80 °C for 1.5 h, cooled to rt and the solution was partitioned between aqueous aqueous ammonium chloride and CH_2Cl_2. The organic layer was extracted with ether, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide 4.7 mg (95%) of enone **192** as a yellow oil: IR (CH_2Cl_2) 2926, 1721, 1633, 1579,

1269, and 1111 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 1.25-1.34 (m, 4H), 1.45-1.48 (m, 1H), 1.65-1.71 (m, 1H), 1.76-1.82, (m, 1H), 1.88-1.96 (m, 1H), 2.03-2.07 (m, 1H), 2.27 (d, 1H, *J* = 6.9 Hz), 2.43 (dd, 1H, *J* = 12.3 and 6.9 Hz), 2.50 (brs, 1H), 2.53 (brs, 1H), 4.09 (brt, 1H, *J* = 13.5 Hz), 4.31 (dd, 1H, *J* = 12.0 and 6.0 Hz), 4.55 (dd, 1H, *J* = 12.0 and 4.6 Hz), 4.95 (d, 1H, *J* = 7.2 Hz), 7.22 (d, 1H, *J* = 7.2 Hz), 7.47 (t, 2H, *J* = 7.6 Hz), 7.60 (t, 1H, *J* = 7.4 Hz) and 8.03 (d, 2H, *J* = 7.4 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 22.1, 22.9, 24.6, 27.4, 27.8, 30.3, 35.6, 51.1, 60.0, 66.8, 97.6, 129.2, 130.0, 130.2, 134.0, 147.1, 166.7, and 193.6; HRMS Calcd for [$C_{20}H_{23}NO_3 + H^+$]: 326.1750. Found: 326.1750.



192

(±)-**77c**
(±)-cylindricine C

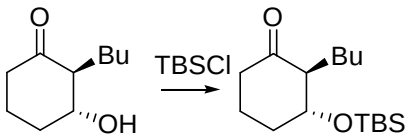
(3:1)

(±)-2-*epi*-**77c**
(±)-2-*epi*-cylindricine C

(+/-)-Cylindricine C ((±)-77c). An oven-dried round bottom flask was charged with 11 mg (53 μmol) of copper bromide-dimethyl sulfide and 0.3 mL of dry THF. The flask was sealed, degassed with argon, and placed in an ice bath. To the resulting slurry was added dropwise 0.3 mL (18.4 μmol) of a 37.0 μM solution of enone **192** in dry THF over the course of 30 min at 0 °C. The reaction mixture was cooled to -78 °C and 8.2 μL (64.5 μmol) of BF_3-OEt_2 was added dropwise over the course of 10 min. To this reaction mixture was added dropwise 28.7 μL (53 μmol) of a 1.86 M solution of *n*-hexylmagnesium bromide in ether over the course of 30 min at -78 °C. The reaction mixture was allowed to stir for an additional 90 min at -78 °C and was then warmed to rt and partitioned between ether and aqueous ammonium chloride. The organic layer was extracted with ether, washed with water, brine, dried with Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash silica

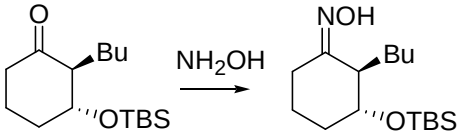
chromatography. The major fraction was immediately added to 5 mL of a 1% NaOH in methanol solution. The reaction mixture was stirred at rt for 2 h and then concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 and 1 N NaOH. The organic layer was extracted with ether, washed with water, brine, dried over Na_2SO_4, and concentrated under reduced pressure to give 3.2 mg (63%) of (±)-cylindricine C ((±)-**77c**) as a colorless oil which exhibited spectroscopic data identical to the material described by Hsung[74]: IR (CH_2Cl_2) 3201, 2926, 2854, 1724, 1633, 1462, 1024, and 804 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 0.88 (t, 3H, *J* = 7.0 Hz), 1.22-1.65 (m, 19H), 1.83 (dd, 1H, *J* = 13.0 and 8.5 Hz), 2.13 (dd, 1H, *J* = 12.5 and 8.0 Hz), 2.23 (dd, 2H, *J* = 13.0 and 3.0 Hz), 2.30 (t, 2H, *J* = 11.4 Hz), 2.88 (brs, 1H), 3.26-3.32 (m, 1H), 3.43 (t, 1H, *J* = 9.3 Hz), and 3.54 (m, 2H) ; ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.6, 22.4, 23.1, 23.3, 24.9, 27.7, 29.3, 30.3, 32.2, 35.8, 36.5, 37.0, 43.1, 50.8, 55.9, 57.1, 58.1, 71.3, and 197.0; HRMS Calcd for [$C_{19}H_{33}NO_2 + H^+$]: 308.2584. Found: 308.2578.

The minor diastereomer was not fully separated from the major diastereomer but exhibited spectroscopic data identical to 2-*epi*-(±)-cylindricine C ((±)-2-*epi*-**77c**) as reported by Hsung[74]: IR (CH_2Cl_2) 3201, 2926, 2854, 1724, 1633, 1462, 1024, and 804 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 0.88 (t, 3H, *J* = 7.0 Hz), 1.22-1.65 (m, 19H), 2.02-2.07 (m, 2H), 2.17 (dd, 1H, *J* = 16.0 and 6.0 Hz), 2.26 (d, 1H, *J* = 10.5 Hz), 2.52-2.53 (m, 1H), 2.65 (dd, 1H, *J* = 15.3 and 5.7 Hz), 2.86 (brs, 1H), 3.22 (dt, 1H, *J* = 6.6 and 1.8 Hz), 3.26-3.32 (m, 1H), 3.36-3.41 (m, 1H), and 3.52-3.57 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.6, 22.4, 23.1, 23.3, 24.9, 27.7, 29.3, 29.9, 32.3, 35.8, 36.5, 37.0, 43.1, 50.8, 55.9, 57.1, 58.1, 66.9, and 197.0; HRMS Calcd for [$C_{19}H_{33}NO_2 + H^+$]: 308.2584. Found: 308.2578.



205 **206**

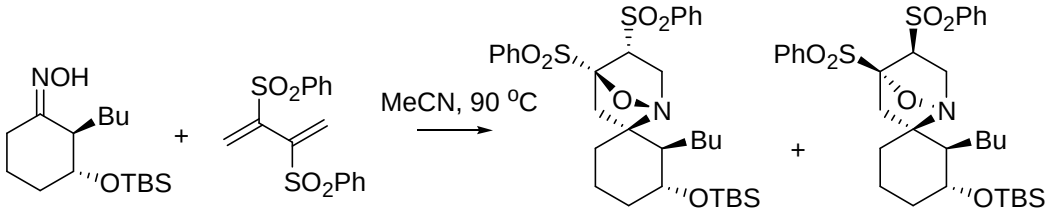
2-Butyl-3-(*t*-butyldimethylsilyloxy)cyclohexanone (206). To a solution of 9.4 g (55 mmol) of 2-butyl-3-hydroxy-cyclohexanone (**205**)[111] in 60 mL of DMF at 0℃ was added 10 g (66 mmol) of TBSCl followed by 9.2 g (135 mmol) of imidazole. The reaction mixture was slowly warmed to 25 ℃ over a period of 3 h. The solution was cooled to 0 ℃, diluted with Et_2O, water was added and the aqueous layer was separated and extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to give 11.4 g (73%) of 2-butyl-3-(*t*-butyldimethylsilyloxy)cyclohexane (**206**) as a yellow oil: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.03 (s, 6H), 0.83-0.91 (m, 3H), 0.86 (s, 9H), 1.14-1.38 (m, 4H), 1.45-1.72 (m, 4H), 1.92-2.10 (m, 2H), 2.17-2.40 (m, 3H) and 3.78 (dt, 1H, *J* = 6.8 and 2.8 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ -4.5, -4.9, 13.9, 17.9, 20.7, 22.8, 25.7, 27.4, 29.8, 31.5, 39.7, 59.6, 74.3, and 212.2.



206 **208**

2-Butyl-3-(*t*-butyldimethylsilyloxy)cyclohexane Oxime (208). To a solution of 10.6 g (37 mmol) of ketone **206** in 360 mL of a 1:1 EtOH/water mixture was added 7.8 g (112 mmol) of hydroxylamine hydrochloride followed by 9.2 g (112 mmol) of sodium acetate. The reaction mixture was heated at reflux at 90 ℃ for 6 h, cooled to 25 ℃, the solvent was removed under reduced pressure and the residue was diluted with CH_2Cl_2. The solution was washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue

was purified using flash silica gel chromatography to give 10.5 g (94%) of the titled oxime **208** as a colorless oil: IR (neat) 3256, 1662, 1463, 1254 and 1088 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.03 (s, 3H), 0.05 (s, 3H), 0.86-0.91 (m, 3H), 0.88 (s, 9H), 1.18-1.38 (m, 4H), 1.40-1.62 (m, 3H), 1.74-1.92 (m, 2H), 2.10-2.26 (m, 2H), 2.76 (dt, 1H, *J* = 14.0 and 4.8 Hz), 3.75-3.82 (m, 1H) and 8.84 (brs, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ -4.8, -4.7, 13.9, 18.0, 20.0, 21.5, 22.7, 25.8, 29.0, 29.5, 30.5, 49.6, 72.9 and 160.4.

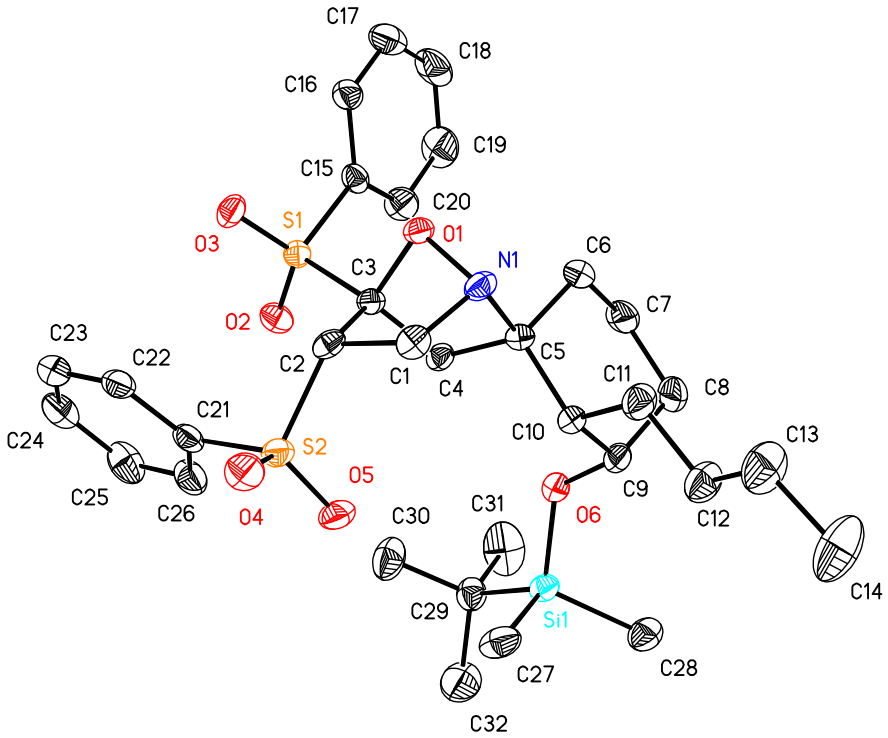


208 **69** **210** **211**

4,5-*endo*-Di(phenylsulfonyl)-2-spiro-(1'-8-butyl-9-(*t*-butyldimethylsilyloxy) cyclohexane)-7-oxo-1-aza-bicyclo[2.2.1]heptanes (210/211). To a solution of 1.05 g (3.5 mmol) of oxime **208** in 12 mL of CH_3CN was added 1.17 g (3.5 mmol) of 2,3-*bis*(phenylsulfonyl)-1,3-butadiene (**69**).[55] The mixture was heated to 90 ℃ for 72 h, cooled to room temperature, and then concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to give 1.16 g (52%) of a 1.5:1 diastereomeric mixture of the titled cycloadducts (**210**/**211**) as a white solid. The two diastereomers were separated by silica gel chromatography. The major diastereomer (**210**) was a white solid: mp 144-145 ℃; IR (neat) 1470, 1445, 1332 and 1154 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 0.10 (s, 3H), 0.20 (s, 3H), 0.83 (d, 1H, *J* = 12.0 Hz), 0.91 (t, 3H, *J* = 6.6 Hz), 0.99 (s, 9H), 1.14-1.52 (m, 10H), 1.55 (s, 2H), 2.04 (dd, 1H, *J* = 13.8 and 2.4 Hz), 2.26

(d, 1H, *J* = 10.8 Hz), 3.40 (d, 1H, *J* = 13.8 Hz), 3.68 (t, 1H, *J* = 12.0 Hz), 3.87 (dd, 1H, *J* = 12.0 and 4.8 Hz), 4.02 (d, 1H, *J* = 2.4 Hz), 4.26 (ddd, 1H, *J* = 11.4, 4.8 and 1.8 Hz), 7.50 (t, 2H, *J* = 7.5 Hz), 7.61 (t, 2H *J* = 7.5 Hz), 7.65 (t, 1H, *J* = 7.5 Hz), 7.71 (t, 1H, *J* = 7.5 Hz), 7.75 (d, 2H, *J* = 7.5 Hz) and 7.97 (d, 2H, *J* = 7.5 Hz); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ -5.4, -4.9, 14.0, 15.2, 18.1, 23.0, 26.0, 26.6, 27.5, 30.6, 32.4, 37.4, 44.5, 52.0, 66.3, 69.2, 74.3, 104.1, 128.7, 129.0, 129.1, 130.1, 134.3, 134.6 and 139.3; Anal. Calcd for $C_{32}H_{47}NO_6S_2Si$: C, 60.63; H, 7.47; N, 2.21; Found: C, 60.81; H, 7.41; N, 2.23.

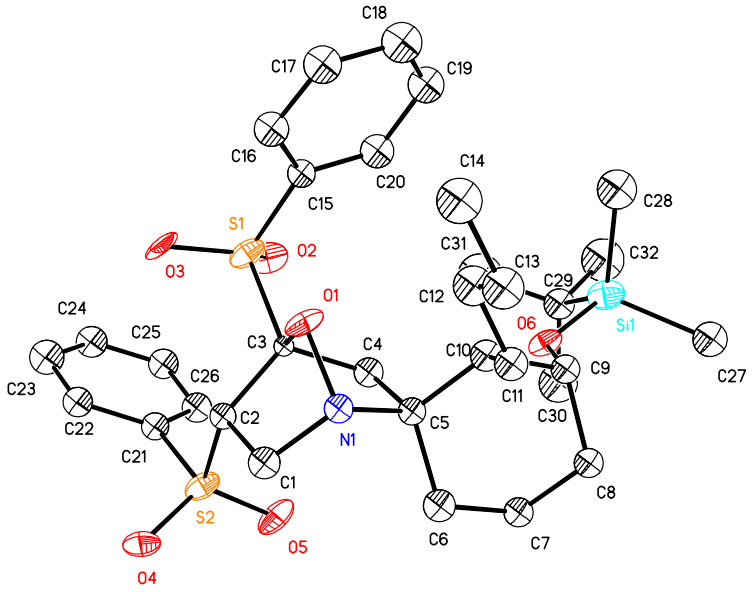
ORTEP representation of **210**:

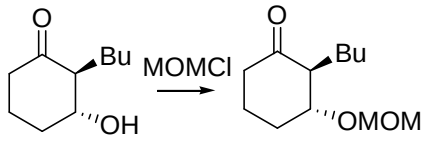


The minor diastereomer (**211**) was also a white solid: mp 150-152 ℃; IR (neat) 1463, 1447, 1329, 1311 and 1155 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 0.02 (s, 6H), 0.76-0.81 (m, 1H), 0.80 (t, 3H, *J* = 6.5 Hz), 0.94 (s, 9H), 1.15-1.04 (m, 4H), 1.32 (dt, 1H, *J* = 13.0 and 4.0 Hz), 1.36-1.40 (m, 1H), 1.44-1.50 (m, 1H),

1.62 (dt, 1H, *J* = 13.5 and 3.5 Hz), 1.73-1.80 (m, 1H), 1.80-1.90 (m, 1H), 2.18 (d, 1H, *J* = 12.5 Hz), 3.01-3.08 (m, 2H), 3.51 (dd, 1H, *J* = 13.0 and 11.0 Hz), 3.86 (d, 1H, *J* = 2.5 Hz), 3.97 (dd, 1H, *J* = 12.5 and 5.0 Hz), 4.13 (dd, 1H, *J* = 11.0 and 5.0 Hz), 7.48 (t, 2H, *J* = 7.5 Hz), 7.62 (t, 2H *J* = 7.5 Hz), 7.65 (t, 1H, *J* = 7.5 Hz), 7.71 (t, 1H, *J* = 7.5 Hz), 7.74 (d, 2H, *J* = 7.5 Hz) and 7.97 (d, 2H, *J* = 7.5 Hz); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ -5.1, -4.6, 14.0, 18.0, 18.1, 22.4, 26.0, 26.6, 27.5, 27.9, 31.5, 39.1, 48.7, 52.3, 67.7, 71.3, 74.1, 105.1, 128.8, 128.9, 129.2, 130.0, 134.3, 135.2 and 139.4; Anal. Calcd for $C_{32}H_{47}NO_6S_2Si$: C, 60.63; H, 7.47; N, 2.21; Found: C, 60.59; H, 7.41; N, 2.23.

ORTEP representation of **211**:

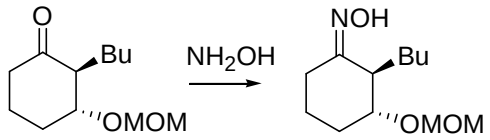




205 **207**

2-Butyl-3-(methoxymethoxy)cyclohexanone (207). To a solution of 16 g (94 mmol) of 2-butyl-3-hydroxy-cyclohexanone (**205**)[111113] in 500 mL of CH_2Cl_2 at 0

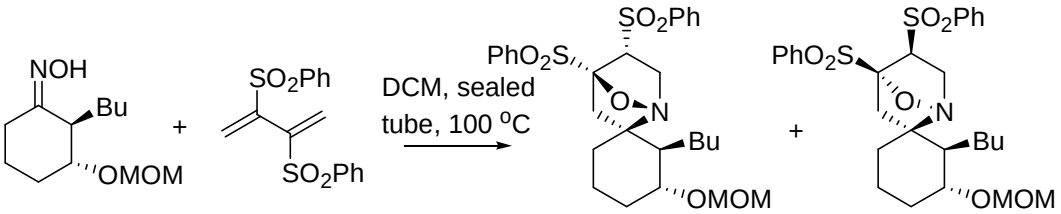
℃ was added 50 mL (282 mmol) of diisopropylethylam ine, followed by 14 mL (188 mmol) of freshly distilled MOM-Cl. The reaction mixture was slowly warmed to 25 ℃ and was stirred overnight. The solution wa s then cooled to 0 ℃ and was quenched with a saturated aqueous NH_4Cl solution. The aqueous layer was separated and extracted with Et_2O, the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to give 17.7 g (88%) of the titled ether **207** as a yellow oil: IR (neat) 1711, 1456, 1148, 1101 and 1039 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 75 MHz) δ 0.44 (t, 3H, *J* = 6.8 Hz), 0.78-0.91 (m, 4H), 1.10-1.25 (m, 3H), 1.25-1.38 (m, 1H), 1.51-1.70 (m, 2H), 1.78-1.86 (m, 1H), 1.90-2.01 (m, 2H), 2.92 (s, 3H), 3.27 (dt, 1H, *J* = 6.8 and 2.9 Hz), 4.18 (d, 1H, *J* = 6.8 Hz) and 4.25 (d, 1H, *J* = 6.8 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 13.8, 20.8, 22.7, 27.3, 28.2, 29.6, 39.4, 55.3, 56.8, 78.6, 94.9 and 211.3; HRMS Calcd for [$C_{12}H_{22}O_3$+ H^+]: 215.1642. Found: 215.1642.



207 **209**

2-Butyl-3-(methoxymethoxy)cyclohexane Oxime (209). To a solution of 5.9 g (27 mmol) of ketone **207** in 140 mL of dry EtOH was added 2.0 g (29 mmol) of hydroxylamine hydrochloride followed by 6.4 mL (78 mmol) of freshly distilled pyridine. The reaction mixture was heated at reflux at 100 ℃ for 2 h, cooled to 25 ℃, the solvent was removed under reduced pressu re and the residue was diluted with CH_2Cl_2. The residue was washed with water, dried over $MgSO_4$, filtered, concentrated under reduced pressure and purified using flash silica gel chromatography to give 6.0 g (96%) of 2-butyl-3-(methoxymethoxy)cyclohex-ane oxime (**209**) as a colorless oil: IR (neat) 3388, 1656, 1456, 1099 and 1037 cm^{-1};

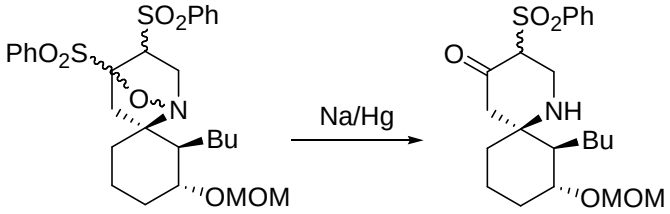
^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, 3H), 1.22-1.37 (m, 4H), 1.41-1.54 (m, 2H), 1.55-1.65 (m, 1H), 1.68-1.87 (m, 3H), 1.92-2.05 (m, 1H), 2.37-2.45 (m, 1H), 2.97 (d, 1H, *J* = 14.0 Hz), 3.35 (s, 3H), 3.76 (s, 1H), 4.64 (s, 2H) and 8.93 (s, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 13.9, 20.0, 27.9, 29.4, 29.7, 37.8, 46.2, 55.3, 75.6, 76.8, 94.3, and 160.8; HRMS Calcd for [$C_{12}H_{23}NO_3$+H^+]: 230.1751. Found: 230.1751.



209 **69** **212** **213**

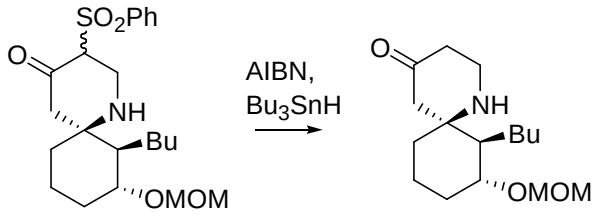
4,5-*endo*-(Diphenylsulfonyl)-2-spiro-(1'-8-butyl-9-(methoxymethoxy) cyclohexane)-7-oxo-1-aza-bicyclo[2.2.1]heptanes (212/213). To a 10 mL sealed tube charged 0.15 g (0.65 mmol) of oxime **209** was added 0.22 g (0.66 mmol) of 2,3-*bis*(phenylsulfonyl)-1,3-butadiene (**69**)[55] and 2.0 mL of CH_2Cl_2. The vessel was sealed and the resulting solution was heated at 100 ℃ for 24 h. The mixture was then cooled to 25 ℃ and concentrated u nder reduced pressure. The residue was purified using flash silica gel chromatography to give 0.25 g (68%) of a 1:1 diastereomeric mixture of cycloadducts (**212**/**213**) as a white solid; mp 136-140 ℃; IR (neat) 1584, 1446, 1322, 1148 and 1040 c m^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.78 (t, 3H, *J* = 6.6 Hz), 0.96-1.14 (m, 5H), 1.19-1.50 (m, 4H), 1.56-1.80 (m, 5H), 2.15 (d, 1H, *J* = 12.0 Hz), 2.74 (d, 1H, *J* = 13.4 Hz), 3.01 (d, 1H, *J* = 13.4 Hz), 3.26 (d, 3H, *J* = 1.5 Hz), 3.58-3.70 (m, 2H), 4.00 (dd, 1H, *J* = 12.6 and 3.8 Hz), 4.26 (dd, 1H, *J* = 6.6 and 1.5 Hz), 4.42 (dd, 2H, *J* = 6.6 and 1.5 Hz), 7.49 (t, 2H, *J* = 7.5 Hz), 7.58-7.75 (m, 4H), 7.82 (d, 2H, *J* = 7.5 Hz) and 8.00 (d, 2H, *J* = 7.5 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.0, 18.8, 22.3, 24.5, 26.3, 27.3, 31.2,

38.6, 45.9, 52.2, 55.2, 66.9, 74.4, 74.9, 94.1, 104.3, 128.5 and 128.7; Anal. Calcd for $C_{28}H_{37}NO_7S_2$: C, 59.66; H, 6.62; N, 2.48; Found: C, 60.02; H, 6.74; N, 2.48.



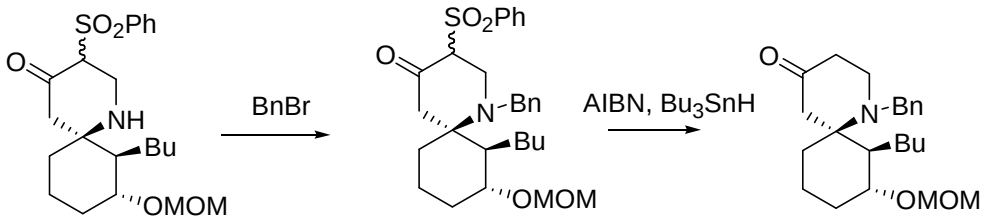
212/213 **214**

3-Benzenesulfonyl-7-butyl-8-(methoxymethoxy)-1-aza-spiro[5.5]undecan-4-one (**214**). To a suspension of 3.4 g (24 mmol) of Na_2HPO_4 and 2.7 g (4.8 mmol) of the 1:1-mixture of cycloadducts (**212/213**) in 50 mL of 2:1 THF/EtOH at 0 ℃ was added 7.7 g (17 mmol) of 5% sodium-mercury amalgam. The resulting yellow suspension was slowly warmed to 25 ℃ and wa s stirred vigorously for 19 h. The reaction mixture was filtered through a pad of Celite and rinsed with Et_2O followed by CH_2Cl_2. The filtrates were then concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to give 1.4 g (69%) of a 1:1 diastereomeric mixture of the titled sulfone **214** as a colorless oil: IR (neat) 3475, 1710, 1308, 1447, 1148 and 1035 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.94 (t, 3H, *J* = 7.0 Hz), 1.03-1.52 (m, 10H), 1.52-1.67 (2H), 1.67-1.81 (m, 1H), 2.01-2.11 (m, 1H), 2.21 (d, 1H, *J* = 13.5 Hz), 3.14 (d, 1H, *J* = 13.5 Hz), 3.18 (dd, 1H, *J* = 15.6 and 4.6 Hz), 3.38 (s, 3H), 3.60 (d, 1H, *J* = 4.6 Hz), 3.72 (dt, 1H, *J* = 9.9 and 4.6 Hz), 3.85 (d, 1H, *J* = 15.6 Hz), 4.60 (d, *J* = 6.9 Hz), 7.10-7.15 (m, 2H), 7.21-7.27 (m, 2H), and 7.39-7.41 (m, 1H) ; ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.1, 18.6, 23.1, 27.0, 32.3, 33.0, 34.0, 41.3, 51.6, 52.2, 55.6, 62.1, 72.2, 78.4, 95.6 and 128.2; HRMS Calcd for $[(C_{22}H_{33}NO_5S) + H]^+$: 424.2152. Found: 424.2147.



214 **215**

7-Butyl-8-(methoxymethoxy)-1-aza-spiro[5.5]undecan-4-one (215). To a solution of 1.3 g (3.1 mmol) of sulfone **214** in 110 mL of dry toluene was added 3.4 mL (12.5 mmol) of *n*-Bu_3SnH. The reaction mixture was heated at reflux before 0.4 g (2.4 mmol) of AIBN was added. After heating at reflux for 5 min, an additional 0.25 g (1.52 mmol) of AIBN was added. After a further 20 min, an additional 0.2 g (1.22 mmol) of AIBN was added. The resulting solution was heated at reflux for 3 h, cooled to 25 ℃ and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to give 0.72 g (82%) of the titled piperidone **215** as a yellow oil: IR (neat) 3341, 1708, 1463, 1142 and 1038 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 75 MHz) δ 0.84 (t, 3H, *J* = 7.1 Hz), 0.98-1.10 (m, 1H), 1.10-1.35 (m, 8H), 1.35-1.58 (m, 5H), 1.62 (dt, 1H, *J* = 13.3 and 4.1 Hz), 1.90-1.98 (m, 1H), 2.00 (d, 1H, *J* = 13.3 Hz), 2.25 (dd, 2H, *J* = 7.1 and 5.1 Hz), 2.64 (d, 1H, *J* = 13.3 Hz), 2.91 (dt, 1H, *J* = 13.3 and 7.1 Hz), 3.12 (dt, 1H, *J* = 13.3 and 5.1 Hz), 3.32 (s, 3H), 3.59 (dt, 1H, *J* = 9.1 and 4.1 Hz), 4.53 (d, 1H, *J* = 7.1 Hz) and 4.66 (d, 1H, *J* = 7.1 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.0, 18.3, 23.2, 27.4, 31.3, 32.5, 33.6, 40.2, 42.7, 50.2, 52.8, 55.4, 60.6, 77.6, 95.2 and 210.1; HRMS Calcd for $[(C_{16}H_{29}NO_3) + H]^+$: 284.2220. Found: 284.2220.

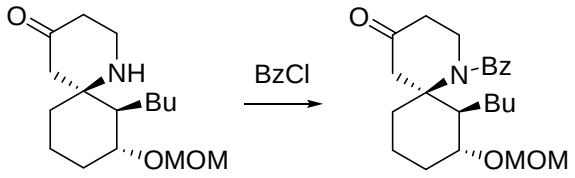


214 **214a** **216**

1-Benzyl-7-butyl-8-(methoxymethoxy)-1-aza-spiro[5.5]undecan-4-one (216). To a suspension of 0.05 g (0.12 mmol) of sulfone **214** and 0.2 g (1.4 mmol) of flame-dried K_2CO_3 in 5 mL of THF was added 170 mL (1.4 mmol) of freshly distilled benzyl bromide. The reaction mixture was heated at reflux for 20 h, cooled, diluted with Et_2O and quenched with a saturated aqueous NH_4Cl solution. The aqueous layer was separated and extracted with Et_2O and the combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to give 0.06 g (92%) of 1-benzyl-3-benzenesulfonyl-7-butyl-8-(methoxymethoxy)-1-aza-spiro[5.5]undecan-4-one (**214a**) as a yellow oil: IR (neat) 3063, 1699, 1305, 1142 and 1034 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.76 (t, 3H, *J* = 7.2 Hz), 0.82-1.20 (m, 6H), 1.21-1.39 (m, 2H), 1.40-1.49 (m, 4H), 1.57 (brs, 1H), 2.58 (d, 1H, *J* = 14.9 Hz), 2.81 (d, 1H, *J* = 12.7 Hz), 3.12 (d, 1H, *J* = 14.9 Hz), 3.28 (s, 3H), 3.41 (d, 1H, *J* = 12.7 Hz), 3.51 (brs, 2H), 4.00 (d, 1H, *J* = 15.9 Hz), 4.31 (d, 1H, *J* = 7.2 Hz), 4.48 (d, 1H, *J* = 7.2 Hz), 7.01-7.10 (m, 2H), 7.15-7.22 (m, 3H), 7.55-7.62 (m, 2H), 7.68-7.74 (m, 2H) and 7.74-7.79 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.0, 17.1, 18.1, 23.1, 25.4, 27.0, 29.7, 31.1, 33.9, 35.5, 42.4, 51.6, 52.3, 55.5, 58.4, 60.2, 74.7, 78.4, 93.8, 95.6, 127.4, 128.2, 128.5, 128.8, 130.2, 131.5, 134.4, 204.0 and 204.4; HRMS Calcd for $[(C_{29}H_{39}NO_5S) + H]^+$: 514.2622. Found: 514.2620.

To a solution of 0.98 mg (1.9 mmol) of the above sulfone (**214a**) in 70 mL of dry toluene was added 2.1 mL (7.6 mmol) of *n*-Bu_3SnH. The reaction mixture

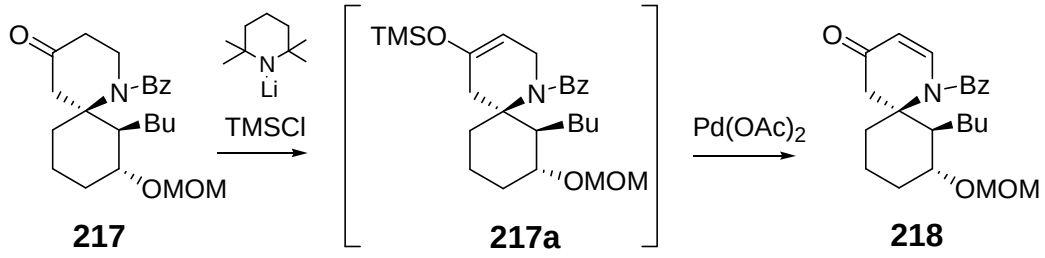
was heated to 110 ℃ and then 0.25 g (1.5 mmol) of AIBN was added. After heating at reflux for 5 min, an additional 0.25 g (1.5 mmol) of AIBN was added. The resulting solution was heated at reflux for 1.5 h, cooled to 25 ℃ and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to give 0.68 g (92%) of the titled piperidone **216** as a yellow oil: IR (neat) 1705, 1454, 1140, 1098 and 1037 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, 3H, *J* = 7.1 Hz), 1.01-1.39 (m, 7H), 1.39-1.60 (m, 5H), 1.69 (d, 1H, *J* = 14.3 Hz), 2.00-2.09 (m, 1H), 2.12 (d, 1H, *J* = 12.5 Hz), 2.34 (dd, 1H, *J* = 14.3 and 8.1 Hz), 2.43-2.58 (m, 1H), 2.56 (d, 1H, *J* = 12.5 Hz), 2.61 (d, 1H, *J* = 12.5 Hz), 3.12 (dd, 1H, *J* = 12.5 and 5.7 Hz), 3.22 (dd, 1H, *J* = 14.0 and 4.3 Hz), 3.36 (s, 3H), 3.55 (dt, 1H, *J* = 10.2 and 4.3 Hz), 4.57 (d, 1H, *J* = 7.1 Hz), 4.71 (d, 1H, *J* = 7.1 Hz), 7.12-7.21 (m, 3H) and 7.23-7.31 (m, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 14.0, 18.5, 23.2, 27.8, 32.0, 32.1, 32.6, 34.1, 46.6, 51.6, 53.0, 53.7, 55.6, 62.3, 78.4, 95.5, 126.1, 128.4, 128.9, 139.9 and 210.4; HRMS Calcd for $[(C_{23}H_{35}NO_3) + H]^+$: 374.2690. Found: 374.2687.



215 **217**

1-Benzoyl-7-butyl-8-(methoxymethoxy)-1-aza-spiro[5.5]undecan-4-one (217). To a solution of 0.14 g (0.49 mmol) of piperidone **215** and 280 µL (2.0 mmol) of Et_3N in 3 mL of CH_3CN at 0 ℃ was added 0.03 g (0.15 mmol) of DMAP followed by 170 µL (1.5 mmol) of freshly distilled benzoyl chloride. The resulting solution was slowly warmed to 25 ℃ and was stirred for 22 h. The solution was concentrated under reduced pressure, diluted with EtOAc and the precipitated triethylammonium salts were filtered. The filtrate was concentrated

under reduced pressure and the residue was purified using flash silica gel chromatography to give 0.15 g (81%) of the titled benzoyl amide **217** as a colorless oil: IR (neat) 1712, 1650, 1371, 1303 and 1036 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.76 (t, 1H, *J* = 6.5 Hz), 0.94 (t, 3H, *J* = 7.1 Hz), 1.03-1.29 (m, 3H), 1.29-1.43 (m, 3H), 1.43-1.83 (m, 5H), 2.18 (d, 1H, *J* = 6.5 Hz), 2.22 (d, 1H, *J* = 19.5 Hz), 2.30-2.48 (m, 1H), 2.61 (d, 1H, *J* = 12.8 Hz), 2.66 (d, 1H, *J* = 14.2 Hz), 3.17 (d, 1H, *J* = 15.5 Hz), 3.36 (s, 3H), 3.50 (d, 1H, *J* = 15.5 Hz), 3.58 (d, 1H, *J* = 14.2 Hz), 3.87 (dd, 1H, *J* = 14.2 and 6.5 Hz), 3.94 (d, 1H, *J* = 19.5 Hz), 4.62 (dt, 2H, *J* = 15.5 and 6.5 Hz) and 7.38-7.63 (m, 5H); [minor rotamer (distinct peaks)] δ 3.38 (s); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.2, 14.4, 17.5, 17.9, 23.5, 24.8, 25.7, 27.1, 30.3, 31.1, 31.7, 41.1, 43.3, 43.6, 43.9, 44.4, 49.0, 50.8, 53.7, 55.6, 63.3, 65.4, 73.8, 74.1, 94.6, 127.2, 128.4, 128.6, 129.0, 130.3, 130.4, 131.2, 133.7, 138.8, 174.2, 176.0, 208.3 and 209.7; HRMS Calcd for $[(C_{23}H_{33}NO_4) + H]^+$: 388.2482. Found: 388.2480.

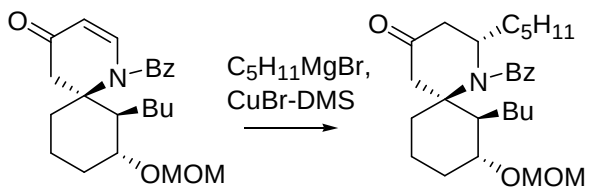


217 **217a** **218**

1-Benzoyl-7-butyl-8-(methoxymethoxy)-1-aza-spiro[5.5]undec-2-en-4-one (218). To a solution of 610 µL (3.6 mmol) of 2,2,6,6-tetramethylpiperidine in 16 mL of THF at 0 ℃ was added 1.5 mL (3.4 mmol) of 2. 25 M *n*-BuLi. After stirring for 1 h at 0 ℃, the reaction mixture was cooled to -78 ℃ and 430 µL (3.4 mmol) of TMSCl and a solution of 0.93 g (2.4 mmol) of ketone **217** in 18 mL of THF was added sequentially. After stirring for 2 h at -78 ℃ and then 1 h at 25 ℃, the

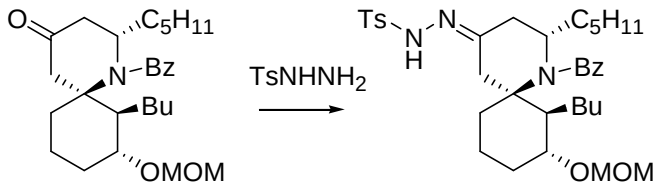
reaction mixture was cooled to 0 ℃ and quenched with a saturated aqueous NH_4Cl solution. The aqueous layer was separated and extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to furnish the crude enol silane (**217a**) which was immediately subjected to the following reaction conditions.

To a solution of the crude enol silane **217a** in 6 mL of a 3:1 CH_3CN/DMSO mixture was added 0.65 g (2.9 mmol) of $Pd(OAc)_2$. The resulting solution was stirred for 41 h at 25 ℃. The resulting suspension was diluted with Et_2O and filtered through a Celite plug. The filtrate was concentrated under reduced pressure and washed with a saturated $NaHCO_3$ solution. The biphasic mixture was extracted with Et_2O and the combined extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to give 0.63 g (68%) of the titled enone **218** as a white solid in 84% yield: mp 113.5-115 ℃; IR (neat) 1669, 1595, 1314, 1242 and 1032 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, 3H, *J* = 7.0 Hz), 1.09-1.91 (m, 11H), 2.30 (d, 1H, *J* = 12.0 Hz), 2.54 (d, 1H, *J* = 16.1 Hz), 3.33 (s, 3H), 3.34-3.42 (m, 1H), 3.83 (d, 1H, *J* = 16.1 Hz), 3.95 (d, 1H, *J* = 2.6 Hz), 4.55 (d, 1H, *J* = 7.0 Hz), 4.58 (d, 1H, *J* = 7.0 Hz), 5.29 (d, 1H, *J* = 8.1 Hz), 7.16 (d, 1H, *J* = 8.1 Hz) and 7.42-7.63 (m, 5H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 14.0, 18.0, 22.7, 26.0, 28.8, 31.1, 39.7, 48.5, 55.3, 69.0, 74.4, 94.4, 107.0, 128.8, 129.3, 132.2, 136.2, 146.5, 172.2 and 194.7; Anal. Calcd for $C_{23}H_{31}NO_4$: C, 71.66; H, 8.11; N, 3.63; Found: C, 71.39; H, 8.20; N, 3.57.



218 **219**

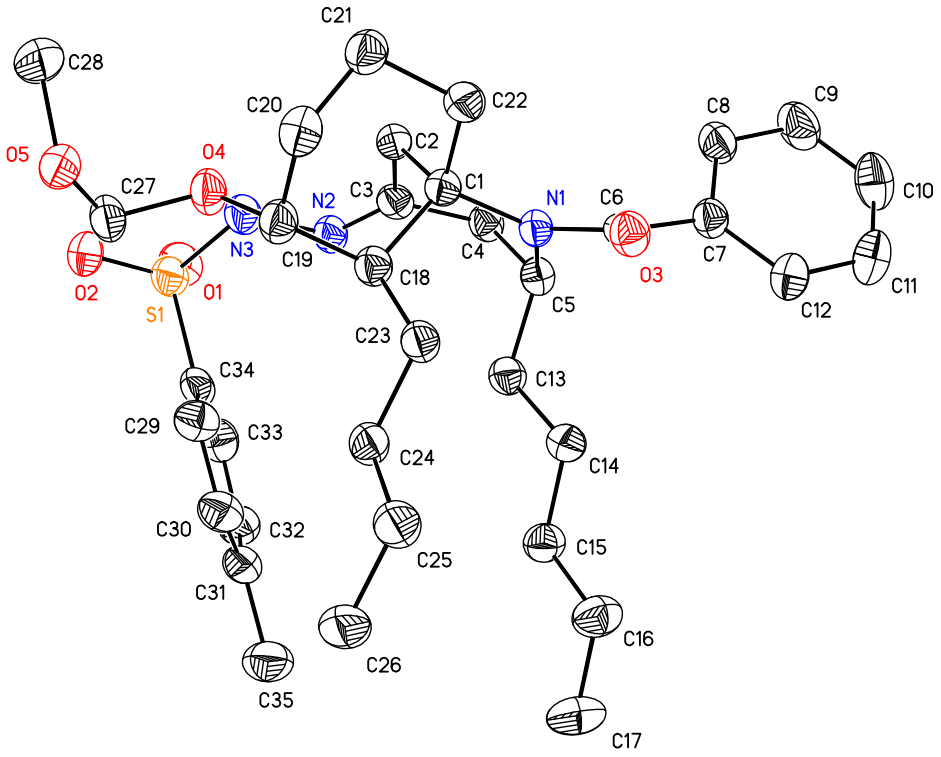
1-Benzoyl-7-butyl-8-(methoxymethoxy)-2-pentyl-1-aza-spiro[5.5]undecan-4-one (219). To a solution of 0.63 g (1.7 mmol) of enone **218** in 16.5 mL of dry THF was added 1.4 g (6.6 mmol) of CuBr-SMe_2. The resulting suspension was stirred for 1 h at room temperature, cooled to -78 ℃ and 900 µL (6.7 mmol) of BF_3-Et_2O was added. After stirring for 1 h at -78 ℃, 2.7 mL (4.9 mmol) of a solution of *n*-pentylmagnesium bromide (2.0 M in Et_2O) was slowly added. The suspension was stirred at -78 ℃ for an additional 3 h before being quenched with 8 mL of a 9:1 saturated aqueous NH_4Cl/NH_4OH solution. Upon warming to 25 ℃, the biphasic mixture was diluted with a further 15 mL of a 9:1 saturated aqueous NH_4Cl/NH_4OH solution and then extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to give 0.68 g (92%) of the titled ketone **219** as a yellow oil: IR (neat) 1722, 1645, 1398, 1348 and 1039 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.79 (t, 3H, *J* = 7.2 Hz), 0.94 (t, 3H, *J* = 7.2 Hz), 0.97-1.10 (m, 5H), 1.10-1.20 (m, 4H), 1.22-1.46 (m, 4H), 1.51-1.67 (m, 4H), 1.74-1.83 (m, 2H), 1.94-2.05 (m, 1H), 2.37 (dd, 1H, *J* = 17.3 and 2.4 Hz), 2.62 (d, 1H, *J* = 16.3 Hz), 2.63 (dd, 1H, *J* = 19.2 and 3.6 Hz), 2.81-2.90 (m, 1H), 3.26 (d, 1H, *J* = 16.3 Hz), 3.37 (s, 3H), 4.04-4.11 (m, 1H), 4.22-4.28 (m, 1H), 4.26 (d, 1H, *J* = 6.7 Hz), 4.68 (d, 1H, *J* = 6.7 Hz), 7.29-7.33 (m, 2H) and 7.37-7.42 (m, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 13.8, 14.1, 18.2, 22.3, 23.4, 26.6, 28.3, 29.7, 31.1, 32.5, 35.1, 37.8, 42.2, 50.7, 52.1, 55.6, 56.5, 64.9, 77.5, 95.6, 125.3, 128.7, 129.1, 139.5, 173.1 and 208.7; HRMS Calcd for $[(C_{28}H_{43}NO_4) + H]^+$: 458.3265. Found: 458.3261.

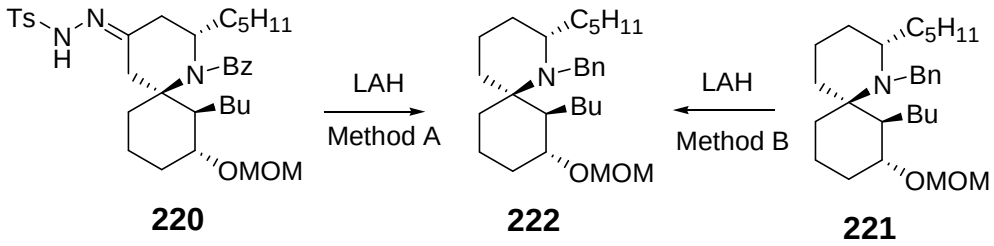


219 **220**

1-Benzoyl-7-butyl-8-(methoxymethoxy)-2-pentyl-1-aza-spiro[5.5]undecan-4-*N*-*p*-toluenesulfonylhydrazone (220). To a solution of 0.16 g (0.35 mmol) of ketone **219** in 800 µL of EtOH was added 0.9 g (0.43 mmol) of *p*-toluenesulfonyl hydrazide. The resulting suspension was heated to 78 ℃ and stirred for 1.5 h. The reaction mixture was cooled to 25 ℃, diluted with CH_2Cl_2 and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to give 0.20 g (92%) of the titled hydrazone **220** as a white solid: mp 128-130 ℃; IR (neat) 3110, 1595, 1344, 1168 and 1001 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.78 (t, 3H, *J* = 7.1 Hz), 0.92 (t, 3H, *J* = 7.1 Hz), 0.96-1.47 (m, 10H), 1.51-1.80 (m, 10H), 1.91 (d, 1H, *J* = 13.5 Hz), 2.08 (d, 1H, *J* = 11.6 Hz), 2.18 (d, 1H, *J* = 12.8 Hz), 2.39 (s, 3H), 2.39-2.50 (m, 1H), 3.53 (s, 3H), 3.81 (dd, 1H, *J* = 13.5 and 1.8 Hz), 3.91 (s, 1H), 4.01-4.12 (m, 1H), 4.86 (d, 1H, *J* = 7.1 Hz), 5.16 (d, 1H, *J* = 7.1 Hz), 7.25 (d, 2H, *J* = 8.2 Hz), 7.31-7.40 (m, 5H), 7.78 (d, 2H, *J* = 8.2 Hz) and 9.98 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.0, 14.4, 17.7, 21.6, 22.5, 23.1, 24.6, 27.1, 29.6, 31.3, 31.6, 34.2, 35.4, 37.9, 39.6, 49.6, 56.5, 59.9, 67.1, 78.3, 96.1, 126.1, 127.7, 128.6, 129.3, 129.7, 135.7, 139.9, 143.2, 152.7 and 174.4; Anal. Calcd for $C_{35}H_{51}N_3O_5S$: C, 67.17; H, 8.21; N, 6.71; Found: C, 66.96; H, 8.25; N, 6.62.

ORTEP representation of **220:**



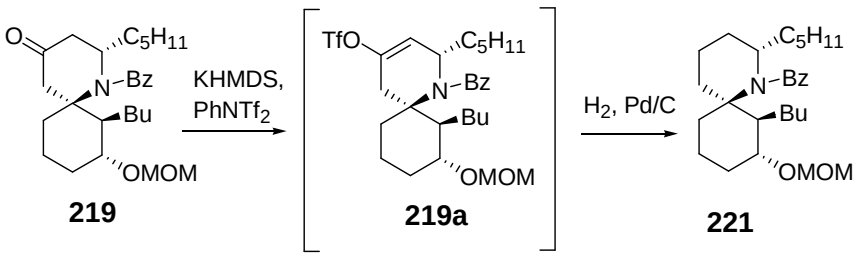


220 **222** **221**

1-Benzyl-7-butyl-8-(methoxymethoxy)-2-pentyl-1-aza-spiro[5.5]undecane (222). (Method A): To a solution of 0.042 g (0.07 mmol) of tosyl hydrazone **220** in 700 μL of dry THF at 0 ℃ was added 0.035 g (0.92 mmol) of $LiAlH_4$. The reaction mixture was heated at reflux for 15 h, cooled to 0 ℃ and then carefully quenched with 50 μL of water, followed by 50 μL of 15% aqueous NaOH, and this was followed by an additional 150 μL of water. The resulting suspension was warmed to room temperature and stirred for an additional 30 min. A portion

of $MgSO_4$ was added and the suspension was stirred for an additional 30 min before being diluted with Et_2O and filtered through a plug of Celite. The filtrate was concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to give 0.014 g (49%) of the titled amine **222** as a colorless oil.

(Method B): To a solution of 0.03 g (0.06 mmol) of amide **221** in 900 μL of dry THF at 0 ℃ was added 0.03 g (0.81 mmol) of $LiAlH_4$. The reaction mixture was heated at reflux overnight for 15 h, cooled to 0 ℃ and then carefully quenched with 50 μL of water, followed by 50 μL of 15% aqueous NaOH, and this was followed by an additional 150 μL of water. The resulting suspension was warmed to 25 ℃ and stirred for an additional 30 min. A portion of $MgSO_4$ was added and the suspension was stirred for an additional 30 min before being diluted with Et_2O and filtered through a plug of Celite. The filtrate was concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to give 0.021 g (84%) of the titled amine **222** as a colorless oil: IR (neat) 1595, 1462, 1150, 1096 and 1041 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 0.68-0.87 (m, 6H), 0.85 (t, 3H, *J* = 7.6 Hz), 1.03-1.30 (m, 10H), 1.40-1.81 (m, 12H), 1.84-1.93 (m, 2H), 3.35 (s, 3H), 3.77 (s, 1H), 3.81 (d, 1H, *J* = 17.1 Hz), 4.57 (d, 1H, *J* = 6.7 Hz), 4.59 (d, 1H, *J* = 6.7 Hz), 7.14 (t, 1H, *J* = 7.6 Hz), 7.25 (t, 2H, *J* = 7.6 Hz) and 7.39 (d, 2H, *J* = 7.6 Hz); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 13.9, 14.0, 14.3, 15.5, 18.5, 22.6, 23.2, 26.3, 27.5, 27.8, 29.7, 31.5, 31.8, 32.1, 33.9, 36.2, 36.7, 47.9, 55.1, 63.6, 76.0, 94.9, 125.7, 127.1, 127.8 and 144.5; HRMS Calcd for $[(C_{28}H_{45}NO_2) + H]^+$: 430.3680. Found: 430.3680.

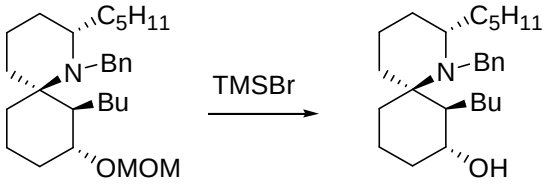


219 **219a** **221**

7-(Butyl-8-(methoxymethoxy)-2-pentyl-1-aza-spiro[5.5]undec-1-yl)-phenyl-methanone (221). To a solution of 0.23 g (0.49 mmol) of ketone **219** in 5 mL of dry THF at -78 ℃ was added 1.2 mL (0.59 mmol) of a solution of KHMDS (0.5 M in toluene) over a period of 15 min. After stirring for 45 min, 0.023 g (0.64 mmol) of $PhNTf_2$ was added and the resulting solution was slowly warmed to 25 ℃ over the course of 17 h. The mixture was then diluted with CH_2Cl_2 and filtered through a plug of neutral alumina. The filtrate was concentrated under reduced pressure and the residue was purified using flash silica gel chromatography to give 0.025 g (85%) of triflate ester **219a** as a colorless oil: IR (neat) 1657, 1418, 1211, 1143 and 1028 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.78 (t, 3H, *J* = 7.2 Hz), 0.92 (t, 3H, *J* = 7.2 Hz), 0.85-1.04 (m, 2H), 1.05-1.23 (m, 4H), 1.29-1.80 (m, 13H), 1.92 (d, 1H, *J* = 10.9 Hz), 2.44 (dt, 1H, *J* = 16.7 and 3.1 Hz), 3.20-3.34 (m, 1H), 3.35 (s, 3H), 3.88 (d, 1H, *J* = 16.7 Hz), 3.93 (s, 1H), 4.53-4.64 (m, 1H), 4.59 (s, 2H), 5.64 (t, 1H, *J* = 3.1 Hz) and 7.34-7.45 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 13.9, 14.2, 18.7, 22.4, 23.4, 24.8, 26.4, 28.1, 30.8, 31.1, 33.4, 37.8, 39.1, 44.3, 55.4, 57.0, 63.8, 73.5, 94.5, 114.5, 126.7, 127.1, 128.5, 129.8, 138.9, 145.9 and 174.1; HRMS Calcd for $[(C_{29}H_{42}NO_6F_3S) + H]^+$: 590.2758. Found: 590.2756.

To a solution of 0.026 g (0.44 mmol) of the above triflate mixture (**219a**) in 21 mL of EtOAc was added 0.065 g (0.88 mmol) of Li_2CO_3 and 0.38 g (3.5 mmol, 40 mol%) of 5% Pd/C. The resulting suspension was stirred for 20 h under a pressurized atmosphere of hydrogen (50 psi). The reaction mixture was diluted with CH_2Cl_2 and filtered through a Celite plug. The filtrate was concentrated under reduced pressure and the resulting residue was purified

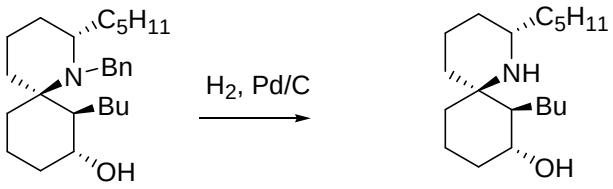
using flash silica gel chromatography to give 0.18 g (92%) of the titled amide **221** as a yellow oil: IR (neat) 1642, 1462, 1351, 1151 and 1039 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.79 (t, 3H, *J* =7.2 Hz), 0.94 (t, 3H, *J* = 7.2 Hz), 0.98-1.10 (m, 2H), 1.10-1.46 (m, 10H), 1.46-1.72 (m, 10H), 1.72-1.88 (m, 3H), 2.02 (d, 1H, *J* = 10.9 Hz), 2.94 (d, 1H, *J* = 13.0 Hz), 3.38 (s, 3H), 3.77-3.88 (m, 1H), 3.95 (d, 1H, *J* = 2.1 Hz), 4.60 (d, 1H, *J* = 6.6 Hz), 4.65 (d, 1H, *J* = 6.6 Hz), 7.31-7.42 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.0, 14.4, 15.5, 18.5, 22.5, 23.4, 26.1, 27.5, 27.7, 29.1, 31.5, 31.9, 34.0, 36.2, 36.7, 46.5, 55.3, 57.2, 63.7, 75.3, 94.7, 125.9, 128.3, 128.6, 141.0 and 174.1; HRMS Calcd for $[(C_{28}H_{45}NO_3) + H]^+$: 444.3472. Found: 444.3469.



222 **223**

1-Benzyl-7-butyl-2-pentyl-1-aza-spiro[5.5]undecan-8-ol (223). To a suspension of 0.02 g (0.05 mmol) of MOM ether **222** and 0.08 g of powdered 4Å molecular sieves in 0.5 mL of dry CH_2Cl_2 at -20 ºC was added 50 mL (0.39 mmol) of freshly distilled trimethylsilylbromide. The resulting suspension was stirred for 3 h at -20 ºC before being warmed to 0 ºC. After stirring for an additional 2 h, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution. The biphasic mixture was diluted with CH_2Cl_2 and filtered through a Celite plug. The filtrate was extracted with CH_2Cl_2 and the combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to give 0.014 g (73%) of the titled alcohol **223** as a colorless oil: IR (neat) 3386, 1451, 1352, 1110 and 1026 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 0.68-0.85 (m, 2H), 0.84

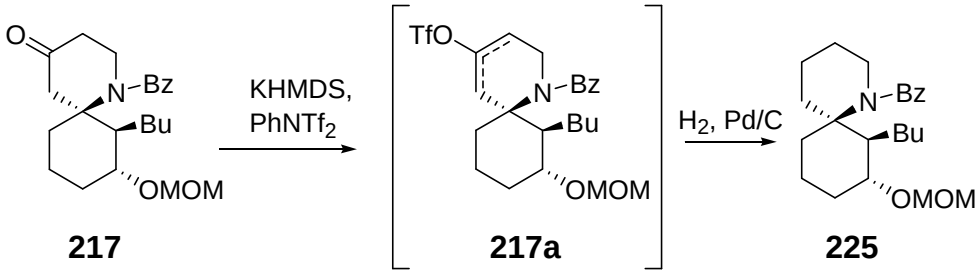
(t, 3H, *J* = 7.6 Hz), 0.86-0.98 (m, 2H), 1.11 (d, 1H, *J* = 3.8 Hz) 1.04-1.17 (m, 4H), 1.17-1.29 (m, 6H), 1.41-1.57 (m, 8H), 1.57-1.70 (m, 6H), 1.70-1.82 (m, 2H), 1.93 (t, 1H, *J* = 8.6 Hz), 3.82 (d, 1H, *J* = 17.1 Hz), 3.97-4.01 (m, 1H), 4.03 (brs, 1H), 7.13 (t, 1H, *J* = 7.6 Hz), 7.25 (t, 2H, *J* = 7.6 Hz) and 7.38 (d, 2H, *J* = 7.6 Hz); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 14.0, 14.1, 22.6, 22.7, 23.6, 25.7, 27.5, 29.3, 29.4, 29.6, 29.7, 30.3, 31.9, 32.8, 34.3, 36.7, 49.9, 55.2, 63.1, 71.1, 125.5, 127.0, 127.6 and 143.9; HRMS Calcd for $[(C_{26}H_{43}NO) + H]^+$: 386.3417. Found: 386.3419.



223 7,8-*epi*-**193**; 7,8-*epi*-PHTx

6-epi-Perhydrohistrionicotoxin (6-epi**-193).** To a solution of 0.04 g (0.0.4 mmol) of amine **223** in 7 mL of EtOH was added 0.07 g of 10% Pd/C. The reaction flask was evacuated and purged with hydrogen 3-times. The reaction mixture was stirred under an atmosphere of hydrogen gas for 18 h. The resulting mixture was filtered through a Celite plug and concentrated under reduced pressure to give 0.03 g (97%) of 6-epi-Perhydrohistrionicotoxin (6-epi-**193**) as a colorless oil: IR (neat) 3351, 1460, 1355, 1261, 1119 and 1033 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 0.76-0.92 (m, 2H), 0.878 (t, 3H, *J* = 7.5 Hz), 0.90 (t, 3H, *J* = 7.5 Hz), 1.07-1.15 (m, 1H), 1.16-1.36 (m, 16H), 1.39-1.48 (m, 2H), 1.51 (dt, 1H, *J* = 13.5 and 4.0 Hz), 1.54-1.61 (m, 4H), 1.67-1.75 (m, 1H), 1.93-1.99 (m, 1H), 2.22 (d, 1H, *J* = 13.5 Hz), 2.46-2.53 (m, 1H) and 3.60 (dt, 1H, *J* = 10.0 and 4.0 Hz); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 14.1, 14.2, 18.9, 20.6, 22.6, 23.3, 25.7, 27.0, 29.7, 30.8, 32.0, 33.3, 34.5, 35.1, 35.9, 37.8, 49.3, 54.9, 56.4 and 72.6. This

compound exhibited identical characteristic data to that reported in the literature.[119]

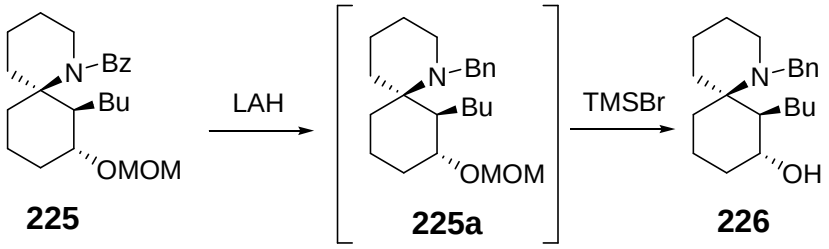


217 **217a** **225**

7-(Butyl-8-(methoxymethoxy)-1-aza-spiro[5.5]undec-1-yl)-phenyl-methanone (225). To a solution of 0.44 mg (1.12 mmol) of ketone **217** in 10 mL of dry THF at -78 ℃ was added 3.0 mL (1.5 mmol) of a solution of KHMDS (0.5 M in toluene), over a period of 15 min. After stirring for 45 min, 0.52 g (1.5 mmol) of $PhNTf_2$ was added and the resulting solution was slowly warmed to 25 ℃ and stirred for 22 h before being diluted with CH_2Cl_2 and filtered through a plug of neutral alumina. The filtrate was concentrated under reduced pressure and the residue was purified using flash silica gel chromatography to give 0.51 g (88%) of a 1:1-mixture of triflate esters (**217a**) as a colorless oil: IR (neat) 1628, 1496, 1418, 1211, 1144 and 1033 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.75 (t, 6H, *J* = 7.0 Hz), 0.82-0.91 (m, 4H), 0.93-1.0 (m, 4H), 1.09-1.85 (m, 16H), 1.69 (s, 2H), 1.70 (s, 2H), 1.93-2.12 (m, 4H), 2.71-2.84 (m, 2H), 3.12 (d, 1H, *J* = 18.4 Hz), 3.21 (d, 1H, *J* = 18.4 Hz), 3.29 (d, 1H, *J* = 8.3 Hz), 3.34 (s, 3H), 3.40 (s, 3H), 3.59 (d, 1H, *J* = 17.5 Hz), 3.65 (d, 1H, *J* = 18.4 Hz), 3.65 (d, 1H, *J* = 18.4 Hz), 3.83 (d, 1H, *J* = 18.4 Hz), 3.94 (s, 1H), 4.01 (d, 1H, *J* = 18.4 Hz), 4.14 (d, 1H, *J* = 17.5 Hz), 4.58 (d, 1H, *J* = 7.6 Hz), 4.61 (d, 1H, *J* = 7.6 Hz), 4.63 (d, 1H, *J* = 7.0 Hz), 4.70 (d, 1H, *J* = 7.0 Hz), 5.59 (s, 1H), 5.62 (s, 1H), 7.36-7.49 (m, 8H) and 7.53 (d, 2H, *J* = 7.0 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 13.8, 14.1, 17.3, 17.7, 22.6, 23.0, 23.3, 24.5, 24.7, 26.5, 26.7, 27.0, 30.6, 31.4, 31.6, 31.8, 34.8, 36.9, 41.3, 43.4,

44.3, 44.5, 55.5, 60.7, 62.2, 73.8, 94.6, 113.4, 114.9, 116.9, 120.0, 127.4, 128.2, 128.6, 128.7, 130.4, 131.0, 137.1, 138.2, 148.3, 149.6, 173.5 and 175.3.

To a solution of 0.51 g (0.99 mmol) of the above triflate mixture (**217a**) in 45 mL of EtOAc was added 0.15 g (2.0 mmol) of Li_2CO_3 and 0.85 g (0.4 mmol, 40 mol%) of 5% Pd/C. The resulting suspension was stirred for 48 h under an atmosphere of hydrogen (60 psi). The reaction mixture was diluted with CH_2Cl_2 and filtered through a Celite plug. The filtrate was concentrated and the resulting residue was purified using flash silica gel chromatography to give 0.34 g (91%) of the titled amide **225** as a yellow oil: IR (neat) 1642, 1390, 1271, 1096 and 1034 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 0.94 (t, 3H, *J* = 7.6 Hz), 1.21-1.81 (m, 15H), 1.97 (d, 1H, *J* = 14.3 Hz), 2.32 (d, 1H, *J* = 10.5 Hz), 2.76 (dt, 1H, *J* = 14.3 and 2.9 Hz), 2.94-3.03 (m, 2H), 3.38 (s, 3H), 3.45 (dt, 1H, *J* = 14.3 and 2.9 Hz), 3.95-3.98 (m, 1H), 4.61 (d, 1H, *J* = 6.7 Hz), 4.65 (d, 1H, *J* = 6.7 Hz) and 7.37-7.40 (m, 5H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 14.1, 18.1, 20.1, 23.1, 25.6, 25.9, 27.0, 31.5, 33.3, 35.5, 40.6, 45.1, 55.2, 64.0, 74.9, 94.6, 126.3, 128.3, 128.9, 140.3 and 173.0; HRMS Calcd for $[(C_{23}H_{35}NO_3) + H]^+$: 374.2690. Found: 374.2700.



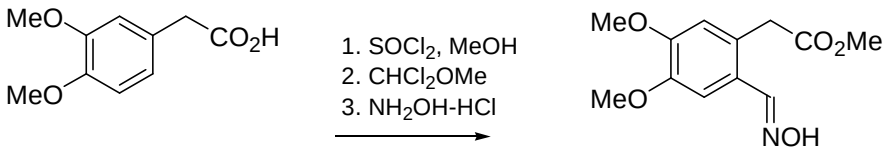
225 **225a** **226**

1-Benzyl-7-butyl-1-aza-spiro[5.5]undecan-8-ol (226). To a solution of 0.13 g (0.35 mmol) of amide **225** in 5.5 mL of dry THF at 0 ℃ was added 0.08 g (2.1 mmol) of $LiAlH_4$. The reaction mixture was heated at reflux for 14 h and then the suspension was cooled to 0 ℃ and was carefully que nched with 100 µL of water, followed by 100 µL of 15% aqueous NaOH, and this was followed by an additional 300 µL of water. The resulting suspension was warmed to 25 ℃ and

was stirred for an additional 30 min. A portion of $MgSO_4$ was added and the suspension was stirred for an additional 30 min before being diluted with Et_2O and filtered through a plug of Celite. The filtrate was concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to give 0.12 g (93%) of 1-benzyl-7-butyl-8-(methoxymethoxy)-1-aza-spiro[5.5]undecane (**225a**) as a colorless oil: IR (neat) 1465, 1450, 1216, 1152, 1098 and 1041 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, 3H, *J* = 6.4 Hz), 0.95-1.09 (m, 1H), 1.19-1.79 (m, 16H), 1.89-2.10 (m, 2H), 2.10-2.23 (m, 1H), 2.44-2.58 (m, 1H), 3.37 (s, 3H), 3.66 (d, 1H, *J* = 14.0 Hz), 3.83-3.89 (m, 1H), 3.92 (d, 1H, *J* = 14.0 Hz), 4.63 (d, 1H, *J* = 7.0 Hz), 4.65 (d, 1H, *J* = 7.0 Hz), 7.20 (t, 1H, *J* = 7.0 Hz), 7.28 (t, 1H, *J* = 6.4 Hz), 7.30 (d, 1H, *J* = 7.0 Hz) and 7.35 (d, 2H, *J* = 7.0 Hz); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 14.0, 18.5, 20.4, 20.7, 23.4, 26.3, 27.0, 31.0, 31.6, 32.6, 33.7, 44.0, 51.2, 55.2, 57.8, 76.6, 95.0, 126.2, 128.0, 128.1 and 142.8; HRMS Calcd. for $[(C_{23}H_{37}NO_2) + H]^+$: 360.2897. Found: 360.2892.

To a suspension of 0.12 g (0.33 mmol) of MOM-ether **225a** and 0.55 g of powdered 4Å molecular sieves in 2.6 mL of dry CH_2Cl_2 at -20 ºC was added 400 mL (2.7 mmol) of freshly distilled trimethylsilylbromide. The resulting suspension was stirred for 3 h at -20 ºC before being warmed to 0 ºC. After stirring for an additional 2 h, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution. The biphasic mixture was diluted with CH_2Cl_2 and filtered through a Celite plug. The filtrate was extracted with CH_2Cl_2 and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to give 0.072 g (71%) of the titled alcohol **226** as a colorless oil: IR (neat) 3386, 1451, 1352, 1110 and 1026 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, 3H, *J* = 7.0 Hz), 1.02-1.18 (m, 1H), 1.18-1.95 (m, 17H), 1.95-2.13 (m, 1H), 2.17-2.28 (m, 1H), 2.42-2.56 (m, 1H), 2.56-2.69 (m, 1H), 3.61 (d, 1H, *J* =

14.0 Hz), 3.93 (d, 1H, *J* = 14.0 Hz), 4.04 (dd, 1H, *J* = 9.5 and 5.0 Hz), 7.21 (t, 1H, *J* = 7.0 Hz), 7.30 (t, 2H, *J* = 7.6 Hz), 7.36 (d, 2H, *J* = 7.0 Hz); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 14.0, 19.0, 20.8, 23.4, 27.0, 29.7, 30.9, 31.4, 33.3, 33.7, 44.3, 49.0, 52.7, 58.6, 72.5, 126.3, 128.0, 128.1 and 142.3.

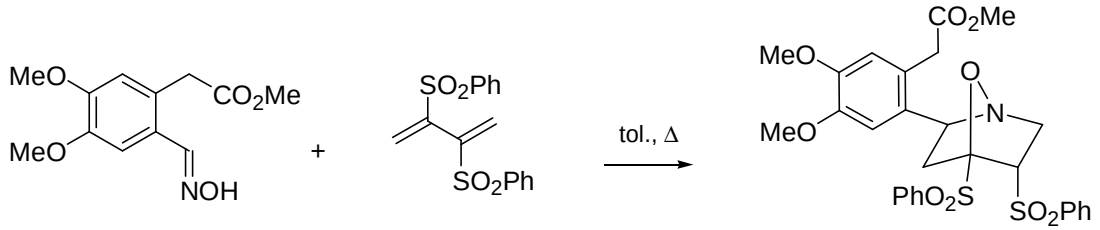


245 **246**

Methyl 2-(2-((hydroxyimino)methyl)-4,5-dimethoxyphenyl)acetate (246). To a solution containing 10.0 g (51 mmol) of 2-(3,4-dimethoxyphenyl)acetic acid (**245**)[168] in 100 mL of methanol at -78 ºC was added 7.5 g (61 mmol) of thionyl chloride. The resulting solution was warmed to room temperature and was stirred overnight (12 h) before being concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with a saturated aqueous $NaHCO_3$ solution and brine. The organic layer was concentrated under reduced pressure to provide 10.1 g (94%) of methyl 2-(3,4-dimethoxyphenyl)acetate[169] which was used in the next step without further purification.

To a solution of 2.0 g (9.5 mmol) of methyl 2-(3,4-dimethoxyphenyl)acetate in 50 mL of CH_2Cl_2 at 0 ℃ was added 2.5 g (19 mmol) of $AlCl_3$ in several portions over a 10 min period. To this mixture was added 1.7 g (13 mmol) of dichloromethylmethyl ether at 0 ℃. The resulting solution was stirred for an additional 1 h at 0 ℃, warmed to room temperature and stirred overnight (12 h). The reaction mixture was poured into ice water and extracted with CH_2Cl_2. The combined organic layer was washed with a 5% aqueous KOH solution, dried over Na_2SO_4 and concentrated under reduced pressure yielding 1.8 g (79%) of methyl 2-(2-formyl-4,5-dimethoxyphenyl)acetate[169] as a yellow solid. The crude product was used in the next step without further purification.

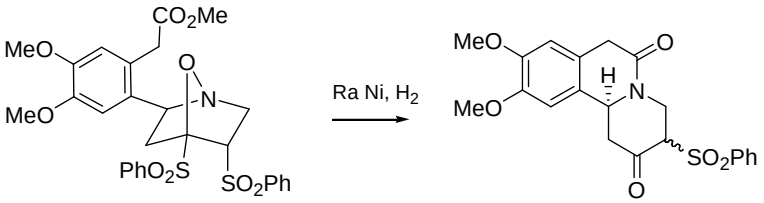
To a solution containing 1.8 g (7.5 mmol) of the above crude ester in 50 mL of methanol was added sequentially 0.6 g (8.2 mmol) of hydroxylamine hydrochloride and 1.2 g (15 mmol) of sodium acetate. After stirring at room temperature for 12 h, the solution was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed with water, brine and dried over Na_2SO_4. Concentration under reduced pressure left behind a residue which was purified using flash silica gel chromatography to give 1.8 g (97%) of the titled oxime **246** as a white solid: mp 120-122 ℃; IR (neat) 3442, 17 31, 1598, 1516, and 1275 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.69 (s, 3H), 3.74 (s, 2H), 3.89 (s, 3H), 3.91 (s, 3H), 6.74 (s, 1H), 7.20 (s, 1H), 8.22 (s, 1H) and 8.33 (s, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 38.8, 52.5, 56.1, 109.8, 114.0, 123.5, 126.2, 148.5, 148.9, 150.4, and 172.0.



246 **69** **247**

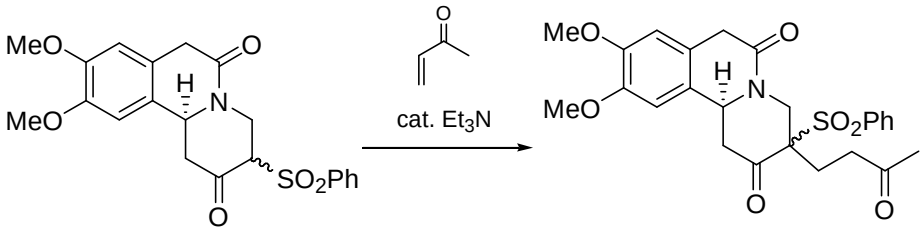
[2-(4,5-*Bis*-benzenesulfonyl-7-oxa-1-aza-bicyclo[2.2.1]hept-2-yl)-4,5-dimethoxy-phenyl]acetic Acid Methyl Ester (247). A mixture containing 3.7 g (11 mmol) of 2,3-*bis*(phenylsulfonyl)-1,3-butadiene (**69**)[55] and 2.6 g (10.1 mmol) of oxime **246** in 165 mL of toluene was heated for 24 h at 125 ℃. The solution was concentrated under reduced pressure and the resulting residue was purified using flash silica gel chromatography to give 4.75 g (80%) of the titled cycloadduct **247** as a white solid: mp 186-187 ℃; IR (neat) 2950, 17 31, 1516, 1445, and 1327 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.08-2.14 (ddd, 1H, *J* = 19.2, 8.4, and 3.6 Hz), 3.41 (s, 3H), 3.56 (d, 1H, *J* = 16.0 Hz), 3.63 (d, 1H, *J* = 16.0

Hz), 3.68-3.71 (m, 1H), 3.74 (s, 3H), 3.77-3.78 (m, 2H), 3.80 (s, 3H), 4.58-4.62 (m, 2H), 6.40 (s, 1H), 6.59 (s, 1H), 7.49-7.53 (m, 2H), 7.63-7.68 (m, 3H), 7.72-7.76 (m, 1H), 7.85-7.87 (m, 2H), and 8.02-8.04 (m, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 38.6, 40.8, 52.6, 55.8, 56.1, 61.4, 67.0, 68.1, 103.1, 109.2, 113.1, 123.3, 129.0, 129.2, 129.8, 130.6, 133.2, 134.9, 135.0, 139.0, 148.3, 148.9, and 171.9; Anal. Calcd for $C_{28}H_{29}NO_9S_2$: C, 57.23; H, 4.97; N, 2.38. Found: C, 55.85; H, 4.83; N, 2.37.



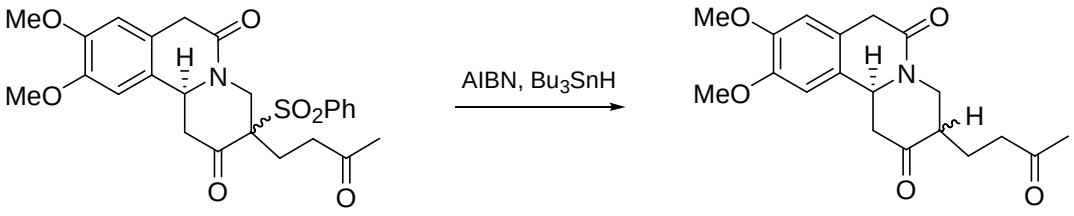
247 **249**

9,10-Dimethoxy-3-(phenylsulfonyl)-3,4-dihydro-1*H*-pyrido[2,1-*a*]isoquinoline-2,6-(7*H*,11*bH*)-dione (249). A solution containing 2.8 g (4.8 mmol) of cycloadduct **247** and 0.28 g of freshly rinsed Raney nickel in 30 mL of THF was refluxed under an atmosphere of hydrogen for 12 h. The resulting solution was filtered through Celite and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to give 1.6 g (81%) of the titled piperidone **249** as a white solid (which in $CDCl_3$ exists as the enol tautomer **249a**): mp 218-219 ℃; IR (neat) 1721, 1654, 1521, 1465, 1450, and 1316 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.91-2.99 (m, 2H), 3.13-3.25 (m, 2H), 3.59-3.65 (m, 2H), 3.83 (s, 3H), 3.87 (s, 3H), 4.76 (d, 1H, *J* = 12.0 Hz), 5.59 (d, 1H, *J* = 15.2 Hz), 6.56 (s, 1H), 6.60 (s, 1H), 7.55-7.62 (m, 2H), 7.67-7.72 (m, 1H), and 7.98-8.03 (m, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 34.9, 41.2, 50.7, 56.1, 56.2, 59.3, 71.4, 107.8, 110.2, 122.6, 122.8, 129.3, 129.4, 129.5, 129.6, 134.8, 136.9, 148.5, 149.3, 167.5, and 197.0; Anal. Calcd for $C_{21}H_{21}NO_6S$: C, 60.71; H, 5.09; N, 3.37. Found: C, 60.32; H, 5.04; N, 3.33.



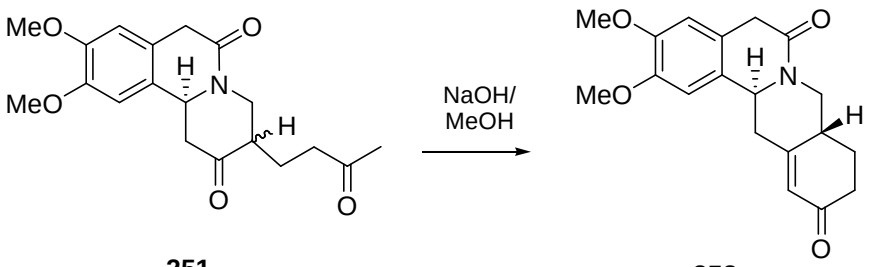
249 **250**

3-Benzenesulfonyl-9,10-dimethoxy-3-(3-oxo-butyl)-3,4,7,11b-tetrahydro-1H-pyrido[2,1-a]isoquinoline-2,6-dione (250). To a suspension of 0.5 g (1.2 mmol) of ketosulfone **249** in 10 mL of a 9:1 mixture of THF/MeOH was added 0.6 g (8.5 mmol) of methyl vinyl ketone. After stirring for 2 h, 0.01 g (0.12 mmol) of triethylamine was added as a 0.8 M solution in THF. The reaction mixture was stirred at room temperature for an additional 18 h, then partitioned between water and CH_2Cl_2. The combined organics were then dried over Na_2SO_4, concentrated under reduced pressure, and purified using flash silica gel chromatography to give 0.49 g (84%) of the titled diketone **250** as an inseparable 1:1 mixture of diastereomers: mp 190-191 °C; IR (neat) 1716, 1650, 1511, 1445, and 1306 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.76-1.84 (m, 1H), 2.14 (s, 3H), 2.26-2.34 (m, 1H), 2.50-2.60 (m, 2H), 2.98 (dd, 1H, *J* = 15.2 and 2.8 Hz), 3.16 (d, 1H, *J* = 14.8 Hz), 3.35 (dd, 1H, *J* = 15.2 and 12.4 Hz), 3.66 (d, 1H, *J* = 20.0 Hz), 3.87-3.90 (m, 7H), 4.79 (d, 1H, *J* = 12.4 Hz), 5.66 (d, 1H, *J* = 15.6 Hz), 6.57 (s, 1H), 6.64 (s, 1H), 7.58-7.62 (m, 2H), 7.70-7.73 (m, 1H), and 7.94-7.96 (m, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 24.8, 30.2, 35.4, 37.7, 44.2, 50.2, 56.2, 56.3, 58.7, 73.9, 107.7, 110.4, 123.0, 123.1, 129.4, 131.0, 134.7, 135.0, 148.6, 149.4, 167.7, 199.8, and 206.5; Anal. Calcd. for $C_{25}H_{27}NO_7S$: C, 61.84; H, 5.60; N, 2.88. Found: C, 61.39; H, 5.77; N, 2.61.



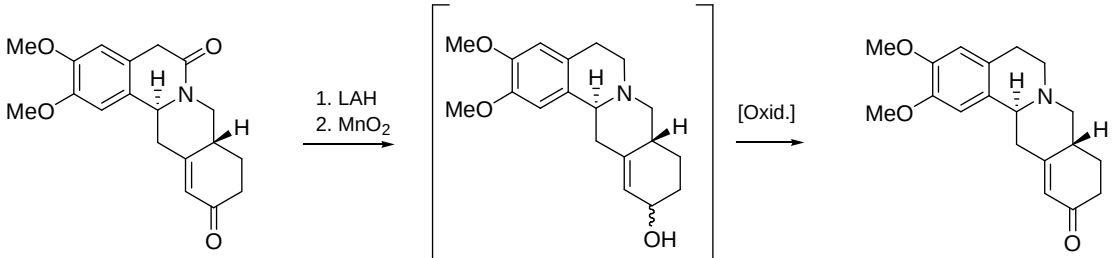
250 **251**

9,10-Dimethoxy-3-(3-oxo-butyl)-3,4,7,11b-tetrahydro-1H-pyrido[2,1-a]isoquinoline-2,6-dione (251). To a solution containing 0.15 g (0.3 mmol) of sulfone **250** and in 9 mL of toluene was added 0.35 g (1.2 mmol) of tributyltin hydride. To this mixture was added 0.054 g (0.33 mmol) of AIBN over the course of 20 min and then the mixture was heated to reflux. The reaction was then concentrated under reduced pressure and the residue was purified using flash silica gel chromatography to give 0.09 g (87%) of an inseparable 1:1 diastereomeric mixture of titled diketone **251** as a white solid: mp 144-145 ℃; IR (neat) 1716, 1644, 1516, 1445, and 1245 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.56-1.62 (m, 1H), 2.05-2.12 (m, 1H), 2.17 (s, 3H), 2.48-2.54 (m, 3H), 2.55-2.62 (m, 1H), 2.65-2.71 (m, 1H), 2.82 (dd, 1H, *J* = 9.2 and 2.0 Hz), 3.70 (d, 2H, *J* = 4.0 Hz), 3.86 (s, 3H), 3.88 (s, 3H), 4.70 (d, 1H, *J* = 8.2 Hz), 5.14 (dd, 1H, *J* = 8.2 and 4.0 Hz), 6.56 (s, 1H), and 6.59 (s, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 20.4, 30.1, 34.6, 41.0, 46.8, 49.1, 51.6, 56.2, 60.1, 107.8, 110.1, 122.3, 123.5, 148.5, 149.3, 167.2, 207.1, and 208.0; Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 64.87; H, 6.62; N, 4.01.



251 **252**

2,3-Dimethoxy-8,8a,9,10,13,13a-hexahydro-5H-isoquino[3,2-a]isoquinoline-6,11-dione (252). To a solution containing 0.06 g (0.17 mmol) of diketone **251** in 5 mL of THF was added 4.4 mL (0.35 mmol) of a 0.08 M solution of sodium methoxide in methanol. The resulting mixture was stirred at 40 ^{o}C for 12 h, concentrated under reduced pressure and purified using flash silica gel chromatography to provide 0.04 g (70%) of a 5:1 diastereomeric mixture of the titled tetracycle **252** as a yellow solid. The major isomer was separated and characterized: mp 237-238 ℃; IR (neat) 1650, 1521, 1465, and 1250 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.63-1.74 (m, 1H), 2.18-2.25 (m, 1H), 2.34-2.47 (m, 3H), 2.51-2.57 (m, 1H), 2.61-2.69 (m, 1H), 2.82 (dd, 1H, *J* = 14.8 and 2.8 Hz), 3.67 (s, 2H), 3.89 (s, 3H), 3.91 (s, 3H), 4.55 (d, 1H, *J* = 10.8 Hz), 5.05 (dd, 1H, *J* = 13.2 and 6.0 Hz), 6.01 (s, 1H), 6.6 (s, 1H), and 6.63 (s, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 25.9, 34.7, 36.5, 36.7, 44.6, 48.1, 56.2, 56.4, 60.1, 108.2, 110.2, 122.5, 124.2, 126.9, 148.5, 160.4, 167.1, and 199.1; Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.19; H, 6.65; N, 4.03.

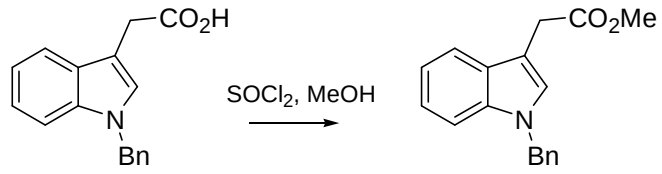


252 **253** **230**

2,3-Dimethoxy-5,6,8,8a,9,10,13,13a-octahydro-isoquino[3,2-a]isoquinolin-11-one (230). To a solution of 100 mg (0.29 mmol) of lactam **252** in 12 mL of a 1:1 mixture of Et_2O/THF at 0 °C was added 100 mg (2.6 mmol) of $LiAlH_4$. The resulting suspension was stirred for 30 min at 0 °C, and then heated at 55 °C and stirred for 1.5 h. The reaction mixture was cooled to 0 °C and sequentially treated with 0.12 mL of water, then 0.12 mL of a 15% aqueous NaOH solution,

and then 0.36 mL of water. The resulting solution was extracted with EtOAc, and the organics were washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure to give 94 mg (94%) of the crude alcohol intermediate **253** as a yellow solid.

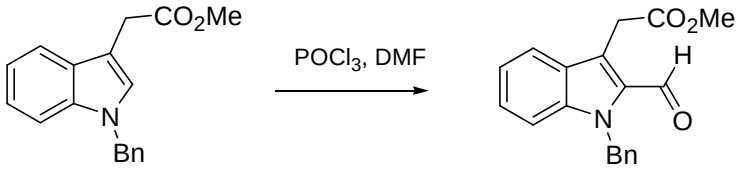
The above crude residue was then brought up in 20 mL of a 1:1 CH_2Cl_2/THF mixture. To this solution was added 0.4 g (4.6 mmol) of manganese dioxide. The resulting suspension was stirred at rt for 72 h and then filtered through a pad of Celite. The filtrates were then concentrated under reduced pressure and purified using flash silica gel chromatography to give 0.7 g (75%) of the titled enone **230** as a yellow solid. The spectral data of this compound is identical to that reported in the literature:[170] mp 182-185 ℃; IR (neat) 1667, 1513, 1464, 1369, 1249 and 1146 cm^{-1}; ^{1}H-NMR (C_6D_6, 600 MHz) δ 1.13-1.22 (m, 1H), 1.25-1.44 (m, 1H), 1.76 (t, 1H, *J* = 11.4 Hz), 1.96 (dt, 1H, *J* = 15.2 and 4.8 Hz), 2.23-2.35 (m, 3H), 2.44 (d, 1H, *J* = 16.2 Hz), 2.62 (d, 1H, *J* = 9.5 Hz), 2.63 (d, 1H, *J* = 11.4 Hz), 2.67-2.72 (m, 1H), 2.67-2.72 (m, 1H), 3.02-3.10 (m, 2H), 3.43 (s, 3H), 3.50 (s, 3H), 5.97 (s, 1H), 6.45 (s, 1H) and 6.56 (s, 1H); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 25.9, 29.1, 36.6, 40.3, 51.3, 55.8, 56.1, 61.9, 62.3, 108.0, 111.4, 125.4, 126.5, 128.7, 147.4, 147.7, 163.4 and 199.5.



precursor-**267** **267**

Methyl 2-(1-Benzyl-1*H*-indol-3-yl)acetate (267). To a solution of 9.0 g (34 mmol) of 2-(1-benzyl-1*H*-indol-3-yl)acetic acid (*precursor*-**267**)[171] in 60 mL of dry MeOH at -78 °C was added 3.0 mL (40.7 mmol) of thionyl chloride. The suspension was slowly allowed to warm to room temperature and was stirred for

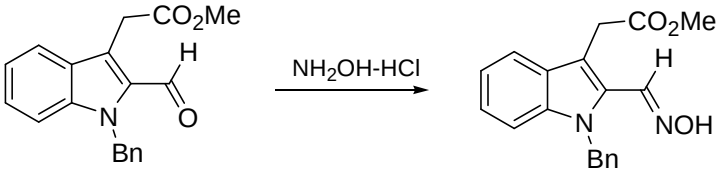
17 h. The resulting deep red solution was concentrated under reduced pressure and the residue was taken up in 100mL of EtOAc. The organics were extracted, washed with a saturated aqueous $NaHCO_3$, then brine, then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was then purified using flash silica gel chromatography to give 8.3 g (88%) of the titled ester **267** as a pale yellow oil: IR (neat) 1737, 1614, 1496, 1164 and 1013 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 3.71 (s, 3H), 3.80 (s, 2H), 5.25 (s, 2H), 7.12 (d, 3H, *J* = 7.6 Hz), 7.16 (t, 1H. *J* = 7.6 Hz), 7.21 (t, 1H, *J* = 7.6 Hz), 7.24-7.32 (m, 4H) and 7.66 (d, 1H, *J* = 7.6 Hz); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 31.0, 49.8, 51.8, 107.4, 109.7, 119.0, 119.3, 121.9, 126.7, 127.0, 127.5, 127.8, 128.6, 136.4, 137.3 and 172.3.



267 **268**

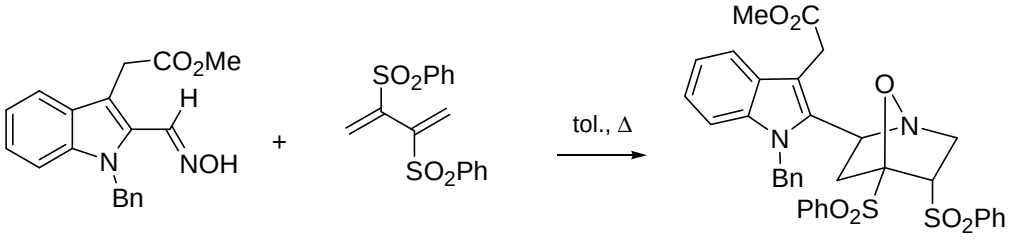
(1-Benzyl-2-formyl-1H-indol-3-yl)-acetic acid methyl ester (268). To a 100 mL flask was charged with 80 mL of DMF was added 6.5 g (43 mmol) of $POCl_3$ and 4.0 g (14 mmol) of indole **267**. The resulting solution was then heated to 50 °C for 15 h, then cooled to room temperature and partitioned between ether and aqueous $NaHCO_3$. The organics were extracted and washed three times with water. The combined organics were then washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to give 2.4 g (56%) of the titled aldehyde **268** as a yellow oil: IR (neat) 2941, 1738, 1664, 1464, 1435, 1351 and 1167 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 3.72 (s, 3H), 4.16 (s, 2H), 5.82 (s, 2H), 7.10 (d, 2H, *J* = 7.1 Hz), 7.20-7.28 (m, 4H), 7.36-7.42 (m, 2H), 7.80 (d, 1H, *J* = 8.1 Hz) and

10.20 (s, 1H); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 29.6, 47.7, 52.3, 110.9, 114.1, 121.1, 121.2, 121.7, 126.4, 127.2, 127.5, 128.5, 131.0, 137.6, 139.2, 170.8 and 181.3.



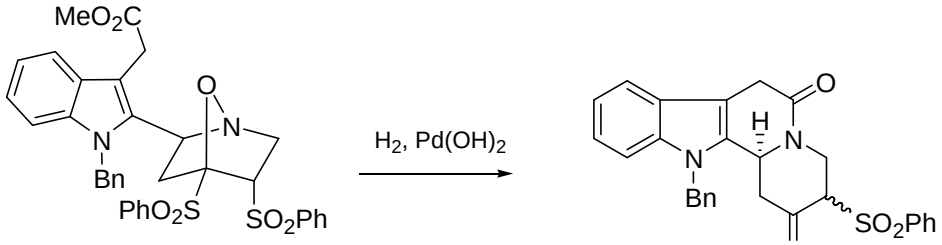
268 **269**

[1-Benzyl-2-(hydroxyimino-methyl)-1H-indol-3-yl]-acetic acid methyl ester (269). To a solution of 5.3 g (17.2 mmol) of aldehyde **268** in 130 mL of MeOH was added 1.6 g (22.4 mmol) of hydroxylamine hydrochloride and 3.6 g (43 mmol) of sodium acetate. The resulting solution was stirred for 23 h and then concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 and washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to give 4.5 g (81%) of the titled oxime **269** as a white solid: mp 121-122 °C; IR (neat) 3355, 1738, 1662, 1453, 1349 and 1256 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.69 (s, 3H), 3.94 (s, 2H), 5.68 (s, 2H), 7.03 (d, 1H, *J* = 8.3 Hz), 7.12-7.18 (m, 1H), 7.20-7.30 (m, 6H), 7.66 (d, 1H, *J* = 8.3 Hz) and 8.39 (s, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 30.4, 48.2, 52.2, 110.1, 112.1, 119.6, 120.4, 124.3, 126.1, 127.2, 127.4, 128.2, 128.6, 137.8, 138.3, 142.4, and 171.7.



269 **69** **272**

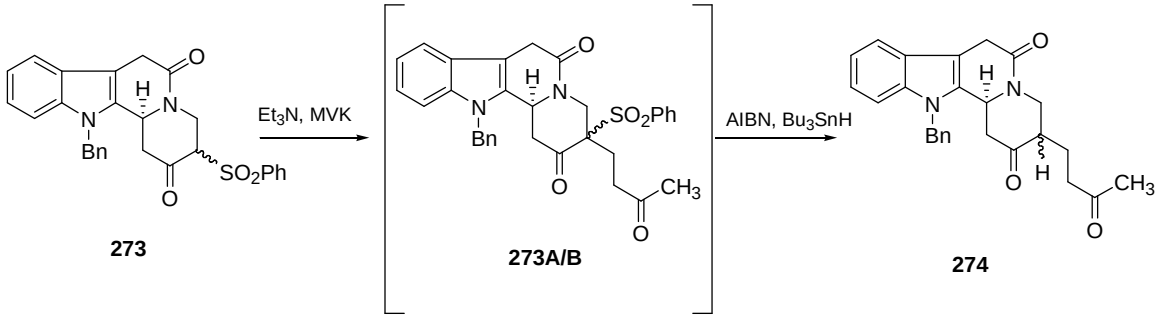
[1-Benzyl-2-(4,5-*bis*-benzenesulfonyl-7-oxa-1-aza-bicyclo[2.2.1]hept-2-yl)-1*H*-indol-3-yl]-acetic Acid Methyl Ester (272). To a 500 mL flask was charged with 5.5 g (17 mmol) of oxime **269** was added 6.2 g (19 mmol) of 2,3-*bis*(phenylsulfonyl)-1,3-butadiene (**69**)[55] and 200 mL of dry toluene. The mixture was heated at reflux for 41 h. The mixture was then concentrated and the residue was purified by flash silica gel chromatography to give 7.9 g (72%) of the titled cycloadduct **272** as a white solid: mp 142-143 °C; IR (neat) 1735, 1637, 1613, 1447 and 1324 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.35-2.40 (m, 1H), 3.38-3.44 (m, 2H), 3.47-3.62 (m, 3H), 3.65 (s, 3H), 4.48-4.54 (m, 1H), 4.83 (t, 1H, *J* = 7.6 Hz), 5.15 (d, 1H, *J* = 17.1 Hz), 5.30 (d, 1H, *J* = 17.1 Hz), 6.98 (d, 2H, *J* = 7.6 Hz), 7.09 (t, 1H, *J* = 7.6 Hz), 7.16 (t, 1H, *J* = 7.6 Hz), 7.18 (d, 1H, *J* = 7.6 Hz), 7.24-7.32 (m, 3H), 7.49 (dd, 1H, *J* = 17.1 and 7.6 Hz), 7.51 (d, 2H, *J* = 7.6 Hz), 7.65 (t, 2H, *J* = 7.6 Hz), 7.70 (t, 1H, *J* = 7.6 Hz), 7.75 (t, 1H, *J* = 7.6 Hz), 7.78 (d, 2H, *J* = 7.6 Hz) and 7.95 (d, 2H, *J* = 7.6 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 29.5, 39.5, 47.1, 51.9, 61.7, 65.0, 67.0, 103.1, 106.6, 109.6, 118.7, 119.9, 122.6, 126.3, 127.5, 127.9, 128.0, 128.7, 129.1, 129.4, 129.6, 130.2, 134.4, 134.7, 135.0, 136.7, 137.5, 138.5 and 172.4; Anal. Calcd for $C_{35}H_{32}N_2O_7S_2$: C, 64.01; H, 4.91; N, 4.27. Found: C, 64.08; H, 5.00; N, 4.14.



272 **273**

3-Benzenesulfonyl-12-benzyl-1,3,4,7,12,12b-hexahydro-indolo[2,3-a]quinolizine-2,6-dione (273). To a 30 mL sealed tube charged with 0.34 g (0.52 mmol) of cycloadduct **272** was added 0.15 g (0.16 mmol) of 20% $Pd(OH)_2$,

50 μL (0.78 mmol) of AcOH, and 3 mL of EtOAc. The resulting mixture was pressurized under an atmosphere of hydrogen (45 psi) and heated at 60 °C for 38 h. The mixture was the cooled and depressurized, then filtered through a pad of Celite. The filtrates were then concentrated under reduced pressure and the crude residue was taken up in CH_2Cl_2 and washed with aqueous $NaHCO_3$. The combined organics were then washed with water, brine, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to give 0.2 g (81%) of a 1:1 diastereomeric mixture the titled ketone **273** as a yellow solid. Subsequent recrystallization from methanol and ether allowed isolation of one diastereomer for characterization purposes: mp 121-122 °C; IR (neat) 1698, 1658, 1449, 1322 and 1148 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.85 (d, 1H, *J* = 14.3 Hz), 3.14 (dd, 1H, *J* = 15.2 and 4.8 Hz), 3.17-3.22 (m, 1H), 3.81 (d, 1H, *J* = 4.8 Hz), 3.89 (d, 1H, *J* = 20.9 Hz), 3.99 (d, 1H, *J* = 20.9 Hz), 4.82 (d, 1H, *J* = 11.4 Hz), 5.22 (d, 1H, *J* = 17.2 Hz), 5.34 (d, 1H, *J* = 17.2 Hz), 5.68 (d, 1H, *J* = 15.2 Hz), 6.88 (d, 2H, *J* = 7.6 Hz), 7.15-7.31 (m, 6H), 7.56 (d, 1H, *J* = 7.6 Hz), 7.60 (t, 2H, *J* = 7.6 Hz), 7.70 (t, 1H, *J* = 7.6 Hz) and 8.03 (d, 2H, *J* = 7.6 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 29.3, 41.7, 47.1, 49.3, 54.7, 71.5, 106.2, 110.0, 118.8, 120.3, 123.2, 125.4, 125.6, 125.7, 127.9, 129.1, 129.2, 129.5, 134.7, 136.4, 136.7, 137.9, 167.8 and 196.1; Anal. Calcd for $C_{28}H_{24}N_2O_4S$: C, 69.40; H, 4.99; N, 5.78. Found: C, 68.58; H, 5.07; N, 5.68.



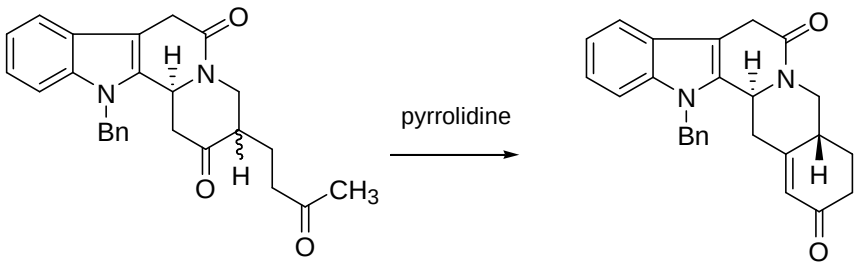
273 **273A/B** **274**

12-Benzyl-3-(3-oxo-butyl)-1,3,4,7,12,12b-hexahydro-indolo[2,3-a]quinolizine-2,6-dione (274). To a solution of 0.63 g (1.3 mmol) of keto sulfone **273** in 15 mL of a 9:1 THF/MeOH mixture was added 0.75 mL (9.0 mmol) of methyl vinyl ketone. To this solution was added 0.35 mL (2.8 mmol) of a 0.8 M solution of Et_3N in THF. The reaction mixture was stirred at room temperature for 24 h and then concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to give 0.70 g (97%) of a 1:1-mixture of diketones **273A** and **273B** as a yellow solid. The diastereomers were separated using flash silica gel chromatography. Data for **273A**: mp 105-106 °C; IR (neat) 1715, 1658, 1600, 1447, 1308 and 1147 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 2.07 (s, 3H), 2.11-2.25 (m, 4H), 2.50-2.56 (m, 1H), 2.60 (dd, 1H, *J* = 18.1 and 11.4 Hz), 2.71-2.78 (m, 1H), 2.88 (dd, 1H, *J* = 17.1 and 4.8 Hz), 2.94 (t, 1H, *J* = 7.6 Hz), 3.38 (t, 1H, *J* = 7.6 Hz), 3.87 (d, 1H, *J* = 15.2 Hz), 3.77-3.90 (m, 2H), 5.18 (d, 1H, *J* = 14.3 Hz), 5.19-5.23 (m, 1H), 5.26 (d, 1H, *J* = 17.1 Hz), 5.32 (d, 1H, *J* = 17.1 Hz), 6.98 (d, 2H, *J* = 7.6 Hz), 7.16-7.20 (m, 1H), 7.22-7.33 (m, 5H), 7.53 (d, 1H, *J* = 7.6 Hz), 7.58 (d, 2H, *J* = 7.6 Hz), 7.71 (t, 1H, *J* = 7.6 Hz) and 7.85 (d, 2H, *J* = 7.6 Hz); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 26.7, 29.3, 29.9, 37.4, 44.6, 47.4, 47.8, 52.7, 75.1, 105.2, 110.1, 118.7, 120.3, 123.1, 125.4, 125.9, 128.0, 129.0, 129.1, 129.2, 129.4, 130.9, 133.9, 134.8, 135.0, 136.5, 137.9, 167.5, 199.6 and 206.6.

Data for **273B**: mp 102-103 °C; IR (neat) 1712, 1649, 1451, 1321, 1266 and 1240 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.73-1.79 (m, 1H), 2.11 (s, 3H), 2.21-2.27 (m, 1H), 2.44-2.57 (m, 2H), 2.89 (dd, 1H, *J* = 15.2 and 1.9 Hz), 3.04 (d, 1H, *J* = 15.2 Hz), 3.34 (dd, 1H, *J* = 15.2 and 12.4 Hz), 3.92 (d, 1H, *J* = 20.9 Hz), 3.99 (d, 1H, *J* = 20.9 Hz), 4.88 (d, 1H, *J* = 12.4 Hz), 5.25 (d, 1H, *J* = 17.1 Hz), 5.38 (d, 1H, *J* = 17.1 Hz), 5.82 (d, 1H, *J* = 15.2 Hz), 6.94 (d, 2H, *J* = 6.7 Hz), 7.17-7.33 (m, 6H), 7.59 (t, 3H, *J* = 8.6 Hz), 7.70 (t, 1H, *J* = 7.6 Hz) and 7.93 (d, 2H, *J* = 7.6 Hz); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 24.6, 29.4, 29.7, 30.1, 37.4, 44.7, 47.2, 49.0,

54.2, 73.8, 106.2, 110.1, 118.8, 120.3, 123.1, 125.5, 125.8, 127.9, 128.1, 129.1, 129.2, 130.7, 134.4, 134.8, 136.5, 137.9, 167.7, 198.8 and 206.2.

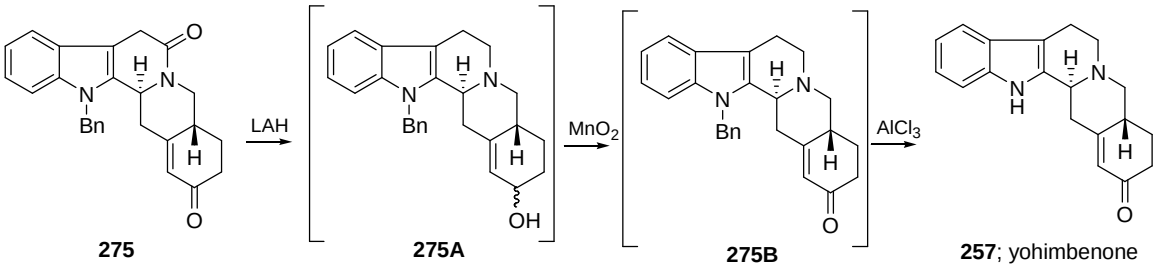
To a solution of 0.25 g (0.45 mmol) of the above mixture of **273A/B** in 15 mL of toluene was added 0.5 mL (1.8 mmol) of *n*-Bu_3SnH. To this mixture was added 0.1 g (0.61 mmol) of AIBN and the solution was heated at reflux for 1 h. The mixture was then cooled to room temperature and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to give 0.18 g (94%) of a 1:1 diastereomeric mixture of the titled diketone **274** as a yellow solid: mp 190-195 °C; IR (neat) 1729, 1648, 1463, 1452, 1236 and 1143 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 1.52-1.64 (m, 1H), 2.10-2.08 (m, 1H), 2.16 (s, 3H), 2.44-2.58 (m, 4H), 2.63-2.72 (m, 1H), 2.74 (dd, 1H, *J* = 13.3 and 2.9 Hz), 3.80-3.94 (m, 2H), 4.81 (dd, 1H, *J* = 12.4 and 2.9 Hz), 5.15 (d, 1H, *J* = 6.7 Hz), 5.24 (d, 1H, *J* = 18.1 Hz), 5.36 (d, 1H, *J* = 18.1 Hz), 6.91 (d, 2H, *J* = 7.6 Hz), 7.17-7.30 (m, 6H) and 7.55 (d, 1H, *J* = 7.6 Hz); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 20.2, 29.3, 30.0, 40.8, 47.1, 47.4, 49.3, 50.2, 55.3, 105.6, 110.1, 118.7, 120.3, 123.1, 125.4, 125.7, 127.9, 129.0, 129.1, 136.5, 137.8, 167.6, 206.1 and 207.8; HRMS Calcd for $[(C_{26}H_{26}N_2O_3) + H]^+$: 415.2016. Found: 415.2010.



274 **275**

13-Benzyl-3,4,4a,5,8,13,13b,14-octahydro-indolo[2',3':3,4]pyrido[1,2-b]isoquinoline-2,7-dione (275). To a solution of 50 mg (0.12 mmol) of diketone **274** in 52 mL of CH_2Cl_2 was added 9.0 μL (0.10 mmol) of pyrrolidine and 6.0 μL (0.10 mmol) of AcOH. The mixture was stirred for 72 h at rt and then

concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to give 40 mg (78%) of a single diastereomer of the titled enone **275** as a yellow solid: mp 195-196 °C; IR (neat) 1713, 1668, 1464, 1454, 1246 and 1191 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.16-2.22 (m, 1H), 2.27-2.38 (m, 3H), 2.42 (t, 1H, *J* = 12.4 Hz), 2.50 (dt, 1H, *J* = 17.2 and 3.8 Hz), 2.55 (dd, 1H, *J* = 14.3 and 1.9 Hz), 2.60-2.68 (m, 1H), 3.79 (dd, 1H, *J* = 21.0 and 1.9 Hz), 3.88 (dd, 1H, *J* = 21.0 and 1.9 Hz), 4.63 (dd, 1H, *J* = 12.4 and 2.9 Hz), 5.06 (dd, 1H, *J* = 13.3 and 5.7 Hz), 5.31 (d, 1H, *J* = 17.2 Hz), 5.36 (d, 1H, *J* = 17.2 Hz), 5.72 (s, 1H), 6.98 (d, 2H, *J* = 6.7 Hz), 7.19 (t, 1H, *J* = 7.6 Hz), 7.24-7.33 (m, 5H) and 7.56 (d, 1H, *J* = 7.6 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 25.5, 29.2, 36.3, 36.4, 43.2, 47.1, 48.5, 55.1, 105.5, 109.8, 118.6, 120.2, 122.9, 125.3, 125.8, 126.7, 127.9, 129.1, 129.8, 136.9, 138.0, 159.1, 167.3 and 198.8; HRMS Calcd for $[(C_{26}H_{24}N_2O_2) + H]^+$: 397.1911. Found: 397.1905.



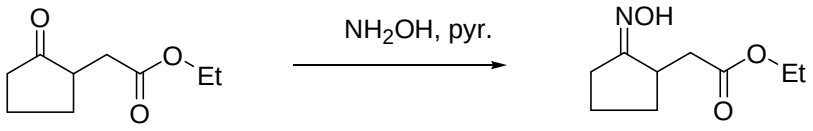
(±)-Yohimbenone (257). To a solution of 0.27 g (0.68 mmol) of lactam **275** in 12 mL of Et_2O was added 0.21 g (5.4 mmol) of $LiAlH_4$. The resulting suspension was stirred for 1 h at 0 °C, and then warmed to rt over the course of 24 h. The reaction mixture was then sequentially treated with 0.27 mL of water, 0.27 mL of a 15% aqueous NaOH solution, and 0.82 mL of water. To the resulting was added anhydrous $MgSO_4$ and this mixture was stirred for an additional 30 minutes. The suspension was then filtered, and the filtrates were concentrated under reduced pressure. The resulting residue was purified using flash silica gel

chromatography to give 0.23 g (88%) of the intermediate alcohol **275A** as a yellow solid: mp 183-184 °C; IR (neat) 3364, 1465, 1350, 1217 and 1182 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 1.77-1.84 (m, 1H), 2.03-2.10 (m, 1H), 2.26-2.35 (m, 2H), 2.40-2.48 (m, 1H), 2.76-2.83 (m, 1H), 2.87 (dt, 1H, *J* = 15.2 and 5.7 Hz), 2.96 (dt, 1H, *J* = 15.2 and 5.7 Hz), 3.12 (dd, 1H, *J* = 18.1 and 11.4 Hz), 3.24-3.29 (m, 1H), 3.65 (dd, 1H, *J* = 10.5 and 2.9 Hz), 4.22 (t, 1H, *J* = 6.7 Hz), 5.29 (s, 2H), 5.34 (s, 1H), 7.00 (d, 2H, *J* = 7.6 Hz), 7.09-7.16 (m, 3H), 7.21-7.31 (m, 3H) and 7.52-7.56 (m, 1H); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 22.3, 24.6, 31.6, 33.7, 37.4, 47.4, 48.1, 58.1, 62.3, 67.4, 108.6, 109.6, 118.2, 119.3, 121.5, 125.3, 125.8, 127.0, 127.3, 128.8, 136.5, 137.6, 137.7 and 140.2.

To a solution of 0.08 g (0.21 mmol) of the above mixture of alcohols **275A** in 20 mL of 1:1 CH_2Cl_2/THF was added 0.2 g (2.1 mmol) of manganese dioxide. The mixture was stirred at rt for 72 h, then filtered through a pad of Celite. The filtrates were then concentrated under reduced pressure and purified using flash silica gel chromatography to give 0.71 g (89%) of ketone **275B** as a yellow solid: mp 149-150 °C; IR (neat) 1665, 1464, 1453, 1264, 1181 and 1028 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 1.53-1.61 (m, 1H), 2.01-2.06 (m, 2H), 2.29-2.36 (m, 1H), 2.42-2.48 (m, 3H), 2.60 (t, 1H, *J* = 12.5 Hz), 2.70-2.77 (m, 1H), 2.84-2.89 (m, 1H), 2.91 (dt, 1H, *J* = 15.0 and 5.0 Hz), 2.98 (dt, 1H, *J* = 15.0 and 5.0 Hz), 3.24-3.31 (m, 2H), 3.77 (dd, 1H, *J* = 10.0 and 4.5 Hz), 5.27 (d, 1H, *J* = 17.5 Hz), 5.31 (d, 1H, *J* = 17.5 Hz), 5.70 (s, 1H), 6.99 (d, 2H, *J* = 7.5 Hz), 7.11-7.20 (m, 3H), 7.22-7.30 (m, 3H) and 7.55 (d, 1H, *J* = 7.0 Hz); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 22.3, 25.7, 34.4, 36.5, 37.8, 47.4, 48.0, 56.9, 61.4, 108.9, 109.6, 118.3, 119.5, 121.9, 125.3, 125.8, 126.8, 127.5, 128.9, 135.6, 137.5, 137.8, 163.0 and 199.3; HRMS Calcd for $[(C_{26}H_{26}N_2O) + H]^+$: 383.2118. Found: 383.2110.

To a solution of 0.05 g (0.12 mmol) of the above ketone **275B** in 10 mL of anhydrous toluene was added 0.6 g (0.47 mmol) of anhydrous $AlCl_3$. The

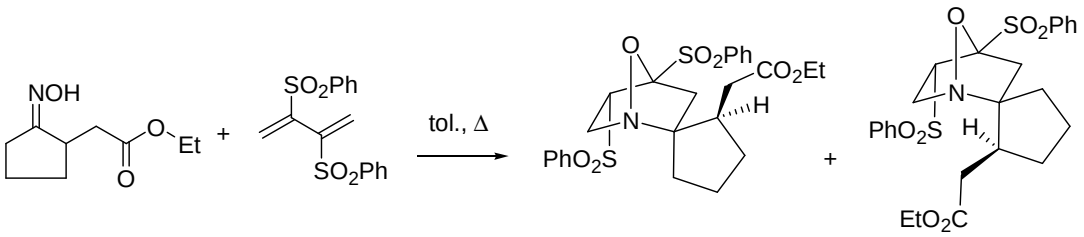
resulting mixture was sonicated at 30 ^{o}C for 5 h. The reaction mixture was then concentrated under reduced pressure. The residue was then partitioned between EtOAc and 5% aqueous NaOH. The organics were collected, washed with water, brine, then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was then purified using flash silica gel chromatography to give 0.03 g (92%) of (±)-yohimbenone (**257**) as a yellow solid. The spectral data of this compound is identical to that reported in the literature:[172] mp 244-245 °C; IR (neat) 3264, 1650, 1449, 1327, 1259 and 1164 cm^{-1}; ^{1}H-NMR (*d*$_6$-DMSO, 600 MHz) δ 1.51-1.65 (m, 1H), 1.97-2.10 (m, 1H), 2.18 (t, 1H, *J* = 11.4 Hz), 2.26-2.43 (m, 3H), 2.62-2.69 (m, 2H), 2.70-2.89 (m, 2H), 3.04-3.15 (m, 2H), 3.19 (dd, 1H, *J* = 11.4 and 6.4 Hz), 3.35 (s, 1H), 5.83 (s, 1H), 6.95 (t, 1H, *J* = 7.3 Hz), 7.03 (t, 1H, *J* = 7.3 Hz), 7.29 (d, 1H, *J* = 8.3 Hz), 7.38 (d, 1H, *J* = 7.3 Hz) and 10.86 (s, 1H); ^{13}C-NMR (*d*$_6$-DMSO, 150 MHz) δ 21.5, 25.6, 36.3, 36.6, 38.2, 51.7, 58.9, 60.9, 106.7, 111.1, 117.7, 118.5, 120.7, 124.6, 126.5, 134.7, 136.1, 163.6 and 198.6.



292 **291**

(2-Hydroxyimino-cyclopentyl)-acetic acid ethyl ester (291). To a RB flask charged with 1.00 g (5.88 mmol) of (2-oxo-cyclopentyl)-acetic acid ethyl ester (**292**)[173] was added 25 mL of ethanol. To this stirring solution was added 0.82 g (11.8 mmol) of hydroxylamine hydrochloride and 1.42 mL (17.6 mmol) of pyridine. The solution was allowed to stir at rt for 24 h, then concentrated under reduced pressure. The crude reside was then brought up in ethyl acetate and transferred to a separatory funnel. The organics were extracted, washed with water, brine, dried using $MgSO_4$, filtered, and concentrated under reduced

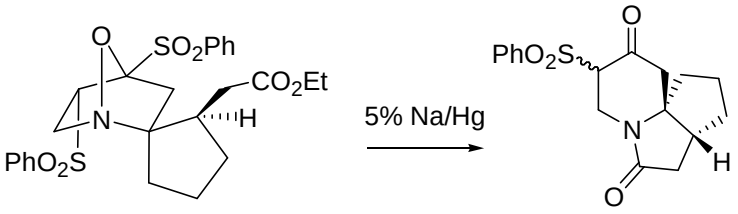
pressure. The crude residue was purified using silica gel chromatography to give 0.97 g (89%) of the titled oxime **291** as a colorless oil: IR (CH_2Cl_2): 3298, 2956, 1677, and 930 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 1.25 (t, 3H, *J* = 6.8 Hz), 1.34-1.44 (m, 1H), 1.58-1.70 (m, 1H), 1.84-1.91 (m, 1H), 2.32-2.45 (m, 2H), 2.55-2.74 (m, 1H), 2.70 (dd, 2H, *J* = 16.4 and 5.2 Hz), 2.87-2.91 (m, 1H), 4.12 (q, 2H, *J* = 6.8 Hz), and 8.24 (br s, 1H); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 14.1, 22.4, 27.0, 31.9, 36.6, 39.6, 60.4, 167.3, and 172.4.



291 **69** **290**-*major* **290**-*minor*

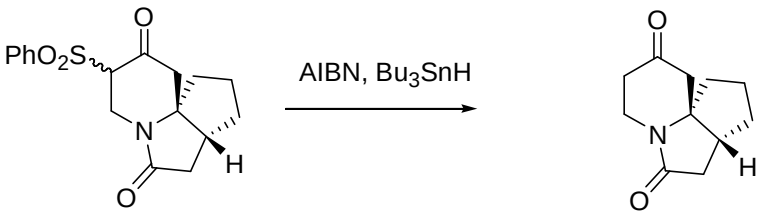
Cycloadduct (290-*major*). To a solution containing 2.0 g (10.8 mmol) of oxime **291** in 50 mL of toluene was added 3.6 g (10.8 mmol) of 2,3-*bis*(phenylsulfonyl)-1,3-butadiene (**69**)[55] at rt. The mixture was heated at reflux for 24 h, then cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 5.6 g (95%) of a 1.3:1 diastereomeric mixture of cycloadducts **290**-*major* and **290**-*minor*. The major isomer, **290**-*major*, was separated and obtained as a colorless oil: IR (neat) 2965, 1729, and 1154 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.19 (t, 3H, *J* = 7.6 Hz), 1.56-1.78 (m, 5H), 1.80-1.92 (m, 2H), 2.02 (dd, 1H, *J* = 15.6 and 3.6 Hz), 2.09 (dd, 1H, *J* = 12.8 and 2.4 Hz), 2.14-2.22 (m, 1H), 3.24 (d, 1H, *J* = 12.8 Hz), 3.66 (dd, 1H, *J* = 12.4 and 10.8 Hz), 3.83 (dd, 1H, *J* = 12.4 and 4.8 Hz), 4.00 (dd, 1H, *J* = 7.2 and 2.0 Hz), 4.04 (dd, 1H, *J* = 7.2 and 2.0 Hz), 4.33 (ddd, 1H, *J* = 10.8, 4.8 and 2.0 Hz), 7.53 (t, 2H, *J* = 7.6 Hz), 7.60-7.70 (m, 3H), 7.73 (t, 1H, *J* = 7.6 Hz), 7.78 (d, 2H, *J* = 7.6), and 7.98 (d, 2H, *J* = 7.6 Hz); ^{13}C-NMR ($CDCl_3$,

100 MHz) δ14.2, 21.3, 28.7, 31.4, 34.4, 40.5, 48.2, 55.0, 60.0, 66.5, 80.2, 103.9, 128.3, 128.8, 129.0, 130.2, 134.2, 134.6, 134.8, 139.1, and 173.0.



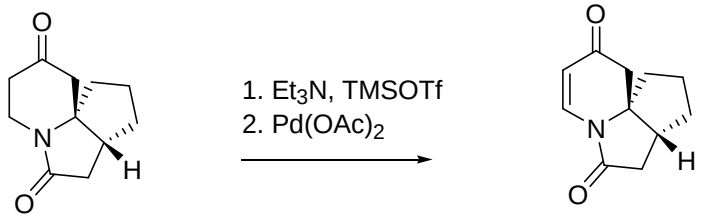
290-*major* **293**

7-Benzenesulfonyl-hexahydro-5*a*-aza-cyclopenta[*c*]indene-5,8-dione (293). To a solution containing 2.6 g (5.0 mmol) of cycloadduct **290**-*major* in 100 mL of THF was added 5.8 g (12.5 mmol) of 5% sodium-mercury amalgam at rt. The mixture was stirred at room temperature for 12 h and then 30 mL of 1 N solution of HCl was added. The resulting mixture was extracted with EtOAc and the combined organics were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 1.25 g (75%) of an inseparable 1:1 diastereomeric mixture of the titled piperidone **293** as a yellow oil; IR (neat) 2943, 1716, and 1684 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.44-1.55 (m, 2H), 1.56-1.76 (m, 3H), 1.96-2.07 (m, 1H), 2.22-2.30 (m, 1H), 2.43-2.52 (m, 1H), 2.58 (dd, 1H, *J* = 13.2 and 0.8 Hz), 2.95 (dd, 1H, *J* = 17.6 and 10.0 Hz), 3.12 (dd, 1H, *J* = 15.2 and 4.8 Hz), 3.31 (d, 1H, *J* = 13.2 Hz), 3.73 (d, 1H, *J* = 4.8 Hz), 4.78 (d, 1H, *J* = 15.2 Hz), 7.62 (t, 2H, *J* = 7.6 Hz), 7.70 (t, 1H, *J* = 7.6 Hz), and 8.02 (d, 2H, *J* = 7.6 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 24.8, 34.3, 35.9, 36.7, 36.9, 41.6, 52.3, 70.7, 72.6, 129.4, 129.6, 134.7, 136.4, 173.7, and 197.3.



293 **294**

Hexahydro-5*a*-aza-cyclopenta[*c*]indene-5,8-dione (294). To a solution containing 1.2 g (3.60 mmol) of sulfone **293** in 50 mL of benzene was added 4.8 mL (18 mmol) of tributyltin hydride and 1.2 g (7.2 mmol) of AIBN. The mixture was heated to reflux for 36 h and then cooled to room temperature. The solvent was then removed under reduced pressure and the residue was subjected to silica gel column chromatography to give 0.58 g (83%) of the titled ketone **294** as a colorless oil: IR (neat) 1729, and 1693 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.39-1.55 (m, 2H), 1.60-1.68 (m, 2H), 1.72 (dd, 1H, *J* = 12.0 and 6.0 Hz), 1.92-2.03 (m, 1H), 2.21 (ddd, 1H, *J* = 18.0, 3.2 and 1.2 Hz), 2.29-2.46 (m, 4H), 2.53 (d, 1H, *J* = 13.6 Hz), 2.78 (dd, 1H, *J* = 18.0 and 10.4 Hz), 2.91 (tdd, 1H, *J* = 13.6, 5.2 and 0.8 Hz), and 4.44 (ddd, 1H, *J* = 13.6, 7.6 and 1.6 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 24.8, 34.2, 35.6, 35.9, 37.3, 40.1, 41.5, 53.0, 72.6, 172.8, and 206.3.

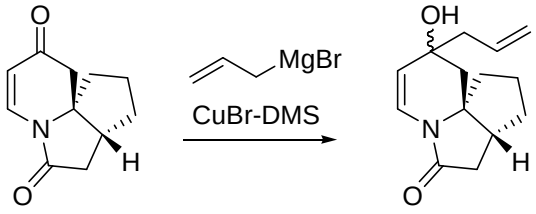


294 **295**

2,3,3a,4-Tetrahydro-1H-5a-aza-cyclopenta[c]indene-5,8-dione (295). To a solution containing 1.7 g (8.8 mmol) of piperidone **294** in 50 mL of CH_2Cl_2 was added 2.9 mL (21 mmol) of triethylamine and then 1.9 mL (10.6 mmol) of TMSOTf at 25 ^{o}C. The solution was stirred at room temperature for 12 h then quenched by the addition of 10 mL of a saturated solution of $NaHCO_3$. The

organics were extracted, washed with water, brine, dried using $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was then immediately taken up in 20 ml of 3:1 MeCN/DMSO.

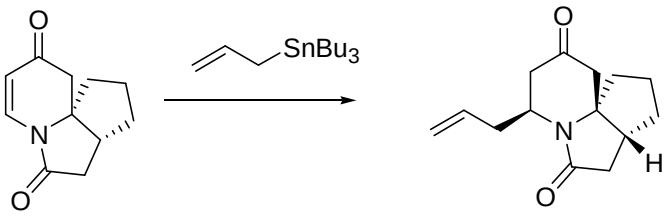
To above solution was added 2.4 g (10.6 mmol) of $Pd(OAc)_2$. The reaction mixture was stirred at room temperature for 36 h then was filtered through a pad of Celite. The filtrates were concentrated under reduced pressure and then partitioned between EtOAc and water. The organics were then extracted and washed with water, brine, then dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography gave 1.3 g (75%) of the titled enone **295** as a white solid: mp 67-68 ^oC; IR (KBr) 1705, and 1689 cm^{-1}; ^1H-NMR ($CDCl_3$ 400 MHz) δ 1.62-2.01 (m, 6H), 2.28 (dd, 1H, *J* = 18.8 and 6.4 Hz), 2.51 (dd, 1H, *J* = 16.0 and 0.8 Hz), 2.54-2.62 (m, 1H), 2.75 (d, 1H, *J* = 16.0 Hz), 2.93 (dd, 1H, *J* = 18.8 and 10.8 Hz), 5.49 (dd, 1H, *J* = 8.0 and 0.8 Hz), and 7.66 (d, 1H, *J* = 8.0 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 24.1, 32.4, 37.0, 38.1, 41.2, 48.5, 71.5, 109.8, 137.5, 171.4, and 193.7.



295 **296**

8-Allyl-8-hydroxy-2,3,3*a*,4,8,9-hexahydro-1*H*-5*a*-aza-cyclopenta[*c*]inden-5-one (296). To a solution containing 0.12 g (0.60 mmol) of enone **295** in 5 mL of THF at –78 ^oC was added 0.9 g (0.63 mmol) of copper bromide-dimethylsulfide complex. The resulting mixture was stirred for 20 min at –78 ^oC and then 756 μL (0.76 mmol) of a 1.0 M solution of allylmagnesium bromide was added. The solution was allowed to warm slowly to 25 ^oC and to this mixture was added a

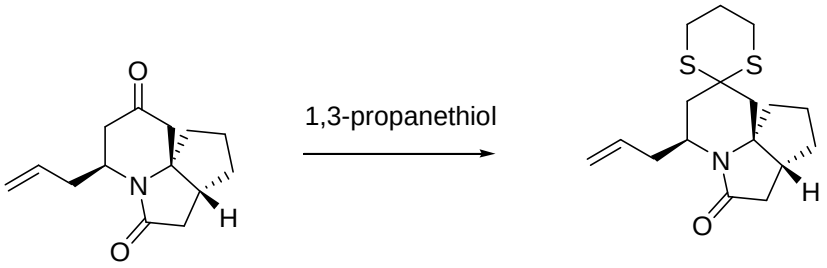
saturated solution of NH_4Cl. The resulting mixture was extracted with EtOAc and the organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 0.11 g (77%) of an inseparable 1:1 diastereomeric mixture of the titled alcohol **296** as a colorless oil: IR (neat) 3402, 2948, and 1673 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.54-1.66 (m, 3H), 1.70-1.81 (m, 4H), 1.82-1.98 (m, 3H), 2.05 (dd, 1H, *J* = 13.6 and 1.6 Hz), 2.17 (dd, 1H, *J* = 18.4 and 6.0 Hz), 2.24-2.34 (m, 2H), 2.39-2.48 (m, 1H), 2.76 (dd, 1H, *J* = 18.4 and 10.8 Hz), 5.19-5.22 (m, 3H), 5.82 (ddt, 1H, *J* = 17.2, 10.0 and 7.2 Hz), and 6.82 (d, 1H, *J* = 8.0 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 24.6, 32.9, 37.1, 38.3, 42.4, 46.6, 47.7, 68.8, 69.1, 115.2, 119.6, 122.8, 132.8, and 172.2.



295 **297**

6-Allyl-hexahydro-5*a*-aza-cyclopenta[*c*]indene-5,8-dione (297). To a solution containing 0.75 g (3.9 mmol) of enone **295** in 15 mL of CH_2Cl_2 at 0 ^oC was added 1.3 mL (4.3 mmol) of allyltributyltin and 0.8 mL (4.3 mmol) of TMSOTf. After stirring for 1 h at 0 ^oC, the mixture was warmed to room temperature and was stirred for an additional 10 min at 25 ^oC. To this solution was added a 1.0 N solution of HCl (10 mL) and the resulting mixture was extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 0.87 g (77%) of a 15:1 diasteromeric mixture of the titled ketone **297** as a

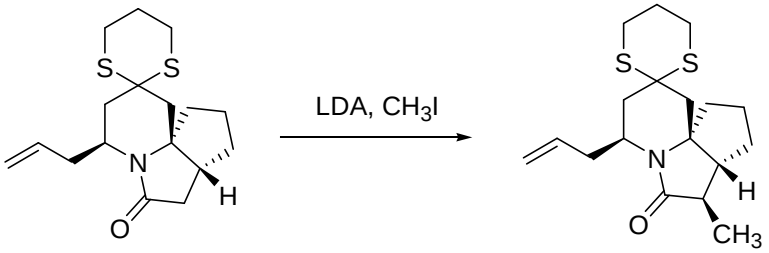
colorless oil. The major diastereomer was then purified and characterized: IR (neat) 2958, 1718, 1685, and 1396 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.34-1.45 (m, 1H), 1.52-1.66 (m, 1H), 1.69-1.86 (m, 3H), 2.00-2.09 (m, 1H), 2.20-2.48 (m, 7H), 2.57 (dd, 1H, *J* = 14.8 and 7.6 Hz), 2.74 (dd, 1H, *J* = 17.2 and 10.4 Hz), 4.67 (ddd, 1H, *J* = 14.8, 8.4 and 4.0 Hz), 5.04-5.13 (m, 2H), and 5.64-5.77 (m, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 25.7, 34.0, 37.3, 39.1, 39.3, 42.9, 43.1, 48.8, 53.0, 72.3, 118.4, 133.9, 173.9, and 206.8.



297 **298**

6-Allyl-hexahydro-5a-aza-cyclopenta[c]indene-5,8-dithia-spiro[5.5]undecane (298). To a solution containing 0.86 g (3.7 mmol) of ketone **297** in 15 mL of CH_2Cl_2 at room temperature was added 0.6 mL (5.5 mmol) of 1,3-propanedithiol and a catalytic amount of BF_3-OEt_2. The solution was stirred for 12 h at rt, then the solvent was removed under reduced pressure. The crude residue was purified by silica gel chromatography to give 1.2 g (99%) of the titled dithiane **298** as a colorless oil: IR (neat) 2948, 1689, and 1397 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.32-1.42 (m, 1H), 1.55-1.74 (m, 2H), 1.76-1.94 (m, 3H), 1.96-2.30 (m, 7H), 2.37 (dd, 1H, *J* = 14.8 and 6.0 Hz), 2.46 (dt, 1H, *J* = 14.4 and 8.1 Hz), 2.56-2.68 (m, 2H), 2.68-2.79 (m, 2H), 2.89 (ddd, 1H, *J* = 14.4, 10.0 and 2.8 Hz), 2.98 (ddd, 1H, *J* = 14.8, 10.0 and 2.8 Hz), 4.20 (quintet, 1H, *J* = 7.2 Hz), 5.20-5.13 (m, 2H), and 5.72-5.86 (m, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 24.8,

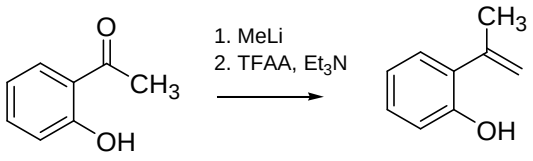
25.4, 26.9, 27.0, 33.4, 36.6, 37.3, 39.3, 41.4, 44.4, 46.3, 48.5, 50.4, 69.7, 117.6, 134.9, and 174.6.



298 **299**

6-Allyl-4-methyl-hexahydro-5a-aza-cyclopenta[c]indene-5,8-dithia-spiro[5.5]undecane (299). To a solution containing 0.5 mL (3.6 mmol) of diisopropylamine in 10 mL of THF at –78 ^{o}C was added 1.5 mL (3.7 mmol) of a 2.5 M solution of *n*-BuLi. After stirring for 30 min, a solution containing 1.1 g (3.4 mmol) of amide **298** in 5 mL of THF was added. The mixture was allowed to stir for 30 min at –78 ^{o}C and 211 μL (3.4 mmol) of iodomethane was added. The reaction mixture was stirred at –78 ^{o}C for an additional 3 h and was then allowed to warm slowly to room temperature. To this mixture was added a saturated solution of NH_4Cl and the resulting solution was extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 0.91 g (79%) of a single diastereomer of ketone **299** as a colorless oil: IR (neat) 2950, 1690, and 1397 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.22 (d, 3H, *J* = 7.2 Hz), 1.40-1.49 (m, 1H), 1.58-1.73 (m, 2H), 1.78-1.95 (m, 4H), 1.96-2.08 (m, 3H), 2.14-2.25 (m, 2H), 2.33 (d, 1H, *J* = 14.4 Hz), 2.39 (dd, 1H, *J* = 14.0 and 9.2 Hz), 2.50 (dt, 1H, *J* = 14.0 and 8.4 Hz), 2.61-2.70 (m, 1H), 2.70-2.81 (m, 2H), 2.91 (ddd, 1H, *J* = 14.4, 10.0 and 2.8 Hz), 3.00 (ddd, 1H, *J* = 14.8, 10.0 and 2.8 Hz), 4.22 (quintet, 1H, *J* = 7.2 Hz), 5.03-5.15 (m, 2H), and 5.74-5.86 (m, 1H); ^{13}C-

NMR ($CDCl_3$, 100 MHz) δ 17.8, 24.8, 25.6, 26.9, 27.0, 32.1, 36.9, 39.1, 41.4, 43.5, 46.5, 48.4, 51.7, 54.7, 67.8, 117.6, 135.0, and 177.0.

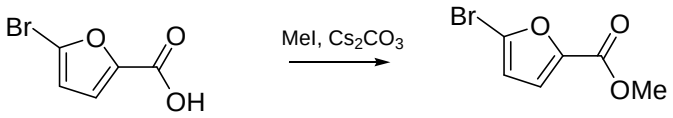


317 **318**

2-Isopropenyl-phenol (318). To a RB flask charged with 5.8 g (42 mmol) of 1-(2-Hydroxy-phenyl)-ethanone (**317**)[174] in 60 mL of dry ether at -78 ^oC was dropwise added 56 mL (90 mmol) of a 1.6 M solution of methyllithium in ether over the course of 1 h. The reaction mixture was warmed to 0 ^oC and allowed to stir for an additional 1 h. The mixture was then transferred to a separatory funnel and partitioned between aqueous NH_4Cl and ether. The organics were extracted, washed with water, brine, dried with $MgSO_4$, then filtered and concentrated under reduced pressure to give 6.3 g of the crude intermediate diol which was immediately dissolved in 50 mL of CH_2Cl_2/MeCN (95:5) and subjected to the following reaction conditions.

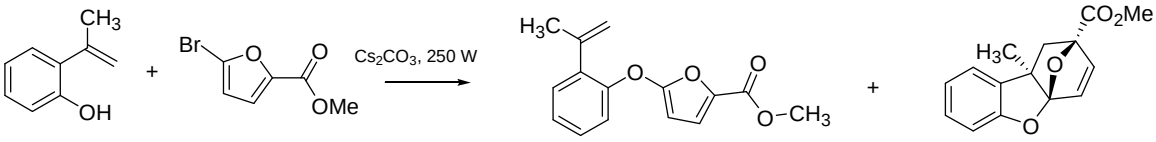
To a solution of the above crude diol in 50 mL of CH_2Cl_2/MeCN (95:5) cooled to 0 ^oC was added 14.6 mL (103.5 mmol) of trifluoroacetic anhydride. To this stirring solution was added 37.4 mL (269 mmol) of triethylamine and a catalytic amount of DMAP. The reaction was then warmed to rt over the course of 2 h, then partitioned between DCM and aqueous NH_4Cl. The organics were extracted, washed with water, brine, dried using $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified using silica gel chromatography to give 5.0 g (90%) of the titled phenol **318** as a pale yellow oil: IR (CH_2Cl_2) 3420, 3010, and 1120 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 2.12 (s, 3H), 2.23 (br s, 1H), 5.15 (s, 1H), 5.40 (s, 1H), 6.90 (t, 1H, J = 6.6 Hz),

6.93 (d, 1H, *J* = 8.4 Hz), and 7.13-7.18 (m, 2H). The spectral data for this compound was identical to the values reported in the literature.[175]



precursor-**321** **321**

5-Bromo-furan-2-carboxylic acid methyl ester (321). To a RB flask charged with 4.6 g (24 mmol) of 5-bromo-furan-2-carboxylic acid (*precursor*-**321**) was added 96 mL of DMF. To this stirring solution was added 2.3 mL (36 mmol) of redistilled methyl iodide and 11.8 g (36 mmol) of cesium carbonate. The reaction mixture was allowed to stir for 24 h at rt then filtered through a pad of Celite. The filtrates were then transferred to a separatory funnel and partitioned between ether and water. The organics were extracted, washed with water, brine, dried using $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified using silica gel chromatography to give 3.7 g (75%) of the titled ester **321** as a white solid; mp 64-65 ^{o}C; IR (CH_2Cl_2) 3021, 1712, and 1140 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.88 (s, 3H), 6.45 (d, 1H, *J* = 3.4 Hz), and 7.12 (d, 1H, *J* = 3.4 Hz). The spectral data for this compound was identical to the values reported in the literature.[176]



318 **321** **322** **323**

2,4a-oxa-bicyclo[2.2.1]heptanyl-9b-methyl-1,2,4a,9b-tetrahydro-dibenzofuran-2-carboxylic acid methyl ester (323). To a microwave vessel charged with 109 mg (0.81 mmol) of 2-isopropenyl-phenol (**318**) was added 3.2 mL of DMF and 168 mg (0.82 mmol) of bromofuran **321**. To this mixture was

added 530 mg (1.60 mmol) of cesium carbonate and the flask was sealed and placed in a microwave reactor which was set to 93 ^{o}C for 55 min under 200 W power. The reaction mixture was then filtered through a pad of Celite, and the filtrates were transferred to a separatory funnel and partitioned between ethyl acetate and water. The organics were extracted, washed with water, brine, dried using $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified using silica gel chromatography to give 75 mg (35%) of the titled bicycloadduct **323** as a colorless oil: IR (CH_2Cl_2) 2922, 2359, 1732, 1644, 1455, and 1375 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 1.12 (s, 3H), 1.89 (d, 1H, *J* = 22.8 Hz), 2.68 (d, 1H, *J* = 22.8 Hz), 3.81 (s, 3H), 6.65 (d, 1H, *J* = 11.4 Hz), 6.75 (d, 1H, *J* = 11.4 Hz), 6.99 (d, 1H, *J* = 13.5 Hz, 1H), 7.02 (d, 1H, *J* = 13.5 Hz), and 7.16-7.25 (m, 2H).

Also recovered from this reaction was 5-(2-Isopropenyl-phenoxy)-furan-2-carboxylic acid methyl ester (**322**) which exhibited limited stability but was fully separated by silica gel purification, giving 95 mg (45%) of **322** as a yellow oil: IR (CH_2Cl_2) 2927, 2359, 2091, 1740, 1456, and 1231 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.10 (s, 3H), 3.86 (s, 3H), 5.08 (s, 1H), 5.16 (m, 1H), 5.33 (d, 1H, *J* = 3.5 Hz), 7.06 (d, 1H, *J* = 8.0 Hz), 7.11 (d, 1H, *J* = 3.5 Hz), and 7.20-7.32 (m, 3H).

IV. X-RAY DATA

Table 1. Crystal data and structure refinement for **210**.

Identification code	HZ2-60s	
Empirical formula	$C_{32}H_{47}NO_6S_2Si$	
Formula weight	633.92	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 11.9551(9) Å	α= 90°.
	b = 18.5416(14) Å	β= 109.276(3)°.
	c = 15.8097(12) Å	γ = 90°.
Volume	3308.0(4) $Å^3$	
Z	4	
Density (calculated)	1.273 Mg/m^3	
Absorption coefficient	2.154 mm^{-1}	
F(000)	1360	
Crystal size	0.42 x 0.25 x 0.16 mm^3	
Theta range for data collection	3.80 to 66.88°.	
Index ranges	-14<=h<=12, -20<=k<=21, -18<=l<=18	
Reflections collected	15780	
Independent reflections	5547 [R(int) = 0.0356]	
Completeness to theta = 66.88°	94.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00 and 0.681082	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5547 / 0 / 385	
Goodness-of-fit on F^2	1.198	
Final R indices [I>2sigma(I)]	R1 = 0.0405, wR2 = 0.1070	
R indices (all data)	R1 = 0.0498, wR2 = 0.1111	
Largest diff. peak and hole	0.310 and -0.275 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **210**. $U_{(eq)}$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U_{(eq)}$
C(1)	10745(2)	1772(1)	9785(1)	27(1)
C(2)	10454(2)	1046(1)	9266(1)	23(1)
C(3)	9184(2)	1226(1)	8655(1)	21(1)
C(4)	9151(2)	1826(1)	7988(1)	22(1)
C(5)	9284(2)	2502(1)	8597(1)	23(1)
C(6)	8081(2)	2876(1)	8416(2)	30(1)
C(7)	7679(2)	3267(1)	7513(2)	36(1)
C(8)	8604(2)	3804(1)	7442(2)	36(1)
C(9)	9794(2)	3442(1)	7618(1)	27(1)
C(10)	10230(2)	3048(1)	8530(1)	24(1)
C(11)	10590(2)	3584(1)	9322(2)	32(1)
C(12)	11435(2)	4183(1)	9260(2)	36(1)
C(13)	11916(3)	4614(1)	10116(2)	48(1)
C(14)	12681(3)	5246(2)	10049(2)	65(1)
C(15)	6774(2)	764(1)	8007(1)	25(1)
C(16)	6200(2)	616(1)	8617(2)	29(1)
C(17)	5035(2)	822(1)	8420(2)	38(1)
C(18)	4457(2)	1179(1)	7631(2)	45(1)
C(19)	5028(2)	1326(1)	7023(2)	45(1)
C(20)	6198(2)	1113(1)	7203(2)	35(1)
C(21)	11173(2)	-57(1)	8334(1)	27(1)
C(22)	11077(2)	-640(1)	8855(2)	29(1)
C(23)	10671(2)	-1288(1)	8450(2)	34(1)
C(24)	10375(2)	-1356(1)	7527(2)	38(1)
C(25)	10497(2)	-779(1)	7017(2)	41(1)
C(26)	10892(2)	-119(1)	7413(2)	36(1)
C(27)	12144(2)	2736(1)	7126(2)	37(1)
C(28)	10692(2)	3906(1)	5908(2)	35(1)
C(29)	10145(2)	2302(1)	5415(1)	32(1)

C(30)	10163(2)	1540(1)	5796(2)	45(1)
C(31)	8886(2)	2472(2)	4808(2)	59(1)
C(32)	10988(3)	2326(2)	4864(2)	55(1)
N(1)	9600(2)	2177(1)	9529(1)	25(1)
O(1)	8764(1)	1567(1)	9321(1)	24(1)
O(2)	8391(1)	274(1)	7382(1)	29(1)
O(3)	8506(1)	-70(1)	8931(1)	29(1)
O(4)	12639(1)	679(1)	9642(1)	34(1)
O(5)	11718(1)	1284(1)	8184(1)	36(1)
O(6)	9698(1)	2942(1)	6901(1)	26(1)
S(1)	8243(1)	453(1)	8219(1)	22(1)
S(2)	11622(1)	781(1)	8851(1)	27(1)
Si(1)	10655(1)	2979(1)	6347(1)	24(1)

Table 3. Bond lengths [Å] and angles [°] for **210**.

C(1)-N(1)	1.495(3)	C(25)-C(26)	1.384(3)
C(1)-C(2)	1.556(3)	C(27)-Si(1)	1.855(2)
C(2)-C(3)	1.542(3)	C(28)-Si(1)	1.859(2)
C(2)-S(2)	1.796(2)	C(29)-C(31)	1.527(3)
C(3)-O(1)	1.452(2)	C(29)-C(30)	1.534(3)
C(3)-C(4)	1.524(3)	C(29)-C(32)	1.535(3)
C(3)-S(1)	1.812(2)	C(29)-Si(1)	1.879(2)
C(4)-C(5)	1.556(3)	N(1)-O(1)	1.473(2)
C(5)-N(1)	1.520(2)	O(2)-S(1)	1.4321(14)
C(5)-C(6)	1.537(3)	O(3)-S(1)	1.4390(14)
C(5)-C(10)	1.547(3)	O(4)-S(2)	1.4403(15)
C(6)-C(7)	1.530(3)	O(5)-S(2)	1.4397(15)
C(7)-C(8)	1.519(3)	O(6)-Si(1)	1.6555(14)
C(8)-C(9)	1.514(3)		
C(9)-O(6)	1.440(2)	N(1)-C(1)-C(2)	105.40(16)
C(9)-C(10)	1.545(3)	C(3)-C(2)-C(1)	98.38(15)
C(10)-C(11)	1.545(3)	C(3)-C(2)-S(2)	123.61(14)
C(11)-C(12)	1.526(3)	C(1)-C(2)-S(2)	111.29(14)
C(12)-C(13)	1.512(3)	O(1)-C(3)-C(4)	104.34(15)
C(13)-C(14)	1.511(4)	O(1)-C(3)-C(2)	98.35(14)
C(15)-C(16)	1.384(3)	C(4)-C(3)-C(2)	112.76(16)
C(15)-C(20)	1.389(3)	O(1)-C(3)-S(1)	107.44(12)
C(15)-S(1)	1.772(2)	C(4)-C(3)-S(1)	116.27(13)
C(16)-C(17)	1.377(3)	C(2)-C(3)-S(1)	115.21(14)
C(17)-C(18)	1.379(3)	C(3)-C(4)-C(5)	100.73(14)
C(18)-C(19)	1.377(3)	N(1)-C(5)-C(6)	106.06(15)
C(19)-C(20)	1.390(3)	N(1)-C(5)-C(10)	111.88(16)
C(21)-C(26)	1.387(3)	C(6)-C(5)-C(10)	110.60(17)
C(21)-C(22)	1.387(3)	N(1)-C(5)-C(4)	102.84(15)
C(21)-S(2)	1.756(2)	C(6)-C(5)-C(4)	110.52(16)
C(22)-C(23)	1.373(3)	C(10)-C(5)-C(4)	114.41(16)
C(23)-C(24)	1.389(3)	C(7)-C(6)-C(5)	111.93(17)
C(24)-C(25)	1.375(3)	C(8)-C(7)-C(6)	111.59(19)

C(9)-C(8)-C(7)	111.01(18)	C(30)-C(29)-C(32)	108.9(2)
O(6)-C(9)-C(8)	108.33(17)	C(31)-C(29)-Si(1)	110.58(17)
O(6)-C(9)-C(10)	110.15(16)	C(30)-C(29)-Si(1)	110.41(15)
C(8)-C(9)-C(10)	112.87(17)	C(32)-C(29)-Si(1)	108.74(17)
C(11)-C(10)-C(9)	111.67(17)	O(1)-N(1)-C(1)	99.70(14)
C(11)-C(10)-C(5)	112.34(16)	O(1)-N(1)-C(5)	98.92(13)
C(9)-C(10)-C(5)	110.15(17)	C(1)-N(1)-C(5)	111.94(15)
C(12)-C(11)-C(10)	115.43(17)	C(3)-O(1)-N(1)	97.12(13)
C(13)-C(12)-C(11)	113.04(19)	C(9)-O(6)-Si(1)	120.01(12)
C(14)-C(13)-C(12)	114.0(2)	O(2)-S(1)-O(3)	120.32(9)
C(16)-C(15)-C(20)	121.3(2)	O(2)-S(1)-C(15)	108.51(9)
C(16)-C(15)-S(1)	119.48(16)	O(3)-S(1)-C(15)	108.33(9)
C(20)-C(15)-S(1)	119.07(17)	O(2)-S(1)-C(3)	106.55(9)
C(17)-C(16)-C(15)	119.0(2)	O(3)-S(1)-C(3)	106.72(9)
C(16)-C(17)-C(18)	120.3(2)	C(15)-S(1)-C(3)	105.45(9)
C(19)-C(18)-C(17)	120.7(2)	O(5)-S(2)-O(4)	118.20(9)
C(18)-C(19)-C(20)	119.9(2)	O(5)-S(2)-C(21)	108.50(10)
C(15)-C(20)-C(19)	118.8(2)	O(4)-S(2)-C(21)	109.16(10)
C(26)-C(21)-C(22)	121.3(2)	O(5)-S(2)-C(2)	110.54(9)
C(26)-C(21)-S(2)	119.59(17)	O(4)-S(2)-C(2)	104.76(9)
C(22)-C(21)-S(2)	119.09(16)	C(21)-S(2)-C(2)	104.87(9)
C(23)-C(22)-C(21)	119.4(2)	O(6)-Si(1)-C(27)	108.56(9)
C(22)-C(23)-C(24)	119.9(2)	O(6)-Si(1)-C(28)	109.95(9)
C(25)-C(24)-C(23)	120.4(2)	C(27)-Si(1)-C(28)	109.69(11)
C(24)-C(25)-C(26)	120.6(2)	O(6)-Si(1)-C(29)	106.55(9)
C(25)-C(26)-C(21)	118.5(2)	C(27)-Si(1)-C(29)	110.49(11)
C(31)-C(29)-C(30)	108.7(2)	C(28)-Si(1)-C(29)	111.52(10)
C(31)-C(29)-C(32)	109.5(2)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **210**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2} U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	25(1)	29(1)	23(1)	1(1)	3(1)	-3(1)
C(2)	21(1)	25(1)	20(1)	5(1)	4(1)	-2(1)
C(3)	20(1)	23(1)	21(1)	0(1)	6(1)	-2(1)
C(4)	23(1)	22(1)	20(1)	4(1)	5(1)	0(1)
C(5)	24(1)	24(1)	21(1)	2(1)	9(1)	1(1)
C(6)	28(1)	29(1)	36(1)	1(1)	15(1)	3(1)
C(7)	29(1)	35(1)	45(1)	11(1)	13(1)	13(1)
C(8)	43(1)	27(1)	39(1)	9(1)	17(1)	9(1)
C(9)	33(1)	21(1)	29(1)	2(1)	13(1)	-1(1)
C(10)	25(1)	22(1)	26(1)	1(1)	10(1)	-1(1)
C(11)	42(1)	27(1)	30(1)	-5(1)	15(1)	-6(1)
C(12)	43(1)	31(1)	33(1)	-3(1)	10(1)	-9(1)
C(13)	57(2)	43(2)	39(2)	-11(1)	8(1)	-16(1)
C(14)	77(2)	47(2)	58(2)	-6(2)	3(2)	-27(2)
C(15)	20(1)	25(1)	28(1)	-4(1)	4(1)	1(1)
C(16)	29(1)	28(1)	31(1)	-5(1)	10(1)	-2(1)
C(17)	32(1)	43(2)	44(2)	-11(1)	17(1)	-4(1)
C(18)	25(1)	50(2)	60(2)	-5(1)	11(1)	7(1)
C(19)	32(1)	46(2)	47(2)	8(1)	0(1)	8(1)
C(20)	28(1)	38(1)	34(1)	3(1)	5(1)	0(1)
C(21)	21(1)	32(1)	29(1)	4(1)	9(1)	7(1)
C(22)	24(1)	34(1)	29(1)	3(1)	11(1)	5(1)
C(23)	32(1)	32(1)	42(1)	2(1)	18(1)	4(1)
C(24)	31(1)	41(1)	44(2)	-10(1)	13(1)	5(1)
C(25)	44(1)	48(2)	29(1)	-5(1)	8(1)	14(1)
C(26)	37(1)	40(1)	32(1)	8(1)	13(1)	14(1)
C(27)	25(1)	44(2)	40(1)	13(1)	8(1)	-2(1)
C(28)	39(1)	34(1)	34(1)	6(1)	14(1)	-3(1)

C(29)	38(1)	31(1)	26(1)	1(1)	10(1)	2(1)
C(30)	65(2)	31(1)	40(1)	-3(1)	19(1)	-5(1)
C(31)	53(2)	56(2)	45(2)	-12(1)	-12(1)	4(1)
C(32)	80(2)	50(2)	47(2)	-8(1)	38(2)	-7(2)
N(1)	27(1)	24(1)	24(1)	-2(1)	9(1)	-8(1)
O(1)	27(1)	24(1)	24(1)	-1(1)	12(1)	-4(1)
O(2)	28(1)	33(1)	26(1)	-5(1)	9(1)	0(1)
O(3)	27(1)	24(1)	32(1)	7(1)	6(1)	-1(1)
O(4)	21(1)	38(1)	38(1)	5(1)	3(1)	-1(1)
O(5)	34(1)	36(1)	43(1)	14(1)	20(1)	2(1)
O(6)	27(1)	25(1)	25(1)	0(1)	8(1)	-2(1)
S(1)	20(1)	22(1)	24(1)	0(1)	5(1)	0(1)
S(2)	21(1)	29(1)	31(1)	7(1)	9(1)	1(1)
Si(1)	23(1)	26(1)	23(1)	3(1)	6(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **210**.

	x	y	z	$U_{(eq)}$
H(1A)	11050	1686	10440	32
H(1B)	11347	2045	9611	32
H(2)	10392	667	9699	27
H(4A)	8390	1830	7486	26
H(4B)	9814	1784	7747	26
H(6A)	7479	2512	8424	36
H(6B)	8141	3228	8900	36
H(7A)	7529	2908	7024	43
H(7B)	6927	3524	7439	43
H(8A)	8343	4019	6834	43
H(8B)	8681	4198	7880	43
H(9)	10390	3820	7613	32
H(10)	10954	2767	8552	28
H(11A)	9862	3809	9370	39
H(11B)	10967	3310	9881	39
H(12A)	12105	3967	9113	43
H(12B)	11013	4513	8765	43
H(13A)	11242	4796	10287	58
H(13B)	12387	4290	10600	58
H(14A)	13353	5071	9881	98
H(14B)	12975	5492	10629	98
H(14C)	12211	5583	9592	98
H(16)	6603	376	9164	35
H(17)	4627	718	8830	46
H(18)	3656	1324	7505	54
H(19)	4622	1572	6482	54
H(20)	6597	1204	6785	42
H(22)	11290	-592	9487	34
H(23)	10593	-1689	8799	41

H(24)	10086	-1803	7245	46
H(25)	10308	-833	6388	49
H(26)	10969	282	7062	43
H(27A)	12429	3118	7575	56
H(27B)	12695	2682	6788	56
H(27C)	12095	2281	7426	56
H(28A)	9885	4057	5561	53
H(28B)	11186	3910	5522	53
H(28C)	11023	4239	6410	53
H(30A)	9615	1516	6140	67
H(30B)	10967	1425	6190	67
H(30C)	9920	1191	5303	67
H(31A)	8637	2116	4324	88
H(31B)	8866	2955	4552	88
H(31C)	8347	2455	5160	88
H(32A)	10739	1968	4382	82
H(32B)	11796	2218	5253	82
H(32C)	10966	2808	4604	82

Table 6. Crystal data and structure refinement for **211**.

Identification code	hz260ms	
Empirical formula	$C_{32}H_{47}NO_6S_2Si$	
Formula weight	633.92	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.0794(17) Å	α= 80.164(8)°.
	b = 11.2603(18) Å	β= 82.222(8)°.
	c = 16.212(2) Å	γ = 69.838(8)°.
Volume	1696.0(5) $Å^3$	
Z	2	
Density (calculated)	1.241 Mg/m^3	
Absorption coefficient	2.101 mm^{-1}	
F(000)	680	
Crystal size	0.16 x 0.13 x 0.02 mm^3	
Theta range for data collection	2.78 to 38.07°.	
Index ranges	-8<=h<=8, -9<=k<=8, -12<=l<=12	
Reflections collected	3969	
Independent reflections	1760 [R(int) = 0.1590]	
Completeness to theta = 38.07°	97.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00 and 0.132910	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1760 / 0 / 221	
Goodness-of-fit on F^2	0.997	
Final R indices [I>2sigma(I)]	R1 = 0.1120, wR2 = 0.2508	
R indices (all data)	R1 = 0.1658, wR2 = 0.2837	
Extinction coefficient	0.0060(13)	
Largest diff. peak and hole	0.517 and -0.368 e.$Å^{-3}$	

Table 7. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for **211**.

$U_{(eq)}$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U_{(eq)}$
C(1)	5454(15)	2571(14)	9661(9)	42(5)
C(2)	4092(15)	2141(14)	9761(9)	32(5)
C(3)	3866(16)	2302(13)	8850(9)	18(4)
C(4)	3358(15)	3684(13)	8429(9)	37(5)
C(5)	4782(15)	4014(14)	8316(9)	29(5)
C(6)	4703(16)	5173(14)	8752(9)	44(5)
C(7)	3956(15)	6452(13)	8254(8)	38(5)
C(8)	4614(15)	6544(14)	7382(9)	36(5)
C(9)	4526(17)	5489(14)	6924(10)	36(5)
C(10)	5300(15)	4170(15)	7397(9)	39(5)
C(11)	6951(15)	3888(14)	7246(9)	42(5)
C(12)	7768(16)	2556(14)	7003(10)	57(6)
C(13)	9354(16)	2294(15)	6816(10)	59(6)
C(14)	10101(17)	957(15)	6583(10)	67(6)
C(15)	3792(16)	993(14)	7539(10)	33(5)
C(16)	5053(16)	-72(15)	7435(11)	48(6)
C(17)	5662(17)	-206(16)	6638(11)	55(6)
C(18)	5186(18)	618(17)	5926(11)	67(6)
C(19)	3929(17)	1616(16)	6008(11)	59(6)
C(20)	3288(17)	1829(16)	6826(10)	51(6)
C(21)	1400(17)	2250(15)	10588(9)	37(5)
C(22)	1687(17)	997(15)	10982(9)	42(5)
C(23)	613(18)	465(17)	11015(10)	62(6)
C(24)	-667(18)	1191(17)	10668(10)	55(6)
C(25)	-911(18)	2397(16)	10267(9)	50(5)
C(26)	167(17)	2950(16)	10231(9)	48(6)
C(27)	2433(16)	7822(14)	5596(9)	58(6)
C(28)	2725(18)	5199(16)	5256(10)	77(7)

C(29)	258(17)	6514(17)	6501(11)	52(6)
C(30)	-201(18)	7462(17)	7113(11)	81(7)
C(31)	80(20)	5298(19)	6937(12)	112(8)
C(32)	-720(20)	7038(18)	5787(12)	100(8)
N(1)	5785(12)	2815(12)	8762(8)	32(4)
O(1)	5342(9)	1858(9)	8471(6)	41(4)
O(2)	1553(11)	1993(10)	8475(6)	47(4)
O(3)	3457(11)	105(11)	9094(7)	48(4)
O(4)	3438(10)	2534(10)	11306(7)	45(4)
O(5)	2219(10)	4277(11)	10236(7)	51(4)
O(6)	3081(11)	5600(9)	6898(6)	38(3)
S(1)	3036(6)	1287(5)	8527(3)	43(2)
S(2)	2779(5)	2931(5)	10522(3)	41(2)
Si(1)	2156(5)	6264(5)	6081(3)	49(2)

Table 8. Bond lengths [Å] and angles [°] for **211**.

C(1)-N(1)	1.451(15)	C(25)-C(26)	1.418(19)
C(1)-C(2)	1.586(18)	C(27)-Si(1)	1.892(15)
C(2)-C(3)	1.496(16)	C(28)-Si(1)	1.850(16)
C(2)-S(2)	1.784(15)	C(29)-C(31)	1.49(2)
C(3)-O(1)	1.479(15)	C(29)-C(30)	1.496(19)
C(3)-C(4)	1.528(17)	C(29)-C(32)	1.527(19)
C(3)-S(1)	1.806(15)	C(29)-Si(1)	1.883(17)
C(4)-C(5)	1.582(17)	N(1)-O(1)	1.465(13)
C(5)-C(10)	1.512(18)	O(2)-S(1)	1.437(9)
C(5)-N(1)	1.514(15)	O(3)-S(1)	1.446(10)
C(5)-C(6)	1.561(17)	O(4)-S(2)	1.446(10)
C(6)-C(7)	1.521(16)	O(5)-S(2)	1.439(11)
C(7)-C(8)	1.482(17)	O(6)-Si(1)	1.641(10)
C(8)-C(9)	1.537(17)		
C(9)-O(6)	1.424(15)	N(1)-C(1)-C(2)	105.3(11)
C(9)-C(10)	1.542(17)	C(3)-C(2)-C(1)	98.1(12)
C(10)-C(11)	1.575(18)	C(3)-C(2)-S(2)	123.4(11)
C(11)-C(12)	1.532(18)	C(1)-C(2)-S(2)	111.8(10)
C(12)-C(13)	1.519(19)	O(1)-C(3)-C(2)	101.5(11)
C(13)-C(14)	1.520(18)	O(1)-C(3)-C(4)	101.1(11)
C(15)-C(20)	1.392(17)	C(2)-C(3)-C(4)	114.9(13)
C(15)-C(16)	1.429(18)	O(1)-C(3)-S(1)	104.4(9)
C(15)-S(1)	1.713(16)	C(2)-C(3)-S(1)	117.6(11)
C(16)-C(17)	1.362(19)	C(4)-C(3)-S(1)	114.2(10)
C(17)-C(18)	1.379(18)	C(3)-C(4)-C(5)	101.0(11)
C(18)-C(19)	1.382(19)	C(10)-C(5)-N(1)	109.3(12)
C(19)-C(20)	1.415(19)	C(10)-C(5)-C(6)	112.0(13)
C(21)-C(26)	1.365(17)	N(1)-C(5)-C(6)	108.5(12)
C(21)-C(22)	1.394(18)	C(10)-C(5)-C(4)	110.5(11)
C(21)-S(2)	1.788(16)	N(1)-C(5)-C(4)	101.6(11)
C(22)-C(23)	1.397(19)	C(6)-C(5)-C(4)	114.4(12)
C(23)-C(24)	1.401(18)	C(7)-C(6)-C(5)	112.8(12)
C(24)-C(25)	1.355(18)	C(8)-C(7)-C(6)	110.9(12)

C(7)-C(8)-C(9)	111.0(13)	C(30)-C(29)-C(32)	107.6(14)
O(6)-C(9)-C(8)	109.8(11)	C(31)-C(29)-Si(1)	110.9(12)
O(6)-C(9)-C(10)	108.7(12)	C(30)-C(29)-Si(1)	110.4(12)
C(8)-C(9)-C(10)	109.6(13)	C(32)-C(29)-Si(1)	110.3(12)
C(5)-C(10)-C(9)	113.2(12)	C(1)-N(1)-O(1)	100.6(11)
C(5)-C(10)-C(11)	113.3(11)	C(1)-N(1)-C(5)	115.5(12)
C(9)-C(10)-C(11)	109.5(13)	O(1)-N(1)-C(5)	99.4(10)
C(12)-C(11)-C(10)	113.4(13)	N(1)-O(1)-C(3)	95.7(9)
C(13)-C(12)-C(11)	114.0(13)	C(9)-O(6)-Si(1)	124.5(9)
C(12)-C(13)-C(14)	111.4(13)	O(2)-S(1)-O(3)	119.2(7)
C(20)-C(15)-C(16)	118.0(15)	O(2)-S(1)-C(15)	108.6(7)
C(20)-C(15)-S(1)	121.8(13)	O(3)-S(1)-C(15)	108.6(7)
C(16)-C(15)-S(1)	119.9(12)	O(2)-S(1)-C(3)	108.1(7)
C(17)-C(16)-C(15)	117.3(15)	O(3)-S(1)-C(3)	105.7(6)
C(16)-C(17)-C(18)	125.5(17)	C(15)-S(1)-C(3)	105.8(7)
C(17)-C(18)-C(19)	118.0(17)	O(5)-S(2)-O(4)	118.1(7)
C(18)-C(19)-C(20)	118.4(17)	O(5)-S(2)-C(2)	110.5(7)
C(15)-C(20)-C(19)	122.4(16)	O(4)-S(2)-C(2)	105.3(7)
C(26)-C(21)-C(22)	124.0(16)	O(5)-S(2)-C(21)	109.0(7)
C(26)-C(21)-S(2)	119.2(13)	O(4)-S(2)-C(21)	108.3(7)
C(22)-C(21)-S(2)	116.8(13)	C(2)-S(2)-C(21)	104.8(7)
C(21)-C(22)-C(23)	116.3(15)	O(6)-Si(1)-C(28)	110.0(6)
C(22)-C(23)-C(24)	119.9(17)	O(6)-Si(1)-C(29)	104.8(7)
C(25)-C(24)-C(23)	122.9(17)	C(28)-Si(1)-C(29)	112.0(8)
C(24)-C(25)-C(26)	117.8(16)	O(6)-Si(1)-C(27)	111.8(7)
C(21)-C(26)-C(25)	119.1(16)	C(28)-Si(1)-C(27)	106.8(8)
C(31)-C(29)-C(30)	108.2(15)	C(29)-Si(1)-C(27)	111.6(7)
C(31)-C(29)-C(32)	109.3(15)		

Symmetry transformations used to generate equivalent atoms:

Table 9. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **211**.

The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2\ hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	27(8)	38(8)	67(9)	-28(7)	8(6)	-19(6)
O(2)	11(9)	59(9)	78(10)	-25(7)	-8(7)	-12(7)
O(3)	63(9)	25(8)	73(10)	-10(8)	-17(7)	-27(7)
O(4)	38(8)	53(9)	53(10)	-20(7)	-12(7)	-19(6)
O(5)	35(8)	30(9)	86(10)	-21(8)	11(6)	-7(7)
O(6)	29(8)	34(8)	56(9)	-8(7)	-22(6)	-7(6)
S(1)	32(4)	36(4)	70(5)	-15(3)	-5(3)	-17(3)
S(2)	28(4)	29(4)	66(5)	-17(3)	0(3)	-8(3)
Si(1)	42(4)	39(4)	63(5)	-17(3)	-10(3)	-1(3)

Table 10. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **211**.

	x	y	z	$U_{(eq)}$
H(1A)	5253	3352	9925	50
H(1B)	6254	1887	9926	50
H(2)	4397	1206	9968	38
H(4A)	2621	4241	8793	45
H(4B)	2987	3754	7881	45
H(6A)	4194	5111	9316	53
H(6B)	5678	5130	8828	53
H(7A)	2943	6552	8245	46
H(7B)	4010	7150	8532	46
H(8A)	5620	6468	7390	43
H(8B)	4122	7389	7074	43
H(9)	4979	5569	6338	43
H(10)	5085	3522	7134	47
H(11A)	7143	4535	6795	50
H(11B)	7306	3977	7765	50
H(12A)	7611	1910	7467	68
H(12B)	7378	2453	6501	68
H(13A)	9755	2390	7315	71
H(13B)	9523	2927	6346	71
H(14A)	10003	327	7064	100
H(14B)	11109	837	6430	100
H(14C)	9674	846	6106	100
H(16)	5450	-662	7902	58
H(17)	6485	-927	6567	67
H(18)	5705	503	5394	81
H(19)	3505	2146	5527	71
H(20)	2485	2569	6891	61
H(22)	2564	530	11214	50
H(23)	751	-387	11273	75

H(24)	-1396	823	10716	66
H(25)	-1776	2855	10019	59
H(26)	33	3797	9963	58
H(27A)	2103	8430	6006	87
H(27B)	1895	8173	5099	87
H(27C)	3443	7670	5431	87
H(28A)	3754	4775	5239	116
H(28B)	2473	5704	4710	116
H(28C)	2249	4555	5381	116
H(30A)	-1122	7466	7402	121
H(30B)	-285	8314	6813	121
H(30C)	503	7228	7526	121
H(31A)	697	4965	7402	168
H(31B)	342	4673	6540	168
H(31C)	-909	5452	7159	168
H(32A)	-554	6377	5426	151
H(32B)	-521	7780	5454	151
H(32C)	-1709	7295	6021	151

Table 11. Crystal data and structure refinement for **220**.

Identification code	MSWA307	
Empirical formula	$C_{35}H_{51}N_3O_5S$	
Formula weight	625.85	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 20.3831(14) Å	α= 90°.
	b = 14.5284(9) Å	β= 90°.
	c = 23.2366(15) Å	γ = 90°.
Volume	6881.1(8) $Å^3$	
Z	8	
Density (calculated)	1.208 Mg/m^3	
Absorption coefficient	1.185 mm^{-1}	
F(000)	2704	
Crystal size	0.88 x 0.24 x 0.09 mm^3	
Theta range for data collection	3.80 to 66.05°.	
Index ranges	-20<=h<=22, -15<=k<=16, -25<=l<=26	
Reflections collected	52658	
Independent reflections	5676 [R(int) = 0.0656]	
Completeness to theta = 66.05°	94.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9009 and 0.4221	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5676 / 0 / 405	
Goodness-of-fit on F^2	1.050	
Final R indices [I>2sigma(I)]	R1 = 0.0457, wR2 = 0.1381	
R indices (all data)	R1 = 0.1128, wR2 = 0.1775	
Extinction coefficient	0.00031(6)	
Largest diff. peak and hole	0.437 and -0.456 e.$Å^{-3}$	

Table 12. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **220**.

$U_{(eq)}$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U_{(eq)}$
C(1)	1210(1)	3956(2)	2020(1)	36(1)
C(2)	1819(1)	4443(2)	1750(1)	38(1)
C(3)	1697(1)	4824(2)	1162(1)	39(1)
C(4)	1517(1)	4097(2)	738(1)	40(1)
C(5)	882(1)	3630(2)	943(1)	38(1)
C(6)	656(1)	2481(2)	1682(1)	36(1)
C(7)	737(1)	1722(2)	1248(1)	39(1)
C(8)	1364(1)	1493(2)	1051(1)	48(1)
C(9)	1456(2)	718(2)	717(1)	61(1)
C(10)	933(2)	172(2)	566(1)	67(1)
C(11)	305(2)	396(2)	754(1)	60(1)
C(12)	210(1)	1164(2)	1097(1)	46(1)
C(13)	277(1)	4227(2)	809(1)	42(1)
C(14)	-385(1)	3763(2)	910(1)	43(1)
C(15)	-959(1)	4308(2)	666(1)	46(1)
C(16)	-1626(1)	3905(2)	813(1)	57(1)
C(17)	-2197(1)	4435(2)	561(1)	67(1)
C(18)	712(1)	4698(2)	2234(1)	38(1)
C(19)	956(1)	5240(2)	2771(1)	43(1)
C(20)	1241(1)	4620(2)	3236(1)	49(1)
C(21)	1761(1)	3970(2)	3006(1)	47(1)
C(22)	1470(1)	3372(2)	2524(1)	43(1)
C(23)	18(1)	4344(2)	2388(1)	40(1)
C(24)	-505(1)	5075(2)	2286(1)	43(1)
C(25)	-1175(1)	4855(2)	2527(1)	56(1)
C(26)	-1670(1)	5599(2)	2385(1)	68(1)
C(27)	1323(1)	6807(2)	2896(1)	49(1)
C(28)	2108(1)	6686(2)	3641(1)	71(1)

C(29)	405(1)	7219(2)	1464(1)	53(1)
C(30)	-259(1)	7226(2)	1337(1)	53(1)
C(31)	-486(1)	7443(2)	790(1)	51(1)
C(32)	-23(2)	7660(2)	371(1)	56(1)
C(33)	642(2)	7631(2)	485(1)	54(1)
C(34)	859(1)	7415(2)	1035(1)	45(1)
C(35)	-1208(2)	7450(2)	651(1)	69(1)
N(1)	933(1)	3325(1)	1558(1)	35(1)
N(2)	1713(1)	5665(1)	989(1)	42(1)
N(3)	1872(1)	6340(2)	1404(1)	47(1)
O(1)	2059(1)	7576(1)	678(1)	62(1)
O(2)	1825(1)	7938(1)	1703(1)	62(1)
O(3)	387(1)	2291(1)	2143(1)	42(1)
O(4)	1431(1)	5951(1)	2608(1)	46(1)
O(5)	1432(1)	6769(1)	3489(1)	53(1)
S(1)	1705(1)	7393(1)	1197(1)	51(1)

Table 13. Bond lengths [Å] and angles [º] for **220**.

C(1)-N(1)	1.521(3)	C(14)-H(14A)	0.9900
C(1)-C(22)	1.540(3)	C(14)-H(14B)	0.9900
C(1)-C(2)	1.561(3)	C(15)-C(16)	1.520(3)
C(1)-C(18)	1.562(3)	C(15)-H(15A)	0.9900
C(2)-C(3)	1.496(3)	C(15)-H(15B)	0.9900
C(2)-H(2A)	0.9900	C(16)-C(17)	1.514(4)
C(2)-H(2B)	0.9900	C(16)-H(16A)	0.9900
C(3)-N(2)	1.286(3)	C(16)-H(16B)	0.9900
C(3)-C(4)	1.490(3)	C(17)-H(17A)	0.9800
C(4)-C(5)	1.535(3)	C(17)-H(17B)	0.9800
C(4)-H(4A)	0.9900	C(17)-H(17C)	0.9800
C(4)-H(4B)	0.9900	C(18)-C(23)	1.547(3)
C(5)-N(1)	1.500(3)	C(18)-C(19)	1.556(3)
C(5)-C(13)	1.540(3)	C(18)-H(18)	1.0000
C(5)-H(5)	1.0000	C(19)-O(4)	1.465(3)
C(6)-O(3)	1.235(3)	C(19)-C(20)	1.522(3)
C(6)-N(1)	1.382(3)	C(19)-H(19)	1.0000
C(6)-C(7)	1.503(3)	C(20)-C(21)	1.516(4)
C(7)-C(12)	1.390(3)	C(20)-H(20A)	0.9900
C(7)-C(8)	1.398(3)	C(20)-H(20B)	0.9900
C(8)-C(9)	1.379(4)	C(21)-C(22)	1.537(3)
C(8)-H(8)	0.9500	C(21)-H(21A)	0.9900
C(9)-C(10)	1.373(4)	C(21)-H(21B)	0.9900
C(9)-H(9)	0.9500	C(22)-H(22A)	0.9900
C(10)-C(11)	1.391(4)	C(22)-H(22B)	0.9900
C(10)-H(10)	0.9500	C(23)-C(24)	1.523(3)
C(11)-C(12)	1.386(4)	C(23)-H(23A)	0.9900
C(11)-H(11)	0.9500	C(23)-H(23B)	0.9900
C(12)-H(12)	0.9500	C(24)-C(25)	1.512(3)
C(13)-C(14)	1.526(3)	C(24)-H(24A)	0.9900
C(13)-H(13A)	0.9900	C(24)-H(24B)	0.9900
C(13)-H(13B)	0.9900	C(25)-C(26)	1.516(4)
C(14)-C(15)	1.523(3)	C(25)-H(25A)	0.9900

C(25)-H(25B)	0.9900	N(1)-C(1)-C(18)	113.62(18)
C(26)-H(26A)	0.9800	C(22)-C(1)-C(18)	111.16(19)
C(26)-H(26B)	0.9800	C(2)-C(1)-C(18)	109.39(18)
C(26)-H(26C)	0.9800	C(3)-C(2)-C(1)	113.68(19)
C(27)-O(5)	1.398(3)	C(3)-C(2)-H(2A)	108.8
C(27)-O(4)	1.429(3)	C(1)-C(2)-H(2A)	108.8
C(27)-H(27A)	0.9900	C(3)-C(2)-H(2B)	108.8
C(27)-H(27B)	0.9900	C(1)-C(2)-H(2B)	108.8
C(28)-O(5)	1.428(3)	H(2A)-C(2)-H(2B)	107.7
C(28)-H(28A)	0.9800	N(2)-C(3)-C(4)	118.2(2)
C(28)-H(28B)	0.9800	N(2)-C(3)-C(2)	129.3(2)
C(28)-H(28C)	0.9800	C(4)-C(3)-C(2)	112.5(2)
C(29)-C(30)	1.385(4)	C(3)-C(4)-C(5)	108.48(18)
C(29)-C(34)	1.391(4)	C(3)-C(4)-H(4A)	110.0
C(29)-H(29)	0.9500	C(5)-C(4)-H(4A)	110.0
C(30)-C(31)	1.388(4)	C(3)-C(4)-H(4B)	110.0
C(30)-H(30)	0.9500	C(5)-C(4)-H(4B)	110.0
C(31)-C(32)	1.392(4)	H(4A)-C(4)-H(4B)	108.4
C(31)-C(35)	1.507(4)	N(1)-C(5)-C(4)	111.50(18)
C(32)-C(33)	1.381(4)	N(1)-C(5)-C(13)	114.46(18)
C(32)-H(32)	0.9500	C(4)-C(5)-C(13)	111.35(19)
C(33)-C(34)	1.387(4)	N(1)-C(5)-H(5)	106.3
C(33)-H(33)	0.9500	C(4)-C(5)-H(5)	106.3
C(34)-S(1)	1.767(3)	C(13)-C(5)-H(5)	106.3
C(35)-H(35A)	0.9800	O(3)-C(6)-N(1)	124.2(2)
C(35)-H(35B)	0.9800	O(3)-C(6)-C(7)	117.9(2)
C(35)-H(35C)	0.9800	N(1)-C(6)-C(7)	117.7(2)
N(2)-N(3)	1.414(3)	C(12)-C(7)-C(8)	119.0(2)
N(3)-S(1)	1.639(2)	C(12)-C(7)-C(6)	120.8(2)
N(3)-H(3N)	0.74(2)	C(8)-C(7)-C(6)	119.7(2)
O(1)-S(1)	1.4321(19)	C(9)-C(8)-C(7)	120.1(3)
O(2)-S(1)	1.4371(19)	C(9)-C(8)-H(8)	119.9
		C(7)-C(8)-H(8)	119.9
N(1)-C(1)-C(22)	109.43(17)	C(10)-C(9)-C(8)	120.7(3)
N(1)-C(1)-C(2)	106.55(17)	C(10)-C(9)-H(9)	119.7
C(22)-C(1)-C(2)	106.34(19)	C(8)-C(9)-H(9)	119.7

C(9)-C(10)-C(11)	119.9(3)	C(16)-C(17)-H(17C)	109.5
C(9)-C(10)-H(10)	120.0	H(17A)-C(17)-H(17C)	109.5
C(11)-C(10)-H(10)	120.0	H(17B)-C(17)-H(17C)	109.5
C(12)-C(11)-C(10)	119.7(3)	C(23)-C(18)-C(19)	105.98(18)
C(12)-C(11)-H(11)	120.1	C(23)-C(18)-C(1)	116.01(19)
C(10)-C(11)-H(11)	120.1	C(19)-C(18)-C(1)	113.43(19)
C(11)-C(12)-C(7)	120.5(3)	C(23)-C(18)-H(18)	107.0
C(11)-C(12)-H(12)	119.7	C(19)-C(18)-H(18)	107.0
C(7)-C(12)-H(12)	119.7	C(1)-C(18)-H(18)	107.0
C(14)-C(13)-C(5)	115.4(2)	O(4)-C(19)-C(20)	110.4(2)
C(14)-C(13)-H(13A)	108.4	O(4)-C(19)-C(18)	111.11(18)
C(5)-C(13)-H(13A)	108.4	C(20)-C(19)-C(18)	113.02(19)
C(14)-C(13)-H(13B)	108.4	O(4)-C(19)-H(19)	107.3
C(5)-C(13)-H(13B)	108.4	C(20)-C(19)-H(19)	107.3
H(13A)-C(13)-H(13B)	107.5	C(18)-C(19)-H(19)	107.3
C(15)-C(14)-C(13)	113.0(2)	C(21)-C(20)-C(19)	112.6(2)
C(15)-C(14)-H(14A)	109.0	C(21)-C(20)-H(20A)	109.1
C(13)-C(14)-H(14A)	109.0	C(19)-C(20)-H(20A)	109.1
C(15)-C(14)-H(14B)	109.0	C(21)-C(20)-H(20B)	109.1
C(13)-C(14)-H(14B)	109.0	C(19)-C(20)-H(20B)	109.1
H(14A)-C(14)-H(14B)	107.8	H(20A)-C(20)-H(20B)	107.8
C(16)-C(15)-C(14)	113.8(2)	C(20)-C(21)-C(22)	109.9(2)
C(16)-C(15)-H(15A)	108.8	C(20)-C(21)-H(21A)	109.7
C(14)-C(15)-H(15A)	108.8	C(22)-C(21)-H(21A)	109.7
C(16)-C(15)-H(15B)	108.8	C(20)-C(21)-H(21B)	109.7
C(14)-C(15)-H(15B)	108.8	C(22)-C(21)-H(21B)	109.7
H(15A)-C(15)-H(15B)	107.7	H(21A)-C(21)-H(21B)	108.2
C(17)-C(16)-C(15)	113.9(2)	C(21)-C(22)-C(1)	112.02(19)
C(17)-C(16)-H(16A)	108.8	C(21)-C(22)-H(22A)	109.2
C(15)-C(16)-H(16A)	108.8	C(1)-C(22)-H(22A)	109.2
C(17)-C(16)-H(16B)	108.8	C(21)-C(22)-H(22B)	109.2
C(15)-C(16)-H(16B)	108.8	C(1)-C(22)-H(22B)	109.2
H(16A)-C(16)-H(16B)	107.7	H(22A)-C(22)-H(22B)	107.9
C(16)-C(17)-H(17A)	109.5	C(24)-C(23)-C(18)	111.9(2)
C(16)-C(17)-H(17B)	109.5	C(24)-C(23)-H(23A)	109.2
H(17A)-C(17)-H(17B)	109.5	C(18)-C(23)-H(23A)	109.2

C(24)-C(23)-H(23B)	109.2	C(29)-C(30)-C(31)	121.5(3)
C(18)-C(23)-H(23B)	109.2	C(29)-C(30)-H(30)	119.2
H(23A)-C(23)-H(23B)	107.9	C(31)-C(30)-H(30)	119.2
C(25)-C(24)-C(23)	115.3(2)	C(30)-C(31)-C(32)	117.7(3)
C(25)-C(24)-H(24A)	108.4	C(30)-C(31)-C(35)	121.6(3)
C(23)-C(24)-H(24A)	108.4	C(32)-C(31)-C(35)	120.7(3)
C(25)-C(24)-H(24B)	108.4	C(33)-C(32)-C(31)	121.6(3)
C(23)-C(24)-H(24B)	108.4	C(33)-C(32)-H(32)	119.2
H(24A)-C(24)-H(24B)	107.5	C(31)-C(32)-H(32)	119.2
C(24)-C(25)-C(26)	111.7(2)	C(32)-C(33)-C(34)	119.8(3)
C(24)-C(25)-H(25A)	109.3	C(32)-C(33)-H(33)	120.1
C(26)-C(25)-H(25A)	109.3	C(34)-C(33)-H(33)	120.1
C(24)-C(25)-H(25B)	109.3	C(33)-C(34)-C(29)	119.6(3)
C(26)-C(25)-H(25B)	109.3	C(33)-C(34)-S(1)	120.9(2)
H(25A)-C(25)-H(25B)	107.9	C(29)-C(34)-S(1)	119.5(2)
C(25)-C(26)-H(26A)	109.5	C(31)-C(35)-H(35A)	109.5
C(25)-C(26)-H(26B)	109.5	C(31)-C(35)-H(35B)	109.4
H(26A)-C(26)-H(26B)	109.5	H(35A)-C(35)-H(35B)	109.5
C(25)-C(26)-H(26C)	109.5	C(31)-C(35)-H(35C)	109.5
H(26A)-C(26)-H(26C)	109.5	H(35A)-C(35)-H(35C)	109.5
H(26B)-C(26)-H(26C)	109.5	H(35B)-C(35)-H(35C)	109.5
O(5)-C(27)-O(4)	113.8(2)	C(6)-N(1)-C(5)	115.69(18)
O(5)-C(27)-H(27A)	108.8	C(6)-N(1)-C(1)	122.62(18)
O(4)-C(27)-H(27A)	108.8	C(5)-N(1)-C(1)	121.39(17)
O(5)-C(27)-H(27B)	108.8	C(3)-N(2)-N(3)	116.8(2)
O(4)-C(27)-H(27B)	108.8	N(2)-N(3)-S(1)	113.55(18)
H(27A)-C(27)-H(27B)	107.7	N(2)-N(3)-H(3N)	120(2)
O(5)-C(28)-H(28A)	109.5	S(1)-N(3)-H(3N)	111(2)
O(5)-C(28)-H(28B)	109.5	C(27)-O(4)-C(19)	112.99(17)
H(28A)-C(28)-H(28B)	109.5	C(27)-O(5)-C(28)	113.6(2)
O(5)-C(28)-H(28C)	109.5	O(1)-S(1)-O(2)	120.04(12)
H(28A)-C(28)-H(28C)	109.5	O(1)-S(1)-N(3)	108.46(13)
H(28B)-C(28)-H(28C)	109.5	O(2)-S(1)-N(3)	103.85(12)
C(30)-C(29)-C(34)	119.7(3)	O(1)-S(1)-C(34)	107.92(13)
C(30)-C(29)-H(29)	120.2	O(2)-S(1)-C(34)	109.35(12)
C(34)-C(29)-H(29)	120.2	N(3)-S(1)-C(34)	106.42(11)

Table 14. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **220**.

The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	34(2)	34(1)	41(1)	-2(1)	0(1)	0(1)
C(2)	33(2)	34(1)	48(1)	-4(1)	-1(1)	0(1)
C(3)	31(2)	37(2)	49(2)	2(1)	7(1)	1(1)
C(4)	39(2)	34(1)	45(1)	2(1)	5(1)	-1(1)
C(5)	42(2)	34(1)	39(1)	-2(1)	3(1)	0(1)
C(6)	30(2)	31(1)	46(1)	2(1)	-3(1)	2(1)
C(7)	41(2)	32(1)	43(1)	1(1)	2(1)	-2(1)
C(8)	45(2)	38(2)	60(2)	-5(1)	4(1)	4(1)
C(9)	62(2)	47(2)	74(2)	-11(2)	13(2)	12(2)
C(10)	88(3)	43(2)	68(2)	-16(2)	13(2)	-1(2)
C(11)	71(2)	51(2)	57(2)	-11(2)	2(2)	-18(1)
C(12)	52(2)	42(2)	45(1)	-1(1)	3(1)	-9(1)
C(13)	42(2)	37(1)	47(1)	5(1)	0(1)	-1(1)
C(14)	41(2)	41(2)	47(1)	2(1)	-2(1)	3(1)
C(15)	42(2)	47(2)	49(2)	5(1)	-2(1)	-1(1)
C(16)	42(2)	66(2)	64(2)	9(2)	1(1)	-3(1)
C(17)	38(2)	93(2)	70(2)	15(2)	0(1)	3(2)
C(18)	39(2)	34(1)	41(1)	0(1)	1(1)	-1(1)
C(19)	39(2)	39(2)	51(2)	-7(1)	4(1)	-5(1)
C(20)	54(2)	45(2)	49(2)	-4(1)	-2(1)	-8(1)
C(21)	51(2)	42(2)	48(2)	3(1)	-8(1)	-6(1)
C(22)	41(2)	38(2)	49(1)	4(1)	-4(1)	-1(1)
C(23)	39(2)	34(1)	46(1)	-1(1)	3(1)	0(1)
C(24)	37(2)	38(1)	54(2)	-4(1)	6(1)	-3(1)
C(25)	41(2)	47(2)	79(2)	-2(2)	10(1)	-3(1)
C(26)	35(2)	59(2)	110(3)	-7(2)	7(2)	0(1)
C(27)	51(2)	34(2)	63(2)	-12(1)	1(1)	-1(1)
C(28)	41(2)	70(2)	102(2)	-24(2)	-17(2)	5(1)
C(29)	50(2)	53(2)	56(2)	5(2)	0(1)	4(1)

C(30)	47(2)	55(2)	58(2)	2(2)	7(1)	7(1)
C(31)	46(2)	51(2)	55(2)	-12(1)	0(1)	10(1)
C(32)	56(2)	61(2)	52(2)	-2(2)	-6(2)	6(1)
C(33)	59(2)	48(2)	54(2)	-1(1)	7(2)	-2(1)
C(34)	47(2)	29(1)	59(2)	2(1)	2(1)	1(1)
C(35)	50(2)	88(2)	70(2)	-14(2)	-2(2)	12(2)
N(1)	36(1)	30(1)	40(1)	-1(1)	0(1)	-1(1)
N(2)	39(1)	35(1)	53(1)	-2(1)	3(1)	-3(1)
N(3)	45(2)	37(1)	58(2)	2(1)	1(1)	-3(1)
O(1)	53(1)	48(1)	86(1)	14(1)	14(1)	-8(1)
O(2)	59(1)	38(1)	88(1)	-10(1)	-13(1)	-8(1)
O(3)	45(1)	36(1)	46(1)	1(1)	5(1)	-3(1)
O(4)	44(1)	35(1)	58(1)	-9(1)	6(1)	-6(1)
O(5)	41(1)	51(1)	66(1)	-19(1)	-7(1)	1(1)
S(1)	44(1)	34(1)	75(1)	3(1)	0(1)	-6(1)

Table 15. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **220**.

	x	y	z	$U_{(eq)}$
H(2A)	1958	4951	2007	46
H(2B)	2186	3997	1729	46
H(4A)	1873	3637	709	48
H(4B)	1449	4375	354	48
H(5)	834	3057	708	46
H(8)	1728	1872	1146	57
H(9)	1884	560	591	73
H(10)	1001	-357	333	80
H(11)	-58	22	647	72
H(12)	-218	1312	1230	56
H(13A)	298	4789	1049	50
H(13B)	300	4422	401	50
H(14A)	-378	3144	731	52
H(14B)	-451	3680	1329	52
H(15A)	-937	4946	815	56
H(15B)	-914	4337	242	56
H(16A)	-1644	3263	671	69
H(16B)	-1674	3887	1237	69
H(17A)	-2179	5075	693	100
H(17B)	-2610	4155	687	100
H(17C)	-2172	4418	140	100
H(18)	659	5154	1916	46
H(19)	567	5560	2940	52
H(20A)	1436	5008	3542	59
H(20B)	883	4255	3411	59
H(21A)	1923	3572	3321	57
H(21B)	2136	4329	2854	57
H(22A)	1107	2997	2682	52
H(22B)	1811	2946	2380	52

H(23A)	-83	3795	2152	47
H(23B)	10	4156	2798	47
H(24A)	-352	5661	2458	51
H(24B)	-547	5174	1866	51
H(25A)	-1144	4788	2950	67
H(25B)	-1328	4261	2367	67
H(26A)	-1526	6185	2551	102
H(26B)	-2099	5431	2545	102
H(26C)	-1707	5661	1966	102
H(27A)	1617	7277	2727	59
H(27B)	866	7006	2826	59
H(28A)	2278	6094	3504	107
H(28B)	2154	6719	4061	107
H(28C)	2357	7188	3464	107
H(29)	549	7081	1843	64
H(30)	-566	7079	1630	64
H(32)	-168	7833	-2	67
H(33)	949	7757	188	65
H(35A)	-1342	8073	541	104
H(35B)	-1457	7253	990	104
H(35C)	-1294	7026	331	104
H(3N)	1783(12)	6265(18)	1711(10)	36(9)

Table 16. Hydrogen bonds for **220** [Å and ٩].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(3)-H(3N)...O(4)	0.74(2)	2.25(2)	2.991(3)	174(3)

Symmetry transformations used to generate equivalent atoms:

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